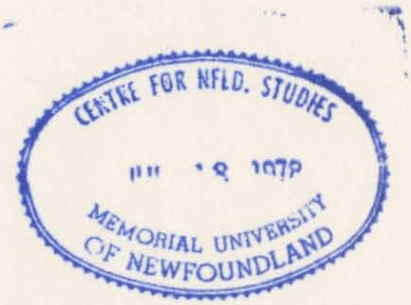
FACIAL SELECTIVITY IN THE DIELS-ALDER REACTION OF SOME INVERSE ELECTRON DEMAND 1,3-CYCLOPENTADIENES AND A TANDEM-ENE APPROACH TO THE SYNTHESIS OF A LINEAR TRIQUINANE

LORI CAROLYN BURRY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FACIAL SELECTIVITY IN THE DIELS-ALDER REACTION OF SOME INVERSE ELECTRON DEMAND 1,3-CYCLOPENTADIENES AND A TANDEM-ENE APPROACH TO THE SYNTHESIS OF A LINEAR TRIQUINANE

by

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B.Sc. (Honors), Memorial University of Newfoundland

St. John's, Newfoundland, 1992

A thesis submitted to the School of Graduate

Studies in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

Department of Chemistry

Memorial University of Newfoundland

St. John's Newfoundland

1998

Abstract

Facial selectivity in the Diels-Alder reaction of 1,2,3,4,5-pentachloro-1,3-cyclopentadiene and its derivatives with OCH_3, H, CH_3 and Br substituents at C-5 is detailed. These dienes which normally react by the inverse-electron-demand mode, reacted with a range of electronically different dienophiles such as *N*-phenylmaleimide, styrene, 4-phenyl-1,2,4-triazoline-3,5-dione, and vinylene carbonate. These dienes were shown to exhibit π-facial selectivity similar to the analogous 1,3-cyclopentadienes which react by the normal-electron-demand mode. The results indicated that both the nature of the dienophile and the substituent at C-5 impart a significant influence on the reaction.

The facial selectivity behavior was also investigated by collaborators using high level *ab initio* calculations. The computational work in conjunction with the experimental data described in this thesis, lead to the conclusion that the mechanism of facial selectivity can be explained on the basis of a steric interaction between the diene and the dienophile. In the transition state, the facial selectivity is a function of both size of the substituent X on the diene and the length of the bond between C-5 and the substituent X. In this way, a larger substituent with a longer C-5—X bond can provide less steric hindrance than a small substituent with a shorter C-5—X bond. This is illustrated in the case of Cl *versus* H, in which addition *syn* to chlorine was preferred with

N-phenylmaleimide. In the case of OMe *versus* Cl, the Cieplak theory predicted addition to the face of the diene anti to the better sigma donor. It was demonstrated, however, that this is not the case. All adducts resulting from additions to 1,2,3,4,5-pentachloro-5-methoxy-1,3-cyclopentadiene (**16**) are *anti* to Cl, which is a poorer sigma donor than OMe.

Tetraene **109** could serve as the precursor for a tandem or cascade ene reaction to produce a linear polyquinane. The "metallo-ene" reaction has been utilized to form polyquinanes through an iterative process, but a cascade scheme is proposed whereby isolation of reaction intermediates would not be required. The synthetic strategy required formation of a precursor similar to tetraene **109** which would be a model to test the viability of the tandem-ene reaction. It was decided to prepare a compound having functionality like that of the triene **111**. Preparation of 2,2-dimethyl-4,6-heptadienal (**128**) by an acid catalyzed condensation of isobutyraldehyde and 1,4-pentadien-3-ol (**142**) was successful. Nucleophilic attack by 3-(*tert*-butyldimethylsilyloxy)-1-octyne (**162**) onto the aldehyde (**128**) gave an acetylenic analogue of the required precursor (**111**).

Acknowledgments

I would like to extend my sincere appreciation to my supervisor, Dr. D. Jean Burnell, for his instruction and guidance throughout the course of my research project.

I would also like to acknowledge Dr. R. Poirier, Mr. J. Xidos and Dr. C. Pye for their collaboration involving the theoretical aspects of this project. Thanks especially to James who helped a lot with the diagrams. I would like to thank Dr. C. Jablonski, Ms. N. Brunet and Mr. D. Miller for NMR spectra, Dr. B. Gregory and Ms. M. Baggs for mass spectra, and Dr. J. Bridson and Mr. D. Miller for X-ray crystallography service.

I thank the entire group for their interest and friendship. Thanks to Ron for all his encouragement, criticism and help throughout our graduate program. Also, I am grateful to my family, Mom, Dad, Kara and Christa for believing it would be finished in good time.

I would like to thank Dr. P. Georghiou and Dr. H. Clase for proofreading and valuable comments and suggestions.

The financial support from both Dr. D. Jean Burnell and Memorial University is gratefully acknowledged.

To my guy, Ron Buckle and my family

you make it all worthwhile

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Glossary of Abbreviations

Anal.	elemental analysis
Ar	aryl
bp	boiling point
BS	4-bromostyrene
calcd	calculated
COD	cyclooctadienyl
dba	dibenzylideneacetone
decomp.	decomposition
DCC	*N*,*N*-dicyclohexylcarbodiimide
DIBAL-H	diisobutylaluminum hydride
DMAD	dimethylacetylenedicarboxylate
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
dppb	1,4-diphenylphosphinobutane
EE	ethoxyethene
Et	ethyl
FMO	frontier molecular orbital
GC-MS	gas chromatography-mass spectrometry
HRMS	high resolution mass spectrum

HOMO	highest occupied molecular orbital
Hz	Hertz
IR	infared (spectroscopy)
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
MA	maleic anhydride
m-CPBA	*meta*-chloroperoxybenzoic acid
MeLi	methyllithium
Me	methyl
MO	molecular orbital
MOM	methoxymethyl
mp	melting point
MS	mass spectrometry
m/z	mass to charge ratio
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance (spectroscopy)
NOE	nuclear Overhauser enhancement
NPM	*N*-phenylmaleimide
NQ	1,4-naphthoquinone
MTAD	4-methyl-1,2,4-triazoline-3,5-dione

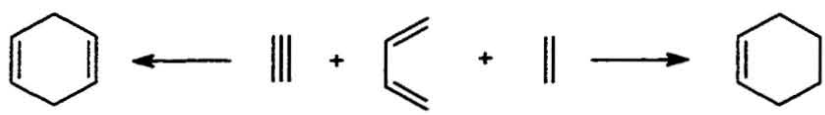
PDC	pyridinium dichromate
PPTS	pyridinium *p*-toluenesulfonate
PTAD	4-phenyl-1,2,4-triazoline-3,5-dione
p-TsOH	*para*-Toluenesulfonic acid
py	pyridine
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
STY	styrene
subl.	sublimation
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
VC	vinylene carbonate

Part 1

FACIAL SELECTIVITY IN THE DIELS-ALDER REACTIONS OF INVERSE-ELECTRON-DEMAND 1,3-CYCLOPENTADIENES

I. Introduction

Since its discovery nearly 70 years ago,[1] the Diels-Alder reaction has become an indispensable tool for the synthetic organic chemist. The Diels-Alder reaction is a thermally allowed [4π+2π] cycloaddition, which creates two new σ bonds at the expense of two π bonds. The reactants are a conjugated diene and a dienophile, which may be an alkene, alkyne, or heterodienophile such as azo (N=N), nitroso (N=O), carbonyl (C=O), or thiocarbonyl (C=S). The resulting product is an unsaturated six-membered carbocycle or heterocycle (Scheme 1).

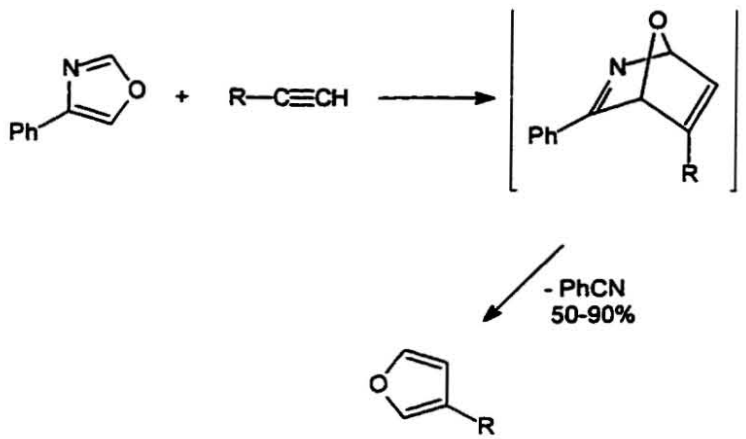


Any carbon may be replaced by a heteroatom such as N or O.

Scheme 1. Depiction of basic Diels-Alder cycloadditions.

The diene component of the reaction may be cyclic or acyclic but, in either case, the conjugated double bonds must be in the *s-cis* conformation to obtain

overlap of the *p*-orbitals of the diene with those of the dienophile.[2] The reaction is reversible and often the retro-Diels-Alder process gives back the starting materials. However, the retro-Diels-Alder reaction is sometimes used synthetically to produce compounds that are difficult to generate otherwise, such as in the case of the furan shown below (Scheme 2).[3]



Scheme 2. Formation of a β-substituted furan by retro-Diels-Alder.

The mechanism by which the Diels-Alder cycloaddition takes place has been the subject of much debate,[4] but it is now generally accepted to be a concerted reaction with both new bonds forming simultaneously. The other proposals involved a diradical[5] or zwitterion[6] intermediate.

The reaction is highly stereoselective and regioselective, giving up to four contiguous stereogenic centers in one step. The outcome of the Diels-Alder reaction is controlled by the substituents on the diene and dienophile. These

substituents act to enhance or inhibit the reactivity and control the regioselectivity and the stereoselectivity. Frontier Molecular Orbital (FMO) theory has been used to explain the reactivity and selectivity in cycloaddition reactions. The Diels-Alder reaction has been classified by Sauer and Sustmann into three general types, according to the three possible arrangements of the HOMO and LUMO molecular orbitals of the reacting partners.[4b] These general types are known as normal-electron-demand, neutral-electron-demand and inverse-electron-demand (Figure 1).

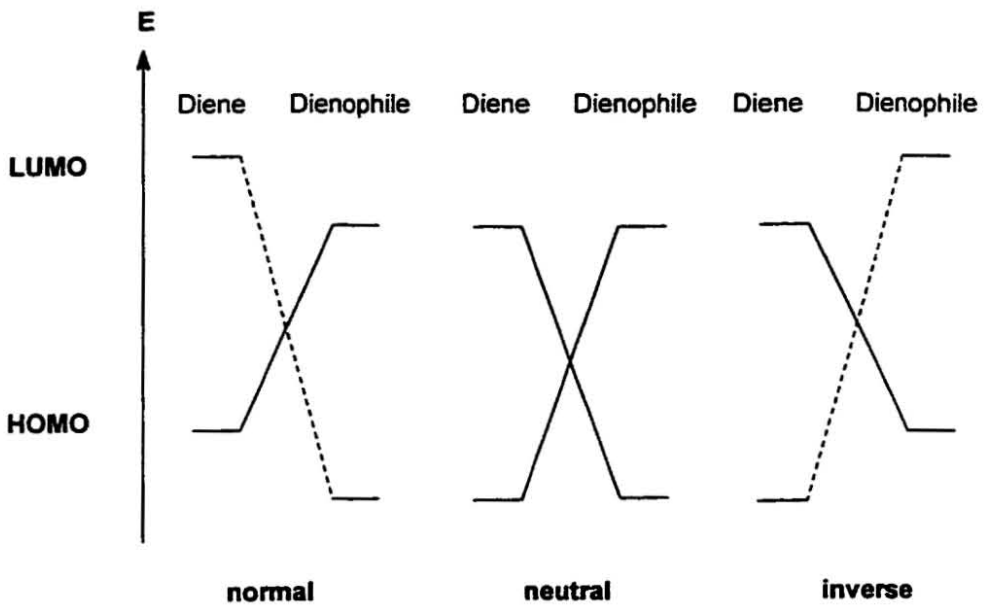


Figure 1. HOMO-LUMO orbital arrangements for the Diels-Alder reaction.

The mode of reactivity depends on the smaller HOMO-LUMO separation that can be achieved by reacting partners. All factors that reduce this energy

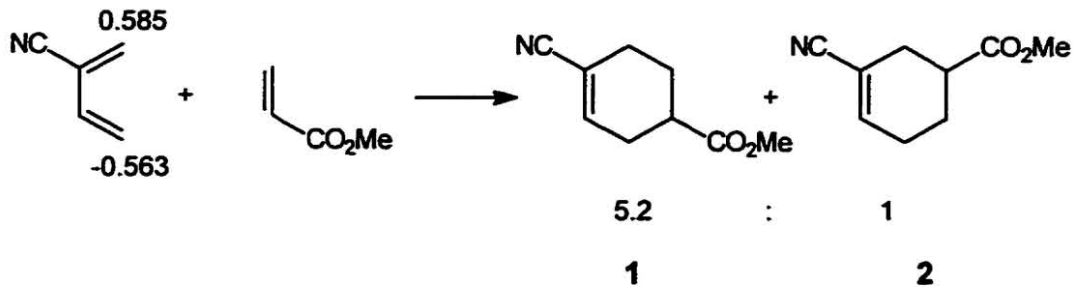
difference help to increase reactivity by stabilization of the transition state. Electron withdrawing groups lower the energy of the molecular orbitals, whereas electron donating groups increase their energy. Thus, in the case of a "normal" Diels-Alder reaction, electron donating substituents on the diene and electron withdrawing substituents on the dienophile will accelerate the reaction. For the inverse-mode Diels-Alder cycloadditions, the opposite substitution pattern also decreases the orbital energy separation, thereby increasing reactivity. The vast majority of research using Diels-Alder cycloadditions has involved the normal-electron-demand process. The research summarized in this thesis, however, has explored the behavior of some inverse-electron-demand dienes.

In theory, a cycloaddition between two unsymmetrically substituted reactants can give two regioisomeric adducts, but usually one adduct is predominant. Predicting the outcomes of Diels-Alder reactions has been the subject of intense study, and the regioselectivity issue has been worked out satisfactorily. Houk and co-workers[7] accounted for the regioselectivity of the Diels-Alder reaction using two generalizations from FMO theory.

1. The principal stabilization of the transition state will arise from interaction of the HOMO-LUMO pairs of addend frontier orbitals which are close in energy.
2. The atoms having the larger terminal coefficients on each addend will become bonded preferentially in the transition state.

Figure 2. Regioselectivity for the normal Diels-Alder addition of 2-ethoxy-1,3-butadiene and methyl acrylate.

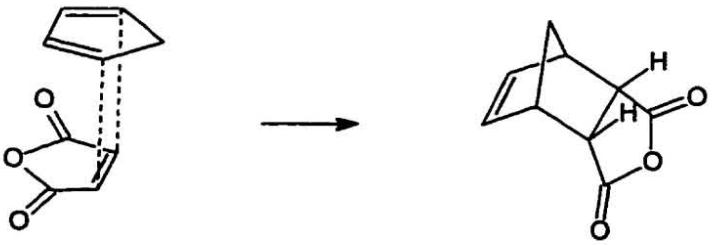
The example in Figure 2 is a normal Diels-Alder reaction,[8] the reaction of 2-ethoxybutadiene with methyl acrylate. It involved the diene HOMO and the dienophile LUMO. The calculated carbon coefficients at the diene and dienophile termini are those of Anh.[9] The larger values indicated the most probable site of reactivity. Therefore, the coefficients predicted a preference in favor of the "*para*" isomer, based on the difference in the HOMO terminal coefficients. For the reaction above, the *para* isomer is produced exclusively. In a case in which the difference in the terminal coefficients is not so pronounced (e.g. Scheme 3) a lower regioselectivity must be expected. The "*para*" isomer **1** is indeed produced along with a smaller amount of the "*meta*" isomer **2**.[10]



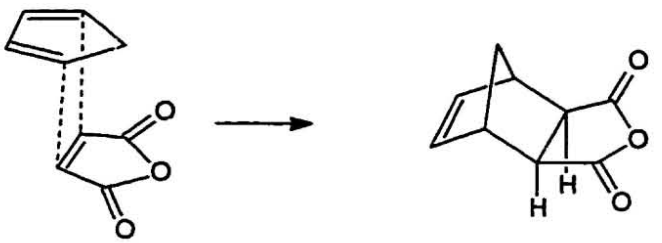
Scheme 3. Regioselectivity for 2-cyano-1,3-butadiene and methyl acrylate.

The possibility of stereoisomerism in the Diels-Alder reaction can arise in two ways, the first being due to topography leading to *endo-exo* isomerism. The *endo* configuration is that in which the bulk of the dienophile is underneath the diene at the transition state. This appears to be the more sterically crowded transition state but, in most cases, it is preferred (Figure 3).

This phenomenon is generally explained using FMO theory. It is thought that a favorable interaction of orbitals on atoms of the diene and dienophile which will ultimately not be bonded in the adduct can account for the preference of *endo* addition despite the inhibitory steric effect.[4b, 11]



***endo* addition product**



exo addition product

Figure 3. *Endo* and *exo* additions in the reaction of maleic anhydride (MA) and cyclopentadiene.

The second effect that can result in the formation of stereoisomers of Diels-Alder adducts is facial selectivity. This arises when the two faces of the π-bonding system of the reacting diene or the dienophile are not equivalent. This leads to diastereomeric products. With a plane-nonsymmetric diene the incoming dienophile may prefer to react with one face of the diene rather than the other (Figure 4).

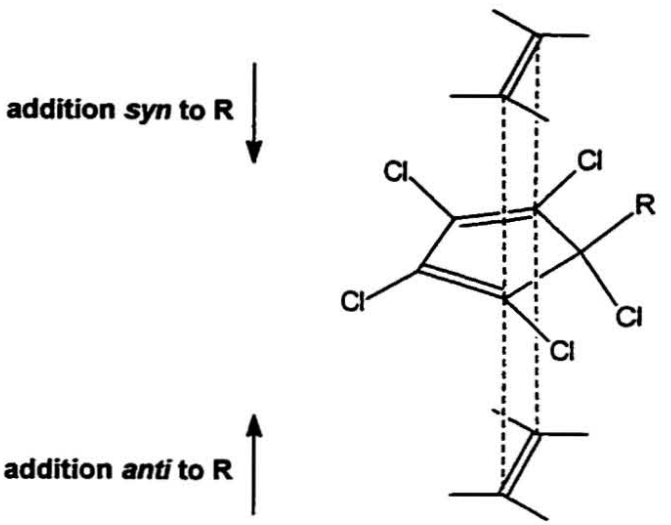


Figure 4. *Syn* and *anti* addition to a 5-substituted 1,2,3,4,5-pentachlorocyclopentadiene.

The investigation of facial selectivity with 1,2,3,4,5-pentachlorinated dienes constitutes the bulk of this thesis. The remainder of the introduction consists of a summary of previous results and theories involving facial selectivity in Diels-Alder reactions.

II. Facial Selectivity: Steric *versus* Electronic Control

Rationalizations for the facial selectivity of the Diels-Alder reaction have been based on steric, torsional and stereoelectronic effects. More than one of these effects may influence the reaction outcome, but ongoing investigations

continue to determine which plays the most important role in governing diastereofacial selectivity for the Diels-Alder reaction.

A study by Burnell and Valenta[12, 13] indicated that steric effects determine the facial selectivity for the tricyclic dienes in Scheme 4 (entries 1 and 2). With these two dienes, the stereoselectivity was attributed to steric interactions between the approaching dienophile *N*-phenylmaleimide (NPM), and the methylene and methine hydrogens on the bridged part of the diene molecules. As shown in Figure 5, the methine hydrogen is pointed directly at the dienophile whereas the methylene hydrogens are angled to either side.

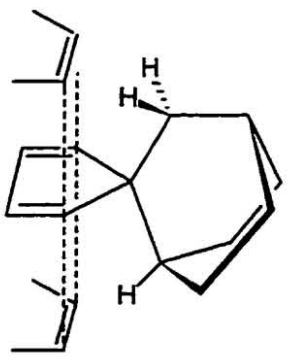
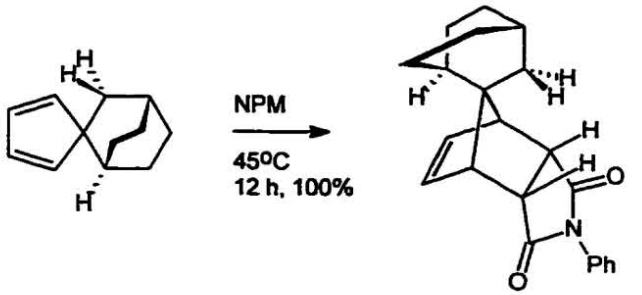
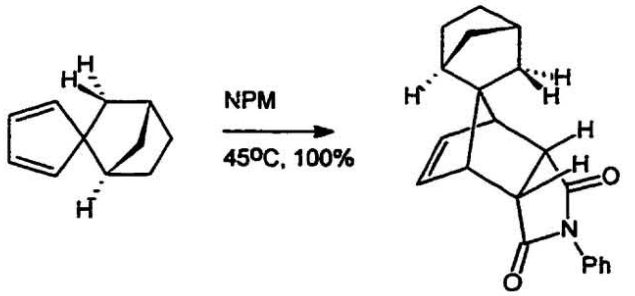
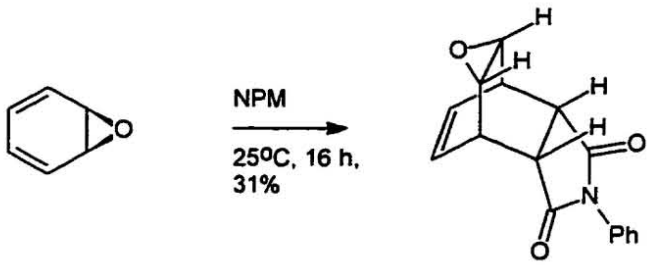
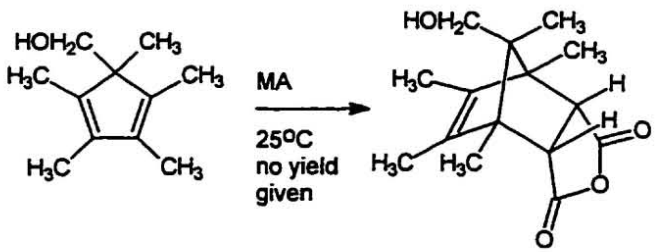


Figure 5. Depiction of two modes of addition to a bridged-ring-substituted 1,3-cyclopentadiene.

Also, an investigation by Gillard and Burnell,[14] utilizing three different benzene oxides as the dienes, gave exclusive addition *anti* to the allylic oxygen. The geometry of the benzene oxides is such that the oxygen is nearly perpendicular to the plane of the diene moiety, whereas the oxirane substituent

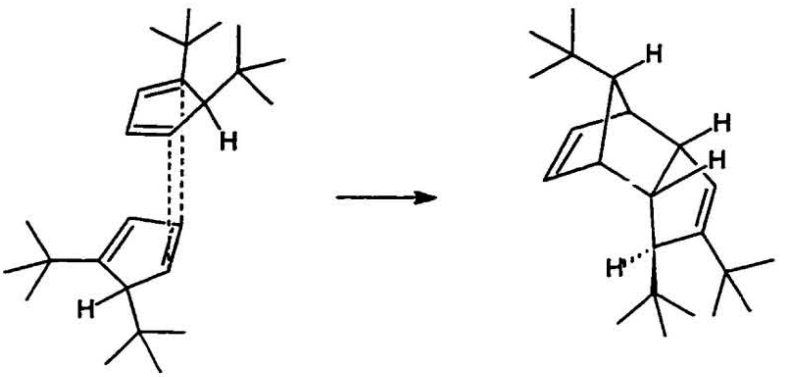
(hydrogens in the case of entry 3, Scheme 4) are roughly coplanar with the diene moiety. Hence, there must be a significant steric interaction between the oxygen and an incoming dienophile on the *syn*-to-oxygen face. The *anti* face is relatively unencumbered, however, resulting in only *anti*-to-oxygen addition of ethylenic and acetylenic dienophiles. This is in marked contrast with many other cases where the presence of an allylic oxygen on the diene gives mainly contrasteric *syn* addition. These *syn*-to-oxygen additions have been explained by electronic phenomena but, the *anti* addition of the oxides were attributed to a steric effect.[14]

Most work with 5-substituted cyclopentadienes concentrated on the elucidation of the extent of facial selectivity when the substituent was a heteroatom. These results, some of which are reported in Schemes 6-8, were accounted for mainly by electronic effects as will be discussed later. There are some examples, however, involving only carbon-based substituents to which it is more difficult to apply electronic factors.[15,16] As shown in entry 4, Scheme 4, the addition of maleic anhydride (MA) to a pentamethylated carbon-based diene was *anti* to the larger CH_2OH group, which lends credence to the concept of steric hindrance being important in Diels-Alder facial selectivity.

Entry	Diels-Alder Reaction	Proportion of Major Adduct	Ref.
1		86%	12
2		69%	13a
3		100%	14
4		95%	15

Scheme 4. Examples of major adducts from Diels-Alder reactions which exhibit the effect of steric hindrance on facial selectivity.

The dimerization of 1,5-di-*tert*-butyl-1,3-cyclopentadiene (Figure 6) occurred via the least sterically hindered transition state to give **3**.[16]

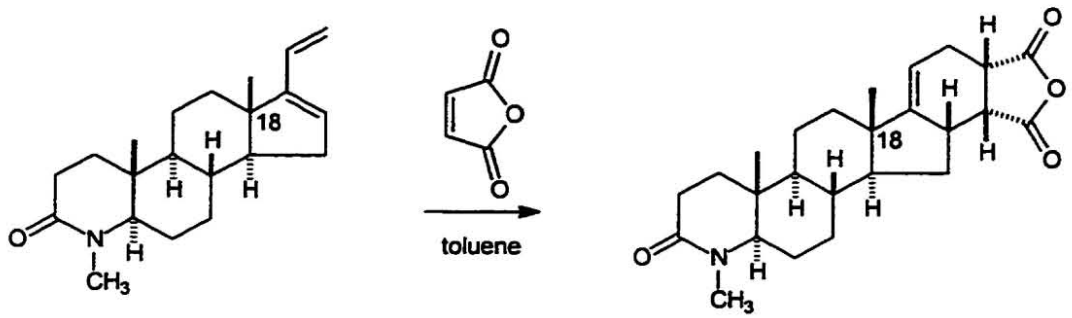


100%

3

Figure 6. The *anti-anti* dimerization of 1,5-di-*tert*-butyl-1,3-cyclopentadiene.

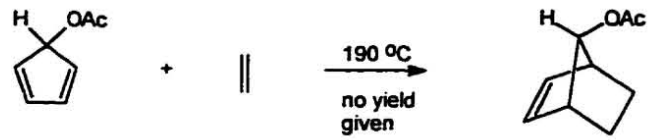
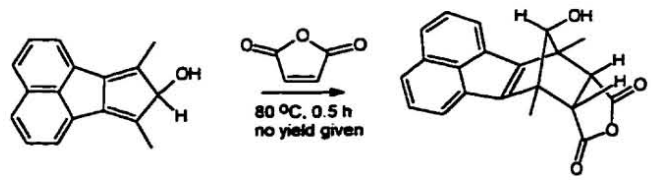
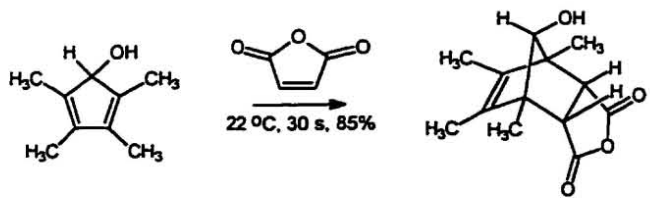
The preference for addition to the less sterically crowded face of a diene has been exploited synthetically in very recent work by Skoda-Földes *et al.*[17] In the synthesis of a pentacyclic steroid, maleic anhydride added to the face of the diene *anti* to the C-18 methyl group, as shown in Scheme 5, to give only **5**.



4 **5**

Scheme 5. Stereoselective reaction of a steroid diene with MA.

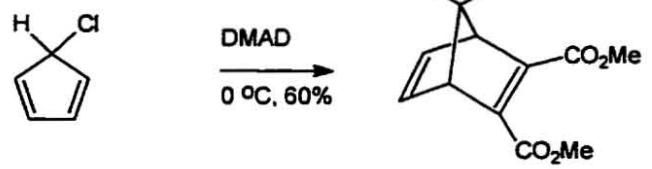
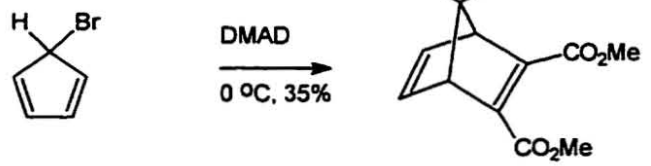
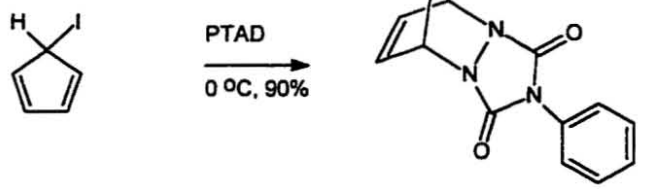
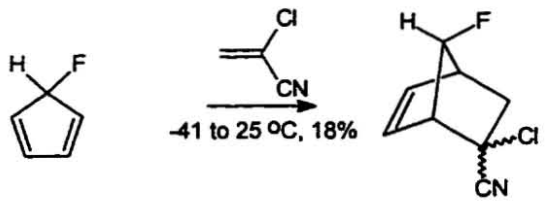
The first example of the cycloaddition of a cyclopentadiene, substituted at the 5-position with a heteroatom, was reported by Woodward and co-workers.[18] 5-Acetoxy-1,3-cyclopentadiene (entry 1, Scheme 6), which had been generated *in situ* from diacetoxydicyclopentadiene, was reacted with ethylene. They found that the product was the result of addition exclusively *syn* to the acetoxy face of the diene. Approximately 25 years later, Jones[19] reacted acetoxy- and hydroxy-substituted cyclopentadienes with several activated dienophiles. The results were exclusively *syn*-to-oxygen and *endo* additions, as shown in Scheme 6 (entries 2 and 3). Jones discussed hydrogen bonding between the hydroxy group of the diene and the dienophiles as a possible explaination of the *syn* addition. He then went on to offer a disproof of this idea, since the acetoxy diene also gave addition *syn* to the oxygen face of the diene when styrene was used

Entry	Diels-Alder Reaction	Proportion of Major Adduct	Ref.
1		100%	18
2		100%	19
3		100%	19
4		100%	20

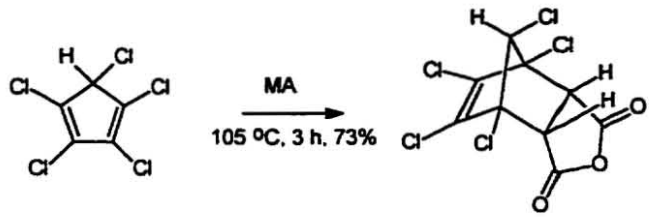
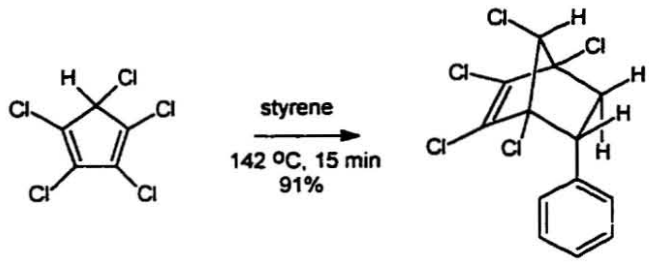
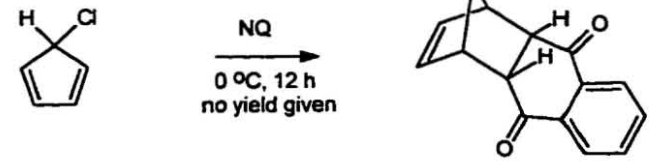
Scheme 6. Additions to dienes with oxygen as the heteroatom substituent.

as the dienophile. Since the use of styrene precludes the possibility of H-bonding, it was concluded that the heteroatom on the diene was responsible for directing the addition *syn* to the oxygen. Fallis and Macaulay[20] examined hydroxy and acetoxy versions of pentamethylcyclopentadiene, and these also gave only addition *syn* to the oxygen functionality (entry 4, Scheme 6).

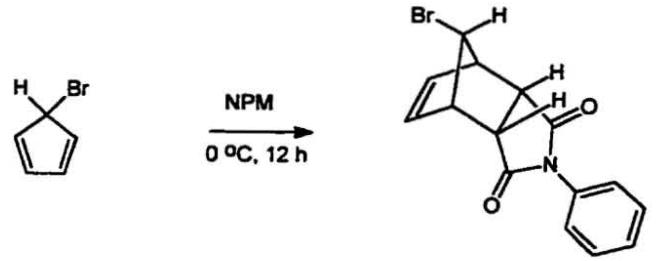
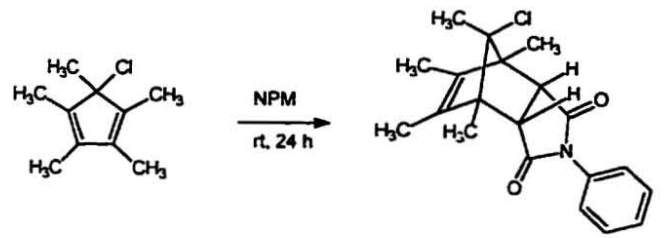
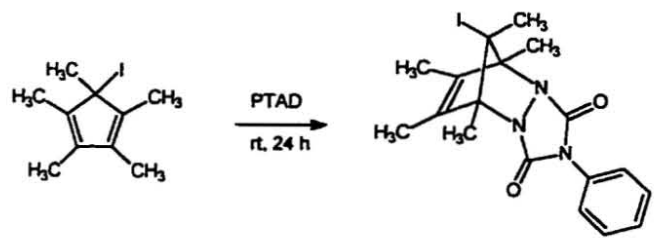
Cyclopentadienes with halogens at the 5-position have also been studied. Breslow carried out reactions with chloro-, bromo-, and iodo-1,3- cyclopentadiene.[21] Upon addition of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD), the chlorodiene gave a mixture of adducts, and the bromo- and iododienes gave addition entirely *anti* to the heteroatom. Sedrati and Franck-Neumann[22] reacted 5-chloro- and 5-bromo-1,3-cyclopentadiene with dimethyl acetylenedicarboxylate (DMAD) to give a mixture for the chlorodiene and 100% *anti* to Br for the bromo diene. Recently, these additions were repeated and data added for several other dienophiles,[23] such as naphthoquinone (NQ), (Scheme 7, entries 8-11). Sik and co-workers[24] synthesized 5-fluoro-1,3-cyclopentadiene and added it to a variety of dienophiles, all of which gave addition *syn* to the fluorine atom. An example (entry 4) is given in Scheme 7.

Entry	Diels-Alder Reaction	Proportion of Major Adduct	Ref.
1		60%	22
2		100%	22
3		100%	21
4		100%	24

Scheme 7. Additions to 5-halogen-substituted 1,3-cyclopentadienes.

Entry	Diels-Alder Reaction	Proportion of Major Adduct	Ref.
5		91%	25
6		99%	25
7		62%	25
8		72%	23

Scheme 7. continued

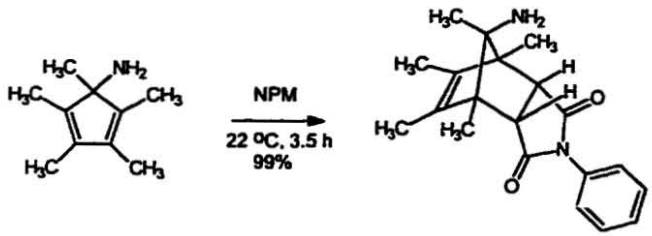
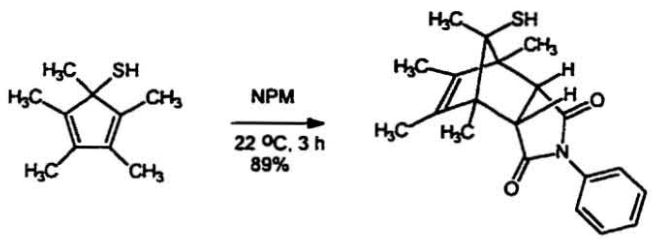
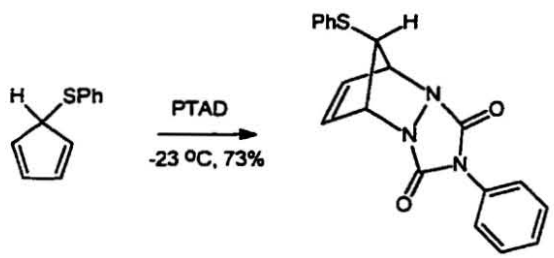
Entry	Diels-Alder Reaction	Proportion of Major Adduct	Ref.
9		85%	23
10		100%	23
11		100%	23

Scheme 7. continued

In 1970 Williamson *et al.*[25] studied the Diels-Alder behavior of pentachlorocyclopentadiene. They reported a large preference for addition *syn* to chlorine with maleic anhydride, which was enhanced by Lewis acid catalysis (Scheme 7, entries 5 and 6). With styrene, however, only 38% of the addition

was *syn* to chlorine. These results were explained as arising from dipole-dipole interactions involving the heteroatom at the 5-position of the diene and the dienophile.

Some examples of nitrogen and sulfur as the heteroatom substituents have been investigated by Fallis and Macaulay.[20] These dienes were derived from pentamethylcyclopentadiene. The dienes substituted at C-5 with nitrogen gave mainly *syn* to nitrogen addition with a number of dienophiles. The sulfur analogues such as SMe and SO_2Me, however, showed a completely opposite trend by giving mainly *anti* addition. The SH-substituted diene, however, showed little selectivity (Scheme 8, entry 2). A study by Isida *et al.*[26a] using sulfur and selenium as the heteroatom substituents gave little selectivity for SPh with ethylenic dienophiles such as NPM and MA, but mainly *anti* to the heteroatom selectivity with PTAD (Scheme 8, entry 3). Larger substituents, such as selenium functional groups, gave additions mostly *anti* to the heteroatom with several dienophiles[26] (Scheme 8, entry 4).

Entry	Diels-Alder Reaction	Proportion of Major Adduct	Ref.
1		100%	20
2		55%	20
3		86%	26b
4		100%	26a

Scheme 8. Additions to cyclopentadienes substituted at C-5 by N, S or Se functional groups.

The earliest theories to explain Diels-Alder addition *syn* to heteroatoms such as O, N, and Cl dealt with ground state electronic effects. The *anti* additions observed with Se, Br and I were assumed to be due to steric effects. Anh[27] proposed that favorable interactions between the frontier molecular orbitals of the diene heteroatom and the dienophile gave rise to *syn* addition (Figure 7).

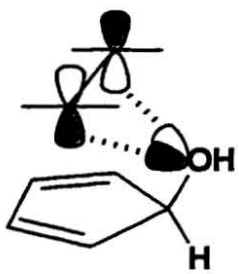


Figure 7. Representation of Anh's proposal for the participation of lone pairs in the Diels-Alder cycloaddition.

In 1976, Fukui *et al.*[28] invoked the "orbital mixing rule" as the explanation for facial selectivity in the Diels-Alder reaction. As shown in Figure 8, it was suggested that when the substituent possessed lone-pair electrons, the non-bonding "lone-pair" orbital perturbed the HOMO of the diene and allowed its mixing with low-lying *s* orbitals of the carbon skeleton, such that the HOMO electron cloud was biased toward the substituent. The *syn* attack by electron-accepting dienophiles is favored by this non-equivalent extension of the diene HOMO. The orbital mixing rule was used to explain Williamson's results with pentachlorocyclopentadiene. The electron-accepting maleic anhydride

prefers *syn* to Cl addition, whereas styrene, which is a poor electron-acceptor, has little preference for addition *syn* to Cl (Scheme 7, entry 7).

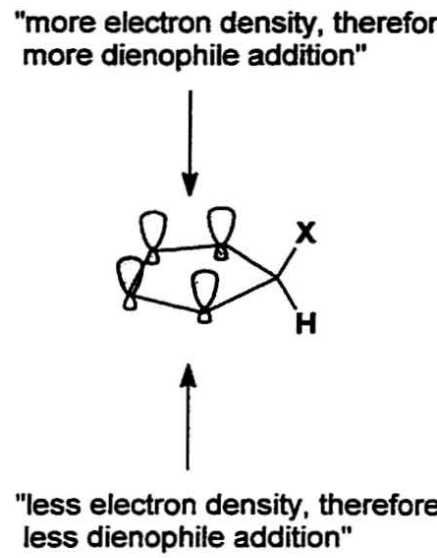
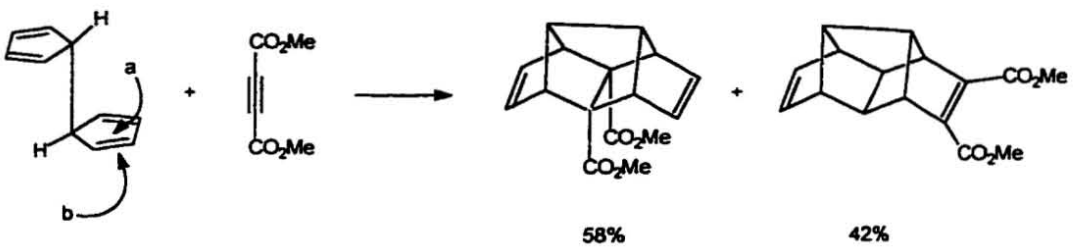


Figure 8. Representation of the "orbital mixing rule", resulting in a facial bias of the diene when heteroatom X is present.

In the case of carbon *versus* hydrogen at C-5 of cyclopentadiene, the electron density difference should be negligible. Thus very little facial selectivity is predicted for these types of dienes. An example of a carbon *versus* hydrogen addition by Paquette and Wyvratt[29] obeys the orbital mixing proposal by Fukui. In Scheme 9, the dienophile attack from face **a** to give **7** (after the second addition of the second cyclopentadiene ring) is only slightly more favored than attack on face **b** to give **8,** as predicted by Fukui.

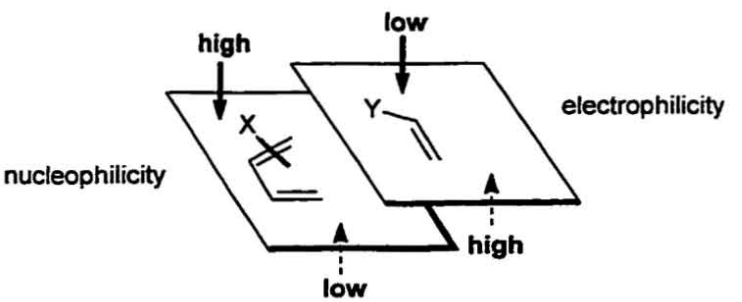


58% 42%

6 **7(via a)** **8(via b)**

Scheme 9. Addition of DMAD to 9,10-dihydrofulvalene **6**.

A third electronic theory proposed by Kahn and Hehre[30] in 1987 suggested that a matching of complementary energy surfaces of diene and dienophile governs the facial selectivity. Simply stated, cycloadditions involving electron-rich dienes and electron-poor dienophiles should occur preferentially from the diene face which is the more nucleophilic onto the face of the dienophile which exhibits the greater electrophilicity.



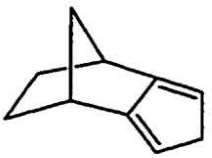
X = electron-donating group
Y = electron-withdrawing group

Figure 9. Depiction of matching reactivity surfaces.

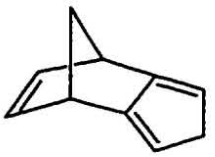
This was used to explain the *syn* to oxygen addition of oxygen-substituted cyclopentadiene by electron-poor dienophiles such as *N*-phenylmaleimide, maleic anhydride and methyl acrylate as seen in Scheme 6. These generalizations should reverse for inverse-electron-demand Diels-Alder reactions.

The facial selectivity of the cycloadditions of compounds such as **9-11** has been examined in considerable detail. Cycloadditions of diene **9** proceeded exclusively from the "below-plane" face with all dienophiles except MA and singlet oxygen. Dienes **10** and **11** behaved similarly. Since the primary reacting carbons of the cyclopentadiene rings are remote from the bridge, steric factors were not considered to be responsible for the overwhelming kinetic preference for below-plane attack of dienophiles on these dienes. Paquette and Gleiter[31a] proposed an orbital-tilting model to explain the addition behavior of these isodicyclopentadienes **9-11**. The explanation given for this behavior involved "tilting" of the terminal diene π lobes as a result of favourable σ/π interactions (Figure 10).

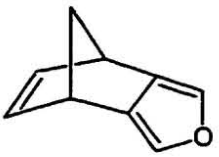
The tilting is considered to be a result of σ orbital mixing with the lowest occupied π orbitals of the diene (π_s). The outcome is a minimization of the degree of the antibonding interaction on the below-plane face of the diene compared with the above-plane face, or, in other words, the below-plane face results in less "repulsion" of the dienophile.



9



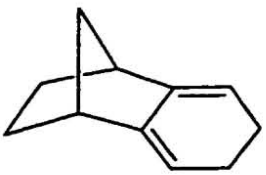
10



11

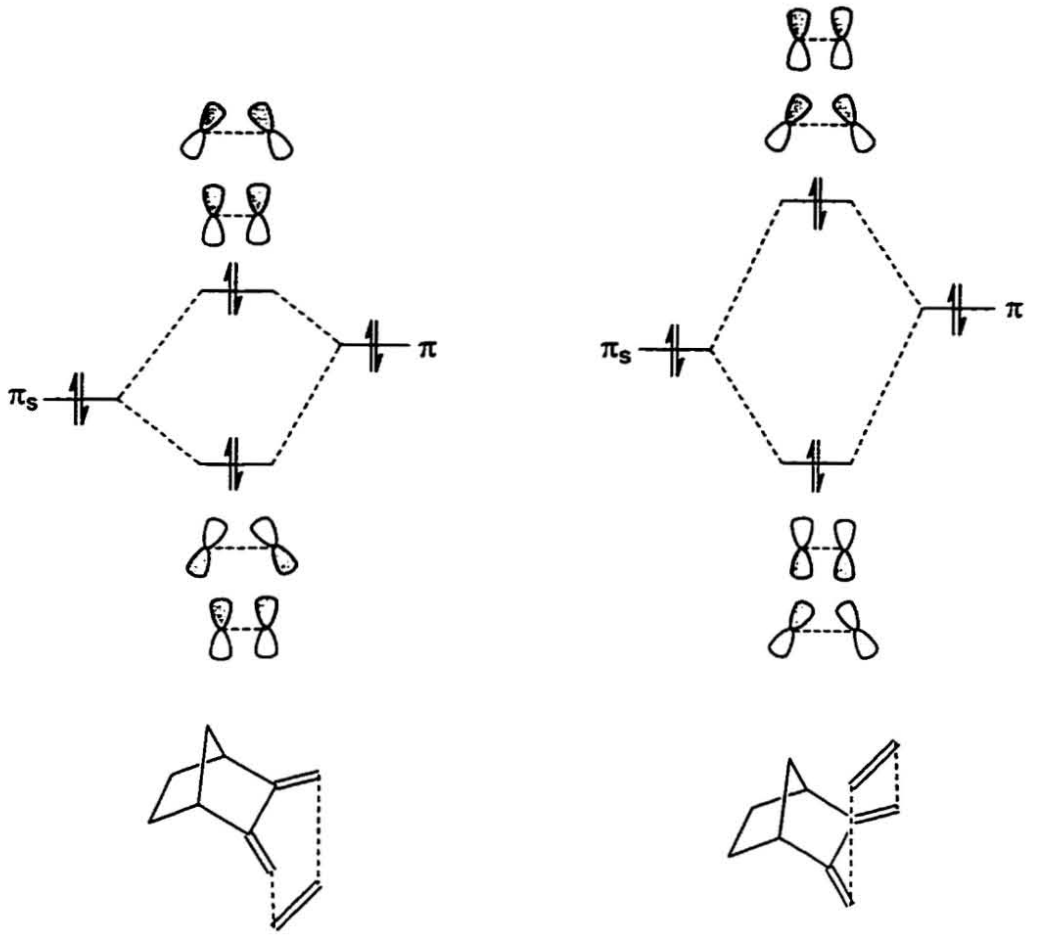
below-plane

Houk stated that below-plane additions are based on a torsional effect.[32] His evidence came from a computational study of Paquette's dienes.



12

Paquette rebutted Houk's torsional idea, however, by studying the π-facial selectivity of diene **12**. It was stated that the energy difference proposed by Houk does not account for the experimental behavior of diene **12**.[31b,c]



below-plane addition **above-plane addition**

Figure 10. Qualitative diagram of the interaction between π_s of the butadiene unit in the bicyclo compound with a π bond from ethylene.

Ginsburg and co-workers[33, 34] studied the cycloadditions of several propellane substrates. The exclusive *anti* to the heteroatom addition for dienes

such as entries 1 and 2 in Scheme 10 were explained by repulsive steric interactions between the five-membered ring and the *syn*-approaching dienophile. It was noted that the diene with the anhydride moiety underwent a complete reversal of facial selectivity when the dienophile was changed to PTAD, (Scheme 10, entry 3). This behavior was rationalized in terms of favorable secondary orbital interactions. An attractive interaction between the π system of the carbonyl groups and the lone-pairs on the nitrogen atoms of the dienophile, as shown in Figure 11, was postulated.

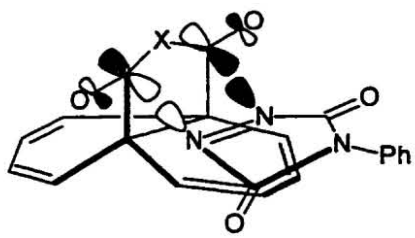
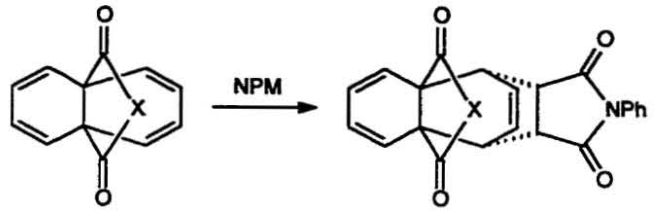
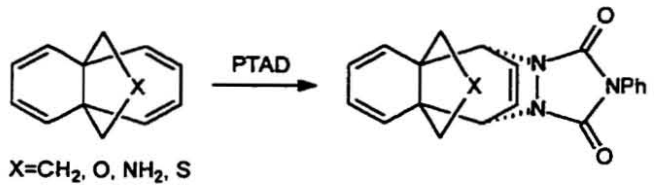
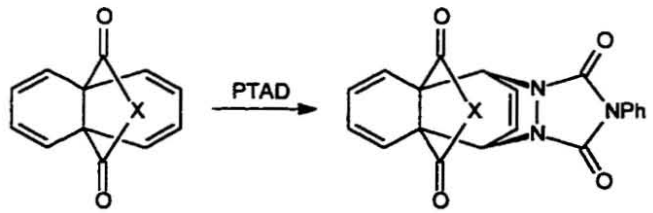


Figure 11. Secondary orbital overlap in the approach of an azo dienophile *syn* to an anhydride-bridged propellane.

Several rationalizations to account for facial selectivity discussed so far have applied to "ground state" properties of the reactants. However, an alternative approach by Cieplak and co-workers[35] used a model based on transition state effects in additions to ketones. The model by Cieplak was related to the Felkin-type transition state structure used to explain facial selectivity in nucleophilic additions to carbonyl groups. The Felkin model explains the stereochemistry of nucleophilic addition to carbonyl groups

Entry	Diels-Alder Reaction	Proportion of Major Adduct	Ref.
1	 X=O, NMe	100%	33
2	 X=CH_2, O, NH_2, S	100%	34
3	 X=O, NMe	100%	34

Scheme 10. Facial selectivities of propellane dienes.

in terms of the stabilizing interaction of the incipient bond with the vicinal σ bonds. Felkin *et al.* postulate that, as seen in Figure 12, a high-lying σ orbital of

the incipient bond ($\sigma_{\ddagger}$) would be delocalized into a vacant σ^* orbital (σ_{CH}) associated with the α-carbon via hyperconjugation.

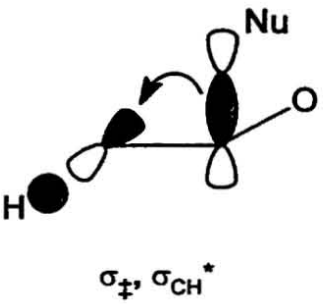
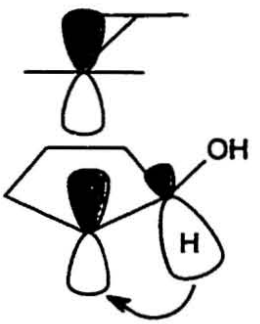


Figure 12. High-lying $\sigma_{\ddagger}$ orbital of the incipient bond delocalized in a hyperconjugative interaction into a vacant σ_{CH}^* orbital **(Felkin-Anh model)**.

This hyperconjugative effect would be optimized when the nucleophile attacks in an antiperiplanar manner. Cieplak's approach suggests transition state stabilization is due to electron donation from an antiperiplanar σ orbital into to a $\sigma_{\ddagger}^*$ orbital, a low-lying vacant orbital of the forming bond. Thus, in the extension of Cieplak's ideas by Fallis and le Noble[36a,b] for prediction of facial selectivity in the Diels-Alder reaction, it was proposed that stabilization of the incipient bond by hyperconjugation of a substituent which is in the antiperiplanar position relative to the forming bond would control the stereochemistry of the addition, as shown in Figure 13. Therefore, cycloadditions of many dienes should prefer addition *anti* to the antiperiplanar σ bond that is the better electron donor. Listed in order of increasing σ-donor ability, some common atom

combinations are $\sigma_{CO} < \sigma_{CN} < \sigma_{CCl} < \sigma_{CC} < \sigma_{CH} < \sigma_{CS}$.[37] Hence, in 5-hydroxy-1,3-cyclopentadiene, a diene that has one face with a carbon-hydrogen bond and the other with a carbon-oxygen bond, addition *syn* to the C-O face should dominate, as was shown for several examples in Scheme 5.



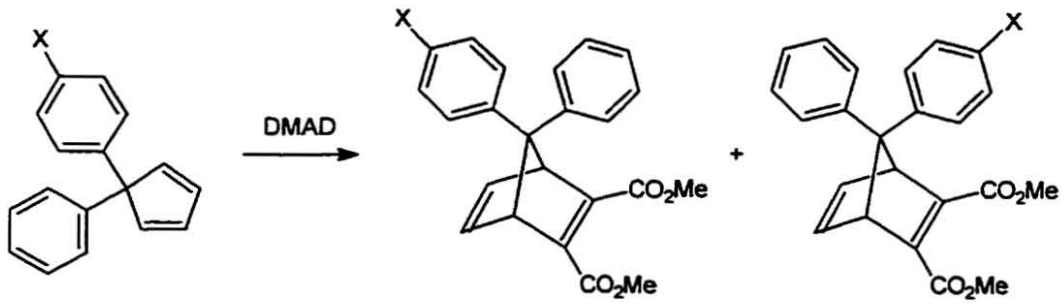
σ_{CH}, $\sigma_{\ddagger}^{*}$

Figure 13. Stabilizing interaction of the incipient bond orbital $\sigma_{\ddagger}^{*}$ with neighboring occupied orbitals σ_{CH} **(Cieplak model).**

Fallis *et al.* adopted this explanation to account for the selectivity observed with N and S as the heteroatoms in studies with pentamethylcyclopentadienes.[20, 36a] As shown in Scheme 7, when carbon and nitrogen substituents were pitted against each other, addition occurred *anti* to the carbon exclusively. This supported Cieplak's theory since the C-C bond is considered to be a better donor than the C-N bond.

Some other results have been offered as support for the validity of the above theory. In a 1992 publication by Halterman *et al.*[38] facial selectivity of

5,5-diarylcyclopentadienes was disclosed. The cyclopentadienes **13-15** were synthesized from the corresponding cyclopentenones. These dienes having substituents X= NO_2, Cl and NMe_2 shown in Table 1 were reacted with DMAD.



13 X=NO_2
14 X=Cl
15 X=$N(Me)_2$

trans cis

Scheme 10. Additions of 5,5-diarylcyclopentadiene with DMAD.

Table 1. Relative amounts of *cis* (*cis* to X) and *trans* (*trans* to X) adducts for Scheme 10.

X	product	% trans	% cis
NO_2	**13**	32	68
Cl	**14**	42	58
$N(Me)_2$	**15**	62	38

The authors stated that the experimental evidence is in agreement with Cieplak's notion that bond formation is predicted to occur opposite the better donor, which was the $N(Me)_2$ group in the Halterman study.

In summary, substituents containing heteroatoms from the first row (X=F, NH_2, OH, OAc) lead overwhelmingly to addition to the diene face *syn* to the heteroatom. Dienes with substituents from the second row (X=SPh, Cl) give both *syn* and *anti* adducts, but with substituents from rows three and four (X=Br, SePh, I), *anti* addition gives the exclusive product. None of the rationalizations discussed can be correct for all of these results.

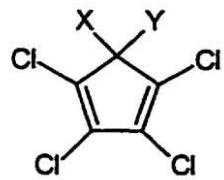
Burnell, Poirier and co-workers[39] proposed a steric model based on an *ab initio* computational examination of the problem. Calculation of "deformation energies"[40] revealed that deformation of the addends at the transition state is the major factor responsible for determining the facial selectivity with 5-substituted cyclopentadienes, not a direct interaction between diene and dienophile. The results presented in the following sections for polychlorinated dienes are discussed as they relate to the prediction of facial selectivity in the Diels-Alder reactions.

In conclusion, for all of the stereoelectronic phenomena implicated in the control of facial selectivity in the Diels-Alder reaction, inverse-electron-demand reactions should reverse the facial preference. As we have discussed, only one study of this type of Diels-Alder reaction was carried out by Williamson in 1970,[25] and it was decided that further examination of this type of system was required.

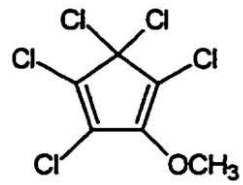
Without a broad range of experimental results to draw on, development of theories for facial selectivity thus far have not taken into account all of the electronic differences affecting the stereochemistry of Diels-Alder reactions.

III. Results and Discussion

(i) 1,2,3,4,5-Pentachloro-5-methoxy-1,3-cyclopentadiene (16)



16 X=Cl, Y=OCH_3
17 X=Y=OCH_3
18 X=Y=Cl



19

As mentioned in Section I. II., there has been only a limited amount of investigation of facial selectivity with inverse-electron-demand dienes. Thus, we decided to examine a series of polychlorinated 1,3-cyclopentadienes. In the normal-electron-demand examples discussed in the Introduction, there are many cases in which the heteroatom is oxygen. Therefore, the work was started by studying facial selectivity with diene **16**, which pitted chlorine against oxygen in a situation in which reactions could proceed through both normal and inverse-electron-demand mechanisms.

The diene **16** was obtained by slow addition of a solution of hexachlorocyclopentadiene **18** to a solution of methanol containing a limiting amount of KOH.[41] The yield of **16** was very poor, but this process avoided the production of the dimethoxydiene **17**, which proved to be very difficult to

separate from **16** by flash chromatography. Diene **16** was obtained as the major component of a 1.5:1 mixture that also contained the preparatively inseparable isomer **19**. However, this mixture could be used in the Diels-Alder reaction because, with a single exception, only adducts from **16** were detected, and **19** remained unchanged after long reaction times.

Diene **16** was reacted with electron-deficient ethylenic dienophiles (*N*-phenylmaleimide, 1,4-naphthoquinone), electron-rich ethylenic dienophiles (vinylene carbonate, ethoxyethylene), styrenes (styrene, 4-bromostyrene, 3-nitrostyrene, 2-vinylnaphthalene), a heteroatomic dienophile (4-phenyl-1,2,4-triazoline-3,5-dione),[42] and an acetylenic dienophile (diethyl acetylenedicarboxylate). The electron-rich dienophiles and the styrenes reacted with **16** in the inverse-electron-demand mode, whereas the electron-poor dienophiles reacted in the normal mode. The mode of reaction was assigned by calculation of HOMO-LUMO (*ab initio* RHF 3-21G) energy differences.[43]

Table 2. Normal-electron-demand HOMO-LUMO (RHF 3-21G) energy differences in Hartrees.[43]

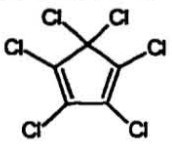
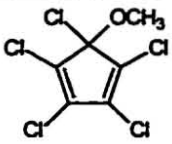
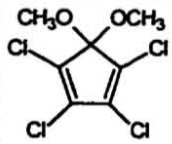
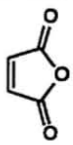
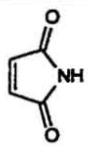
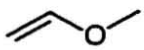
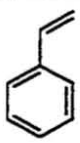
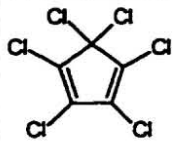
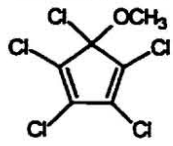
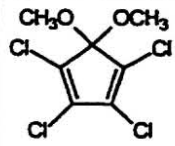
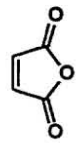
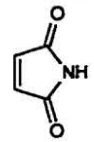
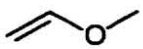
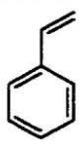
Dienophile		Diene		
	Dienophile LUMO (H)			
Diene HOMO (H)		-0.37811	-0.36471	-0.34519
	0.02548	**0.40359**	**0.39018**	**0.37067**
	0.04555	**0.42366**	**0.41025**	**0.39074**
	0.29376	0.58187	0.56847	0.54895
	0.11155	0.48966	0.47625	0.45674

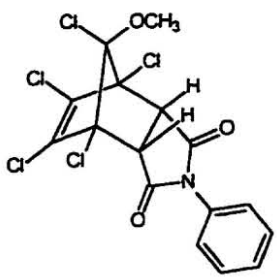
Table 3. Inverse-electron-demand HOMO-LUMO (RHF 3-21G) energy differences in Hartrees.[43]

Dienophile		Diene		
	Dienophile HOMO (H)			
Diene LUMO (H)		0.01439	0.03121	0.0738
	-0.44749	0.46188	0.47869	0.52129
	-0.42203	0.43642	0.45323	0.49583
	-0.33576	**0.35015**	**0.36696**	**0.40956**
	-0.30806	**0.32245**	**0.33926**	**0.38186**

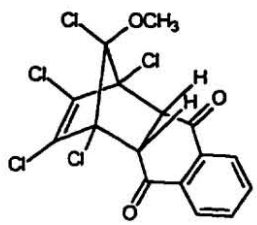
As shown in Tables 2 and 3, the reactions with maleic anhydride and maleimide with **16-18** showed that the normal-electron-demand mode of reaction should be preferred, but the HOMO-LUMO gaps for the reactions of methoxyethylene and styrene with **16-18** were consistent with inverse-electron-demand reactions.

Adducts were not obtained in high yield, but the reactions were followed by GC-MS or ^{1}H NMR spectroscopy and were terminated when a large proportion of diene **16** had been consumed. This was done to pre-empt the possible formation of side-products, such as adducts from the reaction of diene **19**. Facial selectivity in the reactions of **16** with every dienophile was very high: in every case only one adduct derived from **16** was isolated, as shown by structures **20-29**.

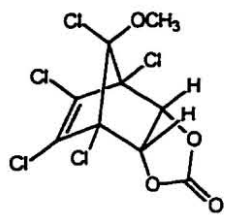
Adducts from ethylenic dienophiles:



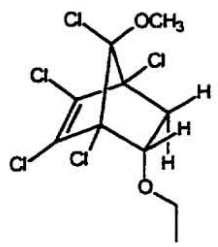
20



21

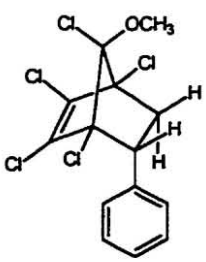


22

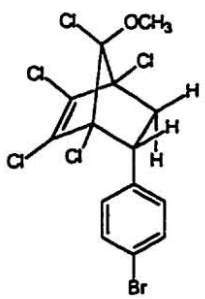


23

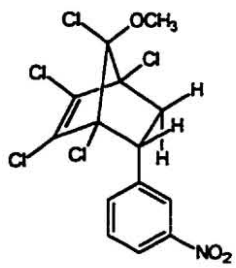
Adducts from styrene dienophiles:



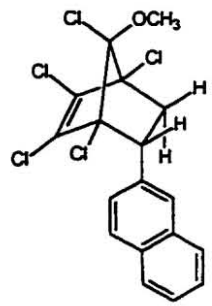
24



25

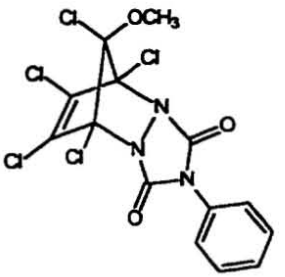


26



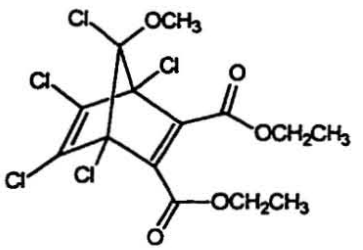
27

Adduct from heteroatomic dienophile:



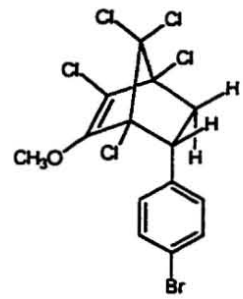
28

Adduct from acetylenic dienophile:



29

These were the only adducts detectable by GC-MS or ^{1}H NMR spectroscopy in the crude reaction product, except in the following instance. With 4-bromostyrene, two adducts were detected in the crude product, but the minor adduct **30** proved, by X-ray crystallography, to be derived from **19**.



30

In an early attempt to assign the stereochemistry of the adducts, a comparison of the ^{13}C NMR data of adducts from dienes **17** and **18** was used. The adducts were generally prepared by heating the reactants at reflux in benzene or toluene. Reaction progress was followed by TLC and the reaction stopped when the dienes were consumed (6h → 5 days). Table 4 shows the data for the ^{13}C NMR chemical shifts for the adducts from dienes **16, 17** and **18**.

Table 4. ^{13}C NMR data for adducts from dienes **16**, **17** and **18**.[a]

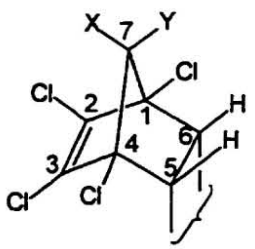
adduct	C-1 C-4	C-2 C-3	C-5 C-6	C-7	OCH_3	other signals[b]
16+NPM **20**	77.7	130.3	51.7	117.2	55.7	C=O: 169.9 Ar: 130.8, 129.4, 129.3, 126.4
17+NPM **31**	75.0	129.3	51.8	114.6	53.0 52.2	C=O: 170.6 Ar: 130.9, 129.3, 129.1, 126.5
18+NPM **41**	79.4	131.0	52.0	103.9	—	C=O: 169.1 Ar: 130.6, 129.4(2C), 126.3

16+VC **22**	79.2	130.2	83.0	114.2	55.8	C=O: 151.7
17+VC **32**	76.5	128.9	83.0	112.1	52.9 52.3	C=O: 152.3
18+VC **42**	80.6	131.5	82.5	98.4	---	C=O: 151.3
16+EE **23**	81.3 76.7	130.9 129.5	83.8 43.5	115.5	54.8	O**C**H_2CH_3: 67.0 OCH_2**C**H_3: 15.3
17+EE **33**	79.0 74.1	129.8 127.9	83.7 43.8	111.7	52.5 51.5	O**C**H_2CH_3: 66.6 OCH_2**C**H_3: 15.3
18+EE **43**	82.4 78.1	131.2 130.1	83.5 43.5	101.1	---	O**C**H_2CH_3: 67.2 OCH_2**C**H_3: 15.4
16+STY **24**	82.7 77.3	130.8 130.5	51.6 41.0	116.1	55.0	Ar: 135.1, 128.9, 128.4, 128.1
17+STY **34**	80.2 74.8	129.6 129.1	51.7 41.9	112.3	52.7 51.7	Ar: 135.8, 129.1, 128.2, 127.8
18+STY **44**	84.1 79.0	131.2 131.0	51.5 40.7	102.8	---	Ar: 134.2, 128.9, 128.5
16+BS **25**	82.5 77.2	131.0 130.3	51.2 41.0	115.9	55.1	Ar: 134.3, 131.5, 130.5, 122.4
17+BS **35**	80.0 74.7	129.8 128.8	51.2 41.8	112.2	52.7 51.7	Ar: 134.9, 131.3, 130.6, 122.1
18+BS **45**	83.9 78.9	131.4 130.8	51.2 40.7	102.7	---	Ar: 133.3, 131.7, 130.5, 122.8

Table 4. continued

16 + PTAD **28**	90.5	129.7	—	109.5	56.0	C=O: 155.4 Ar: 129.5, 128.6, 125.5
18 + PTAD **46**	92.2	under Ar signal	—	97.1	—	C=O: 154.7 Ar: 129.6, 129.5, 128.6, 125.5

a Numbering scheme for the adducts from dienes **16**, **17** and **18**
b Ar = aromatic

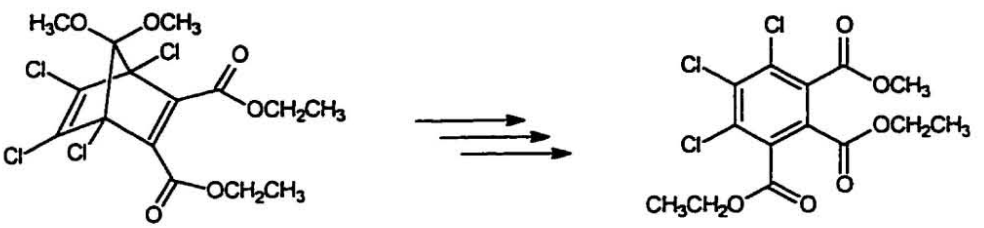


16 X=Cl, Y=OCH_3
17 X=Y=OCH_3
18 X=Y=Cl

As can be seen from Table 4, the ^{13}C NMR signals that might be expected to be diagnostic of the stereochemistry at C-7, such as those for C-2, C-3 and C-5, C-6, do not help to distinguish between the *syn* and *anti* adducts. In most cases these signals are very similar in chemical shift for all three adducts, or the signal for the adduct derived from **16** is centered between those from dienes **17** and **18**.

X-ray crystallography is an unequivocal method to determine whether *syn* or *anti* addition has occurred. The ORTEP diagrams for the X-ray structures of compounds **20-22**, **24**, **25**, **28-30** are shown in **Appendix A**.

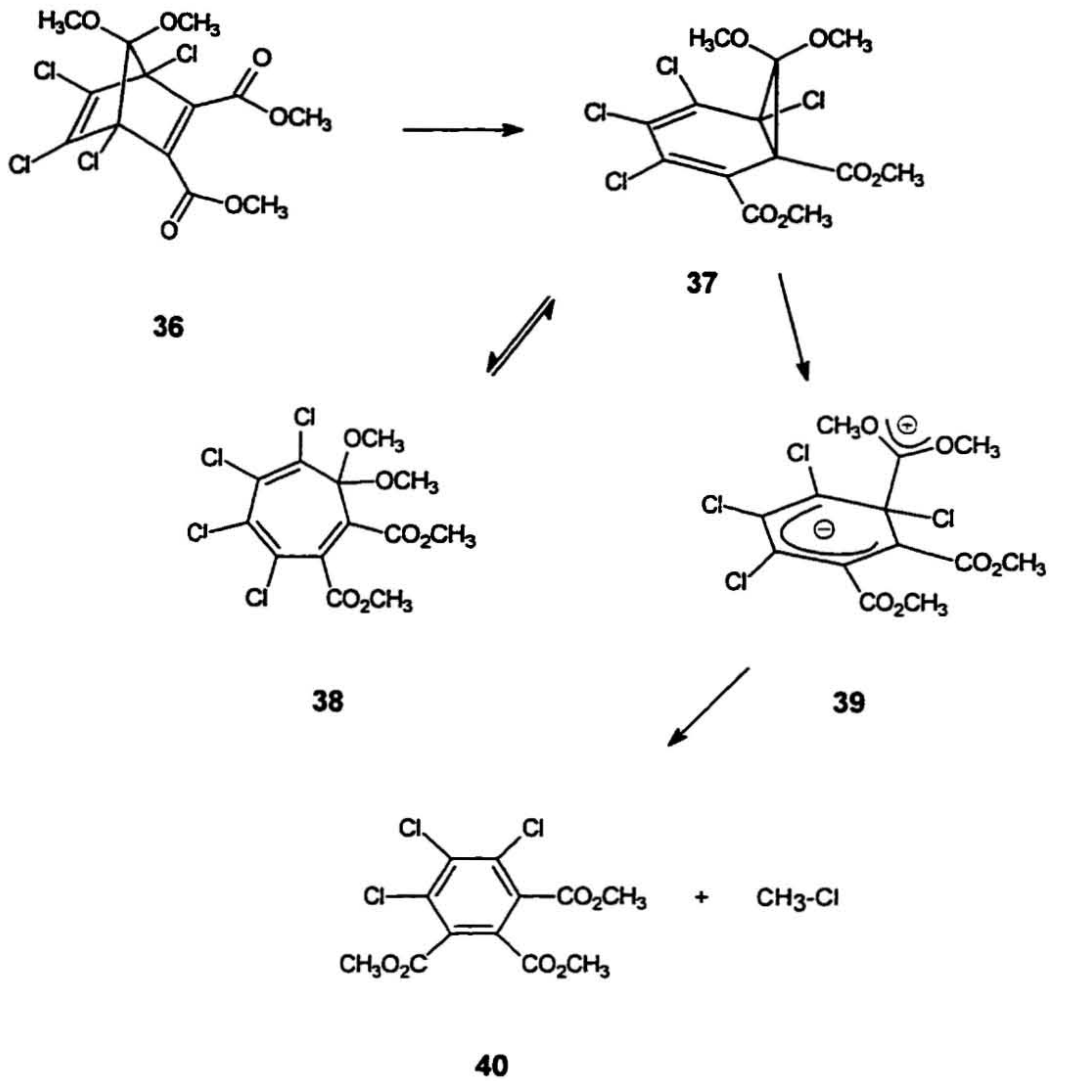
The reaction involving dimethoxy diene **17** and diethyl acetylene-dicarboxylate gave an unexpected product **40**. The NMR spectra of this product suggested a fragmentation reaction had taken place as was shown by the absence of the methoxy signals. Literature precedent was found for this reaction with the substrate from the Diels-Alder reaction of DMAD and diene **17**.[44]



36 **40**

Scheme 11. Aromatization of the norbornadiene ketal from diene **17** and diethyl acetylenedicarboxylate.

The first proposed mechanism for this fragmentation was thought to involve an ionic decomposition pathway.[44c] The more recent publications have expanded this decomposition mechanism to include the cycloheptatriene **38** intermediate as shown in Scheme 12.[44a, 44b]



Scheme 12. Proposed mechanism[44a] for the fragmentation of norbornadiene acetals to give aromatic compounds.

Diene **16** did not react very quickly with any of the dienophiles tested. This suggested that the rate of reaction was retarded very significantly, relative to

5-substituted 1,3-cyclopentadienes, probably by steric hindrance between the dienophile and the chlorines on the termini of the diene moiety of **16**.

The most important result was that the addition was to the face of **16** *syn* to its methoxy group, regardless of the dienophile used. Inverse-electron-demand Diels-Alder reactions have not been addressed in the various rationalizations of facial selectivity, except by Williamson.[25] The fact that the mode of reaction, normal or inverse-electron-demand, had no bearing on the facial selectivity with **16** is not what would be expected for stereoelectronic control of facial selectivity. Comparison of the results with the mechanisms discussed in the Introduction indicate little effect by electronic factors in the case of diene **16**. Fukui's[28] mechanism involving facial bias of the diene π–system in terms of electron density would not be expected to lead to the same result for both electron-rich and electron-poor dienophiles. Kahn and Hehre[30] suggest that the attraction of surfaces based on nucleophilicity should reverse when electron-deficient dienes and electron-rich dienophiles are involved in the Diels-Alder reaction. This is obviously not the case for diene **16**. Anh's[27] idea of the favorable mixing of a lone pair orbital on the heteroatom on the diene with a molecular orbital on the dienophile should also be affected by the electronic properties of the dienophile. The results are also in conflict with Ginsburg's electrostatic interactions,[33] and Williamson's proposal of dipole-dipole interactions.[25] The facial selectivity with **16** was the same as that expected for

the "normal" Diels-Alder reactions in which an oxygen function at C-5 of 1,3-cyclopentadiene very strongly directed addition *syn* to itself,[18, 19, 20] whereas chlorine was less selective.[20, 22]

In an attempt to gain more information regarding the phenomenon controlling the facial selectivity, the relative rates of reactions were determined in an approximate manner for the reactions of dienes **16-18** with styrene. Competitive reactions were carried out in boiling benzene. The relative amounts of the adducts were determined by the integration of ^{1}H NMR spectra of the crude products, and the following equation was used to calculate the relative rates.[45]

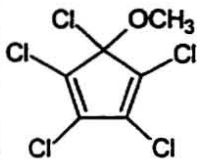
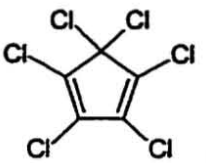
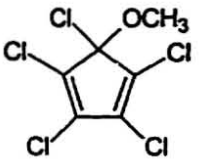
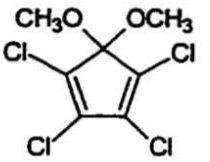
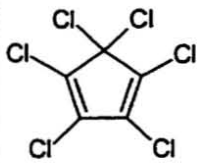
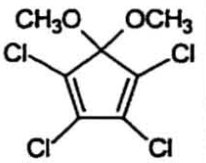
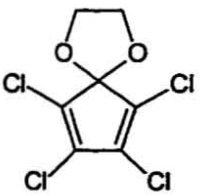
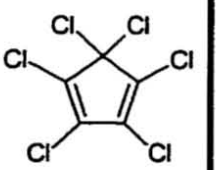
Equation 1

$$\frac{k_a}{k_b} = \frac{\ln \dfrac{[A] - [AC]}{[A]}}{\ln \dfrac{[B] - [BC]}{[B]}}$$

where k_a and k_b are diene reaction rates

[*A*], [*B*] are the initial concentrations of dienes A and B,
and [*AC*], [*BC*] are the final concentrations of adducts A and B.

Table 5. Relative reaction rates for dienes **16**, **17**, **18** and **47** with styrene as the dienophile.

 **16** vs  **18**	 **16** vs  **17**
4 : 1	2 : 1
 **18** vs  **17**	 **47** vs  **18**
1 : 2	62 : 1

As shown in Table 5, the relative reaction rates were 4:2:1, in the order of **16**>**17**>**18**. The difference in rate between **17** and **18** did not reflect the high degree of selectivity of **16**, but this was likely due to a shortcoming of **17** as a model for one face of **16**. The *syn* methoxy of **17** may assume an eclipsed conformation (i.e., dihedral angle of Me—O—C-5—O = 0°) to distance itself from the incoming dienophile, as illustrated by the methoxy group on the lower surface of the diene in Figure 14. However, this would force the *anti* methoxy, represented by the methoxy group on the upper surface of the diene in Figure

14, to lie over the diene and thus to interact with the diene in a sterically unfavorable 1,3- manner.

