Stereoselective Preparation of Highly Substituted Olefins and Synthetic Studies Toward Stresgenin B

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STEREOSELECTIVE PREPARATION OF HIGHLY SUBSTITUTED OLEFINS AND SYNTHETIC STUDIES TOWARD STRESGENIN B

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Alkenoic esters are versatile synthetic intermediates and are contained in many natural products. We have developed methods to stereoselectively prepare substituted alkenoic esters through the *trans*-conjugate addition of a nucleophile and an electrophile across the triple bond of γ-hydroxy-α,β-acetylenic esters. The development and scope of these methods will be discussed. Our preliminary studies toward the synthesis of stresgenin B are also described.

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%	percent
ºC	Celsius
α	alpha
β	beta
γ	gamma
δ	delta
Ac	acetate
aq	aqueous
Bn	benzyl
Bu	butyl
cal	calorie
cat.	catalytic
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
equiv	equivalent
FAB-MS	fast atom bombardment mass spectroscopy
Fmoc	fluorenylmethoxycarbonyl
h	hour
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence
hsp	heat shock protein

HWE	Horner-Wadsworth-Emmons
IR	infrared
K	kelvin
k	kilo
L	liter
M	molar
Me	methyl
Mes	mesityl
min	minute
mL	milliliter
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser enhancement spectroscopy
Ph	phenyl
PhH	benzene
PhMe	toluene
quant	quantitative
Red-Al	sodium bis-(2-methoxyethoxy)aluminum hydride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	trimethylsilyl

*p*TsOH	*p*-toluenesulfonic acid
UV	ultraviolet

1. Introduction

1.1 Stresgenin B

Stereoselective alkene synthesis continues to pose a challenge in organic chemistry.[1,2] Of particular interest are the highly substituted α,β-unsaturated esters due to their usefulness as synthetic intermediates and presence in natural products.[3-32] Stresgenin B, a natural product isolated from the *Streptomyces* sp. AS-9 strain in 1999 by Akagawa et al.,[33] contains an exocylic α,β-alkenoic ester (Figure 1). Stresgenin B was isolated during a search for a selective inhibitor of heat-induced heat-shock protein (hsp) gene expression. Certain cancerous cells produce heat-shock proteins as a defense mechanism in the presence of environmental stimuli such as heat.[34] Hyperthermia is a cancer therapy that exposes tissue to elevated temperatures (40-43 ^{o}C) in an effort to kill cancerous cells or make them susceptible to additional therapies such as radiation or chemotherapy. When certain cancerous cells are exposed to higher temperatures, these cells produce heat-shock proteins that allow them to withstand detrimental effects. Stresgenin B inhibits the heat-induced syntheses of hsp72/73, hsp90, and hsp110, and thus suppressing the thermotolerance gained by the heat-treated cells. The structure and relative stereochemistry of stresgenin B were determined by a combination of high resolution FAB-MS, UV, ^{1}H NMR, ^{13}C NMR, HMQC, HMBC, and NOESY spectroscopy. The goal of this research is to determine the absolute stereochemistry and mode of action of stresgenin B.

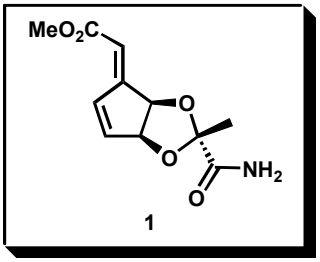
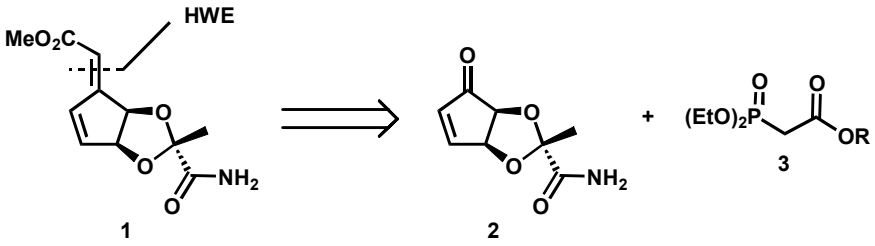


Figure 1. Stresgenin B.

1.2 Approaches to α,β-Unsaturated Esters

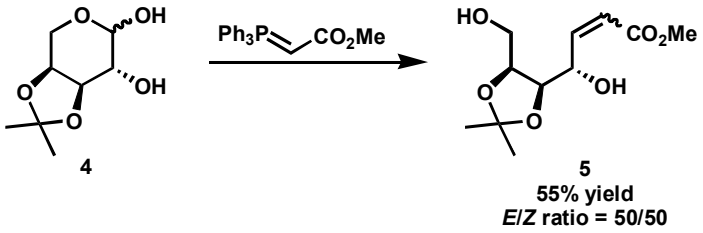
The exocyclic olefin appears to be a potential disconnection point while dissecting stresgenin B in a retrosynthetic fashion (Scheme 1). α,β-Unsaturated esters are often prepared *via* Wittig or Horner-Wadsworth-Emmons (HWE) reactions in which phosphonate-stabilized carbanions preferentially give (*E*)-alkene products.



Scheme 1. Horner-Wadsworth-Emmons reaction to form stresgenin B, **1**.

However, in the presence of an α-hydroxy (or alkoxy) aldehyde, the reaction often generates a mixture of (*E*) and (*Z*)-isomers.[35,36] The reaction conditions can also epimerize the chiral center adjacent to the aldehyde when the α-hydroxy group is present.[35,36] These problems associated with Wittig or HWE conditions make generating the exocyclic olefin in stresgenin B difficult. An example of the difficulty in controlling olefin geometry in the presence of a γ-hydroxy group is shown in Scheme 2. While working toward the synthesis of solandelactone

oxylipins[37], the Martin group required the α,β-(*E*)-unsaturated ester **5**. Subjecting the arabinose derivative **4** to Wittig conditions generated a 50:50 *E*:*Z* mixture of isomers of **5**.[35] Altering the solvent and temperature had a moderate effect on the outcome of the reaction (48% yield, *E*:*Z* ratio = 82:18). While the problem was circumvented by using a different phosphorane reagent, as will be discussed, it does show the difficulty of generating γ-hydroxy-α,β-(*E*)-alkenoic esters.

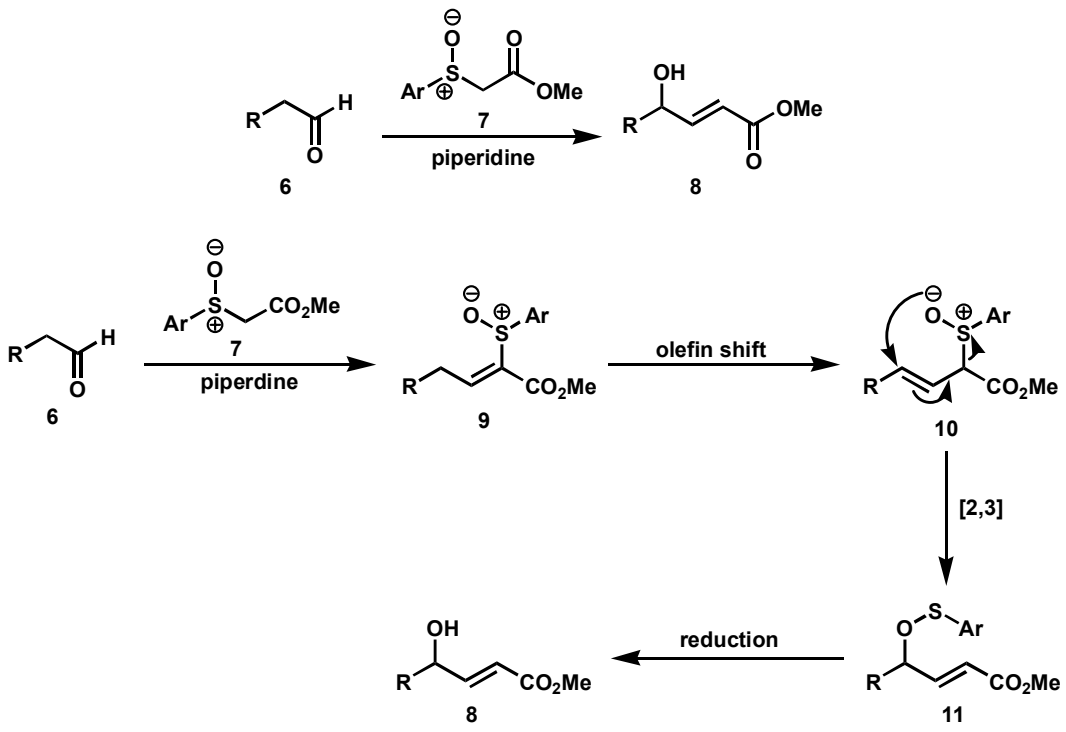


Scheme 2. Wittig reactions with α-hydroxy compound **4**.

1.3 Preparation of γ-hydroxy-α,β-(*E*)-enoates

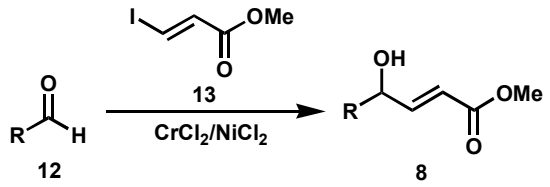
Thus, the limitations of the Wittig approach are that α-alkoxy (or hydroxy) aldehydes are prone to epimerization and often generate a mixture of (*E*) and (*Z*)-isomers[35,36], frequently in preference of the (*Z*)-isomer. Work by Martin et al.[35] has shown that when a tributylphosphine-based Wittig reagent is used instead of a triphenylphosphine-based reagent, the *E*:*Z* ratio can drastically improve, in some cases increasing from 2:3 to 10:1, favoring the (*E*)-isomer (**4** → **5**). In Martin's work, however, the α-hydroxy group must be protected, thereby adding steps to the preparation of the desired product.

The (*E*)-enoate moiety can also be prepared through rearrangement of vinylic sulfoxides (Scheme 3).[38] The method shown in Scheme 3 is moisture-insensitive, but less effective on aldehydes as they become more sterically hindered, while ketones are unreactive.



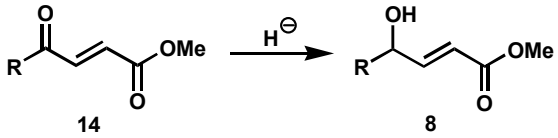
Scheme 3. Rearrangement via vinylic sulfoxides.

The Nozaki-Hiyama-Kishi reaction also provides mild reaction conditions that are compatible with a variety of functional groups (Scheme 4).[39,40] The reaction is highly chemoselective for aldehydes over other carbonyl moieties. A drawback of this approach is that the reaction often requires multiple equiv of chromium with respect to the aldehyde, which limits larger scales reactions due to the cost and toxicity of chromium. Advances to make the reaction catalytic in chromium (7-15 mol%) have been reported by using manganese as the stoichiometric reducing agent.[40] Manganese is cheap and non-toxic, but the use of any quantity of chromium on industrial scales remains hazardous.



Scheme 4. Nozaki-Hiyama-Kishi reaction of aldehyde **12** and vinyl iodide **13**.

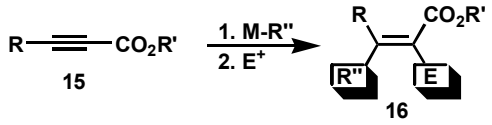
Reduction of enone **14** can also give the desired product **8** (Scheme 5). Substrate- or reagent-controlled reductions can be employed to provide the desired stereochemistry of the resulting alcohol.[41] The enone, however, typically requires multiple steps to prepare.



Scheme 5. Reduction of enone **14** to form γ-hydroxy-α,β-(*E*)-enoate **8**.

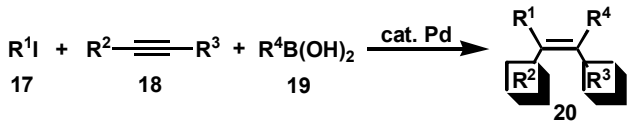
1.4 Preparation of Tri- and Tetra-Substituted Olefins

Organometallic reagents, particularly organocuprates, have been used to prepare β,β-di-substituted alkenoic esters **16** by conjugate *cis*-addition into the corresponding α,β-acetylenic esters **15** (Scheme 6).[42] Methods to obtain the corresponding *trans*-addition product by the addition of an organometallic reagent and electrophile across the triple bond of an alkynoate typically result in poor selectivities.[42]



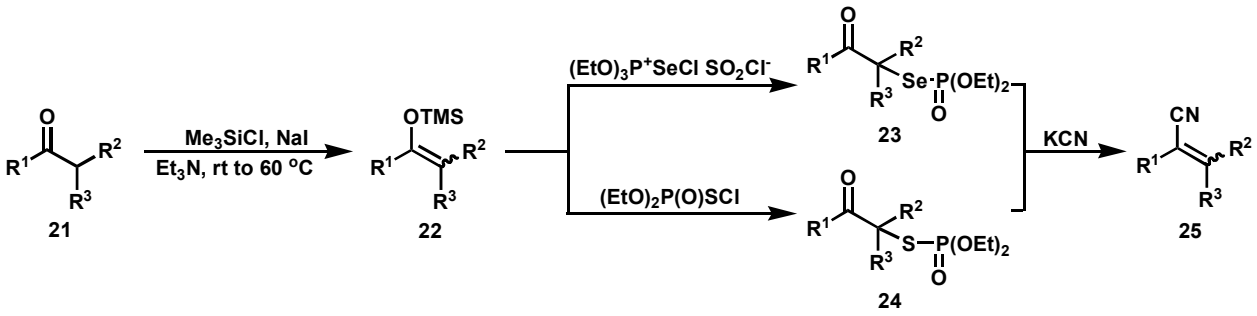
Scheme 6. *cis*-Addition by organometallic reagents.

Tetra-substituted olefins have been prepared by the methods discussed thus far: 1) trapping addition intermediates with electrophiles other than H^+ and 2) by subjecting ketones to Wittig conditions. Controlling the stereoselectivity in the product has proven to be a difficult task. Larock has developed a method for the generation of tetra-substituted olefins initiated by the carbopalladation of alkyne **18** with alkyl iodide **17** (Scheme 7).[43] Subsequent Suzuki coupling of the alkenyl palladium intermediate with boronic acid **19** provides access to the valuable tetra-substituted olefin **20** with excellent control of regio- and stereochemistry.



Scheme 7. Pd catalyzed coupling.

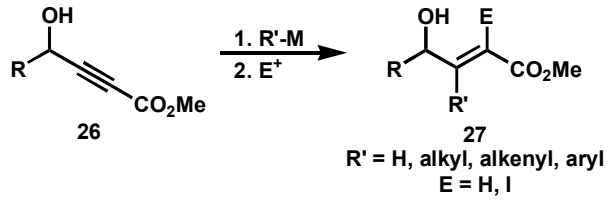
Selenophosphates **23** and thiophosphates **24** have also been used in the preparation of tetra-substituted olefins **25**, incorporating a nitrile as one of the olefinic substituents (Scheme 8).[2] The substituted silyl enol ether **22** is initially prepared from the corresponding ketone **21**, which is then treated with the appropriate salt to afford the seleno- or thiosphosphate intermediate **23** or **24**. These intermediates, when reacted with potassium cyanide and 18-crown-6, provide vinyl nitrile products **25**.



Scheme 8. Seleno- and thiophosphate pathway to tetra-substituted olefins.

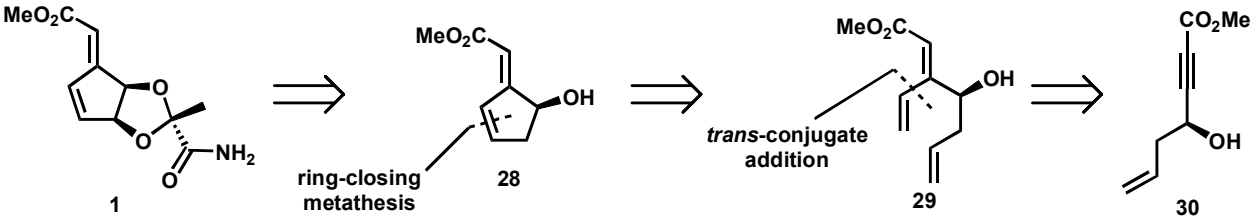
1.5 Goals and Objectives of the Project

We aim to prepare alkenoic ester **27** in a stereoselective manner through the *trans*-conjugate addition of an organometallic reagent and electrophile to the triple bond of alkynoate **26** (Scheme 9). Quenching the reaction with an electrophile will allow for the preparation of di-, tri-, or tetra-substituted olefins. An additional goal is to display the potential of alkenoic esters **27** for diversity-oriented synthesis.



Scheme 9. *trans*-Conjugate addition across the triple bond of γ-hydroxyalkynoate **26**.

Initial progress toward the synthesis of stresgenin B will also be explored. The key step in controlling the exocyclic double bond in stresgenin B will result from the *trans*-conjugate addition of a Grignard reagent to alkynoate **30** and subsequent ring-closing metathesis of triene **29** (Scheme 10).

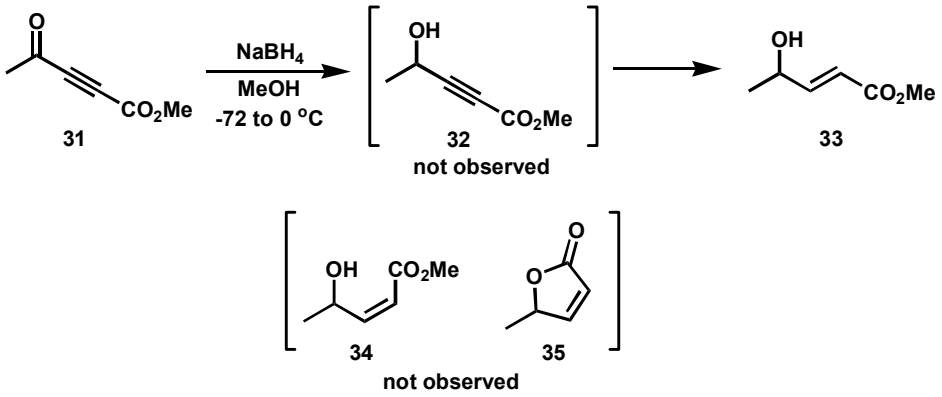


Scheme 10. Retrosynthetic analysis of stresgenin B, **1**.

