ASYMMETRIC DIELS-ALDER STUDIES INVOLVING CHIRAL ACETYLENIC DIESTERS AND INVESTIGATIONS OF AN INTRAMOLECULAR DIELS-ALDER APPROACH TO THE PENTALENOLACTONES

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by

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Abstract

Asymmetric Diels-Alder reactions of 2-(trimethylsilyloxy)cyclohexa-1,3-diene **17a**, 6,6-dimethyl-2-(trimethylsilyloxy)cyclohexa-1,3-diene **17b**, and 5,5-dimethyl-2-(trimethylsilyloxy)cyclohexa-1,3-diene **17c** with several chiral acetylenedicarboxylates were conducted. Modest levels of diastereoselectivity were obtained for several examples.

Semiempirical molecular orbital calculations for the Diels-Alder reactions of 2-hydroxy analogues of these dienes with di-*t*-butyl acetylenedicarboxylate were carried out to help interpret the experimental results. Four transtion states having very similar relative energies were obtained for each diene-dienophile combination. The calculations also supported an asynchronous transition state with the shorter incipient bond nearest the electron-donating trimethylsiloxy group. It follows that the ester group further from the trimethylsiloxy group most likely adopts a "fixed", parallel-planar conformation to activate the triple bond for attack, whereas the other ester is perpendicular to the incoming diene.

(3-Phenylsulfonyl-2-propynyl) 2-(5,5-dimethyl-2-oxocyclohex-3-enyl) ethanoate **223** and ((*E*)-3-phenylsulfonyl-2-propenyl) 2-(5,5-dimethyl-2-(((1,1-dimethylethyl)dimethylsilyl)oxy)cyclohexa-1,3-dienyl)ethanoate **231** could serve as precursors in the synthesis of pentalenolactones. Our synthesis of

these compounds was based on alkylation of 4,4-dimethyl-2-cyclohexen-1-one **20c** with 2-halo esters similar to compound **146**.

Various 2-bromo esters were prepared and converted to their corresponding 2-iodo equivalents via the Finkelstein reaction. These 2-iodo esters were found to undergo alkylation in good yield with 4,4-dimethyl-2-cyclohexen-1-one **20c**. In this manner, (3-phenylthio-2-propynyl) 2-(5,5-dimethyl-2-oxocyclohex-3-enyl)ethanoate **205** was synthesized from (3-phenylthio-2-propynyl) 2-iodoethanoate **204**. Treatment under kinetic conditions gave the desired diene, (3-phenylthio-2-propynyl) 2-(5,5-dimethyl-2-(((1,1-dimethylethyl)dimethylsilyl)oxy)cyclohexa-1,3-dienyl)ethanoate **220**. Activation of the alkyne, by oxidation to the sulfone, gave (3-phenylsulfonyl-2-propynyl) 2-(5,5-dimethyl-2-oxocyclohex-3-enyl)ethanoate **223**.

A similar route involving (*E*)-3-phenylsulfonyl-2-propen-1-ol **227** as the starting alcohol resulted in ((*E*)-3-phenylsulfonyl-2-propenyl) 2-(5,5-dimethyl-2-oxocyclohex-3-enyl)ethanoate **230**. Diene formation under thermodynamic conditions gave ((*E*)-3-phenylsulfonyl-2-propenyl) 2-(5,5-dimethyl-2-(((1,1-dimethylethyl)dimethylsilyl)oxy)cyclohexa-1,3-dienyl)ethanoate **231**.

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To my shining star, Lori

my pillars of strength, Mom and Dad

and my shoulder to lean on, Joy.

Thanks...

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Glossary of abbreviations

*m*CPBA	*meta*-Chloroperoxybenzoic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
de	Diastereomeric excess
4-DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
ee	Enantiomeric excess
Et	Ethyl
GC-MS	Gas chromatography-mass spectrometry
HMDS	1,1,1,3,3,3-Hexamethyldisilazane
HMPA	Hexamethylphosphoric triamide
HPDA	High pressure Diels-Alder
IR	Infrared spectroscopy
KIE	Kinetic isotope effect
LDA	Lithium diisopropylamide
$LiAlH_4$	Lithium aluminum hydride
Me	Methyl
mp	Melting point
Ms	Mesyl = methanesulfonyl
MS	Mass spectrometry

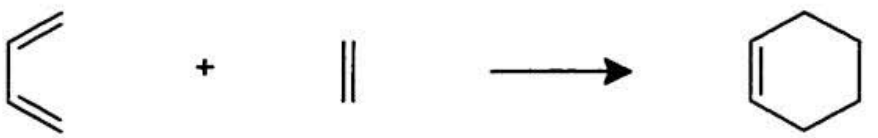
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance spectroscopy
NOE	Nuclear Overhauser effect
PPTS	Pyridinium *p*-toluenesulfonate
RHF	Restricted Hartree-Fock
rt	Room temperature
TBSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCl	Chlorotrimethylsilane
*p*TsOH	*para*-Toluenesulfonic acid monohydrate

Part 1

ASYMMETRIC DIELS-ALDER STUDIES INVOLVING CHIRAL ACETYLENIC DIESTERS

I. Introduction

Since its initial discovery in 1928,[1] the Diels-Alder reaction has found widespread application in the field of organic chemistry and has evolved into an invaluable tool for the synthetic organic chemist. The Diels-Alder reaction is a $[4\pi_s+2\pi_s]$ cycloaddition involving the reaction of a conjugated diene and a dienophile to yield a product referred to as an adduct. The reaction of butadiene and ethylene to give cyclohexene is the simplest example (Scheme 1).



Scheme 1. Basic Diels-Alder reaction.

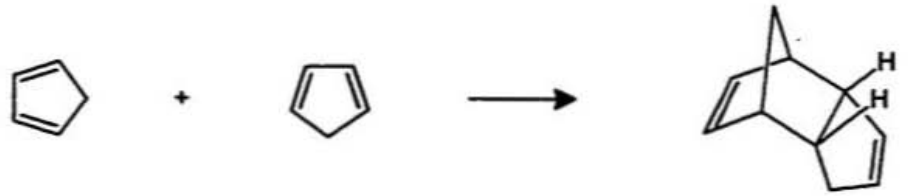
Conjugated dienes may exist in the *s-cis* geometry or the *s-trans* geometry. Only those with the *s-cis* conformation are suitable as Diels-Alder dienes because this allows overlap of the *p*-orbitals (Figure 1a) of the diene and the dienophile in the transition state (Figure 1b).

a b

Figure 1. Diene geometry necessary for a Diels-Alder reaction.

Open-chain dienes such as butadiene and 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene exist in both the *s-cis* and *s-trans* forms. When the Gibbs free-energy difference (ΔG) between the two conformers is large, the rate of reaction for such dienes is affected by the position of equilibrium between the two forms. When the diene substitution pattern is such that steric strain results when the diene is in the *cisoid* form, the diene is very slow to react.

The dienophile in a Diels-Alder reaction can be a molecule containing a double or triple bond which participates as the 2π component in the cycloaddition. In fact, a single compound can participate in a Diels-Alder reaction as both the diene and the dienophile, as in the dimerization of cyclopentadiene (Scheme 2).



Scheme 2. Dimerization of cyclopentadiene.

While the 2π component is usually carbon-based, heteroatomic dienophiles are also routinely used (Figure 2).

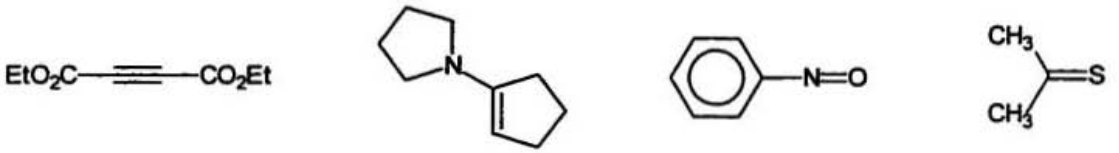


Figure 2. Examples of some commonly used dienophiles.

The reaction rate for a Diels-Alder reaction correlates well with the substituents on the diene and dienophile and is best explained using frontier molecular orbital (FMO) theory. According to this theory, during a [4 + 2] cycloaddition, the highest occupied molecular orbital (HOMO) of one component interacts with the lowest unoccupied molecular orbital (LUMO) of the other. For any Diels-Alder reaction there are two possible interactions: HOMO (diene) - LUMO (dienophile), and LUMO (diene) - HOMO (dienophile). The HOMO - LUMO pair that predominates in the transition state is the one having the smaller energy separation and is responsible for the observed reactivity. Sauer and

Sustmann[2] classified three types of Diels-Alder reactions based on these HOMO - LUMO interactions (Figure 3).

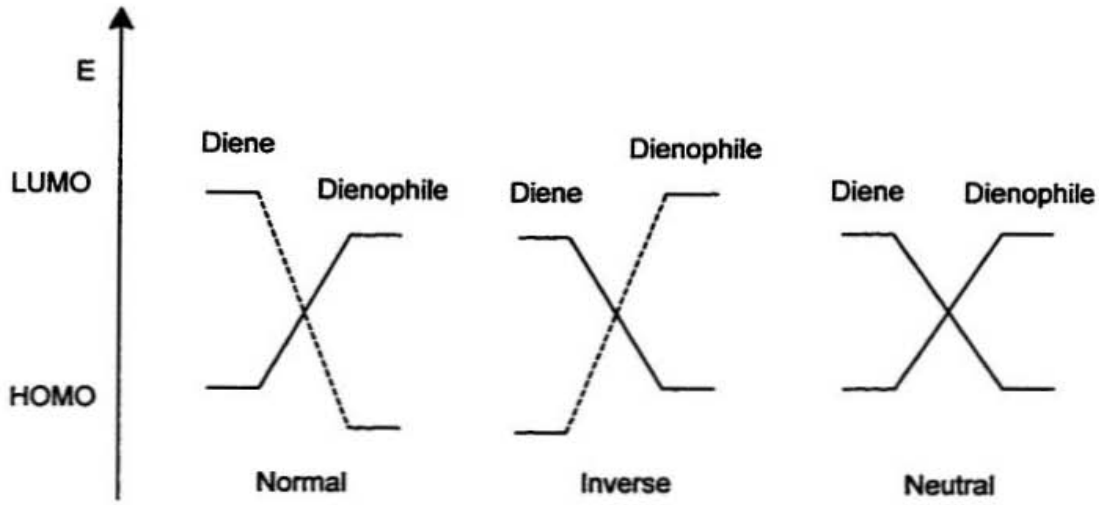
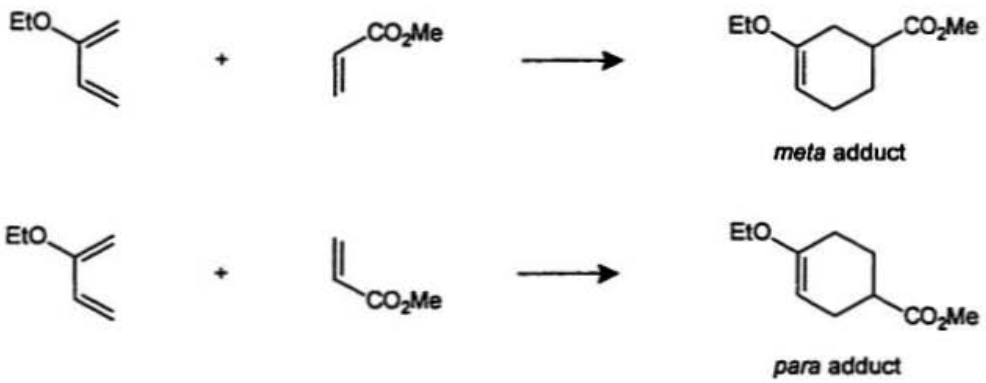


Figure 3. Frontier molecular orbitals for the three types of Diels-Alder reaction.

These are referred to as "normal" electron-demand, "inverse" electron-demand and "neutral" electron-demand Diels-Alder reactions. In the most common type of Diels-Alder, the "normal" electron-demand, the stronger interaction is between the HOMO (diene) and the LUMO (dienophile). Since electron-withdrawing substituents lower the energy of the HOMO and LUMO molecular orbitals and electron-donating substituents increase them, for a "normal" electron-demand Diels-Alder reaction electron-donating substituents on the diene and/or electron-withdrawing substituents on the dienophile will accelerate the reaction. For an "inverse" electron-demand Diels-Alder, the LUMO (diene) - HOMO (dienophile) interaction predominates. Thus, the reaction will be accelerated by

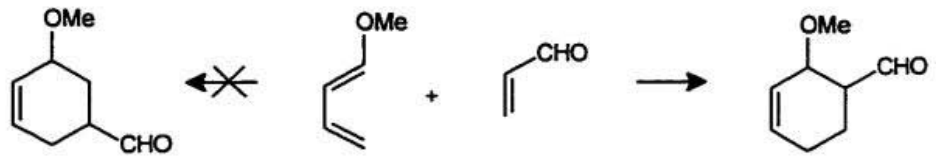
adding electron-withdrawing substituents to the diene and/or electron-donating substituents to the dienophile. Unlike a "normal" Diels-Alder, the presence of electron-withdrawing groups on the dienophile will slow the reaction. In the "neutral" electron-demand Diels-Alder, neither the HOMO (diene) - LUMO (dienophile) nor the LUMO (diene) - HOMO (dienophile) predominates. Both HOMO - LUMO interactions are of similar importance. Any substituent added would result in an increase in reactivity because the gain in stabilization by strengthening one interaction is greater than the loss incurred by weakening the other.

FMO theory can also be used to rationalize the regioselectivity of the Diels-Alder reaction.[3] Diels-Alder reactions between two unsymmetrical addends could result in two regioisomeric adducts, as illustrated for the Diels-Alder reaction of 2-ethoxybutadiene and methyl acrylate (Scheme 3).



Scheme 3. Possible regioisomeric products for the Diels-Alder reaction of 2-ethoxybutadiene and methyl acrylate.

The diene and dienophile could react to give either the "*meta*" adduct or the "*para*" adduct. The terms *ortho*, *meta* and *para* are borrowed from nomenclature associated with disubstituted aromatic systems to describe the relative positions of the substituents for the Diels-Alder adducts. Of the two regioisomers shown above, only the "*para*" product is formed in an appreciable amount.[4] This observation cannot be attributed to electronic effects since replacement of the electron-donating ethoxy substituent with an electron-attracting cyano substituent results in the same regiochemical preference,[5] although the reaction is no longer regiospecific. Steric factors are also unable to account for regioselectivity in the Diels-Alder reaction. Reaction of 1-methoxybutadiene with acrolein gives the more sterically congested "*ortho*" adduct as the only product (Scheme 4).[3a]



Scheme 4. Diels-Alder reaction of 1-methoxybutadiene with acrolein.

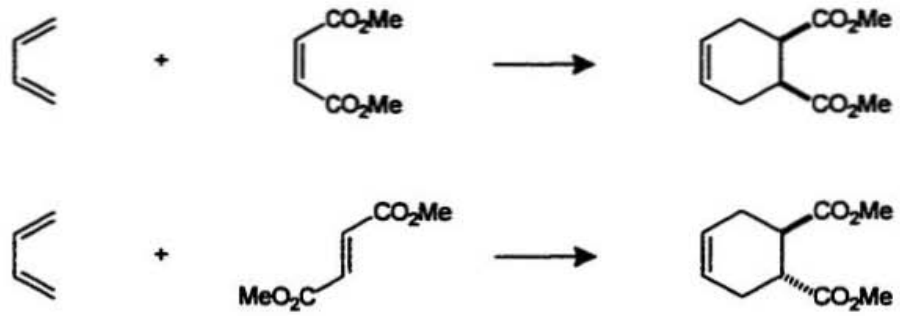
Houk used FMO theory to explain regioselectivity.[6] For symmetrical and/or symmetrically-substituted dienes and dienophiles, the orbital coefficients of the frontier orbitals at the terminal ends are necessarily the same. For unsymmetrical addends, however, the coefficients are not equal, resulting in polarization of the FMO's. Houk concluded that the regioselectivity results from preferential bonding of the larger terminal coefficients on each addend in the

transition state.[6] For the reaction of 2-ethoxybutadiene and methyl acrylate, a "normal" electron-demand Diels-Alder reaction, the principal interaction in the transition state is HOMO (diene) - LUMO (dienophile). The coefficients for this interaction have been calculated by Anh *et al.*[7] and are shown in Figure 4a. Thus, according to FMO theory, it follows that the "*para*" adduct is preferentially formed (Figure 4b).

a b

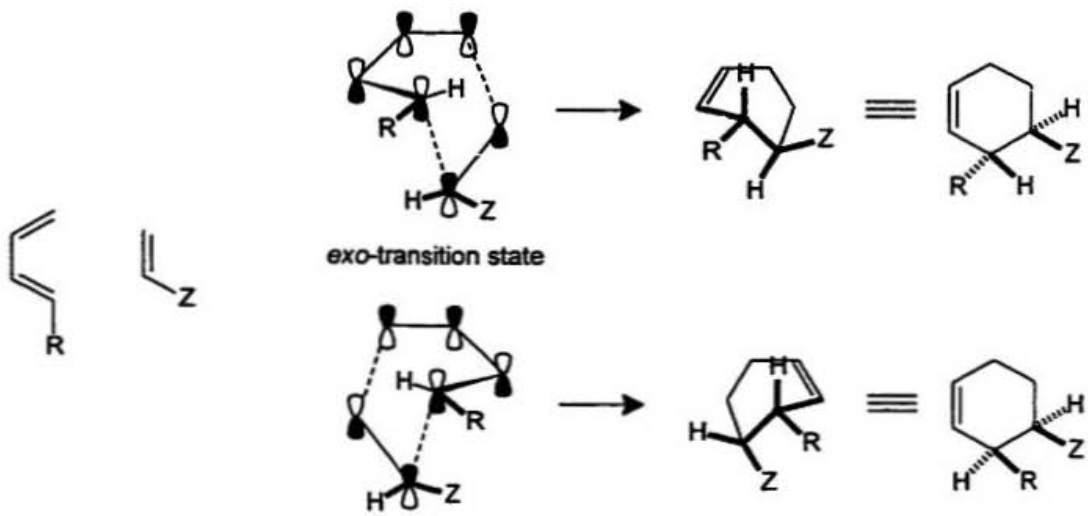
Figure 4. a) Coefficients of the frontier orbitals of 2-ethoxybutadiene and methyl acrylate, and b) preferential overlap of HOMO-LUMO orbitals.

Diels-Alder reactions may result in the formation of as many as four new stereogenic centers. Since the Diels-Alder reaction is highly stereoselective, this accounts for its widespread application in the synthesis of complex natural products. Stereoselectivity is the result of several factors during the cycloaddition. Alder and Stein[8] first observed that the relative configuration of the reactants is conserved in the Diels-Alder adducts and later named this the "*cis* principle." This observation is the result of suprafacial addition of the diene onto the dienophile, and *vice versa*. For example, dimethyl maleate and dimethyl fumarate will react with butadiene to give a cyclohexene product having *cis*- and *trans*-ester functionalities, respectively (Scheme 5).



Scheme 5. Diels-Alder reaction of butadiene with dimethyl maleate and dimethyl fumarate.

For Diels-Alder reactions of unsymmetrical dienes and dienophiles, there are two (racemic) diastereomeric transition states possible, resulting in the corresponding (racemic) diastereomeric products, referred to as the *endo*- and *exo*-adducts (Scheme 6).



Scheme 6. *Endo*- and *exo*-adducts resulting from the Diels-Alder reaction of unsymmetrical addends.

The *endo* transition state usually involves more steric interactions. However, in most Diels-Alder reactions it leads to the major, if not exclusive, product under kinetic conditions. This observation has been attributed to secondary orbital interactions, which stabilize the *endo* mode of addition (Figure 5).

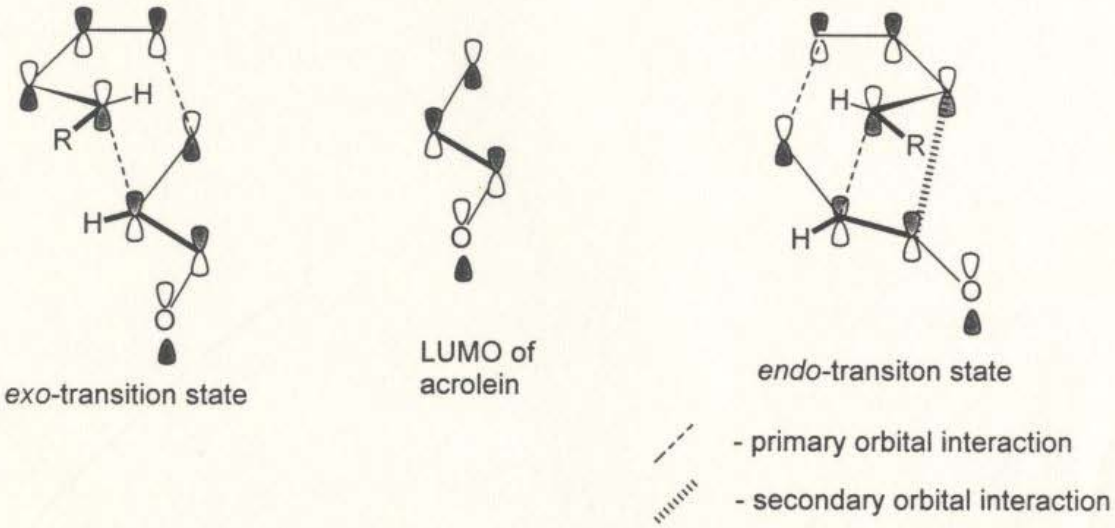


Figure 5. Secondary orbital interactions in the *endo* transition state.

Another aspect of stereoselectivity occurs when the two faces of the diene and/or dienophile are non-equivalent. Cycloaddition may take place preferentially on one face rather than the other. This is referred to as π-facial diastereoselectivity, and the two modes of attack are called *syn*- and *anti*-addition. These terms are used in a relative sense, as illustrated in Figure 6. For the R-substituted cyclopentadiene, the addition of a dienophile to the top face of the diene is considered *syn* to R, whereas the addition of a dienophile to the bottom face of the diene would be considered *anti* to R. This terminology is also applicable for additions to plane-nonsymmetric dienophiles. For the

disubstituted cyclopentenedione shown in Figure 6, addition of a diene to this dienophile can be either *syn* to R_2 or *anti* to R_2.

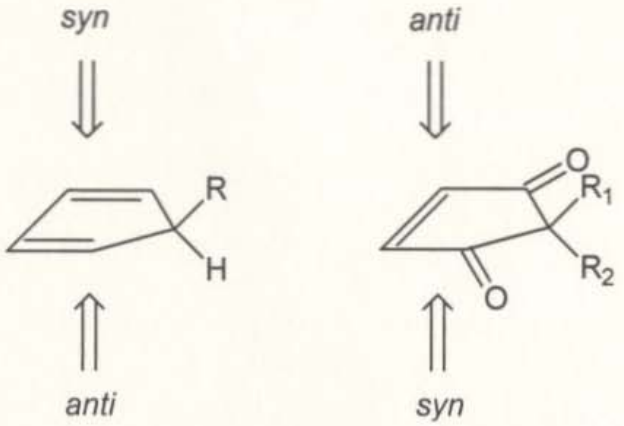


Figure 6. *Syn*- and *anti*-addition to a R-substituted cyclopentadiene and a disubstituted cyclopentenedione.

The first example of the dramatic acceleration of Diels-Alder reactions by catalysis was reported by Yates and Eaton in 1960.[9] Since then, Lewis acid catalyzed Diels-Alder reactions have become increasingly popular, allowing access to adducts using much milder conditions and involving dienophiles of low reactivity. Furthermore, Diels-Alder reactions catalyzed by Lewis acids are not only faster, but tend to be more regioselective and *endo*-selective compared with the non-catalyzed equivalent. For example, reaction of *trans*-1,3-pentadiene and methyl acrylate gave a 9 : 1 *ortho*/*meta* ratio in the absence of catalysis; this increased to 49 : 1 when aluminum trichloride was present.[10] These observations have subsequently been explained using FMO theory.[3a, 11] The increased rate and regioselectivity are due to coordination of the Lewis acid with the electron-withdrawing group of the dienophile, resulting in a net lowering of

II. Asymmetric Diels-Alder Reactions of Chiral Acetylenedicarboxylates.

If at least one of the Diels-Alder components (diene, dienophile or catalyst) is chiral, the possibility of asymmetric induction exists. For the unsymmetrical addends shown in Scheme 6, the absolute configuration of C-1 and C-2 depends on which faces of the diene and dienophile react during the reaction. Ultimately, there are four possible stereoisomeric products, as shown in Figure 7.

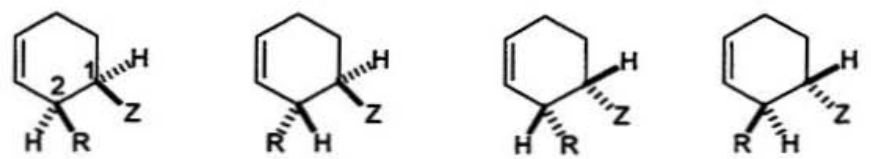
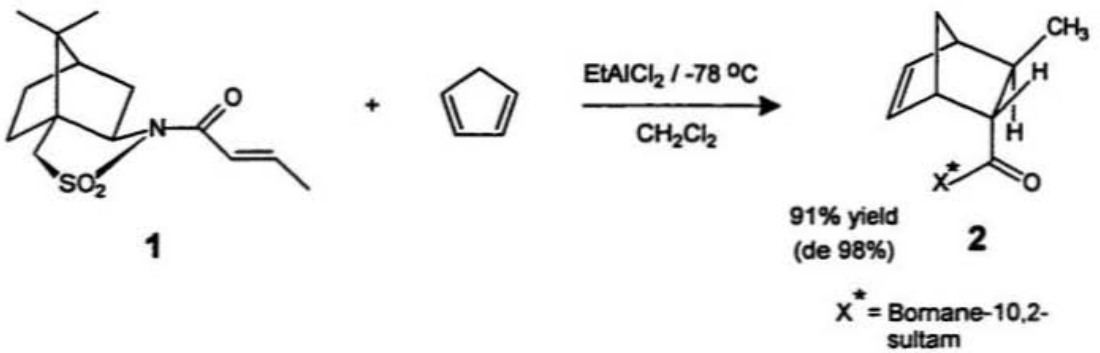


Figure 7. Four possible stereoisomeric products from the Diels-Alder reaction of two unsymmetrical addends.

If either the diene or dienophile shows high facial selectivity, one of the four possible *exo-endo* pairs will predominate. Furthermore, most Diels-Alder reactions give a predominance of the *endo*-product, especially under conditions of catalysis by a Lewis acid. Thus, it is likely that only one of these four products would predominate, resulting in an asymmetric bias.

The vast majority of examples of asymmetric Diels-Alder reactions have so far involved chiral dienophiles.[12] In fact, Koralev and Mur[13] first demonstrated the possibility of asymmetric induction in the Diels-Alder reaction by reacting

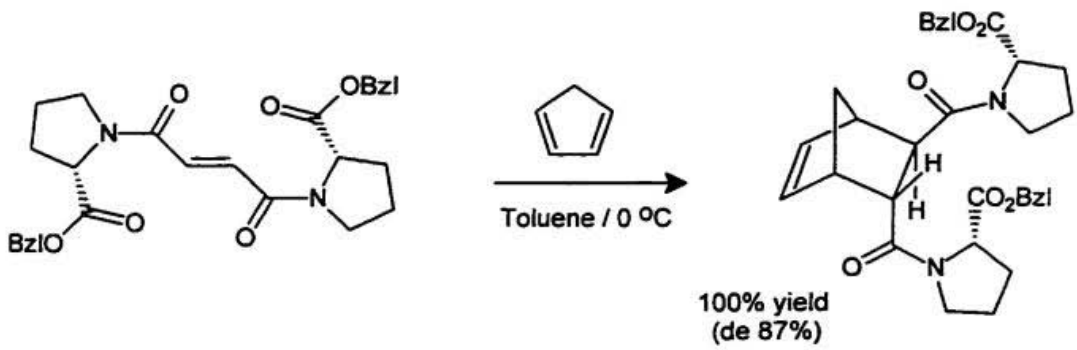
(-)-di-(*R*)-menthyl fumarate with isoprene. Most chiral dienophiles include a chiral auxiliary attached to the dienophile through an ester or amide linkage, allowing for both ease of synthesis and subsequent removal of the auxiliary. The most successful auxiliaries include menthol derivatives, camphor derivatives and oxazolidiones, with the best optical yields generally occurring in the presence of a Lewis acid. One example of the high asymmetric induction attainable for asymmetric Diels-Alder reactions using chiral dienophiles is shown in Scheme 7. Reaction of the camphor-derived sultam **1** with cyclopentadiene in the presence of ethylaluminum dichloride gave **2** in 98% diastereomeric excess (de).[14]



Scheme 7. Asymmetric Diels-Alder reaction of cyclopentadiene with *N*-enoylsultam **1**.[14]

Symmetry has also been used to advantage within chiral dienophiles to enhance stereoselection. Chiral fumarate esters such as **3** have been shown to give high diastereoselectivity,[15, 16] even in the absence of a Lewis acid catalyst. This phenomenon is referred to as the cooperative blocking effect. The

increased diastereoselectivity is a consequence of both auxiliaries directing the diene to the same face of the dienophile. In **3**, the (*S*)-proline benzyl esters have been found to adopt the configuration shown (Scheme 8),[15] with both benzyl esters blocking the *si*-face of the dienophile. Thus, attack of cyclopentadiene is directed preferentially to the *re*-face. Reaction of the acrylate equivalent of **3** with cyclopentadiene under identical conditions gave only 62% diastereoselectivity.[15]

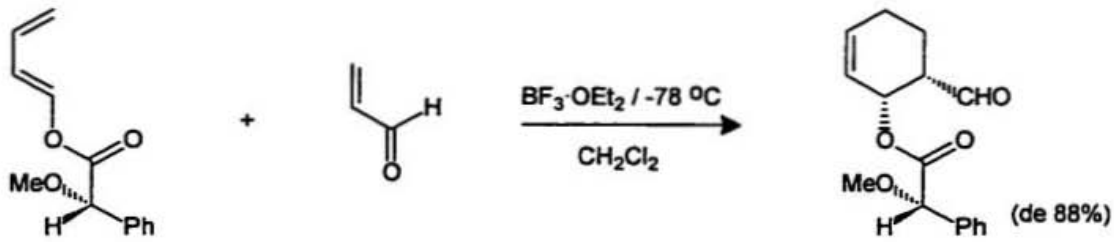


3 **4**

Scheme 8. Increased asymmetric induction by cooperative blocking groups.[15]

There have been fewer examples using chiral dienes than chiral dienophiles. The incorporation of chiral substituents into dienes is not straightforward since most dienes are electron-rich and contain no carbonyl groups for convenient linkages. In most cases, chiral groups have been attached to the diene via an oxygen. This has resulted in problems with diene synthesis as well as difficulties in cleavage of the resulting ethers. The

development of chiral dienes as an integral part of asymmetric Diels-Alder reactions has also been limited by the disappointing diastereoselectivities obtained in many examples. A diene which has given satisfactory results was **5** (Scheme 9),[17] first synthesized by Trost.[18]



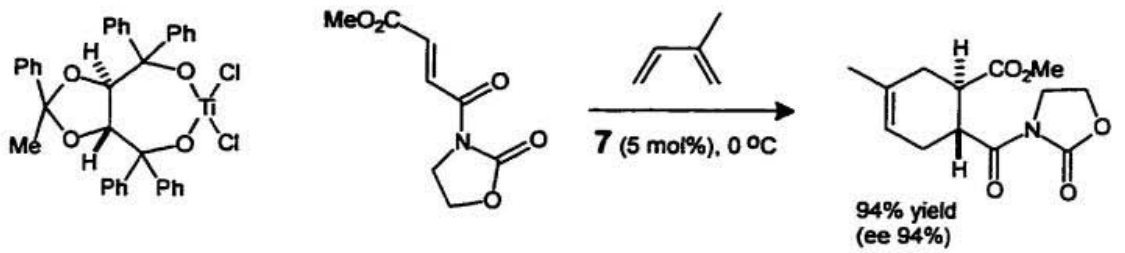
5 **6**

Scheme 9. Asymmetric Diels-Alder reaction of diene **5** with acrolein.[17]

In the past several years, the most popular approach to asymmetric Diels-Alder reactions was to use chiral catalysts, mainly in the form of Lewis acids. Since the diene and dienophile do not require the addition of any chiral groups, steps required to add and remove the chiral auxiliaries are eliminated. Chiral Lewis acid complexes of aluminum, titanium and boron have yielded the best results. For example, the chiral titanium(IV) complex **7**, shown in Scheme 10, was used in the asymmetric Diels-Alder reaction of **8** with isoprene to yield **9** in high enantiomeric excess (ee).[19]

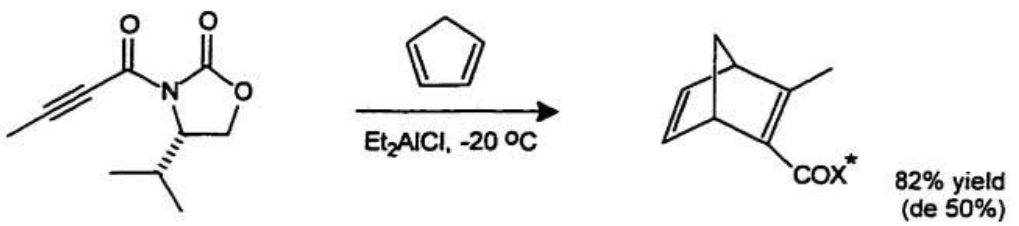
Unlike ethylenic dienophiles, acetylenic dienophiles have been little investigated in asymmetric Diels-Alder reactions. Evans reported an example of

an asymmetric Diels-Alder reaction involving acetylenic imide **10** and cyclopentadiene under Lewis acid conditions to yield **11** in 50% de (Scheme 11).[20]



7 **8** **9**

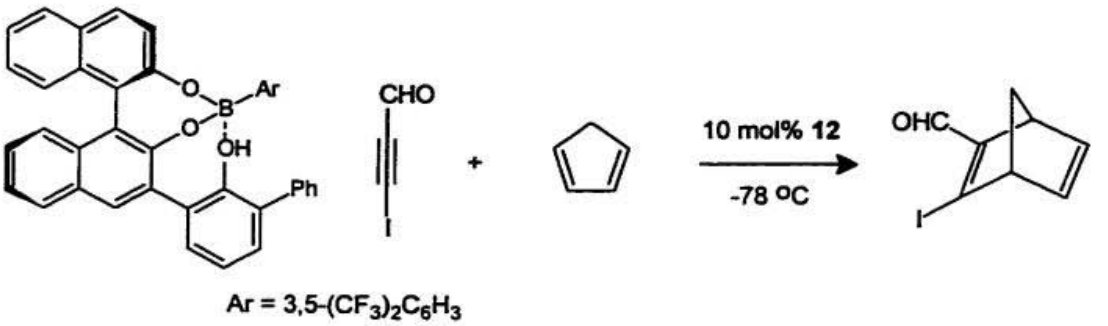
Scheme 10. An example of an asymmetric Diels-Alder reaction utilizing a chiral titanium complex as a catalyst.[19]



10 **11**

Scheme 11. Asymmetric Diels-Alder reaction of chiral imide **10** with cyclopentadiene.[20]

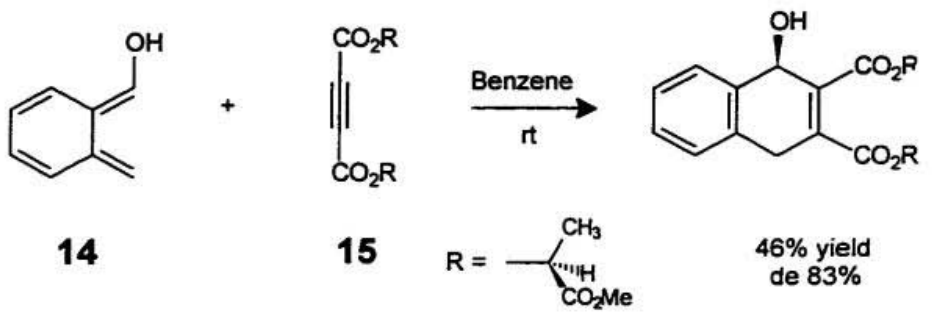
Very recently, Yamamoto reported enantioselective catalytic Diels-Alder reactions of cyclohexadiene and cyclopentadiene with several acetylenic aldehydes.[21] Excellent enantioselectivities were obtained in several examples. Reaction of 3-iodopropynal with cyclopentadiene in the presence of the chiral boron complex **12** gave **13** in good yield with an 81% ee (Scheme 12).[21]



Ar = 3,5-$(CF_3)_2C_6H_3$

12 **13**

Scheme 12. Example of an asymmetric Diels-Alder reaction involving an acetylenic aldehyde in the presence of a chiral catalyst.[21]



14 **15**

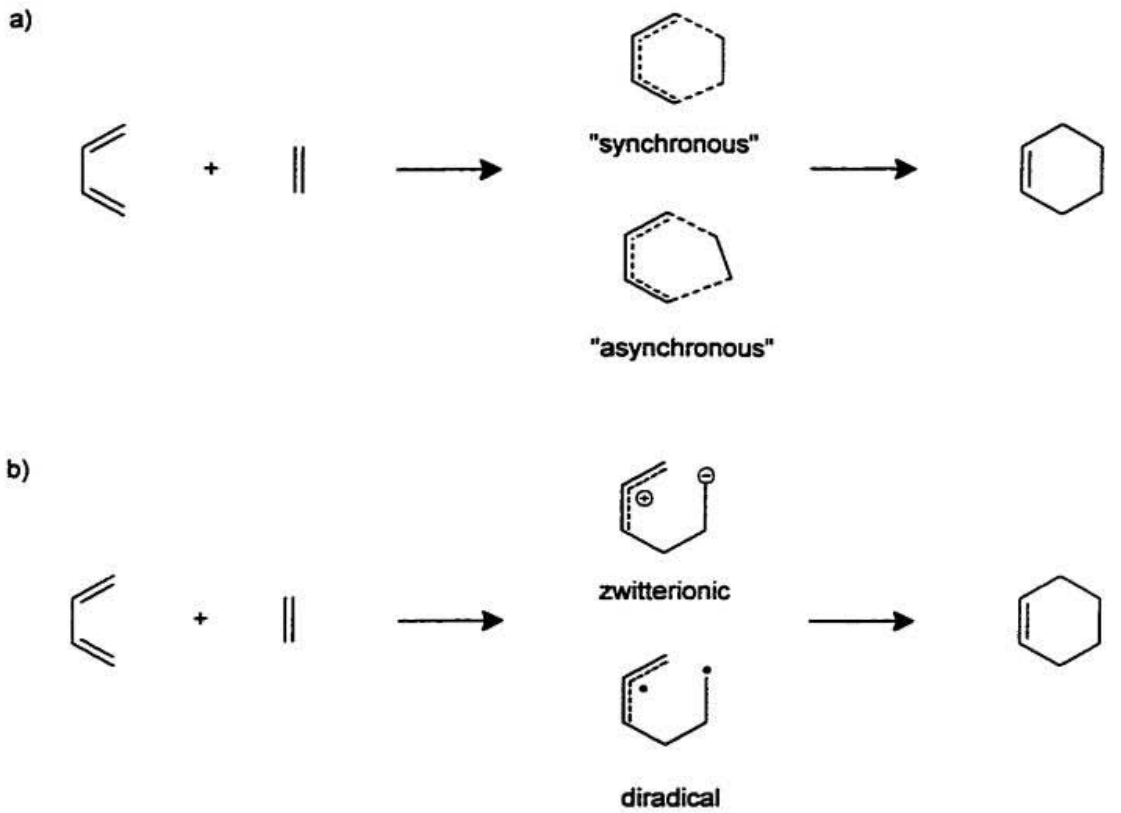
Scheme 13. Asymmetric Diels-Alder reaction of chiral acetylenedicarboxylate **15** with *o*-QDM **14**.[22]

As part of an investigation of aryltetralins, Charlton reported asymmetric Diels-Alder reactions of chiral bis(methyl (*S*)-lactyl) acetylenedicarboxylate (**15**) with various orthoquinodimethanes (*o*-QDM's), phenylbutadiene and an isobenzofuran.[22] The observed diastereoselectivities varied, with ratios of diastereomers ranging from 1 : 1.2 to 1 : 5. The most highly diastereoselective example involved α-hydroxy-*o*-QDM (**14**) shown in Scheme 13, for which

hydrogen-bonding in the transition state was possible. To date, these have been the only studies using chiral acetylenedicarboxylates in asymmetric Diels-Alder reactions.

III. Mechanism of the Diels-Alder Reaction

The mechanism of the Diels-Alder reaction has been debated for over fifty years. A great deal of investigation has been done to unlock the nature of the transition state(s) involved.[2, 23] For a Diels-Alder reaction, the formation of the two new σ bonds may take place in either a concerted or a stepwise fashion, as shown in Scheme 14.

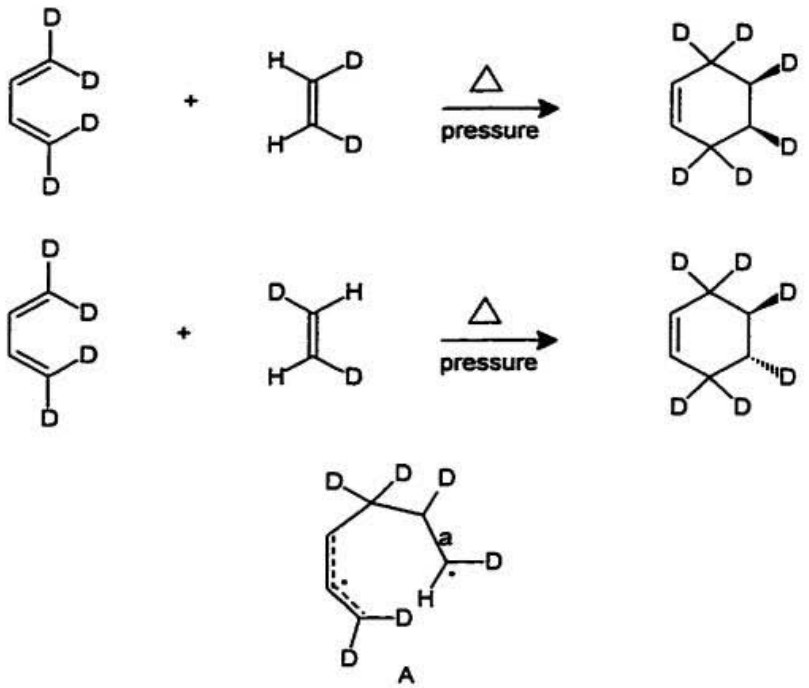


Scheme 14. Possible mechanisms for a Diels-Alder reaction: a) one-step concerted pathway; b) two-step pathway.

For the concerted pathway, both new bonds would be partially formed in a single transition state. If the two bonds are formed to exactly the same extent, it is considered a symmetrical (synchronous) transition state. If one of the new σ bonds is formed to a greater extent than the other, it is referred to as a unsymmetrical (asynchronous) transition state. The stepwise pathway involves the formation of an intermediate having only one of the two new bonds formed. This intermediate could either be diradical or zwitterionic in nature. Subsequently, the second bond is formed to yield the adduct. Thus, the mechanism would involve two kinetically distinct steps.

The first transition state proposal for the Diels-Alder reaction was by Wasserman[24] in 1935. He carried out thermodynamic and kinetic studies of benzoquinone and cyclopentadiene. From this work, he proposed that the dienophile addition to cyclopentadiene was concerted, and that the bond lengths in the transition state should be not much longer than 2.0 Å.[24] Shortly afterwards, Littman proposed diradicals as intermediates in the Diels-Alder reaction.[25] For the next fifty years there was fierce disagreement as to which of these two proposed mechanisms was correct. Sauer and Sustmann[2] sum up the struggle between those who supported the concerted mechanism and those who supported the stepwise mechanism. They state, "Very often, however, and not only in the case of Diels-Alder reactions, one is succumbed to the danger of trying to interpret all reactions of a given type in a uniform way." The modern view holds that there is no mechanism which can be used in exclusivity to

explain all the Diels-Alder cycloadditions. However, the consensus is that most thermal Diels-Alder reactions take place via a concerted, if often an asynchronous, mechanism.



Scheme 15. Diels-Alder reaction of d_4-butadiene with *cis*- and *trans*-dideutereoethylene.[26]

This is supported by several factors, including the *syn* stereospecificity of the Diels-Alder reaction. Addition of dimethyl maleate and dimethyl fumarate to butadiene always results in the *cis*- and *trans*-substituted products, respectively. If the reaction occurred via a stepwise mechanism, it would result in stereochemical scrambling, unless the diradical or zwitterionic intermediate proceeds to product faster than rotation can occur. This possibility was ruled out

for the prototype Diels-Alder reaction of butadiene and ethylene through an elegant study by Houk *et al.*[25] Reaction of 1,1,4,4-tetradeuteriobutadiene with *cis*- and *trans*-dideuterioethylene resulted in the exclusive formation of the *cis*- and *trans*-adducts, respectively (Scheme 15). The potential diradical intermediate A shown in Scheme 15 would have a very low barrier of rotation about bond a. It would be on the order of 0-0.4 kcal/mol.[26] Even if the barrier to cyclization of the diradical were negligible, a mixture of products would have resulted.

Further evidence supporting the concerted nature of the Diels-Alder reaction resulted from asymmetric Diels-Alder reactions carried out by Tolbert and Ali.[27, 28] They attempted to probe Diels-Alder transition state geometry by determining the amount of asymmetric induction resulting from the cycloaddition of dialkyl fumarates containing one or two chiral auxiliary groups with diphenylisobenzofuran and anthracene (Table 1). If the concerted mechanism were operating, the asymmetric induction achieved when two chiral groups are present should be the arithmetic product of that induced when only one chiral group acts independently.

If the mechanism is not concerted, the two chiral groups are in different environments with respect to the new σ bonds, with only one of the groups attached to a bond-forming center in the transition state. Thus, the asymmetric induction due to one chiral group would be greater than that for the other and their results would no longer be additive. The experiments indicated a concerted

mechanism. For example, the diastereomeric ratio obtained for the reaction of methyl *l*-bornyl fumarate with anthracene was 1.25 : 1.[28] Therefore, the predicted asymmetric induction of di-*l*-bornyl fumarate was $(1.25)^2$: 1 (i.e., 1.56 : 1). The diastereomeric ratio of 1.53 produced was within experimental error of the value predicted. The uncatalyzed Diels-Alder reaction was said to exhibit cooperativity in asymmetric induction, indicating that it must take place by a synchronous mechanism. However, this trend was not followed in the presence of Lewis acids. Tolbert and Ali interpreted this observation as an indication of a transition state that was unsymmetrical or asynchronous.[28] However, Konovalov and Kiselev[29] interpreted the catalyzed reaction differently. They reasoned that in a catalyzed reaction one ester group is complexed with aluminum chloride, thus, the other free ester group could no longer be considered equivalent. Therefore, the initial condition for cooperativity of the effect is not fulfilled.

Table 1. Diastereomeric ratios for addition of dialkyl fumarates to anthracene and diphenylisobenzofuran.[27, 28]

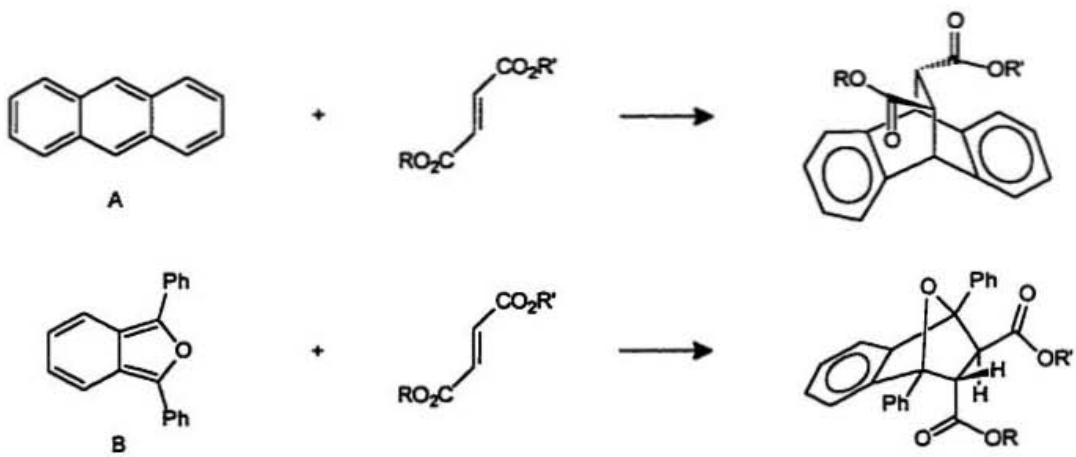


Table 1, cont'd.

Diene	R	R'	diastereomeric ratio
A	Me	Me	1
A	Me	*l*-bornyl	1.25
A	*l*-bornyl	*l*-bornyl	1.53 [1.56[a]]
A	Me	*l*-menthyl	1.18
A	*l*-menthyl	*l*-menthyl	1.36 [1.39[a]]
B	Me	Me	1
B	Me	*l*-bornyl	1.41 (exo)
B	*l*-bornyl	Me	1.53 (endo)
B	*l*-bornyl	*l*-bornyl	2.08 [2.16[a]]

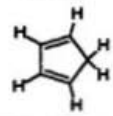
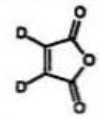
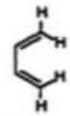
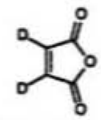
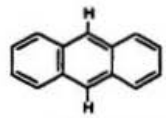
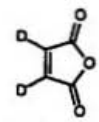
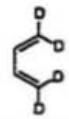
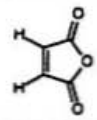
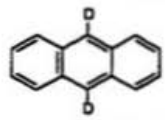
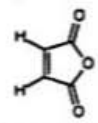
[a] Numbers in brackets represent predicted ratios based on additivity.

KIE's have also been used extensively for elucidating the reaction mechanism of the Diels-Alder reaction.[30] Molecules which differ only in isotopic substitution move along the same potential energy surface. The isotope effect observed for a given reaction is determined by this single potential energy surface, consequently providing a probe as to the nature of a particular transition state. KIE's can be divided into two general types, primary and secondary. A primary KIE can be seen when bonds to an isotopic atom(s) are formed and/or broken in the course of a reaction and secondary KIE's are said to be involved if no bonds to the isotopic atom(s) are formed or broken in the rate-determining

step of a reaction. Secondary KIE's are often only observed when there is some force-constant change between reactant and transition state involving the isotopically substituted position. For example, this could include a change of bond type, such as a change in hybridization or it could involve some change in the spatial environment around the isotopic atom. The Diels-Alder reaction involves a change in hybridization of the four bonding atoms from sp^2 to sp^3 as the reaction proceeds. Therefore, it is well suited for study using these secondary KIE's. Secondary KIE's are usually determined by direct rate measurements on labeled substrates, however, it is possible to measure them at natural abundance. Competitive methods between labeled and unlabeled substrates were often used if the desired precision could not be achieved, especially in the earlier studies.

Van Sickle[31] first reported the use of secondary KIE's to study the Diels-Alder reaction of cyclopentadiene and maleic anhydride. Cyclopentadiene was reacted with a mixture of d_0- and d_2-maleic anhydride of known composition. A small inverse KIE with an average value of 0.943 was obtained for k_H/k_D.[31] Rodin and Van Sickle[32] extended this work by carrying out several other Diels-Alder reactions with the symmetrical addends shown in Table 2.

Table 2. k_H/k_D values for Diels-Alder reactions of various symmetric dienes and dienophiles corrected to 25 °C.[32]

Diene	Dienophile	k_H/k_D (per deuterium)
		0.971
		1.00
		0.952
		0.935
		0.943

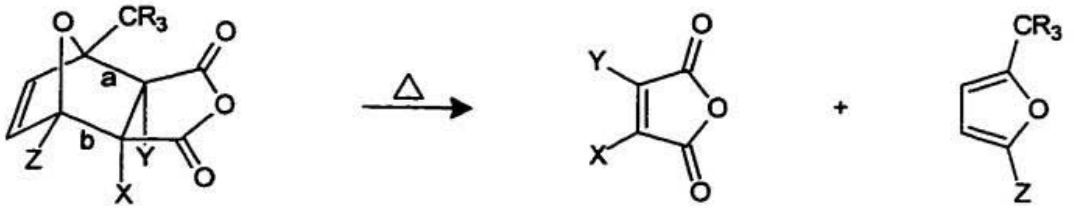
The KIE's were calculated using the equation,

$$\frac{k_H}{k_D} = \frac{\log (a_H / a_H{}^o)}{\log (a_D / a_D{}^o)}$$

$a_H{}^o$ - initial concentration of protio reactant
$a_D{}^o$ - initial concentration of deuterio reactant
a_H - amount remaining after partial reaction completion
a_D - amount remaining after partial reaction completion

An average value for the isotope effect was calculated, corrected to 25 °C, on a per deuterium basis. These small inverse KIE values supported an early Diels-Alder transition state, which is very much like the reactants in nature.

Seltzer followed this work up with a very comprehensive study of the *retro*-Diels-Alder reaction of **16**, derived from 2-methylfuran and maleic anhydride (Scheme 16).[33]



16

a) X = Y = Z = R = H
b) X = Y = D, R = Z = H
c) Z = D, X = Y = R = H
d) X = D, Y = Z = R = H
e) Y = D, X = Z = R = H
f) R = D, X = Y = Z = H

Scheme 16. *Retro*-Diels-Alder reactions of the adducts derived from various deuterated 2-methylfuran and maleic anhydride derivatives.

Six different isomers, having deuterium at various positions, were synthesized and the relative isotopic rates determined.[33]

$$k_a/k_b = 1.16 \pm 0.01$$

$$k_a/k_c = 1.08 \pm 0.01$$

$$k_a/k_f = 1.03 \pm 0.01$$

$$k_d/k_e = 1.00 \pm 0.04$$

The isotopic rate ratio for k_a/k_b was consistent with either a stepwise decomposition (the second step being rapid) with a k_H/k_D of 1.16 for one deuterium atom or a concerted mechanism with an average k_H/k_D of 1.08 per deuterium atom. A k_a/k_c of 1.08 indicates that bond b must be breaking in the

rate determining step. However, the reaction could not be a slow rupture of bond b followed by a fast rupture of bond a because the isotopic rate ratio for k_d/k_e would be much less than the value of 1.00 obtained. This narrowed the possible mechanisms to a stepwise cleavage with an equal probability of bond a or bond b breaking in the rate determining step, followed by fast cleavage of the other bond, or a concerted mechanism with partial cleavage of both bond a and bond b. Seltzer attempted to distinguish between these by deuterating the methyl substituent and studying the effect. The rate ratio for k_a/k_f was interpreted as being too small for a stepwise pathway because a radical on the carbon attached to the methyl should result in much larger secondary KIE's. The Diels-Alder reaction of the slightly unsymmetrical diene, 2-methylfuran, with the symmetrical dienophile, maleic anhydride was found to be consistent with a concerted mechanism, however no conclusions about synchroneity of the reaction were made using these techniques.[33]

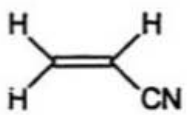
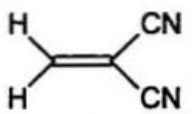
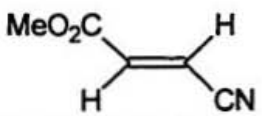
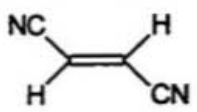
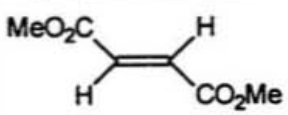
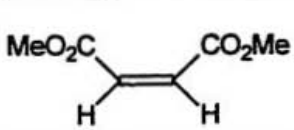
Gajewski *et al.*[34] studied secondary KIE's for the Diels-Alder reactions of isoprene with a variety of dienophiles. They reported KIE's for the Diels-Alder reactions of d_0-, d_2- and d_4-isoprene with a variety of dienophiles. Unlike previous studies, the dienophiles used ranged from symmetrical to very unsymmetrical in type (Table 3). Acrylonitrile reacts with isoprene to give a 3 : 7 mixture of regioisomers. In both cases, the KIE at the α site of acrylonitrile was very small, indicating very weak bond formation. The inverse KIE's at the β site were only half of the maximum value expected, indicating that the transition state

did not have a fully formed bond, therefore was not a diradical. The results suggested an early unsymmetrical transition state. With the more unsymmetrical dienophile, 1,1-dicyanoethene, the results were similar, but a little more extreme. The KIE's at the β site of 1,1-dicyanoethene were half to three-quarters of the maximum, indicating an even more asynchronous transition state, which was approaching a diradical in nature. For the symmetrical or nearly symmetrical dienophiles the KIE's at both C-1 and C-4 of the diene were between one-quarter and one-half of the maximum value expected. Gajewski concluded this was consistent with a nearly synchronous, concerted pathway. However, the possibility of a synchronous transition state was within the limits of experimental error.

A novel study of secondary KIE's in the Diels-Alder reaction was recently reported by Singleton *et al.*[35] Instead of determining KIE's via competition studies of isotopically labeled and unlabeled materials, Singleton determined KIE's for a Diels-Alder reaction at natural abundance. As reactions proceed, the starting materials become enriched in the isotopically slower-reacting components. When the reaction approaches completion, the small KIE's become magnified. Recovery and NMR analysis of the unreacted starting material gave KIE's with high certainty. The methyl group of isoprene was used as the "internal standard" and assumed to have a KIE of 1.00. Analysis of the reacting centers of the diene, positions 1 and 4, revealed that the proportion of ^{13}C increased and the proportion of deuterium decreased (Figure 8). The KIE's

for the non-reacting centres, C_2, C_3 and H_3 were very small, as was expected. Singleton concluded that the results were in line with a concerted mechanism, however, pronounced KIE differences for ^2H substitution on C_1 over C_4 indicated some asynchronicity in bond formation to C_1 *versus* C_4 at the transition state.

Table 3. Diels-Alder reaction of d_0-,d_2- and d_4-isoprene with a variety of symmetric and unsymmetric dienophiles.[34]

Dienophile	Product Regioisomer	d_0/1,1-d_2	d_0/4,4-d_2	Max. expected (Temp. - °C)
	5-cyano	1 / 1.02	1 / 1.10	1.22 (100)
	4-cyano	1 / 1.13	1 / 0.99	
	5,5-dicyano	1 / 1.02	1 / 1.26	1.35 (25)
	4,4-dicyano	1 / 1.28	1 / 0.98	
	isomer 1	1 / 1.09	1 / 1.14	1.35 (25)
	isomer 2	1 / 1.11	1 / 1.12	
		1 / 1.05	1 / 1.05	1.22 (100)
		1 / 1.13	1 / 1.08	1.35 (25)
		1 / 1.09	1 / 1.05	1.22 (100)

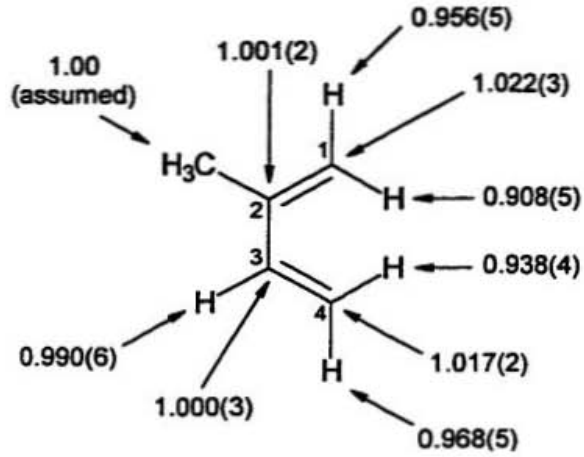
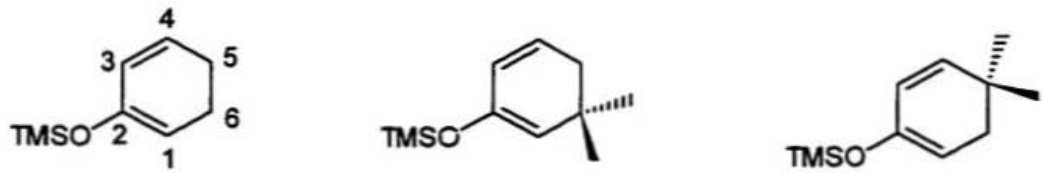


Figure 8. ^{2}H and ^{13}C KIE's for recovered isoprene, with standard deviations in parentheses.[35]

Liu[36] also attempted to study the degree of asynchronicity in the transition state of the uncatalyzed Diels-Alder reaction. The relative reaction rates of dienes **17a-c** (Figure 9) were determined competitively with various symmetrical dienophiles.

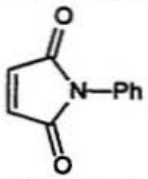
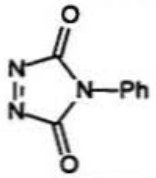
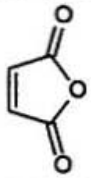
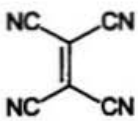


17a **17b** **17c**

Figure 9. Trimethylsilyloxy dienes used in rate studies.

If the Diels-Alder reaction were asynchronous, carbon 1 should be the site of the shorter incipient bond. Therefore, it was theorized that **17b** should react slower than **17c** due to a steric interaction with one of the methyl groups.

Table 4.[36] Ratios of reaction rates determined by competitive experiments for Diels-Alder reactions of dienes **17a-c** with various dienophiles.[a]

entry	dienophile	reaction conditions	relative rate ratios		
			17b : 17c	**17a : 17b**	**17a : 17c**
1		benzene 30 h reflux	(2 : 1)	9 : 1	18 : 1
2		benzene 30 min rt	1.5 : 1	1.1 : 1	1.6 : 1
3		benzene 30 h reflux	(2.3 : 1)	7 : 1	16 : 1
4		benzene 16 h reflux	1 : 1	(27 : 1)	27 : 1
5		benzene 48 h reflux	(11 : 1)	2.3 : 1	25 : 1
6		chloroform 10 min rt	(1 : 4.6)	55 : 1	12 : 1

[a] Ratios in parentheses are derived from the other two results with the same dienophile.

If this steric interaction is not affecting the rate, then one or both of these dienes should react at least with the same rate as **17a**. The results of the comparative rate study are given in Table 4.

For all the dienophiles, excluding *N*-phenyl-1,2,4-triazoline-1,3-dione (PTAD), the cycloadditions of diene **17a** proceeded much faster than those of dienes **17b** and **17c**, indicating there is steric repulsion present in the transition state. The similar rates of reaction of all three dienes with PTAD were rationalized by Liu by considering the Reactivity-Selectivity Principle.[37] It states that the selectivity of a species varies inversely with its reactivity. Since triazolinediones are among the most reactive dienophiles known, the lack of selectivity was not surprising. Tetracyanoethylene reacted with **17c** quite a bit faster than with **17b** indicating the transition state was very unsymmetrical (asynchronous) and that the reaction could have occurred by a different mechanism. The other ethylenic dienophiles had similar relative rates of reaction with dienes **17b** and **17c**. This was consistent with a synchronous or nearly synchronous transition state.

The results for the acetylenic dienophile, diethyl acetylenedicarboxylate, differed substantially from the ethylenic dienophiles in that dienes **17a** and **17b** reacted at similar rates. Furthermore, **17b** reacted faster than **17c**. As mentioned previously, if the transition state were asynchronous, **17c** should have reacted faster. This suggested that the transition state is asynchronous, but

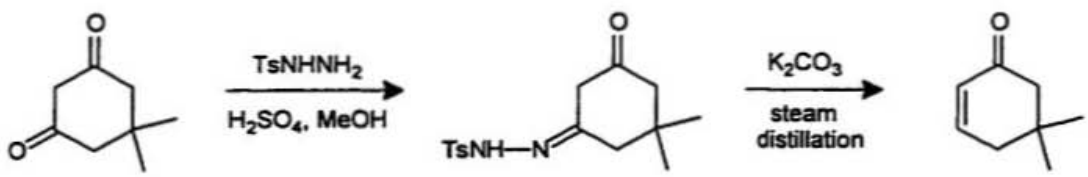
tipped in the opposite direction to tetracyanoethylene, with carbon 4 being the site of the shorter incipient bond! However, the results could still be rationalized two ways by a synchronous pathway. The inductive effect of the dimethyl groups of **17b** may complement the activating effect of the trimethylsiloxy group. Thus, with a sterically less demanding dienophile the steric hindrance is balanced by "electronically derived" rate enhancement. The other possibility is that because there is rotational freedom of the carboxyethyl groups, the ester further from the trimethylsiloxy group may adopt a "fixed", parallel-planar conformation to activate the triple bond, whereas the other ester may be more conformationally mobile. It may rotate to avoid unfavourable steric interactions.

If this explanation were correct, one would expect **17c** to be more sensitive to a chiral auxiliary than **17b** because of the steric interaction of the "*para*" plane-parallel ester with a methyl group. Thus, we decided to synthesize several chiral acetylenedicarboxylates. Asymmetric Diels-Alder reactions of these dienophiles with dienes **17a-c** were carried out to further investigate the surprising rate differences observed with diethyl acetylenedicarboxylate. As well, due to the lack of examples of asymmetric Diels-Alder reactions involving chiral acetylenedicarboxylates, reactions with other dienes were investigated.

IV. Results

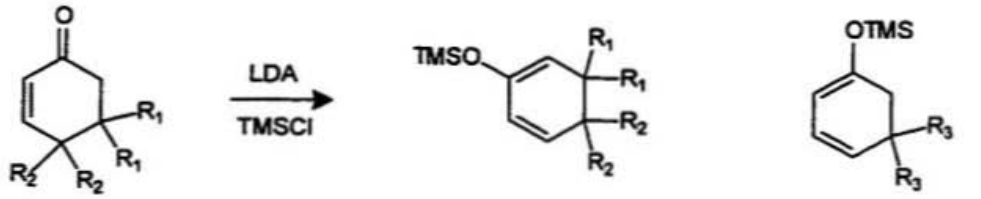
(i). Synthesis of 2-Trimethylsilyl-1,3-cyclohexadienes

Enones **20a-c** were required from which to synthesize the trimethylsilyl dienes for the Diels-Alder reactions with the chiral acetylenedicarboxylates. Of these, only enone **20b** was not commercially available. It was prepared according to Hiegel's procedure[38] via the tosyl hydrazone of 5,5-dimethyl-1,3-cyclohexanedione (Scheme 17). Dienes **17a-c** were prepared according to procedures outlined by Liu[36] (Scheme 18), which involved deprotonation of the required ketones with lithium diisopropylamide (LDA) followed by trapping with chlorotrimethylsilane (TMSCl).[39, 40] Since both kinetic and thermodynamic products are possible for enones **20a** and **20b** that would result in **17a**, **21a** and / or **17b**, **21b** respectively, kinetic conditions were employed. Under these conditions only the desired dienes, **17a** and **17b**, were obtained.



18 **19** **20b**

Scheme 17. Preparation of 5,5-dimethyl-2-cyclohexen-1-one.[38]



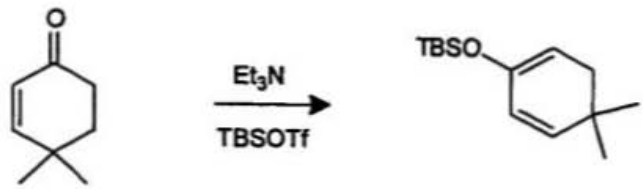
20 **17** **21**

a: $R_1 = R_2 = H$
b: $R_1 = CH_3$, $R_2 = H$
c: $R_1 = H$, $R_2 = CH_3$

a: $R_3 = H$
b: $R_3 = CH_3$

Scheme 18. Synthesis of trimethylsilyl dienes **17a-c**.[36]

Cleavage of the trimethylsilyl group was prevalent if the dienes came in contact with trace amounts of water and/or acid. Therefore, solvents which were used had to be anhydrous and acid-free. The pure dienes, obtained by vacuum distillation, could be stored for several months in the refrigerator (at *ca.* 2-4 °C) under nitrogen.



20c **22**

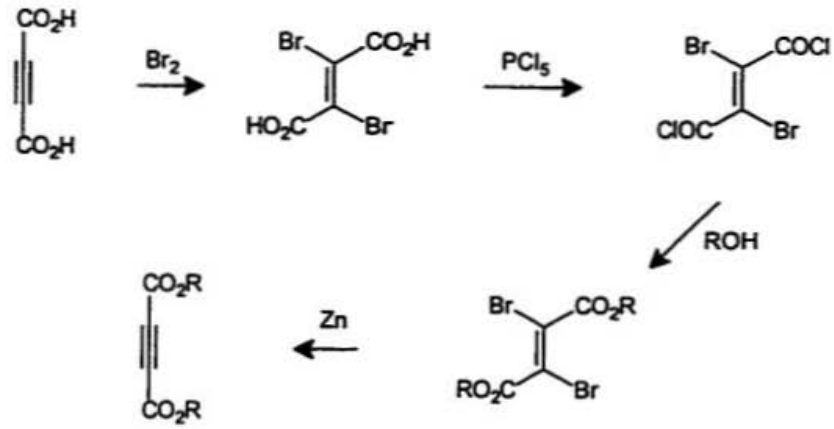
Scheme 19. Synthesis of diene **22** using thermodynamic conditions.

Initially, diene **22** was also prepared in modest yield by deprotonation of **20c** using LDA followed by subsequent trapping with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf). However, **22** was produced more efficiently

by using thermodynamic conditions similar to those described by Danishefsky[41] and Fukumoto.[42] Thus, addition of TBSOTf to a dichloromethane solution of **20c** and triethylamine at 0 °C resulted in complete conversion to **22** in less than thirty minutes (Scheme 19). Initial attempts to purify **22** by flash chromatography led to some product decomposition. However, **22** was obtained in excellent yield by running the crude reaction mixture through a plug of silica gel.

(ii). Synthesis of Chiral Acetylenedicarboxylates

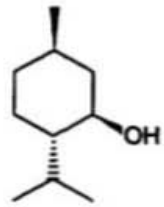
Acetylenedicarboxylates have been commonly used in organic synthesis as dienophiles in intermolecular Diels-Alder reactions. However, the vast majority of examples involve either the dimethyl or diethyl esters. The usual mode of synthesis is by direct esterification of acetylenedicarboxylic acid; however, in some cases addition of the alcohol to the triple bond results in complicated mixtures.[43] In fact, attempts to synthesize diaryl derivatives by way of acid catalysis, by base condensation, and also via acetylenedicarbonyl chloride failed to yield the desired esters in greater than 18% yield.[44] Recently, in an attempt to circumvent this problem, Charlton reported a four-step synthesis of several acetylenedicarboxylates by an indirect route.[22, 45] His approach involved esterification of dibromofumaryl chloride followed by debromination to afford the corresponding acetylenic diesters (Scheme 20).



Scheme 20. Synthesis of acetylenedicarboxylate diesters by way of 2,3-dibromofumaric acid.[45]

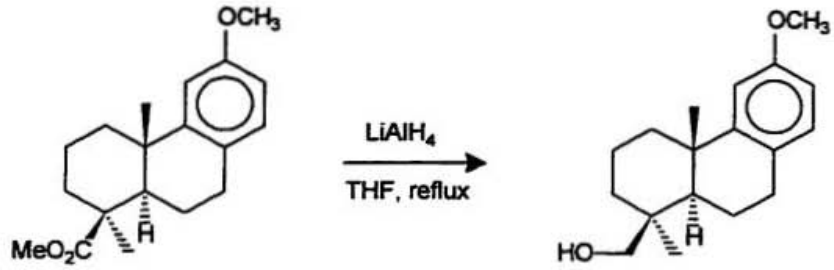
As a result of these synthetic difficulties, only a few chiral acetylenediesters have been reported, including the (-)-menthol[46] and methyl (*S*)-lactate derivatives.[45]

The alcohols that we chose as chiral auxiliaries included (1*R*,2*S*,5*R*)-(-)-menthol (**23**), [(1*S*)-*endo*]-(-)-borneol (**24**), 12-methoxypodocarpa-8,11,13-trien-19-ol (**26**), and (1*R*,2*S*,5*R*)-(-)-8-phenylmenthol (**29**). Compounds **23** and **24** are available commercially (Figure 10). Compound **26** was prepared from methyl *o*-methylpodocarpate (**25**) by reduction of the methyl ester. Reduction using three equivalents of lithium aluminum hydride ($LiAlH_4$) in tetrahydrofuran (THF) proved sluggish at room temperature. The reaction was only about 50% complete after twelve hours. However, smooth conversion of **25** to **26** took place upon heating the reaction mixture to reflux (Scheme 21).



23 **24**

Figure 10. Commercially available chiral auxiliaries.

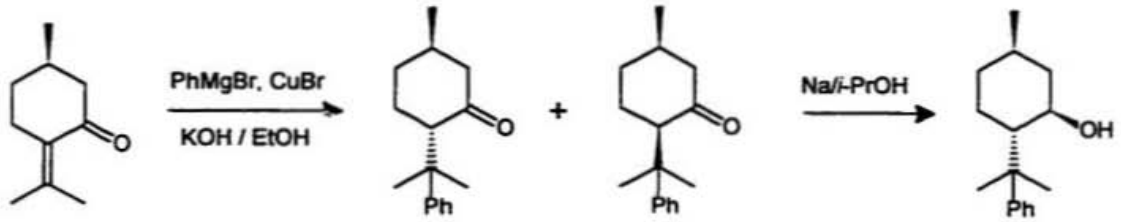


25 **26**

Scheme 21. Reduction of methyl ester **25** to yield chiral auxiliary **26**.

Synthesis of **29** followed procedures outlined by Corey and Ensley[47] and described in depth by Ort.[48] Conjugate addition of phenylmagnesium bromide to (*R*)-(+)-pulegone (**27**) gave the *trans* and the *cis* (1-methyl-1-phenylethyl)-cyclohexanones (**28**) in a ratio of 85 : 15 after equilibration in base (Scheme 22). Flash chromatography of a small portion of this mixture provided homogeneous samples of the epimers and thus permitted complete characterization of both the major (*trans*-**28**) and minor isomers (*cis*-**28**). Following reduction of the ketone mixture by sodium and 2-propanol, the desired alcohol **29**, having chemical shifts

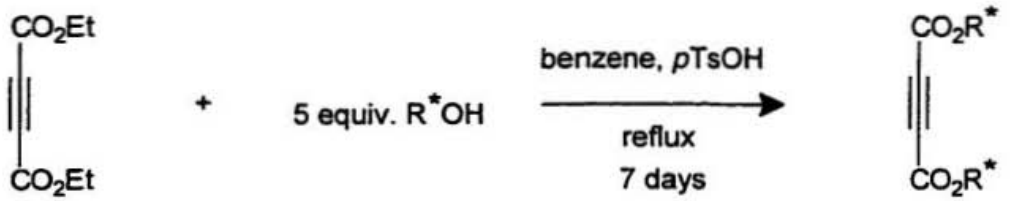
consistent with those reported by Ort,[48] was isolated from a mixture of four diastereomers by careful flash chromatography.



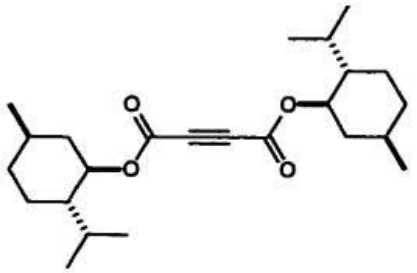
27 *trans*-**28** *cis*-**28** **29**

Scheme 22. Synthesis of (1*R*,2*S*,5*R*)-(-)-8-phenylmenthol (**29**).

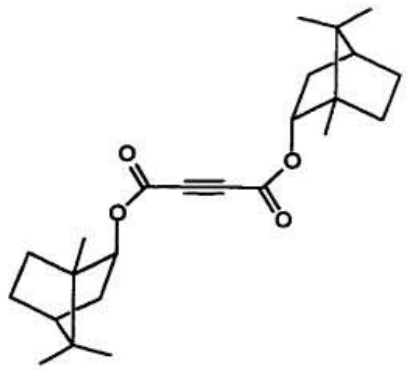
Synthesis of three chiral acetylenediesters was achieved by transesterification of diethyl acetylenedicarboxylate in refluxing benzene with 8 - 10 mol% *p*-toluenesulfonic acid (*p*TsOH) as the acid catalyst (Scheme 23). Reaction of diethyl acetylenedicarboxylate with four or five molar equivalents of **23**, **24** and **26** gave acetylenediesters **30**, **31** and **32**, respectively (Figure 11). The excess alcohol was recovered by flash chromatography and used in subsequent reactions. Under these conditions, optimal yields were obtained after refluxing for about seven days.



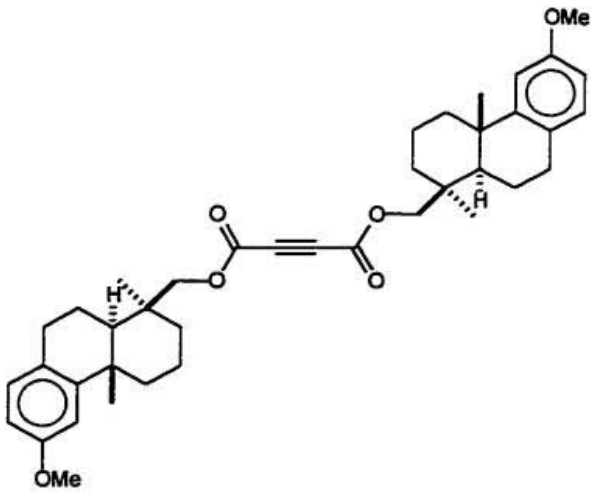
Scheme 23. Synthesis of chiral acetylenedicarboxylates.



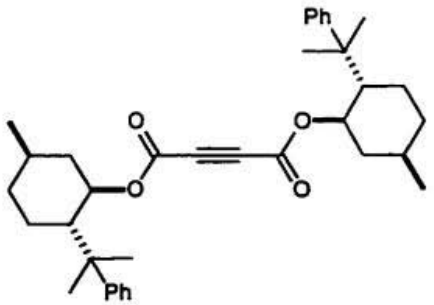
30



31



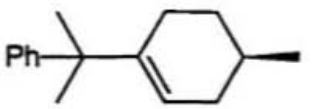
32



33

Figure 11. Chiral acetylene dicarboxylates used in asymmetric Diels-Alder study.

Attempts to synthesize the acetylenediester **33** were not nearly as successful. Reaction of **29** with diethyl acetylenedicarboxylate, utilizing the established conditions, resulted in the appearance of a new non-polar compound, which, according to thin layer chromatography (TLC), seemed consistent with that expected for **33**. However, isolation of this material by flash chromatography provided an impure compound for which the ^{13}C NMR spectrum lacked both the ester and acetylenic signals expected for the product. Unexpected new ^{13}C NMR signals that indicated the presence of a new double bond appeared at δ 144.1 and 119.2. The IR spectrum lacked both an hydroxyl absorption as in **29**, and an ester absorption expected for acetylenedicarboxylate **33**. It was concluded that **29** had slowly dehydrated under the reaction conditions to give **34** as the major product (Figure 12).



34

Figure 12. Reaction byproduct isolated from the attempted transesterification of diethyl acetylenedicarboxylate with **29**.

An attempt was made to synthesize **33** by way of the acetylenedicarbonyl dichloride.[49] Preparation of this dichloride proved problematic since the by-product, phosphorous oxychloride, could not be separated from the desired acid chloride by distillation. Furthermore, efforts to synthesize **33** via Charlton's procedure[22, 45] were also unsuccessful. Attempted transesterification of diethyl

acetylenedicarboxylate by base catalysis using conditions similar to those reported by Decicco,[50] with 4-dimethylaminopyridine (4-DMAP), gave only starting material even after refluxing in benzene for ten days. As well, attempted transesterification using a weaker acid catalyst, oxalic acid, resulted in esterification of the catalyst instead of transesterification of diethyl acetylenedicarboxylate. Ultimately, a low yield of **33** was obtained by heating a benzene solution of **29** and diethyl acetylenedicarboxylate to 70 °C for twelve days with *p*TsOH as the catalyst. Under these conditions, only a small amount of dehydration took place. In fact, nearly 80% of **29** was recovered following reaction at this lower temperature. We conjecture that the addition of the phenyl group to menthol resulted in an increase in the steric hindrance around the alcohol function, compared to **23**, causing the transesterification to be slowed dramatically.

(iii). Asymmetric Diels-Alder Reactions

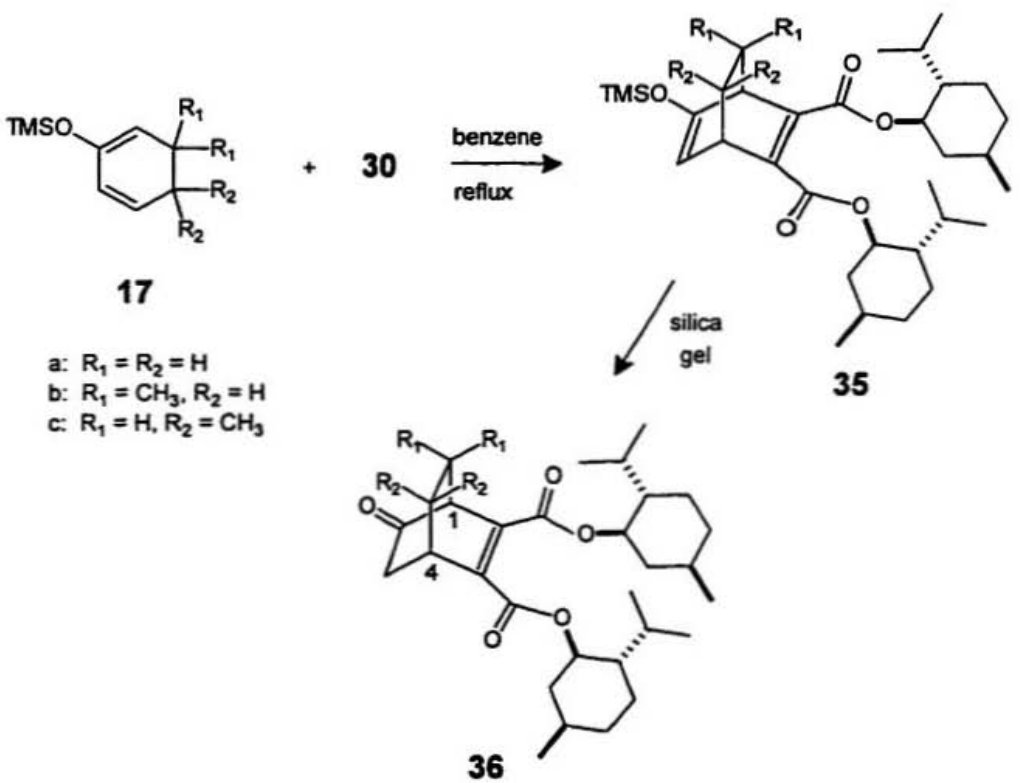
With dienes **17a-c** and several chiral acetylenediesters in hand, Diels-Alder reactions could be carried out, beginning with dienophile **30** (Scheme 24). Reaction of **17a** with an excess of **30** proceeded smoothly to give the expected Diels-Alder adducts **35a**, as a mixture of two inseparable diastereomers, in good yield after only one day of reflux in benzene. Only one of

the two expected diastereomers is shown in Scheme 24, although both were present. Furthermore, we did not attempt to determine which of these was the major adduct. Attempts to purify **35a** by flash chromatography proved troublesome since the silyl enol ether was almost entirely hydrolyzed under these conditions. The column fractions containing **35a** and **36a** were recombined and rechromatographed to give **36a** in good yield. The IR spectrum of **36a** indicated the presence of two distinct carbonyl signals at 1731 cm^{-1} and 1713 cm^{-1}, due to the ketone and unsaturated esters, respectively. ^1H NMR and ^{13}C NMR spectra of **36a** showed that both diastereomers were present in nearly equal amounts. Using $CDCl_3$ as the solvent, no signals were sufficiently separated in the ^1H NMR spectrum to obtain the diastereomeric ratio by integration, but when the solvent was changed to C_6D_6 both of the bridgehead protons, C-1H and C-4H, were resolved to give distinct signals for each diastereomer. ^1H NMR signals for C-1H were found at δ 3.79 and 3.73, whereas those corresponding to C-4H were found at δ 3.16 and 3.10. Accurate integration of these signal pairs using a large number of acquisitions (64) and long delay times (10 sec) to account for T_1 differences gave a diastereomeric ratio of 1.22 : 1.

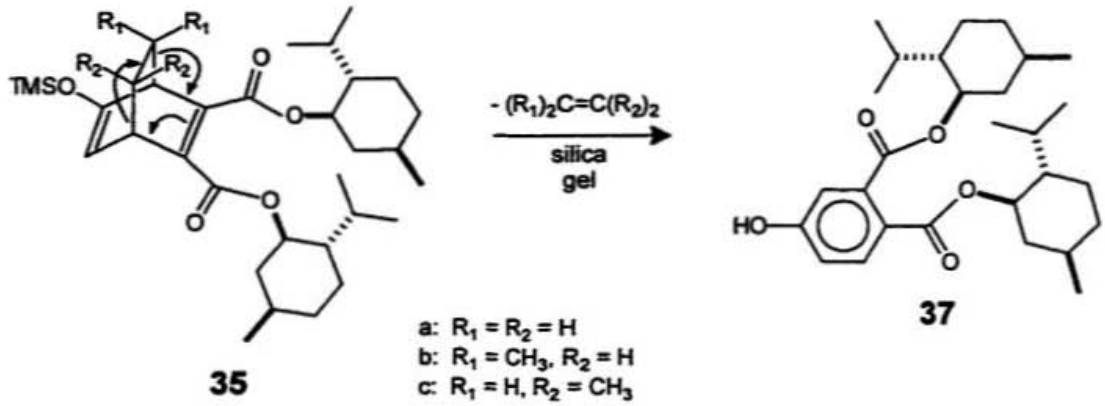
Treatment of **17b** with an excess of **30** gave the expected Diels-Alder adducts **35b** using similar reaction conditions. Subsequent purification yielded **36b** in good yield. The ^1H NMR spectrum in C_6D_6 gave separate signals for both of the bridgehead hydrogens. C-1H signals were found at δ 3.49 and 3.41,

whereas C-4H signals occurred at δ 3.16 and 3.09. Accurate integration gave a diastereomeric ratio of 1.02 : 1.

The Diels-Alder reaction of **17c** with **30** was very sluggish as compared to the corresponding reactions of dienes **17a** and **17b**. Even after extended reaction times only a low yield of **36c** was obtained. ^{1}H NMR signals in C_6D_6 for C-1H occurred at δ 3.74 and 3.67, whereas those for C-4H were found at δ 2.83 and 2.74. The diastereomeric ratio was determined to be 1.45 : 1.



Scheme 24. Asymmetric Diels-Alder adducts obtained from reaction of dienes **17a-c** with dimenthyl acetylenedicarboxylate.

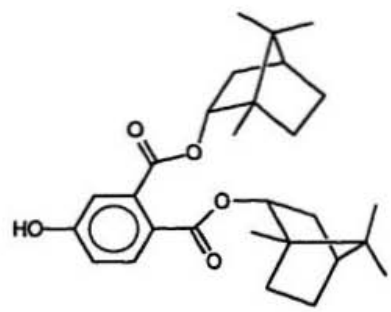


Scheme 25. By-product **37**, formed as a result of *retro*-Diels-Alder reactions of adducts **35a-c**.

Along with the expected Diels-Alder adducts, **35a-c**, a reaction byproduct was also isolated which was common to all three reactions, but in varying amounts. The proportion of this material, with respect to the adducts, tended to increase as a function of reaction time. It was a very UV-active material, and it had a higher polarity than either the initial Diels-Alder adducts, **35a-c**, or the hydrolyzed products, **36a-c**. The IR spectrum contained a broad signal centred at 3361 cm^{-1}, indicating the presence of an acidic hydroxy group and a carbonyl peak at 1710 cm^{-1}. Its ^{1}H NMR spectrum contained aromatic signals at δ 7.70, 6.97 and 6.88, each with an integration of one hydrogen. This indicated a trisubstituted aromatic system containing both electron-donating and electron-withdrawing groups. Its ^{13}C spectrum lacked the ketone signal (*ca.* 210 ppm) common to **36a-c** and contained 6 signals in the double-bond region as compared to 4 (2 pairs) in **36a-c**. This material was assigned the structure **37**,

the result of *retro*-Diels-Alder reactions of the initially formed adducts **35a-c** in the refluxing benzene (Scheme 25). To confirm that the aromatic by-product was only formed from the silyl enol ether adducts, **35a-c**, and not formed from the hydrolyzed keto products, **36a-c**, the synthesis of **37** directly from **36b** was attempted using the original reaction conditions. However, only **36b** was recovered, without a trace of the *retro*-Diels-Alder product, **37**.

Similar Diels-Alder reactions were carried out involving **31** and dienes **17a-c** (Scheme 26). The resulting Diels-Alder adducts (**39a-c**) were hydrolyzed to the corresponding ketones (**40a-c**) before any purification was attempted. This was accomplished by treatment of the reaction residues with dilute HCl in methanol, effecting clean hydrolysis of the silyl enol ethers. Purification of the resulting mixtures by flash chromatography gave ketones **40a-c** in modest to good yield. Once again, a reaction by-product, **38**, (Figure 13) was isolated in varying amounts from each reaction, the result of the *retro*-Diels-Alder reaction of the initial adducts, **39a-c**.



38

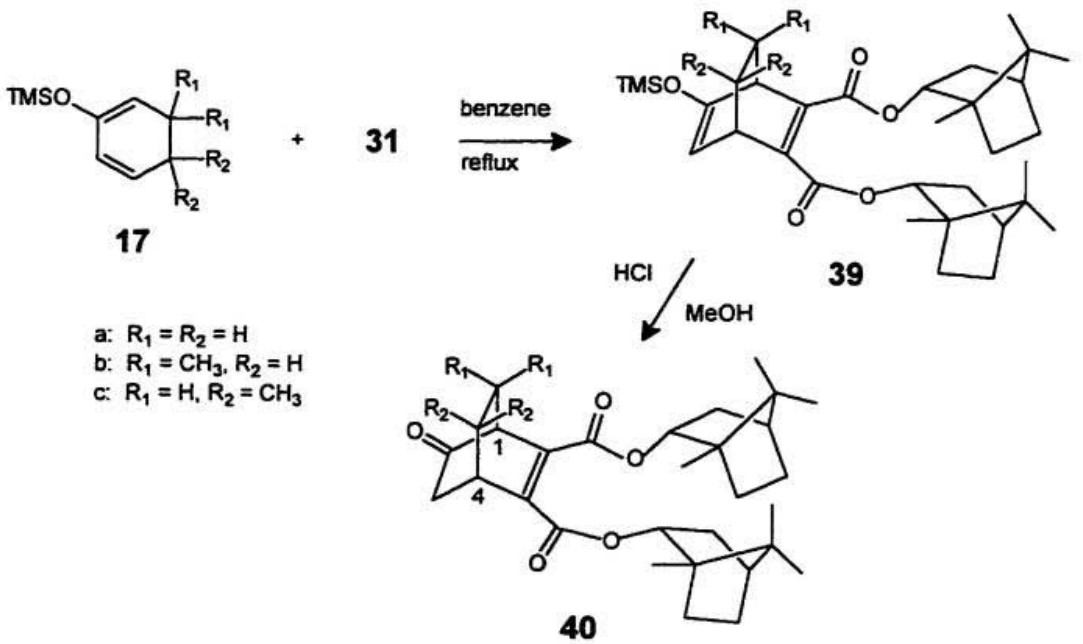
Figure 13. By-product **38**, formed as a result of *retro*-Diels-Alder reactions of adducts **39a-c**.

Treatment of **17a** with three molar equivalents of **31** gave a modest yield of adducts **40a** after refluxing for three days. As for **36a-c**, the only signals in the ^{1}H NMR spectrum which had a possibility of clean separation were those for the bridgehead hydrogens. However, determination of the diastereomeric ratio for **40a** was not as straightforward as discussed previously. The ^{1}H NMR signals for C-1H did not separate in either $CDCl_3$ or C_6D_6, and the signals for C-4H did not separate in $CDCl_3$ and only partially separated in C_6D_6. However, from these partially resolved ^{1}H NMR signals at δ 3.10 and 3.09, the diastereomeric ratio was determined to be 1 : 1.

Diene **17b** was heated with approximately two and one-half equivalents of **31** to give adducts **40b** in 66% yield after five days, following acid treatment. The relative amount of **38** obtained from this reaction was quite high. In fact, the combined yield of purified **40b** and **38** was greater than 94%. This may be an indication that the reaction was heated for longer than necessary, resulting in a significant yield of the *retro*-Diels-Alder product. The diastereomeric ratio of **40b** could only be determined from the C-1H bridgehead proton signal in the ^{1}H NMR spectrum using either C_6D_6 or $CDCl_3$ as the NMR solvent. Integration of the C-1H signals at δ 3.42 and 3.40 in C_6D_6 gave a diastereomeric ratio of 1 : 1.

Similar to our experience with dienophile **30**, the Diels-Alder reaction of diene **17c** with **31** was quite sluggish. A 33% yield of hydrolyzed adducts **40c** was obtained after six days using approximately five and one-half equivalents of

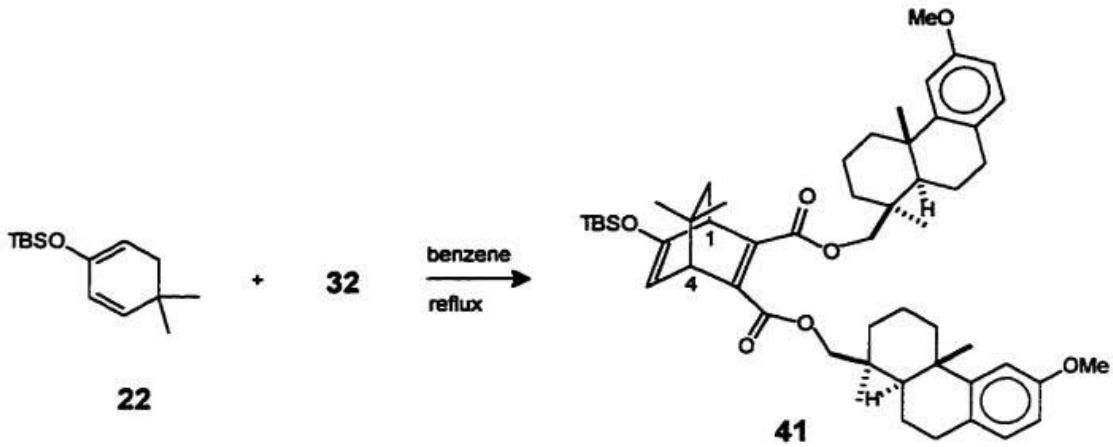
dienophile. This long reaction time resulted in product degradation to give a high yield of the *retro*-Diels-Alder by-product **38** in proportion to the isolated, hydrolyzed products **40c**. The ^{1}H NMR spectrum of **40c** showed C-4H signals at δ 2.70 and 2.67, and integration of these indicated that the diastereomeric ratio was 1.03 : 1.



Scheme 26. Asymmetric Diels-Alder reactions of dienes **17a-c** with dibornyl acetylenedicarboxylate.

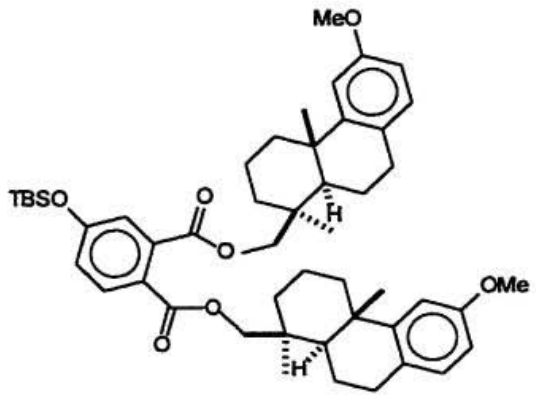
Treatment of diene **22** with **32** gave a 56% yield of the expected Diels-Alder adducts (**41**) after refluxing for nine days using greater than a five-fold excess of diene **22** (Scheme 27). Unlike the adducts obtained from the TMS-dienes (**17a-c**), **41** could be purified by flash chromatography without hydrolysis of the TBS enol ether. In fact, the diastereomers could even be

partially separated during the purification. A diastereomeric ratio of 1 : 1 was determined by integration of the C-1H signals centred at δ 3.29 and 3.26 in the ^{1}H NMR spectrum using $CDCl_3$ as solvent. Along with adducts **41** was isolated **42**, the result of the *retro*-Diels-Alder reaction (Figure 14).



22 **41**

Scheme 27. Asymmetric Diels-Alder reaction of diene **22** with chiral acetylenedicarboxylate **32**.

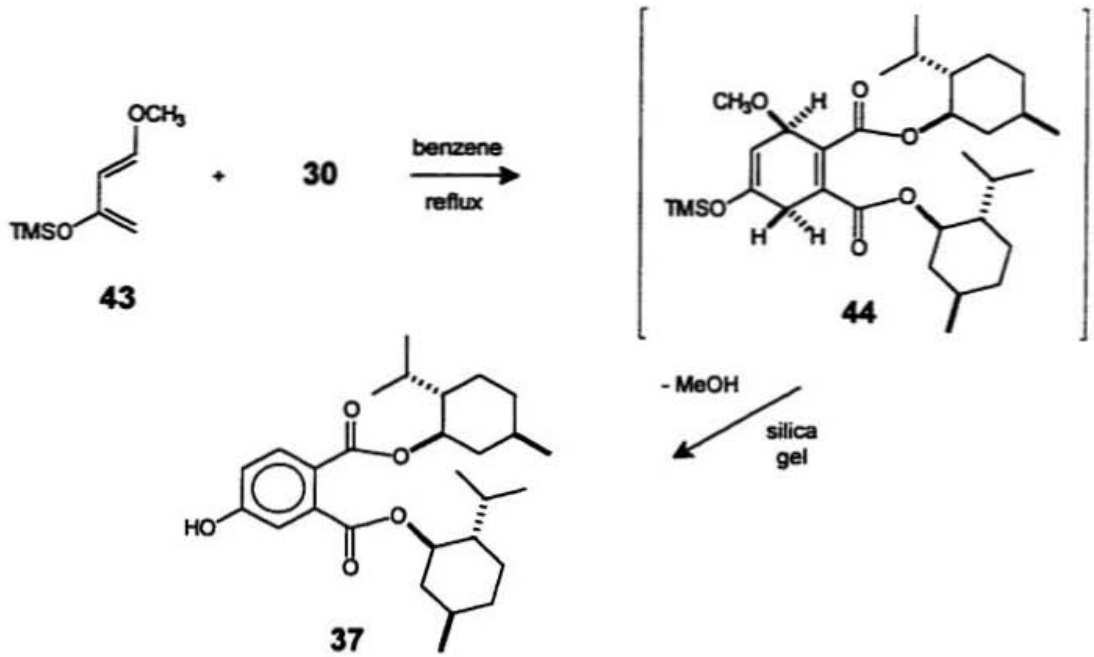


42

Figure 14. *Retro*-Diels-Alder by-product **42**.

Attempted Diels-Alder reaction between **33** and diene **17c** was not as successful. Even after refluxing for ten days with an excess of the diene (approximately fourteen molar equivalents), no new signals were found in the ^{1}H NMR spectrum that were consistent with those expected for a Diels-Alder adduct. The dienophile (**33**) appeared to be very unreactive. Its ^{1}H NMR signals were still present, remaining unchanged throughout the course of the attempted reaction.