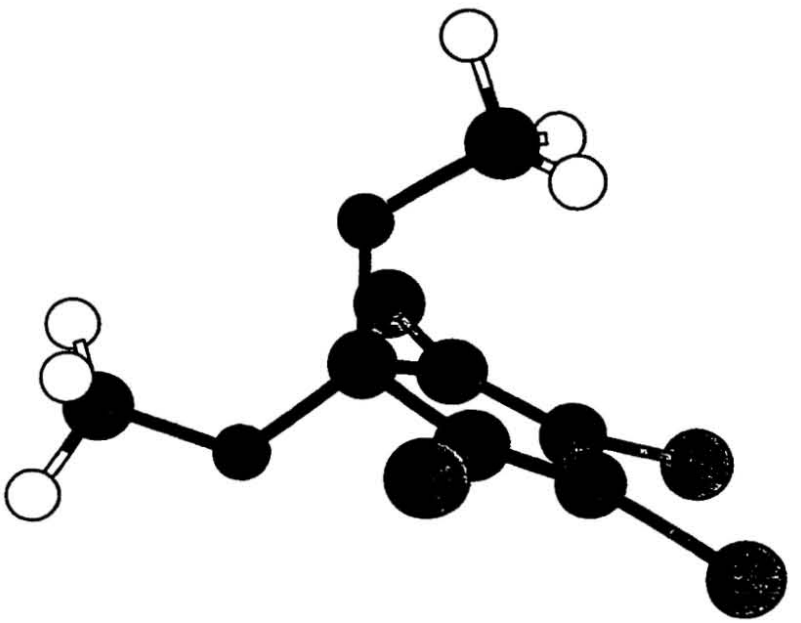
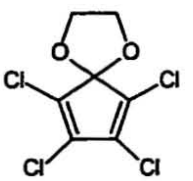


Figure 14. Conformation of diene **17** which would provide steric hindrance for an incoming dienophile

Diene **47** may be a better model for the oxygen-bearing face of **16**, and **47** reacted with styrene approximately 60 times faster than **18**.

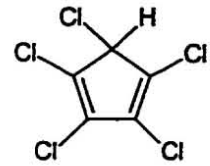


47

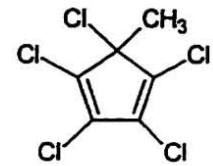
Thus, a diene with a chlorine in the *anti* position reacts more slowly than a diene with an oxygen in the *anti* position. This is not consistent with a popular hypothesis of facial selectivity through σ-donation by an *anti* substituent developed by Cieplak.[35]

The facial selectivity of **16** and the relative rates are entirely consistent with the hypothesis by Burnell, Poirier *et al.*,[39] which is based on an *ab initio* computational study, that a second row atom on C-5 of 1,3-cyclopentadiene imparts a considerable degree of stabilization to the diene moiety in its deformed, transition state geometry mainly when addition is *syn* to these atoms, not *anti*. The hypothesis was formulated from data for only the simple 5-substituted 1,3-cyclopentadienes, and the mechanism by which stabilization occurs is not clear. However, the realization that the hypothesis also holds for electronically different modes of reaction, as was found for diene **16**, is important because this points to a mechanism for the stabilization that is not rooted in a stereoelectronic effect. Indeed, it suggests that facial selectivity for cyclopentadiene derivatives is due mainly to steric or torsional considerations.

(ii) 1,2,3,4,5-Pentachlorocyclopentadiene (49) and 1,2,3,4,5-Pentachloro-5-methyl-1,3-cyclopentadiene (50).

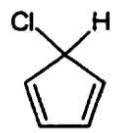


49

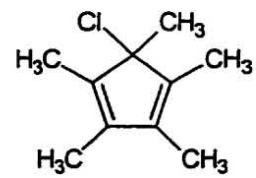


50

These dienes were prepared in order to develop more systematic experimental results for chlorine-substituted dienes. This work was conducted in conjunction with other research from our laboratory which examined the facial selectivity of 5-chloro-1,3-cyclopentadiene (**51**) and 5-chloro-1,2,3,4,5-pentamethyl-1,3-cyclopentadiene (**52**).[23]



51



52

Pentachlorocyclopentadiene (**49**) was first studied by Williamson 28 years ago.[25] We have re-evaluated some of the previously reported reactions, and, to complement this work with a diene electronically related to **49**, we have

assessed for the first time the facial selectivity of reactions involving the pentachloro methyl diene **50**. 1,2,3,4,5-Pentachloro-1,3-cyclopentadiene (**49**) was prepared by a procedure based on that of McBee and Smith.[46]

Hexachlorocyclopentadiene (**18**) was reduced by $SnCl_2 \cdot 2H_2O$ to give the required diene. Maintaining a temperature of approximately 35 °C during the addition of **18** to the $SnCl_2$ solution was necessary in order to obtain a reasonable yield of (**49**).

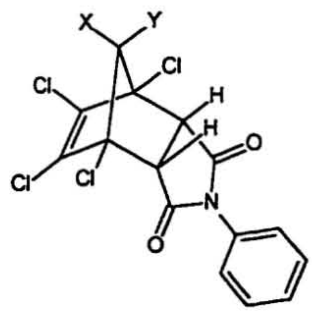
Preparation of the methyl analog **50** was carried out by deprotonation of **49** with *n*-butyllithium followed by addition of iodomethane. Diene **49** dimerizes on standing, therefore the pentachloro methyl diene was produced from freshly prepared **49**.

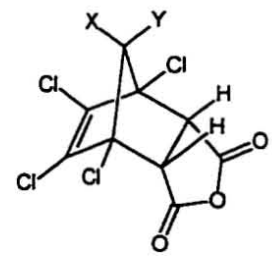
The dienes were reacted with *N*-phenylmaleimide, maleic anhydride (electron-poor, ethylenic), styrene (electron-rich, ethylenic) and 4-phenyl-1,2,4-triazoline-3,5-dione, a reactive heteroatomic dienophile that resembles NPM in its nonreacting portion. It has been implicated in step-wise processes that resemble Diels-Alder reactions.[6b]

In order to compare our results fairly with those of Williamson and co-workers,[25] maleic anhydride (MA) and styrene were also used as dienophiles. The Diels-Alder reactions were followed by TLC or GC-MS. After the diene was mostly consumed, the solvents were evaporated from the reaction mixtures. The adduct ratios were determined by careful integration of the ^{1}H NMR spectra of

these crude reaction mixtures, but in most instances it was also evident from the simplicity of these spectra that the very predominant process was the Diels-Alder reaction i.e., the degree of chemical transformation was very high. Also, every adduct (**53-57, 59, 61-63**) with the exception of **58** and **60** arose by reaction with the intended diene, not a plane-symmetric isomer resulting from a 1,5-sigmatropic rearrangement. The NMR spectra of the crude products of the reactions of **50** with NPM and with MA showed two sets of adduct signals, but the minor adducts proved to be unsymmetrical (tentatively **58** and **60**).

Adducts from NPM and MA with diene **49**:

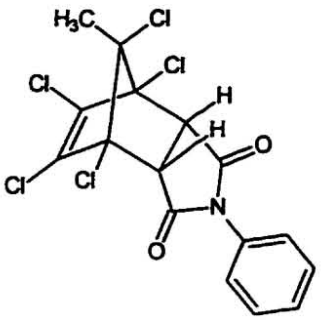




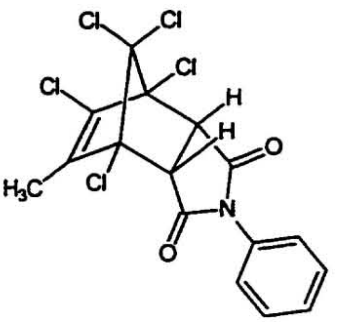
53 X=H, Y=Cl
54 X=Cl, Y=H

55 X=H. Y=Cl
56 X=Cl, Y=H

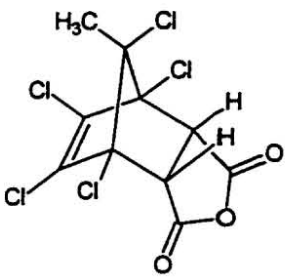
Adducts from NPM and MA with diene **50**:



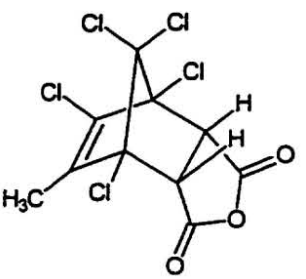
57



58

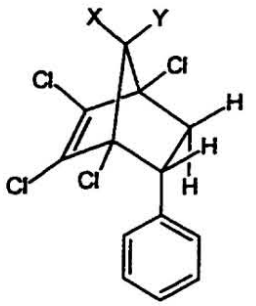


59



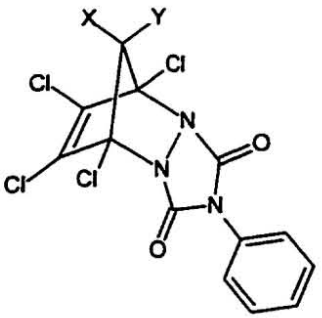
60

Adducts from styrene with dienes **49** and **50**:



61 X=H, Y=Cl
62 X=Cl, Y=H
63 X=Cl, Y=CH_3
64 X=CH_3, Y=Cl

Adducts from PTAD with dienes **49** and **50**:

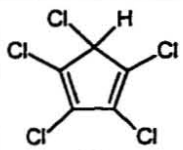
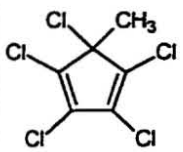


65 X=H, Y=Cl
66 X=Cl, Y=H
67 X=Cl, Y=CH_3
68 X=CH_3, Y=Cl

Facial selectivities for the dienes **49** and **50** are summarized in Table 6. Some effort was made to obtain a sample of each adduct in a form that was homogeneous by NMR. Therefore, almost every adduct mixture was subjected to flash chromatography. This was successful in all cases with exception of the

maleic anhydride adducts. Hydrolysis to give the corresponding diacid occurred on TLC and in solution. Therefore, purification of these adducts was done by careful recrystallization using dry solvents.

Table 6. Relative amounts (%) of the *anti* to Cl adducts from the reactions of diene **49** and diene **50** with various dienophiles.

diene	dienophile			
	NPM	MA	styrene	PTAD
 **49**	42%	37%	67%	78%
 **50**	0%	0%	25%	81%

For many adducts, the relative stereochemistry was determined by measurement of NOE's in the ^{1}H NMR spectra of the homogeneous adducts. Nevertheless, single-crystal X-ray structure determinations were performed on two adducts for which NOE's were impossible, those two being adducts **66** and **67**. For the adducts from NPM and MA with **50**, the negligible NOE results were taken as evidence that the major adducts resulted from addition *syn* to the chlorine atom. An effort was also made to verify that adduct ratios were the result of kinetically controlled processes. Isolated adducts were heated for long

periods at or above the temperatures used for their formation. Only the adducts from PTAD exhibited equilibration behavior under these conditions. Their kinetic adduct ratios were determined by monitoring their formation by ^{1}H NMR spectroscopy as soon as the diene and dienophile had been combined in an NMR tube with $CDCl_3$ as the solvent. For both dienes, the consumption of diene was complete in less than 1 hour.

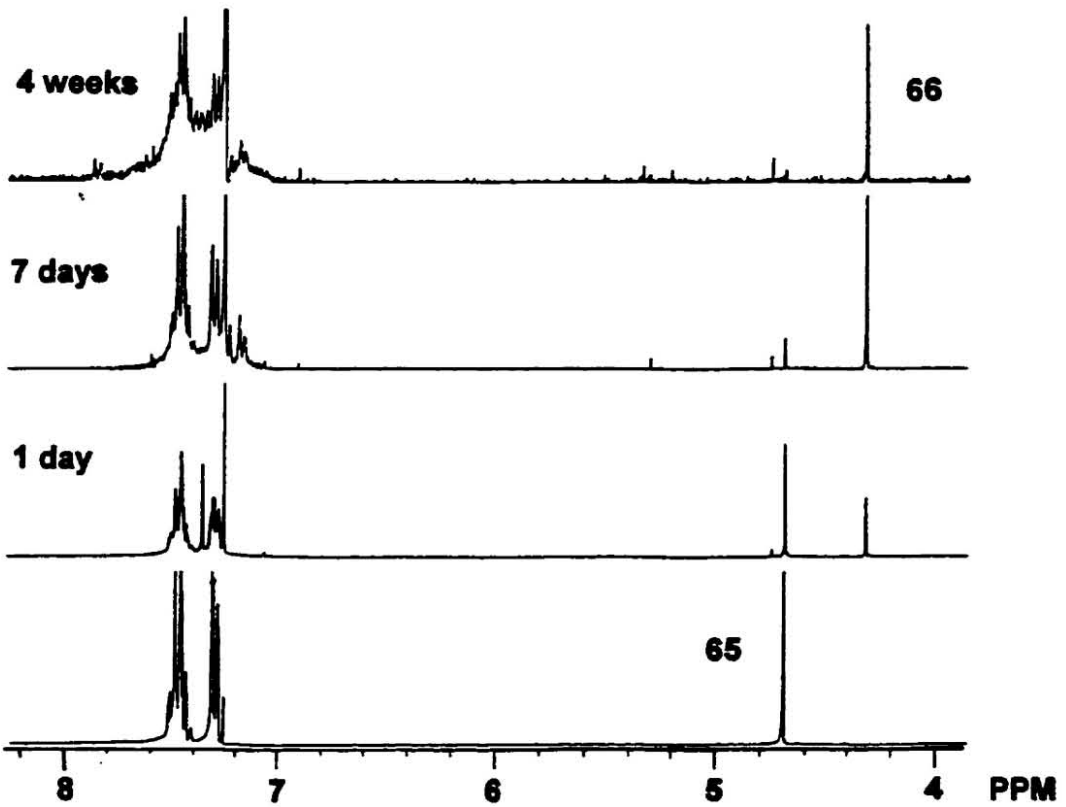


Figure 15. Equilibration of the adducts from diene **49** and PTAD in refluxing benzene

In the Diels-Alder reactions of the 1,3-cyclopentadiene derivatives there must be a steric interaction between the incoming dienophile and the *syn*-substituent at C-5 of the diene, but the computational work by Burnell, Poirier and co-workers[39] suggested that the facial selectivity comes from the energy required to deform the addends into their transition state geometries. It seems that at the transition state the steric hindrance has been translated largely into this deformation because the calculations indicated very little interaction energy (between the dienophile and the diene) at the transition state. Thus, they propose that, with 5-substituted-1,3-cyclopentadienes, facial selectivity can be traced back mainly to the difference in the magnitudes of the dienophile-diene steric interactions, *syn versus anti*. If the reason for the facial selectivity was largely steric, then the pentachlorodiene **49** should react with selectivity similar to that of 5-chloro-1,3-cyclopentadiene (**51**) (21% *anti* to Cl).[23] The selectivity that Williamson[25] reported for the reaction of **49** with MA was 9% *anti* to chlorine **56**, which was significantly more selective than the reaction of **51**. However, in our hands, **49** with MA and NPM showed selectivity more like that of 5-chloro-1,3-cyclopentadiene (**51**). Our results were similar to the selectivity Williamson gave for **49** with another ethylenic dienophile, 1,4-benzoquinone (40% *anti* to chlorine adduct), and we conjecture that the slight attenuation of selectivity of **49** relative to **51** was due to the necessity of reacting **49** at higher temperatures or the fact that in the transition state for *syn* to chlorine addition with **49** the C-5

chlorine must become coplanar with four other chlorines, whereas in **51** the C-5 chlorine becomes coplanar with hydrogens, as shown in Figure 16.

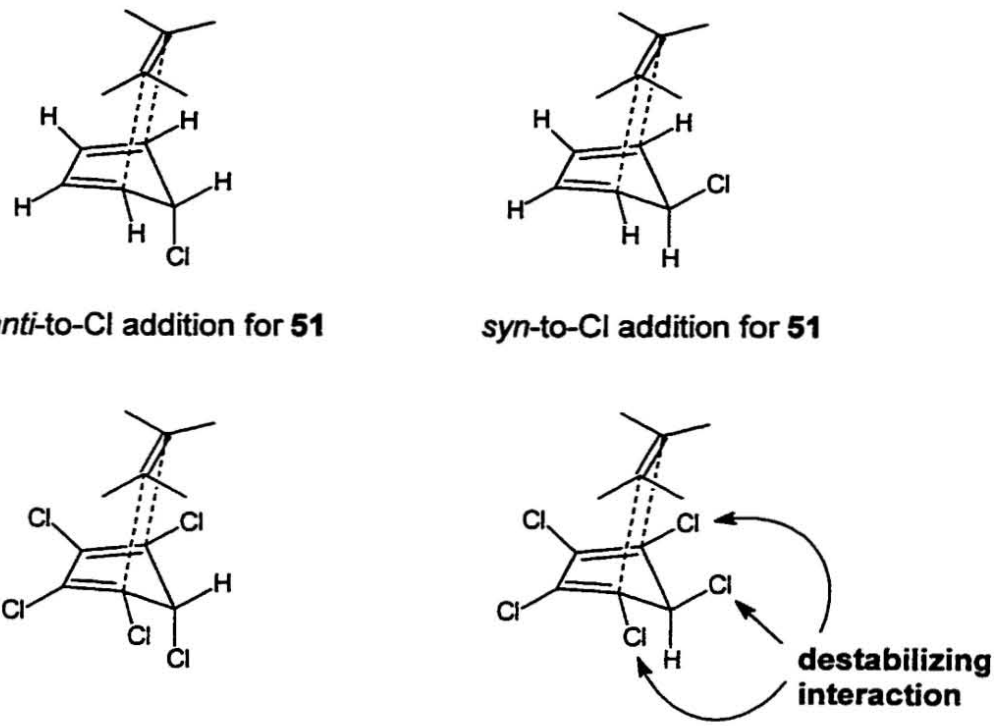


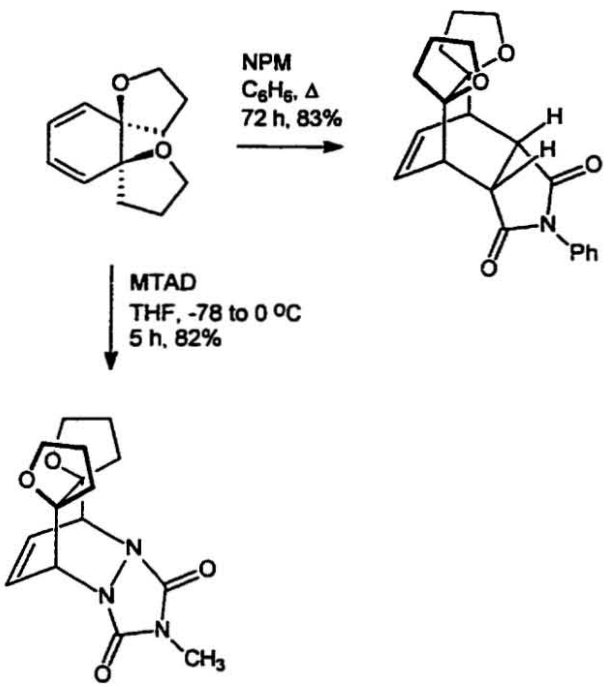
Figure 16. Transition states for 5-chloro *versus* pentachloro dienes

We noticed that, after removal of the reaction solvent, the MA adducts **55** and **56** were sparingly soluble in $CDCl_3$. Hence, the ratio reported previously by Williamson may have been colored by the relative solubilities of the adducts. With PTAD, little steric hindrance toward a *syn*-chlorine was expected, but its

reaction with **49** suggested otherwise because its major adduct **66** was the result of *anti*-addition. The reason for this behavior became apparent from the reaction of **50**, in which a C-5 chlorine was pitted against a methyl group. 1,2,3,4,5-Pentamethyl-1,3-cyclopentadiene (**52**) adds dienophiles mainly to its sterically less hindered face, *anti* to its C-5 methyl.[47]

Diene **49** adds to electron-poor ethylenic dienophiles *syn* to chlorine. In the case of CH_3 versus H, the addition *syn* to H is favored, and for H *versus* Cl, the addition *syn* to Cl is favored, so it follows that in the Cl *versus* CH_3 for diene **50**, addition *syn* to Cl should prevail. This is indeed the case since diene **50** adds NPM and MA exclusively *syn* to chlorine. The PTAD, however, which should not provide a great amount of steric hindrance would be expected to behave similarly and give addition *syn* to Cl in the addition with diene **50**. This was not the experimental result. Instead PTAD added 81% *anti* to the chlorine of **50** giving compound **67** as the major adduct. From these results it was inferred that the reactions of PTAD were also affected by a second phenomenon, which was not steric hindrance. The possibility of an attractive interaction between the C-5 hydrogen of **49** and a nitrogen lone-pair from PTAD, which might have enhanced *anti*-addition, was ruled out because in **50** the C-5 hydrogen had been replaced by a methyl group. What was consistent with these observations was either a destabilizing electrostatic interaction in the *syn* transition state, as might have been expected with a more ionic, less concerted mechanism,[6b] or a

filled-orbital repulsion of the type postulated by Coxon *et al.*[48] Paquette *et al.*[31d] reported similar findings with some dispiro[4.0.4.4]tetradec-11,13-dienes (Scheme 13).



Scheme 13.

The addition of NPM and other ethylenic electron-poor dienophiles occurred *syn* to the oxygen atoms as we have also reported for the polychlorinated diene. The heteroatomic dienophile 4-methyl-1,2,4-triazoline-3,5-dione (MTAD), however, gave addition exclusively *anti* to the oxygen atoms. Paquette in his conclusion supports the idea of a non-concerted mechanism[6] to explain the MTAD Diels-Alder reactions.

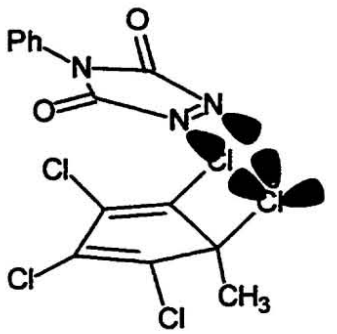
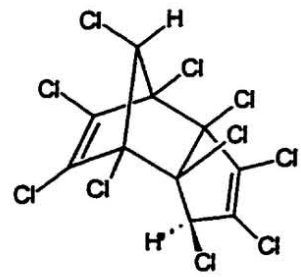


Figure 17. Repulsion of lone-pair orbitals on PTAD and diene **50**

The behavior of **49** and **50** with styrene suggested that the filled-orbital explanation was more plausible. In contrast with the symmetrical dienophiles, styrene, which must react via an unsymmetrical transition state that also is likely to be asynchronous, reacted with **49** (via an *endo* transition state) mainly by *anti*-addition to give **62**. Nevertheless, styrene gave only 25% *anti*-adduct **63** with **50**, completely in accord with an increase in the steric hindrance on the *anti* face. The same trend might have been expected if the selectivity with PTAD were the result of an asynchronous process.

The dimerization of **49** gave only one adduct, **69**, which was the result of addition of both the diene and dienophile partners by their *anti* faces. This result is opposite to that of the addition of other dienophiles to pentachlorocyclopentadiene.[23, 25] Obviously, in this case some other factor is affecting the facial selectivity. Computational work, prompted by this result, is currently underway.

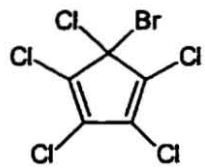


69

A steric factor is defined as a steric interaction between the diene and dienophile which determines the facial selectivity. Therefore, any rationalization for facial selectivity based on steric hindrance must take into account both the "size" of the substituents, and the geometry. There are several empirical measures of size (e.g., *A*-values and van der Waals radii), but all have failings. For these Diels-Alder reactions, using *A* values as a measure of steric hindrance would lead to poor correlation with facial selectivity, because the geometry[39] of these Diels-Alder reactions is very different from that of axial substituents on cyclohexane. Simple van der Waals radii of the substituents do correlate with facial selectivity, with the exception of hydrogen. Hydrogen seems to exert a steric presence larger than its van der Waals radius would suggest, but the steric hindrance provided by a C-H bond, *which uniquely involves an sp³- to s linkage*, may be more than a match for carbon bonds to the atoms that give *syn*-adducts, *viz.* C-F,[24],C-O,[18, 19, 49] C-N,[20] and , as we have shown, C-Cl. Prompted by the results reported here, high-level *ab initio* methods have been used to investigate

the steric influences of these bonds in the Diels-Alder reaction as well as to clarify the source of PTAD's *anti*-directing factor. The computational work by Burnell, Poirier *et al.*[50] determined that the C5–X bond of a 5-substituted 1,3-cyclopentadiene, as well as the substituent X plays a role in the outcome of facial selectivity in the Diels-Alder reaction. A computed steric factor derived from the size and relative position of the centroid of charge of the C5–X bond, is in excellent agreement with the calculated facial selectivities, which in turn are in good agreement with experiment. For example, in the case of Cl *versus* CH_3 the steric factor takes into account the similarity of substituent size, the longer C5–Cl bond and the position of the centroid of charge closer to Cl. These considerations predicted that Cl is "smaller" than CH_3 resulting in preferential addition *syn* to chlorine. The calculations also suggested that for dienophiles such as PTAD with lone-pairs on the reacting centers, the orientation of lone-pairs on the substituent of the diene becomes important.

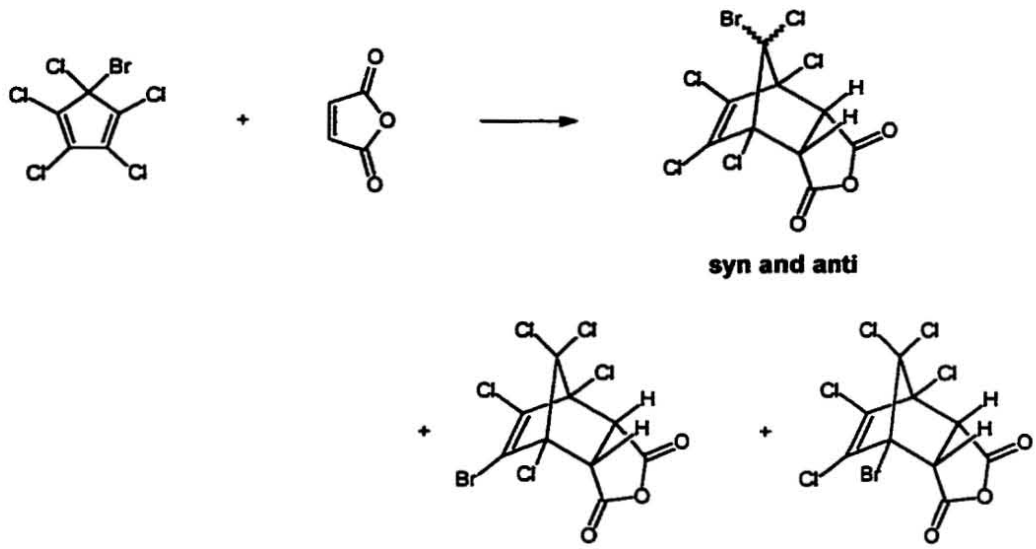
(iii) 5-Bromo-1,2,3,4,5-pentachloro-1,3-cyclopentadiene (70).



70

Diels-Alder reactions of diene **70** had been previously examined by Williamson[25] and Shestakova *et al.*[51] Neither of these studies gave satisfactory facial selectivity results. Shestakova *et al.* reacted diene **70** with a variety of dienophiles, but they were unable to assign unequivocally the stereochemistry of the resulting adducts. Since we had ready access to X-ray crystallography, it was decided to reinvestigate the facial selectivity of Diels-Alder reactions with diene **70**.

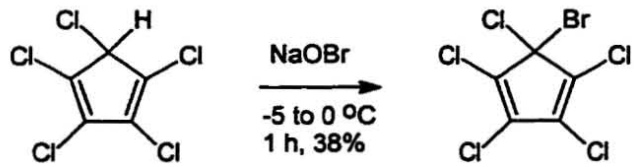
This diene was prepared from freshly distilled 1,2,3,4,5-pentachloro-1,3-cyclopentadiene (**49**). The anion of **49** derived by deprotonation with *n*-butyllithium was treated with a solution of *N*-bromosuccinimide in THF. The product was an orange oil obtained in approximately 80% yield after chromatography. Williamson[25] also attempted to produce this diene and study its facial selectivity. However, he reported that upon reacting the diene with MA, adducts from 1,5-sigmatropic rearrangement of the diene as well as the desired *syn* and *anti* adducts were observed (Scheme 14).



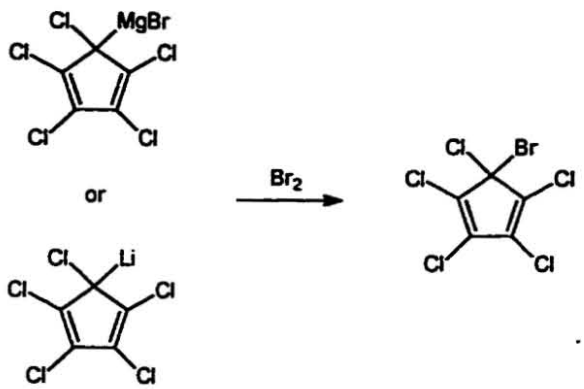
Scheme 14.

He concluded that the diene was thermally unstable, and that the isomerization had occurred during the Diels-Alder experiment. We have not found any evidence of this isomerization during the course of our Diels-Alder reaction since no unsymmetrical adducts were detected.

Shestakova and co-workers[52] prepared diene **70** in 1981 via the following two reactions (Scheme 15):



Scheme 15.

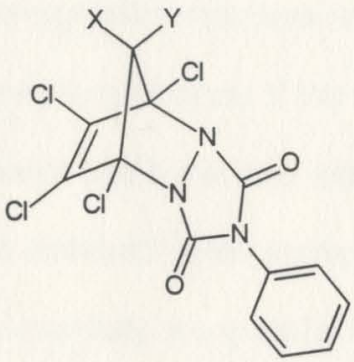


Scheme 15. Continued.

Both methods make it possible to obtain diene **70** in yields ranging between 30-60 %. Our method utilizing NBS gives a better yield and is simpler experimentally compared to the Grignard and organolithium methods. The Russian group reacted diene **70** with various dienophiles,[51] but did not detect unsymmetrical adducts. They concluded that the 1,5-sigmatropic isomers reported by Williamson must have been present in Williamson's starting diene sample as opposed to being produced thermally during the Diels-Alder reaction. Our findings are in agreement that the diene **70** is thermally stable with respect to 1,5-sigmatropic isomerization.

The diene **70** was reacted with a range of dienophiles: *N*-phenylmaleimide and 1,4-naphthoquinone (ethylenic, electron-poor), vinylene carbonate, styrene and 3-nitrostyrene (ethylenic, electron-rich), and 4-phenyl-1,2,4-triazoline-3,5-dione, a heteroatomic dienophile.

Adducts from PTAD:



81 X=Br, Y=Cl
82 X=Cl, Y=Br

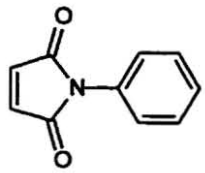
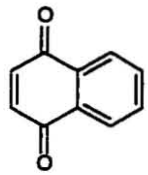
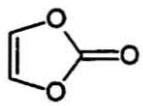
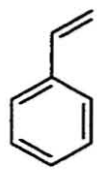
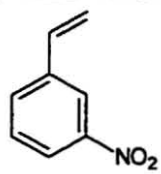
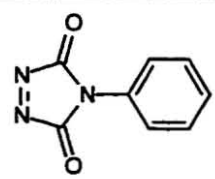
In an attempt to obtain a homogenous sample of each adduct, the crude reaction mixtures were subjected to flash chromatography followed by recrystallization. The only products that were not purified in this way were from diene **70** and vinylene carbonate (due to the instability of these adducts on silica gel, the crude reaction mixture was sublimed and recrystallized). Neither chromatography nor sublimation separated the *syn* and *anti* isomers from any reaction of **70**. Adducts eluted (or sublimed) together, so spectral data were obtained from mixtures.

The adduct ratios were determined by careful integration of the ^{1}H NMR spectra of the crude reaction mixtures, except for adducts **81** and **82** from PTAD. In this case a ratio was determined by integration of an inverse-gated ^{13}C NMR spectrum. The signals for the bridgehead carbons of the major and minor adducts were sufficiently separated to allow such an integration. For the

unequivocal assignment of the stereochemistry, the use of NOE measurements was impossible, therefore, the crystalline mixtures were submitted for X-ray crystallography. Not only were the structures of the major adducts determined in this way, but the relative amounts of the *syn* and *anti* adducts were also confirmed. These ratios were obtained crystallographically by modelling both atoms on the apical carbon as partially occupied by bromines. The approximate adduct ratios were calculated from the levels of bromine occupancy that gave the best refinement (R and R_w). The NMR percentages were determined from the crude adduct mixtures whereas the X-ray percentages applied usually to samples purified by chromatography and recrystallization. Nevertheless, a surprising level of agreement was obtained by both methods. Table 7 gives a summary of the adduct ratios obtained by NMR methods and the corresponding ratios obtained by X-ray analysis.

For the reaction of diene **70** with vinylene carbonate, there was also some adduct produced from reaction of the dienophile with hexachlorocyclopentadiene (**18**). The crude sample contained *syn*, *anti* and hexachloro adducts in a ratio of 1:7.4:3.7. This was a very curious occurrence since the sample of diene **70** did not seem to be contaminated by hexachlorocyclopentadiene (**18**) (by ^{13}C NMR and GC-MS). It is possible that the hexachlorocyclopentadiene was being produced by some free radical mechanism.

Table 7. Proportions of the *anti* (to Br) adduct (%) with diene **70** as determined by NMR and X-ray methods.

dienophile	*anti* to Br by NMR	*anti* to Br by X-ray analysis
	92%	90%
	89%	95%
	88%	96%
	94%[a]	95%
	94%[a]	——
	82%	85%

a. Ratios from samples purified by chromatography.

Chloro-1,3-cyclopentadiene (**51**) prefers addition *syn* to Cl with ethylenic dienophiles such as NPM and NQ.[23] In the case of bromo-1,3-cyclopentadiene, addition *syn* to H is preferred.[23] Hence, if facial selectivity is due only to steric interactions, H must exert more steric hindrance than Cl, and Br must exert more steric hindrance than H. It follows that Br must present more steric hindrance than Cl. In light of the hypothesis by Burnell and Poirier,[39] which states that facial selectivity is a result of the difference in the magnitudes of dienophile-diene interactions rather than electronic factors, the facial preference for addition to 1,3-cyclopentadiene in a normal-electron-demand sense should be the same as for inverse-electron-demand polychlorinated 1,3-cyclopentadiene. For the ethylenic, electron-poor dienophiles NPM and NQ this was indeed the case, as seen in Table 7. If steric interactions are the deciding factor for facial selectivity in Diels-Alder reactions, then an ethylenic, electron-rich dienophile such as vinylene carbonate should behave similarly to NPM and NQ. The experimental results indicate this is so. Vinylene carbonate prefers addition *anti* to bromine. The addition *anti* to Br also applies to the styrenes, which are unsymmetrical ethylenic, electron-rich dienophiles.

For PTAD, as previously discussed, it was expected that the interactions of lone-pairs on the diene and dienophile might influence the facial selectivity. Diene **70** presents lone-pair bearing substituents on both faces so this may explain the slightly lower selectivity with PTAD as a dienophile.

Williamson[25] was interested in studying the behavior of diene **70** to test his hypothesis that facial selectivity is influenced by van der Waals/London type forces. For his results of Diels-Alder reactions with pentachlorocyclopentadiene (**49**), he proposed that chlorine, having a greater polarizability than hydrogen, would be favored for *syn* additions with dienophiles having the largest dipole moments. Since bromine has a greater polarizability than chlorine, he expected preferential reaction *syn* to bromine when chlorine was the competing atom. We have shown experimentally that this is not the case, therefore, the dipole-dipole theory of Williamson does not apply to facial selectivity in these Diels-Alder reactions.

The Cieplak theory[35] involving addition *anti* to the better σ-donor also fails to explain the facial selectivity shown by diene **70**. The C-Cl bond is considered to be a better donor than C-Br.[37] Therefore, by Cieplak's estimation, addition *syn* to Br should be preferred. This is not the case for our results or probably for those of Shestakova *et al.*,[51] despite their failure to assign unequivocally *syn/anti* stereochemistry to the adducts.

We conclude that these results for the addition of diene **70** to various dienophiles support the idea that facial selectivity derives from the energy required to deform the addends into their transition state geometries.[39] This translated into facial selectivity in the Diels-Alder reaction as a result of steric interactions between diene and dienophile.

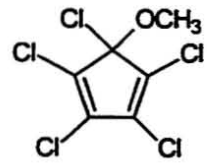
IV. Experimental

General methods

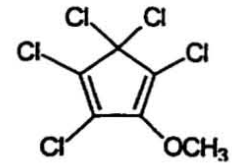
1,4-Naphthoquinone (NQ) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)[42] were purified by sublimation under vacuum. *N*-Phenylmaleimide (NPM) was recrystallized from cyclohexene. All reactions were performed under an atmosphere of nitrogen or argon. Adducts were usually purified by flash chromatography on silica gel with elution by hexane or petroleum ether containing an increasing proportion of ethyl acetate or diethyl ether and then by crystallization. Reaction work-up normally consisted of washing the organic phase with brine and water followed by drying of the organic solution with anhydrous $MgSO_4$. "Ether" refers to diethyl ether. IR spectra (cm^{-1}) were recorded as casts using a Mattson FT-IR instrument. Nuclear magnetic resonance (NMR) spectra were obtained in $CDCl_3$ solution unless otherwise noted, on a General Electric GE 300-NB (300 MHz) instrument; chemical shifts (δ) are relative to internal standards: tetramethylsilane (TMS) for ^1H and the $CDCl_3$ solvent (δ77.0) for ^{13}C NMR. Coupling constants (*J*) are in Hz; *apparent* multiplicities are reported here because in many instances the signals are second order. NOE measurements were on thoroughly degassed $CDCl_3$ solutions. NOE data were obtained from sets of interleaved ^1H experiments (16K) of 8 transients, cycled 12-16 times through the list of irradiated

frequencies. The decoupler was gated on in CW mode for 6 s with sufficient attenuation to give a 70-90% reduction in intensity of the irradiated peak. Frequency changes were preceded by a 60 s delay. Four scans were used to equilibrate spins before data acquisition, but a relaxation delay was not applied between scans at the same frequency. The NOE difference spectra were obtained from zero-filled 32K data tables to which a 1-2 Hz exponential line-broadening function had been applied. NOE data take this form: saturated signal (enhanced signal, enhancement). Mass spectral data were from a V.G. Micromass 7070HS instrument and take the form: *m/z* (% of largest peak). A Hewlett-Packard system (5890 gas chromatograph coupled to a 5970 mass selective detector) equipped with a Hewlett-Packard 12.5-metre fused-silica capillary column with cross-linked dimethylsilicone as the liquid phase was used for gas chromatography-mass spectrometry (GC-MS). Melting points (mp) were determined on a Fisher-Johns melting point apparatus and were uncorrected. Solvents were distilled or were of ACS-grade quality. For X-ray crystallography, all measurements were made by Dr. John N. Bridson or Mr. David O. Miller on a Rigaku AFC6S diffractometer with graphite-monochromated Mo-K_α or Cu-K_α radiation.

1,2,3,4,5-Pentachloro-5-methoxy-1,3-cyclopentadiene (16).



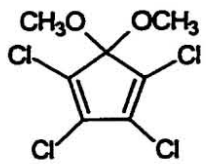
16



19

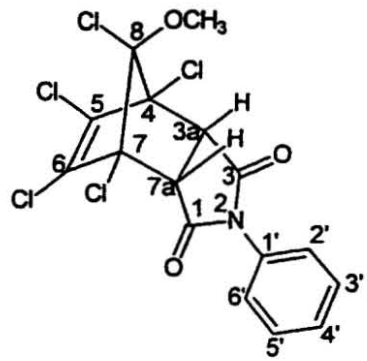
A solution of hexachlorocyclopentadiene (**18**) (6.8 g, 25 mmol) in dry THF (5.0 mL) was added at rt over 1 h to a solution of KOH (1.0 g, 18 mmol) in methanol (0.79 g, 25 mmol) and dry THF (5.0 mL). Stirring was continued for 3 h. The mixture was concentrated under vacuum, and the residue was taken up in CH_2Cl_2. The organic solution was washed with brine, dried and concentrated under vacuum to give an orange oil. Flash chromatography (elution with hexane) provided (300 mg, 6%) of a yellow oil, which was a 1.5:1 mixture (by GC-MS) of **16** and **19**, respectively. For **16**: ^{1}H NMR: δ 3.61 (s). ^{13}C NMR: δ 130.5, 128.8, 98.4, 54.6. MS (GC-MS): 272 (1), 270 (5), 268 (10) and 266 (5) all M^+, 237 (10), 236 (2), 235 (49), 234 (10), 233 (100), 232 (5), 231 (79), 221 (1), 220 (40), 219 (5), 218 (80), 217 (2), 216 (60), 194 (8), 192 (30), 191 (2), 190 (84), 189 (1), 188 (52), 185 (9), 183 (28), 181 (29), 171 (2), 169 (11), 168 (2), 167 (20), 165 (10), 159 (1), 157 (14), 155 (43), 154 (1), 153 (44), 122 (8), 121 (1), 120 (48), 119 (2), 118 (73), 85 (10), 83 (26). For **19**: ^{1}H NMR: δ 4.21 (s). ^{13}C NMR: δ 59.5.

1,2,3,4-Tetrachloro-5,5-dimethoxy-1,3-cyclopentadiene (17).[41]



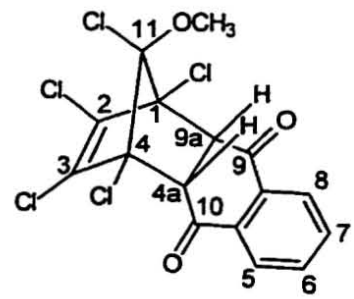
To hexachlorocyclopentadiene (**18**) (1.87 mL, 11.7 mmol) was added a solution of KOH (2.3 g, 41 mmol) in methanol (10 mL) over 15 min. This mixture was stirred at rt for 2.5 h. The methanol was removed under vacuum, and the residue was taken up in ether. This was washed with water and brine, then dried over anhydrous $MgSO_4$ to give a yellow oil after evaporation of the solvent. Flash chromatography (elution with 2% ethyl acetate-hexane) provided **17** as a yellow oil (2.43 g, 79%): IR: 1613, 1212 cm^{-1}. ^1H NMR: δ 3.35 (s). ^{13}C NMR: δ 129.2, 128.4, 104.6, 51.7. MS (GC-MS): 268 (5), 267 (2), 266 (24), 265 (4), 264 (49), 263 (3) and 262 (45) all M^+, 253 (5), 252 (2), 251 (22), 250 (3), 249 (45), 248 (1), 247 (35), 237 (5), 236 (2), 235 (21), 234 (5), 233 (47), 232 (7), 231 (66), 230 (9), 229 (99), 228 (10), 227 (100), 223 (22), 221 (47), 220 (34), 219 (39), 218 (67), 217 (60), 214 (37), 213 (3), 212 (37), 194 (3), 192 (13), 190 (26), 188 (21), 183 (21), 181 (22), 155 (26), 153 (24), 118 (37), 83 (16).

(3aα,4β,7β,7aα,8*s*)-4,5,6,7,8-Pentachloro-3a,4,7,7a-tetrahydro-8-methoxy-2-phenyl-4,7-methano-(2*H*)-isoindole-1,3-dione (20).



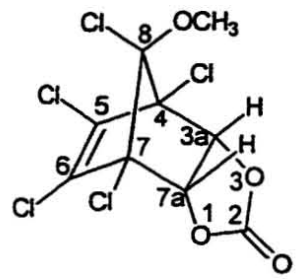
A solution of diene **16** (0.095 g, 0.35 mmol) and *N*-phenylmaleimide (0.093 g, 0.53 mmol) in a 10:1 mixture of CCl_4 and CH_2Cl_2 (11 mL) was heated at reflux for 21 h. The solution was concentrated under vacuum to give a yellow oil. Flash chromatography followed by crystallization from acetone-hexane gave **20** (0.050 g, 32%) as colorless crystals: mp: 223-224 °C. IR: 1721, 1202 cm^{-1}. ^1H NMR: δ 7.51-7.38 (3H, m, C-3'H, C-4'H, C-5'H), 7.14 (2H, m, C-2'H, C-6'H), 3.88 (2H, s, C-3aH, C-7aH), 3.86 (3H, s, OCH_3). ^{13}C NMR: δ 169.9 (C=O), 130.8 (Ar), 130.3 (C-5, C-6), 129.4 (Ar), 129.3 (Ar), 126.4 (Ar), 117.2 (C-8), 77.7 (C-4, C-7) , 55.7 (OCH_3), 51.7 (C-3a, C-7a). MS: 445 (1), 443 (3), 441 (5) and 439 (3) all M^+, 410 (11), 409 (8), 408 (49), 407 (16), 406 (100), 405 (13), 404 (69), 261 (30), 259 (59), 257 (46), 209 (19), 207 (20), 119 (28), 91 (16), 63 (20). HRMS calcd for $C_{16}H_{10}{}^{35}Cl_3{}^{37}ClNO_3$ (M^+ - Cl): 405.9385; found: 405.9396. Anal. calcd for $C_{16}H_{10}Cl_5NO_3$: C, 43.53; H, 2.28; N, 3.17. Found: C, 43.56; H, 2.30; N, 3.20. This structure was determined by X-ray crystallography.

(1α,4α,4aβ,9aβ,11s)-1,2,3,4,11-Pentachloro-1,4,4a,9a-tetrahydro-11-methoxy-1,4-methanoanthracene-9,10-dione (21).



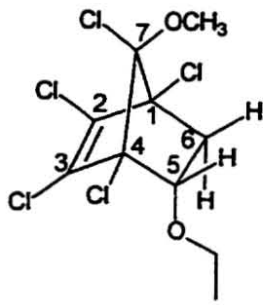
A solution of diene **16** (0.063 g, 0.24 mmol) and 1,4-naphthoquinone (0.041 g, 0.26 mmol) in benzene (10 mL) was heated at reflux for 3 days. Flash chromatography (elution with 10% ethyl acetate-hexane) followed by crystallization from 5:1 hexane-ethyl acetate gave **21** as colorless crystals (30 mg, 29%): mp: 201-202 °C. IR: 1686, 1603, 1203 cm^{-1}. ^1H NMR: δ 8.02 (2H, m, C-5H, C-8H), 7.77 (2H, m), 3.92 (2H, s, C-4aH, C-9aH), 3.88 (3H, s, C-11 OCH_3). ^{13}C NMR: δ 190.1 (C-9, C-10), 135.3 (C-6, C-7), 134.9 (Ar), 130.6 (C-2, C-3), 127.2 (C-5, C-8), 114.7 (C-11), 80.3 (C-1, C-4), 55.6 (OCH_3), 55.1 (C-4a, C-9a). MS: 428 (2), 426(3) and 424 (2) all M^+, 395 (7), 394 (5), 393 (31), 392 (11), 391 (67), 390 (9), 389 (48), 261 (24), 259 (46), 257 (38), 209 (13), 207 (14), 167 (14), 104 (100), 76 (59), 50 (20). HRMS calcd for $C_{16}H_9{}^{35}Cl_3{}^{37}ClO_3$ (M^+ - Cl): 390.9276; found: 390.9264. Anal. calcd for $C_{16}H_9Cl_5O_3$: C, 45.06; H, 2.13. Found: C, 45.16; H, 2.26. This structure was determined by X-ray crystallography.

(3aα,4β,7β,7aα,8s)-4,5,6,7,8-Pentachloro-3a,4,7,7a-tetrahydro-8-methoxy-4,7-methano-1,3-benzodioxol-2-one (22).



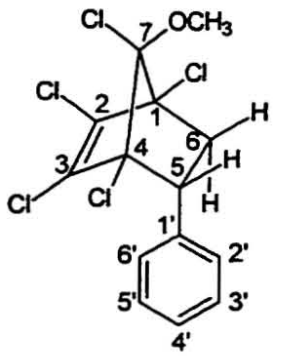
A solution of diene **16** (0.059 g, 0.22 mmol) and vinylene carbonate (0.190 g, 2.20 mmol) in toluene (6.0 mL) was heated at reflux for 8 days. The solution was concentrated under vacuum, and the brown oily residue was filtered through a plug of silica to give an orange oil, which crystallized upon standing at rt.[53] Recrystallization from ethyl acetate-hexane provided **22** as colorless crystals (0.012 g, 15%): mp: 110-111 °C. IR: 1827, 1803, 1604 cm^{-1}. ^1H NMR: δ 5.25 (2H, s, C-3aH, C-7aH), 3.79 (3H, s, OCH_3). NOE data: 5.25 (3.79, 2%), 3.79 (5.25, 5%). ^{13}C NMR: δ 151.7 (C-1, C-3), 130.2 (C-5, C-6), 114.2 (C-8), 83.0 (C-3a, C-7a), 79.2 (C-4, C-7), 55.8 (OCH_3). MS: 356 (1), 354 (2) and 352 (1) all M^+, 323 (11), 322 (5), 321 (49), 320 (10), 319 (100), 318 (8), 317 (79), 268 (8), 233 (18), 231 (15), 91 (56). This structure was determined by X-ray crystallography.

(1*R,4*S**,5*S**,7*R**)-1,2,3,4,7-Pentachloro-5-ethoxy-7-methoxybicyclo[2.2.1] hept-2-ene (23).**



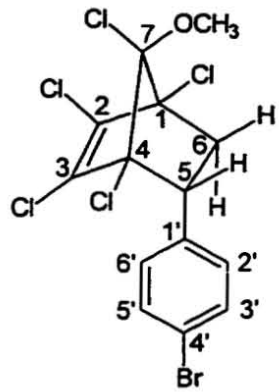
A solution of diene **16** (0.064 g, 0.24 mmol) in ethoxyethylene (8.0 mL) was heated at reflux for 3 days. Concentration of the solution under vacuum followed by flash chromatography (elution with 1% ethyl acetate-hexane) gave **23** as a yellow oil (36 mg, 44%). IR: 3018, 2982, 2954, 1610 cm^{-1}. ^1H NMR: δ 4.36 (1H, dd, *J* = 2.2, 7.5 Hz, C-5H), 3.80 (1H, m, OCH_2CH_3), 3.74 (3H, s, C-7 OCH_3), 3.58 (1H, m, OCH_2CH_3), 2.70 (1H, dd, *J* = 7.5, 12.1 Hz, C-$6H_{exo}$), 1.90 (1H, dd, *J* = 2.2, 12.1 Hz, C-$6H_{endo}$), 1.16 (3H, t, *J* = 7.0 Hz, OCH_2CH_3). NOE data: 4.36 (3.74, 1%; 2.70, 7%), 2.70 (4.36, 12%; 3.74, 2%; 1.90, 21%). ^{13}C NMR: δ 130.9, 129.5 (C-2, C-3), 115.5 (C-7), 83.8 (C-5), 81.3, 76.7 (C-1, C-4), 67.0 (OCH_2CH_3), 54.8 (C-7 OCH_3), 43.5 (C-6), 15.3 (OCH_2CH_3). MS: 344 (4), 342 (13), 341 (2), 340 (19) and 338 (12) all M^+, 307 (4), 305 (9), 303 (7), 233 (26), 231 (21), 216 (19), 214 (37), 212 (100), 211 (17), 210 (100), 93 (46), 79 (59), 61 (52), 29 (72). HRMS calcd for $C_{10}H_{11}{}^{35}Cl_4{}^{37}ClO_2$: 339.9171; found: 339.9171.

(1*R,4*S**,5*R**,7*R**)-1,2,3,4,7-Pentachloro-7-methoxy-5-phenylbicyclo[2.2.1] hept-2-ene (24).**

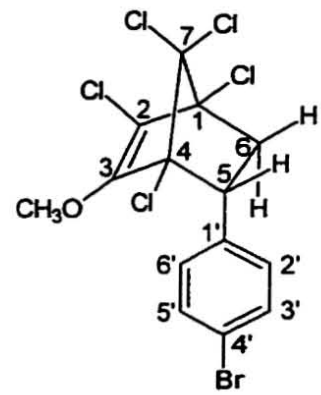


A solution of diene **16** (0.093 g, 0.35 mmol) and styrene (0.035 g, 0.35 mmol) in benzene (8.0 mL) was heated at reflux for 24 h. The solvent was removed under vacuum, and flash chromatography (elution with 1% ethyl acetate-hexane) gave **24** as a pale yellow, crystalline solid (39 mg, 31%): mp: 65-67 °C. IR: 3033, 2952, 2849, 1606, 1456, 1204 cm^{-1}. ^1H NMR (CD_3COCD_3): δ 7.39-7.29 (3H, m, C-3'H, C-4'H, C-5'H), 7.17 (2H, m, C-2'H, C-6'H), 4.00 (1H, dd, *J* = 4.2, 9.2 Hz, C-5H), 3.89 (3H, s, C-7 OCH_3), 2.94 (1H, dd, *J* = 9.1, 12.4 Hz, C-6H_{exo}), 2.52 (1H, dd, *J* = 4.2, 12.4 Hz, C-6H_{endo}). NOE data: 2.94 (4.00, 6%; 3.89, 2%; 2.52, 18%). ^{13}C NMR (CD_3COCD_3): δ 136.1 (C-1'), 131.7, 131.1 (C-2, C-3), 129.8 (Ar), 129.1 (Ar), 128.8 (Ar), 117.6 (C-7), 83.6, 78.2 (C-1, C-4), 55.4 (OCH_3), 52.1 (C-5), 41.4 (C-6). MS: 374 (3), 372 (4) and 370 (3) all M^+, 341 (4), 340 (3), 339 (19), 338 (7), 337 (39), 336 (6), 335 (30), 299 (4), 127 (13), 125 (44), 121(16), 104 (100). HRMS calcd for $C_{14}H_{11}{}^{35}Cl_3{}^{37}ClO$ (M^+ - Cl): 336.9534; found: 336.9518.

(1*R,4*S**,5*R**,7*R**)-5-(4-Bromophenyl)-1,2,3,4,7-pentachloro-7-methoxybicyclo[2.2.1]hept-2-ene (25) and 5-(4-bromophenyl)-1,2,4,7,7-pentachloro-3-methoxybicyclo[2.2.1]hept-2-ene (30).**



25



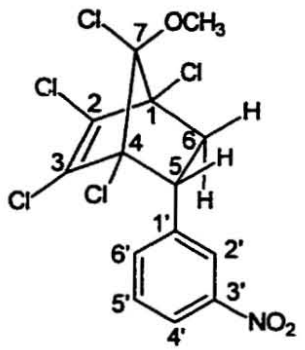
30

A solution of diene **16** (0.091 g, 0.34 mmol) and 4-bromostyrene (0.092 g, 0.50 mmol) in CH_2Cl_2 (8.0 mL) was heated at reflux for 20 h. The solvent was removed under vacuum, and flash chromatography (elution with 1% ethyl acetate-hexane) afforded **25** as a yellow oil (41 mg, 27%). Crystallization occurred after slow evaporation of C_6D_6 from the sample to give colorless crystals of **25**: mp: 99-100.5 °C. IR: 2951, 2850, 1605, 1491, 1451, 1204 cm^{-1}. ^1H NMR: δ 7.45 (2H, broad d, J = 8.5 Hz, C-3'H, C-5'H), 6.96 (2H, br d, J = 8.5 Hz, C-2'H, C-6'H), 3.86 (3H, s, OCH_3), 3.81 (1H, dd, J = 4.2, 9.1 Hz, C-5H), 2.83 (1H, dd, J = 9.1, 12.3 Hz, C-$6H_{exo}$), 2.34 (1H, dd, J = 4.2, 12.3 Hz, C-$6H_{endo}$). ^{13}C NMR: δ 134.3 (Ar), 131.5 (Ar), 131.0 (C-2 or C-3), 130.5 (Ar), 130.3 (C-2 or C3), 122.4 (C-4'), 115.9 (C-7), 82.5, 77.2 (C-1, C4), 55.1 (OCH_3), 51.2 (C-5), 41.0

(C-6). MS: 456 (1), 454 (5), 452 (11), 451 (1), 450 (10) and 448 (4) all M^+, 419 (19), 418 (8), 417 (49), 416 (11), 415 (58), 414 (6), 413 (26), 235 (12), 233 (21), 231 (15), 205 (35), 203 (27), 184 (97), 182 (100). HRMS calcd for $C_{14}H_{10}{}^{79}Br^{35}Cl_4{}^{37}ClO$: 449.8337; found: 449.8341. Anal. calcd for $C_{14}H_{10}BrCl_5O$: C, 37.25; H, 2.23. Found: C, 37.22; H, 2.23. This structure was determined by X-ray crystallography.

Yield of the less polar adduct **30**: <2 mg; colorless crystals: mp: 166-168°C. ^{1}H NMR: δ 7.49 (2H, broad d, J = 8.5 Hz, C-3'H, C-5'H), 7.05 (2H, br d, J = 8.5 Hz, C-2'H, C-6'H), 3.86 (3H, s, OCH_3), 3.83 (1H, dd, J = 4.2, 9.2 Hz, C-5H), 2.89 (1H, dd, J = 9.2, 12.7 Hz, C-6H$_{exo}$), 2.44 (1H, dd, J = 4.2, 12.7 Hz, C-6H$_{endo}$). MS: 452 (2) and 450 (6) both M^+, 417 (6), 415 (6), 272 (7), 270 (25), 268 (39), 266 (25), 251 (8), 249 (35), 247 (72), 245 (58), 236 (26), 235 (34), 234 (51), 233 (68), 232 (42), 231 (49), 205 (100), 203 (79), 184 (71), 103 (53), 77 (61). This structure was determined by X-ray crystallography.

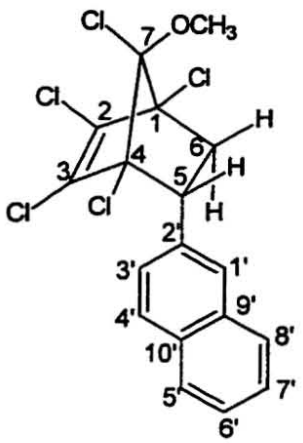
(1*R,4*S**,5*R**,7*R**)-1,2,3,4,7-Pentachloro-7-methoxy-5-(3-nitrophenyl)bicyclo [2.2.1]hept-2-ene (26).**



A solution of diene **16** (0.032 g, 0.12 mmol) and 3-nitrostyrene (0.018 g, 0.12 mmol) in benzene (10 mL) was heated at reflux for 5 days. Removal of the solvent under vacuum followed by flash chromatography (elution with 3% ethyl acetate-hexane) provided **26** as a pale yellow crystalline solid (19 mg, 38%): mp: 106-108 °C. IR: 2954, 1605, 1532, 1350, 1204 cm^{-1}. ^1H NMR (CD_3COCD_3): δ 8.24 (1H, dt, *J* = 7.1, 2.1 Hz, C-2'H), 8.10 (1H, narrow m, C-4'H), 7.74-7.65 (2H, m, C-5'H, C-6'H), 4.27 (1H, dd, *J* = 4.2, 9.1 Hz, C-5H), 3.92 (3H, s, OCH_3), 3.05 (1H, dd, *J* = 9.1, 12.6 Hz, C-6H_{exo}), 2.67 (1H, dd, *J* = 4.2, 12.6 Hz, C-6H_{endo}). NOE data: 3.92 (4.27, 3%; 3.05, 2%), 3.05 (4.27, 12%; 3.92, 1%; 2.67, 18%). ^{13}C NMR (CD_3COCD_3): δ 149.0 (C-3'), 138.7 (C-1'), 136.2 (C-6'), 132.6, 130.7 (C-2, C-3), 130.6 (C-5'), 124.7 (C-2'), 123.8 (C-4'), 117.4 (C-7), 83.4, 78.2 (C-1, C-4), 55.6 (OCH_3), 51.7 (C-5), 41.4 (C-6). MS: 419 (0.4), 417 (0.9) and 415 (0.4) all M^+, 388 (1), 386 (11), 385 (8), 384 (49), 383,(17), 382 (100), 381 (15),

380 (77), 270 (8), 268 (12), 266 (7), 233 (29), 231 (22), 170 (29). HRMS calcd for $C_{14}H_{10}{}^{35}Cl_3{}^{37}ClNO_3$ (M^+ - Cl): 381.9385; found: 381.9407.

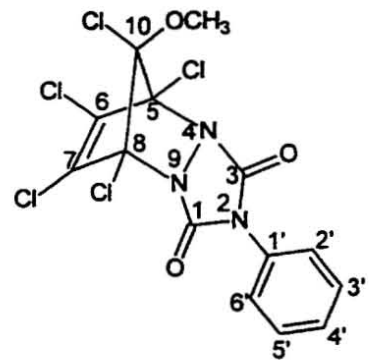
(1*R,4*S**,5*R**,7*R**)-1,2,3,4,7-Pentachloro-7-methoxy-5-(2-naphthyl)bicyclo [2.2.1]hept-2-ene (27).**



A solution of diene **16** (0.034 g, 0.13 mmol) and 2-vinylnaphthalene (0.021 g, 0.14 mmol) in benzene (10 mL) was heated at reflux for 4 days. Removal of the solvent under vacuum gave **27** as a brown oil (14 mg, 26%), which slowly crystallized in the refrigerator: mp: 104-106 °C. IR: 2952, 1606, 1204 cm^{-1}. ^1H NMR: δ 7.84-7.78 (3H, m), 7.56 (1H, broad d, J = 1.5 Hz), 7.49 (2H, symmetrical m), 7.20 (1H, dd, J = 1.9, 7.6 Hz), 4.03 (1H, dd, J = 4.2, 9.1 Hz, C-5H), 3.90 (3H, s, OCH_3), 2.91 (1H, dd, J = 9.1, 12.3 Hz, C-6H_{exo}), 2.54 (1H, dd, J = 4.2, 12.3 Hz, C-6H_{endo}). NOE data: 4.03 (7.56, 9%; 7.20, 7%; 3.90, 0.3%; 2.91, 7%), 3.90 (4.03, 2%; 2.91, 1%), 2.91 (4.03, 9%; 3.90, 1%; 2.54, 14%). ^{13}C NMR (CD_3COCD_3): δ 134.0 (Ar), 133.9 (Ar), 133.7 (Ar), 132.0, 131.2 (C-2, C-3),

129.3 (Ar), 128.7 (Ar), 128.3 (Ar), 127.1 (Ar, 2C), 117.7 (C-7), 83.8, 78.3 (C-1, C-4), 55.5 (OCH_3), 52.3 (C-5), 41.5 (C-6). MS: 426 (1), 424 (4), 423 (1), 422 (6) and 420 (4) all M^+, 389 (3), 387 (5), 385 (4), 236 (4), 175 (20), 171 (12), 154 (100), 153 (12). HRMS calcd for $C_{18}H_{13}{}^{35}Cl_3{}^{37}ClO$ (M^+ - Cl): 386.9690; found: 386.9686.

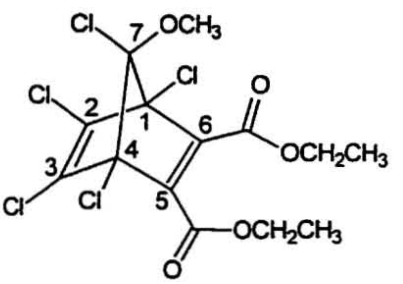
(5*R*,8*S*,10*s*)-5,6,7,8,10-Pentachloro-5,8-dihydro-10-methoxy-2-phenyl-5,8-methano-(1*H*)-[1,2,4]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (28).



A solution of diene **16** (0.063 g, 0.15 mmol) and 4-phenyl-1,2,4-triazoline-3,5-dione (0.053 g, 0.30 mmol) in benzene (7.0 mL) was heated at 75°C overnight. Removal of the solvent under vacuum followed by flash chromatography (elution with 3% ethyl acetate-hexane) gave a yellow solid, which was crystallized from ethanol-ethyl acetate to give **28** as colorless crystals (36 mg, 55%): mp: 99-101 °C. IR: 1802, 1750, 1392, 1219 cm^{-1}. ^1H NMR: δ 7.52-7.40 (3H, m, C-3'H, C-4'H, C-5'H), 7.36 (2H, m, C-2'H, C-6'H), 3.93 (3H, s, OCH_3). ^{13}C NMR: δ 155.4 (C-1, C-3), 129.7 (C-6, C-7), 129.5 (Ar), 128.6 (Ar),

125.5 (Ar), 109.5 (C-10), 90.5 (C-5, C-8), 56.0 (OCH_3). MS: 447 (2), 445 (6), 443 (9) and 441(5) all M^+, 412 (11), 411 (8), 410 (48), 409 (16), 408 (100), 407 (13), 406 (77), 299 (17), 289 (34), 287 (27), 270 (23), 268 (36), 266 (23), 263 (12), 261 (24), 259 (19), 235 (33), 231 (51), 218 (20), 216 (16), 119 (84), 91 (35), 64 (21), 63 (29). HRMS calcd for $C_{14}H_8{}^{35}Cl_3{}^{37}ClN_3O_3$ (M^+ - Cl): 407.9289; found: 407.9284. Anal. calcd for $C_{14}H_8Cl_5N_3O_3$: C, 37.92; H, 1.82; N, 9.47. Found: C, 38.06; H, 1.95; N, 9.35. This structure was determined by X-ray crystallography.

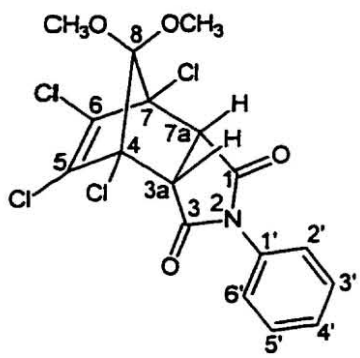
(1*R*,4*S*,7*s*)-1,2,3,4,7-Pentachloro-5,6-bis(ethyloxycarbonyl)-7-methoxy bicyclo[2.2.1]hepta-2,5-diene (29).



A solution of diene **16** (0.117 g, 0.437 mmol) and diethyl acetylene-dicarboxylate (0.272 g, 1.60 mmol) in benzene (10 mL) was heated at reflux for 10 days. Removal of the solvent followed by flash chromatography (elution with 3% ethyl acetate-hexane) gave a pale yellow oil, which crystallized upon refrigeration to give **29** as colorless crystals (81 mg, 42%): mp: 62-64 °C. IR: 2986, 2954, 1731, 1629, 1603, 1206 cm^{-1}. ^1H NMR: δ 4.32 (4H, complex symmetrical m, OCH_2CH_3), 3.77 (3H, s, OCH_3), 1.34 (6H, t, J = 7.1 Hz,

OCH_2CH_3). ^{13}C NMR: δ 160.7 (C=O), 143.3 (C-5, C-6), 137.5 (C-2, C-3), 128.8 (C-7), 81.2 (C-1, C-4), 62.4 (OCH_2), 56.4 (OCH_3), 14.0 (CH_3). MS: no M^+, 407 (2), 406 (1), 405 (8), 404 (3), 403 (16), 402 (2) and 401 (12) all M^+ - Cl; 331 (50), 329 (100), 327 (79), 279 (61), 277 (60), 207 (13), 205 (13), 29 (84). HRMS calcd for $C_{14}H_{13}{}^{35}Cl_3{}^{37}ClO_5$ (M^+ - Cl): 402.9487; found: 402.9469. Anal. calcd for $C_{14}H_{13}Cl_5O_5$: C, 38.35; H, 2.99. Found: C, 38.62; H, 3.09. This structure was determined by X-ray crystallography.

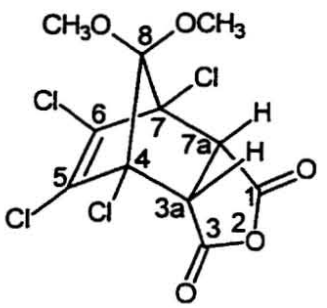
(3aα,4β,7β,7aα)-4,5,6,7-Tetrachloro-3a,4,7,7a-tetrahydro-8,8-dimethoxy-2-phenyl-4,7-methano-(2*H*)-isoindole-1,3-dione (31).



A solution of diene **17** (0.193 g, 0.737 mmol) and *N*-phenylmaleimide (0.139 g, 0.803 mmol) in dichloromethane (15 mL) was heated at reflux for 6 h. Solvent removal provided a white solid. This was crystallized from acetone-hexane to give **31** as colorless crystals (0.067 g, 21%): mp: 159.5-160 °C. IR: 2954, 1721, 1598, 1500, 1383, 1191 cm^{-1}. ^1H NMR: δ 7.48-7.36 (3H, m,

C-3'H, C-4'H, C-5'H), 7.13 (2H, m, C-2'H, C-6'H), 3.79 (2H, s, C-3aH, C-7aH), 3.67 (3H, s, OCH_3), 3.61 (3H, s, OCH_3). ^{13}C NMR: δ 170.6 (C-1, C-3), 130.9 (Ar), 129.3 (Ar), 129.1 (Ar), 126.5 (Ar), signals for quaternary carbons C-5 and C-6 were buried underneath the 129.3 ppm signal, 114.6 (C-8), 75.0 (C-4, C-7), 53.0 (OCH_3), 52.2 (OCH_3), 51.8 (C-3a, C-7a). MS: no M^+, 407 (0.7), 406 (4), 405 (6), 404 (33), 403 (18), 402 (95), 401 (18), 400 (100), 259 (3), 258 (1), 257 (10), 256 (3), 255 (26), 254 (3), 253 (28), 213 (1), 212 (1), 211 (7), 210 (2), 179 (6), 119 (20), 91 (12), 59 (36).

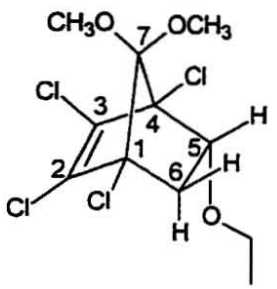
(3aα,4β,7β,7aα)-4,5,6,7-Tetrachloro-3a,4,7,7a-tetrahydro-8,8-dimethoxy-4,7-methano-1,3-benzodioxol-2-one (32).



A solution of diene **17** (0.160 g, 0.61 mmol) and vinylene carbonate (0.192 g, 2.23 mmol) in toluene (6.0 mL) was heated at reflux for 2 days. Solvent was removed under vacuum, and the resulting oil crystallized upon refrigeration. Recrystallization from ethyl acetate-hexane gave **32** as colorless crystals (88 mg, 41%): mp: 137-138 °C. IR: 1837, 1620, 1148 cm^{-1}. ^1H NMR:

δ 5.16 (2H, s, C-3aH, C-7aH), 3.62 (3H, s, OCH_3), 3.60 (3H, s, OCH_3). ^{13}C NMR: δ 152.3 (C-2), 128.9 (C-5, C-6), 112.1 (C-8), 83.0 (C-3a, C-7a), 76.5 (C-4, C-7), 52.9 (OCH_3), 52.3 (OCH_3). MS: no M^+, 319 (4), 318 (4), 317 (32), 316 (11), 315 (100), 314 (11) and 313 (99) all M^+-Cl, 216 (3), 214 (4), 213 (1), 212 (9), 211 (2), 210 (10), 171 (2), 169 (7), 167 (8), 59 (71).

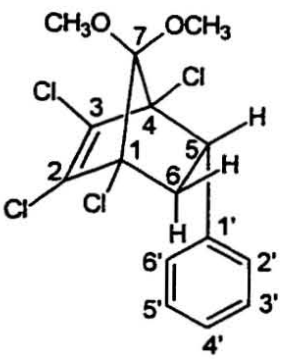
(1*R,4*S**,5*R**)-1,2,3,4-Tetrachloro-5-ethoxy-7,7-dimethoxybicyclo[2.2.1]hept-2-ene (33).**



A solution of diene **17** (0.206 g, 0.78 mmol) and ethoxyethylene (9.0 mL) was heated at reflux for 3 days. Solvent removal gave a yellow oil, which was not purified. ^1H and ^{13}C NMR data were obtained from the crude sample. ^1H NMR: δ 4.27 (1H, dd, J = 2.3, 7.6 Hz, C-5H), 3.75 (1H, m, OCH_2CH_3), 3.57 (3H, s, OCH_3), 3.54 (3H, s, OCH_3), signal for other H of CH_2 buried under the two methoxy signals, 2.61 (1H, dd, J = 7.6, 12.0 Hz, C-$6H_{exo}$), 1.73 (1H, dd, J = 2.3, 12.0 Hz, C-$6H_{endo}$), 1.15 (3H, t, J = 7.0 Hz, OCH_2CH_3). ^{13}C NMR: δ 129.8, 127.9

(C-2, C-3), 111.7 (C-7), 83.7 (C-5), 79.0, 74.1 (C-1, C-4), 66.6 (OCH_2CH_3), 52.5 (OCH_3), 51.5 (OCH_3), 43.8 (C-6), 15.3 (OCH_2CH_3).

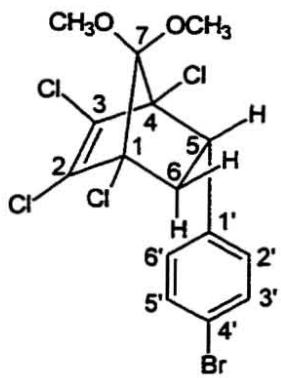
(1*R,4*S**,5*S**)-1,2,3,4-Tetrachloro-7,7-dimethoxy-5-phenylbicyclo[2.2.1]hept-2-ene (34).**



A solution of diene **17** (0.338 g, 1.28 mmol) and styrene (0.188 g, 1.81 mmol) in benzene (10 mL) was heated at reflux for 24 h. Solvent removal was followed by flash chromatography to give an oil, which crystallized after freezing it in liquid nitrogen to yield **34** as colorless crystals (0.119 g, 25%): mp: 75-77 °C. IR: 2951, 1603, 1456, 1192 cm^{-1}. ^1H NMR: δ 7.34-7.27 (3H, m, C-3'H, C-4'H, C-5'H), 7.07 (2H, narrow m, C-2'H, C-6'H), 3.79 (1H, dd, J = 4.4, 9.4 Hz, C-5H), 3.70 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 2.77 (1H, dd, J = 9.4, 12.3 Hz, C-$6H_{exo}$), 2.26 (1H, dd, J = 4.4, 12.3 Hz, C-$6H_{endo}$). ^{13}C NMR: δ 135.8 (C-1'), 129.6 (C-2, C-3), 129.1 (Ar), 128.2 (Ar), 127.8 (Ar), 112.3 (C-7), 80.2, 74.8 (C-1, C-4), 52.7 (OCH_3), 51.7 (2C, OCH_3, C-5), 41.9 (C-6), the quaternary signal for C-2 and C-3 was buried underneath an aromatic signal. MS: no M^+, 338 (0.3),

337 (4), 336 (5), 335 (33), 334 (18), 333 (96), 332 (20), 331 (100) and 329 (2) all M^+-Cl, 299 (2), 298 (1), 297 (8), 296 (2), 295 (13), 188 (12), 187 (11), 186 (35), 152 (28), 151 (14), 150 (12), 125 (32), 121 (56), 104 (19), 103 (11), 91 (30), 77 (30), 59 (85).

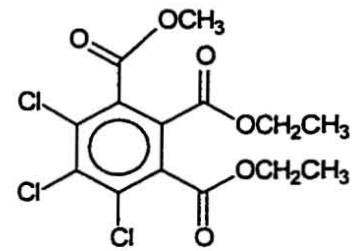
(1*R,4*S**,5*S**)-5-(4-Bromophenyl)-1,2,3,4-tetrachloro-7,7-dimethoxybicyclo-[2.2.1]hept-2-ene (35).**



A solution of diene **17** (0.132 g, 0.50 mmol) and 4-bromostyrene (0.110 g, 0.60 mmol) was heated at reflux in benzene (15 mL) for 4 days. Removal of the solvent followed by flash chromatography gave a white solid. Crystallization from ethyl acetate-hexane produced **35** as colorless crystals (0.144 g, 64%): mp: 114-115 °C. IR: 2950, 1602, 1491, 1193 cm^{-1}. ^1H NMR: δ 7.43 (2H, broad d, *J* = 8.5 Hz, C-3'H, C-5'H), 6.93 (2H, broad d, *J* = 8.5 Hz, C-2'H, C-6'H), 3.75 (1H, dd, *J* = 4.3, 9.4 Hz, C-5H), 3.68 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 2.77 (1H, dd, *J* = 9.4, 12.3 Hz, C-6H_{exo}), 2.17 (1H, dd, *J* = 4.4, 12.3 Hz, C-6H_{endo}). ^{13}C NMR: δ

134.9 (Ar), 131.3 (Ar), 130.6 (Ar), 129.8, 128.8 (C-2, C-3), 122.1 (Ar), 112.2 (C-7), 80.0, 74.7 (C-1, C-4), 52.7 (OCH_3), 51.7 (OCH_3), 51.2 (C-5), 41.8 (C-6). MS: no M^+, 418 (0.1), 417 (2), 416 (3), 415 (19), 414 (12), 413 (68), 412 (20), 411 (100), 410 (14) and 409 (54) all M^+-Cl, 379 (0.9), 378 (0.6), 377 (4), 376 (1), 375 (7), 374 (0.8), 373 (4), 203 (9), 202 (2), 201 (17), 200 (3), 199 (18), 186 (17), 77 (12), 59 (55).

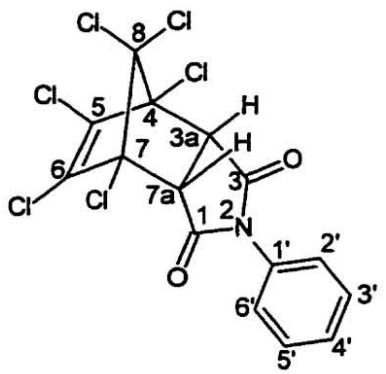
1,2-Bis(carboethoxy)-3-carbomethoxy-4,5,6-trichlorobenzene (40).



The diene **17** (0.088 g, 0.33 mmol) and diethyl acetylenedicarboxylate (1.13 g, 6.66 mmol) were heated at reflux in benzene (7.0 mL) for 5 days. Solvent removal, then flash chromatography (elution with 15% ethyl acetate-hexane) provided **40** as a yellow oil (50 mg, 40%). IR: 2985, 1738, 1554, 1225 cm^{-1}. ^1H NMR ($CD_3C_6D_5$): δ 4.17 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.92 (2H, q, J = 7.2 Hz, OCH_2CH_3), 3.56 (3H, s, OCH_3), 1.10 (3H, t, J = 7.1 Hz, OCH_2CH_3), 0.92 (3H, t, J = 7.2 Hz, OCH_2CH_3). ^{13}C NMR ($CD_3C_6D_5$): δ 164.7 (C=O), 164.1 (C=O), 163.2 (C=O), 136.9 (Ar), 135.1 (Ar), 134.8 (Ar), 132.9 (Ar), 62.7 (OCH_2CH_3), 62.2 (OCH_2CH_3), 52.5 (OCH_3), 13.9 (OCH_2CH_3), 13.8

(OCH_2CH_3). MS: 386 (0.3), 384 (2) and 382 (2) all M^+, 355 (1), 354 (1), 353 (3), 352 (1), 351 (3), 342 (1), 341 (6), 340 (4), 339 (20), 338 (5), 337 (20), 314 (1), 313 (6), 312 (3), 311 (20), 310 (4), 309 (20), 284 (1), 283 (5), 282 (4), 281 (31), 280 (11), 279 (93), 278 (11), 277 (100), 211 (1), 210 (4), 209 (8), 208 (12), 207 (23), 206 (12), 205 (22), 182 (2), 181 (3), 180 (7), 179 (5), 178 (7), 177 (4).

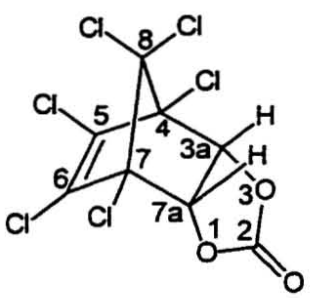
(3aα,4β,7β,7aα)-4,5,6,7,8,8-Hexachloro-3a,4,7,7a-tetrahydro-2-phenyl-4,7-methano-(2*H*)-isoindole-1,3-dione (41).



