University of Alberta

Unconventional Substrates for the Nazarov and Imino-Nazarov Reactions

by

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Abstract

5-Membered carbocycles are ubiquitous in natural products and synthetic drugs. Methods of generating them are therefore valuable, and the ability to do so in a stereospecific and enantioselective manner while making considerable gains in molecular complexity with additional incorporation of versatile handles for further elaboration are even more desirable. In the Nazarov reaction, activation of a dienone by a strong Brønsted or Lewis acid results in the formation of a conjugated pentadienyl cation, which can then undergo conrotatory 4π-electrocyclization to yield a cyclopentenone.

Recent activity in the area of Nazarov chemistry is summarized in Chapter 1. Unconventional substrates are gaining popularity in the Nazarov field due to their potential to eliminate some of the restrictions faced when using the traditional substrates (divinyl ketones). Chapter 2 describes the preparation of 1-alkoxy-2,2-dichloro-1-vinylcyclopropanes, and their application to the Nazarov cyclization. These compounds undergo electrocyclic ring opening of the cyclopropane followed by Nazarov cyclization to furnish chlorinated 2-cyclopentenones. Importantly, this reaction could be done under catalysis by indium(III) chloride in leading examples. Arene traps were tethered through the akoxy-substituent in an effort to effect a novel mode of interrupted Nazarov reaction; however, this reaction was not realized.

During the study of 1-alkoxy-2,2-dichloro-2-vinylcyclopropanes, an unexpected Friedel-Crafts cyclization was observed in some substrates. On further investigation of the process (Chapter 3), it was found that silver(I) bis(trifluoromethanesulfonyl)imide acts as a precatalyst in a Brønsted acid catalyzed intramolecular Friedel-Crafts alkylation of arenes with unactivated alkenes. Electron-rich and electron-deficient arenes as well as heteroaromatic rings reacted with alkenes to afford 5-,6-,7- and 8-membered rings, often generating a quaternary center adjacent to the arene.

In stark contrast to the Nazarov reaction, there is very little knowledge about its nitrogen analogue, the imino-Nazarov reaction. In Chapter 4, our approach to the imino-Nazarov reaction of 1-amino-2,2-dichloro-1-vinylcyclopropanes is reported. The cyclization product is a cyclopenteniminium salt, which is reduced to furnish *cis*-3-amino-4-chlorocyclopentenes. This is the first example of an imino-Nazarov reaction with an electron-rich amine that is retained in the product. These substrates have also afforded the first interrupted imino-Nazarov reaction.

Acknowledgements

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To the Boss: Thanks for giving me a place in your research group and for all of the support and guiding discussions along the way. Thanks for the interest you take not only in our careers during graduate school, but after we leave the group as well.

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List of Standard Abbreviations

σ_p	Hammett parameter for a substituent in the para position on an aromatic ring
Å	angstrom
ABq	AB quartet
Ac	acetyl
Anal. Calcd	analysis calculated
app	apparent
APPI	Atmospheric Pressure Photoionization (mass spectrometry)
aq	aqueous
Ar	aryl
B	an unspecified base
BArF	$[B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$
BINOL	2,2′-dihydroxy-1,1′-dinaphthyl
Bn	benzyl
BORSM	based on recovered starting material
br	indicates that the signal is broad
Bu	butyl
c-hex	cyclohexyl
cat.	indicates that the reagent was used in a catalytic amount
COSY	correlation spectroscopy
Cp	cyclopentadienyl ligand
CSA	(+)-camphorsulfonic acid
d	doublet (spectral)
d.r.	diastereomeric ratio
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCB	1,2-dichlorobenzene

DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
Δ	indicates that the reaction was heated
Δ δAB	difference in chemical shifts of A and B in an Abq
DEPT	distortionless enhancement by polarization transfer
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dt	doublet of triplets
e.e.	enantiomeric excess
E^+	an unspecified electrophile
EI	electron ionization
ESI	electrospray ionization
Et	ethyl
FCC	flash column chromatography
Fmoc	fluorenylmethyloxycarbonyl
g	grams
h	hours
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HMBC	heteronuclear multiple bond coherence
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz

i-Pr	*iso*-propyl
IR	infrared spectroscopy
J	coupling constant
J_{AB}	coupling constant between protons A and B
kcal	kilocalories
LDA	lithium diisopropylamide
M	molarity (concentration)
m	multiplet
M	used to indicate an unspecified metal with unspecified ligands
m.p.	melting point
m/z	mass to charge ratio
M^+	molecular ion
mCPBA	3-chloro-perbenzoic acid
Me	methyl
mg	milligrams
MHz	megahertz
min.	minutes
mL	milliliter
mmol	millimoles
mol	moles
MOM	methoxymethyl
Ms	methanesulfonyl
MS	molecular sieves
n-Pr	propyl
NFSI	*N*-fluoro-*o*-benzenedisulfonimide
NMR	nuclear magnetic resonance
Nu	indicates an unspecified nucleophile
nOe	nuclear Overhauser enhancement
ºC	degrees Celsius

Ph	phenyl
PMB	4-methoxybenzyl
PMP	4-methoxyphenyl
PPA	polyphosphoric acid
ppm	parts per million
Proton Sponge	1,8-bis(dimethylamino)naphthalene, *N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine
q	quartet
r.t.	room temperature
RaNi	Raney Nickel
TROESY	rotating frame Overhauser enhancement spectroscopy
s	singlet
t	triplet
t-Bu	*tert*-butyl
TBAF	tetrabutylammonium fluroride
TBS	*tert*-butyldimethylsilyl
TEBA	benzyltriethylammonium chloride
TES	triethylsilyl
Tf or trifl	trifluoromethansulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
tosylate	*p*-toluenesulfonate
tq	triplet of quartets
triflimide	bis(trifluoromethanesulfonyl)amide

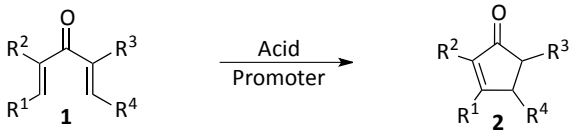
Ts	*p*-toluenesulfonyl

Chapter 1

The Nazarov Reaction

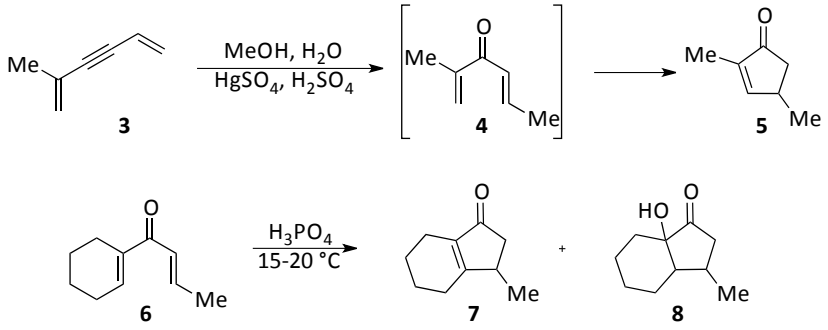
1.1 Nazarov Cyclization

The Nazarov reaction is an excellent way to construct cyclopentenones. This electrocyclic process converts a divinyl ketone to a cyclopentenone under acidic conditions, and has a number of features that impart synthetic clout to its use (Scheme 1.1). The reaction is well studied,[1] occurs with predictable stereochemistry, and catalytic and/or asymmetric procedures have been developed. In addition, reactive intermediates generated en route can be intercepted with bond forming processes to increase the complexity of the Nazarov-derived product. 5-Membered carbocycles are ubiquitous in natural products and synthetic drugs, and thus there is no shortage of applications for methodology that produces them.



Scheme 1.1. The Nazarov Cyclization.

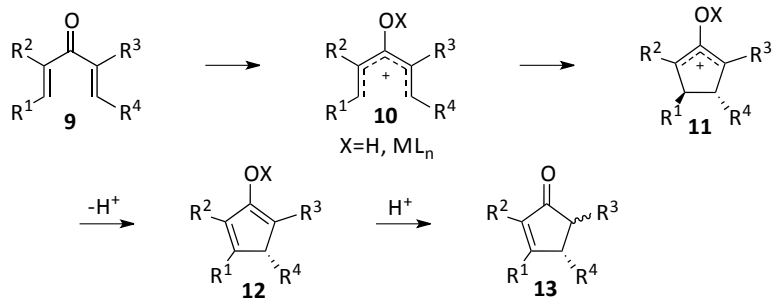
Although in the earliest examples of the cyclization done by I. Nazarov the cross-conjugated dienones were not isolated prior to cyclization, they were later discretely shown to undergo the cyclization step (Scheme 1.2).[2] Dienones have since become accepted as the traditional Nazarov reaction starting materials.



Scheme 1.2. Early Examples of the Nazarov Cyclization.

1.1.1. Mechanistic Aspects

Activation of the dienone by a strong Brønsted or Lewis acid results in the formation of a conjugated pentadienyl cation, which can then undergo conrotatory 4π-electrocyclization. Unless it is intercepted by a trapping group (the "interrupted Nazarov" reaction, *vide infra*), the oxyallyl cation **11** formed from electrocyclization generally experiences elimination of a proton to afford dienol or dienolate **12**. This is followed by tautomerization or protonation to give the cyclopentenone **13** (Scheme 1.3).



Scheme 1.3. Mechanism of the Nazarov Cyclization.

The rotation mode of the reaction is dictated by orbital symmetry. Under thermal conditions, in order for a favourable interaction between the termini of the pentadienyl cation, conrotation is required (Figure 1.1).[3] As a corollary, the stereochemistry of substituents R^1 and R^4 is set by their relationship in the divinyl ketone substrate; in Scheme 1.3, the *E*,*E* geometry necessitates their *trans* disposition in the cyclopentenyl cation. In some cases, the *trans*-isomer is formed regardless of the geometry of the starting dienone.[4] This is explained by a pre-equilibrium where *cis*/*trans* isomerization of the starting material occurs and the *E*,*E* isomer is more reactive toward cyclization.

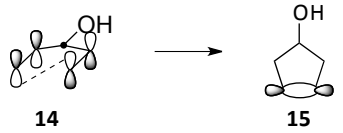
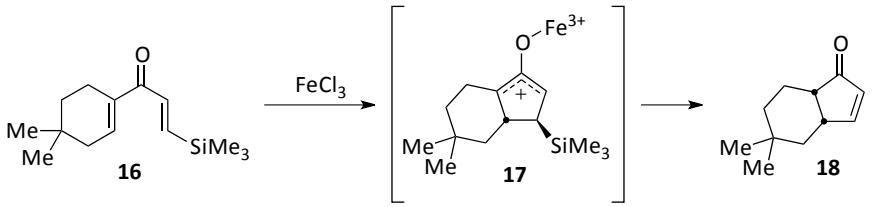


Figure 1.1. Origin of Conrotation in the Nazarov Cyclization.

The relative stereochemistry of R^1 and R^4 is often obliterated *via* elimination to provide **13**. If elimination can be directed outside of the cyclopentene ring, the stereochemical information can be retained. Interrupted Nazarov reactions also preserve both stereogenic centers through nucleophilic attack on the oxyallyl cation, which avoids the elimination entirely.

If elimination is allowed to proceed within the cyclopentanoid ring regioselectivity can be a problem, but generally the more substituted olefin is preferred. This can be attenuated by inclusion of directing elements on the dienone. Silyl groups at the β-position of the dienone can localize the positive charge on the proximal end of the oxyallyl cation and also act as a electrofuge, thus directing the elimination toward the silane regardless of the remaining substituents[5] (Scheme 1.4). Notably, the less substituted olefin can be generated by this method. Stannanes have also been exploited for this task.[6]



Scheme 1.4. Silicon as a Directing Group for Elimination.

The α-cation-stabilizing ability of fluorine has been used to localize the positive charge at one end of the oxyallyl cation, enabling regioselective elimination to yield fluoroalkenes.[7] Oxygen is frequently used in this manner, and esters can direct the elimination to the opposite side of the ring (*vide infra*).

1.2 Catalysis of the Nazarov Reaction

Catalysis of the Nazarov reaction has been a problem with limited solution.[1a] The activating agent must be able to bind to a ketone, and as the product of a Nazarov cyclization is a cyclopentenone, product inhibition is common. Additionally, the metal-bound enolate formed after the Nazarov cyclization can be stable enough such that the catalyst cannot turn over. Catalysis involving unspecialized substrates is rare, and highly reactive polarized substrates

are most often used. For these reasons, catalytic systems have really only been developed for the Nazarov cyclization within the last decade.[1a]

1.2.1. Catalysis Through Two-point Binding

In order to facilitate the cyclization of dienones to encourage feasible catalysis, Frontier and coworkers made use of polarized dienones as substrates for the Nazarov cyclization.[4c, 8] Electron-donating and electron-withdrawing substituents are paired to create a polarized donor-acceptor relationship between the ends of the pentadienyl cation, enhancing reactivity. The reaction could be done using only 2 mol % of copper(II) triflate, and later the more active dicationic iridium catalyst **22** was introduced[9] (Scheme 1.5). The substrate scope included dienones that are capable of binding at two points: the ketone, and either an ester carbonyl or an ether oxygen. This mode of binding enforces the U-shaped conformer necessary for the electrocyclization (Figure 1.2).

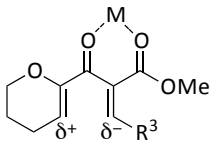


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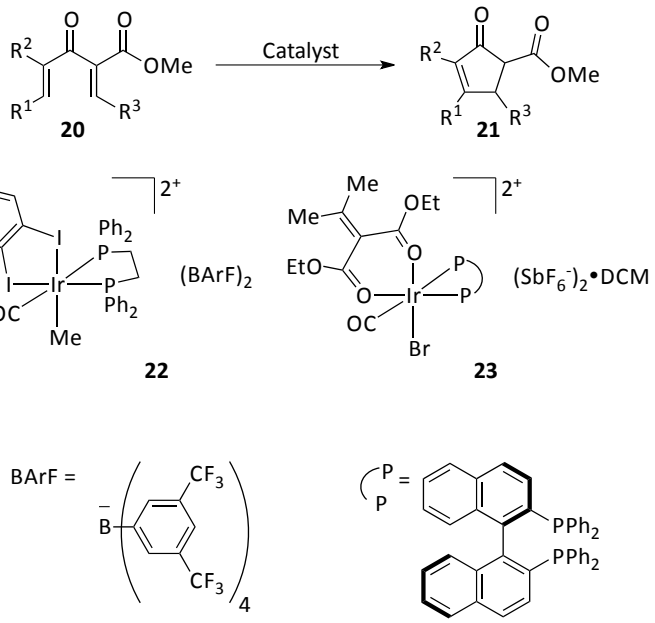
Figure 1.2. Bidentate Coordination of a Polarized Dienone.

Occhiato also took advantage of this type of catalysis with a scandium(III) triflate-catalyzed Nazarov cyclization of 2-(*N*-methoxycarbonylamino)-1,4-pentadien-3-ones,[10] which was quickly followed by a report from the Frontier group utilizing catalytic scandium(III) triflate in the presence of an equivalent of lithium perchlorate to achieve cyclization of heteroaryl carbomethoxy enones.[11]

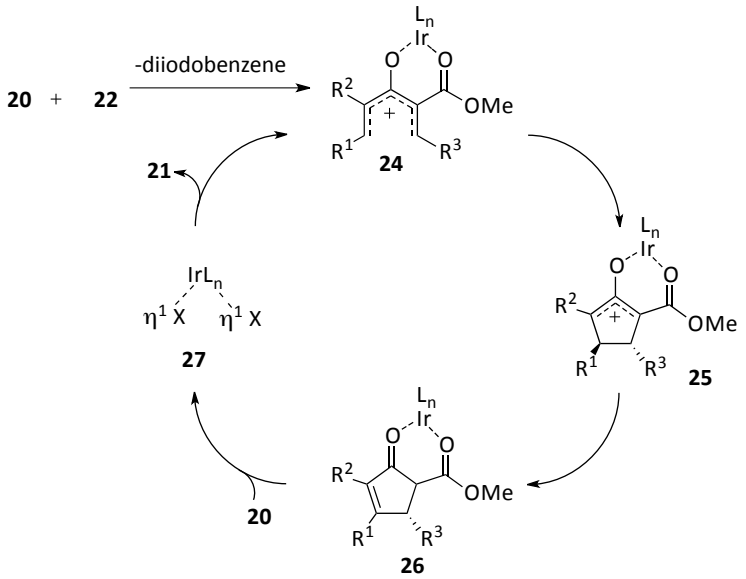


Scheme 1.5. Iridium-Catalyzed Nazarov Cyclization of Polarized Dienones.

Recent work in the area has focused on development of catalysts that open the reaction scope to substrates that are unreactive under the above conditions, new catalysts in the hopes for future asymmetric transformations, and use of known catalytic systems with new substrates.

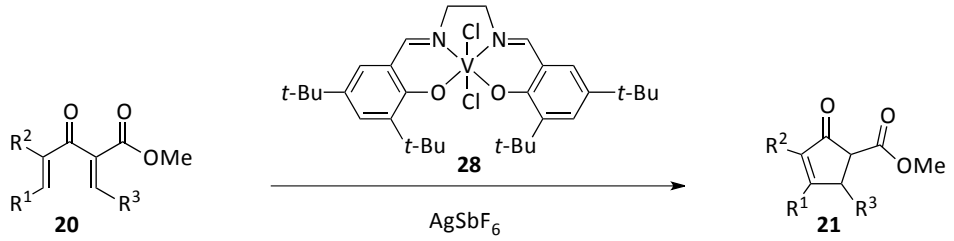
A limitation of the iridium catalyst **22** is that the R^3 substituent must be an electron-donating group. This was overcome with related catalyst **23**, where the methyl ligand is replaced by a bromide, and the bidentate diiodobenzene ligand is exchanged for diethyl isopropylidenemalonate.[12] The higher activity of the catalyst allows the substrate to possess electron-deficient arenes at R^3, and also works with phosphonates, cyano, or nitro groups replacing the ester. These were found to be difficult substrates under catalysis with $Cu(ClO_4)_2$ or the original iridium catalyst. A catalytic cycle based on catalyst **22** is depicted in Scheme 1.6. Catalyst **22** undergoes ligand exchange to form complex **24**. 4π-conrotatory electrocyclization generates **25**, and proton exchange provides **26**. Dissociation of

one carbonyl allows association of another molecule of substrate, forming **27**. Product dissociation to provide **21** and **24** completes the catalytic cycle.



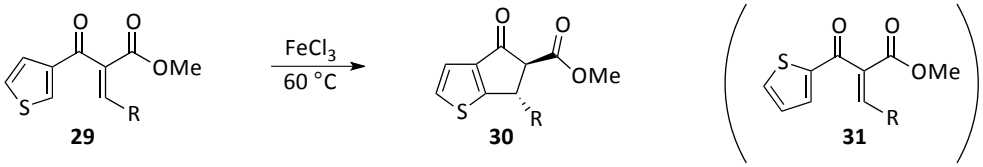
Scheme 1.6. Catalytic Cycle for Iridium-Catalyzed Nazarov Cyclization.

Vanadium complex **28** was activated in a solvent with low coordinating ability to provide a dicationic complex capable of converting dienones substituted with esters at the α-position to cyclopentenones **20** (Scheme 1.7).[13] The dicationic complex was proposed to position two vacant coordination sites *cis*, so as to allow bidentate coordination of the dienone. The reactions were generally complete within minutes. Substrates where the ester was replaced with an amide were inert, and those with an aryl group in place of one olefin were rather unreactive. A substrate incorporating a *p*-nitrophenyl substituent as R^3 could undergo the reaction, although extended reaction time was necessary. In some cases, non-regioselective elimination created product mixtures. A chiral variant of the complex was unable to induce non-racemic product formation.



Scheme 1.7. Vanadium-Catalyzed Nazarov Cyclization of Dienones **20**.

Iron(III) chloride has been applied in the cyclization of 3-thienylenones **29**. Itoh and coworkers found that the catalyst could be used at 10 mol % loading to promote cyclization of **29** in good yields;[14] however, the yields were diminished and reaction times extended when the R group was less able to stabilize a positive charge (Scheme 1.8). Regioisomeric substrates **31** failed to undergo the cyclization.

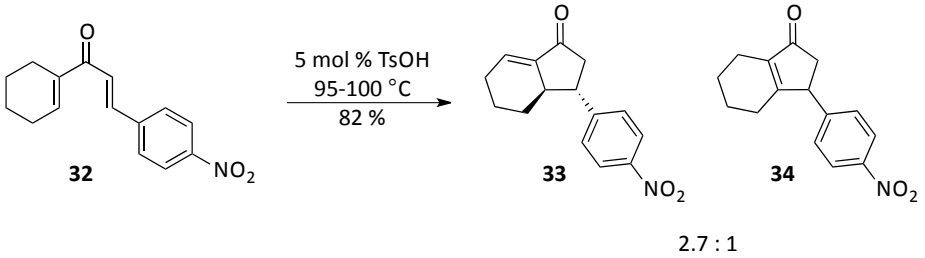


Scheme 1.8. Iron-Catalyzed Cyclization of Thienylenones.

1.2.2. Catalysts Not Requiring Two Binding Sites

Brønsted acids have also found application in catalytic Nazarov cyclizations. $HNTf_2$ [15] and phosphomolybdic acid [16] can promote Nazarov cyclization at 30 and 0.5 mol % respectively. These catalysts have been applied to more reactive polarized Nazarov substrates only. *o*-Benzenedisulfonimide has been used both with α-heteroatom-containing substrates, and a single non-polarized dienone with catalyst loading of 5 to 30 mol %.[17]

Rouden and coworkers employed catalytic *p*-toluenesulfonic acid in their Nazarov cyclizations.[18] Along with dienones containing α-oxygenation, which are more often used in catalytic reactions, simpler dienones such as **32** performed well (Scheme 1.9). The reactions were carried out at high concentration (1M) or without solvent, decreasing waste production from the reactions. In comparison to the dihydropyran-based substrates, which underwent cyclization at ambient temperature in acetonitrile, **32** required treatment with the catalyst in toluene at elevated temperature.

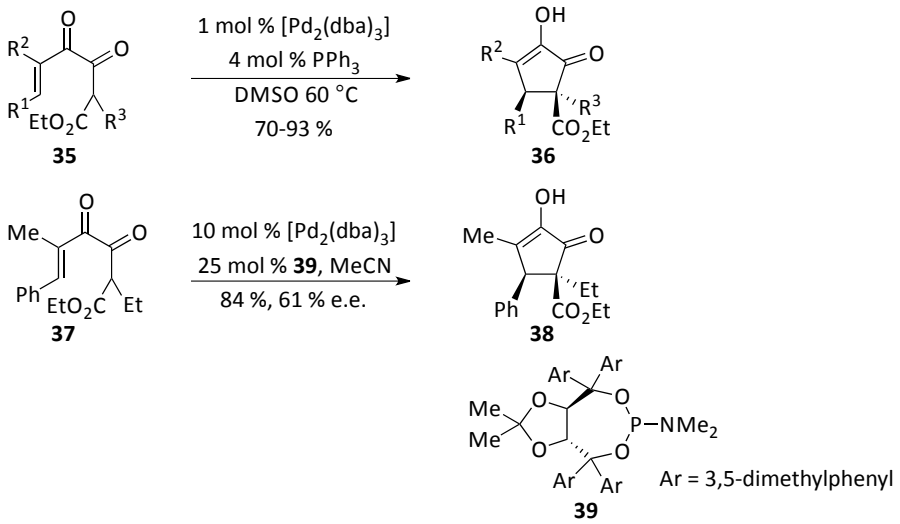


Scheme 1.9. Brønsted Acid-Catalyzed Nazarov Cyclization of Unpolarized Dienone **32**.

1.2.3. Other Modes of Catalysis

Tius and coworkers have previously reported a palladium(II)-catalyzed Nazarov cyclization.[19] Instead of activating the dienone through the carbonyl moiety, the authors propose coordination of the palladium to an olefin to trigger the cyclization. In a more recent report, the same group has used a palladium(0) catalyst to effect cyclization of diketones **35** to the corresponding cyclopentenones *via* the enolized form of the substrate (Scheme 1.10).[20] The mechanistic pathway has yet to be elucidated; however, the neutral reaction conditions of the cyclization are noteworthy. Moderate enantioselectivity has

been reported in a preliminary attempt to extend this methodology to an asymmetric version using chiral phosphoramidite ligand **39**.



Scheme 1.10. Palladium(0)-Catalyzed Nazarov Reaction.

1.2.4. Catalyst-Free Nazarov Cyclizations

It is interesting that with all of the attention catalysis of the Nazarov reaction is receiving, a catalyst is not required at all for some reactions. This was in fact reported by Greaney and coworkers in 2005, where dienones were heated in the polar aprotic solvent *N*,*N*-dimethylformamide to effect cyclization.[21] An ionic liquid, *N*-ethyl-*N*′-methylimidazolium fluoroborate was also used under microwave heating with some success. The reaction scope includes substrates of various substitution patterns (Figure 1.3), but notably not aryl enones and α-carbomethoxydienones.

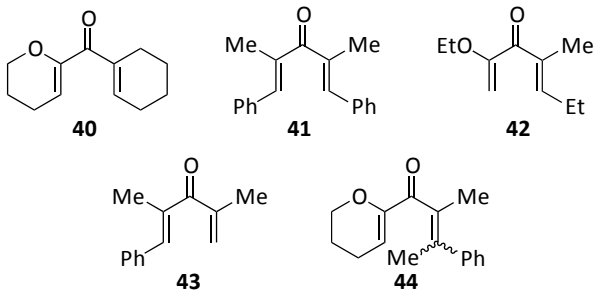
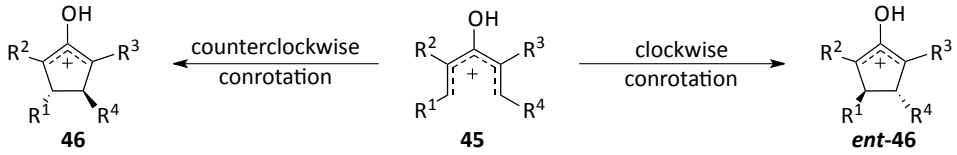


Figure 1.3. Substrates for Reagent-Free Nazarov Cyclization.

1.3 Asymmetric Nazarov Reactions

As alluded to in Section 1.2, one of the major driving forces for establishing a good catalytic Nazarov reaction is that it is a necessary starting point for a catalytic asymmetric Nazarov cyclization (Scheme 1.11). This is a challenging prospect. Although Nazarov reactions can show good diastereoselectivity[4a,22] when there is a strategically placed asymmetric center in the dienone to influence the torquoselectivity, or sense of rotation, of the cyclization, creating an enantioenriched Nazarov product from an achiral dienone is an entirely different challenge. This problem has been solved in part, as described below; however, there is no general method for an asymmetric Nazarov cyclization to date. Enantioselective Nazarov cyclizations that are coupled with further increase in molecular complexity are covered in Section 1.4.



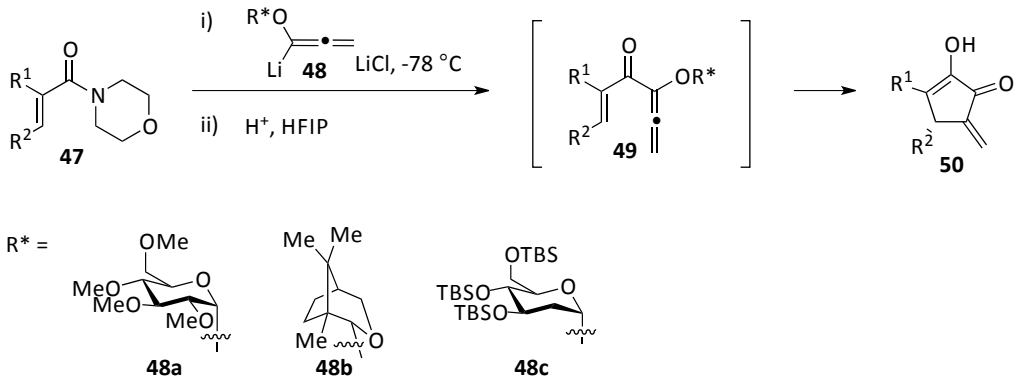
Scheme 1.11. Enantioselectivity in the Nazarov Cyclization.

1.3.1. Chiral Auxiliaries

Chiral auxiliaries attached to the α-position of a dienone have been used for the Nazarov cyclization. The torquoselectivity of the cyclization is biased by the presence of the auxiliary such that the product is diastereoenriched. The first group involves the traceless auxiliaries developed by the Tius group, and the second group is based on chiral oxazolidinones.

The Nazarov cyclization of allenyl enones with an oxygen-substituted allene is very favourable.[23] Relief of allenic strain and the small steric requirements of the allene contribute to the ease of the reaction, along with the benefit of stabilization of the oxyallyl cation by the oxygen substituent and additional conjugation with the remaining π-bond from the former allene. Additionally, when the R group on the oxygen can leave as a stable cation, the termination step is fast and irreversible. These allenylenones are so reactive that they must be formed *in situ*, and cyclization is effected by addition of a proton source at low temperature.

The Tius group first published work on traceless chiral auxiliaries for the allenyl ether Nazarov cyclization in 2000. The term "traceless" can be applied to these auxiliaries due to their departure as stabilized oxocarbenium ions following the cyclization; thus, no additional steps are required for their removal. The first auxiliary was derived from glucose (**48a**),[24a] followed by an improved version based on camphor (**48b**, Scheme 1.12).[24b, 25] Continued improvement in enantioselectivity was seen in allenyl vinyl ketones with auxiliary **48c**.



Scheme 1.12. Chiral Auxiliaries for the Nazarov Cyclization of Allenyl Ethers.

The mode of action of these chiral auxiliaries was not obvious, and after studying the behavior of a variety of auxiliaries, the authors proposed the transition structure depicted in Figure 1.4.[26] In transition state **51**, the chiral auxiliary departure is concurrent with the Nazarov cyclization step. Therefore, there is a developing positive charge at the anomeric carbon. This charge can be stabilized by a ring-inversion of the auxiliary so that the axial C-O bond at C-3 of the ring can donate electron density to the deficient anomeric carbon.[27] This conformation positions the C-4 siloxy substituent in an axial orientation, and pointing toward the incipient 5-membered ring. The ring-oxygen can provide stabilization to the forming ring through a charge-dipole interaction, thus positioning the forming ring beneath the auxiliary for maximum influence. In such a conformation, substituent R^2 preferentially rotates away from the auxiliary to give the major enantiomer.

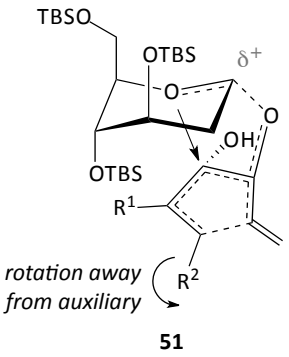
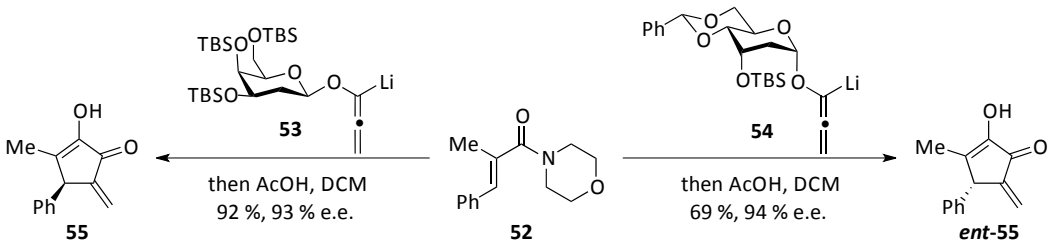


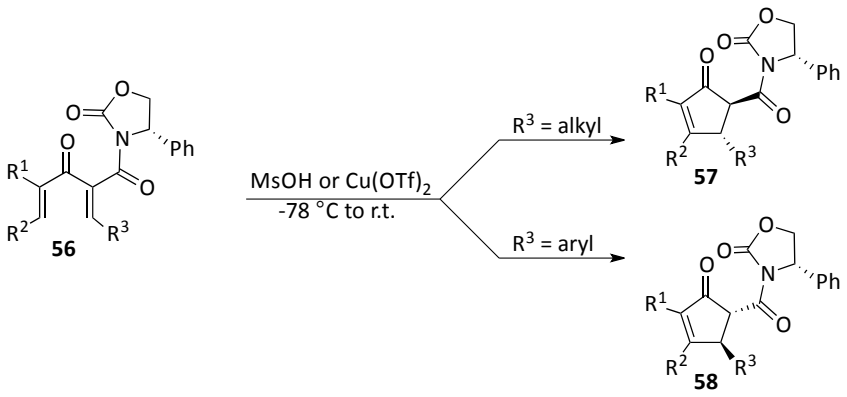
Figure 1.4. Proposed Transition State with Auxiliary **48c**.

Based on this model, lithioallenylethers **53** and **54** were developed to provide access to both enantiomers of ***55*** with high levels of enantioselectivity (Scheme 1.13).



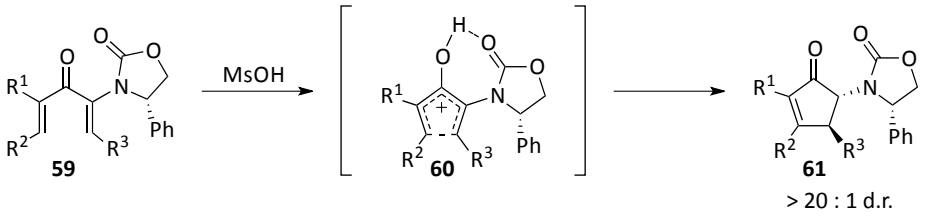
Scheme 1.13. Rationally Designed Chiral Auxiliaries.

The Pridgen group, followed by the Flynn group have been involved in the use of oxazolidinone-based chiral auxiliaries for the Nazarov cyclization.[28,29] In the original version, the auxiliary was spaced through a carbonyl at the α-position of the dienones. Interestingly, Flynn and coworkers observed that the major diastereomer obtained using the same auxiliary is different when R^3 is alkyl than when R^3 is and aryl group (Scheme 1.14).



Scheme 1.14. Nazarov Reactions with Oxazolidinone Chiral Auxiliary (Major Diastereomers Depicted).

In a very recent publication, the Flynn group again applied the oxazolidinone as a chiral auxiliary, but this time without the carbonyl spacer (Scheme 1.15).[30,31] With the nitrogen bound directly to the α-position of the dienone, its electron density can be donated to the oxyallyl cation to help encourage cyclization. The diastereoselectivities are much improved from the previous work. A chelate formed between the two carbonyls with the acid promoter is implicated in the torquoselectivity of the reaction, where the oxazolidinone is held such that the phenyl group blocks rotation toward it. Flynn and coworkers were also able to use their methodology in the context of the interrupted Nazarov reaction (Section 1.4.1). Interestingly, although in most cases a heteroatom substituent at the α-position of the substrate will bias elimination toward the proximal end of the oxyallyl cation, the double-bond regiochemistry of the products observed by Flynn are distal to the oxazolidinone in all cases. The auxiliary can be removed reductively by treatment with lithium naphthalenide or samarium diiodide.



Scheme 1.15. Oxazolidinone Chiral Auxiliary for the Nazarov Cyclization.

1.3.2. Lewis Acid Catalysts

After a single example of an asymmetric Nazarov cyclization utilizing a scandium-pybox complex,[32] Aggarwal and Belfield, in 2003, completed a more in depth inquiry into asymmetric Nazarov cyclizations utilizing a chiral Lewis acid.[33] A chiral copper(II) complex was used at 50-100 mol % loading, and while this illustrated proof of principle that the torquoselectivity of the Nazarov cyclization could be controlled by an external source of chirality, the high catalyst loading rendered the reaction impractical. Since then, much effort has been directed at producing a practical catalytic asymmetric Nazarov cyclization. There are still few methods that provide useful levels of enantioselectivity.

More recently, Kawatsura and Itoh have also used pybox ligands in their work on cobalt and iron catalysts for the asymmetric Nazarov reaction (Figure 1.5). The reaction yields were generally rather low, and it was necessary to optimize the reaction conditions for each substrate, using either catalyst **62** or **63** with various solvents. Despite this, in some cases good enantioselectivity was observed (up to 93 %), although 50 mol % loading of the catalyst was used.

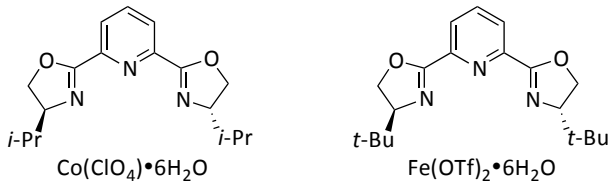
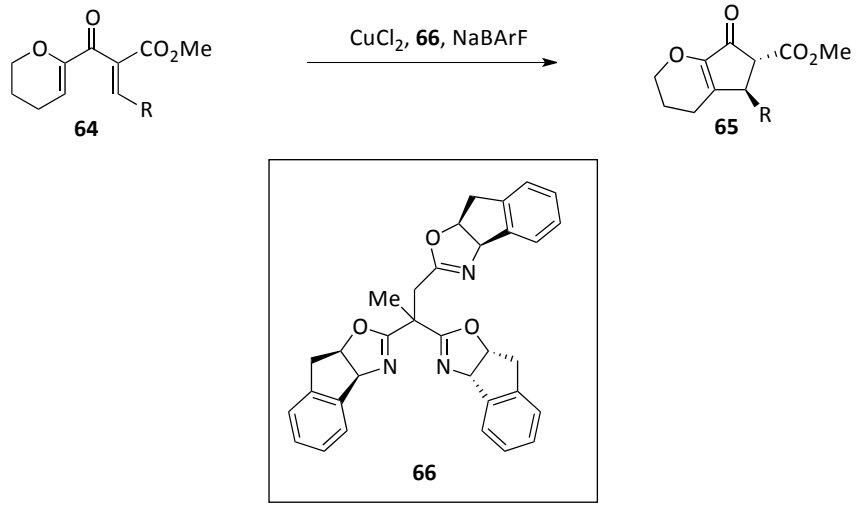


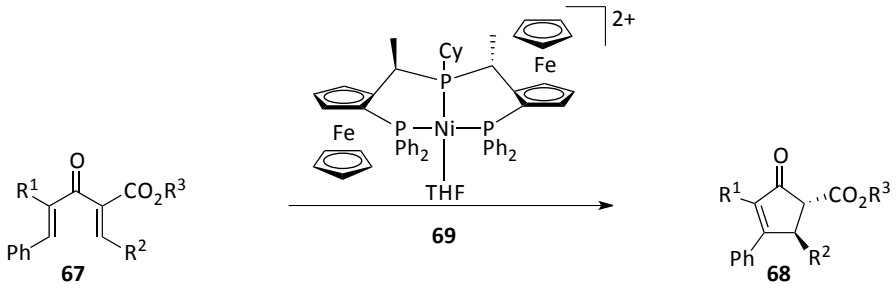
Figure 1.5. Catalyst Systems for Kawatsura and Itoh's Asymmetric Nazarov Reaction.

Tang and coworkers used a copper(II) tris(oxazoline) complex to carry out their asymmetric Nazarov cyclization (Scheme 1.16).[34] The substrates contain both an α-oxygen, and an α-ester, and so are highly reactive. This ligand fared much better than the pybox ligands, and enantioselectivity of up to 98 % was achieved with 10 mol % loading of copper(II). The yields were also good except when R was an electron-deficient arene. Unfortunately, this was the only site where variation was examined.



Scheme 1.16. Enantioselective Nazarov Cyclization With Tris(oxazoline) Ligand **66**.

Togni and Walz have developed an enantioselective Nazarov cyclization with a substantially different ligand system. Nickel(II) complex **69** was utilized with dienones **67** to provide enantioenriched cyclopentenones **68** (Scheme 1.17).[35] Enantioselectivities of up to 88 % were produced using 10 mol % **69**, a considerable improvement in catalyst loading from the groundbreaking work of Aggarwal, although the reaction is quite slow. Although R^2 was always an electron-rich arene, various substitution at R^1 was tolerated.



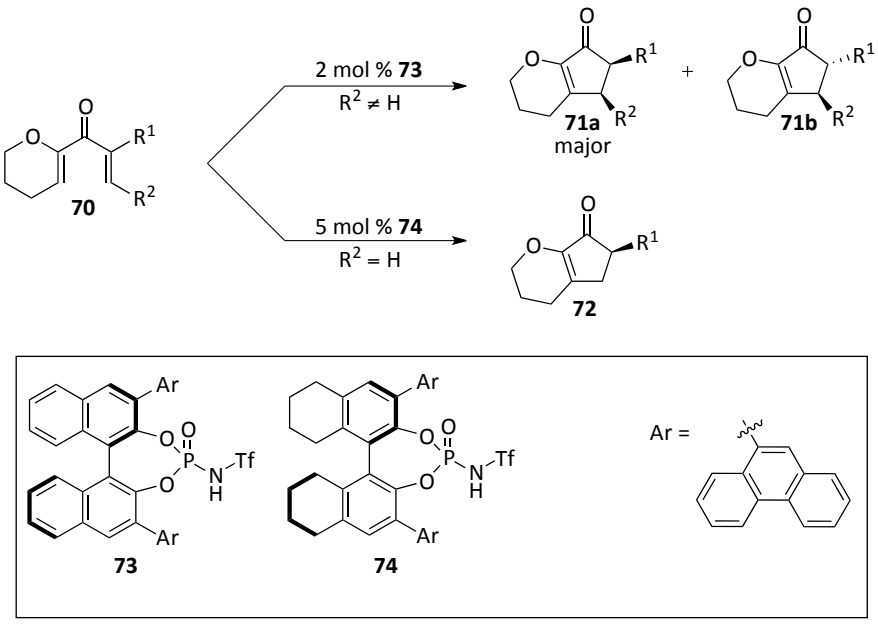
Scheme 1.17. Asymmetric Nazarov Cyclization Using a Ni(II)-Pigiphos Complex.

1.3.3. Brønsted Acid Catalysts

Rueping and coworkers introduced Brønsted acids as enantioselective catalysts for the Nazarov cyclization in 2007.[36] This work represents the first use of an organocatalyst in an enantioselective electrocyclization. BINOL-derived *N*-triflyl phosphoramide **73** was used at a low catalyst loading to provide the cyclopentenones **71a** in good yield and up to 98 % e.e. (Scheme 1.18).

Key features of the substrate are that the α-oxygen assists in stabilizing the intermediate oxyallyl cation and also plays a role in directing the elimination to the ring fusion, avoiding product mixtures from unselective elimination. The torquoselectivity of the cyclization is controlled by the chiral ion pair generated by proton transfer from the catalyst to the dienone. Unfortunately,

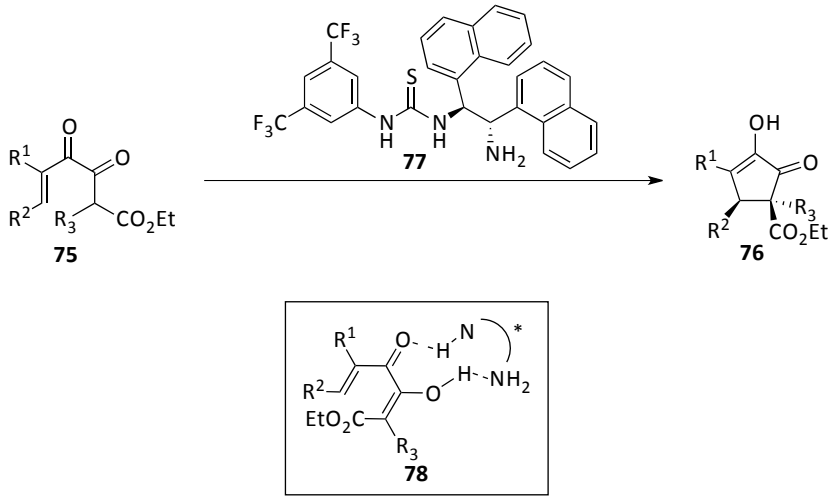
tautomerization of the dienol formed after elimination is only moderately selective for the kinetically favoured *cis*-product; however, epimerization with basic alumina can convert the preferred isomer to the *trans* diastereomer. The scope of this reaction was recently broadened to include acyclic α-alkoxydienones.



Scheme 1.18. Chiral Phosphoramide Catalysis of the Nazarov Reaction.

In a following publication, a related phosphoramide was used to catalyze the Nazarov cyclization of substrates lacking the β-substituent.[37] Although the cyclization step does not create a stereogenic center that is retained in the product, the catalyst is now responsible for enantioselective protonation of the enol. Previously, enantioselective protonation was achieved using a scandium-pybox complex.[38] Enantioselectivities of up to 78 % were possible using phosphoramide **74**, and the diastereoselectivity problem was avoided by using substrates with R^2 = H.

Tius and coworkers have used bifunctional thiourea catalyst **77** to convert keto-enones **75** to optically enriched cyclopentenones **76** (Scheme 1.19).[39] Catalyst loading is relatively high (10 mol %), and the process suffers from prolonged reaction times ranging from a few days to several weeks. Nonetheless, enantioselectivity up to 97 % is obtained, and the product yields range from good to excellent. The catalyst acts as both an acid and a base, simultaneously activating the carbonyl and enol to catalyze the reaction.



Scheme 1.19. Asymmetric Thiourea-Catalyzed Nazarov Cyclization.

1.4 Step-Economy and the Nazarov Reaction

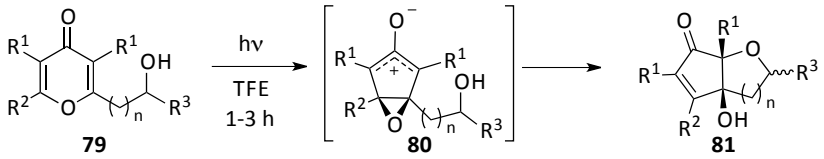
While the Nazarov cyclization is a powerful tool for cyclopentenone synthesis, this is not the limit of the reaction's capabilities. The reactive oxyallyl cation intermediate can be harnessed to provide access to a diverse range of scaffolds *via* nucleophilic attack in the interrupted Nazarov reaction to build up complex molecules quickly. Nazarov reaction conditions are also compatible with a variety of subsequent transformations where the enol or enolate

intermediate can act as a nucleophile, providing one-pot sequences that eliminate needless workup steps and minimize solvent waste.

1.4.1. Interrupted Nazarov Reactions

Prompted by the work of Barltrop[40] and Pavlik[41] implicating nucleophilic attack on oxyallyl cations generated during the photolysis of pyrones, West and coworkers began exploiting the reactivity of the oxyallyl cation.

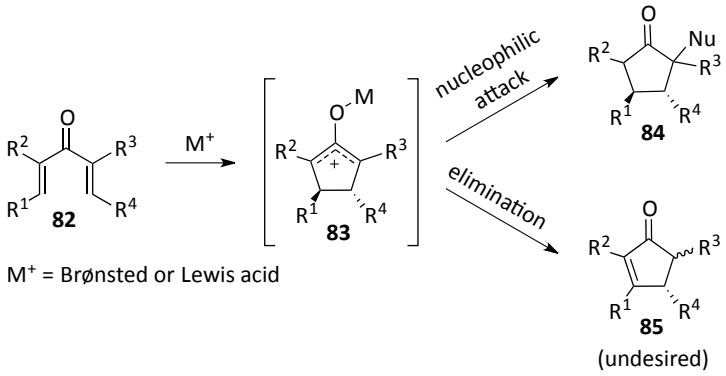
For the initial investigation, a hydroxylic nucleophile was chosen to intercept the oxyallyl cation (Scheme 1.20).[42] As the major competing reaction to the desired outcome was intramolecular rearrangement to the corresponding 2-pyrone, West and coworkers reasoned that increasing the effective concentration of the trapping element by tethering it to the 4-pyrone would give the now intramolecular interrupted process an advantage over the rearrangement. As a bonus, the product would possess an additional ring. Photochemically induced charge separation in the 4-pyrone precursor followed by electrocyclization led to the zwitterion **80**, which was then attacked by the tethered nucleophile.



Scheme 1.20. Trapping of a Photochemically Generated Oxyallyl Cation with a Tethered Hydroxyl.

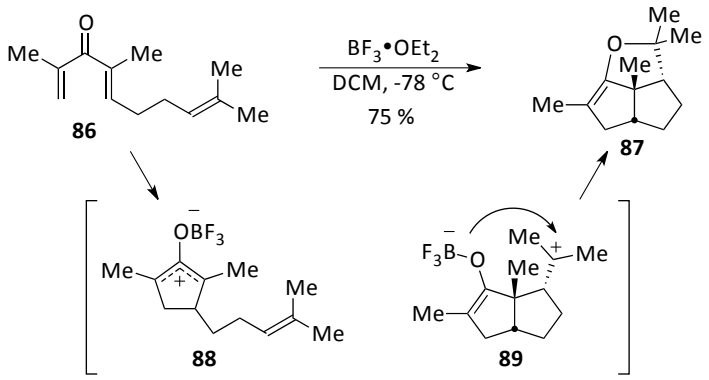
The intermolecular process was also viable.[43] West then investigated other trapping agents: alkenes,[44] arenes,[45] butadienes,[46] acetonitrile,[47] and carboxylic acids.[48]

While the photochemical Nazarov cyclization of 4-pyrones had served well in the investigation of oxyallyl cation reactivity, there are some limitations associated with the pyrone substrates. For example, the structural diversity of the products was limited to 4-hydroxy 2-cyclopentenones. Generation of the oxyallyl cation *via* acid mediated electrocyclization of divinyl ketones would prove very useful (Scheme 1.21). The products that can be obtained from the dienone precursors are highly substituted cyclopentanes. As a beneficial corollary, the stereochemistry established by the electrocyclization is retained in the product.



Scheme 1.21. The Interrupted Nazarov Reaction.

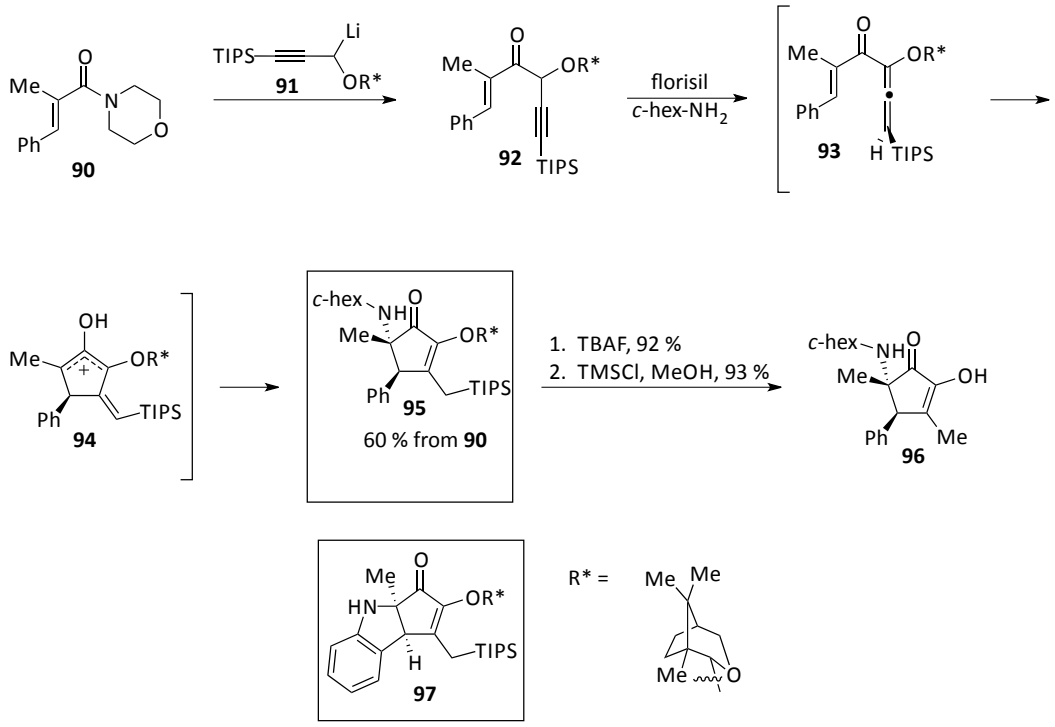
The first premeditated interrupted Nazarov reaction was conducted by West and coworkers in 1998. Trienones, exemplified by **86,** were subjected to boron trifluoride diethyletherate to form polycyclic hemiketals (Scheme 1.22).[49] Fortunately, the trapping process proved to be highly diastereoselective, resulting from a compact transition state. Attack of the resulting enolate on the tertiary carbocation led to the observed product.



Scheme 1.22. Alkene Trapping of the Nazarov Intermediate.

West and others have since developed a plethora of interrupted Nazarov reactions.[1d] The subject of this section is methodology that was developed from 2006 until the present.

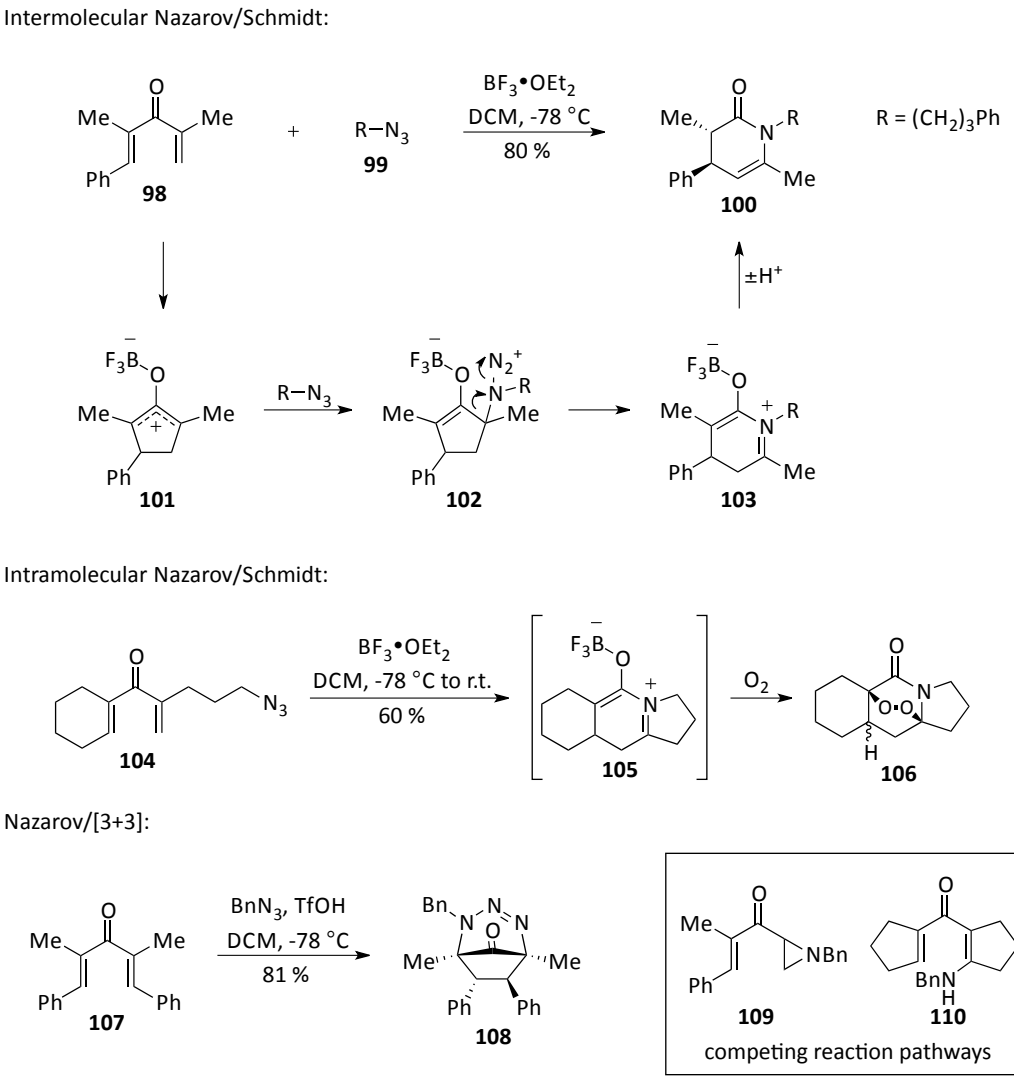
Amines as nucleophilic traps for the interrupted Nazarov cyclization of *in situ* generated allenyl vinyl ketones were introduced by Tius in 2005.[50] In 2007, a diastereoselective variant utilizing a chiral auxiliary was disclosed.[51] The amine invariably attacked the non-oxygen substituted portion of the oxyallyl cation, and on the less hindered face (opposite to the phenyl substituent in **95**). In intramolecular examples, the stereochemistry of the incoming amine was reversed due to the constraints in forming a bicyclic system, and product **97** was observed. Although the interruption event precludes the possibility of a traceless auxiliary, contrasting to the uninterrupted reaction (*vide supra*), the auxiliary was cleaved in good yield when **95** was subjected to TMSCl in methanol.



Scheme 1.23. Amine-Interrupted Nazarov Cyclization.

West and coworkers have used azides in the interrupted Nazarov reaction in first an intramolecular fashion, then later intermolecularly (Scheme 1.24).[52] This represents the first example where the nucleophilic atom possesses a leaving group, resulting in an interesting interrupted Nazarov/Schmidt rearrangement sequence to produce dihydropyridones **100**. These are the only examples of a Nazarov reaction in which a ring expansion occurs to form a 6-membered heterocycle rather than a cyclopentenone. When oxygen was not rigorously excluded from the reaction medium, peroxy-bridged compounds **106** were produced, but only in the intramolecular cases.

In the intermolecular sense, the azide attacked at the least hindered position of the oxyallyl cation, in agreement with previous work. This resulted in excellent regio- and stereoselectivities, although protonation of the boron enolate **103** could result in production of epimers in some cases.

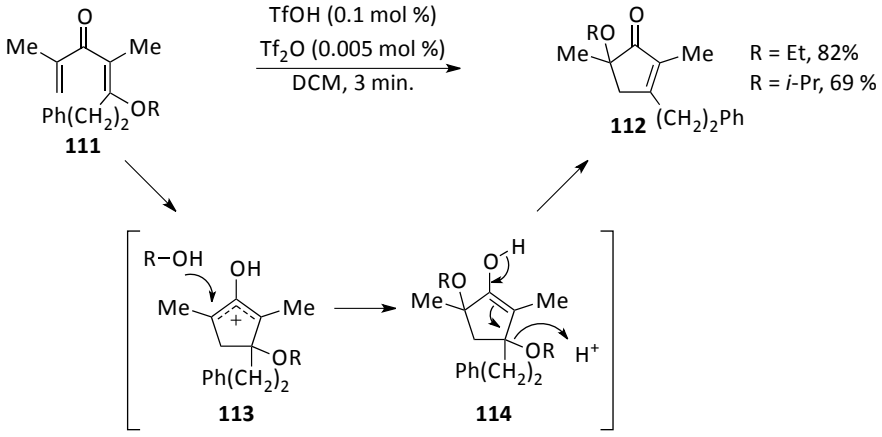


Scheme 1.24. Azide-Interrupted Nazarov Cyclizations.

In addition to that, when the reaction is promoted by TfOH at low temperature a [3+3] cycloaddition between the oxyallyl cation and the azide occurs to generate the novel ring system of compounds **108** (Scheme 1.24).[53] When substrates that are a bit sluggish to undergo Nazarov cyclization are used, competing products **109** and **110** were observed.

The first examples of interrupted Nazarov reactions involved trapping by oxygen nucleophiles.[54] Hydroxyl nucleophiles were also deliberately applied to

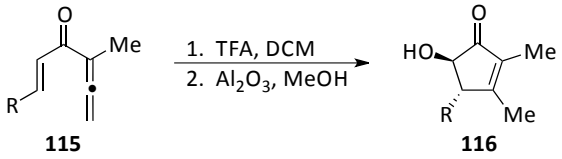
photochemically generated oxyallyl zwitterions (*vide supra*). Shindo and coworkers brought this reactivity into the realm of catalysis utilizing alcohols that were generated *in situ* from β-alkoxydienone substrates (Scheme 1.25).[55] This type of reactivity was precedented in a report on the Nazarov cyclization of β-thiodienones.[56] Shindo and coworkers made use of methyl, ethyl, and isopropyl ethers, producing interrupted Nazarov products **112** in good yield. Crossover experiments demonstrated that the nucleophile is derived intermolecularly. The β-alkoxy substituent is required for the reaction to proceed in a catalytic manner.



Scheme 1.25. Interruption of the Nazarov Cyclization with an Alcohol.

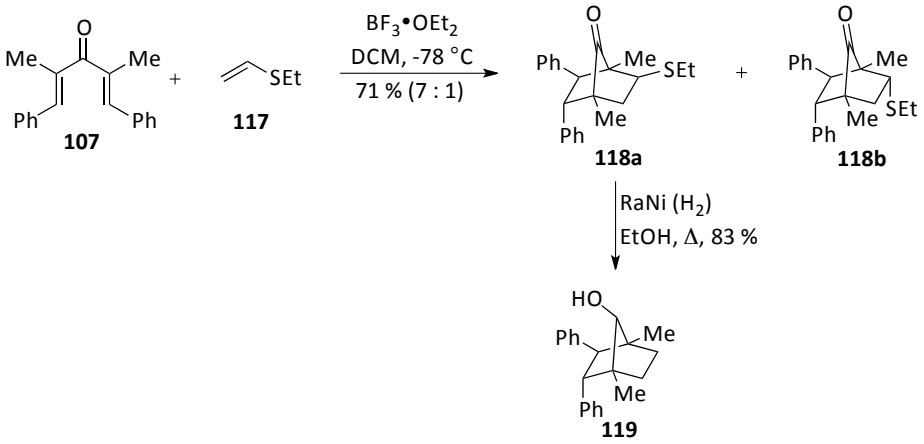
An asymmetric version of this process was disclosed in 2009 utilizing 10 mol % scandium(III) with a pybox ligand.[57] A very limited substrate scope was examined, and enantioselectivities varied widely from racemic to 91 %. The yields were also modest under these conditions.

Burnell has used trifluoroacetic acid as both a promoter and trapping agent in the Nazarov cyclization of allenyl vinyl ketones (Scheme 1.26).[58] Hydrolysis of the intermediate trifluoroacetates under mild conditions gave α-hydroxycyclopentenones **116**.



Scheme 1.26. Trifluoroacetate Interrupted Nazarov Cyclization.

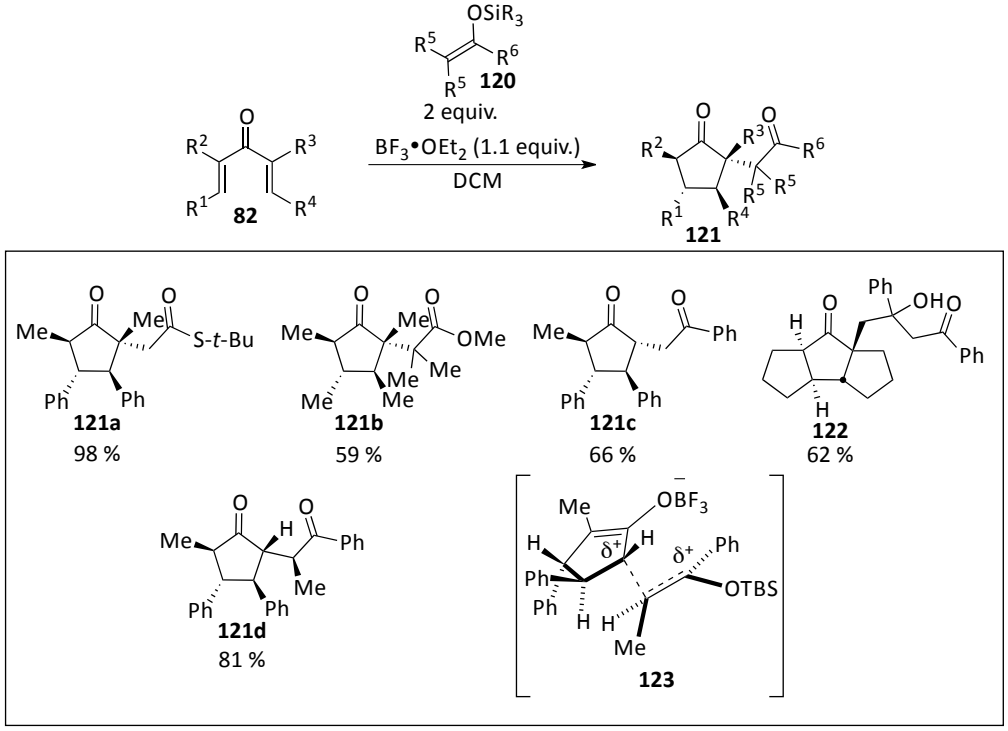
Vinyl sulfides and silyl enol ethers have been added to the alkene class of nucleophiles in the interrupted Nazarov reaction. In 2007, Mahmoud and West utilized vinyl sulfides to perform a [3+2] reaction with the Nazarov intermediate (Scheme 1.27).[59] While substitution on the vinyl sulfide was poorly tolerated and diastereoselectivity was often poor, the thioether of products **118** added versatility to the method. For example, compound **118a** could be reduced with Raney nickel to generate **119**, whereas the interrupted Nazarov cyclization with ethylene would not be feasible.



Scheme 1.27. Use of Vinyl Sulfides for the Interrupted Nazarov Cyclization.

Burnell demonstrated the first example using silyl enol ethers as traps for the Nazarov reaction of (*E*)-4-methyl-1-phenyl-1,4,5-hexatrien-3-one.[60] Wu and West followed this up in 2011.[61] These nucleophiles produce addition products

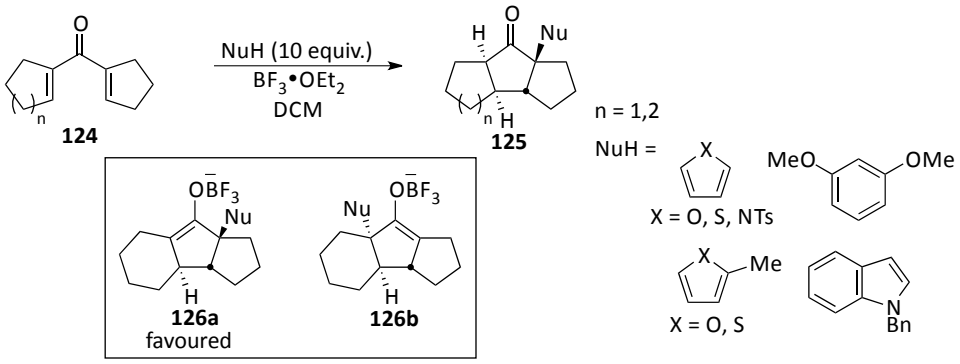
121 rather than [3+2] adducts generated by reaction with allyl silanes and vinyl sulfides, constituting the equivalent of a homologous Mukaiyama aldol reaction (Scheme 1.28). Products **121** are furnished in good yield, and complete diastereoselectivity is observed for the trapping event. Compound **122** is an anomaly, being the product of cascade trapping. Product **121d** was generated from the reaction of an *E*-alkene, generating an exocyclic stereogenic center. Impressively, compound **121d** was formed as a single diastereomer. The authors proposed that transition state **123** accounts for this selectivity, orienting the alkene such that the developing positive charge may receive additional stabilization through proximity to the formal negative charge.



Scheme 1.28. Homologous Mukaiyama Reactions.

Arene trapping works well in intramolecular reactions, as demonstrated by West in 2001.[62] The intermolecular reaction was not observed until 2008. A

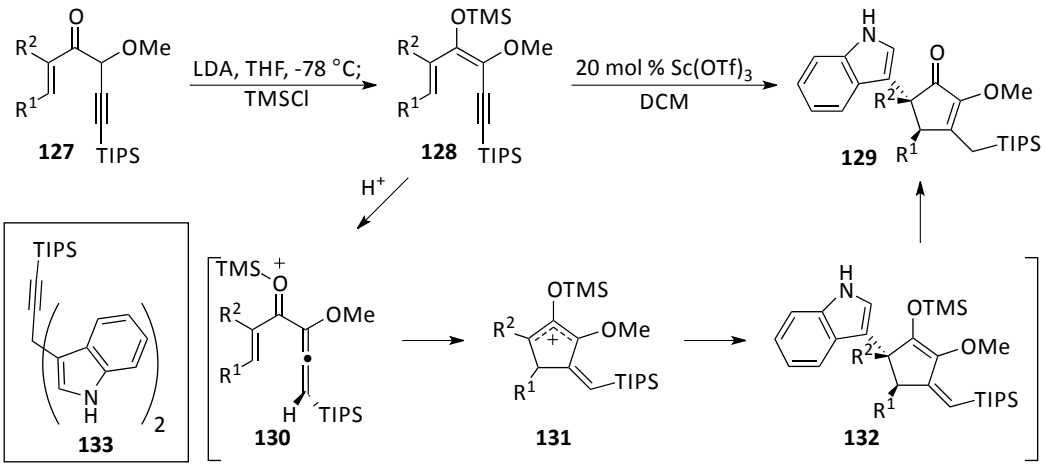
limited scope of dienones which are slow to undergo elimination underwent the reaction with appropriately nucleophilic arenes, including various heteroaromatic compounds (Scheme 1.29).[63] Trapping occurred such that *cis*-fusion of the rings resulted. Good regioselectivity could be observed when n = 2, which is rationalized as occurring to produce the least strained enolate **126a**.



Scheme 1.29. Arene Trapping in Nazarov Reactions of Cyclic Dienones.

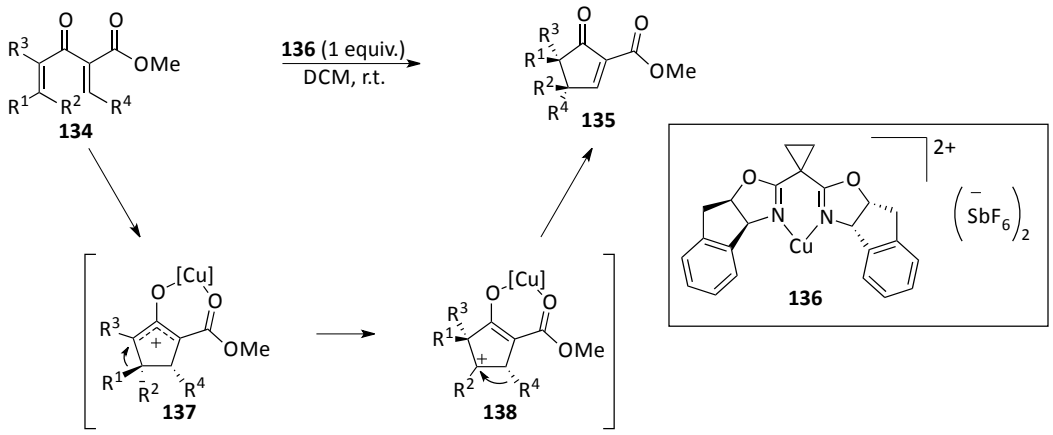
Allenyl vinyl ketones can also be applied to the arene interrupted Nazarov cyclization, as demonstrated by Basak and Tius. Instead of isomerizing the propargyl ketones to the respective allenes, trimethylsilyl enol ethers **128** were utilized as the allenyl vinyl ketone precursors (Scheme 1.30).[64] This was necessitated by the production of side product **133** when the propargyl ketones were employed directly, possibly due to a retro-benzoin condensation of substrates **127** in the presence of the indole. The reaction of compounds **128** is catalyzed by 20 mol % scandium triflate, though Basak and Tius proposed that the actual role of the catalyst is to generate a strong Brønsted acid *in situ* through reaction with adventitious water. Protonation of the substrate appears to occur exclusively at the alkyne to generate the allene (**130**). Nazarov cyclization followed by indole attack gave compounds **129** with complete regio- and diastereoselectivity. In a report by Burnell, the regiochemistry is less certain. The allenes used lacked terminal substitution and so attack of the nucleophile at

the exocyclic alkene was in competition with the expected attack at the α-position.[65] Pyrroles and indoles served as nucleophiles.



Scheme 1.30. Indole Interrupted Nazarov Reaction.

While Wagner-Meerwein shifts have been implicated as a problem with the Nazarov reaction of certain substrate classes, the process can be deliberately evoked. Motoyoshiya demonstrated this under rather harsh reaction conditions in 1991.[66] Frontier and coworkers also embraced this process in an elegant demonstration of diastereo- and chemoselectivity, providing substantial improvement in yield, selectivity, and substrate scope.[67] Using a stoichiometric amount of promoter **136**, dienones **134** could be converted to rearrangement products **135** in high yield with excellent diastereoselectivity (Scheme 1.31). Importantly, spirocycles can be formed when R^1 and R^3 are part of a ring. The products arise from Nazarov cyclization of **134** followed by sequential 1,2-migrations. Because the conrotatory nature of the Nazarov cyclization sets the relative stereochemistry of R^1 and R^4 and the Wagner-Meerwein shifts are suprafacial, the overall process occurs with predictable relative stereochemistry. Additionally, the promoter is chiral and enantioselectivities of 29 to 64 % were observed.



Scheme 1.31. Nazarov Cyclization with Sequential Wagner-Meerwein Shifts.

This sequence is highly chemoselective; in general, the choice of migrating group falls in line nicely with the order aryl > H > *i*-Pr > Me. As an exception to this trend, hydrogen shift is preferred over that of a hindered aryl group, where intermediate **139** becomes highly strained and migration is disfavoured for steric reasons (Figure 1.6).

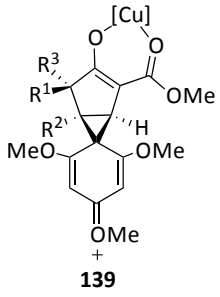
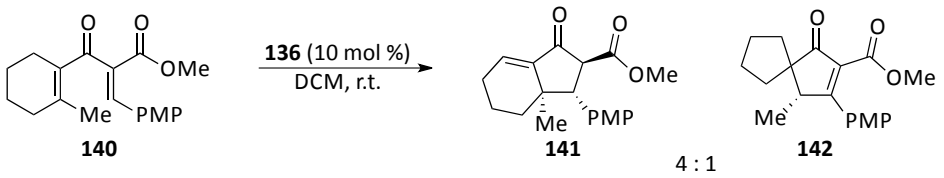


Figure 1.6. Unfavourable Migration of a 2,4,6-Trimethoxyphenyl Group.

When **136** is applied in a catalytic amount, the normal course of the Nazarov cyclization gives exocyclic elimination product **141** in preference to the Wagner-Meerwein rearrangement product (Scheme 1.32). This dichotomy, as well as the observation that only very non-coordinating counterions are tolerated

in the reaction medium, implied that if weak Lewis bases are present, the elimination pathway will be dominant.



Scheme 1.32. Preference for Simple Nazarov Product with Catalytic **136**.

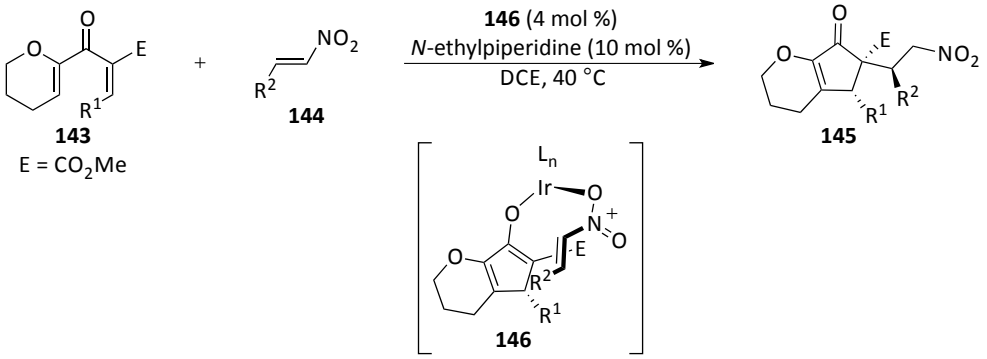
In a later publication, $[(MeCN)_5Cu(SbF_6)_2]$ was used to promote the reaction. This catalyst could be used at 10 mol % loading in combination with 90 mol % NaBArF. It was put forth that the role of the weak Lewis acid is to coordinate to a carbonyl moiety in order to suppress the elimination event.

1.4.2. Reactions Following Nazarov Cyclization

The advances in catalytic conditions for the Nazarov cyclization (Section 1.2) has not only allowed the reaction to proceed under mild conditions and opened up the realm of asymmetric catalysis, but also allowed the development of one-pot protocols for further elaboration of the product cyclopentenones. The catalysts enable mild conditions that will not destroy the reacting partners, and also catalyze the subsequent bond formation of the cyclopentenone with electrophiles. The most popular transformations applied in this way are Michael additions and reaction with electrophilic halogen sources.

Frontier and coworkers were the first to demonstrate a one-pot Nazarov cyclization/Michael addition in 2007. Iridium complex **146** (see Section 1.2.1) catalyzes both the Nazarov cyclization step, and the addition to nitrostyrenes **144** (Scheme 1.33).[68] *N*-Ethylpiperidine is employed as a co-catalyst to facilitate the Michael addition. This high-yielding transformation occurs with good

diastereoselectivity, varying from 8:1 to 15:1. Although the Michael addition proceeds to create a *trans*-relationship between R^1 and the electrophile, addition to either face of the nitroalkene can occur to provide stereoisomers at R^2. The Michael addition is reversible, and so the diastereoselectivity should reflect the thermodynamic stabilities of the products. Overall, three adjacent stereogenic centers (two of which are quaternary) are formed with high diastereocontrol in a single operation.

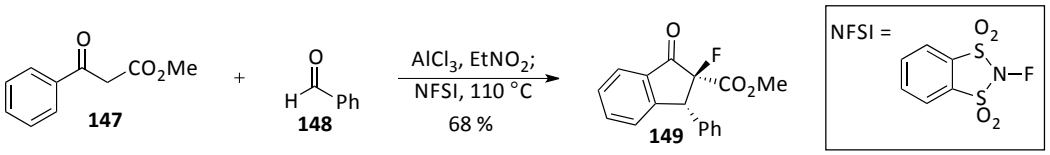


Scheme 1.33. The First Tandem Nazarov Cyclization/Michael Addition.

Itoh and coworkers subsequently reported a similar reaction catalyzed by $FeCl_3 \cdot Al_2O_3$.[69] Pyrroloenones were employed with acrylonitrile and methacrolein, although in these reactions the Michael acceptors could not be added until the Nazarov reaction was complete. Catalyst recycling was achieved when an ionic liquid (1-butyl-3-methylimidazolium triflimide) was used as the solvent.

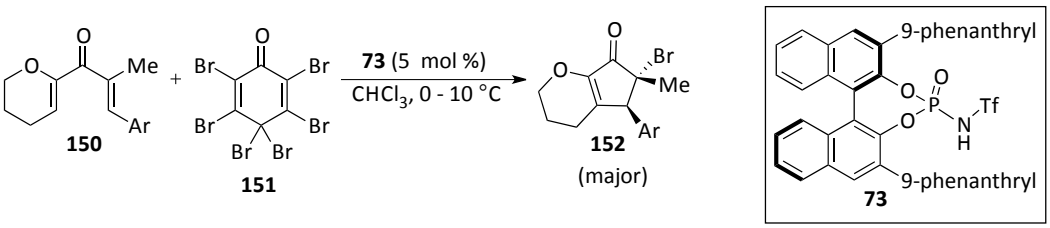
Tandem Nazarov/electrophilic halogenation was introduced by the Ma group in 2007. 10 mol % copper(II) triflate was used to convert aryl enones and electrophilic fluorine source NFSI to 2-fluoroindanones.[70] Iron(II) triflate can also catalyze this process, as demonstrated by Itoh and coworkers.[71] A preference was shown for attack from the less hindered side of the nuclophile to produce a *trans*-relationship between R^2 and the fluorine. Additionally, the step economy of the process can be further streamlined by generating the substrate with an *in situ*

Knoevenagel condensation when an equivalent of aluminum chloride is used in place of the copper catalyst (Scheme 1.34).[72] Diastereoselectivity was excellent, with ratios of > 20 : 1 (*trans*/*cis*) observed in all of the examples examined. This latter process was also useful for chlorination and bromination with *N*-chlorosuccinimide and *N*-bromosuccinimide respectively.[73]



Scheme 1.34. Tandem Knoevenagel/Nazarov/Halogenation of Aryl Ketoesters.

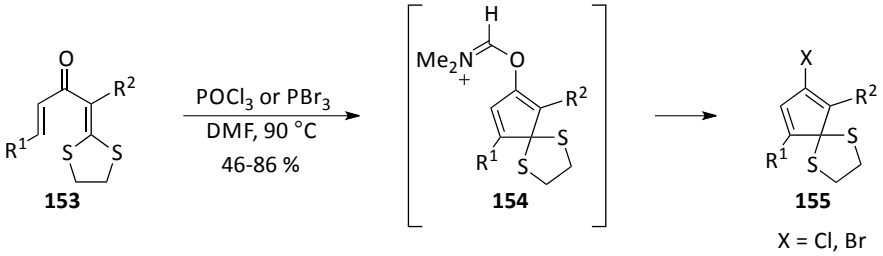
Asymmetric Nazarov/bromination was reported by Rueping and Ieawsuwan in 2011. Five mol % of catalyst **73**, previously employed in their enantioselective Nazarov cyclization (Section 1.3.3), was used to catalyze cyclization of dienones **150** and subsequent bromination with 2,4,4,6-tetrabromocyclohexa-2,5-dienone (Scheme 1.35). α-Bromocyclopentenes **152** were formed in good to excellent enantioselectivity, with moderate to good diastereoselectivity in favour of the *trans* product.



Scheme 1.35. Asymmetric Nazarov/Halogenation Sequence.

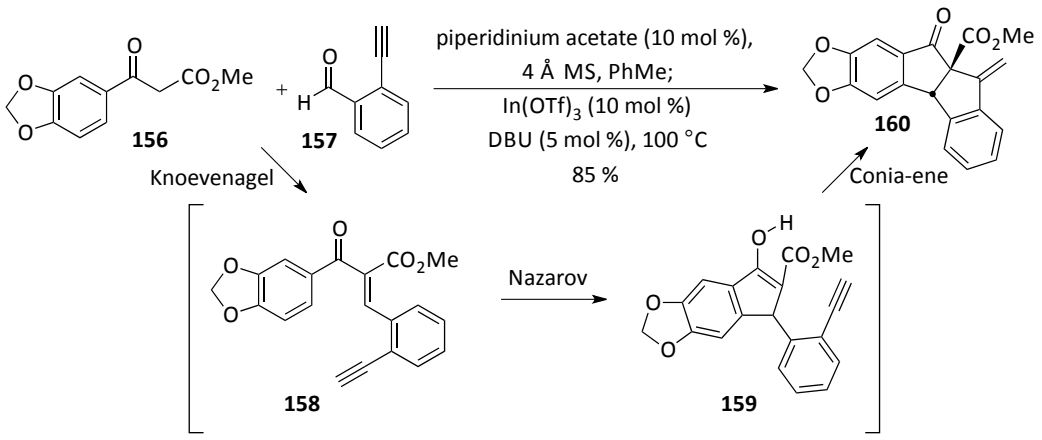
Nucleophilic halogenation in the interrupted Nazarov cyclization[74] and electrophilic halogenation (above) produce α-halocyclopentenones. Halogenation

of the incipient carbonyl is also possible when the Nazarov cyclization is promoted by the Vilsmeier reagent (Scheme 1.36). Under these conditions, presumed intermediate **154** goes on to produce chlorocyclopentadienes **155**.[75] R^1 was limited to aryl substituents, whereas R^2 could be either alkyl or aromatic. When the cyclopentadiene is not 5,5-disubstituted, regioisomeric mixtures can result.



Scheme 1.36. Nazarov/Halovinylation Sequence.

Zhang and coworkers reported a one-pot Knoevenagel/Nazarov/Conia-ene sequence (Scheme 1.37).[76] 5- to 7-membered rings are generated during the Conia-ene stage, and the *E*-alkene is the sole or dominant isomer for substituted alkynes. The yields of the one-pot procedure are generally higher than when the Knoevenagel and Nazarov/Conia-ene steps are done separately.

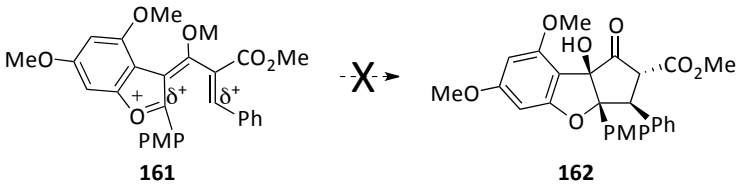


Scheme 1.37. One-Pot Knoevenagel/Nazarov/Conia-ene Reaction.

1.5 Recent Synthetic Applications of the Nazarov Cyclization

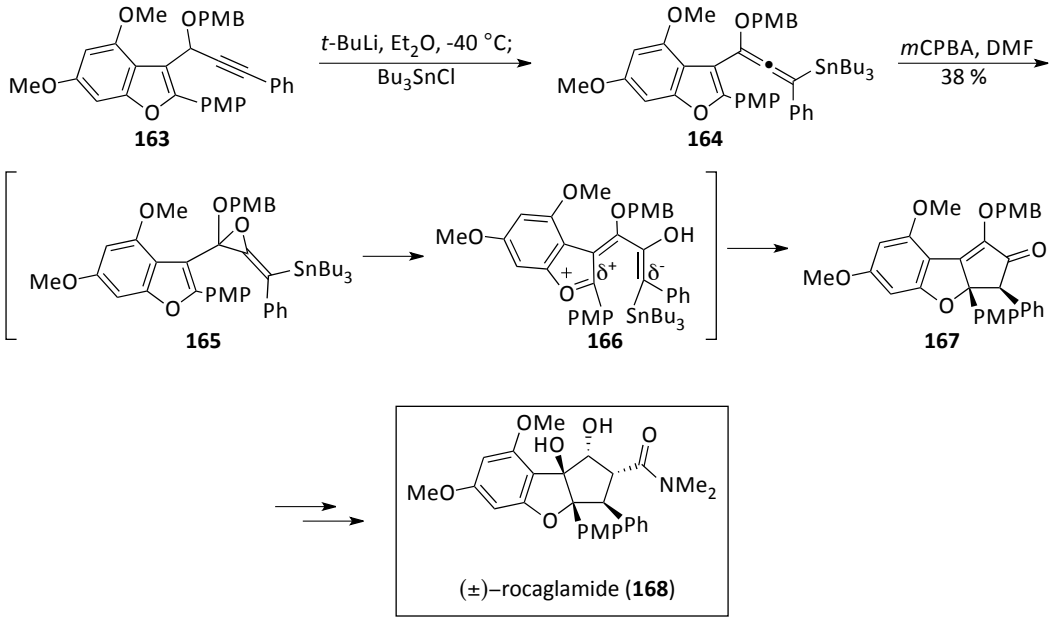
1.5.1. Rocaglamide and Methyl Rocaglate

Rocaglamide (**168**) exhibits a highly oxygenated 1*H*-cyclopenta[*b*]-benzofuran framework, and was isolated from *Aglaia elliptifolia* in 1982.[77] Frontier and coworkers developed a novel Nazarov cyclization of a non-traditional dienone surrogate in their total synthesis of this compound.[78] In an early approach, cyclization of **161** followed by hydroxyl trapping was expected to give hydroxycyclopentanone **162** (Scheme 1.38). Attempts to effect this cyclization failed. This was explained by the cation stabilizing ability of the oxygenated benzofuran, rendering polarization of the putative pentadienyl cation in an unproductive acceptor-acceptor fashion.



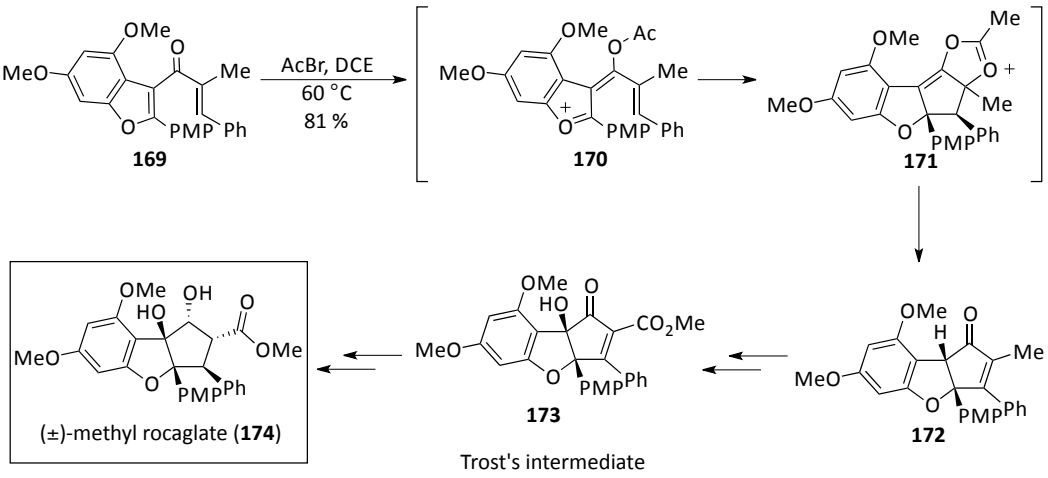
Scheme 1.38. Acceptor-Acceptor Polarization in **161**.

The solution to this problem was to replace the electron-withdrawing ester with an electron-donating group to provide donor-acceptor polarization. Frontier and coworkers envisioned vinyl allene **164** as an unconventional precursor to the 3-oxidopentadienyl cation (Scheme 1.39). Epoxidation of the allene with *m*CPBA yielded labile allene oxide **165**, which upon opening triggered the Nazarov cyclization. Cyclopentenone **167** was produced in 38 % yield over two steps. From this intermediate, the synthesis was completed in seven steps.



Scheme 1.39. Unconventional Nazarov Cyclization in Frontier's Total Synthesis of (±)-Rocaglamide.

In formal synthesis of the closely related compound methyl rocaglate, another interesting Nazarov reaction was developed by Magnus and coworkers.[79] Similar lack of reactivity was proving to be a problem with the Nazarov cyclization of **169**, although there was no ester substituent on the alkene portion. A number of Lewis acids were not capable of evoking the Nazarov reaction; $SnCl_4$, $AlCl_3$, $TiCl_4$, and $Sc(OTf)_3$ were all tried (Scheme 1.40). Finally, acetyl bromide was able to effect the desired transformation in good yield. This was unprecedented in the Nazarov literature; however, it is somewhat reminiscent of Wang and Liu's use of the Vilsmeier reagent.[75] The reaction is thought to proceed through Nazarov cyclization of acetylated pentadienyl cation **170**. The authors propose interesting interrupted Nazarov intermediate **171**, which collapses to the desired cyclopentenone upon elimination.



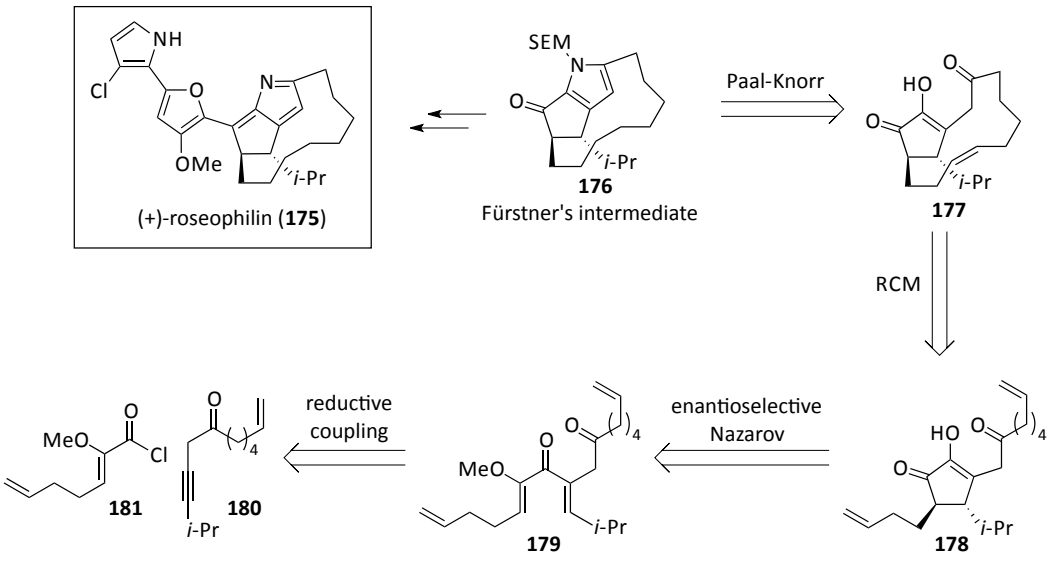
Scheme 1.40. Acetyl Bromide-Mediated Nazarov Cyclization in Magnus' Formal Synthesis of (±)-Methyl Rocaglate.

1.5.2. Roseophilin

The Nazarov cyclization has been used in the synthesis of the *ansa*-bridged macrocycle roseophilin in numerous total and formal syntheses.[25,80]

Recently, the Flynn group reported a formal synthesis of (+)-roseophilin using the chiral Brønsted acid catalyst developed by Rueping. This represents the first example where a catalytic asymmetric Nazarov cyclization is used to control the absolute stereochemistry in the synthesis of a natural product.

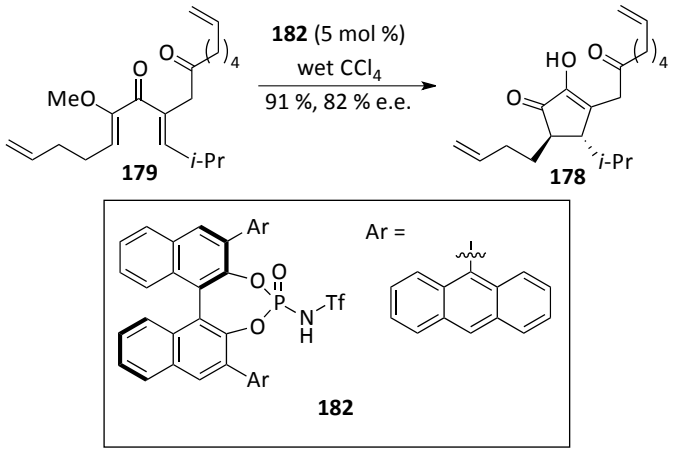
Kerr and Flynn targeted Fürstner's intermediate **176** (Scheme 1.41). The pyrrole would be installed by the Paal-Knorr pyrrole synthesis, and the 13-membered ring would be formed using ring-closing metathesis. An enantioselective Nazarov cyclization would set the absolute stereochemistry and provide all of the necessary functionality for the pyrrole formation later. The dienone was constructed by a reductive coupling of acid chloride **181** with alkyne **180**; this methodology was previously utilized by Flynn and coworkers for the synthesis of related dienones.[29]



Scheme 1.41. Key Steps in Flynn's Formal Synthesis of (+)-Roseophilin.

The phosphoramide catalyst that was used for the Nazarov key step was slightly modified from that used by Rueping,[36] with anthracenyl groups appended to the BINOL moiety. Wet carbon tetrachloride as solvent produced higher

enantioselectivity than chloroform, giving cyclopentenone **178** in 91 % yield and 82 % enantiomeric excess (Scheme 1.42).



Scheme 1.42. Asymmetric Nazarov Cyclization of **179**.

1.6 Conclusions

Current activity in the Nazarov field has focused on developing better catalysts, asymmetric variants, increase in synthetic efficiency, and applications to complex targets.

The most obvious limitation for the catalytic reactions (asymmetric included) is the narrow substrate scope, where polarization in the substrates is often a requirement for a successful reaction. Although the catalysts are not general, polarized substrates yield functionalized cyclopentenones adorned with useful synthetic handles.

The Nazarov reaction is suitable for application to enhanced step-economy in interrupted Nazarov cyclizations and one-pot protocols. Interrupted Nazarov reactions in particular take advantage of the stereospecific nature of the electrocyclization, and the versatility of these reactions will undoubtedly lead to

applications in the synthesis of complex targets. Efforts to increase the products available from these types of processes are ongoing.

Another recent pursuit in Nazarov chemistry is use of non-traditional substrates for the Nazarov reaction in efforts to overcome limitations imposed by dienone substrates. This is the topic of Chapter 2.

1.7 References

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Chapter 2

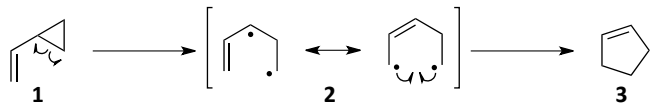
Nazarov Cyclization of 2-Alkoxy-1,1-dichloro-2-vinylcyclopropanes

2.1 Sequential Ring Opening-Annulation Reactions of Vinylcyclopropanes

Halogenated and non-halogenated vinylcyclopropanes are strained molecules that provide access to a number of cyclic products. The angle strain energy associated with the cyclopropane ring is higher than any other cycloalkane at 27.5 kcalmol^{-1}, with cyclobutane a close second at 26.3 kcalmol^{-1} and the larger rings substantially lower.[1] The consequence of this ring strain is that the C-C bonds can be cleaved more easily than would be expected in an equivalent linear structure. The C-C bonds of cyclopropane have considerable π-character and can participate in conjugation with appropriate substituents. This is apparent in vinylcyclopropane, where the vinyl group is oriented orthogonal to the cyclopropane ring. The bond lengths of the cyclopropane are distorted, with the bonds proximal to the vinyl group lengthened to 1.520 Å, as compared to the distal C-C bond at 1.510 Å.[2]

2.1.1. Thermal Reactions of Vinylcyclopropanes

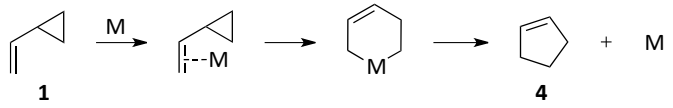
Vinylcyclopropanes can be transformed into cyclopentenes when subjected to temperatures in the range of 200-350 °C.[3] This reaction is thought to proceed *via* a radical mechanism (Scheme 2.1). Homolytic cleavage of the strained cyclopropane C-C bond yields biradical **2**; subsequent bond formation at the termini of the pentenyl biradical gives the cyclopentene. Interestingly, although the process requires a great deal of energy to initiate the homolytic cleavage, the reaction has been calculated to be exothermic by 21.7 kcalmol^{-1} for the parent structure.[4]



Scheme 2.1. Thermal Vinylcyclopropane-Cyclopentene Rearrangement.

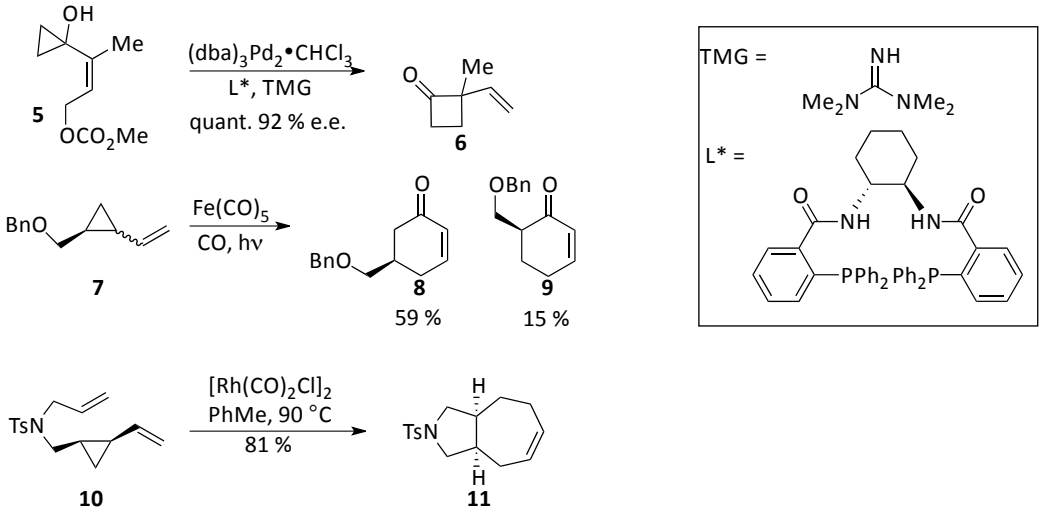
2.1.2. Metal-Catalyzed Reactions of Vinylcyclopropanes

The vinylcyclopropane–cyclopentene rearrangement can be performed at lower temperatures utilizing catalysis by palladium, platinum, nickel, rhodium or ruthenium.[3] When donor-acceptor cyclopropanes are used, Lewis acids suffice to promote the rearrangement.[3c] A general mechanism for the metal-catalyzed cycloisomerization is depicted in Scheme 2.2.



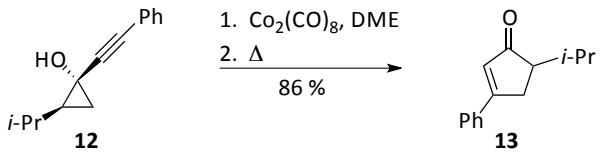
Scheme 2.2. Metal-catalyzed Vinylcyclopropane-Cyclopentene Rearrangement.

A diversity of other ring sizes is also accessible from the vinylcyclopropane system. Examples include the ring expansion of vinylcyclopropanols to cyclobutanones under palladium catalysis [5] and the generation of cyclohexenones *via* a formal [5+1] reaction between the vinylcyclopropane, which provides the C-5 component, and carbon monoxide.[6] Reaction of vinylcyclopropanes with tethered alkenes and alkynes, as well as intermolecular variations, provides access to cycloheptenes,[7] cycloheptadienes,[8] and cycloheptenones.[9] Representatives of these reaction types are given in Scheme 2.3.



Scheme 2.3. Metal-Catalyzed Reactions of Vinylcyclopropanes.

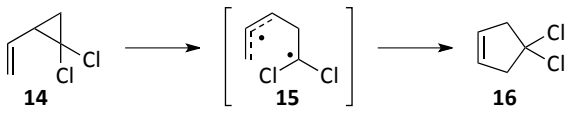
Additionally, 2-cyclopentenones can be accessed from alkynylcyclopropanols. Coordination of the alkyne moiety with $Co_2(CO)_8$, results in the generation of a hexacarbonyldicobalt complex, which rearranges under thermal conditions to give the desired compounds. (Scheme 2.4).[10]



Scheme 2.4. Formation of a 2-Cyclopentenone from Alkynylcyclopropanol **12**.

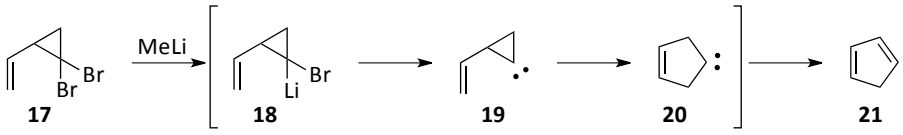
2.1.3. Reactions of *gem*-Dihalovinylcyclopropanes

1,1-Dihalo-2-vinylcyclopropanes are excellent substrates for the vinylcyclopropane-cyclopentene rearrangement (Scheme 2.5). The rearrangement of 1,1-dichloro-2-vinylcyclopropane (**14**) occurs at a lower temperature, 200 ºC,[11] than that required for unsubstituted vinylcyclopropane (340 ºC).[12] This is due to the higher radical-stabilizing ability of the *gem*-dichloro-substituted carbon relative to the parent structure.[13]



Scheme 2.5. Vinylcyclopropane-cyclopentene Rearrangement of 1,1-Dichloro-2-vinylcyclopropane.

Furthermore, cyclopropylcarbenes (**19**), which can be formed under lithium-halogen exchange conditions, undergo the Skattebøl rearrangement to afford cyclopentadienes (Scheme 2.6).[14]



Scheme 2.6. The Skattebøl Rearrangement.

gem-Dihalocyclopropanes are also prone to thermal or Lewis acid assisted dehalogenation with concomitant 2π-disrotatory electrocyclic ring opening[15,16] to form reactive 2-haloallyl cations (Figure 2.1). The rotation sense of the ring opening is governed by substituent size, where the larger substituent (R_L) will prefer outward rotation, such that steric repulsion between the internally rotating substituents will be minimal.[17] The halogen which is initially removed is also dictated by this preference, as the electron density of the breaking cyclopropane bond provides anchimeric assistance through interaction with the σ* of the C-X bond.[15a-c, 18] Thus, outward rotation of R_L will occur with the departure of X_A.

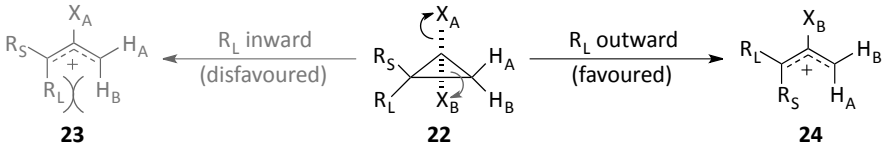


Figure 2.1. Ring Opening of *gem*-Dihalocyclopropanes.

The 2-haloallyl cation generated from **25** can either undergo elimination to yield a 1,3-diene (**26**) or be attacked by a variety of internal nucleophiles, such as tethered alkenes, arenes, carboxylates, and carbamates (Figure 2.2).[19] External nucleophiles, including halides, acetates, water, phenols, alcohols, cyanate, amines, arenes and thiolates are also competent.

