REGIOSELECTIVITY IN DIELS-ALDER REACTIONS AND PROBING THE USE OF THE GEMINAL ACYLATION REACTION FOR THE FORMATION OF A STEROID

TONYA S.L. CHINN

Regioselectivity in Diels-Alder Reactions and Probing the Use of the Geminal Acylation Reaction for the Formation of a Steroid

by

Tonya S. L. Chinn
(B.Sc. Honours, Memorial University, 2001)

A thesis submitted to the School of Graduate Studies

in partial fulfillment of the requirements for the degree of

Master of Science

Department of Chemistry

Memorial University of Newfoundland

St. John's, Newfoundland and Labrador

May 2005

Abstract

Regioselectivity in Diels-Alder reactions is usually explained using frontier molecular orbital and/or electrostatic rationales. Steric interactions may play an important role in determining stereoselectivity. Thus, a hypothesis was suggested by the Burnell group that steric hindrance might contribute significantly to regioselectivity as well. Attempts to test this hypothesis focused on methyl-substituted *para*-benzoquinones. Dienes which were used had structures such that the regiochemical bias would be due to a steric factor rather than an electronic one. Previous work by the Burnell group dealt with dienes which did not show any such bias. This document deals with cyclic dienes to alleviate some prior problems. 2,6-Dimethyl-*para*-benzoquinone was initially used as the dienophile since many compounds found in nature have two methyl groups with a 1,3-relationship within them. Various dienes were used with this dienophile using various conditions, but unsatisfactory results required a change in the dienes to make them more stable and a change in the dienophile towards a better steric probe. Diels-Alder reactions with the new dienes and dienophiles were carried out under various conditions, still producing no satisfactory results. New dienophiles, *N*-phenylmaleimide and 2-methyl-*N*-phenylmaleimide, were used with the same dienes in an attempt to learn about the reactivity of the dienes and obtain Diels-Alder adducts. Some success was seen with these dienophiles. All of the results are summarized, along with modifications that had to be made to the Diels-Alder substrates.

The geminal acylation reaction can be applied to many ketones and acetals. The

various routes that were devised towards the synthesis of a steroid skeleton, via a double geminal acylation, as well as modifications to the original routes, are discussed. The first attempts involved the Michael addition of silyl enol ethers to α,β-unsaturated ketones to give diketones. Some success was achieved, but due to some undesired results, substrates had to be modified. These modifications led to substrates which could be used as precursors to natural products, and a route was devised for future work on this objective. The second route towards the required diketones used ozonolysis and was successful. The third and fourth routes involved alkylations, which proved to be difficult. Various conditions were tried and some showed positive results. Some new information dealing with the reactivity of alkylation substrates as well as double alkylations was discovered. Also, several substrates were more difficult to produce than anticipated. Various routes were attempted and the substrates were obtained. Some results, such as the reductive succinoylation, seen before in the Burnell group were observed with this work as well. Possible precursors to other natural molecules were obtained and routes are proposed towards such molecules.

Acknowledgements

I would like to thank, first and foremost, Jean Burnell for his guidance, not only with this Masters project, but with various projects I have been a part of throughout my chemistry career. I would also like to thank him for the monumental support, knowledge, and advice he has provided during my undergraduate and Masters degrees. I also need to thank Christine Elliott, Angela Blanchard, Rhea Melanson, Guanglin Bao, Christopher Morrison, and Anne McCarthy, past members of the Burnell group, who have passed on much of their knowledge about chemistry, lab procedures and thesis writing to me. Rolf Vermeij, Jiang Li, and especially Ian Pottie, Krista Hawco, and Teizi Satou, who have given me much advice about chemistry and equipment, need to be thanked, and I do so with much gratitude. All of these people have taught me lab skills and chemistry that could not be found in a book.

Many thanks are given to Graham Bodwell for chemical knowledge he has passed on to me and for being available for questions in Dr. Burnell's absence. I would also like to thank David Miller and Rosemary Harvey for all their help with the NMR facilities, and Patrick Hannon for the use of lab equipment under his supervision. These people have also contributed greatly to my undergraduate and Masters degrees. A special thanks to faculty, staff and fellow students of the Memorial University Chemistry Department who have made both these degrees successful and something I will carry with me and cherish forever.

I thank Dr. Burnell, the Memorial University Chemistry Department, and Memorial University of Newfoundland for financial support and allowing me to work with Dr. Jean Burnell's group which has broadened my knowledge greatly

Last, but not least, I would like to thank my parents, loved ones, and friends for providing support throughout my university career.

Table of Contents

List of Figures

List of Schemes

Glossary of Abbreviations

Ac	acetate
ATR	attenuated total reflectance
bd	broad doublet
bm	broad medium
bw	broad weak
C-1	carbon-1
cm	centimeter
^{13}C NMR	carbon nuclear magnetic resonance
CNDO/2	complete neglect of differential overlap
d (for NMR)	doublet
d	days
dd	doublet of doublets
DME	1,2-dimethoxyethane
DMP	Dess-Martin periodinane
ESR	electronic spin resonance
Et	ethyl
FMO	frontier molecular orbital
g	grams
h	hours
HMPA	hexamethylphosphoramide
^{1}H NMR	proton nuclear magnetic resonance
HOMO	highest occupied molecular orbital

IR	infrared spectrometry
J	coupling constant (*J* value)
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
m (for IR)	medium
m (for NMR)	multiplet
Me	methyl
MeOH	methanol
mg	milligrams
min	minute
mL	milliliter
mmol	millimole
MO	molecular orbital
mol	mole
mp	melting point
P	protecting group
PDC	pyridinium dichromate
Ph	phenyl
ppm	parts per million
p-TsOH	*para*-toluenesulfonic acid
RAMP	(*R*)-(+)-1-amino-2-methoxymethylpyrrolidine
ref.	reference
rt	room temperature

s (for NMR)	singlet
s (for IR)	strong
SAMP	(*S*)-(-)-1-amino-2-methoxymethylpyrrolidine
t	triplet
TBS	*tert*-butyldimethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tr	triphenylmethyl
trityl	triphenylmethyl
w	weak

1. Regioselectivity in Diels Alder Reactions

1.1 Introduction

Regioselectivity in Diels-Alder reactions is often explained using electrostatic and/or frontier molecular orbital (FMO) considerations. This involves the favorable overlap between the larger coefficients of the HOMO of the diene and the LUMO of the dienophile during the transition state.[1] In other words, FMO theory proposes that regioselectivity is controlled by the interaction of the end of the diene with the larger coefficient in its HOMO, and the end of the dienophile with the larger coefficient in its LUMO. The closer the two orbitals are in energy, the more strongly the orbitals will interact. The overlap is greatest when the diene attacks the site in the dienophile which has the larger LUMO coefficient. Thus, this is the predicted site of attack.[2] FMO theory uses these interactions to predict the regioselectivity of Diels-Alder reactions. The reaction in Scheme 1 illustrates an example where the experimental result corresponds with the FMO prediction of regioselectivity.[2, 3]

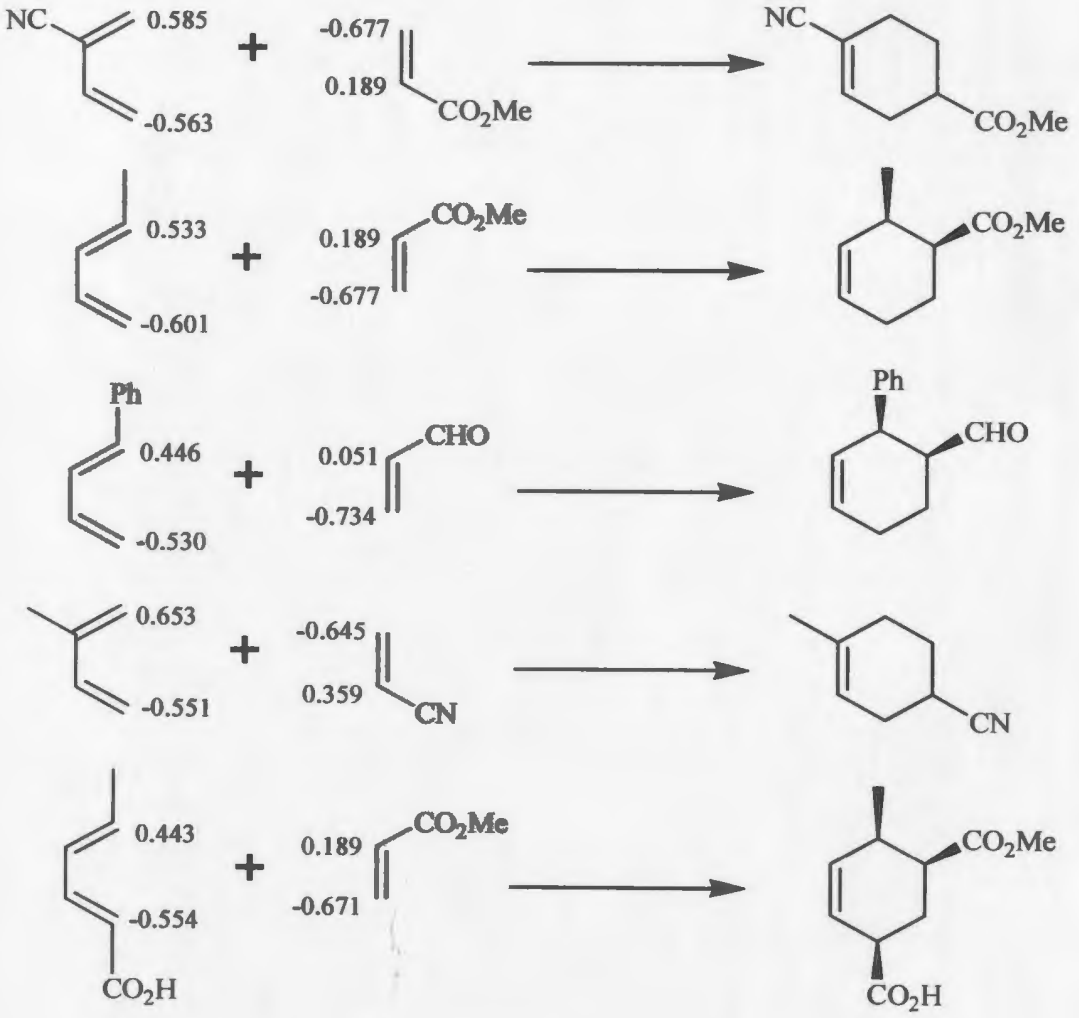
Many studies have used FMO theory to predict the regioselectivity of Diels-Alder reactions.[3] Anh *et al.*[3b] have applied FMO theory to approximately 100 examples of the

Scheme 1

Coefficients of frontier orbitals determined by Hückel methods

Diels-Alder reaction. Some examples from his work, with major products shown, are provided in Scheme 2. The more nucleophilic site of a diene is the terminus with the higher HOMO coefficient. A relationship between experimentally measured quantities and the site of attack has been found by Houk *et al.*[2] using ESR spectra. The hyperfine

Scheme 2



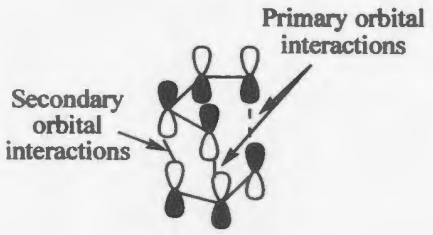
Coefficients of frontier orbitals determined by Hückel methods.

couplings observed in these spectra of a radical anion of a molecule are related to the site of attack on the neutral molecule. The hyperfine couplings correlate with the spin

densities of a site, and the spin densities are related to the coefficients of the singly occupied orbital of the radical anion. This singly occupied orbital is the LUMO of the neutral molecule. They found a clear correspondence between the magnitudes of the LUMO coefficients and the preferential site of attack by nucleophiles for both donor- and acceptor-substituted benzoquinones. Many of Houk's studies used benzoquinones and naphthoquinones.

Alston[4] found that where the generalizations of the FMO theory have failed, regioselectivity could be predicted when secondary orbital interactions are considered. Secondary orbital interactions refer to overlap between pairs of atomic orbitals involved in the reorganization of the π system, but such interactions do not participate directly in the breakage or formation of σ bonds (Figure 1).[5] One such example is the prediction of

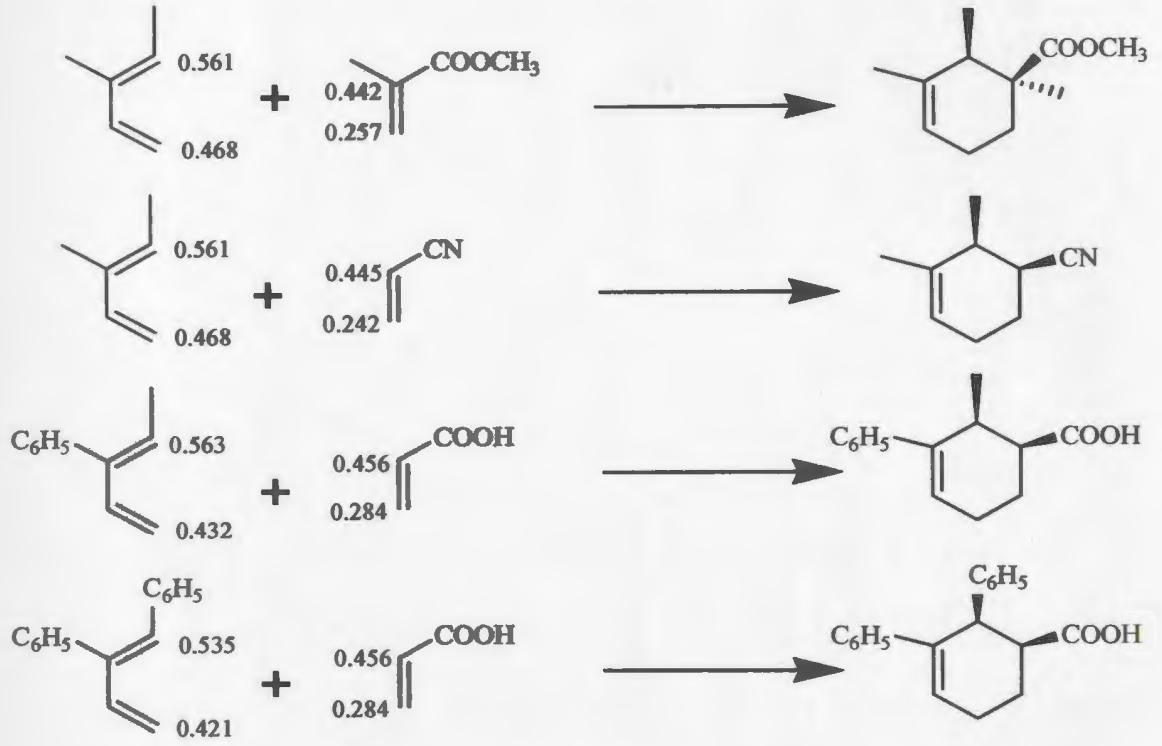
Figure 1: Secondary orbital interactions.



the regioselectivity of 1,2-disubstituted butadienes in Diels-Alder reactions. Primary orbital interactions could not predict the observed regioselectivity of the reactions in Scheme 3, as well as many other reactions (not shown).[4] However, when secondary orbital interactions were included in the FMO theory calculations, the preferred regioisomer was successfully predicted each time.[4] Alston found that the secondary orbital coefficient of the dienophile would interact preferentially with the larger

secondary orbital coefficient of the diene. Even though FMO theory has successfully predicted the regioselectivity of many Diels-Alder reactions, it has its drawbacks. Accurate predictions using FMO analysis assumes that the relative energies of the frontier

Scheme 3



Coefficients of frontier orbitals determined by CNDO/2 methods.

MO's at the ground state will not be significantly altered during the transition state. Bach *et al.*[6] found this is not the case. He found that the energies do indeed change at the transition state. He stated that "large geometric perturbations occur on going from the ground state to the transition state that result in significant destabilization of key frontier orbitals." He found that the prediction, based upon ground state arguments, that the two-electron HOMO-LUMO interaction is stabilizing and will have the largest influence on the regiochemistry of the reaction is not translated to the transition state. He attributed

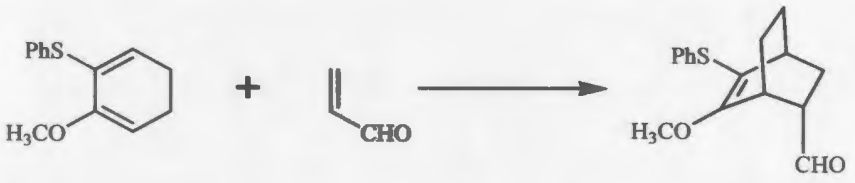
the shortcomings of FMO treatments of the Diels-Alder reaction to this destabilization of frontier orbitals at the transition state.

Hehre *et al.*[7] recognized that a drawback to the FMO theory is in misassigning the regioproduct in cycloadditions to dienes substituted by two different groups or by the same group in different diene positions. He attributed the shortcomings of FMO theory to the assumption of additivity of substituent effects on orbital coefficients or to

Scheme 4

equating a difference in orbital coefficients to regiochemical preferences. FMO theory correctly suggested that a methoxy substituent will dominate a methyl group in a 1,4-disubstituted diene when directing regioselectivity (Scheme 4), and properly ordered the relative directing abilities of acetoxy and ethyl groups in the 1,4 positions. However, FMO theory failed to show that a phenyl substituent is a much better regiodirector than a methyl group when they are in the 1,4 positions of a diene. FMO theory also fails to indicate phenyl and chloro substituents are better regiodirectors than methyl substituents,

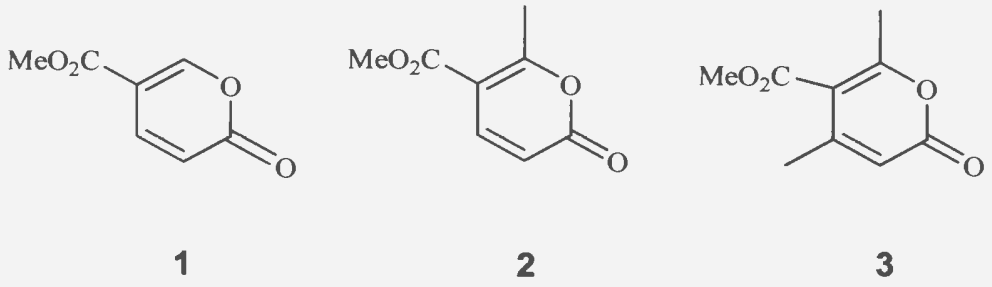
Scheme 5



and also that 2-ethoxy, 2-acetoxy, 2-trichloroacetoxy, 2-phenyl and 2-chloro substituents are not as strongly regiodirecting as a methyl group in the 1-position of butadiene. In Scheme 5, the product shown is another experimental result, where FMO theory predicted that the methoxy group should be a stronger director.

There is a recognition that steric effects can greatly influence facial selectivity and reaction rate in Diels-Alder reactions. It has been seen in many cases that the Diels-Alder reaction is highly facially selective, and the main factor that controls this selectivity is steric effects, which force the diene to attack preferentially the less sterically demanding, or more open, surface.[8] Steric interactions also influence the rate of Diels-Alder reactions, slowing the reaction if the steric effects are large.[9] For example, 5-methoxycarbonyl-2-pyrone (**1**) reacts faster than 5-methoxycarbonyl-6-methyl-2-pyrone (**2**), which reacts much faster than 5-methoxycarbonyl-4,6-dimethyl-2-pyrone (**3**)

Figure 2: Pyrones which react at different rates due to sterics.



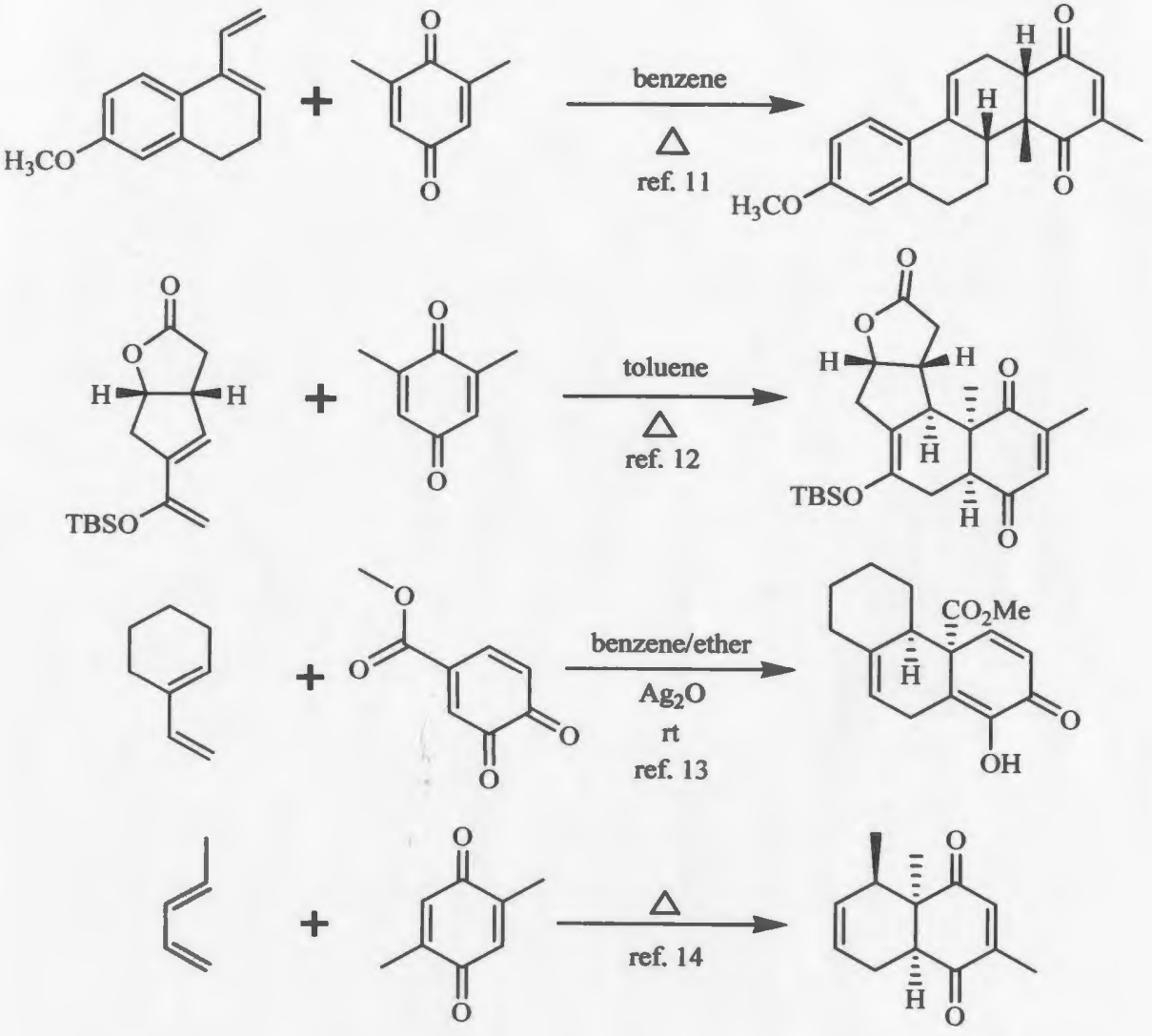
1 **2** **3**

(Figure 2). This difference in rate has been attributed to steric influences.[9] Endo/exo selectivity, previously explained using secondary orbital considerations, is now believed to be controlled largely by steric effects.[5, 10] However, steric effects are almost never implicated when referring to regiochemical control. It is possible the other major facet of

the Diels-Alder reaction, regioselectivity, might also be controlled by previously underappreciated steric influences.

Some synthetic examples, such as the formation of various steroids by Valenta *et al.*,[11] the assembly of kempane diterpene precursors by Liu and Burnell,[12] work by Pitea *et al.*,[13] and by Reusch *et al.*[14] (Scheme 6), contradict predictions made when using FMO theory. More selectivity is seen than orbital coefficients suggest. It appears that at least

Scheme 6

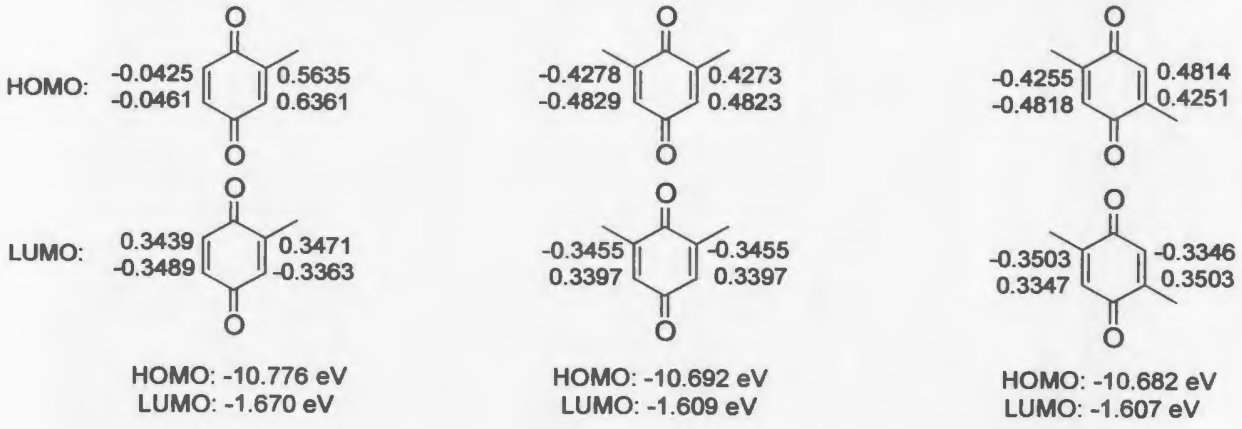


one other factor is controlling the regiochemistry in these examples. In each case, the less hindered termini of the diene and dienophile came together. Furthermore, high regioselectivity was seen, with the major products being the ones shown, in at least a 4:1 ratio with the minor product. There does not seem to be a convincing FMO-based explanation that accounts for such high selectivity since, in each case, the coefficients of the diene or the dienophile are very similar. According to FMO theory, the LUMO and HOMO with the larger coefficients would overlap, thus determining the regiochemistry. However, in Scheme 6, the coefficients of one of the two reacting partners in each reaction has very little bias. FMO theory would predict approximately a 1:1 mixture of the two possible regioisomers since there is probably no significantly larger orbital coefficient on either of the two reacting partners in each of the cases in Scheme 6. Thus, FMO theory does not seem to explain the regioselectivities shown in Scheme 6. It is possible that this orbital bias is so small that it might be insignificant, and there may be a different reason for the high regioselectivity. The results make more sense when steric effects are taken into consideration. It is highly likely that the two new bonds forming in the Diels-Alder reaction do not form synchronously, and that at the transition state, one bond would have formed more completely than the other. Thus, the two incipient bonds would be quite different in length. It would make sense for the more complete bond to form between the two less hindered ends of the diene and the dienophile, forcing the two more hindered ends to form the second bond. The reactions in Scheme 6 are four examples where the regioselectivity is very high and there is an indication that steric effects may play a role. In each case, the less substituted, less sterically hindered, end of

the diene joins with the less substituted, less sterically hindered, end of the dienophile.

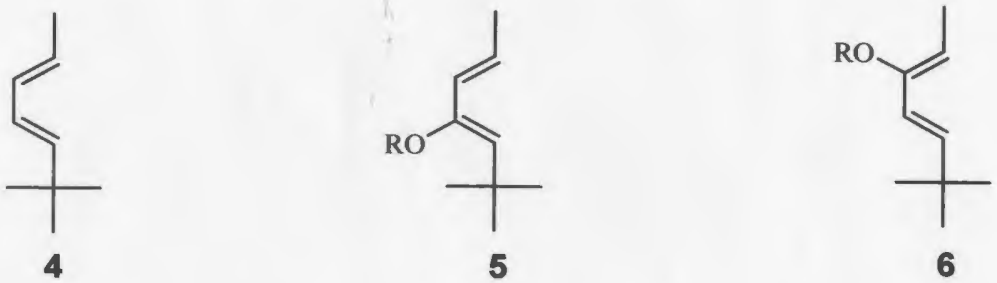
The goal of the work described in this thesis was to find experimental evidence for high regioselectivity where the FMO theory would fail to predict the regiochemical outcome, especially in cases where there are small differences between the HOMO and LUMO coefficients. Dimethyl-*para*-benzoquinones were chosen as the dienophiles to probe the steric versus electronic considerations. There were three reasons for this choice. The first was that quinones are the only examples for which there has been a

Figure 3: Results of HOMO-LUMO calculations carried out on quinones.



suggestion that steric effects may play a role in determining the regiochemistry of Diels-Alder reactions.[15] The second was that quinones are synthetically important

Figure 4: Dienes used in previous steric vs. electronic investigations.

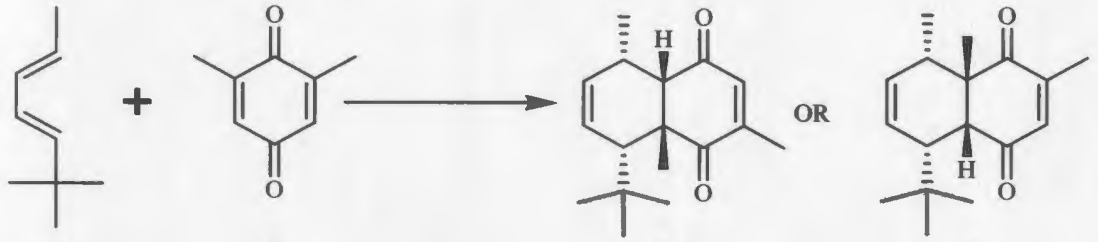


4 **5** **6**

dienophiles.[11, 12] The third was that calculations done by Xidos and Burnell show there is very little LUMO bias in these types of quinones.[16] Results of these calculations done using B3LYP/6-31G* reporting orbital coefficients perpendicular to the plane of the dienophile can be seen in Figure 3. 2,6-Dimethyl-*para*-benzoquinone was chosen initially since many substances found in nature, such as various steroids, contain two methyl groups in a 1,3 relationship. Furthermore, the difference in the C-2 and C-3 LUMO coefficients very small and is smaller than that found in other methyl-substituted quinones.

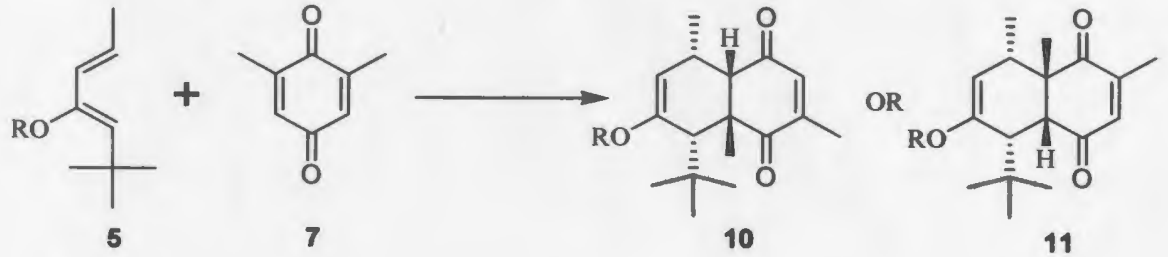
In order to prove a steric involvement, the dienes needed to have a structure such that most of the regiochemical bias would be due to a steric factor rather than an

Scheme 7



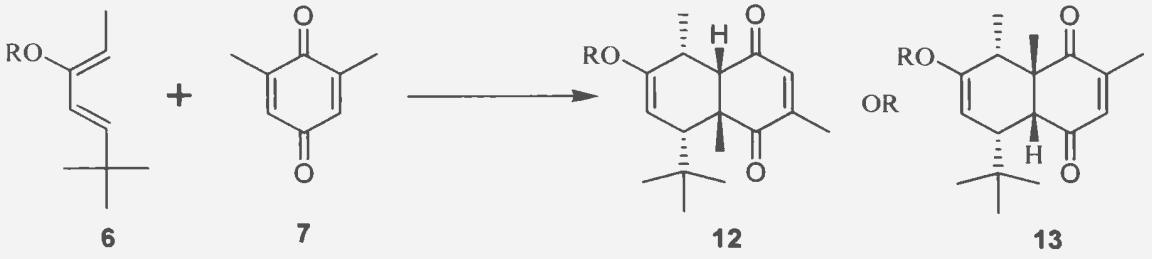
electronic one. Previous work in this investigation[17] involved dienes **4**, **5**, and **6** (Figure 4). The reaction in Scheme 7 was to be carried out to investigate regiochemical bias with

Scheme 8



diene **4**, which might have two possible endo-addition products, **8** and **9**. If the hypothesis of "less-hindered" goes to "less-hindered" holds true, **8** would be the preferred product. If diene **4** showed regiochemical bias and **8** was the major product, then the reaction involving diene **5** in Scheme 8 was to be carried out to investigate the effect of introducing an electronic or orbital bias. If **10** was the major product, then a steric effect would be more important. If **11** was the major product, then an electronic or orbital effect could be deduced to be more important. If the major product of the reaction in Scheme 7 were **9**, then the reaction involving diene **6** in Scheme 9 was to be carried out.

Scheme 9

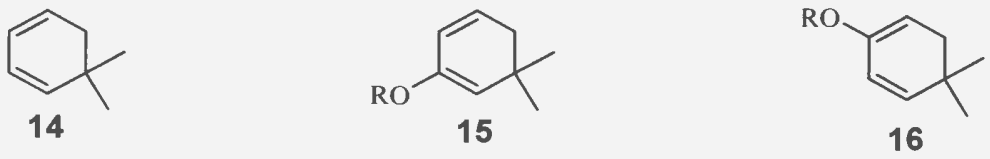


6 **7** **12** **13**

In the case where **12** was the major product, then a steric effect would be more important. If **13** was the major product, then an electronic or orbital effect would be more important. These predictions are based on the orbital difference of the diene since the dienophile would create very little orbital bias. The investigation of steric versus electronic/orbital effects using dienes **4**, **5**, and **6** was therefore undertaken.[17] However, problems were encountered. One problem was the difficulty in making and storing the dienes due to their low boiling points and ease of polymerization. The second, major problem was that diene **4** showed no bias in regioselectivity when reacted with 2,6-dimethyl-*para*-

benzoquinone (**7**). The two possible products **8** and **9** were obtained in a 1:1 ratio. A result which had some regiochemical bias was therefore required to further test the predictions of steric involvement which came about due to results such as those in Scheme 6. What was likely was that the steric differences presented by dienes **4**, **5**, and **6** were not in an effective location, especially the steric difference created by the *t*-butyl group at C5. The fact that the dienes were not rigid and the bond between the two double bonds can rotate to have a thermodynamically more favoured *s*-trans orientation might also have played a role in the undesirable results. This orientation could give rise more easily to a less reactive diene. In light of these problems, new dienes, **14**, **15**, and **16**, shown in Figure 5, were considered. The rigidity created by the ring the single bond

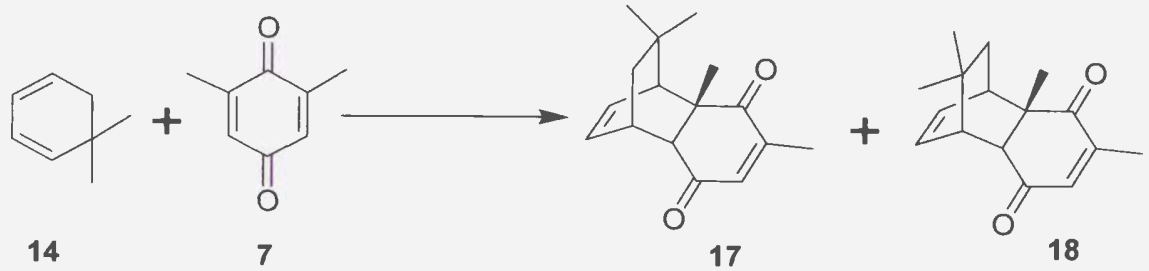
Figure 5: Proposed cyclic dienes for the steric vs. electronic investigations.



14 **15** **16**

between the two double bonds to be *s*-cis, and forces the sterically different characteristics, the CH_2 and the gem-dimethyl group, to be in a location where they would

Scheme 10



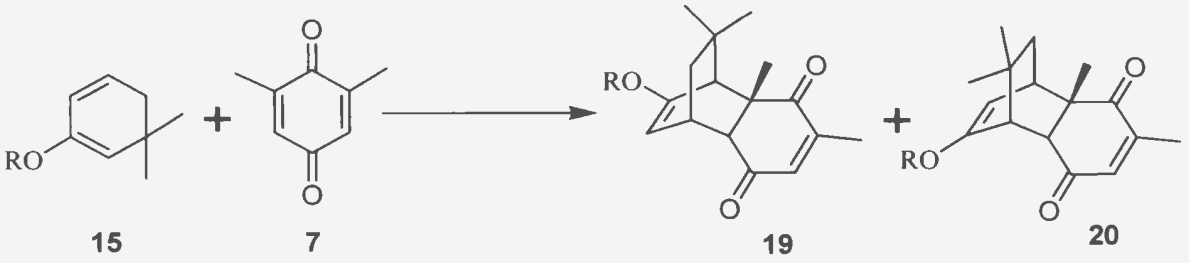
14 **7** **17** **18**

more effectively impede approach by the dienophile. This would potentially create more

of a steric interaction than the less rigid methyl and *t*-butyl groups in the three dienes **4**, **5**, and **6** previously considered.

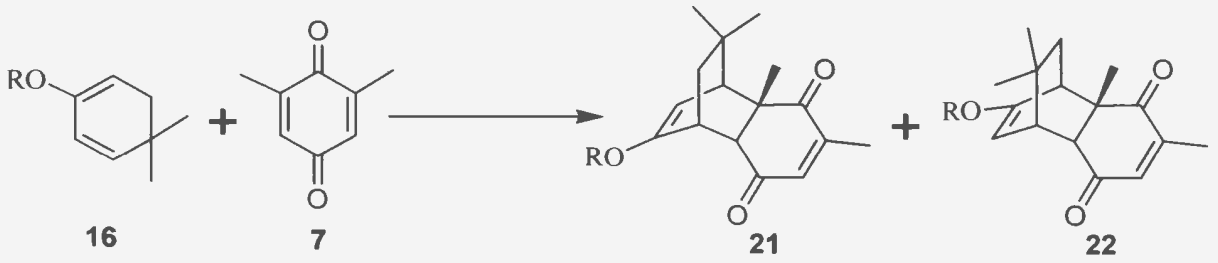
The reaction between diene **14** and 2,6-dimethyl-*para*-benzoquinone (**7**) in Scheme 10, which would be carried out to investigate the initial regiochemical bias,

Scheme 11



would have two possible "endo" products, **17** and **18**. If the reaction in Scheme 10 shows bias, then the reactions in Scheme 11 and Scheme 12 with dienes **15** and **16**, respectively, would be carried out to introduce electronic or orbital effects to see if the regioselectivity, relative to the gem-dimethyl group, would change. If **19** and **21** are the major products,

Scheme 12

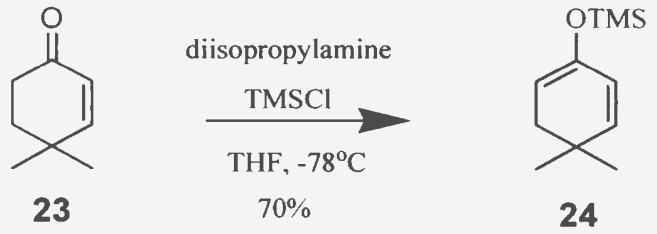


respectively, then steric effects would still be dominant. If **20** and **22** are the major products, then it can be deduced that electronic or orbital effects would be more important. If adducts of the same type as the major adduct in Scheme 10 persisted in Schemes 11 and 12, then a steric effect would be more dominant.