2. Results and Discussion

2.1 Background

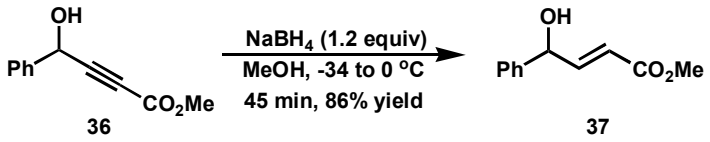
During synthetic studies toward FR901464, ynoate **31** was reduced with $NaBH_4$ in an attempt to isolate alkynoate **32** (Scheme 11). However, the reduction of ynoate **31** with $NaBH_4$ in MeOH provided γ-hydroxy-α,β-(*E*)-enoate **33**, instead of the expected alcohol **32**.[44]



Scheme 11. Reduction of ynoate **31**.

Neither alcohol **34** nor lactone **35** were detected by ^1H NMR spectroscopy, leading to further exploration into the mechanism of this apparent *trans*-addition of two hydrogen atoms across a triple bond. For isolation purposes, the higher molecular weight phenyl-substituted alkynoate **36**

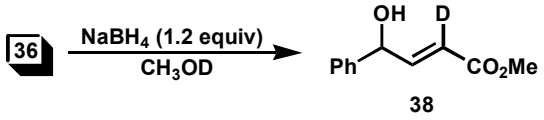
was used to probe the *trans*-enoate formation (Scheme 12). Accordingly, treatment of **36** with $NaBH_4$ in MeOH afforded alkenoate **37** in 86% yield.



36 37

Scheme 12. Reduction of phenyl alkynoate **36**.

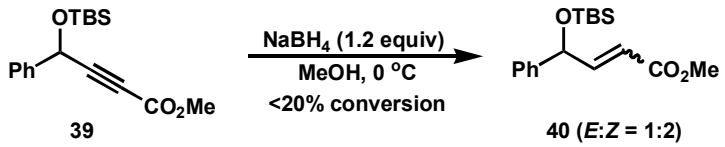
Deuterium labeling studies provided valuable information on the mechanism of this reduction. Treatment of **36** with $NaBH_4$ in CD_3OD gave the (*E*)-alkenoate **38** with deuterium incorporation α to the ester, indicating that hydride delivery occurs at the β carbon of the alkynoate (Scheme 13).



38

Scheme 13. Reduction of **36** in CD_3OD.

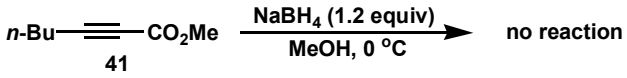
To determine the role of the hydroxy group in the reduction, the TBS-protected derivative **39** was subjected to the reaction conditions (1.2 equiv of $NaBH_4$ in MeOH at -30 ^oC); however, **39** was recovered in a quantitative yield. After warming this mixture to 0 ^oC, poor conversion to **40** was observed. Analysis of the ^1H NMR spectrum of the crude reaction mixture showed approximately 15% conversion to the alkenoate **40** with an *E*:*Z* ratio of 1:2, favoring the (*Z*)-isomer (Scheme 14).



Scheme 14. Reduction of TBS-protected derivative.

2.2 Continued Control Reactions

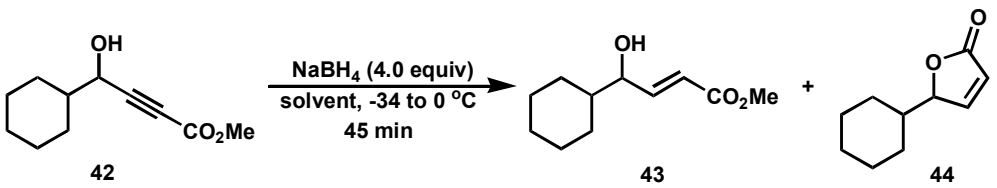
With the above results, we continued to study the mechanism of the $NaBH_4$ reduction of alkynoate **36**. Additional investigation into the role of the hydroxy group led to the reduction of alkynoate **41**, which lacks a γ-hydroxy group. Alkynoate **41** was recovered with no evidence of the reduced product (Scheme 15). These results suggest that γ-oxygenation facilitates the reaction. Importantly, the γ-hydroxy group accelerates the reduction affording only the (*E*)-enoate.



Scheme 15. Attempted reduction of alkynoate **41**.

When alkynoate **42** was reduced with $NaBH_4$ and MeOH (Table 1, Run 7), the ratio of *E*:*Z* isomers was 5.5:1. In order to optimize the reaction conditions, solvents were screened to determine which gave the highest *E*:*Z* ratios and yields for the desired (*E*)-alkenoate **43** (Table 1). In cases where the solvent was not an alcohol, MeOH was added (solvent:MeOH = 9:1) to form the reactive intermediate shown in Scheme 16.[45] The ratio of **43**:**44** ranged from 2.5:1 in THF to 9:1 in Et_2O while the yield of the reaction ranged from 9% in CH_2Cl_2 to 75% in MeOH. These results do not exhibit a correlation between polarity or coordination ability of each solvent with yield and ratio of olefin isomers. Although MeOH afforded the product in a modest 5.5:1

ratio, the yield was 23% greater than the next best solvent (EtOAc, 52% yield). Thus, MeOH remained the solvent for the optimized reduction conditions with $NaBH_4$.



42 43 44

run	solvent	43:44	yield (43+44)
1	THF	2.5:1	27%
2	CH_2Cl_2	7.5:1	9%
3	EtOAc	8:1	52%
4	Et_2O	9:1	19%
5	DMF	7:1	13%
6	*i*-PrOH	8.5:1	15%
7	MeOH	5.5:1	75%

Table 1. Solvent effect on $NaBH_4$ reduction.

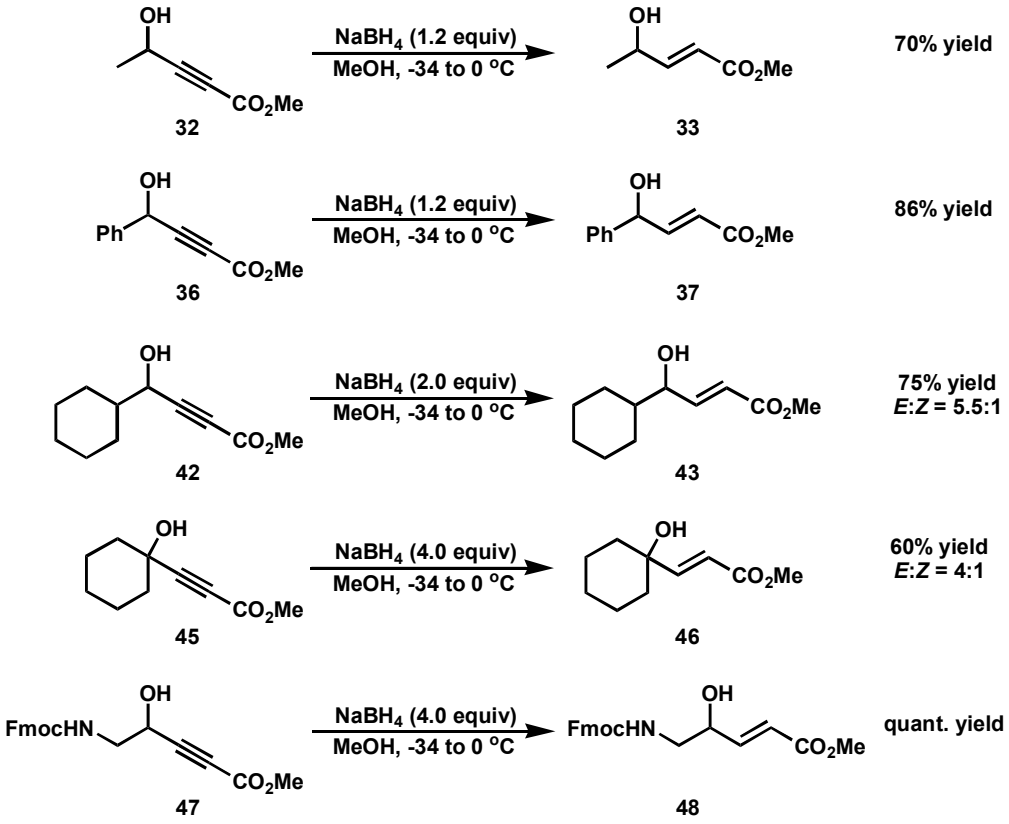
$$NaBH_4 + MeOH \rightarrow NaBH_3(OMe) + H_2$$

Scheme 16. Preparation of $NaBH_3(OMe)$.

2.3 Demonstrating the Scope of the $NaBH_4$ Reduction of γ-Hydroxyalkynoates

In order to examine the scope of this reduction, a number of γ-hydroxyalkynoates were prepared and subjected to our optimized reaction conditions (Scheme 17). When acetylenic esters **32** and **36** were subjected to the optimized conditions, the corresponding (*E*)-enoates **33** and **37** were isolated in 70% and 86% yield, respectively. When the acetylenic esters **42** and **45** were reacted under the provided conditions, yields were 75% and 60%, respectively. Unfortunately, the stereoselectivity decreased for these more sterically demanding propargylic alcohols affording mixtures of olefin isomers (*E*:*Z* = 4.0-5.5:1). If the reaction proceeds through the proposed mechanism shown in Scheme 21, then as the size of the R group increases, it

becomes more difficult for a solvent molecule to coordinate to alkoxide **59**, which could result in addition to the allenolate from the opposite face, providing the *cis*-isomer. Since the reducing species in the reaction (hydride) is basic, it was necessary to determine if the reaction conditions were compatible with base-sensitive functional groups. When the Fmoc-protected amino alcohol **47** was submitted to the reaction conditions, the desired alkenoate **48** was isolated in a quantitative yield with complete control of olefin geometry.

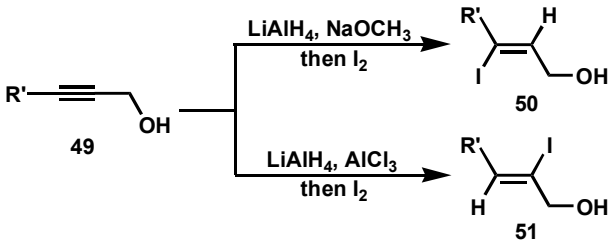


Scheme 17. $NaBH_4$ reduction of acetylenic esters.

2.4 Development of Red-Al Reductions of γ-Hydroxyalkynoates

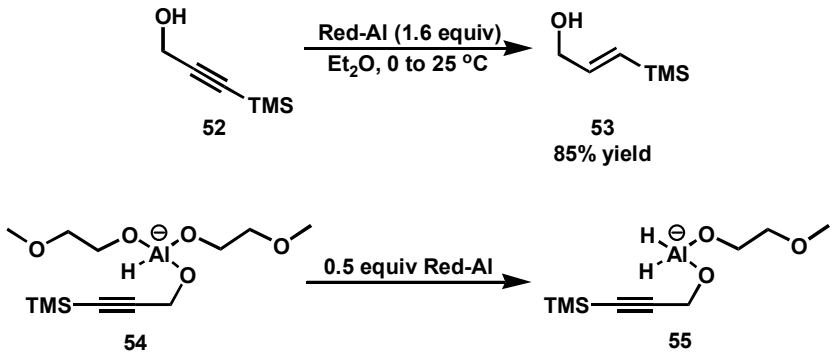
We were unhappy with the low *E*/*Z* ratios obtained for the more sterically hindered acetylenic esters and we decided to investigate other reducing agents that had been reported for

the reduction of propargyl alcohols. Corey and coworkers have shown that propargyl alcohols could be reduced with $LiAlH_4$, and the resultant vinylalanes could be trapped to incorporate an electrophile β or γ to the alcohol (Scheme 18).[46] When sodium methoxide is the additive in the reduction shown in Scheme 18, the electrophile is incorporated γ to the alcohol, providing tri-substituted olefin **50**, while aluminum trichloride provides incorporation of electrophiles at the β position to afford tri-substituted olefin **51**. However, these reductions must be carried out with $LiAlH_4$ in refluxing THF, which raises serious concerns of functional group compatibility.



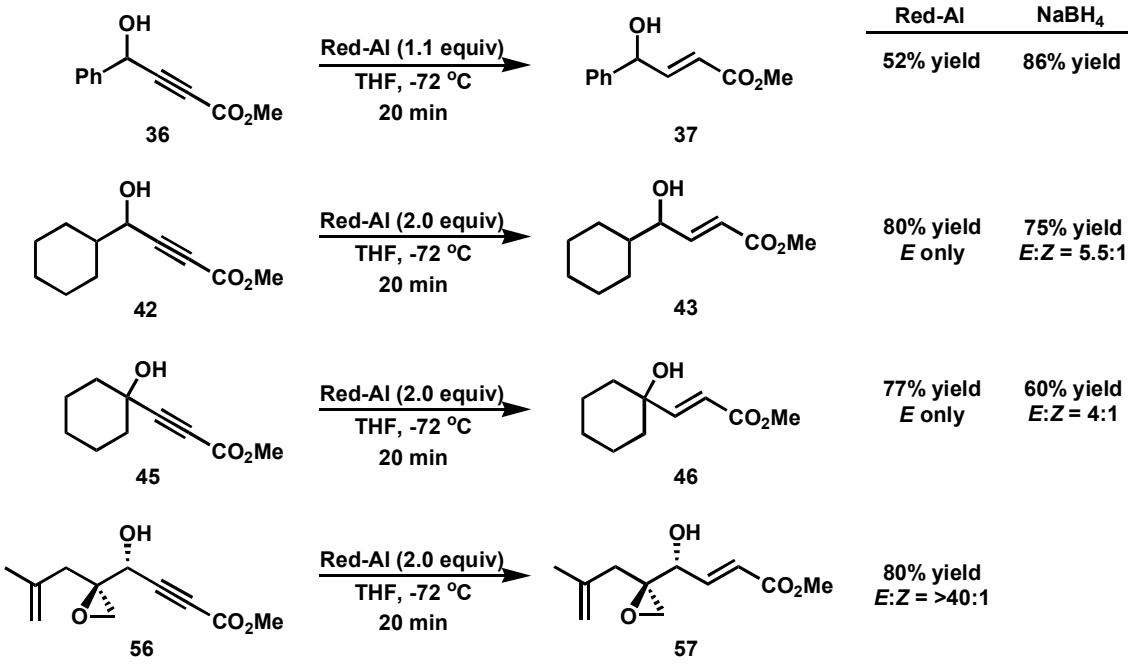
Scheme 18. $LiAlH_4$ reduction of propargyl alcohols.

In a related study on the reduction of propargyl alcohols, Denmark and coworkers prepared the (*E*)-alkene **53**, which results from the *trans*-reduction of the TMS-propargyl alcohol **52**.[47] Sodium bis-(2-methoxyethoxy)aluminum hydride (Red-Al or SMEAH) in diethyl ether (0 → 25 ^{o}C) provided **53** in 85% yield (Scheme 19). Interestingly, the reaction required 1.6 equiv of Red-Al to reduce **52**, as 1.1 equiv did not provide the desired product, even in refluxing diethyl ether. The authors hypothesized that the additional 0.5 equiv of Red-Al generated the reactive species **55**, in which the dihydrido species could reduce the alkyne faster than species **54**.



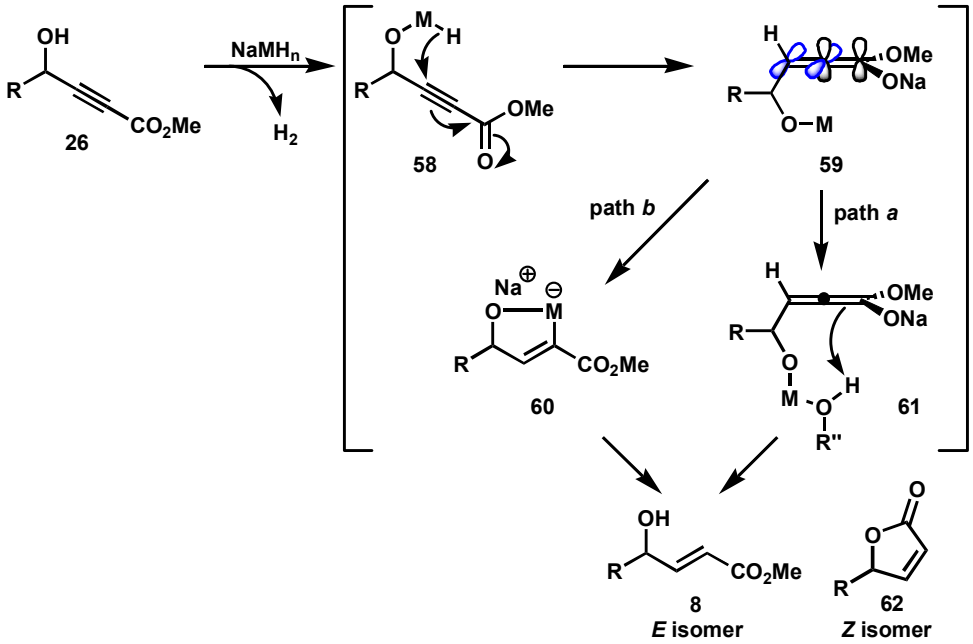
Scheme 19. Red-Al reduction of TMS-alkyne **52**.

