University of Alberta

Efficient Intermolecular [3+2] Trapping of the Nazarov Intermediate with Vinyl Sulfides

by

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To the memory of my father "Dr. Murshid S. Mahmoud"

To my mother

To my husband Farook ♥

To my children Omar, Huda and Yahya

Abstract

Tandem or "domino" processes have emerged as a powerful tool for organic synthesis. In these reactions, multiple new bonds or rings are formed in a single stereoselective operation generating complex polycyclic systems. Trapping the Nazarov intermediate with suitable nucleophiles is one of these processes. It is called the interrupted Nazarov reactions. This project is an example of the interrupted Nazarov reactions. Several simple 1,4-pentadien-3-ones were prepared and then treated with $BF_3 \cdot OEt_2$ to undergo Nazarov cyclization to produce oxyallyl cations. Generating this cationic intermediate in the present of electron-rich vinyl sulfides yielding functionalized bicyclo[2.2.1]heptanone products. Although this trapping occurred *via* stepwise cationic [3+2] cycloaddition, the diastereoselectivity of the products was good. This methodology resulted in the formation of three carbon-carbon bonds and up to six new stereocenters.

The ability to transfer a sulfur group in the bicyclo[2.2.1]heptanone products to another functionality was also examined. The polycyclic products contain a sulfur functionality was successfully desulfurized by treating it with Raney nickel. In the process, the carbonyl group was also reduced to an alcohol. In another modification of the sulfide moiety, the functionalized bicyclo[2.2.1]heptanone product was oxidized by m-CPBA to its corresponding sulfoxide. Stirring the sulfoxide product in refluxing toluene successfully eliminated the sulfoxide group and furnished the alkene.

Acknowledgment

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List of Abbreviations

Anal.	Elemental analysis
app.	Apparent
APT	Attached proton test
Ar	Aryl
Bn	Benzyl
brs	Broad singlet
Calcd.	Calculated
COSY	Homonuclear correlation spectroscopy
conc.	Concentrated
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
dq	Doublet of quartets
DCM	Dichloromethane
EI	Electron impact
equiv.	Equivalents
ESI	Electrospray ionization
Et	Ethyl
FTIR	Fourier-transform infrared
h.	hour/hours
HMBC	Heteronuclear multiple bond correlation
HMQC	Heteronuclear multiple quantum correlation
HRMS	High resolution mass spectrometry

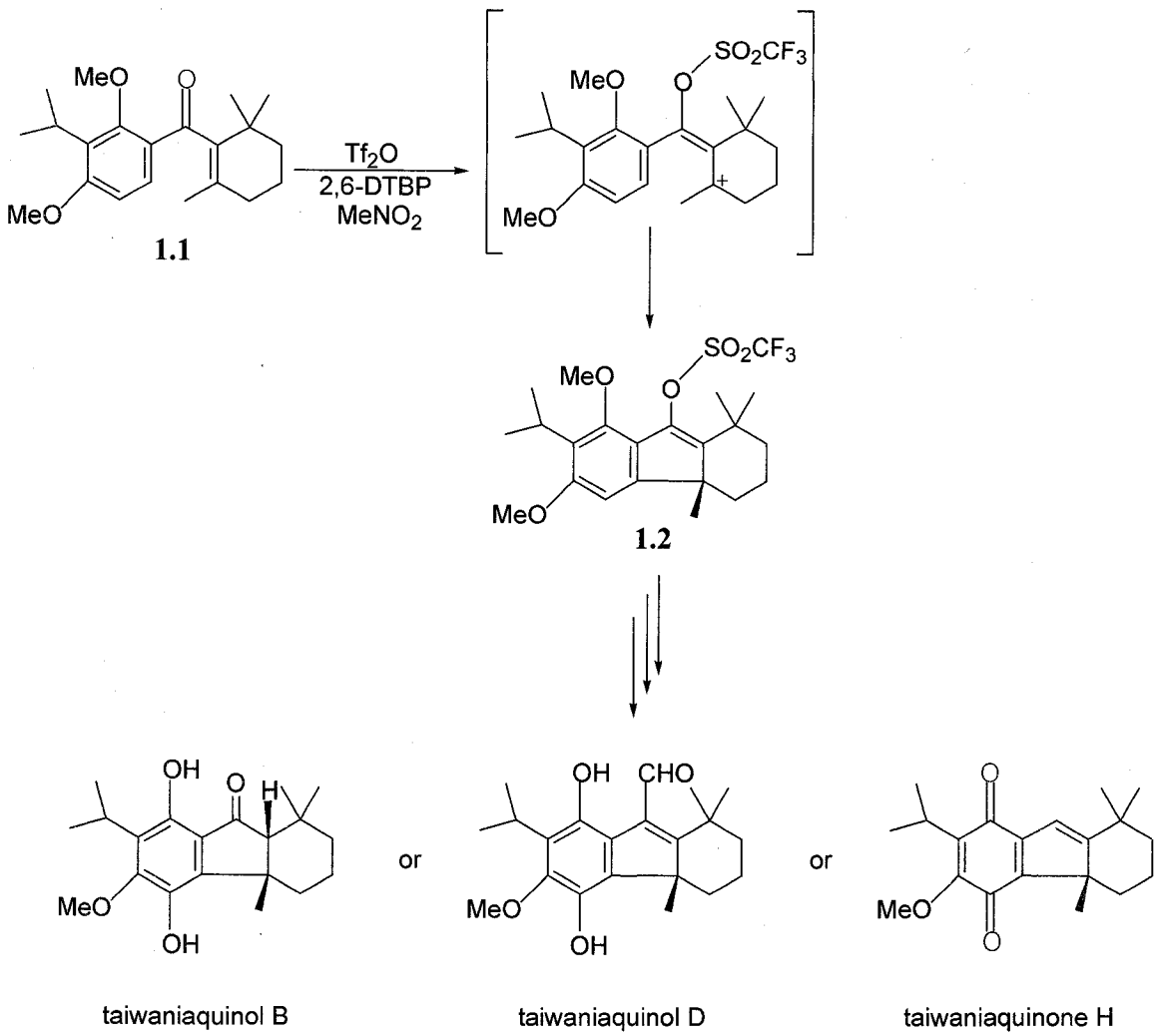
HSQC	Heteronuclear single quantum correlation
IR	Infrared
LA	Lewis acid
m	Multiplet
m-CPBA	meta-Choroperoxybenzoic acid
Me	Methyl
mg	Milligrams
min	Minute/minutes
mL	Milliliters
mmol	Millimoles
m.p.	Melting point
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
Ph	phenyl
ppm	Parts per million
q	quartet
R	Generic alkyl group
Rf	Retention factor (in chromatography)
rt	Room temperature
s	Singlet
t	Triplet
TLC	Thin layer chromatograph

Chapter 1 The interrupted Nazarov reaction

1.1 Introduction

In Nature, there is a great abundance of products that exist or are produced without human interference. Some of these compounds are biologically active and may have useful applications. However, extracting such compounds from their natural sources is not always an easy or cost-effective task. Therefore, finding methods for synthesizing these products in the lab is a more practical alternative.

Many of these natural products contain five-membered rings, which led to the development of several methods for their preparation in synthetic organic chemistry. The Nazarov cyclization is one such method, which is especially powerful in generating cyclopentenone rings from acyclic cross-conjugated dienones.[1] For example, the Taiwaniaquinoids are a family of compounds marked by a tricyclic [6-5-6] ring system with several of its members having biological activity as aromatase inhibitors. A synthetic approach towards this unusual family was recently developed by Trauner and coworkers based on the Nazarov reaction.[2] In their approach, aryl vinyl ketone **1.1** was prepared and then treated with triflic anhydride in the presence of a hindered base (2,6-di-*tert*-butylpyridine; 2,6-DTBP). Under these conditions, aryl vinyl ketone **1.1** undergoes 4π electrocyclization followed by deprotonation to yield **1.2** via aromatic Nazarov reaction. This intermediate **1.2** was then used as a key intermediate to prepare several members of the Taiwaniaquinoid family (Scheme 1.1).



Scheme 1.1 Synthesis of Taiwaniaquinoids via Nazarov cyclization

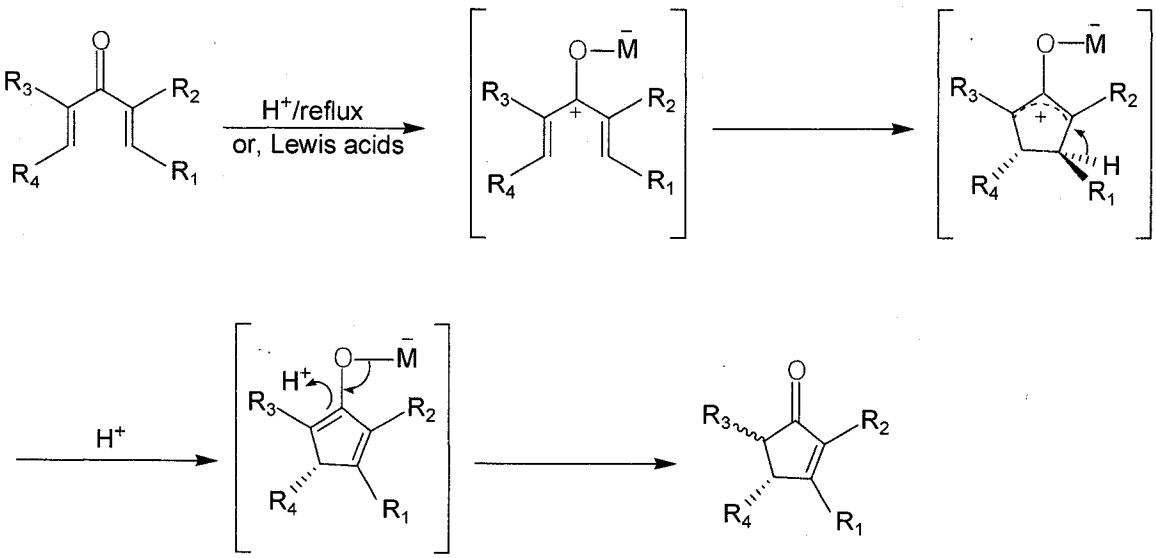
However, the challenges associated with synthesis increase substantially with the increase in molecular complexity. Such molecular structures are prepared through many demanding steps, which include the formation of multiple new bonds and rings. Carrying out many chemical steps in a linear sequence can be very inefficient and time consuming. Therefore, it is highly desirable to design new reactions that form several new chemical bonds in a single process. In this project we devise new methods in which two simple molecular partners are induced to combine with the formation of three new carbon-

carbon bonds. In the process, the molecular complexity of the products is greatly increased, compared to the starting material, and the overall sequence is significantly shortened.

One method that proved to be very useful in organic synthesis is the tandem or "domino" processes.[3,1g] In these reactions, multiple new bonds or rings are formed, thus greatly increasing the molecular complexity in a single step. Trapping the Nazarov intermediate with a suitable nucleophile is considered to be one of these processes. It is called the "interrupted Nazarov reaction." This chapter will provide a brief review of the basic Nazarov reaction, its interrupted variant, and also discuss some examples of the reactions of vinyl sulfides with various electrophiles.

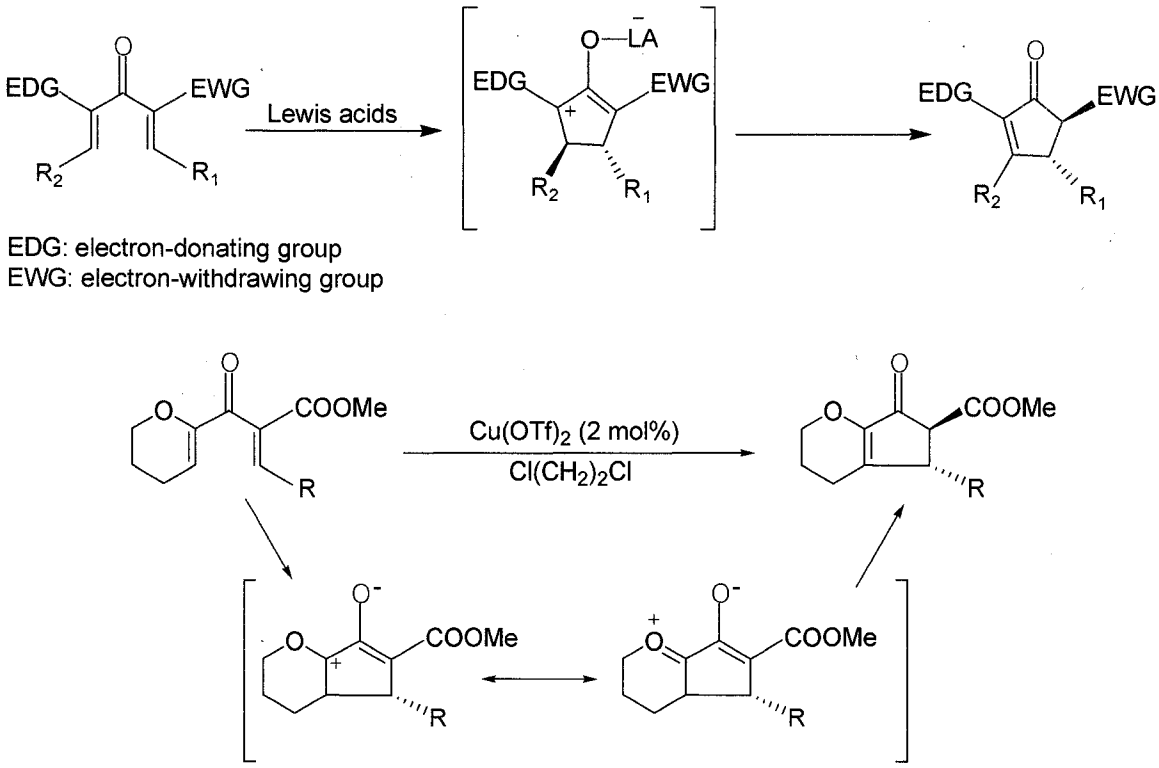
1.2 Nazarov reaction

The Nazarov cyclization is considered as an electrocyclic reaction where 1,4-dien-3-ones undergo ring closure to form cyclopentenones. Thermally, this reaction is initiated with protic or Lewis acid to generate a pentadienyl cation, which undergoes a conrotatory 4π electrocyclization to produce the five-membered ring oxyallyl intermediate. Elimination of a proton followed by protonation of the transient enolate furnishes the cyclopentenones with up to two new stereocenters (Scheme 1.2).[4]

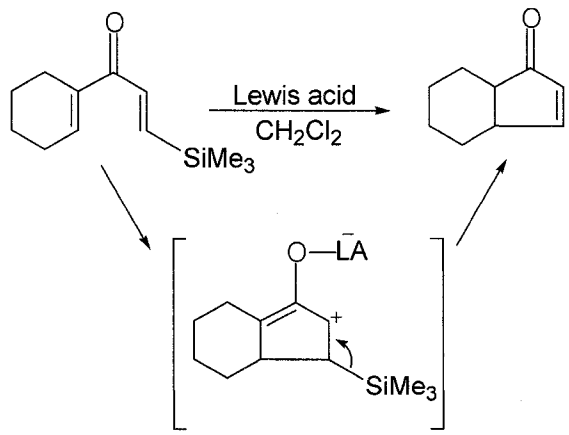


Scheme 1.2 The proposed mechanism of Nazarov cyclization

However the regioselectivity of the elimination step is quite low, producing a mixture of products. Recently a lot of effort has been done to control of the termination step of the Nazarov reaction.[5] For example, the conjugated system in the Nazarov cyclization can be polarized by using electron-donating and withdrawing groups as substituents. This polarization facilitates the cyclization and gives better regioselectivity in the elimination step (Scheme 1.3).[6] Also the ability of silicon to stabilize the β-carbocations was used to direct the introduction of the new double bond in Nazarov cyclization (Scheme 1.4).[7]



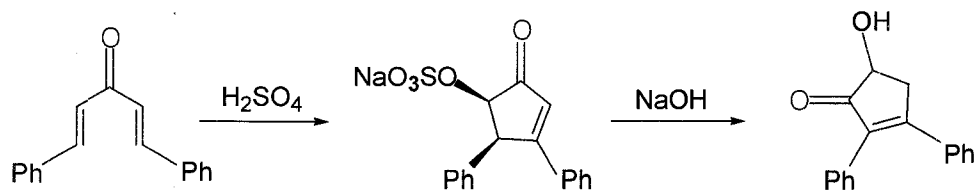
Scheme 1.3 A polarized Nazarov cyclization



Scheme 1.4 Silicon-Directed Nazarov cyclization

1.3 Interrupted Nazarov cyclization

The initial electrocyclization in Nazarov reaction results in a new carbon-carbon bond and a reactive oxyallyl intermediate. In 1972, an unexpected product resulting from apparent solvent capture of this intermediante was reported (Scheme 1.5).[8] This result suggested that the lifetime of the oxyallyl cation intermediate is long enough to be trapped with a suitable nucleophile. Trapping the cationic Nazarov intermediate with a suitable nucleophile provides a one-step process that potentially forms several carbon–carbon bonds at once and increases molecular complexity in a single step. Recently, West and coworkers have reported a number of examples of trapping the cationic Nazarov cyclization intermediate via intra- and intermolecular fashion, as will be discussed in the next two sections.



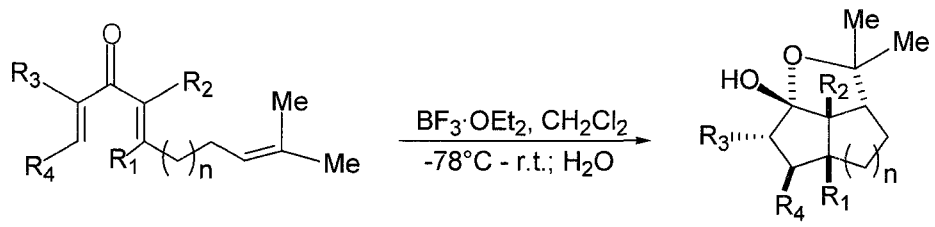
Scheme 1.5 Solvent capture of the oxyallyl intermediate

1.4 Intramolecular trapping of Nazarov intermediate

1.4.1 Cycloisomerization of acyclic trienone

In this example, the Nazarov oxyallyl intermediate was trapped via cationic cyclization onto pendant olefins in a single step. The acyclic, achiral trienones were

treated with $BF_3{\cdot}OEt_2$ to furnish diquinanes (Table 1.1).[9] In the processes of cyclization, the reaction was activated with the Lewis acid to form a pentadienyl cation, which underwent a conrotatory 4π electrocyclization to form an oxyallyl cation intermediate. This cation was trapped by the pendant olefin, in a 5-exo fashion, to generate the tertiary carbocation, which was subsequently trapped with the boron enolate oxygen. This is possible only if the final ring closure occurs in endo-disposed geometry of the generated tertiary carbocation through a compact transition state. The hydration of the strained enol ether via the selective protonation from the convex face produced the hemiketal **1.4** (Scheme 1.6). In this methodology, two carbon-carbon bonds and up to five new stereocenters were formed in one pot reaction.

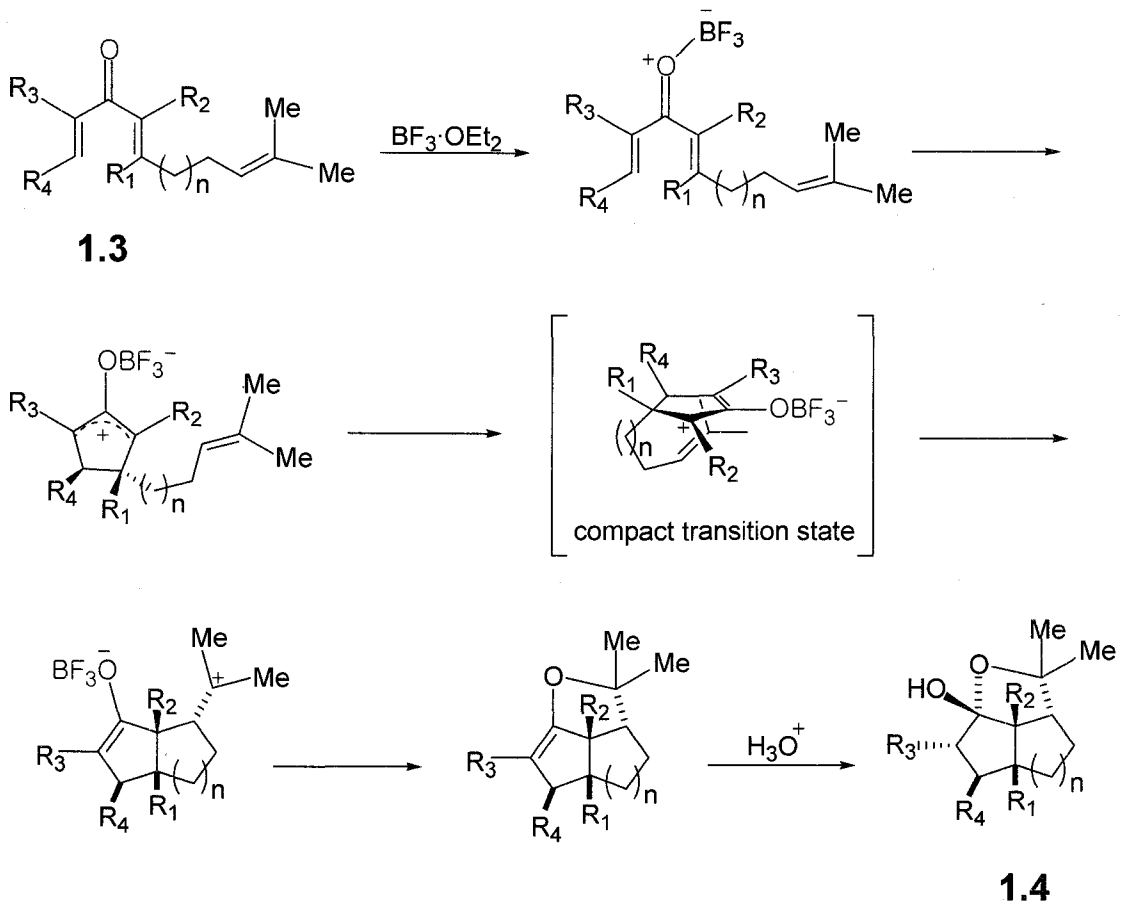


1.3 **1.4**

entry	dienone	R_1	R_2	R_3	R_4	n	Yield(%)
1	1.3a	H	Me	Me	H	1	75
2	1.3b	H	Me	$C(CH_3)_3$	H	1	89
3	1.3c	H	Me	CH_2CH_3	Me	1	73
4	1.3d	H	Me	$(CH_2)_4$		1	62
5	1.3e	H	Me	Me	H	2	42
6	1.3f	Me	H	Me	H	1	a

[(a)] Complex mixture of products.

Table 1-1 Cycloisomerization of acyclic trienone

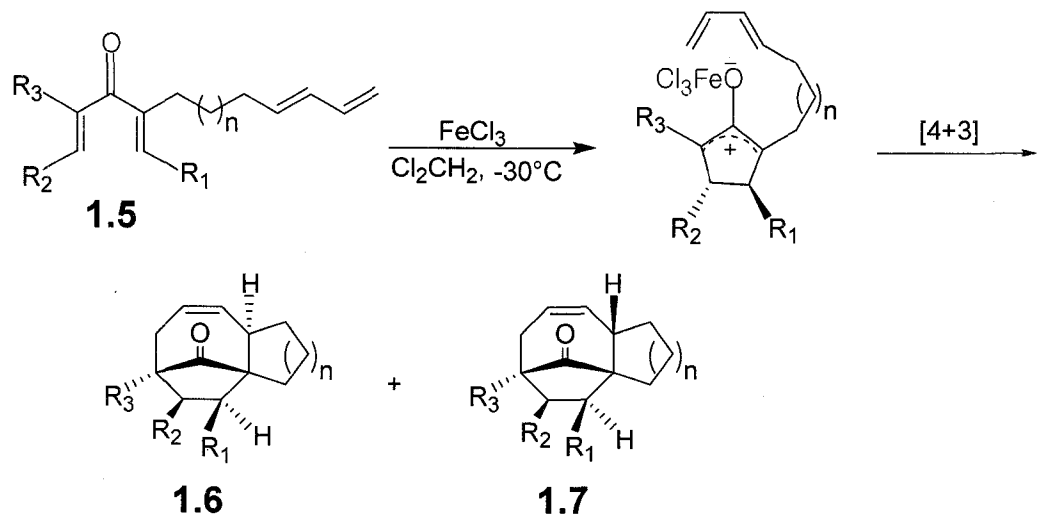


Scheme 1.6 Cycloisomerization of acyclic trienone

1.4.2 Cycloisomerization of acyclic tetraenones

This is another example of a tandem reaction where a 1,4-diene-3-one bearing a pendant 1,3-diene undergoes Nazarov cyclization followed by an intramolecular [4+3] cycloaddition to produce tricyclic compounds. Three new carbon-carbon bonds were formed and up to five new stereocenters (Table 1.2).[10] This reaction showed a complete facial selectivity where the diene approached from the less hindered face of the oxyallyl cation in the cycloaddition process. Also, cases with a three-carbon tether led to low

exo/endo selectivity. However, with a four-carbon tether, complete exo selectivity was seen.

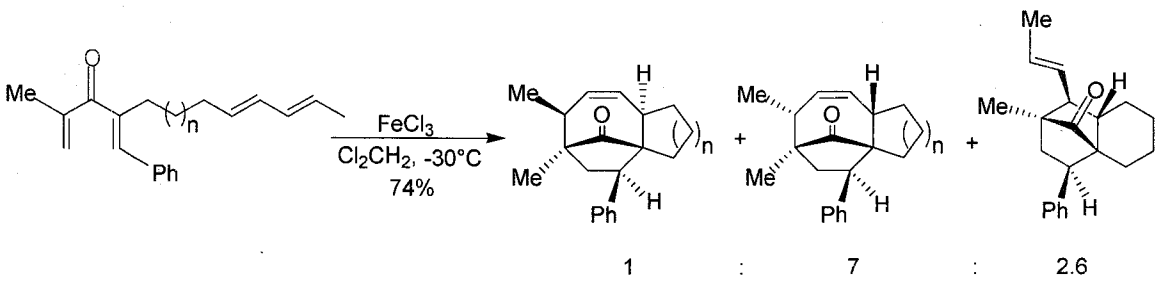


entry	substrate	R_1	R_2	R_3	n	yield (%)	ratio 1.6:1.7
1	1a	Me	H	Me	1	65	1.3:1
2	1a	Ph	H	Me	1	72	1.3:1
3	1a	Me	H	Me	2	67	0:1
4	1b	Ph	H	Me	2	75	0:1
5	1b	H	$(CH_2)_4$		1	98	1.4:1

Table 1-2 Intramolecular [4+3] cycloaddition

In a case in which the 1,3-diene possessed a methyl group on its terminus, the reaction led to three products in a combined yield of 74% (Scheme 1.7). The exo isomer of the [4+3] adduct was the major one and a formal [3+2] adduct was the second major

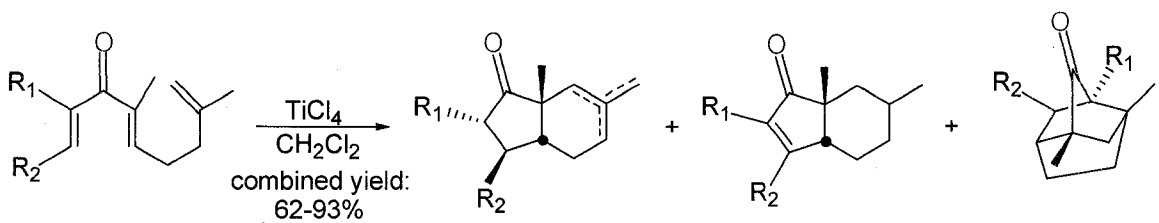
isomer. Its formation can be explained based on a stepwise nucleophilic trapping of the oxyallyl cation, followed by enolate closure onto the resulting allylic carbocation.



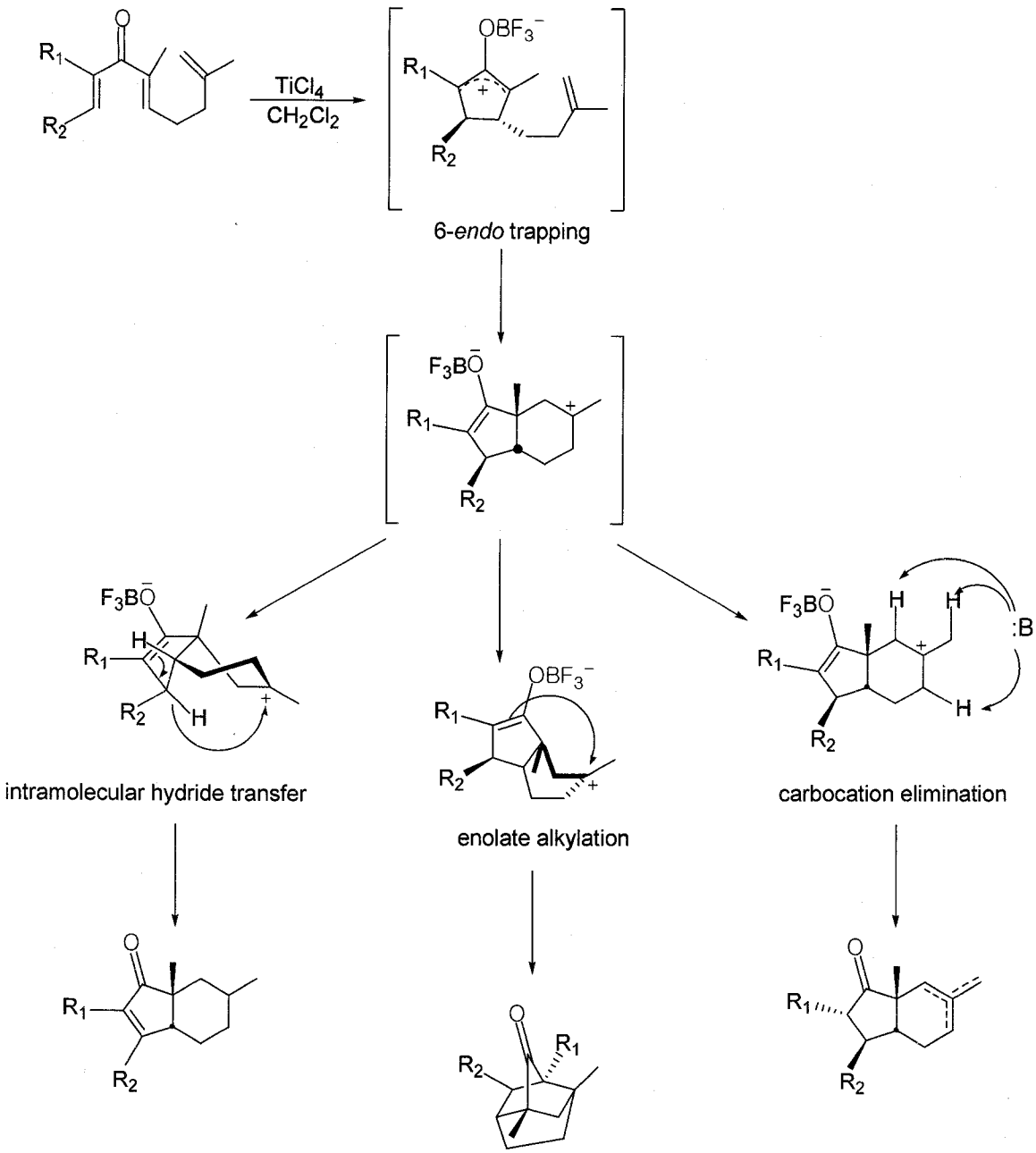
Scheme 1.7 Cycloisomerization of acyclic tetraenones

1.4.3 6-endo trapping of the Nazarov oxyallyl intermediate

So far, we saw that the Nazarov oxyallyl intermediate can be trapped by the pendant olefin in a 5- or 6-*exo* cation-olefin cyclization to produce diquinane or hydrindane products. However, the hydrindane skeleton can also be assembled by trapping the Nazarov intermediate in 6-*endo* cationic cyclization (Scheme 1.8).[11] In this process the starting trienone was treated with $BF_3 \cdot OEt_2$ at -78 °C followed by warming to 0 °C and workup to generate carbocationic hydrindane intermediates. These intermediates undergo several termination events to furnish the final products (Scheme 1.9).



Scheme 1.8 6-Endo trapping of the Nazarov oxyallyl intermediate

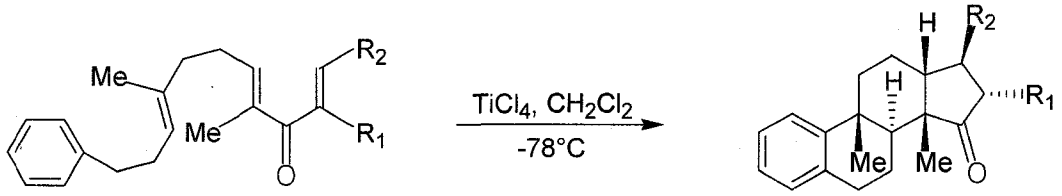


Scheme 1.9 Termination events to furnish the final products

1.4.4 Cascade polycyclization of aryltrienones

In this neat methodology, West and coworkers converted simple aryl trienone precursors, through cascade cationic polycyclization processes, into tetra-or pentacyclic

skeletons. This conversion was accomplished with high-yield and diastereoselectivity (Table 1.3).[12]



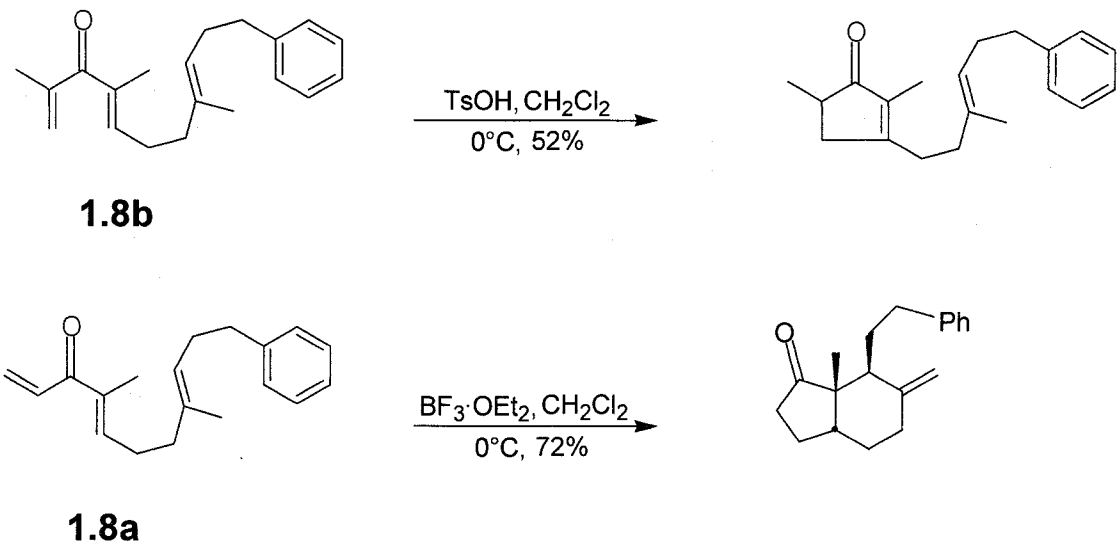
1.8 **1.9**

entry	substrate	R_1	R_2	Product	Yield (%)
1	1.8a	H	H	1.9a	--[b]
2	1.8b	Me	H	1.9b	99
3	1.8c	Me	Et	1.9c	73
4	1.8d	$(CH_2)_4$		1.9d	98
5	1.8e	$(CH_2)_4$		1.9e	74

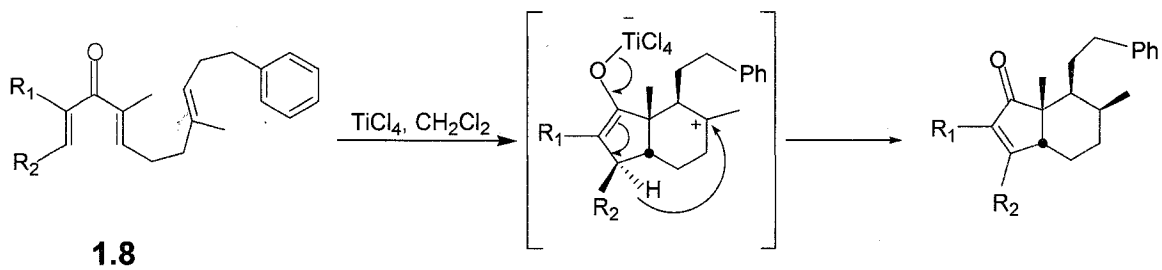
[(b)] Oligomeric material was isolated.

Table 1-3 Cascade polycyclization of aryltrienones

To study the reaction conditions, **1.8b** was treated with protic acid; under this condition the "traditional" Nazarov cyclization product was formed. However, treating **1.8a** with $BF_3{\cdot}OEt_2$ at 0°C furnished the hydrindenone adduct (Scheme 1.10). In the previous two cases, the formation of the elimination product ceased the production of the desired cascade cyclization product. Switching to strong Lewis acid like $TiCl_4$ and reducing the temperature to -78°C, aryl trienone cleanly produced the cascade polycyclization product. The formation of minor products in the case of **1.8c** and **1.8e** was explained based on an intramolecular hydride transfer process (Scheme 1.11).



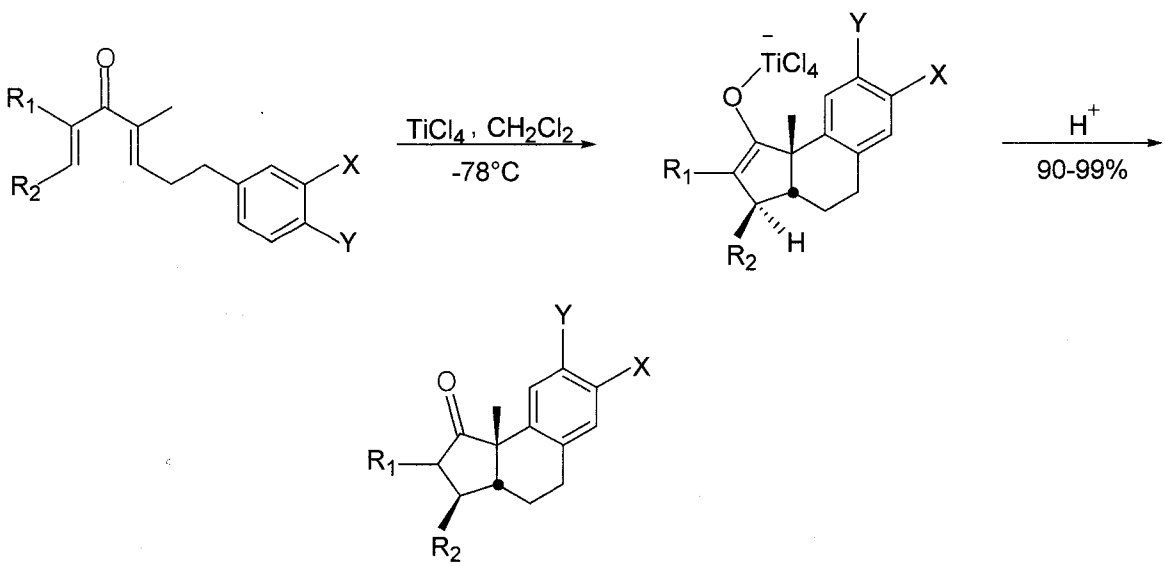
Scheme 1.10 The formation of the elimination product



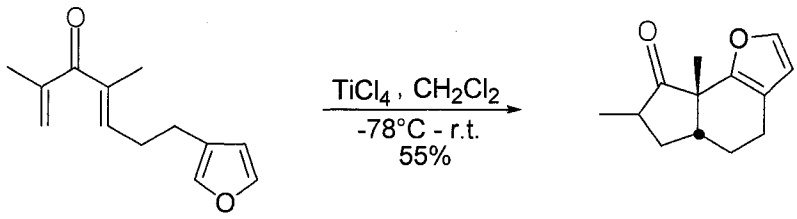
Scheme 1.11 Intramolecular hydride transfer process

1.4.5 Trapping of the Nazarov intermediate with substituted arenes

This example of the interrupted Nazarov cyclization relied on the trapping of the Nazarov oxyallyl intermediate via electrophilic aromatic substitution. In this single chemical step, aryl dienones were converted into benzohydrindenones in high-yield and stereoselectivity (Scheme 1.12).[13] Initially, unsubstituted phenyl was used with $BF_3{\cdot}OEt_2$ and $TiCl_4$ as a Lewis acids; however, no trapping products where obtained. Using more electron-rich arenes in the presence of $TiCl_4$, rapidly and cleanly produced the arene-fused hydrindenones. Replacing the pendant aryl group in the aryl dienones with furan and treating it with the $TiCl_4$ furnished furohydrindenone in 55% yield (Scheme 1.13).