1.2 Results and Discussion

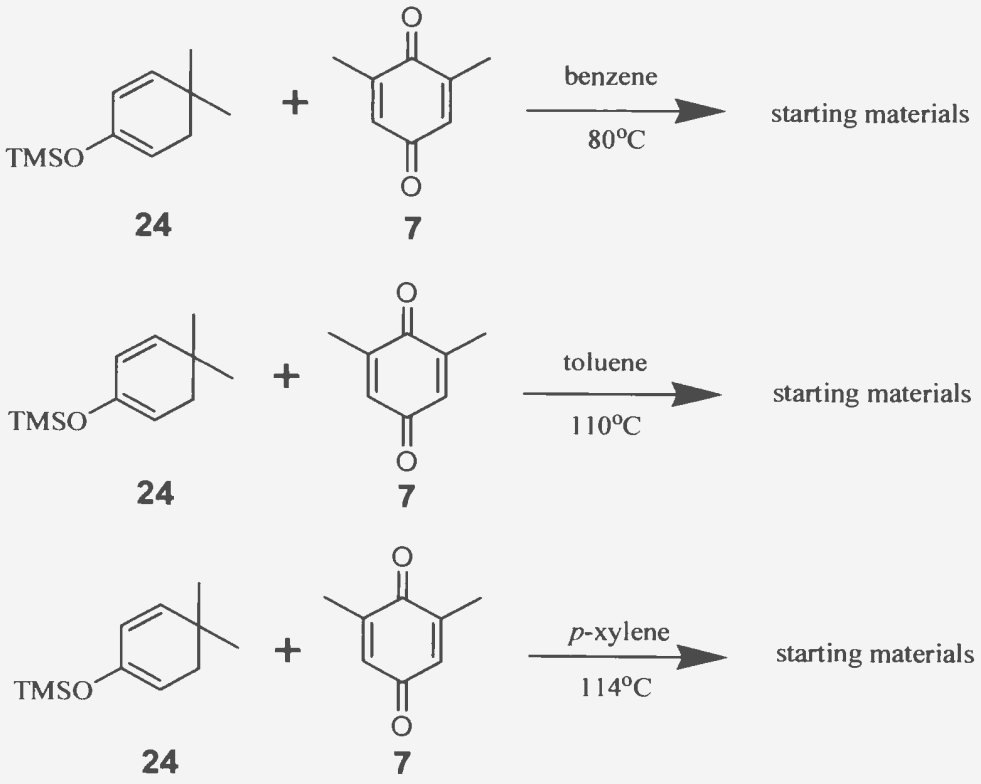
The initial work that had to be carried out was to synthesize dienes **14**, **15** and **16**.[18] This was done using lithium diisopropylamine and TMSCl on the substrate **23** to

Scheme 13



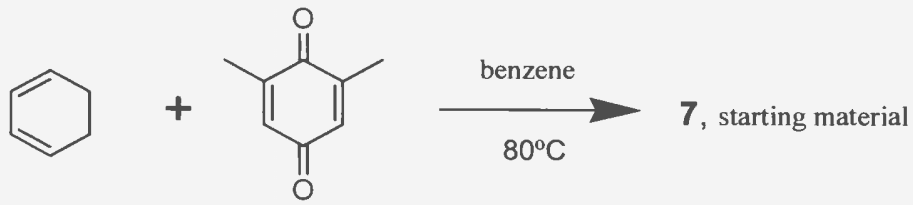
give the silyl enol ether **24** (Scheme 13). A TMS protecting group was chosen as opposed to a TBS group because TMS is less bulky. Before dienes **14** and **15** were

Scheme 14



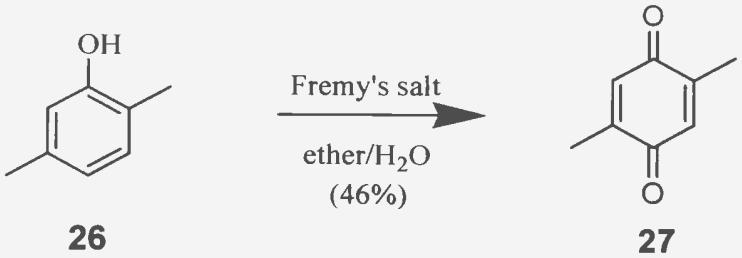
synthesized, Diels-Alder reactions were attempted, over time periods which ranged from 24 to 96 hours, using **24** and 2,6-dimethyl-*para*-benzoquinone (**7**). Diene **24** was added to **7** and heated in refluxing benzene only to return starting materials (93% recovery) (Scheme 14). Since the reaction yielded no desirable result, the temperature was increased and the reaction was carried out in a higher boiling solvent. Diene **24** and quinone **7** were heated in refluxing toluene, but only enone **23** and starting materials were recovered (92% recovery). The same two substrates were subjected to even harsher

Scheme 15



conditions, refluxing in *p*-xylene, only to experience no Diels- Alder reactivity and the return of both starting materials (87% recovery). A simpler diene was chosen instead of using **14** and **15,** which were of similar complexity to **24**, to try to obtain a Diels-Alder

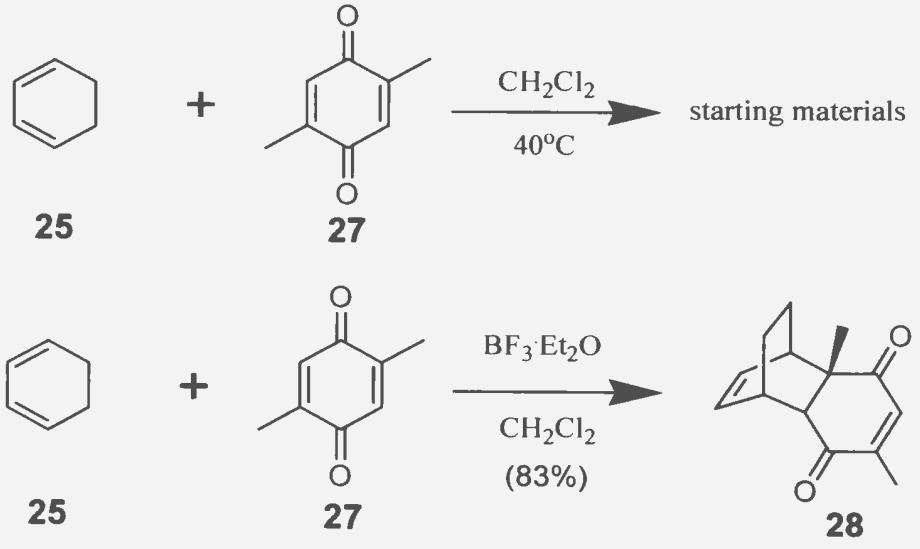
Scheme 16



adduct. 1,3-Cyclohexadiene (**25**) was chosen as the diene. This was combined with the same dienophile **7** in benzene under reflux conditions (Scheme 15). Unfortunately, only

the unreacted quinone was recovered again (57% recovery). However, more satisfactory results may be obtained with 2,5-dimethyl-*para*-benzoquinone (**27**). Compound **27** was considered to be a better probe for a potential steric interaction since the two carbonyls are chemically identical in the ground state. This quinone was synthesized from 2,5-dimethylphenol (**26**) using Fremy's salt in an emulsion of ether and water[19] (Scheme 16). 1,3-Cyclohexadiene (**25**) was added to **27** in dichloromethane at room temperature and allowed to react for 16 h, but only starting materials were retrieved (43% recovery) (Scheme 17). However, once a mixture of **25** and **27** was heated and $BF_3 \cdot Et_2O$ was

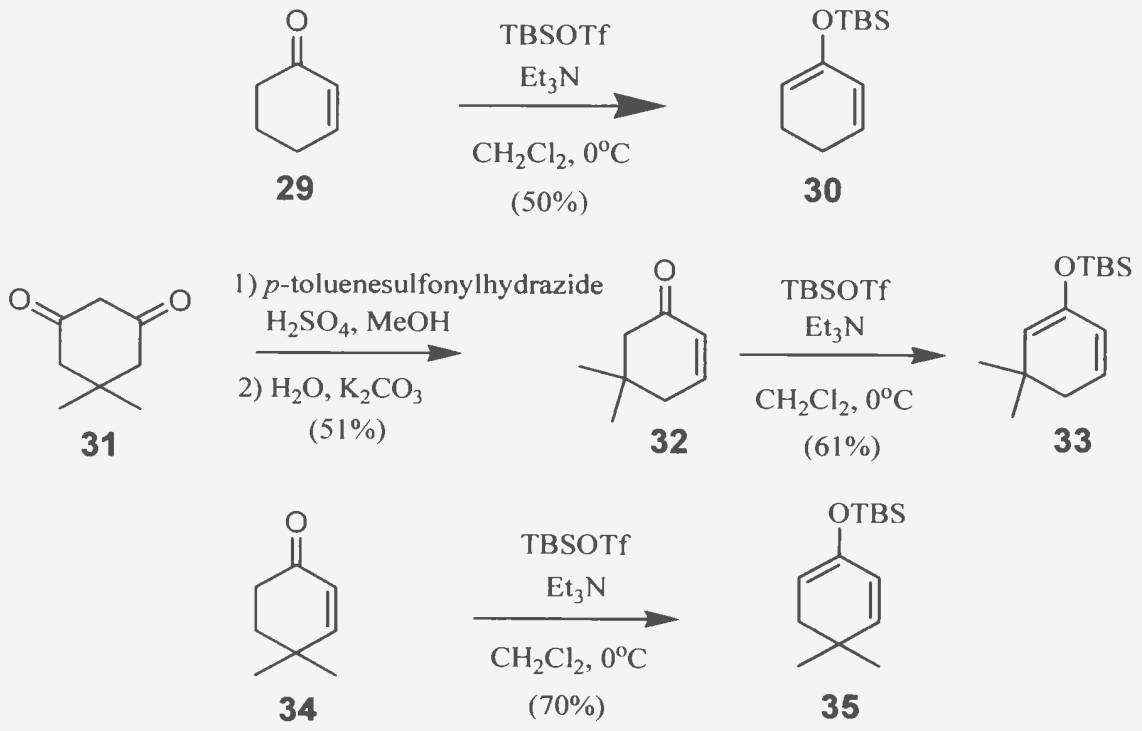
Scheme 17



added, the Diels-Alder adduct **28** was obtained in a 83% yield. Due to this positive result with **25** and the undesirable recovery of the enone seen in some instances, it was thought there was a possibility that the diene **24**, which contained the TMS group, may have been proto-desilylated. However, if dienes containing a TBS group were used in the Diels-Alder reactions, the possibility existed that the bulkiness of the TBS group could slow

down the hydrolysis process and provide a better chance for an adduct to form. Even though TBS dienes would be easier to handle, easier to store, and would be less susceptible to proto-desilylation, we were not sure the bulkier TBS group would not have an effect on the reaction due to an additional steric contribution. Nonetheless, the TBS group was needed, so it was hoped the size of the protecting group had no significant effect on the reaction.

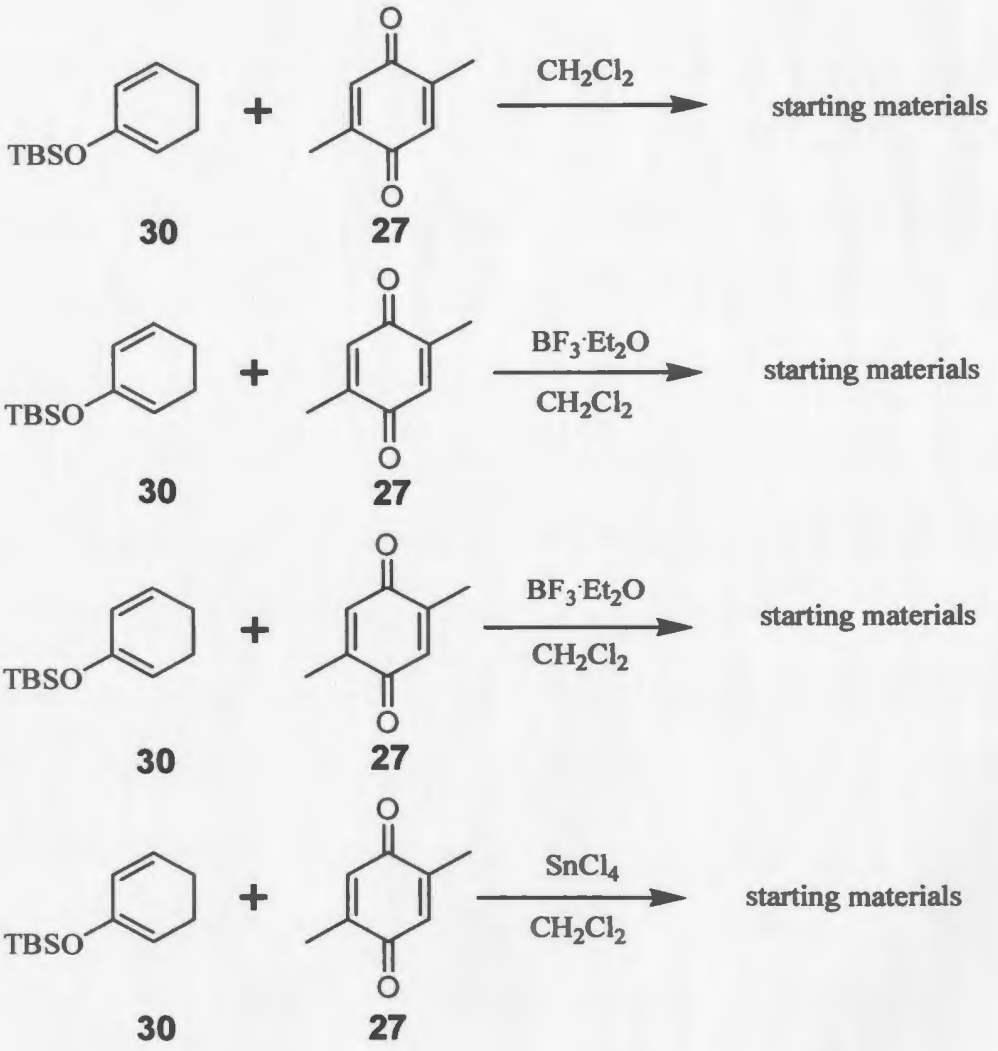
Scheme 18



Dienes **30**, **33**, and **35** were prepared from 2-cyclohexen-1-one (**29**), 5,5-dimethyl-2-cyclohexen-1-one (**32**) and 4,4-dimethyl-2-cyclohexen-1-one (**34**), respectively, using TBSOTf and triethylamine in dichloromethane[18] (Scheme 18). Enone **32** was formed from dimedone (**31**) using *para*-toluenesulfonylhydrazide and sulfuric acid in methanol

followed by the addition of water and potassium carbonate. Diels-Alder reactions were then attempted using these dienes.

Scheme 19



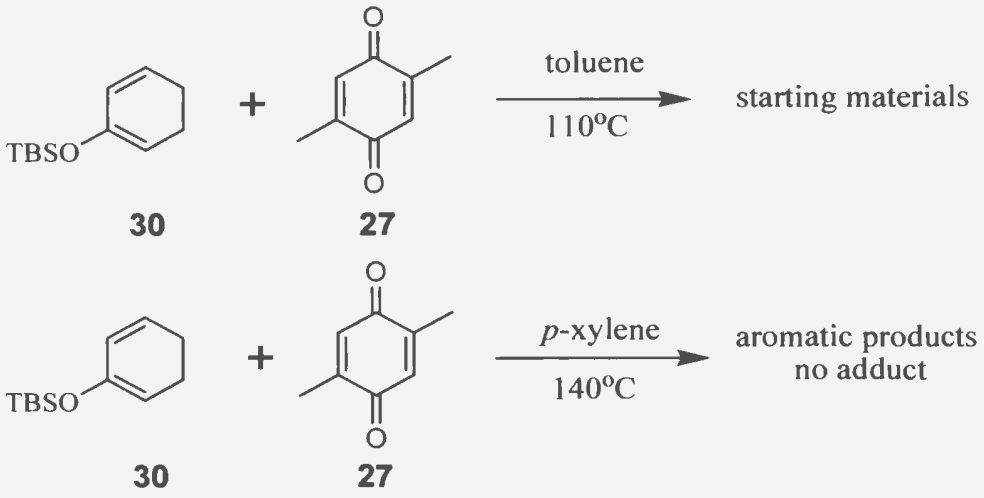
The nonmethylated diene **30** was combined with quinone **27** under mild conditions, refluxing in dichloromethane, but only starting materials were recovered (89% recovery) (Scheme 19). A Diels-Alder adduct from **30** and **27** was desired at this point, even if it was obtained using conditions that may affect regioselectivity, in order to

find out what the spectroscopic data of the desired adduct looked like. Attempts to obtain this Diels-Alder adduct involved the use of Lewis acid catalysts. Lewis acids often influence the regioselectivity of Diels-Alder reactions, but when used with **27**, this would not make a difference since steric versus electronic effects would still be probed. Addition of a Lewis acid to **27** largely changes its LUMO, and thus, its coefficients. Once the Lewis acid is added, the double bonds are no longer identical, so the coefficients of each double bond are no longer identical. The diene has a choice to which double bond it adds, similar to giving it a choice between two different molecules with which to react. If the diene is biased, it could be determined which effect is dominant, steric or electronic, depending on the adduct formed. One adduct would form as the result of steric effects dominating, and the other adduct would form as the result of electronic effects dominating. Unfortunately, the attempts were futile when $BF_3 \cdot Et_2O$ was used, with or without heat (Scheme 19), and only the enone and/or starting materials were seen in the resulting material (68-74% recovery). The results were unchanged with $SnCl_4$ (Scheme 19) with no evidence seen for Diels-Alder adduct formation, and only starting materials were recovered (79% recovery). Other Lewis acids were not tried since no Diels-Alder reactivity had been seen. There is a good chance that if *no* reactivity at all was seen, none would be seen with more reactive Lewis acids. If *some* reactivity had occurred with $BF_3 \cdot Et_2O$, or $SnCl_4$, then more reactive Lewis acids such as $AlCl_3$ would have been tried due to the good chance of increasing Diels-Alder reactivity.

The same two substrates, **30** and **27**, were subjected to higher reaction temperatures (Scheme 20). Again, only starting materials were obtained when these two

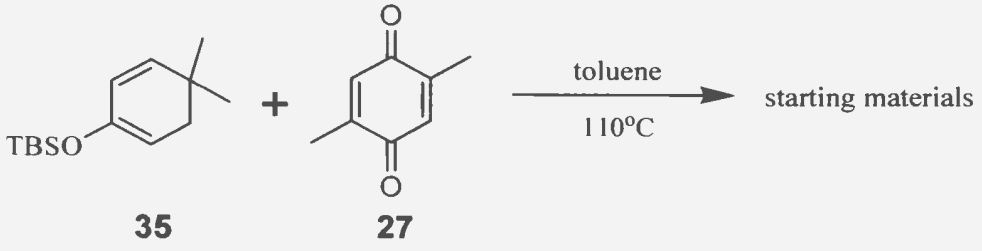
were heated at 110°C in toluene in a sealed tube (92% recovery). When heated at 140°C

Scheme 20



in *p*-xylene, in a sealed tube, only unidentified aromatic products were seen with no sign of starting materials or desired products. Quinones are known to act as oxidizing agents, so it is possible that the quinone was aromatizing the diene. The crude NMR suggested aromatic compounds but since no Diels-Alder adduct was present, it was not purified. Due to these results with the nonmethylated diene, it was decided to carry out Diels-Alder

Scheme 21

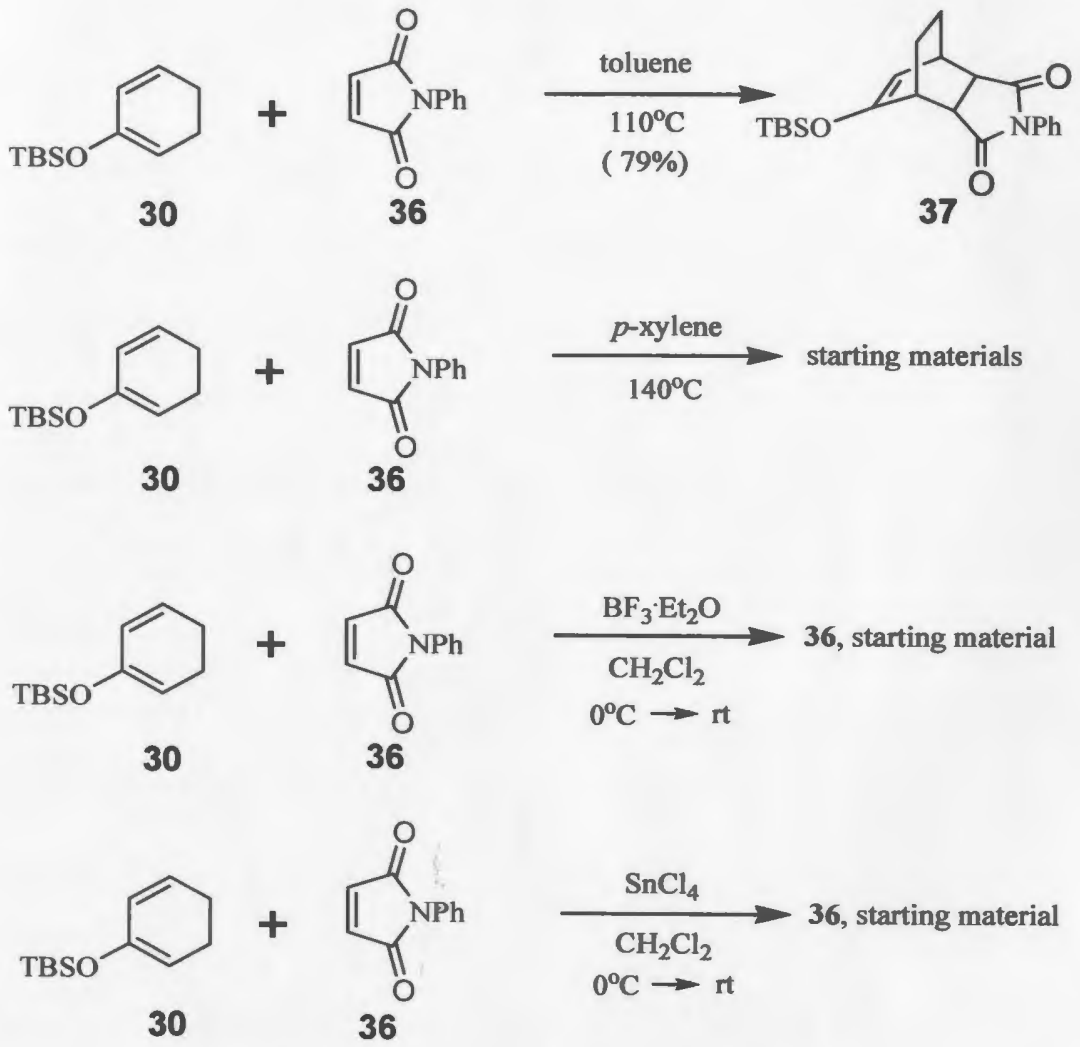


reactions with the methylated diene **35** since it would not be aromatized as easily. Diene **35** was combined with dienophile **27** and heated at 110°C in toluene in a sealed tube. With great disappointment, only starting materials were obtained (91% recovery)

(Scheme 21). It was decided to abandon the quinones as the dienophiles to try to learn more about how the dienes themselves behave.

N-Phenylmaleimide (**36**) was chosen as the new dienophile since it is generally a more reactive dienophile and high temperatures would be needed less for it to react. We were hoping to get a Diels-Alder adduct at lower temperatures where compounds are less

Scheme 22



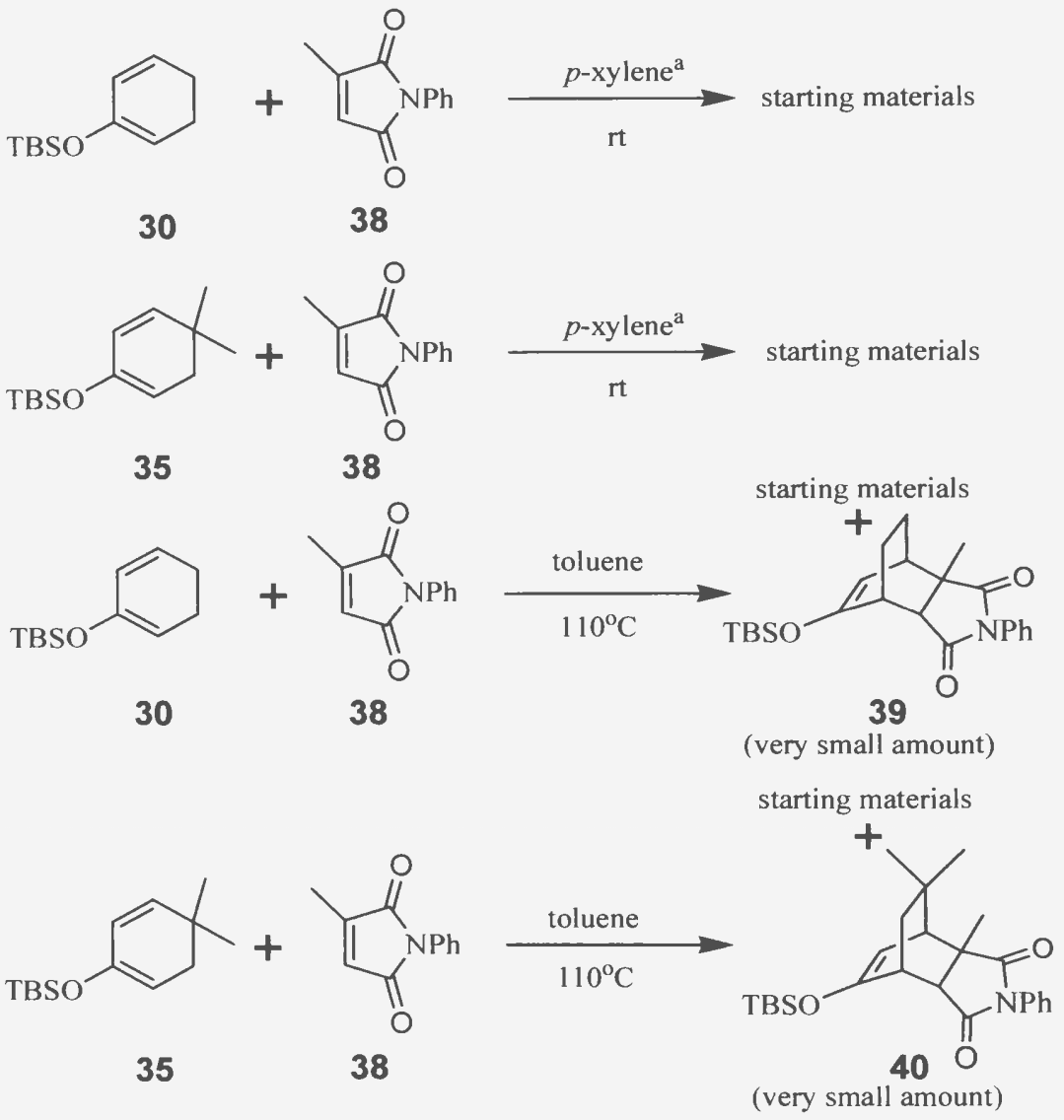
likely to aromatize. *N*-Phenylmaleimide was first reacted with the nonmethylated diene **30** (Scheme 22) in toluene and heated at 110 °C in a sealed tube. The Diels-Alder adduct

37 was formed in a 79% yield. To be consistent with previous experimental work with the quinones, the same two substrates, **30** and **36**, were heated at 140 °C in *p*-xylene in a sealed tube, but only starting materials were the result (93% recovery). Since Diels-Alder reactions are reversible, it is likely that heating at 140 °C in *p*-xylene in a sealed tube is too extreme for the Diels-Alder adduct to stay intact. Enough energy was provided for the reverse reaction to occur, causing the adduct to revert back to starting materials. If this were the case, it would appear as if no reaction had occurred and that the starting materials were unchanged. Thus, the retro-Diels-Alder is the preferred reaction at 140 °C in *p*-xylene in a sealed tube. Still keeping with the same reaction conditions as with the quinones, *N*-phenylmaleimide was combined with **30** in the presence of $BF_3 \cdot H_2O$ and $SnCl_4$ (Scheme 22), but the results were no more promising than previous Diels-Alder reactions carried out which involved Lewis acids. Only the dienophile was recovered (69-75% recovery), along with some intractable material.

Since there was some success with *N*-phenylmaleimide as the dienophile, it was decided to choose a dienophile that better matched the steric characteristics of the methyl quinones and still have similarities to *N*-phenylmaleimide. Thus, 2-methyl-*N*-phenylmaleimide (**38**) was chosen. This compound would be a reasonably efficient dienophile due to its electron-deficient double bond, it would not aromatize the dienes, and it should have a similar steric effect as the methyl quinones **7** and **27**. Dienophile **38** was combined with the nonmethylated diene **30** and heated at 110 °C in toluene in a sealed tube. Some starting materials were recovered as well as a small amount of the adduct, **39** (Scheme 23). The adduct is believed to have the regiochemistry shown since

maleimides are known to add exclusively endo.[20] The same two substrates, **30** and **38**, were combined in *p*-xylene at room temperature for fourteen days, but only starting

Scheme 23



a. A very long reaction time was anticipated, so *p*-xylene was used, at room temperature, to avoid evaporation of solvent.

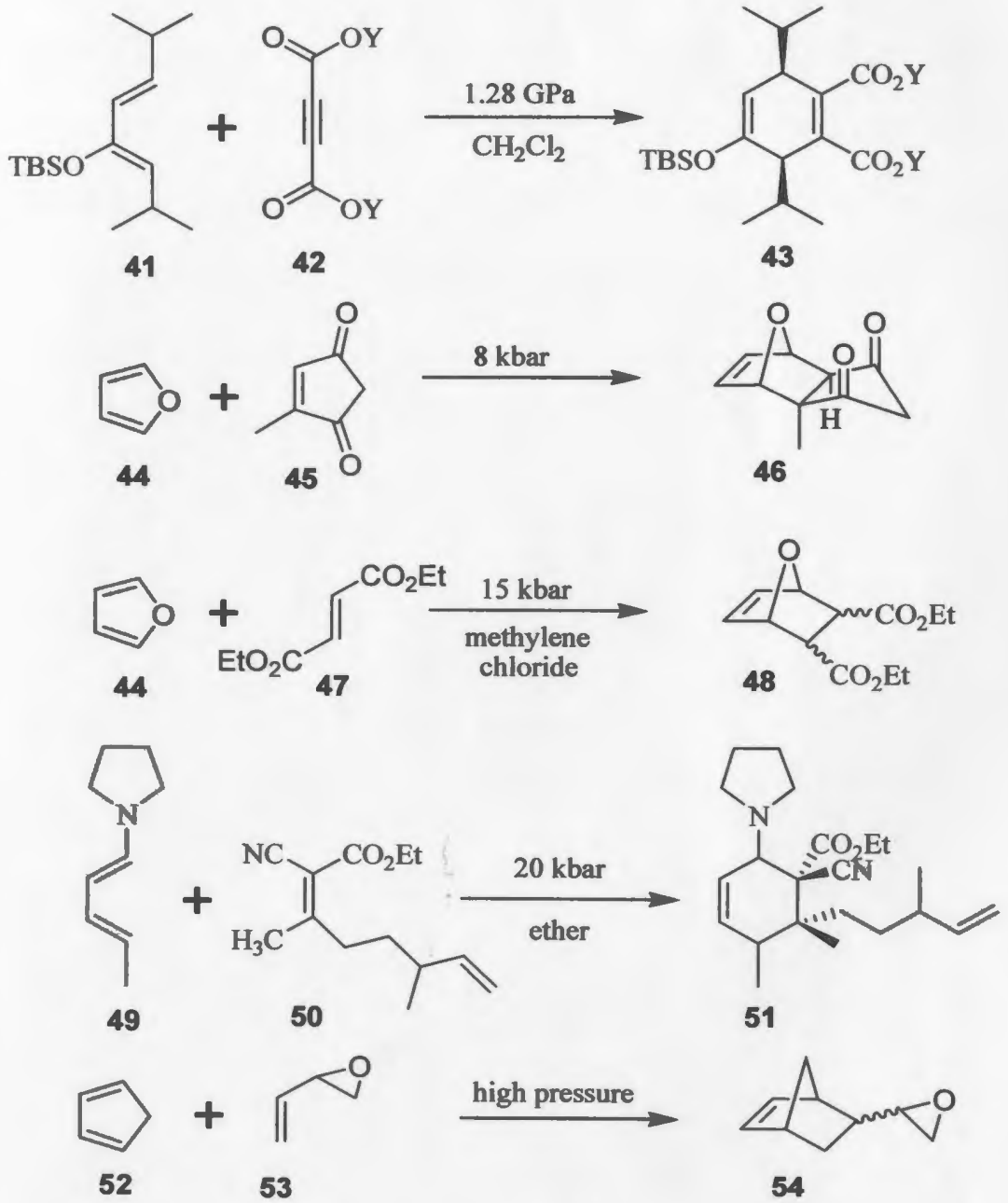
materials (71% recovery) were seen in the extracted material. Dienophile **38** was also reacted with the methylated diene **35**, by both heating at 110 °C in toluene in a sealed tube and stirring at room temperature in *p*-xylene. Again, a small amount of adduct was seen

when the reaction was heated at 110 °C in toluene, but only starting materials (74% recovery) were recovered from stirring in *p*-xylene at room temperature (Scheme 23). It should be noted that in none of the reactions in which the maleimides were used as the dienophile did any aromatic material appear in the product. This is consistent with the hypothesis that the quinones were aromatizing the dienes since aromatic material was seen when quinones were used as the dienophiles.

1.3 Conclusions and Future Work

It seems that the molecules discussed in this chapter will only show consistent Diels-Alder reactivity under extreme conditions, and even then, only with certain dienes and dienophiles as the substrates. In more extreme conditions, the adduct seems to revert

Scheme 24



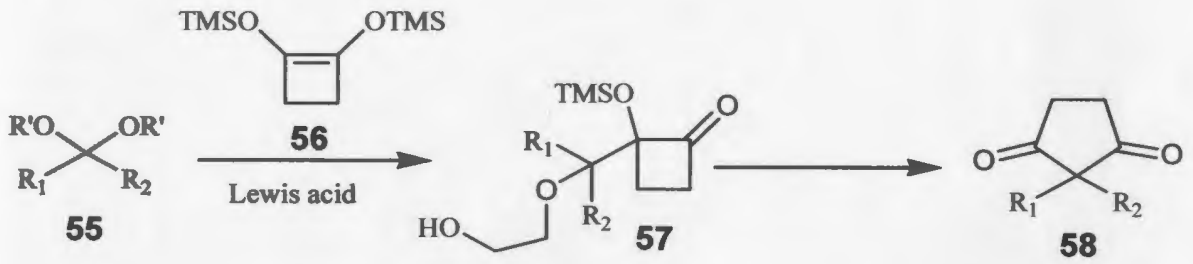
back to starting materials. Even catalysts could not force these substrates to come together. Thus, high pressure systems are most likely what will be needed for the substrates to react in an expected way. Precedence for high pressure systems being successful where thermal conditions were not has been established by a number of groups. Examples of such reactions can be seen in Scheme 24. The Burnell[21] group observed no reaction between diene **41** and dienophile **42** after 5 days under reflux in benzene but obtained the desired adduct **43** at 1.28 GPa. Dauben's[22] attempt to react **44** and **45** under thermal conditions, yielded **46** in only 2%, but the yield increased dramatically to 97% when the reaction was carried out at high pressure. Dauben[23] also increased yields of **48** and **51** by using high pressure systems as did Welker *et al.*[24] in producing **54** after thermal conditions gave very low yields. Therefore, the project was put on hold until a high pressure system becomes routinely available to the Burnell group.

2. Probing the Use of the Geminal Acylation Reaction for the Formation of a Steroid Skeleton

2.1 Introduction

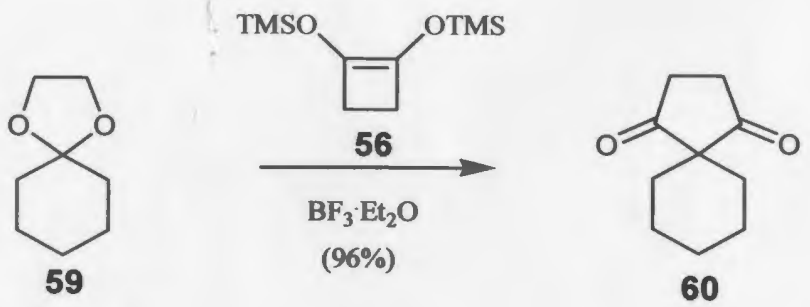
The geminal acylation reaction is the net replacement of a carbon-oxygen double bond by two geminally substituted acyl groups.[25] Kuwajima found that the reaction of acetals with 1,2-bis[(trimethylsilyl)oxy]cyclobutene (**56**) passed through a pinacol intermediate by an aldol addition. This reaction was initiated by a Lewis acid or a fluoride catalyst. A general outline of this reaction can be seen in Scheme 25.

Scheme 25



Kuwajima[25] reported that $TiCl_4$ was the most effective Lewis acid for geminal acylation with aldehydes and aliphatic acetals. This is not surprising since Mukaiyama[26] had found

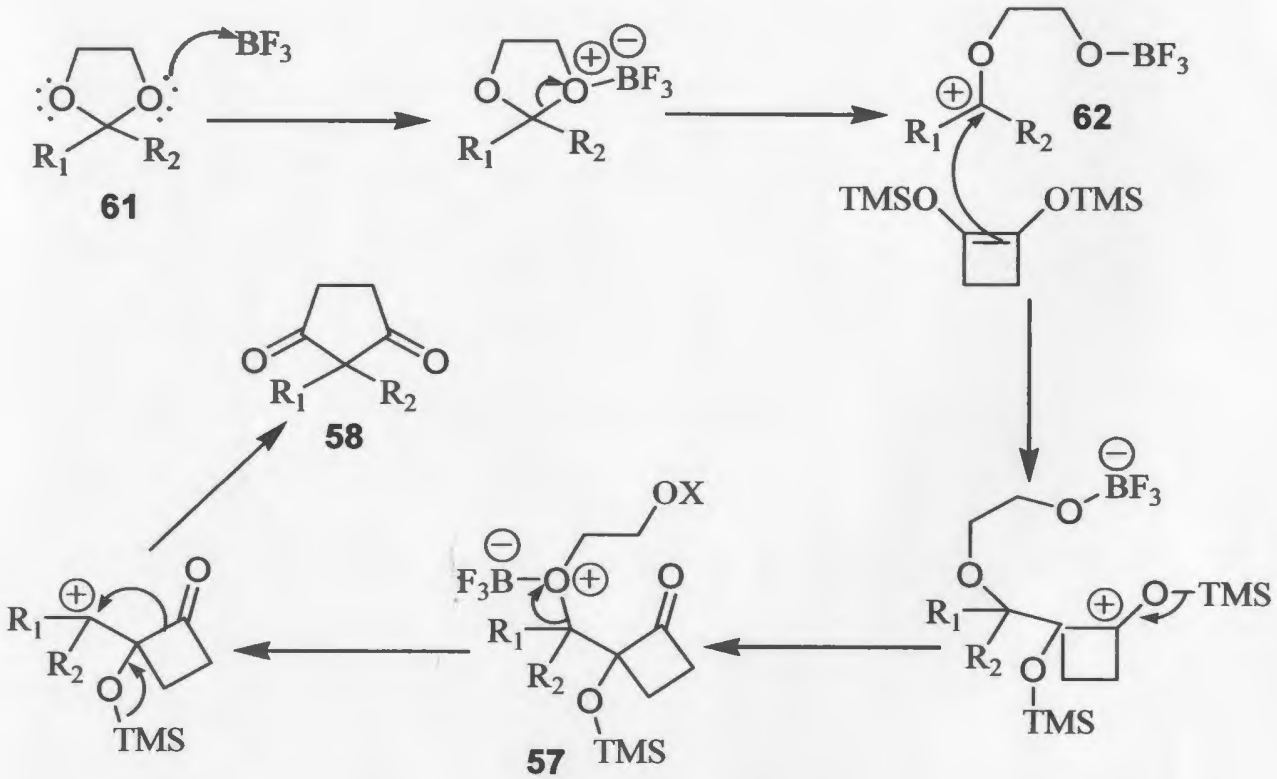
Scheme 26



that $TiCl_4$- catalyzed reactions of silyl enol ethers with acetals gave the desired products in good yields. Kuwajima reported that $BF_3{\cdot}Et_2O$ gave the best results with more reactive acetals. He claimed that ketones were not susceptible to geminal acylation conditions and did not react under various acidic and basic conditions.[25] This was consistent with the reported absence of reactivity of silyl enol ethers with ketones in other systems.[27]

The Burnell group discovered two factors which added to Kuwajima's findings (Scheme 26).[28] The first was that the proposed two-step process can be carried out in one pot, often in a higher yield, by using two to three equivalents of **56** and a large excess of $BF_3{\cdot}Et_2O$. The second was that this $BF_3{\cdot}Et_2O$ one-step process yields the 2,2-

Scheme 27

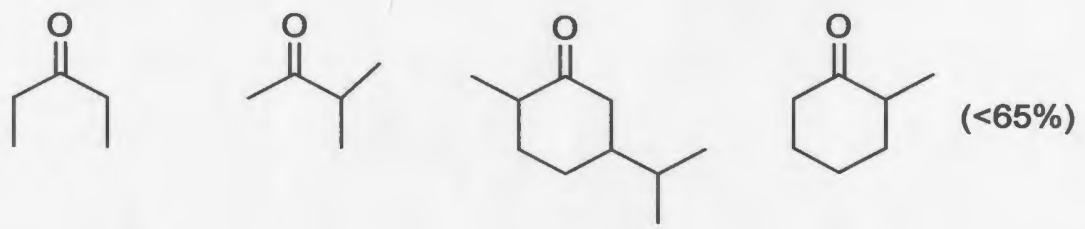


disubstituted- 1,3-cyclopentanedione **60** from the ketone in satisfactory yields when a

small volume of H_2O, equal to the volume of $BF_3{\cdot}Et_2O$, is added to the medium containing the cyclobutanone intermediate. This discovery now allowed the geminal acylation reaction to be carried out directly on ketones and not just with their corresponding acetals. Burnell proposed that the addition of H_2O and acid must facilitate the rearrangement by hydrolysis of one or both of the (trimethylsilyl)oxy groups of the no-longer-isolated cyclobutanone intermediate **57**.[28] In saying this, acetals are often the preferred of the two starting material options since they are known to coordinate more strongly with the Lewis acid than their parent ketone.[29] The mechanism of the geminal acylation reaction is illustrated on an acetal in Scheme 30. The initial Mukaiyama-like aldol reaction is initiated by coordination of the Lewis acid with an oxygen of the acetal **61**. This activates the tertiary carbon, making it susceptible to nucleophilic attack. The double bond in 1,2-bis(trimethylsilyloxy)cyclobutene **62** acts as the nucleophile. The nucleophilic attack is facilitated by the loss of one (trimethylsilyl)oxy group to give the cyclobutanone intermediate **57**. This is followed by acid-initiated acyl migration similar to a pinacol rearrangement to afford the 2,2-disubstituted 1,3-diketone **58**.

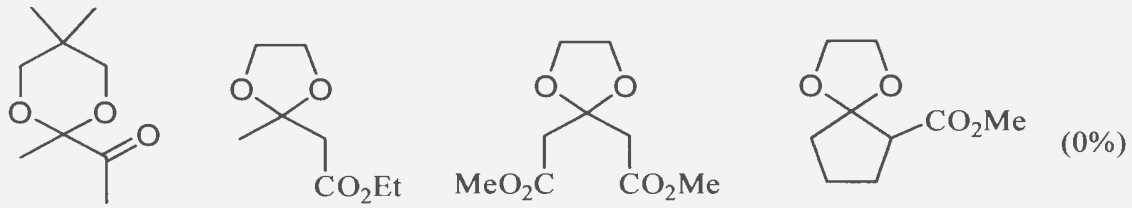
The yields of the geminal acylation reaction are very sensitive to the steric environment of the ketone or acetal. Work done by Jenkins and Burnell[28] showed that α-

Figure 6: α-methylated substrates of geminal acylation reactions.