After screening reducing agents ($NaBH_3CN$, $^nBu_4NBH_4$, and BH_3) to improve the selectivity in the reduction of alkynoates **42** and **45**, we found Red-Al afforded the desired products with excellent *E*:*Z* ratios along with improved yields (Scheme 20). Red-Al reduction of alcohols **42** and **45** provided only the (*E*)-isomers **43** and **46** (*E*/*Z* ratio determined from analyzing ^1H NMR spectra) along with improved yields (80% and 77%, respectively) while the $NaBH_4$ reduction of the same alcohols provided moderate *E*:*Z* ratios of the alkenoate products. Reduction of **36** with 1.1 equiv Red-Al gave a 52% yield of alkenoate **37**. This moderate yield may arise from a situation similar to Denmark's, in which an additional 0.5 equiv is required to make a stronger reducing species to complete the reaction. To determine if the reaction conditions were compatible with potentially electrophilic functional groups, epoxy alcohol **56** was subjected to Red-Al reduction to provide the desired product **57** in 80% yield with an *E*:*Z* ratio of >40:1.



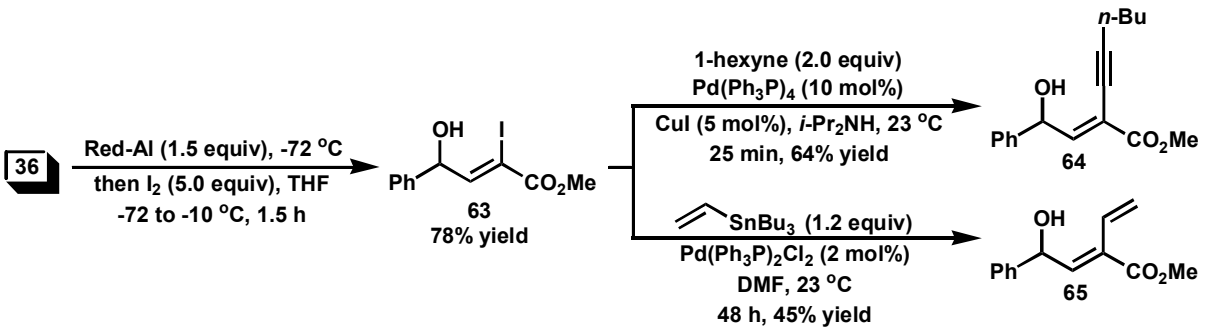
Scheme 20. Red-Al reduction of acetylenic esters.

On the basis of observations made thus far, the mechanism shown in Scheme 21 is proposed for the reduction of **26**. The reaction is initiated by an acid-base reaction of **26** and $NaMH_n$ to afford the metal alkoxide **58**. Intramolecular conjugate reduction provides allenolate **59** which can produce **8** according to one of two pathways. The metal alkoxide **61** can direct protonation to the α-face of the allenolate affording, after workup, **8** (path *a*). Alternatively, the metallocycle **60** may be formed from allenolate **59** and upon workup, only the (*E*)-product is observed (path *b*). This second pathway is consistent with lack of over-reduced product in our reactions. If path *a* is functioning, then we should expect significant amounts of the saturated γ-hydroxyesters. Nevertheless, if the reaction proceeds through either of these pathways, it should be possible to quench the reaction with various electrophiles to produce α,β-di-substituted alkenoates in a stereoselective fashion.



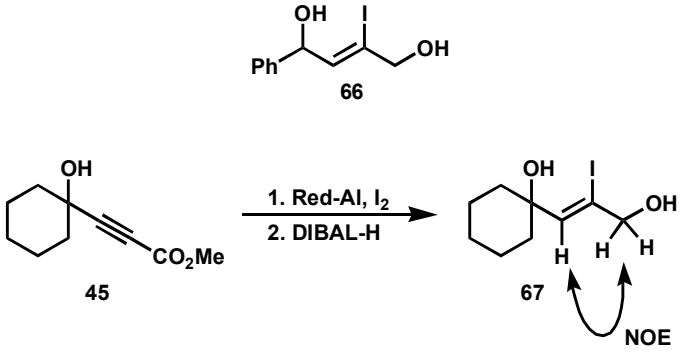
Scheme 21. Plausible mechanisms for hydride reduction of alkynoate **26**.

To test this hypothesis, Red-Al reduction of phenyl derivative **36** was quenched with iodine, providing vinyl iodide **63** in 78% yield (Scheme 22). Vinyl halides are valuable precursors in organic synthesis as divergence points in diversity-oriented approaches to library synthesis.[48] For example, vinyl iodide **63** was coupled with 1-hexyne in a Sonogashira reaction[49] and with tributyl(vinyl)tin in a Stille reaction[50] to provide the conjugated enyne **64** and diene **65** in 64% and 45% yield, respectively (not optimized).



Scheme 22. Preparation of tri-substituted olefins **63**, **64**, and **65**.

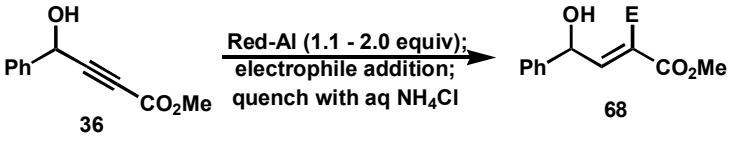
To unambiguously determine the olefin geometry of vinyl iodide **63**, diol **66** was prepared by DIBAL-H reduction of compound **63** (Scheme 23). NOE experiments proved unsuccessful with diol **66**, presumably due to the molecule's rapid tumbling in solution. Diol **67** was prepared from propargyl alcohol **45** in the same manner. The indicated NOE enhancement between the vinyl proton and methylene protons confirms the *cis* geometry.



Scheme 23. Determination of olefin geometry.

Unfortunately, we have not been able to trap our intermediate allenolates with other electrophiles (Table 2). To improve the yield of iodide incorporation, N-iodosuccinimide (NIS) was used as the source of I^+; however, only the disubstituted olefin **68** was observed. To prepare

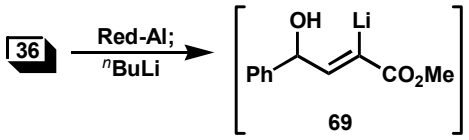
a silyl allenolate or vinyl tin species, the reaction was quenched with TMSCl or Me_3SnCl as the electrophilic source, again only yielding the *trans*-olefin **68** (E = H). To directly form a C-C bond with the Red-Al reduction conditions rather than using Pd-coupling reactions, benzaldehyde was added to the reaction mixture after alkynoate **36** had been reduced with Red-Al, yet again providing the *trans*-olefin **68** (E = H).



electrophile	result
NIS	E = H (trans olefin)
TMSCl	E = H (trans olefin)
Me_3SnCl	E = H (trans olefin)
benzaldehyde	E = H (trans olefin)

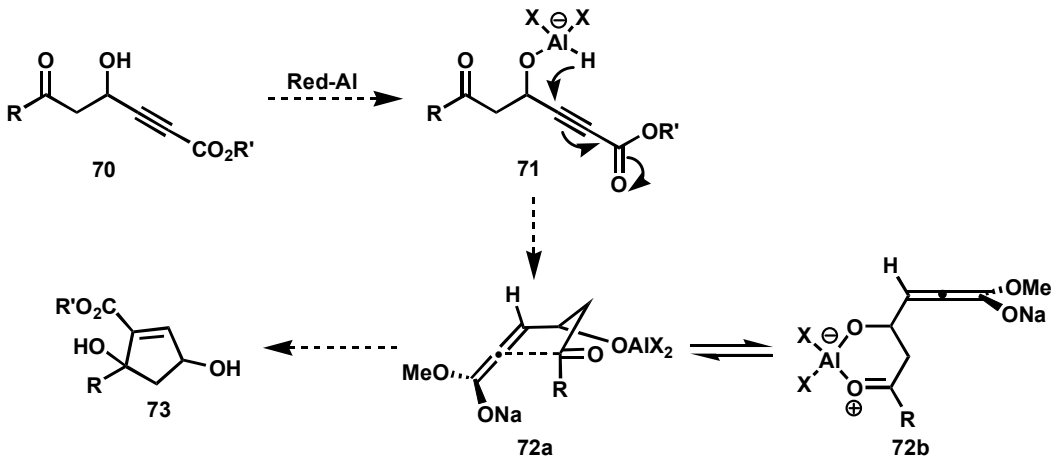
Table 2. Attempts to trap Red-Al reduction with electrophiles.

It is possible that the vinyl aluminum species that forms during the Red-Al reduction is not nucleophilic enough to react with certain electrophiles, providing only the *trans*-olefin product unless iodine is used. To increase the nucleophilicity of the vinyl-metal intermediate, future work will examine the addition of a lithium species (^{n}BuLi) to the reaction after Red-Al reduction to yield the more nucleophilic vinyl lithium **69** *in situ* (Scheme 24). This more nucleophilic species may be capable of reacting with various electrophiles to produce the tri-substituted olefin **68**.



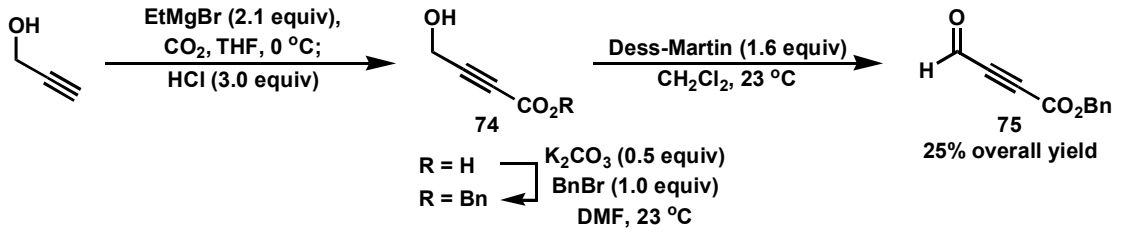
Scheme 24. Preparation of vinyl lithium **69**.

Despite unfruitful attempts of trapping the Red-Al reduction with various electrophiles, further elaboration of the Red-Al reduction of alkynoates was investigated. Since the intermolecular trapping of the vinyl aluminum species only transpired with iodine, the intramolecular route was examined (Scheme 25). We hypothesized that by incorporating a carbonyl in a 1,3-relationship with the propargyl alcohol that following Red-Al reduction of alkynoate **70**, the favored intermediate for cyclization would be **72a**, compared to the aluminum coordinating to two oxygen atoms. In this intermediate, the carbonyl group should be positioned for intramolecular nucleophilic attack by allenolate **72**, providing cyclic diol **73** after acidic workup.



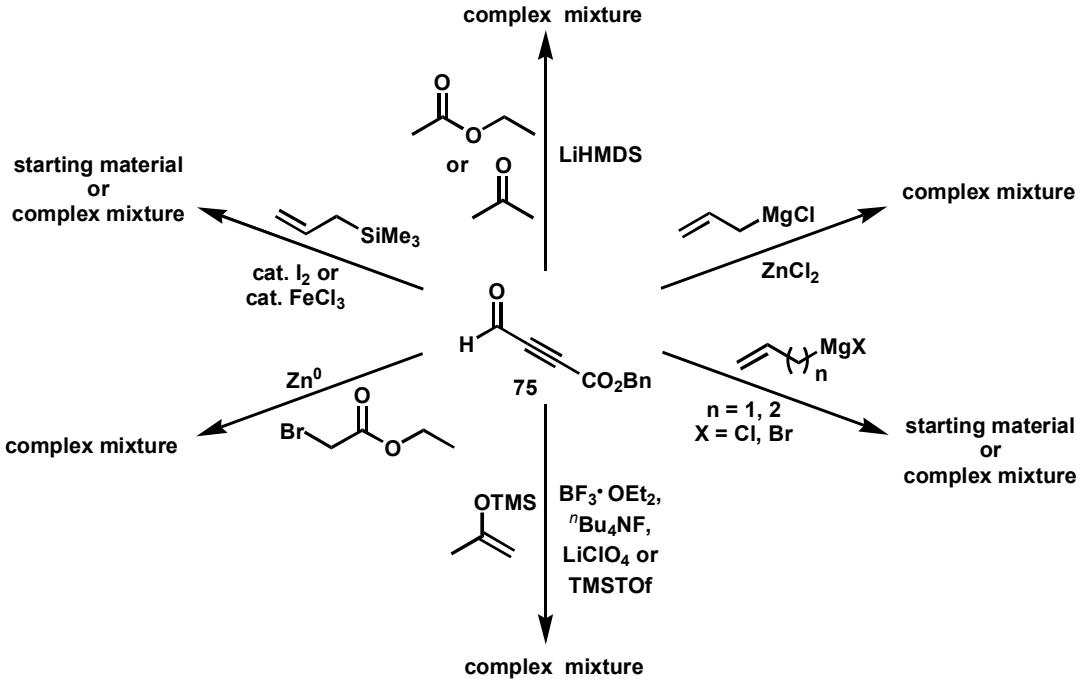
Scheme 25. Cyclization of alkynoate **70** with Red-Al.

Preparation of alkynoate **70** started with dianion formation of propargyl alcohol followed by quenching with CO_2 and HCl to yield commercially available carboxylic acid **74** (R = H) (Scheme 26). The crude product was reacted with K_2CO_3 and BnBr to give ester **74** (R = Bn).[51] The crude product was again carried on, this time through Dess-Martin periodinane oxidation to yield aldehyde **75** in 25% overall yield from propargyl alcohol.



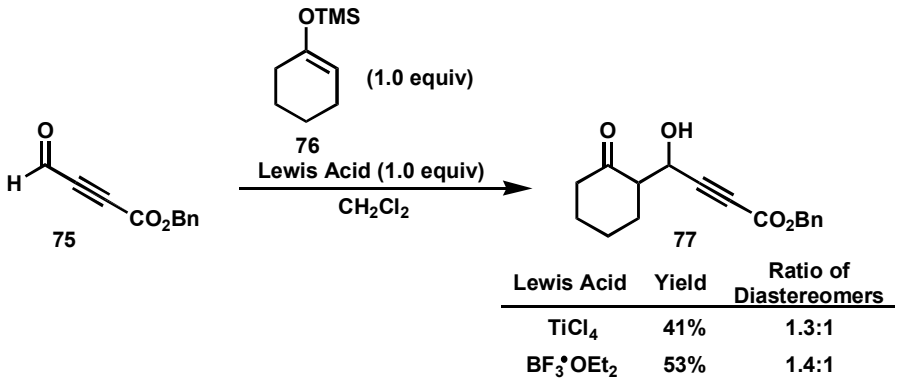
Scheme 26. Prepartion of aldehyde **75**.

Direct allylation and ozonolysis of aldehyde **75** was initially thought to give the requisite aldehyde **70** (R = H); however, various methods of addition into aldehyde **75** proved unsuccessful (Scheme 27). Use of allyl and homoallyl Grignard reagents gave complex mixtures or starting material. Changing the organometallic species to allyl zinc through transmetalation of allyl magnesium chloride also provided a complex mixture. Attempting to add the allyl group in a milder method also provided the starting aldehyde or a complex mixture when allyltrimethylsilane was the allylating agent with catalytic I_2 or $FeCl_3$.[52,53] The addition of an ester into aldehyde **75** was explored: 1) Reformatsky reactions with Zn dust[54] or Rieke Zn[55] and ethyl bromoacetate and 2) addition of the enolate derived from ethyl acetate. Ester addition attempts led to complex mixtures. Mukaiyama additions with the silyl enol ether of acetone and various Lewis acids also provided complex mixtures when reacted with aldehyde **75**. The difficulty of addition into aldehyde **75** may be due to its multiple electrophilic sites and sites for reactivity: 1) 1,2-addition into the aldehyde or ester functionality and 2) conjugate addition into the alkyne due to the presence of two electron-withdrawing groups present on either side of the triple bond.



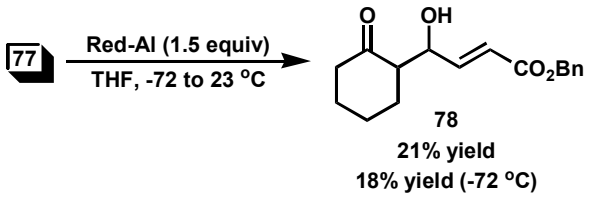
Scheme 27. Attempted additions to aldehyde **75**.

Initial success of addition into aldehyde **75** resulted from the Mukaiyama reaction of silyl enol ether **76** with BF_3•OEt2 or $TiCl_4$ as the Lewis acid (Scheme 28). Although both Lewis acids yielded the desired alkynoate **77**, BF_3•OEt2 gave both higher yield and slightly improved ratio of diastereomers. Increased amounts of BF_3•OEt_2 did improve the ratio of diastereomers (1.9:1), but also decreased the yield (45%).



Scheme 28. Mukaiyama reactions with aldehyde **77**.

Alkynoate **77** was reacted with Red-Al at -72 ^{o}C in THF, only to yield the reduced alkenoate product **78** in 18% yield (Scheme 29). In an attempt to promote cyclization, the reaction temperature was warmed to 23 ^{o}C, yielding alkenoate **78** in 21% yield. This result may be due to the low nucleophilicity of the intermediate vinyl aluminum species, which could be rectified through transmetalation. Producing a more reactive species would promote cyclization, although reversibility of the reaction may become problematic.

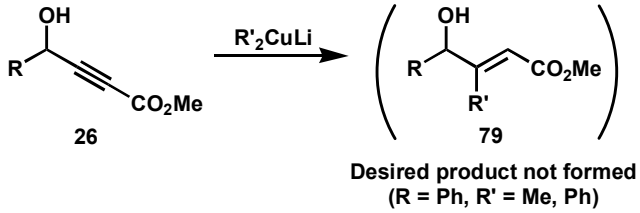


Scheme 29. Attempted cyclization of alkynoate **77**.