The Diels-Alder reaction of hexachlorocyclopentadiene (**18**) and NPM gave **41** as a beige solid, and the crude sample was crystallized from acetone-hexane to provide **41** as colorless crystals: mp: 223-225 °C. IR: 1722 cm^{-1}. ^1H NMR: δ 7.51-7.39 (3H, m, C-3'H, C-4'H, C-5'H), 7.13 (2H, narrow m, C-2'H, C-6'H), 4.00 (2H, s, C-3aH, C-7aH). ^{13}C NMR: δ 169.1 (C-1, C-3), 131.0 (C-5, C-6), 130.6 (Ar), 129.4 (2C, Ar), 126.3 (Ar), 103.9 (C-8), 79.4 (C-4, C-7), 52.0 (C-3a, C-7a). MS: 451 (2), 449 (9), 447 (21), 445 (24) and 443 (13) all M^+,

414 (1), 413 (0.4), 412 (3), 411 (0.9), 410 (5), 409 (0.3), 408 (3), 270 (1), 269 (2), 268 (1), 267 (16), 266 (3), 265 (46), 264 (6), 263 (70), 262 (4), 261 (43), 241 (2), 240 (0.2), 239 (5), 238 (0.5), 237 (7), 236 (0.1), 235 (5), 173 (100), 119 (54), 91 (22), 77 (12), 64 (15), 54 (22).

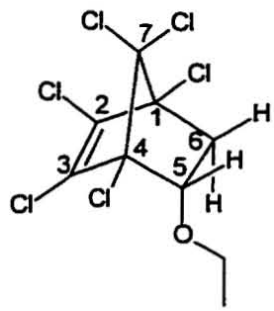
(3aα,4β,7β,7aα)-4,5,6,7,8,8-Hexachloro-3a,4,7,7a-tetrahydro-4,7-methano-1,3-benzodioxol-2-one (42).



A solution of hexachlorocyclopentadiene (**18**) (0.085 g, 0.31 mmol) and vinylene carbonate (0.267 g, 0.310 mmol) in toluene (7.0 mL) was heated at reflux for 4 days. Upon removal of the last traces of solvent under vacuum, the oil crystallized. Crystallization from ethyl acetate-hexane yielded **42** as colorless crystals (60 mg, 54%): mp: 110 °C (subl.). IR: 3020, 1832, 1600 cm^{-1}. ^{1}H NMR: δ 5.38 (2H, s, C-3aH, C-7aH). ^{13}C NMR: δ 151.3 (C-1, C-3), 131.5 (C-5, C-6), 98.4 (C-8), 82.5 (C-3a, C-7a), 80.6 (C-4, C-7). MS: 364 (1), 362 (6), 360 (14), 358 (16) and 356 (8) all M^{+}, 278 (8), 277 (9), 276 (34), 275 (4), 274 (78), 273 (5), 272 (100), 271 (3), 270 (49), 257 (0.6), 256 (2), 255 (4), 254 (11), 253

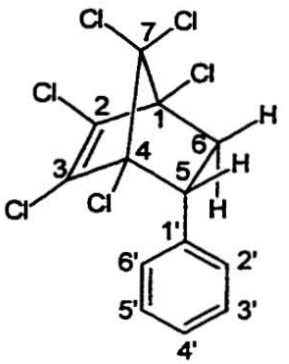
(12), 252 (31), 251 (19), 250 (47), 249 (12), 248 (31), 242 (1), 241 (11), 240 (3), 239 (33), 238 (4), 237 (53), 236 (3), 235 (33), 220 (3), 219 (2), 218 (13), 217 (8), 216 (29), 215 (14), 214 (21), 213 (10), 109 (8), 108 (21). HRMS calcd. for $C_8H_2{}^{35}Cl_4{}^{37}ClO_3$: 357.8105; found: 357.8112.

(1*R,4*S**,5*S**)-1,2,3,4,7,7-Hexachloro-5-ethoxybicyclo[2.2.1]hept-2-ene (43).**



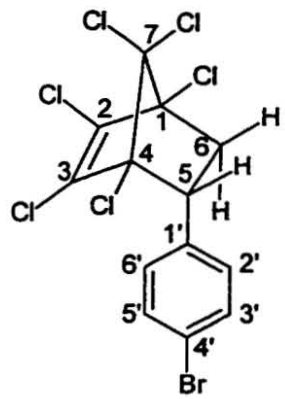
The diene **18** (0.851 g, 3.12 mmol) and ethoxyethylene (10 mL) were heated at reflux for 2 days. Removal of the excess ethoxyethylene and flash chromatography (elution with 5% ethyl acetate-hexane) gave **43** as a yellow oil (0.88 g, 83%). ^{1}H NMR: δ 4.45 (1H, dd, *J* = 2.3, 7.4 Hz, C-5H), 3.83 (1H, dq, *J* = 7.0, 9.3 Hz, C-5 O**C**H_2CH$_3$), 3.60 (1H, dq, *J* = 7.0, 9.3 Hz, O**C**H_2CH$_3$), 2.85 (1H, dd, *J* = 7.4, 12.7 Hz, C-6H$_{exo}$), 1.97 (1H, dd, *J* = 2.3, 12.7 Hz, C-6H$_{endo}$), 1.17 (3H, t, *J* = 7.0 Hz, OCH$_2$**C**H$_3$). ^{13}C NMR: δ 131.2, 130.1 (C-2, C-3), 101.1 (C-7), 83.5 (C-5), 82.4, 78.1 (C-1, C-4), 67.2 (O**C**H_2CH$_3$), 43.5 (C-6), 15.4 (OCH$_2$**C**H$_3$).

(1*R,4*S**,5*R**)-1,2,3,4,7,7-Hexachloro-5-phenylbicyclo[2.2.1]hept-2-ene (44).**



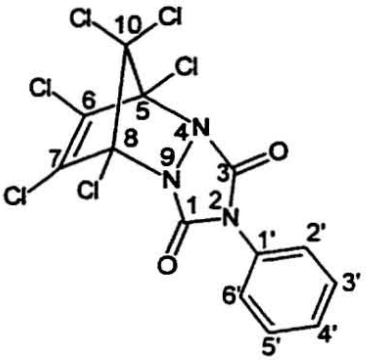
A solution of diene **18** (2.72 g, 10.0 mmol) and styrene (1.56 g, 15.0 mmol) was heated at reflux in benzene (10 mL) for 24 h. Removal of the solvent followed by refrigeration overnight yielded a colorless solid. The remaining styrene was removed from the solid by filtration via centrifugation. Crystallization from methanol-hexane afforded **44** as colorless crystals (1.61 g, 43%): mp: 72-74 °C. IR: 1603 cm^{-1}. ^1H NMR: δ 7.40-7.32 (3H, narrow m, C-3'H, C-4'H, C-5'H), 7.11 (2H, narrow m, C-2'H, C-6'H), 3.99 (1H, dd, *J* = 4.3, 9.1 Hz, C-5H), 2.93 (1H, dd, *J* = 9.1, 13.0 Hz, C-6H_{exo}), 2.51 (1H, dd, *J* = 4.3, 13.0 Hz, C-6H_{endo}). ^{13}C NMR: δ 134.2 (Ar), 131.2, 131.0 (C-2, C-3), 128.9 (Ar), 128.5 (Ar), 102.8 (C-7), 84.1 and 79.0 (C-1 and C-4), 51.7 (C-5), 40.7 (C-6). MS: 376 (0.9) and 374 (0.1) both M^+, 276 (0.1), 274 (1), 272 (1), 240 (1), 239 (5), 238 (2), 237 (7), 236 (1), 235 (4), 127 (29), 125 (87), 104 (100), 103 (15), 78 (16), 77 (10).

(1*R,4*S**,5*R**)-5-(4-Bromophenyl)-1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-ene (45).**



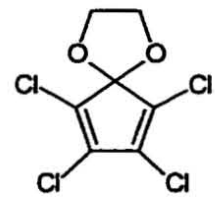
Hexachlorocyclopentadiene (**18**) (0.760 g, 2.79 mmol) and 4-bromostyrene (1.02 g, 5.57 mmol) were heated at reflux in benzene (8.0 mL) for 24 h. Removal of the solvent followed by standing overnight at rt gave a colorless solid. Crystallization from ethyl acetate-hexane provided **45** as colorless crystals (1.20 g, 94%): mp: 132-133 °C. IR: 3051, 2963, 1603 cm^{-1}. ^1H NMR: δ 7.47 (2H, broad d, *J* = 8.5 Hz, C-3'H, C-5'H), 7.00 (2H, broad d, *J* = 8.5 Hz, C-2'H, C-6'H), 3.95 (1H, dd, *J* = 4.3, 9.1 Hz, C-5H), 2.93 (1H, dd, *J* = 9.1, 13.1 Hz, C-$6H_{exo}$), 2.44 (1H, dd, *J* = 4.3, 13.1 Hz, C-$6H_{endo}$). ^{13}C NMR: δ 133.3 (Ar), 131.7 (Ar), 131.4, 130.8 (C-2, C-3), 130.5 (Ar), 122.8 (Ar), 102.7 (C-7), 83.9, 78.9 (C-1, C-4), 51.2 (C-5), 40.7 (C-6). MS: 460 (0.1), 458 (1), 456 (2), 454 (1) and 452 (0.2) all M^+, 208 (2), 207 (25), 206 (8), 205 (100), 204 (6), 203 (79), 185 (8), 184 (83), 183 (9), 182 (81), 103 (31), 102 (13), 77 (34), 51 (13).

5,6,7,8,10,10-Hexachloro-5,8-dihydro-2-phenyl-5,8-methano-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (46).



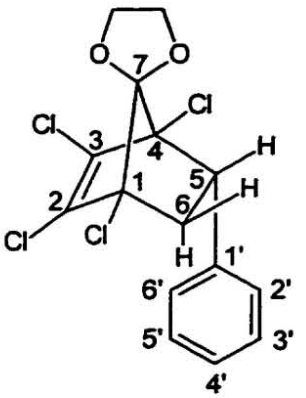
A solution of hexachlorocyclopentadiene (**18**) (0.120 g, 0.44 mmol) and 4-phenyl-1,2,4-triazoline-3,5-dione (0.077 g, 0.44 mmol) in benzene (7.0 mL) was heated at reflux for 6 h. Removal of the solvent followed by flash chromatography (elution with 5% ethyl acetate-hexane) gave **46** as colorless crystals (0.142 g, 73%): mp: 131-133 °C (decomp.). IR: 3067, 1809, 1754, 1596 cm^{-1}. ^1H NMR: δ 7.52-7.44 (3H, m, C-3'H, C-4'H, C-5'H), 7.30 (2H, m, C-2'H, C-6'H). ^{13}C NMR: δ 154.7 (C-1, C-3), 129.6 (Ar), 129.5 (Ar), 128.6 (Ar), 125.5 (Ar), signals for quaternary carbons C-6 and C-7 were buried under an aromatic signal, 97.1 (C-10), 92.2 (C-5, C-8). MS: 451 (0.4), 449 (1), 447 (1) and 445 (0.7) all M^+, 416 (1), 415 (0.7), 414 (4), 413 (1), 412 (7), 411 (0.7), 410 (4), 280 (0.9), 279 (0.2), 278 (7), 277 (2), 276 (29), 275 (4), 274 (68), 273 (4), 272 (86), 271 (3), 270 (45), 243 (2), 242 (0.9), 241 (14), 240 (2), 239 (42), 238 (4), 237 (67), 236 (2), 235 (412), 119 (100), 91 (47), 64 (28).

6,7,8,9-Tetrachloro-1,4-dioxaspiro[4.4]nona-6,8-diene (47).[41]



A solution of potassium hydroxide (2.5 g, 44 mmol) and ethanediol (4.0 g, 66 mmol) in THF (3.0 mL) was stirred at rt for 30 minutes. To this was added a solution of hexachlorocyclopentadiene (**18**) (3.0 g, 11 mmol) in THF (3.0 mL). The mixture was stirred at rt overnight. The resulting yellow solution was diluted with ether and washed with water and brine, then dried over anhydrous $MgSO_4$. Concentration of the solution under vacuum followed by flash chromatography (elution with 3% ethyl acetate-hexane) gave **48** as colorless crystals (0.86 g, 31%): mp: 63-65 °C. IR: 1623, 1205 cm^{-1}. ^1H NMR: δ 4.33 (s). ^{13}C NMR: δ 130.0, 128.6, 120.5, 67.4. MS: 266 (5), 265 (2), 264 (22), 263 (4) 262 (43), 261 (3) and 260 (35) all M^+, 232 (1), 231 (4), 230 (3), 229 (31), 228 (8), 227 (95), 226 (8), 225 (100), 210 (7), 209 (2), 208 (35), 207 (4), 206 (70), 205 (4), 204 (57), 187 (2), 186 (1), 185 (19), 184 (3), 183 (57), 182 (4), 181 (59), 173 (4), 172 (1), 171 (16), 170 (2), 169 (30), 168 (2), 167 (29), 166 (1), 165 (17), 155 (26), 153 (27), 120 (24), 118 (37), 83 (17), 43 (17).

(1*R,4*S**,5*S**)-1,2,3,4-Tetrachloro-5-phenylspiro[bicyclo[2.2.1]hept-2-ene-7,2'-[1.3]dioxolane] (48).**



A solution of diene **47** (0.056 g, 0.22 mmol) and styrene (0.034 g, 0.32 mmol) in benzene (5.0 mL) was heated at reflux for 24 h. Solvent removal gave **48** as a yellow oil, which was not purified (0.069 g, 87%). IR: 2904, 1595, 1278, 1246, 1221 cm^{-1}. ^1H NMR: δ 7.31 (3H, m, C-3'H, C-4'H, C-5'H), 7.09 (2H, narrow m, C-2'H, C-6'H), 4.36-4.21 (4H, symmetrical m, OCH_2CH_2O), 3.81 (1H, dd, *J* = 4.5, 9.4 Hz, C-5H), 2.77 (1H, dd, *J* = 9.4, 12.3 Hz, C-$6H_{exo}$), 2.31 (1H, dd, *J* = 4.5, 12.3 Hz, C-$6H_{endo}$). ^{13}C NMR: δ 136.2 (Ar), 129.8 (C-2 or C-3), 129.0 (Ar), 128.5 (Ar), 128.0 (Ar), 121.7 (C-7), 79.2, 73.6 (C-1, C-4), 67.9, 66.7 (OCH_2CH_2O), 51.6 (C-5), 41.5 (C-6), the signal for C-2 or C-3 may be underneath the aromatic signals. MS: no M^+, 335 (4), 334 (6), 333 (35), 332 (17), 331 (100), 330 (18) and 329 (100) all M^+-Cl, 296 (1), 295 (8), 294 (3), 293 (12), 253 (4), 252 (1), 251 (10), 250 (2), 249 (11), 186 (24), 152 (20), 125 (30), 86 (13), 84 (19), 77 (13), 51 (11).

Competitive reactions of dienes 16, 17, 18 and 47 with styrene as the dienophile.

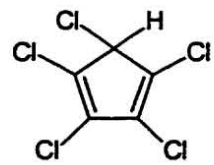
Diene **16** (0.081 mmol) and diene **18** (0.59 mmol) were placed in benzene (15 mL) with styrene (0.60 mmol) and heated to reflux overnight. The solvent was removed under vacuum, and ^{1}H NMR analysis of the residue showed signals for unreacted diene **16**, as well as adducts **24** and **44** in a ratio of 1:2.0. The ratio of reaction rates of diene **16** versus diene **18** calculated by Equation 1 was 4:1.

Diene **16** (0.068 mmol) and diene **17** (0.20 mmol) were placed in benzene (15 mL) with styrene (0.050 mmol) and heated to reflux for 2 days. The solvent was removed under vacuum, and ^{1}H NMR analysis of the residue showed signals for both unreacted dienes **16** and **17**, as well as adducts **24** and **34** in a ratio of 1.7:1. The ratio of reaction rates of diene **16** versus diene **17** calculated by Equation 1 was 2:1.

Diene **17** (0.58 mmol) and diene **18** (0.73 mmol) were placed in benzene (10 mL) with styrene (0.34 mmol) and heated to reflux overnight. The solvent was removed under vacuum, and ^{1}H NMR analysis of the residue showed signals for unreacted diene **17**, as well as adducts **34** and **44** in a ratio of 1.3:1. The ratio of reaction rates of diene **17** versus diene **18** calculated by Equation 1 was 2:1.

Diene **18** (0.37 mmol) and diene **47** (0.37 mmol) were placed in benzene (6.0 mL) with styrene (0.21 mmol) and heated to reflux overnight. The solvent was removed under vacuum, and ^{1}H NMR analysis of the residue showed signals for unreacted diene **47**, as well as adducts **44** and **48** in a ratio of 1:5.1. The ratio of reaction rates of diene **18** versus diene **47** calculated by Equation 1 was 1:62.

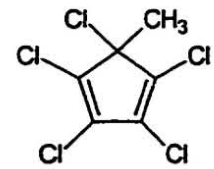
1,2,3,4,5-Pentachloro-1,3-cyclopentadiene (49).



A solution of hexachlorocyclopentadiene (**18**) (20.4 g, 74.9 mmol) in acetone (8.0 mL) was cooled in an ice bath as a solution of $SnCl_2 \bullet H_2O$ (17.2 g, 76.7 mmol) in acetone (30 mL) was added at a rate such as to maintain the temperature of the diene solution in the 30-35 °C range. After addition was complete (approximately 10 min), the brown solution was stirred at rt for 1 h. The acetone was removed under vacuum, and the residue was taken up in CCl_4. This solution was washed with water and brine, then dried over $CaCl_2$. Vacuum distillation (73-76 °C at 4 mm Hg) provided **49** as a yellow liquid (12.1 g, 68%). IR: 2938, 1603 cm^{-1}. ^{1}H NMR: δ 4.75 (s). ^{13}C NMR: δ 129.6, 129.0, 60.2. MS: 244 (0.3), 242 (5), 240 (14), 238 (22) and 236 (14) all M^+, 207 (11), 205 (49), 203

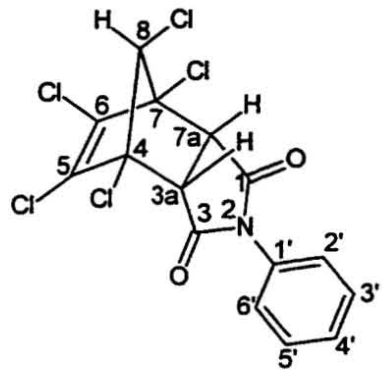
(100), 201 (79), 171 (2), 169 (7), 167 (8), 135 (2), 133 (9), 131 (13), 98 (6), 96 (20), 61 (22), 60 (11).

1,2,3,4,5-Pentachloro-5-methyl-1,3-cyclopentadiene (50).

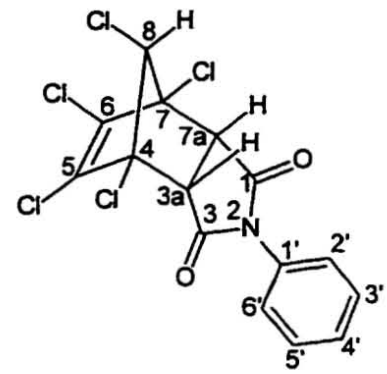


A 2.5 M solution of *n*-butyllithium (2.2 mL, 2.5 M in hexanes, 5.5 mmol) in hexanes was added dropwise to a solution of **49** (1.01 g, 4.25 mmol) in dry THF (40 mL) at -78 °C. Iodomethane (0.35 mL, 5.5 mmol) was added, and the mixture was allowed to warm slowly to rt. The solution was concentrated under vacuum, and the brown residue was redissolved in CH_2Cl_2. The solution was washed with water and brine, then dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by flash chromatography with hexane as the eluent gave **50** (0.719 g, 67%) as an orange oil. IR: 1601 cm^{-1}. ^1H NMR: δ 1.69 (s). ^{13}C NMR: δ 134.3, 127.4, 69.7, 23.8. MS: 258 (1), 256 (7), 254 (24), 252 (34) and 250 (22) all M^+, 239 (3), 237 (5), 235 (3), 223 (0.5), 221 (10), 219 (48), 217 (100), 215 (75), 186 (3), 184 (24), 182 (76), 180 (79), 149 (0.7), 147 (5), 145 (16), 143 (10), 109 (23), 108 (17), 74 (26).

(3aα,4β,7β,7aα,8*s*)-(53) and (3aα,4β,7β,7aα,8*r*)-4,5,6,7,8-Pentachloro-3a,4,7,7a-tetrahydro-2-phenyl-4,7-methano-(2*H*)-isoindole-1,3-dione (54).



53



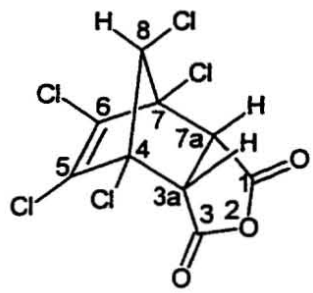
54

A solution of pentachlorocyclopentadiene (**49**) (0.550 g, 2.31 mmol) and *N*-phenylmaleimide (0.126 g, 0.728 mmol) in benzene (10 mL) was heated at reflux overnight. The solvent was removed under vacuum, and ^{1}H NMR analysis indicated the presence of two adducts. Crystals which formed from the crude reaction mixture were rinsed with petroleum ether and then recrystallized from acetone to give the *syn*-to-chlorine adduct **53** as colorless crystals (0.128 g, 43%). Flash chromatography (elution with 40% ethyl acetate-hexane) of the petroleum ether rinse of the crude reaction mixture gave the *anti*-to-chlorine adduct (0.049 g, 16%). It was recrystallized from hexane-methanol to give **54** as colorless crystals. For the *syn*-to-chlorine adduct **53**: mp: 286-287 °C. IR: 1714 cm^{-1}. ^{1}H NMR: δ 7.48-7.44 (3H, m, C-3'H, C-4'H, C-5'H), 7.16 (2H, m, C-2'H, C-6'H), 4.33 (1H, s, C-8H), 4.00 (2H, s, C-3aH, C-7aH). ^{13}C NMR: δ

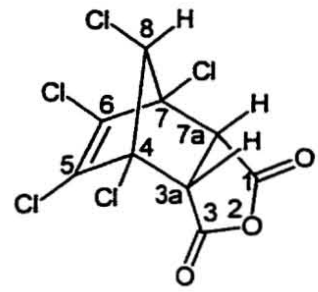
169.7 (C-1, C-3), 131.7, 130.7 (Ar, C-5 and C-6), 129.3 (Ar), 129.2 (Ar), 126.4 (Ar), 80.2 (C-8), 73.4 (C-4, C-7), 52.6 (C-3a, C-7a). MS: 417 (1), 415 (6), 413 (17), 411 (27) and 409 (17) all M^+, 244 (0.2), 242 (2), 240 (6), 238 (10), 236 (6), 235 (0.3), 233 (1), 231 (7), 229 (14), 227 (11), 209 (0.1), 207 (0.7), 205 (4), 203 (8), 201 (6), 173 (100), 119 (23), 91 (17), 54 (17). HRMS calcd for $C_{15}H_8{}^{35}Cl_4{}^{37}ClNO_2$: 410.8968; found: 410.8949. Anal. calcd for $C_{15}H_8Cl_5NO_2$: C, 43.78; H, 1.96; N, 3.40; Found: C, 43.29; H, 1.89; N, 3.39.

For the *anti*-to-chlorine adduct **54**: mp: 221-223 °C. IR: 1722 cm^{-1}. ^1H NMR: δ 7.51-7.42 (3H, m, C-3'H, C-4'H, C-5'H), 7.15 (2H, m, C-2'H, C-6'H), 4.47 (1H, s, C-8H), 3.78 (2H, s, C-3aH, C-7aH). NOE data: 4.47 (3.78, 6%), 3.78 (4.47, 14%). ^{13}C NMR: δ 169.1 (C-1, C-3), 130.7, 130.0 (Ar, C-5 and C-6), 129.5 (Ar), 126.4 (Ar), 81.4 (C-8), 74.6 (C-4, C-7), 51.9 (C-3a, C-7a). MS: 415 (2), 413 (6), 411 (8) and 409 (5) all M^+, 242 (1), 240 (4), 238 (7), 236 (4), 233 (0.5), 231 (4), 229 (9), 227 (7), 207 (0.6), 205 (3), 203 (6), 201 (5), 173 (100), 119 (15), 91 (13), 54 (15). Anal. calcd for $C_{15}H_8Cl_5NO_2$: C, 43.78; H, 1.96; N, 3.40. Found: C, 43.20; H, 2.02; N, 3.36.

(3aα,4β,7β,7aα,8*s*)- (55) and (3aα,4β,7β,7aα,8*r*)-4,5,6,7,8-Pentachloro-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1,3-dione (56).



55



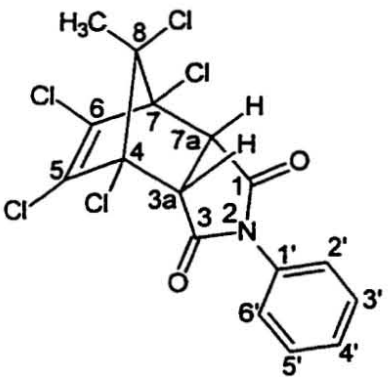
56

A solution of pentachlorocyclopentadiene (**49**) (0.306 g, 1.28 mmol) and maleic anhydride (0.190 g, 1.92 mmol) in toluene (10 mL) was heated at reflux for 6 h. Heating was continued at 60-70 °C for another 2 days. The solution was concentrated under vacuum, and ^{1}H NMR analysis indicated the presence of two adducts. The crude reaction mixture was crystallized from ethyl acetate-hexane to yield 50 mg (12%) of colorless crystals of **55**. The second adduct **56**, could not be separated from the remaining maleic anhydride and **55**. For the *syn*-to-chlorine adduct **55**: mp: 211-212 °C. IR: 1864, 1788, 1588 cm^{-1}. ^{1}H NMR: δ 4.33 (1H, s, C-8H), 4.14 (2H, s, C-3aH, C-7aH). [^{1}H NMR for corresponding diacid: δ 4.14 (1H, s, C-8H), 4.01 (2H, s, C-3aH, C-7aH)]. ^{13}C NMR: δ 164.5 (C-1, C-3), 132.3 (C-5, C-6), 80.3 (C-8), 73.4 (C-4, C-7), 54.1 (C-3a, C-7a). MS: 340 (2), 338 (7), 336 (11) and 334 (6) all M$^+$, 303 (2), 301 (4), 299 (3), 261 (2), 259 (6), 257 (14), 255 (10), 244 (4), 242 (21), 240 (71), 238

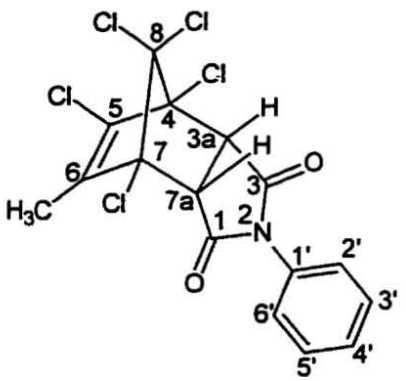
(100), 236 (68), 233 (5), 231 (21), 229 (45), 227 (36), 207 (4), 205 (17), 203 (34), 201 (26), 159 (13), 157 (20), 96 (19). HRMS calcd for $C_9H_3{}^{35}Cl_4{}^{37}ClO_3$: 335.8495; found: 335.8466. Anal. calcd for $C_9H_3Cl_5O_3$: C, 32.14; H, 0.90; found: C, 31.92; H, 0.95.

For the *anti* adduct **56** (from a mixture containing the *syn* adduct and MA): ^{1}H NMR: δ 4.45 (1H, s, C-8H), 4.00 (2H, s, C-3aH, C-7aH). [^{1}H NMR of corresponding diacid: δ 4.32 (1H, s, C-8H), 3.80 (2H, s, C-3aH, C-7aH). NOE data: 4.32 (3.80, 12%)].

(3aα,4β,7β,7aα,8*s*)-4,5,6,7,8-Pentachloro-3a,4,7,7a-tetrahydro-8-methyl-2-phenyl-4,7-methano-(2*H*)-isoindole-1,3-dione (57).



57



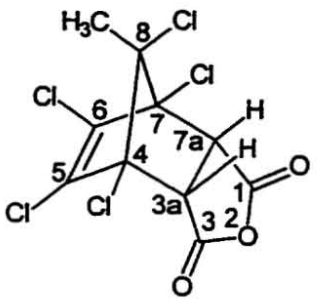
58

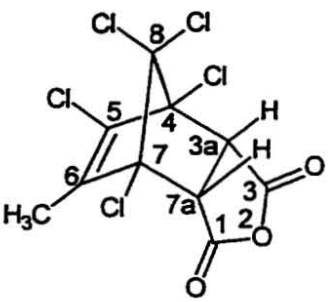
A solution of diene **50** (0.084 g, 0.33 mmol) and *N*-phenylmaleimide (0.092 g, 0.53 mmol) in benzene (10 mL) was heated at reflux for 6 days. The reaction did not appear to be complete, so reflux was continued in toluene for 24

h. The solution was concentrated under vacuum, and ^{1}H NMR analysis of the crude reaction mixture indicated the presence of one symmetrical adduct and a minor amount of an unsymmetrical adduct, likely **58**. Flash chromatography (elution with 10% ethyl acetate-hexane) gave 75 mg (53%) of a beige solid. Crystallization from dichloromethane-hexane provided colorless needles (mp: 207-209 °C) that were still contaminated with the second adduct **58**, so spectral data are for these needles: IR: 1782, 1721 cm^{-1}. ^{1}H NMR: δ 7.48-7.37 (3H, m, C-3'H, C-4'H, C-5'H), 7.13 (2H, m, C-2'H, C-6'H), 4.06 (2H, s, C-3aH, C-7aH), 1.65 (3H, s, C-8 CH_3). ^{13}C NMR: δ 170.1 (C-1, C-3), 130.8, 130.5 (Ar, C-5 and C-6), 129.3 (Ar), 129.2 (Ar), 126.4 (Ar), 91.6 (C-8), 77.7 (C-4, C-7), 53.6 (C-3a, C-7a), 18.8 (CH_3). MS: 431 (1), 429 (9), 427 (25), 425 (38) and 423 (24) all M^+, 394 (0.9), 392 (5), 390 (10), 388 (8), 256 (2), 254 (8), 252 (12), 250 (7), 247 (3), 245 (14), 243 (29), 241 (22), 173 (100), 119 (98). HRMS calcd for $C_{16}H_{10}{}^{35}Cl_5NO_2$: 422.9153; found: 422.9170. Anal. calcd for $C_{16}H_{10}Cl_5NO_2$: C, 45.16; H, 2.37; N, 3.29; found: C, 44.97; H, 2.41; N, 3.27.

Readily discerned signals for putative **58**: ^{1}H NMR: δ 3.88 (1H, d, J = 7.5 Hz), 3.60 (1H, d, J = 7.5 Hz), 1.73 (3H, s). ^{13}C NMR: δ 51.4 and 49.7 (C-3a, C-7a), 11.7 (CH_3).

(3aα,4β,7β,7aα,8s)-4,5,6,7,8-Pentachloro-3a,4,7,7a-tetrahydro-8-methyl-4,7-methanoisobenzofuran-1,3-dione (59).



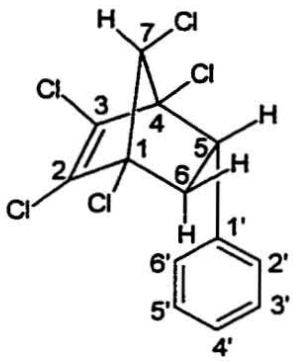


59 **60**

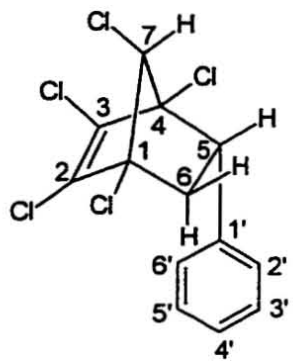
A solution of the diene **50** (0.150 g, 0.590 mmol) and maleic anhydride (0.071 g, 0.72 mmol) in toluene (4.0 mL) was heated at reflux for 5 days. The solvent was removed under vacuum. In the ^{1}H NMR spectrum of the crude sample, there were signals for a minor unsymmetrical adduct, likely to be **60**, in addition to the major symmetrical adduct. Crystallization from petroleum ether-ethyl acetate failed to separate the adducts but gave 50 mg (25%) of pale yellow needles. For the *syn*-to-chlorine adduct (from mixture containing small amount of **60**): mp: 135 °C (subl.). IR: 1785. ^{1}H NMR: δ 4.22 (2H, s, C-3aH, C-7aH), 1.63 (3H, s, C-8 CH_3). ^{13}C NMR: δ 164.8 (C-1, C-3), 131.0 (C-5, C-6), 91.8 (C-8), 77.6 (C-4, C-7), 55.0 (C-3a, C-7a), 18.7 (CH_3). MS: 354 (1), 352 (6), 350 (8) and 348 (5) all M^+, 319 (1), 317 (9), 315 (17), 313 (13), 258 (2), 256 (12), 254 (36), 252 (58), 250 (38), 247 (11), 245 (48), 243 (100), 241 (77), 219 (17), 217 (34), 215 (27), 209 (25), 207 (55), 205 (47), 182 (22), 180 (23), 172 (24),

171 (22), 170 (36), 86 (42), 85 (67), 83 (73). Signals for putative **60**: ^{1}H NMR: δ 4.06 (1H, d, $J \approx 7.5$ Hz), 3.79 (1H, d, $J \approx 7.5$ Hz), 1.72 (3H, s).

(1*R,4*S**,5*R**,7*R**)- (61) and (1*R**,4*S**,5*R**,7*S**)-1,2,3,4,7-Pentachloro-5-phenylbicyclo[2.2.1]hept-2-ene (62).**



61



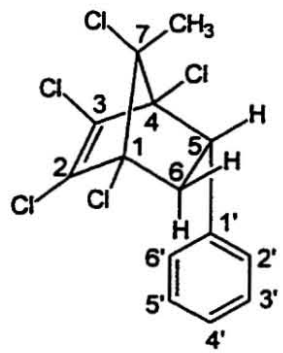
62

A solution of pentachlorocyclopentadiene **49** (0.400 g, 1.68 mmol) and styrene (0.183 g, 1.76 mmol) in *p*-xylene (10 mL) was heated at 100 °C for 12 h. The solvent was removed under vacuum, and ^{1}H NMR analysis of the crude sample indicated the presence of two adducts. Flash chromatography (elution with 10% ethyl acetate-hexane) gave 0.150 g of a mixture of the *syn*-to-chlorine adduct **61** and the dimerized diene. Also, a 0.260 g (45%) sample of the *anti*-to-chlorine **62** adduct was isolated as an orange oil. For **61** (from a mixture containing a small amount of the dimer of **49**): ^{1}H NMR: δ 7.35-7.29 (3H, m, C-3'H, C-4'H, C-5'H), 7.10 (2H, m, C-2'H, C-6'H), 4.18 (1H, d, J = 1.7 Hz, C-7H),

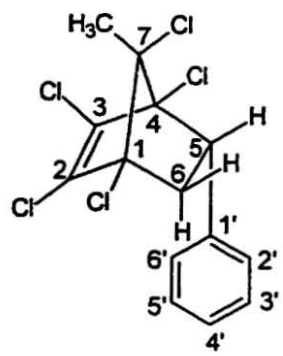
3.96 (1H, dd, J = 4.4, 9.5 Hz, C-5H), 2.90 (1H, dd, J = 9.5, 12.8 Hz, C-6H_{exo}), 2.40 (1H, ddd, J = 1.7, 4.4, 12.8 Hz, C-6H_{endo}). ^{13}C NMR: δ 134.4 (Ar), 132.1, 131.9 (C-2, C-3), 128.8 (Ar), 128.4 (Ar), 128.1 (Ar), 77.9 (C-1 or C-4), 77.5 (C-7), 72.7 (C-1 or C-4), 52.2 (C-5), 40.8 (C-6).

For **62**: IR: 1599, 1277 cm^{-1}. ^{1}H NMR: δ 7.34 (3H, narrow m, C-3'H, C-4'H, C-5'H), 7.10 (2H, narrow m, C-2'H, C-6'H), 4.49 (1H, s, C-7H), 3.72 (1H, dd, J = 4.9, 9.5 Hz, C-5H), 2.74 (1H, dd, J = 9.5, 12.9 Hz, C-6H_{exo}), 2.58 (1H, dd, J = 4.9, 12.9 Hz, C-6H_{endo}). NOE data: 4.49 (3.72, 6%; 2.74, 2%), 3.72 (7.10, 2%; 4.49, 10%, 2.74, 4%). ^{13}C NMR: δ 134.8 (Ar), 130.2, 129.8 (C-2, C-3), 128.6 (Ar), 128.4 (Ar), 128.3 (Ar), 81.2 (C-7), 79.8, 74.1 (C-1, C-4), 52.7 (C-5), 41.7 (C-6). MS: 342 (0.3, M^+), 240 (2), 238 (3), 236 (2), 205 (2), 203 (3), 201 (3), 125 (11), 104 (100), 78 (8), 77 (6).

(1*R,4*S**,5*S**,7*R**)- (63) and (1*R**,4*S**,5*S**,7*S**)-1,2,3,4,7-Pentachloro-7-methyl-5-phenylbicyclo[2.2.1]hept-2-ene (64).**



63



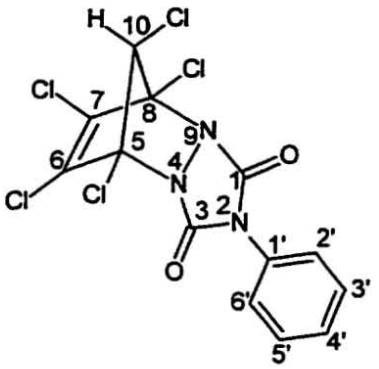
64

A solution of the diene **50** (0.090 g, 0.36 mmol) and styrene (0.111 g, 1.07 mmol) in toluene (4.0 mL) was heated at reflux for 9 days. The solvent was removed under vacuum, and ^{1}H NMR analysis of the crude reaction mixture indicated the presence of two adducts. Flash chromatography gave 0.62 g (49%) of **64** as a colorless liquid, which crystallized upon refrigeration, 0.17 g (14%) of **63** as a pale yellow solid, and 0.15 g (12%) of a mixture of **63** and **64**. Recrystallization of **63** from ethyl acetate-hexane gave colorless crystals. Recrystallization of **64** from ethyl acetate-petroleum ether also provided colorless crystals. For the *anti*-to-chlorine adduct **63**: mp: 94-96 °C. IR: 1603 cm^{-1}. ^{1}H NMR: δ 7.36-7.31 (3H, m, C-3'H, C-4'H, C-5'H), 7.10 (2H, m, C-2'H, C-6'H), 3.65 (1H, dd, J = 4.6, 9.1 Hz, C-5H), 2.66 (1H, dd, J = 9.1, 13.2 Hz, C-6H$_{exo}$), 2.51 (1H, dd, J = 4.6, 13.2 Hz, C-6H$_{endo}$), 1.81 (3H, s, CH$_3$). NOE data: 3.65 (2.66, 5%; 1.81, 2%), 2.66 (3.65, 2%; 2.51, 7%; 1.81, 0.7%), 2.51 (2.66, 9%), 1.81

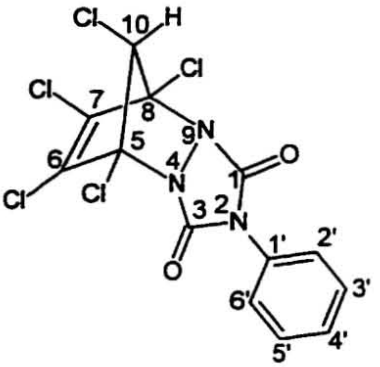
(3.65, 8%; 2.66, 3%). ^{13}C NMR: δ 134.9 (Ar), 132.0 (C-2 or C-3), 128.9 (Ar), 128.6 (C-2 or C-3), 128.4 (Ar), 91.8 (C-7), 83.0, 77.2 (C-1, C-4), 51.5 (C-5), 40.4 (C-6), 20.9 (CH_3). MS: 358 (0.3), 356 (0.6) and 354 (0.3) all M^+, 256 (2), 254 (7), 252 (12), 250 (8), 219 (2), 217 (4), 215 (3), 196 (2), 194 (2), 182 (3), 180 (3), 125 (21), 104 (100). Anal. calcd for $C_{14}H_{11}Cl_5$: C, 47.17; H, 3.11; found: C, 47.44; H, 2.92.

For the *syn*-to-chlorine adduct **64**: mp: 54-55 °C. IR: 1601 cm^{-1}. ^1H NMR: δ 7.36-7.28 (3H, m, C-3'H, C-4'H, C-5'H), 7.11 (2H, m, C-2'H, C-6'H), 4.07 (1H, dd, J = 4.2, 9.2 Hz, C-5H), 2.97 (1H, dd, J = 9.2, 12.7 Hz, C-6H_{exo}), 2.41 (1H, dd, J = 4.2, 9.2 Hz, C-6H_{endo}), 1.63 (3H, s, CH_3). NOE data: 4.07 (7.11, 2%; 2.97, 4%), 2.97 (4.07, 4%; 2.41, 11%), 2.41 (7.11, 2%; 2.97, 11%). ^{13}C NMR: δ 135.2 (Ar), 130.6 (C-2 or C-3), 129.0 (Ar), 128.5 (Ar), 128.0 (Ar), 88.6 (C-7), 82.5, 77.2 (C-1, C-4), 52.9 (C-5), 41.3 (C-6), 19.8 (CH_3). MS: 358 (1), 356 (2) and 354 (1) all M^+, 258 (2), 256 (14), 254 (44), 252 (59), 250 (44), 237 (1), 235 (5), 233 (19), 231 (34), 229 (25), 221 (4), 219 (16), 217 (33), 215 (26), 198 (21), 196 (52), 194 (55), 186 (4), 184 (9), 182 (27), 180 (23), 127 (19), 125 (71), 104 (100). Anal. calcd for $C_{14}H_{11}Cl_5$: C, 47.17; H, 3.11; found: C, 47.32; H, 3.03.

(5*R*,8*S*,10*s*)- (65) and (5*R*,8*S*,10*r*)-5,6,7,8,10-Pentachloro-5,8-dihydro-2-phenyl-5,8-methano-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (66).



65



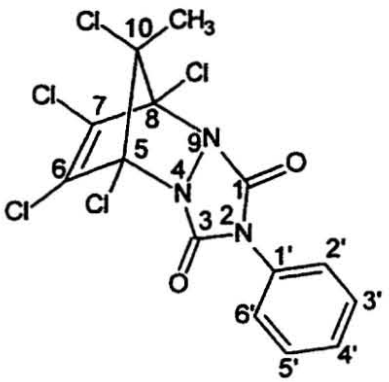
66

A solution of pentachlorocyclopentadiene (**49**) (0.262 g, 1.10 mmol) and 4-phenyl-1,2,4-triazoline-3,5-dione (0.193 g, 1.10 mmol) in benzene (10 mL) were heated at 70 °C overnight. The reaction mixture was still red in the morning, which indicated an excess of the dienophile. Extra diene was added dropwise until the distinctive red colour of the dienophile had faded to give a pale yellow solution. Solvent removal under vacuum, followed by flash chromatography (elution with 15% ethyl acetate-petroleum ether) gave the separated *syn* and *anti* adducts. Crystallization from petroleum ether-ether-methanol gave 0.136 g (30 %) of the *anti*-to-chlorine adduct **66** as beige crystals and 0.139 g (31%) of the *syn*-to-chlorine adduct **65** as beige crystals. For the *syn*-to-chlorine adduct **65**: mp: 160-165 °C (decomp.). IR: 1805, 1742 cm^{-1}. ^1H NMR: δ 7.51-7.39 (3H, m, C-3'H, C-4'H, C-5'H), 7.29 (2H, m, C-2'H, C-6'H), 4.33

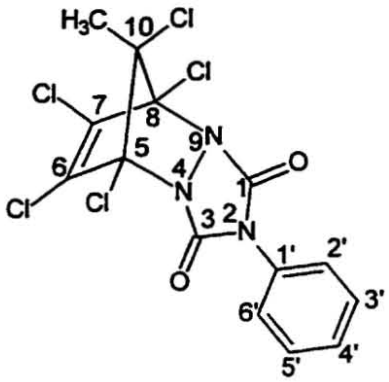
(1H, s, C-10H). ^{13}C NMR: δ 155.4 (C-1, C-3), 129.8 (Ar or C-6, C-7), 129.5 (2C, Ar), 129.4 (Ar or C-6, C-7), 125.5 (Ar), 87.4 (C-10), 74.7 (C-5, C-8). MS: 415 (0.2), 413 (0.7) and 411 (0.2) all M^+, 244 (4), 242 (21), 240 (66), 238 (100), 236 (64), 207 (14), 205 (64), 203 (88), 202 (43), 201 (69), 119 (91), 91 (53), 64 (31). Anal. calcd for $C_{13}H_6Cl_5N_3O_2$: C, 37.76; H, 1.46; N, 10.16; found: C, 37.82; H, 1.49; N, 10.23.

For the *anti*-to-chlorine adduct **66**: mp: 144-145 °C, 148°C (decomp.). IR: 1806, 1750 cm^{-1}. ^1H NMR: δ 7.49-7.44 (3H, m, C-3'H, C-4'H, C-5'H), 7.30 (2H, m, C-2'H, C-6'H), 4.70 (1H, s, C-10H). ^{13}C NMR: δ 155.2 (C-1, C-3), 129.5 (many resonances), 128.0 (Ar or C-6, C-7), 125.5 (Ar), 89.2 (C-10), 75.8 (C-5, C-8). MS: 415 (2), 413 (3) and 411 (2) all M^+, 244 (1), 242 (7), 240 (21), 238 (33), 236 (21), 207 (5), 205 (24), 203 (3), 202 (3), 201 (36), 119 (100), 91 (80), 64 (43). Anal. calcd for $C_{13}H_6Cl_5N_3O_2$: C, 37.76; H, 1.46; N, 10.16; found: C, 37.53; H, 1.53; N, 10.14. The structure of **66** was determined by X-ray crystallography.

(5*R*,8*S*,10*r*)- (67) and (5*R*,8*S*,10*s*)-5,6,7,8,10-Pentachloro-5,8-dihydro-10-methyl-5,8-methano-(1*H*)-[1,2,4]triazolo[1,2-a]pyridazine-1,3(2*H*)-dione (68).



67



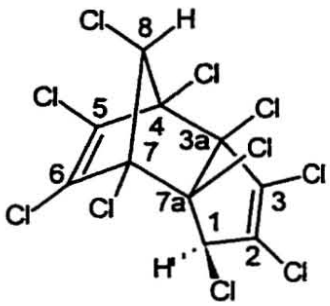
68

A solution of diene **50** (0.167 g, 0.66 mmol) and 4-phenyl-1,2,4-triazoline-1,3-dione (0.122 g, 0.70 mmol) in benzene (10 mL) was heated at reflux for 24 h. The solution was concentrated under vacuum, and ^{1}H NMR analysis indicated the presence of two adducts. Flash chromatography (elution with 1% ethyl acetate-hexane) gave 0.180 g (64%) of a mixture of *syn* and *anti* adducts, as well as 0.065 g (23%) of a 10:1 mixture of *syn* to *anti* as a colorless solid. Crystallization of the larger sample from ether-dichloromethane-methanol gave 0.134 g of the *anti*-to-chlorine adduct **67** as colorless crystals. For the *anti*-to-chlorine adduct **67**: mp: 129-131 °C (turning pink at 125 °C). IR: 1805, 1750 cm^{-1}. ^{1}H NMR: δ 7.47-7.41 (3H, m, C-3'H, C-4'H, C-5'H), 7.29 (2H, m, C-2'H, C-6'H), 1.91 (3H, s, CH_3). ^{13}C NMR: δ 155.3 (C-1, C-3), 129.6 (Ar or C-6, C-7), 129.4 (Ar), 129.1 (Ar or C-6, C-7), 125.5 (Ar), 91.9 (C-10), 86.4 (C-5, C-8),

20.7 (CH_3). MS: 429 (0.9), 427 (2) and 425 (0.8) all M^+, 392 (0.8), 390 (0.4), 275 (0.6), 273 (2), 258 (3), 256 (20), 254 (64), 252 (100), 250 (63), 221 (5), 219 (21), 217 (44), 215 (34), 186 (0.8), 184 (8), 182 (25), 180 (26), 119 (38), 91 (21), 64 (13). Anal. calcd for $C_{14}H_8Cl_5N_3O_2$: C, 39.33; H, 1.89; N, 9.83; found: C, 39.34; H, 1.93; N, 10.03. The structure of **67** was determined by X-ray crystallography.

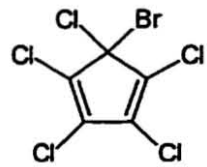
For the *syn*-to-chlorine adduct **68**: mp: 163-166 °C but first turning pink at 147 °C. IR: 1802, 1749 cm^{-1}. ^1H NMR: δ 7.50-7.42 (3H, m, C-3'H, C-4'H, C-5'H), 7.30 (2H, m, C-2'H, C-6'H), 1.63 (3H, s, CH_3). ^{13}C NMR: δ 155.4 (C-1, C-3), 129.8 (Ar or C-6, C-7), 129.4 (Ar), 128.1 (Ar or C-6, C-7), 125.5 (Ar), 91.4 (C-10), 84.5 (C-5, C-8), 19.4 (CH_3). MS: 429 (0.1), 427 (0.6) and 425 (0.1) all M^+, 394 (0.8), 392 (2), 390 (1), 275 (1), 273 (3), 271 (2), 258 (3), 256 (20), 254 (64), 252 (100), 250 (62), 223 (0.5), 221 (6), 219 (29), 217 (60), 215 (47), 186 (1), 184 (12), 182 (36), 180 (38), 119 (54), 91 (54), 64 (18). Anal. calcd for $C_{14}H_8Cl_5N_3O_2$: C, 39.33; H, 1.89; N, 9.83; found: C, 39.25; H, 1.89; N, 9.92.

(1*R,3aα,4β,7β,7aα,3*R**)-1,2,3,3a,4,5,6,7,7a,8-Decachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene (69).**



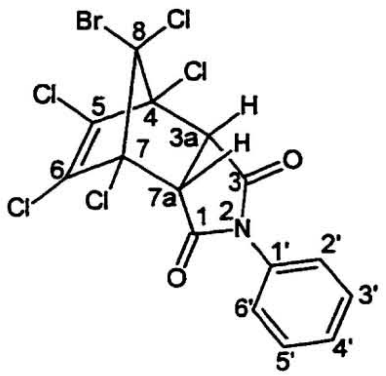
Dimerization of 1,2,3,4,5-pentachloro-1,3-cyclopentadiene (**49**) occurred in the refrigerator over ~4 weeks. Only one adduct from diene **49** was detected. It was crystallized from dichloromethane/hexane to give **69** as colorless crystals: mp: 234-236 °C. IR: 1625, 1610 cm^{-1}. ^1H NMR: δ 5.02 (1H, s), 4.93 (1H, s). ^{13}C NMR: δ 134.7, 134.3, 131.6, 129.5 (C-2, C-3, C-5, C-6), 86.2, 82.3, 82.0, 81.7 (C-3a, C-4, C-7, C-7a), 78.7 (C-8), 64.7 (C-1). MS: no M^+, 443 (0.1), 441 (0.5), and 439 (0.1) all M^+-Cl, 373 (0.6), 372 (0.4), 371 (1), 370 (0.7), 369 (1), 368 (0.7), 367 (0.5), 338 (2), 337 (0.4), 336 (4), 335 (0.6), 334 (5), 333 (0.3), 332 (3), 267 (0.2), 266 (4), 265 (1), 264 (7), 263 (1), 262 (6), 244 (3), 243 (1), 242 (21), 241 (4), 240 (64), 239 (6), 238 (100), 237 (4), 236 (64), 207 (4), 206 (1), 205 (17), 204 (2), 203 (34), 202 (2), 201 (27), 170 (0.4), 169 (1), 168 (3), 167 (4), 166 (2), 133 (3), 132 (5), 131 (5), 96 (4). Anal. calcd for $C_{10}H_2Cl_{10}$: C, 25.20; H, 0.42. Found: C, 25.08; H, 0.42. This structure was determined by X-ray crystallography.

5-Bromo-1,2,3,4,5-pentachloro-1,3-cyclopentadiene (70).

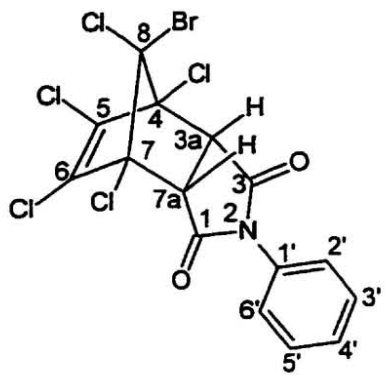


A 2.5 M solution of *n*-butyllithium (1.7 mL, 2.5 M in hexanes, 4.3 mmol) in hexanes was added dropwise to a solution of **49** (0.790 g, 3.32 mmol) in dry THF (30 mL) at -78 °C. *N*-Bromosuccinimide (0.804 g, 4.51 mmol) in THF (15 mL) was added, and the mixture was allowed to warm slowly to rt. The solution was concentrated under vacuum, and the orange residue was taken up in ether. The organic solution was washed with water and brine, then dried over anhydrous $MgSO_4$. Concentration of the solution under vacuum followed by flash chromatography with hexane as the eluent gave **70** (0.834 g, 79%) as an orange oil. IR: 1599 cm^{-1}. ^{13}C NMR: δ 133.8, 127.3, 67.7. MS: 322 (1), 320 (5), 318 (9), 316 (10) and 314 (4) all M^+, 285 (3), 283 (8), 281 (10), 279 (4), 243 (3), 241 (21), 239 (68), 237 (100), 235 (61), 169 (5), 167 (14), 165 (16), 145 (4), 143 (13), 141 (13), 134 (30), 132 (14), 130 (23), 97 (10), 95 (31), 60 (20).

(3aα,4β,7β,7aα,8*s*)- (71) and (3aα,4β,7β,7aα,8*r*)-8-Bromo-4,5,6,7,8-pentachloro-3a,4,7,7a-tetrahydro-2-phenyl-4,7-methano-(2*H*)-isoindole-1,3-dione (72).



71



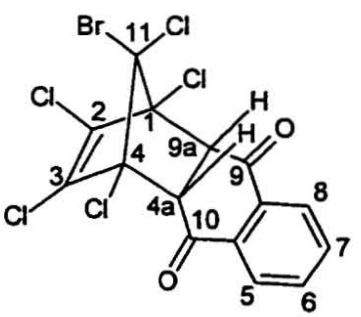
72

A solution of diene **70** (0.122 g, 0.385 mmol) and *N*-phenylmaleimide (0.125 g, 0.724 mmol) in toluene (10 mL) was heated at reflux for 3 weeks. The solution was concentrated under vacuum, and ^{1}H NMR analysis indicated the presence of two adducts. Flash chromatography (elution with 5% ethyl acetate-hexane) resulted in the adducts **71** and **72**, as well as the excess *N*-phenylmaleimide eluting together. This mixture was refluxed in dichloromethane with diene **17** to consume the extra NPM. Flash chromatography (elution with 4% ethyl acetate-hexane) of the resulting mixture gave 0.083 g (44%) of a colorless solid. Crystallization from acetone-hexane gave colorless needles, and the ^{1}H NMR analysis indicated that this was still a mixture of *syn* and *anti* adducts **71** and **72**. Mp: 235-236 °C. IR: 1723 cm^{-1}. ^{1}H

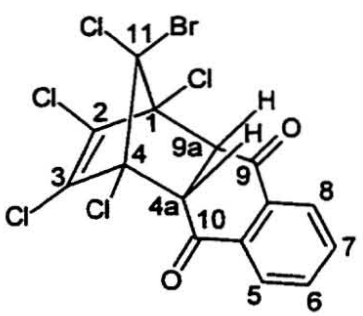
NMR: δ 7.50-7.38 (3H, m, C-3'H, C-4'H, C-5'H), 7.16-7.09 (2H, m, C-2'H, C-6'H), 4.02 (2H, s, C-3aH, C-7aH). ^{13}C NMR: δ 169.1 (C-1, C-3), 132.1, 130.6 (Ar, C-5 and C-6), 129.5 (Ar), 126.4 (Ar), 95.2 (C-8), 79.9 (C-4, C-7), 51.4 (C-3a, C-7a). MS: 497 (1), 495 (6), 493 (21), 491 (39), 489 (28) and 487 (15) all M^+, 460 (0.3), 458 (2), 456 (4), 454 (4), 452 (2), 313 (2), 311 (11), 309 (29), 307 (35), 305 (15), 269 (0.7), 267 (4), 265 (12), 263 (18), 261 (12), 243 (0.4), 241 (2), 239 (7), 237 (11), 235 (7), 173 (100), 119 (19), 91 (15), 54 (17). Anal. calcd for $C_{15}H_7BrCl_5NO_2$: C, 36.74; H, 1.44; N, 2.86; found: C, 36.75; H, 1.52; N, 2.83.

Readily discernible signals for the minor adduct **72**: ^{1}H NMR: δ 4.08 (2H, s, C-3aH, C-7aH). ^{13}C NMR: δ 94.6 (C-8). The structure and the adduct ratio were confirmed by X-ray crystallography.

(1α,4α,4aβ,9aβ,11*r*)- (73) and (1α,4α,4aβ,9aβ,11*s*)-11-Bromo-1,2,3,4,11-pentachloro-1,4,4a,9a-tetrahydro-1,4-methanoanthracene-9,10-dione (74).



73

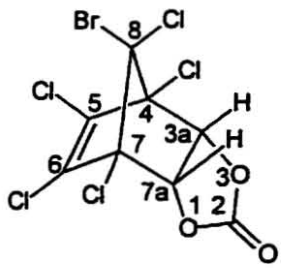


74

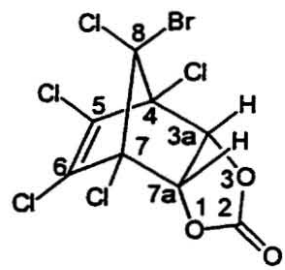
A solution of the diene **70** (0.191 g, 0.0603 mmol) and 1,4-naphthoquinone (0.193 g, 0.122 mmol) in toluene (4.0 mL) were heated at reflux for 4 weeks. Removal of the solvent gave a brown oil. ^{1}H NMR analysis of the crude sample indicated two adducts. Flash chromatography (elution with 15% ethyl acetate-petroleum ether) gave 0.130 g (45%) of a beige solid, which was a mixture of **73** and **74**. Crystallization from ether-petroleum ether gave colorless crystals of the adduct mixture. Mp: 139-140°C. ^{1}H NMR: δ 8.02 (2H, symmetrical m, C-5H, C-8H), 7.80 (2H, symmetrical m, C-6H, C-7H), 4.09 (2H, s, C-4aH, C-9aH). ^{13}C NMR: δ 189.1 (C-9, C-10), 135.2 (C-6, C-7), 134.7 (C-8a, C-10a), 132.3 (C-2, C-3), 93.6 (C-11), 82.3 (C-1, C-4), 54.2 (C-4a, C-9a). MS: 480 (1), 479 (0.8), 478 (4), 477 (2), 476 (8), 475 (2), 474 (8) 473 (0.7) and 472 (3) all M^+, 445 (0.2), 444 (0.1), 443 (2), 442 (1), 441 (4), 440 (1), 439 (5), 438 (0.7), 437 (3), 435 (0.2), 402 (0.5), 401 (1), 400 (0.5), 399 (3), 398 (2), 397 (8), 396 (2), 395 (12), 394 (2), 393 (7), 366 (0.4). 365 (1), 364 (2), 363 (2), 362 (6), 361 (4), 360 (14), 359 (6), 358 (13), 357 (4), 356 (3), 326 (3), 325 (9), 324 (6), 323 (10), 322 (12), 321 (3), 320 (43), 319 (5), 318 (83), 317 (5), 316 (81), 315 (2), 314 (33), 245 (0.7), 238 (9), 237 (100), 236 (6), 235 (61), 169 (22), 167 (64), 158 (12), 104 (66), 76 (98), 50 (41).

Readily discernible signals for minor adduct **74**: ^{1}H NMR: δ 4.16 (2H, s, C-4aH, C-9aH). The structure and the adduct ratio were confirmed by X-ray crystallography.

(3aα,4β,7β,7aα,8*s*)- (75) and (3aα,4β,7β,7aα,8*r*)-8-Bromo-4,5,6,7,8-pentachloro-3a,4,7,7a-tetrahydro-4,7-methano-1,3-benzodioxol-2-one (76).



75

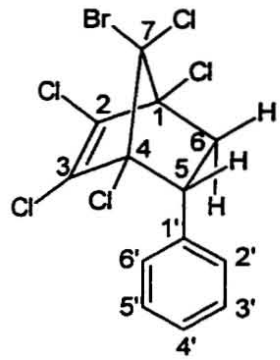


76

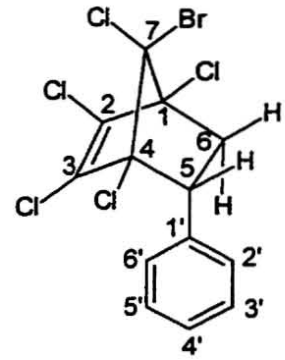
A solution of the diene **70** (0.274 g, 0.863 mmol) and vinylene carbonate (0.089 g, 1.03 mmol) were heated together at 150 °C for 3 h. Removal of the excess vinylene carbonate under high vacuum gave a brown, oily residue, which crystallized upon refrigeration. Sublimation of the sample gave a colorless solid, (31 mg, 9%). Crystallization of the solid from ether-petroleum ether gave colorless crystals. ^{1}H NMR analysis indicated the presence of three adducts. From GC-MS one adduct seemed to be that from hexachlorocyclopentadiene (**18**) plus vinylene carbonate, **42**. Data were obtained for this mixture of three adducts. Mp: 145-165 °C (subl.). IR: 1822 cm^{-1}. ^{1}H NMR: δ 5.44 (s) for **76**, 5.40 (s) for **75**, 5.37 (s) for **42**. ^{13}C NMR for major adduct **75**: δ 151.3 (C-1, C-3), 132.7 (C-5, C-6), 88.8 (C-8), 81.1 (C-4, C-7), 82.0 (C-3a, C-7a). MS (GC-MS) for **75** and **76**: 406 (3), 404 (14) and 402 (11) all M^{+}, 322 (18), 320 (59), 319 (7), 318 (98), 317 (2), 316 (100), 314 (38), 296 (15), 294 (18), 292 (9), 254 (2), 252

(16), 251 (7), 250 (23), 249 (2), 248 (16), 241 (17), 239 (59), 238 (3), 237 (86), 236 (2), 235 (55), 218 (17), 217 (10), 216 (40), 215 (21), 214 (34), 213 (16), 145 (17), 144 (10), 143 (33), 142 (4), 141 (15), 108 (40), 73 (19). The structure and the adduct ratio were determined by X-ray crystallography.

(1*R,4*S**,5*R**,7*R**)- (77) and (1*R**,4*S**,5*R**,7*S**)-7-Bromo-1,2,3,4,7-pentachloro-5-phenylbicyclo[2.2.1]hept-2-ene (78).**



77



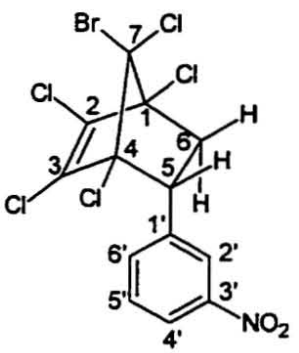
78

A solution of diene **70** (0.089 g, 0.28 mmol) and styrene (0.044 g, 0.42 mmol) in benzene (4.0 mL) was heated at reflux for 6 days. Solvent removal under vacuum followed by flash chromatography (elution with 1% ether-petroleum ether) gave an inseparable mixture of *syn* and *anti* adducts, 0.075 g (63%). Crystallization from ethyl acetate-hexane gave colorless crystals composed of **77** and **78**. Mp: 67-68 °C. IR: 1603 cm^{-1}. ^1H NMR: δ 7.33 (3H, narrow m, C-3'H, C-4'H, C-5'H), 7.10 (2H, narrow m, C-2'H, C-6'H), 4.01 (1H, dd, J = 4.3, 9.1 Hz, C-5H), 2.96 (1H, dd, J = 9.1, 12.9 Hz, C-6H_{exo}), 2.51 (1H, dd, J =

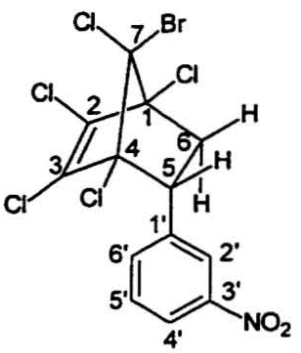
4.3. 12.9 Hz, C-6H_{endo}). ^{13}C NMR: δ 134.3 (Ar), 132.3 and 132.2 (C-2 and C-3), 128.9 (Ar), 128.5 (Ar), 94.6 (C-7), 84.5 and 79.4 (C-1 and C-4), 51.1 (C-5), 39.9 (C-6). MS: 424 (0.5), 420 (0.5) and 418 (0.1) all M^+, 243 (0.2), 241 (1), 239 (3), 238 (0.7), 237 (5), 236 (0.5), 235 (4), 234 (0.8), 233 (3), 127 (16), 125 (55), 104 (100), 103 (10), 78 (11), 77 (7), 51 (6). Anal. calcd for $C_{13}H_8BrCl_5$: C, 37.06; H, 1.91; found: C, 37.08; H, 1.73.

Readily discernible signals for the minor adduct **78**: ^{1}H NMR: δ 4.07 (1H, dd, J = 4.1, 9.1 Hz, C-5H). ^{13}C NMR: δ 52.1 (C-5) and 41.1 (C-6). The structure and the adduct ratio determined by X-ray crystallography.

(1*R,4*S**,5*R**,7*R**)- (79) and (1*R**,4*S**,5*R**,7*S**)-7-Bromo-1,2,3,4,7-pentachloro-5-(3-nitrophenyl)bicyclo[2.2.1]hept-2-ene (80).**



79



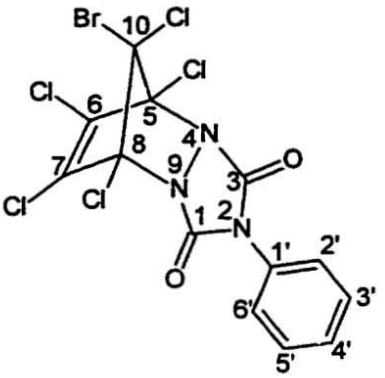
80

Diene **70** (0.235 g, 0.741 mmol) and 3-nitrostyrene (0.166 g, 1.11 mmol) in toluene (4.0 mL) were heated at reflux for 3 days. Removal of the solvent gave a brown oil, which contained both adducts and some remaining dienophile.

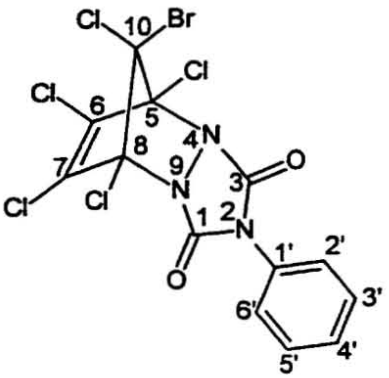
Flash chromatography (elution with 10 % ether-petroleum ether) gave a beige solid, (0.124 g, 36%), which was still a mixture of both adducts. This was crystallized from petroleum ether-ethyl acetate-ether to give colorless crystals. These crystals contained both major and minor adducts **79** and **80**. The following spectral data are for this mixture. Mp: 116-117 °C. IR: 1601, 1530, 1349 cm^{-1}. ^1H NMR: δ 8.22 (1H, d, *J* = 8.1 Hz, C-2'H), 8.02 (1H, narrow m, C-4'H), 7.58-7.43 (2H, m, C-5'H, C-6'H), 4.14 (1H, dd, *J* = 4.3, 9.6 Hz, C-5H), 3.05 (1H, dd, *J* = 9.6, 13.1 Hz, C-6H_{exo}), 2.54 (1H, dd, *J* = 4.3, 13.1 Hz, C-6H_{endo}). ^{13}C NMR: δ 148.2 (C-3'), 136.7 (C-1'), 134.7 (C-6'), 133.2, 131.6 (C-2, C-3), 129.6 (C-5'), 123.9 (C-2'), 123.5 (C-4'), 93.9 (C-7), 84.3, 79.2 (C-1, C-4), 50.8 (C-5), 39.9 (C-6). MS: 471 (0.6), 470 (0.2), 469 (2), 468 (0.5), 467 (3), 466 (0.6), 465 (3), 464 (0.1) and 463 (1) all M^+, 324 (2), 323 (1), 322 (14), 321 (3), 320 (50), 319 (6), 318 (99), 317 (6), 316 (100), 315 (2), 314 (38), 310 (2), 300 (0.8), 299 (10), 298 (2), 297 (25), 296 (2), 295 (31), 294 (1), 293 (14), 243 (3), 242 (1), 241 (19), 240 (3), 239 (57), 238 (5), 237 (88), 236 (3), 235 (55), 220 (2), 219 (0.7), 218 (5), 217 (1), 216 (11), 215 (1), 214 (9), 172 (9), 170 (28), 149 (15), 133 (14), 103 (33), 77 (34).

Readily discernible signals for the minor adduct **80**: ^1H NMR: δ 4.20 (1H, dd, *J* = 4.8, 9.8 Hz, C-5H). ^{13}C NMR: δ 51.8 (C-5), 41.1 (C-6).

(5*R*,8*S*,10*s*)- (81) and (5*R*,8*S*,10*r*)-10-Bromo-5,6,7,8,10-pentachloro-5,8-dihydro-5,8-methano-(1*H*)-[1,2,4]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (82).



81



82

A solution of diene **70** (0.147 g, 0.460 mmol) and 4-phenyl-1,2,4-triazoline-1,3-dione (0.088 g, 0.48 mmol) in benzene (10 mL) was heated at reflux for two days. The solution was concentrated under vacuum. Flash chromatography (elution with 5% ethyl acetate-hexane) afforded an inseparable mixture of **81** and **82**, (0.188 g, 83%). Crystallization of the mixture from dichloromethane-hexane gave colorless crystals composed of **81** and **82**: mp: 137-140 °C, but first turning pink at 130 °C. IR: 1804, 1749 cm^{-1}. ^{13}C NMR: δ 154.6 (C-1, C-3), 129.6 (Ar), 129.5 (Ar), 129.4 (Ar or C-6, C-7), 125.5 (Ar), 92.8 (C-10), 87.0 (C-5, C-8). MS: no M^+, 460 (0.4), 458 (2), 456 (2) and 454 (1) all M^+-Cl, 324 (0.6), 322 (5), 320 (18), 316 (34), 314 (13), 287 (0.3), 285 (3), 283 (7), 281 (8), 279 (4), 243 (3), 241 (20), 239 (64), 237 (100), 235 (62), 119 (68), 91

(31), 64 (19). Anal. calcd for $C_{13}H_5BrCl_5N_3O_2$: C, 31.71; H, 1.02; N, 8.53; found: C, 31.69; H, 1.00; N, 8.50.

Readily discernible signals for the minor adduct **82**: ^{13}C NMR: δ 127.8 (C-6, C-7), 86.4 (C-10). The structure and the adduct ratio were confirmed by X-ray crystallography.

Part II

A TANDEM-ENE APPROACH TO THE SYNTHESIS OF A LINEAR TRIQUINANE.

I. Introduction

The ene reaction was first recognized in 1943 by Alder *et al.*[54] The classical ene reaction involves the thermal reaction of an alkene bearing an allylic hydrogen (an "ene") with an electron-deficient unsaturated compound (an "enophile") to form two σ-bonds with migration of the π-bond (Scheme 16).

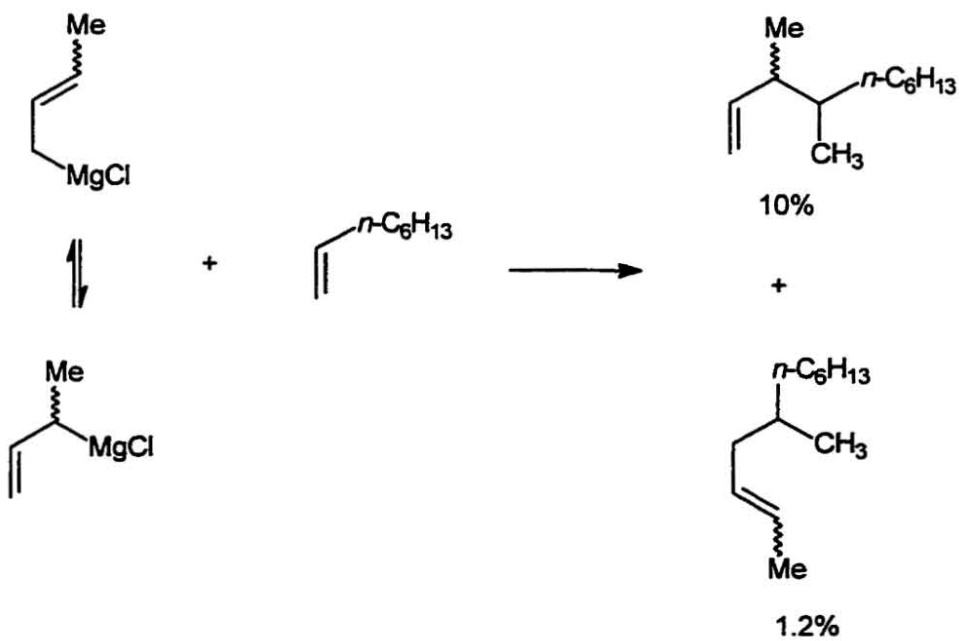
ene enophile

Scheme 16. Depiction of a classical ene reaction.

The ene reaction is defined as a six-electron pericyclic process and is mechanistically related to the better known Diels-Alder reaction. In the ene reaction the two electrons of the allylic C-H σ-bond replace the two π-electrons of the diene in the Diels-Alder reaction. Thus, the activation energy is greater and

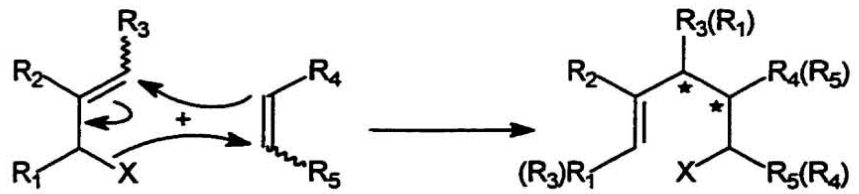
higher temperatures are generally required compared to the Diels-Alder reaction. That is the main reason why ene reactions found limited use in organic synthesis for a long time.

Starting in 1970, Lehmkuhl *et al.*[55] studied the addition of allylic Grignard reagents to alkenes or alkynes. It was found that these substrates reacted in a way analogous to the classical ene process with the hydrogen on the ene being replaced by a metal, i.e., magnesium. Despite the extensive work of Lehmkuhl, this type of reaction received virtually no attention as a tool in organic synthesis due to problems with low regio- and stereoselectivity, as well as low overall efficiency, as illustrated by Scheme 17.



Scheme 17. Example of low efficiency and selectivity for early magnesium ene reactions.

Additions of allylmetal compounds to alkenes and alkynes were classified by Oppolzer[56] as "metallo-ene" reactions (Scheme 18).

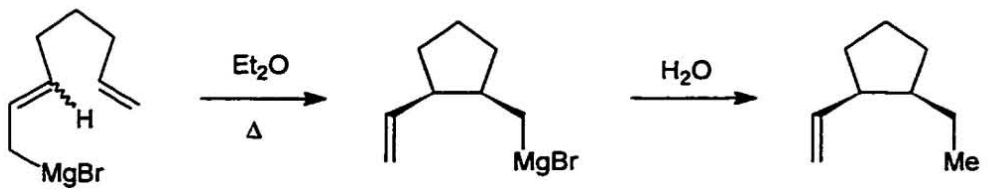


ene enophile

X=Metal

Scheme 18. Metallo-ene Reaction.

The applicability of the reactions improved dramatically when it was discovered by Felkin *et al.*[57] that when the metallo-ene reactions were carried out in an intramolecular manner they were more selective and efficient (Scheme 19).



67%

Scheme 19.

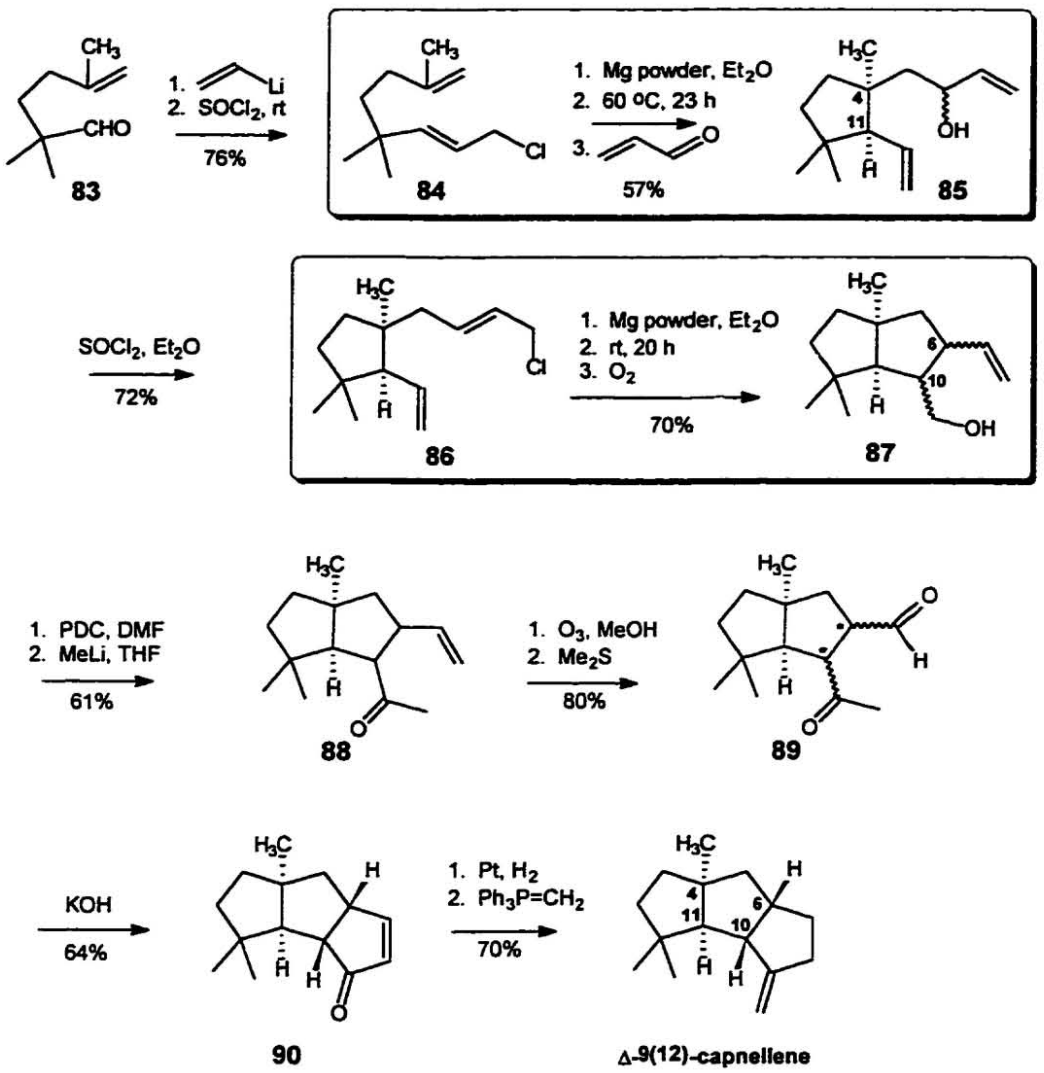
After several reports of results similar to Felkin's, the challenge of using the metallo-ene for natural product synthesis in turn spurred much exploration and extension of this methodology, particluarly by Oppolzer's group. The list of

useful metals has been extended to include zinc, lithium, palladium, platinum and nickel, in addition to the earliest examples using magnesium.