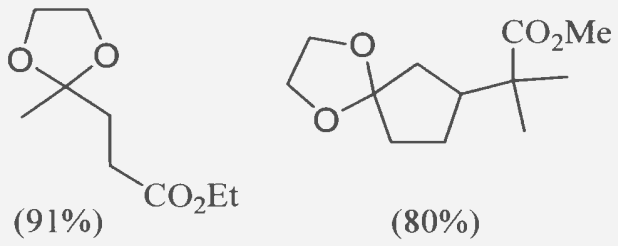
methylated substrates do not give products in useful yields in the geminal acylation reaction, (Figure 6). When there is a carbonyl α to, or an ester β to the ketone moiety (Figure 7), the geminal acylation reaction is inhibited completely [30]. However, molecules with an ester γ to the acetal moiety, or further away (Figure 8), react normally when

Figure 7: Geminal acylation substrates containing α or β carbonyl.



exposed to geminal acylation conditions.[28] The sensitivity towards substitution could place significant limits on the usefulness of the geminal acylation reaction, but it can also be used as an advantage, as Wu and Burnell showed in their synthesis of isokhusimone. In this synthesis, the doubly acetalized substrate **63** was subjected to geminal acylation

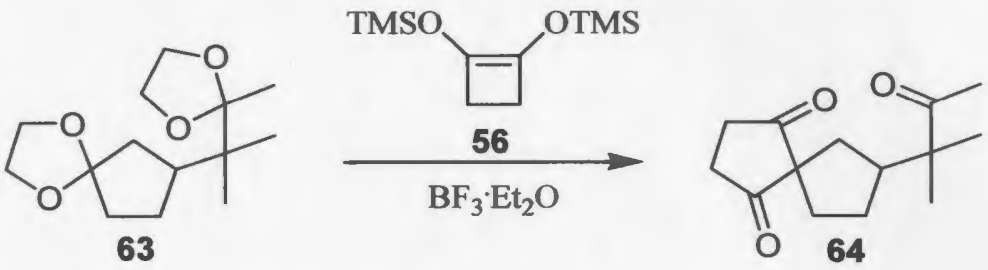
Figure 8: Geminal acylation substrates containing γ esters.



conditions and the less hindered acetal reacted efficiently to give the 1,3-pentanedione moiety (Scheme 28), whereas the more hindered acetal only underwent hydrolysis during work-up, to give **64** in a very good yield.[30] When the acetal contains alkyl or aryl substituents, the trend seen is that yields decrease as the alkyl substituents become larger

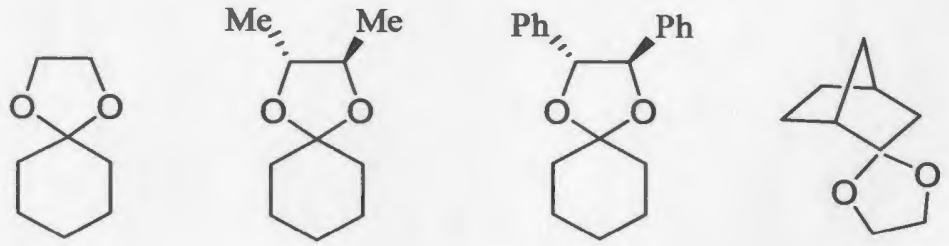
(Figure 9). Compounds **65** and **66** gave yields of 48% and 0%, respectively, whereas reactions with the unsubstituted acetal **59** proceeded under geminal acylation conditions with a 96% yield.[30] Thus, acetals with certain alkyl substituents such as that in **66** resist

Scheme 28



reactivity and can be seen as protecting groups in geminal acylation conditions.[30] The reason why alkyl substituents on the acetal impede reactivity is not known, but it is possible that the acetal reacts differently. It is possible that the oxygen-carbon bond with the alkyl group may be broken to produce a carbocation.

Figure 9: Acetals with alkyl substituents used as geminal acylation substrates.

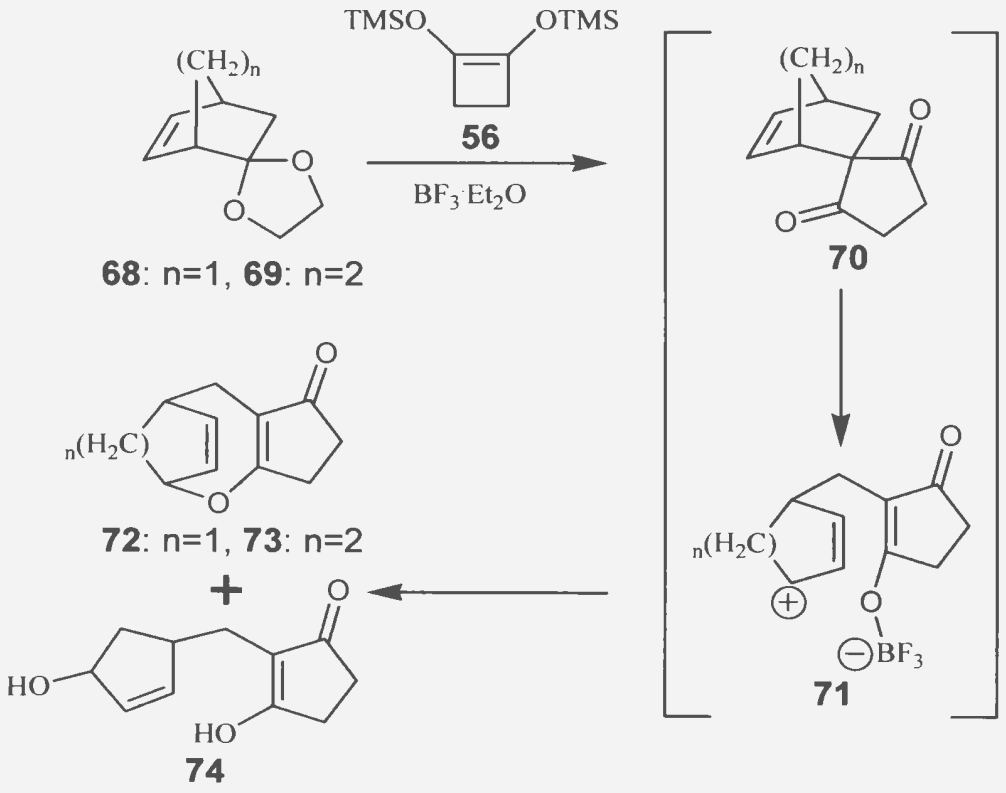


59 (96%) **65** (48%) **66** (0%) **67** (82%)

Compound **56** may attack this carbocation instead of the tertiary one. Bicyclic compounds such as **67** are more reactive than α-methylated substrates and give the desired geminal acylation product in very acceptable yields even though **67** is α substituted.[30] Reactions of some unsaturated bicyclic systems were unsuccessful under

geminal acylation conditions. Products were obtained which must have been derived from initial geminal acylation products followed by the rupture of the bicyclic framework (Scheme 29). Acetal **68** gave only a 12% yield of **72**, the consequence of an intermediate allylic cation **71** closing onto an enol oxygen. The major product seen from this substrate was **74,** which was likely the result of hydrolysis of **72** during work-up, rather than the

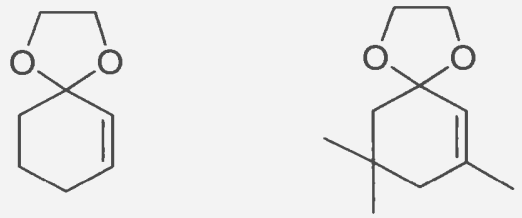
Scheme 29



capture of water by **71**, since efforts were made to exclude water from the reaction medium. On the other hand, acetal **69** gave **73** in a 56% yield as the only isolated product.[30] Reactions failed under geminal acylation conditions with acetals like those in Figure 10 which are derived from conjugated cyclic enones, where the double bond remained in the α,β-position during acetalization. This is likely due to the stabilization

of the positive charge on the tertiary carbon by the double bond rendering the carbocation sufficiently unreactive so that it does not attack **56**, leading to recovered enone through

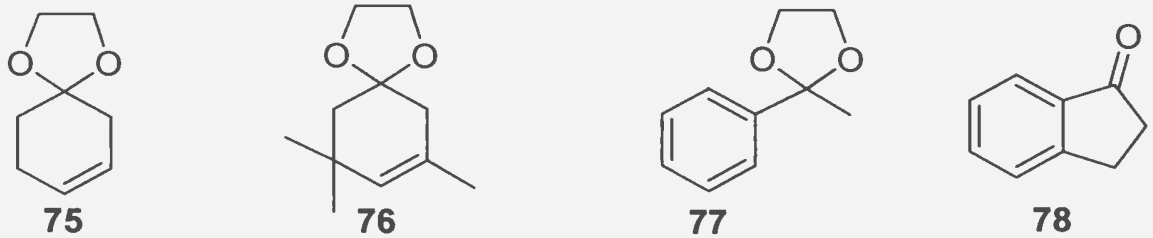
Figure 10: α, β-Unsaturated cyclic acetals.



(0%) (0%)

aqueous work up. Also, undesired products may result from 1,4 additions.[28, 30] However, substrates, such as **75** and **76**, where the double bond of the cyclic enone migrates to the

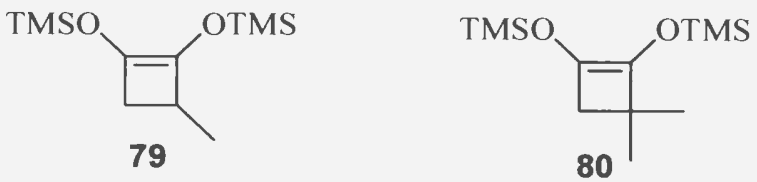
Figure 11: β,γ-Unsaturated cyclic and α-aromatic acetals.



75 (75%) **76** (72%) **77** (77%) **78** (75%)

β,γ-position during acetalization and compounds with aromatic components α to the acetal or ketone, such as **77** and **78**, underwent geminal acylation in very good yields[28, 30] (Figure 11).

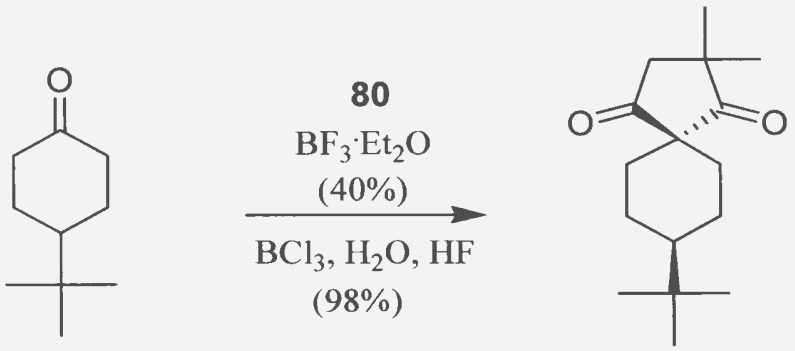
Figure 12: Mono and dimethylated 1,2-bis[(trimethylsilyl)oxy] cyclobutene.



79 **80**

Crane, Jenkins and Burnell[31] carried out modifications to the geminal acylation reaction that included the use of 3-methyl-1,2-bis[(trimethylsilyl)oxy]cyclobutene (**79**) and 3,3-dimethyl-1,2-bis[(trimethylsilyl)oxy]cyclobutene (**80**) as the nucleophiles (Figure 12). This modification is very useful since methyl or gem-dimethyl substituents appear in many natural products.[31] Reactions of **80** with ketones gave better yields than with acetals, and unhindered substrates gave the best yields.[31] They found that geminal

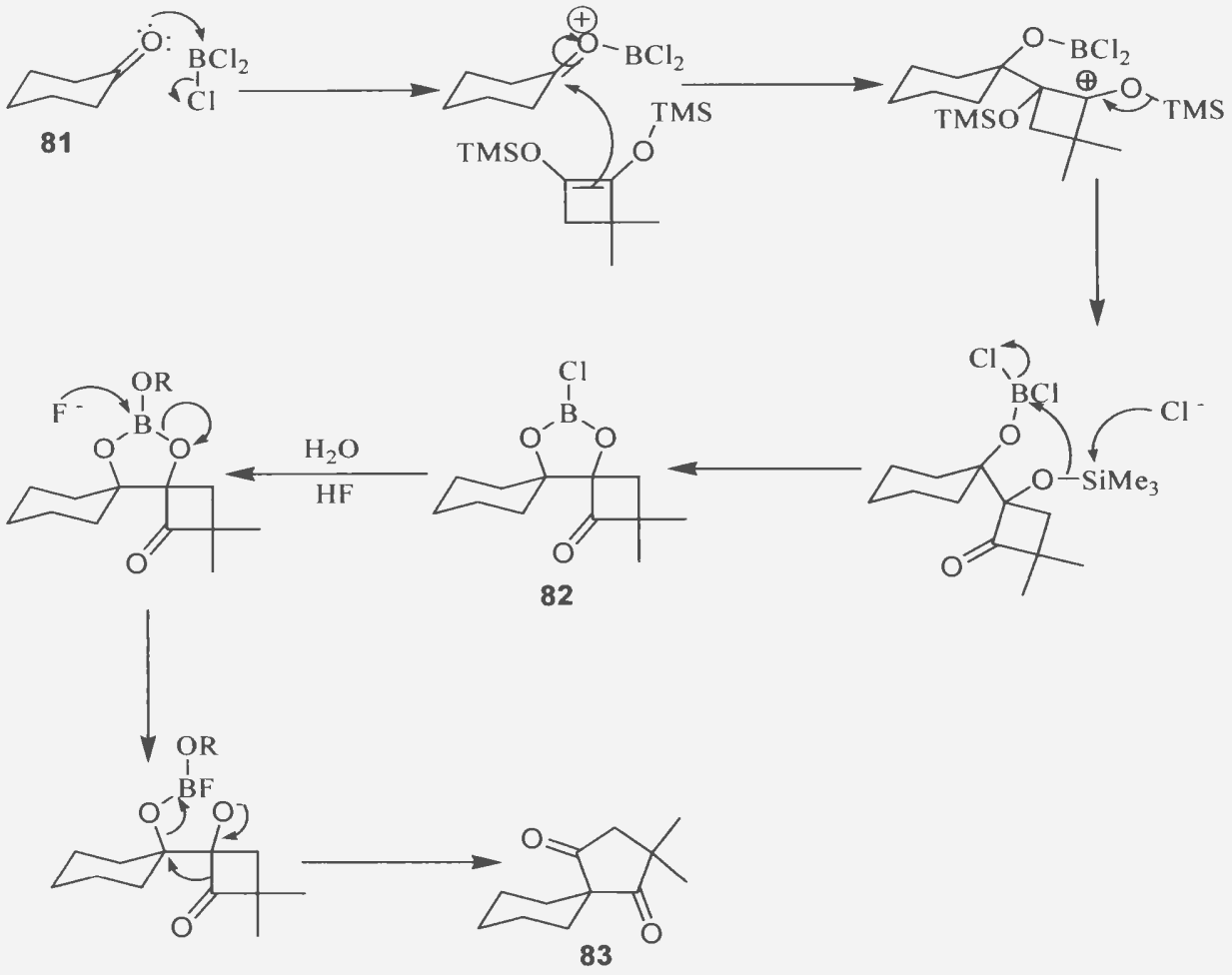
Scheme 30



acylation reactions with **80** were more successful when BCl_3 was the Lewis acid used (Scheme 30). They proposed that this was due to a difference in the mechanisms that BCl_3 and $BF_3{\cdot}Et_2O$ facilitate.[32] The proposed mechanism for the geminal acylation reaction with BCl_3 is shown in Scheme 31. The initial aldol reaction is induced by the formation of a cyclic borate **82** in which two B-Cl bonds are broken and two O-B bonds are formed. This inhibits subsequent equilibration of the aldol product. This is the key difference with the $BF_3{\cdot}Et_2O$-catalyzed mechanism, since $BF_3{\cdot}Et_2O$ allows for the equilibration of the cyclobutanone intermediate, which leads to significant amounts of a furanone by-product **84** (Scheme 32). The process seen in Scheme 32 may invoke direct attack on the carbocation, but the alkene was isolated by the Burnell group. Thus, the

carbocation is probably deprotonated prior to the formation of the furanone. Furanones were never observed in reactions with **56** and **79** so a carbocationic intermediate was suspected. Upon addition of water, hydrofluoric acid and trifluoroacetic acid, the acyl migration proceeded to yield the 2,2-disubstituted-1,3-cyclopentanedione product **83**.[32]

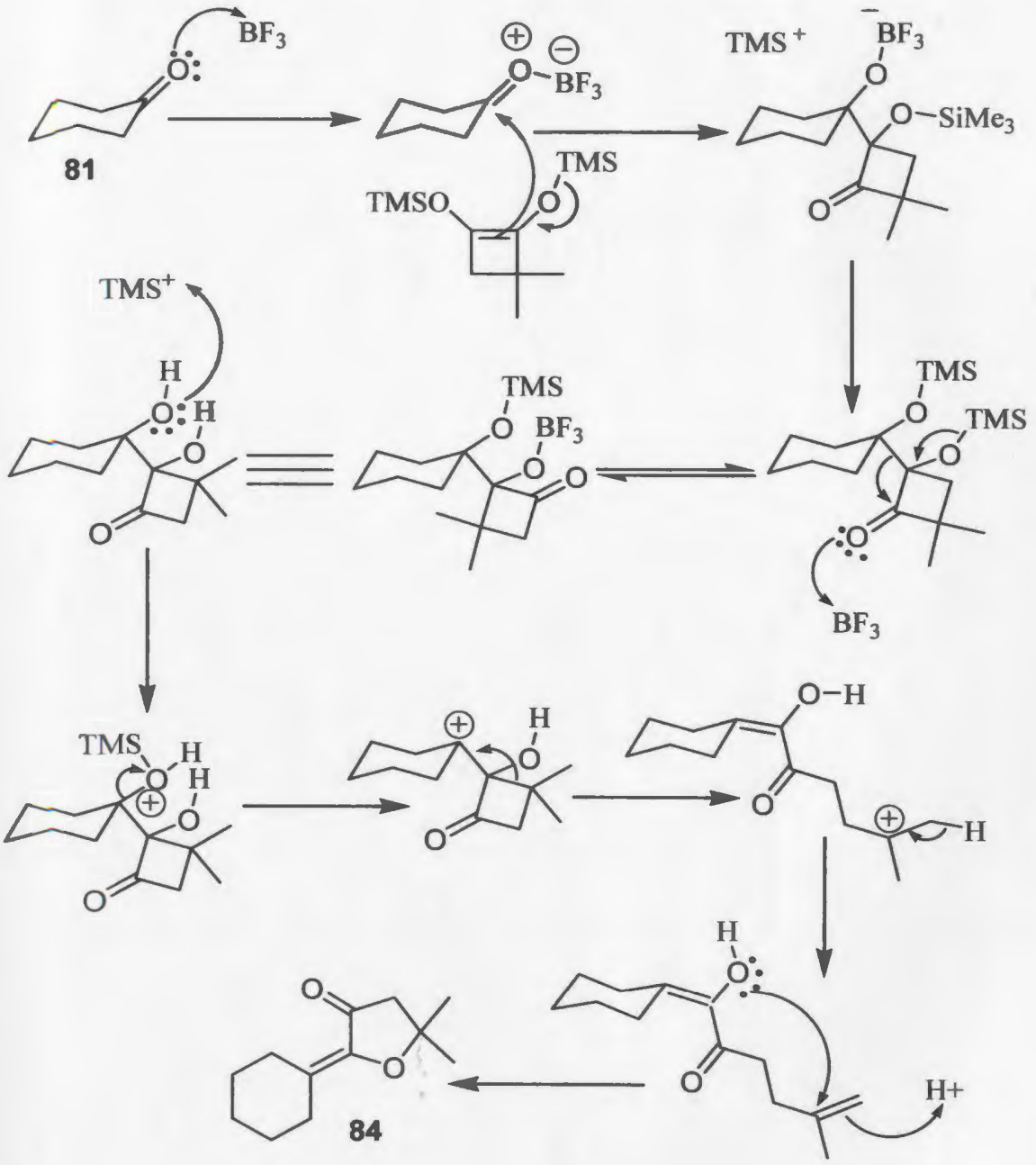
Scheme 31



Studies were carried out with **79** on the relative stereochemistry at the spiro center. Cyclobutanones from acetals undergo rearrangement to cyclopentanediones by inversion at the cyclohexyl C-1 with little stereochemical scrambling.[31] This was also true for the processes with **56** for both acetals and ketones. This means thatthe

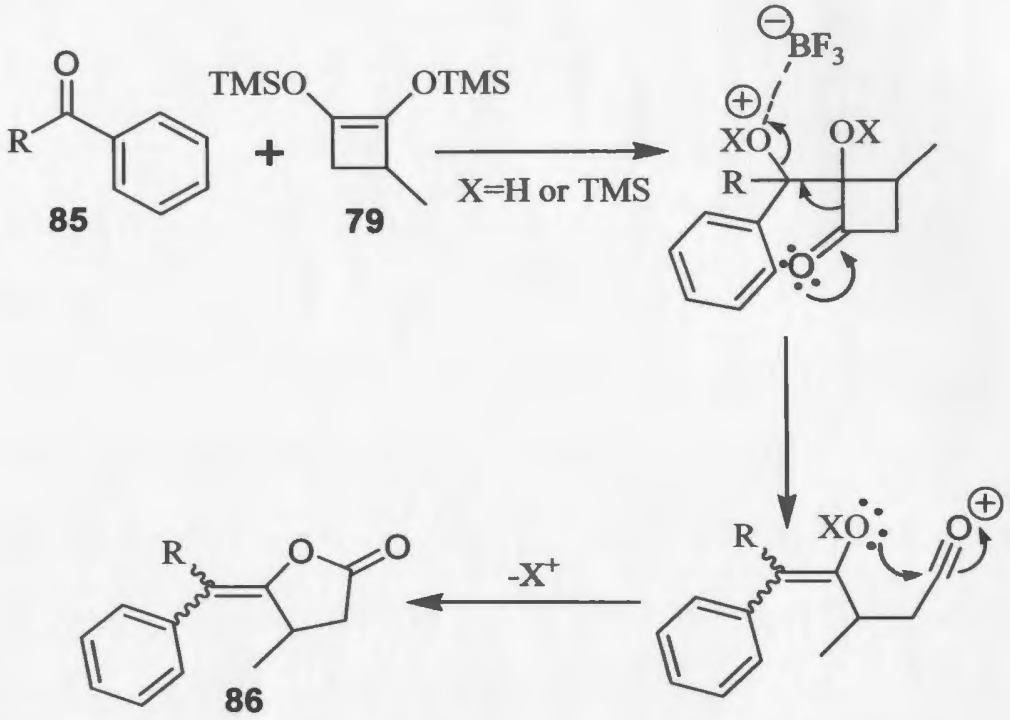
stereochemistry of the cyclopentanedione derived from acetals was largely determined by

Scheme 32



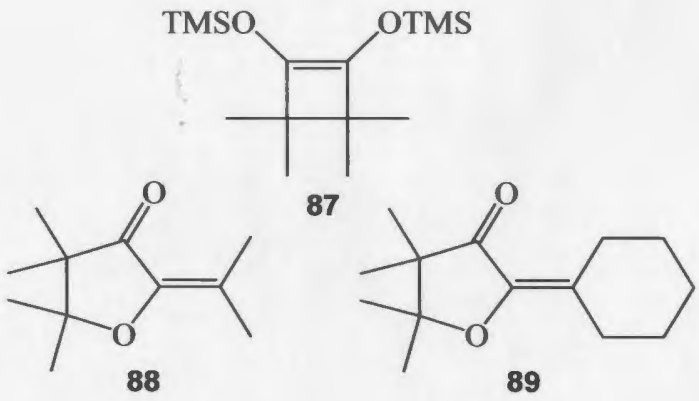
the stereochemical preference in the first aldol reaction. The stereochemistry of the cyclopentanediones from ketones was generally the opposite of this and seemed to

Scheme 33



indicate some equilibration of the cyclobutanone.[31] Compound **80** generally gave poorer yields than **79** under geminal acylation conditions, but produced cyclopentanediones with

Figure 13: TetraMe-bis[TMSO]cyclobutene and geminal acylation furanone products.



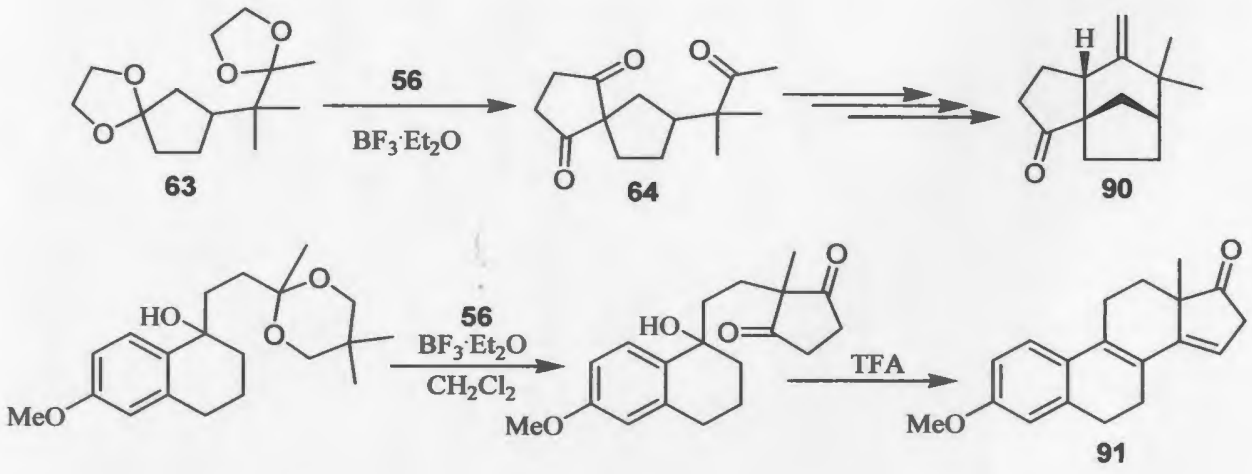
much higher stereoselectivity.[31]

Reactions of aromatic ketones, such as **85**, with **79** and **80** produced minor amounts of lactones, such as **86**, (Scheme 33), but proceed to give 1,3 diketones in fair to good yields under anhydrous conditions, whereas geminal acylation reactions of saturated ketones with **79** and **80** required H_2O .[33]

Reactions were also carried out with **87** on acetone and cyclohexanone, but no cyclopentanedione products were seen. Only furanones **88** and **89**, respectively, were isolated (Figure 13).

The geminal acylation reaction is a powerful C-C bond forming tool. It introduces a 1,3-cyclopentanedione substructure, which is useful for the synthesis of many natural products.[29] Some examples include Wu and Burnell's syntheses of a sesquiterpene, isokhusimone (**90**)[30, 31] and the estrone derivative **91**.[34] The use of the geminal acylation reaction in these syntheses can be seen in Scheme 34.

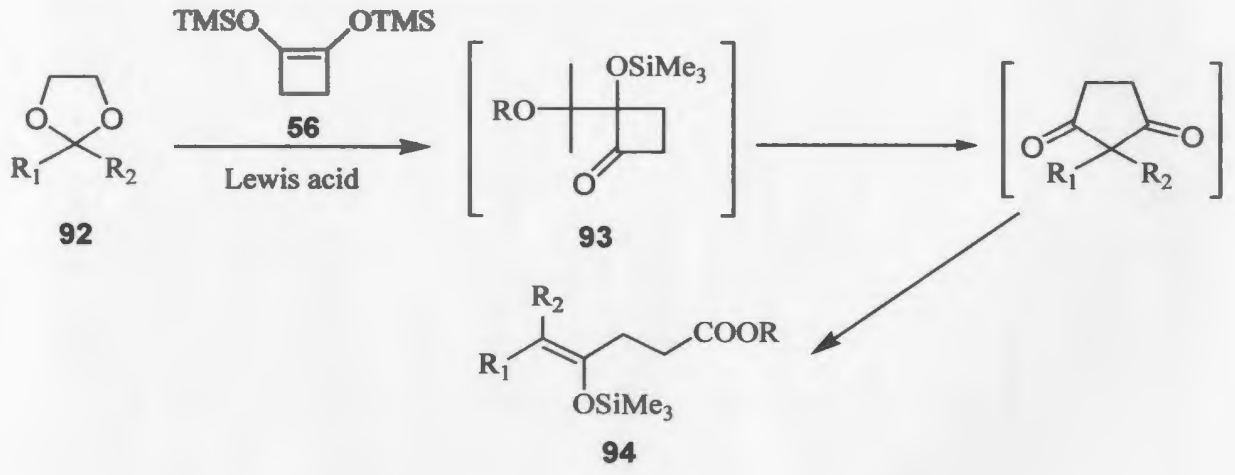
Scheme 34



Instances have been encountered where the cyclobutanone ring **93** has been

cleaved under acidic conditions (Scheme 35). Certain Lewis acids ($AlCl_3$, $TiCl_4$, $SnCl_4$, $SbCl_5$) permit **56** to be reactive enough to transform **92** into a γ-keto ester quantitatively, with $SnCl_4$ providing the highest yield of **94** in a one-pot process. Isolation of the intermediate **93** can be avoided using this Lewis acid.[35] This process is known as reductive succinoylation of a ketone function, and it was found that susceptibility to ring cleavage greatly depended on the structure of the substrate. For example, the aldol products obtained from cyclohexanone and cyclopentanone acetals underwent reductive succinoylation easily in the presence of a small amounts of the catalyst. On the other

Scheme 35

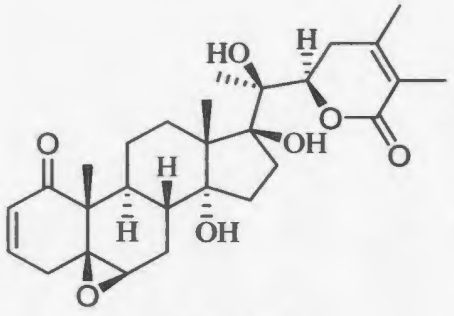


hand, acetone acetal was not susceptible to reductive succinoylation and underwent geminal acylation effectively.[25] The reductive succinoylation process was also used to explain the low yielding geminal acylations when a series of acetals derived from ketones with α-methyl groups were used as the substrates.[30] Work was done on the use of acetals bearing alkyl substituents as well as modifications to the geminal acylation reaction conditions, but the reductive succinoylation process still posed a problem.[36] This

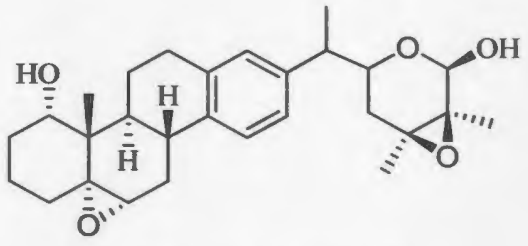
behaviour was observed during the course of work which will be presented in this document. However, in these instances, $BF_3{\cdot}Et_2O$ and BCl_3 were the Lewis acids involved. Even though this reaction pathway has been used in a positive way, since **94** can react with various electrophiles,[35] to synthesize *dl*-lanceol for example,[25] it was undesired in the work presented in this document, and posed problems which hindered the productivity of this research.

There is a need for synthetic steroids which have an oxygen functionality at C-1[37-39] since many biologically-active steroids and analogues have this characteristic. Some examples can be seen in Figure 14. We proposed that the geminal acylation reaction

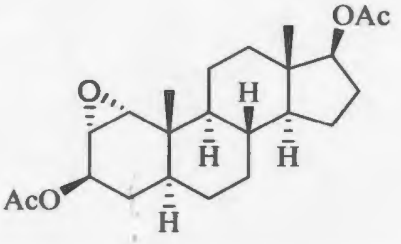
Figure 14: Steroids with oxygen functionality at C-1.



(+)-withanolide E



2,3-dihydrosalpichrolide B



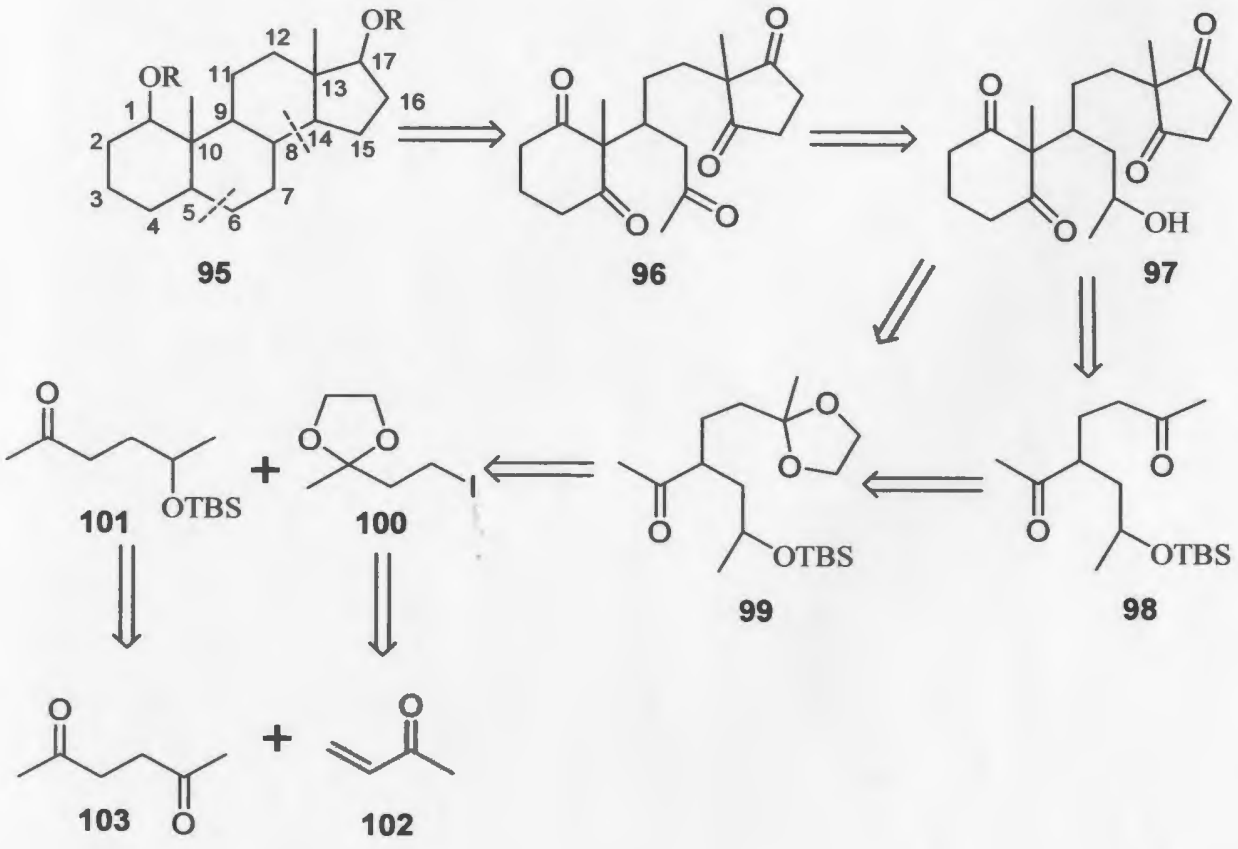
3b-acetoxy-1a,2a-epoxyandrostane

might be utilized in the synthesis of a C-1 oxygenated steroid. The remainder of this document describes proposed routes to obtain this goal and attempts to follow these routes along with conclusions as to why certain processes happened and others did not.

2.2 Retrosynthetic Analysis

A proposed route to a steroid skeleton with oxygen functionality at C-1 and C-17 is outlined in Scheme 36. Retrosynthetic cuts were made in the analysis as indicated by the broken lines on the steroid skeleton **95**, which left the pentaketone **96** as the target compound. One of these carbonyls can be obtained by oxidation of the alcohol **97**. The two 1,3-diketone components, and thus the A- and D-rings of the steroid could be the result of two geminal acylation reactions to the diketone **98** using 1,2-bis[(trimethylsilyl)oxy]cyclobutene and 1,2-bis[(trimethylsilyl)oxy]cyclopentene. The two carbonyl functionalities in **98** could be distinguished by obtaining one from an

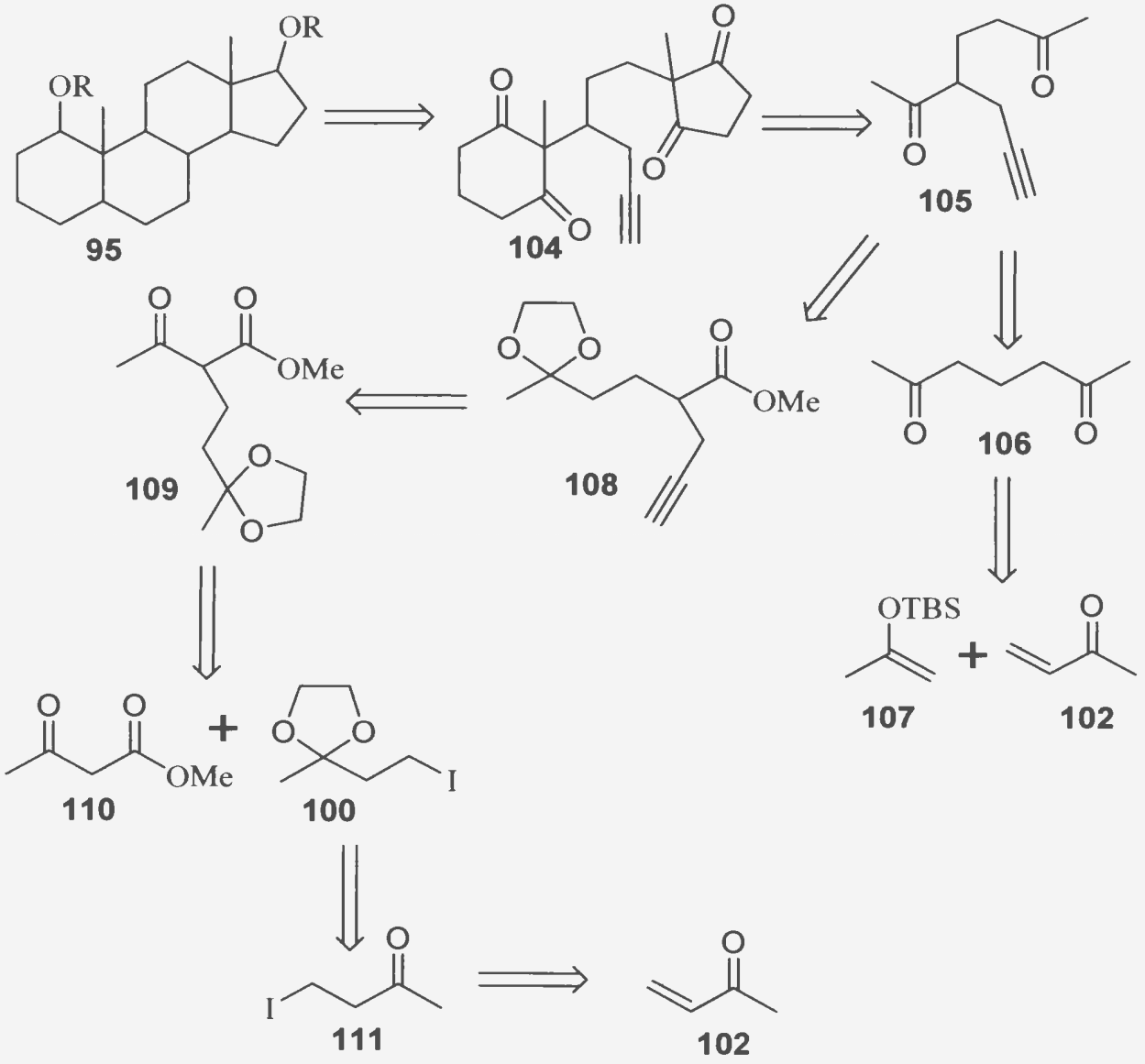
Scheme 36



acetal, as in **99**. This molecule could come from alkylation of the protected ketoalcohol **101** with the iodoacetal **100**. These molecules could be obtained from 2,5-hexanedione and 3-buten-2-one, two readily available compounds.

Scheme 37 illustrates a second route to the steroid skeleton, which is similar to the first except having an acetylene moiety, which can be converted to ketone **96** when

Scheme 37



needed. Again the pentaketone **96** , described previously in Scheme 36, would be obtained. The required diketone with the acetylene functionality **105** could come from alkylation of 2,6-heptanedione (**106**) with propargyl bromide. Since 2,6-heptanedione is not commercially available, it would have to be prepared. This could be achieved through the Michael addition of the silyl enol ether **107** to 3-buten-2-one (**102**).

A modification to this last route can be seen in Scheme 37 as well. The diketone with the acetylene component **105** can be derived from the dialkylation of methyl acetoacetate (**110**) with the iodoketal **100** and propargyl bromide since previous work with this system displayed a loss of an acyl group.[39] The iodoketal could be prepared from 3-buten-2-one (**102**).