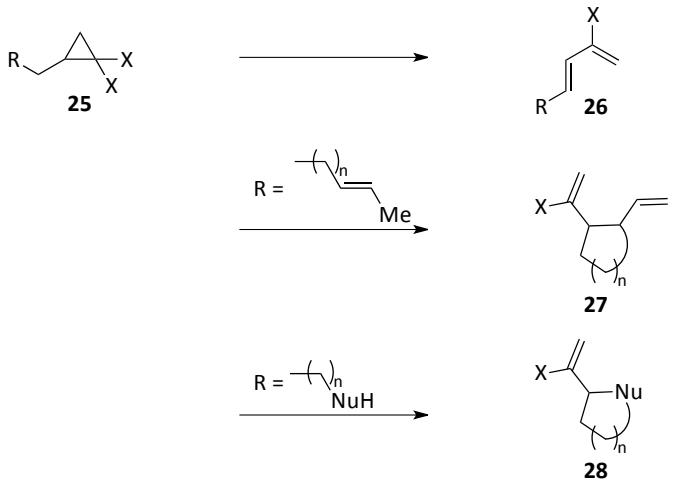
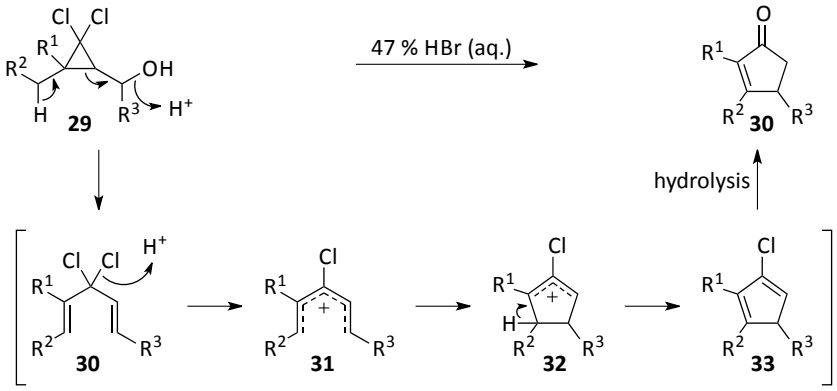


Figure 2.2. Reactions of *gem*-Dihalocyclopropanes.

Hiyama and coworkers have shown that dichlorocyclopropylalcohols (**29**) can be converted to cyclopentenones (**30**) on exposure to acid (Scheme 2.7).[20] The mechanism proposed by the authors involves conjugate dehydration followed by chloride departure to form a 3-chloropentenyl cation (**31**), which undergoes 4π-electrocyclization to give chlorocyclopentenyl cation **32**. Elimination, followed by hydrolysis of vinyl chloride **33,** provides the observed 2-cyclopentenone **30**.



Scheme 2.7. Conversion of Cyclopropylcarbinols to 2-Cyclopentenones.

2.2 Non-Traditional Substrates for the Nazarov Reaction: 1,1-Dichloro-2-siloxy-2-vinylcyclopropanes

The Nazarov reaction traditionally involves the 4π-electrocyclic closure of a pentadienyl cation generated through activation of a divinyl ketone (Figure 2.3).[21] There are, however, some limitations involved with the use of divinyl ketones as pentadienyl cation precursors. For example, the need to activate a carbonyl causes problems in both catalysis and reaction scope. Dienones often require strong acids as promoters for the cyclization, and this can lead to decomposition of acid-sensitive substrates. Also, as discussed in Chapter 1, catalytic Nazarov cyclizations are often limited to dienones with two Lewis basic sites, restricting the reaction scope significantly. Additionally, as both the substrate and product of the reaction are ketones, a catalyst must bind to the carbonyl of the dienone in preference to that of the cyclopentenone to avoid product inhibition. This is a significant challenge in practice, and often results in high catalyst loadings and slow reactions. For these reasons, new modes of activation are desirable and redesigned dienone surrogates must be examined.

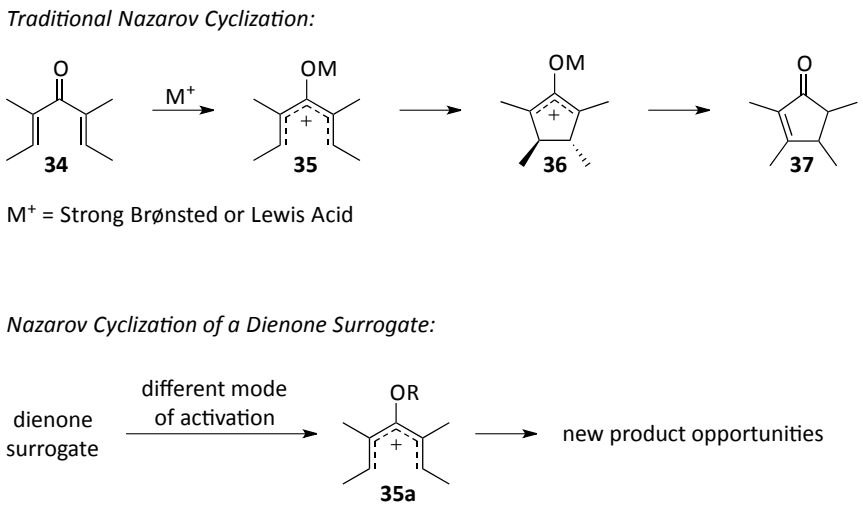
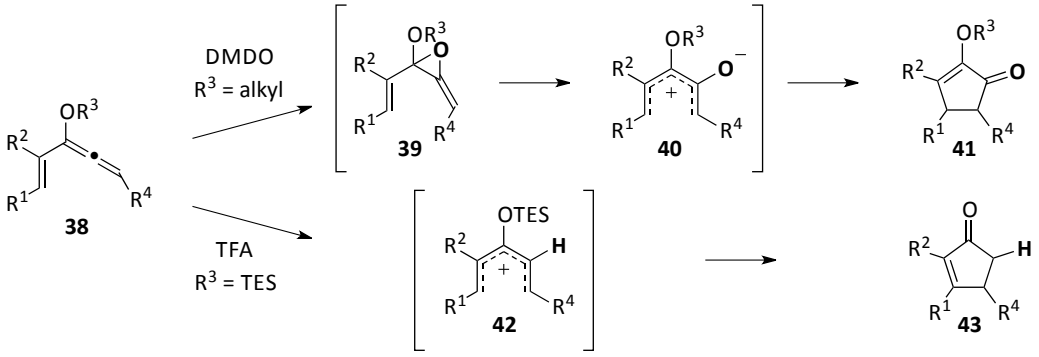


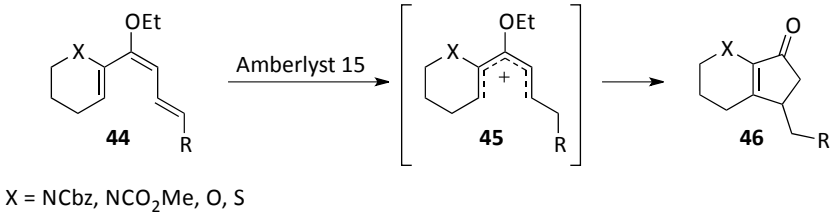
Figure 2.3. Dienone Surrogates for the Nazarov Cyclization.

In a recent trend, alternate substrates that generate the 3-oxo-pentadienyl cation directly, rather than acting as precursors to divinylketones, have started to emerge. An advantage to developing these new types of substrates is the potential to use activating agents other than strong acids, as exemplified by the Frontier group's work on activation of vinyl alkoxyallenes with DMDO (Scheme 2.8).[22] In this variant of the Nazarov cyclization, the activation step targets the allene and also produces a carbon-oxygen bond. Wu and West have investigated the activation of vinyl siloxyallenes by trifluoroacetic acid.[23]



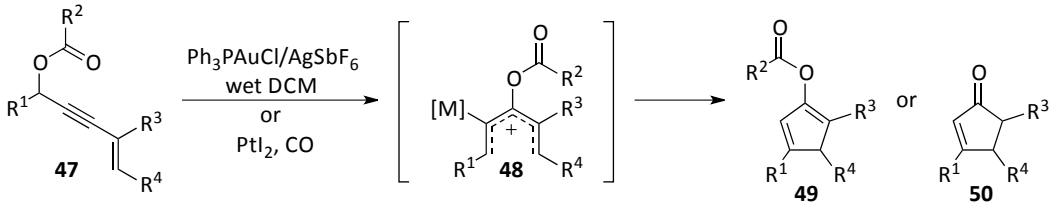
Scheme 2.8. Vinylallenes as Substrates for the Nazarov Reaction.

Occhiato *et al*. have shown that the 3-oxopentadienyl cation can be generated by protonation of triene **44** with the acidic resin Amberlyst 15 (Scheme 2.9).[24]



Scheme 2.9. Trienes as Substrates for the Nazarov Reaction.

Gold- or platinum-catalyzed [3,3]-rearrangement/Nazarov cyclization sequences employing vinyl or aryl propargyl acetates respectively as Nazarov substrates have also been reported (Scheme 2.10).[25] Notably, substrates **47** lead to the less-substituted cyclopentenone alkene under these conditions because the alkene is formed at the site of the gold-substituted carbon.



Scheme 2.10. [3,3]-Rearrangement/Nazarov Cascade.

2.2.1. Nazarov Cyclization of 1,1-Dichloro-2-siloxy-2-vinylcyclopropanes

While vinylcyclopropanes had long been recognized as precursors of cyclopentenes *via* thermal rearrangement (*vide infra*), their suitability as unconventional Nazarov substrates was only recently examined by Grant and West. They envisioned the tandem electrocyclic cyclopropane-opening/Nazarov cyclization sequence depicted in Figure 2.4.

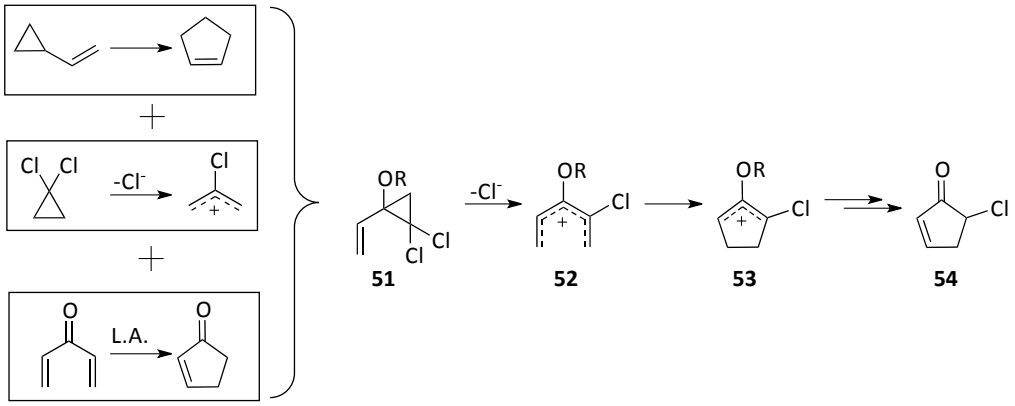
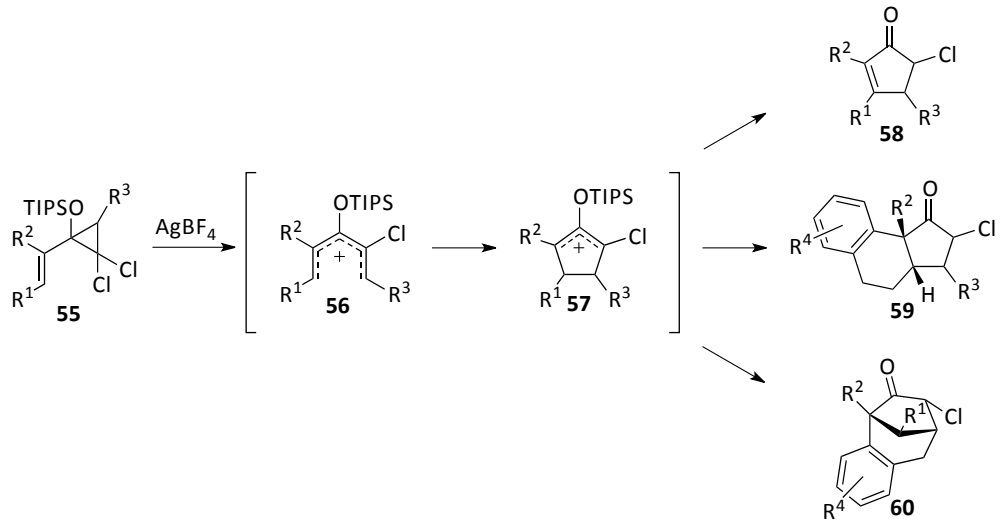


Figure 2.4. Conceptualization of Sequential Ring-Opening/Nazarov Cyclization Process.

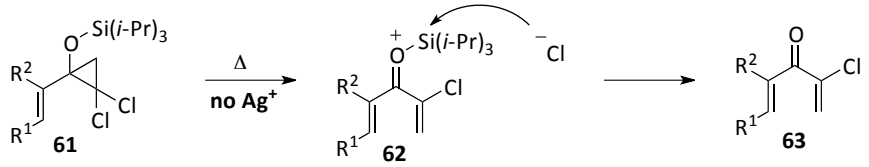
Grant and West have demonstrated that when the vinyl-bearing cyclopropane carbon is substituted with a siloxy group (R = TIPS in Figure 2.4), a cyclopentenone is formed on exposure to silver fluoroborate.[26,27] Silver(I)-assisted departure of the chloride, accompanied by electrocyclic ring opening of the cyclopropane, and subsequent cyclization of the resultant 3-oxidopentadienyl cation leads to the cyclopentenyl cation. From there, either elimination, giving rise to a 2-cyclopentenone **58**, or intramolecular electrophilic aromatic substitution, generating products **59** and **60**, are possible (Scheme 2.11). Notably, the products of these reactions contain either a vinyl chloride, which could be used in coupling reactions,[28] or an α-chloroketone, amenable to substitution chemistry.[29] Furthermore, silver fluoroborate is a mild alternative to a strong acid, and thus development of this chemistry may prove fruitful in expanding the scope of Nazarov and interrupted-Nazarov chemistry.



Scheme 2.11. Nazarov Chemistry of 1,1-Dichloro-2-vinyl-2-siloxycyclopropanes.

2.3 Nazarov Cyclization of 1-Alkoxy-1,1-dichloro-2-vinylcyclopropanes

The precedent for electrocyclic ring opening of dichlorocyclopropanes under thermal conditions, without the need for a Lewis acid, is an attractive strategy for a reagent-free version of the sequential ring-opening/Nazarov cyclization. When siloxy cyclopropanes (**61**) are used, this reaction is not feasible. This is because the chloride ions generated are not sequestered as silver chloride, and can participate in premature desilylation of the 3-siloxypentadienyl cation **62** (Scheme 2.12). In this case the observed product is no longer the desired cyclopentenone, but rather dienone **63**. In light of this result, it can be postulated that if the substituent on the oxygen were less prone to removal by nucleophiles this problem could be alleviated, leading to reagent-free formation of cyclopentenones.



Scheme 2.12. Premature Desilylation.

As dienone substrates preclude substitution on the oxygen atom, interrupted Nazarov cyclizations using these traditional substrates with internal nucleophiles have been limited to tethers α or β to the oxygen-bearing carbon (Figure 2.5).[30] In contrast, cyclopropanols are amenable to substitution on the oxygen atom. This opens up potential for an unprecedented mode of trapping, with the nucleophile being tethered through the oxygen.

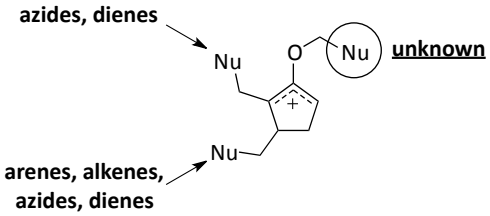


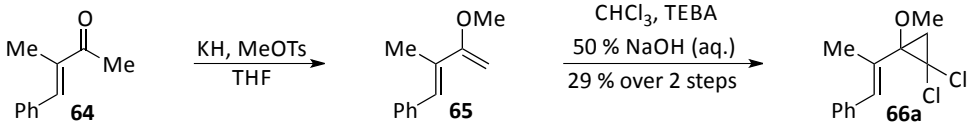
Figure 2.5. Modes of Interrupted Nazarov.

The goal of this project was to find solutions to the above-mentioned limitations associated with the ring-opening/Nazarov cyclization of siloxycyclopropanes and the interrupted Nazarov reaction. Redesign of the dichlorocyclopropane substrates to include an alkoxy group, rather than siloxy, could allow nucleophiles to be tethered through the oxygen. Additionally, we believed that the use of a less labile substituent on the oxygen of the cyclopropanol, such as an alkyl ether, could conceivably produce a successful reagent-free ring-opening/Nazarov cyclization sequence. We postulated that 2-alkoxy-1,1-dichloro-2-vinylcyclopropanes should undergo an analogous reaction

to what had been observed with the siloxy substrates; however, the substitution of the alkyl ether for the silyl ether could have a significant impact on the reaction conditions that would be required.

2.3.1. Initial Findings and Optimization

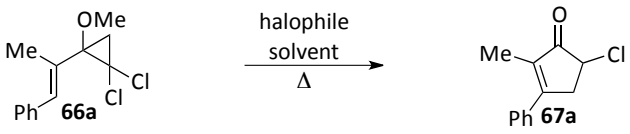
In the study prior to this work, the 1,1-dichloro-2-siloxy-2-vinylcyclopropane substrates were prepared from the corresponding enones.[26,27] An analogous synthesis was possible for the methoxy-substituted compound **66a** (Scheme 2.13). Deprotonation of 3-methyl-4-phenyl-3-buten-2-one (**64**) with potassium hydride in the presence of methyl tosylate provided methyl enol ether **65**. Cyclopropanation under phase transfer conditions[31] occurred with complete regioselectivity for the more electron rich double bond, and produced methoxycyclopropane **66a** in 29 % yield over two steps. This substrate was used in our initial optimization studies.



Scheme 2.13. Preparation of Cyclopropane **66a**.

The Nazarov reactions of the siloxycyclopropanes initially investigated by Grant and West could be accomplished using one and a half equivalents of silver fluoroborate in dichloromethane at room temperature. Unfortunately, the alkoxy analogues were unreactive under those conditions. A screening of reaction solvents was performed using methoxycyclopropane **66a** as the test substrate. It was found that although **66a** was not fully consumed, the reaction occurred in

optimal yield when the halophile silver triflimide was used in 1,2-dichloroethane at reflux. All reactions were run with a substrate concentration of 0.05 M.



solvent	halophile (equivalents)	time	yield (%) (**66a** : **67a**)
DCE	$AlCl_3$ (1)	3 d	not observed
DCE	$FeCl_3$ (1)	3 d	not observed
DCE	---	3 d	1 : 0
DCE	$AgBF_4$ (1)	3 d	39 (1:1.4)
MeCN	$AgBF_4$ (1)	5 d	--- (2.2:1)
DCE	$AgNTf_2$ (1)	3 d	74 (1:6.3)
MeCN	$AgNTf_2$ (1)	5 d	--- (1.9:1)
DCB	$AgNTf_2$ (2)	2 h	28
DCE	$AgNTf_2$ (1.1)	6 d	61
DCE	$AgNTf_2$ (1.5)	1 d	58
DCE	$AgNTf_2$ (2)	1 d	65

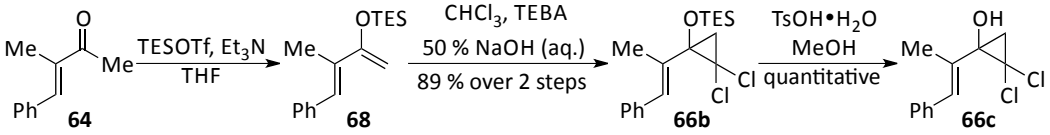
Table 2.1. Optimization of Ring Opening/Nazarov Cyclization of Alkoxycyclopropanes.

Interestingly, acetonitrile was not a particularly good solvent for the reaction, whereas with the analogous siloxy compounds it was found to be the solvent of choice.[32] This may be due to a higher barrier for ring-opening in the alkoxycyclopropanes. A solvent with a lower coordinating ability would allow

the silver(I) to be more electrophilic and more readily assist in chloride departure. In 1,2-dichlorobenzene (b.p. 180 °C) with two equivalents of silver triflimide, the starting material was consumed in only two hours. At this temperature, however, a significant amount of decomposition diminished the overall product yield. Changing the silver(I) source from silver tetrafluoroborate to silver triflimide was also beneficial in a practical sense, as it is much less hygroscopic and therefore is much easier to handle.

2.3.2. Preparation of 2-Alkoxy-1,1-dichloro-2-vinylcyclopropanes

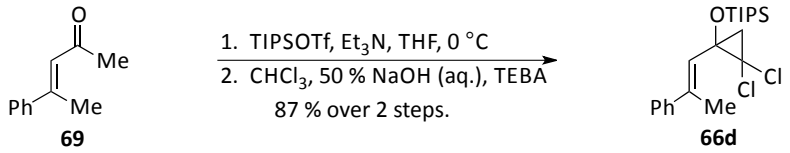
It was of interest to examine the effect of a simple alcohol substitution on the cyclopropane ring, thus cyclopropanol **66c** was prepared from enone **64** (Scheme 2.14). In analogous manner to the siloxycyclopropanes of the previous study,[26,27] enone **64** was converted to triethylsilyl enol ether **68**, and subsequently cyclopropanated to provide vinylcyclopropane **66b** in 89 % yield over the two steps. The triethylsilyl group was removed in quantitative yield by exposure of **66b** to *p*-toluenesulfonic acid monohydrate in methanol. Fortunately, the deprotection reaction was quite clean; cyclopropanol **66c** was rather labile and not amenable to purification.



Scheme 2.14. Preparation of Cyclopropanol **66c**.

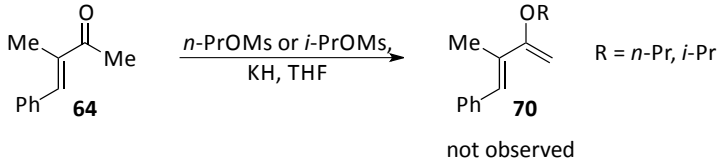
Siloxycyclopropane **66d** was used to test whether the Nazarov process would tolerate disubstitution at the terminus of the alkene. It was prepared from

known enone **69**, which was converted to a silyl enol ether and then cyclopropanated to provide **66d** in 87 % yield over two steps (Scheme 2.15).



Scheme 2.15. Preparation of Cyclopropane **66d**.

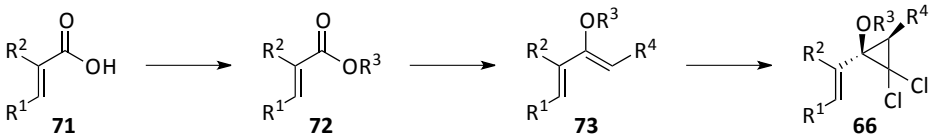
Effort was then put into producing substrates with different alkyl groups on the oxygen to examine the effect of this variation on the Nazarov cyclization. Unfortunately, the conditions that had been used to prepare methoxy enol ether **65** could not be extended to formation of propyl and isopropyl enol ethers **70**. Enone **64** was recovered unchanged from these attempts (Scheme 2.16). A more robust route for synthesis of these compounds was needed, and is described below.



Scheme 2.16. Failed Enol Ether Formation from **64**.

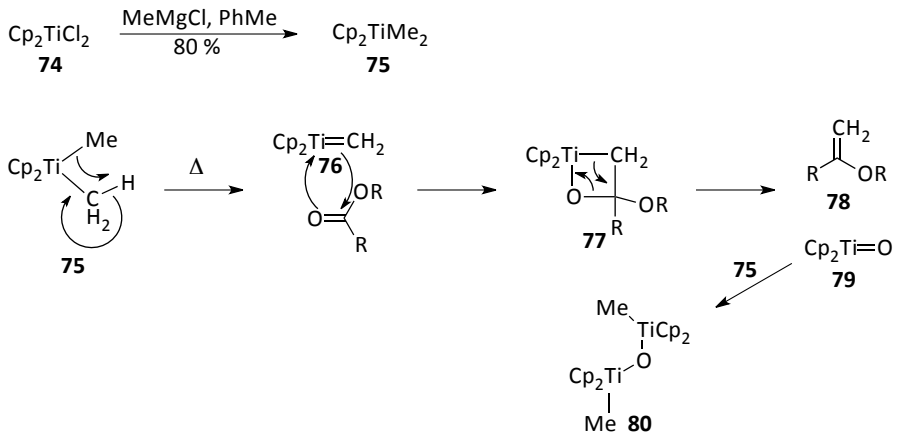
Although common Wittig-type reagents typically do not react with esters, the more nucleophilic titanium analogs can easily convert esters to enol ethers by methylenation or alkylidenation.[33] A general route to 2-alkoxy-1,1-dichloro-2-vinylcyclopropanes is given in Scheme 2.17. It was envisioned that R^1 and R^2 would be introduced in the form of readily available α,β-unsaturated carboxylic acids **71**, which would be esterified to add R^3. Methylenation or alkylidenation

would incorporate R^4, and subsequent cyclopropanation would complete the substrate synthesis.



Scheme 2.17. General Synthetic Route to 2-Alkoxy-1,1-dichloro-2-vinylcyclopropanes.

The Petasis reagent, dimethyltitanocene (**75**), is easily synthesized from titanocene dichloride by Payack's procedure (Scheme 2.18),[34] and can be stored in the refrigerator as a standardized solution for a few months. On heating, α-elimination of methane yields titanium methylidene **76**. A formal [2+2] reaction between the ester and the titanium carbenoid generates titanocycle **77**. This is followed by a retro [2+2], releasing enol ether **78** and byproduct **79**, which proceeds to form dimer **80** with a second equivalent of dimethyltitanocene.[35] The substrate scope for the Petasis reagent encompasses an impressive variety of carbonyls, including acid anhydrides, thioesters, and imides.[36] Additionally, this titanium methylidene had previously been utilized for the synthesis of 2-alkoxy-1,3-butadienes,[36,37] and so this methylenation approach appeared to be an excellent candidate for our needs.

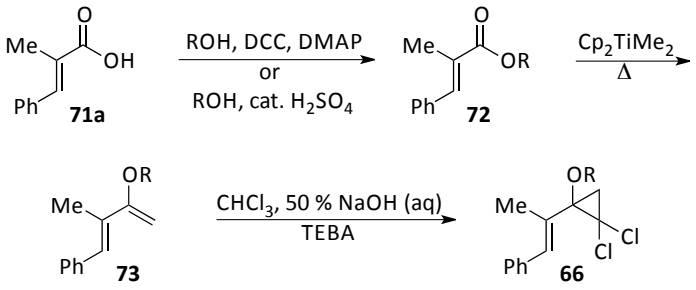


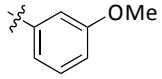
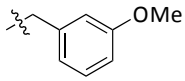
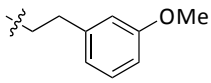
Scheme 2.18. Synthesis of the Petasis Reagent and Mechanism of Methylenation.

Cyclopropanes **66e**-**j** were synthesized in order to examine the effect of the oxygen substituent. Compounds **66h**-**j** held additional value, as they were used to examine the possibility of an interrupted Nazarov reaction. α-Methylcinnamic acid (**71a**) was converted to cyclopropanes **66e**-**j** in the following three-step sequence (Table 2.2). The *n*-propyl and isopropyl esters, **72a** and **72b,** were synthesized by Fisher esterification in 92 and 91 % yield respectively. Methylenation with the Petasis reagent produced the 2-alkoxy-1,3,-butadienes **73a** and **73b** in good yield, and cyclopropanation with dichlorocarbene generated **66e** in 91 % yield and **66f** in 81 %. It is important to note that if the cyclopropanation time is extended past seven minutes, the yield of the reaction decreases substantially. Therefore, each enol ether was first subjected to a small-scale version of the reaction that was closely monitored by TLC (every minute) to determine what reaction time was necessary to consume the enol ether, but not begin to destroy the desired dichlorocyclopropane product.

Esters **72c**-**f** were obtained by *N*,*N*′-dicyclohexylcarbodiimide-mediated coupling of **71a** with the requisite alcohols in good yields. The esters were then subjected to dimethyltitanocene, with heating, to form the corresponding 2-alkoxy-1,3-butadienes. Purification by flash column chromatography using basic

alumina (Brockman activity III), however, did not remove all of the titanocene-containing contaminants, as was evident by ^{1}H NMR, and so accurate yields for this step are unavailable. Cyclopropanation of these compounds went smoothly, and cyclopropanes **66g-j** were acquired in 29 to 45 % yield from the respective esters.

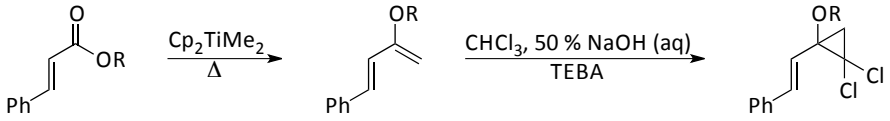


entry	R	ester (yield, %)	enol ether (yield, %)	cyclopropane (yield, %)
1	*n*-Pr	**72a** (92)[a]	**73a** (85)	**66e** (91)
2	*i*-Pr	**72b** (91)[a]	**73b** (92)	**66f** (81)
3	*t*-Bu	**72c** (81)	73c	**66g** (29 over 2 steps)
4		**72d** (74)	73d	**66h** (45 over 2 steps)
5		**72e** (73)	73e	**66i** (41 over 2 steps)
6		**72f** (56)	73f	**66j** (38 over 2 steps)

[a]These esters were prepared by Fischer esterification (see experimental section). The others were synthesized using DCC-mediated coupling.

Table 2.2. Synthesis of *gem*-Dichlorocyclopropanes **66e** to **66j**.

To ascertain the importance of the α-methyl substituent on the vinyl group, four cinnamic acid-derived dichlorocyclopropanes were synthesized. Cinnamic acid (**71b**) was converted to 3-methoxybenzylcinnamate (**72j**) in 86 % by the DCC-mediated coupling outlined in Table 2.2. The other cinnamate esters were either known in the literature[38] or commercially available. In the same manner as for the previous substrates, the esters were methylenated and cyclopropanated to obtain dichlorocyclopropanes **66g-j** (Table 2.3).



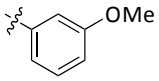
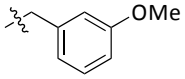
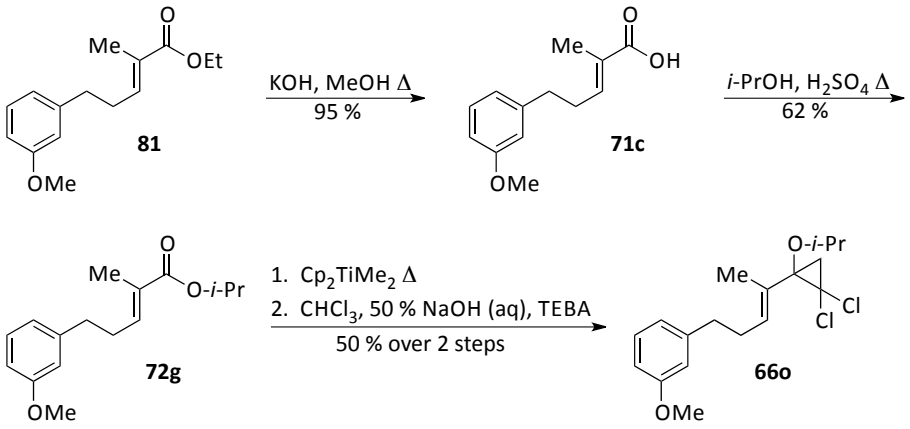
entry	R	ester	cyclopropane (yield over 2 steps, %)
1	*n*-Pr	**72g**	**66k** (45)
2	Bn	**72h**	**66l** (70)
3		**72i**	**66m** (23)
4		**72j**	**66n** (23)

Table 2.3. Synthesis of Cyclopropanes **66k**-**n**.

In order to provide a control substrate to test the interrupted Nazarov reaction in analogy to that of the siloxycyclopropanes, compound **66o** was also desired. To obtain **66o**, known ester **81**[39] was first saponified with potassium hydroxide in methanol to provide carboxylic acid **71c**. Subsequent esterification of **71c** with isopropanol, and application of the above described methylenation/cyclopropanation sequence gave **66o** in 50 % yield over two steps (Scheme 2.19).

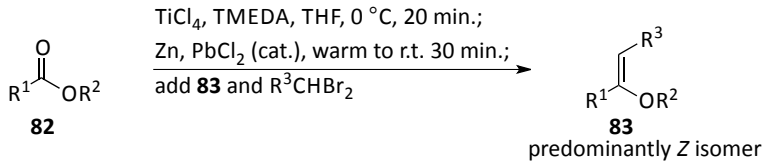


Scheme 2.19. Preparation of Cyclopropane **66o**.

Although suitable for a number of desired substrates, there are three major drawbacks associated with dialkyltitanocene reagents. The reagents will undergo β-hydride elimination if possible, making them generally unsuitable for alkylidenation reactions. Also, the titanium methylidene can react with the enol ether product. This can be circumvented by employing a sacrificial ester that reacts with the titanium methylidene more slowly than the substrate, but more rapidly than the product.[40] Finally, because the reaction is performed in the solvent the dimethyltitanocene is stored in (a combination of toluene – b.p. 110 °C – and tetrahydrofuran), isolation of low molecular weight and volatile products can be problematic.

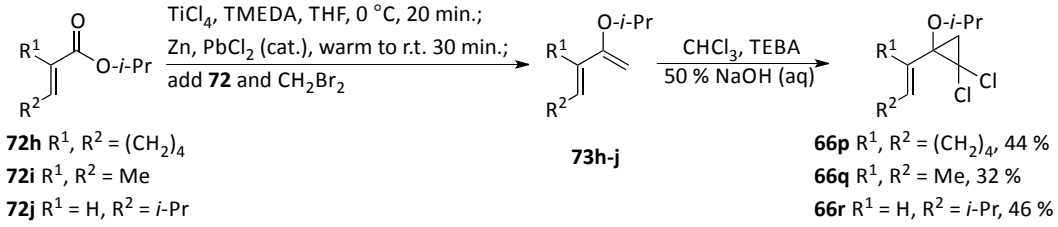
For methylenation of volatile esters, Takai and Utimoto's method[41] proved to be more successful (Scheme 2.20). The reagent is pre-formed from titanium tetrachloride, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, zinc dust and a catalytic amount of lead(II) chloride. The ester is then introduced concurrently with a 1,1-dibromoalkane, resulting in the formation of enol ether **83**. Although methylenation is generally lower yielding than alkylidenation, this procedure was still able to generate the desired enol ethers in synthetically useful amounts. The

mechanism of the reaction and the structure of the active titanium species have not been fully elucidated.



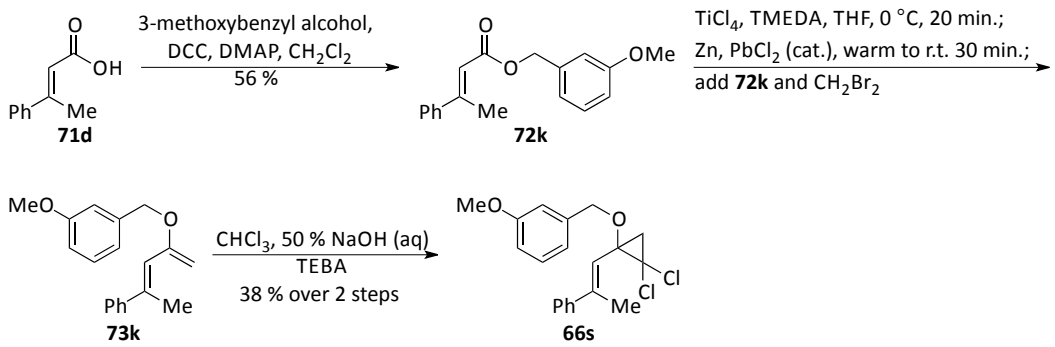
Scheme 2.20. Takai-Utimoto Alkylidenation.

Cyclopropanes **66p**-**r** were needed to examine the scope of the alkene substitution pattern. Low molecular weight esters **72h**-**j** were methylenated using the Takai-Utimoto methodology (Scheme 2.21). Cyclopropanation with dichlorocarbene gave *gem*-dichlorocyclopropanes **66p**-**r** in moderate yields over two steps.



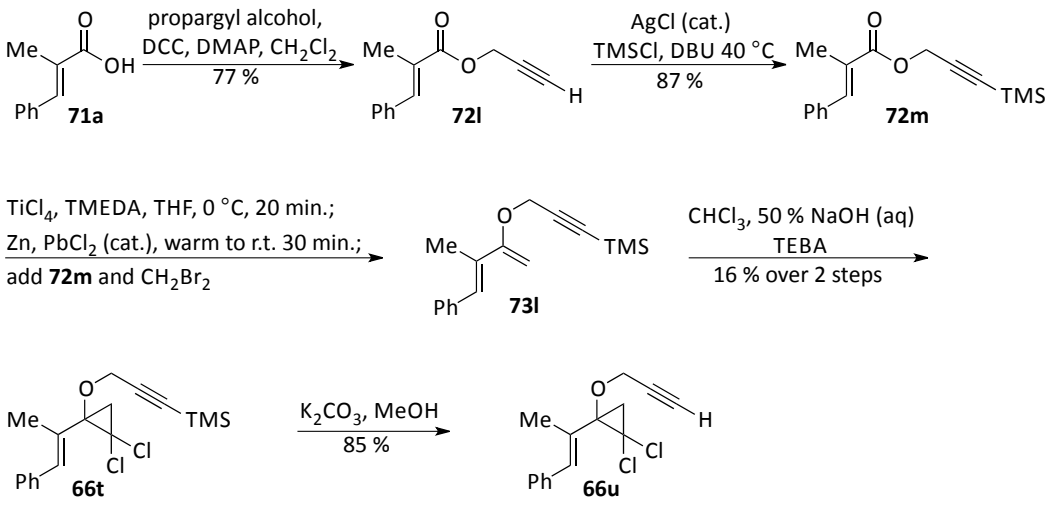
Scheme 2.21. Synthesis of Cyclopropanes **66p**-**r**.

Compound **66s** was used to examine the combination of β,β-disubstitution of the alkene with a potential arene-interrupted Nazarov cyclization. The methylenation reaction of ester **72k**, which was complicated by decomposition when the Petasis reagent was used, could be accomplished under Takai-Utimoto conditions. This allowed access to **66s** in 38 % yield over two steps (Scheme 2.22).



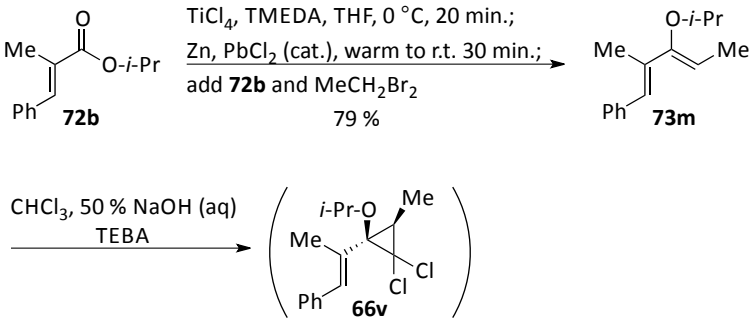
Scheme 2.22. Preparation of Cyclopropane **66s**.

Alkyne **66u** was synthesized to examine an alkyne as a trap for an interrupted Nazarov reaction. Petasis conditions were also unsuitable for the methylenation of alkyne-containing compound **72l**. Instead, compound **66u** was prepared as shown in Scheme 2.23. Esterification of α-methylcinnamic acid (**71**) with propargyl alcohol provided ester **72l**. Initially, exposure of **72l** to the Takai-Utimoto conditions resulted in decomposition, making it necessary to first protect the terminal alkyne. This was accomplished by conversion to the silylated derivative under silver chloride catalysis, yielding 87 % of ester **72m**. Subsequent Takai-Utimoto methylenation followed by cyclopropanation gave propargyloxy cyclopropane **66t,** albeit in poor yield. Deprotection of the alkyne provided the desired cyclopropane (**66u)** in 85 % yield.



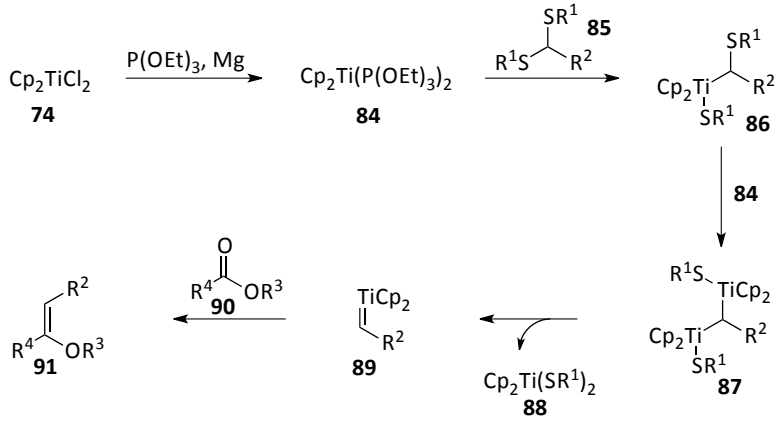
Scheme 2.23. Synthesis of Cyclopropane **66u**.

To determine whether or not further substitution on the cyclopropanes is tolerated in the Nazarov reaction of alkoxycyclopropanes, we synthesized cyclopropane **66v**. Pentadiene **73m**, which was needed as a precursor to **66v,** was prepared using Takai-Utimoto alkylidenation conditions (Scheme 2.24). Starting from precursor **72b**, pentadiene **73m** was synthesized in 79 % with greater than 20 to 1 selectivity for the *Z*-isomer. Stereospecific cyclopropanation of **73m** with dichlorocarbene ensured that the methyl and isopropoxy groups would be *cis* to one another in the cyclopropane product (**66v**). Since compound **66v** was not amenable to chromatographic purification, the crude product was taken on to the Nazarov reaction.



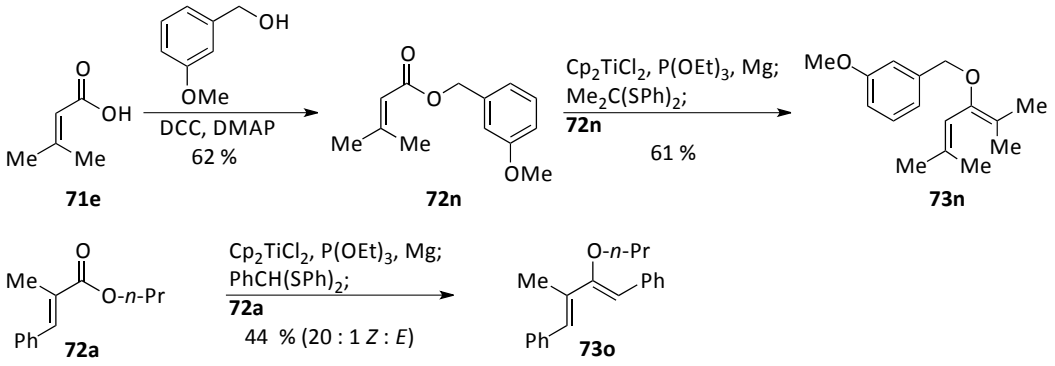
Scheme 2.24. Preparation of Cyclopropane **66v**.

In the literature, there have been no reports of either benzylidenation or synthesis of tetra-substituted alkenes by the Takai-Utimoto method. Chemistry developed by Takeda and coworkers[42] has proven useful for both of these endeavors; however, there are no previous examples reported using α,β-unsaturated esters. Takeda's method for alkylidenation is outlined in Scheme 2.25. Titanocene dichloride is first reduced by magnesium in the presence of triethyl phosphite to form Ti(II) complex **84**. Two equivalents of **84** undergo oxidative addition with a dithioacetal (**85**) to produce **87**, which then disproportionates to form reactive titanium carbenoid **89** and titanium complex **88**. Carbenoid **89** then reacts with the ester, in the same manner as shown for the Petasis reagent (Scheme 2.18), to give the desired enol ether product (**91**).



Scheme 2.25. Potential Mechanism for Takeda's Alkylidenation Reaction.

Our use of Takeda's alkylidenation procedure with unsaturated ester **72n** provided tetra-substituted enol ether **73n** in moderate yield. Benzylidenation of **72a** yielded 44 % of butadiene **73o** in a 20 : 1 ratio of isomers (Scheme 2.26). It is well known that the *Z*-isomer dominates under these reaction conditions, except in cases where a very bulky ester is used. The stereochemistry of **73o** was confirmed by rOe experiments, which showed a correlation between the methine of the enol ether moiety and the vinyl methyl group in the major isomer (Figure 2.6). The cyclopropanes derived from **73n**,**o** were not amenable to purification, thus the crude cyclopropane was directly subjected to Nazarov conditions.



Scheme 2.26. Preparation of Dienes **73n** and **73o**.

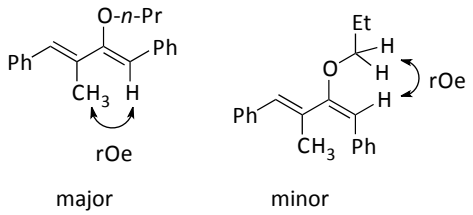
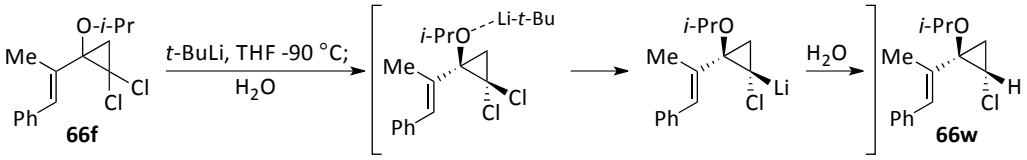


Figure 2.6. Relevant TROESY Correlations of **73o**.

To determine whether non-chlorinated cyclopentenones could be produced by the ring-opening/Nazarov sequence, dichlorocyclopropane **66f** was selectively mono-dehalogenated to provide **66w** (Scheme 2.27). Lithium-halogen exchange at -90 ºC followed by a low temperature quench of the anion with water afforded a single diastereomer of **66w**. The diastereoselectivity is postulated to arise through chelation of the lithium by the isopropoxy oxygen, which presumably leads to the *trans*-isomer of **66w** depicted below; however, nOe experiments could not confirm or reject this. Although compound **66w** was not stable to purification, the reaction was reasonably clean and high yielding, and so the crude material could be subjected to the Nazarov conditions.

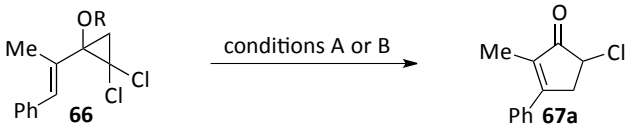


Scheme 2.27. Mono-dehalogenation of **66f**.

2.3.3. Variation of the Oxygen Substituent

With these substrates in hand, the effect of different substituents on the oxygen was examined and the results are shown in Table 2.4. Magnesium sulfate

proved to be a useful additive, presumably due to its function as a scavenger of adventitious water.

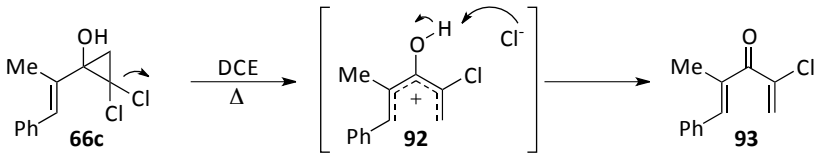


entry	cyclopropane	R	conditions[a]	Time (h)	yield (%)
1	**66x**	TIPS	A		99[b]
2	**66g**	*t*-Bu	B	0.5	59 (52[c])
3	**66f**	*i*-Pr	B	18	77 (74[c])
4	**66e**	*n*-Pr	B	18	65 (40[c])
5	**66a**	Me	B	72	74[c]
6	**66c**	H	B	0.75	41

[a]Conditions: A: 1 equiv. $AgBF_4$, MeCN, reflux. B: 1 equiv. $AgNTf_2$, 1,2-dichloroethane, 2 equiv. $MgSO_4$ reflux. [b]This result is from reference 32. [c]No $MgSO_4$ was added.

Table 2.4. Effect of the Oxygen Substituent on Nazarov Cyclization Efficiency.

Looking at the results of Table 2.4, it can be seen that the triisopropylsilyl group is clearly superior to any of the alkyl groups. The alkyl substituents performed in the order *i*-Pr > Me > *n*-Pr > *t*-Bu, and even a simple hydrogen was allowable, though the yield was the lowest of the group. Notably, in contrast to the siloxycyclopropanes, the alkoxy-substituted cyclopropanes remained intact upon heating in dichloroethane. Compound **66c**, however, was converted to dienone **93** (Scheme 2.28).



Scheme 2.28. Conversion of **66c** to Dienone **93**.

Reaction times varied substantially between the alkoxycyclopropanes in the order *t*-Bu << *i*-Pr ~ *n*-Pr << Me, with times of 30 minutes, 18 hours, and 72 hours respectively. The trend may be rationalized by looking at two related factors: the facility of the *gem*-dichlorocyclopropane ring-opening step, and the ability of the substituent on the oxygen to enforce the reactive "U"-conformation of the pentadienyl cation.

A greater drive for cyclopropane ring-opening is seen with larger substituents. This is due to the fact that steric bulk increases the strain in the small ring, with the resultant increase in ground-state energy presumably lowering the activation barrier for ring-opening. The methyl-substituted cyclopropane was not fully consumed after a prolonged reaction time, whereas the reactions of the larger alkyl groups were much faster. A-values are a measure of the size of a group, where a larger number is given to a larger group and H is assigned as 0 (Table 2.5). Although the size difference between the methyl and *n*-propyl groups does not appear large enough to produce the disparity between reaction rates of those two cyclopropanes, the general trend can be noted.

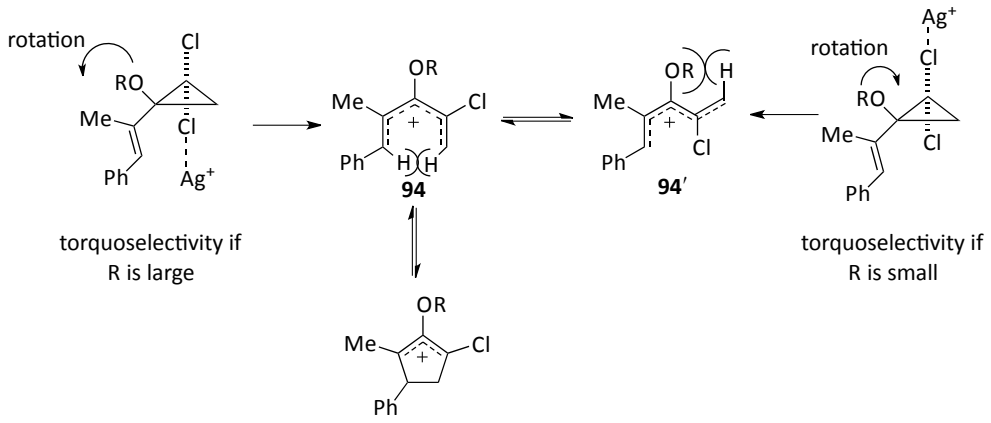
The hydroxyl-substituted cyclopropane **66c** appears to be an exception to this trend, as it the smallest of the series, yet reacts relatively quickly (2 hours and 45 minutes). One explanation for this is that the hydroxyl group is a better electron donor. While the alkoxy groups have a similar ability to push electron density onto the cyclopropane to aid in ring-opening (σ_p ~ -0.25 to -0.27), the hydroxyl group has a σ_p value of -0.37,[43] indicating a greater ability for donation.

It is also possible that the hydroxyl group can expedite the chloride departure by way of hydrogen bonding.[17]

alkyl group	A-value[1]	reaction time (h)
t-Bu	4.7	0.5
i-Pr	2.2	18
n-Pr	1.8	18
Me	1.7	72 (incomplete)

Table 2.5. Size of Alkyl Group and Nazarov Reaction Time.

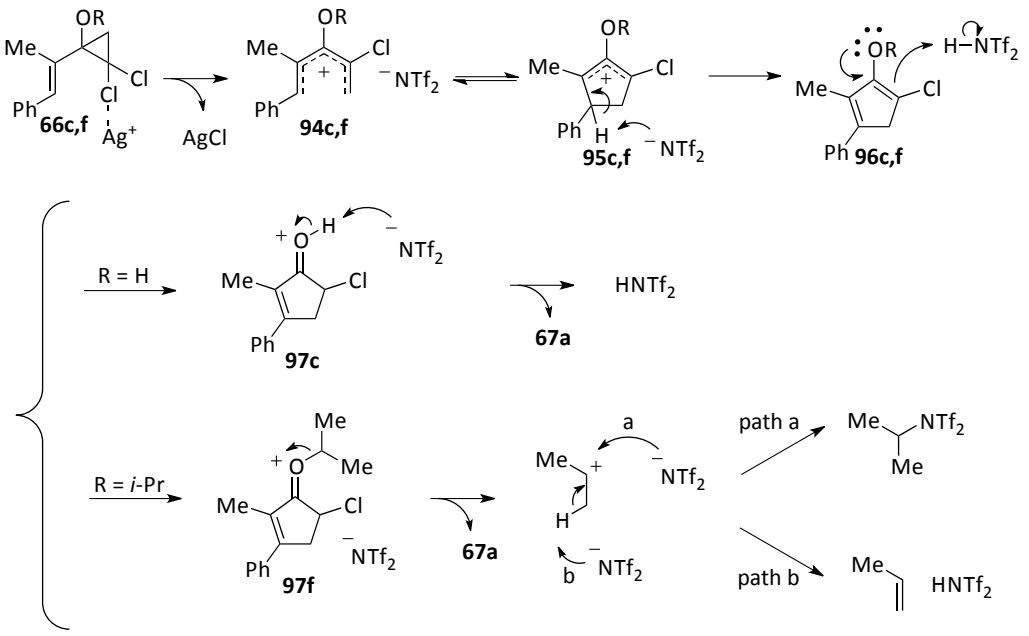
It is worth noting that when there is a bulky group on the oxygen, ring opening of the cyclopropane should lead to the conformation of the pentadienyl cation that is required for the Nazarov cyclization (Scheme 2.29). This is because the cyclopropane ring is opened in a disrotatory fashion, and there is a propensity for the outward rotation of a larger substituent. Although in the original siloxycyclopropane opening/Nazarov reaction sequence, there is evidence to suggest that bond rotation is faster than the cyclization event,[26,27] there is an additional role played by the oxygen substituent. A large group will help push the equilibrium of pentadienyl cation rotamers **94** and **94′** to the U conformation, rather than the sickle conformation, by bumping into the terminal hydrogen in conformation **94′**. This rationalization implies that a larger group on the oxygen should lead to a higher yield. Unfortunately, this was not observed in practice, suggesting that other factors are involved in the outcome of the reaction.



Scheme 2.29. Effect of Oxygen Substituent Size on the Nazarov Cyclization.

The reason for the differences in yields of the various substrates is unclear. There is no direct correlation associated with either the steric bulk of the alkyl groups or in electron-donating abilities of the substituents tested. Although these factors may play a role, they are not significant enough to be the cause of the yield variation. It is also possible that the termination of the reaction plays a role. In reactions where a strong acid is likely to be a substantial byproduct, the yields are found to be lower.

For example, in the reaction of hydroxycyclopropane **66c**, an equivalent of acid is produced from **97c**. This reaction has the lowest yield (Scheme 2.30). In the reaction of isopropoxycyclopropane **66f**, the isopropyl group may be able to leave as secondary cation. Although the side products have not been observed for the reactions in Table 2.5, the isopropyl cation may then be attacked by the triflimide[44] (path a), or undergo elimination to produce $HNTf_2$ or another strong acid (path b). If path a is predominant, less acid will be produced. Additionally, when product cyclopentenone **67a** is exposed to one equivalent of $HNTf_2$ at reflux over a 24-hour period, the yield of recovered material is only 86 %. This indicates that when the acid is present, the product yield can be depressed.



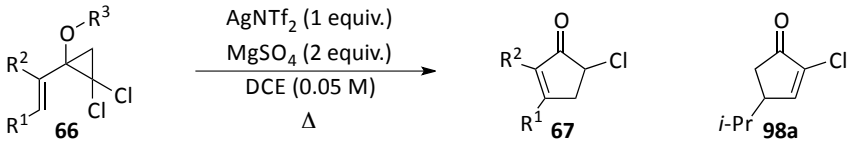
Scheme 2.30. Byproducts of the Nazarov Cyclization.

2.3.4. Variation of Non-Oxygen Substituents

Due to the superior performance of the isopropyl group among the alkyl substituents tested, it was used in the majority of the later-prepared substrates. Alkyl-substituted cyclopropanes **66kp**-**r** were subjected to the optimized conditions and the results are shown in Table 2.6.

Cyclopentenone **67b** was produced in approximately 30 % yield from **66p**. Compound **67b** could not be be purified from contaminants, and the actual yield is somewhat lower. The majority of the material balance was a complex mixture of unidentifiable products. A trace amount of dimethyl-substituted cyclopentenone **67c** could be seen in the ^{1}H NMR spectrum of the crude product for the reaction of **66q**, but this compound could not be isolated for characterization. Compound **66k** provided cyclopentenone **67d**, which could not be purified from contaminants, in poor yield. Unexpectedly, **98a** was the sole product isolated from the reaction of **66r**. The analogous siloxycyclopropane had

given **98a** as a minor product, the major product being the regioisomer 5-chloro-3-isopropyl-2-cyclopentenone (57 %, 1.7:1).[26]

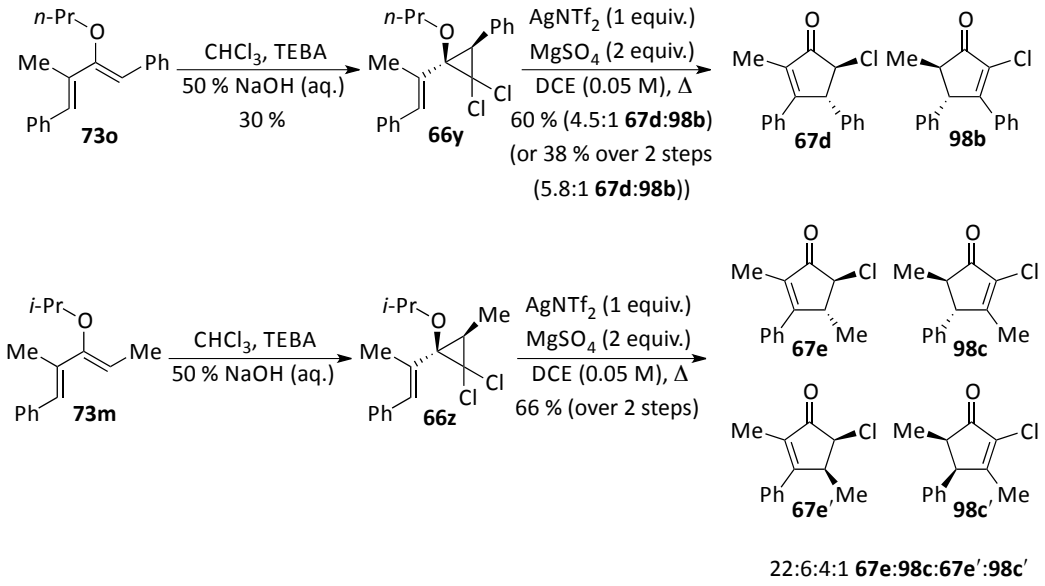


entry	substrate	R^1	R^2	R^3	product	yield (%)
1	**66p**	$(CH_2)_4$		*i*-Pr	**67b**	< 30 %
2	**66q**	Me	Me	*i*-Pr	**67c**	trace
3	**66k**	Ph	H	*n*-Pr	**67d**	< 10 %
4	**66r**	*i*-Pr	H	*i*-Pr	**98a**	44

Table 2.6. Nazarov Reactions of Cyclopropanes **66k**,**p**-**r**.

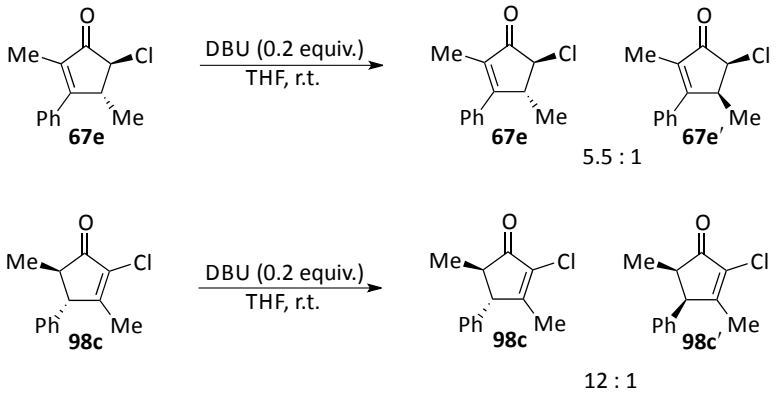
Incorporation of an additional substituent on the cyclopropane was well tolerated, and produced tetra-substituted cyclopentenones as mixtures of isomers (Scheme 2.31). Phenylcyclopropane **66y** furnished regioisomeric cyclopentenones **67d** and **98b**, favouring placement of the olefin away from the electronegative chlorine. This is because the positive charge of the cyclopentenyl cation is more stabilized at the methyl-substituted carbon, as evidenced by trapping experiments,[27] and leads to preferential formation of the methyl-substituted olefin. Each regioisomer was formed as a single diastereomer. The relative stereochemistry of the compounds was determined based on literature precedent. Coupling constants between the methine protons for the *trans*-isomers of 2-cyclopentenones are typically in the range of 2-3 Hz, while the coupling constants of the *cis*-isomers range between 6 and 7.5 Hz.[45,26] Purification of **66y** was unreliable, and so the reaction was done with the crude cyclopropane mixture in subsequent experiments. For this enol ether, selectivity was poor in the cyclopropanation step, and the result was a 3.1 : 1 ratio of cyclopropane **66y** to an

unidentified compound. Cyclopentenones **67d** and **98b** were produced in 38 % yield over two steps, in a 5.8 : 1 ratio. Due to decomposition of **66y** during purification, the yield over two steps is higher than that when **66y** was isolated. Similar regioselectivity was observed in the reaction of **66z**; however, each regioisomer was present as a set of diastereomers, favouring the more stable *trans* isomers.



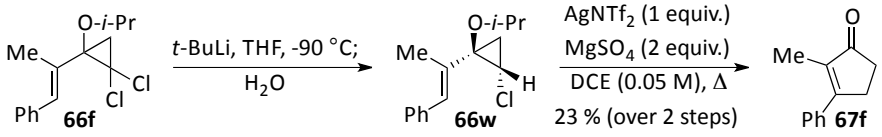
Scheme 2.31. Nazarov Reactions of **66y**,**z**.

The ratios of the *cis*/*trans* isomers reflect the thermodynamic stabilities of the compounds. When pure **67e** was subjected to catalytic 1,8-diazabicyclo[5.4.0]undec-7-ene, the equilibrium ratio of isomers observed matches the relative amounts of **67e** and **67e′** isolated from the original Nazarov reaction (Scheme 2.32). The equilibration between **98c** and **98c′** lies somewhat closer to the *trans* isomer than the *cis* as compared to what was isolated from the initial reaction.



Scheme 2.32. Equilibrium Distribution of *cis*/*trans* Isomers.

Subjection of monochlorocyclopropane **66w** to the Nazarov conditions resulted in a diminished yield of the cyclopentenone (23 %) relative to that of the analogous dichlorocyclopropane (77 %). The reaction, however, was significantly faster in this case, requiring only 30 minutes as compared to 18 hours for the dichloro-analogue (Scheme 2.33).



Scheme 2.33. Nazarov Reaction of Chlorocyclopropane **66w**.

This differences between the reactivity of the mono- and dichloro-analogues can be rationalized in the following points: 1) The ring opening of a monochlorocyclopropane is known to occur faster than that of a dichlorocyclopropane. This is because the developing positive charge is not destabilized by an electron-withdrawing substituent.[17] 2) The chlorine substituent on the oxyallyl cation is stabilizing by resonance,[46] so its presence would help to push the equilibrium between the open chain and ring-closed cations to favour the

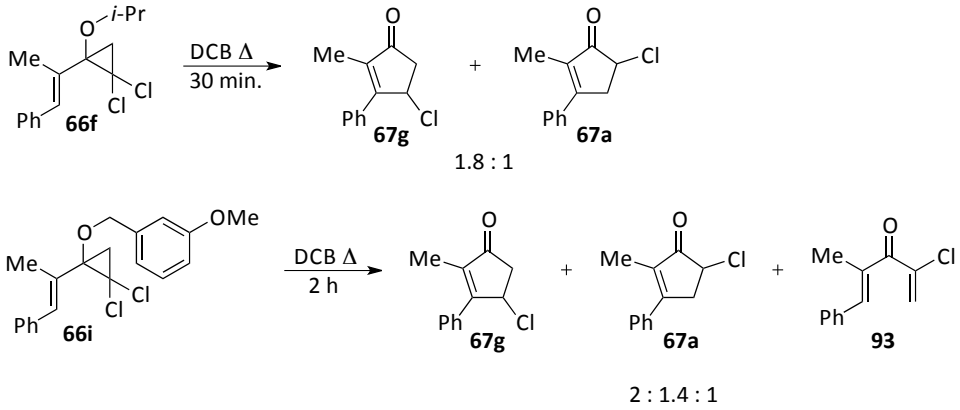
closed ring. 3) An additional role of the α-substituents in the Nazarov cyclization is to provide steric bulk, which helps to enforce the reactive "U"-conformation of the pentadienyl cation versus the unreactive sickle conformation; in the dichloro case, the chlorine is beneficial at this position. Looking again at the resulting reaction outcomes, point 1 explains the increased rate and points 2 and 3 explain the diminished yield for the monochlorocyclopropane (**66w**) relative to the analogous dichlorocyclopropane (**66f**).

2.3.5. Catalytic and Metal-Free Reaction Conditions

Metal-free Nazarov Cyclization

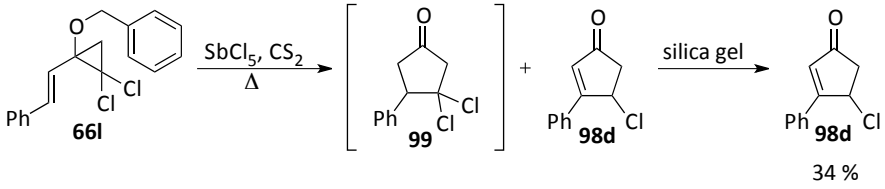
As it was not desirable to use a full equivalent of a silver salt to promote the halocyclopropane Nazarov reaction, and the alkyl oxygen substituents were shown to be more stable than the corresponding silyl groups, we thought a reagent-free Nazarov reaction was worth investigation.

It was initally found that cyclopropane **66f** could be heated at reflux for 24 hours in 1,2-dichloroethane (83 ºC) with no reaction, suggesting that a higher temperature was necessary to cause ring opening. When the cyclopropane was heated at reflux in 1,2-dichlorobenzene (180 ºC), the starting material was consumed within thirty minutes. Although significant decomposition occurred, examination of the ^{1}H NMR spectrum of the crude product revealed that Nazarov cyclization had occurred to provide **67a** (minor), as well as cyclopentenone **67g** (major) (Scheme 2.34). A similar result was obtained from the reaction of **66i**, but in this case the uncyclized dienone was also present.



Scheme 2.34. Reagent-Free Reactions of Cyclopropanes **66f**,**i**.

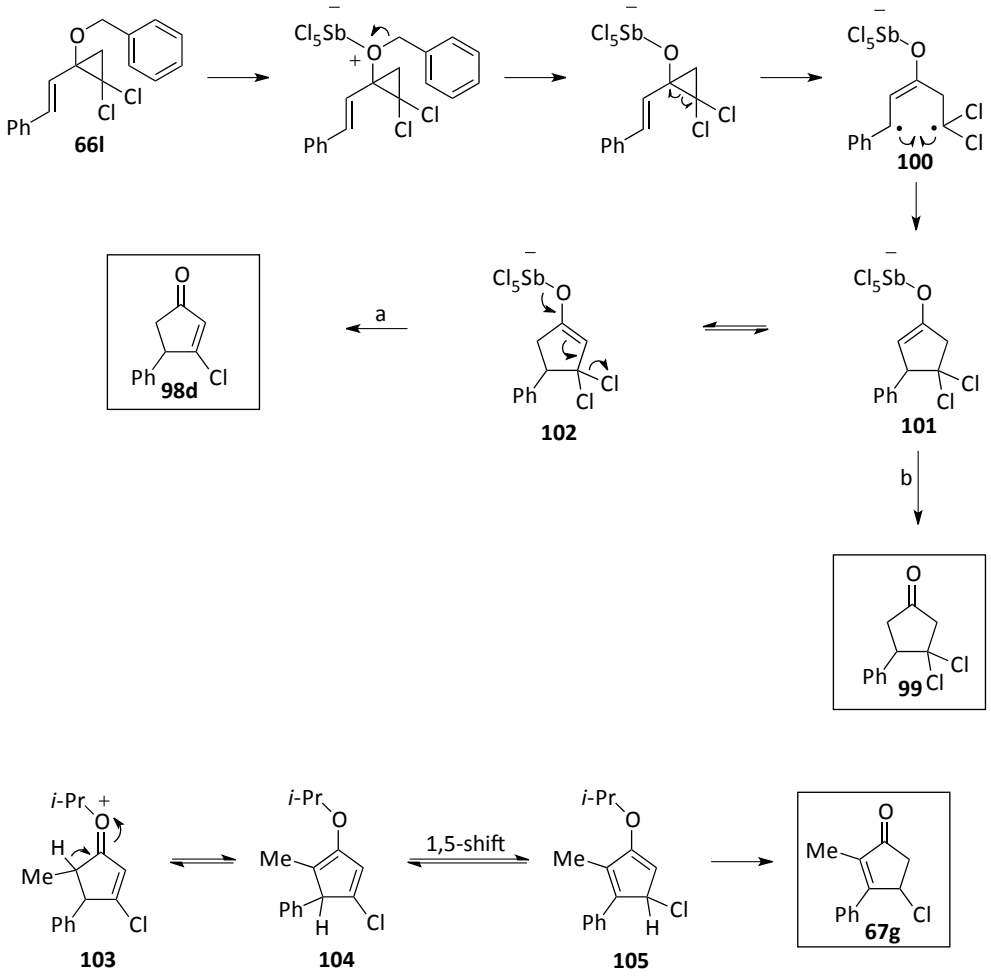
An experiment with benzyloxycyclopropane **66l** provided insight as to how **67g** may be formed. When **66l** was subjected to antimony pentachloride in carbon disulfide, a mixture of **98d** and its presumed precursor **99** was produced (Scheme 2.35). Upon chromatographic purification, only **98d** could be isolated, and in 34 % yield.



Scheme 2.35. Reaction of Cyclopropane **66l** with $SbCl_5$.

It is likely that **98d** is formed *via* a vinylcyclopropane-cyclopentene rearrangement (Scheme 2.36). The benzyl group could be removed after coordination of the antimony pentachloride to the oxygen. The cyclopropane bond could then be cleaved to provide dually stabilized biradical **100**, which would cyclize to cyclopentene **101**. On protonation, the unstable dichloroketone **99** would be formed (path b). Alternatively, isomerization could produce enolate

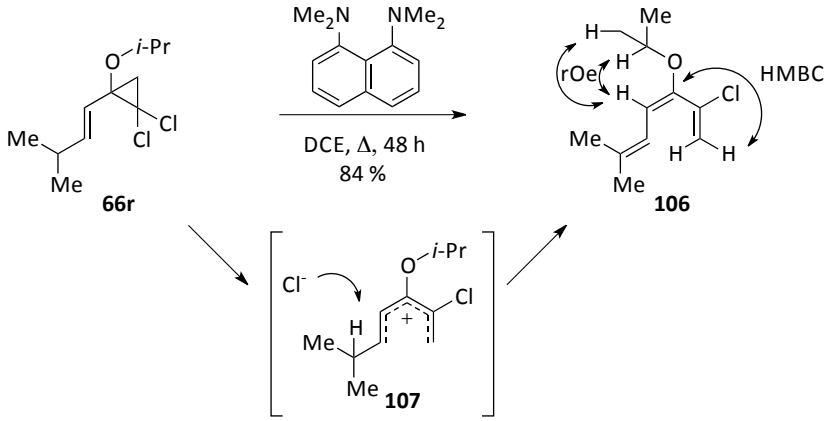
102, which would eliminate a chloride to generate **98d**. For cyclopentenone **67g**, deprotonation followed by a 1,5-hydride shift could conceivably lead to **105**, where the double bond is tetra-substituted.



Scheme 2.36. Proposed Mechanism for the Formation of **98d**, **99** and **67g**.

Cyclopropane **66r** proved to be more labile than the styryl cyclopropanes and underwent reaction in 1,2-dichloroethane at reflux. The sole reaction product was the result of an electrocyclic ring opening followed by deprotonation to form triene **106**. When the reaction was done in the presence of Proton Sponge, **106**

was isolated in 84 % yield (Scheme 2.37). The connectivity of **106** was determined by HMBC experiments. A key correlation, as well as the TROESY correlations that led to the assignment of the geometry of the internal double bond, are shown below.



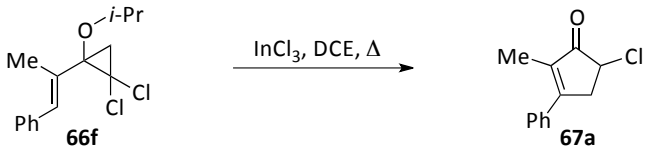
Scheme 2.37. Reaction of **66r** to Produce Triene **106**.

Due to the fact that the non-dehalogenative ring opening of the cyclopropanes is in competition with the desired electrocyclic ring opening of the cyclopropanes at these temperatures, it is unlikely that appropriate conditions can be found to effect an efficient ring-opening/Nazarov cyclization sequence under reagent-free conditions. Also, as elimination can be faster than Nazarov cyclization when the chloride is not sequestered, the alkyl-substituted alkenes are not suitable for reagent-free Nazarov cyclization either.

Catalytic Nazarov Cyclization

Discouraged by the results of the metal-free reactions, our next step was to try to minimize the quantity of metal used. Silver salts were not amenable to this end, so we next explored the use of indium(III) chloride. Indium salts have been previously reported to activate allylic halides.[47] When cyclopropane **66f** was

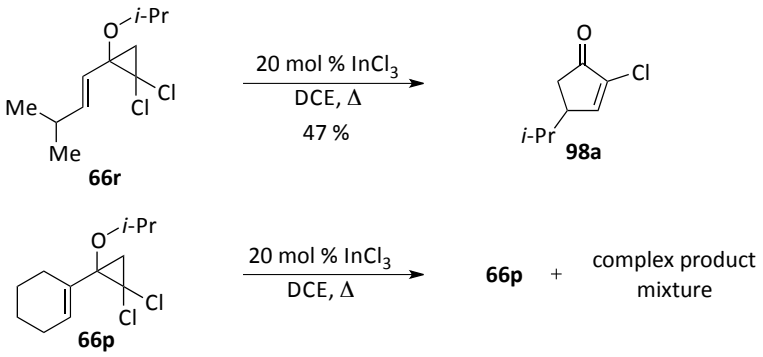
allowed to react with an equivalent of indium chloride in 1,2-dichloroethane at reflux, cyclopentenone **67a** was formed in 84 % yield (Table 2.7). More importantly, when the loading of indium chloride was reduced to 20 mol %, 64 % (86 % BORSM) of **67a** could be obtained after 17 hours when the reaction was run with a 0.1 M concentration of the substrate. The reaction could be pushed to completion by increasing the concentration to 0.2 M, although the yield was not improved.



entry	$InCl_3$ (mol %)	substrate concentration (M)	time (h)	yield (%)
1	100	0.1	23	84
2	20	0.1	17	64
3	20	0.2	19	61

Table 2.7. $InCl_3$-Catalyzed Nazarov Cyclization of **66f**.

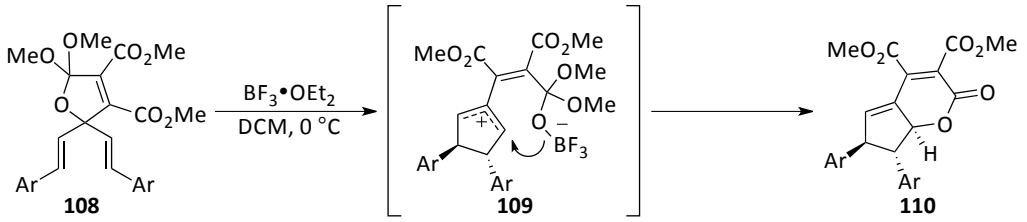
Cyclopropane **66r** also underwent the desired cyclization under indium chloride catalysis in comparable yield to the silver(I)-mediated cyclization (Scheme 2.38). Although **66p** was partially consumed after twenty hours, there was no trace of the expected cyclopentenone. Compound **66p** has been identified as a poor Nazarov substrate, so these results conform to those observed under previous conditions.



Scheme 2.38. $InCl_3$-Catalyzed Nazarov Cyclizations.

2.4 Attempted Interrupted Nazarov Reaction of 2-Alkoxy-1,1-dichloro-2-vinylcyclopropanes

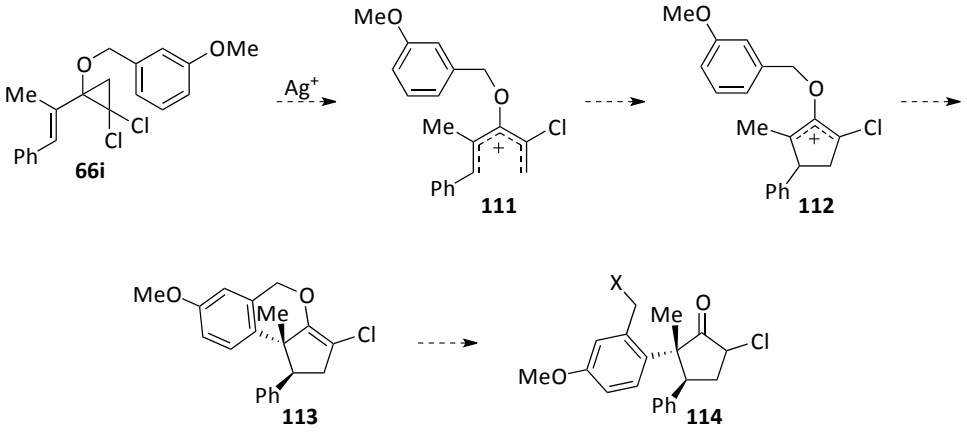
With the results from the above investigations in hand, we felt we knew the system well enough to attempt an interrupted Nazarov reaction. In a related reaction to our desired transformation, cyclopentenyl cation **109** was trapped by a nucleophile tethered through the 2-position. The all-carbon tether incorporated a *cis*-alkene (Scheme 2.39).[48] In this case, the alkene orients the nucleophile such that its proximity to the allyl cation could facilitate bond-formation.



Scheme 2.39. Nair's Synthesis of Bicyclic Lactones.

The phenylpropenyl-substituted cyclopropanes had performed well, and so we continued to use this scaffold. Since arenes are known to trap the Nazarov

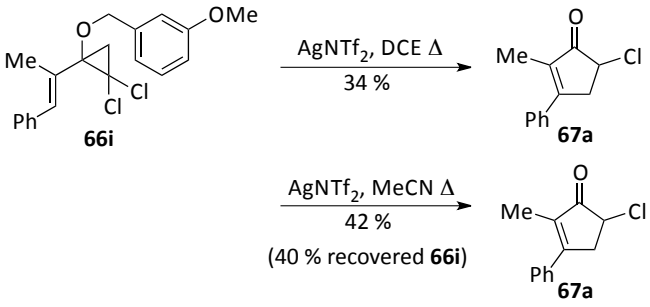
intermediate in the siloxy version of the halocyclopropane Nazarov reaction,[27] arene trapping was a logical starting point. The 3-methoxybenzyl ether moiety appeared to be the ideal nucleophile because the electron-donating methoxy group is positioned *para* to the carbon which would presumably attack the oxyallyl cation. We were optimistic that the ring-opening and cyclization sequence would be followed by nucleophilic attack on the methyl-substituted terminus of the oxyallyl cation. Subsequent rearomatization would provide **113** (Scheme 2.40). Although compound **113** may be stable under the reaction conditions, prior knowledge that the corresponding ketones are produced in the non-interrupted version of the reaction implies that the product observed might be a ring-opened compound such as **114**.



Scheme 2.40. Proposed Interrupted Nazarov Reaction.

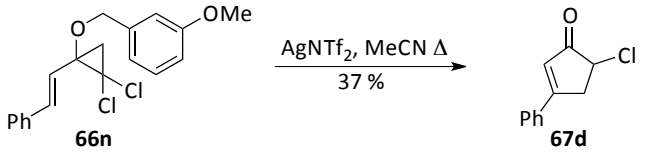
When **66i** was subjected to silver triflimide in 1,2-dichloroethane at reflux, 34 % of 2-cyclopentenone **67a** was obtained with no trace of the desired interrupted Nazarov product (Scheme 2.41). Changing the solvent to acetonitrile, the solvent of choice for the interrupted Nazarov reaction with the siloxycyclopropanes, provided little improvement. After five days at reflux, the reaction was stopped, though incomplete, and 5-chloro-2-cyclopentenone **67a** was

isolated in 42 % yield. As in the first example, there was no evidence of an interrupted Nazarov reaction. The use of 2,2,2-trifluoroethanol as the solvent provided a lower yield of cyclopentenone **67a**, and use of either silver fluoroborate or silver hexafluoroantimonate was also futile.



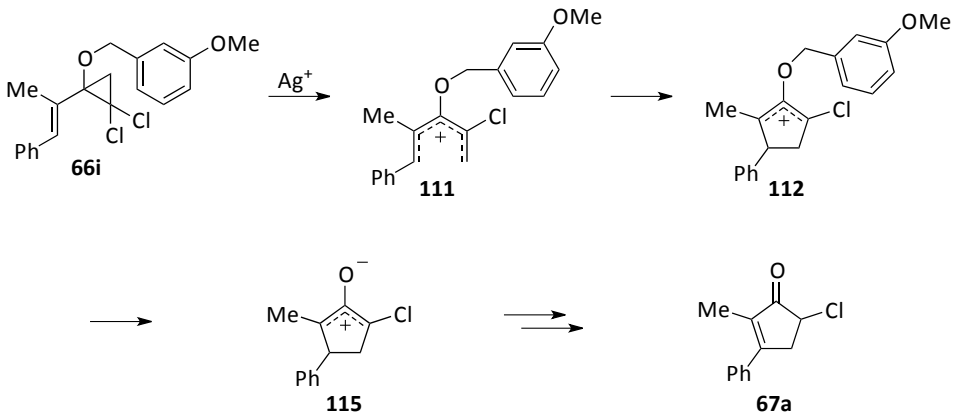
Scheme 2.41. Attempted Interrupted Nazarov Reaction of **66i**.

Although it was discouraging to obtain simple Nazarov products, substrate-based optimization could possibly lead to the desired reactivity. Perhaps the fully substituted oxyallyl cation was too sterically hindered for the trapping event to take place; this has been a problem in the reaction of a siloxycyclopropane with a phenyl trap tethered through the vinyl moiety.[27] Substrate **66n**, lacking the methyl substituent, could perhaps overcome this obstacle. Disappointingly, only cyclopentenone **67d** was isolated under all conditions applied, and a maximum yield of 37 % was realized with acetonitrile as the solvent (Scheme 2.42).



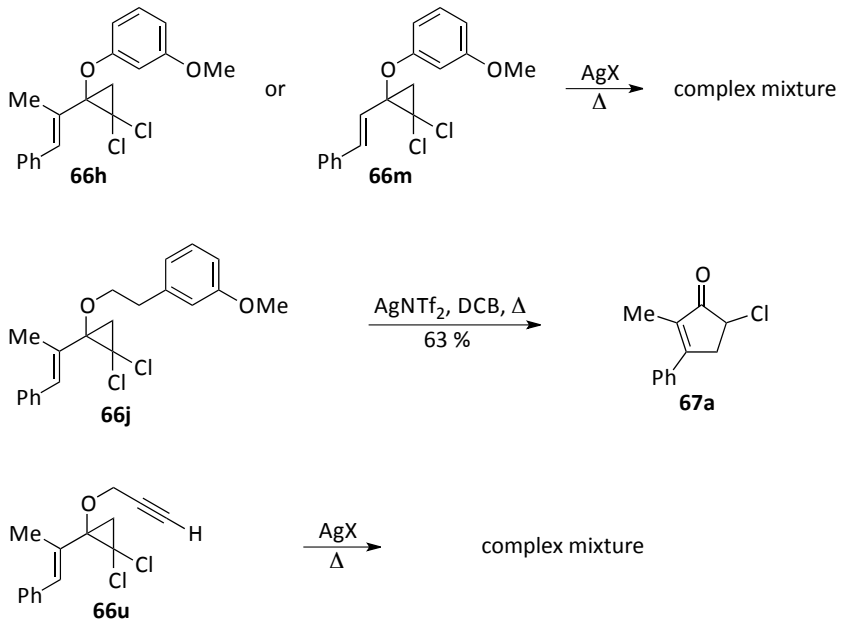
Scheme 2.42. Attempted Interrupted Nazarov Reaction of **66n**.

The observation of only simple cyclopentenone products in these cases may be the result of early loss of the methoxybenzyl group on oxygen. If this substituent were removed prior to elimination, zwitterion **115** would result, which would preclude the intended intramolecular trapping event (Scheme 2.43).



Scheme 2.43. Possible Premature Debenzylation of **112**.

Compounds **66h**, **66m** and **66j** were subjected to Nazarov conditions with the hope that changing the tether length would have a beneficial effect on the reaction (Scheme 2.44). In addition to testing cyclization to 5- and 7-membered rings, if the interrupted process were to occur we would also gain insight into whether the poorer leaving group ability of these alkoxy substituents, relative to the benzyl cation, would influence the outcome. This increased stability could perhaps prevent premature dealkylation, if that was a factor affecting previous substrates. Phenyl ethers **66h** and **66m** decomposed under the reaction conditions applied, and **66j** was rather unreactive, requiring a higher temperature to effect cyclopropane opening. When **66j** was subjected to silver triflimide in 1,2-dichlorobenzene at reflux, cyclopentenone **67a** was obtained in 63 % yield. Nothing corresponding to an interrupted Nazarov product was observed.



Scheme 2.44. Attempted Interrupted Nazarov Reactions.

Another potential rationale for the lack of interrupted Nazarov product could be that the chosen nucleophile is too sterically encumbered to approach the allyl cation. Figure 2.7 depicts a conformation of intermediate **112** positioning the arene for attack on the oxyallyl cation. The methyl substituent must be positioned under the aryl ring, and the aromatic proton is placed on top of the cyclopentenyl cation. These two interactions will raise the energy of conformation **112**, inhibiting nucleophilic attack by the arene. On the other hand, a propargyl oxyallyl cation (**116**) should be better able to adopt the conformation shown in Figure 2.7.

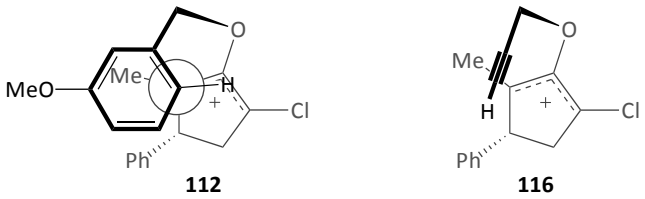
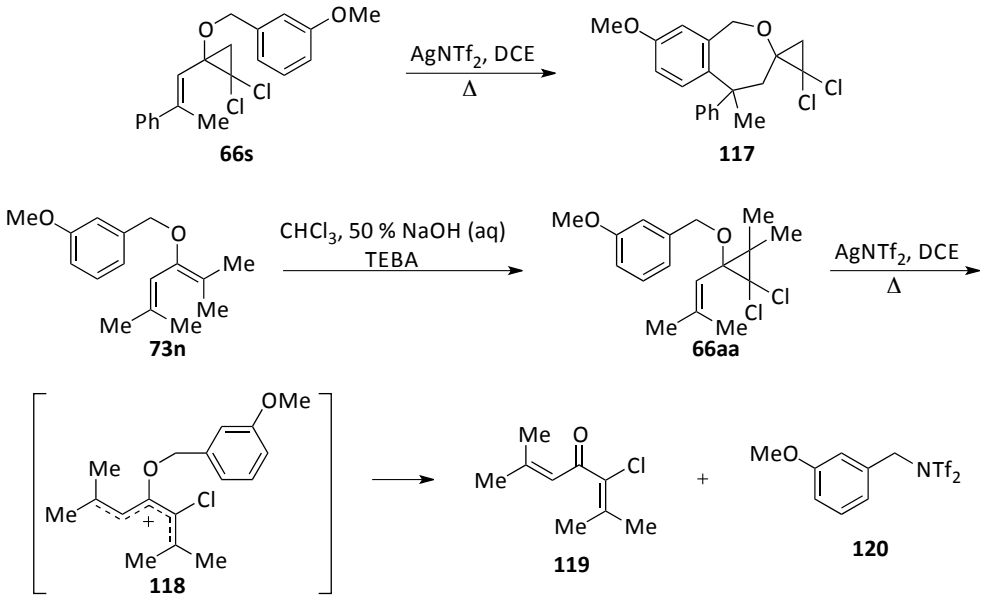


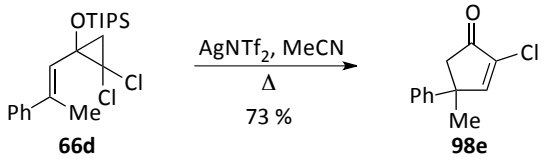
Figure 2.7. Proposed Conformations of Intermediates **112** and **116**.

Although unknown in the Nazarov literature,[49] we were initially intrigued by the idea of using an alkyne nucleophile because of its small size, and thus its approach to the cyclopentenyl cation with relatively little steric interference, which could lead to an interrupted Nazarov reaction. In the event, however, subjection of **66u** to Nazarov conditions resulted in decomposition to a complex product mixture (Scheme 2.44).

If the interrupted Nazarov reaction pathway is possible, then the eliminative process is out-competing it. When the preferred elimination pathway is blocked by replacement of the hydrogen with a methyl group in cyclopropane **66s** (Scheme 2.45), elimination should become more difficult, and could perhaps be slow enough that the interrupted Nazarov could occur. Unexpectedly, **66s** underwent a Friedel-Crafts reaction to produce **117** rather than dehalogenative cyclopropane ring opening; this process is detailed in Chapter 3. The same phenyl-methyl substitution on the olefin was shown to be permissible for the Nazarov reaction when the arene was replaced in siloxycyclopropane **66d** (Scheme 2.46).



Scheme 2.45. Attempts at Blocking the Elimination Process.

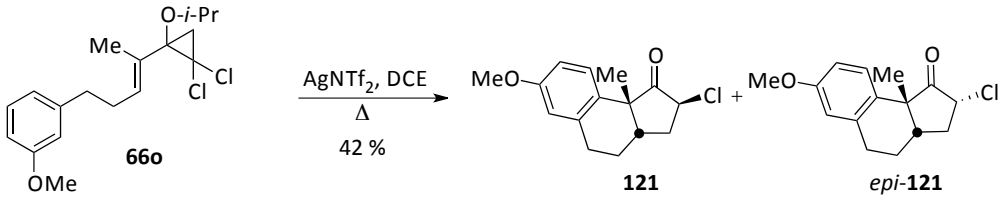


Scheme 2.46. Nazarov Cyclization of Cyclopropane **66d**.

When the possibility of elimination was blocked in cyclopropane **66aa**, a new problem arose. The Nazarov cyclization of pentadienyl cation **118** did not occur at all; known dienone **119**[50] and a 3-methoxybenzyl-containing product, whose spectral data were consistent with triflimide **120**,[51] were the only products observed in the crude NMR spectrum. Seeing as the termini of the pentadienyl cation are substituted such that there is severe steric clash between the internal substituents in the U conformation, lack of cyclization is not entirely surprising.

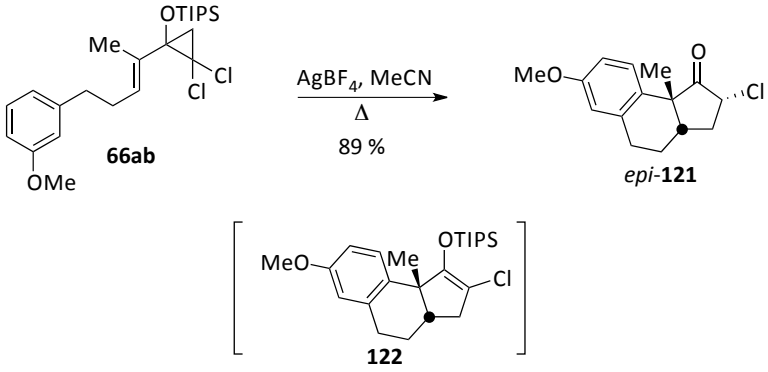
It was important to us to find out if any mode of trapping was possible for the alkoxycyclopropanes. In order to garner this information, compound **66o**,

with the trapping moiety tethered through the alkene, was subjected to Nazarov conditions (Scheme 2.47). Reassuringly, the expected benzohydrindanones were formed in 42 % yield as a 1.1 : 1 ratio of **121** and *epi*-**121**.



Scheme 2.47. Interrupted Nazarov Reaction of **66o**.

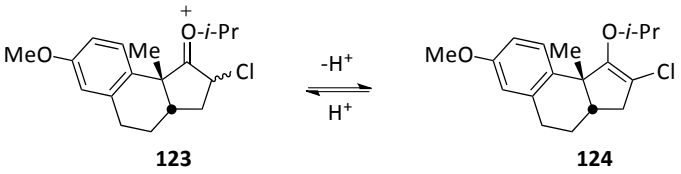
Previously, siloxycyclopropane **66ab** was shown to undergo an interrupted Nazarov reaction to produce *epi*-**121** as a single diastereomer (Scheme 2.48).[27] The selectivity in this case is likely the result of kinetic protonation of the silyl enol ether intermediate on the more accessible convex face.[32]



Scheme 2.48. Interrupted Nazarov Reaction of **66ab**.

Epi-**121** is a known compound, and the relative stereochemistry has been unambiguously determined by X-ray crystallographic analysis.[27] The *cis* relationship between the angular methyl and the chloro-substitutents in **121** was

implied by the very weak intensity of the nOe correlation between the methyl protons and the methine proton α to the ketone. The epimeric relationship of **121** to *epi*-**121** was confirmed by conversion of *epi*-**121** to **121** with 1,8-diazabicyclo[5.4.0]undec-7-ene. The epimerization reaction resulted in a 1.1 : 1 ratio of **121** to *epi*-**121**, confirming that the ratio of epimers obtained from the reaction is under thermodynamic control *via* epimerization of **123** (Scheme 2.49).



123 **124**

Scheme 2.49. Epimerization of **123**.

2.5 Conclusions

Electrocyclic ring opening of 2-alkoxy-1,1-dichlorocyclopropanes followed by Nazarov cyclization has been demonstrated. These substrates require harsher reaction conditions than the analogous siloxy compounds, and the reaction occurs to generate α-chlorocyclopentenones with somewhat lower efficiency, particularly for substrates containing cyclic alkenes.

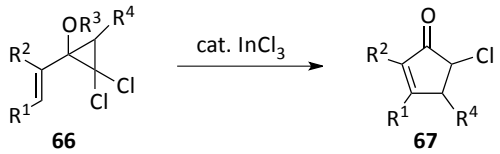
Although most substrates are unreactive in 1,2-dichloroethane at reflux without the addition of silver salts, the silver-free reaction does occur at higher temperatures. In these cases, the Nazarov cyclization was found to be a minor pathway, producing 5-chlorocyclopentenones, and the major products were isomeric 4-chlorocyclopentenones. In addition, a competing eliminative pathway has been shown to produce a triene, rather than any cyclized product at all. These competing non-Nazarov pathways do not allow for a practical reagent-free Nazarov cyclization.

An interrupted Nazarov cyclization with a nucleophile tethered through the oxygen has not been realized, despite variations on the reaction conditions and changes in tether length, nucleophile, or alkene substitution of the substrates. The reason for this lack of reactivity has not been elucidated, though the problem may be that the geometry is not favourable. In a related example by Nair and coworkers, incorporation of a *cis*-alkene in the tether may make bond-formation more favourable than in the present study (Scheme 2.39).[48]

We have also discovered that indium(III) chloride can activate *gem*-dichlorocyclopropanes for dehalogenative ring opening. This application is unprecedented in the literature, and has been put to use in the electrocyclic ring opening/Nazarov cyclization reaction. The reaction can be done catalytically with a 20 mol % catalyst loading. Preliminary work has shown that the yields and selectivities are similar to the silver(I)-mediated process.

2.6 Future Work

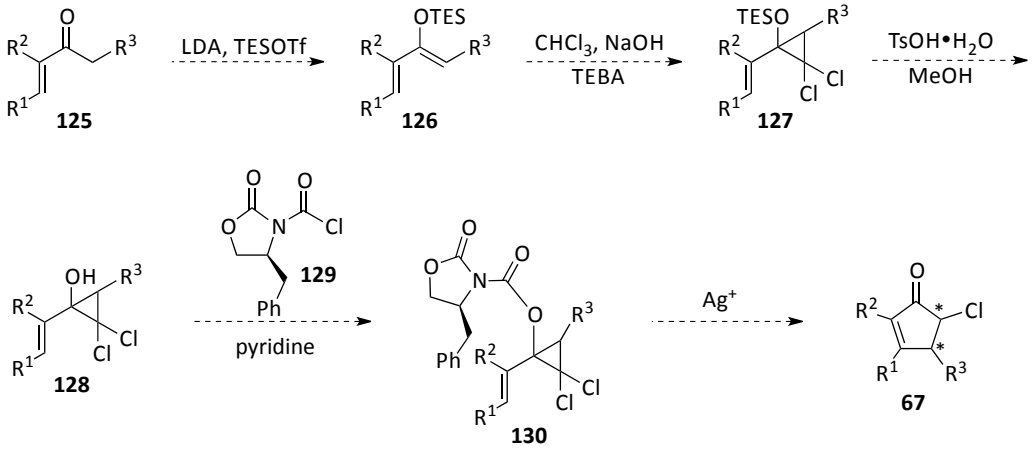
Although the reagent-free Nazarov cyclization of alkoxycyclopropanes is complicated by other reaction pathways, the indium(III) chloride-catalyzed Nazarov reaction shows promise (Scheme 2.50). This mode of activation is quite novel in the Nazarov field, and may be applicable to dichlorocyclopropanes that correspond to dienones which would be difficult to activate in a catalytic manner.



66 **67**

Scheme 2.50. Catalytic Nazarov Cyclization.

A benefit to using alkoxy cyclopropanes as Nazarov substrates is that the oxygen substituent can be varied at will. Incorporation of a chiral auxiliary at this position is not known, and may lead to a practical asymmetric Nazarov reaction. The auxiliary could be attached to cyclopropanol **128**, which would then be subjected to a halophile to produce enantio-enriched cyclopentenones (Scheme 2.51). This method of substrate synthesis could allow for rapid screening of a variety of auxiliaries, such as the Evans auxiliary depicted below.



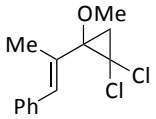
Scheme 2.51. Proposed Asymmetric Nazarov Cyclization.

2.7 Experimental

2.7.1. General Information

Reactions were carried out in flame-dried glassware under an atmosphere of argon. Tetrahydrofuran (Na/benzophenone), diethyl ether (Na/benzophenone), dichloromethane (CaH_2), 1,2-dichloroethane (CaH_2), acetonitrile (CaH_2), and toluene (CaH_2) were distilled prior to use, and chloroform was filtered through potassium carbonate. Thin layer chromatography was performed on glass plates precoated with 0.25 mm Kieselgel 60 F254 (Merck). Flash chromatography columns were packed with 230-400 mesh silica gel (Silicycle), or 150 mesh basic alumina (Sigma-Aldrich) which was deactivated with 6 % water prior to use. Silver bis(trifluoromethanesulfonyl)imide was prepared from silver carbonate.[52] Titanium tetrachloride was distilled under argon prior to use. Zinc dust was rinsed sequentially with 5 % HCl, water, methanol, and ether, and then dried at 100 ºC in vacuo overnight prior to use. *N*,*N*,*N*′,*N*′-tetramethylethylenediamine was distilled over calcium hydride and stored over potassium hydroxide. Titanocene dichloride was purified by Soxhlet extraction with dichloromethane. Dimethyltitanocene was prepared by the method of Payack.[34] Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 MHz, 400 MHz, or 500 MHz and coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, etc. The chemical shifts are reported on the δ scale (ppm) and the spectra are referenced to residual solvent peaks: $CDCl_3$ (7.26 ppm, ^{1}H; 77.26 ppm, ^{13}C), as internal standard. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz or 125 MHz, and the chemical shifts are accurate to one decimal place.

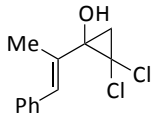
2.7.2. Experimental Procedures and Characterization



1,1-dichloro-2-methoxy-2-(1-phenyl-[*1E*]-1-propen-2-yl)cyclopropane (66a). Methyl tosylate (0.71 mL, 4.7 mmol) was added to a stirred suspension of potassium hydride (876 mg, 21.8 mmol) in 18.6 mL THF. A solution of (*E*)-4-phenyl-3-methyl-3-buten-2-one[26] (0.500 g, 3.12 mmol) in 65 mL THF was introduced *via* cannula, and the reaction was allowed to progress for 35 minutes before it was quenched by addition of 40 mL of saturated ammonium chloride. The reaction mixture was extracted three times with ethyl acetate. The combined extract was washed with brine then dried over sodium sulfate, filtered, and concentrated. The crude material was dissolved in hexanes and eluted through a plug of basic alumina (Brockman activity III) with hexanes to remove the major impurities to provide 214 mg of (*E*)-1-phenyl-3-methoxy-2-methyl-1,3-butadiene (**65**) as a pale yellow oil, which was used without further purification.

Crude **65** (174 mg, ~1.0 mmol) was dissolved in 8.3 mL chloroform. Benzyltriethylammonium chloride (68 mg, 0.30 mmol) was added followed by 50 % aqueous sodium hydroxide (14.4 mL, 180 mmol), and the biphasic mixture was stirred vigorously for 20 min. The reaction was quenched by the addition of water and the layers were separated. The aqueous portion was extracted three times with dichloromethane. The combined organic extract was dried over magnesium sulfate, filtered, and concentrated to a light yellow oil. Purification by FCC (2 % ether in hexanes) provided the product as a colourless oil, 194 mg, 29 % over 2 steps. IR (dichloromethane cast film) 2994, 2935, 2828, 1493, 1447, 1075 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.31 (m, 4H), 7.30-7.25 (m, 1H), 6.53 (br s, 1H), 3.33 (s, 3H), 2.11 (d, *J* = 1.3 Hz, 3H), 1.95 (d, *J* = 8.4 Hz, 1H), 1.68 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 132.2, 132.1,

129.2, 128.5, 127.5, 73.8, 64.0, 55.1, 29.8, 15.7; HRMS (EI, M^+) calculated for $C_{13}H_{14}OCl_2$, m/z 256.0422; found m/z 256.0425.

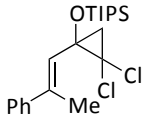


2,2-dichloro-1-(1-phenyl-[*1E*]-1-propen-2-yl)cyclopropanol (66c). Triethylamine (0.49 mL, 3.5 mmol) was added dropwise to a solution of (*E*)-3-methyl-4-phenyl-butene-2-one (224 mg, 1.40 mmol) in 4.7 mL THF at 0 ºC. Triethylsilyl trifluoromethanesulfonate (0.41 mL, 1.8 mmol) was subsequently added, and the reaction was stirred for 1 h. 2.5 mL of hexanes, 0.5 mL of triethylamine and 3 mL of saturated sodium bicarbonate were added, and the layers were separated. The organic layer was washed with water then brine, dried over magnesium sulfate, filtered, and concentrated to provide (*E*)-3-triethylsiloxy-2-methyl-1-phenyl-1,3-butadiene (**68**) as 415 mg pale yellow oil. The crude product was used directly in the following transformation.