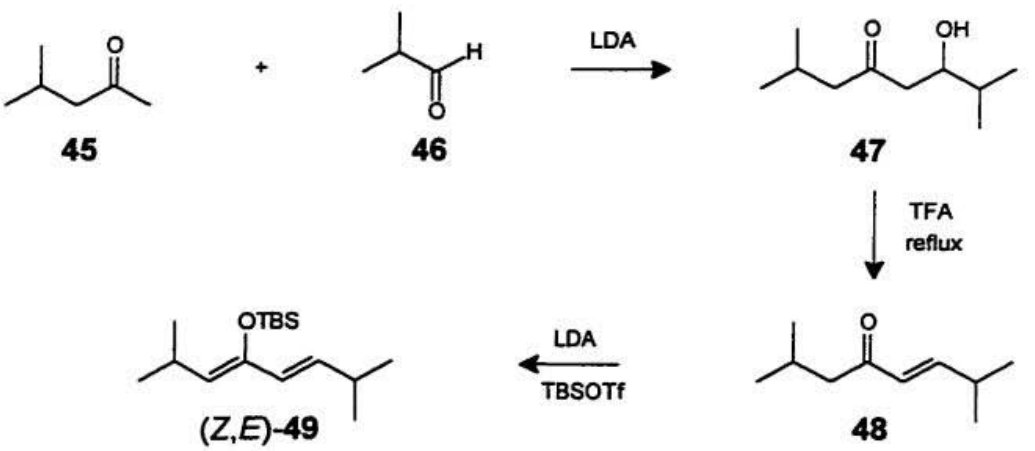
Several other attempts to find asymmetric bias of chiral acetylenedicarboxylates included the Diels-Alder reaction of **30** with 1-methoxy-3-(trimethylsilyl)-1,3-butadiene (Danishefsky's diene) (**43**), as shown in Scheme 28. A slight excess of **30** with **43** in refluxing benzene did not yield the expected Diels-Alder adducts (**44**). Analysis of the ^{1}H NMR spectrum of the isolated product showed a material with three aromatic protons at δ 7.70, 6.97 and 6.88. Also, a broad peak at 3361 cm^{-1} in the IR spectrum indicated the presence of an hydroxy group. These values were identical with those observed for **37**, the *retro*-Diels-Alder byproduct isolated from the reaction of **30** with dienes **17a-c**. Apparently, the initially formed adduct quickly aromatized to **37** with a concomitant loss of methanol.



Scheme 28. Attempted asymmetic Diels-Alder reaction of Danishefsky's diene and dimenthyl acetylenedicarboxylate.

Diene **49** was synthesized according to Rubin's procedure (Scheme 29).[51] Deprotonation of 4-methyl-2-pentanone (**45**) with LDA under kinetic conditions followed by alkylation with isobutyraldehyde (**46**) gave β-hydroxy ketone **47** upon protonation. Crude **47** was dehydrated by refluxing in dichloromethane with trifluoroacetic acid (TFA) to yield enone **48** as the major product. Deprotonation of **48** with LDA under kinetic conditions, followed by treatment with TBSOTf gave **49** as a mixture of two products, which were separated by flash chromatography. Theoretically, four geometric isomers were possible as products from this reaction, (*E*,*E*)-**49**, (*Z*,*E*)-**49**, (*Z*,*Z*)-**49** and (*E*,*Z*)-**49**. However, because the

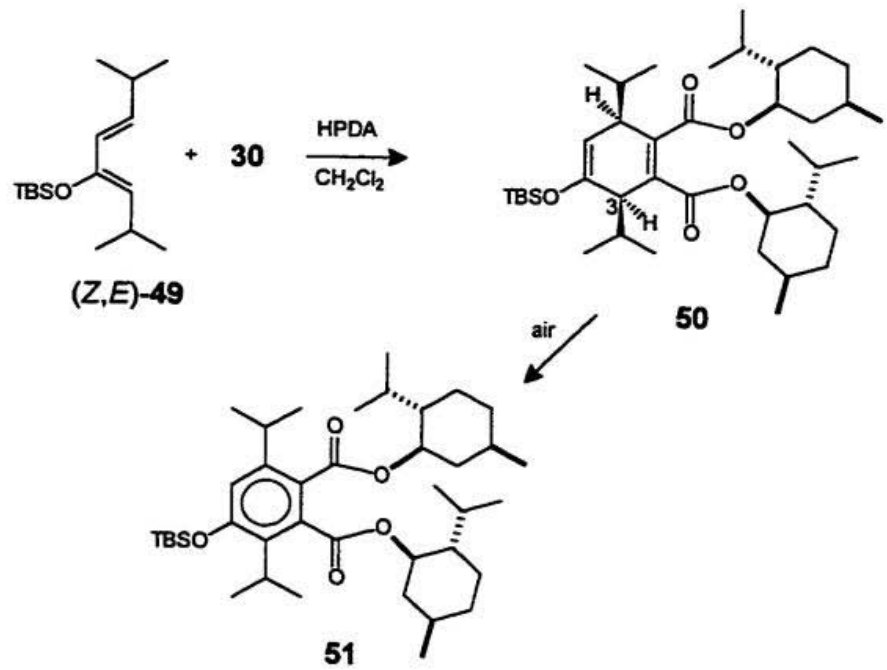
reaction was carried out under kinetic conditions, isomerization of the (*E*)-alkene present in **48** was not likely. Therefore, the two products were very likely (*E*,*E*)-**49** and (*Z*,*E*)-**49**. To differentiate between the two, NOE experiments were undertaken, saturating the C-3H signals at δ 4.51 and 4.59 in the ^{1}H NMR spectrum, for the major and minor compounds, respectively. The major constituent of **49** gave an NOE to the C-5 and/or C-6 hydrogen(s), thus, this compound was (*Z*,*E*)-**49**. The minor product was consistent with (*E*,*E*)-**49**, giving no measurable NOE to the C-5 and/or C-6 hydrogen(s) and a small NOE to the methyl groups attached to silicon.



Scheme 29. Synthesis of diene (*Z*,*E*)-**49** from 4-methyl-2-pentanone (**45**).

Initial attempts to utilize (*Z*,*E*)-**49** as a diene in a Diels-Alder reaction with **30** were not successful. Reaction of an excess of **30** with (*Z*,*E*)-**49** in refluxing benzene gave no indication of adduct formation after five days. Attempts using longer reaction times and higher boiling solvents such as toluene resulted in

complex mixtures which made adduct isolation impossible. Diels-Alder adducts **50** were finally obtained using high pressure Diels-Alder (HPDA) conditions. The HPDA reaction (185,000 psi) of **30** with **49** in dichloromethane at room temperature gave a 24% yield of adducts **50** (Scheme 30).

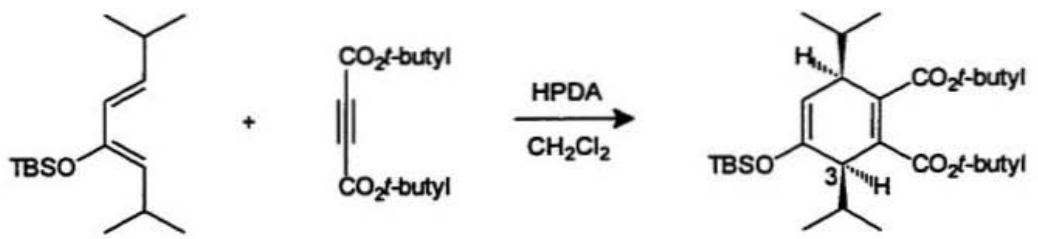


Scheme 30. High pressure Diels-Alder reaction of diene (*Z*,*E*)-**49** with dimenthyl acetylenedicarboxylate.

This was supported by the presence of two pairs of ester signals and four pairs of double bond signals in the ^{13}C NMR spectrum of the product. The ^{13}C NMR spectrum indicated the formation of two diastereomers in a nearly 2 : 1 ratio. The only diastereomeric signals to separate cleanly in the ^{1}H NMR spectrum were those due to C-3H, centred at δ 3.06 and 3.01. Accurate integration of the

^{1}H NMR signals for C-3H gave a diastereomeric ratio of 1.78 : 1. Adducts **50** could not be fully characterized because the sample readily underwent aerial oxidation to give the aromatic diester **51**. The ^{13}C NMR spectrum of **51** contained about one-half of the number of signals present in **50**, a mixture of diastereomers. An aromatic signal appeared in the ^{1}H NMR spectrum of **51** at δ 6.77.

There was some question as to whether the ratio measured was the diastereomeric ratio of the Diels-Alder adduct or the ratio of *cis* and *trans* isomers, the result of a double Michael reaction. To ensure that **50** was in fact a mixture of Diels-Alder adducts, the HPDA reaction of (*Z*,*E*)-**49** and di-*tert*-butyl acetylenedicarboxylate (**52**) was carried out under similar conditions (Scheme 31). Adduct **53** showed only one set of ^{1}H NMR signals, including a single signal for C-3H centred at δ 3.02. This was strong evidence that adducts **50** were the result of a Diels-Alder reaction, since only one isomer was formed in reacting the non-chiral acetylenedicarboxylate **52** with diene (*Z*,*E*)-**49**.



(*Z*,*E*)-**49** **52** **53**

Scheme 31. High pressure Diels-Alder reaction of diene (*Z*,*E*)-**49** with **52**.

V. Discussion and Modeling Studies

(i). Experimental Findings

The syntheses of dienophiles **30**, **31**, and **32** by transesterification of diethyl acetylenedicarboxylate with alcohols **23**, **24**, and **26** respectively, in the presence of an acid catalyst proceeded smoothly. However, attempted reactions to synthesize **33** by the same procedure using **29** were surprisingly sluggish, by comparison. The cause for this lack of reactivity was not obvious. Both **23** and **29** are secondary alcohols with very similar structures, yet the relative rates of reaction are substantially different. Synthesis of **30** by Charlton's method was also straightforward, however, reaction of **29** with dibromofumaryl chloride using identical conditions was not nearly as successful. For compound **23**, the methyl groups of the isopropyl group may have rotated away from the reacting alcohol center, however, for compound **29**, steric interactions with either a methyl or phenyl group could not be avoided. The increase in steric bulk around the alcohol center inhibited the reaction considerably.

Chiral dienophile **31** gave little or no diastereoselectivity in the asymmetric Diels-Alder reactions with dienes **17a-c**. All diastereomeric ratios were, within experimental error, 1 : 1. These results were discouraging since camphor derivatives have been shown to be effective chiral auxiliaries in other asymmetric

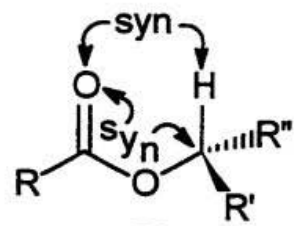
Diels-Alder reactions.[52, 53] For instance, Tolbert had successfully used dibornyl fumarate to induce asymmetric induction in reactions with several diene systems, including anthracene and 1,3-diphenylisobenzofuran.[27, 28] For the uncatalyzed Diels-Alder reaction with anthracene, dibornyl fumarate gave higher diastereoselectivity than the dimenthyl equivalent. For a given dienophile, no single chiral auxiliary has been shown to be capable of asymmetric induction with a wide variety of dienes, thus, the lack of diastereoselectivity observed for the Diels-Alder reactions of **31** with **17a-c** could merely indicate that **24** was unsuitable as a chiral auxiliary in the present study.

Other camphor derivatives were also considered as possible chiral auxiliaries, including **54** and **55** (Figure 15).[52] In comparison to **24**, most of these have increased substitution on the carbon immediately next to the alcohol. Because of the considerable difficulties encountered in synthesizing acetylenic esters of more congested alcohols, e.g. **33**, we did not pursue this idea any further.

54 **55**

Figure 15. Other examples of camphor-derived chiral auxiliaries.[52]

The Diels-Alder reaction of **32** with diene **22** also gave little evidence of diastereoselectivity. We thought that by using a very large chiral auxiliary, the chance of interaction with the diene would be greater. Each unit was so large that we anticipated that the number of conformers might be limited, since some possible conformations would involve unfavourable steric interactions between the auxiliaries. However, for dienophile **32**, the closest stereogenic carbon is four bonds away from the nearest incipient bond. Thus, the geometrical differences may have been too distant to induce diastereoselection during the Diels-Alder reaction.



56

Figure 16. Preferred conformation of aliphatic esters.[17]

The lack of chiral induction may also have been related to a lack of rigidity in the ester conformation of dienophile **32**. A syn-periplanar arrangement of the ester group (angle O=C-O-C near 0 °) has been shown to be the lowest energy conformation of aliphatic esters.[54] Furthermore, a hydrogen of the attached alkyl group also prefers to be syn to the carbonyl oxygen (Figure 16).[17] For **32**, there are two hydrogens present on the first carbon of the chiral auxiliary. Therefore, there are at least two preferred conformations for the chiral auxiliary with respect

to the attached carbonyl. The steric preference exhibited towards an incoming diene by one conformer may be cancelled by the other, resulting in little diastereoselectivity.

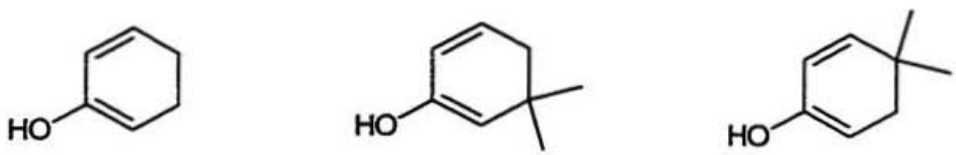
Unlike chiral dienophiles **31** and **32**, **30** proved to be capable of asymmetric induction with dienes **17a** and **17c**. The level of diastereoselectivity observed for these uncatalyzed Diels-Alder reactions was lower than we anticipated, but selectivity was comparable with Charlton's results for bis(methyl (*S*)-lactyl) acetylenedicarboxylate in reactions with dienes for which hydrogen-bonding in the transition state was not possible.[22] As we had predicted, diene **17c** showed chiral induction whereas diene **17b** did not. This supported our hypothesis of a synchronous transition state in which the "para" ester of the acetylenedicarboxylate is planar and the ester closer to the trimethylsiloxy group is free to rotate. However, the observation of diastereoselectivity for the Diels-Alder reaction of **17a** with **30** was surprising. We had hypothesized that the only important interaction in the transition state would be between one of the *gem*-dimethyls of the diene and the incoming dienophile. Diene **17a** contains no dimethyl group. The only substituent making the diene unsymmetrical is the 2-silyloxy group. Therefore, its role in the asymmetric Diels-Alder reactions of dienes **17a-c** with the chiral acetylenedicarboxylates may have been prematurely discounted.

Since **23** had shown some promising results, we decided to use **29** as a chiral auxiliary. Compound **29** had been shown to be much more effective than **23** in many instances.[12] As mentioned previously, a lot of effort was expended to synthesize the corresponding acetylenedicarboxylate, **33**. Consequently, we were disappointed when **33** did not react with **17c**. The steric bulk of **33** may have prevented the asymmetric Diels-Alder reaction from occurring.

A 1.78 : 1 diastereomeric ratio was obtained for the asymmetric Diels-Alder reaction of (*Z*,*E*)-**49** and **30**. Again, only the 2-silyloxy substituent renders the diene unsymmetrical. Rubin *et al.* had reported that (*Z*,*E*)-**49** was quite unreactive. Their attempts to effect a Diels-Alder reaction of this diene with C_{60} using thermal conditions (25-110 °C) had failed.[51] We experienced similar results until the high pressure Diels-Alder reaction was attempted. The success of this technique has been attributed to large negative activation volumes.[12, 55] The diastereomeric ratio obtained for adducts **50** was the highest we observed for our uncatalyzed asymmetric Diels-Alder reactions. The degree of chiral induction we observed for the asymmetric Diels-Alder reactions of **30** with various dienes appeared to be linked to the steric bulk of the diene. Diene **17a**, with a 2-silyloxy group, gave a de of 10%, diene **17c**, with a 2-silyloxy group and a *gem*-dimethyl group, gave a de of 18%, and (*Z*,*E*)-**49**, with a 2-silyloxy group and two isopropyl groups, gave a de of 28%. As the steric bulk increases, so does the asymmetric induction.

(ii). Modeling Studies

To aid in the understanding of our experimental results, *semiempirical* molecular orbital calculations at the AM1[56] level were used to identify the transition states for the Diels-Alder reactions of di-*t*-butyl acetylenedicarboxylate with the 2-hydroxy analogues of dienes **17a-c** (Figure 17).



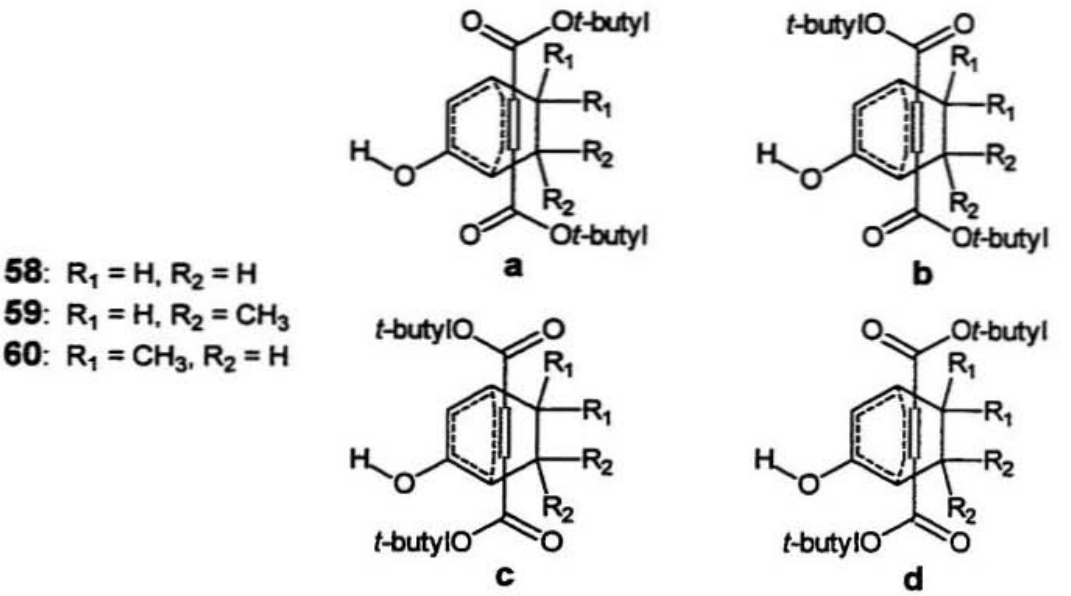
57a **57b** **57c**

Figure 17. Dienes **57a-c** used in molecular orbital calculations.

Di-*t*-butyl acetylenedicarboxylate appeared well suited as a dienophile for these theoretical studies because the *t*-butyl group has 3-fold symmetry about the point of attachment, thus the number of different alkoxy conformations to be calculated was minimized. Also, the *t*-butyl group compared well, in terms of steric bulk, to the environments around the alcohol functionalities of the chiral auxiliaries used in the experimental work. Di-*t*-butyl acetylenedicarboxylate contained fewer atoms than the chiral dienophiles, which reduced the computer time needed for the calculations. Similarly, **57a-c** were used as the dienes to reduce the size of the calculations.

The transition states were obtained using the SPARTAN® computational package. The AM1 calculations yielded four potential transition states for the Diels-Alder reaction of di-*t*-butyl acetylenedicarboxylate with each diene (Figure 18 and Appendix A). Frequency calculations gave only one negative eigenvalue for each, confirming that all four were indeed transition states. In all cases the ester groups were found to be parallel, or nearly parallel to the plane of the reacting diene. However, the transition states differed in the conformations of the ester-carbonyls with respect to the diene. Each carbonyl group of the acetylenedicarboxylate could be orientated either towards or away from, the 4π component of the diene during reaction, corresponding to the four transition states depicted in Figure 18.

Some geometrical and energetic properties for the calculated transition states of the Diels-Alder reactions of di-*t*-butyl acetylenedicarboxylate with dienes **57a-c** are tabulated in Tables 5-7. The distances between reacting carbons have been labeled r_1 and r_2, with r_1 referring to the distance between carbon 1 of the diene and the corresponding acetylenic carbon and r_2 referring to the distance between carbon 4 of the diene and the corresponding acetylenic carbon. Computed heats of formation (ΔH_f) have also been provided for each transition state.



58: $R_1 = H$, $R_2 = H$
59: $R_1 = H$, $R_2 = CH_3$
60: $R_1 = CH_3$, $R_2 = H$

Figure 18. Transition states obtained from AM1 calculations for the Diels-Alder reactions of dienes **57a-c** with di-*t*-butyl acetylenedicarboxylate.

Table 5. Transition state properties calculated by AM1 for the Diels-Alder reaction of diene **57a** with di-*t*-butyl acetylenedicarboxylate.

Transition states	r_1 (Å)	r_2 (Å)	ΔH_f (kcal/mol)
58a	2.041	2.241	-119.8
58b	2.045	2.239	-119.9
58c	2.045	2.245	-119.9
58d	2.043	2.245	-120.1
Avg. value	2.044	2.242	

Table 6. Transition state properties calculated by AM1 for the Diels-Alder reaction of diene **57b** with di-*t*-butyl acetylenedicarboxylate.

Transition states	r_1 (Å)	r_2 (Å)	ΔH_f (kcal/mol)
59a	2.041	2.263	-125.1
59b	2.044	2.261	-125.1
59c	2.048	2.252	-125.3
59d	2.048	2.252	-125.5
Avg. value	2.045	2.257	

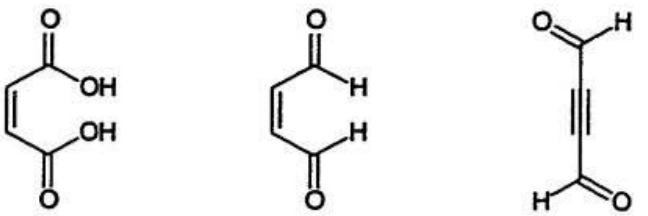
Table 7. Transition state properties calculated by AM1 for the Diels-Alder reaction of diene **57c** with di-*t*-butyl acetylenedicarboxylate.

Transition states	r_1 (Å)	r_2 (Å)	ΔH_f (kcal/mol)
60a	2.082	2.209	-125
60b	2.074	2.217	-125
60c	2.076	2.222	-125.1
60d	2.084	2.216	-125.3
Avg. value	2.079	2.216	

For the computational studies, the relative energies of all four transition states obtained for each diene (**57a-c**) were essentially identical. In fact, the energy difference between the lowest energy transition state (**d**) and the highest energy transtion state (**a**) was less than 0.5 kcal/mol for any given diene (**57a-c**) and dienophile (**52**) combination. The results of the computational studies indicated that the chiral inductions that we did observe may be as good as can be expected with simple chiral acetylenedicarboxylates and dienes **17a-c**. For

the non-chiral acetylenediester **52**, there are four different transition states with nearly identical energies. Thus, experimentally one should expect reaction to take place via all four planar conformations of the dienophile if the chiral acetylene dicarboxylates behave in the same manner. We might therefore expect very little chiral induction because different conformers of the dienophile might react with different, even opposite steric biases.

The computational work also revealed that the transition states are asynchronous for dienes **57a-c**, but not tipped in the direction suggested by the rate studies. The shorter incipient bond is near the electron-donating trimethylsiloxy group, as we would have intuitively expected. This may be an indication that the symmetrical dienophile may not be symmetrical in the transition state of the Diels-Alder. Unpublished work by Singleton and Leung predicted asynchronous transition structures for the Diels-Alder reactions of butadiene, a symmetrical diene, with maleic acid (**61**), malealdehyde (**62**), and acetylene dicarboxaldehyde (**63**) (Figure 19).[57] The prediction of unsymmetical transition states for these RHF calculations, at first glance, seems quite surprising considering that both the diene and dienophiles are symmetrical. For maleic acid and malealdehyde, strong steric and electronic interactions between the substituents may result in geometrical adjustments, causing the dienophiles to become unsymmetrical. However, no such interactions will exist for acetylene dicarboxaldehyde. This may be an indication that the corresponding aldehydes are not co-planar in the transition state.



61 **62** **63**

Figure 19. Dienophiles used by Singleton and Leung for computational studies.[57]

Our AM1 calculations indicated very little conformational bias in the achiral acetylenedicarboxylate. However, we did obtain modest asymmetric induction in some instances. This contradiction implies that a higher level of calculation would be required to expose potentially larger differences in the transition state energies. A recent *ab initio* study by Morokuma *et al.*[58] of the Diels-Alder reaction between acetylenedicarboxylic acid and cyclopentadiene has shown the transition state to be extremely unsymmetrical. One of the carboxyl groups adopts a plane-parallel conformation, with respect to the incoming diene, while the other carboxyl is perpendicular and retained overlap with the second, non-reacting π-bond of the acetylene moiety. Morokuma *et al.* attribute the lack of symmetry to activation of the acetylene by the parallel-planar carboxyl, which makes the dienophile carbon that is further from the parallel-planar carbonyl more positively charged, and thus more reactive. An X-ray structure of dimenthyl acetylenedicarboxylate (**30**) indicates that this conformational preference might also be present in more complex, chiral

acetylenedicarboxylates.[59] In the solid state, the ester groups were found to be orthogonal to each other, which suggested the possibility of resonance interaction between the carboxyls and the two mutually perpendicular π systems of the alkyne. If this conformational rigidity for **30** were also present in solution, it could explain the diastereoselectivity in our Diels-Alder reactions.

Our AM1 calculations supported an asynchronous transition state for which carbon 1 (Figure 9) is the site of the shorter incipient bond. Furthermore, our experimental results with dimenthyl acetylenedicarboxylate (**30**) seemed to indicate a conformational preference in the transition state even though the AM1 calculations were unable to explain this. Thus, the ester group further from the trimethylsiloxy group most likely adopts a "fixed", parallel-planar conformation to activate the triple bond for attack, whereas the other ester is perpendicular to the incoming diene. This would explain the large difference in relative reaction rates observed by Liu for dienes **17a-b**, as compared to diene **17c**. For diene **17c**, the parallel-planar ester will interact with the methyl groups of the diene, whereas for dienes **17a-b** this unfavourable steric interaction is absent. Furthermore, a higher degree of diastereoselectivity for the Diels-Alder reaction of **30** with diene **17c**, as compared to dienes **17a-b**, would be expected.

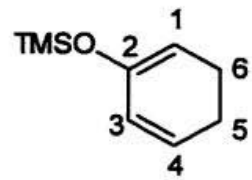
VI. Experimental

General Methods

Diisopropylamine, pyridine, and triethylamine were freshly distilled from CaH_2. THF was freshly distilled from sodium/benzophenone. Other solvents were distilled or were of ACS Grade. Sodium iodide and zinc(II) chloride were dried for 6 h at 60 °C and 80 °C, respectively, under vacuum, and stored in a desiccator until used. Activated zinc metal was prepared by washing with 6 M HCl, water, acetone, and diethyl ether, and then dried under vacuum for 2 h. All reactions were performed under dry nitrogen or argon. Solutions were dried after work-up with either anhydrous $MgSO_4$, K_2CO_3 or Na_2SO_4. Products were usually purified by flash chromatography on silica gel with elution with hexane or petroleum ether containing an increasing proportion of ethyl acetate or diethyl ether. IR spectra were recorded as thin films on 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 for ^1H) instrument. For ^1H NMR, chemical shifts are relative to internal tetramethylsilane (TMS). ^{13}C NMR spectra are at 75 MHz in $CDCl_3$ unless otherwise noted; chemical shifts are relative to the solvent resonance. Coupling constants (*J*) are in Hz; *apparent* multiplicities are reported here because in many instances the signals are second order. The assignment of NMR signals were made on the basis of chemical shift considerations as well as APT, COSY, and HETCORR

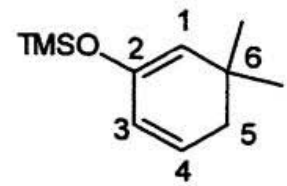
experiments where ambiguities remained. NOE measurements were on thoroughly degassed $CDCl_3$ solutions. NOE data were obtained from sets of interleaved ^1H experiments (16K) of 8 transients cycled 12-16 times through the list of irradiated frequencies. The decoupler was gated on a continuous wave mode 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. 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 are reported as: saturated signal (enhanced signal, enhancement). Mass spectral data were from a V.G. Micromass 7070HS instrument and are reported as: *m/e* (% 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 stationary phase was used for gas chromatography-mass spectrometry (GC-MS). Melting points (mp) were determined on a Fisher-Johns melting point apparatus and are uncorrected.

2-(Trimethylsilyloxy)cyclohexa-1,3-diene (17a).



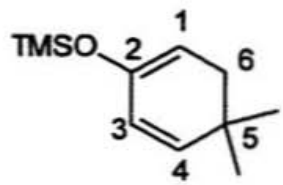
n-Butyllithium (1.6 M in hexanes, 12 mL, 19 mmol) was added dropwise to a solution of diisopropylamine (1.74 g, 17.2 mmol) in THF (55 mL) at 0 °C. This solution was maintained at 0 °C for 30 min, then it was cooled to -78 °C for 30 min. A solution of 2-cyclohexen-1-one (1.50 g, 15.6 mmol) in THF (10 mL) was added dropwise to the solution. After 1 h, TMSCl (3.56 g, 32.8 mmol) was added, and the mixture was maintained at -78 °C for a further 1.5 h before it was allowed to warm to rt. After stirring for 1 h, the THF was evaporated, and the residue was taken up in anhydrous pentane (60 mL). The LiCl precipitate was removed by filtration. Evaporation of the pentane followed by vacuum distillation (35-37 °C at 3 mm Hg) gave **17a** (2.05 g, 78%) as a colourless liquid. IR: 3048, 3025 (weak), 2957, 1649, 1594, 1401, 1251, 1198, 909 cm^{-1}. ^1H NMR: δ 5.86 (1H, dt, J = 4.0, 9.9 Hz, C-4H), 5.69 (1H, dq, J = 1.8, 9.9 Hz, C-3H), 4.88 (1H, dt, J = 1.8, 4.0 Hz, C-1H), 2.22-2.03 (4H, m, C-5H_2, C-6H_2), 0.19 (9H, s, $(CH_3)_3Si$). ^{13}C NMR: δ 148.0 (C-2), 128.9 (C=C), 126.3 (C=C), 102.4 (C-1), 22.6 (CH_2), 21.7 (CH_2), 0.2 ($(CH_3)_3Si$). MS: 169 (12, M^+ + 1), 168 (10, M^+), 167 (9), 151 (7), 147 (20), 145 (11), 86 (59), 75 (30), 73 (100), 68 (8), 67 (9), 58 (10).

6,6-Dimethyl-2-(trimethylsilyloxy)cyclohexa-1,3-diene (17b).



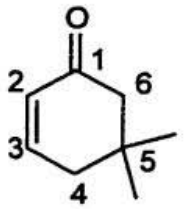
n-Butyllithium (1.6 M in hexanes, 11 mL, 17 mmol) was added dropwise to a solution of diisopropylamine (1.34 g, 13.2 mmol) in THF (40 mL) at 0 °C. This solution was maintained at 0 °C for 30 min, then it was cooled to -78 °C for 30 min. A solution of 5,5-dimethyl-2-cyclohexen-1-one (1.50 g, 12.1 mmol) in THF (5.0 mL) was added dropwise to the solution. After 1 h, TMSCl (2.75 g, 25.3 mmol) was added, and the mixture was maintained at -78 °C for a further 2 h before it was allowed to warm to rt. After stirring for 1.5 h, the THF was evaporated, and the residue was taken up in anhydrous pentane (60 mL). The LiCl precipitate was removed by filtration. Evaporation of the pentane followed by vacuum distillation (29-31 °C at 0.8 mm Hg) gave **17b** (1.89 g, 80%) as a colourless liquid. IR: 3047 (weak), 3018 (weak), 2958, 1649, 1592, 1401, 1252 (broad), 846 (broad) cm^{-1}. ^1H NMR: δ 5.76 (1H, dt, J = 4.1, 10.0 Hz, C-4H), 5.66 (1H, dq, J = 1.8, 10.0 Hz, C-3H), 4.65 (1H, symmetrical m, C-1H), 2.05 (2H, dd, J = 1.8, 4.1 Hz, C-5H_2), 1.00 (6H, s, 2 x C-6**CH_3**), 0.18 (9H, s, $(CH_3)_3Si$). ^{13}C NMR: δ 146.5 (C-2), 127.5 (C=C), 125.1 (C=C), 114.8 (C-1), 38.0 (C-5), 31.8 (C-6), 28.7 (2 x C-6**CH_3**), 0.1 ($(CH_3)_3Si$). MS: 197 (3, M^+ +1), 196 (10, M^+), 181 (100), 165 (53), 105 (4), 91 (10), 82 (18), 75 (20), 73 (77).

5,5-Dimethyl-2-(trimethylsilyloxy)cyclohexa-1,3-diene (17c).



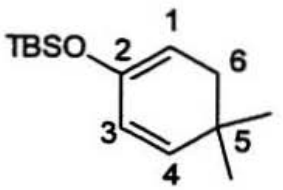
n-Butyllithium (2.5 M in hexanes, 4.7 mL, 12 mmol) was added dropwise to a solution of diisopropylamine (1.08 g, 10.7 mmol) in THF (40 mL) at 0 °C. After 30 min, a solution of 4,4-dimethyl-2-cyclohexen-1-one (1.20 g, 9.66 mmol) in THF (5.0 mL) was added dropwise. After 1 h, TMSCl (2.20 g, 20.3 mmol) was added, and the reaction mixture was maintained at 0 °C for a further 2 h before it was allowed to warm to rt. After 1 h the THF was evaporated, and the residue was taken up in anhydrous pentane (60 mL). The LiCl precipitate was removed by filtration. Evaporation of the pentane followed by vacuum distillation (29-31 °C at 0.8 mm Hg) gave **17c** (1.45 g, 76%) as a colourless liquid. IR: 3041, 3017 (weak), 2958, 1653, 1596, 1404, 1377, 1251, 1205, 897, 845 cm^{-1}. ^1H NMR: δ 5.55 (2H, m, C-3H, C-4H), 4.79 (1H, tt, J = 1.4, 4.6 Hz, C-1H), 2.12 (2H, d, J = 4.6 Hz, C-6H_2), 1.01 (6H, s, 2 x C-5**C**H_3), 0.19 (9H, s, $(CH_3)_3Si$). ^{13}C NMR: δ 147.1 (C-2), 140.1 (C-4), 123.7 (C-3), 101.5 (C-1), 37.0 (C-6), 31.2 (C-5), 27.7 (2 x C-5**C**H_3), 0.2 ($(CH_3)_3Si$). MS (from GC-MS): 196 (28, M^+), 182 (16), 181 (100), 165 (46), 75(24), 73 (62), 45 (17).

5,5-Dimethyl-2-cyclohexen-1-one (20b).



Concentrated H_2SO_4 (5 drops) was added to a solution of 5,5-dimethyl-1,3-cyclohexanedione (5.67 g, 40.4 mmol) and *p*-toluenesulfonhydrazide (7.66 g, 41.1 mmol) in methanol (100 mL). After 20 min, a beige precipitate began to form. After stirring for 12 h, the methanol was evaporated under vacuum. Potassium carbonate (44.2 g, 320 mmol) and water (200 mL) were added. This resulted in a slightly exothermic reaction with a colour change from beige to orange. Steam distillation of the resulting mixture yielded a largely aqueous distillate (1 L). This mixture was saturated with NaCl and extracted with diethyl ether (4 x 65 mL). The combined ether extracts were washed with brine (40 mL), and then dried ($MgSO_4$). Solvent evaporation followed by flash chromatography (elution with 3% ethyl acetate-hexane) gave **20b** (2.28 g, 46%) as a colourless oil. IR: 3036 (weak), 2960, 1679, 1469 (weak), 1389, 1243 cm^{-1}. ^1H NMR: δ 6.88 (1H, dt, J = 4.1, 10.1 Hz, C-3H), 6.03 (1H, dt, J = 2.0, 10.1 Hz, C-2H), 2.28 (2H, s, C-6H_2), 2.26 (2H, dd, J = 2.0, 4.1 Hz, C-4H_2), 1.06 (6H, s, 2 x C-5**C**H_3). ^{13}C NMR: δ 199.9 (C-1), 148.4 (C-3), 128.8 (C-2), 51.7 (C-6), 39.8 (C-4), 33.8 (C-5), 28.2 (2 x C-5**C**H_3). MS: 125 (1, M^+ + 1), 124 (11, M^+), 109 (3), 81 (6), 68 (100).

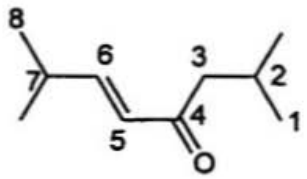
5,5-Dimethyl-2-((1,1-dimethylethyl)-dimethylsilyl)oxy)cyclohexa-1,3-diene (22).



A solution of 4,4-dimethyl-2-cyclohexen-1-one (0.238 g, 1.92 mmol) in dichloromethane (10 mL) was cooled to 0 °C, and triethylamine (0.30 g, 0.41 mL, 3.0 mmol) was added dropwise. After 10 min, TBSOTf (0.73 g, 0.64 mL, 2.8 mmol) was added, and the ice bath was removed after 15 min. After 45 min, the orange mixture was poured into diethyl ether (100 mL). The organic solution was washed with a saturated aqueous $NaHCO_3$ solution (2 x 15 mL), and brine (15 mL), and then dried ($MgSO_4/K_2CO_3$). Solvent evaporation followed by flash chromatography (elution with 3% diethyl ether-petroleum ether) gave **22** (0.436 g, 95%) as a colourless oil. IR: 2958, 1654, 1472, 1363, 1254, 1206, 891, 839, 782 cm^{-1}. ^1H NMR: δ 5.56-5.54 (2H, m, C-3H, C-4H), 4.80-4.75 (1H, symmetrical m, C-1H), 2.11 (2H, d, J = 4.6 Hz, C-6H_2), 1.01 (6H, s, 2 x C-5$\mathbf{CH_3}$), 0.93 (9H, s, ($\mathbf{CH_3}$)$_3$C(CH$_3$)$_2$Si), 0.13 (6H, s, (CH$_3$)$_3$C($\mathbf{CH_3}$)$_2$Si). ^{13}C NMR: δ 147.4 (C-2), 139.9 (C-4), 123.9 (C-3), 101.5 (C-1), 37.0 (C-6), 31.2 (C-5), 27.7 (2 x C-5$\mathbf{CH_3}$), 25.7 (($\mathbf{CH_3}$)$_3$C(CH$_3$)$_2$Si), 18.1 ((CH$_3$)$_3$$\mathbf{C}$(CH$_3$)$_2$Si), 0.13 ((CH$_3$)$_3$C($\mathbf{CH_3}$)$_2$Si). MS: 239 (4, M^+ + 1), 238 (17, M^+), 224 (6), 223 (31), 182 (11), 181 (45), 167 (9),

165 (11), 127 (5), 126 (37), 107 (10), 105 (6), 91 (14), 77 (7), 75 (100), 73 (59), 59 (15).

(*E*)-2,7-Dimethyl-5-octen-4-one (48).

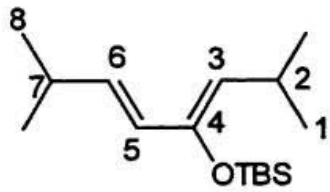


To a solution of diisopropylamine (5.2 g, 7.2 mL, 51 mmol) in THF (10 mL) cooled to 0 °C was added *n*-butyllithium (2.5 M in hexanes, 20 mL, 51 mmol) dropwise over 10 min. After a further 10 min, the mixture was cooled to -78 °C and 4-methyl-2-pentanone (4.99 g, 49.8 mmol) in THF (8.0 mL) was added dropwise. After stirring for 20 min, isobutyraldehyde (3.60 g, 49.9 mmol) in THF (10 mL) was added dropwise. The reaction was allowed to warm to rt over 6 h to yield a yellow, gelatinous mixture. This was quenched with water (25 mL), and the organic layer separated. The aqueous layer was acidified with 3 M aqueous HCl (35 mL), and it was extracted with diethyl ether (3 x 35 mL). The combined organic solutions were washed with water (20 mL), a saturated aqueous $NaHCO_3$ solution (20 mL), and brine (20 mL), and then dried (Na_2SO_4). The crude β-hydroxy ketone **47** was obtained after the solvent was removed by evaporation.

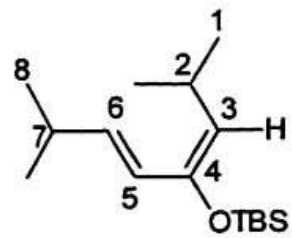
The crude **47** was added to a solution of dichloromethane (20 mL) and trifluoroacetic acid (5.9 g, 4.0 mL, 0.052 mol). The mixture was heated to reflux

for 12 h. After cooling, the mixture was diluted with diethyl ether (100 mL) and washed with water (15 mL), a saturated aqueous $NaHCO_3$ solution (15 mL) and brine (15 mL). After drying (Na_2SO_4) and solvent evaporation, vacuum distillation (75 °C at 2-3 mm Hg) gave **48** (4.07 g, 53%) as a yellow oil. IR: 2960, 1696, 1671, 1628, 1467, 1366 cm^{-1}. ^1H NMR: δ 6.78 (1H, dd, *J* = 6.6, 16.0 Hz, C-6H), 6.04 (1H, dd, *J* = 1.4, 16.0 Hz, C-5H), 2.52-2.38 (1H, d of septets, *J* = 1.4, 6.6 Hz, C-7H), 2.41 (2H, d, *J* = 6.8 Hz, C-$3H_2$), 2.16 (1H, septet, *J* = 6.8 Hz, C-2H), 1.07 (6H, d, *J* = 6.6 Hz, C-7**CH_3**, C-$8H_3$), 0.94 (6H, d, *J* = 6.8 Hz, C-$1H_3$, C-2**CH_3**). ^{13}C NMR: δ 200.9 (C-4), 153.3 (C-6), 127.9 (C-5), 49.1 (C-3), 31.0 (C-7), 25.1 (C-2), 22.7 (2 x CH_3), 21.3 (2 x CH_3). MS: 308 (0.5, 2 M^+), 265 (24), 181 (7), 179 (4), 155 (5, M^+ + 1), 154 (4, M^+), 153 (9), 139 (7), 124 (16), 111 (10), 97 (20), 85 (100), 69 (18), 57 (47), 55 (10).

(*Z*,*E*)-2,7-Dimethyl-4-(((1,1-dimethylethyl)dimethylsilyl)oxy)-3,5-octadiene (*Z*,*E*-49) and (*E*,*E*)-2,7-dimethyl-4-(((1,1-dimethylethyl)dimethylsilyl)oxy)-3,5-octadiene (*E*,*E*-49).



(*Z*,*E*)-**49**

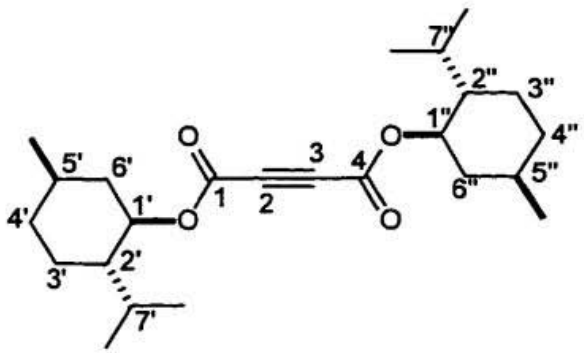


(*E*,*E*)-**49**

A solution of diisopropylamine (0.16 g, 0.23 mL, 1.6 mmol) in THF (10 mL) was cooled to 0 °C and *n*-butyllithium (2.5 M in hexanes, 0.59 mL, 1.5 mmol) was added dropwise. After stirring for 10 min, the solution was cooled to -78 °C. Dropwise addition of **48** (0.208 g, 1.35 mmol) in THF (3.0 mL) over 10 min resulted in a pale yellow solution. After stirring at -78 °C for 40 min, TBSOTf (0.39 g, 0.34 mL, 1.5 mmol) was added. The mixture was maintained at -78 °C overnight, then slowly allowed to warm to rt. Most of the THF was evaporated, and the mixture was diluted with pentane (40 mL). The resulting precipitate was removed by filtration. Solvent evaporation followed by flash chromatography (elution with 1% ethyl acetate-hexane) gave (*Z*,*E*)-**49** (0.251 g, 69%) and (*E*,*E*)-**49** (0.021 g, 6%) as colourless oils. For (*Z*,*E*)-**49**. IR: 3028 (weak), 2959, 1623, 1464, 1362, 1256, 1010, 839, 808, 778 cm^{-1}. ^1H NMR: δ 5.75-5.73 (2H, m, C-5H, C-6H), 4.51 (1H, d, *J* = 9.7 Hz, C-3H), 2.78-2.61 (1H, m, C-2H), 2.38-2.22 (1H, m, C-7H), 0.998 (6H, d, *J* = 6.7 Hz, C-7$\mathbf{CH_3}$, C-8H_3), 0.995 (9H, s, ($\mathbf{CH_3}$)$_3$C(CH$_3$)$_2$Si), 0.95 (6H, d, *J* = 6.7 Hz, C-1H_3, C-2$\mathbf{CH_3}$), 0.11 (6H, s, (CH$_3$)$_3$C($\mathbf{CH_3}$)$_2$Si). NOE data: 4.51 (5.75-5.73, 5%; 2.78-2.61, 1%). ^{13}C NMR: δ 146.3 (C-4), 136.2 (C-6), 125.9 (C-5), 121.0 (C-3), 30.8 (C-7), 26.0 (($\mathbf{CH_3}$)$_3$C(CH$_3$)$_2$Si), 24.9 (C-2), 23.1 (C-1, C-2$\mathbf{CH_3}$), 22.4 (C-7$\mathbf{CH_3}$, C-8), 18.5 ((CH$_3$)$_3$**C**(CH$_3$)$_2$Si), -3.7 ((CH$_3$)$_3$C($\mathbf{CH_3}$)$_2$Si). MS: 269 (2, M^+ +1), 268 (7, M^+), 253 (26), 225 (36), 211 (7), 169 (17), 153 (7), 93 (8), 77 (8), 75 (100), 74 (8), 73 (94), 59 (15), 57 (9).

For (*E*,*E*)-**49**. ^{1}H NMR: δ 6.14 (1H, d, *J* = 15.3 Hz, C-5H), 5.95 (1H, dd, *J* = 6.9, 15.3 Hz, C-6H), 4.59 (1H, d, *J* = 9.7 Hz, C-3H), 2.58 (1H, d of septets, *J* = 6.6, 9.7 Hz, C-2H), 2.37 (1H, septet, *J* = 6.9 Hz, C-7H), 1.02 (6H, d, *J* = 6.8 Hz, 2 x CH_3), 0.98 (6H, d, *J* = 6.7 Hz, 2 x CH_3), 0.96 (9H, s, $(\mathbf{CH_3})_3C(CH_3)_2Si$), 0.12 (6H, s, $(CH_3)_3C(\mathbf{CH_3})_2Si$). NOE data: 4.59 (2.58, 1%; 0.12, 0.5%).

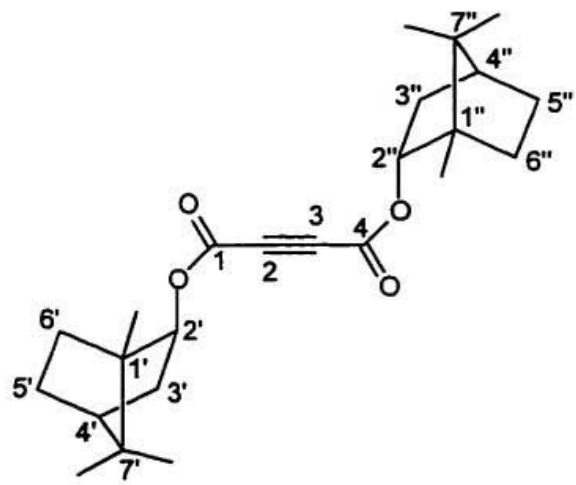
Dimenthyl acetylenedicarboxylate (30).



Diethyl acetylenedicarboxylate (2.45 g, 2.30 mL, 14.4 mmol), (1*R*,2*S*,5*R*)-(-)- menthol (10.05 g, 64.3 mmol) and *p*TsOH (0.251 g, 1.32 mmol) were dissolved in benzene (50 mL). The mixture was heated to reflux, and reaction progress was monitored by TLC. After 7 days, evaporation of the solvent under vacuum yielded a yellow oil. Flash chromatography (elution with 3% ethyl acetate-hexane) gave **30** (5.40 g, 96%) as a colourless solid: mp: 135-136 °C. IR: 2960, 2924, 1712, 1263 cm^{-1}. ^{1}H NMR: δ 4.84 (2H, dt, *J* = 4.5, 10.8 Hz, C-1'H, C-1"H), 2.06-1.99 (2H, m, C-6'H_e, C-6"H_e), 1.98-1.82 (2H, doublet of septets, *J* = 2.7, 6.9 Hz, C-7'H, C-7"H), 1.75-1.64 (4H, m, C-3'H_e,

C-3"H_e, C-4'H_e, C-4"H_e), 1.56-1.39 (4H, m, C-2'H, C-2"H, C-5'H, C-5"H), 1.14-0.97 (4H, m, C-3'H_a, C-3"H_a, C-6'H_a, C-6"H_a), 0.92 (6H, d, *J* = 6.9 Hz, C-7'**CH_3**, C-7"**CH_3**), 0.91-0.84 (2H, m, C-4'H_a, C-4"H_a), 0.91 (6H, d, *J* = 6.9 Hz, C-7'**CH_3**, C-7"**CH_3**), 0.76 (6H, d, *J* = 7.0 Hz, C-5'**CH_3**, C-5"**CH_3**). ^{13}C NMR: δ 151.6 (2 x C=O), 77.5 (C-1', C-1"), 74.8 (C≡C), 46.7 (C-2', C-2"), 40.4 (C-6', C-6"), 33.9 (C-4', C-4"), 31.4 (C-5', C-5"), 26.0 (C-7', C-7"), 23.1 (C-3', C-3"), 21.9 (C-7'**CH_3**, C-7"**CH_3**), 20.7 (C-7'**CH_3**, C-7"**CH_3**), 16.0 (C-5'**CH_3**, C-5"**CH_3**). MS: no M^+; 155 (1), 139 (27), 138 (97), 137 (7), 124 (4), 123 (40), 97 (14), 96 (27), 95 (100), 83 (71), 82 (30), 81 (80), 69 (40), 67 (19), 57 (29), 55 (54). Anal. calcd. for $C_{24}H_{38}O_4$: C 73.79, H 9.81; found: C 73.87, H 9.75.

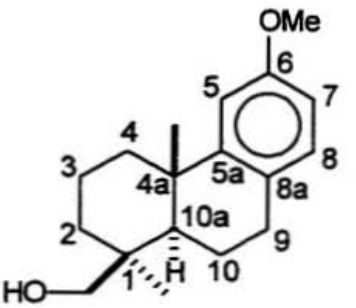
Dibornyl acetylenedicarboxylate (31).



Diethyl acetylenedicarboxylate (1.0 g, 0.94 mL, 5.9 mmol), [(1*S*)-*endo*]-(-)-borneol (4.0 g, 26 mmol), and *p*TsOH (0.12 g, 0.63 mmol) were dissolved in

benzene (25 mL). The mixture was heated to reflux, and reaction progress was monitored by TLC. After 7 days, evaporation of the solvent under vacuum yielded a yellow oil. Flash chromatography (elution with 1% ethyl acetate-hexane) gave **31** (1.95 g, 86%) as colourless crystals: mp: 87-88 °C. IR: 2957, 2883, 1719, 1454, 1379, 1258 cm^{-1}. ^1H NMR: δ 5.02 (2H, ddd, J = 2.1, 3.4, 9.9 Hz, C-2'H, C-2"H), 2.45-2.34 (2H, m, C-3'H, C-3"H), 2.02-1.89 (2H, m, C-5'H, C-5"H), 1.85-1.68 (4H, m, C-4'H, C-4"H, C-6'H, C-6"H), 1.41-1.23 (4H, m, C-5'H, C-5"H, C-6'H, C-6"H), 1.07 (2H, dd, J = 3.4, 14.0 Hz, C-3'H, C-3"H), 0.90 (6H, s, C-7'$\mathbf{CH_3}$, C-7"$\mathbf{CH_3}$), 0.89 (6H, s, C-7'$\mathbf{CH_3}$, C-7"$\mathbf{CH_3}$), 0.87 (6H, s, C-1'$\mathbf{CH_3}$, C-1"$\mathbf{CH_3}$). ^{13}C NMR: δ 152.4 (2 x C=O), 83.4 (C-2', C-2"), 74.9 (C≡C), 49.0 and 48.0 (C-1', C-1", C-7', C-7"), 44.7 (C-4', C-4"), 36.4 (C-3', C-3"), 27.9 (CH_2), 26.9 (CH_2), 19.6 (C-7'$\mathbf{CH_3}$, C-7"$\mathbf{CH_3}$), 18.8 (C-7'$\mathbf{CH_3}$, C-7"$\mathbf{CH_3}$), 13.4 (C-1'$\mathbf{CH_3}$, C-1"$\mathbf{CH_3}$). MS: 387 (1, M^+ +1), 386 (4, M^+), 250 (0.5), 249 (0.9), 153 (4),137 (45), 136 (82), 121 (31), 110 (44), 109 (15), 108 (12), 95 (100), 93 (39), 92 (11), 81 (48), 80 (15), 79 (8), 69 (20), 67 (13), 55 (17). HRMS: calcd for $C_{24}H_{34}O_4$: 386.2455; found: 386.2479.

(1*S*,4a*S*,10a*R*)-1,2,3,4,4a,9,10,10a-Octahydro-6-methoxy-1,4a-dimethyl-1-phenanthrenemethanol (26).

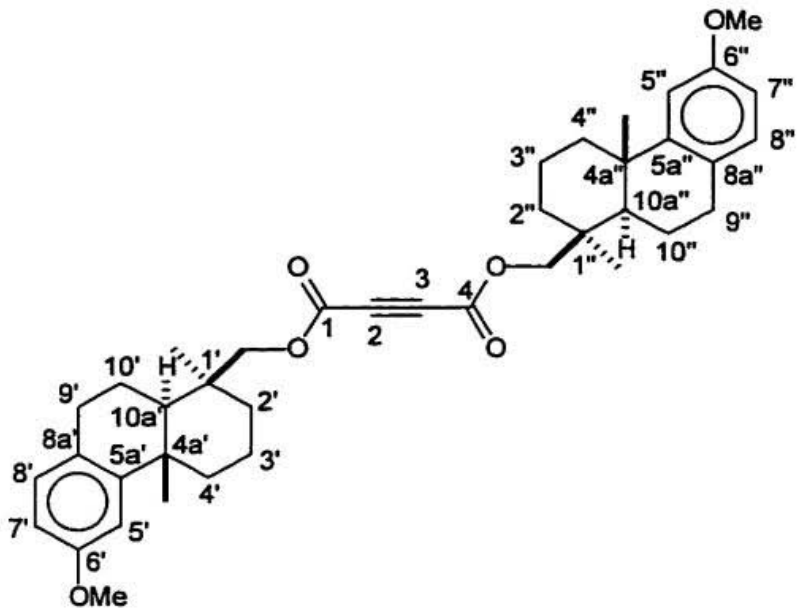


A suspension of $LiAlH_4$ (1.56 g, 41.1 mmol) in THF (20 mL) was cooled to 0 °C and a solution of methyl *o*-methylpodocarpate (**25**) (4.16 g, 13.8 mmol) in THF (30 mL) was added dropwise over 30 min. The mixture was maintained at 0 °C for 3 h, then allowed to warm slowly to rt. TLC after 15 h indicated only 50% conversion, therefore, the mixture was heated to reflux for 24 h. The mixture was then cooled to 0 °C and a solution of 9 : 1 methanol/water (20 mL) was added dropwise resulting in gas evolution. This was followed by dropwise addition of 10% aqueous NH_4Cl (30 mL). After stirring for 1h, the mixture was diluted with diethyl ether (100 mL), water (50 mL), and a saturated aqueous NH_4Cl solution (40 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (4 x 75 mL). Aqueous HCl (1M, 20 mL) was used to neutralize the aqueous layer after the second ether extraction. The combined organic solutions were washed with water (30 mL), and brine (30 mL), and then dried ($MgSO_4$). Solvent evaporation gave a thick yellow oil, which was

purified by flash chromatography (elution with a solvent gradient from 20 to 30% ethyl acetate-petroleum ether) to provide **26** (3.57 g, 94%) as a colourless oil, which crystallized upon standing: mp: 93-93.5 °C. IR: 3384 (broad), 2927, 1610, 1574 (weak), 1501, 1467, 1376, 1247, 1042 cm^{-1}. ^1H NMR: δ 6.95 (1H, d, *J* = 8.4 Hz, C-8H), 6.80 (1H, d, *J* = 2.6 Hz, C-5H), 6.66 (1H, dd, *J* = 2.6, 8.4 Hz, C-7H), 3.86 (1H, d, *J* = 10.9 Hz, C-1**CH**OH), 3.77 (3H, s, C-6O**CH_3**), 3.54 (1H, d, *J* = 10.9 Hz, C-1**CH**OH), 2.92-2.70 (2H, m, C-9H_2), 2.33-2.24 (1H, symmetrical m, C-4H_e), 2.02-1.85 (2H, m, C-2H_e, C-10H_e), 1.80-1.56 (3H, m, C-3H_2, C-10H_a), 1.51-1.38 (2H, m, C-4H_a, C-10aH), 1.35-1.24 (1H, m, C-1CH_2**OH**), 1.18 (3H, s, C-4a**CH_3**), 1.10-0.95 (1H, m, C-2H_a), 1.05 (3H, s, C-1**CH_3**). NOE data: 6.95 (6.66, 4%; 2.92-2.70, 1%), 6.80 (3.77, 2%; 2.33-2.24, 10%; 1.18, 1%), 2.92-2.70 (6.95, 6%; 2.02-1.85, 1%), 2.33-2.24 (6.80, 10%; 1.51-1.38, 5%; 1.18, 1%), 2.02-1.85 (2.92-2.70, 1%; 1.80-1.56, 2%; 1.10-0.95, 1%), 1.51-1.38 (2.33-2.24, 6%; 1.10-0.95, 1%), 1.18 (6.95, 4%; 3.86, 13%; 3.54, 4%; 2.33-2.24, 2%). ^{13}C NMR: δ 157.6 (C-6), 151.0 (C-5a), 129.8 (C-8), 127.1 (C-8a), 110.9 (C-7), 110.2 (C-5), 65.2 (C-1**CH_2**OH), 55.2 (C-6O**CH_3**), 51.1 (C-10a), 38.9 (C-4), 38.7 and 37.9 (C-1, C-4a), 35.1 (C-2), 30.1 (C-9), 26.8 (C-1**CH_3**), 25.6 (C-4a**CH_3**), 19.2 (C-10), 19.0 (C-3). MS: 275 (20, M^+ + 1), 274 (100, M^+), 259 (8), 243 (6), 242 (7), 241 (37), 229 (7), 215 (4), 213 (4), 201 (16), 199 (8), 187 (12), 185 (10), 175 (9), 174 (11), 173 (37), 172 (9), 171 (27), 162

(10), 161 (78), 159 (22), 158 (11), 148 (11), 147 (73), 135 (17), 134 (13), 129 (10), 128 (12), 121 (36), 115 (15), 91 (14), 81 (13), 55 (18).

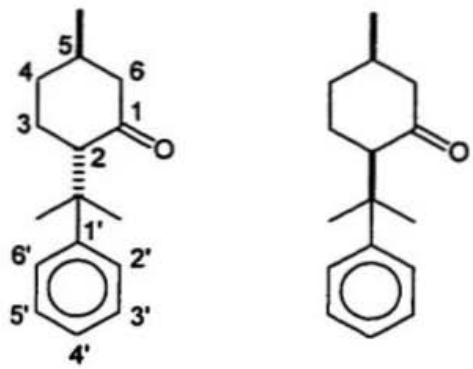
Bis(1*S*,4a*S*,10a*R*)-1,2,3,4,4a,9,10,10a-octahydro-6-methoxy-1,4a-dimethyl-1-phenanthrenemethyl) acetylenedicarboxylate (32).



Diethyl acetylenedicarboxylate (0.276 g, 1.62 mmol), **26** (2.02 g, 7.36 mmol) and *p*TsOH (0.024 g, 0.12 mmol) were dissolved in benzene (15 mL). The mixture was heated to reflux and reaction progress was monitored by TLC. After 7 days, evaporation of the solvent under vacuum yielded a yellow oil. Flash chromatography (elution with a solvent gradient from 10 to 20% ethyl acetate-petroleum ether) provided **32** (0.905 g, 89%) as a colourless solid: mp: 65-67 °C. IR: 2930, 1720, 1610, 1574 (weak), 1502, 1469, 1376 (weak), 1248,

1044, 788 cm^{-1}. ^1H NMR: δ 6.96 (2H, d, *J* = 8.4 Hz, C-8'H, C-8"H), 6.80 (2H, d, *J* = 2.6 Hz, C-5'H, C-5"H), 6.67 (2H, dd, *J* = 2.6, 8.4 Hz, C-7'H, C-7"H), 4.53 (2H, d, *J* = 11.2 Hz, C-1'**C**HOH, C-1"**C**HOH), 4.15 (2H, d, *J* = 11.2 Hz, C-1'**C**HOH, C-1"**C**HOH), 3.77 (6H, s, C-6'O**C**H_3, C-6"O**C**H_3), 2.95-2.71 (4H, m, C-9'H_2, C-9"H_2), 2.35-2.25 (2H, symmetrical m, C-4'H_e, C-4"H_e), 2.04-1.94 (2H, m, C-10'H_e, C-10"H_e), 1.88-1.39 (12H, m, C-2'H_e, C-2"H_e, C-3'H_2, C-3"H_2, C-4'H_a, C-4"H_a, C-10'H_a, C-10"H_a, C-10a'H, C-10a"H), 1.20 (6H, s, C-4a'**C**H_3, C-4a"**C**H_3), 1.18-1.05 (2H, m, C-2'H_a, C-2"H_a), 1.08 (6H, s, C-1'**C**H_3, C-1"**C**H_3). ^{13}C NMR: δ 157.8 (C-6', C-6"), 152.2 (2 x ester C=O), 150.4 (C-5a', C-5a"), 129.8 (C-8', C-8"), 126.8 (C-8a', C-8a"), 111.1 (C-7', C-7"), 110.2 (C-5', C-5"), 74.9 (C-2, C-3), 69.5 (C-1'**C**H_2OH, C-1"**C**H_2OH), 55.2 (C-6'O**C**H_3, C-6"O**C**H_3), 51.1 (C-10a', C-10a"), 38.6 (C-4', C-4"), 37.8 and 37.3 (C-1', C-1", C-4a', C-4a"), 35.6 (C-2', C-2"), 29.9 (C-9', C-9"), 27.1 (C-1'**C**H_3, C-1"**C**H_3), 25.6 (C-4a'**C**H_3, C-4a"**C**H_3), 19.2 (C-10', C-10"), 18.8 (C-3', C-3"). MS: 627 (8, M^+ + 1), 626 (27, M^+), 625 (65), 370 (2), 369 (3), 257 (6), 256 (11), 255 (8), 243 (4), 242 (9), 241 (38), 199 (12), 187 (18), 185 (24), 175 (14), 174 (18), 173 (39), 172 (15), 171 (27), 161 (100), 159 (23), 158 (11), 148 (7), 147 (53), 135 (13), 134 (12), 121 (34), 95 (12), 91 (9), 83 (11), 81 (15), 69 (11), 55 (27). HRMS: calcd for $C_{40}H_{50}O_6$: 626.3605; found: 626.3625.

(2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone (*trans*-28) and (2*R*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanone (*cis*-28).



trans-**28** *cis*-**28**

To a suspension of magnesium (5.55 g, 0.228 mol) in diethyl ether (30 mL) was added one-tenth of a solution of bromobenzene (39.3 g, 0.250 mol) in diethyl ether (50 mL). The mixture was heated to reflux until Grignard reagent began to form. After the initial reflux subsided, addition of the bromobenzene solution was continued with stirring at such a rate that gentle reflux was maintained. After the addition was complete, the red-brown solution was heated to reflux for 1 h, then cooled to rt using an ice bath.

A suspension of copper(I) bromide (2.2 g, 0.015 mol) in diethyl ether (30 mL) was cooled to -20 °C and stirred vigorously while the solution containing the Grignard reagent was added dropwise via a canula using nitrogen pressure. The resulting green-black solution was stirred at -20 °C for 30 min. A solution of (*R*)-(+)-pulegone (17.0 g, 0.112 mol) in diethyl ether (25 mL) was added dropwise, with stirring over 2.5 h, and the resulting solution was kept at -20 °C

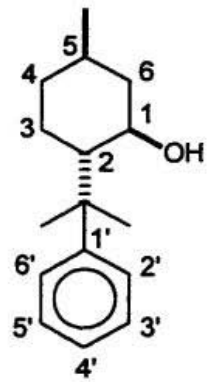
overnight. The dark green solution was then carefully poured into ice-cold 2M aqueous HCl (150 mL) with vigorous stirring. The organic layer was separated and filtered while the aqueous layer was saturated with NH_4Cl and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (20 mL), and the solvent was evaporated under reduced pressure to yield a crude oily product (~ 35 g).

This crude product was added to a solution of ethanol (300 mL), water (40 mL) and KOH (35.0 g, 0.624 mol) and refluxed for 3 h. The mixture was concentrated to 100 mL under reduced pressure, and water (250 mL) was added. The aqueous layer was saturated with NaCl and extracted with diethyl ether (4 x 60 mL). After drying ($MgSO_4$) and solvent evaporation, the crude mixture was distilled under reduced pressure (1.5 mm Hg). Four fractions were collected. Fractions 1 and 2 (boiling range: up to 135 °C) contained mostly biphenyl. Fraction 3 (boiling range: 135-142 °C) contained primarily ketone **28** and a little biphenyl, whereas fraction 4 (boiling range: 142-147 °C) contained the main quantity of ketone **28**. Fraction 3 was decanted away from the crystalline biphenyl into fraction 4 to give **28** (20.4 g, 79 %) as a yellow oil. This crude product was used directly in the reduction step. A small sample was purified by flash chromatography (elution with 4% ethyl acetate-hexane). For *trans*-**28**. IR: 3089 (weak), 3058 (weak), 2954, 1711, 1600 (weak), 1446 cm^{-1}. ^1H NMR: δ 7.29 (4H, m, C-2'H, C-3'H, C-5'H, C-6'H), 7.16 (1H, m, C-4'H), 2.67

(1H, ddd, J = 1.1, 4.7, 12.7 Hz, C-2H), 2.24 (1H, ddd, J = 2.2, 3.9, 12.5 Hz, C-6H_e), 2.01 (1H, dt, J = 0.8, 12.5 Hz, C-6H_a), 1.92-1.66 (3H, m, C-3H_e, C-4H_e, C-5H), 1.53-1.13 (2H, m, C-3H_a, C-4H_a), 1.46 (3H, s, C-2C**CH_3**Ph), 1.40 (3H, s, C-2C**CH_3**Ph), 0.96 (3H, d, J = 6.1 Hz, C-5**CH_3**). ^{13}C NMR: δ 211.1 (C-1), 149.8 (C-1'), 127.9 (C-3', C-5'), 125.7 (C-2', C-6'), 125.4 (C-4'), 59.4 (C-2), 52.2 (C-6), 38.9 (C-2**C**$(CH_3)_2$Ph), 36.1 (C-5), 34.6 (C-4), 28.9 (C-3), 26.5 (C-2C**CH_3**Ph), 23.7 (C-2C**CH_3**Ph), 22.2 (C-5**CH_3**). MS: 231 (1, M^+ + 1), 230 (8, M^+), 131 (2), 120 (11), 119 (100), 112 (31), 111 (3), 91 (20), 79 (4), 77 (3), 41 (13). HRMS: calcd for $C_{16}H_{22}O$: 230.1670; found: 230.1672.

For *cis*-**28**. IR: 3096 (weak), 3058 (weak), 2958, 1710, 1620 (weak) cm^{-1}. ^{1}H NMR: δ 7.32 (4H, m, C-2'H, C-3'H, C-5'H, C-6'H), 7.18 (1H, m, C-4'H), 2.66 (1H, dd, J = 6.3, 10.0 Hz, C-2H), 2.48 (1H, dd, J = 5.7, 13.0 Hz, C-6H_e), 2.34-2.20 (1H, m, C-5H), 1.99 (1H, ddd, J = 1.6, 4.7, 13.0 Hz, C-6H_a), 1.80-1.20 (4H, m, C-3H_e, C-3H_a, C-4H_e, C-4H_a), 1.46 (3H, s, C-2C**CH_3**Ph), 1.43 (3H, s, C-2C**CH_3**Ph), 0.90 (3H, d, J = 7.4 Hz, C-5**CH_3**). ^{13}C NMR: δ 212.3 (C-1), 149.3 (C-1'), 128.0 (C-3', C-5'), 125.9 (C-2', C-6'), 125.6 (C-4'), 59.6 (C-2), 50.3 (C-6), 39.5 (C-2**C**$(CH_3)_2$Ph), 32.2 (C-5), 31.2 (C-4), 27.2 (C-2C**CH_3**Ph), 24.8 (C-3), 24.0 (C-2C**CH_3**Ph), 19.3 (C-5**CH_3**). MS: 231 (1, M^+ + 1), 230 (5, M^+), 131 (2), 120 (9), 119 (100), 112 (29), 111 (4), 91 (19), 79 (4), 77 (3), 41 (11). HRMS: calcd for $C_{16}H_{22}O$: 230.1670; found: 230.1667.

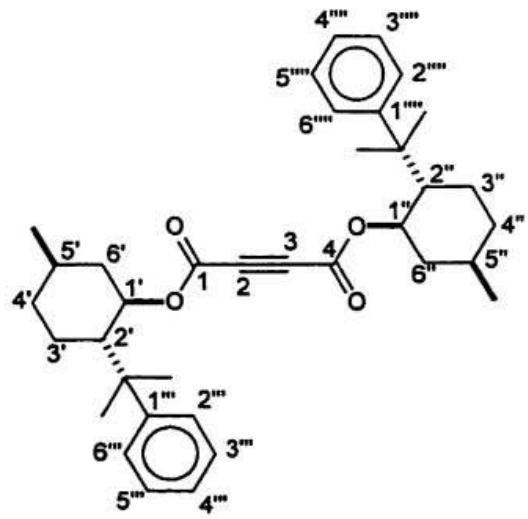
(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol (29).



A suspension of sodium (6.03 g, 0.262 mol) in toluene (90 mL) was heated to reflux. A solution of 2-propanol (15.0 g, 19.1 mL, 0.250 mmol) and *cis*- and *trans*-**28** (*ca.* 19.5 g, 84.7 mmol) in toluene (20 mL) were added dropwise to this mixture over 90 min. The rate of addition was such that controlled refluxing was maintained. The mixture was refluxed for 8 h, and the resulting yellow-orange solution was cooled to 0 °C. Ethanol was added slowly until most of the sodium was quenched. The mixture was then poured into ice-water (100 mL) after diluting with diethyl ether (125 mL). The organic layer was separated, and the aqueous layer was saturated with NaCl and extracted with diethyl ether (4 x 50 mL). The combined organic layers were washed with brine (25 mL) and dried ($MgSO_4$). Solvent evaporation gave a red oil which was vacuum distilled (138-143 °C at *ca.* 0.5 mm Hg) to yield crude **29** (15.3 g, 78%), composed of 4 epimers as a yellow oil. Careful column chromatography of ~1-5 g samples (elution with 4% ethyl acetate-hexane) gave **29** (8.24, 42%) as a colourless oil. IR: 3564, 3430 (broad), 3088 (weak), 3057 (weak), 3030 (weak), 2919, 1600,

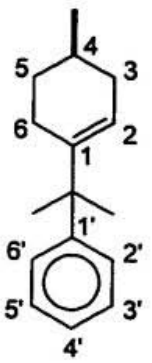
1496, 1455, 1368, 1030 cm^{-1}. ^1H NMR: δ 7.42-7.37 (2H, m, C-2'H, C-6'H), 7.35-7.28 (2H, m, C-3'H, C-5'H), 7.18 (1H, m, C-4'H), 3.53 (1H, symmetrical m, C-1H), 1.84 (1H, symmetrical m, C-6H_e), 1.76-1.58 (3H, m, C-2H, C-3H_e, C-4H_e), 1.39 (1H, m, C-5H), 1.42 (3H, s, C-2C**CH_3**Ph), 1.29 (3H, s, C-2C**CH_3**Ph), 1.12-0.77 (3H, m, C-3H_a, C-4H_a, C-6H_a), 0.87 (3H, d, J = 6.6 Hz, C-5**CH_3**). ^{13}C NMR: δ 151.3 (C-1'), 128.4 (C-3', C-5'), 125.7 (C-2', C-4', C-6'), 72.9 (C-1), 54.1 (C-2), 45.3 (C-6), 39.7 (C-2**C**$(CH_3)_2$Ph), 34.8 (C-4), 31.5 (C-5), 28.7 (C-2C**CH_3**Ph), 26.4 (C-3), 24.2 (C-2C**CH_3**Ph), 22.0 (C-5**CH_3**). MS: 232 (0.6, M^+), 214 (6), 120 (36), 119 (100), 118 (51), 105 (26), 95 (11), 91 (51), 86 (8), 84 (13), 79 (10), 77 (8), 55 (9).

Bis((1*R*,2*S*,5*R*)-8-phenylmenthyl) acetylenedicarboxylate (33) and (4*R*)-4-methyl-1-(1-methyl-1-phenylethyl)cyclohexene (34).



33

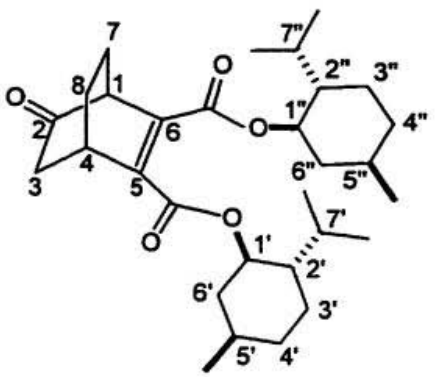
A solution of **29** (0.448 g, 1.93 mmol), diethyl acetylenedicarboxylate (0.0935 g, 0.550 mmol) and *p*TsOH (0.018 g, 0.095 mmol) in benzene (15 mL) was heated to 70 °C for 14 days. Solvent evaporation followed by flash chromatography (elution with 6% ethyl acetate-petroleum ether) gave **33** (11.1 mg, 4 %) as a yellow oil, **34** (25.1 mg, 6%) as a colourless oil and **29** (0.348 g, 78%) was recovered as a colourless oil. For **33**. IR: 3058 (weak), 3024 (weak), 2955, 1715, 1257, 1028 cm^{-1}. ^1H NMR: δ 7.33-7.25 (8H, m, C-2'''H, C-2''''H, C-3'''H, C-3''''H, C-5'''H, C-5''''H, C-6'''H, C-6''''H), 7.18-7.11 (2H, m, C-4'''H, C-4''''H), 4.90 (2H, dt, *J* = 4.4, 10.7 Hz, C-1'H, C-1"H), 2.04-1.86 (4H, m, C-2'H, C-2"H, C-6'H_e, C-6"H_e), 1.66-1.32 (6H, m, C-3'H_e, C-3"H_e, C-4'H_e, C-4"H_e, C-5'H, C-5"H), 1.34 (6H, s, C-2'C**CH_3**Ph, C-2"C**CH_3**Ph), 1.27 (6H, s, C-2'C**CH_3**Ph, C-2"C**CH_3**Ph), 1.20-0.75 (6H, m, C-3'H_a, C-3"H_a, C-4'H_a, C-4"H_a, C-6'H_a, C-6"H_a), 0.88 (6H, d, *J* = 6.5 Hz, C-5'**CH_3**, C-5"**CH_3**). ^{13}C NMR: δ 151.2 (C-1''', C-1''''), 150.3 (C-1, C-4), 128.1 (C-3''', C-3'''', C-5''', C-5''''), 125.5 (C-4''', C-4''''), 125.4 (C-2''', C-2'''', C-6''', C-6''''), 77.6 (C-1', C-1"), 74.6 (C-2, C-3), 50.5 (C-2', C-2"), 41.3 (C-6', C-6"), 39.8 (C-2'**C**$(CH_3)_2$Ph, C-2"**C**$(CH_3)_2$Ph), 34.2 (C-4', C-4"), 31.4 (C-5', C-5"), 26.7 (C-3', C-3"), 26.6 (C-2'C(**CH_3**)$_2$Ph, C-2"C(**CH_3**)$_2$Ph), 21.7 (C-5'**CH_3**, C-5"**CH_3**). MS: 542 (1, M^+), 423 (1), 327 (1), 215 (14), 214 (27), 120 (28), 119 (100), 118 (47), 105 (47), 95 (9), 91 (33), 81 (7), 79 (6), 69 (5), 55 (10).



34

For **34**. IR: 3056 (weak), 3022 (weak), 2923, 1600, 1493, 1454 cm^{-1}. ^1H NMR: δ 7.34-7.23 (4H, m, C-2'H, C-3'H, C-5'H, C-6'H), 7.15 (1H, m, C-4'H), 5.67 (1H, m, C-2H), 2.21 (1H, m, C-3H_e), *ca.* 1.90-1.40 (5H, m, C-3H_a, C-4H, C-5H_e, C-6H_2), 1.39 (3H, s, C-1C**CH_3**Ph), 1.36 (3H, s, C-1C**CH_3**Ph), *ca.* 1.25-0.95 (1H, m, C-5H_a), 0.93 (3H, d, J = 6.7 Hz, C-4**CH_3**). ^{13}C NMR: δ 149.4 (C-1'), 144.1 (C-1), 127.9 (C-3', C-5'), 126.1 (C-2', C-6'), 125.4 (C-4'), 119.2 (C-2), 43.5 (C-1**C**$(CH_3)_2$Ph), 34.2 (C-3), 31.6 (C-5), 29.1 (C-1C**CH_3**Ph), 28.4 (C-4), 27.6 (C-1C**CH_3**Ph), 25.6 (C-6), 21.8 (C-4**CH_3**). MS: 215 (11, M^+ + 1), 214 (60, M^+), 200 (14), 199 (84), 171 (26), 157 (27), 144 (13), 143 (76), 131 (11), 129 (31), 128 (12), 119 (100), 118 (10), 117 (11), 115 (11), 105 (22), 95 (32), 91 (69), 79 (15), 77 (17), 69 (16), 55 (19). HRMS: calcd for $C_{16}H_{22}$: 214.1720; found: 214.1719.

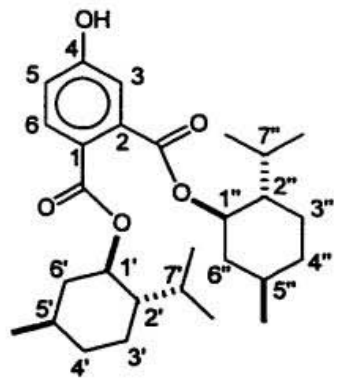
Dimenthyl bicyclo[2.2.2]oct-5-en-2-one-5,6-dicarboxylate (36a) and dimenthyl 4-hydroxyphthalate (37).



36a

Diene **17a** (0.254 g, 1.51 mmol) and acetylenic dienophile **30** (3.00 g, 7.68 mmol) were added to benzene (40 mL). The dienophile was dissolved with stirring, and the mixture was heated to reflux for 27 h. Solvent evaporation followed by the addition of a small amount of pentane gave partial precipitation of the excess dienophile. Flash chromatography (elution with 1.5% ethyl acetate-hexane) gave a mixture of the TMS enol ether **35a** (minor) and the corresponding ketone **36a** (major). Flash chromatography (elution with solvent gradient from 1 to 7% ethyl acetate-hexane) gave **36a** (0.461 g, 63%) as a pale yellow oil and **37** (0.069 g, 10%) as a white solid. For **36a** (a 1.22 : 1 diastereomeric mixture). IR: 2956, 2871, 1731, 1713, 1639, 1454, 1377, 1263 cm^{-1}. ^1H NMR: δ 4.87-4.74 (2H, m, C-1'H, C-1"H), 3.59 (1H, m, C-1H), 3.37 (1H, m, C-4H), 2.25-1.37 (18H, m, C-2'H, C-2"H, C-$3H_2$, C-3'H_e, C-3"H_e, C-4'H_e, C-4"H_e, C-5'H, C-5"H, C-6'H_e, C-6"H_e, C-$7H_2$, C-7'H, C-7"H, C-$8H_2$), 1.17-0.81

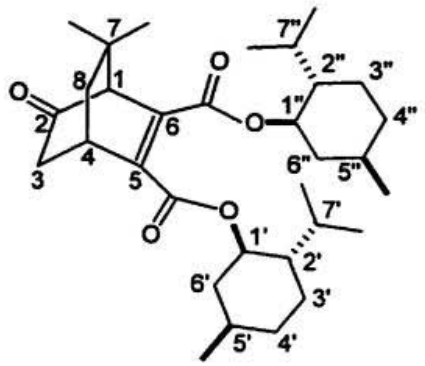
(18H, m, C-3'H_a, C-3"H_a, C-4'H_a, C-4"H_a, C-6'H_a, C-6"H_a, 2 x C-7'$\mathbf{CH_3}$, 2 x C-7"$\mathbf{CH_3}$), 0.80 (1.5H, d, J = 7.1 Hz, C-5'$\mathbf{CH_3}$ or C-5"$\mathbf{CH_3}$), 0.79 (1.5H, d, J = 7.1 Hz, C-5'$\mathbf{CH_3}$ or C-5"$\mathbf{CH_3}$), 0.77 (3H, J = 7.1 Hz, C-5'CH_3 or C-5"CH_3). ^{13}C NMR: (Some ^{13}C signals are present for both diastereomers, others overlap and appear as one. Theoretically, this C_{30} compound could have 60 ^{13}C signals.) δ 209.12 and 209.07 (C-2), 165.2 and 165.1 (ester C=O), 163.7 (2C, ester C=O), 143.3 and 143.1 (C-5), 134.0 and 133.7 (C-6), 75.60, 75.56, and 75.5 (4C, C-1', C-1"), 49.6 (2C, C-1), 46.8, 46.74 and 46.70 (4C, C-2', C-2"), 40.6 and 40.5 (4C, C-6', C-6"), 39.0 (2C, C-3), 35.10 and 35.06 (C-4), 34.1 (4C, C-4', C-4"), 31.3 (4C, C-5', C-5"), 26.13, 26.08, 26.0 and 25.9 (C-7', C-7"), 24.0 and 23.9 (C-8), 23.3 and 23.2 (4C, C-3', C-3"), 22.73 and 22.69 (C-7), 22.0 (4C, C-7'$\mathbf{CH_3}$, C-7"$\mathbf{CH_3}$), 20.8 and 20.7 (4C, C-7'$\mathbf{CH_3}$, C-7"$\mathbf{CH_3}$), 16.2 and 16.1 (4C, C-5'$\mathbf{CH_3}$, C-5"$\mathbf{CH_3}$). MS: 348 (4, M^+ - 138), 210 (100), 193 (3), 192 (24), 150 (3), 151 (6), 139 (23), 138 (4), 123 (7), 97 (10), 95 (10), 85 (17), 83 (93), 81 (13), 69 (25), 57 (23), 55 (32). HRMS: calcd for $C_{20}H_{28}O_5$ (M^+ - $C_{10}H_{18}$): 348.1935; found: 348.1929.



37

For **37**: mp: 175-176 °C. IR: 3361 (broad), 2956, 1710, 1603, 1580, 1455, 1277 (broad), 1128 cm^{-1}. ^1H NMR: δ 7.70 (1H, d, *J* = 8.5 Hz, C-6H), 7.40 (1H, br m, OH), 6.97 (1H, d, *J* = 2.6 Hz, C-3H), 6.88 (1H, dd, *J* = 2.6, 8.5 Hz, C-5H), 4.91 (2H, apparent dq, *J* = 4.2, 11.1 Hz, C-1'H, C-1"H), 2.30-2.07 (2H, m, C-6'H_e, C-6"H_e), 2.03-1.89 (2H, symmetrical m, C-7'H, C-7"H), 1.84-1.37 (8H, m, C-2'H, C-2"H, C-3'H_e, C-3"H_e, C-4'H_e, C-4"H_e, C-5'H, C-5"H), 1.20-0.85 (6H, m, C-3'H_a, C-3"H_a, C-4'H_a, C-4"H_a, C-6'H_a, C-6"H_a), 0.93 (3H, d, *J* = 6.4 Hz, C-7'**CH_3** or C-7"**CH_3**), 0.92 (3H, d, *J* = 6.7 Hz, C-7'**CH_3** or C-7"**CH_3**), 0.90 (3H, d, *J* = 7.1 Hz, C-7'**CH_3** or C-7"**CH_3**), 0.89 (3H, d, *J* = 7.3 Hz, C-7'**CH_3** or C-7"**CH_3**), 0.83 (3H, d, *J* = 6.9 Hz, C-5'**CH_3** or C-5"**CH_3**), 0.79 (3H, d, *J* = 7.0 Hz, C-5'**CH_3** or C-5"**CH_3**). ^{13}C NMR: δ 168.4 (ester C=O), 165.9 (ester C=O), 158.7 (C-4), 136.6 (C-2), 131.6 (C-6), 122.7 (C-1), 116.8 (C-5), 115.3 (C-3), 76.0 and 75.2 (C-1', C-1"), 47.1 (C-2', C-2"), 40.7 and 40.3 (C-6', C-6"), 34.3 (C-4', C-4"), 31.5 (C-5', C-5"), 26.2 and 26.0 (C-7', C-7"), 23.4 and 23.3 (C-3', C-3"), 22.1 (C-7'**CH_3**, C-7"**CH_3**), 20.9 (C-7'**CH_3**, C-7"**CH_3**), 16.4 and 16.2 (C-5'**CH_3**, C-5"**CH_3**). MS: no M^+, 321 (3), 184 (9), 183 (100), 166 (9), 165 (63), 139 (18), 138 (38), 123 (15), 97 (12), 96 (11), 95 (47), 83 (30), 82 (14), 81 (34), 69 (33), 67 (11), 57 (23), 55 (42). Anal. calcd. for $C_{28}H_{42}O_5$: C 73.31, H 9.24; found: C 73.37, H 9.17.

Dimenthyl 7,7-dimethylbicyclo[2.2.2]oct-5-en-2-one-5,6-dicarboxylate (36b) and dimenthyl 4-hydroxyphthalate (37).

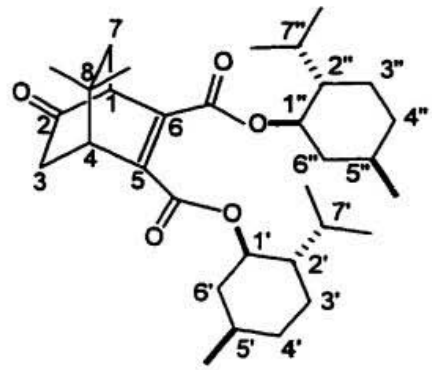


36b

Diene **17b** (0.228 g, 1.16 mmol) and acetylenic dienophile **30** (3.17 g, 8.12 mmol) were added to benzene (40 mL). The dienophile was dissolved with stirring, and the mixture was heated to reflux for 30 h. Solvent evaporation followed by the addition of a small amount of pentane gave partial precipitation of the excess dienophile. Flash chromatography (elution with 3% ethyl acetate-hexane) was initially unsuccessful. The column fractions were recombined and flash chromatography using Fluorisil (elution with 7.5% ethyl acetate-hexane) gave **36b** (0.401 g, 67%) as a colourless oil and **37** (0.034 g, 6%) as a white solid. For **36b** (a 1.02 : 1 diastereomeric mixture). IR: 2956, 2871, 1736, 1713, 1657, 1265, 1238 cm^{-1}. ^1H NMR: δ 4.86-4.73 (2H, m, C-1'H, C-1"H), 3.27 (1H, m, C-4H), 3.22 (0.5 H, s, C-1H), 3.19 (0.5H, s, C-1H), 2.23-1.99 (4H, m, C-3H_2, C-6'H_e, C-6"H_e), 1.96-1.78 (2H, m, C-7'H, C-7"H), 1.75-1.36 (10H, m, C-2'H, C-2"H, C-3'H_e, C-3"H_e, C-4'H_e, C-4"H_e, C-5'H, C-5"H,

C-8H_2), 1.11-0.82 (18H, m, C-3'H_a, C-3"H_a, C-4'H_a, C-4"H_a, C-6'H_a, C-6"H_a, 2 x C-7'$\mathbf{CH_3}$, 2 x C-7"$\mathbf{CH_3}$), 1.11 (3H, s, C-7$\mathbf{CH_3}$), 1.00 (1.5H, s, C-7$\mathbf{CH_3}$), 0.99 (1.5H, s, C-7$\mathbf{CH_3}$), 0.79 (3H, d, J = 6.9 Hz, C-5'$\mathbf{CH_3}$ or C-5"$\mathbf{CH_3}$), 0.75 (3H, d, J = 6.9 Hz, C-5"$\mathbf{CH_3}$ or C-5'$\mathbf{CH_3}$). ^{13}C NMR: δ 209.2 and 209.1 (C-2), 165.5 and 165.4 (ester C=O), 163.83 and 163.78 (ester C=O), 142.9 and 142.8 (C-5), 133.8 and 133.4 (C-6), 75.44, 75.41 and 75.3 (4C, C-1', C-1"), 62.2 and 61.9 (C-1), 46.8, 46.74 and 46.72 (4C, C-2', C-2"), 40.5 (4C, C-6', C-6"), 39.7 (2C, C-8), 37.44 and 37.37 (C-3), 35.6 and 35.38 (C-4), 35.5 and 35.43 (C-7), 34.1 (4C, C-4', C-4"), 31.3 (4C, C-5', C-5"), 30.4 (2C, C-7$\mathbf{CH_3}$), 29.6 and 29.4 (C-7$\mathbf{CH_3}$), 26.3, 26.2, 25.9 and 25.8 (C-7', C-7"), 23.5, 23.4 and 23.0 (4C, C-3', C-3"), 22.0 (4C, C-7'$\mathbf{CH_3}$, C-7"$\mathbf{CH_3}$), 20.8 and 20.6 (4C, C-7'$\mathbf{CH_3}$, C-7"$\mathbf{CH_3}$), 16.4 and 16.0 (4C, C-5'$\mathbf{CH_3}$, C-5"$\mathbf{CH_3}$). MS: 515 (0.3, M^+ +1), 377 (4), 376 (15), 240 (8), 239 (57), 238 (100), 222 (4), 221 (19), 220 (98), 179 (12), 178 (19), 139 (56), 138 (15), 123 (8), 97 (27), 95 (29), 84 (13), 83 (100), 81 (33), 69 (69), 67 (11), 57 (60). HRMS: calcd for $C_{22}H_{32}O_5$ (M^+ - $C_{10}H_{18}$): 376.2248; found: 376.2221.

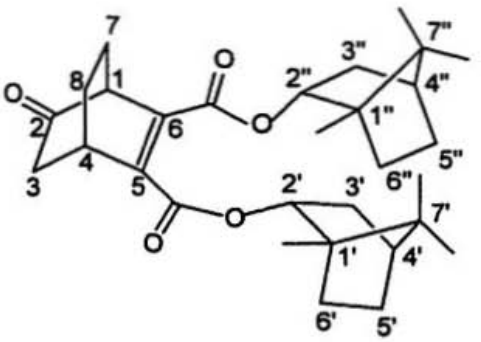
Dimenthyl 8,8-dimethylbicyclo[2.2.2]oct-5-en-2-one-5,6-dicarboxylate (36c) and dimenthyl 4-hydroxyphthalate (37).



Diene **17c** (0.155 g, 0.787 mmol) and acetylenic dienophile **30** (2.22 g, 5.68 mmol) were added to benzene (40 mL). The mixture was heated to reflux for 5 days. Solvent evaporation followed by the addition of a small amount of pentane gave partial precipitation of the excess dienophile. Flash chromatography (elution with 5% ethyl acetate-hexane) gave poor separation. The column fractions were recombined, and flash chromatography (elution with 2.5% ethyl acetate-hexane) gave **36c** (0.145 g, 36%) as a colourless oil and **37** (0.044 g, 12%) as a white solid. For **36c** (a 1.45 : 1 diastereomeric mixture). IR: 2956, 2871, 1734, 1712, 1639, 1265, 1240 cm^{-1}. ^1H NMR: δ 4.88-4.74 (2H, m, C-1'H, C-1"H), 3.45 (1H, m, C-1H), 2.90 (0.41H, t, J = 2.7 Hz, C-4H), 2.85 (0.59H, t, J = 2.7 Hz, C-4H), 2.47 (1H, dd, J = 2.7, 18.9 Hz, C-3H), 2.16-2.03 (3H, m, C-3H, C-6'H_e, C-6"H_e), 1.96-1.79 (2H, symmetrical m, C-7'H, C-7"H), 1.79-1.35 (10H, m, C-2'H, C-2"H, C-3'H_e, C-3"H_e, C-4'H_e, C-4"H_e, C-5'H, C-5"H, C-7H_2), 1.16 (3H, s, C-8CH_3), 1.14-0.87 (18H, m, C-3'H_a, C-3"H_a, C-4'H_a, C-4"H_a,

C-6'H_a, C-6"H_a, 2 x C-7'CH_3, 2 x C-7"CH_3), 1.06 (3H, s, C-8CH_3), 0.80-0.75 (6H, m, C-5'CH_3, C-5"CH_3). ^{13}C NMR: δ 209.5 and 209.4 (C-2), 165.4 and 165.3 (ester C=O), 164.2 and 164.0 (ester C=O), 144.4 and 143.9 (C-5), 133.6 and 133.2 (C-6), 75.61, 75.57, 75.5 and 75.4 (C-1', C-1"), 51.6 and 51.2 (C-1), 47.0, 46.9, 46.80, 46.76 and 46.7 (6C, C-4, C-2', C-2"), 40.6, 40.5 and 40.4 (4C, C-6', C-6"), 38.7 (2C, C-7), 35.5 and 35.4 (C-3), 34.14 (4C, C-4', C-4"), 34.08 (2C, C-8), 31.5, 31.4 and 31.3 (6C, C-8CH_3, C-5', C-5"), 28.2 (2C, C-8CH_3), 26.3, 26.0 and 25.9 (4C, C-7', C-7"), 23.6, 23.3, 23.2 and 23.1 (C-3', C-3"), 22.0 (4C, C-7'CH_3, C-7"CH_3), 20.8 and 20.6 (4C, C-7'CH_3, C-7"CH_3), 16.5, 16.3, 16.1 and 16.0 (C-5'CH_3, C-5"CH_3). MS: 515 (0.1, M^+ +1), 377 (1), 376 (4), 238 (100), 221 (4), 220 (26), 179 (5), 139 (17), 138 (5), 123 (3), 97 (10), 95 (12), 83 (51), 81 (10), 69 (21), 57 (19), 55 (34). HRMS: calcd for $C_{22}H_{32}O_5$ (M^+ - $C_{10}H_{18}$): 376.2248; found: 376.2251.

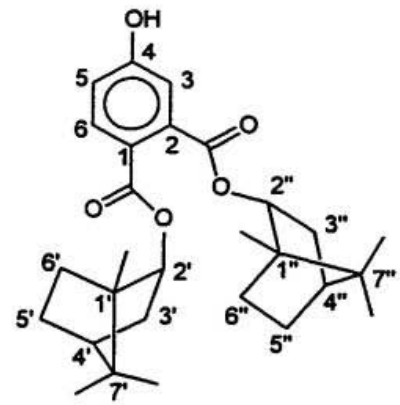
Dibornyl bicyclo[2.2.2]oct-5-en-2-one-5,6-dicarboxylate (40a) and dibornyl 4-hydroxyphthalate (38).



40a

Diene **17a** (0.124 g, 0.737 mmol) and the acetylenic dienophile **31** (0.819 g, 2.12 mmol) were added to benzene (25 mL). The mixture was heated to reflux for 3 days. Following solvent evaporation, methanol (10 mL) and 0.5 M aqueous HCl (0.5 mL) were added to the mixture. This was stirred for 1 h then diluted with diethyl ether (20 mL) and ethyl acetate (10 mL). The organic solution was washed with brine (5 mL) and water (5 mL), and then dried ($MgSO_4$). Solvent evaporation followed by flash chromatography (elution with 4% ethyl acetate-hexane) gave **40a** (0.162 g, 46%) as a yellow solid and **38** (0.037 g, 11%) as a white solid. For **40a** (a 1 : 1 diastereomeric mixture): mp: 130-131 °C. IR: 2955, 2879, 1730, 1715, 1639, 1454, 1258 cm^{-1}. ^1H NMR: δ 5.08-4.96 (2H, m, C-2'H, C-2"H), 3.63 (1H, m, C-1H), 3.41 (1H, m, C-4H), 2.46-2.31 (2H, symmetrical m, C-3'H, C-3"H), 2.23 (1H, m, C-3H), 2.14 (1H, dd, J = 2.4, 18.6 Hz, C-3H), 2.08-1.63 (10H, m, C-4'H, C-4"H, C-5'H, C-5"H, C-6'H, C-6"H, C-$7H_2$, C-$8H_2$), 1.37-1.21 (4H, m, C-5'H, C-5"H, C-6'H, C-6"H), 1.16-1.02 (2H, m, C-3'H, C-3"H), 0.92 (3H, s, CH_3), 0.91 (3H, s, CH_3), 0.884 (3H, s, CH_3), 0.876 (3H, s, CH_3), 0.87 (3H, s, CH_3), 0.86 (1.5H, s, CH_3), 0.85 (1.5H, s, CH_3). ^{13}C NMR: δ 209.2 and 209.1 (C-2), 165.8 (2C, ester C=O), 164.3 (2C, ester C=O), 143.4 and 143.3 (C-5), 134.1 (2C, C-6), 81.44, 81.40, 81.34 and 81.27 (C-2', C-2"), 49.82 and 49.78 (C-1), 49.02, 48.97, 47.93 and 47.89 (8C, C-1', C-1", C-7', C-7"), 44.8 (4C, C-4', C-4"), 39.1 and 39.0 (C-3), 36.6, 36.4 and 36.3 (4C, C-3', C-3"), 35.24 and 35.20 (C-4), 28.0, 27.94, 27.90 and 27.2 (8C, C-5',

C-5", C-6', C-6"), 24.1 and 24.0 (C-8), 22.8 and 22.7 (C-7), 19.4 (4C, C-7'CH_3, C-7"CH_3), 18.8 (4C, C-7'CH_3, C-7"CH_3), 13.60 and 13.56 (4C, C-1'CH_3, C-1"CH_3). MS: 483 (1, $M^+ + 1$), 482 (2, M^+), 347 (3), 346 (11), 211 (1), 210 (10), 153 (15), 138 (69), 137 (100), 136 (49), 135 (10), 122 (3), 121 (20), 109 (32), 108 (8), 107 (8), 95 (35), 93 (17), 81 (73), 69 (17), 67 (10). HRMS: calcd for $C_{20}H_{26}O_5$ ($M^+ - C_{10}H_{16}$): 346.1779; found: 346.1773.