2.3 Results and Discussion

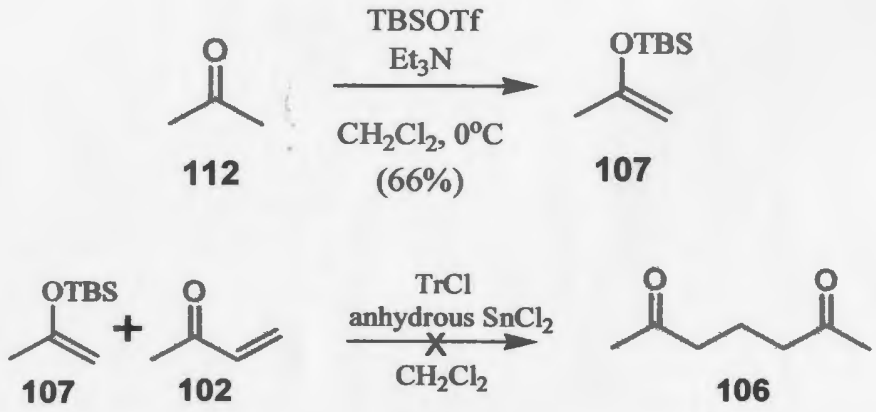
2.3.1 Endeavors Towards the Steroid Skeleton Originating with 2,6-Heptanedione

The first attempts towards the synthesis of 2,6-heptanedione followed a procedure by Mukaiyama and Kobayashi, which involved the Michael addition of silyl enol ethers to α,β- unsaturated ketones to give diketones.[41] Such a reaction is catalyzed by the combination of a neutral molecule and a weak Lewis acid under mild conditions. The catalyst that Mukaiyama developed was the combination of trityl chloride (TrCl) as the neutral molecule and tin(II) chloride as the weak Lewis acid. The exact catalytic mechanism by which this reaction proceeds is unknown. What is known is that the

Figure 15: Coordination of TrCl to Lewis acid.

catalyst is formed by the neutral molecule coordinating to the Lewis acid, in the fashion

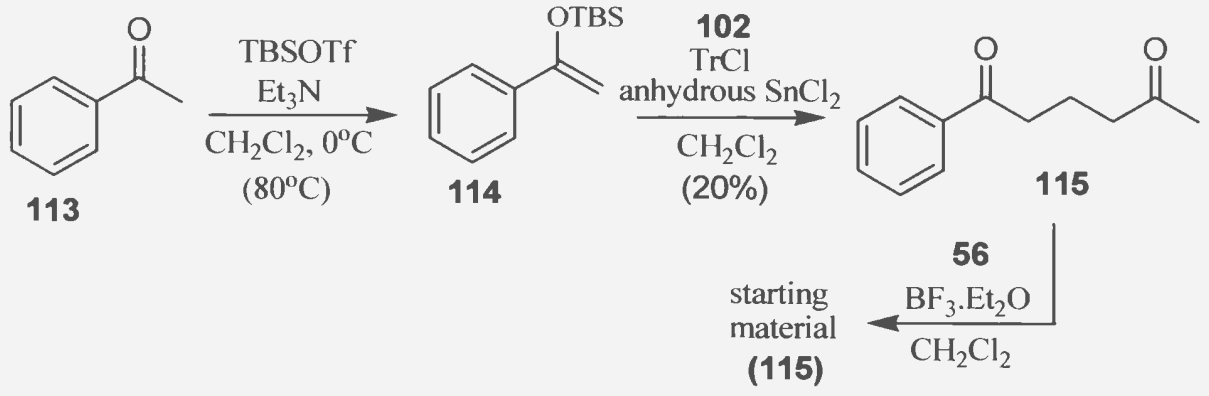
Scheme 38



depicted in Figure 15, to generate a partial positive charge on the trityl moeity.

To make 2,6-heptanedione by Mukaiyama's procedure, the silyl enol ether of acetone **107** was needed. Compound **107** was obtained in a 66% yield by treating acetone with TBSOTf and Et_3N in CH_2Cl_2. This silyl ether was then reacted with 3-buten-2-one under Mukaiyama's conditions in the hope of forming the desired diketone (Scheme 38). However, only trityl-protected compounds and intractable material were seen. It was unclear as to why the reaction was not working, but a low recovery of starting material or product indicated that the volatility of both starting materials, and even the product, could be causing problems. Evidence of polymerization was also seen in the ^1H NMR spectra. To test the reaction, a starting material with a larger molecular mass and less likely to polymerize, the silyl enol ether of acetophenone **114** that was prepared the same way as the previous silyl enol ether, was reacted under the modified Michael addition conditions with 3-buten-2-one. The expected diketone **115** was obtained, but in only a 20% yield (Scheme 39). The remainder of the material was acetophenone and trityl-protected compounds. The recovery of acetophenone and not enone indicates the problem was with

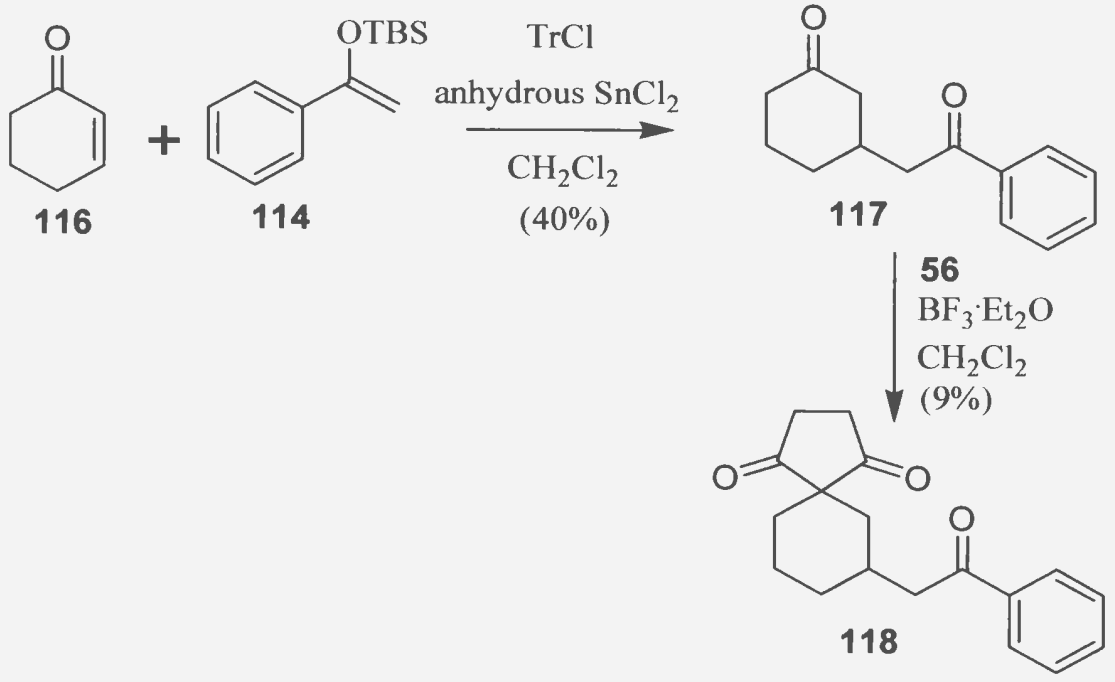
Scheme 39



the enone.

Enones **116** and **102** may be participating in another reaction in these modified Michael additions. In the interest of learning more about the geminal acylation reaction with unsymmetrical diketones, the geminal acylation conditions were applied to **115**, but unfortunately only starting material was recovered. The modest success with the larger molecule under Mukaiyama's Michael addition conditions was consistent with our hypothesis of smaller molecules causing problems, so a larger unsaturated ketone, 2-cyclohexen-1-one (**116**), was chosen for the next reaction. This Michael acceptor was reacted with **114**, and the expected diketone **117** was obtained in a 40% yield (Scheme 40). The higher yield was not surprising since the product (**117**) was less volatile than the

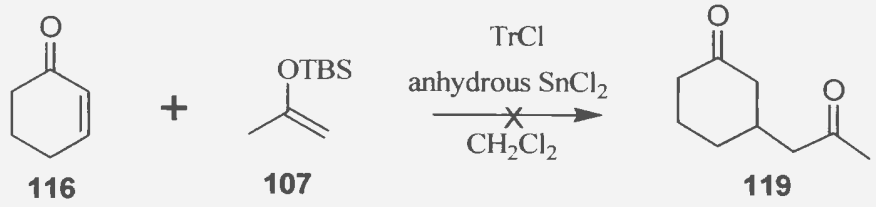
Scheme 40



others, **106** and **115**. The unsymmetrical diketone (**117**) was subjected to geminal

acylation conditions. The mono reacted product **118** was isolated but in a 9% yield only. This product was the expected one because it was felt that resonance stabilization would stabilize the carbonyl α to the aryl. The stabilization would render this carbonyl component less susceptible to the geminal acylation conditions than the aliphatic ketone. Low yielding mono-geminal acylation reactions, such as the one in Scheme 40, were not uncommon. Previous members of the Burnell group have seen low yields of monoreacted product as the result of geminal acylation reactions when there is another oxygen atom near the reaction site.[40] This type of molecule (**118**) would be of interest to learn about and synthesize since applying a McMurray coupling to molecules like **118**

Scheme 41

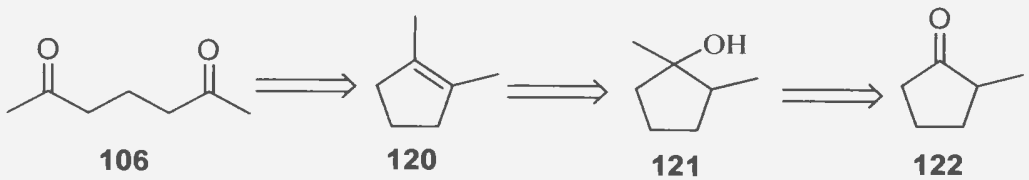


116 **107** **119**

would yield ring systems of natural products such as 3,4-anhydro-13,14-dihydroxyfloridanolide, a sesquiterpene lactone of the *seco*-prezizane type.[42]

Since there had been some success reacting the cyclic enone **116** with **114**, **116** was subjected to Mukaiyama's modified Michael addition conditions with **107**, but only

Scheme 42

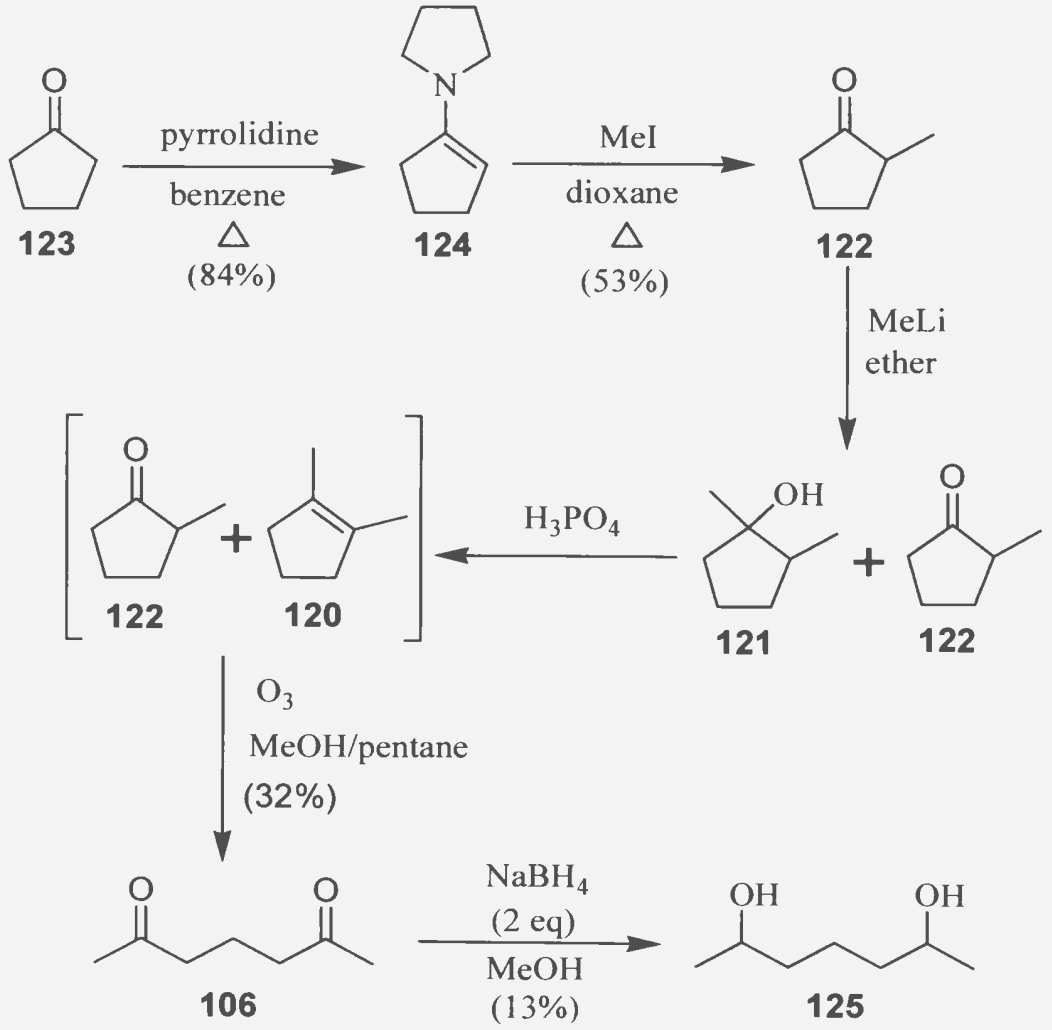


106 **120** **121** **122**

intractable material was obtained (Scheme 41). Different molar equivalents of catalysts (0.05, 0.1, 0.3, 1) and an excess of each starting material, up to double proportions were tried, but no trace of **119** was ever found.

Even though Mukaiyama's modified Michael additions appeared to work in some instances such as **116** with **114**, the yields were always low. In the instance which was most important to this research, i.e., to form 2,6-heptanedione, the reaction did not work

Scheme 43



at all. Thus, an alternative route was explored. A second route by which the desired

diketone **106** might be synthesized is outlined retrosynthetically in Scheme 42.

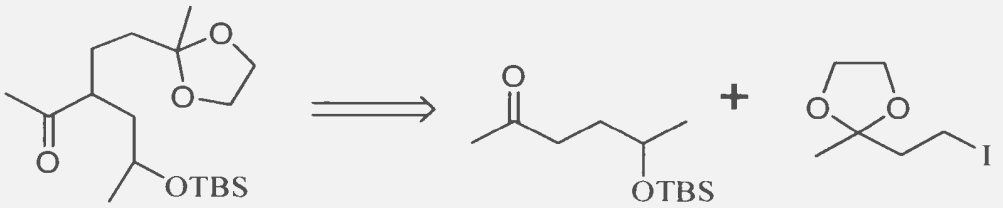
2,6-Heptanedione might be derivable from 1,2-dimethylcyclopentene (**120**) via ozonolysis. This can be mapped back to 1,2-dimethylcyclopentan-1-ol (**121**) through elimination and this, in turn, might be derived from 2-methylcyclopentanone (**122**) by attack of an organometallic reagent. In the forward direction, the enamine of **123** was obtained in a 84% yield from cyclopentanone and pyrrolidine in benzene (Scheme 43). The enamine was then alkylated with iodomethane in dioxane in a 53% yield to provide the α-methyl ketone **122**. This was followed by reaction with MeLi in ether in the hope of obtaining the alcohol **121**. Although some **121** was obtained, starting material was also recovered along with **121** in a 1:1 ratio. The mixture was not simply subjected to more MeLi because it was believed that some of the MeLi acted as a base and formed an enolate which would prevent subsequent reaction of MeLi with the carbonyl group. Thus, the use of additional MeLi would not change this behaviour. Compounds **121** and **122** could not be separated on silica since they co-eluted, so they were carried through an elimination reaction with phosphoric acid as a mixture since only the alcohol should react. The resulting mixture was not isolated and the solvent was not removed due to the danger of losing any alkene given its low boiling point. In light of this, the mixture was subjected to ozonolysis conditions. The reaction proceeded in the desired way with only the alkene reacting to give the diketone **106**. Since the diketone was less volatile, **121** and **122** were evaporated under a stream of nitrogen upon work-up. Thus, the need for separation was eliminated. Both carbonyls of this diketone were then reduced to afford the diol **125**. The formation of a mixture of diastereomers was not a concern since the

alcohols would eventually be reoxidized into ketones after a few other steps. Compound **125** was to be carried through a synthetic route similar to one which will be seen later with 2,5-hexanediol (Scheme 49), but unfortunately time did not permit for it to be done and included in this document. Research using compound **125** in a route similiar to the one in Scheme 52 can be carried out by future members of the Burnell group.

2.3.2 Working Towards the Steriod Skeleton via Alkylation

This route required a protected ketoalcohol **101** as the substrate and an iodoacetal **100** as the alkylating agent (Scheme 44). These compounds were derived from

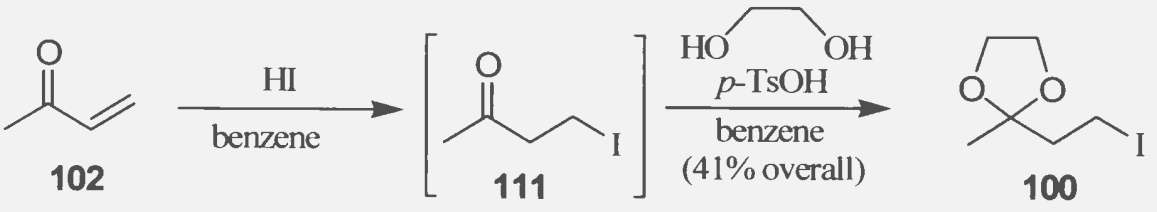
Scheme 44



99 **101** **100**

2,5-hexanedione and 3-buten-2-one, respectively. Compound **100** was prepared in a 41% overall yield by first treating 3-butene-2-one with hydroiodic acid in benzene, and then reacting the resulting iodide **111** with ethylene glycol and *p*-toluenesulfonic acid (Scheme 45).

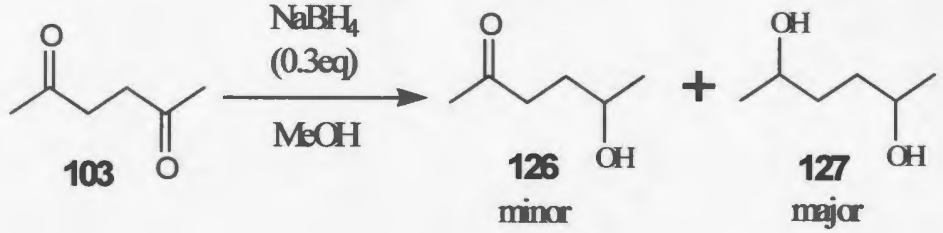
Scheme 45



102 **111** **100**

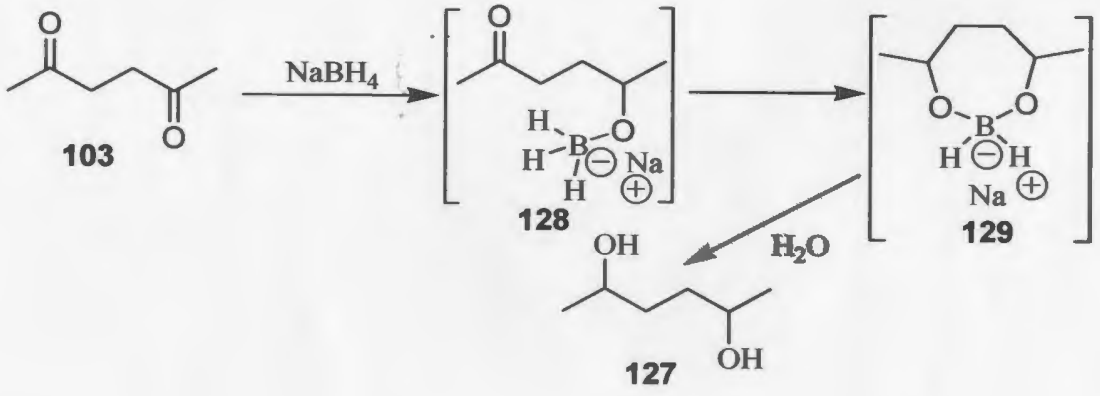
The synthesis of the protected ketoalcohol **101** began with attempts to mono-reduce 2,5-hexanedione (**103**) using 0.1 molar equivalents of $NaBH_4$ in MeOH. Only starting material was recovered. The $NaBH_4$ was tested with cyclohexanone, and it provided cyclohexanol in a 98% yield, so the reagent was not the problem. Upon treating **103** with 0.3 equivalents of $NaBH_4$, the desired mono-reduced product **126** was obtained, but only as a minor product (4:1) (Scheme 46). The major product was the doubly reduced product **127**. Different molar equivalents (1.0, 1.5) of the reducing agent were

Scheme 46



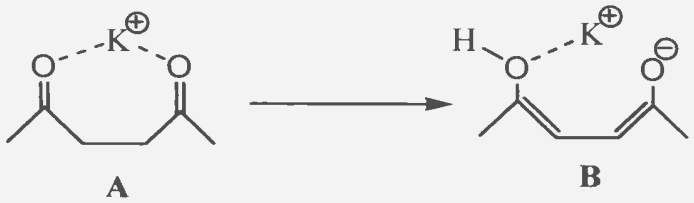
tried, but they gave no better results. It seemed that the rate of reduction of the second carbonyl was faster than the first reduction. Once the first hydride adds, a borotrihydride **128** is formed (Scheme 47). The second reduction would occur intramolecularly to give a

Scheme 47



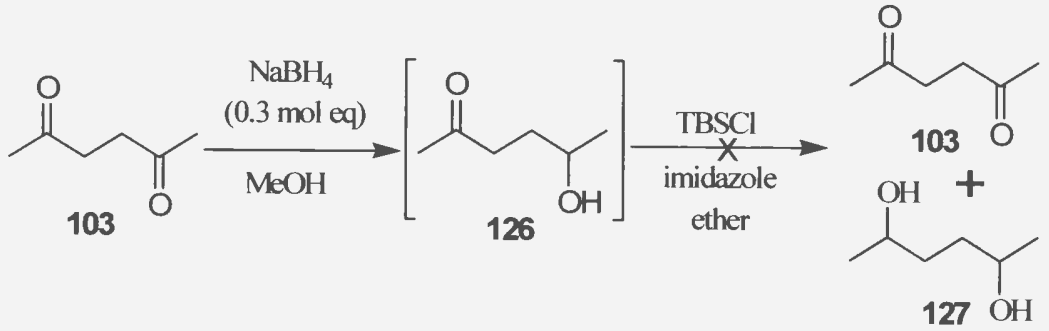
cyclic borate **129**. The unreactivity of the cyclic borate **129** is surprising since the transition state seems to involve a seven-membered ring. Normally this would not be anticipated as a problem, but 7-exo-trig reactions would allow for this ring closure, unlike if the transition state were a five- or six-membered ring. However, it did pose a problem. The doubly reduced product indicates that this intramolecular reaction appears to be faster than the intermolecular reduction, or the reduction of the first carbonyl. It was decided to try a different reducing agent since many are available. K-Selectride® was chosen since it only has one hydride to deliver. Therefore, the intramolecular reduction seen in Scheme 47 was much less likely. K-Selectride® was added to a solution of the diketone **103** in

Figure 16: Enol/Enolate form ion of the K-Selectride® ligand.



THF, but it gave an unexpected result. The material obtained contained only starting material. There was no reason to believe the K-Selectride® had decomposed since it was simultaneously being used in other reactions, which proceeded in the expected manner. It

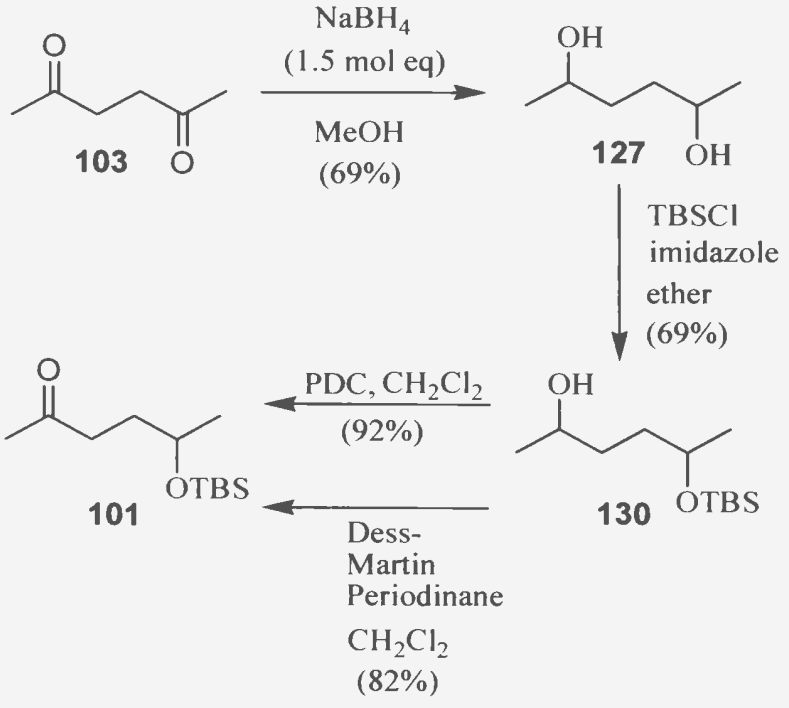
Scheme 48



is conceivable that K-Selectride® functioned as a base, rather than a nucleophile when presented with diketone **103**. Bidentate co-ordination of **103** to the potassium ion would afford complex **A** (Figure 16), which could then proceed to enolate **B** upon deprotonation and enolization in either order. Complex **B** would be unreactive toward K-Selectride®, either as a base or a nucleophile, and thus would deliver the starting material **103** upon work-up.

Further attempts to obtain the ketoalcohol **101** in reasonable yield were futile as well. Efforts were made to protect the mono-reduced product *in situ* by first adding $NaBH_4$ in MeOH, and, once the methanol was removed, adding TBSCl and imidazole in ether (Scheme 48). The hope was that the mono-reduced product would form and then be protected before the second ketone would be reduced. This was based on the

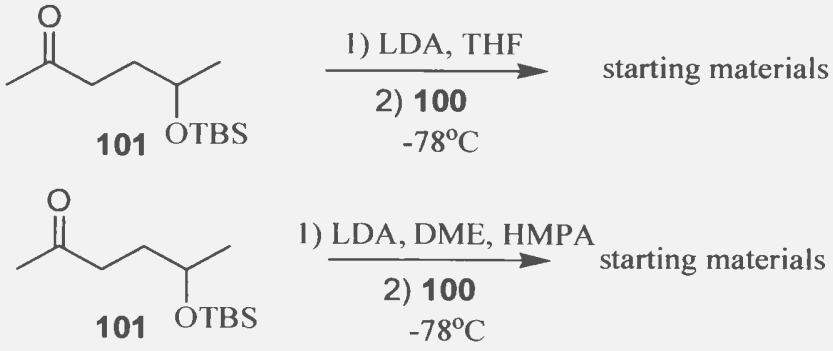
Scheme 49



presumption that the reduction of the second alcohol was directly related to the reduction of the first. Thus, by not having any of the first alcohol present but instead having it protected, it was hoped the second reduction would not take place as quickly. However, only starting material and the diol **127** were seen. It was possible that, after the addition of $NaBH_4$, the putative borotrihydride **128** shown in Scheme 47 was not reactive towards TBSCl. Thus, the TBS did not add to the oxygen and the reaction proceeded as outlined in Scheme 47, again yielding the diol **127**. Thus, the protected alcohol ketone would not be obtained using this general strategy.

A new approach that did not require mono-reduction and proceeded through **127** was implemented to obtain **101** (Scheme 49). 2,5-Hexanedione was reduced to the diol using an excess of $NaBH_4$ in methanol. Protection with 0.45 molar equivalents of TBSCl and 0.5 molar equivalents of imidazole in ether provided the mono-protected alcohol **130**. The fact that none of the di-protected alcohol was seen indicated that the first protection was faster than the second. That the first protection hindered the second was interesting since the hydroxyl groups were a fair distance apart. Compound **130** was then oxidized

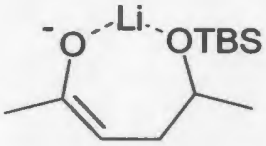
Scheme 50



using two different agents, pyridinium dichromate and Dess-Martin periodinane (DMP). PDC was the superior oxidizing agent in this case since it gave the protected ketoalcohol in 92% yield, and DMP gave **101** in a 82% yield.

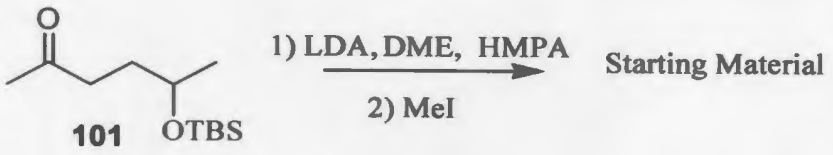
Now that both alkylating substrates had been synthesized, the next step along this route to the steroid skeleton was the alkylation. The initial alkylation reaction was attempted with LDA in THF (Scheme 50). However, this yielded none of the desired product, so an additive, HMPA, was added to the reaction. Again, no positive result was obtained; only starting materials were recovered. It was thought that the iodoacetal might not be a very good alkylating agent. Also, the anion may be stabilized by the OTBS component and the oxygens on the acetal once the iodoketal is in the vicinity of the

Figure 17: Intramolecular complexation of oxygens and lithium.



alkylating substrate (Figure 17). If this were the case, the iodide component would not be able to get near the anion for a nucleophilic attack to occur. There is evidence, with the chiral auxiliaries SAMP and RAMP, to support the hypothesis that remote oxygen atoms can stabilize an anion.[42] The reaction mixture was warmed to 0 °C, in an effort to

Scheme 51

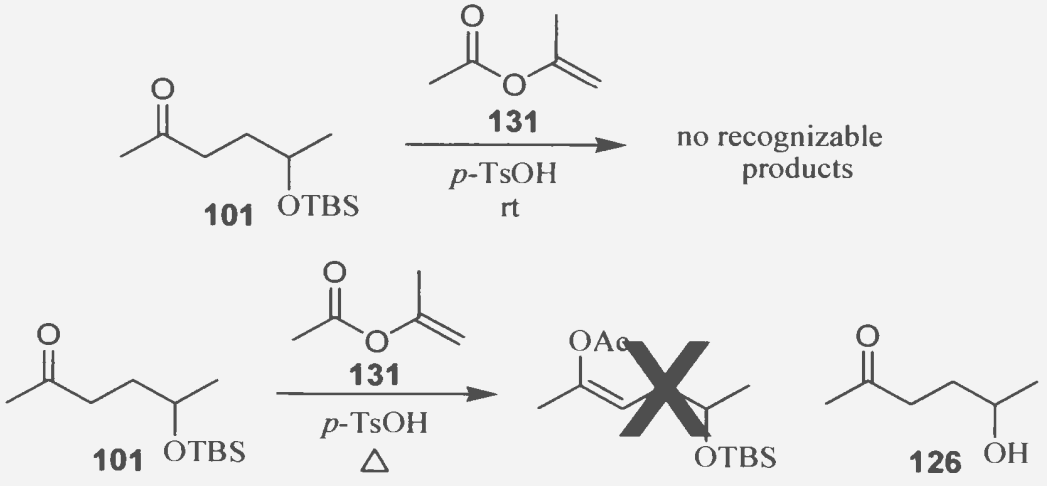


equilibrate the kinetic enolate to the more stable enolate. The warming process, would support remote oxygen stabilization and inadvertently keep the reaction from proceeding in the desired fashion.

Due to these results, a simpler alkylating agent, iodomethane, was applied (Scheme 51). It, too, was added to a solution of **101** and LDA in DME along with the same additive, HMPA, but unfortunately, only starting material made up the recovered matter. This indicated there may have been a problem with both of the alkylating substrates **100** and **101**.

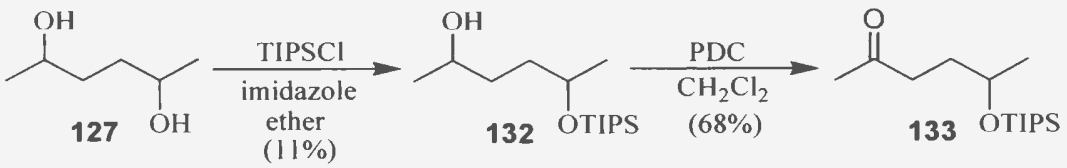
Another way the alkylation product **99** might have been obtained was through the enol acetate of the protected alcohol/ketone. Two procedures to produce an enol acetate of **101** were tried using *p*-toluenesulfonic acid and isopropenyl acetate as the solvent, one at room temperature and one under reflux conditions (Scheme 52). Neither gave desirable results. The reaction at room temperature gave no recognizable products, and the one at reflux gave only deprotected alcohol. The procedure was modified by

Scheme 52



refluxing in benzene to incorporate a Dean-Stark apparatus to remove any water that might evolve and inhibit the reaction, but the result was unchanged. Since the deprotected alcohol was seen, it was decided to protect the alcohol with a more robust protecting group to avoid loss of the protecting group. The diol **127** was monoprotected

Scheme 53

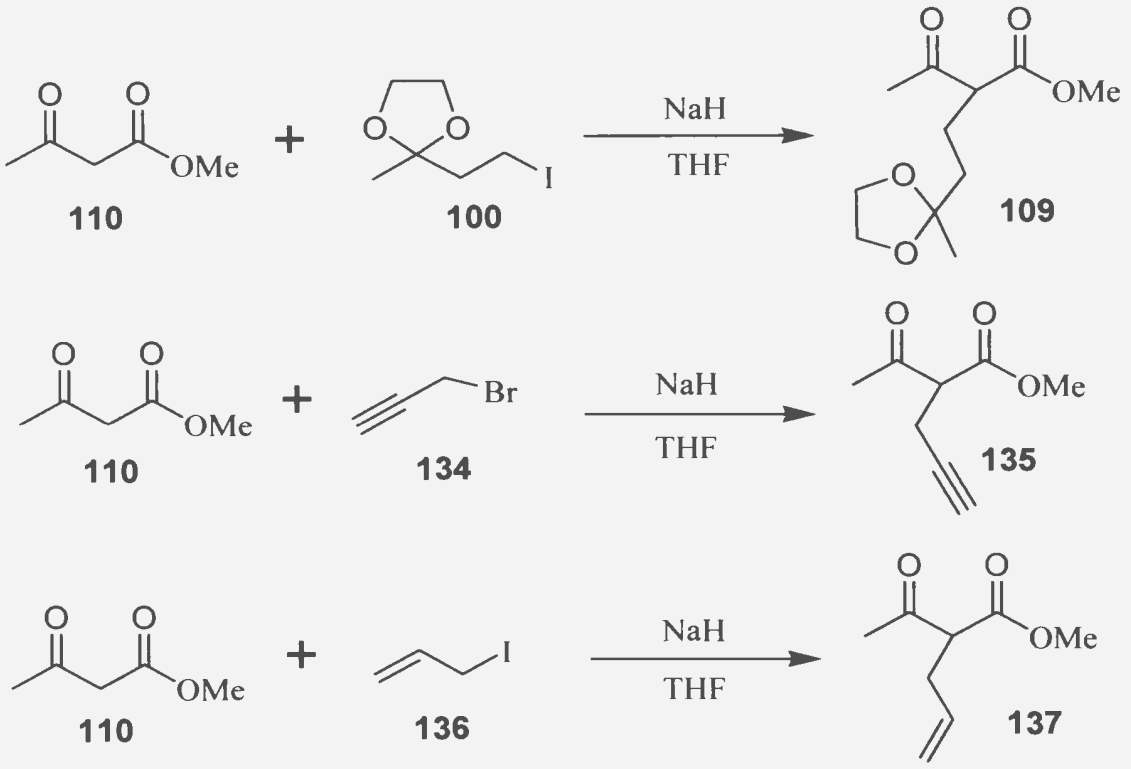


in the same way as the protection in Scheme 50 with 0.45 molar equivalents of TIPSCl and 0.5 molar equivalents of imidazole in ether. Oxidation with PDC gave the protected ketoalcohol **133** along with what seemed to be very large amounts of TIPS-X impurities. This product needs to be purified before any attempts to make the enol acetate are carried out on it. Since time constraints prohibited further investigation of this reaction product, this purification would have to be attempted by someone else in the Burnell group.

2.3.3 Making the Steroid Skeleton through the Double Alkylation of Methyl Acetoacetate

A third route towards **98** utilized a double alkylation of methyl acetoacetate. The third oxygen functionality in **98** could come from a variety of alkylating substrates

Scheme 54

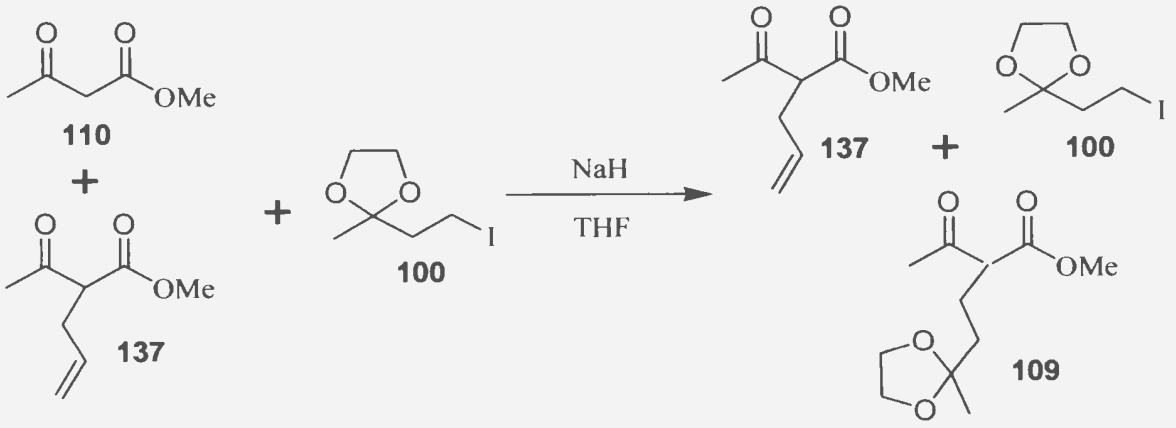


containing functionality that could easily be converted to a ketone. The three alkylating substrates chosen to work with were the iodoacetal **100**, propargyl bromide and allyl iodide. Each reaction used sodium hydride as the base. The iodoacetal **100** was the first alkylating agent tried since this compound already contains an oxygen functionality in the

required site. Compound **109** was obtained but in a 7% yield only. This result was similar to other alkylation reactions conducted with this iodoacetal (Scheme 54). When the alkylating agent was changed to propargyl bromide, the expected product **135** was obtained with a yield of 66%. This result was encouraging, and so, propenyl iodide was subjected to an alkylation reaction with methyl acetoacetate, again using sodium hydride. Since iodides are generally better electrophiles than bromides, it was thought that a higher yield of **137** would result when propenyl iodide was used. However, a significant change in yield was not found to occur. Unfortunately, the reactions never went to completion since, one or sometimes both, starting materials were always recovered. The propargyl bromide and propenyl iodide were not seen in the product mixture probably due their volatility. This characteristic may not have been a factor which prevented completion of the reaction since an excess of these reagents, up to 1.5 molar equivalents, was used. It seemed that these products **109**, **135**, and **137** (Scheme 54) decomposed on silica, so subsequent reactions were carried out on the crude mixtures. It was later discovered that column chromatography using neutral alumina purified these mixtures very efficiently, but time did not permit subsequent reactions to be carried out on the pure products.

The iodoacetal **100** was added to crude **137** along with NaH in THF and the compounds shown in Scheme 55 were obtained. Both starting materials were recovered, along with the product **109**, of alkylation of **100** with **110**. This was a little puzzling at first since it seemed as if an exchange of a whole alkyl group had taken place. However, this was not the case. Compound **137** had been carried through the reaction sequence

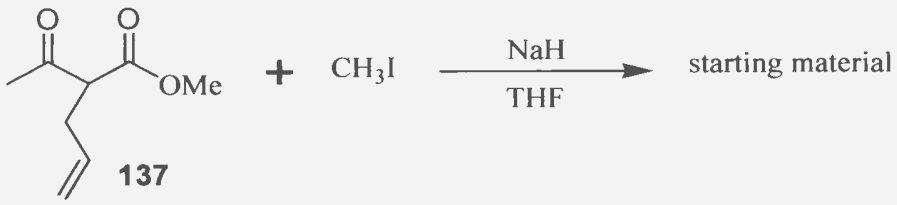
Scheme 55



as the major component of a crude mixture which had contained methyl acetoacetate. It can be presumed that the methyl acetoacetate had reacted with some of the iodoacetal **100** in an alkylation reaction to yield **109**. However, the amount of **109** produced was low (4:1, **137**:**109**). This concurred with the amount of methyl acetoacetate mixed with **137** to start with since the ratio of **137** to **110** was 4:1, also. The alkylation of methyl acetoacetate with **100** indicated that the reaction conditions were appropriate for alkylation, but due to the absence of dialkylated product, the monoalkylation also suggested that the monoalkylated substrate **137** will react significantly more slowly than the unalkylated substrated **110**. It was obvious these molecules needed to be purified before they could be used in subsequent reactions.

Since some previous reactions indicated problems with the iodoacetal as an alkylating agent, a simpler one, iodomethane, was tested (Scheme 56). Compound **137** was combined with iodomethane still in the presence of NaH and THF, but unfortunately only starting material was obtained. The double alkylation of methyl acetoacetate is a

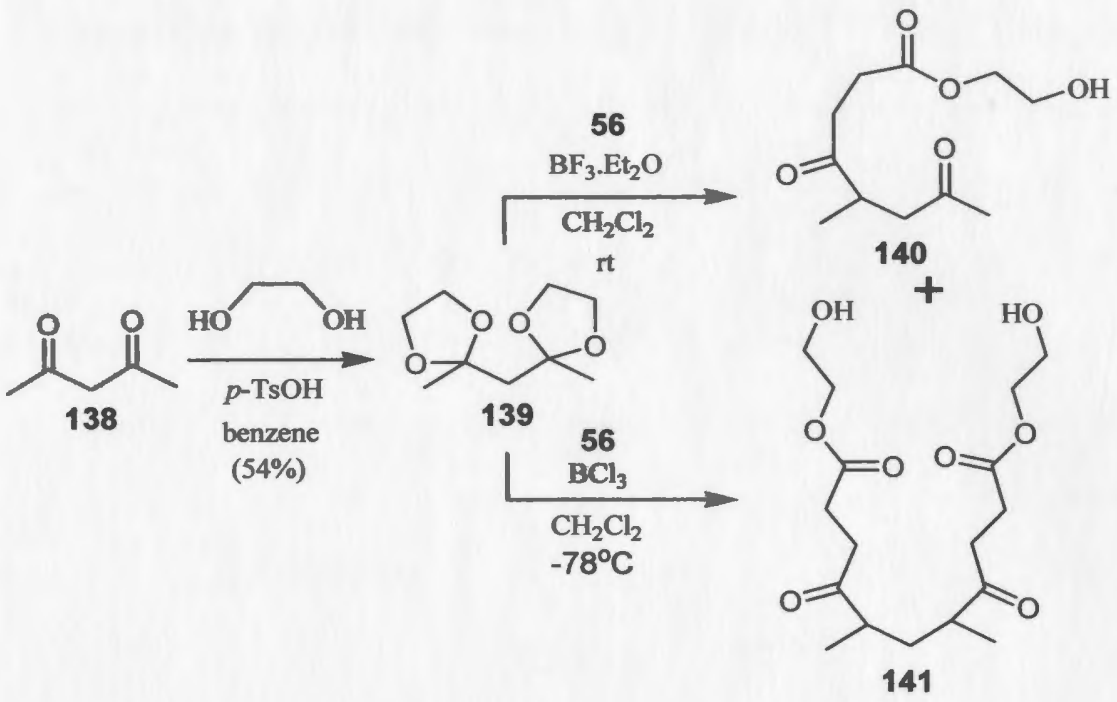
Scheme 56



difficult task to achieve, especially the second alkylation.