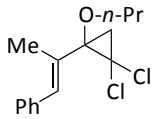
(*E*)-3-Triethylsiloxy-2-methyl-1-phenyl-1,3-butadiene (**68**) was cyclopropanated in the same manner as for **66a** for 15 minutes. Purification of the crude reaction mixture by flash column chromatography (5 % dichloromethane in hexanes) provided (*E*)-1,1-dichloro-2-triethylsilyloxy-2-(1-phenyl-[2*E*]-propen-2-yl)cyclopropane (**66b**) as a colourless oil, 419 mg, 81 % over 2 steps. IR (dichloromethane cast film) 3025, 2957, 2878, 1586, 1495, 1459, 1412, 1379, 1257, 1074 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 7.38-7.34 (m, 2H), 7.29-7.24 (m, 3H), 6.47 (br s, 1H), 2.11-2.07 (m, 4H), 1.67 (d, *J* = 8.5 Hz, 1H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.71-0.59 (m, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 137.0, 136.1, 129.6, 129.1, 128.5, 127.3, 68.8, 64.4, 32.3, 16.0, 7.0, 5.5; HRMS (APPI, M^+) calculated for $C_{18}H_{26}Cl_2OSi$, m/z 356.1124; found m/z 356.1126.

p-Toluenesulfonic acid monohydrate (194 mg, 1.02 mmol) was added to a stirred solution of **66b** (122 mg, 0.340 mmol) in 17 mL methanol. After 30 min., the reaction mixture was poured into ice water and extracted three times with ether. The combined extract was washed with saturated aqueous sodium

bicarbonate then brine, dried over magnesium sulfate, filtered, and concentrated to provide (*E*)-2,2-dichloro-1-(1-phenyl-[2*E*]-propen-2-yl)cyclopropanol (**66c**) as a white solid, 91 mg, quantitative. Purification of the product was unnecessary. IR (cast film) 3282, 3060, 2950, 2858, 1491, 1441, 1380, 1240, 1054 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.31-7.24 (m, 3H), 6.58 (br s, 1H), 2.69 (br s, 1H), 2.13-2.10 (m, 4H), 1.75 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 133.8, 131.0, 129.2, 128.5, 127.5, 67.8, 64.4, 32.2, 15.7; HRMS (EI, M^+) calculated for $C_{12}H_{12}Cl_2O$, m/z 242.0265; found m/z 242.0263.



1,1-dichloro-2-(2-phenyl-[*1E*]-1-propen-1-yl)-2-triisopropylsiloxycyclopropane (66d). Compound **66d** was synthesized in an analogous manner to **66b** (see **66c**). Cyclopropanation time was 25 minutes. FCC (5 % dichloromethane in hexanes) provided the product as a colourless oil, 170 mg, 87 %; IR (neat) 3031, 2946, 2893, 2868, 1635, 1495, 1464, 1446, 1246 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.39 (m, 2H), 7.37-7.33 (m, 2H), 7.32-7.28 (m, 1H), 5.96 (br s, 1H), 2.28 (d, *J* = 1.3 Hz, 3H), 1.81 (d, *J* = 8.2 Hz, 1H), 1.65 (d, *J* = 8.2 Hz, 1H), 1.16-1.05 (m, 21H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.4, 142.3, 128.6, 128.1, 126.0, 125.1, 66.2, 61.4, 35.5, 18.4, 18.22, 18.20, 13.1; HRMS (APPI, M+H) calculated for $C_{21}H_{33}Cl_2OSi$, m/z 399.1672; found m/z 399.1667.

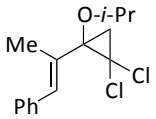


1,1-dichloro-2-(1-phenyl-[*1E*]-1-propen-2-yl)-2-propoxycyclopropane (66e). Concentrated sulfuric acid (0.05 mL) was added to a solution of α-methylcinnamic acid (0.500 g, 3.08 mmol) in propanol (2.3 mL, 31 mmol). The solution was heated at 80 ºC for 20 h, then cooled and concentrated. Water was added, followed by ether, and the solution was transferred to a separatory funnel.

The layers were separated, and the aqueous was extracted two times with ether. The combined extracts were washed sequentially with 5 % sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated to a yellow oil. FCC (4 % ethyl acetate in hexanes) provided propyl (*E*)-α-methylcinnamate (**72a**) as a colourless oil, 574 mg, 92 %. IR (neat) 3058, 2968, 2879, 1708, 1635, 1576, 1448, 1253, 1114 cm^{-1}; ^{1}H NMR 7.69 (s, 1H), 7.42-7.29 (m, 5H), 4.18 (t, *J* = 6.7 Hz, 2H), 1.29 (d, *J* = 1.3 Hz, 3H), 1.75 (app sextet, *J* = 7.1 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 138.9, 136.2, 129.9, 128.9, 128.6, 128.5, 66.7, 22.3, 14.3, 10.8; HRMS (EI, M^+) calculated for $C_{13}H_{16}O_2$, m/z 204.1150; found m/z 204.1154; Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.17; H, 7.83.

In a flame-dried flask under argon, dimethyltitanocene (0.43 M in toluene/THF, 23 mL, 9.8 mmol) was added to propyl (*E*)-α-methylcinnamate (**72a**, 1.00 g, 4.90 mmol). The flask was wrapped in foil to prevent exposure to light, and the solution was heated to 90 ºC for 6 h. After cooling, basic alumina Brockman activity III was added to the flask. The mixture bubbled and lightened from deep red-orange to pale orange, and then it was concentrated. The resulting solid was placed on top of a basic alumina Brockman activity III plug and the enol ether was eluted with ether and concentrated to a dark orange oil. The crude product was subjected to flash column chromatography (hexanes, basic alumina Brockman activity III) to provide (*E*)-2-methyl-1-phenyl-3-propoxy-1,3-butadiene (**73a**) as a pale yellow oil, 848 mg, 85 %. Partial data is reported. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (m, 2H), 7.31-7.28 (m, 2H), 7.26-7.21 (m, 1H), 7.14 (br s, 1H), 4.41 (d, *J* = 2.4 Hz, 1H), 4.21 (d, *J* = 2.4 Hz, 1H), 3.77 (t, *J* = 6.5 Hz, 2H), 2.01 (d, *J* = 1.3 Hz, 3H), 1.85-1.78 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H); ^{13}C APT (125 MHz, $CDCl_3$) δ 161.4 (C), 138.1 (C), 132.1 (C), 129.4 (CH), 128.1, 126.7 (CH), 126.5 (CH), 83.7 (CH_2), 69.2 (CH_2), 22.5 (CH_2), 14.9 (CH_3), 10.9 (CH_3); HRMS (EI, M-$C_3H_7^+$) calculated for $C_{11}H_{11}O$, m/z 159.0810; found m/z 159.0811.

(*E*)-2-Methyl-1-phenyl-3-propoxy-1,3-butadiene (**73a**) was cyclopropanated in the same manner as in the synthesis of **66a** for 7 minutes. Purification by FCC (20 % dichloromethane in hexanes) gave 1,1-dichloro-2-(1-phenyl-[*1E*]-1-propen-2-yl)-2-propoxycyclopropane (**66e**) as a colourless oil, 645 mg, 91 %. IR (neat) 3024, 2963, 2879, 1493, 1443, 1410, 1236, 1076 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.30 (m, 4H), 7.29-7.24 (m, 1H), 6.50 (br s, 1H), 3.51 (dt, *J* = 9.0, 6.3 Hz, 1H), 3.28 (dt, *J* = 9.0, 6.3 Hz, 1H), 2.10 (d, *J* = 1.1, 3H), 1.95 (d, *J* = 8.3 Hz, 1H), 1.67-1.57 (m, 3H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 133.0, 131.5, 129.2, 128.5, 127.4, 72.8, 69.6, 64.2, 30.2, 23.1, 15.8, 11.0; HRMS (EI, M^+) calculated for $C_{15}H_{18}Cl_2O$, m/z 284.0735; found m/z 284.0736; Anal. Calcd for $C_{15}H_{18}Cl_2O$: C, 63.17; H, 6.36, Found: C, 62.94; H, 6.77.

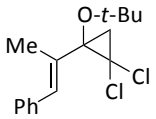


1,1-dichloro-2-isopropoxy-2-(1-phenyl-[*1E*]-1-propen-2-yl)cyclopropane (66f). Isopropyl (*E*)-α-methylcinnamate (**72b**) was synthesized in the same manner as **72a**. FCC 4 % ethyl acetate in hexanes provided as a colourless oil, 568 mg, 91 %. IR (neat) 3057, 2980, 1707, 1635, 1448, 1359, 1256, 1105 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.42-7.37 (m, 4H), 7.35-7.28 (m, 1H), 5.14 (septet, *J* = 6.3 Hz, 1H), 2.11 (d, *J* = 1.4 Hz, 3H), 1.33 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.4, 138.6, 136.3, 129.9, 129.3, 128.6, 128.4, 68.4, 22.2, 14.3; HRMS (EI, M^+) calculated for $C_{13}H_{16}O_2$, m/z 204.1150; found m/z 204.1147.

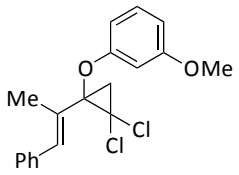
(*E*)-3-Isopropoxy-2-methyl-1-phenyl-1,3-butadiene (**73b**) was synthesized from **72b** by the same procedure as for **73a**. FCC (hexanes on basic alumina Brockman activity III) provided **73b** as a pale yellow oil, 919 mg, 92 %. IR (neat) 3024, 2977, 2925, 1669, 1584, 1444, 1370, 1270, 1126 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (m, 2H), 7.31-7.28 (m, 2H), 7.24-7.20 (m, 1H), 7.10 (br s, 1H), 4.49 (d, *J* = 2.3 Hz, 1H), 4.37 (septet, *J* = 6.1 Hz, 1H), 4.23 (d, *J* = 2.3 Hz,

1H), 2.00, (d, *J* = 1.3 Hz, 3H), 1.33 (d, *J* = 6.1 Hz, 6H); HRMS (EI, M-$C_3H_7^+$) calculated for $C_{11}H_{11}O$, m/z 159.0810; found m/z 159.0803.

1,1-Dichloro-2-isopropoxy-2-(1-phenyl-[*1E*]-1-propen-2-yl)cyclopropane (**66f**) was synthesized from **73b** by the same procedure as for **66a**; cyclopropanation time was 7 minutes. FCC (20 % dichloromethane in hexanes) provided as a colourless oil, 574 mg, 81 %. IR (neat) 3025, 2976, 2931, 1493, 1445, 1381, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.21 (m, 5H), 6.51 (s, 1H), 3.86 (septet, *J* = 6.2 Hz, 1H), 2.11 (d, *J* = 1.4 Hz, 3H), 2.03 (d, *J* = 8.2 Hz, 1H), 1.73 (d, *J* = 8.2 Hz, 1H), 1.21 (d, *J* = 6.2 Hz, 3H), 1.17 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 134.6, 130.8, 129.2, 128.5, 127.4, 72.3, 71.6, 64.0, 30.8, 23.3, 23.1, 16.1; HRMS (EI, M^+) calculated for $C_{15}H_{18}Cl_2O$, m/z 284.0735; found m/z 284.0728.



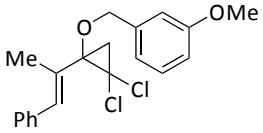
2-*tert*-butoxy-1,1-dichloro-2-(1-phenyl-[*1E*]-1-propen-2-yl)cyclopropane (66g). *t*-Butyl α-methylcinnamate (**72c**) was converted to **66g** in the same manner as for **66e**. Cyclopropanation time was 5 minutes. FCC (30 % dichloromethane in hexanes) provided **66g**, 714 mg, 29 % over two steps, as a white solid; m.p. 56-59 ºC; IR ($CDCl_3$ cast film) 3057, 3024, 2979, 2872, 1599, 1493, 1474, 1366, 1180, 769 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.31-7.24 (m, 2H), 7.28-7.24 (m, 1H), 6.51 (br s, 1H), 2.22 (d, *J* = 8.5 Hz, 1H), 2.13 (s, 3H), 1.90 (d, *J* = 8.5 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 136.9, 130.1, 129.1, 128.5, 127.3, 79.0, 68.9, 64.2, 32.6, 29.5, 16.7; HRMS (APPI, [M+H-*t*BuCl]$^+$) calculated for $C_{12}H_{12}ClO$, m/z 207.0577; found m/z 207.0542; Anal. Calcd for $C_{16}H_{20}Cl_2O$: C, 64.22; H, 6.74 Found: C, 64.57; H, 6.77.



1,1-dichloro-2-(3-methoxyphenoxy)-2-(1-phenyl-[*1E*]-1-propen-2-yl)cyclopropane (66h). α-Methylcinnamic acid (**71a**) (0.500 g, 3.08 mmol) was dissolved in 31 mL dichloromethane. 3-Methoxyphenol (0.51 mL, 4.6 mmol) was added *via* syringe, followed by 4-*N*,*N*-dimethylaminopyridine (57 mg, 0.47 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (0.700 g, 3.39 mmol). The mixture was allowed to stir overnight, and then magnesium sulfate was added, and the mixture was filtered through Celite. The solution was concentrated, and purification by FCC (gradient 5, 7, 10 % ethyl acetate in hexanes) provided 3-methoxyphenyl α-methylcinnamate (**72d**), 612 mg, 74 %, as a colourless oil; IR ($CHCl_3$ cast film) 3058, 2960, 2836, 1724, 1630, 1608, 1593, 1490, 1138 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (br s, 1H), 7.49-7.40 (m, 4H), 7.39-7.33 (m, 1H), 7.31 (app triplet, *J* = 8.2 Hz, 1H), 6.81 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.77 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.75-6.72 (m, 1H), 3.82 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 160.8, 152.4, 140.9, 135.9, 130.0, 128.9, 128.7, 128.1, 114.2, 112.0, 107.9, 55.7, 14.5 (one aromatic carbon signal is missing due to incidental overlap); HRMS (EI, M^+) calculated for $C_{17}H_{16}O_3$, m/z 268.1100; found m/z 268.1098.

3-Methoxyphenyl α-methylcinnamate (**72d**) was converted to 1,1-dichloro-2-(3-methoxyphenoxy)-2-(1-phenyl-[*1E*]-1-propen-2-yl)cyclopropane (**66h**) in the same manner as for **66e**. Cyclopropanation was done at 0 ºC for 45 minutes. FCC (5 % ethyl acetate in hexanes) provided **72d** as a colourless oil, 231 mg, 45 % over 2 steps; IR (neat) 3085, 3003, 2956, 2835, 1593, 1489, 1466, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.32 (m, 2H), 7.30-7.23 (m, 3H), 7.16 (app t, *J* = 8.2 Hz, 1H), 6.67-6.63 (m, 2H), 6.63-6.61 (m, 1H), 6.56 (ddd, *J* = 8.3, 2.4, 0.9 Hz, 1H), 3.78 (s, 3H), 2.38 (d, *J* = 9.0 Hz, 1H), 2.11 (d, *J* = 1.4 Hz,

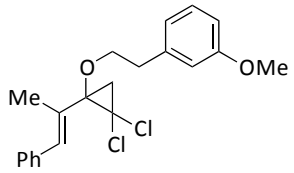
3H), 1.86 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 157.8, 136.5, 132.8, 131.7, 130.0, 129.2, 128.5, 127.5, 109.5, 108.0, 103.7, 70.9, 63.4, 55.6, 30.6, 15.8; HRMS (APPI, [M+H]) calculated for $C_{19}H_{19}O_2Cl_2$, m/z 349.0757; found m/z 349.0753.



1,1-dichloro-2-(3-methoxybenzyloxy)-2-(1-phenyl-[*1E*]-1-propen-2-yl)cyclopropane (66i). α-Methylcinnamic acid (**71a**) was converted to 3-methoxybenzyl α-methylcinnamate (**72e**) by the same procedure as for **72d** (see **66h**). FCC (gradient 5, 7, 10 % ethyl acetate in hexanes) provided the product, 1.28 g, 73 % as a colourless oil; IR (neat) 3056, 3000, 2937, 2836, 1705, 1633, 1599, 1490, 1451 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (br s, 1H), 7.42-7.38 (m, 4H), 7.35-7.29 (m, 2H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.79 (br s, 1H), 6.88 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.26 (s, 2H), 3.84 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 160.0, 139.5, 138.0, 136.1, 129.91, 129.87, 128.6, 120.5, 113.9, 113.8, 66.7, 55.5, 14.4 (2 aromatic carbon signals are missing due to incidental overlap); HRMS (EI, M^+) calculated for $C_{18}H_{18}O_3$, m/z 282.1256; found m/z 282.1252.

3-Methoxybenzyl α-methylcinnamate (**72e**) was converted to 1,1-dichloro-2-(3-methoxyphenoxy)-2-(1-phenyl-[*1E*]-1-propen-2-yl)cyclopropane (**66i**) by the same procedure as for **66e**. Cyclopropanation was done at 0 ºC for 13 minutes. FCC (5 % ethyl acetate in hexanes) provided **66i** as a colourless oil, 381 mg, 41 % over 2 steps; IR (neat) 3056, 3000, 2954, 2836, 1665, 1603, 1587, 1491, 1455 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.31 (m, 4H), 7.30-7.22 (m, 2H), 6.93-6.89 (m, 2H), 6.85-6.80 (m, 1H), 6.57 (br s, 1H), 4.60 (d, *J* = 11.8 Hz, 1H), 4.44 (d, *J* = 11.8 Hz, 1H), 3.80 (s, 3H), 2.14 (d, *J* = 1.4 Hz, 3H), 1.99 (d, *J* = 8.4 Hz, 1H), 1.72 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 139.3, 136.6, 132.7, 132.2, 129.7, 129.3, 128.6, 127.5, 120.0, 113.6, 113.2, 73.2, 69.8,

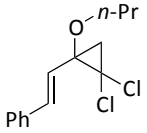
64.0, 55.4, 30.5, 15.9; HRMS (APPI, [M-Cl]) calculated for $C_{20}H_{20}O_2Cl$, m/z 327.1146; found m/z 327.1139.



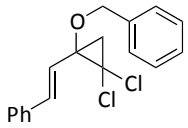
1,1-dichloro-2-(2-(3-methoxyphenoxy)ethoxy)-2-(1-phenyl-[*1E*]-1-propen-2-yl)cyclopropane (66j). α-Methylcinnamic acid (**71a**) was converted to 2-(3-methoxyphenyl)ethyl α-methylcinnamate (**72f**) by the same procedure as for **72d** (see **66h**). FCC (10 % ethyl acetate in hexanes) provided the product, 852 mg, 56 % as a colourless oil; IR (neat) 3055, 2998, 2956, 2835, 1707, 1634, 1603, 1585, 1490, 1453, 1259 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (br s, 1H), 7.42-7.36 (m, 4H), 7.36-7.29 (m, 1H), 7.24 (app t, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 7.4 Hz, 1H), 6.84-8.82 (m, 1H), 6.70 (dd, *J* = 8.2, 2.6 Hz, 1H), 4.43 (t, *J* = 7.0 Hz, 2H), 3.80 (s, 3H), 3.02 (t, *J* = 7.0 Hz, 2H), 2.11 (d, *J* = 1.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 160.0, 139.9, 139.2, 136.2, 129.9, 129.7, 128.7, 128.62, 128.56, 121.6, 115.0, 112.2, 65.6, 55.4, 35.5, 14.3; HRMS (ESI, [M+Na]) calculated for $C_{19}H_{20}O_3Na$, m/z 319.1305; found m/z 319.1300; Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80 Found: C, 77.25; H, 6.79.

2-(3-Methoxyphenyl)ethyl α-methylcinnamate (**72f**) was converted to 1,1-dichloro-2-(2-(3-methoxyphenoxy)ethoxy)-2-(1-phenyl-[*1E*]-1-propen-2-yl)cyclopropane (**66j**) by the same procedure as for **66e**. Cyclopropanation was done at 0 ºC for 5 minutes. FCC (5 % ethyl acetate in hexanes) provided **66j** as a colourless oil, 407 mg, 38 % over 2 steps; IR (neat) 3025, 2952, 2870, 1602, 1585, 1490, 1466, 1438, 1260 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.29 (m, 2H), 7.27-7.21 (m, 3H), 7.16 (app t, *J* = 7.7 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, H), 6.75-6.70 (m, 2H), 6.44 (br s, 1H), 3.78-3.69 (m, 4H), 3.57-3.45 (m, 1H), 2.91-2.78 (m, 2H), 1.99 (s, 3H), 1.87 (d, *J* 8.2 Hz, 1H), 1.49 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 140.6, 136.6, 132.8, 131.7, 129.5, 129.2, 128.5, 127.4, 121.6, 115.0, 112.0, 73.0, 69.0, 64.0, 55.4, 36.5, 30.2, 15.8; HRMS (APPI,

[M+H]) calculated for $C_{21}H_{23}O_2Cl_2$, m/z 377.1075; found m/z 377.1056; [M-Cl] calculated for $C_{21}H_{22}O_2Cl$, m/z 341.1308; found m/z 341.1293; Anal. Calcd for $C_{21}H_{22}O_2Cl_2$: C, 66.85; H, 5.88 Found, C, 66.48; H, 5.89.

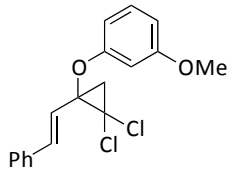


1,1-dichloro-2-(1-phenyl-[*1E*]-ethen-2-yl)-2-propylcyclopropane (66k). Propyl cinnamate (**72g**) was converted to (**66k**) by the same procedure as for **66e**. Cyclopropanation time was 15 minutes. FCC (2 % ether in hexanes) provided **66k** as a colourless oil, 134 mg, 49 % over 2 steps; IR ($CDCl_3$ cast film) 3028, 2963, 2933, 2877, 1599, 1496, 1449, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.40 (m, 2H), 7.37-7.32 (m, 2H), 7.30-7.25 (M, 1H), 6.78 (d, *J* = 16.0 Hz, 1H), 6.26 (d, *J* = 16.0 Hz, 1H), 3.68 (dt, *J* = 8.8, 6.4 Hz, 1H), 3.48 (dt, *J* = 8.8, 6.8 Hz, 1H), 1.82 (ABq, 2H, $\Delta\delta_{AB}$ = 0.06, *J* = 8.4 Hz), 1.67 (app sextet, *J* = 7.1 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 134.2, 129.0, 128.4, 126.8, 124.5, 70.3, 67.9, 65.3, 32.8, 23.3, 10.9; HRMS (APPI, M+H) calculated for $C_{14}H_{17}Cl_2O$ m/z 271.0651; found m/z 271.0649; (M-Cl) calculated for $C_{14}H_{16}ClO$ m/z 235.0884; found m/z 235.0875.

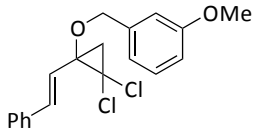


2-benzyloxy-1,1-dichloro-2-(1-phenyl-[*1E*]-1-ethen-2-yl)cyclopropane (66l). (*E*)-3-Benzyloxy-1-phenyl-1,3-butadiene[37] was converted to (**66l**) by the same prodecure as for **66e**. Cyclopropanation time was 15 minutes. FCC (2.5 % ether in hexanes) provided **66l** as a white solid, 328 mg, 96 %; m.p. 43-45 °C; IR (neat) 3063, 3029, 2929, 2875, 1598, 1497, 1454, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.47 – 7.27 (m, 10 H), 6.86 (d, *J* = 16.0 Hz, 1H), 6.36 (d, *J* = 16.0 Hz, 1H), 4.81 (d, *J* = 11.2 Hz, 1H), 4.67 (d, *J* = 11.2 Hz, 1H), 1.95 (d, *J* = 8.4 Hz, 1H), 1.86 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 136.2, 134.8,

129.0, 128.7, 128.5, 128.1, 127.9, 126.9, 123.9, 70.6, 68.2, 65.2, 33.1; HRMS (APPI, [M-Cl]) calculated for $C_{18}H_{16}OCl$, m/z 283.0884; found m/z 283.0882.



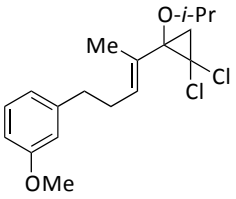
1,1-dichloro-2-(3-methoxyphenoxy)-2-(1-phenyl-[*1E*]-ethen-2-yl)cyclopropane (66m). 3-Methoxyphenyl cinnamate (**72i**)[38] was converted to (**66m**) by the same procedure as for **66e**. Cyclopropanation was done at 0 ºC for 22 minutes. FCC (5 % ethyl acetate in hexanes) provided **66m** as a colourless oil, 125 mg, 23 % over 2 steps; IR ($CHCl_3$ cast film) 3027, 3003, 2959, 2835, 1603, 1491, 1450, 1146 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 4H), 7.28-7.23 (m, 1H), 7.21-7.15 (m, 1H), 6.73 (d, *J* = 16.0 Hz, 1H), 6.62-6.55 (m, 3H), 6.31 (d, *J* = 16.0 Hz, 1H), 3.79 (s, 3H), 2.05 (ABq, 2H, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 157.3, 136.1, 134.2, 130.1, 128.9, 128.4, 126.9, 123.5, 109.2, 107.7, 103.4, 66.4, 64.9, 55.6, 34.0; HRMS (APPI, [M+H]) calculated for $C_{18}H_{17}O_2Cl_2$, m/z 335.0606; found m/z 335.0588.



1,1-dichloro-2-(3-methoxybenzyloxy)-2-(1-phenyl-[*1E*]-ethen-2-yl)cyclopropane (66n). Cinnamic acid was converted to 3-methoxybenzyl cinnamate (**72j**) by the same procedure as for **72d** (see **66h**). FCC (10 % ethyl acetate in hexanes) provided the product as a colourless oil, 1.566 g, 86 %; IR (neat) 3060, 3002, 2956, 2836, 1713, 1637, 1603, 1587, 1492, 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 16.0 Hz, 1H), 7.56-7.50 (m, 2H), 7.42-7.36 (m, 3H), 7.31 (app t, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.98-6.96 (m, 1H), 6.89 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.50 (d, *J* = 16.0 Hz, 1H), 5.23 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 160.0, 145.4, 137.8, 134.6, 130.6,

129.9, 129.1, 128.4, 120.7, 118.1, 114.0, 113.9, 66.4, 55.5; HRMS (EI, M^+) calculated for $C_{17}H_{16}O_3$, m/z 268.1100; found m/z 268.1097.

3-Methoxybenzyl cinnamate (**72j**) was converted to 1,1-dichloro-2-(3-methoxybenzyloxy)-2-(1-phenyl-[*1E*]-ethen-2-yl)cyclopropane (**66n**) by the same procedure as for **66e**. Cyclopropanation time was 5 minutes. FCC (5 % ethyl acetate in hexanes) provided **66n** as a colourless oil, 148 mg, 23 % over 2 steps IR ($CHCl_3$ cast film) 3058, 3028, 2938, 2836, 1604, 1587, 1491, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.41 (m, 2H), 7.38-7.33 (m, 2H), 6.97-6.93 (m, 2H), 6.88-6.81 (m, 2H), 6.34 (d, *J* = 16.1 Hz, 1H), 4.78 (d, *J* = 11.4 Hz, 1H), 4.63 (d, *J* = 11.4 Hz, 1H), 3.81 (s, 3H), 1.94 (d, *J* = 8.4 Hz, 1H), 1.85 (d, *J* = 8.4 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 139.2, 136.1, 134.8, 129.7, 129.0, 128.5, 126.9, 123.9, 120.0, 113.7, 113.2, 70.5, 68.2, 65.2, 55.5, 33.0; HRMS (APPI, [M+H]) calculated for $C_{19}H_{19}O_2Cl_2$, m/z 349.0757; found m/z 349.0757; [M-Cl] calculated for $C_{19}H_{18}O_2Cl$, m/z 313.0995; found m/z 131.0980.

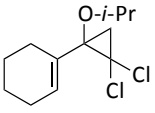


1,1-dichloro-2-isopropoxy-2-(5-(3-methoxyphenyl)-[2*E*]-2-penten-2-yl)cyclopropane (66o). Ethyl (*E*)-5-(3-methoxyphenyl)-2-methyl-2-pentenoate[39] (2.23 g, 8.85 mmol) was dissolved in 18 mL methanol, and potassium hydroxide pellets were added (2.48 g, 44.2 mmol). The mixture was heated at reflux for 1 h, then cooled and poured into water. The solution was acidified with concentrated hydrochloric acid, and then extracted three times with ether. The combined extract was dried over magnesium sulfate, filtered, and concentrated to 1.862 g white solid, 95 %: m.p. 44-47 °C; IR (neat) 3300-2500, 1694, 1642, 1602, 1489, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (app triplet, *J* = 7.7 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.81-6.73 (m, 3H), 3.80 (s, 3H), 2.77-2.71 (m, 2H), 2.52 (app quartet, *J* = 7.6 Hz, 2H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4,

160.0, 144.1, 142.9, 129.7, 127.9, 121.0, 114.4, 111.7, 55.4, 34.8, 30.9, 12.2; HRMS (EI, M^+) calculated for $C_{13}H_{16}O_3$, m/z 220.1099; found m/z 220.1100; Anal. Calcd for $C_{13}H_{16}O_3$: C 70.89; H, 7.32 Found C, 71.15; H, 7.54.

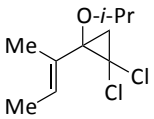
Acid **71c** was converted to isopropyl (*E*)-5-(3-methoxyphenyl)-2-methyl-2-pentenoate (**72g**) by the same procedure as for **72d** (see **66e**). FCC (10 % ethyl acetate in hexanes) provided the product as a colourless oil, 739 mg, 62 %; IR (neat) 2980, 2938, 2836, 1707, 1649, 1602, 1585, 1489, 1455, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23-7.18 (m, 1H), 6.81-6.73 (m, 4H), 5.05 (septet, *J* = 6.2 Hz, 1H), 3.80 (s, 3H), 2.75-2.70 (m, 2H), 2.51-2.44 (m, 2H), 1.79-1.78 (m, 3H), 1.26 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 159.9, 143.2, 140.8, 129.7, 129.1, 121.0, 114.4, 111.6, 67.9, 55.4, 35.1, 30.8, 22.1, 12.6; HRMS (EI, M^+) calculated for $C_{16}H_{22}O_3$, m/z 262.1569; found m/z 262.1571; Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45 Found C, 73.17; H, 8.59.

Ester (**72g**) was converted to 1,1-dichloro-2-isopropoxy-2-(5-(3-methoxyphenyl)-[2*E*]-2-penten-2-yl)cyclopropane (**66o**) by the same procedure as for **66e**. Cyclopropanation time was 8 minutes. FCC (5 % ethyl acetate in hexanes) provided the product as a pale yellow oil, 320 mg, 57 % over two steps; IR (dichloromethane cast film) 2974, 2934, 2835, 1602, 1585, 1489, 1455 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (app t, *J* = 7.7 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H) 6.74-6.70 (m, 2H), 5.47 (tq, *J* = 7.3, 1.3 Hz, 1H), 3.79 (s, 3H), 3.63 (septet, *J* = 6.2 Hz, 1H), 2.73-2.60 (m, 2H), 2.46-2.39 (m, 2H), 1.82-1.79 (m, 4H), 1.56 (d, *J* = 8.2 Hz, 1H), 1.10 (d, *J* = 6.2 Hz, 3H), 1.06 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 143.4, 132.3, 131.0, 129.5, 121.1, 114.6, 111.3, 71.6, 71.0, 63.8, 55.4, 35.5, 30.6, 29.4, 23.3, 22.9, 14.2; HRMS (APPI, M^+) calculated for $C_{18}H_{25}Cl_2O_2$, m/z 343.1226; found m/z 343.1234; [M-Cl] calculated for $C_{18}H_{24}ClO_2$, m/z 307.1459; found m/z 307.1464.



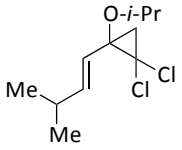
1,1-dichloro-2-(1-cyclohexenyl)-2-isopropoxycyclopropane (66p). A flame-dried flask under argon was charged with 30 mL THF, and then cooled to 0 ºC. A solution of titanium tetrachloride (1.3 mL, 11.9 mmol) in 4.7 mL dichloromethane was added, resulting in the formation of a yellow slurry. Tetramethylethylenediamine (3.56 mL, 23.8 mmol) was added, and the brown mixture was stirred for 20 min. before activated zinc dust (1.748 g, 26.7 mmol) and lead(II) chloride (41 mg, 0.148 mmol) were added. The mixture was allowed to warm to r.t. and stir for 30 min. until the mixture turned bright blue. A solution of isopropyl cyclohexene-1-carboxylate (**72h**, 0.500 g, 2.97 mmol) and dibromomethane (0.44 mL, 6.2 mmol) in 7.6 mL THF was added *via* cannula, and the reaction was stirred at room temperature until the starting material was consumed as judged by TLC. After cooling to 0 ºC, sodium methoxide (643 mg, 11.9 mmol) was added and after 20 min., 30 mL of 0.5 % triethylamine in ether. The slurry was filtered through basic alumina Brockman activity III, and the solution was concentrated to provide the crude enol ether, which was used directly in the next step.

Cyclopropanation by the same procedure as for **66a** (30 minutes) gave the crude cyclopropane, which was purified by FCC (1 % ethyl acetate in hexanes) to provide **66p** as a yellow oil, 326 mg, 44 % over 2 steps. IR (neat) 2975, 2931, 2859, 1449, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.76-5.72 (m, 1H), 3.75 (septet, *J* = 6.2, 1H), 2.36-2.26 (m, 1H), 2.18-2.04 (m, 3H), 1.82 (d, *J* = 8.1 Hz, 1H), 1.73-1.58 (m, 4H), 1.56, (d, *J* = 8.1 Hz, 1H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.11 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 128.8, 71.2, 70.6, 64.0, 30.1, 26.0, 25.5, 23.4, 23.1, 22.7, 22.5; HRMS (APPI, M^+) calculated for $C_{12}H_{18}Cl_2O$, m/z 248.0729; found m/z 248.0729.

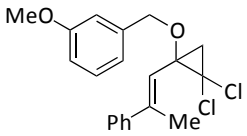


1,1-dichloro-2-isopropoxy-2-([2*E*]-2-buten-2-yl)cyclopropane (66q). Isopropyl tiglate (**72i**) was converted to **66q** by the same procedure as for **66p**. FCC (2 %

ethyl acetate in hexanes) provided **66q**, 99 mg, as a colourless oil, 32 % over 2 steps. IR (neat) 2976, 1453, 1382, 1237, 1116 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.55 (q, *J* = 6.8 Hz, 1H), 3.73 (septet, *J* = 6.2 Hz, 1H), 1.84-1.81 (m, 4H), 1.68 (d, *J* = 6.8 Hz, 3H), 1.58 (d, *J* = 8.1 Hz, 1H), 1.15 (d, *J* = 6.2 Hz, 3H), 1.10 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.4, 126.2, 71.7, 71.0, 63.9, 30.5, 23.2, 23.0, 13.9, 13.5; HRMS (APPI, M^+) calculated for $C_{10}H_{16}Cl_2O$, m/z 222.0573; found m/z 222.0563.



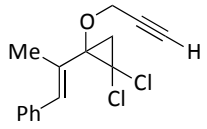
1,1-dichloro-2-isopropoxy-2-(3-methyl-[1*E*]-1-buten-1-yl)cyclopropane (66r). Isopropyl (*E*)-4-methyl-2-pentenoate (**72j**) was converted to **66r** by the same procedure as for **66p** (5 minute cyclopropanation). FCC 2 % ethyl acetate in hexanes provided the cyclopropane as a yellow oil, 339 mg, 46 % over 2 steps; IR (neat) 2965, 2871, 1466, 1119, 1061 cm^{-1}; ^1H NMR (MHz, CDCl3) δ 5.80 (dd, *J* = 15.5, 6.8 Hz, 1H), 5.60 (d, *J* = 15.5 Hz, 1H), 3.85 (septet, *J* = 6.2 Hz, 1H), 2.39 (app octet, *J* = 6.7 Hz, 1H), 1.21 (d, *J* = 6.2 Hz, 3H), 1.16 (d, *J* = 6.2 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 1.02 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 123.5, 71.1, 67.0, 64.8, 31.2, 31.0, 23.4, 23.2, 22.4 [one methyl carbon signal is missing due to incidental overlap]; HRMS (APPI, M-Cl) calculated for $C_{11}H_{18}ClO$, m/z 201.1041; found m/z 201.1039.



1,1-dichloro-2-(3-methoxybenzyloxy)-2-([1*E*]-2-phenylpropen-1-yl)cyclopropane, (72k). β-methylcinnamic acid was converted to 3-methoxybenzyl (*E*)-β-methylcinnamate (**72k**) by the same procedure as for **72d** (see **66h**). FCC (5 % ethyl acetate in hexanes) provided **72k** as a colorless oil, 489 mg, 56 %: IR (neat) 3057, 3001, 2836, 1714, 1629, 1587, 1491, 1156, 768

cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.40-7.35 (m, 3H), 7.29 (app. t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.96-9.94 (m, 1H), 6.87 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.21 (br q, *J* = 1.3 Hz, 1H), 5.19 (s, 2H), 3.82 (s, 3H), 2.61 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 160.0, 156.6, 142.4, 138.1, 129.9, 129.3, 128.8, 126.6, 120.6, 117.0, 113.9, 113.8, 65.9, 55.5, 18.3; HRMS (EI, M^+) for $C_{18}H_{18}O_3$ calculated 282.1256, found m/z 282.1245.

72k was converted to **66s** by the same procedure as for **66p**. Cyclopropanation time was 1.5 minutes. Purification by FCC (5 % ethyl acetate in hexanes) yielded **66s** as a colorless oil, 1.03 g, 38 % over 2 steps: IR (neat) 3056, 2939, 2835, 1604, 1588, 1492,1267, 1051, 777, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.45 (m, 2H), 7.40-7.30 (m, 3H), 7.27-7.22 (m, 1H), 6.95-6.91 (m, 2H), 6.85-6.81 (m, 1H), 6.21 (br s, 1H), 4.70 (d, *J* = 10.8 Hz, 1H), 4.65 (d, *J* = 10.7 Hz, 1H), 3.79 (s, 3H), 2.30 (d, *J* = 1.1 Hz, 3H), 2.05 (d, *J* = 8.1 Hz, 1H), 1.69 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 146.5, 142.0, 139.4, 129.7, 128.7, 128.3, 126.1, 120.7, 120.4, 113.63, 113.58, 70.0, 64.7, 64.4, 55.4, 34.7, 17.6; HRMS (APPI, $[M+H]^+$) for $C_{20}H_{21}Cl_2O_2$, 363.0919, found m/z 363.0918.



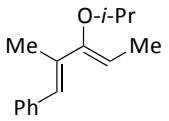
1,1-dichloro-2-(1-phenyl-[*1E*]-1-propen-2-yl)-2-propargyloxycyclopropane (66u). α-Methylcinnamic acid (**71a**) was converted to propargyl α-methylcinnamate (**72l**) by the same procedure as for **72d** (see **66h**). FCC (5 % ethyl acetate in hexanes) provided the product as a colourless oil, 1.42 g, 77 %; IR (neat) 3292, 3059, 2945, 2129, 1713, 1633, 1492, 1449, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (q, *J* = 1.5 Hz, 1H), 7.42-7.39 (m, 4H), 7.37-7.32 (m, 1H), 4.83 (d, *J* = 2.4 Hz, 2H), 2.50 (t, *J* = 2.4 Hz, 1H), 2.14 (d, *J* = 1.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 140.3, 135.9, 130.0, 128.75, 128.66, 127.9,

78.2, 75.0, 52.6, 14.3; HRMS (EI, M^+) calculated for $C_{13}H_{12}O_2$, m/z 200.0837, found m/z 200.0833.

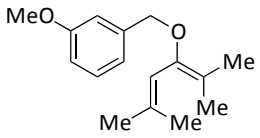
Propargyl α-methylcinnamate (**72l**) (1.238 g, 6.183 mmol) was dissolved in 6.2 mL dichloromethane. Silver chloride (177 mg, 1.24 mmol) and DBU (1.8 mL, 12 mmol) were added to the reaction flask, and then the mixture was heated to 40 ºC. TMSCl (1.6 mL, 12 mmol) was added, and the reaction was stirred at that temperature for 24 hours. The mixture was cooled, diluted with hexanes, and washed twice with a saturated solution of sodium bicarbonate, twice with 1 M hydrochloric acid, water, then brine, and dried over magnesium sulfate, filtered, and concentrated to a colourless oil. FCC (5 % ethyl acetate in hexanes) provided **72m** as a colourless oil, 1.459 g, 87 %; IR (neat) 3059, 2961, 2900, 2186, 1635, 1576, 1492, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (q, J = 1.4 Hz, 1H), 7.42-7.39 (m, 4H), 7.36-7.30 (m, 1H), 4.83 (s, 2H), 2.14 (d, J = 1.4 Hz, 3H), 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 140.0, 136.0, 130.0, 128.7, 128.6, 128.1, 99.6, 92.2, 53.4, 14.3, 0.0; HRMS (EI, M^+) calculated for $C_{16}H_{20}O_2Si$, m/z 272.1233, found m/z 272.1218; Anal. Calcd for $C_{16}H_{20}O_2Si$: C, 70.54; H, 7.40 Found C, 70.65; H, 7.63.

Ester **72m** was converted to dichlorocyclopropane **66t** by the same procedure as for **66p** (cyclopropanation time 2 minutes). FCC (gradient 100 % hexanes to 4 % ethyl acetate in hexanes) provided the product as a colourless oil, 201 mg, 16 % over 2 steps. Compound **66t** was contaminated with a small amount of the deprotected compound **66u**; IR (neat) 3026, 2959, 2900, 2858, 2178, 1600, 1576, 1494, 1412 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.23 (m, 5H), 6.60 (br s, 1H), 4.17 (ABq, 2H, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 15.9 Hz), 2.10 (s, 3H), 1.98 (ABq, 2H, $\Delta\delta_{AB}$ = 0.06, J_{AB} = 8.4 Hz), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.6, 133.0, 131.9, 129.3, 128.5, 127.6, 101.2, 92.5, 73.1, 63.2, 56.7, 31.0, 15.9, -0.1; HRMS (ESI, M+Na) calculated for $C_{18}H_{22}OSiCl_2Na$, m/z 375.0709, found m/z 375.07185.

Cyclopropane **66t** (50 mg, 0.14 mmol) was dissolved in 0.28 mL methanol. Potassium carbonate (3 mg, 0.02 mmol) was added to the flask, and the reaction was allowed to stir at room temperature for 40 minutes. The reaction was diluted with water, and the solution was extracted three times with ether. The combined extract was washed with water then brine, dried over magnesium sulfate, filtered, and concentrated to a colourless oil. FCC (5 % ethyl acetate in hexanes) provided 1,1-dichloro-2-(1-phenyl-[*1E*]-1-propen-2-yl)-2-propargyloxy-cyclopropane (**66u**) as a colourless oil, 33 mg, 85 %; IR ($CHCl_3$ cast film) 3298, 3025, 2919, 2860, 2122, 1599, 1576, 1493, 1441, 1412, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H), 6.60 (br s, 1H), 4.24 (ABX, 2H, $\Delta\delta_{AB}$ = 0.09, J_{AB} = 15.6 Hz, J_{AX} = 2.5 Hz, J_{BX} = 2.4 Hz), 2.43 (X part, app triplet, J = 2.4 Hz, 1H), 2.11 (d, J = 1.4 Hz, 3H), 1.99 (ABq, 2H, $\Delta\delta_{AB}$ = 0.06, J_{AB} = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 133.0, 131.8, 129.3, 128.6, 127.6, 79.4, 75.3, 73.1, 63.1, 55.8, 30.7, 15.9.



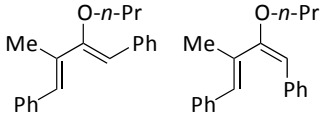
(1*E*,3*Z*)-3-isopropoxy-2-methyl-1-phenyl-1,3-pentadiene (73m). Isopropyl α-methylcinnamate (**72b**) was converted to **73m** by the same procedure as for **66p**, substituting 1,1-dibromoethane for dibromomethane. FCC (hexanes on basic alumina, Brockmann activity III) provided the product as a colourless oil, 1.268 g, 79 %, >20:1 *Z* : *E*. IR (neat) 3057, 2974, 2859, 1637, 1599, 1490, 1445, 1369, 1108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.32 (m, 2H), 7.32-7.28 (m, 2H), 7.24-7.20 (m, 1H), 6.79 (br s, 1H), 5.29 (q, J = 6.9 Hz, 1H), 4.08 (septet, J = 6.2 Hz, 1H), 1.98 (s, 3H), 1.76 (d, J = 6.9 Hz, 3H), 1.27 (d, J = 6.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 138.4, 133.6, 129.5, 128.3, 126.58, 126.56, 110.4, 72.0, 22.6, 15.5, 12.0; HRMS (EI, M^+) calculated for $C_{15}H_{20}O$, 216.1514; found m/z 216.1512; Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32, found: C, 83,18; H, 9.23.



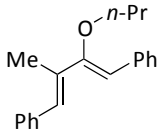
3-(3-methoxybenzyloxy)-2,5-dimethyl-2,4-hexadiene (73n). Senecoic acid (**71e**) was converted to 3-methoxybenzyl senecoate (**72n**) by the same procedure as for **72d** (see **66h**). Purification by FCC (10 % ethyl acetate in hexanes) provided **72n** as a colorless oil, 1.780 g, 62 %: IR (neat) 2941, 2837, 1718, 1650, 1604, 1456, 1226, 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (app t, *J* =7.9 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 6.92-6.90 (m, 1H), 6.85 (dd, *J* = 8.3 Hz, 2.6 Hz, 1H), 5.75 (app septet, *J* = 1.4 Hz, 1H), 5.11 (s, 2H), 3.81 (s, 3H), 2.19 (d, *J* = 1.2 Hz, 3H), 1.90 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 159.9, 157.6, 138.2, 129.8, 120.5, 116.0, 113.8, 113.7, 65.4, 55.5, 27.7, 20.5; HRMS (EI, M^+) $C_{13}H_{16}O_3$ calculated 220.1099, found m/z 220.1102.

Titanocene dichloride (5.36 g, 21.5 mmol), powdered 4 Å molecular sieves (2.15 g), and magnesium turnings (654 mg, 26.9 mmol) were combined in a round bottom flask and then flame-dried under vacuum. The flask was cooled, then 40 mL THF was added, followed by triethylphosphite (7.0 mL, 42 mmol). The resulting suspension was stirred for 3h at room temperature. 2,2-Di(thiophenyl)propane (1.54 g, 5.92 mmol) in 10 mL THF was added *via* cannula in a dropwise fashion. After 5 minutes, a solution of **72n** (1.184 g, 5.38 mmol) in 10 mL THF was added *via* cannula. The reaction was stirred at room temperature for 18 hours, and then quenched with 5 % aqueous sodium hydroxide and stirred for 45 minutes. The mixture was filtered through Celite. Ether was added to the filtrate, and the layers were separated. The ether solution was washed with water then brine, dried over magnesium sulfate, filtered, and concentrated. FCC (hexanes on basic alumina, Brockman activity III) provided a mixture of the desired compound and residual triethyl phosphite. The triethylphosphite was distilled off by Kugelrohr distillation at reduced pressure (0.5 mmHg) up to 80 ºC to provide 3-(3-methoxybenzyloxy)-2,5-dimethyl-2,4-hexadiene (**73n**) as a pale

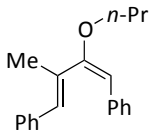
yellow oil, 812 mg, 61 %; IR (neat) 2967, 2912, 2855, 1655, 1604, 1588, 1490, 1455 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25-7.21 (m, 1H), 6.93-6.90 (m, 2H), 6.83-6.79 (m, 1H), 5.64-5.61 (m, 1H), 4.59 (s, 2H), 3.81 (s, 3H), 1.82 (d, *J* = 1.4 Hz, 3H), 1.72 (d, *J* = 0.9 Hz, 3H), 1.63 (d, *J* = 1.2 Hz, 3H), 1.54 (s, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 145.6, 140.7, 139.0, 129.4, 120.2, 118.8, 115.5, 113.32, 113.29, 70.9, 55.4, 25.9, 20.2, 19.6, 17.4; HRMS (EI, M^+) calculated for $C_{16}H_{22}O_2$ m/z 246.1620; found m/z 246.1619.



(1*Z*,3*E*)-3-methyl-1,4-diphenyl-2-propoxy-1,3-butadiene and (1*E*,3*E*)-3-methyl-1,4-diphenyl-2-propoxy-1,3-butadiene (73o). Compound **73o** was prepared from propyl α-methylcinnamate (**72d**) and α,α-di(thiophenyl)toluene in the same manner as **73n**. The crude product was purified by FCC (5 % ether in hexanes on basic alumina Brockman activity III) to provide the product as a colourless oil, 305 mg, 44 % yield as a 20 : 1 mixture of *Z* to *E* isomers. Data given are for the mixture: IR (neat) 3053, 2963, 2876, 1613, 1489, 1445, 1080, 696; HRMS (EI, M^+) calculated for $C_{20}H_{22}O$, m/z 278.1670; found m/z 278.1670.

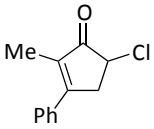


Major isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.71-7.69 (m, 2H), 7.40-7.32 (m, 6H), 7.28-7.24 (m, 1H), 7.22-7.18 (m, 1H), 7.04 (br s, 1H), 6.08 (s, 1H), 3.71 (t, *J* = 6.7 Hz, 2H), 2.11 (d, *J* = 1.2 Hz, 3H), 1.84-1.76 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 137.9, 136.2, 133.0, 129.4, 128.9, 128.3, 128.2, 128.0, 126.8, 126.6, 113.5, 72.6, 23.5, 15.4, 10.7.

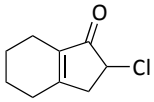


Minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (s, 1H), 5.69 (s, 1H), 3.84 (t, *J* = 6.5 Hz, 2H), 2.04 (d, *J* = 1.5 Hz, 3H), 1.06 (t, *J* = 7.4 Hz, 3H).

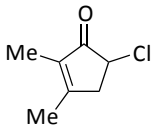
General Procedure for Nazarov Reactions:



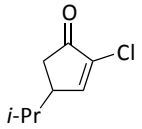
5-chloro-2-methyl-3-phenyl-2-cyclopentenone (67a). Cyclopropane **66f** (50.1 mg, 0.175 mmol) was dissolved in 3.5 mL 1,2-dichloroethane (0.05 M **66f**). Magnesium sulfate (42 mg, 0.35 mmol, 2 equiv.) followed by silver triflimide (68 mg, 0.18 mmol, 1 equiv.) was added to the reaction flask, and the resulting mixture was heated to reflux. After 18 hours, the mixture was cooled and filtered through a silica plug, which was rinsed with dichloromethane. The filtrate was concentrated under reduced pressure, and the crude cyclopentenone was purified by FCC (15 % ethyl acetate in hexanes) to provide the product as a white solid, 26.9 mg, 74 %. The data for this compound are in agreement with that previously reported.[26]



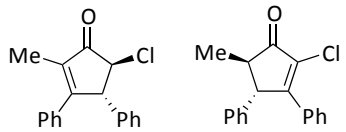
$\Delta^{1,6}$-8-chloro-bicyclo[4.3.0]nonen-7-one (67b). The above procedure was used to convert 1,1-dichloro-2-(1-cyclohexenyl)-2-isopropoxycyclopropane (**66p**, 30 mg, 0.12 mmol) to **67b**. Flash column chromatography (gradient hexanes to 20 % ethyl acetate in hexanes) provided the product (slightly impure) as a pale yellow oil, 7.0 mg, < 34 %. The data for this compound are in agreement with that previously reported.[26]



5-chloro-2,3-dimethyl-2-cyclopentenone (67c). The above procedure was used to convert 1,1-dichloro-2-isopropoxy-2-([2*E*]-2-buten-2-yl)cyclopropane (**66q**, 25 mg, 0.11 mmol) to **67c**. The presence of **67c** was implied by the following data: ^{1}H NMR (MHz, $CDCl_3$) δ 4.24 (dd, *J* = 6.8, 2.4, 1H), 3.11 (dd, *J* = 18.8, 6.9 Hz, 1H), 2.68 (d, *J* = 18.8 Hz, 1H), 2.07 (s, 3H), 1.76 (s, 3H).



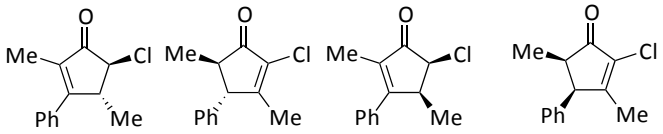
2-chloro-4-isopropyl-2-cyclopentenone (98a). The above procedure was used to convert 1,1-dichloro-2-isopropoxy-2-(3-methyl-[1*E*]-1-buten-1-yl)cyclopropane (**66r**, 30 mg, 0.13 mmol) to **98a**. Flash column chromatography (10 % ethyl acetate in hexanes) provided the product as a colourless oil, 10.4 mg, 50 %. The data for this compound are in agreement with that previously reported.[26]



***trans*-5-chloro-2-methyl-3,4-diphenyl-2-cyclopentenone (67d) and *trans*-2-chloro-5-methyl-3,4-diphenylcyclopentenone (98b)**. 3-Methyl-1,4-diphenyl-2-propoxy-1,3-butadiene (**73o**, 50.3 mg, 0.181 mmol) was cyclopropanated by the same procedure as for **66a** (cyclopropanation time was 40 minutes), and then the crude cyclopropane was subjected to Nazarov conditions (40 minutes). FCC (2 % acetone, 10 % dichloromethane in petroleum ether) provided the cyclopentenones **67d** and **98b**, 23.1 mg, 45 %, in a 5.9 : 1 ratio as an inseparable mixture. Data given is for the mixture; IR ($CHCl_3$ cast film) 3062, 3029, 2923, 1715, 1617, 1603, 1573, 1496, 1454 cm^{-1}; HRMS (EI, M^+) calculated for $C_{18}H_{15}ClO$ m/z 282.0812; found m/z 282.0814.

67d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.08 (m, 10 H), 4.56-4.52 (m, 1H), 4.20 (d, *J* = 2.9 Hz, 1H), 2.10 (d, *J* = 2.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 166.4, 139.6, 136.4, 134.3, 130.0, 129.3, 128.8, 127.9, 127.8, 62.7, 58.2, 10.7. One aromatic carbon signal is missing due to incidental overlap.

98b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.08 (m, 10H), 4.10 (d, *J* = 2.7 Hz, 1H), 2.51 (qd, *J* = 7.4, 2.7 Hz, 1H), 1.41 (d, *J*= 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 164.6, 141.2, 132.6, 130.7, 129.0, 128.6, 127.6, 127.4, 55.7, 50.3, 15.6. Two of the aromatic carbon signals are missing due to incidental overlap.



***trans*-5-chloro-2,4-dimethyl-3-phenyl-2-cyclopentenone (67e)**, ***trans*-2-chloro-3,5-dimethyl-4-phenyl-2-cyclopentenone (98c)**, ***cis*-5-chloro-2,4-dimethyl-3-phenyl-2-cyclopentenone (67e′) and *cis*-2-chloro-3,5-dimethyl-4-phenyl-2-cyclopentenone (98c′)**. (1*E*,3*Z*)-3-Isopropoxy-2-methyl-1-phenyl-1,3-pentadiene (**73m**, 100 mg, 0.462 mmol) was cyclopropanated by the same procedure as for **66a** (reaction time was 15 minutes), and then the crude cyclopropane was subjected to Nazarov conditions (30 minute reaction time) to provide cyclopentenones **67e**, **98c**, **67e′** and **98c′**. FCC (10 % ether in petroleum ether) followed by preparatory TLC (20 % ether in petroleum ether) provided **98c** (10.3 mg, 10 %); **67e** (45.1 mg, 44 %); **67e′** and **98c′** as a 2 : 1 mixture (14.7 mg, 13 %).

67e: white solid; m.p. 80-83 ºC; IR ($CHCl_3$ cast film) 2967, 2929, 2874, 1713, 1623, 1573, 1450 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.43 (m, 3H), 7.37-7.34 (m, 2H), 3.98 (d, *J* = 2.9 Hz, 1H), 3.46-3.38 (m, 1H), 1.91 (d, *J* = 2.1 Hz, 3H), 1.21 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 169.7, 134.7, 134.3, 130.0, 129.0, 128.3, 61.5, 47.1, 17.9, 10.1; HRMS (EI, M^+) calculated for $C_{13}H_{13}ClO$, 220.0655; found m/z 220.0658.

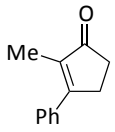
98c: white solid; m.p. 84-86 ºC; IR ($CHCl_3$ cast film) 3028, 2968, 2873, 1725, 1626, 1493, 1454 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.37 (m, 2H), 7.36-7.32 (m, 1H), 7.17-7.13 (m, 2H), 3.47 (br s, 1H), 2.48 (qd, *J* = 7.4, 2.4 Hz, 1H); 1.98 (s, 3H), 1.33 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6,

169.5, 140.2, 131.9, 129.4, 127.9, 127.8, 57.7, 50.0, 15.9, 15.3; HRMS (EI, M^+) calculated for $C_{13}H_{13}ClO$, 220.0655; found m/z 220.0653.

67e′ and **98c′** mixture: Oily white solid; data given is for the mixture. IR ($CHCl_3$ cast film) 3060, 2977, 2933, 2875, 1713, 1627, 1494, 1453 cm^{-1}; HRMS (EI, M^+) calculated for $C_{13}H_{13}OCl$ m/z 220.0655; found m/z 220.0651.

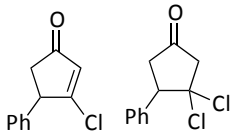
67e′, major: ^1H NMR (500 MHz, $CDCl_3$) δ 7.51-7.27 (m, 5H), 4.65 (d, *J* = 6.6 Hz, 1H), 3.66-3.59 (m, 1H), 1.93 (d, *J* = 1.7 Hz, 3H), 1.16 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 170.6, 134.8, 134.0, 129.9, 129.1, 127.8, 60.4, 40.9, 17.3, 10.2.

98c′, minor: ^1H NMR (500 MHz, $CDCl_3$) δ 7.51-7.27 (m, 5H), 4.11 (d, *J* = 7.0 Hz, 1H), 2.90-2.83 (m, 1H), 2.03-2.02 (m, 3H), 0.75 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.0, 169.2, 137.4, 132.6, 129.0, 128.3, 127.9, 53.6, 44.5, 16.4, 12.5.



2-methyl-3-phenyl-2-cyclopentenone (67f). Cyclopropane **66f** (25 mg, 0.088 mmol) was dissolved in 0.5 mL ether. The flask was cooled in a toluene/liquid nitrogen slurry (-95 ºC), and *t*-butyllithium (0.12 mL, 1.6 M in pentane, 0.19 mmol) was added dropwise *via* syringe. After stirring for 10 minutes, 1 drop of water dissolved in 0.5 mL THF was added, and the reaction was allowed to warm slowly to room temperature. The solution was transferred to a separatory funnel, washed with water then brine, dried over magnesium sulfate, filtered, and concentrated to provide 1-chloro-2-isopropoxy-2-(1-phenyl-[1*E*]-1-propen-2-ylcyclopropane (**66w**) as a pale yellow oil, 20.9 mg, 94 % crude. Partial data is reported: ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.31 (m, 4H), 7.27-7.23 (m, 1H), 6.59 (br s, 1H), 3.82 (app septet, *J* = 6.2 Hz, 1H), 3.30 (dd, *J* = 8.5, 4.9 Hz, 1H), 2.07 (d, *J* = 1.4 Hz, 3H), 1.49 (dd, *J* = 8.5, 7.3 Hz, 1H), 1.40 (dd, *J* = 7.3, 4.9 Hz, 1H), 1.14 (d, *J* = 6.2 Hz, 3H), 1.10 (d, *J* = 6.2 Hz, 3H).

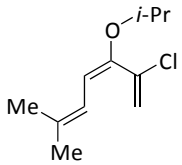
Chlorocyclopropane **66w** was subjected to Nazarov conditions (30 minute reaction time). FCC (gradient, 2, 5, 7, 10 % ethyl acetate in hexanes) provided, **67f**, 5.5 mg, 36 % over two steps. The data for this compound are in agreement with that reported in the literature.[53]



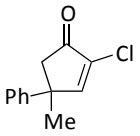
3-chloro-4-phenyl-2-cyclopentenone (98d) and **3,3-dichloro-4-phenylcyclopentanone (99)**. Cyclopropane **66l** (49.9 mg, 0.157 mmol) was dissolved in 31 mL carbon disulfide. Antimony pentachloride (22 μL, 0.17 mmol) was added *via* syringe and the solution was heated to reflux for 10 minutes. After cooling, the mixture was filtered through a small silica plug, eluted with dichloromethane, and concentrated. A mixture of compounds **98d** and **99** were observed in the NMR spectra of the crude mixture. FCC (10 % ethyl acetate in hexanes) gave **98d** as a pale yellow oil, 10.5 mg, 34 %. IR (neat) 3087, 3030, 2927, 1713, 1588, 1496, 1455, 1406 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.35 (m, 2H), 7.34-7.30 (m, 1H), 7.19-7.16 (m, 2H), 6.39 (d, *J* = 1.7 Hz, 1H), 4.16 (app dt, *J* = 7.3, 2.0 Hz, 1H), 3.08 (dd, *J* = 18.8, 7.3 Hz, 1H), 2.58 (dd, *J* = 18.8, 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 173.2, 139.1, 132.2, 129.4, 128.2, 127.6, 51.9, 46.6; HRMS (EI, M^+) calculated for $C_{11}H_9ClO$, m/z 192.0342; found, m/z 192.0337.

Partial data is reported for **99**, as it was observed as a mixture with **98d**.

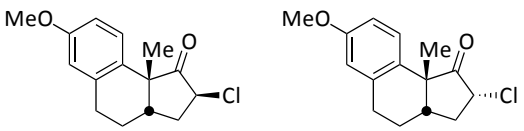
^1H NMR (500 MHz, $CDCl_3$) δ 4.07 (dd, *J* = 12.1, 7.7 Hz, 1H), 3.51 (d, *J* = 18.3 Hz, 1H), 3.29 (d, *J* = 18.3 Hz, 1H), 3.02 (dd, *J* = 18.8, 12.0 Hz, 1H), 2.78 (dd, *J* = 18.8, 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 134.1, 129.7, 128.9, 128.5, 90.1, 61.1, 57.7, 42.5.



(*E*)-2-chloro-3-isopropoxy-6-methylhepta-1,3,5-triene (106). 1,1-Dichloro-2-isopropoxy-2-(3-methyl-[1*E*]-1-buten-1-yl)cyclopropane (**66r**) (20 mg, 0.084 mmol) was dissolved in 1.7 mL 1,2-dichloroethane. Proton sponge (*N,N,N′,N′*-tetramethyl-1,8-diaminonaphthalene) (36 mg, 0.17 mmol) was added to the reaction flask, and the resulting solution was heated to reflux for 48 hours. After cooling, the solution was filtered through silica and concentrated. FCC (5 % ethyl acetate in hexanes) gave **106** as a pale yellow oil, 14.3 mg, 84 %; IR (neat) 2976, 2929, 2875, 1618, 1594, 1181 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.01 (d, *J* = 11.2 Hz, 1H), 5.85 (d, *J* = 11.2 Hz, 1H), 5.67 (s, 1H), 5.49 (s, 1H), 4.21 (septet, *J* = 6.1 Hz, 1H), 1.78 (s, 3H), 1.74 (s, 3H), 1.25 (d, *J* = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 134.2, 134.0, 120.4, 119.8, 109.3, 70.8, 26.5, 22.2, 18.6. Due to extensive fragmentation, the molecular ion was not seen in the mass spectrum.



2-chloro-4-methyl-4-phenyl-2-cyclopentenone (98e). 1,1-Dichloro-2-(2-phenyl-[*1E*]-1-propen-1-yl)-2-triisopropylsiloxycyclopropane (**66d**, 25 mg, 0.063 mmol) was dissolved in 1.3 mL 1,2-dichloroethane. Silver triflimide (24 mg, 0.063 mmol) was added and the solution was heated to reflux for 18 hours. The resulting mixture was cooled, filtered through a plug of silica and concentrated. FCC (10 % ethyl acetate in hexanes) provided the product as a pale yellow oil, 9.5 mg, 73 %; IR (neat) 3060, 2968, 2928, 1728, 1600, 1496, 1446 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.39-7.33 (m, 2H), 7.30-7.24 (m, 3H) 2.76 (ABq, 2H, $\Delta\delta_{AB}$ = 0.09, J_{AB} = 18.9 Hz), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 164.0, 144.8, 134.2, 129.2, 127.4, 125.8, 51.0, 45.8, 27.7; HRMS (EI, M^+) calculated for $C_{12}H_{11}ClO$, m/z 206.0498; found m/z 206.0495.



2-chloro-7-methoxy-9b-methyl-2,3,3a,4,5,9b-hexahydro-cyclopenta[a]naphthalen-1-ones (121) and (*epi*-121). 1,1-Dichloro-2-isopropoxy-2-(5-(3-methoxyphenyl)-[*2E*]-2-penten-2-yl)cyclopropane (**66o**, 50 mg, 0.15 mmol) was converted to **121** and *epi*-**121** using the general Nazarov procedure above. FCC (gradient 10, 11, 12, 13, 14, 15 % ethyl acetate in hexanes) provided **121**, 9.0 mg, 22 %, and *epi*-**121**, 8.1 mg, 20 %, as colourless resins.

121: IR (neat) 2927, 2859, 1750, 1608, 1575 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl^{3}$) δ 7.45 (d, J = 8.8 Hz, 1H), 6.76 (dd, J = 8.8, 2.8 Hz, 1H), 6.60 (d, J = 2.8 Hz, 1H), 4.25 (dd, J = 7.6, 4.4 Hz, 1H), 3.76 (s, 3H), 2.86 – 2.73 (m, 2H), 2.63-2.57 (m, 1H), 2.33 (ddd, J = 14.2, 9.0, 7.8 Hz, 1H), 2.18 (ddd, J = 14.2, 6.8, 4.4 Hz, 1H), 1.79 (ddd, J = 13.9, 11.1, 5.6 Hz, 1H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 212.8, 158.5, 137.3, 130.1, 127.1, 114.0, 113.2, 57.1, 55.4, 50.3, 40.3, 34.1, 28.1, 26.3, 22.8; HRMS (EI, M^+) calculated for $C_{15}H_{17}O_2Cl$ m/z 264.0917; found m/z 264.0916.

Data for *epi*-**121** is in agreement with that previously reported.[27]

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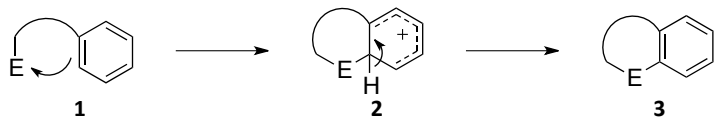
Chapter 3

Superacid-catalyzed Friedel-Crafts Cyclization of Unactivated Alkenes

3.1 Friedel-Crafts Cyclization of Unactivated Alkenes

The Friedel-Crafts reaction occupies a prominent position in the chemist's toolbox for the addition of carbon functionality to arene moieties, and intramolecular versions are well established. A general depiction of this reaction is shown in Scheme 3.1, where an aromatic group tethered to an electrophilic carbon, E, is cyclized to benzocycloalkane **3**. Attack of the arene on "E" leads to Wheland intermediate **2**, followed by loss of a proton to give product **3**.

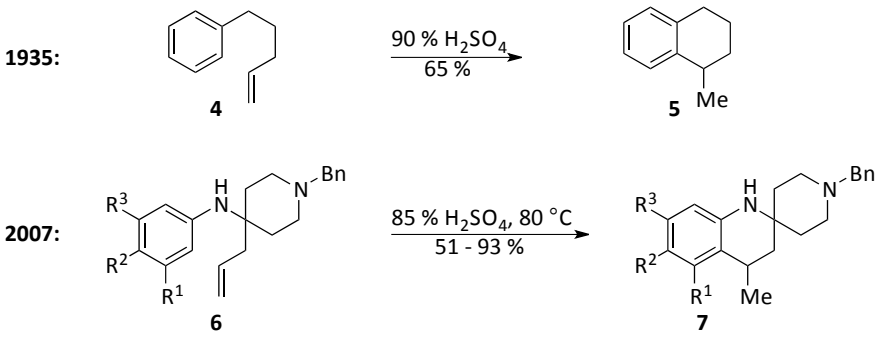


Scheme 3.1. Friedel-Crafts Cyclization.

There are a number of precursors to **1** that are possible; however, this discussion will be limited to the use of alkenes. Alkenes can function as the electrophilic partners in intramolecular Friedel-Crafts reactions, though typically this is limited to Michael acceptor alkenes activated by Brønsted or Lewis acid,[1,2] as these polarized compounds are more readily activated by acidic promoters. Allylic alcohols have also received substantial recent attention.[3]

3.1.1 Friedel-Crafts Cyclization of Unactivated Alkenes with Stoichiometric Brønsted Acids

Brønsted acid-mediated intramolecular Friedel-Crafts alkylation of simple alkenes which do not possess allylic functionalization is a well-established reaction, and has remained largely unchanged. Sulfuric acid is one of the classic reagents for this reaction, as exemplified by the cyclization of 5-phenyl-1-pentene (**4**) to 1-methyltetralin (**5**).[4] Recently tetrahydroquinoline **7** was synthesized in the same manner to examine the biological activity of this scaffold.[5]

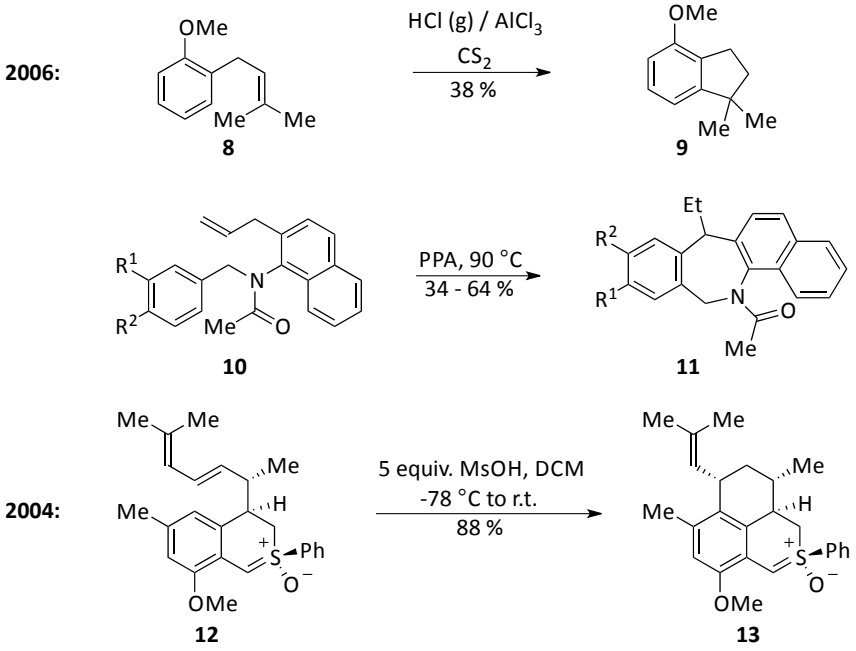


Scheme 3.2. Sulfuric Acid Mediated Friedel-Crafts Cyclization.

While development of new Lewis acid catalysts has received recent attention, the classical Brønsted acid reagents sulfuric acid, polyphosphoric acid, aluminum chloride, and hydrogen fluoride continue to be the reagents of choice

for the Brønsted acid-mediated reaction. Here aluminum chloride is categorized as a Brønsted acid because the active reagent is generated from the reaction of aluminum chloride with adventitious water.[6]

While the substrates have become more elaborate, the reaction conditions are largely the same (Scheme 3.3). A combination of hydrogen chloride and aluminum chloride was used to cyclize 1-aryl-2-butene **8** to indane **9** in moderate yield,[7] and polyphosphoric acid has found application in synthesis of benzazepines **11**.[8]



Scheme 3.3. Friedel-Crafts Cyclizations Utilizing Brønsted Acids.

There has also been some recent use of sulfonic acids. Excess methanesulfonic acid was used to perform the diastereoselective cyclization of diene **12** to **13** (Scheme 3.3).[9]

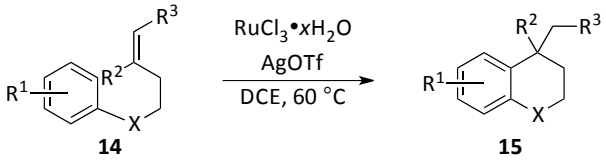
There are a number of problems associated with use of large excesses of these strong acids. Along with poor functional group tolerance, isomerization of

the alkene prior to cyclization often occurs, as in the formation of benzazepine **11**. The reaction is theoretically completely atom-economical in terms of the substrate; however, the waste associated with use of superstoichiometric promoters for the cyclization can be costly in an industrial setting.

3.1.2 Catalytic Friedel-Crafts Cyclizations of Unactivated Alkenes

Although catalytic Friedel-Crafts cyclization of unactivated alkenes has only been observed in very limited examples, these simple alkenes participate in these cyclizations in the presence of promoters such as $In(OTf)_3$, $RuCl_3$/AgOTf, and $PtCl_2$.

$RuCl_3$/AgOTf has been used by Sames and coworkers to synthesize tetralins and heteroatom-containing analogs (Scheme 3.4).[10] Sixty-seven metal salts were screened, and a combination of $RuCl_3$ and AgOTf was found optimal for catalysis of the hydroarylation reaction. The authors proposed that ruthenium activates the double bond and electrophilic aromatic substitution occurs at the more substituted terminus of the activated olefin. The resulting carbon-ruthenium bond then undergoes protiodemetallation to provide the cyclized product and complete the catalytic cycle.

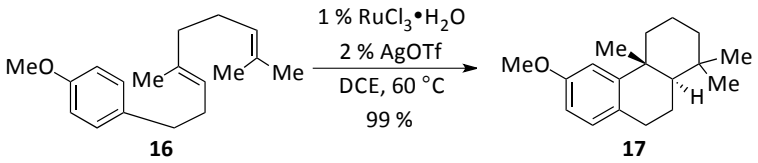


Scheme 3.4. $RuCl_3$/AgOTf Catalyzed Friedel-Crafts Cyclization.

Mono-, di- and trisubstituted alkenes are permitted in the reaction. Indoles are tolerated, albeit in reduced yield. Regioselectivity is moderate for *meta*-

substituted arenes, with a preference to cyclization *para* to the substituent, so as to avoid formation of a congested 1,2,3-trisubstituted benzene ring.

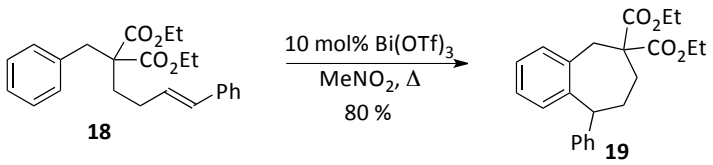
It was also possible to close two rings in a cascade version of the reaction (Scheme 3.5).



Scheme 3.5. Cascade Cyclization of Aryldiene **16**.

$In(OTf)_3$ also catalyzes this transformation, as described by Tan and coworkers.[11] This investigation was conducted in order to identify a more economical alternative to the ruthenium catalyst, and also to minimize byproducts due to olefin isomerization, which can account for as much as 8 % of the material balance. The results of In(III) versus Ru(III) catalysis proved to be similar; however, the In(III) system was ineffective for cyclization of internal alkenes and was not capable of the cascade cyclization depicted in Scheme 3.5. In both of these attempts, an intractable mixture resulted. The byproducts observed in the Ru(III)-catalyzed reaction were not found when the reaction was run under $In(OTf)_3$ catalysis. The authors report that merely passing the reaction mixture through a plug of silica was sufficient as a purification step.

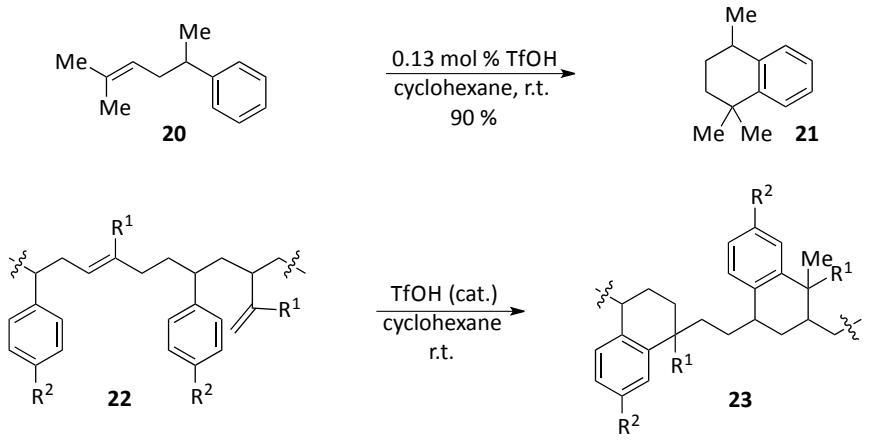
In 2011, Duñach and coworkers replaced the $In(OTf)_3$ catalyst with $Bi(OTf)_3$ due to its lower toxicity.[12] They made use of substituted tethers, and were able to perform a cascade cyclization forming two new rings. Additionally, this method was amenable to synthesis of medium rings (Scheme 3.6).



Scheme 3.6. $Bi(OTf)_3$-Catalyzed Closure of a Medium Ring.

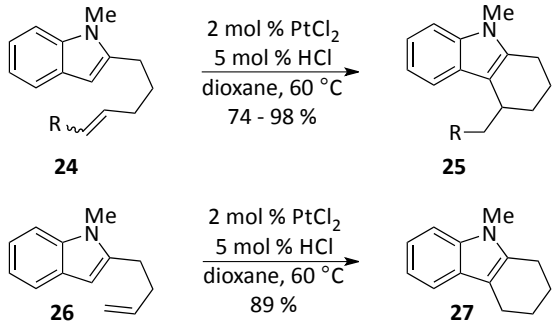
It is interesting to note that in all of the above reactions, the triflate counterion is present. It has been established that hydrolysis of $Bi(OTf)_3$ and $In(OTf)_3$ in the presence of traces of water can lead to a triflic acid-catalyzed reaction.[13] Ruthenium salts have also been implicated.[14] Although Sames and coworkers tested the reaction with 5 mol % triflic acid and found that there was only a 16 % yield of the cyclized product, this may have been too high of a catalyst loading to test with. Hartwig and coworkers have demonstrated that for a number of reactions, significant decomposition occurs with amounts of triflic acid larger than 1 mol %, while use of the lower catalyst loading gives clean reaction and much higher yields. Therefore, further investigation is necessary before proposing the active catalyst in these reactions, and it is possible that triflic acid is involved.

In fact, a triflic acid-catalyzed Friedel-Crafts cyclization of unactivated alkenes has been reported in the context of polymer chemistry (Scheme 3.7).[15] The authors tested the cyclization on a model substrate, and found that only 0.13 mol % triflic acid was necessary to convert hexene **20** to tetralin **21** in 90 % yield. These reaction conditions translated successfully to the styrene-diene copolymer.



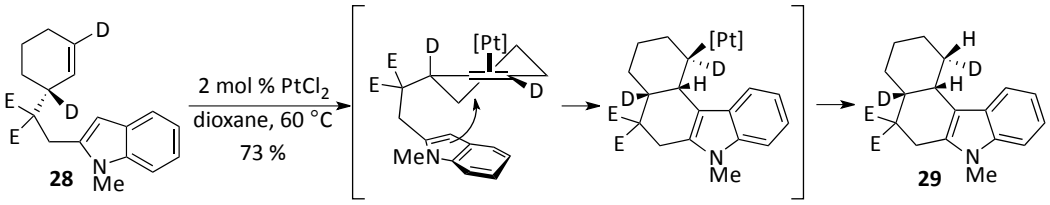
Scheme 3.7. Triflic Acid-catalyzed Friedel-Crafts Cyclization of a Polymer.

Widenhoefer and coworkers demonstrated that intramolecular hydroarylation of olefins with indoles was feasible under platinum(II) catalysis.[16] Alkenylindoles **24** were subjected to $PtCl_2$ and a small amount of hydrochloric acid with heating to produce cyclized compounds **25** (Scheme 3.8). The hydrochloric acid was necessary to facilitate protiodemetallation in order to eliminate side products due to aromatization. Free NH-containing indoles were tolerated. Notably, anti-Markovnikov product **27** was the sole product of the reaction of **26**; this result is due to attack by the indole at the least hindered terminus of the olefin-metal complex (Scheme 3.8).



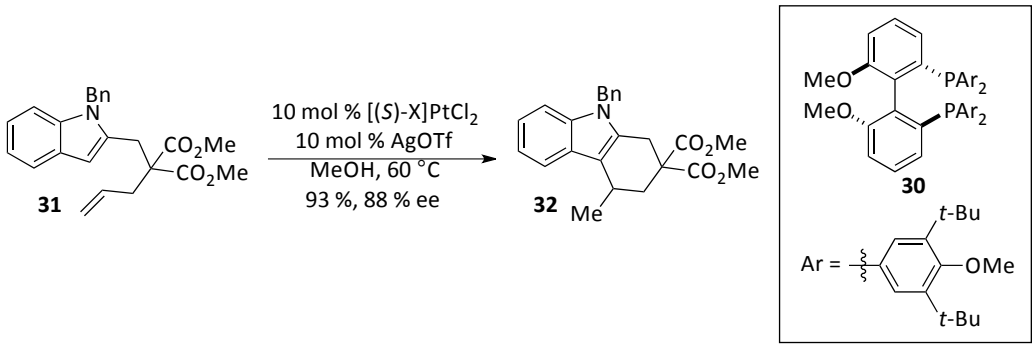
Scheme 3.8. Intramolecular Hydroarylation of Olefins with Indoles.

The authors clarified that the reaction does not involve CH-activation of the indole, but rather coordination of the metal to the alkene, followed by indole attack *trans* to the metal and protiodemetallation. Deuterated alkene **28** gave exclusively *anti*-**29**, whereas *syn* addition of the indole moiety and platinum would have occurred in a CH-activation mechanism by way of alkene insertion into the platinum-carbon bond (Scheme 3.9).



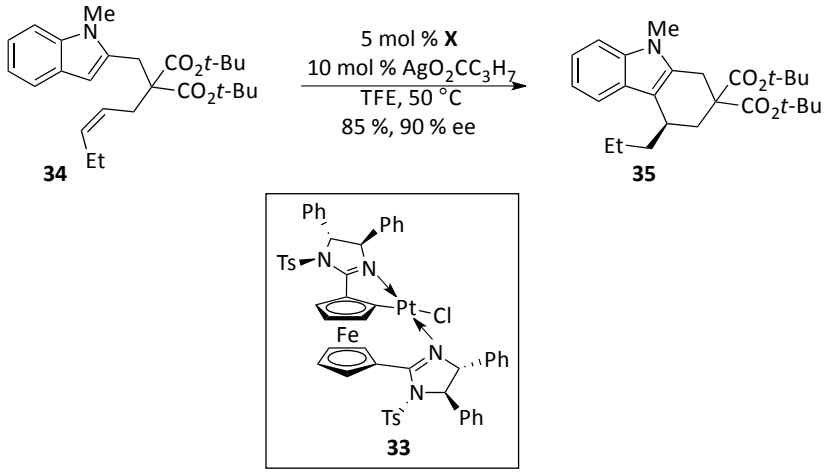
Scheme 3.9. Evidence of *trans* attack on Pt-olefin complex.

The same group reported an asymmetric variation of the platinum-catalyzed hydroarylation reaction in 2006.[17] A ligand screen identified the ligand **30** as capable of inducing asymmetric cyclization (Scheme 3.10). Control experiments demonstrated that triflic acid or AgOTf in the presence of **30** were not capable of catalyzing this transformation in the absence of platinum.



Scheme 3.10. Asymmetric Cyclization of Alkenylindoles.

Peters and Huang designed a more elaborate catalyst for asymmetric platinum-catalyzed cyclization of indoles onto unactivated alkenes.[18] Platinacycle **33** was able to catalyze the cyclization of internal alkenes in an asymmetric fashion (Scheme 3.11), whereas Widenhoefer and coworkers reported only cyclizations of terminal alkenes.



Scheme 3.11. Asymmetric Cyclization of Alkenylindoles Catalyzed by Platinacycle **33**.

3.2 Brønsted Acid Catalyzed Friedel-Crafts Cyclization of Simple Alkenes

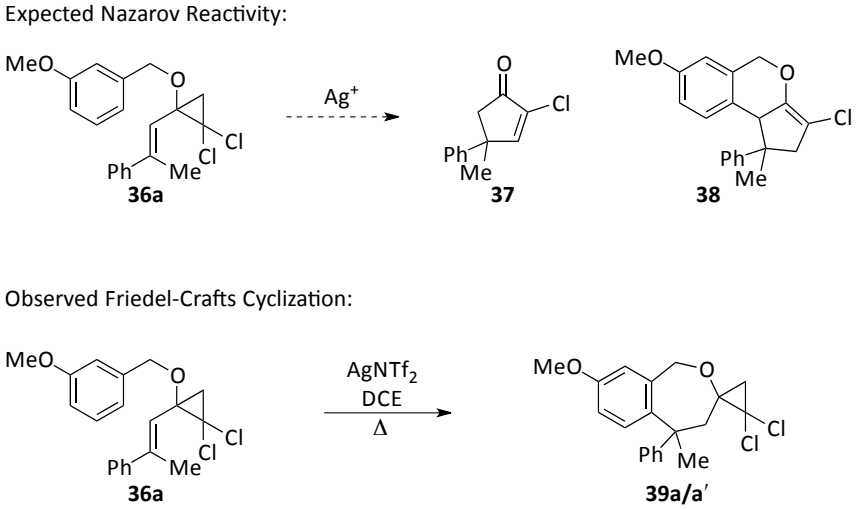
Development of a Brønsted acid-catalyzed Friedel-Crafts cyclization with simple alkenes is long overdue. Although analogous metal-catalyzed reactions are receiving more attention, they are more useful for alkenes with less substitution, whereas Brønsted acids preferentially activate more highly substituted alkenes. With the advent of modern "superacids,"[19] it stands to reason that the cyclization of simple alkenes should be amenable to catalysis, and this has been shown in a triflic acid catalyzed cyclization of arene-alkene units in a

polymeric system.[15] However, to our knowledge there has been no definitive work on the optimization and scope of this reaction, despite the recent interest in the corresponding metal-catalyzed versions.

Here we describe a Brønsted acid catalyzed intramolecular Friedel-Crafts alkylation between a wide range of aromatic partners and simple alkenes with $AgNTf_2$ as the acid precursor, or directly by addition of $HNTf_2$.[20] The reaction is high-yielding, convenient, and atom-economical.

3.2.1 Introduction – Initial Findings

In an attempt to interrupt the Nazarov cyclization with an arene tethered through the C-3 oxygen (*Chapter 2*), benzylic ether **36a** was prepared and its behavior in the presence of 1 equivalent of $AgNTf_2$ examined (Scheme 3.12).



Scheme 3.12. Unexpected Friedel-Crafts Reaction of **36a**.

Neither the expected Nazarov process nor the corresponding interrupted Nazarov process occurred to any observable extent to produce either **37** or **38** respectively. The product of this reaction appeared to be a 1.2 : 1 mixture of

diastereomers with the molecular formula $C_{20}H_{20}O_2Cl_2$, indicating that the product was isomeric with the starting material. Examination of the spectroscopic data of the major isomer revealed that the *gem*-dichlorocyclopropane remained intact, as did the benzyl ether, and there was a new isolated methylene with protons at 2.81 and 2.58 ppm with a geminal coupling constant of 15.7 Hz. There was also one less aromatic proton relative to **36a**, and a coupling pattern consistent with a 1,2,4-trisubstituted benzene (Figure 3.1) evidenced by the following signals: An aromatic proton at 7.08 ppm which appeared as a doublet with a coupling constant of 8.7 Hz, indicating an *ortho* relationship with the proton at 6.81 ppm, a doublet of doublets with coupling constants 8.7 and 2.9 Hz. The 2.9 Hz coupling constant was shared by the proton at 6.74 ppm, indicating a *meta* relationship. Lack of an observed coupling between the 6.81 and 6.74 ppm protons is consistent with a *para* orientation. The methylene protons had HMBC correlations to the cyclopropane carbon at 66.6 ppm and a quaternary carbon at 46.6 ppm. This quaternary carbon showed HMBC cross peaks to the methyl singlet at 1.87 ppm. HMBC correlation between the methyl singlet and the *ipso* carbon of the phenyl group at 148.6 ppm as well as one or both the carbons of the trisubstituted aromatic at 139.3 and 137.7 ppm confirmed that the product of the reaction arose from the Friedel-Crafts reaction of **36a**, and was in fact 1,3,4,5-tetrahydro-2-benzoxepin **39a**.

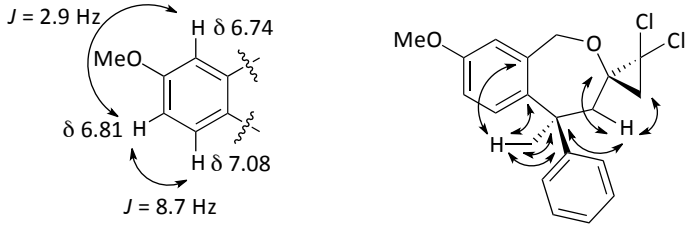


Figure 3.1. 1,3,4-Trisubstituted Aromatic Moiety and Key HMBC Correlations of **39a**.

Compound **39a** was assigned as having a trans relationship between the chlorine-bearing carbon and the phenyl group due to the presence of an rOe correlation between the cyclopropane methylene and the phenyl protons. This correlation was absent in the *cis* diastereomer **39a′** (Figure 3.2). It is expected that the phenyl substituent has a predisposition for pseudoaxial orientation in this compound because the rOe enhancement between the cyclopropane protons and the phenyl group is observed. In an equatorial orientation, it is unlikely that they would be in close enough proximity. This result is not surprising because in conformational studies of 1-methyl-1-phenylcyclohexane, the lower energy conformer also positions the phenyl group in an axial orientation.[21]

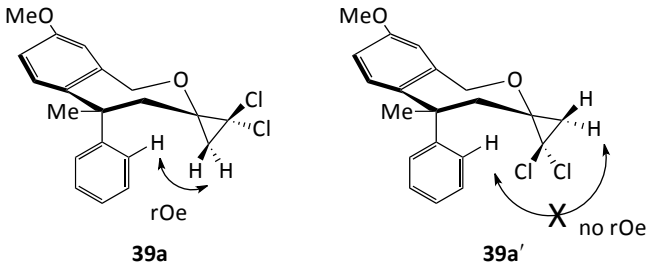
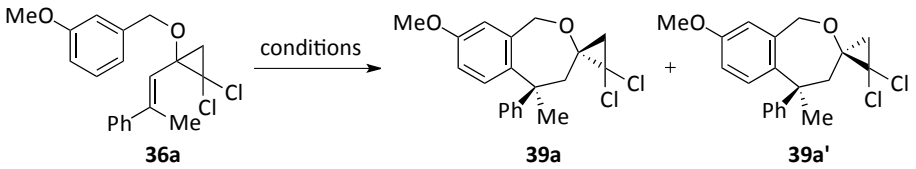


Figure 3.2. Relevant TROESY Correlations in **39a** and **39a′**.

The unexpected formation of **39a** is notable for the following reasons: first, no evidence of dechlorinative cyclopropane opening is observed, despite the presence of a full equivalent of the Ag(I) salt. Also, the selective 7-*endo* cyclization demonstrates that this process can form medium-sized rings. Optimization studies indicated a strong counterion effect; $AgNTf_2$ is superior to other silver salts (AgOTf, $AgSbF_6$ and $AgBF_4$), and that the catalyst loading could be reduced to 10 mol % (Table 3.1).



36a **39a** **39a'**

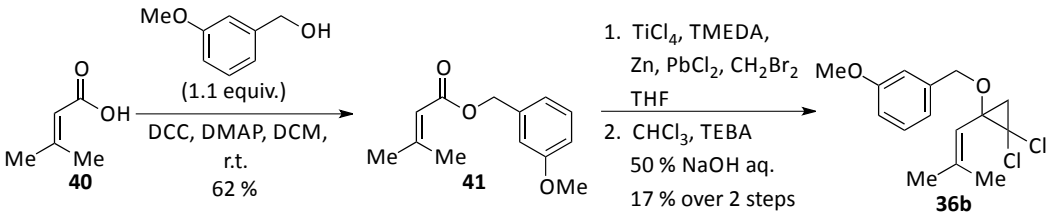
entry	catalyst (mol %)	solvent	temp.	ratio **36a** : **39a** : **39a′**	yield (%)
1	$AgBF_4$ (100)	DCE	Reflux	decomposition	
2	$AgSbF_6$ (100)	DCE	Reflux	decomposition	
3	AgOTf (100)	DCE	Reflux	0 : 1.3 : 1	35
4	$AgNTf_2$ (100)	DCE	Reflux	0 : 1 : 1.2	27
5	AgOTf (20)	DCE	Reflux	8 : 1 : undetermined	
6	AgOTf (10)	DCE	Reflux	1 : 0 : 0	
7	$AgNTf_2$ (20)	DCE	r.t.	1 : 0 : 0	
8	$AgNTf_2$ (20)	MeCN	reflux	1 : 0 : 0	
9	$AgNTf_2$ (20)	TFE	Reflux	0 : 1 : 1.6	23
10	$AgNTf_2$ (10)	DCM	Reflux	0 : 43 : 36	79
11	$AgNTf_2$ (20)	DCM	r. t.	0 : 1.7 : 1	62
12	$AgNTf_2$ (5)	DCM	Reflux	1.5 : 1.8 : 1	

Table 3.1. Optimization of Friedel-Crafts Cyclization.

Silver(I) salts are also known to activate multiple bonds toward nucleophilic attack, and thus appear as good candidates for catalysis of such a process.[22] To date, reported examples of arene alkylation by alkenes under silver catalysis involve AgOTf-mediated intermolecular addition of 1,3-dienes to phenols,[23] hydroarylation of silver-activated enones,[24] and AgOTf-catalyzed intramolecular allylation of arenes by allylic alcohols.[25]

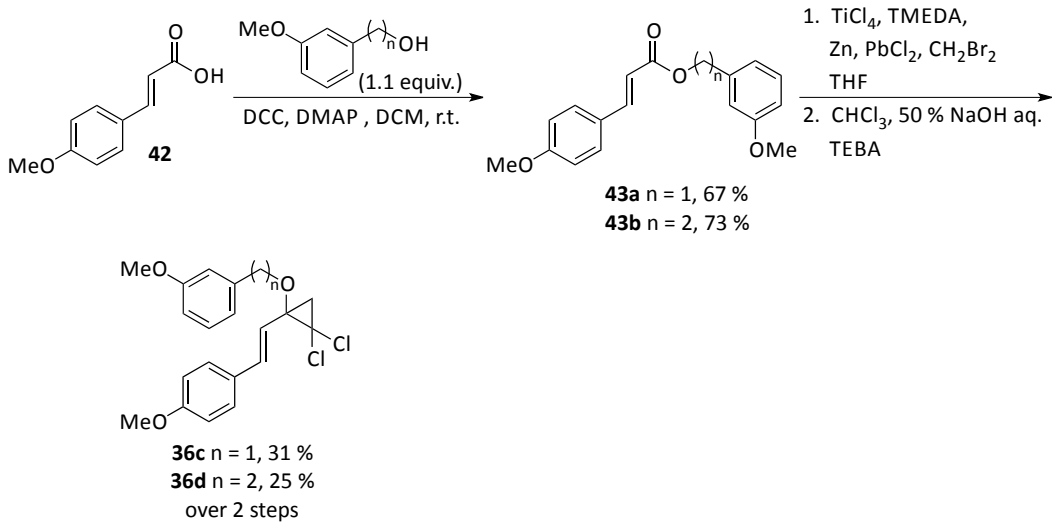
3.2.2 Synthesis of Friedel-Crafts Substrates

Substrate **36a** was synthesized as detailed in Chapter 2. In order to test the reaction with variations on the structure of dichlorocyclopropane **36a**, compounds **36b** to **36d** were synthesized. In analogy to **36a**, senecoic acid (**40**) was converted to ester **41** in 62 % yield by *N*,*N*′-dicyclohexylcarbodiimide mediated esterification with 3-methoxybenzyl alcohol. Compound **41** was methylenated under the conditions developed by Takai and Utimoto, [26] and then dichlorocyclopropanated under phase-transfer conditions to provide Friedel-Crafts substrate **36b** in 17 % yield over 2 steps (Scheme 3.13).



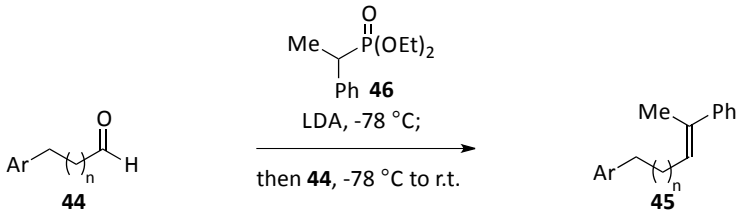
Scheme 3.13. Preparation of *gem*-Dichlorocyclopropane **36b**.

4-Methoxycinnamic acid (**42**) was converted to *gem*-dichlorocyclopropanes **36c** and **36d** in the same manner (Scheme 3.14).



Scheme 3.14. Preparation of *gem*-Dichlorocyclopropanes **36c** and **36d**.

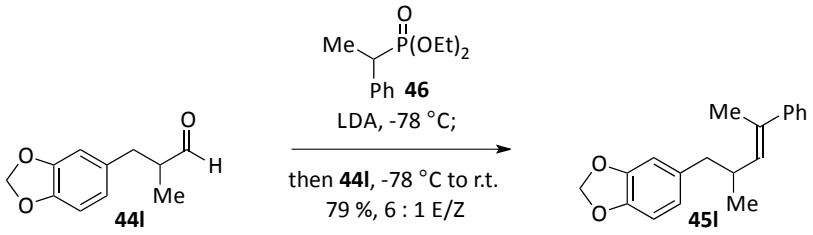
Simplified substrates were prepared so as to investigate the effect of various tether lengths and arene substitution. Alkenes **45a** to **45k** were synthesized in one step from the known aldehyde precursors by Horner-Wadsworth-Emmons reaction with the anion of diethyl 1-phenylethylphosphonate, **46** (Table 3.2). The yields of these reactions were moderate at best, but because the route allowed rapid assembly of the desired compounds, the reactions were not subjected to further optimization.



entry	substrate	Ar	n	product	yield (%)	E/Z ratio
1	**44a**	2-MeO-C_6H_4	1	**45a**	56	16 : 1
2	**44b**	3-MeO-C_6H_4	1	**45b**	35	10 : 1
3	**44c**	4-MeO-C_6H_4	1	**45c**	46	12 : 1
4	**44d**	2-Me-C_6H_4	1	**45d**	26	12 : 1
5	**44e**	3-Me-C_6H_4	1	**45e**	44	13 : 1
6	**44f**	3-F-C_6H_4	1	**45f**	42	20 : 1
7	**44g**	3-Cl-C_6H_4	1	**45g**	32 (*E*), 2 (*Z*)	
8	**44h**	Ph	1	**45h**	44	20 : 1
9	**44i**	3-MeO-C_6H_4	0	**45i**	47	8 : 1
10	**44j**	3,4-MeO-C_6H_3	2	**45j**	37	10 : 1
11	**44k**	3-furyl	1	**45k**	23	9 : 1

Table 3.2. Preparation of Olefins **45a** to **45k**.

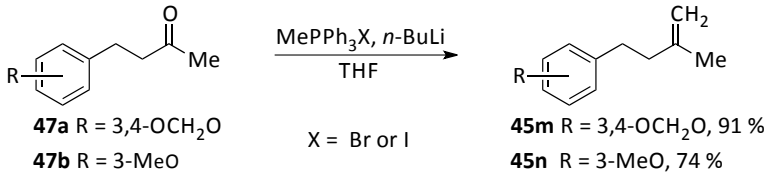
In order to investigate the diastereoselectivity of the Friedel-Crafts cyclization, commercially available 2-methyl-3-(3,4-methylenedioxy-phenyl)propanal **44l** was also converted to **45l** by means of a Horner-Wadsworth-Emmons reaction (Scheme 3.15).



Scheme 3.15. Preparation of Alkene **45l**.

With the exception of aryl chloride **45g**, the *E*/*Z* mixtures were inseparable. The vinyl protons in the major (*E*) isomers were consistently 0.2 to 0.3 ppm downfield from the minor isomers due to the deshielding effect of the *cis* phenyl substituent.

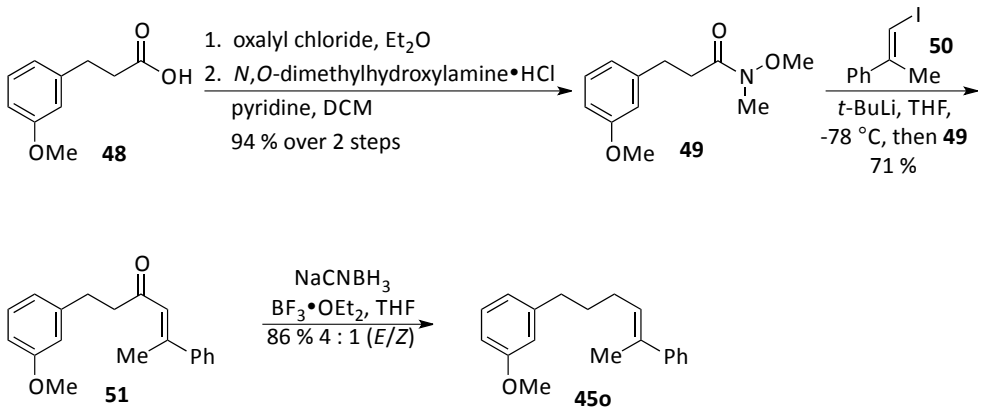
With the intention of investigating an *exo* mode of cyclization, substrates **45m** and **45n** were desired (Scheme 3.16). Commercially available 4-(3,4-methylenedioxyphenyl)-2-butanone, **47a**, and known ketone 4-(3-methoxyphenyl)-2-butanone, **47b**, were methylenated in 91 % and 74 % yield respectively.



Scheme 3.16. Preparation of Terminal Alkenes **45m** and **45n**.

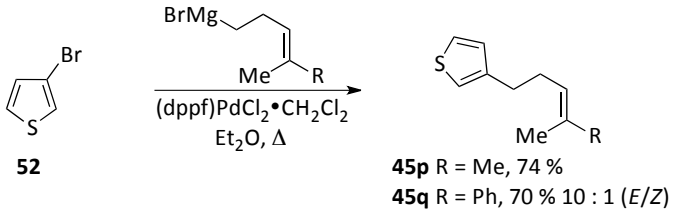
The synthesis of 3-carbon-tethered substrate **45o** began with conversion of 3-(3-methoxyphenyl)propionic acid, **48**, to the corresponding Weinreb amide **49** in 94 % yield over two steps, followed by alkylation with the lithium/halogen exchange product of vinyl iodide **50**[27] to give enone **51** in 71 % yield. Removal of the ketone functionality with boron trifluoride diethyl etherate and sodium

cyanoborohydride[28] provided the desired compound as a 4 : 1 (*E*/*Z*) mixture in 86 % yield (Scheme 3.17).



Scheme 3.17. Preparation of Alkene **45o**.

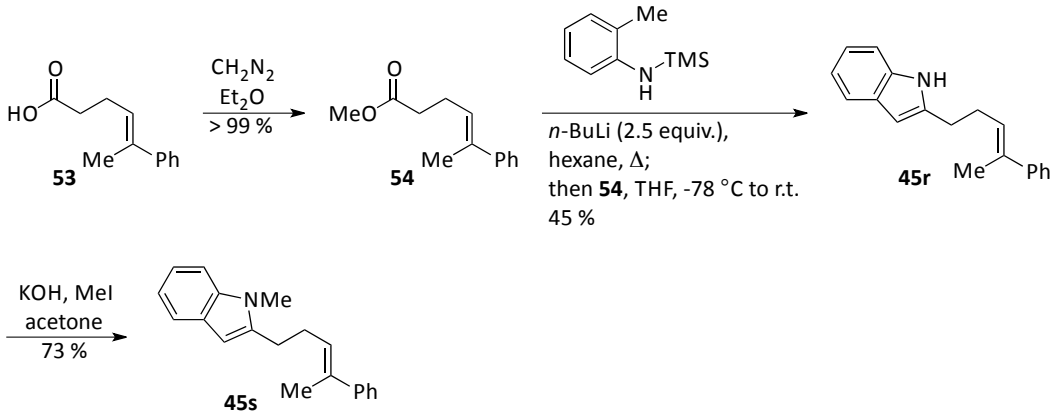
Along with furan **45k**, other heteroaromatic substrates were useful in determining the scope of the Friedel-Crafts cyclization. Commercially available 3-bromothiophene (**52**) was subjected to a Kumada cross-coupling reaction[29] to provide known compound thiopyrillene (**45p**)[30] and thiophene **45q** in 74 and 70 % respective yields (Scheme 3.18).



Scheme 3.18. Preparation of Thiophenes **45p** and **45q**.

Known pentenoic acid **53** [31] was esterified with diazomethane in quantitative yield. Indole **45r** was formed in 45 % yield by the reaction of the

dianion of *N*-trimethylsilyl-*o*-toluidine and methyl ester **54** (Scheme 3.19).[32] Methylation of **45r** with iodomethane provided indole **45s**.