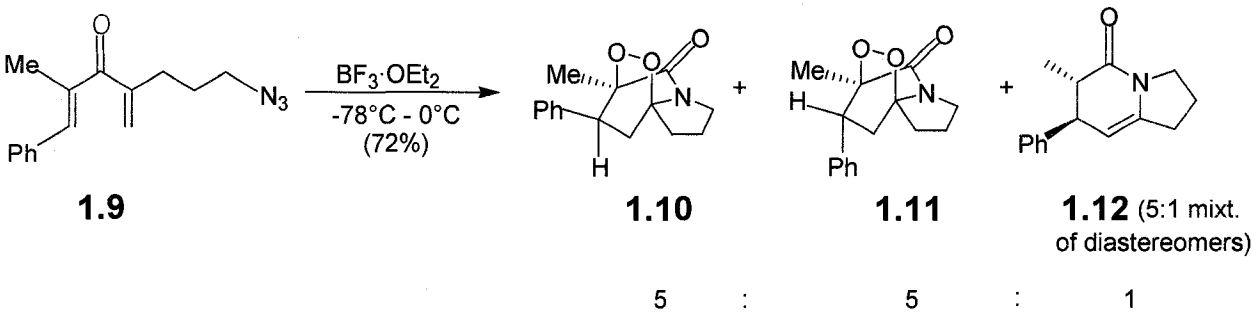
Scheme 1.12 Trapping of the Nazarov intermediate with substituted arenes



Scheme 1.13 Trapping of the Nazarov intermediate with furan

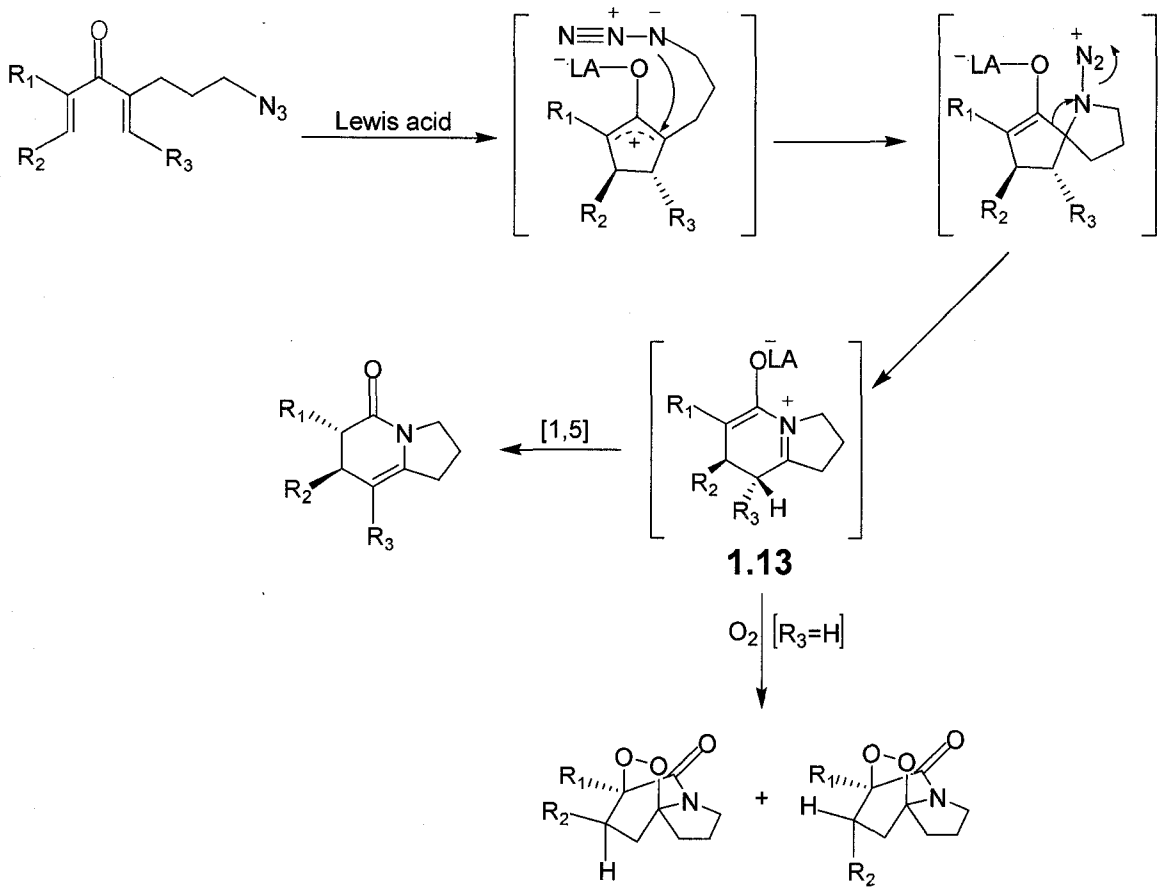
1.4.6 Inramolecular azide trapping of the Nazarov intermediate

The previous sections showed that trapping the Nazarov cyclization intermediate in intramolecular fashion with nucleophiles increased the molecular complexity in one step. Several polycyclic compounds were prepared by using these tandem processes. However, in all cases the nucleophiles were carbon π nucleophiles. Recently, West and coworkers disclosed a new methodology where pendent azides were used as heteronucleophiles to trap the Nazarov cyclization intermediate in intramolecular fashion.[14] This provides a convenient method to synthesis polycyclic systems containing heterocyclic rings. Their initial focus was to use dienones with pendent azide side chains to undergo 1,3-dipolar cycloaddition. To achieved that, **1.9** was prepared and treated with $BF_3{\cdot}OEt_2$ at -78°C followed by warming to 0°C. Under these conditions the starting material disappeared and three products formed (Scheme 1.14).[14] To their surprise, diastereomeric endoperoxides **1.10** and **1.11** were the major products. The third compound dihydropyridone **1.12** was the minor product.



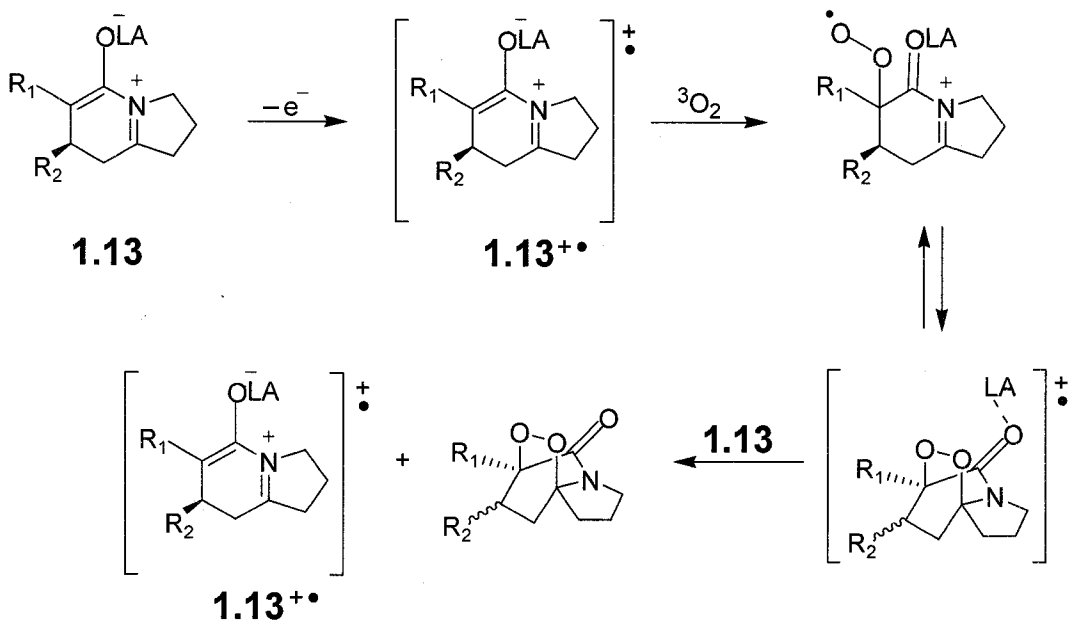
Scheme 1.14 Azide trapping and peroxide formation

It was suggested that all the three products formed from the same intermediate **1.13** (Scheme 1.15). The proposed mechanism for the formation of this intermediate begins with attaching the Lewis acid to the oxygen atom of the 1,4-diene-3-one to form the Nazarov cyclization intermediate followed by nucleophilic capture of the allyl carbocation by the internal nitrogen atom to form a zwitterion. The zwitterion, after that, undergoes bond migration which leads to the release of dinitrogen to form intermediate **1.13**. Intermediate **1.13** can undergo 1,5-hydrogen shift to form dihydropyridone products. However, trapping this intermediate with adventitious oxygen resulted in the formation of the two major diastereomeric endoperoxides products. When the oxygen is rigorously excluded from the reaction, only **1.12** is isolated in 70% yield.

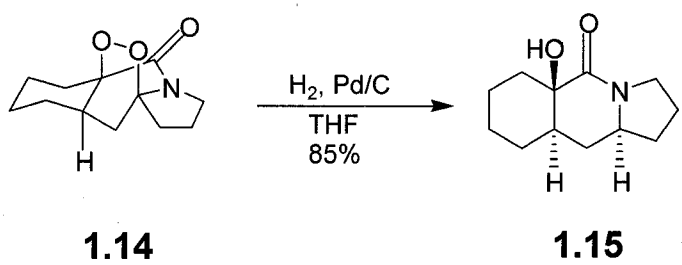


Scheme 1.15 Proposed mechanism of azide trapping

The lifetime of the 1,4-dipole intermediate **1.13** is expected to be limited due to the 1,5-hydrogen shift pathway. However the rigidity of the bi- and tricyclic1,4-dipole intermediate in this study seems to decrease the rate of the 1,5-hydrogen shift, which subsequently will increase the lifetime of the betaines **1.13** and make it available to be trapped by the oxygen. The proposed mechanism for trapping intermediate **1.13** with oxygen is *via* cation radical chain mechanism as in Scheme 1.16. Reducing peroxide **1.14** under catalytic hydrogenation conditions furnished the α-hydroxylactams **1.15** (Scheme 1.17).



Scheme 1.16 Cation radical chain mechanism for peroxide formation

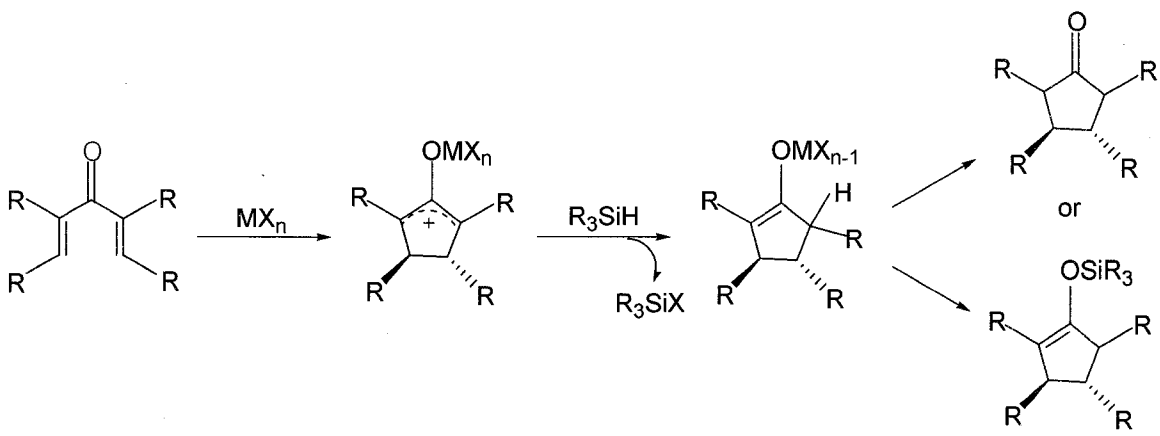


Scheme 1.17 Reduction of the peroxide bridge

1.5 Intermolecular trapping of Nazarov intermediate

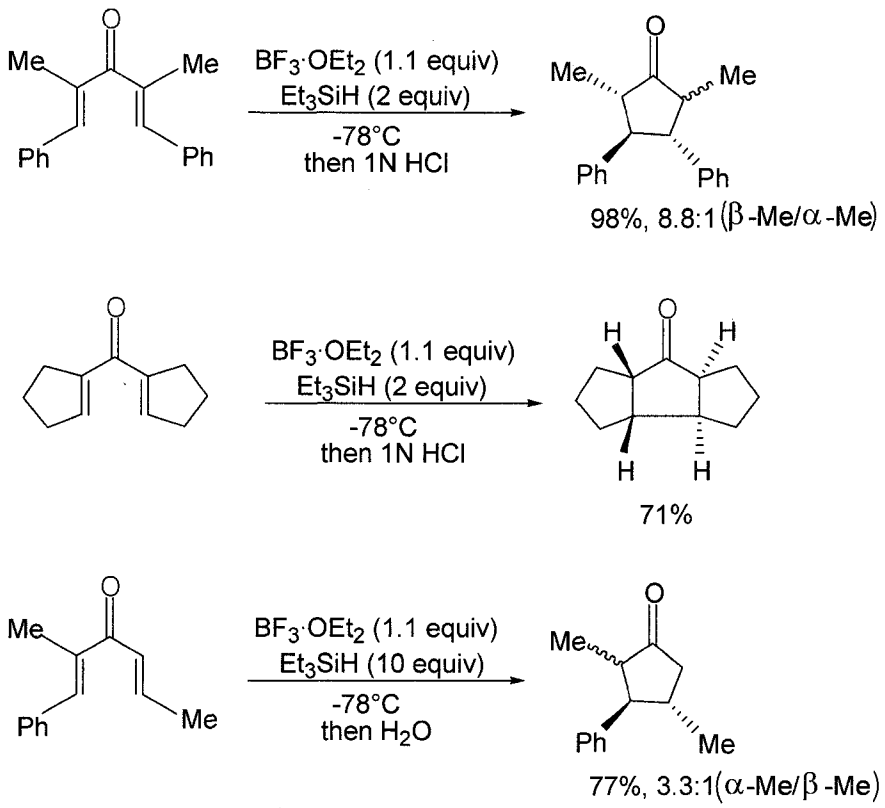
1.5.1 The reductive Nazarov cyclization

Among the cyclopentannulation processes, Nazarov cyclization has emerged as a rapid method to prepare cyclopentenones from 1,4 diene-3-ones. However, termination of the Nazarov cyclization by elimination usually destroys any diastereoselectivity involving the new formed carbon-carbon bond. In 1998, Giese and West showed that the elimination step of the Nazarov cyclization could be avoided by reducing the generated oxyallyl intermediate in an intermolecular hydride delivery with the Lewis acid–stable hydride source Et_3SiH. So, in a single step, acyclic dienones are converted into cyclopentanones, or their enol silanes, with preservation of the newly formed stereocenters (Scheme 1.18).[15]

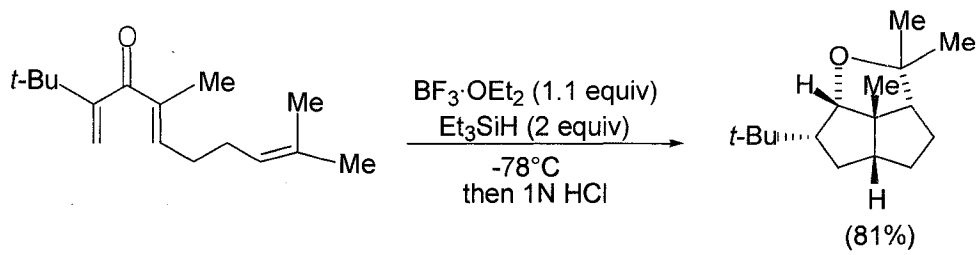


Scheme 1.18 The reductive Nazarov cyclization

In this methodology, several dienones were trapped in the presence of the $BF_3{\cdot}OEt_2$ as a Lewis acid and Et_3SiH as a hydride source to form the cyclopentanones in high yield and diastereoselectivity (Scheme 1.19). Subjecting a dienone, bearing a pendant alkene, to this reaction condition, exclusively produced the tricyclic compound. This product resulted from 5-*exo* cyclization followed by ionic hydrogenation of the resulting enol ether (Scheme 1.20).



Scheme 1.19 The formation of the cyclopentanones via reductive Nazarov cyclization

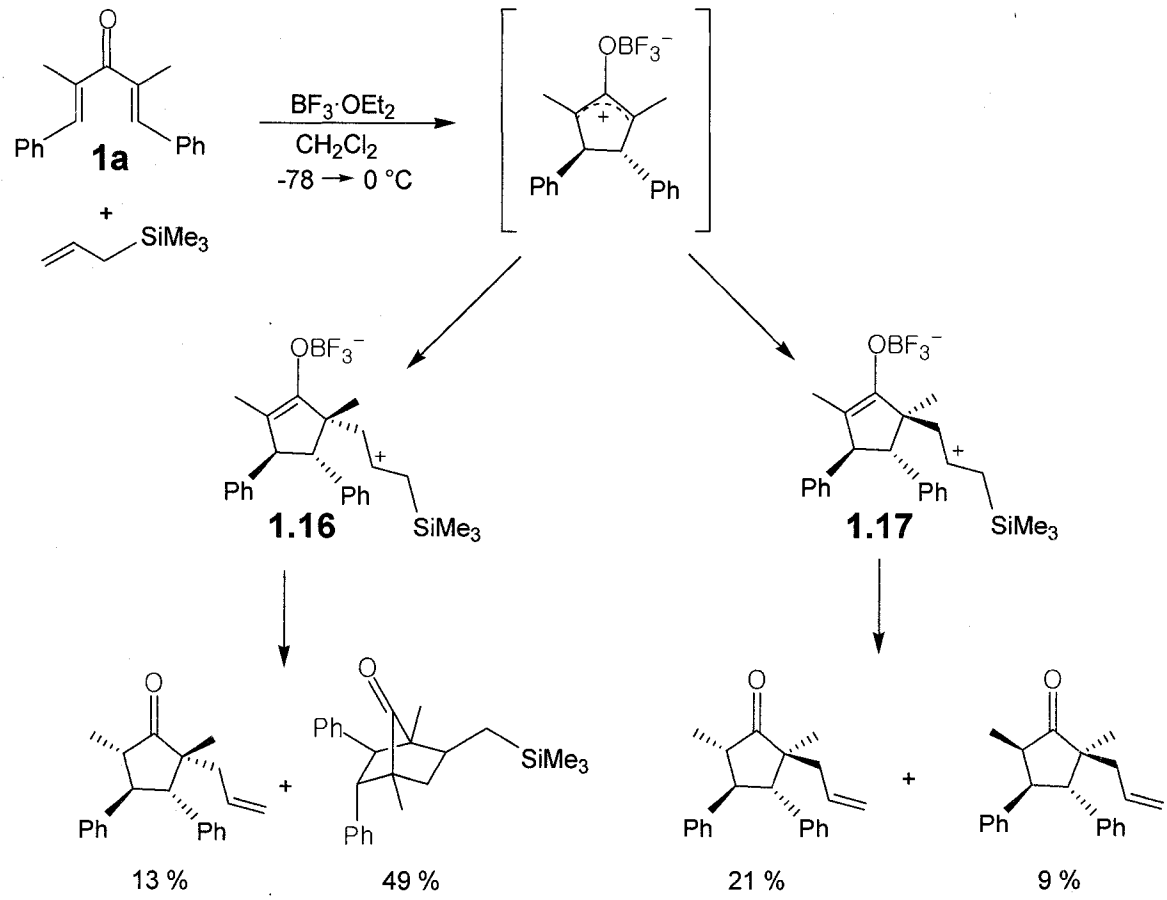


Scheme 1.20 The formation of the tricyclic compound via tandem processes

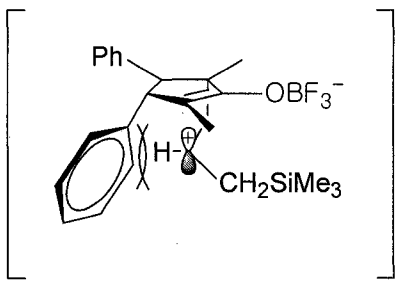
1.5.2 Domino electrocyclization/[3+2] cycloadditions with allylsilanes

The high-yield and stereoselectivity of the intermolecular trapping of the Nazarov cyclization intermediate with the silyl hydride encouraged West and coworkers to investigate the reactivity of the oxyallyl cations generated during the Nazarov cyclization toward carbon nucleophiles. Allylsilanes, which are quite nucleophilic and stable to Lewis acidic conditions, were used in this methodology. Initially, $BF_3{\cdot}OEt_2$ was added to the mixture of 1,4-dien-3-ones and allyltrimethylsilane. This resulted in the formation of bicyclo[2.2.1]heptanone as a major product in combination with three diastereomeric allylated cyclopentanones (Scheme 1.21).[16]

The majority of the allylated compounds (30% yield) resulted due to allyltrimethylsilane approaching the oxyallyl cation intermediate from the face opposite to the adjacent phenyl group. However, the bicyclic compound resulted due to allyltrimethylsilane approaching the oxyallyl cation intermediate from the same face of the adjacent phenyl group. Failure to observe any bicyclic product from intermediate 1.17 was explained by the steric effect in the transition state for ring closure (Scheme 1.22). This is discussed in detail in chapter 2.



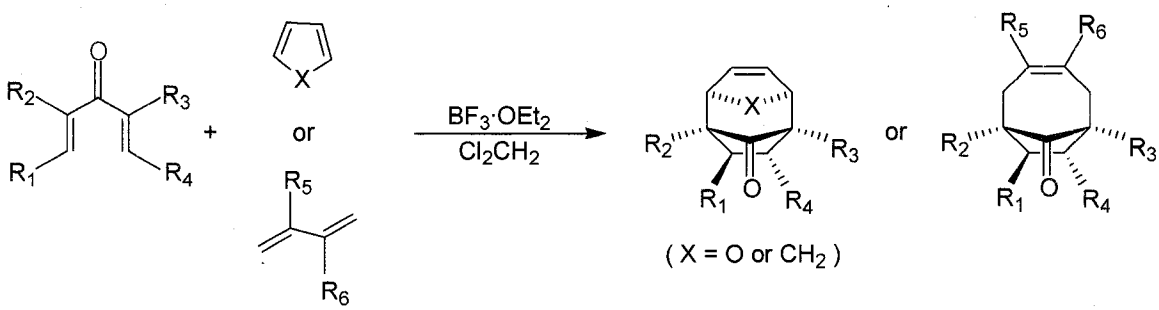
Scheme 1.21 [3+2] cycloadditions of **1a** with a allyltrimethylsilane.



Scheme 1.22 The steric effect in the transition state for ring closure

1.5.3 Intermolecular [4+3] trapping of the Nazarov intermediate with 1,3-Dienes

Many synthetic methods have been developed to prepare cyclooctanoid ring systems, such as intramolecular [4+4] cycloaddition.[17] However, in 2003, West and coworkers came up with a new methodology where 1,4-dien-3-ones and 1,3-dienes undergo Nazarov electrocyclization followed by intermolecular [4+3] cycloaddition in the presence of $BF_3{\cdot}OEt_2$ to furnish keto-bridged cyclooctenes in good yield and diastereroselectivity (Scheme 1.23).[18] Cyclic dienes, such as cyclopentadiene and furan, and acyclic dienes, such as isoprene and 2,3-dimethylbutadiene, have been examined. In all cases, only *endo* isomers were formed, strongly suggesting that the cycloaddition step occurs via compact transition state (Scheme 1.23).



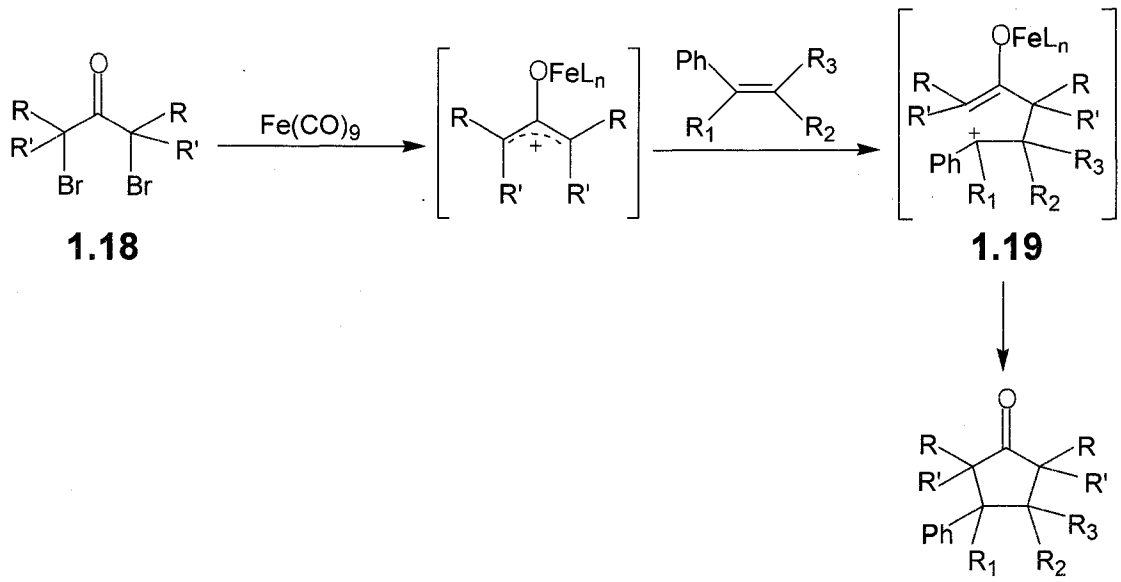
Scheme 1.23 Intermolecular [4+3] cycloaddition

1.6 Alkenes as nucleophiles

1.6.1 Alkenes as nucleophiles in cationic [3+2] cycloaddition

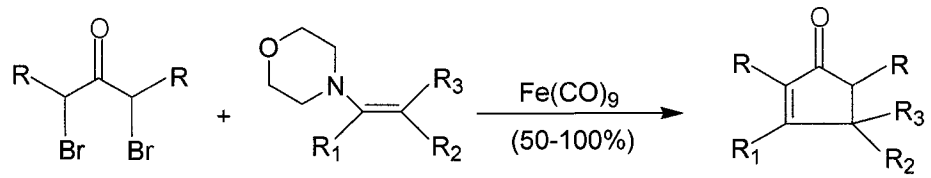
One way of producing cyclopentanone derivatives is the coupling between 2-oxyallyl cations and olefins.[19] This coupling occurs via cationic [3+2] cycloaddition which is classified as $[\pi 2_s + \pi 2_s]$ process. According to the principle of conservation of orbital symmetry such a cycloaddition is thermally forbidden.[20] So, the cationic [3+2] cycloaddition does not occur in a concerted manner but rather via stepwise mechanism.[19] An example of the stepwise [3+2] cycloaddition was discussed earlier in section 1.5.2. In this neat methodology the oxyallyl carbocation intermediate, which was generated during Nazarov cyclization, was trapped with allysilane in a formal [3+2] fashion to generate bicyclo[2.2.1]heptanone as a major product.

In the literatures,[19] the 2-oxyallyl cation intermediate was generated in situ by treating α,α'-dibromo ketones **1.18** with $Fe_2(CO)_9$. Then, these allyl cation species were trapped by certain olefins to produce the cyclopentenones (Scheme 1.24). It was found that these olefins should be aryl substituted alkenes to be able to trap the allyl cation intermediate. Simple aliphatic olefins such as isobutylene failed to undergo this cycloaddition. Also, the yield of the products depends on the ability of the substituents on the alkene terminus to stabilize the carbocation species **1.19**. For example, when styrene was used the yield was 65%. However, using α-cyclopropylstyrene the yield increased to 95%. This is because both phenyl and cyclopropyl groups are able to stabilize the carbocation intermediate **1.19**.[19a]

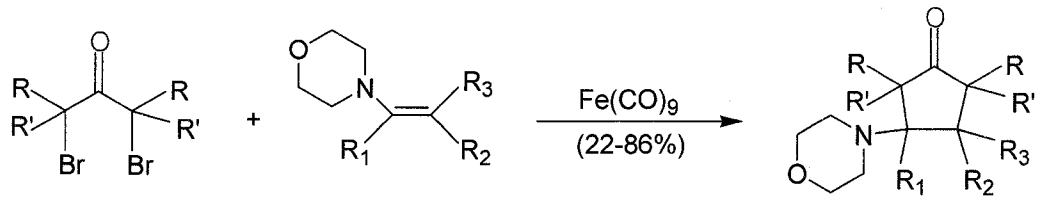


Scheme 1.24 The mechanism of the addition of the aryl alkenes to the 2-oxyallyl cation intermediates

Morpholine enamines were also used as activated olefins to trap the 2-oxyallyl cation intermediate. In the process, the generated allyl cation species undergoes cationic [3+2] cycloaddition with the morpholine enamines followed by spontaneous elimination of morpholine, after silica gel chromatography, to produce cyclopentenones in good yields (Scheme 1.25). [21] However, if the α,α'-dibromo ketones **1.18** bear no hydrogen atoms at the α-position of the carbonyl group, no elimination of morpholine will occur and the products will be β–morpholino ketones **1.20** (Scheme 1.26). [19b,21,22]



Scheme 1.25 The formation of the cyclopentenones



1.18 **1.20**

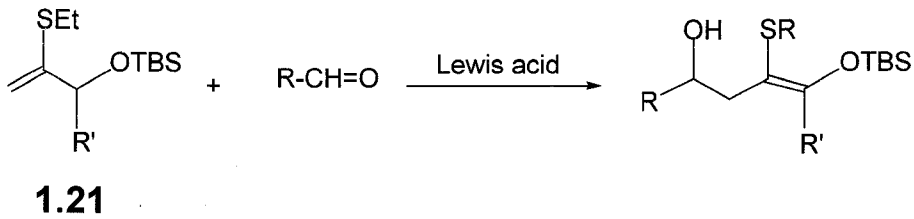
Scheme 1.26 The formation of the β–morpholino ketone

The ability of the activated alkenes such as morpholine enamines to trap the 2-oxyallyl cation intermediate encouraged us to try enamines as nucleophiles in trapping the cationic Nazarov intermediate. Morpholine cyclohexene enamine and pyrrolidine cyclopentene enamine were used in the presence of $BF_3 \cdot OEt_2$ to trap the 2-oxyallyl cation intermediate that resulted from 2,4-dimethyl-1,5-diphenylpenta-1,4-dien-3-one. The starting material, however, was not consumed. Using $SnCl_4$ instead of $BF_3 \cdot OEt_2$ as Lewis acid also did not consume the 1,4-dien-3-one. When $TiCl_4$ was used, the starting material disappeared producing the simple Nazarov product combined together with a complex mixture of other products. Getting these results lead us to think of different types of activated alkenes, such as vinyl sulfides.

1.7 Vinyl sulfides as nucleophiles

Vinyl sulfides are also considered to be highly reactive nucleophiles. They were used in ene reactions with carbonyl compounds in intermolecular fashion.[23] Normal alkenes

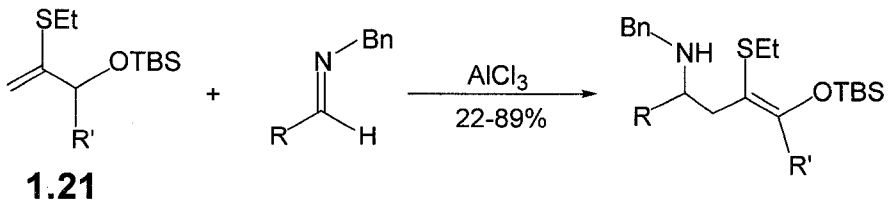
react only with active enopiles such as formaldehyde. However, less reactive aldehydes need a highly activated alkene to react with. [24] It was found that 2-(alkylthio)-allyl silyl ethers **1.21** are very effective nucleophiles for this type of ene reaction. Treating a mixture of **1.21** and aldehydes with Lewis acid resulted in the formation of the corresponding enol silyl ethers of γ-hydroxyaldehydes in high yields (Scheme 1.27).[23b]



1.21

Scheme 1.27 Ene reaction of aldehydes with 2-(alkylthio)-allyl silyl ethers.

This methodology worked very well with a wide range of aldehydes including aliphatic, aromatic and α, β-unsaturated examples. Not only can **1.21** react with various types of aldehydes to produce the desired products, but it can also undergo ene reaction with the less reactive aldimines. This reaction generates the enol silyl ether moiety as well as the protected amino group (Scheme 1.28).[25]



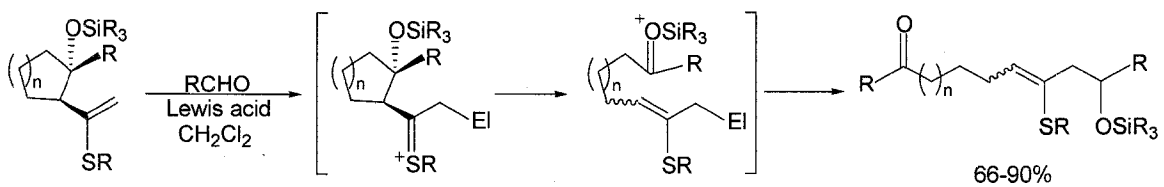
1.21

Scheme 1.28 Ene reaction of N-benzylimines with 2-(alkylthio)-allyl silyl ethers.

Also, simple vinyl sulfides, without the silyl ether group, proved to be very reactive nucleophiles. They reacted readily with wide range of the aldehydes and 3-(alkylthio)-2-siloxyallyl cationic species in the presence of a Lewis acid to produce the desired products in high yield and regioselictivity.[23,26,28] Examples of these reactions will be discussed in the following two sections.

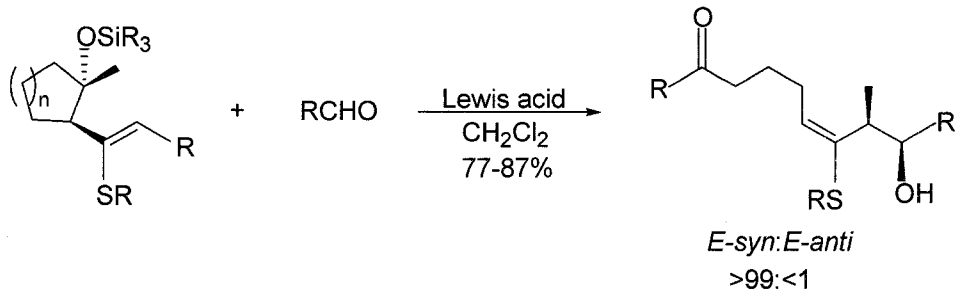
1.7.1 Selective formation and cleavage of carbon-carbon bonds

Forming and breaking carbon-carbon bonds are very important processes in organic synthesis. In 1993, Kuwajima and coworkers came up with a methodology that included tandem carbon-carbon bonds formation and cleavage. Substrates containing an alkenyl sulfide and a β-siloxy group were treated with a carbon electrophile in the presence of a Lewis acid, leading to the formation of carbon-carbon bond and thionum ion. This thionum ion readily converted to the more stable silyloxonium ion via carbon-carbon bond cleavage (Scheme 1.29).[26] The reaction went smoothly with aliphatic, aromatic and α,β-unsaturated aldehydes as an electrophiles. The Lewis acids $TiCl_3(O^iPr)$ or TMSCl-$ZnCl_2$ cleanly induced the desired transformation with high yield and 1:1 mixture of two geometrical isomers.

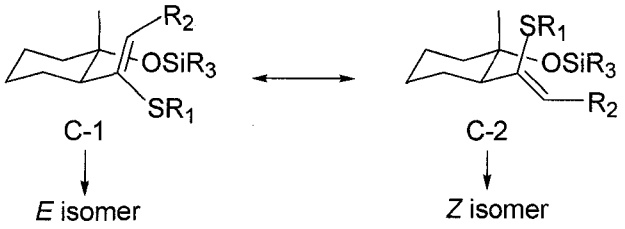


Scheme 1.29 Vinyl sulfides act as nucleophiles in a tandem carbon-carbon bond formation-cleavage type reaction.

To study the stereochemistry of this reaction, terminally substituted vinyl sulfides were subjected to the reaction conditions. Only $TiCl_4$ and $TiCl_3(O^iPr)$ induced the reaction to yield the desired produced with almost a complete *E* and *syn* selectivity and high yield (Scheme 1.30). This stereochemistry was explained based on the energy difference between the two conformations C-1 and C-2 (Table 1.4). Since C-1 is more stable than C-2, the *E* isomer was the major product. Also, the more stable chair-like transition state for the initial addition to the aldehyed led to the formation of the *syn* product (Scheme 1.31).



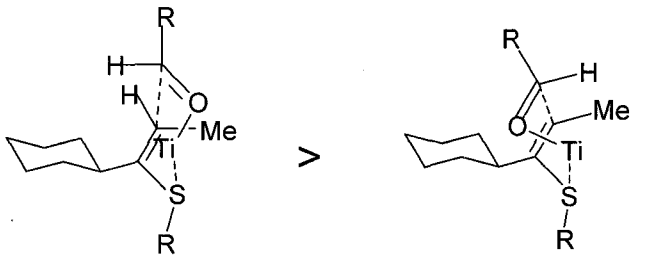
Scheme 1.30 The stereoselectivity of the tandem carbon-carbon bond formation-cleavage type reaction.



	C-1(kcal/mol)	C-2(kcal/mol)	ΔE^a(kcal/mol)
R_1=R_2=Me	-120.68	-119.22	1.46
R_1=Ph, R_2=H	-75.75	-75.41	0.34

[a] Energy difference between C-1 and C-2

Table 1-4 Calculate energies for conformers of starting materials



chair like transition state (More stable) > boat like transition state (Less stable)

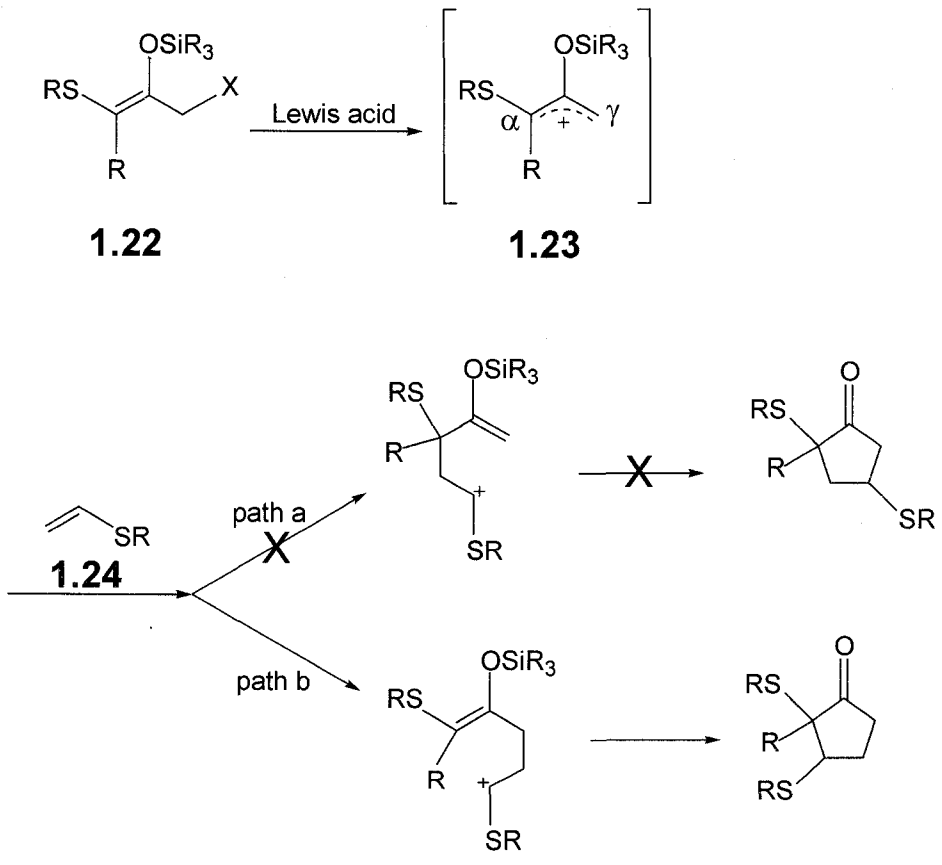
Scheme 1.31 Cyclic transition state models

1.7.2 [3+2]-cycloaddition

Preparation of cyclopentanones via cationic [3+2] cycloaddition has some limitations arising from the stepwise mechanism.[27] However, the high reactivity[23] and the ability of sulfur atom –in certain cases- to play an important role in controlling the

stereochemistry of the products[26, 28] encouraged Kuwajima and coworkers to use vinyl sulfides as precursors in the synthesis of cyclopentanones.