As a side project, some work was done on the geminal acylation reaction with a diacetal as the substrate (Scheme 57). 2,4-Pentanedione was converted into diacetal **139** using ethylene glycol and *p*-TsOH. Then the geminal acylation was carried out, both with BF_3·EtO and BCl_3. In both cases, it appeared that the compound was singly and doubly geminally acylated, but then subsequent reactions with ethylene glycol gave **140** and **141**. The mono- and di-1,3-cyclopentanedione moieties seemed to have formed but then each underwent reductive succinoylation which has been seen previously in Kuwajima's work[25] and by the Burnell group.[30a] The 1,2-ethanediol (or derivative) generated during the reaction participates in an acid-catalyzed ring opening of the acylation product which led to ketoesters **140** and **141**. The majority of cases of reductive succinoylation seen in the Burnell group were seen with α-methylated substrates and some α-alkylated substrates in Kuwajima's group. Both groups predicted that the ease of ring cleavage depends on the structure of the substrate. The reductive succinoylation seen with **139** may be due to the fact that each acetal has a pseudo α-methyl substituent disguised as the

Scheme 57

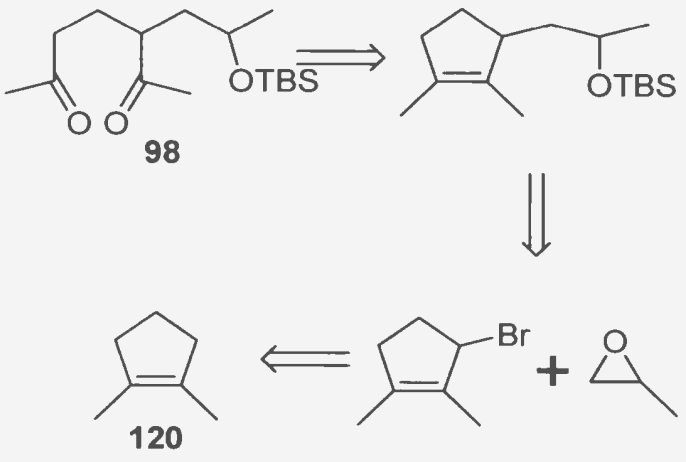


quaternary carbon in each adjacent acetal. Thus, these reductive succinoylation results follow those previously seen with α-methylated substrates.

2.4 Conclusions and Future Work

The synthesis of steroid backbones is a very delicate and complicated process. The routes proposed in this document may be feasible but require some modifications. Since long-chain diketones are not readily available, and Mukaiyama's procedure did not seem to work well with volatile and easily polymerized substrates, a new process to form them will have to be found. Ozonolysis procedures proved to be slightly more successful, but research to drive reactions to completion would have to be performed. A possible retrosynthetic route which does not involve alkylation but does utilize alkene **120** and ozonolysis can be seen in Scheme 58.

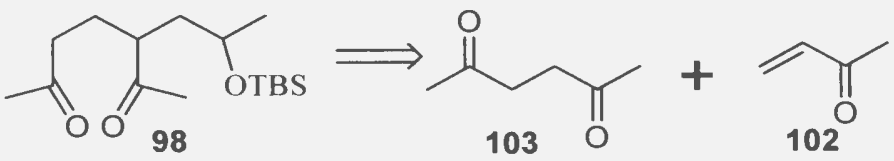
Scheme 58



Due to problems seen with alkylating the iodoketal **100**, the alcohol **101**, and methyl acetoacetate **110** such as only partial alkylation or no alkylation at all, more research will need to be carried out to find more suitable alkylating routes. Certain

features of the alkyl group are required. Thus, the alkylating agent **100** would be unchanged. Precedence has been set for the alkylation of methyl acetoacetate.[44] However, effects of solvent, temperature, concentration, and the counter ion would need to be studied. Different additives such as HMPA and LiCl would have to be included in order to attempt to improve the yields of alkylation. An alternative to direct alkylation could be investigated. A possible retrosynthetic route where a Michael addition instead of an alkylation could be used is shown in Scheme 59.

Scheme 59

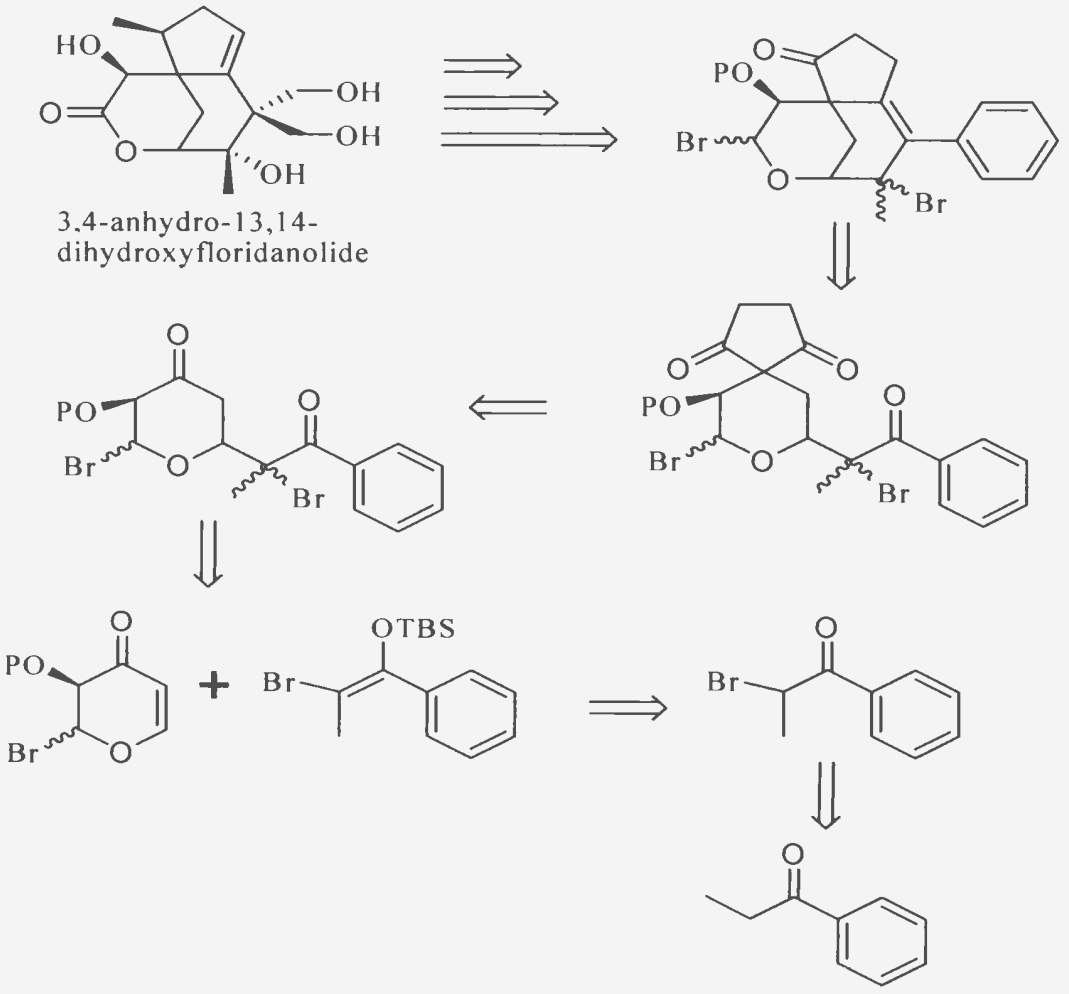


Successful geminal acylation reactions performed upon substrates such as **117** would prove to be beneficial since McMurry couplings carried out on these products such as **118** would lead to many natural products such as 3,4-anhydro-13,14-dihydroxyfloridanolide (Scheme 60). Research carried out in this thesis has begun the foundation for this. A possible retrosynthetic route can be seen in Scheme 60. The McMurry coupling may be useful to make steroids in an alternate way as well. Two possible retrosynthetic routes are proposed in Schemes 61 and 62.

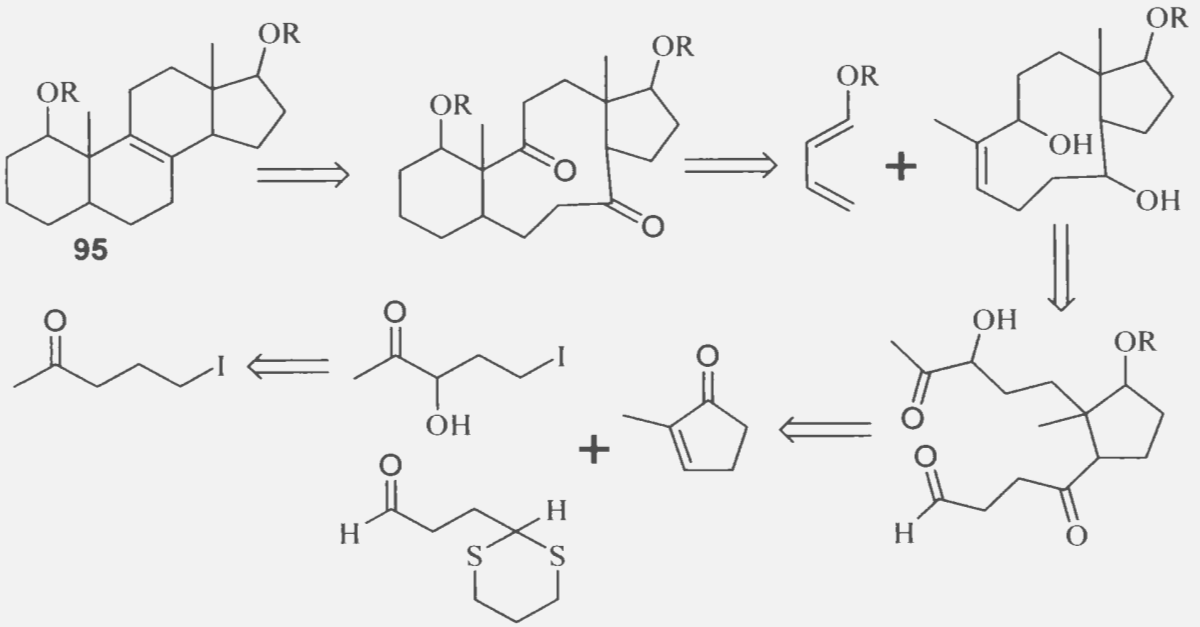
Much of this research seems to give rise to finding ways to go along with mother nature's wishes, as opposed to fighting them. An example of this is the preparation of **101** which was achieved in an improved yield, as was shown in Scheme 49. Many of the

problems seen here could be overcome by changing procedures.

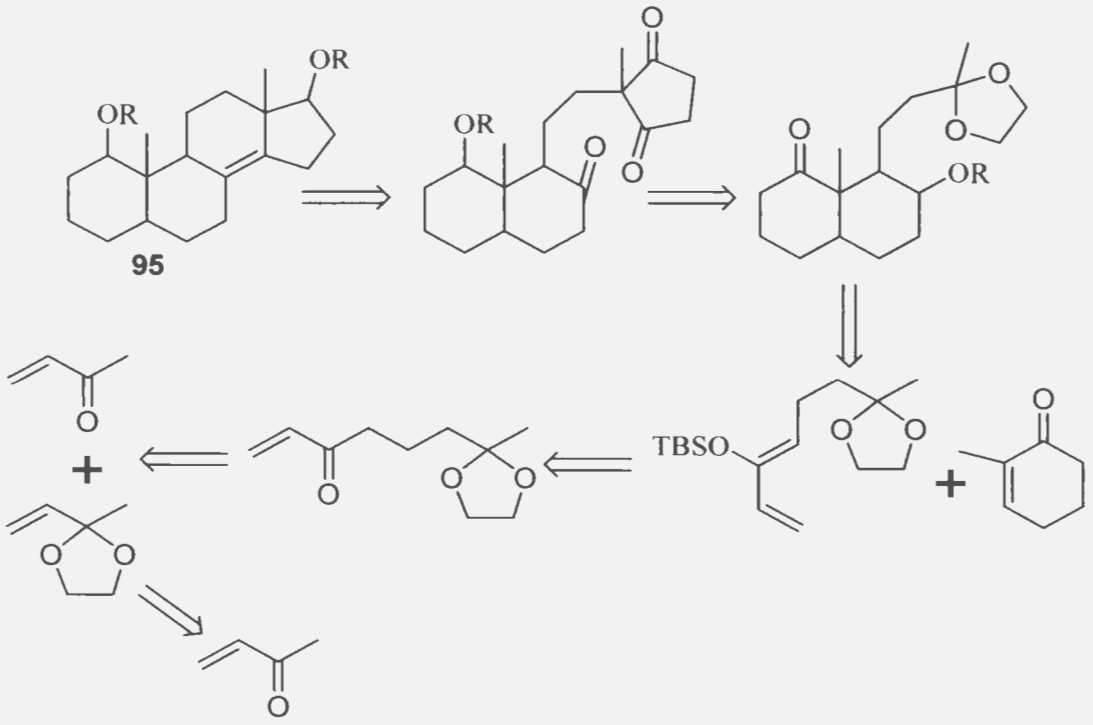
Scheme 60



Scheme 61



Scheme 62



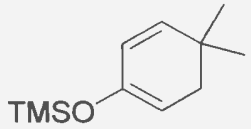
Experimental

General Experimental Procedures:

All reactions were performed under oxygen-free nitrogen. Dichloromethane was dried and distilled from calcium hydride and stored over molecular sieves. THF was distilled from sodium/benzophenone immediately before use. Concerns about the volatility of some products led us to be cautious when removing solvents under reduced pressure. Thus, in some NMRs trace amounts of solvent are found.

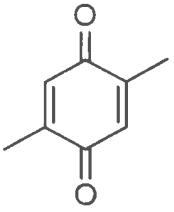
Thin layer chromotography (TLC) was done on Macherey-Magel Polygram® SIL G/UV_{254} precoated silica plates. Silica gel 60 (230-400 mesh) was used for flash chromotography. Melting points were measured using a Fisher-Johns melting point apparatus and are uncorrected.

Nuclear magnetic resonance (NMR) spectra were obtained using a General Electric GN-300NB spectrometer operating at 300.1 MHz and a Bruker AVANCE 500 MHz spectrometer operating at 500.0 MHz for ^{1}H NMR, and a Bruker AVANCE 500 MHz spectrometer operating at 500.0 MHz for ^{13}C NMR. $CDCl_3$ was used as the solvent. Chemical shifts are reported in ppm and are relative to tetramethylsilane (δ = 0.00 ppm) for ^{1}H NMR and $CDCl_3$ (δ = 77.0 ppm) for ^{13}C NMR. Infrared (IR) spectra were acquired on neat samples using a Bruker Tensor 27 spectrophotometer equipped with a MIRacle ATR accessory unit. Gas chromatography-mass spectrometry (GC-MS) for selected compounds were performed on a Hewlett Packard 5710A gas chromatograph using a Finnigan MAT ion trap detector.



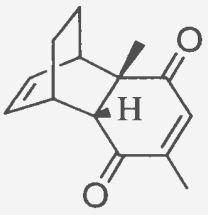
5,5-Dimethyl-2-(trimethylsilyloxy)-1,3-cyclohexadiene (24)

According to a procedure by Buckle,[18] *n*-butyllithium (6.0 mL, 9.6 mmol) was added dropwise to a solution of diisopropylamine (1.25 mL, 8.92 mmol) in THF (20 mL) at 0 °C. The mixture was cooled to -78 °C, and a solution of 4,4-dimethyl-2-cyclohexen-1-one (1.1 mL, 8.4 mmol) in THF (6 mL) was added dropwise. The resulting mixture was stirred for 1.5 h. TMSCl (1.1 mL, 8.7 mmol) was added, and the mixture was stirred for 1.5 h. The mixture was warmed to room temperature and stirred for 45 min. The THF was removed under reduced pressure, leaving a residue. This residue was dissolved in pentane (20 mL). The pentane was removed under reduced pressure to give an orange, transparent liquid (0.92 g, 56%): IR ν_{max} 3045 (m), 3021 (w), 2946 (m), 1650 (s), 1598 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.55 (2H, d, J = 1.4 Hz), 4.83-4.77 (1H, m), 2.11 (2H, d, J = 4.7 Hz), 1.01 (6H, s), 0.19 (9H, s). ^{13}C NMR ($CDCl_3$): δ 147.1, 140.1, 127.6, 101.2, 37.3, 30.9, 26.6, 0.1. MS *m/z* (%): 53 (38), 67 (44), 81 (48), 82 (64), 96 (100), 124 (24), 147 (7) 197 (3, $M^+ + 1$).



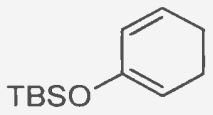
2, 5-Dimethyl-*para*-benzoquinone (27)

According to a procedure by Zimmer,[19] a mixture of Fremy's salt (4.80 g, 8.94 mmol) and sodium acetate solution (1.0 M, 8 mL) was added to a solution of 2,5-dimethylphenol (0.48 g, 3.9 mmol) in ether (10 mL). The mixture was stirred for 2 h, and then extracted with ether (3 × 50 mL). The combined organic layers were washed with H_2O (50 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give **27** as a bright reddish-orange solid (0.25 g, 46%). mp: 70-71 °C. IR ν_{max} 3056 (w), 1663 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.70 (2H, q, J = 1.7 Hz), 2.1 (6H, d, J = 1.7 Hz). ^{13}C NMR ($CDCl_3$): δ 188.0, 145.8, 133.3, 15.4.



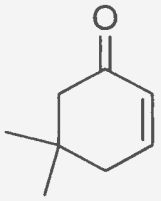
cis-2,5-Dimethyltricyclo[6.2.2.0^{2,7}]dodeca-4,9-diene-3,6-dione (28)

1,3-Cyclohexadiene (0.03 mL, 0.3 mmol) was added to a solution of **27** (20 mg, 0.15 mmol) in CH_2Cl_2 (15 mL). The mixture was heated at reflux for 48 h, then cooled to 0 °C. $BF_3{\cdot}Et_2O$ (5.7 μL, 0.045 mmol) was added, and the mixture was stirred at room temperature for 48 h. Water was added (10 mL), and the reaction mixture was extracted with ether (3 ×15 mL). The combined organic layers were washed with 0.1 M aqueous NaOH solution (20 mL) and H_2O (20 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography yielded **28** as a yellow solid (32 mg, 83%): mp: 59-61 °C (lit.[23] 60-62°C). IR ν_{max} 3043 (w), 2958 (m), 2870 (w), 1656 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.51 (1H, s), 6.29 (1H, t, J = 7.3 Hz), 6.10 (1H, t, J = 7.3 Hz), 3.08-3.01 (1H, m), 2.93-2.87 (1H, m), 2.51 (1H, s), 1.94 (3H, s), 1.91-1.84 (2H, m), 1.78-1.70 (2H, m), 1.32 (3H, s). ^{13}C NMR ($CDCl_3$): δ 203.0, 200.6, 150.4, 139.4, 136.6, 132.2, 58.5, 51.2, 39.4, 37.3, 26.5, 26.2, 19.0, 16.5.



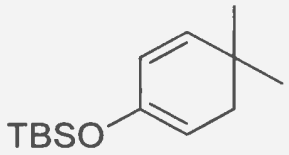
2-(*tert*-Butyldimethylsilyloxy)-1,3-cyclohexadiene (30)

Compound **30** was prepared using a procedure by Buckle.[18] A solution of 2-cyclohexen-1-one (0.25 mL, 2.6 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C and Et_3N (0.56 mL, 4.0 mmol) was added slowly. After 15 min, TBSOTf (0.72 mL, 3.1 mmol) was added. The mixture was stirred for 30 min, warmed to room temperature for 2 h, poured into ether (100 mL), and washed with aqueous saturated $NaHCO_3$ (2 × 16 mL) followed by brine (16 mL). The combined organic layers were dried over $MgSO_4/K_2CO_3$, and the solvent was removed under reduced pressure to give **30** as an orange, transparent liquid (0.27 g, 50%): IR ν_{max} 2910 (m), 1667 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.91-5.82 (1H, m), 5.73-5.65 (1H, m), 4.89-4.82 (1H, m), 2.21-2.09 (4H, m), 0.93 (9H, s), 0.15 (6H, s). ^{13}C NMR ($CDCl_3$): δ 146.2, 128.9, 124.6, 101.9, 22.5, 21.4, 0.1, -3.4.



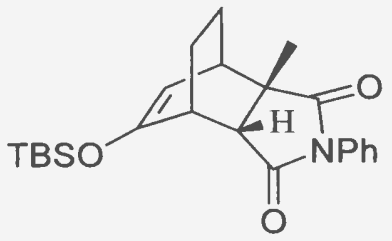
5,5-Dimethyl-2-cyclohexen-1-one (32)

According to a procedure by Buckle,[18] *p*-toluenesulfonhydrazide (11.3 g, 60.4 mmol) was dissolved in MeOH (150 mL). 5,5-Dimethyl-1,3-cyclohexanedione (8.47 g, 60.4 mmol) was added followed by 8 drops of concentrated H_2SO_4. The mixture was stirred overnight and concentrated under vacuum. H_2O (300 mL) was added followed by potassium carbonate (66.3 g, 476 mmol). The mixture was steam distilled, and the distillate was saturated with NaCl and extracted with ether (4 × 100 mL). The combined organic extracts were washed with brine (60 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give **32** as a bright yellow, transparent liquid (3.12 g, 51%): IR ν_{max} 3589 (bw), 2958 (m), 1653 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.88 (1H, dt, J = 4.1, 10.2 Hz), 6.05 (1H, dt, J =2.0, 10.1 Hz), 2.29 (2H, s), 2.34-2.22 (2H, m), 1.06 (6H, s). ^{13}C NMR ($CDCl_3$): δ 199.9, 148.3, 129.0, 51.8, 39.9, 33.9, 28.3.



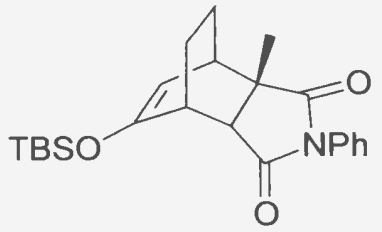
2-(*tert*-Butyldimethylsilyloxy)-5,5-dimethyl-1,3-cyclohexadiene (35)

Based on a procedure by Buckle,[18] 4,4-dimethyl-2-cyclohexen-1-one (0.25 mL, 1.9 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. Et_3N (0.41 mL, 2.9 mmol) was added dropwise. After 10 min, TBSOTf (0.64 mL, 2.8 mmol) was added. After 15 min, the mixture was warmed to room temperature and stirred for 1 h. The mixture was poured into ether (100 mL) and the solution was washed with aqueous saturated $NaHCO_3$ (2 × 15 mL) followed by brine (15 mL). The solution was dried over $MgSO_4/K_2CO_3$, and the solvent was removed under reduced pressure to give **35** as an orange-yellow, transparent liquid with a chemical yield based on integration of the crude NMR since the impurities could not be removed without destroying the product (0.48 g, 79%): IR ν_{max} 3401 (bw), 2907 (m), 1681 (m), cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.55 (2H, q), 4.81-4.74 (1H, m), 2.11 (2H, d, J = 4.6 Hz), 1.01 (6H, s), 0.93 (9H, s), 0.13 (6H, s). ^{13}C NMR ($CDCl_3$): δ 159.9, 158.5, 126.8, 124.9, 71.3, 45.7, 36.1, 34.4, 27.7, -3.0, -3.6.



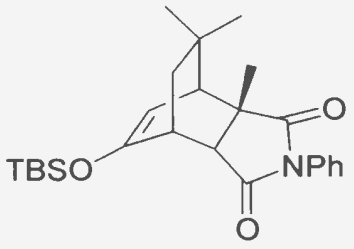
***cis*-endo-8-(*tert*-Butyldimethylsilyloxy)-4-phenyl-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (37)**

A solution of **30** (3.68 mg, 0.146 mmol) and *N*-phenylmaleimide (20 mg, 0.12 mmol) in dry toluene (20 mL) was sealed in a glass tube. The mixture was heated at 120 °C for 7 d. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure to give **37** as a white solid (0.035 g, 79%): mp: 154-157 °C. IR ν_{max} 3065 (w), 2943 (m), 2856 (w), 1733 (w), 1694 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.49-7.18 (5H, m), 4.98 (1H, dd, J = 6.9, 2.6 Hz), 3.27-3.19 (1H, m), 3.18-3.05 (1H, m), 3.04-2.89 (2H, m), 1.67-1.56 (4H, m), 0.89 (9H, s), 0.17 (3H, s), 0.12 (3H, s). ^{13}C NMR ($CDCl_3$): δ 178.1, 177.3, 154.8, 132.1, 128.9, 128.3, 126.4, 100.8, 45.2, 44.4, 38.1, 32.7, 25.2, 24.1, 17.9, -4.6, -4.7.



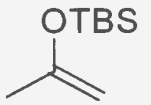
endo-8-(*tert*-Butyldimethylsilyloxy)-2-methyl-4-phenyl-4-azatricyclo[5.2.2.$0^{2,6}$]undec-8-ene-3,5-dione (39)

A solution of 2-methyl-*N*-phenylmaleimide (21.5 mg, 0.115 mmol) and diene **30** (31.9 mg, 0.152 mmol) in toluene (10 mL) was sealed in a glass tube. The solution was heated at 115 °C for 2 d. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure to yield **39** as a yellow oil with a chemical yield based on the integration of the crude ^{1}H NMR spectrum (ca. 4 mg, 8%): ^{1}H NMR ($CDCl_3$): δ 7.30-7.15 (5H, m), 5.91-5.69 (1H, m), 2.24-2.02 (7H, m), 1.43 (3H, s), 0.93 (9H, s), 0.12 (6H, s).



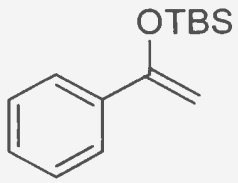
endo-8-(*tert*-Butyldimethylsilyloxy)-2,10,10-trimethyl-4-phenyl-4-aza-tricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (40)

A solution of 2-methyl-*N*-phenylmaleimide (20.5 mg, 0.110 mmol) and diene **35** (36.2 mg, 0.151 mmol) in toluene (10 mL) was sealed in a glass tube. The solution was heated at 115 °C for 2 d. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure to yield **40** as a yellow oil with a chemical yield based on integration of the crude NMR (3.07 mg, 7%): ^{1}H NMR ($CDCl_3$): δ 7.30-7.12 (5H, m), 5.85-5.74 (1H, m), 2.00-1.95 (1H, m), 1.32-1.01 (4H, m), 1.13 (3H, s), 1.00 (6H, s), 0.91 (9H, s), 0.12 (6H, s).



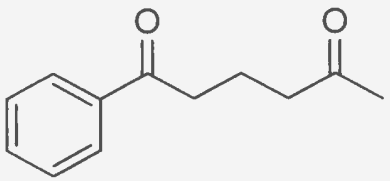
2-(*tert*-Butyldimethylsilyoxy)-1-propene (107)

Compound **107** was prepared using a procedure by Buckle.[18] A solution of acetone (0.25 mL, 3.4 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C, and Et_3N (0.47 mL, 3.4 mmol) was added dropwise. After 10 min, TBSOTf (0.78 mL, 3.40 mmol) was added. After 20 min, the mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was poured into ether (100 mL) and washed with aqueous saturated $NaHCO_3$ (2 × 15 mL) and brine (15 mL). The combined organic layers were dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure to give **107** as a clear liquid (0.39 g, 66%): IR ν_{max} 2930 (m), 1636 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.04 (2H, s), 1.77 (3H, s), 0.91 (9H, s), 0.15 (6H, s). ^{13}C NMR ($CDCl_3$): δ 156.2, 91.2, 25.7, 22.7, 18.1, -2.9, -4.6.



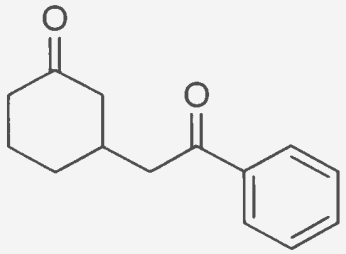
1-(*tert*-Butyldimethylsilyoxy)-1-phenylethene (114)

According to a procedure by Buckle,[18] a solution of acetophenone (0.97 mL, 8.3 mmol) in dry CH_2Cl_2 (30 mL) was cooled to -78 °C, and Et_3N (1.75 mL, 12.6 mmol) was added dropwise. After 25 min, TBSOTf (2.87 mL, 12.5 mmol) was added, and the mixture was stirred for 20 min. The mixture was warmed to room temperature and stirred for 17 h. The mixture was poured into ether (200 mL) and washed with aqueous saturated $NaHCO_3$ (2 × 30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure to give crude **114** as an orange, transparent liquid (2.45 g, 80%): IR ν_{max} 2930 (m), 1614 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.68-7.59 (2H, m), 7.37-7.23 (3H, m), 4.89 (1H, d, J = 1.7 Hz), 4.42 (1H, d, J = 1.8 Hz), 1.00 (9H, s), 0.21 (6H, s). ^{13}C NMR ($CDCl_3$): δ 164.3, 161.2, 155.3, 152.0, 149.2, 129.6, 28.7, 15.2, -2.9.



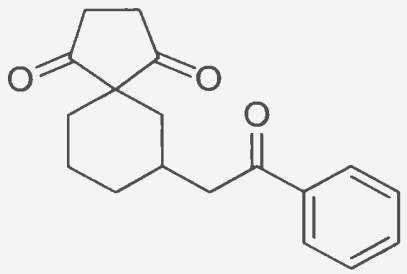
1-Phenyl-1,5-hexanedione (115)

Compound **115** was prepared according to a procedure by Mukaiyama.[41] $SnCl_2$ (135 mg, 0.0712 mmol), dried under reduced pressure at 100 °C for 2 h, and chlorotriphenylmethane (trityl chloride) (0.0201 g, 0.0721 mmol) were dissolved in CH_2Cl_2 (1 mL). This mixture was stirred for 45 min. The mixture was cooled to -78 °C. Compound **114** (0.333 g, 1.42 mmol) and 3-buten-2-one (0.12 mL, 1.4 mmol) were dissolved in CH_2Cl_2 (4 mL), and added to the $SnCl_2$/TrCl solution. This mixture was stirred for 100 min. The mixture was warmed to room temperature and poured into aqueous saturated $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography yielded **115** as a pale, yellow liquid (165 mg, 6%): IR ν_{max} 3058 (w), 2922 (m), 1709 (s), 1676 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.01-7.89 (2H, m), 7.62-7.51 (1H, m), 7.50-7.40 (2H, m), 3.03 (2H, t, J = 7.1 Hz), 2.58 (2H, t, J = 7.1 Hz), 2.16 (3H, s), 2.02 (2H, quintet, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 208.7, 199.9, 137.1, 133.4, 129.0, 128.4, 42.7, 37.4, 30.1, 18.2.



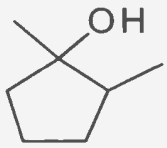
3-(2-Phenyl-2-oxoethyl)cyclohexanone (117)

According to a procedure by Mukaiyama,[41] trityl chloride (301 mg, 0.108 mmol) and $SnCl_2$ (201 mg, 0.106 mmol) were dissolved in CH_2Cl_2 (1 mL). The mixture was stirred for 30 min. The mixture was cooled to -78 °C, and a solution of 2-cyclohexen-1-one (0.10 mL, 1.0 mmol) and **114** (269 mg, 1.15 mmol) in CH_2Cl_2 (4 mL) was added. The mixture was stirred for 100 min, warmed to room temperature and poured into aqueous saturated $NaHCO_3$ (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography yielded **117** as a yellow solid (0.903 g, 40%): mp: 74-75 °C. IR ν_{max} 3062 (w), 2918 (m), 1711 (s), 1680 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.01-7.88 (2H, m), 7.63-7.52 (1H, m), 7.51-7.41 (2H, m), 3.08-2.90 (2H, m), 2.63-1.88 (7H, m), 1.81-1.41 (2H, m). ^{13}C NMR ($CDCl_3$): δ 211.1, 198.8, 137.4, 133.5, 128.9, 128.2, 47.8, 44.7, 41.2, 34.8, 31.3, 25.0.



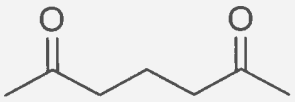
7-(2-Phenyl-2-oxoethyl)spiro[4.5]decane-1,4-dione (118)

Based on a procedure by Crane,[33] a solution of **56** (992 mg, 0.399 mmol) in dry CH_2Cl_2 (3 mL) was added to **118** (58.3 mg, 0.270 mmol). $BF_3{\cdot}Et_2O$ (0.045 mL, 0.36 mmol) was added, and the mixture was stirred for 23 h. The mixture was washed with H_2O (2 × 10 mL). The aqueous layers were re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. The mixture was filtered through a layer of charcoal, a layer of Florisil® and then flushed with CH_2Cl_2 (100 mL) and ether (100 mL). The solvent was removed under reduced pressure, and flash chromatography was carried out on the residue to yield **118** as a cloudy, white, viscous oil (7.1 mg, 9%): IR ν_{max} 3056 (w), 2934 (m), 1706 (s), 1669 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.98-7.89 (2H, m), 7.63-7.52 (1H, m), 7.51-7.40 (2H, m), 3.01-2.88 (4H, m), 2.86 (2H, d, J = 6.4 Hz), 1.81-1.62 (5H, m), 1.54-1.35 (2H, m), 1.26 (2H, t, J = 7.8 Hz). MS *m/z* (%): 51 (19), 77 (71), 105 (100), 120 (81), 164 (47), 284 (1, M^+).



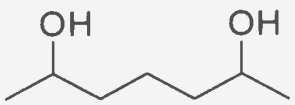
1,2-Dimethyl-1-cyclopentanol (121)

Compound **121** was prepared based on a procedure from the Memorial University of Newfoundland 2003 Chemistry 2400 laboratory manual.[45] 2-Methylcyclopentanone (1.03 g, 11.5 mmol) was dissolved in ether and was cooled to 0 °C. MeLi (1.6 M solution in hexanes, 16 mL, 22 mmol) was added dropwise, and the mixture was warmed to room temperature and stirred for 24 h. The mixture was quenched with saturated NH_4Cl (12 mL). The organic layer was washed with aqueous saturated $NaHCO_3$ (25 mL) and brine (25 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield the diastereomers of **121** in a 2:1 ratio as a clear, colorless mixture with 2-methylcyclopentanone **122** having a chemical yield based on integration of the crude NMR (0.46 g, 38%): ^{1}H NMR ($CDCl_3$): δ 1.84-1.40 (7H, m), 1.57 (1H, bd, J = 2.3 Hz), 1.26 (3H, s), 1.17 (3H, s), 0.94 (3H, d, J = 6.9 Hz), 0.89 (3H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$): δ 80.1, 44.0, 37.8, 32.1, 26.1, 20.8, 12.6.



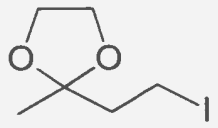
2,6-Heptanedione (106)

Compound **106** was prepared according to a procedure from the Memorial University of Newfoundland 2003 Chemistry 2400 laboratory manual.[45] A mixture containing **120**, **121**, and **122** (3.50 g, 36.3 mmol) was dissolved in concentrated H_3PO_4 (4.6 mL). The mixture was distilled using a fractional distillation apparatus. The fraction with a boiling range of 85-95 °C was washed with H_2O (10 mL), aqueous saturated $NaHCO_3$ (10 mL), H_2O (10 mL) and dried over $MgSO_4$. The $MgSO_4$ was extracted with pentane and filtered. The filtrate was not concentrated. MeOH (5 mL) was added to the filtrate, and the solution was cooled to -78 °C. Ozone was bubbled through the mixture until a light blue color was produced (30 min). Me_2S (4 mL) was added, and the mixture was warmed to room temperature. N_2 was blown over the mixture overnight to remove excess O_3. The residue was washed with aqueous 5% $CuSO_4$ (3 × 10 mL). The organic layers were dried over $MgSO_4$ and filtered. The filtrate was extracted with ether. The solution was concentrated by blowing N_2 (due to the instability of the compound, the solution was not evaporated to dryness.) over the surface to give the crude product **106** as a yellow, transparent oil (0.637 g, 16%): IR ν_{max} 3400 (bw), 2939 (m), 1707 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.47 (4H, t, J = 7.1 Hz), 2.13 (6H, s), 1.85 (2H, quintet, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 208.6, 42.4, 29.8, 17.6.



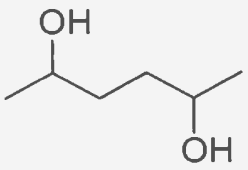
2,6-Heptanediol (125)

Based on a procedure by Melanson,[40] $NaBH_4$ (0.264 g, 6.99 mmol) was added in portions to a solution of crude **106** (0.395 g, 3.08 mmol) in MeOH (65 mL). The reaction mixture was stirred at room temperature for 48 h. H_2O was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL). The combined aqueous layers were re-extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated by blowing N_2 over the surface of the solution followed by simple distillation to yield **125** as a transparent, colorless oil and a mix of the *meso* and the racemic diastereomers (0.0540 g, 13%): IR ν_{max} 3335 (bs), 2931 (s), 1711 (w) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.81 (2H, quintet, J = 6.1 Hz), 1.63-1.43 (6H, m), 1.20 (6H, d, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$): δ 71.3, 39.5, 30.1, 14.6.



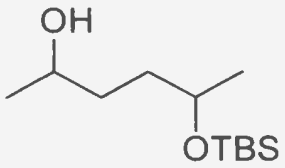
2-(2-Iodoethyl)-2-methyl-1,3-dioxolane (100)

Based on a procedure by Stowell,[46] aqueous concentrated HI (5.4 mL, 72 mmol) was added to a solution of 3-buten-2-one (2.51 g, 35.8 mmol) in benzene (30 mL). The mixture was stirred for 2 h. The two layers were separated, and the organic layer was poured into aqueous saturated $NaHCO_3$ (30 mL). The organic layer was washed with aqueous saturated $NaHCO_3$ (3 × 30 mL) and brine (30 mL). The combined aqueous layers were re-extracted with benzene (2 × 25 mL). The combined organic layers were dried over $MgSO_4$. The filtered mixture was added to *p*-TsOH (0.206 g, 1.09 mmol), and ethylene glycol (2.2 mL, 39 mmol) was added. The mixture was heated at reflux for 4 h, and H_2O was removed using a Barrett apparatus. The cooled mixture was washed with aqueous saturated $NaHCO_3$ (2 × 25 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to yield a greenish black liquid. This liquid was passed through neutral alumina (10 cm x 1 cm) using hexanes (85 mL) as the eluting solvent. The solution was concentrated under reduced pressure to yield **100** as a yellow, transparent liquid (1.78 g, 21%): IR ν_{max} 2933 (m), 1624 (w), 532 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.99-3.88 (4H, m), 3.20-3.13 (2H, m), 2.32-2.24 (2H, m), 1.31 (3H, s). ^{13}C NMR ($CDCl_3$): δ 109.4, 64.5, 44.0, 23.5, -2.4.



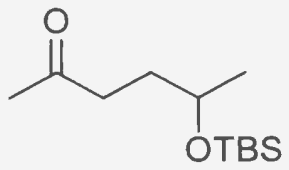
2,5-Hexanediol (127) as a diastereomeric mixture

Based on a procedure by Melanson,[40] $NaBH_4$ (2.49 g, 65.7 mmol) was added in portions to a 0 °C solution of 2,5-hexandione (5.01 g, 43.9 mmol) in MeOH (80 mL). The mixture was stirred for 24 h. H_2O (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (60 mL), and the aqueous layers were re-extracted with ethyl acetate (4 × 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography was carried out using 50% EtOAc/hexane as the eluting solvent to yield **127** as a pale, yellow oil (3.55 g, 69%): IR ν_{max} 3320 (bs), 2966 (s), 2930 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.89-3.77 (2H, m), 2.06 (2H, bs), 1.66-1.46 (4H, m), 1.21 (6H, d, J = 6.1 Hz). ^{13}C NMR ($CDCl_3$): δ 68.2, 67.6, 36.0, 34.8, 23.7, 23.1.



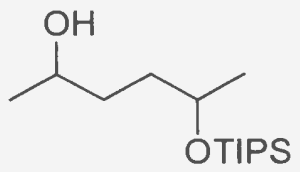
5-(*tert*-Butyldimethylsilyloxy)-2-hexanol (130)

According to a procedure by Melanson,[40] the mixture of diastereomers **127** (0.75 g, 6.4 mmol) was dissolved in dry ether (7 mL) and TBSCl (0.43 g, 2.9 mmol) was added, followed by imidazole (0.22 g, 3.2 mmol). The mixture was stirred at room temperature for 24 h. H_2O (6 mL) was added, and the mixture was extracted with ether (3 × 7 mL). The combined organic layers were washed with H_2O (2 × 6 mL) and brine (6 mL), dried over $MgSO_4$, and concentrated under reduced pressure to yield **130** as a pale, yellow oil (0.16 g, 24%): IR ν_{max} 3334 (bw), 2929 (bm) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.96-3.72 (2H, m), 1.69-1.49 (4H, m), 1.29-1.12 (6H, m), 0.90 (9H, s), 0.10 (6H, s). ^{13}C NMR ($CDCl_3$): δ 68.4, 65.8, 35.9, 35.0, 31.6, 25.6, 23.8, 18.0, 15.2, -3.6.