2.5 Carbon-Carbon Bond Formation Using the γ-Hydroxy Directed *trans*-Conjugate Addition

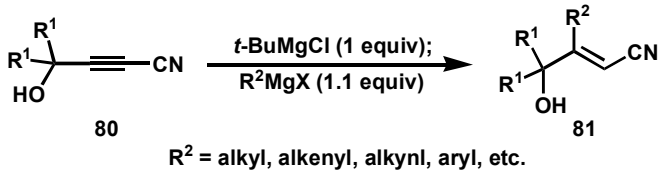
To expand the scope of the *trans*-conjugate addition reaction towards C-C bond forming reactions and β,β-di-substituted alkenoates, a suitable reagent was pursued that would deliver a

carbon nucleophile to the β carbon of alkynoate **26** directed by the γ-hydroxy group. Initially, dialkylcuprate-mediated conjugate addition into various alkynoates was investigated; however, various conditions (Me_2CuLi, Ph_2CuLi, range of temperatures, range of additives) failed to give the desired alkenoate **79** (Scheme 30).



Scheme 30. Attempted organocuprate addition.

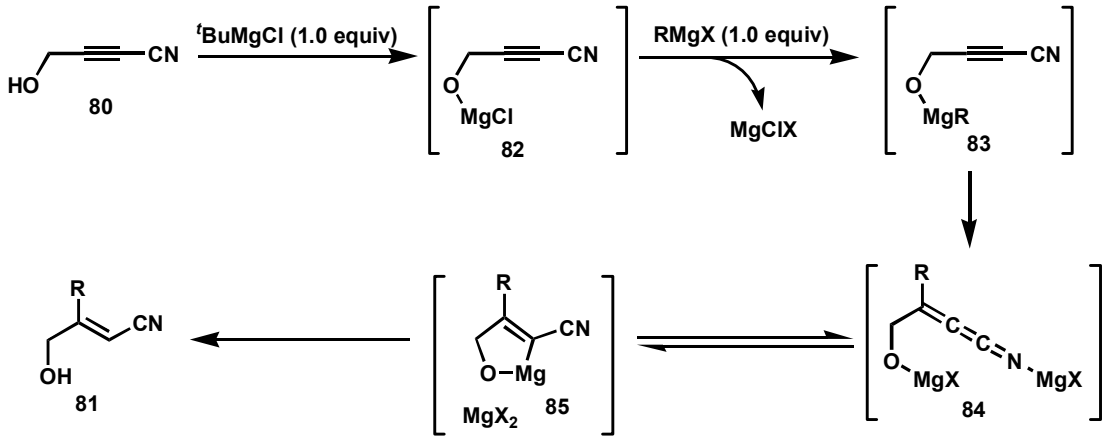
Investigations to find a suitable organometallic reagent capable of adding a carbon nucleophile in a *trans*-conjugate fashion to alkynoates **26** led to a study by the Fleming group that showed Grignard reagents were able to add carbon nucleophiles in a conjugate fashion to γ-hydroxy-α,β-acetylenic nitriles (Scheme 31).[56]



Scheme 31. Conjugate addition into γ-hydroxy-α,β-acetylenic nitrile **80**.

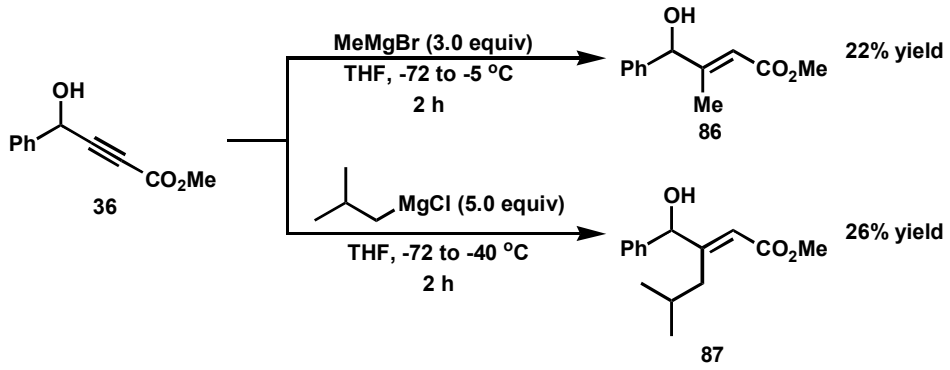
This reaction utilizes ^{t}BuMgCl (1.0 equiv) to deprotonate alcohol **80** (R^1 = H) to prepare the initial alkoxide **82** (Scheme 32). At this point, a different Grignard reagent is added to the reaction, which displaces the chloride atom on the magnesium, forming the reactive

organomagnesium species **83**. The nucleophilic carbon is then added in a conjugate addition fashion to the acetylenic nitrile, forming magnesiated alkenenitrile **84** that is in equilibration with the cyclic compound **85**. Quenching the reaction with a proton source generates tri-substituted vinyl cyano-species **81**.



Scheme 32. Proposed mechanism on *trans*-conjugate addition towards γ-hydroxy-α,β-acetylenic nitriles.

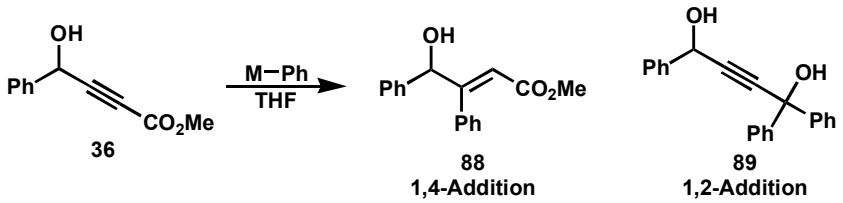
With this precedent in mind, phenyl alkynoate **36** was reacted with 3.0 equiv of MeMgBr in an attempt to prepare the β,β-di-substituted alkenoate **86** (Scheme 33). After changing various reaction conditions, the optimum isolated yield was 22%. To test the ability of a different sp^3 Grignard reagent to complete the conjugate addition, ^{i}BuMgCl was reacted with **36** to provide alkenoate **87** in a 26% yield. These results denote that *trans*-conjugate additions of sp^3-hybridized carbon nucleophiles into γ-hydroxyalkynoates require further investigation.



Scheme 33. sp^3 conjugate Grignard additions to alkynoate **36**.

In an effort to couple **36** with sp^2-hybridized carbon nucleophiles, PhMgBr was reacted with **36** in THF at -72 to -40 °C to yield alkenoate **88**:alkynoate **36** in a 3:1 ratio (Table 3, run 1). To improve the yield, the reaction was warmed to various temperatures. The highest yield resulted from allowing the reaction to warm to -20 °C, providing alkenoate **88** in 64% yield (91% based on recovered starting material). Warming the reaction further did not lead to increased yields. Various additives (BF3•OEt2, AgOTf, $AuCl_3$, $NiCl_2$, $Zn(OTf)_2$, $InCl_3$, or $TiCl_4$) were then included in the reaction with PhMgBr under the optimized conditions (3.0 equiv PhMgBr, THF, -72 to -20 °C) in an effort to enhance the electrophilicity of the triple bond by activating either the alkyne directly or by coordinating the ester. Reactions with an additive resulted in lower yields (40-50%) in comparison to the optimized reaction conditions. It is possible that PhMgBr reacted with some of the additives to generate a less reactive organometallic reagent, which would be responsible for the decrease in yield. Altering the organometallic species was the next route for reaction optimization, and as stated above, Ph_2CuLi failed to yield the desired product. Addition of the more nucleophilic PhLi at low temperatures (-72 to -40 °C) in THF led to recovery of alkynoate **36**. Warming the reaction to 23 °C resulted in the 1,2-addition product **89** rather than the desired 1,4-addition product **88**. This was an expected result due to the

increased nucleophilicity of PhLi and the inability of a lithium atom to form an intermediate analogous to **60**. Various additives ($InCl_3$, $AlCl_3$, or $GaCl_3$) were added to the reaction of alkynoate **36** with PhLi, however, the 1,2-addition product was still generated.



run	M	equiv	temp (°C)	results
1	MgBr	3.0	-72 to -40	3 : 1 (88 : 36)
2	MgBr	3.0	-43 to -20	64% yield 88
3	Li	3.0	-72 to -40	no reaction
4	Li	3.0	-72 to 23	89

Table 3. Phenyl addition to alkynoate **36**.

Continued efforts to improve the phenyl addition to alkynoate **36** led to utilization with $ZnPh_2$ as the organometallic reagent (Table 4). The reaction of $ZnPh_2$ with alkynoate **36** resulted in recovery of starting material when the temperature was increased from -72 to -40 °C. When the reaction was warmed to 0 °C, the ^1H NMR showed a 1:1.5 ratio of alkenoate **88**:starting alkynoate **36**. Since the reaction seemed to proceed at warmer temperatures, the reaction was started at -43 °C and allowed to warm to 0 °C, when it was quenched with a protic solvent. The reaction was conducted with a variety of metals and ligands in an effort to improve the yield of the desired alkenoate, however, only a handful of additives had any effect on the reaction. The metals and ligands were initially used in catalytic amounts (5-10 mol%), then subsequently increased if they promoted the desired reaction. The ligands were added in attempts to increase

the nucleophilicity of the Zn species,[57] while the metals were added with the anticipation of activating the alkynoate for conjugate addition. The highest yield obtained for the $ZnPh_2$ addition was in the presence of 0.5 equiv of $InCl_3$ after 0.1 equiv showed improvement of the conjugate addition reaction. Increasing the amount of $InCl_3$, however, did not result in an increased yield of product. The addition of ethylene glycol (0.1 equiv) to the reaction mixture resulted in a 1:1.2 mixture of alkenoate **88**:alkynoate **36**. The metals and ligands shown in Table 4 that are not highlighted resulted in isolation of the alkynoate **36**. Extending the carbon chain by one and using 1,3-propanediol as the additive resulted in no reaction. Utilizing $ZnPh_2$ in the conjugate addition towards alkynoates such as **36** may prove to be beneficial with further optimization.

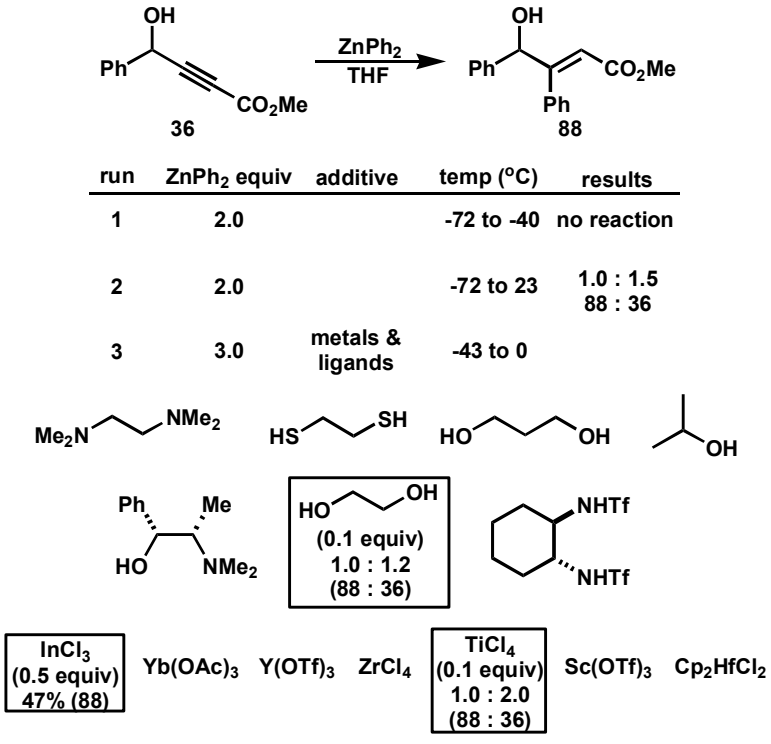
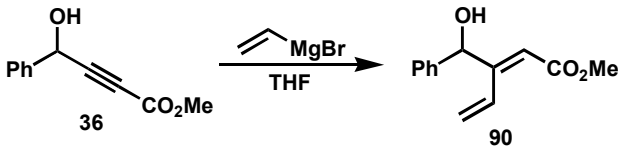


Table 4. $ZnPh_2$ conjugate addition toward alkynoate **36**.

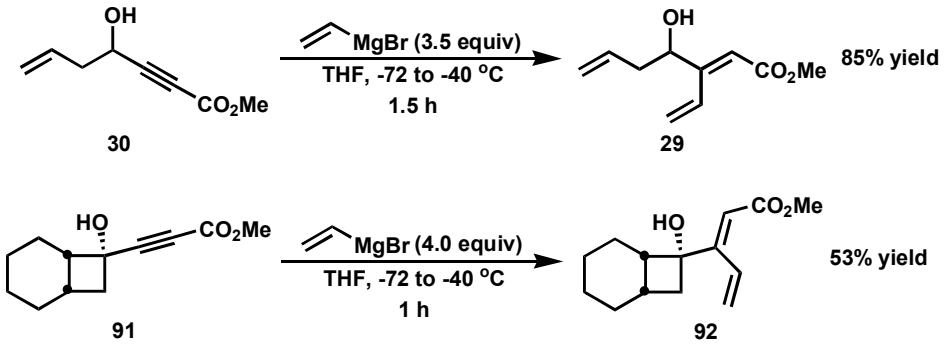
Following studies of phenyl addition into alkynoate **36**, CH_2=CHMgBr was examined as an additional sp^2 carbon source (Table 5). When 3.0 equiv of CH_2=CHMgBr were reacted with alkynoate **36** at -72 °C, diene **90** was afforded in 52% yield (run 1). Increasing the amount of Grignard reagent to 5.0 equiv to promote product formation increased the yield to 68% (run 2), however 5.0 equiv of CH_2=CHMgBr was deemed excessive, so other routes to optimize the reaction were investigated. Including a coordinating additive such as DMPU decreased the yield dramatically to <10% (run 3), so other coordinating additives were not studied further. Increasing the temperature of the reaction was examined in a fashion similar to the phenyl addition to alkynoate **36**. When the mixture was quenched at -60 °C, the yield of diene **90** improved to 80% (run 4). Allowing the reaction to warm to -40 °C before quenching provided the desired diene **90** in 90% yield (run 5). Additional warming of the reaction did not result in increased yields. The optimum concentration in THF proved to be 0.1 M, although increasing or decreasing the concentration (0.05 – 0.4 M) diminished the yields only slightly.



run	equiv of Grignard	additive	temp	yield
1	3.0	-	-72	52%
2	5.0	-	-72	68%
3	3.0	DMPU	-72	<10%
4	3.0	-	-72 to -60	80%
5	3.0	-	-72 to -40	90%

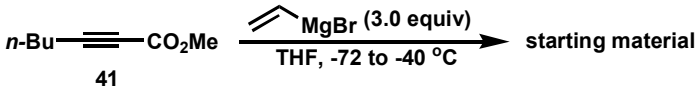
Table 5. Optimizing CH_2=CHMgBr addition to **36**.

With satisfactory conditions determined (3.0 equiv of CH_2=CHMgBr, 0.1 M concentration, THF, -72 to -40 ^oC), the mechanism and scope of the reaction were then investigated. The reaction conditions were applied to the non-aromatic enyne **30** resulting in the isolation of triene **29** in 85% yield (Scheme 34). The reaction did, however, require a slight increase in the amount of CH_2=CHMgBr (3.5 equiv). Sterically hindered alkynoate **91** required 4.0 equiv of CH_2=CHMgBr to provide diene **92** in 53% yield. In each of the cases, however, no 1,2-addition was observed under the reaction conditions.



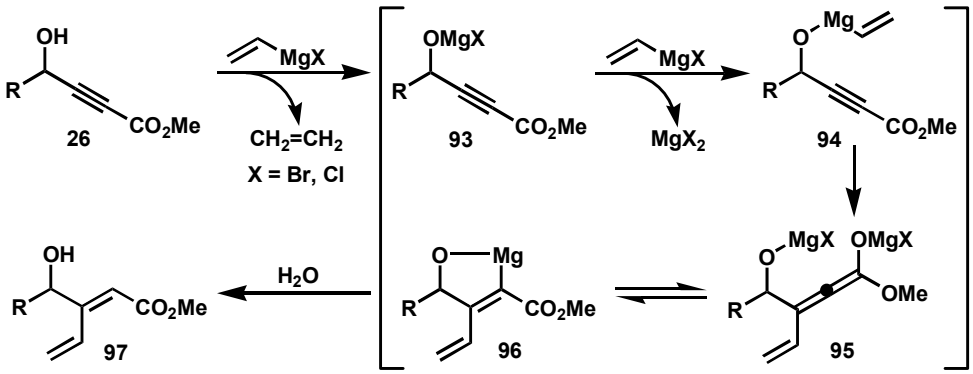
Scheme 34. Conjugate sp^2 Grignard addition into acetylenic esters.

To determine if the hydroxy group constituted a role similar to the case when $NaBH_4$ or Red-Al is used to reduce alkynoate **26**, CH_2=CHMgBr was reacted with alkynoate **41**, which lacks a γ-hydroxy group. When alkynoate **41** was subjected to the optimized reaction conditions, starting material was obtained with no evidence of either 1,4-conjugate addition or direct 1,2-addition to the ester (Scheme 35). This result is further evidence that the reaction is directed by the hydroxy group in a similar mechanism as that hypothesized for $NaBH_4$ or Red-Al reduction of the corresponding alkynoates.



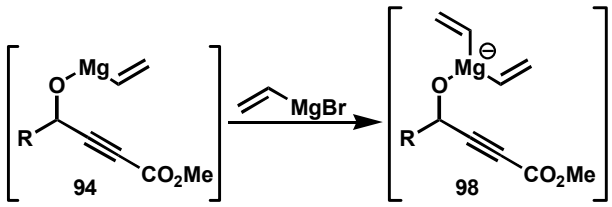
Scheme 35. CH_2=CHMgBr reaction with alkynoate **41**.

The mechanism that we propose is analogous to Fleming's,[56] as depicted in Scheme 36. The first equivalent of Grignard reagent deprotonates the alcohol proton to produce one equivalent of ethylene gas and the magnesium alkoxide **93**, which then reacts with the second equivalent of Grignard reagent to form the alkenylmagnesium species **94**. This intermediate delivers the vinyl group to the β carbon of the acetylenic ester, resulting in allenolate **95**, which is presumably in equilibrium with the cyclic species **96**. Quenching the reaction with a protic solvent allows for the isolation of diene **97**. Interestingly, when CH_2=CHMgCl is used as the Grignard reagent for the *trans*-conjugate addition of a carbon nucleophile to alkynoate **26**, no reaction occurs. This result may be due to the inability of CH_2=CHMgCl to form reactive intermediate **94** from alkoxide **93**.