The intramolecular "metallo-ene type" reactions are entropically favored resulting in lowered activation energies relative to classical ene reactions, thereby giving reactions that occur under milder conditions than those for the classical ene. This factor made the intramolecular "metallo-ene" an attractive tool for the synthetic organic chemist.

Examples of synthetic successes follow. Oppolzer utilized iterative intramolecular "magnesium-ene" reactions to synthesize (±)–$\Delta^{9(12)}$-capnellene[58] (Scheme 20).

In the first key step, **84** to **85**, the sterically congested bond between C-4 and C-11 was formed with high stereochemical control to give a *cis* orientation of the substituents. Trapping the Grignard intermediate with acrolein set up the second magnesium-ene cyclization. Scavenging the bicyclic magnesium-ene product with oxygen gave the alcohol **87** as a 3:2 mixture of *cis* and *trans* stereoisomers. Oxidation of the primary alcohol followed by treatment with methyllithium gave the methoxy ketones **88**. Ozonolysis of **88** followed by reductive work-up with dimethyl sulfide gave **89**.

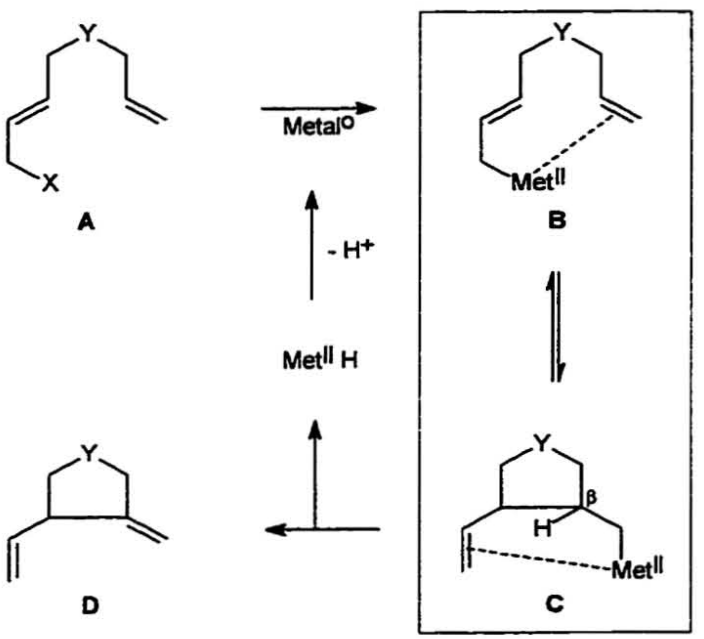


Scheme 20. Synthesis of Δ-$^{9(12)}$-capnellene by Oppolzer[58]

This kinetically derived mixture was, however, epimerized at either C-6 or C-10 resulting in the thermodynamic *cis* ring junction after the base-catalyzed aldol condensation to provide **90**. Finally, hydrogenation of the double bond and

methylenation with a salt-free solution of $Ph_3P=CH_2$ gave the product (±)–$\Delta^{9(12)}$-capnellene, a *cis-anti-cis* linear triquinane.

Oppolzer then became interested in extending the metallo-ene reaction to include the transfer of transition metals. The magnesium-ene is limited in the way that a halogen function must be present to form the pre-ene substrate. Transition metals such as Pd, Pt and Ni, however, held greater potential in terms of functional group compatibility and stereochemical control.

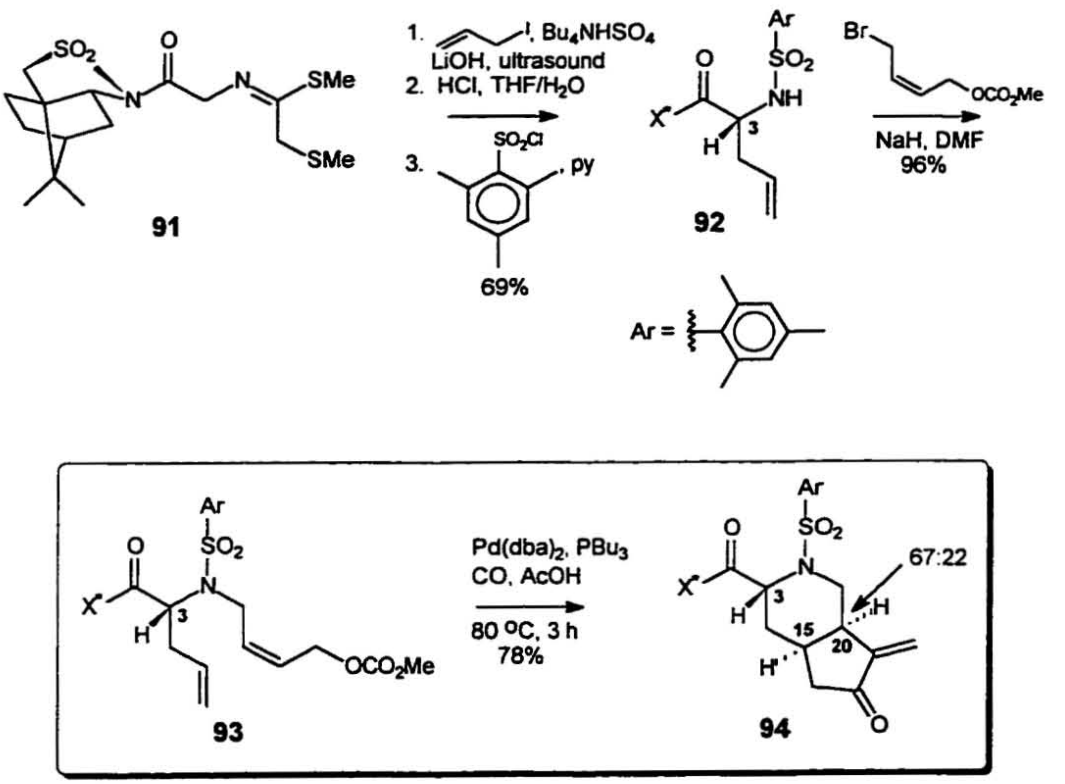


X = OAc, OH, OTHP
Y = $C(SO_2Ar)_2$, $C(CO_2Me)_2$, CH_2, NR, O

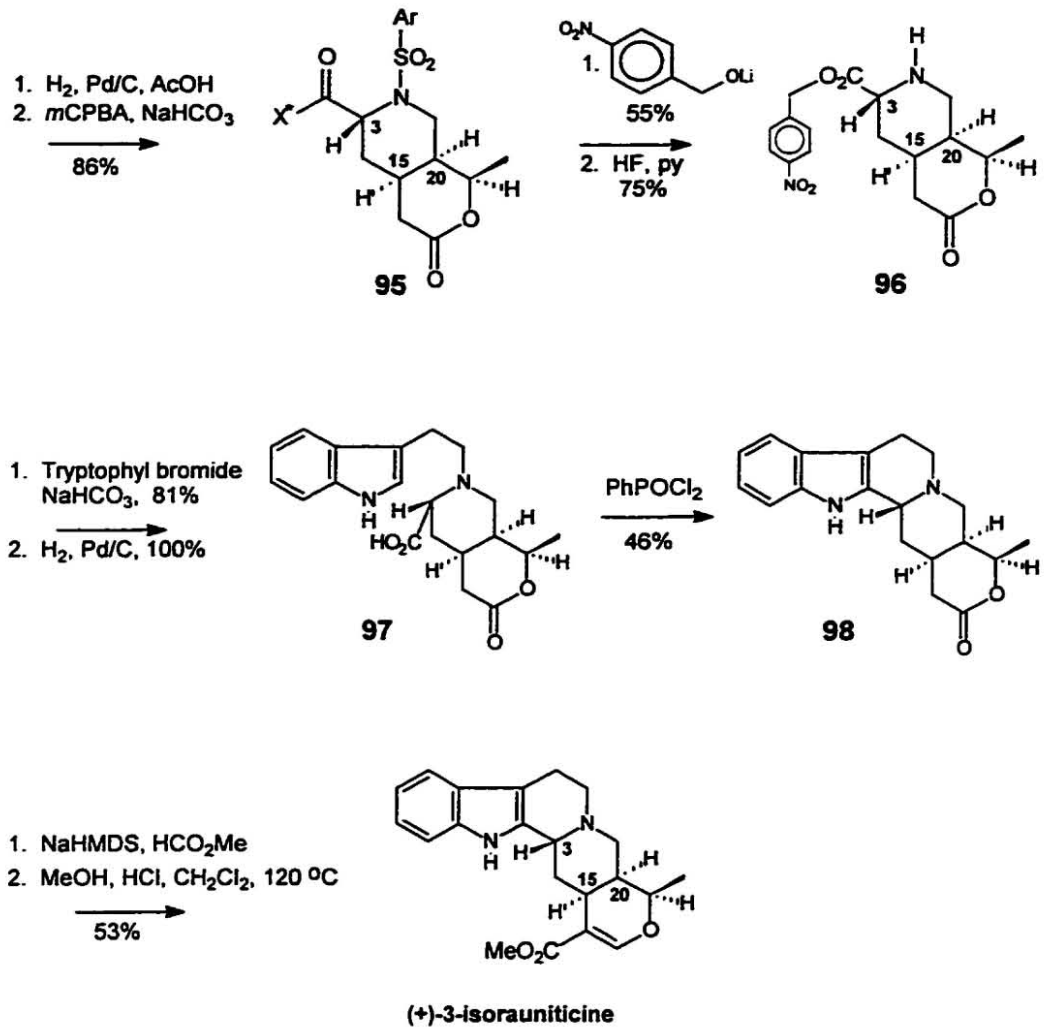
Scheme 21.

The intramolecular metallo-ene step (B→C) is followed by β-hydride elimination (C→D), which regenerates a metal(0) species that continues the catalytic cycle by oxidative addition to allyl derivatives A (Scheme 21).

An example of the palladium-ene reaction in organic synthesis is illustrated by the synthesis of (+)-3-isorauniticine by Oppolzer *et al.* (Scheme 22).[59]



Scheme 22. Synthesis of (+)-3-isorauniticine by Oppolzer *et al.*[59]



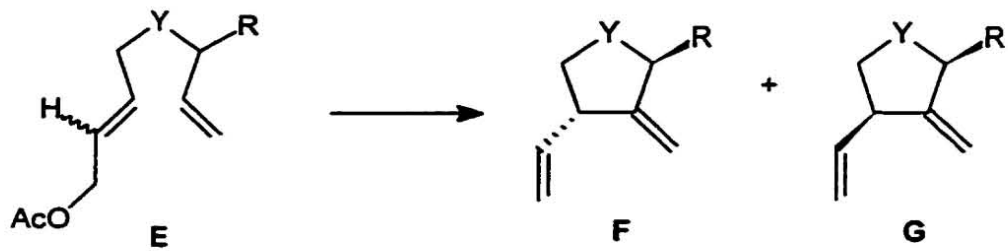
Scheme 22. continued.

The enantioselective construction of 3-isorauniticine (Scheme 22) begins with the formation of the stereocenter C-3 by asymmetric *C*-alkylation of the

commercially available chiral glycinate equivalent, **91**. This center induces the new centers C-15 and C-20 in the key step involving the Pd-catalyzed cyclization/carbonylation/β-elimination cascade. The minor C-20 epimer was removed by flash chromatography to give the desired diastereomer **94** in 52% yield. The remaining steps included catalytic hydrogenation of **94** from the less hindered face and Baeyer-Villiger oxidation to yield lactone **95**. Removal of the chiral auxiliary and cleavage of the sulfonamide gave **96** and *N*-alkylation with tryptophyl bromide provided **97**. Finally, $PhPOCl_2$-mediated Rapoport cyclization,[60] formylation of lactone **98** with sodium hexamethyldisilazane (NaHMDS), and acid-promoted Korte rearrangement[61] provided pure (+)-3-isorauniticine.

The analogous Ni(0)-catalyzed transformations proved to be less straightfoward. After some experimentation, it was determined that the utility of the Ni(0) complexes depended strongly on the metal ligands.[56a,b] A 1:1 mixture of $Ni(cyclooctadienyl)_2$ (COD) and 1,4-diphenylphosphinobutane (dppb) and $Ni(CO)_3$ and triphenylphosphine were found to be most useful. The Ni(0) catalyzed intramolecular-ene is more stereoselective than with Pd when the substrate has pre-existing stereogenic centers, as shown in Table 8.

Table 8. Comparison of Stereoselectivity for Pd and Ni ene reactions.[56d, 62]



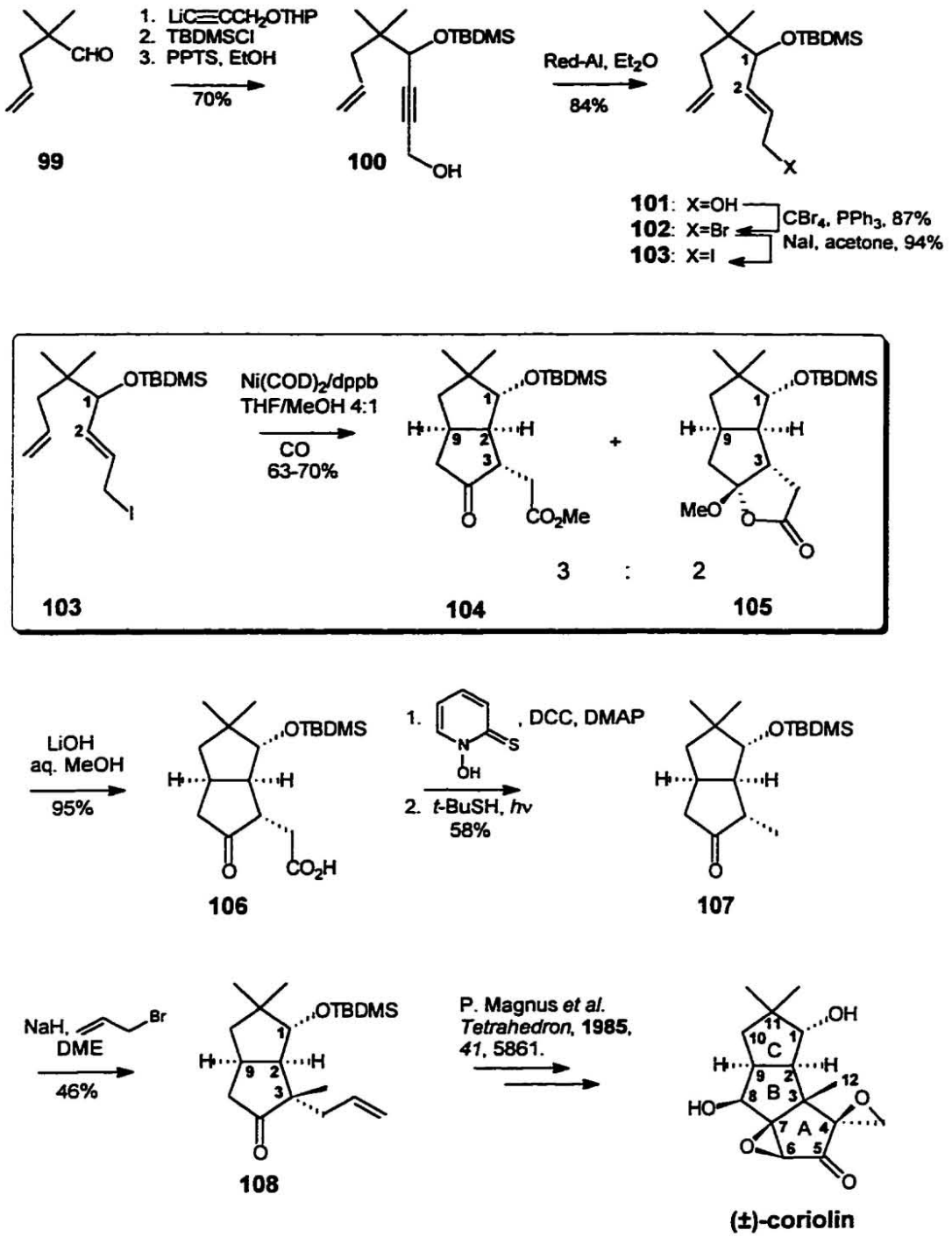
E F G

Y	R	Catalyst[a] (mol%)	Yield % (F+G)	Ratio F/G
O	*n*-C_6H_{13}	Pd (5)	62	52/48
O	*n*-C_6H_{13}	Ni (10)	79	>99/<1
CH_2	CH_2OBn	Pd (10)	67	72/28
CH_2	CH_2OBn	Ni (10)	88	97/3

a. Pd = $Pd(dba)_2/PPh_3$ (1:3), AcOH, 80 °C
Ni = $Ni(COD)_2$, dppb (1:1), THF, 20-51 °C

Oppolzer *et al.*[63] designed a formal synthesis of coriolin, another linear triquinane, around the Ni(0)-catalyzed tandem cyclization/carbonylation reaction of the iododiene **103**, (Scheme 23).

Oppolzer's synthetic plan for the coriolin precursor **108** involved formation of the C-2–C-9 bond coupled with CO insertion, which would generate the B and C rings in one step. In light of the model studies outlined in Table 8, they expected to achieve excellent induction from the chiral center present at C-1 during the Ni(0) catalysis. Hence, the synthesis was designed around this



Scheme 23. Formal synthesis of (±)–coriolin by Oppolzer *et al.*[63]

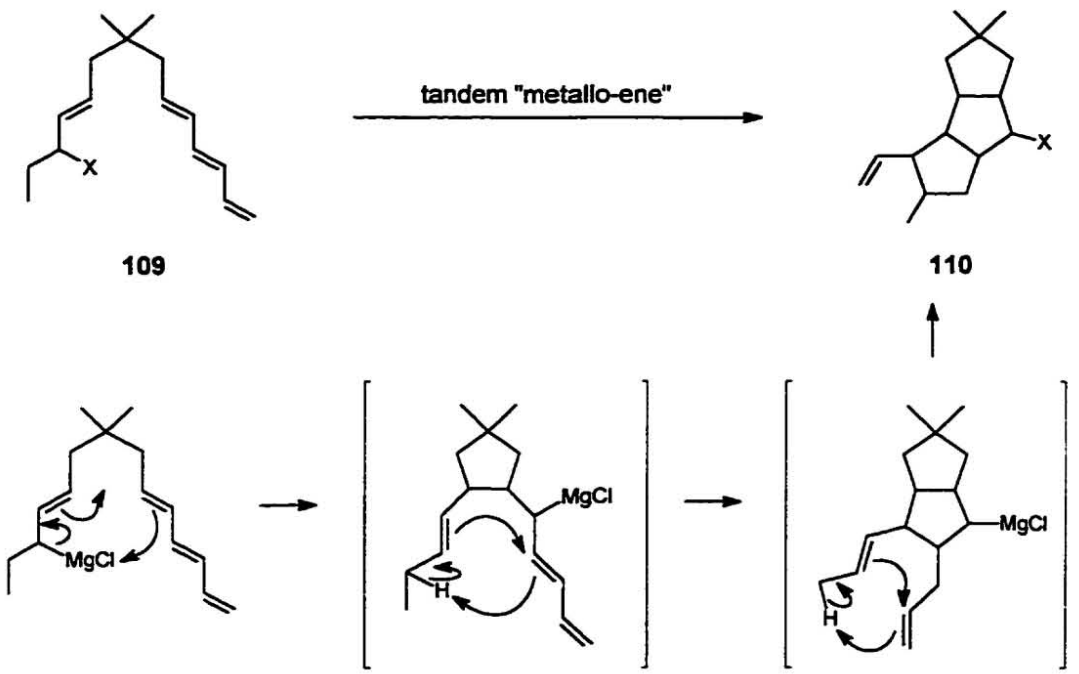
key step. 2,2-Dimethyl-4-pentenal (**99**) was converted to the iododiene **103** in six steps. The key step, the Ni(0)-catalyzed ene reaction, gave a 3:2 mixture of the expected bicyclo ketoester **104** and the isomeric lactone **105**. Mild saponification with LiOH gave only oxo-acid **106**. Since no other stereoisomer was detected, the cyclization from **103** to **104** + **105** was completely stereoselective within experimental error. This was followed by a Barton-type decarboxylation with *N*-hydroxy-2-thiopyridone and photolysis with *t*-butylthiol. Stereoselective C-3 allylation of **107** by successive treatment with NaH and allyl bromide gave Magnus' coriolin precursor **108**.[64]

As can be seen from the preceding examples, the "metallo-ene" reaction is synthetically very useful. There have been no examples, however, of its use in a tandem or cascade ene sequence to form a polyquinane. Oppolzer's iterative ene synthesis of Δ-9(12)-capnellene is not a true cascade sequence, since the intermediates are isolated between steps.

For a tandem or cascade series of reactions the process should involve two or more consecutive reactions in which subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step.[65] These sequential transformations are understood to involve bond-making or bond-breaking without isolation of any intermediates.

We decided to explore the possibility of extending the "metallo-ene" reaction to a tandem sequence. This combination could give a highly selective

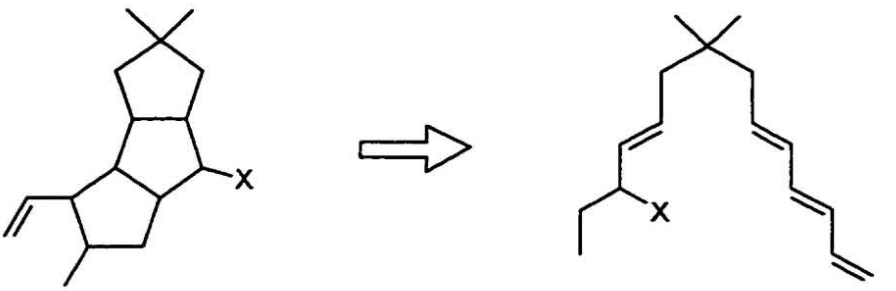
and efficient route to polyquinanes. In our specific retro-synthetic plan, the aim was to use this strategy to form a linear triquinane **110** from the tetraene compound **109**. The key step is outlined below (Scheme 24).



Scheme 24.

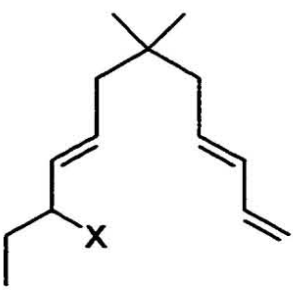
II. Results and Discussion

To explore the possibility of a tandem-ene step in forming a linear triquinane, a substrate such as **109** was required.



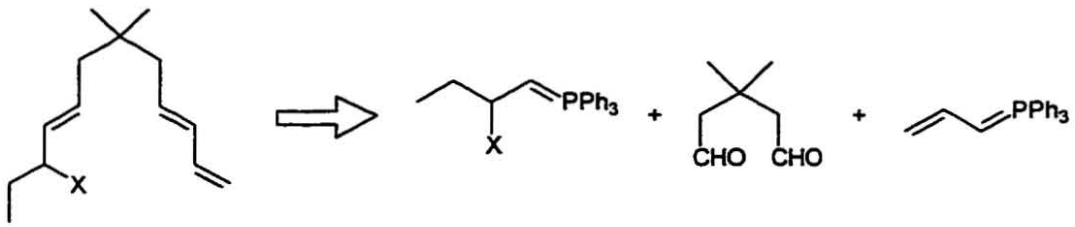
110 **109**

In the synthetic plan, compound **109** was the ultimate ene precursor. The investigation was started, however, by aiming to make a substrate resembling **111**. This compound could undergo two consecutive ene reactions to give a diquinane. This was a reasonable model to determine whether or not a more ambitious tandem process would be successful.



111

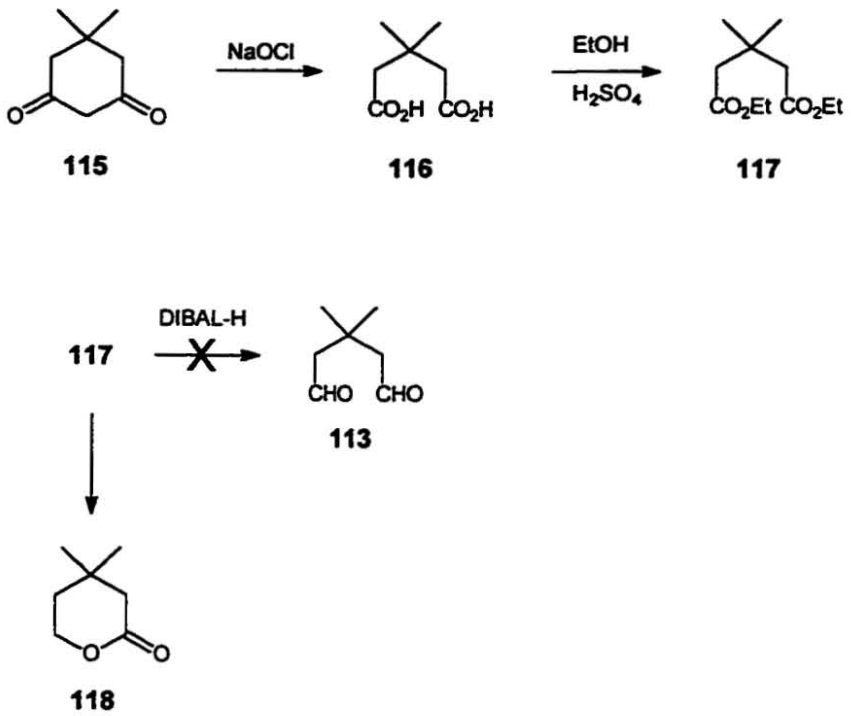
To synthesize **111** it was initially proposed to use a double Wittig strategy (Scheme 25). This reaction could only expect a maximum yield of 50% of the desired substrate **111**, but if it was formed in a single step then this would be a highly efficient way of reaching the ene precursor .



111 **112** **113** **114**

Scheme 25.

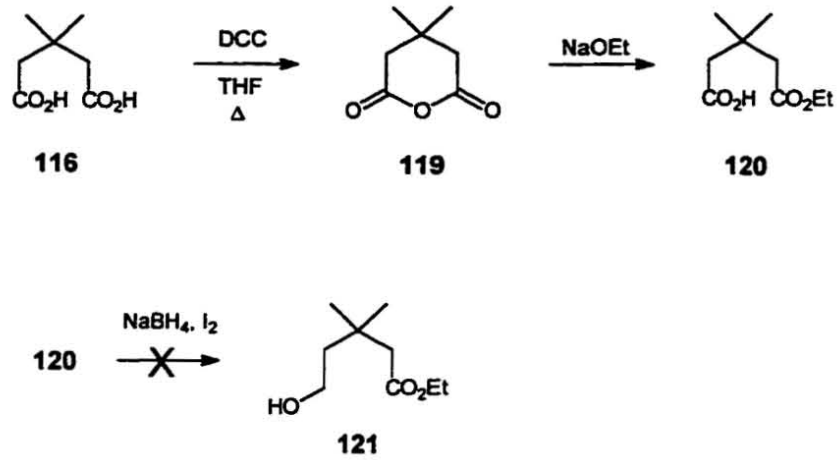
This strategy, however, proved to be a difficult one to implement since the five-carbon chain dialdehyde **113** was difficult to isolate. This chain length tends to cyclize onto itself[66] as opposed to remaining acyclic as was required. It was attempted to make the dialdehyde from the corresponding diacid, known as 3,3-dimethylglutaric acid. The diacid **116** was prepared by oxidation of dimedone **115** following a literature procedure[67] (Scheme 26).



Scheme 26.

This was followed by formation of the diethyl ester **117** in 85% yield. All attempts to reduce the diester under mild conditions with diisobutylaluminum hydride (DIBAL-H), however, did not produce any isolable dialdehyde **113**. In most cases, the only recognizable product was the lactone **118**, which was of little use for the double Wittig plan. The double Wittig idea was set aside at that point. A Wittig strategy was still pursued to form **111,** but working on one side of the molecule at a time was the new approach. In order to do this, the 3,3-dimethyl- glutaric anhydride **119** was formed from the corresponding acid

116 in 49% yield using 1,3-dicyclohexylcarbodiimide (DCC) and converted to the mono-ethyl ester **120**, in 40% yield (Scheme 27).

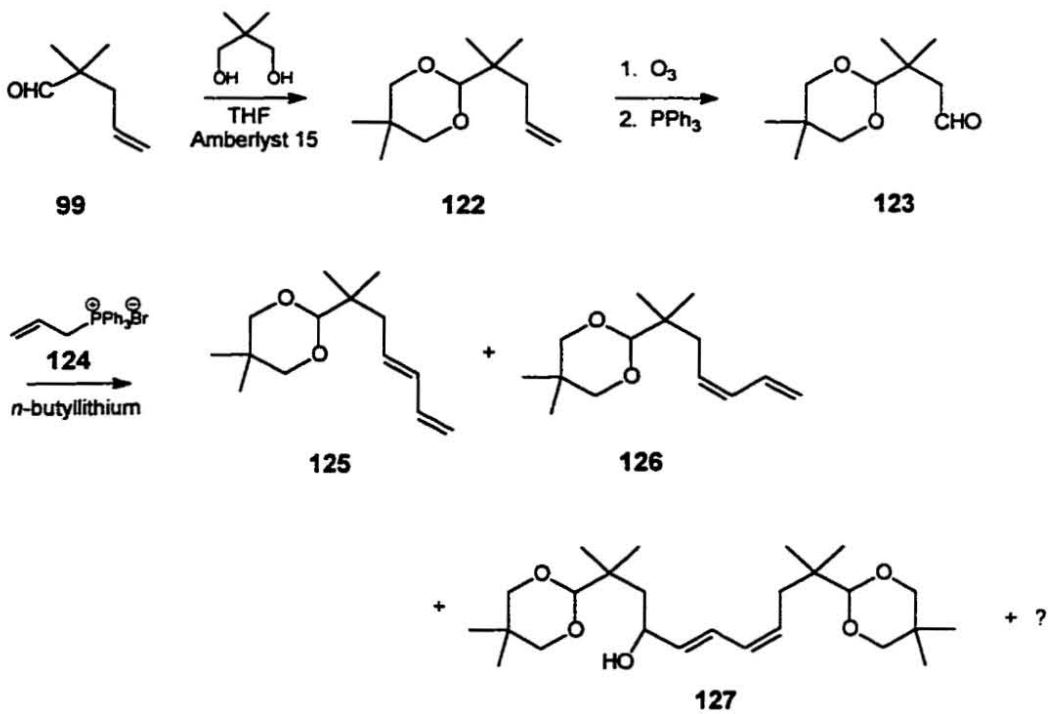


Scheme 27.

A 1991 paper by Kanth and Periasamy[68] gave examples of selective reduction of carboxylic acids to alcohols in the presence of an ester using sodium borohydride/iodine. They did not, however, investigate a substrate with the ester and acid as part of a five-carbon chain as in the substrate **120**. Once again the only recognizable substance in the product was the lactone **118**. The ethyl ester had been completely cleaved.

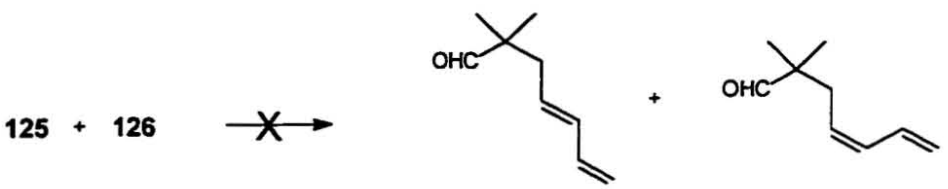
At this point it was realized that while preparing one side of the molecule for the Wittig reaction the remaining side of the molecule would have to be protected with something hardier than an ester group. A preparation of 2,2-dimethyl-4- pentenal (**99**) by Brannock[69] spurred a new idea to prepare a

substrate suitable for the Wittig reaction with allyltriphenylphosphorane **114**. The aldehyde **99** was protected as a cyclic acetal with 2,2-dimethyl-1,3-propanediol to give **122** in 85% yield. This alkene was then treated with ozone to cleave the double bond and give an aldehyde **123** in 85% yield which was suitable to undergo a Wittig reaction. The allyltriphenylphosphonium bromide **124**, prepared from allyl bromide and triphenylphosphine,[70] was treated with *n*-butyllithium (2.5 M solution in hexanes) to give the required ylid **114**. Reaction with the aldehyde **123** gave a nearly equivalent mixture of *trans* and *cis* dienes, **125** and **126** in 31% yield, as well as two unexpected compounds (Scheme 28).



Scheme 28.

The production of the nearly equivalent mixture of *cis* and *trans* isomers **125** and **126** should not be a problem since both isomers should lead to the *cis*-substituted cyclopentane derivatives by ene processes.[71] One of the unexpected products may be **127**, for which the NMR data would be consistent. Johnson[72] states that allylic ylides may react at both the α and γ carbons due to isomerization of the ylid double bond. The result would be a compound like **127**, which has linked together two molecules of the aldehyde **123**. The second unexpected product was not readily identified by its ^{1}H NMR spectra. The shortcoming of the cyclic acetal as a protecting group for the aldehyde was revealed in the next step, since attempts to remove it were unsuccessful (Scheme 29). Extremely forcing conditions were thought to be of little use since they would have resulted in destruction of the diene functionality.



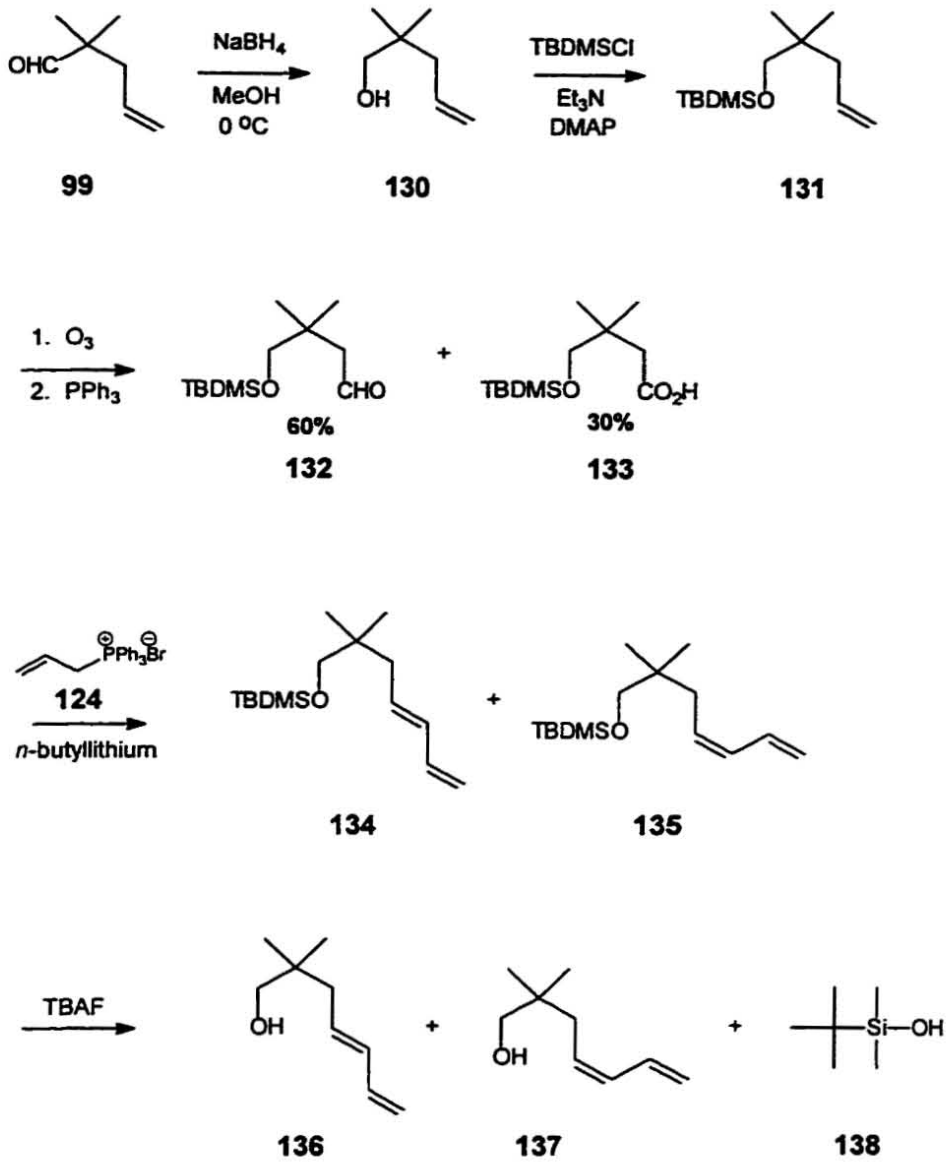
128 **129**

Scheme 29.

Since the acetal had proved to be a poor choice of protecting group, the next choice was the use of a silyl ether.[72] Once more the synthetic sequence was started from the aldehyde **99**. It was reduced with sodium borohydride in

85% yield to give the corresponding alcohol **130**. This alcohol was then protected as the *tert*-butyldimethylsilyl (TBDMS) ether **131**. Similar to the protected alkene in Scheme 28, this terminal alkene was ozonolized to give the desired aldehyde **132** in 60% yield. This aldehyde proved to be very easily oxidized in air, thus a portion of the sample was the corresponding carboxylic acid **133**. The amount of carboxylic acid was kept low by carefully excluding air and moisture during isolation.

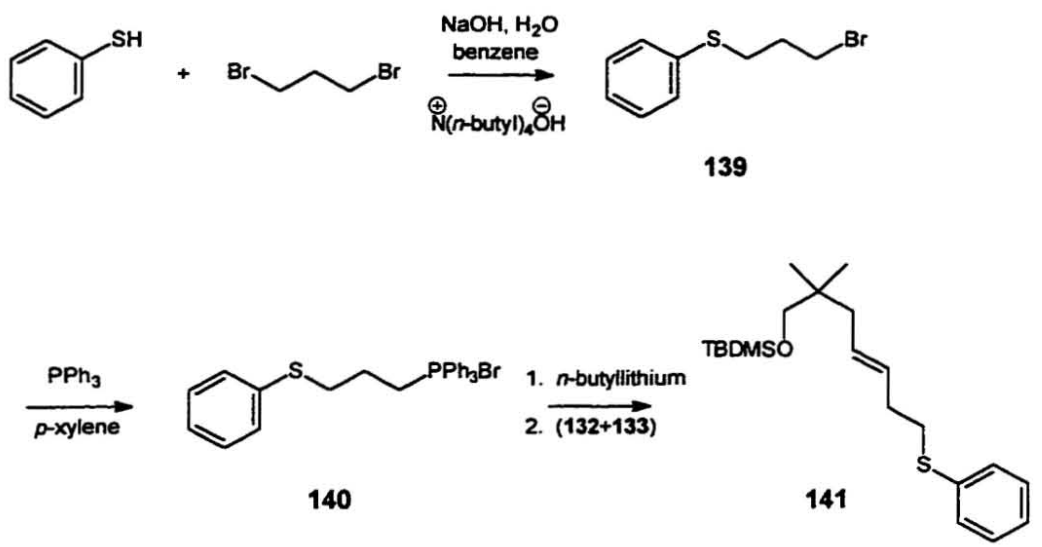
The aldehyde-acid mixture was subjected to the Wittig reaction conditions with allyltriphenylphosphorane produced *in situ* from **124** and *n*-butyllithium. A nearly equal mixture of the *trans* and *cis* dienes **134** and **135** was again produced in low 29% yield. In this case none of the product from γ-carbon attack of the ylid was isolated. Removal of the silyl ether protecting group provided another unexpected hurdle. The TBDMS group was easily cleaved with tetrabutylammonium fluoride (TBAF), but the by-product *tert*-butyldimethylsilanol (**138**), boiled at nearly the same temperature as the desired *trans* and *cis* alcohols, **136** and **137** (Scheme 30). The inability to purify the alcohols would have been a problem in continuing with this approach, and the low boiling points of the test molecules would have been a problem throughout the synthesis.



Scheme 30.

To circumvent the problems inherent to small molecules, it was thought that a larger ylid with functionality which could later be converted to a terminal

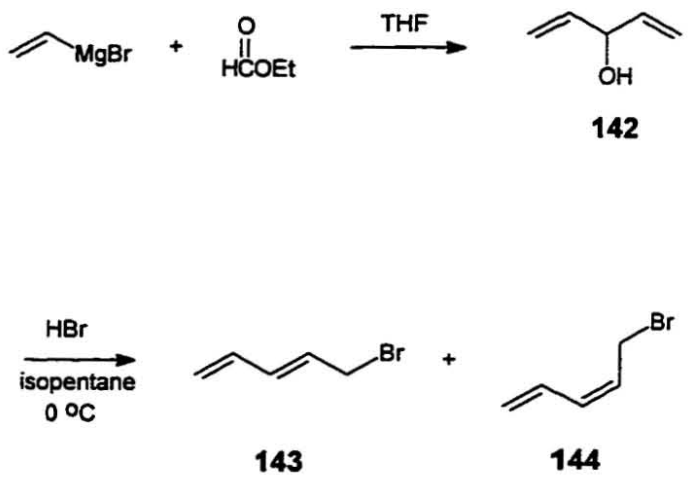
diene would allow separation of the desired substrate from the by-product **138**. To pursue this strategy the bromosulfide **139** was prepared from thiophenol and 1,3-dibromopropane using phase-transfer technology.[74] Bromosulfide **139** was converted to the ylid salt **140** in a modest 56% yield. Wittig reaction with the aldehyde-acid mixture (**132** and **133**) gave the corresponding alkene **141** in 27% yield (Scheme 31).



Scheme 31.

This route was halted, however, when a more direct and efficient method was found to synthesize the alcohol **136**. Wender *et al.*[75] described the preparation of this alcohol via alkylation of methyl isobutyrate with pentadienyl bromide. Pentadienyl bromide (**143**) is a relatively unstable species which must

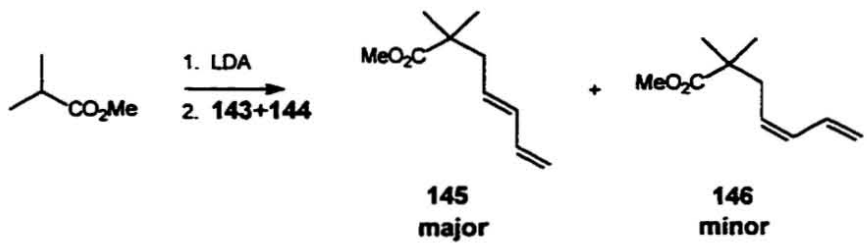
be freshly prepared before use. It was formed in 73% yield[76] from 1,4-pentadien-3-ol (**142**) (Scheme 32), which is commercially available but rather expensive. Compound **142** was prepared by the Grignard reaction of vinyl magnesium bromide with ethyl formate.[77] The pentadienyl bromide produced consisted of major and minor, *trans* and *cis*, dienes **143** and **144**. This mixture was used for the alkylation step.



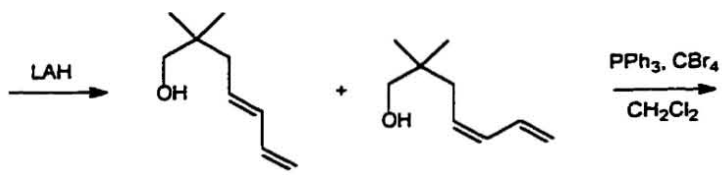
Scheme 32.

Alkylation of methyl isobutyrate with lithium diisopropylamide (LDA) and pentadienyl bromides **143** and **144** gave the mixture of methyl esters **145** and **146** in a 78% yield after distillation. Alcohols **136** and **137** were obtained by lithium aluminum hydride (LAH) reduction of the esters **145** and **146**. Following this success was the required task of assembling the remaining side of the molecule to obtain the ene substrate **111**. The strategy involved conversion of

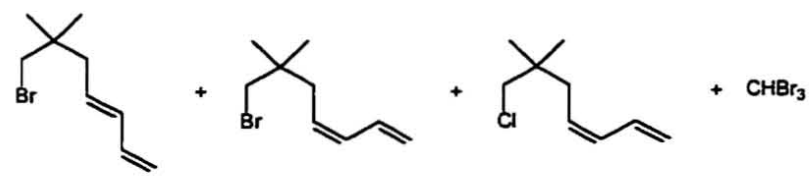
the alcohols **136** and **137** to the bromides **147** and **148** as shown in Scheme 33, followed by formation of the corresponding Grignard reagents. Attack of these Grignard reagents on an appropriate aldehyde could complete the formation of **111**.



145 **major** **146** **minor**



136 **137**

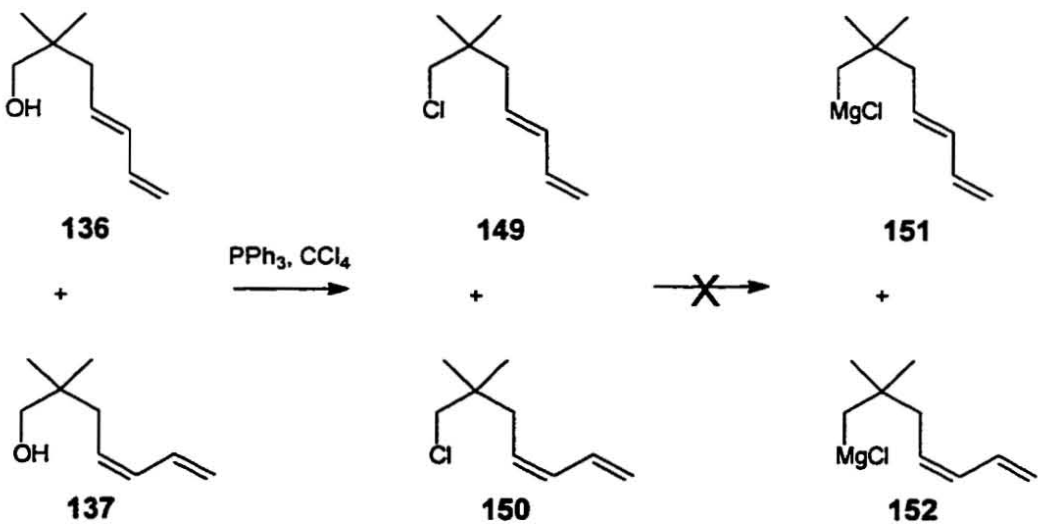


147 **148** **149**

Scheme 33.

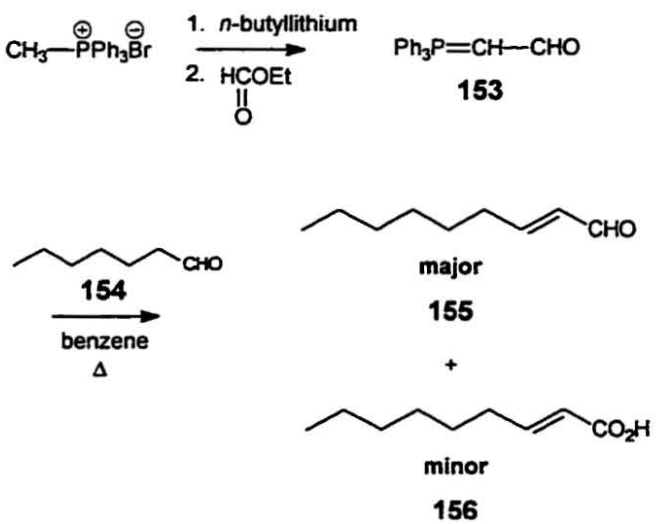
The production of the bromide from the alcohol via triphenylphosphine/carbon tetrabromide gave the desired products **147** and **148**, as well as some chloride **149** for a combined yield of approximately 80%. Unfortunately, the remaining CBr_4 and the by-product bromoform ($CHBr_3$) were not separable from the halogenated dienes (**147**, **148** and **149**). Once again, it was believed that carrying on without purification would cause problems later in the synthesis.

The next approach involved making the chloride version of **147** and **148** (Scheme 34). Chlorination of the alcohols **136** and **137** with triphenylphosphine and carbon tetrachloride resulted in a 64% yield of the desired dienes **149** and **150**. In this case the by-product, chloroform ($CHCl_3$), was easily removed under vacuum.



Scheme 34.

In order to conduct the planned Grignard reaction an α,β-unsaturated aldehyde was required. Thus, 2-nonenal was prepared by the following Wittig reaction (Scheme 35). Formyltriphenylphosphorane (**153**) was prepared from methyltriphenylphosphorane generated *in situ* with *n*-butyllithium and ethyl formate. The resulting ylid was produced in 33% yield. Reaction of the ylid **153** with heptanal (**154**) in refluxing benzene gave the aldehyde **155** in 31% yield. The aldehyde was the major product, but a minor amount of the carboxylic acid **156** was also detected.

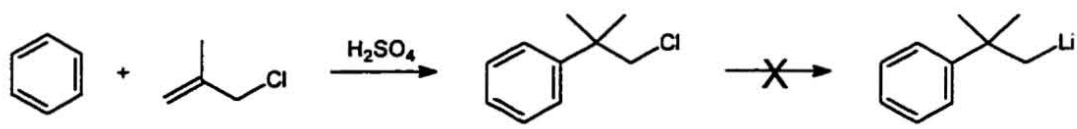


Scheme 35.

Having a suitable aldehyde in hand we were ready to carry out the Grignard reaction to form the remaining portion of the molecule, which would

resemble compound **111**. Formation of the Grignard reagent from the less reactive chloride, however, did not succeed. Several standard methods using Mg(0) were employed in addition to a procedure for activated magnesium from $MgCl_2$ and lithium naphthalide.[78] Only scrupulously dry magnesium chloride will be successful for this procedure[79] and it was believed that failure with this method using the chlorides **149** and **150** was because the $MgCl_2$ was not sufficiently dry.

It was thought that perhaps lithium would succeed where magnesium had failed to generate organometallic reagents from **149** and **150**. This was tried with 1-chloro-2-methyl-2-phenylpropane (**157**) as a test molecule. Neophyl chloride (**157**) was formed in 33% yield from benzene and methallyl chloride (Scheme 36)[80].

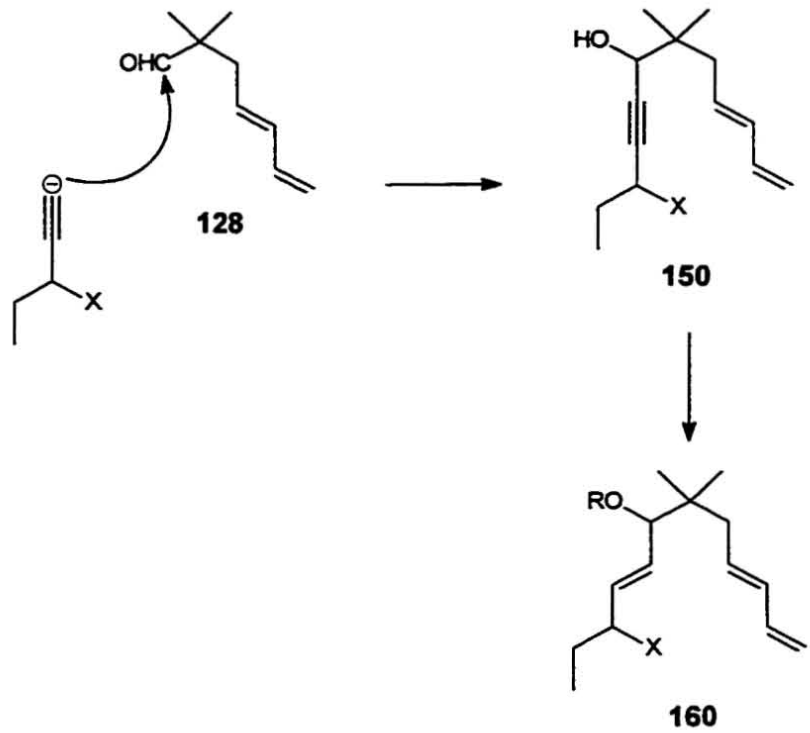


157 **158**

Scheme 36.

However, attempts to form the neophyl lithium (**158**) using *tert*-butyllithium and finely divided lithium metal were unsuccessful. The unchanged neophyl chloride (**157**) was recovered in every case. The more reactive iodide has been

converted to the organolithium in some cases[81] for neopentyl-type carbons. The chloride, however, appears to be quite unreactive with both lithium and magnesium. For this reason the approach to forming the remaining portion of **111** changed from attack of a neopentyl-type carbon onto to an aldehyde, to the attack of an appropriate fragment onto the neopentyl carbon (Scheme 37).

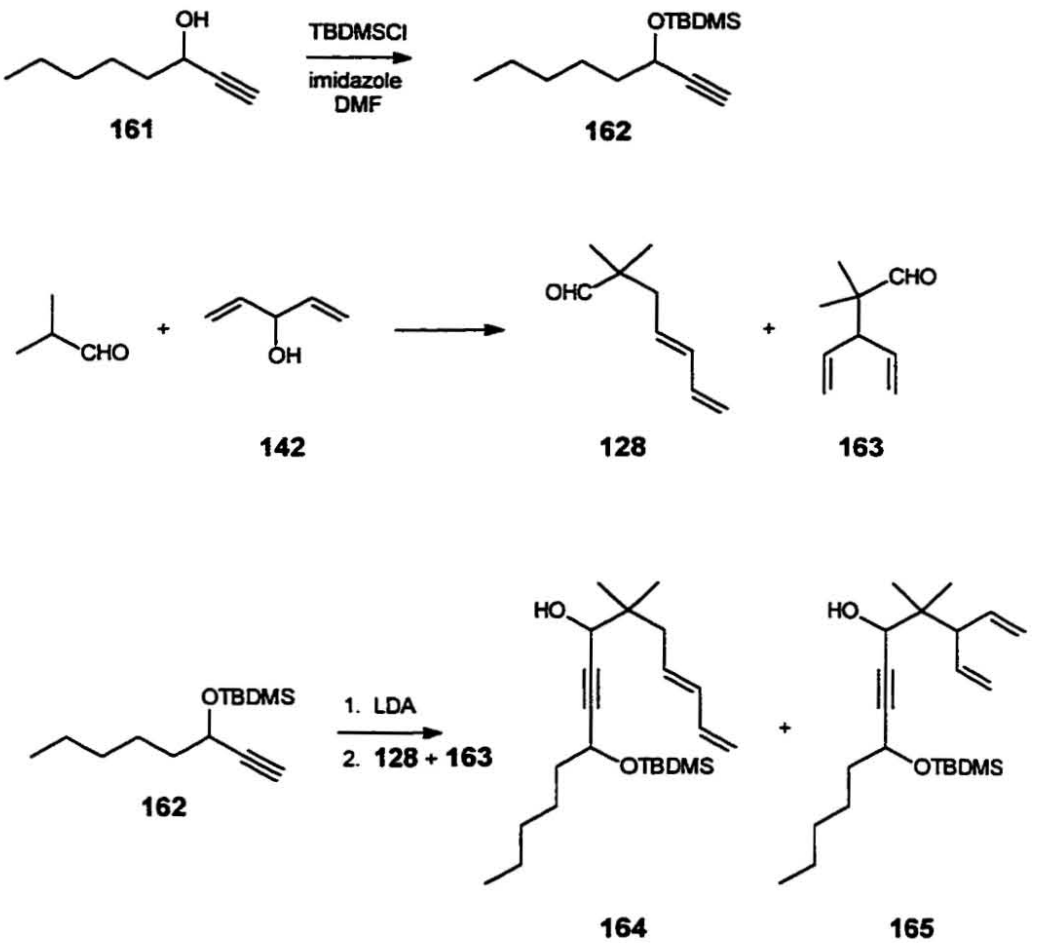


Scheme 37.

It was thought that an alkyne would be useful as such a nucleophile owing to its relatively compact size. Following the alkyne attack, the synthetic plan involved protection of the resulting hydroxy group followed by selective

hydrogenation of the triple bond to give a substrate **160**, which would resemble the original compound **111**.

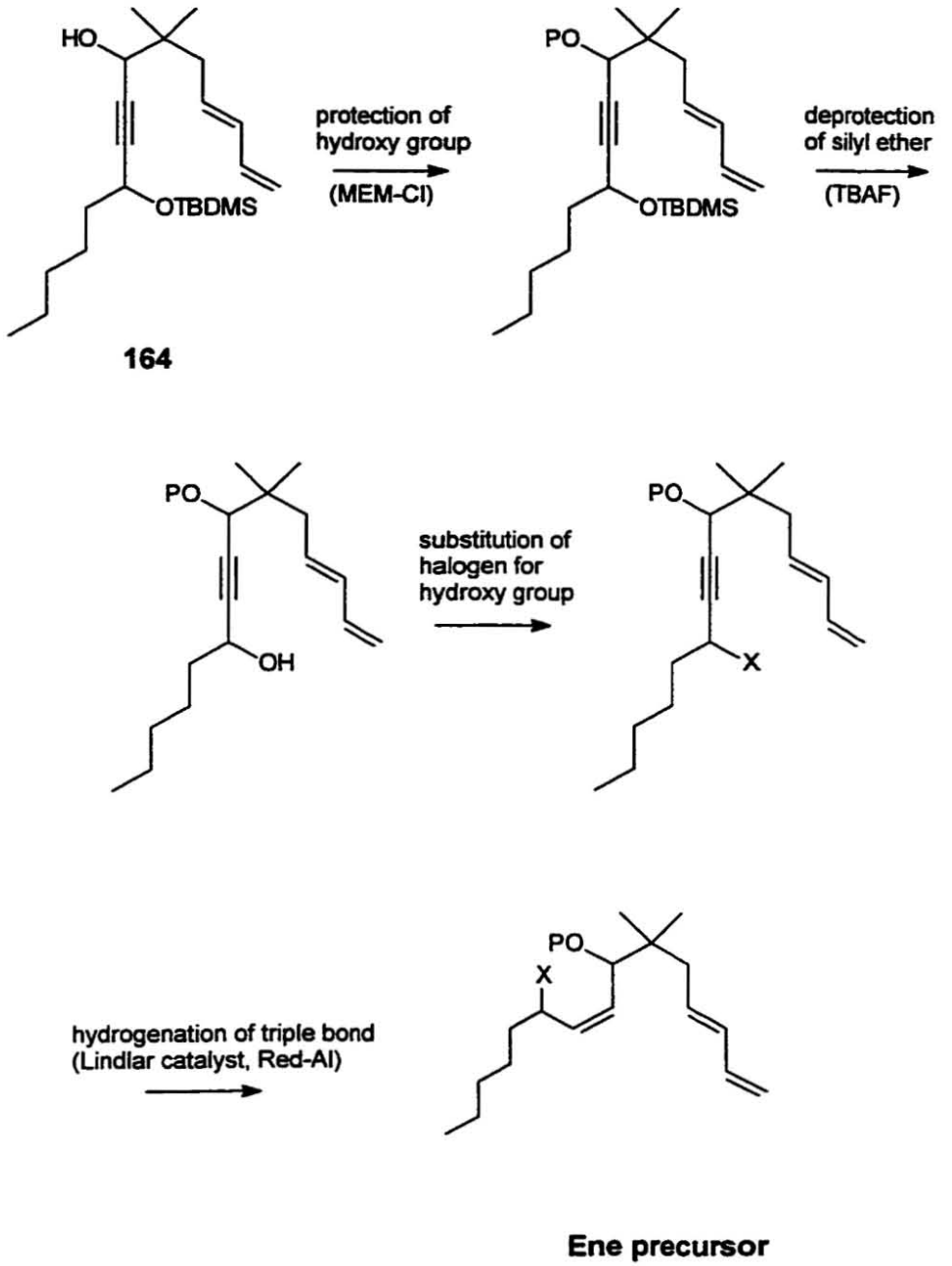
The alkyne chosen was commercially available 1-octyn-3-ol (**161**). It was protected as a silyl ether with TBDMSCl to give a 72% yield of **162** (Scheme 38).



Scheme 38.

The required aldehyde **128** was prepared using an acid-catalyzed condensation between isobutyraldehyde and divinylcarbinol (**142**). This type of

reaction had yielded the 2,2-dimethyl-4-pentenal (**99**) used earlier in the synthesis.[69] The result was a 42% yield of compounds **128** and **163** in a 3:1 ratio. This inseparable mixture was used in the next step. The alkyne **162** was deprotonated using LDA at -78 °C followed by addition of the mixture of aldehydes **128** and **163**. The result was a 4% yield of **164** as well as a 4% yield of **165** from addition to **163**. A large proportion of the starting alkyne was also recovered. There appeared to be a single diastereomer isolated for the samples of **164** and **165**. The yield was low, however, and therefore flash chromatography may have failed to provide the other diastereomers in detectable quantities. In any case, diastereoselectivity was not expected for this experiment. This reaction has obviously not been optimized and some further work is required but an entry is indicated to provide compounds of the type required for tandem ene processes. This includes protection of the hydroxy group, selective hydrogenation of the triple bond, removal of the silyl ether and conversion of the resulting hydroxy group to a halogen. Ideas for future work are outlined in Scheme 39.

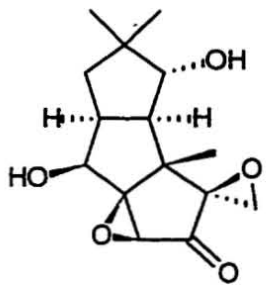


164

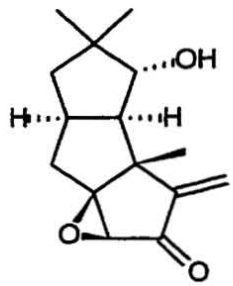
Ene precursor

Scheme 39.

With progress in the synthesis having reached compound **164**, it is believed that a route to the substrates similar to **111** has been uncovered. A bonus using this strategy is the presence of an oxygen functionality on the carbon which neighbors the quaternary carbon with the *gem*-dimethyl groups. This oxygen functionality is present in some natural linear triquinanes, such as coriolin and hypnophilin.[82]



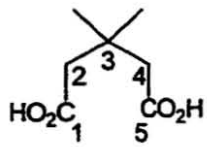
coriolin



hypnophilin

III. Experimental[83]

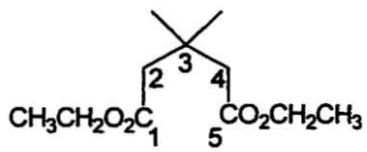
3,3-Dimethylglutaric acid (116).



To a solution of NaOH (80.0 g, 2.00 mol) in water (110 mL) was added 446 g of crushed ice. Then Cl_2 was bubbled into this solution until 58 g had been absorbed. Dimedone (**115**) (25.0 g, 0.178 mol) was dissolved in a solution of KOH (23.2 g, 0.413 mol) in water (190 mL). The resulting yellow solution was then added dropwise, with stirring, to the sodium hypochlorite solution. A maximum temperature of 42 °C was observed during the addition. After the addition was complete, the reaction mixture was stirred for 7 h at rt. While continuing to stir, Na_2SO_3 (18.0 g, 0.174 mol) was added to the reaction mixture. This was followed by acidification to pH 1 using concentrated HCl. The solution was left to stand at rt overnight. The excess water was removed by simple distillation until a precipitate began to form in the distillation flask. The residue was cooled to rt and 100 mL of ether, as well as enough water to redissolve the precipitate were added. This solution was extracted with ether (3 x 75 mL). The ether extracts were combined and dried over $MgSO_4$. Evaporation of the solvent gave the product **116** as a white crystalline solid (18.9 g, 67%). Recrystallization of a small sample from benzene gave colorless crystals: mp: 99-101 °C. IR:

3020, 1709 cm^{-1}. ^1H NMR: δ 11.64 (2H, broad s, CO_2H), 2.52 (4H, s, C-2H, C-4H), 1.17 (6H, s, 2 x CH_3). ^{13}C NMR: δ 178.6 (C-1, C-5), 44.6 (C-2, C-4), 32.3 (C-3), 27.7 (CH_3). MS: no M^+, 142 (13, M^+-H_2O), 127 (17), 114 (25), 101 (36), 83 (46), 59 (100), 55 (33), 43 (47), 41 (27).

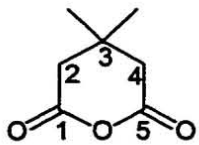
Diethyl, 3,3-dimethylglutarate (117).



3,3-Dimethylglutaric acid (**116**) (18.1 g, 0.113 mol) was dissolved in absolute ethanol (200 mL). To this was added 1.3 mL of concentrated sulfuric acid. After several days of stirring at rt the esterification was not complete. The mixture was heated at reflux for 24 h. The ethanol was removed under vacuum, and the residue was extracted with ether. The combined ether layers were washed with 0.1M NaOH, brine and then dried over $MgSO_4$. Concentration under vacuum gave the crude diester, which was purified by vacuum distillation. The product was collected over 97-105°C at 3 mm Hg to give **117** as a colorless liquid (14.2 g, 58%). Also, a 3:1 mixture of diester and mono-ester (8.7 g) was collected in the range 105-108°C at 3 mm Hg. A total yield of 85% was achieved for production of the diethyl ester. IR: 2981, 1734, 1468, 1370 cm^{-1}. ^1H NMR: δ 4.12 (4H, q, J = 7.2 Hz, O**C**H_2CH_3), 2.41 (4H, s, C-2H, C-4H), 1.26 (6H, t, J = 7.1

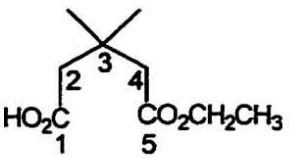
Hz, OCH_2CH_3), 1.12 (6H, s, CH_3). ^{13}C NMR: δ 171.6 (C-1, C-5), 59.8 (OCH_2CH_3), 45.1 (C-2), 32.4 (C-3), 27.4 (C-3 CH_3), 14.1 (OCH_2CH_3). MS: 216 (M^+, 1), 171 (100), 170 (20), 155 (2), 143 (27), 142 (47), 129 (72), 127 (16), 101 (23), 88 (15), 87 (53), 83 (55), 73 (11), 69 (20), 60 (19).

3,3-Dimethylglutaric anhydride (119).



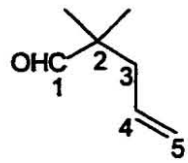
To a solution of 3,3-dimethylglutaric acid (**116**) (3.70 g, 23.1 mmol) in THF (40 mL) was added dicyclohexylcarbodiimide (7.11 g, 34.4 mmol) suspended in THF (20 mL). The resulting mixture was stirred at rt under a $CaCl_2$ drying tube for 3 days. Reaction progress was slow, therefore the mixture was heated at 50 °C for a further 7 days. The reaction was stopped and the residue filtered through Celite. Concentration of the filtrate gave crystals coated with a yellow oil. This oil was removed by rinsing the crystals with ether. The result was **119** as a white crystalline solid (1.61 g, 49%): mp: 125-126 °C. IR: 2967, 2936, 2878, 1811, 1774 cm^{-1}. ^1H NMR: δ 2.61 (4H, s, C-2H, C-4H), 1.15 (6H, s, CH_3). ^{13}C NMR: δ 166.2 (C-1, C-5), 43.7 (C-2, C-4), 29.4 (C-3), 27.4 (CH_3). MS: 143 (M^++H, 0.6), 98 (0.3), 70 (32), 56 (100).

3,3-Dimethylglutaric acid, mono-ethyl ester (120).



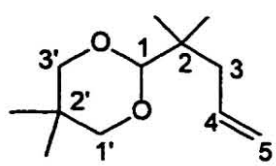
Sodium metal (0.450 g, 19.6 mmol) was added to absolute ethanol (10 mL). When the evolution of H_2 gas had subsided, 3,3-dimethylglutaric anhydride (**119**) (1.98 g, 13.9 mmol) was washed in with 2 mL of absolute ethanol. The solution was refluxed for 20 h. The ethanol was removed under vacuum, and the residue was taken up in water. This was extracted with ether. Then the aqueous layer was acidified with 3M HCl and extracted twice with ether. The combined ether layers were washed with water and brine and dried over $MgSO_4$. Concentration under vacuum gave the crude monoester. The product was purified by vacuum distillation to give **120** as a colorless liquid (1.05 g, 40%): bp: 142-150°C at 25 mm Hg. IR: 3600-2400 (broad, strong), 1731, 1710 cm^{-1}. ^1H NMR: δ 11.5-10.5 (1H, broad s, CO_2H), 4.13 (2H, q, J = 7.1 Hz, $O\mathbf{CH_2}CH_3$), 2.48 (2H, s, C-2H), 2.44 (2H, s, C-4H), 1.26 (3H, t, J = 7.2 Hz, $OCH_2\mathbf{CH_3}$), 1.15 (6H, s, 2 x CH_3). ^{13}C NMR: δ 177.9 (C-1), 172.0 (C-5), 60.2 ($O\mathbf{CH_2}CH_3$), 45.0 and 44.0 (C-2 and C-4), 32.4 (C-3), 27.6 (2 x CH_3), 14.1 ($OCH_2\mathbf{CH_3}$).

2,2-Dimethyl-4-pentenal (99).



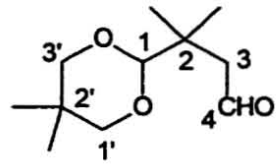
To a 3-necked flask equipped with a stopper, thermometer, and fractionating column topped with a Dean-Stark trap was added allyl alcohol (12 mL, 0.18 mol), 2-methylpropanal (24 mL, 0.26 mol), *p*-TsOH (0.100 g, 0.526 mmol), and *p*-cymene (30 mL). The fractionating column was wrapped with glass wool, and the temperature of the solution was slowly increased to 145 °C over 36 h. After this time, approximately 2.5 mL of water had been evolved. The reaction was stopped, and the product was collected by fractional distillation to give **99** as a colorless liquid (12.0 g, 61%): bp: 116-128 °C. IR: 2977, 1703 cm^{-1}. ^1H NMR: δ 9.48 (1H, s, C-1H), 5.70 (1H, symmetrical m, C-4H), 5.10-5.01 (2H, m, C-5H), 2.22 (2H, dt, *J* = 7.5, 1.1 Hz, C-3H), 1.06 (6H, s, 2 x CH_3). ^{13}C NMR: δ 205.5 (C-1), 133.0 (C-4), 118.2 (C-5), 45.5 (C-2), 41.3 (C-3), 21.0 (2 x CH_3). MS: 113 (M^++1, 8), 83 (65), 55 (74).

2,2-Dimethyl-4-pentenal, 2,2-dimethyl-1,3-propane acetal (122).



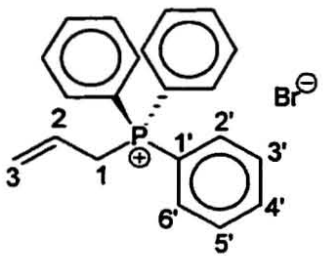
A solution of 2,2-dimethyl-4-pentenal (**99**) (9.96 g, 88.8 mmol) and 2,2-dimethyl-1,3-propanediol (46.2 g, 0.444 mol) in THF (100 mL) was stirred overnight at rt with approximately 0.75 g of Amberlyst 15®. The catalyst was removed by filtration and the THF was removed under vacuum. Water was added, and the residue was extracted with ether, then the combined ether layers were washed with water and brine, and then dried over anhydrous K_2CO_3. Evaporation of the solvent gave the crude product as a colorless liquid. The last traces of dimethylpropanediol were removed by filtration through a short silica gel column (elution with 10% ethyl acetate-hexane) to give **122** as a colorless liquid (15.2 g, 85%). IR: 2956, 2845, 1639, 1474, 1393, 1115 cm^{-1}. ^1H NMR: δ 5.82 (1H, symmetrical m, C-4H), 5.06-4.96 (2H, m, C-5H), 4.04 (1H, s, C-1H), 3.59 (2H, d, J = 10.8 Hz, C-1'H_e, C-3'H_e), 3.36 (2H, d, J = 10.8 Hz, C-1'H_a, C-3'H_a), 2.09 (2H, d, J = 7.5 Hz, C-3H), 1.15 (3H, s, C-2' $(CH_3)_e$), 0.91 (6H, s, 2 x CH_3), 0.67 (3H, s, C-2' $(CH_3)_a$). ^{13}C NMR: δ 135.2 (C-4), 117.0 (C-5), 106.8 (C-1), 77.2 (C-1', C-3'), 42.1 (C-3), 37.6, 30.1 (C-2, C-2'), 22.9 (C-2' CH_3), 21.9 (2 x CH_3), 21.7 (C-2' CH_3). MS: 198 (M^+, 0.4), 197 (2), 141 (8), 115 (100), 83 (10), 71 (11), 69 (92), 56 (22), 55 (18).

2,2-Dimethyl-1,4-butanedial, 1-(2,2-dimethyl-1,3-propane acetal) (123).



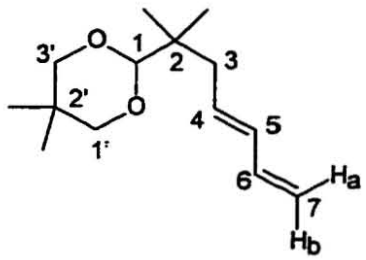
A solution of the acetal **122** (14.7 g, 74.2 mmol) in dichloromethane (250 mL) was cooled to -78 °C using a Dry Ice/acetone bath. Ozone (O_3) was bubbled through the solution until a persistent blue color was reached (~1 h). This was followed by bubbling N_2 through the solution to remove the excess O_3. Then triphenylphosphine (19.0 g, 72.4 mmol) was added, and the mixture was allowed to warm to rt overnight. The solution was washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent under vacuum gave the crude product, which was purified by flash chromatography (elution with 10% ethyl acetate-hexane) using a short silica gel column to give **123** as a yellow oil (12.6 g, 84%). IR: 2961, 2868, 1698 cm^{-1}. ^1H NMR: δ 9.83 (1H, t, *J* = 3.1 Hz, C-4H), 4.13 (1H, s, C-1H), 3.60 (2H, d, *J* = 10.1 Hz, C-1'H_e, C-3'H_e), 3.38 (2H, d, *J* = 10.1 Hz, C-1'H_a, C-3'H_a), 2.35 (2H, d, *J* = 3.1 Hz, C-3H), 1.13 (3H, s, C-2' $(CH_3)_e$), 1.08 (6H, s, C-2 2 x CH_3), 0.71 (3H, s, C-2' $(CH_3)_a$). ^{13}C NMR: δ 203.0 (C-4), 106.1 (C-1), 77.1 (C-1', C-3'), 51.0 (C-3), 38.0, 30.0 (C-2, C-2'), 23.4 (C-2 2 x CH_3), 22.9, 21.6 (C-2' 2 x CH_3). MS: 199 (M^+-1, 3), 183 (5), 158 (21), 156 (20), 115 (100), 113 (9), 85 (14), 72 (25), 71 (19), 70 (13), 69 (88), 57 (17), 56 (40).

Allyltriphenylphosphonium bromide (124).

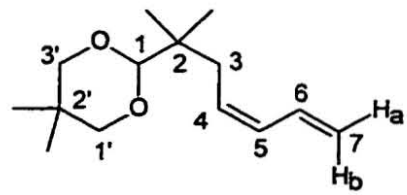


Allyl bromide (2.90 g, 24.0 mmol) and triphenylphosphine (5.02 g, 19.1 mmol) were dissolved in benzene (6.0 mL). The solution was stirred overnight at rt, and the resulting suspension was refluxed for 1 h. The white precipitate was isolated by suction filtration. It was washed with cold benzene and dried under vacuum for several hours. The result was **124** as a white solid (6.87 g, 94%): mp: 200-205 °C. ^{1}H NMR: δ 7.89-7.79 (9H, m, C-3'H, C-4'H, C-5'H), 7.74-7.67 (6H, m, C-2'H, C-6'H), 5.80-5.55 (2H, m, C-3H), 5.40 (1H, symmetrical m, C-2H), 4.77 (2H, dd, *J* = 6.8, 15.5 Hz, C-1H). ^{13}C NMR: δ 135.0 (3 x C-4'), 133.7 (d, *J* = 9.0 Hz, 3 x C-2', 3 x C-6'), 130.2 (d, *J* = 12.9 Hz, 3 x C-3', 3 x C-5'), 126.1 (d, *J* = 12.7 Hz, C-3), 122.9 (d, *J* = 9.6 Hz, C-2), 117.7 (d, *J* = 86.5 Hz, C-1'), 28.7 (d, *J* = 48.6 Hz, C-1).

(4*E*)-2,2-Dimethyl-4,6-heptadienal, 2,2-dimethyl-1,3-propane acetal (125) and (4*Z*)-2,2-dimethyl-4,6-heptadienal, 2,2-dimethyl-1,3-propane acetal (126).



125



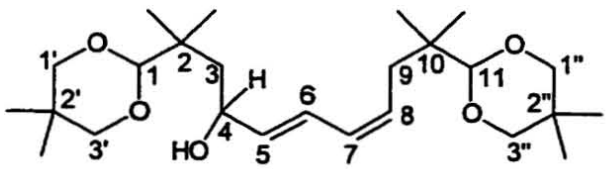
126

Allyltriphenylphosphonium bromide (**124**) (34.1 g, 90.0 mmol) in dry THF (80 mL) was cooled to 0 °C. To this, *n*-butyllithium (43.2 mL, 2.5 M in hexanes, 108 mmol) was added dropwise. The dark red ice-cold solution was stirred for 30 min. The aldehyde **123** (12.1 g, 60.7 mmol) in THF (10 mL) was added to the ylid solution over 30 min using a syringe pump. The resulting solution was warmed to rt and stirred for 1 h. The THF was removed under vacuum, and the residue was taken up in ether. The ether portion was washed with water, and the aqueous layer was re-extracted with ether. The combined ether layers were then washed with water and brine and dried over $MgSO_4$. Concentration of the solution under vacuum followed by filtration through a short silica gel column to remove the triphenylphosphine oxide gave 9.30 g of a yellow oil. ^1H NMR analysis of the residue along with TLC indicated *cis* and *trans* dienes as well as two other products. Flash chromatography (elution with 5% ethyl acetate-hexane) gave 4.24 g (31%) of a 1:1 mixture of *trans* and *cis* dienes, **125** and **126**

and 1.43 g of a viscous oil and 1.04 g of a yellow liquid. From the text by Johnson,[72] one of the two unknown fractions could be **127**. Data were obtained for the mixture of *trans* **125** and *cis* **126** dienes. For **125** (clearly discernible signals): ^{1}H NMR: δ 6.33 (1H, m, C-6H), 5.73 (1H, m, C-4H), 4.95 (1H, dd, J = 1.5, 10.1 Hz, C-7H$_b$), 2.11 (2H, d, J = 7.8 Hz, C-3H), 0.92 (6H, s, C-2 2 x CH$_3$). ^{13}C NMR: δ 137.3 (C-6), 133.4 (C-5), 131.6 (C-4), 106.8 and 106.5 (C-1(*E*) and C-1(*Z*)), 40.8 (C-3), 38.4 and 38.2 (C-2(*E*) and C-2(*Z*)).

For **126** (clearly discernible signals): ^{1}H NMR: δ 6.68 (1H, symmetrical m, C-6H), 5.51 (1H, symmetrical m, C-4H), 5.17 (1H, dd, J = 2.0, 16.9 Hz, C-7H$_b$), 2.20 (2H, dd, J = 1.2, 8.3 Hz, C-3H), 0.98 (6H, s, C-2 2 x CH$_3$). ^{13}C NMR: δ 132.6 (C-6), 131.2 (C-5), 128.9 (C-4), 116.8 (C-7), 35.4 (C-3).

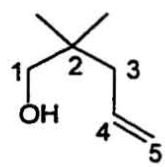
For **125** and **126** (overlapping signals): ^{1}H NMR: δ 6.13-6.00 (2H, m, C-5H(*E*) and C-5H(*Z*)), 5.11-5.05 (2H, m, C-7H$_a$(*E*) and C-7H$_a$(*Z*)), 4.03 (2H, s, C-1H(*E*) and C-1H(*Z*)), 3.62-3.57 (4H, m, C-1'H$_e$(*E*), C-3'H$_e$(*E*), C-3'H$_e$(*Z*), C-3'H$_e$(*Z*)), 3.38-3.33 (4H, m, C-1'H$_a$(*E*), C-3'H$_a$(*E*), C-3'H$_a$(*Z*), C-3'H$_a$(*Z*)), 1.16 (6H, s, C-2' (CH$_3$)$_e$(*E*) and C-2' (CH$_3$)$_e$(*Z*)), 0.69 (6H, s, C-2' (CH$_3$)$_a$(*E*) and C-2' (CH$_3$)$_a$(*Z*)). ^{13}C NMR: δ 77.2 (C-1'H(*E*), C-1'H(*Z*), C-3'H(*E*) and C-3'H(*Z*)), 30.2 (C-2'(*E*) and C-2'(*Z*)), 22.9 (C-2' (CH$_3$)$_e$(*E*) and C-2' (CH$_3$)$_e$(*Z*)), 22.0 (C-2 2CH$_3$(*E*) and C-2 2CH$_3$(*Z*)), 21.7 (C-2' (CH$_3$)$_a$(*E*) and C-2' (CH$_3$)$_a$(*Z*)).