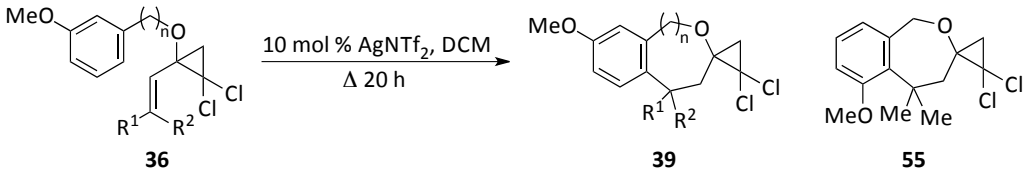


Scheme 3.19. Preparation of Indoles **45r** and **45s**.

3.2.3 Friedel-Crafts Reaction of *gem*-Dichlorocyclopropane-containing Substrates

Compound **36a** reacted under the optimized reaction conditions to furnish **39a** in 79% yield as a 1.9 : 1 mixture of diastereomers (Table 3.3, entry 1). Three other dichlorocyclopropane substrates **36b–d** were also examined, and all underwent similar cyclization to **39b–d**. These structural variations demonstrate that the reaction does not require aryl substitution on the alkene (entry 2), it tolerates disubstituted alkenes (entries 3-4), and even an 8-membered ring can be formed with reasonable efficiency when a suitable tether is used (entry 4). The structure of **39d** was confirmed by X-ray crystallography (see appendix IV). Dimethyl substrate **36b** produced minor amounts of the regioisomer **55**, which is the result of alkylation *ortho* to the methoxy group (entry 2). This can be attributed to both the lower stability of a tertiary carbocation relative to the aryl-stabilized cation intermediates, as well as decreased steric hindrance by the

dimethyl substitution rather than bulkier aryl substitution in the newly formed quaternary center. These factors allow the congested 1,2,3-trisubstituted arene **55** to compete with the less congested isomer **39b** for substrate **36b** and not for the other three substrates in Table 3.3.



36 **39** **55**

entry	substrate	R^1	R^2	n	yield (%)[b] / product ratio
1	**36a**	Ph	Me	1	79/1.9:1[a]
2	**36b**	Me	Me	1	43/2.4:1[b]
3	**36c**	4-$MeOC_6H_4$	H	1	64/1:1[a]
4	**36d**	4-$MeOC_6H_4$	H	2	52/1:1[a]

[a]Ratio of diastereoisomers of **39**. [b]Ratio of regioisomers **39b** and **55**.

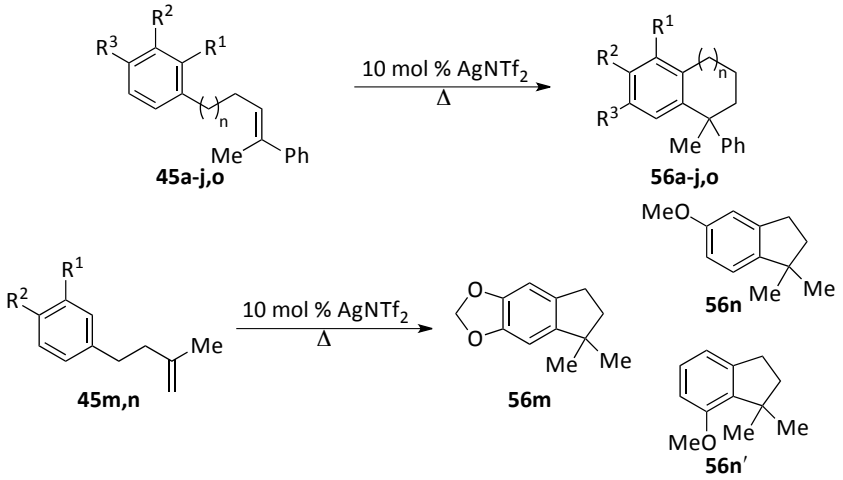
Table 3.3. Friedel-Crafts Reactions of Cyclopropane Substrates.

3.2.4 Friedel-Crafts Reactions of Simplified Substrates

The role, if any, of the cyclopropane ring in the success of this unexpected annulation process is an important question. Conceivably, the presence of a quaternary center in the tether might enhance the rate of cyclization as a manifestation of the *gem*-dialkyl effect.[33] With this in mind, several simplified substrates lacking the dichlorocyclopropane moiety were prepared and their reactivity examined under the optimized conditions (Table 3.4).

For the initial series, the olefin substitution pattern was held constant, while arene substitution and tether length were varied. Under the standard

conditions, substrates **45a–j,o** cyclized efficiently in an *endo* fashion to furnish aryl-substituted tetralins **56a–j,o** (entries 1–9). In early experiments, it was noted that the yield for **56a** is somewhat lower than the other electron-rich examples (entries 1, 3–6), though still in an acceptable range (77%). In an effort to achieve better conversion and more convenient reaction times, microwave heating was investigated (Table 3.5); the optimized conditions led to near quantitative formation of **56a** (Table 3.4, entry 2).



entry	substrate	product(s)	R^1	R^2	R^3	n	method[a]	yield (%)[b]
1	**45a**	**56a**	OMe	H	H	1	A	77
2	**45a**	**56a**	OMe	H	H	1	B	98
3	**45b**	**56b**	H	OMe	H	1	A	99
4	**45c**	**56c**	H	H	OMe	1	A	99
5	**5d**	**56d**	Me	H	H	1	A	90
6	**45e**	**56e**	H	Me	H	1	A	97
7	**45f**	**56f**	H	F	H	1	B	99
8	**45g**	**56g**	H	Cl	H	1	B	90
9	**45h**	**56h**	H	H	H	1	B	98
10	**45i**	**56i**	H	OMe	H	0	A	76
11	**45j**	**56j**	H	OMe	OMe	2	A	30
12	**45o**	**56o**	H	OMe	H	2	A	56
13	**45m**	**56m**	(OCH_2O)		---	1	B	83
14	**45n**	**56n**, **56n′**	OMe	H	---	1	B	90 (2:8:1)[b]

[a]Method A: substrates **45** were dissolved in DCM (0.05 M) with $AgNTf_2$ (10 mol %) and stirred at reflux until **45** was consumed (20–48 h). Method B: substrates **45** were dissolved in 1,2-dichloroethane (0.05 M or 0.1 M) with $AgNTf_2$ (10 mol %) in a microwave reaction vial and heated at 180 °C for 5 min–1 h. [b]Ratio of **56n** to **56n′**

Table 3.4. Effect of Arene Substitution, Tether Length, and Olefin.

entry	solvent	mol % of $AgNTf_2$	temperature (°C)	time (min)	yield **56h** (%)
1	DCM	20	100	60	30 [a]
2	DCM	20	100	150	98
3	DCM	20	100	210	83
4	DCM	10	100	210	45 [a]
5	DCE	20	180	60	99
6	DCE	20	180	30	95
7	DCE	10	180	60	93
8	DCE	10	180	15	98
9	DCE	10	180	10	62 [a]
10	DCE	0	180	15	0

[a]Product yield was calculated using the ^{1}H NMR ratio of an inseparable mixture of **56h** and unconsumed **45h**.

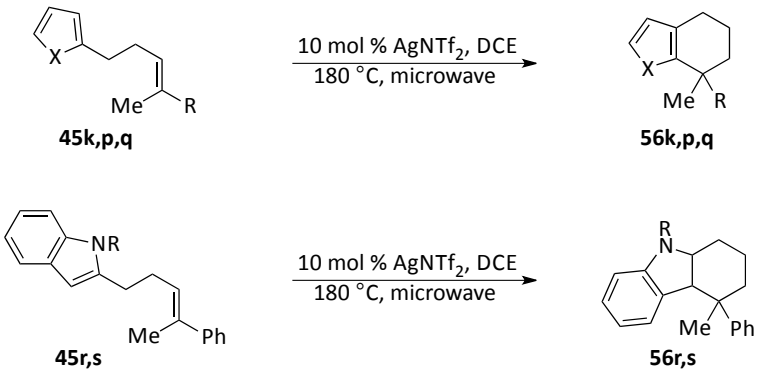
Table 3.5. Optimization of Microwave Heating Conditions.

Electron-deficient 3-halophenyl substrates were both cleanly converted to tetralins **56f,g** in excellent yields under the microwave conditions (Table 3.4, entries 7-8). Catalytic Friedel-Crafts alkylations utilizing alkene electrophiles and electron-deficient arenes are rare, and typically involve arene allylation by allylic halides or alcohols. The tolerance of halogen substitution [34] suggests the possibility of sequential C-C bond formation by Friedel-Crafts alkylation followed by various transition metal-catalyzed cross-coupling processes. Tether length was also examined (entries 10–12). The 5-endo cyclization of **45i** proceeds in 76% yield to furnish indane **56i** (entry 10), conforming to the Markovnikov selectivity observed in the previous cases. On the other hand,

longer tethers provide benzocycloheptenes **56j**,**o** in only moderate yields (entries 11-12). The contrast between these results and the higher yielding formation of **36a** and **36c** suggests that the ether linkage and cyclopropane present in their precursors may enhance the cyclization process. Finally, 1,1-disubstitution on the alkene effects a reversal in cyclization regiochemistry (entries 13–14), affording indanes **56m**,**n** in high yields *via* a 5-*exo* mode.

3.2.5 Friedel-Crafts Reaction of Heteroaromatics

Several heteroaromatic substrates were also examined (Table 3.6). Although unreactive under the originally optimized conditions, these compounds undergo smooth cyclization with microwave heating to afford tetrahydrobenzothiophenes **56q**,**p**[35] (entries 1-2), tetrahydrobenzofuran **56k** (entry 3), and tetrahydrocarbazoles **56r**,**s** (entries 4-5). Diminished reactivity with the electron-rich heteroaromatic substrates was initially surprising, given their higher nucleophilicity relative to the arenes of Table 3.4. Competing acid-catalyzed decomposition pathways may contribute to the reduced yields observed in some cases.



entry	substrate	product	X	R	yield(%)[b]
1	**45q**	**56q**	S	Ph	96
2	**45p**	**56p**	S	Me	79 (10:1)[c]
3	**45k**	**56k**	O	Ph	78
4	**45r**	**56r**	-	-	93
5	**45s**	**56s**	-	-	98

[a]For a description of reaction conditions, see Method B in Table 3.4. [b]Yields given are for pure product after chromatographic purification. [c]Ratio of tetrahydrobenzothiophene and tetrahydroisobenzothiophene regioisomers.

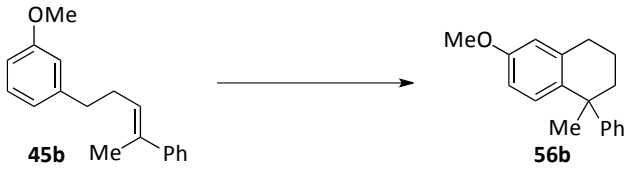
Table 3.6. Cyclizations of Heteroaromatic Substrates.[a]

3.2.6 Catalyst Identity

Metal triflates and triflimides are known to be prone to hydrolysis. As a result, they can act as precatalysts to form the corresponding Brønsted acids, which are the active catalysts in a number of studies.[36] With this in mind, the "Ag(I)-catalyzed" Friedel-Crafts reaction of substrate **45b** described above was examined in greater depth (Table 3.7). To probe the nature of the actual catalyst, substrate **45b** was subjected to cyclization conditions in the presence of $AgNTf_2$

with or without added water, $HNTf_2$, and other Brønsted acids. When the reaction components were filtered through dry potassium carbonate under argon to remove the residual water from the dichloromethane[37] as well as any trace $HNTf_2$ that may be in the $AgNTf_2$, no reaction occurred upon extended stirring, supporting the need for trace acid to catalyze this reaction (entry 1). $HNTf_2$ itself proved to be a very effective catalyst for the process, and the reaction proceeded to completion within 1 h with only 0.5 % loading of the acid (entry 2). Increasing the catalyst loading to 1 % $HNTf_2$ has little effect on the yield of **56b**; however, the time required for the consumption of **45b** was significantly reduced (entry 3). Conversely, decreasing the catalyst to 0.1 % led to an unacceptable reaction time and inconsistent yields.

A controlled amount of water was added to **45b** and $AgNTf_2$ to demonstrate that hydrolysis of the silver salt by amounts of water available in "dry" dichloromethane[14] can lead to generation of sufficient Brønsted acid active catalyst to effect conversion of **45b** to **56b**. In all of these cases, reactivity was at least partially restored, with 0.5 mol % water being optimal, and higher concentrations led to apparent inhibition of the reaction (entries 4-6). In entry 7, $AgNTf_2$ was used in combination with $HNTf_2$ to check for an additive effect; however, the results did not differ significantly from the use of $HNTf_2$ alone. Finally, other strong Brønsted acids failed to catalyze the cyclization, with the exception of triflic acid in moderate yield.



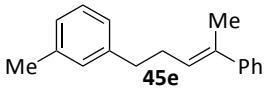
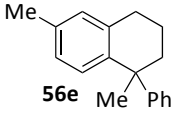
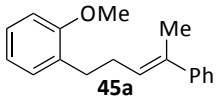
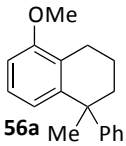
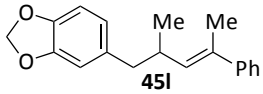
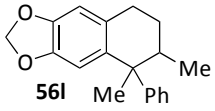
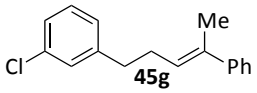
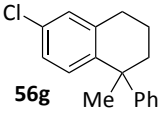
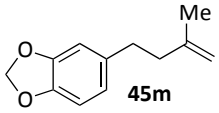
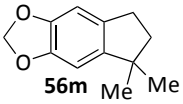
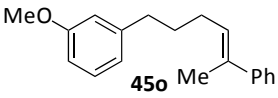
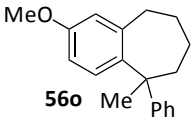
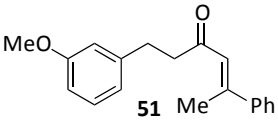
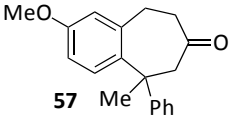
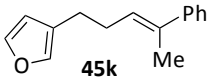
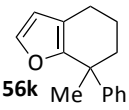
Entry	$AgNTf_2$ (mol %)	Brønsted acid (mol %)	H_2O (mol %)	Time (h)	Yield of **56b** (%)
1	10	-	-	24	0
2	-	$HNTf_2$ (0.5)	-	1	94
3	-	$HNTf_2$ (1.0)	-	0.25	89
4	10	-	0.5	24	96
5	10	-	1	24	70[b]
6	10	-	10	24	36[b]
7	10	$HNTf_2$ (0.5)	-	1	96
8	-	$TsOH•H_2O$ (0.5)	-	1	NR
9	-	MsOH (0.5)	-	1	NR
10	-	CSA (0.5)	-	1	NR
11	-	TfOH (0.5)	-	1	38[b]

[a]Reaction conditions: 0.05 M substrate in DCM at reflux. [b]Product yield was calculated using the ^{1}H NMR ratio of an inseparable mixture of **45b** and **56b**.

Table 3.7. Effect of Added Water or Brønsted Acid.

3.2.7 $HNTf_2$ Catalyzed Friedel-Crafts Cyclization

When the optimized reaction conditions were applied to a selection of substrates (Table 3.8), it was found that in the majority of cases it was necessary to increase the catalyst loading to 1 % and employ microwave heating in 1,2-dichloroethane to encourage expedient and complete reaction of the substrate.

entry	substrate	reaction conditions [a]	product	yield (%)	yield using $AgNTf_2$ (%)
1	 **45e**	A	 **56e**	92	97
2	 **45a**	B	 **56a**	80	98
3	 **45l**	B	 **56l**	90 (2.8: 1 dr)	--
4	 **45g**	B	 **56g**	87	90
5	 **45m**	B	 **56m**	74	83
6	 **45o**	C	 **56o**	60	56
7	 **51**	D	 **57**	NR	NR
8	 **45k**	B	 **56k**	56	78

[a]Reaction Conditions: A) 0.5 mol % $HNTf_2$ in DCM at reflux, 2h; B) 1.0 mol % $HNTf_2$ in DCE, 180 °C, microwave heating, 5 min. to 2 h; C) 1.0 mol % $HNTf_2$ in DCM at reflux, 20h; D) 1.0 mol % $HNTf_2$, CD_2Cl_2, reflux, 21 h; then 100 °C (microwave), 30 min.

Table 3.8. Scope of $HNTf_2$ Catalyzed Cyclization of Arene-tethered Olefins.

Enone **51** was unreactive under the conditions employed, which may arise from preferential *s-cis* conformation of the enone moiety.[38]

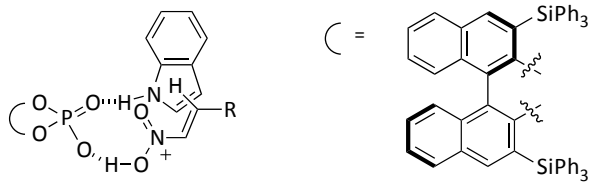
In most cases the yield is lower when $HNTf_2$ is used relative to use of $AgNTf_2$ as a precatalyst. It is possible that less than 1 mol % of $HNTf_2$ is produced from the precatalyst, and the yields of Table 3.8 could conceivably improve on more rigorous case-by-case optimization of catalyst loading.

3.3 Conclusions

Silver bis(trifluoromethanesulfonyl)imide acts as a precatalyst for intramolecular Friedel-Crafts alkylation of various aromatic moieties with unactivated alkenes. A spectrum of electron-rich to electron-deficient arenes are all capable substrates. The active catalyst is formed in the presence of water, even at concentrations available in dichloromethane dried in the traditional manner. The mild conditions are showcased by the preference for cyclization over the expected dehalogenation of *gem*-dichlorocyclopropanes, and generality is exhibited by the formation of 5-,6-,7- and 8-membered rings through either *endo*- or *exo*-cyclization modes. This method provides access to a variety of useful polycyclic products, including those with handles for further elaboration.

3.4 Future Directions

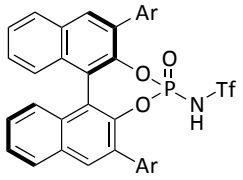
It may be possible to use a chiral Brønsted acid to convert aryl alkenes to cyclized products. This is precedented with the Friedel-Crafts cyclization of Michael acceptors with indoles.[39] In some cases, the N-H of the indole is necessary for obtaining good yields and selectivities, where the hydrogen bond donor participates in the postulated transition state **57** (Figure 3.3).



57

Figure 3.3. Transition State for an Asymmetric Friedel-Crafts Reaction.

Strongly acidic *N*-triflyl phosphoramides **58** may be able to catalyze the Friedel-Crafts cyclization of unactivated alkenes. This mode of asymmetric induction applied to indoles or other arenes tethered to alkenes, if successful, would lead to an unprecedented asymmetric Brønsted acid-catalyzed Friedel-Crafts cyclization of unactivated alkenes.



58

Figure 3.4. Chiral Brønsted Acids **58**.

3.5 Experimental

3.5.1 General Information

Reactions were carried out in flame-dried glassware under an atmosphere of either argon or nitrogen. Tetrahydrofuran (Na/benzophenone), dichloromethane (CaH_2), and diethyl ether (Na/benzophenone) were either distilled prior to use or were used as received (DriSolv® Anhydrous solvents from EMD). Microwave heating was carried out in a Biotage Initiator microwave reactor, using 2-5 mL vials. Reaction temperature was determined through measurement of the vial surface temperature using an infrared sensor, then correction for internal temperature by the unit's processor using a proprietary algorithm. Thin layer chromatography was performed on glass plates precoated with 0.25 mm Kieselgel 60 F254 (Merck). Flash chromatography columns were packed with 230-400 mesh silica gel (Silicycle). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 MHz, 400 MHz, or 500 MHz and coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, etc. The chemical shifts are reported on the δ scale (ppm) and the spectra are referenced to residual solvent peaks: $CDCl_3$ (7.26 ppm, ^{1}H; 77.06 ppm, ^{13}C), or CD_3CN (1.94 ppm, ^{1}H; 118.26 ppm, ^{13}C) as internal standard. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz or 125 MHz, and the chemical shifts are accurate to one decimal place. Silver bis(trifluoromethanesulfonyl)imide from Sigma Aldrich was dried under vacuum at 100 °C overnight prior to use, or was prepared from silver carbonate.[40] There was no difference between 1,2-dichloroethane that was distilled from CaH_2 or that used directly from the bottle.

General Friedel-Crafts Procedures

For silver triflimide as a precatalyst

Condition A:

In a flame-dried flask under argon, the substrate was dissolved in dry dichloromethane at a concentration of 0.05 M. 10 mol % silver bis(trifluoromethanesulfonyl)imide was added, and the reaction was protected from light and stirred at reflux for the specified time. On completion, the solution was filtered through a plug of silica, eluted with dichloromethane and concentrated under reduced pressure to provide the crude product.

Condition B:

In a flame-dried microwave vial under argon or nitrogen, the substrate was dissolved in 1,2-dichloroethane at a concentration of 0.05 M. 10 mol % silver bis(trifluoromethanesulfonyl)imide was added either as a solid or as a 0.2 M solution in 1,2-dichloroethane. The reaction was heated in the microwave at 180 °C for the specified time before it was filtered through a plug of silica, and eluted with dichloromethane. The resulting solution was concentrated under reduced pressure to provide the crude product.

Procedure for Friedel-Crafts Reactions in Table 3.7:

A round bottom flask (the reaction flask) equipped with a stir bar and Vigreux column capped with a septum were flame-dried under vacuum. A plug of cotton was inserted into a 3 mL syringe, and the syringe was capped with a septum and purged with argon. K_2CO_3 (dried under vacuum in the presence of P_2O_5) was added to the syringe, and the syringe was connected to a needle that was long enough to reach the reaction flask through the Vigreux column. The needle was inserted through the column, and the system was purged with argon. A second flask (the mixing flask) was flame-dried and purged with argon. **45b** (50 mg) was added to the mixing flask, the flask was purged again, and then dry

dichloromethane (0.5 mL) was added *via* syringe. The resultant solution was transferred *via* cannula to the K_2CO_3-containing syringe, and filtered into the reaction flask. The mixing flask was rinsed with 0.5 mL dichloromethane, which was transferred to the reaction flask in the same manner. Dichloromethane (1 mL) was added to the mixing flask, and a solution of silver bis(trifluoromethanesulfonyl)imide in 1,2-dichloroethane (0.10 mL, 0.198 M) was added. The solution was mixed, and then transferred through the filter into the reaction vessel. The mixing flask and filter were rinsed twice with dichloromethane (1 mL + 1 mL), and the filter setup was removed. The appropriate additive was added directly to the reaction flask (water as a 0.12 M solution (determined by Karl-Fischer titration),[41] and $HNTf_2$ as a solution in 1,2-dichloroethane), and the solution was heated to reflux. The workup and purification was performed in the same manner as for the other Friedel-Crafts reactions.

Trifluoromethanesulfonimide conditions:

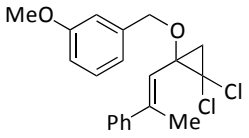
Condition C:

In a flame-dried flask under argon, the substrate was dissolved in dichloromethane at a concentration of 0.05 M. The appropriate amount of trifluoromethanesulfonimide was added as a solution in dichloromethane, and the solution was heated to reflux. On completion, the reaction was quenched by addition of saturated Na_2CO_3 (aq). The layers were separated, and the aqueous was extracted three times with dichloromethane. The combined extract was washed with water then brine, dried over magnesium sulfate, filtered, and concentrated to provide the crude product, which was purified by flash column chromatography.

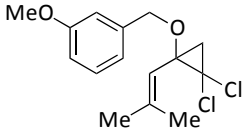
Condition D:

In a flame-dried microwave vial under argon or nitrogen, the substrate was dissolved in 1,2-dichloroethane at a concentration of 0.05 M. 1 mol % trifluoromethanesulfonimide was added as a solution in dichloromethane. The reaction was heated in the microwave at 180 °C for the specified time before the reaction was quenched by addition of saturated Na_2CO_3 (aq). The layers were separated, and the aqueous was extracted three times with dichloromethane. The combined extract was washed with water then brine, dried over magnesium sulfate, filtered, and concentrated to provide the crude product, which was purified by flash column chromatography.

3.5.2 Experimental Procedures and Characterization



1,1-dichloro-2-(3-methoxybenzyloxy)-2-((*1E*)-2-phenylpropen-1-yl)cyclopropane, (36a). The preparation of this compound can be found in Chapter 2.



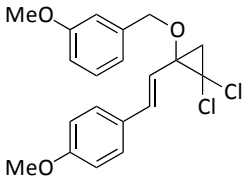
1,1-dichloro-2-(3-methoxybenzyloxy)-2-(2-methylpropen-1-yl)cyclopropane, (36b). *N*,*N*-dimethylaminopyridine (238 mg, 1.95 mmol) followed by *N*,*N*-dicyclohexylcarbodiimide (2.95 g, 14.3 mmol) was added to a solution of senecoic acid (**40**, 1.30 g, 13.0 mmol) and 3-methoxybenzyl alcohol (1.8 mL, 14.3 mmol) in 130 mL dichloromethane. The mixture was stirred overnight at room temperature before it was filtered through Celite and concentrated. Purification by flash column chromatography (10 % ethyl acetate in hexanes) provided 3-

methoxybenzyl senecoate (**41**) as a colorless oil, 1.780 g, 62 %: IR (neat) 2941, 2837, 1718, 1650, 1604, 1456, 1226, 1143 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (app t, *J* =7.9 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 6.92-6.90 (m, 1H), 6.85 (dd, *J* = 8.3 Hz, 2.6 Hz, 1H), 5.75 (app septet, *J* = 1.4 Hz, 1H), 5.11 (s, 2H), 3.81 (s, 3H), 2.19 (d, *J* = 1.2 Hz, 3H), 1.90 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 159.9, 157.6, 138.2, 129.8, 120.5, 116.0, 113.8, 113.7, 65.4, 55.5, 27.7, 20.5; HRMS (EI, M^+) $C_{13}H_{16}O_3$ calculated 220.1099, found m/z 220.1102.

At 0 °C, *N,N,N′,N′*-tetramethylethylenediamine (8.0 mL, 53 mmol) was added via syringe to titanium tetrachloride (2.0 M in DCM, 13.3 mL, 26.6 mmol) in 60 mL THF. The solution was stirred for 20 min. at that temperature, then zinc dust (3.91 g, 59.8 mmol) followed by lead (II) chloride (92 mg, 0.33 mmol) were added and the mixture was stirred at room temperature for 30 min. until the solution phase was bright blue. A solution of 3-methoxybenzyl senecoate (1.46 g, 6.64 mmol) and dibromomethane (1.0 mL, 14.6 mmol) in 10 mL THF was added *via* cannula, and the mixture was allowed to stir overnight. The flask was placed in an ice bath and triethylamine (6.6 mL) and saturated aqueous potassium carbonate (9.2 mL) were added sequentially. The mixture was stirred for 20 min., after which 0.5 % triethylamine in ether was added and the slurry was filtered through basic alumina (Brockman activity III). The solution was concentrated, then dissolved in hexane and filtered again to remove additional solid, and concentrated to a yellow oil (913 mg) that was used directly in the next step.

The crude enol ether (200 mg) was dissolved in 7.7 mL of chloroform. Benzyltriethylammonium chloride (64 mg, 0.28 mmol) was added, followed by 13.2 mL of 50 % aqueous sodium hydroxide. The reaction was stirred vigorously for 15 min., then quenched by the addition of water. The layers were separated, and the aqueous layer was extracted three times with dichloromethane. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated to a brown oil. Flash column chromatography (5 % ethyl acetate in

hexanes) provided **36b** as a pale yellow oil, 184 mg, 41 % over 2 steps: IR (neat) 2999, 2937, 2836, 1604, 1588, 1491, 1456, 1268, 1067, 777, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.22 (m, 1H), 6.93-6.90 (m, 2H), 6.84-6.80 (m, 1H), 5.61-5.59 (m, 1H), 4.61 (d, *J* = 10.8 Hz, 1H), 4.57 (d, *J* = 10.8 Hz, 1H), 3.80 (s, 3H), 1.91 (d, *J* = 8.1 Hz, 1H), 1.87 (d, *J* = 1.2 Hz, 3H), 1.85 (d, *J* = 1.4 Hz, 3H), 1.55 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 145.1, 139.7, 129.6, 120.3, 118.3, 113.6, 113.5, 69.6, 64.6, 64.4, 55.4, 34.5, 25.8, 19.8; HRMS (APPI, $[M+H]^+$) calcd for $C_{15}H_{19}O_2Cl_2$, 301.0762, found m/z 301.0759.

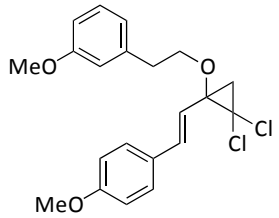


1,1-dichloro-2-(3-methoxybenzyloxy)-2-((*1E*)-1-(4-methoxyphenyl)ethen-2-yl)cyclopropane, (36c). 3-Methoxybenzyl (*E*)-4-methoxycinnamate **(43a)** was prepared in a manner analogous to 3-methoxybenzyl senecoate (see **36b**). Purification by flash column chromatography (20 % ethyl acetate in hexanes) yielded the product as a colorless oil, 1.678 g, 67 %: IR (neat) 3003, 2957, 1710, 1634, 1604, 1513, 1254, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 16.0 Hz, 1H), 7.51-7.44 (m, 2H), 7.31 (dd, *J* = 7.9, 7.8 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.97-6.94 (m, 1H), 6.93-6.85 (m, 3H), 6.36 (d, *J* = 16.0 Hz, 1H), 5.22 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 161.7, 160.0, 145.1, 138.0, 130.0, 129.9, 127.3, 120.6, 115.5, 114.6, 114.0, 113.9, 66.3, 55.6, 55.5; HRMS (EI, M^+) for $C_{18}H_{18}O_4$ calcd 298.1205, found 298.1204.

At 0°C, *N,N,N′,N′*-tetramethylethylenediamine (4.4 mL, 29 mmol) was added via syringe to a solution of titanium tetrachloride (1.6 mL, 14 mmol) in 36 mL THF. The solution was stirred for 20 min. at that temperature, then zinc dust (2.13 g, 32.6 mmol) followed by lead (II) chloride (50 mg, 0.18 mmol) were added and the mixture was stirred at room temperature for 30 min. until the solution was bright blue. A solution of 3-methoxybenzyl (*E*)-4-methoxycinnamate (1.08 g, 3.62 mmol) and dibromomethane (0.56 mL, 8.0

mmol) in 9 mL THF was added via cannula, and the mixture was allowed to stir overnight. The flask was placed in an ice bath and triethylamine (3.6 mL) followed by saturated aqueous potassium carbonate (4.9 mL) were added and the mixture was stirred for 20 min., after which 0.5 % triethylamine in ether was added and the mixture was filtered through basic alumina (Brockman activity III). The solution was concentrated, then dissolved in hexane and filtered again to remove additional solid, and concentrated to a yellow oil (894 mg) that was used directly in the next step.

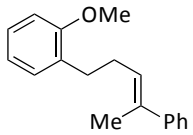
The crude enol ether (858 mg) was dissolved in 24 mL of a 1 : 1 mixture of chloroform and dichloromethane. Benzyltriethylammonium chloride (200 mg, 0.87 mmol) was added, the solution was cooled to 0 °C, and 42 mL of 50 % aqueous sodium hydroxide was added. The reaction was stirred vigorously for 8 min., and then the reaction was quenched by the addition of water. The layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated to a brown oil. Purification by flash column chromatography (15 % ethyl acetate in hexanes) yielded **36c** as a colorless oil, 421.7 mg, 31 % over 2 steps: IR (thin film) 3034, 2954, 2838, 1609, 1585, 1510, 1274, 1240 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.34 (m, 2H), 7.29-7.24 (m, 1H), 6.99-6.93 (m, 2H), 6.91-6.86 (m, 2H), 6.86-6.82 (m, 1H), 6.77 (d, *J* = 16.0 Hz, 1H), 6.21 (d, *J* = 16.0 Hz, 1H), 4.77 (d, *J* = 11.5 Hz, 1H), 4.62 (d, *J* = 11.5 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 1.91 (d, *J* = 8.4 Hz, 1H), 1.83 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz in $CDCl_3$) δ 160.01, 159.95, 139.2, 134.4, 129.7, 128.9, 128.2, 121.4, 119.9, 114.4, 113.7, 113.1, 70.3, 68.3, 65.2, 55.6, 55.5, 32.8; HRMS (ESI,[$M+Na]^+$) for $C_{20}H_{20}$ Cl_2O_3 calcd, 401.0687, found: m/z 401.0684; Anal. Calcd for $C_{20}H_{20}$ Cl_2O_3: C, 63.33; H, 5.32. Found: C, 63.41; H, 5.35.



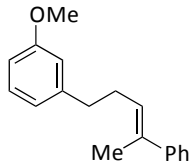
1,1-dichloro-2-((*1E*)-1-(4-methoxyphenyl)ethen-2-yl)-2-(2-(3-methoxyphenyl)ethoxy)cyclopropane, (36d). 2-(3-methoxyphenyl)ethyl (*E*)-4-methoxycinnamate (**43b**) was synthesized in a manner analogous to 3-methoxybenzyl senecoate (see **36b**) to afford 1.137 g of the product as a colorless oil after flash column chromatography (15 % ethyl acetate in hexanes), 73 %: IR (neat) 3002, 2956, 2836, 1707, 1633, 1603, 1512, 1253, 1164 cm^{-1}; ^{1}H NMR (500 MHz in $CDCl_3$) δ 7.66 (d, *J* = 16.0 Hz, 1H), 7.50-7.46 (m, 2H), 7.25 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.94-6.90 (m, 2H), 6.88 (d, *J* = 7.5 Hz, 1H), 6.84 (s, 1H), 6.81 (dd, *J* = 8.0, 2.6 Hz, 1H), 6.32 (d, *J* = 16.0 Hz, 1H), 4.43 (t, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.01 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR (125 MHz in $CDCl_3$) δ 167.4, 161.6, 159.9, 144.7, 139.7, 129.9, 129.7, 127.3, 121.5, 115.7, 114.9, 114.5, 110.1, 65.0, 55.6, 55.4, 35.5; HRMS (EI, M^+) for $C_{19}H_{20}O_4$ calculated 312.1362, found m/z 312.1363; Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.78; H, 6.42.

Compound **36d** was prepared in a manner analogous to **36b** (cyclopropanation time was 23 min.). Flash column chromatography (10 % ethyl acetate in hexanes) provided the product as a colorless oil, 269.2 mg, 25 % over two steps from 2-(3-methoxyphenyl)ethyl (*E*)-4-methoxycinnamate: IR (neat) 3003, 2953, 2836, 1607, 1512, 1252, 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.21 (dd, *J* = 7.7, 7.6 Hz, 1H), 6.88-6.84 (m, 2H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.80-6.76 (m, 2H), 6.56 (d, 16.0 Hz, 1H), 6.08 (d, 16.0 Hz, 1H), 3.91 (ddd, *J* = 9.0, 6.9, 6.8 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.74 (ddd, *J* = 9.0, 7.1, 7.1 Hz, 1H), 2.94-2.89 (m, 2H), 1.77 (d, *J* = 8.3 Hz, 1H), 1.74 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.90, 159.86, 140.4, 133.9, 129.6, 128.9, 128.1, 121.7, 121.6, 115.1, 114.3, 112.0, 69.5, 68.2, 65.2, 55.6, 55.4, 36.6, 32.7; HRMS

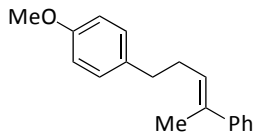
(EI, M^+) for $C_{21}H_{22}Cl_2O_3$ calculated 392.0946, found m/z 392.0948; Anal. Calcd for $C_{21}H_{22}Cl_2O_3$: C, 64.13; H, 5.64. Found: C, 64.16; H, 6.02.



(*E*)-5-(2-methoxyphenyl)-2-phenyl-2-pentene, (45a). At 0°C, freshly distilled diisopropylamine (0.62 mL, 4.4 mmol) was added dropwise to a solution of *n*-butyllithium (1.6 M in hexanes, 2.8 mL, 4.4 mmol) in 4.0 mL THF. After stirring for 20 min., the solution was cooled to -78 °C and diethyl 1-phenylethylphosphonate (**46**, 969 mg, 4.00 mmol) was added via syringe. The solution was stirred for 40 min. at -78 °C before 3-(2-methoxyphenyl)propanal (**44a**, 657 mg, 4.00 mmol) was added via cannula as a solution in 4 mL THF. The solution was allowed to warm to room temperature overnight before the reaction was quenched by the addition of saturated ammonium chloride. The aqueous layer was extracted three times with ether. The combined extract was washed with water then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to a yellow oil. Flash column chromatography (2 % ethyl acetate in hexanes) provided **45a** as a colourless oil, 5728 mg, 56 % as a 16 : 1 mixture of *E* to *Z* isomers: IR (neat) 3022, 2937, 2834, 1600, 1588, 1493, 1464, 1243, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (m, 2H), 7.33-7.27 (m, 2H), 7.24-7.15 (m, 3H), 6.93-6.85 (m, 2H), 5.87 (tq, *J* = 7.2, 1.3 Hz, 1H), 3.85 (s, 3H), 2.80-2.74 (m, 2H), 2.54-2.46 (m, 2H), 1.99 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 144.3, 135.3, 130.7, 130.2, 128.35, 128.31, 127.3, 126.7, 125.9, 120.6, 110.5, 55.5, 30.5, 29.3, 15.9; HRMS (EI, M^+) for $C_{18}H_{20}O$ calcd, 252.1514, found: m/z 252.1513; Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.57; H, 8.05.

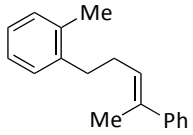


(*E*)-5-(3-methoxyphenyl)-2-phenyl-2-pentene, (45b). At 0°C, diethyl 1-phenylethylphosphonate (**46**, 296 mg, 1.22 mmol) in 1.2 mL THF was added via cannula to a solution of *n*-butyllithium (1.6 M in hexane, 0.76 ml, 1.2 mmol) in 0.8 mL THF. The solution was stirred at that temperature for 30 min., during which the solution became a pale reddish-orange. 3-(3-methoxyphenyl)propanal (**44b**, 200 mg, 1.2 mmol) as a solution in 1.2 mL THF was added via cannula, and the pale yellow solution was allowed to stir until the reaction was judged complete by TLC analysis. The reaction was quenched by the addition of saturated aqueous ammonium chloride, and the aqueous layer was extracted three times with ether. The combined extract was washed with water then brine, dried over magnesium sulfate, filtered, and concentrated. The resulting yellow oil was purified by flash column chromatography (5 % ethyl acetate in hexanes) to afford **45b** as a colorless oil, 107.9 mg, 35 %, as a mixture of 10 : 1 *E* to *Z* isomers: IR (neat) 3054, 2937, 1601, 1584, 1489, 1261, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.34 (m, 2H), 7.34-7.28 (m, 2H), 7.25-7.19 (m, 2H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.80-6.78 (m, 1H), 6.76 (dd, *J* = 8.1, 2.6 Hz), 5.82 (tq, *J* = 7.2, 1.3 Hz, 1H), 3.80 (s, 3H), 2.75 (t, *J* = 7.8 Hz, 2H), 2.52 (dt, *J* = 7.7, 7.3 Hz, 2H), 1.99 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 144.1, 143.9, 135.7, 129.5, 128.4, 127.6, 126.8, 125.9, 120.2, 114.5, 111.4, 55.4, 36.1, 30.9, 16.1; HRMS (EI, M^+) for $C_{18}H_{20}O$ calculated 252.1514, found m/z 252.1515; Anal. Calcd for $C_{18}H_{20}O$, 85.67; H, 7.99. Found: C, 85.45; H, 8.09.

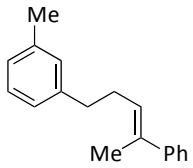


(E)-5-(4-methoxyphenyl)-2-phenyl-2-pentene, (45c). Compound **45c** was prepared in a manner analogous to **45a**. Flash column chromatography (40 %

dichloromethane in hexanes) provided the product as a colorless oil, 353 mg, 46 %, as a mixture of 12 : 1 *E* to *Z* isomers. IR (neat) 3029, 2933, 2834, 1612, 1512, 1443, 1246 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 144.2, 135.6, 134.4, 129.6, 128.4, 127.7, 126.8, 125.9, 114.0, 55.5, 35.2, 31.2, 16.0; Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.29; H, 8.01. IR, HRMS and ^1H NMR data is consistent with the reported values.[42]

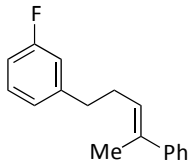


(*E*)-5-(2-methylphenyl)-2-phenyl-2-pentene, (45d). Compound **45d** was prepared in a manner analogous to **45a**. Flash column chromatography (2 % ethyl acetate in hexanes) provided the product as a colorless oil, 221 mg, 26 %, as a mixture of 12 : 1 *E* to *Z* isomers. IR (neat) 3058, 2939, 2865, 1598, 1494, 1445, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.36 (m, 2H), 7.34-7.28 (m, 2H), 7.25-7.10 (m, 5H), 5.86 (tq, *J* = 7.2, 1.3 Hz, 1H), 2.79-2.72 (m, 2H), 2.53-2.45 (m, 2H), 2.36 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 140.4, 136.2, 135.6, 130.4, 129.1, 128.4, 127.8, 126.8, 126.24, 126.19, 125.9, 33.4, 29.7, 19.6, 16.0; HRMS (EI, M^+) for $C_{18}H_{20}$ calcd, 236.1565, found: m/z 236.1567.

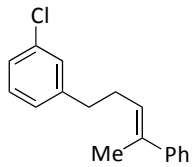


(*E*)-5-(3-methylphenyl)-2-phenyl-2-pentene, (45e). Compound **45e** was prepared in a manner analogous to **45a**. Flash column chromatography (15 % dichloromethane in hexanes) provided the product as a colorless oil, 306 mg, 44 %, as a mixture of 13 : 1 *E* to *Z* isomers: IR (neat) 3023, 2921, 2857, 1609, 1493, 1444, 758, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (m, 2H), 7.34-7.28 (m, 2H), 7.26-7.17 (m, 2H), 7.01-7.08 (m, 3H), 5.83 (tq, *J* = 7.3, 1.4 Hz, 1H), 2.77-2.71 (m, 2H), 2.56-2.48 (m, 2H), 2.36 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 142.2, 138.1, 135.6, 129.6, 128.5, 128.4, 127.8, 126.81,

126.79, 125.9, 125.7, 36.0, 31.1, 21.7, 16.0; HRMS (EI, M^+) for $C_{18}H_{20}$ calcd, 236.1565, found: m/z 236.1565; Anal. Calcd for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.66; H, 8.58.

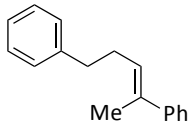


(*E*)-5-(3-fluorophenyl)-2-phenyl-2-pentene, (45f) Compound **45f** was prepared in a manner analogous to **45a**. Flash column chromatography (gradient from hexanes to 5 % ethyl acetate in hexanes) provided the product as a colorless oil, 117 mg, 42 %, as a mixture of 20 : 1 *E* to *Z* isomers: IR (neat) 3063, 2936, 2864, 1616, 1588, 1487, 1446, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.21 (m, 6H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.97-6.87 (m, 2H), 5.79 (t, *J* = 7.1 Hz, 1H), 2.80-2.75 (m, 2H), 2.56-2.50 (m, 2H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, *J* = 245.1 Hz), 144.8 (d, *J* = 7.2 Hz), 144.0, 136.0, 129.9 (d, *J* = 8.3 Hz), 128.4, 127.1, 126.9, 125.9, 124.4 (d, *J* = 2.7 Hz), 115.5 (d, *J* = 20.8 Hz), 113.0 (d, *J* = 21.0 Hz), 35.8 (d, *J* = 1.6 Hz), 30.6, 16.1; HRMS (EI, M^+) for $C_{17}H_{17}F$ calculated, 240.1314, found: m/z 240.1314.

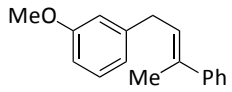


(*E*)-5-(3-chlorophenyl)-2-phenyl-2-pentene, (45g). Compound **45g** was prepared in a manner analogous to **45a**. Flash column chromatography (hexanes) provided the product as a colorless oil, 283 mg, 32 %. 18 mg, 2 % of the *Z*-isomer was also isolated: IR (neat) 3036, 2933, 1598, 1573, 1494, 1475, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.38-7.28 (m, 4H), 7.26-7.16 (m, 4H), 7.11 (d, *J* = 7.2 Hz, 1H), 5.77 (tq, *J* = 7.2, 1.3 Hz, 1H), 2.77-2.72 (m, 2H), 2.55-2.48 (m, 2H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 144.0, 136.1, 134.3, 129.8,

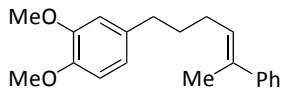
128.9, 128.4, 127.04, 126.95, 126.91, 126.3, 125.9, 35.7, 30.7, 16.1; HRMS (EI, M^+) for $C_{17}H_{17}Cl$ calcd, 256.1019, found: m/z 256.1018.



(*E*)-2,5-diphenyl-2-pentene, (45h). Compound **45h** was prepared in a manner analogous to **45a**. Flash column chromatography (2 % ethyl acetate in hexanes) provided the product as a colorless oil, 496 mg, 44 %, as a 20 : 1 mixture of *E* to *Z* isomers: IR (neat) 3060, 3027, 2923, 1999, 1495, 1453, 758, 697 cm^{-1}; HRMS (EI, M^+) for $C_{17}H_{18}$ calcd, 222.1408, found: m/z 222.1408; Anal. Calcd for $C_{17}H_{18}$: C, 91.41; H, 8.23. Found: C, 91.84; H, 8.16. ^1H NMR and ^{13}C NMR data are consistent with the reported values.[43]

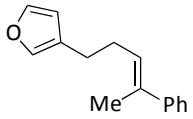


(*E*)-1-(3-methoxyphenyl)-3-phenyl-2-butene, (45i). Compound **45i** was prepared in a manner analogous to **45a**. Flash column chromatography (40 % dichloromethane in hexanes) provided the product as a colorless oil, 342 mg, 47 %, as a mixture of 8 : 1 *E* to *Z* isomers: IR (neat) 3029, 2938, 1600, 1490, 1453, 1261, 762, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.40 (m, 2H), 7.35-7.29 (m, 2H), 7.27-7.20 (m, 2H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.82-6.80 (m, 1H), 6.76 (dd, *J* = 8.3, 2.6 Hz, 1H), 5.98 (tq, *J* = 7.4, 1.4 Hz, 1H), 3.81 (s, 3H), 3.56 (d, *J* = 7.4 Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 143.9, 142.9, 136.1, 129.7, 128.4, 127.0, 126.8, 126.0, 121.1, 114.5, 111.5, 55.4, 35.2, 16.2; HRMS (EI, M^+) for $C_{17}H_{18}O$ calcd, 238.1358, found: m/z 238.1360; Anal. Calcd for $C_{17}H_{18}O$: C, 85.68; H, 7.61. Found: C, 85.24; H, 7.61.

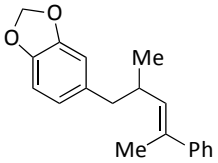


(*E*)-6-(3,4-dimethoxyphenyl)-2-phenyl-2-hexene, 45j. Compound **45j** was prepared in a manner analogous to **45a**. Flash column chromatography (10 %

ethyl acetate in hexanes) provided the product as a colorless oil, 378 mg, 37 %, as a 10 : 1 mixture of *E* to *Z* isomers: IR (neat) 3055, 2934, 2856, 1591, 1516, 1464, 1262, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.36 (m, 2H), 7.34-7.28 (m, 2H), 7.25-7.20 (m, 1H), 6.8 (d, *J* = 7.9 Hz, 1H), 6.76-6.72 (m, 2H), 5.81 (tq, *J* = 7.2, 1.3 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 2.63 (t, *J* = 7.2, 1.3 Hz, 2H), 2.24 (app q, *J* = 7.3 Hz, 2H), 2.02 (s, 3H), 1.78 (app pentet, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 147.2, 144.0, 135.2, 135.1, 128.2, 126.6, 125.6, 120.3, 111.9, 111.3, 56.0, 55.9, 35.2, 31.5, 28.4, 15.9 [One aromatic carbon signal is missing due to incidental overlap]; HRMS (EI, M^+) for $C_{20}H_{24}O_2$ calcd, 296.1776, found: m/z 296.1775; Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16 . Found: C, 80.77; H, 8.18.

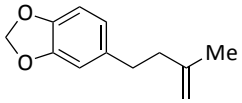


3-((*E*)-2-phenyl-2-penten-5-yl)furan, (44k). Compound **44k** was prepared in a manner analogous to **45a**. Purification by flash column chromatography (2 % ethyl acetate in hexanes) provided **44k** as a colorless oil, 364 mg, 23 %: IR (neat) 3030, 2921, 2856, 1598, 1494, 1445, 1025, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 3H), 7.33-7.29 (m, 2H), 7.27-7.26 (m, 1H), 7.25-7.21 (m, 1H), 6.33-6.32 (m, 1H), 5.83-5.79 (m, 1H), 2.61-2.57 (m, 2H), 2.50-2.45 (m, 2H), 2.03-2.02 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 142.9, 139.2, 135.7, 128.4, 127.7, 126.8, 125.9, 124.9, 111.3, 29.5, 25.0, 16.1; HRMS (EI, M^+) for $C_{15}H_{16}O$ calcd 212.1201, found m/z 212.1197.

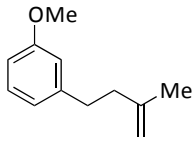


(*E*)-4-methyl-5-(3,4-methylenedioxyphenyl)-2-phenyl-2-pentene, (**45l**). Compound **45l** was prepared in a manner analogous to **45a**. Flash column chromatography (hexanes to 5 % ethyl acetate in hexanes gradient) provided the

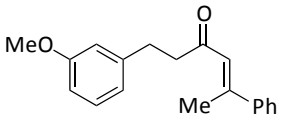
product as a colourless oil, 2.527 g, 79 %, as a mixture of 5.9 : 1 *E* to *Z* isomers: IR (neat) 2958, 2923, 1488, 1439, 1242, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 4H), 7.25-7.20 (m, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 1.6 Hz, 1H), 5.93 (s, 2H), 5.58 (dq, *J* = 9.4, 1.6 Hz, 1H), 2.83-2.72 (m, 1H), 2.59 (dd, *J* = 7.0, 3.1 Hz, 2H), 1.90 (d, *J* = 1.6 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 145.5, 134.7, 133.9, 128.1, 126.5, 125.7, 122.1, 109.6, 107.9, 100.7, 43.5, 35.5, 20.5, 15.9 (1 aromatic carbon signal is missing due to incidental overlap); HRMS (EI, M^+) for $C_{19}H_{20}O_2$ calcd, 280.1463, found: m/z 280.1462.



2-methyl-4-(3,4-methylenedioxyphenyl)-1-butene, (45m). At 0 °C, *n*-butyllithium (1.6 M in hexanes, 6.5 mL, 10 mmol) was added dropwise to methyltriphenylphosphonium bromide (3.72 g, 10.4 mmol) in 50 mL THF. The mixture was stirred for 20 min. at that temperature, then allowed to warm to room temperature and stirred for a further 20 min. before 4-(3,4-methylenedioxyphenyl)-2-butanone (**47a**, 1.00 g, 5.20 mmol) was added *via* cannula as a solution in 5.0 mL THF. The solution was allowed to stir overnight before it was quenched by the addition of water. The aqueous layer was extracted three times with ether, and the combined extract was washed with water then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. Flash column chromatography (2 % ethyl acetate in hexanes) afforded the **45m** as a pale yellow oil, 906 mg, 91 %: IR (neat) 2936, 1649, 1503, 1490, 1443, 1245, 1042 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 1.6 Hz, 1H), 6.64 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.92 (s, 2H), 4.74 (s, 1H), 4.70 (s, 1H), 2.70-2.65 (m, 2H), 2.30-2.25 (m, 2H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 145.8, 145.5, 136.3, 121.2, 110.5, 109.0, 108.3, 101.0, 40.1, 34.2, 22.8; HRMS (EI, M^+) for $C_{12}H_{14}O_2$ calcd, 190.0994, found, 190.0996.



4-(3-methoxyphenyl)-2-methyl-2-butene, (45n). *n*-Butyllithium (0.88 mL, 1.6 M in hexanes, 1.4 mmol) was added dropwise to methyltriphenylphosphonium iodide (568 mg, 1.4 mmol) in 7.0 mL THF at 0°C, and the solution was stirred 20 minutes before it was warmed to room temperature and stirred for a further 20 minutes. 4-(3-methoxyphenyl)-2-butanone (**47b**, 125 mg, 0.703 mmol) was added as a solution in 1.0 mL THF, and the reaction was allowed to stir overnight. After the reaction was quenched with saturated ammonium chloride, it was extracted three times with ether, the combined extracts were washed with water then brine, dried over magnesium sulfate, filtered, and concentrated. Purification by flash column chromatography (gradient, hexanes to 5 % ethyl acetate in hexanes) provided **45n** as a colorless oil, 92.3 mg, 74 %: IR (neat) 3081, 2938, 2835, 1651, 1602, 1584, 1489, 1453, 1258, 1151, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.19 (m, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.77-6.73 (m, 2H), 4.76 (s, 1H), 4.73 (s, 1H), 3.81 (s, 3H), 2.78-2.72 (m, 2H), 2.36-2.30 (m, 2H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 144.6, 143.1, 128.5, 120.0, 113.4, 110.3, 109.4, 54.4, 38.7, 33.5, 21.9; HRMS (EI, M^+) for $C_{12}H_{16}O$ calculated 176.1201, found m/z 176.1200.

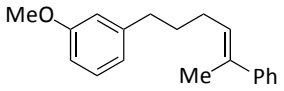


(*E*)-1-(3-methoxyphenyl)-5-phenyl-4-hexen-3-one (51). Oxalyl chloride (0.47 mL, 5.5 mmol) was added in a dropwise fashion *via* syringe to a stirring solution of 3-(3-methoxyphenyl)propionic acid (**48**, 0.500 g, 2.77 mmol) in ether (2.8 mL). The solution was stirred at room temperature overnight, then concentrated under reduced pressure. The resulting crude acid chloride was dissolved in 28 mL dichloromethane, then cooled to 0 °C. *N*,*O*-dimethylhydroxylamine hydrochloride (0.513 g, 5.26 mmol) was added, followed by pyridine (0.67 mL,

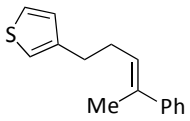
8.3 mmol). The solution was allowed to warm to room temperature, and was quenched by the addition of water after four hours. The aqueous layer was extracted three times with dichloromethane, dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by flash column chromatography (70 % ethyl acetate in hexanes) provided *N*-methoxy-*N*-methyl 3-(3-methoxyphenyl)propionamide (**49**) as a pale yellow oil, 580 mg, 94 %: IR (neat) 2939, 2836, 1665, 1602, 1585, 1489, 1263, 783 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 7.21 (app t, *J* = 7.8 Hz, 1H), 6.85-6.72 (m, 3H), 3.80 (s, 3H), 3.62 (s, 3H), 3.81 (s, 3H), 2.99-2.90 (m, 2H), 2.77-2.65 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 159.9, 143.2, 129.7, 121.0, 114.4, 111.6, 61.5, 55.4, 33.9, 32.5, 31.0; HRMS (EI, M^+) for $C_{12}H_{17}NO_3$ calcd, 223.1208, found: m/z 223.1208; Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27 . Found: C, 64.68; H, 7.67; N, 6.24.

At -78°C, *t*-butyllithium (1.7 M in pentane, 0.88 mL, 1.5 mmol) was added to a solution of (*E*)-1-iodo-2-phenyl-1-propene[27] (**50**, 208 mg, 0.75 mmol) in 0.75 mL ether. The solution was stirred at that temperature for 30 minutes before it was added *via* cannula to a solution of *N*-methoxy-*N*-methyl 3-(3-methoxyphenyl)propionamide (**49**, 100 mg, 0.500 mmol) in 0.5 mL ether. The resulting solution was warmed to 0°C after 30 min. and stirred for an additional two hours at that temperature before quenching by the addition of water. The aqueous layer was extracted three times with ether, washed with water then brine, dried over magnesium sulfate, filtered, and concentrated. Flash column chromatography (7 % ethyl acetate in hexanes) provided (*E*)-1-(3-methoxyphenyl)-5-phenyl-4-hexen-3-one (**51**) as a colorless oil, 99.5 mg, 71 %: IR (neat) 3056, 2937, 2835, 1682, 1602, 1492, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.43 (m, 2H), 7.40-7.35 (m, 3H), 7.21 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 6.79-6.77 (m, 1H), 6.75 (dd, *J* = 8.1, 2.6 Hz, 1H), 6.48 (q, *J* = 1.3 Hz, 1H), 3.80 (s, 3H), 2.99-2.93 (m, 2H), 2.90-2.85 (m, 2H), 2.56 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 160.0, 154.4, 143.2, 142.8,

129.7, 129.3, 128.8, 126.7, 124.3, 121.0, 114.4, 111.6, 55.4, 46.5, 30.5, 18.7; HRMS (EI, M^+) for $C_{19}H_{20}O_2$ calculated 280.1463, found m/z 280.1464; Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.53; H, 7.33.

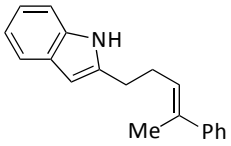


(*E*)-6-(3-methoxyphenyl)-2-phenyl-2-hexene, (45o). Boron trifluoride diethyl etherate (0.26 mL, 2.1 mmol) followed by sodium cyanoborohydride (134 mg, 2.14 mmol) were added to a solution of (*E*)-1-(3-methoxyphenyl)-6-phenyl-4-hexen-3-one (**51**) in 2.4 mL THF. The solution was stirred at room temperature for 45 min. before it was quenched by the addition of water. The aqueous layer was extracted three times with ether, then the combined extract was washed with water then brine, dried over magnesium sulfate, filtered, and concentrated. Flash column chromatography provided the **45o** as a colorless oil, 164.4 mg, 86 % as a 4 : 1 mixture of *E* to *Z* isomers: IR (neat) 3028, 2936, 2858, 1601, 1584, 1492, 1454, 1262, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.36 (m, 2H), 7.35-7.29 (m, 2H), 7.25-7.14 (m, 2H), 6.81 (d, J = 7.6 Hz, 1H), 6.77-6.71 (m, 2H), 5.80 (tq, J = 7.2, 1.3 Hz, 1H), 3.81 (s, 3H), 2.67 (t, J = 7.6 Hz, 2H), 2.25 (app q, J = 7.3 Hz, 2H), 2.02 (s, 3H), 1.80 (app pentet, J = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 144.4, 144.2, 135.3, 129.5, 128.4, 128.4, 126.8, 125.9, 121.2, 114.5, 111.3, 55.4, 35.9, 31.4, 28.6, 16.1. HRMS (EI, M^+) for $C_{19}H_{22}O$ calculated 266.1670, found m/z 266.1675.



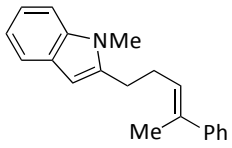
3-((*E*)-2-phenyl-2-penten-5-yl)thiophene, (45q). At 0 °C, 4-phenylpent-3-enyl-1-magnesium bromide[31] (0.26 M in ether, 7.0 mL, 1.8 mmol) was added dropwise to a mixture of 3-bromothiophene (0.155 mL, 1.65 mmol) and [1,1′-bis(piphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (13 mg, 0.017 mmol) in 1.5 mL ether. After the addition was complete, the solution was heated to reflux for 20 h. The mixture was cooled to 0 °C and

quenched with 2 M HCl. The aqueous layer was extracted three times with ether, and the combined extract was washed with water then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to a brown oil, 435.6 mg. 261.4 mg of the crude product was purified by preparatory HPLC (C-18 column, gradient of acetonitrile/aqueous trifluoroacetic acid (0.06 %)) to provide **45q** as a colorless oil, 160.4 mg, 70 % as a mixture of 10 : 1 *E* to *Z* isomers: IR (neat) 3027, 2920, 2855, 1493, 1445, 833, 754, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.19 (m, 6H), 7.02-6.97 (m, 2H), 5.82 (t, *J* = 7.4 Hz, 1H), 2.83-2.78 (m, 2H), 2.58-2.50 (m, 2H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 142.6, 135.7, 128.5, 128.4, 127.6, 126.8, 125.9, 125.5, 120.5, 30.4, 30.0, 16.0; HRMS (EI, M^+) for $C_{15}H_{16}S$ calcd 228.0973, found m/z 228.0975.



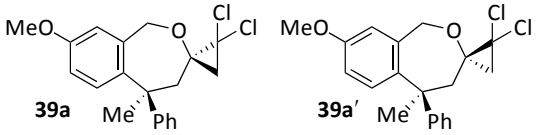
2-((*E*)-2-phenyl-2-penten-5-yl)indole, (45r). A solution of diazomethane in toluene was added dropwise to a solution of (*E*)-5-phenylhex-4-enoic acid[31] (**53**, 1.264 g, 6.643 mmol) in 6.6 mL ether until the solution remained a yellow color. The remaining diazomethane was quenched by the addition of acetic acid, and then the solution was washed with water followed by saturated sodium bicarbonate and finally brine before it was dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was judged to be ≥98% pure by NMR analysis, and was not subjected to any subsequent purification procedures; methyl (*E*)-5-phenylhex-4-enoate **(54)** was obtained as a colorless oil, 1.356 g, >99 %: IR (neat) 3023, 2951, 1735, 1494, 1436, 1159 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.35 (m, 2H), 7.34-7.28 (m, 2H), 7.26-7.21 (m, 1H), 5.73 (t, *J* = 7.0 Hz, 1H), 3.70 (s, 3H), 2.58-2.51 (m, 2H), 2.50-2.45 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 143.8, 136.5, 128.4, 127.0, 126.2, 125.9, 51.8, 34.2, 24.5, 16.1; HRMS (EI, M^+) for $C_{13}H_{16}O_2$ calculated 204.1150, found m/z 204.1153.

n-Butyllithium (6.9 mL, 1.6 M in hexane, 11 mmol) was added dropwise to a solution of *N*-trimethylsilyl-*o*-toluidine[32] (794 mg, 4.43 mmol) in 22 mL hexanes (dried over 3 Å molecular sieves) at 0 °C. The solution was heated to reflux for 6 hours before it was cooled to -78°C and then methyl (*E*)-5-phenylhex-4-enoate (**54**, 1.36 g, 6.64 mmol) was added as a solution in 6.8 mL THF. After warming to room temperature, stirring was continued for 1 h. The reaction was quenched by addition of brine. The aqueous layer was extracted three times with ether, and then the combined extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated to a yellow oil. Flash column chromatography (gradient from hexanes to 15 % ethyl acetate in hexanes) provided **45r** as a white solid, 526.1 mg, 45 %: m.p. 101.5-104.3 °C; IR (cast film, dichloromethane) 3396, 2949, 1713, 1494, 1443, 1413, 1289, 786, 749, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.41-7.28 (m, 5H), 7.27-7.21 (m, 1H), 7.15 – 7.06 (m, 2H), 6.31 (s, 1H), 5.88 (tq, *J* = 7.1, 1.3 Hz, 1H), 2.94 (t, *J* = 7.5 Hz, 2H), 2.65 (app q, *J* = 7.2 Hz, 2H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 139.5, 136.4, 136.2, 129.0, 128.5, 127.1, 127.0, 125.9, 121.3, 120.1, 119.9, 110.6, 100.0, 28.8, 28.4, 16.1; HRMS (EI, M^+) for $C_{19}H_{19}N$ calcd 261.1518, found m/z 261.1518.



1-methyl-2-((*E*)-2-phenyl-2-penten-5-yl)indole, (45s). Compound **45r** (150 mg, 0.957 mmol) was added to a suspension of powdered potassium hydroxide (483 mg, 8.61 mmol) in acetone. Iodomethane (119 μL, 1.91 mmol) was added, and the mixture was stirred for 2 h before the addition of water. The solution was extracted three times with ether, and the combined extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. Flash column chromatography (gradient of hexanes to 5 % ethyl acetate in hexanes) yielded **45s** as a white powder, 193 mg, 73 %: m.p. 92.1-95.5 °C; IR (cast film,

dichloromethane) 3054, 2937, 1544, 1467, 1444, 1400, 1343, 747, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.8 Hz, 1H), 7.40-7.36 (m, 2H), 7.34-7.28 (m, 3H), 7.26-7.20 (m, 1H), 7.20-7.14 (m, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.32 (s, 1H), 5.89 (t, *J* = 7.0 Hz, 1H), 3.70 (s, 3H), 2.93-2.87 (m, 2H), 2.69-2.62 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 140.9, 137.6, 136.1, 128.4, 128.1, 127.2, 127.0, 125.9, 120.9, 120.1, 119.5, 109.0, 99.1, 29.7, 28.1, 27.0, 16.1; HRMS (EI, M^+) for $C_{20}H_{21}N$ calcd 275.1674, found m/z 275.1676.

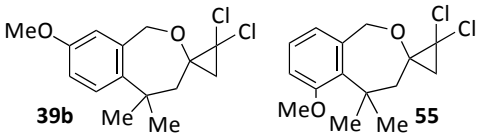


***trans*-2′,2′-dichloro-8-methoxy-5-methyl-5-phenyl-1,3,4,5-tetrahydro-spiro-[2-benzoxepin-3,1′-cyclopropane], 39a** and ***cis*-2′,2′-dichloro-8-methoxy-5-methyl-5-phenyl-1,3,4,5-tetrahydro-spiro-[2-benzoxepin-3,1′-cyclopropane], 39a′.** Compound **36a** (20 mg, 0.055 mmol) was subjected to Friedel-Crafts conditions A (20 h) followed by flash column chromatography (gradient hexanes to 10 % ethyl acetate in hexanes) to provide the product as a colorless resin, 15.9 mg, 79 % as a 1.5 : 1 mixture of **39a** to **39a′**. Further purification by pTLC (2 elutions with 10 % ethyl acetate in hexanes) allowed for samples of each diastereoisomer to be collected for analysis.

39a: IR (neat) 3057, 2957, 2836, 1612, 1502, 1465, 1284, 770 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 7.26-7.21 (m, 2H), 7.18-7.12 (m, 3H), 7.08 (d, *J* = 8.7 Hz, 1H), 6.81 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.74 (d, *J* = 2.9 Hz, 1H), 4.93 (d, *J* = 14.8 Hz, 1H), 4.80 (d, *J* = 14.8 Hz, 1H), 3.78 (s, 3H), 2.81 (d, *J* = 15.7 Hz, 1H), 2.58 (d, *J* = 15.7 Hz, 1H), 1.82 (s, 3H), 1.28 (d, *J* = 8.8 Hz, 1H), 1.21 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (CD_3CN, 125 MHz) δ 158.6, 149.9, 140.6, 138.7, 132.2, 128.7, 128.2, 126.8, 114.2, 113.8, 71.55, 67.5, 64.4, 55.9, 41.3, 45.2, 33.7, 31.8; HRMS (APPI, $[M+H]^+$) for $C_{20}H_{21}Cl_2O_2$ calculated 363.0913, found m/z 363.0916.

39a′: IR (neat) 3056, 2954, 2836, 1611, 1501, 1465, 1284, 751 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 7.27-7.24 (m, 2H), 7.24-7.19 (m, 1H),

6.62-6.57 (m, 3H), 5.30 (d, *J* = 15.1 Hz, 1H), 4.77 (d, *J* = 15.1 Hz, 1H), 3.76 (s, 3H), 3.43 (d, *J* = 15.6 Hz, 1H), 1.87 (s, 3H), 1.81 (d, *J* = 8.6 Hz, 1H), 1.71 (d, *J* = 15.6 Hz, 1H), 1.59 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 151.6, 139.9, 138.8, 133.0, 128.2, 126.9, 126.1, 112.9, 112.6, 71.3, 66.4, 61.9, 55.2, 47.6, 45.2, 34.4, 27.4; HRMS (EI, M^+) for $C_{20}H_{20}Cl_2O_2$ calculated 362.0840, found m/z 362.0842.

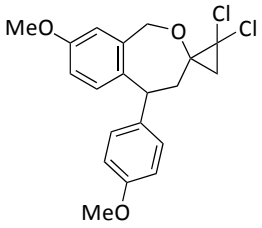


2′,2′-dichloro-8-methoxy-5,5-dimethyl-1,3,4,5-tetrahydro-spiro-[2-benzoxepin-3,1′-cyclopropane], 39b and **2′,2′-dichloro-6-methoxy-5,5-dimethyl-1,3,4,5-tetrahydro-spiro-[2-benzoxepin-3,1′-cyclopropane], 55.** Compound **36b** (47.5 mg, 0.158 mmol) was subjected to Friedel-Crafts conditions A (20 h) followed by purification by flash column chromatography (40 % dichloromethane in hexanes) to provide **39b**, 14.3 mg colorless resin, 30 %. The minor isomer was further purified by pTLC (5 % ether in hexanes) to provide **55**, 6.3 mg white solid, 13 %.

39b: IR ($CDCl_3$ cast film) 2959, 2867, 1612, 1575, 1502, 1466, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8 Hz, 1H), 6.81 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.59 (d, *J* = 2.8 Hz, 1H), 5.09 (d, *J* = 14.8 Hz, 1H), 4.74 (d, *J*, = 14.8 Hz, 1H), 3.79 (s, 3H), 2.72 (d, *J* = 15.2 Hz, 1H), 1.91 (d, *J* = 15.4 Hz, 1H), 1.76 (d, *J* = 8.5 Hz, 1H), 1.55 (d, *J* = 8.4 Hz, 1H), 1.50 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 139.7, 138.8, 128.7, 114.0, 113.0, 72.1, 67.1, 63.3, 55.5, 44.6, 38.9, 34.2, 31.0 [1 aliphatic carbon signal is missing due to incidental overlap]; HRMS (APPI, M^+) for $C_{15}H_{18}Cl_2O_2$ calculated 300.0678, found m/z 300.0678.

55: m.p. 100-102 °C; IR 2958, 2836, 1576, 1449, 1259, 1075, 790 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (app t, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.63 (d, *J* = 7.4 Hz), 5.21 (d, *J* = 15.1 Hz, 1H), 4.71 (d, *J* = 15.1 Hz, 1H), 3.84 (s, 3H),

3.05 (d, *J* = 15.8 Hz, 1H), 1.77-1.70 (m, 2H), 1.63 (d, *J* = 8.6 Hz, 1H), 1.58 (s, 3H), 1.56 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 139.4, 135.0, 127.6, 121.3, 111.9, 71.6, 66.7, 62.4, 55.5, 46.0, 40.5, 33.9, 30.5, 26.2; HRMS (APPI, $[M-Cl]^+$) for $C_{15}H_{18}ClO_2$ calculated 265.099, found, 265.099.

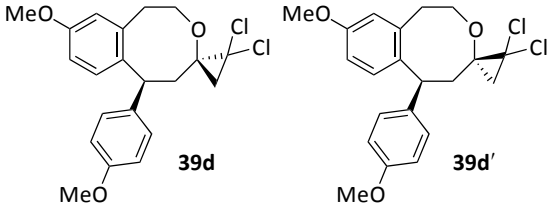


2′,2′-dichloro-8-methoxy-5-(4-methoxyphenyl)-1,3,4,5-tetrahydro-spiro-[2-benzoxepin-3,1′-cyclopropane] 39c and **39c′.** Subjection of **36c** (25 mg, 0.066 mmol) to Friedel-Crafts conditions A (20 h) followed by flash column chromatography (gradient hexanes to 10 % ethyl acetate in hexanes) provided the product as a colorless resin, 16.1 mg, 64 % as a 1.3 : 1 mixture of diastereomers **39c** (major) and **39c′**. Further purification by flash column chromatography (gradient, 5-15 % ethyl acetate in hexane) allowed for samples of each diastereomer to be collected for characterization.

39c: IR ($CDCl_3$ cast film) 3000, 2957, 2836, 1611, 1583, 1512, 1464, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.14 (m, 2H), 6.96-6.91 (m, 2H), 6.77 (d, *J* = 2.7 Hz, 1H), 6.64 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.52 (d, *J* = 8.6 Hz, 1H), 4.92 (d, *J* = 13.8 Hz, 1H), 4.84 (d, *J* = 13.8 Hz, 1H), 4.40 (d, *J* = 10.1 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 2.83 (ddd, *J* = 14.2, 11.1, 1.5 Hz, 1H), 2.20 (dd, *J* = 14.4, 1.9 Hz, 1H), 1.76 (dd, *J* = 8.2, 1.4 Hz, 1H), 1.52 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 158.0, 138.4, 136.4, 136.3, 130.1, 129.8, 114.9, 114.4, 112.7, 72.2, 69.2, 65.0, 55.57, 55.56, 45.1, 40.1, 32.8; HRMS (APPI, $[M+H]^+$) for $C_{20}H_{21}Cl_2O_3$ calculated 379.0862, found m/z 379.0867.

39c′: IR ($CDCl_3$ cast film) 3001, 2958, 2836, 1612, 1581, 1513, 1253, 1043 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 7.20-7.16 (m, 2H), 6.95-6.91 (m, 2H), 6.87 (d, *J* = 2.7 Hz, 1H), 6.70 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.54 (d, *J* = 8.5 Hz, 1H), 5.14 (d, *J* = 13.9 Hz, 1H), 4.69 (d, *J* = 13.9 Hz, 1H), 4.62 (d, *J* = 10.0 Hz, 1H), 3.79 (s, 3H),

3.75 (s, 3H), 2.60 (dd, *J* = 14.8Hz, 10.1 Hz, 1H), 2.35 (d, *J* = 14.6 Hz, 1H), 1.60 (d, *J* = 8.6 Hz, 1H), 1.46 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 158.1, 139.0, 136.9, 135.6, 129.9, 129.7, 115.2, 114.2, 112.8, 72.8, 69.4, 64.2, 55.6, 55.5, 45.8, 40.7, 35.1; HRMS (APPI, $[M+H]^+$) for $C_{20}H_{21}Cl_2O_3$ calculated 379.0862, found m/z 379.0866.

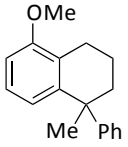


***trans*-2′,2′-dichloro-9-methoxy-6-(4-methoxyphenyl)-1,2,5,6-tetrahydro-spiro-[2-benzoxocine-4,1′-cyclopropane], 39d** and ***cis*-2′,2′-dichloro-9-methoxy-6-(4-methoxyphenyl)-1,2,5,6-tetrahydro-spiro-[2-benzoxocine-4,1′-cyclopropane], 39d′.** Subjection of **36d** (156.6 mg, 0.398 mmol) to Friedel-Crafts conditions A (20 h) followed by purification by flash column chromatography (gradient 10-20 % ethyl acetate in hexanes) provided 82.8 mg of a 1:1 mixture of diastereomers **39d** and **39d′**, 52 %. A sample was further purified by flash column chromatography (slow gradient 10-20 % ethyl acetate in hexanes) to obtain each isomer for analysis.

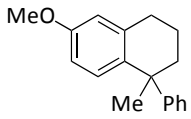
39d: white solid, m.p. 72-76 °C; IR ($CDCl_3$ cast film) 3056, 2930, 2856, 1608, 1578, 1492, 1464, 1252 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.14 (m, 2H), 6.92-6.87 (m, 2H), 6.72 (d, *J* = 2.6 Hz, 1H), 6.66 (d, *J* = 8.6 Hz, 1H), 6.61 (dd, *J* = 2.7 Hz, 1H), 4.34 (d, *J* = 10.6 Hz, 1H), 3.81 (s, 3H), 3.79-3.68 (m, 5H), 3.24 (ddd, *J* = 13.8, 10.8, 7.0 Hz, 1H), 2.81-2.67 (m, 2H), 2.25 (dd, *J* = 14.1, 1.7 Hz, 1H), 1.95 (dd, *J* = 2.4, 9.0 Hz, 1H), 1.57 (d, *J* = 8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 158.2, 138.3, 137.7, 137.2, 129.6, 129.5, 114.9, 114.2, 112.2, 68.1, 66.6, 64.8, 55.6, 55.4, 43.6, 42.0, 34.1, 29.2; HRMS (APPI, $[M+H]^+$) for $C_{21}H_{23}Cl_2O_3$ calculated 393.1019, found, m/z 393.1029.

39d′: colourless resin; IR ($CDCl_3$ cast film) 3000, 2953, 2835, 1610, 1512, 1464, 1083 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.18 (m, 2H), 6.90-6.86 (m, 2H),

6.68 (d, *J* = 8.5 Hz, 1H), 6.66 (d, *J* = 2.6 Hz, 1H), 6.61 (dd, *J* = 8.5, 2.7 Hz, 1H), 4.79 (dd, *J* = 12.6, 4.4 Hz, 1H), 4.11-4.16 (m, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.64-3.54 (m, 1H), 3.40 (app t, *J* = 11.9 Hz, 1H), 3.00 (ddd, *J* = 13.3, 4.5, 2.1 Hz, 1H), 2.58 (d, *J* = 15.5 Hz, 1H), 1.76 (app t, *J* = 12.9 Hz, 1H), 1.36 (dd, *J* = 9.7, 1.9 Hz, 1H), 0.39 (d, *J* = 9.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 158.2, 139.8, 136.7, 135.9, 129.4, 128.9, 115.1, 113.9, 112.5, 68.6, 66.0, 64.0, 55.5, 55.4, 42.9, 40.6, 37.4, 30.4; HRMS (APPI, $[M+H]^+$) for $C_{21}H_{23}Cl_2O_3$ calculated 393.1019, found, m/z 393.1022.

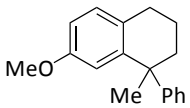


5-methoxy-1-methyl-1-phenyl-1,2,3,4-tetrahydronaphthalene, (56a). Subjection of **45a** (50.0 mg, 0.198 mmol) to Friedel-Crafts conditions B (20 min.) followed by purification by flash column chromatography (15 % dichloromethane in hexanes) yielded the product as a colorless gum, 49.3 mg, 98 %. Subjection of **45a** (50.0 mg, 0.198 mmol) to conditions A (20 h), 38.8 mg, 77 % of **56a** was produced: IR (neat) 3058, 2935, 2835, 1581, 1494, 1459, 1247, 1050, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.20 (m, 2H), 7.17- 7.10 (m, 3H), 7.08 (app t, *J* = 8.2 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 3.86 (s, 3H), 2.73 (t, *J* = 6.6 Hz, 2H), 2.03 (ddd, *J* = 13.1, 8.3, 3.1 Hz, 1H), 1.86 (ddd, *J* = 13.1, 9.4, 2.8 Hz, 1H), 1.81-1.72 (m, 4H), 1.68-1.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 151.7, 145.8, 128.0, 127.7, 126.6, 126.0, 125.6, 121.6, 106.9, 55.5, 43.1, 41.3, 30.2, 23.9, 19.0; HRMS (EI, M^+) for $C_{18}H_{20}O$ calculated 252.1514, found m/z 252.1515.

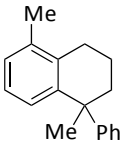


6-methoxy-1-methyl-1-phenyl-1,2,3,4-tetrahydronaphthalene, (56b). Compound **45b** (42.8 mg, 0.170 mmol) was subjected to Friedel-Crafts conditions A (20 h). The crude product was judged to be ≥98% pure by NMR analysis, and

was not subjected to any subsequent purification procedures, 42.8 mg colorless oil, >99 %: IR (neat) 3056, 2933, 2869, 1608, 1500, 1464, 1257, 1029, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.21 (m, 2H), 7.17-7.10 (m, 3H), 6.92 (d, *J* = 8.6 Hz, 1H), 6.71-6.64 (m, 2H), 3.80 (s, 3H), 2.82 (app t, *J* = 6.5 Hz, 2H), 2.04 (ddd, *J* = 13.2, 9.3, 2.9 Hz, 1H), 1.87 (ddd, *J* = 13.2, 9.3, 2.9 Hz, 1H), 1.81-1.72 (m, 1H), 1.71 (s, 3H), 1.70-1.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 152.0, 138.6, 136.8, 130.4, 128.0, 127.6, 125.6, 113.3, 112.6, 55.4, 42.6, 41.8, 30.8, 30.3, 19.8; HRMS (EI, M^+) for $C_{18}H_{20}O$ calcd, 252.1514, found: m/z 252.1512; Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.86, 8.34.

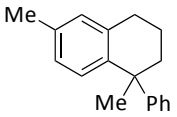


7-methoxy-1-methyl-1-phenyl-1,2,3,4-tetrahydronaphthene, (56c). Compound **45c** (50.0 mg, 0.198 mmol) was subjected to Friedel-Crafts conditions A (48 h). The crude product was judged to be ≥98% pure by NMR analysis, and was not subjected to any subsequent purification procedures, 50.0 mg colorless oil, > 99 %: IR (neat) 3056, 2933, 2834, 1610, 1494, 1443, 1238, 1047, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.23 (m, 2H), 7.21-7.12 (m, 3H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.76 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.57 (d, *J* = 2.7 Hz, 1H), 3.72 (s, 3H), 2.80 (app t, *J* = 6.5 Hz, 2H), 2.06 (ddd, *J* = 13.3, 8.2, 3.1 Hz, 1H), 1.89 (ddd, *J* = 13.3, 9.3, 3.0 Hz, 1H), 1.82 (m, 4H), 1.71-1.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 151.6, 145.7, 130.0, 129.6, 128.0, 127.6, 125.7, 114.3, 112.2, 55.4, 43.4, 41.7, 30.3, 29.6, 19.9; HRMS (EI, M^+) for $C_{18}H_{20}O$ calculated, 252.1514, found, m/z 252.1517; Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.42; H, 8.08.

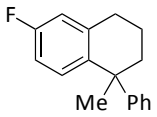


1,5-dimethyl-1-phenyl-1,2,3,4-tetrahydronaphthalene, (56d). Compound **45d** (50 mg, 0.21 mmol) was subjected to Friedel-Crafts conditions A (40 h).

Purification by flash column chromatography (5 % dichloromethane in hexanes) gave the product as a colourless oil, 45.4 mg, 84 %: IR (neat) 3058, 2933, 2867, 1493, 1472, 1444, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26-7.22 (m, 2H), 7.17-7.11 (m, 3H), 7.05-7.00 (m, 2H), 6.91-6.87 (m, 1H), 2.72-2.68 (m, 2H), 2.29 (s, 3H), 2.05 (ddd, *J* = 13.1, 8.3, 3.0 Hz, 1H), 1.87 (ddd, *J* = 13.2, 9.6, 2.8 Hz, 1H), 1.81-1.77 (m, 1H), 1.74 (s, 3H), 1.72-1.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 144.5, 136.4, 135.9, 128.0, 127.7, 127.5, 127.3, 125.6, 125.5, 43.3, 41.2, 30.5, 27.6, 20.3, 19.5; HRMS (EI, M^+) for $C_{18}H_{20}$ calcd, 236.1565, found: m/z 236.1567; Anal. Calcd for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.50; H, 8.55.

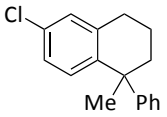


1,6-dimethyl-1-phenyl-1,2,3,4-tetrahydronaphthalene, (56e). Compound **45e** (50.0 mg, 0.21 mmol) was subjected to Friedel-Crafts conditions A (48 h). The crude product was judged to be ≥98% pure by NMR analysis, and was not subjected to any subsequent purification procedures, 48.7 mg colorless oil, 97 %: IR (neat) 3055, 2932, 2868, 1494, 1444, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.21 (m, 2H), 7.18-7.11 (m, 3H), 6.96 (s, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 2.83 (app t, *J* = 6.4 Hz, 2H), 2.32 (s, 3H), 2.05 (ddd, *J* = 13.3, 8.4, 3.1 Hz, 1H), 1.88 (ddd, *J* = 13.3, 9.1, 3.0 Hz, 1H), 1.82-1.73 (m, 1H), 1.72 (s, 3H), 1.71-1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 141.6, 137.1, 135.3, 129.7, 129.3, 128.0, 127.6, 127.0, 125.6, 42.8, 21.8, 30.5, 30.3, 21.2, 19.8; HRMS (EI, M^+) for $C_{18}H_{20}$ calculated, 236.1565, found m/z 236.1567; Anal. Calcd for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.32; H, 8.62.

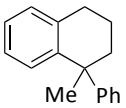


6-fluoro-1-methyl-1-phenyl-1,2,3,4-tetrahydronaphthalene, (56f). Compound **45f** (25.0 mg, 0.104 mmol) was subjected to Friedel-Crafts conditions B (20

min.). The crude product was judged to be ≥98% pure by NMR analysis, and was not subjected to any subsequent purification procedures, 24.9 mg, 99 %: IR (neat) 2934, 1586, 1493, 1236, 757, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.22 (m, 2H), 7.20-7.14 (m, 1H), 7.14-7.08 (m, 2H), 6.95 (dd, *J* = 8.5, 6.0 Hz, 1H), 6.85-6.76 (m, 2H), 2.83 (t, *J* = 6.4 Hz, 2H), 2.06 (ddd, *J* = 13.3, 8.4, 3.1 Hz, 1H), 1.88 (ddd, *J* = 13.3, 9.2, 3.0 Hz, 1H), 1.83-1.61 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.0 (d, *J* = 244.1 Hz), 151.5, 140.3 (d, *J* = 3.0 Hz), 139.4 (d, *J* = 7.0 Hz), 131.0 (d, *J* = 8.0 Hz), 128.1, 127.6, 125.8, 115.0 (d, *J* = 19.9 Hz), 113.3 (d, *J* = 21.0 Hz), 42.8, 41.6, 30.6, 30.3, 19.6; HRMS (EI, M^+) for $C_{17}H_{17}F$ calcd 240.1314, found m/z 240.1316.

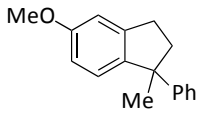


6-chloro-1-methyl-1-phenyl-1,2,3,4-tetrahydronaphthalene, (56g). Compound **45g** (22.5 mg, 0.0876 mmol) was subjected to Friedel-Crafts conditions B; substrate concentration was 0.1 M, 1 h. The crude product was judged to be ≥98% pure by NMR analysis, and was not subjected to any subsequent purification procedures, colorless oil, 20.3 mg, 90 %: IR (neat) 2933, 1595, 1481, 1444, 1029, 756, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.22 (m, 2H), 7.20-7.14 (m, 1H), 7.14-7.08 (m, 3H), 7.06 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 2.83 (t, *J* = 6.4 Hz, 2H), 2.05 (ddd, *J* = 13.4, 8.5, 3.2 Hz, 1H), 1.87 (ddd, *J* = 13.4, 9.1, 3.0 Hz, 1H), 1.83-1.61 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 143.2, 139.2, 131.5, 130.9, 128.8, 128.1, 127.5, 126.3, 125.9, 42.9, 41.5, 30.4, 30.2, 19.6; HRMS (EI, M^+) for $C_{17}H_{17}Cl$ calcd 258.0989, found m/z 258.0993.

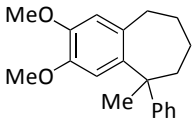


1-methyl-1-phenyl-1,2,3,4-tetrahydronaphthalene, (56h). Compound **45h** (50.2 mg, 0.226 mmol) was subjected to Friedel-Crafts conditions B (15 min.).

The crude product was judged to be ≥98% pure by NMR analysis, and was not subjected to any subsequent purification procedures, 49.6 mg, 98 %: IR (neat) 3020, 2930, 1490, 1443, 1029, 752, 698 cm^{-1}; HRMS (EI, M^+) for $C_{17}H_{18}$ calcd 222.1408, found m/z 222.1408; ^1H NMR and ^{13}C NMR data are in agreement with those previously reported.[44]

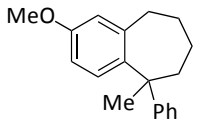


5-methoxy-1-methyl-1-phenylindane, (56i). Compound **45i** (50.0 mg, 0.210 mmol) was subjected to Friedel-Crafts conditions A (48 h). Purification by flash column chromatography (40 % dichloromethane in hexanes) provided the product as a colorless oil, 38.2 mg, 76 %: IR (neat) 3057, 2959, 2867, 1606, 1491, 1251, 1029, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.24 (m, 2H), 7.24-7.15 (m, 3H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.85 (s, 1H), 6.78 (dd, *J* = 8.4, 2.3 Hz, 1H), 3.84 (s, 3H), 2.92-2.84 (m, 2H), 2.42 (ddd, *J* = 12.6, 7.3, 5.4 Hz, 1H), 2.23 (ddd, *J* = 12.5, 7.8, 7.8 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 149.6, 145.5, 143.3, 128.2, 126.8, 125.9, 125.0, 112.7, 110.0, 55.6, 51.6, 44.8, 30.8, 28.0; HRMS (EI, M+) for $C_{17}H_{18}O$ calculated 238.1358, found m/z 238.1354; Anal. Calcd for $C_{17}H_{18}O$: C, 85.68; H, 7.61. Found: C, 85.62; H, 7.62.

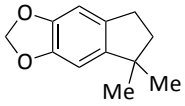


7,8-dimethoxy-1-methyl-1-phenylbenzocycloheptene, (56j). Compound **45j** (30.0 mg, 0.112 mmol) was subjected to Friedel-Crafts conditions A (20 h). Purification by flash column chromatography provided **56j** as a white solid, 9.3 mg, 30 %: m.p. 106-110 °C; IR ($CDCl_3$ cast film) 3056, 2930, 2853, 1605, 1578, 1516, 1445, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.21 (m, 2H), 7.15 (app t, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 7.7 Hz, 1H), 7.05-7.01 (m, 2H), 6.99 (s, 1H), 6.65 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 2.51-2.28 (m, 3H), 1.96-1.77 (m, 3H), 1.76-1.66 (m, 1H), 1.63 (s, 3H), 1.42-1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

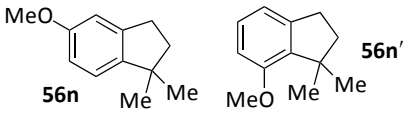
148.9, 146.8, 146.3, 138.9, 136.6, 128.4, 127.2, 125.5, 114.7, 112.6, 56.4, 56.0, 47.5, 40.4, 36.4, 36.0, 27.9, 26.9; HRMS (EI, M^+) for $C_{20}H_{24}O_2$ calcd, 296.1776, found: m/z 296.1781.



7-methoxy-1-methyl-1-phenylbenzocycloheptene, (56o). Compound **45o** (47.2 mg, 0.177 mmol) was subjected to Friedel-Crafts conditions A (20 h). Purification by pTLC (5% ether in hexanes) gave the product as a colorless oil, 24.1 mg, 51 %: IR (cast film, dichloromethane) 3057, 2930, 2856, 1606, 1578, 1492, 1445, 1252, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.7 Hz, 1H), 7.28-7.20 (m, 2H), 7.19-7.11 (m, 1H), 7.05-6.99 (m, 2H), 6.75 (dd, *J* = 8.7, 2.8, 1H), 6.68 (d, *J* = 2.8 Hz, 1H), 3.83 (s, 3H), 2.52-2.43 (m, 1H), 2.43-2.29 (m, 2H), 2.00-1.86 (m, 1H), 1.86-1.68 (m, 3H), 1.61 (s, 3H), 1.40-1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 149.1, 145.6, 139.0, 128.7, 128.4, 127.2, 125.5, 117.1, 110.0, 55.4, 47.2, 40.5, 37.0, 36.2, 27.8, 27.0; (EI, M^+) for $C_{19}H_{22}O$ calcd, 266.1670, found: m/z 266.1674.



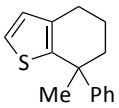
1,1-dimethyl-5,6-methylenedioxyindane, (56m). Compound **45m** (40.0 mg, 0.210 mmol) was subjected to Friedel-Crafts conditions B (5 min.). Purification by flash column chromatography provided **56m** as a colourless oil, 33.4 mg, 83 %: IR (neat) 2953, 2862, 1475, 1301, 1244, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.65 (s, 1H), 6.61 (s, 1H), 5.90 (s, 2H), 2.79 (t, *J* = 7.2 Hz, 2H), 1.92 (t, *J* = 7.2 Hz, 2H), 1.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 146.5, 145.9, 135.4, 105.3, 103.1, 101.0, 44.0, 42.1, 30.2, 28.9; (EI, M^+) for $C_{12}H_{14}O_2$ calcd, 190.0994, found: m/z 190.0995; Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.55; H, 7.53.



5-methoxy-1,1-dimethylindane, (56n), and **7-methoxy-1,1-dimethylindane, (56n′).** Compound **45n** (30.0 mg, 0.170 mmol) was subjected to Friedel-Crafts conditions B (20 min.). The crude product was judged to be ≥98% pure by NMR analysis, and was not subjected to any subsequent purification procedures, 27.1 mg colorless oil, 90 %, 2.8 : 1 mixture of **56n** to **56n′**. The data given are for the mixture: IR (neat) 2950, 2862, 1606, 1587, 1492, 1456, 1249, 1142, 1047, 745 cm^{-1}; HRMS (EI, M^+) for $C_{12}H_{16}O$ calculated 176.1201, found m/z 176.1198.

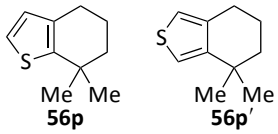
56n: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.1 Hz, 1H), 6.76-6.71 (m, 2H), 3.78 (s, 3H), 2.86 (t, *J* = 7.2 Hz, 2H, overlap with **56n′**), 1.92 (t, *J* = 7.2 Hz, 2H, partial overlap with **56n′**), 1.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 145.1, 144.5, 122.7, 112.4, 110.1, 55.6, 43.5, 42.0, 30.4, 29.1.

56n′ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (app t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 8.1 Hz, 1H), 3.82 (s, 3H), 2.86 (m, 2H, overlap with **56n**), 1.91 (t, *J* = 7.4 Hz, 2H, partial overlap with **56n**), 1.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 145.3, 138.7, 128.0, 117.3, 108.9, 55.3, 45.2, 42.2, 30.8, 27.4.



6-methyl-6-phenyl-3,4,5,6-tetrahydrobenzo[*b*]thiophene, (56q). Compound **45q** (30.0 mg, 0.131 mmol) was subjected to Friedel-Crafts conditions B (20 min.). The crude product was judged to be ≥98% pure by NMR analysis, and was not subjected to any subsequent purification procedures, 28.9 mg colorless oil, 96 %: IR (neat) 2931, 1494, 1442, 1024, 698 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.30-7.24 (m, 2H), 7.20-7.15 (m, 4H), 6.82 (d, *J* = 5.1 Hz, 1H), 2.73 (ddd, *J* = 16.4, 6.1, 3.9 Hz, 1H), 2.65 (ddd, *J* = 16.4, 9.7, 5.9 Hz, 1H), 2.12 (ddd, *J* = 13.0, 6.1, 2.8 Hz, 1H), 1.91 (ddd, *J* = 13.0, 11.7, 2.7 Hz, 1H), 1.78-1.67 (m, 4H), 1.62-

1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 144.3, 136.6, 128.0, 127.5, 127.2, 126.1, 123.2, 24.3, 41.7, 31.5, 26.0, 13.6; HRMS (EI, M^+) for $C_{15}H_{16}S$ calcd 228.0973, found m/z 228.0974.

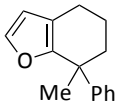


56p **56p′**

7,7-dimethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene, (56p), 4,4-dimethyl-4,5,6,7-tetrahydrobenzo[*c*]thiophene, (56p′). Compound **45p** (30.0 mg, 0.180 mmol) was subjected to Friedel-Crafts conditions B (20 min.). The crude product was judged to be ≥98% pure by NMR analysis, and was not subjected to any subsequent purification procedures, 28.3 mg colourless oil, 79 %, as an inseparable 10:1 mixture of **56p** to **56p′**. The data given are for the mixture: IR (neat) 2958, 2931, 2864, 1455, 1362, 1195, 707 cm^{-1}; HRMS (EI, M^+) for $C_{10}H_{14}S$ calculated 166.0816, found m/z 166.0816.

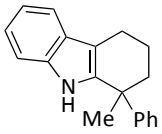
56p: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 5.1 Hz, 1H), 6.71 (d, *J* = 5.1 Hz, 1H), 2.61 (t, *J* = 6.3 Hz, 2H), 1.88-1.80 (m, 2H), 1.72-1.66 (m, 2H), 1.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 134.5, 127.6, 121.7, 39.4, 34.2, 32.8, 26.2, 20.3.[35]

56p′: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 3.1 Hz, 1H), 6.84-6.82 (m, 1H), 2.71 (t, *J* = 6.5 Hz, 2H), 1.62-1.58 (m, 2H), 1.80-1.75 (m, 2H), 1.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.8, 118.7, 39.2, 33.9, 32.2, 26.7, 20.4 [two carbons of the thiophene were not seen in the ^{13}C NMR spectrum].[35]

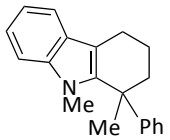


6-methyl-6-phenyl-3,4,5,6-tetrahydrobenzofuran, (56k). Compound **45k** (49.9 mg, 0.235 mmol) was subjected to Friedel-Crafts conditions B (2.5 min.). Purification by flash column chromatography (7 % dichloromethane in hexanes) provided **56k** as a colorless oil, 39.0 mg, 78 %: IR (neat) 3059, 2968, 2933, 2850, 1600, 1503, 1495, 1454, 1445, 1152, 891 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ

7.37 (d, *J* = 1.9 Hz, 1H), 7.32-7.28 (m, 2H), 7.22-7.19 (m, 1H), 7.12-7.09 (m, 2H), 6.30 (d, *J* = 1.9 Hz, 1H), 2.53-2.50 (m, 2H), 2.15 (ddd, *J* = 13.3, 6.2, 2.7 Hz, 1H), 1.92-1.86 (m, 1H), 1.76-1.70 (m, 1H), 1.69 (s, 3H), 1.59-1.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 148.5, 141.1, 128.2, 126.8, 126.1, 118.0, 110.4, 41.3, 41.2, 27.2, 22.8, 20.3; HRMS (EI, M^+) for $C_{15}H_{16}O$ calcd 212.1201, found m/z 212.1197; Anal. Calcd for $C_{15}H_{16}O$: C, 84.46; H, 7.62. Found: C, 84.46; H, 7.60.

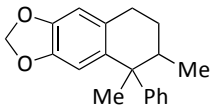


4-methyl-4-phenyl-1,2,3,4-tetrahydrocarbazole, (56r). Compound **45r** (50.0 mg, 0.191 mmol) was subjected to Friedel-Crafts conditions B (20 min.). The crude product was judged to be ≥98% pure by NMR analysis, and was not subjected to any subsequent purification procedures, 46.9 mg off-white powder, 93 %: m.p. 170-172 °C; IR (thin film, dichloromethane) 3402, 3052, 2933, 1582, 1489, 1460, 1322, 738, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.35-7.07 (m, 8H), 6.96-6.90 (m, 1H), 2.80 (t, *J* = 6.3 Hz, 2H), 2.10 (ddd, *J* = 13.2, 8.2, 2.7 Hz, 1H), 2.00-1.84 (m, 5H), 1.80-1.69 (m, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 136.2, 134.8, 128.1, 127.2, 127.1, 125.7, 121.0, 120.7, 119.2, 116.9, 110.6, 42.9, 40.2, 28.3, 23.9, 20.0; HRMS (EI, M^+) for $C_{19}H_{19}N$ calcd 261.1518, found m/z 261.1516.



4,9-dimethyl-4-phenyl-1,2,3,4-tetrahydrocarbazole, (56s). Compound **45s** (30.2 mg, 0.110 mmol) was subjected to Friedel-Crafts conditions B (20 min.). The crude product was judged to be ≥98% pure by NMR analysis, and was not subjected to any subsequent purification procedures, 29.8 mg pale yellow solid, 98 %: m.p. 111-115 °C; IR (thin film, dichloromethane) 3056, 2931, 1469, 1412, 1372, 737, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.20 (m, 5H), 7.18-7.10

(m, 3H), 6.91 (app t, *J* = 7.6 Hz, 1H), 3.69 (s, 3H), 2.79-2.75 (m, 2H), 2.12-2.05 (m, 1H), 1.96-1.87 (m, 2H), 1.84 (s, 3H), 1.78-1.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 137.4, 136.4, 128.0, 127.3, 126.5, 125.6, 120.6, 120.5, 118.7, 116.0, 108.7, 42.7, 40.4, 29.4, 28.6, 22.7, 19.9; HRMS (EI, M^+) for $C_{20}H_{21}N$ calcd 127.1674, found m/z 275.1676.



1,2-dimethyl-6,7-methylenedioxy-1-phenyl-1,2,3,4-tetraydronaphthalene (56l). Subjection of **45l** (49.7 mg, 0.178 mmol) to Friedel-Crafts conditions D (15 min.) followed by purification by flash column chromatography (2 % ethyl acetate in hexanes) yielded the product as a colorless gum, 45.1 mg, 74 % as a 2.8 : 1 mixture of inseparable diastereomers. The relative configuration of the isomers was unable to be assigned by NMR spectroscopic techniques. Data given is for the mixture: IR (neat) 2953, 2912, 1600, 1501, 1481, 1227, 1038 cm^{-1}; HRMS (EI, M^+) for $C_{19}H_{20}O_2$ calculated 280.1463, found m/z 280.1466.

major isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.20 (m, 4H), 7.18-7.14 (m, 1H), 6.54 (s, 1H), 6.19 (s, 1H), 5.84 (d, *J* = 1.5 Hz, 1H), 5.83 (d, *J* = 1.5 Hz, 1H), 2.78-2.73 (m, 1H), 2.45 (dd, *J* = 16.0, 11.7 Hz, 1H), 2.13-2.03 (m, 1H), 1.79 (dt, *J* = 13.4, 2.4 Hz, 1H), 1.66 (s, 3H), 1.02 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 145.9, 145.7, 138.5, 130.0, 128.2, 127.5, 125.8, 109.5, 108.2, 100.8, 51.4, 44.8, 39.8, 29.8, 26.8, 22.4.

minor isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.20 (m, 2H), 7.16-7.14 (m, 1H), 7.04-7.02 (m, 2H), 6.63 (s, 1H), 6.59 (s, 1H), 5.93 (d, *J* = 1.5 Hz, 1H), 5.89 (d, *J* = 1.5 Hz, 1H), 2.75-2.70 (m, 1H), 2.42 (dd, *J* = 16.1, 11.0 Hz, 1H), 2.13-2.03 (m, 1H), 1.93 (d, *J* = 12.1 Hz, 1H), 1.69 (s, 3H), 0.88 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 146.2, 146.0, 136.1, 131.0, 127.9, 127.6, 125.6, 108.4, 108.3, 100.9, 50.0, 43.8, 39.5, 31.4, 25.1, 22.3.

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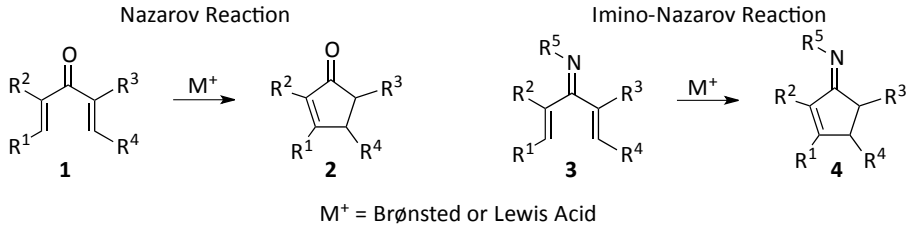
Chapter 4

Imino-Nazarov Reaction of Aminocyclopropanes

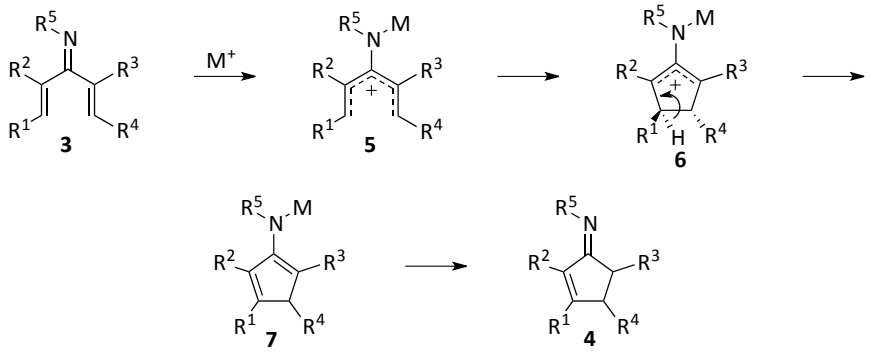
4.1 Imino-Nazarov Cyclization

The term "Nazarov" reaction traditionally refers to the activation of a divinyl ketone to generate cyclopentenones (Scheme 4.1). This reaction has received a lot of attention in the literature; substituent effects, a range of promoters, catalytic and asymmetric variants, and interrupted Nazarov reactions have all been studied (Chapter 1). In stark contrast, there is very little knowledge about its nitrogen analogue, the imino-Nazarov reaction.