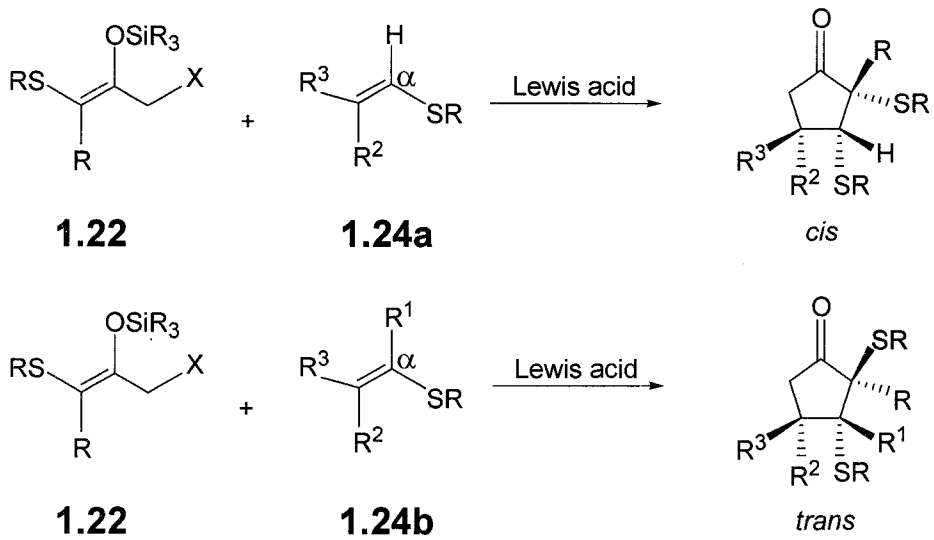
In this methodology, vinyl sulfides were used as nucleophiles to react with the 1-(alkylthio)-2-siloxyallyl cationic species via [3+2] cycloaddition to furnish cyclopentanoid compounds in high regio- and stereoselectivity. In the processes, **1.22** was treated with $EtAlCl_2$ as a Lewis acid to produce the cationic species **1.23**. This allylic species has two reactive sites, α- and γ- to the sulfide. It was found that the vinyl sulfides predominantly reacted at the γ- position through path b, as in Scheme 1.32.[29]



Scheme 1.32 [3+2] cyclopentanone annulation.

Also, it has been found that the reactivity of **1.22** with vinyl sulfides has several sterochemical outcomes:

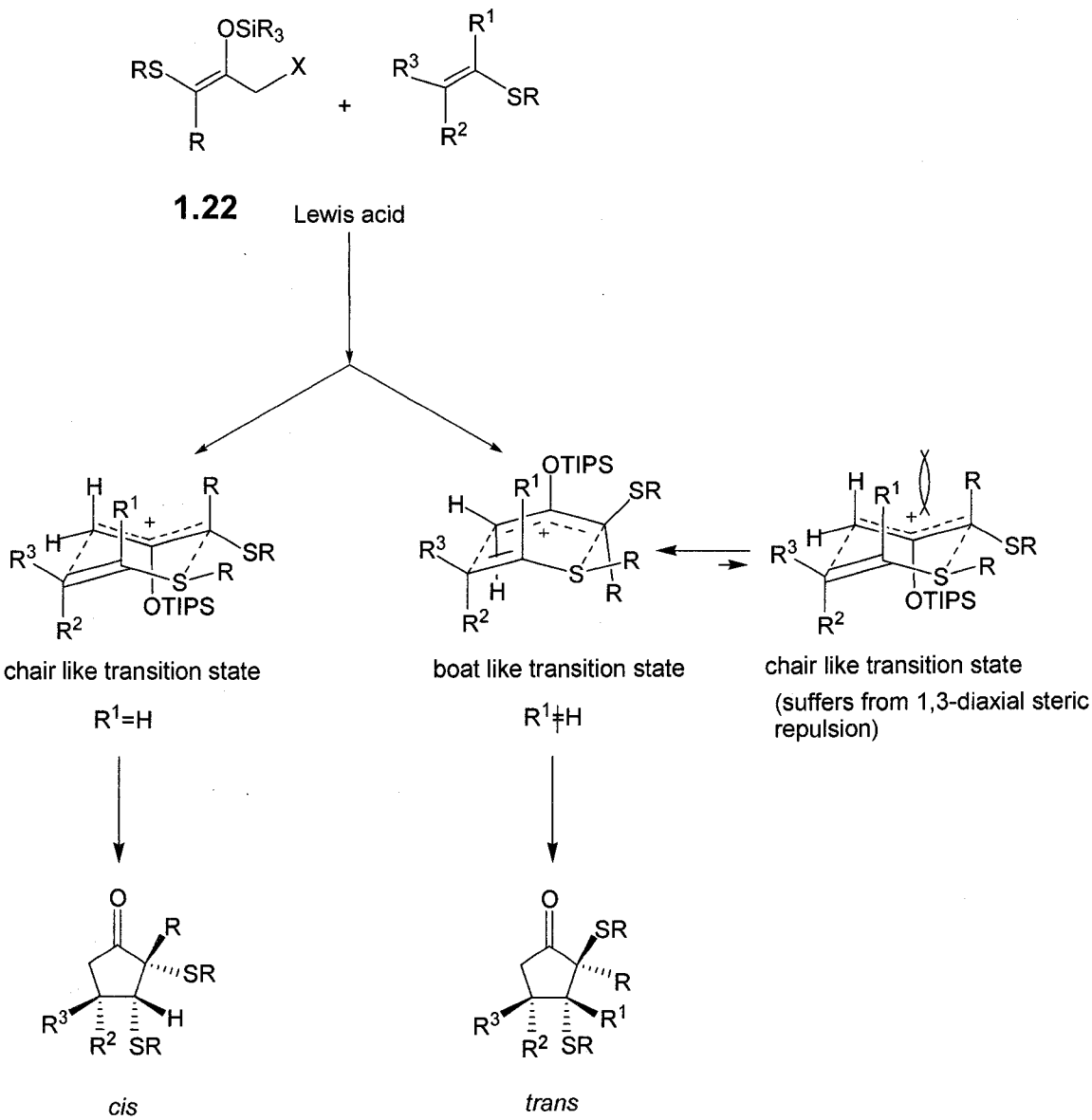
1. The substituent at the α-position of the vinyl sulfides **1.24** has a great influence in the stereochemistry of the product. Thus, if the α-substituent is a hydrogen atom in the vinyl sulfide (e.g. **1.24a**), the two alkylthio groups in the product will be *cis* to each other. However, if the vinyl sulfide has an alkyl group at this position (e.g. **1.24b**), the RS groups in the product will be *trans* (Scheme 1.33).



Scheme 1.33 The effect of the substituent at the α–position of a vinyl sulfide on the stereochemistry of the product.

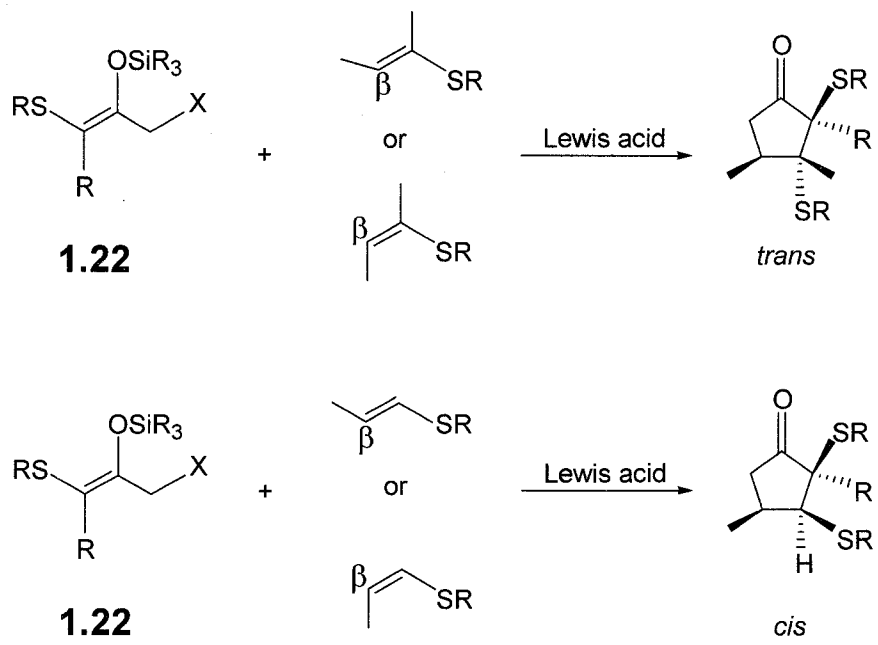
The high selectivity of this stepwise [3+2] cycloaddition reaction can be explained based on a six-membered cyclic transition state, involving either chair-like

transition states or boat-like transition states. In cases with a hydrogen at the α-position, the reaction proceeds through a chair-like transition state, which leads to the *cis* isomer. However, if the substituent at the α-position is an alkyl group, the reaction goes through a boat-like transition state. This avoids the 1,3-diaxial steric repulsion between the alkyl and methyl group in the chair like transition state and result in the *trans* isomer (Scheme 1.34).

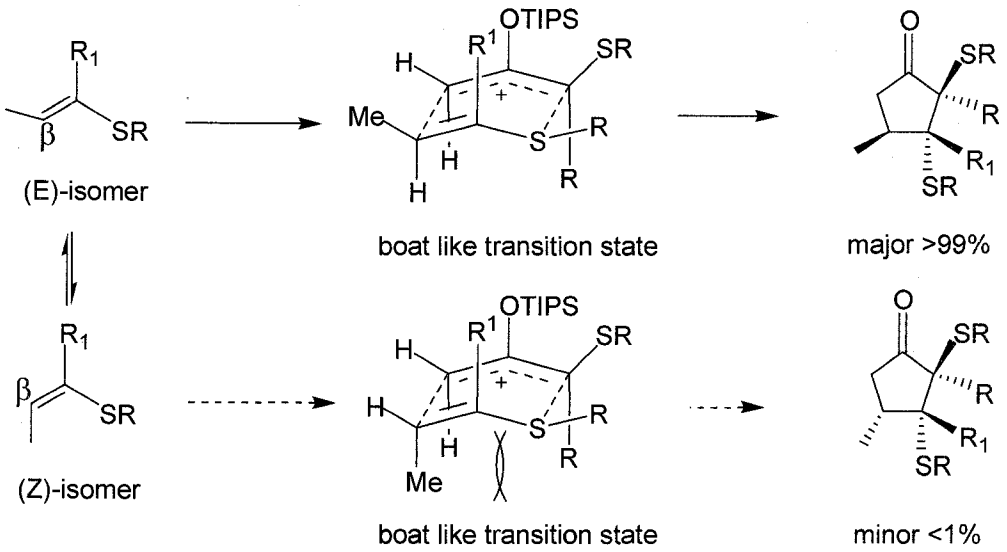


Scheme 1.34 Six-membered cyclic transition states for [3+2] cycloaddition reaction

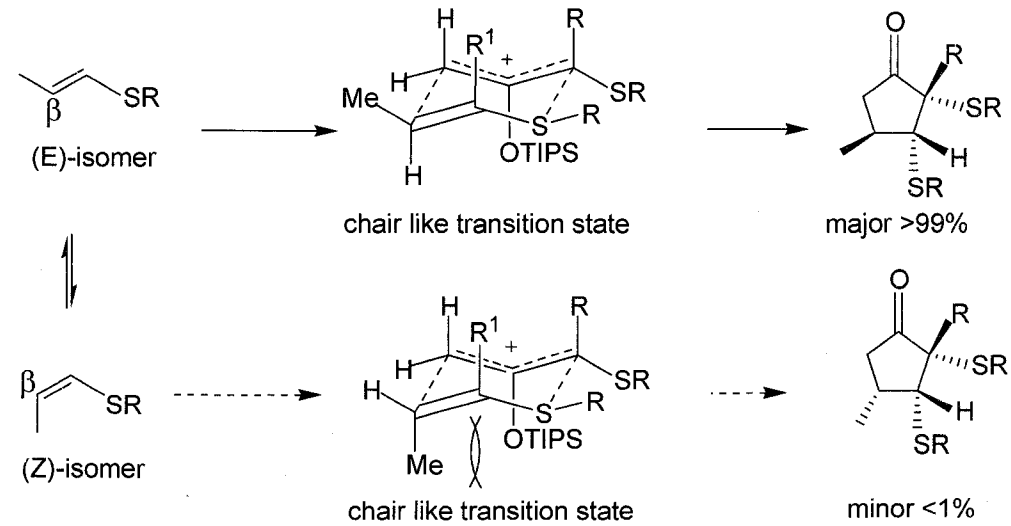
2. A vinyl sulfide with a β-substituent has two geometrical isomers, *cis* and *trans*. Subjecting either isomer to the reaction condition produced the same diastereomer as the major product (Scheme 1.35), which seems to arise from the *trans* vinyl sulfide. This is expected since the cyclic transition state of the addition of the *trans* vinyl sulfide to the 1-(alkylthio)-2-siloxyallyl cationic species suffers less steric effect compared to the cyclic transition state of the addition of the *cis* vinyl sulfide to the 1-(alkylthio)-2-siloxyallyl cationic species (Scheme 1.36). Also they found that treatment of the *cis* isomer with $EtAlCl_2$ produced a mixture of geometrical isomers. This suggests that the *cis* vinyl sulfide rapidly changes its configuration under the same reaction condition.



Scheme 1.35 The effect of the substituent at the β–position of a vinyl sulfide on the stereochemistry of the product.



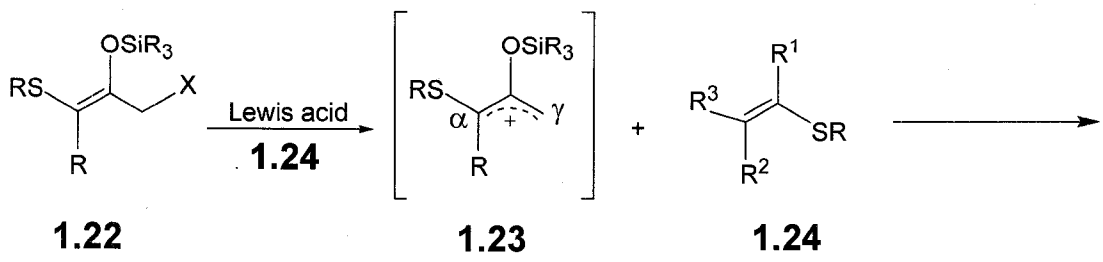
-The substituent at the α-position of the vinyl sulfides (R_1) is an alkyl group



-The substituent at the α-position of the vinyl sulfides (R_1) is hydrogen

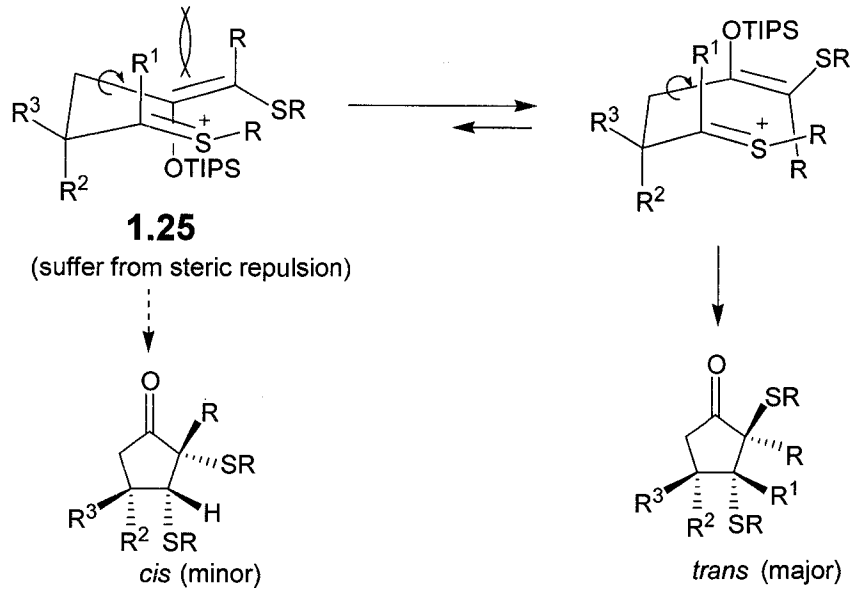
Scheme 1.36 Six-membered cyclic transition states for [3+2] cycloaddition reaction

The influence of the substituent at the α-position of the vinyl sulfides **1.24** on the stererochemistry of the product can also be explained based on the stepwise mechanism with an intermediate that can undergo free rotation. It can be argued that the vinyl sulfide **1.24** attacks the γ- position of the 1-(alkylthio)-2-siloxyallyl cationic species **1.23** and forms intermediate **1.25**. If the α-substituent is an alkyl group in the vinyl sulfide, the free rotation around the carbon – carbon bond in intermediate **1.25** leads to ring closing of this intermediate **1.25** in two transition states, which are in equilibrium. However, the equilibrium is shifted towards the transition state where the steric effect is minimal. Ring closing of this transition state produced the major isomer (Scheme 1.37). However, if the vinyl sulfide has a hydrogen atom at this position, it seems that the carbon-carbon bond formation, which results in the formation of the major isomer, is faster relative to the bond rotation to generate the minor isomer (Scheme 1.37).



1.22 **1.23** **1.24**

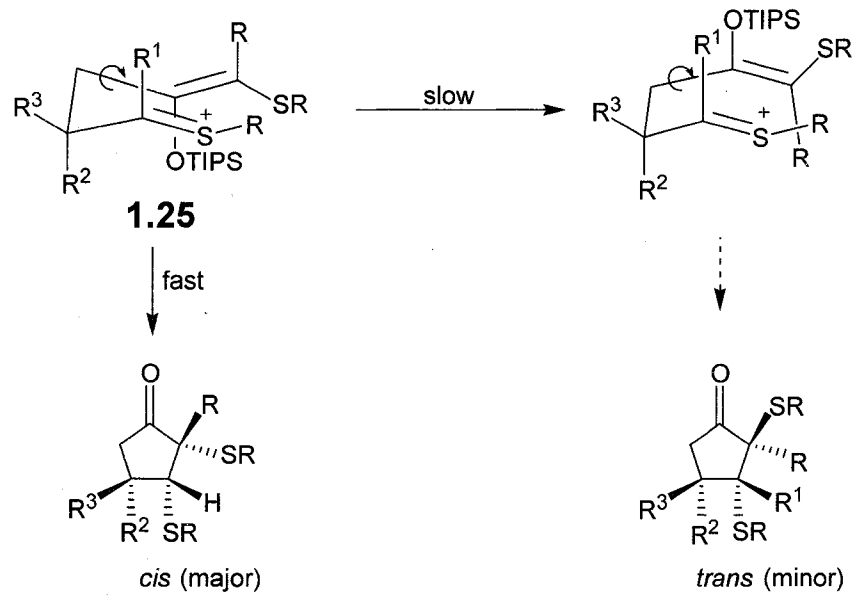
-The substituent at the α -position of the vinyl sulfides (R_1) is an alkyl groug



1.25
(suffer from steric repulsion)

cis (minor) *trans* (major)

-The substituent at the α -position of the vinyl sulfides (R_1) is hydrogen



1.25

cis (major) *trans* (minor)

Scheme 1.37 The transition states required for ring closing of intermediate **1.25**

1.8 Summary

This chapter provided a brief introduction to the Nazarov reaction and its importance in organic synthesis. Also, many example of the interrupted Nazarov cyclization were discussed. In these methodologies, the generated oxyallyl intermediate during the Nazarov reaction was trapped with different types of electron-rich carbon nucleophiles to form several carbon-carbon bonds in high regio- and steroselectivity. A review of the literature indicates that vinyl sulfides are effective nucleophiles for trapping carbocationic electrophiles. Given this background, we embarked on a study of vinyl sulfides as intermolecular traps in the interrupted Nazarov reaction (see Chapter 2).

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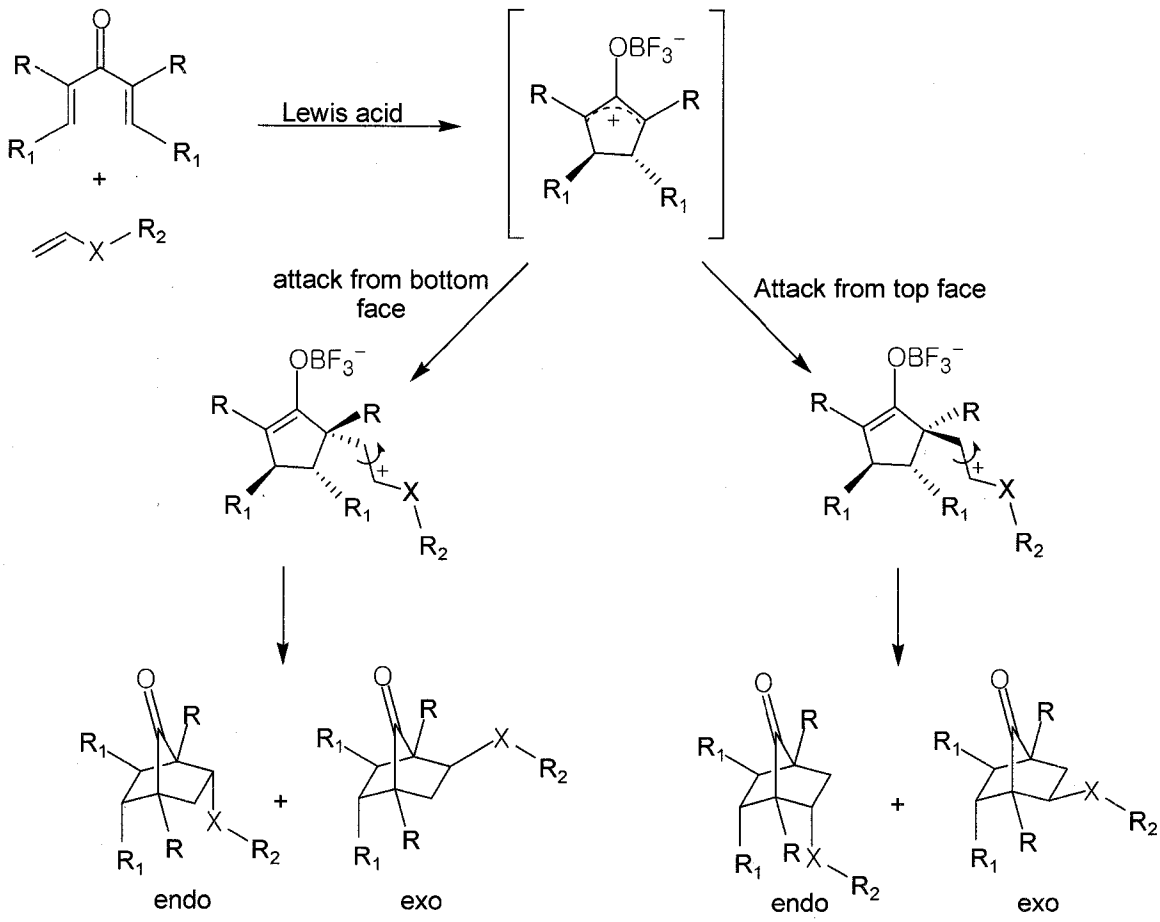
Chapter 2 The synthesis of bicyclo[2.2.1]heptanones

2.1 Introduction

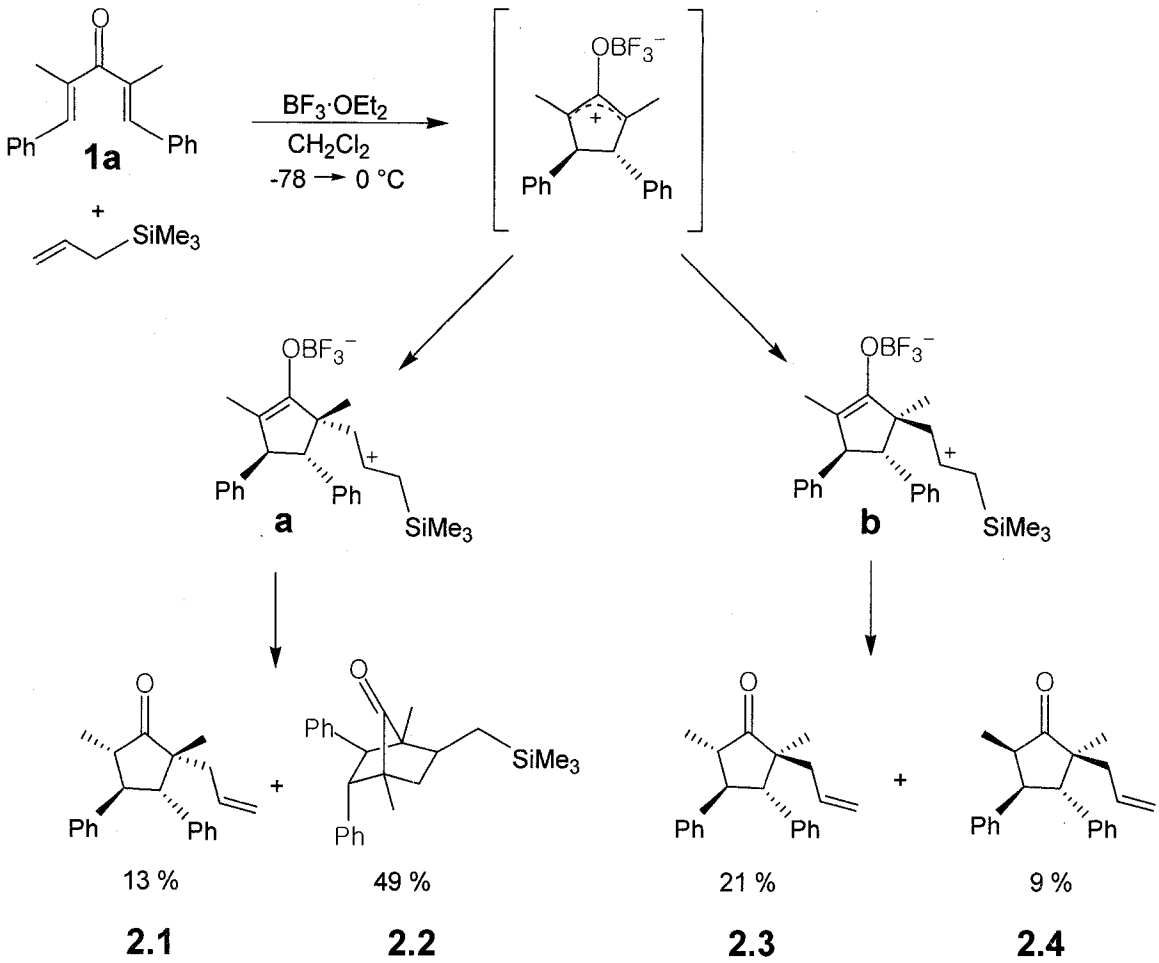
As we noted in chapter one, the initial electrocyclization in Nazarov reaction results in a new carbon–carbon bond and a reactive oxyallyl intermediate. Trapping the cationic Nazarov intermediate with a suitable nucleophile forms up to three carbon–carbon bonds in a single transformation. Certain classes of electron-rich alkenes can be considered appropriate for this trapping. They can trap the Nazarov intermediate in a 3+2 annulation process to give bicyclo[2.2.1]heptanones. As we discussed in Chapter 1 section 1.6.1, the cationic [3+2] cycloaddition reactions are thermally forbidden via concerted transition state since 4π electrons are involved.[1] Therefore, this [3+2] cycloaddition will take place in stepwise manner. The proposed mechanism of this trapping is shown in Scheme 2.1.

In 2000, West and coworkers described the first examples of intermolecular trapping of the Nazarov oxyallyl intermediate by allylsilanes in a stepwise 3+2 annulation process to give bicyclo[2.2.1]heptanones. In their initial experiments, they treated the mixture of **1a** and allytrimethylsilane with $BF_3{\cdot}OEt_2$ at low temperature, and they got three diastereomeric allylated cyclopentanones (**2.1**, **2.3**, **2.4**) in a combined yield of 43 % along with 49 % of bicyclo[2.2.1]heptanone **2.2** (Scheme 2.2). Also, it was found that replacing trimethylsilyl with a bulkier silyl group, to suppress desilylation and favour the [3+2] pathway, yielded 50 % of the [3+2] adduct as a mixture of *endo* and *exo*

diastereomers with little or none of the simple allylation product. Using $SnCl_4$ as a Lewis acid instead of $BF_3{\cdot}OEt_2$ still gave the *endo* and *exo* [3+2] adducts, but in a different ratio.[2]



Scheme 2.1 The step-wise [3+2] annulation process to give bicyclo[2.2.1]heptanones.



Scheme 2.2 The intermolecular trapping of the Nazarov oxyallyl intermediate by allylsilanes

These results encouraged us to investigate a different type of electron-rich alkene for this trapping. Vinyl sulfides were nominated to be used to trap the cationic Nazarov intermediate. As discussed in chapter one, they can be considered as electron-rich alkenes, which should permit effective nucleophilic trapping. [3] It was shown that vinyl sulfides underwent efficient [3+2] cycloaddition with different types of cationic species

to furnish five-member ring products. [4] Also, unlike allylsilanes, vinyl sulfides should not be subject to a competing elimination step. Therefore, [3+2] trapping was expected to be the major pathway. The polycyclic products contain a sulfur functionality which can be readily transformed into other functional groups. Also, many natural products and biologically active compounds contain such heteroatoms.[5] Thus, the central question of this project was: can vinyl sulfides be used as effective partners in [3+2] type trapping of the Nazarov intermediate?

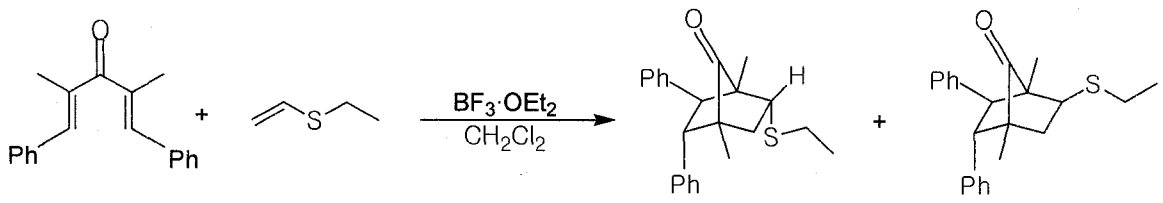
2.2 Attempted intermolecular [3+2] cycloaddition of substituted dienones with vinyl sulfides.

To study this type of reaction, several 1,4-dien-3-ones were prepared following the literature procedures. These dienones are 2,4-dimethyl-1,5-diphenylpenta-1,4-dien-3-one, **1a**,[6] 2,4-dimethyl-1-phenylpenta-1,4-dien-3-one, **1b**,[7] cyclohexen-1-yl propen-2-yl ketone, **1c**[7] and 1,5-diisopropyl-2,4-dimethyl-1,4-pentadien-3-one, **1d**.[8] These dienones were selected because they, with the exception of **1d**, undergo [4+3] cycloaddition smoothly with 1,3-dienes and furnish keto-bridged cyclooctenes in good yield.[7]

Two of the vinyl sulfides used, ethyl vinyl sulfide **2a** and phenyl vinyl sulfide **2b**, were commercially available. The third vinyl sulfide β-(phenylthio)styrene, **2c** used in our work was prepared using a literature procedure.[9] This substituted vinyl sulfide chosen to study the effect of a non-hydrogen substituent at the vinyl terminus on the regioselectivity of this type of reaction.

2.2.1 Attempted intermolecular [3+2] cycloaddition of 2,4-dimethyl-1,5-diphenylpenta-1,4-dien-3-one, 1a, with vinyl sulfides.

In our initial experiments, we followed the same reaction conditions that West and coworkers used to trap 1,4-dien-3-ones with allysilanes.[2] So, to a mixture of ten equivalents of ethyl vinyl sulfide **2a** and one equivalent of **1a** in dichloromethane, 1.2 equivalents of $BF_3 \cdot OEt_2$ was added at –78°C. TLC analysis indicated that the starting material had disappeared after 30 minutes; however, the reaction was very messy. The crude ^1H NMR spectrum showed the disappearance of the peaks of the alkene protons. This encouraged us to separate the products by column chromatography. Two of the products were isolated and fully characterized. The structure of **4** was first determined by 1D NMR and 2D NMR data, and then later confirmed by X-ray crystallography (see Appendix A). A discussion of the structural assignments can be found in section 2.3 of this chapter. The ratio of **3** to **4** was 1:7 and the combined yield was 60% (Table 2.1) entry 1.



1 : 7

1a **2a** 3 4

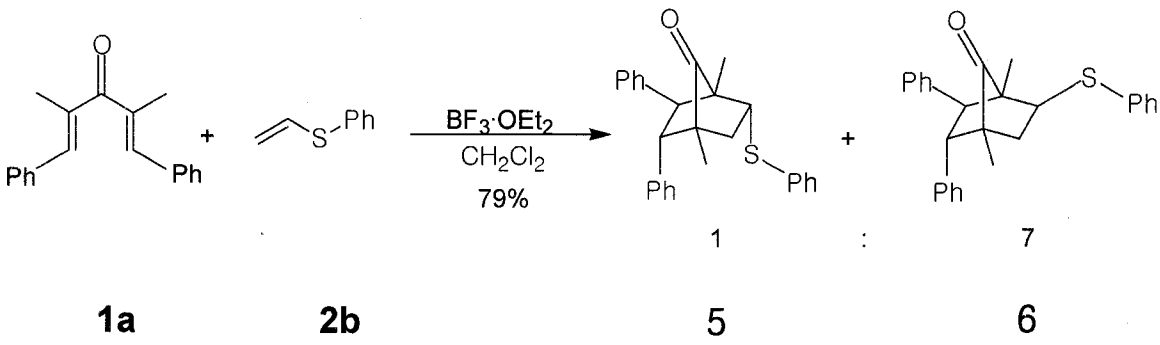
entry	$BF_3{\cdot}OEt_2$ (equivalents)	2a (equivalents)	Yield (%)
1	1.2	10	60
2	1	5	70
3	1.2	4	70
4	1	4	71
5	1	3	68
6	1	2	65
7	0.5	2	40

Table 2-1 Treatment of **1a** with different ratios of **2a** and $BF_3{\cdot}OEt_2$

In an attempt to get a cleaner reaction, the number of equivalents of ethyl vinyl sulfide was reduced to five, four, three and two equivalents. TLC analysis suggested a cleaner reaction at lower sulfide equivalents; however, the yield of the trapping products was reduced by 3-6% when the number of equivalents of ethyl vinyl sulfide was less than 4 equivalents (Table 2.1). Also when the number of equivalents of $BF_3{\cdot}OEt_2$ was reduced to 0.5 equivalent, the yield dropped from 65% to 40% (entry 5 – 6).

The optimized reaction condition from Table 2.1 entry 4 was then applied to the reaction of **1a** with **2b**. So, to a mixture of four equivalents of phenyl vinyl sulfide **2b** and one equivalent of **1a** in dichloromethane was added one equivalent of $BF_3{\cdot}OEt_2$ at –

78°C. TLC analysis suggested consumption of the starting material in 30 minutes. Two products were isolated and fully characterized by 1D NMR and 2D NMR data. The ratio of **5** to **6** was 1:7 in a combined yield of 79% (Scheme 2.3).

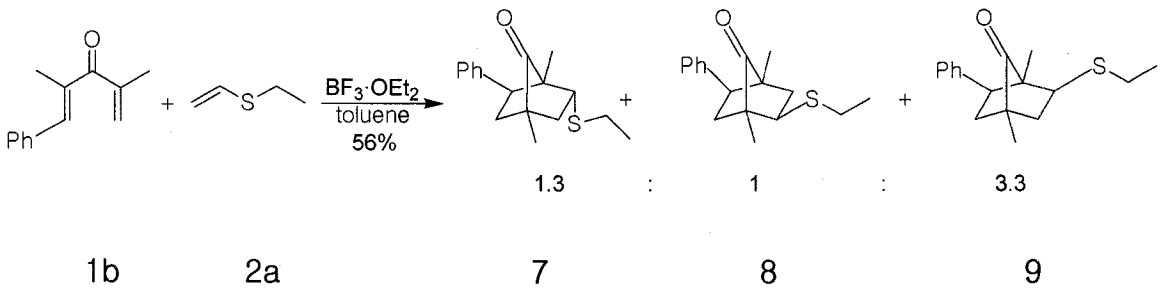


Scheme 2.3 Intermolecular [3+2] cycloaddition of **1a** with phenyl vinyl sulfide **2b**.

The positive result that we got so far from the previous two reactions encouraged us to apply the same reaction conditions on the reaction of **1a** with **2c**. So, to a mixture of four equivalents of β-(phenylthio)styrene **2c,** and one equivalent of **1a** in dichloromethane was added one equivalent of $BF_3{\cdot}OEt_2$ at –78°C. The starting material disappeared in fifteen minutes, producing a complex mixture of products. Attempts to optimize the reaction through systematic variation of stoichiometry, temperature or solvent failed to improve the outcome, yielding a complex mixture of unidentifiable products. Accordingly, this reaction was not pursued further.

2.2.2 Intermolecular [3+2] cycloaddition of 2,4-dimethyl-1-phenylpenta-1,4-dien-3-one, 1b, with vinyl sulfide.

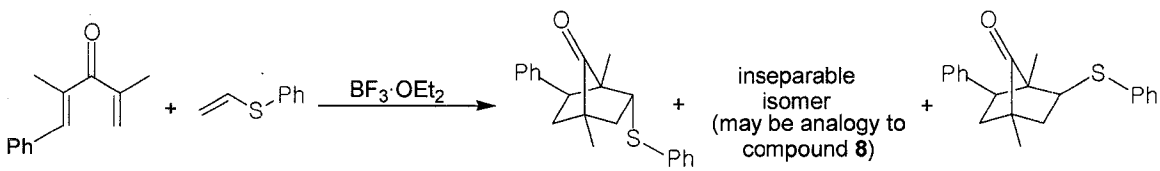
Even though **1b** is known to be less reactive than the previous dienone **1a**, we decided to start by applying the same optimised condition of **1a**. However, adding one equivalent of $BF_3{\cdot}OEt_2$ to a mixture of four equivalents of the ethyl vinyl sulfide **2a** and one equivalent of **1b** in dichloromethane at –78°C resulted in a messy reaction with incomplete consumption of the starting material. So, 1.5 equivalents of $BF_3{\cdot}OEt_2$ were used instead and the reaction mixture was left to stir overnight. Under these conditions, the starting material disappeared but the reaction was still very messy. Changing the solvent to toluene provided a cleaner reaction which generated 1.3:1:3.3 mixture of three isomers in 56% combined yield (Scheme 2.4). The structures of these products were identified by NMR and 2D NMR spectral analysis.



Scheme 2.4 Intermolecular [3+2] cycloaddition of **1b** with ethyl vinyl sulfide **2a**.

The new optimized conditions found for the previous reaction were applied to the reaction of **1b** with **2a**. So, to a mixture of four equivalents of phenyl vinyl sulfide **2b** and one equivalent of **1b** in dichloromethane was added 1.5 equivalents of $BF_3{\cdot}OEt_2$ at –

78°C. Fortunately, the starting material disappeared after two hours, yielding three products **10, 11** and **12** (2:1:5) ratio in 83% combined yield. Based on the previous observations with toluene as a solvent, with relatively clean reaction and complete consumption of the starting material, the reaction was repeated in toluene to see the effect. Performing the reaction in toluene changed the ratio of products to 3.3:1:3.3 respectively and the yield increased to 86%. Products **10** and **12** were isolated and characterized (Table 2.2) while product **11** could not be separated from the other isomers. Therefore, only partial ^{1}H NMR data could be reported. The ratios were calculated based on ^{1}H NMR spectra.

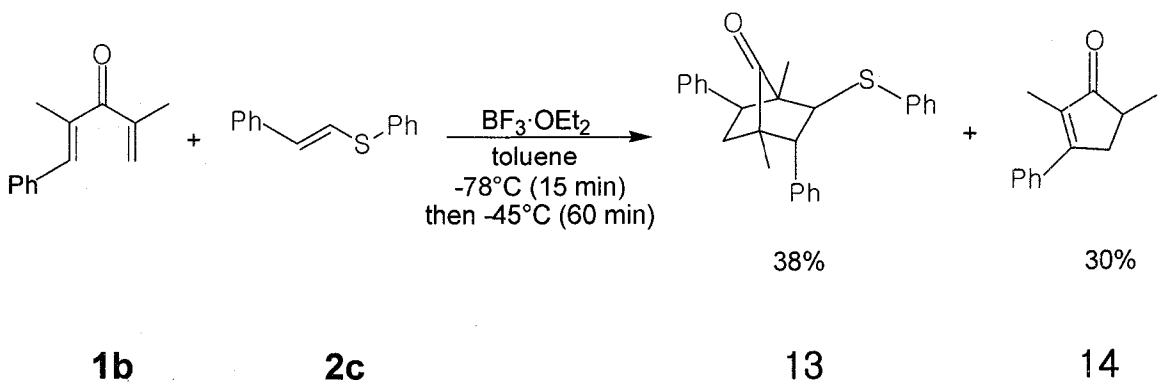


1b **2b** 10 **11** 12

entry	solvent	Ratio of (10:11:12)	Yield (%)
1	dichloromethane	2 : 1 : 5	83
2	toluene	1 : 0.3 : 1	86

Table 2-2 the effect of solvent on the intermolecular [3+2] cycloaddition of **1b** with **2b**

The same optimized conditions, found for the previous two reactions, were applied to the reaction of **1b** with **2c**. However, since **1b** is less bulky than **1a**, we had more hopes for this reaction to occur. The procedure involved adding 1.5 equivalents of $BF_3{\cdot}OEt_2$ at -78°C to a mixture of four equivalents of *β*-(phenylthio)styrene **2c** and one equivalent of **1b** in toluene. Immediately a product started to form. However, from TLC we noticed that the polarity of this product was more than what is expected for the trapping product. The temperature was then increased to -45°C. After one hour, a new product was formed and the starting material was consumed. Two products were isolated and fully characterized. One of them was the trapping product **13** in 33% yield, and the other one, which formed first, was the simple Nazarov product **14** in 34% yield. Since **14** was formed first, at lower temperature, the number of equivalents of $BF_3{\cdot}OEt_2$ was reduced to 1.2 in an attempt to suppress its formation and increase the yield of **13**. The yield for the trapping product **13** increased to 38% and of the simple Nazarov product **14** decreased to 30% (Scheme 2.5). In another attempt to increase the yield of **13**, the 1.2 equivalents of $BF_3{\cdot}OEt_2$ was added to the reaction mixture at -45°C; however the simple Nazarov product, **14**, was the major product under these conditions.