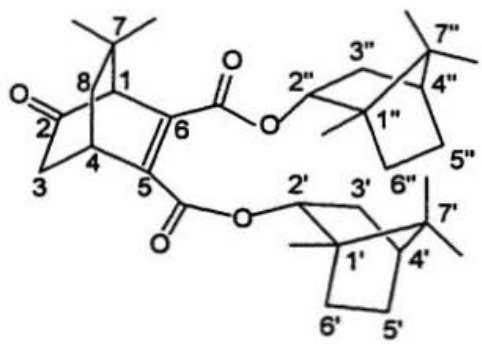


38

For **38**: mp: 214-215 °C. IR: 3371 (broad), 3021 (weak), 2957, 1709, 1605, 1580, 1453 cm^{-1}. ^1H NMR: δ 7.70 (1H, d, J = 8.5 Hz, C-6H), 7.57 (1H, br s, OH), 7.03 (1H, d, J = 2.5 Hz, C-3H), 6.91 (1H, dd, J = 2.5, 8.5 Hz, C-5H), 5.06 (2H, symmetrical m, C-2'H, C-2"H), 2.42 (2H, symmetrical m, C-3'H, C-3"H), 2.07-1.85 (2H, m, C-5'H, C-5"H), 1.85-1.65 (4H, m, C-4'H, C-4"H, C-6'H, C-6"H), 1.41-1.18 (5H, m, C-3'H or C-3"H, C-5'H, C-5"H, C-6'H, C-6"H), 1.13 (1H, dd, J = 3.4, 13.8 Hz, C-3'H or C-3"H), 0.92 (6H, s, 2 x CH_3), 0.89 (3H, s, CH_3), 0.88 (6H, s, 2 x CH_3), 0.87 (3H, s, CH_3). ^{13}C NMR: δ 169.4 (ester C=O), 167.0 (ester

C=O), 159.2 (C-4), 136.2 (C-2), 131.5 (C-6), 122.4 (C-1), 117.1 (C-5), 115.6 (C-3), 82.0 and 81.2 (C-2', C-2"), 48.9 and 47.9 (C-1', C-1", C-7', C-7"), 44.8 (C-4', C-4"), 36.5 and 36.1 (C-3', C-3"), 28.0, 27.9, 27.3 and 27.1 (C-5', C-5", C-6', C-6"), 19.7 (C-7'$\mathbf{CH_3}$, C-7"$\mathbf{CH_3}$), 18.8 (C-7'$\mathbf{CH_3}$, C-7"$\mathbf{CH_3}$), 13.5 (C-1'$\mathbf{CH_3}$, C-1"$\mathbf{CH_3}$). MS: 455 (0.6, $M^+ + 1$), 454 (3, M^+), 318 (0.1), 302 (0.6), 301 (2), 183 (2), 153 (1), 138 (12), 137 (100), 136 (6), 95 (12), 93 (8), 81 (50), 69 (12), 67 (8), 55 (7). HRMS: calcd for $C_{28}H_{38}O_5$: 454.2717; found: 454.2686.

Dibornyl 7,7-dimethylbicyclo[2.2.2]oct-5-en-2-one-5,6-dicarboxylate (40b) and dibornyl 4-hydroxyphthalate (38).



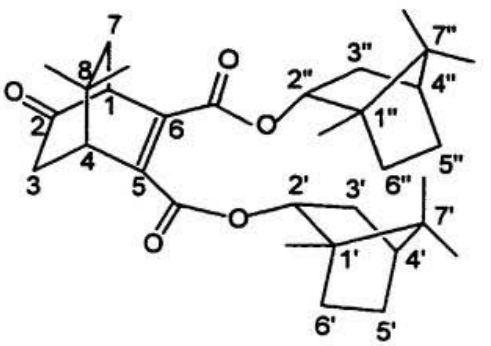
40b

Diene **17b** (0.122 g, 0.619 mmol) and acetylenic dienophile **31** (0.542 g, 1.40 mmol) were added to benzene (25 mL). The mixture was heated to reflux for 5 days. Following solvent evaporation, methanol (10 mL) and 0.5 M aqueous HCl (0.5 mL) were added to the mixture. This was stirred for 1 h then diluted with diethyl ether (20 mL) and ethyl acetate (10 mL). The organic solution was

washed with brine (5 mL) and water (5 mL), and then dried ($MgSO_4$). Solvent evaporation followed by flash chromatography (elution with 7% ethyl acetate-hexane) gave **40b** as a yellow solid (0.208 g, 66 %) and **38** (0.077g, 28%). For **40b** (a 1 : 1 diastereomeric mixture): mp: 189-190 °C. IR: 2957, 2875, 1732, 1713, 1640, 1265, 1234 cm^{-1}. ^1H NMR: δ 5.07-4.94 (2H, m, C-2'H, C-2"H), 3.33 (1H, m, C-4H), 3.23 (0.5H, s, C-1H), 3.22 (0.5H, s, C-1H), 2.41-2.31 (2H, m, C-3'H, C-3"H), 2.20 (1H, m, C-3H), 2.08 (1H, dd, *J* = 2.3, 18.5 Hz, C-3H), 1.96-1.53 (8H, m, C-4'H, C-4"H, C-5'H, C-5"H, C-6'H, C-6"H, C-8H_2), 1.38-1.06 (6H, m, C-3'H, C-3"H, C-5'H, C-5"H, C-6'H, C-6"H), 1.13 (3H, s, C-7**CH_3**), 1.05 (1.5H, s, C-7**CH_3**), 1.04 (1.5H, s, C-7**CH_3**), 0.92 (3H, s, CH_3), 0.91 (3H, s, CH_3), 0.882 (3H, s, CH_3), 0.878 (3H, s, CH_3), 0.87 (3H, s, CH_3), 0.86 (1.5H, s, CH_3), 0.84 (1.5H, s, CH_3). ^{13}C NMR: δ 209.0 and 208.9 (C-2), 165.8 (2C, ester C=O), 164.5 (2C, ester C=O), 142.8 and 142.6 (C-5), 134.4 and 134.1 (C-6), 81.25, 81.20, 81.1 and 81.0 (C-2', C-2"), 62.4 and 62.3 (C-1), 48.92, 48.89, 48.83 and 47.81 (8C, C-1', C-1", C-7', C-7"), 44.71 and 44.66 (4C, C-4', C-4"), 39.8 and 39.7 (C-8), 37.4 and 37.3 (C-3), 36.6, 36.22 and 36.17 (4C, C-3', C-3"), 35.6 and 35.52 (C-7), 35.48 and 35.3 (C-4), 30.4 (2C, C-7**CH_3**), 29.7 and 29.6 (C-7**CH_3**), 27.9, 27.8 and 27.1 (8C, C-5', C-5", C-6', C-6"), 19.6 (4C, C-7'**CH_3**, C-7"**CH_3**), 18.7 (4C, C-7'**CH_3**, C-7"**CH_3**), 13.50 and 13.46 (4C, C-1'**CH_3**, C-1"**CH_3**). MS: 511 (0.4, $M^+ + 1$), 510 (0.6, M^+), 375 (2), 374 (7), 239 (3), 238 (23), 179 (2), 178 (1), 153 (8), 138 (33), 137 (100), 136 (19), 121 (8), 109 (12), 95 (21), 93 (12), 81

(80), 69 (20), 67 (10), 57 (14), 55 (12). HRMS: calcd for $C_{32}H_{46}O_5$: 510.3343; found: 510.3325.

Dibornyl 8,8-dimethylbicyclo[2.2.2]oct-5-en-2-one-5,6-dicarboxylate (40c) and dibornyl 4-hydroxyphthalate (38).

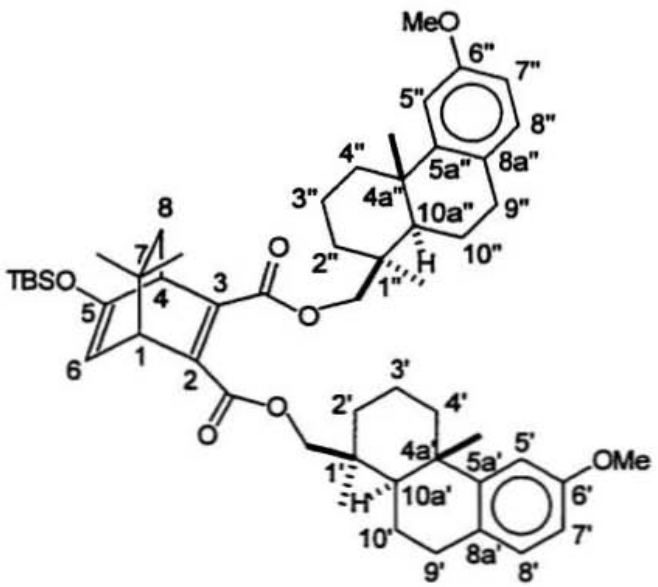


40c

Diene **17c** (0.122 g, 0.622 mmol) and the acetylenic dienophile **31** (1.35 g, 3.49 mmol) were added to benzene (25 mL). The dienophile was dissolved with stirring, and the mixture was heated to reflux for 6 days. Following solvent evaporation, methanol (10 mL) and 0.5 M aqueous HCl (0.5 mL) were added to the residue. This was stirred for 1 h then diluted with diethyl ether (20 mL) and ethyl acetate (10 mL). The organic solution was washed with brine (5 mL), and water (5 mL), and then dried ($MgSO_4$). Solvent evaporation followed by flash chromatography (elution with 5% ethyl acetate-petroleum ether) gave **40c** (0.104 g, 33 %) as a white solid and **38** (0.050 g, 18%) as a white solid. For **40c** (a 1.03 : 1 diastereomeric mixture): mp: 177-178 °C. IR: 2957, 2875, 1731, 1712,

1639, 1454, 1267 cm^{-1}. ^1H NMR: δ 5.10-4.94 (2H, m, C-2'H, C-2"H), 3.51 (1H, m, C-1H), 2.90 (0.5H, t, *J* = 2.5 Hz, C-4H), 2.88 (0.5H, t, *J* = 2.5 Hz, C-4H), 2.49 (1H, dd, *J* = 2.5, 19.0 Hz, C-3H), 2.46-2.31 (2H, m, C-3'H, C-3"H), 2.12 (1H, dd, *J* = 2.5, 19.0 Hz, C-3H), 1.92-1.61 (8H, m, C-4'H, C-4"H, C-5'H, C-5"H, C-6'H, C-6"H, C-$7H_2$), 1.40-1.03 (6H, m, C-3'H, C-3"H, C-5'H, C-5"H, C-6'H, C-6"H), 1.18 (3H, s, C-8$\mathbf{CH_3}$), 1.10 (1.5H, s, C-8$\mathbf{CH_3}$), 1.09 (1.5H, s, C-8$\mathbf{CH_3}$), 0.93 (3H, s, CH_3), 0.91 (3H, s, CH_3), 0.89 (3H, s, CH_3), 0.88-0.86 (6H, m, 2 x CH_3), 0.85 (3H, s, CH_3). ^{13}C NMR: 209.3 and 209.2 (C-2), 166.2 (2C, ester C=O), 164.4 (2C, ester C=O), 145.3 and 145.0 (C-5), 133.1 and 132.8 (C-6), 81.4, 81.3, 81.2 and 81.1 (C-2', C-2"), 51.4 and 51.2 (C-1), 49.0, 48.9, 47.9 and 47.8 (8C, C-1', C-1", C-7', C-7"), 47.3 and 47.1 (C-4), 44.8 (4C, C-4', C-4"), 38.8 and 38.7 (C-7), 36.5, 36.4, 36.30 and 36.26 (C-3', C-3"), 35.5 and 35.4 (C-3), 34.3 and 34.3 (C-8), 31.6 and 31.5 (C-8$\mathbf{CH_3}$), 28.2 (2C, C-8$\mathbf{CH_3}$), 27.91, 27.86, 27.21 and 27.17 (8C, C-5', C-5", C-6', C-6"), 19.6 (4C, C-7'$\mathbf{CH_3}$, C-7"$\mathbf{CH_3}$), 18.8 (4C, C-7'$\mathbf{CH_3}$, C-7"$\mathbf{CH_3}$), 13.5 (4C, C-1'$\mathbf{CH_3}$, C-1"$\mathbf{CH_3}$). MS: 511 (0.1, M^+ + 1), 510 (0.3, M^+), 375 (1), 374 (6), 239 (3), 238 (20), 220 (2), 179 (2), 138 (24), 137 (100), 136 (13), 121 (6), 109 (8), 108 (3), 95 (23), 93 (11), 82 (9), 81 (76), 69 (24), 67 (16), 57 (7), 55 (10). HRMS: calcd for $C_{22}H_{30}O_5$ (M^+ - $C_{10}H_{16}$): 374.2092; found: 374.2084.

7,7-Dimethyl-5-(((1,1-dimethylethyl)dimethylsilyl)oxy)bicyclo[2.2.2]octa-2,5-diene-2,3-dicarboxylate, bis((1*S*,4a*S*,10a*R*)-1,2,3,4,4a,9,10,10a-octahydro-6-methoxy-1,4a-dimethyl-1-phenanthrenemethyl) ester (41) and 4-(((1,1-dimethylethyl)dimethylsilyl)oxy)phthalic acid, bis((1*S*,4a*S*,10a*R*)-1,2,3,4,4a,9,10,10a-octahydro-6-methoxy-1,4a-dimethyl-1-phenanthrenemethyl)ester (42).



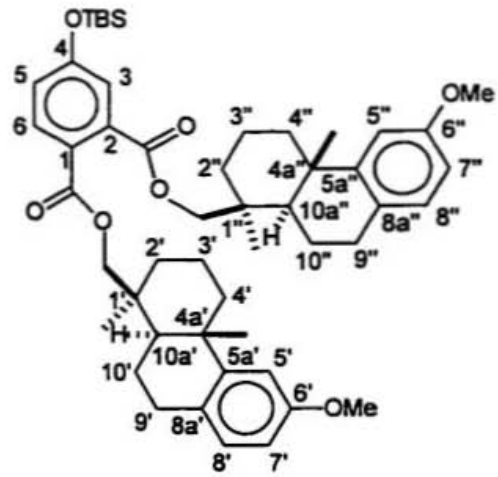
41

Diene **22** (0.328 g, 1.38 mmol) and acetylenic dienophile **32** (0.164 g, 0.262 mmol) were added to benzene (3.5 mL). The mixture was heated to reflux for 9 days. Reaction progress was monitored by TLC. Solvent evaporation, followed by flash chromatography (elution with a solvent gradient from 5 to 12.5% diethyl ether-petroleum ether) gave **41** (0.127 g, 56%) as a colourless oil

and **42** (0.040 g, 19%) as a viscous yellow oil. For **41**. IR: 2931, 1712, 1650, 1631, 1610, 1502, 1470, 1260, 1249 cm^{-1}. ^1H NMR: δ 6.95 (2H, d, J = 8.4 Hz, C-8'H, C-8"H), 6.80 (2H, d, J = 2.3 Hz, C-5'H, C-5"H), 6.66 (2H, dd, J = 2.3, 8.4 Hz, C-7'H, C-7"H), 5.18-5.14 (1H, symmetrical m, C-6H), 4.50-4.40 (2H, m, C-1'**CH**O, C-1"**CH**O), 4.15-4.05 (2H, symmetrical m, C-1'**CH**O, C-1"**CH**O), 3.76 (6H, s, C-6'O**CH_3**, C-6"O**CH_3**), 3.52 (1H, m, C-4H), 3.29 (0.5H, d, J = 6.6 Hz, C-1H), 3.26 (0.5H, d, J = 6.6 Hz, C-1H), 2.94-2.70 (4H, m, C-9'H_2, C-9"H_2), 2.34-2.24 (2H, m, C-4'H_e, C-4"H_e), 2.05-1.27 (16H, m, C-2'H_e, C-2"H_e, C-3'H_2, C-3"H_2, C-4'H_a, C-4"H_a, C-8H_2, C-10'H_2, C-10"H_2, C-10a'H, C-10a"H), 1.22 (6H, s, C-4a'**CH_3**, C-4a"**CH_3**), 1.17 (3H, s, C-7**CH_3**), 1.08-0.82 (11H, m, C-1'**CH_3**, C-1"**CH_3**, C-2'H_a, C-2"H_a, C-7**CH_3**), 0.92 (4.5H, s, 0.5 x (**CH_3**)$_3$C(CH_3)$_2$Si), 0.91 (4.5H, s, 0.5 x (**CH_3**)$_3$C(CH_3)$_2$Si), 0.139 (3H, s, (CH_3)$_3$C**CH_3**Si), 0.136 (3H, s, (CH_3)$_3$C**CH_3**Si). ^{13}C NMR: δ 166.7 and 166.5 (ester C=O), 166.1 and 166.0 (ester C=O), 158.8 and 158.6 (C-5), 157.7 (4C, C-6', C-6"), 150.6 (4C, C-5a', C-5a"), 145.8, 145.5, 140.4 and 139.9 (C-2, C-3), 129.8 (4C, C-8', C-8"), 126.9 (4C, C-8a', C-8a"), 111.0 (4C, C-7', C-7"), 110.2 and 110.1 (4C, C-5', C-5"), 103.9 and 103.8 (C-6), 67.5 and 67.3 (4C, C-1'**CH_2**O, C-1"**CH_2**O), 55.2 (4C, C-6'O**CH_3**, C-6"O**CH_3**), 51.2 (5C, C-10a', C-10a", C-1), 51.1 (C-1), 46.4 and 46.3 (C-4), 40.1 (2C, C-8), 39.1 (2C, C-7), 38.7 (4C, C-4', C-4"), 37.9 (4C, C-4a', C-4a"), 37.46, 37.41 and 37.36 (4C, C-1', C-1"), 35.96, 35.90, 35.86 and 35.8 (4C, C-2', C-2"), 30.8 and 30.6 (C-7**CH_3**), 30.06, 30.02 and 29.97 (4C, C-9',

C-9"), 27.7, 27.34 and 27.30 (6C, C-7$\mathbf{CH_3}$, C-1'$\mathbf{CH_3}$, C-1"$\mathbf{CH_3}$), 25.6 (10C, C-4a'$\mathbf{CH_3}$, C-4a"$\mathbf{CH_3}$, $(\mathbf{CH_3})_3C(CH_3)_2Si$), 19.34, 19.29, 19.25 and 19.21 (C-10', C-10"), 18.9 (4C, C-3', C-3"), 18.0 (2C, $(CH_3)_3\mathbf{C}(CH_3)_2Si$), -4.5 and -4.6 (4C, $(CH_3)_3C(\mathbf{CH_3})_2Si$). MS: 553 (0.9), 552 (2), 297 (5), 280 (3), 279 (16), 274 (3), 273 (4), 257 (33), 256 (87), 255 (20), 254 (8), 241 (16), 221 (8), 187 (9), 186 (8), 185 (27), 175 (15), 174 (21), 173 (23), 172 (10), 171 (11), 162 (12), 161 (100), 159 (10), 147 (25), 121 (13), 83 (9), 69 (8), 55 (19).

Distinct signals for the 2 diastereomers were obtained by comparison of ^{13}C NMR spectra of samples enriched in one diastereomer or the other. First diastereomer: 166.5, 166.1, 158.6, 145.5, 140.4, 103.9, 46.4, 37.46, 35.96, 35.8, 19.34, 19.21. Second diastereomer: 166.7, 166.0, 158.8, 145.8, 139.9, 103.8, 46.3, 37.41, 35.90, 35.86, 19.29, 19.25.



42

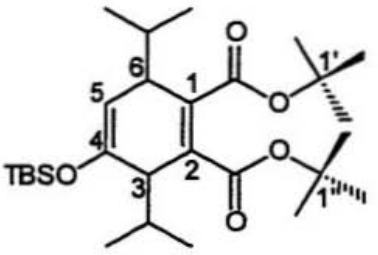
For **42**. IR: 2930, 1723, 1605, 1573, 1502, 1471, 1263 cm^{-1}. ^1H NMR: δ 7.73 (1H, d, *J* = 8.5 Hz, C-6H), 7.04 (1H, d, *J* = 2.4 Hz, C-3H), 6.96 (2H, d, *J* = 8.4 Hz, C-8'H, C-8"H), 6.94 (1H, dd, *J* = 2.4, 8.5 Hz, C-5H), 6.82 (2H, symmetrical m, C-5'H, C-5"H), 6.67 (2H, dd, *J* = 2.6, 8.4 Hz, C-7'H, C-7"H), 4.58 (1H, d, *J* = 11.0 Hz, C-1'**CH**O or C-1"**CH**O), 4.54 (1H, d, *J* = 11.0 Hz, C-1'**CH**O or C-1"**CH**O), 4.22 (1H, d, *J* = 11.0 Hz, C-1'**CH**O or C-1"**CH**O), 4.18 (1H, d, *J* = 11.0 Hz, C-1'**CH**O or C-1"**CH**O), 3.78 (6H, s, C-6'O**CH_3**, C-6"O**CH_3**), 2.96-2.71 (4H, m, C-9'H_2, C-9"H_2), 2.35-2.26 (2H, m, C-4'H_e, C-4"H_e), 2.07-1.38 (14H, m, C-2'H_e, C-2"H_e, C-3'H_2, C-3"H_2, C-4'H_a, C-4"H_a, C-10'H_2, C-10"H_2, C-10a'H, C-10a"H), 1.26 (3H, s, C-4a'**CH_3** or C-4a"**CH_3**), 1.24 (3H, s, C-4a'**CH_3** or C-4a"**CH_3**), 1.18-0.95 (2H, m, C-2'H_a, C-2"H_a), 1.11 (3H, s, C-1'**CH_3** or C-1"**CH_3**), 1.09 (3H, s, C-1'**CH_3** or C-1"**CH_3**), 0.99 (9H, s, (**CH_3**)$_3$C(CH_3)$_2$Si), 0.24 (6H, s, (CH_3)$_3$C(**CH_3**)$_2$Si). ^{13}C NMR: δ 168.2 and 166.7 (ester C=O), 158.5 (C-4), 157.7 (2C, C-6', C-6"), 150.7 (2C, C-5a', C-5a"), 135.9 (C-2), 131.2 (C-6), 129.8 (2C, C-8', C-8"), 127.0 (2C, C-8a', C-8a"), 123.7 (C-1), 121.5 (C-5), 119.9 (C-3), 111.0 (2C, C-7', C-7"), 110.2 (2C, C-5', C-5"), 68.3 and 68.2 (C-1'**CH_2**O, C-1"**CH_2**O), 55.2 (2C, C-6'O**CH_3**, C-6"O**CH_3**), 51.3 (2C, C-10a', C-10a"), 38.7 (2C, C-4', C-4"), 37.9 (2C, C-4a', C-4a"), 37.5 and 37.4 (C-1', C-1"), 36.0 (2C, C-2', C-2"), 30.1 (2C, C-9', C-9"), 27.5 and 27.4 (C-1'**CH_3**, C-1"**CH_3**), 25.7 (2C, C-4a'**CH_3**, C-4a"**CH_3**), 25.6 (**CH_3**)$_3$C(CH_3)$_2$Si), 19.3 (2C, C-10', C-10"), 19.0 (C-3', C-3"), 18.2 ((CH_3)$_3$**C**(CH_3)$_2$Si), -4.4 (CH_3)$_3$C(**CH_3**)$_2$Si). MS: 552 (1, M^+ - 256), 297 (4), 280

(3), 279 (16), 274 (6), 273 (4), 257 (31), 256 (85), 255 (20), 254 (8), 241 (18), 221 (15), 187 (10), 185 (25), 175 (14), 174 (20), 173 (24), 172 (10), 171 (11), 162 (13), 161 (100), 159 (11), 147 (26), 121 (16), 83 (9), 69 (8), 55 (19).

Attempted Diels-Alder between Danishefsky's diene and dimenthyl acetylenedicarboxylate (30).

A solution of 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (0.180 g, 1.04 mmol) and **30** (0.453 g, 1.16 mmol) in benzene (15 mL) was heated to reflux under a nitrogen atmosphere. Reaction progress was monitored by TLC. The reaction was stopped after 5 days and the solvent evaporated under vacuum. Flash chromatography (elution with 5% ethyl acetate-hexane) gave **37** (0.368 g, 77%) as a white solid: mp: 175-176 °C.

3,6-bis (1-Methylethyl)-4-(((1,1-dimethylethyl)dimethylsilyl)oxy)cyclohexa-1,4-diene-1,2-dicarboxylic acid, bis-(1,1-dimethylethyl) ester (53).

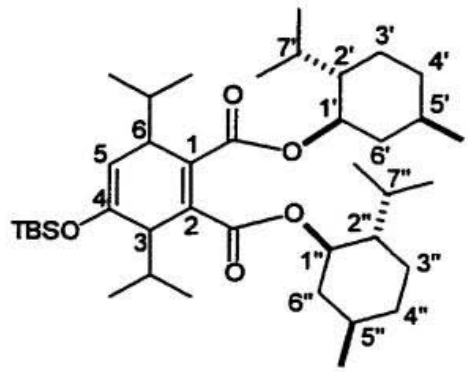


Diene **49** (0.0764 g, 0.285 mmol) and di-*tert*-butyl acetylenedicarboxylate (0.287 g, 1.27 mmol) were added to a high pressure reaction vessel.

Dichloromethane (2 mL) was added and the mixture subjected to high pressure (12,585 atm or 185,000 psi) for 1 day.* The mixture was removed and TLC indicated most of the diene had reacted. Flash chromatography (elution with 5% diethyl ether-35% hexane-petroleum ether) gave **53** (0.0276 g, 20%) as a yellow oil. IR: 2961, 1721, 1680, 1473, 1393, 1367, 1255, 1156, 845 cm^{-1}. ^1H NMR: δ 4.76 (1H, d, *J* = 4.1 Hz, C-5H), 3.10 (1H, dt, *J* = 4.1, 6.2 Hz, C-6H), 3.02 (1H, dd, *J* = 3.0, 6.2 Hz, C-3H), 2.15-2.02 (1H, m, C-6**CH**$(CH_3)_2$), 2.00 (1H, doublet of septets, *J* = 3.0, 7.0 Hz, C-3**CH**$(CH_3)_2$), 1.49 (18H, s, 2 x OC$(\mathbf{CH_3})_3$), 1.07 (3H, d, *J* = 7.0 Hz, C-3CH**CH_3**), 0.98 (3H, d, *J* = 6.7 Hz, C-6CH**CH_3**), 0.97-0.94 (3H, m, C-3CH**CH_3**), 0.94 (9H, s, $(\mathbf{CH_3})_3C(CH_3)_2Si$), 0.86 (3H, d, *J* = 6.7 Hz, C-6CH**CH_3**), 0.19 (3H, s, $(CH_3)_3C\mathbf{CH_3}Si$), 0.18 (3H, s, $(CH_3)_3C\mathbf{CH_3}Si$). ^{13}C NMR: δ 168.3 (ester C=O), 166.6 (ester C=O), 151.0 (C-4), 140.0 and 133.7 (C-1, C-2), 99.5 (C-5), 81.2 and 81.1 (2 x O**C**$(CH_3)_3$), 46.1 (C-3), 45.4 (C-6), 32.4 (C-3**CH**$(CH_3)_2$, 31.1 (C-6**CH**$(CH_3)_2$), 28.0 (2 x OC$(\mathbf{CH_3})_3$), 25.9 ($(\mathbf{CH_3})_3C(CH_3)_2Si$), 22.5 (C-3CH**$CH_3$**), 21.4 (C-6CH**$CH_3$**), 19.7 (C-3CH**$CH_3$**), 18.6 (C-6)CH**$CH_3$**),18.1 ($(CH_3)_3\mathbf{C}(CH_3)_2Si$), -4.3 ($(CH_3)_3C(\mathbf{CH_3})_2Si$). MS: no M^+, 409 (0.2), 365 (5), 339 (5), 321 (5), 305 (3), 298 (7), 297 (35), 280 (20), 279 (100), 221 (7), 165 (5), 86 (17), 84 (26), 75 (8), 73 (32), 57 (63).

* Note: Reactants sent to Dr. Michael Kerr at Acadia University, Wolfville, Nova Scotia for the high pressure Diels-Alder reaction. An unknown amount of the diene was lost in transit, therefore the reaction yield must actually be higher.

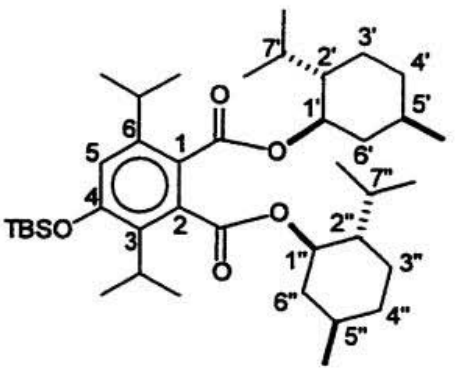
3,6-bis (1-Methylethyl)-4-((1,1-dimethylethyl)-dimethylsilyl)oxy)cyclohexa-1,4-diene-1,2-dicarboxylic acid, dimenthyl ester (50) and 3,6-bis (1-methylethyl)-4-(((1,1-dimethylethyl)dimethylsilyl)oxy)phthalic acid, dimenthyl ester (51).



50

Diene **49** (46.6 mg, 0.174 mmol) and acetylenic dienophile **30** (0.308 g, 0.789 mmol) were added to a high pressure reaction vessel. Dichloromethane (2.0 mL) was added, and the mixture was subjected to high pressure (12,585 atm or 185,000 psi) for 3 days. The mixture was removed after each 24 h period, and reaction progress was monitored by TLC. The dichloromethane was evaporated using a stream of nitrogen. Flash chromatography (elution with 2.5% ethyl acetate-hexane) gave poor separation. Preparative thin layer chromatography using the same solvent system yielded **50** (0.0277 g, 24%) as a colourless oil. For **50**, only ^{1}H NMR and ^{13}C NMR are given. The adduct oxidized to the corresponding aromatic compound (**51**) before complete spectral analysis was done. The aromatic by-product was fully characterized. For **50**: ^{1}H

NMR: δ 4.81-4.69 (3H, m, C-5H, C-1'H, C-1"H), 3.18 (1H, m, C-6H), 3.09-3.04 (0.64H, dd, *J* = 2.5, 6.2 Hz, C-3H), 3.03-2.99 (0.36H, dd, *J* = 2.2, 6.2 Hz, C-3H), 2.28-1.81 (6H, m, C-3**CH**, C-6CH, C-6'H_e, C-6"H_e, C-7'H, C-7"H), 1.74-1.24 (8H, m, C-2'H, C-2"H, C-3'H_e, C-3"H_e, C-4'H_e, C-4"H_e, C-5'H, C-5"H), 1.16-0.80 (39H, m, 2 x C-3CH**CH_3**, 2 x C-6CH**CH_3**, **$(CH_3)_3$**C**$(CH_3)_2$**Si, C-3'H_a, C-3"H_a, C-4'H_a, C-4"H_a, C-6'H_a, C-6"H_a, 2 x C-7'**CH_3**, 2 x C-7"**CH_3**), 0.80-0.72 (6H, m, C-5'**CH_3**, C-5"**CH_3**), 0.20 (3H, s, $(CH_3)_3$C**CH_3**Si), 0.18 (3H, s, $(CH_3)_3$C**CH_3**Si). ^{13}C NMR: δ 168.6 and 168.3 (ester C=O), 166.6 and 165.8 (ester C=O), 151.5 and 150.4 (C-4), 142.4 and 138.9 and 131.3 (C-1, C-2), 99.9 and 98.7 (C-5), 75.1, 74.9 and 74.7 (4C, C-1', C-1"), 47.2, 47.1 and 47.0 (4C, C-2', C-2"), 46.5 and 46.3 (C-3), 45.4 and 45.2 (C-6), 40.6, 40.5, 40.4 and 40.3 (C-6', C-6"), 34.3 and 34.2 (4C, C-4', C-4"), 33.3, 32.3, 31.4, 31.2, and 30.5 (8C, C-3**CH**$(CH_3)_2$, C-6**CH**$(CH_3)_2$, C-5', C-5"), 26.03, 25.96, 25.86, 25.7 and 25.5 (10C, **$(CH_3)_3$**C**$(CH_3)_2$**Si, C-7', C-7"), 23.7, 23.3, 23.0 and 22.8 (6C, C-3CH**CH_3**, C-3', C-3"), 22.1 (4C, C-7'**CH_3**, C-7"**CH_3**), 21.4, 21.2, 21.0, 20.9 and 20.8 (6C, C-6CH**CH_3**, C-7'**CH_3**, C-7"**CH_3**), 19.4 (2C, C-3CH**CH_3**), 18.8, 18.5, 18.3 and 18.2 (4C, C-6CH**CH_3**, $(CH_3)_3$**C**$(CH_3)_2$Si), 16.3, 15.8 and 15.7 (4C,C-5'**CH_3**, C-5"**CH_3**), -4.2 and -4.3 (4C, $(CH_3)_3$C(**CH_3**)$_2$Si).



51

For **51**: IR: 2957, 1720, 1591, 1463, 1326, 1263, 1192, 830 cm^{-1}. ^1H NMR: δ 6.77 (1H, s, C-5H), 4.88-4.78 (2H, symmetrical m, C-1'H, C-1"H), 3.18 (1H, septet, *J* = 6.7 Hz, C-6**CH**$(CH_3)_2$), 2.93 (1H, septet, *J* = 7.0 Hz, C-3**CH**$(CH_3)_2$), 2.37-2.00 (4H, m, C-6'H_e, C-6"H_e, C-7'H, C-7"H), 1.75-1.36 (8H, m, C-2'H, C-2"H, C-3'H_e, C-3"H_e, C-4'H_e, C-4"H_e, C-5'H, C-5"H), 1.33 (3H, d, *J* = 6.9 Hz, C-3CH**CH**$_3$ or C-6CH**CH**$_3$), 1.32 (3H, d, *J* = 6.9 Hz, C-3CH**CH**$_3$ or C-6CH**CH**$_3$), 1.21 (3H, d, *J* = 7.2 Hz, C-6CH**CH**$_3$ or C-3CH**CH**$_3$), 1.18 (3H, d, *J* = 7.2 Hz, C-6CH**CH**$_3$ or C-3CH**CH**$_3$), 1.15-0.80 (6H, m, C-3'H_a, C-3"H_a, C-4'H_a, C-4"H_a, C-6'H_a, C-6"H_a), 1.03 (9H, s, (**CH**$_3$)$_3$C$(CH_3)_2$Si), 0.95 (3H, d, *J* = 6.7 Hz, C-7'**CH**$_3$ or C-7"**CH**$_3$), 0.94 (3H, d, *J* = 6.5 Hz, C-7'**CH**$_3$ or C-7"**CH**$_3$), 0.89 (3H, d, *J* = 7.1 Hz, C-7"**CH**$_3$ or C-7'**CH**$_3$), 0.88 (3H, d, *J* = 7.1 Hz, C-7"**CH**$_3$ or C-7'**CH**$_3$), 0.81 (3H, d, *J* = 6.9 Hz, C-5'**CH**$_3$ or C-5"**CH**$_3$), 0.80 (3H, d, *J* = 7.0 Hz, C-5'**CH**$_3$ or C-5"**CH**$_3$), 0.33 (3H, s, $(CH_3)_3$C**CH**$_3$Si), 0.32 (3H, s, $(CH_3)_3$C**CH**$_3$Si). ^{13}C NMR: δ 169.1 (ester C=O), 168.4 (ester C=O), 156.3 (C-4), 145.7 (C-6), 135.4 (C-3),

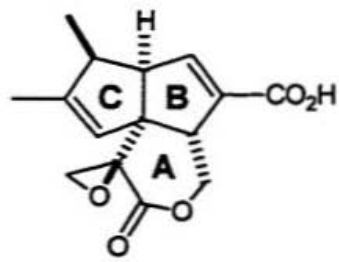
131.9 (C-2), 123.0 (C-1), 116.7 (C-5), 76.0 and 75.8 (C-1', C-1"), 46.9 and 46.8 (C-2', C-2"), 40.5 and 40.0 (C-6', C-6"), 34.2 (C-4', C-4"), 31.5 (C-5', C-5"), 31.1 and 30.3 (C-3**CH**$(CH_3)_2$, C-6**CH**$(CH_3)_2$), 26.2 ($(\mathbf{CH_3})_3C(CH_3)_2Si$), 25.5 and 25.2 (C-7', C-7"), 24.3 and 24.0 (C-3CH($\mathbf{CH_3}$)$_2$ or C-6CH($\mathbf{CH_3}$)$_2$), 23.0 and 22.8 (C-3', C-3"), 22.1 (C-7'$\mathbf{CH_3}$, C-7"$\mathbf{CH_3}$), 21.0 (C-7'$\mathbf{CH_3}$, C-7"$\mathbf{CH_3}$), 20.8 and 20.6 (C-6CH($\mathbf{CH_3}$)$_2$ or C-3CH($\mathbf{CH_3}$)$_2$, 18.8 ($(CH_3)_3\mathbf{C}(CH_3)_2Si$), 16.1 and 15.6 (C-5'$\mathbf{CH_3}$, C-5"$\mathbf{CH_3}$), -3.6 ($(CH_3)_3C(\mathbf{CH_3})_2Si$). MS: no M^+, 518 (0.2), 517 (0.5), 381 (3), 380 (10), 379 (4), 365 (4), 364 (13), 363 (43), 362 (59), 361 (22), 335 (8), 334 (23), 307 (11), 306 (25), 305 (100), 279 (7), 139 (4), 138 (5), 137 (2), 123 (4), 97 (10), 95 (18), 86 (14), 84 (27), 83 (53), 81 (18), 73 (43), 69 (31), 67 (9), 57 (25), 55 (47).

Part II.

INVESTIGATIONS OF AN INTRAMOLECULAR DIELS-ALDER APPROACH TO THE PENTALENOLACTONES

I. Introduction

In 1957 Celmer, at the Pfizer pharmaceutical company, reported the isolation of a new antibiotic from a *Streptomyces* broth culture.[60] The substance, initially named PA-132, was subsequently called pentalenolactone (**64**) (Figure 20).



64

Figure 20. Pentalenolactone.

This sesquiterpene lactone has been found to exhibit a broad spectrum of activity against a wide variety of organisms, including Gram-positive and Gram-negative bacteria. It has been shown to block glycolysis by selective inhibition of glyceraldehyde-3-phosphate dehydrogenase from both prokaryotic (*Escherichia coli*, *Bacillus subtilis*) as well as eukaryotic sources (yeast, spinach,

rabbit muscle).[61] This irreversible inactivation of glyceraldehyde-3-phosphate dehydrogenase results from specific reaction with all four active-site cysteines of the tetrameric enzyme.[62] Pentalenolactone has also been reported to exhibit potent and specific antiviral activity.[63]

Further work with various *Streptomyces* species revealed that pentalenolactone was produced along with numerous co-metabolites. These include pentalenolactones A-B, D-H and O-P (Figure 21).[64] From a typical fermentation, pentalenolactone was obtained as the major component while the other pentalenolactones were isolated as minor components.[61] The isolation of pentalenene (**66**), the parent sesquiterpene hydrocarbon, along with these new members of the pentalenolactone family sparked a multitude of biosynthetic studies. These lactones were thought to represent possible intermediates or shunt metabolites.

Early labeling studies by Cane supported a mevalonic pathway.[65] Furthermore, the role of pentalenene (**66**) as a precursor of the more oxidized pentalenolactones was established by feeding experiments.[66] In 1992, as a result of intensive investigation, Cane proposed a biosynthetic pathway for the formation of pentalenolactone in *Streptomyces* species (Scheme 32).[61] Pentalenene (**66**) is formed from enzyme-catalyzed cyclization of *trans*,*trans*-farnesyl pyrophosphate (**65**). Oxidation of pentalenene (**66**) is thought to result in the formation of deoxypentalenic acid (**67**).

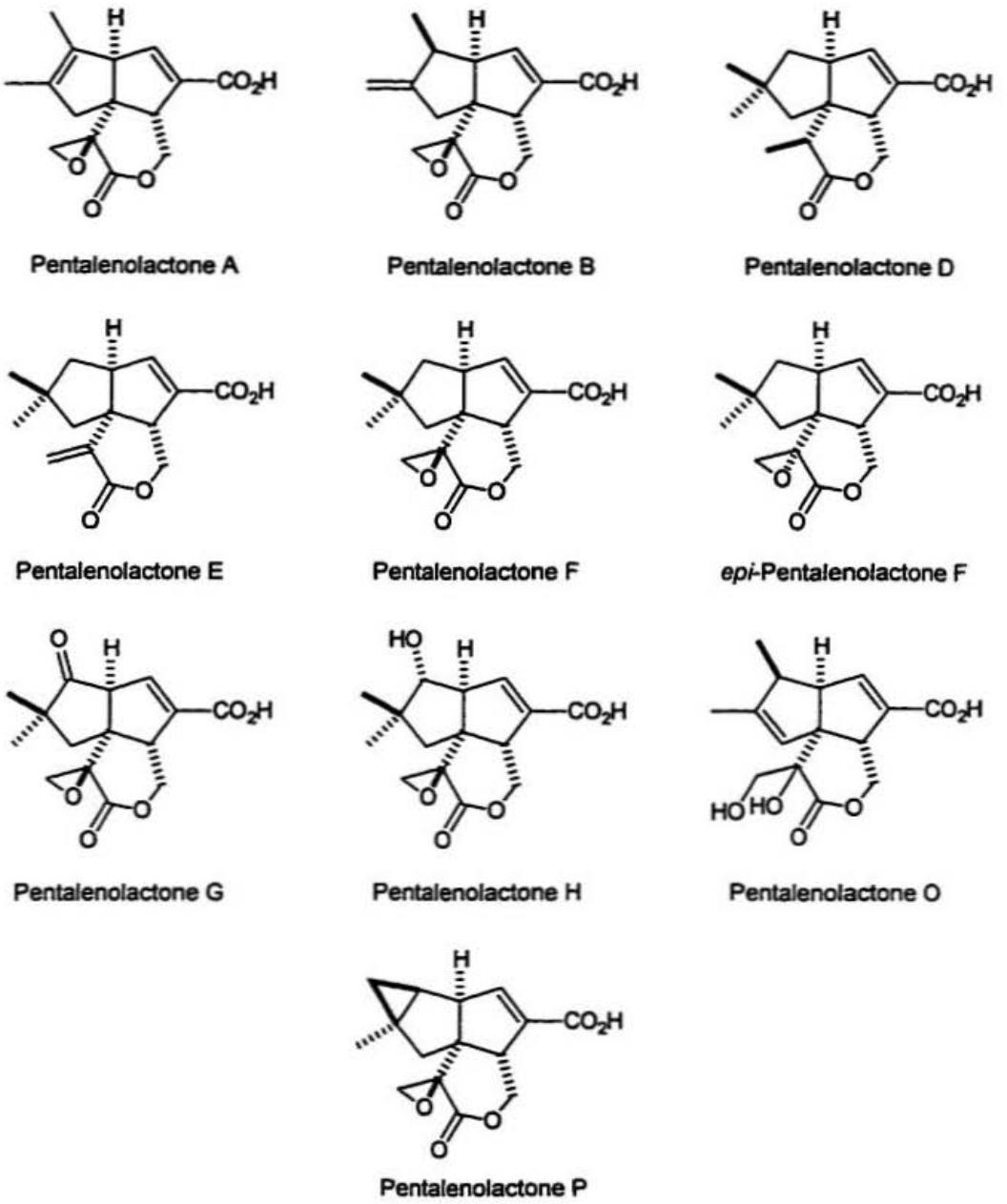
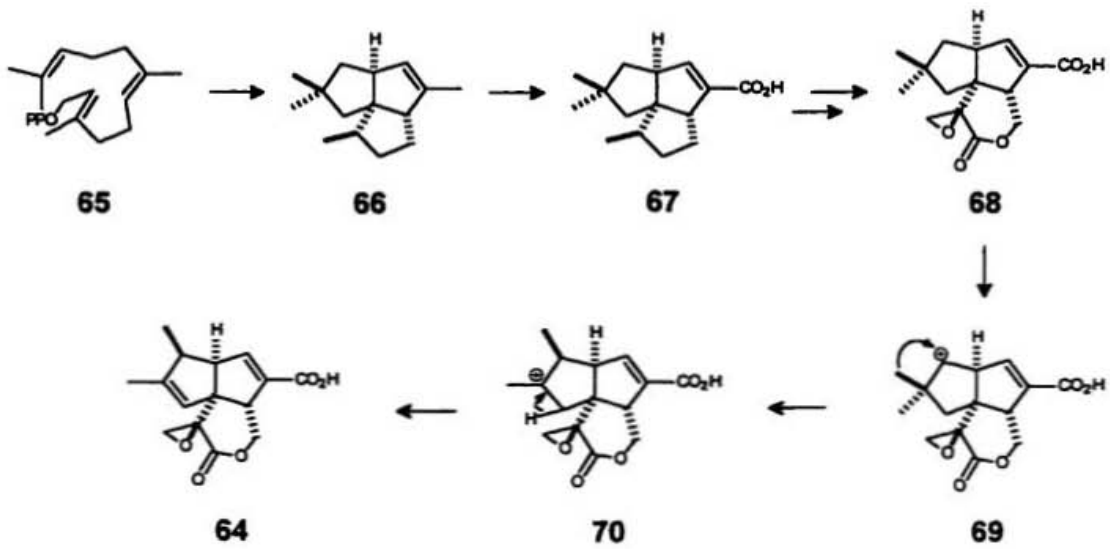


Figure 21. Pentalenolactones isolated from *Streptomyces* species.

Subsequent oxidative cleavage, dehydrogenation, and epoxidation would yield pentalenolactone F (**68**). Generation of an intermediate such as **69**, followed by

methyl migration and proton loss, would result in pentalenolactone (**64**). The pentalenolactones not part of the main biosynthetic pathway were said to be a result of rearrangement or oxidation of various intermediates.

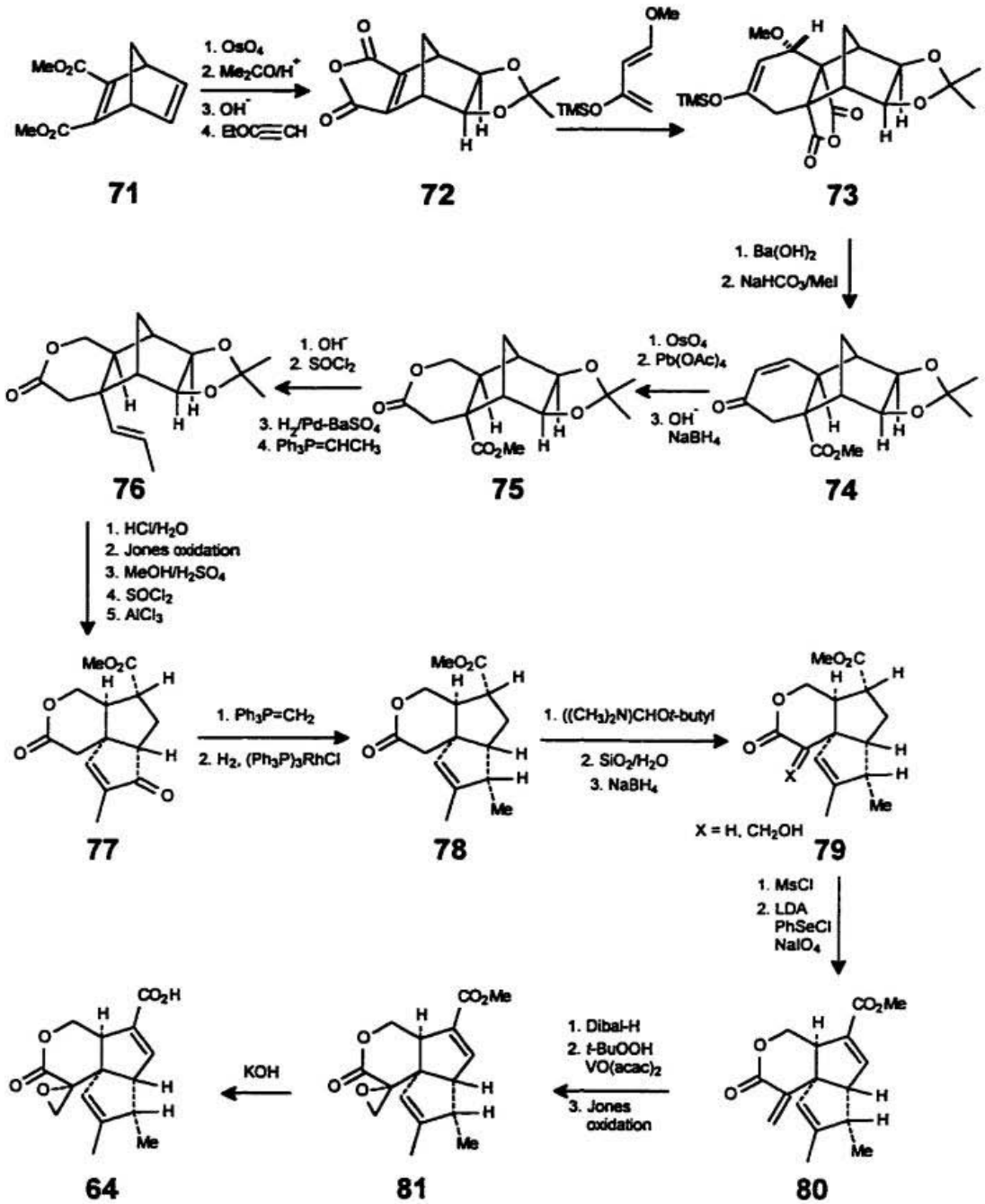


Scheme 32. Cane's proposed biosynthetic pathway for pentalenolactone.[61]

As a result of their interesting biogenesis and promising biological properties, the synthesis of pentalenolactones aroused considerable interest. Access to this family of sesquiterpenes offers a formidable challenge. Synthesis requires not only construction of a functionalized diquinane core, but also introduction of an α-oxy δ-lactone moiety in a stereoselective manner as well as creation of a quaternary carbon centre. To date, total syntheses of pentalenolactone, pentalenolactone E, pentalenolactone F, pentalenolactone G

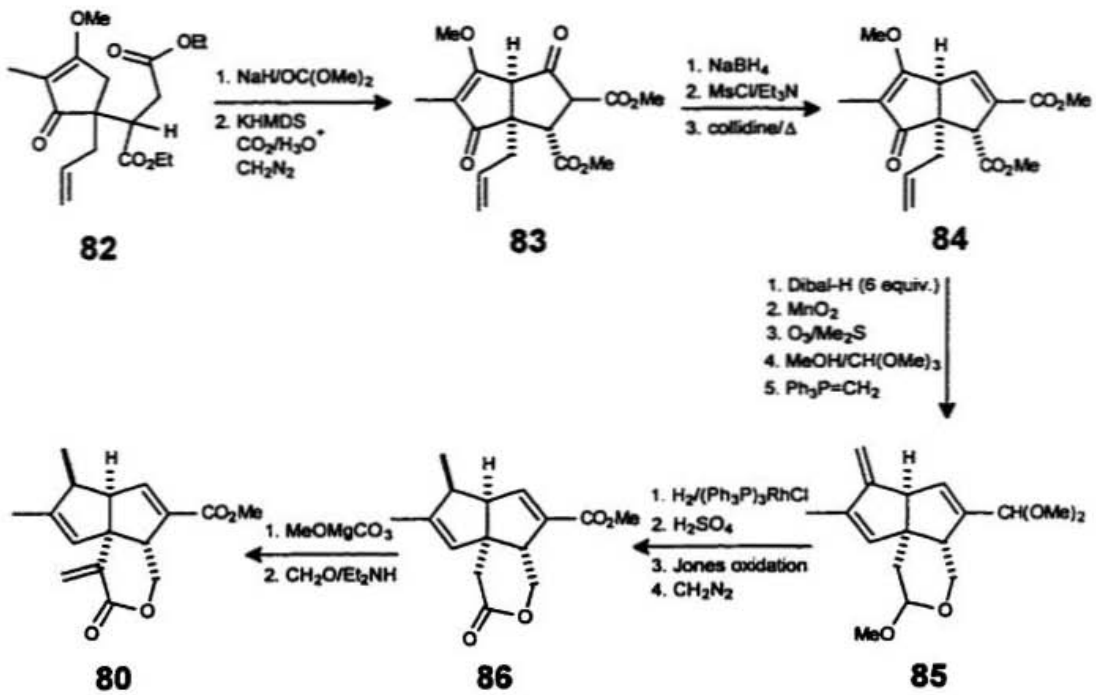
and pentalenolactone P have been reported, however, only one of these has been a chiral synthesis.

The first total synthesis of a member of the pentalenolactone family of antibiotics was of pentalenolactone itself. Danishefsky's approach used Diels-Alder methodology to control several key stereocenters and to elaborate the δ-lactone ring system (Scheme 33).[67, 68] The Diels-Alder adduct (**71**) of dimethyl acetylenedicarboxylate and cyclopentadiene was used as the starting material. Diol formation was followed by acetonide formation, saponification and dehydration to give **72**. Reaction of **72** with Danishefsky's diene resulted in the formation of the Diels-Alder adduct **73**. Treatment with $Ba(OH)_2$ resulted in unmasking of the enone, hydrolysis to the diacid, and decarboxylation to give **74**. Formation of the A-ring lactone present in pentalenolactone, followed by ester reduction and Wittig olefination gave **76**. Unmasking of the diol was followed by oxidative cleavage and selective methylation. Ring C was synthesized using a Darzen's type condensation of the (*E*)-alkene and an acid chloride. Following introduction of the stereoselective C-ring methyl group, formation of the α-methylene lactone was accomplished by way of the enaminolactone in 60% yield. Introduction of B-ring unsaturation to give **80** in modest yield was followed by epoxide formation via the hemiacetal using Sharpless technology. Saponification yielded the desired pentalenolactone in a disappointing 12% yield from **80**. Danishefsky's synthesis required 33 synthetic operations in a 0.2% overall yield.



Scheme 33. Danishefsky's synthesis of pentalenolactone.[67, 68]

Schlessinger achieved a formal synthesis of pentalenolactone by selective acylation and alkylation of enolate ions to generate a BC ring system with appropiate functionalization for introduction of the fused δ-lactone ring.[69, 70] Enolate generation from the vinylogous ester of compound **82** resulted in cyclization to give the desired bicyclo[3.3.0]octane (Scheme 34). Introduction of the B-ring ester gave **83**, which possessed the *cis* relationship between the allyl group and the carboxylate residue required for lactone formation. To form the required unsaturated ester present in ring B, the unconjugated ketone was reduced and subsequently eliminated. Lactone formation was accomplished by initial formation of the lactol, followed by oxidation.

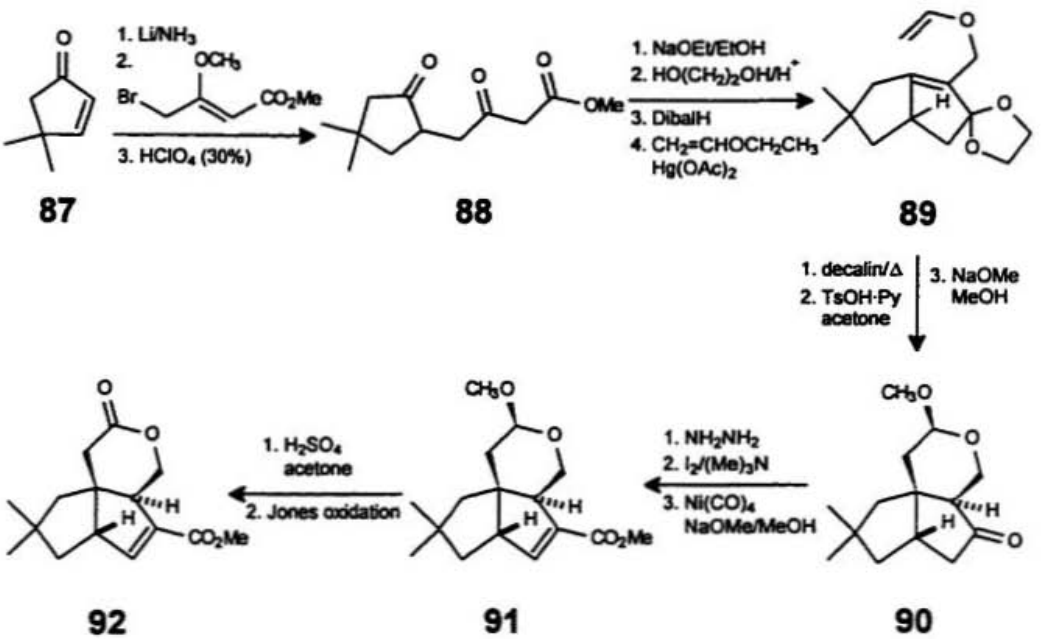


Scheme 34. Schlessinger's formal synthesis of pentalenolactone.[69, 70]

Introduction of the stereoselective methyl of ring C was accomplished in a similar manner to Danishefsky, however, reduction gave a disappointing 2 : 1 mixture of methyl group epimers. Formation of the α-methylene lactone was accomplished in modest yield, however, it was accompanied by a "fortuitous experimental event."[69, 70] The 2 : 1 epimeric methyl mixture was now determined to be the desired β-methyl isomer, exclusively! Schlessinger's formal synthesis was a dramatic improvement, with 10 fewer steps and a 10-fold increase in overall yield.

Unlike pentalenolactone, pentalenolactone E contains a *gem*-dimethyl group. The first synthesis of pentalenolactone E, as the methyl ester, was accomplished by Paquette (Scheme 35).[71, 72] His strategy was also centred around formation of a suitably constructed bicyclo[3.3.0] ring system. Regiospecific enolate formation of 4,4-dimethyl-2-cyclopentenone, followed by condensation with 3-methoxy-4-bromocrotonate, gave **88**, after hydrolysis of the vinyl ether. Cyclization, in the presence of sodium ethoxide, gave the desired diquinane ring system. Ketal formation and reduction of the ester were followed by vinyl ether formation (**89**). Claisen rearrangement initially gave a product containing an aldehyde and exocyclic methylene. Attack of methoxide on the aldehyde, followed by intramolecular Michael addition to the unmasked enone gave **90** as a single stereoisomer. Introduction of the B ring ester was accomplished via the vinyl iodide, however, a 2.2 : 1 mixture of regioisomers was produced. Furthermore, unmasking of the δ-lactone also led to a mixture of

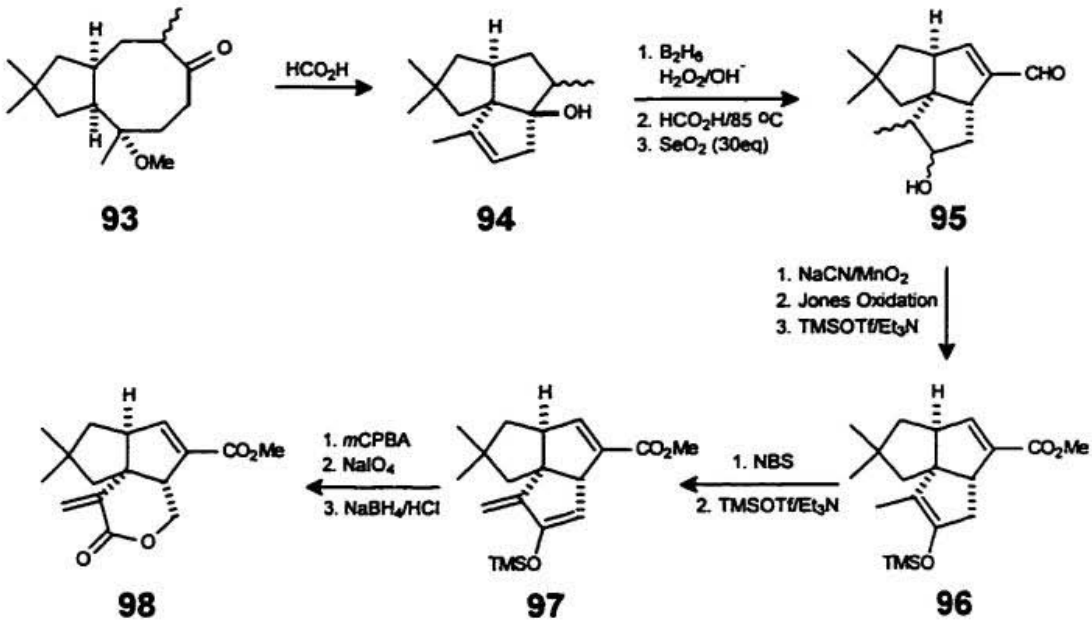
double bond isomers (2.5 : 1) with the minor product being the desired **92**. Completion of the total synthesis for pentalenolactone E was accomplished using the protocol established by Schlessinger in the synthesis of pentalenolactone.



Scheme 35. Paquette's synthesis of pentalenolactone E methyl ester.[71, 72]

Cyclization of farnesyl pyrophosphate results in humulene, a biosynthetic precursor to the pentalenolactones.[66] Matsumoto *et al.* carried out extensive investigations of biomimetic cyclizations of humulene and its derivatives. This work resulted in the synthesis of pentalenolactones E and F (Scheme 36).[73] Transannular cyclization of compound **93** resulted in **94**, closely related to pentalenene (**66**). All the carbons for the ABC ring system of the pentalenolactones were in place. Hydroboration-oxidation and elimination were

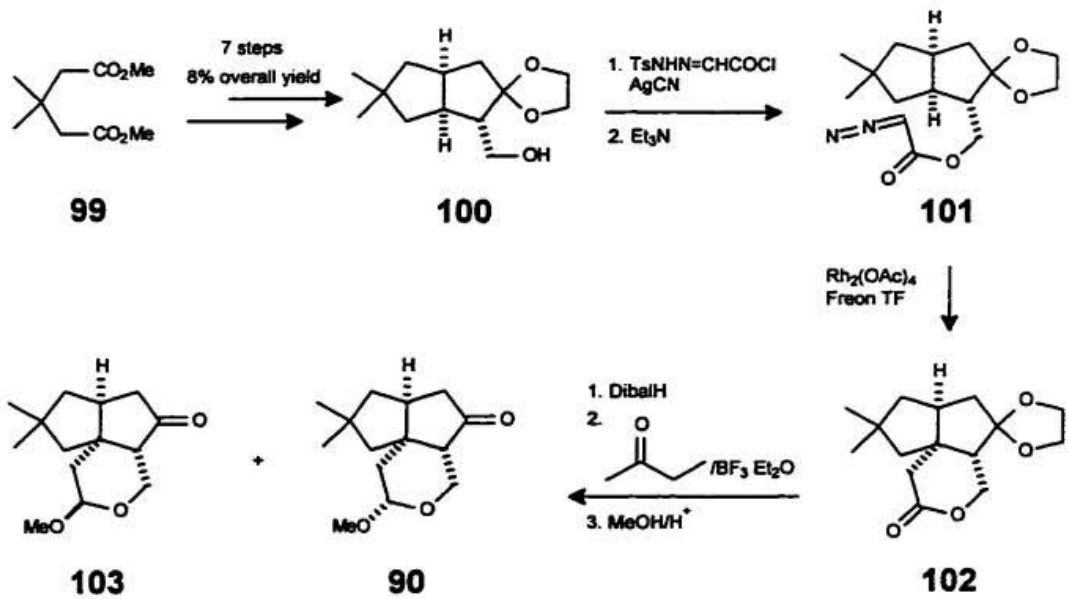
followed by oxidation of the B-ring methyl. Several synthetic transformations resulted in the silyl enol ether **96** as the major product, with the less-substituted enol ether as a reaction by-product. Formation of the corresponding α-bromo ketone was followed by synthesis of diene **97**. Epoxide formation, oxidative cleavage, and reduction gave pentalenolactone E methyl ester (**98**) in 14 steps from **93**, in an overall yield of 4%. Oxidation of the α-methylene gave pentalenolactone F methyl ester in low yield.



Scheme 36. Synthesis of pentalenolactone E by Matsumoto *et al.*[73]

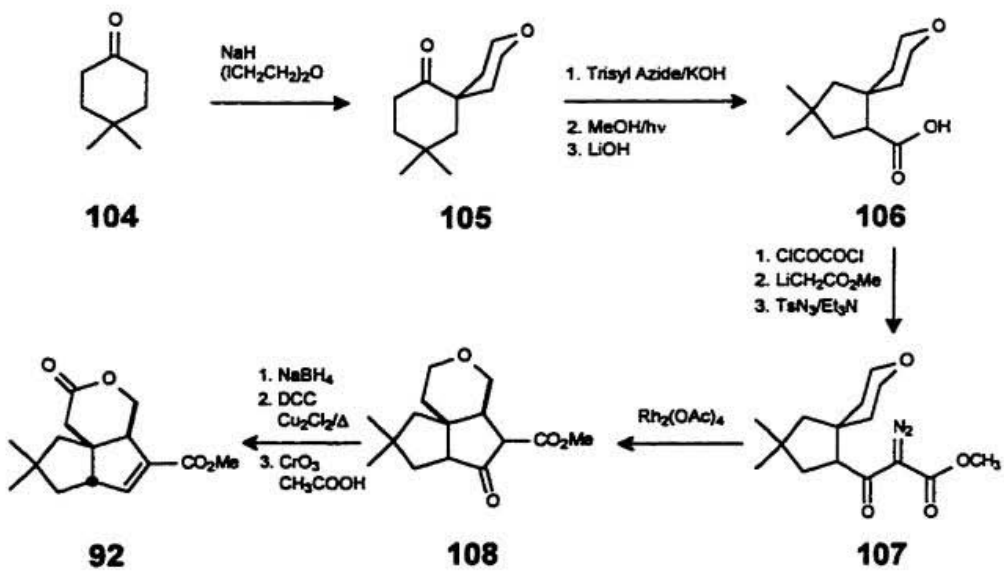
Cane has not only been instrumental in the biosynthetic studies of pentalenolactones, he has also made valuable synthetic contributions. In 1984, Cane and Thomas reported a formal synthesis of pentalenolactone E based on

an intramolecular carbene reaction at an unactivated bridgehead C-H bond to generate the A-ring (Scheme 37).[74] The diquinane ring system was constructed in ten steps from 3,3-dimethylglutarate in an overall yield of 8%. Compound **100** was strikingly similar to **89**, found in Paquette's synthesis, although Cane's approach to **100** was centered around an intermolecular [2 + 2] reaction. Treatment of **100** with glyoxalyl chloride tosylhydrazone in the presence of silver cyanide gave the desired glyoxalyl ester. Subsequent treatment with triethylamine gave the desired diazo ester (**101**). Carbene insertion gave 45% of the desired lactone (**102**). Reduction, deketalization and treatment with acidic methanol gave **90** and **103**. Compound **90** had been an intermediate in Paquette's synthesis of pentalenolactone E, however, both compounds were suited to the purpose of elaboration to pentalenolactone E.



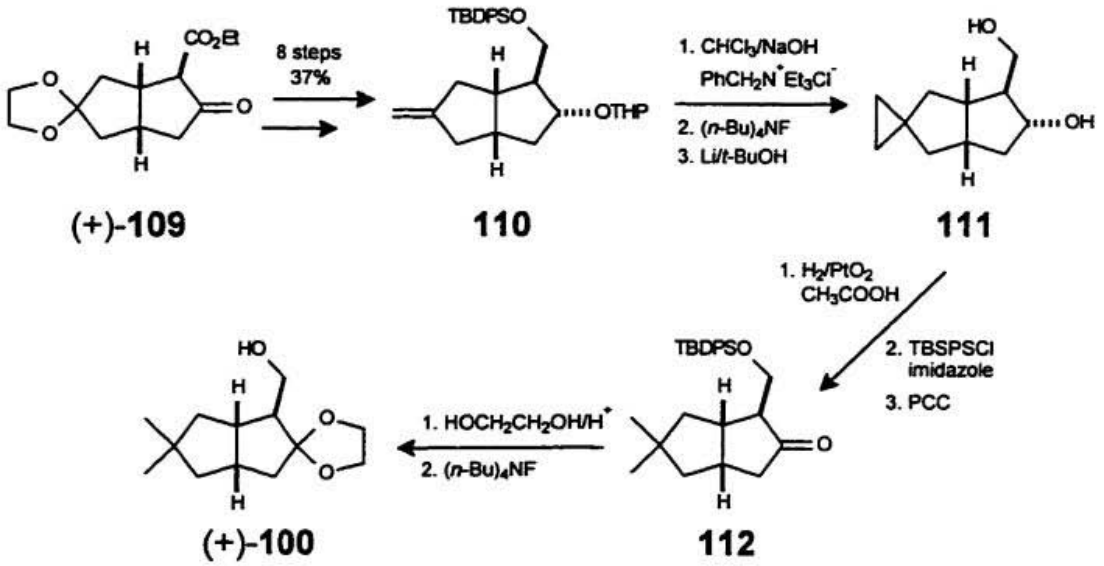
Scheme 37. Formal synthesis of pentalenolactone E by Cane and Thomas.[74]

Taber and Schuchardt's approach to pentalenolactone E differed from the previous attempts, which had been centered around dissection of the A-ring lactone, leading to a bicyclo[3.3.0]octan-3-one. Their approach involved dissection of the C-ring, leaving a spiro precursor with the AB ring system intact (Scheme 38).[75, 76] Similar to Cane and Thomas, the key step of the synthesis was an intramolecular C-H insertion, which took place in high yield to give **108**. Reduction and elimination of the ketone was followed by an oxidation to yield **92**, completing the formal synthesis of pentalenolactone E. The oxidation step proved unsatisfactory, taking place in 30% yield, with only a 3 : 1 preference for oxidation of the less-hindered methylene. By taking advantage of symmetry to simplify the synthesis, **92** could be formed in only eleven steps from 4,4-dimethylcyclohexanone. The key step was very successful, however the overall yield was poor.



Scheme 38. Formal synthesis of pentalenolatone E by Taber *et al.*[75, 76]

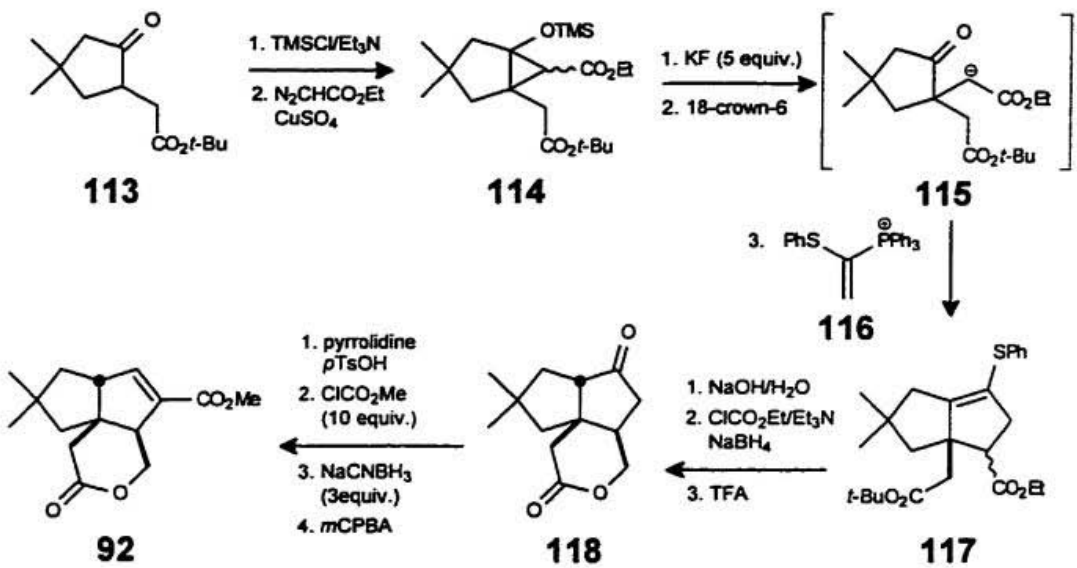
Mori and Tsuji reported the formal synthesis of chiral pentalenolactone E methyl ester in 1988 (Scheme 39).[77] Key to the enantioselective synthesis was the baker's yeast-mediated kinetic resolution of diquinane **109**. Cyclopropanation of **110** with dichlorocarbene gave **111**, after reductive dechlorination. Hydrogenolytic cleavage, followed by functional group manipulation gave the desired bicyclic alcohol (+)-**100**. Compound (+)-**100** was subsequently converted into (-)-pentalenolactone E methyl ester using procedures previously described.[71, 72, 74]



Scheme 39. Synthesis of chiral bicyclic alcohol (+)-**100** by Mori and Tsuji.[77]

Marino and Silveira applied a general route to annulated cyclopentanones, via a stepwise [3 + 2] process, to the formal synthesis of the methyl ester of pentalenolactone E (Scheme 40).[78] Formation of the silyl enol

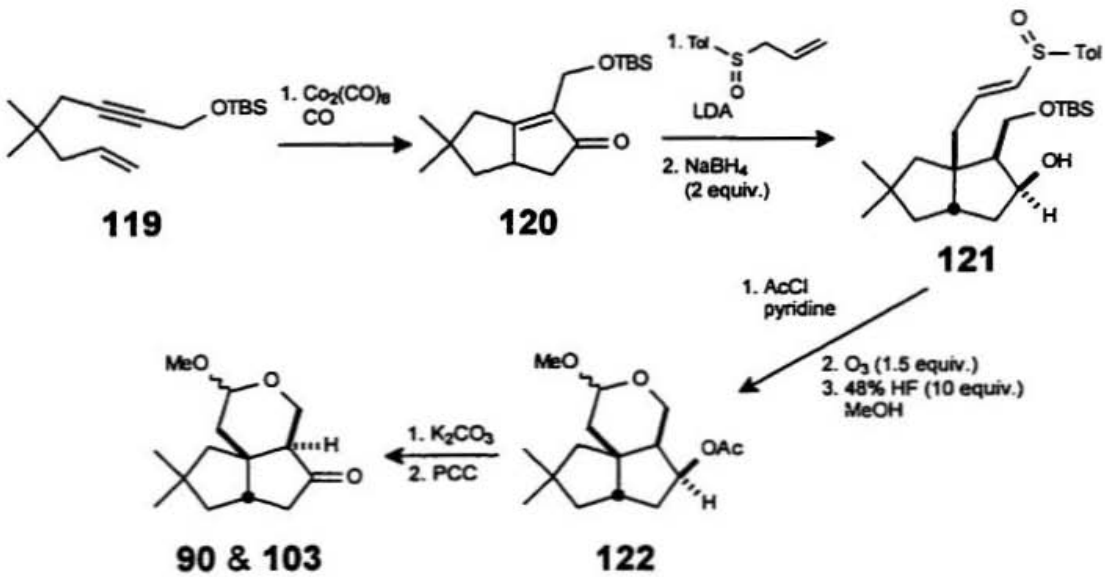
ether of **113**, followed by cyclopropanation, gave the key intermediate **114**. Fluoride ion-mediated formation of the γ-oxo ester enolate **115** followed by an addition-cyclization sequence gave diquinane **117** in excellent yield. A 1 : 1 mixture of *cis*/*trans* stereoisomers was obtained. Hydrolysis of the ethyl ester improved the ratio marginally. These isomers were separated, and the *cis* isomer carried on to **92**, a key intermediate of Paquette's synthesis.[71, 72] Compound **92** was synthesized from 4,4-dimethyl-2-cyclopentenone in 13 steps, with an overall yield of 11%.



Scheme 40. Synthesis of **92** by Marino and Silveira.[78]

The intramolecular Pauson-Khand reaction has also proven useful for formation of the diquinane system of the pentalenolactones.[79, 80] Hua *et al.* used this reaction along with a 1,4-addition reaction of sulfinylallyl anion as part of a

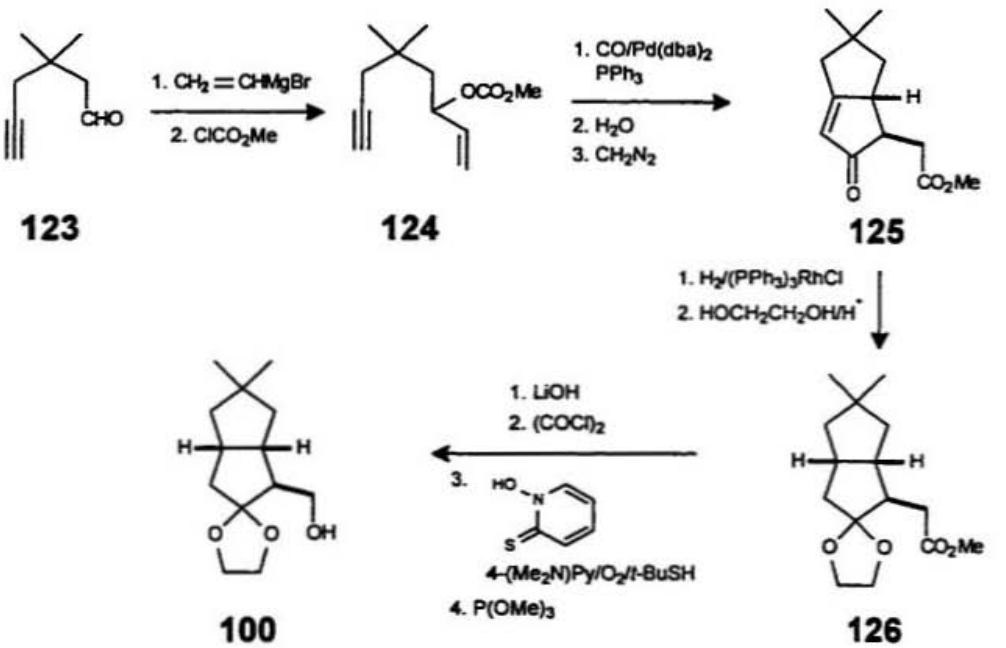
formal synthesis of pentalenolactone E (Scheme 41).[80, 81] Cobalt carbonyl promoted co-cyclization provided diquinane **120** in good yield. Reaction of the anion of *p*-tolyl allyl sulfoxide with **120** gave the expected 1,4-adduct. After reducing the ketone, attempted acetylation gave an unexpected result. It was found that acetylation was accompanied by reduction of the sulfoxide to a sulfide. Subsequent ozonolysis and fluoride ion-mediated lactonization yielded **122**. Functional group manipulation yielded a mixture of epimeric acetals (**90** and **103**). This constituted a formal synthesis since these had been carried on to pentalenolactone E by both Paquette[71, 72] and Cane.[74]



Scheme 41. Formal synthesis of pentalenolactone E by Hua *et al.*[80, 81]

Previous syntheses of pentalenolactone E by Cane and Thomas[74] as well as Mori and Tsuji[77] had used bicyclic alcohol **100** as an intermediate. Oppolzer

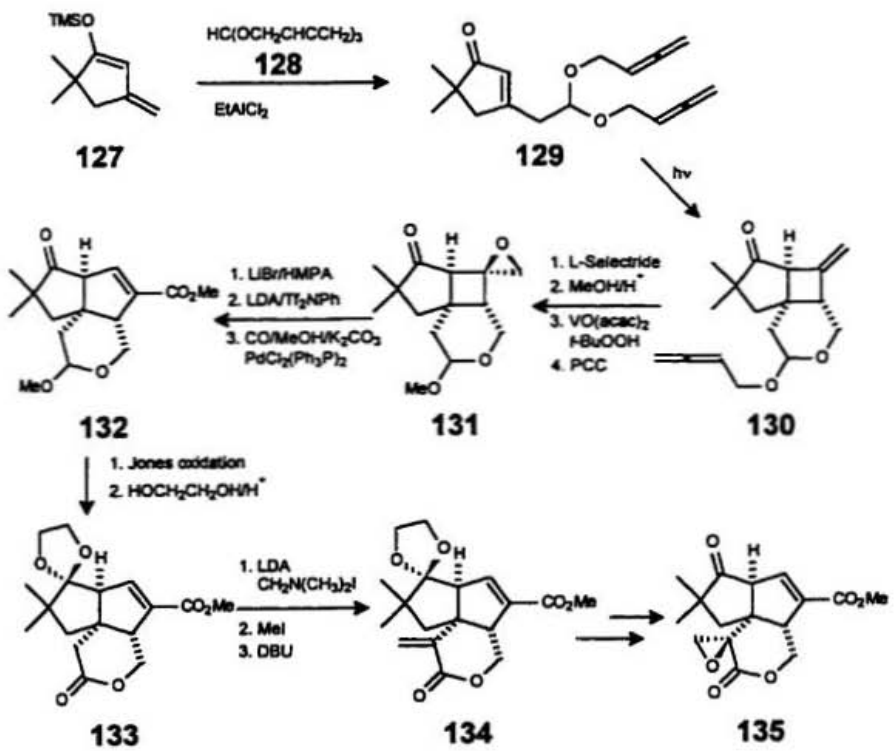
and co-workers[82] have described a synthesis of **100** using a palladium-catalyzed, tandem intramolecular allylation-carbonylation sequence (Scheme 42). Reaction of aldehyde **123** with vinylmagnesium bromide and trapping with methyl chloroformate gave carbonate **124**. This intermediate was set up for the crucial allylation-carbonylation step, which took place in modest yield to give bicyclooctenone **125**. Oppolzer *et al.*[82] used Barton's radical-chain method to reduce **126** to the required alcohol (**100**). This eleven step procedure provided alcohol **100** in 20% overall yield.



Scheme 42. Synthesis of **100** by Oppolzer and co-workers.[82]

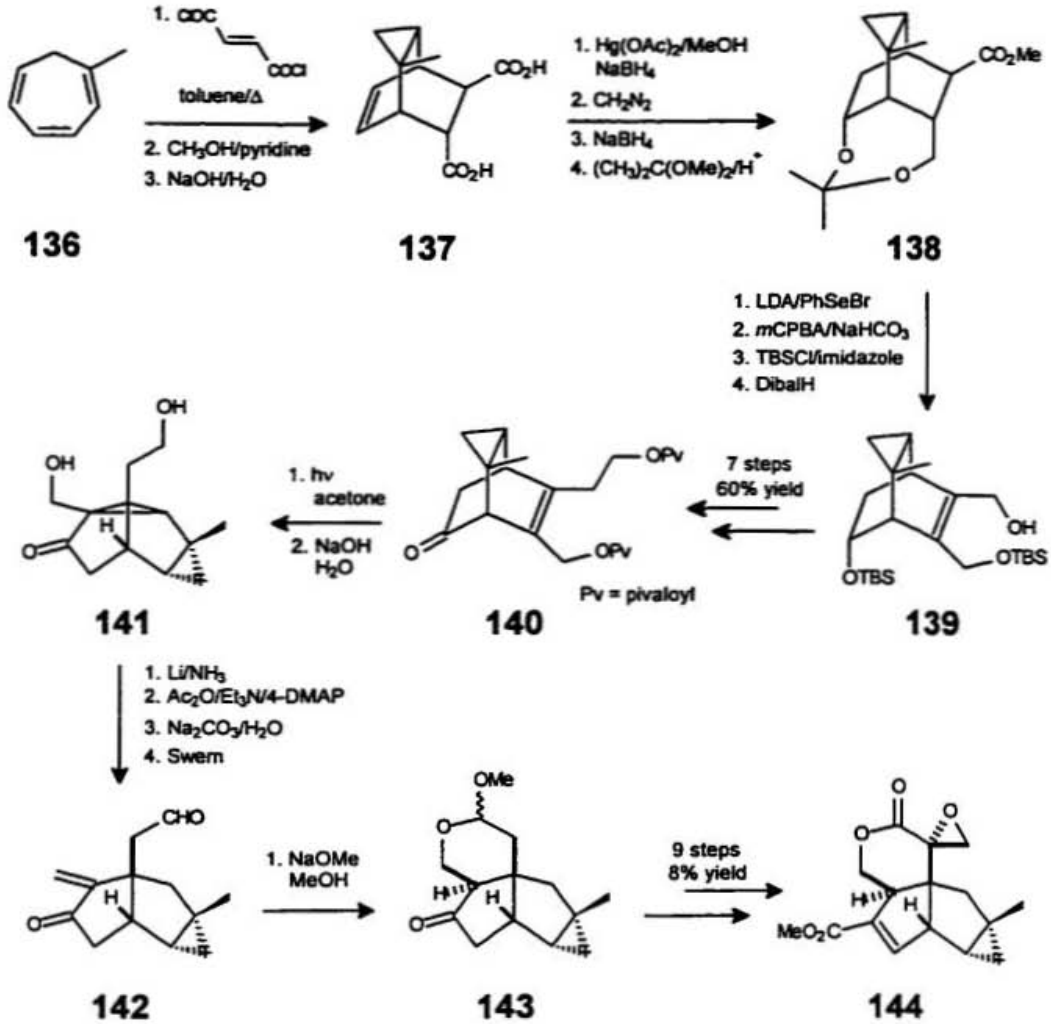
Unlike pentalenolactone E, there has been only one total synthesis of the more highly oxygenated pentalenolactone G. Pirrung and Thomson used the intramolecular photochemical cycloaddition of enone-acetals to form the A-ring

lactone (Scheme 43).[83, 84] Lewis acid-catalyzed condensation of orthoformate **128** with dienol ether **127** gave enone acetal **129** in good yield. Photochemical reaction gave **130**, having the required *cis* stereochemistry for the lactone ring. Reduction, allenic glycoside exchange for methyl, epoxidation and oxidation gave **131**. Ring expansion in the presence of lithium bromide followed by conversion of the B-ring ketone to a cyclopentene-carboxylate, using Stille methodology, gave **132**. Following oxidation and ketalization, introduction of the α-methylene group lead to **134**. Several more synthetic steps gave the desired pentalenolactone G methyl ester. Pirrung has also used this methodology in a formal synthesis of pentalenolactone E methyl ester.[84]



Scheme 43. Synthesis of pentalenolactone G methyl ester by Pirrung and Thomson.[83, 84]

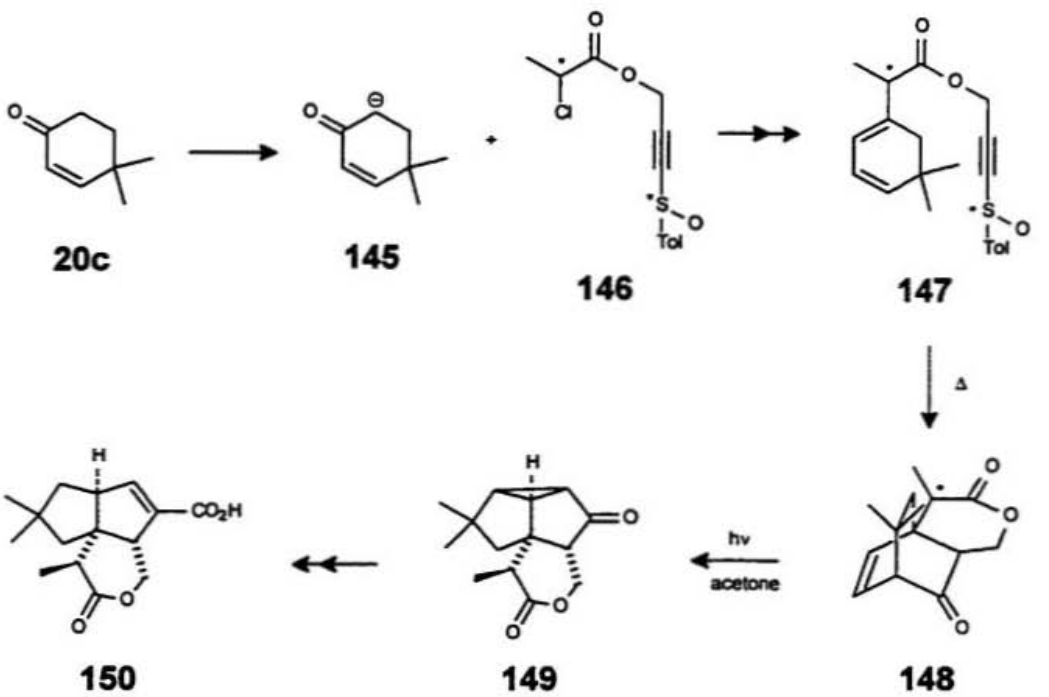
The first total synthesis of pentalenolactone P methyl ester was disclosed by Paquette *et al.* in 1992 (Scheme 44).[85, 86] In synthesizing this compound, a strategy was developed that was completely tolerant to the cyclopropane ring on the congested concave surface of the core diquinane framework. Diels-Alder reaction of 1-methylcycloheptatriene and fumaryl chloride, using either high pressure or thermal conditions, gave **137**, after modification. The stereochemical course of the Diels-Alder reaction was affected by the steric role of the methyl group. This resulted in *endo* addition of the proximal carbonyl, allowing for differentiation of acid residues through lactone formation. Esterification of the free acid, reduction of the lactone, and protection gave acetonide **138**. Formation of the α,β-unsaturated ester was accompanied by acetal cleavage. Silylation of the diol, followed by reduction of the ester gave **139**. In the key step of the synthesis, oxa-di-π-methane rearrangement of **140** resulted in **141** in excellent yield, following saponification. Treatment of diol **141** with acetic anhydride and triethylamine resulted in protection of the primary alcohol and formation of the α,β-unsaturated ketone **142**, after oxidation. Compound **143** was formed using the same procedure previously described by Paquette[71, 72] for pentalenolactone E. Formation of the cyclopentene-carboxylate closely followed the conditions used by Pirrung and Thomson[84] in the synthesis of pentalenolactone G. Introduction of the α-methylene moiety, followed by oxidation, completed the 32-step synthesis of pentalenolactone P methyl ester.



Scheme 44. Paquette's synthesis of pentalenolactone P methyl ester.[85, 86]

The goal of our research was to develop a short, high-yielding route to one of the two main types of pentalenolactones, those with *gem*-dimethyls in the C ring (Scheme 45). Furthermore, realization of this route would lead to pentalenolactones in optically active form. Using enone **20c** as our starting material, enolate formation (**145**) and alkylation with a chiral 2-halo ester such as **146** could lead to **147**. Compound **146** could be derived from chiral 2-chloro

propionyl chloride and an appropriate alcohol, containing a chiral alkynyl sulfoxide. Intramolecular Diels-Alder reaction of **147** would lead to **148**, after hydrolysis. In the key step, oxa-di-π-methane rearrangement of **148** would lead to pentalenolactone precursor **149**, having the ABC ring system and *cis*-fused lactone already in place. Reduction and homologation would provide pentalenolactone D (**150**). This route provides ample opportunity for introduction of other functionalities which would make all the *gem*-dimethyl pentalenolactones accessible (Figure 21).



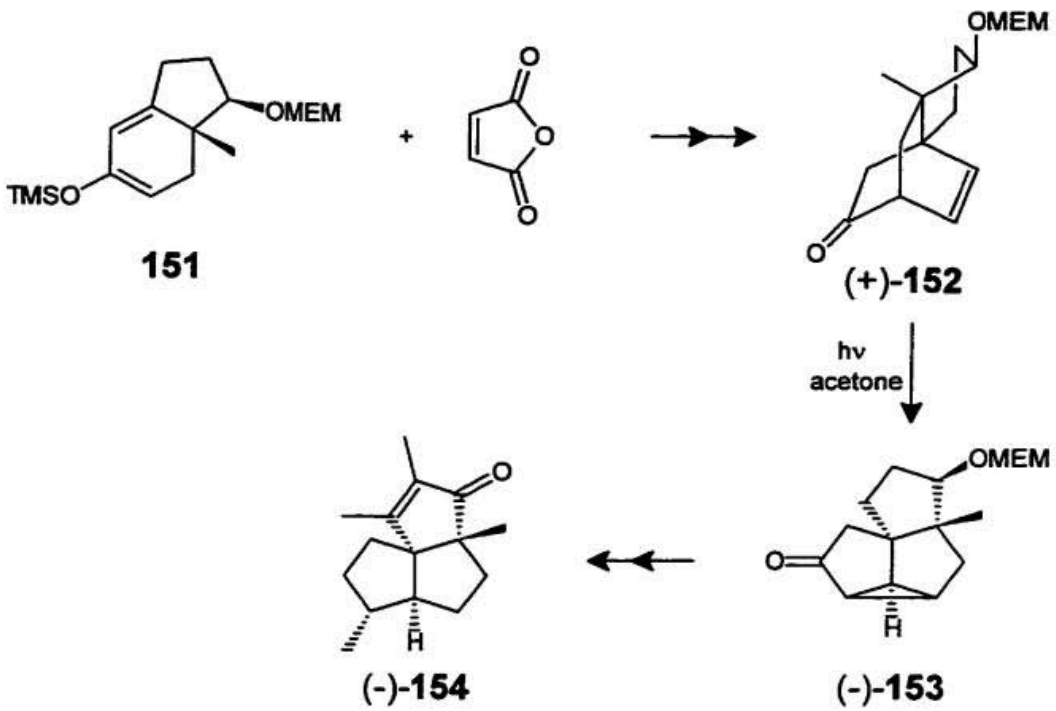
Scheme 45. Proposed synthetic route to pentalenolactones containing *gem*-dimethyls.

II. Results and Discussion

The use of an oxa-di-π-methane rearrangement of a bicyclo[2.2.2]octenone as the key step of a synthesis is not a novel concept. A large amount of work with these bridged bicyclic ketones has shown their photochemical reactivity to be quite general.[87] The oxa-di-π-methane rearrangements show a high degree of stereochemical control, proceed in high yield and can be carried out at high concentrations.[87] Furthermore, optically active compounds undergo enantiospecific rearrangements. These features have resulted in the application of the oxa-di-π-methane rearrangement in the syntheses of a number of natural products, especially sesquiterpenes containing two or three fused five-membered rings. The bicyclo[2.2.2]octenones required for these rearrangements are easily assembled using a Diels-Alder reaction. Therefore, precedence exists to allow the design of syntheses in which the photochemical rearrangement is preceded by a Diels-Alder reaction.

As shown in Scheme 44, Paquette *et al.* applied this methodology in the synthesis of pentalenolactone P methyl ester.[85, 86] This approach was also utilized by Demuth and Hinsken in the first total synthesis of enantiomerically pure (-)-silphiperfol-6-en-5-one (**154**) (Scheme 46).[88] Intermolecular Diels-Alder reaction of diene **151** with maleic anhydride gave (+)-**152**, after electrolytic decarboxylation. Photochemical rearrangement of (+)-**152** afforded triquinane

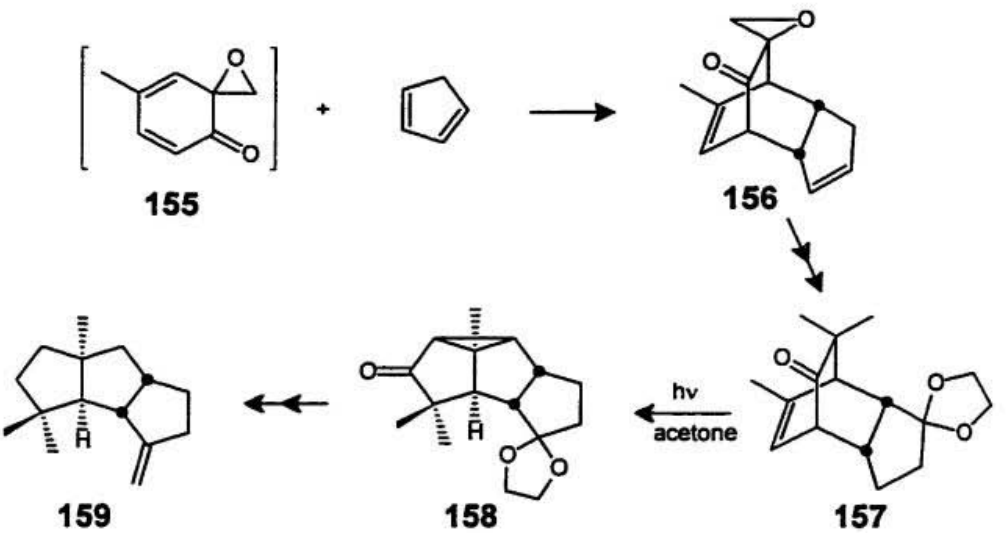
(-)-**153** in 70% yield. Further functional group manipulation completed the synthesis of (-)-silphiperfol-6-en-5-one (**154**).



Scheme 46. Total synthesis of enantiomerically pure (-)-silphiperfol-6-en-5-one by Demuth and Hinsken.[88]

Very recently, Singh *et al.* disclosed the total synthesis of racemic $\Delta^{9(12)}$-capnellene, a linear triquinane, using the Diels-Alder-oxa-di-π-methane rearrangement strategy (Scheme 47).[89] Spiro-epoxycyclohexa-2,4-dienone **155** was accessible from the corresponding hydroxymethyl *p*-cresol derivative by oxidation. Capture of this diene by Diels-Alder reaction with cyclopentadiene gave **157**, after several synthetic operations. Oxa-di-π-methane rearrangement of **157** gave triquinane **158** in 64% yield, possessing the desired stereochemical

disposition of rings, substituents and function groups present in $\Delta^{9(12)}$-capnellene. The synthesis was completed in 13 synthetic operations from the *p*-cresol derivative.

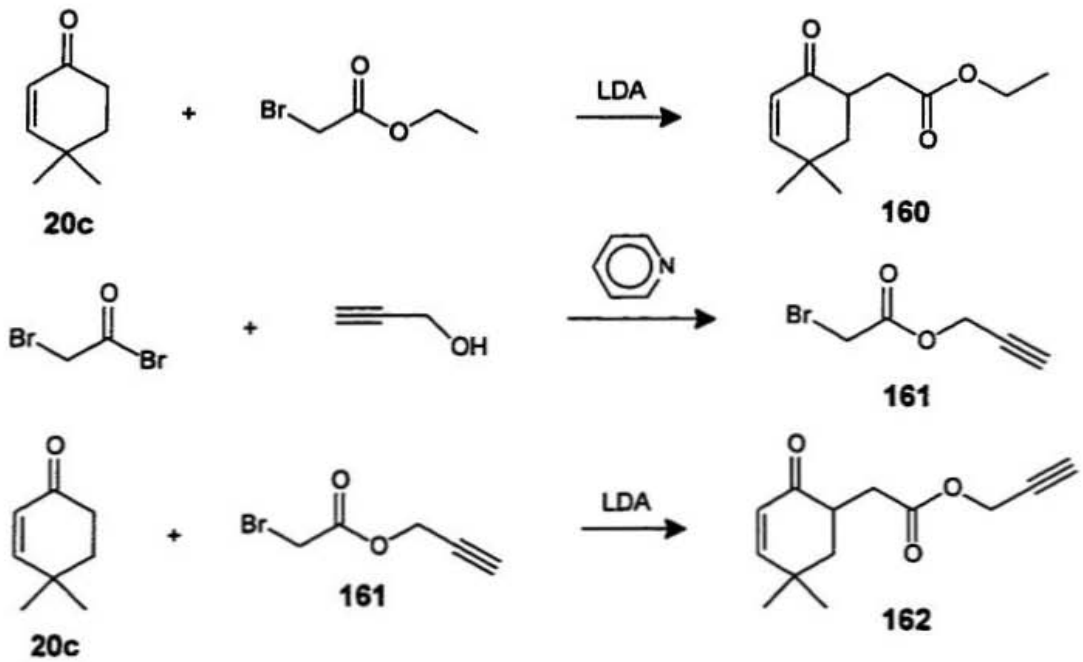


Scheme 47. Synthesis of $\Delta^{9(12)}$-capnellene by Singh and co-workers.[89]

(i). Initial Alkylation Studies

Initially, model studies for the alkylation of 4,4-dimethyl-2-cyclohexen-1-one (**20c**) with simple 2-halo esters were undertaken. The enolate of **20c** was formed by deprotonation with a slight excess of LDA at -78 °C. Attempted alkylation with ethyl bromoacetate gave the expected γ-keto ester **160** in 38% yield (Scheme 48). This yield was not considered discouraging since the conditions had not been optimized. We then attempted alkylation with a 2-halo ester which more closely resembled **146**. Addition of bromoacetyl bromide to a 0

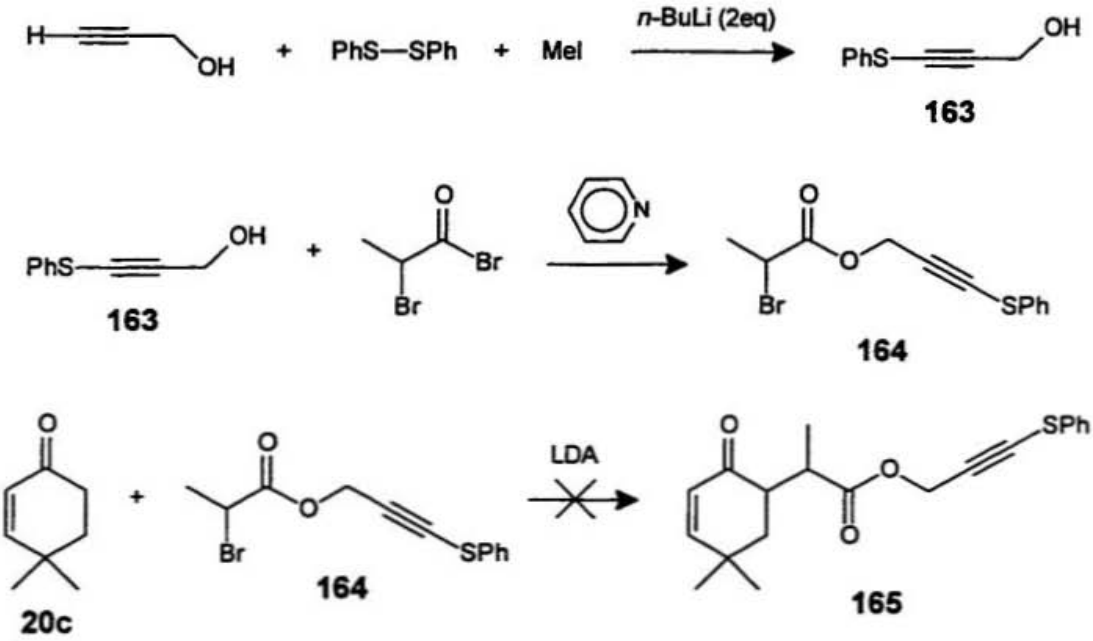
°C solution of pyridine and 2-propynol in diethyl ether gave **161** in 85% yield (Scheme 48). Reaction of **161** with **20c** gave the expected γ-keto ester **162** in only 9% yield after flash chromatography. It appeared that the identity of the 2-halo ester affected the reaction outcome. Compound **161** has an acidic alkynyl hydrogen which is not present in ethyl bromoacetate. Due to this concern, we decided to replace the hydrogen with another substituent.