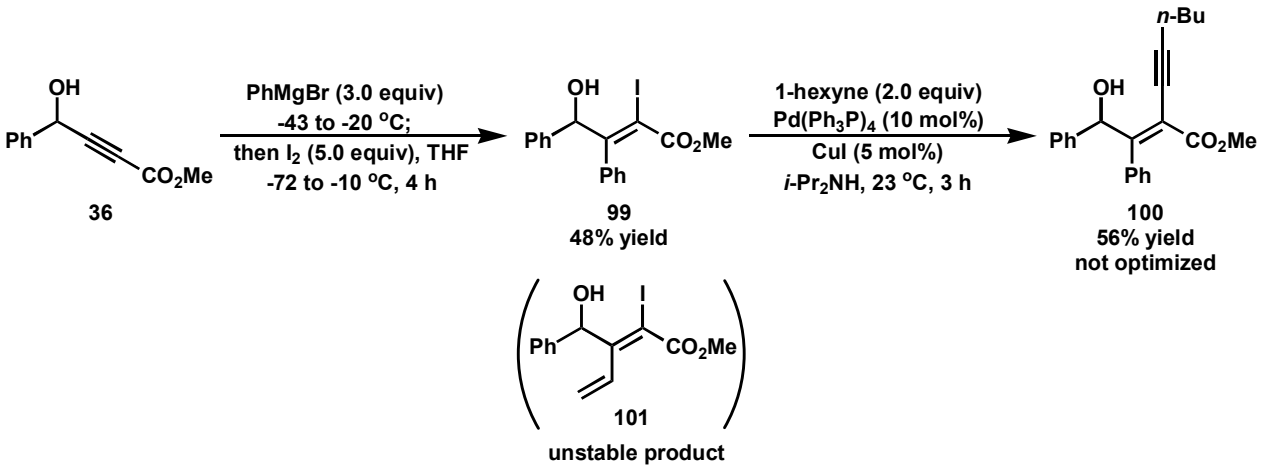
Scheme 36. Hydroxy directed *trans*-conjugate Grignard addition.

If the reaction does proceed through the mechanism shown above, then 2.0 equiv of CH_2=CHMgBr should be adequate to complete the reaction. However, the reaction proceeds to completion with 3.0 equiv of CH_2=CHMgBr, leaving the possibility of a different intermediate forming in solution, such as the magnesium ate complex shown in Scheme 37. The ate complex **98** is more nucleophilic than intermediate **94**, which may explain the increased yields when 3.0 equiv of CH_2=CHMgBr is used. To test this hypothesis, a control experiment was conducted with alkynoate **36** and 1.5 equiv of CH_2=CHMgBr. Alkynoate **36** was recovered in a quantitative yield, providing support for the formation of ate complex **98**.



Scheme 37. Formation of ate complex **98**.

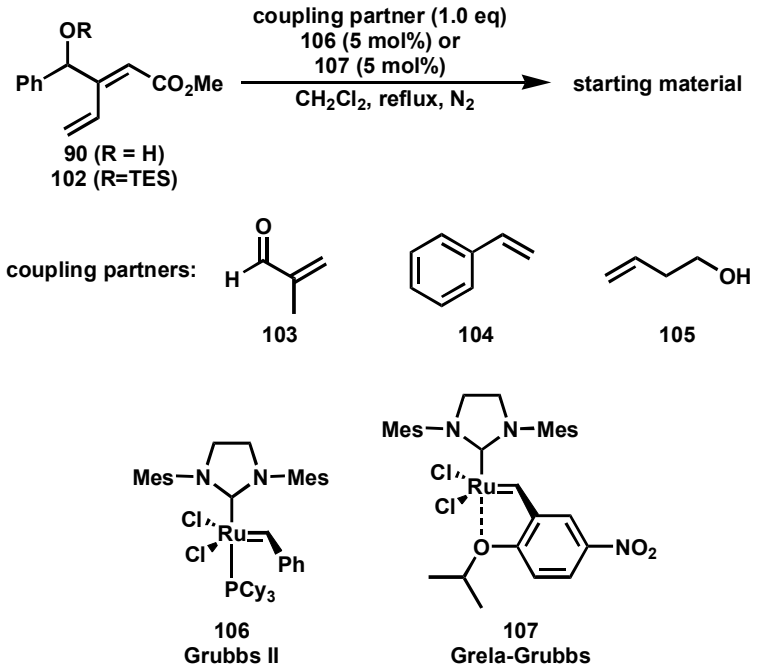
If the reaction proceeds through the proposed mechanism in a similar fashion to that hypothesized for the hydride reduction of acetylenic esters, then it is conceivable to quench the reaction with various electrophiles to derivatize the α carbon in a stereoselective fashion. To test this hypothesis, PhMgBr addition into **36** was quenched with iodine to furnish vinyl iodide **99** in 48% yield (Scheme 38). This low yield is due in part to the decomposition of **99** during purification. Vinyl iodide **99** was subjected to Sonogashira[49] conditions with 1-hexyne to provide the highly conjugated tetra-substituted olefin **100** in 56% yield (not optimized). Use of CH_2=CHMgBr in the corresponding addition and quenching with iodine to provide vinyl iodide **101** led to poor yields due to product instability during purification.



Scheme 38. Preparation of tetra-substituted olefins **99** and **100**.

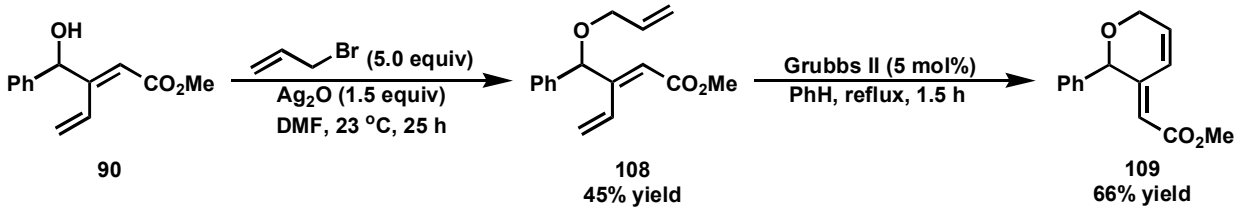
To elaborate the *trans*-conjugate addition of CH_2=CHMgBr to alkynoate **36**, the subsequent diene was used in cross-metathesis reactions with ruthenium catalysts and various terminal olefins (Scheme 39). Initial attempts to couple diene **90** with aldehyde **103** using Grubbs II[58] (5 mol%) in refluxing CH_2Cl_2 provided starting material from the reaction mixture. Since aldehyde **103** is an electron-poor coupling partner, less electron-deficient terminal olefins were used under similar reaction conditions. Still, when styrene or alcohol **105** was used in the cross-metathesis with diene **90** and Grubbs II, only starting material was recovered. To determine if the free alcohol was hindering the reaction, TES ether **102** was subjected to the same reaction conditions as diene **90** (Grubbs II (5 mol%), refluxing CH_2Cl_2, aldehyde **103**, styrene, or alcohol **105**), but starting material was recovered from all the reaction mixtures. The more reactive ruthenium catalyst **107**[59] (Grela-Grubbs) was also unsuccessful in cross-metathesis reactions between diene **90** and any of the used attempted coupling partners. While diene **90** proved to be ineffective in coupling with various terminal olefins, it may be due to the inherent

nature of the diene, in particular how the diene is conjugated and electron-poor due to the ester substituent.



Scheme 39. Attempted cross-metathesis reactions.

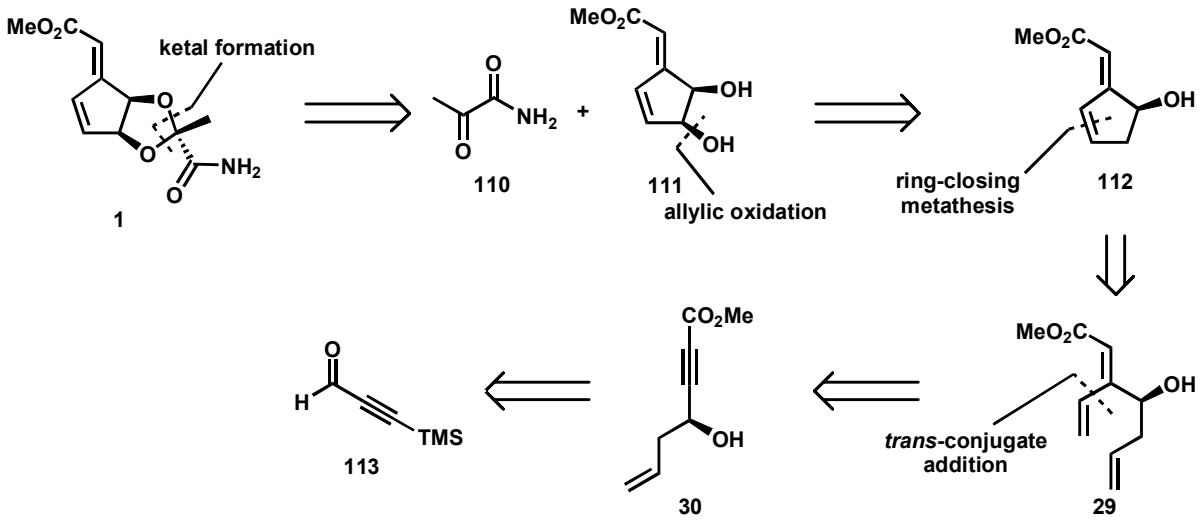
As stated previously, controlling the stereochemistry of exocyclic tri-substituted olefins presents a challenge in the synthesis of complex molecules, since most methods have difficulty controlling the *E*:*Z* selectivity. To address this issue in the context of the *trans*-conjugate addition to acetylenic esters, diene **90** was treated with allyl bromide and Ag_2O to give allyl ether **108** in 45% yield (Scheme 40). Ring-closing metathesis with Grubbs II[58] of the triene provided cyclic compound **109** in 66% yield. This strategy can be employed to control the stereochemistry of the exocyclic alkenoate in the preparation of stresgenin B through utilizing the *trans*-conjugate addition of Grignard reagents toward alkynoates.



Scheme 40. Preparation of exocyclic compound **109**.

2.6 Initial Synthetic Studies Towards Stresgenin B

The retrosynthetic analysis of stresgenin B ensued with controlling the stereochemistry of the exocyclic double bond through the *trans*-conjugate Grignard addition into an acetylenic ester. Scheme 41 shows the retrosynthetic analysis of **1**, commencing with ketal formation to give diol **111** and α-keto-amide **110**. In order to determine which diastereomer would be favored during ketal formation, it was necessary to compare **1** and **114** (Figure 2). Initial calculations with CAChe (MM3 force field) have shown a 0.56 kcal/mol energy difference favoring the desired diastereomer **1** during ketal formation. This calculation indicates that the desired diastereomer **1** will be thermodynamically favored during ketal formation. Diol **111** will be prepared through allylic oxidation of cyclic compound **112** by activation of the C-H bond directly.[60] Cyclic compound **112** will be derived from the ring-closing metathesis of triene **29**, which will be prepared through a key *trans*-conjugate addition of CH_2=CHMgBr to alkynoate **30**, prepared from commercially available aldehyde **113**.



Scheme 41. Retrosynthetic analysis of stresgenin B (**1**).

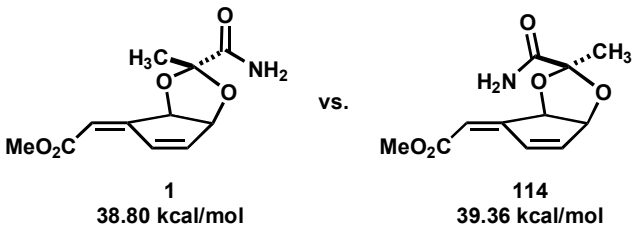
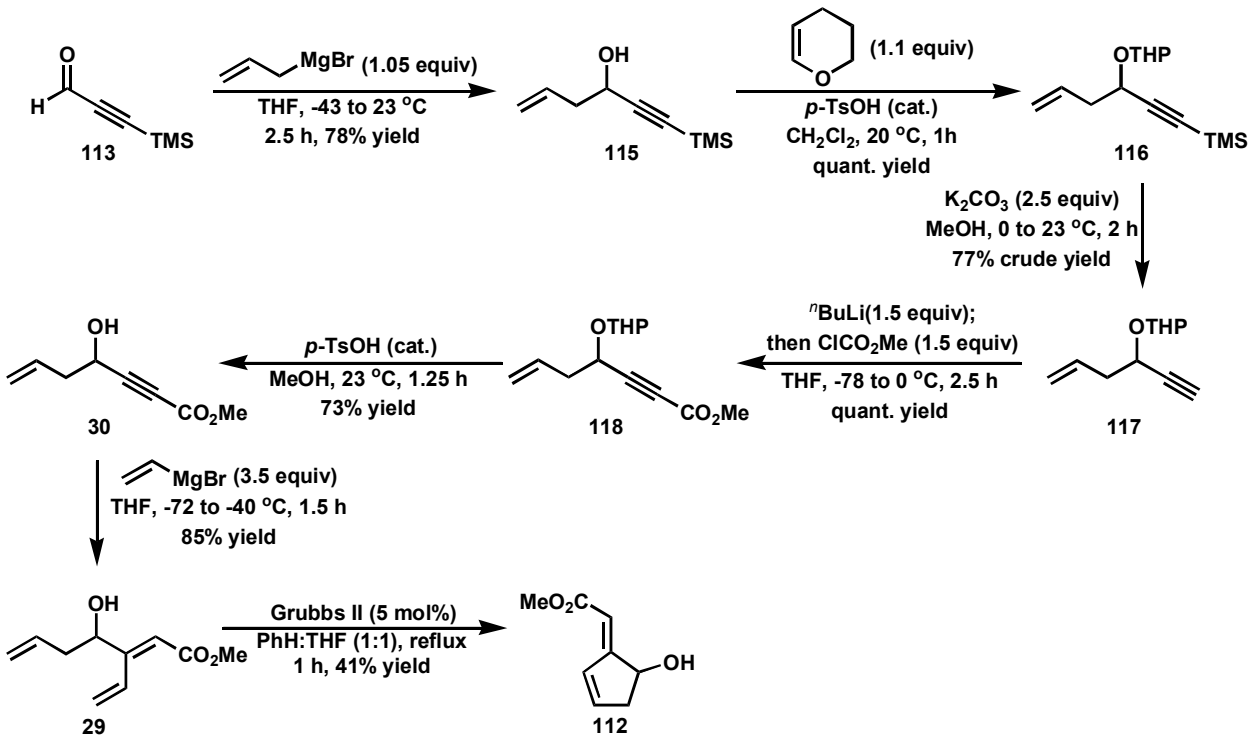


Figure 2. Energy values for stresgenin B diastereomers **1** and **114**.

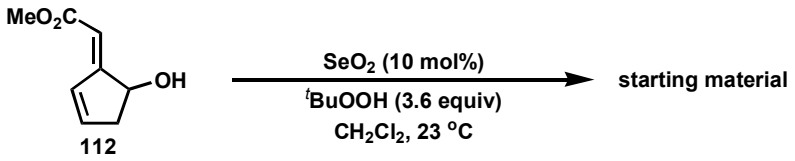
The synthesis of racemic stresgenin B started with the addition of allylmagnesium bromide into aldehyde **113**, yielding the known homoallylic alcohol **115** in 78% yield (Scheme 42). Protection of this alcohol as the THP ether **116** and subsequent TMS deprotection with K_2CO_3 in MeOH provided terminal alkyne **117** in 77% yield (two steps). Deprotonation of **117** and reaction with methyl chloroformate provided alkynoate **118** in quantitative yield. THP deprotection provided free alcohol **30** in 73% yield. As previously stated, the *trans*-conjugate addition into alkynoate **30** with CH_2=CHMgBr in THF furnished triene **29** in 85% yield.

Ensuing ring-closing metathesis with Grubbs II in refluxing benzene:THF (1:1) resulted in the isolation of cyclic compound **112**.



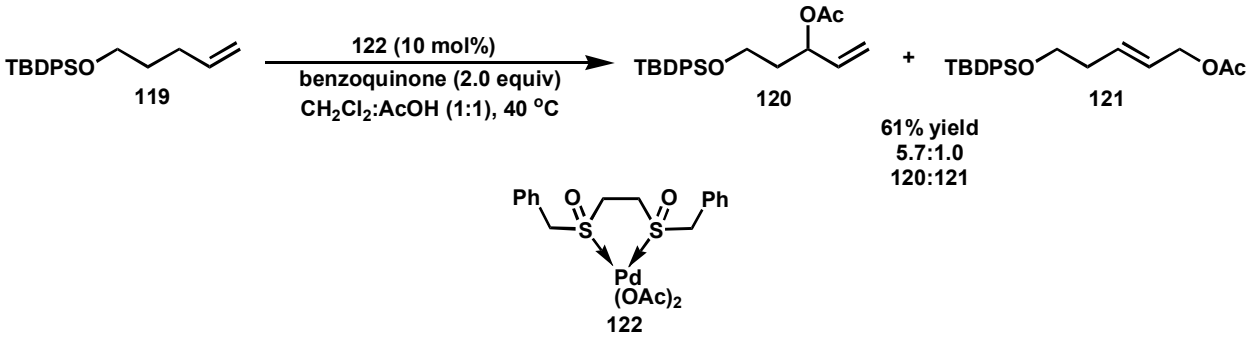
Scheme 42. Initial steps toward stresgenin B.

To incorporate the second hydroxy group, different allylic oxidation conditions were explored. Selenium dioxide has been shown to oxidize allylic carbons, mainly in linear systems.[61] When alcohol **112** was subjected to the reaction conditions, however, starting material was recovered (Scheme 43).