127

Readily discernible signals for the putative **127**: ^{1}H NMR: δ 6.57-5.50 (4H, m, C-5H, C-6H, C-7H, C-8H), 4.14 (1H, s, C-1H or C-11H), 4.04 (1H, s, C-1H or C-11H), 3.98 (1H, s, C-4H), 3.64-3.57 (4H, m, C-1'H_e, C-3'H_e, C-1"H_e, C-3"H_e), 3.43-3.37 (4H, m, C-1'H_a, C-3'H_a, C-1"H_a, C-3"H_a), 2.22 (2H, d, C-3H or C-9H), 2.21 (2H, d, C-3H or C-9H), 1.18 and 1.15 (6H, s, C-2' $(CH_3)_e$ and C-2" $(CH_3)_e$), 0.97 and 0.93 (12H, s, C-2 2 x CH_3 and C-10 2CH_3), 0.71 and 0.69 (6H, s, C-2' $(CH_3)_a$ and C-2" $(CH_3)_a$).

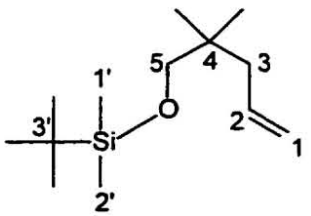
2,2-Dimethyl-4-penten-1-ol (130).



Sodium borohydride (1.58 g, 41.8 mmol) was placed in methanol (10 mL) and the mixture was cooled in an ice bath. The aldehyde **99** (2.00 g, 17.8 mmol) was added dropwise over approximately 5 minutes. It was stirred at 0 °C for a further 5 min until gas evolution had slowed. The solution was then stirred in a warm water bath for 5-10 min. The methanol was removed under vacuum, and

the residue was taken up in ether. The ether solution was washed with NH_4Cl(aq), water and brine and then dried over anhydrous K_2CO_3. After evaporation of the solvent, the result was **130** as a colorless liquid (1.73 g, 85%): ^{1}H NMR: δ 5.83 (1H, m, C-4H), 5.08-4.98 (2H, m, C-5H), 3.30 (2H, s, C-1H), 2.27 (1H, broad s, OH), 2.02 (2H, d, J = 7.6 Hz, C-3H), 0.88 (6H, s, C-2 2 x CH_3). ^{13}C NMR: δ 135.2 (C-4), 117.0 (C-5), 71.5 (C-1), 43.2 (C-3), 35.4 (C-2), 23.7 (C-2 2 x CH_3).

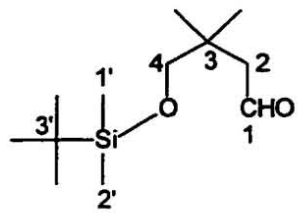
5-(*tert*-Butyldimethylsilyloxy)-4,4-dimethyl-1-pentene (131).



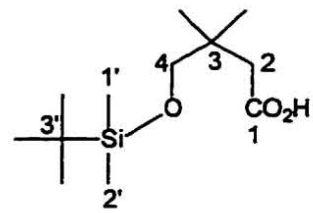
A solution of alcohol **130** (2.40 g, 21.0 mmol), *tert*-butylchlorodimethylsilane (3.70 g, 25.0 mmol), triethylamine (3.5 mL, 25 mmol) and 4,4-dimethylaminopyridine (0.50 g, 4.1 mmol) in dichloromethane (20 mL) was stirred at rt overnight under a nitrogen atmosphere. The solution was washed with NH_4Cl(aq), water and brine and then dried over $MgSO_4$. Concentration of the solution under vacuum followed by flash chromatography (elution with 10% ethyl acetate-hexane) gave **132** as a colorless liquid (4.24 g, 88%). IR: 3077, 2958, 2858, 1640, 1472, 1256 cm^{-1}. ^{1}H NMR: δ 5.78 (1H, m, C-2H), 5.00 (1H, broad s, C-1H), 4.96 (1H, symmetrical m, C-1H), 3.21 (2H, s, C-5H), 1.96 (2H, d,

J = 8.1 Hz, C-3H), 0.88 (9H, s, *t*-Bu), 0.87 (6H, s, C-4 2 x CH_3), 0.00 (6H, s, $Si(CH_3)_2$). ^{13}C NMR: δ 135.7 (C-2), 116.7 (C-1), 71.3 (C-5), 43.2 (C-3), 35.6 (C-4), 25.9 (C-3' 3 x CH_3), 23.9 (C-4 2 x CH_3), 18.3 (C-3'), -5.53 ($Si(CH_3)_2$). MS: no M^+, 214 (0.7), 213 (3), 173 (4), 172 (13), 171, (85), 143 (19), 129 (12), 115 (10), 99 (25), 75 (100), 73 (34), 59 (8).

4-(*tert*-Butyldimethylsilyloxy)-3,3-dimethyl-1-pentanal (132).



132



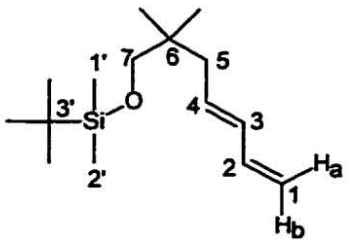
133

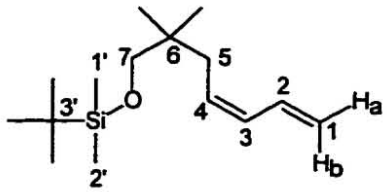
The TBDMS-protected alcohol **131** (5.95 g, 26.0 mmol) was dissolved in dichloromethane (100 mL). This solution was cooled to -78 °C using a Dry Ice/acetone bath. Ozone was bubbled through the solution until a blue color persisted (approximately 30 min). This was followed by bubbling nitrogen through the solution to remove the excess O_3. Then triphenylphosphine (6.14 g, 23.4 mmol) was added to the cold solution. The solution was allowed to warm slowly to rt overnight under a N_2 atmosphere. The aldehyde was easily oxidized in air so an aqueous work-up was not performed. Instead the solution was diluted with hexane to precipitate the triphenylphosphine oxide. This was removed by filtration through Celite. Flash chromatography (elution with hexane)

through a short plug of neutral alumina removed the last trace of triphenylphosphine oxide to give 5.39 g of a colorless liquid. ^{1}H NMR analysis showed a 2:1 mixture of aldehyde and acid. Thus, the sample was 66% aldehyde by mass. Therefore, 3.56 g (60%) of aldehyde **132** was produced in addition to 1.83 g (30%) of the carboxylic acid **133**. The aldehyde and acid were not separated and spectral data were obtained for the mixture. IR: 2957, 2931, 2858, 1709, 1473 cm^{-1}. ^{1}H NMR: δ 9.80 (1H, t, *J* = 3.1 Hz, C-1H), 3.32 (2H, s, C-4H), 2.24 (2H, d, *J* = 3.1 Hz, C-2H), 0.98 (6H, s, C-3 2 x CH_3), 0.86 (9H, s, *t*-Bu), 0.00 (6H, s, $Si(CH_3)_2$). ^{13}C NMR: δ 203.1 (C-1), 71.7 (C-4), 52.8 (C-2), 36.2 (C-3), 25.8 (*t*-Bu), 24.5 (C-2 2 x CH_3), 18.2 (C-3'), -5.69 ($Si(CH_3)_2$).

Readily discernible signals for the acid **133**: ^{1}H NMR: δ 11.5 (1H, broad s, C-1H), 3.34 (2H, s, C-4H), 2.27 (2H, s, C-2H), 0.97 (6H, s, C-2 2 x CH_3), 0.87 (9H, s, *t*-Bu), 0.07 (6H, s, $Si(CH_3)_2$). ^{13}C NMR: δ 177.8 (C-1), 71.4 (C-4), 42.9 (C-2), 35.3 (C-3), 24.1 (C-3 2 x CH_3).

(3*E*)-7-(*tert*-Butyldimethylsilyloxy)-6,6-dimethylhepta-1,3-diene (134) and (3*Z*)-7-(*tert*-butyldimethylsilyloxy)-6,6-dimethylhepta-1,3-diene (135).





134 **135**

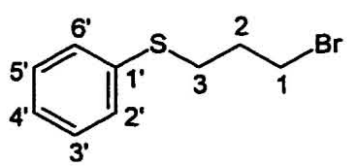
Allyltriphenylphosphonium bromide (**124**) (25.3 g, 66.1 mmol) was stirred in anhydrous THF (65 mL) under nitrogen. To this was added *n*-butyllithium (29.1 mL, 2.5 M in hexanes, 73 mmol) over 30 min. The flask was cooled in ice during the addition of the base. The resulting red-orange slurry was stirred at rt for a further 30 min. Then the aldehyde-acid mixture (**132** and **133**) (5.19 g, 22.0 mmol) was dissolved in THF (7.0 mL) and added to the ylid solution over 30 min. The solution was also cooled in ice during this addition. After the aldehyde addition was complete the mixture was stirred at rt for 1 h. The excess ylid was quenched by adding 1M HCl until a neutral solution was obtained. The THF was removed under vacuum, and the residue was extracted with ether. The combined ether layers were washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a yellow oil. Flash chromatography (elution with 5% ethyl acetate-hexane) gave a colorless liquid, 1.09 g, (29%). ^{1}H NMR analysis indicated a mixture of *trans* and *cis* dienes **134** and **135**. Spectra were obtained for this mixture. IR: 2955, 2931, 2858, 1653, 1472 cm^{-1}. For **134** (clearly discernible signals): ^{1}H NMR: δ 6.29 (1H, m, C-2H),

5.67 (1H, m, C-4H), 4.92 (1H, d, J = 10.2 Hz, C-1H_b), 3.21 (2H, s, C-7H), 1.99 (2H, d, J = 7.2 Hz, C-5H), 0.81 (6H, C-6 2 x CH_3). ^{13}C NMR: δ 137.3 (C-2), 133.3 (C-3), 132.1 (C-4), 114.6 (C-1), 71.2 and 71.1 (C-7(*E*) and C-7(*Z*)), 41.8 (C-5).

For **135** (clearly discernible signals): ^{1}H NMR: δ 6.65 (1H, symmetrical m, C-2H), 5.47 (1H, symmetrical m, C-4H), 5.14 (1H, d, J = 17.0 Hz, C-1H_b), 3.20 (2H, s, C-7H), 2.11 (2H, d, J = 8.2 Hz, C-5H). ^{13}C NMR: δ 132.7 (C-2), 131.0 (C-3), 129.4 (C-4), 116.7 (C-1), 36.2 (C-5).

For **134** and **135** (overlapping signals): ^{1}H NMR: δ 6.10-5.97 (2H, m, C-3H(*E*) and C-3H(*Z*)), 5.07-5.02 (2H, m, C-1H_a(*E*) and C-1H_a(*Z*)), 0.88 (18H, s, C-3' 3CH_3(*E*) and C-3' 3CH_3(*Z*)), 0.00 (12H, s, C-1'H(*E*), C-1'H(*Z*), C'2'H(*E*), C-2'H(*Z*)). ^{13}C NMR: δ 36.4 (C-5(*E*) and C-5(*Z*)), 25.9 (C-3' 3CH_3(*E*) and C-3' 3CH_3(*Z*)), 24.0 (C-6 2CH_3(*E*) and C-6 2CH_3(*Z*)), 18.3 (C-3'(*E*) and C-3'(*Z*)), -5.5 (C-1'(*E*), C-1'(*Z*), C'2'(*E*), C-2'(*Z*)).

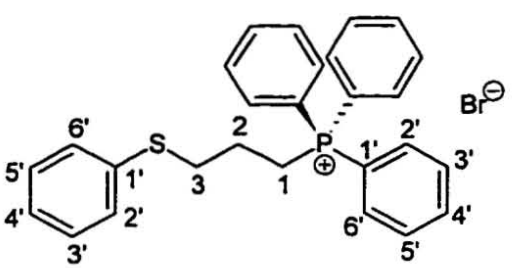
(3-Bromopropyl)phenylsulfide (139).



Sodium hydroxide (2.81 g, 70.3 mmol) was dissolved in distilled water (45 mL). To this was added benzene (45 mL), and the solution was stirred under

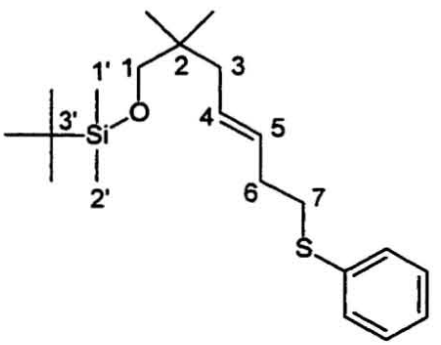
nitrogen. Thiophenol (4.77 g, 43.3 mmol) and 1,3-dibromopropane (21.8 g, 108 mmol) were added followed by *t*-butylammonium hydroxide (0.5 mL, 1.0 M in water, 0.5 mmol). The resulting cloudy solution was stirred for a further 40 min. The organic and aqueous phases were separated, and the organic layer was washed with 10% NaOH and brine and then dried over anhydrous Na_2SO_4. Evaporation of the solvent gave 23.5 g of a yellow liquid. Flash chromatography (elution with hexane) gave **139** as a colorless liquid (8.16 g, 82%). IR: 1584, 1480, 1439 cm^{-1}. ^1H NMR: δ 7.35-7.15 (5H, m, C-2'H, C-3'H, C-4'H, C-5'H, C-6'H), 3.50 (2H, t, J = 6.4 Hz, C-1H), 3.05 (2H, t, J = 6.9 Hz, C-3H), 2.12 (2H, quintet, J = 6.6 Hz, C-2H). ^{13}C NMR: δ 135.4 (C-1'), 128.3 (Ar), 128.8 (Ar), 126.1 (Ar), 31.9, 31.8 and 31.6 (C-1, C-2 and C-3). MS: 233 (7), 232 (65), 231 (6) and 230 (65) all M^+, 151 (5), 123 (100), 110 (44), 109 (20), 77 (11), 65 (14), 51 (13).

Triphenyl(3-thiophenylpropyl)phosphonium bromide (140).



(3-Bromopropyl)phenylsulfide (**139**) (4.00 g, 17.3 mmol) and triphenylphosphine (13.6 g, 51.9 mmol) were heated at reflux in *p*-xylene (20 mL) for 3 days. Suction filtration gave **140** as a white solid (4.80 g, 56%), mp: 144-145 °C. ^{1}H NMR: δ 7.83-7.75 (8H, m, Ar), 7.74-7.72 (6H, m, Ar), 7.60-7.14 (6H, m, Ar), 4.17 (2H, symmetrical m, C-1H), 3.42 (2H, dt, *J* = 1.1, 6.4 Hz, C-3H), 1.97 (2H, symmetrical m, C-2H). ^{13}C NMR: δ 134.9 (3 x C-4"), 134.4 (C-1'), 133.3 (d, *J* = 9.0 Hz, 3 x C-2" and 3 x C-6"), 130.4 and 130.2 (C-2', C-6', C-8' and C-5'), 128.9 (d, *J* = 10.1 Hz, 3 x C-3" and 3 x C-5"), 126.0 (C-4'), 117.8 (d, *J* = 85.5 Hz, 3 x C-1"), 32.9 (d, *J* = 18.6 Hz, C-1), 21.4 and 20.7 (C-2 and C-3).

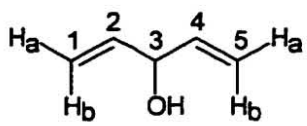
1-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-7-thiophenyl-4-heptene (141).



The ylid salt **140** (1.01 g, 2.03 mmol) was stirred in benzene under nitrogen. To this *n*-butyllithium (0.7 mL, 2.5 M in hexanes, 2 mmol) was added dropwise. The aldehyde **132** (0.410 g, 1.78 mmol) was dissolved in benzene (3.0 mL), and this solution was added dropwise to the ylid solution. The resulting mixture was stirred at rt for 1 h. The benzene solution was washed with water

and brine and dried over $MgSO_4$. Evaporation of the solvent followed by flash chromatography (elution with 5% dichloromethane-hexane) gave **141** as a pale yellow oil (0.176 g, 27%). ^1H NMR: δ 7.35-7.16 (5H, m, ArH), 5.52-5.48 (2H, m, C-4H, C-5H), 3.21 (2H, s, C-1H), 2.93 (2H, t, *J* = 7.6 Hz, C-7H), 2.38 (2H, symmetrical m, C-6H), 1.94 (2H, d, *J* = 6.0 Hz, C-3H), 0.89 (9H, s, *t*-Bu), 0.81 (6H, s, C-2 2 x CH_3), 0.01 (6H, s, $Si(CH_3)_2$).

1,4-Pentadien-3-ol (142).



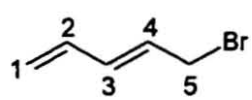
Cold bromoethene (127.7 g, 1.194 mol) was added to dry THF (300 mL) under a stream of argon at -78 °C. Small portions (*ca.*10 mL) of bromoethane and the bromoethene solution were added to Mg turnings (24.2 g, 0.995 mol) to initiate the reaction. The remainder of the bromoethene solution was added over 2.5 h while keeping the temperature near 80 °C. After the addition was complete the reaction mixture was heated at approximately 65 °C for 1 h, and then it was kept under an argon atmosphere overnight at rt.

Ethyl formate (35.0 mL, 0.433 mol) in THF (40 mL) was added over 2 h while keeping the vigorously stirred solution at a temperature below 40 °C with an ice bath. When the addition was complete and the solution cooled to rt, a saturated solution of aqueous NH_4Cl (200 mL) was added slowly. The aqueous

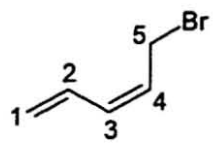
phase was extracted with ether, and the combined ether layers were washed with water and brine and dried over $MgSO_4$.

The ether and some THF was removed by simple distillation under an argon atmosphere. The remainder of the THF was removed at 100 mm Hg. Finally, fractional distillation gave the product **142** as a colorless liquid (18.5 g, 51%): bp: 55-60 °C at 75-80 mm Hg. ^{1}H NMR: δ 5.87 (2H, ddd, J = 5.9, 10.3, 17.1 Hz, C-2H, C-4H), 5.25 (2H, symmetrical m, C-1H_b, C-5H_b), 4.60 (1H, symmetrical m, C-3H), 3.17 (1H, broad s, OH). ^{13}C NMR: δ139.3 (C-2, C-4), 115.2 (C-1, C-5), 73.8 (C-3).

(*E*)-5-Bromo-1,3-pentadiene (143).



143



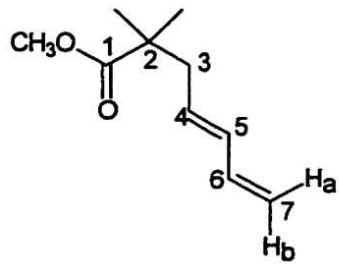
144

1,4-Pentadien-3-ol (**142**) (5.00 g, 59.4 mmol) in isopentane (12 mL) was cooled to 0 °C in an ice bath. HBr (48% in H_2O) (11.2 g, 66.6 mmol) was added dropwise over 15 min while keeping the reaction temperature near 2-3 °C. The solution was stirred for a further 1.5 h at 0 °C and then at rt for 1 h. The organic and aqueous phases were separated, and the aqueous layer was extracted with ether. The combined ether layers were washed with water, 1M aqueous

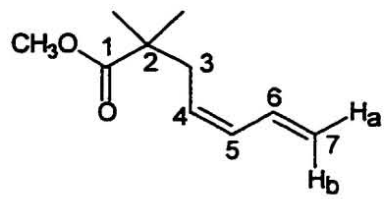
$NaHCO_3$ and brine and dried over $MgSO_4$. Concentration of the solution under vacuum followed by vacuum distillation gave the product **143** as a bright yellow liquid (6.46 g, 73%): bp: 50-52 °C at 28 mm Hg. ^1H NMR analysis of the product indicated a 20:1 mixture of the *E*-compound **143** and the *Z*-compound **144**. Data were obtained for the mixture. IR: 3088, 3033, 3012, 2971, 1600 cm^{-1}. For **143**: ^1H NMR: δ 6.40-6.23 (2H, m, C-2H, C-3H), 5.88 (1H, symmetrical m, C-4H), 5.32-5.14 (2H, m, C-1H), 4.02 (2H, d, J = 7.6 Hz, C-5H). ^{13}C NMR: δ135.5 and 135.2 (C-2 and C-3), 129.1 (C-4), 119.4 (C-1), 32.8 (C-5).

Readily discernible signals for the minor compound **144**: ^1H NMR: δ 4.12 (2H, d, J = 8.5 Hz, C-5H). ^{13}C NMR: δ 133.3 and 130.3 (C-2 and C-3), 126.2 (C-4), 120.8 (C-1), 26.9 (C-5).

Methyl (*E*)-2,2-dimethyl-4,6-heptadienoate (145).



145



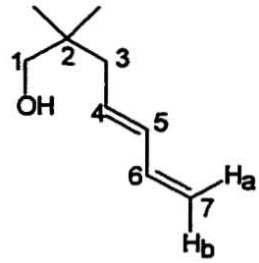
146

A solution of diisopropylamine (1.45 g, 14.3 mmol) in dry THF (30 mL) was cooled to -78 °C. *n*-Butyllithium (5.2 mL, 2.5 M in hexanes, 13 mmol) was

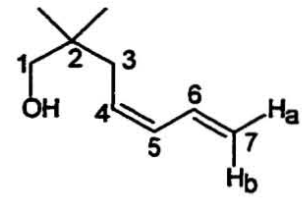
added dropwise. This was stirred for 15 min and methyl isobutyrate (1.22 g, 11.9 mmol) in THF (4.0 mL) was added over 15 min. The resulting solution was stirred for 1 h, and **143** (2.10 g, 14.3 mmol) in THF (2.0 mL) was added over 15 min. The solution warmed slowly to rt overnight. The THF was removed under vacuum, and the residue was redissolved in ether. This ether solution was washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent followed by vacuum distillation gave **145** as a colorless liquid (1.56 g, 78%): bp: 62-66 °C at 5.5 mm Hg. ^{1}H NMR analysis indicated a 20:1 ratio of major and minor products. The minor product likely due to reaction with the *cis* bromide **144** to give **146**. Data are given for the mixture. IR: 2974, 1735, 1603, 1471 cm^{-1}. For **145**: ^{1}H NMR: δ 6.29 (1H, m, C-6H), 6.06 (1H, m, C-5H), 5.60 (1H, m, C-4H), 5.11 (1H, dd, J = 1.1, 17.1 Hz, C-7H_a), 4.98 (1H, dd, J = 1.1, 10.2 Hz, C-7H_b), 3.66 (3H, s, C-2 2 x CH_3). ^{13}C NMR: δ 177.8 (C-1), 136.8 and 134.0 (C-5 and C-6), 130.0 (C-4), 115.6 (C-7), 51.6 (CO_2**CH_3**), 43.4 (C-3), 42.6 (C-2), 24.8 (C-2 2 x CH_3). MS: 169 (2) and 168 (14) both M^+, 109 (27), 108 (15), 93 (11), 68 (13), 67 (100).

Readily discernible signals for the minor product **146**: ^{1}H NMR: δ 3.65 (3H, s, CO_2**CH_3**), 2.43 (2H, d, J = 8.2 Hz, C-3H), 1.19 (6H, s, C-2 2 x CH_3). ^{13}C NMR: δ 131.9 and 131.7 (C-5 and C-6), 127.3 (C-4), 117.7 (C-7), 38.1 (C-3).

(*E*)-2,2-Dimethyl-4,6-heptadien-1-ol (136).



136



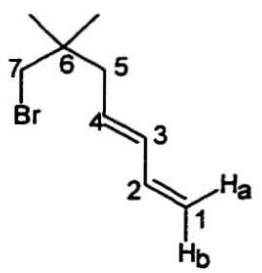
137

Lithium aluminum hydride (2.98 g, 78.6 mmol) suspended in anhydrous ether (55 mL) was cooled in an ice-bath. Methyl ester **145** (4.40 g, 26.2 mmol) in ether (10 mL) was added over 30 min. The solution was allowed to warm to rt slowly, and then it was stirred overnight. A 9:1 mixture of methanol/water was added slowly to the reaction mixture followed by 1M aqueous NH_4Cl (10 mL). When gas evolution had slowed, the organic and aqueous phases were separated, and the aqueous layer was re-extracted with ether. The combined ether layers were washed with water and brine and dried over $MgSO_4$. Concentration of the solution under vacuum followed by flash chromatography (elution with 15% petroleum ether-ethyl acetate) gave **136** as a pale yellow liquid (3.12 g, 85%). ^{1}H NMR analysis indicated a 20:1 ratio of compound **136** and compound **137**. Data are given for the mixture. IR: 3359 (broad), 3009, 2959, 2872, 1650, 1602, 1472, 1385 cm^{-1}. For **136**: ^{1}H NMR: δ 6.32 (1H, m, C-6H), 6.08 (1H, m, C-5H), 5.72 (1H, m, C-4H), 5.11 (1H, dd, J = 1.1, 16.8 Hz, C-7H$_a$), 4.98 (1H, dd, J = 1.1, 10.2 Hz, C-7H$_b$), 3.32 (2H, s, C-1H), 2.04 (2H, d, J = 7.4

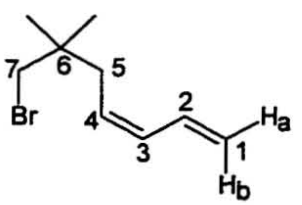
Hz, C-3H), 1.62 (1H, broad s, OH), 0.88 (6H, s, C-2 2 x CH_3). ^{13}C NMR: δ 137.0 and 133.5 (C-5 and C-6), 131.4 (C-4), 115.2 (C-7), 71.6 (C-1), 41.9 (C-3), 36.0 (C-2), 23.9 (C-2 2 x CH_3). MS: 140 (M^+, 1), 125 (12), 109 (4), 99 (55), 81 (20), 55 (78).

Readily discernible signals for the minor compound **137**: ^1H NMR: δ 2.16 (2H, d, J = 8.2 Hz, C-3H), 0.90 (6H, C-2 2 x CH_3). ^{13}C NMR: δ 117.4 (C-7), 36.8 (C-3).

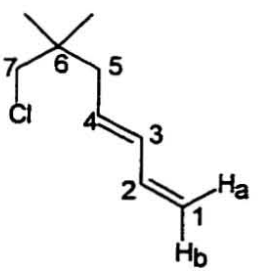
(*E*)-7-Bromo-6,6-dimethyl-1,3-heptadiene (147).



147



148



149

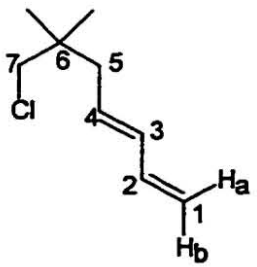
The alcohol **136** (1.45 g, 10.3 mmol) and tetrabromoethane (4.11 g, 12.4 mmol) were dissolved in dichloromethane (6.0 mL), and the solution was cooled in an ice bath. Triphenylphosphine (2.98 g, 11.4 mmol) in dichloromethane (6.0 mL) was added over 1 h. After the addition was complete, the solution was warmed to rt over 2 h. The mixture was then heated at reflux for 3 days. The solution was diluted with pentane and washed with aqueous $NaHCO_3$, water and

brine and then dried over $MgSO_4$. Concentration of the solution under vacuum followed by flash chromatography (elution with petroleum ether) gave the product **147** as a yellow liquid (0.227 g, 11%). Also obtained from the column was a fraction which was a mixture of remaining CBr_4, the by-product, bromoform ($CHBr_3$) and the desired bromide **147**, 2.58 g. From GC-MS analysis this mixture contained approximately 1.44 g of the bromide **147** for an overall yield of *ca.* 80%. Both of these fractions were also contaminated by the chloride isomer **149** and a small amount of the *cis* compound **148**. Data were obtained for the fraction containing the bromide isomers **147** and **148** and the chloride isomer **149**. For **147**: ^{1}H NMR: δ 6.33 (1H, m, C-2H), 6.11 (1H, m, C-3H), 5.65 (1H, m, C-4H), 5.13 (1H, d, J = 17.2 Hz, C-1H$_a$), 5.01 (1H, dd, J = 1.3, 10.2 Hz, C-1H$_b$), 3.27 (2H, s, C-7H), 2.13 (2H, d, J = 6.9 Hz, C-5H), 1.02 (6H, s, C-6 2 x CH_3). MS from GC-MS: 205 (0.6), 204 (6), 203 (0.7) and 202 (6) all M^+, 148 (8), 146 (10), 137 (15), 135 (16), 123 (3), 109 (5), 107 (4), 91 (6), 68 (25), 67 (100), 56 (12), 55 (59).

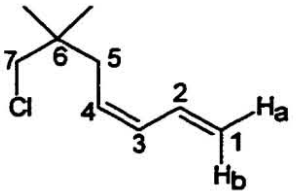
Readily discernible signals for the *cis* isomer **148**: ^{1}H NMR: δ 3.29 (2H, s, C-7H), 2.25 (2H, d, J = 8.2 Hz, C-5H), 1.03 (6H, s, C-6 2 x CH_3).

Readily discernible signals for the chloride isomer **149**: ^{1}H NMR: δ 3.26 (2H, s, C-7H), 0.98 (6H, s, C-6 2 x CH_3).

(*E*)-7-Chloro-6,6-dimethyl-1,3-heptadiene (149).



149



150

The alcohol **136** (0.403 g, 2.88 mmol) was dissolved in carbon tetrachloride (10 mL). To this was added dropwise, a solution of triphenylphosphine (0.989 g, 3.77 mmol). The solution was heated to reflux for 2 days. The solution was diluted with dichloromethane and washed with aqueous $NaHCO_3$, aqueous NaOCl solution (4%), water and brine and then dried over $MgSO_4$. Evaporation of the solvent followed by flash chromatography (elution with 5% ethyl acetate-petroleum ether) gave **149** as a yellow oil (0.267 g, 64%). ^1H NMR analysis indicated a 20:1 ratio of major *E* diene **149** and minor *Z* diene **150**. Data were obtained for the mixture of these two isomers. (The sample seemed to be volatile). IR: 3011, 2963, 1650, 1602 cm^{-1}. For **149**: ^1H NMR: δ 6.31 (1H, m, C-2H), 6.10 (1H, m, C-3H), 5.67 (1H, m, C-4H), 5.13 (1H, dd, *J* = 1.2, 16.8 Hz, C-1H_a), 5.00 (1H, dd, *J* = 1.2, 10.1 Hz, C-1H_b), 3.26 (2H, s, C-7H), 2.10 (2H, d, *J* = 7.7 Hz, C-5H), 0.98 (6H, s, C-6 2 x CH_3). ^{13}C NMR: δ 136.9 and 134.3 (C-2 and C-3), 130.2 (C-4), 115.6 (C-1), 55.2 (C-7), 42.2 (C-5), 36.0 (C-6),

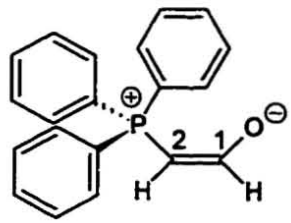
25.0 (C-6 2 x CH_3). MS: 160 (1), 150 (0.7) and 158 (6) all M^+, 123 (2), 109 (12), 93 (9), 92 (4), 91 (34), 69 (12), 68 (33), 67 (90), 55 (77).

Readily discernible signals for the minor *cis* isomer **150**: ^{1}H NMR: δ 3.35 (2H, s, C-7H), 2.22 (2H, d, J = 8.4 Hz, C-5H), 0.99 (6H, s, C-6 2 x CH_3).

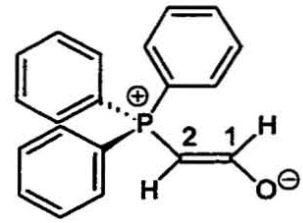
(1-Oxoethylene)triphenylphosphorane (153).

$$\underset{2}{Ph_3P{=}CH}\text{–}\underset{1}{CHO}$$

Methyltriphenylphosphonium bromide (10.6 g, 29.6 mmol) was suspended in dry ether (100 mL) under an argon atmosphere. To this was added *n*-butyllithium (13 mL, 2.5 M, 33 mmol) dropwise. This solution was stirred at rt for 40 min. This solution was added to ethyl formate (3.1 mL, 38 mmol) in ether (50 mL). The result was a white precipitate. This was stirred for a further 30 min. The solution was extracted with 1M HCl. The acidic extracts were made alkaline with 3M NaOH. This alkaline solution was then extracted with benzene and the combined benzene layers dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a tan-coloured solid. Crystallization from acetone gave **153** as pale yellow crystals (2.97 g, 33%): mp: 188-190 °C (decomp.). The ^{1}H NMR analysis indicated the presence of the *Z* **153a** and *E* **153b** isomers of the ylid.



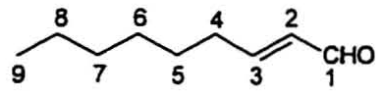
153a



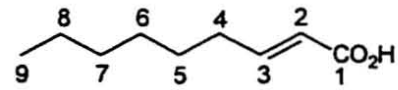
153b

Data were obtained for this mixture. ^{1}H NMR: δ 9.01 (1H, dd, *J* = 3.5, 38.3 Hz, C-1H(*Z*)), 8.28 (1H, dd, *J* = 3.4, 10.8 Hz, C-1H(*E*)), 7.70-7.43 (15H, m, Ar-H from *Z* and *E* isomers), 4.06 (1H, dd, *J* = 10.8, 19.4 Hz, C-2H(*E*)), 3.66 (1H, dd, *J* = 3.8, 24.4 Hz, C-2H(*Z*)). ^{13}C NMR: δ 181.7 and 181.6 (C-1*E* and C-1*Z*), 133.2 (Ar), 133.0 (Ar), 132.9 (Ar), 132.7 (Ar), 132.2 (Ar), 128.9 (Ar), 128.8 (Ar), 56.2 (d, *J* = 110.4 Hz, C-2), 54.7 (d, *J* = 99.6 Hz, C-2). MS: 304 (50) and 303 (100) both M^{+}, 276 (6), 275 (29), 185 (13), 183 (31), 165 (9), 77 (10), 51 (7).

2-Nonenal (155).



155



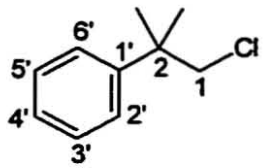
156

Heptanal (**154**) (0.818 g, 7.16 mmol) and the ylid **153** (2.57 g, 8.44 mmol) were dissolved in benzene (50 mL) and heated to reflux overnight. The solvent was then removed under vacuum, and the residue was taken up in ether. This ether solution was washed with water, and the resulting aqueous layer was

extracted with ether. The combined ether layers were washed with brine and dried over $MgSO_4$. Concentration of the solution under vacuum gave a yellow liquid, which was purified by vacuum distillation to give **155** as a pale yellow oil (0.291 g, 30%): bp: 88-90 °C at 9 mm Hg. ^{1}H NMR analysis of the sample indicated a 5:1 ratio of aldehyde **155** and carboxylic acid **156**. Data were obtained for this mixture. IR: 2957, 2930, 2858, 1692, 1638 cm^{-1}. For **155**: ^{1}H NMR: δ 9.50 (1H, d, *J* = 7.9 Hz, C-1H), 6.87 (1H, dt, *J* = 15.6, 7.2 Hz, C-3H), 6.12 (1H, ddt, *J* = 1.4, 15.6, 7.8 Hz, C-2H), 2.34 (2H, symmetrical m, C-4H), 1.56-1.43 (2H, m, C-5H), 1.42-1.23 (6H, m, C-6H, C-7H, C-8H), 0.89 (3H, m, C-9H). ^{13}C NMR: δ 194.1 (C-1), 159.1 (C-3), 132.3 (C-2), 32.6 (C-4), 31.4 (C-5), 28.7 (CH_2), 27.7 (CH_2), 22.4 (C-8), 13.9 (C-9). MS: 140 (M^+, 2), 139 (16), 113 (6), 99 (12), 97 (6), 73 (45), 69 (23), 55 (52), 43 (100).

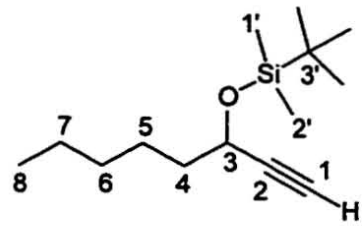
Readily discernible signals for the carboxylic acid **156**: ^{1}H NMR: δ 10.8 (1H, broad s, CO_2H), 7.07 (1H, dt, *J* = 7.0, 15.5 Hz, C-3H), 5.78 (1H, dt, *J* = 1.5, 15.5 Hz, C-2H), 2.27-2.18 (2H, symmetrical m, C-4H). ^{13}C NMR: δ 171.1 (C-1), 151.9 (C-3), 120.5 (C-2), 32.2 (C-4).

1-Chloro-2,2-dimethyl-2-phenylethane (157).



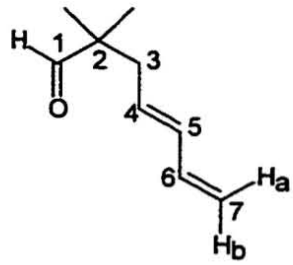
A mixture of benzene (43.7 g, 0.559 mol) and concentrated H_2SO_4 (1.5 mL, 27 mmol) was cooled in an ice bath. Methallyl chloride (17.2 g, 0.190 mol) was added dropwise at such a rate as to keep the temperature near 10 °C. After the addition was complete, the solution was stirred at between 10 and 15 °C for 1 h. The aqueous phase was separated from the organic phase, and organic phase was washed with distilled water until the aqueous washing was at pH 7. The organic layer was dried over anhydrous Na_2SO_4. Concentration under vacuum followed by vacuum distillation gave the product **157** as a colorless liquid (10.6 g, 33%): bp: 95-99 °C at 10 mm Hg. IR: 2971, 1601, 1498 cm^{-1}. ^1H NMR: δ 7.46-7.27 (5H, m, Ar-H), 3.72 (2H, s, C-1H), 1.51 (6H, s, C-2 2 x CH_3). ^{13}C NMR: δ 145.9 (C-1'), 128.3, 126.4 and 125.9 (C-2', C-3', C-4', C-5' and C-6'), 56.3 (C-1), 39.7 (C-2), 26.4 (C-2 2 x CH_3). MS: 170 (1) and 168 (4) both M^+, 119 (100), 117 (8), 91 (46), 79 (9), 77 (8).

3-(*tert*-Butyldimethylsilyloxy)-1-octyne (162).

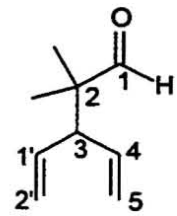


1-Octyn-3-ol (**161**) (0.656 g, 5.20 mmol), *tert*-butylchlorodimethylsilane (1.03 g, 6.85 mmol) and imidazole (0.728 g, 10.7 mmol) were dissolved in dimethylformamide (50 mL) and stirred under argon for 2 days. The yellow solution was diluted with petroleum ether and then washed with aqueous $NaHCO_3$, water and brine and then dried over anhydrous K_2CO_3 and $MgSO_4$. Concentration of the solution under vacuum followed by flash chromatography (elution with 20% ethyl acetate-petroleum ether) gave **162** as a pale yellow liquid (0.899 g, 72%). IR: 3314, 2958, 2931, 2859, 1472 cm^{-1}. ^1H NMR: δ 4.31 (1H, td, J = 2.0, 6.4 Hz, C-3H), 2.34 (1H, d, J = 2.0 Hz, C-1H), 1.70-1.61 (2H, m, C-4H), 1.48-1.35 (2H, m, C-5H), 1.35, 1.22 (4H, m, C-6H, C-7H), 0.89 (9H, s, *t*-Bu), 0.85 (3H, s, C-8H), 0.12 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$). ^{13}C NMR: δ 85.8 (C-2), 71.8 (C-1), 62.8 (C-3), 38.6 (C-4), 31.5 (C-6), 25.8 (*t*-Bu), 24.7 (C-5H), 22.6 (C-7), 18.2 (C-3'), 14.0 (C-8), -4.57 ($SiCH_3$), -5.08 ($SiCH_3$). MS: no M^+, 217 (7), 215 (20), 199 (13), 173 (8), 147 (9), 127 (12), 109 (47), 99 (22), 83 (19), 81 (12), 75 (100), 73 (89), 67 (38), 57 (21), 55 (29).

(*E*)-2,2-Dimethyl-4,6-heptadienal (128) and 2,2-dimethyl-3-vinyl-4-pentenal (163).



128



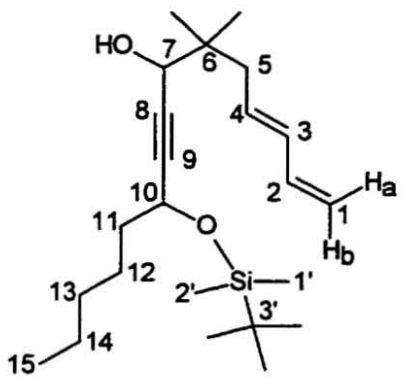
163

1,4-Pentadien-3-ol (**142**) (2.56 g, 30 5 mmol), 2-methylpropanal (4.39 g, 60.9 mmol) and *p*-TsOH (approximately 0.1 g) were dissolved in benzene (50 mL). The solution was heated at reflux for 4 days. The solution was then cooled and washed with 1M aqueous $NaHCO_3$, water and brine and then dried over $MgSO_4$. Evaporation of the solvent followed by flash chromatography (elution with 7% ethyl acetate-petroleum ether) gave **128** as a pale yellow oil (1.77 g, 42%). ^1H NMR analysis indicated a 3:1 ratio of **128** and a minor product **163**. Data were obtained for the mixture. IR: 3012, 2971, 2932, 2808, 1727, 1651, 1603, 1468 cm^{-1}. For **128**: ^1H NMR: δ 9.48 (1H, s, C-1H), 6.29 (1H, m, C-6H), 6.08 (1H, m, C-5H), 5.58 (1H, symmetrical m, C-4H), 5.11 (1H, m, C-7H_b), 5.01 (1H, d, J = 10.0 Hz, C-7H_a), 2.24 (2H, d, J = 7.2 Hz, C-3H), 1.06 (6H, s, C-2 2 x CH_3). ^{13}C NMR: δ 205.7 (C-1), 136.6 and 134.5 (C-5 and C-6), 128.2 (C-4), 116.1 (C-7), 46.1 (C-2), 40.1 (C-3), 21.2 (C-2 2 x CH_3). MS: 138 (M^+, 3), 123 (2), 110 (10), 95 (12), 81 (7), 77 (4), 67 (100).

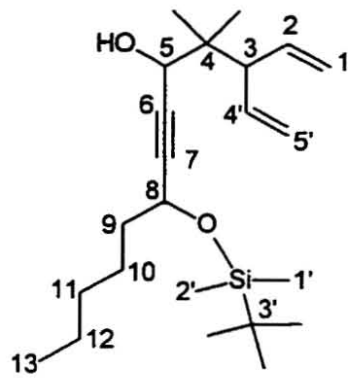
Readily discernible signals for the minor compound **163**: ^{1}H NMR: δ 9.49 (1H, s, C-1H), 5.82-5.69 (2H, m, C-4H, C-1'H), 2.94 (1H, t, *J* = 8.4 Hz, C-3H), 1.04 (6H, s, C-2 2CH_3). ^{13}C NMR: δ 135.7 (C-4, C-1'), 117.7 (C-5, C-2'), 53.7 (C-3), 19.2 (C-2 CH_3).

(E)-10-(*tert*-Butyldimethylsilyloxy)-6,6-dimethylpentadeca-1,3-dien-8-yn-7-ol (164) and

8-(*tert*-Butyldimethylsilyloxy)-4,4-dimethyl-3-vinyltridec-1-en-6-yn-5-ol (165).



164



165

A solution of diisopropylamine (0.152 g, 1.50 mmol) in THF (7.0 mL) was cooled to -78 °C using a Dry Ice/acetone bath. *n*-Butyllithium (0.60 mL, 2.5 M in hexanes, 1.4 mmol) was added dropwise. Stirring was continued for a further 20 min. Then the protected yn-ol **162** (0.309 g, 1.28 mmol) in THF (4.0 mL) was added to the cold solution over 15 min. After the addition was complete, the solution was stirred at -78 °C for 1 h. The aldehyde **128** (0.209 g, 1.51 mmol) in

THF (2.0 mL) was added dropwise. The reaction mixture was allowed to warm slowly to rt overnight. The THF was removed under vacuum, and the residue was redissolved in ether. This was washed with water, and the resulting aqueous phase was re-extracted with ether. The combined ether layers were washed with brine and dried over $MgSO_4$. Concentration of the solution gave a yellow liquid. ^1H NMR analysis of the crude sample indicated the presence of a large proportion of the starting alkyne compound **162**, in addition to a minor amount of the desired product. Also present was the compound **165**, resulting from attack on the minor aldehyde component **163** that had contaminated the aldehyde **128** sample. Purification by flash chromatography (elution with 12% ether-petroleum ether) gave **164** as a pale yellow oil (0.020 g, 4.1%). Also isolated was the compound **165** as a yellow oil (0.020 g, 4.1%) and the remaining 3-(*tert*-butyldimethylsilyloxy)-1-octyn-3-ol (**162**), 0.180 g.

Data for the desired product **164**: IR: 2958, 2931, 2859, 2249, 1650, 1602, 1472 cm^{-1}. ^1H NMR: δ 6.33 (1H, m, C-2H), 6.09 (1H, m, C-3H), 5.73 (1H, m, C-4H), 5.11 (1H, dd, J = 1.3, 17.0 Hz, C-$1H_a$), 4.98 (1H, dd, J = 1.3, 10.1 Hz, C-$1H_b$), 4.38 (1H, t, J = 6.3 Hz, C-10H), 4.09 (1H, dd, J = 1.6, 6.1 Hz, C-7H), 2.16 (2H, symmetrical m, C-5H), 1.71-1.62 (2H, m, C-11H), 1.58 (1H, s, C-7 OH), 1.43-1.22 (6H, m, C-12H, C-13H, C-14H), 0.97 (3H, s, C-6 CH_3), 0.95 (3H, s, C-6 CH_3), 0.91 (9H, s, C-3' $3CH_3$), 0.90 (3H, s, C-15H), 0.13 (3H, s, C-1'H), 0.10 (3H, s, C-2'H). ^{13}C NMR: δ 137.1 (C-2), 133.9 (C-3), 131.1 (C-4), 115.3 (C-1), 88.2

and 83.1 (C-8 and C-9), 70.2 (C-7), 63.0 (C-10), 41.4 (C-5), 39.3 (C-6), 38.8 (C-11), 31.5 (C-13), 25.8 (*t*-Bu), 24.9 (C-12), 22.7 (C-14), 22.6 (C-6 2 x CH_3), 18.3 (C-3'), 14.0 (C-15), -4.5 ($SiCH_3$), -4.9 ($SiCH_3$). MS: 378 (M^+, 0.3), 321 (2), 253 (2), 175 (19), 159 (4), 113 (11), 105 (12), 83 (12), 75 (100), 73 (45), 67 (54), 57 (10), 55 (18).

Data for compound **165**: IR: 3078, 2960, 2932, 2859, 1632, 1464 cm^{-1}. ^1H NMR: δ 5.93-5.76 (2H, m, C-2H C-4'H), 5.15-5.05 (4H, m, C-1H, C-5'H), 4.39 (1H, t, J = 6.5 Hz, C-8H), 4.23 (1H, dd, J = 1.5, 6.5 Hz, C-5H), 2.98 (1H, t, J = 8.7 Hz, C-3H), 1.74-1.63 (2H, m, C-9H), 1.58 (1H, s, C-5 OH), 1.44-1.25 (6H, m, C-10H, C-11H, C-12H), 0.97 (3H, s, C-4 CH_3), 0.93 (3H, s, C-4 CH_3), 0.91 (9H, s, *t*-Bu), 0.89 (3H, s, C-13H), 0.13 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$). ^{13}C NMR: δ 137.9 and 137.3 (C-2, C-4'), 116.7 and 116.6 (C-1, C-5'), 88.3 and 83.1 (C-6, C-7), 69.2 (C-5), 63.0 (C-8), 54.4 (C-3), 41.0 (C-4), 38.8 (C-9), 31.5 (C-11), 25.8 (*t*-Bu), 24.9 (C-10), 22.6 (C-12), 20.1 (C-4 CH_3), 19.6 (C-4 CH_3), 18.2 (C-3'), 14.0 (C-13), -4.5 ($SiCH_3$), -5.0 ($SiCH_3$). MS: no M^+, 321(2), 253 (3), 215 (3), 183 (5), 175 (89), 109 (12), 105 (18), 95 (14), 83 (20), 75 (100), 73 (68), 67 (76), 57 (12), 55 (21).

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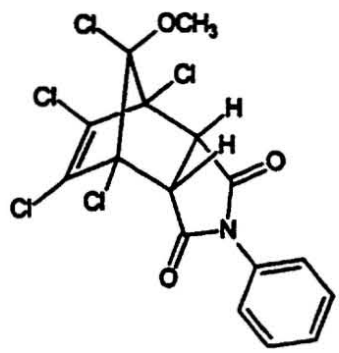
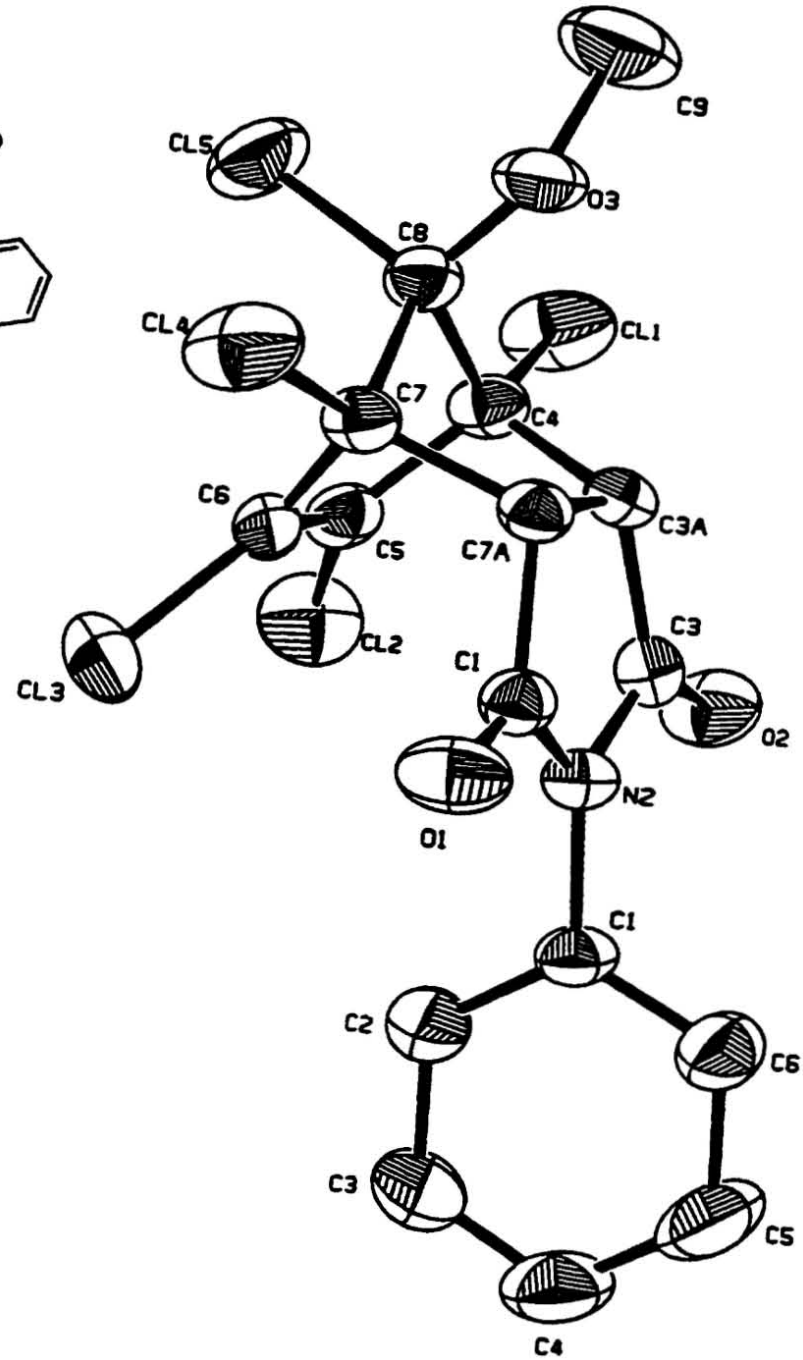
83. For General Methods, see *Part I*: section I.IV.

Appendix A

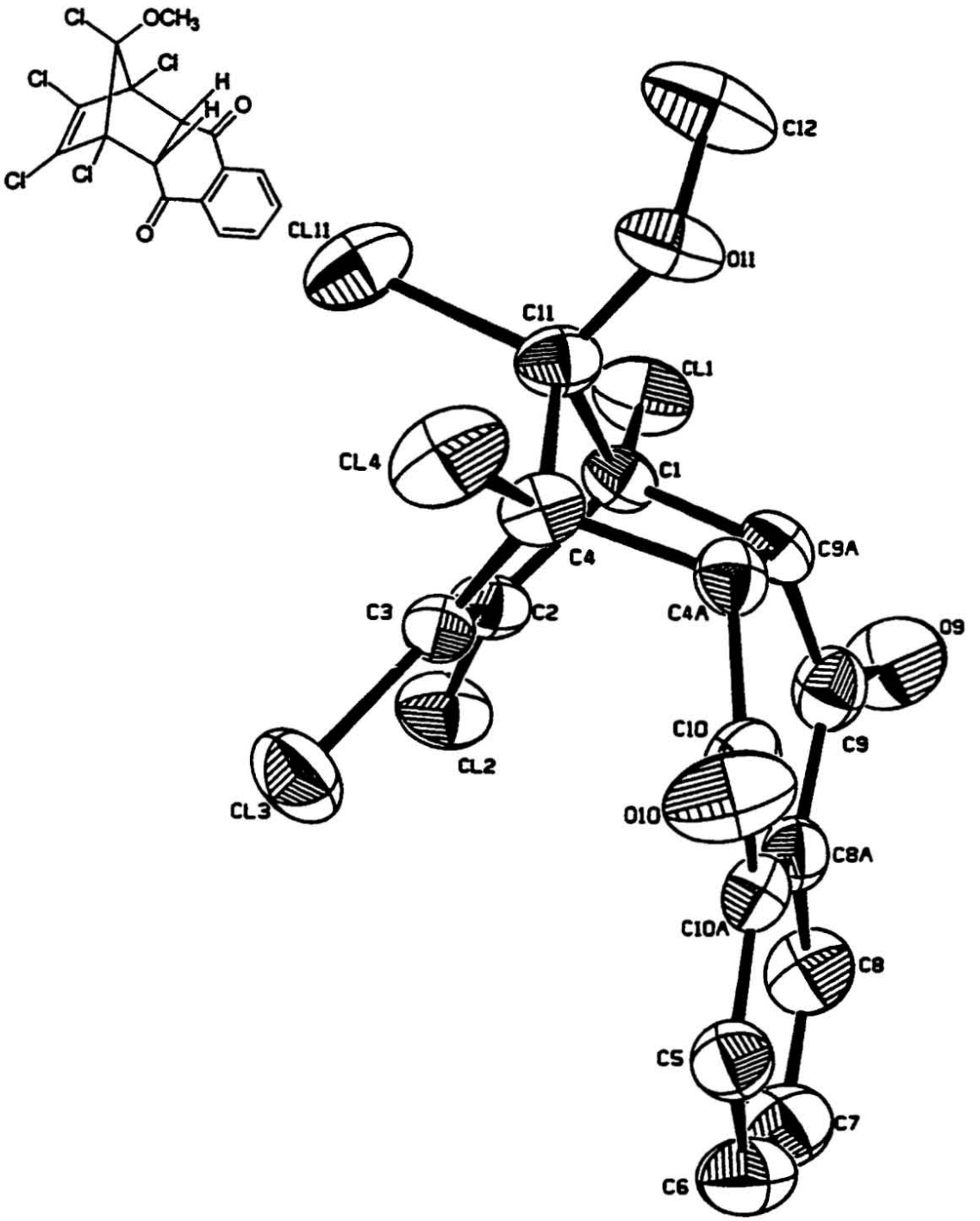
ORTEP diagrams for those compounds where the stereochemistry was assigned using X-ray crystallography. These data were collected and the structures solved by Dr. John N. Bridson and Mr. David O. Miller. For the instrument employed see ***General Methods*** *section* ***I.IV.***

Adduct 20 Space Group: Pbca (#61)

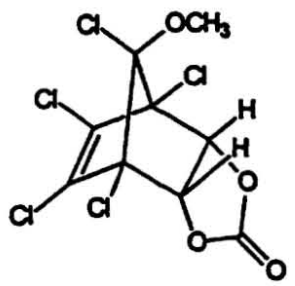


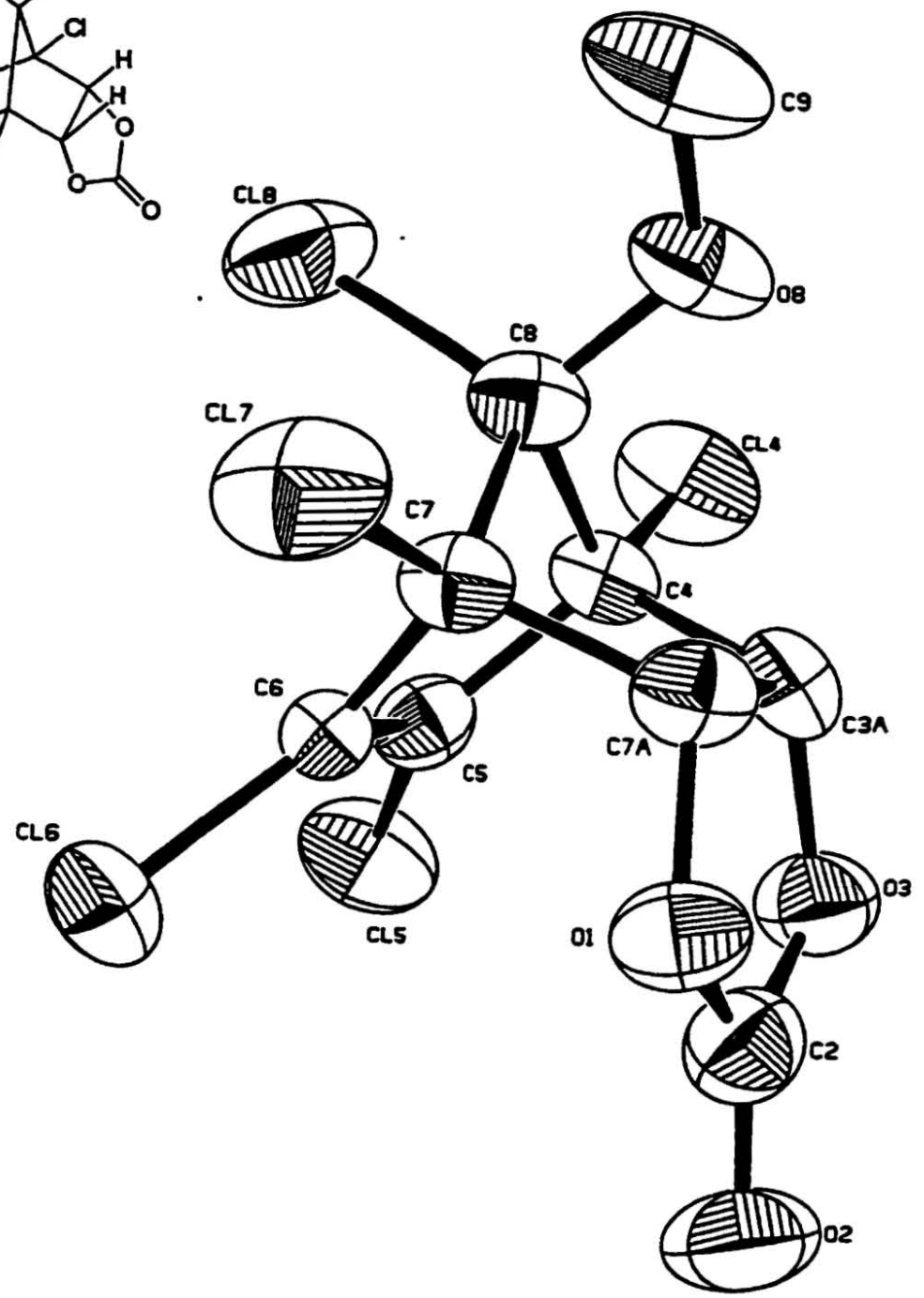


Adduct 21 **Space Group: $P\bar{1}$ (#2)**

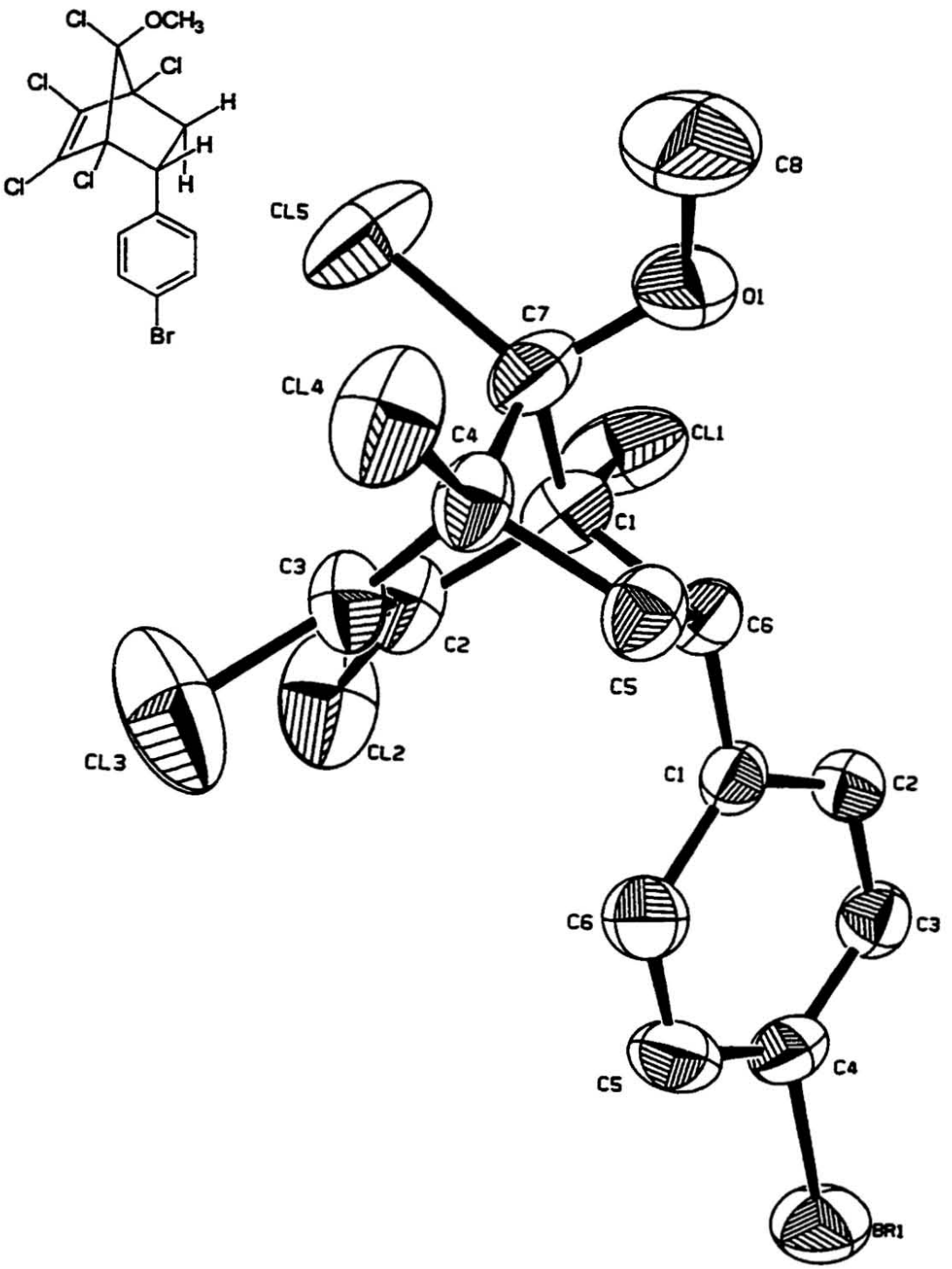


Adduct 22 **Space group: P_n (#7)**

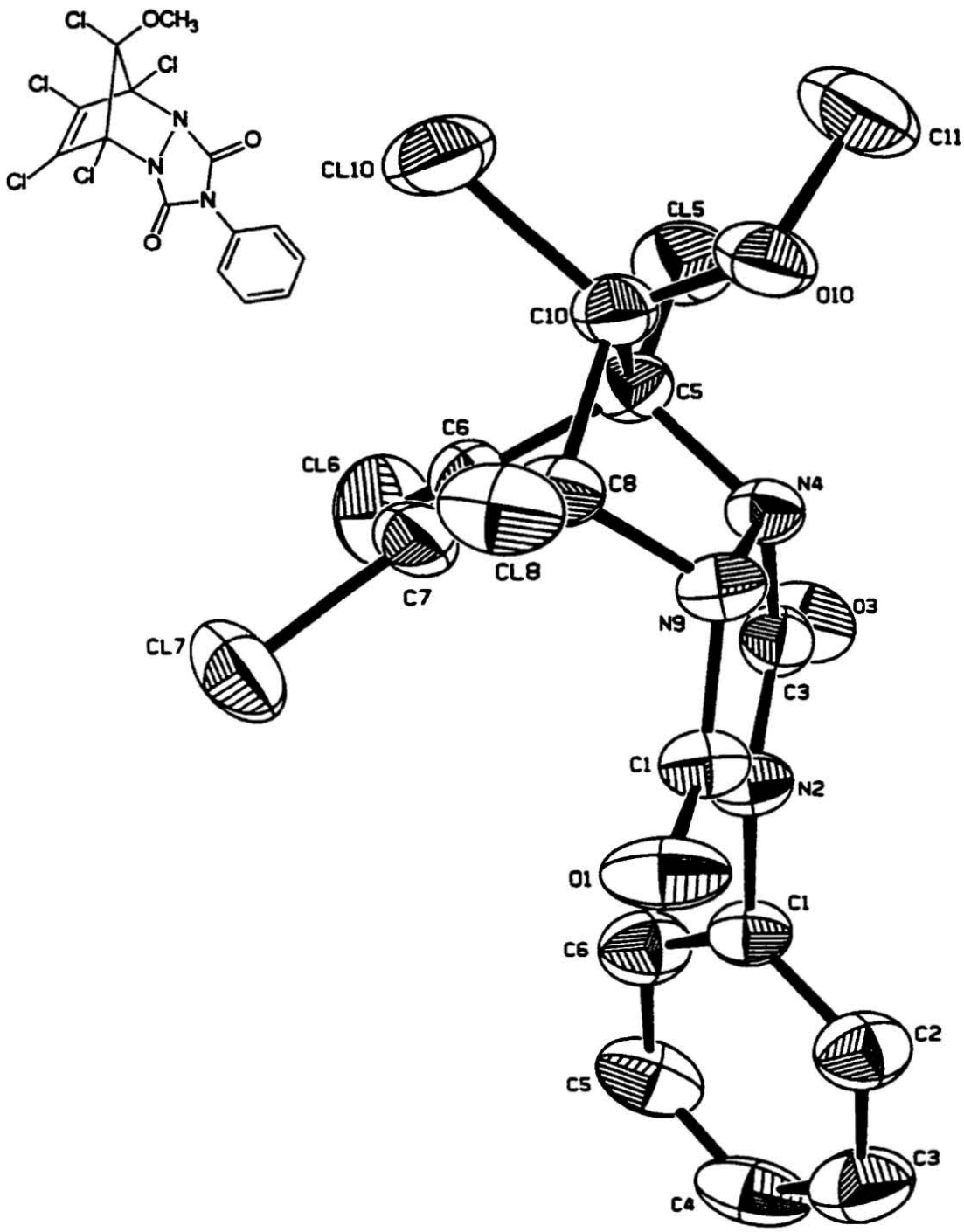




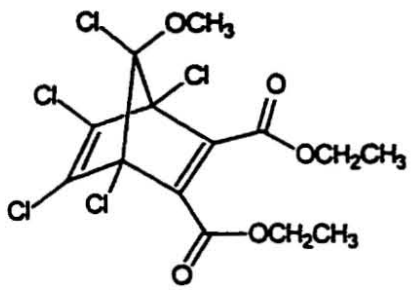
Adduct 25 Space group: $P2_1/c$ (#14)

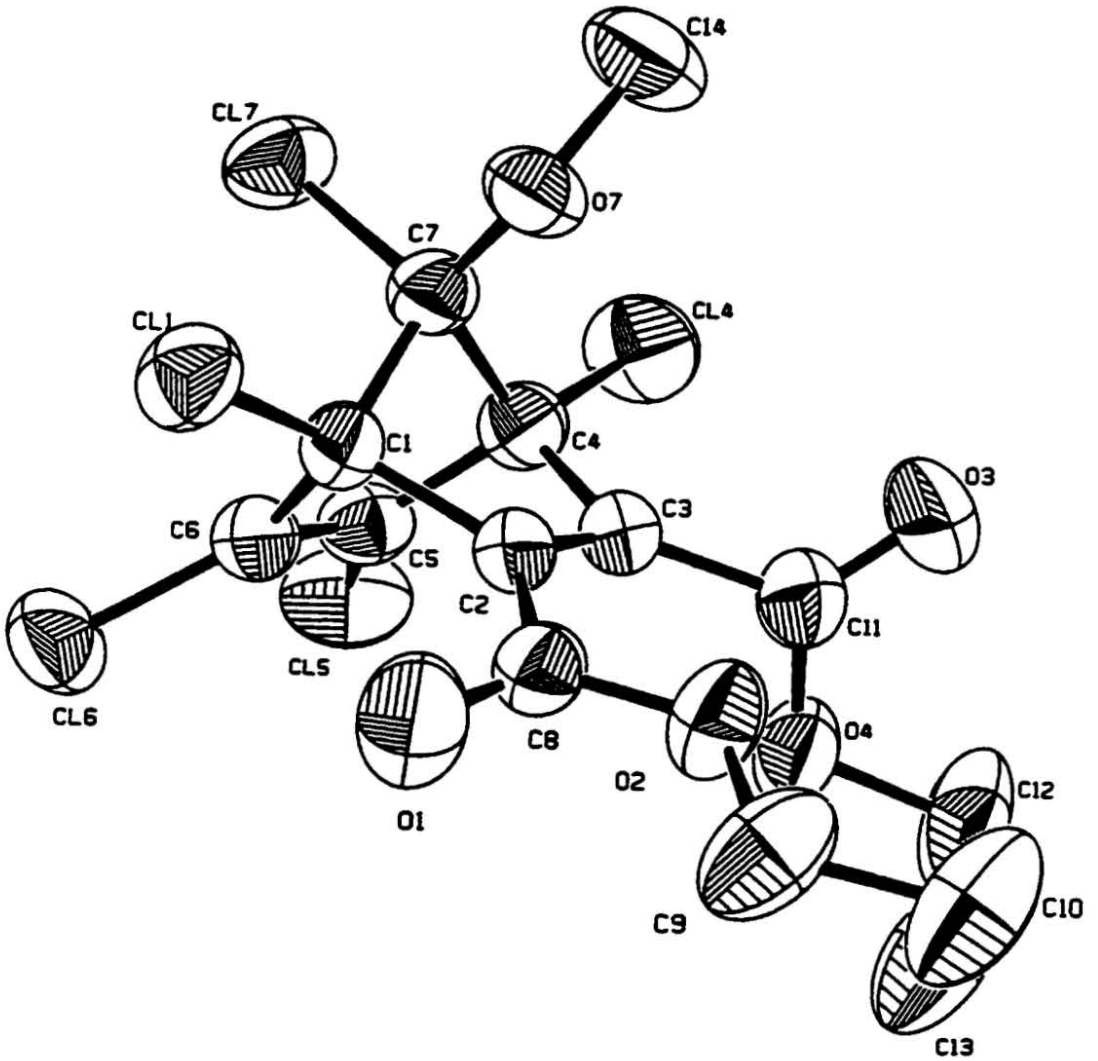


Adduct 28 Space group: $P\bar{1}$ (#2)

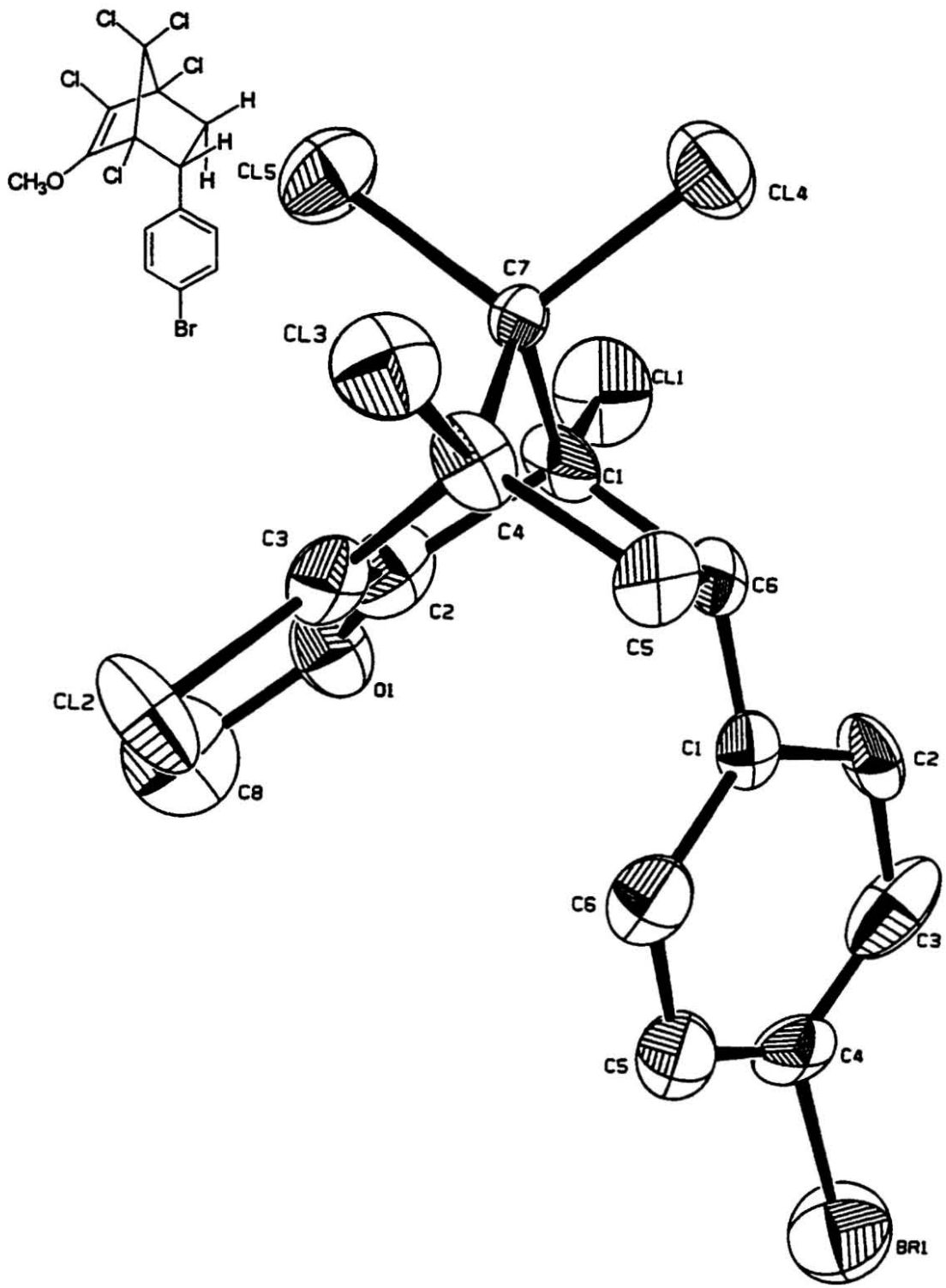


Adduct 29 Space group: $P\bar{1}$ (#2)