Scheme 48.

Magee and Kabanyane had reported a convenient procedure for the preparation of alkynyl phenyl sulfides.[90] Formation of the dianion of 2-propynol at -30 °C using *n*-butyllithium, followed by treatment with a pre-mixed solution of phenyl disulfide and iodomethane in THF, gave **163** in 84% yield (Scheme 49).

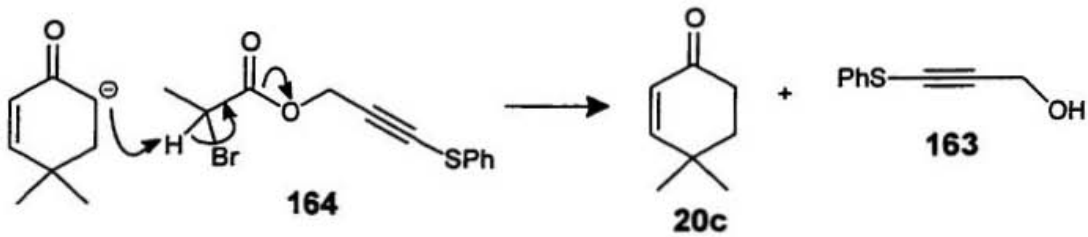
Reaction of **163** with a slight excess of 2-bromopropionyl bromide and pyridine resulted in the expected 2-bromo ester (**164**) in 96% yield. The use of a slight excess of the acid bromide instead of a stoichiometric or slight excess of alcohol always gave a higher yield. This is most likely a result of some unavoidable degradation of the moisture-sensitive acid bromide.



Scheme 49.

Compound **164** was well-suited to the pentalenolactone synthesis since it contained the eventual A-ring methyl and a dienophile suitable for an intramolecular Diels-Alder reaction. Attempted alkylation of **20c** with **164** did not result in **165** (Scheme 49). Instead, alcohol **163** was isolated in 83% yield,

based on the starting 2-bromo ester (**164**). TLC and crude ^{1}H NMR showed that **20c** remained unchanged. The enolate of **20c** appeared to have abstracted the proton α to the carboxyl of **164**, resulting in its subsequent degradation (Scheme 50). This result illustrated that 2-bromo esters were not suitable as alkylating agents for enone **20c** since proton abstraction occurred preferentially over the desired S_N2 substitution. Podraza and Bassfield had reported that alkylation of 3-methyl-2-cyclohexen-1-one and 2-cyclohexen-1-one with ethyl bromoacetate, using similar conditions, gave the desired γ-keto esters in good yields.[91] These contrasting results indicated there may be a steric effect present due to the dimethyl group in **20c**.

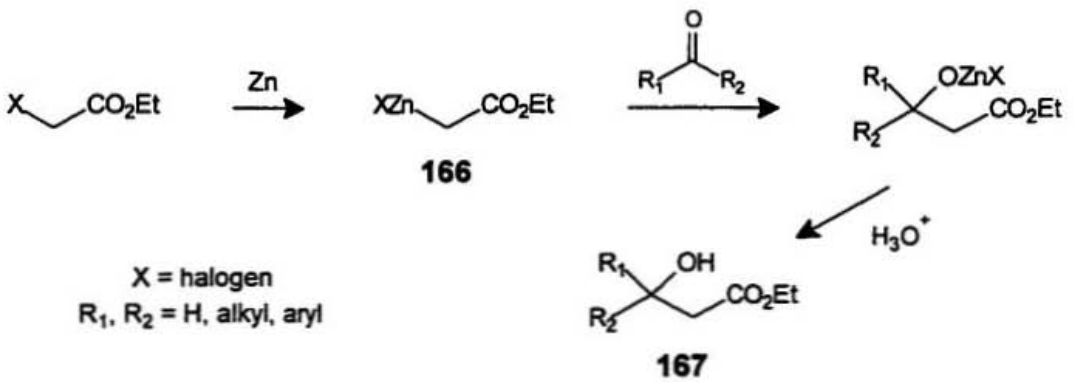


Scheme 50.

These initial alkylation reactions were discouraging. Although 2-bromo esters, containing functionalities amenable to the synthesis of *gem*-dimethyl pentalenolactones, could be prepared in high yield, attempted alkylations to form synthetic precursors to **147** did not appear to be accessible using our initial approach.

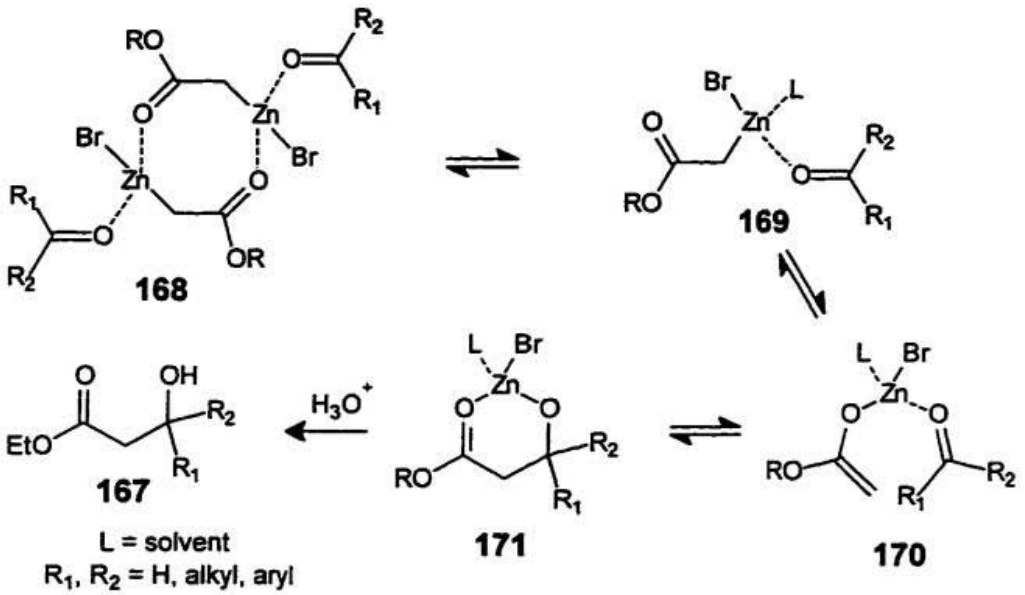
(ii). Reformatsky Approach

The Reformatsky reaction in its classical form, as shown in Scheme 51, is the reaction of a carbonyl compound, usually an aldehyde or ketone, with an α-halo ester in the presence of zinc metal to furnish, after hydrolysis, a β-hydroxy ester.[92] Since its discovery, the scope of the Reformatsky reaction has been extended beyond these very restricted conditions. Furstner broadened the definition to include all reactions resulting from metal insertions into carbon-halogen bonds activated by carbonyl- or carbonyl-derived groups in vicinal or vinylogous positions with a variety of electrophiles.[93]



Scheme 51. Classical Reformatsky reaction.

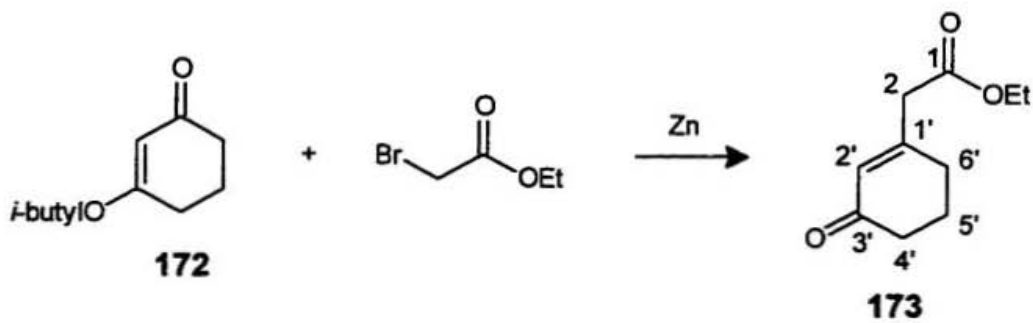
The reaction can be regarded as being similar to the Grignard reaction with **166** as an intermediate analogous to RMgX. The exact nature of intermediate **166** has been the subject of much controversy.[37]



Scheme 52. The minimum energy reaction path for the Reformatsky reaction obtained from computational studies.[95]

X-Ray crystallography of the solid intermediate indicated the Reformatsky reagent was dimeric, possessing characteristics of both the *C*- and *O*-metallated enolates.[94] Dewar and Merz used computational studies to obtain the minimum energy reaction path for this reaction, shown in Scheme 52.[95] These results reinforced the dimeric nature of the Reformatsky reagent (**168**), however, reaction involved the formation of a *C*-metallated monomer (**169**), which underwent a (1,3)-shift to give the *O*-metallated enolate (**170**). Intermediate **170** underwent C-C bond formation through a metallo-Claisen rearrangement to give the β-hydroxy ester (**167**) after hydrolysis.

Our interest in the Reformatsky reaction stemmed from work by Panouse and Sannie.[96] They had reported that the Reformatsky reaction of enone **172** with ethyl bromoacetate gave an undisclosed yield of the 3-substituted enone **173** (Scheme 53). For compound **173**, introduction of a methyl group at C-2, a dimethyl group at C-5', and modification of the ester group would yield an intermediate well-suited to our approach to the pentalenolactones. A similar reaction sequence involving modified reagents was thus attempted.

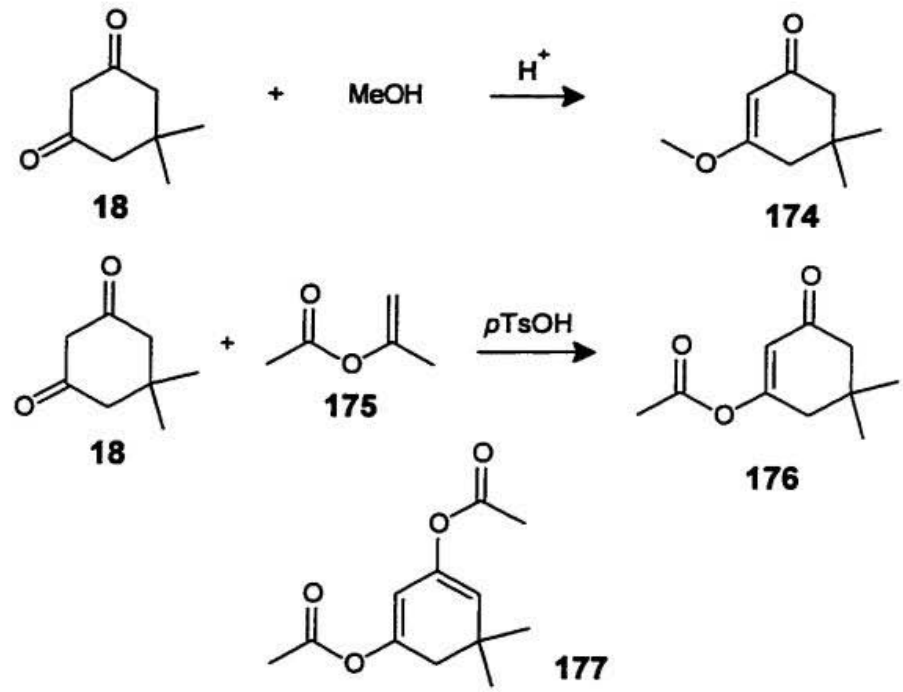


172 **173**

Scheme 53. Reformatsky reaction reported by Panouse and Sannie.[96]

The *gem*-dimethyl group required in the synthesis could be easily accommodated using derivatives of the commercially available 5,5-dimethyl-1,3-cyclohexanedione (**18**). Reaction of **18** with excess methanol in the presence of an acid catalyst furnished a 95% yield of the desired enone (**174**), after chromatography (Scheme 54). Also, **18** was reacted with a slight excess of isopropenyl acetate (**175**) at 60 °C using benzene as the solvent. An 81% yield of **176** was obtained following distillation. Early attempts to synthesize **176** in refluxing benzene appeared to be highly successful, with isolated yields

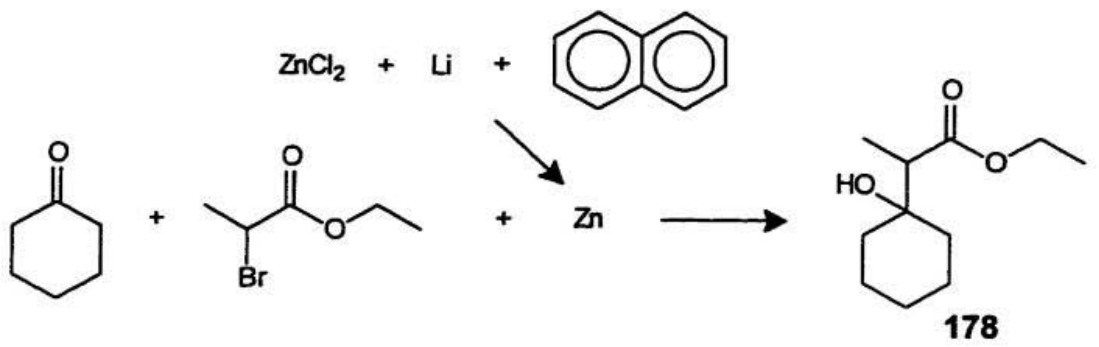
greater than 90%. However, once yields appeared to top 100%, it was soon realized that the diacetoxy derivative (**177**) was being produced as a by-product. By reducing the temperature and closely monitoring the reaction progress by TLC, this could be avoided.



Scheme 54.

There are two general strategies for activating zinc to be used in the Reformatsky reaction involving either cleaning of the metal surface to remove the deactivating zinc oxide layer or achieving a fine distribution of metal, usually accomplished by reduction of zinc halides. Of these two methods, the second has been shown to result in higher yields under much milder conditions. As a result, we reduced zinc(II) chloride using lithium naphthalide, following a

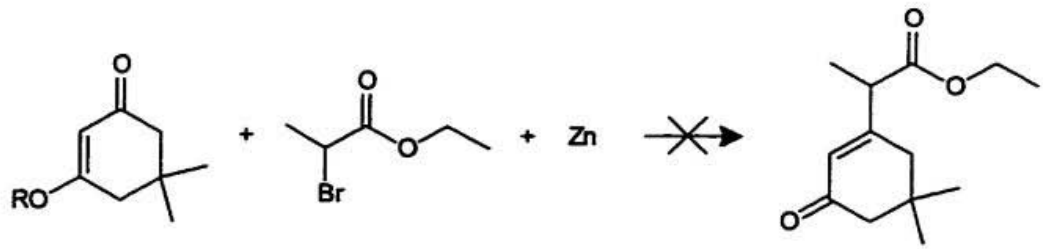
procedure originally reported by Rieke,[97] to generate activated zinc suitable for our Reformatsky reactions.



Scheme 55.

To test this procedure a simplified Reformatsky reaction, involving a saturated ketone, was attempted. Reduction of pre-dried zinc(II) chloride with lithium naphthalide in 1,2-dimethoxyethane after stirring for fifteen hours yielded activated zinc as a fine black powder. Subsequently, this was used in the Reformatsky reaction of ethyl 2-bromopropionate and cyclohexanone to furnish a 72% unoptimized yield of β-hydroxy ester **178** (Scheme 55). Attempted Reformatsky reactions of enones **174** and **176** with ethyl 2-bromopropionate, using identical conditions, did not result in **179** (Table 8). Compound **174** was recovered unchanged whereas **176** hydrolyzed to give 5,5-dimethyl-1,3-cyclohexanedione (**18**). Several attempts to circumvent this by changing the reaction solvent, the identity of the halide and the amount of reducing agent were all unsuccessful (Table 8).

Table 8. Unsuccessful Reformatsky reaction conditions.



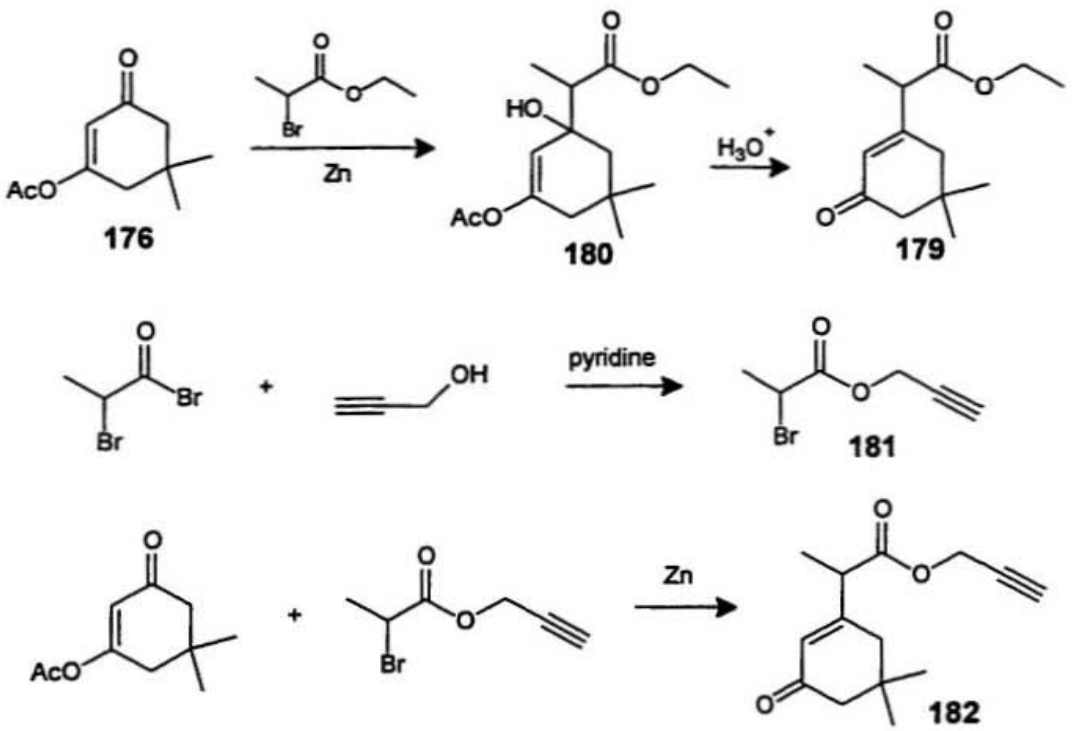
174 : R = CH_3
176 : R = CH_3CO

179

enone	equivalents of lithium used	solvent	zinc halide
174	2	diethyl ether	$ZnCl_2$
174	2	THF	$ZnCl_2$
174	2	1,2-dimethoxyethane	$ZnBr_2$
174	4	diethyl ether	$ZnBr_2$
176	2	diethyl ether	$ZnCl_2$
176	3	1,2-dimethoxyethane	$ZnCl_2$

Following the initial attempts using activated zinc derived from zinc halides, we decided to try the classical Reformatsky conditions. Zinc metal (20 mesh) was activated by washing with dilute hydrochloric acid, and a mixture of benzene and diethyl ether was used as the solvent. This solvent mixture had been shown to be superior to benzene alone, especially for less reactive ketones.[98] Reaction of ethyl 2-bromopropionate and **174** under Reformatsky conditions failed to show any indication of product. Once again, only starting material was recovered. Reaction with **176** proved to be more fruitful.

Compound **176** reacted with the Reformatsky reagent derived from activated zinc metal and ethyl 2-bromopropionate to form **179** in 67% yield, after acidic hydrolysis (Scheme 56). Initially, it was suspected the product might be β-hydroxy ester **180**, however, the absence of a hydroxyl signal in the IR spectrum suggested otherwise. Unmasking of the enone probably occurred during the acidic workup.



Scheme 56.

We now hoped to introduce a modified 2-halo ester possessing a potential dienophile. The synthesis of a suitable 2-bromo ester proved to be straightforward. 2-Bromopropanoyl bromide reacted with 2-propynol, in the

presence of pyridine, to give a 93% yield of **181** (Scheme 56). The Reformatsky reaction of **181** with enone **176** furnished the desired enone **182** in 62% yield, utilizing the usual benzene-diethyl ether solvent. It was anticipated that diene formation would yield a product suitable for an intramolecular Diels-Alder reaction.

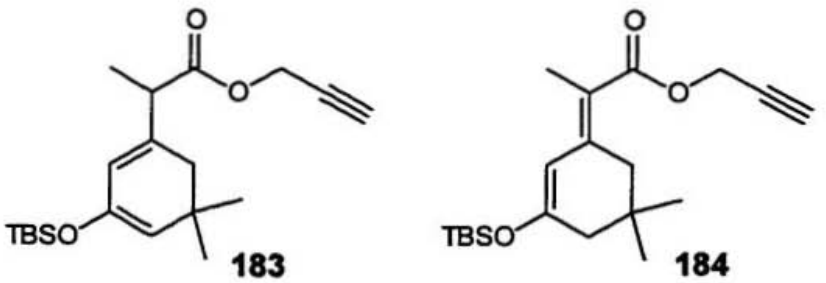
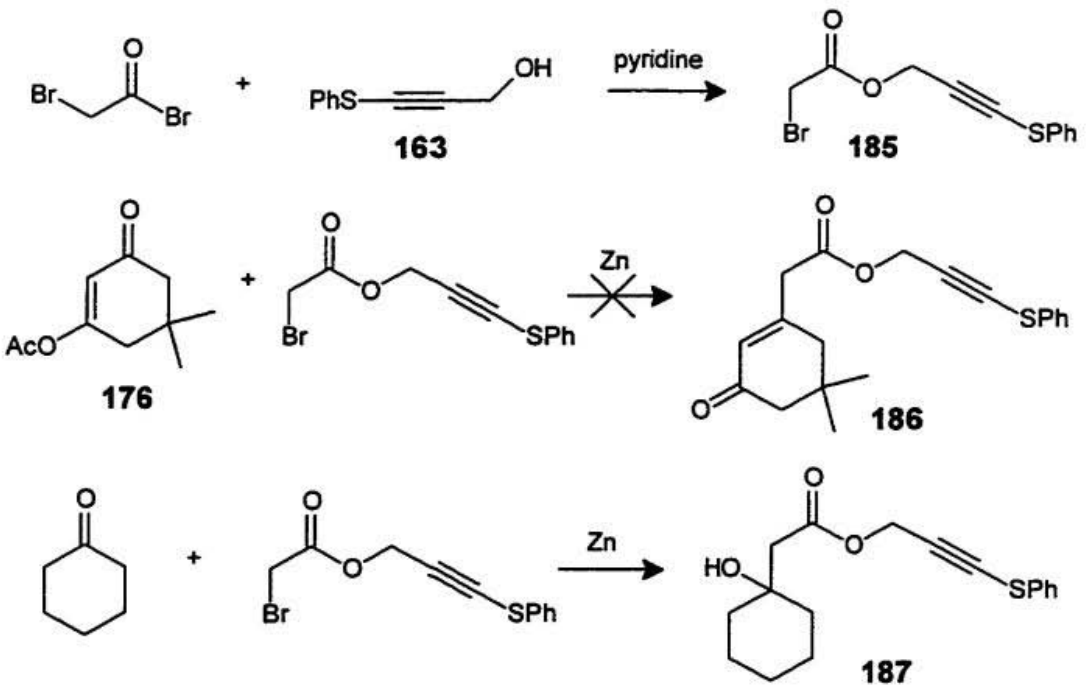


Figure 22. Expected and observed products for the attempted diene formation.

However, deprotonation of **182** with one equivalent of LDA, followed by the addition of TBSCl at -78 °C did not give the desired diene **183** (Figure 22). The crude ^{13}C NMR spectrum indicated a silyl enol ether had formed concurrently with the disappearance of the enone carbonyl signal of **182** at δ 199.5. As would be expected for diene **183**, the sp^2 carbon region now contained four signals, however, it appeared that only one of these had attached protons. This was supported by the presence of only one double bond proton at δ 5.73 in the ^1H NMR spectrum. Furthermore, the ^1H and ^{13}C NMR signals for the 2-propynyl ester portion remained intact. Deprotonation had removed the

proton α to the ester, resulting in the conjugated silyl enol product **184** (Figure 22).

The addition of two equivalents of base was contemplated, but it was feared that problems would arise as a result of the acidic alkynyl hydrogen. Thus, we synthesized **185** in 95 % yield from the corresponding acid bromide and 3-substituted alcohol (Scheme 57). Surprisingly, the attempted Reformatsky reaction of **185** with enone **176** resulted in no indication of desired product. Only signals representative of enone **176** and the debrominated **185** were observed.



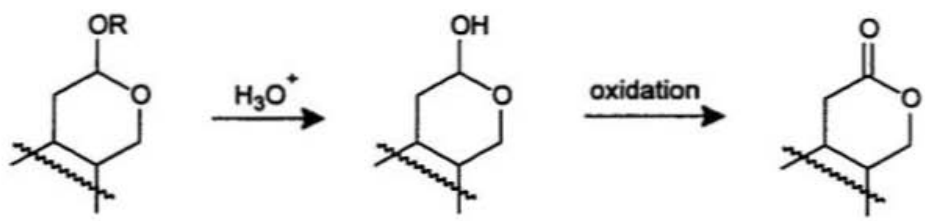
Scheme 57.

The Reformatsky reaction of **185** and cyclohexanone gave only a 44% yield of the expected product (**187**). Compound **163**, resulting from degradation of **185**,

was also obtained in 12% yield, based on the amount of starting 2-bromo ester. This lack of desired reactivity was a little baffling considering the earlier results. Rather than pursue this avenue any further, we chose to explore a new route based on 2-halo acetals.

(iii). The Acetal Approach

In many synthetic studies, cyclic hemi-acetals have often been used as synthetic precursors for lactones. In fact, several total syntheses of the pentalenolactones have used this approach to form the A ring lactone.[69-72, 80-81, 83-86] As illustrated in Scheme 58, acidic hydrolysis of cyclic hemi-acetal **188** would result in a lactol, which could be oxidized to the corresponding lactone (**189**).



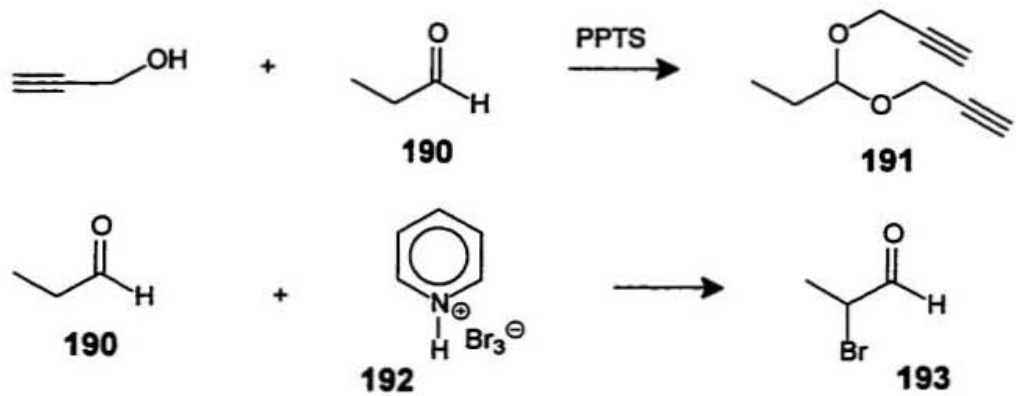
188 **189**

Scheme 58.

The results of the Reformatsky reactions and the initial alkylation attempts both seemed to indicate the relatively acidic α-proton of the 2-halo esters was

causing problems. Our approach was to alkylate **20c** with a 2-halo acetal, which could be converted to a lactone following the intramolecular Diels-Alder reaction.

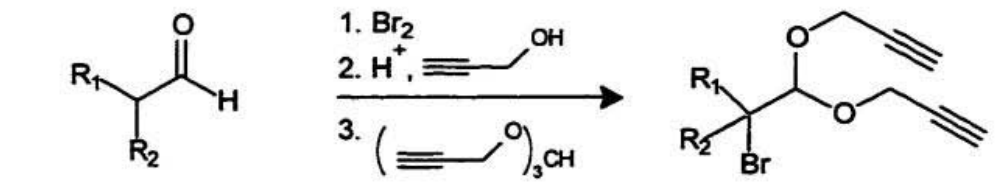
Acetal **191** was obtained in 50% yield by reacting two equivalents of propargyl alcohol with propionaldehyde (**190**) in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) (Scheme 59). Thus , we



Scheme 59.

assumed that the same reaction with 2-bromopropionaldehyde (**193**) would yield a 2-bromo acetal suitable for alkylation. Preparation of **193** was not straightforward. The actual bromination of **190** was accomplished using pyridinium bromide perbromide (**192**),[99] however isolation proved to be difficult. Within minutes of removing the solvent, **193** had polymerized. As a result, purification, by distillation or otherwise, was impossible. This problem could be bypassed by adding benzene, the solvent to be used for the acetylation, before removing the diethyl ether used in the bromination step. Reaction of this solution

of **193** with two equivalents of propargyl alcohol yielded an inseparable mixture of mono- and di-2-propynyl acetals.

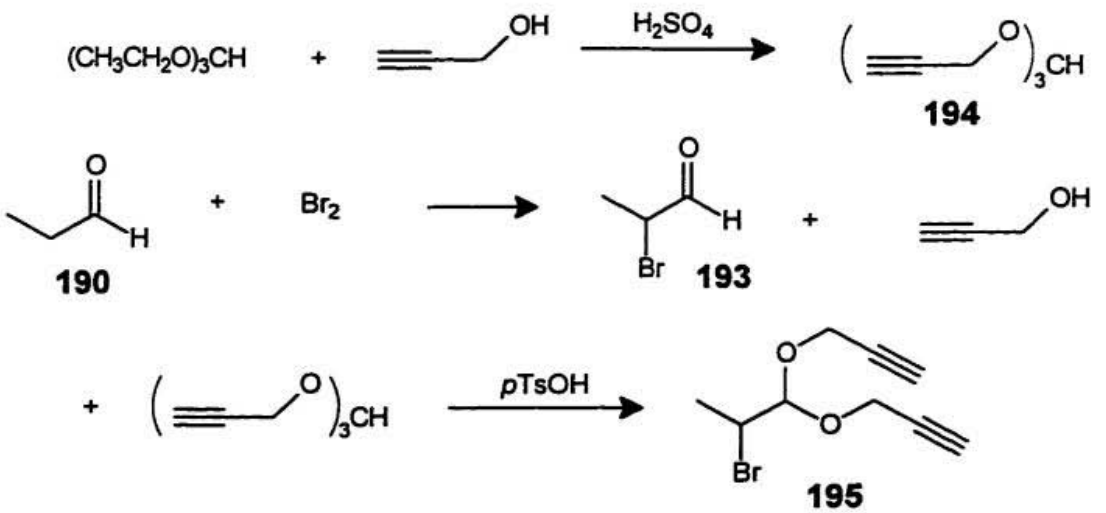


R_1, R_2 = Me, Et, Pr, Bu

194

Scheme 60.

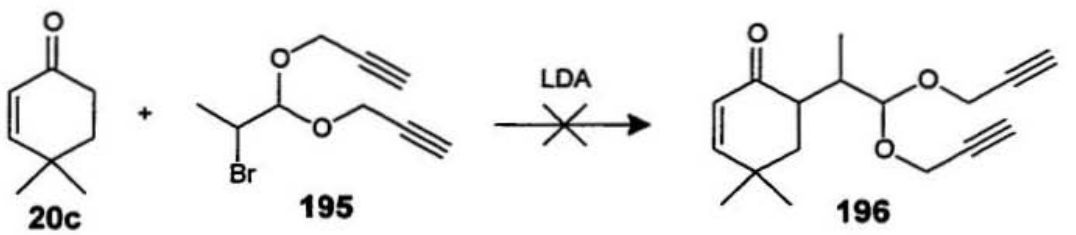
Okabe and Tada had described the preparation of 2-bromo acetals similar to **195** involving more complex aldehydes (Scheme 60).[100] We adapted this procedure to propionaldehyde (**190**). Azeotropic removal of ethanol from a benzene solution of triethyl orthoformate and excess 2-propynol yielded the desired orthoformate **194**, after distillation (Scheme 61).



Scheme 61.

Following Okabe and Tada's procedure, an ethereal solution of **190** was reacted with one equivalent of bromine. The resulting 2-bromopropanal (**193**) was used directly in the synthesis of **195** by refluxing in the presence of four equivalents of 2-propynol and a small amount of orthoformate **194**. A 38% yield of 2-bromo acetal **195** was obtained after distillation.

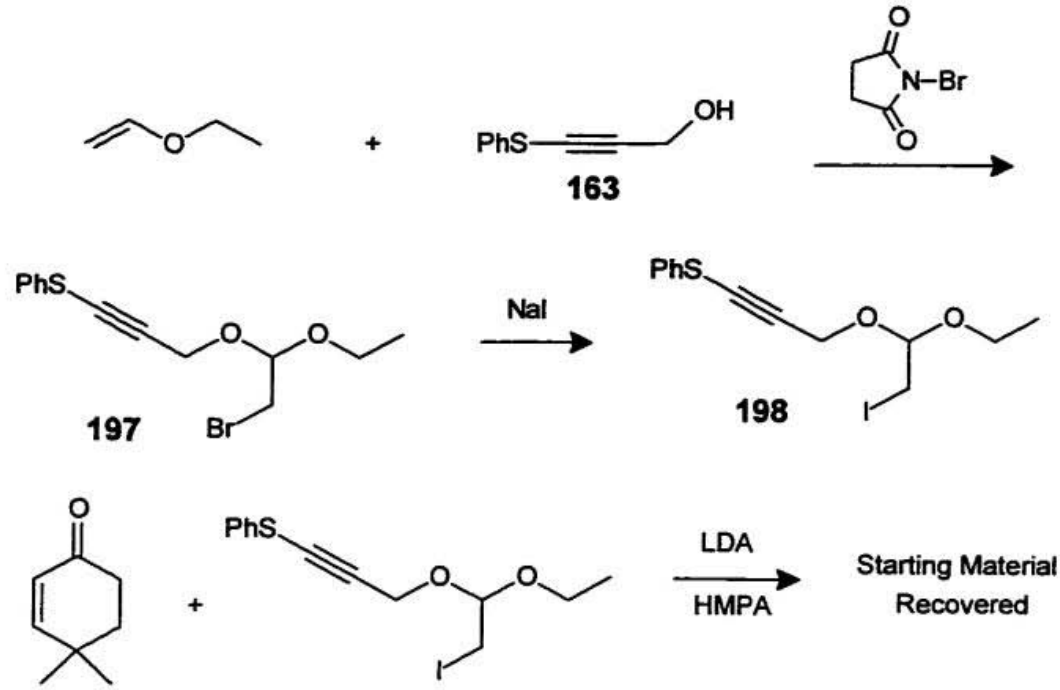
Deprotonation of **20c** with LDA at -78 °C, followed by the addition of **195** gave none of the expected product (**196**) (Scheme 62). The crude ^{1}H NMR spectrum indicated **20c** to be unchanged while the 2-bromo acetal had partially decomposed.



20c **195** **196**

Scheme 62.

We were concerned that **195** was not reactive enough as an alkylating agent for **20c**. For **195**, if the reaction was to occur, the bromine would be displaced from a secondary carbon. By using a primary carbon as the reacting center and using a better leaving group, we hoped to improve our chance for alkylation.

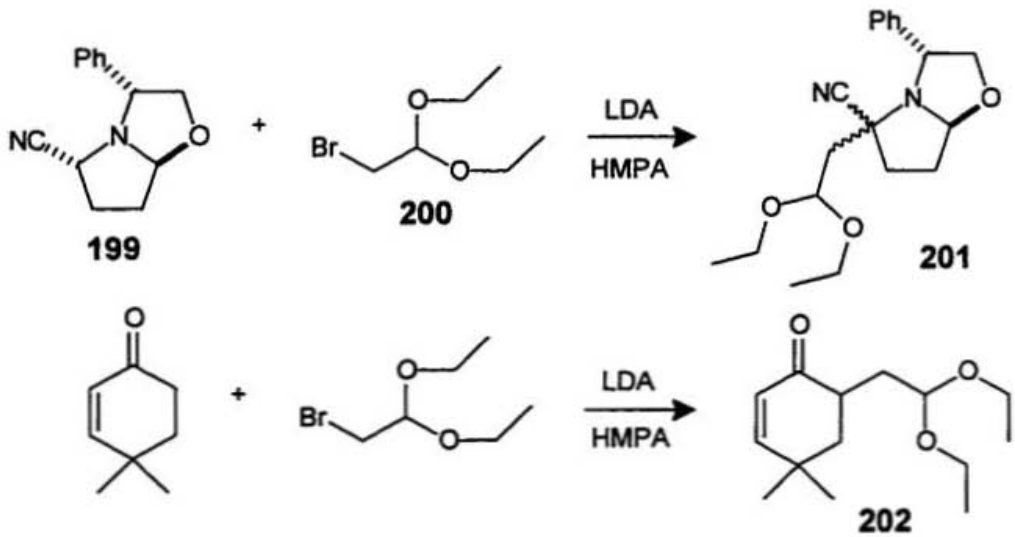


Scheme 63.

Several groups had reported the synthesis of various 2-halo acetals by reacting alkyl vinyl ethers with alcohols in the presence of *N*-bromosuccinimide.[101] Using a similar approach, reaction of ethyl vinyl ether with **163** gave a 75% yield of **197** (Scheme 63). Compound **197** was reacted with a slight excess of sodium iodide in refluxing acetone for two days. The ^{1}H NMR spectrum of the crude reaction mixture showed the reaction to be 40% complete. With the addition of three equivalents of sodium iodide and refluxing for a further two days, **198** was obtained in 78% yield. Attempted alkylation of **20c** with **198** in the usual manner resulted in no reaction (Scheme 63). In fact,

the "crude" ^{1}H NMR spectrum was so clean that the *only* signals present were those for the two starting materials.

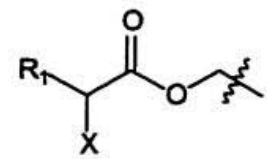
Following this disappointing result, it appeared that any attempt to alkylate **20c** with a 2-halo acetal would be unsuccessful. However, recent work by Royer *et al.* sparked our interest in this area once more.[102] They had reported alkylation of **199** with two equivalents of 2-bromoethanal diethyl acetal (**200**) at -78 °C using three equivalents of LDA and five equivalents of HMPA (Scheme 64). Compound **201** was obtained in 84% yield. We reacted **20c** with **200** using the same conditions. GC-MS indicated that only starting materials were present.



Scheme 64.

(iv). Alkylation Studies Revisited

As a result of the limited success with the Reformatsky approach and the apparent unreactivity of 2-halo acetals as alkylating agents for **20c**, we reexamined our initial alkylation approach to intermediate **147**. The 2-bromo esters used in the initial studies were quite unreactive as alkylating agents for enone **20c** (Figure 23).



X = Br

R_1 = H, CH_3

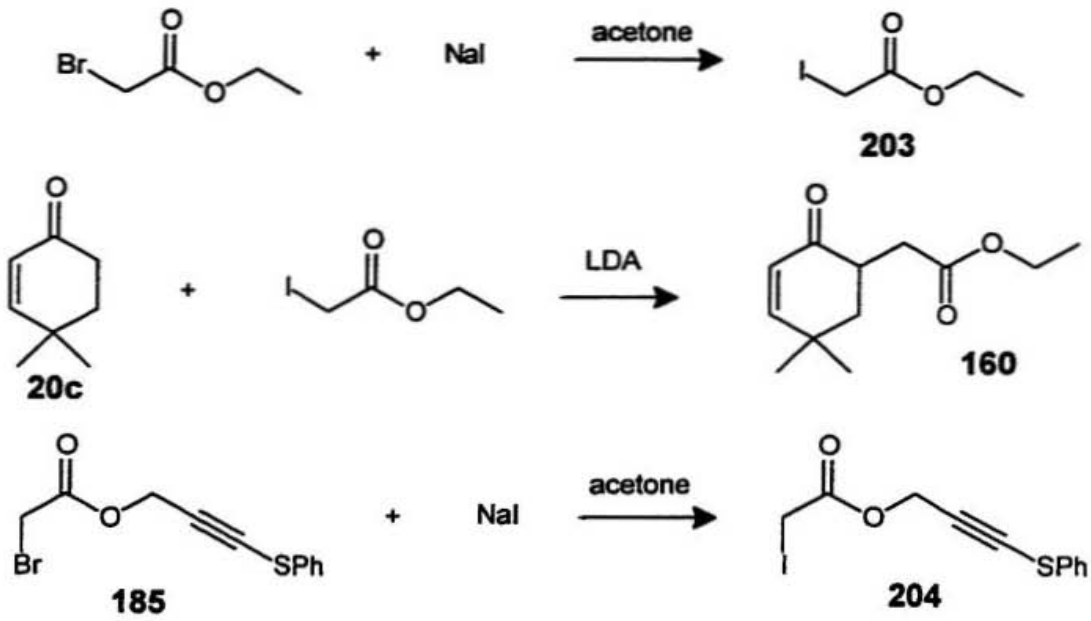
Figure 23. 2-Halo esters used in the initial alkylation studies.

Introduction of a better leaving group might result in the α-carbon being more receptive to attack. Thus, we decided to substitute iodine in place of bromine. α-Iodo esters are not generally available commercially, however they have been synthesized by deprotonation of the corresponding ester with a strong base, followed by the addition of iodine.[103] This would not lead to chiral α-halo esters, therefore we took a different approach. Our intention was to synthesize 2-iodo esters from the readily accessible 2-bromo esters by halide exchange, sometimes called the Finkelstein reaction (Scheme 65).[37] This is an equilibrium process, that takes advantage of the fact that sodium iodide is very much more soluble in acetone than is sodium bromide.

Scheme 65.

The reaction of commercially available ethyl bromoacetate with sodium iodide in refluxing acetone gave an 84% yield of ethyl 2-iodoacetate (**203**) (Scheme 66). Alkylation of **20c** with **203** proceeded smoothly, in THF at -78 °C, to give a 79% yield of the desired enone **160**. This was a substantial improvement over the 38% reported for ethyl 2-bromoacetate. The α-iodo version of **185** was prepared in a similar manner using Finkelstein conditions to give an excellent yield of **204**. We found that reduction of the temperature to about 45 °C resulted in a higher yield of product, with minimal decomposition.

Deprotonation of **20c** with LDA, followed by the addition of **204** resulted in 50% conversion to the desired product (**205**) by ^{1}H NMR. Addition of approximately two equivalents of HMPA resulted in a 70% yield of purified **205** (Scheme 67). Finally, we had found a viable method for alkylating **20c** with α-halo esters. Several by-products were also isolated, resulting from degradation of **204** in a similar manner to that shown in Scheme 50. Compounds **163** and **206** were obtained in 15 and 7% yields, respectively, based on **204** (Figure 24).



Scheme 66.

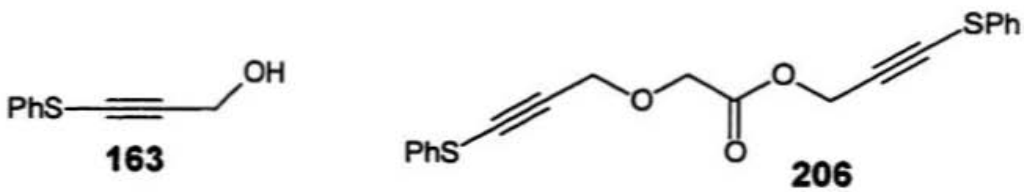
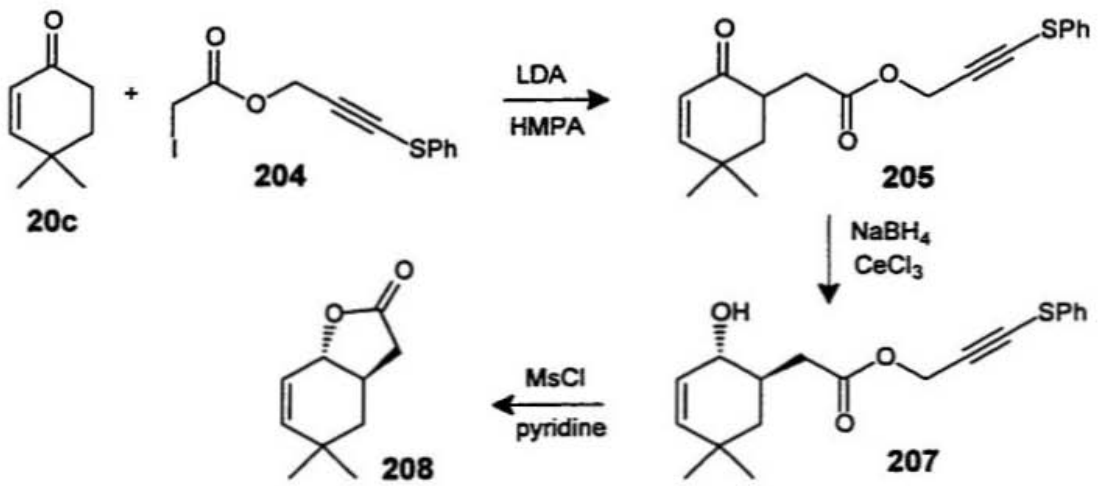


Figure 24. By-products isolated along with compound **205**.

Conversion of the enone **205** to a diene suitable for the intramolecular Diels-Alder appeared to be possible using two general methods. The ketone could be reduced and eliminated or converted to its silyl enol ether. Initially, we chose the reduction-elimination sequence. Reduction of **205** using $NaBH_4$, in the presence of $CeCl_3$, gave an 80% yield of the desired allylic alcohol **207** (Scheme 67). The ratio of *trans* : *cis* isomers was determined from the crude ^1H NMR

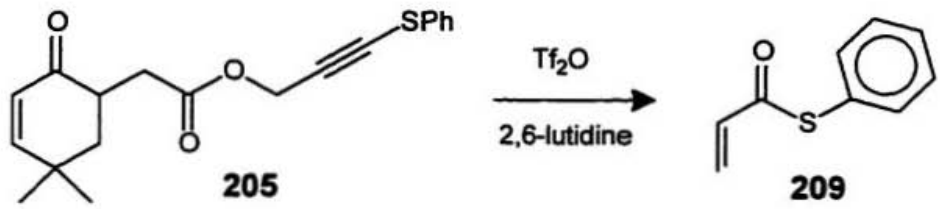
spectrum to be 21 : 1. We assumed the approach of the reducing agent would be opposite that of the newly-added ester functionality to give the *cis* isomer as the major product, however, NOE experiments indicated otherwise. The large ester substituent most likely occupies the equatorial position. Since the ester and the *gem*-dimethyls have a 1,3-relationship, the equatorial methyl will be on the same side of the ring as the ester. As a result, the reducing agent must have approached from the same side as these substituents to avoid the axial methyl group, thereby giving the *trans* isomer as the major product.



Scheme 67.

Attempted mesylation of **207** at 0 °C with two equivalents of mesyl chloride in the presence of excess pyridine appeared successful by TLC. However, the yield obtained was never greater than 50%. The only recognizable product was lactone **208**, the result of cyclization (Scheme 67).

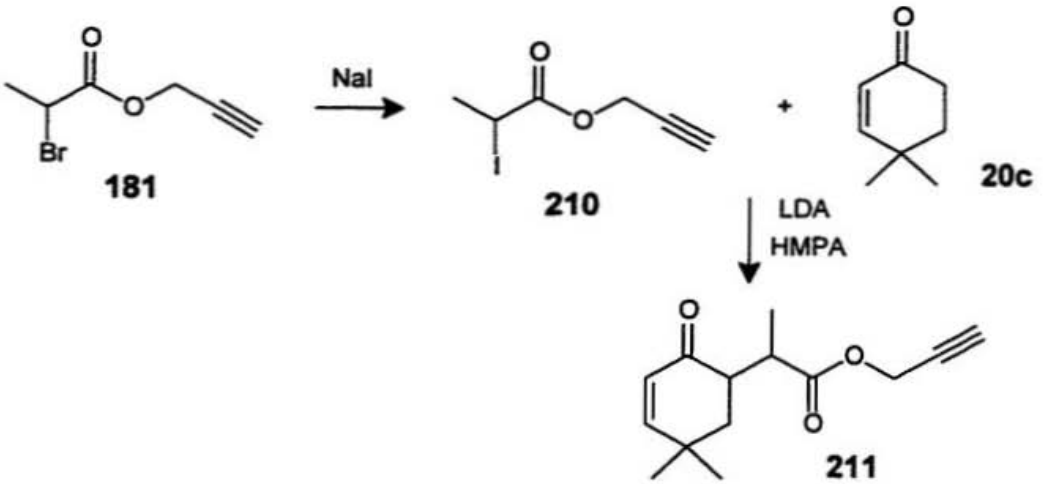
As an alternative to the reduction-elimination sequence, we attempted to convert the ketone of **205** to an alkene by way of an enol triflate.[104] Following a procedure by Jigajinni and Wightman,[105] compound **205** was reacted with triflic anhydride, in the presence of 2,6-lutidine. Instead of forming the desired enol triflate, the only compound obtained upon purification was **209**, in 47% yield (Scheme 68). The reaction conditions were obviously too harsh for **205**, resulting in cleavage of the ester and hydrolysis of the alkyne.



Scheme 68.

As part of our synthetic investigations, several other enone esters were synthesized in good yield. Unlike **205**, these substrates contained the A-ring methyl group required in the pentalenolactone synthesis. The Finkelstein reaction of **181** gave **210** in 89% yield. Deprotonation of **20c** using one equivalent of LDA, followed by the addition of **210** gave **211** in 62% yield (Scheme 69). The diastereomeric ratio was determined to be 3.0 : 1 from the crude ^{1}H NMR spectrum. Using a similar sequence, **213** was obtained in 73% overall yield from commercially available ethyl 2-bromopropanoate (Scheme 70).

The diastereomeric ratio of **213** was found to be very similar to that of **211**, at 2.9 : 1.

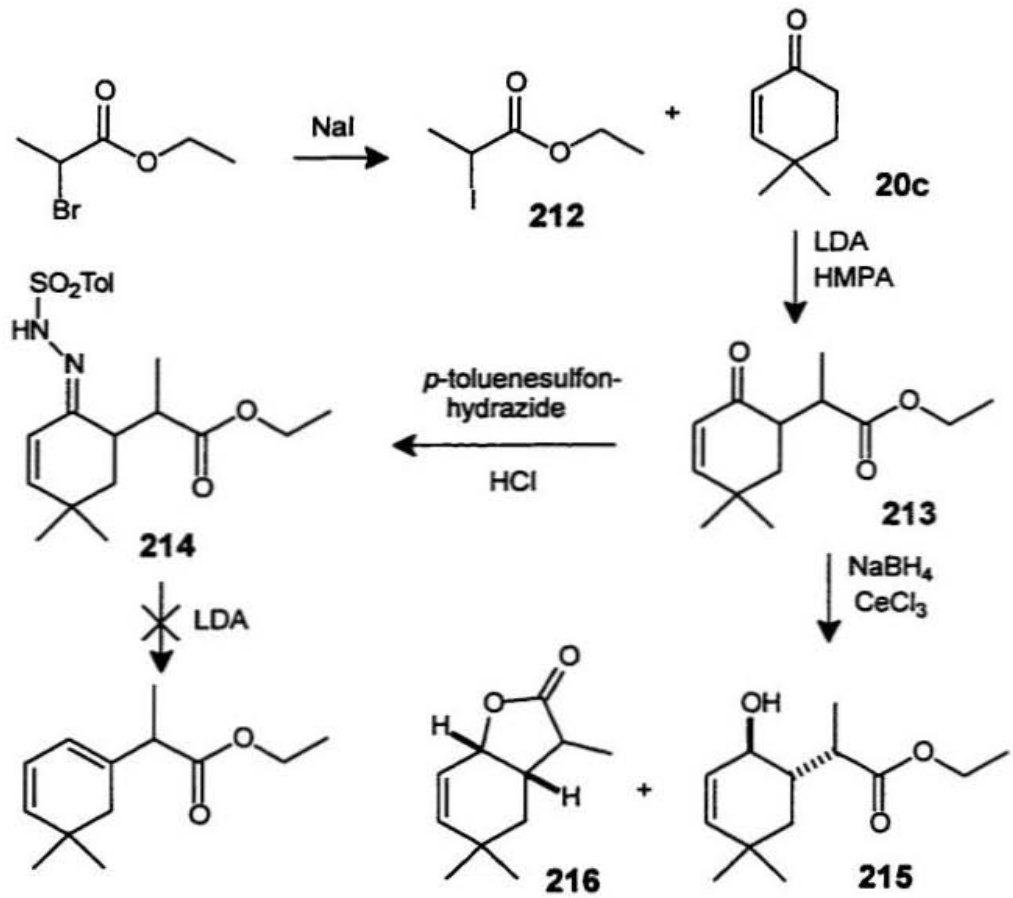


Scheme 69.

In an attempt to convert the enone of **213** directly to a diene, we employed the Shapiro reaction.[106] Following a procedure successfully used by Grieco,[106c] treatment of **213** with *p*-toluenesulfonhydrazide gave a 78% yield of tosylhydrazone **214** (Scheme 70). Treatment of **214** in THF at 0 °C with five equivalents of LDA, however, failed to yield the expected diene product. The crude ^{1}H NMR spectrum indicated that **214** was still present, unchanged. The origin of this inactivity is unclear, however, deprotonation α to the ester may result in a stable anion which undergoes no further reaction.

Sodium borohydride reduction of **213** in methanol at 0 °C resulted in the desired alcohol (**215**) in 69% yield (Scheme 70). This yield was surprisingly low

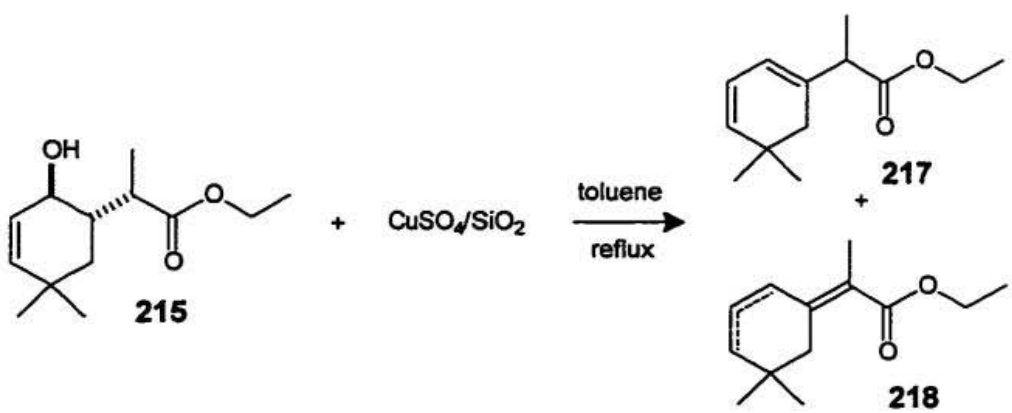
for such an uncomplicated cyclohexenone derivative. Compound **216**, the lactone by-product, was also obtained in 8% yield along with the recovery of 11% of the starting material. We found that increasing the reaction time to allow all of **213** to react resulted in a proportionate increase in the amount of by-product formed. Lactone formation for alcohol **215** seemed to be occurring faster than for **207**.



Scheme 70.

Previous experiments to eliminate the allylic alcohol using basic conditions had been fruitless. We attempted to synthesize diene **217** using Nishiguchi's

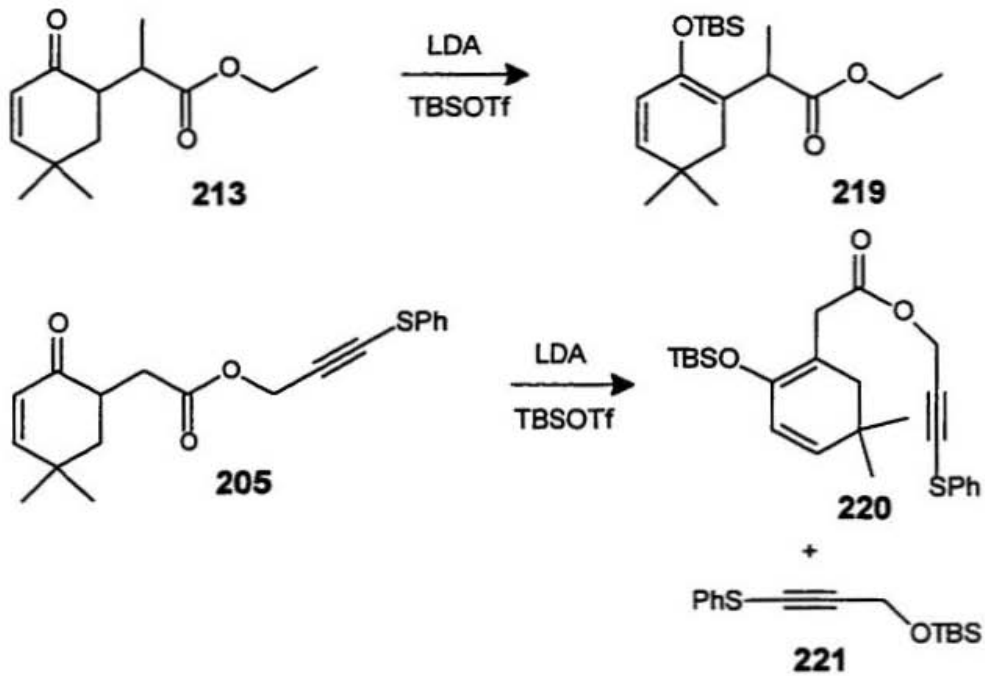
method.[107] A mixture of SiO_2 and $CuSO_4$(3 : 1 by weight) was pre-dried at 240 °C for one hour. Compound **215** was refluxed with a suspension of this material in toluene. The TLC indicated the formation of two new compounds of very similar polarity. They could not be separated by flash chromatography, however, the mass spectrum showed a molecular ion of *m/e* 208, consistent with the expected diene **217**. The absence of an hydroxyl absorption in the IR spectrum was consistent with this. Unexpectedly, the carbonyl region contained two strong absorptions at 1732 and 1709 cm^{-1}. Some double bond migration had occurred following dehydration, resulting in a mixture of **217** and **218** (Scheme 71). The migration of the alkene was a blow to our strategy. This result indicated double bond migration would be probable at high temperature, the condition necessary for any attempted Diels-Alder reaction.



Scheme 71.

Double bond migration could be avoided if the silyl enol ether of **213** were synthesized. Using conditions similar to those reported by Reusch[108] and

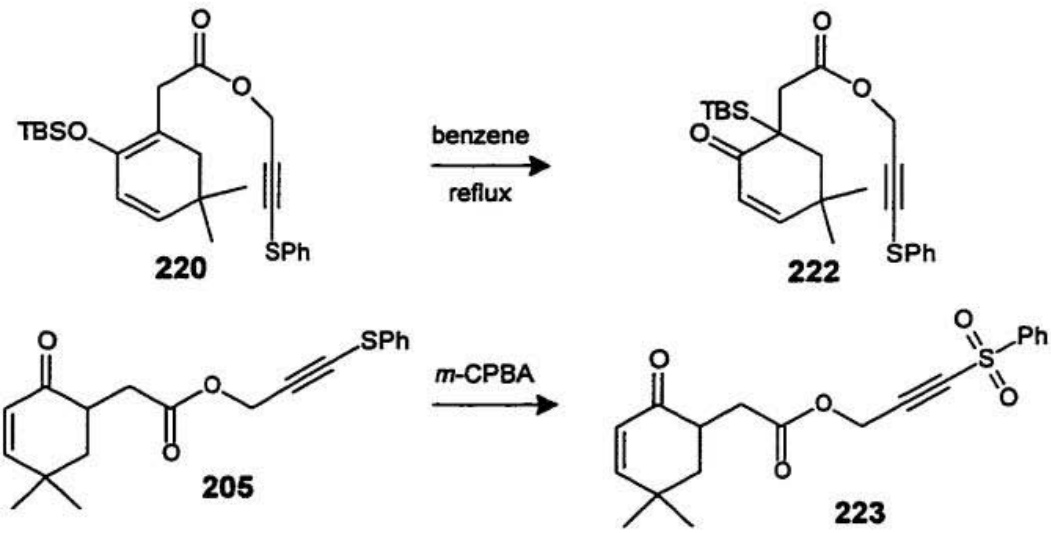
Ireland,[109] deprotonation of **213** was effected using one equivalent of LDA at -78 °C. Addition of TBSOTf gave diene **219** in 25% yield, after purification by flash chromatography. Although the yield was poor, we attempted the same reaction with **205**, using identical conditions. We were pleased when a 51% yield of **220** was obtained (Scheme 72). Compound **220** was accompanied by an 8% yield of **221**, probably the result of some degradation in the presence of strong base, and a 20% recovery of starting material. Finally, we had a substrate suitable for the intramolecular Diels-Alder reaction.



Scheme 72.

Towards this end, **220** was refluxed in benzene for twelve days, while monitoring reaction progress by TLC. Flash chromatography yielded a

compound for which the IR spectrum contained absorption maxima at 2198, 1745 and 1682 cm^{-1}, consistent with the presence of an alkyne, ester, and unsaturated ketone, respectively. The ^{13}C NMR spectrum was strikingly similar to the starting enone **205**, except for the characteristic TBS signals at δ 25.9, 18.3 and -3.5. Instead of reacting in a Diels-Alder fashion, **220** had undergone a silyl migration to give **222**, which must be a more thermodynamically stable product (Scheme 73).



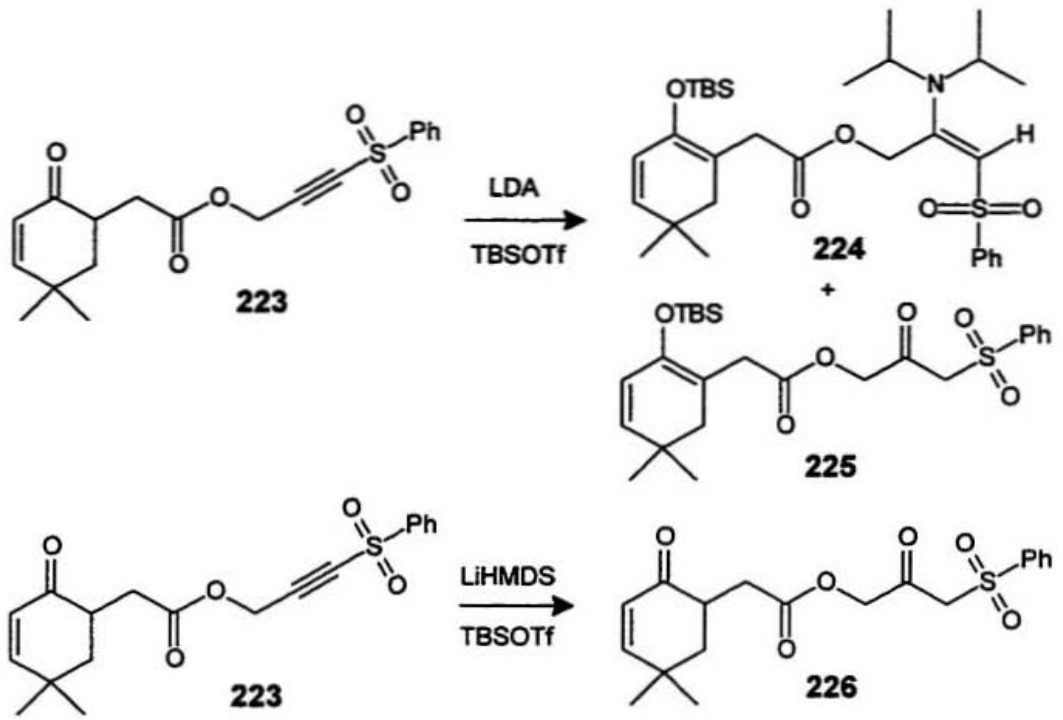
Scheme 73.

The apparent lack of reactivity of **220** in the intramolecular Diels-Alder reaction prompted us to explore methods to activate the dienophile. Oxidation of **205** using three equivalents of *m*CPBA, in a mixed solvent consisting of dichloromethane and chloroform, gave an 94% yield of sulfone **223** (Scheme 73). Separation problems plagued the first few experiments, however the use of

K_2CO_3 instead of the usual $NaHCO_3$ remedied the problem, successfully removing the *m*-chlorobenzoic acid produced in the reaction.

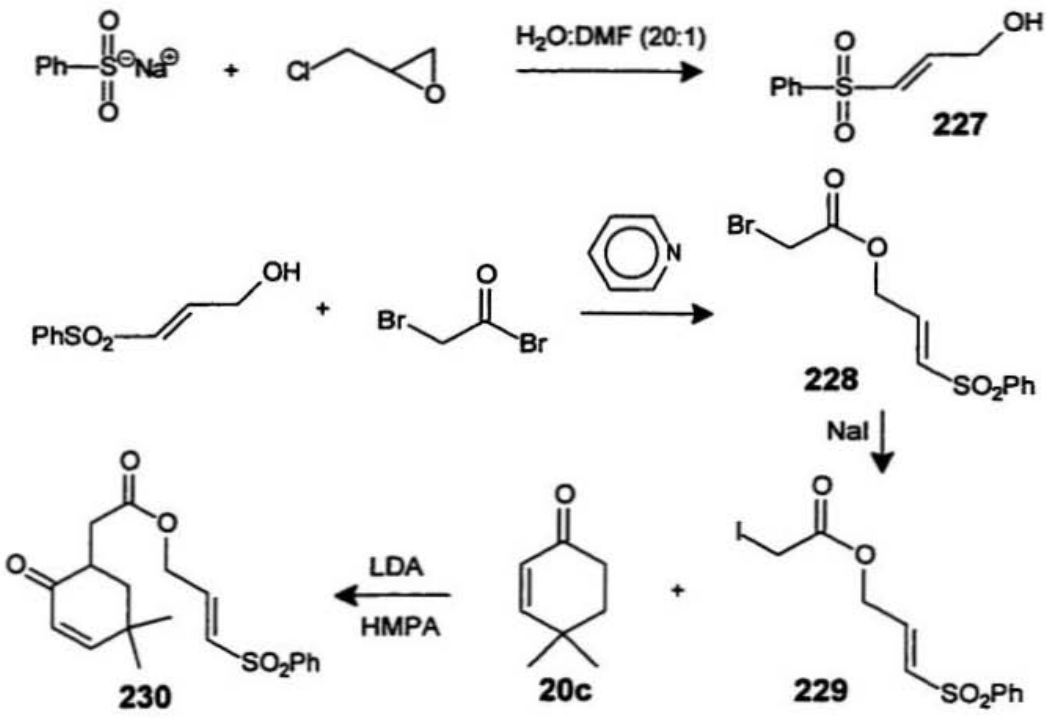
Formation of the enolate of **223** using kinetic conditions, followed by treatment with TBSOTf, gave an inseparable mixture of two compounds in a 2.1 : 1 ratio. The ^1H NMR spectrum indicated both compounds contained a TBS group and other signals compared favourably with diene formation. Surprisingly, there was no absorption in the alkyne region (2000 - 2200 cm^{-1}) of the IR spectrum. This was confirmed by the absence of the alkyne carbon signals in the ^{13}C NMR spectrum, which for **223** appeared at δ 88.0 and 82.6. The ^1H NMR spectrum revealed that LDA had added to the alkynyl sulfone, by 1,4-addition, resulting in enamine **224** (Scheme 74). Subsequent hydrolysis, either on workup or during purification, gave **225** as the minor component. Additions of LDA are rarely observed since it is considered a non-nucleophilic base. This seemed to indicate the alkynyl sulfone was quite prone to a Michael-type addition.

Therefore, we decided to attempt diene formation using a base known to be even less nucleophilic. Deprotonation of **223** with lithium hexamethyldisilazide (LiHMDS) at -78 °C in THF, followed by the addition of TBSOTf resulted in a 53% yield of **226** (Scheme 74). Again, the alkyne had been attacked in a Michael fashion, most likely by LiHMDS. Unlike the previous experiment, no TBS diene was isolated. It may have been hydrolyzed during the workup.



Scheme 74.

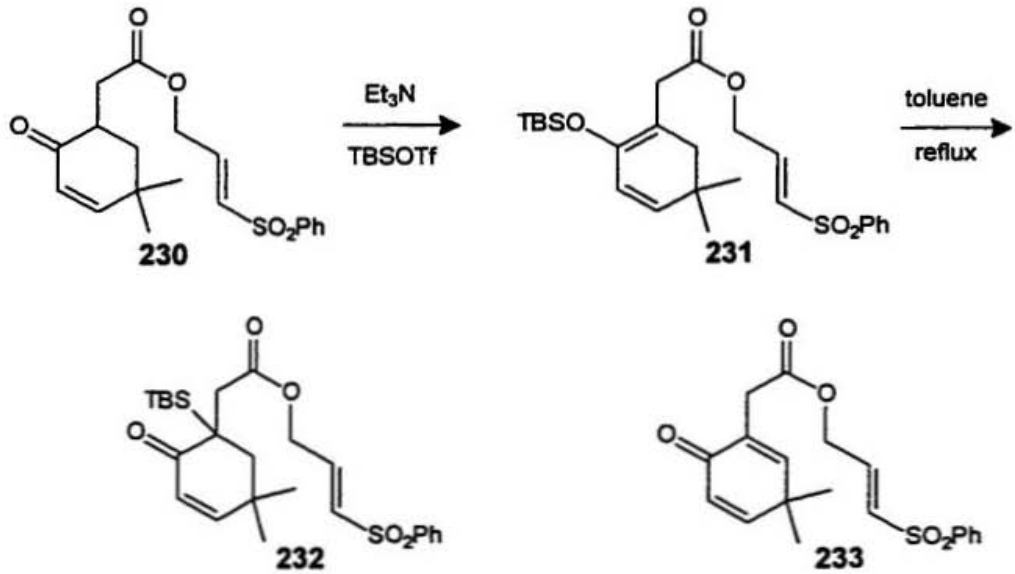
Since the alkynyl sulfone was so prone to 1,4-addition, we turned to the synthesis of a vinyl sulfone equivalent of **223**. The synthesis of alcohol **227** had been previously reported by Jackson *et al.*[110] 1-Chloro-2,3-epoxypropane (epichlorohydrin) and two equivalents of sodium benzenesulfinate were refluxed in a mixed solvent of water and DMF (20 : 1) to yield **227** in 72% yield (Scheme 75). The reaction of a basic solution of **227** with bromoacetyl bromide, in diethyl ether at 0 °C, gave **228** in 88% yield. Treatment of **228** with sodium iodide, in acetone at 40 °C, proceeded cleanly to give **229**. The alkylation of **20c** with **229** using the usual kinetic conditions gave **230** in 58% yield (Scheme 75).



Scheme 75.

As an alternative to the formation of the TBS diene using kinetic conditions, we reacted **230** with TBSOTf and triethylamine in dichloromethane at 0 °C.[41, 42] To our delight, an 83% yield of **231** was obtained using these thermodynamic conditions (Scheme 76). The reaction was complete after about fifteen minutes. Compound **231** was refluxed in toluene for six days. TLC indicated the formation of several new compounds. Flash chromatography of the crude sample resulted in the isolation of four compounds, including a 12% recovery of **231**. A 7% yield of the hydrolyzed diene (**230**) was also obtained. The IR spectrum of the third component showed absorption maxima consistent

with an ester, at 1745 cm^{-1}, and a conjugated carbonyl, at 1680 cm^{-1}. The ^1H NMR spectrum indicated the vinyl sulfone was still present, with a doublet of triplets at δ 6.97 and another at δ 6.59. Comparison of the ^1H NMR and ^{13}C NMR spectral data for **222** with this new compound confirmed that **231** had undergone a TBS migration in a similar manner to **220** to give **232** in 29% yield (Scheme 76). The IR spectrum of the fourth compound was consistent with the presence

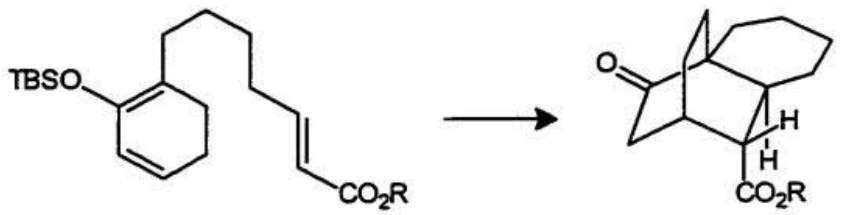


Scheme 76.

of a saturated ester and an unsaturated ketone, containing absorption maxima at 1745 and 1666 cm^{-1}. The ^1H NMR spectrum showed the vinyl sulfone component to be unchanged. The double bond region of the ^{13}C NMR spectrum contained ten signals, the same number present in the ^{13}C NMR spectrum of **231** and two more than the eight present in **230**. There were no signals in the ^1H and

^{13}C NMR spectra characteristic of a TBS moiety. Thus, the compound was assigned the structure **233**. Compound **233** probably formed as a result of elimination of the TBS group in **232**. The attempted intramolecular Diels-Alder reaction of **231** failed to yield the desired adduct.

In contrast, the intramolecular Diels-Alder reaction of a similar system, **234** was reported by Fukumoto *et al.*[42] to give the expected adduct **235** (Scheme 77). Several key differences between **231** and **234** may have led to the sharp contrast in reactivity. The *gem*-dimethyl group of **231** may have played a steric role, preventing the diene and dienophile from obtaining the necessary overlap for the Diels-Alder reaction to occur. Another obvious difference was the all-carbon tether of **234** *versus* the ester group present in the tether of **231**. A literature search revealed that this fact may have been an important factor.



234 **235**

Scheme 77.[42]

It has been reported by Boeckman *et al.* that trienes containing an ester in the chain linking the diene and dienophile are resistant to cyclization.[111] His attempts to cyclize **236** were unsuccessful (Figure 25).[111b] The unreactive nature of **236** was attributed to an unfavourable lack of overlap of the ester oxygen

non-bonding electrons with the carbonyl group in the reactive conformation (**237**). Jung and Gervay attributed the reduced reactivity to a minimization of the dipole effect.[112] Thus, **238** is preferred over **239**, the conformation required for the intramolecular Diels-Alder to occur.

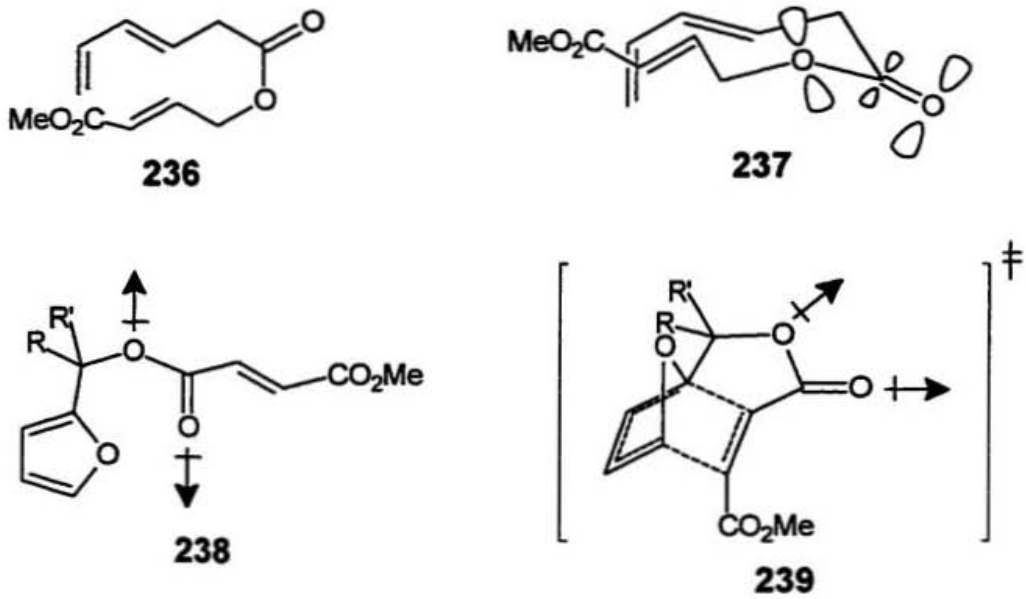
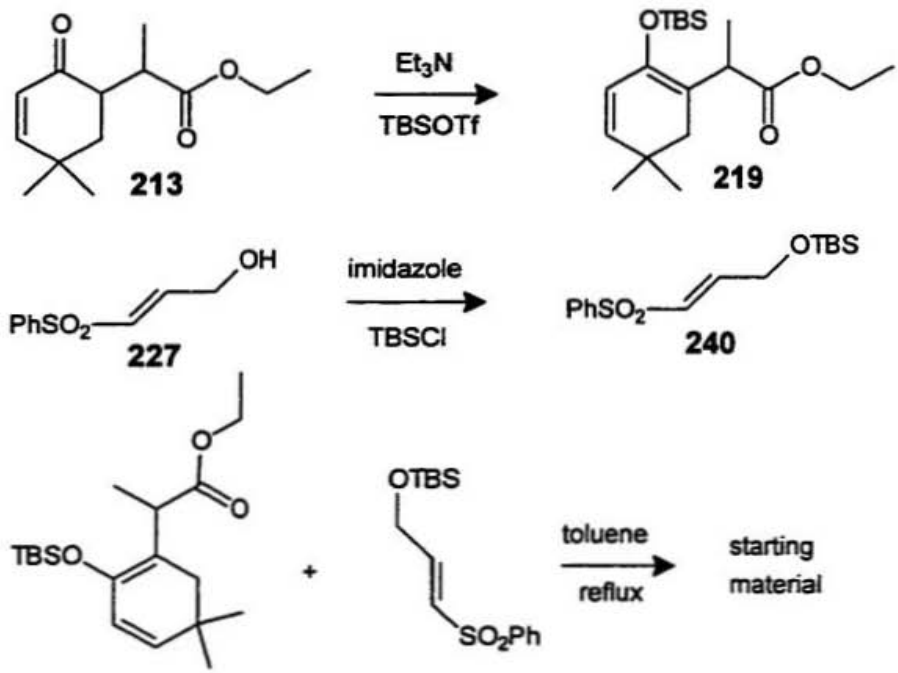


Figure 25.[111b, 112] Theories put forward to explain the failure of intramolecular Diels-Alder reactions involving dienophiles attached by ester-containing tethers.

With the lack of success in cyclizing **231**, we turned to an intermolecular Diels-Alder approach. Formation of the silyl enol ether of **213** with TBSOTf and triethylamine at 0 °C in dichloromethane yielded a 72% yield of **219** (Scheme 78), as compared with 25% using kinetic conditions. Following a procedure used by Jackson *et al.*,[110] protected-alcohol **240** was synthesized in 88% yield by treatment of **227** with TBSCl and imidazole, in DMF at 25 °C. Refluxing of **219**

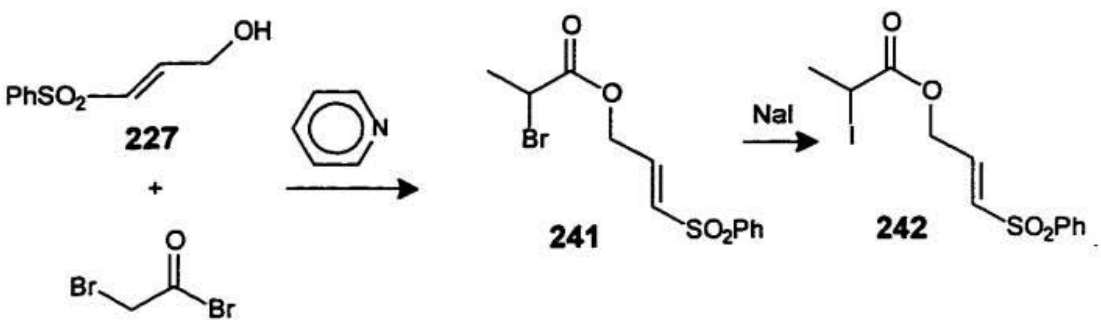
with three and one-half equivalents of **240** in toluene for six days gave no indication of adduct. TLC revealed that only the two starting materials were present, unchanged. This result seemed to indicate that the *gem*-dimethyl group might have been playing a bigger role than originally thought, since the ester-containing tether was no longer present.



Scheme 78.

This result was useful since the previous intramolecular Diels-Alder substrates, **220** and **231**, had experienced a significant amount of TBS migration at reflux temperatures for extended periods of time. Introduction of the methyl group α to the ester seemed to have slowed or stopped this process. The synthesis of a substrate, equivalent to **231** with the methyl present, might provide

a compound which could be subjected to higher reaction temperatures, possibly resulting in the desired Diels-Alder adduct. Furthermore, Jung and Gervay have shown that **238**, when R = Me, R' = H, shows roughly four times the rate of cycloaddition exhibited by **238**, where R = R' = H.[112] Introduction of alkyl groups in the tether led to conformational changes, resulting in rate increases. Our work in this area has only been partially completed. To date, the required 2-iodo ester (**242**) has been synthesized in 88% overall yield from 2-bromopropionyl bromide and **227** (Scheme 79).



Scheme 79.

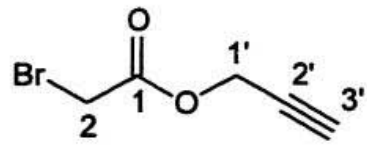
Other future work includes the attempted high pressure Diels-Alder reaction of TBS diene **231**. Since the reaction is carried out at room temperature the migration may not be a problem. Also, we intend to take advantage of the incredible susceptibility of alkynyl sulfones to undergo 1,4-addition. Initially, we hope to react **20c** with a sulfone equivalent of alcohol **163** by a double Michael reaction. If this if successful, elaboration of both substrates could result in the

formation of the bicyclo[2.2.2]octanone required for the synthesis of the *gem*-dimethyl pentalenolactones.

In our initial approach to the pentalenolactones, we were expecting the photochemical step to be the key step of the synthesis. To present, this has not materialized because we have not been successful in forming the required Diels-Alder adduct, however, our work has exposed some novel chemistry and expanded some old ideas. The alkylation of enones and ketones with α-halo esters has often been used in synthetic schemes. However, when the halide is not attached to a primary center, yields have often been very low. Our use of the Finkelstein reaction to convert the readily accessible α-chloro and bromo esters to their more reactive iodo equivalents provides a convenient high-yielding route to alkylating with secondary α-halo esters. The intriguing migration of the TBS group in refluxing benzene and toluene might be used to advantage in future syntheses of natural products. This reaction can provide access to enones from their corresponding ketones using neutral conditions. Also, the incredible susceptibility of the alkynyl sulfones to undergo Michael addition with amine bases provides a convenient route for the conversion of an alkyne to a ketone. In its usual form, the Reformatsky reaction is often used for the formation of β-hydroxy esters or α,β-unsaturated esters. Our work has expanded its scope as a source of vinylogous β-enone esters by attacking 3-substituted enones.

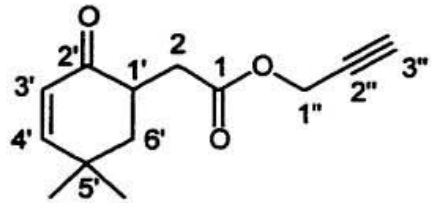
III. Experimental[113]

(2-Propynyl) 2-bromoethanoate (161).



2-Propynol (1.47 g, 26.2 mmol) in diethyl ether (50 mL) was cooled to 0 °C. Pyridine (2.24 g, 2.29 mL, 28.3 mmol) was added dropwise, and the solution was stirred for 15 min. Bromoacetyl bromide (4.40 g, 1.90 mL, 28.3 mmol) was added dropwise resulting in the immediate formation of a white precipitate. The reaction mixture was stirred for 5 h while slowly warming to rt. The pyridinium salt was removed by filtration through a sintered-glass funnel containing Celite. The filtrate was washed with 2 M aqueous HCl (15 mL), brine (10 mL) and dried ($MgSO_4$). Solvent evaporation followed by flash chromatography (elution with 20% ethyl acetate-hexane) yielded **161** (3.27 g, 85%) as a colourless oil. IR: 3294, 2131, 1746, 1437, 1371, 1280, 1153 cm^{-1}. ^1H NMR: δ 4.78 (2H, d, J = 2.3 Hz, C-1'H_2), 3.89 (2H, s, C-2H_2), 2.54 (1H, t, J = 2.3 Hz, C-3'H). ^{13}C NMR: δ 166.4 (C-1), 76.6 (C-2'), 75.7 (C-3'), 53.5 (C-1'), 25.1 (C-2). MS: no M^+, 123 (28), 121 (29), 97 (65), 95 (14), 93 (16), 83 (16), 69 (7), 56 (23), 55 (8), 42 (21), 39 (100).

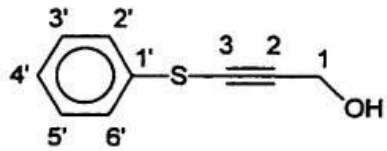
(2-Propynyl) 2-(5,5-dimethyl-2-oxocyclohex-3-enyl)ethanoate (162).



A THF (20 mL) solution of diisopropylamine (0.317 g, 0.439 mL, 3.13 mmol) was cooled to 0 °C. *n*-Butyllithium (2.5 M in hexanes, 1.5 mL, 3.6 mmol) was added dropwise. The reaction mixture was cooled to -78 °C after 1 h and 4,4-dimethyl-2-cyclohexen-1-one (0.300 g, 2.42 mmol) was added dropwise in THF (10 mL) to the solution. After stirring for a further 1.5 h, compound **161** (0.469 g, 2.65 mmol) was added to the reaction mixture. The solution was left to slowly warm to rt overnight. The THF was removed under vacuum, and the reaction mixture was diluted with diethyl ether (80 mL). After quenching with water (25 mL), the organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 x 30 mL). The combined organic layers were washed with brine (20 mL) and dried ($MgSO_4$). Solvent evaporation followed by flash chromatography (elution with 20% ethyl acetate-hexane) gave **162** (0.049 g, 9%) as a colourless oil. IR: 3287, 2962, 2128 (weak), 1743, 1679, 1378, 1160 cm^{-1}. ^1H NMR: δ 6.63 (1H, dd, J = 2.0, 10.0 Hz, C-4'H), 5.85 (1H, d, J = 10.0 Hz, C-3'H), 4.72 (2H, d, J = 2.4 Hz, C-1"H_2), 3.04 (1H, m, C-1'H), 2.93 (1H, dd, J = 6.0, 16.5 Hz, C-2H), 2.49 (1H, t, J = 2.4 Hz, C-3"H), 2.30 (1H, dd, J = 6.9, 16.5 Hz, C-2H), 1.89 (1H, ddd, J = 2.0, 4.9, 13.4 Hz, C-6'H), 1.76 (1H, apparent

t, J = 13.4 Hz, C-6'H), 1.25 (3H, s, C-5'**CH_3**), 1.16 (3H, s, C-5'**CH_3**). ^{13}C NMR: δ 199.0 (C-2'), 171.6 (C-1), 159.0 (C-4'), 125.9 (C-3'), 77.6 (C-2''), 74.8 (C-3''), 51.9 (C-1''), 42.2 (C-6'), 39.7 (C-1'), 34.2 (C-2), 33.7 (C-5'), 30.4 (C-5'**CH_3**), 25.1 (C-5'**CH_3**). MS: 220 (11, M^+), 205 (16), 165 (23), 164 (29), 136 (11), 123 (10), 122 (15), 121 (11), 96 (100), 82 (11), 81 (24), 67 (17), 55 (8), 53 (11). HRMS: calcd for $C_{13}H_{16}O_3$: 220.1099; found: 220.1099.

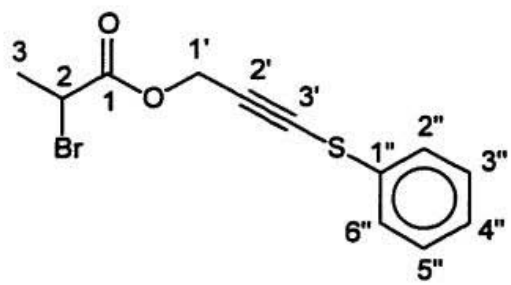
3-Phenylthio-2-propyn-1-ol (163).



A THF (120 mL) solution of 2-propynol (2.00 g, 2.08 mL, 35.7 mmol) was cooled to -30 °C. Diphenyl disulfide (8.42 g, 38.6 mmol) and iodomethane (5.6 g, 2.4 mL, 39 mmol) were dissolved in THF (30 mL), and stirred for 1 h at rt. *n*-Butyllithium (2.5 M in hexanes, 30 mL, 75 mmol) was added dropwise over 20 min to the cooled alcohol solution. Near the end of the addition, the solution thickened; however, warming it for a few minutes seemed to reverse this. After stirring for a further 30 min at -30 °C, the sulfide solution was added over 15 min, and the mixture warmed to rt overnight. Solvent evaporation was followed by dilution with diethyl ether (150 mL). This was washed with water (35 mL) and 0.1 M HCl (35 mL). The resulting aqueous layer was extracted with diethyl ether (3 x 30 mL), and the combined organic layers were washed with brine (35 mL) and

dried ($MgSO_4$). Solvent evaporation followed by flash chromatography (elution with 20% ethyl acetate-hexane) gave **163** (4.92, 84%) as a yellow oil. IR: 3339 (broad), 3061 (weak), 2186, 1583, 1478, 1442, 1065, 997, 739, 688 cm^{-1}. ^1H NMR: δ 7.43 (2H, m, C-2'H, C-6'H), 7.33 (2H, m, C-3'H, C-5'H), 7.22 (1H, m, C-4'H), 4.49 (2H, s, C-1H_2), 2.12 (1H, br s, OH). ^{13}C NMR: δ 132.1 (C-1'), 129.2 (C-3', C-5'), 126.7 (C-4'), 126.3 (C-2', C-6'), 97.3 (C-2), 73.0 (C-3), 51.9 (C-1). MS: 166 (5, $M^+ + 2$), 165 (11, $M^+ + 1$), 164 (100, M^+), 163 (10), 147 (10), 134 (11), 110 (14), 103 (24), 102 (12), 91 (14), 87 (63), 86 (8), 78 (16), 77 (25), 71 (11), 69 (13), 65 (7), 59 (16), 58 (9).

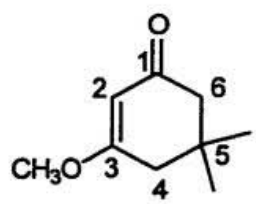
(3-Phenylthio-2-propynyl) 2-bromopropionate (164).



3-Phenylthio-2-propyn-1-ol (**163**) (2.18 g, 13.3 mmol) in diethyl ether (70 mL) was cooled to 0 °C. Pyridine (1.37 g, 1.40 mL, 17.3 mmol) was added dropwise, and the reaction was stirred for 1 h. Dropwise addition of 2-bromopropanoyl bromide (3.73 g, 1.81 mL, 17.3 mmol) resulted in the formation of a yellow precipitate. After stirring at 0 °C for 2 h the reaction was warmed to rt. After 12 h, the pyridinium salt was removed by filtration using a

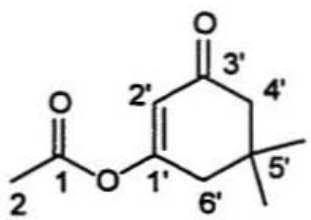
sintered-glass funnel containing Celite. The organic layer was washed with 1 M aqueous HCl (10 mL), a saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL). Drying ($MgSO_4$) and solvent evaporation gave a red-orange oil, which was purified by flash chromatography (elution with 10% ethyl acetate-hexane) to give **164** (3.80 g, 96%) as an orange oil. IR: 3075 (weak), 2199, 1746, 1583, 1479, 1443, 1330, 1214, 1150, 740, 688 cm^{-1}. ^1H NMR: δ 7.43 (2H, m, C-2"H, C-6"H), 7.35 (2H, m, C-3"H, C-5"H), 7.26 (1H, m, C-4"H), 5.00 (2H, m, C-1'H_2), 4.41 (1H, q, J = 7.0 Hz, C-2H), 1.85 (3H, d, J = 7.0 Hz, C-3H_3). ^{13}C NMR: δ 169.5 (C-1), 131.7 (C-1"), 129.3 (C-3", C-5"), 126.9 (C-4"), 126.5 (C-2", C-6"), 92.3 (C-2'), 75.6 (C-3'), 54.4 (C-1'), 39.4 (C-2), 21.5 (C-3). MS: 300 (23, M^+), 298 (24, M^+), 220 (15), 219 (100), 164 (18), 163 (40), 147 (39), 146 (67), 145 (38), 137 (5), 135 (11), 121 (9), 109 (13), 107 (14), 103 (68), 102 (50), 91 (18), 87 (17), 77 (37), 70 (14), 69 (35), 51 (36). HRMS: calcd for $C_{12}H_{11}{}^{79}BrO_2S$: 297.9663; found: 297.9682 and for $C_{12}H_{11}{}^{81}BrO_2S$: 299.9642; found: 299.9644.

3-Methoxy-5,5-dimethyl-2-cyclohexen-1-one (174).



Amberlyst 15 ® ion-exchange resin (*ca.* 1 g) was added to a methanol (250 mL) solution of 5,5-dimethyl-1,3-cyclohexanedione (5.00 g, 35.7 mmol). After stirring for 2 days at rt, the resin was removed by adding Celite (*ca.* 10 g) to the reaction solution and filtering through a plug of silica gel (elution with 50% ethyl acetate-hexane). The solvent was removed under vacuum, and the resulting oil was purified by flash chromatography (elution with 30% ethyl acetate-hexane) to yield **174** (5.23 g, 95%) as a colourless oil. IR: 2960, 1658, 1610, 1462, 1375, 1224, 1155, 1016, 824 cm^{-1}. ^1H NMR: δ 5.37 (1H, s, C-2H), 3.70 (3H, s, OCH_3), 2.28 (2H, s, C-4H_2), 2.21 (2H, s, C-6H_2), 1.08 (6H, s, 2 x C-5**CH_3**). ^{13}C NMR: δ 199.2 (C-1), 176.8 (C-3), 101.0 (C-2), 55.5 (OCH_3), 50.6 (C-6), 42.5 (C-4), 32.4 (C-5), 28.1 (2 x C-5**CH_3**). MS: 154 (30, M^+), 139 (7), 98 (100), 69 (29), 68 (70), 41 (11), 40 (25).

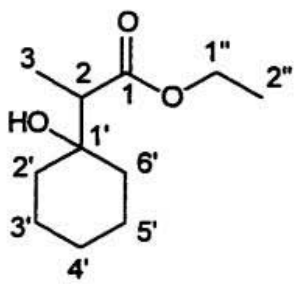
5,5-Dimethyl-3-oxocyclohex-1-enyl ethanoate (176).



A benzene (25 mL) solution of 5,5-dimethyl-1,3-cyclohexanedione (8.04 g, 57.4 mmol), isopropenyl acetate (6.29 g, 6.91 mL, 62.8 mmol) and *p*TsOH (80.4 mg, 0.423 mmol) was heated to 60 °C. After 18 h, solvent evaporation under vacuum gave a red solution. After adding K_2CO_3 (65.2 mg, 0.472 mmol),

vacuum distillation (94-96 °C at 3.5 mm Hg) gave **176** (8.41 g, 81%) as a colourless oil. IR: 2962, 1771, 1673, 1643, 1361, 1198, 1181, 1116 cm^{-1}. ^1H NMR: δ 5.91 (1H, t, *J* = 1.1 Hz, C-2'H), 2.42 (2H, d, *J* = 1.1 Hz, C-6'H_2), 2.27 (2H, s, C-4'H_2), 2.22 (3H, s, C-2H_3), 1.11 (6H, s, 2 x C-5'**C**H_3). ^{13}C NMR: δ 199.4 (C-3'), 168.0 and 167.4 (C-1, C-1'), 116.4 (C-2'), 50.7 (C-4'), 42.1 (C-6'), 33.1 (C-5'), 28.1 (2 x C-5'**C**H_3), 21.2 (C-2). MS: 182 (6, M^+), 140 (12), 125 (6), 84 (63), 69 (15), 43 (100), 41 (10).

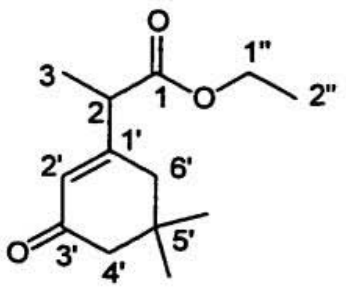
Ethyl 2-(1-hydroxycyclohexyl)propanoate (178).



Zinc(II) chloride (3.27 g, 24.0 mmol) and naphthalene (0.65 g, 5.1 mmol) were added to 1,2-dimethoxyethane (20 mL). Lithium (0.396 g, 57.1 mmol), which had been cut in small pieces, was added, and the reaction was stirred at rt for *ca.* 15 h. Shortly after the addition, the reaction mixture turned dark and was somewhat exothermic. Stirring was stopped and the black powder settled to the bottom of the round-bottomed flask. After 90 min, the bulk of the solvent was removed by syringe, and the remainder of the solvent was removed under vacuum. Diethyl ether (25 mL) was added, followed by one-tenth of the ethyl

2-bromopropanoate (3.91 g, 2.80 mL, 21.6 mmol), and the flask was equipped with a reflux condenser. After cooling to 0 °C, a mixture of the remaining ester and cyclohexanone (2.12 g, 21.6 mmol) was added over 15 min. Removal of the ice bath resulted in the reaction mixture heating to reflux. The reflux rate was controlled using the ice bath, and once the reaction ceased to reflux, it was heated externally to reflux for 2 h. The reaction solution was poured into ice-cold 0.1 M aqueous HCl (20 mL), and diethyl ether (50 mL) was added. After stirring for 15 min the organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried ($MgSO_4$). Solvent evaporation and flash chromatography (elution with 5% ethyl acetate-hexane) gave **178** (3.10 g, 72%) as a colourless oil. IR: 3515, 2936, 1727, 1182 cm^{-1}. ^1H NMR: δ 4.17 (2H, symmetrical m, C-1"H_2), 3.04 (1H, s, OH), 2.49 (1H, q, J = 7.2 Hz, C-2H), 1.75-1.15 (10H, m, C-2'H_2, C-3'H_2, C-4'H_2, C-5'H_2, C-6'H_2), 1.28 (3H, t, J = 7.1 Hz, C-2"H_3), 1.19 (3H, d, J = 7.2 Hz, C-3H_3). ^{13}C NMR: δ 176.9 (C-1), 71.2 (C-1'), 60.4 (C-1"), 47.8 (C-2), 36.9, 33.8 (C-2', C-6'), 25.6, 21.9, 21.5 (C-3', C-4', C-5'), 14.1 (C-2"), 11.4 (C-3). MS: 200 (3, M^+), 183 (11), 157 (28), 144 (21), 111 (17), 109 (15), 102 (100), 99 (66), 98 (28), 81 (53), 74 (67), 69 (14), 57 (16), 56 (30), 55 (42). HRMS: calcd for $C_{11}H_{20}O_3$: 200.1411; found: 200.1417.