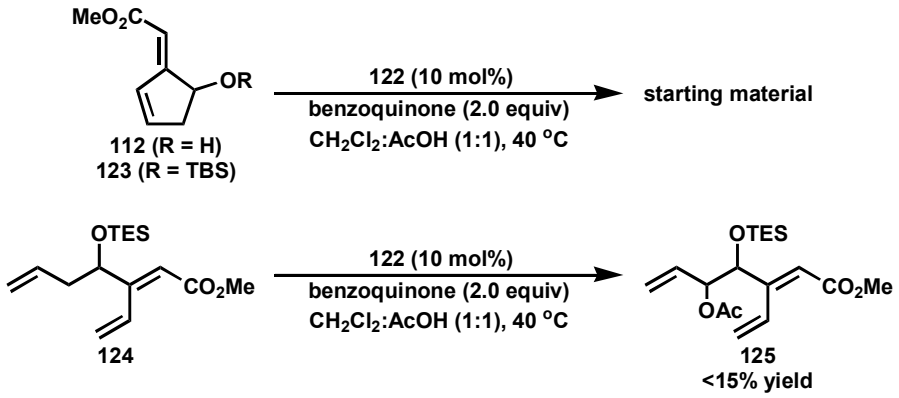
Scheme 43. Attempted SeO_2 oxidation.

Recently, White *et al*. have developed the palladium bis-sulfoxide catalyst **122** to oxidize allylic C-H bonds (Scheme 44).[62] Again, most of the substrates oxidized with this method are linear, although non-functionalized six-member rings have successfully been oxidized.



Scheme 44. Allylic oxidation with Pd bis-sulfoxide catalyst.

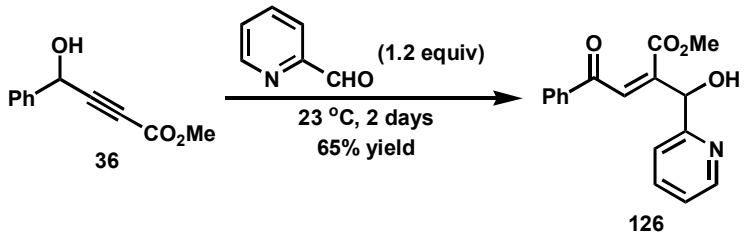
When alcohol **112** was reacted with Pd bis-sulfoxide catalyst **122**, benzoquinone, methylene chloride, and acetic acid at 40 °C, starting material was recovered (Scheme 45). To determine if the hydroxy group impedes the oxidation, TBS ether **123** was subjected to the same reaction conditions. However, no oxidation occurred and starting material was recovered. Although the allylic oxidation of alcohol **112** has proven problematic, initial attempts to oxidize the protected triene **124** prior to ring-closing metathesis have revealed there is promise for the Pd bis-sulfoxide allylic oxidation pathway.



Scheme 45. Attempted Pd bis-sulfoxide oxidation.

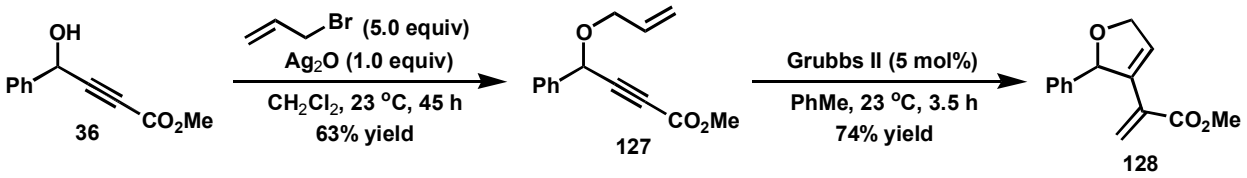
2.7 Use of γ-Hydroxy-α,β-Acetylenic Esters as a Pluripotent Precursor for Diversity-Oriented Synthesis

Preliminary investigations have involved diversifying the alkynoates used as starting materials in the *trans*-conjugate addition reactions, such as that shown in Scheme **46**. The Morita-Baylis-Hillman[63,64] type reaction between alkynoate **36** and 2-pyridinecarboxaldehyde proceeds at 23 °C over 2 days to yield enone **126**. While initial studies have shown the reaction to be specific for 2-pyridinecarboxyaldehyde, further exploration will provide a novel way to obtain functionalized compounds such as **126** from readily available starting materials.



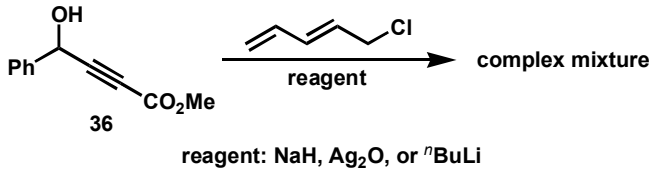
Scheme 46. Morita-Baylis-Hillman type reaction.

In addition to preparing tri- and tetra-substituted olefins, we envisioned utilizing alkynoate **36** in a variety of cycloaddition reactions. The *O*-allylation of **36** with allyl bromide and silver oxide yielded enyne **127** (63% yield) (Scheme 47). Ring-closing metathesis of enyne **127** in the presence of Grubbs II afforded diene **128**, which is structurally distinct from the other derivatives described thus far.



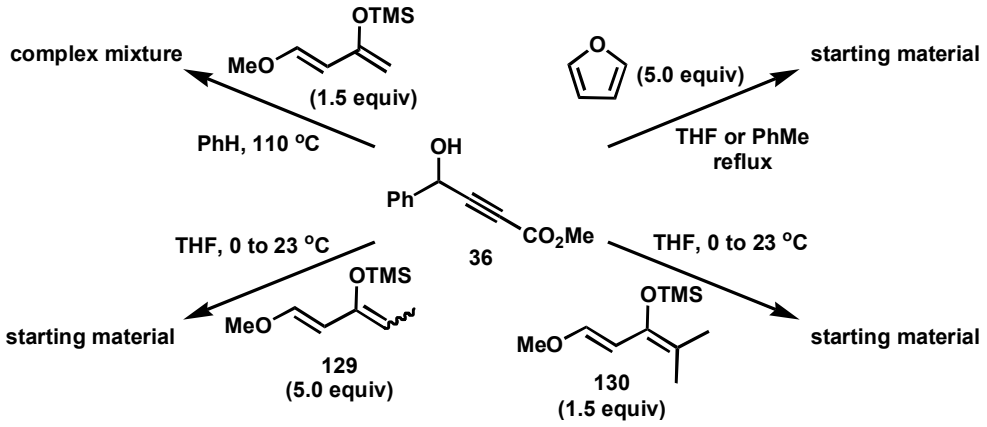
Scheme 47. Enyne metathesis formation of diene **128**.

We next investigated Diels-Alder reactions with alkynoate **36** and various dienes. To utilize the alkyne as the dienophile in an intramolecular Diels-Alder reaction, a diene would need to be tethered to the molecule. Etherification attempts of alkynoate **36** with 1-chloro-2,4-pentadiene[65] and various reagents (NaH, Ag_2O, or ^{n}BuLi) all provided complex mixtures (Scheme 48). The basic reagents used for the etherification may have promoted a retro-addition along with the possibility of a newly formed alkoxide adding to another alkynoate molecule in solution. Future work will focus on a mild etherification technique compatible with alkynoate **36**.



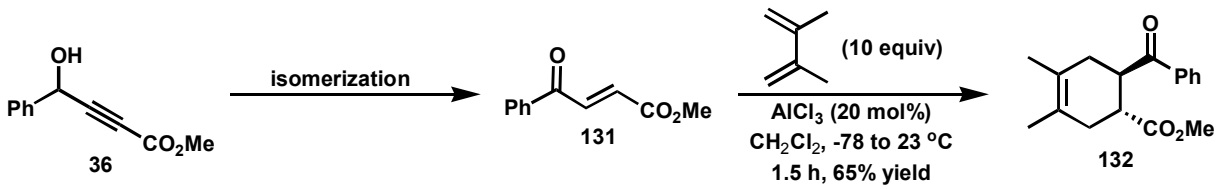
Scheme 48. Attempts to prepare intramolecular Diels-Alder substrate.

The intermolecular Diels-Alder reaction with alkynoate **36** and various dienes also proved difficult (Scheme 49). A mixture of furan and **36** in either refluxing THF or PhMe afforded starting material. In an effort to use a more reactive diene, the Kitahara-Danishefsky diene was reacted with alkynoate **36**, this time producing a complex mixture. Variations of Kitahara-Danishefsky's diene (**129** and **130**), provided recovery of starting material.



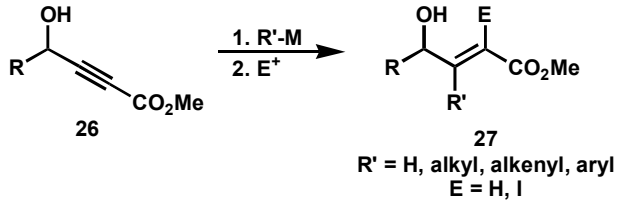
Scheme 49. Intermolecular Diels-Alder reactions.

To advance the Diels-Alder reaction of alkynoate **36**, it seemed necessary to increase the reactivity of the starting material. Examples in the literature have shown that enone substrates, similar to enone **131**, are capable of reacting with 2,3-dimethyl-1,3-butadiene and $AlCl_3$ to provide products analogous to cyclohexene **132** (Scheme 50).[66] Commercially available enone **131** (Interchim Intermediates) is nothing more than the isomerization product of alkynoate **36**. In accordance with literature precedent, enone **131** afforded cyclohexene **132** through the $AlCl_3$ catalyzed Diels-Alder reaction with 2,3-dimethyl-1,3-butadiene in 65% yield.



Scheme 50. Diels-Alder reaction of enone **131**.

3. Conclusion



We have demonstrated the *trans*-conjugate addition of a nucleophile and electrophile across the triple bond of alkynoate **26**. Initial work demonstrated that either $NaBH_4$ or Red-Al are capable of preparing γ-hydroxy-α,β-(*E*)-alkenoate **27** (R' = H, E = H) from the corresponding γ-hydroxy-α,β-alkynoates, utilizing the γ-hydroxyl to control the reduction. Trapping these intermediates with iodine allowed for the formation of tri-substituted olefins **27** (R' = H, E = I), which are suitable for use in a variety of coupling reactions. The procedure was then modified to incorporate the addition of carbon nucleophiles into alkynoate **26** through the use of Grignard reagents, thus yielding β,β-di-substituted alkenoate **27** (R' = alkyl, alkenyl, aryl; E = H). These reactions could also be trapped with iodine to generate tetra-substituted olefin **27** (R' = alkyl, alkenyl, aryl; E = I) in a stereoselective fashion, which could be used further for diverse coupling reactions. The *trans*-conjugate Grignard addition into alkynoates also led to the ability to control the geometry of exocyclic olefins, which was adapted toward the total synthesis of stresgenin B.

We have also demonstrated that γ-hydroxy-α,β-alkynoates can serve as building blocks for diversity-oriented synthesis. Alkynoate **36**, specifically, was capable of undergoing a variety of reactions to form skeletally and/or functionally distinct molecules.

4. Experimental

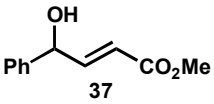
General Techniques All reactions were carried out with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium-benzophenone, and methylene chloride (CH_2Cl_2) was distilled from calcium hydride. Acetonitrile was dried over 3Å molecular sieves. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials, unless otherwise stated.

All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm E. Merck silica gel plates (60F-254) using UV-light (254 nm) with anisaldehyde in ethanol and heat as developing agents. TSI silica gel (230-400 mesh) was used for flash column chromatography. NMR spectra were recorded on AM300 or AM500 (Bruker) instruments and calibrated using a solvent peak or tetramethylsilane as an internal reference. The following abbreviations are used to indicate the multiplicities; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. High-resolution mass spectra were obtained by using EBE geometry.

General procedure for reduction of propargylic alcohol 42 with $NaBH_4$. Sodium borohydride (1.2 – 4.0 mmol) was added to a solution of alcohol **42** (1.0 mmol) in MeOH (4.0 mL) in one portion at –34 °C. The mixture was allowed to warm to 0 ºC then was quenched with saturated aqueous NH_4Cl (60 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (20 mL x 1). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL x 1) and brine (30 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel chromatography (EtOAc in hexanes) to afford an inseparable mixture of alcohol **43** and lactone **44**.

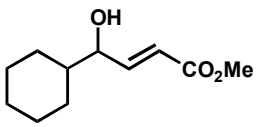
General procedure for reduction of propargylic alcohol 42 with Red-Al. Alcohol **42** (1.0 mmol) in THF (5.0 mL) was added to a solution of Red-Al (2.0 mmol) in THF (4.0 mL) dropwise at –72 °C under a nitrogen atmosphere. After stirring at –72 °C for 20 min, the solution was quenched with 0.1 M HCl* (53 mL). The solution was concentrated under reduced pressure to remove THF and was then diluted with EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (20 mL x 1). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (15 mL x 1) and brine (15 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified through a plug of silica gel to afford an inseparable mixture of alcohol **43** and lactone **44**.

*In the case of acid-sensitive compounds, 1 M Rochelle's salt can be used in lieu of HCl.



37

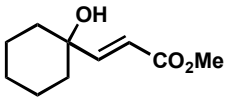
^{1}H NMR spectrum was consistent with literature: Burgess, K.; Cassidy, J.; Henderson, I. *J. Org. Chem.* **1991**, *56*, 2050-2058. Data for (*E*)-4-hydroxy-4-phenyl-but-2-enoic acid methyl ester (**37**): yellow oil; R_f 0.26 (30% EtOAc in hexanes); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 7.47-7.28 (m, 5H), 7.05 (dd, 1H, J = 15.6, 4.8 Hz), 6.18 (dd, 1H, J = 15.6, 1.7 Hz), 5.36 (dd, 1H, J = 4.7, 1.6 Hz), 3.73 (s, 3H).



43

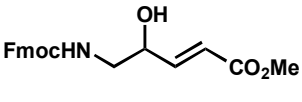
^{1}H NMR spectrum was consistent with literature: Naka, T.; Koide, K. *Tetrahedron Lett.* **2003**, *44*, 443-445. Data for (*E*)-4-cyclohexyl-4-hydroxy-but-2-enoic acid methyl ester (**43**): yellow oil; R_f 0.31 (30%

EtOAc in hexanes); ^{1}H NMR (300 MHz, 293 K, $CDCl_3$) δ = 6.98 (dd, 1H, *J* = 15.7, 5.2 Hz), 6.04 (dd, 1H, *J* = 15.7, 1.7 Hz), 4.10 (td, 1H, *J* = 5.3, 1.5 Hz), 3.75 (s, 3H), 1.85-1.67 (m, 5H), 1.60-1.49 (m, 2H), 1.28-1.02 (m, 4H).



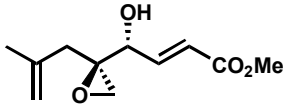
46

^{1}H NMR spectrum was consistent with literature: Tanikaga, R.; Nozaki, Y.; Tamura, T.; Kaji, A. *Synthesis* **1983**, 134-135. Data for (*E*)-3-(1-hydroxy-cyclohexyl)-acrylic acid methyl ester (**46**): yellow oil; R_f 0.44 (30% EtOAc in hexanes); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 7.04 (d, 1H, *J* = 15.7 Hz), 6.07 (d, 1H, 15.7 Hz), 3.74 (s, 3H), 1.70-1.52 (m, 7H), 1.35-1.25 (m, 3H).



48

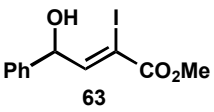
Data for (*E*)-5-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-hydroxy-pent-2-enoic acid methyl ester (**48**): white powder; mp 139.8-141.5 °C; R_f 0.32 (50% EtOAc in hexanes); IR (film) 3354 (broad, O-H), 2924, 1718 (C=O), 1532, 1450, 1260, 741 cm^{-1}; ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 7.76 (d, 2H, *J* = 7.4 Hz), 7.59-7.53 (m, 2H), 7.40 (apparent t, 2H, *J* = 7.4 Hz), 7.31 (td, 2H, *J* = 7.4, 1.1 Hz), 6.90 (br dd, 1H, *J* = 15.6, 4.1 Hz), 6.16 (br d, 1H, *J* = 15.6 Hz), 5.25-5.17 (m, 1H), 4.45-4.39 (m, 2H), 4.20 (broad t, 1H, *J* = 6.6 Hz), 3.73 (s, 3H), 3.22-3.11 (m, 2H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 166.6, 157.5, 146.7, 143.7, 141.3, 127.7, 127.1, 125.0, 121.7, 120.0, 70.8, 67.0, 51.7, 47.1, 46.1; HRMS (EI+) calcd for $C_{21}H_{21}NO_5$ (M^+) 367.1420; found 367.1424 *m/z*.



57

Data for (*E*)-4-hydroxy-4-[2-(2-methyl-allyl)-oxiranyl]-but-2-enoic acid methyl ester (**57**): clear oil; R_f 0.24 (30% EtOAc in hexanes); IR (film)

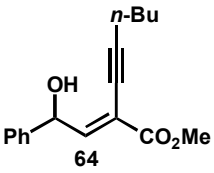
3458 (broad, O-H), 2921, 1724 (C=O), 1652, 1437, 1270, 1171 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 6.95 (dd, 1H, *J* = 15.7, 5.1 Hz), 6.14 (dd, 1H, *J* = 15.7, 1.7 Hz), 4.89-4.86 (m, 1H), 4.80-4.78 (m, 1H), 4.35-4.29 (m, 1H), 3.75 (s, 3H), 2.89 (d, 1H, *J* = 4.6 Hz), 2.71 (d, 1H, *J* = 4.7 Hz), 2.47 (br d, 1H, *J* = 14.7 Hz), 2.34 (br d, 1H, *J* = 14.6 Hz), 1.76 (s, 3H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 166.4, 145.0, 140.6, 122.4, 114.8, 72.0, 59.8, 51.7, 49.5, 39.1, 23.3; HRMS (EI+) calcd for $C_{11}H_{13}O_3$ (M^+ - H_3O) 193.0865; found 193.0861 *m/z*.