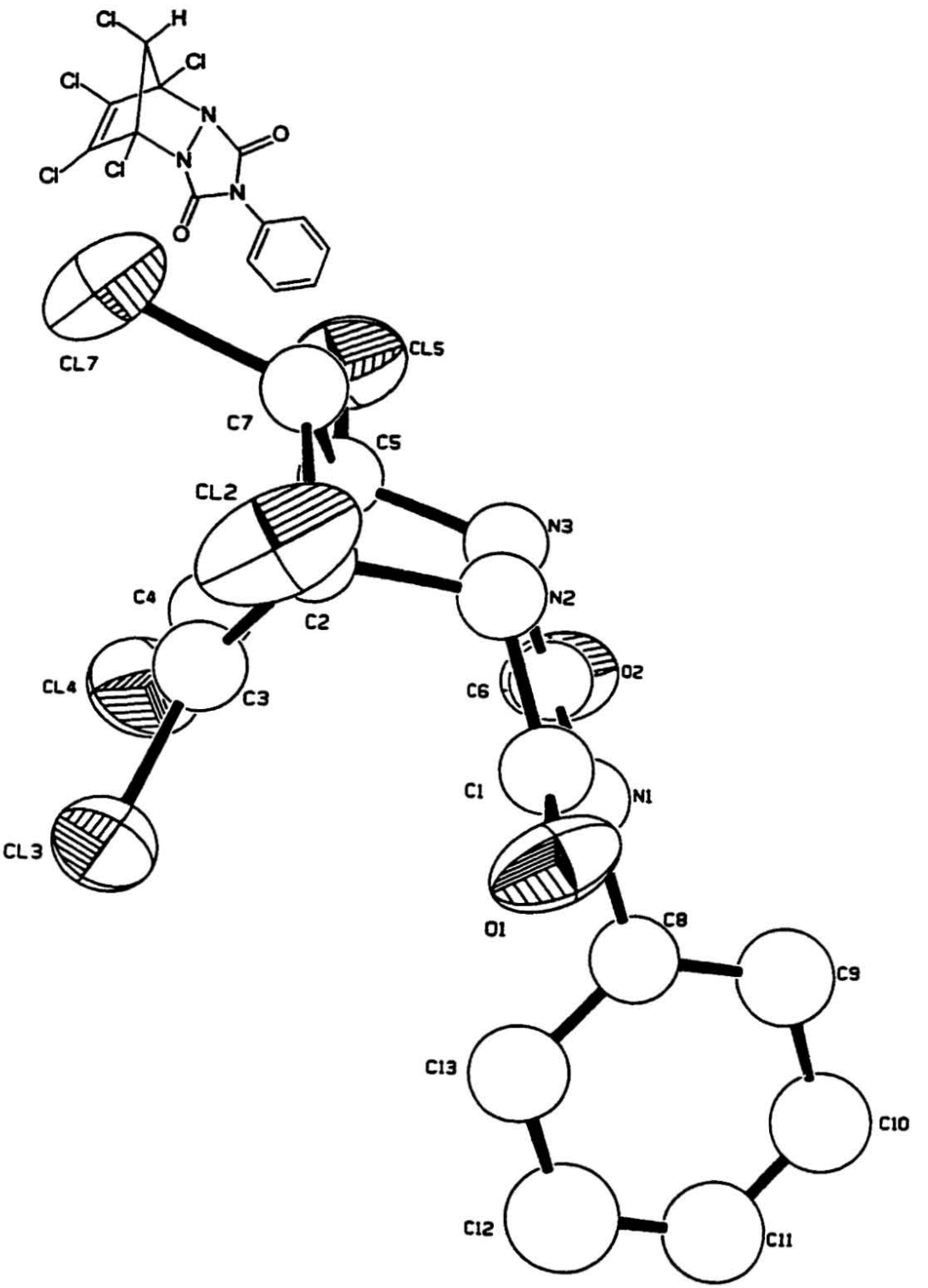




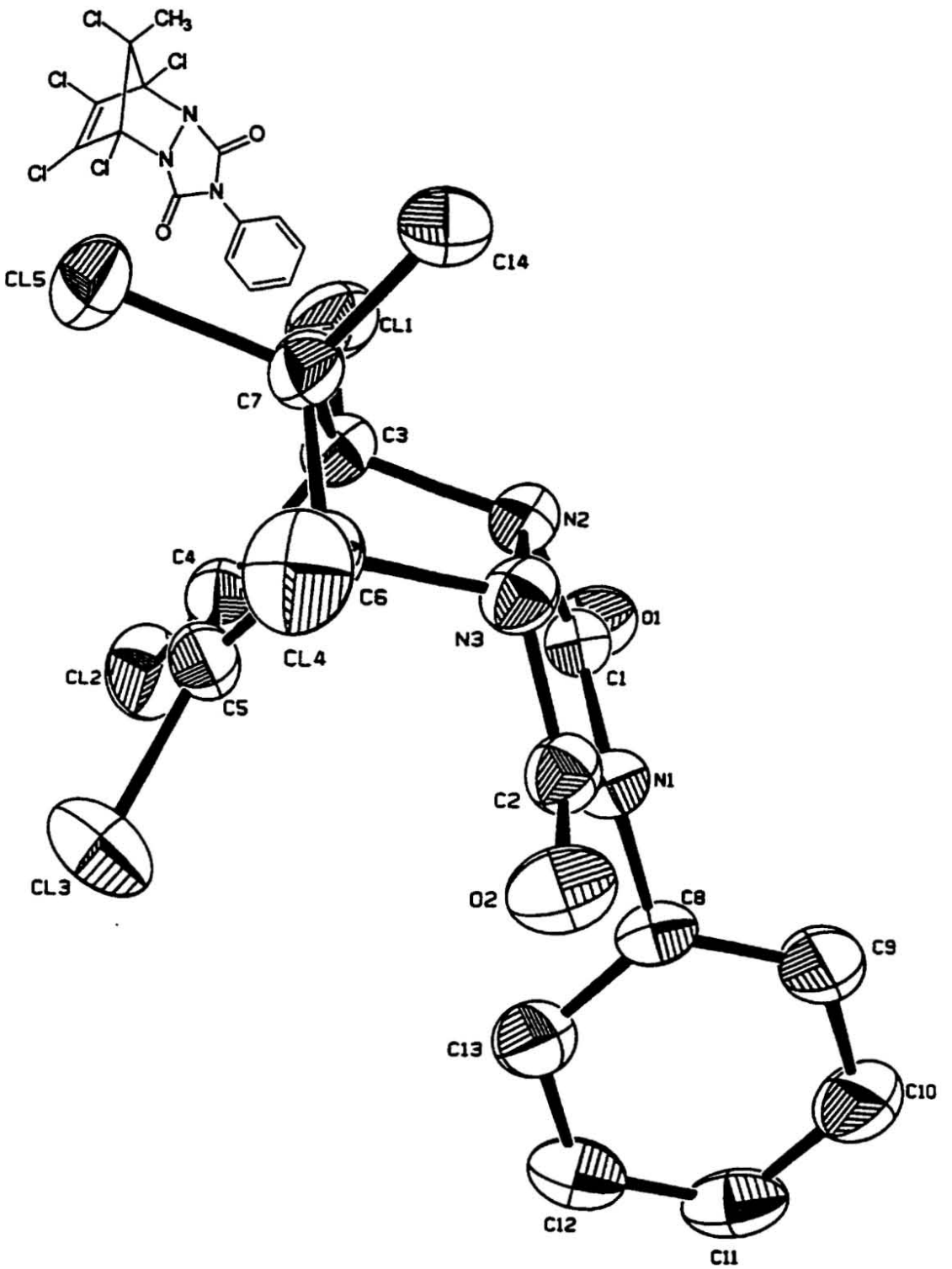
Adduct 30 Space group: $P\bar{1}$ (#2)



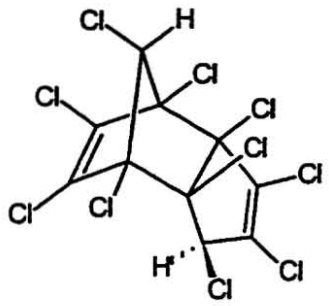
Adduct 66 Space group: Pbca (#61)

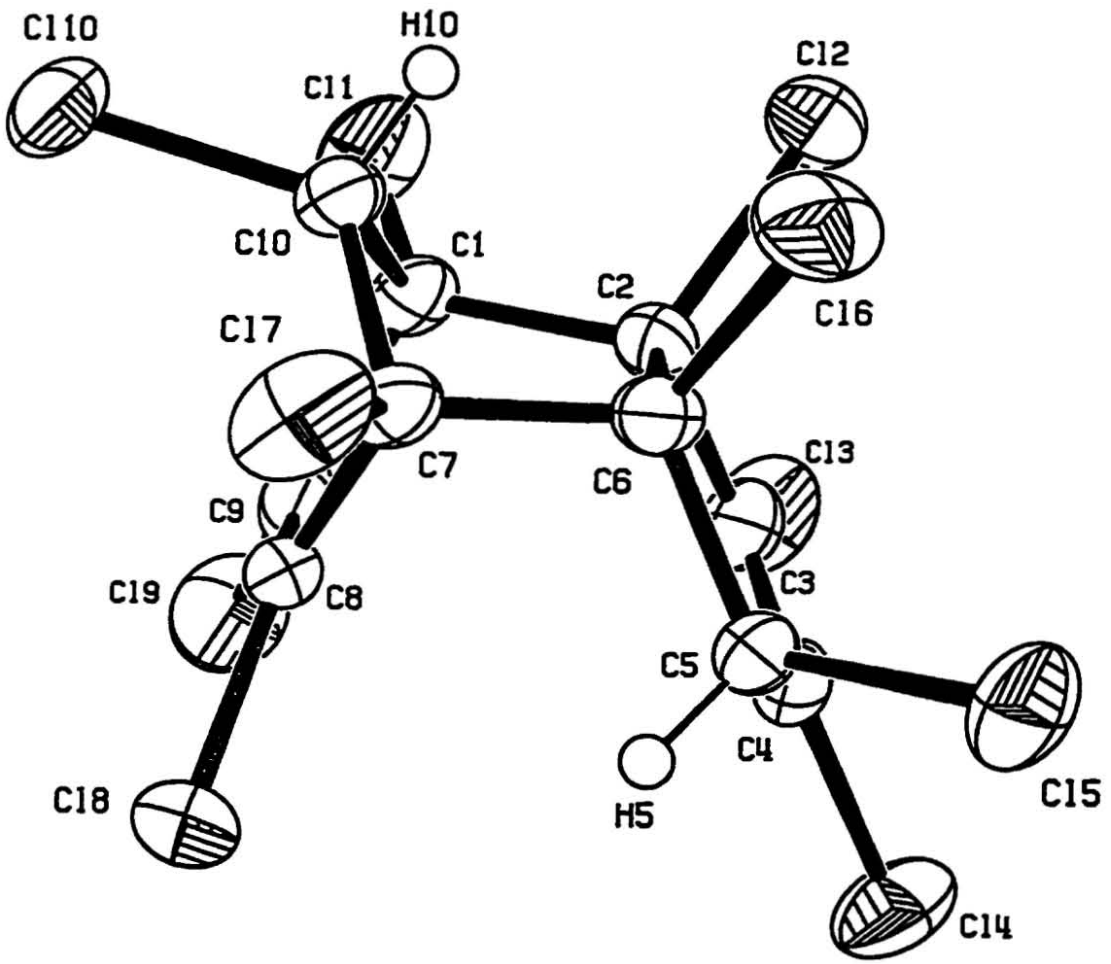


Adduct 67 Space group: $P2_1/c$ (#14)

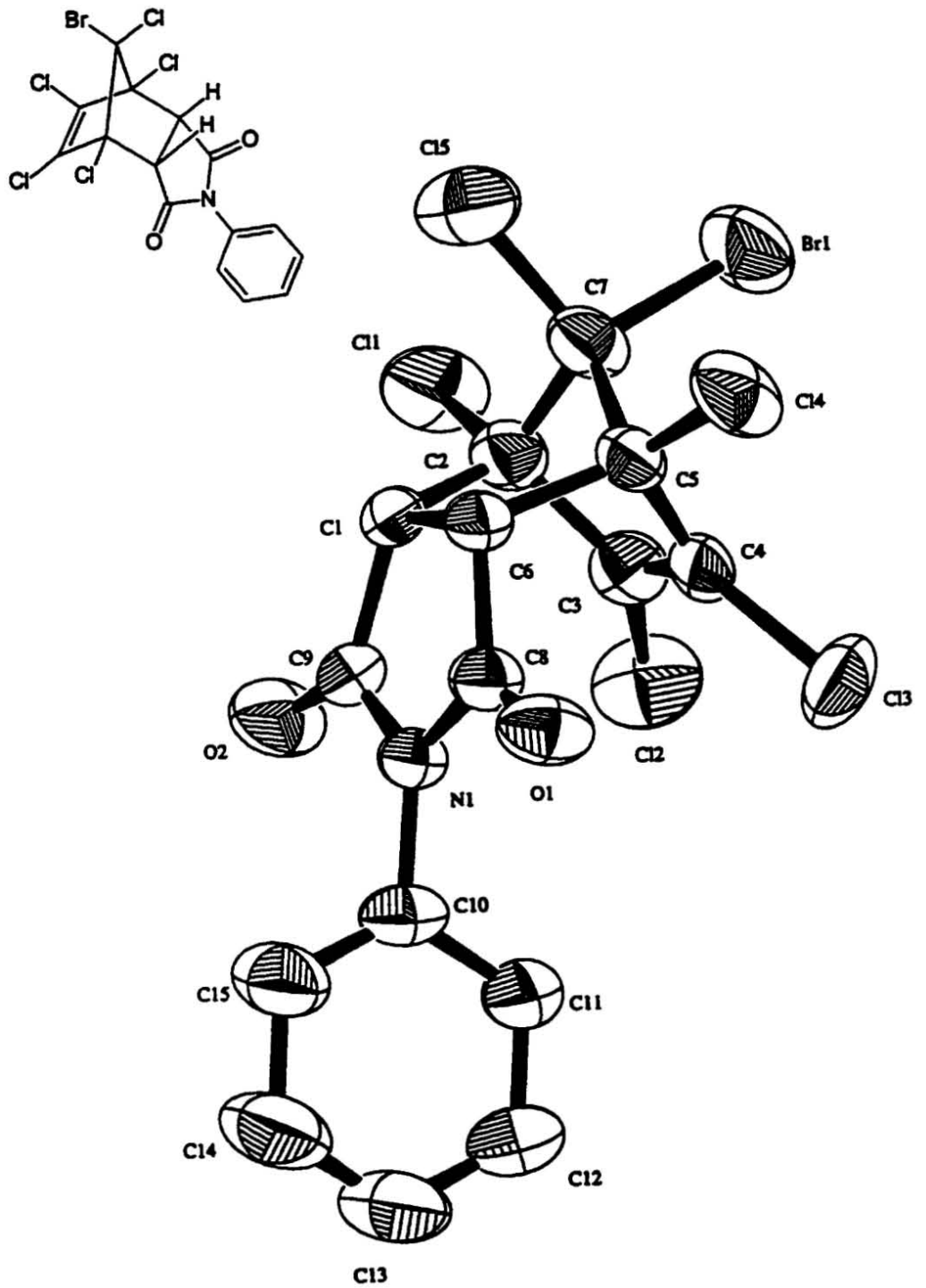


Adduct 69 Space group: $Pca2_1$ (#29)

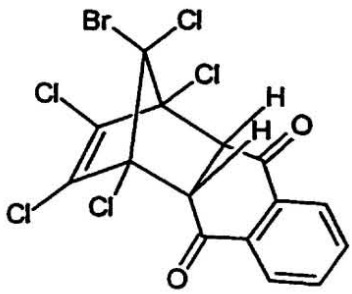


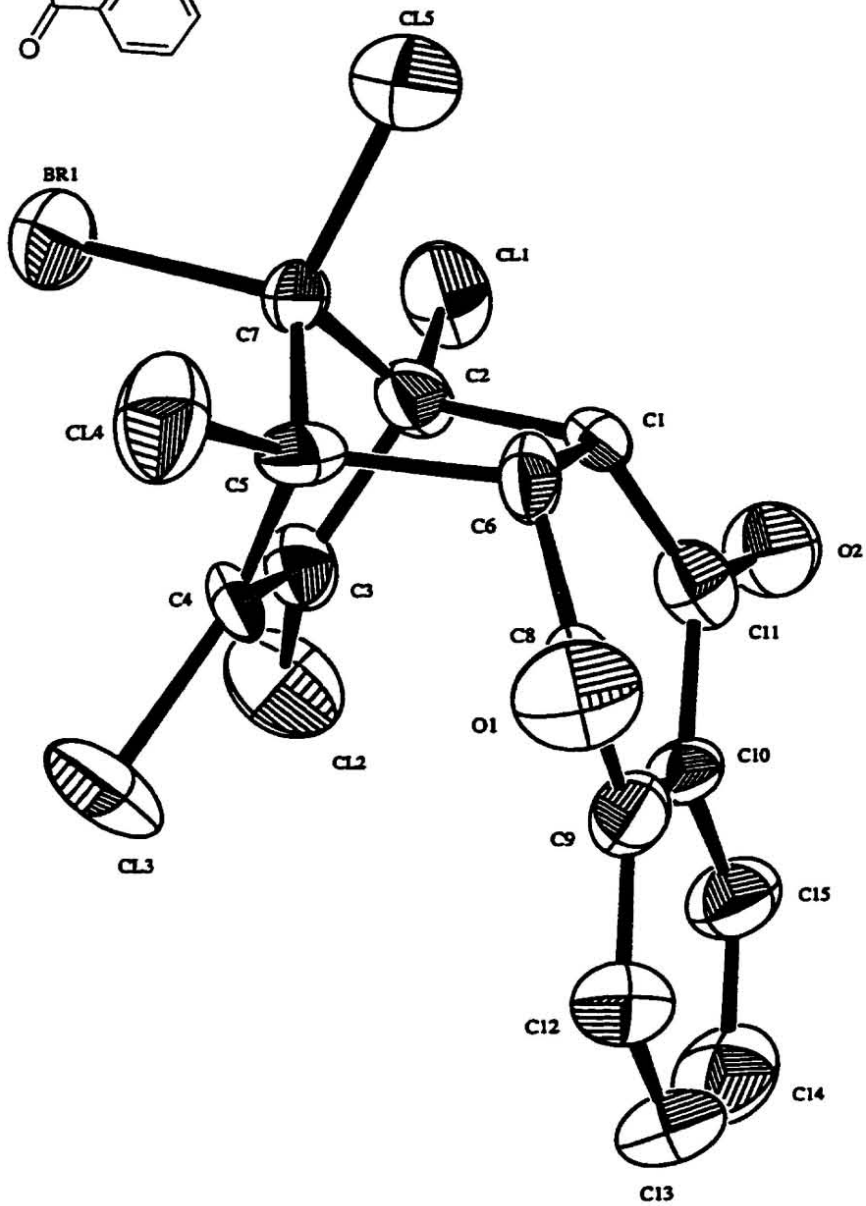


Adduct 71 Space group: $P2_1/c$ (#14)

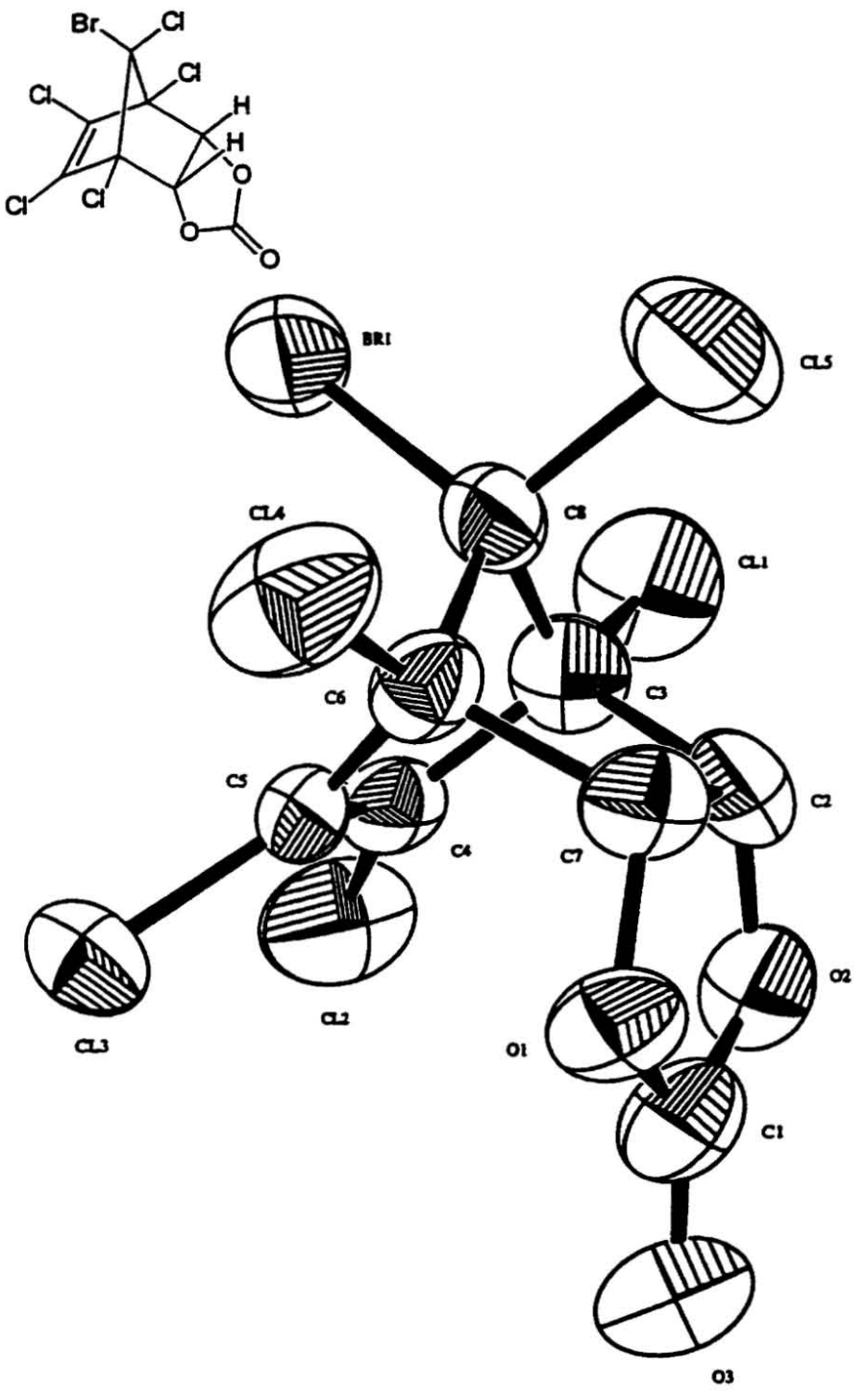


Adduct 73 Space group: $P\bar{1}$ (#2)

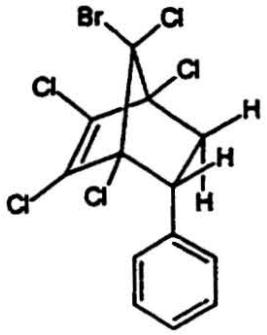


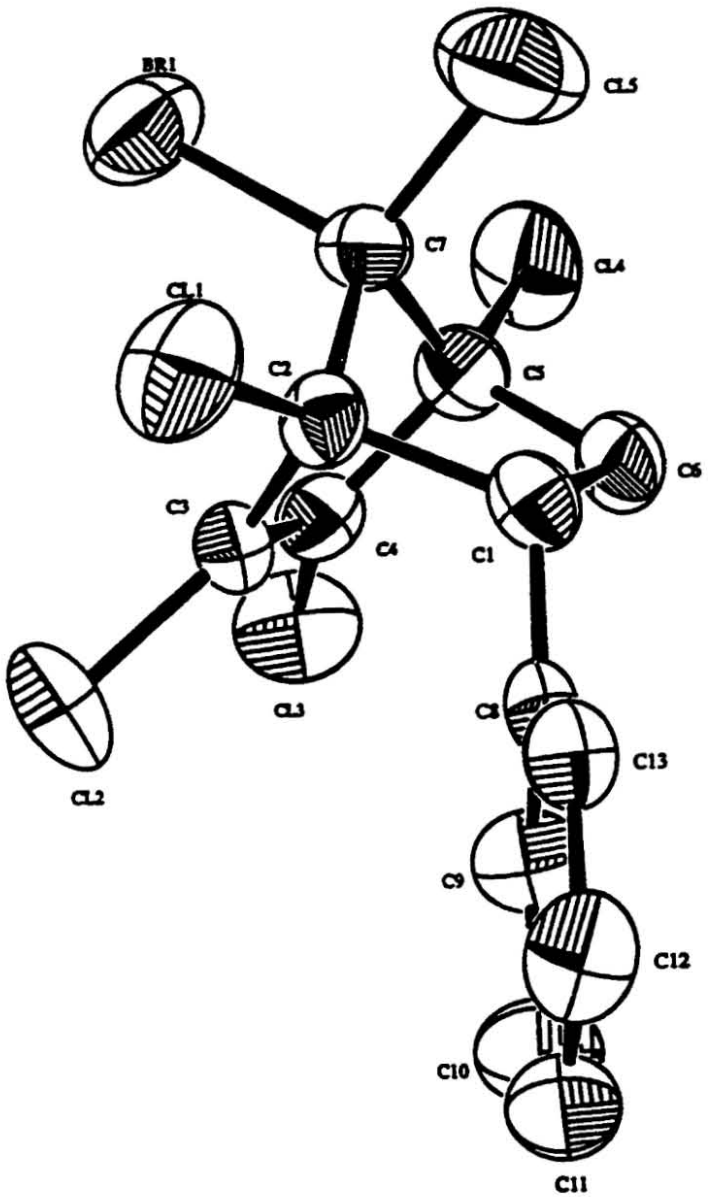


Adduct 75 Space group: $P2_1/c$ (14)

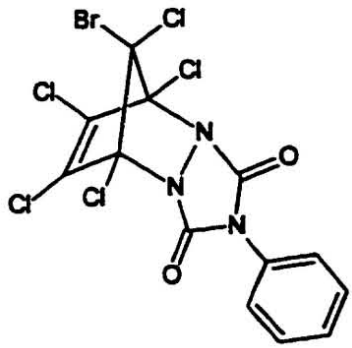


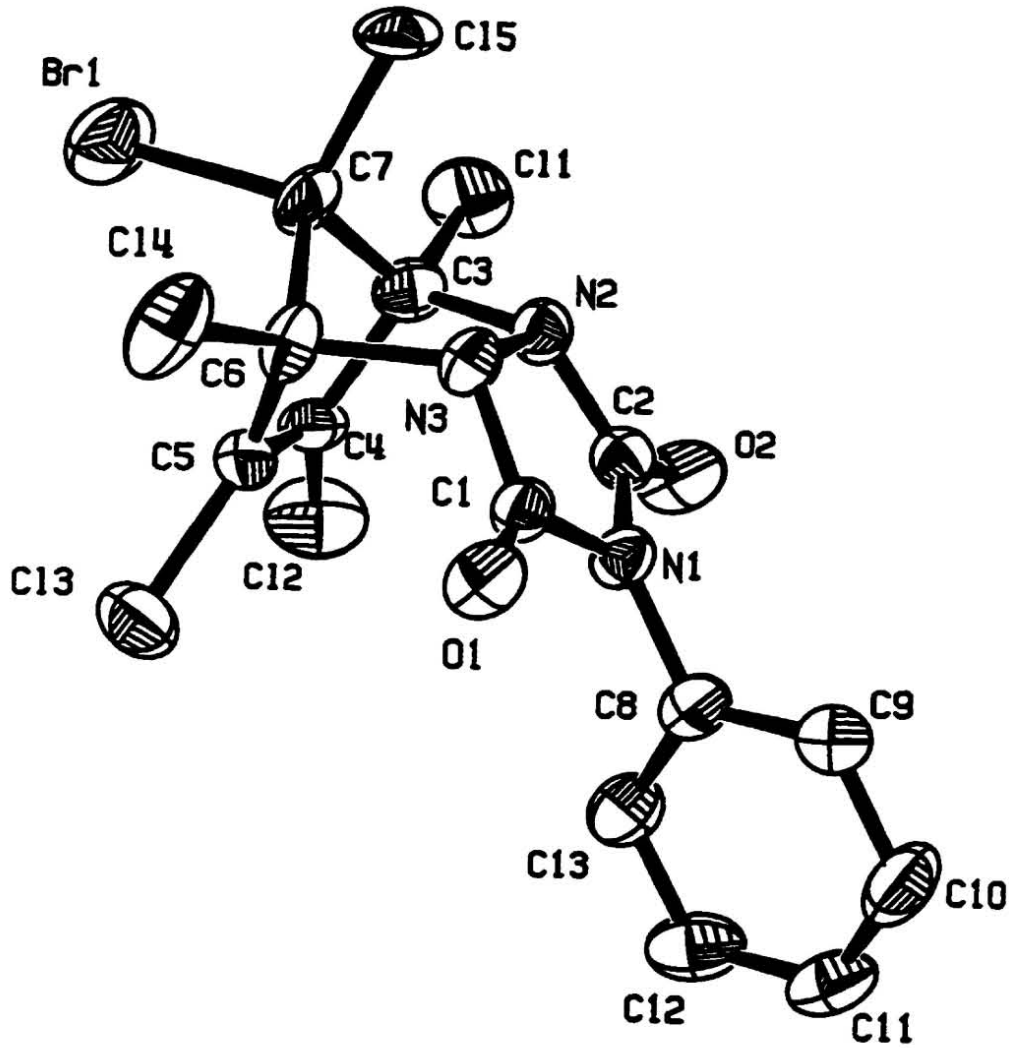
Adduct 77 Space group: $P2_1/c$ (#14)





Adduct 81 Space group: $P2_1/c$ (#14)

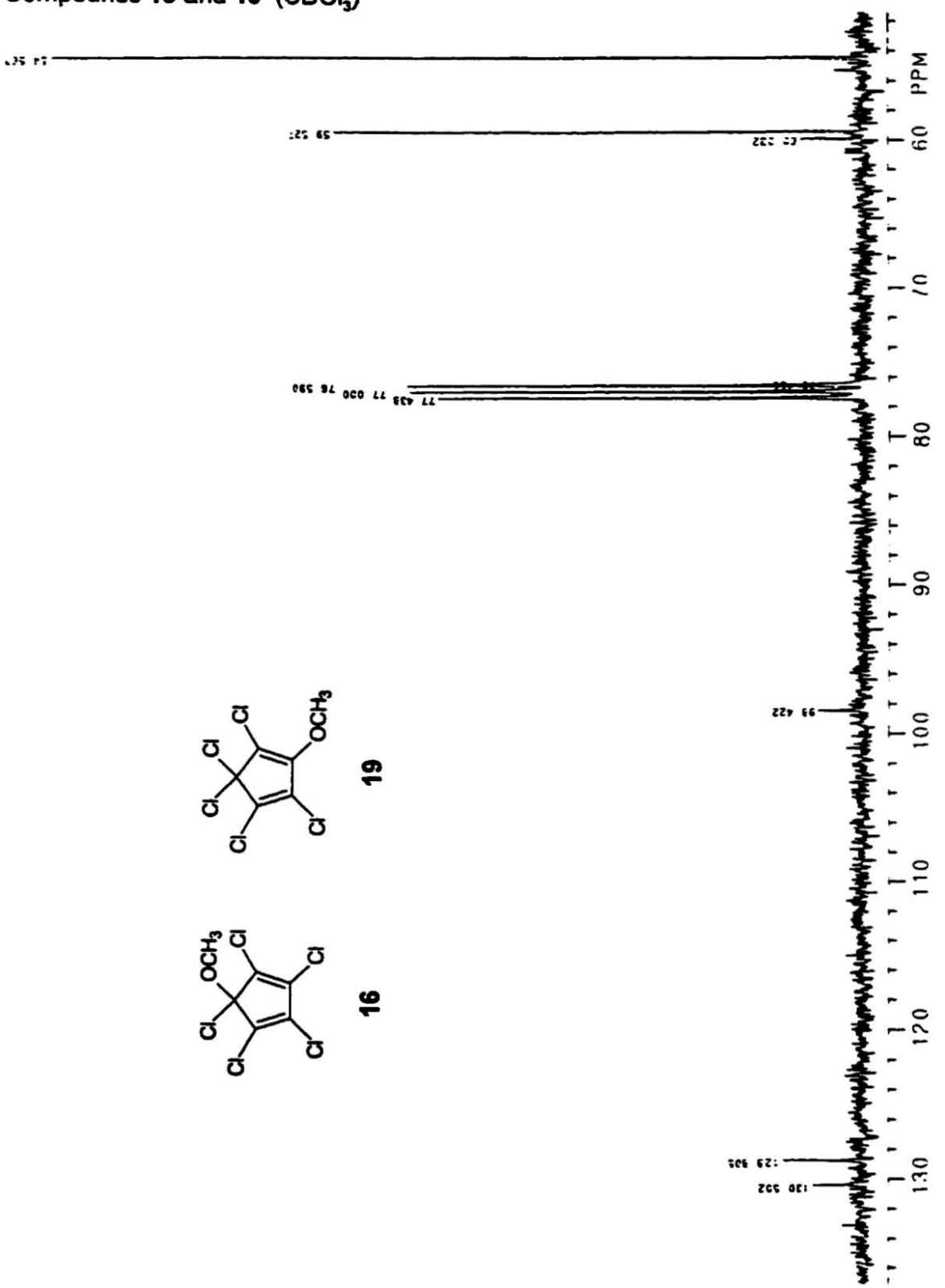




Appendix B

NMR Spectra for selected compounds are arranged in the order in which they appear in the text. For the instrument employed see ***General Methods*** *section* ***I.IV.***

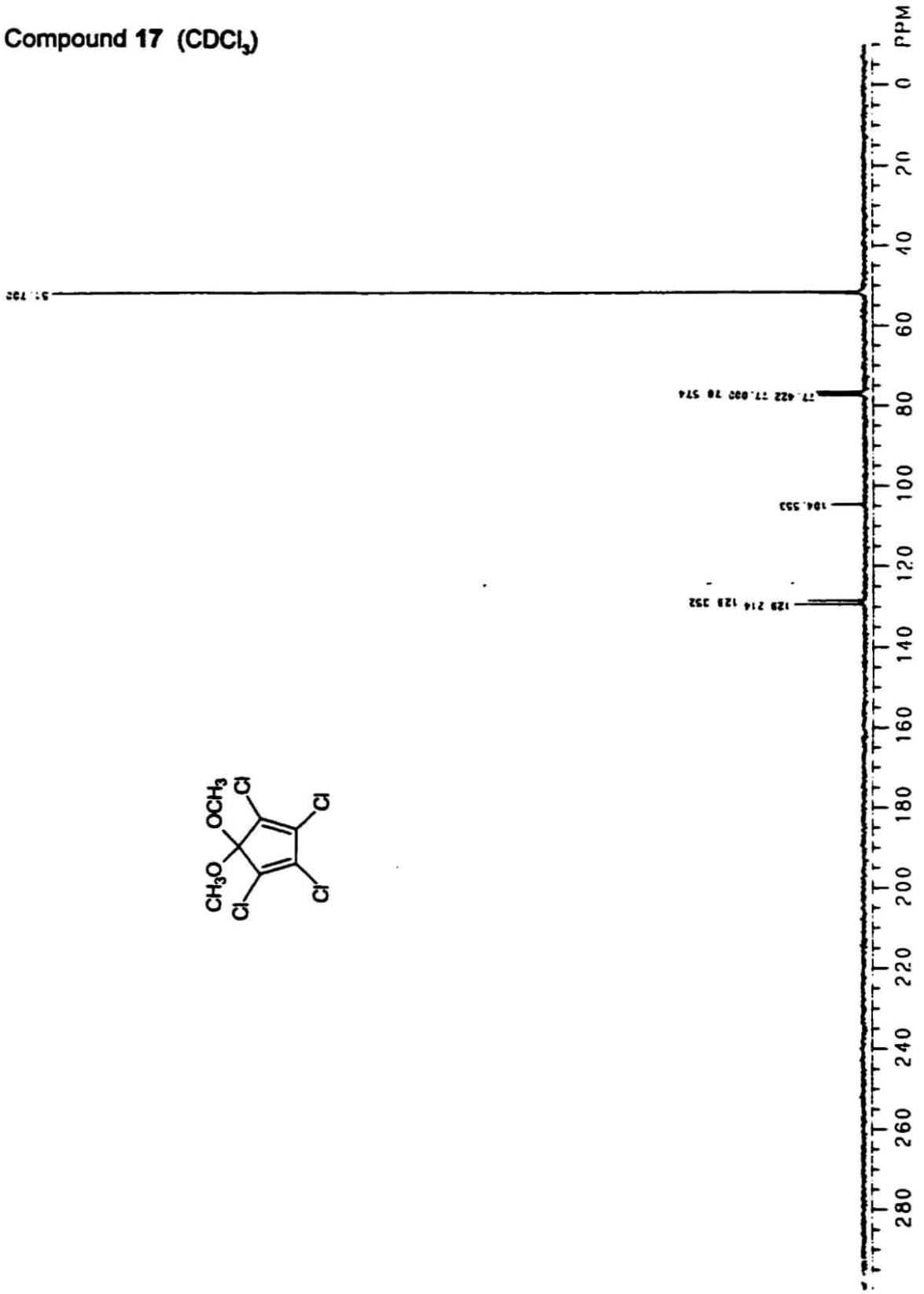
Compounds 16 and 19 ($CDCl_3$)



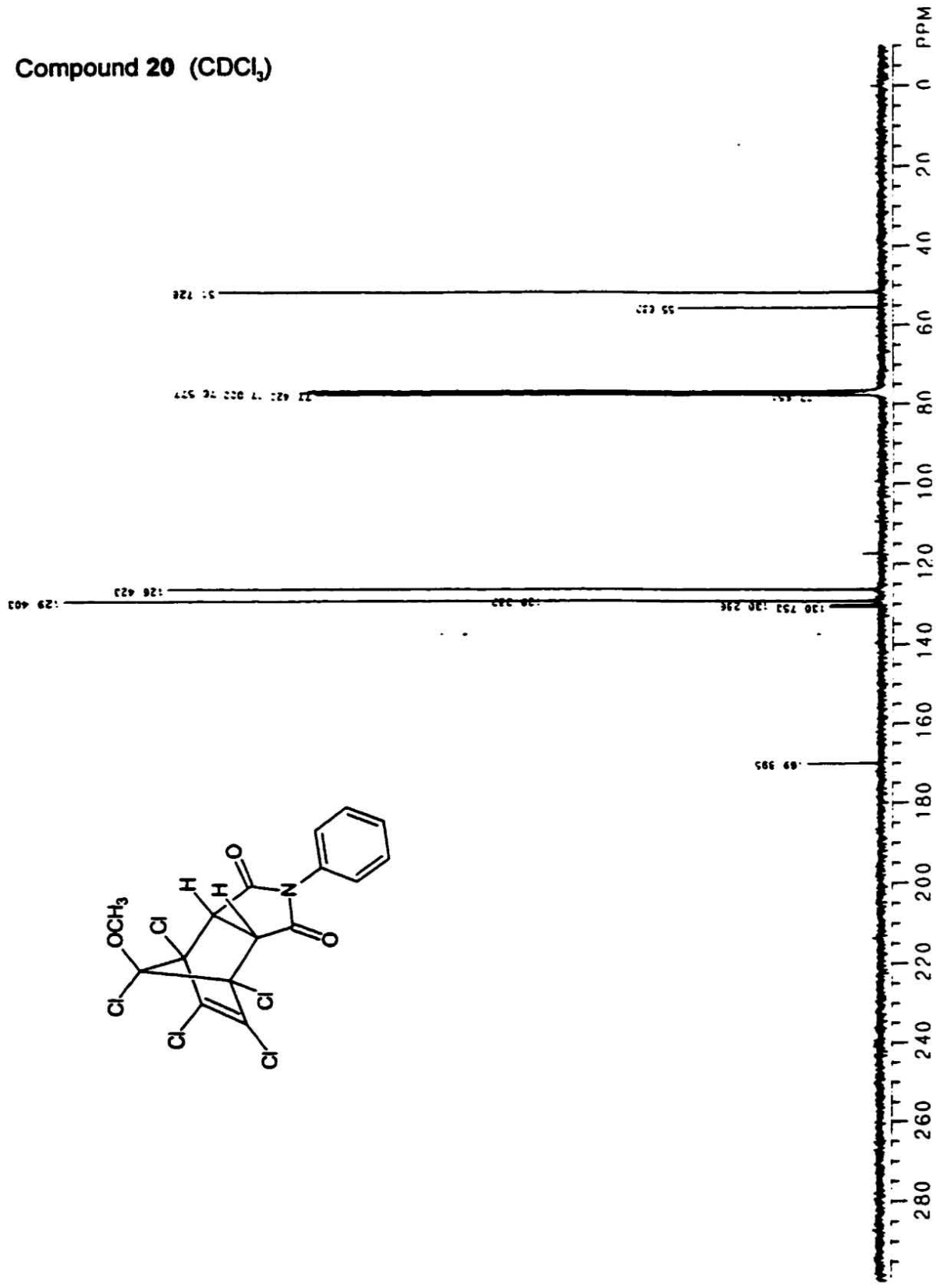
19

16

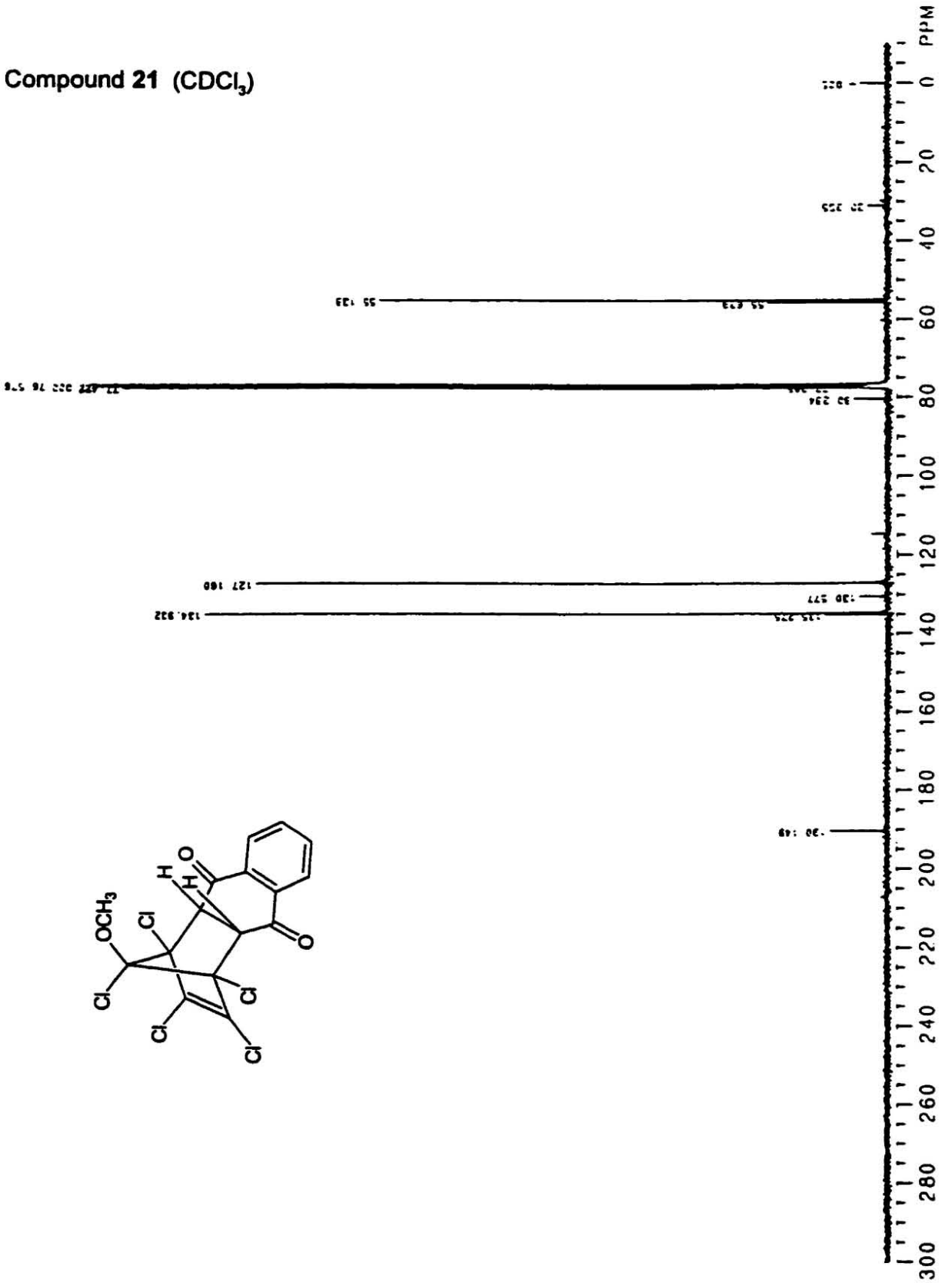
Compound 17 ($CDCl_3$)



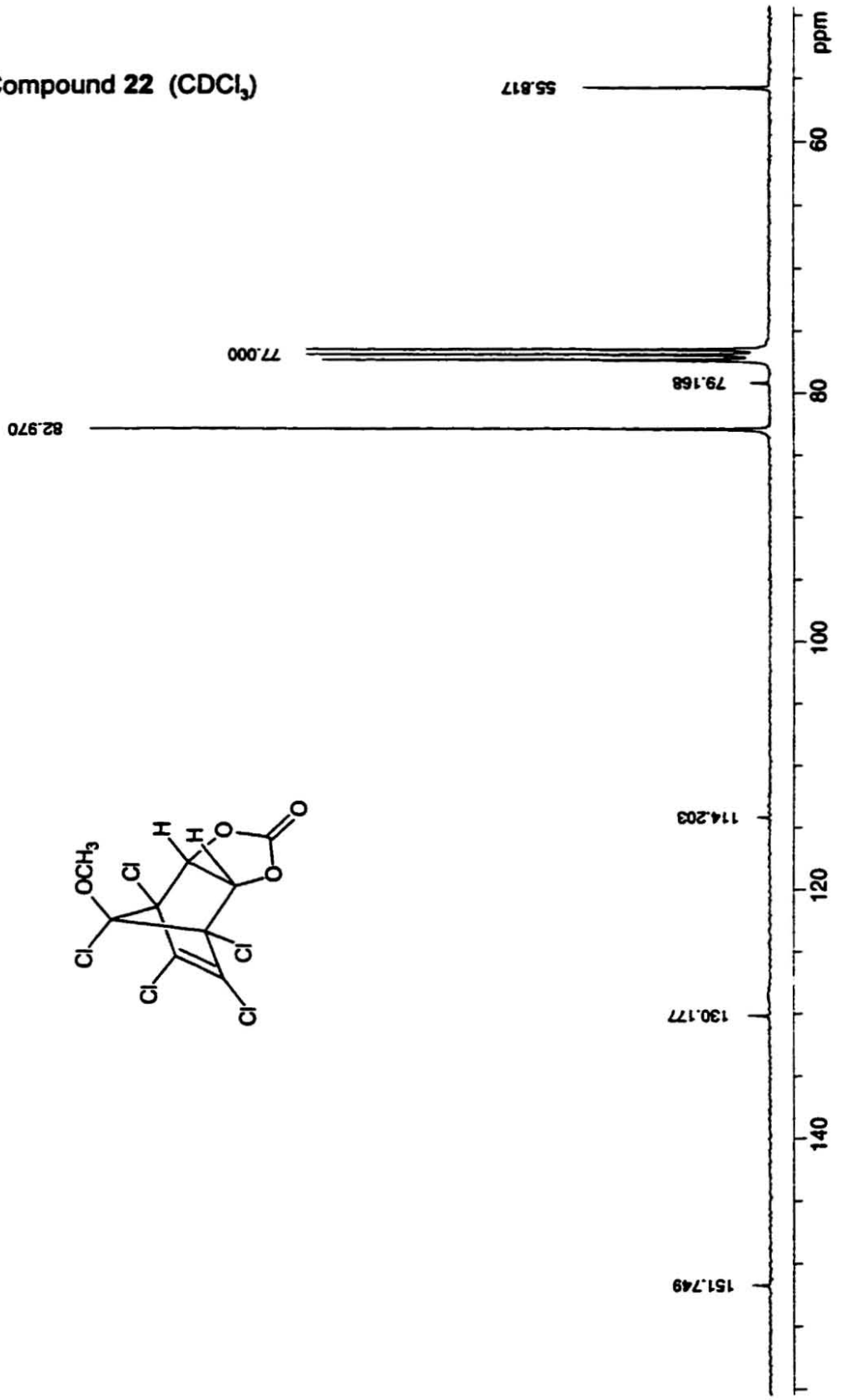
Compound 20 ($CDCl_3$)



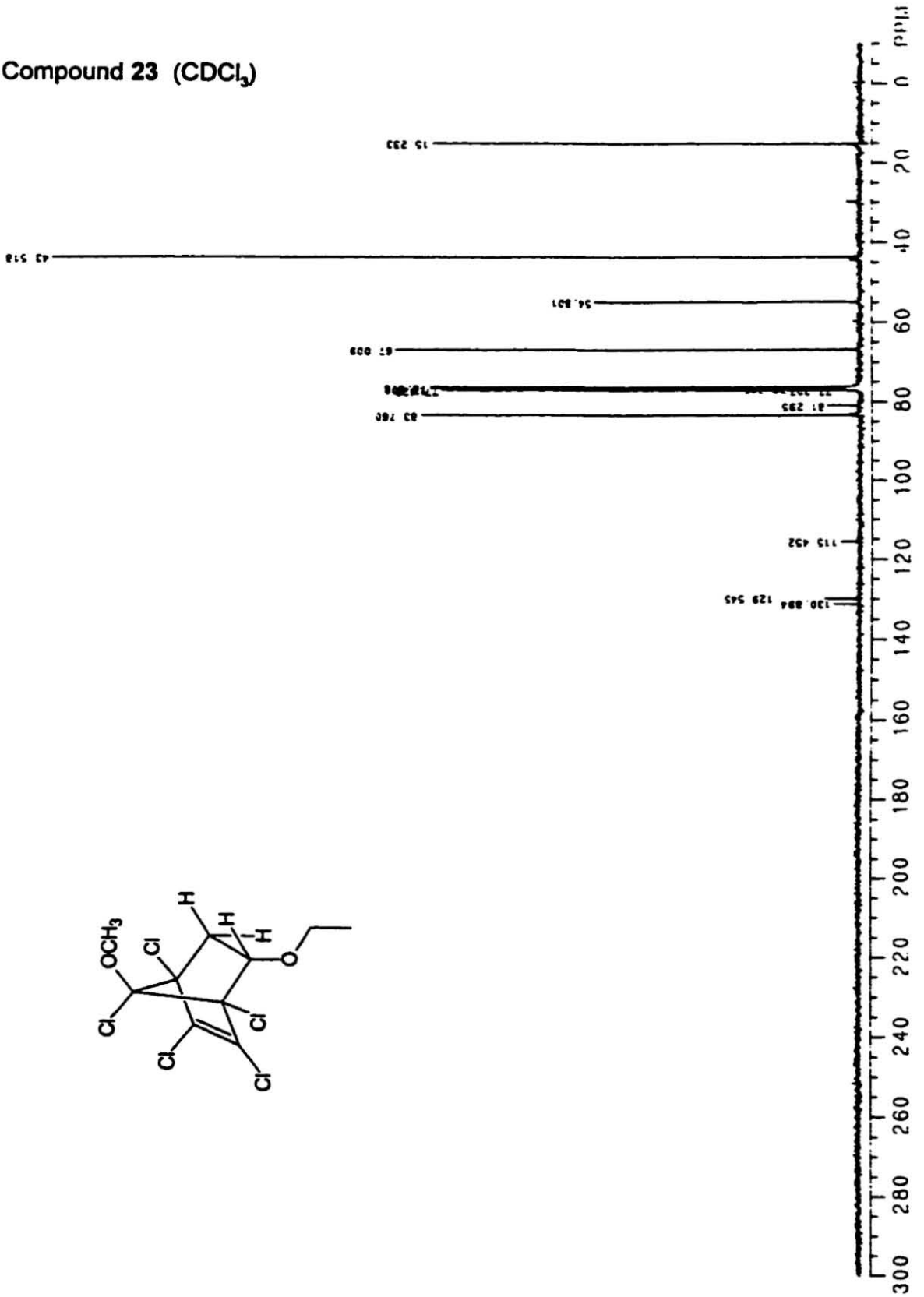
Compound 21 ($CDCl_3$)



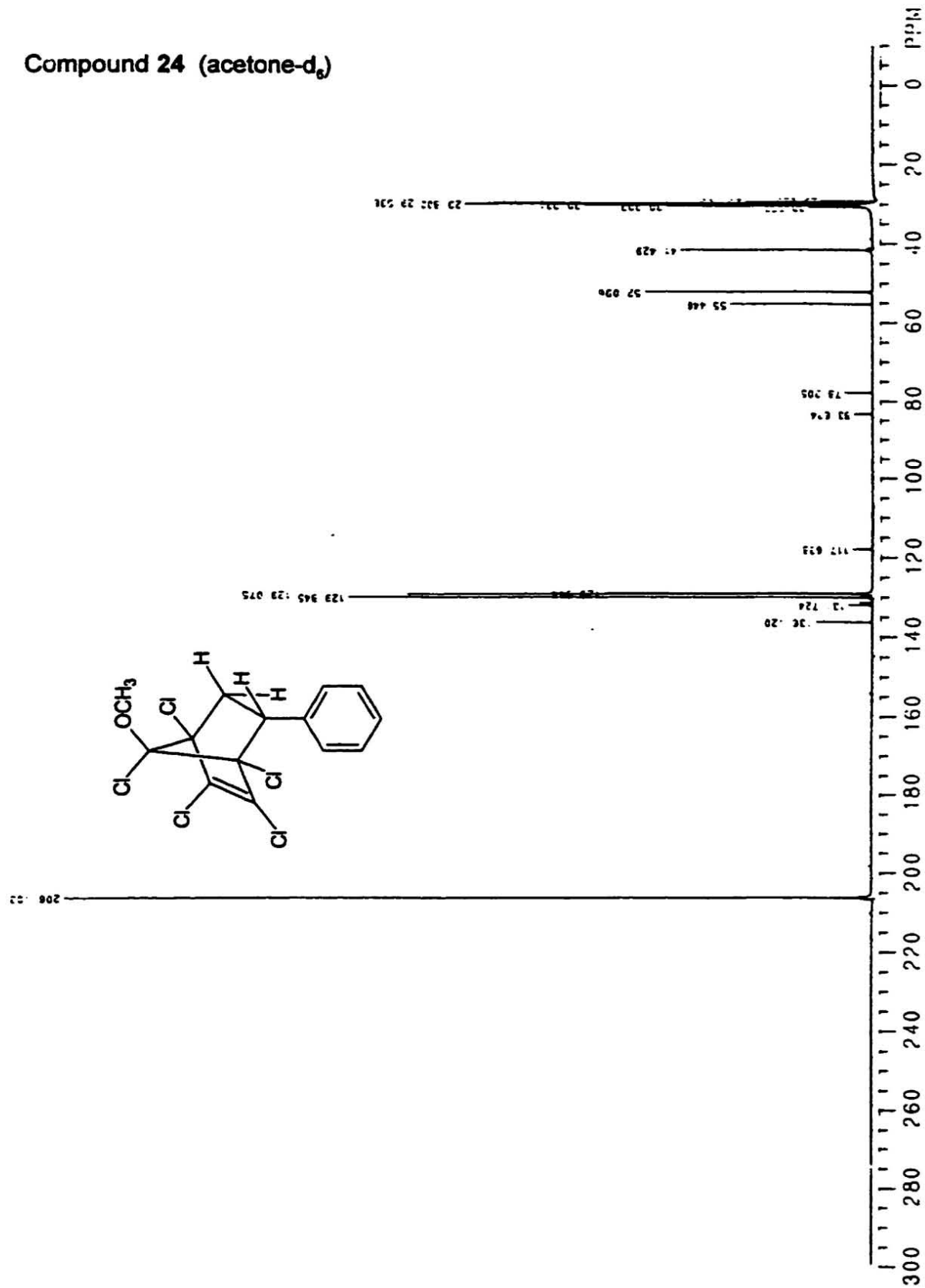
Compound **22** ($CDCl_3$)



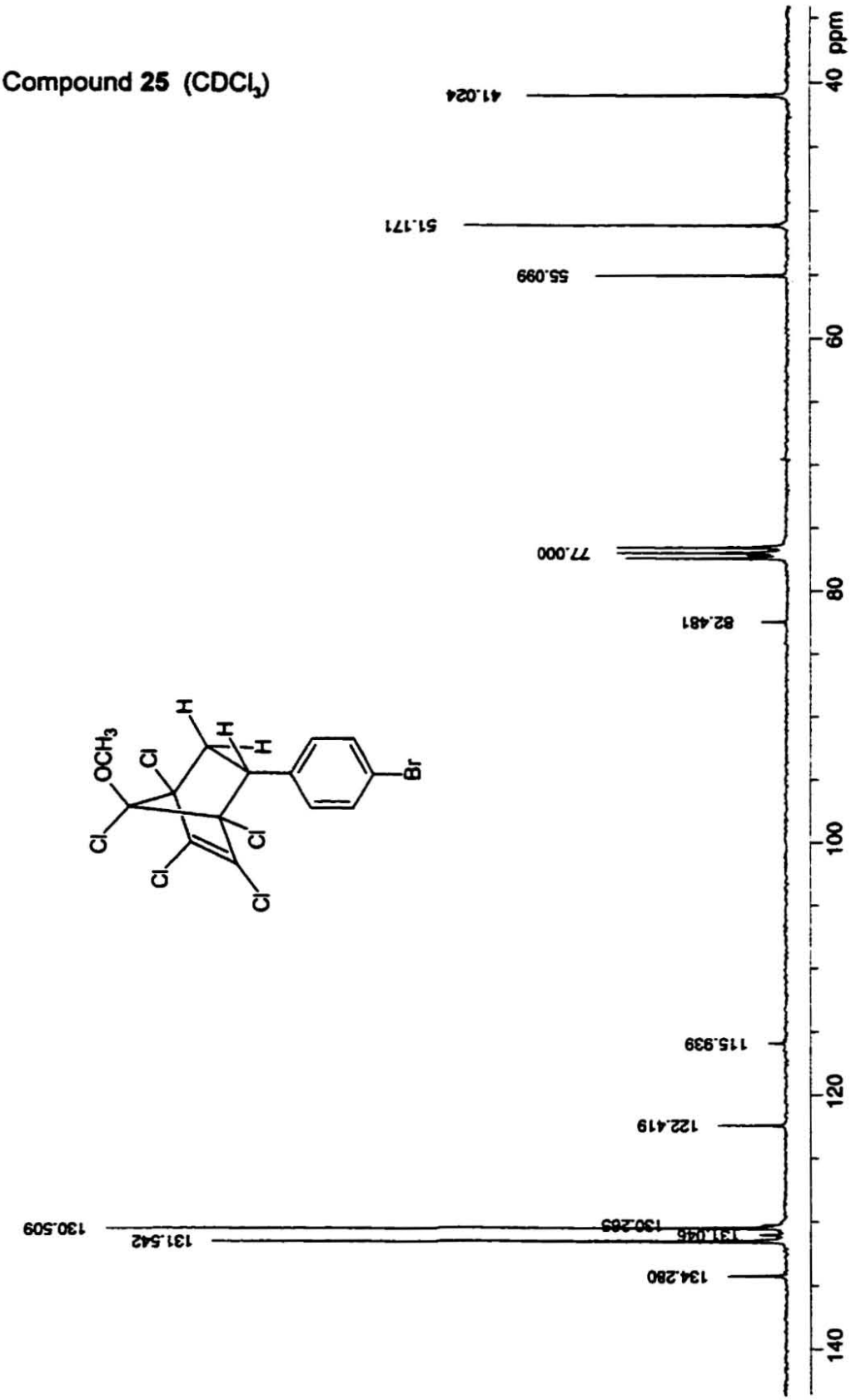
Compound **23** ($CDCl_3$)



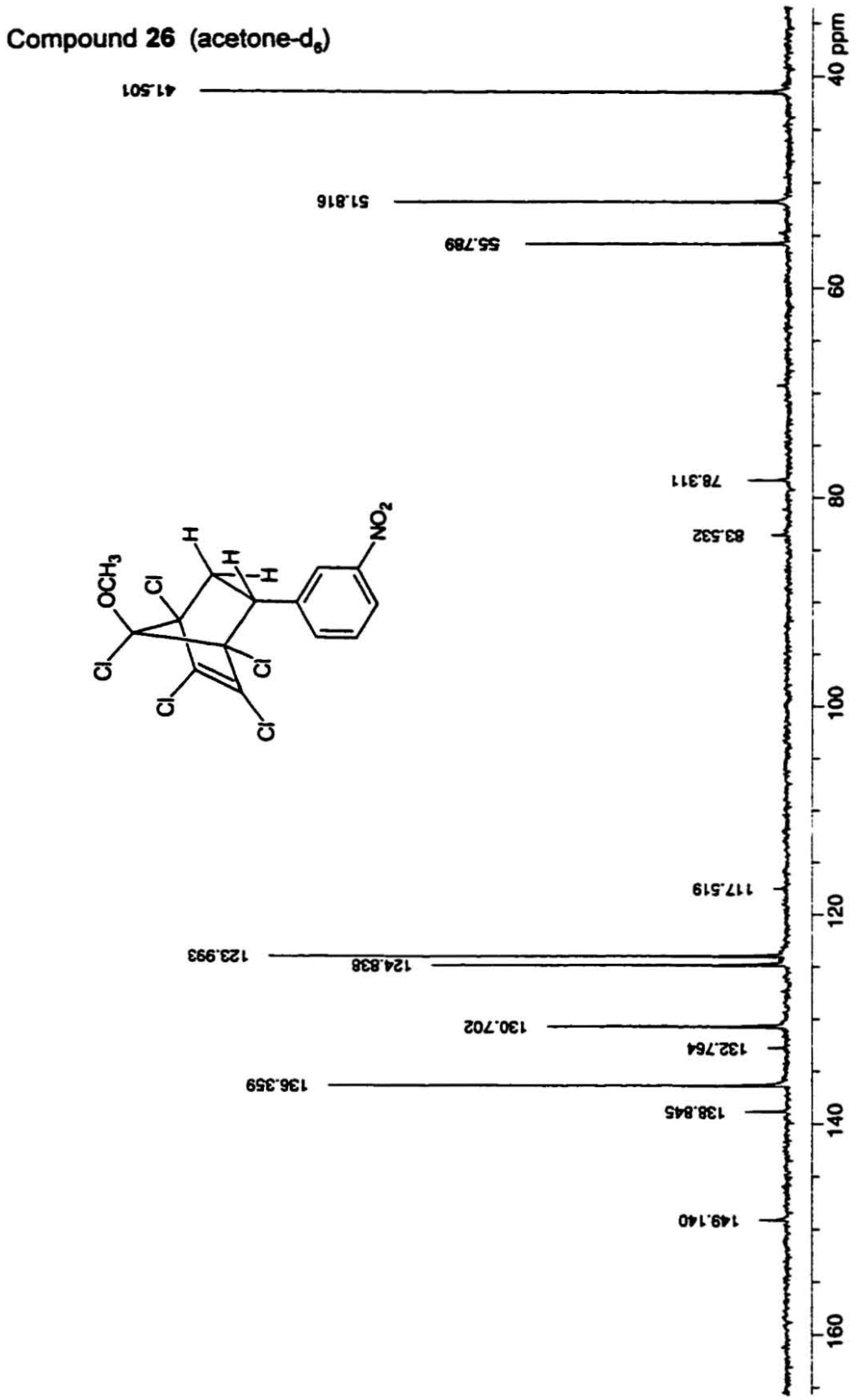
Compound 24 (acetone-d_6)



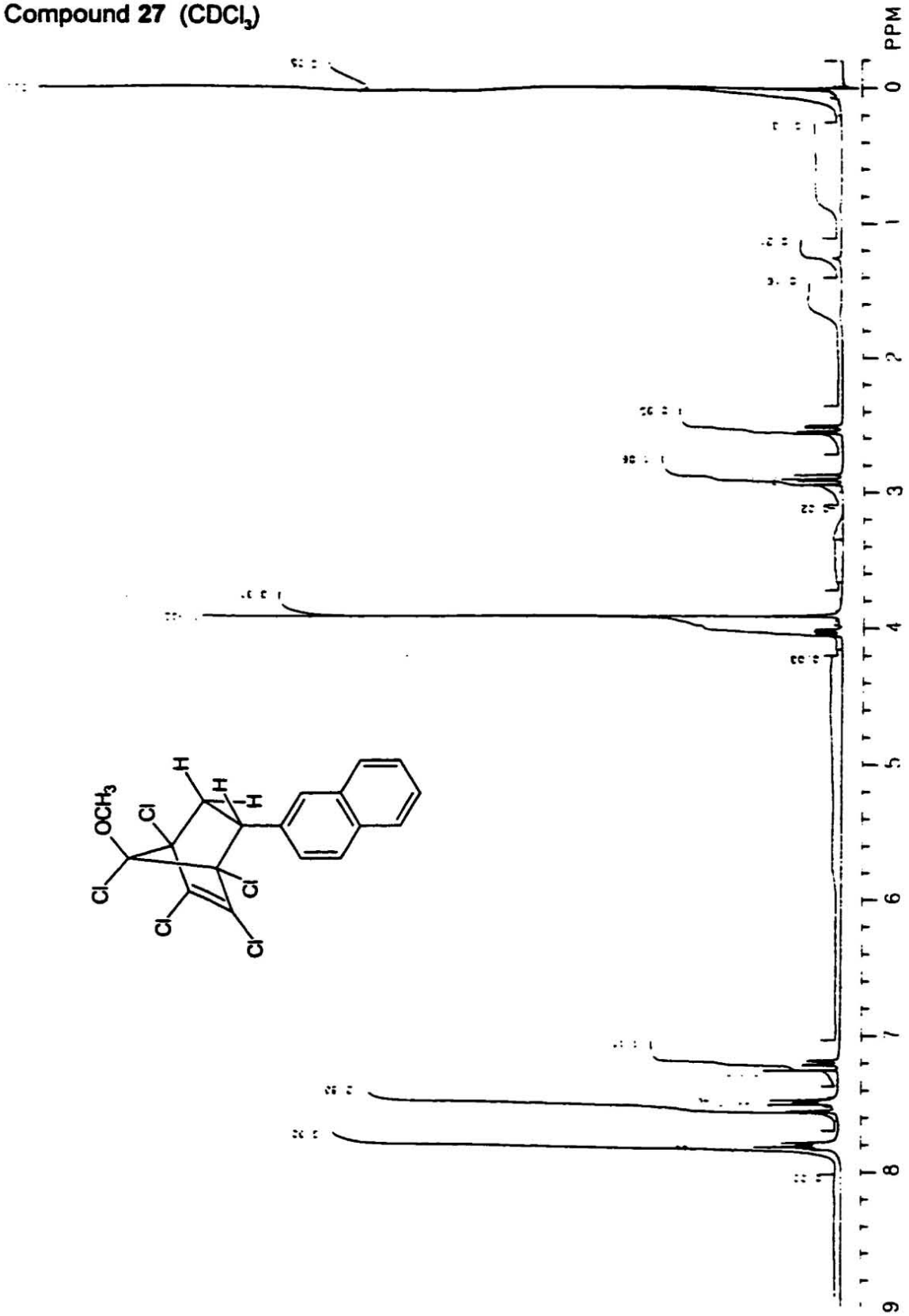
Compound **25** ($CDCl_3$)



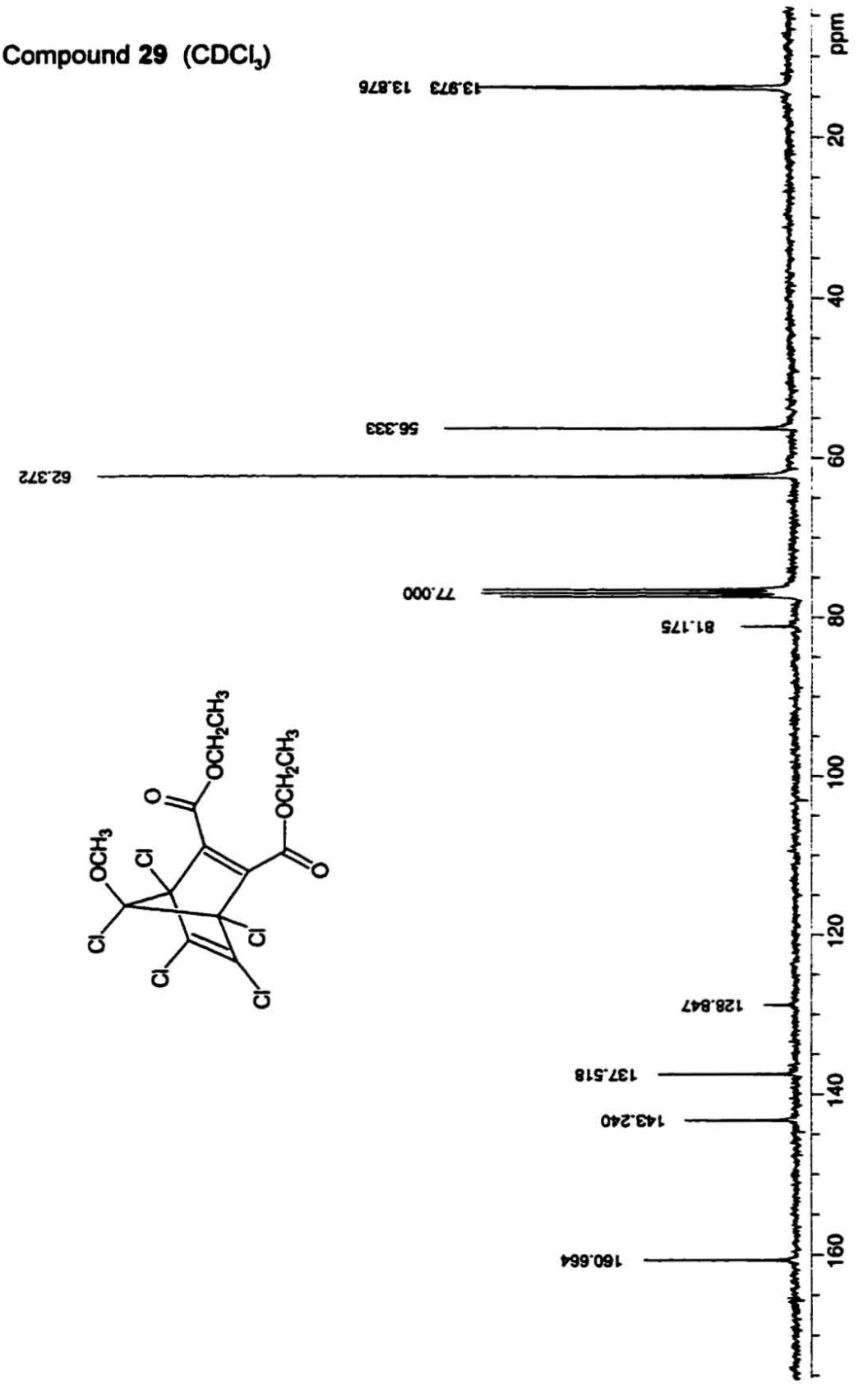
Compound **26** (acetone-d_6)



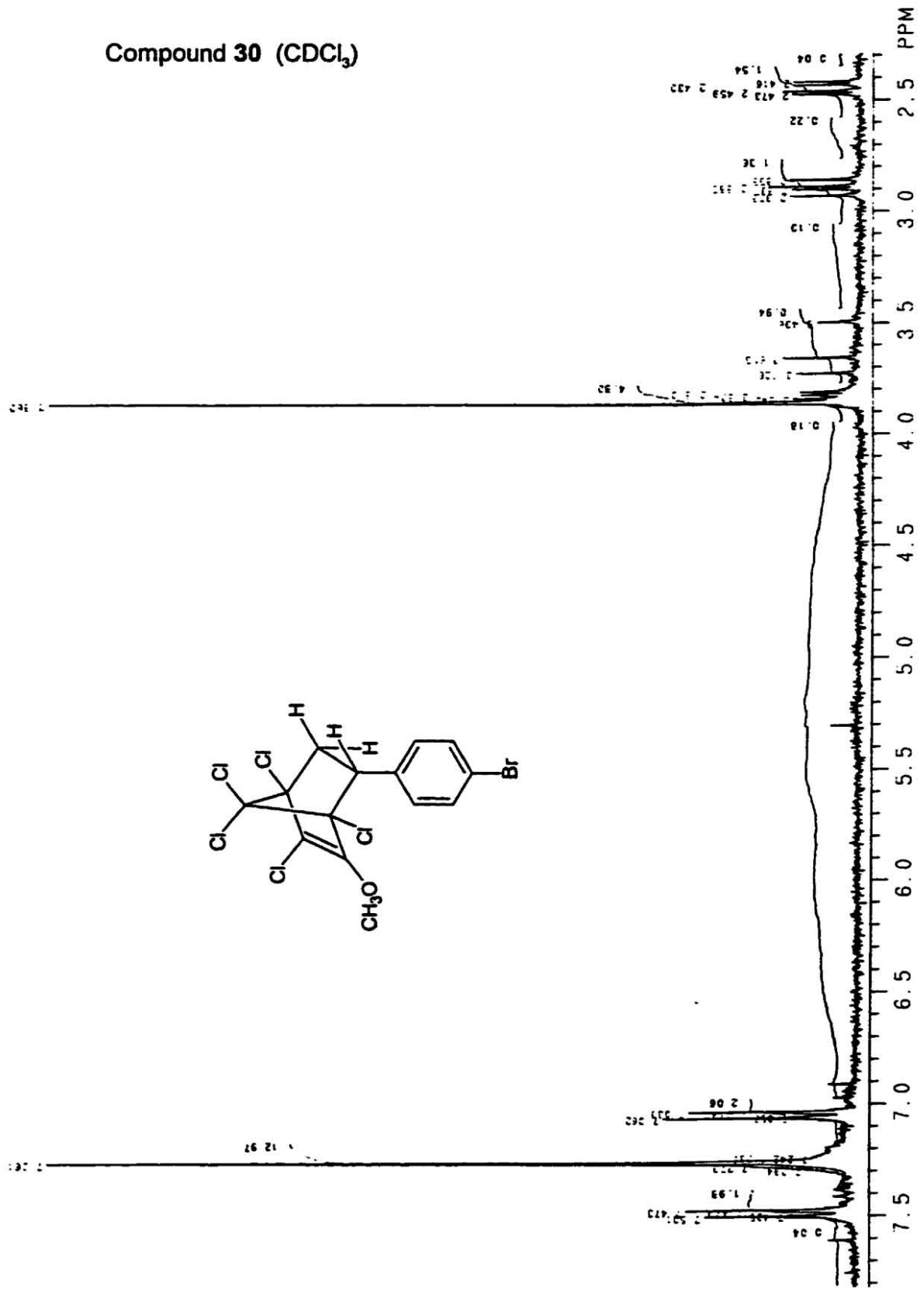
Compound 27 ($CDCl_3$)



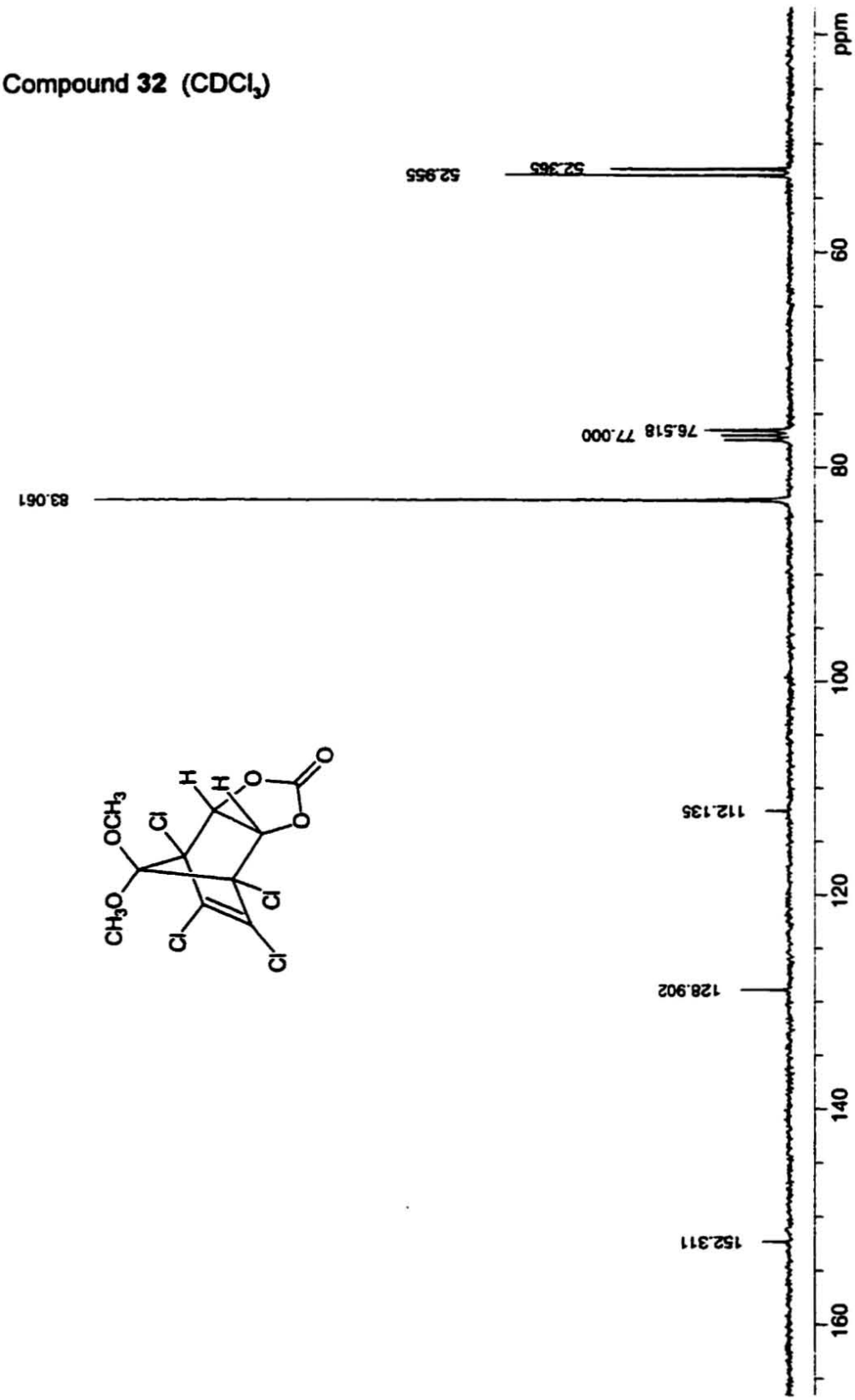
Compound **29** ($CDCl_3$)



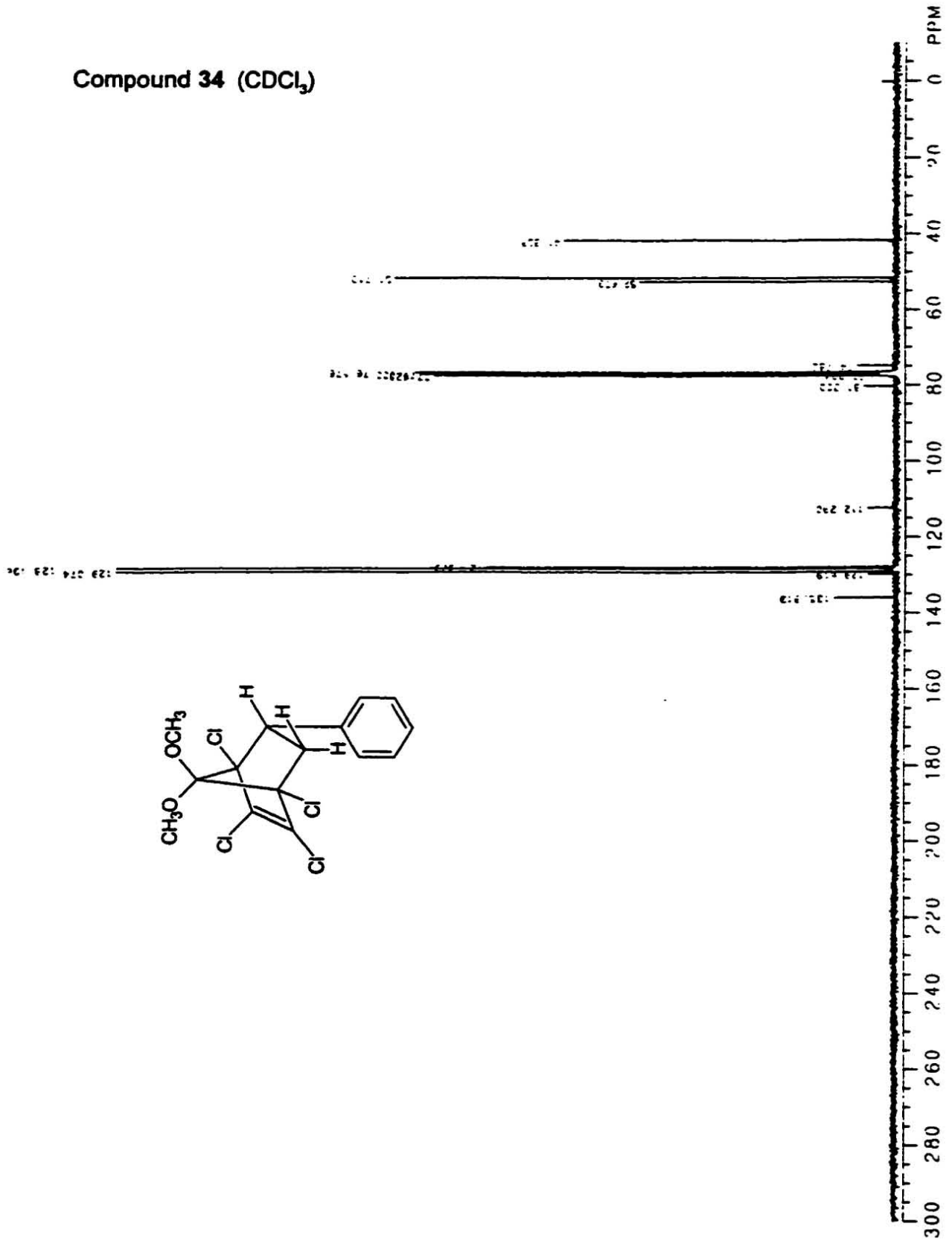
Compound **30** ($CDCl_3$)