Scheme 4.1. Imino-Nazarov Reaction.

The imino-Nazarov reaction should proceed similarly to the Nazarov reaction, where activation of a divinylimine precursor leads to 3-aminopentadienyl cation **5** (Scheme 4.2). Conrotatory 4π-electrocyclization gives 2-aminocyclopentenyl cation **6**, and elimination followed by tautomerization gives cyclopentenimine **4**.



Scheme 4.2. Mechanism of the Imino-Nazarov Reaction.

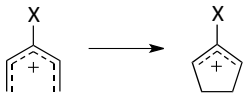
In practice, replacement of oxygen by nitrogen has significant consequences. Few synthetic routes are available in the literature for synthesis of the required divinylimine precursors; routes including non-hydrogen R^2 and R^3 substituents are especially scarce.[1] These methods are typically used to generate *N*-tosylimines. Moreover, the electronic properties of the pentadienyl cation C-3 substituent have a large impact on whether or not the cyclization will be energetically favourable.

4.1.1 Effect of C-3 Substitution of the Pentadienyl Cation

Calculations on the pentadienyl cation indicate that the cyclization to the cyclopentenyl cation is exothermic by 19.9 kcalmol^{-1} (Table 4.1).[2] The Nazarov cyclization (Chapter 1), in which C-3 is oxygen-substituted, is somewhat less

exothermic due to resonance stabilization of the open form of the cation. The oxygen imparts no exceptional stabilization to the cyclopentenyl cation, so the overall effect is to lower the energy of the starting material with no corresponding effect on the product. This results in a higher activation energy, and a more product-like transition state.

The popularity of the Nazarov reaction compared to the cyclization of non-oxygenated pentadienyl cations stems not from relative ease of the cyclization step itself, but more facile generation of the pentadienyl cation. Additionally, the synthetic handles that result are convenient for further manipulation. The reaction is exothermic overall; the exchange of a π-bond for a σ-bond in the cyclization step more than compensates for the effect of the oxygen.



X	energy of cyclization ($kcalmol^{-1}$)[a]
H	-19.9
OH	-3.2
NH_2	7.0

[a] Values are taken from reference 2.

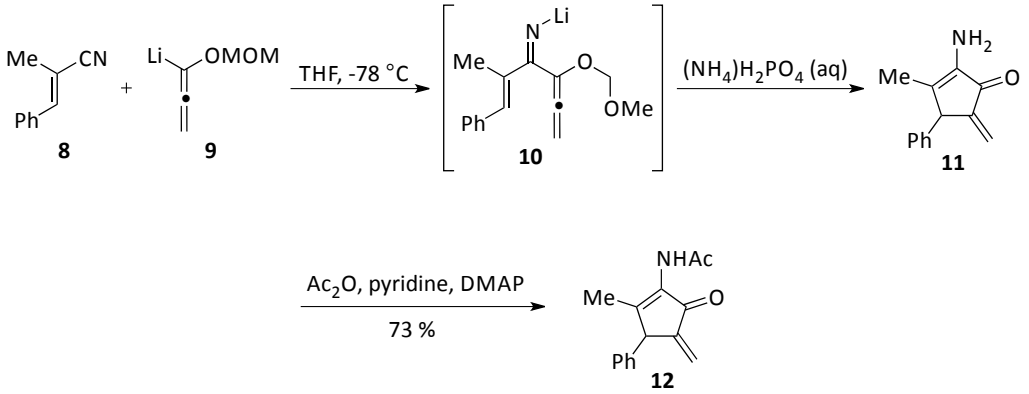
Table 4.1. Energy of Cyclization for Pentadienyl Cations.

Nitrogen is less electronegative than oxygen (Pauling electronegativities of 3.04 and 3.44 respectively), and therefore is better able to stabilize cations through resonance donation. When the pentadienyl cation is substituted with nitrogen at C-3, a correspondingly larger effect is seen than that in the traditional Nazarov cyclization. For the parent system, with all hydrogen substitution except for the amino group, the 3-aminopentadienyl cation is sufficiently stabilized such that the cyclization is endothermic; consequentially the activation barrier is

higher, and the transition state is later. It must be emphasized here that the calculations have been done for the *parent* system. The substitution pattern of the reacting species can be adjusted to stabilize the cyclopentenyl cation and compensate for the detrimental effect of the C-3 nitrogen.

4.1.2 Imino-Nazarov Reactions

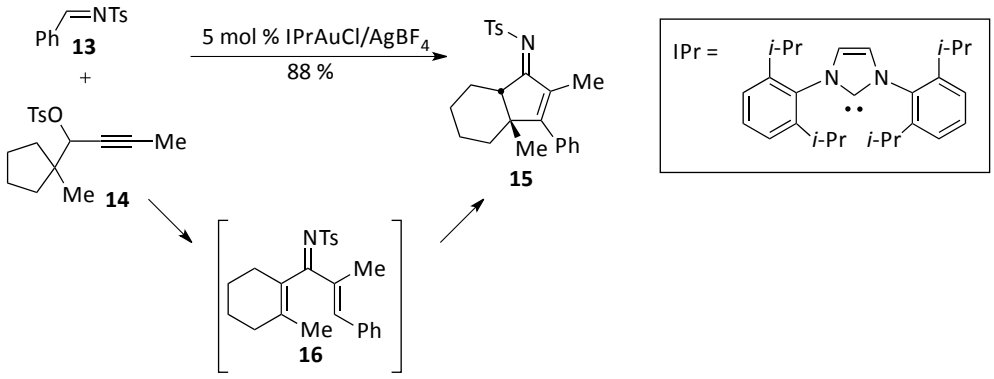
There are only three reports of imino-Nazarov cyclizations. Tius demonstrated the first example of an imino-Nazarov cyclization in 2001.[3] Cyclization of an *in situ* generated allenyl-vinyl imine was driven to the cyclic product by relief of allenic strain, as well as irreversible loss of a MOM protecting group (Scheme 4.3). The product was converted to acetamide **12** to facilitate purification and storage. Non-hydrogen substitution on nitrogen is not available by this method.



Scheme 4.3. Imino-Nazarov Reaction of Allenylvinylimines.

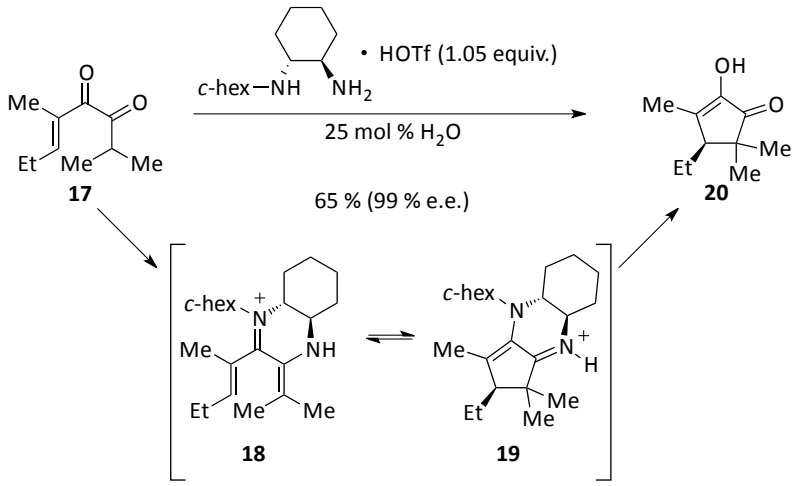
In 2009, González reported a process to convert propargyl tosylates and tosylimines to cyclopentenimines, which they proposed to occur *via* a gold(I)-catalyzed imino-Nazarov cyclization of divinylimine intermediate **16**.[4] This work

was limited to deactivated tosyl imines, which reduces the ability of nitrogen to inhibit the cyclization.



Scheme 4.4. Imino-Nazarov Cyclization of Proposed Intermediate **16**.

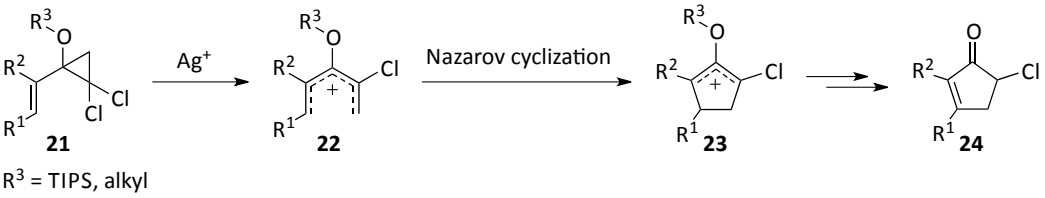
The most recent example of an imino-Nazarov is from the Tius group, where an enantio-enriched diamine reacts with an α-ketoenone to produce divinyl iminium **18** (Scheme 4.5). Intermediate **18** undergoes cyclization to ultimately provide enantio-enriched cyclopentenones.[5] This reaction is enabled by stabilization of the cyclic allyl cation by the second nitrogen. Thus, choice of appropriate flanking substituents for the allyl cation can compensate for the endergonic contribution of the nitrogen atom at C-3 to the cyclization process.



Scheme 4.5. Imino-Nazarov Cyclization to Access Enantioenriched Cyclopentenones.

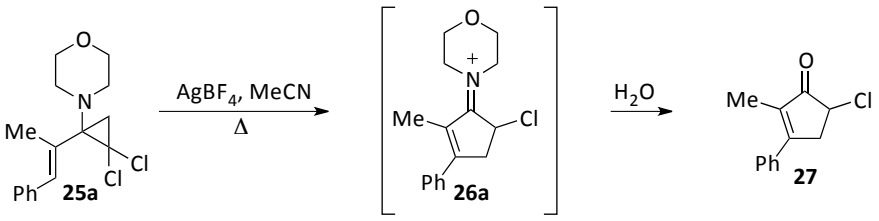
4.2 Imino-Nazarov Reaction of 2-Amino-1,1-dichloro-2-vinylcyclopropanes

Development of non-traditional substrates for the Nazarov cyclization[6] is an area of interest in the West group. Grant and West have reported the use of 1,1-dichloro-2-siloxy-2-vinylcyclopropanes as precursors to pentadienyl cations **22** which undergo the Nazarov cyclization (Scheme 4.6), as well as an interrupted variant of the process.[6c,e] The scope of this reaction has been expanded to include 2-alkoxy-1,1-dichloro-2-vinylcyclopropanes (Chapter 2).



Scheme 4.6. Electrocyclic Cyclopropane-Opening/Nazarov Cyclization Sequence.

We were interested to apply this method to the imino-Nazarov cyclization, in particular to include substrates in which the nitrogen atom is substituted with electron-donating groups, and also to retain the nitrogen in the products. These two criteria have not been met simultaneously prior to this work. In the West group, it was shown that morpholinocyclopropane **25a** could be converted to 5-chloro-2-cyclopentenone (**27**) by exposure to silver fluoroborate in acetonitrile at reflux (Scheme 4.7).[7] This presumably occurs *via* an imino-Nazarov cyclization in analogy to the reactions of the oxygenated cyclopropanes in Chapter 2 to form iminium **26a**, and subsequent hydrolysis to cyclopentenone **27**.

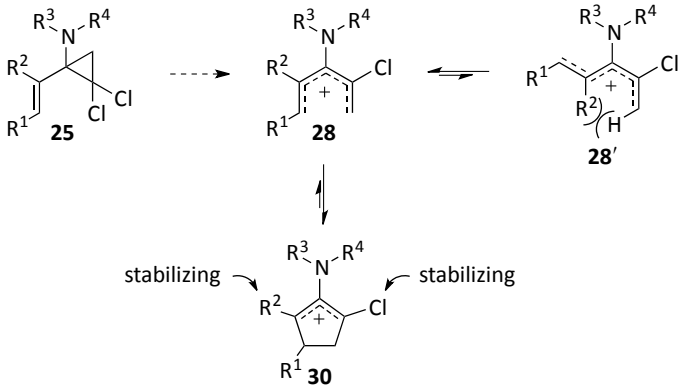


Scheme 4.7. Nazarov Cyclization of Aminocyclopropane **25a**.

4.2.1 Synthesis of 2-Amino-1,1-dichloro-2-vinylcyclopropanes

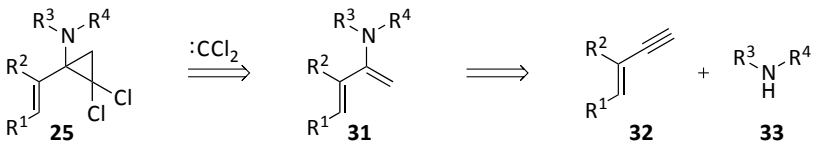
Being aware of the potential difficulties in effecting cyclization of a divinyliminium ion, substrates were designed such that cyclopentenyl cation **30**

could obtain extra stabilization from substituents at both termini. A chlorine and alkyl group at either end of the allyl cation is expected to impart sufficient stabilization[8] to overcome the innately unfavourable cyclization in the parent system (Scheme 4.8). Additionally, non-hydrogen substituents at this position help to enforce the "U" conformer of the pentadienyl cation (**28**), which is the necessary geometry for cyclization. The R^1, R^3 and R^4 substituents were varied to examine the effect of different types of substitution at those positions.



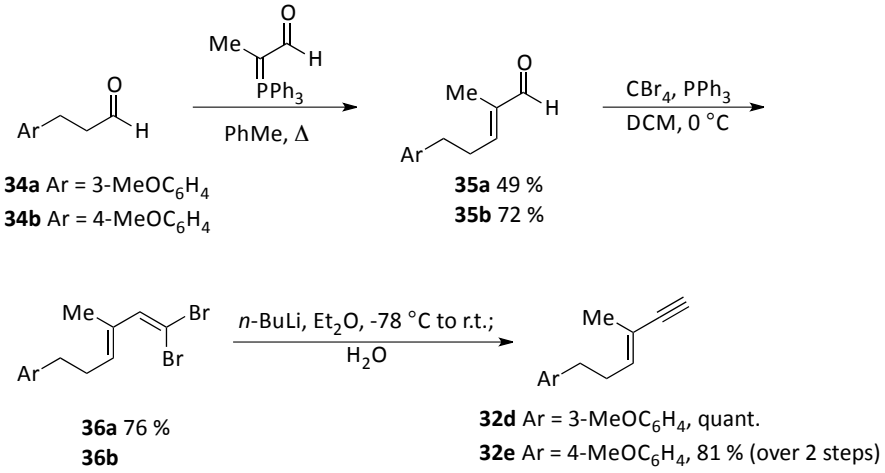
Scheme 4.8. Factors Influencing Substrate Design.

In analogy to the 1-alkoxy-2,2-dichloro-1-vinylcyclopropanes, the amino congeners could arise from regioselective cyclopropanation with dichlorocarbene at the more electron-rich alkene of aminodiene **31** (Scheme 4.9). 2-Amino-1,3-dienes are rare in the literature, and there are few methods for their preparation. Two methods were reported by the Barluenga group: one involving a Buchwald-type coupling of 2-chloro-1,3-dienes,[9] and one involving aminomercuration of enynes.[10] Both routes were attempted; however, the aminomercuration route was ultimately more productive.



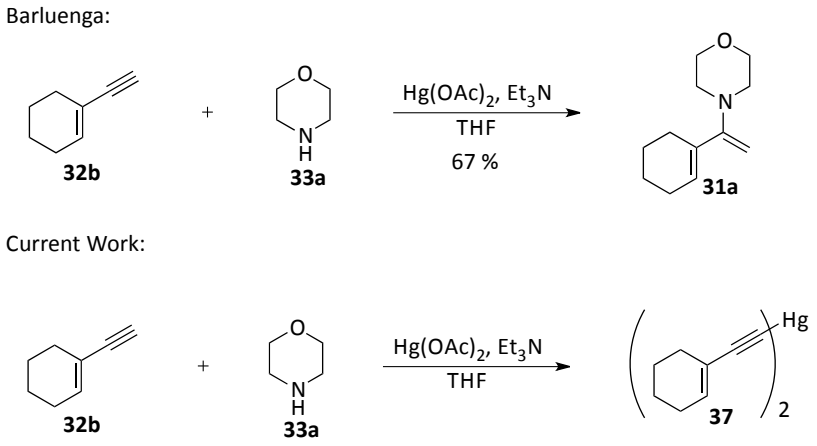
Scheme 4.9. Synthetic Plan for Substrate Preparation.

Two of the requisite enynes were commercially available (1-ethynylcyclohexene (**32b**) and 3-methyl-3-buten-1-yne (**32c**)), 3-methyl-3-phenyl-3-buten-1-yne (**32a**) was prepared as previously disclosed,[7] and the remaining compounds were prepared from the corresponding unsaturated aldehydes. Compounds **35a** and **35b** were synthesized from isomeric propanals in moderate yield by reaction with 2-(triphenylphosphoranylidene)propanal (Scheme 4.10). Enals **35a** and **35b** were treated with carbon tetrabromide and triphenylphosphine to generate dibromoolefins **36a** and **36b.** Compounds **36** were subjected to *n*-butyllithium followed by water to give the required enynes **32d** and **32e** in good yield for the combined two steps.



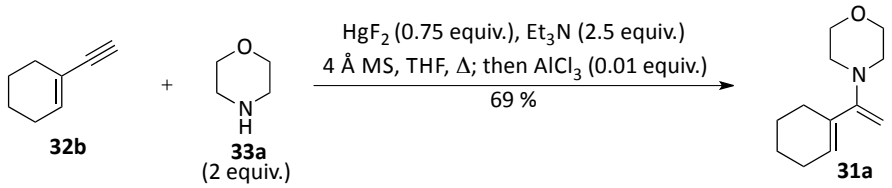
Scheme 4.10. Preparation of Enynes **32d** and **32e**.

Barluenga and coworkers reported that enynes and secondary amines are converted to 2-amino-1,3-butadienes in the presence of mercury(II) acetate and triethylamine in tetrahydrofuran at room temperature.[10] This did not work in our hands; a compound which is likely bisalkynylmercurial **37** was formed instead and did not react further (Scheme 4.11).[11] Barluenga and coworkers have implicated an alkynylmercury halide or acetate as the species that leads to productive reaction.[12] Modification of the aminomercuration conditions was necessary.



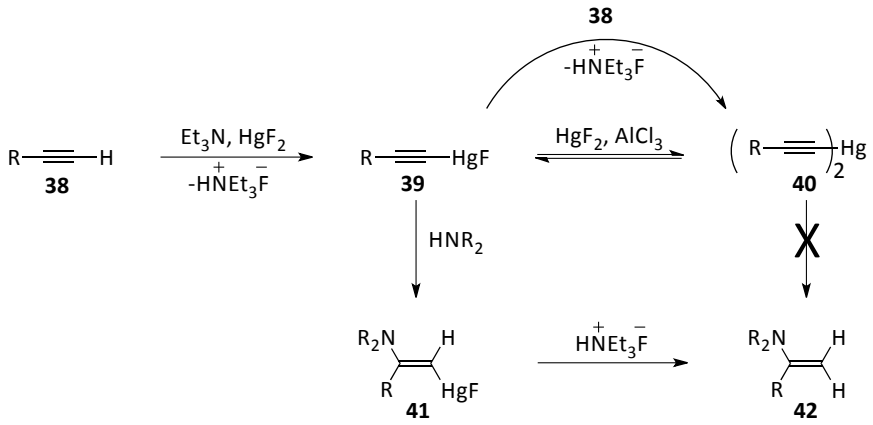
Scheme 4.11. Aminomercuration Under Barluenga's Conditions.

After some experimentation, conditions that produced consistent results were determined. Mercury(II) fluoride gave better results than the acetate, chloride, or bromide salts. The reaction was performed at reflux rather than room temperature, and 4 Å molecular sieves were added to decrease hydrolysis of the product by adventitious water. Addition of a catalytic amount of aluminum chloride after an empirically determined period of three hours was found to be essential to achieving consistent results (Scheme 4.12).



Scheme 4.12. Revised Aminomercuration Conditions.

Aluminum chloride has been used as a catalyst to promote redistribution of ligands on mercury,[13] and it may promote the redistribution so as to make the needed alkynylmercury fluoride (Scheme 4.13).

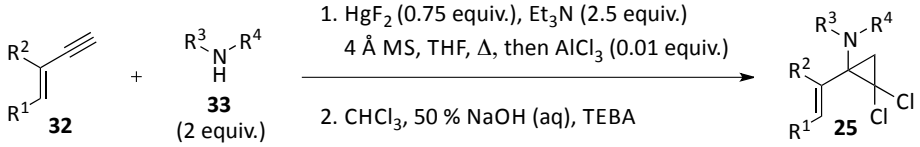


Scheme 4.13. Aminomercuration of Terminal Alkynes.

2-Amino-1,3-butadienes are labile toward hydrolysis, and decompose at a rate such that they should be used within days of synthesis. As these compounds are not amenable to most purification methods, the lower molecular weight compounds were purified by Kugelrohr distillation. The compounds that could not be distilled at a reasonable temperature were carried on as the crude material. Unfortunately, although the crude samples looked reasonably pure by NMR spectroscopy and were visibly homogeneous, metallic mercury could be seen

forming at the bottom of the storage vessel over time. Therefore, we were unable to speculate on the yield for the aminomercuration step in cases where distillation was not possible. Mercury was also observed during distillation; when the temperature approached 200 ºC, metallic mercury could be seen in the receiving flask.

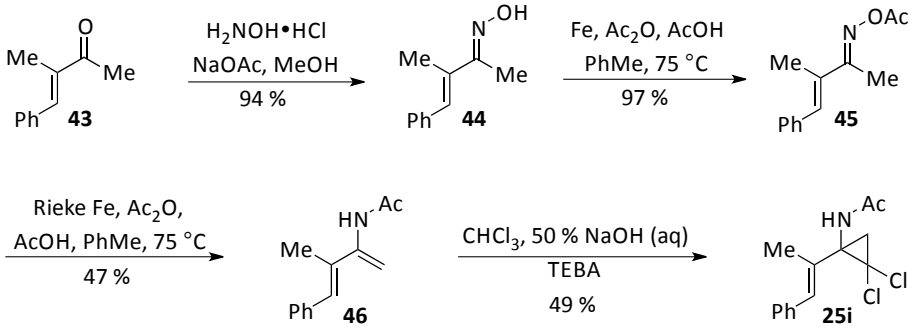
Aminodienes prepared by this method were cyclopropanated under phase-transfer conditions[14] to provide 2-amino-1,1-dichloro-2-vinylcyclopropanes **25a**-**h** in 14-46 % yield over the two steps (Table 4.2).



entry	enyne	amine	cyclopropane	yield (%)
1	**32a** R^1, R^2 = Ph, Me	**33a** R^3, R^4 = $CH_2CH_2OCH_2CH_2$	**25a**	46
2	**32a**	**33b** R^3, R^4 = Me, Bn	**25b**	42
3	**32a**	**33c** R^3, R^4 = Me, Ph	**25c**	14
4	**32c** R^1, R^2 = H, Me	**33a**	**25d**	34
5	**32b** R^1, R^2 = $(CH_2)_4$	**33a**	**25e**	44
6	**32c** R^1, R^2 = CH_2CH_2-(3-$MeOC_6H_4$), Me	**33a**	**25f**	38
7	**32c**	**33b**	**25g**	37
8	**32d** R^1, R^2 = CH_2CH_2-(4-$MeOC_6H_4$), Me	**33a**	**25h**	26

Table 4.2. Preparation of 1-Amino-2,2-dichloro-1-vinylcyclopropanes **25a**-**h**.

Additionally, we were interested in the reactivity of electronically deactivated cyclopropyl acetamide **25i**. Known enone **43** was converted to the corresponding oxime (Scheme 4.14). The first attempt to synthesize enamide **46** resulted in the acetylation of **44**, but no further reaction. The iron powder had been washed with hydrochloric acid and then dried under vacuum prior to use. Resubjection of **45** to the reaction conditions with freshly prepared Rieke iron yielded the desired enamide. Unlike the enamines previously prepared, **46** was sufficiently stable to purify by flash column chromatography using silica gel, and was isolated in 47 % yield. The enamide was cyclopropanated under the standard conditions, and cyclopropane **25i** was provided in 49 % yield.

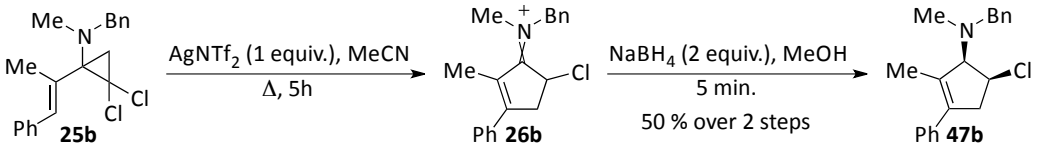


Scheme 4.14. Preparation of Cyclopropane **25i**.

4.2.2 Imino-Nazarov Cyclization - Initial Results

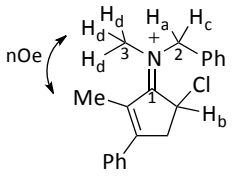
As mentioned above, when morpholinocyclopropane **25a** was subjected to the reaction conditions previously developed for the siloxycyclopropanes,[7] 5-chloro-2-methyl-3-phenyl-2-cyclopentenone (**27**) was the only isolable product. If this compound derives from hydrolysis of the product of an imino-Nazarov cyclization, then either 1) the iminium was sensitive to atmospheric moisture on workup or 2) the water was introduced with the silver fluoroborate as a result of its hygroscopicity.

With hopes of avoiding the hydrolysis, cyclopropane **25b** was subjected to the less hygroscopic silver triflimide in acetonitrile at reflux (Scheme 4.15). After a simple filtration and removal of solvent, none of the hydrolysis product was observed. Two new compounds, which appeared to be geometric isomers, were detected by NMR. The downfield shifts in both the ^{1}H and ^{13}C NMR spectra suggested that the products were iminium species **26b** (Table 4.3).



Scheme 4.15. Imino-Nazarov Reaction/Reduction Sequence.

The iminium salt was reduced with sodium borohydride in methanol to provide *cis*-3-amino-4-chlorocyclopentene **47b** in excellent diastereoselectivity and moderate yield over the two steps. A small amount of unreacted cyclopropane was also recovered. Extending the Nazarov reaction time or increasing the amount of silver triflimide in attempt to reach full conversion resulted in diminished yield.



26b

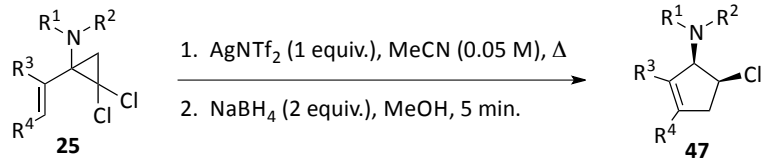
H	Chemical Shift (ppm)	C	Chemical Shift (ppm)
a	5.48	1	186
b	5.49	2	62.7
c	4.98	3	42.4
d	3.62		

Table 4.3. Selected Chemical Shifts in $CDCl_3$ at 500 MHz (^1H) and 125 MHz (^{13}C) for Iminium Salt **26b**.

Despite the modest yield, this result marks the first example in which an imino-Nazarov reaction was carried out with an electron-rich nitrogen that is retained in the product.

4.2.3 Substituent Effects on the Imino-Nazarov Cyclization

The results obtained with **25b** suggested that the aminocyclopropane approach offered a viable method for effecting the imino-Nazarov reaction with a strongly electron-donating nitrogen substituent at C-3, an unprecedented observation. Moreover, the cyclized product, an unsaturated iminium salt, was sufficiently robust to permit its isolation and subsequent reduction. Given the ready access to aminocyclopropane derivatives **25a-e**,**i**, we set out to examine the scope of this process (Table 4.4).



25 **47**

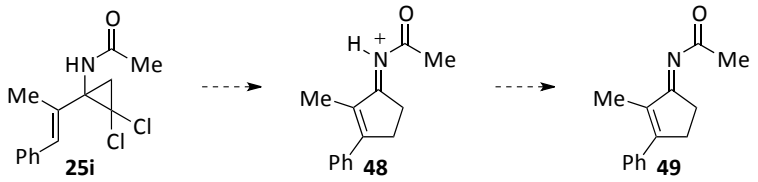
entry	substrate	R^1	R^2	R^3	R^4	time (h)	product	yield (%)
1	**25a**	$CH_2CH_2OCH_2CH_2$		Me	Ph	8.5	**47a**	50
2	**25b**	Me	Bn	Me	Ph	5	**47b**	50
3	**25c**	Me	Ph	Me	Ph	3	**47c**	48
4	**25i**	H	Ac	Me	Ph	24	---	0
5	**25d**	$CH_2CH_2OCH_2CH_2$		Me	H	2	**47d**	22
6	**25e**	$CH_2CH_2OCH_2CH_2$		C_4H_8		0.17	**47e**	12

Table 4.4. Imino-Nazarov/Reduction Sequence.

The substituents on the nitrogen were varied while the remainder of the substrate remained constant to determine what types of secondary amines were permissible. There was no difference in yield when the amine portion was changed from benzylmethylamine (entry 2) to a cyclic amine (entry 1) or an aryl amine (entry 3). In contrast to the other aminocyclopropanes, the reaction of **25c** went to completion. Acetamide **25i** was inert to the standard reaction conditions (entry 3). Although the reaction conditions used for the Nazarov reactions of siloxy-, alkoxy- and aminocyclopropanes vary, the reactivity trend appears to be OSi > Oalkyl ~ $N(alkyl)_2$ >> NAc.

When the temperature was increased to 180 ºC (1,2-dichlorobenzene) in an attempt to effect ring opening, **25i** decomposed to an intractable mixture of products. Compound **25i** was particularly interesting as a substrate because if the reaction progressed in the same manner as for the aminocyclopropanes, *N*-acyliminium **48** would be formed (Scheme 4.16). Compound **48** could then

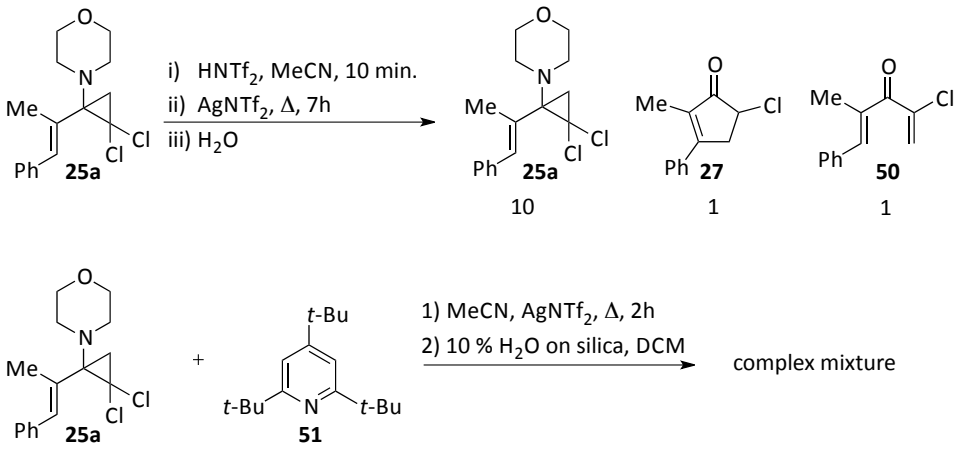
undergo loss of a proton to give *N*-acylimine **49** as a neutral compound, rendering a subsequent reduction step unnecessary.



Scheme 4.16. Hypothetical Imino-Nazarov Reaction of Acetamide **25i**.

Morpholinocyclopropane **25d**, bearing only a methyl substituent on the alkene cyclized to provide **47d** in 22 % yield (entry 5). The reaction stalls at a 1 : 1 ratio of product to starting material, irrespective of whether the imino-Nazarov reaction is run for one to four hours. Cyclohexenylcyclopropane **25e** also underwent the cyclization in poor yield. It appeared that the initial reaction of **25e** was quite fast, as substantial precipitation of silver chloride was observed within 5 minutes of heating. The reaction failed to run to completion on prolonged stirring, during which time the product iminium species was subject to decomposition. A short reaction time of 10 minutes allowed the most reproducible result, with an average yield of 12 % (entry 6).

In an attempt to determine whether acid generated under the reaction conditions could be preventing complete reaction of the aminocyclopropanes, cyclopropane **25a** was treated with one equivalent of $HNTf_2$ prior to addition of silver triflimide (Scheme 4.17). Unreacted starting material was the predominant component of the mixture after 7 hours at reflux, indicating that deactivation by *N*-protonation could be a factor. Compound **25a** is consumed within two hours when the hindered base 2,4,6-tri-*tert*-butylpyridine is added as an acid scavenger; however, these conditions do not lead to observable Nazarov products.



Scheme 4.17. Effect of Acid on the Imino-Nazarov Cyclization of **25a**.

Reduction of the iminium ions occurs exclusively to form a single diastereomer in all of the above examples. The coupling constants for the methine protons of the cyclopentene ring vary between 7.1 and 7.5 Hz. The relative stereochemistry was tentatively assigned as *cis* by comparison to related 3,4-disubstituted cyclopentenes;[15] however, a firm assignment was not possible for these compounds. Hydride addition to the less hindered face of the iminium, opposite to the chlorine results in the proposed stereochemistry (Figure 4.1).

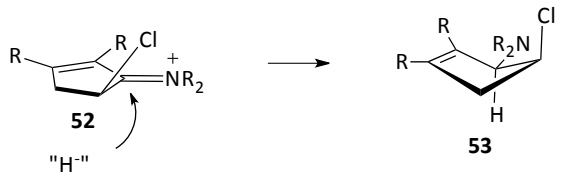
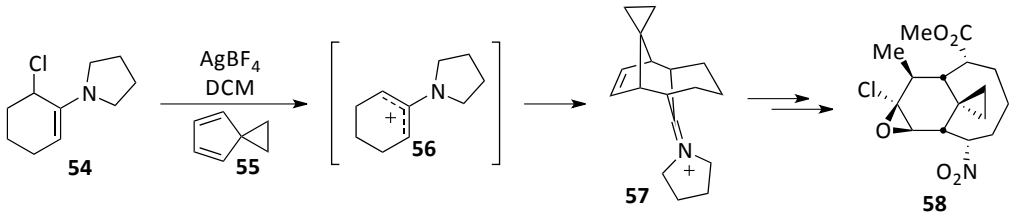


Figure 4.1. Selectivity Model for Iminium Reduction.

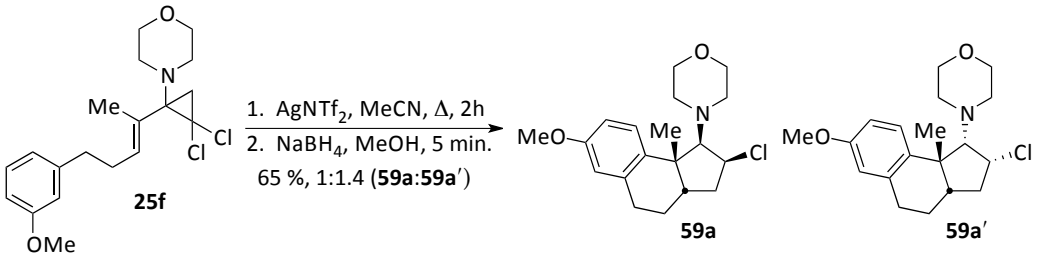
4.2.4 Interrupted Imino-Nazarov Reaction

The West group and others have had much experience in reactions of 2-oxyallyl cations,[16] however, the reactions of the corresponding amino compounds are less often seen in the literature, and unprecedented in the Nazarov subset. Aminoallyl cations are generated from α-chloroenamines[17] or imines,[18] or methyleneaziridines[19] and reacted with dienes or alkenes to obtain cycloaddition products. Cha used an intermolecular [4+3]-cycloaddition involving an aminoallyl cation as an integral step in a synthetic approach toward taxane diterpenes (Scheme 4.18).[17b]



Scheme 4.18. [4+3]-Cycloaddition of a 2-Aminoallyl Cation.

When a 3-methoxyphenyl group was appended to an imino-Nazarov substrate, an interrupted imino-Nazarov reaction of **25f** proceeded smoothly. Tricyclic amines **59a** and **59a′** were generated in a 1:1.4 ratio in 65 % combined yield (Scheme 4.19).



Scheme 4.19. Interrupted Imino-Nazarov Reaction of **25f**.

The structure of the minor isomer **59a** was confirmed by X-ray crystallographic analysis (see appendix V). The relative stereochemistry of the major product **59a'** was assigned based on TROESY correlations shown in Figure 4.2.

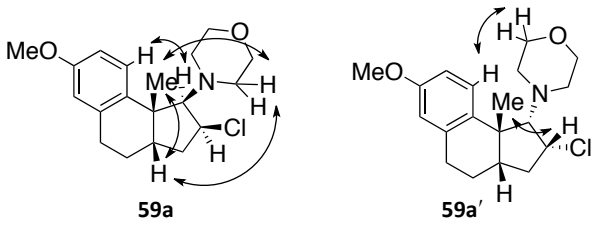
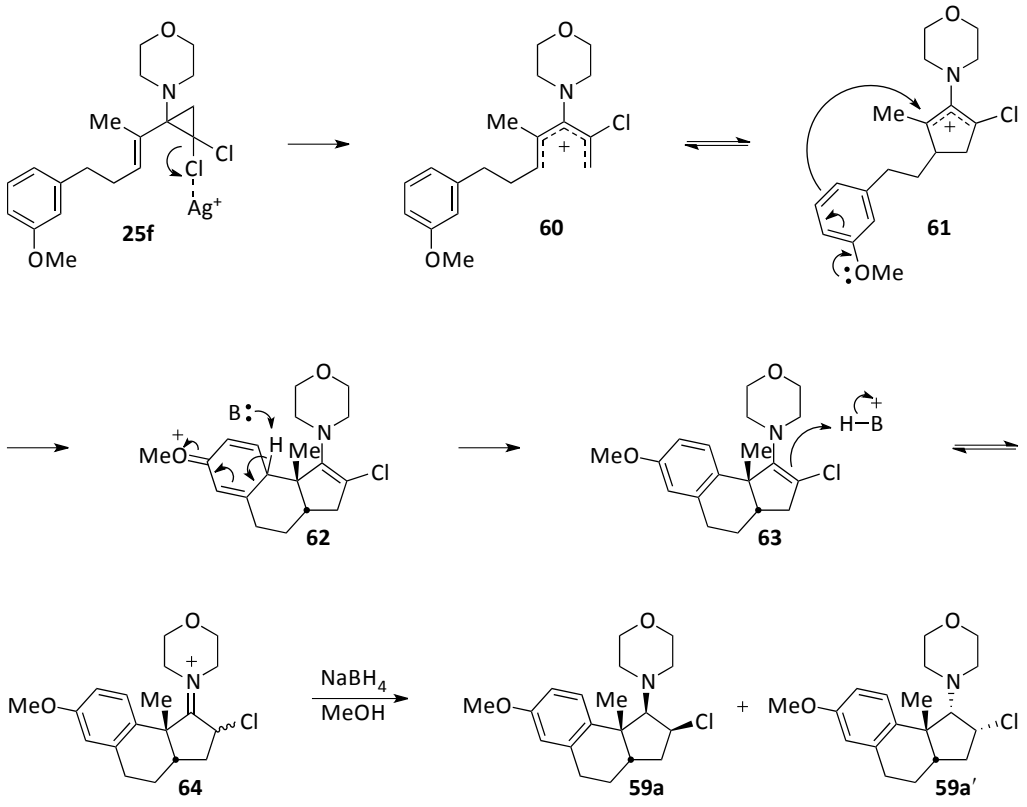


Figure 4.2. Relevant TROESY Correlations for Compounds **59a** and **59a′**.

A mechanism for the formation of tricyclic amines **59a** and **59a′** is proposed in Scheme 4.20. Chloride departure and 2π-electrocyclic ring opening of the cyclopropane gives cation **60**, which undergoes Nazarov cyclization to produce 2-aminoallyl cation **61**. Electrophilic aromatic substitution followed by protonation of the resulting enamine forms iminium salts **64**. The protonation step is reversible, and so the ratio of epimers obtained at this stage should reflect the thermodynamic stabilities of iminiums **64**. This is also observed in the interrupted Nazarov cyclization of the analogous isopropoxycyclopropane (Chapter 2).

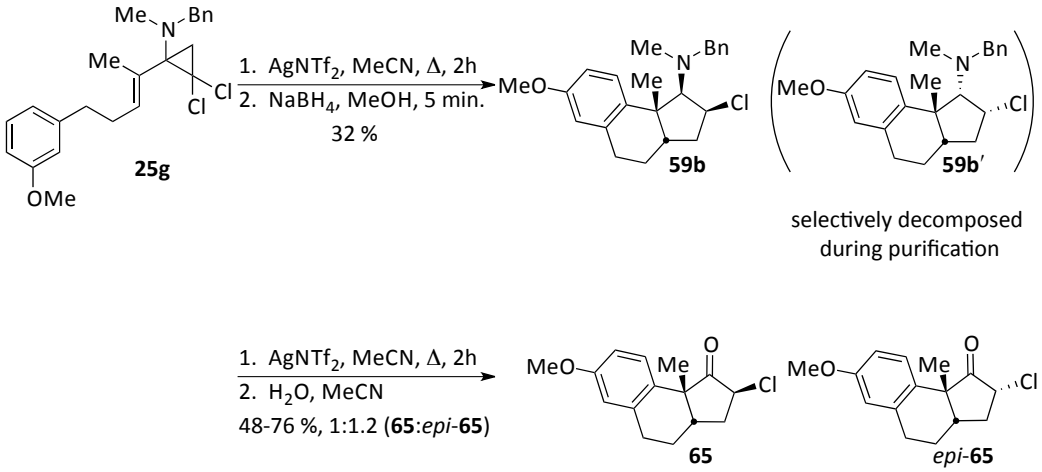
The stereochemical course of iminium reduction of the tricyclic structure is dictated by the geometry of the chlorine substituent, as in the non-interrupted imino-Nazarov cyclizations. Attack of borohydride from the face opposite to the chlorine again exclusively leads to the *cis* relationship between the amine and the chlorine.



Scheme 4.20. Mechanism of the Interrupted Imino-Nazarov Reaction.

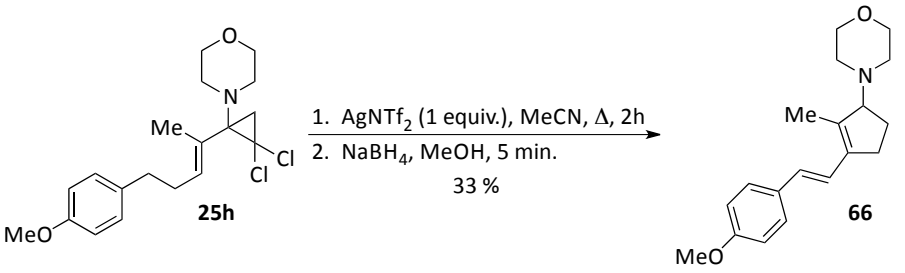
N-benzyl-*N*-methylaminocyclopropane **25g** also underwent the interrupted Nazarov reaction producing two diastereoisomeric compounds in a 1.2:1 ratio (Scheme 4.21). The major isomer, presumably **59b′**, was not stable to chromatography. The minor isomer, **59b**, was isolated in 32 % yield. The relative stereochemistry of **59b** was tentatively assigned based on 1D-TROESY

data. In an effort to establish yields for the Nazarov step, the crude iminium was subjected to hydrolysis. The combined yield of ketones **65** and *epi*-**65** was inconsistent between runs, ranging from 76 % to 48 %; however, the ratio of **65** to *epi*-**65** remained constant.



Scheme 4.21. Interrupted Imino-Nazarov Cyclization of **25g**.

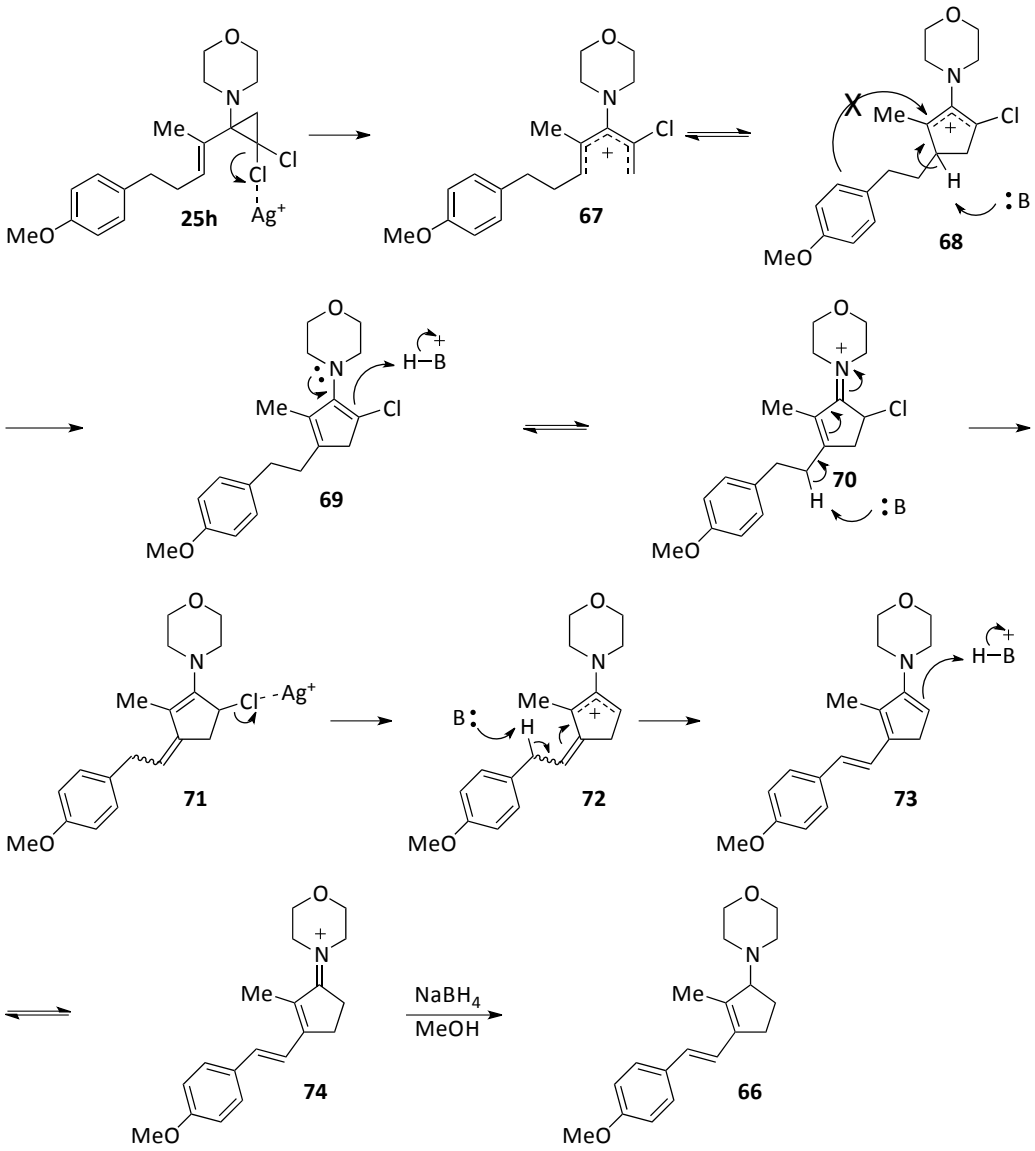
Substrate **25h** did not undergo the interruption event. Presumably, the carbon *meta* to the methyl ether on the arene is not sufficiently electron-rich to effect the nucleophilic attack on the aminoallyl cation. Unexpectedly, when the reaction was run with one equivalent of silver triflimide, dechlorinated product **66** was isolated (Scheme 4.22).



Scheme 4.22. Unexpected Production of a Dechlorinated Cyclopentenylamine.

A possible mechanism for the formation of **66** is shown Scheme 4.23. Silver(I)-assisted departure of a chloride with concomitant 2π-electrocyclic ring-opening of the cyclopropane would generate pentadienyl cation **67**. Subsequent Nazarov cyclization would yield 2-aminoallyl cation **68**. Failure of nucleophilic attack by the arene allowed elimination to proceed, generating intermediate **71**. Compounds of this structure are known to undergo dechlorination to produce allyl cations[17] (Scheme 4.18), and this has been observed previously in the interrupted variant of the siloxycyclopropane Nazarov.[6e] Loss of chloride gives a second allyl cation **72**. Elimination would lead to doubly unsaturated iminium **74**, which would give the isolated dienylamine **66** on reduction with sodium borohydride.

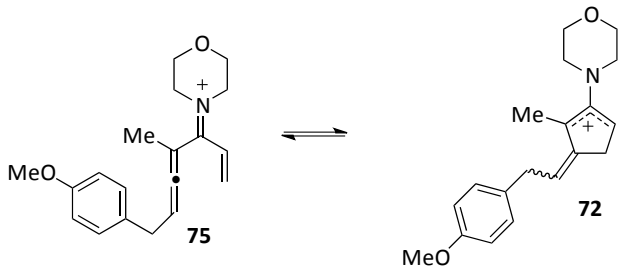
Failure of the 4-methoxyphenyl moiety to trap the Nazarov intermediate **68** is congruent with the results of a study of the interrupted Nazarov cyclization of 1,1-dichloro-2-siloxy-2-vinylcyclopropanes, where a phenyl group could not intercept an oxyallyl cation with a similar substitution pattern to **68**.[6e] In addition, the 3-methoxyphenyl group was an effective trap, as is the case with aminocyclopropane substrate **25g**.



Scheme 4.23. Mechanism for Production of **66**.

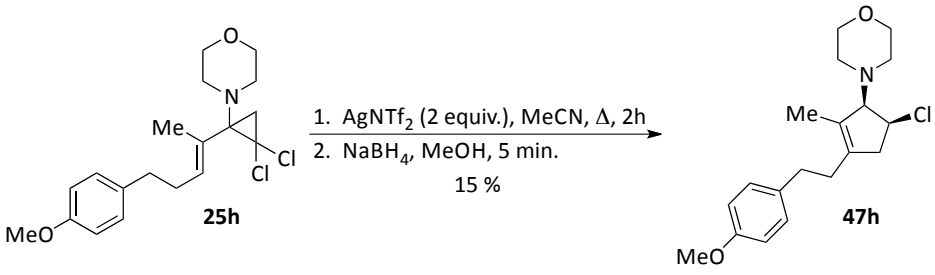
Proposed intermediate **72** is interesting because it would be produced from a hypothetical Nazarov cyclization of allenyl precursor **75** (Scheme 4.24). The retro-Nazarov reaction[20] of **72** does not appear to be a substantial pathway in this reaction. This may indicate that two stabilizing α-substituents on the 3-aminopentadienyl cation are not strictly required for a productive imino-Nazarov

reaction. Allenic strain generated in the ring-opening reaction may also play a role in inhibiting the retro-Nazarov pathway.



Scheme 4.24. Equilibrium of Open and Closed Cations **75** and **72**.

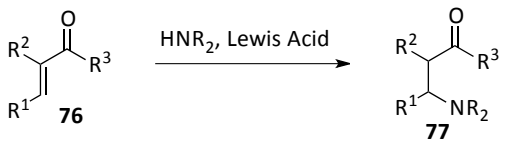
We expected that additional silver triflimide would aid in the second dechlorination step, from enamine **71** to **72**. In an effort to increase the yield of **66**, **25h** was exposed to two equivalents of silver triflimide, with all other reaction conditions remaining unchanged. Only imino-Nazarov product **47h** was isolated; there was no trace of compound **66** (Scheme 4.25). This was a surprising result, given our expectations for the experiment, and it is not clear why the reaction course was shifted so dramatically.



Scheme 4.25. Imino-Nazarov Cyclization of **25h** in the Presence of Excess $AgNTf_2$.

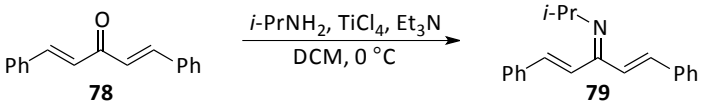
4.2.5 Dienones as Precursors for the Imino-Nazarov Reaction

An often-cited fundamental problem with divinylimines as Nazarov substrates is that they cannot be prepared from divinylketone precursors. The normal product from the reaction of an amine with an α,β-unsaturated ketone is conjugate addition product **77** (Scheme 4.26). This is also the reason enamine preparation from these enones is problematic.



Scheme 4.26. Michael Addition of Amines to α,β-Unsaturated Ketones.

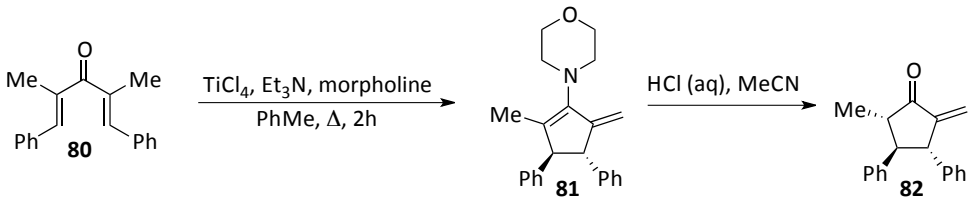
In the few instances divinylimines have been prepared from divinyl ketones,[1] most examples lack α-substituents, as exemplified by production of **79** from dibenzylideneacetone (Scheme 4.27).[1a]



Scheme 4.27. Synthesis of a Divinylimine.

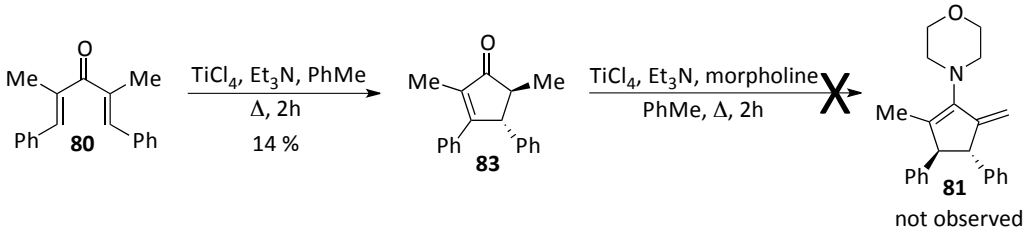
We thought that a similar reaction performed with a secondary amine would produce a divinyliminium and trigger Nazarov cyclization. Dienone **80**, bearing two electron-donating methyl substituents, was chosen to test this hypothesis (Scheme 4.28). Ketone **80** was added to a mixture of morpholine, titanium tetrachloride and triethylamine in toluene, and then heated to reflux.

Upon workup, **81** was observed as the major product. Although the enamine was not purified, hydrolysis under acidic conditions provided enone **82**,[21] supporting the assigned structure.



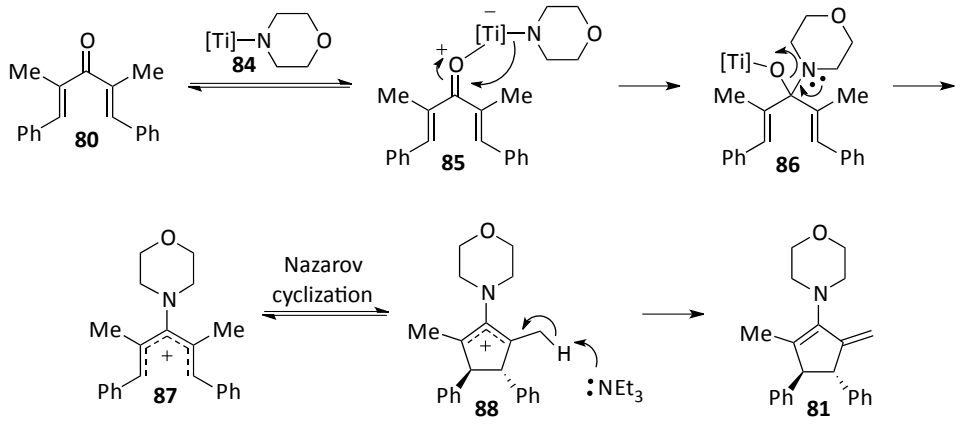
Scheme 4.28. Imino-Nazarov Reaction of Dienone **80** and Morpholine.

Control experiments demonstrated that although **80** can be converted to cyclopentenone **83** under the reaction conditions in the absence of morpholine, **83** does not appear to be an intermediate in the formation of enamine **81** (Scheme 4.29).



Scheme 4.29. Cyclopentenone **83** is not a Precursor to **81**.

A mechanism for the formation of **81** is proposed in Scheme 4.30. Dienone **80** coordinates to morpholine-bound titanium species **84**. Morpholine transfer followed by iminium formation gives 3-aminopentadienyl cation **85**. Intermediate **87** undergoes 4π-conrotatory electrocyclization to give 2-aminocyclopentenyl cation **88**, and elimination gives the product enamine **81**.



Scheme 4.30. Mechanism for Imino-Nazarov Reaction of Dienone **80** with Morpholine.

While this result is very preliminary, it demonstrates a synthetically straightforward method to access divinyliminium species for the imino-Nazarov cyclization.

4.3 Conclusions

The first examples of an imino-Nazarov cyclization with an electron-rich nitrogen to produce cyclopentenes retaining the nitrogen have been demonstrated. 1-Amino-2,2-dichloro-1-vinylcyclopropanes undergo an electrocyclic ring-opening of the cyclopropane followed by Nazarov cyclization to produce cyclopenteniminiums. The iminiums are easily reduced with sodium borohydride to provide cyclopentenylamines in moderate yields. The reaction is tolerant of cyclic amines, anilines, and alkyl-substituted amine moieties. This is considerably expanded from previous imino-Nazarov reactions.

The first interrupted imino-Nazarov reaction has been demonstrated utilizing a tethered 3-methoxyphenyl nucleophile. The arene trap must be suitably electron-rich in order for this process to occur.

4.4 Future Directions

This and other[3,4,5] preliminary reports of the imino-Nazarov cyclization represent the beginning of a quest to understand and exploit the imino-Nazarov cyclization. An expanded study of substituent effects will be essential in this endeavor. All of the substrates so far examined have been substituted at both α-positions of the pentadienyl cation. This substitution pattern must be varied in order to understand the boundaries within which the imino-Nazarov reaction is operational.

The substitution in this study was limited not only because we thought it would help promote the cyclization, but also because the route for substrate synthesis required this substitution pattern. The aminomercuration requires that R^2 is not hydrogen, and also that the reactant is a terminal alkyne (Figure 4.3).[10]

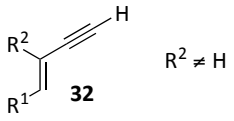
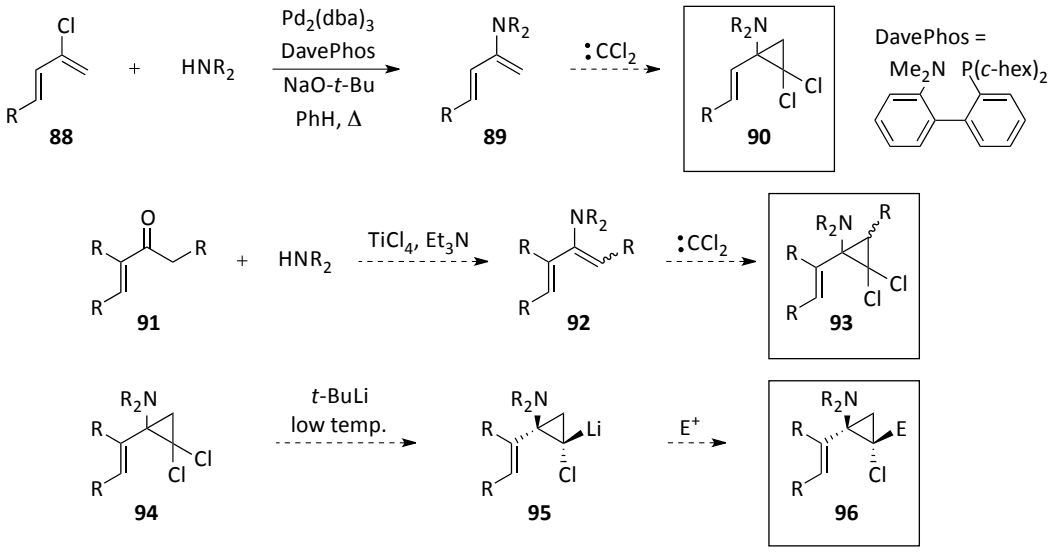


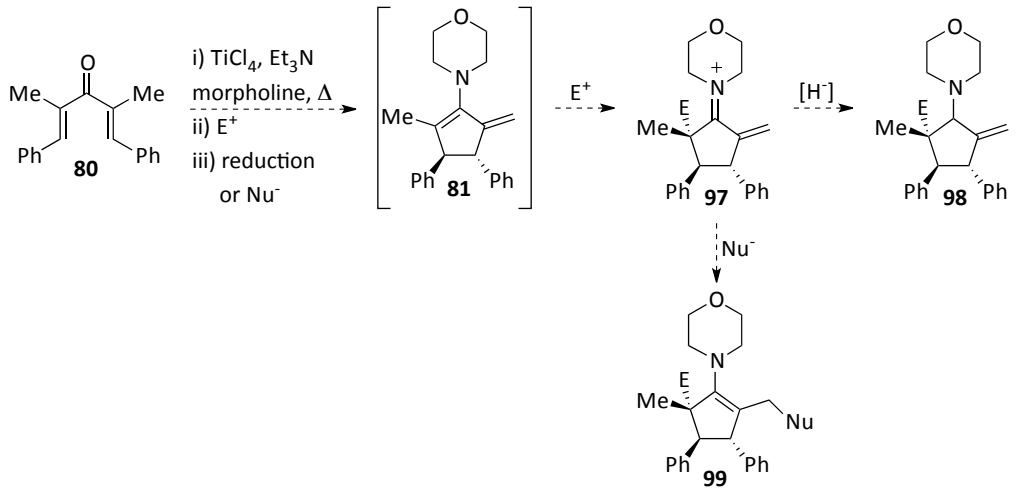
Figure 4.3. Acceptable Substrates for Aminomercuration.

Compounds of type **90** may be available utilizing a Buchwald-type coupling of chlorodienes **88** and secondary amines to form enamines **89** (Scheme 4.31).[9] A titanium-mediated enamine synthesis[22] could conceivably give entry to enamines **92** to provide more highly substituted aminocyclopropanes **93**. It may be possible to remove the chlorine substituent with lithium-halogen exchange, followed by reaction with an appropriate electrophile.



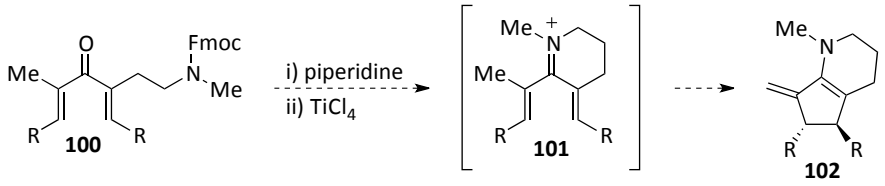
Scheme 4.31. Possible Routes to Aminocyclopropanes **90**, **93** and **96**.

Imino-Nazarov cyclization of an *in situ* generated divinyl iminium provides a simpler entry to divinyliminium species. A number of dienones are readily available, as well as partner amines. Optimization of this process could provide the first practically useful imino-Nazarov reaction. In addition, under the basic conditions of the cyclization, enamine **81** was produced (Scheme 4.32). This enamine functionality could provide a handle for subsequent bond formation with an electrophile, potentially in a one-pot fashion, to generate products **97**. Reduction would provide functionalized cyclopentanes **98** in a short sequence. Also, the initial product from electrophilic functionalization of the enamine is a conjugated eniminium, which could be further functionalized by 1,4-addition in an extended sequence to furnish compounds **99**.



Scheme 4.32. One-pot Imino-Nazarov Reactions.

Intramolecular delivery of the amine may also be possible, leading to structures such as **102** that have been inaccessible by previous Nazarov chemistry (Scheme 4.33).[23]



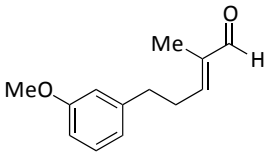
Scheme 4.33. Intramolecular Amine Delivery to Form Heterocycle **102**.

4.5 Experimental

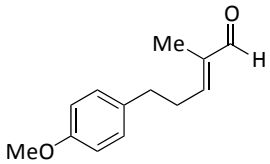
4.5.1 General Information

Reactions were carried out in flame-dried glassware under an atmosphere of argon. Tetrahydrofuran (Na/benzophenone), diethyl ether (Na/benzophenone), dichloromethane (CaH_2), acetonitrile (CaH_2), toluene (CaH_2), and triethylamine (CaH_2) were distilled prior to use, and chloroform was filtered through potassium carbonate. Methanol was dried over activated 3Å molecular sieves. Thin layer chromatography was performed on glass plates precoated with 0.25 mm Kieselgel 60 F254 (Merck). Flash chromatography columns were packed with 230-400 mesh silica gel (Silicycle), or 150 mesh neutral alumina (Sigma-Aldrich). Carbon tetrabromide was dissolved in dichloromethane, dried over magnesium sulfate and filtered prior to use to remove residual water in the commercial reagent. Mercury(II) fluoride and mercury(II) acetate were dried over phosphorus pentoxide under vacuum prior to use. Silver bis(trifluoromethanesulfonyl)imide was prepared from silver carbonate.[24] Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 MHz, 400 MHz, or 500 MHz and coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, etc. The chemical shifts are reported on the δ scale (ppm) and the spectra are referenced to residual solvent peaks: $CDCl_3$ (7.26 ppm, ^{1}H; 77.26 ppm, ^{13}C), as internal standard. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz or 125 MHz, and the chemical shifts are accurate to one decimal place.

4.5.2 Experimental Procedures and Characterization

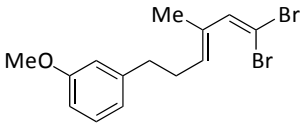


(*E*)-5-(3-methoxyphenyl)-2-methyl-2-pentenal (35a). 3-(3-methoxyphenyl)-propanal (**34a**, 1.706 g, 10.4 mmol) was dissolved in 100 mL toluene. 2-(triphenylphosphoranylidene)propanal (3.64 g, 11.4 mmol) was added, and the mixture was heated at reflux for 2 days. The mixture was allowed to cool to room temperature and concentrated. Ether was added, and the flask was placed in a sonicator bath for 1h. Filtration and concentration gave the crude product. FCC (8, 10 % ethyl acetate in hexanes) provided **35a** as a pale yellow oil, 1.057 g, 49 %. IR (DCM cast film) 2939, 2835, 2762, 2714, 1685, 1642, 1602, 1585, 1489, 1454, 1262, 1153 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.22 (app t, *J* = 7.9 Hz, 1H), 6.81-6.74 (m, 3H); 6.50 (dq, *J* = 7.2, 1.4 Hz, 1H), 3.80 (s, 3H), 2.82-2.78 (m, 2H), 2.71-2.65 (m, 2H), 1.70 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 160.0, 153.4, 142.5, 140.1, 129.8, 121.0, 114.5, 111.6, 55.4, 34.7, 30.7, 9.4; HRMS (EI, M^+) calculated for $C_{13}H_{16}O_2$ m/z 204.1150; found m/z 204.1146.

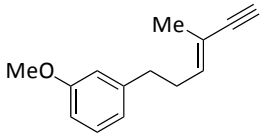


(*E*)-5-(4-methoxyphenyl)-2-methyl-2-pentenal (35b). This compound was synthesized in a manner analogous to **35a**. FCC (7 % ethyl acetate in hexanes) provided **35b** as a colourless oil, 755 mg, 72 %; IR (neat) 2997, 2934, 2835, 2714, 1686, 1644, 1612, 1513, 1247 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.13-7.09 (m, 2H), 6.86-6.82 (m, 2H), 6.49 (tq, *J* = 7.2, 1.4 Hz, 1H), 3.80 (s, 3H), 2.79-2.74 (m, 2H), 2.67-2.62 (m, 2H), 1.70-1.67 (m, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 195.4, 158.4, 153.6, 140.1, 132.9, 129.5, 114.2, 55.5, 33.8, 31.2, 9.4; HRMS (EI, M^+) calculated for $C_{13}H_{16}O_2$ m/z 204.1150, found m/z 204.1143.

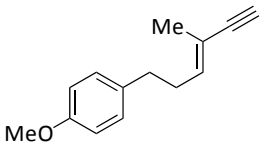


(3*E*)-1,1-dibromo-6-(3-methoxyphenyl)-3-methyl-1,3-hexadiene (36a). A solution of carbon tetrabromide (4.31 g, 13.0 mmol) in 10 mL dichloromethane was added to a stirred solution of triphenylphosphine (6.82 g, 26.0 mmol) in 20 mL dichloromethane at 0 ºC. After 15 minutes of stirring, (*E*)-5-(3-methoxyphenyl)-2-methyl-2-pentenal (**35a**) was added (1.33 g, 6.51 mmol) as a solution in 10 mL dichloromethane. After stirring for 1 h, the reaction was quenched with water, and the resulting layers were separated. The aqueous was extracted once with dichloromethane. Ether was added to the combined extract, the mixture was filtered, dried over magnesium sulfate, filtered, then concentrated. Ether was added to the crude mixture, and it was sonicated for 1 hour. The mixture was filtered and concentrated. Hexanes was added, and filtration followed by concentration yielded the dibromide as a yellow oil of sufficient purity, 1.799 g, 76 %. IR (DCM cast film) 2998, 2936, 2833, 1602, 1584, 1488, 1465, 1262 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23-7.18 (m, 1H), 6.92 (s, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.76-6.73 (m, 2H), 5.70-5.65 (m, 1H), 3.80 (s, 3H), 2.70-2.66 (m, 2H), 2.40 (app q, *J* = 7.6 Hz, 2H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 143.4, 141.0, 134.7, 132.5, 129.6, 121.1, 114.5, 111.4, 86.5, 55.4, 35.4, 30.1, 15.5; HRMS (EI, M-Br) calculated for $C_{14}H_{16}OBr$ m/z 279.0384; found m/z 279.0386.

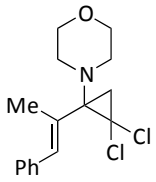


(*E*)-6-(3-methoxyphenyl)-3-methylhex-3-en-1-yne (32d). *n*-Butyllithium (3.9 mL, 2.5 M in hexanes, 9.8 mmol) was added to a solution of (3*E*)-1,1-dibromo-6-

(3-methoxyphenyl)-3-methyl-1,3-hexadiene (**36a**) (1.772 g, 4.921 mmol) in 16 mL ether at -78 ºC. The solution was allowed to slowly warm to room temperature and stir 17 h. Water was then added, the layers were separated, and the aqueous was extracted once with hexanes. The combined extract was washed with water then brine, dried over magnesium sulfate, filtered, and concentrated to a pale yellow oil, 1.030 g, quantitative. IR (DCM cast film) 3287, 3028, 2938, 2859, 2094, 1585, 1489, 1454, 1437, 1262, 1153, 1051 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.16 (m 1H), 6.81-6.71 (m, 3H), 6.02-5.95 (m, 1H), 3.28 (s, 3H), 2.76 (s, 1H), 2.71-2.62 (m, 2H), 2.46-2.35 (m, 2H), 1.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 143.3, 138.8, 129.6, 121.0, 117.8, 114.4, 111.5, 87.0, 74.0, 55.4, 35.3, 30.4, 17.2; HRMS (EI, M^+) calculated for $C_{14}H_{16}O$ m/z 200.1201; found m/z 200.1198.

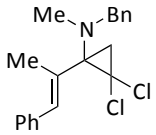


(*E*)-6-(4-methoxyphenyl)-3-methylhex-3-en-1-yne (32e). This compound was synthesized in a manner analogous to **32d**. Compound **32e** was isolated as a pale yellow oil, 584 mg, 81 % over 2 steps. IR ($CDCl_3$ cast film) 3287, 2932, 2856, 2093, 1612, 1584, 1513, 1465, 1247 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12-7.07 (m, 2H), 6.85-6.81 (m, 2H), 5.98 (tq, J = 7.4, 1.5 Hz, 1H), 3.79 (s, 3H), 2.76 (s, 1H), 2.65-2.61 (m, 2H), 2.40-2.35 (m, 2H), 1.74-1.73 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 138.9, 133.7, 129.5, 117.7, 114.1, 87.1, 73.9, 55.5, 34.4, 30.8, 17.2; HRMS (EI, M^+) calculated for $C_{14}H_{16}O$ m/z 200.1201; found m/z 200.1203.

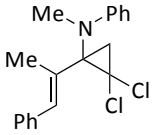


1,1-dichloro-2-morpholino-2-(1-phenyl-[2*E*]-propen-2-ylcyclopropane (25a). Mercury(II) fluoride (1.26 g, 5.27 mmol), powdered 4 Å molecular sieves (1.4 g), tetrahydrofuran (18 mL), triethylamine (2.5 mL, 17.6 mmol), (*E*)-4-phenyl-3-methyl-3-buten-1-yne (1.00 g, 7.03 mmol), and morpholine (1.23 mL, 14.1 mmol) were sequentially added to a round bottom flask, and the mixture was stirred and heated to reflux for 3 h. The mixture was then cooled to room temperature, and aluminum chloride (9 mg, 0.07 mmol) was added. The mixture was heated to reflux for 19 h, then cooled. Hexane was added, and the mixture was filtered through Celite and concentrated. The resulting oil was dissolved in hexanes, filtered through Celite and concentrated to provide the enamine as a yellow oil, 2.519 g, which was carried on in crude form.

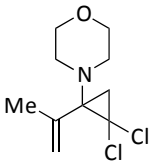
The crude enamine (2.51 mg) was dissolved in 91 mL chloroform. 50 % aqueous sodium hydroxide (157 mL, 1.96 mol) was added followed by benzyltriethylammonium chloride (745 mg, 3.27 mmol), and the reaction was stirred vigorously for 30 min., and then diluted with water. The layers were separated, and the aqueous was extracted three times with dichloromethane. The combined extract was washed with water then brine, dried over magnesium sulfate, filtered, and concentrated to a brown film. FCC (7 % ethyl acetate in hexanes) provided the desired compound as an off-white solid, 1.021 g, 46 % over 2 steps. The data for this compound is in agreement with that previously reported.[7]



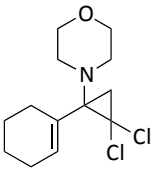
1-(*N*-benzyl-*N*-methylamino)-2,2-dichloro-1-(1-phenyl-[1*E*]-propen-2-yl)cyclopropane (25b). This compound was prepared in a manner analogous to **25a**. Cyclopropanation time was 35 minutes. FCC (3 % ethyl acetate in hexanes) provided the desired compound as an off-white solid, 180 mg, 42 % over 2 steps. M.p. (decomp.) 85 ºC; IR (dichloromethane cast film) 3061, 3026, 2950, 2945, 1600, 1494, 1447 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.24 (m, 10H), 6.51 (s, 1H), 3.99 (d, *J* = 13.4 Hz, 1H), 3.75 (d, *J* = 13.4 Hz, 1H), 2.32 (s, 3H), 2.23 (s, 3H), 1.85 (d, *J* = 6.9 Hz, 1H), 1.77 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 137.1, 133.4, 131.2, 129.3, 128.6, 128.51, 128.50, 127.2, 127.2, 67.8, 62.4, 59.2, 38.4, 35.9, 20.4; HRMS (ESI, M+H) calculated for $C_{20}H_{22}NCl_2$ m/z 346.1124; found m/z 346.1128.



1,1-dichloro-2-(*N*-methyl-*N*-phenylamino)-2-(1-phenyl-[1*E*]-propen-2-yl)cyclopropane (25c). This compound was prepared in a manner analogous to **25a**. Cyclopropanation time was 60 minutes. FCC (15 % dichloromethane in hexanes provided the desired compound as an off-white solid, 324 mg, 14 % over 2 steps; m.p. 76-78 ºC; IR ($CHCl_3$ cast film) 3024, 2892, 2821, 1599, 1500, 1344 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.32 (m, 2H), 7.30-7.22 (m, 5H), 6.92-6.88 (m, 2H), 6.81 (tt, *J* = 7.3, 1.0 Hz, 1H), 6.71 (s, 1H), 3.35 (s, 3H), 2.47 (d, *J* = 8.0 Hz, 1H), 2.08 (d, *J* = 1.3 Hz, 3H), 1.93 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 137.0, 133.5, 131.3, 129.3, 129.1, 128.4, 127.2, 118.0, 114.0, 67.6, 58.3, 40.2, 34.3, 17.9; HRMS (ESI, M+H) calculated for $C_{19}H_{20}NCl_2$ m/z 332.0967; found m/z 332.0965.

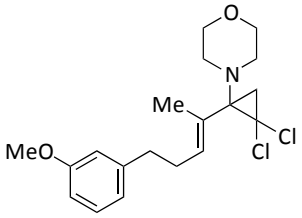


1,1-dichloro-2-morpholino-2-[*E*]-propen-2-ylcyclopropane (25d). This compound was prepared in a manner analogous to **25a**. Cyclopropanation time was 2 minutes. FCC (7 % ethyl acetate in hexanes) provided the desired compound as a shiny white solid, 411 mg, 34 % over 2 steps; m.p. 54-56 ºC; IR (dichloromethane cast film) 2958, 2855, 2828, 1637, 1116 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (app pentet, J = 1.5 Hz, 1H), 4.89-4.88 (m, 1H), 3.67-3.64 (m, 4H), 2.79-2.73 (m, 2H), 2.65-2.60 (m, 2H), 1.93 (dd, J = 1.5, 0.8 Hz, 3H), 1.58 (d, J = 6.8 Hz, 1H), 1.52 (d, J = 6.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 119.6, 67.7, 66.6, 59.1, 50.4, 34.5, 23.2; HRMS (ESI, M+H) calculated for $C_{10}H_{16}NOCl_2$ m/z 236.0603; found m/z 236.0599.

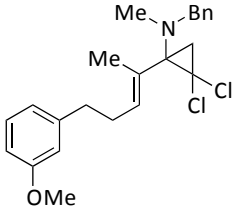


1,1-dichloro-2-cyclohexen-1-yl-2-morpholinocyclopropane (25e). This compound was prepared in a manner analogous to **25a**. The intermediate enamine was purified by Kugelrohr distillation (100 ºC, 0.5 mmHg) to provide the known enamine **31a**[10a] as a colourless liquid, 1.34 g, 69 %. Cyclopropanation time was 15 minutes. The crude cyclopropane was purified by flash column chromatography (20 % ethyl acetate in hexanes) to provide the desired compound as a white solid, 467 mg, 65 %; m.p. 75-77 ºC; IR (DCM cast film) 2933, 2855, 1655, 1451, 1116; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62-5.59 (m, 1H), 3.67-3.62 (m, 4H), 2.78-2.72 (m, 2H), 2.65-2.60 (m, 2H), 2.26-2.19 (m, 1H), 2.16-2.05 (m, 3H), 1.75-1.64 (m, 2H), 1.58-1.49 (m, 3H), 1.46 (d, J = 6.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.4, 130.8, 67.7, 67.1, 59.4, 50.5, 34.1, 30.3, 25.4, 22.9,

22.5; HRMS (ESI, M+H) calculated for $C_{13}H_{20}NOCl_2$ m/z 276.0916; found m/z 276.0911.

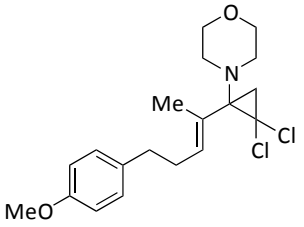


1,1-dichloro-2-morpholino-2-(5-(3-methoxyphenyl)-[2*E*]-penten-2-yl)cyclopropane (25f). This compound was prepared in a manner analogous to **25a**. Cyclopropanation time was 15 minutes. Flash column chromatography (10 % ethyl acetate in hexanes) provided the product as a pale yellow solid, 136 mg, 48 % over 2 steps; m.p. 56-59ºC; IR (dichloromethane cast film) 3008, 2953, 2852, 2833, 1609, 1581, 1489, 1454, 1265 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22-7.17 (m, 1H), 6.78 (br d, *J* = 7.5 Hz, 1H), 6.75-6.72 (m, 2H), 5.38-5.34 (m, 1H), 3.80 (s, 3H), 3.67-3.59 (m, 4H), 2.70-2.63 (m, 4H), 2.53-2.47 (m, 2H), 2.41 (app q, *J* = 7.6 Hz, 2H); 1.79 (s, 3H), 1.53-1.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 143.5, 134.1, 129.6, 128.6, 121.1, 114.6, 111.3, 67.6, 66.9, 60.8, 55.4, 50.4, 35.7, 34.8, 29.8, 18.4; HRMS (ESI, M+H) calculated for $C_{19}H_{26}NO_2Cl_2$ m/z 370.1335; found m/z 370.1337.

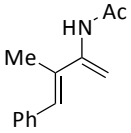


1-(*N*-benzyl-*N*-methylamino)-2,2-dichloro-1-(5-(3-methoxyphenyl)-[2*E*]-penten-2-yl)cyclopropane (25g). This compound was prepared in a manner analogous to **25a**. Cyclopropanation time was 12 minutes. FCC (2 % ethyl acetate in hexanes) provided **25g** as a pale yellow thick oil, 284 mg, 37 % over two steps; IR (neat) 2938, 2795, 1663, 1601, 1585, 1492, 1454 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.26 (m, 4H), 7.24-7.19 (m, 2H), 6.81 (br d, *J* = 7.7 Hz,

1H), 6.77-6.74 (m, 2H), 5.45 (br t, *J* = 7.2 Hz, 1H), 3.82-3.76 (m, 4H), 3.52 (d, *J* = 13.4 Hz, 1H), 2.78-2.67 (m, 2H), 2.53-2.42 (m, 2H), 2.13 (s, 3H), 1.87 (s, 3H), 1.63-1.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 143.6, 139.5, 133.7, 129.5, 129.2, 128.6, 128.4, 127.2, 121.2, 114.6, 111.3, 67.7, 61.6, 59.1, 55.4, 38.3, 35.7, 35.6, 29.8, 18.4; HRMS (ESI, M+H) calculated for $C_{23}H_{28}Cl_2NO$ m/z 404.1542, found m/z 404.1538.



1,1-dichloro-2-(5-(3-methoxyphenyl)-[2*E*]-penten-2-yl)-2-morpholinocyclopropane (25h). This compound was prepared in a manner analogous to **25a**. Cyclopropanation time was 16 minutes. FCC (10 % ethyl acetate in hexanes) provided **25h** as an off-white powder, 275 mg, 26 % over two steps; m.p. 61-65 ºC; IR (neat) 2967, 2852, 1612, 1512, 1453 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11-7.07 (m, 2H), 6.84-6.81 (m, 2H), 5.36 (br t, *J* = 7.1 Hz, 1H), 3.79 (s, 3H), 3.69-3.60 (m, 4H), 2.72-2.60 (m, 4H), 2.56-2.47 (m, 2H), 2.42-2.33 (m, 2H), 1.78 (s, 3H), 1.54-1.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 134.2, 134.0, 129.5, 128.5, 114.0, 67.6, 67.0, 60.8, 55.5, 50.3, 34.8, 34.7, 30.1, 18.4; HRMS (ESI, M+H) calculated for $C_{19}H_{26}Cl_2NO_2$ m/z 370.1335, found m/z 370.1330.

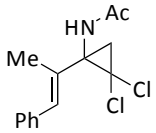


3-acetamido-3-methyl-1-phenyl-1,3-butadiene (46). Hydroxylamine hydrochloride (477 mg, 6.86 mmol) was dissolved in 3.1 mL methanol. Sodium acetate (563 mg, 6.86 mmol) was added, and the resulting mixture was stirred for 30 minutes. (*E*)-2-methyl-1-phenyl-1-buten-3-one (**43**, 1.00 g, 6.24 mmol) was

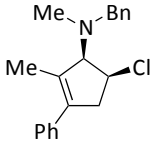
added in one portion, and the reaction was allowed to stir 4 hours. Water was added, and the product was removed by filtration. No further purification was necessary. 2-Methyl-1-phenyl-1-buten-3-one oxime (**44**) was provided as a white powder, 1.030 g, 94 %. Data for this compound are consistent with that reported in the literature.[25]

Oxime **44** (993 mg, 5.67 mmol) was dissolved in 16 mL toluene. Acetic anhydride (1.6 mL, 17 mmol) and acetic acid (0.95 mL, 17 mmol) were added, followed by iron powder (697 mg, 12.5 mmol). The mixture was heated at 75 ºC for 8 hours, then allowed to cool and filtered. The filtrate was washed twice with 2M aqueous sodium hydroxide, then dried over magnesium sulfate, filtered, and concentrated to a white solid. 1.20 g of the acetylated oxime **45** was isolated, 97 %. IR (neat) 3068, 2971, 2859, 1767, 1625, 1575 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.36 (m, 2H), 7.35-7.32 (m, 2H), 7.31-7.27 (m, 1H), 7.05 (br s, 1H), 2.25 (s, 3H), 2.25 (s, 3H), 2.16 (d, J = 1.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 164.6, 136.8, 134.2, 134.2, 129.6, 128.5, 127.8, 20.2, 14.7, 12.8; HRMS (ESI, M+Na) calculated for $C_{13}H_{15}NO_2Na$ m/z 240.0995, found m/z 240.0993.

Compound **45** was resubjected to the above conditions. The acetic anhydride was freshly distilled over phosphorus pentoxide, some acetic anhydride was added to the acetic acid and it was distilled, and freshly prepared Rieke iron was used. The reaction was worked up after two hours, and FCC (40 %, 50 % ethyl acetate in hexanes) provided the desired enamide (**46**) as a white solid, 310 mg, 45 %; m.p. 97-100ºC; IR (neat) 3231, 3140, 3026, 2923, 2822, 1659, 1613, 1546, 1446 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H), 6.69 (br s, 1H), 6.61 (br s, 1H), 5.66 (br s, 1H), 5.21 (br s, 1H), 2.16 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 141.9, 137.4, 134.6, 129.4, 128.5, 127.2, 127.0, 106.0, 30.0, 15.9; HRMS (EI, M+Na) calculated for $C_{13}H_{15}NONa$ m/z 224.1046, found m/z 224.1041.

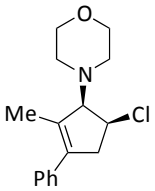


1-acetamido-2,2-dichloro-3-(1-phenyl-[1*E*]-propen-2-yl)cyclopropane (25i). Enamide **46** was subjected to the standard cyclopropanation conditions (15 min.) and FCC (40 % ethyl acetate in hexanes) to provide **25i** as a tan solid, 184 mg, 49 %; m.p. (decomposed) 142 ºC; IR (neat film) 3241, 3200, 3038, 2860, 1661, 1549, 1447 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.27-7.24 (m, 2H), 7.23-7.18 (m, 1H), 6.67 (s, 1H), 6.35 (br s, 1H), 2.38 (d, *J* = 8.8 Hz, 1H), 2.01 (d, *J* = 1.1 Hz, 3H), 2.00 (s, 3H), 1.93 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 136.9, 132.5, 131.8, 129.3, 128.4, 127.2, 64.5, 49.2, 33.0, 23.8, 16.2; HRMS (ESI, M+H) calculated for $C_{14}H_{16}Cl_2NO$ m/z 284.0603; found m/z 284.0602.

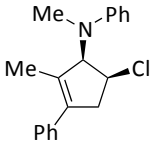


***cis*-3-(*N*-benzyl-*N*-methylamino)-4-chloro-1-phenyl-2-methylcyclopentene (47b).** Cyclopropane **25b** (60 mg, 0.17 mmol) was dissolved in 3.5 mL acetonitrile. Silver triflimide (66 mg, 0.17 mmol) was added, and the solution was heated to reflux for 5h, during which the solution became a raspberry red and white precipitate was formed. The mixture was allowed to cool to room temperature, and then filtered through a pad of Celite and concentrated to a dark oil. The oil was dissolved in 2 mL methanol, taking no precaution to exclude the ambient atmosphere, and sodium borohydride (13 mg, 0.34 mmol) was added in one portion. The reaction bubbled vigorously, and some black precipitate was formed. After 5 minutes, the reaction mixture was poured into water, and 2M sodium hydroxide (~ 0.2 mL) was added to ensure the solution was basic. The mixture was extracted three times with dichloromethane. The combined extract was washed with water then brine, dried over magnesium sulfate, filtered, and

concentrated. FCC (10 % dichloromethane, 1 % ethyl acetate, 0.5 % triethylamine in hexanes) provided the product as a colourless resin, 28.4 mg, 53 % (54 % BORSM) and 2.0 mg recovered starting material, 3 %. IR (neat) 3060, 2933, 2854, 1600, 1494, 1451 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.22 (m, 10H), 4.73-4.67 (m, 1H), 4.15 (s, 2H), 3.94 (d, *J* = 7.3 Hz, 1H), 3.16-3.03 (m, 2H), 2.53 (s, 3H), 1.97-1.94 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2, 137.1, 136.0, 134.9, 128.48, 128.47, 128.43, 128.0, 127.3, 126.9, 75.1, 60.4, 58.7, 46.3, 37.4, 14.6; HRMS (ESI, M+H) calculated for $C_{20}H_{23}NCl$ m/z 312.1514; found m/z 312.1507.

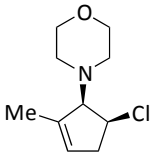


***cis*-4-chloro-1-phenyl-2-methyl-3-morpholinocyclopentene (47a).** Cyclopropane **25a** (100 mg, 0.320 mmol) was subjected to Nazarov conditions (8.5 h, see **47b**) followed by reduction and FCC (10 % dichloromethane, 5 % ethyl acetate, 0.5 % triethylamine in hexanes) to provide the product as a thick colourless oil that quickly darkened to a brown oil on standing, 47.1 mg, 53 % (57 % BORSM), and 7.3 mg recovered starting material. IR (neat) 3055, 2952, 2852, 1600, 1495, 1446, 1115; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.33 (m, 2H), 7.31-7.25 (m, 2H), 4.64-4.58 (m, 1H), 3.72-3.58 (m, 5H), 3.12-3.01 (m, 3H), 3.01-2.89 (m, 3H), 1.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 136.7, 134.1, 128.5, 127.9, 127.5, 75.8, 68.3, 59.4, 49.8, 46.2, 14.9; HRMS (ESI, M+H) calculated for $C_{16}H_{21}NOCl$ m/z 278.1306; found m/z 278.1302.

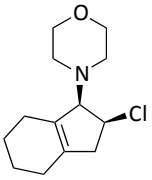


***cis*-4-chloro-1-phenyl-2-methyl-3-(*N*-methyl-*N*-phenylamino)cyclopentene (47c).** Cyclopropane **25c** (100 mg, 0.301 mmol) was subjected to Nazarov

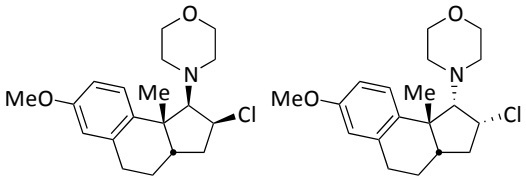
conditions (7.5 h, see **47b**) followed by reduction and FCC (15 % dichloromethane in hexanes) to provide the product as a pale yellow solid, 45.4 mg, 50 %; m.p. 69-71 ºC; IR (chloroform cast film) 3057, 2926, 2854, 1597, 1504, 1444 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 -7.24 (m, 7H), 6.90-6.86 (m, 2H), 6.75 (app dt, *J* = 7.3, 0.9 Hz, 1H), 4.98 (d, *J* = 7.5 Hz, 1H), 4.85 (ddd, *J* = 8.0, 7.5, 6.5 Hz, 1H), 3.31 (ddq, *J* = 16.5, 8.0, 1.9 Hz, 1H), 3.16-3.07 (m, 1H), 2.91 (s, 3H), 1.85-1.83 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 136.8, 136.7, 133.4, 129.3, 128.6, 127.9, 127.7, 117.0, 112.9, 70.6, 58.4, 46.7, 33.7, 14.5; HRMS (ESI, M+H) calculated for $C_{19}H_{21}NCl$ m/z 298.1357; found m/z 298.1351.



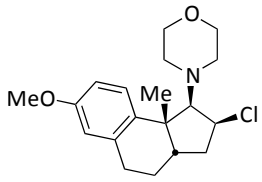
***cis*-4-chloro-2-methyl-3-morpholinocyclopentene (47d).** Cyclopropane **25d** (70.1 mg, 0.297 mmol) was subjected to Nazarov conditions (2 h, see **47b**) followed by reduction and FCC (10 % dichloromethane, 5 % ethyl acetate, 0.5 % triethylamine in hexanes) to provide the product as a colourless oil which darkened to brown, 13.9 mg, 23 % (29 % BORSM) and 16.4 mg recovered starting material, 23 %; IR (chloroform cast film) 2953, 2852, 1584, 1116 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 (br s, 1H), 4.46-4.50 (m, 1H), 3.70-3.61 (m, 4H), 3.49 (d, *J* = 7.1 Hz, 1H), 3.01-2.94 (m, 2H), 2.87-2.81 (m, 2H), 2.72 (dddq, *J* = 16.3, 8.2, 3.5, 1.7 Hz, 1H), 2.46 (dddq, *J* = 16.2, 8.1, 4.6, 2.6 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 126.4, 73.2, 68.1, 60.3, 49.7, 42.3, 16.6; HRMS (ESI, M+H) calculated for $C_{10}H_{17}NOCl$ m/z 202.0993; found m/z 202.0989.



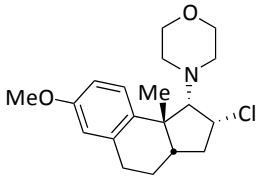
$\Delta^{1,6}$-8-chloro-7-mopholinobicyclo[4.3.0]nonene (47e). Cyclopropane **25e** (25.9 mg, 0.0938 mmol) was subjected to Nazarov conditions (10 min., see **47b**) followed by reduction and FCC (10 % dichloromethane, 5 % ethyl acetate, 0.5 % triethylamine in hexanes) to provide the product as a colourless oil which darkened to brown, 3.3 mg, 14 % (16 % BORSM) and 3.2 mg recovered starting material, 12 %. IR ($CDCl_3$ cast film) 2927, 2853, 1448, 1116 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.50-4.45 (m, 1H), 3.69-3.61 (m, 4H), 3.48 (d, *J* = 7.4 Hz, 1H), 2.89-2.84 (m, 2H), 2.81-2.76 (m, 2H), 2.61 (dd, *J* = 15.9, 8.2 Hz, 1H), 2.50-2.43 (m, 1H), 2.15-1.88 (m, 4H), 1.72-1.51 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2, 133.8, 73.4, 68.1, 59.6, 50.0, 45.7, 25.9, 25.8, 23.1 (one of the aliphatic cyclohexenyl carbons is missing due to incidental overlap); HRMS (ESI, M+H) calculated for $C_{13}H_{21}ClNO$ m/z 242.1306; found m/z 242.1302.



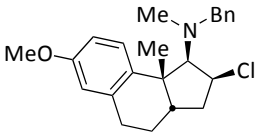
2-chloro-7-methoxy-9b-methyl-1-morpholino-2,3,3a,4,5,9b-hexahydro-cyclopenta[a]naphthalenes (59a) and (59a′). Cyclopropane **25f** (50.1 mg, 0.135 mmol) was subjected to Nazarov conditions (2 h, see **47b**) followed by reduction and FCC (10 % ethyl acetate, 0.5 % triethylamine in hexanes). The first compound to elute was **59a**, 4.9 mg white solid, 25 % followed by **59a′**, 6.9 mg white solid that quickly turned pale pink, 35 %.



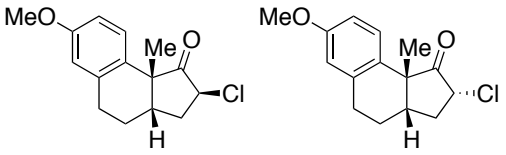
59a: mp 108-110 ºC; IR (dichloromethane cast film) 3001, 2964, 2857, 1609, 1499, 1470, 1139 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.7 Hz, 1H), 6.74 (dd, *J* = 8.7 , 2.8 Hz, 1H), 6.55 (d, *J* = 2.8 Hz, 1H), 4.26-4.21 (m, 1H), 3.80-3.66 (m, 7H), 3.21 – 3.16 (m, 2H), 3.02 (d, *J* = 5.2 Hz, 1H), 2.99-2.93 (m, 2H), 2.79-7.71 (m, 1H), 2.60-2.54 (m, 2H), 2.17 (ddd, *J* = 13.9, 10.1, 7.2 Hz, 1H), 2.12-2.05 (m, 1H), 1.88-1.80 (m, 1H), 1.69 (ddd, *J* = 13.3, 7.9, 3.8 Hz, 1H), 1.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 137.8, 137.6, 128.9, 113.1, 113.0, 79.6, 68.3, 61.1, 55.4, 52.9, 47.5, 42.8, 39.1, 27.8, 25.8, 24.3; HRMS (ESI, M+H) calculated for $C_{19}H_{27}NO_2Cl$ m/z 336.1725; found m/z 336.1719.



59a′: mp 84-90 ºC; IR (dichloromethane cast film) 3001, 2958, 2855, 2805, 1609, 1572, 1499, 1462, 1169 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.7 Hz, 1H), 6.75 (dd, *J* = 8.7, 2.9 Hz, 1H), 4.51 (td, *J* = 7.2, 5.6, Hz, 1H), 3.78 (s, 3H), 3.58-3.52 (m, 2H), 3.44-3.38 (m, 2H), 2.93 (d, *J* = 5.6 Hz, 1H), 2.87-2.78 (m, 5H), 2.60 (dt, *J* = 16.1, 5.1 Hz, 1H), 2.43 (ddd, *J* = 13.6, 8.5, 7.2 Hz, 1H), 2.07-1.91 (m, 3H), 1.68-1.62 (m, 1H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 138.4, 133.4, 132.4, 112.5, 111.6, 79.1, 67.4, 61.4, 55.3, 52.5, 46.5, 44.2, 39.8, 36.3, 27.2, 24.8; HRMS (ESI, M+H) calculated for $C_{19}H_{27}NO_2Cl$ m/z 336.1725; found m/z 336.1726.

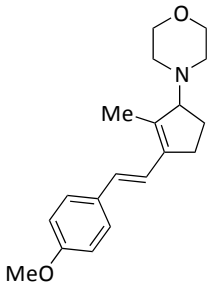


1-(*N*-benzyl-*N*-methylamino)-2-chloro-7-methoxy-9b-methyl-2,3,3a,4,5,9b-hexahydro-cyclopenta[a]naphthalene (59b). Cyclopropane **25g** (35.4 mg, 0.0875 mmol) was subjected to Nazarov conditions (2h, see **47b**) followed by reduction and FCC (10 % DCM, 5 % toluene, 0.5 % triethylamine in hexanes on neutral alumina). The major isomer (**59b′**) could not be recovered. Compound **59b** was provided as a colourless film, 10.5 mg, 32 %; IR (neat) 3026, 2925, 2855, 1736, 1608, 1584, 1498, 1453 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.43 (m, 2H), 7.37-7.33 (m, 2H), 7.29-7.25 (m, 1H), 7.00 (d, *J* = 8.7 Hz, 1H), 6.66 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.51 (d, *J* = 2.7 Hz, 1H), 4.23-4.14 (m, 3H), 3.75 (s, 3H), 3.37 (d, *J* = 5.8 Hz, 1H), 2.84-2.75 (m, 1H), 2.70 (s, 3H), 2.66-2.60 (m, 1H), 2.59-2.53 (m, 1H), 2.38-2.29 (m, 1H), 2.20-2.13 (m, 1H), 1.87-1.80 (m, 1H), 1.75-1.68 (m, 1H), 1.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 141.3, 137.8, 137.6, 129.1, 128.8, 128.5, 127.0, 113.2, 112.9, 62.4, 61.6, 55.4, 48.9, 43.0, 39.4, 39.3, 27.8, 25.4, 24.0 (one aliphatic carbon is missing due to incidental overlap); HRMS (EI, M^+) calculated for $C_{23}H_{29}NOCl$ m/z 369.1859, found m/z 369.1856.



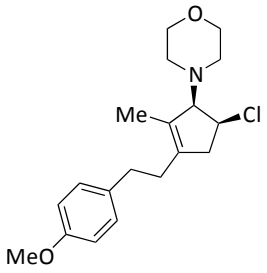
2-chloro-7-methoxy-9b-methyl-2,3,3a,4,5,9b-hexahydro-cyclopenta[a]naphthalen-1-ones (65) and (*epi*-65). Cyclopropane **25b** (20 mg, 0.049 mmol) was subjected to Nazarov conditions (2h, see **47b**), and then 1 mL acetonitrile and 1 mL water was added. The solution was allowed to stand overnight, then it was transferred to a separatory funnel and water was added. The solution was extracted three times with dichloromethane. The combined

extract was washed with water then brine, dried over magnesium sulfate, filtered, and concentrated to a brown film. FCC (10 % DCM, 2 % ethyl acetate in hexanes) provided the products, 10 mg, 76 % in a 1.2 : 1 ratio. Data for **65** is consistent with that reported for the same compound in Chapter 2. Data for *epi*-**65** is consistent with that previously reported.[6e]



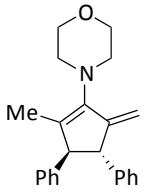
1-(4-methoxycinnamyl)-2-methyl-3-morpholinocyclopentene (66).

Cyclopropane **25h** (30.0 mg, 0.0810 mmol) was subjected to Nazarov conditions (2h, see **47b**) followed by reduction and FCC (10 % acetone, 1 % triethylamine in hexanes) provided **66** as a white solid, 8.2 mg, 33 %; m.p. 93-95 ºC; IR (chloroform cast film) 3030, 2849, 2811, 1604, 1511, 1453, 1247 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.35 (m, 2H), 6.97 (d, *J* = 16.0 Hz, 1H), 6.88-6.84 (m, 2H), 6.42 (d, *J* = 16.0 Hz, 1H), 3.83-3.77 (m, 4H), 3.73-3.64 (m, 4H), 2.58-2.45 (m, 2H), 2.45-2.40 (m, 4H), 2.00-1.93 (m, 1H), 1.85 (s, 3H), 1.79-1.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 137.4, 136.9, 131.0, 128.9, 127.7, 121.5, 114.3, 75.4, 67.8, 55.6, 48.8, 31.6, 19.8, 12.7; HRMS (ESI, M+H) calculated for $C_{19}H_{26}NO_2$ m/z 300.1958; found m/z 300.1954.



4-chloro-1-(1-(4-methoxyphenyl)eth-2-yl)-2-methyl-3-morpholinocyclopentene (**47h**). Cyclopropane **25h** (50.2 mg, 0.135 mmol) was

dissolved in 2.7 mL acetonitrile. Silver triflimide (105 mg, 0.27 mmol) was added, and the solution was heated to reflux for 2h. The reaction mixture became deep reddish brown with white precipitate. The mixture was cooled to room temperature, filtered through a pad of Celite and concentrated. The reduction step was performed under ambient atmosphere. The crude iminium was immediately dissolved in 1.5 mL methanol, and sodium borohydride (10 mg, 0.27 mmol) was added in a single portion. The mixture was stirred for 5 min., and then transferred to a separatory funnel containing water. Some 2 M NaOH was added, and the solution was extracted three times with dichloromethane. The combined extract was washed with water then brine, dried over magnesium sulfate and concentrated. FCC (10 % ethyl acetate, 1 % triethylamine in hexanes) provided an inseparable mixture of **47h** and remaining **25h**, 11.3 mg in a 2.4 : 1 ratio, corresponding to 17 % **47h** (18 % BORSM). The data reported is for the mixture. IR ($CHCl_3$ cast film) 2950, 2851, 1611, 1512, 1451 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.09-7.05 (m, 2H), 6.82-6.78 (m, 2H), 4.44-4.38 (m, 1H), 3.77 (s, 3H), 3.43 (br d, *J* = 7.3 Hz, 1H), 3.60-3.48 (m, 4H), 2.77-2.44 (m, 9H), 2.33-2.22 (m, 1H), 1.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 134.1, 134.0, 133.5, 129.5, 113.9, 74.9, 68.2, 59.6, 55.5, 49.5, 45.1, 33.0, 30.1, 13.3; HRMS (ESI, M+H) calculated for $C_{19}H_{27}ClNO_2$ m/z 336.1725; found m/z 336.1718.