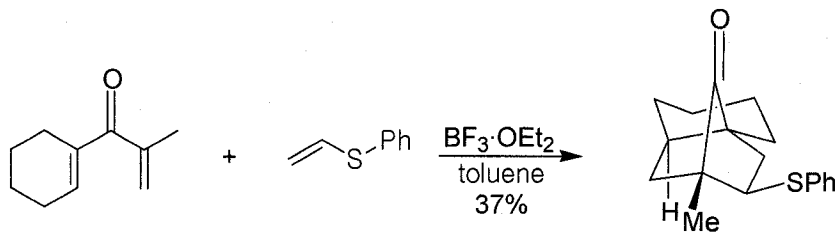


Scheme 2.5 Intermolecular [3+2] cycloaddition of **1b** with **2c**

2.2.3 Intermolecular [3+2] cycloaddition of cyclohexen-1-yl propen-2-yl ketone,1c, with vinyl sulfide.

Since it is known that the reactivity of **1c** is similar to that of **1b** and less than that of **1a**,[7,8] we began by using the optimized conditions of the reaction of **1b**. So, to a solution of four equivalents of ethyl vinyl sulfide, **2a**, and one equivalent of **1c** in toluene, was added 1.5 equivalents of $BF_3{\cdot}OEt_2$ at –78°C. Under these conditions the starting material was not consumed. The number of equivalents of $BF_3{\cdot}OEt_2$ was then increased to two equivalents. Still the starting material was not consumed even after the temperature was raised to 40°C. From the results that we got so far and also from the coming sections, it seems that the reactivity of the ethyl vinyl sulfide toward the Nazarov intermediates is less than that of phenyl vinyl sulfide. Also, control experiments indicate consumption of the ethyl vinyl sulfide in the presence of $BF_3{\cdot}OEt_2$ at –78°C. Since the reactivity of **1c** is less than that of **1a**, this may explain the recovery of **1c**.

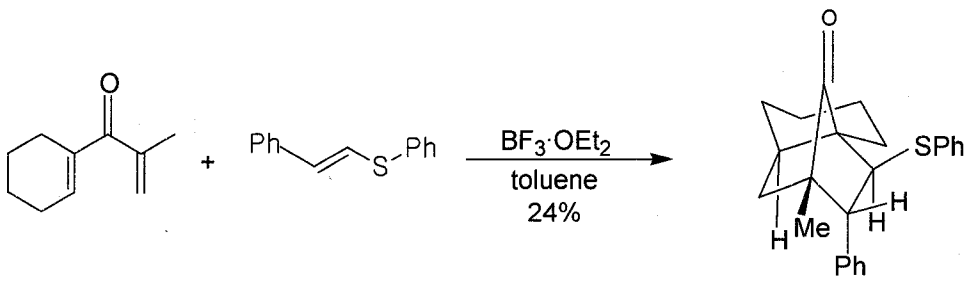
For the reaction of **1c** with **2b**, we started by adding two equivalents of $BF_3{\cdot}OEt_2$ to the mixture of four equivalents of phenyl vinyl sulfide **2b** and one equivalent of **1c** in toluene at –78°C. After stirring at low temperature for 15 min, the temperature was raised to room temperature. After one hour the starting material was consumed. One product, **15**, was isolated in 37% yield (Scheme 2.6).



1c 2b 15

Scheme 2.6 Intermolecular [3+2] cycloaddition of **1c** with **2b**

Following a similar procedure as above, for the reaction of **1c** with **2c**, the starting material disappeared in two hours. One product, **16**, was isolated in 24% yield (Scheme 2.7).



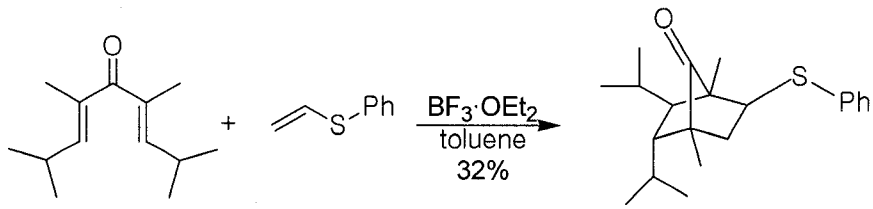
1c 2c 16

Scheme 2.7 Intermolecular [3+2] cycloaddition of **1c** with **2c**

2.2.4 Intermolecular [3+2] cycloaddition of 1,5-diisopropyl-2,4-dimethyl-1,4-pentadien-3-one, 1d, with vinyl sulfide.

To study the reactivity of dienone **1d** with **2a** we applied the same reaction condition as above. However, under these conditions, the starting material was not consumed even when the temperature was raised to 40°C.

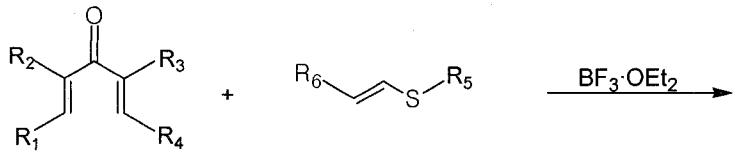
In the reaction of **1d** with **2b**, we mixed four equivalents of phenyl vinyl sulfide and one equivalent of **1d** in toluene and then added two equivalents of $BF_3 \cdot OEt_2$. The reaction mixture was left to stir overnight and the starting material disappeared. One trapping product, **17**, was isolated and fully characterized. The yield was 32% (Scheme 2.8).



1d 2b 17

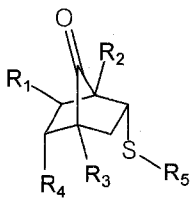
Scheme 2.8 Intermolecular [3+2] cycloaddition of **1d** with **2b**

Table 2.3 summarizes the results and reaction conditions for the trapping experiments discussed above. The reaction of **1a** with vinyl sulfides **2a** and **2b** produced similar results (entries 1 and 2). However, the reaction of vinyl sulfide **2c** with the Nazarov cationic intermediate resulted in either a complex mixture (entry 3) or low yield (entries 7 and 9). The dienone **1b** was also trapped by **2a** and **2b**, although a third isomer was seen in these cases (entries 4 and 6). The less reactive dinones **1c** and **1d** were not trapped with vinyl sulfide **2a** (entries 8 and 11) and their trapping yield with **2b** is relatively low (entries 9 and 12).

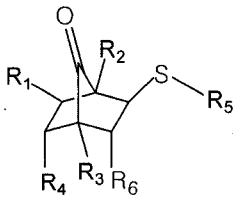


1a-d

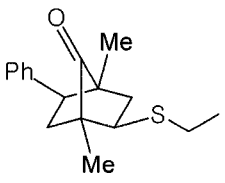
2a (R_5= C_2H_5; R_6= H)
2b (R_5= Ph; R_6= H)
2c (R_5= Ph; R_6= Ph)



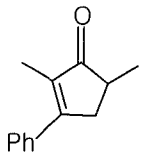
3 (R_5= C_2H_5)
5 (R_5= Ph)
7 (R_5= C_2H_5)
10 (R_5= Ph)



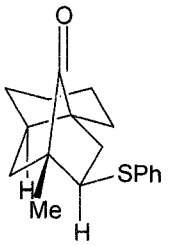
4 (R_5= C_2H_5; R_6= H)
6 (R_5= Ph; R_6= H)
9 (R_5= C_2H_5; R_6= H)
12 (R_5= Ph; R_6= H)
13 (R_5= Ph; R_6= Ph)
16 (R_5= Ph; R_6= Ph)
17 (R_5= Ph; R_6= H)



8



14



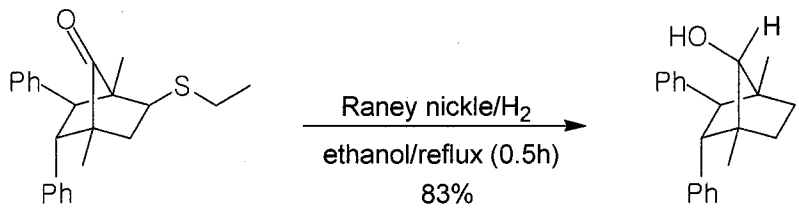
15

entry	dienone	R_1	R_2	R_3	R_4	vinyl sulfid	solvent	BF_3·OEt_2 (equiv)	products (% yield)
1	**1a**	Ph	Me	Me	Ph	**2a**	CH_2Cl_2	1	**3** + **4** (71; 1:7)
2	**1a**	Ph	Me	Me	Ph	**2b**	CH_2Cl_2	1	**5** + **6** (79; 1:7)
3	**1a**	Ph	Me	Me	Ph	**2c**	CH_2Cl_2	1 - 0.5	Complex mixture
4	**1b**	Ph	Me	Me	H	**2a**	toluene	1.5	**7** + **8** + **9** (56; 4:3:10)
5	**1b**	Ph	Me	Me	H	**2b**	CH_2Cl_2	1.5	**10** +**11** + **12** (83; 12.5:6:30)
6	**1b**	Ph	Me	Me	H	**2b**	toluene	1.5	**10** +**11** + **12** (86; 10:3:10)
7	**1b**	Ph	Me	Me	H	**2c**	toluene	1.5	**13** (38) + **14** (30)
8	**1c**	$(CH_2)_4$		Me	H	**2a**	toluene	2	NR
9	**1c**	$(CH_2)_4$		Me	H	**2b**	toluene	2	**15** (37)
10	**1c**	$(CH_2)_4$		Me	H	**2c**	toluene	2	**16** (24)
11	**1d**	*i*-Pr	Me	Me	*i*-Pr	**2a**	toluene	2	NR
12	**1d**	*i*-Pr	Me	Me	*i*-Pr	**2b**	toluene	2	**17** (32)

Table 2-3 Summary of the intermolecular [3+2] cycloaddition of **1a-d** with **2a-c**

2.2.5 Further transformations involving the sulfide functionality

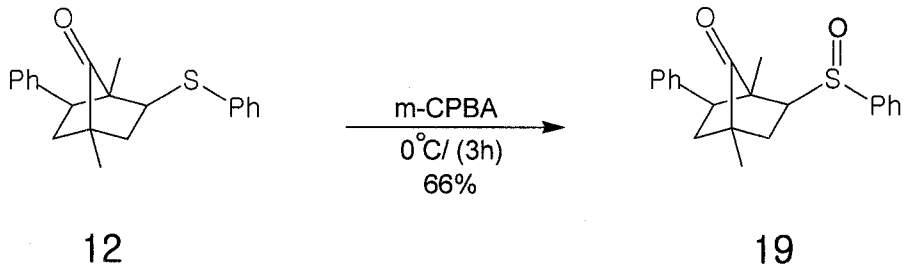
Finally, the ability of transferring sulfur group to another functionality was examined using adducts **4** and **12**. Following the literature procedure,[10] adduct **4** was successfully desulfurized by treating it with Raney nickel in ethanol at reflux for 0.5 hour. The desulfurized product **18** was purified in silica gel chromatography and obtained in 83% yield (Scheme 2.9). In the process, the carbonyl group was also reduced to an alcohol. The structure of compound **18** was identified by NMR and 2D NMR spectral analysis. Obtaining compound **18** as the only isomer can be explained based on the observation that the carbonyl group was reduced from the same side where the desulfonzation occurred. Moreover, the other side of adduct **4** is blocked by two phenyl groups.



4 18

Scheme 2.9 Desulfurization of compound **4**

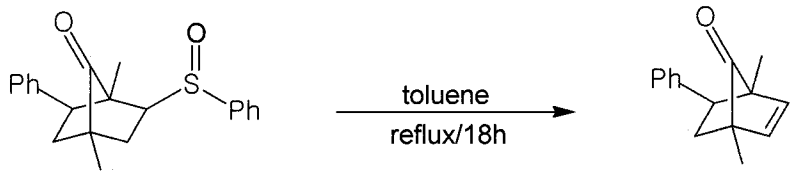
In another modification of the sulfide moiety, adduct **12** was oxidized by 1.1 equivalents of m-CPBA at 0°C to its corresponding sulfoxide **19** (Scheme 2.10).[11] The product was purified in silica gel chromatography to give pure material in 66% yield. The structure of compound **19** was identified by NMR spectral analysis.



12 19

Scheme 2.10 The formation of the sulfoxide

Stirring compound **19** in refluxing toluene for eighteen hours successfully eliminated the sulfoxide group and furnished alkene **20** (Scheme 2.11).[12] Unfortunately, compound **20** was unstable to silica gel chromatography, even after pretreatment with 2% triethylamine. Since the crude ^{1}H NMR spectra was almost clean and alkene **20** was the major product, compound **20** was identified without purification based on NMR spectral analysis, mass spectra and IR spectra, as will be seen later in this chapter.



19 20

Scheme 2.11 Sulfoxide elimination to form alkene **20**

2.3 Structure determination of the novel products

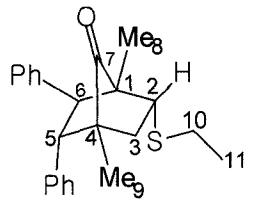
Up to this point, we produced the reaction conditions in which simple dienones undergo 3+2 cycloaddition with the vinyl sulfides. In some cases, as seen in Table 2.3, we got more than one isomer, but with good selectivity. Careful examination of the 1D and 2D NMR data of the products, as will be seen later, showed that all the minor isomers have the same relative stereochemistry. The same generalization also applies to all major isomers.

Furthermore, the IR spectra indicated the presence of a carbonyl group in each isomer. The frequencies of these carbonyl groups appeared in the range of 1757-1769 cm^{-1}. The carbonyl stretching frequency typically appears in the range of 1720-1708 cm^{-1} for aliphatic ketones. However, ring strain increases this frequency in cyclic ketones, as is seen for the simple cycloalkanones such as cyclohexanone (1715 cm^{-1}), cyclopentanone (1745 cm^{-1}) and cyclobutanone (1780 cm^{-1}).[13] The values obtained for the various [3+2] cycloadducts are consistent with ketones contained within a strained, bicyclic framework.

2.3.1 Structure determination of bicyclic compound 3, 5, 7 and 10 (The minor isomers)

We will start by identifying the structure of compound **3**. The HRMS showed the molecular formula for compound **3** to be $C_{23}H_{26}OS$. The structure of compound **3** was determined based on 1D and 2D NMR data. The ^{13}C NMR spectrum showed that there were ten sp^3 carbons in the molecule. From the APT spectrum it was apparent that three

of these carbons were methines, two were methylenes, three were methyl groups and two were quaternary carbons. Also, from the HMQC experiment we could assign which proton attached to which carbon (Table 2.4).



3

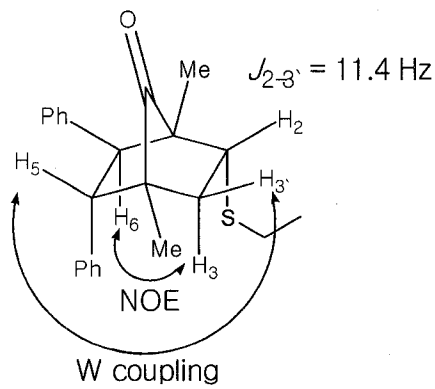
Carbon Number	δ_C (ppm)	δ_H (ppm) of correlated protons
4	49.6 (C)	
5	56.2 (CH)	3.17 (dd, 1H, J = 8.1, 2.0 Hz)
6	47.5 (CH)	4.17 (d, 1H, J = 8.1 Hz)
1	51.9 (C)	
2	48.3 (CH)	2.71 (dd, 1H, J = 11.4, 6.6 Hz)
3	34.1 (CH_2)	1.93 (dd, 1H, J = 13.7, 6.6 Hz) 1.46 (ddd, 1H, J = 13.7, 11.4, 2.2 Hz)
7	214.9 (C=O)	
9	13.9 (CH_3)	1.00 (s, 3H)
8	12.8 (CH_3)	0.96 (s, 3H)
10	26.8 (CH_2)	2.25 (dq, 2H, J = 7.5, 2.8 Hz)
11	15.2 (CH_3)	1.01 (t, 3H, J = 7.3 Hz)

Table 2-4 Chemical shifts of compound **3**

H Number	δ_H (ppm)	Multiplicity	Coupling constant (Hz)	COSY correlations
H_6	4.17	d	8.1	H_5
H_5	3.17	dd	8.1, 2.0	H_6, $H_{3'}$
H_2	2.71	dd	11.4, 6.6	H_3, $H_{3'}$
H_3	1.93	dd	13.7, 6.6	$H_{3'}$, H_2
$H_{3'}$	1.46	ddd	13.7, 11.4, 2.2	H_3, H_5, H_2

Table 2-5 The coupling constants used for determination of the configuration of isomer **3**

The 2D COSY spectrum of compound **3** showed that H_5 experiences long range W- coupling with $H_{3'}$. This indicated that both H_5 and $H_{3'}$ occupy *exo* positions, and that the phenyl group attached to C_5 is therefore *endo* (Scheme 2.12). Also the coupling constant between H_2 and H_3 was found to be 6.6 Hz; however, the coupling constant between H_2 and $H_{3'}$ was 11.4 Hz (Table 2.5). This suggested that H_2 and $H_{3'}$ are *cis*, with a dihedral angle of around 0°, whereas H_2 and H_3 are *trans*.[14] The TROESY spectrum showed that H_6 correlated to H_3, but there was no correlation between H_2 and H_6. These correlations supported the stereochemical assignment at C_2 (Scheme 2.12).

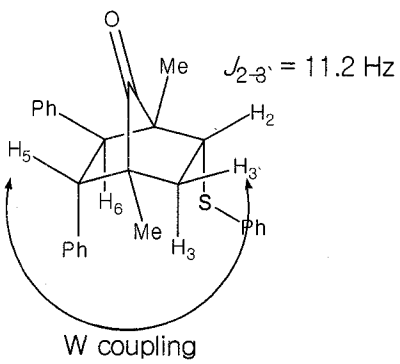


3

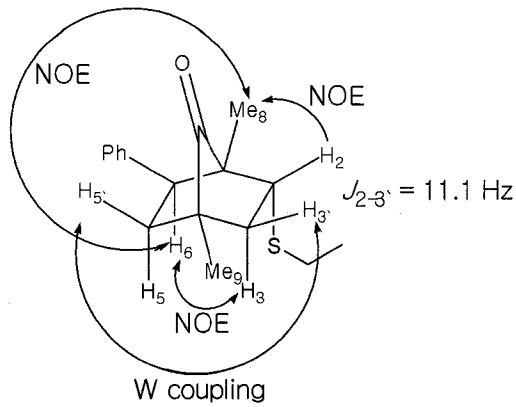
Scheme 2.12 The W-coupling and the NOE effect in compound **3**

Following the same steps as above, we determined the structure of compounds **5**, **7** and **10.** The HRMS identified the molecular formula for compound **5** as $C_{27}H_{26}OS$, compound **7** as $C_{17}H_{22}OS$ and compound **10** as $C_{21}H_{22}OS$. Following the same procedure

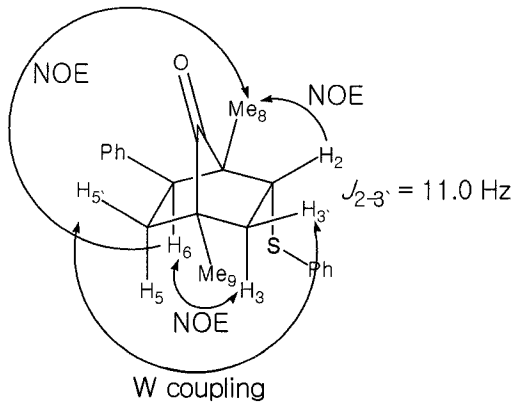
of structural investigation, as discussed above, we concluded that all these compounds have the same relative stereochemistry. The 2D COSY spectra are summarized in Table 2.6 for compound **5**, Table 2.7 for compound **7**, and Table 2.8 for compound **10**. Scheme 2.9 shows the key evidence for the structure determination of these compounds. For example, the TROESY spectrum for compound **7** showed that H_2 correlated to methyl C_8. Also H_6 correlated to methyl C_8. These correlations confirmed the regiochemistry to be as shown, with the ethyl sulfide and phenyl group adjacent to the same bridgehead. The correlation between H_3 and H_6 suggested the *syn* relationship between H_3 and H_6. For compound **10**, The TROESY spectrum showed that H_6 and H_2 correlated to methyl C_8, as was discussed above for compound **7**. Also, H_3 correlated to H_5 and H_6. This suggested that H_6, H_5, and H_3 are all *syn* to each other and in close proximity. There was no correlation between H_2 and either H_6 or H_5. This implied that H_2 was in the exo orientation (Scheme 2.13).



5

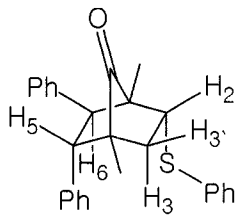


7



10

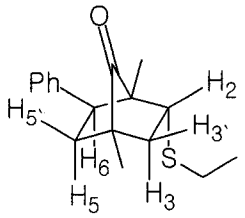
Scheme 2.13 The W-coupling and the NOE effects in compounds **5**, **7** and **10**



5

H Number	δ_H (ppm)	Multiplicity	Coupling constant (Hz)	COSY correlations
H_6	4.27	d	8.0	H_5
H_2	3.28	dd	11.2, 6.5	H_3, $H_{3'}$
H_5	3.18	dd	8.1, 2.1	H_6, $H_{3'}$
H_3	2.02	dd	13.8, 6.5	$H_{3'}$, H_2
$H_{3'}$	1.43	ddd	13.6, 11.2, 2.2	H_3, H_5, H_2

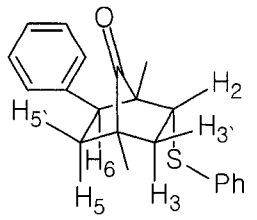
Table 2-6 The coupling constants used for determination of the configuration of isomer **5**



7

H Number	δ_H (ppm)	Multiplicity	Coupling constant (Hz)	COSY correlations
H_6	3.65	dd	10.6, 5.8	H_5, $H_{5'}$
H_2	2.62	dd	11.1, 6.1	H_3, $H_{3'}$
H_5	1.88	dd	12.7, 10.6	H_6, $H_{5'}$
$H_{3'}$	1.84	ddd	12.7, 11.2, 3.4	$H_{5'}$, H_3, H_2
$H_{5'}$	1.64	ddd	12.7, 5.8, 3.4	H_5, H_6, $H_{3'}$
H_3	1.42	dd	12.7, 6.1	$H_{3'}$, H_2

Table 2-7 The coupling constants used for determination of the configuration of isomer **7**



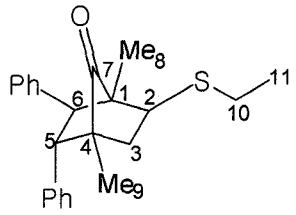
10

H Number	δ_H (ppm)	Multiplicity	Coupling constant (Hz)	COSY correlations
H_6	3.75	dd	J=10.6, 5.7	$H_{5'}$, H_5
H_2	3.22	dd	J=11.0, 5.9	H_3, $H_{3'}$
H_5	1.93	dd	J=12.8, 10.6	H_6, $H_{5'}$
$H_{3'}$	1.83	ddd	J=13.0, 11.0, 3.5	$H_{5'}$, H_3, H_2
$H_{5'}$	1.67	ddd	J=12.8, 5.7, 3.5	H_5, $H_{3'}$
H_3	1.51	dd	J=13.0, 6.0	$H_{3'}$, H_2

Table 2-8 The coupling constants used for determination of the configuration of isomer **10**

2.3.2 Structure determination of bicyclic compound 4, 6, 9, 12, 13, 16 and 17 (The major isomers)

From HRMS we learned that the molecular formula for compound **4** was $C_{23}H_{26}OS$. The structure of **4** was first determined by 1D NMR and 2D NMR data, and then later confirmed by X-ray crystallography (See Appendix A). ^{13}C NMR spectrum showed that there were ten sp^3 carbons in the molecule. APT experiment indicated that three of these carbons were methines, two were methylenes, three were methyl groups and two were quaternary carbons. In Table 2.9, we could assign which proton was attached to which carbon depending on the data from HMQC experiment.



4

Carbon Number	δ_C (ppm)	δ_H (ppm) of correlated protons
4	48.4 (C)	
5	55.7 (CH)	3.13 (s, 2H)
6	55.6 (CH)	3.13 (s, 2H)
1	51.7 (C)	
2	48.6 (CH)	3.06 (dd, 1H, J = 10.0, 4.8 Hz)
3	35.1 (CH_2)	2.40 (dd, 1H, J = 14.1, 10.1 Hz)
		1.36 (dd,1H, J = 14.1, 4.7 Hz)
7	214.9 (C=O)	
9	14.0 (CH_3)	0.99 (s, 3H)
8	14.4(CH_3)	1.11 (s, 3H)
10	25.5 (CH_2)	2.26 (q, 2H, J = 7.5 Hz)
11	11.6 (CH_3)	1.03 (t, 3H, J = 7.5 Hz)

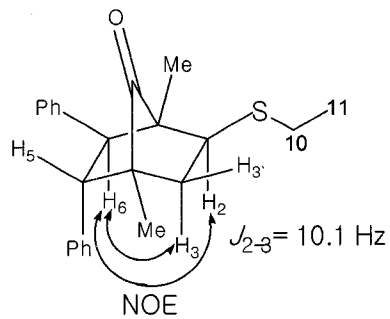
Table 2-9 Chemical shifts of compound **4**

H Number	δ_H (ppm)	Multiplicity	Coupling constant (Hz)	COSY correlations
H_2	3.06	dd	10.0, 4.8	H_3, $H_{3'}$
H_3	2.40	dd	14.1, 10.1	$H_{3'}$, H_2
$H_{3'}$	1.36	dd	14.1, 4.7	H_3, H_2

Table 2-10 The coupling constants used for determination of the configuration of isomer **4**.

To our surprise, both protons H_5 and H_6 have the same chemical shift in ^{1}H NMR spectrum and their peak is an apparent singlet with integration value of two protons (Table 2.9). The 2D COSY spectrum of compound **4** did not show any long range W-

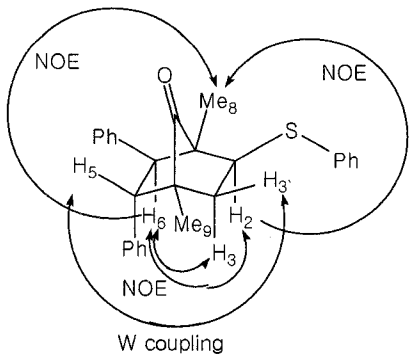
coupling between H_5 and $H_{3'}$. However the coupling constant between H_2 and H_3 was found to be 10.1 Hz; and the coupling constant between H_2 and $H_{3'}$ was 4.8 Hz (Table 2.10). This suggested that H_2 and H_3 are *cis*, with a dihedral angle of around 0°, whereas H_2 and $H_{3'}$ are *trans*. Also, the TROESY spectrum showed that H_6 was in close proximity to H_3 and H_2 (Scheme 2.14). This confirmed that H_3, H_6 and H_2 were *syn* to each other. From the NMR data we determined the structure of compound **4** to be as in Scheme 2.10. Further support came from X-ray data, from which the structure of compound **4** was determined without ambiguity (Scheme 2.14).



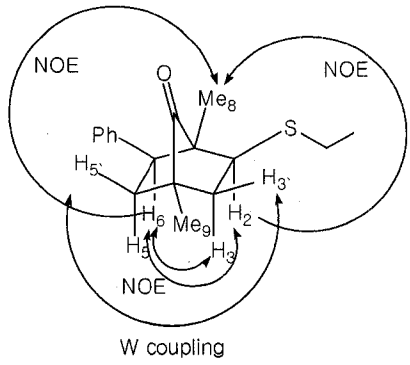
4

Scheme 2.14 The NOE effect in compound **4**

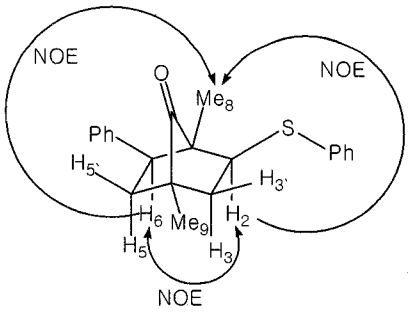
Following the same steps as above, we determined the structure of compounds **6**, **9**, **12**, **13**, **16**, and **17**. It was found that all these compounds have the same relative stereochemistry. Scheme 2.15 shows the key evidence for the structure determination of these compounds.



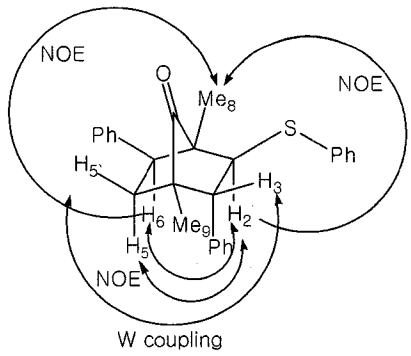
6



9



12



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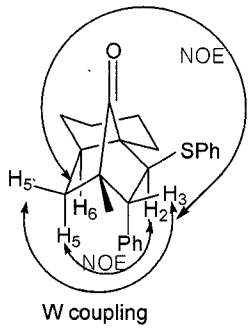
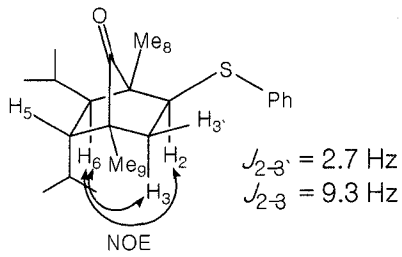


16

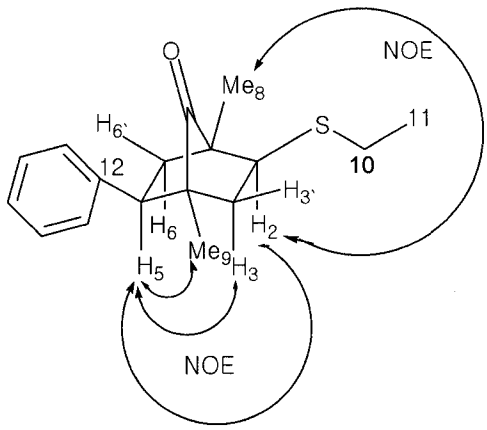


13

Scheme 2.15 The W-coupling and the NOE effects in compounds **6**, **9**, **12**, **13**, **16**, and **17**

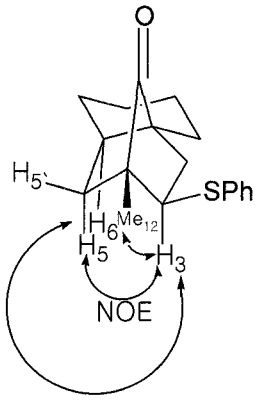
2.3.3 Structure determination of bicyclic compounds 8 and 15

From HRMS we learned that the molecular formula for compound **8** was $C_{17}H_{22}OS$. The HMBC data for compound **8** showed a correlation between H_5 and C_{12} on the phenyl group. The TROESY spectrum showed that H_2 was in close proximity to methylene C_{10}, methyl C_{11}, and methyl C_8. Also, H_5 showed a correlation with methyl C_9. This suggested that the ethyl vinyl sulfide and the phenyl group were on opposite sides of the molecule. Finally, correlations were observed between H_2, H_6, H_5 and H_3, providing evidence that these hydrogens were all *syn* to each other (Scheme 2.16).



8

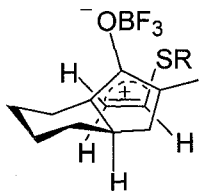
Scheme 2.16 The NOE effects in compounds **8**



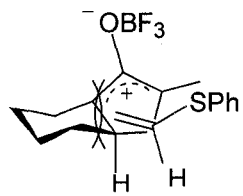
15

Scheme 2.17 The NOE effects in compounds **15**

From HRMS the molecular formula for compound **15** was found to be $C_{18}H_{22}OS$. The TROESY spectrum of compound **15** showed that H_3 correlated to methyl C_{12}, so the phenyl sulfide group and the methyl group were determined to be on adjacent carbons. Also, H_3 correlated to H_5 and H_6. This indicated that H_3, H_5, and H_6 are all *syn* to each other and in close proximity (Scheme 2.17). The orientation of H_6 is expected to be down in compound **15** and also **16**. This is because of the concave shape of the cyclopentenyl cation from **1c**. The vinyl sulfide will preferentially approach the bicyclic cationic species from the convex face to result in H_6 oriented down (Scheme 2.18).



convex face

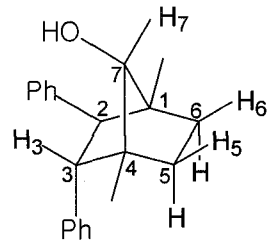


concave face

Scheme 2.18 The steric effect when the vinyl sulfide approaches the cationic intermediate from the concave face

2.3.4 Structure determination of compounds 18, 19 and 20

The HRMS of the product from treatment of compound **4** with Raney nickel showed the molecular formula for compound **18** to be $C_{21}H_{24}O$, indicating the loss of sulfur and the addition of two hydrogen atoms. Also, the ^{13}C NMR spectrum indicated the presence of nine sp^3 carbons in the molecule, and the peak for carbonyl group was no longer present. From the HMQC experiment we could assign which proton attached to which carbon (Table 2.11).



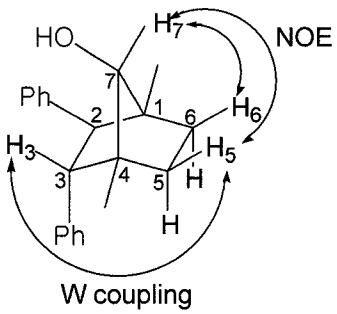
18

Carbon Number	δ_C (ppm)	δ_H (ppm) of correlated protons
2	58.4 (CH)	3.13 (d, 1H, J = 8.33 Hz)
3	59.3 (CH)	3.76 (dd, 1H, J = 8.4, 1.9 Hz)
5	26.5 (CH_2)	1.74 (ddd, 1H, J = 13.1, 10.1, 5.7 Hz)
		1.00-0.92 (m,1H)
6	37.5 (CH_2)	1.48-1.34 (m, 2H)
7	88.6 (HC-OH)	3.06 (s, 1H)
		1.12 (s, 1H)

Table 2.11 Chemical shifts of compound **18**

To confirm the presence of a hydroxyl group, few drops of D_2O were added to compound **18** in the NMR tube. After running the ^1H NMR spectra again the peak at 1.12 ppm disappeared. This is seen as an indication that this peak is due to the hydroxyl group.

The TROESY spectrum showed that H_7 correlated to H_5 and H_6. These correlations supported the stereochemical assignment at C_7 (Scheme 2.19). Furthermore, the IR spectrum did not show any carbonyl group peak. However, there was an hydroxyl group stretch observed in the range of 3583-3466 cm^{-1}.



18

Scheme 2.19 The NOE effects in compounds **18**

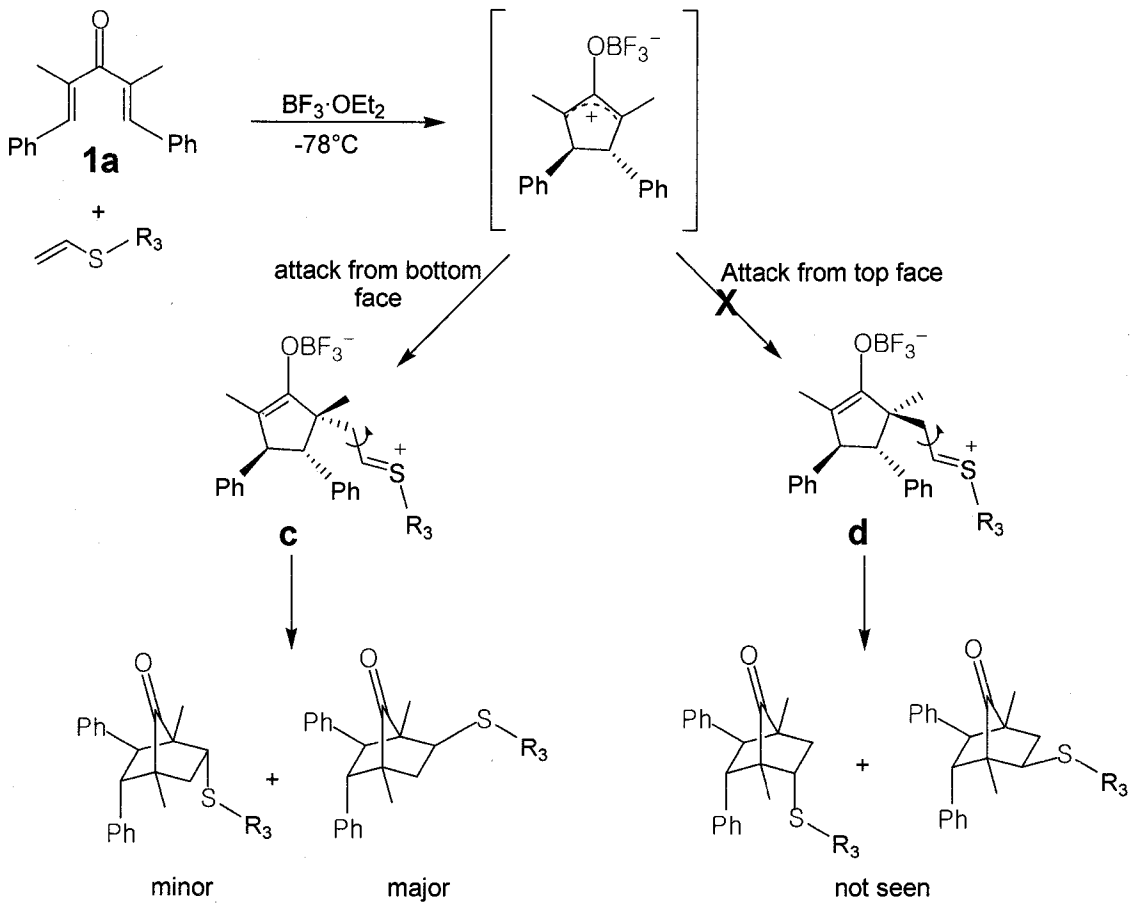
Regarding the oxidation of compound **12**, the mass spectrum identified the molecular formula for compound **19** as $C_{21}H_{22}O_2S$, indicating the presence of one additional oxygen atom. Since compound **12** has carbonyl group, there is a possibility of a competing Baeyer-Villiger oxidation, which results in the formation of the lactone. The IR spectrum showed that compound **19** was the sulfoxide, not the lactone, since the frequency of the carbonyl group was 1759 cm^{-1}. If compound **19** is lactone, the frequency of the carbonyl group should be around 1770 cm^1. Also, in the IR spectrum, a

strong band was observed at 1047 cm^{-1}, which was for the stretching of the sulfoxide group.

Refluxing compound **19** in toluene for eighteen hours resulted in formation of product **20**. From the HRMS we learned that the molecular formula for compound **20** was $C_{15}H_{16}O$ which is less than the molecular formula for compound **19** by C_6H_6OS. This indicated that compound **19** underwent sulfoxide elimination to produce alkene **20**. Also, the ^{13}C NMR spectrum for compound **19** showed that there were eight unique sp^3 carbons in the molecule, while compound **20** has only six sp^3 carbons and six sp^2 carbons. The IR spectrum showed that the carbonyl group peak appeared at 1779 cm^{-1}. This is expected since the strain in the bicyclic compound **20** is high due to presence of the additional double bond.