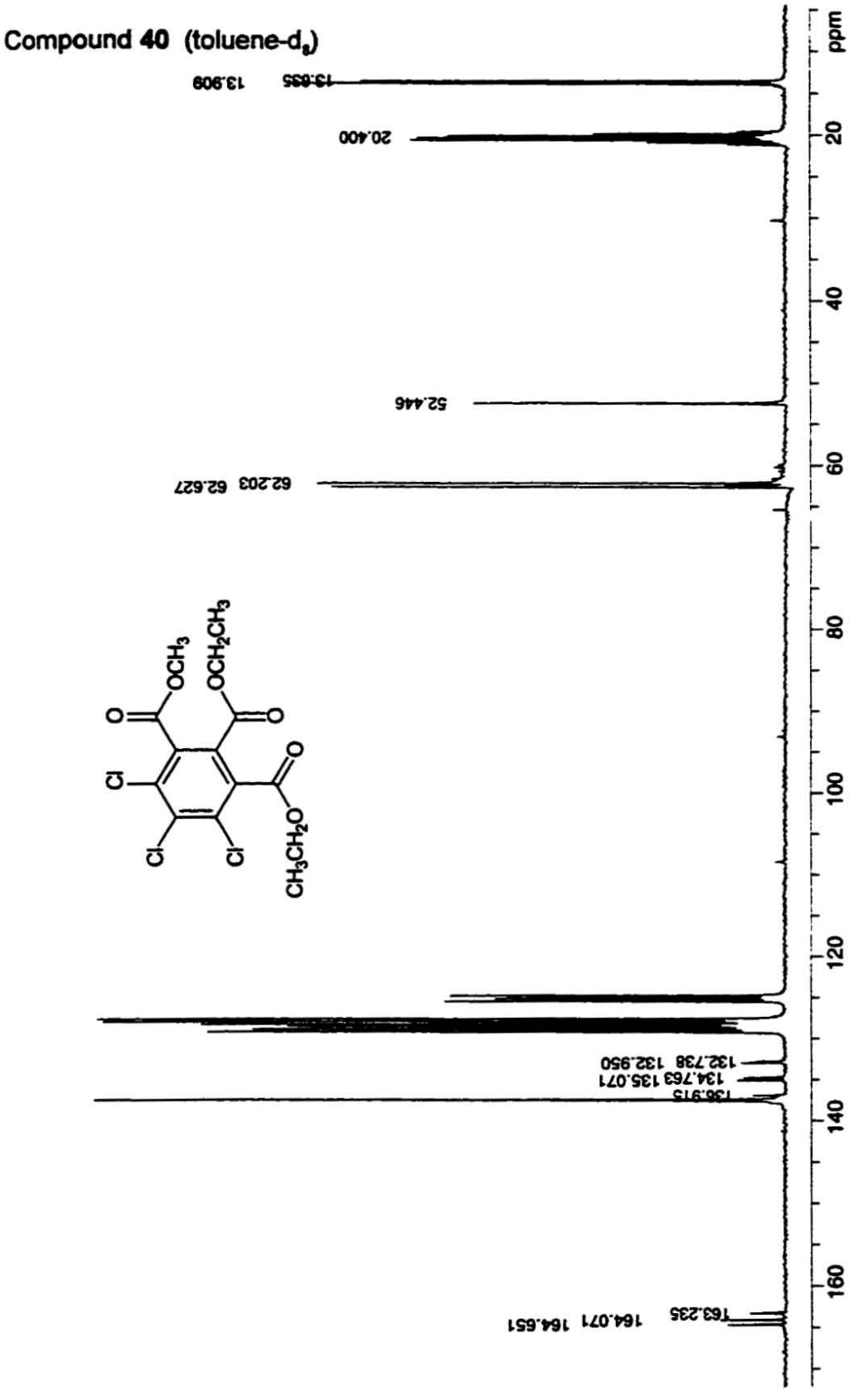
Compound **32** ($CDCl_3$)

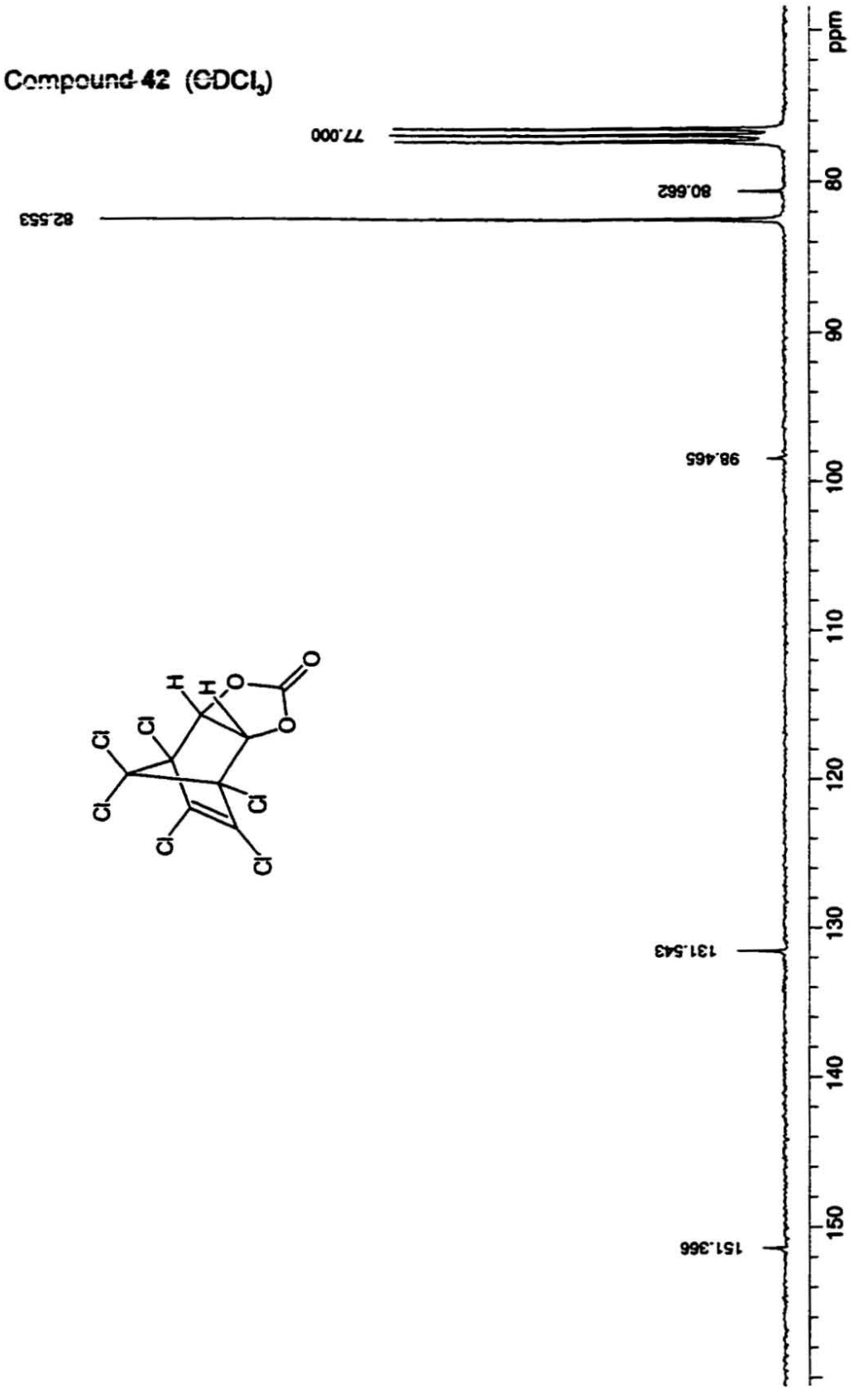


Compound 34 ($CDCl_3$)

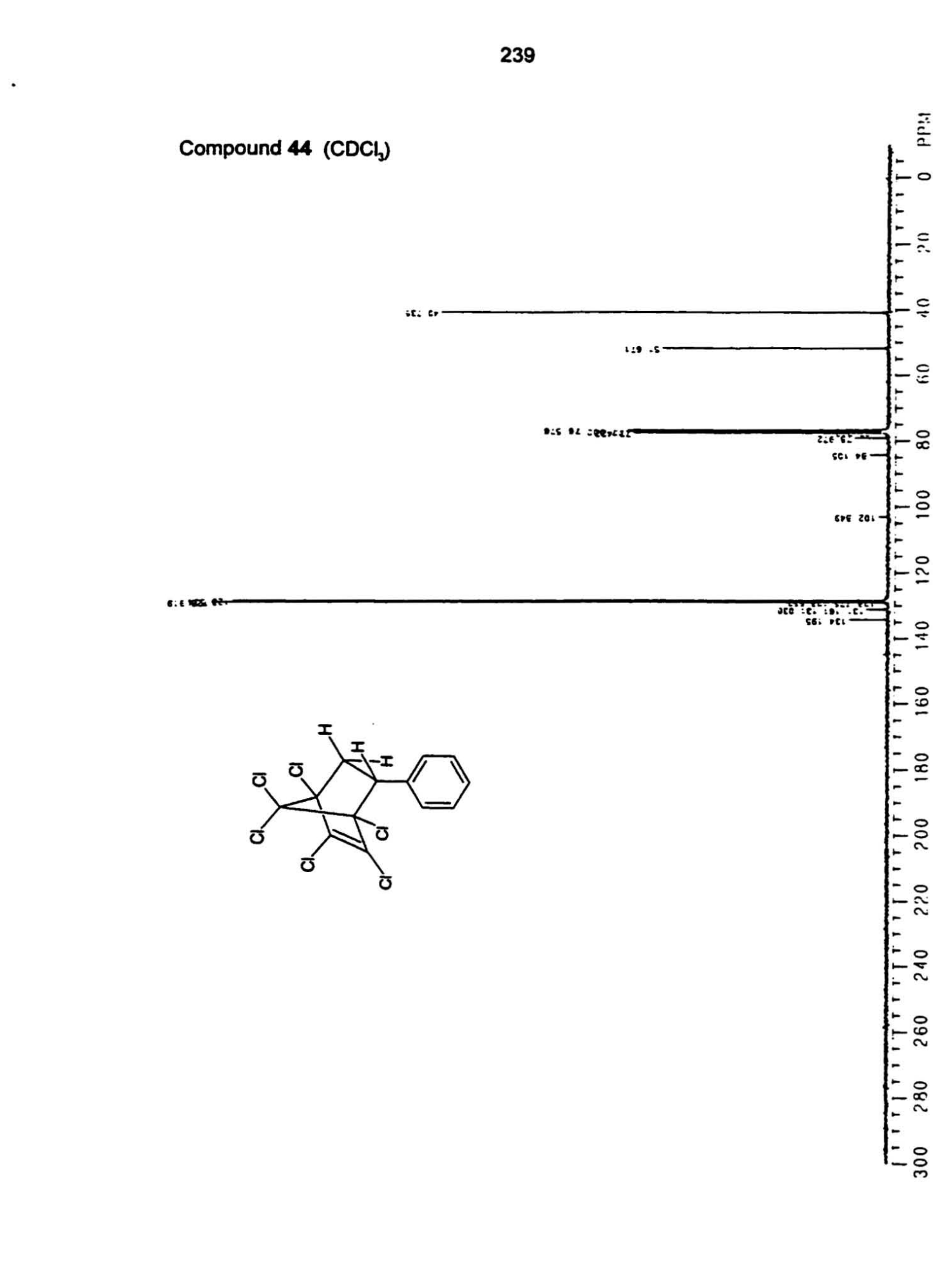


Compound **40** (toluene-d_8)

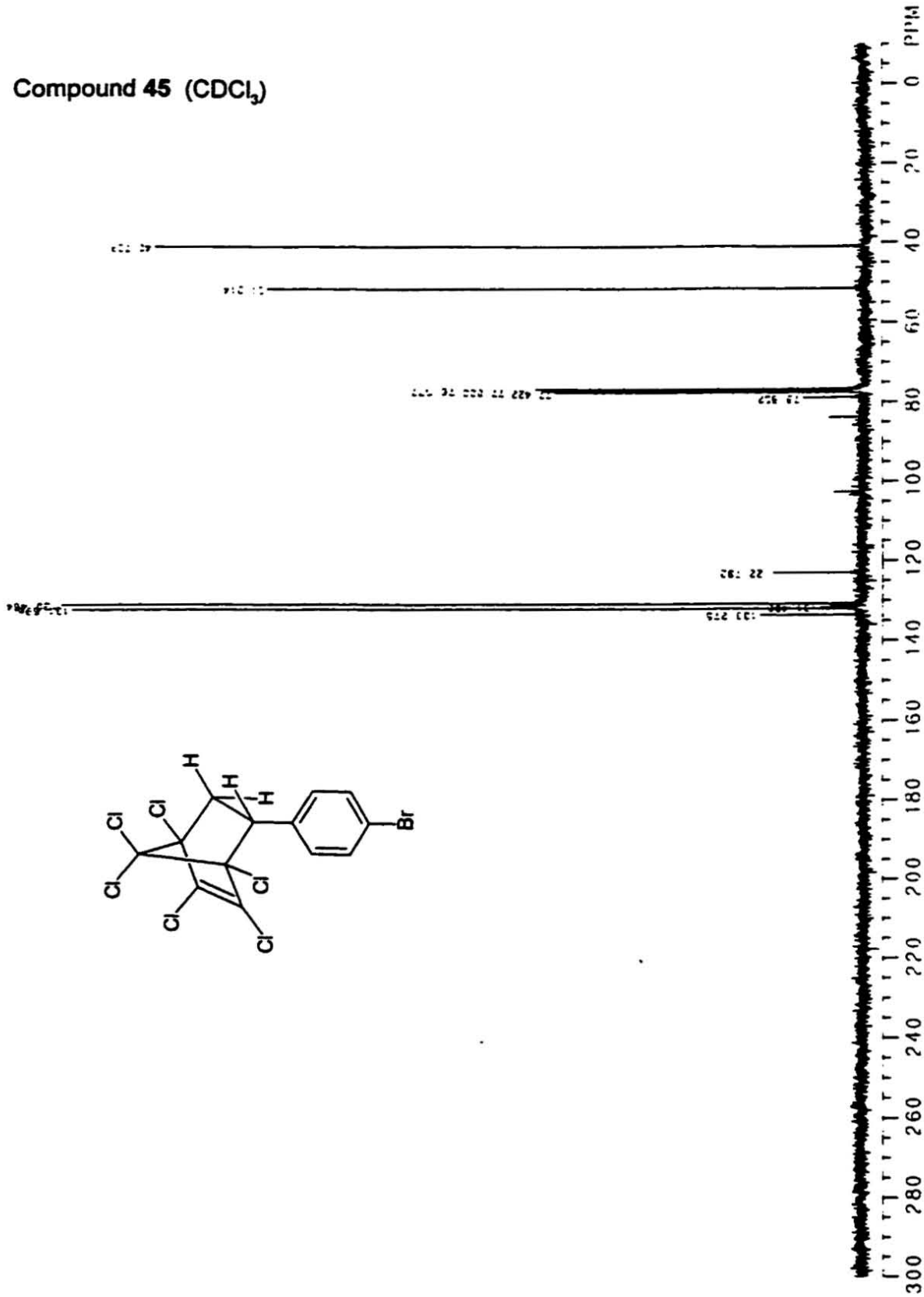



Compound 42 (CDCl3)
77.000
80.662
82.553
98.465
131.543
151.366
ppm
80
90
100
110
120
130
140
150
O
O
O
H
H
Cl
Cl
Cl
Cl
Cl
Cl

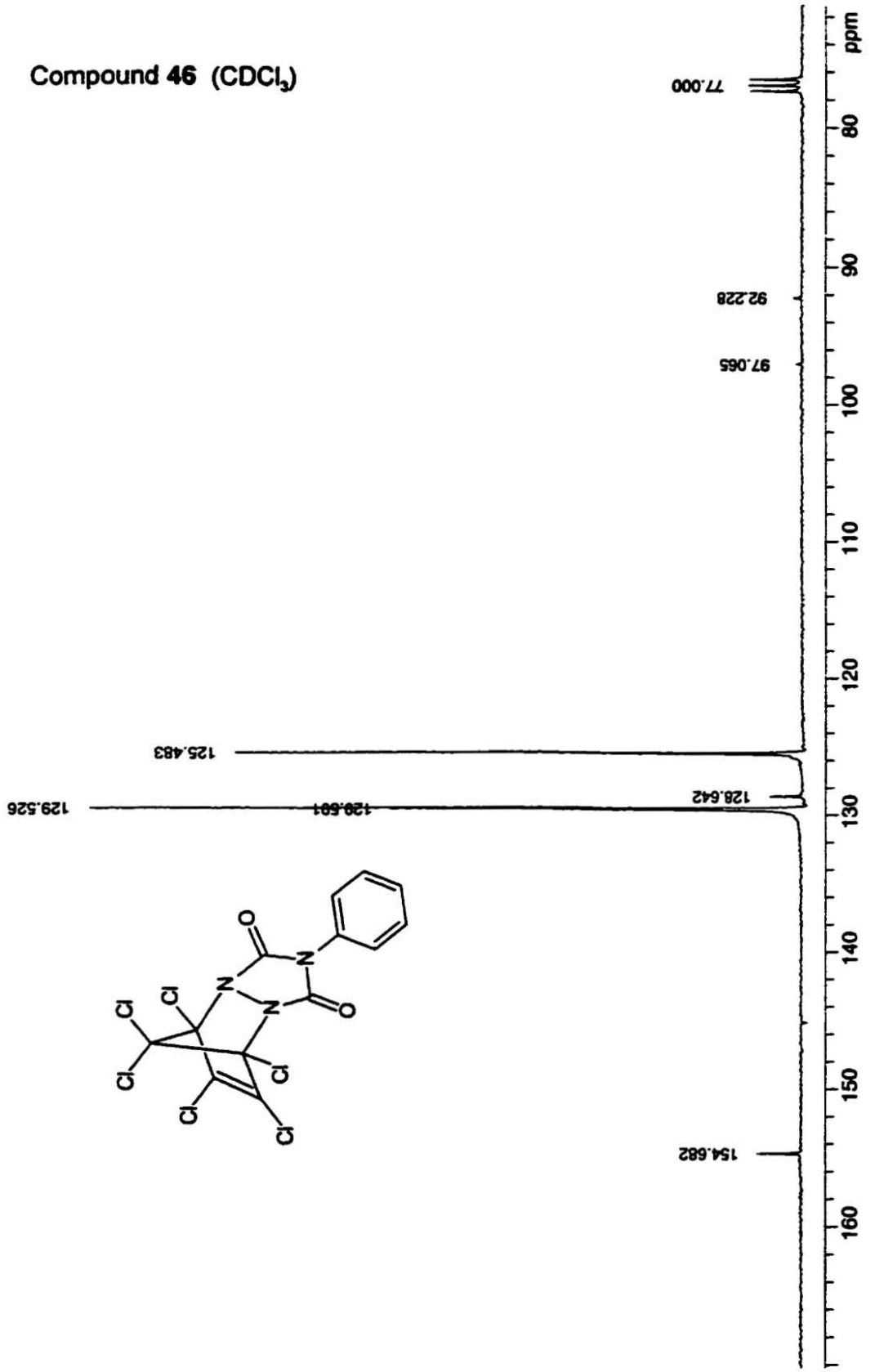
Compound 44 ($CDCl_3$)



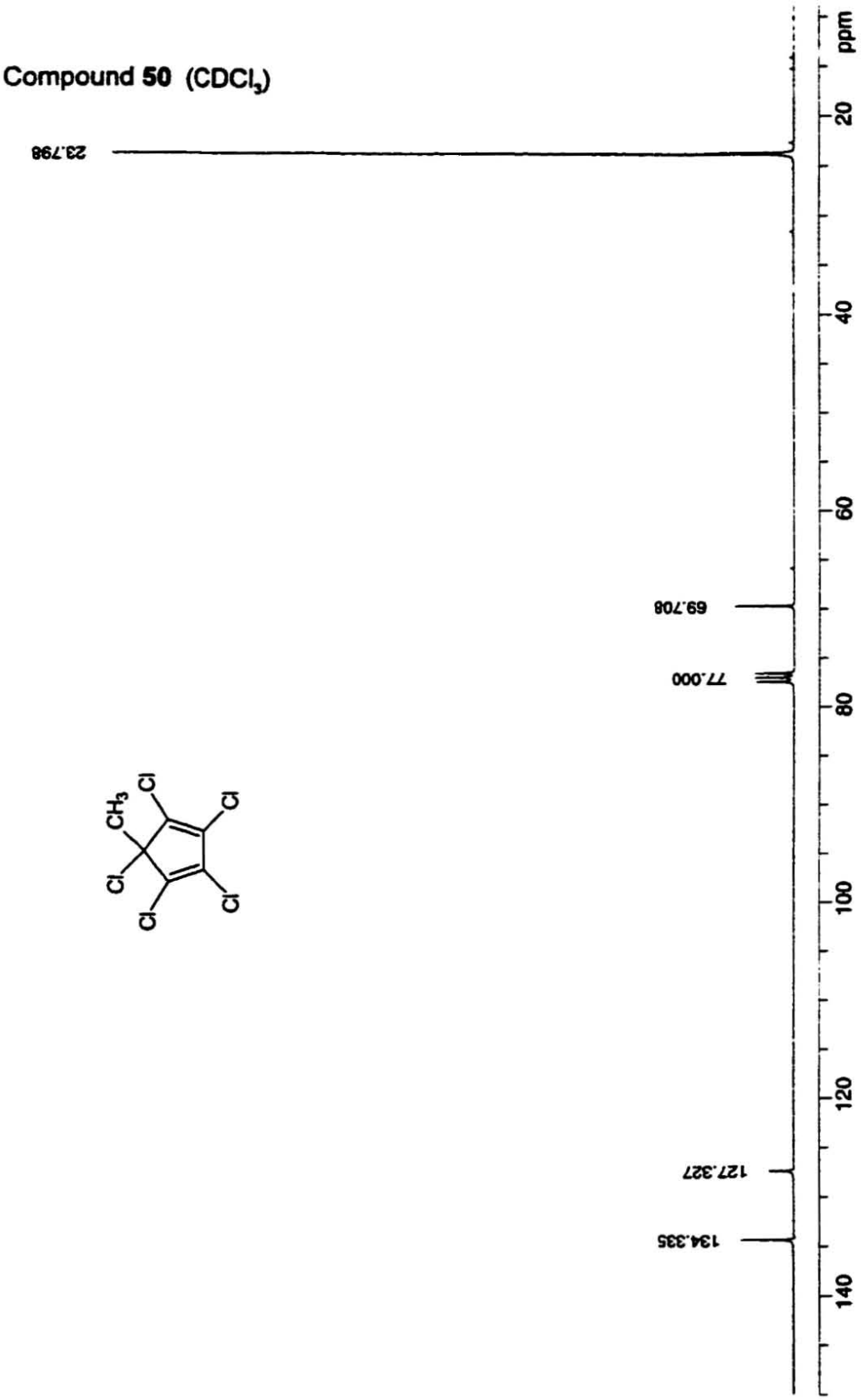
Compound 45 ($CDCl_3$)



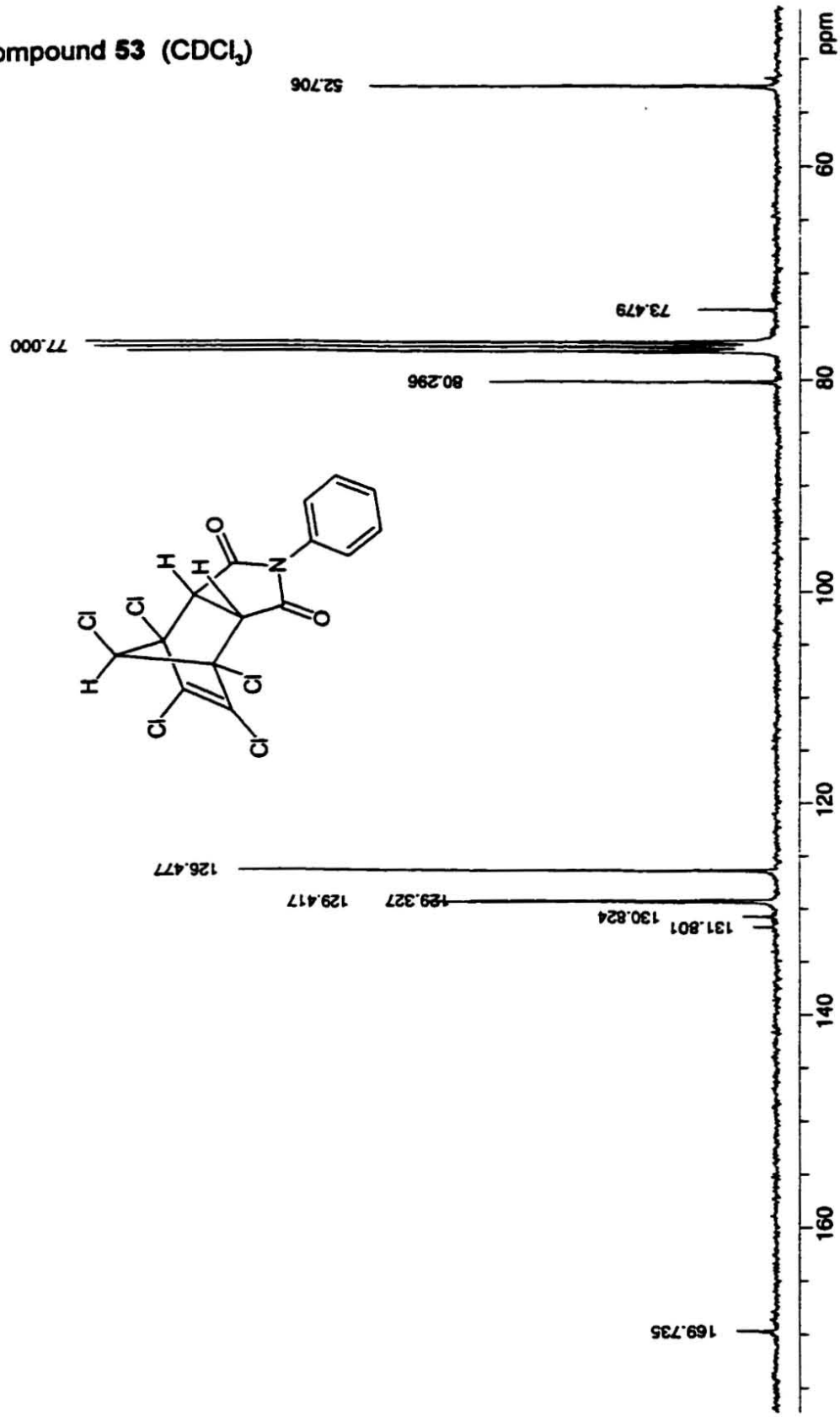
Compound **46** ($CDCl_3$)



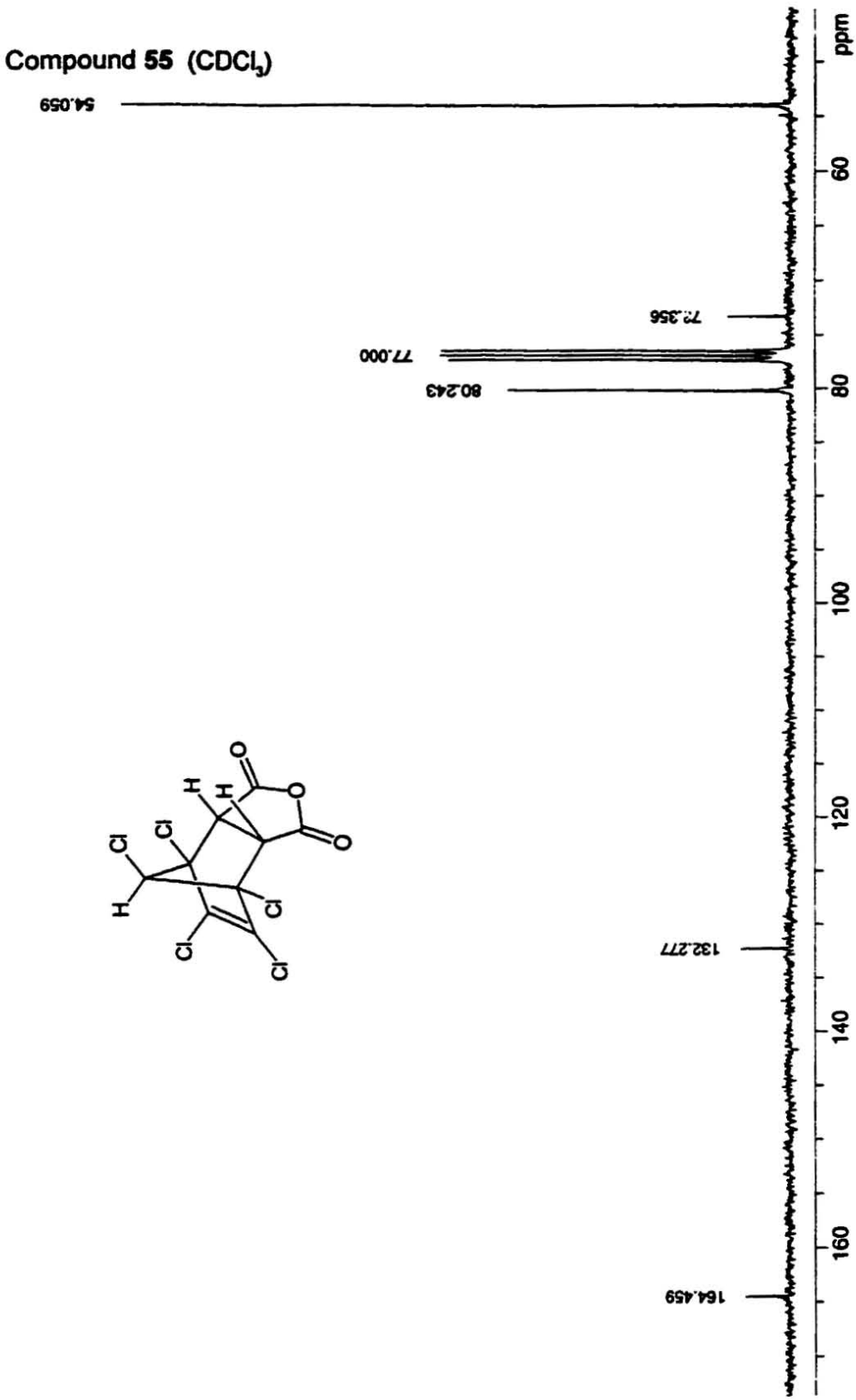
Compound **50** ($CDCl_3$)



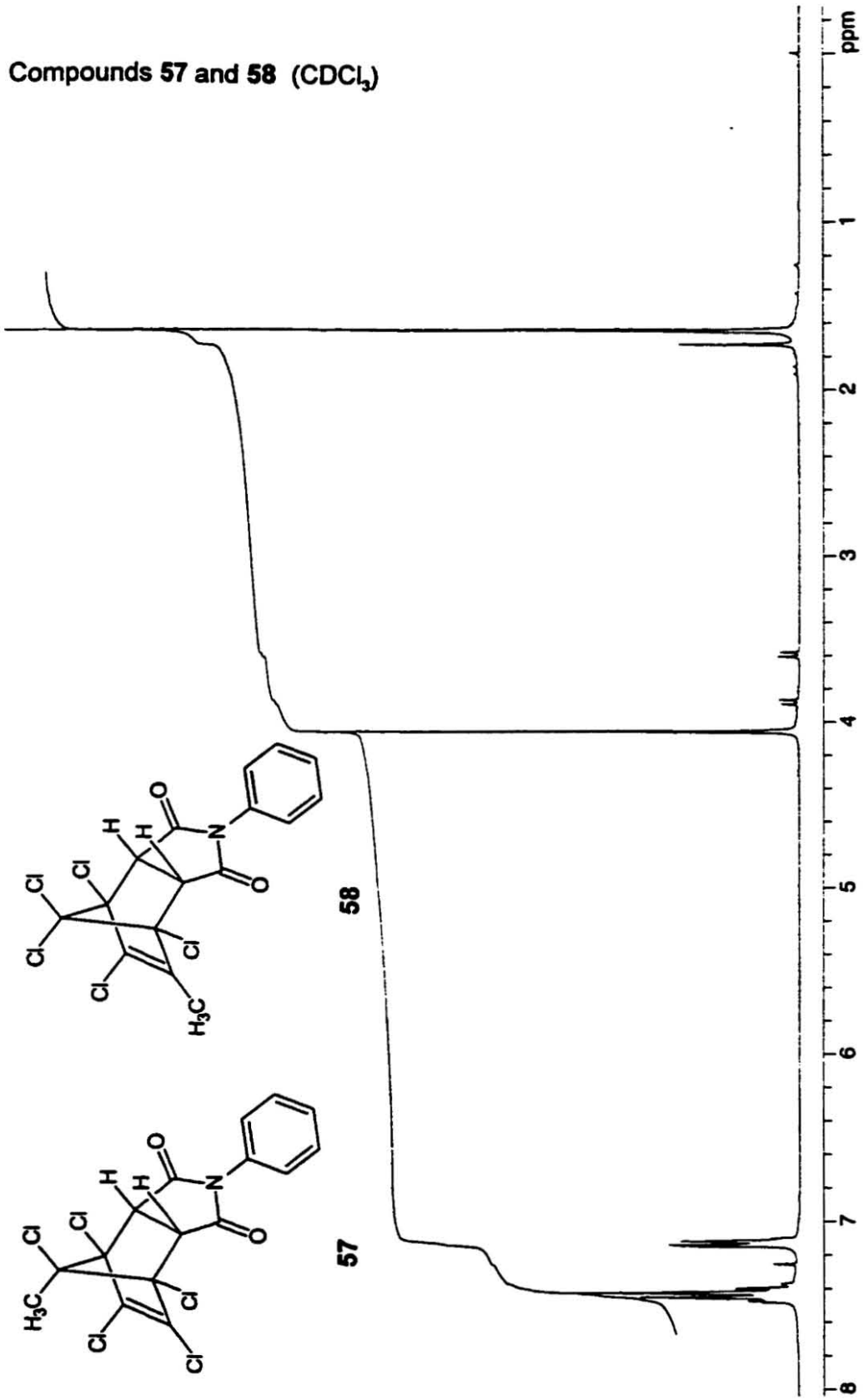
Compound **53** ($CDCl_3$)



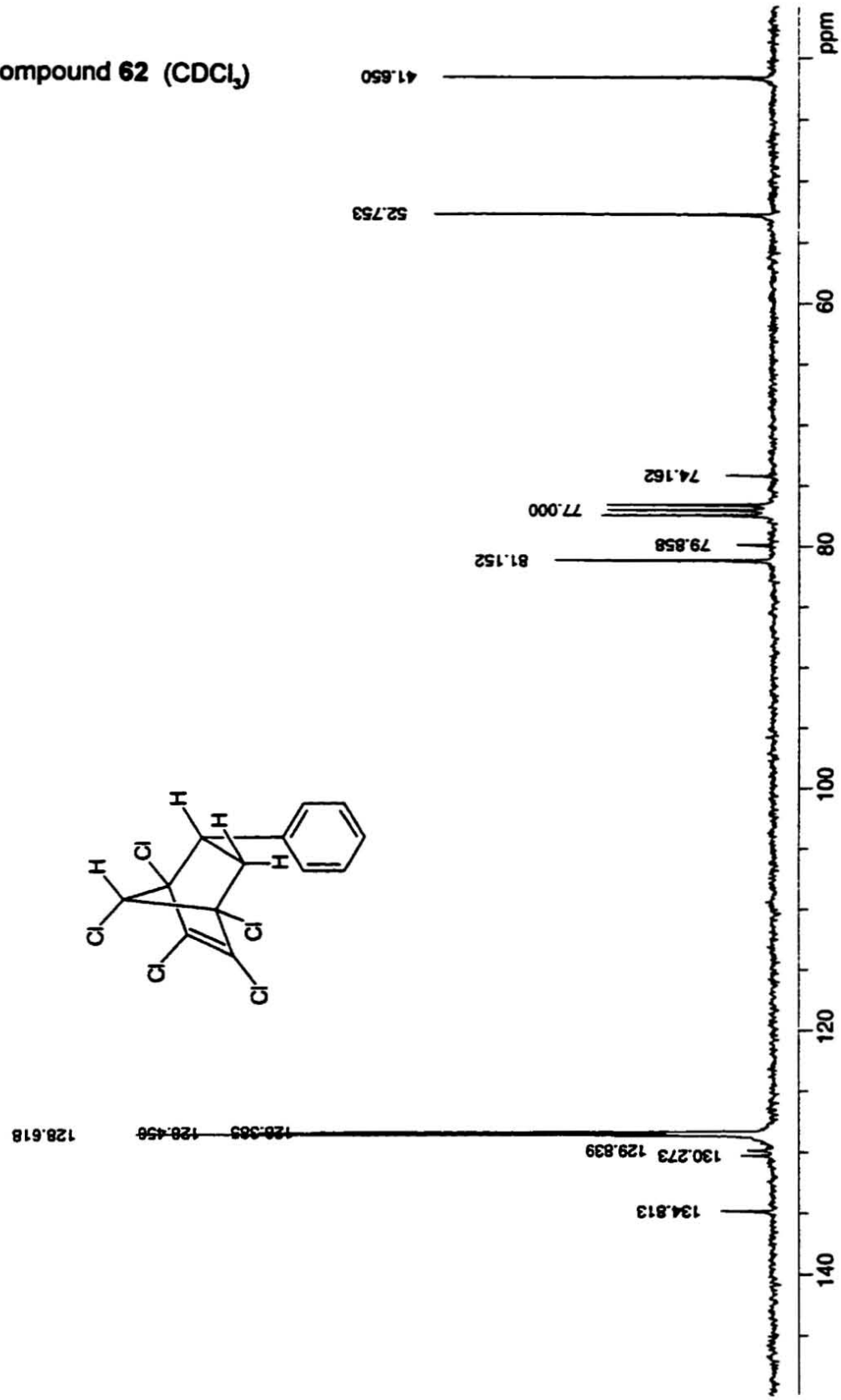
Compound **55** ($CDCl_3$)



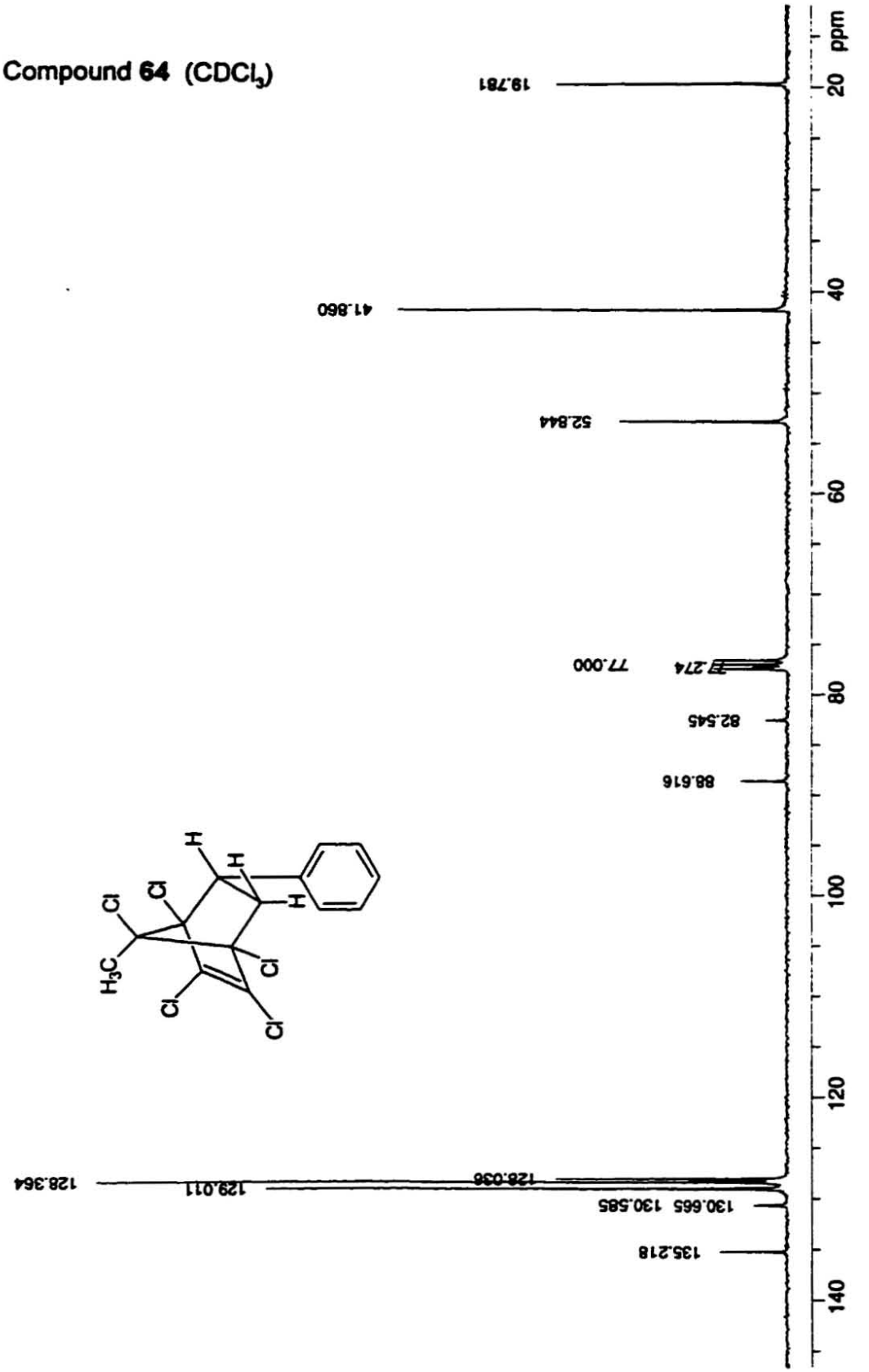
Compounds 57 and 58 ($CDCl_3$)



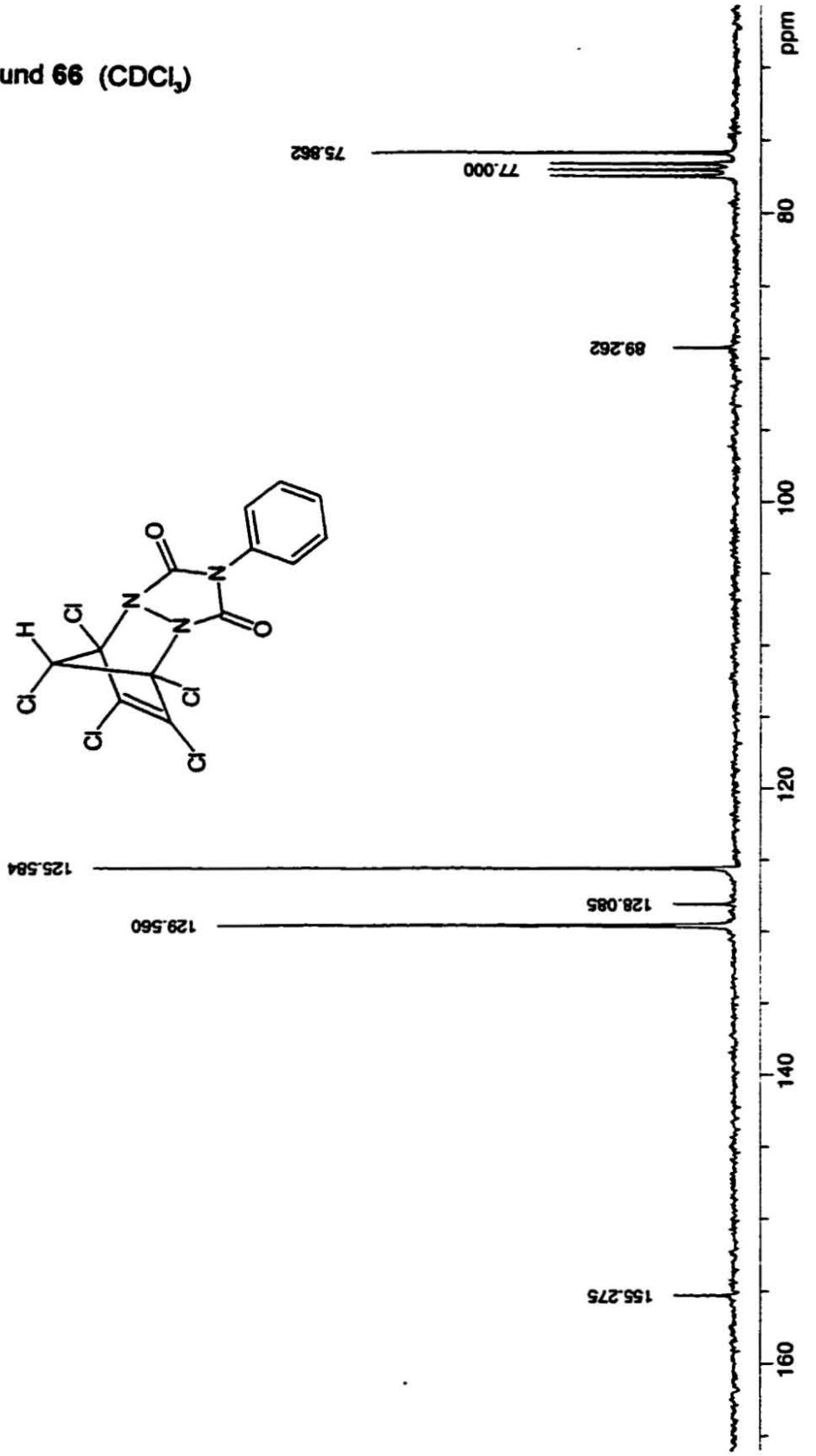
Compound **62** ($CDCl_3$)



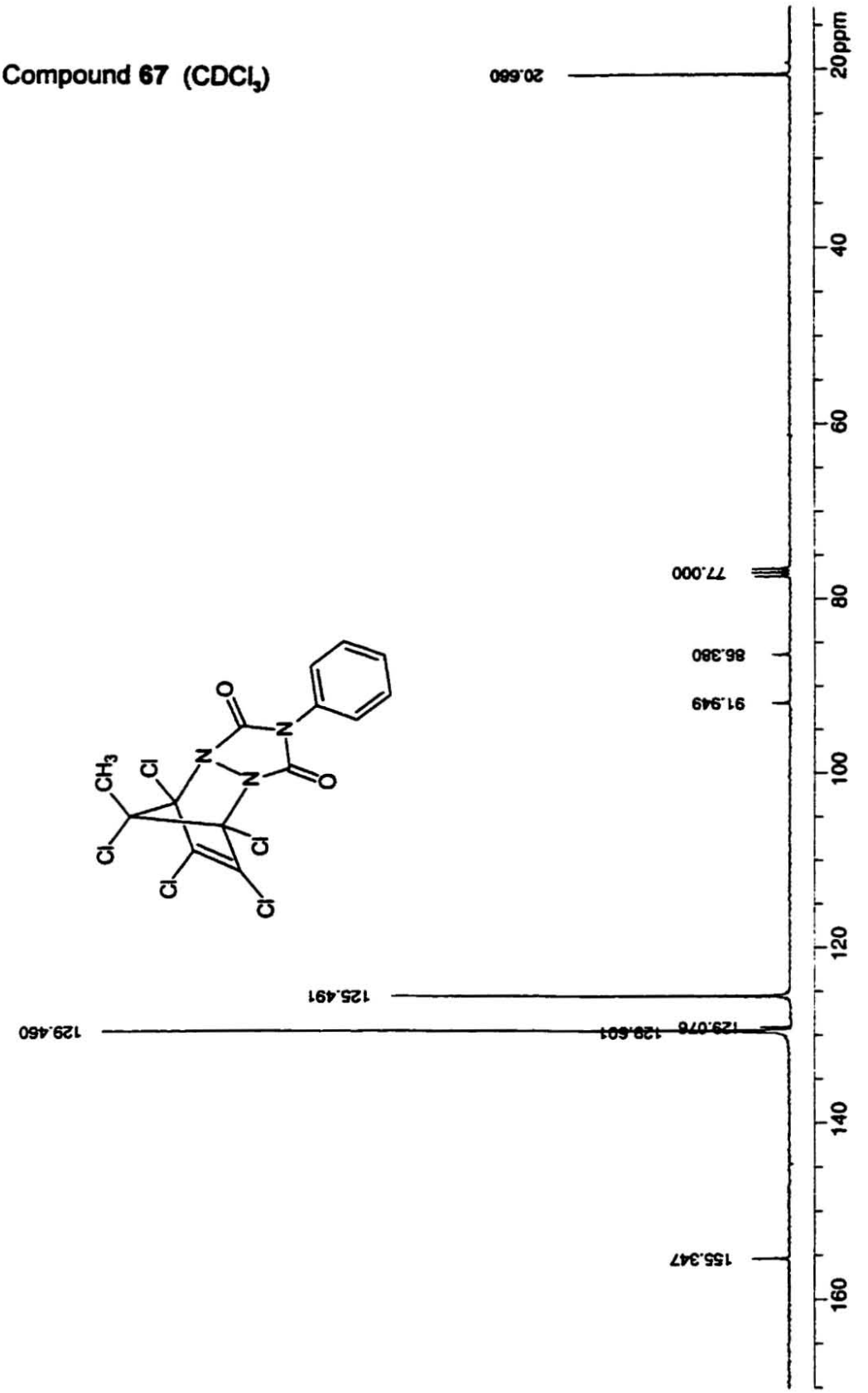
Compound **64** ($CDCl_3$)



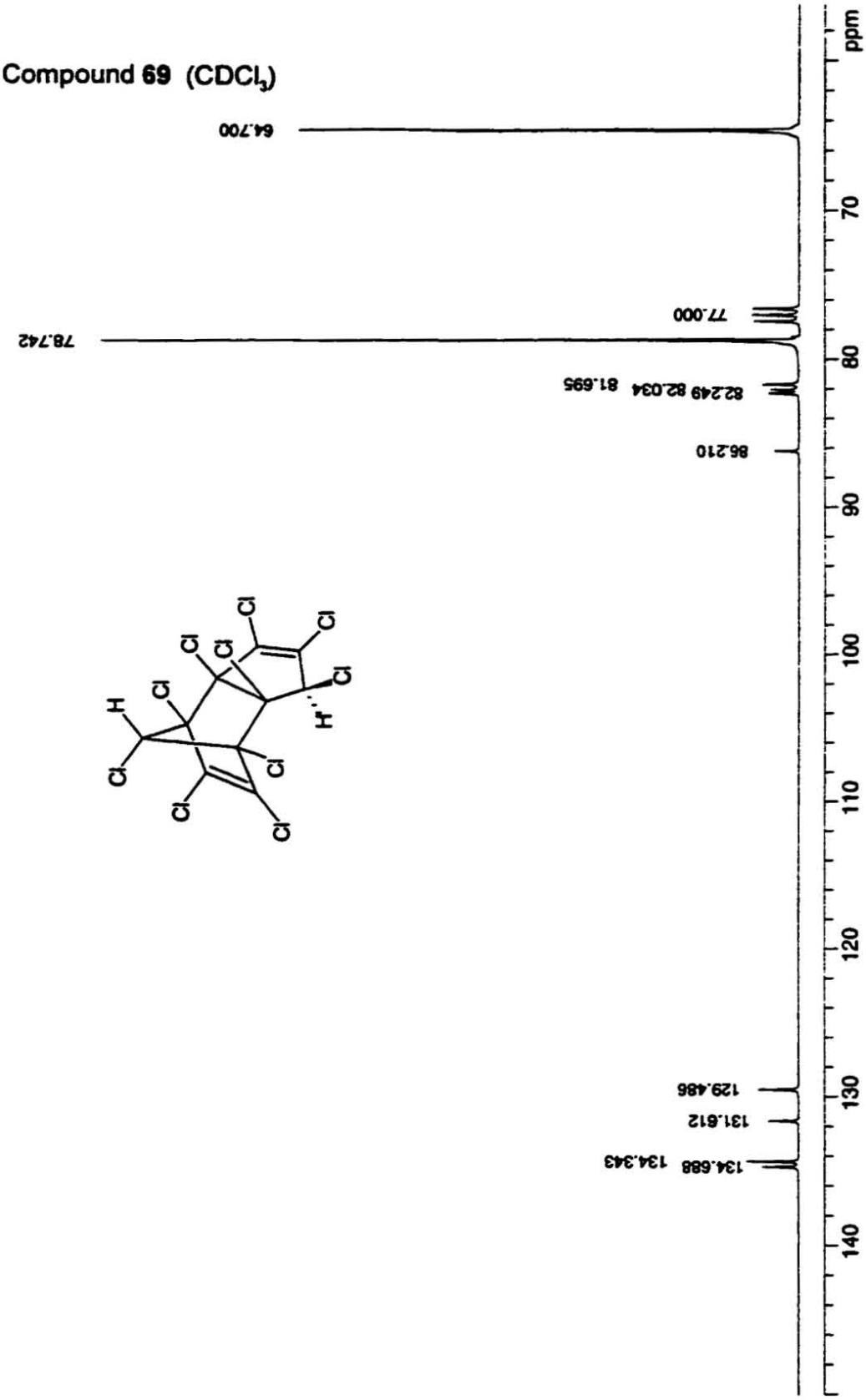
Compound **66** ($CDCl_3$)

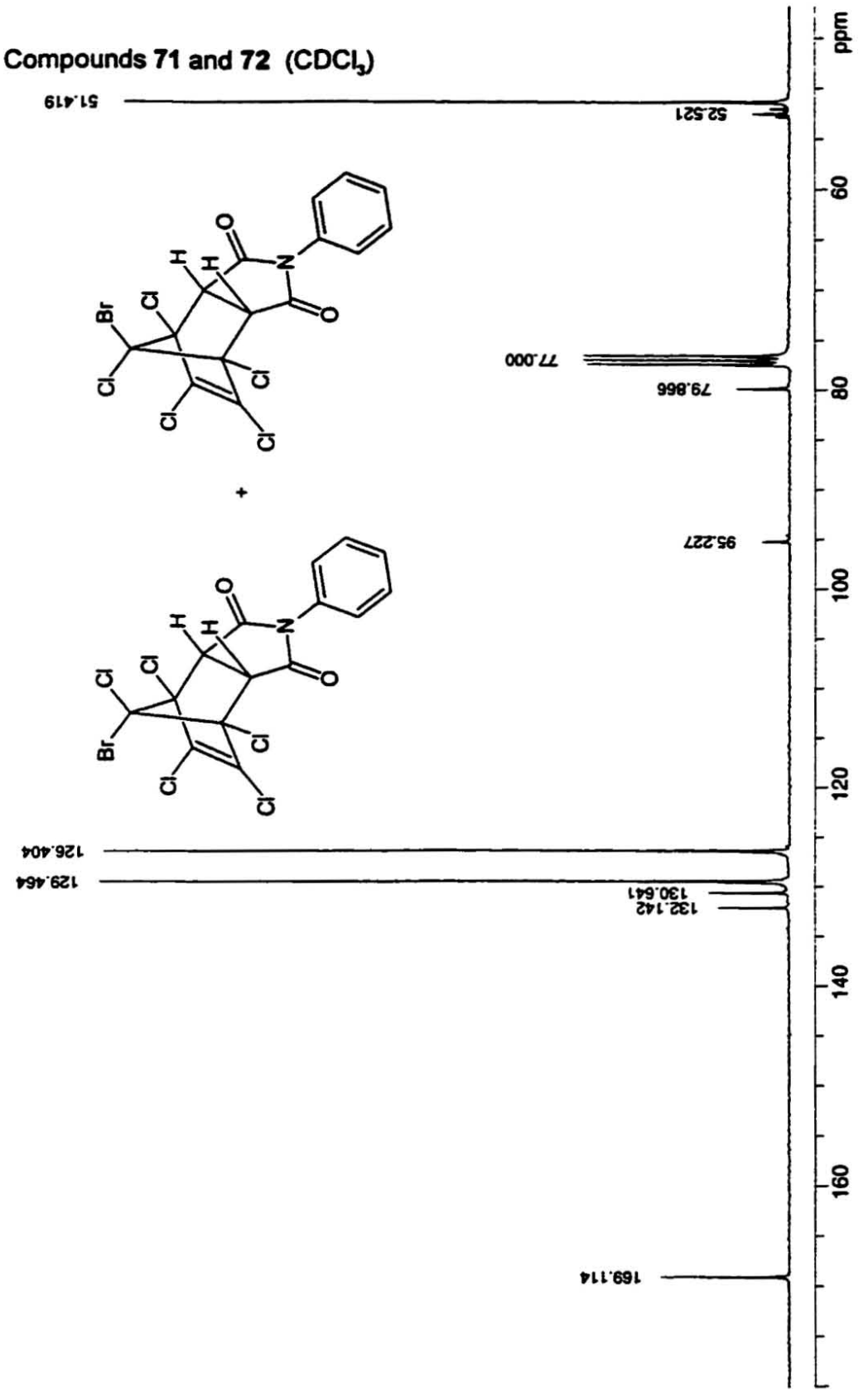


Compound **67** ($CDCl_3$)

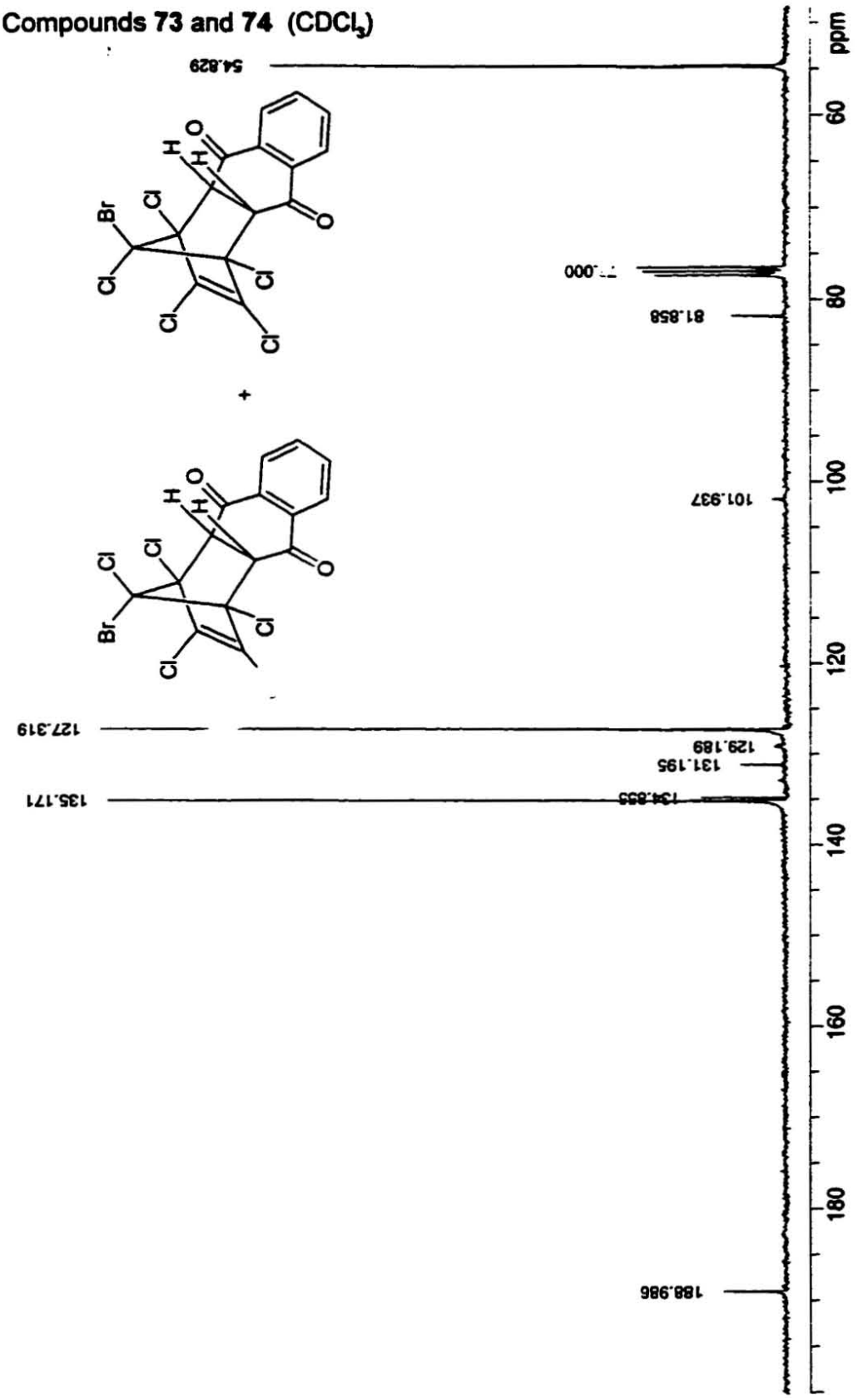


Compound **69** ($CDCl_3$)

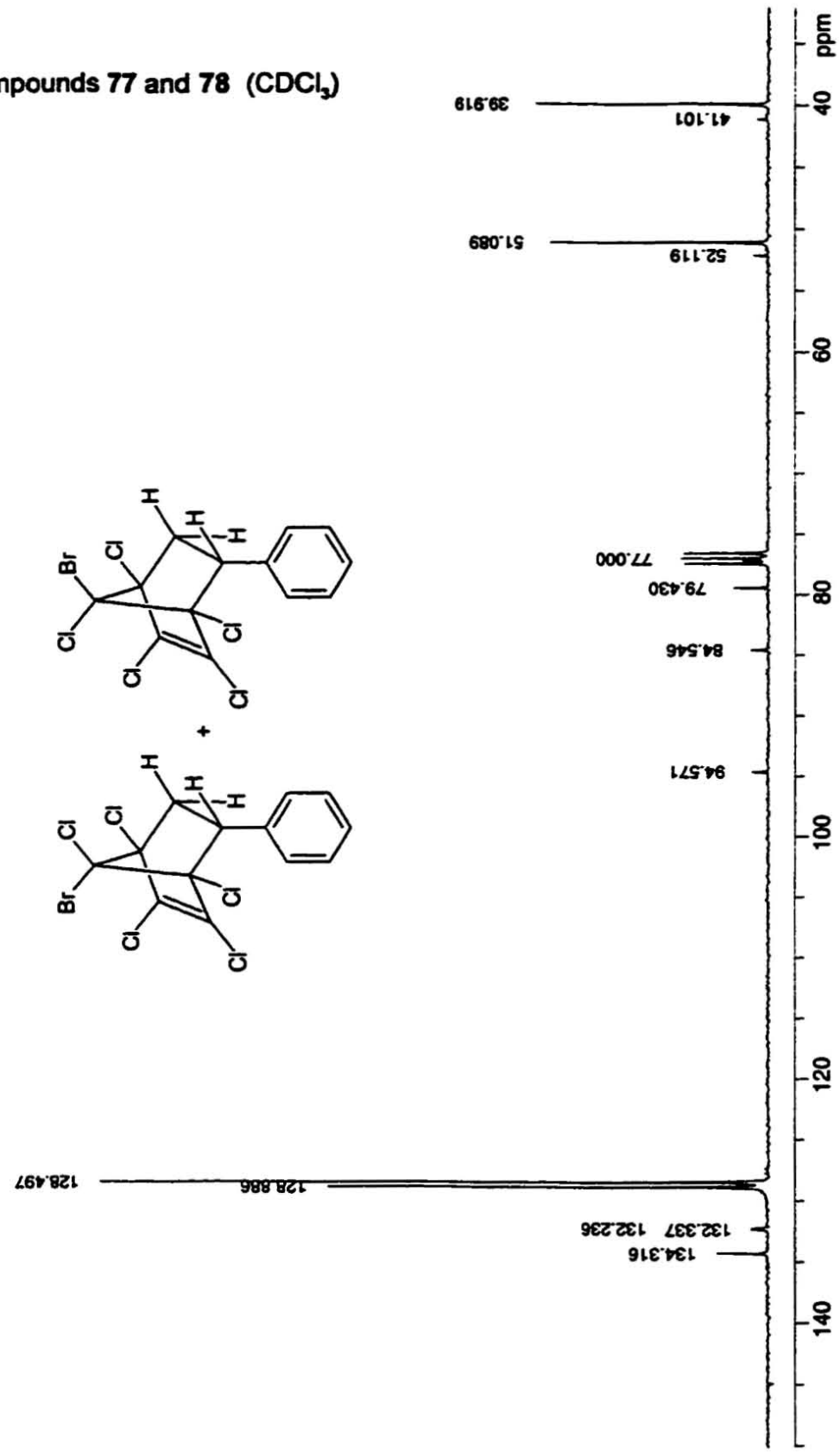


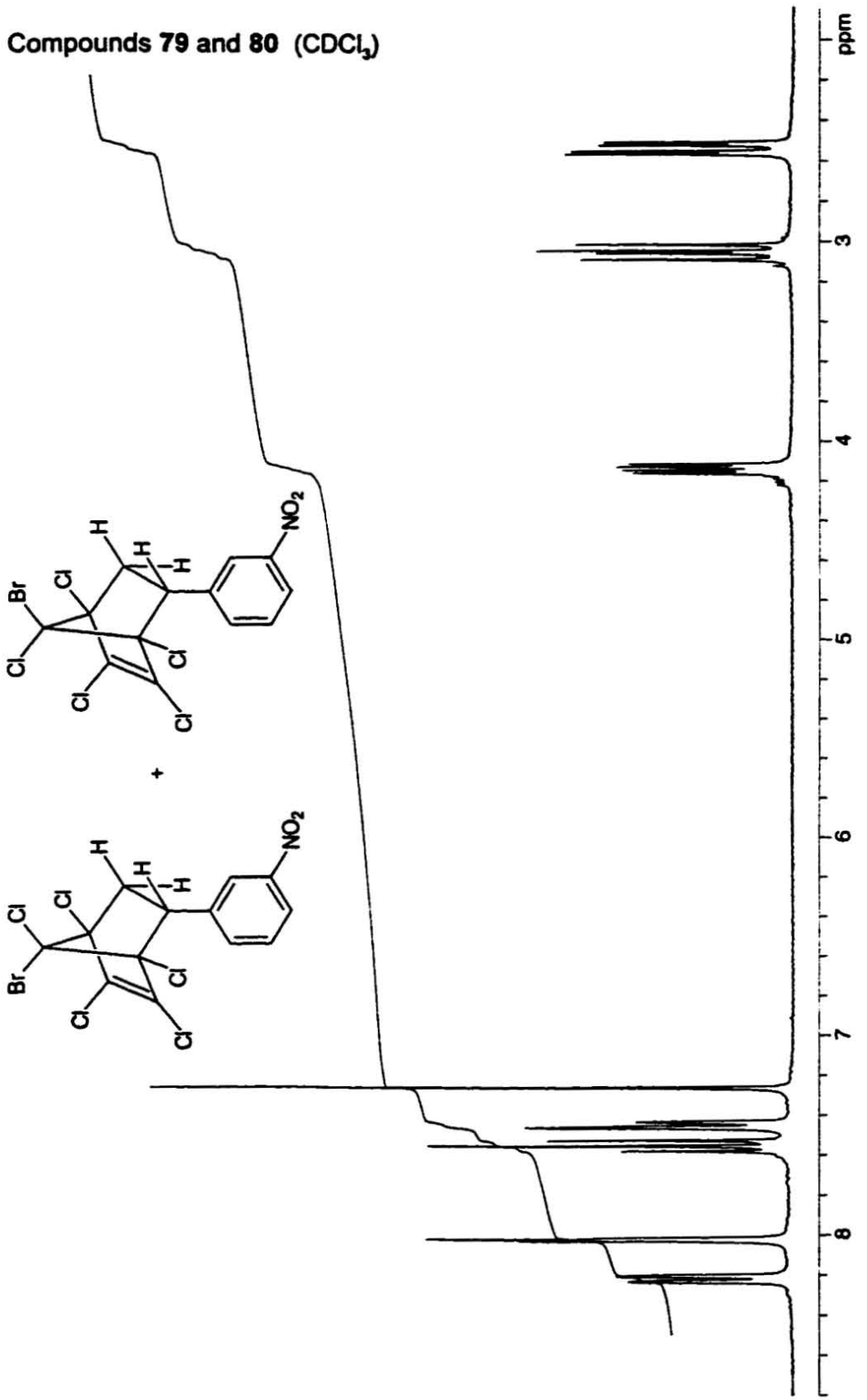

Compounds 71 and 72 (CDCl3)
51.419
52.521
77.000
79.866
95.227
126.404
129.464
130.641
132.142
159.114
ppm
60
80
100
120
140
160
O
N
O
H
H
Br
Cl
Cl
Cl
Cl
Cl
+
O
N
O
H
H
Cl
Cl
Br
Cl
Cl
Cl

Compounds 73 and 74 ($CDCl_3$)

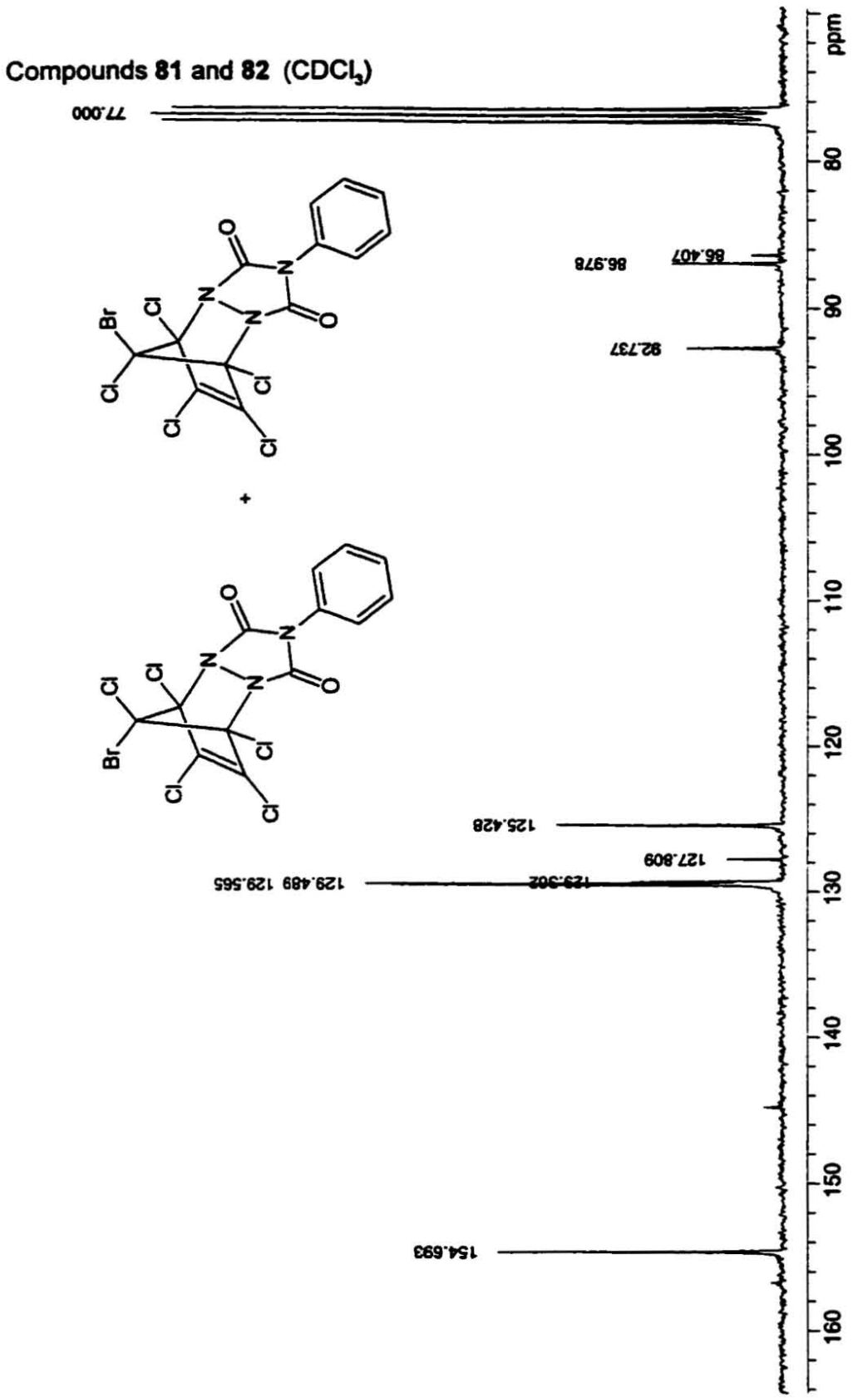


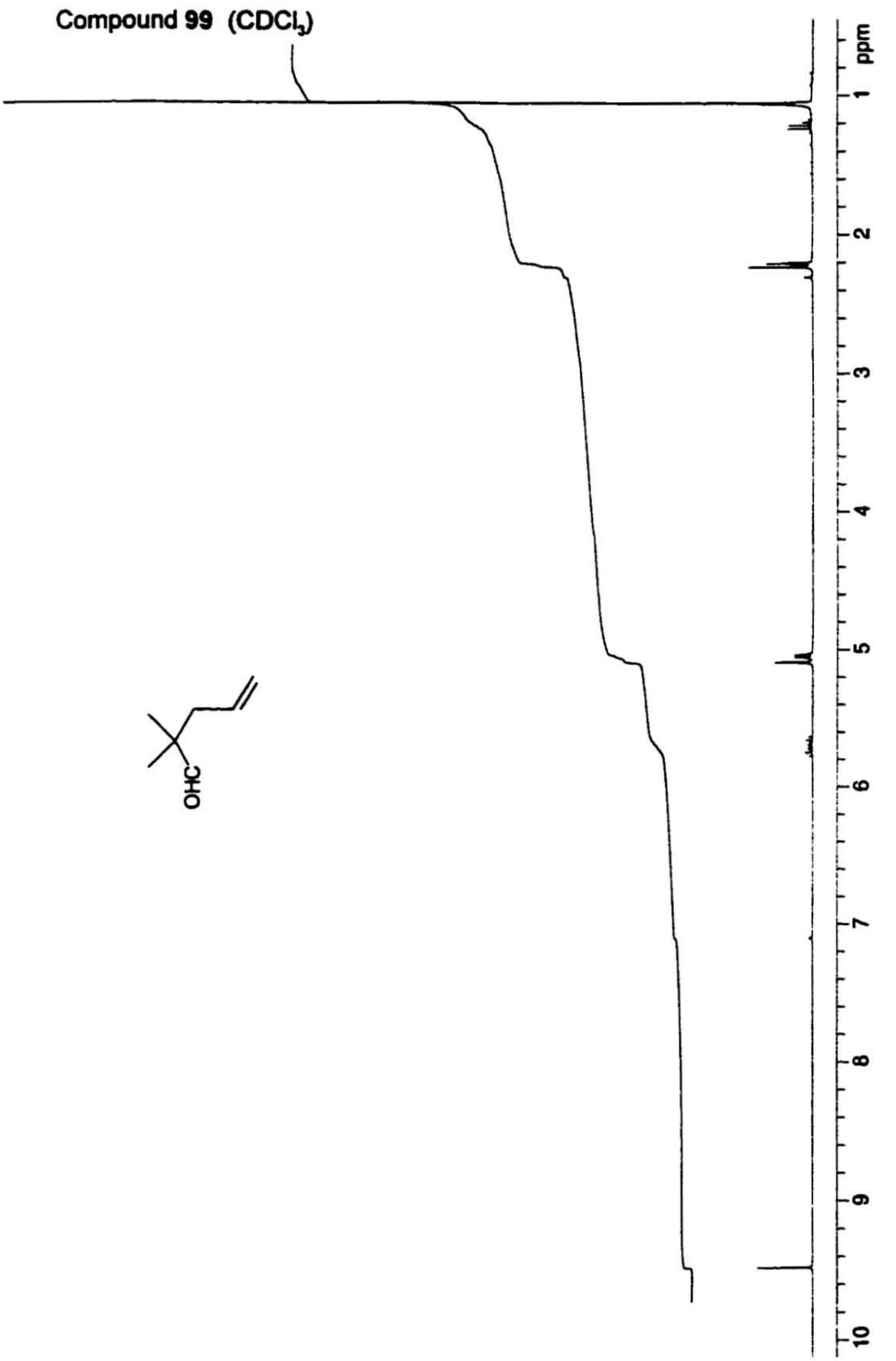
Compounds **77** and **78** ($CDCl_3$)



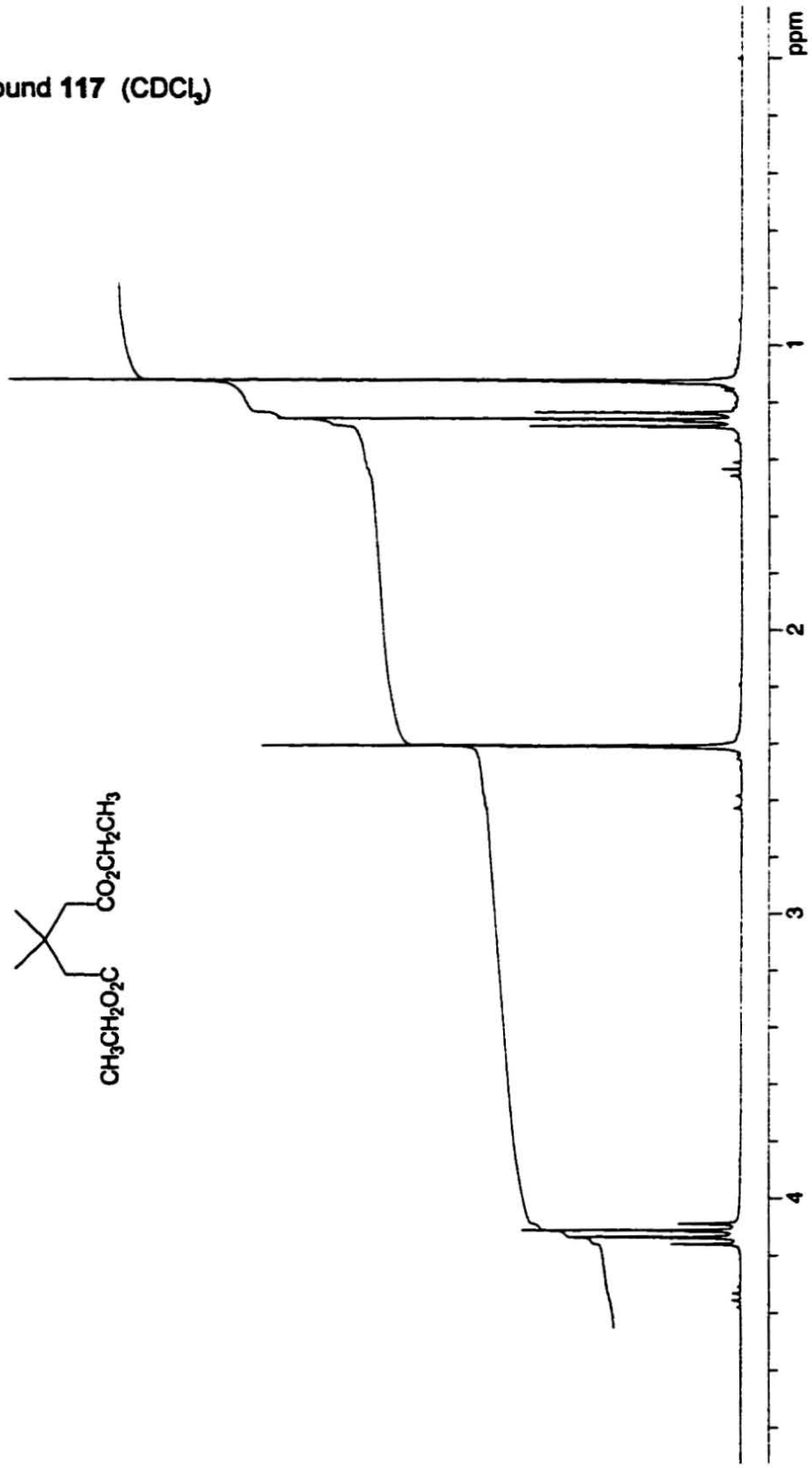

Compounds 79 and 80 (CDCl3)
ppm
3
4
5
6
7
8
NO2
Br
Cl
H
+

Compounds **81** and **82** ($CDCl_3$)