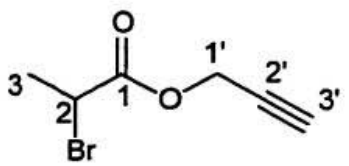
Ethyl 2-(5,5-dimethyl-3-oxocyclohex-1-enyl)propanoate (179).



To a mixed solvent of diethyl ether (10 mL) and benzene (5 mL) was added activated Zn metal (20 mesh, granular) (1.92 g, 29.4 mmol). Ethyl 2-bromopropanoate (2.79 g, 2.00 mL, 15.4 mmol) and **176** (2.03 g, 11.1 mmol) were added to the addition funnel along with diethyl ether (5 mL) and benzene (15 mL). One-tenth of this mixture and a few crystals of iodine were added to the reaction mixture. Upon heating to a gentle reflux, the iodine colour soon faded. The remainder of the ester mixture was added alternately with the iodine (3.89 g, 15.3 mmol) over the next 45 min. The mixture was refluxed for a further 4 h and carefully poured into a mixture of ice (*ca.* 25 mL) and concentrated HCl (20 mL). Diethyl ether (50 mL) was added, and the solution was stirred for 10 min. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 x 35 mL). The combined organic layers were washed with water (10 mL), an aqueous saturated solution of $NaHCO_3$ (20 mL), an aqueous saturated solution of $Na_2S_2O_3$ (15 mL), and brine (15 mL) and then dried ($MgSO_4$). Solvent evaporation followed by flash chromatography (elution with 25% ethyl acetate-hexane) yielded **179** (1.65 g, 67%) as a colourless oil. IR:

2979, 1737, 1672, 1468, 1390, 1194 cm^{-1}. ^1H NMR: δ 5.97 (1H, s, C-2'H), 4.16 (2H, q, J = 7.1 Hz, C-1"H_2), 3.29 (1H, q, J = 7.2 Hz, C-2H), 2.24 (2H, s, C-4'H_2), 2.22 (2H, AB quartet, J = 17.6 Hz, C-6'H_2), 1.34 (3H, d, J = 7.2 Hz, C-3H_3), 1.25 (3H, t, J = 7.1 Hz, C-2"H_3), 1.05 (3H, s, C-5'**CH_3**), 1.03 (3H, s, C-5'**CH_3**). ^{13}C NMR: δ 199.7 (C-3'), 172.2 (C-1), 160.2 (C-1'), 125.8 (C-2'), 61.0 (C-1"), 51.0 (C-4'), 47.0 (C-2), 41.5 (C-6'), 33.5 (C-5'), 28.2 (C-5'**CH_3**), 27.7 (C-5'**CH_3**), 14.9 (C-3), 14.0 (C-2"). MS: 224 (32, M^+), 209 (13), 167 (10), 151 (13), 136 (11), 135 (100), 123 (19), 112 (22), 81 (10), 67 (10), 55 (9), 53 (10). HRMS: calcd for $C_{13}H_{20}O_3$: 224.1411; found: 224.1407.

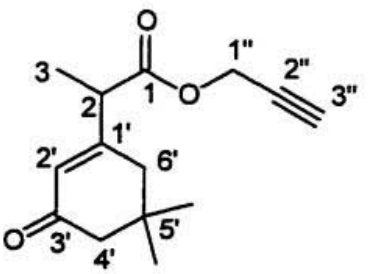
(2-Propynyl) 2-bromopropanoate (181).



A diethyl ether (10 mL) solution of 2-propynol (0.19 g, 0.19 mL, 3.3 mmol) was cooled to 0 °C. After 5 min pyridine (0.31 g, 0.31 mL, 3.9 mmol) was added. After stirring for 30 min, 2-bromopropanoyl bromide (0.62 g, 0.30 mL, 2.8 mmol) was added dropwise, resulting in the immediate formation of a pale yellow solid. After warming to rt over 3 h, the pyridinium salt was removed by filtration through a sintered-glass funnel containing Celite. The filtrate was diluted with diethyl ether (40 mL) and washed with 1M HCl (10 mL), and 5% aqueous $NaHCO_3$ (10 mL), and then dried ($MgSO_4$). Flash chromatography (elution with 10% ethyl

acetate-hexane) gave **181** (0.509 g, 93%) as a pale yellow oil. IR: 3295, 2131 (weak), 1746, 1447, 1377, 1334, 1218, 1155 cm^{-1}. ^1H NMR: δ 4.77 (2H, symmetrical m, C-1'H_2), 4.40 (1H, q, J = 7.0 Hz, C-2H), 2.53 (1H, t, J = 2.5 Hz, C-3'H), 1.85 (3H, d, J = 7.0 Hz, C-3H_3). ^{13}C NMR: δ 169.4 (C-1), 76.7 (C-2'), 75.6 (C-3'), 53.3 (C-1'), 39.2 (C-2), 21.5 (C-3). MS: no M^+, 137 (12), 135 (14), 111 (33), 109 (42), 107 (42), 56 (10), 55 (12), 39 (100).

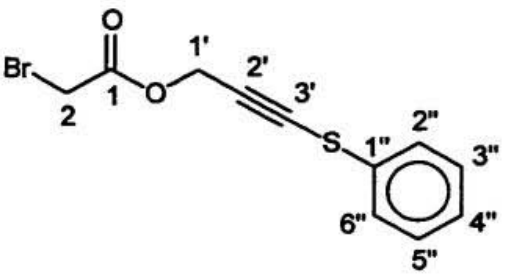
(2-Propynyl) 2-(5,5-dimethyl-3-oxocyclohex-1-enyl)propanoate (182).



To a mixed solvent of diethyl ether (10 mL) and benzene (5 mL) was added activated Zn metal (20 mesh, granular) (0.438 g, 6.70 mmol). Compound **181** (0.657 g, 3.44 mmol) and **176** (0.451 g, 2.46 mmol) were added to the addition funnel along with diethyl ether (5 mL) and benzene (10 mL). One-tenth of this mixture and a few crystals of iodine were added to the reaction mixture. Upon heating to a gentle reflux, the iodine colour soon faded. The remainder of the ester mixture was added alternately with the iodine (0.931 g, 3.67 mmol) over the next 30 min. The mixture was refluxed for a further 2.5 h, and carefully poured into a mixture of ice (~ 25 mL) and concentrated HCl (15 mL). Diethyl

ether (40 mL) was added, and the solution was stirred for 15 min. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with water (10 mL), a saturated aqueous $NaHCO_3$ solution (20 mL), a saturated aqueous $Na_2S_2O_3$ solution (15 mL), and brine (15 mL) and then dried ($MgSO_4$). Solvent evaporation followed by flash chromatography (elution with 15% ethyl acetate-hexane) yielded **182** (0.359 g, 62%) as a colourless oil. IR: 3282, 2961, 2127 (weak), 1744, 1667, 1460, 1369, 1171 cm^{-1}. ^1H NMR: δ 5.97 (1H, s, C-2'H), 4.70 (2H, symmetrical m, C-1"H_2), 3.34 (1H, q, J = 7.1 Hz, C-2H), 2.49 (1H, t, J = 2.5 Hz, C-3"H), 2.24 (2H, s, C-4'H_2), 2.23 (2H, symmetrical m, C-6'H_2), 1.37 (3H, d, J = 7.1 Hz, C-3H_3), 1.05 (3H, s, C-5'**CH_3**), 1.04 (3H, s, C-5'**CH_3**). ^{13}C NMR: δ 199.5 (C-3'), 171.4 (C-1), 159.3 (C-1'), 126.2 (C-2'), 77.1 (C-2"), 75.2 (C-3"), 52.4 (C-1"), 51.0 (C-4'), 46.8 (C-2), 41.5 (C-6'), 33.6 (C-5'), 28.2 (C-5'**CH_3**), 27.8 (C-5'**CH_3**), 14.9 (C-3). MS: 234 (50, M^+), 219 (23), 167 (12), 135 (100), 123 (26), 121 (11), 107 (11), 95 (18), 93 (11), 91 (14), 83 (10), 81 (17), 79 (12), 77 (9), 67 (17), 55 (17), 53 (20). HRMS: calcd for $C_{14}H_{18}O_3$: 234.1255; found: 234.1246.

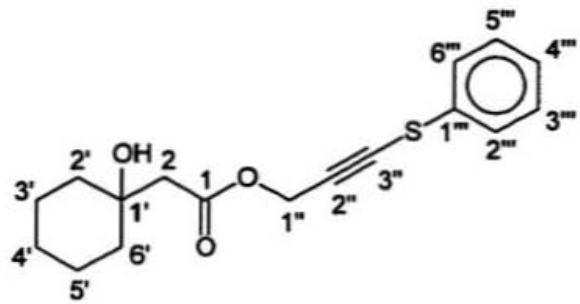
(3-Phenylthio-2-propynyl) 2-bromoethanoate (185).



A diethyl ether (80 mL) solution of **163** (3.00 g, 18.3 mmol) was cooled to 0 °C. Pyridine (1.9 g, 1.9 mL, 24 mmol) was added dropwise, and the mixture was stirred for 1 h. Bromoacetyl bromide (4.8 g, 2.1 mL, 24 mmol) was added dropwise resulting in the formation of a cream-coloured precipitate. After stirring at 0 °C for 2 h, the mixture was warmed to rt and stirred for another 12 h. The pyridinium salt was removed by filtration using a sintered-glass funnel containing Celite and washed with diethyl ether (4 x 20 mL). The filtrate was washed with 1M aqueous HCl (10 mL), a saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL). Drying ($MgSO_4$) and solvent evaporation gave a red-orange oil, which was purified by flash chromatography (elution with 10% ethyl acetate-hexane) to yield **185** (4.97 g, 95%) as a yellow oil. IR: 3074 (weak), 2198, 1746, 1583, 1479, 1442, 1366, 1274, 1141, 965, 740, 688 cm^{-1}. ^1H NMR: δ 7.40 (2H, m, C-2"H, C-6"H), 7.32 (2H, m, C-3"H, C-5"H), 7.22 (1H, m, C-4"H), 4.97 (2H, s, C-1'H_2), 3.86 (2H, s, C-2H_2). ^{13}C NMR: δ 166.3 (C-1), 131.4 (C-1"), 129.2 (C-3", C-5"), 126.8 (C-4"), 126.3 (C-2", C-6"), 92.3 (C-2'), 75.6 (C-3'), 54.5 (C-1'), 25.3 (C-2). MS: 286 (19, M^+), 284 (19, M^+), 206 (12), 205 (92), 164 (16),

163 (31), 147 (39), 146 (62), 145 (45), 135 (17), 123 (11), 121 (17), 109 (10), 103 (100), 102 (64), 95 (10), 93 (11), 91 (27), 87 (20), 77 (59), 70 (21), 69 (53), 65 (12), 56 (13), 51 (62), 50 (17). HRMS: calcd for $C_{11}H_9{}^{79}BrO_2S$: 283.9507; found: 283.9496 and for $C_{11}H_9{}^{81}BrO_2S$: 285.9486; found: 285.9496.

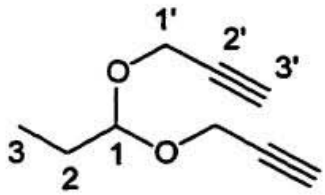
(3-Phenylthio-2-propynyl) 2-(1-hydroxycyclohexyl)ethanoate (187).



Activated zinc metal (20 mesh, granular) (0.381 g, 5.83 mmol) was added to a THF (20 mL) solution of cyclohexanone (0.269 g, 2.74 mmol). THF (10 mL), **185** (0.665 g, 2.33 mmol) and benzene (5.0 mL) were added to the addition funnel. About one-tenth of this solution was added to the reaction mixture along with a small amount of iodine. The reaction was heated to reflux, and the remainder of the ester solution was added alternately with the iodine (0.74 g, 2.92 mmol) over 15 min. The mixture was refluxed for a further 4 h and poured into a mixture of ice (25 mL) and concentrated HCl (15 mL). Diethyl ether (50 mL) was added, and the solution was stirred for 10 min. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic layers were washed with a saturated aqueous $NaHCO_3$

solution (2 x 20 mL), a saturated aqueous $Na_2S_2O_3$ solution (10 mL), and brine (10 mL) and then dried ($MgSO_4$). Solvent evaporation followed by flash chromatography (elution with 15% ethyl acetate-hexane) gave **187** (0.309, 44%) as a pale yellow oil and **163** (78 mg, 12%) as a colourless oil. For **187**. IR: 3497 (broad), 3061 (weak), 2933, 2198, 1729, 1479, 1443, 1169, 1125 cm^{-1}. ^1H NMR: δ 7.42 (2H, m, C-2'''H, C-6'''H), 7.34 (2H, m, C-3'''H, C-5'''H), 7.24 (1H, m, C-4'''H), 4.93 (2H, s, C-1''H_2), 3.16 (1H, broad s, OH), 2.53 (2H, s, C-2H_2), 1.70-1.27 (10H, m, C-2'H_2, C-3'H_2, C-4'H_2, C-5'H_2, C-6'H_2). ^{13}C NMR: δ 172.0 (C-1), 131.7 (C-1'''), 129.2 (C-3''', C-5'''), 126.8 (C-4'''), 126.4 (C-2''', C-6'''), 92.9 (C-2''), 74.9 (C-3''), 70.1 (C-1'), 53.0 (C-1''), 45.2 (C-2), 37.3 (C-2', C-6'), 25.5 (C-4'), 21.9 (C-3', C-5'). MS: 304 (15, M^+), 164 (45), 163 (39), 162 (16), 147 (100), 146 (27), 145 (14), 135 (9), 123 (10), 110 (11), 103 (79), 102 (28), 99 (31), 98 (11), 87 (12), 86 (21), 81 (38), 77 (21), 69 (13), 55 (20), 51 (14). HRMS: calcd for $C_{17}H_{20}O_3S$: 304.1132; found: 304.1131.

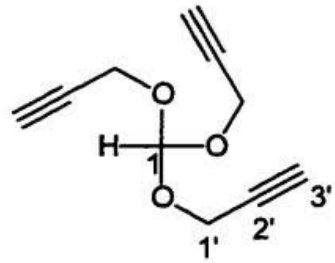
1,1-Bis(2-propynoxy)propane (191).



A benzene (35 mL) solution of 2-propynol (11.6 g, 12.0 mL, 206 mmol), propanal (6.0 g, 7.5 mL, 103 mmol) and pyridinium *p*-toluenesulfonate (*ca.* 0.20

g, *ca.* 0.80 mmol) was heated to 45 °C. The reaction solution was stirred for 12 h, then refluxed for a further 8 h. The yellow-orange solution was then vacuum distilled (58-61 °C at *ca.* 2.5 mm Hg) to yield **191** (7.81 g, 50%) as a colourless oil. IR: 3295, 2972, 2120, 1465, 1351, 1121, 1056 cm^{-1}. ^1H NMR: δ 4.74 (1H, t, J = 5.8 Hz, C-1H), 4.24 (4H, d, J = 2.4 Hz, 2 x C-1'H_2), 2.44 (2H, t, J = 2.4 Hz, 2 x C-3'H), 1.69 (2H, dq, J = 5.8, 7.4 Hz, C-2H_2), 0.95 (3H, t, J = 7.4 Hz, C-3H_3). ^{13}C NMR: δ 102.5 (C-1), 79.7 (2 x C-2'), 74.1 (2 x C-3'), 53.0 (2 x C-1'), 26.1 (C-2), 8.6 (C-3). MS: no M^+, 137 (5), 123 (18), 97 (38), 77 (12), 70 (15), 67 (10), 57 (41), 55 (24), 39 (100).

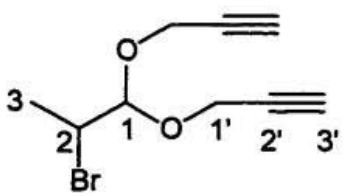
Tris(2-propynoxy)methane (194).



A benzene (300 mL) solution of 2-propynol (39.2 g, 699 mmol), triethyl orthoformate (14.8 g, 99.9 mmol), and H_2SO_4 (6 drops) was heated to 50 °C for 12 h. After replacing the condenser with a distillation column, the reaction was heated to reflux, and the ethanol was slowly removed azeotropically over 2 - 3 h. Once 125 mL had been collected, benzene (100 mL) and 2-propynol (9.63 g, 172 mmol) were added, and the ethanol was removed azeotropically once again.

After repeating the process again, the ^{1}H NMR spectrum of the distillate showed no sign of ethanol. The reaction was cooled to rt and a saturated aqueous $NaHCO_3$ solution (100 mL) was added. The resulting mixture was extracted with diethyl ether (2 x 100 mL). The combined ether layers were washed with a saturated $NaHCO_3$ solution (20 mL) and dried (K_2CO_3). Solvent evaporation gave a yellow-brown oil, which was vacuum distilled (84-92 °C at 3.5 mm Hg) to yield **194** (6.62 g, 37%) as a yellow oil. IR: 3294, 2123, 1093, 1048 cm^{-1}. ^{1}H NMR: δ 5.64 (1H, s, C-1H), 4.31 (6H, d, J = 2.5 Hz, 3 x C-1'H$_2$), 2.47 (3H, t, J = 2.5 Hz, 3 x C-3'H). ^{13}C NMR: δ 110.1 (C-1), 78.6 (3 x C-2'), 74.7 (3 x C-3'), 52.3 (3 x C-1'). MS: no M$^+$, 177 (2, M$^+$ -1), 139 (2), 124 (7), 123 (100), 77 (13), 65 (9), 55 (25), 41 (29), 39 (96).

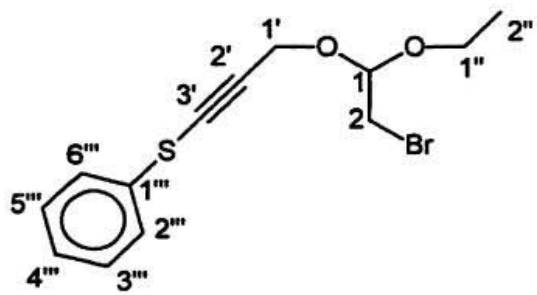
2-Bromo-1,1-bis(2-propynoxy)propane (195).



Bromine (6.9 g, 2.2 mL, 43 mmol) in dichloromethane (2.0 mL) was added to a diethyl ether (10 mL) solution of propanal (2.5 g, 3.1 mL, 43 mmol) over 45 min, using a water bath to moderate the temperature. The reaction mixture was stirred for 24 h at rt, and benzene (20 mL) was added. This solution was cooled to 0 °C and K_2CO_3 (4.3 g) and $Na_2S_2O_3$ (1.15 g) were added. The reaction

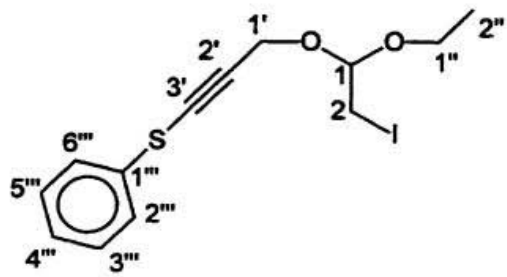
mixture was then warmed to rt, and it was stirred a further 3 h. The precipitated salts were removed by filtration, and the filtrate was placed in a round-bottomed flask along with *p*TsOH (0.25 g) and 2-propynol (9.63 g, 10.0 mL, 172 mmol). The flask was equipped with a condenser, and the mixture was refluxed for 2.5 h. Upon cooling, a saturated aqueous $NaHCO_3$ solution (50 mL) was added, and the mixture was extracted with diethyl ether (3 x 40 mL). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (20 mL) and dried (K_2CO_3). Solvent evaporation followed by vacuum distillation (90-93 °C at *ca.* 5 mm Hg) gave **195** (3.74 g, 38%) as a pale yellow oil. IR: 3294, 2121, 1448, 1352, 1080, 1048 cm^{-1}. ^1H NMR: δ 4.87 (1H, d, *J* = 4.9 Hz, C-1H), 4.38 (4H, m, 2 x C-1'H_2), 4.13 (1H, dq, *J* = 4.9, 6.9 Hz, C-2H), 2.51 (2H, t, *J* = 2.4 Hz, 2 x C-3'H), 1.70 (3H, d, *J* = 6.9 Hz, C-3H_3). ^{13}C NMR: δ 102.3 (C-1), 78.8 (2 x C-2'), 75.2 (C-3'), 75.1 (C-3'), 55.6 (C-1'), 55.4 (C-1'), 47.8 (C-2), 20.0 (C-3). MS: no M^+, 177 (18), 175 (17), 123 (76), 113 (10), 77 (19), 67 (11), 65 (11), 57 (11), 55 (25), 41 (40), 39 (100).

2-Bromo-1-ethoxy-1-(3-phenylthio-2-propynoxy)ethane (197).



Compound **163** (0.654 g, 3.98 mmol) and *N*-bromosuccinimide (0.850 g, 4.77 mmol) in dichloromethane (20 mL) were cooled to -30 °C. 1-Ethoxyethene (0.34 g, 0.45 mL, 4.76 mmol) was diluted in dichloromethane (2.5 mL) and added dropwise over 1 h. The reaction was kept at -30 °C for 3 h then left to warm to rt overnight. The reaction mixture was diluted with dichloromethane (60 mL) and washed with water (10 mL), 2 M aqueous HCl (10 mL), and brine (10 mL) and then dried ($MgSO_4$). Flash chromatography (elution with 5% ethyl acetate-hexane) gave **197** (0.937 g, 75%) as a yellow oil. IR: 3061 (weak), 2976, 2184, 1582, 1479, 1442, 1345, 1120, 1061, 1024, 740, 688 cm^{-1}. ^1H NMR: δ 7.43 (2H, m, C-2'''H, C-6'''H), 7.34 (2H, m, C-3'''H, C-5'''H), 7.25 (1H, m, C-4'''H), 4.91 (1H, t, J = 5.4 Hz, C-1H), 4.53 (2H, s, C-1'H_2), 3.70 (2H, symmetrical m, C-1"H_2), 3.43 (2H, d, J = 5.4 Hz, C-2H_2), 1.25 (3H, t, J = 7.1 Hz, C-2"H_3). ^{13}C NMR: δ 132.1 (C-1'''), 129.3 (C-3''', C-5'''), 126.8 (C-4'''), 126.5 (C-2''', C-6'''), 100.3 (C-1), 94.6 (C-2'), 74.2 (C-3'), 63.0 (C-1"), 55.1 (C-1'), 31.6 (C-2), 15.2 (C-2"). MS: 316 (0.9, M^+), 314 (0.9, M^+), 153 (10), 151 (10), 149 (7), 148 (29), 147 (100), 135 (17), 125 (21), 123 (23), 121 (11), 116 (9), 115 (79), 109 (8), 103 (64), 91 (17), 77 (27), 71 (27), 70 (10), 69 (17), 53 (13), 51 (22). HRMS: calcd for $C_{13}H_{15}{}^{79}BrO_2S$: 313.9976; found: 313.9978 and for $C_{13}H_{15}{}^{81}BrO_2S$: 315.9955; found: 315.9970.

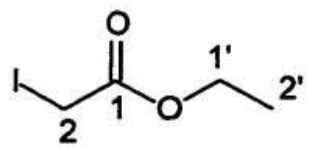
1-Ethoxy-2-iodo-1-(3-phenylthio-2-propynoxy)ethane (198).



Compound **197** (0.937 g, 2.97 mmol) in acetone (3.0 mL) was added dropwise to an acetone (4.0 mL) solution of sodium iodide (0.542 g, 3.61 mmol). The reaction mixture was heated to reflux for 48 h. Analysis of a small sample by ^{1}H NMR spectroscopy indicated 40% conversion to product. Additional sodium iodide (1.20 g, 8.01 mmol) was added, and the mixture was refluxed for a further 48 h. The resulting NaBr was removed by filtration through a sintered-glass funnel containing Celite. Solvent evaporation yielded a white precipitate in an orange oil. Pentane (40 mL) and diethyl ether (20 mL) were added and the solution again filtered. The filtrate was dried ($MgSO_4$), and the solvent evaporated to yield **198** (0.843 g, 78%) as an orange oil. IR: 3060 (weak), 2975, 2184, 1583, 1479, 1341, 1111, 1059, 1023, 739 cm^{-1}. ^{1}H NMR: δ 7.44 (2H, m, C-2'''H, C-6'''H), 7.35 (2H, m, C-3'''H, C-5'''H), 7.25 (1H, m, C-4'''H), 4.83 (1H, t, J = 5.4 Hz, C-1H), 4.51 (2H, s, C-1'H_2), 3.67 (2H, symmetrical m, C-1"H_2), 3.28 (2H, d, J = 5.4 Hz, C-2H_2), 1.25 (3H, t, J = 7.1 Hz, C-2"H_3). ^{13}C NMR: δ 132.1 (C-1'''), 129.3 (C-3''', C-5'''), 126.8 (C-4'''), 126.5 (C-2''', C-6'''), 100.4 (C-1), 94.7 (C-2'), 74.1 (C-3'), 62.6 (C-1"), 54.9 (C-1'), 15.1 (C-2"), 5.0

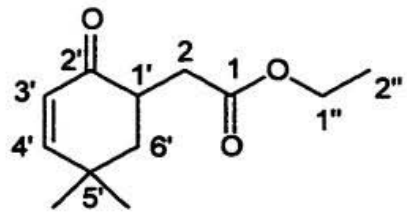
(C-2). MS: 362 (2, M^+), 235 (2), 199 (10), 171 (27), 149 (10), 148 (40), 147 (100), 135 (14), 121 (14), 116 (10), 115 (76), 109 (8), 104 (9), 103 (70), 91 (19), 77 (33), 71 (25), 70 (14), 69 (17), 51 (27). HRMS: calcd for $C_{13}H_{15}IO_2S$: 361.9839; found: 361.9815.

Ethyl 2-iodoethanoate (203).



Sodium iodide (15.1 g, 0.101 mol) was dissolved in acetone (110 mL) and ethyl bromoacetate (14.0 g, 84.0 mmol) was added dropwise, resulting in immediate precipitate formation. The reaction mixture was heated to reflux for 12 h then cooled to rt and filtered through a sintered-glass funnel, washing with acetone (2 x 15 mL). The volume of the red-orange solution was reduced to 30 mL under vacuum and pentane (120 mL) was added, resulting in a grey-green precipitate. Filtration, drying ($MgSO_4$) and solvent evaporation gave **203** (15.2 g, 84%) as a pale yellow oil. IR: 2982, 1732, 1417, 1366, 1264 cm^{-1}. ^1H NMR: δ 4.21 (2H, q, J = 7.1 Hz, C-1'H_2), 3.69 (2H, s, C-2H_2), 1.28 (3H, t, J = 7.1 Hz, C-2'H_3). ^{13}C NMR: δ 168.7 (C-1), 62.0 (C-1'), 13.8 (C-2'), -5.3 (C-2). MS: 214 (60, M^+), 186 (45), 169 (46), 142 (13), 141 (23), 128 (4), 127 (8), 87 (46), 59 (13), 45 (10), 29 (100).

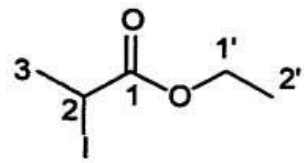
Ethyl 2-(5,5-dimethyl-2-oxocyclohex-3-enyl)ethanoate (160).



A THF (10 mL) solution of diisopropylamine (0.195 g, 0.270 mL, 1.93 mmol) was cooled to -30 °C. *n*-Butyllithium (2.5 M in hexanes, 0.71 mL, 1.77 mmol) was added dropwise, and, after stirring for 20 min, 4,4-dimethyl-2-cyclohexen-1-one (0.203 g, 1.61 mmol) in THF (2.0 mL) was added dropwise. After stirring for 1 h, compound **203** (0.429 g, 2.00 mmol) was added, and the reaction was kept at -30 °C for 2 h, then left to warm slowly to rt overnight. After removing the solvent under vacuum, the reaction mixture was diluted with diethyl ether (50 mL) and quenched with water (10 mL). The organic layer was washed with brine (10 mL) and dried ($MgSO_4$). Solvent evaporation followed by flash chromatography (elution with 15% ethyl acetate-hexane) gave **160** (0.273 g, 79%) as a colourless oil. IR: 2962, 1736, 1681, 1470, 1374, 1266, 1178 cm^{-1}. ^1H NMR: δ 6.62 (1H, dd, *J* = 2.0, 10.0 Hz, C-4'H), 5.84 (1H, d, *J* = 10.0 Hz, C-3'H), 4.18 (2H, symmetrical m, C-1"H_2), 3.02 (1H, m, C-1'H), 2.88 (1H, dd, *J* = 5.5, 16.5 Hz, C-2H), 2.24 (1H, dd, *J* = 7.1, 16.5 Hz, C-2H), 1.87 (1H, ddd, *J* = 2.0, 4.9, 13.1 Hz, C-6'H), 1.75 (1H, apparent t, *J* = 13.1 Hz, C-6'H), 1.28 (3H, t, *J* = 7.2 Hz, C-2"H_3), 1.24 (3H, s, C-5'$\mathbf{CH_3}$), 1.15 (3H, s, C-5'$\mathbf{CH_3}$). ^{13}C NMR: δ 199.4 (C-2'), 172.5 (C-1), 159.0 (C-4'), 126.1 (C-3'), 60.5 (C-1"), 42.4 (C-6'), 39.8

(C-1'), 34.5 (C-2), 33.7 (C-5'), 30.5 (C-5'CH_3), 25.2 (C-5'CH_3), 14.2 (C-2''). MS: 210 (15, M^+), 195 (28), 165 (46), 164 (30), 149 (12), 137 (11), 136 (18), 123 (17), 122 (18), 121 (30), 108 (10), 96 (100), 95 (10), 93 (11), 81 (29), 79 (10), 77 (11), 68 (11), 67 (23), 53 (16). HRMS: calcd for $C_{12}H_{18}O_3$: 210.1255; found: 210.1246.

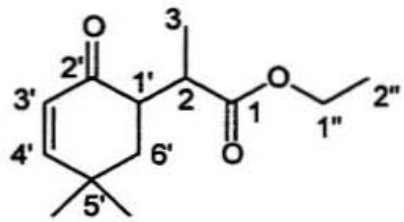
Ethyl 2-iodopropanoate (212).



Ethyl 2-bromopropanoate (8.0 g, 5.7 mL, 44 mmol) was added dropwise to an acetone (60 mL) solution of sodium iodide (9.28 g, 61.9 mmol), resulting in precipitation of NaBr about halfway through the addition. The solution was heated to 40 °C overnight. The sodium bromide was removed by filtration through a sintered-glass funnel containing Celite. Solvent evaporation followed by the addition of pentane (100 mL) and diethyl ether (40 mL) resulted in the formation of a green precipitate. The solution was again filtered, using a sintered-glass funnel, and dried ($MgSO_4$). Solvent evaporation gave **212** (9.34 g, 93%) as a yellow oil. IR: 2982, 1731, 1446, 1369, 1330, 1208, 1135 cm^{-1}. ^1H NMR: δ 4.47 (1H, q, J = 7.0 Hz, C-2H), 4.21 (2H, dq, J = 1.5, 7.1 Hz, C-1'H_2), 1.96 (3H, d, J = 7.0 Hz, C-3H_3), 1.28 (3H, t, J = 7.1 Hz, C-2'H_3). ^{13}C NMR: δ

171.8 (C-1), 61.7 (C-1'), 23.3 (C-3), 13.7, 13.2 (C-2, C-2'). MS: 228 (22, M$^+$), 183 (8), 155 (22), 101 (42), 73 (9), 45 (12), 29 (100).

Ethyl 2-(5,5-dimethyl-2-oxocyclohex-3-enyl)propanoate (213).

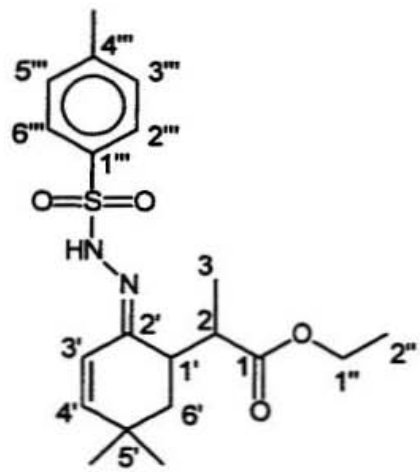


A THF (50 mL) solution of diisopropylamine (2.7 g, 3.7 mL, 27 mmol) and HMPA (8.7 g, 8.4 mL, 48 mmol) was cooled to -78 °C. *n*-Butyllithium (2.5 M in hexanes, 9.9 mL, 24.7 mmol) was added dropwise, and, after stirring for 20 min, 4,4-dimethyl-2-cyclohexen-1-one (2.92 g, 23.5 mmol) in THF (5.0 mL) was added dropwise over 15 min. After 1 h, compound **212** (6.07 g, 26.6 mmol) in THF (5.0 mL) was added over 10 min. The reaction was kept at -78 °C for 18 h, then warmed to rt for 2 h. The reaction mixture was quenched with water (10 mL) and most of the THF was removed under vacuum. After the addition of diethyl ether (200 mL), the solution was washed with water (4 x 10 mL), and brine (20 mL) and then dried ($MgSO_4$). Solvent evaporation yielded a pale yellow oil. Flash chromatography (elution with 15% ethyl acetate-petroleum ether) gave **213** (4.10 g, 78%) as a colourless oil, composed of two diastereomers. The diastereomeric ratio was determined to be 2.9 : 1 by ^{1}H NMR spectroscopy. Major isomer: IR: 3021 (weak), 2962, 1732, 1682, 1468, 1393, 1195, 1178,

1062 cm^{-1}. ^1H NMR: δ 6.61 (1H, dd, *J* = 1.1, 10.0 Hz, C-4'H), 5.82 (1H, d, *J* = 10.0 Hz, C-3'H), 4.17 (2H, symmetrical m, C-1"H_2), 3.10-2.99 (2H, m, C-1'H, C-2H), 1.76 (2H, m, C-6H_2), 1.28 (3H, t, *J* = 7.1 Hz, C-2"H_3), 1.22 (3H, s, C-5'CH_3), 1.17 (3H, s, C-5'CH_3), 1.09 (3H, d, *J* = 7.0 Hz, C-3H_3). ^{13}C NMR: δ 199.0 (C-2'), 175.9 (C-1), 158.7 (C-4'), 126.4 (C-3'), 60.3 (C-1"), 44.9 (C-1'), 37.9 (C-2, C-6'), 33.5 (C-5'), 30.6 (C-5'CH_3), 24.9 (C-5'CH_3), 14.2 (C-2"), 12.7 (C-3). MS: 224 (8, M^+), 209 (21), 179 (34), 178 (13), 163 (10), 151 (27), 150 (12), 135 (22), 125 (11), 124 (96), 123 (39), 122 (8), 109 (38), 96 (100), 95 (19), 81 (22), 69 (14), 67 (21), 55 (27), 53 (17). HRMS: calcd for $C_{13}H_{20}O_3$: 224.1411; found: 224.1413.

Minor isomer: IR: 3020 (weak), 2962, 1731, 1680, 1468, 1378, 1198, 1152, 1066 cm^{-1}. ^1H NMR: δ 6.60 (1H, dd, *J* = 2.0, 10.0 Hz, C-4'H), 5.84 (1H, d, *J* = 10.0 Hz, C-3'H), 4.13 (2H, dq, *J* = 0.6, 7.1 Hz, C-1"H_2), 3.01 (1H, m, C-2H), 2.83 (1H, dt, *J* = 4.5, 14.0 Hz, C-1'H), 1.93 (1H, m, C-6H), 1.75 (1H, ddd, *J* = 2.1, 4.8, 13.0 Hz, C-6H), 1.24 (3H, t, *J* = 7.1 Hz, C-2"H_3), 1.21 (3H, d, *J* = 7.2 Hz, C-3H_3), 1.20 (3H, s, C-5'CH_3), 1.17 (3H, s, C-5'CH_3). ^{13}C NMR: δ 198.8 (C-2'), 174.6 (C-1), 158.4 (C-4'), 126.7 (C-3'), 60.4 (C-1"), 45.4 (C-1'), 38.6 (C-2, C-6), 33.5 (C-5'), 30.7 (C-5'CH_3), 25.4 (C-5'CH_3), 14.2 (C-2"), 13.3 (C-3). MS: 224 (10, M^+), 209 (13), 179 (38), 178 (15), 168 (14), 163 (10), 151 (24), 150 (13), 135 (21), 124 (79), 123 (32), 109 (51), 96 (100), 95 (26), 91 (10), 81 (23), 69 (13), 67 (21), 55 (26), 53 (17). HRMS: calcd for $C_{13}H_{20}O_3$: 224.1411; found: 224.1406.

Ethyl 2-(5,5-dimethyl-2-[(4-methylphenylsulfonyl)hydrazono]-3-cyclohexenyl)propanoate (214).

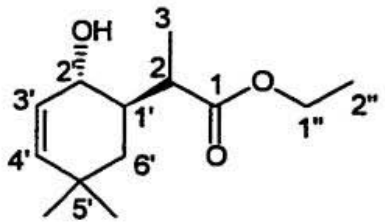


Enone **213** (0.704 g, 3.14 mmol) in THF (3 mL) was added to a THF (25 mL) solution of *p*-toluenesulfonhydrazide (0.591 g, 3.17 mmol). Concentrated HCl (5 drops) was added, and the reaction was stirred under a N_2 atmosphere for 48 h at rt. Dry benzene (10 mL) was added, the solvent was evaporated, and the process was repeated. The resulting yellow viscous oil was purified by flash chromatography (elution with 25% ethyl acetate-petroleum ether) to give **214** (0.95 g, 78%) as a viscous yellow oil. The product contained a mixture of two diastereomers. IR (for mixture): 3216, 2961, 1730, 1339, 1168, 786 cm^{-1}. Distinguishable NMR signals for the minor diastereomer are reported separately. For the major diastereomer: ^1H NMR: δ 7.87 (2H, d, J = 8.2 Hz, C-2'''H, C-6'''H), 7.69 (1H, broad s, NH), 7.31 (2H, d, J = 8.2 Hz, C-3'''H, C-5'''H), 6.11 (1H, d, J = 10.2 Hz, C-3'H), 6.07 (1H, d, J = 10.2 Hz, C-4'H), 4.16 (2H,

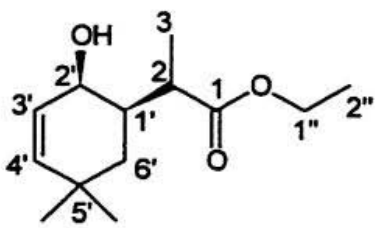
symmetrical m, C-1"H_2), 3.07 (2H, m, C-1'H, C-2H), 2.42 (3H, s, C-4'''$\mathbf{CH_3}$), 1.55 (1H, m, C-6'H), *ca.* 1.30 (1H, m, C-6'H), 1.26 (3H, t, *J* = 7.1 Hz, C-2"H_3), 1.07 (3H, s, C-5'$\mathbf{CH_3}$), 1.03 (3H, s, C-5'$\mathbf{CH_3}$), 0.88 (3H, d, *J* = 6.8 Hz, C-3H_3). ^{13}C NMR: δ 176.1 (C-1), 152.9 (C-2'), 151.5 (C-4'), 143.9 and 135.4 (C-1''', C-4'''), 129.4 (C-3''', C-5'''), 128.2 (C-2''', C-6'''), 113.6 (C-3'), 60.4 (C-1"), 38.4 and 38.3 (C-1', C-2), 37.8 (C-6'), 33.7 (C-5'), 30.4 (C-5'$\mathbf{CH_3}$), 25.8 (C-5'$\mathbf{CH_3}$), 21.6 (C-4'''$\mathbf{CH_3}$), 14.2 (C-2"), 11.9 (C-3). MS: 392 (1, M^+), 347 (6), 237 (10), 208 (13), 179 (40), 137 (33), 135 (41), 120 (12), 119 (24), 108 (18), 107 (79), 105 (15), 96 (11), 95 (11), 93 (51), 92 (21), 91 (74), 79 (19), 77 (27), 67 (11), 65 (28), 55 (16), 53 (11). HRMS: calcd for $C_{18}H_{23}O_3N_2S$ (M^+ - C_2H_5O): 347.1428; found: 347.1456.

For minor diastereomer: ^{1}H NMR: δ 2.95 (1H, dt, *J* = 4.8, 13.0 Hz, C-1'H), 2.74 (1H, symmetrical m, C-2H), 1.21 (3H, t, *J* = 7.2 Hz, C-2"H_3), 1.05 (3H, s, C-5'$\mathbf{CH_3}$). ^{13}C NMR: δ 174.7 (C-1), 151.4 (C-4'), 143.8 (C-1''' or C-4'''), 128.4 (C-2''', C-6'''), 113.8 (C-3'), 60.3 (C-1"), 39.9 and 39.1 (C-1', C-2), 39.7 (C-6'), 33.8 (C-5'), 26.2 (C-5'$\mathbf{CH_3}$), 14.1 (C-2"), 12.9 (C-3).

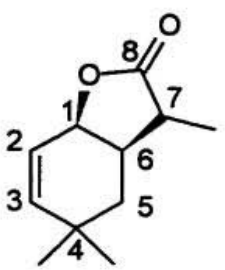
Ethyl (2*R,1'*R**,2'*R**)-2-(2-hydroxy-5,5-dimethylcyclohex-3-enyl)propanoate (*trans*-215), ethyl (2*R**,1'*R**,2'*S**)-2-(2-hydroxy-5,5-dimethylcyclohex-3-enyl) propanoate (*cis*-215) and (1*S**,6*R**,7*S**)-4,4,7-trimethyl-9-oxabicyclo[4.3.0] non-2-en-8-one (216).**



trans-**215**



cis-**215**



216

Enone **213** (0.513 g, 2.29 mmol) and $CeCl_3 \cdot 7H_2O$ (1.06 g, 2.84 mmol) were added to methanol (15 mL), and the solution was cooled to 0 °C. $NaBH_4$ (0.103 g, 2.72 mmol) was added in one portion, resulting in gas evolution. The reaction was stirred for 12 h before it was quenched with a saturated aqueous NH_4Cl solution (10 mL). Following evaporation of most of the methanol, a saturated aqueous NH_4Cl solution (30 mL) and water (30 mL) were added, and the resulting solution was extracted with diethyl ether (3 x 50 mL) and ethyl

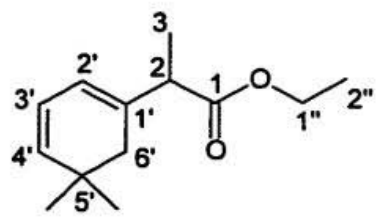
acetate (50 mL). The combined organic layers were washed with brine (15 mL) and dried ($MgSO_4$). Solvent evaporation, followed by flash chromatography (elution with 20% ethyl acetate-petroleum ether) gave **213** (0.107 g, 11%) as a yellow oil, **216** (0.060 g, 8%) as a yellow oil, and **215** (0.691, 69%) as a colourless oil. Compound **215** was composed of two diastereomers. IR (for mixture): 3417 (broad), 3015 (weak), 2957, 1731, 1466, 1373, 1193, 1046 cm^{-1}. MS (for mixture): no M^+, 211 (9), 181 (12), 180 (31), 170 (21), 165 (23), 137 (17), 125 (35), 124 (100), 119 (19), 109 (41), 107 (54), 102 (30), 98 (38), 97 (58), 96 (17), 95 (11), 93 (18), 91 (22), 83 (23), 81 (18), 79 (18), 77 (22), 74 (29), 71 (11), 70 (21), 69 (31), 67 (26), 65 (11), 57 (14), 55 (58), 53 (27). HRMS (for mixture): calcd for $C_{13}H_{22}O_3$: 226.1568; found: 226.1542; calcd for $C_{12}H_{19}O_3$ ($M^+ - CH_3$): 211.1333; found: 211.1343. Distinguishable signals for the minor diastereomer are reported separately. For the major diastereomer: ^1H NMR: δ 5.47 (2H, m, C-3'H, C-4'H), 4.16 (2H, symmetrical m, C-1"H_2), 3.97 (1H, d, J = 9.0 Hz, C-2'H), 2.87 (1H, dq, J = 4.6, 7.6 Hz, C-2H), 2.08 (1H, m, C-1'H), 1.53 (1H, broad s, OH), *ca.* 1.30 (2H, m, C-6'H_2), 1.26 (3H, t, J = 7.1 Hz, C-2"H_3), 1.11 (3H, d, J = 7.6 Hz, C-3H_3), 1.01 (3H, s, C-5'**CH_3**), 0.99 (3H, s, C-5'**CH_3**). ^{13}C NMR: δ 176.6 (C-1), 139.1 (C-4'), 128.4 (C-3'), 69.7 (C-2'), 60.3 (C-1"), 41.9 (C-1'), 39.6 (C-2), 37.2 (C-6'), 33.0 (C-5'), 31.0 (C-5'**CH_3**), 27.7 (C-5'**CH_3**), 14.3 (C-2"), 11.3 (C-3).

For minor diastereomer: ^{1}H NMR: δ 2.78 (1H, dq, *J* = 3.1, 7.3 Hz, C-2H), 1.92 (1H, m, C-1'H). ^{13}C NMR: δ 138.5 (C-4'), 68.9 (C-2'), 60.5 (C-1''), 42.4 (C-1'), 40.7 (C-2), 38.9 (C-6'), 29.0 (C-5'**CH$_3$**), 27.9 (C-5'**CH$_3$**), 13.3 (C-2'').

For **216**: ^{1}H NMR: δ 5.89 (1H, d, *J* = 10.0 Hz, C-3H), 5.77 (1H, dd, *J* = 4.5, 10.0 Hz, C-2H), 4.79 (1H, apparent t, *J* = 4.5 Hz, C-1H), 2.42 (1H, dq, *J* = 1.5, 7.6 Hz, C-7H), 2.28 (1H, symmetrical m, C-6H), 1.54 (1H, ddd, *J* = 1.2, 4.8, 13.2 Hz, C-5H), 1.36 (3H, d, *J* = 7.6 Hz, C-7**CH$_3$**), 1.31 (1H, t, *J* = 13.2 Hz, C-5H), 1.05 (3H, s, C-4**CH$_3$**), 1.00 (3H, s, C-4**CH$_3$**). NOE data: 4.79 (5.77, 2%; 2.28, 2%). ^{13}C NMR: δ 177.3 (C-8), 144.8 (C-3), 119.8 (C-2), 73.2 (C-1), 43.1 (C-6), 38.5 and 38.4 (C-5, C-7), 31.9 (C-4), 30.1 (C-4**CH$_3$**), 27.2 (C-4**CH$_3$**), 15.5 (C-7**CH$_3$**). MS (from GC-MS): 180 (11, M$^+$), 165 (5), 152 (11), 125 (10), 124 (100), 121 (22), 109 (20), 107 (29), 96 (18), 95 (12), 93 (54), 91 (32), 82 (13), 81 (13), 79 (21), 77 (25), 69 (45), 67 (33), 65 (12), 55 (38), 53 (21), 51 (12).

Attempted dehydration of 215.

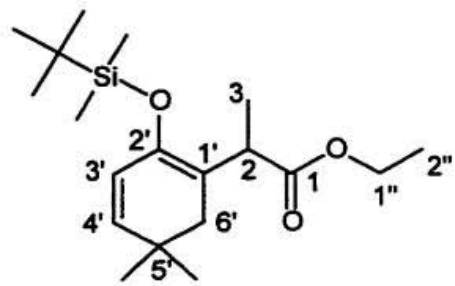
Ethyl 2-(5,5-dimethyl-1,3-cyclohexadienyl)propanoate (217).



$CuSO_4/SiO_2$ (0.524 g SiO_2, 0.175 g $CuSO_4$) and toluene (10 mL) were added to a round-bottomed flask. The allylic alcohol **215** (0.193 g, 0.852 mmol)

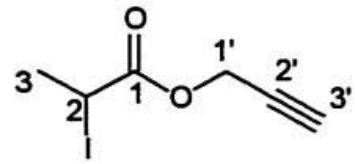
was added and the mixture heated to reflux. The reaction was monitored by TLC and removed after 1h. The reaction mixture was filtered to remove a solid. The filtrate was washed with diethyl ether (3 x 10 mL). After solvent evaporation, flash chromatography (elution with 7.5% ethyl acetate-petroleum ether) gave an inseparable mixture of various double bond isomers of **217** (0.096 g, 54%) as a colourless oil. IR (mixture): 2955, 1733, 1709, 1620 (weak), 1587 (weak), 1462, 1230, 1188, 1099. Readily discernible signals for the ^{1}H NMR of the mixture: δ 6.43 (1H, dt, J = 2.2, 10.2 Hz, C=CH), 5.99 (1H, dt, J = 4.3, 10.2 Hz, C=CH), 5.90-5.71 (2H, m, 2 x C=CH), 5.47 (1H, m, C=CH), 4.21 (2H, q, J = 7.1 Hz, O**CH$_2$**CH$_3$), 4.16 (2H, q, J = 7.2 Hz, O**CH$_2$**CH$_3$), 3.15 (1H, q, J = 6.9 Hz, CH$_3$**CH**), 1.31 (3H, t, J = 7.1 Hz, OCH$_2$**CH$_3$**), 0.96 (6H, s, (**CH$_3$**)$_2$C), 0.91 (6H, s, (**CH$_3$**)$_2$C). MS (mixture): 208 (21, M$^+$), 193 (12), 147 (13), 135 (26), 133 (30), 120 (14), 119 (100), 107 (22), 105 (23), 102 (12), 91 (36), 79 (17), 77 (25), 65 (12).

Ethyl 2-(5,5-dimethyl-2-(((1,1-dimethylethyl)dimethylsilyl)oxy) -1,3-cyclohexadienyl)propanoate (219).



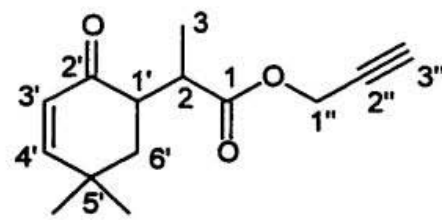
A dichloromethane (3.0 mL) solution of **213** (0.222 g, 0.989 mmol) was cooled to 0 °C. Following dropwise addition of triethylamine (0.17 g, 0.23 mL, 1.7 mmol), TBSOTf (0.414 g, 0.360 mL, 1.57 mmol) was added and the reaction was slowly warmed to rt. After 2 h, the reaction mixture was poured into diethyl ether (100 mL) and washed with a saturated aqueous $NaHCO_3$ solution (3 x 15 mL), and brine (20 mL) and then dried (K_2CO_3). Solvent evaporation followed by flash chromatography (elution with 9% diethyl ether-hexane) gave **219** (0.241 g, 72%) as a colourless oil. IR: 3021 (weak), 2957, 1731, 1656, 1464, 1377, 1282, 1253, 1205, 1107, 869, 839, 779 cm^{-1}. ^1H NMR: δ 5.62 (1H, d, J = 9.8 Hz, C-3'H), 5.49 (1H, d, J = 9.8 Hz, C-4'H), 4.11 (2H, q, J = 7.1 Hz, C-1"H_2), 3.88 (1H, q, J = 7.1 Hz, C-2H), 2.07 (1H, d, J = 16.2 Hz, C-6'H), 1.92 (1H, d, J = 16.2 Hz, C-6'H), 1.23 (3H, t, J = 7.1 Hz, C-2"H_3), 1.17 (3H, d, J = 7.1 Hz, C-3H_3), 1.00 (3H, s, C-5'**CH_3**), 0.96 (12 H, s, C-5'**CH_3**, **$(CH_3)_3$**C$(CH_3)_2$Si), 0.15 (3H, s, $(CH_3)_3$C**CH_3**Si), 0.13 (3H, s, $(CH_3)_3$C**CH_3**Si). ^{13}C NMR: δ 174.8 (C-1), 142.2 (C-2'), 138.6 (C-4'), 123.4 (C-3'), 112.4 (C-1'), 60.3 (C-1"), 37.8 (C-2), 37.1 (C-6'), 31.5 (C-5'), 27.9 (C-5'**CH_3**), 26.7 (C-5'**CH_3**), 25.8 (**$(CH_3)_3$**C$(CH_3)_2$Si), 18.1 ($(CH_3)_3$**C**$(CH_3)_2$Si), 14.4 (C-3), 14.2 (C-2"), -3.9, -4.1 ($(CH_3)_3$C(**CH_3**)$_2$Si). MS: 338 (8, M^+), 293 (8), 292 (18), 281 (16), 277 (16), 265 (35), 249 (11), 177 (12), 91 (9), 75 (52), 73 (100), 59 (13). HRMS: calcd for $C_{19}H_{34}O_3Si$: 338.2275; found: 338.2263.

(2-Propynyl) 2-iodopropanoate (210).



To a solution of sodium iodide (1.48 g, 9.87 mmol) in acetone (15 mL) was added **181** (1.40 g, 7.35 mmol), resulting in immediate precipitate formation. The mixture was heated to 40 °C for 12 h, then cooled to rt and filtered through a sintered-glass funnel. Solvent evaporation, followed by the addition of pentane (100 mL) and diethyl ether (30 mL) resulted in a grey-green precipitate. Filtration, drying ($MgSO_4$) of the filtrate, and solvent evaporation gave **210** (1.55 g, 89%) as a pale yellow oil. IR: 3293, 2130 (weak), 1738, 1446, 1375, 1331, 1199, 1130 cm^{-1}. ^1H NMR: δ 4.75 (2H, symmetrical m, C-1'H_2), 4.52 (1H, q, J = 7.0 Hz, C-2H), 2.53 (1H, t, J = 2.5 Hz, C-3'H), 1.98 (3H, d, J = 7.0 Hz, C-3H_3). ^{13}C NMR: δ 171.1 (C-1), 76.8 (C-2'), 75.5 (C-3'), 53.2 (C-1'), 23.2 (C-3), 11.7 (C-2). MS: 238 (11, M^+), 183 (2), 155 (15), 127 (7), 111 (27), 56 (10), 55 (13), 53 (11), 39 (100). HRMS: calcd for $C_6H_7IO_2$: 237.9493; found: 237.9489.

(2-Propynyl) 2-(5,5-dimethyl-2-oxocyclohex-3-enyl)propanoate (211).

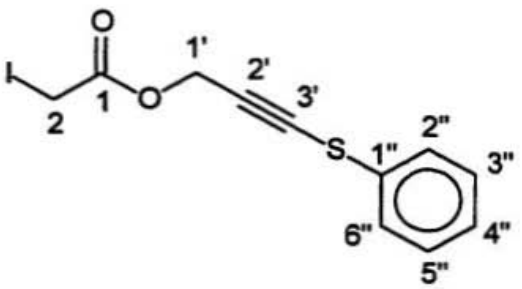


A THF (15 mL) solution of diisopropylamine (0.56 g, 0.77 mL, 5.5 mmol) and HMPA (1.8 g, 1.7 mL, 9.9 mmol) was cooled to -78 °C. *n*-Butyllithium (2.5 M in hexanes, 2.10 mL, 5.23 mmol) was added dropwise, and the LDA solution warmed to 0 °C over 15 min. After recooling to -78 °C, 4,4-dimethyl-2-cyclohexen-1-one (0.612 g, 4.93 mmol), diluted in THF (1.0 mL), was added dropwise over 5 min. After 1 h, **210** (1.42 g, 5.97 mmol) in THF (1.0 mL) was added dropwise. The reaction was maintained at -78 °C for 18 h, then warmed to rt for 2 h. The reaction mixture was quenched with water (4 mL) and most of the THF was removed under vacuum. After the addition of diethyl ether (100 mL), the solution was washed with water (3 x 15 mL), and brine (10 mL) and then dried ($MgSO_4$). Solvent evaporation followed by flash chromatography (elution with 15% ethyl acetate-petroleum ether) gave **211** (0.721 g, 63%) as a pale yellow oil, composed of two diastereomers. The diastereomeric ratio was determined to be 3.0 : 1 by ^{1}H NMR spectroscopy. Major isomer: IR: 3270, 2962, 2128, 1741, 1679, 1460, 1378, 1168, 1063 cm^{-1}. ^{1}H NMR: δ 6.62 (1H, dd, *J* = 1.6, 10.0 Hz, C-4'H), 5.83 (1H, d, *J* = 10.0 Hz, C-3'H), 4.73 (2H, symmetrical m, C-1"H_2), 3.16-2.99 (2H, m, C-1'H, C-2H), 2.48 (1H, t, *J* = 2.4 Hz, C-3"H), 1.83-1.68 (2H, m, C-6'H_2), 1.23 (3H, s, C-5'**C**H_3), 1.17 (3H, s, C-5'**C**H_3), 1.12 (3H, d, *J* = 7.0 Hz, C-3H_3). ^{13}C NMR: δ 198.7 (C-2'), 175.1 (C-1), 158.8 (C-4'), 126.3 (C-3'), 77.8 (C-2"), 74.6 (C-3"), 51.9 (C-1"), 44.9 (C-1'), 37.9 (C-2), 37.8 (C-6'), 33.6 (C-5'), 30.6 (C-5'**C**H_3), 24.9 (C-5'**C**H_3), 12.6 (C-3). MS: 234 (3,

M$^+$), 219 (8), 179 (13), 178 (8), 151 (12), 135 (11), 124 (100), 123 (20), 122 (7), 109 (24), 96 (83), 95 (15), 81 (19), 69 (11), 67 (20), 55 (23), 53 (17). HRMS: calcd for $C_{14}H_{18}O_3$: 234.1255; found: 234.1265.

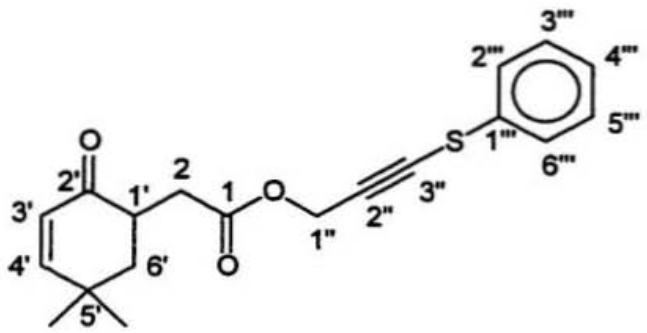
Minor isomer: IR: 3271, 3022 (weak), 2962, 2128, 1742, 1679, 1468, 1379, 1192, 1144, 1066 cm^{-1}. ^{1}H NMR: δ 6.61 (1H, dd, *J* = 2.0, 10.0 Hz, C-4'H), 5.84 (1H, d, *J* = 10.0 Hz, C-3'H), 4.68 (2H, symmetrical m, C-1"H_2), 3.03 (1H, m, C-2H), 2.90 (1H, dt, *J* = 4.4, 14.1 Hz, C-1'H), 2.44 (1H, t, *J* = 2.5 Hz, C-3"H), 1.96 (1H, m, C-6'H), 1.76 (1H, ddd, *J* = 2.1, 4.7, 13.0 Hz, C-6'H), 1.23 (3H, d, *J* = 7.2 Hz, C-3H_3), 1.21 (3H, s, C-5'**C**H_3), 1.17 (3H, s, C-5'**C**H_3). ^{13}C NMR: δ 198.5 (C-2'), 173.8 (C-1), 158.6 (C-4'), 126.6 (C-3'), 77.2 (C-2"), 74.6 (C-3"), 51.9 (C-1"), 45.4 (C-1'), 38.7 (C-6'), 38.4 (C-2), 33.6 (C-5'), 30.6 (C-5'**C**H_3), 25.3 (C-5'**C**H_3), 13.0 (C-3). MS: 234 (3, M$^+$), 219 (5), 179 (16), 178 (24), 151 (12), 135 (12), 124 (100), 123 (23), 122 (6), 109 (45), 96 (87), 95 (29), 91 (12), 81 (25), 77 (11), 69 (13), 68 (11), 67 (25), 55 (30), 53 (22). HRMS: calcd for $C_{14}H_{18}O_3$: 234.1255; found: 234.1264.

(3-Phenylthio-2-propynyl) 2-iodoethanoate (204).



Compound **185** (1.66 g, 5.82 mmol) in acetone (5.0 mL) was added dropwise to an acetone (20 mL) solution of sodium iodide (1.20 g, 8.01 mmol), and the mixture was heated to 50 °C overnight. The sodium bromide was removed by filtration through a sintered-glass funnel containing Celite. Solvent evaporation under vacuum, followed by the addition of pentane (40 mL) and diethyl ether (30 mL) resulted in the formation of a white precipitate. This was again removed by filtration through a sintered-glass funnel containing Celite. Drying ($MgSO_4$) and solvent evaporation under vacuum gave **204** (1.86 g, 97 %) as a pale yellow oil. IR: 3054 (weak), 2198, 1738, 1582, 1479, 1442, 1248, 1086, 740 cm^{-1}. ^1H NMR: δ 7.43 (2H, m, C-2"H, C-6"H), 7.35 (2H, m, C-3"H, C-5"H), 7.25 (1H, m, C-4"H), 4.97 (2H, s, C-1'H_2), 3.75 (2H, s, C-2H_2). ^{13}C NMR: δ 168.1 (C-1), 131.6 (C-1"), 129.3 (C-3", C-5"), 126.9 (C-4"), 126.5 (C-2", C-6"), 92.4 (C-2'), 75.7 (C-3'), 54.6 (C-1'), -6.3 (C-2). MS: 332 (22, M$^+$), 206 (10), 205 (68), 169 (13), 164 (41), 163 (34), 147 (36), 146 (43), 145 (33), 141 (10), 135 (17), 127 (5), 121 (13), 111 (13), 109 (11), 103 (100), 102 (59), 91 (36), 87 (16), 86 (10), 78 (8), 77 (51), 70 (17), 69 (40), 65 (11), 55 (14), 51 (52), 50 (12). HRMS: calcd for $C_{11}H_9IO_2S$: 331.9370; found: 331.9400.

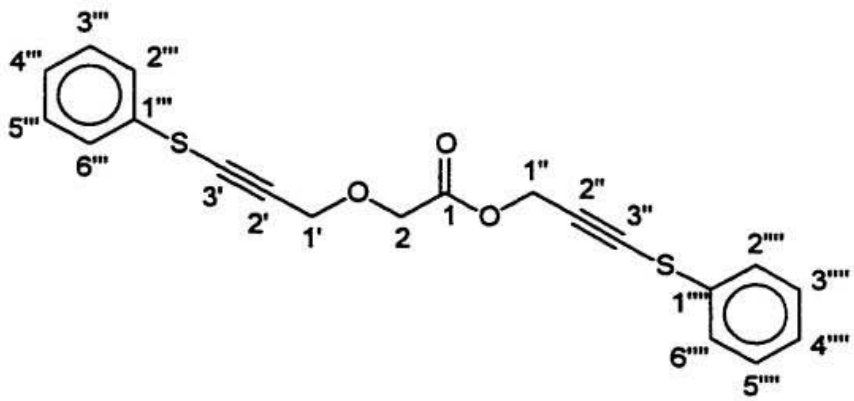
(3-Phenylthio-2-propynyl) 2-(5,5-dimethyl-2-oxocyclohex-3-enyl)ethanoate (205) and (3-phenylthio-2-propynyl) 2-(3-phenylthio-2-propynoxy)ethanoate (206).



205

To a solution of THF (20 mL) and HMPA (0.90 g, 0.87 mL, 5.0 mmol) was added diisopropylamine (0.31 g, 0.42 mL, 3.0 mmol) dropwise. The solution was cooled to -78 °C and *n*-butyllithium (2.5 M in hexanes, 1.0 mL, 2.5 mmol) was added dropwise. After stirring for 20 min, 4,4-dimethyl-2-cyclohexen-1-one (0.315 g, 2.54 mmol) in THF (3.0 mL) was added dropwise over 15 min. After 1 h, **204** (0.916 g, 2.76 mmol) was added over 20 min. The mixture was kept at -78 °C overnight before it slowly warmed to rt. After removing the solvent, the residue was diluted with diethyl ether (100 mL) and washed with water (3 x 10 mL), and brine (10 mL) and then dried ($MgSO_4$). Solvent evaporation followed by flash chromatography (15% ethyl acetate-hexane) gave **205** (0.580 g, 70%) as a colourless oil and **206** (0.036 g, 7%) as a pale yellow oil. For **205**: IR: 3060 (weak), 2961, 2197, 1743, 1680, 1583, 1479, 1376, 1265, 1156 cm^{-1}. ^1H

NMR: δ 7.43 (2H, m, C-2'''H, C-6'''H), 7.34 (2H, m, C-3'''H, C-5'''H), 7.24 (1H, m, C-4'''H), 6.62 (1H, dd, *J* = 1.3, 10.0 Hz, C-4'H), 5.84 (1H, d, *J* = 10.0 Hz, C-3'H), 4.95 (2H, s, C-1''H_2), 3.04 (1H, apparent septet, C-1'H), 2.94 (1H, dd, *J* = 5.7, 16.3 Hz, C-2H), 2.31 (1H, dd, *J* = 7.0, 16.3 Hz, C-2H), 1.88 (1H, ddd, *J* =1.6, 4.7, 12.9 Hz, C-6'H), 1.75 (1H, t, *J* = 13.5 Hz, C-6'H), 1.22 (3H, s, C-5'**CH_3**), 1.13 (3H, s, C-5'**CH_3**). ^{13}C NMR: δ 199.1 (C-2'), 171.8 (C-1), 159.1 (C-4'), 131.9 (C-1'''), 129.2 (C-3''', C-5'''), 126.8 (C-4'''), 126.4 (C-2''', C-6'''), 126.0 (C-3'), 93.4 (C-2''), 74.5 (C-3''), 53.1 (C-1''), 42.2 (C-6'), 39.9 (C-1'), 34.6 (C-2), 33.7 (C-5'), 30.4 (C-5'**CH_3**), 25.2 (C-5'**CH_3**). MS: 328 (4, M^+), 165 (100), 147 (15), 146 (29), 145 (15), 123 (11), 109 (7), 103 (30), 102 (19), 77 (13), 69 (9), 67 (8), 51 (8). HRMS: calcd for $C_{19}H_{20}O_3S$: 328.1132; found: 328.1117.



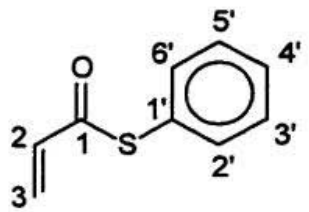
206

For **206**: IR: 3060 (weak), 2193, 1759, 1583, 1479, 1442, 1187, 1116, 739 cm^{-1}. ^{1}H NMR: δ 7.42 (4H, m, C-2'''H, C-2''''H, C-6'''H, C-6''''H), 7.33 (4H, m, C-3'''H, C-3''''H, C-5'''H, C-5''''H), 7.23 (2H, m, C-4'''H, C-4''''H), 5.00 (2H, s,

C-1"H_2), 4.56 (2H, s, C-1'H_2), 4.29 (2H, s, C-2H_2). ^{13}C NMR: δ 169.2 (C-1), 131.9 and 131.7 (C-1''', C-1''''), 129.3 (C-3''', C-3'''', C-5''', C-5''''), 126.83 and 126.77 (C-4''', C-4''''), 126.4 (C-2''', C-2'''', C-6''', C-6''''), 93.8 and 92.6 (C-2', C-2"), 75.5 and 75.4 (C-3', C-3"), 65.9 (C-2), 59.4 (C-1'), 53.4 (C-1"). MS: 368 (2, M$^+$), 221 (21), 163 (12), 147 (59), 103 (100), 77 (25), 69 (14), 51 (14).

Attempted formation of the enol triflate of 205.

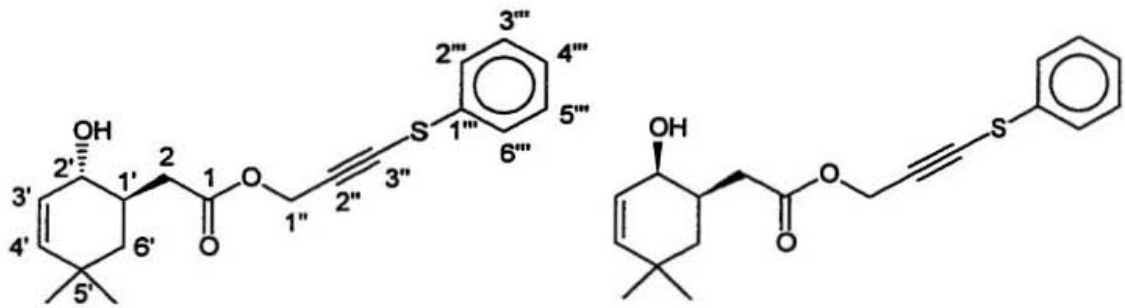
Phenylthio 2-propenoate (209).



A dichloromethane (15 mL) solution of **205** (0.177 g, 0.540 mmol) was cooled to -15 °C and triflic anhydride (0.20 g, 0.70 mmol) was added. The reaction mixture turned yellow soon after addition. 2,6-Lutidine (81 mg, 0.76 mmol) was added dropwise, and the mixture was stirred for 3 h. The brown solution was diluted with dichloromethane (75 mL) and washed with 1 M HCl (15 mL) and saturated aqueous $NaHCO_3$ solution (15 mL). After drying ($MgSO_4$) and solvent evaporation, flash chromatography (elution with 10% ethyl acetate-hexane) gave **209** (23.7 mg, 27%) as a yellow oil. IR: 3076 (weak), 1683, 1632, 1478, 1441, 1393, 1159, 994, 776 cm^{-1}. ^{1}H NMR: δ 7.43 (5H, m, Ph), 6.43 (2H, m, C-3H_2), 5.77 (1H, dd, J = 2.2, 9.0 Hz, C-2H). ^{13}C NMR: δ

188.4 (C-1), 134.6, 134.4, 129.5, 129.2, 127.4. MS: 164 (10, M$^+$), 109 (7), 65 (7), 55 (100). HRMS: calcd for C_9H_8OS: 164.0295; found: 164.0290.

(3-Phenylthio-2-propynyl) (1'*R,2'*R**)-2-(2-hydroxy-5,5-dimethyl cyclohex-3-enyl)ethanoate (*trans*-207) and (3-phenylthio-2-propynyl) (1'*R**,2'*S**)-2-(2-hydroxy-5,5-dimethylcyclohex-3-enyl)ethanoate (*cis*-207).**



trans-**207** *cis*-**207**

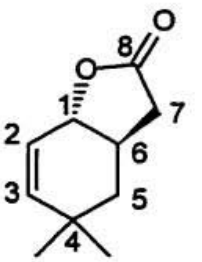
$CeCl_3 \cdot 7H_2O$ (0.378 g, 1.04 mmol) and **205** (0.284 g, 0.863 mmol) were added to methanol (5 mL) and cooled to 0 °C. Addition of $NaBH_4$ (41.7 mg, 1.10 mmol) resulted in gas evolution. After 30 min, the ice bath was removed, and the mixture was stirred for 1.5 h. Following solvent evaporation, diethyl ether (60 mL), water (30 mL) and NH_4Cl (10 mL) were added to the residue. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed to yield an orange oil. Flash chromatography (elution with 40% ethyl acetate-hexane) gave **207** (0.228 g, 80%) as an inseparable mixture of *trans*-**207**

and *cis*-**207**. The *trans* : *cis* ratio was determined to be 21 : 1 by integration of the ^{1}H NMR spectrum of the crude sample. IR (for mixture): 3476, 3061 (weak) 3016 (weak), 2957, 2197, 1742, 1583, 1479, 1442, 1267, 1154 cm^{-1}. For *trans*-**207**: ^{1}H NMR: δ 7.42 (2H, m, C-2'''H, C-6'''H), 7.34 (2H, m, C-3'''H, C-5'''H), 7.23 (1H, m, C-4'''H), 5.47 (2H, apparent s, C-3'H, C-4'H), 4.93 (2H, s, C-1''H_2), 3.87 (1H, apparent t, *J* = 8.3 Hz, C-2'H), 2.76 (1H, dd, *J* = 5.7, 15.2 Hz, C-2H), 2.29 (1H, dd, *J* = 7.6, 15.2 Hz, C-2H), 2.17-2.00 (2H, m, C-1'H, **OH**), 1.53 (1H, dd, *J* = 2.5, 13.2 Hz, C-6'H), 1.27 (1H, apparent t, C-6'H), 1.03 (3H, s, C-5'**CH_3**), 0.96 (3H, s, C-5'**CH_3**). NOE data (for mixture): 5.47 (3.87, 3%; 1.03, 1%; 0.96, 1%), 3.87 (5.47, 2%; 2.76, 1%; 2.29, 2%; 1.27, 1%), 2.76 (3.87, 1%; 2.29, 10%), 2.29 (5.47, 1%; 2.76, 10%; 1.27, 1%), 2.17-2.00 (5.47, 2%; 2.76, 3%; 2.29, 1%; 1.27, 1%; 1.03, 1%), 1.53 (2.29, 1%; 1.27, 6%; 1.03, 1%; 0.96, 1%), 1.27 (3.87, 2%; 2.76, 1%; 2.29, 1%; 1.53, 12%; 0.96, 1%). ^{13}C NMR: δ 172.9 (C-1), 139.1 (C-4'), 131.9 (C-1'''), 129.2 (C-3''', C-5'''), 127.9 (C-3'), 126.8 (C-4'''), 126.4 (C-2''', C-6'''), 93.3 (C-2''), 74.5 (C-3''), 72.2 (C-2'), 53.0 (C-1''), 41.7 (C-6'), 38.3 (C-2), 37.3 (C-1'), 32.9 (C-5'), 30.8 (C-5'**CH_3**), 28.0 (C-5'**CH_3**). MS (for mixture): no M$^+$, 183 (3), 165 (68), 164 (33), 163 (15), 148 (27), 147 (98), 146 (14), 145 (11), 134 (19), 123 (13), 121 (13), 115 (23), 110 (52), 109 (15), 108 (16), 107 (32), 103 (100), 102 (24), 95 (16), 93 (17), 91 (22), 87 (29), 83 (13), 82 (15), 79 (15), 78 (11), 77 (56), 70 (12), 69 (52), 67 (20), 65 (16), 55 (41), 53 (14), 51 (46), 50 (13).

For *cis*-**207**: distinct signals in ^{1}H and ^{13}C NMR for the minor product. ^{1}H NMR: δ 2.87 (1H, dd, *J* = 8.0, 17.4 Hz, C-2H), 1.04 (3H, s, C-5'CH_3), 1.00 (3H, s, C-5'CH_3). ^{13}C NMR: δ 51.9 (C-1"), 30.1 (C-5'CH_3), 26.7 (C-5'CH_3).

Attempted mesylation of *cis*-207 and *trans*-207.

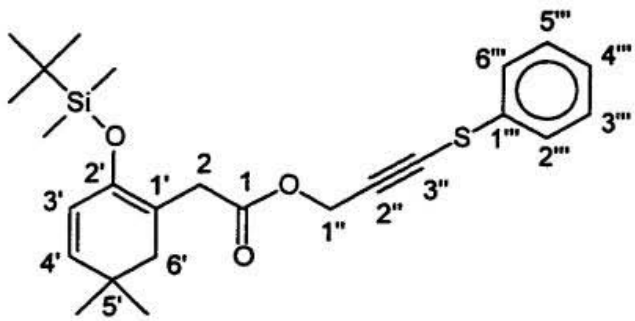
(1*R,6*R**)-4,4-Dimethyl-9-oxabicyclo[4.3.0]non-2-en-8-one (208).**



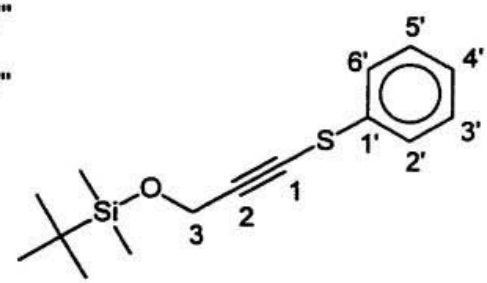
A pyridine (2.9 g, 3.0 mL, 37 mmol) solution of **207** (0.141 g, 0.427 mmol) was cooled to 0 °C. Mesyl chloride (0.063 g, 0.550 mmol) was added dropwise, and the reaction was stirred at 0 °C for 12 h. A white solid was removed by filtration. The organic solvent was removed by vacuum distillation to yield a dark orange oil. Ethyl acetate (60 mL) was added, and the organic layer was washed with water (3 x 5 mL) and NaCl (10 mL). After drying ($MgSO_4$), the solvent was removed, and the residual pyridine was removed using a vacuum pump to provide an orange oil (0.099 g). It was composed of **208** and **163**, in a ratio of 1.3 : 1, respectively. For **208**: ^{1}H NMR: δ 5.93 (1H, d, *J* = 10.0 Hz, C-3H), 5.79 (1H, dd, *J* = 4.5, 10.0 Hz, C-2H), 4.71 (1H, apparent t, *J* = 4.5 Hz, C-1H), 2.88 (1H, dd, *J* = 8.1, 17.4 Hz, C-7H), 2.65 (1H, m, C-6H), 2.26 (1H, d, *J* = 17.4 Hz,

C-7H), 1.50 (1H, ddd, J = 1.2, 4.8, 13.2 Hz, C-5H), 1.27 (1H, m, C-5H), 1.05 (3H, s, C-4CH_3), 1.01 (3H, s, C-4CH_3). MS (from GC-MS): 166 (11, M^+), 151 (9), 138 (12), 124 (22), 110 (100), 107 (35), 105 (23), 95 (17), 93 (21), 91 (42), 82 (42), 81 (13), 79 (42), 77 (23), 69 (23), 67 (40), 65 (18), 55 (37), 53 (24), 51 (21).

(3-Phenylthio-2-propynyl) 2-(5,5-dimethyl-2-(((1,1-dimethylethyl) dimethylsilyl)oxy)-1,3-cyclohexadienyl)ethanoate (220) and 3-(((1,1-dimethylethyl)dimethylsilyl)oxy)-1-phenylthio-1-propyne (221).



220



221

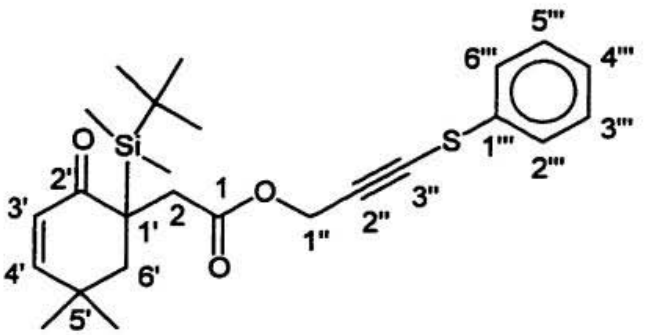
A THF (10 mL) solution of diisopropylamine (0.08 g, 0.10 mL, 0.74 mmol) was cooled to -78 °C. *n*-Butyllithium (2.5 M in hexanes, 0.27 mL, 0.68 mmol) was added dropwise. After 20 min, **205** (0.212 g, 0.645 mmol) in THF (2.5 mL) was added dropwise. After 60 min, TBSOTf (0.25 g, 0.22 mL, 0.97 mmol) was added, and the reaction was stirred overnight. Following solvent evaporation, the residue was diluted with diethyl ether (100 mL), and washed with water (2 x 10 mL) and brine (10 mL). After drying ($MgSO_4$) and solvent evaporation, flash

chromatography (elution with a solvent gradient of 3 to 27% ethyl acetate-hexane) gave **205** (0.043 g, 20%) as a colourless oil, **220** (0.145 g, 51%) as a yellow oil and **221** (0.015 g, 8%) as a colourless oil. For **220**: IR: 3040 (weak), 2956, 2198 (weak), 1744, 1663, 1583, 1480, 1377, 1254, 1217, 1140 cm^{-1}. ^1H NMR: δ 7.46-7.20 (5H, m, C-2'''H, C-3'''H, C-4'''H, C-5'''H, C-6'''H), 5.60 (1H, d, J = 9.8 Hz, C-3'H), 5.51 (1H, d, J = 9.8 Hz, C-4'H), 4.90 (2H, s, C-1''H_2), 3.20 (2H, s, C-2H_2), 2.12 (2H, s, C-6'H_2), 1.00 (6H, s, 2 x C-5'**CH_3**), 0.94 (9H, s, (**CH_3**)$_3$C(CH_3)$_2$Si), 0.12 (6H, s, (CH_3)$_3$C(**CH_3**)$_2$Si). ^{13}C NMR: δ 171.1 (C-1), 143.8 (C-2'), 139.1 (C-4'), 132.0 (C-1'''), 129.2 (C-3''', C-5'''), 126.7 (C-4'''), 126.4 (C-2''', C-6'''), 123.1 (C-3'), 106.5 (C-1'), 93.6 (C-2''), 74.6 (C-3''), 41.1 (C-6'), 35.1 (C-2), 31.8 (C-5'), 27.6 (2 x C-5'**CH_3**), 25.7 ((**CH_3**)$_3$C(CH_3)$_2$Si), 18.1 ((CH_3)$_3$**C**(CH_3)$_2$Si), -4.1 ((CH_3)$_3$C(**CH_3**)$_2$Si).

For **221**: IR: 3076 (weak), 2956, 2187 (weak), 1584, 1472, 1443, 1363, 1256, 1096, 837 cm^{-1}. ^1H NMR: δ 7.44-7.20 (5H, m, Ph), 4.55 (2H, s, C-3H_2), 0.92 (9H, s, (**CH_3**)$_3$C(CH_3)$_2$Si), 0.14 (6H, s, (CH_3)$_3$C(**CH_3**)$_2$Si). ^{13}C NMR: δ 132.7 (C-1'), 129.1 (C-3', C-5'), 126.5 (C-4'), 126.3 (C-2', C-6'), 98.1 (C-2), 71.7 (C-1), 52.6 (C-3), 25.8 ((**CH_3**)$_3$C(CH_3)$_2$Si), 18.3 ((CH_3)$_3$**C**(CH_3)$_2$Si), -5.1 ((CH_3)$_3$C(**CH_3**)$_2$Si). MS: no M^+, 221 (24), 192 (17), 191 (100), 167 (42), 148 (9), 147 (88), 103 (62), 77 (28), 75 (47), 73 (52), 69 (17), 59 (15), 57 (17), 51 (20).

Attempted Diels-Alder reaction of 220.

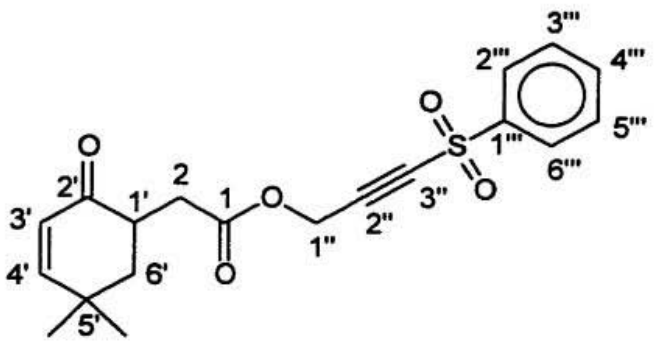
(3-Phenylthio-2-propynyl) 2-(5,5-dimethyl-1-((1,1-dimethylethyl) dimethylsilyl)-2-oxocyclohex-3-enyl)ethanoate (222).



A solution of **220** in benzene (2.0 mL) was heated to reflux under a nitrogen atmosphere. The reaction progress was monitored by TLC. After 12 days the solvent was evaporated under vacuum. Flash chromatography (elution with 5% ethyl acetate-hexane) gave **222** (12.5 mg, 21%) as a colourless oil and **205** (0.114 g, 25%) as a colourless oil along with an undetermined amount of the starting diene. For **222**: IR: 2958, 2198 (weak), 1745, 1682, 1254, 1178, 1146, 1070, 838 cm^{-1}. ^1H NMR: δ 7.42 (2H, m, C-2'''H, C-6'''H), 7.36 (2H, m, C-3'''H, C-5'''H), 7.25 (1H, m, C-4'''H), 6.67 (1H, dd, *J* = 1.4, 10.2 Hz, C-4'H), 5.92 (1H, d, *J* = 10.2 Hz, C-3'H), 4.92 (1H, doublet, *J* = 16.5 Hz, C-1''H), 4.86 (1H, doublet, *J* = 16.5 Hz, C-1''H), 2.97 (1H, d, *J* = 15.4 Hz, C-2H), 2.74 (1H, d, *J* = 15.4 Hz, C-2H), 2.22 (1H, d, *J* = 14.4 Hz, C-6'H), 2.12 (1H, dd, *J* = 1.4, 14.4 Hz, C-6'H), 1.29 (3H, s, C-5'$\mathbf{CH_3}$), 1.12 (3H, s, C-5'$\mathbf{CH_3}$), 0.84 (9H, s, $(\mathbf{CH_3})_3C(CH_3)_2Si$), 0.22 (3H, s, $(CH_3)_3C\mathbf{CH_3}Si$), -0.06 (3H, s, $(CH_3)_3C\mathbf{CH_3}Si$). ^{13}C NMR: δ 196.1 (C-2'),

169.7 (C-1), 159.7 (C-4'), 131.8 (C-1'''), 129.3 (C-3''', C-5'''), 126.8 (C-4'''), 126.4 (C-2''', C-6'''), 124.6 (C-3'), 93.2 (C-2''), 74.8 (C-3''), 53.0 (C-1''), 46.9 (C-6'), 42.9 (C-2), 33.5 (C-5'), 30.9 (C-5'$\mathbf{CH_3}$), 29.4 (C-5'$\mathbf{CH_3}$), 25.9 ($(\mathbf{CH_3})_3C(CH_3)_2Si$), 18.3 ($(CH_3)_3\mathbf{C}(CH_3)_2Si$), -2.9 ($(CH_3)_3C\mathbf{CH_3}Si$), -3.5 ($(CH_3)_3C\mathbf{CH_3}Si$), C-1' signal must be overlapped. MS: no M^+, 149 (15), 148 (35), 147 (100), 104 (10), 103 (100), 96 (26), 81 (7), 77 (15), 75 (35), 73 (26), 69 (10), 57 (8).

(3-Phenylsulfonyl-2-propynyl) 2-(5,5-dimethyl-2-oxocyclohex-3-enyl) ethanoate (223).

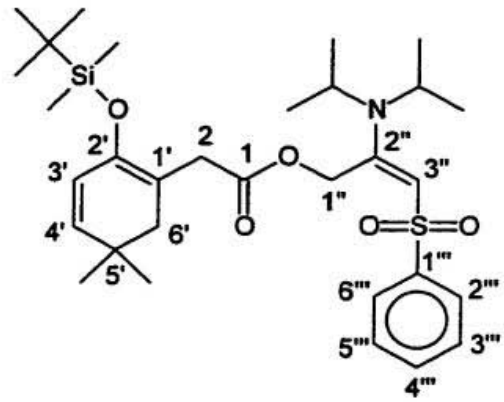


A dichloromethane (40 mL) solution of **205** (0.429 g, 1.31 mmol) was cooled to 0 °C. *m*-CPBA (55%, 0.804 g, 2.56 mmol) was dissolved in chloroform (20 mL), and this was added over 5 min. The ice bath was removed, and the reaction mixture was stirred for 12 h. TLC indicated the reaction to be incomplete, therefore more *m*-CPBA (55%, 0.519 g, 1.65 mmol) was added, and the solution was stirred a further 12 h. A saturated aqueous Na_2CO_3 solution (60 mL), water (50 mL) and dichloromethane (50 mL) were added, and this was

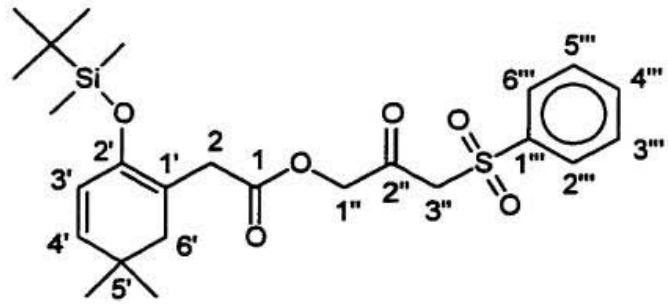
stirred for 5 min. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (4 x 50 mL). The combined organic layers were washed with brine (30 mL) and dried ($MgSO_4$), and the solvent was removed. Flash chromatography (elution with 40% ethyl acetate-petroleum ether) gave **223** (0.445 g, 94%) as a white solid: mp: 87.5-88.0 °C. IR: 2962, 2214, 1749, 1677, 1447, 1336, 1164, 1088, 732 cm^{-1}. ^1H NMR: δ 8.02 (2H, m, C-2""H, C-6""H), 7.71 (1H, m, C-4""H), 7.60 (2H, m, C-3""H, C-5""H), 6.63 (1H, dd, *J* = 2.0, 10.0 Hz, C-4'H), 5.83 (1H, d, *J* = 10.0 Hz, C-3'H), 4.86 (1H, doublet, *J* = 16.7 Hz, C-1"H), 4.80 (1H, doublet, *J* = 16.7 Hz, C-1"H), 3.03 (1H, m, C-1'H), 2.85 (1H, dd, *J* = 6.3, 16.6 Hz, C-2H), 2.29 (1H, dd, *J* = 6.6, 16.6 Hz, C-2H), 1.84 (1H, ddd, *J* = 2.0, 5.1, 13.1 Hz, C-6'H), 1.75 (1H, apparent t, *J* = 13.1 Hz, C-6'H), 1.24 (3H, s, C-5'$\mathbf{CH_3}$), 1.16 (3H, s, C-5'$\mathbf{CH_3}$). ^{13}C NMR: δ 198.8 (C-2'), 171.2 (C-1), 159.2 (C-4'), 140.9 (C-1""), 134.5 (C-4""), 129.4 (C-3"", C-5""), 127.6 (C-2"", C-6""), 125.8 (C-3'), 88.0 (C-2"), 82.6 (C-3"), 50.9 (C-1"), 42.2 (C-6'), 39.8 (C-1'), 34.1 (C-2), 33.8 (C-5'), 30.4 (C-5'$\mathbf{CH_3}$), 25.2 (C-5'$\mathbf{CH_3}$). MS: 360 (2, M^+), 181 (1), 165 (13), 164 (14), 125 (12), 123 (7), 122 (13), 121 (7), 115 (9), 96 (100), 91 (7), 82 (7), 81 (21), 77 (27), 68 (8), 67 (19), 65 (7), 53 (13), 51 (16). HRMS: calcd for $C_{19}H_{20}O_5S$: 360.1030; found: 360.1021.

Attempted TBS diene formation from 223.

((*E*)-2-(Bis(1-methylethyl)amino)-3-phenylsulfonylprop-2-enyl) 2-(5,5-dimethyl-2-(((1,1-dimethylethyl)dimethylsilyl)oxy)cyclohexa-1,3-dienyl)ethanoate (224) and (2-oxo-3-phenylsulfonylpropyl) 2-(5,5-dimethyl-2-(((1,1-dimethylethyl)dimethylsilyl)oxy)cyclohexa-1,3-dienyl)ethanoate (225).



224



225

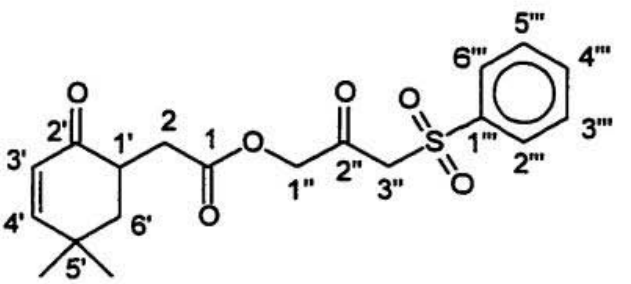
A solution of diisopropylamine (0.067 g, 0.660 mmol) in THF (5.0 mL) was cooled to 0 °C and *n*-butyllithium (2.5 M in hexanes, 0.24 mL, 0.60 mmol) was

added dropwise. The solution was stirred for 20 min, then added to a THF (7.0 mL) solution of **223** (0.207 g, 0.574 mmol) cooled to -78 °C. TBSOTf (0.212 g, 0.804 mmol) was added to the solution of **223** 5 min before dropwise addition of the LDA solution. This was maintained at -78 °C for 4 h, then warmed to rt. Solvent evaporation was followed by the addition of diethyl ether (150 mL). The organic solution was washed with water (2 x 15 mL) and brine (15 mL), and then dried ($MgSO_4$). Following solvent evaporation, flash chromatography (elution with 25% ethyl acetate-hexane) gave 0.118 g of an inseparable mixture of **224** and **225** as a yellow oil. ^{1}H NMR analysis of the mixture indicated a ratio of 2.1 : 1 of **224** and **225**. IR (for mixture): 2957, 1738, 1662 (weak), 1562, 1254, 1135, 1082 cm^{-1}. For **224** from the spectra of the mixture: ^{1}H NMR: δ 7.92-7.44 (5H, m, Ph), 5.56 (1H, d, J = 9.9 Hz, C-3'H or C-4'H), 5.49 (1H, d, J = 9.9 Hz, C-3'H or C-4'H), 5.33 (1H, s, C-3"H), 5.08 (2H, s, C-1"H_2), 3.73 (2H, septet, J = 6.9 Hz, 2 x $(CH_3)_2$**C**HN), 2.99 (2H, s, C-2H_2), 2.00 (2H, s, C-6'H_2), 1.25 (12H, d, J = 6.9 Hz, 2 x (**C**$H_3)_2$CHN), 0.99 (6H, s, 2 x C-5'**C**H_3), 0.92 (9H, s, (**C**$H_3)_3$C($CH_3)_2$Si), 0.09 (6H, s, ($CH_3)_3$C(**C**$H_3)_2$Si). ^{13}C NMR: δ 170.6 (C-1), 150.6 (C-2"), 146.0 (C-1""), 143.6 (C-2'), 139.1 (C-4'), 131.6 (C-4""), 128.8 (C-3"", C-5""), 126.2 (C-2"", C-6""), 123.0 (C-3'), 106.2 (C-1'), 98.7 (C-3"), 58.0 (C-1"), 48.4 (2 x ($CH_3)_2$**C**HN), 41.1 (C-6'), 34.9 (C-2), 31.8 (C-5'), 27.6 (2 x C-5'**C**H_3), 25.7 ((**C**$H_3)_3$C($CH_3)_2$Si), 20.2 (2 x (**C**$H_3)_2$CHN), 18.0 (($CH_3)_3$**C**($CH_3)_2$Si), -4.1 (($CH_3)_3$C(**C**$H_3)_2$Si).

For **225** from the spectra of the mixture: ^{1}H NMR: δ 7.92-7.44 (5H, m, Ph), 5.61 (1H, d, *J* = 10.0 Hz, C-3'H or C-4'H), 5.53 (1H, d, *J* = 10.0 Hz, C-3'H or C-4'H), 4.91 (2H, s, C-1"H_2), 4.20 (2H, s, C-3"H_2), 3.25 (2H, s, C-2H_2), 2.11 (2H, s, C-6'H_2), 1.00 (6H, s, 2 x C-5'**CH_3**), 0.94 (9H, s, (**CH_3**)$_3$C(CH_3)$_2$Si), 0.11 (6H, s, (CH_3)$_3$C(**CH_3**)$_2$Si). ^{13}C NMR: δ 170.8 (C-1), 143.6 (C-2'), 139.2 (C-4'), 138.3 (C-1'''), 134.5 (C-4'''), 129.4 (C-3''', C-5'''), 128.4 (C-2''', C-6'''), 123.0 (C-3'), 106.2 (C-1'), 68.3 and 64.2 (C-1", C-3"), 41.0 (C-6'), 34.6 (C-2), 31.8 (C-5'), 27.6 (2 x C-5'**CH_3**), 25.7 ((**CH_3**)$_3$C(CH_3)$_2$Si), 18.0 ((CH_3)$_3$**C**(CH_3)$_2$Si), -4.1 ((CH_3)$_3$C(**CH_3**)$_2$Si).

Attempted TBS diene formation.

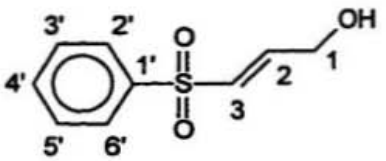
(2-Oxo-3-phenylsulfonylpropyl) 2-(5,5-dimethyl-2-oxocyclohex-3-enyl) ethanoate (226).



To a solution of 1,1,1,3,3,3-hexamethyldisilazane (0.105 g, 0.650 mmol) in THF (3.0 mL), cooled to 0 °C, was added *n*-butyllithium (1.6 M in hexanes, 0.37 mL, 0.60 mmol) dropwise. This solution was maintained at 0 °C for 30 min, then added to a -78 °C solution of **223** (0.196 g, 0.542 mmol) in THF (10 mL). After 5 min, TBSOTf (0.21 g, 0.78 mmol) was added to the orange solution. The

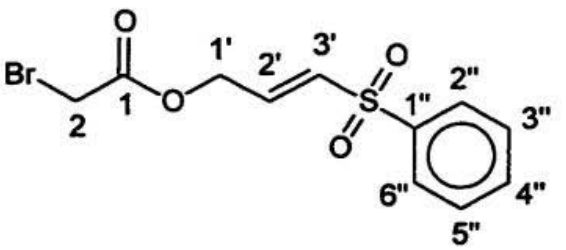
mixture was maintained at -78 °C for 6 h, then it was allowed to warm to rt. After quenching with water, the solvent was removed and replaced by diethyl ether (150 mL). The solution was washed with water (2 x 15 mL) and brine (15 mL), and then dried ($MgSO_4$). Solvent evaporation followed by flash chromatography (50% ethyl acetate-hexane) gave **226** (0.110 g, 53%) as a white solid. IR: 3065 (weak), 2962, 1738, 1678, 1326, 1157, 788 cm^{-1}. ^1H NMR: δ 7.92 (2H, m, C-2'''H, C-6'''H), 7.68 (1H, m, C-4'''H), 7.58 (2H, m, C-3'''H, C-5'''H), 6.63 (1H, dd, *J* = 2.0, 10.0 Hz, C-4'H), 5.84 (1H, d, *J* = 10.0 Hz, C-3'H), 4.90 (2H, s, C-1''H_2), 4.32 (1H, doublet, *J* = 13.8 Hz, C-3''H), 4.26 (1H, doublet, *J* = 13.8 Hz, C-3''H), 3.07 (1H, m, C-1'H), 2.94 (1H, dd, *J* = 6.2, 16.2 Hz, C-2H), 2.34 (1H, dd, *J* = 6.6, 16.2 Hz, C-2H), 1.91 (1H, ddd, *J* = 2.0, 4.8, 13.6 Hz, C-6'H), 1.76 (1H, apparent t, *J* = 13.6 Hz, C-6'H), 1.23 (3H, s, C-5'**CH_3**), 1.15 (3H, s, C-5'**CH_3**). ^{13}C NMR: δ 199.1 (C-2'), 192.2 (C-2''), 171.7 (C-1), 159.3 (C-4'), 138.3 (C-1'''), 134.4 (C-4'''), 129.3 (C-3''', C-5'''), 128.4 (C-2''', C-6'''), 125.9 (C-3'), 68.5 and 64.0 (C-1'', C-3''), 42.1 (C-6'), 39.9 (C-1'), 34.1 (C-2), 33.8 (C-5'), 30.4 (C-5'**CH_3**), 25.1 (C-5'**CH_3**). MS: 377 (0.6, M^+ - 1), 362 (1), 166 (11), 165 (100), 164 (24), 141 (9), 137 (6), 136 (10), 125 (19), 123 (17), 121 (18), 109 (8), 108 (17), 96 (78), 95 (11), 93 (15), 91 (16), 81 (22), 79 (13), 78 (19), 77 (91), 69 (12), 67 (29), 65 (12), 55 (12), 53 (21), 51 (39), 50 (14).