2.4 Proposed mechanism and transition state

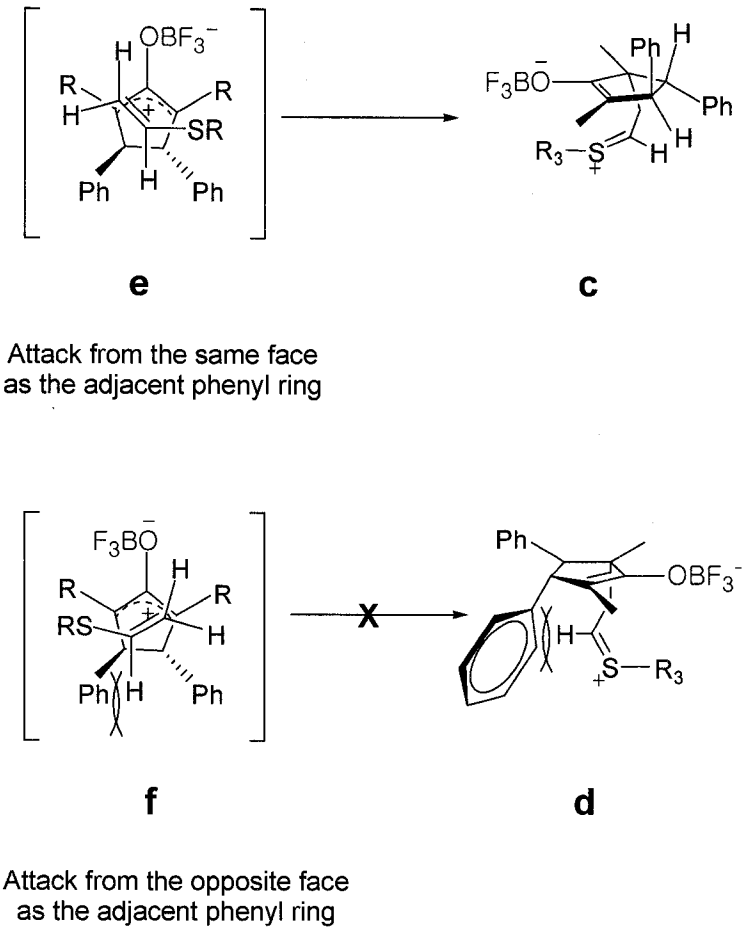
At the beginning of this chapter we showed the proposed mechanism of trapping the Nazarov intermediate with electron-rich alkenes (Scheme 2.1). This mechanism can be used as a starting point to explain the regioselectivity of the products that we got from trapping the dienones with vinyl sulfides. Starting with dienone **1a**, theoretically, trapping of the resulting cyclopentenyl cation from **1a** with vinyl sulfides **2a** or **2b** could produce four isomers with their enantiomers. However, experimentally, we only saw two isomers, in a 1:7 ratio. Nucleophilic attack of the β carbon atom of these vinyl sulfides at one of the oxyallyl cation termini can happen from either the same face as the neighbouring phenyl ring to produce intermediate **c**, or from the opposite face to produce intermediate **d** (Scheme 2.20).



Scheme 2.20 The proposed mechanism of trapping the Nazarov intermediate with vinyl sulfide

However, the products that we observed were formed from collapsing of zwitterion **c**. None of the bicyclic products derived from zwitterion **d** were observed. This can be explained based on a compact transition state with the olefin π system underneath the allyl cation.[15] If this is the case, it is actually better to have the unsubstituted end of the vinyl sulfide coming in next to the phenyl group to minimize the

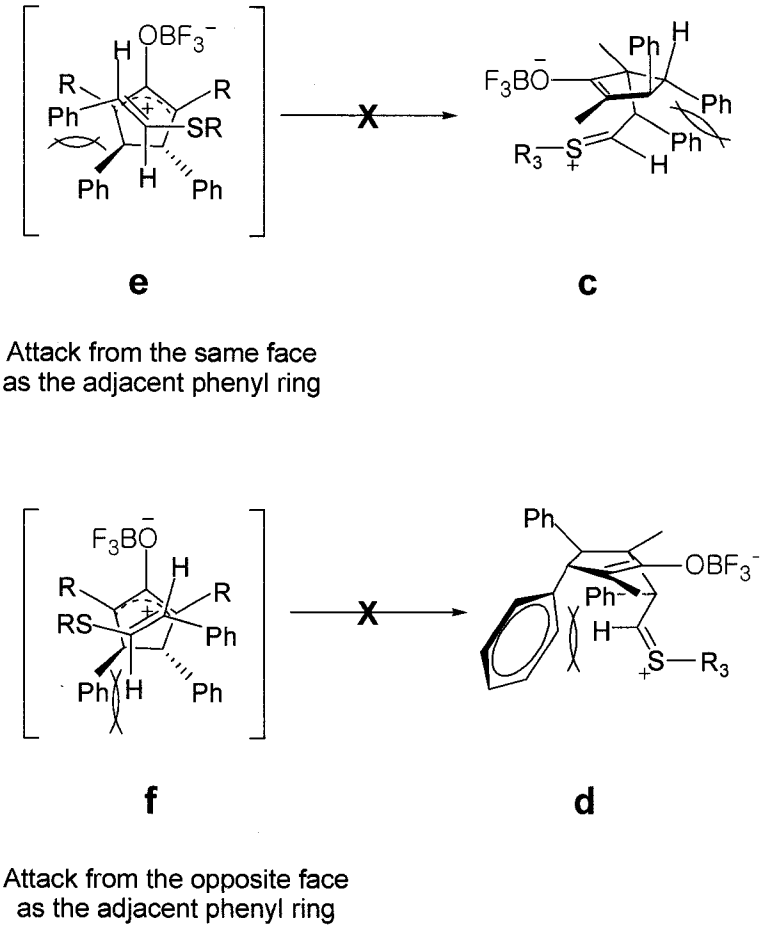
steric effect. Zwitterion **c** may form through compact transition state **e** where the attack happened from the same face as the adjacent phenyl ring (Scheme 2.21). Failure to see any bicyclic products derived from zwitterion **d** may be due to the unfavourable steric effects in the compact transition state **f** (Scheme 2.21).



Scheme 2.21 The compact transition states required for forming zwitterions **c** and **d**

Failure to trap **1a** with **2c** offers additional evidence that this trapping may occur via a compact transition state. It can be argued that the cyclopentenyl cation from **1a** is

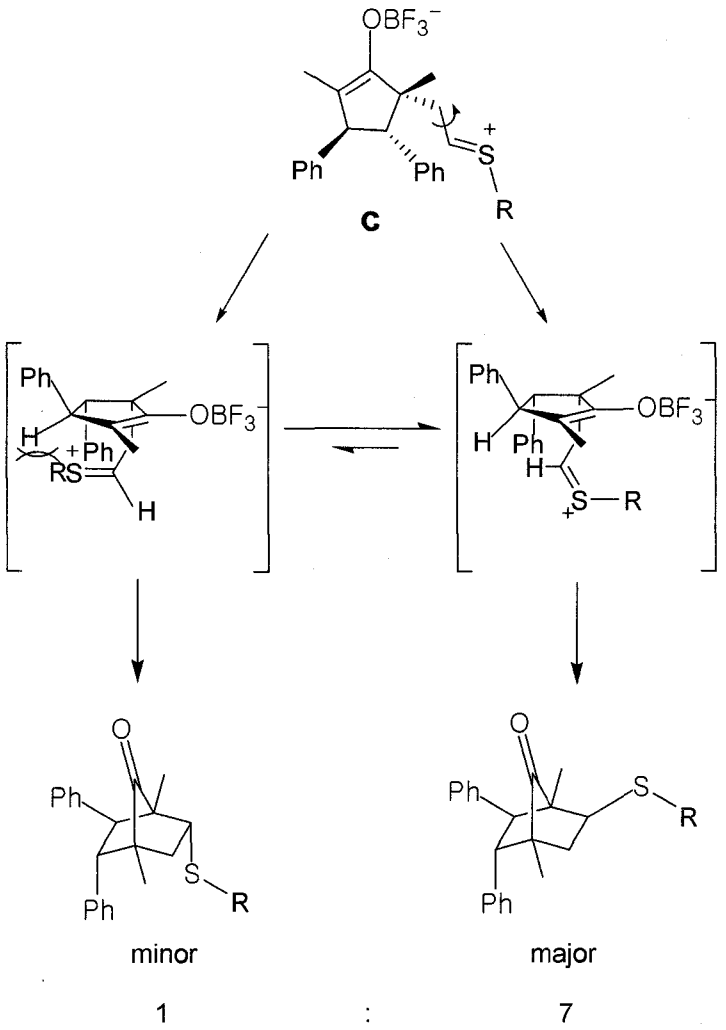
sterically hindered due to the phenyl group on each face. This hindrance could prevent *β*-(phenylthio)styrene **2c**, from closely approaching the cyclopentenyl cation from either face of the molecule (Scheme 2.22).



Scheme 2.22 The steric effect in the compact transition states required for trapping **1a** with **2c**

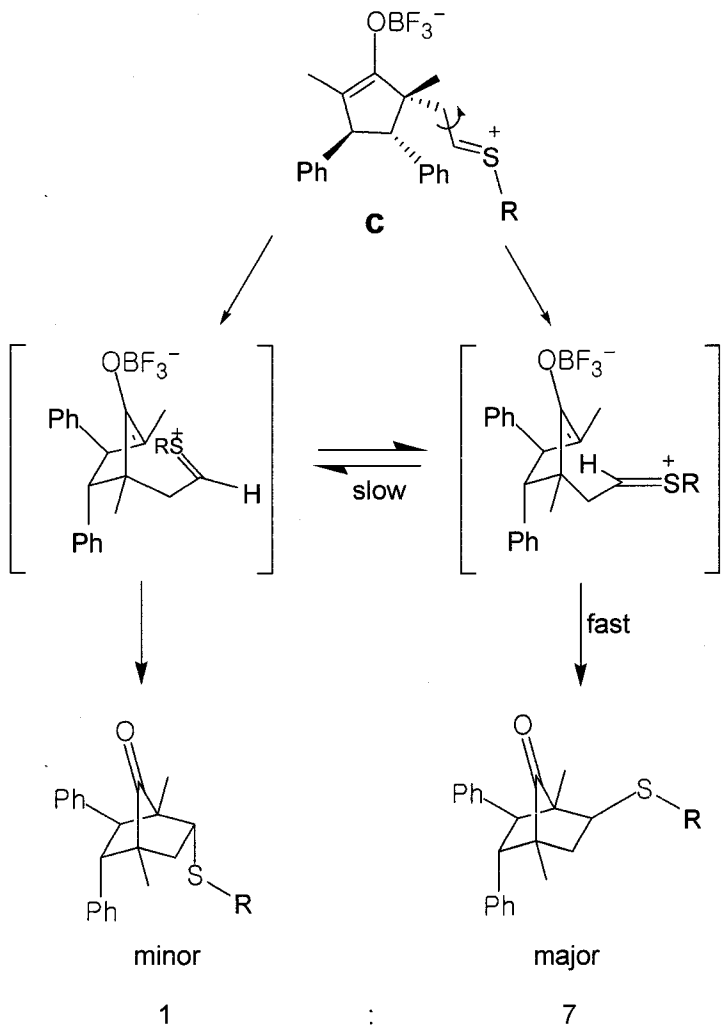
As mentioned earlier, trapping of the resulting cyclopentenyl cation from **1a** with vinyl sulfides **2a** or **2b** produces two isomers in a 1:7 ratio. Having these two isomers in this ratio can be explained based on the free rotation around the carbon – carbon bond in

zwitterions **c**, as in Scheme 2.20. This rotation leads to ring closing of this zwitterions **c** in two transition states, which are in equilibrium. However, the equilibrium is shifted towards the transition state where the steric effect is minimal. Ring closing of this transition state produced the major isomer (Scheme 2.23).



Scheme 2.23 Transition states required for ring closure of zwitterion **c**

Also, it is possible that the carbon-carbon bond formation, which results in the formation of the major isomer, is faster relative to the bond rotation to generate the minor isomer (Scheme 2.24).[16]



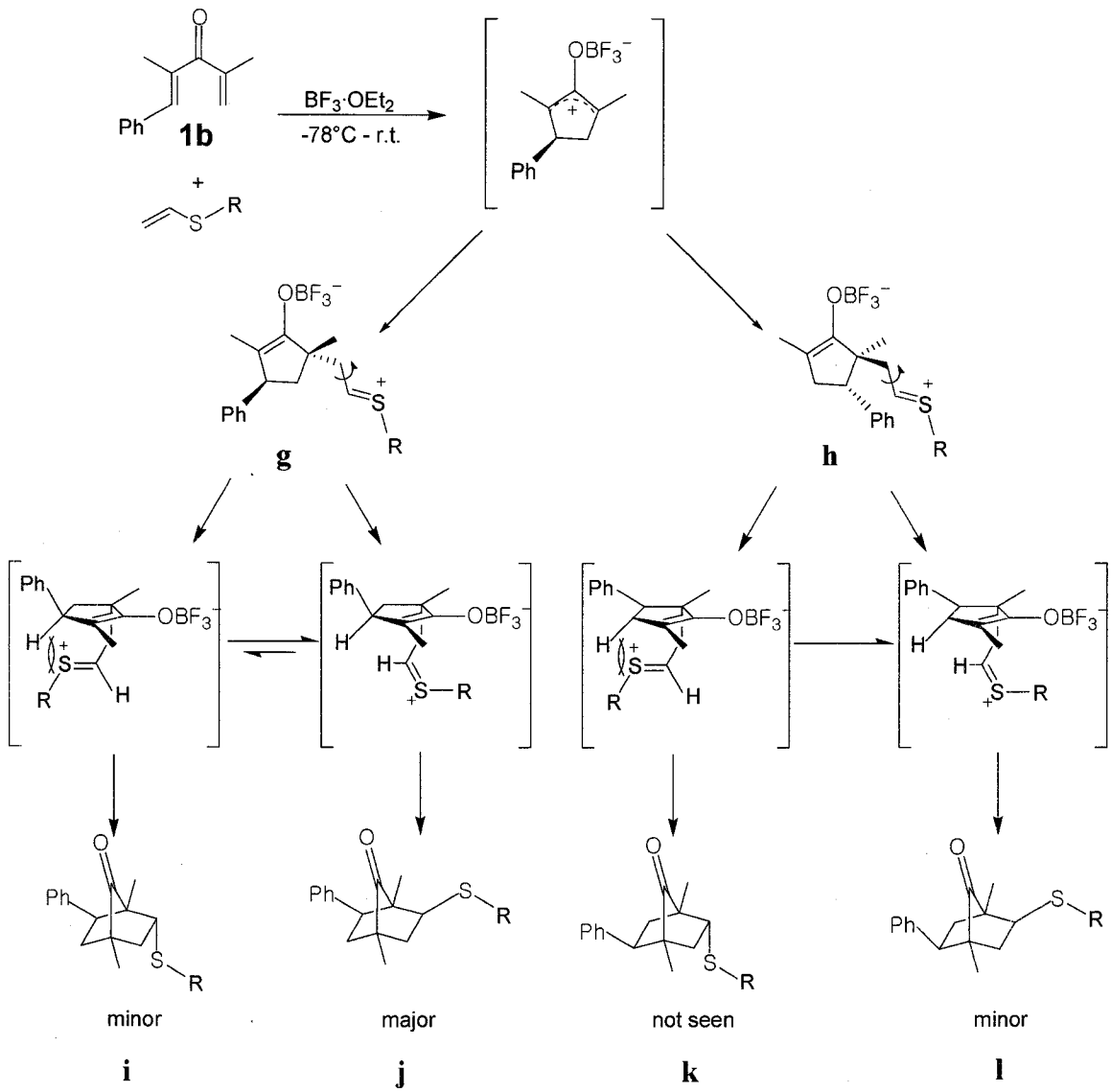
Scheme 2.24 Carbon-carbon bond formation versus bond rotation

Moving to the case where the resulting cyclopentenyl cation from **1b** was trapped with vinyl sulfides **2a** or **2b**, we noticed the formation of three isomers. We expect to see more isomers in this case than in the previous one, since the dienone **1b** has only one

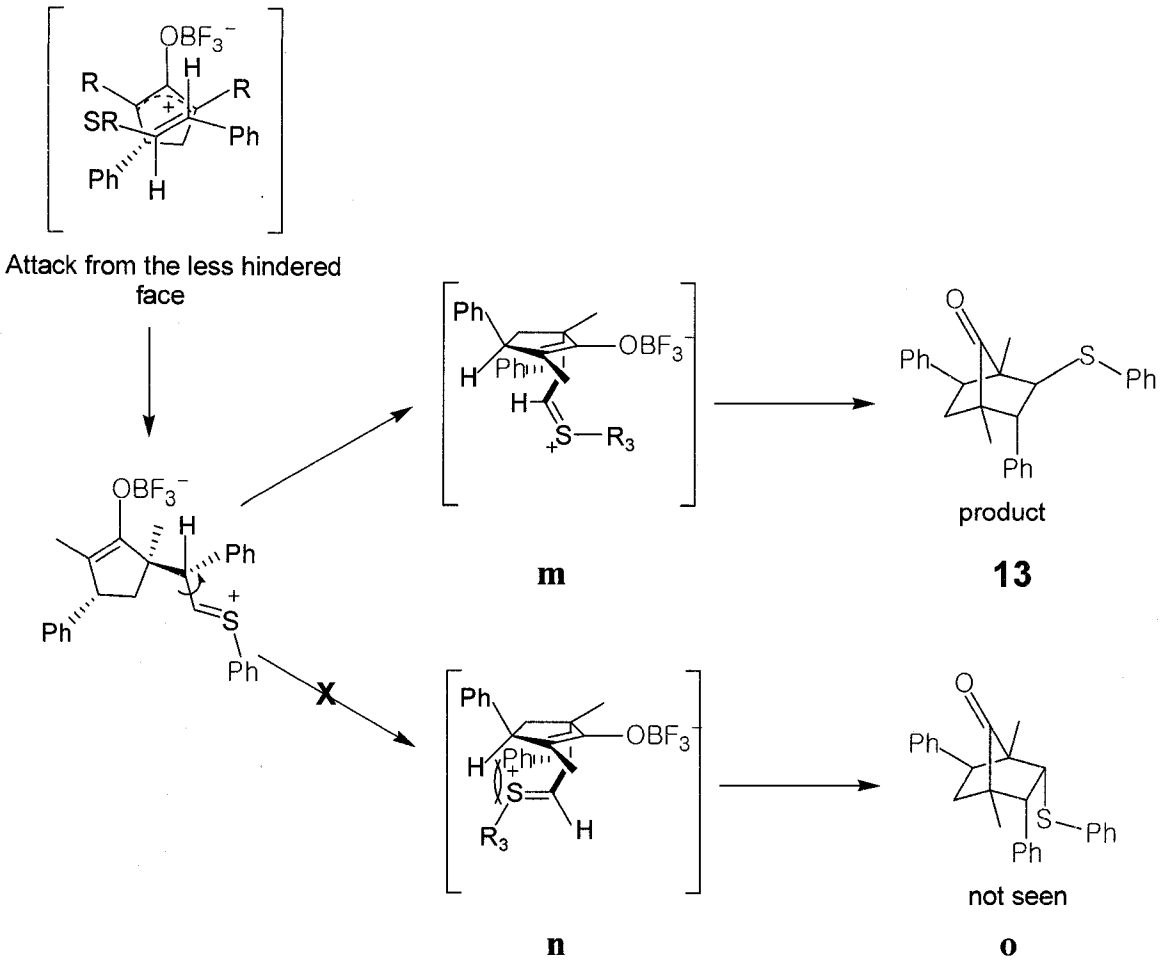
phenyl group. Therefore, one of the faces of the reactive oxyallyl intermediate resulting from **1b** is more available than the other face. As a result, the nucleophilic attack of the β carbon atom on the vinyl sulfides occurs at one of the oxyallyl cation termini from the less hindered face, the face opposite the phenyl group, and produces two zwitterions **g** and **h** (Scheme 2.25). The collapse of zwitterion **g** would result in the formation of the observed isomers **i** and **j**. Only **l** was observed as a result of zwitterion **h**. The favourable formation of **j** and **l** can be explained based on the transition state where the steric effect is minimal (Scheme 2.25).

The difference in ratio between these isomers is less than that for trapping **1a** with **2a** and **2b**. The ratio was 1:7 in the case of trapping **1a** and it was 1.3:1:3.3 and 3.3:1:3.3 in the case of trapping **1b** with **2a** and **2b** respectively. This is probably because the free rotation around the carbon – carbon bond in zwitterion **g**, which has no phenyl group at that face, is faster than that of zwitterion **c** (Scheme 2.23).

Also, we did notice that **1b** can be trapped by disubstituted vinyl sulfide **2c** in the presence of $BF_3{\cdot}OEt_2$ to produce compound **13**. The formation of this compound, as the only isomer, can be explained based on steric effects. Nucleophilic attack of the β carbon atom on the vinyl sulfides occurs, via compact transition state, at one of the cation termini. This would occur from the less hindered face, the face opposite the phenyl group, to produce a zwitterion (Scheme 2.26). Compound **13** would be formed when this zwitterion collapsed via intermediate **m**. This is expected since the steric repulsion is minimal in this intermediate. Trapping **1c** with **2c** resulted in compound **16**, which has the same regioselectivity as compound **13** (Table 2.3).



Scheme 2.25 Transition states required for ring closure of zwitterions **g** and **h**



Scheme 2.26 Transition states required for forming and ring closure of the zwitterion

For the dienones **1c** and **1d**, we noticed that they have less reactivity towards the vinyl sulfides than **1a** and **1b** (Table 2.3).[7,8] Also, a single trapping product was observed from their reaction. For instance, trapping **1c** with **2b** should produce at least three isomers as in the case of trapping **1b** with **2b**. Also trapping **1d** with **2b** should produce two isomers as in the case of trapping **1a** with **2b**. In both cases only one isomer was observed, which has the same regioselectivity as that of the major isomer in the other cases. Due to the low yield, we argue that minor isomers could have been produced in small quantities that are very difficult to detect.

2.5 Conclusion

In this work, we disclosed a new reaction in which two simple unsaturated precursors were induced, using $BF_3 \cdot OEt_2$, to combine with the formation of three new carbon – carbon bonds and up to five contiguous stereocenters. This was achieved by trapping the cationic Nazarov intermeduates with vinyl sulfides in a one pot reaction to form densely functionalized bicyclo[2.2.1]heptanones. Several dieneones and vinyl sulfides were examined producing good-to-moderate yields with relatively high regioselectivity. The sulfur group in the resulting adducts provides a useful handle for further elaboration, thus making this methodology both convenient and potentially broad in its scope. For example, the sulfur group could be removed with Raney nickel or eliminated after being oxidized to sulfoxide. The resulting double bond can be converted to many functionalities.

The regioselectivity observed in these reactions was similar to that reported by West and coworkers in trapping the Nazarov oxyallyl intermediate by allylsilanes. As explained earlier, this regioselectivity was based on the compact transition state. Also, as mentioned in Chapter 1, this is not the only case in which allyl cations are proposed to react with unsaturated traps via a compact transition state. The trapping of the Nazarov oxyallyl intermediate with 1,3-dienes in a bimolecular version of the [4+3] cycloaddition to furnish keto-bridged cyclooctenes, and the trapping of the Nazarov intermediate from acyclic trienone in an intramolecular fashion by pendant olefins, occurred via compact transition states.[17]

In addition, when West and coworkers trapped the Nazarov oxyallyl intermediate by allylsilanes, using $BF_3 \cdot OEt_2$ as a Lewis acid, the *exo* adduct was the major product.

However, when they used $SnCl_4$ as a Lewis acid instead of $BF_3 \cdot OEt_2$, the reaction gave the *endo* adducts as a major products. In this work, $BF_3 \cdot OEt_2$ was used as a Lewis acid and the *exo* products were the major isomers. So, for future work, we suggest using $SnCl_4$ as a Lewis acid instead of $BF_3 \cdot OEt_2$ to study its effect on the ratio between the *exo* and *endo* products.

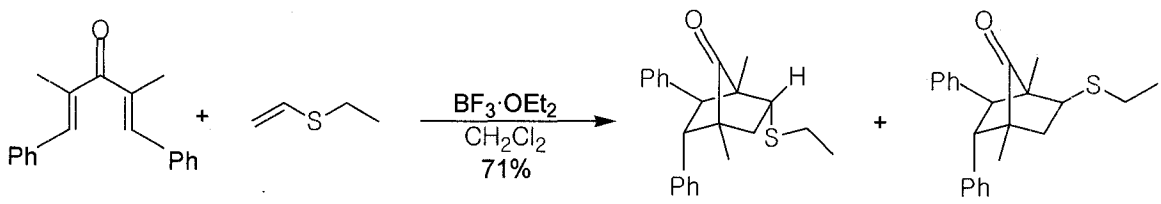
As an extension to this work, the scope of this methodology can be investigated further by applying it over a wider rang of dienones such as 1-phenyl-2,5-dimethyl-1,4-pentadien-3one. This dienone has unsymmetrical termini on the oxyallyl intermediate, where one terminus has a methyl group and the other has a hydrogen atom. It would be valuable to know how the regoiselectivity would be affected by such an unsymmetrial substitution. Another type of dienone, worth trying in the interrupted Nazarov reactions, is a dienone bearing pendant vinyl sulfide. Intramolecular trapping may be more efficient, permitting the use of more sterically demanding reaction partners.

One can also search for a reaction condition that increases the yield and selectivity of this methodology, especially in the case of less reactive dienones, such as **1c** and **1d**. This might be achieved using a stronger Lewis acid, such as BF_2OTf, which can be prepared by mixing TMSOTf with $BF_3 \cdot OEt_2$.[18] Finally, different classes of electron-rich alkenes can be used for this trapping. For example, 1,1-bis(alkylsulfanyl)-1-alkene. Also, enamies can be examined in this reaction using Lewis acids different from the ones mentioned in chapter one.

2.6 Experimental Section

General Information: All air or moisture sensitive reactions were carried out in oven dried (165°C) glassware under an argon atmosphere. Reagents and solvents were transferred by oven-dried syringes or cannulae and were added into the reaction flask through rubber septa. All anhydrous solvents were distilled prior to their use: dichloromethane from calcium hydride, toluene from sodium metal. Thin layer chromatography was performed on glass plates precoated with 0.25mm Kieselgel 60 F254 (Merck). Flash chromatography columns were packed with 230-400 mesh silica gel (Merck). β-(Phenylthio)styrene was prepared according to literature procedures.[1] Commercial reagents were used without further purification unless otherwise noted.

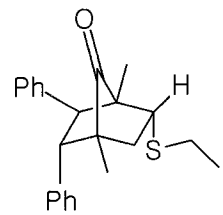
Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz or 500 MHz and coupling constants (*J*) are reported in Hertz (Hz). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz or 125 MHz and are reported (ppm) relative to the center line of the triplet from benzene-d (128.10 ppm). Infrared (IR) spectra were measured with a Mattson FTIR 3000 infrared spectrometer. Mass spectra were determined on a Finnigan Mat 95 high resolution gas chromatography/mass spectrometer with Finnigan Mat ICIS II operating system.



1 : 7

1a **2a** **3** **4**

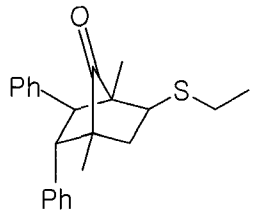
1,4-dimethyl-5,6-diphenyl-2-phenylthiobicyclo[2.2.1]heptan-7-one, 3 and 4: $BF_3{\cdot}OEt_2$ (0.024 mL, 0.19 mmol) was added to a solution of 2,4-dimethyl-1,5-diphenylpenta-1,4-dien-3-one **1a** (0.050 g, 0.19 mmol) and ethyl vinyl sulfide **2a** (0.077 mL, 0.76 mmol) in CH_2Cl_2 (22 mL) at –78°C. After 30 min., the reaction was quenched at -78°C by addition of sat. $NaHCO_3$ (15 mL) and the mixture was then allowed to warm to room temperature. The organic layer was separated and dried ($MgSO_4$). Solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (packed by 2% triethylamine in hexane) (1:40 ether/hexanes as the eluent) yielding two isomers **3** (0.0059 g, 9.0 %) and **4** (0.041 g, 63%).



3

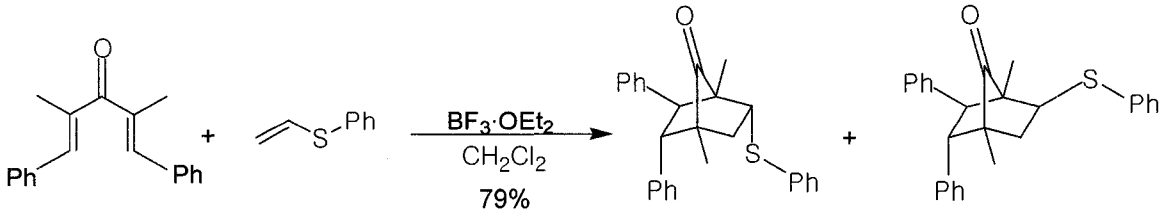
1,4-dimethyl-5,6-diphenyl-2-ethylthiobicyclo[2.2.1]heptan-7-one, 3: White solid: m.p. 129-130°C; R_f 0.50 (1:9 EtOAc/hexanes); IR (Cast film) 3062, 3028, 2962, 2926, 2870, 1761, 1601, 701 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 7.43-7.16 (m, 3H), 7.14-6.90 (m, 7H), 4.17 (d, 1H, J = 8.1 Hz), 3.17 (dd, 1H, J = 8.1, 2.0 Hz), 2.71 (dd, 1H, J = 11.4, 6.6

Hz), 2.28-2.21 (m, 2H), 1.93 (dd,1H, J = 13.7, 6.6 Hz), 1.46 (ddd, 1H, J = 13.7, 11.4, 2.2 Hz), 1.01 (t, 3H, J = 7.3 Hz), 1.00 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 214.9, 142.9, 137.3, 130.3, 128.7, 128.7, 128.4, 127.2, 126.9, 56.2, 51.9, 49.6, 48.3, 47.5, 34.1, 26.8, 15.2, 13.9, 12.8; HRMS for $C_{23}H_{26}OS$ calcd 350.1704, found: m/z 350.1703.



4

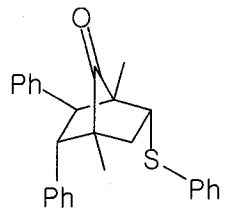
1,4-dimethyl-5,6-diphenyl-2-ethylthiobicyclo[2.2.1]heptan-7-one, 4: White solid: m.p. 119-120°C; R_f 0.47 (1:9 EtOAc/hexanes); IR (Cast film) 3061, 3028, 2965, 2926, 2868, 1949, 1879, 1758, 701 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 7.13-6.93 (m, 10H), 3.13 (s, 2H), 3.06 (dd, 1H, J = 10.0, 4.8 Hz), 2.40 (dd, 1H, J = 14.1, 10.1 Hz), 2.26 (q, 2H, J = 7.5 Hz), 1.36 (dd,1H, J = 14.1, 4.7 Hz), 1.11 (s, 3H), 1.03 (t, 3H, J = 7.5 Hz), 0.99 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 214.9, 143.0, 137.9, 129.4, 128.7, 128.5, 128.4, 127.2, 127.1, 55.6, 55.5, 51.7, 48.5, 48.3, 35.0, 25.3, 14.3, 13.9, 11.5; HRMS for $C_{23}H_{26}OS$ calcd 350.1704, found: m/z 350.1708.



1 : 7

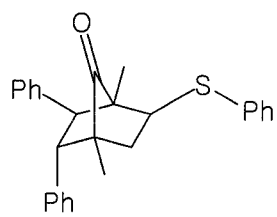
1a **2b** 5 6

1,4-dimethyl-5,6-diphenyl-2-ethylthiobicyclo[2.2.1]heptan-7-one, 5 and 6: The previously outlined procedure was used with phenyl vinyl sulfide **2b** (0.10 mL, 0.76 mmol) as the trapping reagent. The residue was purified by chromatography on silica gel (packed by 2% triethylamine in hexane) (1:40 ether/hexanes as the eluent) yielding two isomers, **5** (0.0071 g, 10 %) and **6** (0.0.049 g, 69 %).



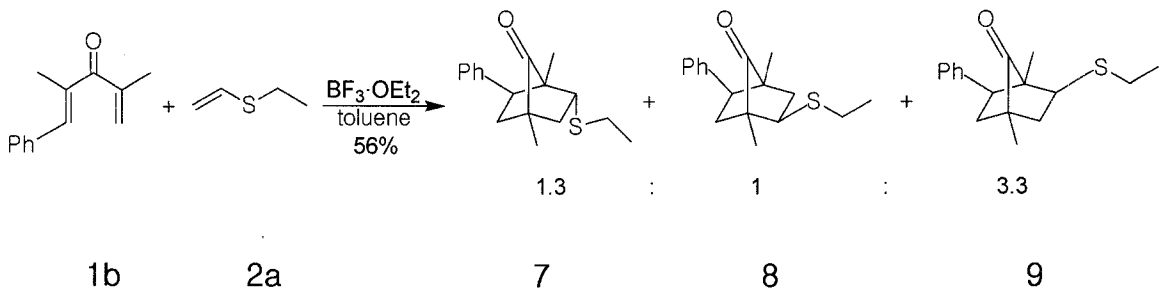
5

1,4-dimethyl-5,6-diphenyl-2-phenylthiobicyclo[2.2.1]heptan-7-one, 5: White solid: m.p. 146-147°C; R_f 0.50 (1:9 EtOAc/hexanes); IR (Cast film) 3059, 3026, 2958, 2923, 2866, 1765, 1461, 701 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.45-6.92 (m, 15H), 4.27 (d, 1H, J = 8.0 Hz), 3.28 (dd, 1H, J = 11.2, 6.5 Hz), 3.18 (dd, 1H, J = 8.1, 2.1 Hz), 2.02 (dd, 1H, J = 13.8, 6.5 Hz), 1.43 (ddd,1H, J = 13.6, 11.2, 2.2 Hz), 0.95 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 214.4, 142.9, 137.5, 135.5, 132.4, 130.6, 129.4, 129.0, 129.0, 128.7, 128.3, 127.5, 127.3, 56.4, 52.4, 51.5, 49.8, 47.7, 34.0, 14.1, 13.0; HRMS for $C_{27}H_{26}OS$ calcd 398.1704, found: m/z 398.1702.



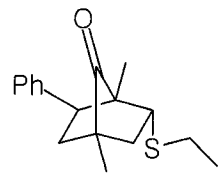
6

1,4-dimethyl-5,6-diphenyl-2-phenylthiobicyclo[2.2.1]heptan-7-one, 6: White solid: m.p. 135-136°C; R_f 0.47 (1:9 EtOAc/hexanes); IR (Cast film) 3060, 3028, 2962, 2926, 2867, 1950, 1879, 1758, 701 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 7.31-6.88 (m, 15H), 3.72 (dd, 1H, J = 9.7, 4.2 Hz), 3.22 (d, 1H, J = 7.5 Hz), 3.12 (dd, 1H, J = 7.5, 2.0 Hz), 2.45 (dd, 1H, J = 14.2, 9.6 Hz), 1.46 (ddd,1H, J = 14.2, 4.1, 2.2 Hz), 1.10 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 214.3, 142.6, 137.6, 135.9, 130.9, 129.4, 129.1, 128.7, 128.5, 128.5, 127.2, 127.2, 126.6, 55.4, 55.1, 51.7, 50.2, 48.2, 35.1, 13.9, 11.6; HRMS for $C_{27}H_{26}OS$ calcd 398.1704, found: m/z 398.1709; Anal. Calcd for $C_{27}H_{26}OS$: C, 81.36; H, 6.58; S, 8.05. Found: C, 81.29; H, 6.62; S, 7.76.



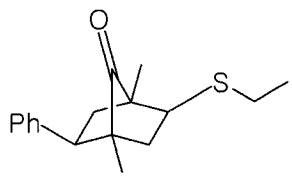
1,4-dimethyl-6-phenyl-2-ethylthiobicyclo[2.2.1] heptan-7-one, 7, 8, and 9: $BF_3{\cdot}OEt_2$ (0.036 mL, 0.29 mmol) was added to a solution of (*E*)-2,4-dimethyl-1-phenylpenta-1,4-dien-3-one **1b** (0.035 g, 0.19 mmol) and ethyl vinyl sulfide **2a** (0.077 mL, 0.76 mmol) in toluene (22 mL) at –78°C. The reaction mixture was allowed to stir overnight and was then quenched by addition of sat. $NaHCO_3$ (15 mL). The organic layer was separated and dried ($MgSO_4$). Solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (packed by 2% triethylamine in hexane) (1:40

ether/hexanes) yielding three isomers **7** (0.0075 g, 13 %), **8** (0.0058 mmol, 10 %), and **9** (0.019 g, 33 %).



7

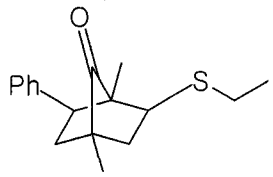
1,4-dimethyl-6-phenyl-2-ethylthiobicyclo[2.2.1]heptan-7-one, 7: White solid: R_f 0.47 (1:9 EtOAc/hexanes); IR (Cast film) 3063, 3029, 2960, 2927, 2868, 1761, 701 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.08-6.90 (m, 5H), 3.65 (dd, 1H, J = 10.6, 5.8 Hz), 2.62 (dd, 1H, J = 11.1, 6.1 Hz), 2.23-2.18 (m, 2H), 1.88 (dd, 1H, J = 12.7, 10.6 Hz), 1.84 (ddd, 1H, J = 12.7, 11.2, 3.4 Hz), 1.64 (ddd, 1H, J = 12.7, 5.8, 3.4 Hz), 1.42 (dd, 1H, J = 12.7, 6.1 Hz), 1.00 (t, 3H, J = 7.4 Hz), 0.99 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 215.0, 144.2, 128.8, 128.6, 126.8, 51.3, 47.1, 43.8, 42.4, 41.6, 41.6, 26.8, 15.3, 14.6, 12.9; HRMS for $C_{17}H_{22}OS$ calcd 274.1391, found: m/z 274.1400.



8

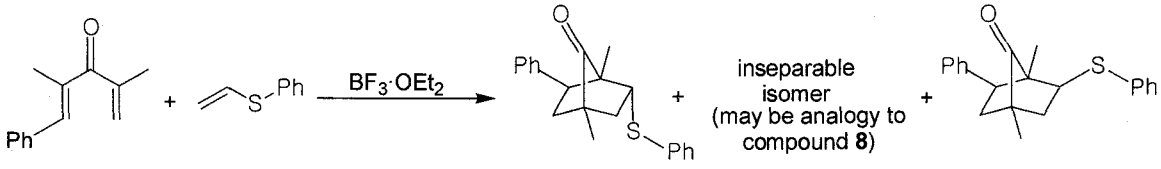
1,4-dimethyl-5-phenyl-2-ethylthiobicyclo[2.2.1]heptan-7-one, 8: White solid: R_f 0.46 (1:9 EtOAc/hexanes); IR (Cast film) 3029, 2961, 2926, 2868, 1757, 701 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.10-6.91 (m, 5H), 2.72 (dd, 1H, J = 10.0, 5.2 Hz), 2.50 (dd, 1H, J =

10.4, 5.7 Hz), 2.23 (q, 2H, J = 7.4 Hz), 1.95 (dd, 1H, J = 13.2, 10.0 Hz), 1.78 (dd, 1H, J = 13.5, 10.1Hz), 1.70 (dd, 1H, J = 13.5, 5.6 Hz), 1.59 (dd, 1H, J = 13.3, 5.2 Hz), 1.25 (s, 3H), 1.04 (t, 3H, J = 7.4 Hz), 0.66 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 214.7, 144.3, 128.7, 128.3, 126.9, 48.1, 47.0, 46.6, 46.6, 43.8, 42.5, 25.4, 14.8, 13.3, 13.11; HRMS for $C_{17}H_{22}OS$ calcd 274.1391, found: m/z 274.1394.



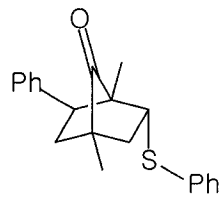
9

1,4-dimethyl-6-phenyl-2-ethylthiobicyclo[2.2.1]heptan-7-one, 9: White solid: m.p. 106-108°C; R_f 0.45 (1:9 EtOAc/hexanes); IR (Cast film) 3029, 2962, 2926, 2868, 1757, 701 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 7.10-6.91 (m, 5H), 2.79 (dd, 1H, J = 10.1, 4.8 Hz), 2.56 (dd, 1H, J = 10.5, 5.5 Hz), 2.23-2.18 (m, 2H), 1.94 (dd, 1H, J = 12.9, 10.1 Hz), 1.77 (dd, 1H, J = 12.7, 10.8 Hz), 1.65-1.56 (m, 2H), 1.03 (s, 3H), 1.01 (t, 3H, J = 7.4 Hz), 0.93 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 214.7, 144.2, 128.8, 128.2, 127.0, 49.3, 48.1, 42.7, 42.4, 42.0, 41.2, 25.4, 14.6, 14.4, 11.4; HRMS for $C_{17}H_{22}OS$ calcd 274.1391, found: m/z 274.1394.



1b **2b** 10 **11** 12

1,4-dimethyl-6-phenyl-2-phenylthiobicyclo[2.2.1]heptan-7-one, 10, 11, and 12: $BF_3{\cdot}OEt_2$ (0.036 mL, 0.29 mmol) was added to a solution of (*E*)-2,4-dimethyl-1-phenylpenta-1,4-dien-3-one **1b** (0.035 g, 0.19 mmol) and phenyl vinyl sulfide **2b** (0.10 mL, 0.76 mmol) in CH_2Cl_2 (22 mL) at –78°C. After two hours, the reaction was quenched at -78°C by addition of sat. $NaHCO_3$ (15 mL) and the mixture was then allowed to warm to room temperature. The organic layer was separated and dried ($MgSO_4$). Solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (packed by 2% triethylamine in hexane) (1:40 ether/hexanes) yielding three isomers **10**, **11**, and **12** (2.1:1:5). Performing the same reaction in toluene provided a different ratio of products (3.3:1:3.3), **10** (0.023 g, 37 %), **11** (12 %), and **12** (0.023 g, 37 %).