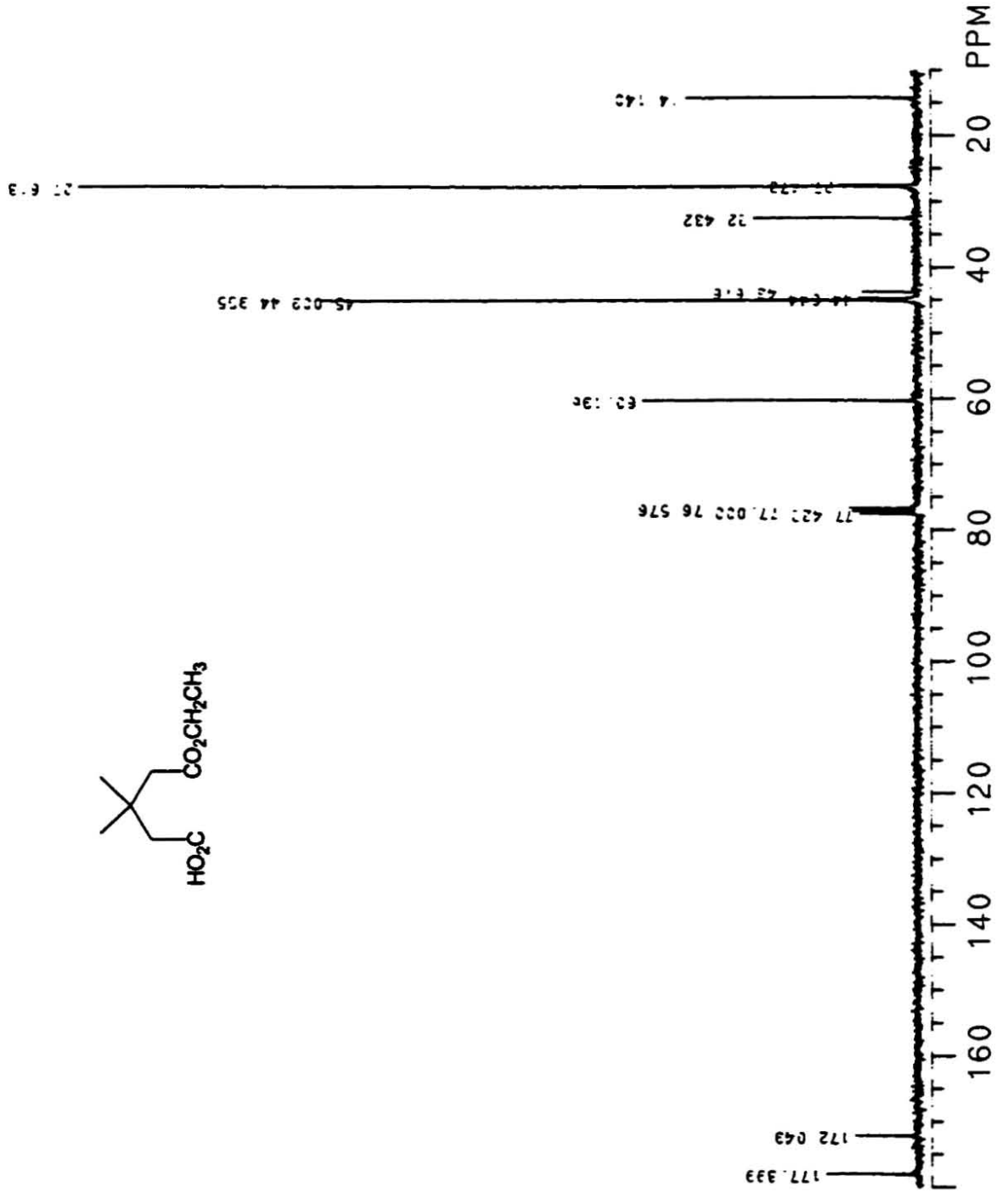


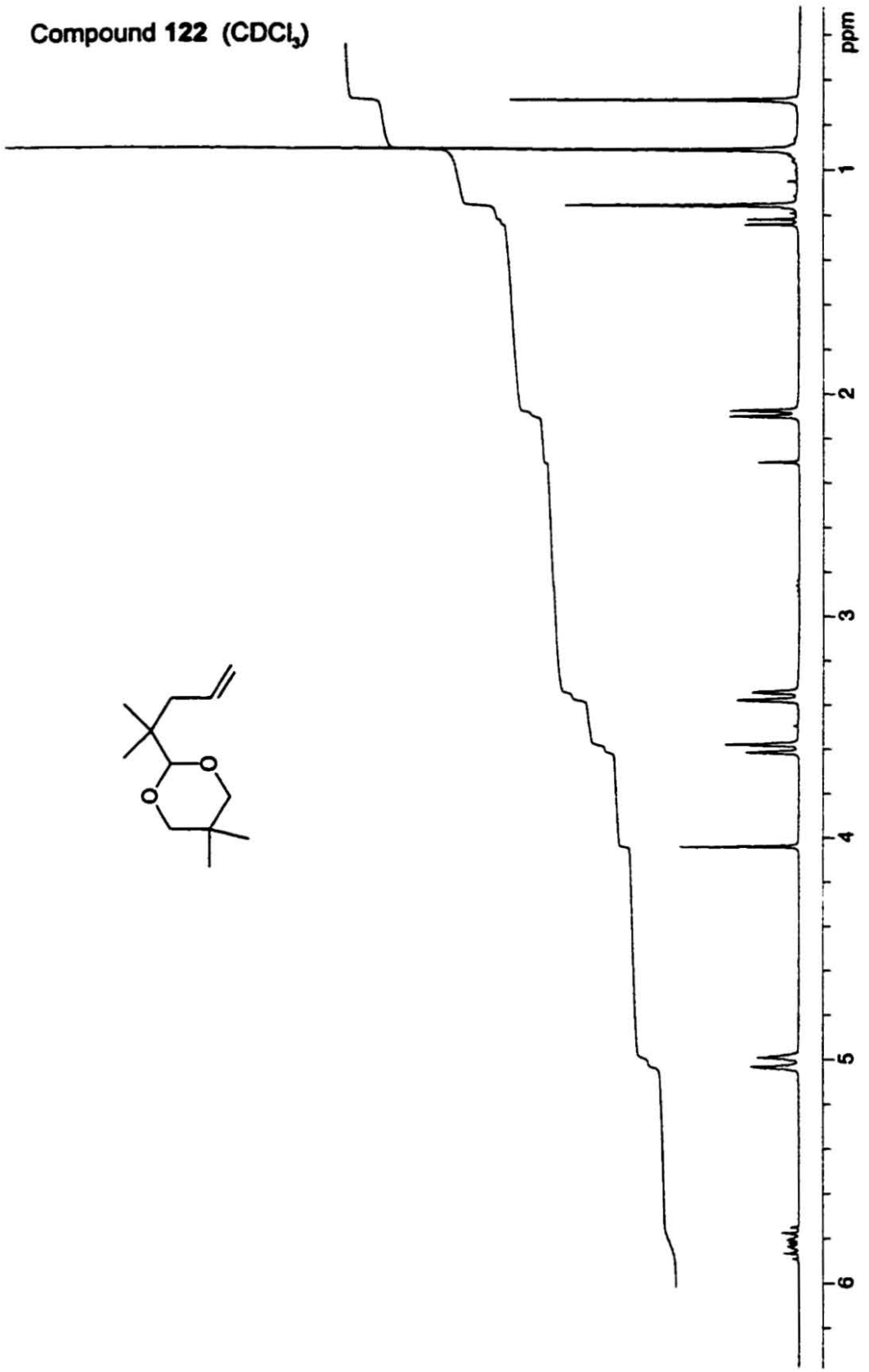

Compound 99 (CDCl3)
OHC
ppm
1
2
3
4
5
6
7
8
9
10

Compound **117** ($CDCl_3$)

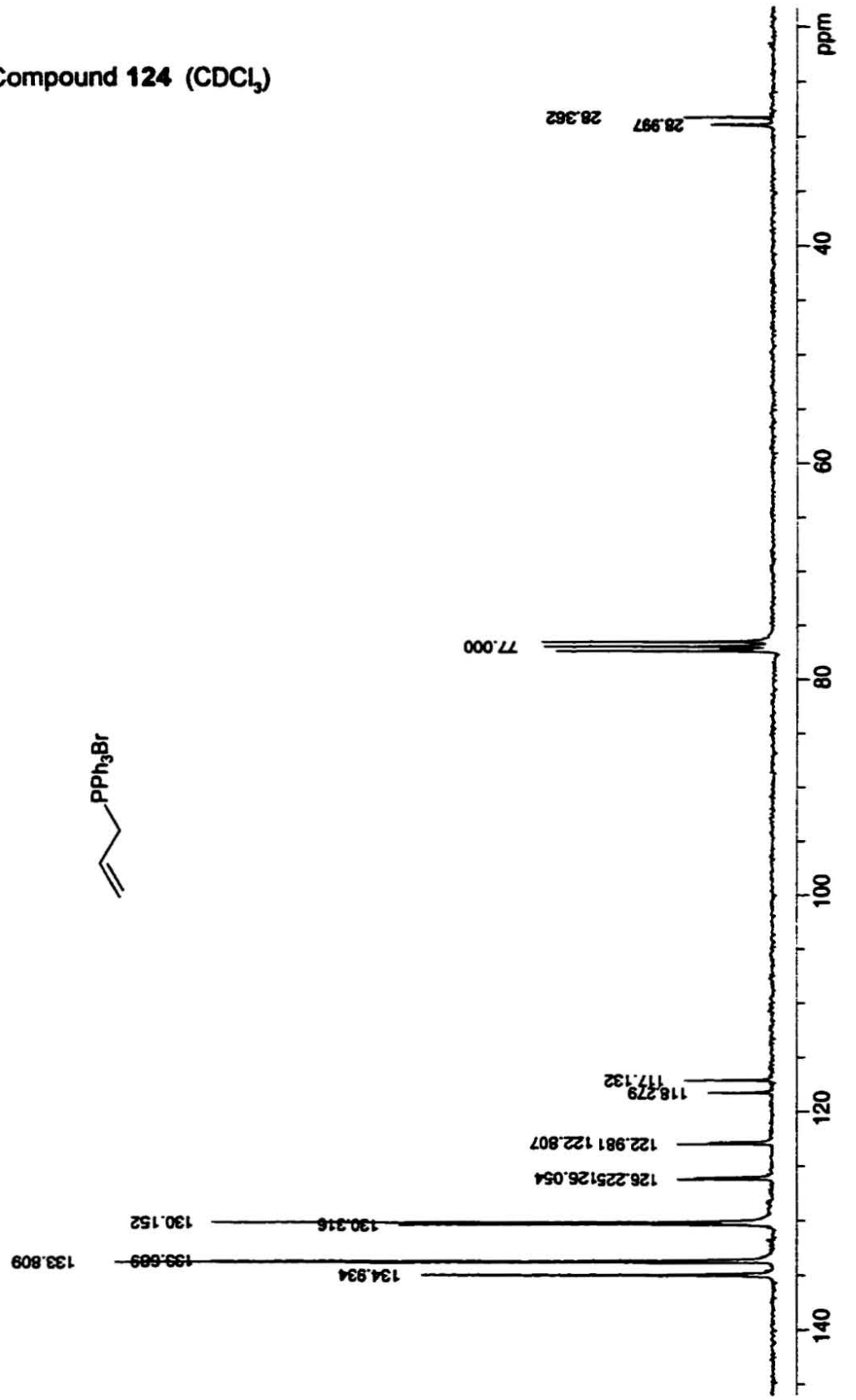


Compound **120** ($CDCl_3$)

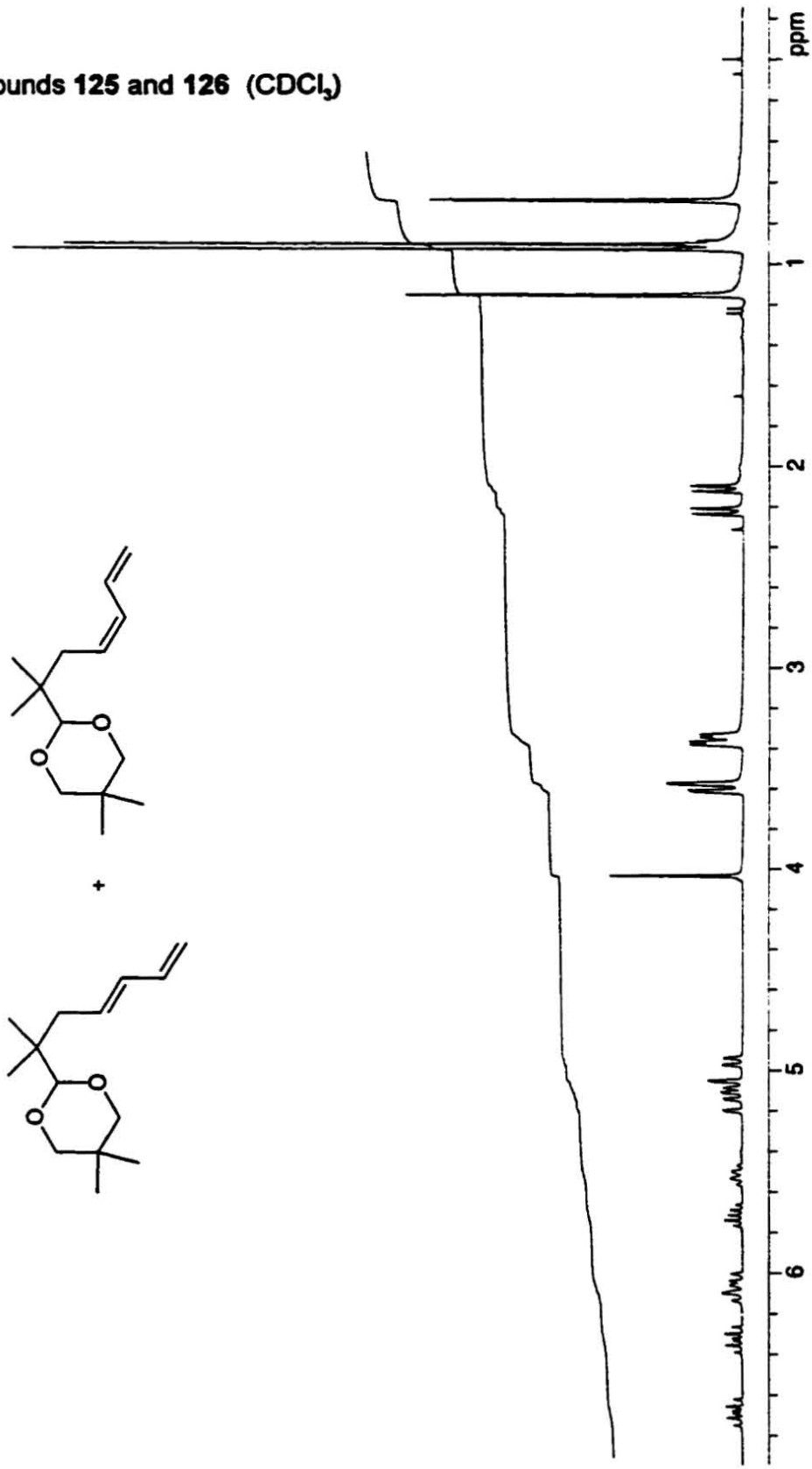



Compound 122 (CDCl3)
ppm
1
2
3
4
5
6

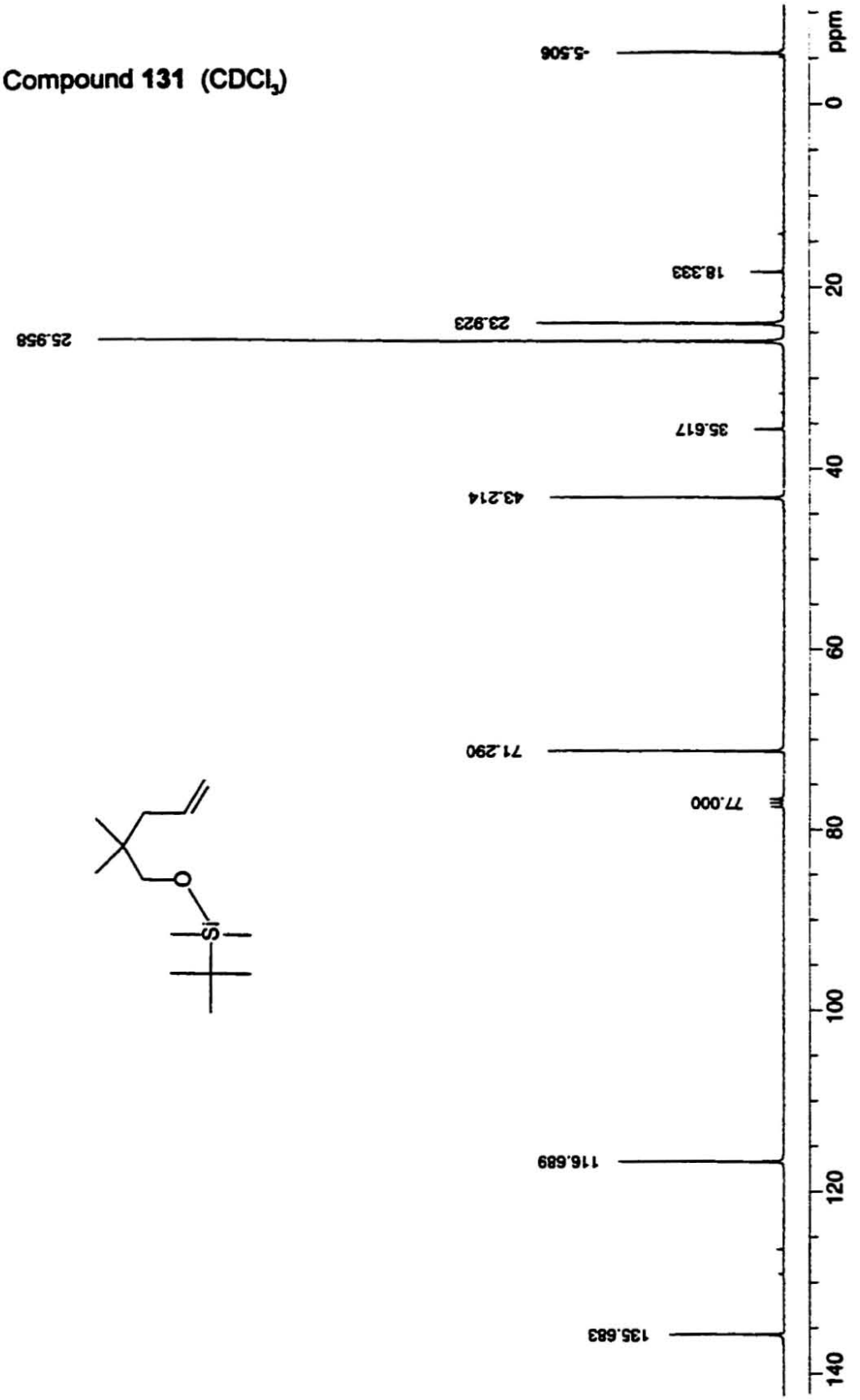
Compound **124** ($CDCl_3$)



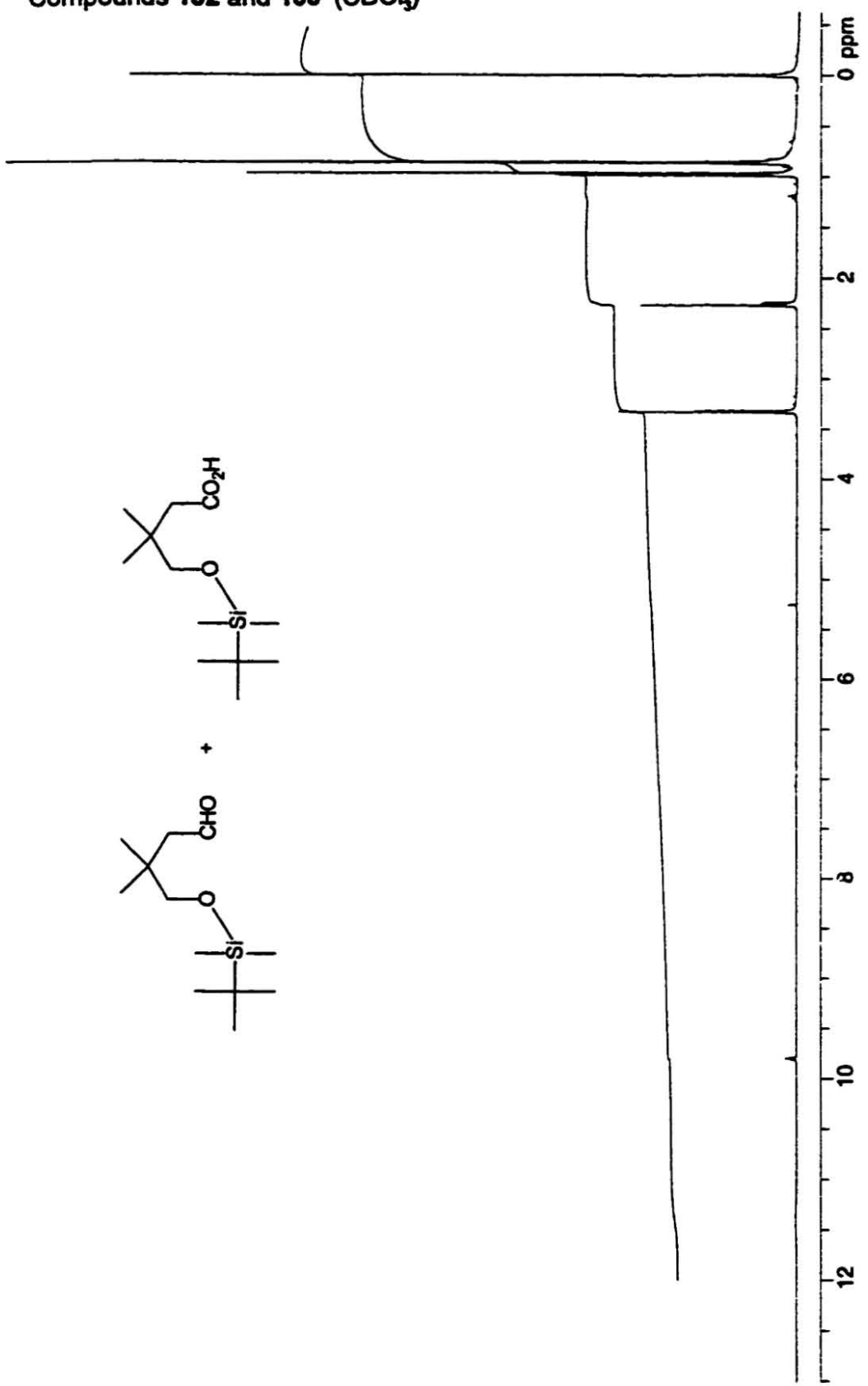
Compounds 125 and 126 ($CDCl_3$)



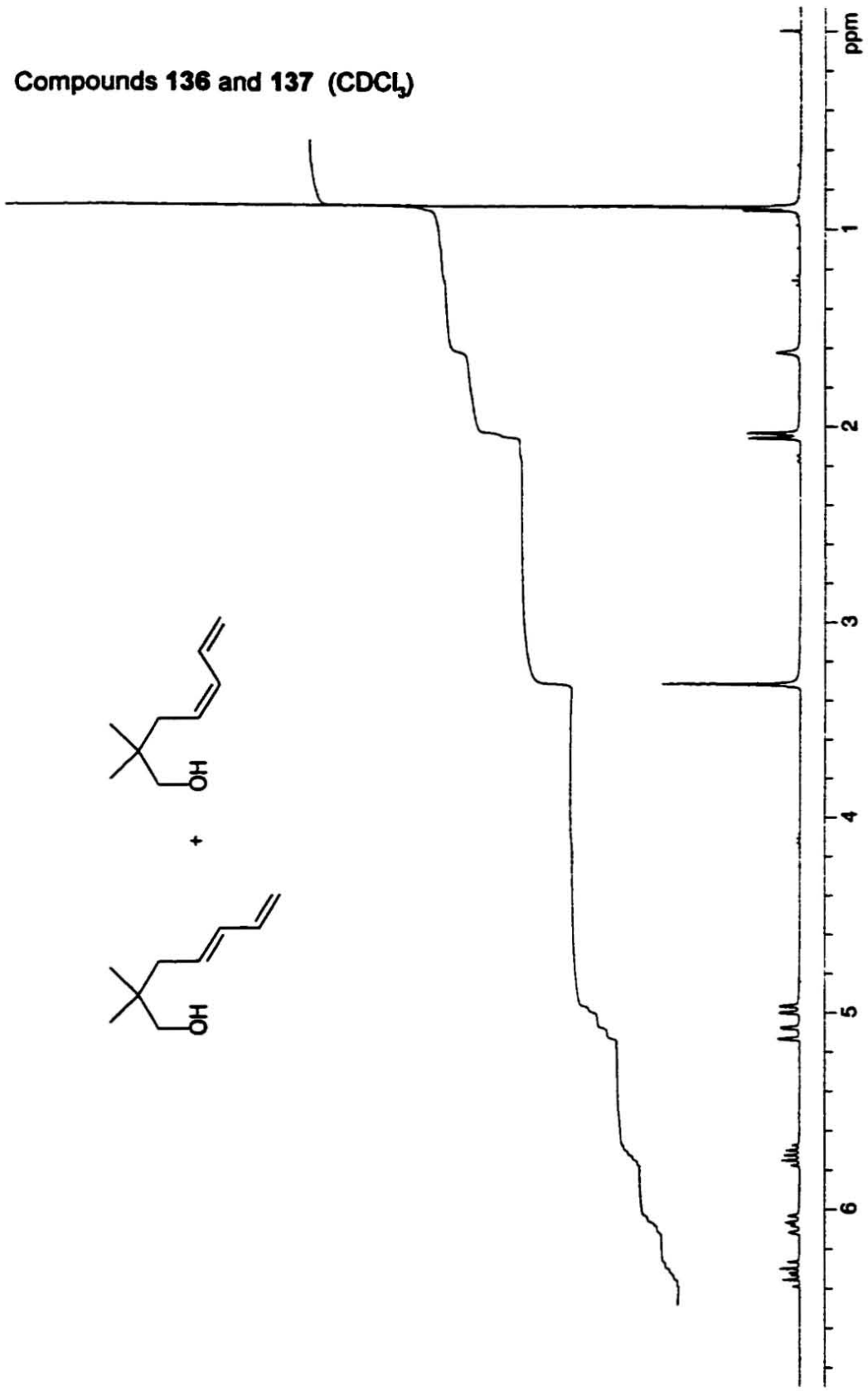
Compound 131 ($CDCl_3$)



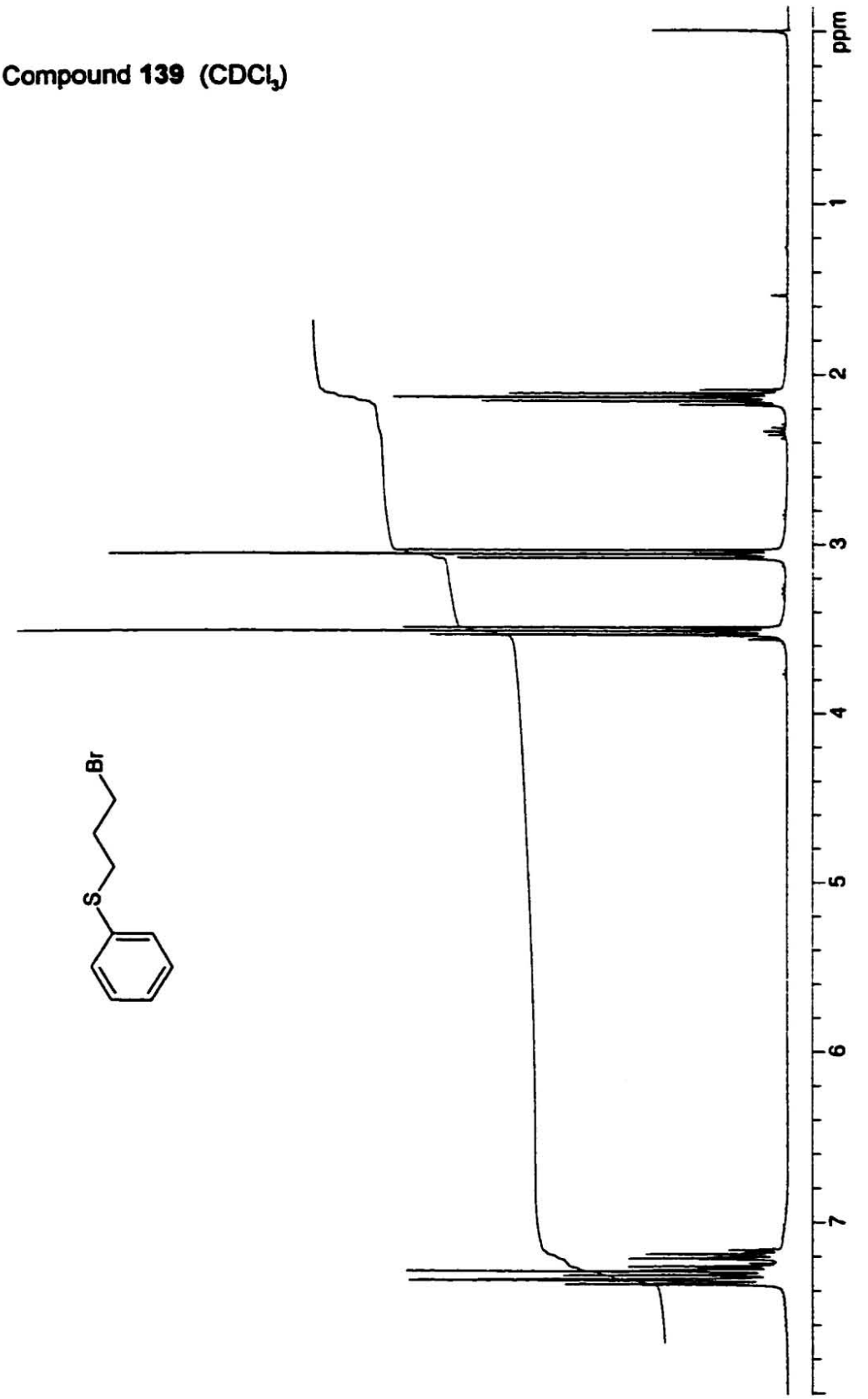
Compounds **132** and **133** ($CDCl_3$)



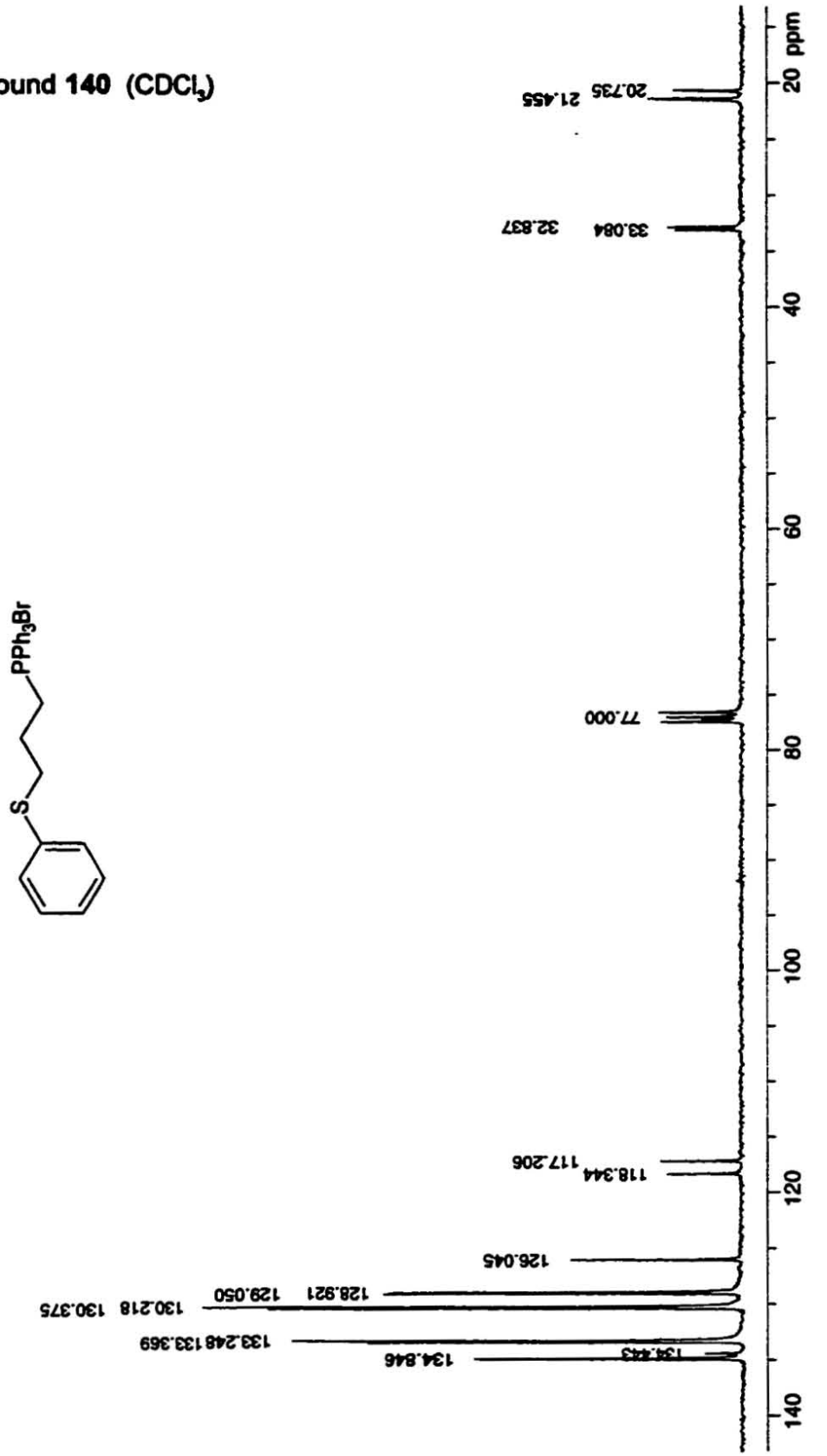
Compounds 136 and 137 ($CDCl_3$)

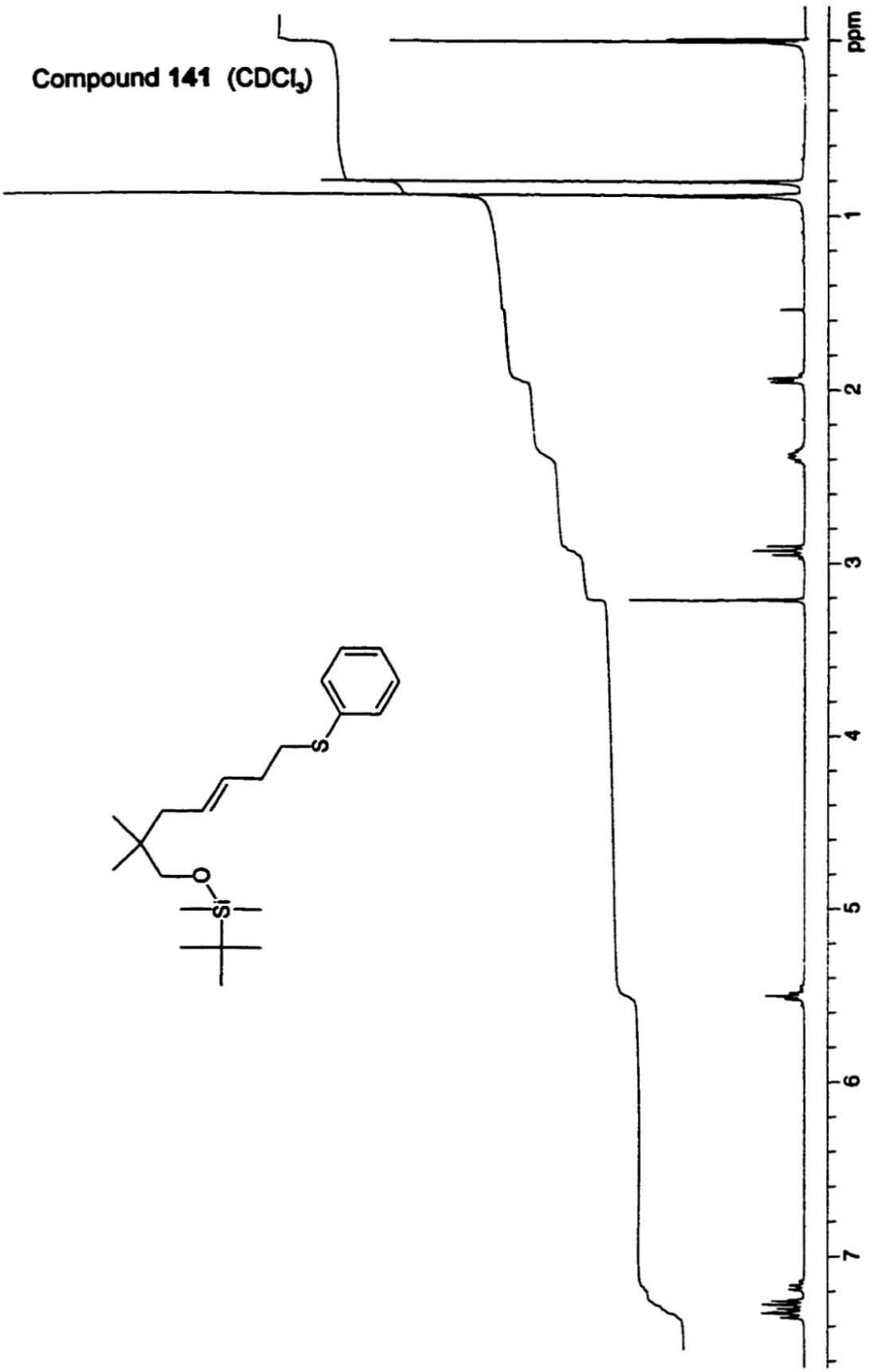


Compound **139** ($CDCl_3$)

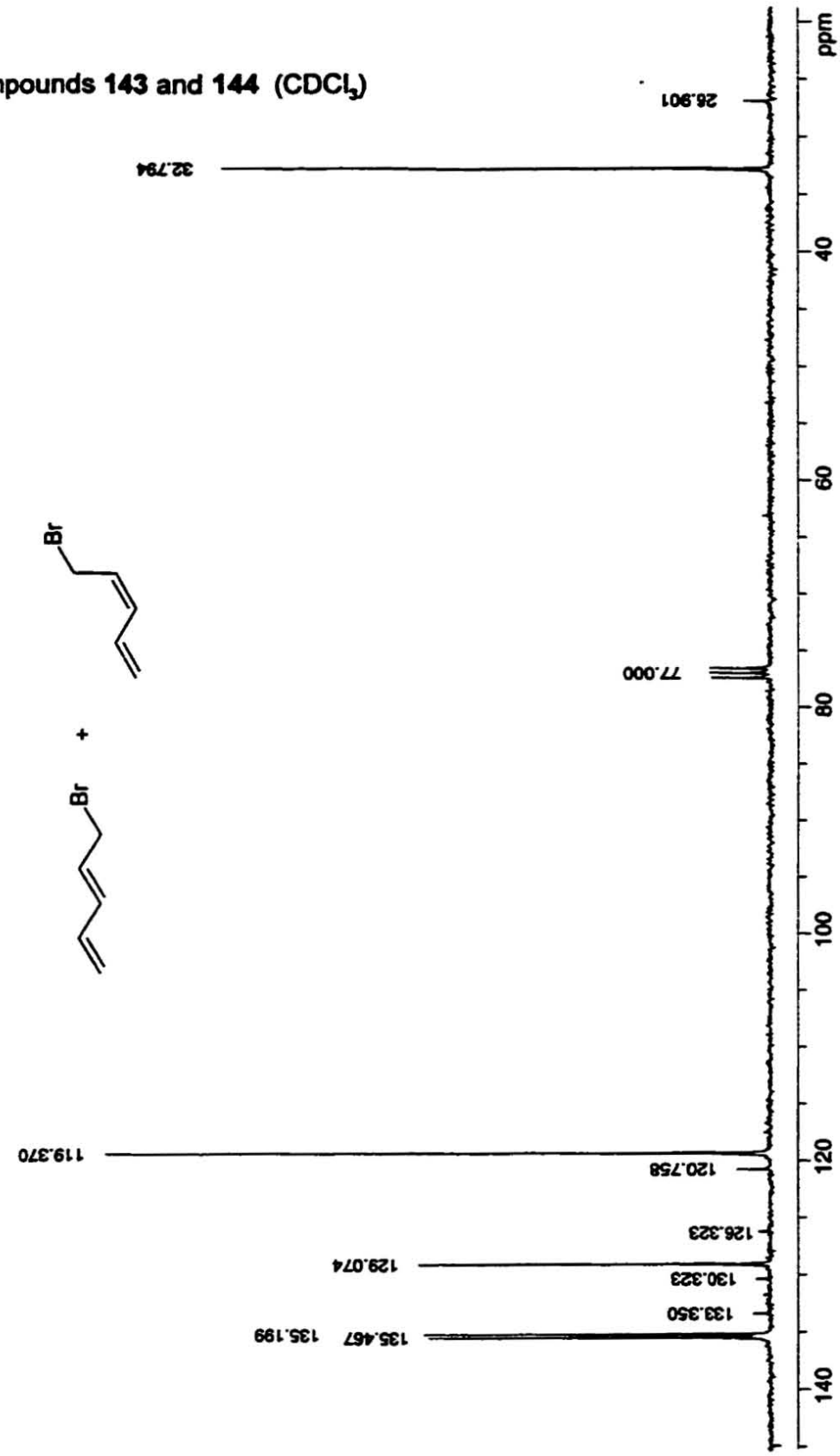


Compound 140 ($CDCl_3$)

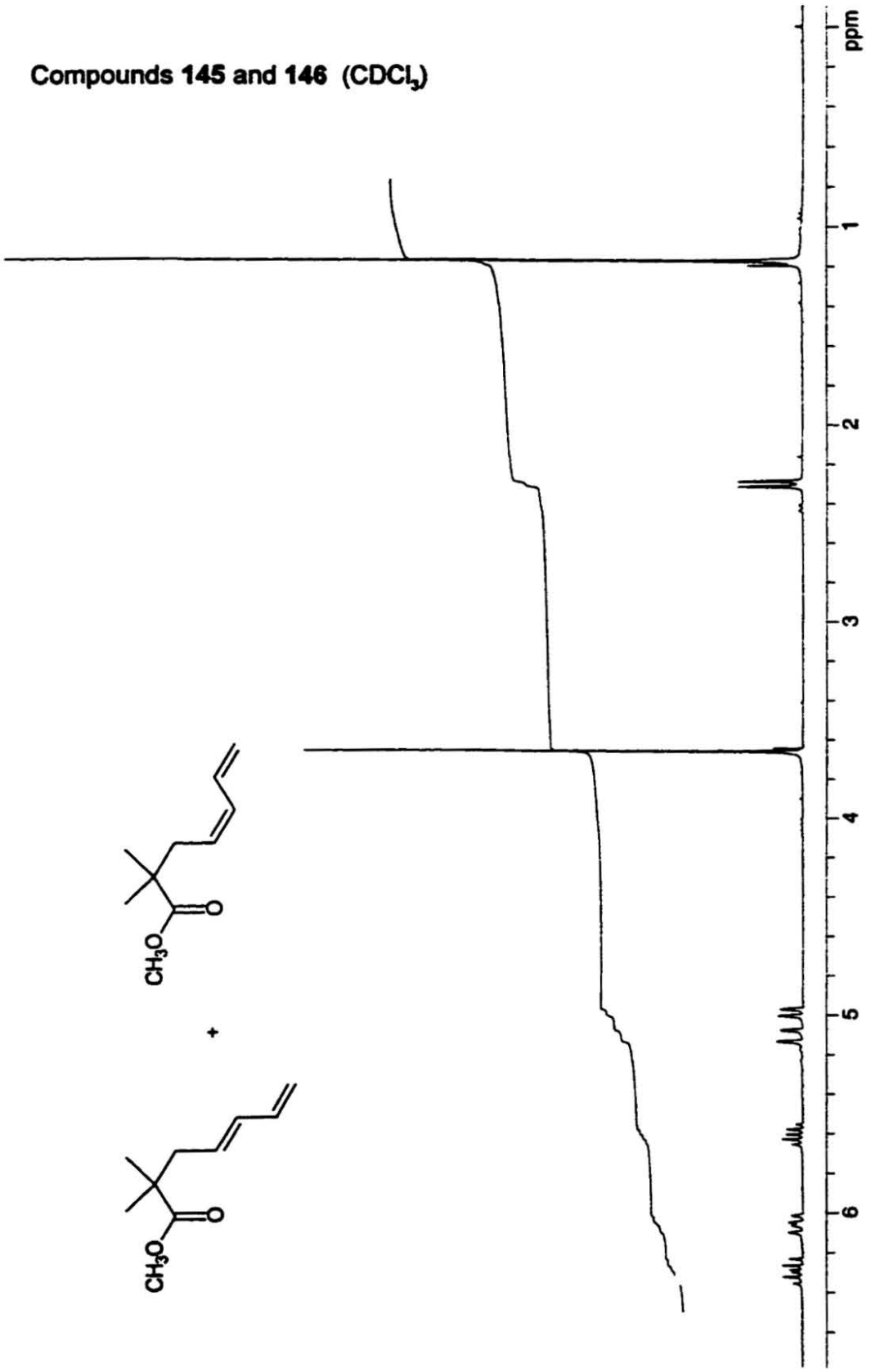



Compound 141 (CDCl3)
ppm
1
2
3
4
5
6
7
S
O
Si

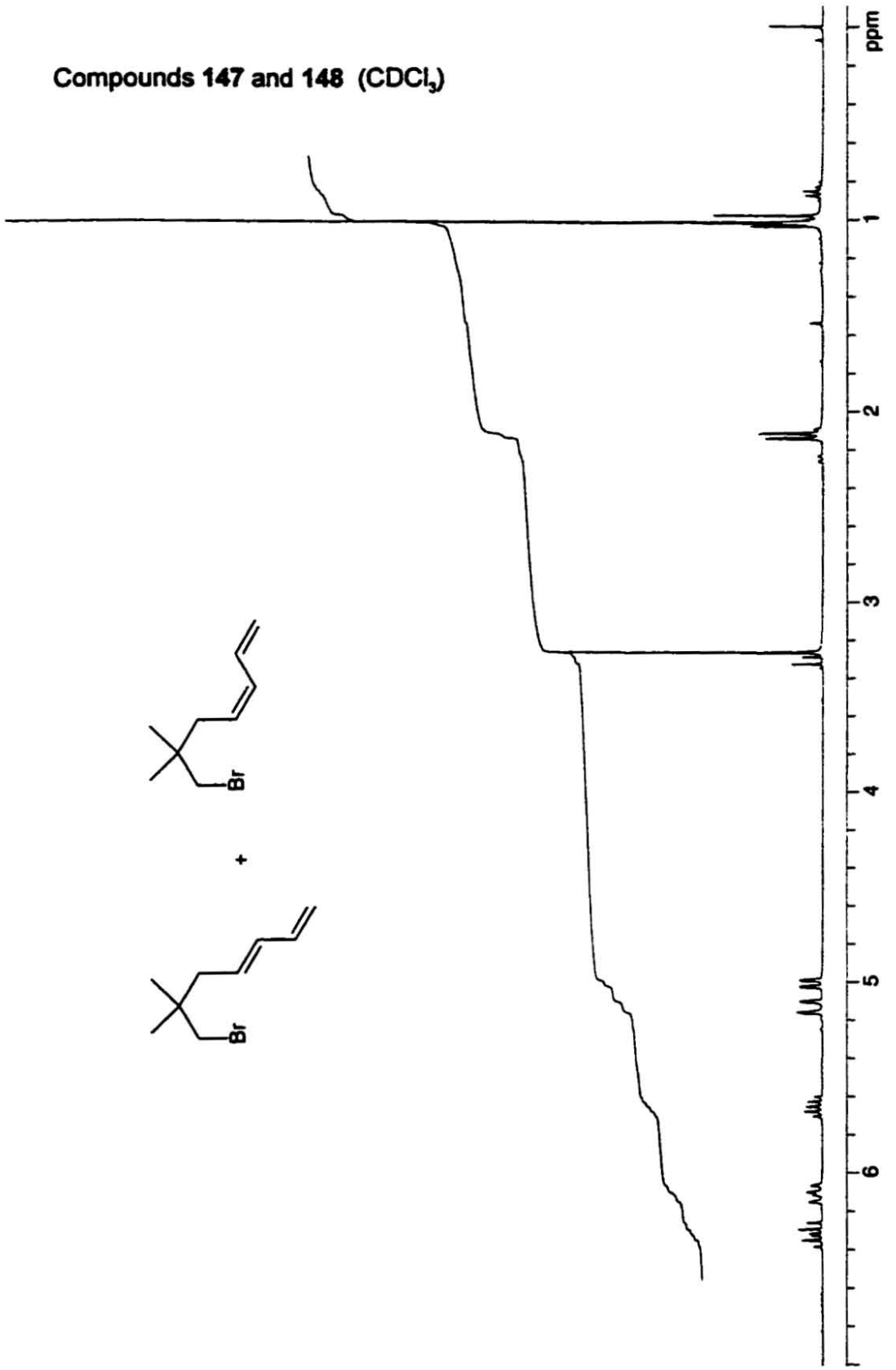
Compounds **143** and **144** ($CDCl_3$)



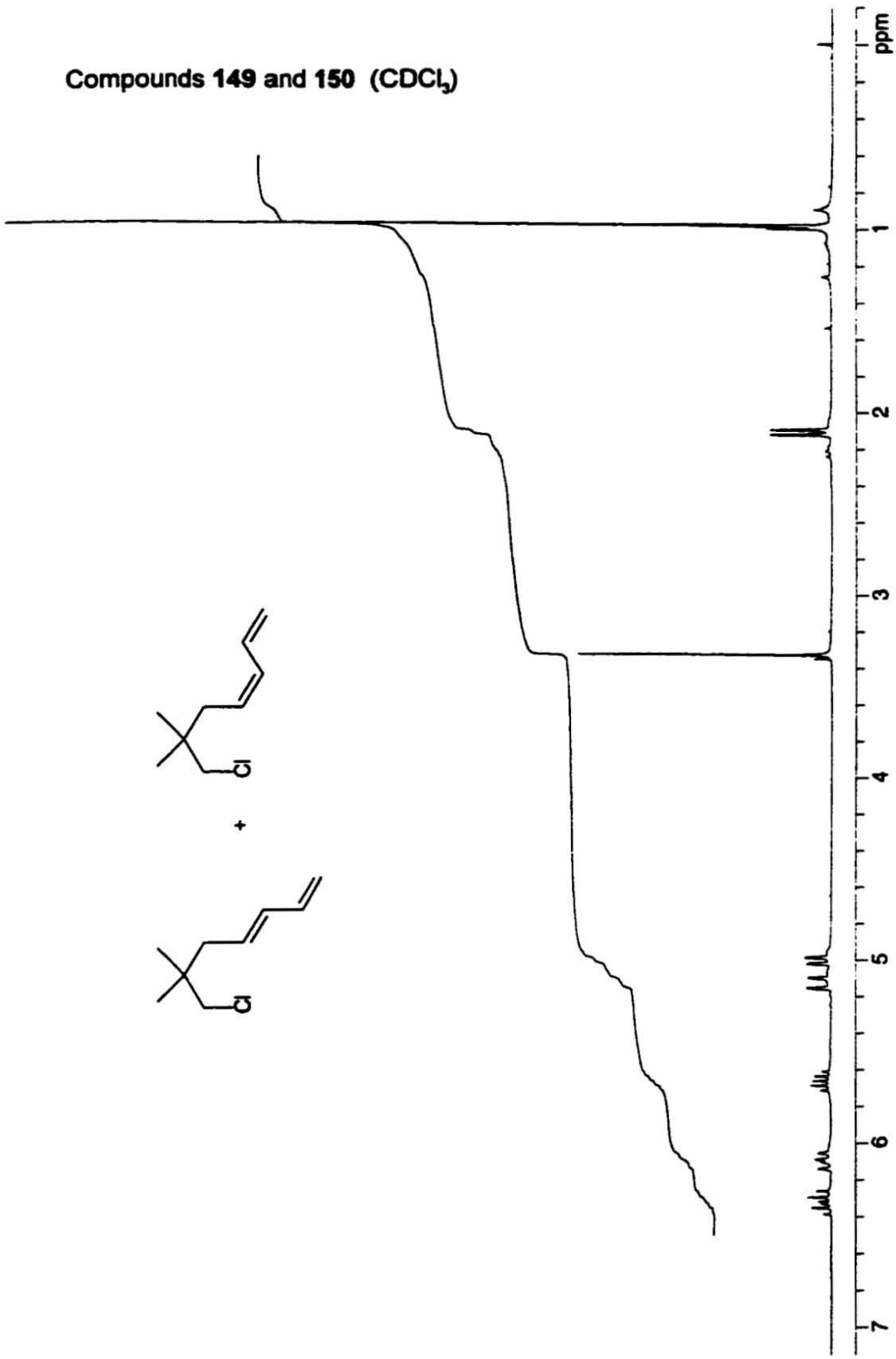
Compounds 145 and 146 ($CDCl_3$)



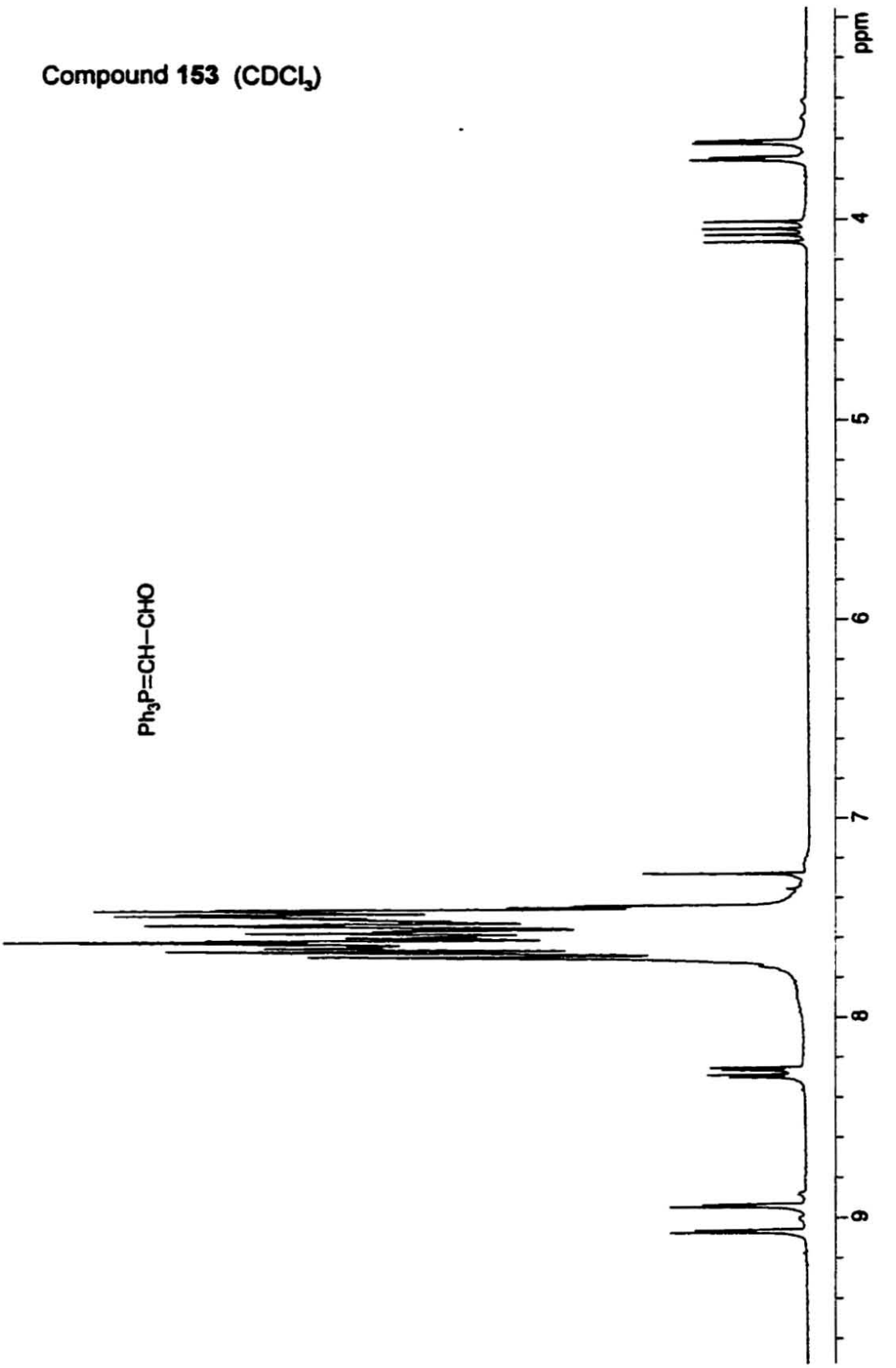
Compounds 147 and 148 ($CDCl_3$)

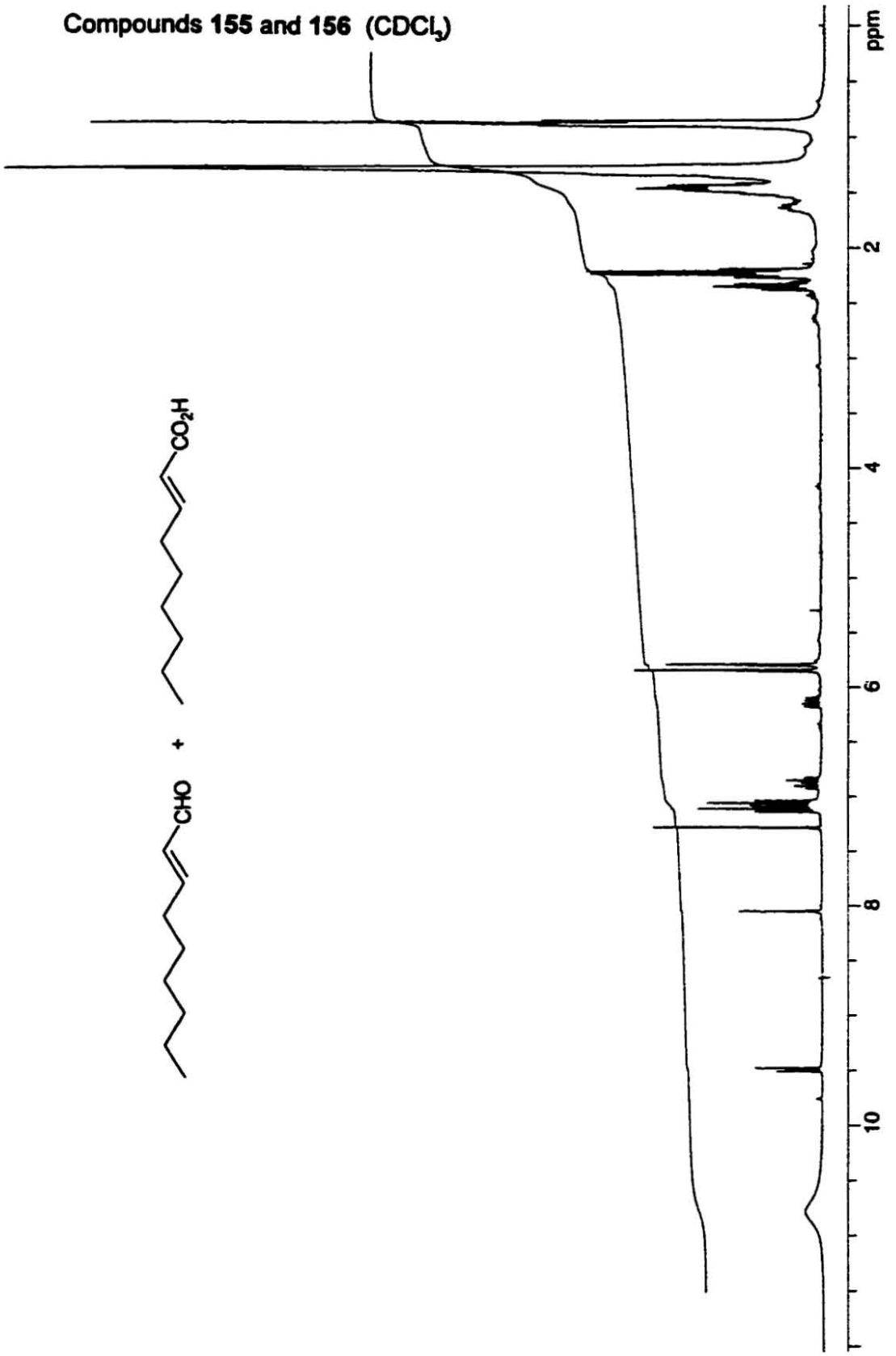


Compounds **149** and **150** ($CDCl_3$)

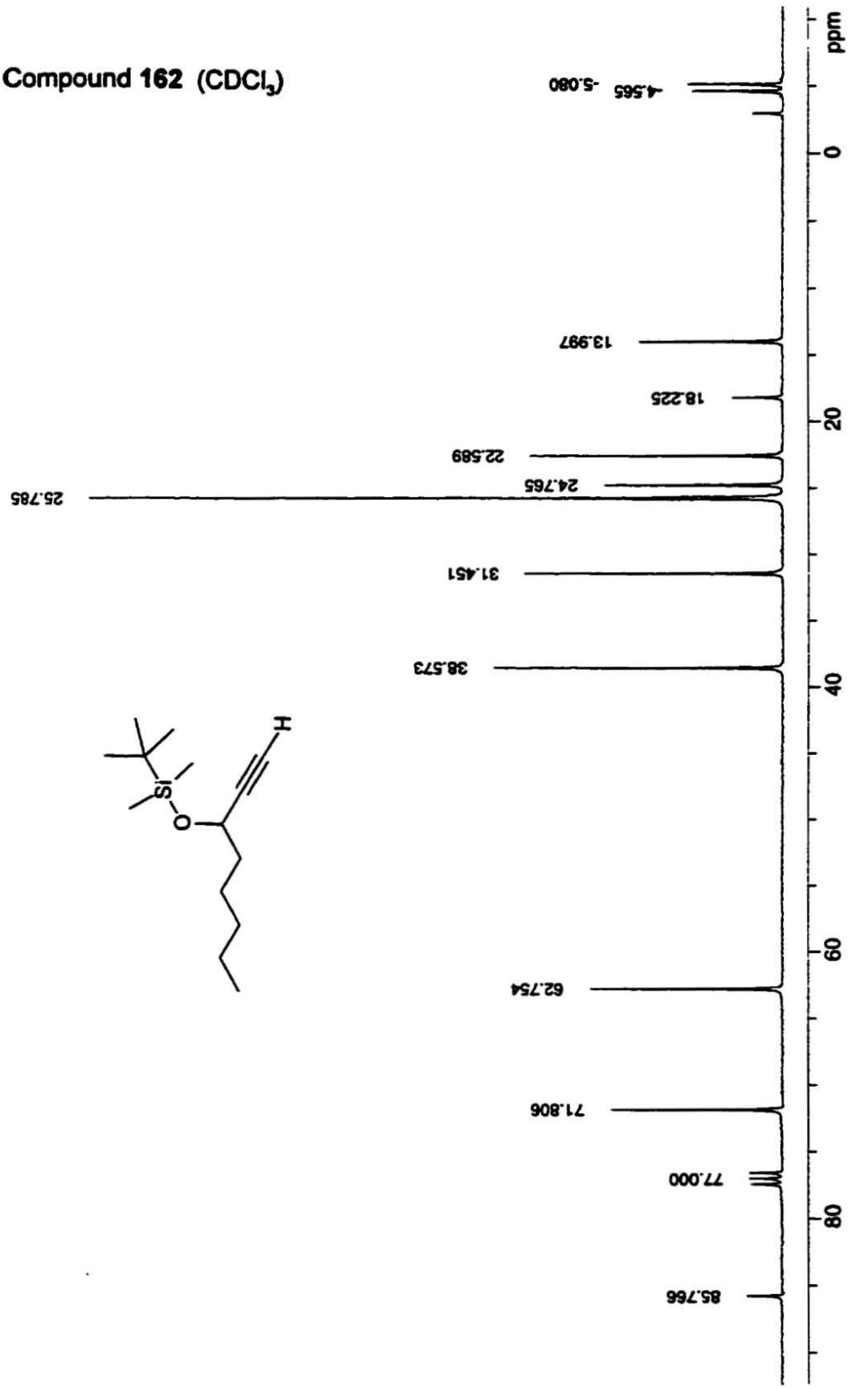


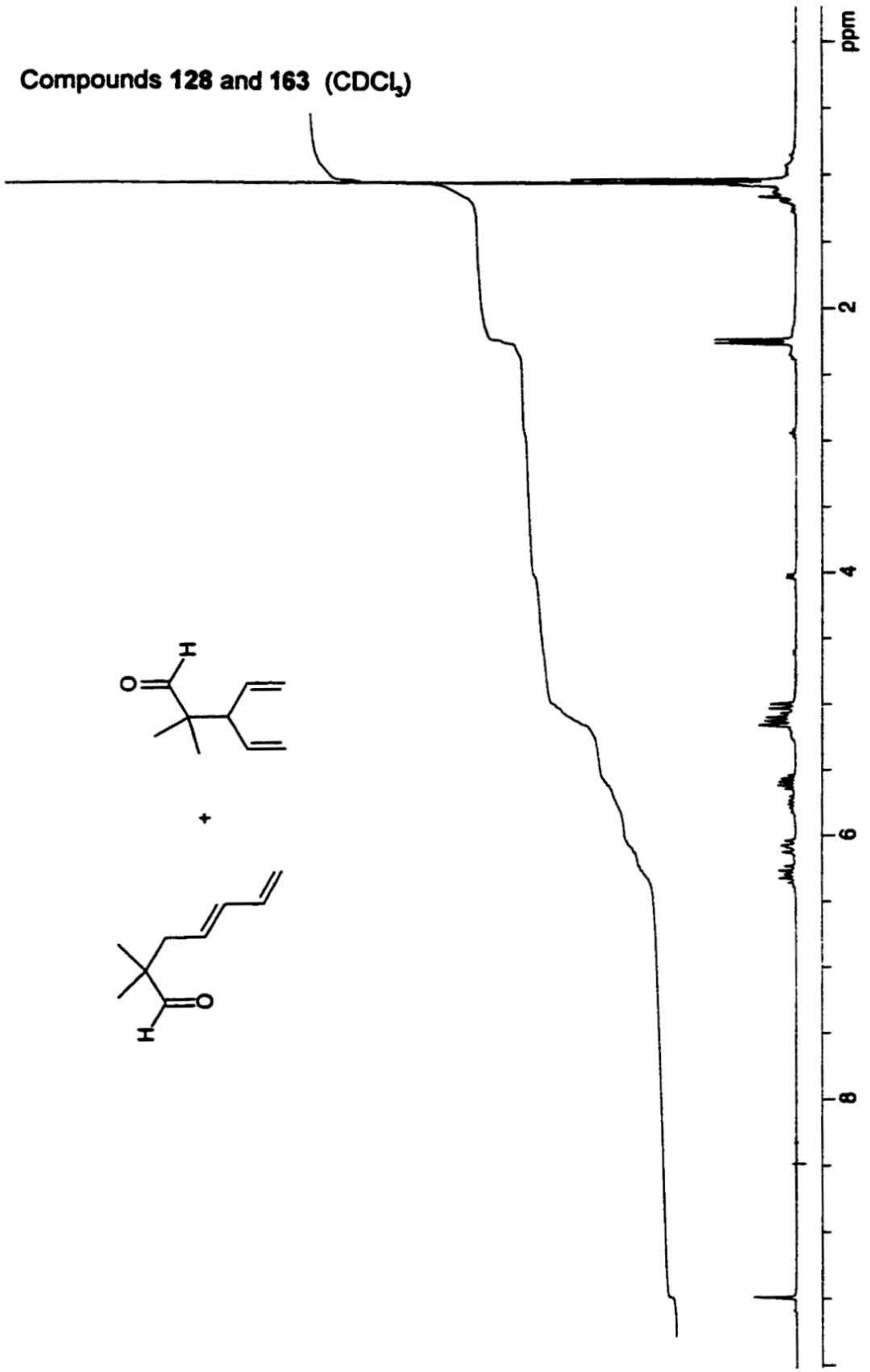
Compound **153** ($CDCl_3$)



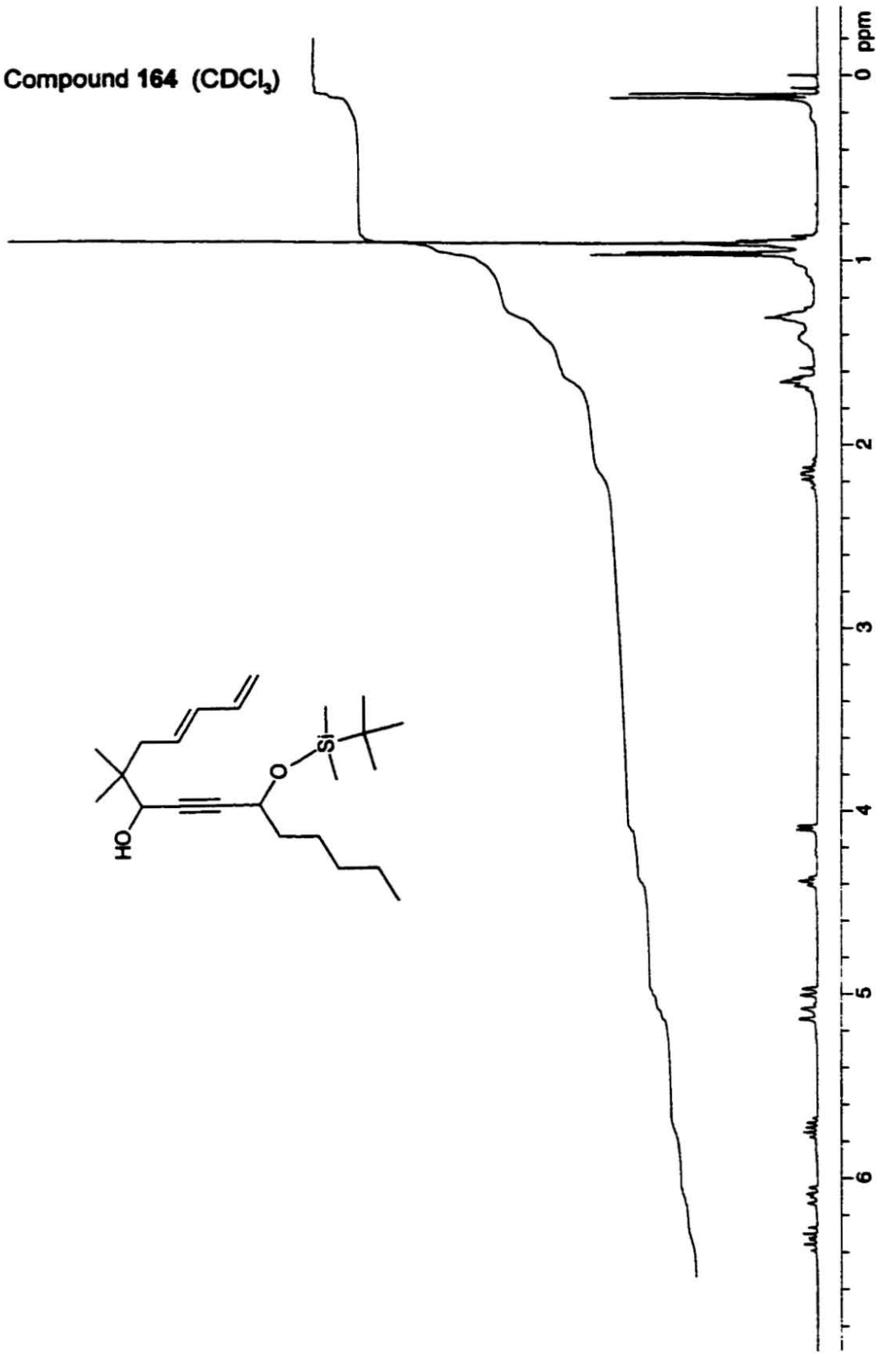

Compounds 155 and 156 (CDCl3)
CO2H
+
CHO
ppm
2
4
6
8
10

Compound **162** ($CDCl_3$)




Compounds 128 and 163 (CDCl3)
ppm
2
4
6
8
O
H
+
O
H

Compound **164** ($CDCl_3$)



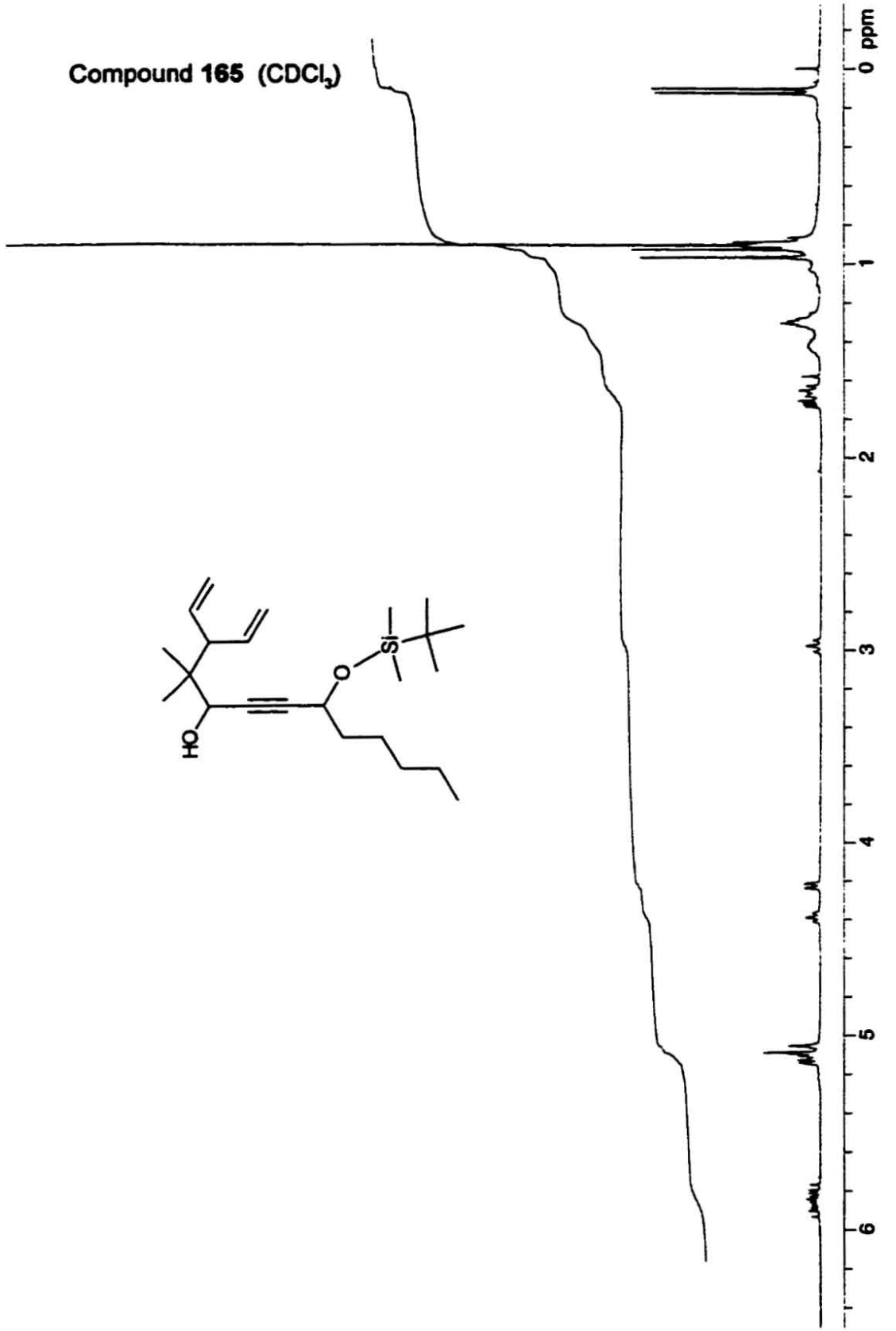
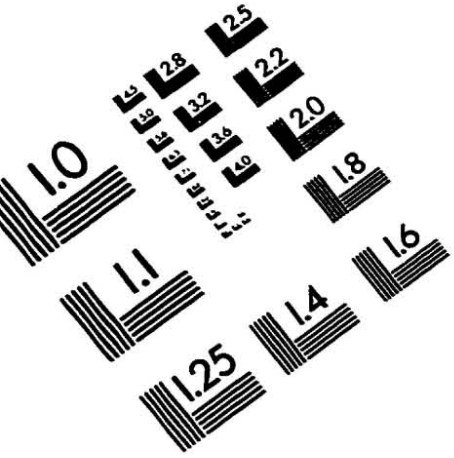
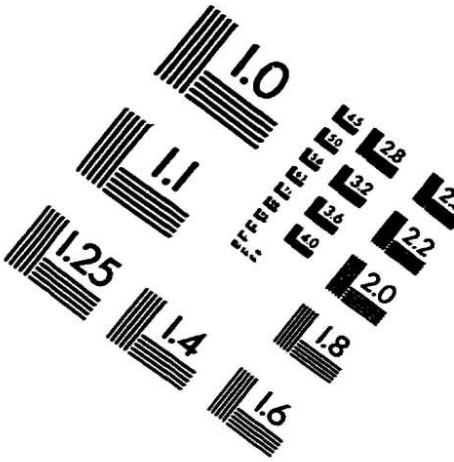
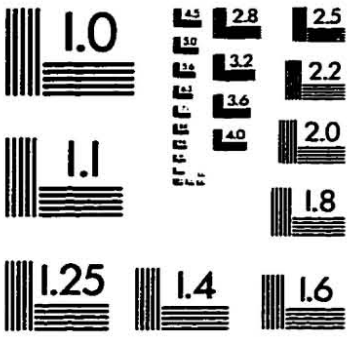
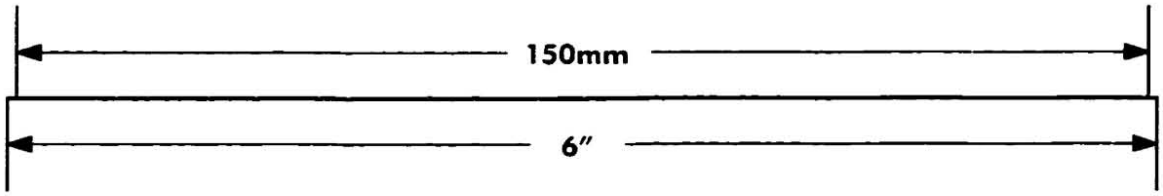

Compound 165 (CDCl3)
HO
O
Si
0 ppm
1
2
3
4
5
6

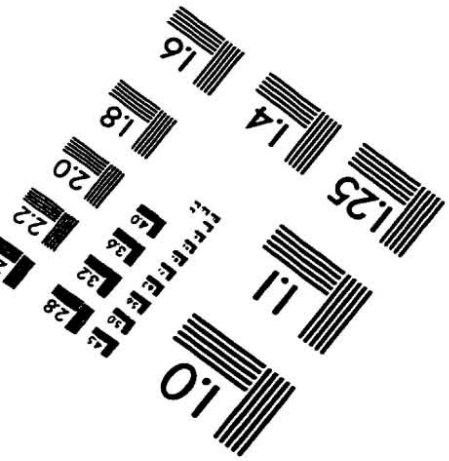
IMAGE EVALUATION
TEST TARGET (QA–3)

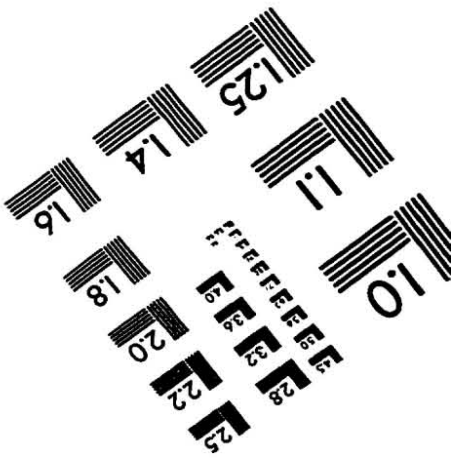












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