(*E*)-3-Phenylsulfonyl-2-propen-1-ol (227).



Benzenesulfinic acid sodium salt (8.36 g, 50.9 mmol) was dissolved in a solution of DMF (5.0 mL) and water (100 mL). After dissolving the salt, epichlorohydrin (9.6 g, 8.1 mL, 0.10 mol) was added, and the solution was heated to reflux whereupon a white solid began to precipitate. Refluxing was stopped after 6 h, and the reaction was cooled to rt and stirred for 18 h. The mixture was cooled in an ice bath, and the white solid was collected by filtration through a sintered-glass funnel. The solid was washed with ice-cold water (2 x 15 mL), partially dried under suction and dried under vacuum (*ca.* 1 mm Hg, 60 °C) for about 10 h. Recrystallization from acetone gave **227** (7.21 g, 72%) as colourless crystals: mp: 142.0-142.5 °C. IR: 3491, 3054, 1630 (w), 1454, 1285, 1142, 1085 cm^{-1}. ^1H NMR (CD_3COCD_3): δ 7.92 (2H, m, C-2'H, C-6'H), 7.72 (1H, m, C-4'H), 7.64 (2H, m, C-3'H, C-5'H), 7.08 (1H, m, C-2H), 6.71 (1H, apparent dt, J = 2.3, 14.4 Hz, C-3H), 4.37 (3H, m, C-1H_2, **OH**). ^{13}C NMR (CD_3COCD_3): δ 148.0 (C-2), 142.3 (C-1'), 134.2 (C-4'), 130.3 (C-3', C-5'), 130.1 (C-3), 128.3 (C-2', C-6'), 61.1 (C-1). MS: 198 (2, M^+), 170 (10), 169 (100), 125 (33), 97 (9), 94 (13), 91 (17), 78 (38), 77 (76), 65 (7), 57 (50), 51 (52), 50 (14).

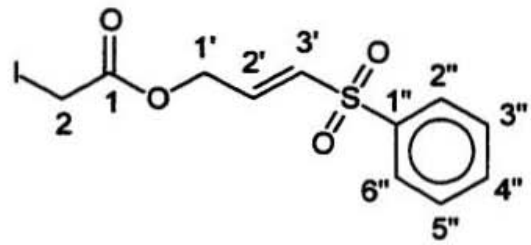
((*E*)-3-Phenylsulfonyl-2-propenyl) 2-bromoethanoate (228).



(*E*)-3-Phenylsulfonyl-2-propen-1-ol (**227**) (1.06 g, 5.35 mmol) was suspended in THF (60 mL). Pyridine (0.55 g, 0.56 mL, 7.0 mmol) was added dropwise, and the reaction was stirred for 30 min. Bromoacetyl bromide (1.4 g, 0.61 mL, 7.0 mmol) was added dropwise at rt, resulting in a cream-coloured precipitate and the generation of heat. After stirring the mixture overnight, the pyridinium bromide salt was removed by filtration through a sintered-glass funnel containing Celite. The THF was removed, and the residue was diluted with diethyl ether (100 mL). The organic layer was washed with 1 M aqueous HCl (10 mL), a saturated aqueous $NaHCO_3$ solution (10 mL), and brine (10 mL), and then dried ($MgSO_4$). Solvent evaporation followed by flash chromatography (elution with 40% ethyl acetate-petroleum ether) gave **228** (1.50 g, 88%) as a pale yellow oil. IR: 3060, 1745, 1636 (weak), 1447, 1316, 1281, 1147, 1086 cm^{-1}. ^1H NMR: δ 7.90 (2H, m, C-2"H, C-6"H), 7.66 (1H, m, C-4"H), 7.56 (2H, m, C-3"H, C-5"H), 6.99 (1H, dt, J = 4.0, 15.1 Hz, C-2'H), 6.63 (1H, dt, J = 2.1, 15.1 Hz, C-3'H), 4.88 (2H, dd, J = 2.1, 4.0 Hz, C-1'H_2), 3.86 (2H, s, C-2H_2). ^{13}C NMR: δ 166.3 (C-1), 139.6 (C-1"), 138.2 (C-2'), 133.7 (C-4"), 131.8 (C-3'), 129.4 (C-3", C-5"), 127.8

(C-2", C-6"), 62.8 (C-1'), 24.9 (C-2). MS: 320 (0.05, M$^+$), 199 (9), 198 (73), 197 (15), 181 (11), 179 (59), 177 (62), 169 (22), 143 (9), 125 (100), 123 (80), 121 (84), 97 (18), 95 (14), 93 (14), 84 (11), 78 (24), 77 (92), 57 (51), 51 (28). Anal. calcd. for $C_{11}H_{11}BrO_4S$: C 41.40, H 3.47; found: C 41.37, H 3.25.

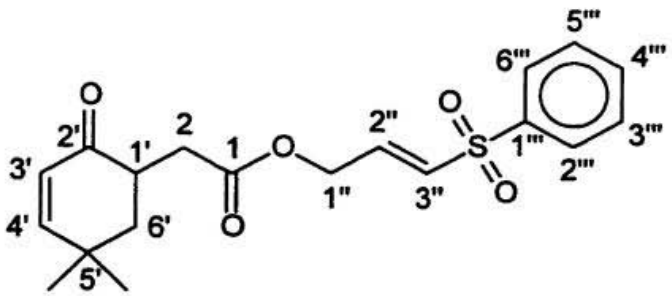
((*E*)-3-Phenylsulfonyl-2-propenyl) 2-iodoethanoate (229).



A solution of sodium iodide (2.43 g, 16.2 mmol) in acetone (12 mL) was cooled to 0 °C, and the bromoester **228** (4.22 g, 13.2 mmol) in acetone (5.0 mL) was added dropwise resulting in the immediate formation of a white precipitate. The reaction was heated to 40 °C for 12 h, and the sodium bromide was removed from the red solution by filtration through a sintered-glass funnel containing Celite. Solvent evaporation followed by flash chromatography (elution with 40% ethyl acetate-petroleum ether) gave **229** (4.64 g, 96%) as a pale yellow solid: mp: 57-58 °C. IR: 3058, 1739, 1640 (weak), 1447, 1308, 1265, 1147, 1097 cm^{-1}. ^{1}H NMR: δ 7.90 (2H, m, C-2"H, C-6"H), 7.66 (1H, m, C-4"H), 7.56 (2H, m, C-3"H, C-5"H), 7.00 (1H, dt, J = 4.0, 15.2 Hz, C-2'H), 6.66 (1H, dt, J = 2.1, 15.2 Hz, C-3'H), 4.85 (2H, dd, J = 2.1, 4.0 Hz, C-1'H$_2$), 3.72 (2H, s, C-2H$_2$).

^{13}C NMR: δ 167.8 (C-1), 139.7 (C-1"), 138.4 (C-2'), 133.7 (C-4"), 131.6 (C-3'), 129.4 (C-3", C-5"), 127.8 (C-2", C-6"), 62.5 (C-1'), -6.9 (C-2). MS: 366 (0.5, M$^+$), 239 (4), 225 (36), 198 (22), 197 (13), 181 (61), 169 (100), 168 (9), 141 (16), 125 (70), 97 (12), 78 (14), 77 (52), 57 (16), 51 (11). Anal. calcd. for $C_{11}H_{11}IO_4S$: C 36.08, H 3.03; found: C 36.07, H 2.84.

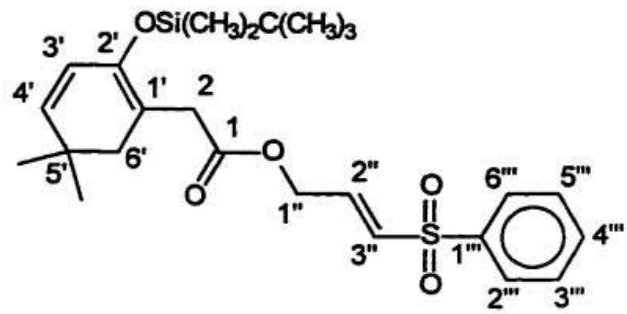
((*E*)-3-Phenylsulfonyl-2-propenyl) 2-(5,5-dimethyl-2-oxocyclohex-3-enyl) ethanoate (230).



A solution of diisopropylamine (0.10 g, 0.13 mL, 0.95 mmol) and HMPA (0.32 g, 0.32 mL, 1.8 mmol) in THF (8.0 mL) was cooled to 0 °C. *n*-Butyllithium (2.5 M in hexanes, 0.40 mL, 1.0 mmol) was added dropwise, and the solution was stirred for 30 min. 4,4-Dimethyl-2-cyclohexen-1-one (0.109 g, 0.879 mmol) in THF (2.0 mL) was then added dropwise, and the mixture was stirred for a further 40 min. After cooling to -78 °C and stirring for 20 min, **229** (0.354 g, 0.965 mmol) in THF (3.0 mL) was added over 5 min. The mixture was maintained at -78 °C for 18 h, then warmed to rt. Solvent evaporation was followed by dilution with diethyl ether (200 mL). The organic solution was

washed with water (3 x 10 mL), and brine (15 mL), and then dried ($MgSO_4$). Solvent evaporation gave a yellow oil, which was purified by flash chromatography (elution with 30% ethyl acetate-petroleum ether) to give **230** (0.184 g, 58%) as a pale yellow oil. IR: 3060 (weak), 2962, 1743, 1677, 1639, 1447, 1319, 1283, 1148, 1086 cm^{-1}. ^1H NMR: δ 7.91 (2H, m, C-2'''H, C-6'''H), 7.64 (1H, m, C-4'''H), 7.55 (2H, m, C-3'''H, C-5'''H), 7.00 (1H, dt, *J* = 3.9, 15.2 Hz, C-2"H), 6.67 (1H, dt, *J* = 2.0, 15.2 Hz, C-3"H), 6.62 (1H, dd, *J* = 1.8, 10.0 Hz, C-4'H), 5.81 (1H, d, *J* = 10.0 Hz, C-3'H), 4.83 (2H, symmetrical m, C-1"H_2), 3.02 (1H, m, C-1'H), 2.82 (1H, dd, *J* = 6.5, 16.6 Hz, C-2H), 2.30 (1H, dd, *J* = 6.2, 16.6 Hz, C-2H), 1.84 (1H, ddd, *J* = 1.9, 5.4, 13.2 Hz, C-6H), 1.75 (1H, apparent t, *J* = 13.2 Hz, C-6H), 1.22 (3H, s, C-5'**CH_3**), 1.14 (3H, s, C-5'**CH_3**). ^{13}C NMR: δ 199.0 (C-2'), 171.5 (C-1), 159.2 (C-4'), 139.8 (C-1'''), 139.3 (C-2"), 133.5 (C-4'''), 131.2 (C-3"), 129.7 (C-3''', C-5'''), 127.7 (C-2''', C-6'''), 125.8 (C-3'), 61.5 (C-1"), 42.3 (C-6'), 39.8 (C-1'), 34.3 (C-2), 33.7 (C-5'), 30.4 (C-5'**CH_3**), 25.1 (C-5'**CH_3**). MS: 362 (4, M^+), 181 (8), 165 (48), 164 (25), 125 (25), 123 (11), 122 (14), 96 (100), 86 (17), 84 (27), 81 (20), 77 (28), 67 (16), 59 (15), 53 (10), 51 (12). HRMS: calcd for $C_{19}H_{22}O_5S$: 362.1187; found: 362.1190.

((*E*)-3-Phenylsulfonyl-2-propenyl) 2-(5,5-dimethyl-2-(((1,1-dimethylethyl) dimethylsilyl)oxy)cyclohexa-1,3-dienyl)ethanoate (231).

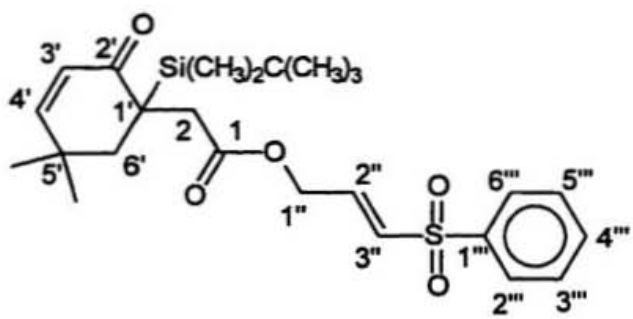


A solution of **230** (0.136 g, 0.374 mmol) in dichloromethane (2.0 mL) was cooled to 0 °C and triethylamine (60 mg, 0.083 mL, 0.59 mmol) was added dropwise. After stirring for 10 min, TBSOTf (0.14 g, 0.12 mL, 0.53 mmol) was added dropwise, and the reaction slowly warmed to rt. After 2 h, the mixture was poured into diethyl ether (100 mL) and washed with a saturated aqueous $NaHCO_3$ solution (3 x 15 mL), and brine (10 mL), and then dried ($MgSO_4/K_2CO_3$). Solvent evaporation followed by flash chromatography (elution with 15% ethyl acetate-hexane) gave **231** (0.147 g, 83%) as a colourless oil. IR: 3062 (weak), 2956, 1743, 1662, 1322, 1254, 1214, 1149, 1087 cm^{-1}. ^1H NMR: δ 7.89 (2H, m, C-2'''H, C-6'''H), 7.64 (1H, m, C-4'''H), 7.54 (2H, m, C-3'''H, C-5'''H), 6.99 (1H, dt, *J* = 3.9, 15.2 Hz, C-2"H), 6.55 (1H, dt, *J* = 2.2, 15.2 Hz, C-3"H), 5.58 (1H, d, *J* = 9.4 Hz, C-3'H), 5.50 (1H, d, *J* = 9.4 Hz, C-4'H), 4.78 (2H, dd, *J* = 2.2, 3.9 Hz, C-1"H_2), 3.16 (2H, s, C-2H_2), 2.06 (2H, s, C-6'H_2), 0.96 (6H, s, 2 x C-5'**CH_3**), 0.90 (9H, s, (**CH_3**)$_3$C(CH_3)$_2$Si), 0.08 (6H, s, (CH_3)$_3$C(**CH_3**)$_2$Si). ^{13}C NMR: δ 170.7

(C-1), 143.9 (C-2'), 139.9 (C-1'''), 139.5 (C-2''), 139.2 (C-4'), 133.6 (C-4'''), 131.3 (C-3''), 129.3 (C-3''', C-5'''), 127.8 (C-2''', C-6'''), 122.9 (C-3'), 106.0 (C-1'), 61.3 (C-1''), 41.3 (C-6'), 35.1 (C-2), 31.7 (C-5'), 27.5 (2 x C-5'CH_3), 25.6 ($(CH_3)_3C(CH_3)_2Si$), 18.0 ($(CH_3)_3C(CH_3)_2Si$), -4.1 ($(CH_3)_3C(CH_3)_2Si$). MS: 476 (7, M$^+$), 461 (3), 420 (13), 419 (44), 252 (12), 251 (53), 239 (18), 238 (75), 237 (18), 235 (10), 223 (12), 210 (10), 209 (13), 199 (13), 195 (18), 194 (59), 193 (13), 181 (13), 179 (39), 135 (14), 125 (37), 117 (11), 105 (24), 77 (15), 75 (42), 73 (100), 59 (14). HRMS: calcd for $C_{25}H_{36}O_5SSi$: 476.2051; found: 476.2047.

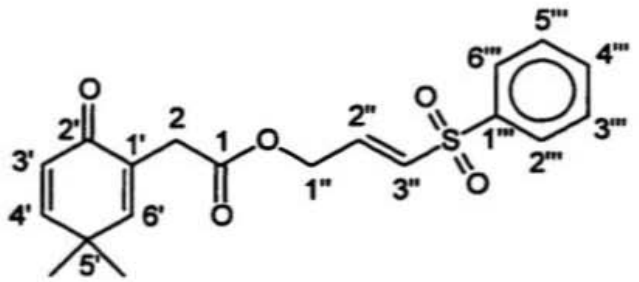
Attempted intramolecular Diels-Alder reaction of 231.

((*E*)-3-Phenylsulfonyl-2-propenyl) 2-(5,5-dimethyl-1-((1,1-dimethylethyl) dimethylsilyl)-2-oxocyclohex-3-enyl)ethanoate (232) and ((*E*)-3-phenylsulfonyl-2-propenyl) 2-(5,5-dimethyl-2-oxocyclohexa-3,6-dienyl)ethanoate (233).



232

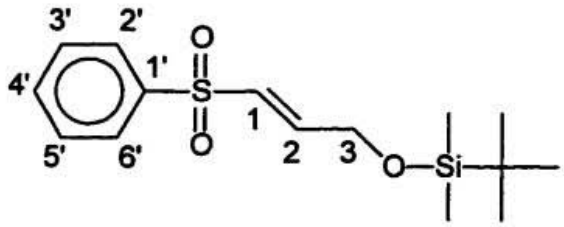
A solution of **231** (74.6 mg, 0.156 mmol) in toluene (2.5 mL) was heated to reflux, and reaction progress was monitored by TLC. After 6 days, the solvent was evaporated, and flash chromatography of the residue (elution with 15% ethyl acetate-petroleum ether) gave **230** (6.6 mg, 12%) as a colourless oil, **231** (5 mg, 7%) as a pale yellow oil, **232** (22 mg, 29%) as a colourless oil, and **233** (10 mg, 18%) as a colourless oil. For **232**: IR: 3062 (weak), 2958, 1745, 1680, 1447, 1321, 1254, 1150, 1087 cm^{-1}. ^1H NMR: δ 7.91 (2H, m, C-2'''H, C-6'''H), 7.65 (1H, m, C-4'''H), 7.56 (2H, m, C-3'''H, C-5'''H), 6.97 (1H, dt, J = 4.0, 15.1 Hz, C-2"H), 6.65 (1H, dd, J = 1.4, 10.2 Hz, C-4'H), 6.59 (1H, dt, J = 1.7, 15.1 Hz, C-3"H), 5.87 (1H, d, J = 10.2 Hz, C-3'H), 4.74 (2H, symmetrical m, C-1"H_2), 2.94 (1H, d, J = 15.5 Hz, C-2H), 2.68 (1H, d, J = 15.5 Hz, C-2H), 2.17 (1H, d, J = 14.5 Hz, C-6'H), 2.07 (1H, dd, J = 1.6, 14.5 Hz, C-6'H), 1.28 (3H, s, C-5'$\mathbf{CH_3}$), 1.12 (3H, s, C-5'$\mathbf{CH_3}$), 0.80 (9H, s, $(\mathbf{CH_3})_3C(CH_3)_2Si$), 0.15 (3H, s, $(CH_3)_3C\mathbf{CH_3}Si$), -0.08 (3H, s, $(CH_3)_3C\mathbf{CH_3}Si$). ^{13}C NMR: δ 196.1 (C-2'), 169.4 (C-1), 159.7 (C-4'), 139.9 (C-1'''), 139.0 (C-2"), 133.6 (C-4'''), 131.5 (C-3"), 129.3 (C-3''', C-5'''), 127.8 (C-2''', C-6'''), 124.5 (C-3'), 74.7 (C-1'), 61.5 (C-1"), 47.1 (C-6'), 42.9 (C-2), 33.5 (C-5'), 30.9 (C-5'$\mathbf{CH_3}$), 29.5 (C-5'$\mathbf{CH_3}$), 25.7 ($(\mathbf{CH_3})_3C(CH_3)_2Si$), 18.2 ($(CH_3)_3\mathbf{C}(CH_3)_2Si$), -2.9 and -3.5 ($(CH_3)_3C(\mathbf{CH_3})_2Si$). MS: no M^+, 435 (13), 237 (18), 209 (21), 195 (15), 181 (14), 163 (11), 135 (8), 126 (7), 125 (100), 117 (11), 97 (8), 96 (37), 81 (8), 77 (17), 75 (30), 73 (24).



233

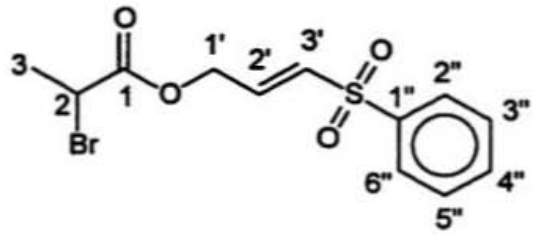
For **233**: IR: 3057 (weak), 2968, 1745, 1666, 1637, 1447, 1408, 1309, 1147, 1101 cm^{-1}. ^1H NMR: δ 7.91 (2H, m, C-2'''H, C-6'''H), 7.64 (1H, m, C-4'''H), 7.56 (2H, m, C-3'''H, C-5'''H), 6.98 (1H, dt, *J* = 4.0, 15.1 Hz, C-2''H), 6.84 (1H, dd, *J* = 2.9, 9.9 Hz, C-4'H), 6.74 (1H, m, C-6'H), 6.61 (1H, dt, *J* = 2.1, 15.1 Hz, C-3''H), 6.17 (1H, d, *J* = 9.9 Hz, C-3'H), 4.81 (2H, dd, *J* = 2.1, 4.0 Hz, C-1''H_2), 3.32 (2H, d, *J* = 0.7 Hz, C-2H_2), 1.27 (6H, s, 2 x C-5'**CH_3**). ^{13}C NMR: δ 184.7 (C-2'), 170.0 (C-2), 156.8 (C-4'), 154.9 (C-6'), 139.9 (C-1'''), 139.2 (C-2''), 133.5 (C-4'''), 131.2 (C-3''), 130.7 (C-1'), 129.3 (C-3''', C-5'''), 127.8 (C-2''', C-6'''), 126.6 (C-3'), 61.7 (C-1''), 38.3 (C-5'), 35.1 (C-2), 26.8 (2 x C-5'**CH_3**). MS: 360 (0.8, M^+), 219 (1), 181 (8), 179 (5), 163 (25), 162 (100), 161 (17), 147 (10), 135 (56), 134 (52), 125 (36), 121 (7), 107 (17), 106 (11), 105 (12), 97 (11), 92 (13), 91 (48), 79 (14), 77 (46), 65 (13), 53 (9), 51 (19).

(*E*)-3-(((1,1-Dimethylethyl)dimethylsilyl)oxy)-1-phenylsulfonyl-1-propene (240).



(*E*)-3-Phenylsulfonyl-2-propen-1-ol (**227**) (1.13 g, 5.70 mmol) was dissolved in DMF (10 mL). A solution of imidazole (0.438 g, 6.43 mmol) in DMF (5.0 mL) was added dropwise, followed by the addition of TBSCl (0.953 g, 6.32 mmol) in DMF (5.0 mL). This was stirred at rt overnight. The mixture was diluted with petroleum ether (200 mL) and washed with a saturated aqueous $NaHCO_3$ solution (3 x 15 mL) and brine (2 x 15 mL). Drying (K_2CO_3), followed by solvent evaporation yielded **240** (1.56 g, 88%) as a colourless oil. IR: 3065 (weak), 2955, 1638, 1447, 1308, 1258, 1146 cm^{-1}. ^1H NMR: δ 7.90 (2H, m, C-2'H, C-6'H), 7.58 (3H, m, C-3'H, C-4'H, C-5'H), 7.04 (1H, dt, J = 2.9, 14.6 Hz, C-2H), 6.61 (1H, dt, J = 2.3, 14.6 Hz, C-1H), 4.38 (2H, t, J = 2.4 Hz, C-$3H_2$), 0.88 (9H, s, $(\mathbf{CH_3})_3C(CH_3)_2Si$), 0.05 (6H, s, $(CH_3)_3C(\mathbf{CH_3})_2Si$). ^{13}C NMR: δ 145.8 (C-2), 140.5 (C-1'), 133.2 (C-4'), 129.3 (C-1), 129.2 (C-3', C-5'), 127.6 (C-2', C-6'), 61.4 (C-3), 25.7 ($(\mathbf{CH_3})_3C(CH_3)_2Si$), 18.3 ($(CH_3)_3\mathbf{C}(CH_3)_2Si$), -5.5 ($(CH_3)_3C(\mathbf{CH_3})_2Si$). MS: no M^+, 297 (1), 257 (4), 256 (8), 255 (43), 141 (2), 135 (34), 125 (11), 115 (6), 114 (12), 113 (100), 99 (11), 97 (7), 77 (26), 75 (39), 73 (27), 59 (9), 57 (7).

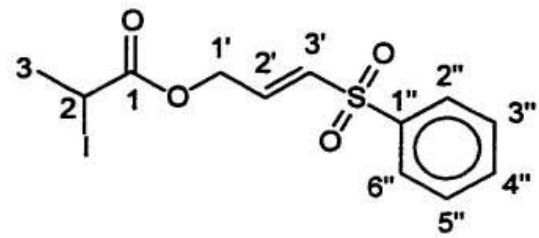
((*E*)-3-Phenylsulfonyl-2-propenyl) 2-bromopropanoate (241).



A suspension of (*E*)-3-phenylsulfonyl-2-propen-1-ol (**227**) (2.31 g, 11.7 mmol) in THF (100 mL) was cooled to 0 °C, and pyridine (1.2 g, 1.2 mL, 0.015 mol) was added dropwise. After 15 min, 2-bromopropanoyl bromide (3.2 g, 1.5 mL, 0.015 mol) was added, resulting in the formation of a cream-coloured precipitate. The mixture was stirred overnight, during which time it slowly warmed to rt. The mixture was filtered through a sintered-glass funnel containing Celite. The solvent was removed from the filtrate under vacuum, and the residue was redissolved in diethyl ether (200 mL). The solution was washed with 1M aqueous HCl (20 mL), water (20 mL), a saturated aqueous $NaHCO_3$ solution (20 mL), and brine (15 mL), and then dried ($MgSO_4$). Solvent evaporation followed by flash chromatography (40% ethyl acetate-petroleum ether) gave **241** (3.60g, 93%) as a yellow oil. IR: 3060, 1746, 1638, 1447, 1319, 1281, 1218, 1148, 1086 cm^{-1}. ^1H NMR: δ 7.90 (2H, m, C-2"H, C-6"H), 7.75 (1H, m, C-4"H), 7.56 (2H, m, C-3"H, C-5"H), 7.00 (1H, dt, J = 3.9, 15.2 Hz, C-2'H), 6.65 (1H, dt, J = 2.0, 15.2 Hz, C-3'H), 4.88 (2H, m, C-1'H_2), 4.40 (1H, q, J = 6.9 Hz, C-2H), 1.87 (3H, d, J = 6.9 Hz, C-3H_3). ^{13}C NMR: δ 169.2 (C-1), 139.6 (C-1"), 138.5 (C-2'), 133.7 (C-4"), 131.6 (C-3'), 129.3 (C-3", C-5"), 127.7 (C-2", C-6"), 62.4 (C-1'),

39.0 (C-2), 21.4 (C-3). MS: 334 (1), 332 (1) both M^+, 199 (7), 198 (58), 197 (21), 193 (48), 191 (51), 181 (13), 169 (14), 137 (65), 135 (66), 126 (9), 125 (100), 109 (53), 107 (54), 97 (15), 78 (20), 77 (83), 57 (19), 56 (25), 55 (16). Anal. calcd. for $C_{12}H_{13}BrO_4S$: C 43.26, H 3.93; found: C 43.30, H 4.08.

((*E*)-3-Phenylsulfonyl-2-propenyl) 2-iodopropanoate (242).



A solution of sodium iodide (1.84 g, 12.3 mmol) in acetone (8.0 mL) was cooled to 0 °C and **241** (3.21 g, 9.65 mmol), dissolved in acetone (5.0 mL), was added dropwise. White solid began to form in the yellow solution after several minutes. After heating at 40 °C for 12 h, the insoluble sodium bromide was removed by filtration using a sintered glass funnel containing Celite. Solvent evaporation followed by flash chromatography (elution with 40% ethyl acetate-petroleum ether) gave **242** (3.48 g, 95%) as a yellow oil. IR: 3059 (weak), 1738, 1638 (weak), 1447, 1319, 1282, 1200, 1148, 1086 cm^{-1}. ^1H NMR: δ 7.90 (2H, m, C-2"H, C-6"H), 7.65 (1H, m, C-4"H), 7.56 (2H, m, C-3"H, C-5"H), 7.01 (1H, dt, J = 3.9, 15.2 Hz, C-2'H), 6.68 (1H, dt, J = 2.0, 15.2 Hz, C-3'H), 4.86 (2H, symmetrical m, C-1'H), 4.51 (1H, q, J = 7.0 Hz, C-2H), 1.95 (3H, d, J = 7.0 Hz, C-$3H_3$). ^{13}C NMR: δ 170.9 (C-1), 139.7 (C-1"), 138.6 (C-2'), 133.7 (C-4"),

131.6 (C-3'), 129.4 (C-3", C-5"), 127.8 (C-2", C-6"), 62.2 (C-1'), 23.1 (C-3), 11.5 (C-2). MS: 380 (0.1, M^+), 254 (1), 253 (8), 239 (9), 198 (7), 197 (10), 183 (39), 182 (17), 181 (100), 155 (47), 126 (7), 125 (94), 97 (13), 78 (11), 77 (53), 57 (7), 56 (23), 55 (35). Anal. calcd. for $C_{12}H_{13}IO_4S$: C 37.91, H 3.45; found: C 38.17, H 3.42.

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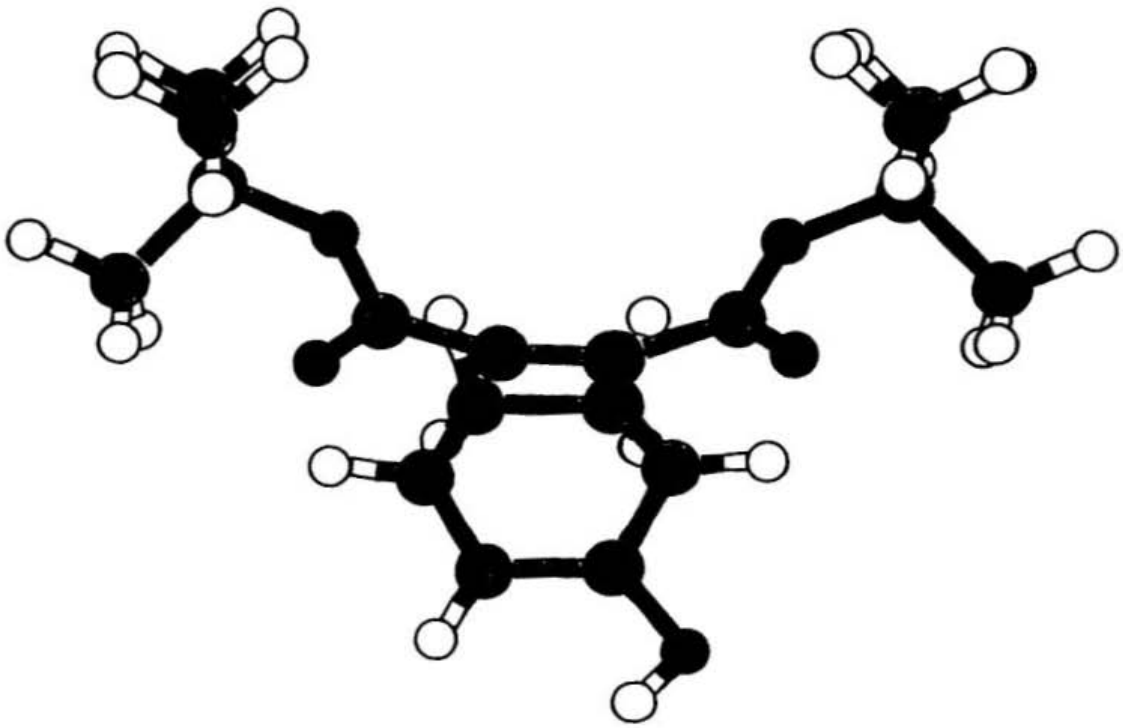
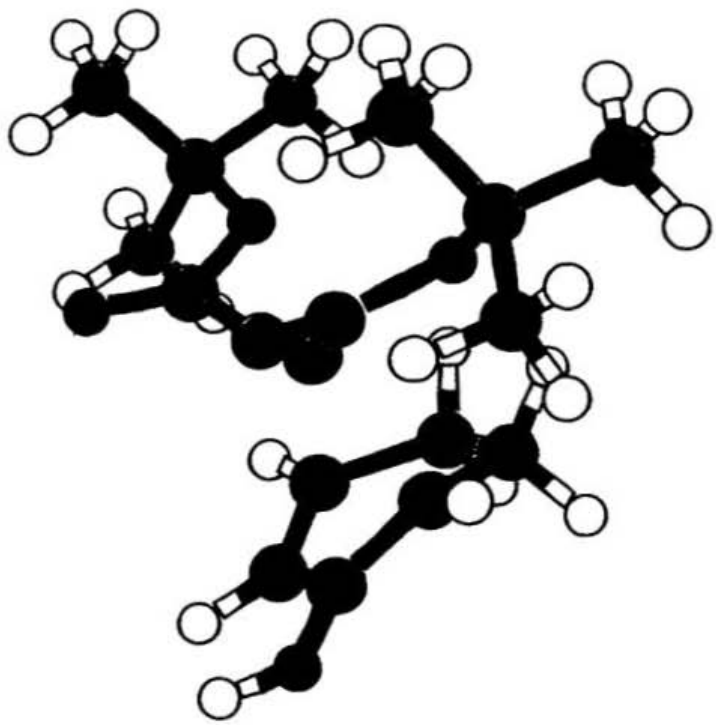
113. For general methods see *Part I*, section VI.

Appendix A

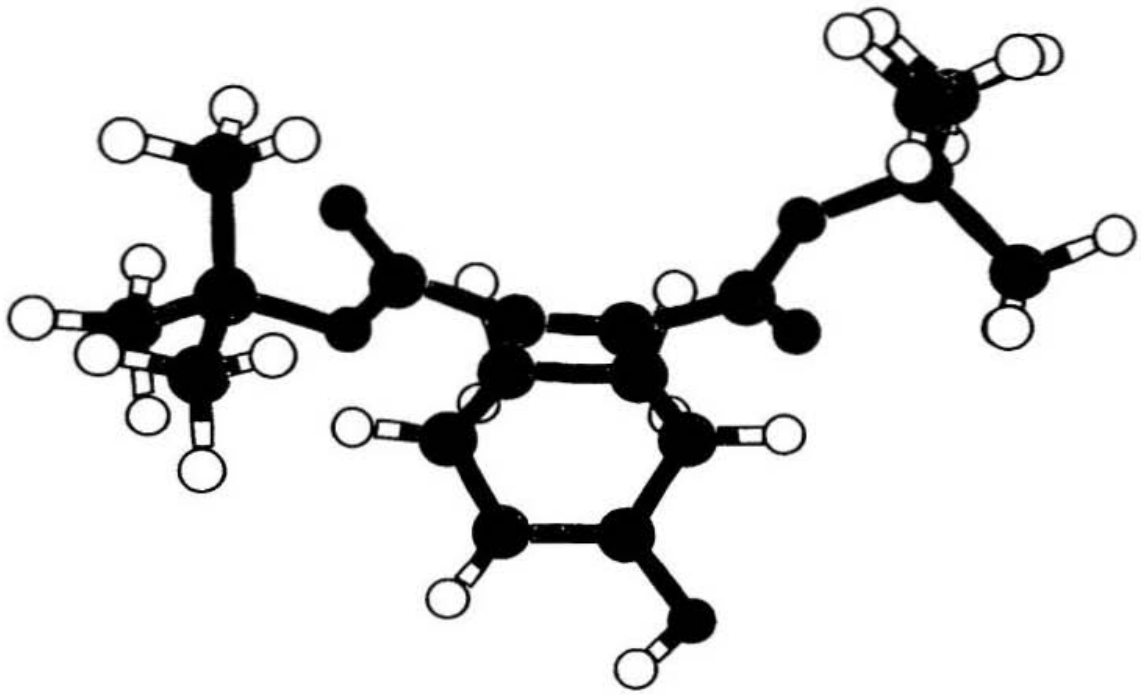
Transition structures obtained from *Semiempirical* molecular orbital calculations at the AM1 level using the SPARTAN® computational package.

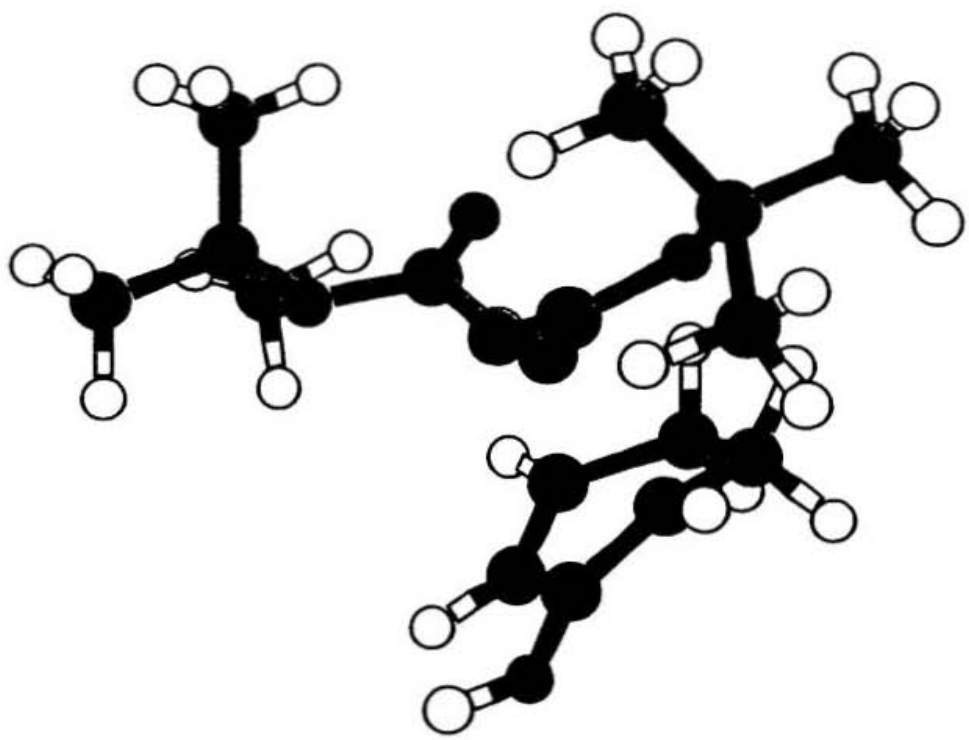
Transition Structure **58a**



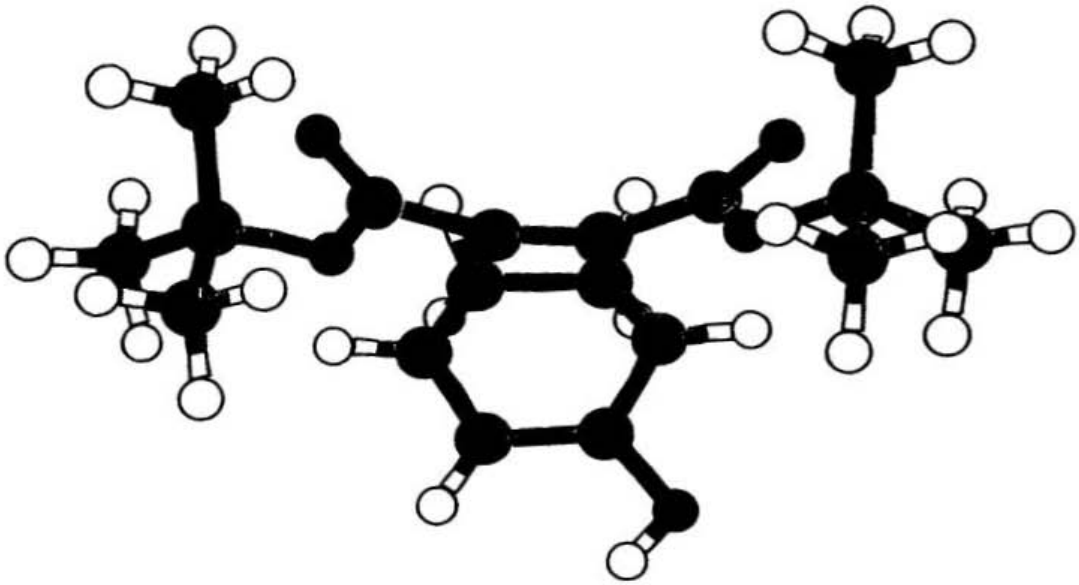


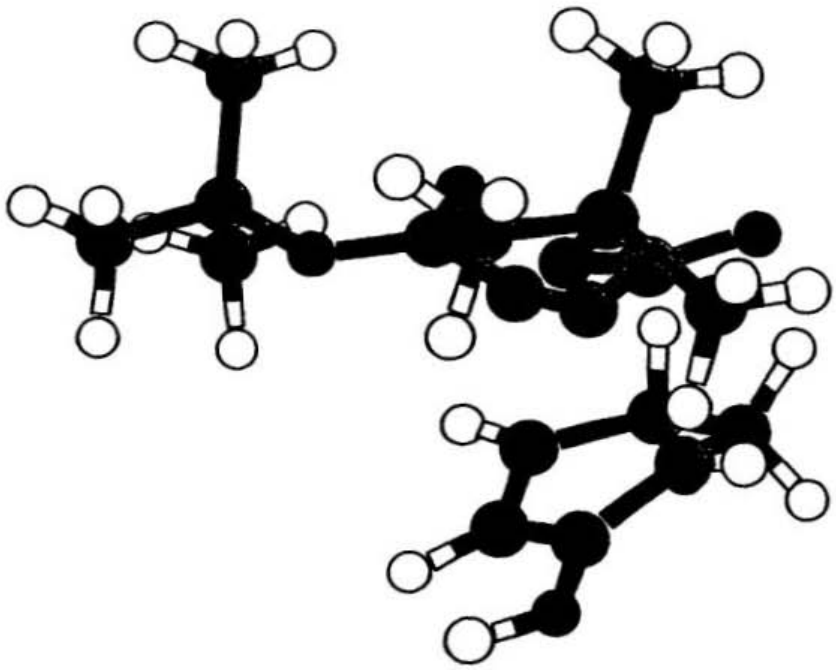
Transition Structure **58b**



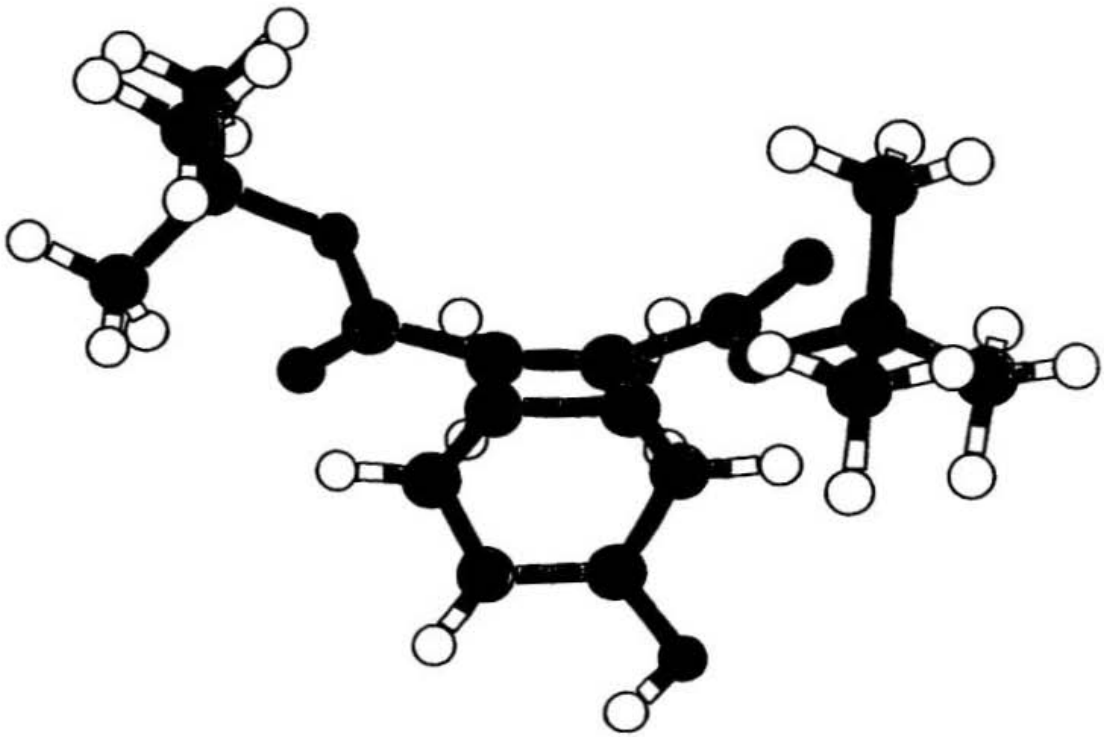


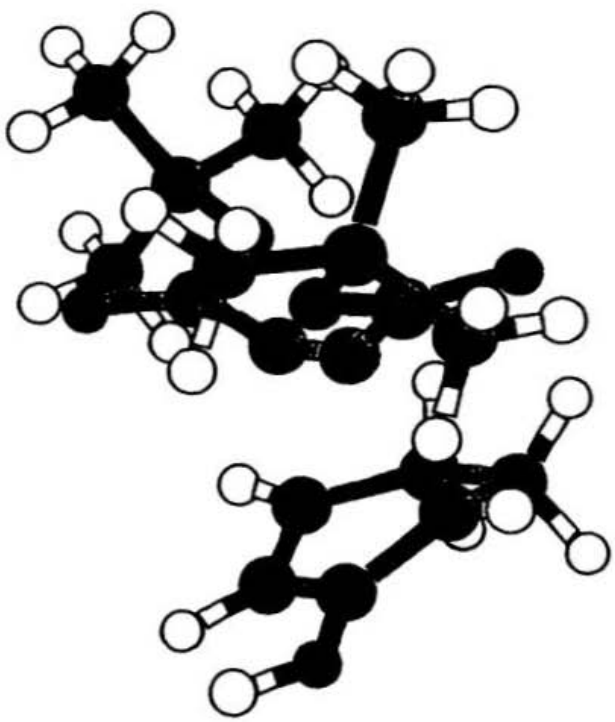
Transition Structure **58c**



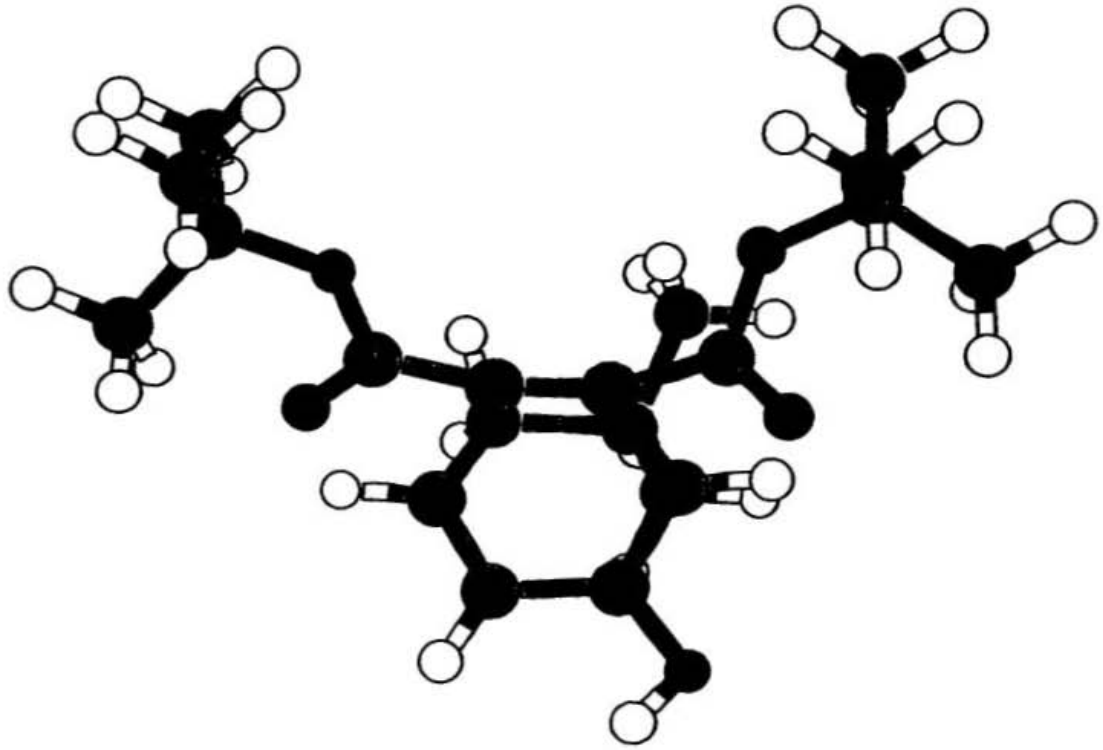


Transition Structure **58d**

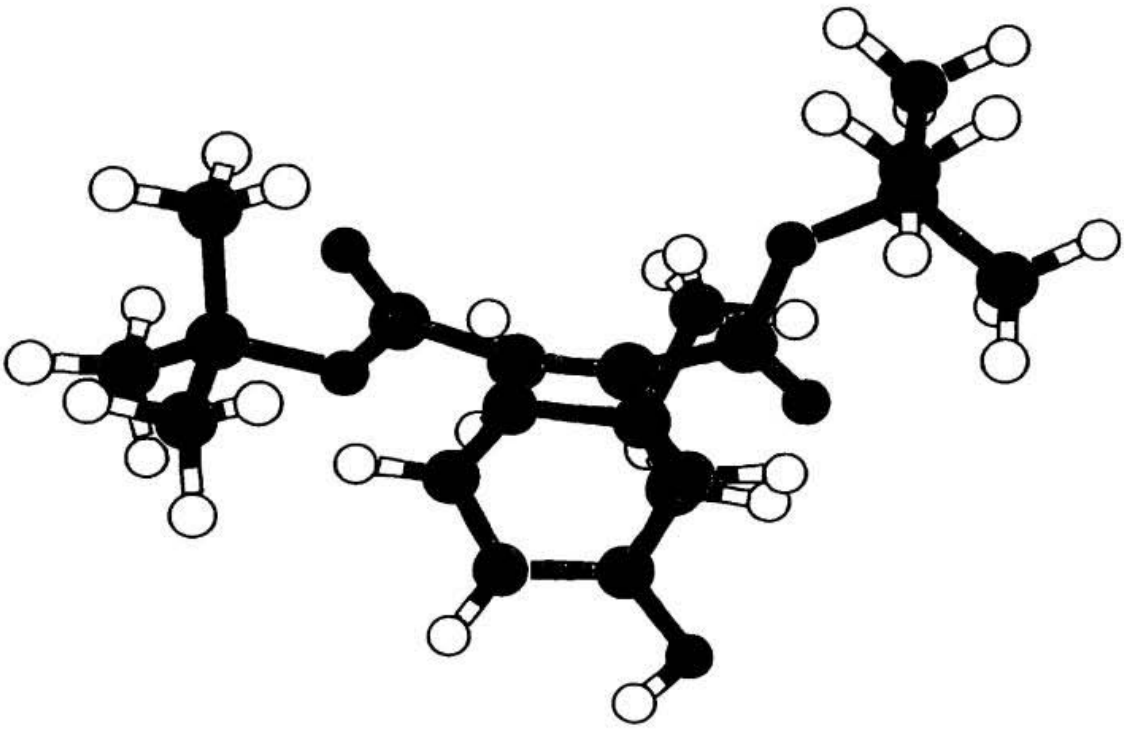


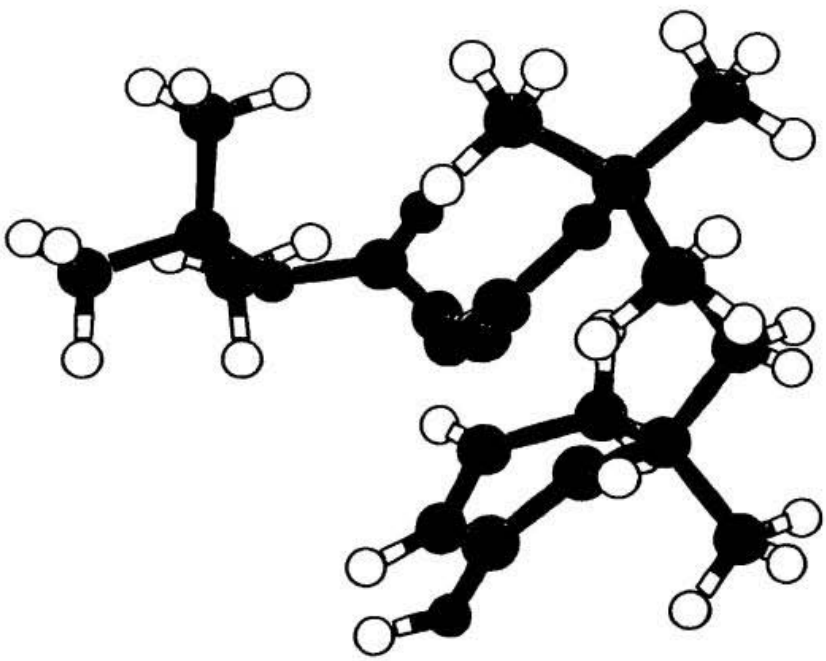


Transition Structure **59a**

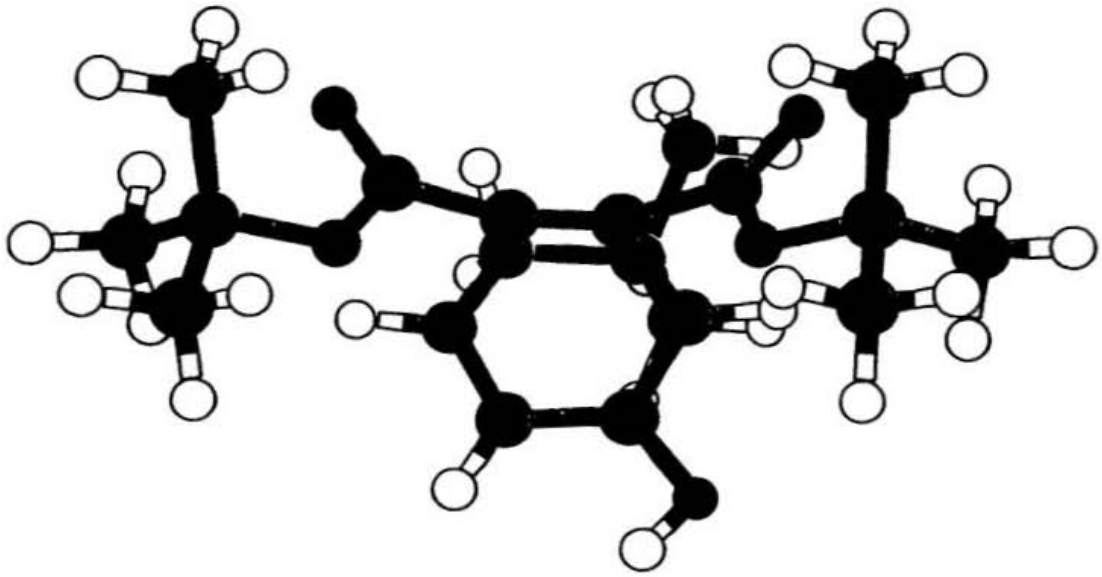


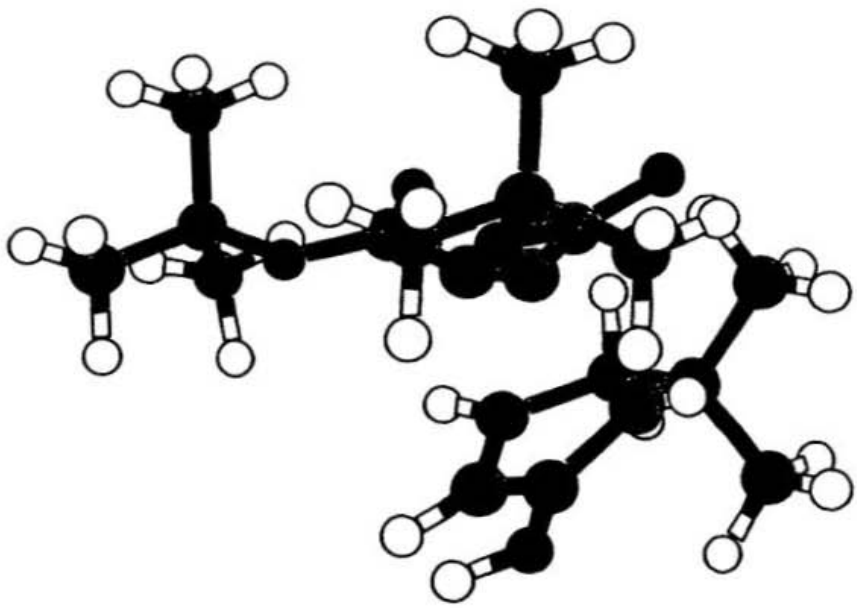
Transition Structure **59b**



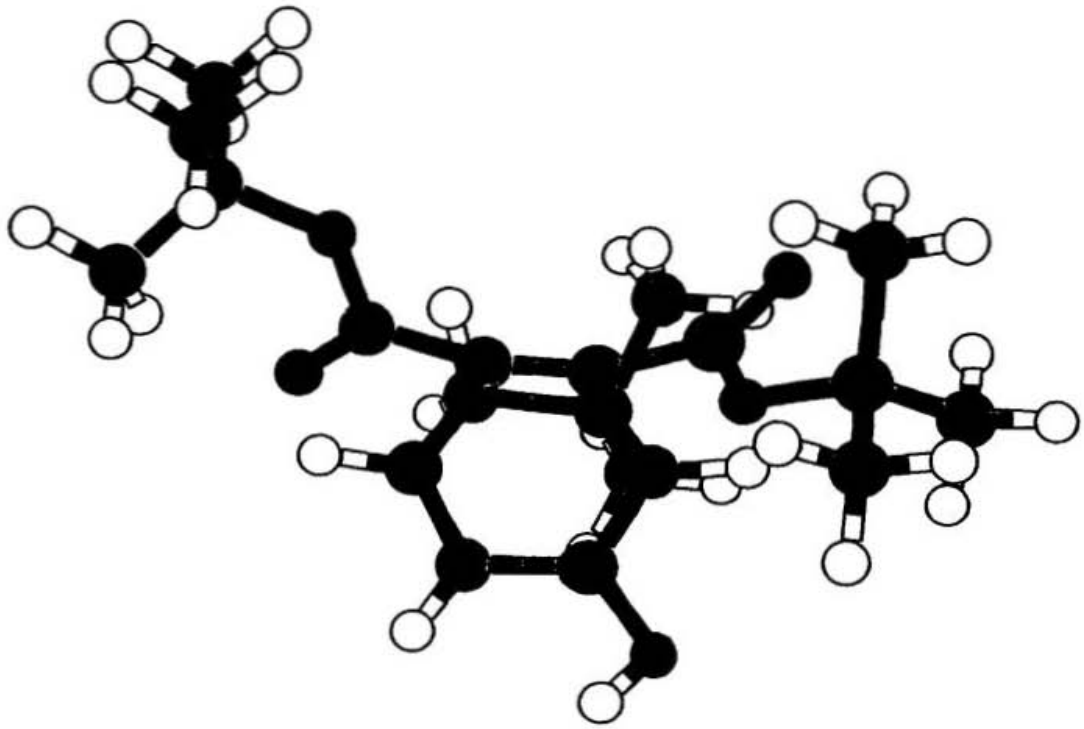


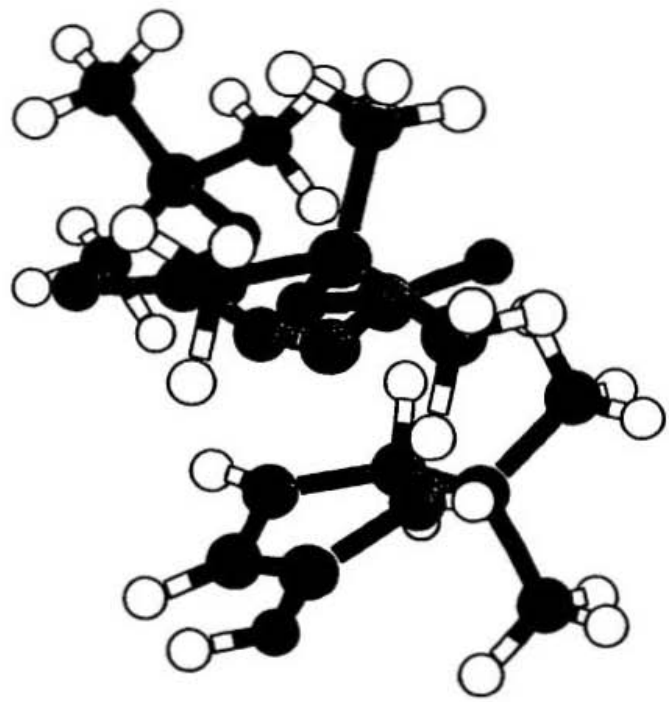
Transition Structure **59c**



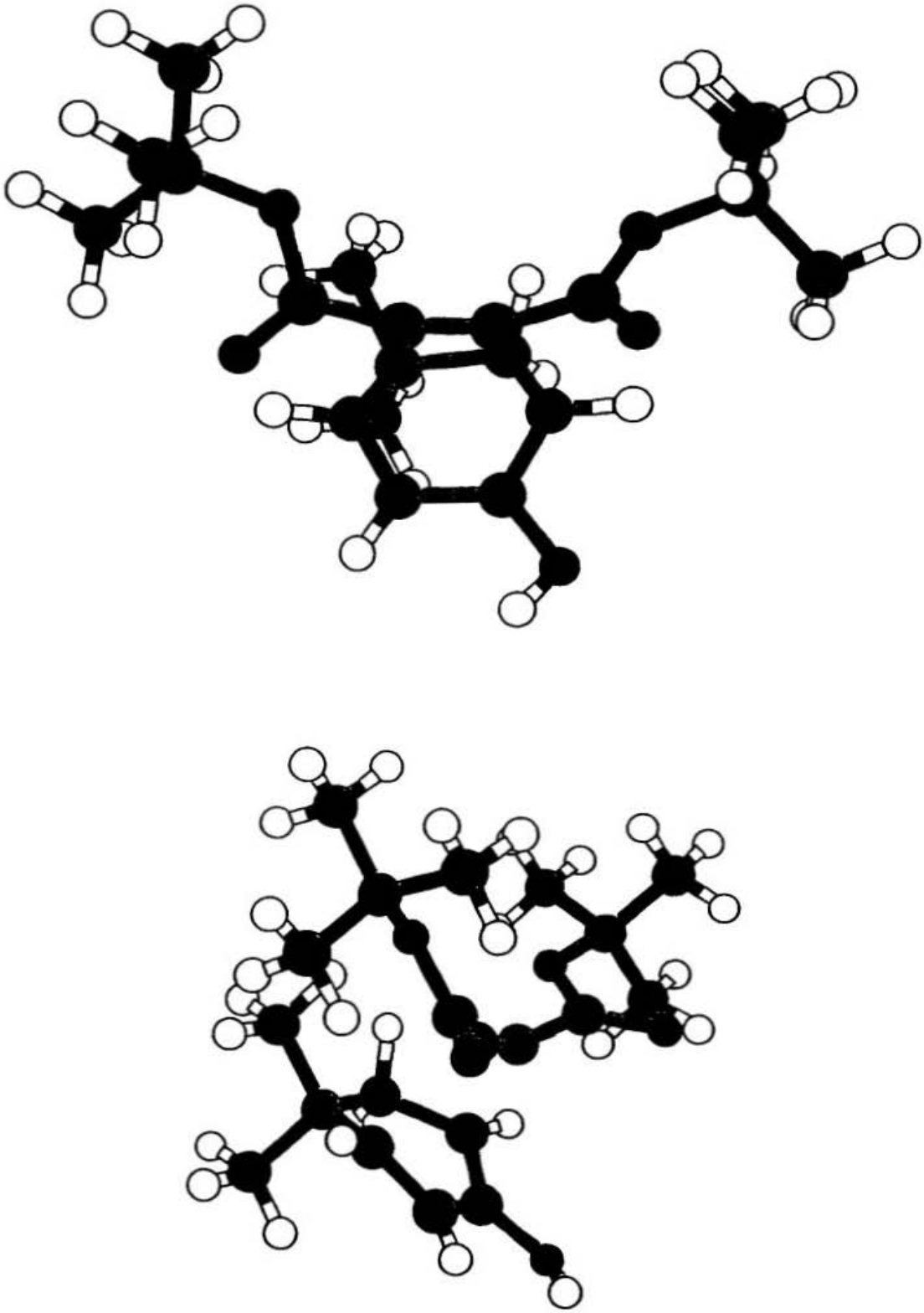


Transition Structure **59d**

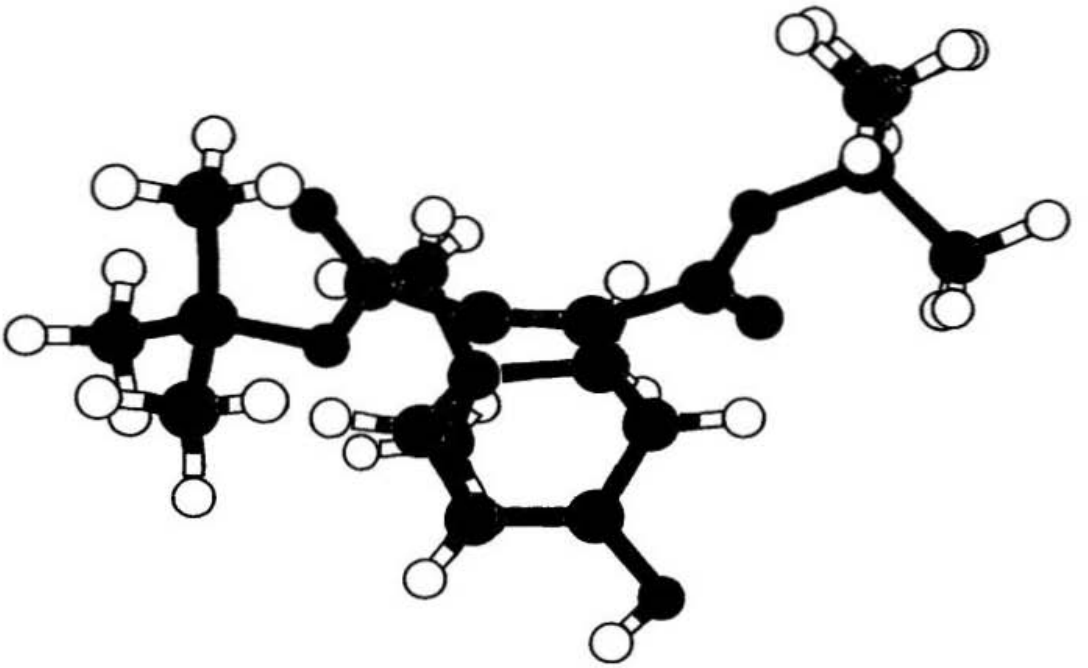


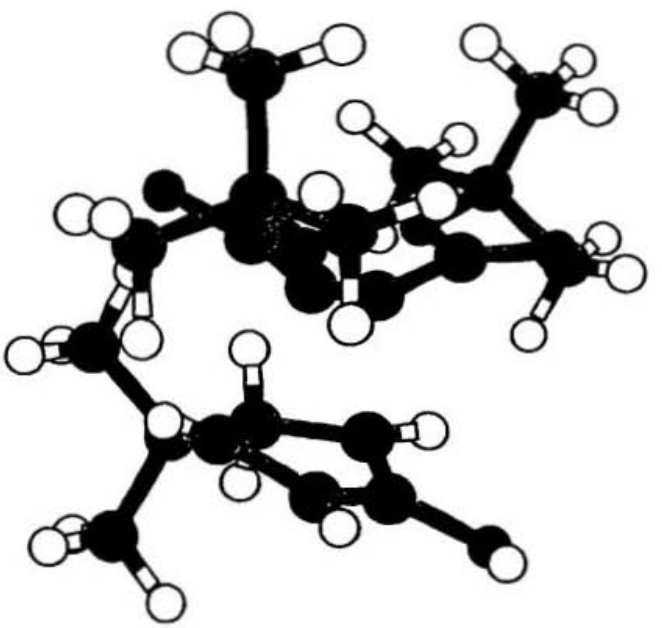


Transition Structure **60a**

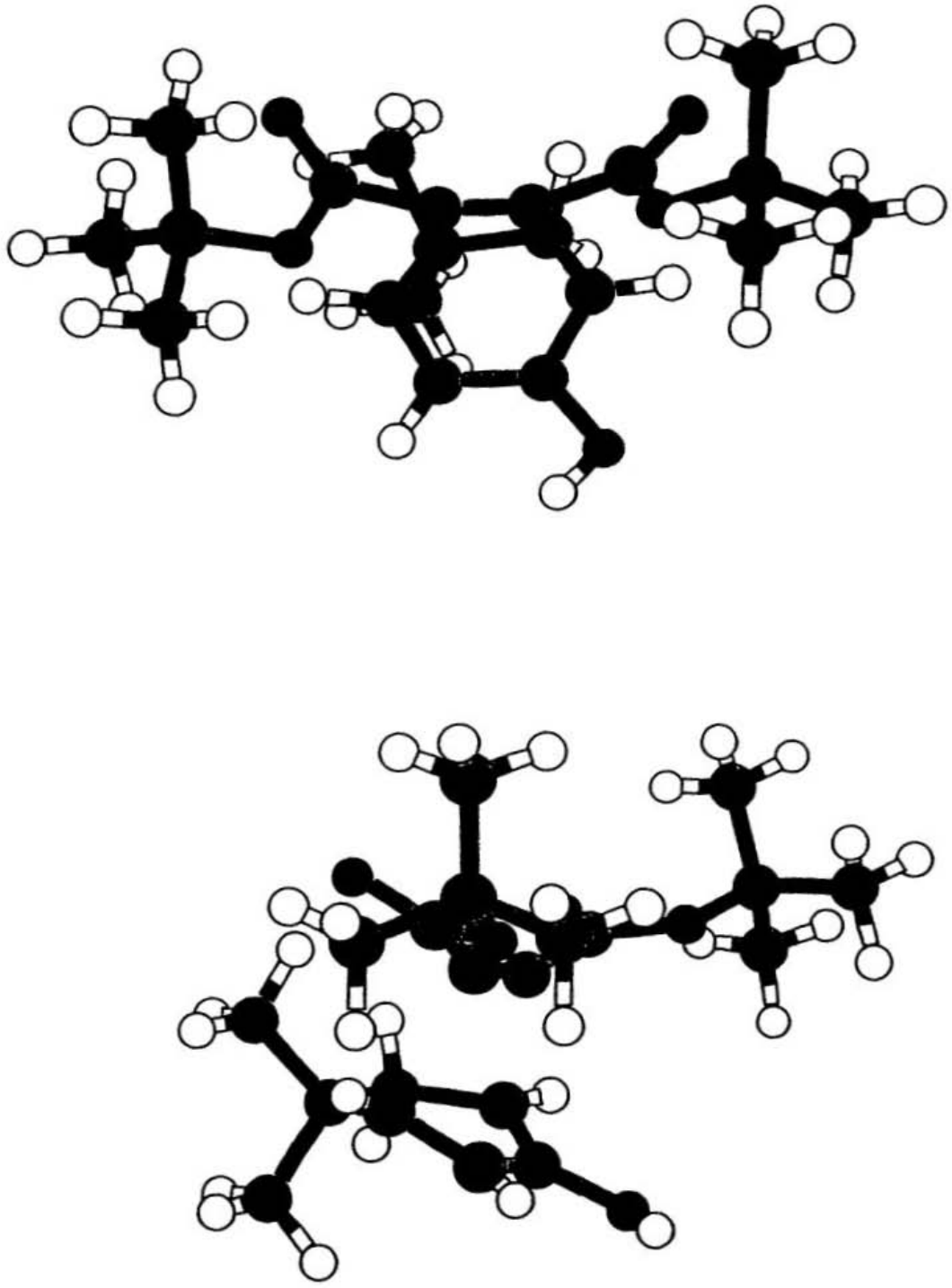


Transition Structure **60b**

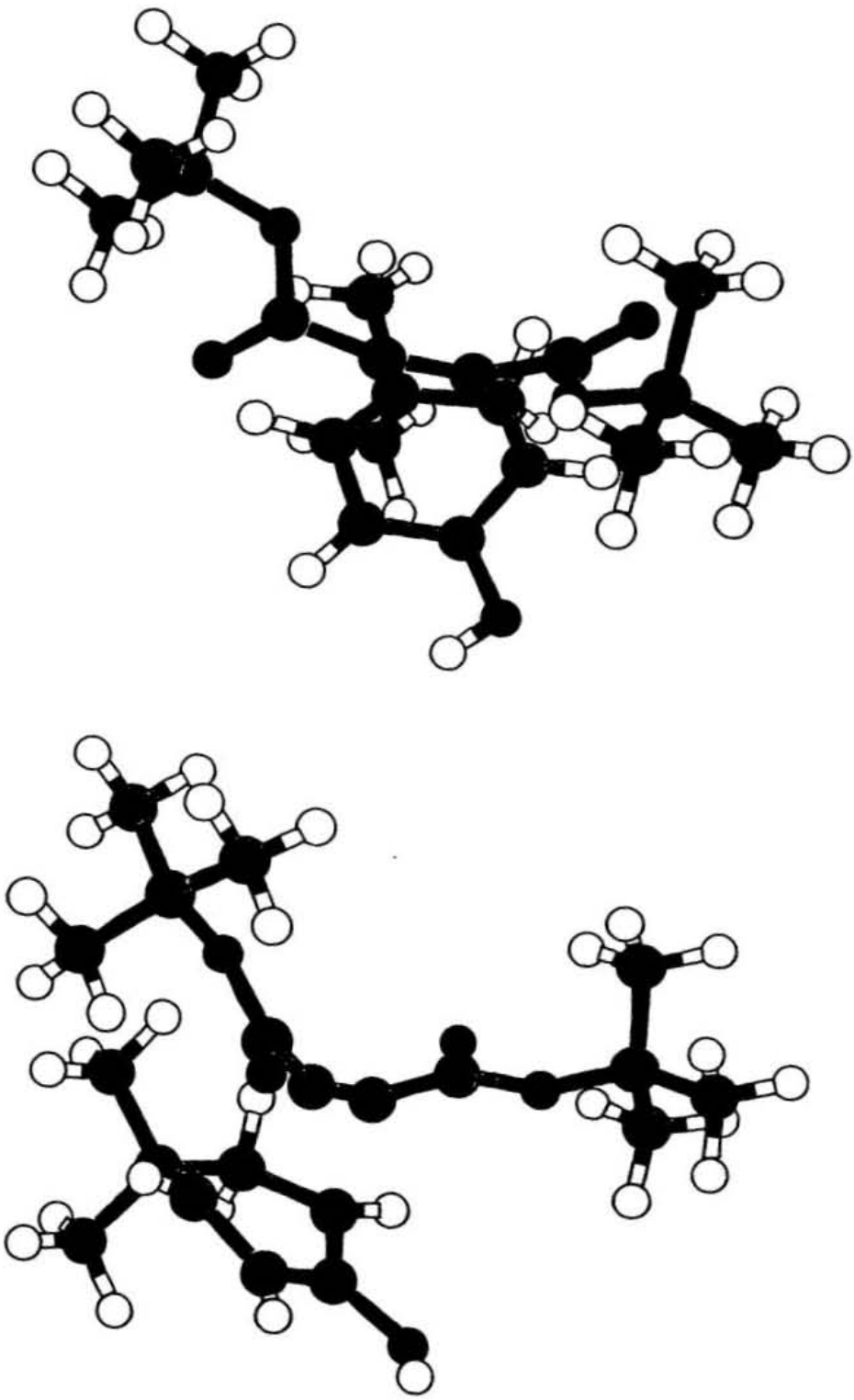




Transition Structure **60c**



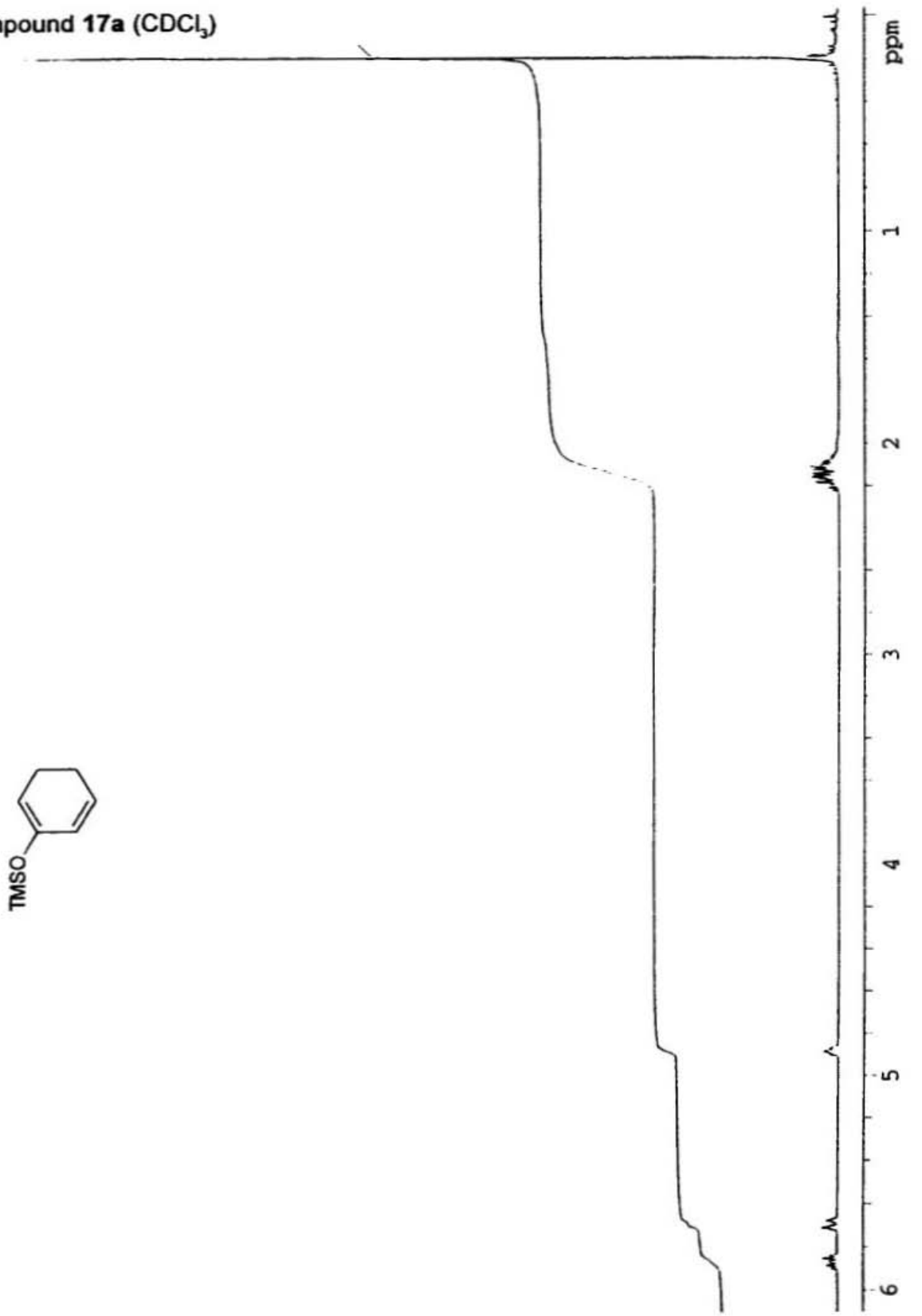
Transition Structure **60d**



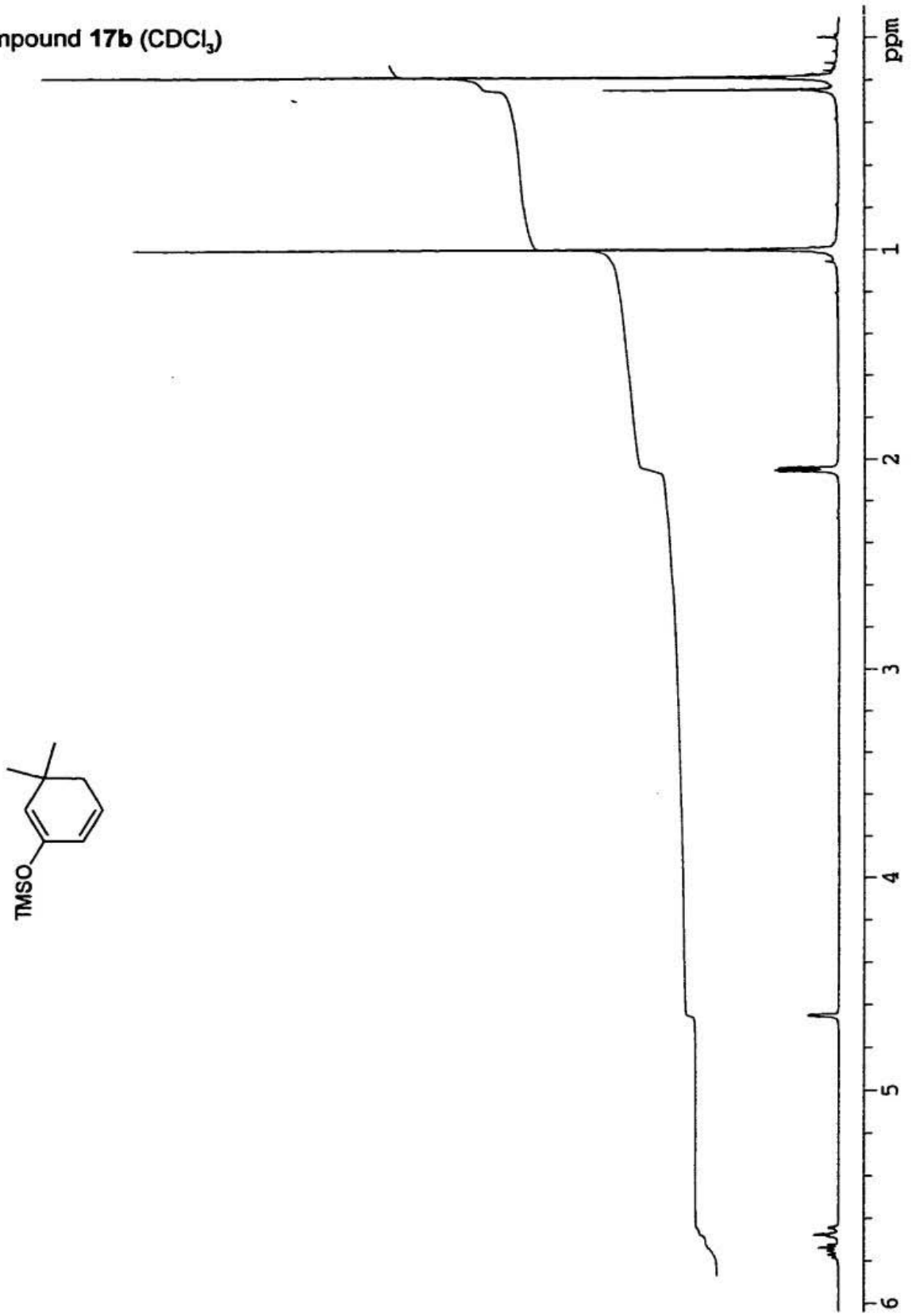
Appendix B

The selected ^{1}H NMR spectra of the synthetic samples were arranged according to the order in which they appear in the text. For the instrument employed, see **General Methods** in Part one.

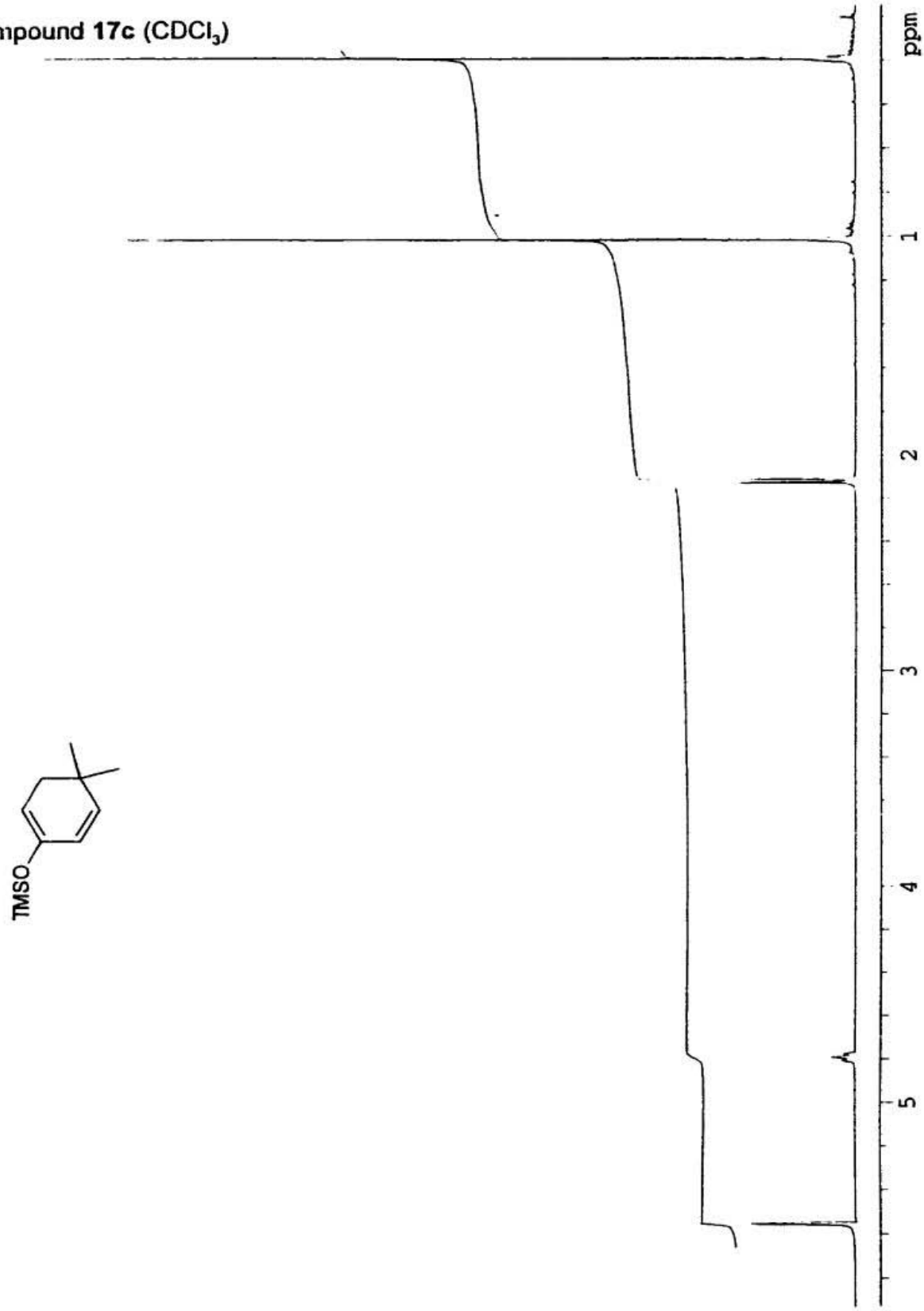
Compound **17a** ($CDCl_3$)



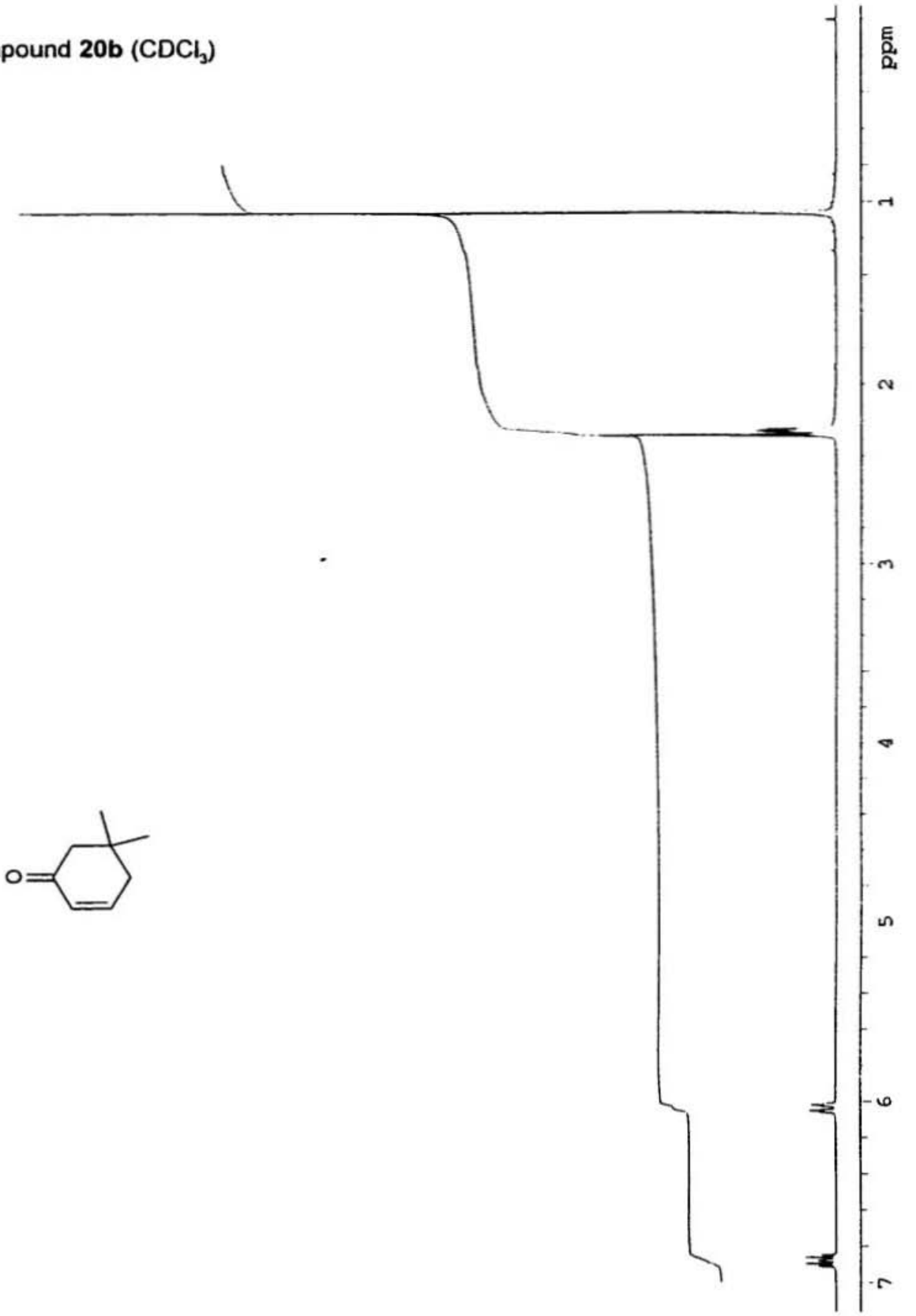
Compound **17b** ($CDCl_3$)



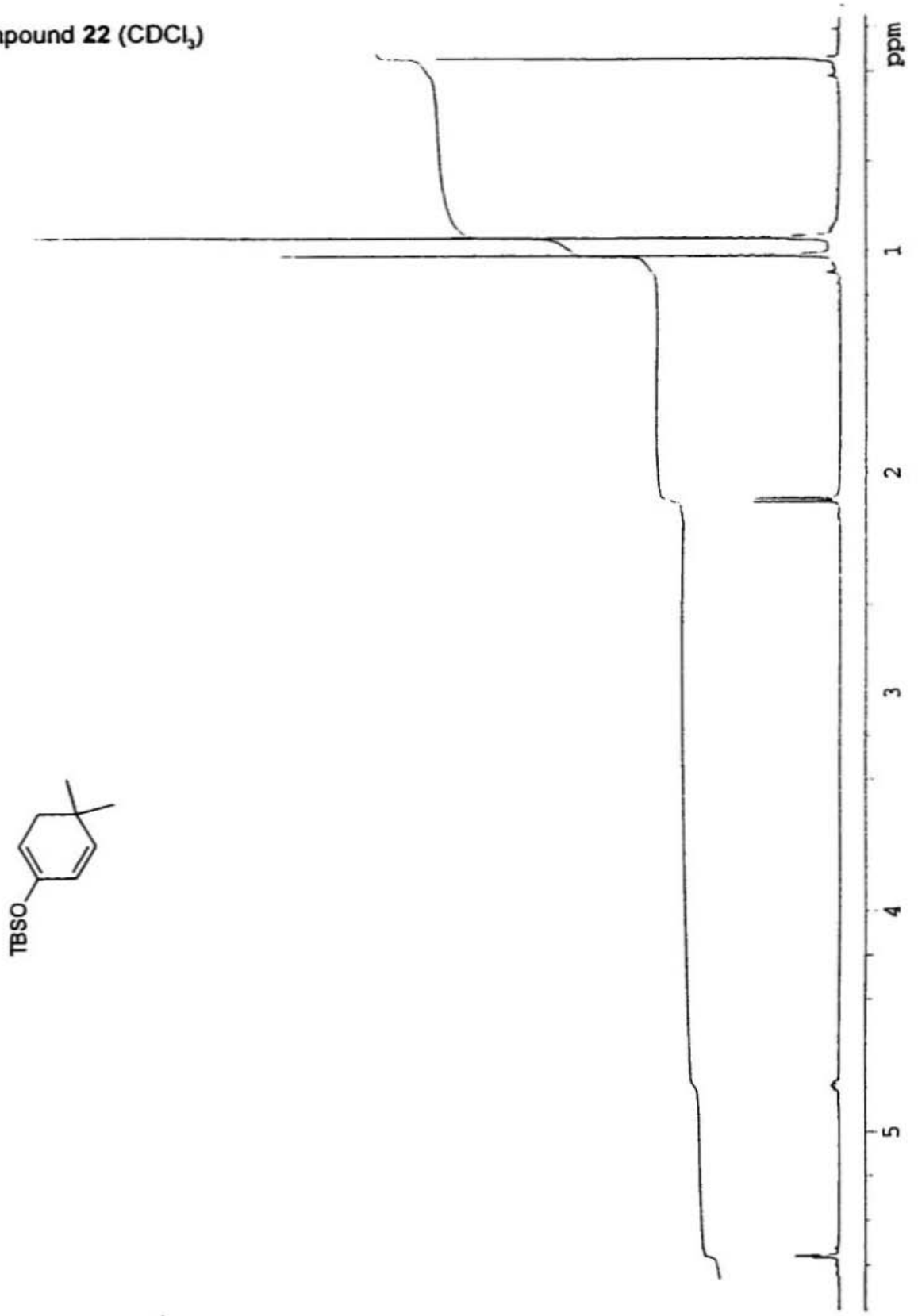
Compound **17c** ($CDCl_3$)



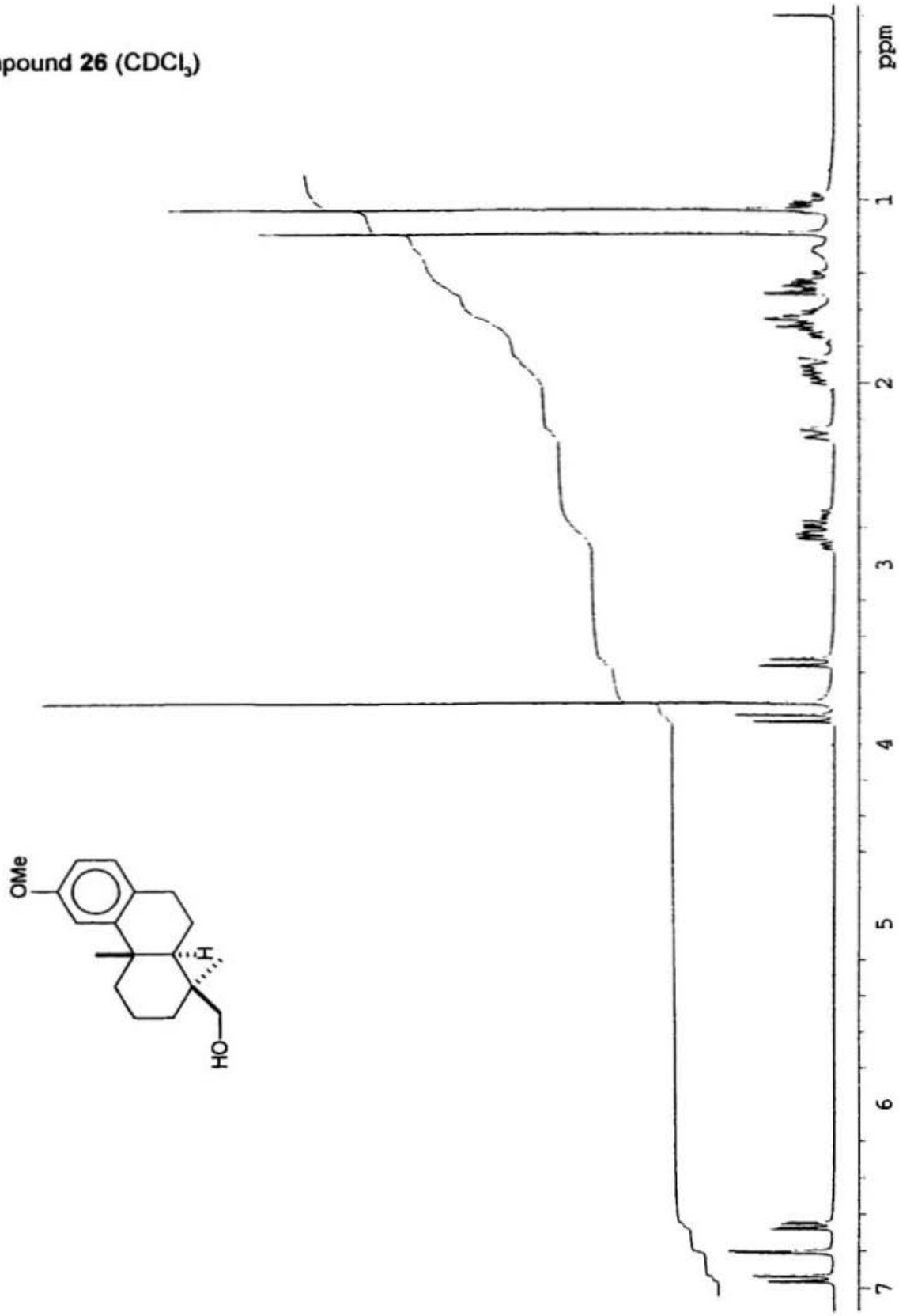
Compound **20b** ($CDCl_3$)



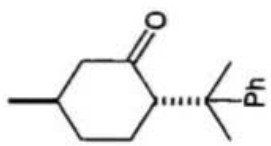
Compound **22** ($CDCl_3$)