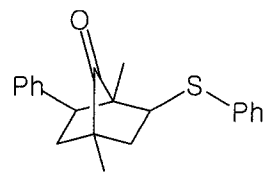


10

1,4-dimethyl-6-phenyl-2-phenylthiobicyclo[2.2.1]heptan-7-one, 10: White solid: R_f 0.47 (1:9 EtOAc/hexanes); IR (Cast film) 3061, 3029, 2959, 2926, 2868, 1760, 701 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 7.30-7.22 (m, 2H), 7.10-6.90 (m, 8H), 3.75 (dd, 1H, *J* = 10.6, 5.7 Hz), 3.22 (dd, 1H, *J* = 11.0, 5.9 Hz), 1.93 (dd, 1H, *J* = 12.8, 10.6 Hz), 1.83 (ddd, 1H, *J* = 13.0, 11.0, 3.5 Hz), 1.67 (ddd, 1H, *J* = 12.8, 5.7, 3.5 Hz), 1.51 (dd, 1H, *J* = 13.0, 6.0 Hz), 0.98 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 214.3, 144.1,

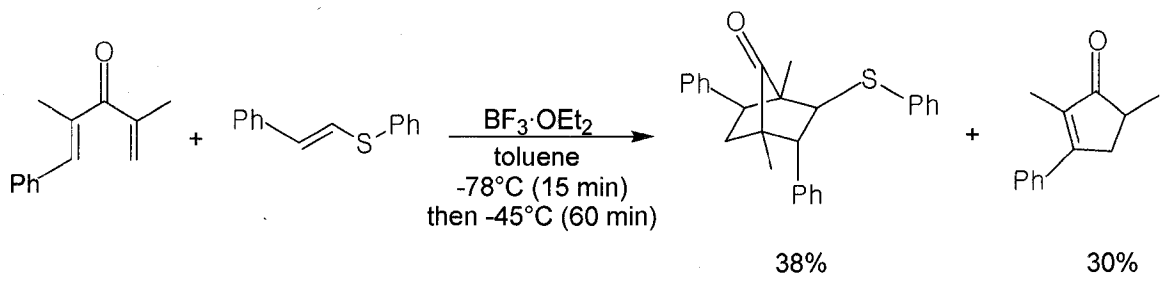
135.8, 132.0, 129.4, 128.9, 128.7, 127.3, 127.1, 51.7, 49.9, 43.9, 42.1, 41.7, 41.5, 14.7, 12.9; HRMS for $C_{21}H_{22}OS$ calcd 322.1391, found: m/z 322.1389.

1,4-dimethyl-6-phenyl-2-phenylthiobicyclo[2.2.1]heptan-7-one, 11: The sample was contaminated with the other two isomers, thus complete spectral data could not be reported: R_f 0.45 (1:9 EtOAc/hexanes); Partial ^{1}H NMR (C_6D_6, 400 MHz) δ 7.27-7.23(m, 2H), 7.11-6.96 (m, 8H), 3.35 (dd, 1H, J = 9.6 , 4.6 Hz), 2.47 (dd, 1H, J = 10.8 , 5.7 Hz), 1.24 (s, 3H), 0.73 (s, 3H).



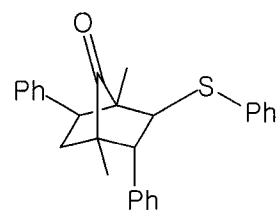
12

1,4-dimethyl-6-phenyl-2-phenylthiobicyclo[2.2.1]heptan-7-one, 12: White solid: m.p. 109-110°C ; R_f 0.43 (1:9 EtOAc/hexanes); IR (Cast film) 3061, 3029, 2957, 2926, 2868, 1757, 701 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 7.24-7.21 (m, 2H), 7.08-6.88 (m, 8H), 3.43 (dd, 1H, J = 9.5, 4.2 Hz), 2.62 (dd, 1H, J = 10.6 , 5.9 Hz), 1.93 (dd, 1H, J = 13.0, 9.5 Hz), 1.78-1.57 (m, 3H), 0.98 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 214.0, 143.8, 136.1, 130.8, 129.1, 128.8, 128.3, 127.1, 126.5, 50.6, 49.8, 49.0, 42.6, 42.1, 41.2, 14.6, 11.4; HRMS for $C_{21}H_{22}OS$ calcd 322.1391, found: m/z 322.1393; Anal. Calcd for $C_{21}H_{22}OS$: C, 78.22; H, 6.88; S, 9.94. Found: C, 78.1095; H, 6.93; S, 10.28.



1b **2c** **13** **14**

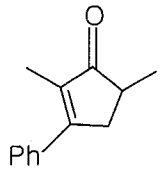
1,4-dimethyl-3,6-diphenyl-2-phenylthiobicyclo[2.2.1]heptan-7-one, 13: $BF_3{\cdot}OEt_2$ (0.029 mL, 0.23 mmol) was added to a solution of (*E*)2,4-dimethyl-1-phenylpenta-1,4-dien-3-one **1b** (0.035 g, 0.19 mmol) and *β*-(phenylthio)styrene **2c** (0.161 g, 0.76 mmol) in toluene (22 mL) at –78°C. The reaction was stirred for 15 min. at –78°C before the temperature was raised to -45°C. After one hour, the reaction was quenched by addition of sat. $NaHCO_3$ (15 mL). The organic layer was separated and dried ($MgSO_4$). Solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (packed by 2% triethylamine in hexane) (1:40 ether/hexanes) yielding the trapping product **13** (0.031 g, 38 %), and the simple Nazarov product **14** (0.011g, 30 %).



13

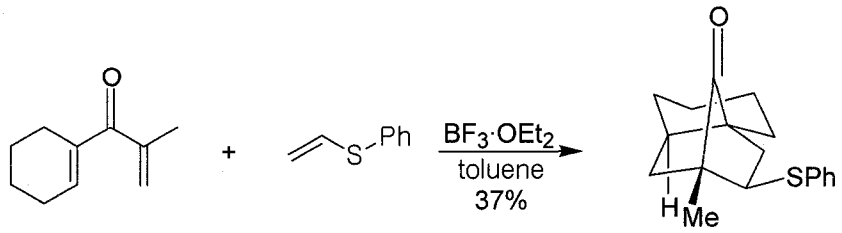
1,4-dimethyl-3,6- diphenyl-2-phenylthiobicyclo[2.2.1]heptan-7-one, 13: White solid: m.p. 132-134°C; R_f 0.46 (1:9 EtOAc/hexanes); IR (Cast film) 3061, 3029, 2961, 2926,

1760, 701 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.24-7.20 (m, 2H), 7.12-6.80 (m, 13H), 3.95 (d, 1H, J = 6.6 Hz), 3.06 (dd, 1H, J = 6.8, 2.2 Hz), 2.90 (dd, 1H, J = 10.5, 5.4 Hz), 2.22 (dd, 1H, J = 14.2, 10.7 Hz), 1.41 (ddd, 1H, J = 13.9, 5.4, 2.2 Hz), 1.08 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 214.5, 143.9, 138.0, 135.5, 132.6, 129.4, 129.0, 128.8, 128.6, 127.9, 127.4, 127.2, 127.1, 57.6, 55.9, 52.8, 49.6, 48.6, 34.2, 13.8, 11.8; HRMS for $C_{27}H_{26}OS$ calcd 398.1704, found: m/z 398.1711.



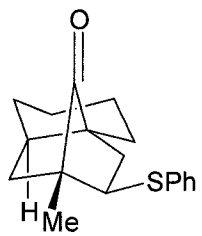
14

1-Phenyl-2,4-dimethylcyclopent-1-en-3-one, 14: The spectral data are consistent with the literature data. [19] ^1H NMR (C_6D_6, 400 MHz) δ 7.20-7.09 (m, 5H), 2.54 (ddq, 1H, J = 17.4, 7.0, 2.0 Hz), 2.23-2.13 (m, 1H), 2.06-1.97 (m, 1H), 1.90 (app. t, 3H, J = 1.5 Hz), 1.10 (d, 3H, J = 5.4 Hz); HRMS for $C_{13}H_{14}O$ calcd 186.1044, found: m/z 186.1044.



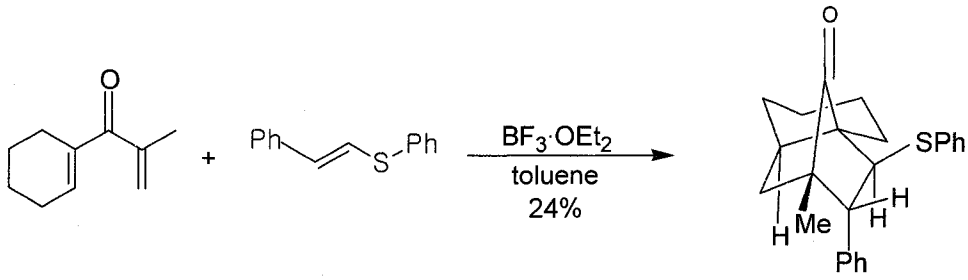
1c 2b 15

Compound, 15: $BF_3{\cdot}OEt_2$ (0.048 mL, 0.38 mmol) was added to a solution of cyclohexen-1-yl propen-2-yl ketone **1c** (0.029 g, 0.19 mmol) and phenyl vinyl sulfide **2b** (0.10 mL, 0.76 mmol) in toluene (22 mL) at –78°C. The reaction was stirred for 15 min. before the temperature was raised to room temperature. After one hour the reaction was quenched by addition of sat. $NaHCO_3$ (15 mL). The organic layer was separated and dried ($MgSO_4$). Solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (packed by 2% triethylamine in hexane) (1:40 ether/hexanes) yielding one isomer **15** (0.019 g, 37%).



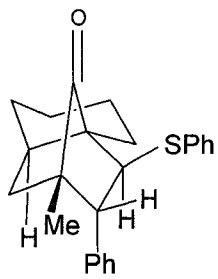
15

Compound, 15: White solid: R_f 0.60 (1:9 EtOAc/hexanes); IR (Cast film) 2929, 2864, 1769, 740 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 7.21-7.18 (m, 2H), 7.03-6.96 (m, 3H), 3.25 (dd, 1H, J = 9.5, 3.9 Hz), 1.85-1.80 (m, 1H), 1.75 (dd, 1H, J = 13.3, 9.5 Hz), 1.67-1.55 (m, 3H), 1.49-1.35 (m, 3H), 1.19-1.15 (m, 1H), 1.14 (s, 3H), 0.94 (dd, 1H, J=12.9, 3.3 Hz), 0.90-0.76 (m, 2H), 0.70-0.63 (m, 1H); ^{13}C NMR (C_6D_6, 125 MHz) δ 212.9, 136.3, 130.5, 129.1, 126.3, 49.7, 46.8, 45.4, 42.5, 40.1, 37.7, 33.7 26.1, 25.2, 23.0, 13.7; HRMS for $C_{18}H_{22}OS$ calcd 286.1391, found: m/z 286.1389.



1c 2c 16

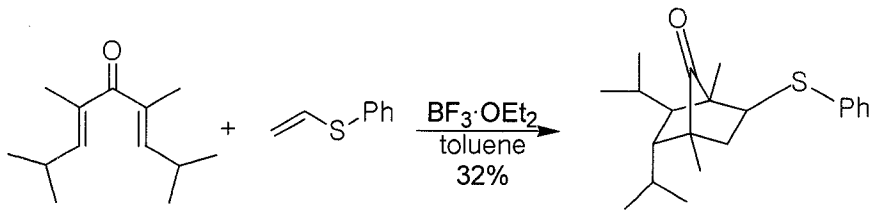
Compound, 16: $BF_3{\cdot}OEt_2$ (0.048 mL, 0.38 mmol) was added to a solution of cyclohexen-1-yl propen-2-yl ketone **1c** (0.029 g, 0.19 mmol) and *β*-(phenylthio)styrene **2c** (0.16 g, 0.76 mmol) in toluene (22 mL) at –78°C. The reaction was allowed to stir for 15 min. before the temperature was raised to room temperature. After two hours the reaction was quenched by addition of sat. $NaHCO_3$ (15 mL). The organic layer was separated and dried ($MgSO_4$). Solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (packed by 2% triethylamine in hexane) (1:40 ether/hexanes) yielding one isomer, **16** (0.016g, 24%).



16

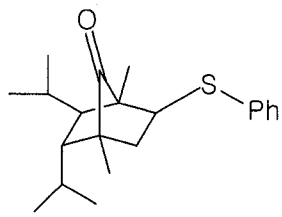
Compound, 16: White solid: R_f 0.59 (1:9 EtOAc/hexanes); IR (Cast film) 2930, 2866, 1760, 742 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.26-7.22 (m, 2H), 7.14-6.80 (m, 8H), 3.66 (d, 1H, J = 7.0 Hz), 2.95 (dd, 1H, J = 7.1, 2.1 Hz), 2.65 (br.d, 1H, J = 13.8 Hz), 1.89 (dd, 1H, J = 13.3, 9.7 Hz), 1.64 (ddd, 1H, J = 13.1, 3.5, 3.5 Hz), 1.58-1.54 (m, 1H), 1.51-1.44

(m, 1H), 1.41-1.34 (m, 2H), 1.24 (dd, 1H, J = 13.6, 4.8 Hz), 0.87 (s, 3H), 0.86-0.80 (m, 1H), 0.70 (m, 1H), 0.48 (ddd, 1H, J = 13.3, 2.3, 2.3 Hz); ^{13}C NMR (C_6D_6, 100 MHz) δ 213.4, 137.8, 135.4, 132.9, 129.4, 128.8, 128.3, 128.2, 127.1, 56.9, 55.8, 51.1, 48.2, 38.6, 34.7, 32.7, 25.1, 24.9, 23.4, 14.0; HRMS for $C_{24}H_{26}OS$ calcd 362.1704, found: m/z 362.1707.



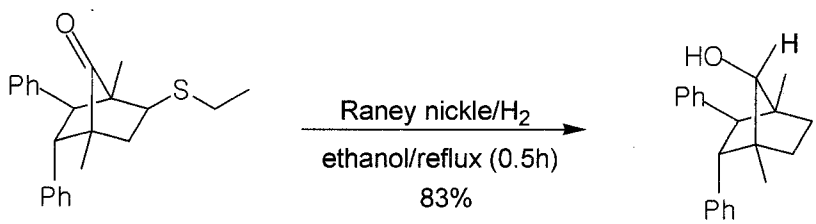
1d 2b 17

5,6-Diisopropyl-1,4-dimethyl-2-phenylthiobicyclo[2.2.1]heptan-7-one, 17: $BF_3{\cdot}OEt_2$ (0.048 mL, 0.39 mmol) was added to a solution of 1,5-diisopropyl-2,4-dimethyl-1,4-pentadien-3-one **1d** (0.037 g, 0.19 mmol) and phenyl vinyl sulfide **2b** (0.10 mL, 0.76 mmol) in toluene (22 mL) at –78°C. The reaction mixture was allowed to stir overnight before being quenched by addition of sat. $NaHCO_3$ (15 mL). The organic layer was separated and dried ($MgSO_4$). Solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (packed by 2% triethylamine in hexane) (1:40 ether/hexanes) yielding one isolated isomer, **17** (0.021, 32%).



17

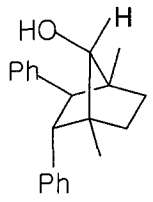
5,6-diisopropyl-1,4-dimethyl-2-phenylthiobicyclo[2.2.1]heptan-7-one, 17: White solid: R_f 0.60 (1:9 EtOAc/hexanes); IR (Cast film) 3057, 2959, 2931, 2873, 1763, 739 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.28-7.24 (m, 2H), 7.03-6.89 (m, 3H), 3.73 (dd, 1H, *J* = 9.3, 2.7 Hz), 1.80 (dd, 1H, *J* = 13.4, 9.3 Hz), 1.63 (dd, 1H, *J* = 13.4, 2.7 Hz), 1.55-1.46 (m, 1H), 1.45-1.40 (m, 1H), 1.35 (s, 3H), 1.07-1.02 (m, 2H), 1.02 (s, 3H), 0.78 (d, 3H, *J* = 7.3 Hz), 0.77 (d, 3H, *J* = 6.6 Hz), 0.74 (d, 3H, *J* = 7.1 Hz), 0.73 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (C_6D_6, 100 MHz) δ 213.8, 136.4, 130.5, 129.0, 126.3, 52.9, 51.0, 50.5, 45.6, 45.2, 42.4, 32.2, 31.6, 22.9, 21.5, 20.6, 18.7, 14.8, 14.5; HRMS for $C_{21}H_{30}OS$ calcd 330.2018, found: m/z 330.2017.



4 **18**

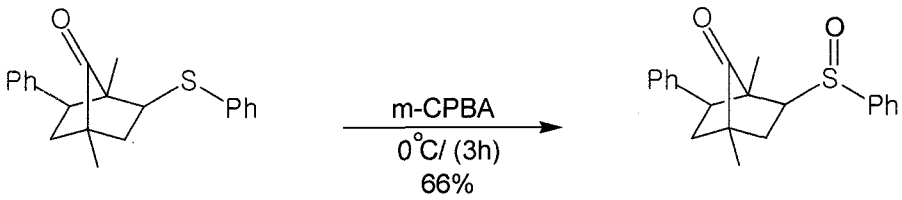
1,4-dimethyl-2,3-diphenyl bicyclo[2.2.1]heptan-7-ol, 18: Compound **4** (0.019 g, 0.054 mmol) was dissolved in 2mL of ethanol and added to a suspension of 0.1 g of Raney nickel in 10 mL of ethanol. The reaction mixture was heated at reflux for 0.5 h, cooled to room temperature, and filtered through a pad of Celite. Solvent was removed under

reduced pressure, and the residue was purified by chromatography on silica gel (1:25 ether/hexanes) yielding compound **18** (0.013 g, 83 %).



18

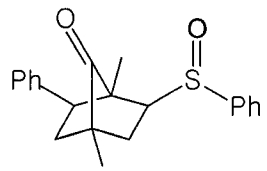
1,4-dimethyl-2,3-diphenyl bicyclo[2.2.1]heptan-7-ol, 18: White solid: m.p. 124-126°C; R_f 0.29 (1:9 EtOAc/hexanes); IR (Cast film) 3583, 3466, 2948, 2923, 2870, 1945, 1812 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.57-7.53 (m, 2H), 7.24-7.16 (m, 3H), 7.14-7.00 (m, 5H), 3.76 (dd, 1H, J = 8.4, 1.9 Hz), 3.13 (d, 1H, J = 8.3 Hz), 3.06 (s, 1H), 1.74 (ddd, 1H, J = 13.1, 10.1, 5.7 Hz), 1.48-1.34 (m, 2H), 1.12 (br. s, 1H), 1.00-0.92 (m, 1H), 0.91 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 144.0, 140.2, 130.7, 129.6, 128.2, 128.2, 126.6, 126.2, 88.5, 59.3, 58.4, 50.4, 48.7, 37.5, 26.5, 17.2, 17.2; HRMS for $C_{21}H_{24}O$ calcd 292.1827, found: m/z 292.1831.



12 **19**

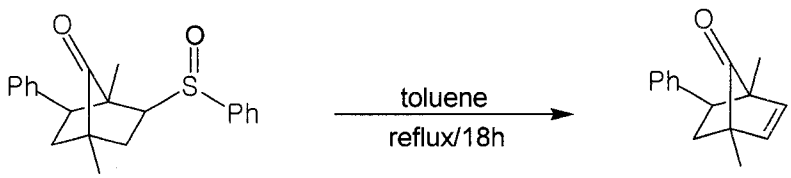
Compound 19: Compound **12** (0.020 g, 0.062 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C in an ice bath. A solution of m-CPBA (77 % pure) (0.015 g, 0.068 mmol) in CH_2Cl_2 (3 mL) was added dropwise over 30 min. After being stirred for 3 h,

the reaction mixture was washed with sat. $NaHSO_3$, sat. Na_2CO_3, and brine, then the organic layer was dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (1:1 ether/hexanes) yielding compound **19** (0.014 g, 66 %).



19

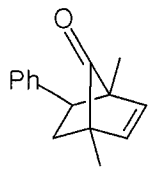
Compound 19: White solid: m.p. 153-155°C; R_f 0.15 (7:2 ether/hexanes); IR (Cast film) 2960, 2928, 2871, 1759, 1047 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 7.51-7.46(m, 2H), 7.08-6.98 (m, 6H), 6.88-6.84 (m, 2H), 2.95 (dd, 1H, J = 10.3, 6.6 Hz), 2.64 (app. t, 1H, J = 7.8 Hz), 1.57-1.53 (m, 2H), 1.36 (s, 3H), 1.03-0.92 (m, 2H), 0.89 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 213.8, 143.5, 142.7, 131.4, 129.1, 128.9, 128.3, 127.3, 126.7, 68.0, 50.1, 49.7, 42.6, 40.1, 33.2, 14.3, 11.5; HRMS (ES+) for $C_{21}H_{22}O_2SNa$ calcd [MNa] 361.1233, found [MNa]: m/z 361.1231.



19 20

Compound 20: Compound **19** (0.014 g, 0.041 mmol) was dissolved in 20 mL of toluene and the reaction was stirred at reflux for 18 h. Then the reaction mixture was cooled to

room temperature, and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (4 mL) and transferred to another flask leaving undissolved black materials behind. The solvent was removed under reduced pressure yielding compound **20** (crude: 0.0076 g, 87%). As mentioned in section 2.2.5, compound 20 decomposes in silica gel chromatography, even after pretreatment with 2 % triethylamine.



20

Compound 20: The sample was contaminated with other products. IR (Cast film) 2960, 2927, 2870, 1954, 1869, 1779 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.42-7.38 (m, 2H), 6.04 (d, 1H, J = 6.8 Hz), 6.01 (d, 1H, J = 6.8 Hz), 2.49 (dd, 1H, J = 10.6, 5.8 Hz), 1.73 (dd, 1H, J = 12.5, 10.7 Hz), 1.64 (dd, 1H, J = 12.6, 5.8 Hz), 1.21 (s, 3H), 0.87 (s, 3H), 3 aryl protons could not be assigned due to overlap with impurity; ^{13}C NMR (C_6D_6, 100 MHz) δ 207.6, 142.4, 139.5, 138.5, 128.9, 128.8, 127.0, 53.8, 49.9, 48.6, 40.2, 12.5, 10.6; HRMS for $C_{15}H_{16}O$ calcd 212.1201, found: m/z 212.1203.

2.7 Bibliography

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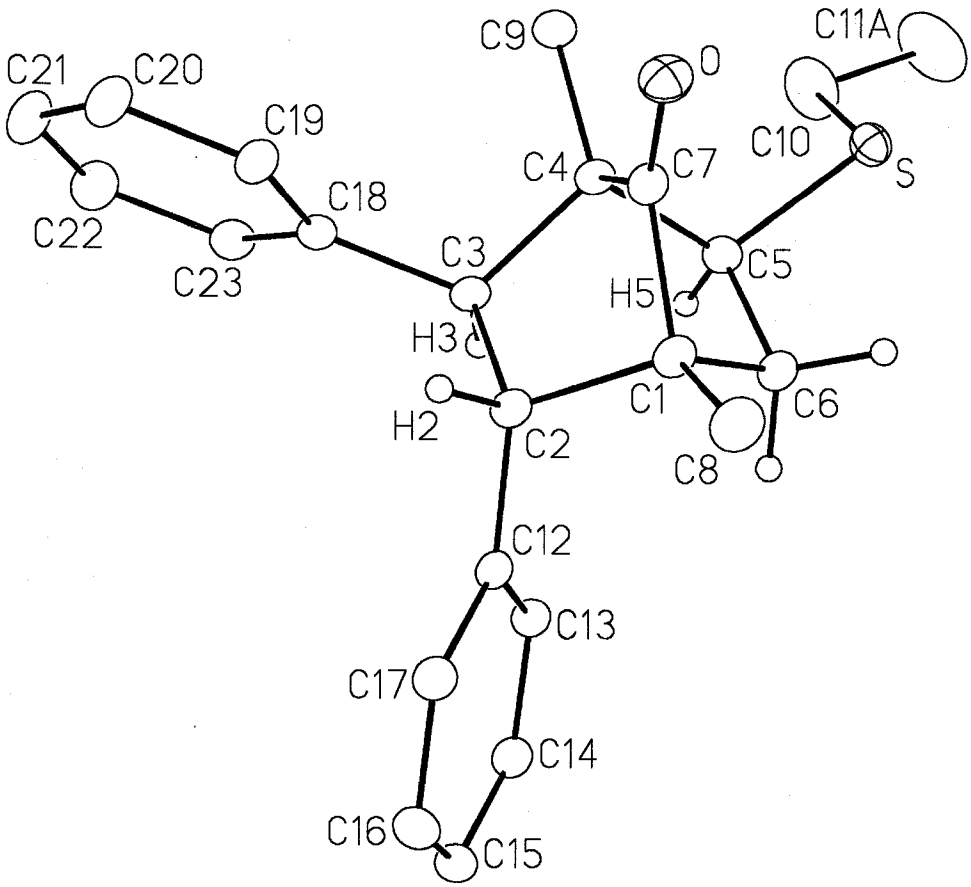
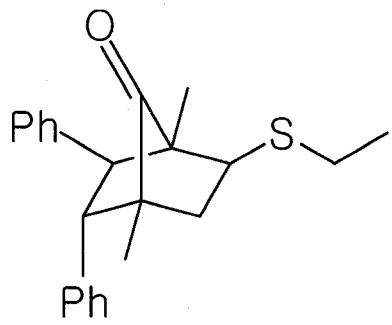
Appendix

A-X-ray diffraction data of compound **4**





compound **4**

Table 1. Crystallographic Experimental Details of compound **4**

A. Crystal Data	
formula	$C_{23}H_{26}OS$
formula weight	350.50
crystal dimensions (mm)	0.57 × 0.37 × 0.31
crystal system	monoclinic
space group	$P2_1/c$ (No. 14)
unit cell parameters[a]	
a (Å)	9.9150 (14)
b (Å)	12.7028 (18)
c (Å)	16.374 (2)
β (deg)	105.3721 (18)
V (Å^3)	1988.6 (5)
Z	4
ρ_{calcd} (g cm^{-3})	1.171
μ (mm^{-1})	0.170
B. Data Collection and Refinement Conditions	
diffractometer	Bruker PLATFORM/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ω scans (0.4°) (10 s exposures)
data collection 2θ limit (deg)	52.78
total data collected	12563 ($-12 \le h \le 12$, $-15 \le k \le 15$, $-20 \le l \le 19$)
independent reflections	4053 (R_{int} = 0.0228)
number of observed reflections (*NO*)	3241 [$F_o^2 \ge 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–86*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–93*[d])
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.9492–0.9093
data/restraints/parameters	4053 [$F_o^2 \ge -3\sigma(F_o^2)$] / 1[e] / 229
goodness-of-fit (*S*)[f]	1.032 [$F_o^2 \ge -3\sigma(F_o^2)$]
final R indices[g]	
R_1 [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0376
wR_2 [$F_o^2 \ge -3\sigma(F_o^2)$]	0.1009
largest difference peak and hole	0.258 and –0.162 e Å^{-3}

[a]Obtained from least-squares refinement of 4818 reflections with $5.16° < 2\theta < 52.38°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.

[d]Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993.

[e]The C10–C11A and C10–C11B distances were constrained to be equal (within 0.001 Å) during refinement.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0458P)^2 + 0.6447P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters of compound **4**

Atom	*x*	*y*	*z*	U_{eq}, Å^2
S	-0.20088(4)	0.43874(3)	0.14081(3)	0.03893(13)*
O	-0.04987(12)	0.19180(9)	0.28501(7)	0.0431(3)*
C1	0.02244(16)	0.36021(12)	0.35945(9)	0.0319(3)*
C2	0.18363(15)	0.37419(11)	0.37443(9)	0.0301(3)*
C3	0.20503(14)	0.37101(11)	0.28285(8)	0.0286(3)*
C4	0.05745(15)	0.33870(11)	0.22491(9)	0.0293(3)*
C5	-0.03157(15)	0.44090(11)	0.21811(9)	0.0312(3)*
C6	-0.05553(16)	0.45305(12)	0.30805(10)	0.0346(3)*
C7	-0.00060(15)	0.27896(12)	0.28891(9)	0.0318(3)*
C8	-0.02395(19)	0.32954(15)	0.43717(11)	0.0473(4)*
C9	0.05695(17)	0.28190(13)	0.14377(9)	0.0375(4)*
C10	-0.1585(2)	0.4808(2)	0.04515(12)	0.0689(6)*
C11A[a,b]	-0.2917(12)	0.5210(12)	-0.0147(7)	0.100(4)*
C11B[a,c]	-0.2830(15)	0.4787(15)	-0.0315(9)	0.100(4)*
C12	0.24912(15)	0.46528(12)	0.42990(9)	0.0304(3)*
C13	0.25029(15)	0.56763(12)	0.39979(9)	0.0333(3)*
C14	0.31386(16)	0.64862(13)	0.45320(10)	0.0384(4)*
C15	0.37706(16)	0.62876(14)	0.53770(11)	0.0429(4)*
C16	0.37527(17)	0.52799(15)	0.56871(10)	0.0454(4)*
C17	0.31256(16)	0.44710(13)	0.51552(10)	0.0381(4)*
C18	0.32387(15)	0.30046(12)	0.27514(9)	0.0302(3)*
C19	0.33367(16)	0.19617(12)	0.30179(10)	0.0375(4)*
C20	0.44291(18)	0.13270(14)	0.29385(12)	0.0471(4)*
C21	0.54509(19)	0.17252(16)	0.25952(13)	0.0538(5)*
C22	0.53652(18)	0.27490(16)	0.23195(12)	0.0515(5)*
C23	0.42643(17)	0.33859(13)	0.23936(10)	0.0386(4)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$. [a]Refined with common anisotropic displacement parameters. [b]Refined with an occupancy factor of 0.55. [c]Refined with an occupancy factor of 0.45.

Table 3. Selected Interatomic Distances (Å) of compound **4**

Atom1	Atom2	Distance
S	C5	1.8151(15)
S	C10	1.807(2)
O	C7	1.2051(18)
C1	C2	1.561(2)
C1	C6	1.534(2)
C1	C7	1.520(2)
C1	C8	1.514(2)
C2	C3	1.5698(19)
C2	C12	1.508(2)
C3	C4	1.5728(19)
C3	C18	1.512(2)
C4	C5	1.557(2)
C4	C7	1.525(2)
C4	C9	1.5107(19)
C5	C6	1.560(2)
C10	C11A	1.510(4)[a]
C10	C11B	1.510(4)[a]
C12	C13	1.392(2)
C12	C17	1.395(2)
C13	C14	1.389(2)
C14	C15	1.382(2)
C15	C16	1.379(3)
C16	C17	1.383(2)
C18	C19	1.390(2)
C18	C23	1.388(2)
C19	C20	1.384(2)
C20	C21	1.379(3)
C21	C22	1.372(3)
C22	C23	1.390(2)

[a]Distances constrained to be equal during refinement.

Table 4. Selected Interatomic Angles (deg) of compound **4**

Atom 1	Atom 2	Atom 3	Angle
C5	S	C10	102.44(9)
C2	C1	C6	110.18(12)
C2	C1	C7	97.93(11)
C2	C1	C8	115.05(13)
C6	C1	C7	98.78(11)
C6	C1	C8	115.97(13)
C7	C1	C8	116.48(13)
C1	C2	C3	103.82(11)
C1	C2	C12	116.19(12)
C3	C2	C12	116.71(12)
C2	C3	C4	104.07(11)
C2	C3	C18	113.62(11)
C4	C3	C18	114.58(11)
C3	C4	C5	104.16(11)
C3	C4	C7	100.12(11)
C3	C4	C9	116.15(12)
C5	C4	C7	98.85(11)
C5	C4	C9	117.75(12)
C7	C4	C9	116.93(13)
S	C5	C4	116.05(10)
S	C5	C6	108.40(10)
C4	C5	C6	103.90(11)
C1	C6	C5	105.14(11)
O	C7	C1	129.88(14)
O	C7	C4	129.97(14)
C1	C7	C4	100.15(11)
S	C10	C11A	107.4(8)
S	C10	C11B	112.9(10)
C2	C12	C13	123.12(13)
C2	C12	C17	119.07(14)
C13	C12	C17	117.81(14)
C12	C13	C14	120.94(14)
C13	C14	C15	120.31(15)
C14	C15	C16	119.43(15)
C15	C16	C17	120.34(15)
C12	C17	C16	121.16(16)

C3	C18	C19	122.00(13)
C3	C18	C23	120.16(14)
C19	C18	C23	117.83(14)
C18	C19	C20	121.14(15)
C19	C20	C21	120.18(17)
C20	C21	C22	119.60(16)
C21	C22	C23	120.32(16)
C18	C23	C22	120.92(16)

Table 5. Torsional Angles (deg) of compound **4**

Atom 1	Atom 2	Atom 3	Atom 4	Angle
C10	S	C5	C4	-87.15(14)
C10	S	C5	C6	156.46(13)
C5	S	C10	C11A	-159.3(5)
C5	S	C10	C11B	176.1(7)
C6	C1	C2	C3	-63.21(14)
C6	C1	C2	C12	66.35(16)
C7	C1	C2	C3	39.23(13)
C7	C1	C2	C12	168.80(12)
C8	C1	C2	C3	163.43(13)
C8	C1	C2	C12	-67.01(17)
C2	C1	C6	C5	68.22(14)
C7	C1	C6	C5	-33.64(14)
C8	C1	C6	C5	-158.88(14)
C2	C1	C7	O	122.47(17)
C2	C1	C7	C4	-57.07(12)
C6	C1	C7	O	-125.57(17)
C6	C1	C7	C4	54.89(13)
C8	C1	C7	O	-0.7(2)
C8	C1	C7	C4	179.77(13)
C1	C2	C3	C4	-8.14(14)
C1	C2	C3	C18	-133.42(12)
C12	C2	C3	C4	-137.39(12)
C12	C2	C3	C18	97.33(15)
C1	C2	C12	C13	-83.41(17)
C1	C2	C12	C17	96.93(16)
C3	C2	C12	C13	39.66(19)
C3	C2	C12	C17	-140.00(14)
C2	C3	C4	C5	75.83(13)
C2	C3	C4	C7	-26.07(13)
C2	C3	C4	C9	-152.96(13)
C18	C3	C4	C5	-159.50(12)
C18	C3	C4	C7	98.59(13)
C18	C3	C4	C9	-28.29(18)
C2	C3	C18	C19	52.62(18)
C2	C3	C18	C23	-128.44(14)
C4	C3	C18	C19	-66.84(18)

C4	C3	C18	C23	112.11(15)
C3	C4	C5	S	169.95(9)
C3	C4	C5	C6	-71.17(13)
C7	C4	C5	S	-87.18(12)
C7	C4	C5	C6	31.69(13)
C9	C4	C5	S	39.68(17)
C9	C4	C5	C6	158.56(13)
C3	C4	C7	O	-127.40(16)
C3	C4	C7	C1	52.14(13)
C5	C4	C7	O	126.38(16)
C5	C4	C7	C1	-54.08(13)
C9	C4	C7	O	-1.0(2)
C9	C4	C7	C1	178.50(12)
S	C5	C6	C1	125.14(11)
C4	C5	C6	C1	1.14(14)
C2	C12	C13	C14	-179.02(13)
C17	C12	C13	C14	0.6(2)
C2	C12	C17	C16	179.33(14)
C13	C12	C17	C16	-0.3(2)
C12	C13	C14	C15	-0.2(2)
C13	C14	C15	C16	-0.6(2)
C14	C15	C16	C17	0.9(3)
C15	C16	C17	C12	-0.4(2)
C3	C18	C19	C20	179.70(14)
C23	C18	C19	C20	0.7(2)
C3	C18	C23	C22	179.86(14)
C19	C18	C23	C22	-1.2(2)
C18	C19	C20	C21	0.4(3)
C19	C20	C21	C22	-1.1(3)
C20	C21	C22	C23	0.7(3)
C21	C22	C23	C18	0.5(3

Table 6. Anisotropic Displacement Parameters (U_{ij}, Å^2) of compound **4**

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S	0.0371(2)	0.0392(2)	0.0383(2)	0.00353(17)	0.00620(16)	0.00090(16)
O	0.0519(7)	0.0288(6)	0.0513(7)	0.0005(5)	0.0185(5)	-0.0063(5)
C1	0.0379(8)	0.0304(8)	0.0308(8)	0.0007(6)	0.0150(6)	0.0002(6)
C2	0.0366(8)	0.0266(7)	0.0279(7)	0.0014(6)	0.0100(6)	0.0031(6)
C3	0.0343(7)	0.0255(7)	0.0276(7)	-0.0018(6)	0.0110(6)	-0.0030(6)
C4	0.0346(7)	0.0262(7)	0.0287(7)	-0.0026(6)	0.0111(6)	-0.0024(6)
C5	0.0342(7)	0.0262(7)	0.0326(8)	0.0007(6)	0.0080(6)	-0.0007(6)
C6	0.0353(8)	0.0342(8)	0.0354(8)	-0.0043(6)	0.0113(6)	0.0027(6)
C7	0.0328(7)	0.0274(8)	0.0362(8)	0.0011(6)	0.0106(6)	0.0017(6)
C8	0.0533(10)	0.0543(11)	0.0410(9)	0.0022(8)	0.0246(8)	-0.0017(8)
C9	0.0407(8)	0.0390(9)	0.0336(8)	-0.0076(7)	0.0112(6)	-0.0035(7)
C10	0.0644(13)	0.0974(17)	0.0417(11)	0.0244(11)	0.0084(9)	-0.0016(12)
C11A[a]	0.095(2)	0.144(11)	0.045(4)	0.029(5)	-0.010(3)	-0.019(4)
C11B[a]	0.095(2)	0.144(11)	0.045(4)	0.029(5)	-0.010(3)	-0.019(4)
C12	0.0306(7)	0.0330(8)	0.0286(7)	-0.0020(6)	0.0097(6)	0.0049(6)
C13	0.0353(8)	0.0333(8)	0.0308(7)	-0.0017(6)	0.0077(6)	0.0031(6)
C14	0.0378(8)	0.0334(9)	0.0443(9)	-0.0050(7)	0.0115(7)	0.0008(6)
C15	0.0357(8)	0.0476(10)	0.0426(9)	-0.0155(8)	0.0058(7)	-0.0017(7)
C16	0.0435(9)	0.0580(11)	0.0301(8)	-0.0043(8)	0.0018(7)	0.0059(8)
C17	0.0414(8)	0.0412(9)	0.0309(8)	0.0013(7)	0.0082(6)	0.0072(7)
C18	0.0312(7)	0.0318(8)	0.0283(7)	-0.0053(6)	0.0093(6)	-0.0033(6)
C19	0.0373(8)	0.0327(9)	0.0477(9)	-0.0031(7)	0.0203(7)	-0.0009(6)
C20	0.0467(9)	0.0352(9)	0.0645(12)	-0.0039(8)	0.0238(9)	0.0047(7)
C21	0.0445(10)	0.0539(12)	0.0717(13)	-0.0104(10)	0.0304(9)	0.0069(8)
C22	0.0436(9)	0.0603(12)	0.0604(11)	-0.0076(9)	0.0308(9)	-0.0067(9)

C23 0.0412(8) 0.0408(9) 0.0368(8) -0.0032(7) 0.0158(7) -0.0068(7)

The form of the anisotropic displacement parameter is:
$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

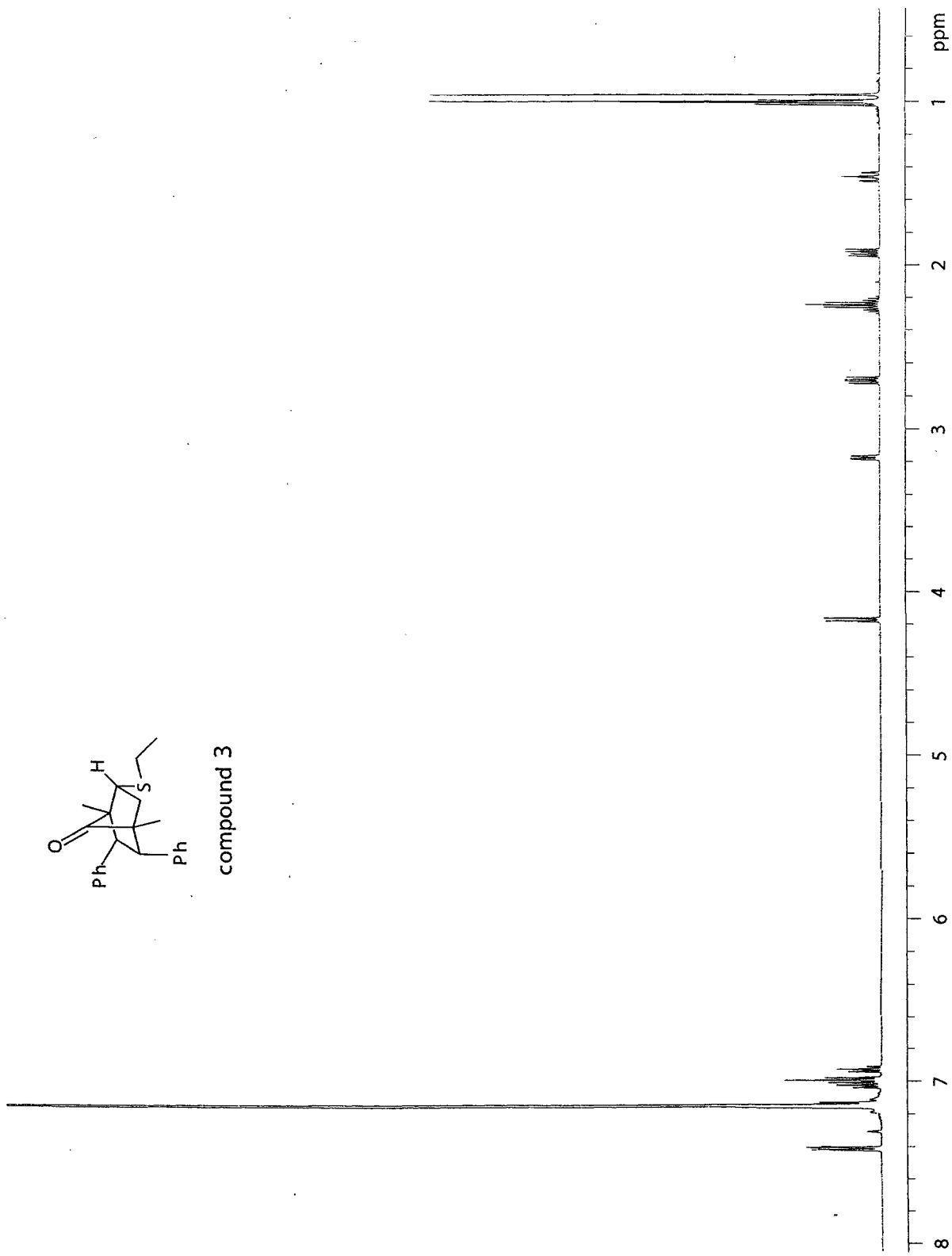
[a]Refined with common anisotropic displacement parameters.