***trans*-1-methyl-3-methylidene-2-morpholino-4,5-diphenylcyclopentene (81).** Toluene (15 mL), triethylamine (0.26 mL, 1.9 mmol) and morpholine (66 μL, 0.76 mmol) were combined and cooled in an ice bath. Titanium(IV) chloride (0.080 mL, 0.76 mmol) in 1 mL toluene was added, followed by (*E*,*E*)-2,4-dimethyl-1,5-diphenyl-1,4-pentadien-3-one (**80**, 200 mg, 0.762 mmol). The resulting mixture was immediately transferred to a pre-heated oil bath, and heated

at reflux for 2 hours. The resulting mixture was cooled to room temperature, filtered through Celite and concentrated. Hexanes was added and a second filtration was done, followed by concentration to provide the crude product. The presence of **81** was implied by the following data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.08 (m, 10 H), 5.09 (s, 1H), 4.55 (s, 1H), 3.80 (app t, *J* = 4.6 Hz, 4H), 3.65-3.63 (m, 1H), 3.55 (br s, 1H), 3.27-3.22 (m, 2H), 3.21-3.16 (m, 2H), 1.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 146.7, 145.6, 144.5, 135.0, 128.8, 128.7, 127.78, 127.76, 126.8, 126.5, 102.8, 68.3, 62.7, 57.4, 51.0, 14.4; HRMS (EI, M^+) calculated for $C_{23}H_{25}NO$ m/z 331.1936, found m/z 331.1942.

4.6 References

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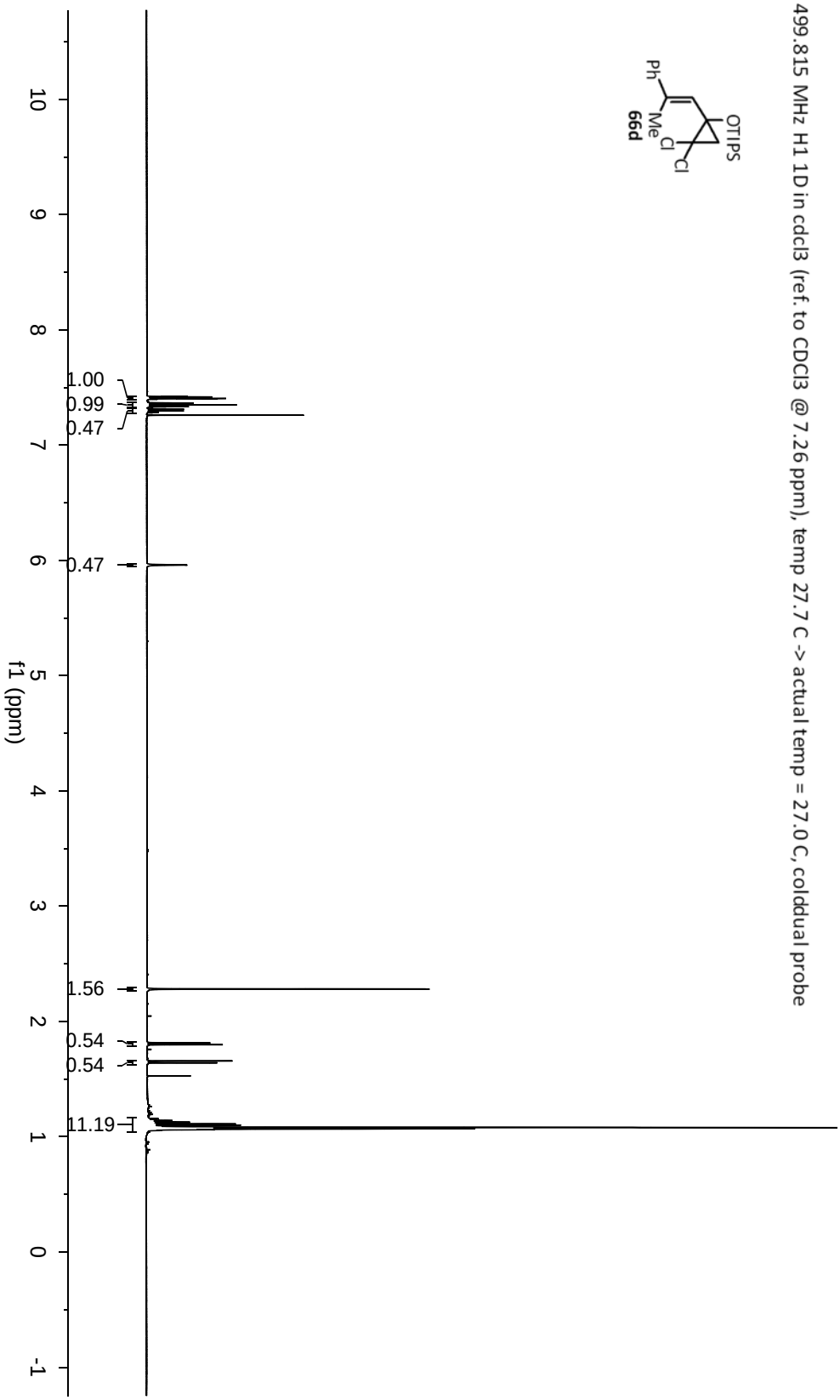
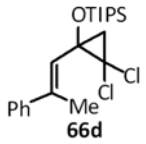
Appendix I: Selected NMR Spectra

(Chapter 2)

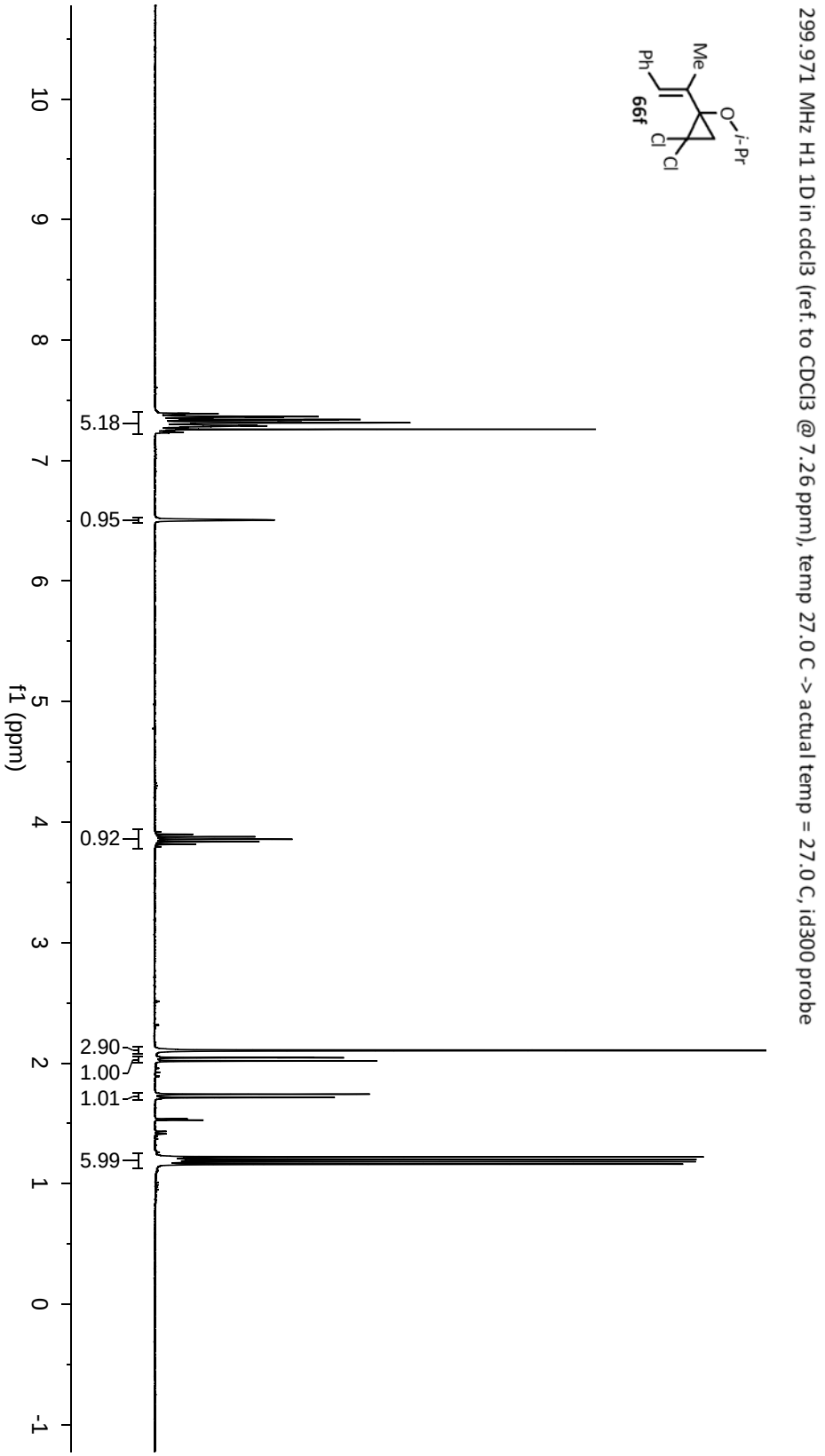

499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
OTIPS
Ph
Me
Cl
Cl
66d
1.00
0.99
0.47
0.47
1.56
0.54
0.54
11.19
f1 (ppm)
10
9
8
7
6
5
4
3
2
1
0
-1

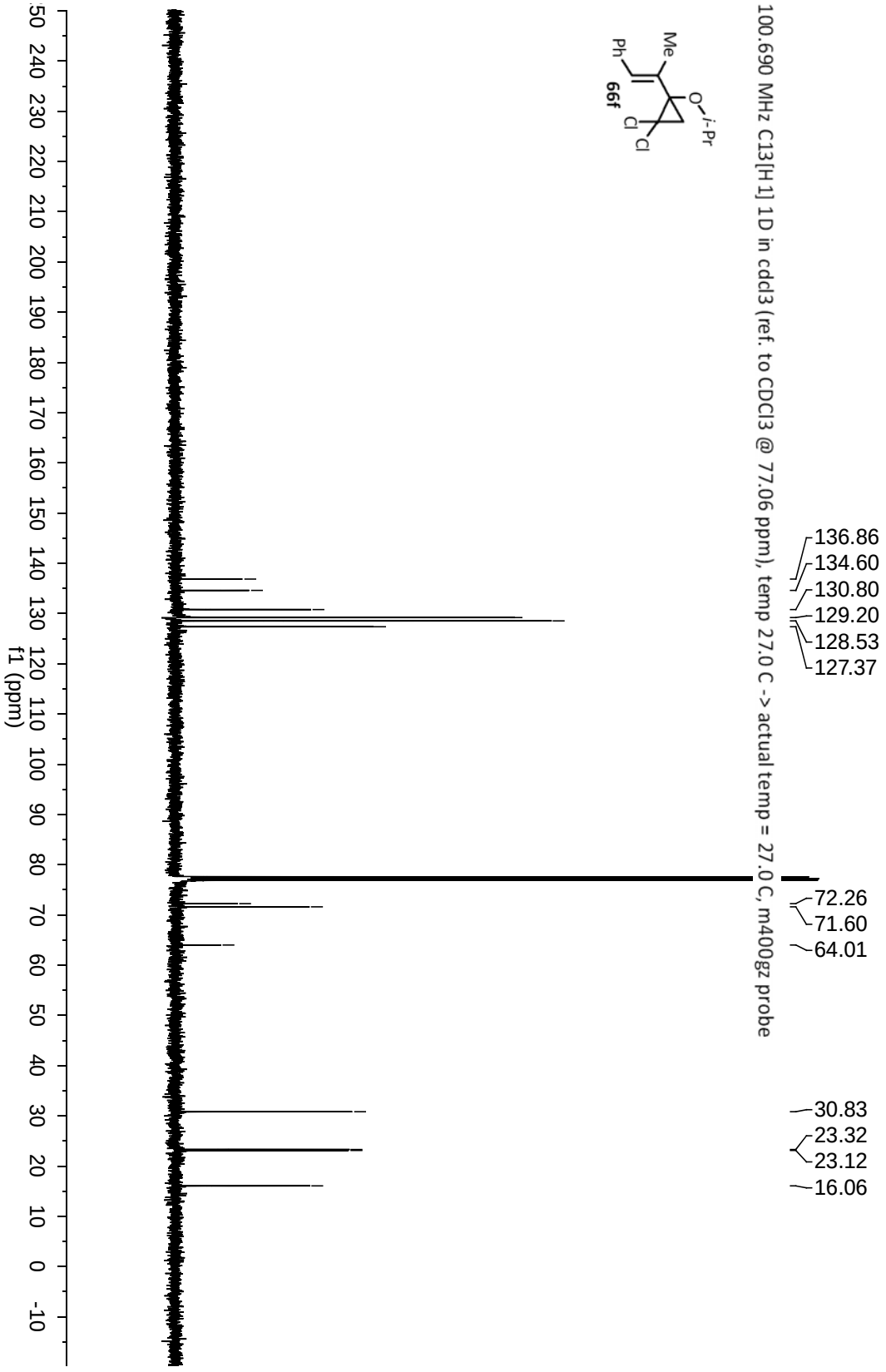
145.41
142.32
128.63
128.05
126.04
125.07
66.21
61.40
35.55
18.42
18.26
18.23
18.20
13.11

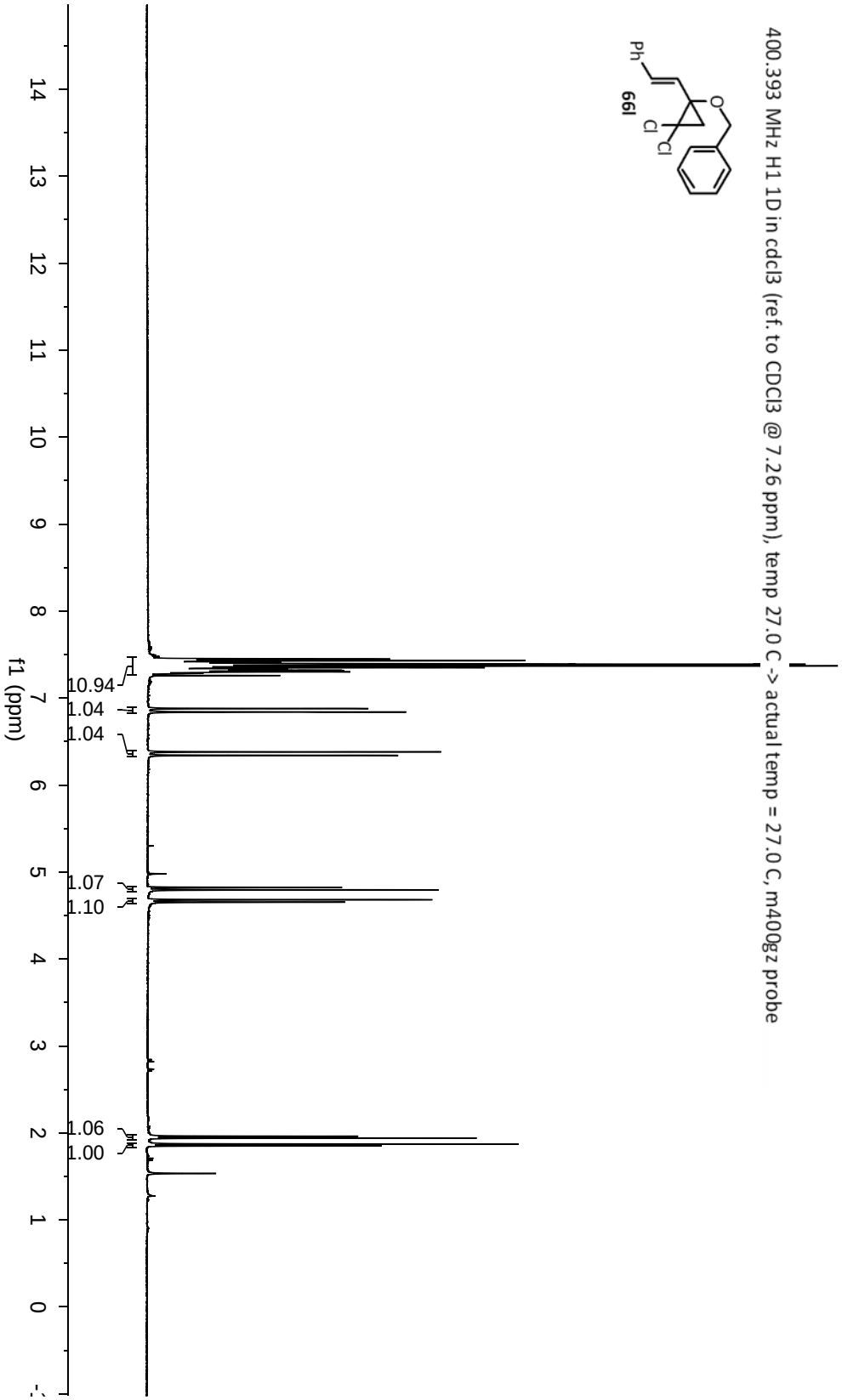
125.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

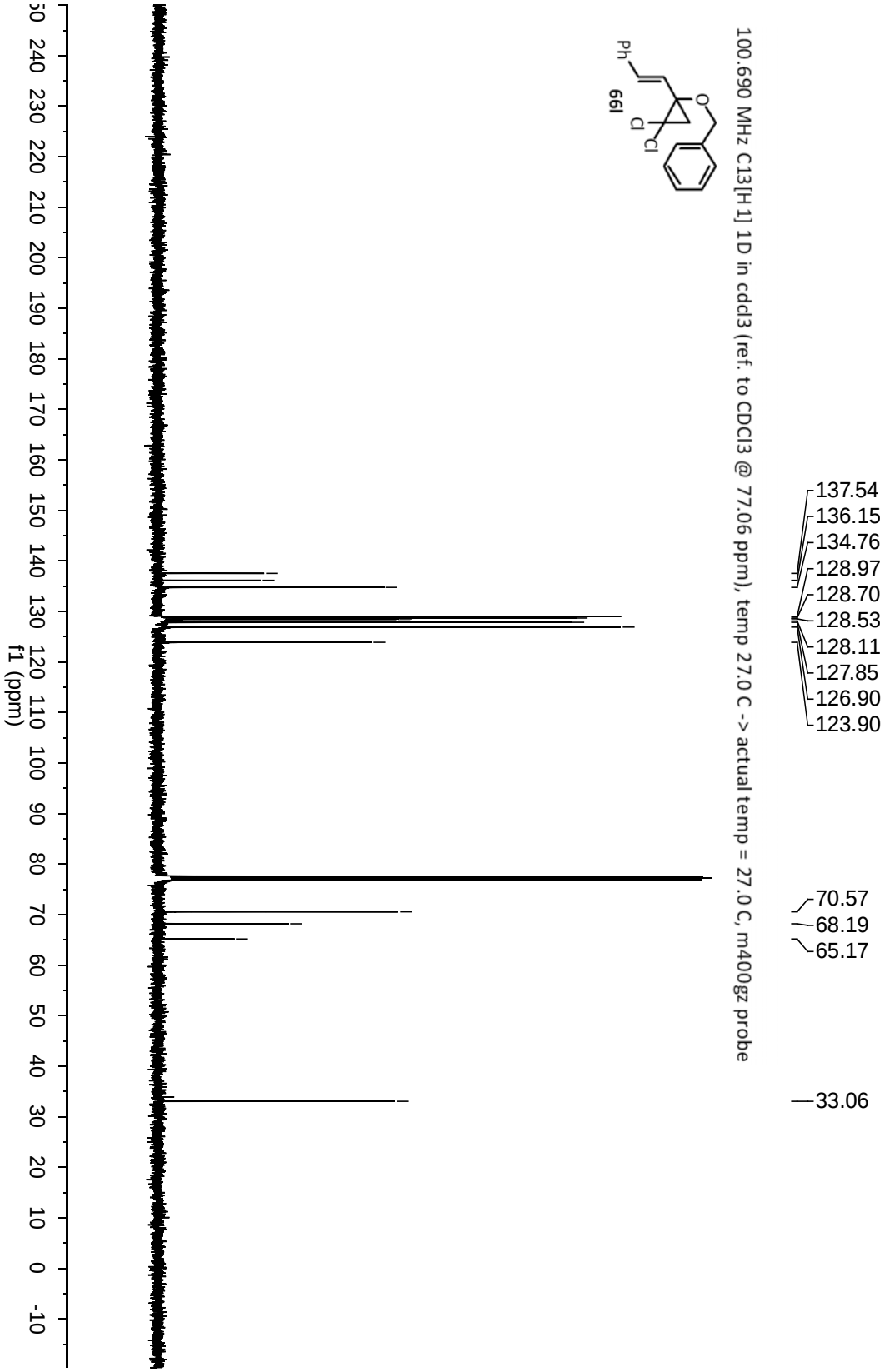


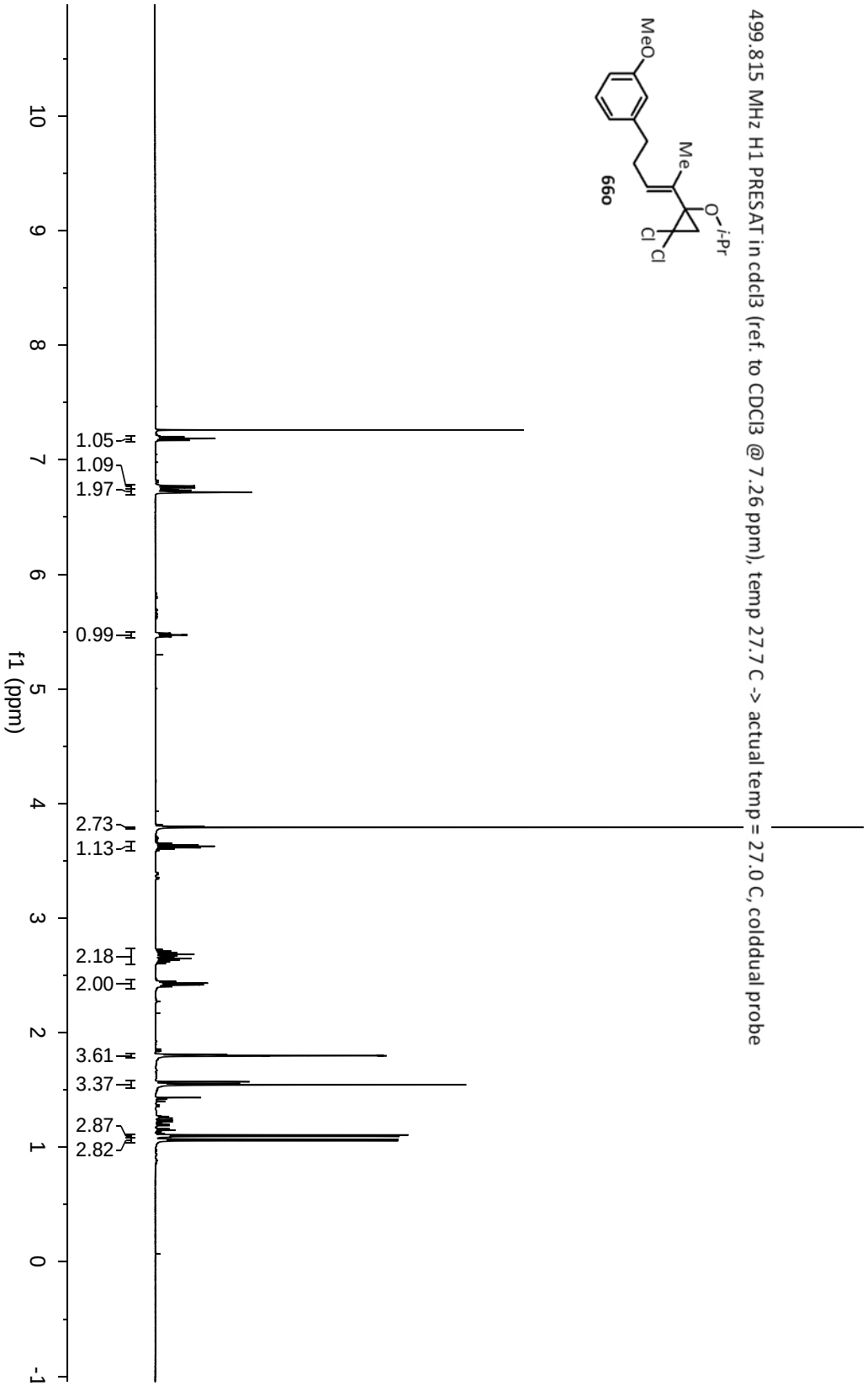
66d


299.971 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, id300 probe
Ph
Me
O
i-Pr
Cl
Cl
66f
5.18
0.95
0.92
2.90
1.00
1.01
5.99
f1 (ppm)
10
9
8
7
6
5
4
3
2
1
0
-1


100.690 MHz C13[H1] 1D in cdd3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Me
O
i-Pr
Ph
66f
Cl
Cl
136.86
134.60
130.80
129.20
128.53
127.37
72.26
71.60
64.01
30.83
23.32
23.12
16.06
f1 (ppm)

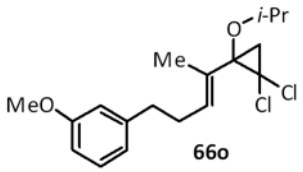

400.393 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
66l
Ph
Cl
Cl
O
f1 (ppm)
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
10.94
1.04
1.04
1.07
1.10
1.06
1.00


100.690 MHz C13[H1] 1D in cdd3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Ph
O
Cl
Cl
66l
137.54
136.15
134.76
128.97
128.70
128.53
128.11
127.85
126.90
123.90
70.57
68.19
65.17
33.06
f1 (ppm)
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

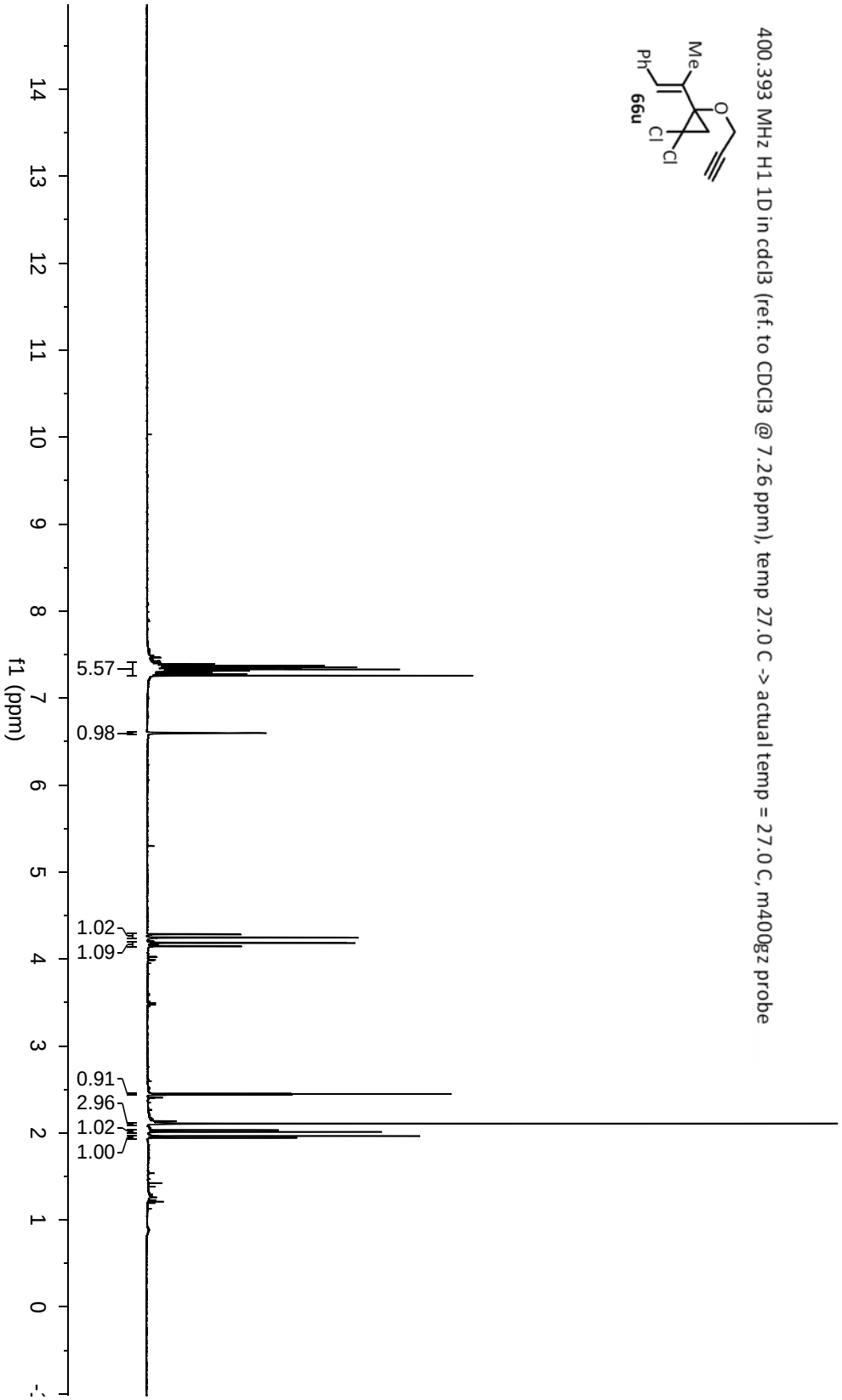

499.815 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
MeO
Me
O
i-Pr
Cl Cl
66o
f1 (ppm)
10
9
8
7
6
5
4
3
2
1
0
-1
1.05
1.09
1.97
0.99
2.73
1.13
2.18
2.00
3.61
3.37
2.87
2.82

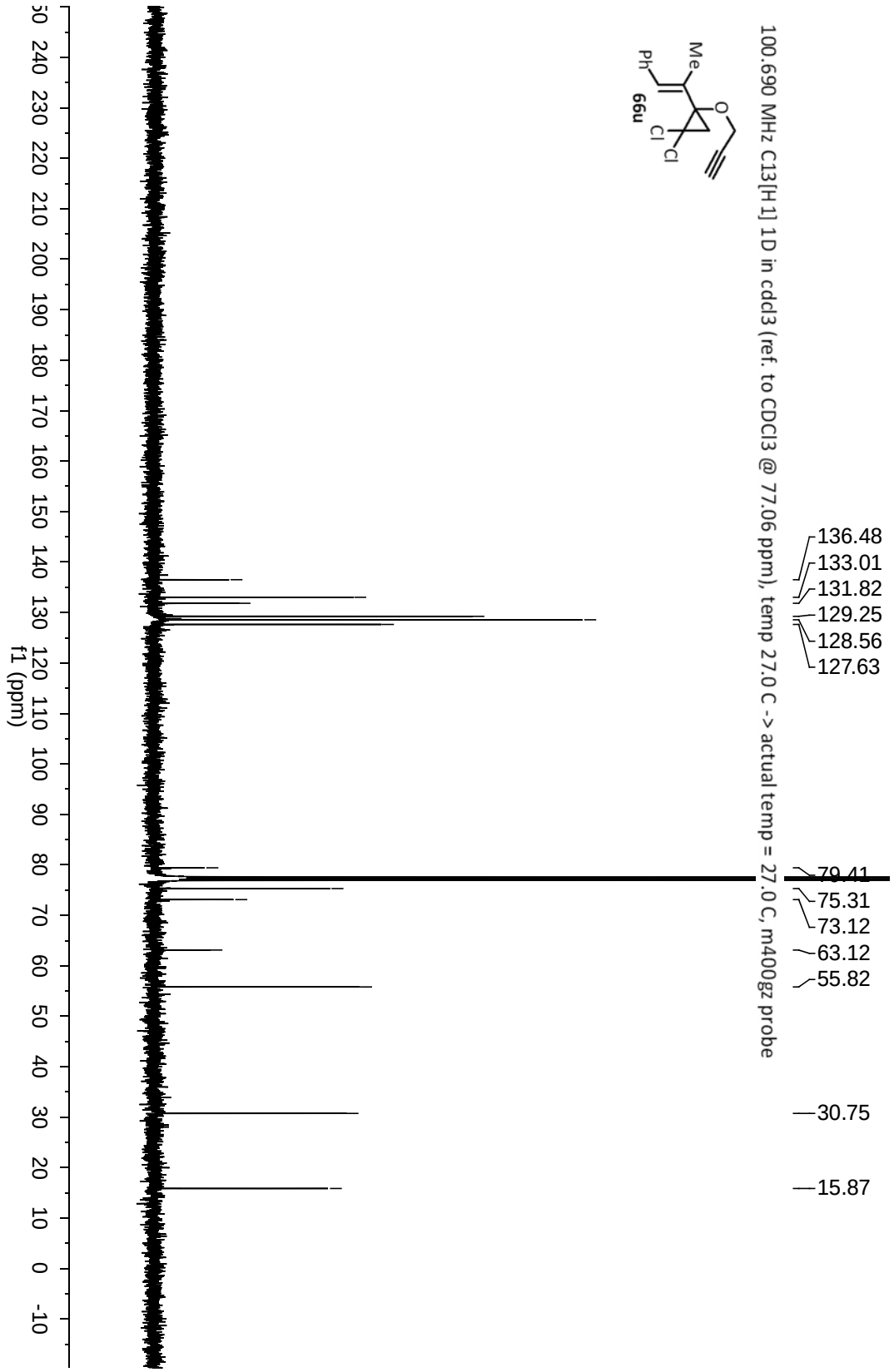
159.89
143.40
132.30
131.01
129.54
121.06
114.59
111.31
71.58
71.01
63.77
55.39
35.54
30.58
29.46
23.26
22.90
14.21

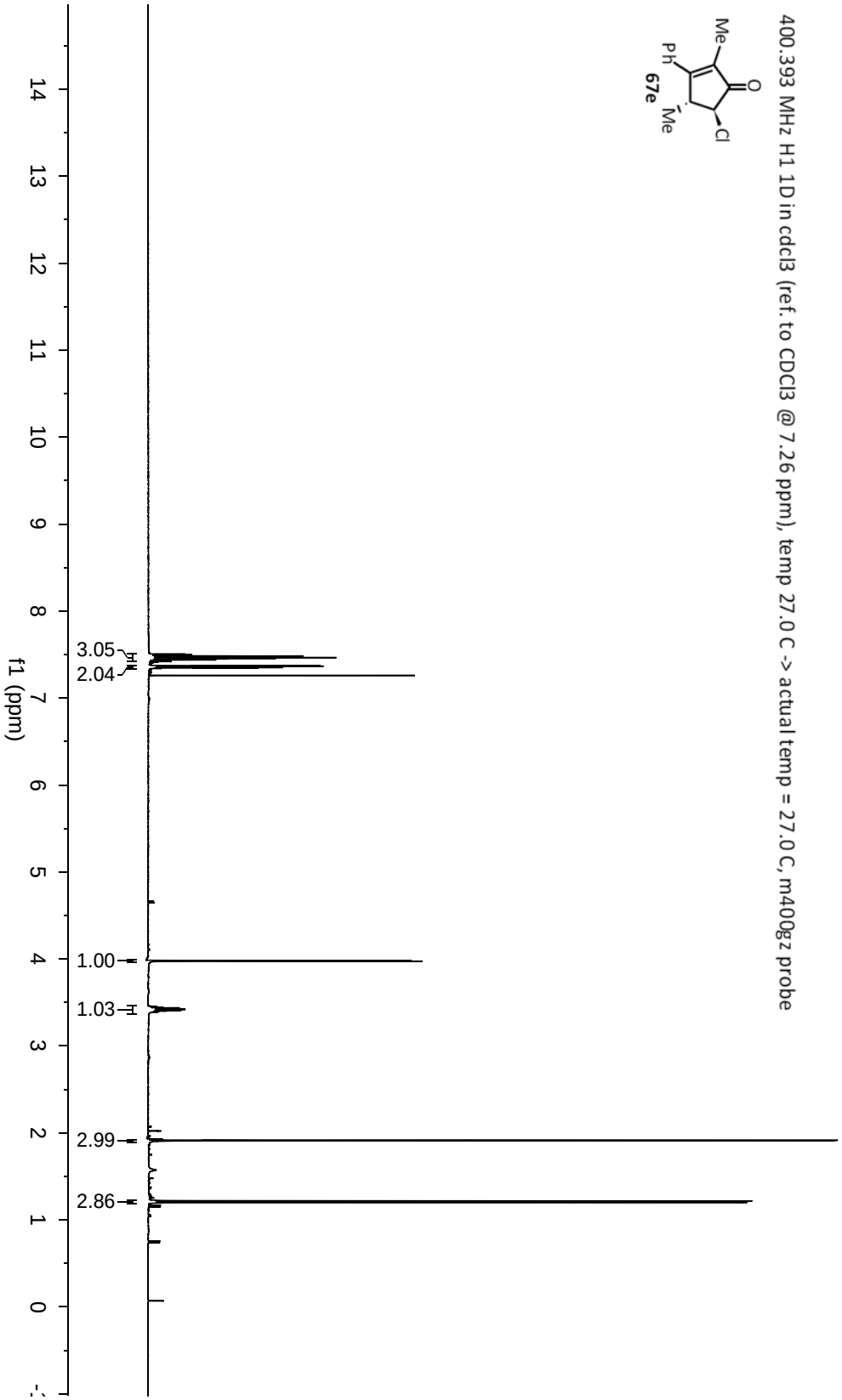
125.693 MHz C13[H 1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

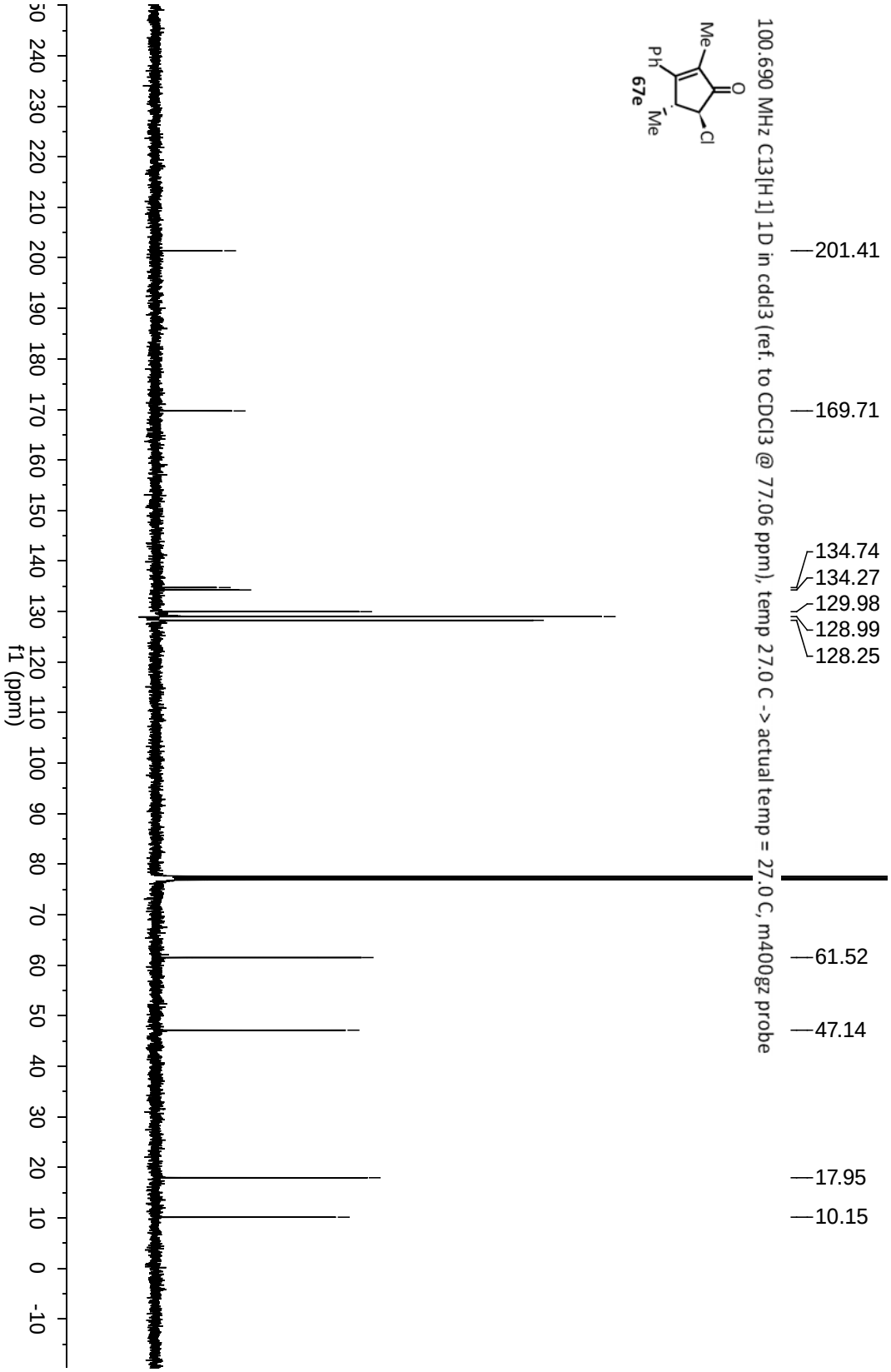


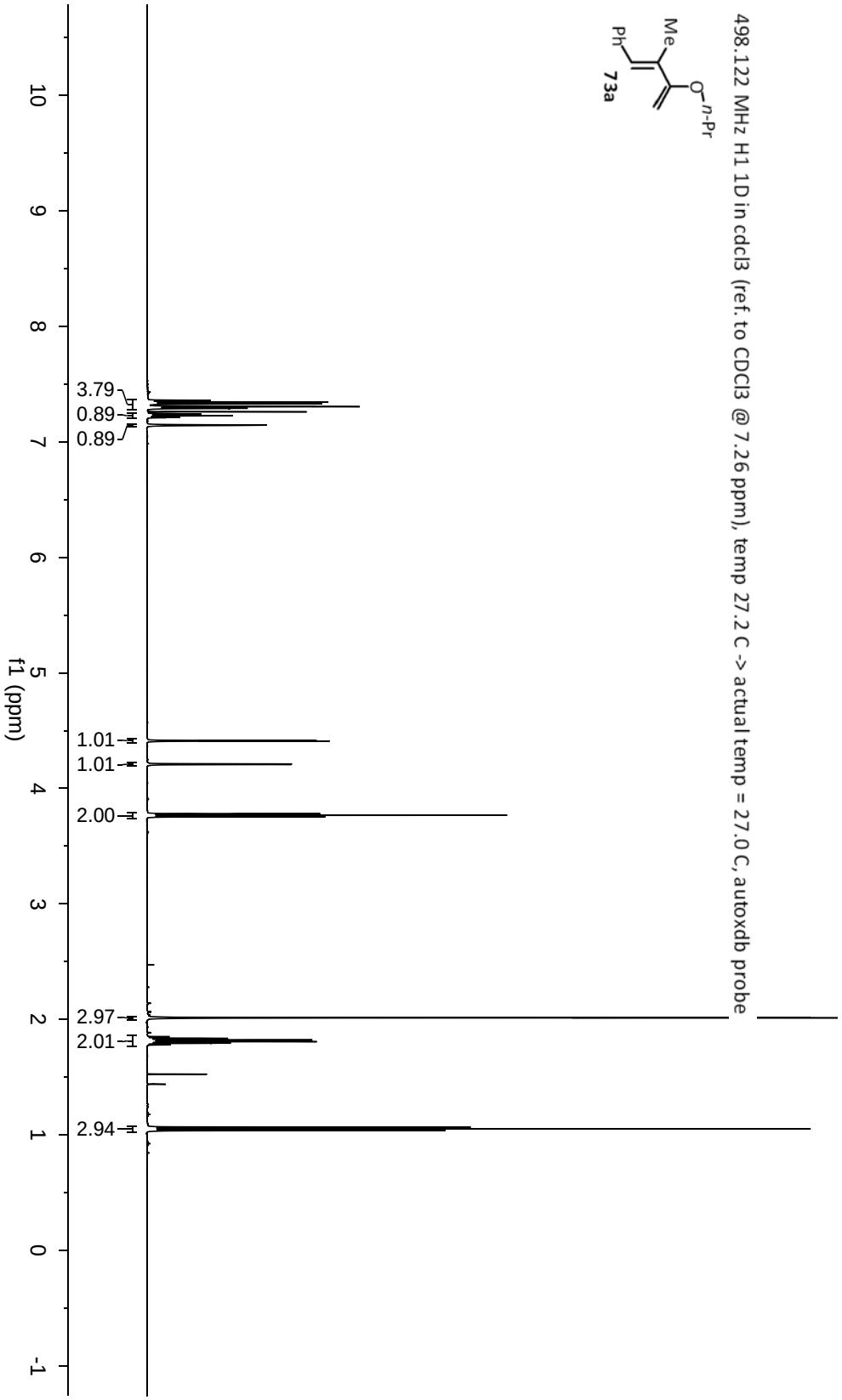
66o


400.393 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
66u
Me
Ph
O
Cl
Cl
f1 (ppm)
5.57
0.98
1.02
1.09
0.91
2.96
1.02
1.00


100.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Me
Ph
66u
Cl
Cl
O
136.48
133.01
131.82
129.25
128.56
127.63
79.41
75.31
73.12
63.12
55.82
30.75
15.87
f1 (ppm)
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

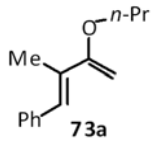

400.393 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Me
Ph
Me
Cl
O
67e
f1 (ppm)
3.05
2.04
1.00
1.03
2.99
2.86


Me
Ph
O
Cl
Me
67e
100.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
201.41
169.71
134.74
134.27
129.98
128.99
128.25
61.52
47.14
17.95
10.15
f1 (ppm)
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

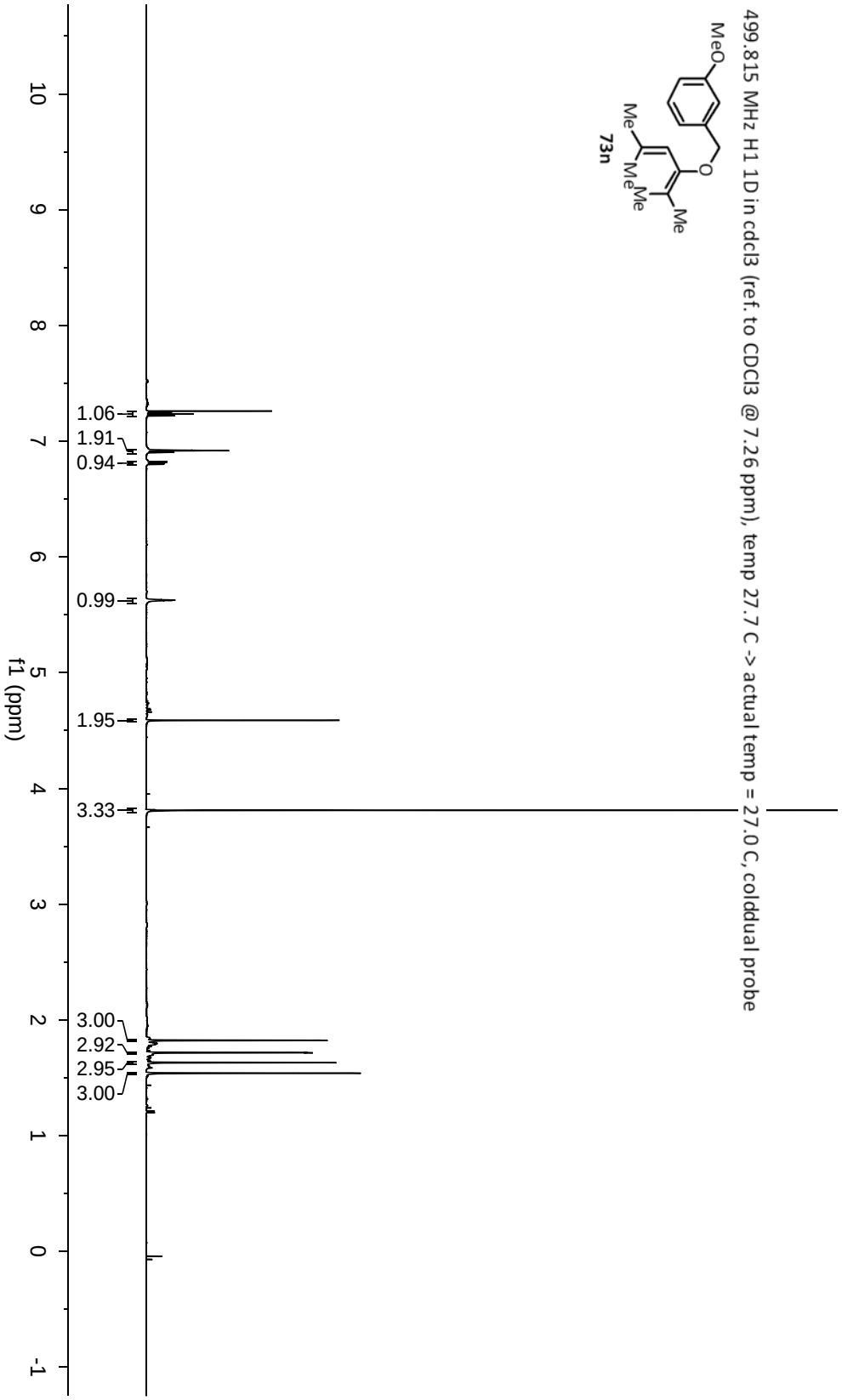

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe
Ph
Me
O
n-Pr
73a
3.79
0.89
0.89
1.01
1.01
2.00
2.97
2.01
2.94
f1 (ppm)
10
9
8
7
6
5
4
3
2
1
0
-1

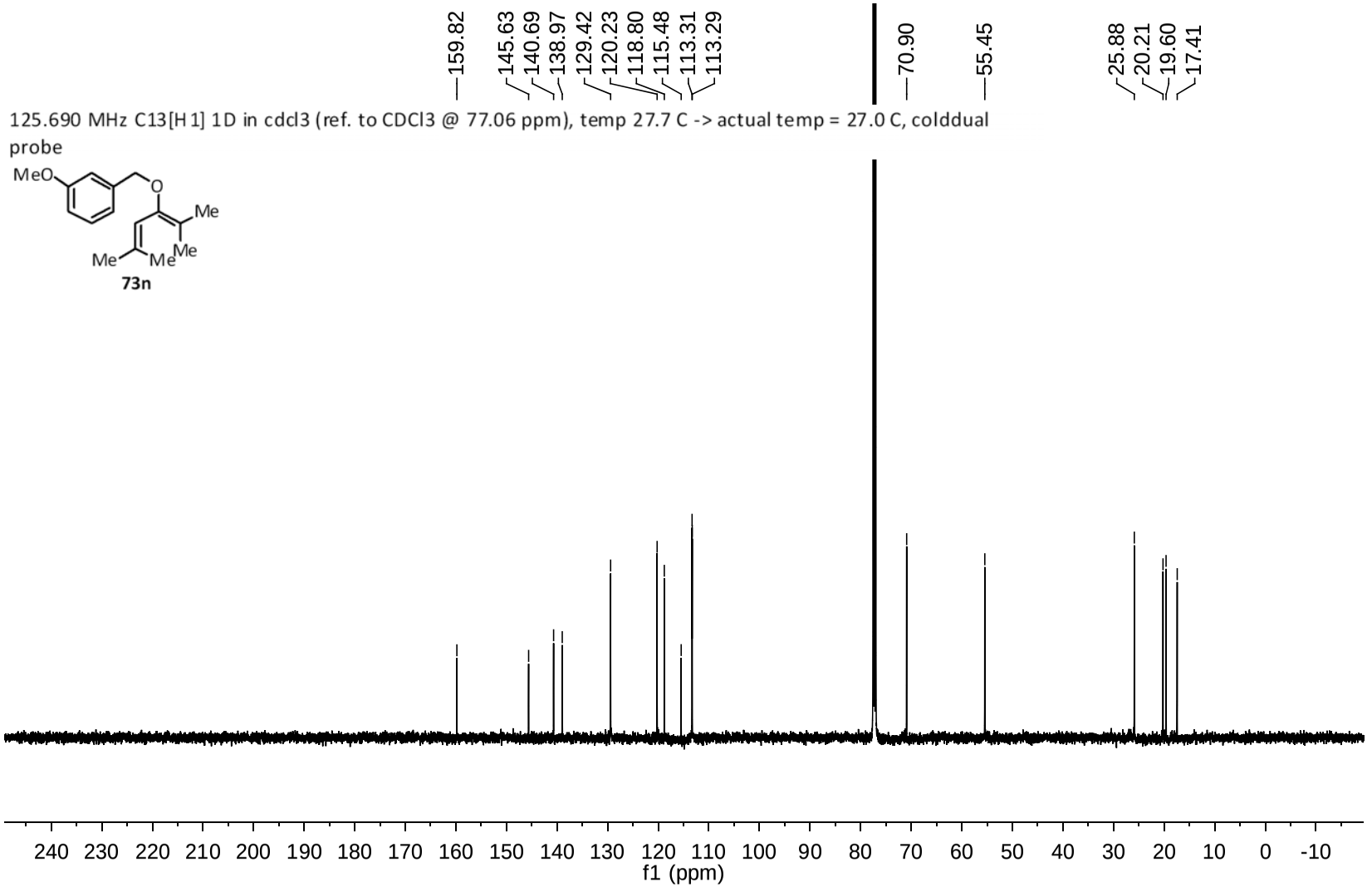
125.267 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

C & CH2 same, CH & CH3 opposite side of solvent signal

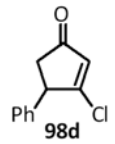


73a

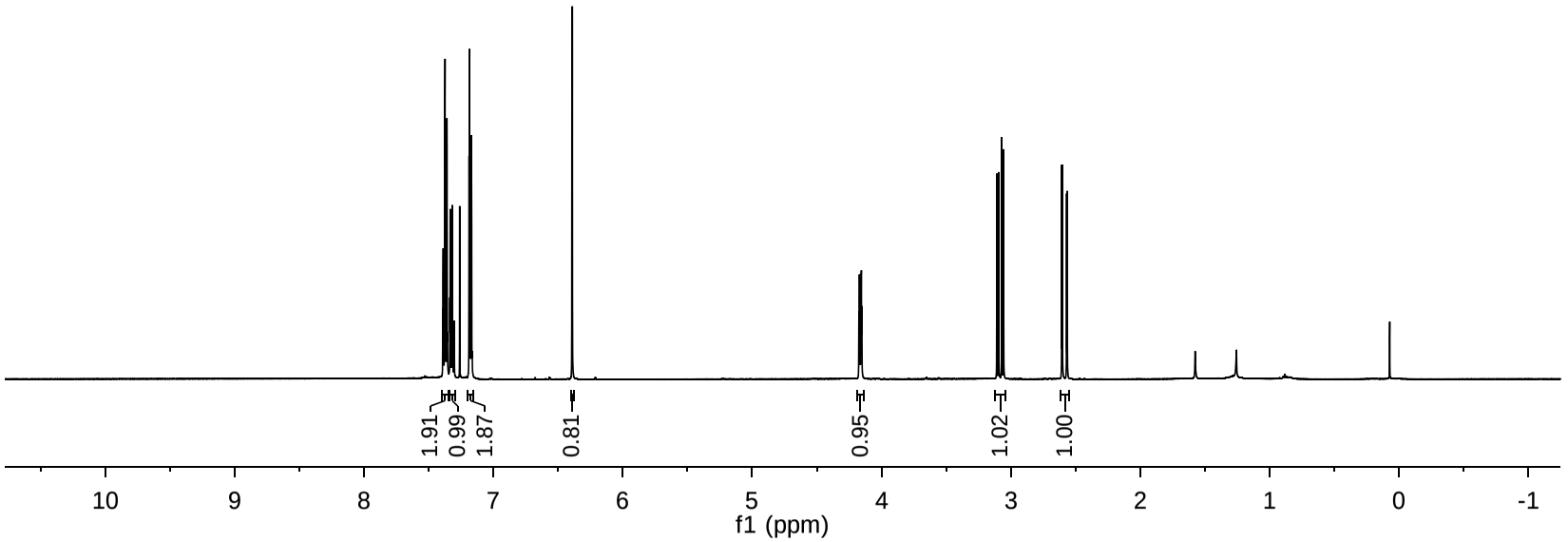

499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
MeO
Me
Me
Me
O
Me
73n
f1 (ppm)
10
9
8
7
6
5
4
3
2
1
0
-1
1.06
1.91
0.94
0.99
1.95
3.33
3.00
2.92
2.95
3.00

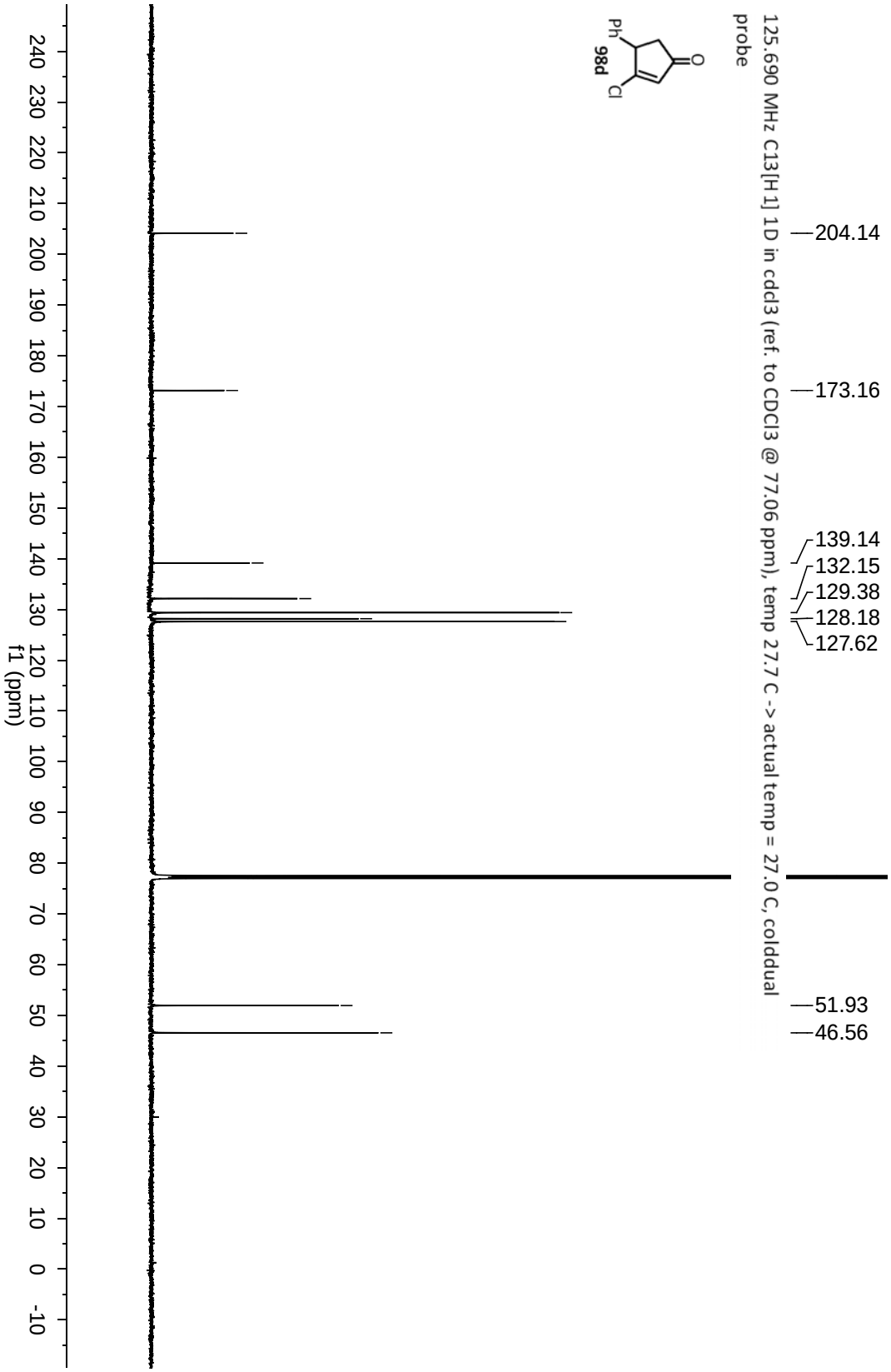

159.82
145.63
140.69
138.97
129.42
120.23
118.80
115.48
113.31
113.29
70.90
55.45
25.88
20.21
19.60
17.41
125.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
MeO
O
Me
Me
Me
Me
73n
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe



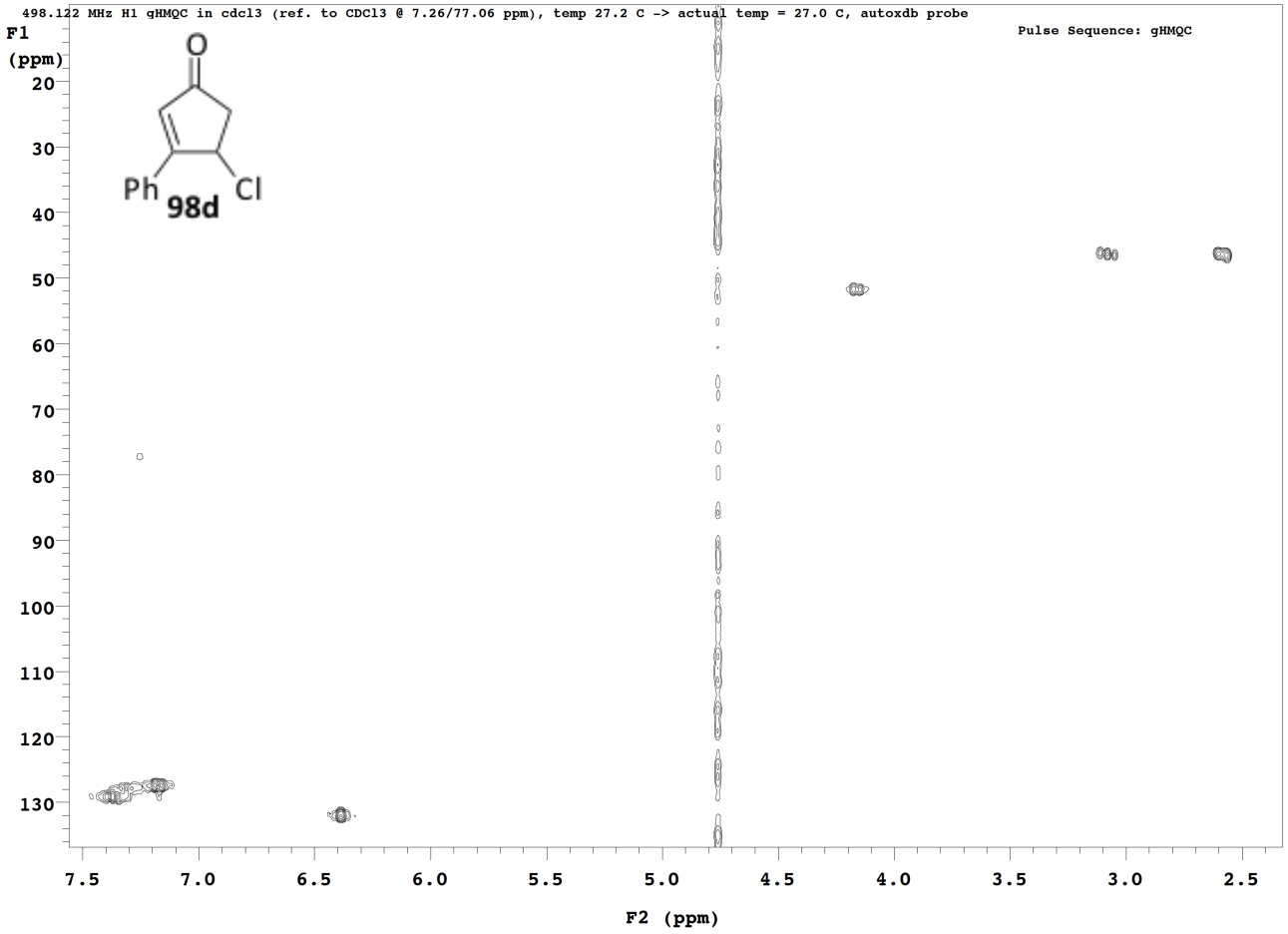
98d



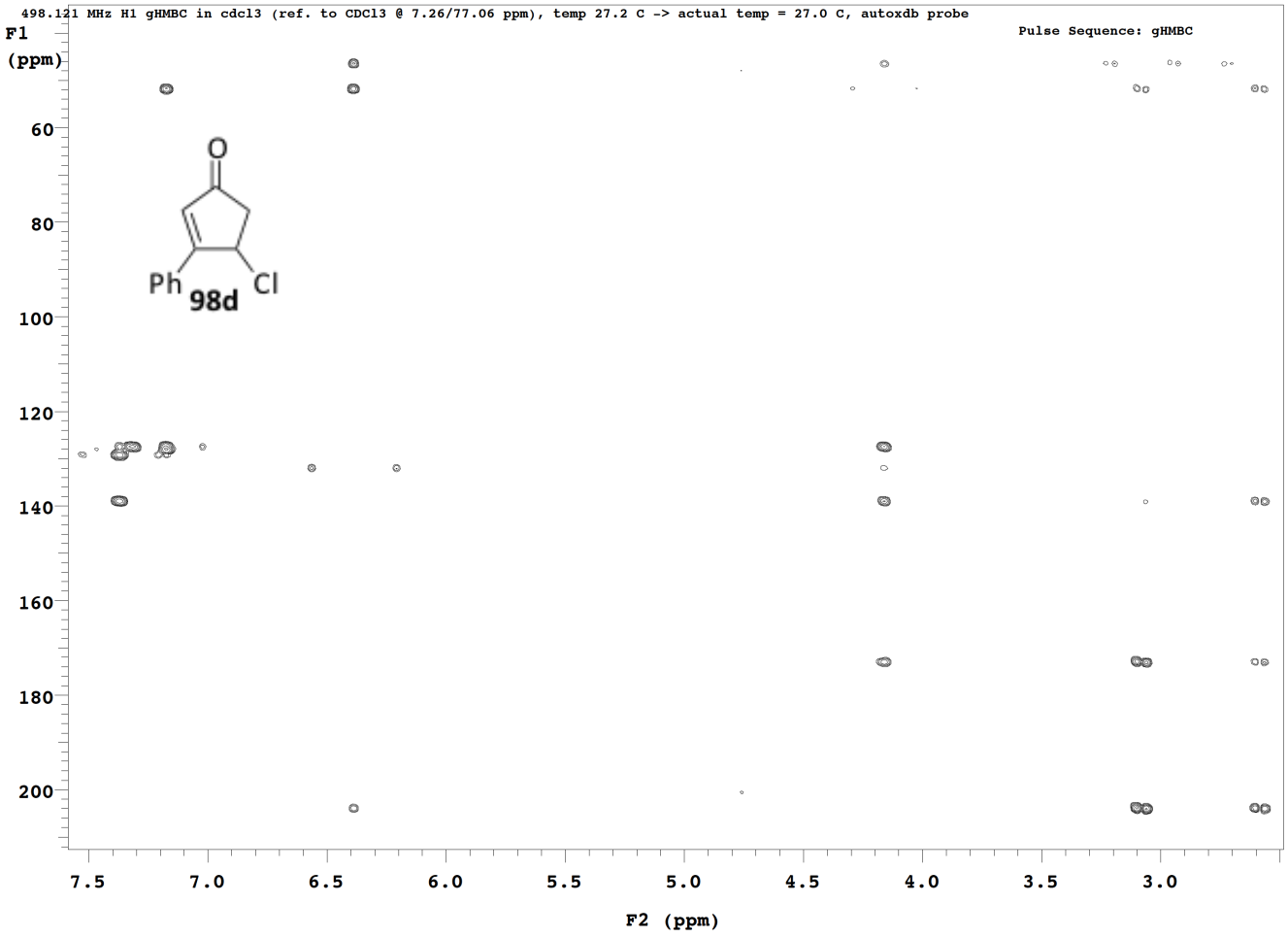

98d
Ph
Cl
O
125.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
204.14
173.16
139.14
132.15
129.38
128.18
127.62
51.93
46.56
f1 (ppm)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

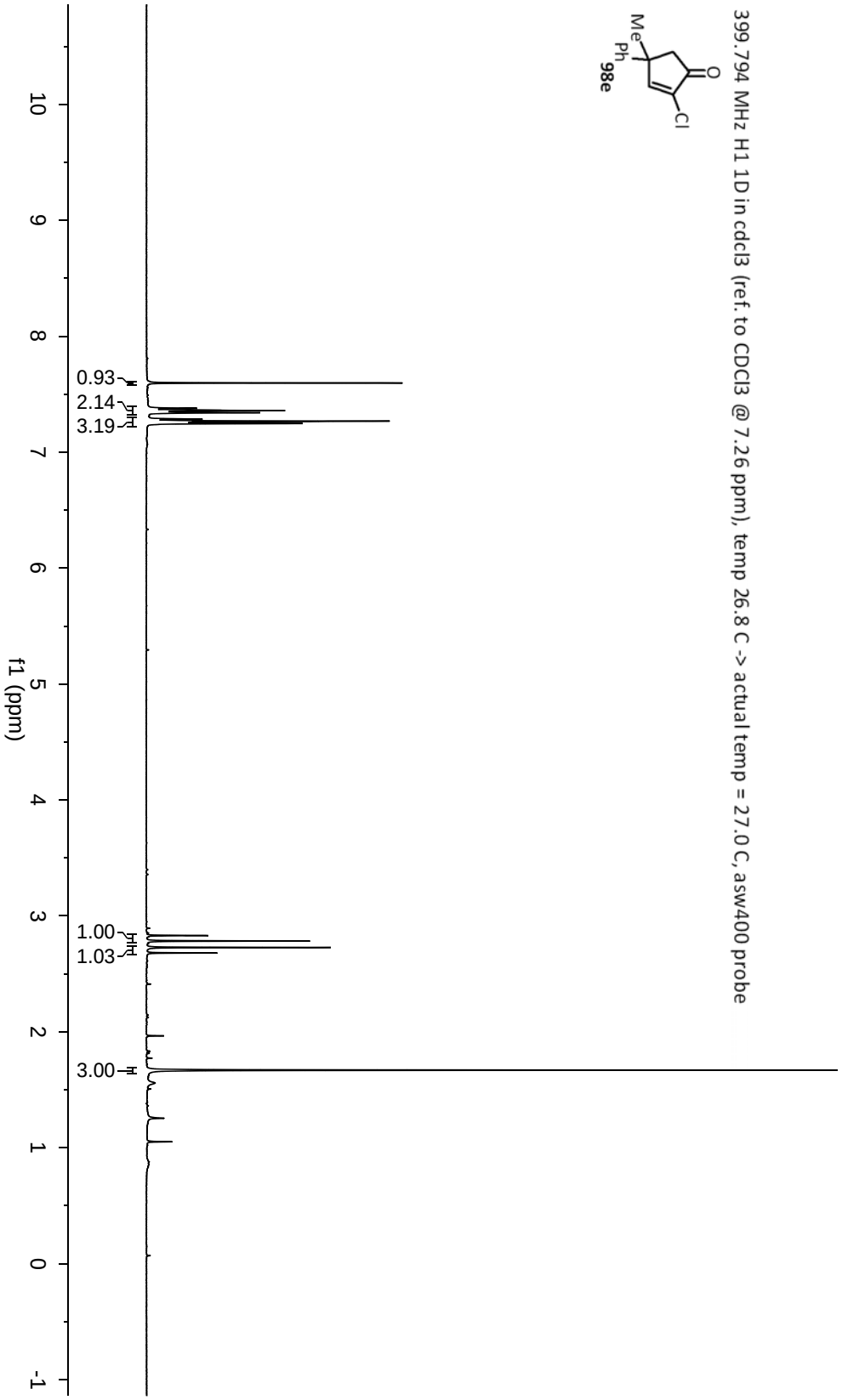
SB-11-89PA1
20120313

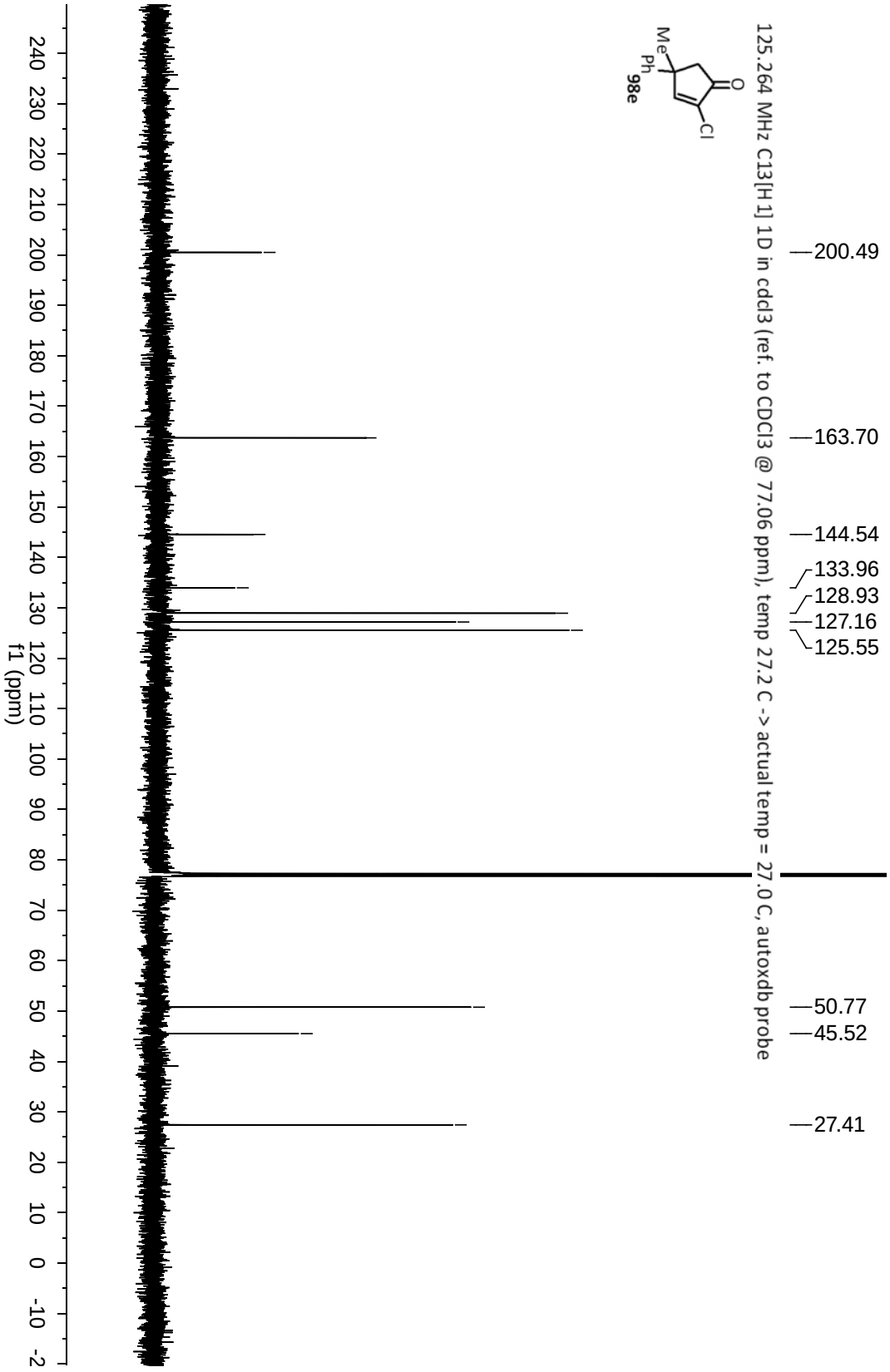
498.122 MHz H1 gHMQC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

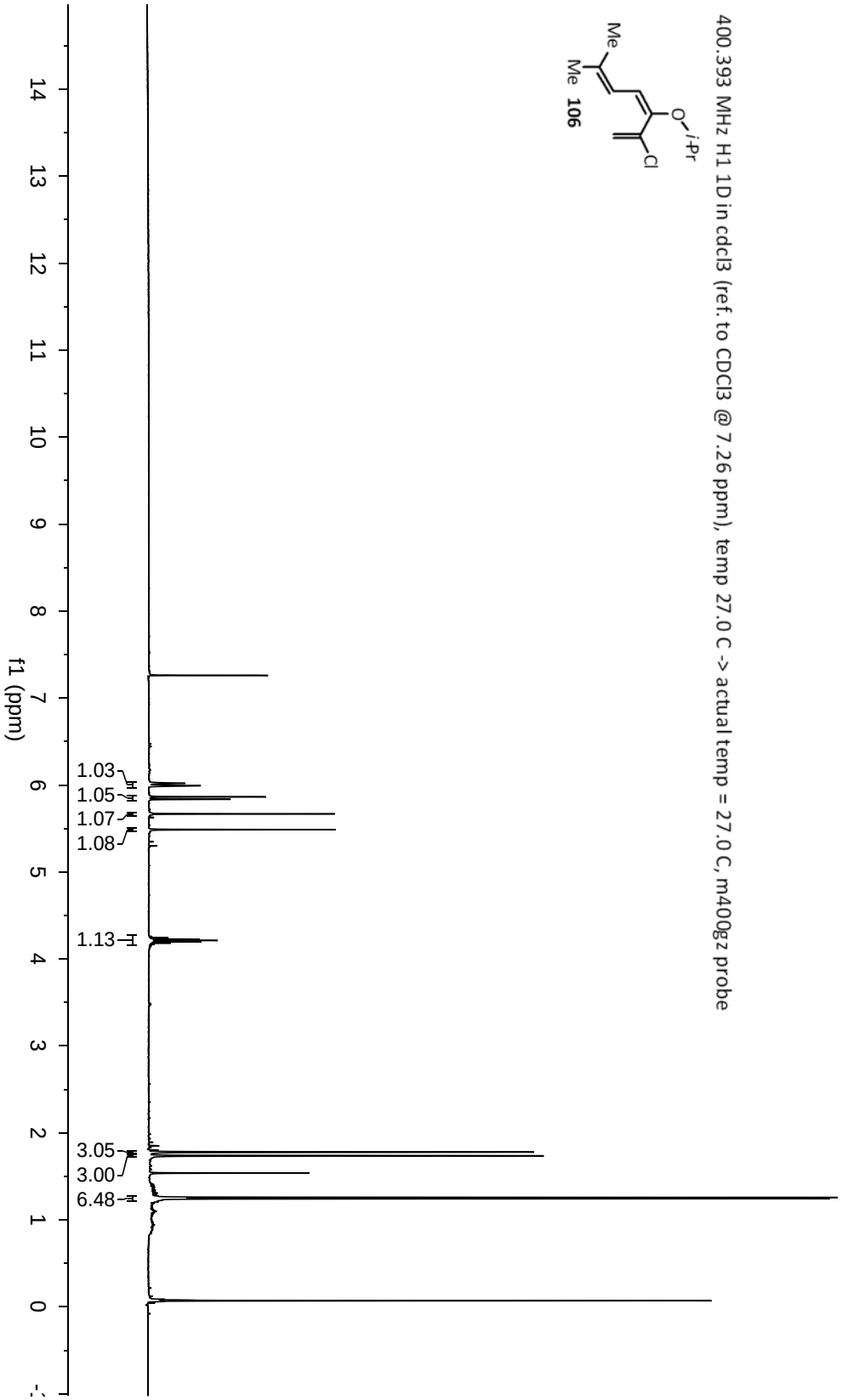


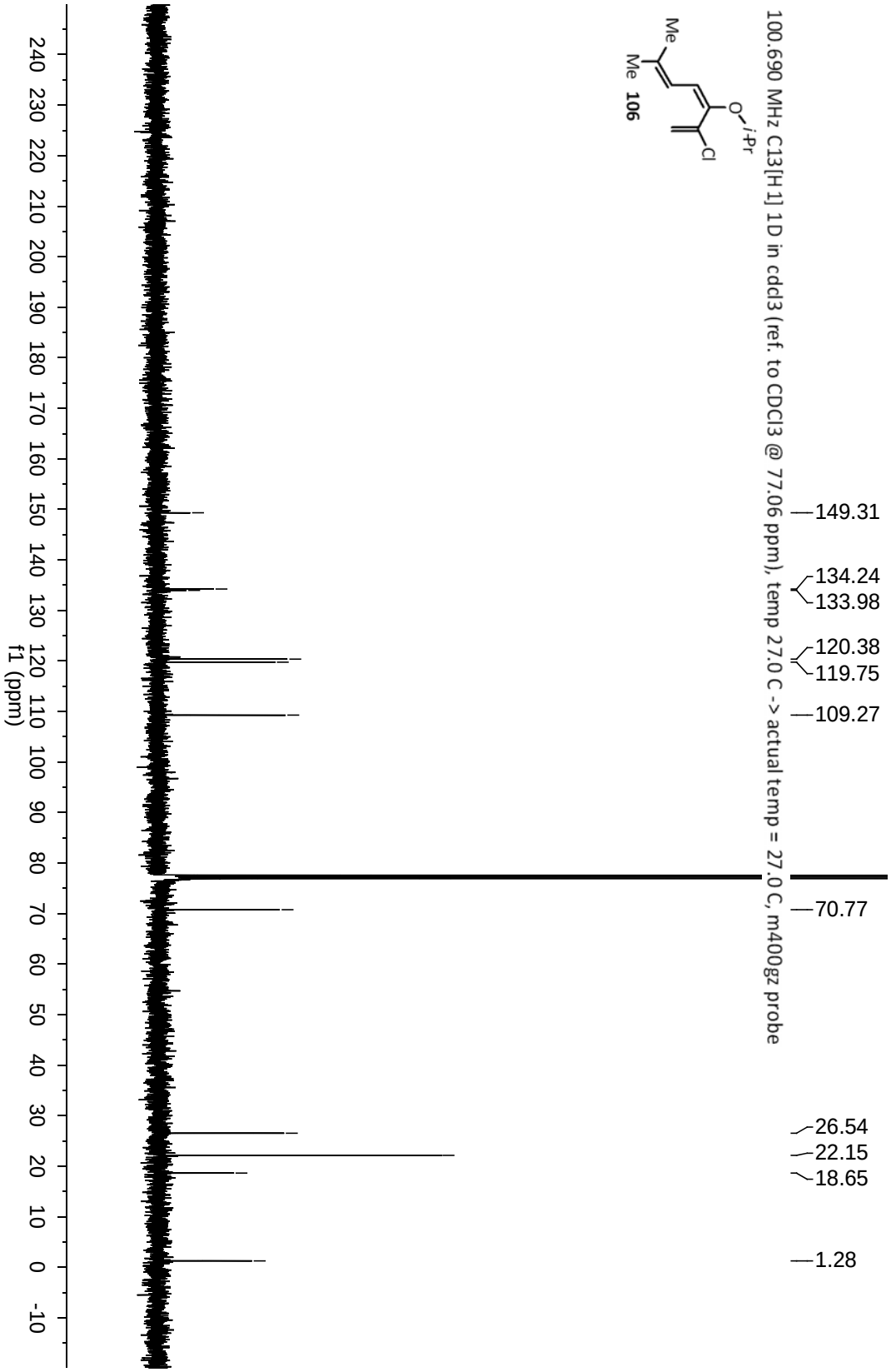
SB-11-89PA1
20120313



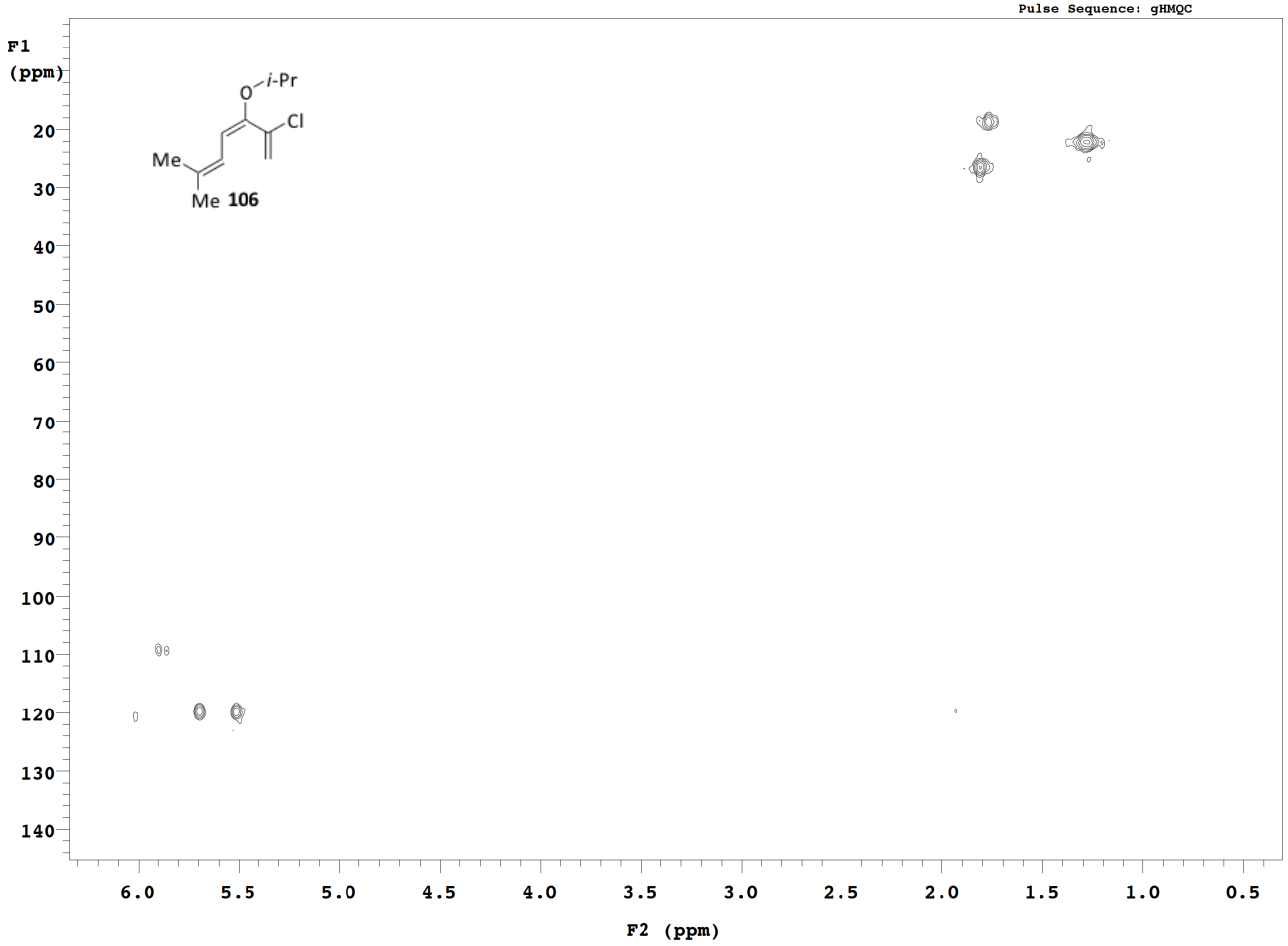

399.794 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe
98e
Me
Ph
O
Cl
0.93
2.14
3.19
1.00
1.03
3.00
f1 (ppm)
10
9
8
7
6
5
4
3
2
1
0
-1


125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe
98e
Me
Ph
O
Cl
200.49
163.70
144.54
133.96
128.93
127.16
125.55
50.77
45.52
27.41
f1 (ppm)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -2

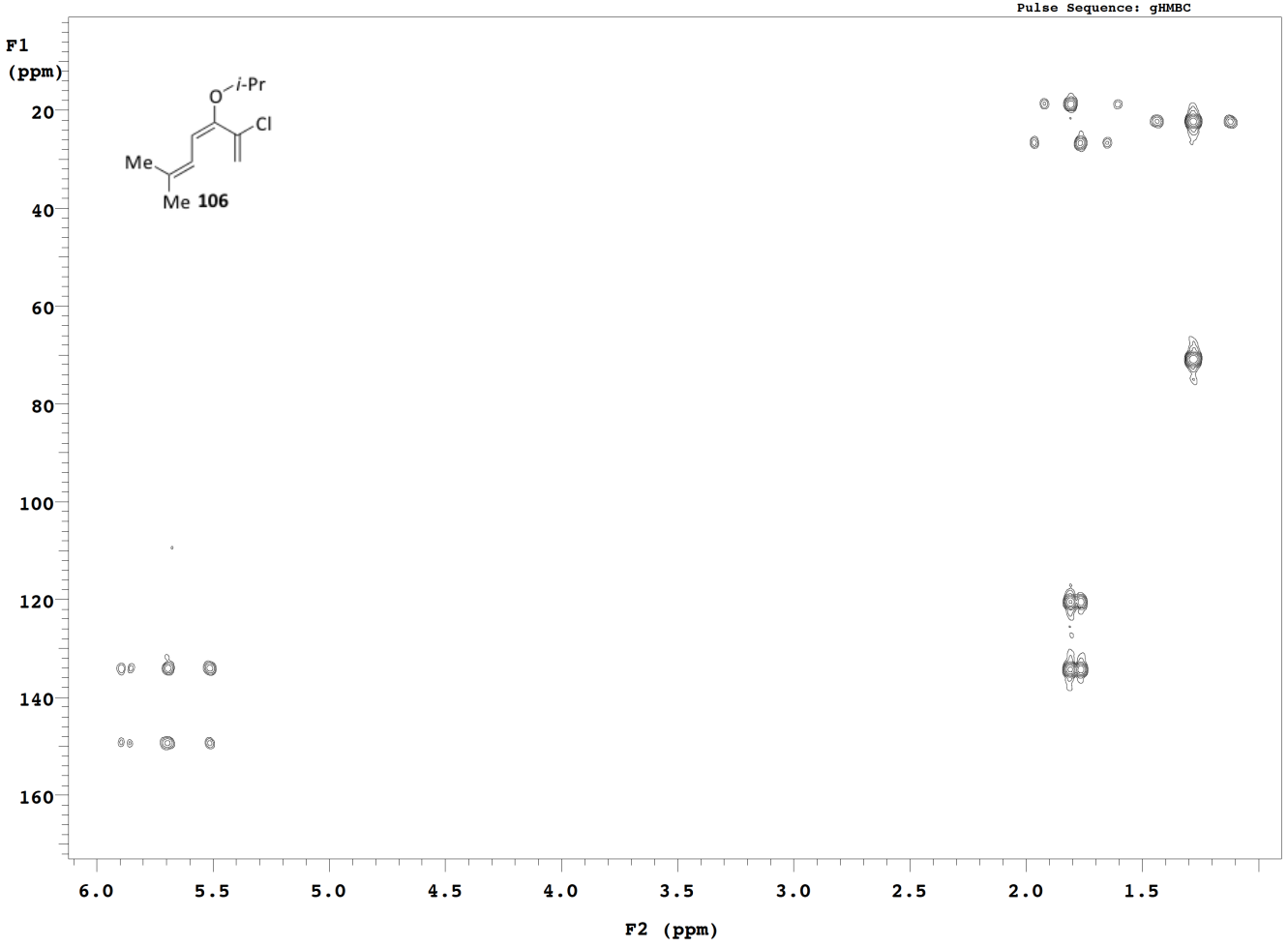

400.393 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Me
Me
O
i-Pr
Cl
106
f1 (ppm)
1.03
1.05
1.07
1.08
1.13
3.05
3.00
6.48


100.690 MHz C13[H 1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Me
Me
106
O
i-Pr
Cl
149.31
134.24
133.98
120.38
119.75
109.27
70.77
26.54
22.15
18.65
1.28
f1 (ppm)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

Sara, SB-4-168-B
400.393 MHz H1 gHMQC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Pulse Sequence: gHMQC

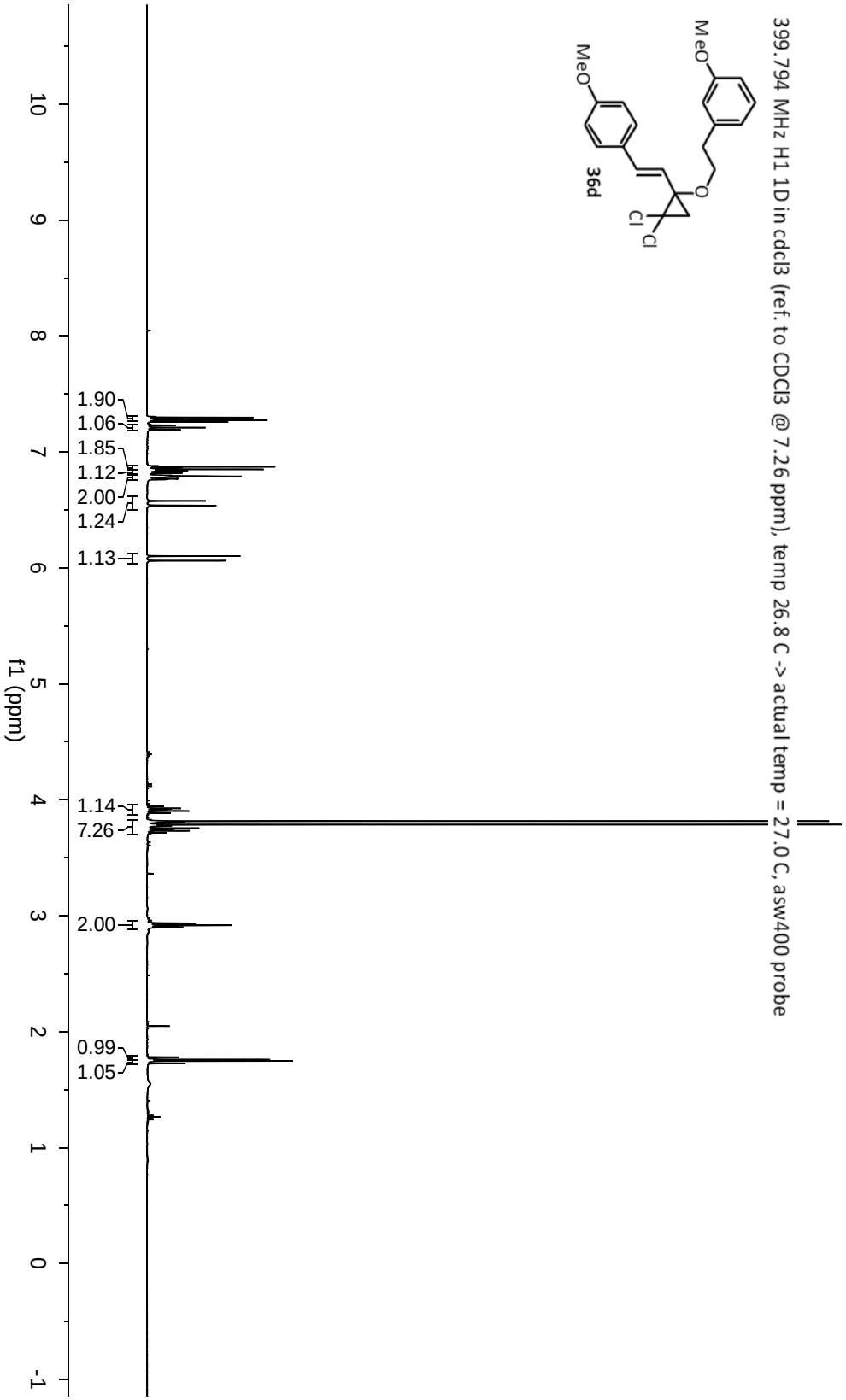


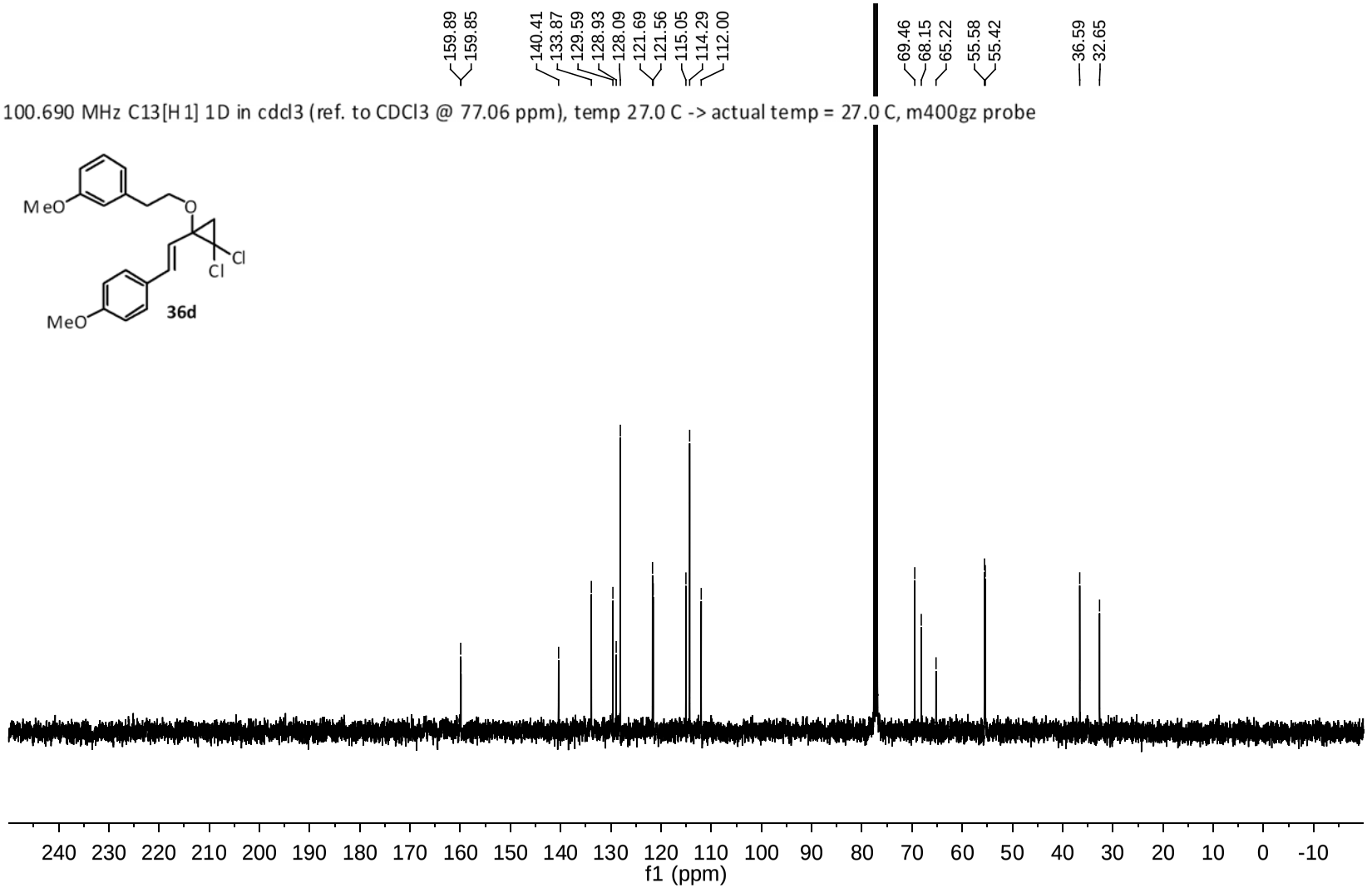
Sara, SB-4-168-B
400.393 MHz H1 gHMBC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Pulse Sequence: gHMBC

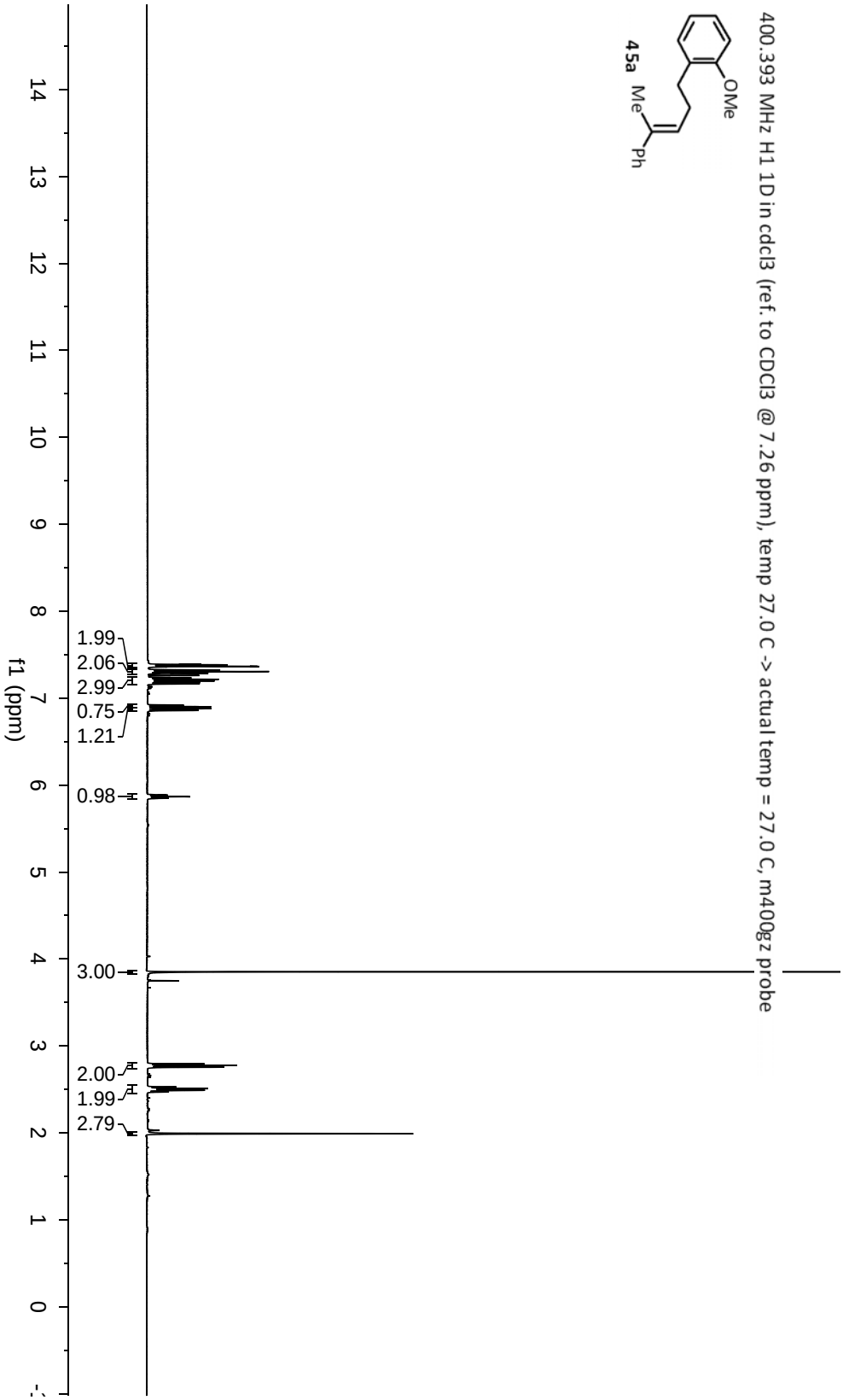


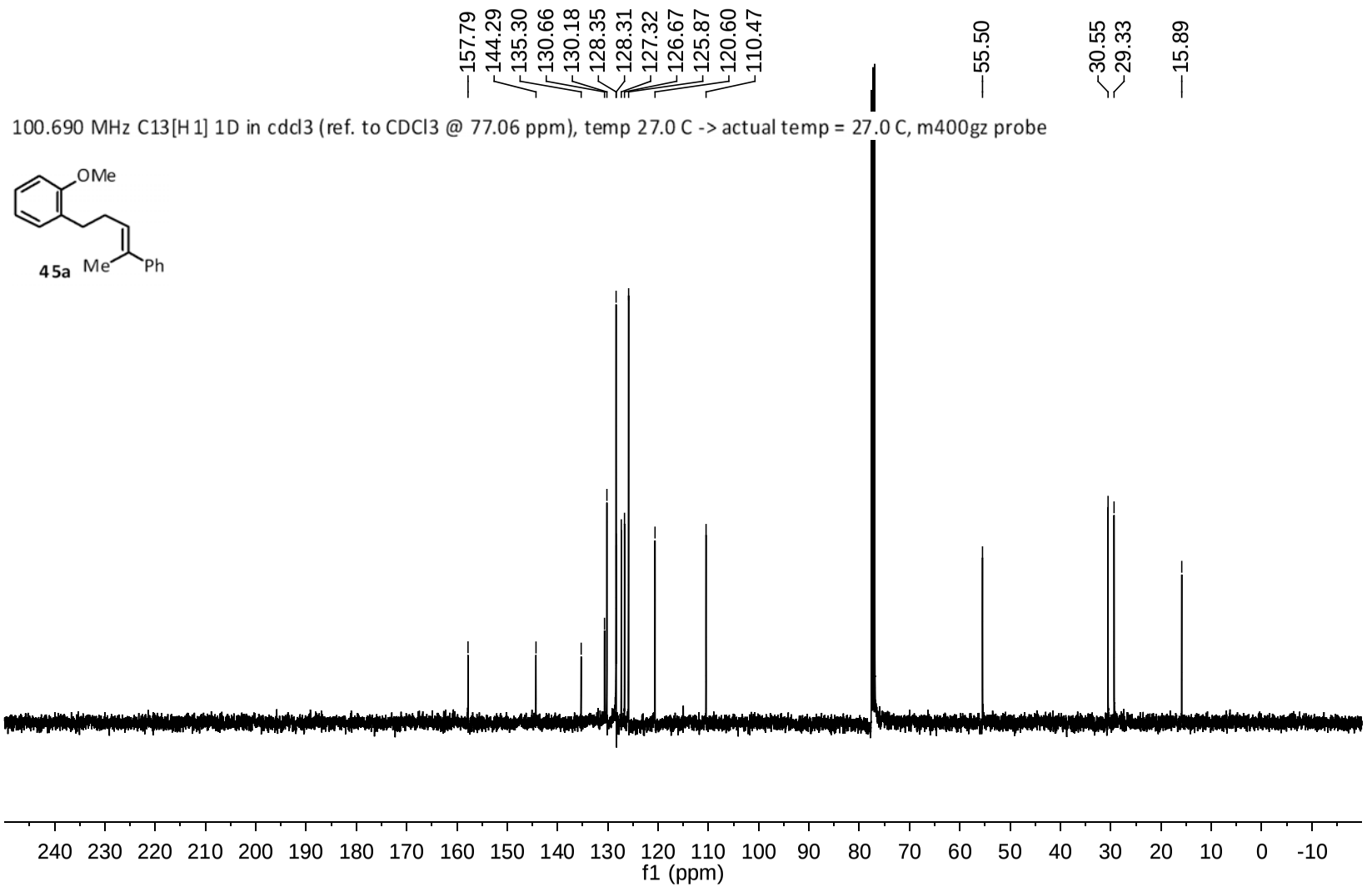
Appendix II: Selected NMR Spectra

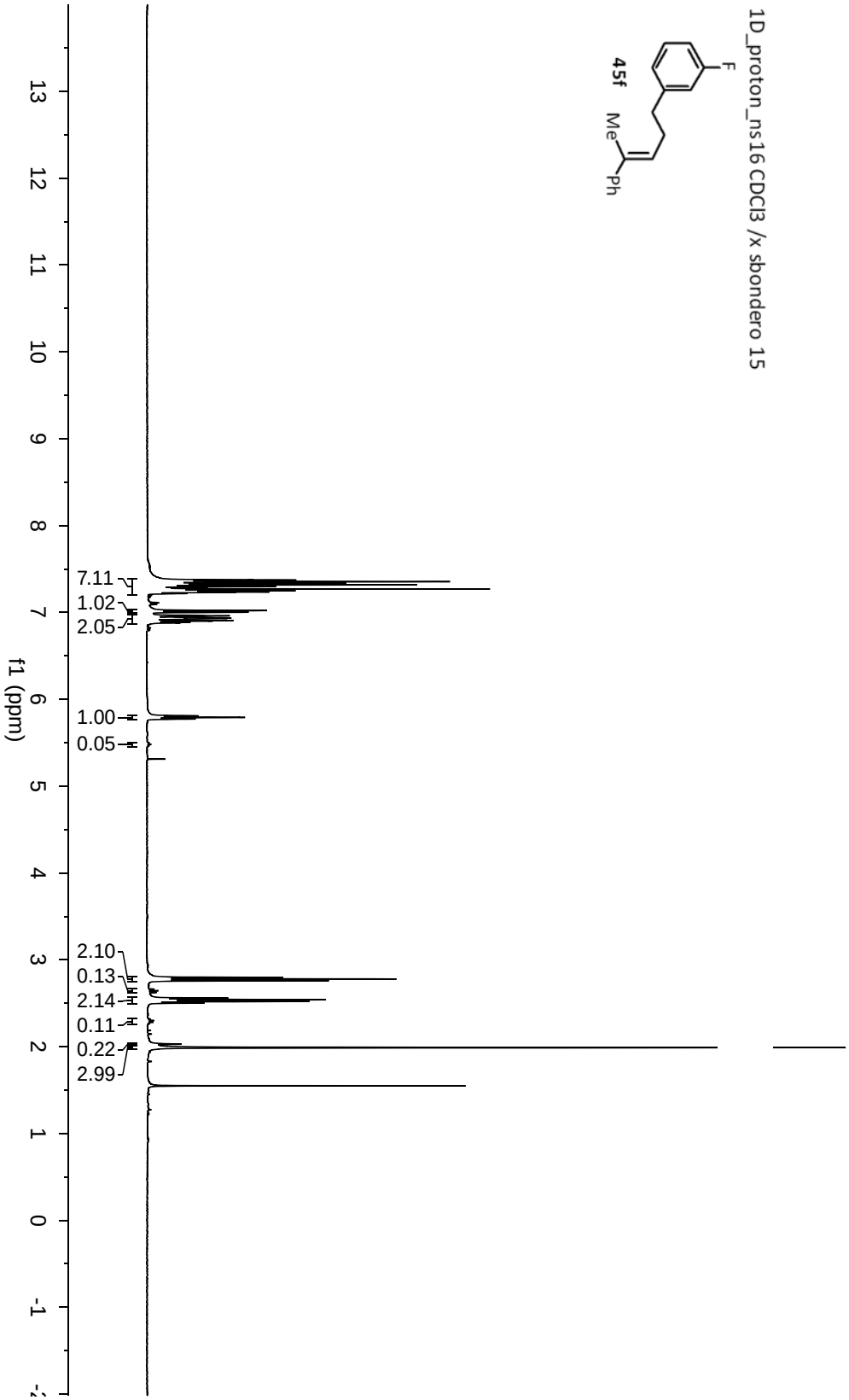
(Chapter 3)