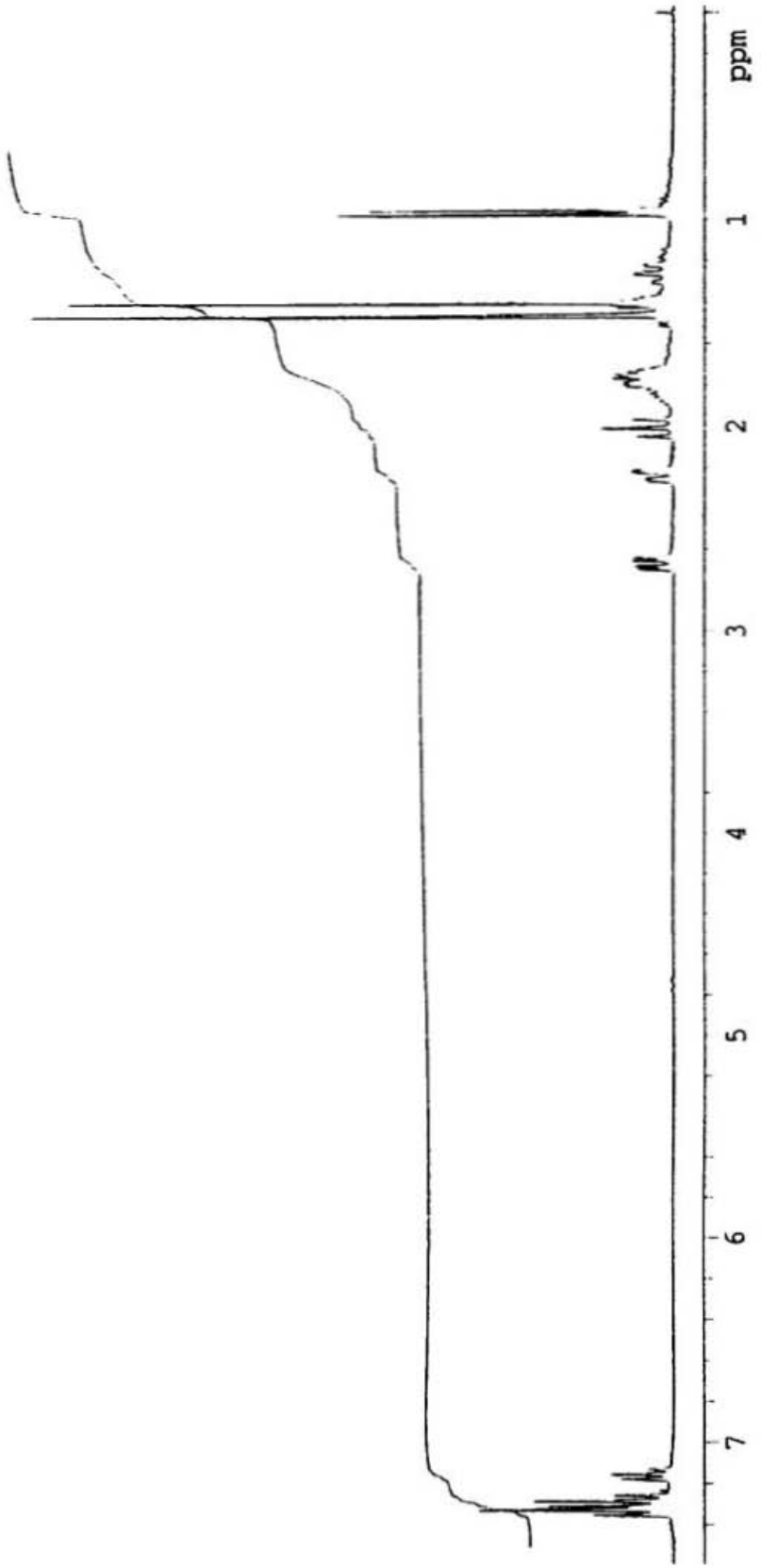


Compound **26** ($CDCl_3$)

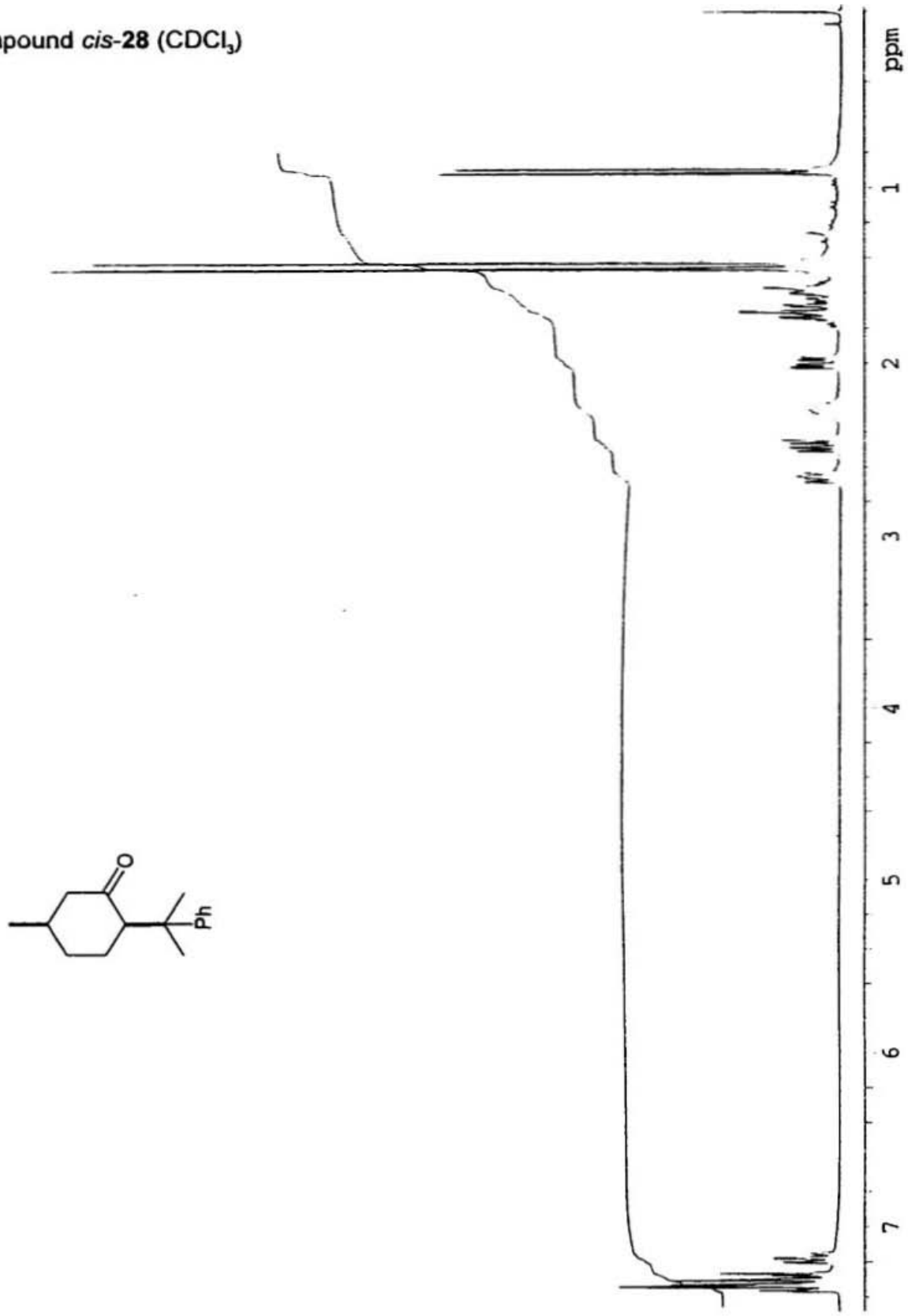


Compound *trans*-**28** ($CDCl_3$)

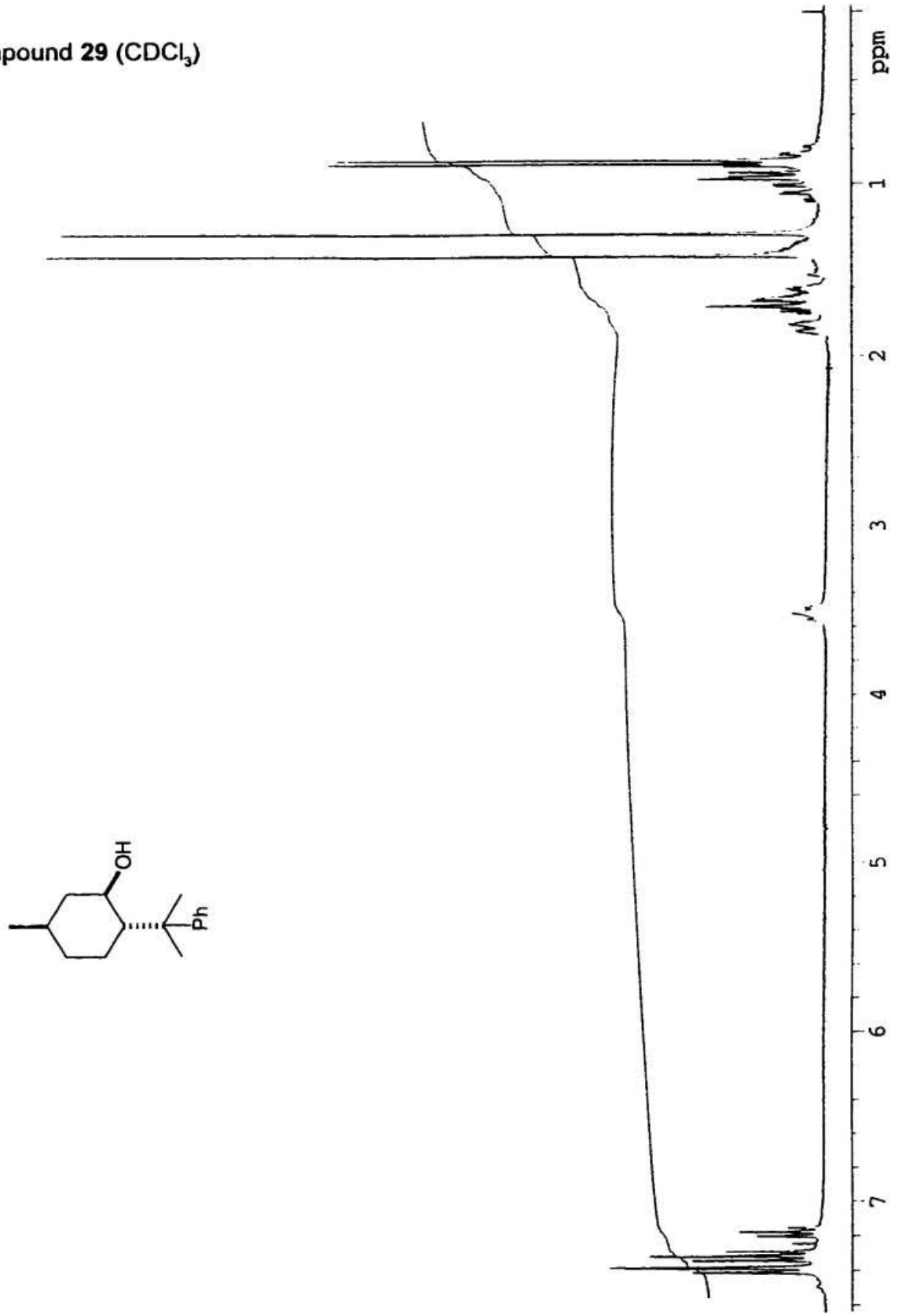




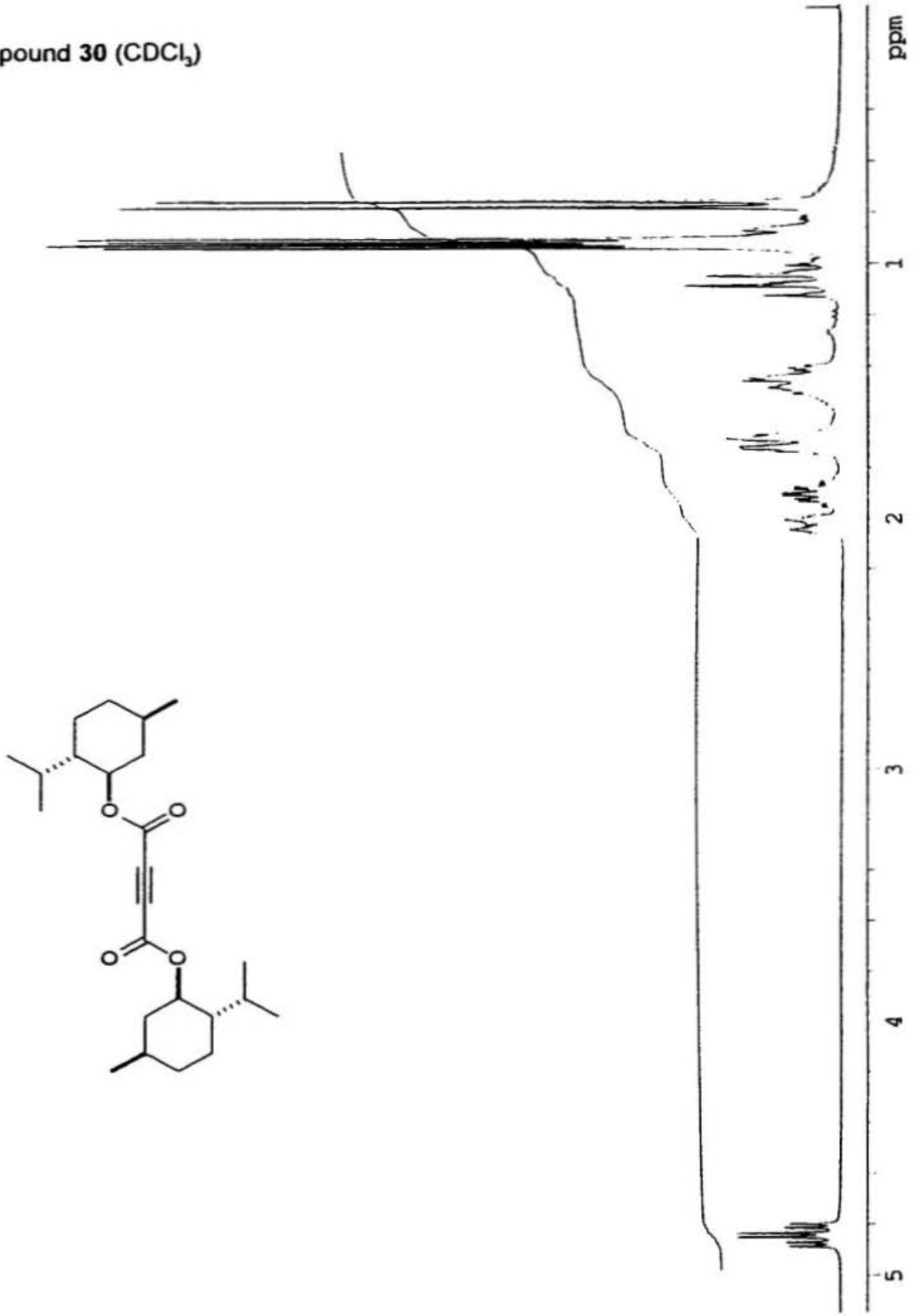
Compound *cis*-**28** ($CDCl_3$)



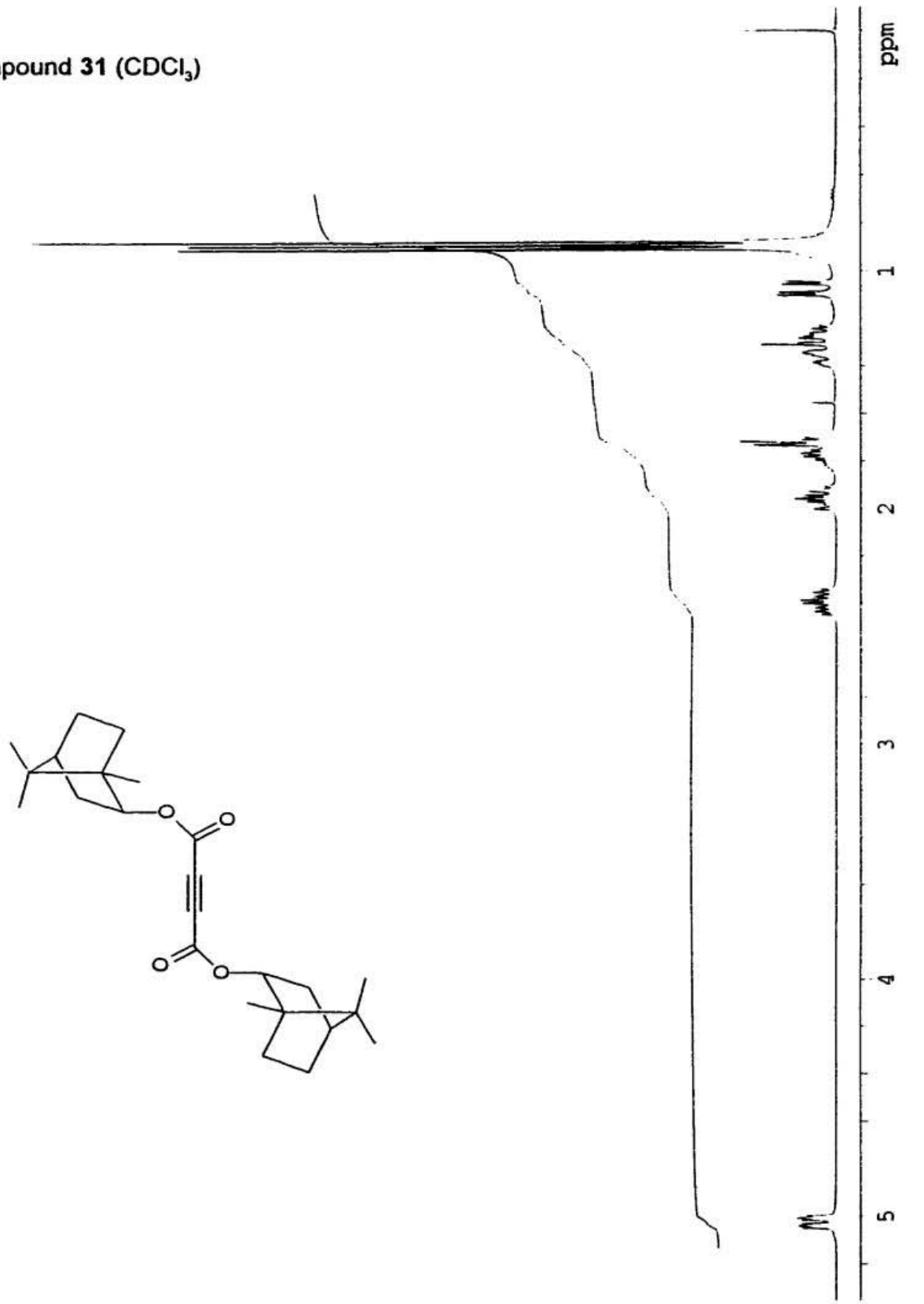
Compound **29** ($CDCl_3$)



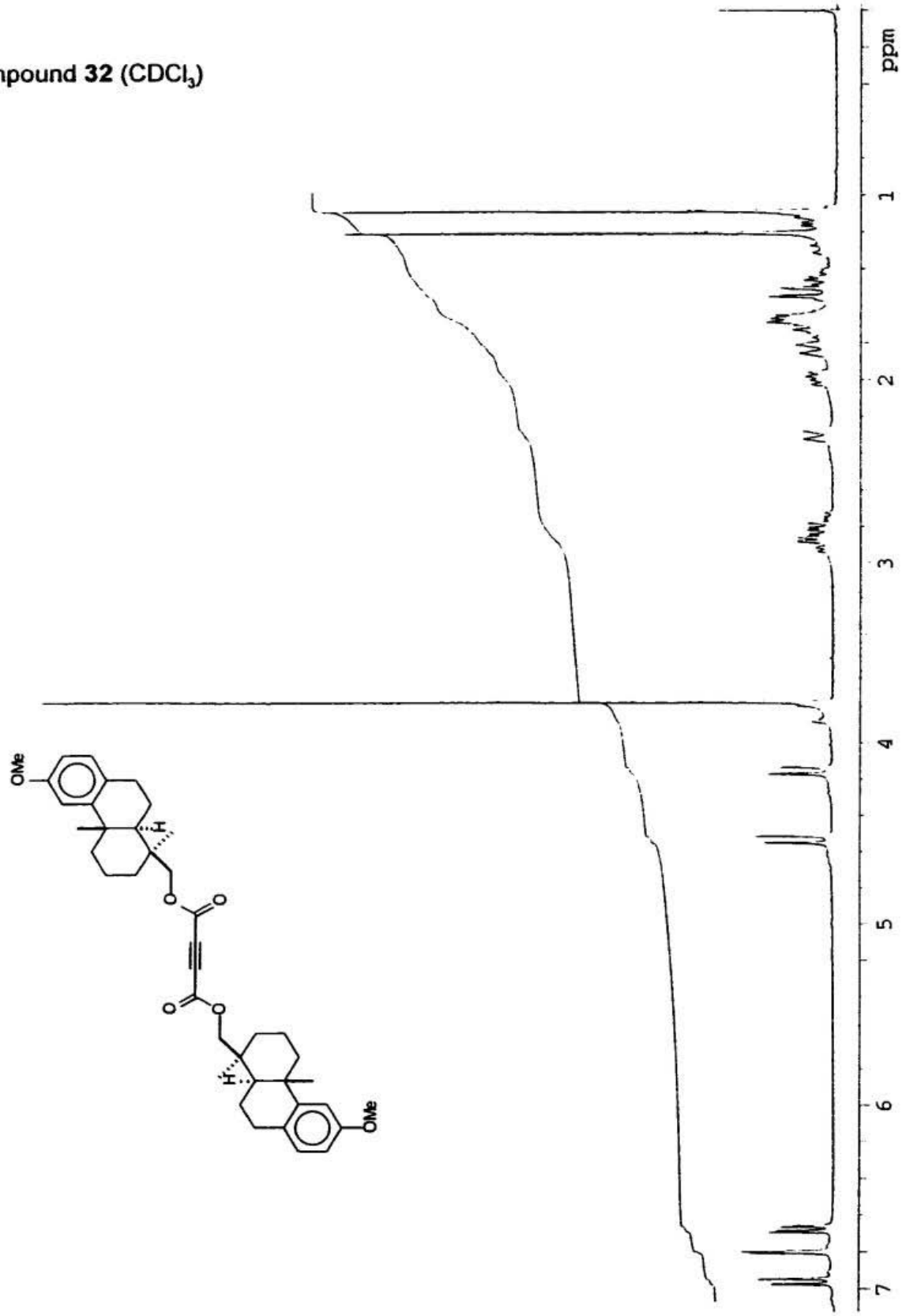
Compound **30** ($CDCl_3$)



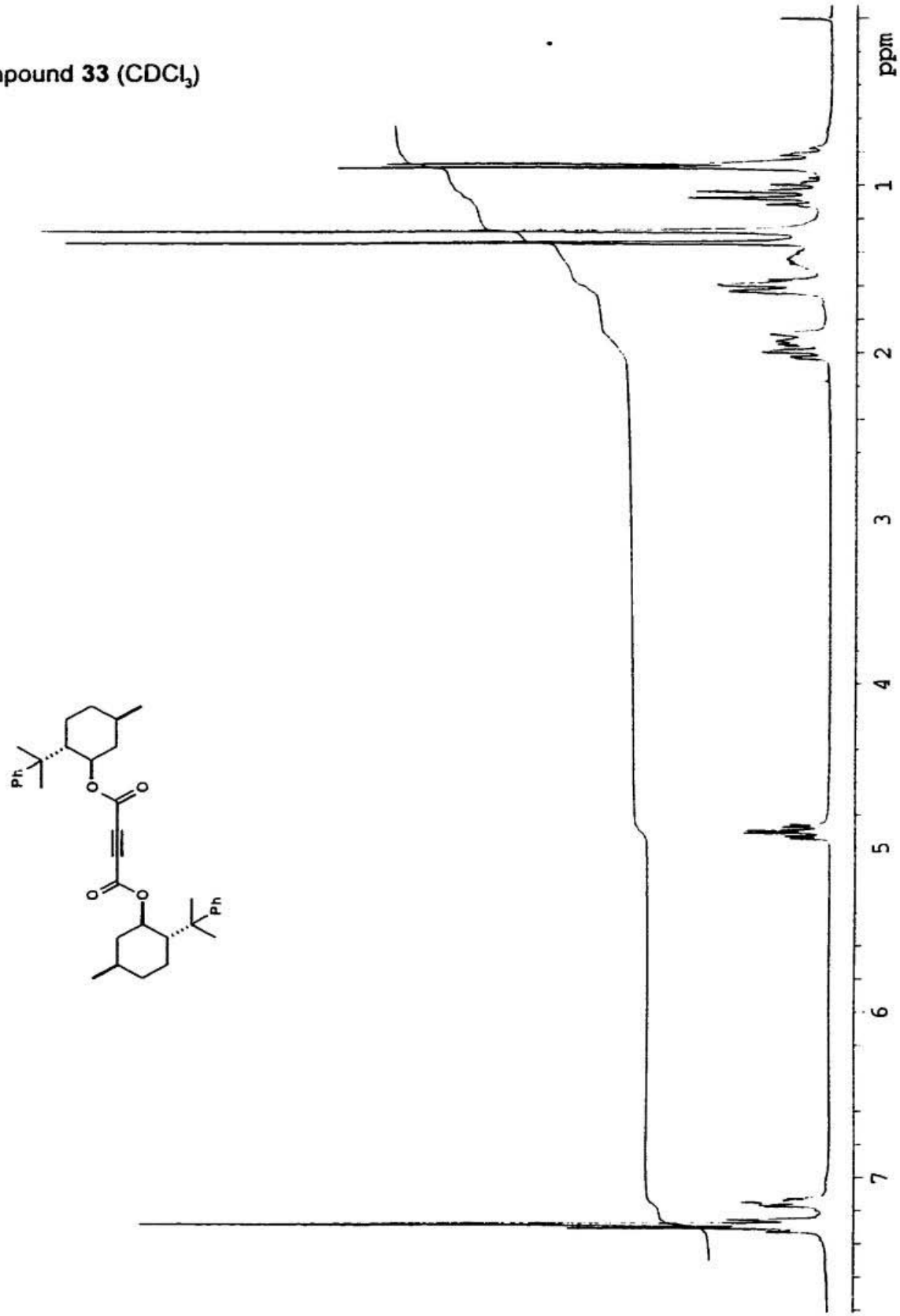
Compound **31** ($CDCl_3$)



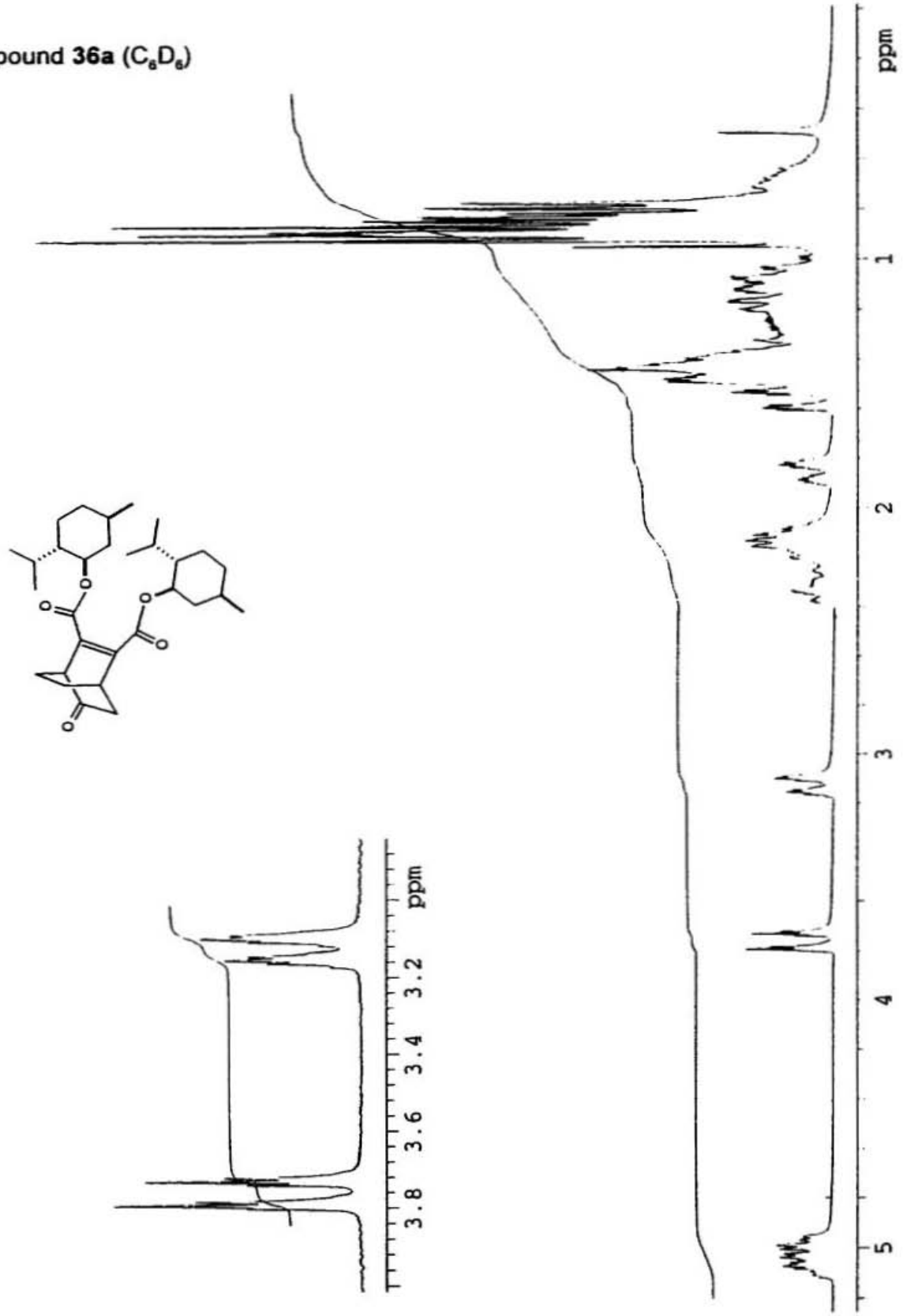
Compound **32** ($CDCl_3$)



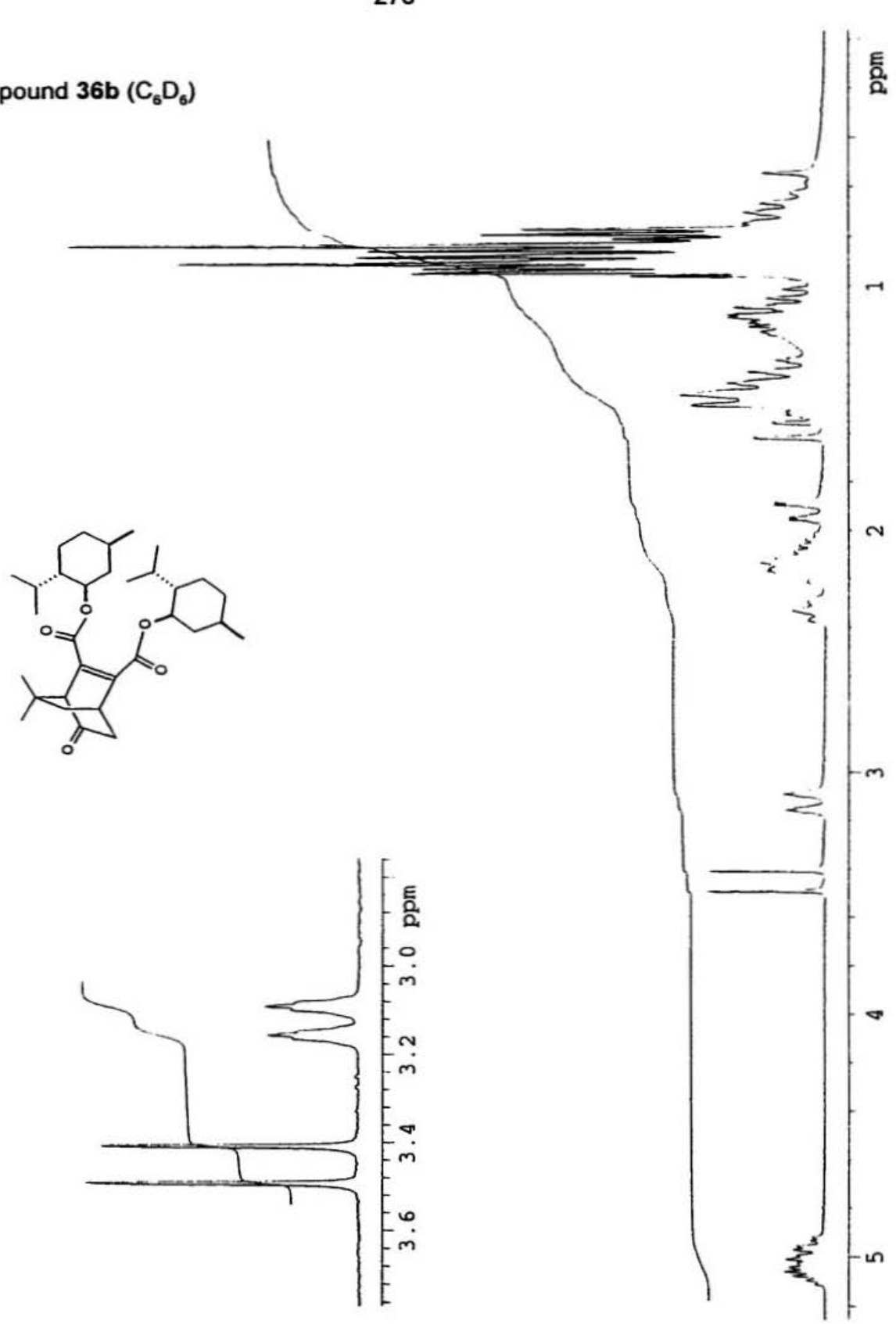
Compound **33** ($CDCl_3$)



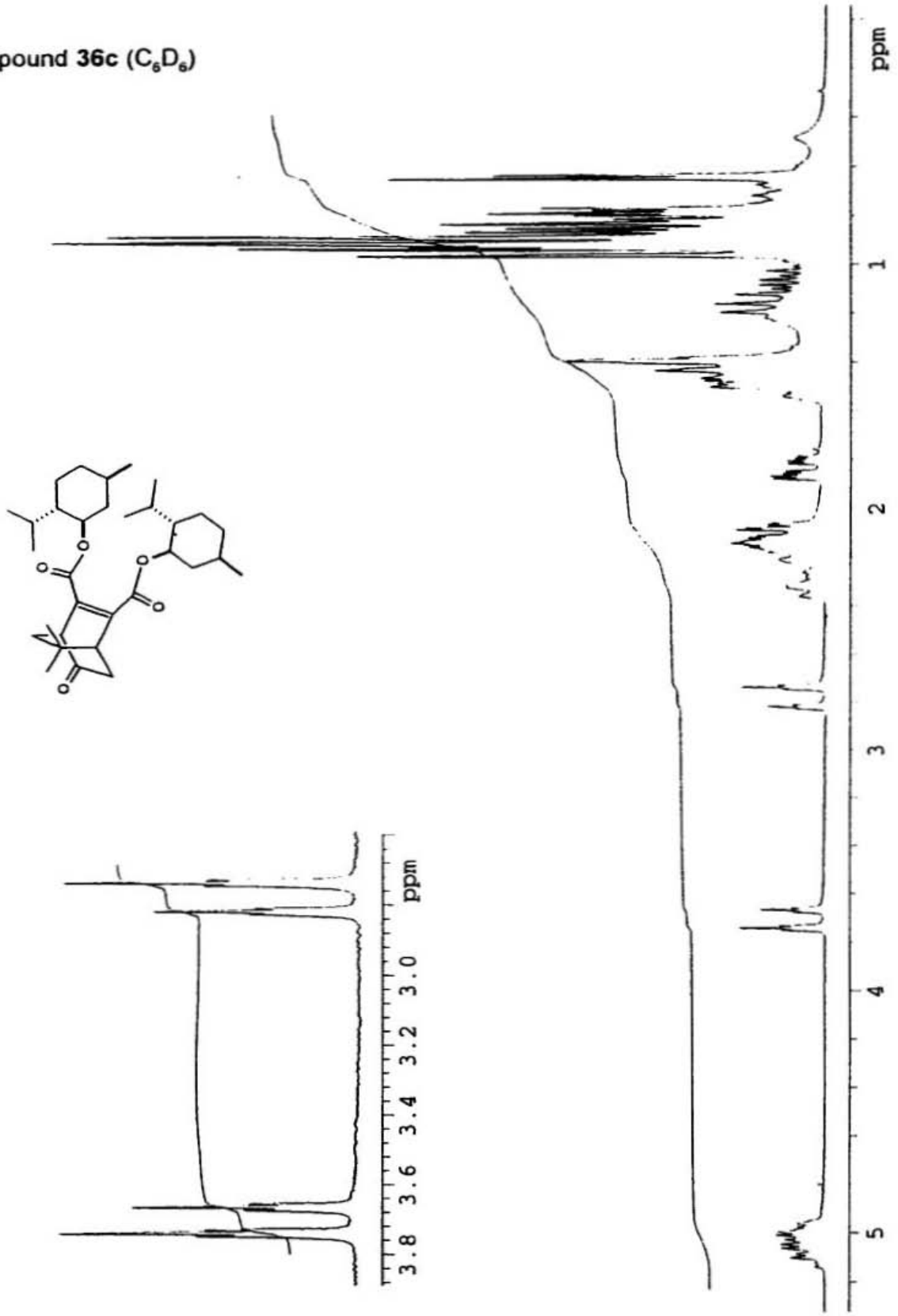
Compound **36a** (C_6D_6)



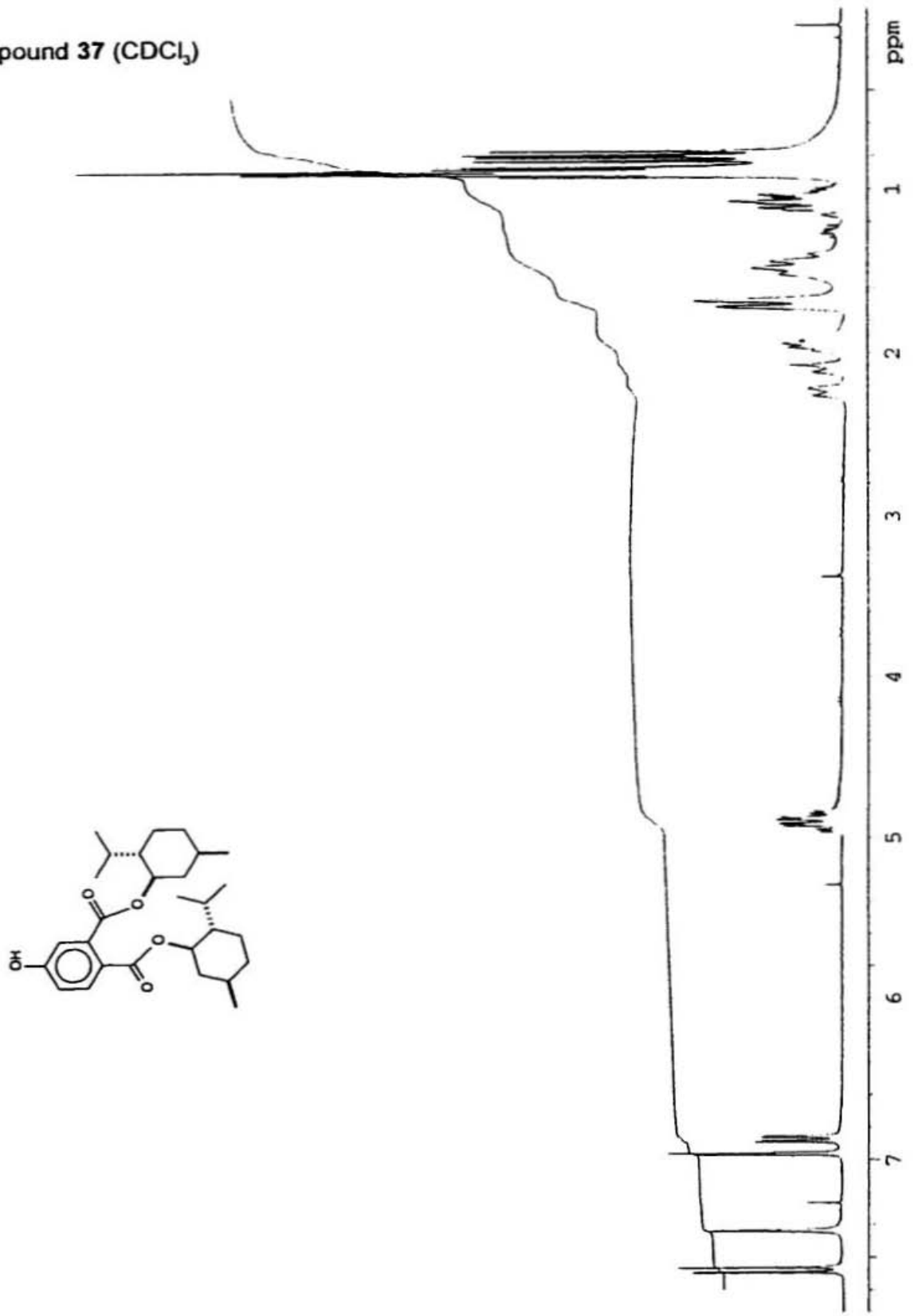
Compound **36b** (C_6D_6)



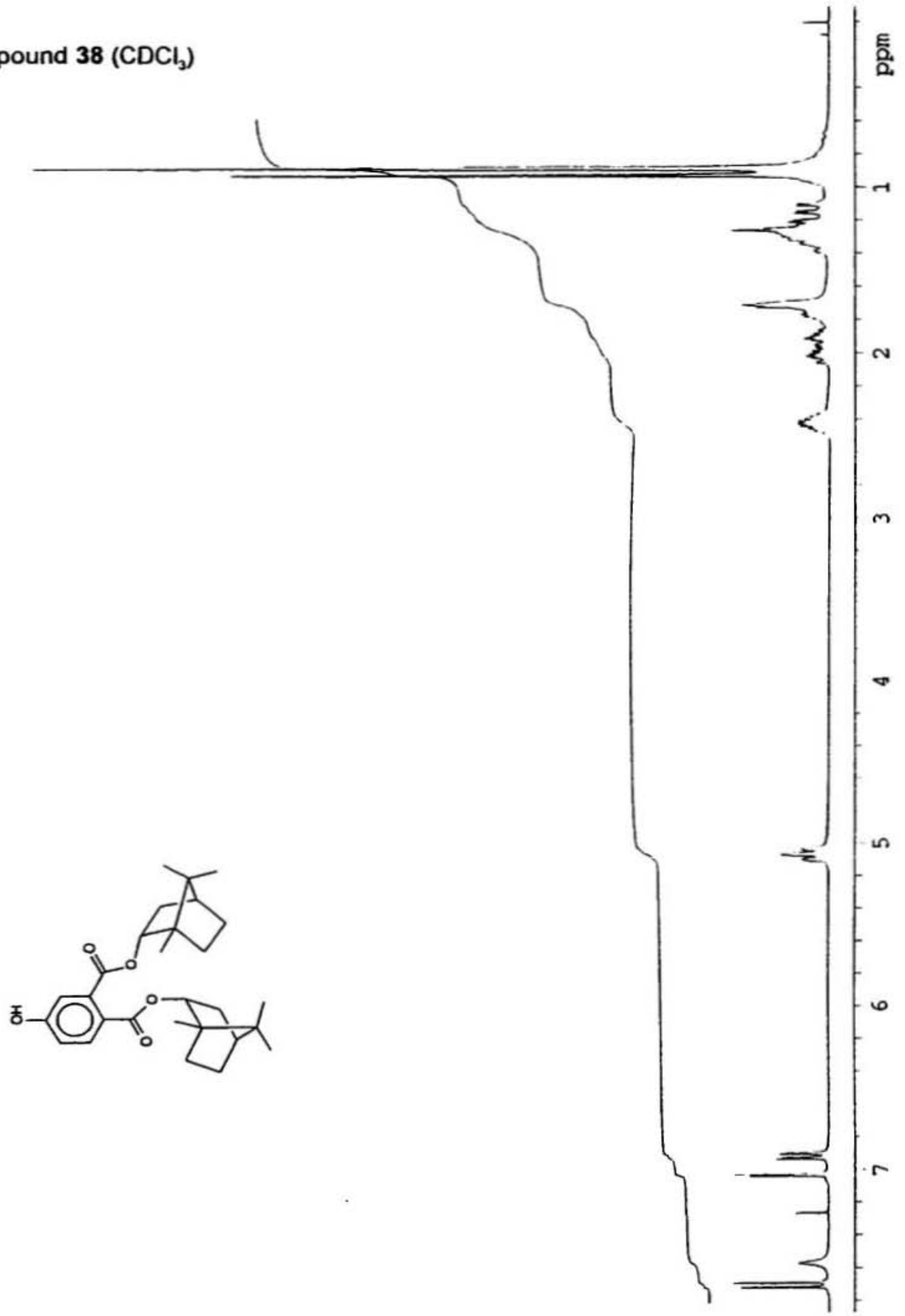
Compound **36c** (C_6D_6)



Compound **37** ($CDCl_3$)

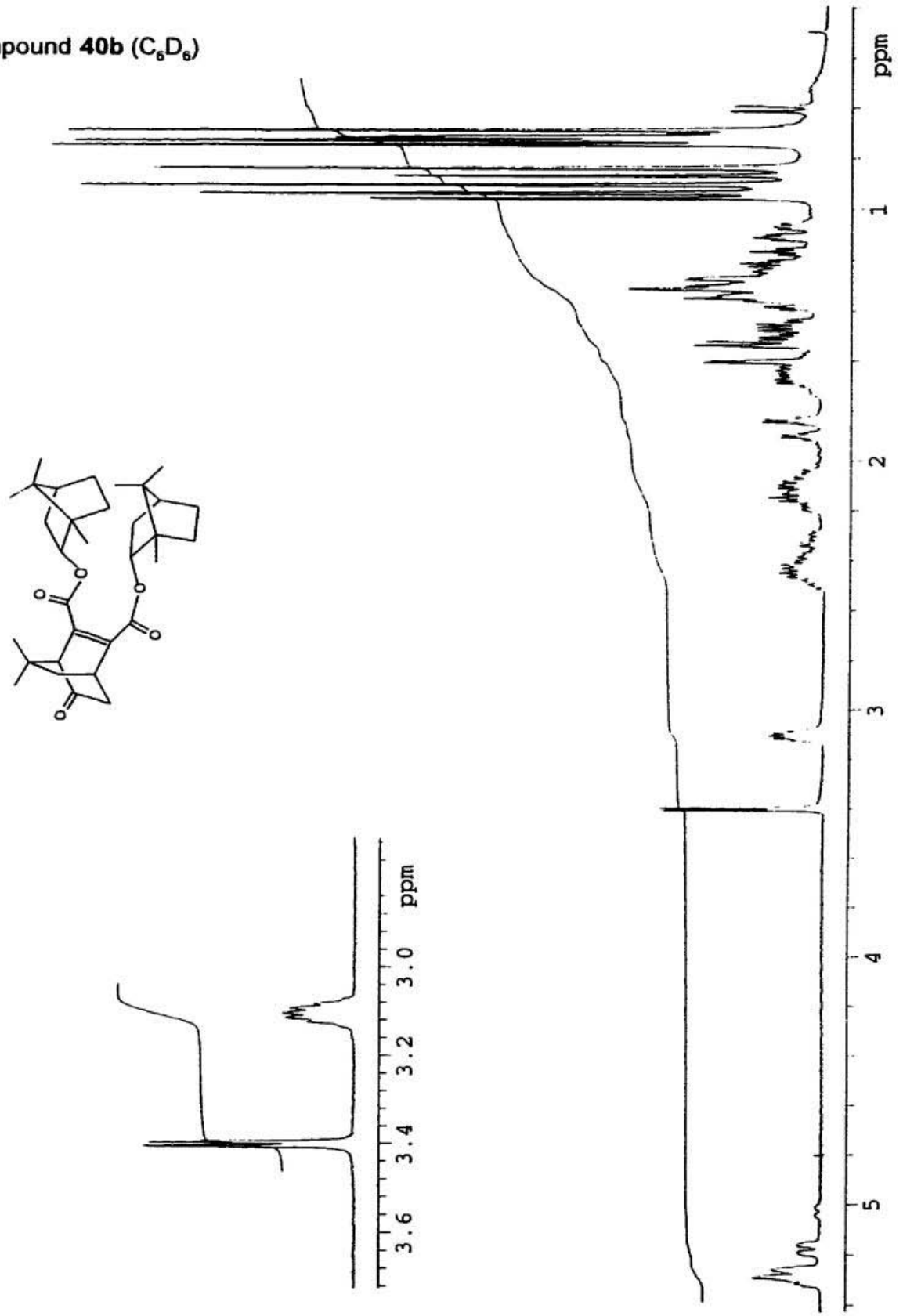


Compound **38** ($CDCl_3$)

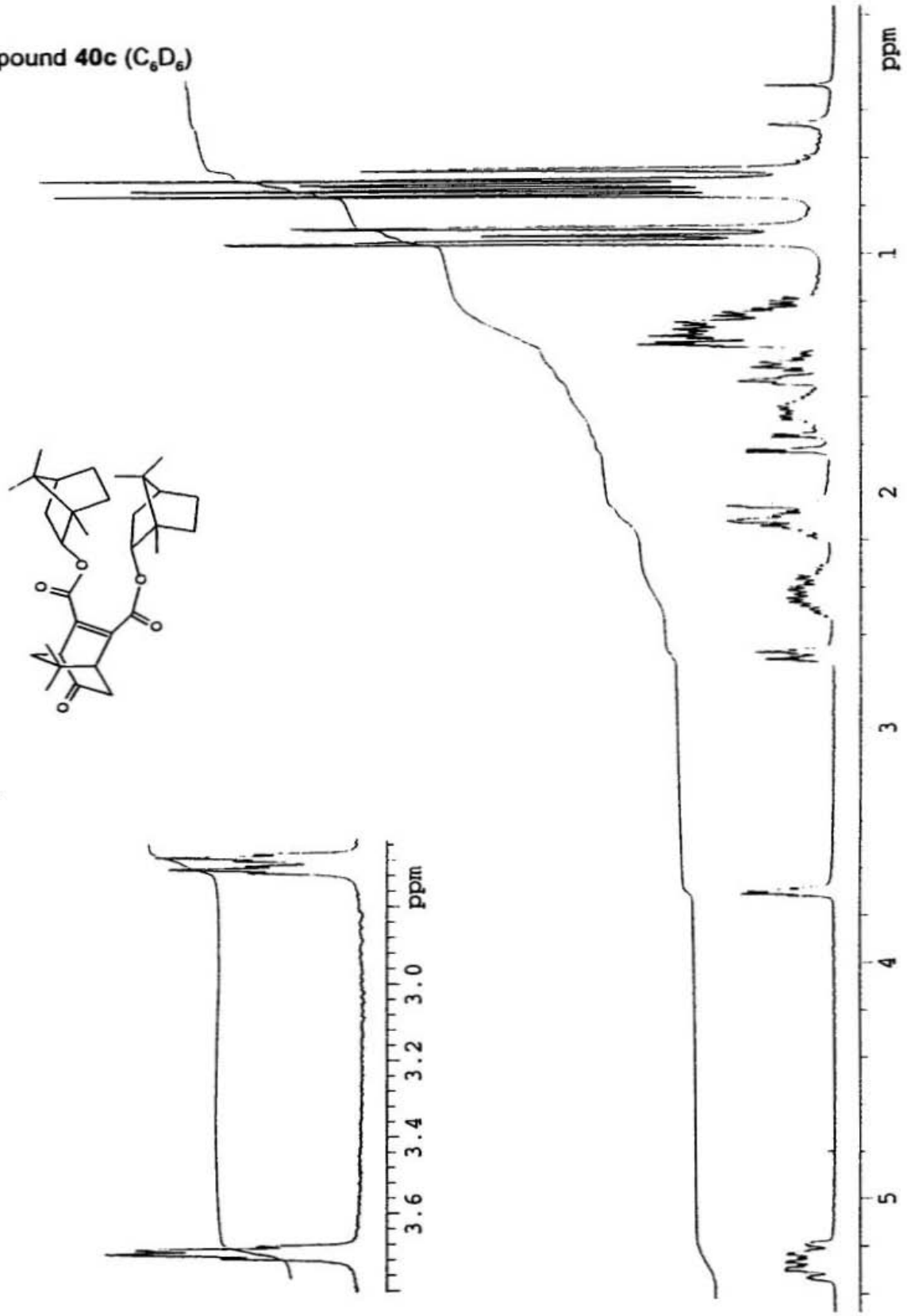


Compound **40a** (C_6D_6)

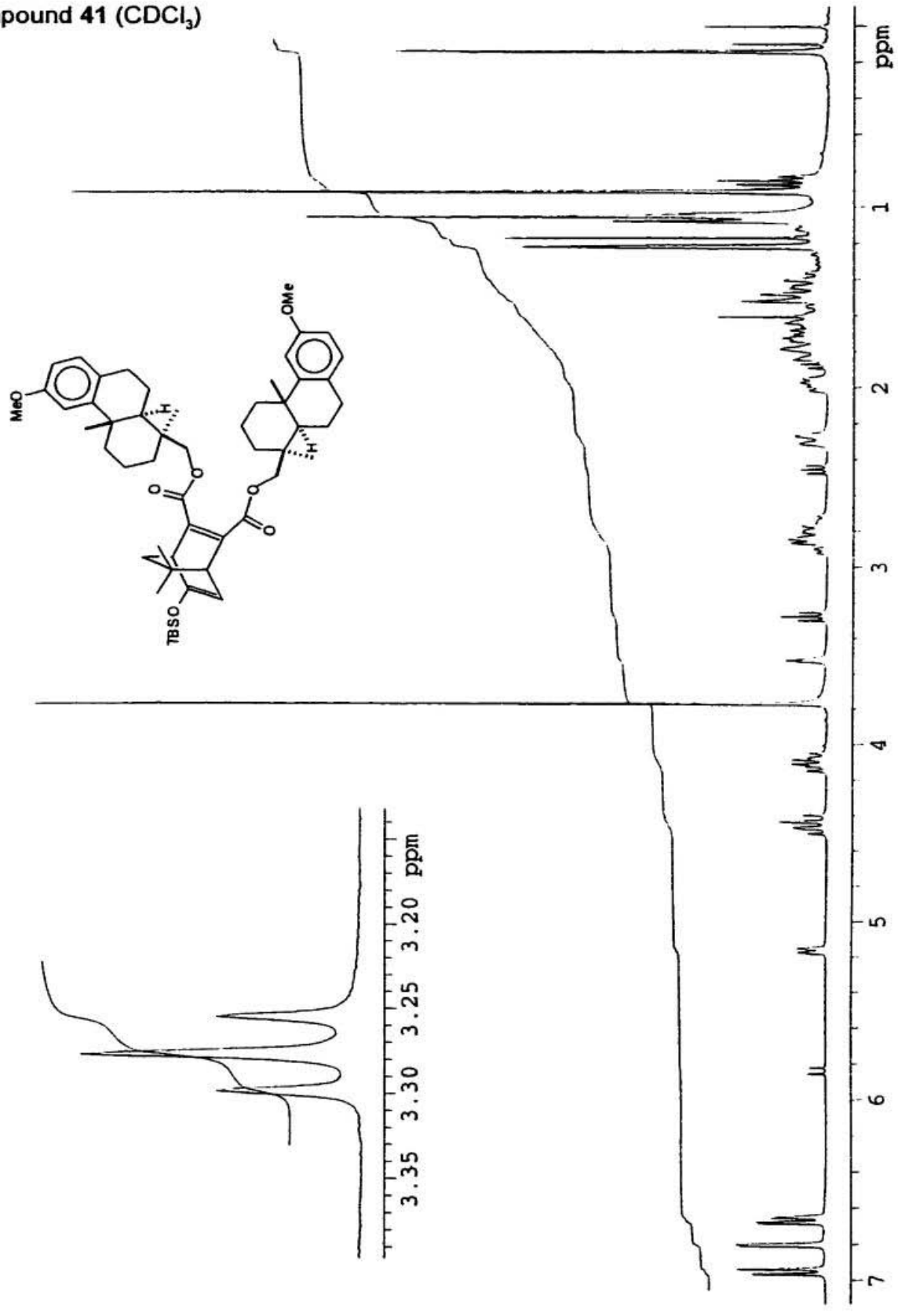
Compound **40b** (C_6D_6)



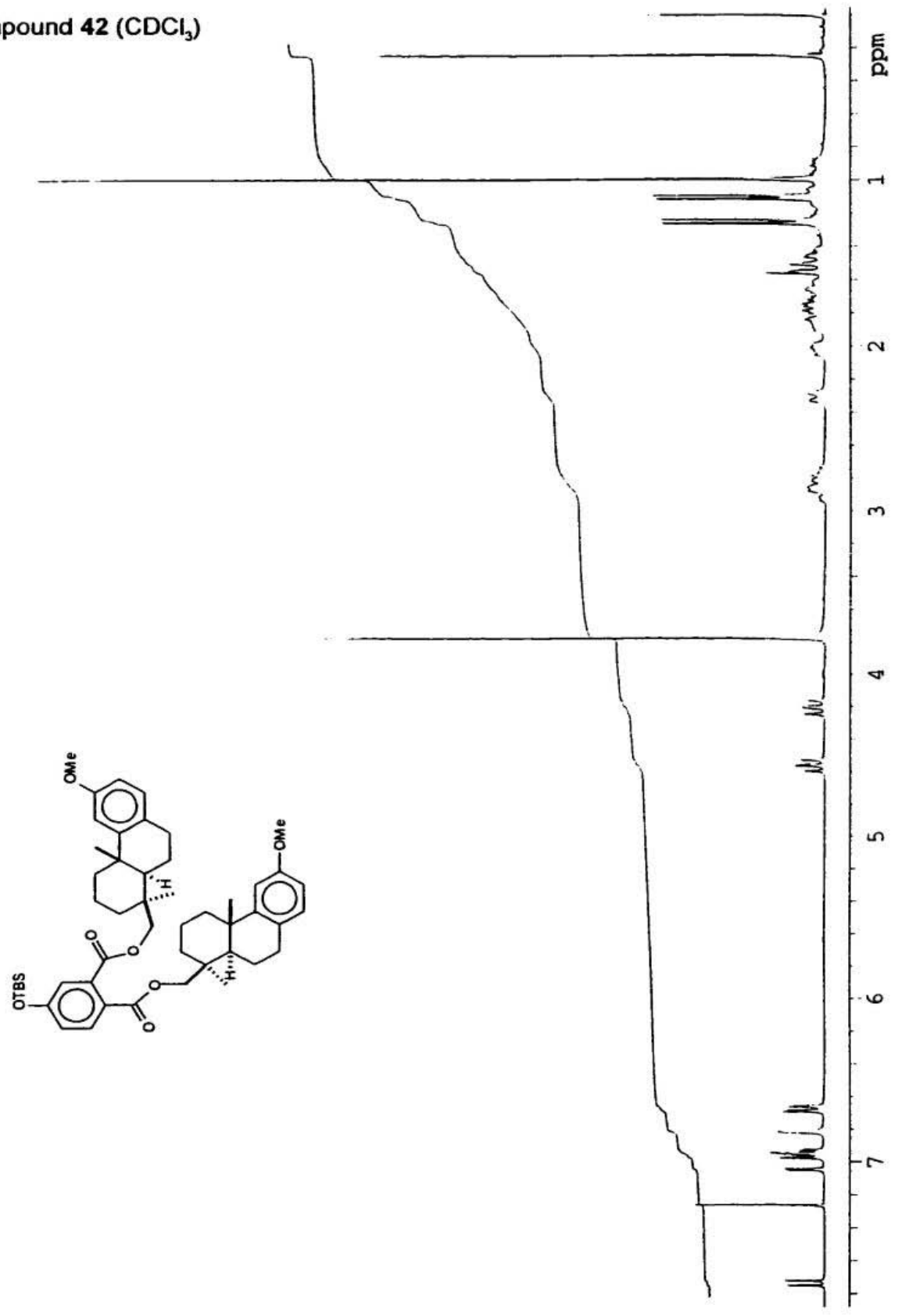
Compound **40c** (C_6D_6)



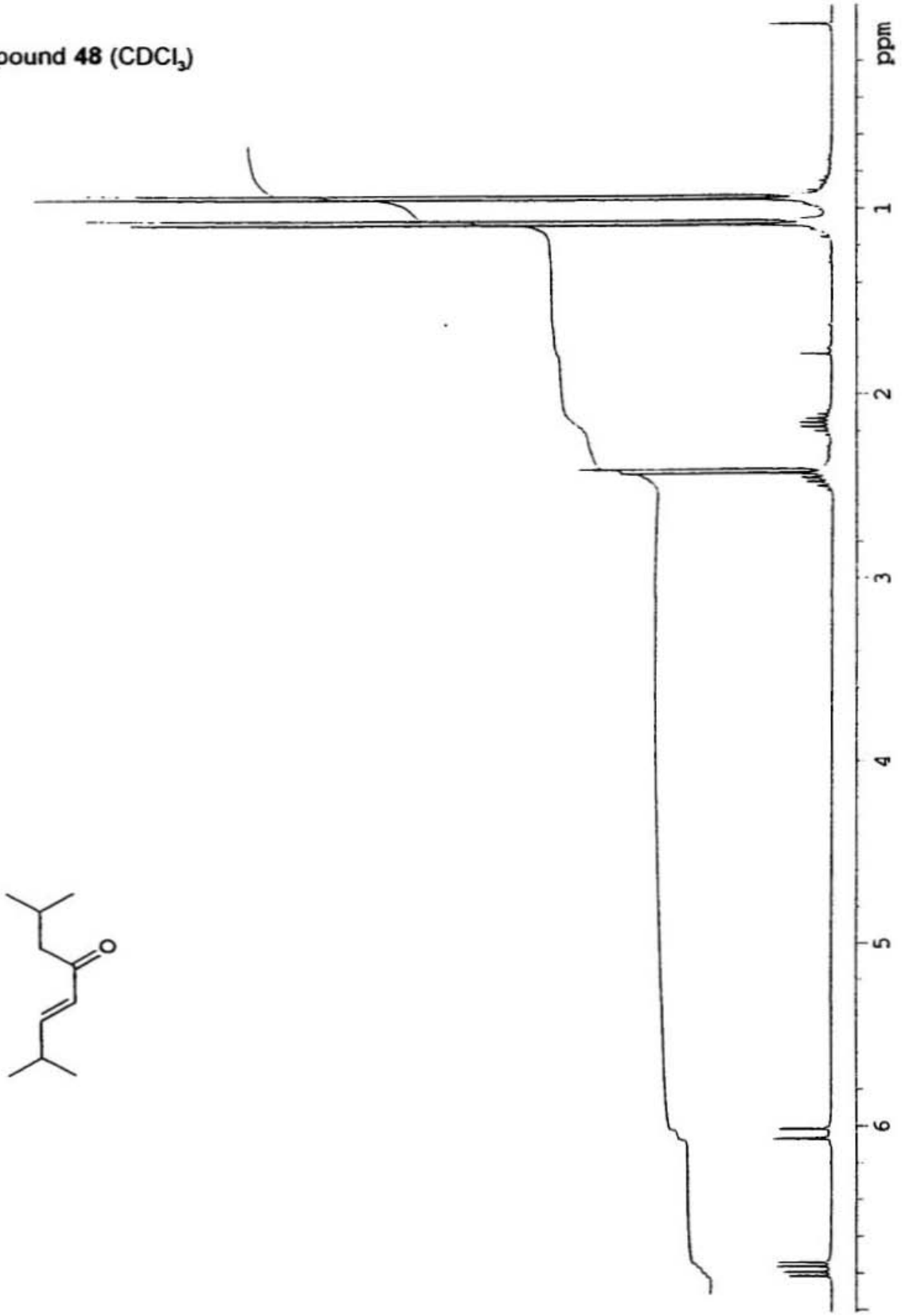
Compound **41** ($CDCl_3$)



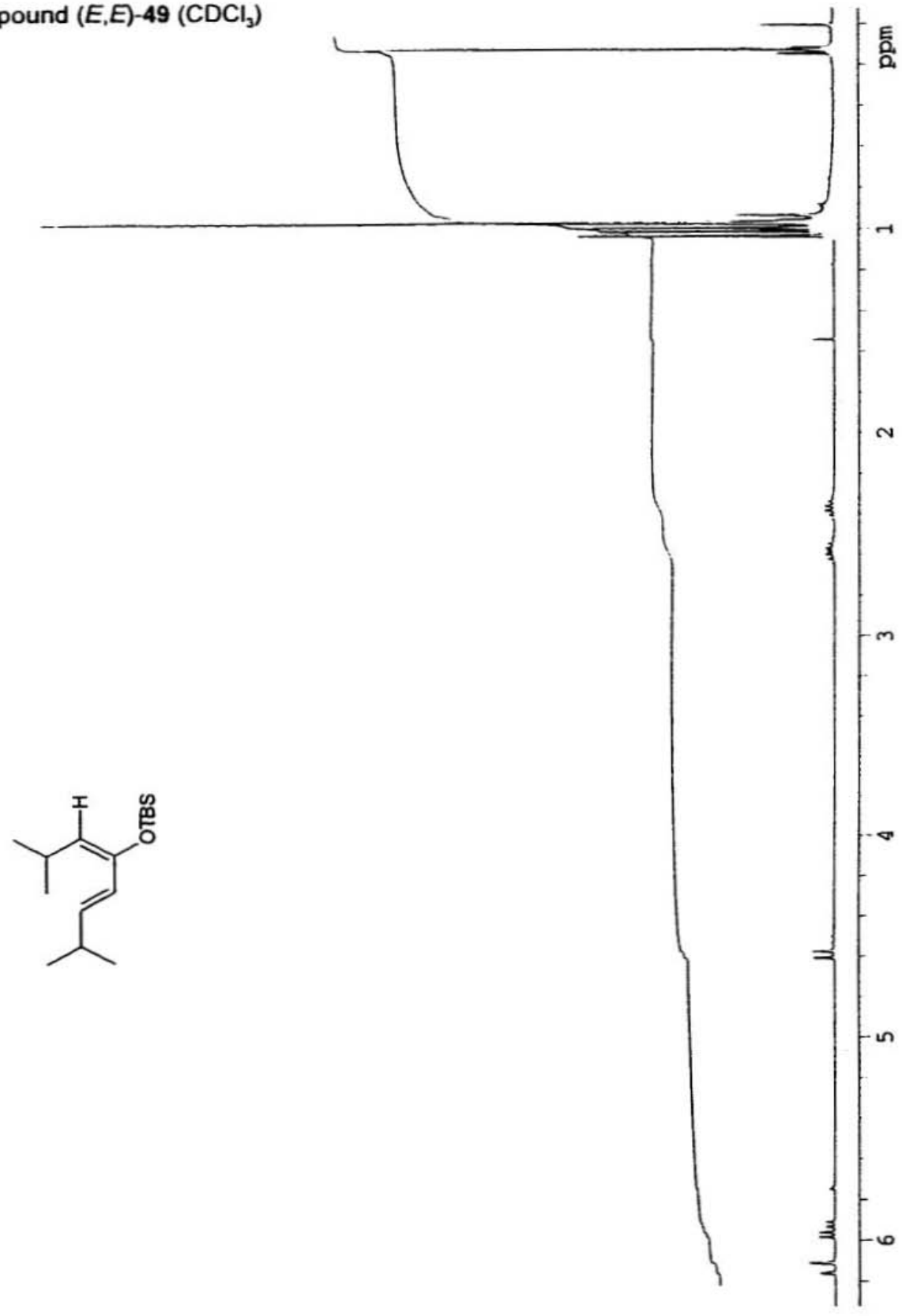
Compound **42** ($CDCl_3$)



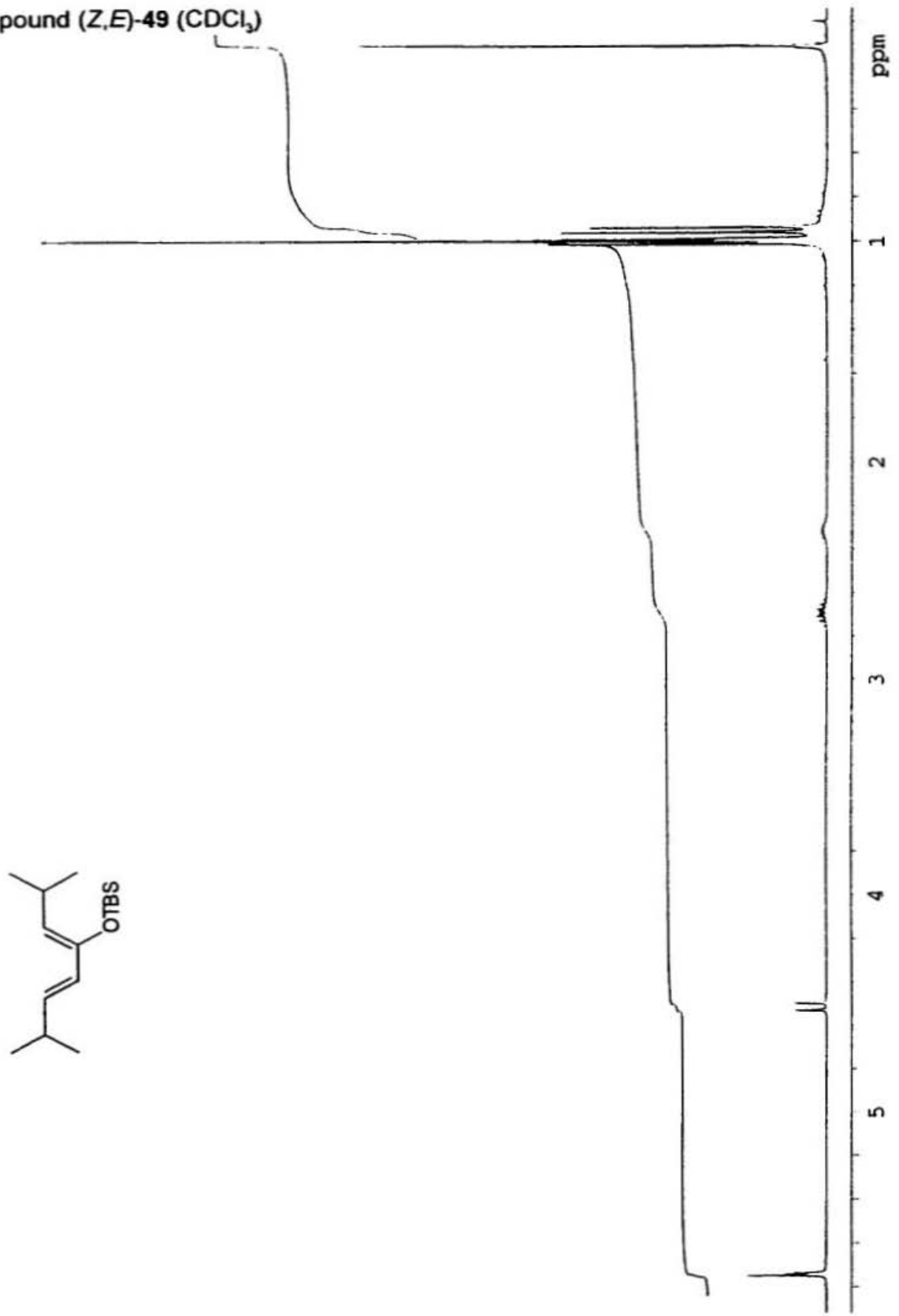
Compound **48** ($CDCl_3$)



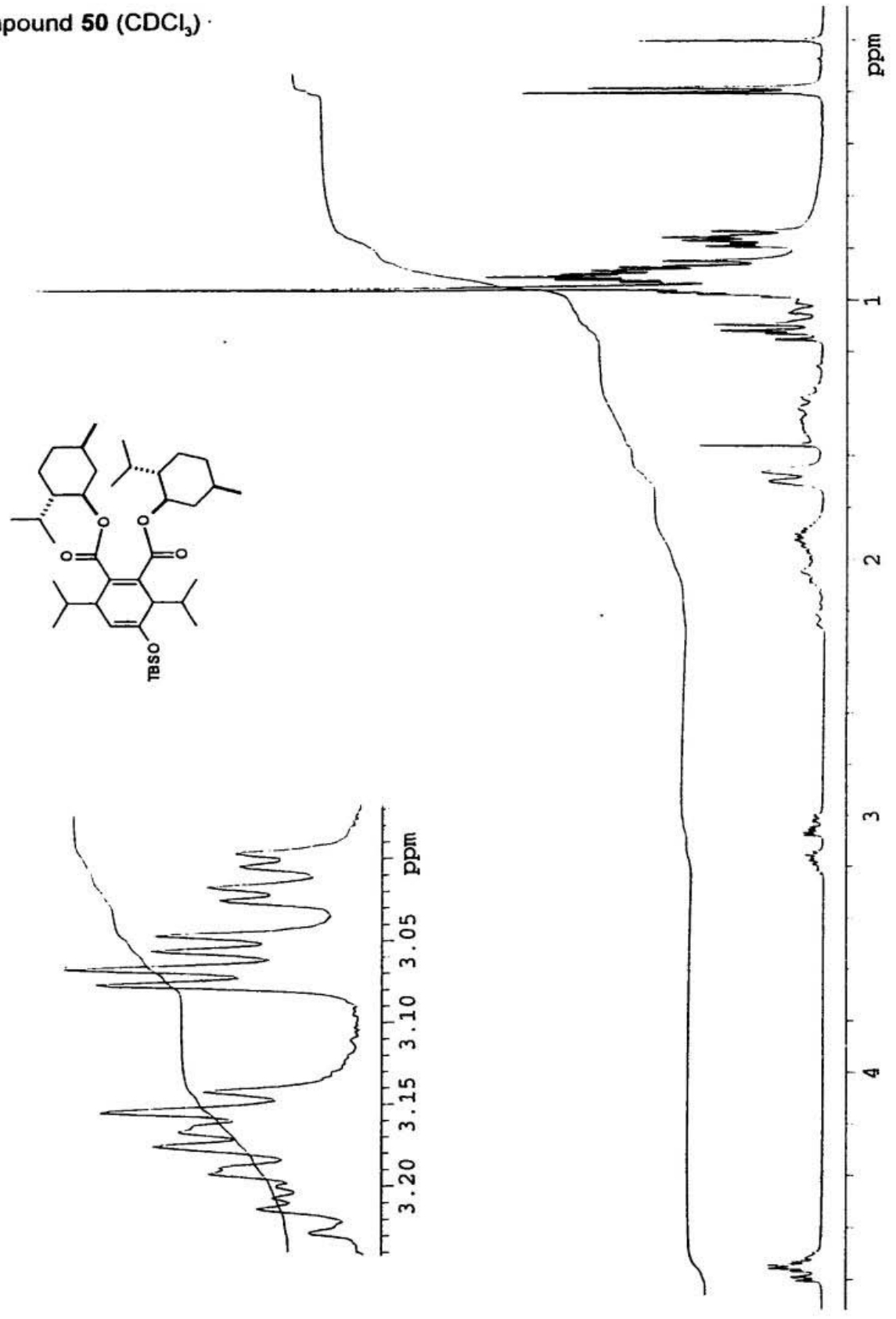
Compound (*E*,*E*)-**49** ($CDCl_3$)



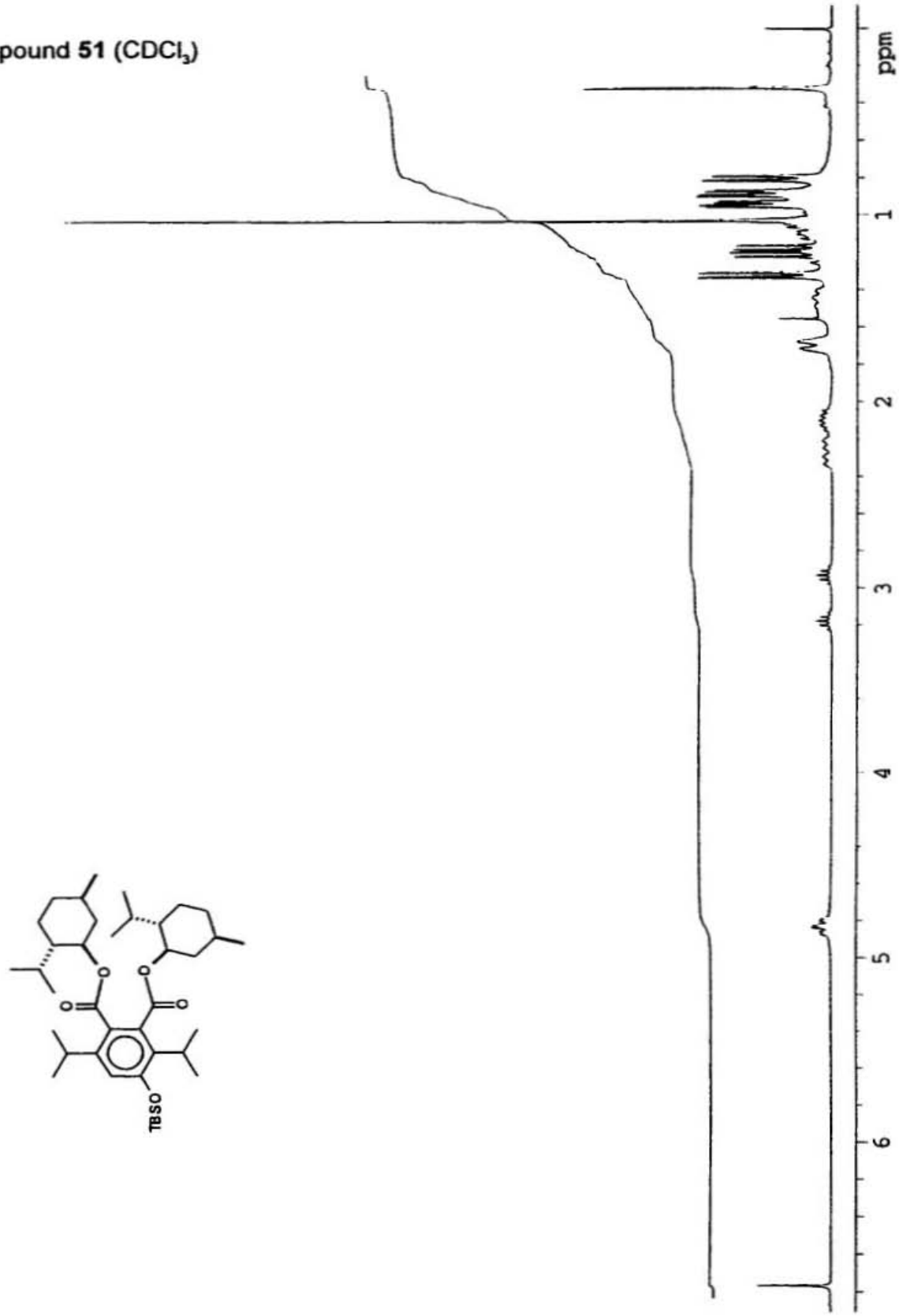
Compound (*Z*,*E*)-**49** ($CDCl_3$)



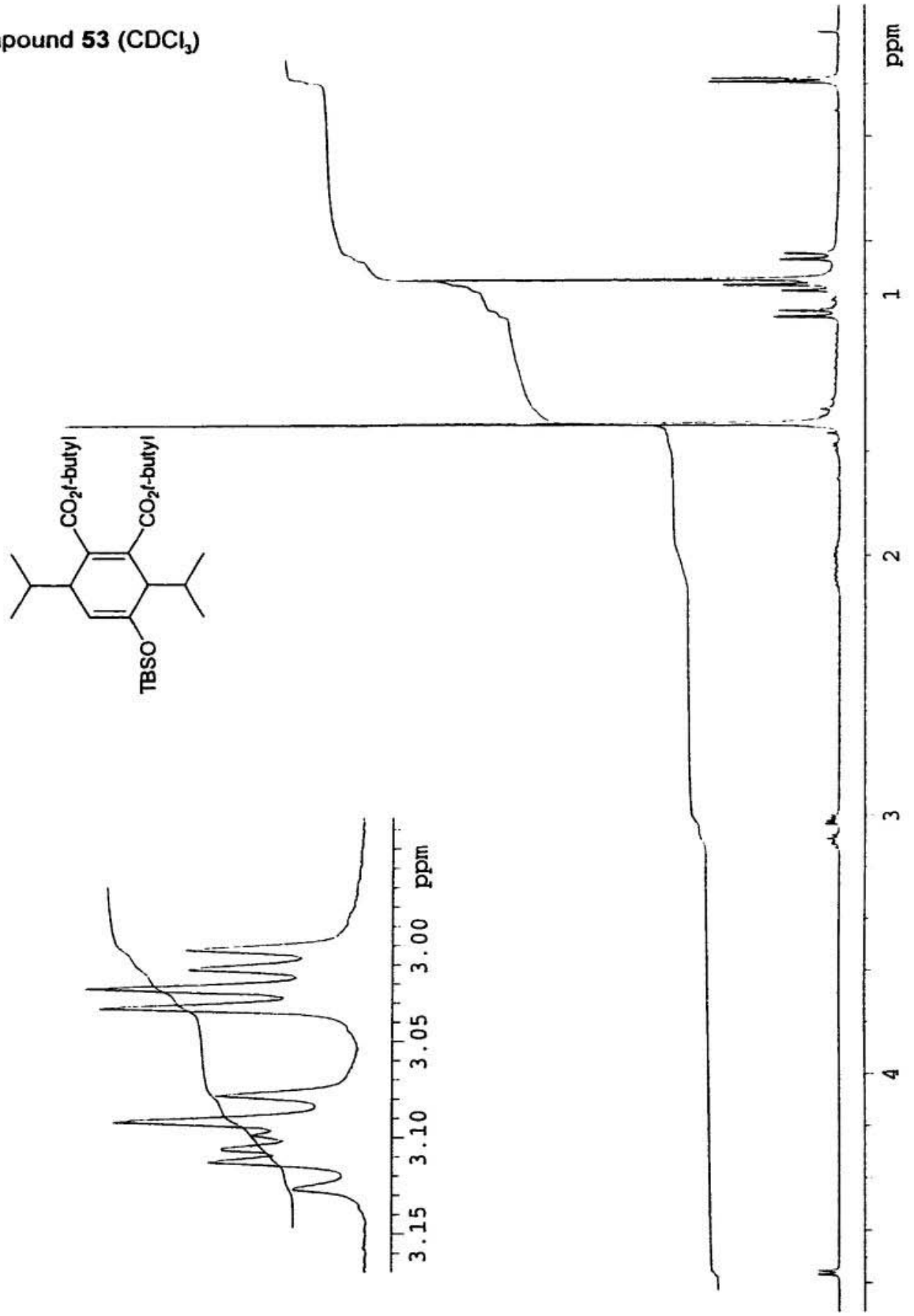
Compound **50** ($CDCl_3$)



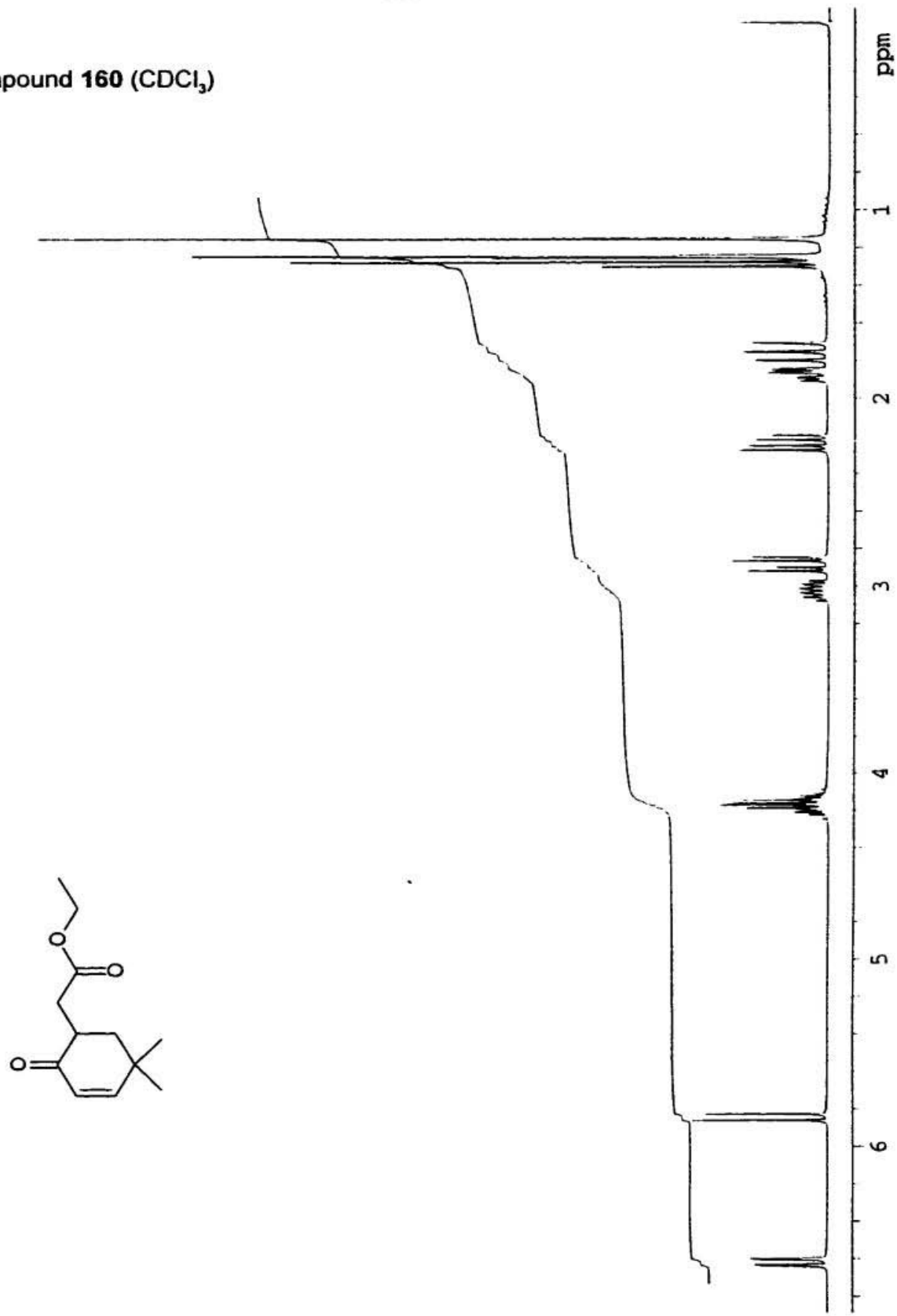
Compound **51** ($CDCl_3$)



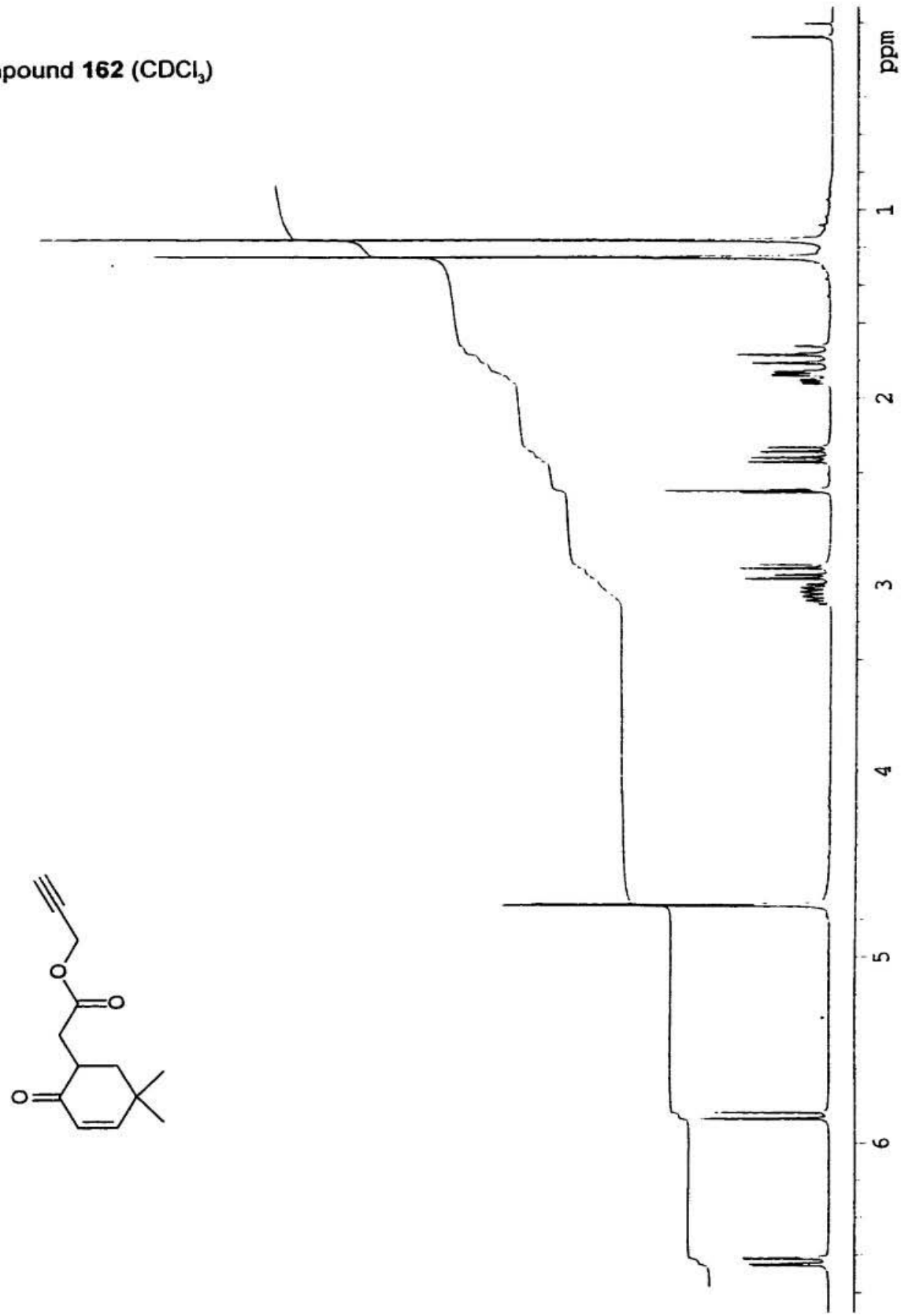
Compound **53** ($CDCl_3$)



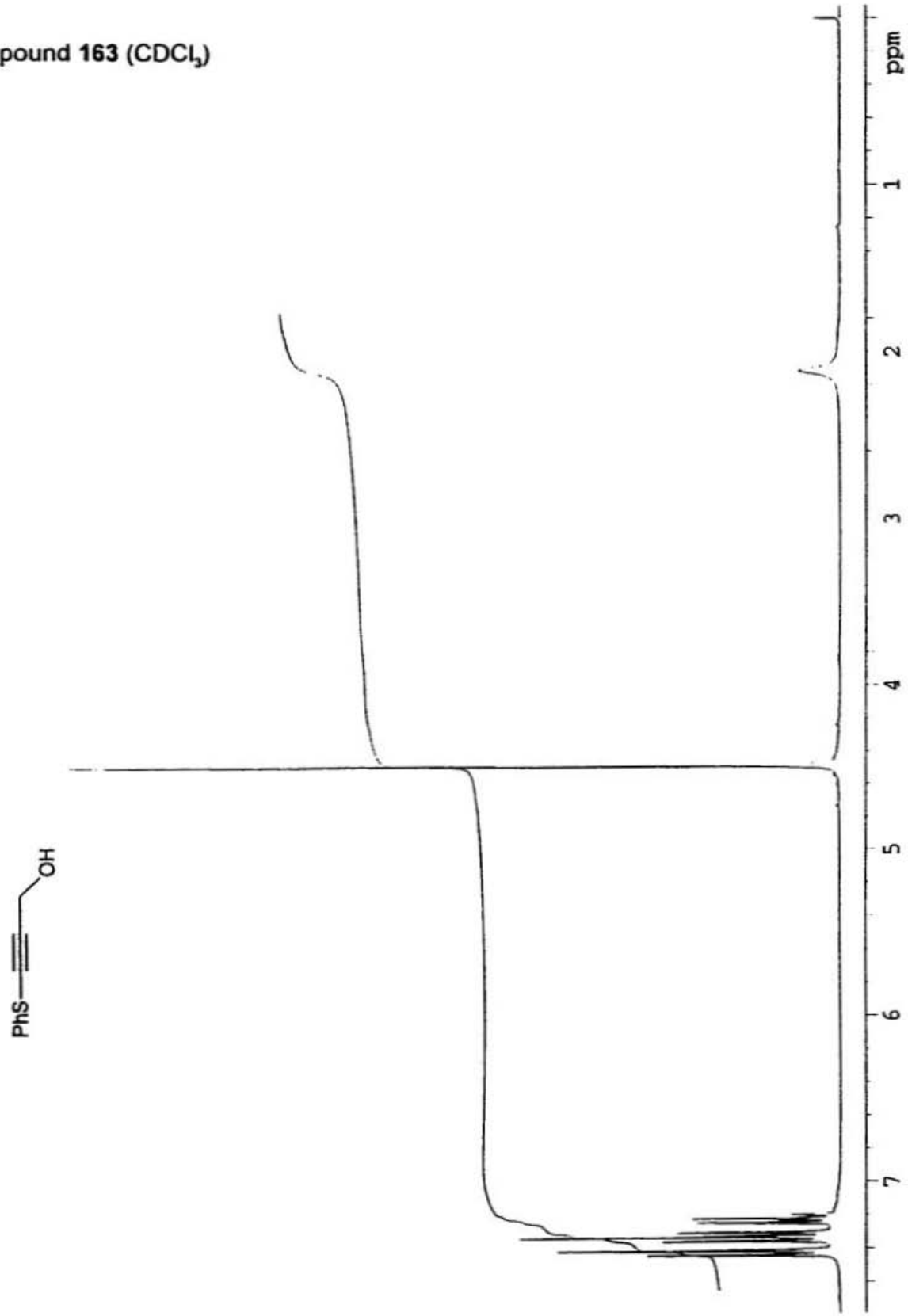
Compound **160** ($CDCl_3$)



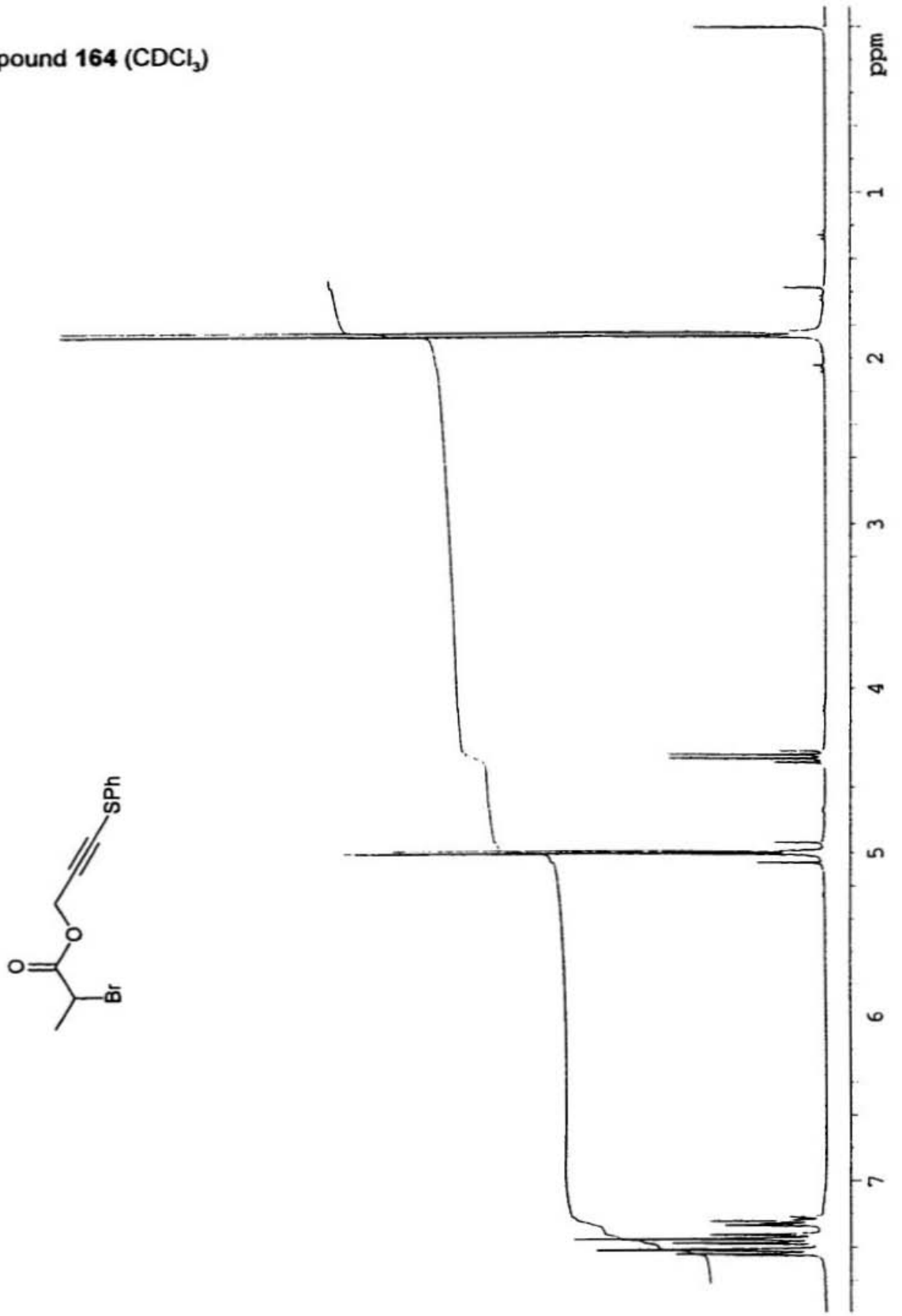
Compound **162** ($CDCl_3$)



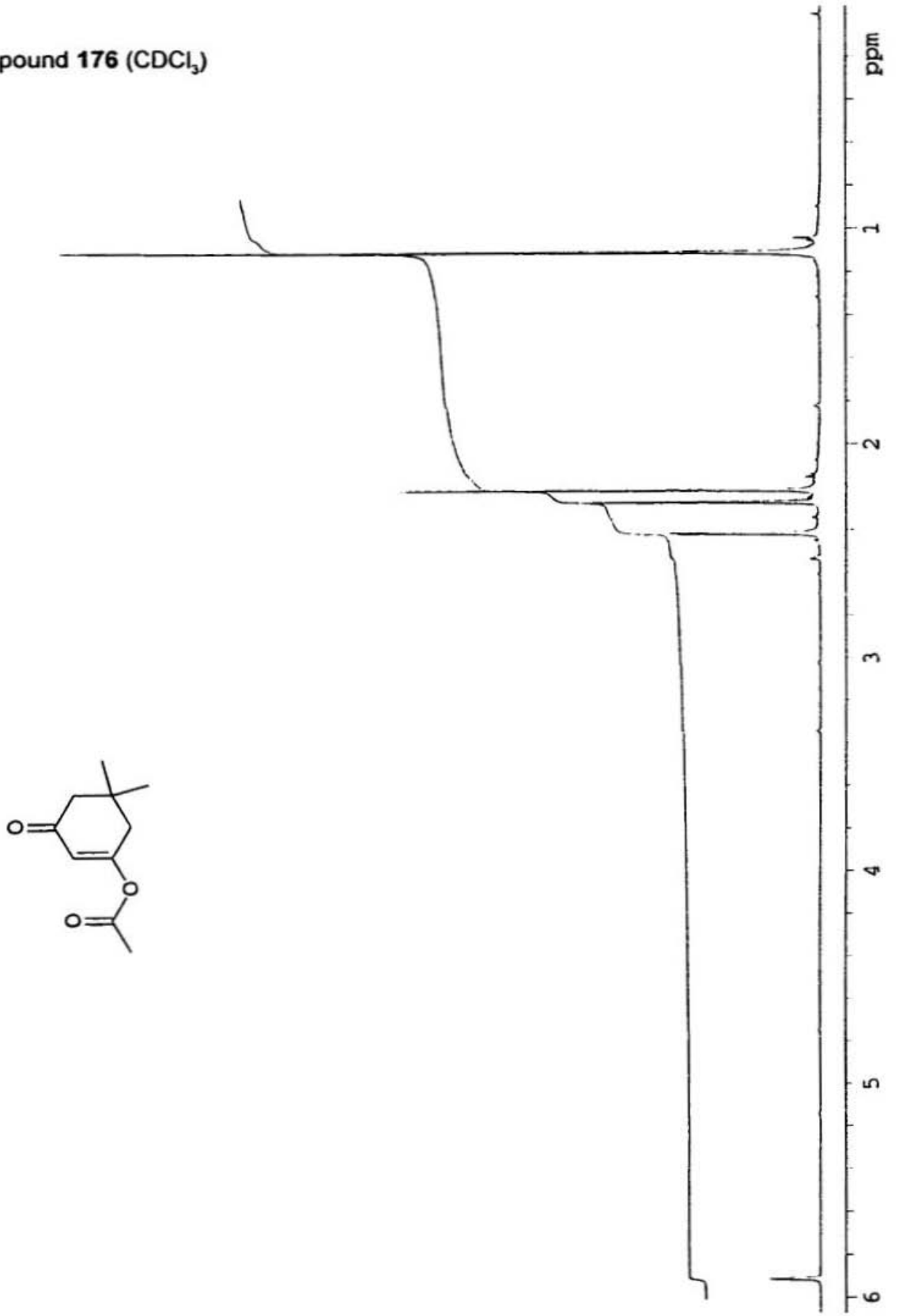
Compound **163** ($CDCl_3$)