63

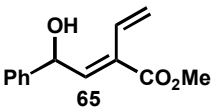
Preparation of (*Z*)-4-hydroxy-2-iodo-4-phenyl-but-2-enoic acid methyl ester (63). Alcohol **36** (477 mg, 2.51 mmol) in THF (12.5 mL) was added to a solution of Red-Al (1.17 g of a 65+wt % solution in toluene, 3.76 mmol) in THF (7.5 mL) dropwise at –72 °C under a nitrogen atmosphere. The mixture was stirred for 40 min at –72 °C then iodine (3.18 g, 12.5 mmol) dissolved in THF (25 mL) was added dropwise to the solution at –72 ºC. The solution was allowed to warm to –10 ºC over 50 min, upon which the solution was quenched with a 10% aqueous solution of $Na_2S_2O_3$ (15 mL). The solution was concentrated under reduced pressure to remove THF and was then diluted with EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (30 mL x 1). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (30 mL x 1) and brine (30 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified through a plug of silica gel (5 mL) to afford vinyl iodide **63** (622 mg, 78% yield) as a clear oil. Data for vinyl iodide **63**: R_f 0.32 (30% EtOAc in hexanes); IR (film) 3427 (broad, O-H), 2951, 1720 (C=O), 1257, 699 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.52-7.47 (m, 2H), 7.42-7.33 (m, 4H, vinyl proton in aromatic region), 5.57 (d, 1H, *J* = 8.0 Hz), 3.81 (s, 3H), 2.27

(br s, 1H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 163.2, 152.2, 140.2, 128.9, 128.6, 126.4, 93.9, 77.8, 53.8; HRMS (EI+) calcd for $C_{11}H_{11}IO_3$ (M^+) 317.9753, found 317.9767 *m/z*.



64

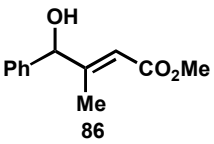
Preparation of 2-[2-hydroxy-2-phenyl-eth-(*E*)-ylidene]-oct-3-ynoic acid methyl ester (64). $Pd(PPh_3)_4$ (12.1 mg, 10.5 μmol) was dissolved in *i*-Pr_2NH (0.21 mL) under a nitrogen atmosphere. Vinyl iodide **63** (33.4 mg, 0.105 mmol) in *i*-Pr_2NH (0.40 mL) was added dropwise to the flask, followed by dropwise addition of 1-hexyne (24.1 μL, 0.210 mmol) and addition of CuI (0.9 mg, 5.3 μmol). After 25 min, the solution was concentrated under reduced pressure. The mixture was then diluted with Et_2O (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 mL x 1). The combined organic layers were washed with brine (10 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel (5 mL) column chromatography (5 → 30% EtOAc in hexanes) to afford enyne **64** (18.3 mg, 64% yield) as a yellow oil**.** Data for enyne **64**: R_f 0.33 (30% EtOAc in hexanes); IR (film) 3432 (broad, O-H), 3030, 2956, 2929, 2872, 2228 (C≡C), 1727 (C=O), 1436, 1238, 1145, 1012, 756, 699 cm^{-1}; ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 7.46-7.42 (m, 2H), 7.39-7.27 (m, 3H), 7.17 (d, 1H, *J* = 8.6 Hz), 5.80 (d, 1H, *J* = 8.6 Hz), 3.77 (s, 3H), 2.46 (t, 2H, *J* = 6.9 Hz), 1.65-1.53 (m, 2H), 1.52-1.41 (m, 2H), 0.94 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 165.1, 150.2, 141.2, 128.7, 128.1, 126.0, 116.9, 99.4, 73.7, 72.2, 52.6, 30.5, 22.0, 19.3, 13.6; HRMS (EI+) calcd for $C_{17}H_{20}O_3$ (M^+) 272.1412, found 272.1409 *m/z*.



65

Preparation of (*E*)-4-hydroxy-4-phenyl-2-vinyl-but-2-enoic acid methyl ester (65). $Cl_2Pd(PPh_3)_2$ (2.6 mg, 3.7 μmol) was dissolved in THF (0.4 mL)

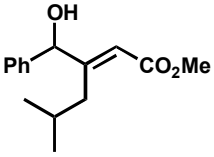
under a nitrogen atmosphere. Vinyl iodide **63** (58.8 mg, 0.185 mmol) in THF (0.5 mL) was added dropwise to the flask, followed by dropwise addition of tributyl(vinyl)tin (64.9 μL, 0.222 mmol). After 48 h the mixture was quenched with 10% NH_4OH (2 mL). The mixture was concentrated under reduced pressure to remove THF and was then diluted with Et_2O (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 mL x 1). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel (8 mL) column chromatography (10 → 40% EtOAc in hexanes) to afford diene **65** (18.0 mg, 45% yield) as a pale yellow oil**.** Data for diene **65**: R_f 0.32 (30% EtOAc in hexanes); IR (film) 3427 (broad, O-H), 2952, 1721 (C=O), 1436, 1234, 699 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.47-7.28 (m, 5H), 6.86 (br d, 1H, *J* = 9.0 Hz), 6.56 (dd, 1H, *J* = 17.6, 11.4 Hz), 5.66 (dd, 1H, *J* = 9.0, 4.0 Hz), 5.58 (dd, 1H, *J* = 17.6, 1.6 Hz), 5.46 (ddd, 1H, *J* = 11.4, 1.4, 1.0 Hz), 3.78 (s, 3H), 2.22 (d, 1H, *J* = 4.0 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 167.1, 142.2, 141.8, 131.0, 128.8, 128.2, 126.5, 126.3, 121.5, 70.2, 52.1; HRMS (EI+) calcd for $C_{13}H_{14}O_3$ (M^+) 218.0943, found 218.0942 *m/z*.



86

Preparation of (*E*)-4-hydroxy-3-methyl-4-phenyl-but-2-enoic acid methyl ester (86). Methylmagnesium bromide (0.51 mL, 3.0 M in Et_2O, Aldrich) was added dropwise to a solution of alkynoate **36** (97.1 mg, 0.511 mmol) in THF (2.6 mL) at –72 ºC under a nitrogen atmosphere. The solution was allowed to warm to –5 ºC over 2 h and was then quenched with 1 M NaH_2PO_4 (5 mL). The solution was concentrated under reduced pressure to remove THF and was then diluted with Et_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (5 mL x 1). The combined organic

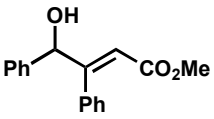
layers were then washed with water (10 mL x 1) and brine (7 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel (8 mL) chromatography (5 → 40% EtOAc in hexanes) to afford an inseparable mixture of alkenoate **86** and alkynoate **36** (3:1 ratio, 30.5 mg, 22% yield of alkenoate **86**) as a pale yellow oil. Data for alkenoate **86**: R_f 0.28 (30% EtOAc in hexanes); IR (film) 3438 (broad, O-H), 2950, 1717 (C=O), 1221, 1151, 701 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.37-7.31 (m, 5H), 6.28 (dq, 1H, J = 1.3, 1.3 Hz), 5.14 (br s, 1H), 3.73 (s, 3H), 1.99 (dd, 1H, J = 1.3, 0.2 Hz); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 167.3, 158.7, 140.6, 128.7, 128.4, 126.9, 114.6, 78.4, 51.1, 15.6; HRMS (EI+) calcd for $C_{12}H_{14}O_3$ (M^+) 206.0943; found 206.0940 *m/z*.



87

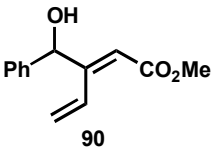
Preparation of (*E*)-3-(hydroxy-phenyl-methyl)-5-methyl-hex-2-enoic acid methyl ester (87). Isobutylmagnesium bromide (1.70 mL, 2.0 M in Et_2O, Aldrich) was added dropwise to a solution of alkynoate **36** (127 mg, 0.676 mmol) in THF (6.76 mL) at –72 ºC under a nitrogen atmosphere. The solution was allowed to warm to –40 ºC over 2 h then was quenched with saturated aqueous NH_4Cl (8 mL). The solution was concentrated under reduced pressure to remove THF then was diluted with Et_2O (8 mL). The layers were separated and the aqueous layer was extracted with Et_2O (8 mL x 1). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (10 mL x 1) and brine (10 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified through a plug of silica gel (5 mL) to afford an inseparable mixture of alkenoate **87** and alkynoate **36** (1:1.7 ratio, 120 mg, 26% yield of alkenoate **87**) as a pale yellow oil. Data for alkenoate **87**: R_f 0.45 (30% EtOAc in hexanes); IR (film) 3432 (broad, O-H), 2956, 1717 (C=O), 1255, 700 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.39-7.30 (m, 5H),

6.37 (br s, 1H), 5.22 (br s, 1H), 3.72 (s, 3H), 2.94 (dd, 1H, *J* = 12.5, 7.4 Hz), 2.01 (br d, 1H, *J* = 2.9 Hz), 1.89 (hep, 1H, *J* = 6.8 Hz), 1.77 (d, 1H, *J* = 12.5 Hz), 1.75 (d, 1H, *J* = 12.5 Hz), 0.91 (d, 3H, *J* = 6.5 Hz), 0.90 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 167.2, 162.0, 141.0, 128.8, 128.5, 127.4, 115.0, 77.2, 51.0, 38.0, 28.4, 22.8, 22.4; HRMS (EI+) calcd for $C_{15}H_{18}O_2$ (M^+ - H_2O) 230.1307; found 230.1309 *m/z*.



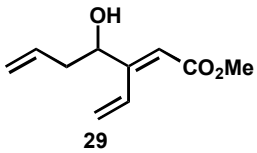
88

Preparation of (*E*)-4-hydroxy-3,4-diphenyl-but-2-enoic acid methyl ester (88). Phenylmagnesium bromide (0.66 mL, 3.0 M in Et_2O, Aldrich) was added dropwise to a solution of alkynoate **36** (126.3 mg, 0.664 mmol) in THF (3.3 mL) at –43 ºC under a nitrogen atmosphere. The solution was allowed to warm to –20 ºC over 30 min and was then quenched with saturated aqueous NH_4Cl (10 mL). The solution was concentrated under reduced pressure to remove THF and was then diluted with Et_2O (6 mL). The layers were separated and the aqueous layer was extracted with Et_2O (7 mL x 1). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (15 mL x 1) and brine (15 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel (8 mL) chromatography (5 → 30% EtOAc in hexanes) to afford alkenoate **88** (112.0 mg, 63% yield) as a yellow-orange oil. Data for alkenoate **88**: R_f 0.39 (30% EtOAc in hexanes); IR (film) 3434 (broad, O-H), 2950, 2925, 1712 (C=O), 1222, 1164, 700 cm^{-1}; ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 7.61-7.54 (m, 1H), 7.42-7.19 (m, 7H), 6.92-6.89 (m, 2 H), 6.44 (d, 1H, *J* = 1.4 Hz), 5.44 (br s, 1H), 3.55 (s, 3H), 2.24 (d, 1H, *J* = 3.3 Hz); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 166.5, 159.5, 139.9, 136.9, 128.4, 128.2, 127.8, 127.7, 127.0 116.2, 78.0, 51.2; HRMS (EI+) calcd for $C_{17}H_{16}O_3$ (M^+) 268.1099; found 268.1100 *m/z*.



90

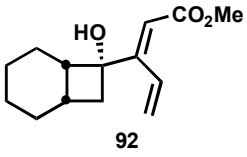
Preparation of (*E*)-3-(hydroxy-phenyl-methyl)-penta-2,4-dienoic acid methyl ester (90). CH_2=CHMgBr (0.31 mL, 1.0 M in THF) was added dropwise to a solution of alkynoate **36** (19.4 mg, 0.102 mmol) in THF (1.0 mL) at –72 ºC under a nitrogen atmosphere. The solution was allowed to warm to –40 ºC over 2 h then was quenched with saturated aqueous NH_4Cl (4 mL). The solution was concentrated under reduced pressure to remove THF then was diluted with Et_2O (4 mL). The layers were separated and the aqueous layer was extracted with Et_2O (4 mL x 1). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (5 mL x 1) and brine (5 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified through a plug of silica gel (5 mL) to afford an inseparable mixture of alkynoate **36** and diene **90** (14:1 ratio, 23.5 mg, 90% yield of diene **90**) as a pale yellow oil. Data for diene **90**: R_f 0.32 (30% EtOAc in hexanes); IR (film) 3420 (broad, O-H), 2952, 1716 (C=O), 1252, 1161, 700 cm^{-1}; ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 7.56 (br dd, 1H, J = 18.1, 11.6 Hz), 7.41-7.29 (m, 5H), 6.32 (br s, 1H), 5.68 (br s, 1H), 5.46 (ddd, 1H, J = 18.1, 1.5, 0.7 Hz), 5.37 (ddd, 1H, J = 11.6, 1.5, 0.9 Hz), 3.76 (s, 3H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 166.9, 154.1, 141.3, 131.3, 128.7, 128.2, 127.1, 121.2, 116.6, 73.2, 51.3; HRMS (EI+) calcd for $C_{13}H_{14}O_3$ (M^+) 218.0943; found 218.0943 *m/z*.



29

Preparation of (*E*)-4-hydroxy-3-vinyl-hepta-2,6-dienoic acid methyl ester (29). CH_2=CHMgBr (44.4 mL, 1.0 M in THF) was added dropwise to a solution of alkynoate **30** (1.71 g, 11.1 mmol) in THF (111 mL) at –72 ºC under a nitrogen atmosphere. The solution was allowed to warm to –40 ºC over 1.5 h then was quenched with 1M NaH_2PO_4 (90 mL). The solution was concentrated under reduced pressure to

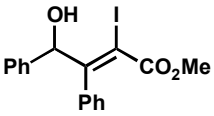
remove THF then was diluted with Et_2O (60 mL). The layers were separated and the aqueous layer was extracted with Et_2O (60 mL x 1). The combined organic layers were then washed with brine (150 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified through a plug of silica gel (5 mL) to afford an inseparable mixture of alkynoate **30** and triene **29** (1:5 ratio, 1.72 g, 85% yield of triene **29**) as a pale yellow oil. Data for triene **29**: R_f 0.41 (30% EtOAc in hexanes); IR (film) 3454 (broad, O-H), 2950, 1717 (C=O), 1436, 1235, 1161, 923 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.62 (br dd, 1H, J = 18.1, 11.6 Hz), 6.09 (s, 1H), 5.91-5.77 (m, 1H), 5.55 (d, 1H, J = 18.2 Hz), 5.46 (dd, 1H, J = 11.6, 0.8 Hz), 5.21 (br s, 1H), 5.18-5.15 (m, 1H), 4.74-4.70 (m, 1H), 3.73 (s, 3H), 2.61-2.53 (m, 1H), 2.31-2.21 (m, 1H), 1.89 (br s, 1H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 166.9, 155.4, 133.8, 131.6, 119.6, 118.7, 115.5, 69.3, 51.2, 41.7; HRMS (EI+) calcd for $C_{10}H_{14}O_3$ (M^+) 182.0943; found 182.0939 *m/z*.



92

Preparation of (*E*)-3-((*R*)-7-hydroxy-bicyclo[4.2.0]oct-7-yl)-penta-2,4-dienoic acid methyl ester (92). CH_2=CHMgBr (0.93 mL, 1.0 M in THF) was added dropwise to a solution of alkynoate **91** (65.2 mg, 0.310 mmol) in THF (3.1 mL) at –72 ºC under a nitrogen atmosphere. The solution was allowed to warm to –40 ºC over 1 h then was quenched with saturated aqueous NH_4Cl (6 mL). The solution was concentrated under reduced pressure to remove THF then was diluted with Et_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (5 mL x 1). The combined organic layers were then washed with water (10 mL x 1) and brine (10 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel (8 mL) chromatography (5 → 25% EtOAc in hexanes) to afford diene **92** (48.2 mg,

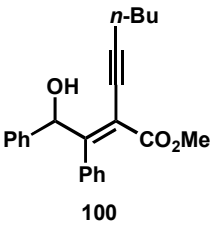
54% yield) as a colorless oil. Data for diene **92**: R_f 0.27 (15% EtOAc in hexanes); IR (film) 3450 (O-H), 2924, 2851, 1719 (C=O), 1167 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.44 (ddd, 1H, *J* = 18.2, 11.7, 0.7 Hz), 5.98 (br s, 1H), 5.69 (dd, 1H, *J* = 18.2, 1.5 Hz), 5.54 (ddd, 1H, *J* = 11.7, 1.5, 0.7 Hz), 3.74 (s, 3H), 2.62-2.48 (m, 2H), 2.42-2.30 (m, 2H), 2.25-2.10 (m, 1H), 2.03-1.93 (m, 1H), 1.91-1.62 (m, 2H), 1.54-1.43 (m, 2H), 1.28-1.24 (m, 1H), 1.20-1.07 (m, 1H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 166.9, 155.3, 130.1, 122.3, 115.8, 76.0, 51.4, 42.3, 36.3, 25.9, 24.5, 22.2, 21.7, 21.3; HRMS (EI+) calcd for $C_{14}H_{20}O_3$ (M^+) 236.1412; found 236.1410 *m/z*.