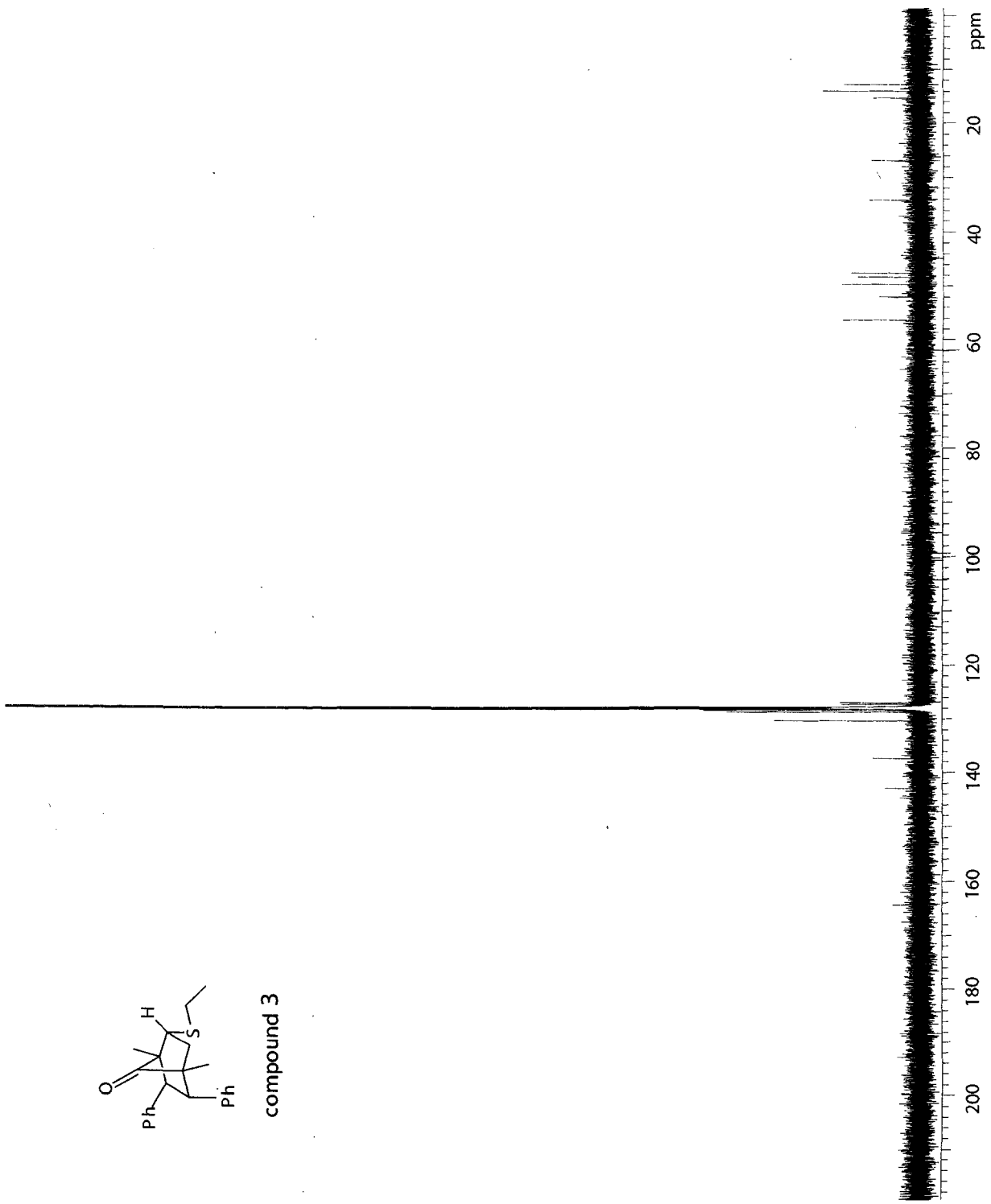
Table 7. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms of compound **4**

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H2	0.2280	0.3089	0.4037	0.036
H3	0.2259	0.4442	0.2672	0.034
H5	0.0239	0.5021	0.2064	0.037
H6A	-0.0173	0.5208	0.3340	0.042
H6B	-0.1565	0.4500	0.3050	0.042
H8A	-0.0075	0.3884	0.4773	0.057
H8B	0.0295	0.2680	0.4640	0.057
H8C	-0.1239	0.3123	0.4205	0.057
H9A	0.1134	0.2177	0.1571	0.045
H9B	0.0964	0.3279	0.1079	0.045
H9C	-0.0393	0.2633	0.1137	0.045
H10A[a]	-0.0872	0.5373	0.0581	0.083
H10B[a]	-0.1207	0.4211	0.0192	0.083
H10C[b]	-0.1207	0.5533	0.0533	0.083
H10D[b]	-0.0846	0.4344	0.0348	0.083
H11A[a]	-0.2724	0.5443	-0.0676	0.120
H11B[a]	-0.3277	0.5803	0.0115	0.120
H11C[a]	-0.3615	0.4645	-0.0269	0.120
H11D[b]	-0.2541	0.5016	-0.0815	0.120
H11E[b]	-0.3556	0.5261	-0.0224	0.120
H11F[b]	-0.3201	0.4069	-0.0405	0.120
H13	0.2070	0.5823	0.3419	0.040
H14	0.3139	0.7180	0.4316	0.046
H15	0.4213	0.6841	0.5741	0.051
H16	0.4173	0.5140	0.6269	0.054
H17	0.3127	0.3780	0.5377	0.046
H19	0.2642	0.1680	0.3259	0.045
H20	0.4475	0.0615	0.3121	0.056
H21	0.6210	0.1293	0.2550	0.065
H22	0.6062	0.3024	0.2077	0.062
H23	0.4213	0.4092	0.2197	0.046

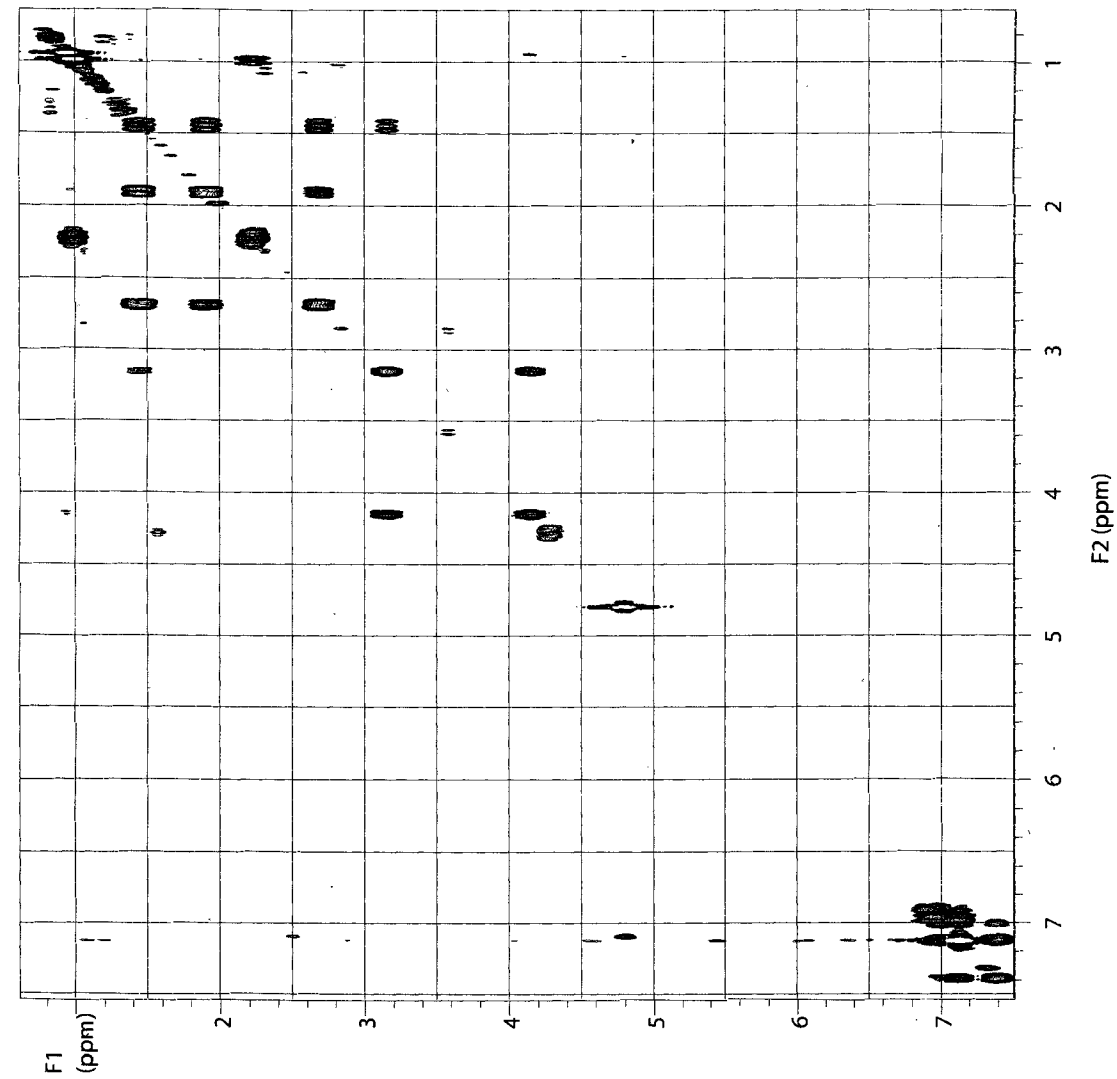
[a]Included with an occupancy factor of 0.55. [b]Included with an occupancy factor of 0.45.

B-Selected NMR spectra





compound 3



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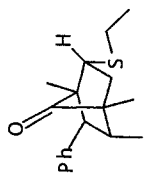

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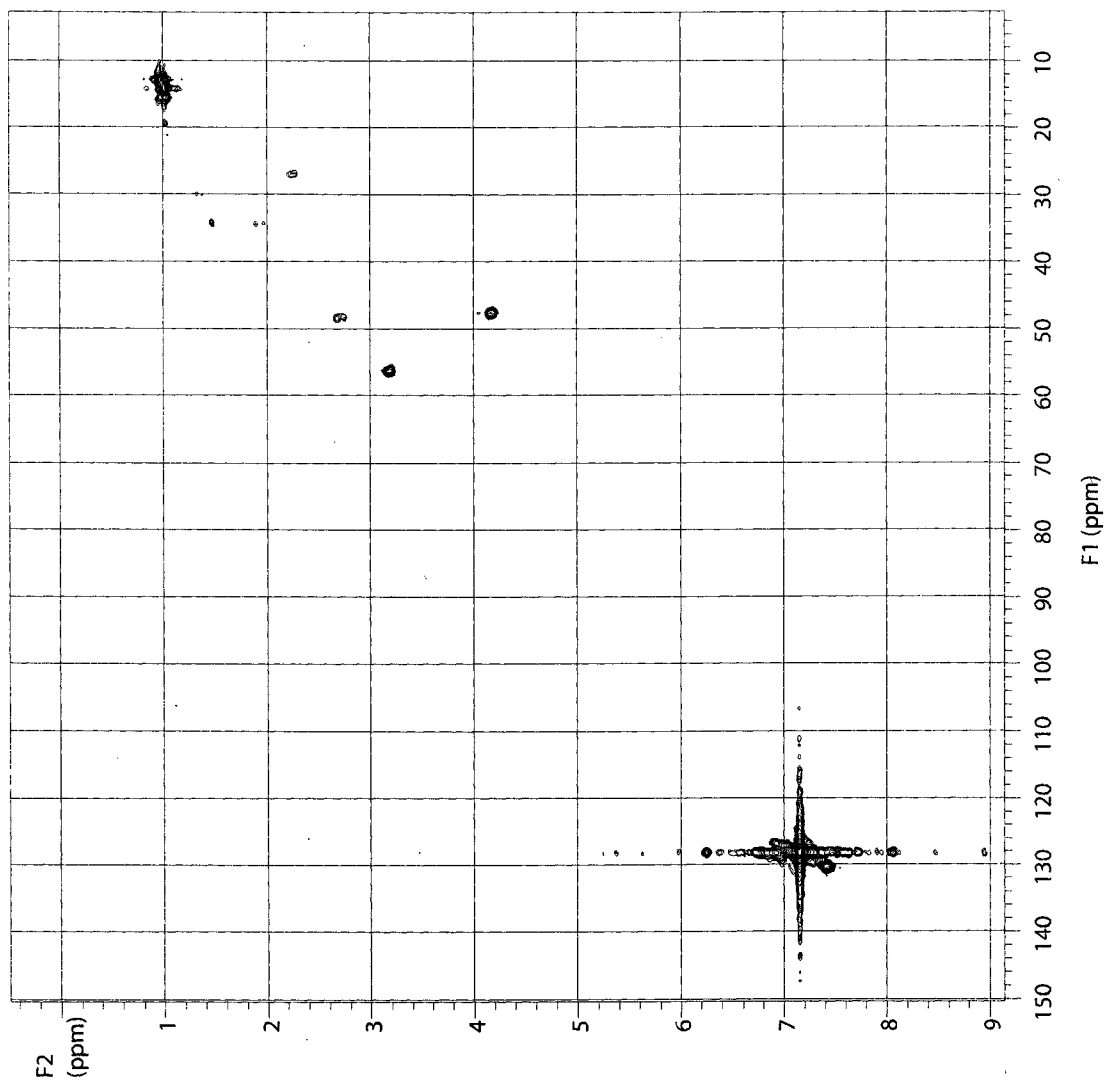

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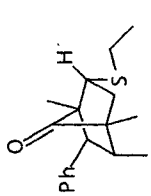

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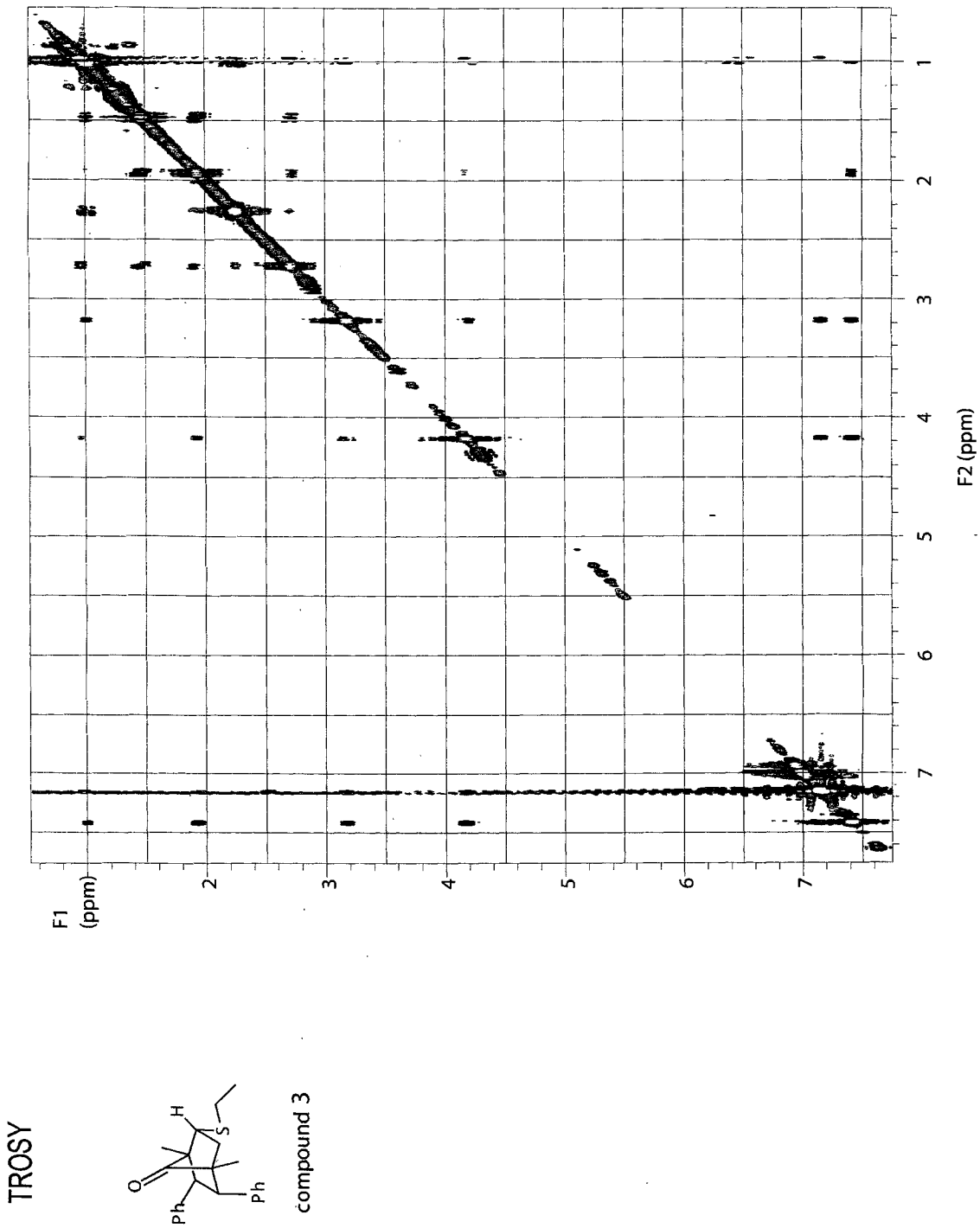
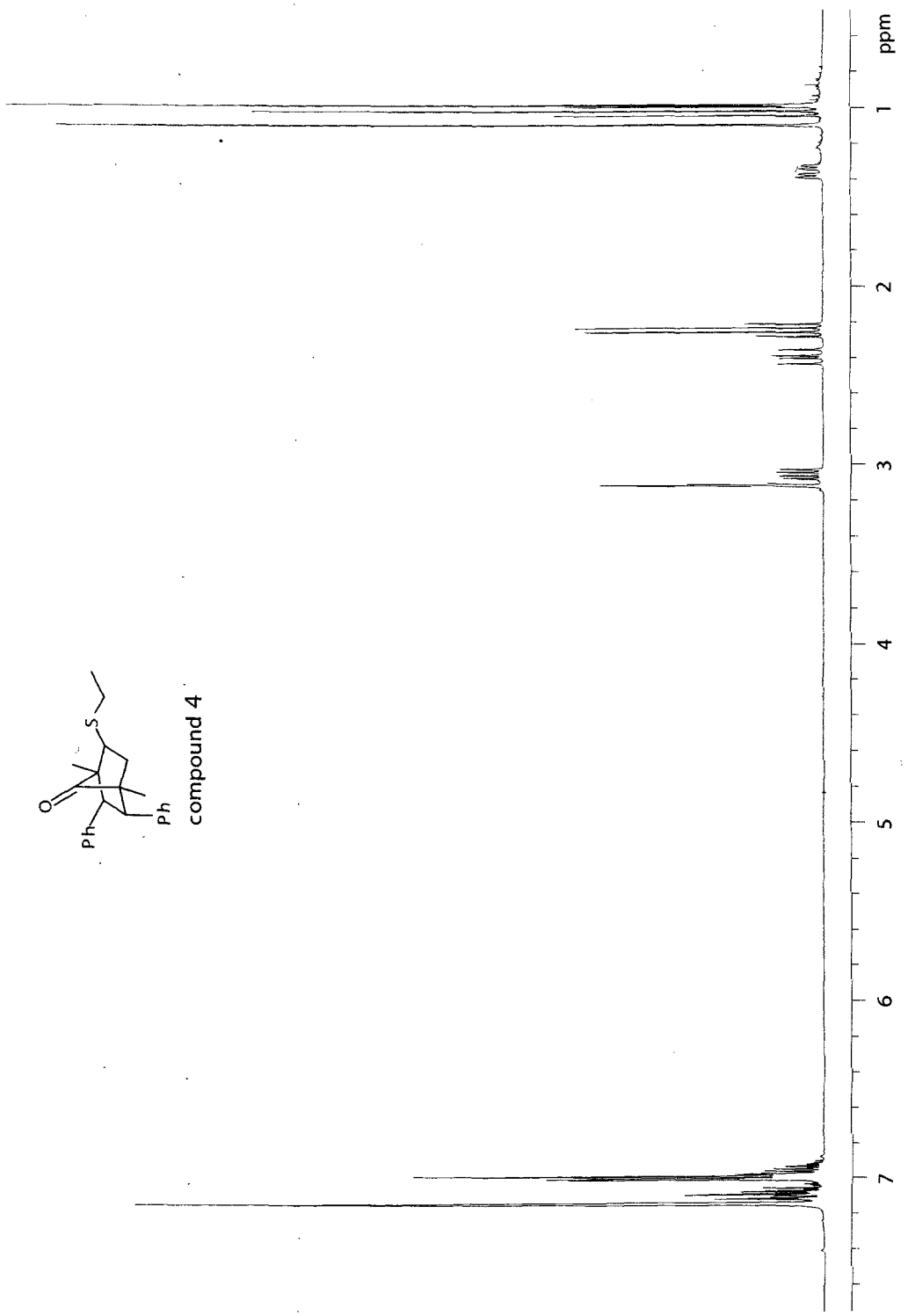
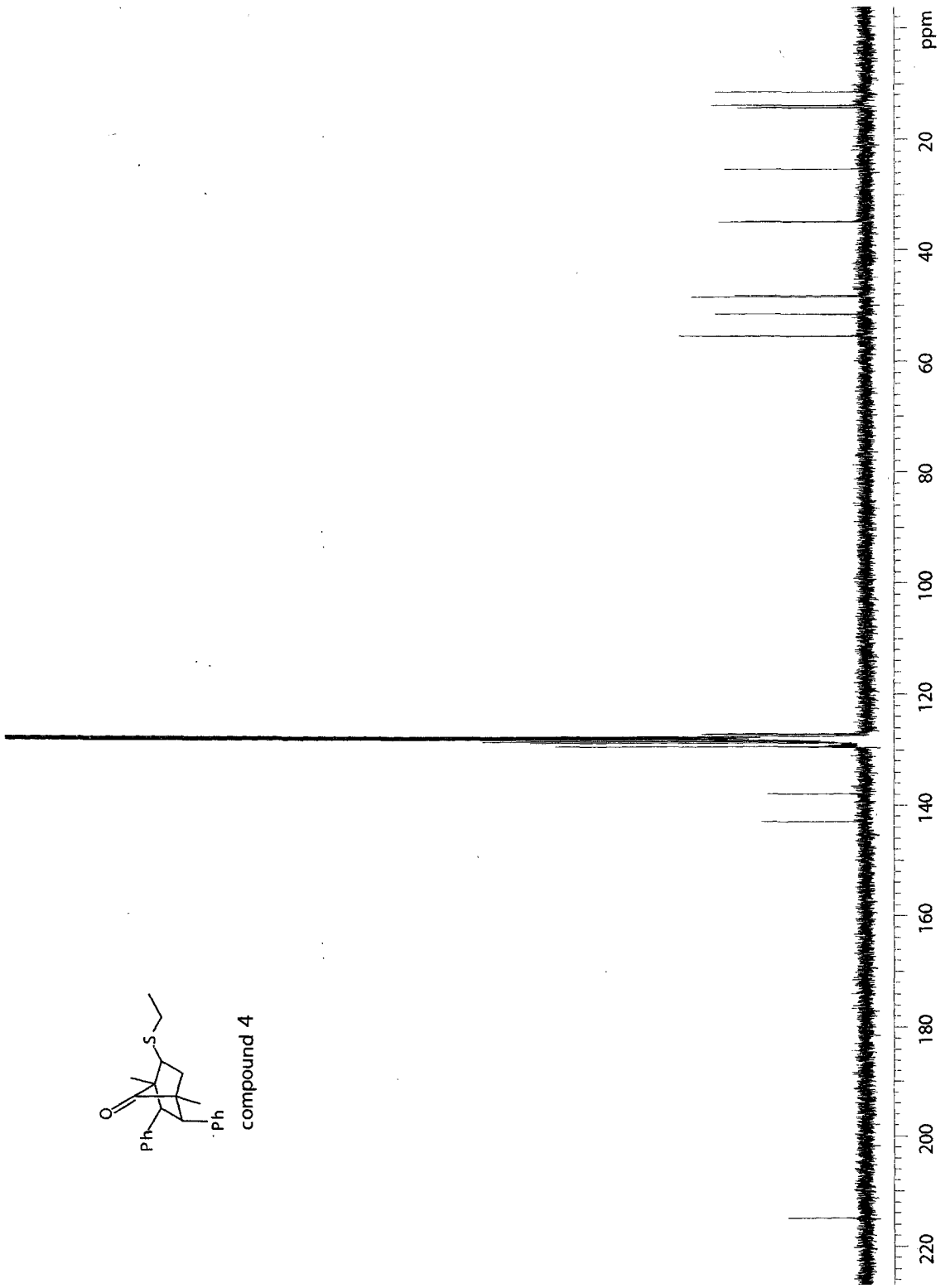
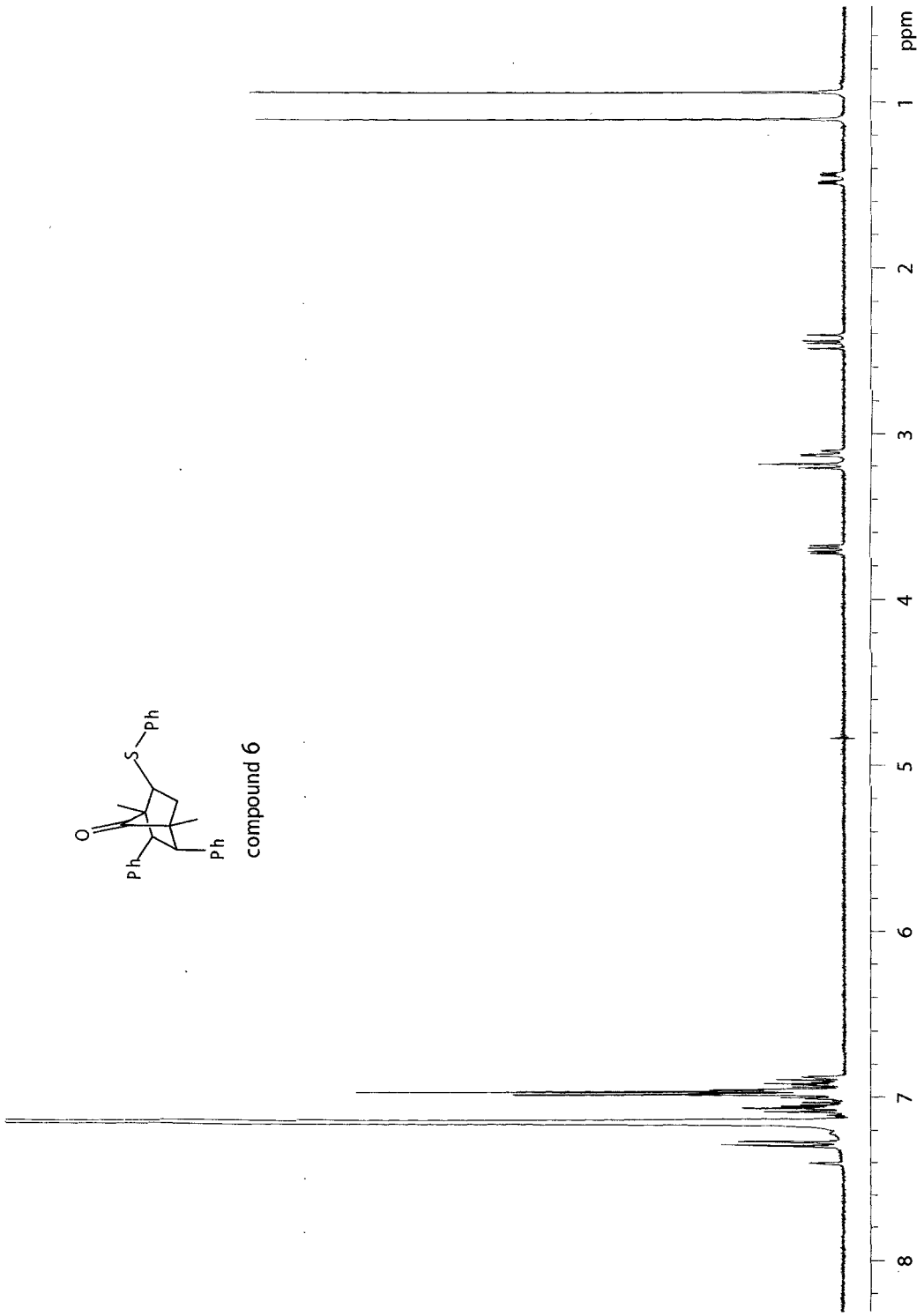
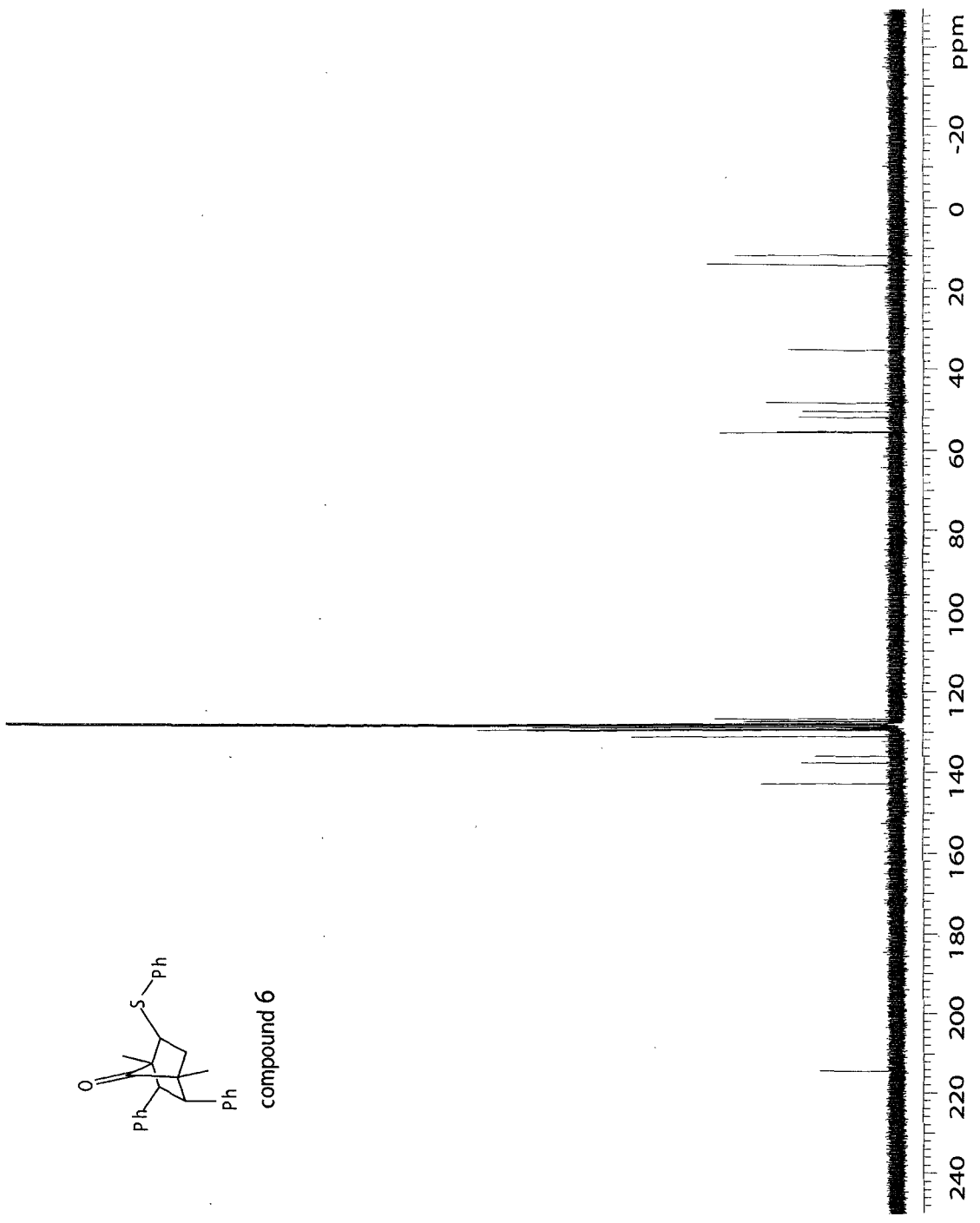


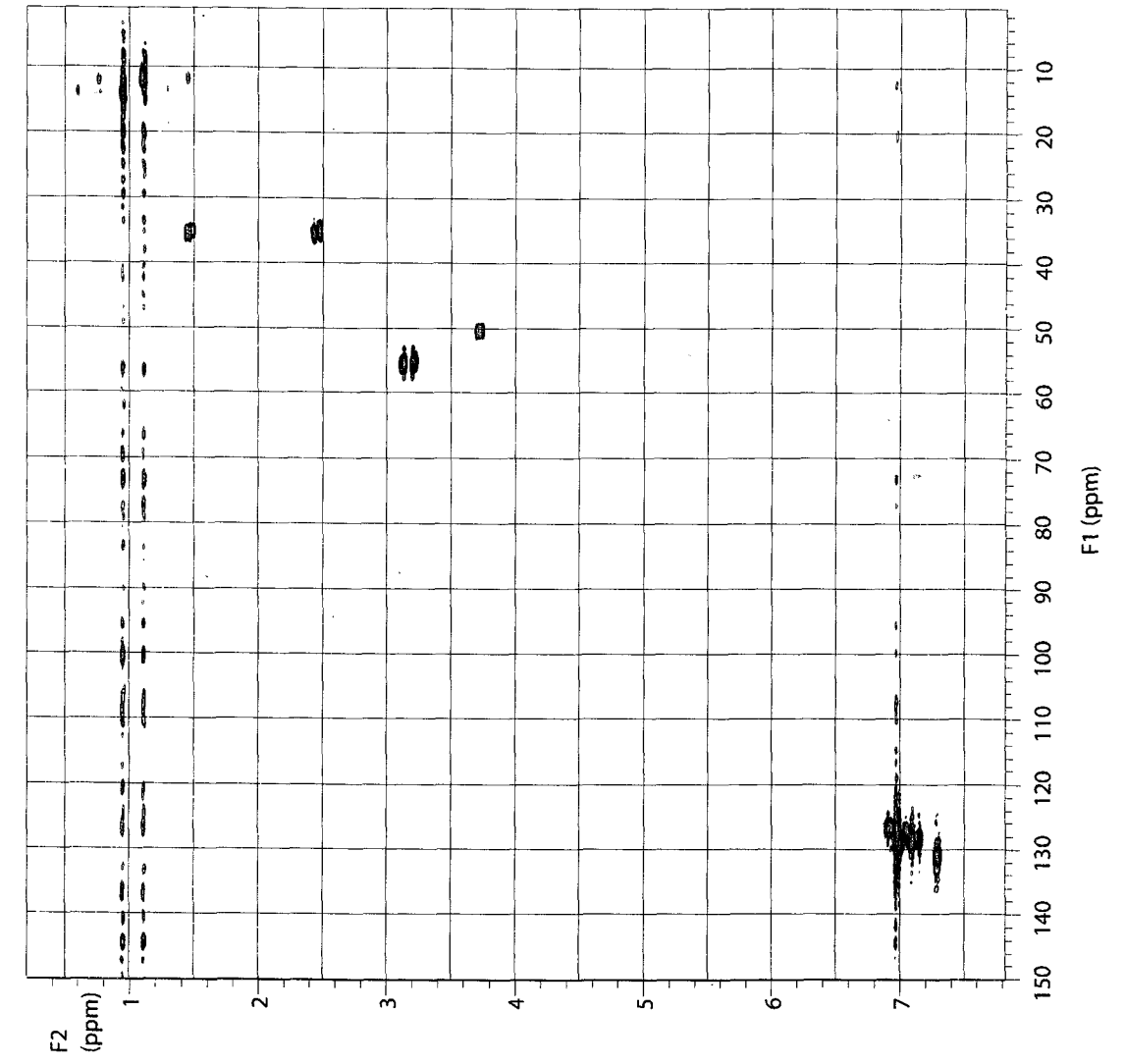




compound 4







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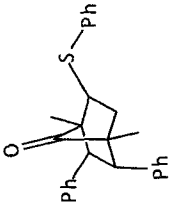
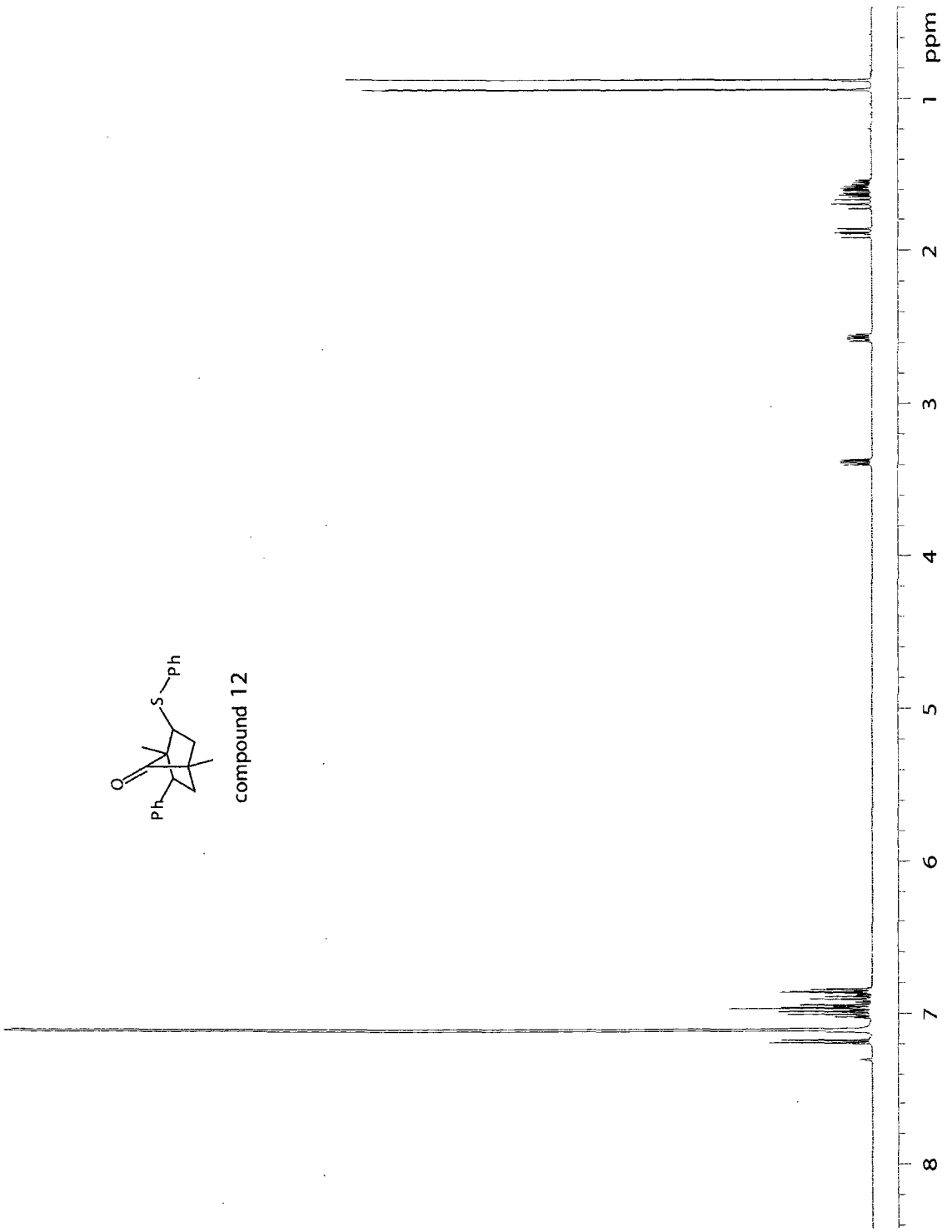
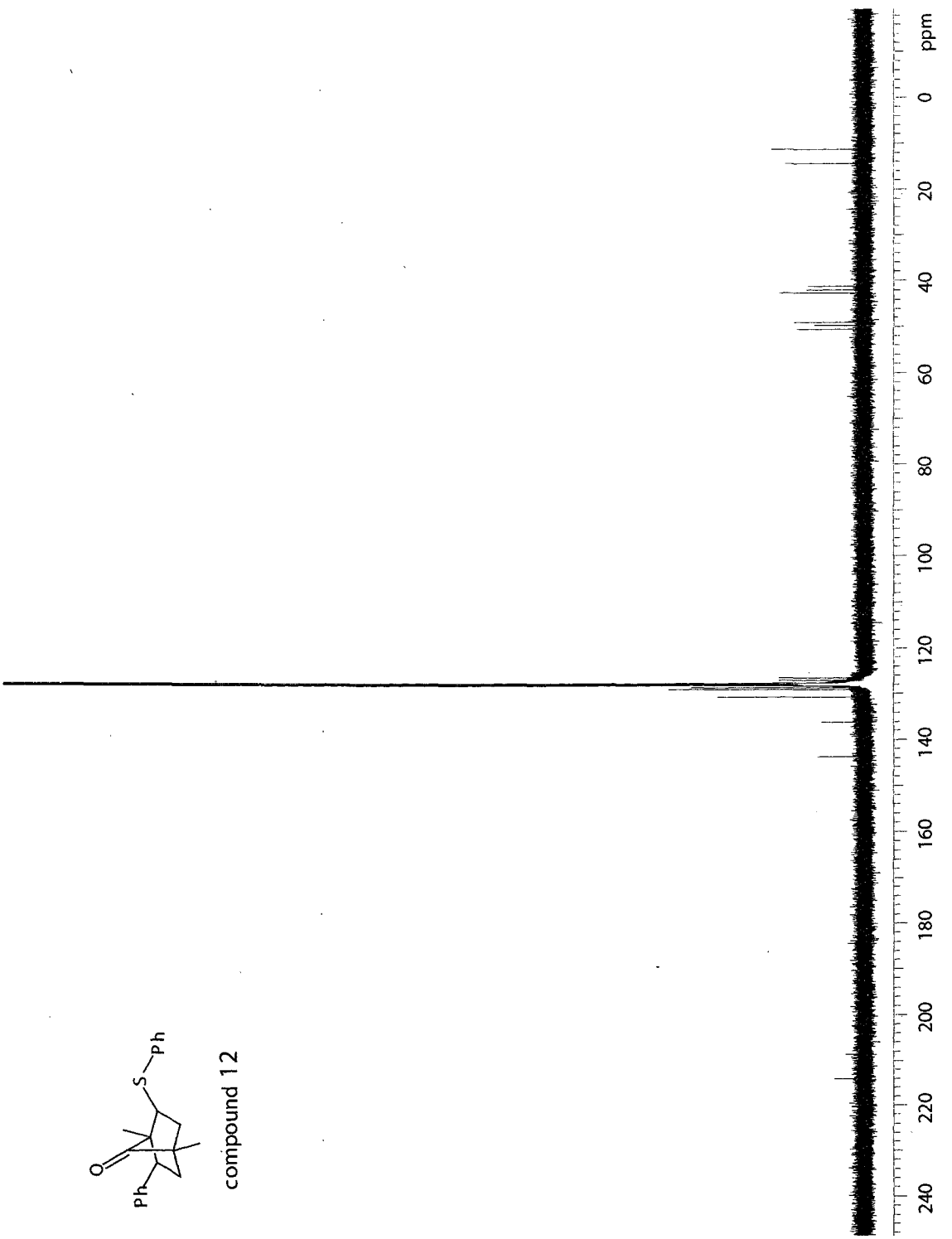