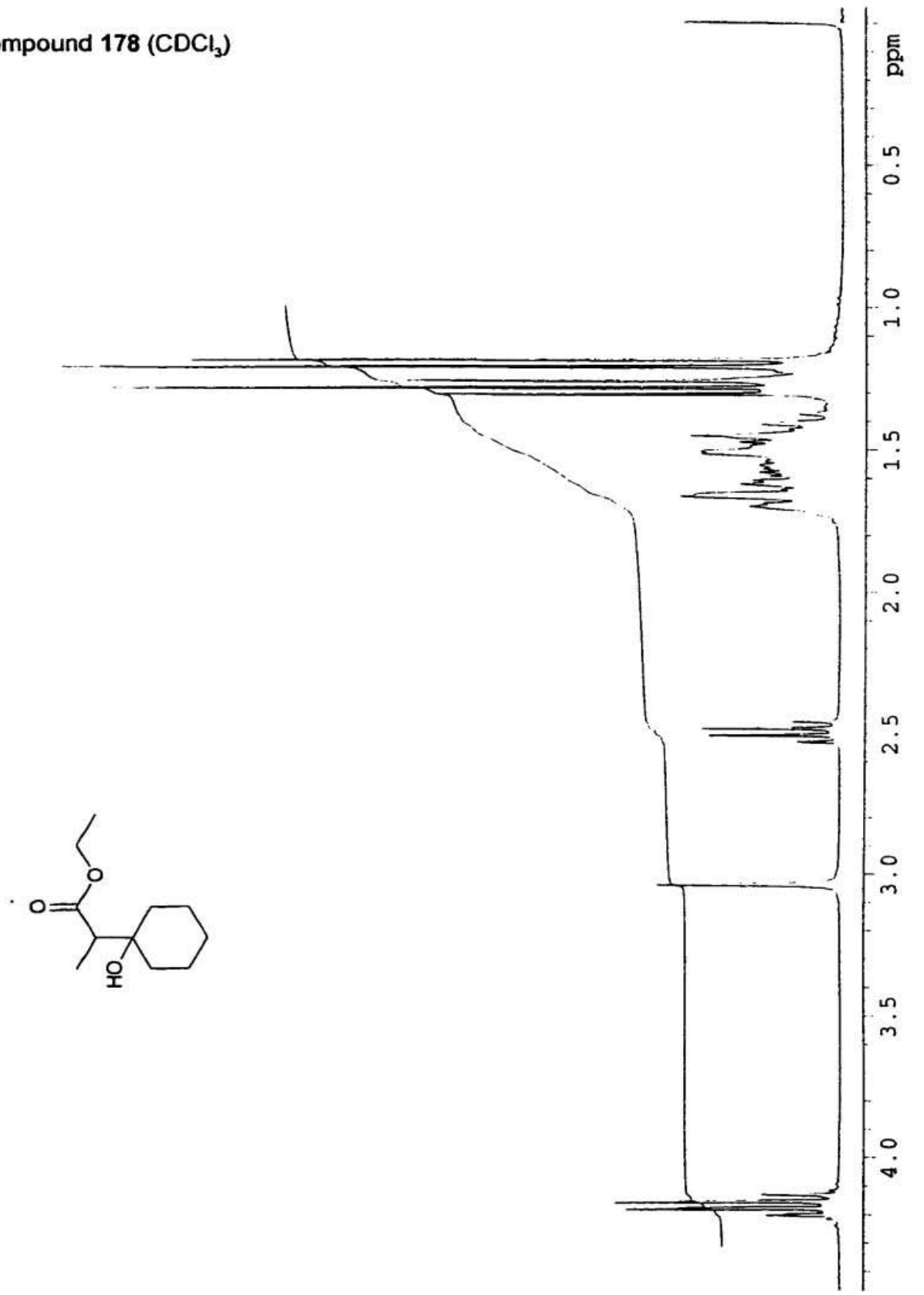
Compound **164** ($CDCl_3$)



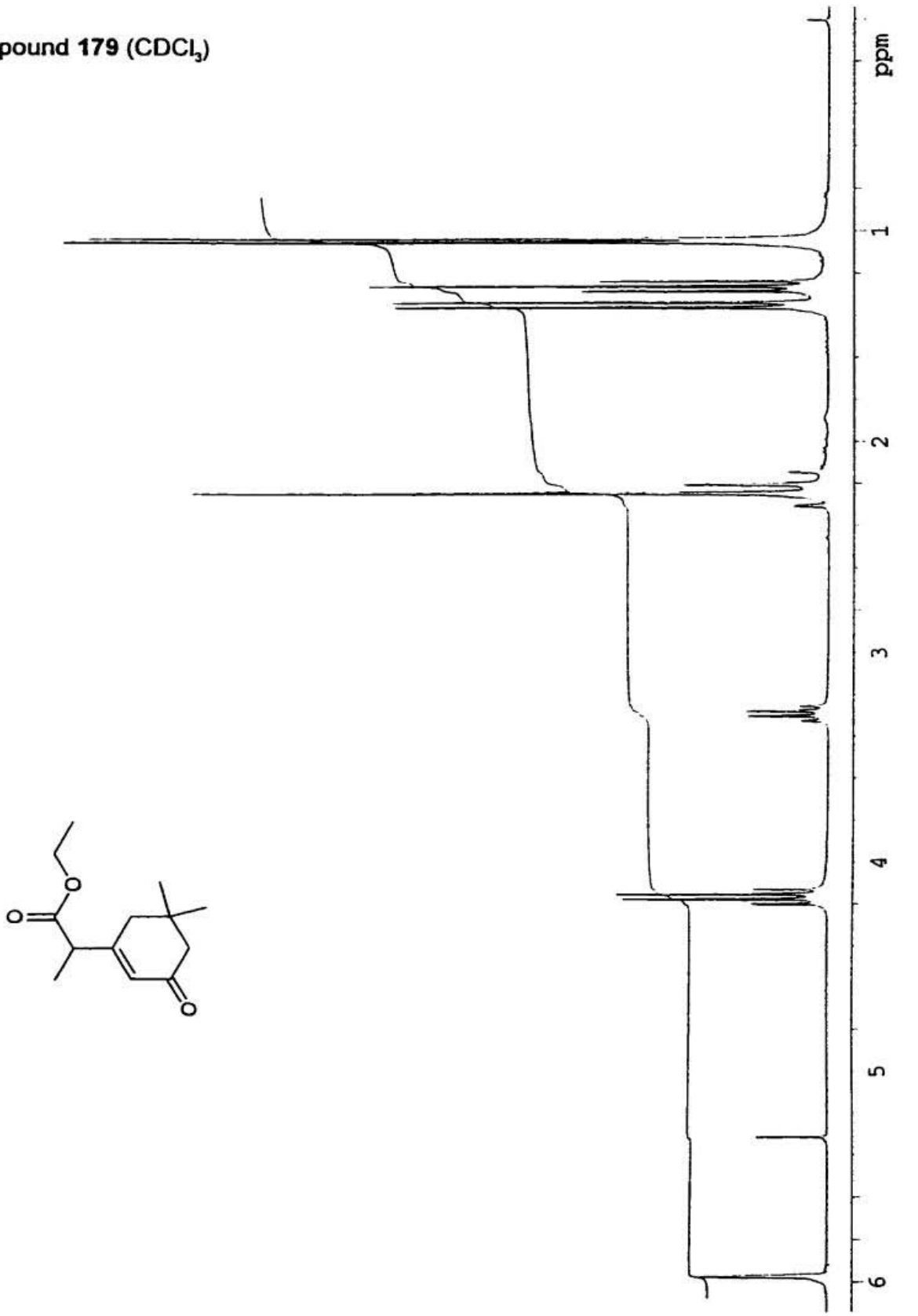
Compound **176** ($CDCl_3$)



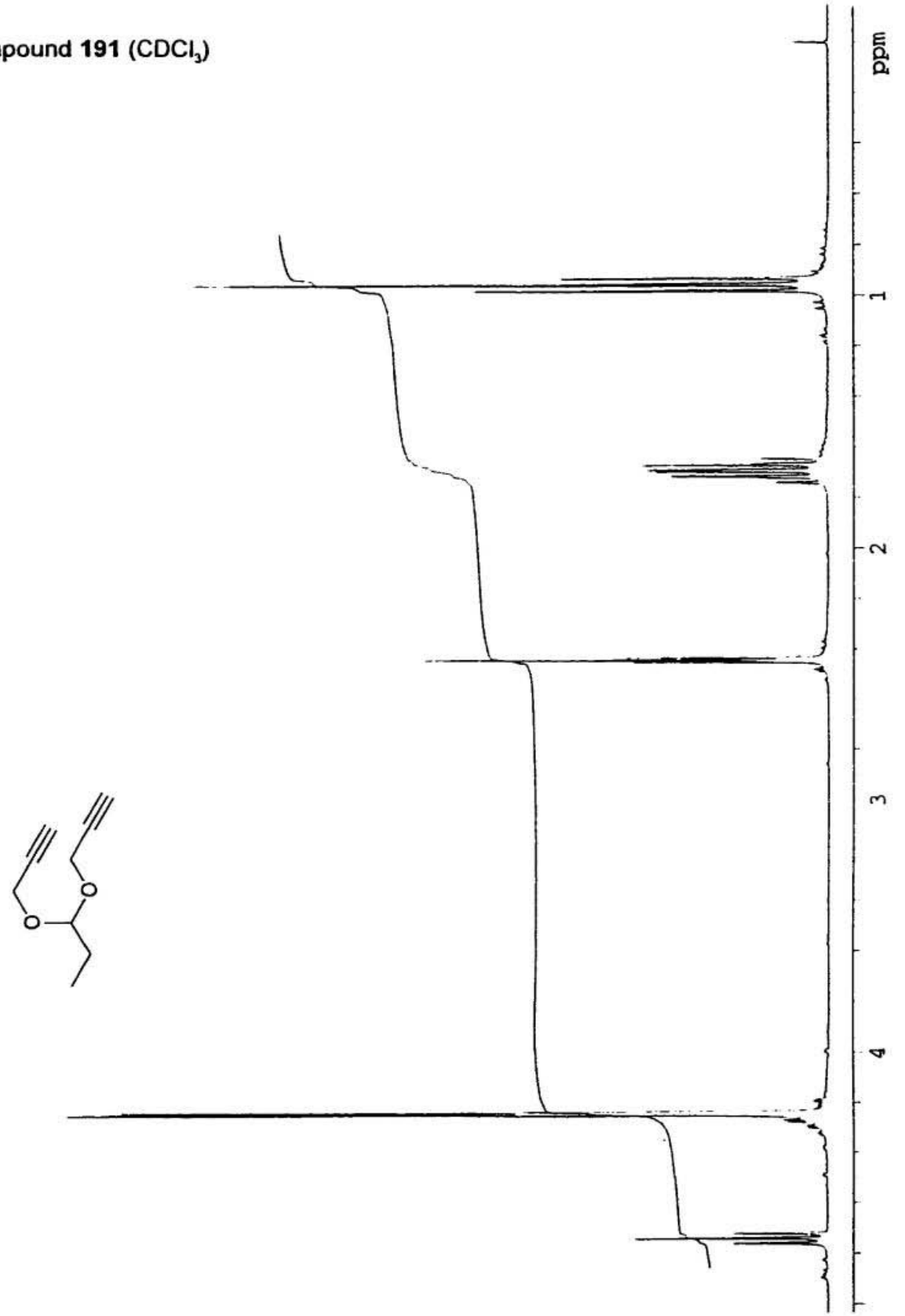
Compound **178** ($CDCl_3$)



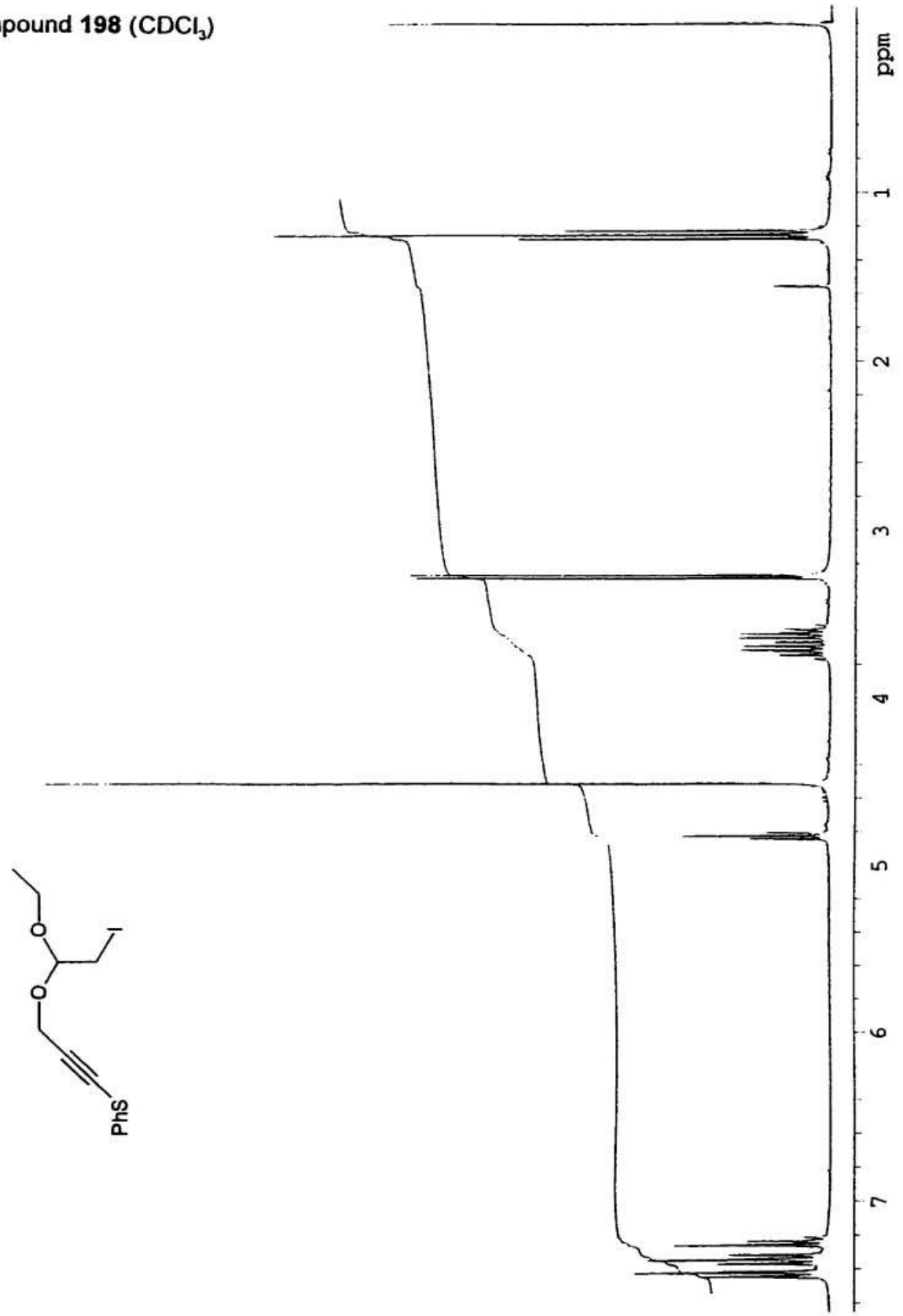
Compound **179** ($CDCl_3$)



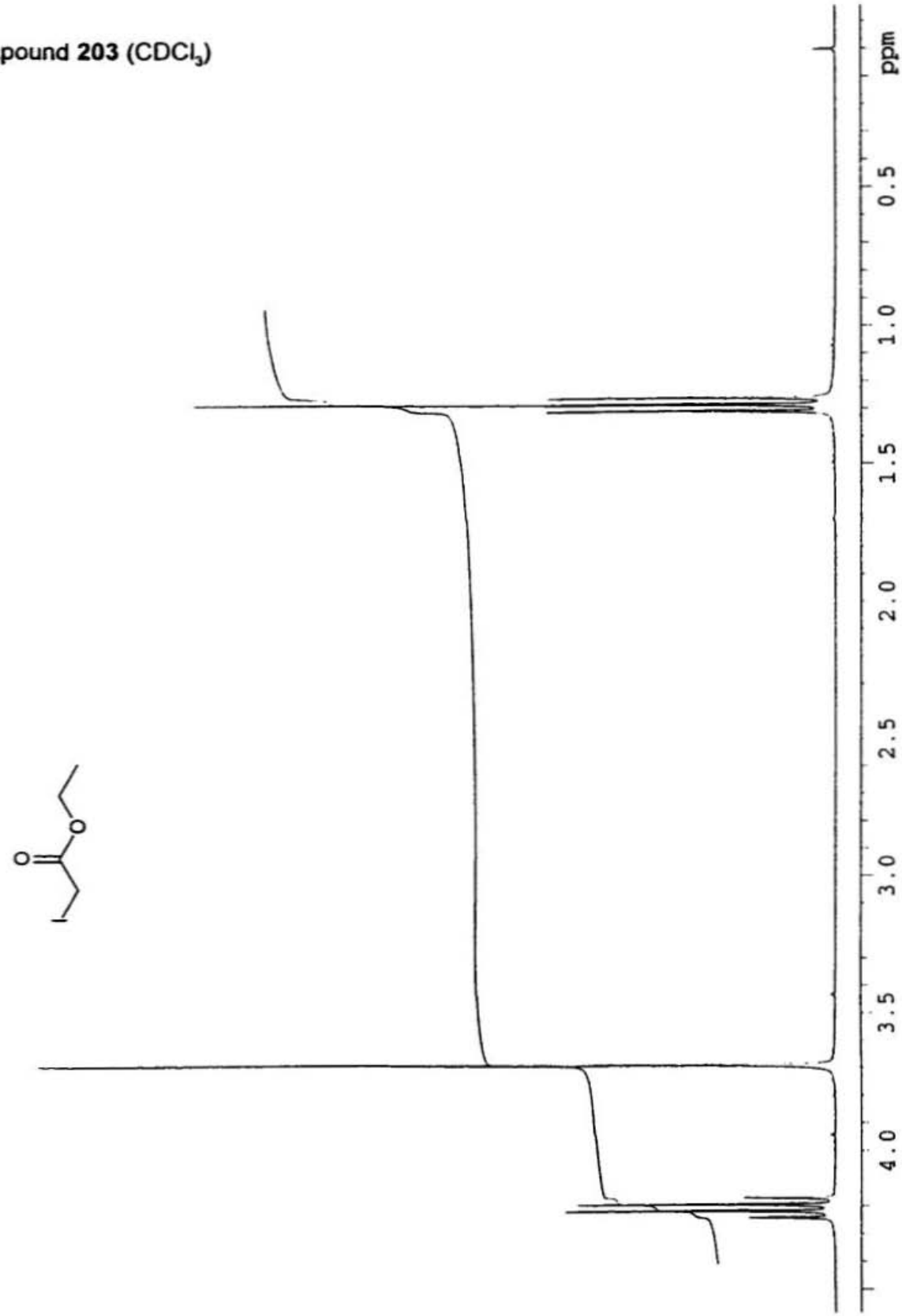
Compound **191** ($CDCl_3$)



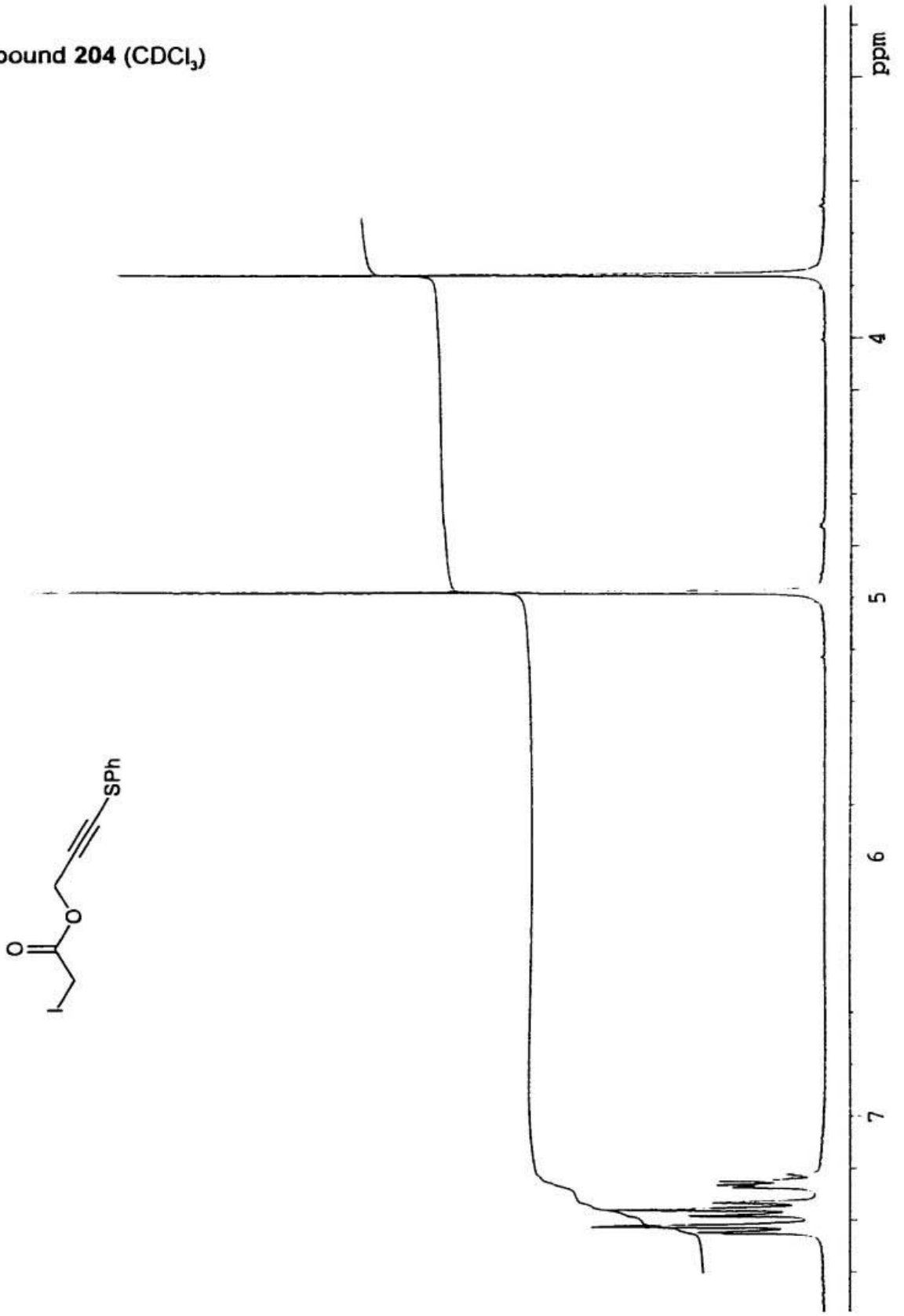
Compound **198** ($CDCl_3$)



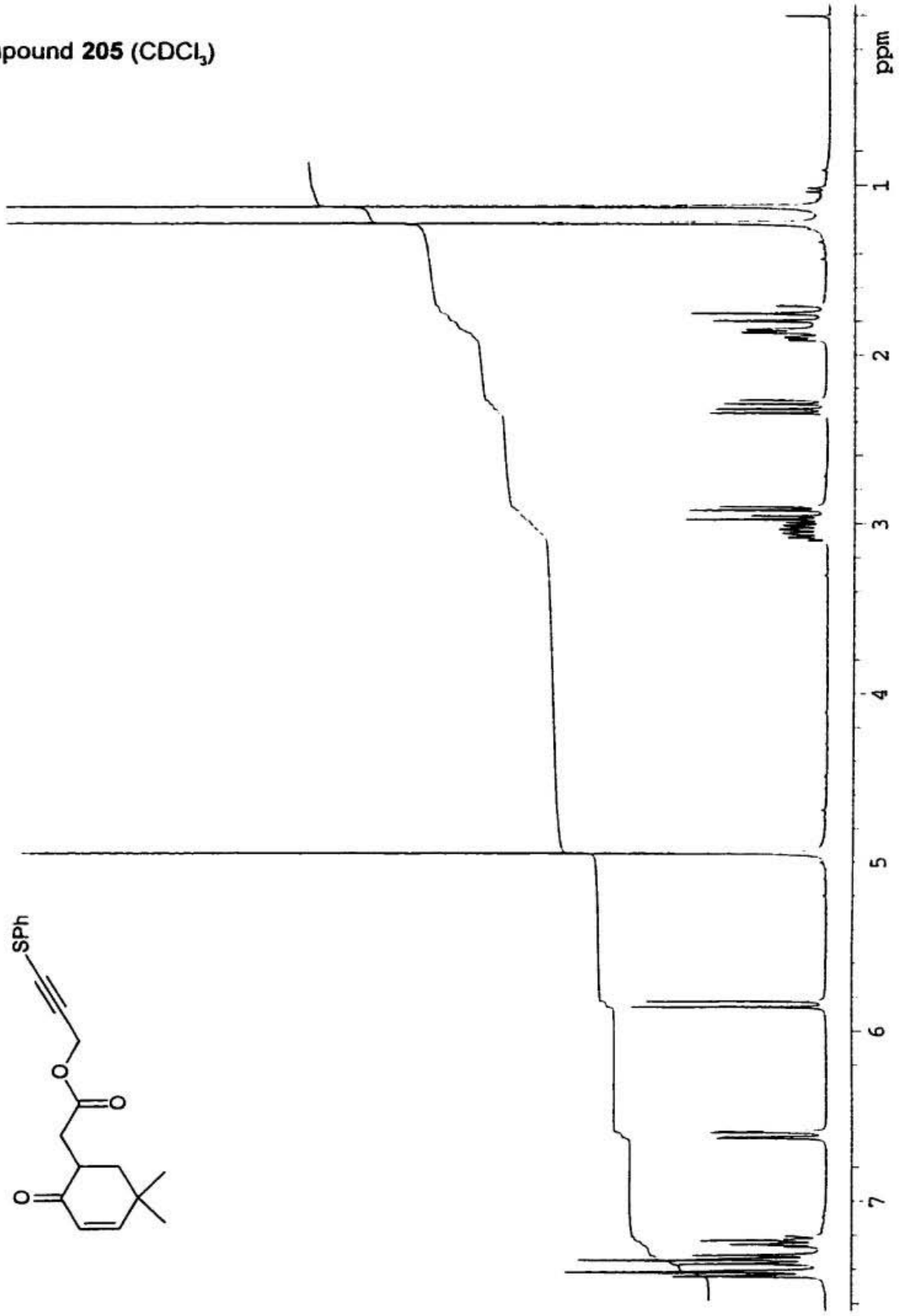
Compound **203** ($CDCl_3$)



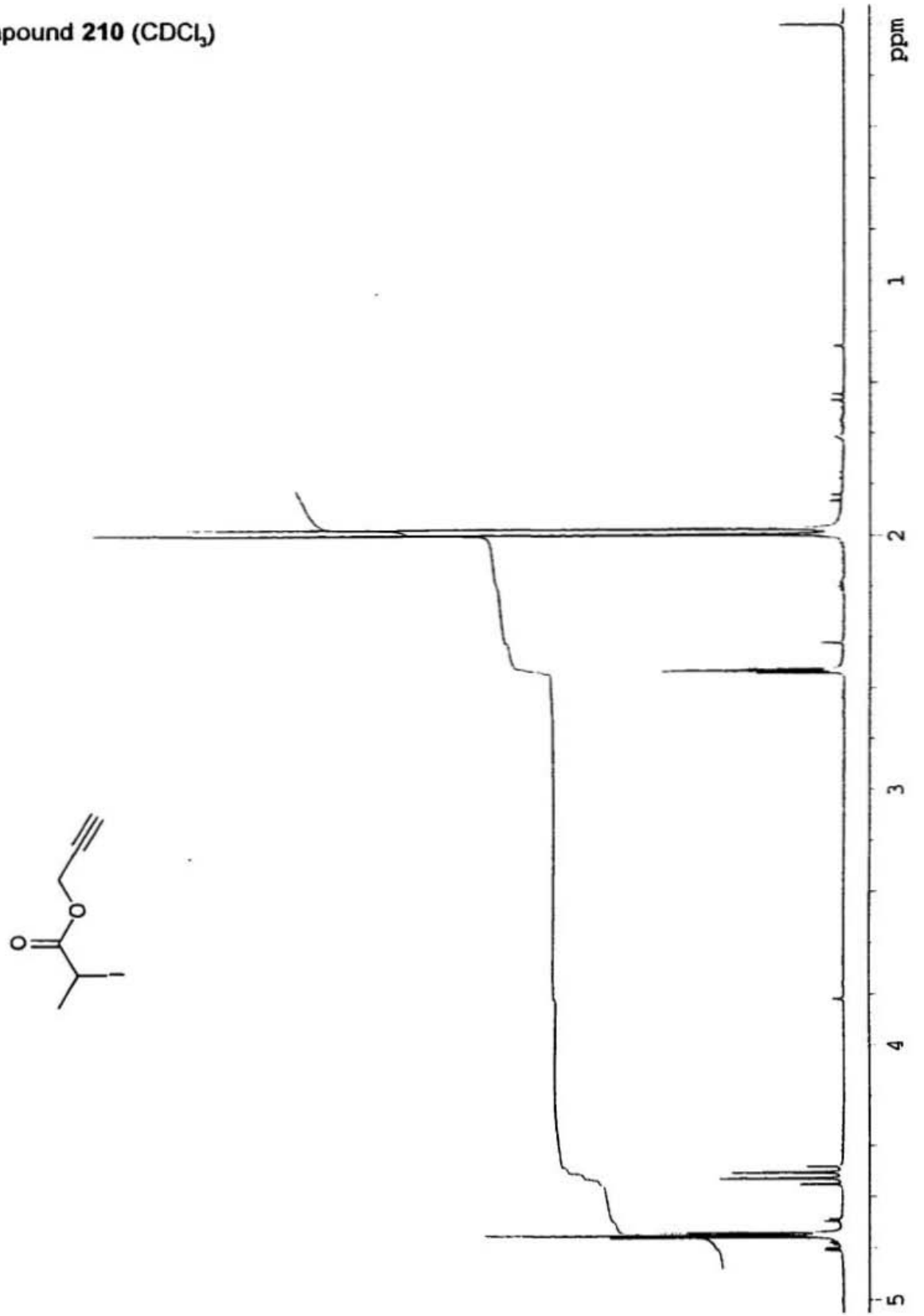
Compound **204** ($CDCl_3$)



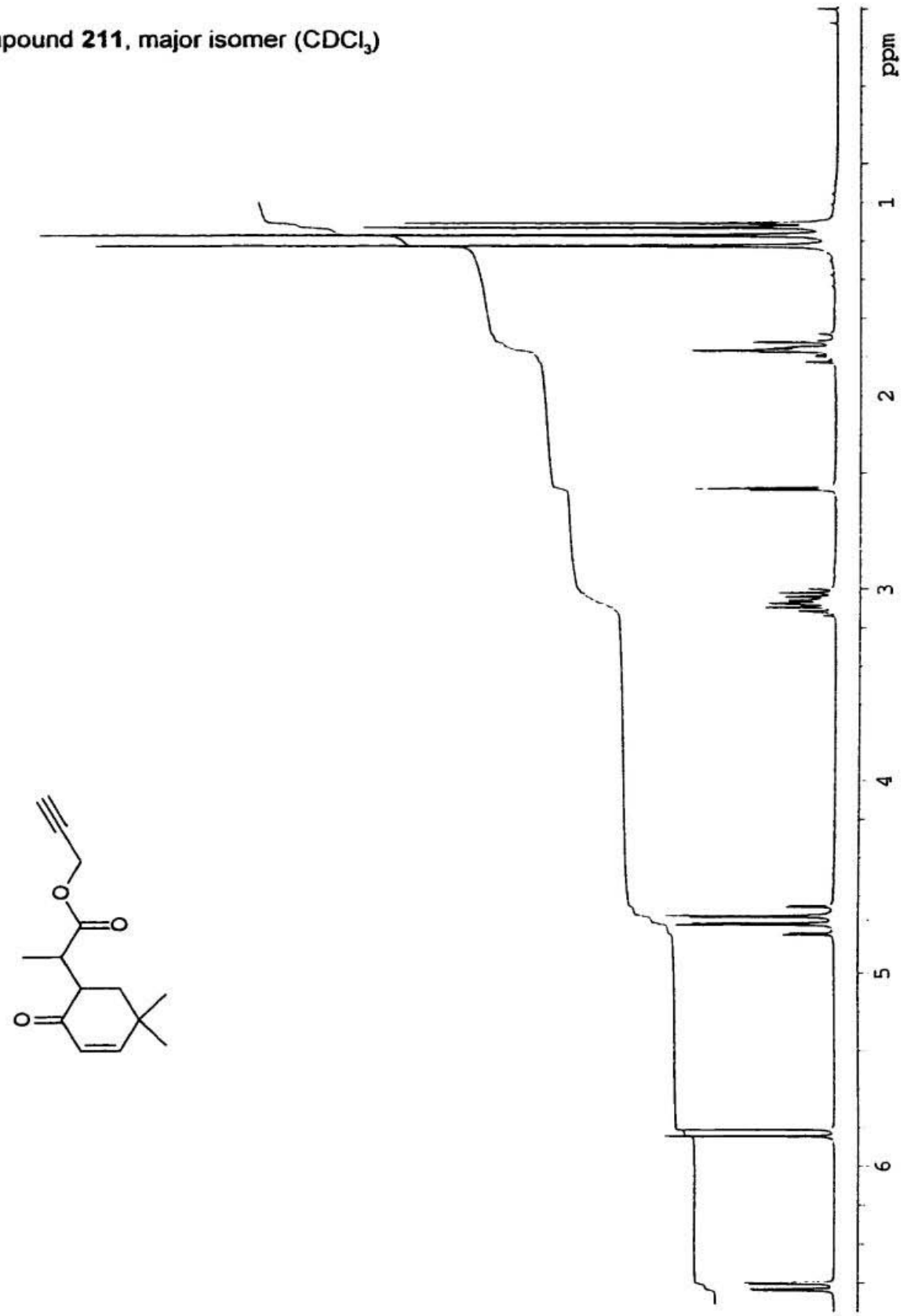
Compound **205** ($CDCl_3$)



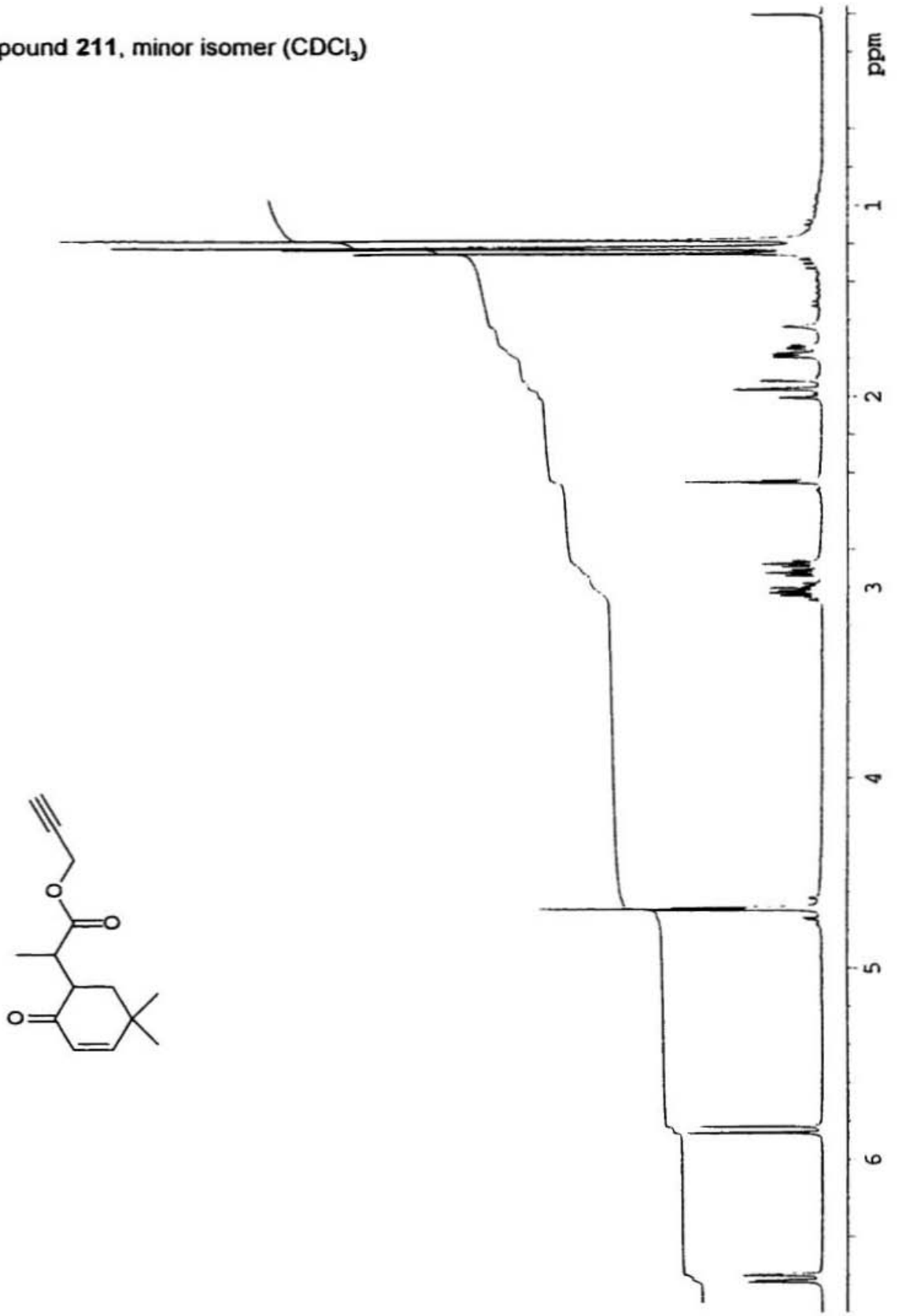
Compound **210** ($CDCl_3$)



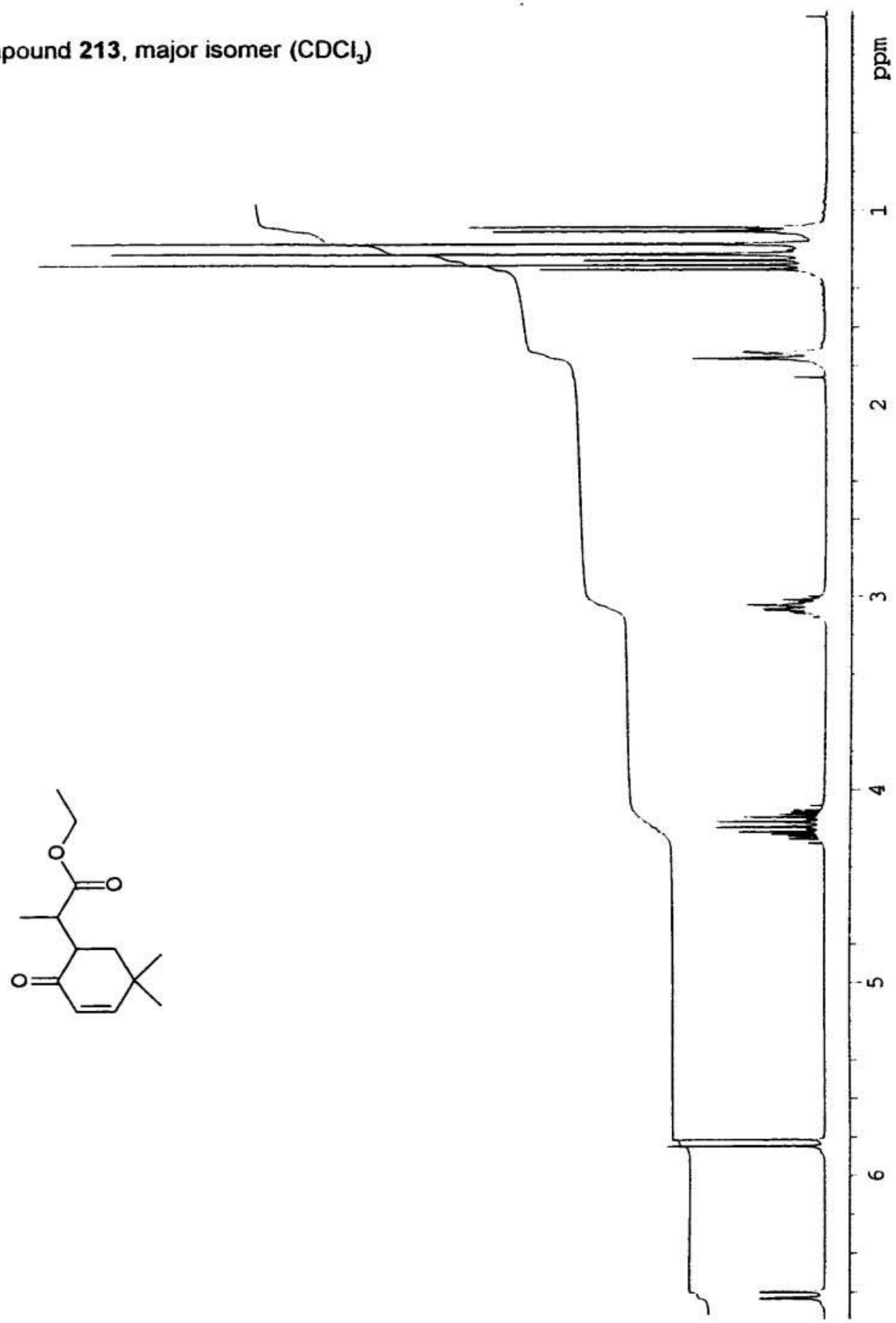
Compound **211**, major isomer ($CDCl_3$)



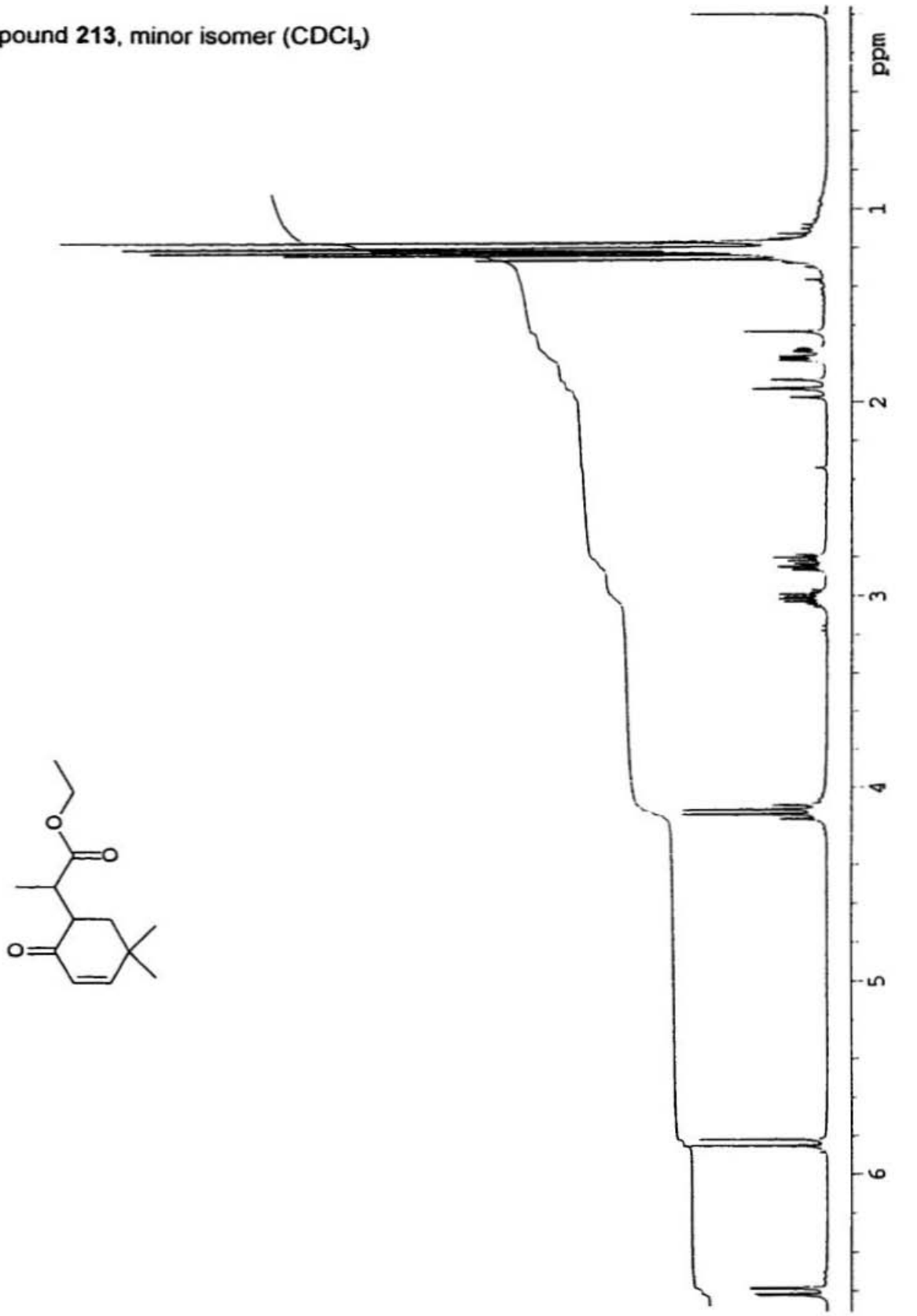
Compound **211**, minor isomer ($CDCl_3$)



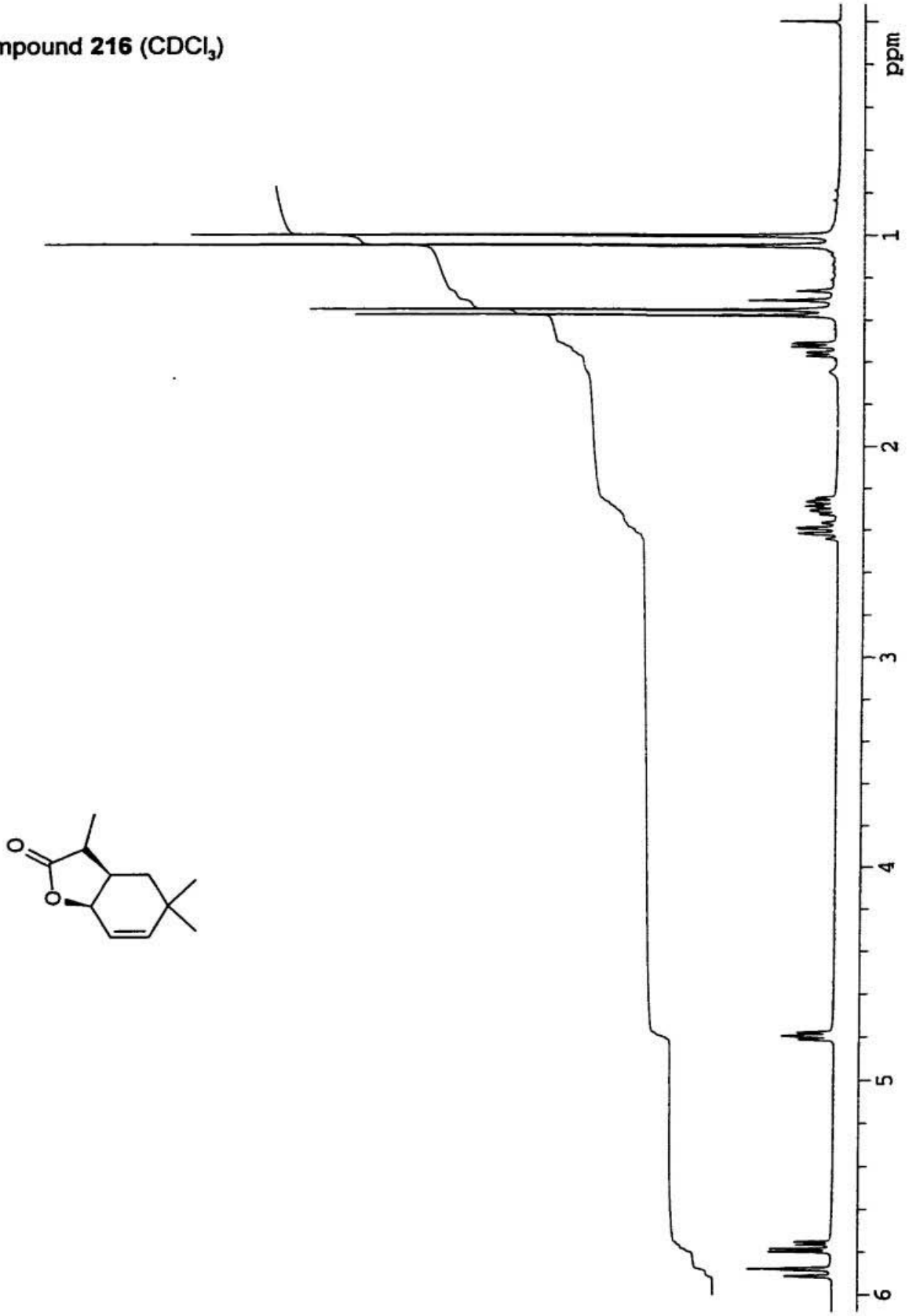
Compound **213**, major isomer ($CDCl_3$)



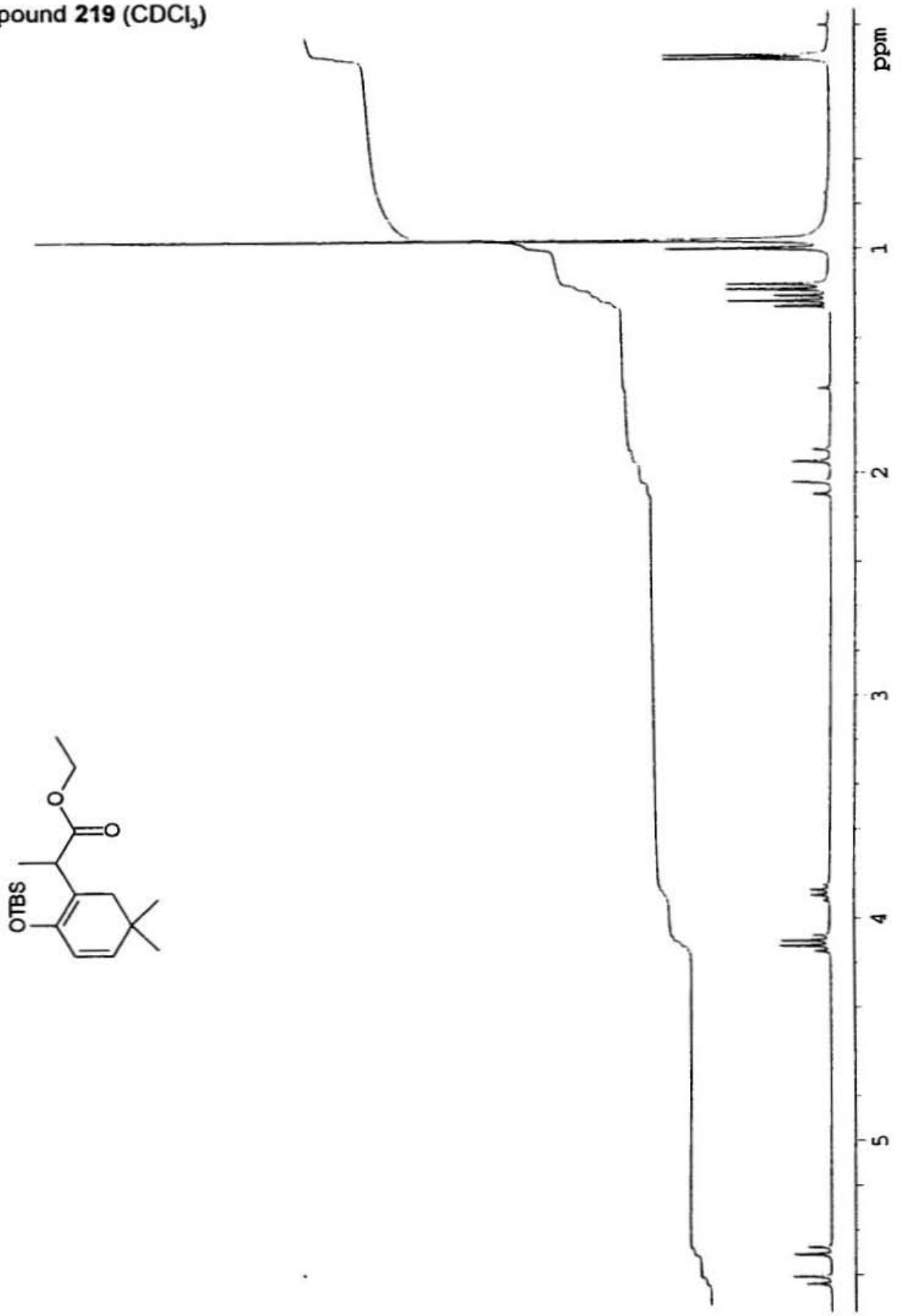
Compound **213**, minor isomer ($CDCl_3$)



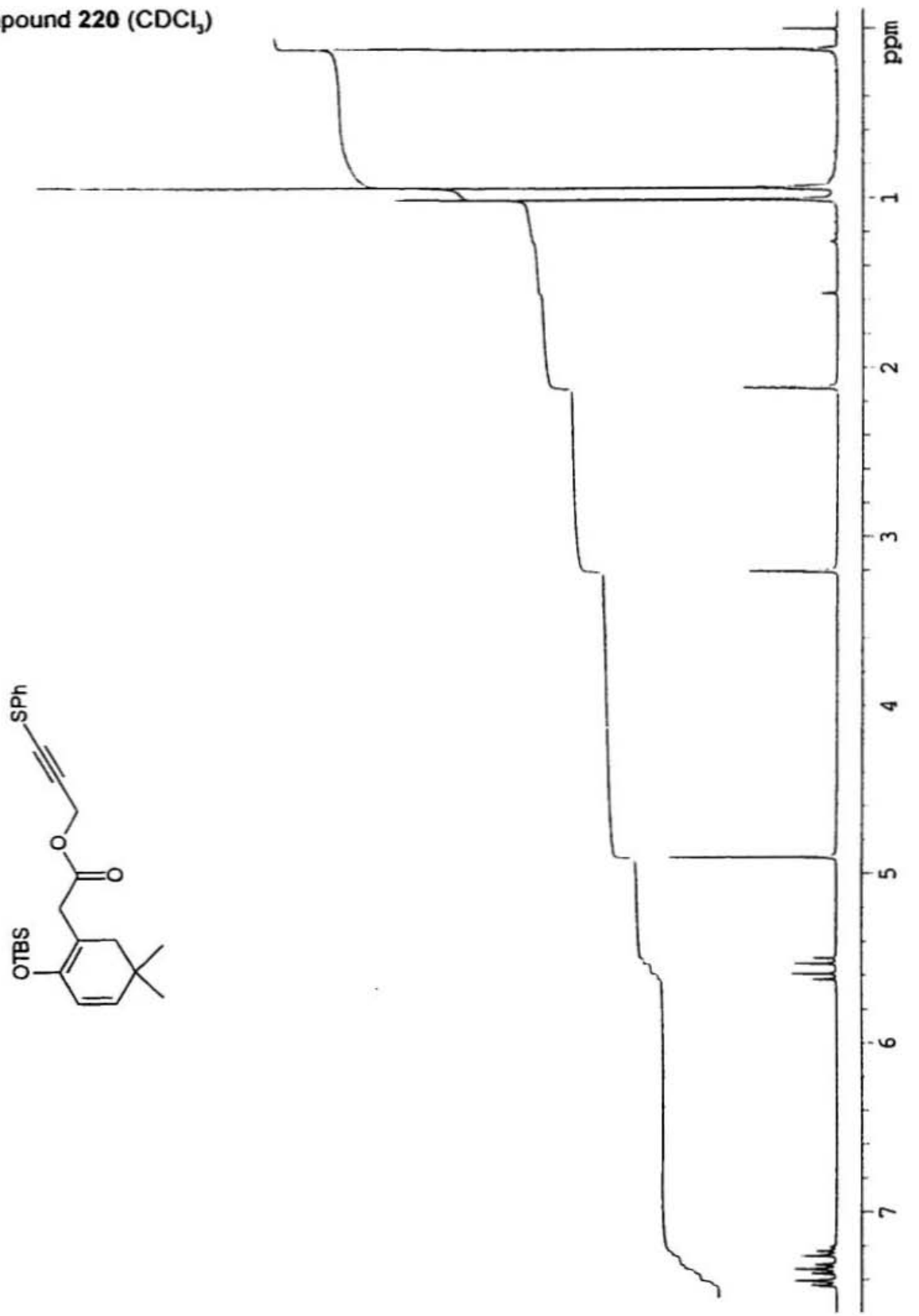
Compound **216** ($CDCl_3$)



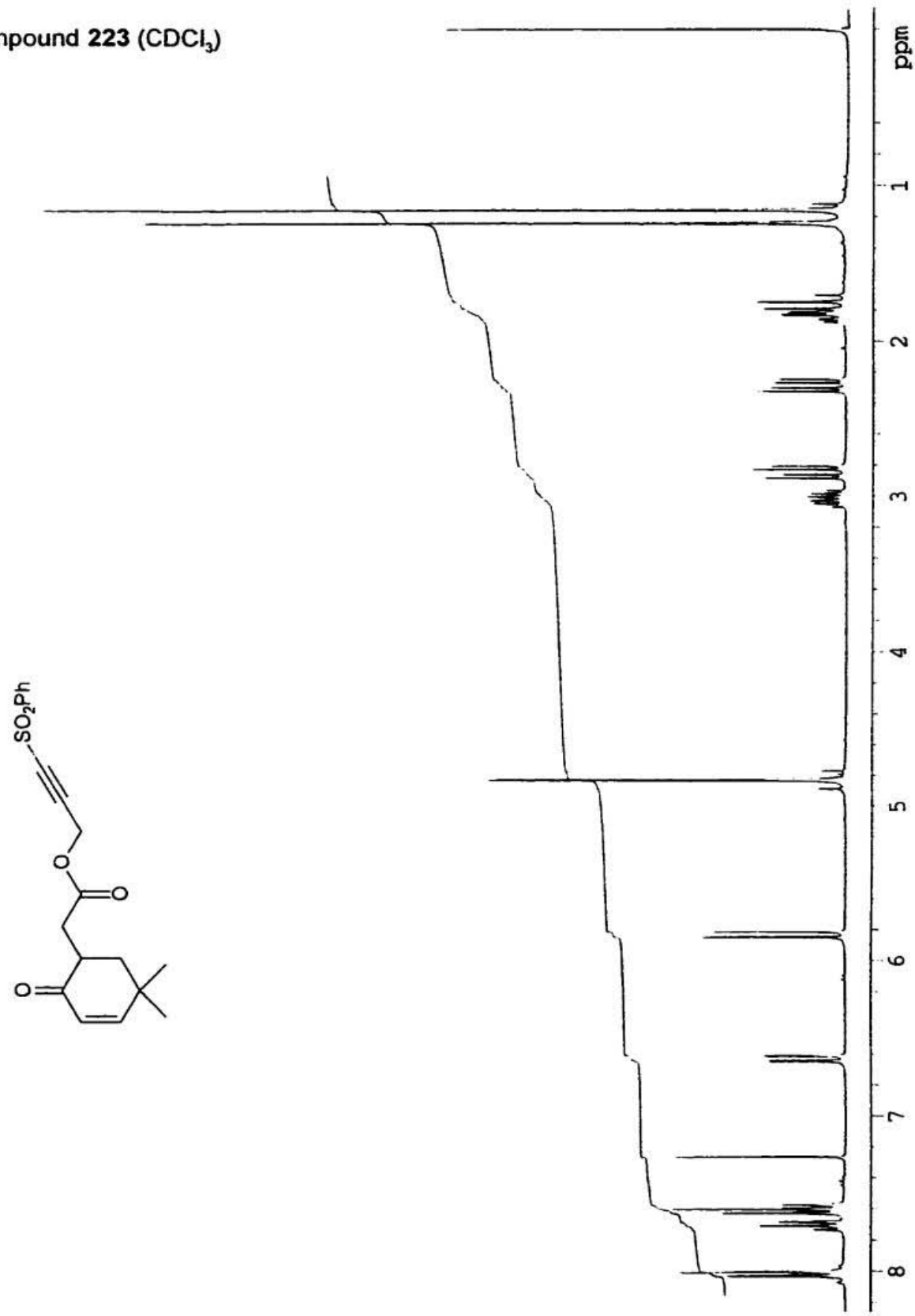
Compound **219** ($CDCl_3$)



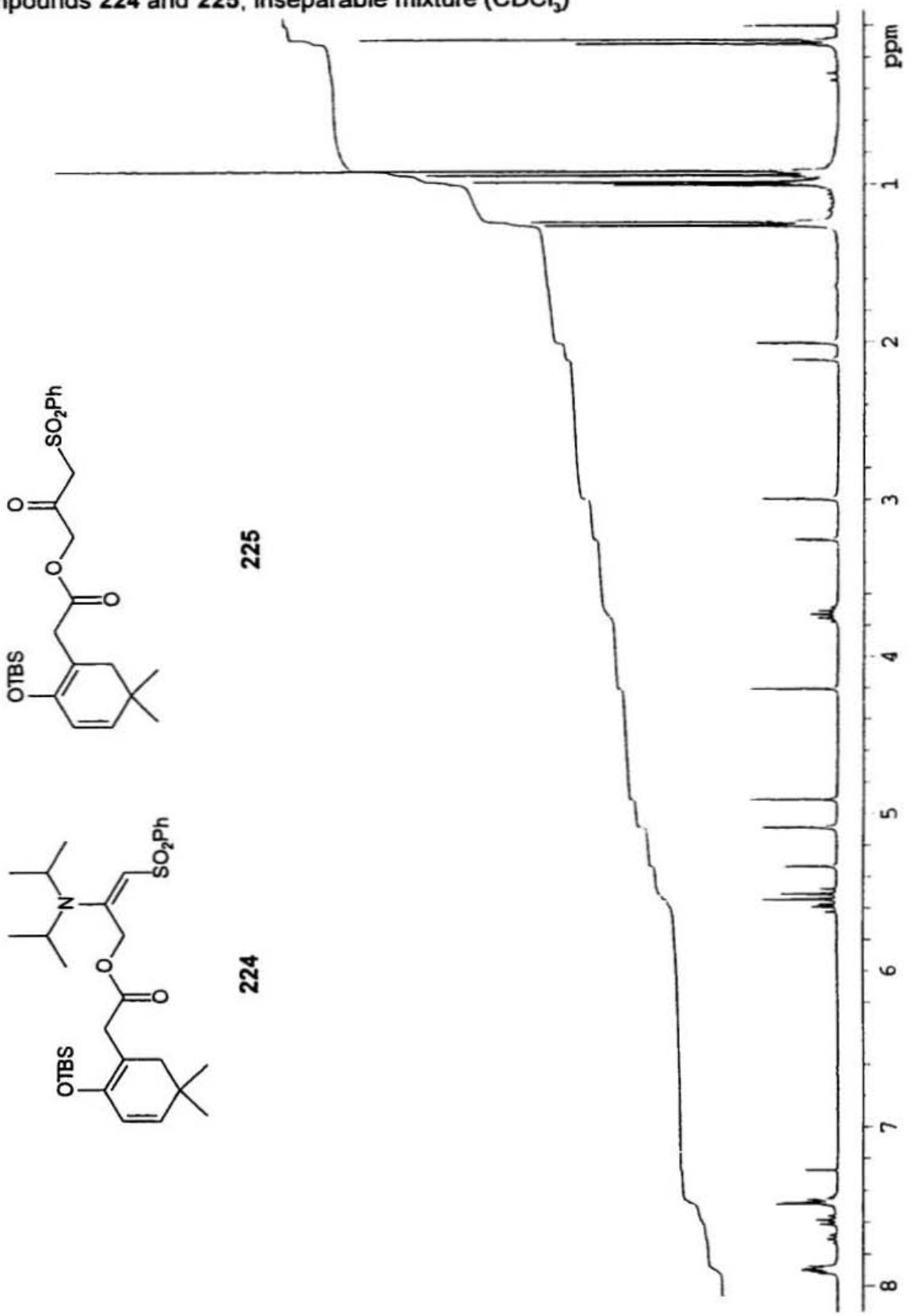
Compound **220** ($CDCl_3$)



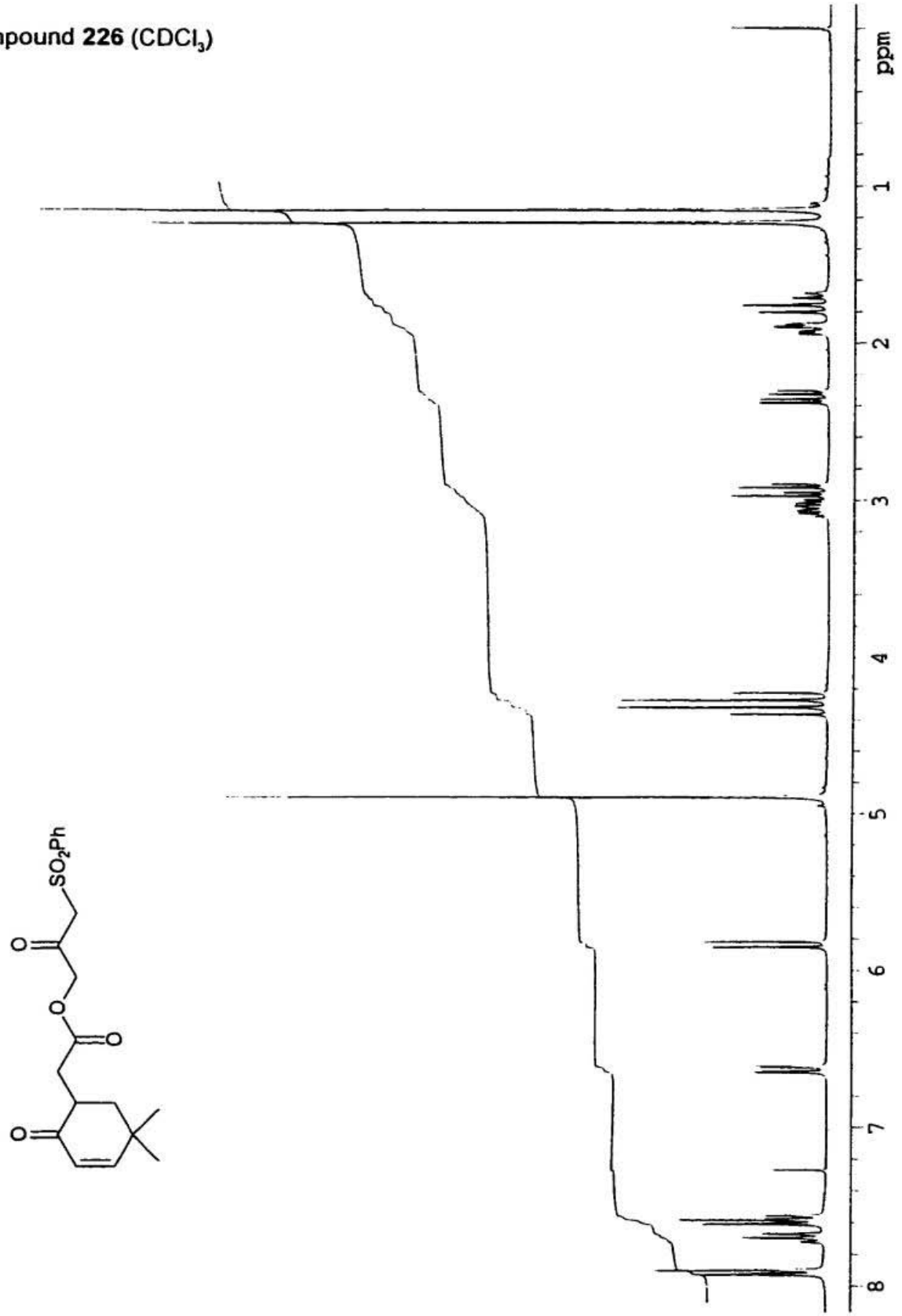
Compound **223** ($CDCl_3$)



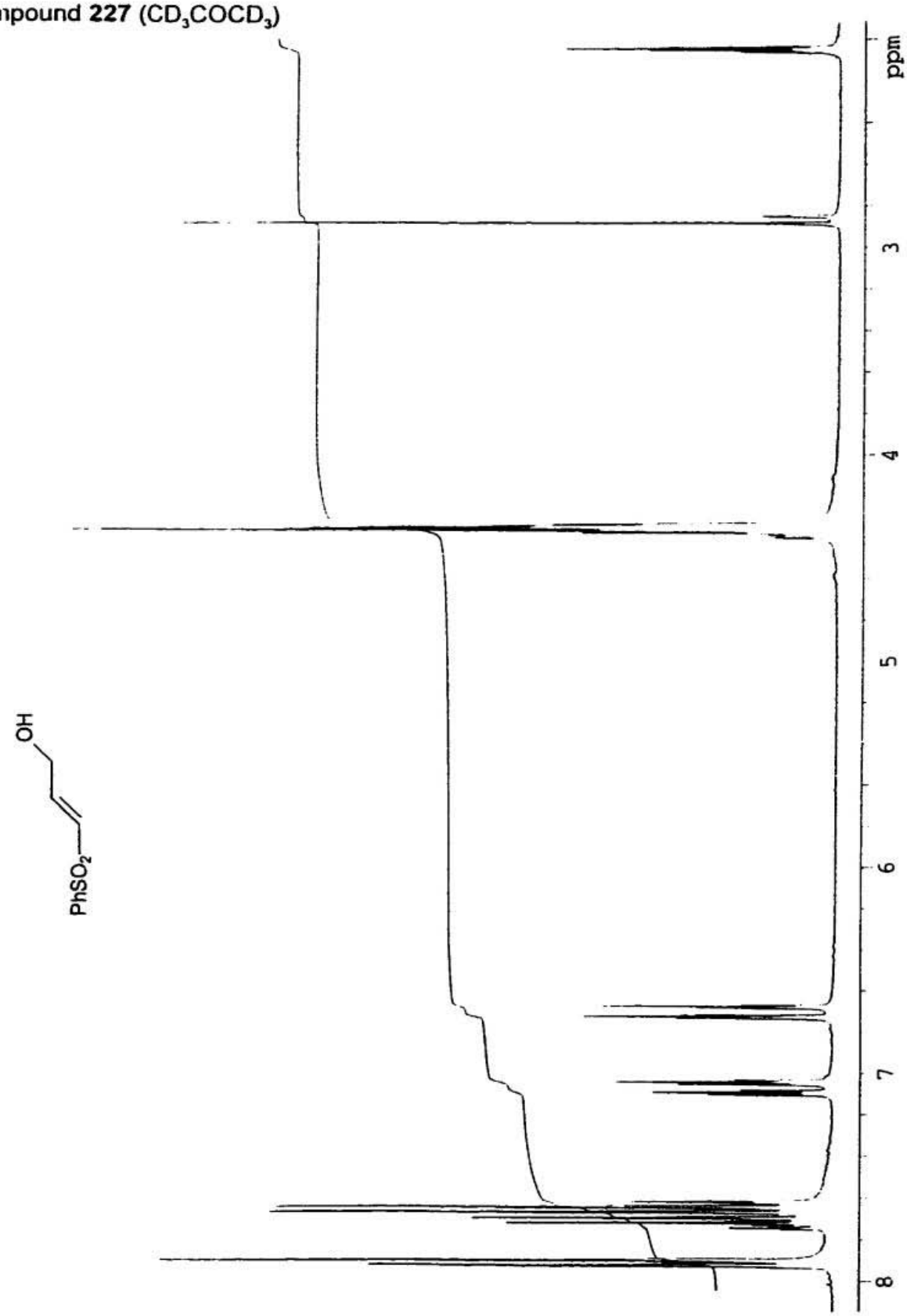
Compounds **224** and **225**, inseparable mixture ($CDCl_3$)



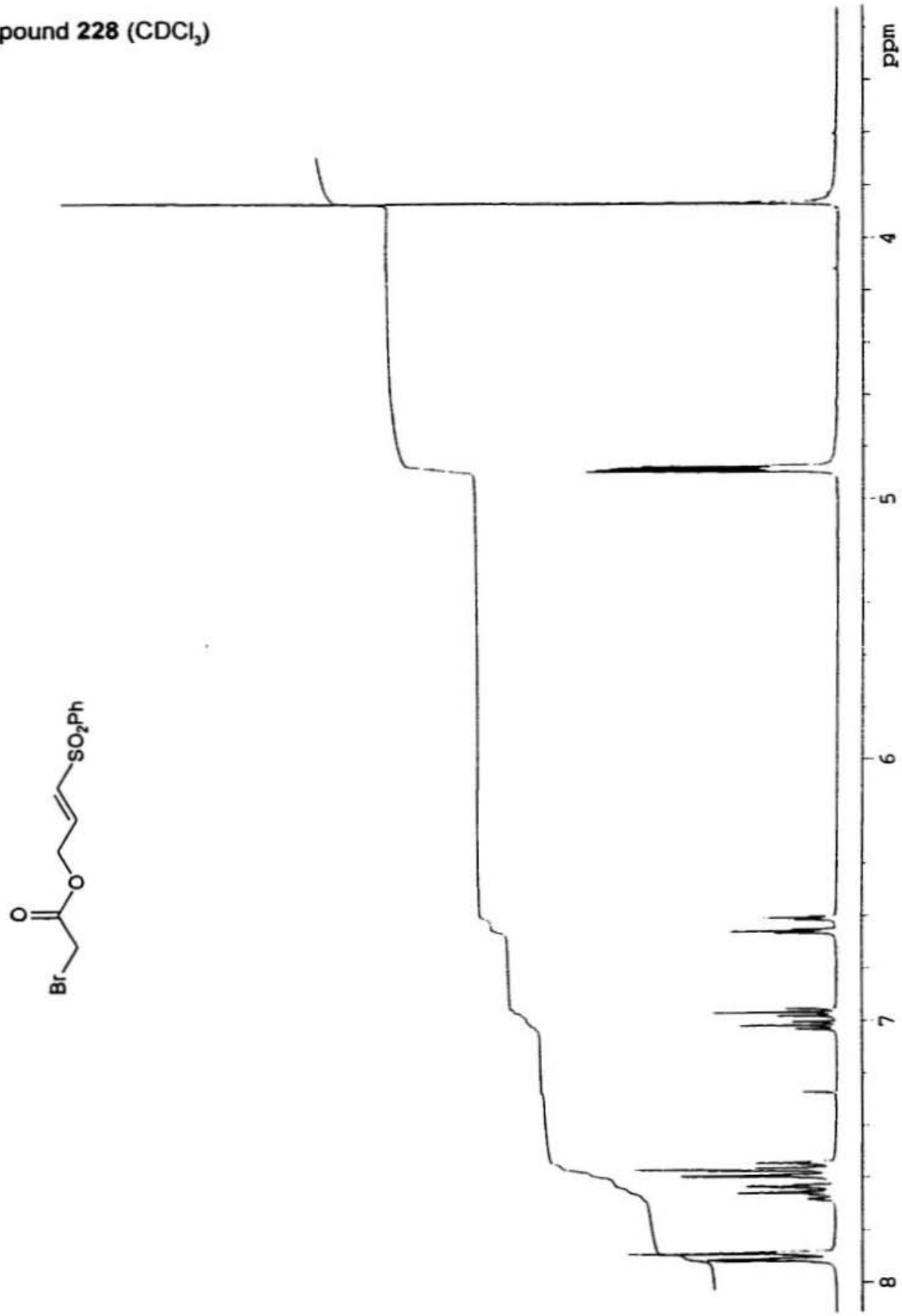
Compound **226** ($CDCl_3$)



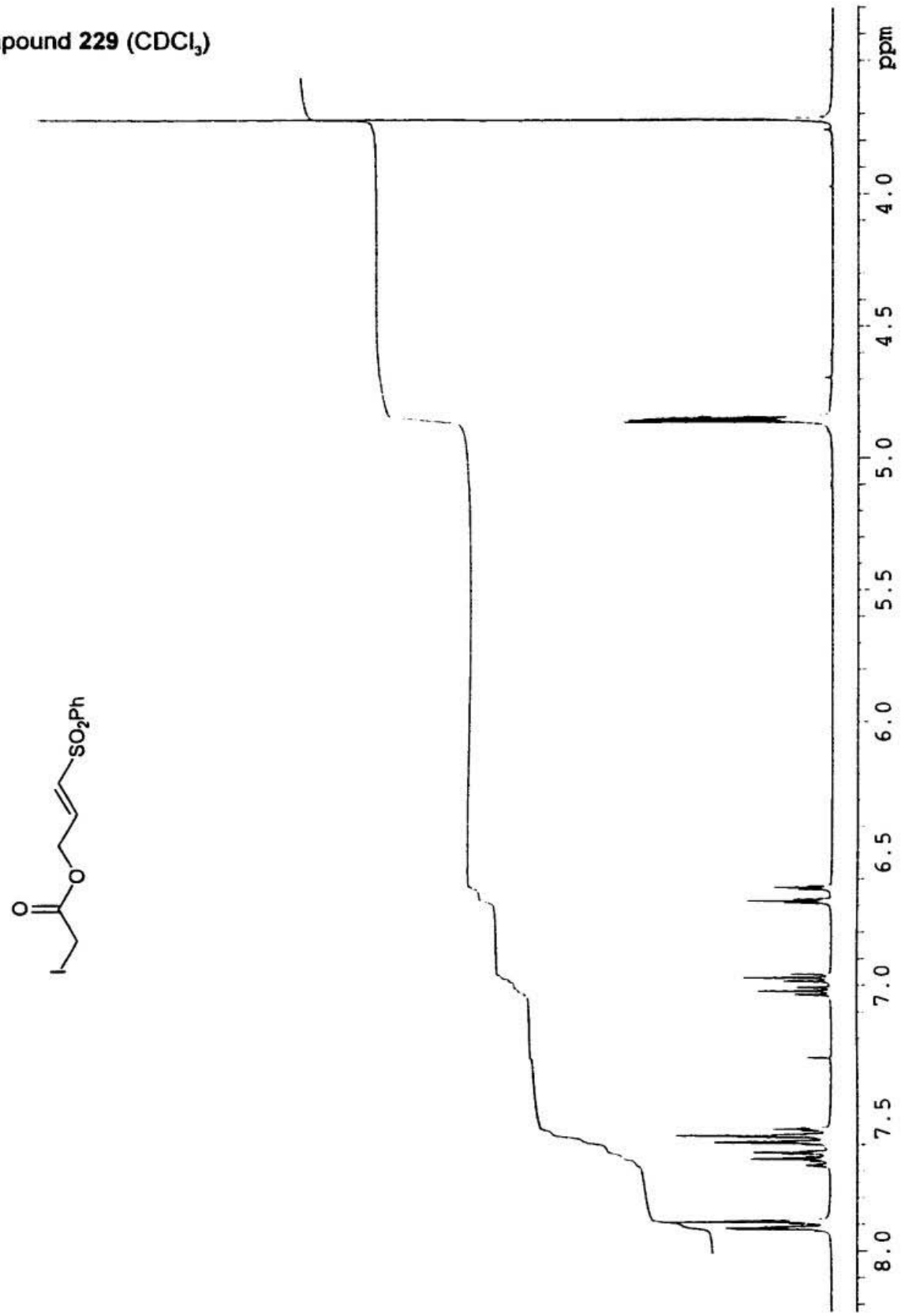
Compound **227** (CD_3COCD_3)



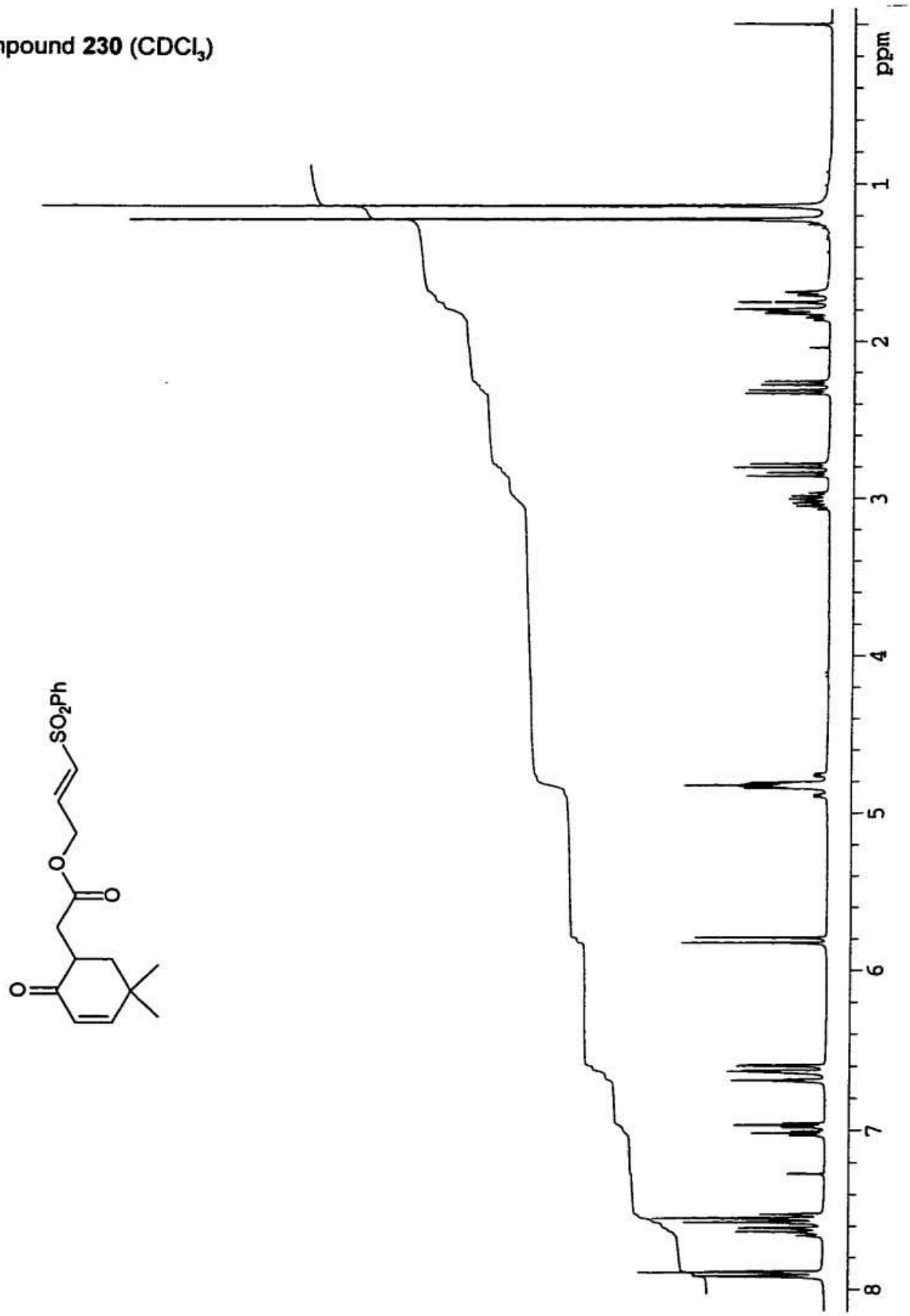
Compound **228** ($CDCl_3$)



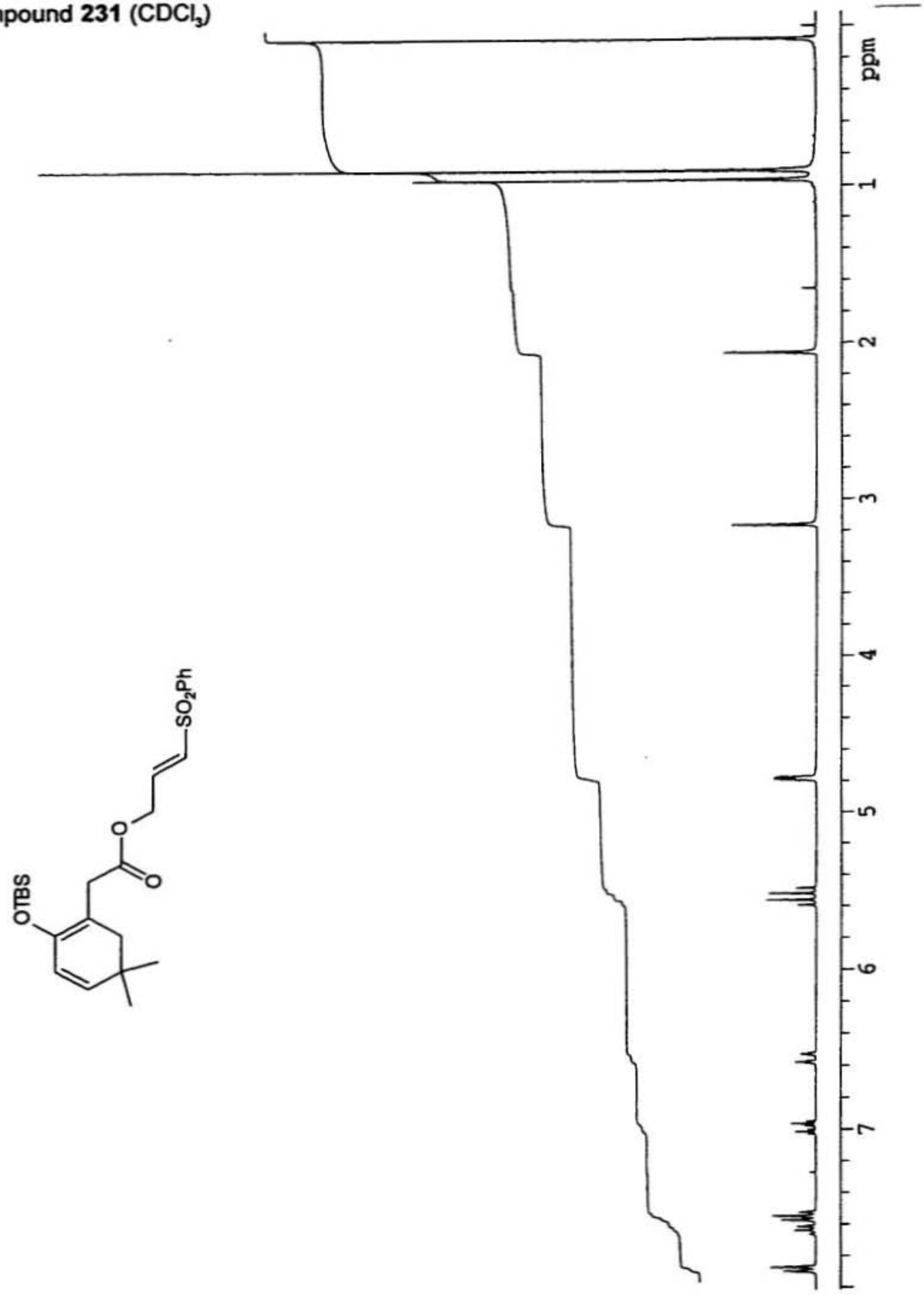
Compound **229** ($CDCl_3$)



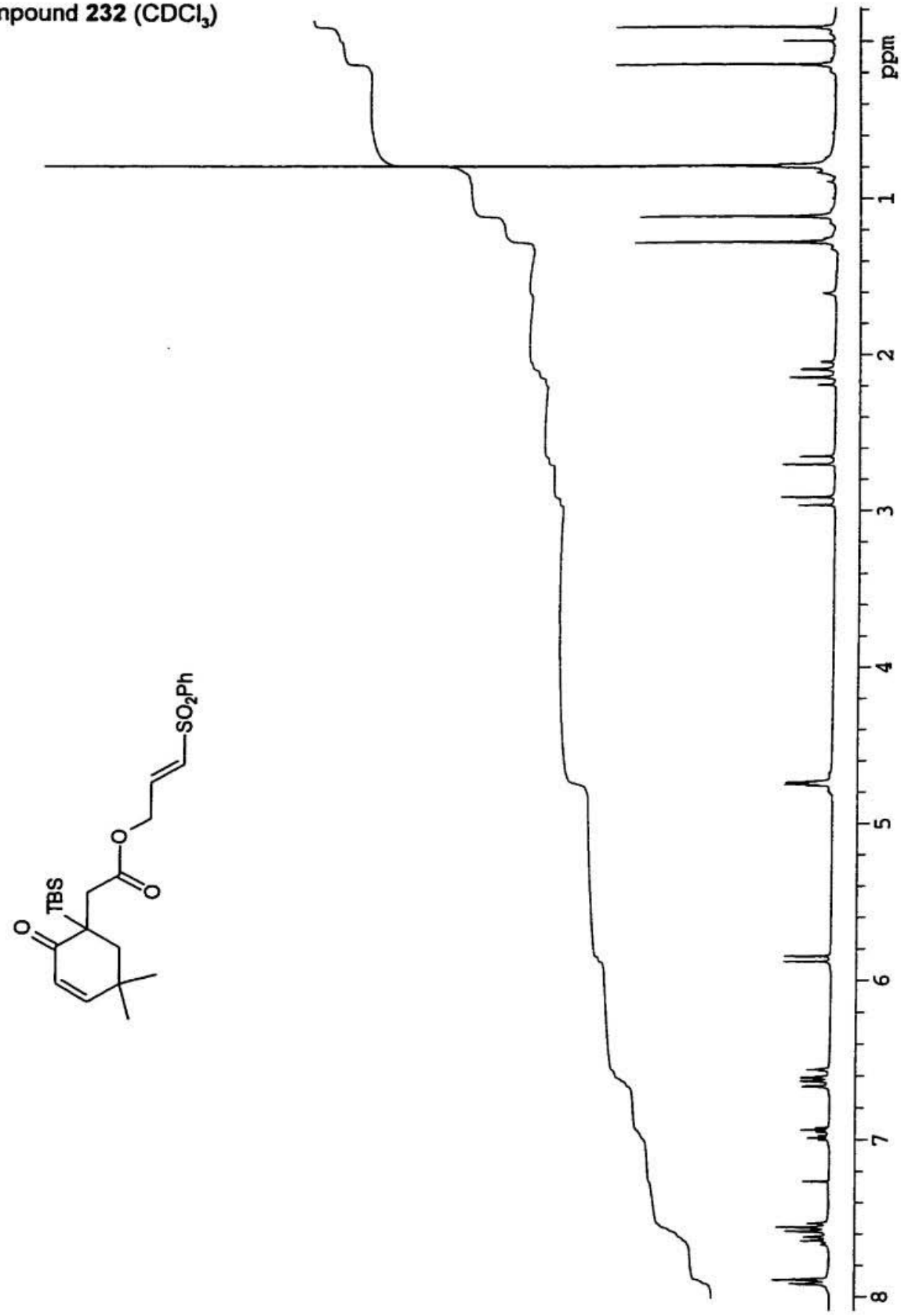
Compound **230** ($CDCl_3$)



Compound **231** ($CDCl_3$)



Compound **232** ($CDCl_3$)



Compound **233** ($CDCl_3$)

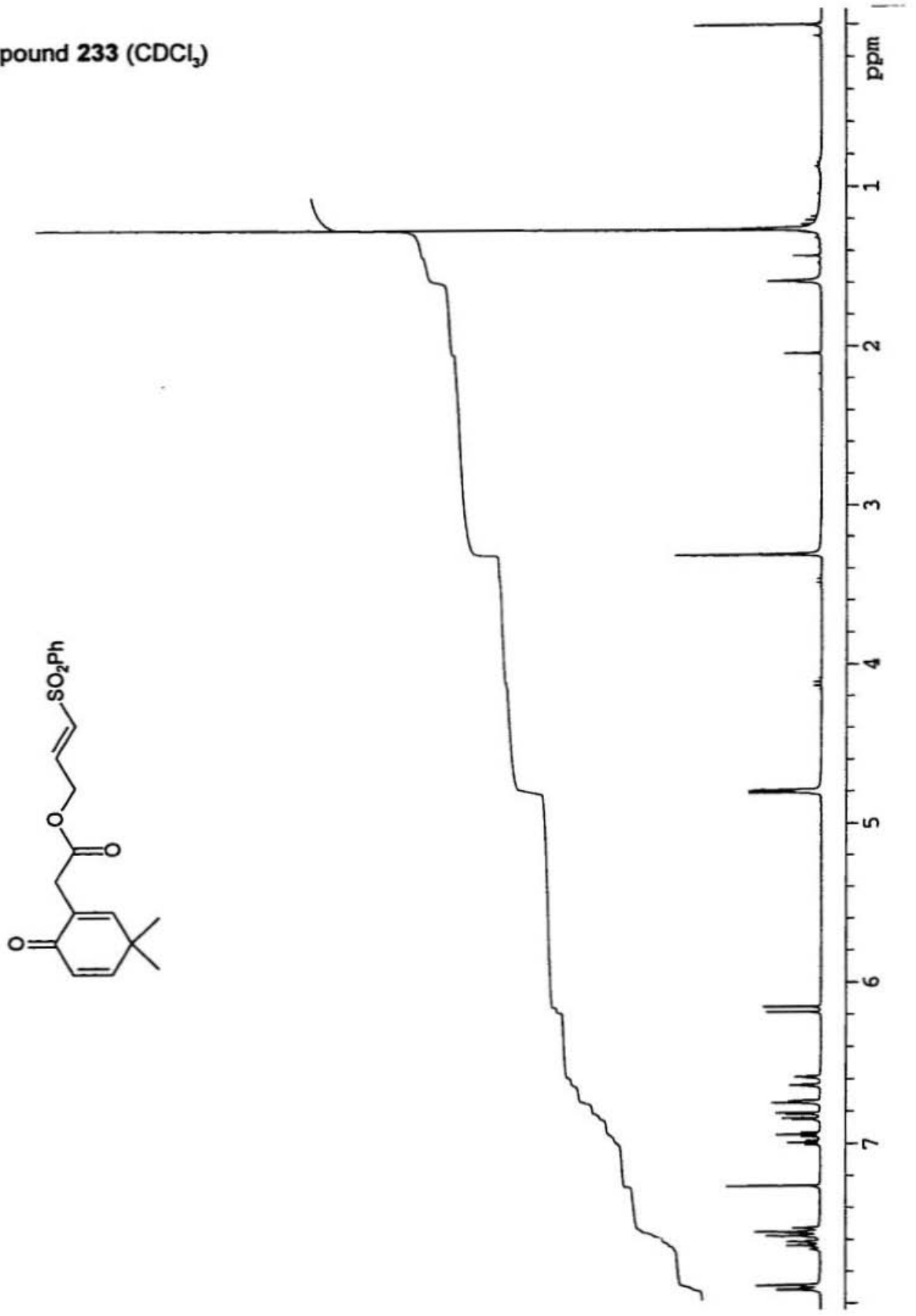
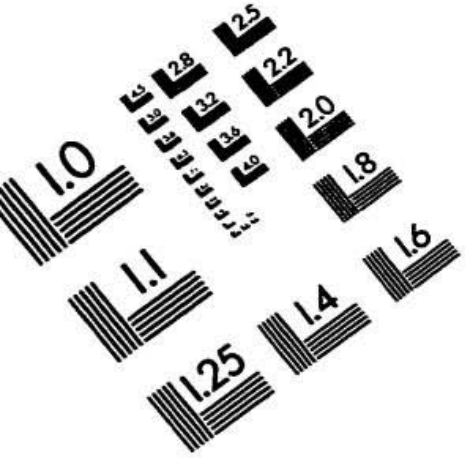
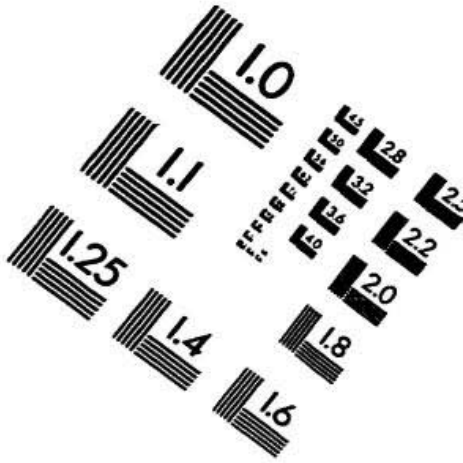
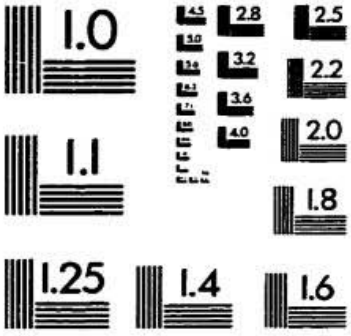
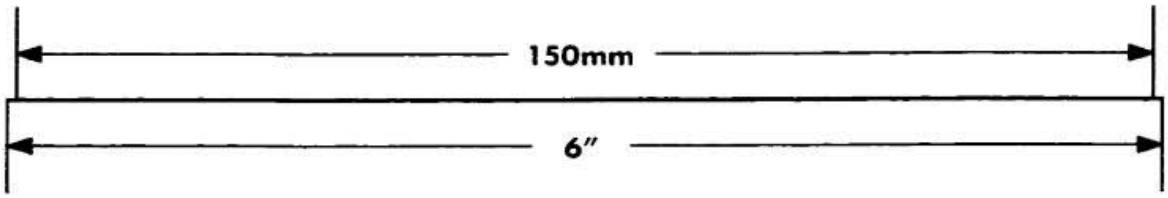


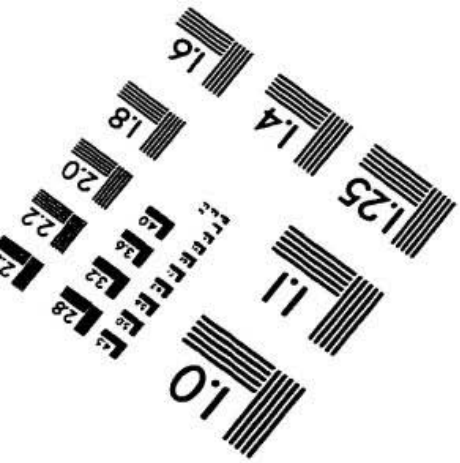
IMAGE EVALUATION
TEST TARGET (QA–3)

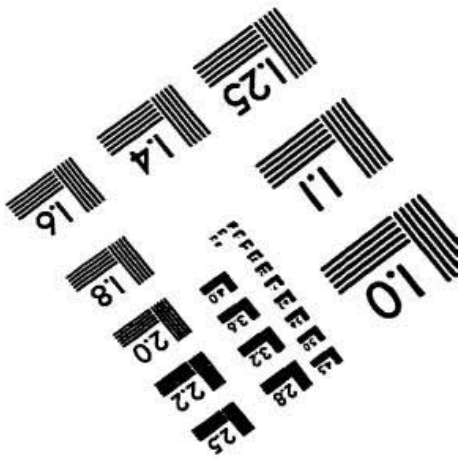












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