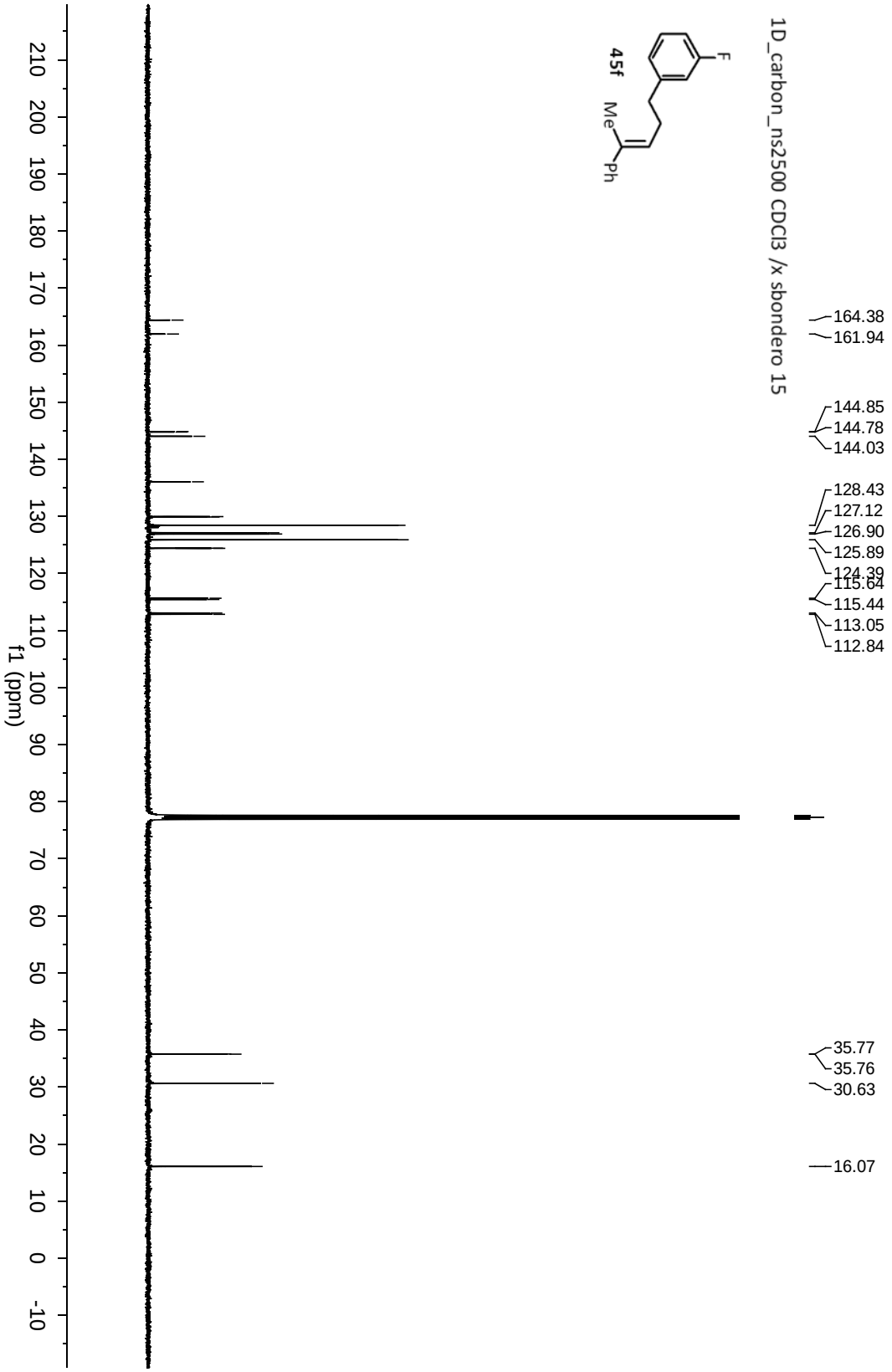

399.794 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe
MeO
MeO
O
Cl
Cl
36d
f1 (ppm)
10
9
8
7
6
5
4
3
2
1
0
-1
1.90
1.06
1.85
1.12
2.00
1.24
1.13
1.14
7.26
2.00
0.99
1.05

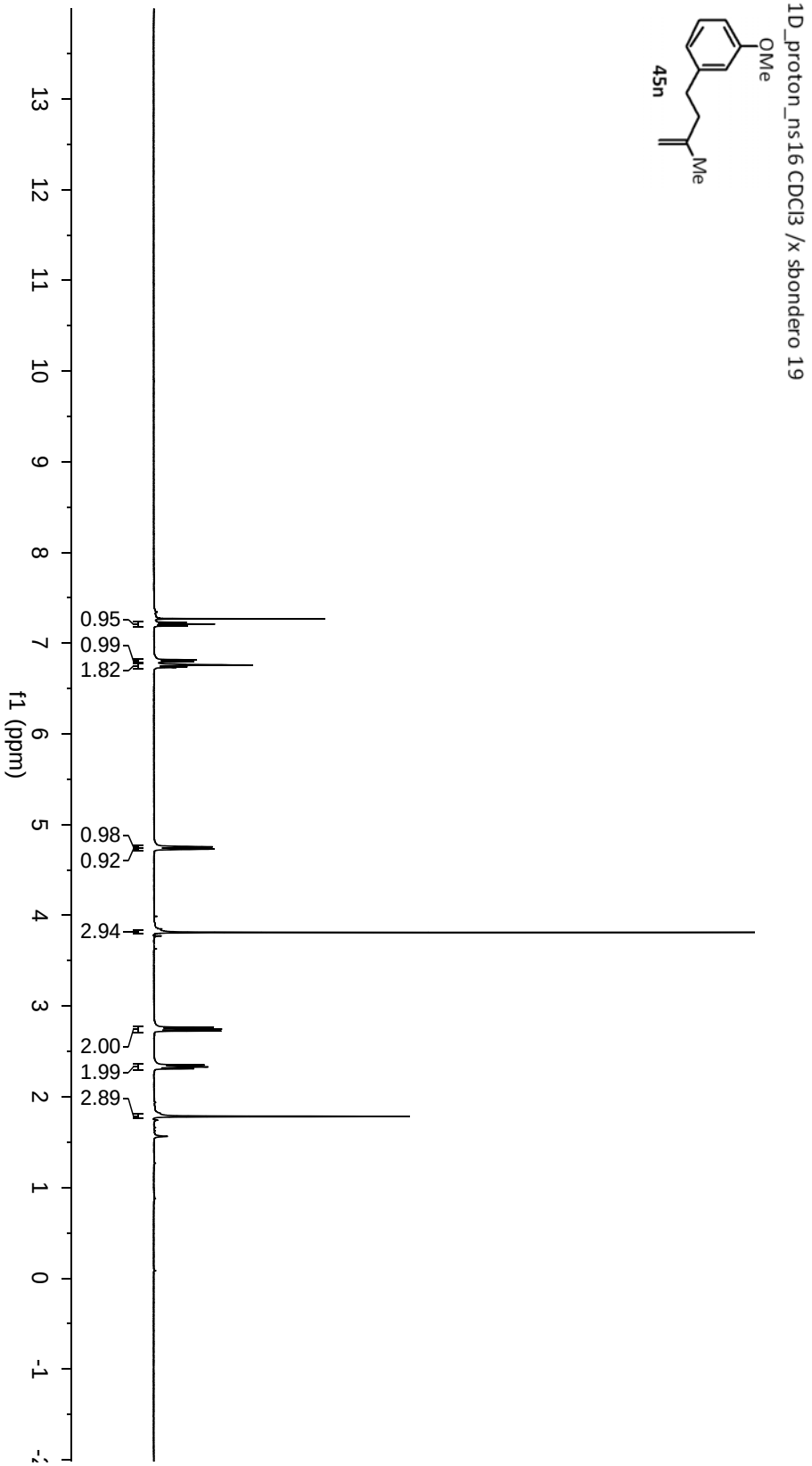

159.89
159.85
140.41
133.87
129.59
128.93
128.09
121.69
121.56
115.05
114.29
112.00
69.46
68.15
65.22
55.58
55.42
36.59
32.65
100.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
MeO
O
Cl
Cl
MeO
36d
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

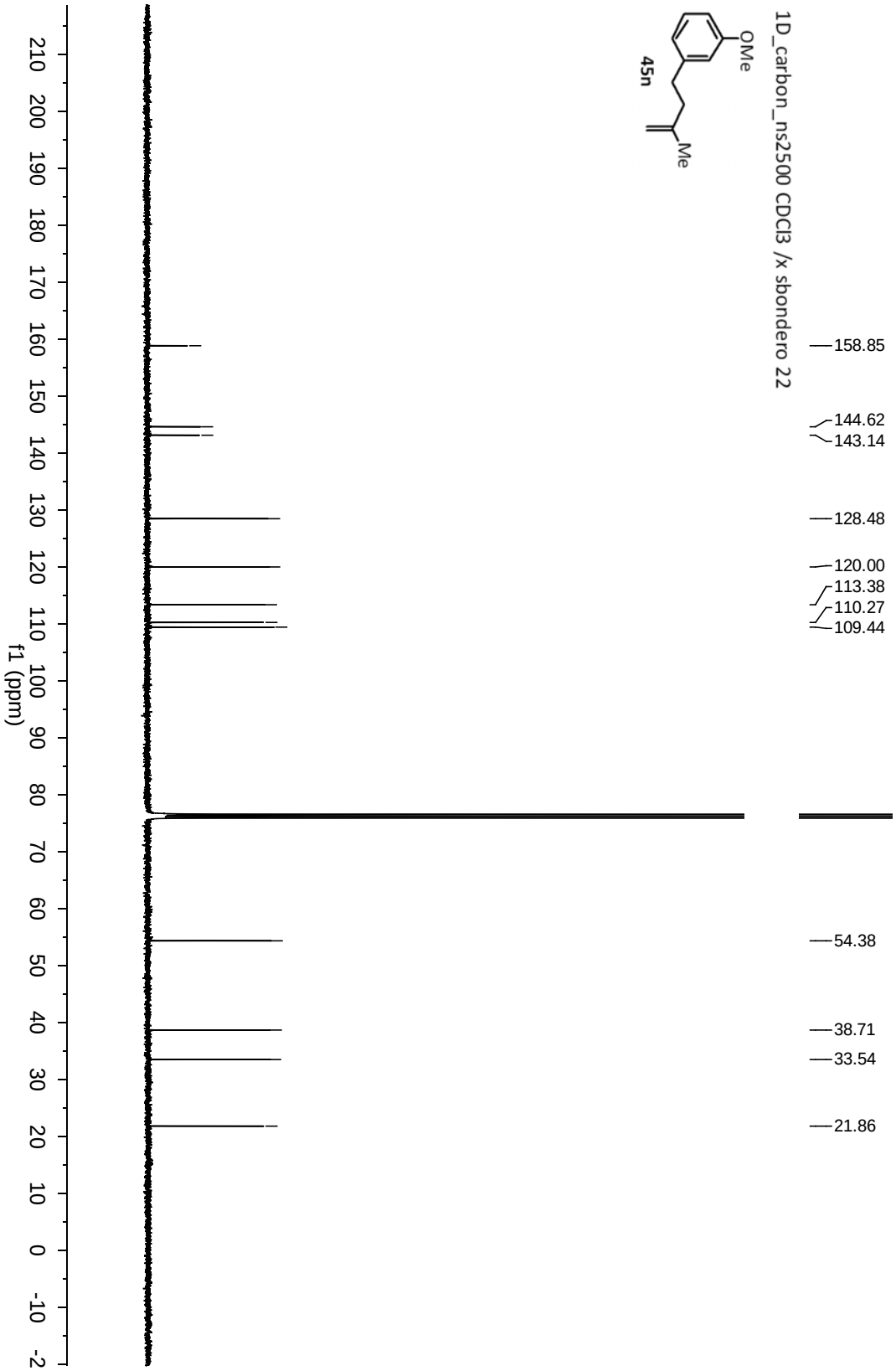

400.393 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
45a
OMe
Me
Ph
f1 (ppm)
1.99
2.06
2.99
0.75
1.21
0.98
3.00
2.00
1.99
2.79

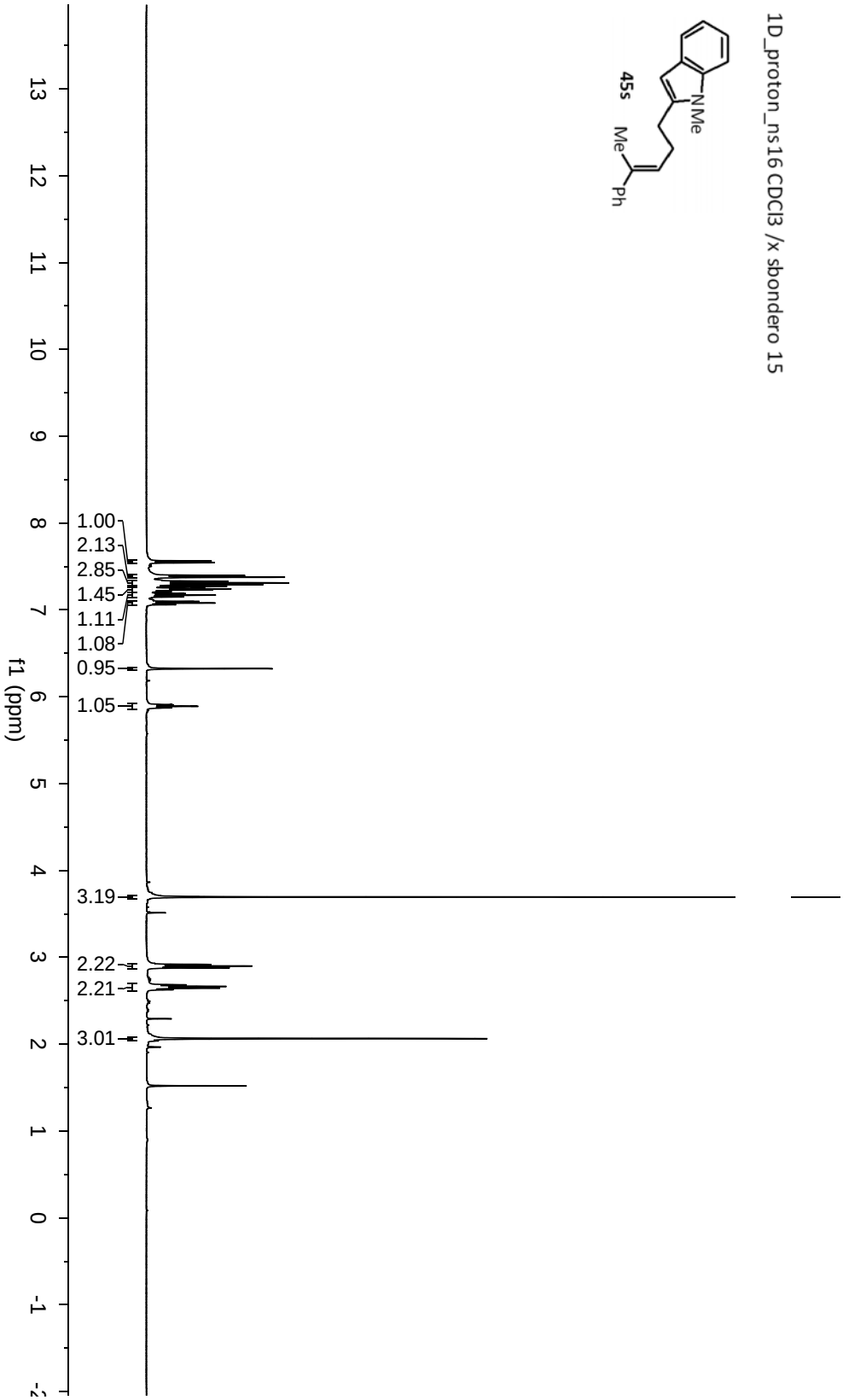

157.79
144.29
135.30
130.66
130.18
128.35
128.31
127.32
126.67
125.87
120.60
110.47
55.50
30.55
29.33
15.89
100.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
OMe
Me
Ph
45a
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

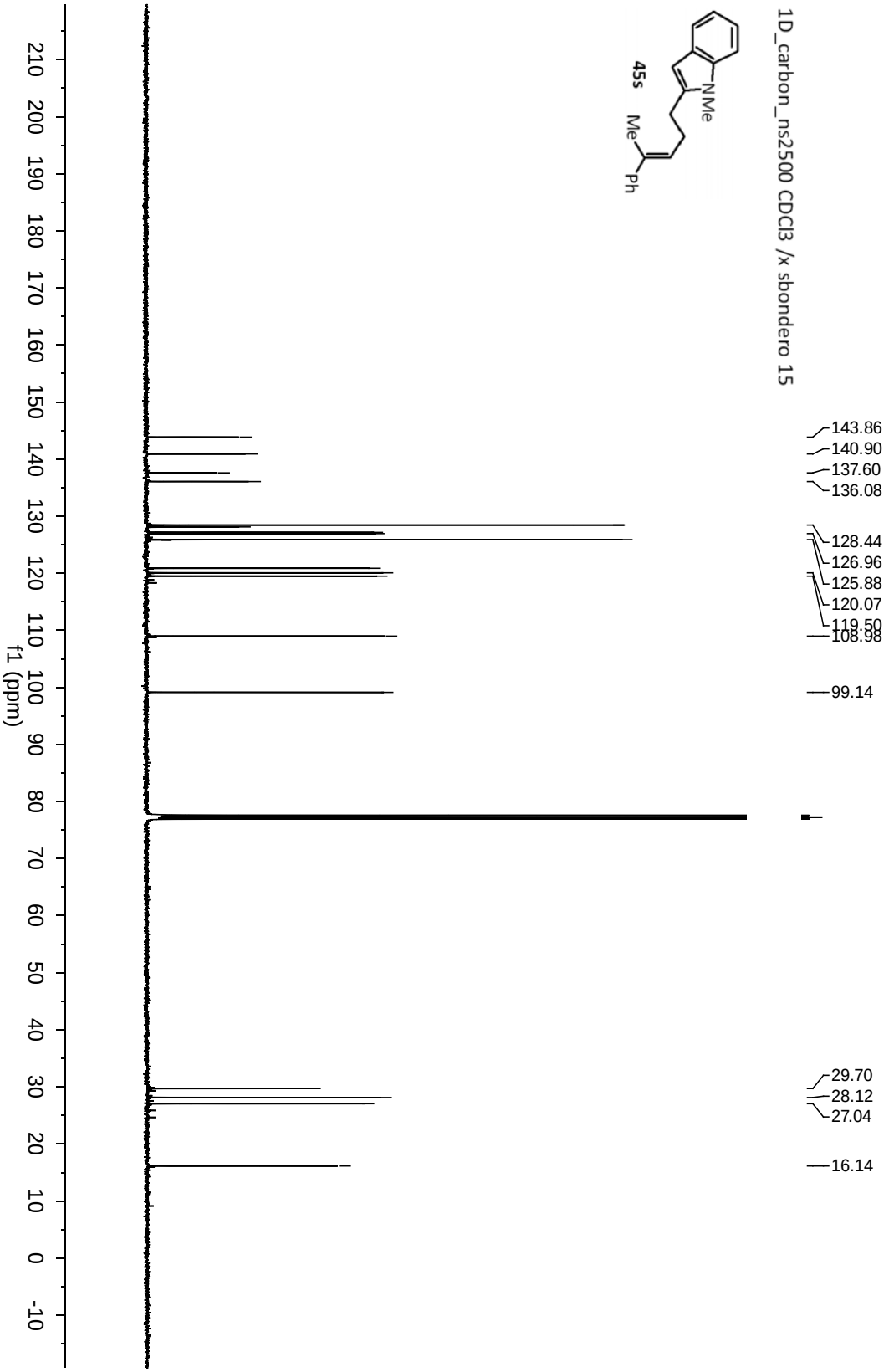

1D_proton_ns16 CDCl3 /x sbondero 15
45f
F
Me
Ph
f1 (ppm)
7.11
1.02
2.05
1.00
0.05
2.10
0.13
2.14
0.11
0.22
2.99

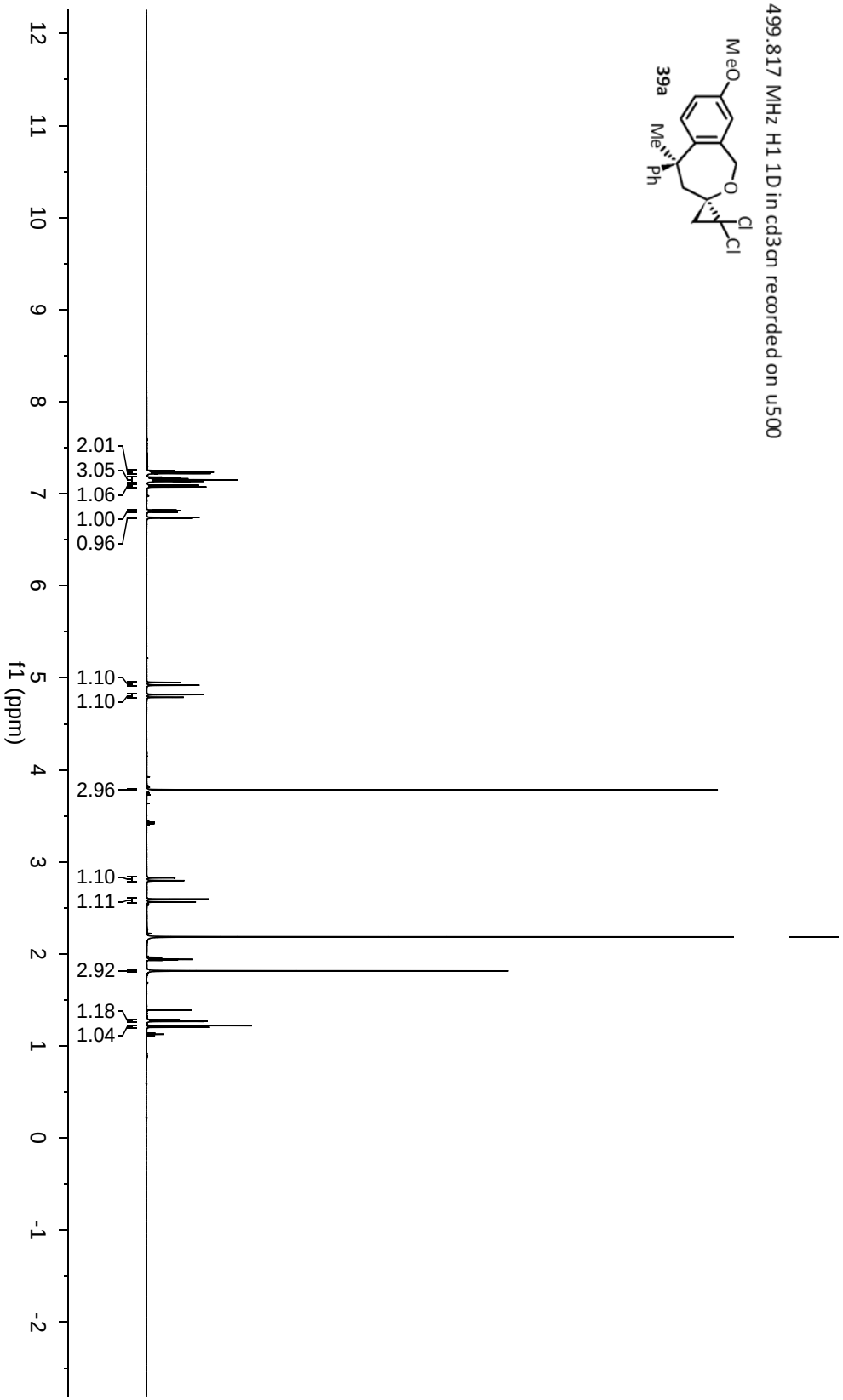

1D_carbon_ns2500 CDCl3 /x sbondero 15
45f
F
Me
Ph
164.38
161.94
144.85
144.78
144.03
128.43
127.12
126.90
125.89
124.39
115.64
115.44
113.05
112.84
35.77
35.76
30.63
16.07
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

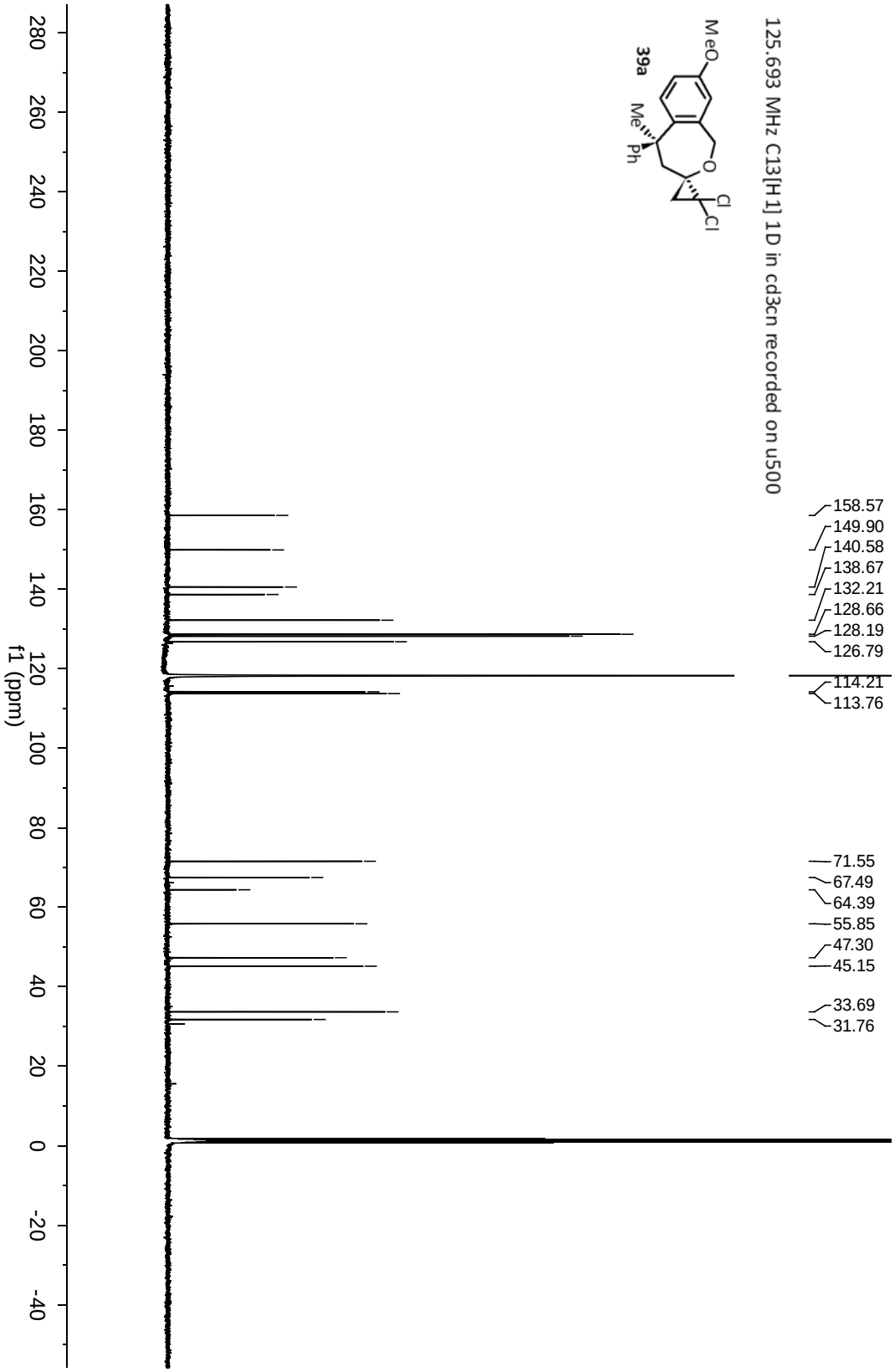

1D_proton_ns16 CDCl3 /x sbondero 19
45n
OMe
Me
f1 (ppm)
0.95
0.99
1.82
0.98
0.92
2.94
2.00
1.99
2.89


1D_carbon_ns2500 CDCl3 /x sbondero 22
45n
OMe
Me
158.85
144.62
143.14
128.48
120.00
113.38
110.27
109.44
54.38
38.71
33.54
21.86
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -2


1D_proton_ns16 CDCl3 /x sbondero 15
45s
NMe
Me
Ph
f1 (ppm)
1.00
2.13
2.85
1.45
1.11
1.08
0.95
1.05
3.19
2.22
2.21
3.01

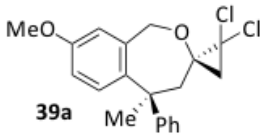

1D_carbon_ns2500 CDCl3 /x sbondero 15
45s
NMe
Me
Ph
143.86
140.90
137.60
136.08
128.44
126.96
125.88
120.07
119.50
108.98
99.14
29.70
28.12
27.04
16.14
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


499.817 MHz H1 1D in cd3cn recorded on u500
39a
MeO
Me
Ph
O
Cl
Cl
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
2.01
3.05
1.06
1.00
0.96
1.10
1.10
2.96
1.10
1.11
2.92
1.18
1.04

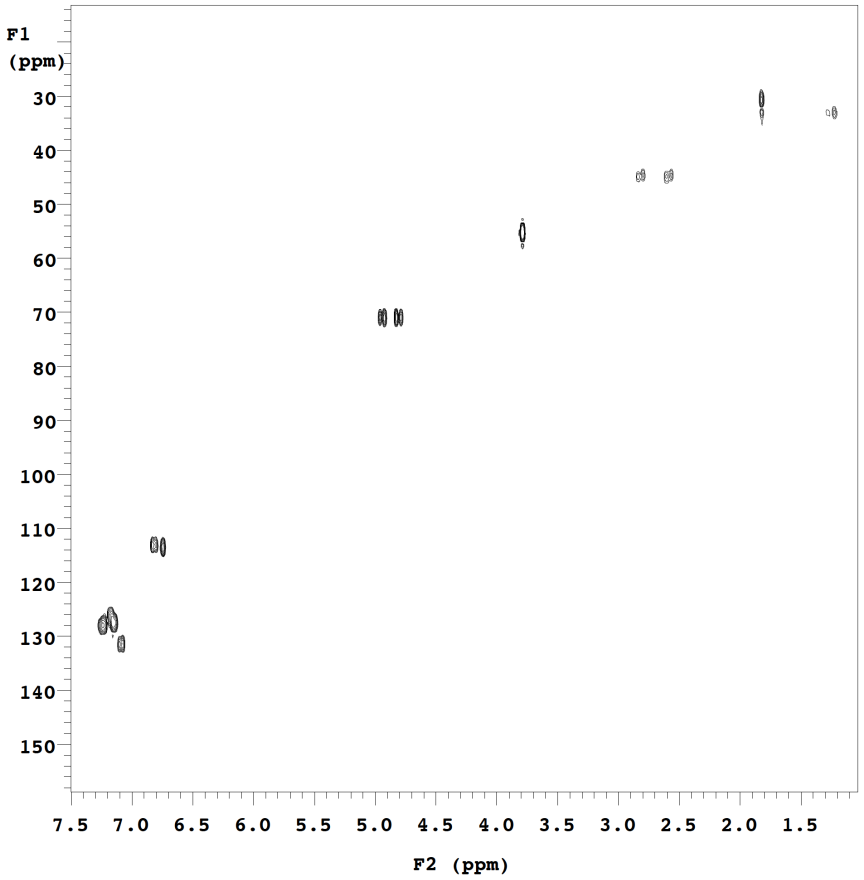

125.693 MHz C13[H1] 1D in cd3cn recorded on u500
MeO
39a
Me
Ph
O
Cl
Cl
158.57
149.90
140.58
138.67
132.21
128.66
128.19
126.79
114.21
113.76
71.55
67.49
64.39
55.85
47.30
45.15
33.69
31.76
f1 (ppm)
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40

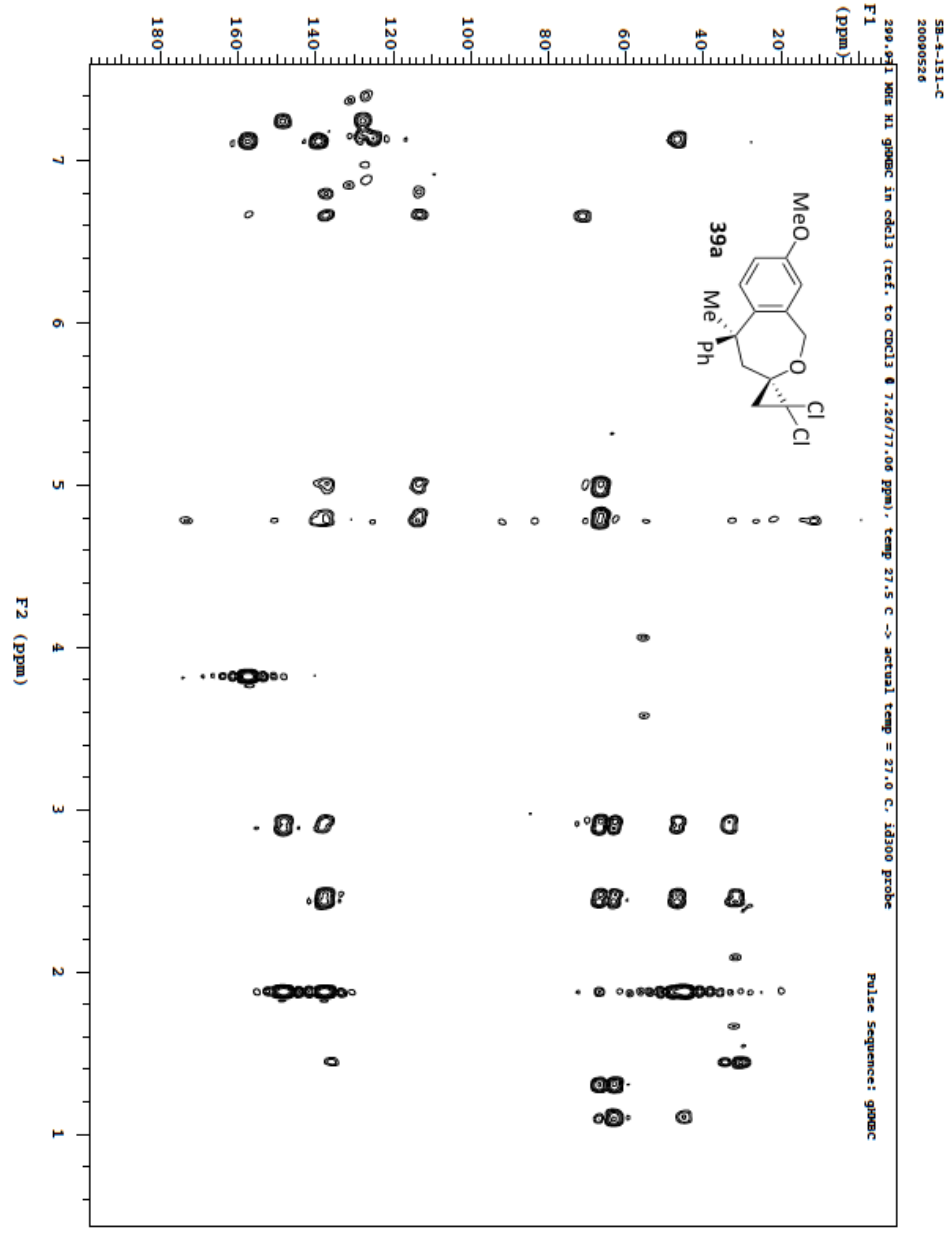
Sara, SB-7-135-PB1
400.395 MHz H1 gHSQC in cd3cn, temp 27.0 C -> actual temp = 27.0 C, m400gz probe

Pulse Sequence: gHSQC



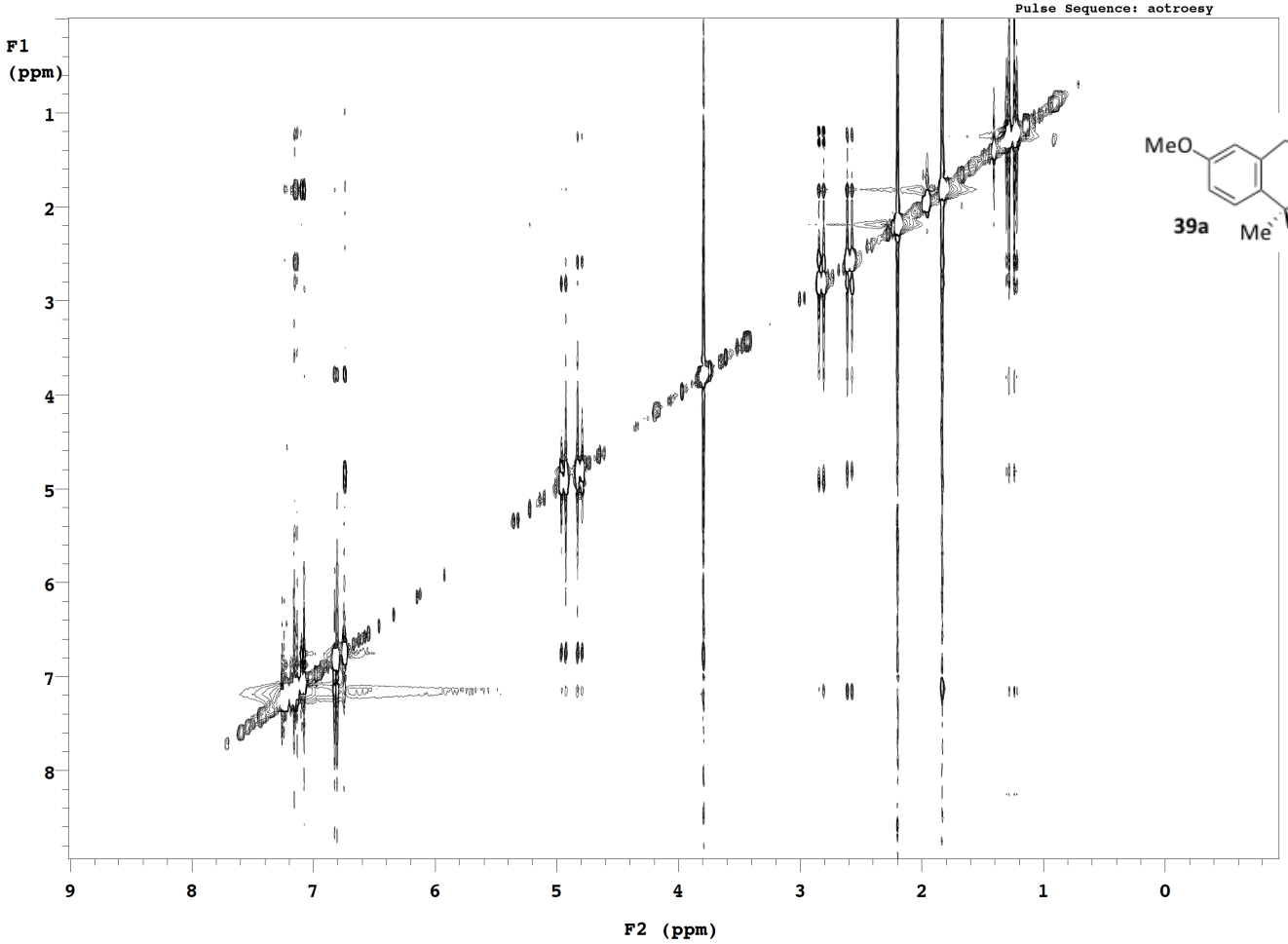
39a




SB-4-151-C
20090526
299.911 MHz H1 gHMBC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm), temp 27.5 C -> actual temp = 27.0 C, id300 probe
Pulse Sequence: gHMBC
F1 (ppm)
F2 (ppm)
MeO
39a
Me
Ph
O
Cl
Cl

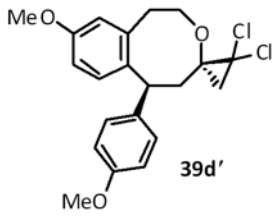
Sara, SB-7-135-PB1
400.395 MHz H1 aotroesy in cd3cn, temp 27.0 C -> actual temp = 27.0 C, m400gz probe

Pulse Sequence: aotroesy

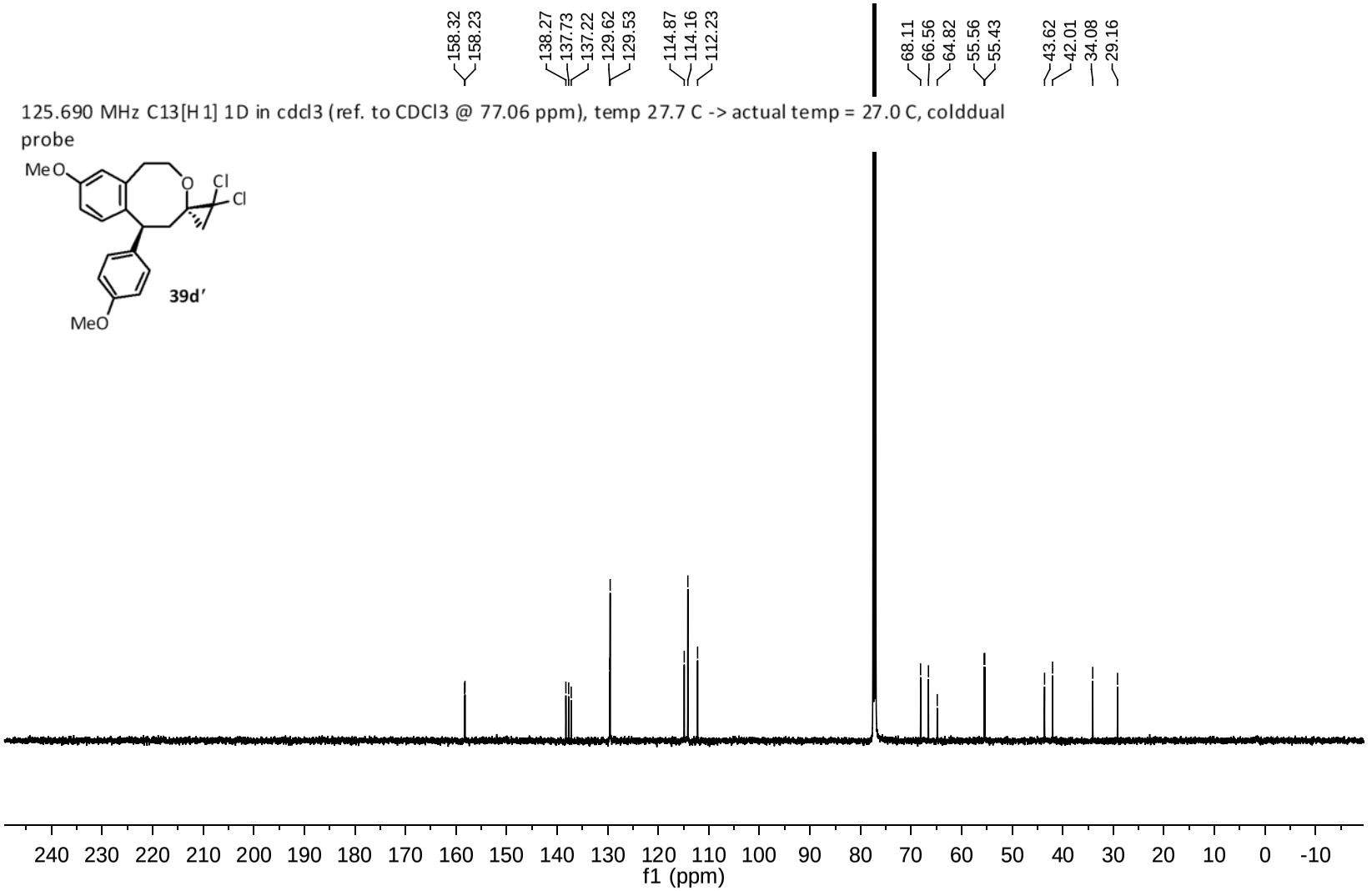


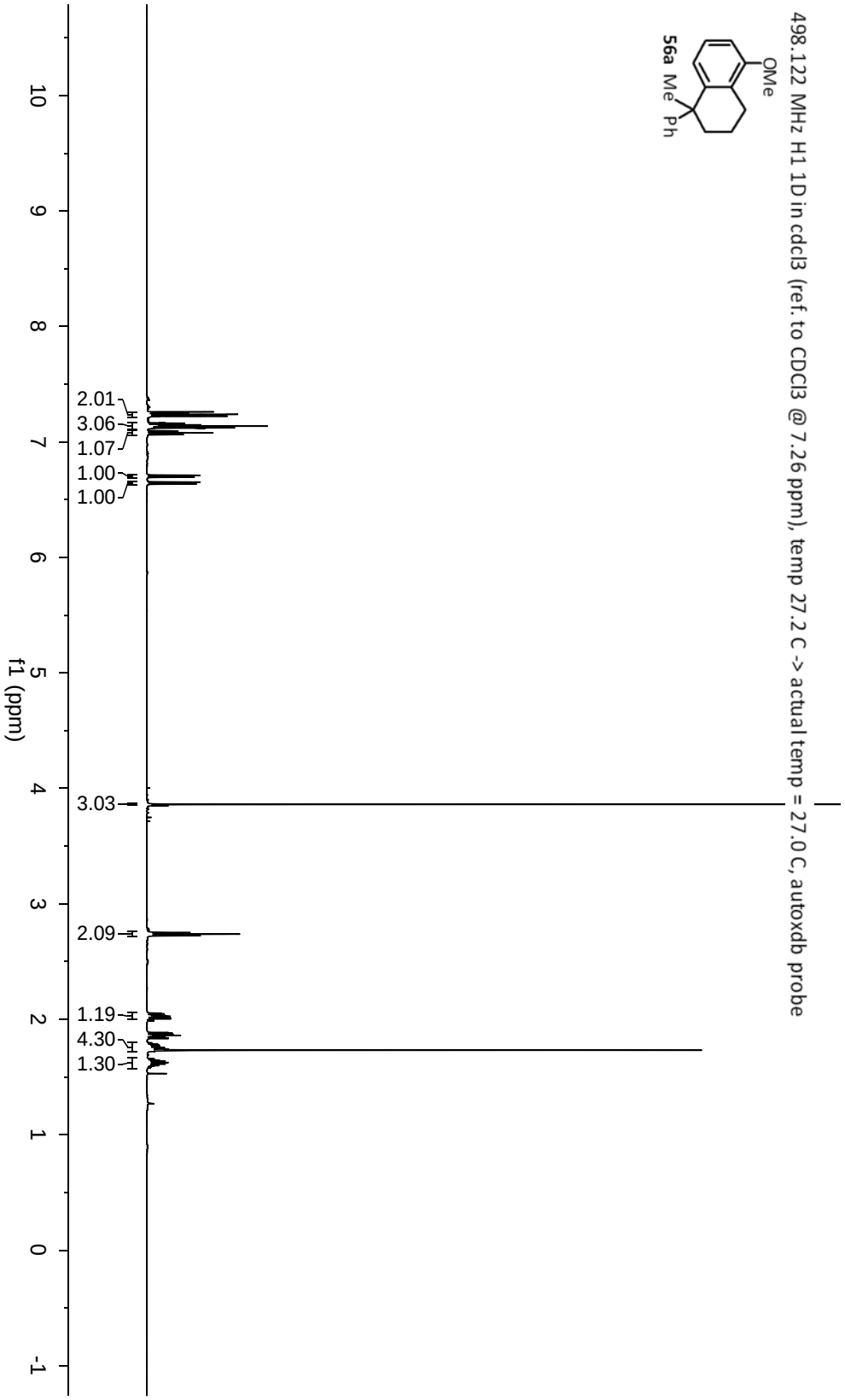
39a

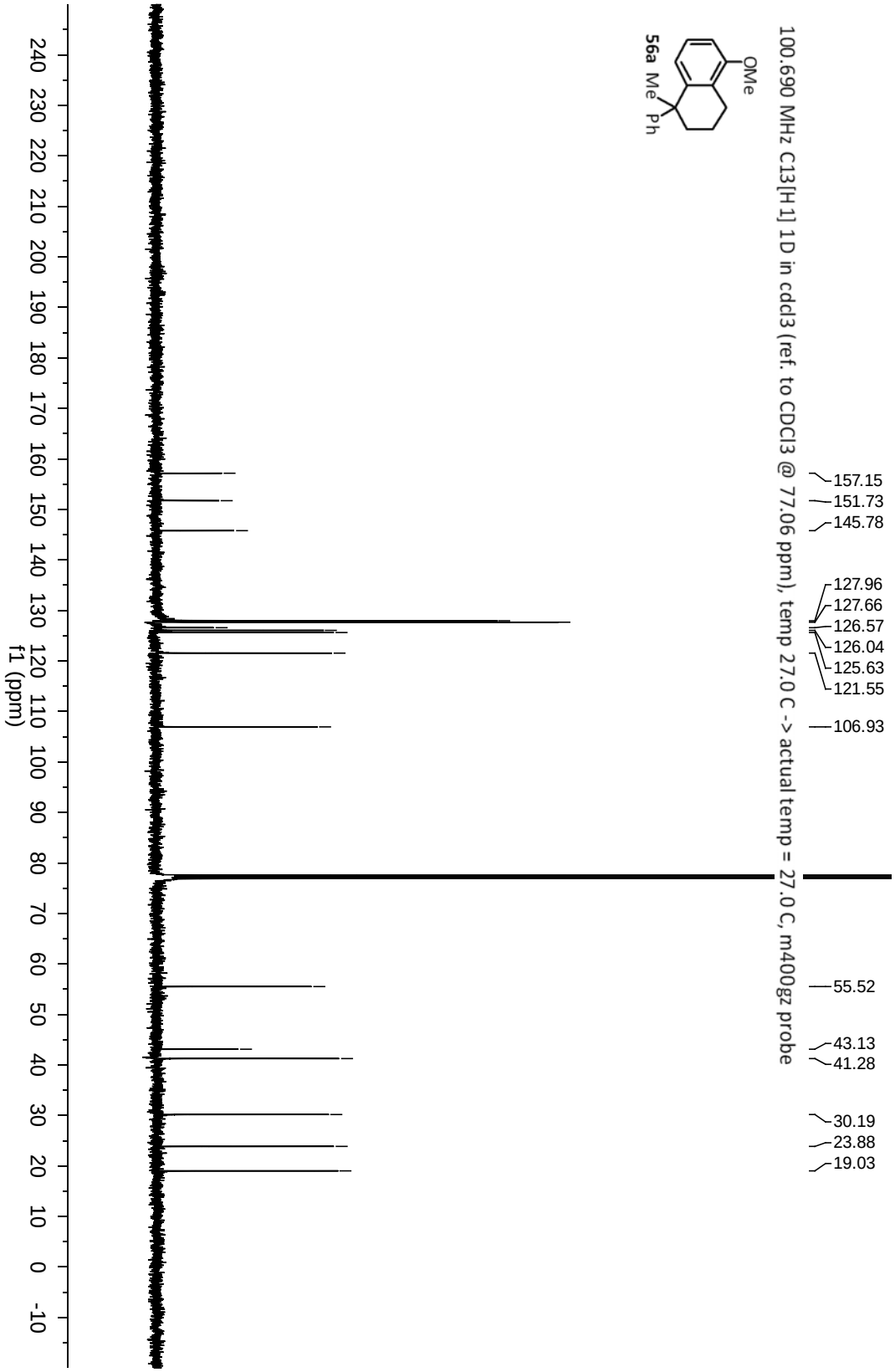
499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

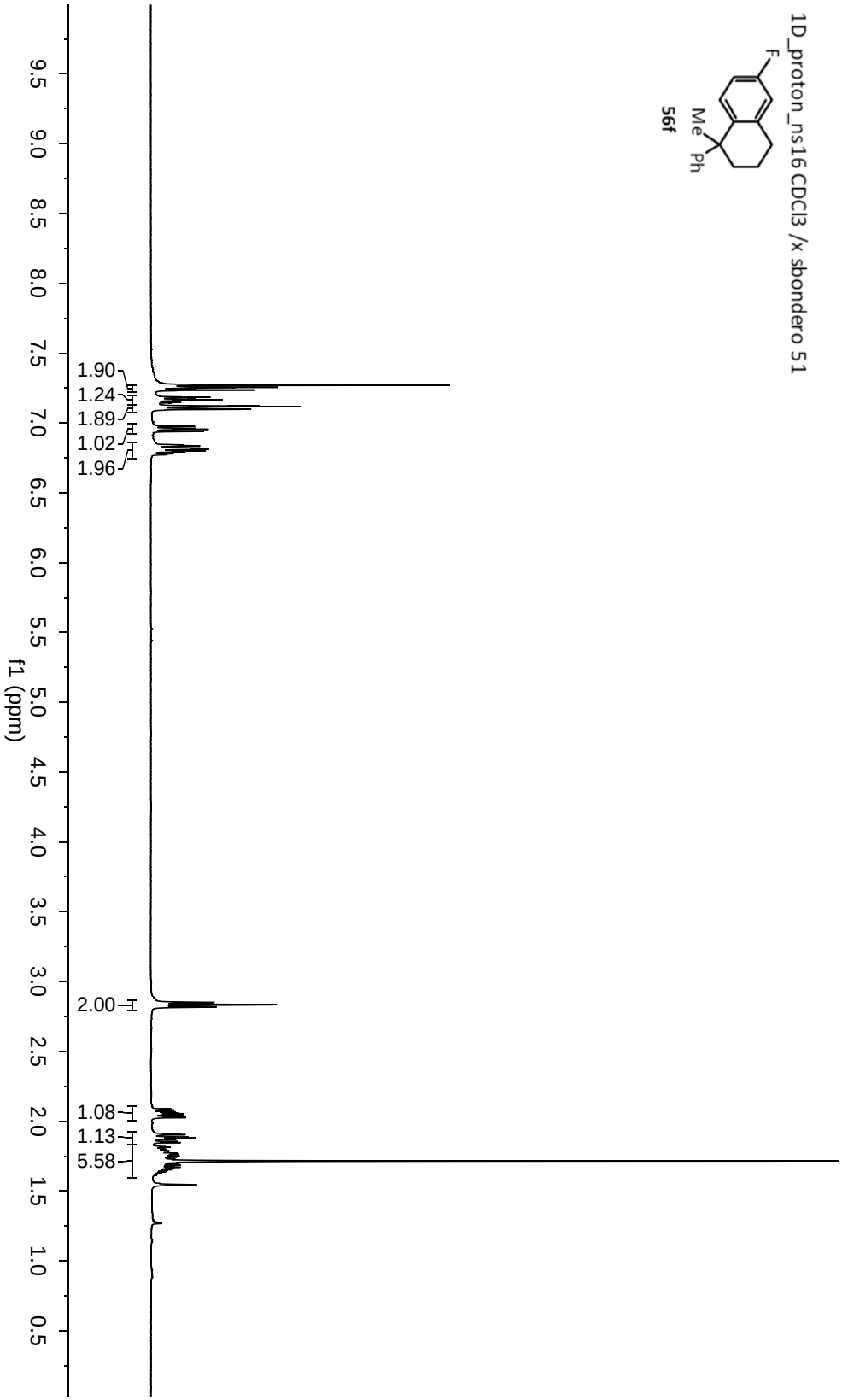


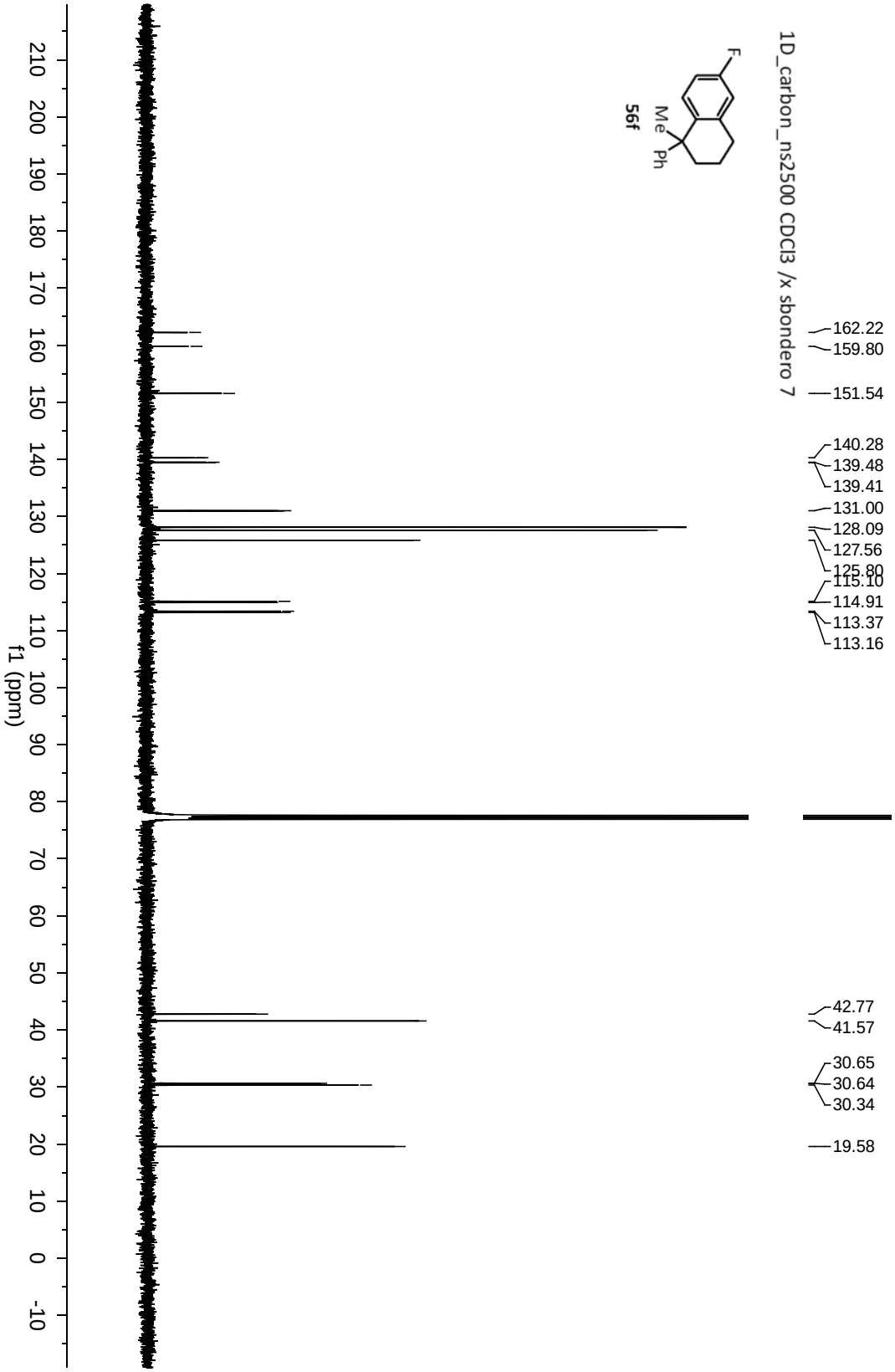
39d′

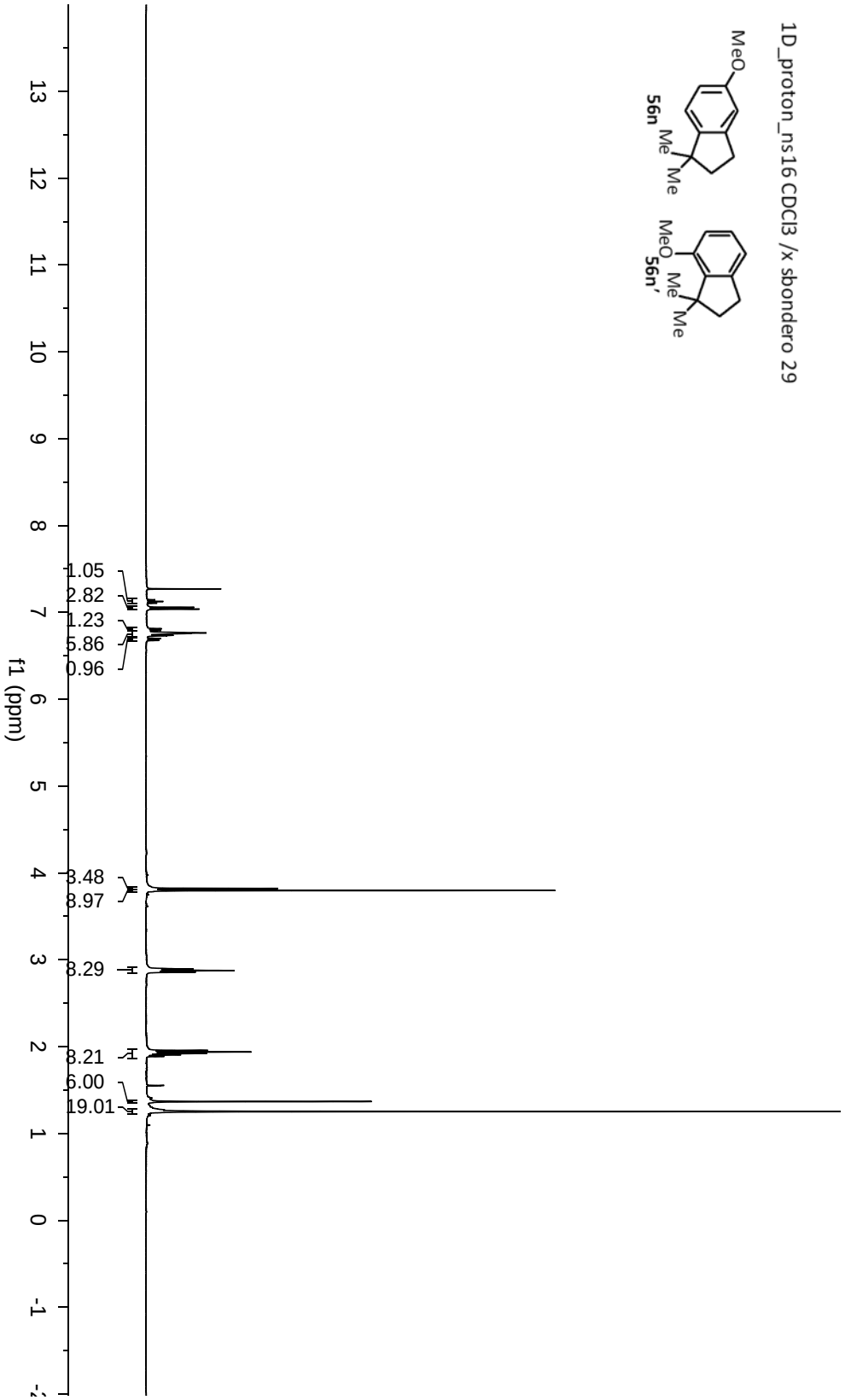

158.32
158.23
138.27
137.73
137.22
129.62
129.53
114.87
114.16
112.23
68.11
66.56
64.82
55.56
55.43
43.62
42.01
34.08
29.16
125.690 MHz C13[H 1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
MeO
O
Cl
Cl
39d'
MeO
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

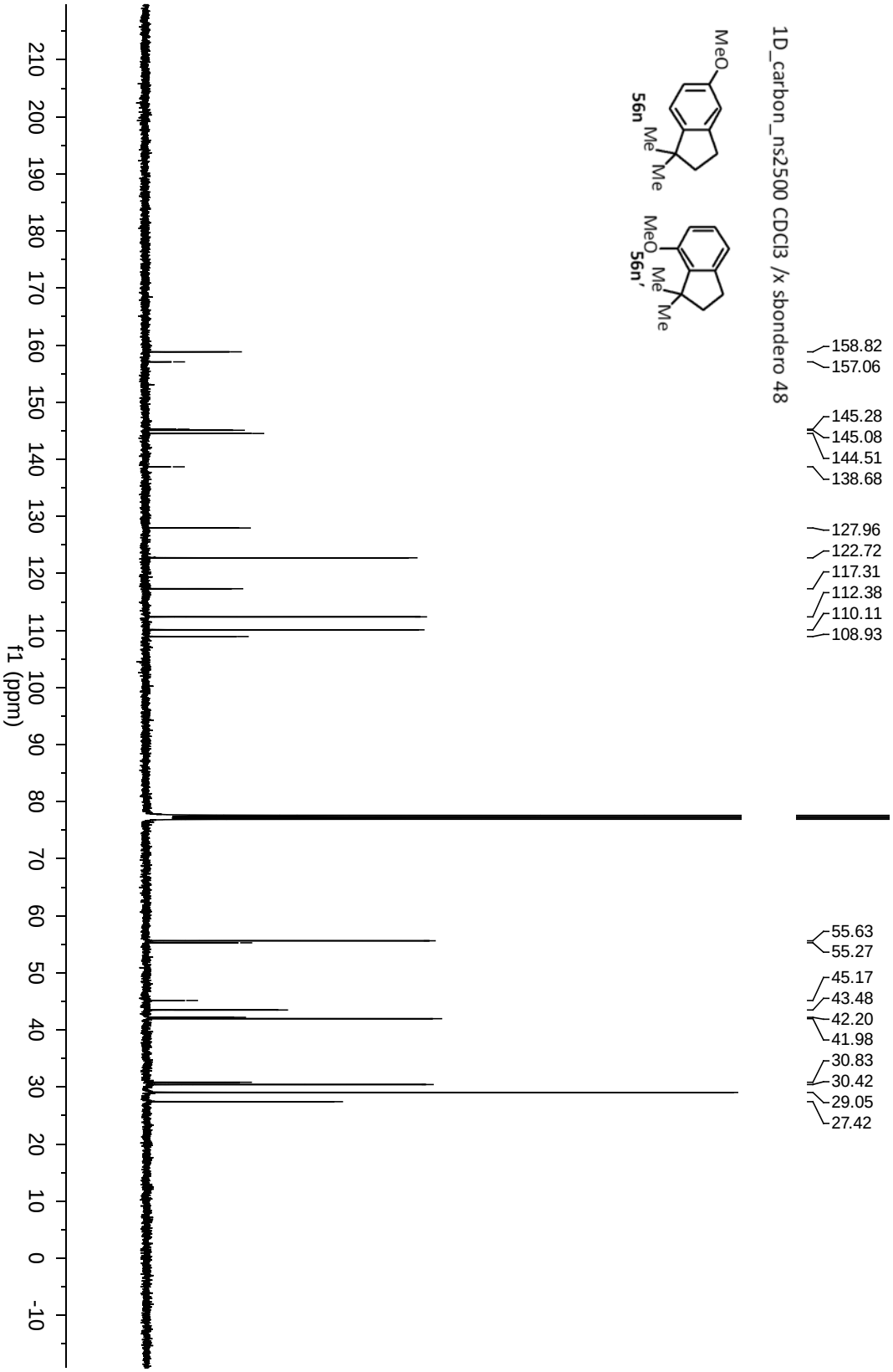

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe
OMe
56a Me Ph
2.01
3.06
1.07
1.00
1.00
3.03
2.09
1.19
4.30
1.30
f1 (ppm)
10
9
8
7
6
5
4
3
2
1
0
-1

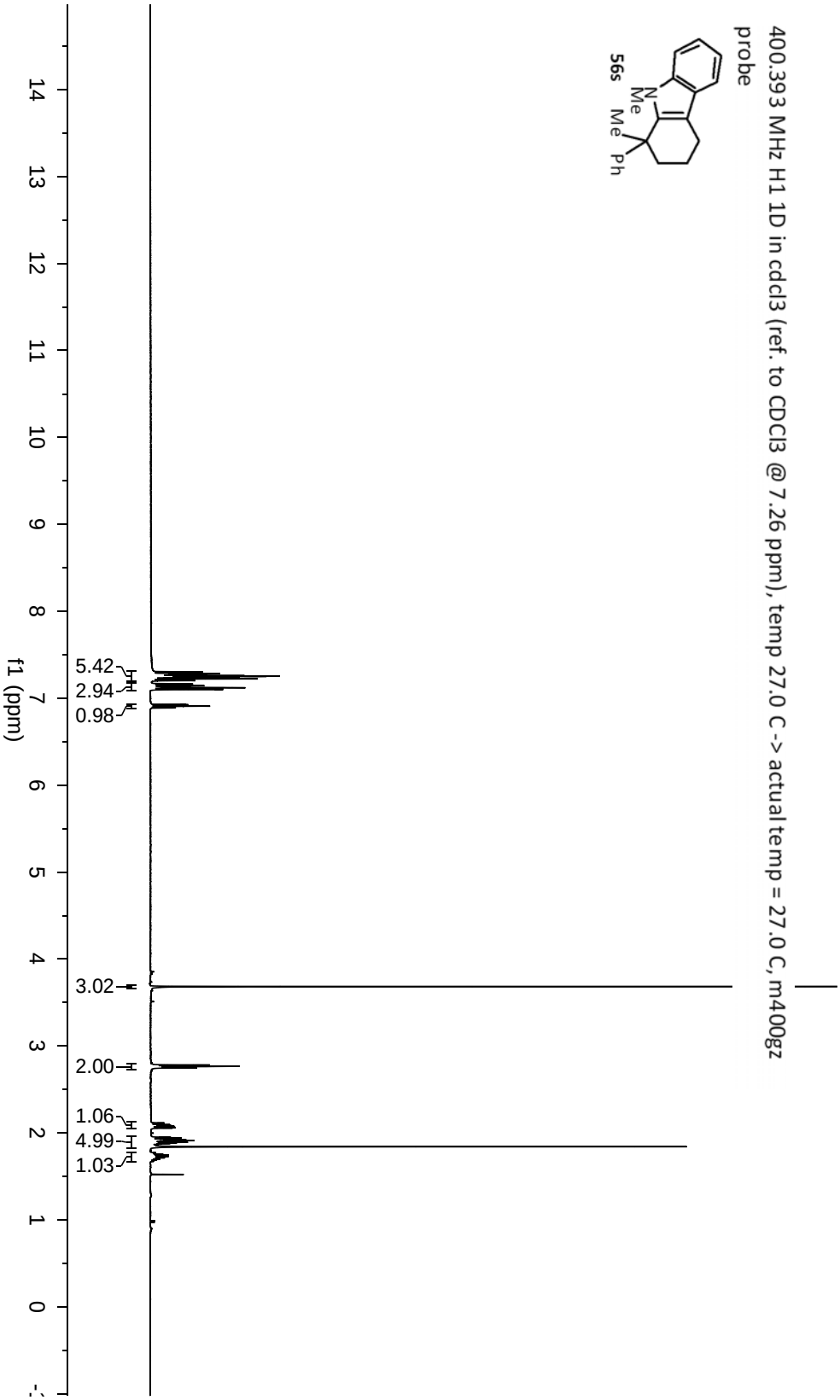

100.690 MHz C13[H 1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
OMe
56a Me Ph
157.15
151.73
145.78
127.96
127.66
126.57
126.04
125.63
121.55
106.93
55.52
43.13
41.28
30.19
23.88
19.03
f1 (ppm)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

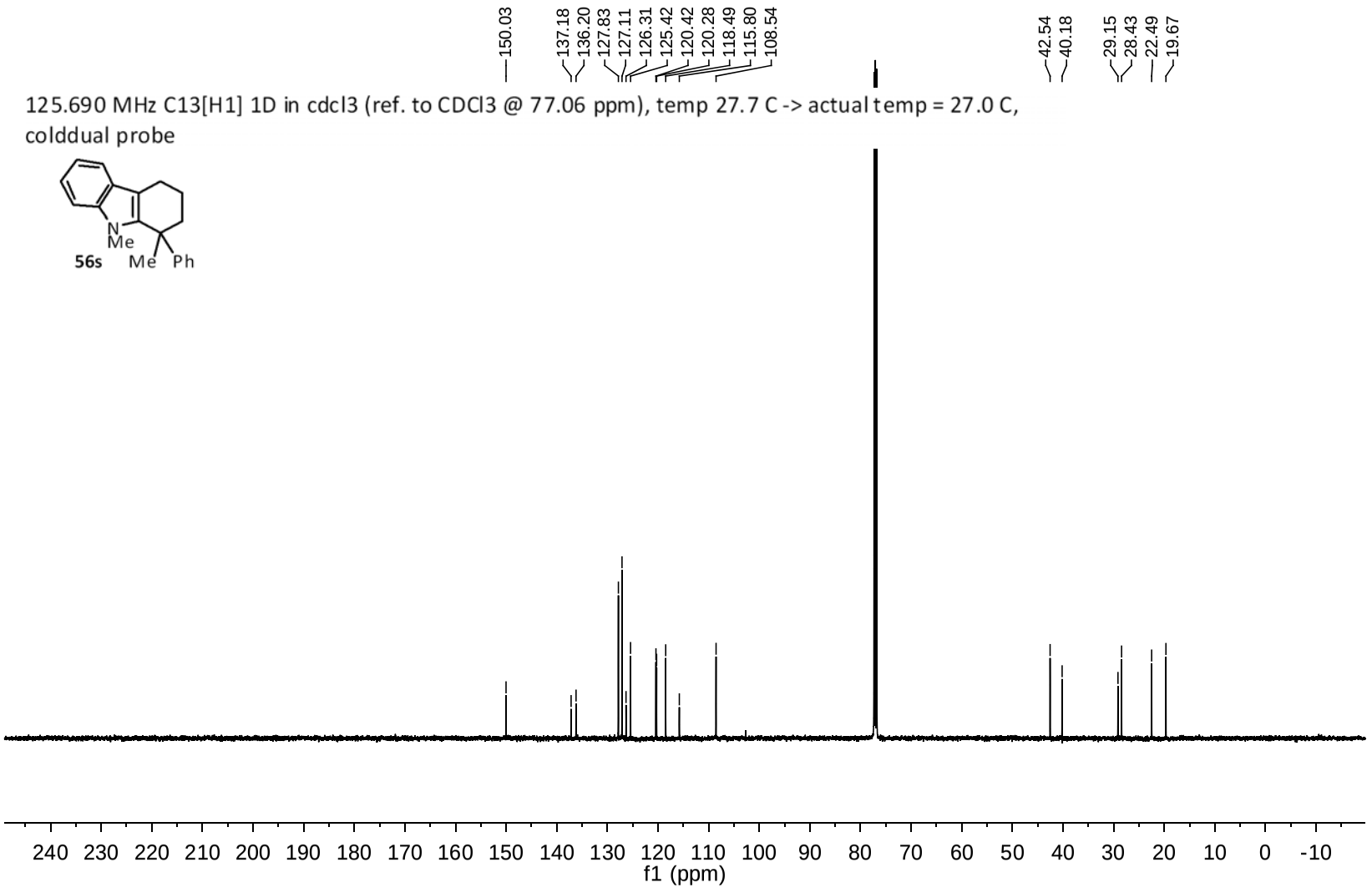

1D_proton_ns16 CDCl3 /x sbondero 51
F
Me
Ph
56f
1.90
1.24
1.89
1.02
1.96
2.00
1.08
1.13
5.58
f1 (ppm)
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


1D_carbon_ns2500 CDCl3 /x sbondero 7
56f
F
Me
Ph
162.22
159.80
151.54
140.28
139.48
139.41
131.00
128.09
127.56
125.80
115.10
114.91
113.37
113.16
42.77
41.57
30.65
30.64
30.34
19.58
f1 (ppm)


1D_proton_ns16 CDCl3 /x sbondero 29
MeO
Me
Me
56n
MeO
Me
Me
56n'
f1 (ppm)
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
1.05
2.82
1.23
5.86
0.96
3.48
8.97
8.29
8.21
6.00
19.01

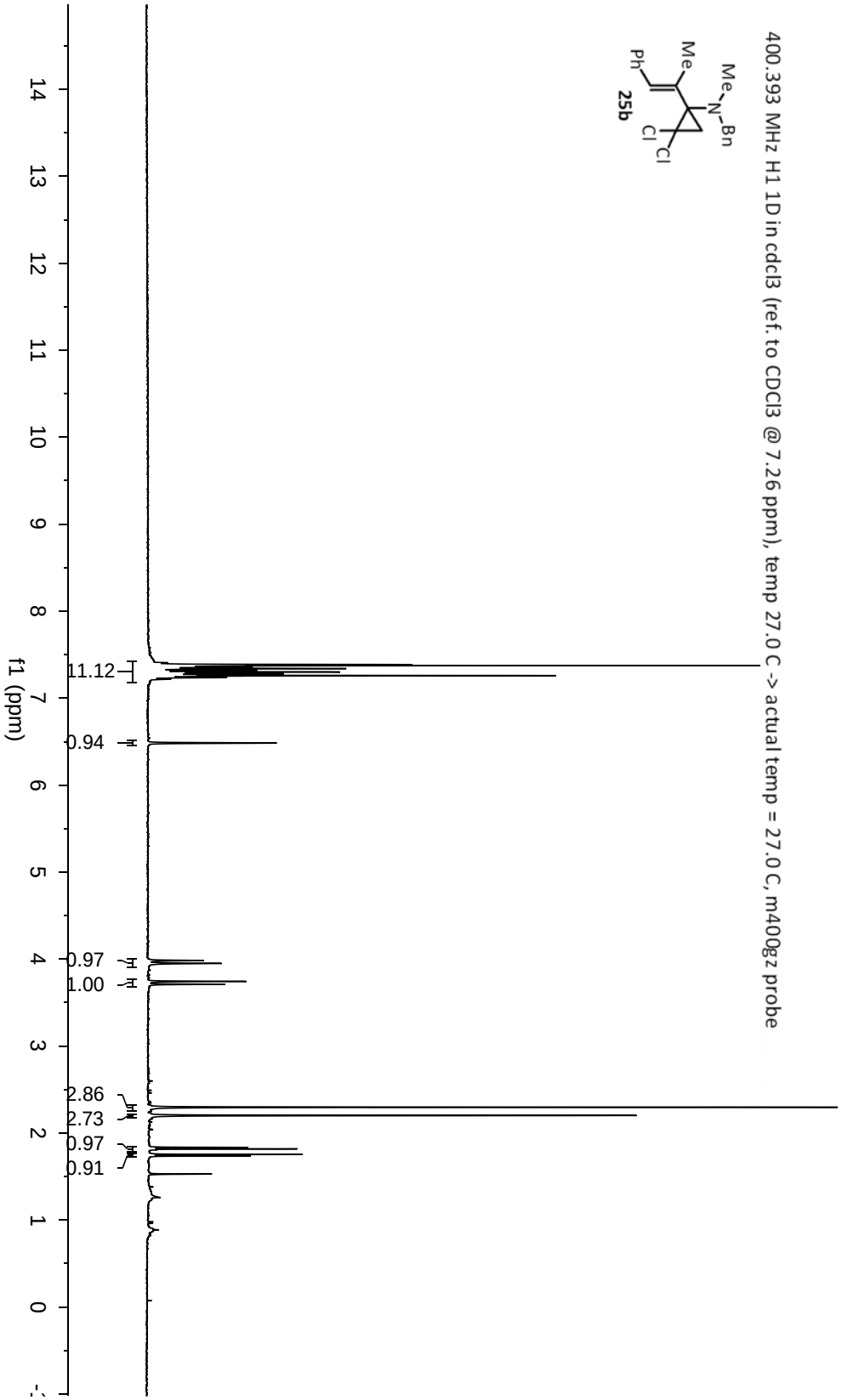

1D_carbon_ns2500 CDCl3 /x sbondero 48
MeO
Me
Me
56n
MeO
Me
Me
56n'
158.82
157.06
145.28
145.08
144.51
138.68
127.96
122.72
117.31
112.38
110.11
108.93
55.63
55.27
45.17
43.48
42.20
41.98
30.83
30.42
29.05
27.42
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

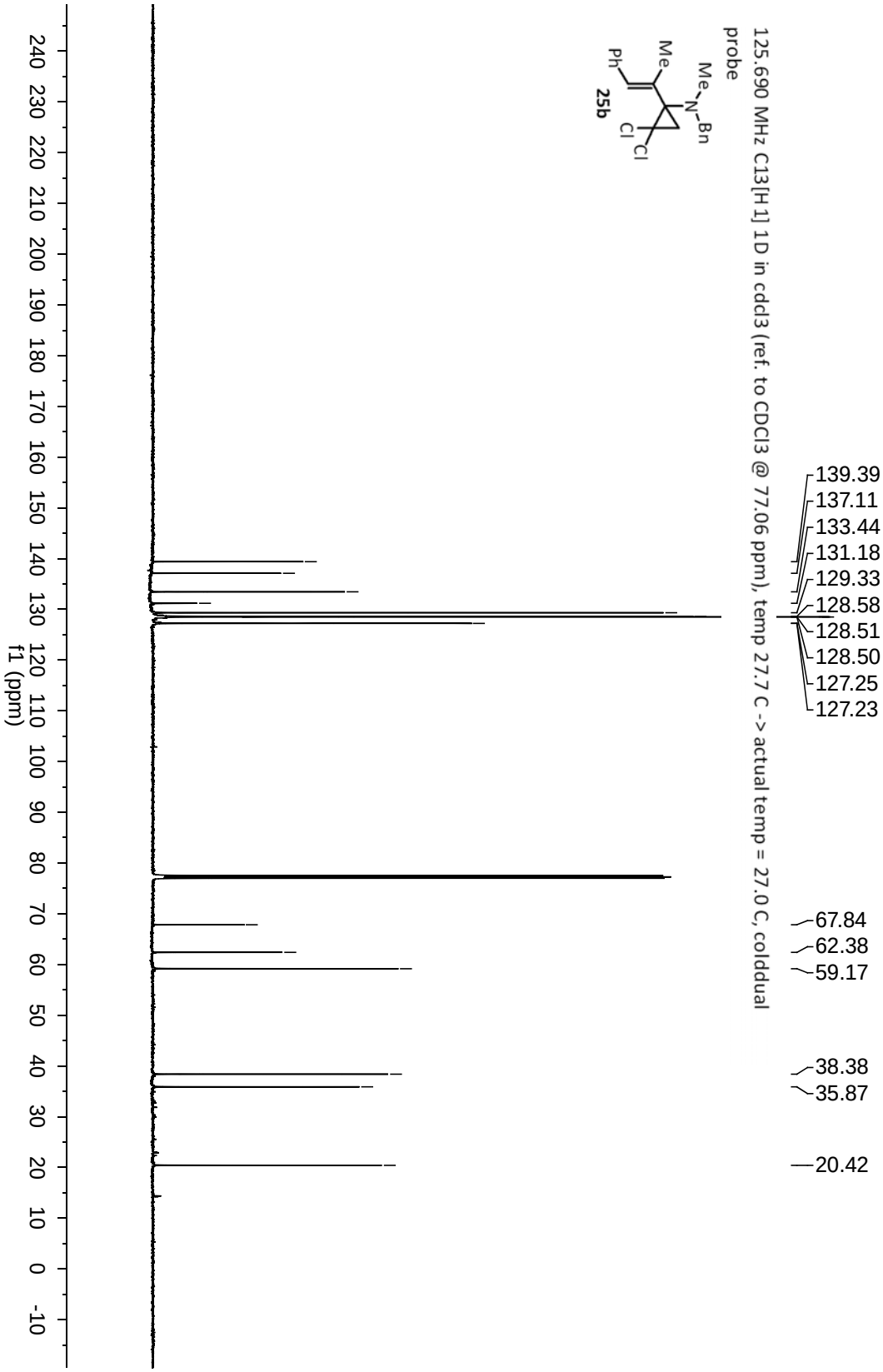

400.393 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
56s
N
Me
Me
Ph
f1 (ppm)
5.42
2.94
0.98
3.02
2.00
1.06
4.99
1.03

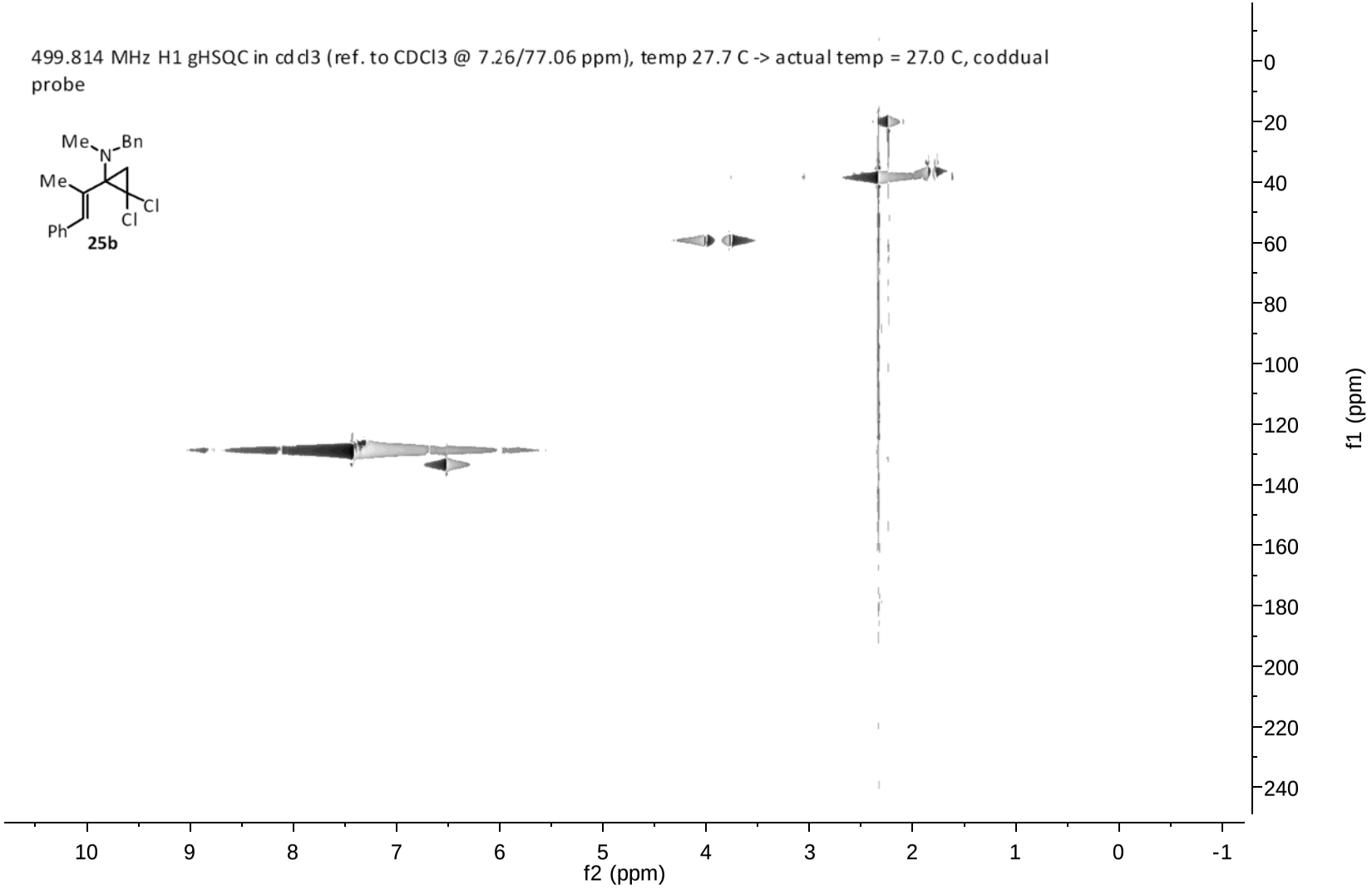

150.03
137.18
136.20
127.83
127.11
126.31
125.42
120.42
120.28
118.49
115.80
108.54
42.54
40.18
29.15
28.43
22.49
19.67
125.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C,
colddual probe
N
Me
56s Me Ph
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

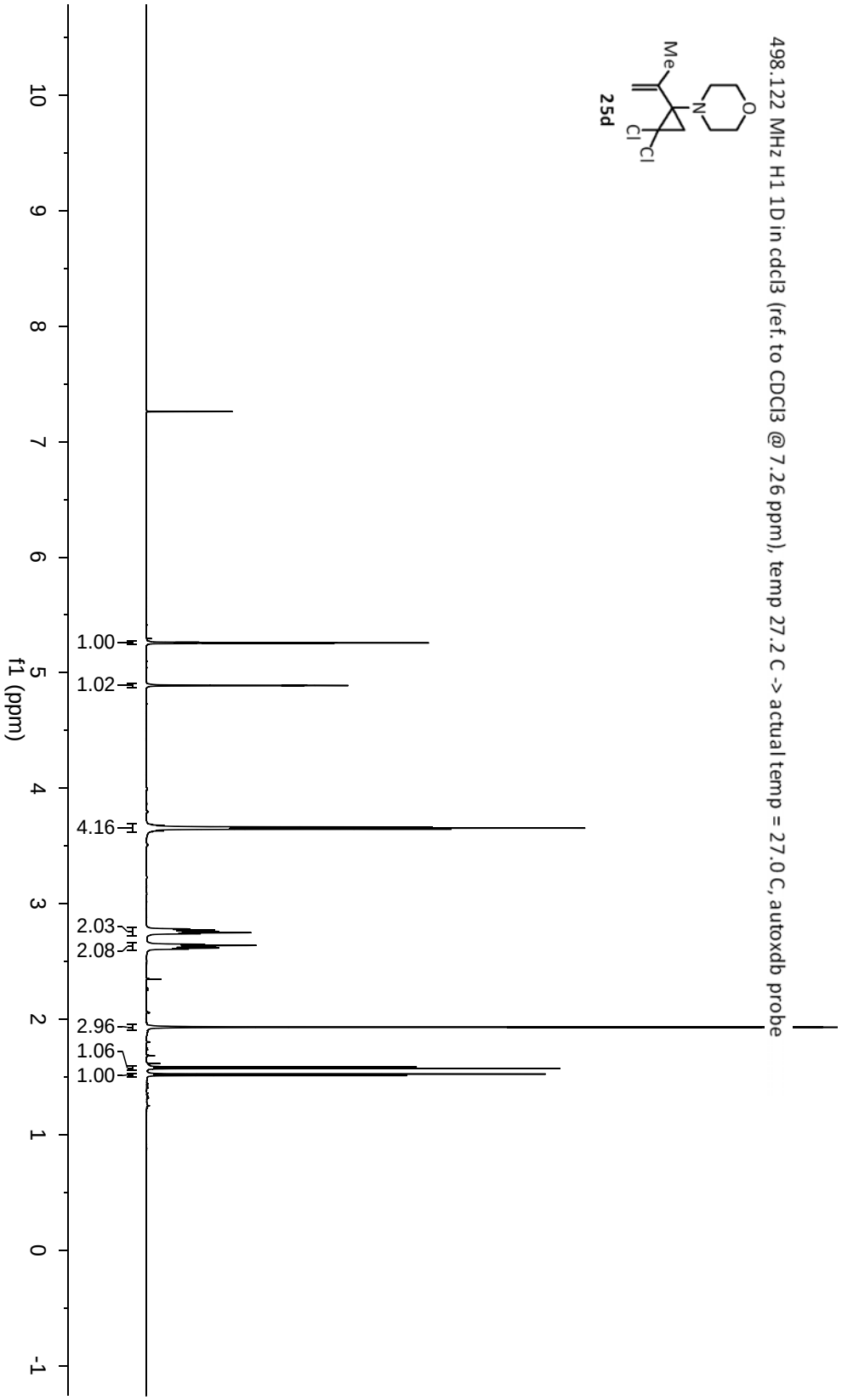
Appendix III: Selected NMR Spectra

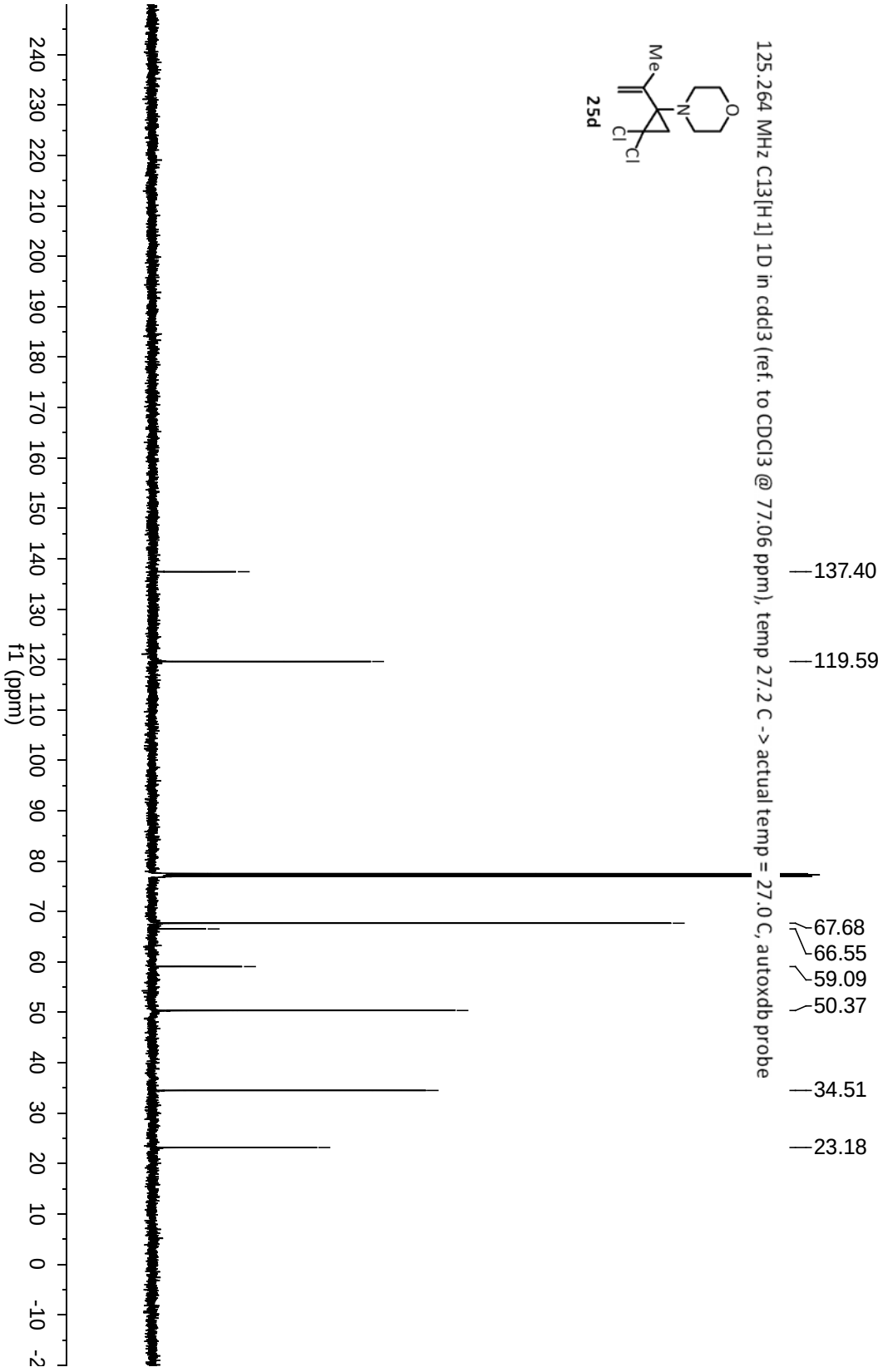
(Chapter 4)

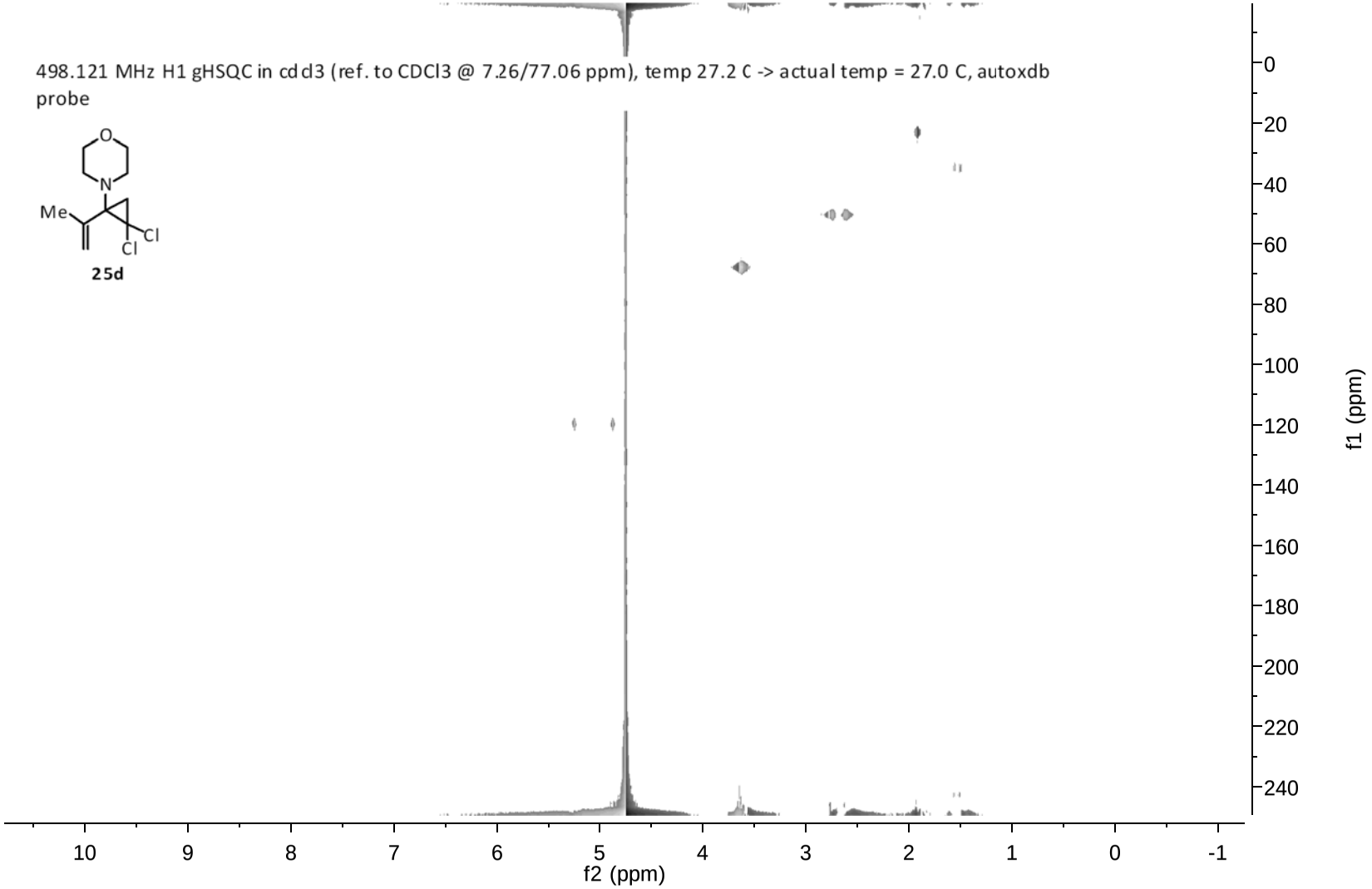

400.393 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Me
N
Bn
Me
Ph
Cl
Cl
25b
f1 (ppm)
11.12
0.94
0.97
1.00
2.86
2.73
0.97
0.91