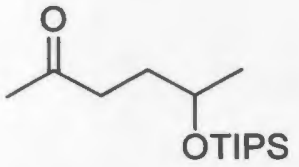
5-(*tert*-Butyldimethylsilyloxy)-2-hexanone (101)

Acccording to a procedure by Martin,[47] PDC (0.162 g, 0.431 mmol) was suspended in dry CH_2Cl_2 (5 mL), and a solution of **130** (0.105 g, 0.452 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise. The mixture was heated at reflux for 24 h under a drying tube containing $CaCl_2$ in the condenser. The mixture was diluted with ether, run through Celite, and the Celite was flushed with ether (150 mL). The mixture was then washed with H_2O (6 × 25 mL), and the combined aqueous layers were re-extracted with ether (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give **100** as a yellowish-brown liquid (0.454 g, 92%): IR ν_{max} 3430 (bw), 2909 (s), 1705 (w) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.82 (1H, m), 2.55-2.46 (2H, m), 2.15 (3H, s), 1.82-1.48 (2H, m), 1.12 (3H, d, J = 6.4 Hz), 0.88 (9H, s), 0.05 (3H, s), 0.04 (3H, s). ^{13}C NMR ($CDCl_3$): δ 203.2, 66.1, 38.7, 35.9, 34.8, 31.2, 25.7, 15.7, -3.4.



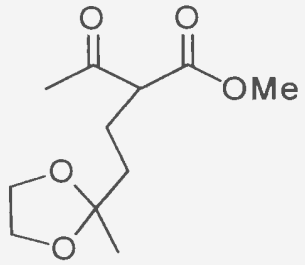
5-(Triisopropylsilyloxy)-2-hexanol (132)

Compound **132** was prepared based on a procedure by Melanson.[40] TIPSCl (0.53 mL, 2.5 mmol) was added to a solution of **127** (0.649 g, 5.49 mmol) in dry ether (6 mL). This was followed by the addition of imidazole (0.188 g, 2.76 mmol). Dry ether (4 mL) was added, and the mixture was stirred overnight. H_2O (6 mL) was added and the aqueous layer was extracted with ether (3 × 7 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure to yield **132** as a pale, yellow oil. Since impurities could not be separated without destroying the product, a chemical yield is reported based on integration of the crude NMR (0.52 g, 11%): ^{1}H NMR ($CDCl_3$): δ 3.90-3.81 (2H, m), 1.69-1.50 (4H, m), 1.32-1.19 (3H, m), 1.18 (6H, d, J = 6.1 Hz), 1.14-1.02 (18H, m). ^{13}C NMR ($CDCl_3$): δ 68.3, 67.9, 65.7, 35.9, 35.0, 23.7, 23.4, 17.7, 12.3.



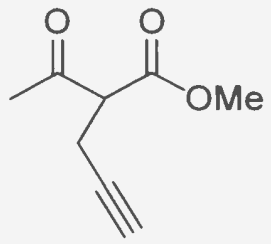
5-(Triisopropylsilyloxy)-2-hexanone (133)

According to a procedure by Martin,[47] compound **132** (0.520 g, 1.89 mmol) in dry CH_2Cl_2 (20 mL) was added to a suspension of PDC (0.790 g, 2.10 mmol) in dry CH_2Cl_2 (30 mL). The mixture was heated at reflux for 24 h with a drying tube containing $CaCl_2$ in the condenser. The mixture was diluted with ether (60 mL) and flushed through celite followed by ether (250 mL). The solvent was reduced by 75%, and the residue was washed with H_2O (5 × 60 mL). The aqueous layers were re-extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (80 mL), 0.01 M HCl (4 × 15 mL), dried over $MgSO_4$, and concentrated under reduced pressure to yield **133** as a reddish-brown, thick oil. Since impurities could not be removed without destroying the product, a chemical yield is reported based on integration of the crude NMR (0.251 g, 68%): IR ν_{max} 3448 (bw), 2892 (s), 1711 (w) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.09-3.981 (1H, m), 2.53 (2H, t, J = 9.1 Hz), 2.15 (3H, s), 1.81-1.68 (2H, m), 1.15 (3H, d, J = 6.3 Hz), 1.10 (21H, s). ^{13}C NMR ($CDCl_3$): δ 209.1, 67.4, 39.1, 33.2, 29.3, 23.3, 17.7, 12.3.



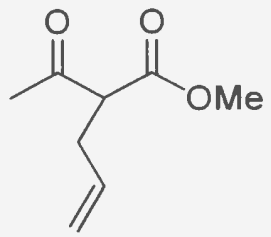
Methyl 2-(3-dioxolanobutyl)-3-oxobutanoate (109)

According to a procedure by Melanson,[40] a solution of methyl acetoacetate (0.74 mL, 6.9 mmol) in dry THF (9 mL) was added dropwise to a solution of NaH (0.172 g, 7.18 mmol) in dry THF (9 mL). A solution of **100** (1.50 g, 6.21 mmol) in dry THF (9 mL) was added to the mixture. The mixture was heated at reflux for 20 h, after which time it was cooled to room temperature and washed with brine (2 × 10 mL). The combined aqueous layers were re-extracted with EtOAc (6 × 10 mL). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography was carried out on the residue using neutral alumina with 20% EtOAc/hexane as the eluting solvent to yield **109** as an orange-brown liquid (0.14 g, 7%): IR ν_{max} 3469 (bw), 2955 (bm), 1716 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.98-3.88 (4H, m), 3.74 (3H, s), 3.50 (1H, t, J = 7.4 Hz), 2.24 (3H, s), 2.03-1.91 (2H, m), 1.69-1.58 (2H, m), 1.32 (3H, s). ^{13}C NMR ($CDCl_3$): δ 203.0, 170.2, 109.3, 83.7, 64.6, 52.3, 36.2, 28.9, 23.7, 22.6.



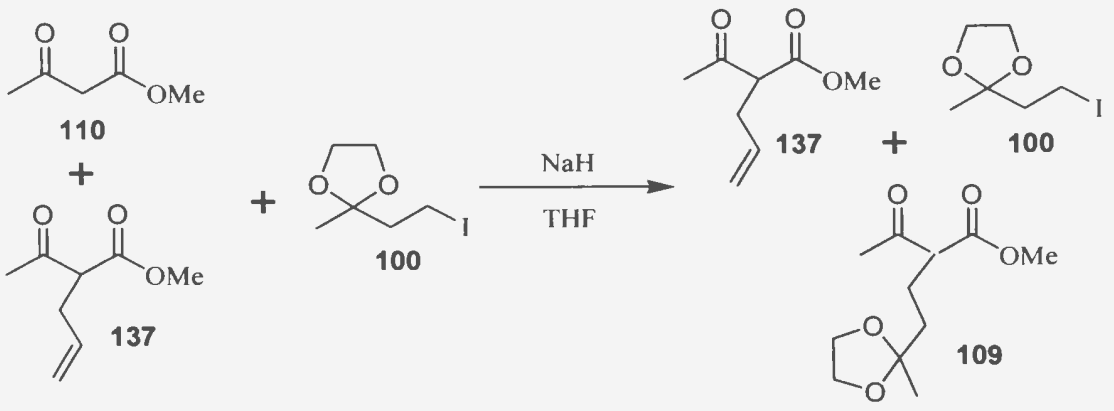
Methyl 3-oxo-2-(2-propynyl)butanoate (135)

Based on a procedure by Melanson,[40] methyl acetoacetate (0.94 mL, 8.7 mmol) in dry THF (10 mL) was added dropwise to a suspension of NaH (0.292 g, 12.2 mmol) in dry THF (10 mL). A solution of propargyl bromide (1.38 mL, 15.5 mmol) in dry THF (5 mL) was added to the reaction mixture. The mixture was heated at reflux for 24 h, cooled, and washed with brine (2 × 25 mL). The combined aqueous layers were re-extracted with EtOAc (4 × 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give **135** as an orange, transparent liquid with a chemical yield based on integration of the crude NMR (1.10 g, 66%): ^{1}H NMR ($CDCl_3$): δ 3.78 (3H, s), 3.75 (1H, t, J = 7.5 Hz), 2.73 (1H, m), 2.33 (3H, s), 2.01 (1H, t, J = 2.8 Hz).

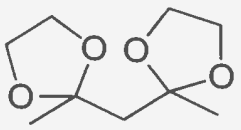


Methyl 3-oxo-2-(2-propenyl)butanoate (137)

According to a procedure by Melanson,[40] methyl acetoacetate (0.94 mL, 8.7 mmol) in THF (15 mL) was added to a solution of NaH (0.301 g, 12.5 mmol) in THF (30 mL). After 10 min, a solution of allyl iodide (0.79 mL, 8.6 mmol) in THF (15 mL) was added. The mixture was heated at reflux for 42 h after which time it was cooled and washed with brine (2 × 25 mL). The combined aqueous layers were extracted with ethyl acetate (4 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield **137** an orange-brown, transparent liquid with a chemical yield based on integration of the crude NMR (1.10 g, 65%): ^{1}H NMR ($CDCl_3$): δ 5.81-5.66 (1H, m), 5.17-5.04 (2H, m), 3.74 (3H, s), 3.55 (1H, t, J = 7.3 Hz), 2.60 (2H, m), 2.24 (3H, s).

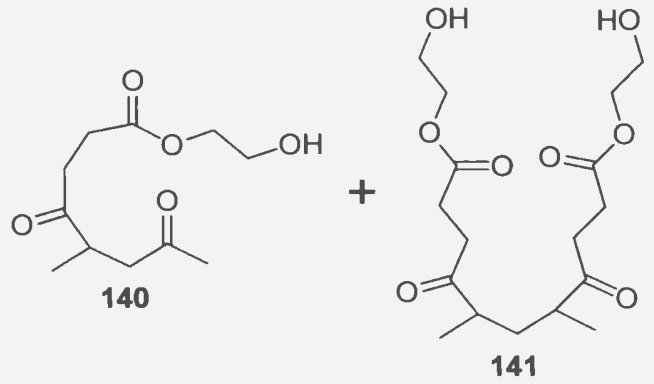


Based on a procedure by Melanson,[40] the mixture containing compounds **110**, and **137** (0.5016 g, 1.842 mmol) dissolved in dry THF (4 mL) was added to a solution of NaH (0.0849 g, 3.538 mmol) in dry THF (2 mL). A solution of compound **100** (0.8533 g, 3.538 mmol) in dry THF (4 mL) was added. The mixture was refluxed for 44 h. The mixture was cooled to room temperature and washed with brine (2 × 10 mL). The aqueous layers were re-extracted with ethyl acetate (6 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield a mixture of **100**, **109**, **137** as an orange, transparent liquid (1.1645 g, 79%). NMR signals for these compounds have been reported previously in this document.



2,4-Pentandione diacetal (139)

Based on a procedure by Stowell,[46] *p*-TsOH (0.196 g, 1.03 mmol) was added to a solution of 2,4-pentanedione (10.0 g, 100 mmol) in benzene (120 mL) followed by the addition of ethylene glycol (12.3 mL, 220 mmol). A Dean-Stark apparatus was attached to the reaction flask, and the mixture was heated at reflux for 48 h. The mixture was cooled to room temperature and washed with saturated $NaHCO_3$ (2 × 100 mL). The combined aqueous layers were re-extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield **139** as a yellow, transparent liquid (10.2 g, 54%): IR ν_{max} 3502 (bw), 2933 (bw) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.87 (8H, s), 2.03 (2H, s), 1.43 (6H, s). ^{13}C NMR ($CDCl_3$): δ 108.8, 64.4, 46.4, 24.8.



140 + 141

5-Methyl-4,7-dioxooctanoic acid, (2-hydroxyethyl) ester (140) and 5,7-dimethyl-4,8-dioxoundecanedioic acid, bis(2-hydroxyethyl) ester (141)

Compound **139** (0.501 g, 2.66 mmol) was dissolved in CH_2Cl_2 (1 mL) and cooled to -78 °C. BCl_3 (4.3 mL, 4.3 mmol) followed by **56** (0.988 g, 4.29 mmol) were added to the reaction mixture. The mixture was warmed to room temperature overnight. The mixture was then cooled to -78 °C and HF (2.2 mL, 0.13 mmol) dissolved in MeOH (8.7 mL, 0.21 mmol) was added, and the mixture was stirred for 15 min. The mixture was warmed to room temperature and stirred for 1.5 h. The mixture was concentrated under reduced pressure and TFA (8 mL, 0.1 mol) was added. The mixture was stirred overnight, washed with H_2O (2 × 50 mL), and back-extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were washed with brine (4 × 60 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a mixture of **140** and **141** as a cloudy, yellow oil (a trace amount): ^{1}H NMR ($CDCl_3$): δ 4.22 (6H, t, J = 4.8 Hz), 3.84 (6H, t, J = 7.5 Hz), 2.81 (6H, t, J = 4.7 Hz), 2.51 (3H, t, J = 4.8 Hz), 2.34-2.29 (6H, m), 2.11 (2H, d, J = 6.2 Hz), 2.05 (3H, s), 1.68 (9H, d, J = 6.1 Hz).

References

1) Smith, M.; March, J. March's Advanced Organic Chemistry. 5th ed. John Wiley & Sons Inc., New York. 1068 (2001), 847.

2) Rozeboom, M. D.; Tegno-Larsson, I.-M.; Houk, K. N. *J. Org. Chem.* **1981**, *46*, 2338-2345.

3)(a) Houk, K. N.; *Acc. Chem. Res.* **1975**, *8*, 361-369. (b) Elsentein, O.; Lefour, J. M.; Anh, N. T.; Hudson, R. F. *Tetrahedron*, **1977**, *33*, 523-531. (c) Eplotis, N. D. *J. Am. Chem. Soc.* **1973**, *95*, 5624-5632.

4) Alston, P. V.; Ottenbrite, R. M.; Cohen, T. *J. Org. Chem.* **1978**, *43*, 1864-1867.

5) Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *Acc. Chem. Res.* **2000**, *33*, 658-664.

6) Bach, R. D.; McDouall, J. J. W.; Schlegel, H. B.; Wolber, G. J. *J. Org. Chem.* **1989**, *54*, 2931-2935.

7) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381-7396.

8)(a) Capaccio, C. A. I.; Varela, O. *J. Org. Chem.* **2002**, *67*, 7839-7846. (b) Carreno, M. C.; Garcia-Cerrada, S.; Urbano, A.; Vitta, C. D. *J. Org. Chem.* **2000**, *65*, 4355-4363. (c) Bachmann, C.; Boker, N.; Mondon, M.; Gesson, J.-P. *J. Org. Chem.* **2000**, *65*, 8089-8092. (d) Abad, A.; Agullo, C.; Castelblanque, L.; Cunat, A. C.; Navarro, I..; Ramirez de Arellano, M. C. *J. Org. Chem.* **2000**, *65*, 4189-4192. (e) Muray, E.; Alvarez-Larena, A.; Piniella, J. F.; Branchadell, V.; Ortuno, R. M. *J. Org. Chem.* **2000**, *65*, 388-396. (f) Hou, G. F.; Peddinti, R. K.; Liao, C.-C. *Org. Lett.* **2002**, *4*, 2477-2480. (g) Huang, Y.; Iwama, T.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 1163-1166. (h) Chou, Y.-Y.; Peddinti, R. K.; Liao, C.-C. *Org. Lett.* **2003**, *5*, 1637-1640.

9) Chen, C.-H.; Liao, C.-C. *Org. Lett.* **2000**, *2*, 2049-2052.

10) Xidos, J. D.; Gosse, T. L.; Burke, E. D.; Poirier, R. A.; Burnell, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 5482-5488.

11) Dickinson, R. A.; Kubela, R.; MacAlpine, G. A.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1972**, *50*, 2377-2380.

12) Liu, C. J.; Burnell, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 9584-9585.

13) Pitea, D.; Gastaldi, M.; Orsini, F.; Pelizzoni, F.; Mugnoli, A.; Abbondanti, E. *J. Org. Chem.* **1985**, *50*, 1853-1859.

14) Tou, J. S.; Reusch, W. *J. Org. Chem.* **1980**, *45*, 5012-5014.

15) Bohlmann, F.; Mathar, W.; Schwarz, H. *Chem. Ber.* **1977**, *110*, 2028-2045.

16) Mercer, D.; Pye, C. C.; Burnell, D. J. Unpublished work.

17) Burnell, D. J.; Chinn, T.S.L. Unpublished work.

18) Buckle, R. N.; Liu, P.-Y.; Roberts, E. W. D.; Burnell, D. J. *Tetrahedron*, **1999**, *55*, 11455-11464.

19) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229-246.

20) Sauer, J. *Angew. Chem. Int. Ed.* **1967**, *6*, 16-33.

21) Buckle, R. N.; Burnell, D. J.; *Tetrahedron*, **1999**, *55*, 14829-14838.

22) Dauben, W. G.; Lam, J. Y. L.; Guo, Z. R. *J. Org. Chem.* **1996**, *61*, 4816-4819.

23)(a) Dauben, W. G.; Krabbenhoft, H. O. *J. Am. Chem. Soc.* **1976**, *98*, 1992-1993. (b) Dauben, W. G.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1974**, *96*, 3664-3666.

24) Franks, M. A.; Hyatt, J. A.; Welker, M. E. *Org. Proc. Res. Dev.* **2001**, *5*, 514-518.

25) Shimada, J.; Hashimoto, K.; Kim, G. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759-1773.

26) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503-7509.

27)(a) Stork, G.; Hudrik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464-4465. (b) Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. *J. Org. Chem.* **1983**, *48*, 932-945. (c) Sato, T.; Otera, J.; Nazaki, H. *J. Am. Chem. Soc.* **1990**, *112*, 901-902.

28) Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 1485-1491.

29) Kuwajima, I.; Nakamura, E.; Shimizu, M.; Noyori, R.; Yokoyama, K.; Sakata, J. *J. Am. Chem. Soc.* **1977**, *99*, 1265-1267.

30)(a) Wu, Y.-J.; Strickland, D. W.; Jenkins, T. J.; Liu, P.-Y.; Burnell, D. J. *Can. J. Chem.* **1993**, *71*, 1311-1318. (b) Burnell, D. J.; Wu, Y. -J. *Can. J. Chem.* **1990**, 68, 804-811.

31) Crane, S. N.; Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1997**, *62*, 8722-8729.

32) Crane, S. N.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 5708-5710.

33) Crane, S. N.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 1352-1355.

34) Burnell, D. J.; Wu, Y.-J. *Can. J. Chem.* **1989**, *67*, 816-819.

35) Nakamura, E.; Hashimoto, K.; Kuwajima, I. *J. Org. Chem.* **1977**, *42*, 4166-4167.

36) McCarthy, A. M.; Burnell, D.J. M. Sc. Thesis, Memorial University of Newfoundland, **2003**.

37) Perez-Medrano, A.; Grieco, P. *J. Am. Chem. Soc.* **1991**, *113*, 1057-1059.

38) Bado, S.; Mareggiuni, G.; Amiano, N.; Burton, G.; Veleiro, A. S. *J. Agric. Food Chem.* **2004**, *52*, 2875-2878.

39) Torrini, I.; Maione, A. M.; Calcagni, A. *J. Chem. Soc. Perkin Trans. 1.* **1980**, 440-443.

40) Melanson, R. A.; Burnell, D.J. M. Sc. Thesis, Memorial University of Newfoundland, **2000**.

41) Mukaiyama, T.; Kobayashi, S.; Tamura, M.; Sagawa, Y. *Chem. Lett.* **1987**, 491-494.

42) Schmidt, T. J.; Müller, E.; Fronczek, F. R. *J. Nat. Prod.* **2001**, *64*, 411-414.

43) Enders, D.; Zampon, A.; Raabe, G.; Runsink, J. *Synthesis*. **1993**, 725-728.

44) Ono, N.; Yoshimura, T.; Saito, T.; Tamura, R.; Tanikaga, R.; Kaji, A. *Bull. Chem. Soc. Jap.* **1979**, *52*, 1716-1719.

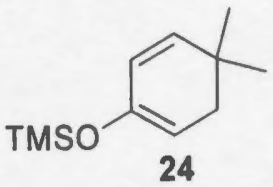
45) Chemistry 2400 Laboratory Manual, Memorial University of Newfoundland, **2003**.

46) Stowell, J. C.; King, B. T.; Hauck, H. F., Jr. *J. Org. Chem.* **1983**, *48*, 5381-5382.

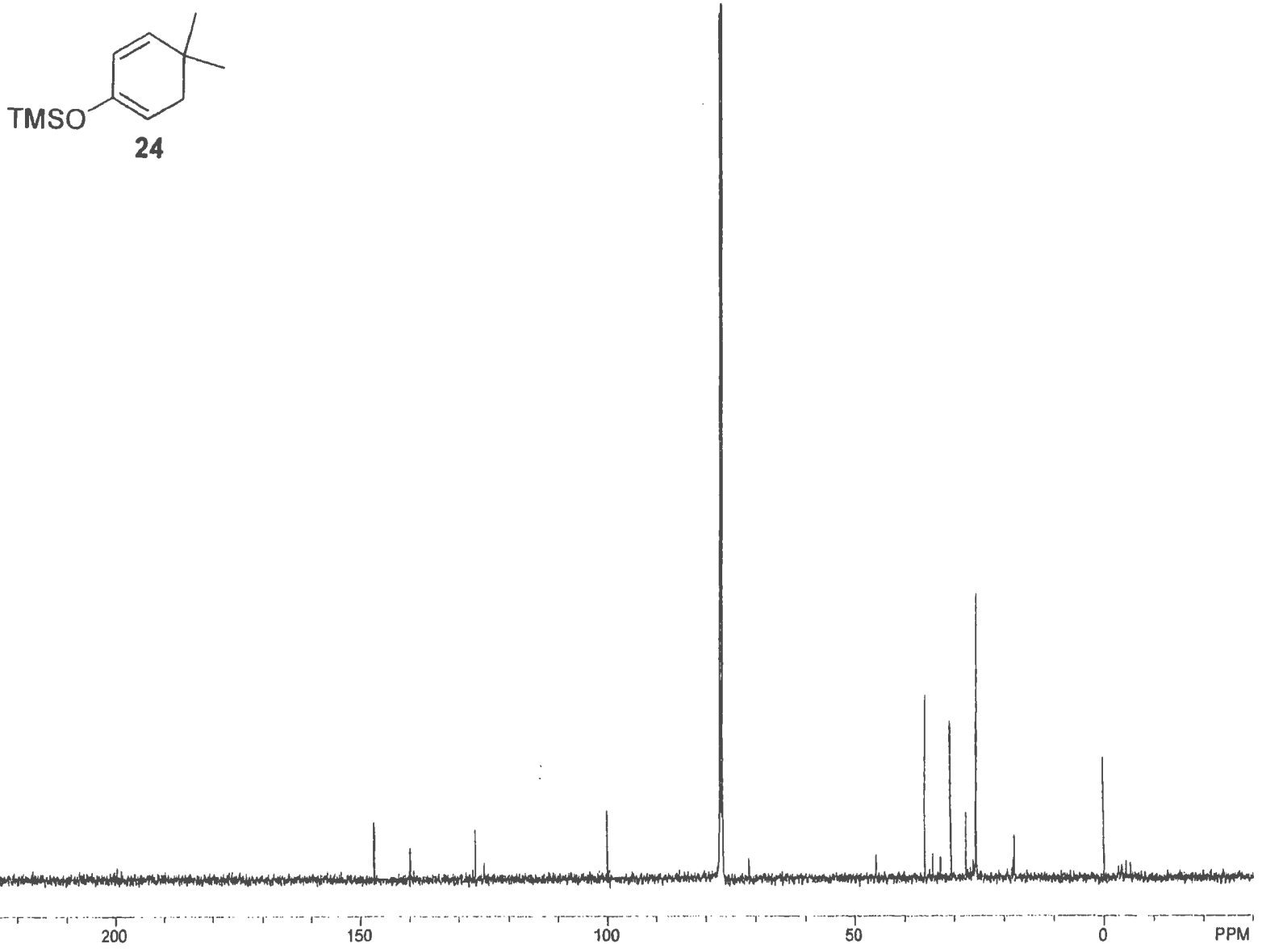
47) Martin, C. J.; Bess, D. B. *J. Org. Chem.* **1983**, *48*, 4155-4156.