compound 6





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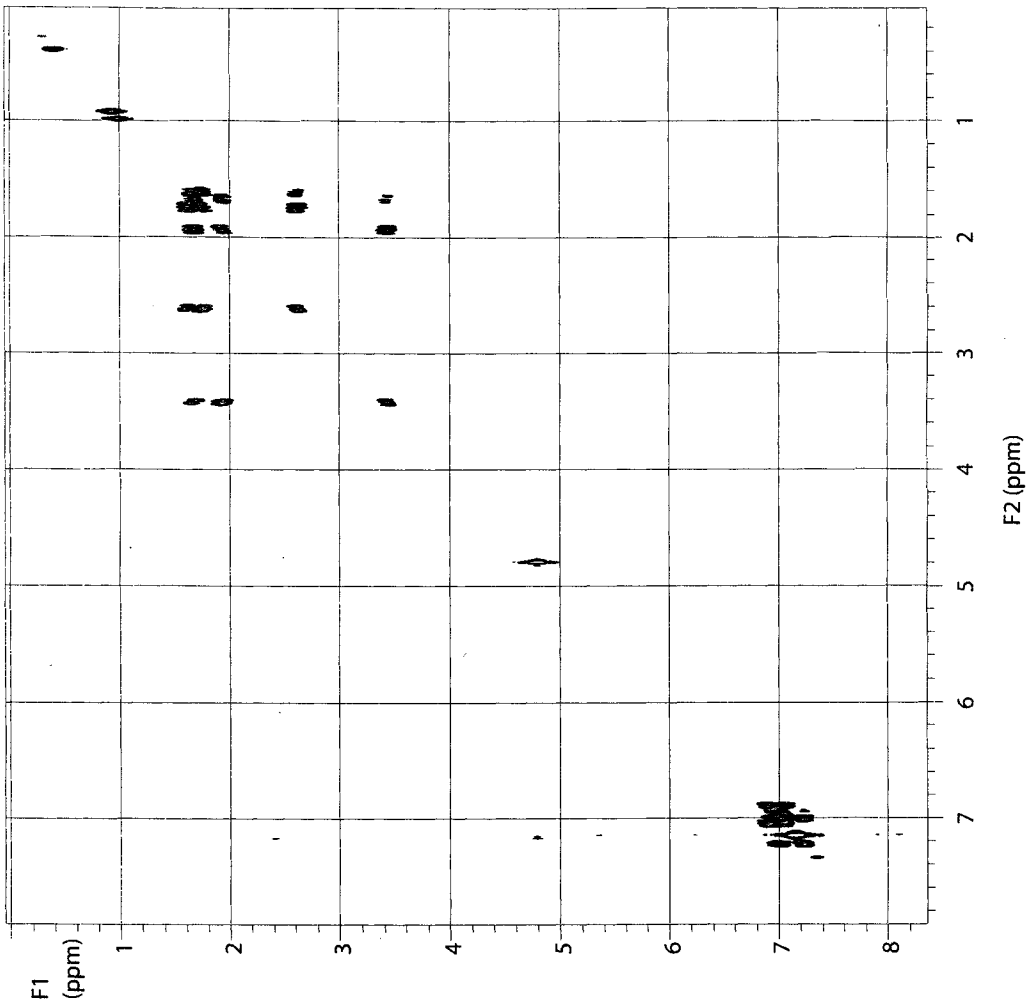
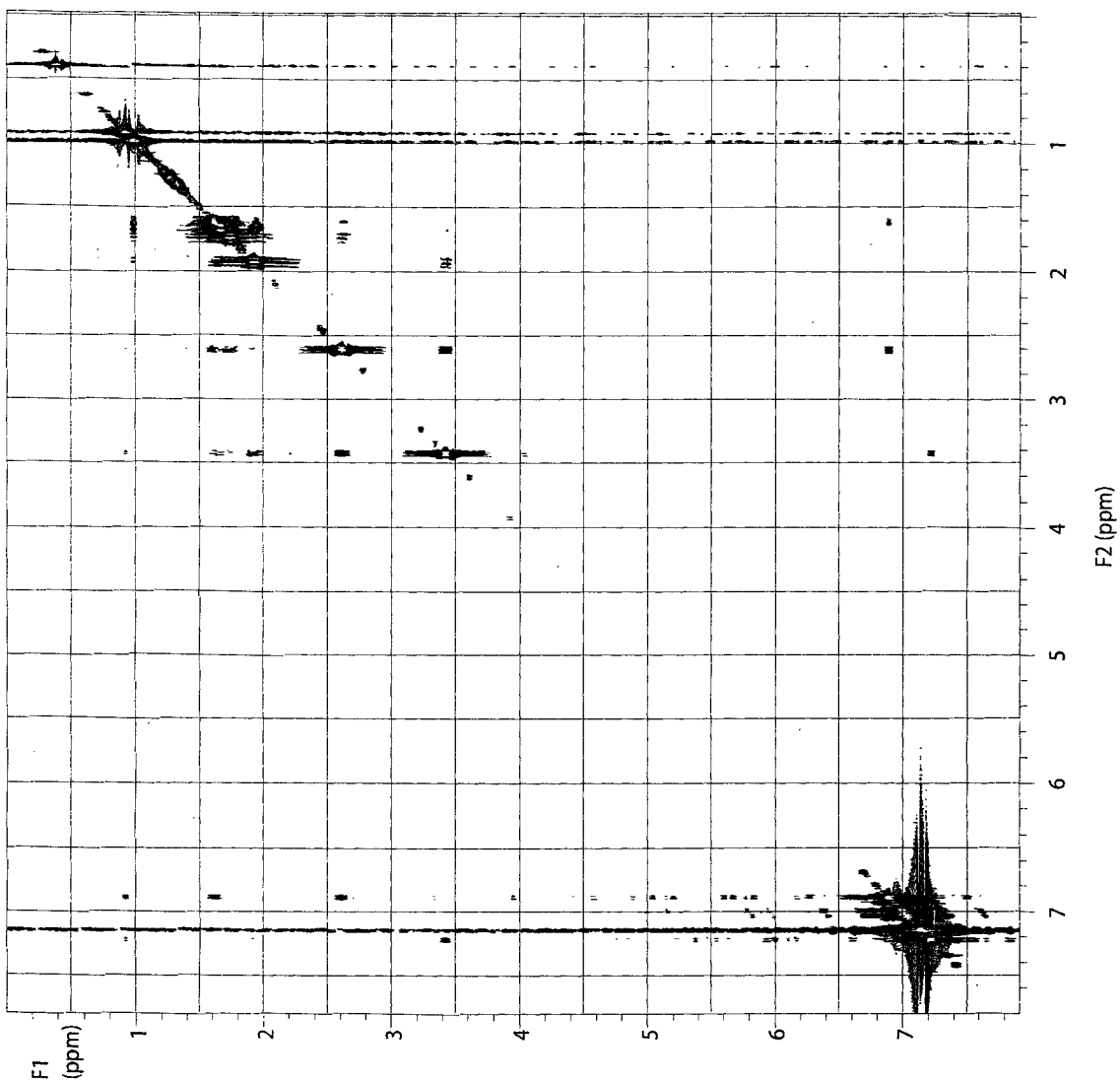


COSY

compound 12



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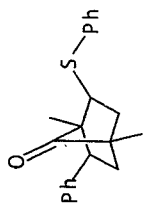

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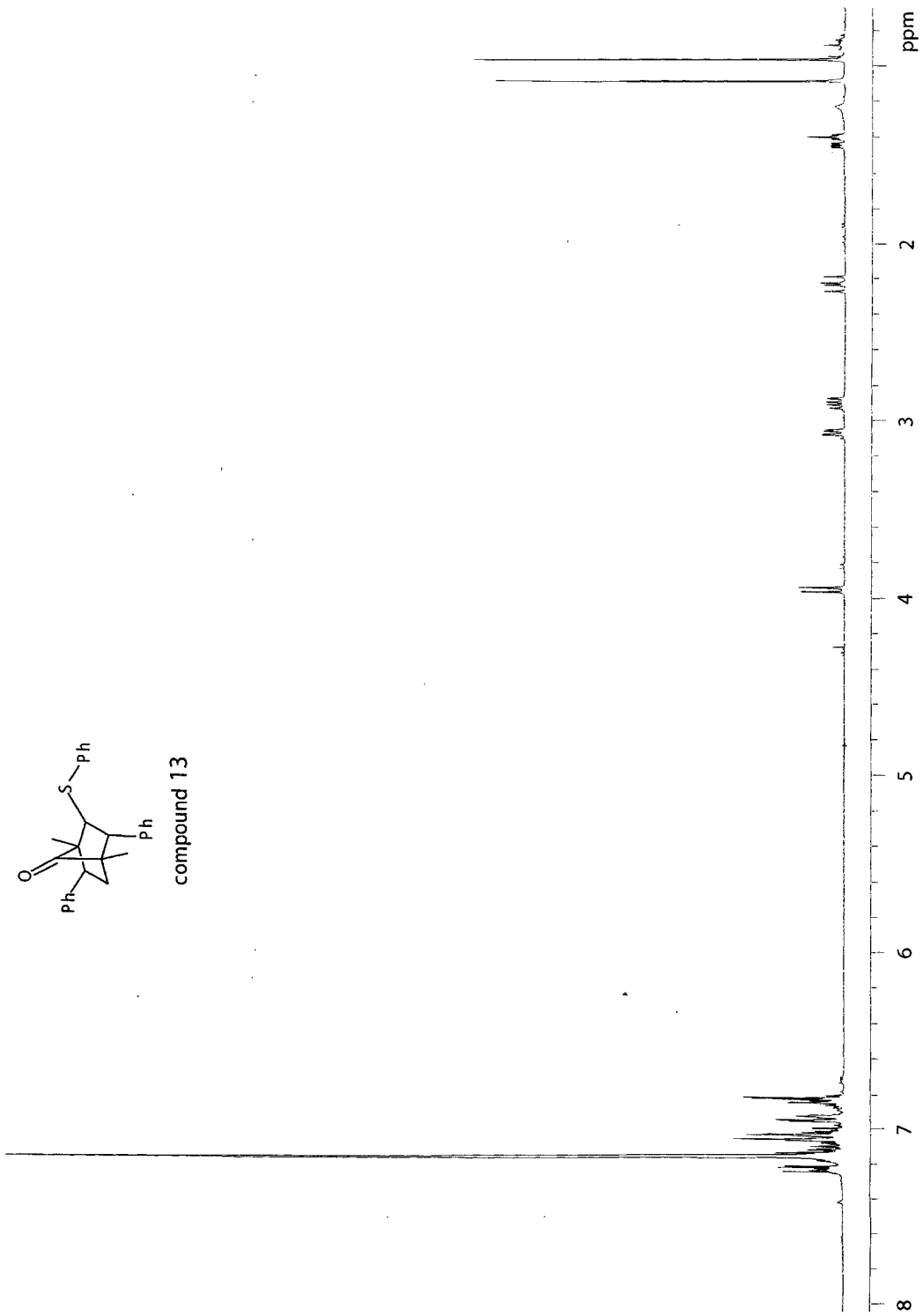

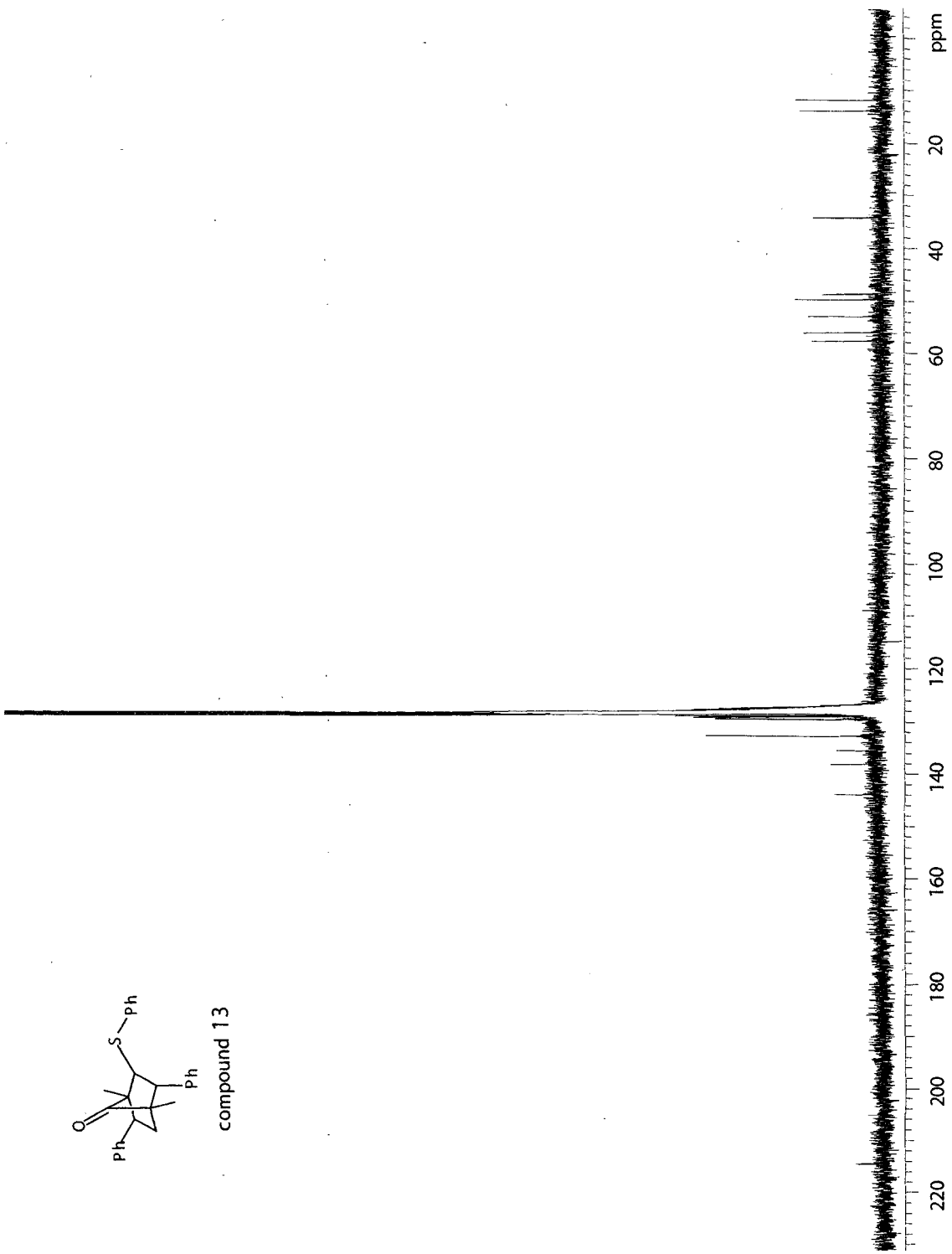

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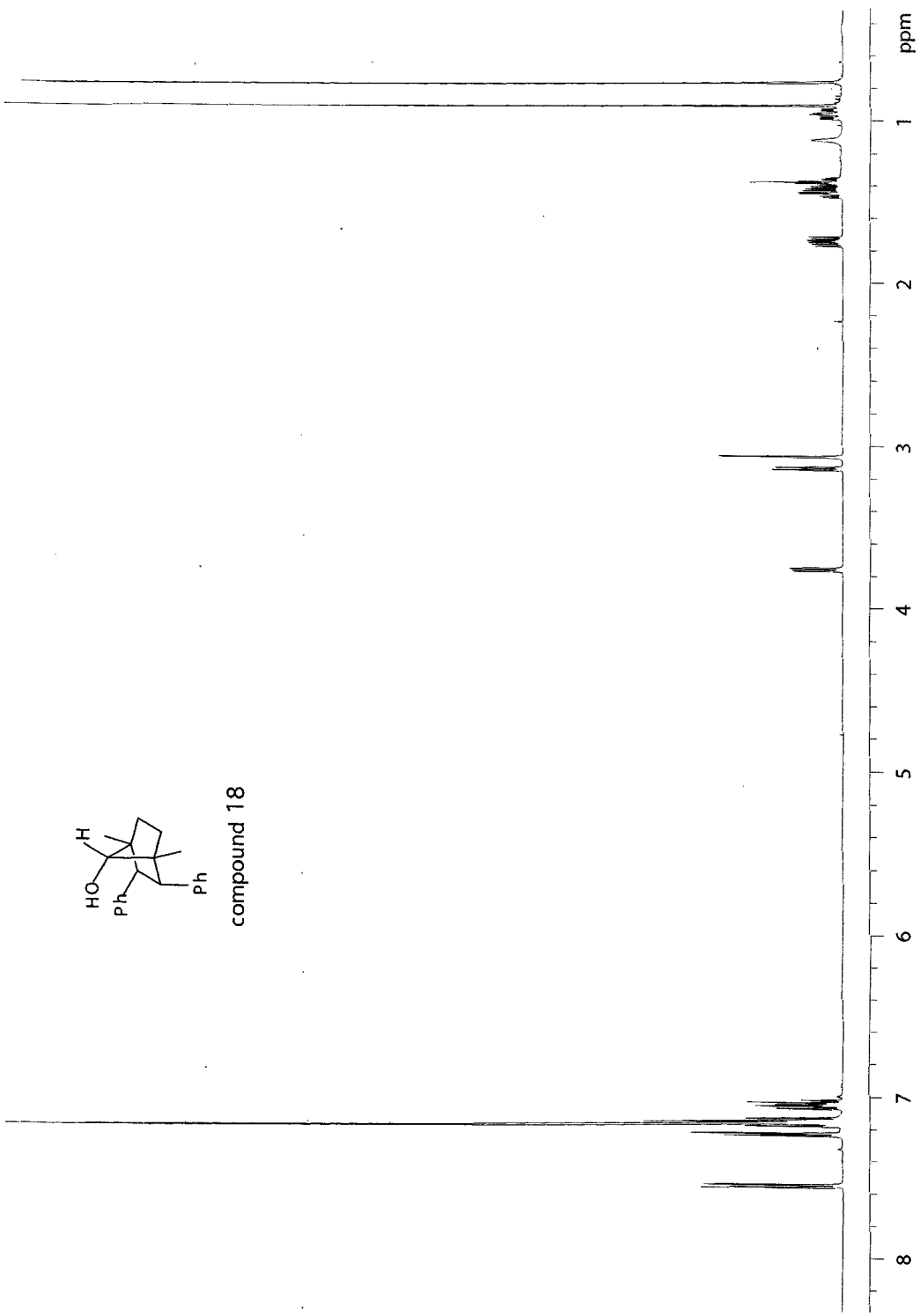

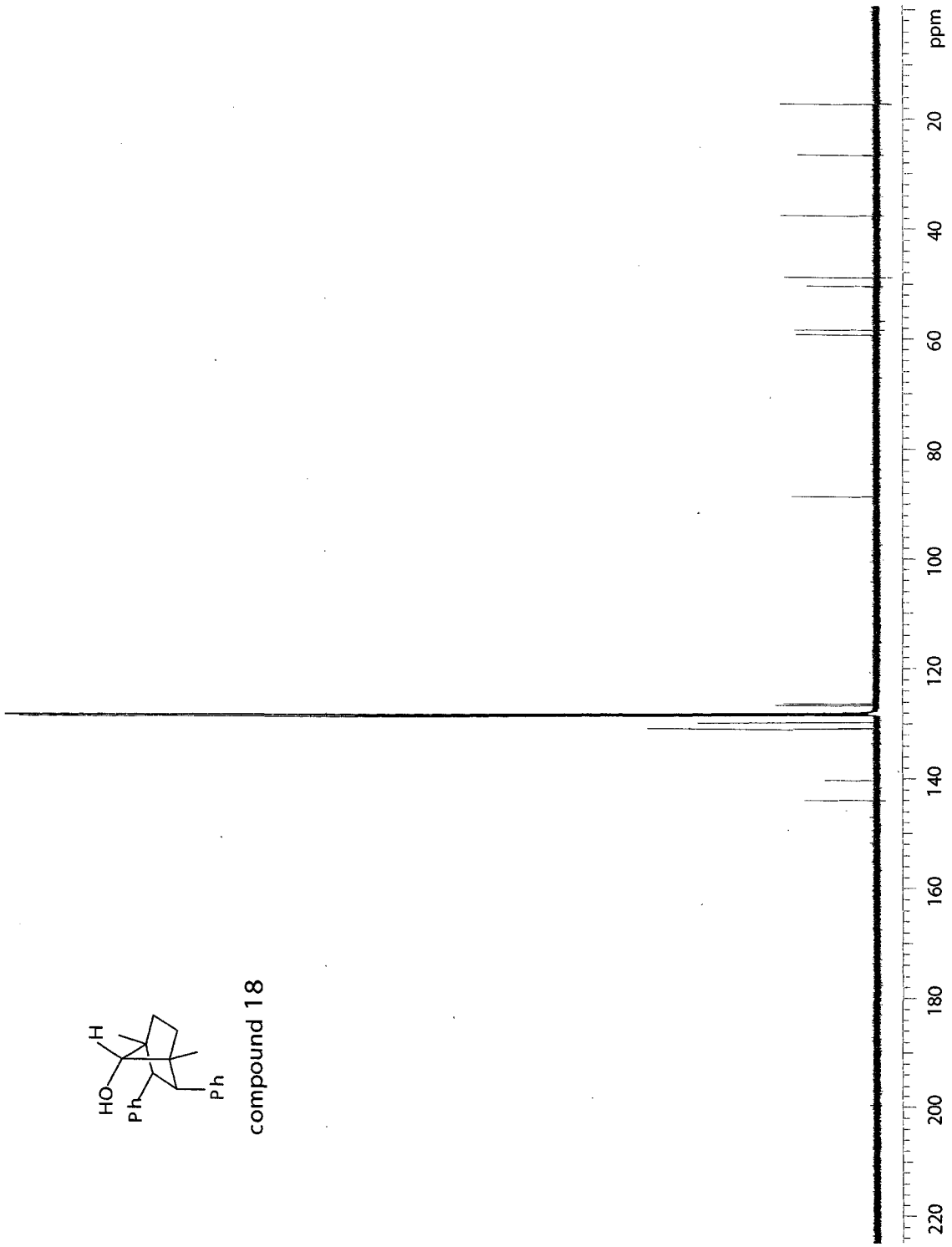

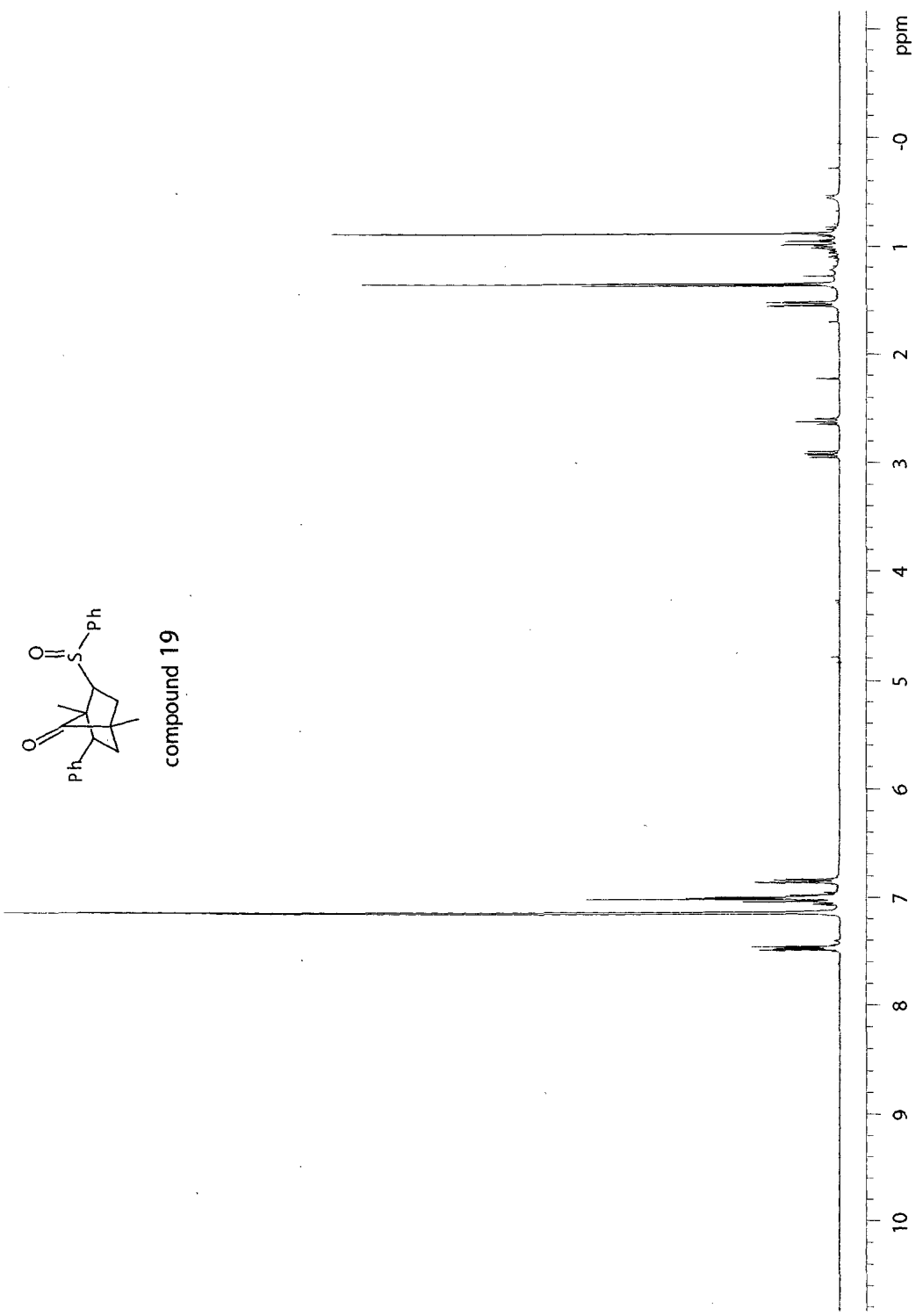

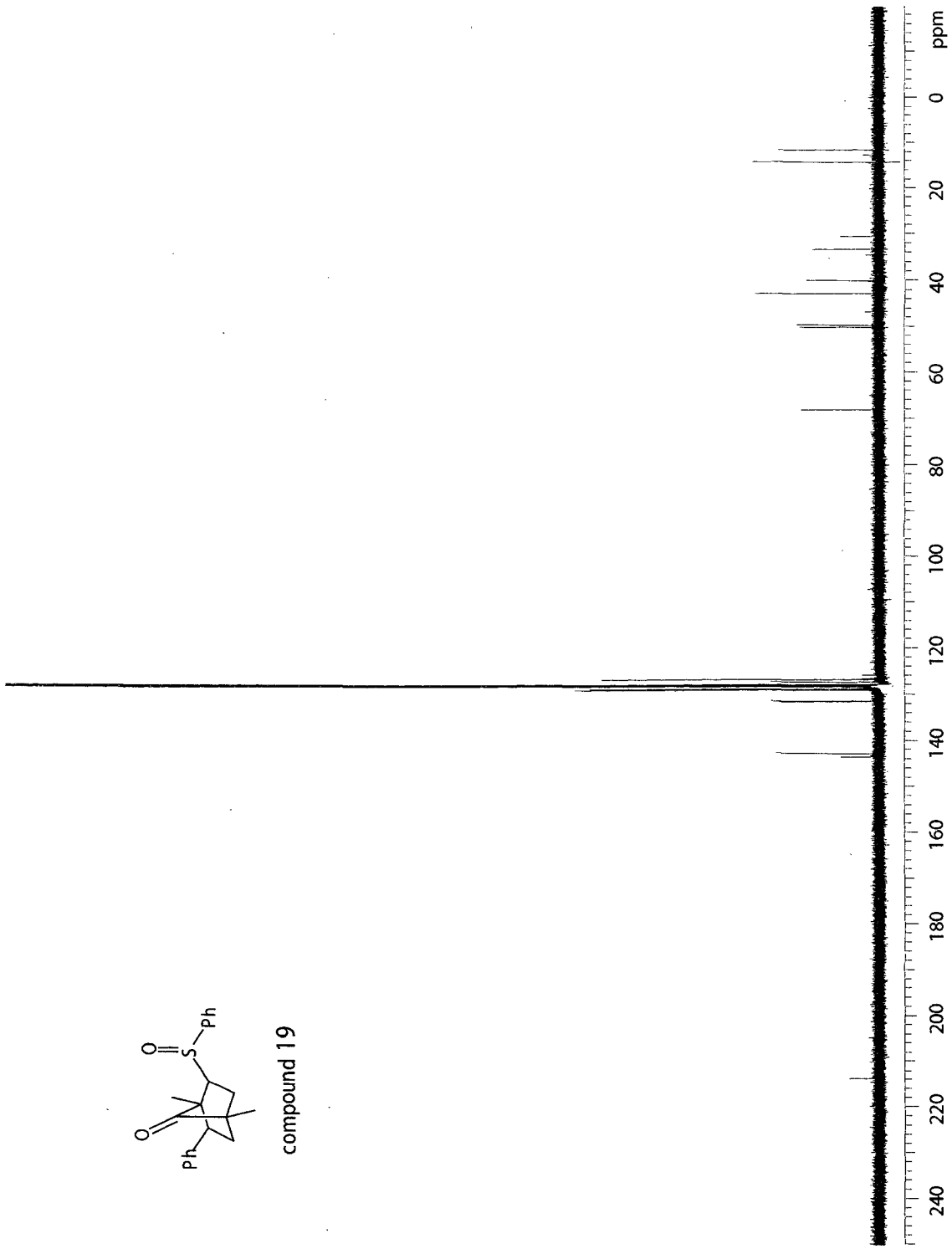

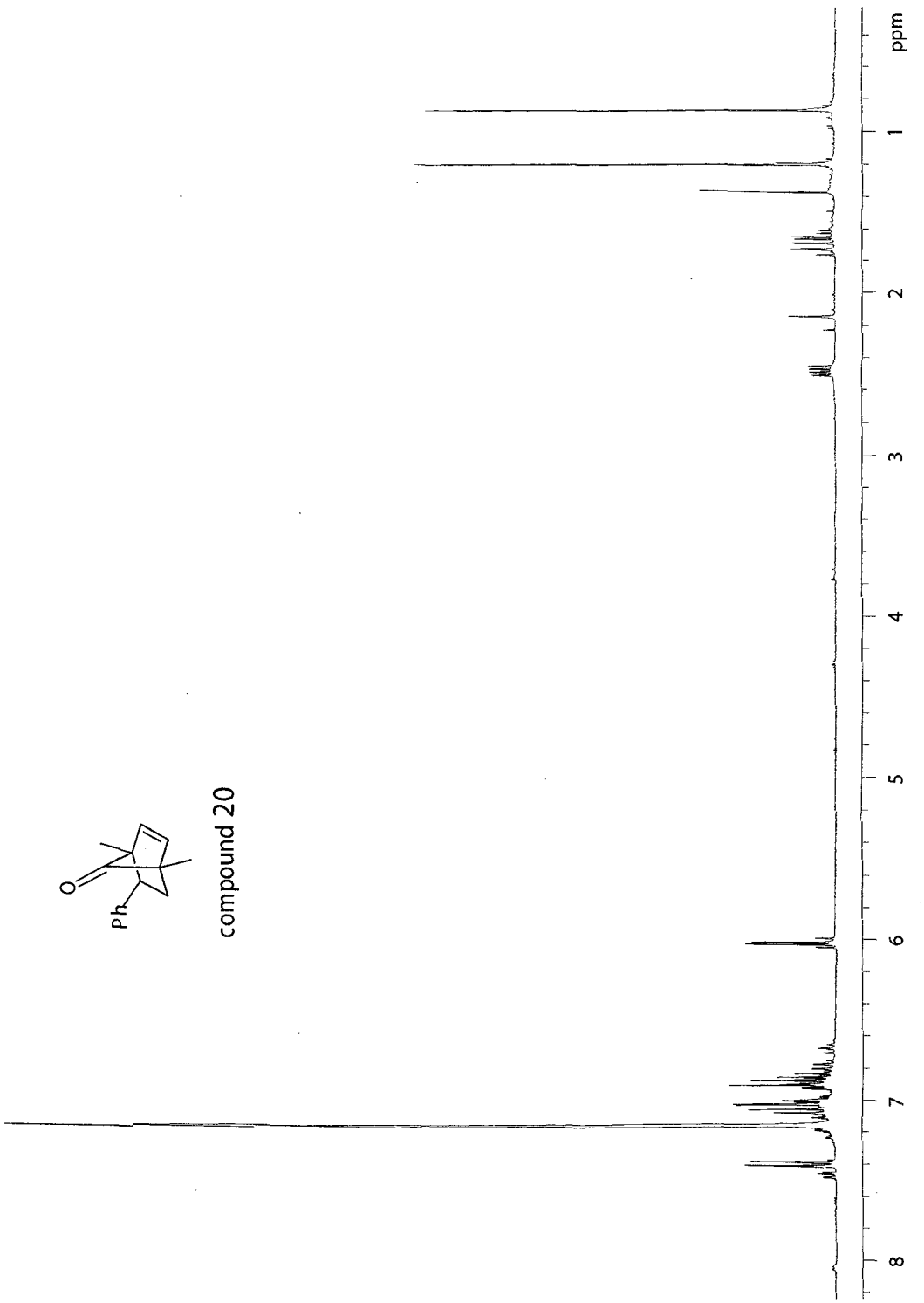

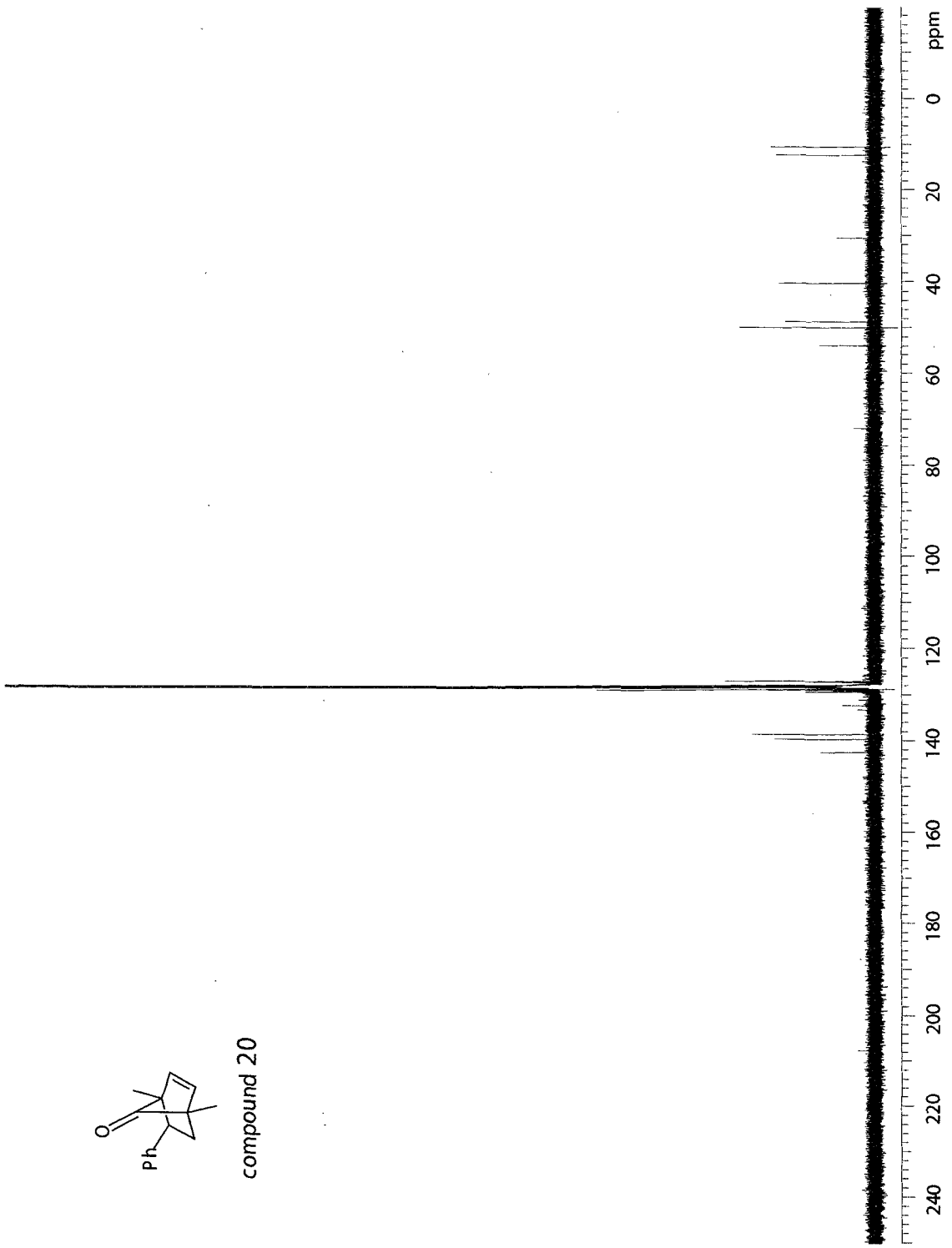

compound 20