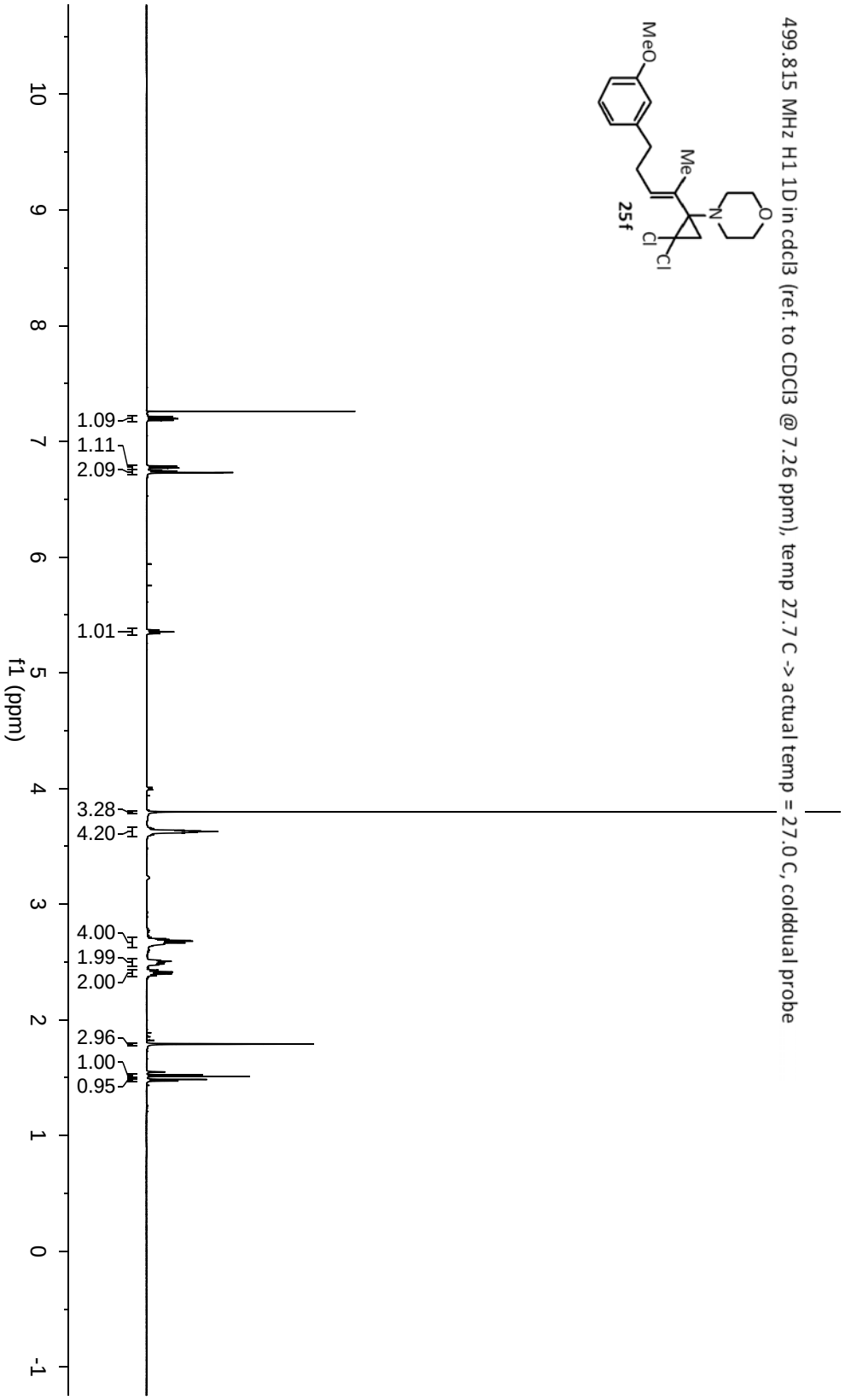

125.690 MHz C13[H 1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual
probe
25b
Me
Ph
Me
N
Bn
Cl
Cl
f1 (ppm)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
139.39
137.11
133.44
131.18
129.33
128.58
128.51
128.50
127.25
127.23
67.84
62.38
59.17
38.38
35.87
20.42


499.814 MHz H1 gHSQC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, coddual probe
Me
N
Bn
Me
Cl
Cl
Ph
25b
f2 (ppm)
f1 (ppm)


498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe
25d
Me
O
N
Cl
Cl
f1 (ppm)
10
9
8
7
6
5
4
3
2
1
0
-1
1.00
1.02
4.16
2.03
2.08
2.96
1.06
1.00

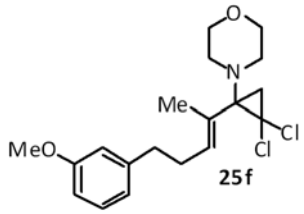

125.264 MHz C13[H 1] 1D in cdd3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe
25d
Me
N
O
Cl
Cl
137.40
119.59
67.68
66.55
59.09
50.37
34.51
23.18
f1 (ppm)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -2


498.121 MHz H1 gHSQC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb
probe
O
N
Me
Cl
Cl
25d
0
20
40
60
80
100
120
140
160
180
200
220
240
f1 (ppm)
10
9
8
7
6
5
4
3
2
1
0
-1
f2 (ppm)

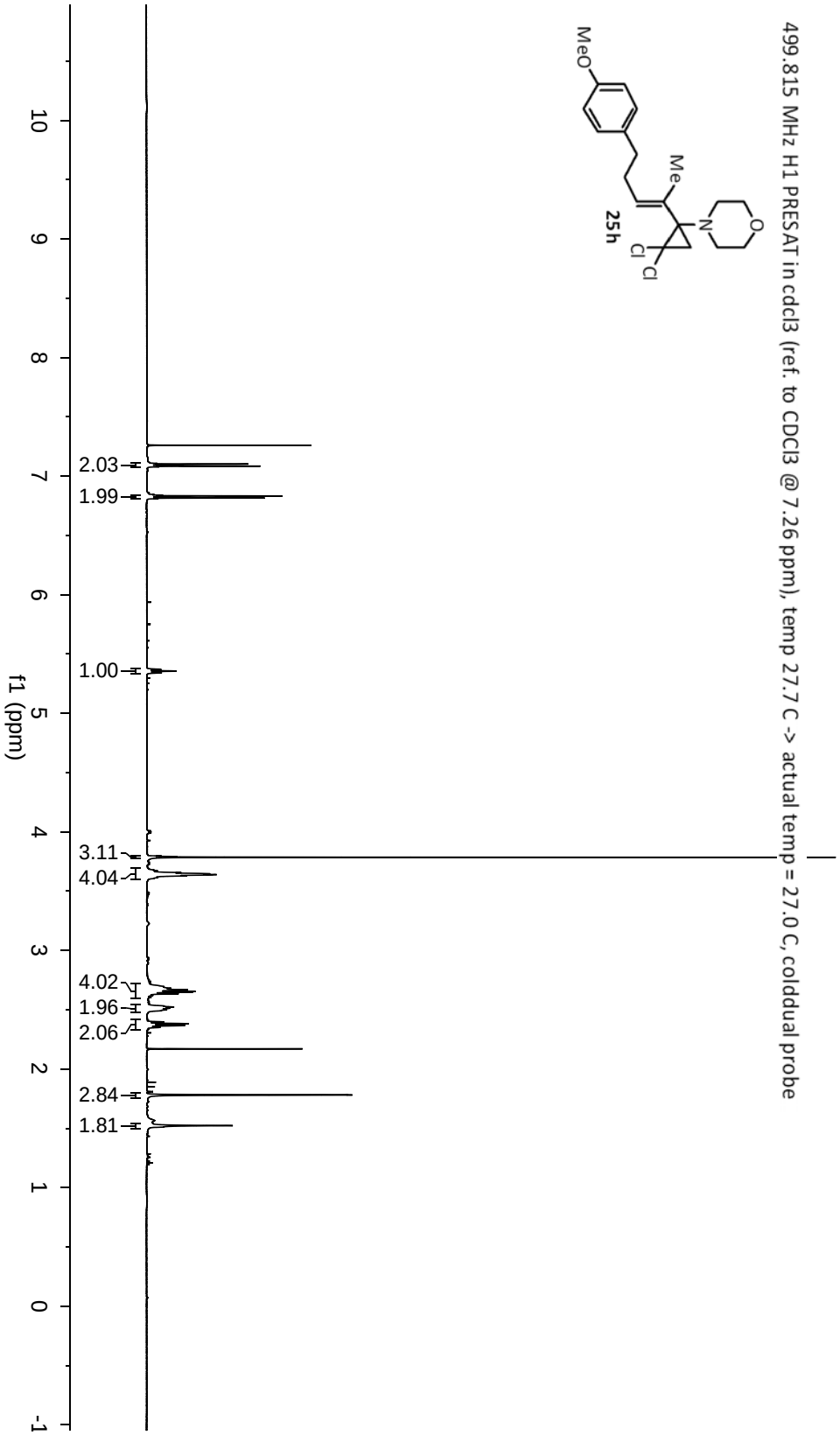

499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
MeO
Me
N
O
Cl
Cl
25f
f1 (ppm)
10
9
8
7
6
5
4
3
2
1
0
-1
1.09
1.11
2.09
1.01
3.28
4.20
4.00
1.99
2.00
2.96
1.00
0.95

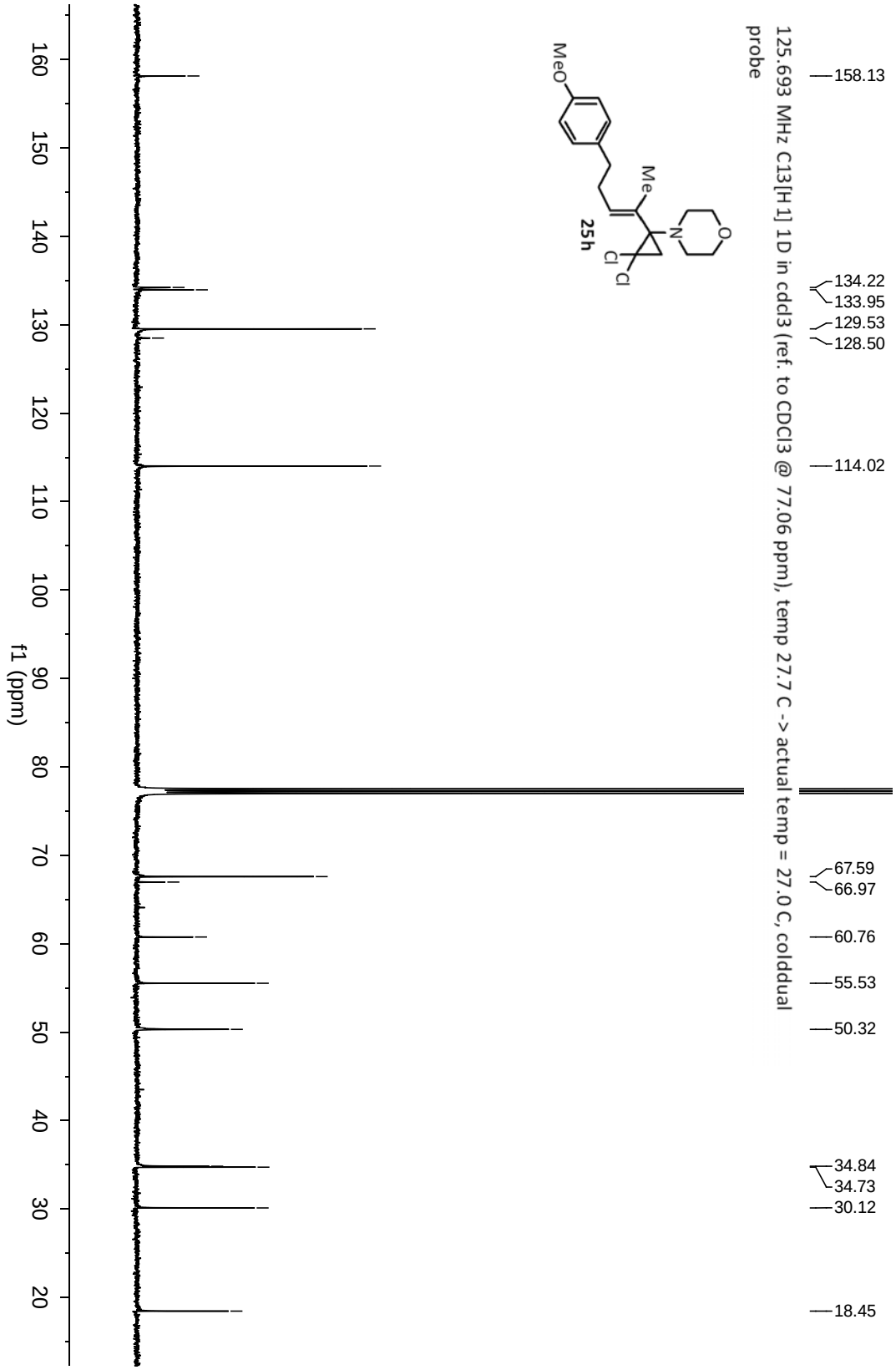
159.91
143.48
134.13
129.55
128.61
121.06
114.61
111.33
67.56
66.90
60.75
55.40
50.35
35.67
34.81
29.78
18.45

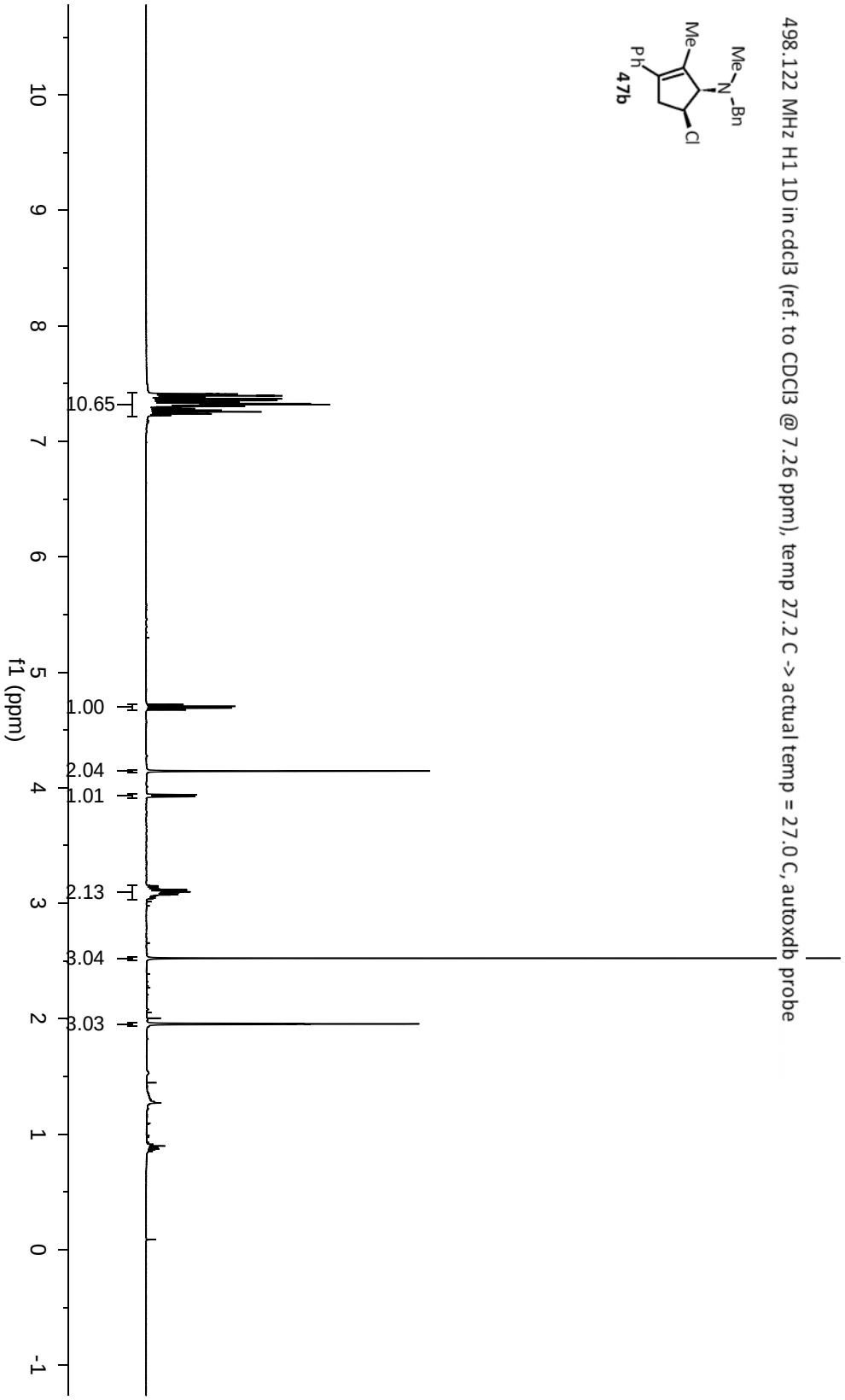
125.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

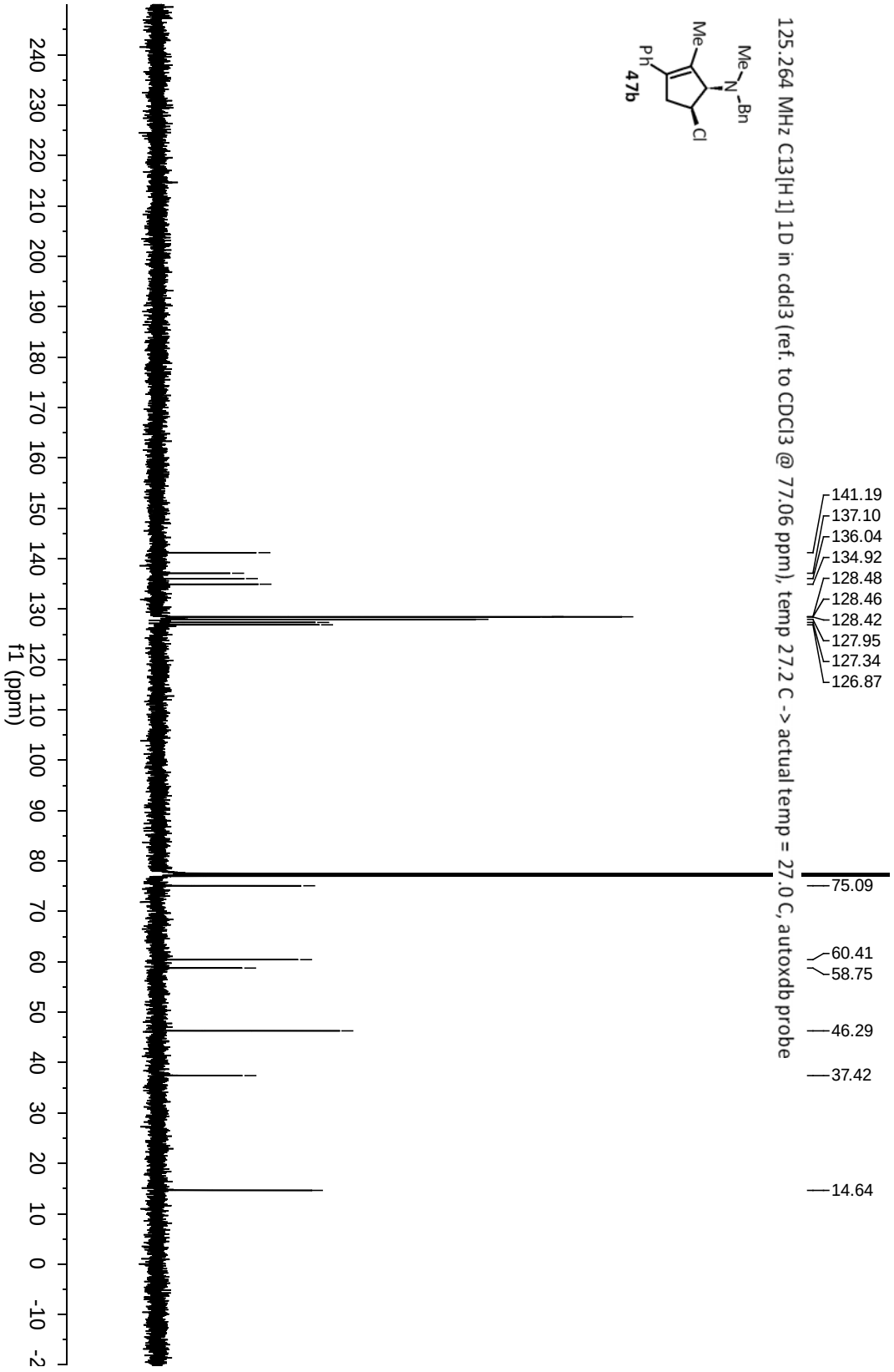


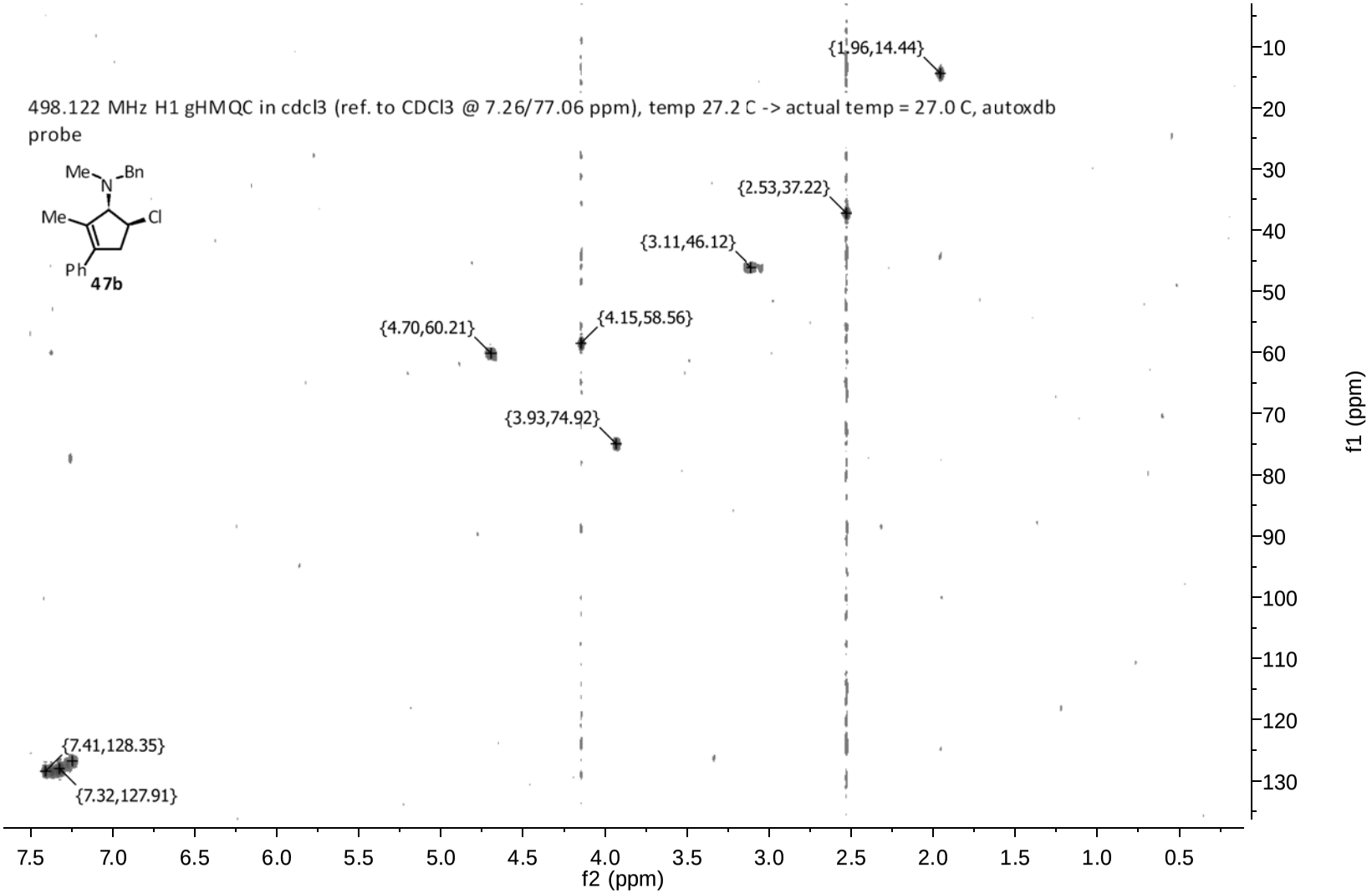
25f


499.815 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
MeO
Me
N
O
Cl
Cl
25h
f1 (ppm)
10
9
8
7
6
5
4
3
2
1
0
-1
2.03
1.99
1.00
3.11
4.04
4.02
1.96
2.06
2.84
1.81

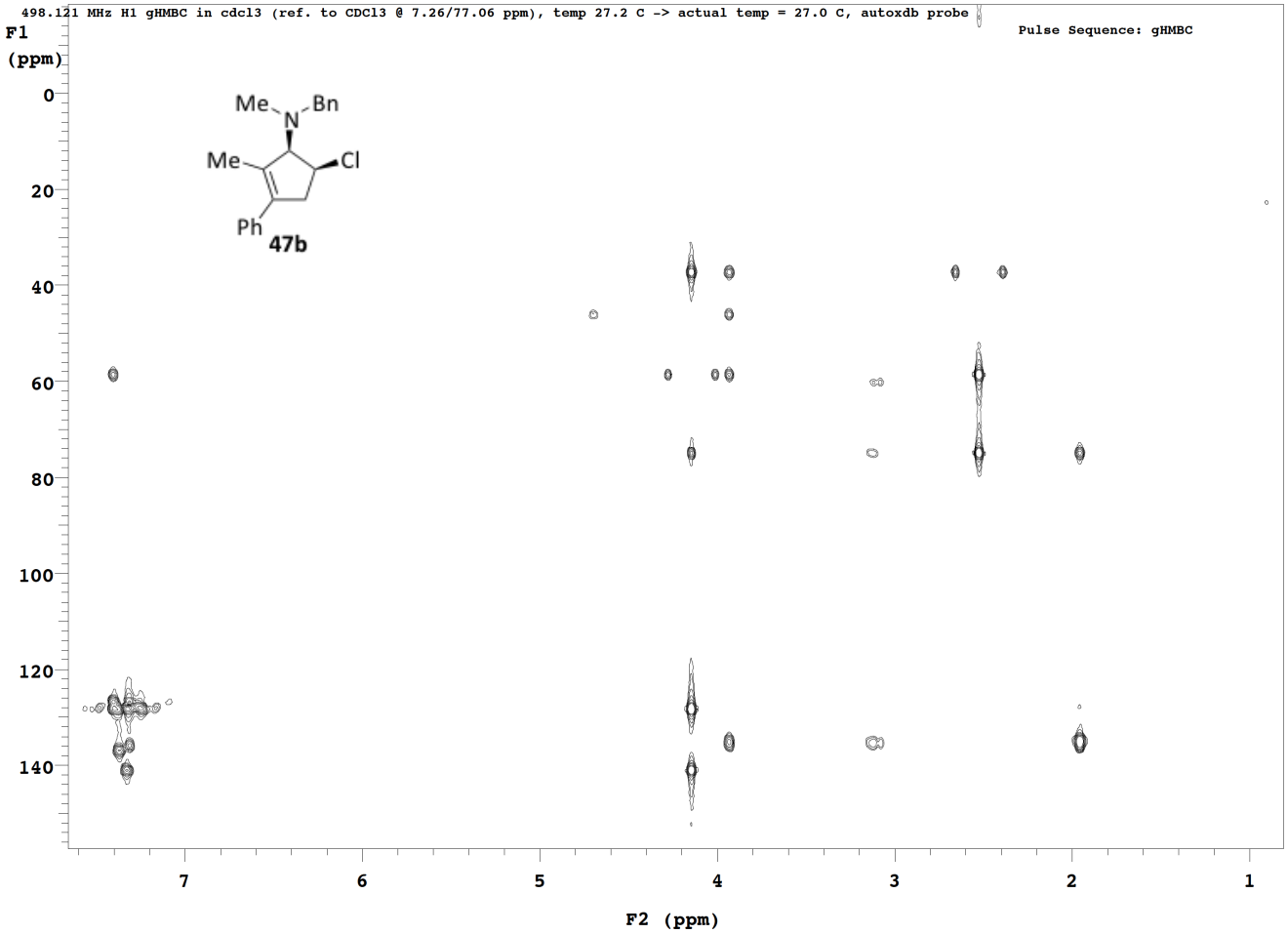

125.693 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
158.13
134.22
133.95
129.53
128.50
114.02
67.59
66.97
60.76
55.53
50.32
34.84
34.73
30.12
18.45
MeO
Me
N
O
Cl
Cl
25h
f1 (ppm)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20


498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe
Me
Me
N
Bn
Ph
Cl
47b
10.65
1.00
2.04
1.01
2.13
3.04
3.03
f1 (ppm)
10
9
8
7
6
5
4
3
2
1
0
-1

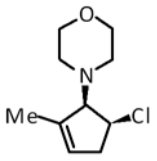

125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe
Me
Me
N
Bn
Ph
Cl
47b
141.19
137.10
136.04
134.92
128.48
128.46
128.42
127.95
127.34
126.87
75.09
60.41
58.75
46.29
37.42
14.64
f1 (ppm)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -2


498.122 MHz H1 gHMQC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb
probe
Me
N
Bn
Me
Cl
Ph
47b
{1.96,14.44}
{2.53,37.22}
{3.11,46.12}
{4.15,58.56}
{4.70,60.21}
{3.93,74.92}
{7.41,128.35}
{7.32,127.91}
f2 (ppm)
f1 (ppm)

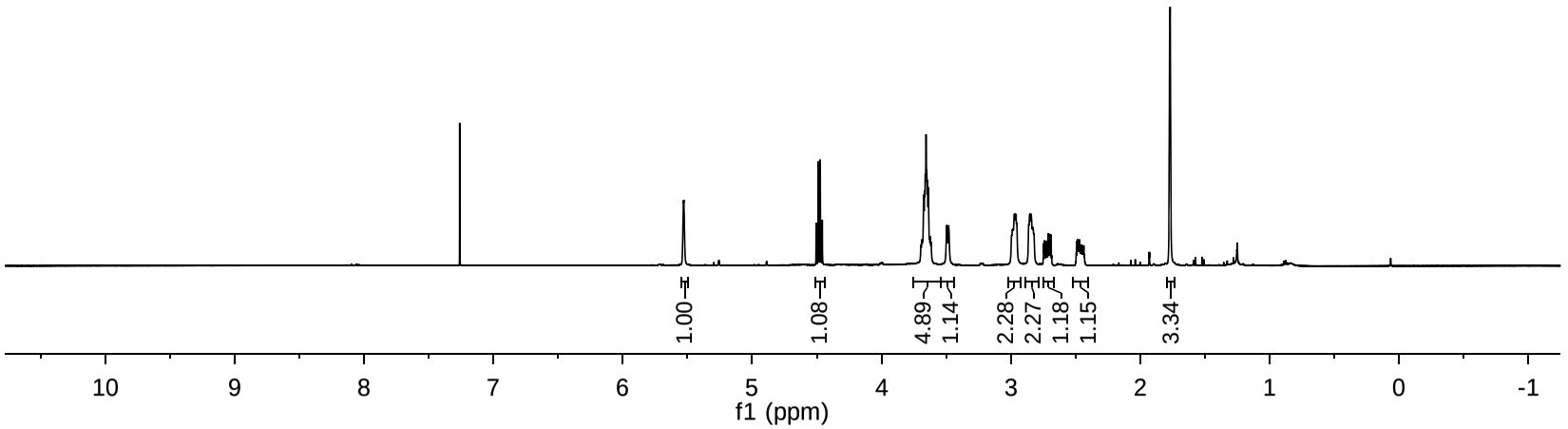
SB-11-103PA2
20120320

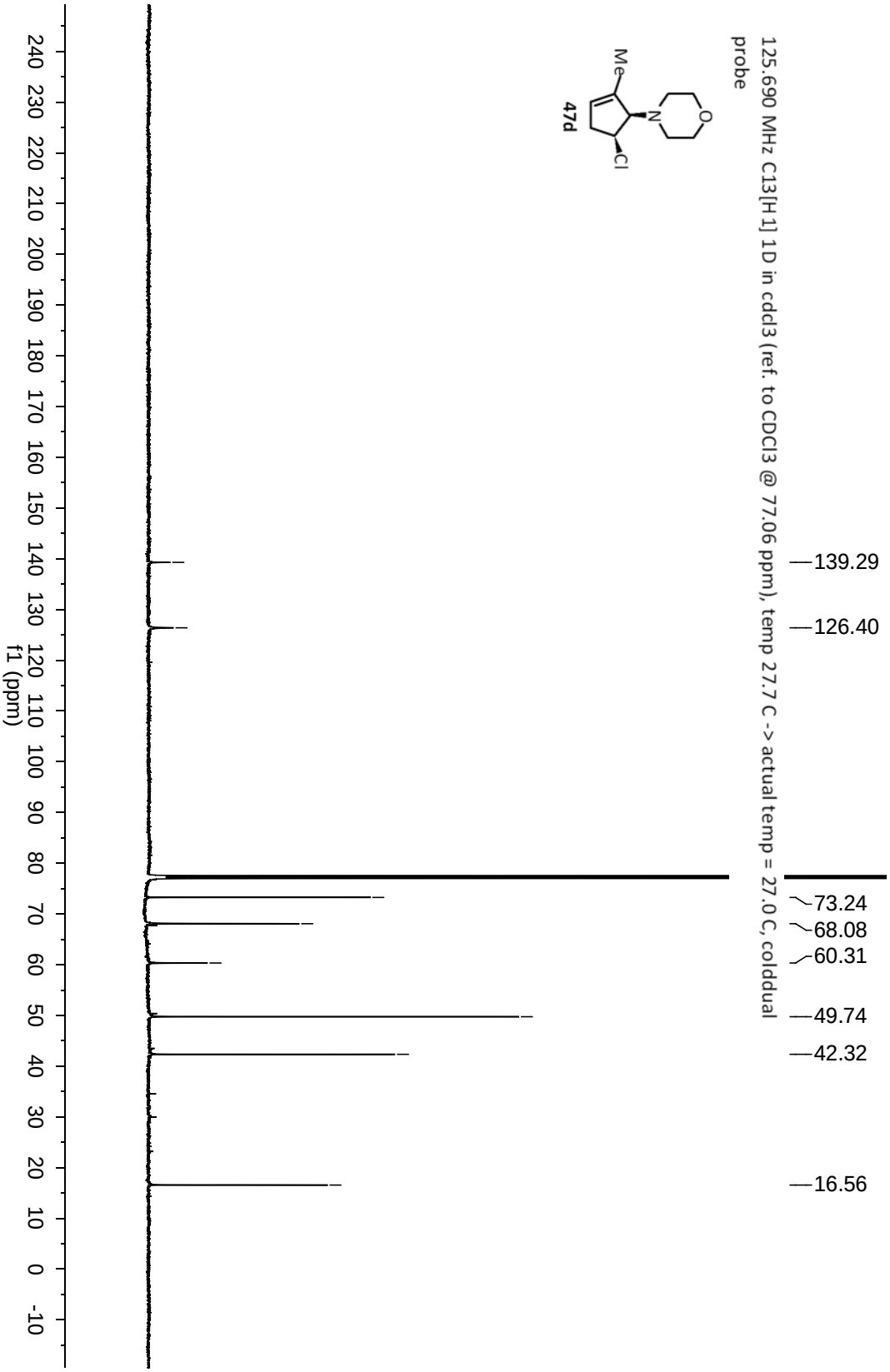


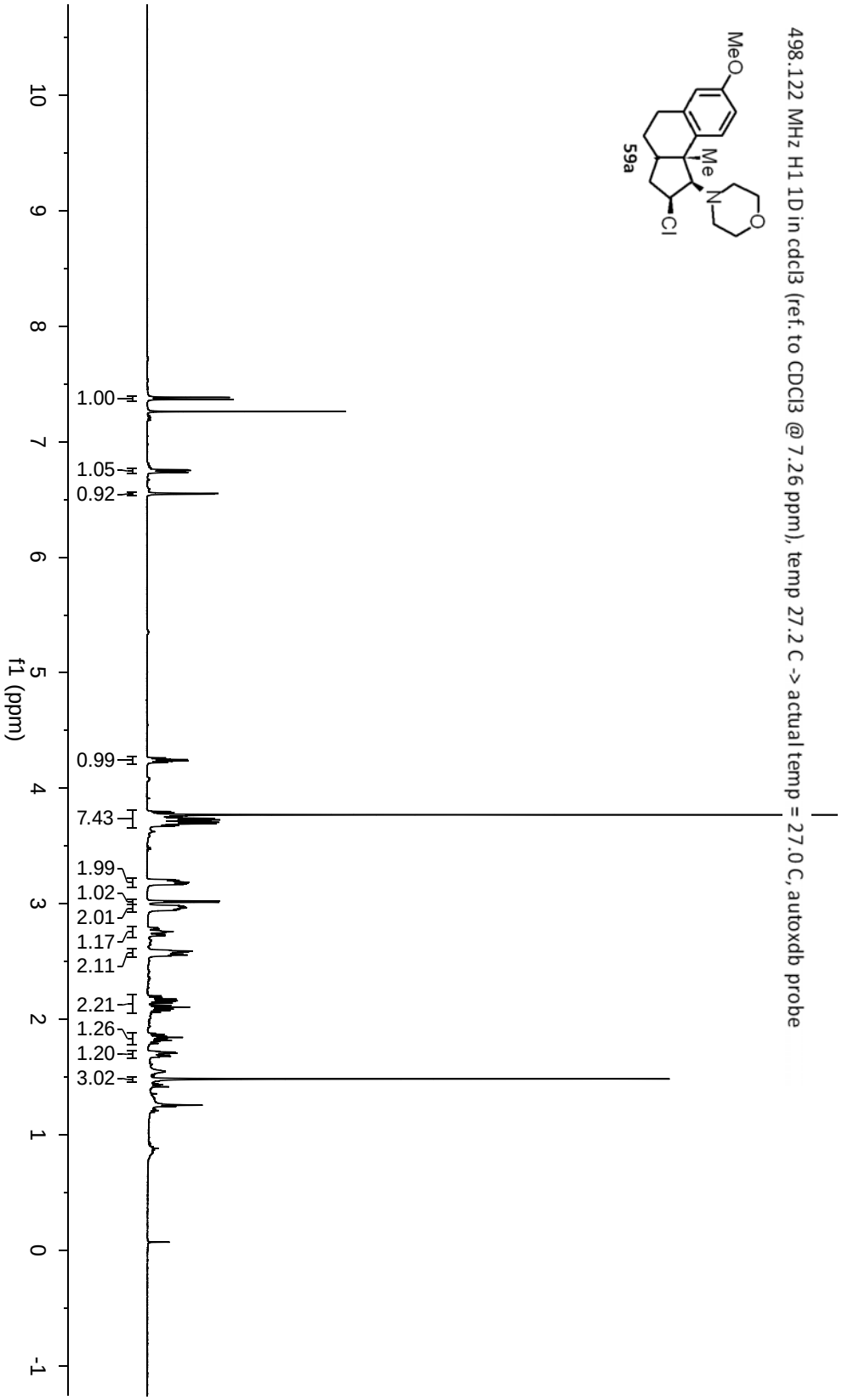
499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

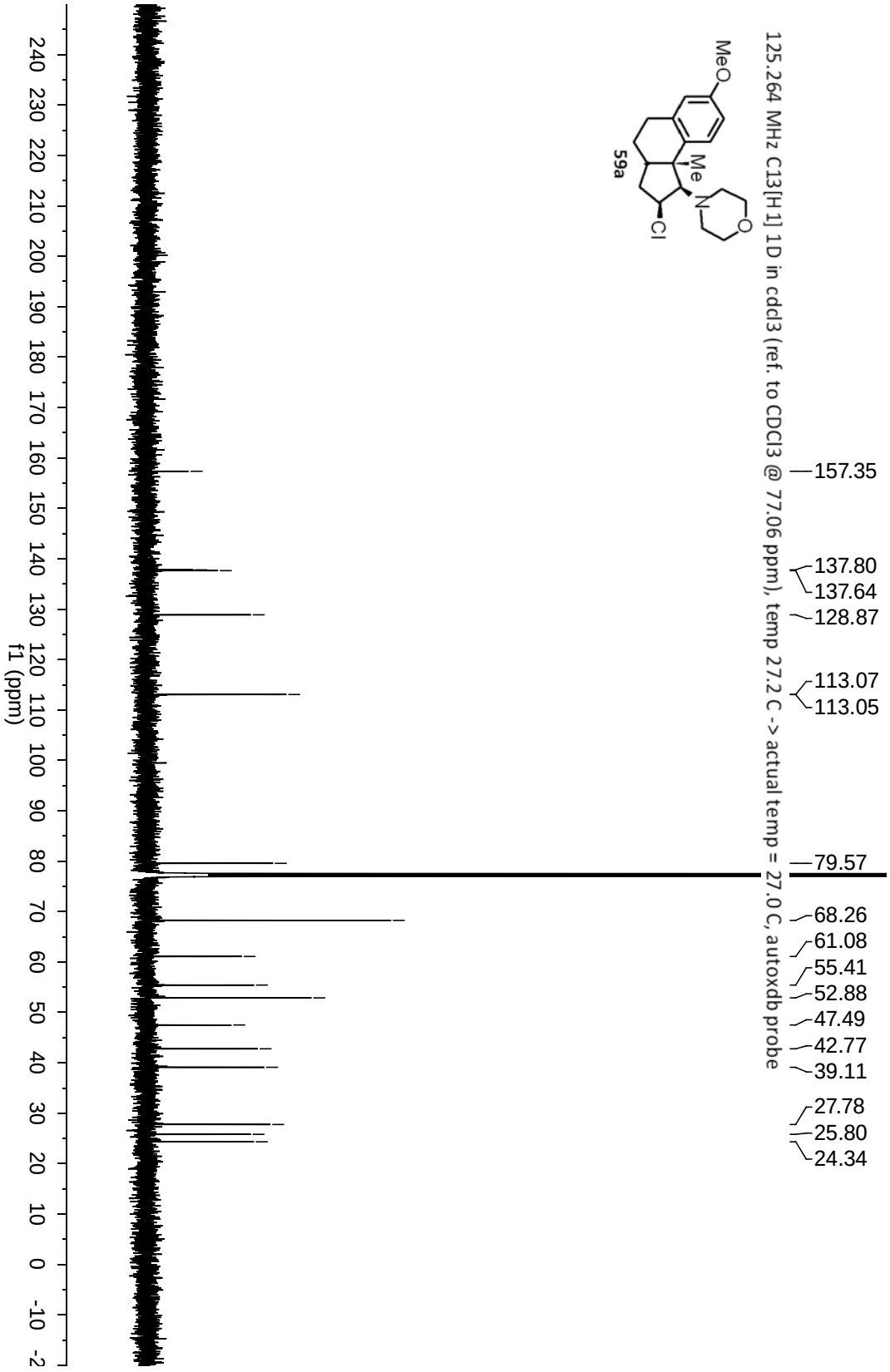


47d

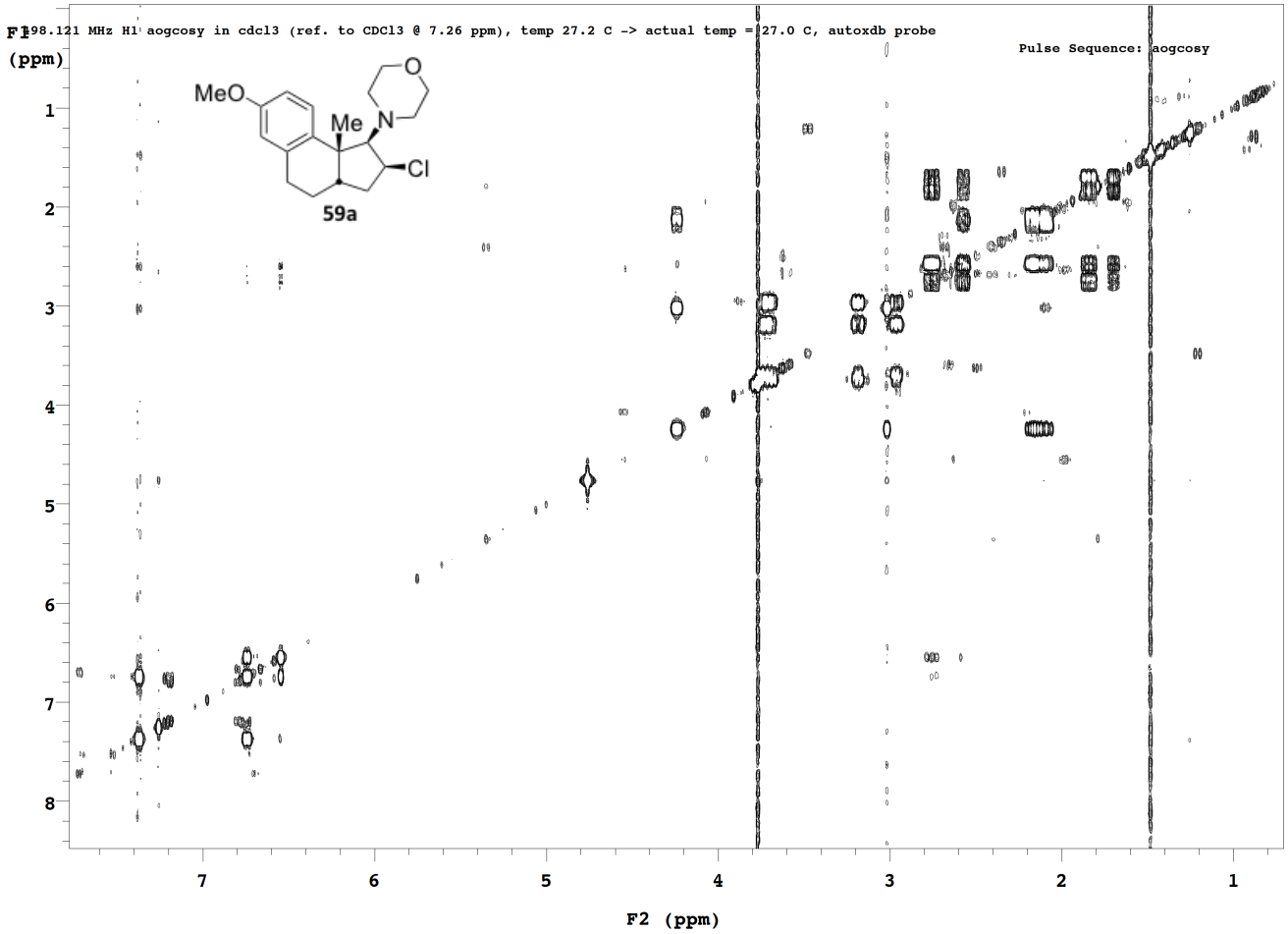



125.690 MHz C13[H 1] 1D in cdd3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
47d
Me
N
O
Cl
139.29
126.40
73.24
68.08
60.31
49.74
42.32
16.56
f1 (ppm)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

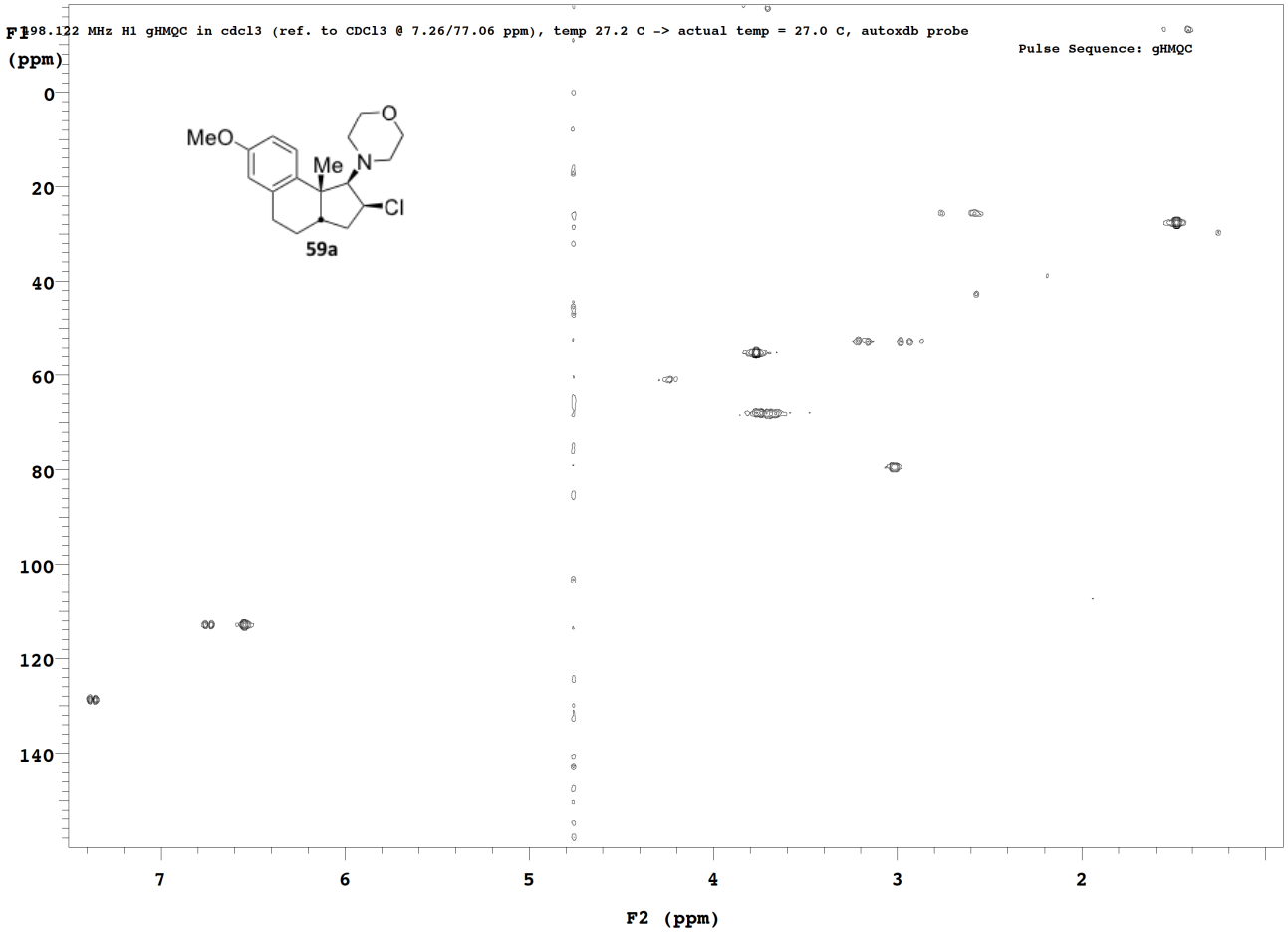

498.122 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe
MeO
Me
N
O
Cl
59a
f1 (ppm)
10
9
8
7
6
5
4
3
2
1
0
-1
1.00
1.05
0.92
0.99
7.43
1.99
1.02
2.01
1.17
2.11
2.21
1.26
1.20
3.02


MeO
Me
N
O
Cl
59a
125.264 MHz C13[H 1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe
157.35
137.80
137.64
128.87
113.07
113.05
79.57
68.26
61.08
55.41
52.88
47.49
42.77
39.11
27.78
25.80
24.34
f1 (ppm)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -2

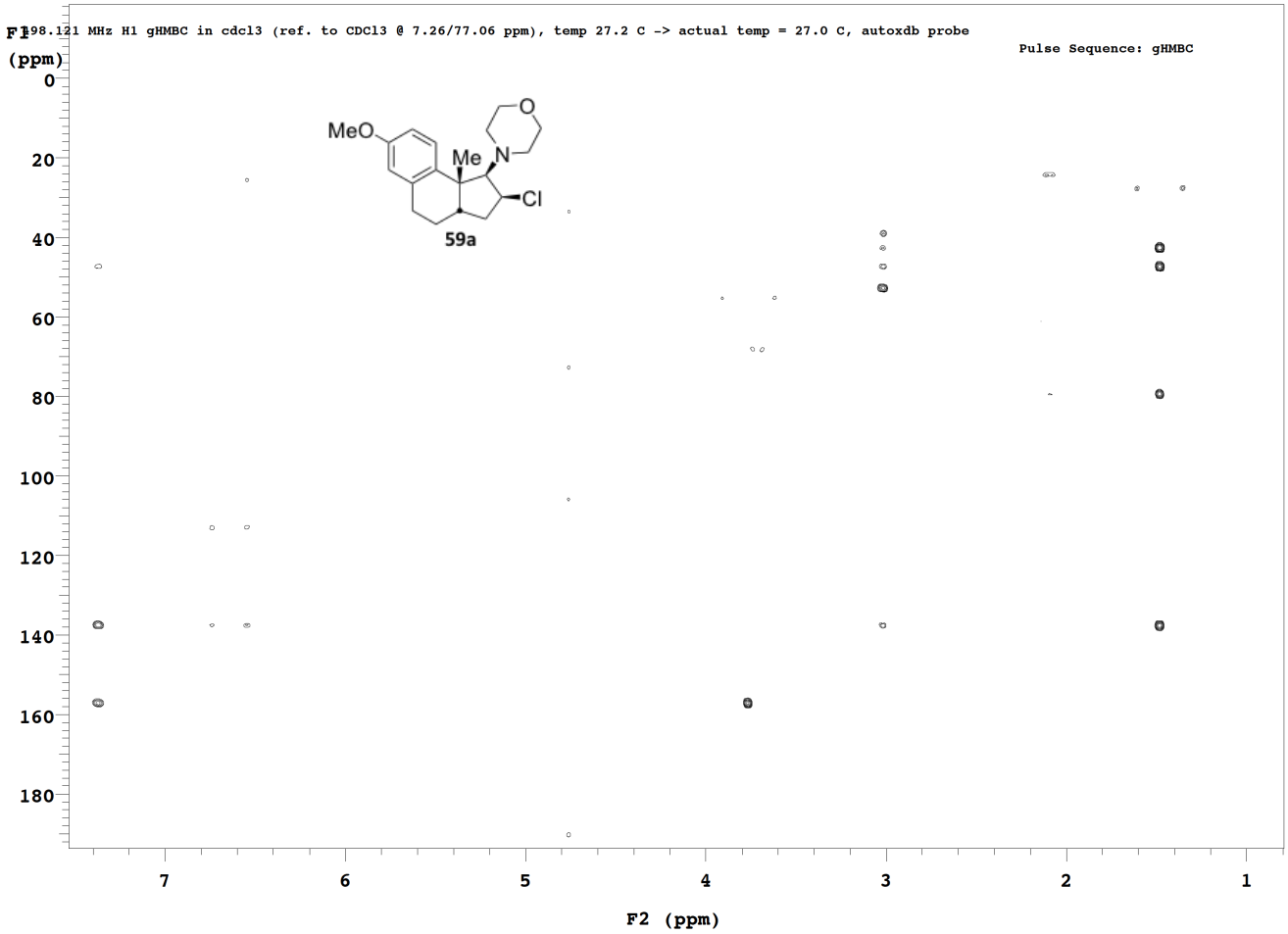
SB-11-101PA1
minor diastereomer
20120319



SB-11-101PA1
minor diastereomer
20120319



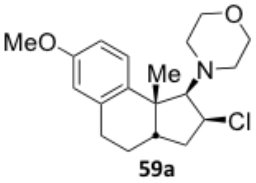
SB-11-101PA1
minor diastereomer
20120319



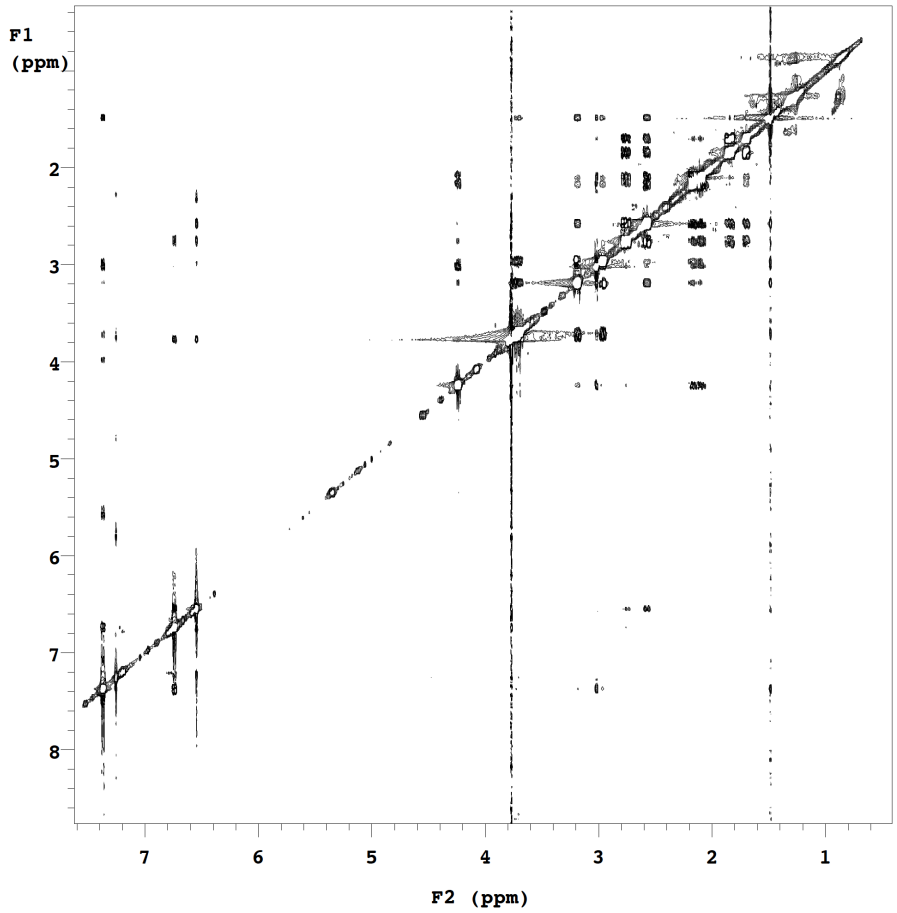
SB-11-101PA1
minor diastereomer
20120319

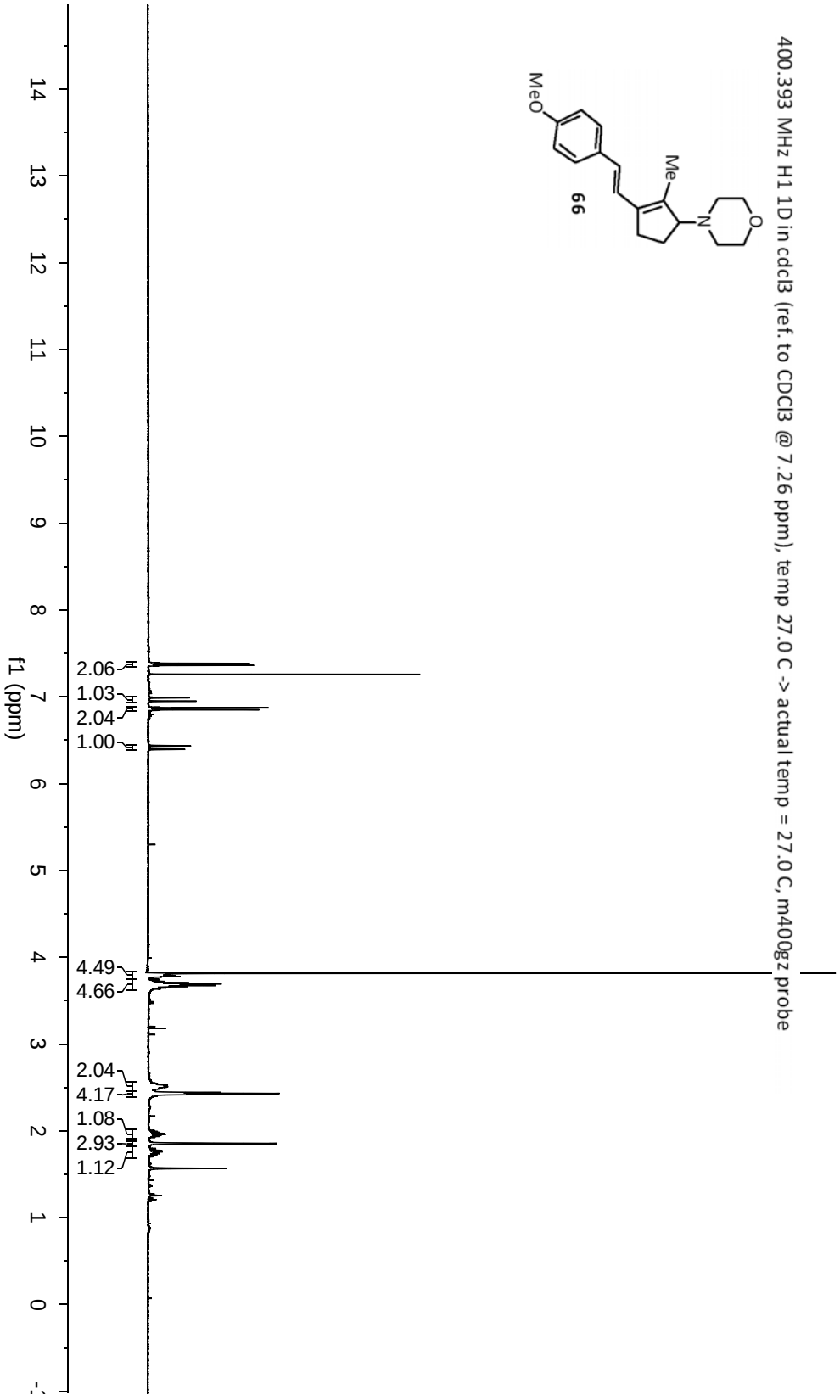
498.121 MHz H1 aotroesy in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe

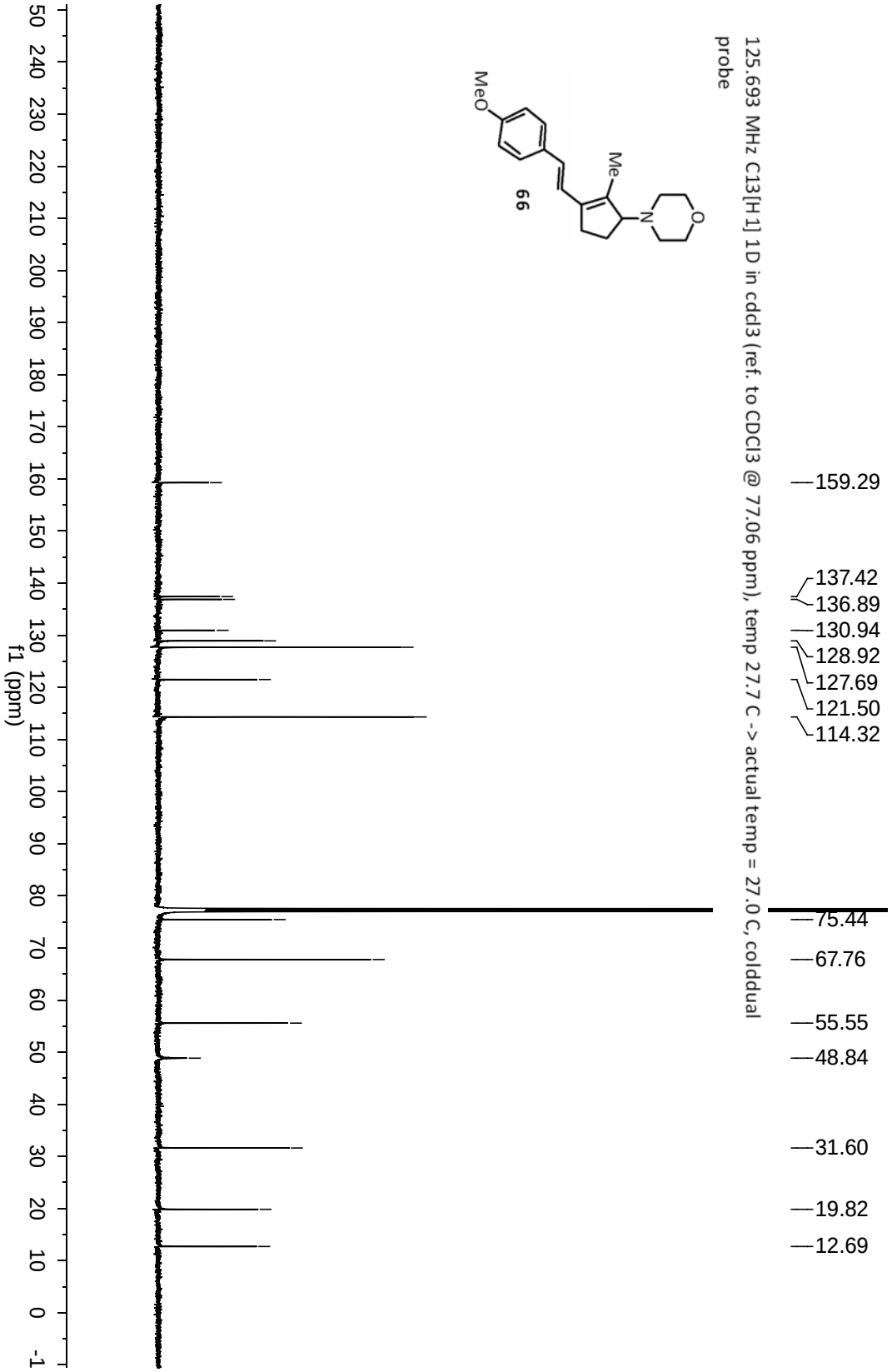
Pulse Sequence: aotroesy



59a

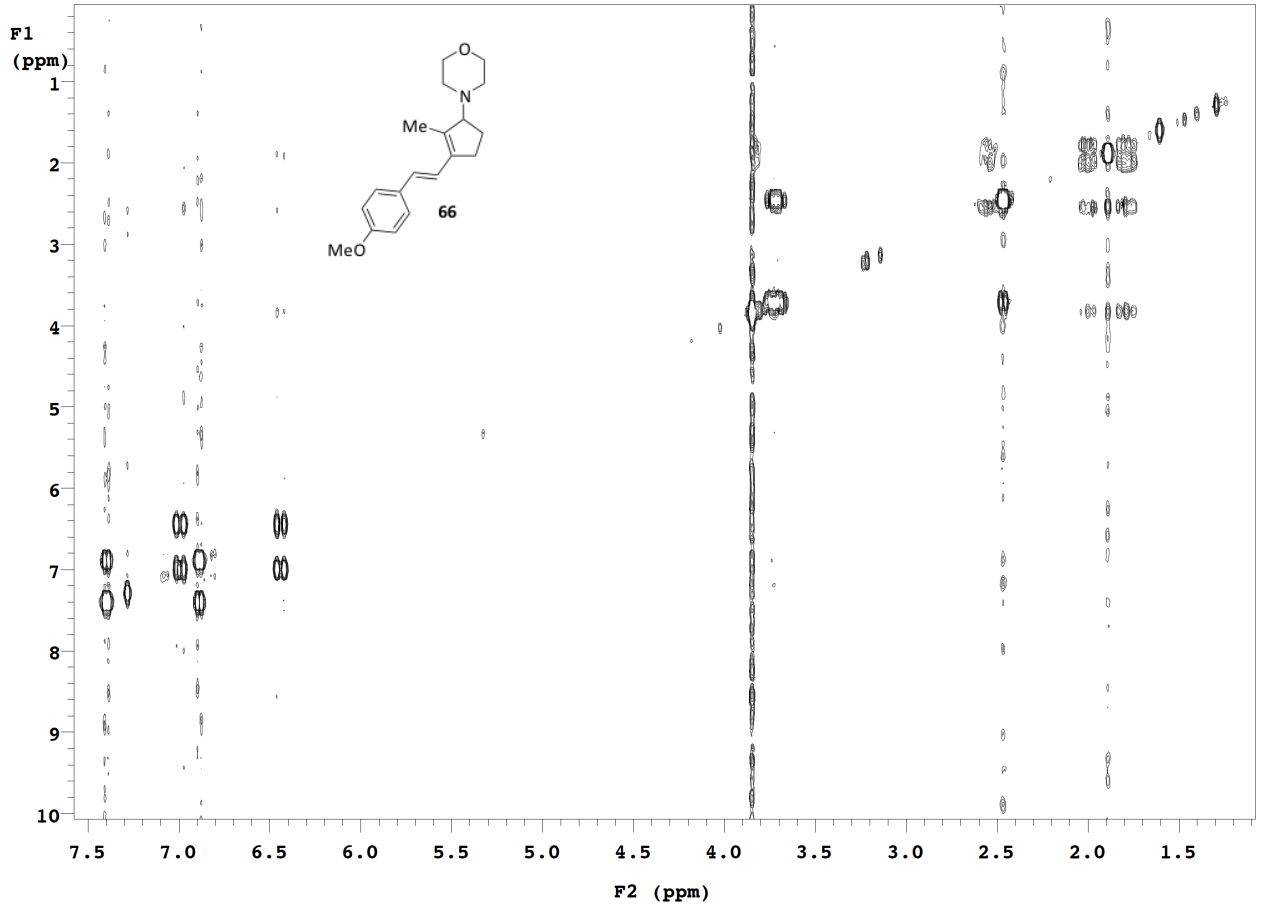



400.393 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
MeO
Me
N
O
66
f1 (ppm)
2.06
1.03
2.04
1.00
4.49
4.66
2.04
4.17
1.08
2.93
1.12

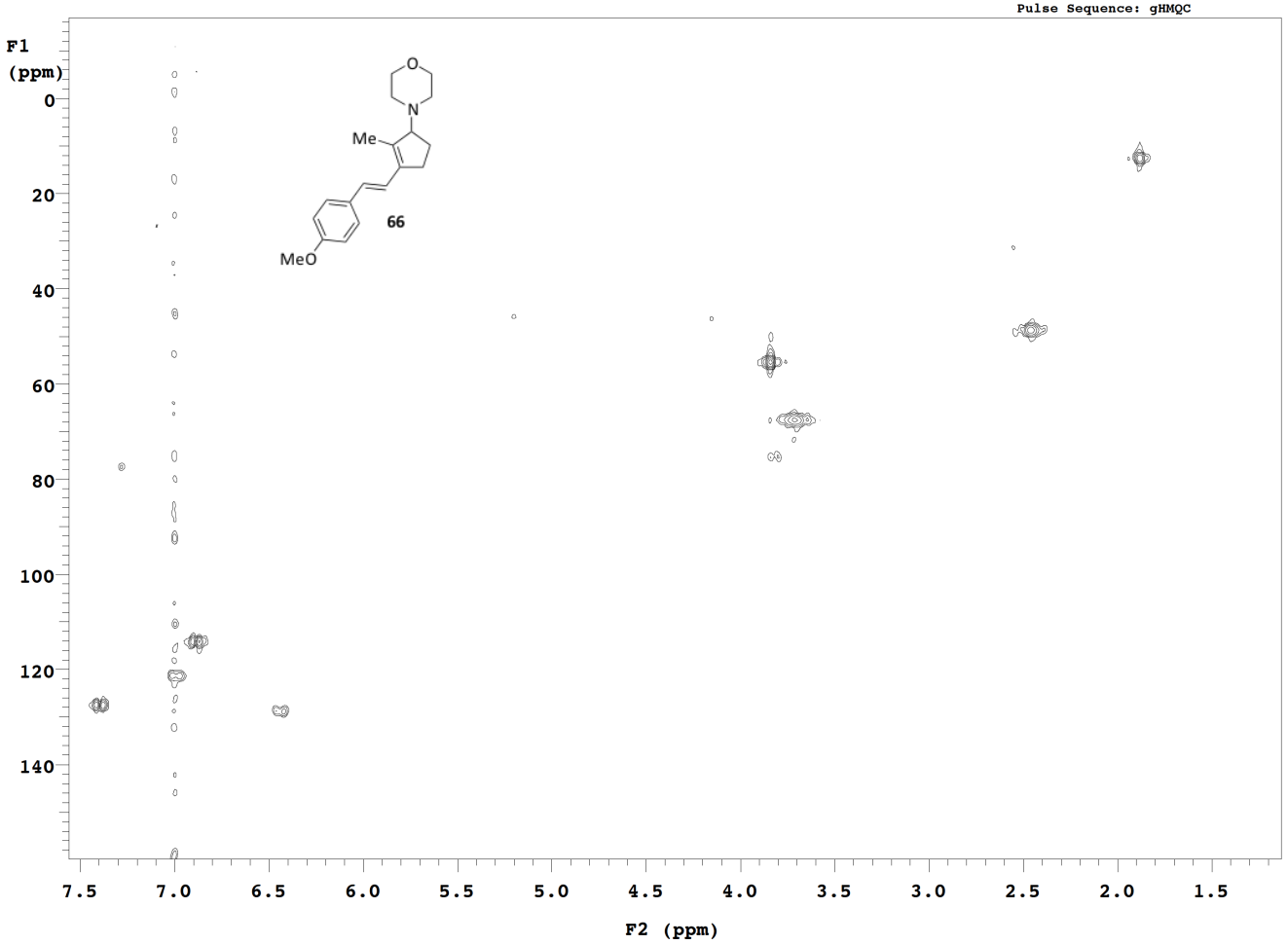

125.693 MHz C13[H 1] 1D in cdd3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual
probe
MeO
Me
N
O
66
159.29
137.42
136.89
130.94
128.92
127.69
121.50
114.32
75.44
67.76
55.55
48.84
31.60
19.82
12.69
f1 (ppm)
50 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1

Sara, SB-12-69PB3
400.393 MHz H1 aogcosy in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

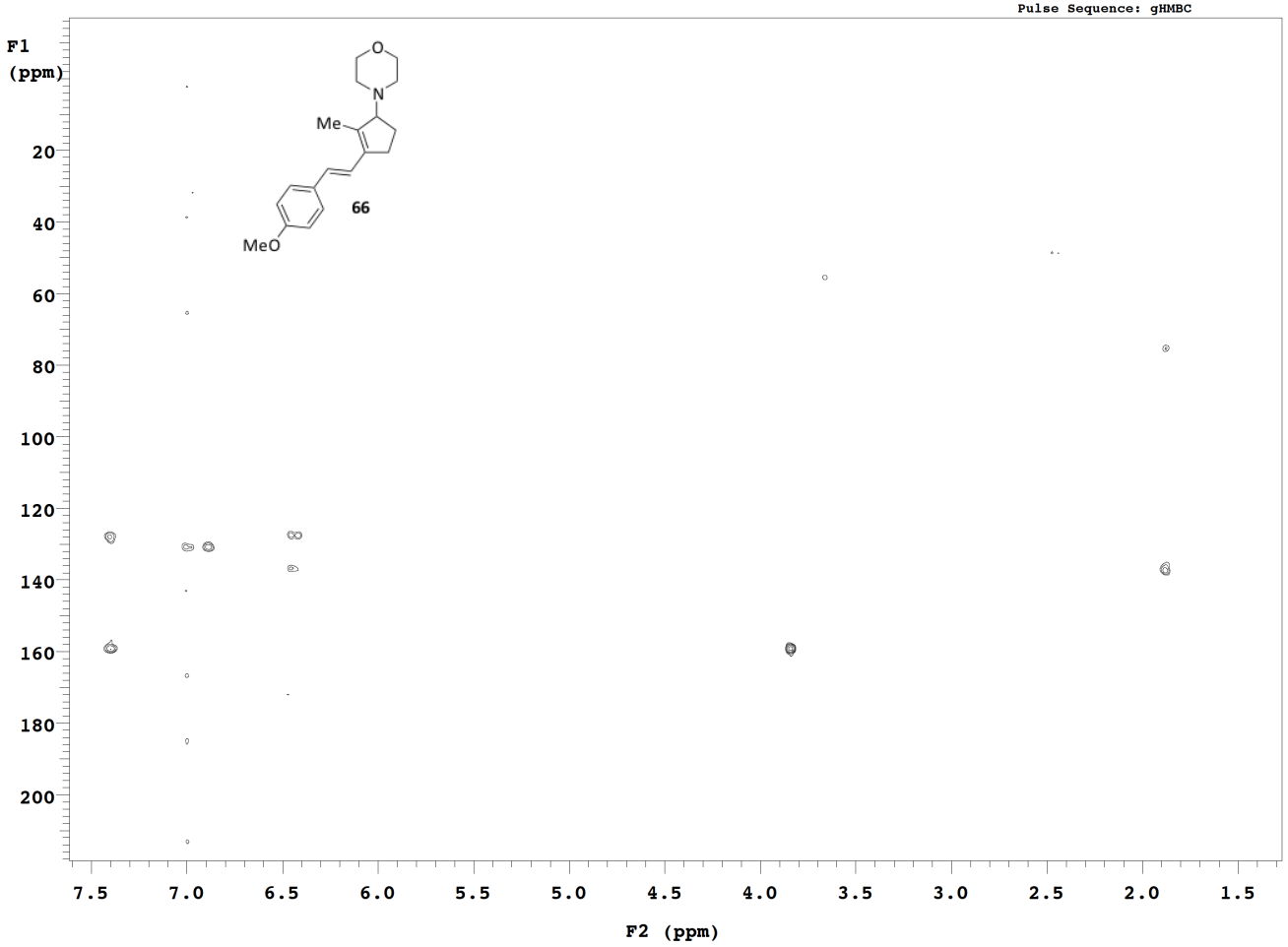
Pulse Sequence: aogcosy



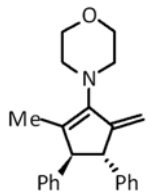
Sara, SB-12-69PB3
400.393 MHz H1 gHMQC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Pulse Sequence: gHMQC



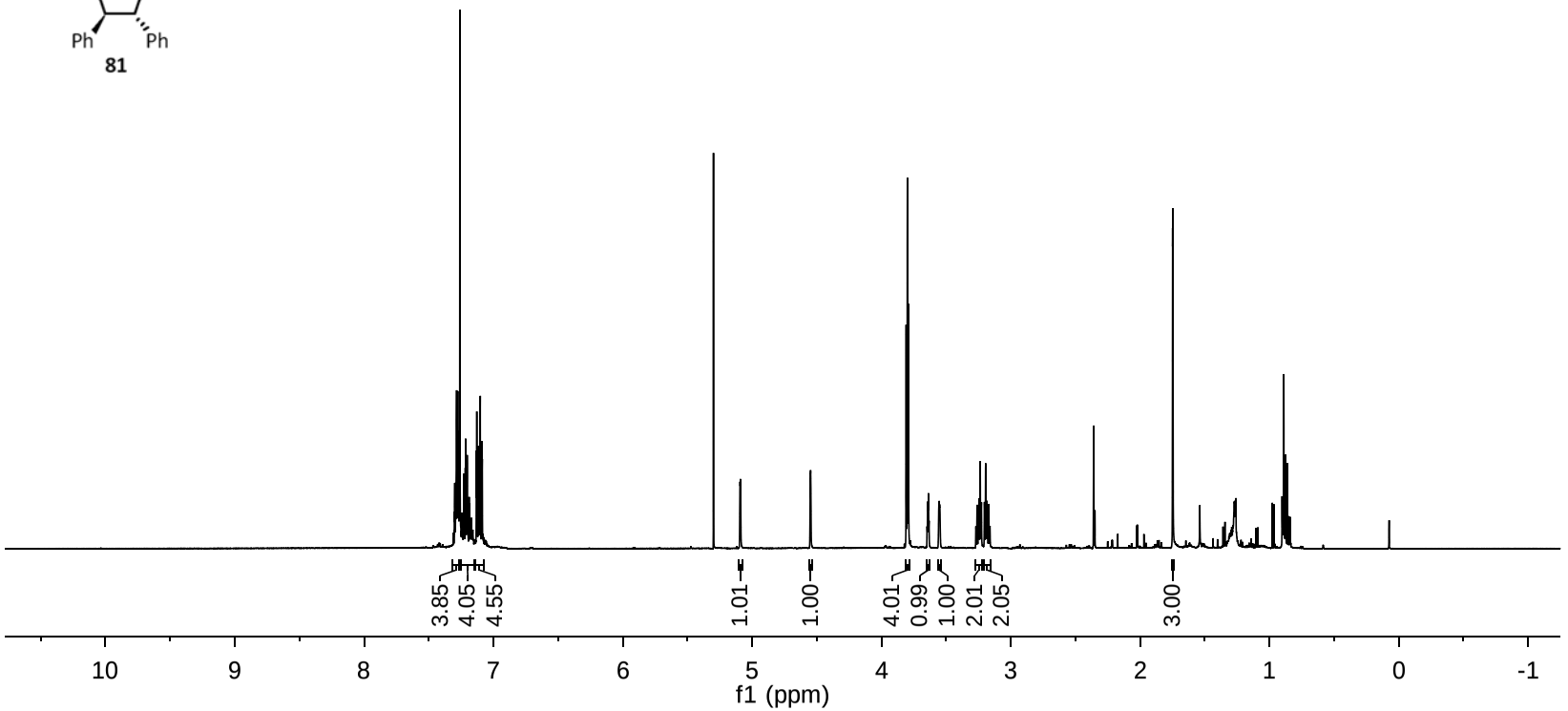
Sara, SB-12-69PB3
400.393 MHz H1 gHMBC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Pulse Sequence: gHMBC

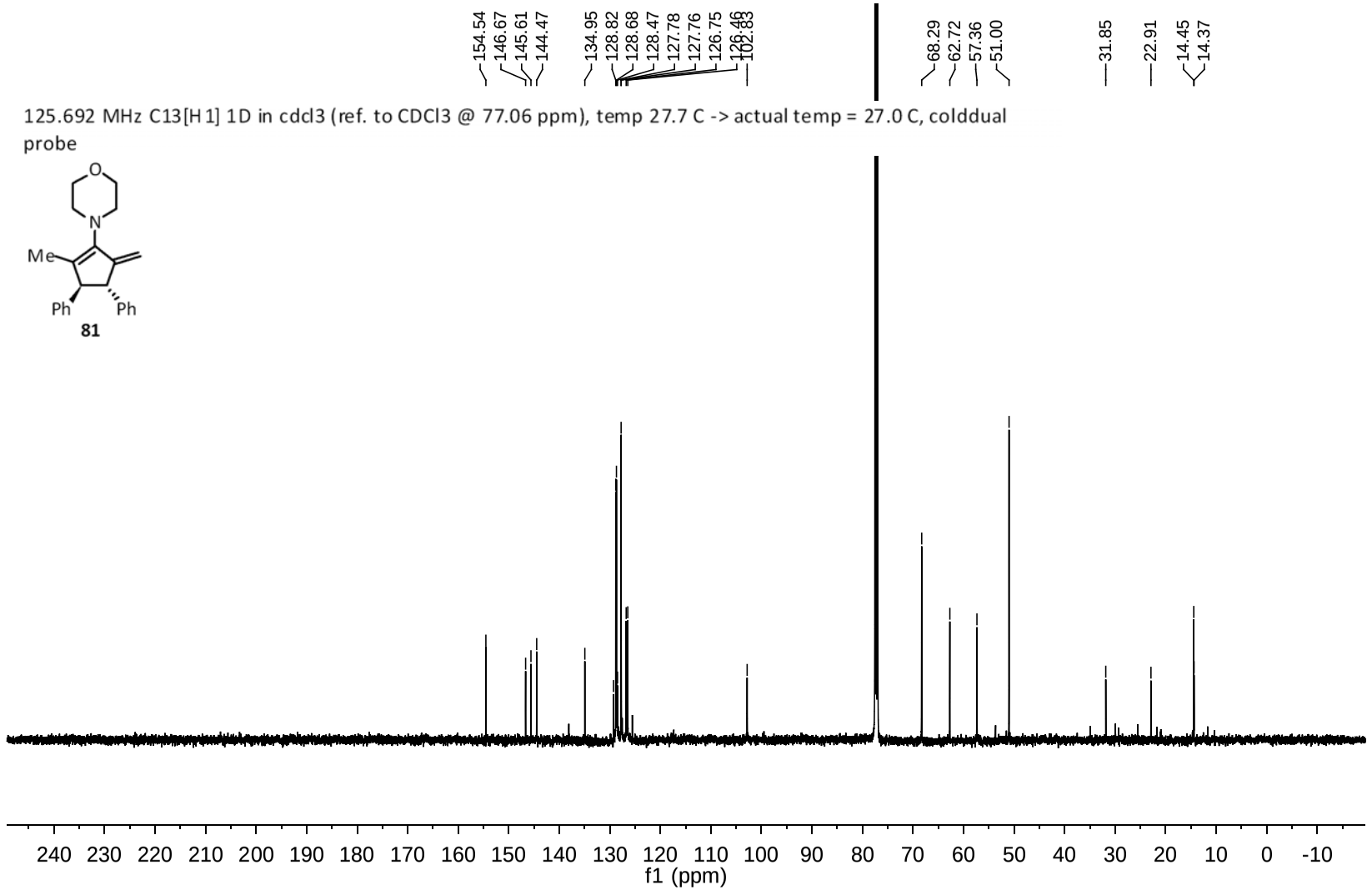


499.815 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe



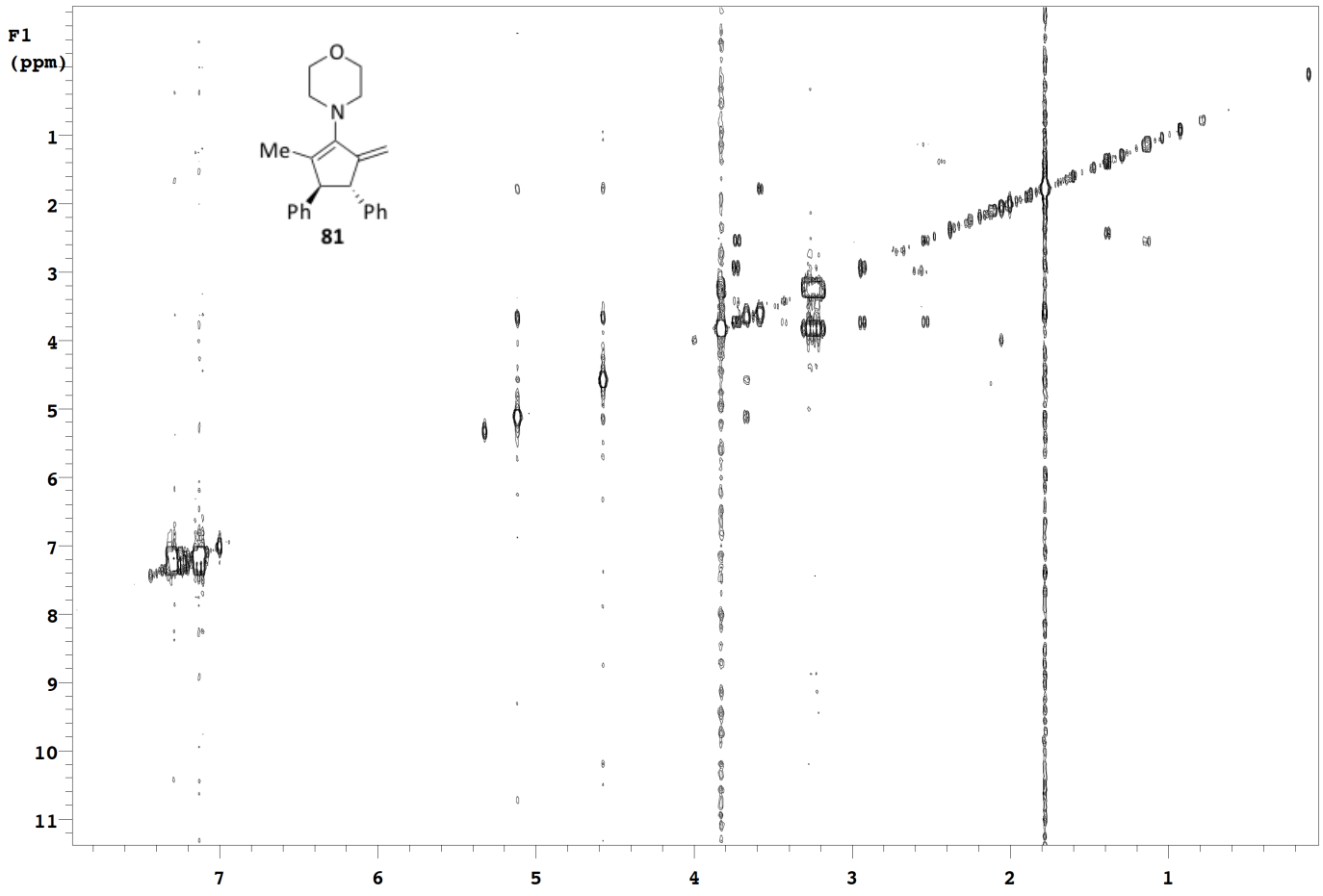
81



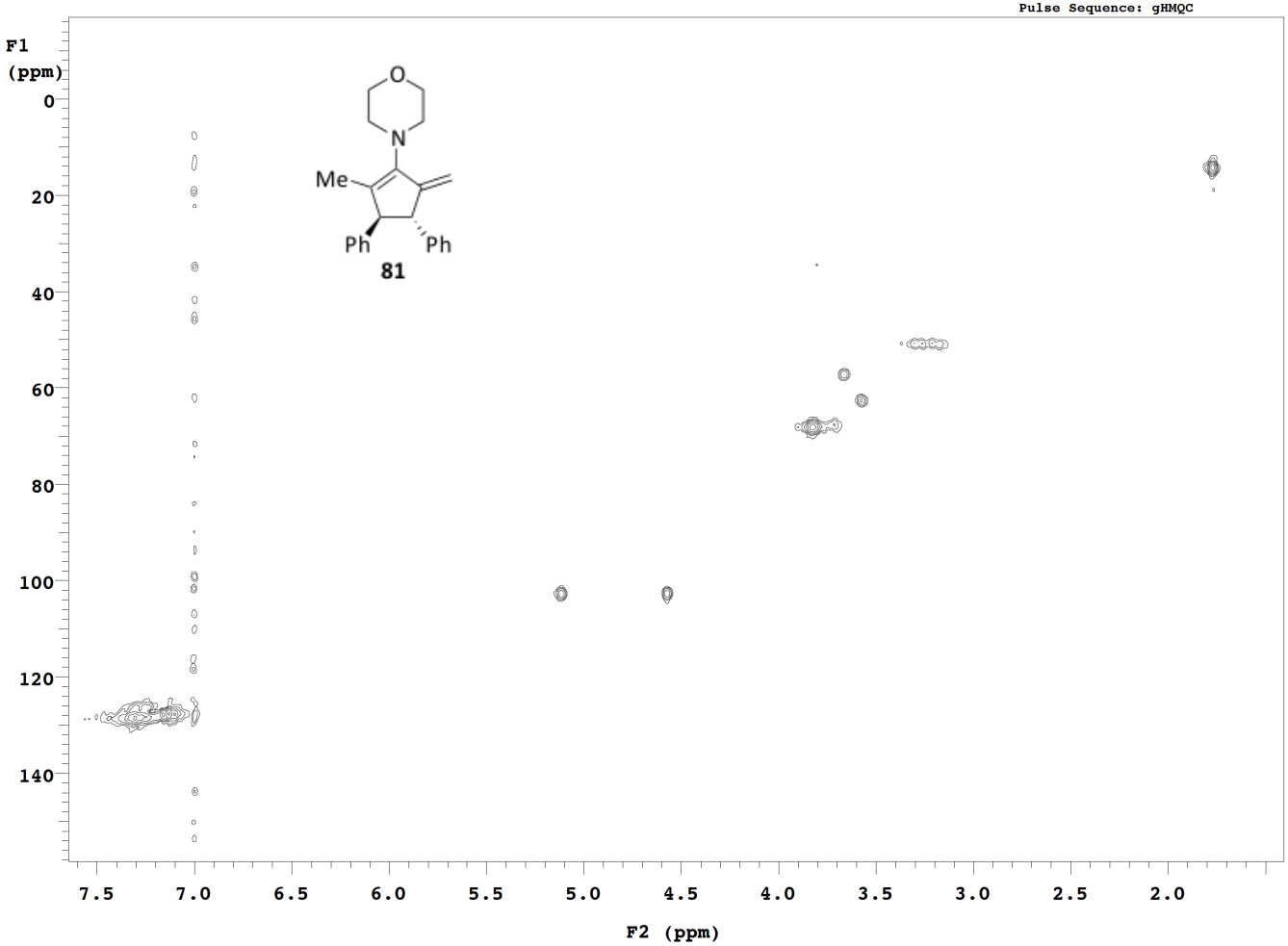

154.54
146.67
145.61
144.47
134.95
128.82
128.68
128.47
127.78
127.76
126.75
68.29
62.72
57.36
51.00
31.85
22.91
14.45
14.37
125.692 MHz C13[H 1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
O
N
Me
Ph
Ph
81
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Sara, SB-11-73
400.393 MHz H1 aogcosy in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

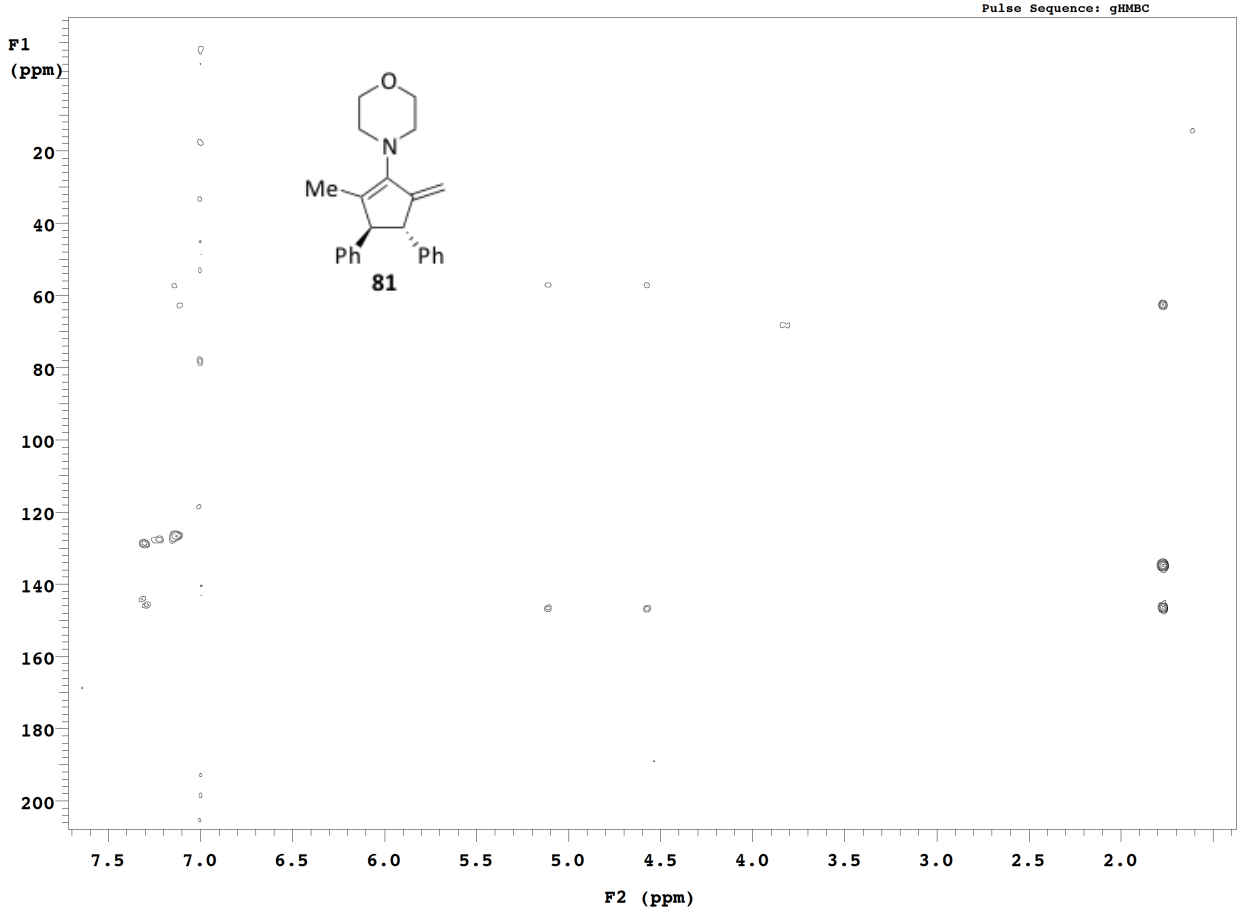
Pulse Sequence: aogcosy



Sara, SB-11-73
400.393 MHz H1 gHMQC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Pulse Sequence: gHMQC



Sara, SB-11-73
400.393 MHz H1 gHMBC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
Pulse Sequence: gHMBC



Appendix IV: X-ray Crystallographic Data For Compound 39d

(Chapter 3)

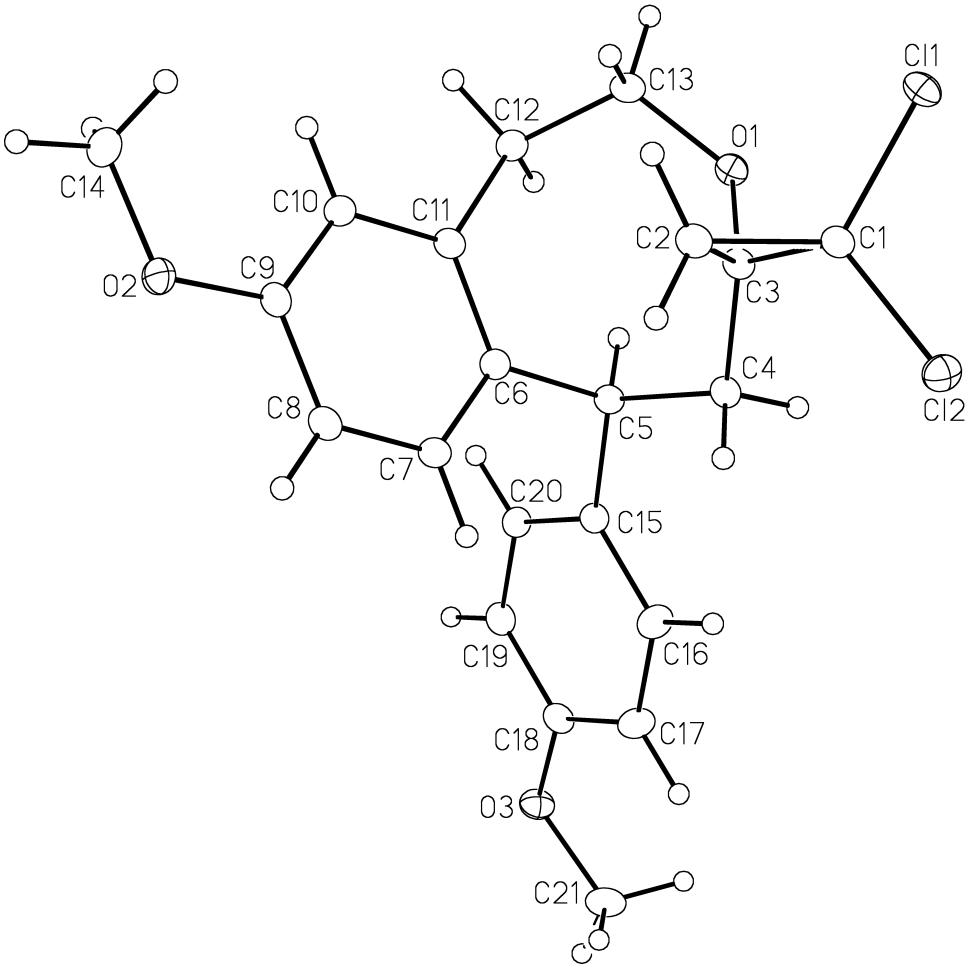
STRUCTURE REPORT

XCL Code: FGW1011 **Date:** 7 October 2010

Compound: 2',2'-dichloro-9-methoxy-6-(4-methoxyphenyl)-1,2,5,6-tetrahydrospiro{3-benzoxocine-4,1'-cyclopropane}

Formula: $C_{21}H_{22}Cl_2O_3$

Supervisor: F. G. West **Crystallographer:** M. J. Ferguson



Compound 39d

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{21}H_{22}Cl_2O_3$
formula weight	393.29
crystal dimensions (mm)	0.42 × 0.28 × 0.24
crystal system	orthorhombic
space group	$Pna2_1$ (No. 33)
unit cell parameters[a]	
	a (Å) 11.4369 (13)
	b (Å) 12.3026 (14)
	c (Å) 27.375 (3)
	V (Å^3) 3851.7 (8)
	Z 8
ρ_{calcd} (g cm^{-3})	1.356
μ (mm^{-1})	0.355
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–100
scan type	ω scans (0.3°) (20 s exposures)
data collection 2θ limit (deg)	54.88
total data collected	32097 (-14 ≤ h ≤ 14, -15 ≤ k ≤ 15, -35 ≤ l ≤ 35)
independent reflections	8733 (R_{int} = 0.0402)
number of observed reflections (*NO*)	8045 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXD*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–97*[d])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9197–0.8644
data/restraints/parameters	8733 / 0 / 470
Flack absolute structure parameter[e]	0.16(4)
goodness-of-fit (*S*)[f] [all data]	1.051
final R indices[g]	
	R_1 [$F_o^2 \geq 2\sigma(F_o^2)$] 0.0462
	wR_2 [all data] 0.1328
largest difference peak and hole	0.704 and –0.444 e Å^{-3}

[a]Obtained from least-squares refinement of 9197 reflections with $4.86° < 2\theta < 54.12°$.

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

[c]Schneider, T. R.; Sheldrick, G. M. *Acta Crystallogr*. **2002**, *D58*, 1772-1779.

[d]Sheldrick, G. M. *Acta Crystallogr*. **2008**, *A64*, 112–122.

[e]Flack, H. D. *Acta Crystallogr*. **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr*. **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst*. **2000**, *33*, 1143–1148. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration. The value observed herein is indicative of racemic twinning, and was accomodated during the refinement (using the *SHELXL-93* TWIN instruction [see reference *d*]).

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0995P)^2 + 0.2902P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

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

Appendix V: X-ray Crystallographic Data For Compound 59a

(Chapter 4)

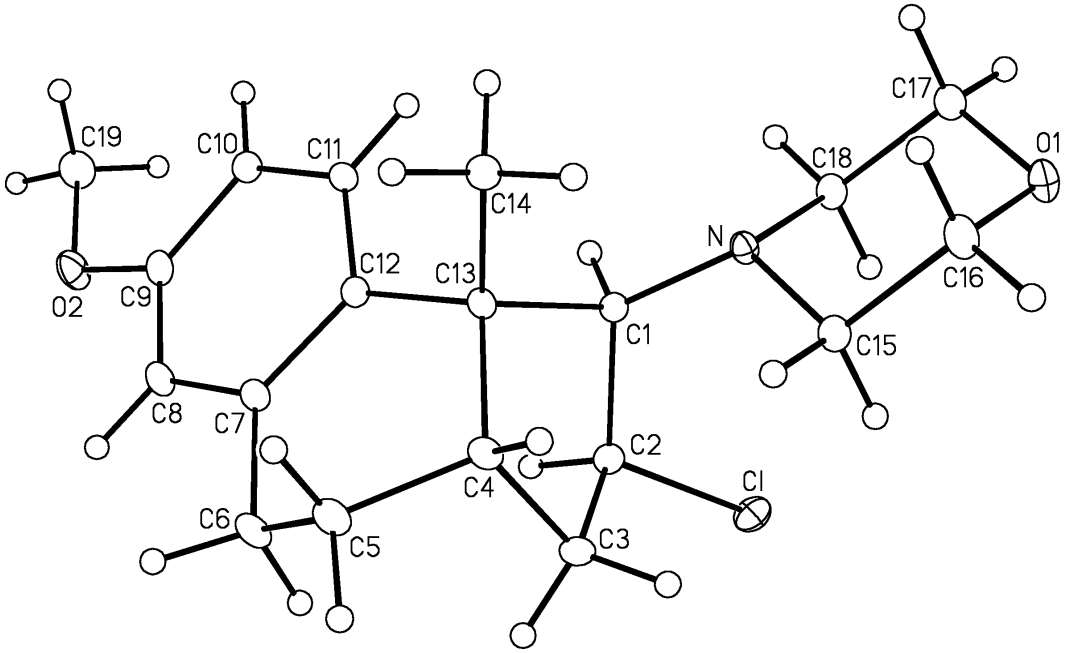
STRUCTURE REPORT

XCL Code: FGW1201 **Date:** 10 April 2012

Compound: 4-(2-chloro-7-methoxy-9*b*-methyl-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-cyclopenta[*a*]naphthalen-1-yl)morpholine

Formula: $C_{19}H_{26}ClNO_2$

Supervisor: F. G. West **Crystallographer:** M. J. Ferguson



Compound 59a

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{19}H_{26}ClNO_2$
formula weight	335.86
crystal dimensions (mm)	0.49 × 0.19 × 0.13
crystal system	monoclinic
space group	$P2_1/c$ (No. 14)
unit cell parameters[a]	
a (Å)	5.9630 (5)
b (Å)	13.8664 (12)
c (Å)	20.4254 (17)
β (deg)	93.7580 (10)
V (Å^3)	1685.2 (2)
Z	4
ρ_{calcd} (g cm^{-3})	1.324
μ (mm^{-1})	0.237
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–100
scan type	ω scans (0.3°) (20 s exposures)
data collection 2θ limit (deg)	53.74
total data collected	13792 (-7 ≤ h ≤ 7, -17 ≤ k ≤ 17, -25 ≤ l ≤ 25)
independent reflections	3617 (R_{int} = 0.0358)
number of observed reflections (*NO*)	3018 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–97*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–97*[c])
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.9694–0.8936
data/restraints/parameters	3617 / 0 / 210
goodness-of-fit (S)[d] [all data]	1.041
final R indices[e]	
	R_1 [$F_o^2 \geq 2\sigma(F_o^2)$] 0.0386
	wR_2 [all data] 0.1014
largest difference peak and hole	0.294 and –0.254 e Å^{-3}

[a]Obtained from least-squares refinement of 5886 reflections with 5.88° < 2θ <

52.76°.

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

[c]Sheldrick, G. M. *Acta Crystallogr*. **2008**, *A64*, 112–122.

[d]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0485P)^2 + 0.6519P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

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