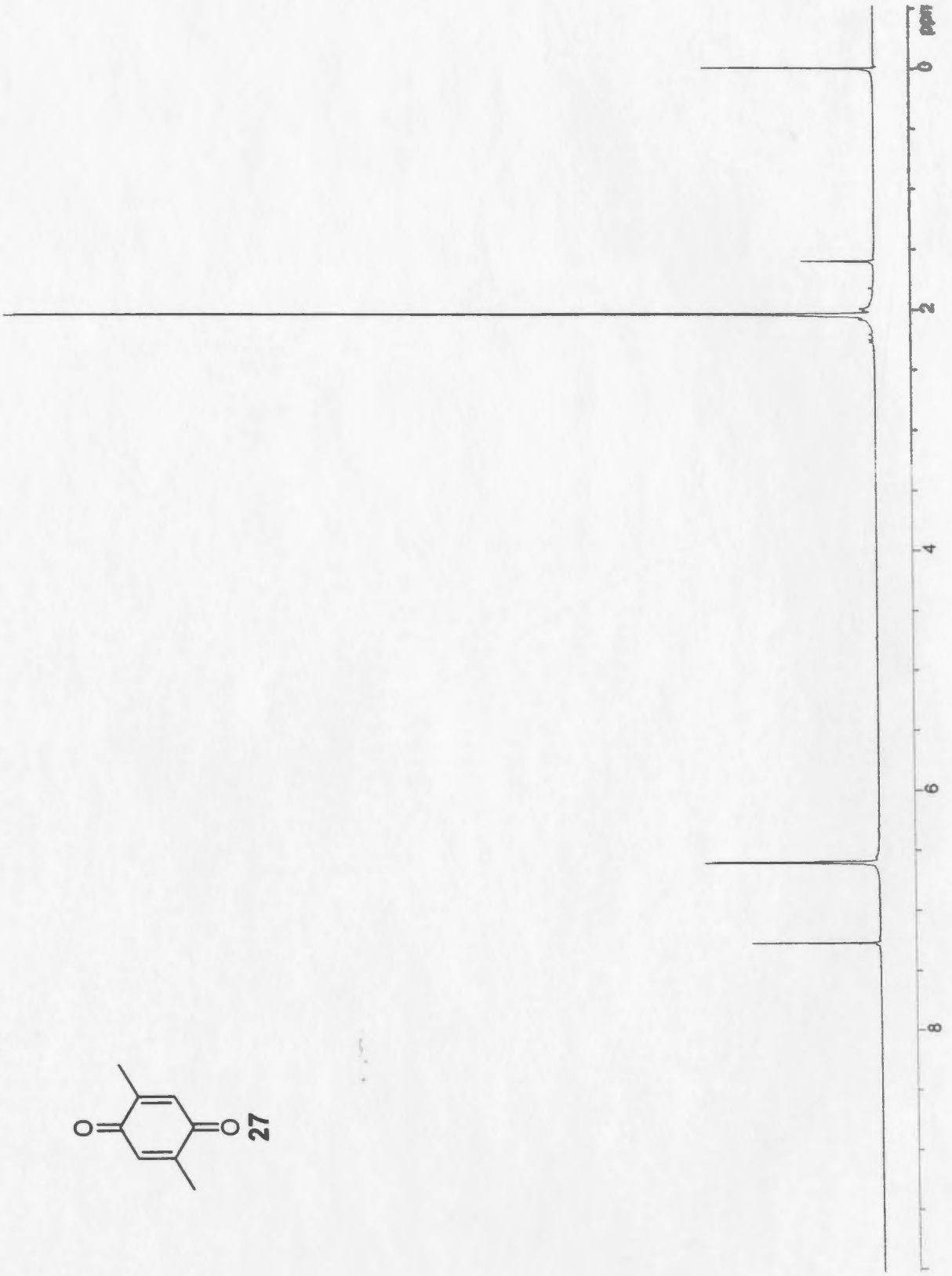
Appendix A

^{1}H and ^{13}C NMR Spectra

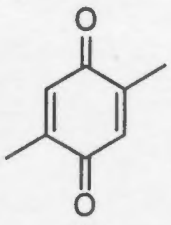


24

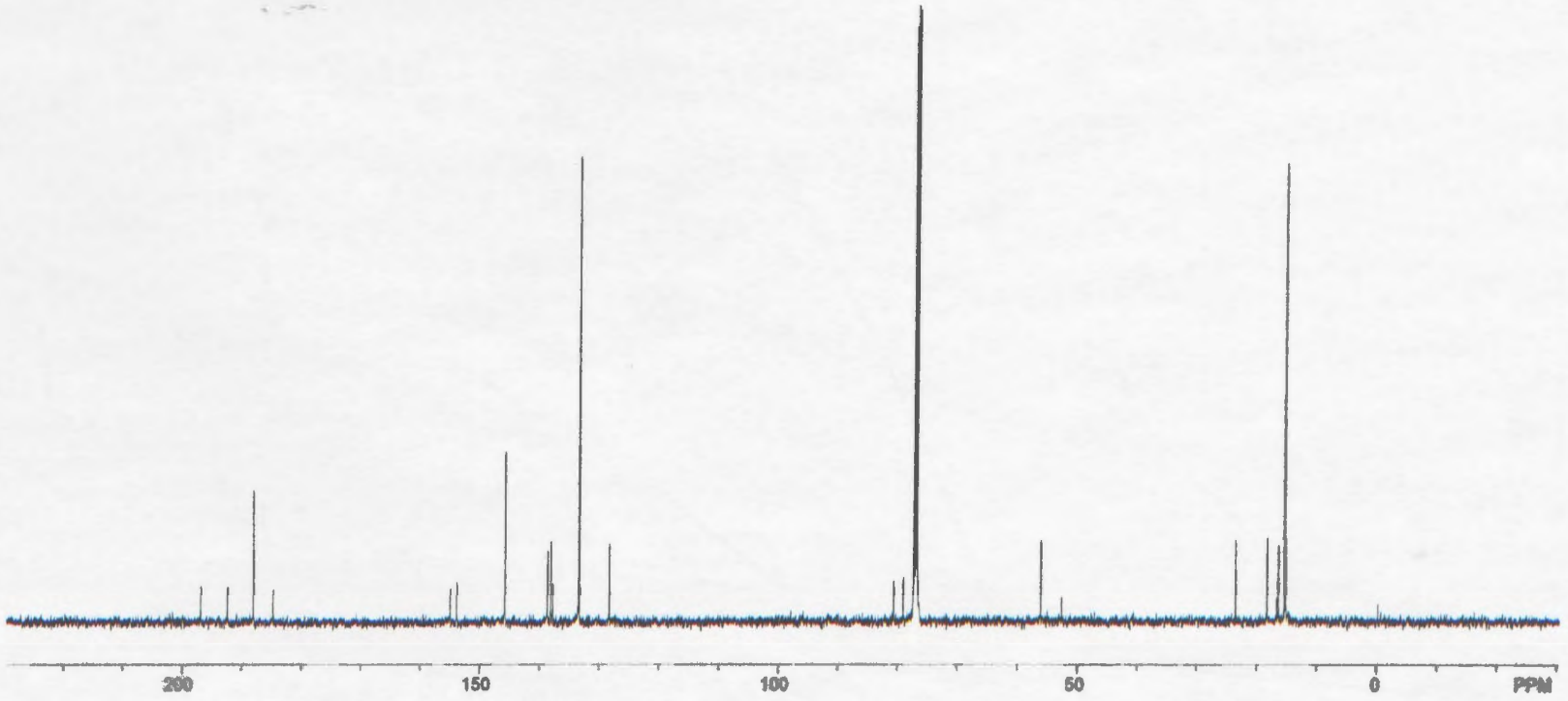

TMSO
24
200
150
100
50
0
PPM

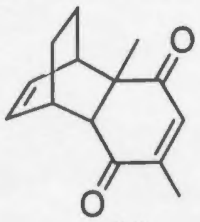


27

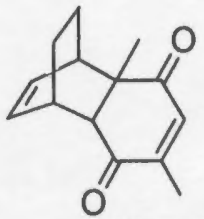


27

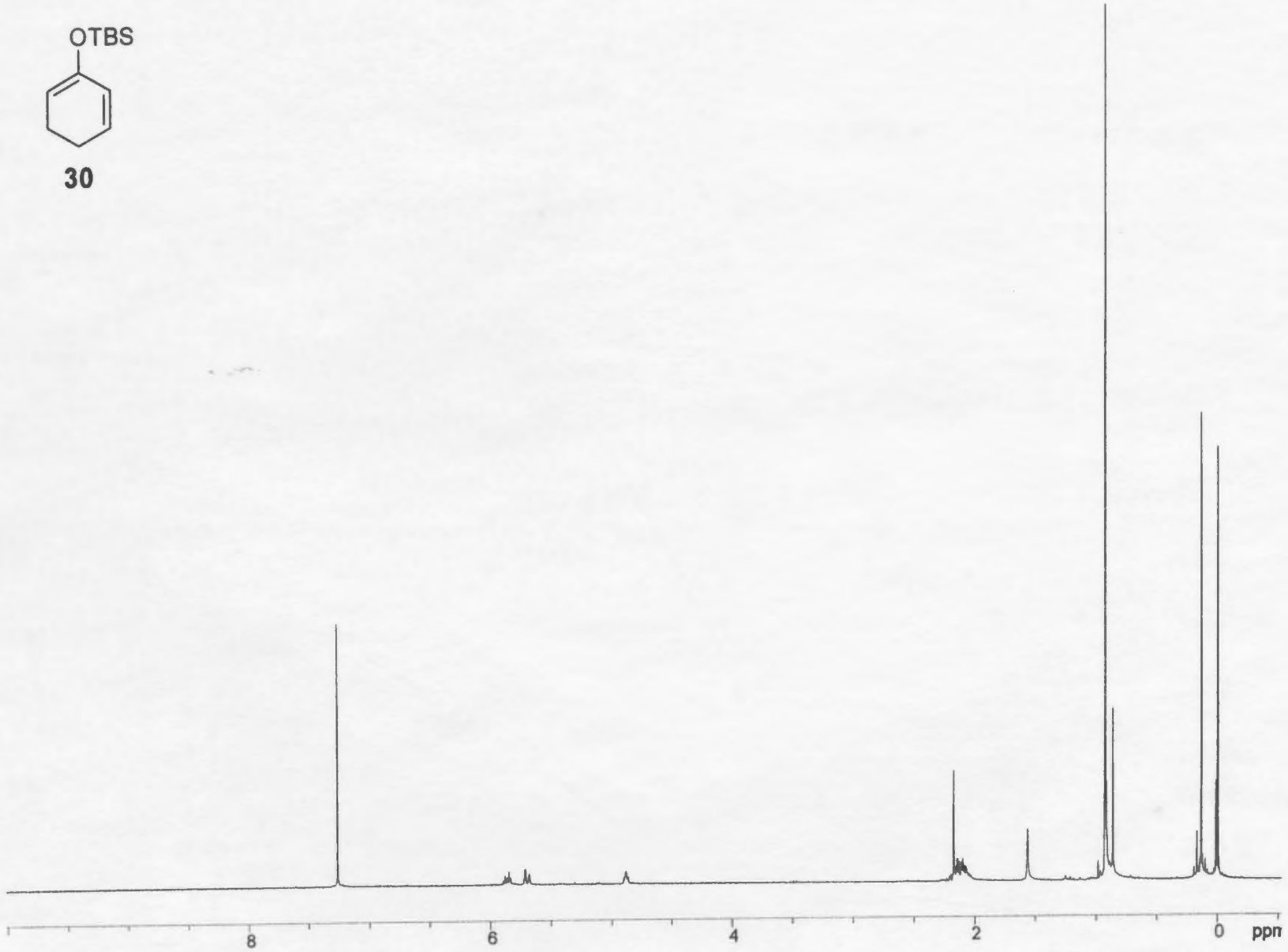


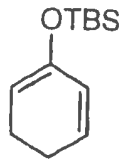


28

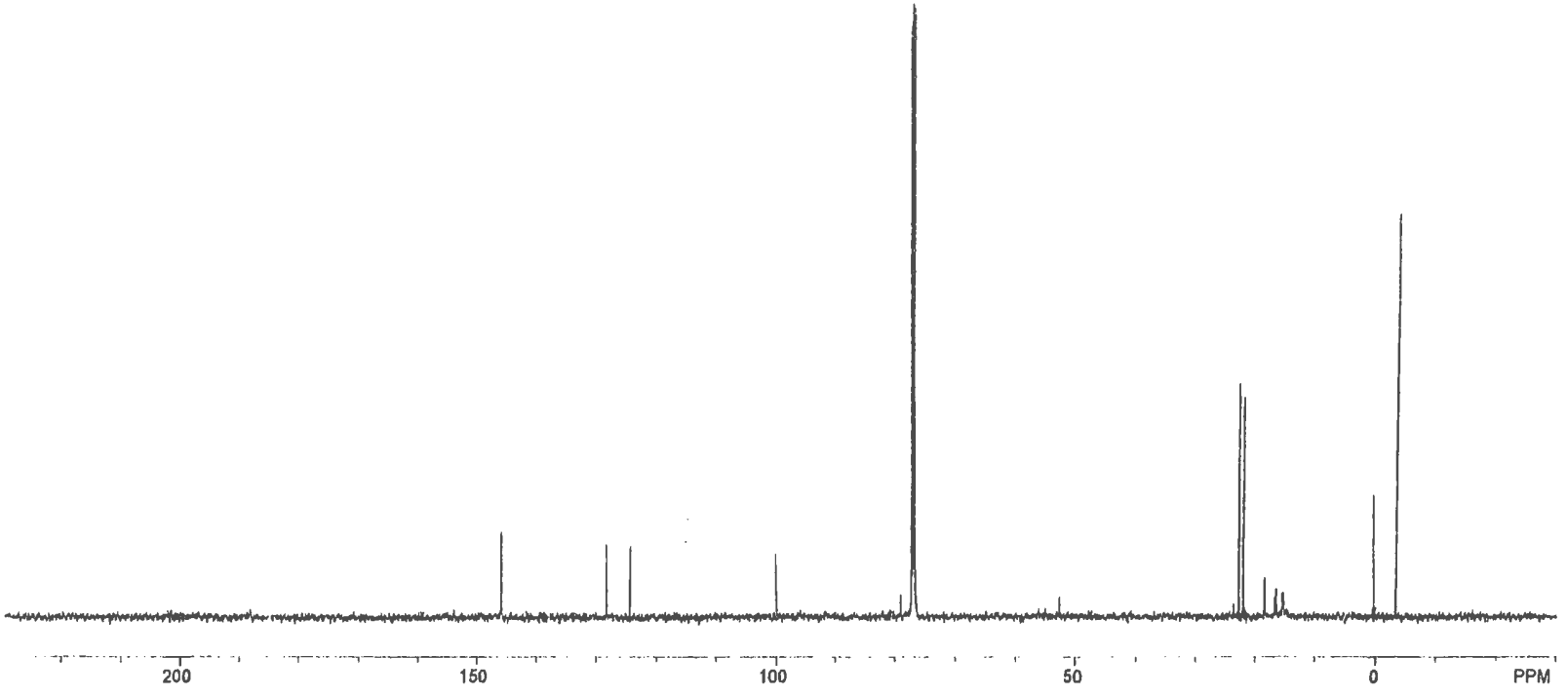


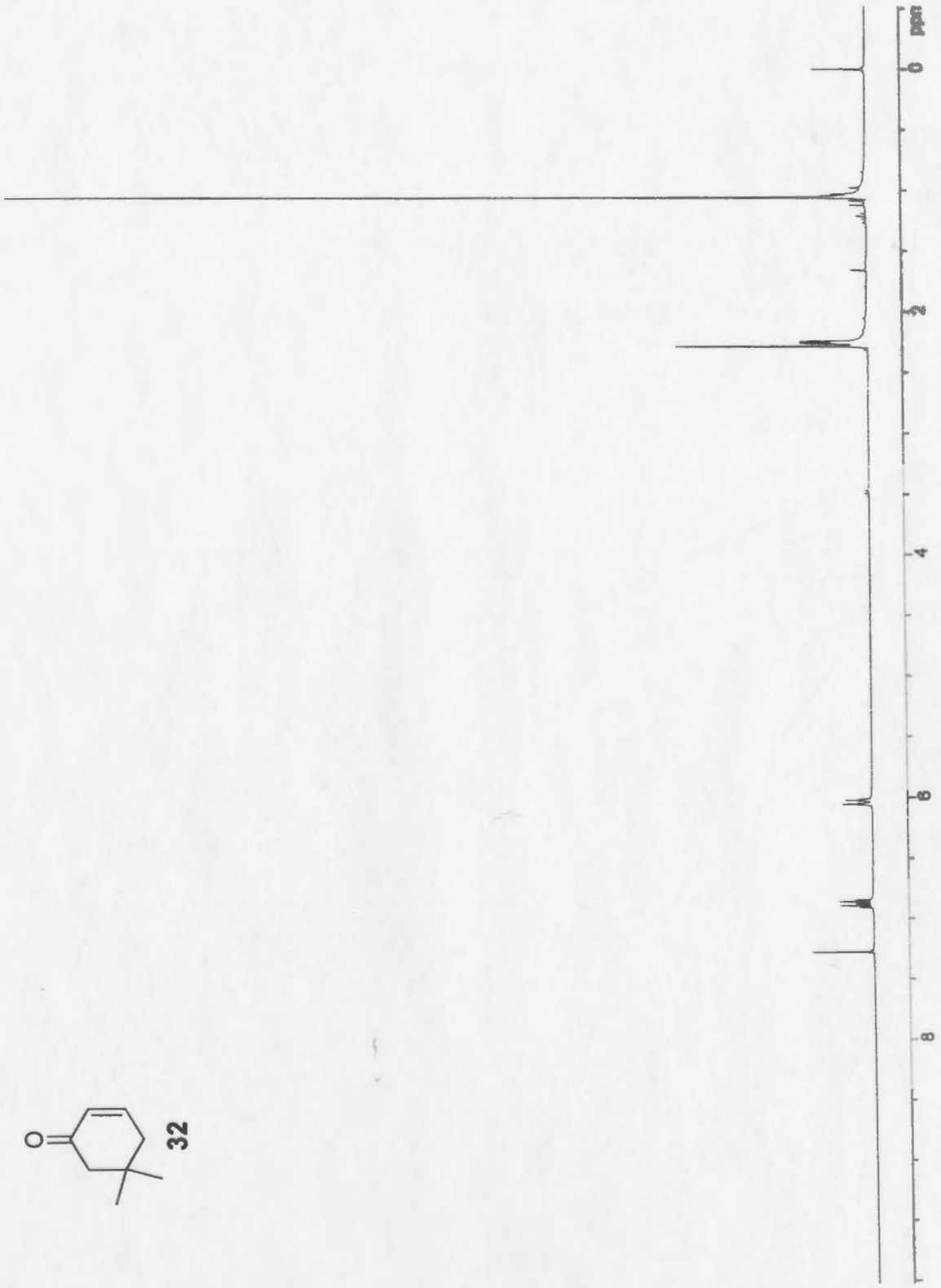
28


OTBS
30
8
6
4
2
0
ppm

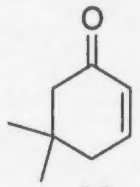


30

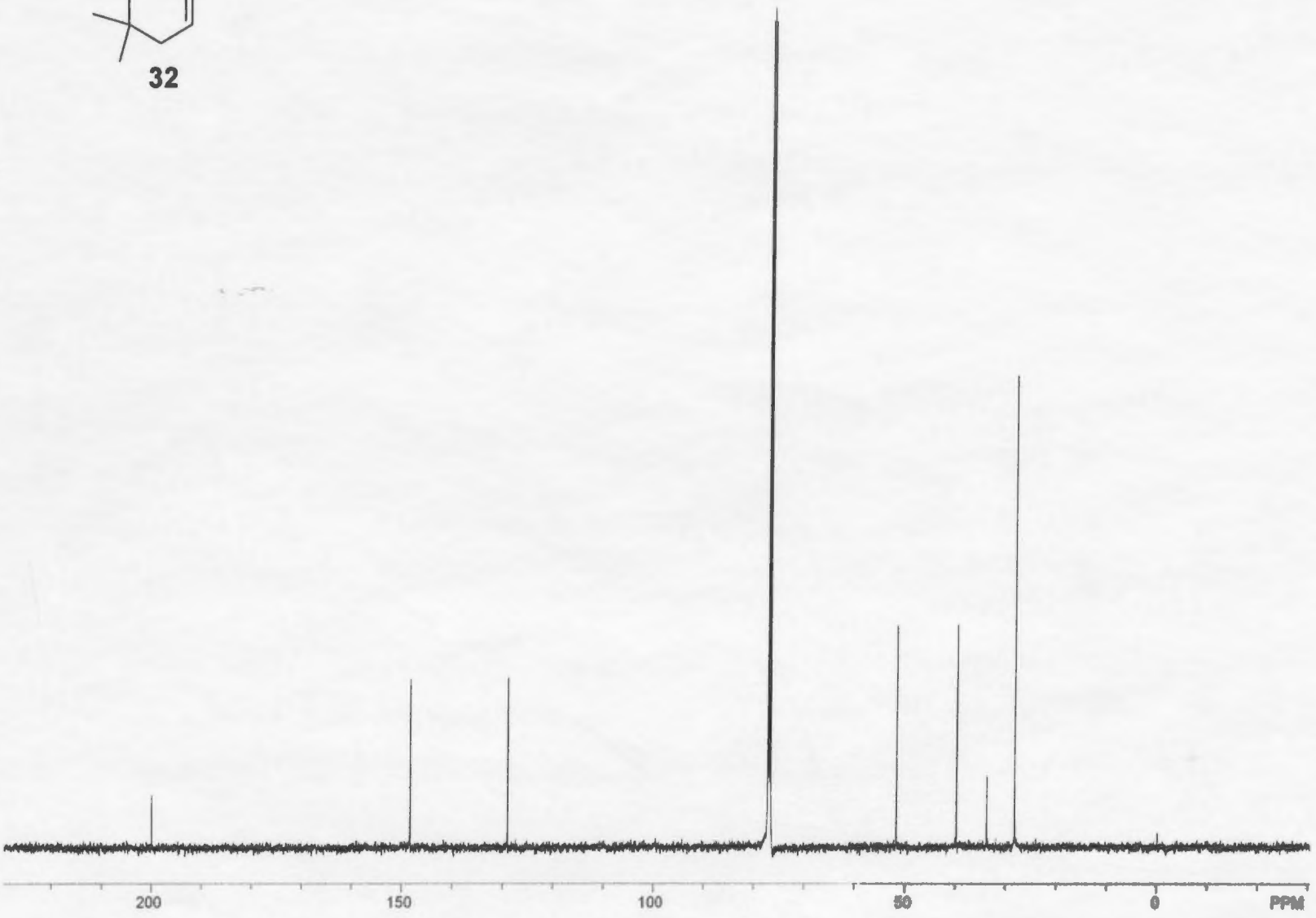


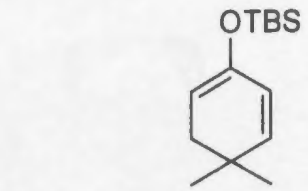


32

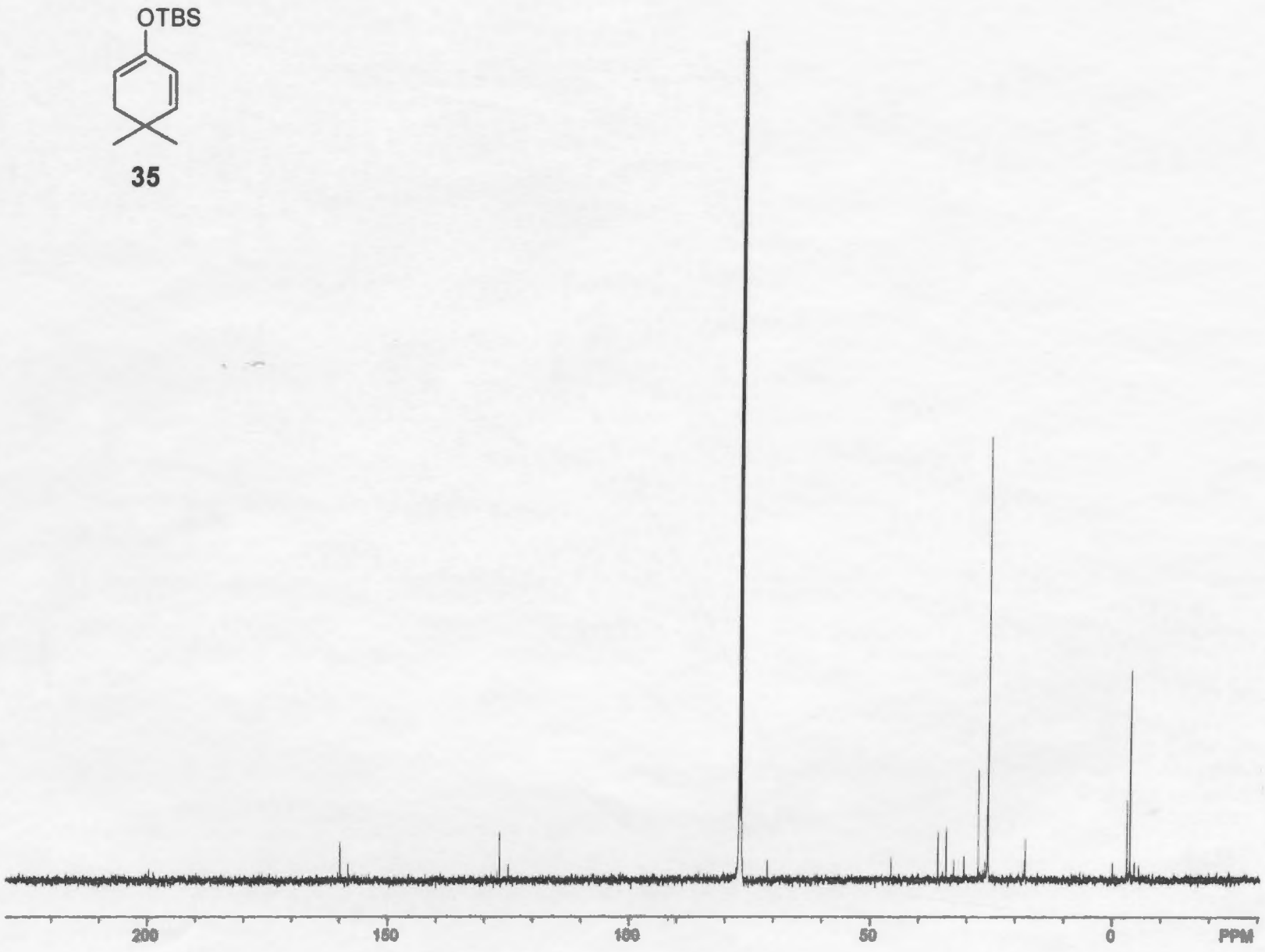


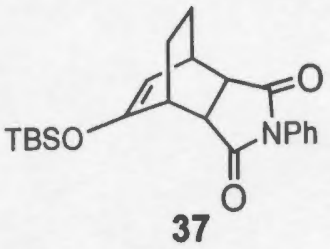
32



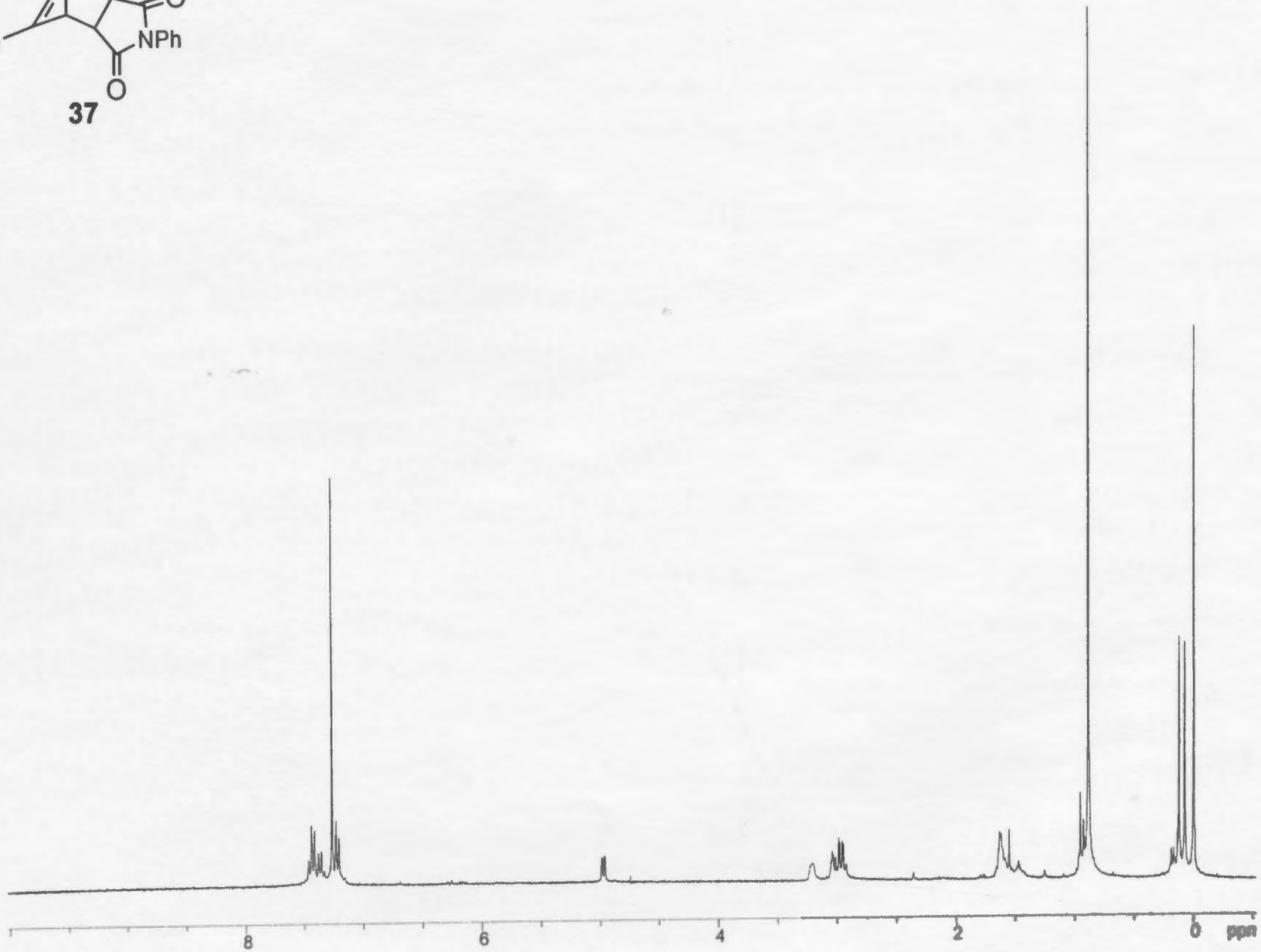


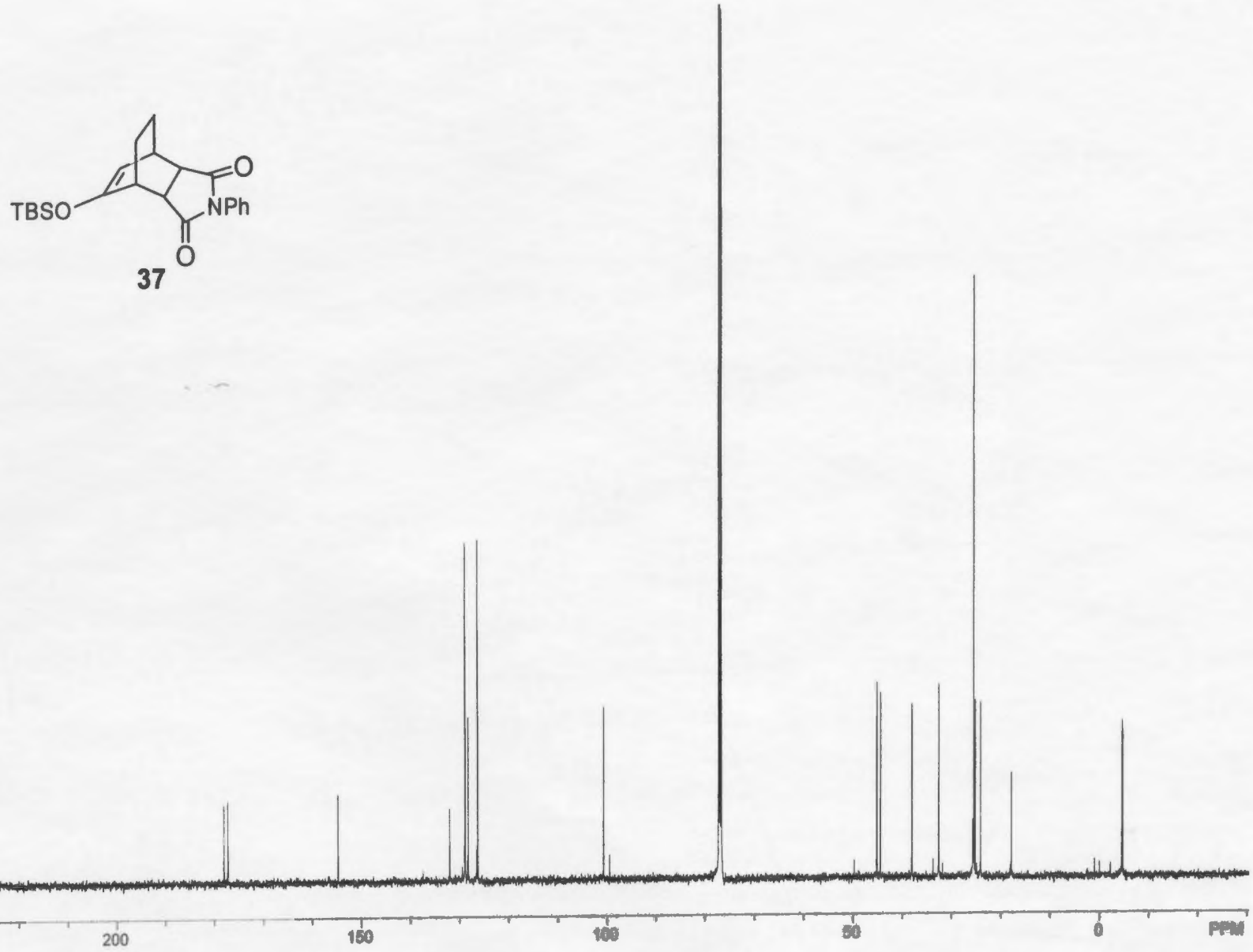
35

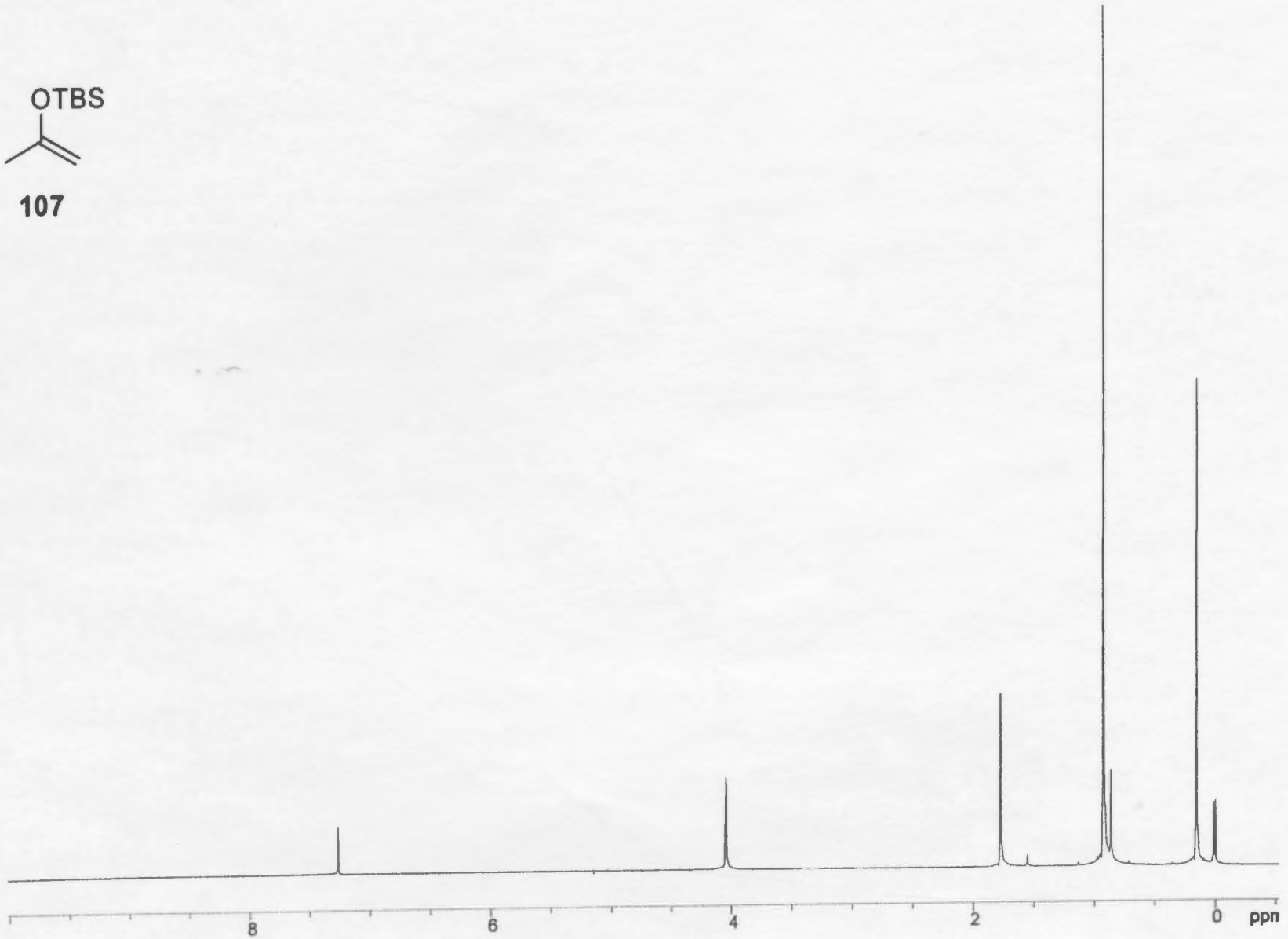

OTBS
35
200
150
100
50
0
PPM

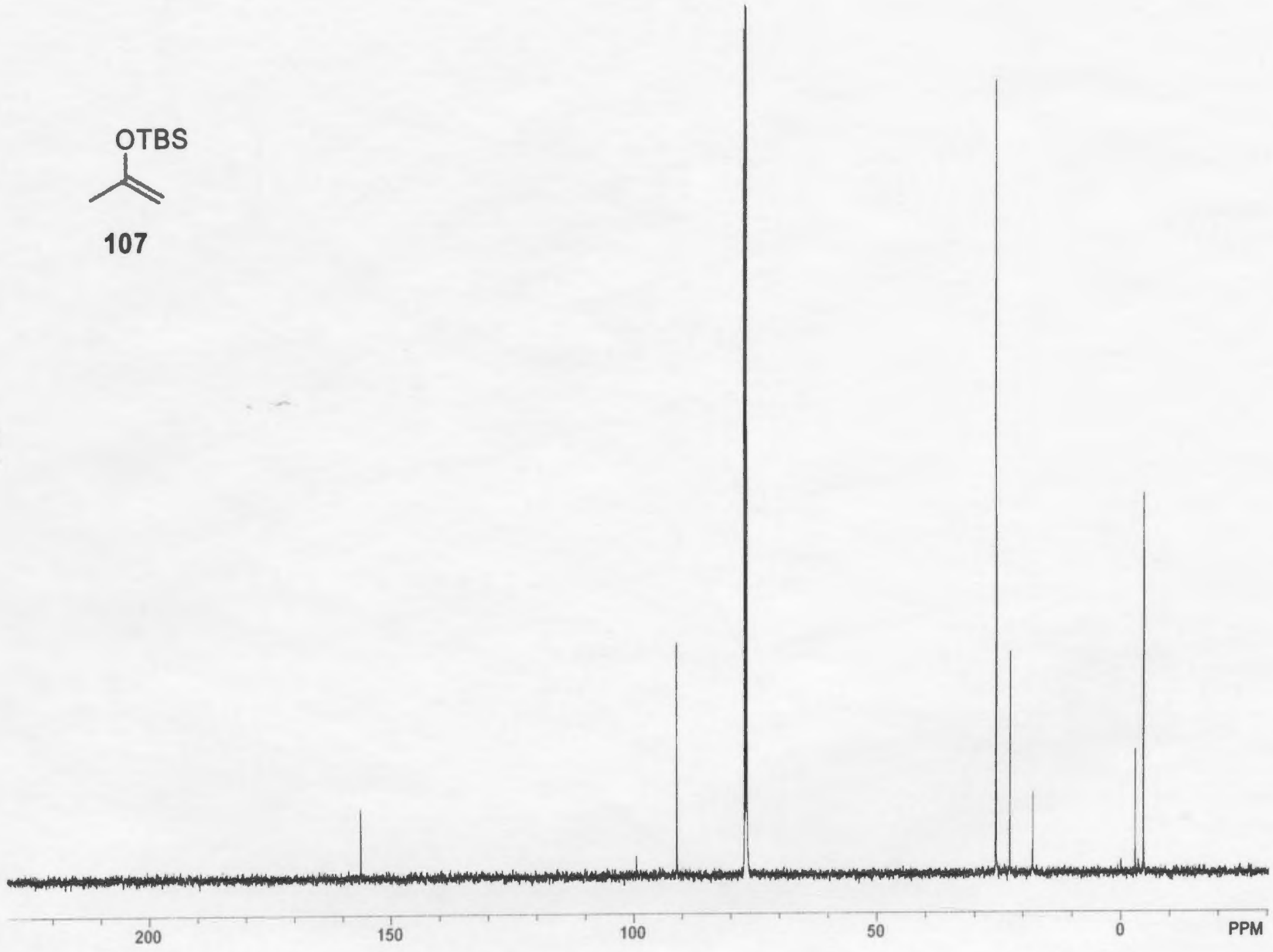


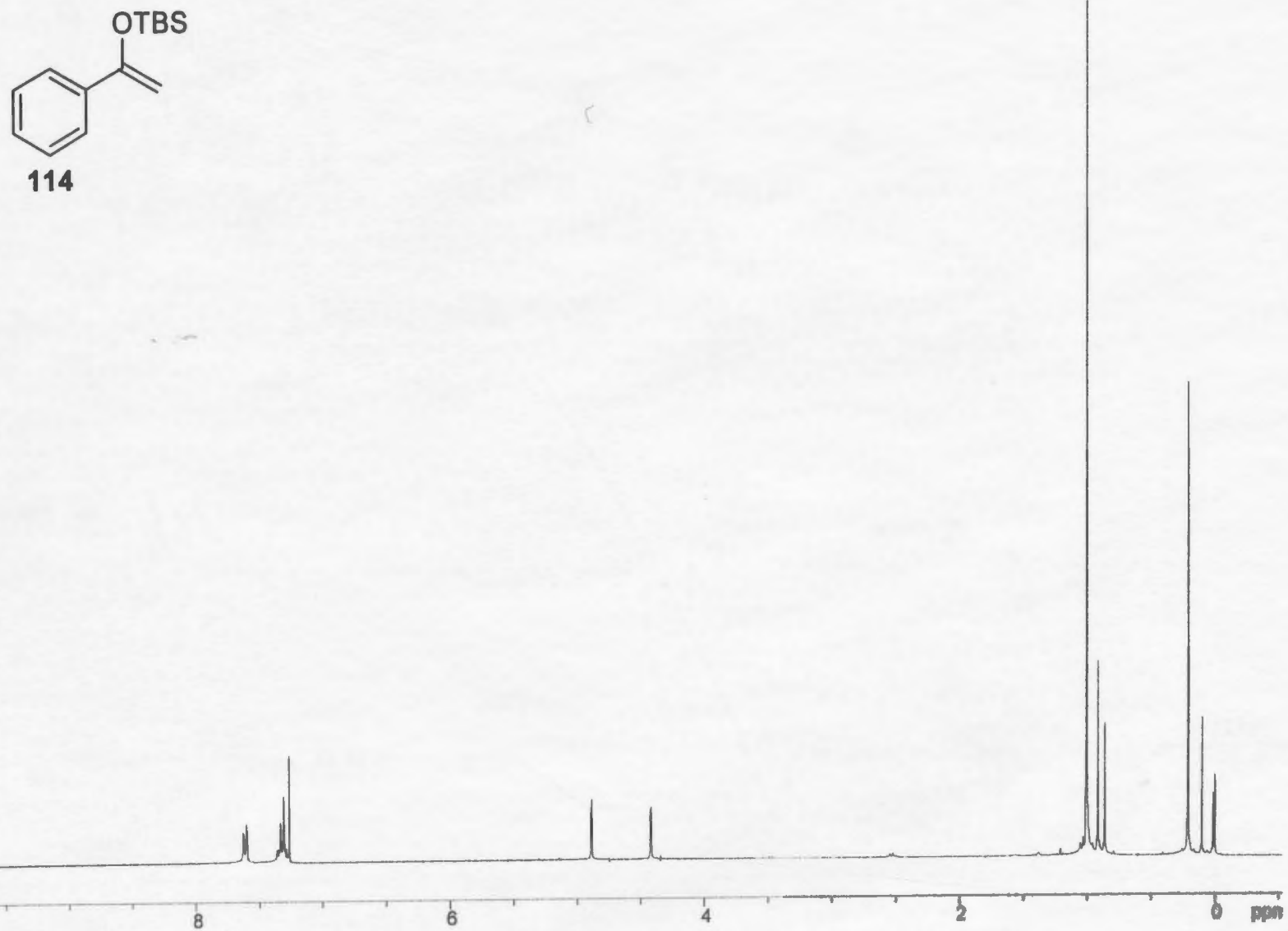
37



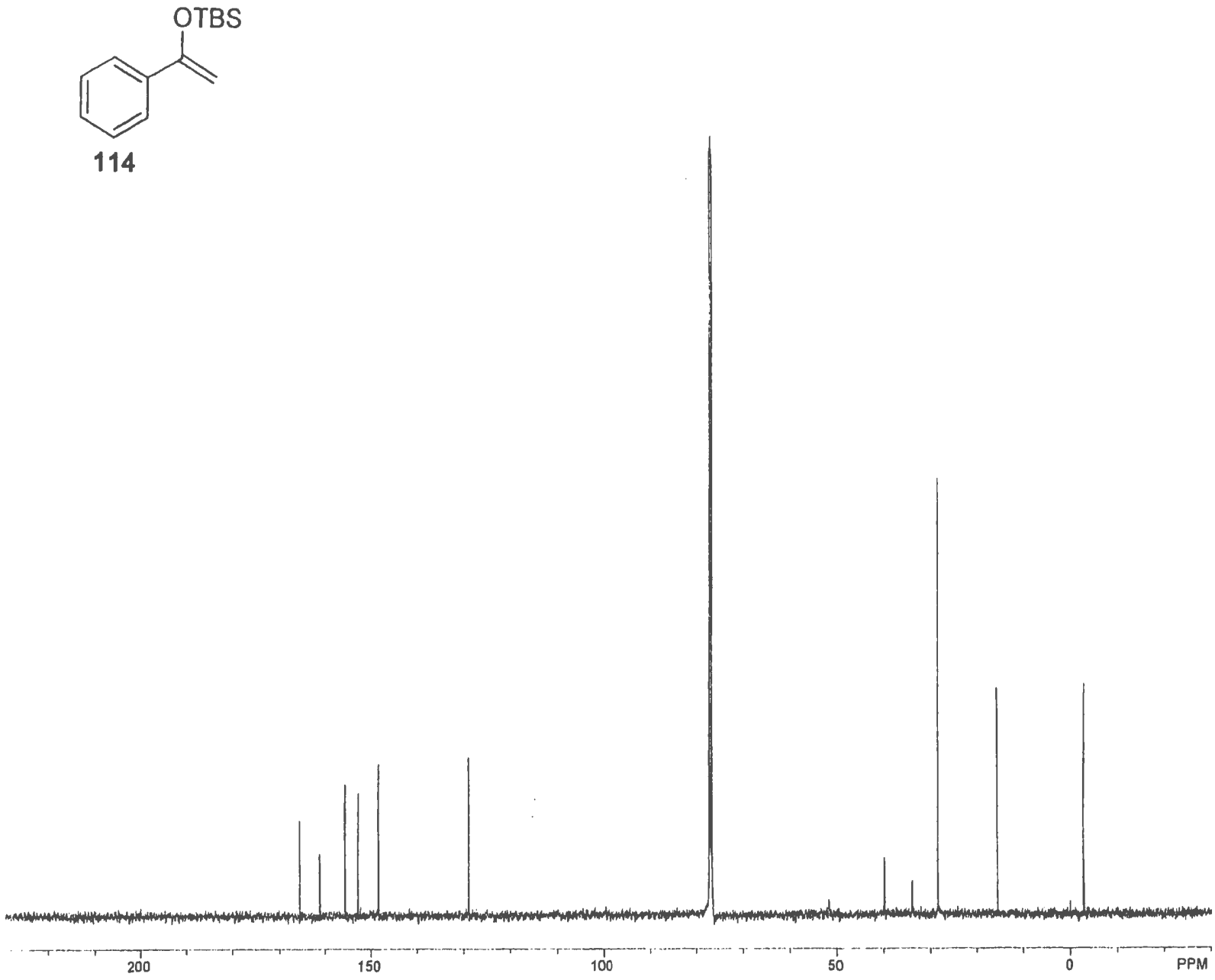

TBSO
O
NPh
O
37
200
150
100
50
0
PPM

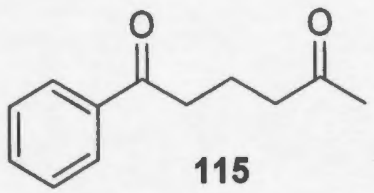

OTBS
107
8
6
4
2
0
ppm


OTBS
107
200
150
100
50
0
PPM

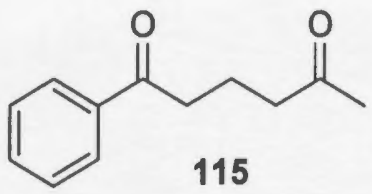


114

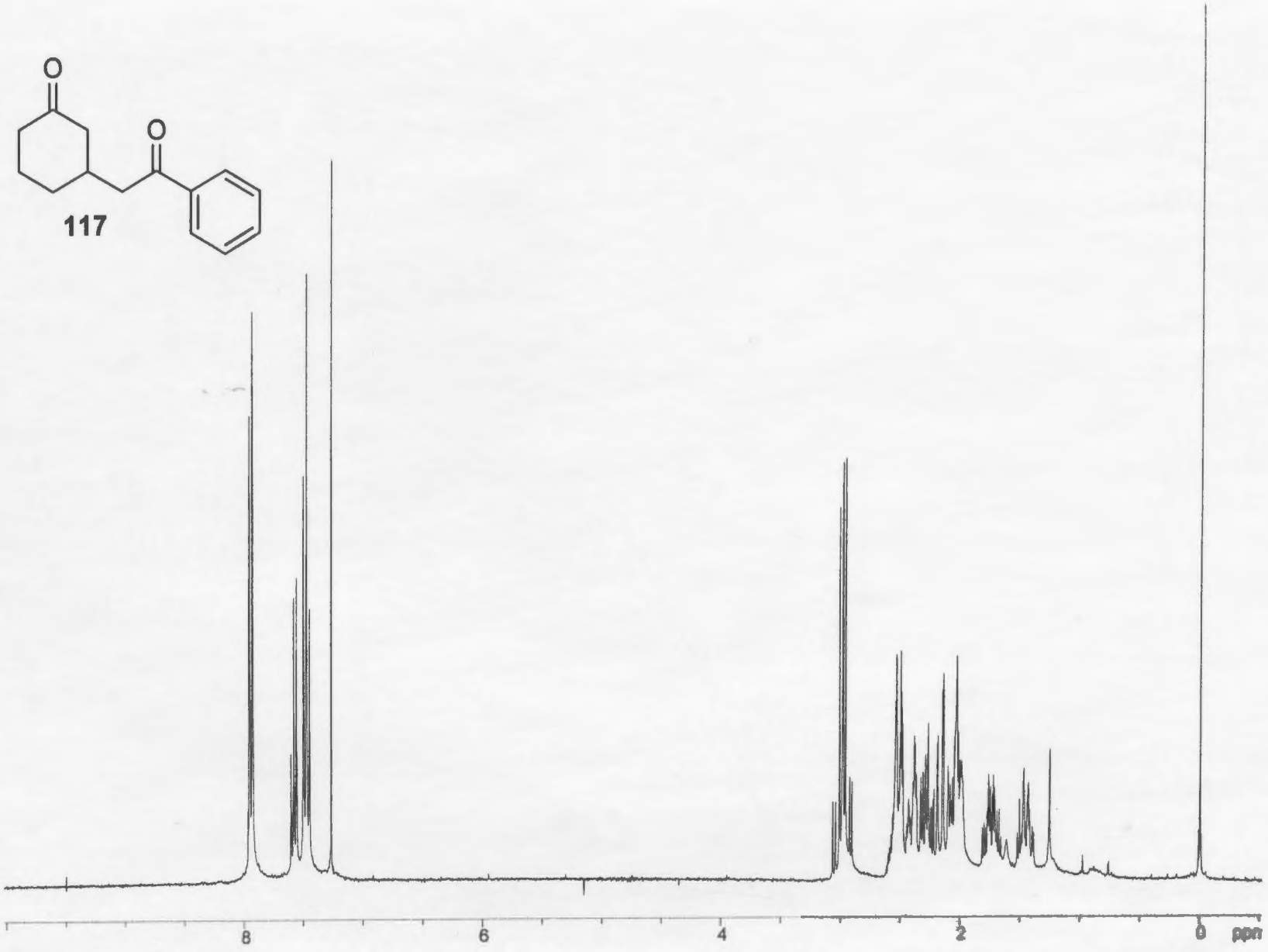

OTBS
114
200
150
100
50
0
PPM

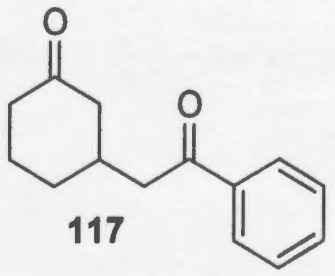


115

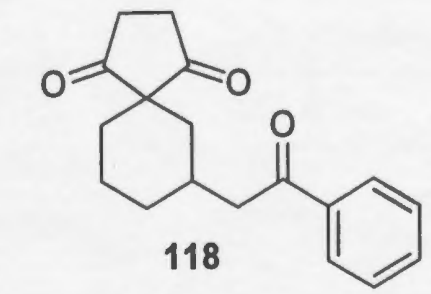


115

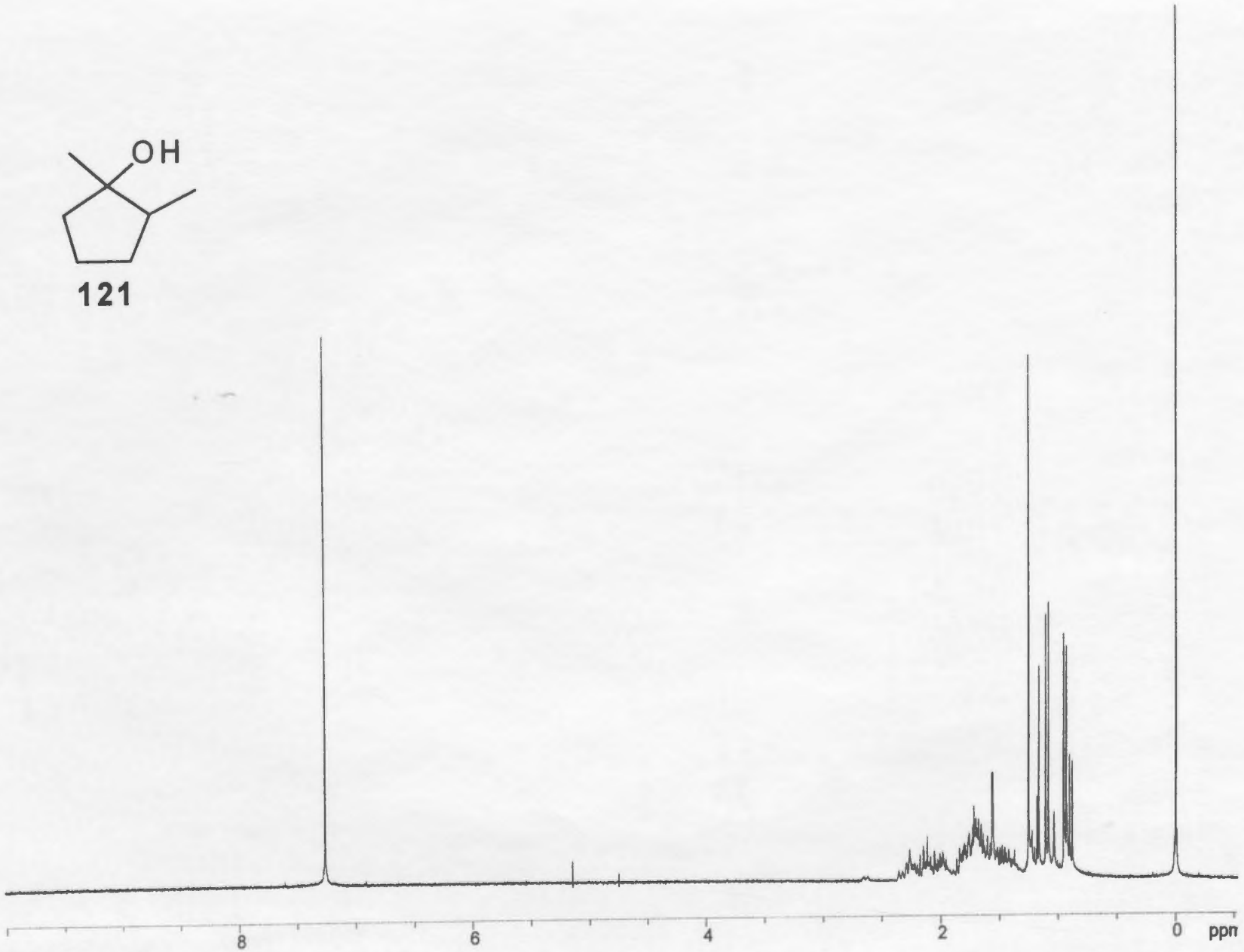

O
O
117
8
6
4
2
0
ppm

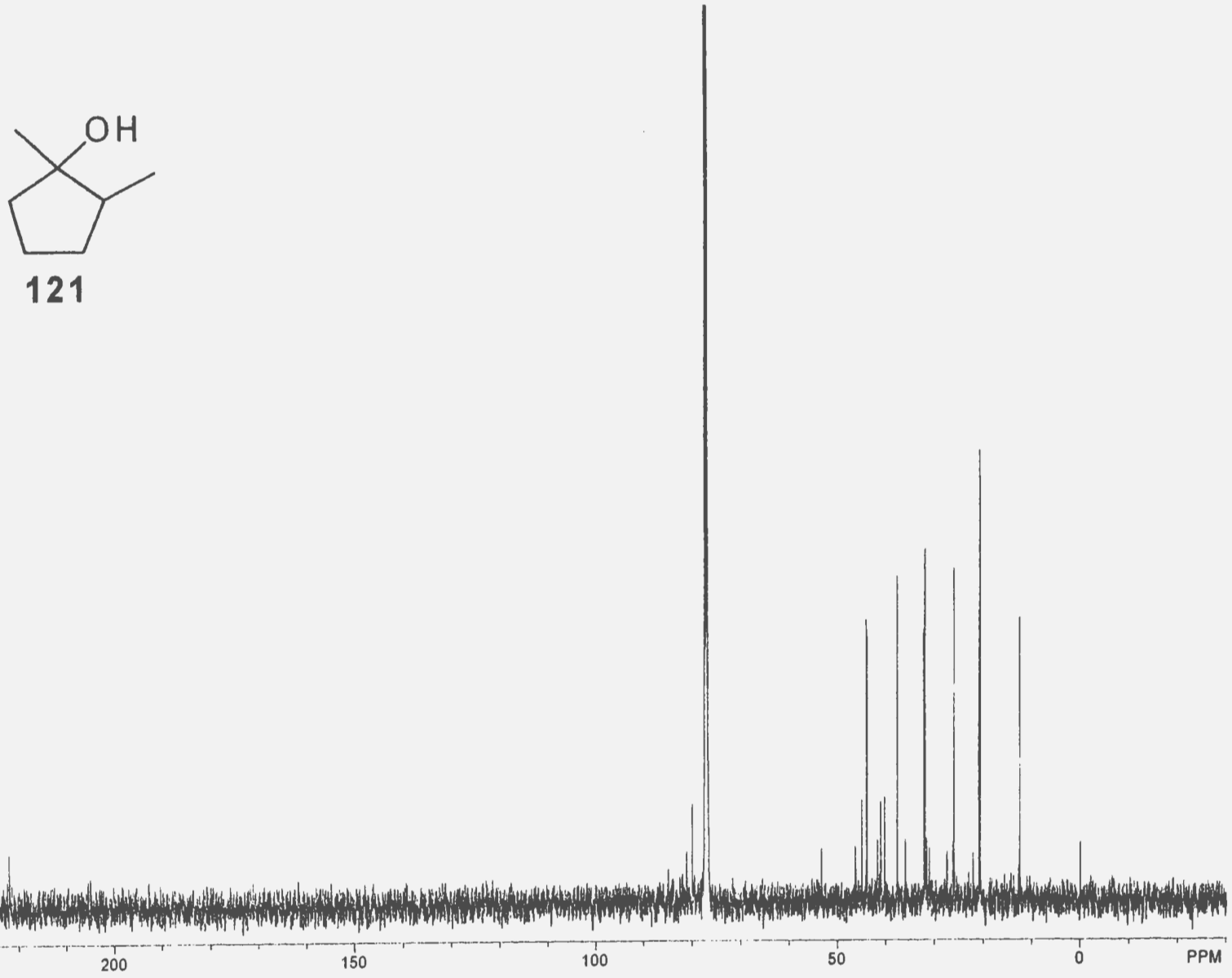


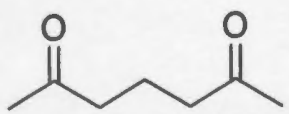
117



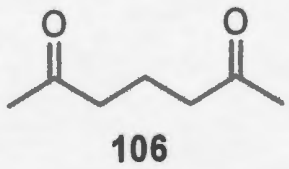
118


OH
121
8
6
4
2
0
ppm

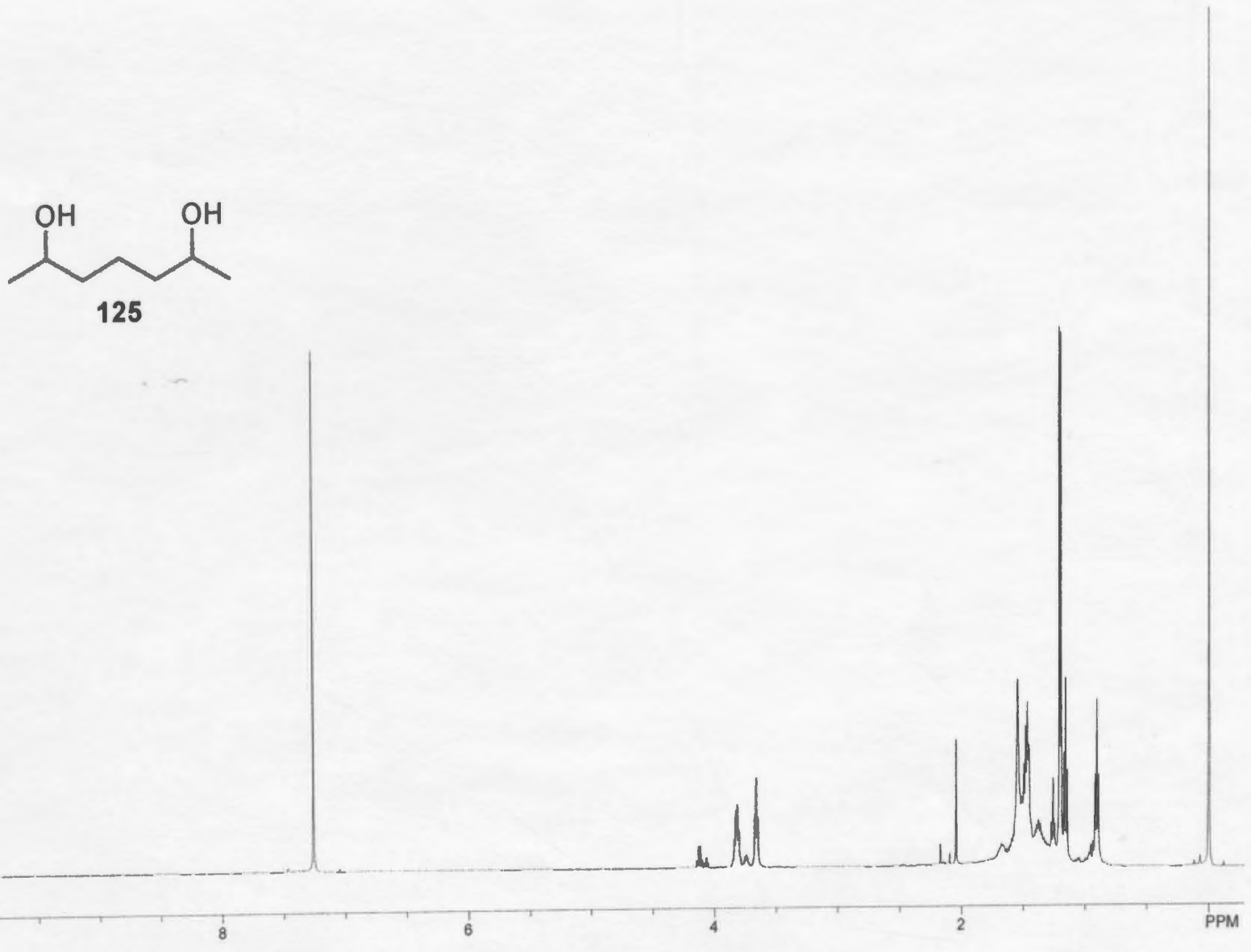

OH
121
200
150
100
50
0
PPM

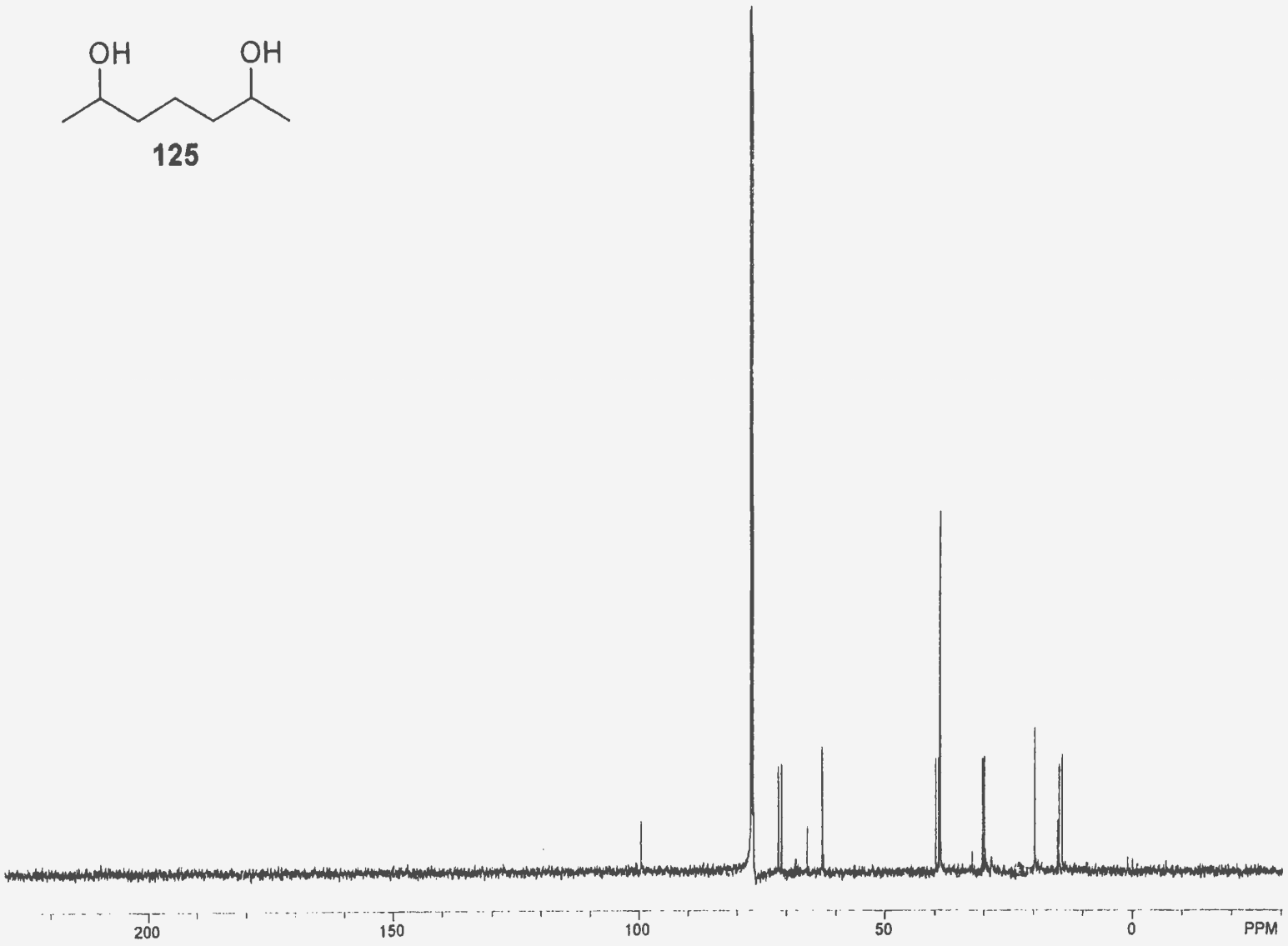


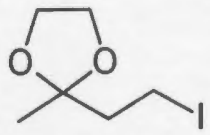
106



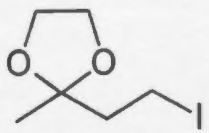
106


OH
OH
125
10
8
6
4
2
PPM

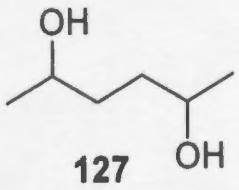

OH
OH
125
200
150
100
50
0
PPM



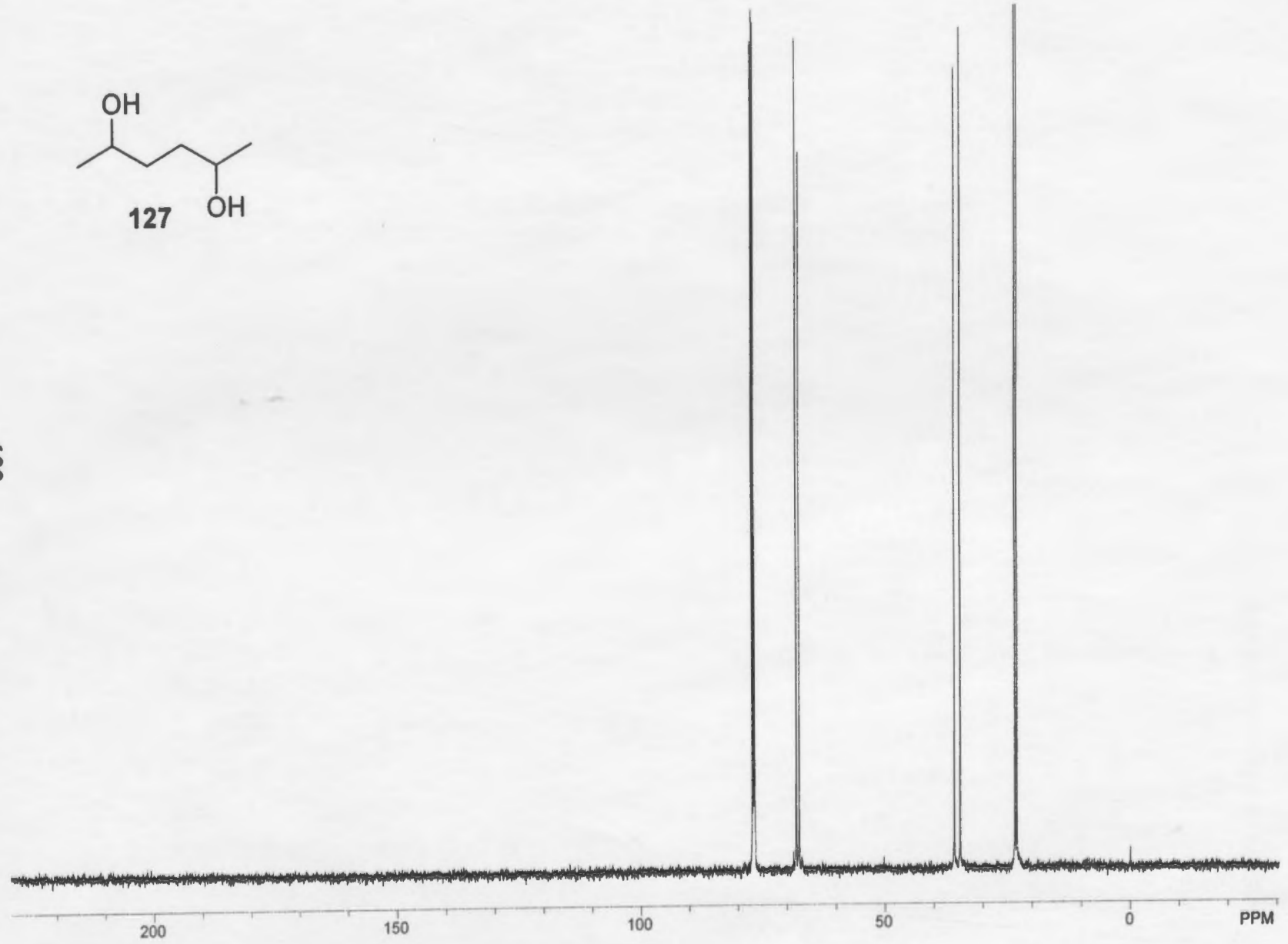
100

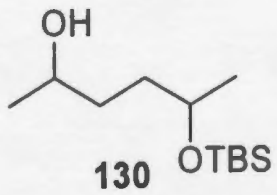


100

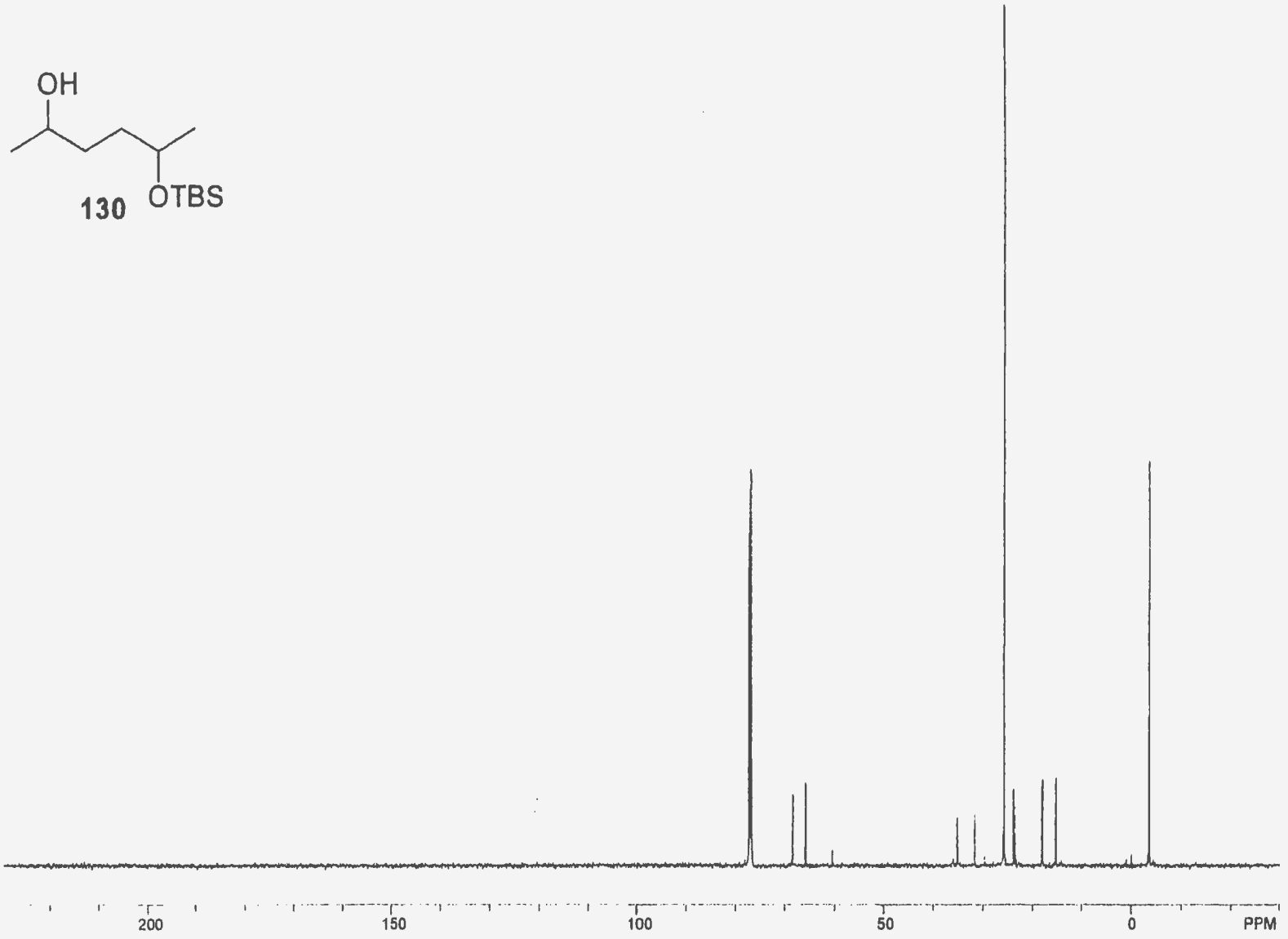


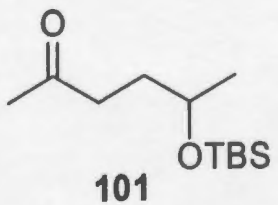
127


OH
OH
127
200
150
100
50
0
PPM

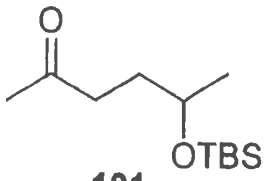


130


OH
OTBS
130
200
150
100
50
0
PPM

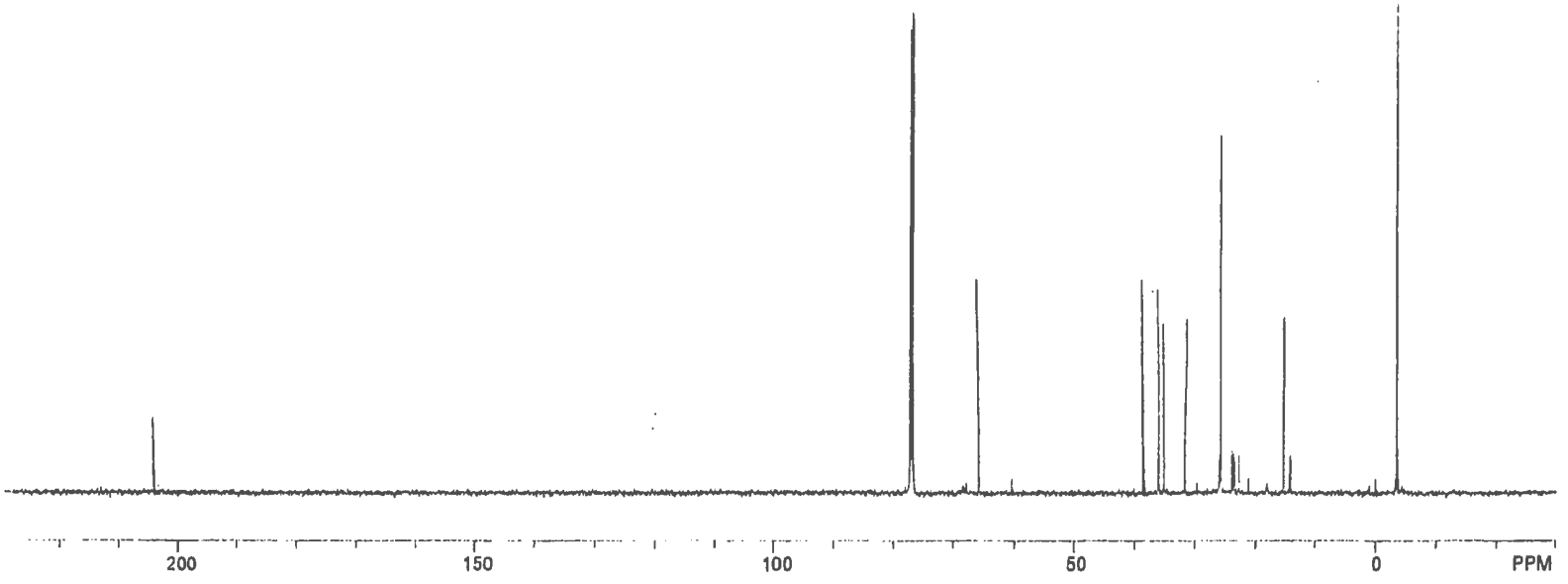


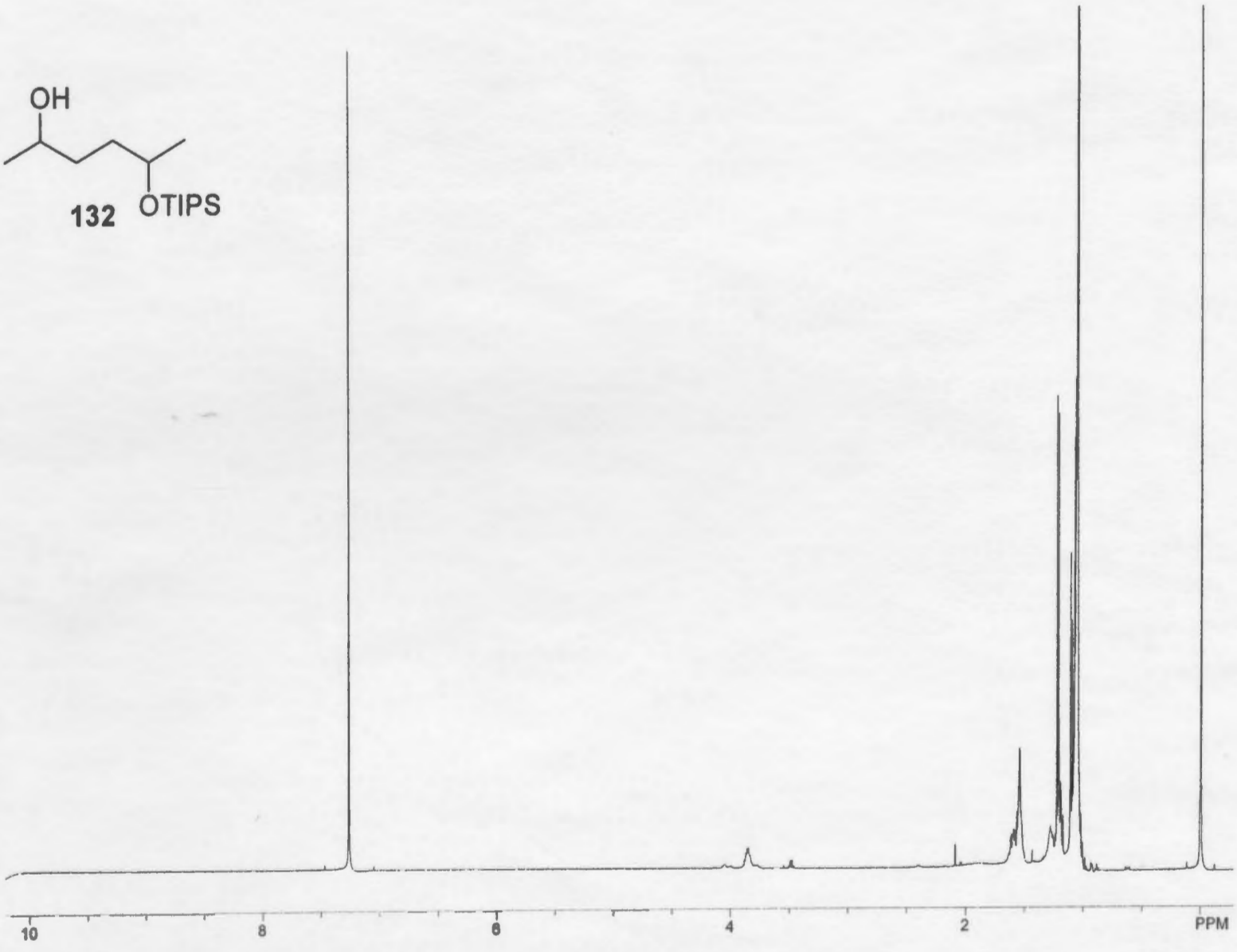
101

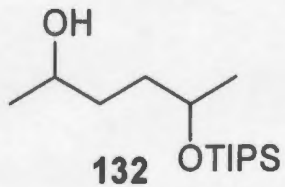


101

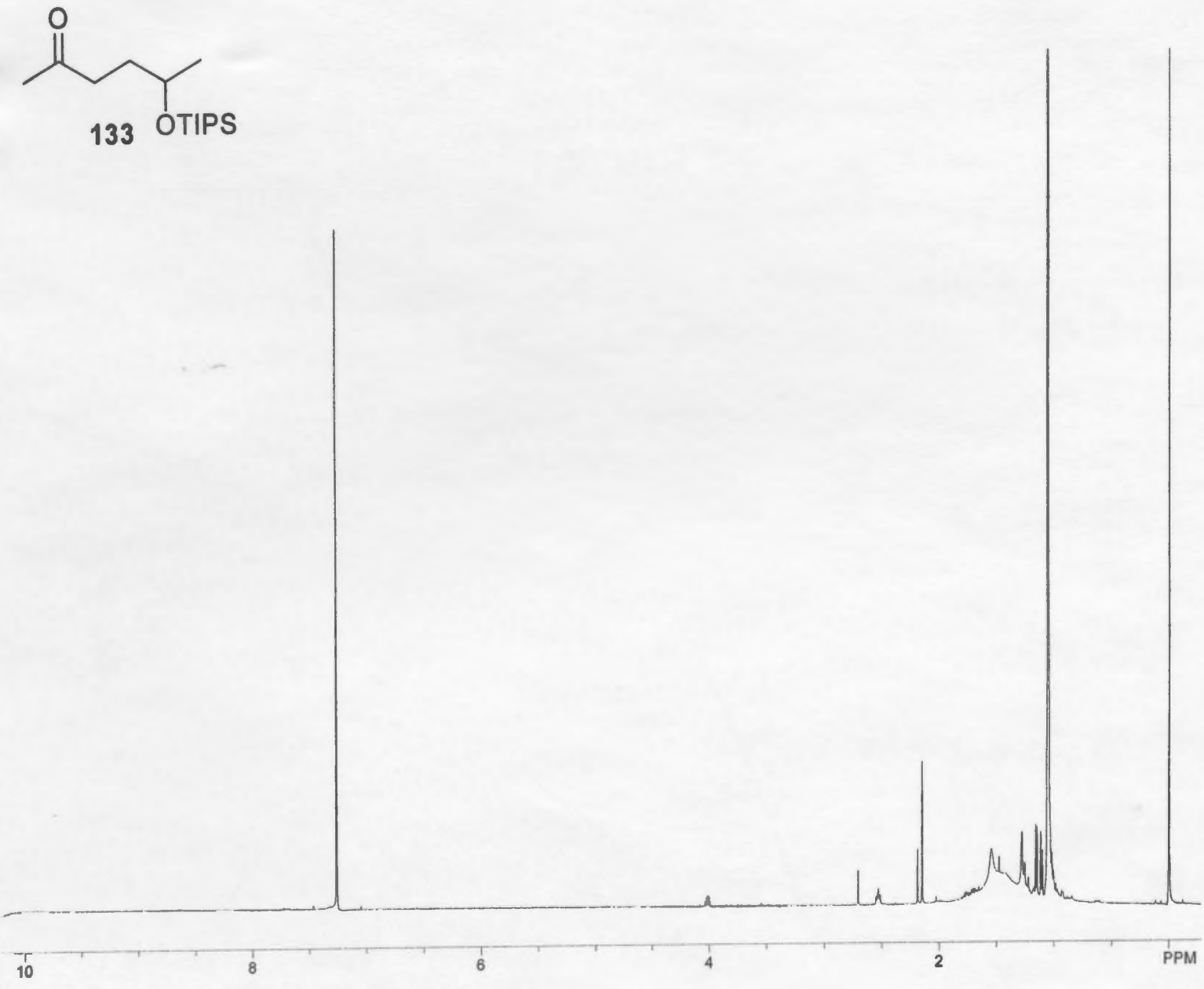
137



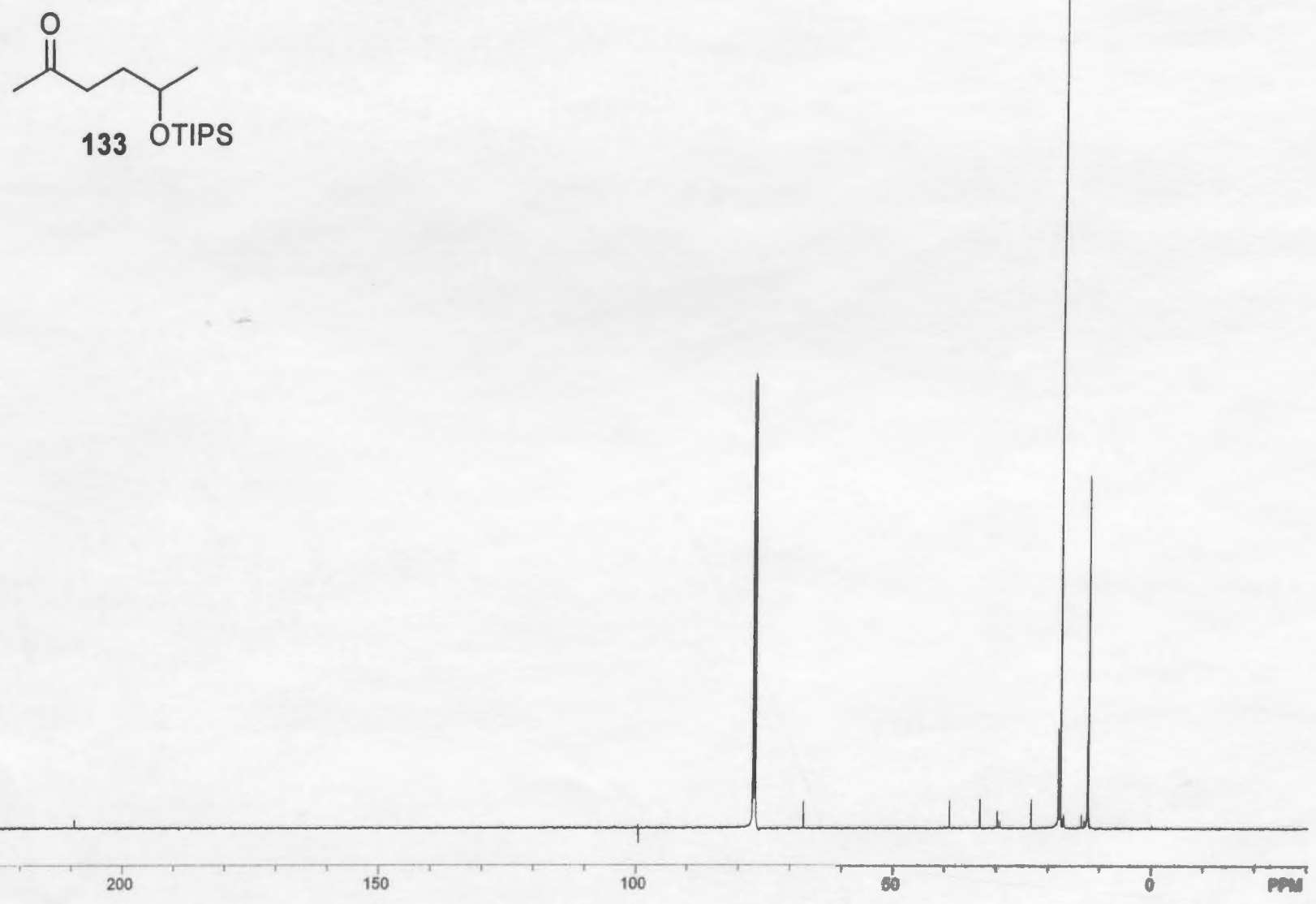

OH
OTIPS
132
10
8
6
4
2
PPM



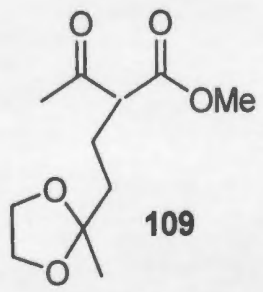
132



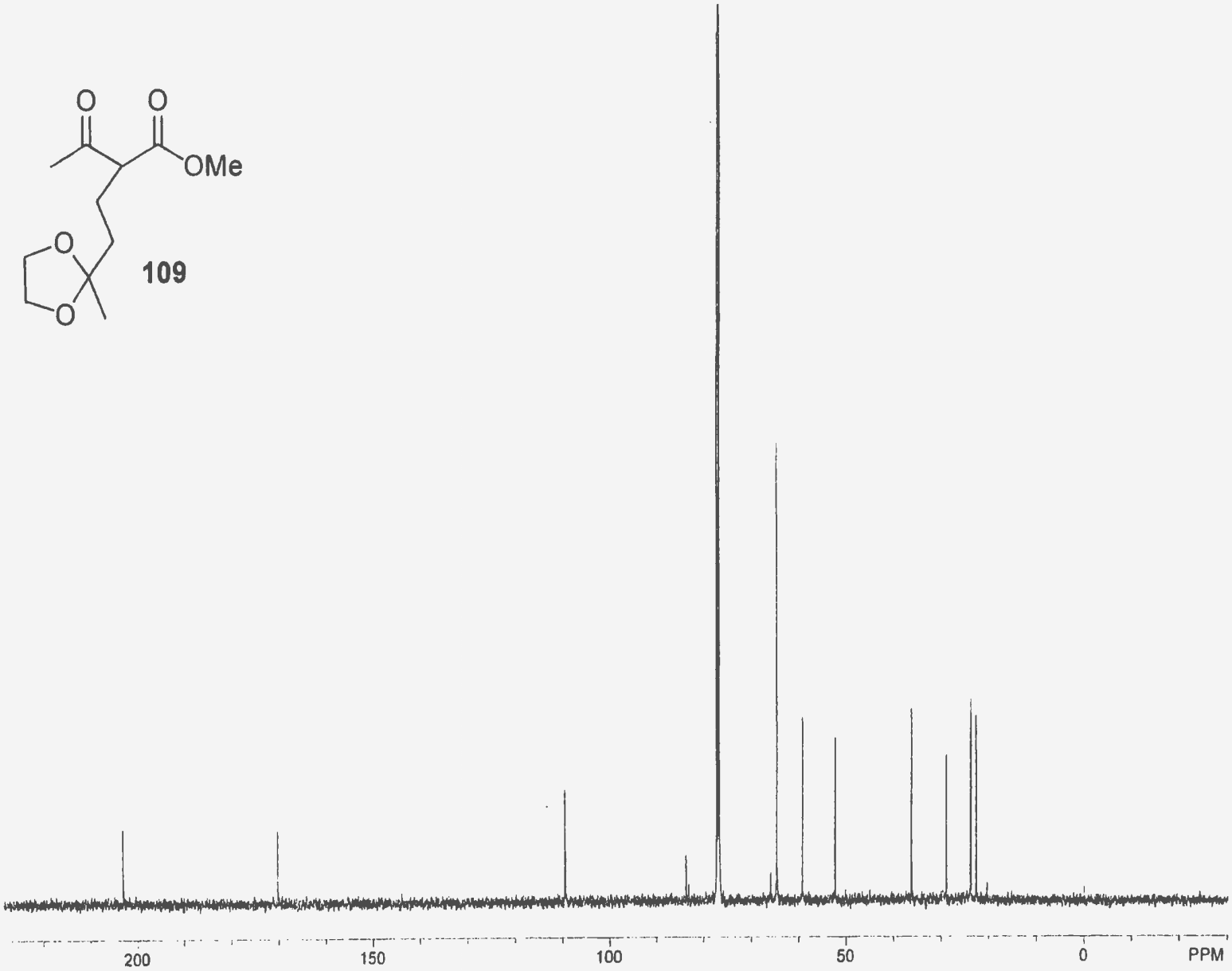
133

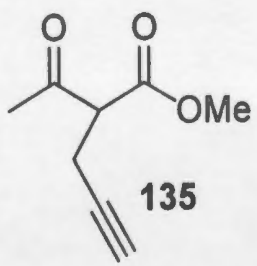


133

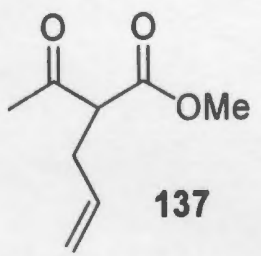


109

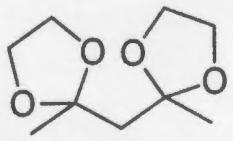

O
O
OMe
O
O
109
200
150
100
50
0
PPM



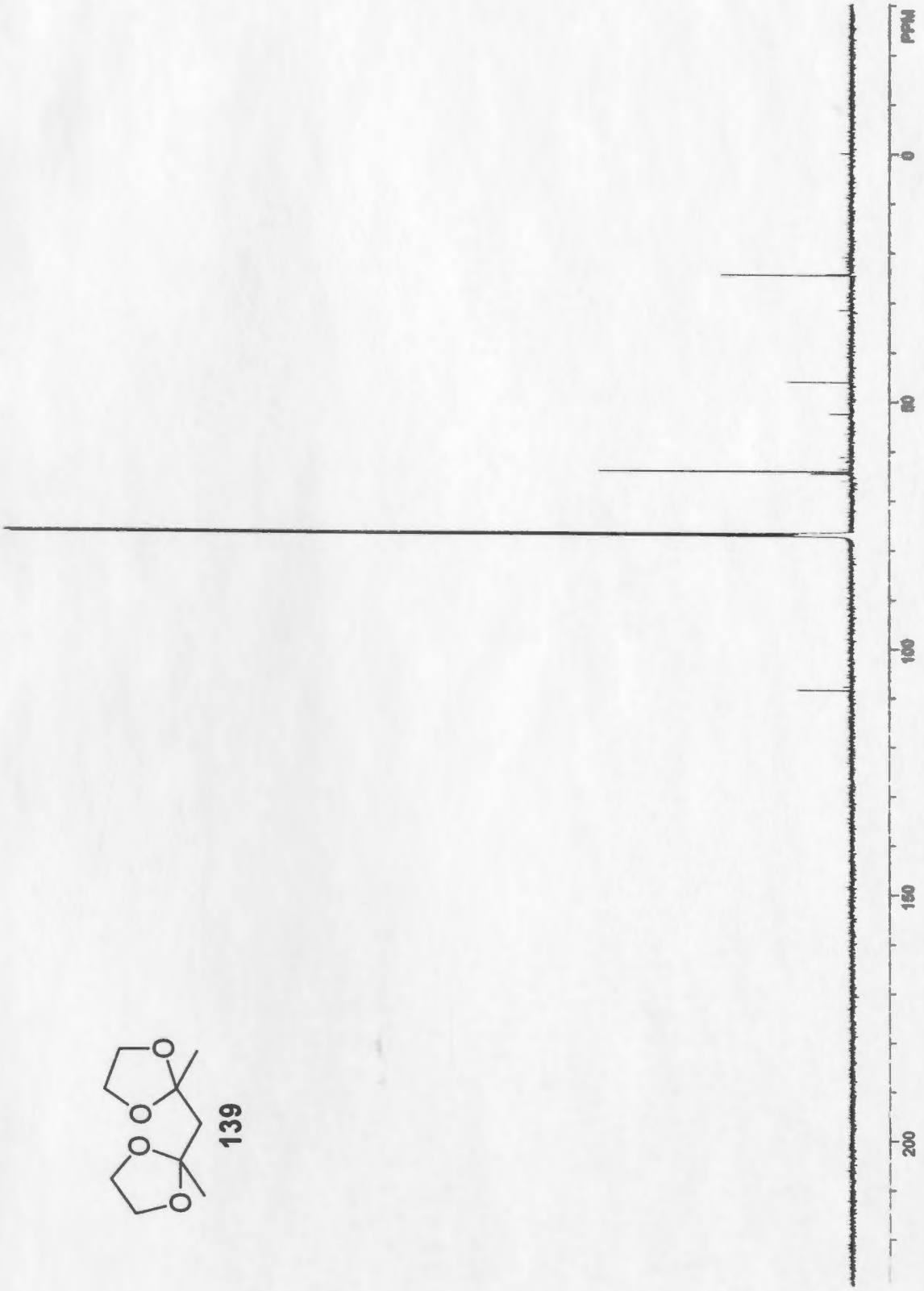
135



137



139



139