99

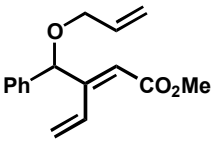
Preparation of (*Z*)-4-hydroxy-2-iodo-3,4-diphenyl-but-2-enoic acid methyl ester (99). Phenylmagnesium bromide (3.78 mL, 3.0 M in Et_2O) was added dropwise to a solution of alkynoate **36** (720 mg, 3.78 mmol) in THF (19 mL) at –43 ºC under a nitrogen atmosphere. The solution was allowed to warm to –20 ºC over 1 h then was cooled to –72 ºC. Iodine (4.80 g, 18.9 mmol) in THF (38 mL) was then added dropwise at –72 ºC. The solution was allowed to warm to –20 ºC over 3 h then was quenched with saturated aqueous sodium sulfite until the solution turned light orange. The solution was concentrated under reduced pressure to remove THF then was diluted with Et_2O (45 mL). The layers were separated and the aqueous layer was extracted with Et_2O (50 mL x 1). The combined organic layers were then washed with water (150 mL x 1) and brine (150 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel (50 mL) chromatography (5 → 30% EtOAc in hexanes) to afford vinyl iodide **99** (722 mg, 48% yield) as an orange oil. Data for vinyl iodide **99**: R_f 0.24 (30% EtOAc in hexanes); IR (film) 3446 (br, O-H), 1726 (C=O), 1229, 701 cm^{-1}; ^1H NMR (300 MHz, 293K,

$CDCl_3$) δ 7.40-7.17 (m, 8H), 6.89-6.81 (m, 2H), 6.11 (d, 1H, *J* = 7.0 Hz), 4.73 (s, 1H), 3.44 (s, 3H), 2.07 (d, 1H, *J* = 7.0 Hz). ^{13}C NMR and HRMS analyses were prevented due to facile decomposition.



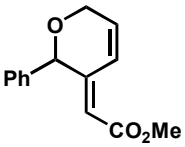
100

Preparation of 2-[2-hydroxy-1,2-diphenyl-eth-(*E*)-ylidene]-oct-3-ynoic acid methyl ester (100). $Pd(PPh_3)_4$ (32.5 mg, 28.1 μmol) was dissolved in *i*-Pr_2NH (0.55 mL). Vinyl iodide **99** (111 mg, 0.281 mmol) in *i*-Pr_2NH (1.10 mL) was added dropwise to the solution followed by dropwise addition of 1-hexyne (65 μL, 0.56 mmol) and addition of CuI (2.7 mg, 14 μmol). After 3 h at 23 °C, the reaction was concentrated under reduced pressure to a crude residue. The residue was then diluted with Et_2O (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (5 mL x 1). The combined organic layers were then washed with water (10 mL x 1) and brine (10 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel (8 mL) chromatography (5 → 40% EtOAc in hexanes) to afford enyne **100** (55.2 mg, 56% yield) as a pale amber oil. Data for enyne **100**: R_f 0.28 (20% EtOAc in hexanes); IR (film) 3452 (br, O-H), 1728 (C=O), 1200, 1173, 702 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.39-7.18 (m, 8H), 6.89-6.84 (m, 2H), 6.34 (d, 1H, *J* = 7.5 Hz), 3.48 (s, 3H), 2.46 (t, 2H, *J* = 6.9 Hz), 2.21 (d, 1H, *J* = 7.6 Hz), 1.64-1.52 (m, 2H), 1.50-1.36 (m, 2H), 0.91 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 166.0, 156.4, 140.7, 135.5, 128.5, 128.2, 128.0, 127.6, 127.5, 125.7, 116.6, 99.2, 75.5, 74.4, 52.0, 30.4, 22.0, 19.4, 13.5; HRMS (EI+) calcd for $C_{23}H_{24}O_3$ (M^+) 348.1725; found 348.1729 *m/z*.



108

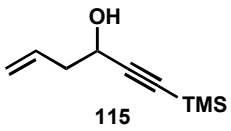
Preparation of (*E*)-3-(allyloxy-phenyl-methyl)-penta-2,4-dienoic acid methyl ester (108). Allyl bromide (84 μL, 0.97 mmol) was added dropwise to a solution of diene **90** (53.0 mg, 0.243 mmol) in DMF (0.243 mL) at 23 °C under a nitrogen atmosphere. The flask was then covered in aluminum foil, followed by the addition of Ag_2O (84.4 mg, 0.364 mmol). The solution was allowed to stir at 23 °C for 25 h then was diluted with Et_2O (7 mL) and filtered through a Celite plug (3 mL). The solution was washed with water (40 mL x 7) and brine (40 mL x 1), then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel (4 mL) chromatography (0 → 20% EtOAc in hexanes) to afford triene **108** (28.2 mg, 45% yield) as a pale yellow oil. Data for triene **108**: R_f 0.33 (10% EtOAc in hexanes); IR (film) 2949, 2923, 1717 (C=O), 1227, 1158, 700 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.55 (br dd, 1H, J = 18.0, 11.5 Hz), 7.36-7.28 (m, 5H), 6.26 (br s, 1H), 5.99-5.87 (m, 1H), 5.56 (d, 1H, J = 18.1 Hz), 5.37 (br d, 1H, J = 11.5 Hz), 5.32-5.26 (m, 2H), 5.21 (br d, 1H, J = 10.4 Hz), 4.06-3.92 (m, 2H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 166.8, 152.7, 139.6, 134.3, 131.6, 128.5, 128.0, 127.4, 121.2, 117.4, 117.0, 79.7, 69.8, 51.3.



109

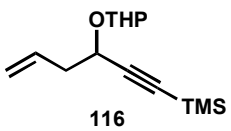
Preparation of [2-phenyl-6*H*-pyran-(3*E*)-ylidene]-acetic acid methyl ester (109). Triene **108** (14.8 mg, 57.3 μmol) was dissolved in benzene (1.2 mL) under a nitrogen atmosphere. Grubbs II (2.4 mg, 2.9 μmol) was added at 23 °C. The solution was refluxed for 1 h, cooled to 23 °C, then was concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel (4 mL) chromatography (0 → 20% EtOAc in hexanes) to afford diene **109** (8.7 mg, 66% yield) as a pale brown oil. Data for diene **109**: R_f 0.36 (15% EtOAc in hexanes); IR (film) 2924, 2853, 1719 (C=O), 1240, 701 cm^{-1}; ^1H NMR (300

MHz, 293K, $CDCl_3$) δ 7.68 (br d, 1H, *J* = 10.4 Hz), 7.40-7.31 (m, 5H), 6.28 (m, 1H), 5.23-5.21 (m, 2H), 4.38 (ddd, 1H, *J* = 18.3, 2.6, 2.6 Hz), 4.24 (ddd, 1H, *J* = 18.2, 2.5, 2.5 Hz), 3.69 (s, 3H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 166.5, 148.9, 137.8, 135.1, 128.5, 128.4, 128.1, 122.8, 114.4, 78.8, 64.0, 51.2; HRMS (EI+) calcd for $C_{14}H_{14}O_3$ (M^+) 230.0943; found 230.0944 *m/z*.



115

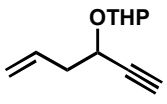
Preparation of 1-trimethylsilanyl-hex-5-en-1-yn-3-ol (115). Aldehyde **113** (7.6 g, 60 mmol) in THF (60.1 mL) was added dropwise to a solution of allylmagnesium bromide (63 mL, 1.0 M in Et_2O) at –40 °C under a nitrogen atmosphere. The cooling bath was removed and the reaction was warmed to 23 ^oC over 2 h then was quenched with 0.5 M HCl until the solution reached pH 4.0. The solution was concentrated under reduced pressure to remove THF then was diluted with Et_2O (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (100 mL x 1). The combined organic layers were then washed with water (200 mL x 2) and brine (200 mL x 2), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel (300 mL) chromatography (0 → 20% EtOAc in hexanes) to afford propargyl alcohol **115** (7.9 g, 78% yield) as an orange oil. ^1H NMR spectrum was consistent with literature: Darvesh, S.; Grant, A.S.; MaGee, D.I.; Valenta, Z. *Can. J. Chem.* **1991**, *69*, 712-731. Data for propargyl alcohol **115**: R_f 0.55 (25% EtOAc in hexanes); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 5.95-5.82 (m, 1H), 5.23-5.20 (m, 1H), 5.17-5.16 (m, 1H), 4.44-4.38 (m, 1H), 2.49-2.45 (m, 2H), 1.87 (d, 1H, *J* = 5.9 Hz), 0.17 (br s, 9H).



116

Preparation of trimethyl-[3-(tetrahydro-pyran-2-yloxy)-hex-5-en-1-ynyl]-silane (116). Dihydropyran (4.7 mL, 51 mmol) was added to a

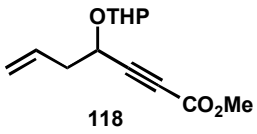
solution of propargyl alcohol **115** (7.9 g, 47 mmol) in CH_2Cl_2 (186 mL) at 23 °C under a nitrogen atmosphere. *p*-Toluenesulfonic acid monohydrate (89 mg, 0.47 mmol) was added to the solution while the temperature was maintained at 20 °C. The reaction was diluted with Et_2O (200 mL) after 1 h. The reaction mixture was washed with a solution of sat. aqueous $NaHCO_3$ (80 mL), brine (80 mL), and water (160 mL). The layers were separated and the aqueous layer was extracted with Et_2O (200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel (300 mL) chromatography (0 → 10% EtOAc in hexanes) to afford THP ether **116** (12.3 g, quant. yield) as a 2:1 inseparable mixture of diastereomers. Data for THP ether **116**: yellow oil; R_f 0.35 (5% EtOAc in hexanes); IR (film) 2944, 2172 (C≡C), 1250, 1022, 843 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 5.97-5.81 (m, 1H), 5.19-5.07 (m, 2H), 4.98 (m, 1H), 4.79-4.77 (m, 0.5H), 4.42 (t, 1H, J = 6.7 Hz), 4.31 (t, 0.5H, J = 6.7 Hz), 4.04-3.98 (m, 0.5H), 3.84-3.76 (m, 1H), 3.53-3.48 (m, 1H), 2.56-2.42 (m, 2H), 1.92-1.47 (m, 4H), 1.30-1.23 (m, 1H), 0.90-0.86 (m, 1H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 133.7, 133.5, 117.7, 117.5, 105.1, 104.0, 97.7, 95.2, 90.3, 89.4, 67.1, 64.8, 62.0, 61.8, 40.1, 30.3, 30.2, 25.4, 19.1, 18.8, -0.14; HRMS (EI+) calcd for $C_{14}H_{24}O_2Si$ (M^+) 252.1546; found 252.1533 *m/z*.



117

Preparation of 2-(1-ethynyl-but-3-enyloxy)-tetrahydro-pyran (117). K_2CO_3 (11 g, 79 mmol) was added to a solution of THP-ether **116** (7.99 g, 31.7 mmol) in MeOH (32 mL) at 0 °C under a nitrogen atmosphere. The solution was kept at 0 °C for 30 min then was warmed to 23 °C over 1.5 h then was quenched with EtOAc (50 mL) and saturated aqueous NH_4Cl (50 mL). The solution was concentrated under reduced pressure to remove MeOH and EtOAc then was diluted with Et_2O (30 mL). The layers were separated and the

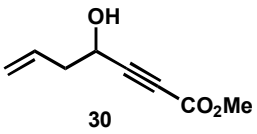
aqueous layer was extracted with Et_2O (30 mL x 1). The combined organic layers were then washed with brine (60 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting crude yellow oil (4.37 g, 77% crude yield) was carried on to the next step without further purification.



118

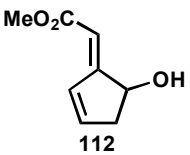
Preparation of 4-(tetrahydro-pyran-2-yloxy)-hept-6-en-2-ynoic acid methyl ester (118). ^{n}BuLi (23 mL, 1.6M in hexane) was added dropwise to a solution of terminal alkyne **117** (4.37 g, 24.3 mmol) in THF (8.7 mL) at –78 ^{o}C under a nitrogen atmosphere and was allowed to stir 10 min. Methyl chloroformate was added dropwise and the solution was allowed to stir at –78 ^{o}C for 10 min, then the solution was allowed to warm to 0 ^{o}C over 2 h then was quenched with saturated aqueous NH_4Cl (120 mL). The solution was concentrated under reduced pressure to remove THF then was diluted with Et_2O (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (100 mL x 1). The combined organic layers were then washed with brine (200 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified through a plug of silica gel to afford alkynoate **118** (6.70 g, quant. yield) as a pale yellow oil. Data for alkynoate **118**: R_f 0.26 (10% EtOAc in hexanes); IR (film) 2947, 2359, 2237 (C≡C), 1720 (C=O), 1251, 1023 cm^{-1}; ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 5.95-5.77 (m, 1H), 5.23-5.20 (m, 0.5H), 5.18-5.13 (m, 1H), 4.93-4.92 (m, 1H), 4.79-4.78 (m, 0.5H), 4.58 (t, 1H, J = 6.6 Hz), 4.40 (t, 0.5H, J = 6.6 Hz), 4.02-3.94 (m, 1H), 3.78 (s, 3H), 3.77 (s, 1.5H), 3.60-3.49 (m, 0.5H), 2.58-2.50 (m, 2H), 1.89-1.52 (m, 8H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 153.8, 153.6, 132.6, 132.4, 128.3, 118.6, 118.4, 98.4, 95.9, 87.1, 86.1, 77.1, 76.4, 66.4, 64.1, 62.3, 61.9, 52.6, 52.5,

39.4, 39.2, 30.2, 30.1, 25.3, 19.0, 18.6 HRMS (EI+) calcd for $C_{13}H_{18}O_4$ (M^+) 238.1205; found 238.1204 *m/z*.



30

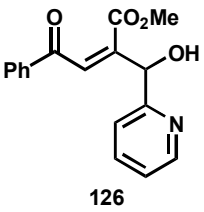
Preparation of 4-hydroxy-hept-6-en-2-ynoic acid methyl ester (30). *p*-Toluenesulfonic acid monohydrate (3 mg, 0.02 mmol) was added to a solution of alkynoate **118** (83 mg, 0.35 mmol) in MeOH (0.35 mL) at 23 ^oC under a nitrogen atmosphere. The solution was allowed to stir for 1.25 h then was quenched with $NaHCO_3$ (5 mg, 0.05 mmol). The solution was concentrated under reduced pressure to a crude oil and was then diluted with Et_2O (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (5 mL x 1). The combined organic layers were then washed with brine (10 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel (5 mL) chromatography (0 $\rightarrow$ 30% EtOAc in hexanes) to afford alkynoate **30** (39 mg, 73% yield) as a yellow oil. Data for alkynoate **30**: R_f 0.30 (30% EtOAc in hexanes); IR (film) 3418 (broad, O-H), 2956, 2239 (C≡C), 1716 (C=O), 1436, 1255, 1046, 752 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 5.92-5.79 (m, 1H), 5.25-5.23 (m, 1H), 5.19 (m, 1H), 4.55 (m, 1H), 3.80 (s, 3H), 2.69-2.67 (m, 1H), 2.55-2.50 (m, 2H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 153.7, 131.8, 119.8, 87.6, 76.4, 61.2, 52.8, 41.1.



112

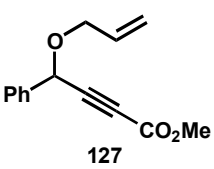
Preparation of [5-hydroxy-cyclopent-2-en-(*E*)-ylidene]-acetic acid methyl ester (112). Triene **29** (74.0 mg, 0.406 mmol) in THF (2 mL) was added to a solution of Grubbs II (16.7 mg, 20.3 μmol) in benzene (2 mL) at 23 °C under a nitrogen atmosphere. The solution was refluxed for 1 h then was quenched with water (4 mL) at 23 °C. The solution was concentrated under reduced pressure to remove THF then was diluted

with Et_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (7 mL x 1). The combined organic layers were then washed with brine (20 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel (7 mL) chromatography (0 → 30% EtOAc in hexanes) to afford diene **112** (25.8 mg, 41% yield) as a brown oil. Data for diene **112**: R_f 0.17 (30% EtOAc in hexanes); IR (film) 3411 (br, O-H), 2917, 2849, 1709 (C=O), 1637, 1216, 1142, 778 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.24 (m, 1H), 6.52-6.48 (m, 1H), 5.82 (m, 1H), 4.80-4.78 (m, 1H), 3.74 (s, 3H), 2.95-2.85 (m, 1H), 2.47-2.39 (m, 1H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 167.3, 165.3, 144.4, 130.2, 109.5, 73.4, 51.2, 41.2; HRMS (EI+) calcd for $C_8H_{10}O_3$ (M^+) 154.0630; found 154.0625 *m/z*.



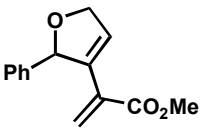
126

Preparation of (*Z*)-2-(hydroxy-pyridin-2-yl-methyl)-4-oxo-4-phenyl-but-2-enoic acid methyl ester (126). A round-bottom flask was charged with alkynoate **36** (172 mg, 0.906 mmol) and 2-pyridinecarboxaldehyde (105 μL, 1.09 mmol). The solution was allowed to stir at 23 °C for 2 days. The resulting residue was purified by silica gel (20 mL) chromatography (0 → 40% EtOAc in hexanes) to afford enone **126** (175 mg, 65% yield) as a pink-brown solid. Data for enone **126**: mp 90.1-92.1 °C; R_f 0.25 (30% EtOAc in hexanes); IR (KBr) 2952, 1708 (C=O), 1656 (C=O), 1436, 1398, 1147, 1125, 992, 786, 701 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 8.64 (d, 1H, J = 4.8 Hz), 7.70 (td, 1H, J = 7.7, 1.6 Hz), 7.49-7.30 (m, 6H), 6.37 (br s, 1H), 6.26-6.25 (m, 1H), 5.67 (d, 1H, J = 1.9 Hz), 3.44 (s, 3H), 1.56 (br s, 1H); ^{13}C NMR (125 MHz, 293 K, $CDCl_3$) δ 169.1, 166.4, 154.5, 149.4, 137.7, 137.0, 128.6, 128.4, 128.3 (x2), 124.6, 121.0, 109.5, 106.1, 92.3, 83.2, 50.8; HRMS (EI+) calcd for $C_{17}H_{15}NO_4$ (M^+) 297.1001; found 297.1010 *m/z*.



127

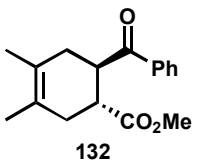
Preparation of 4-allyloxy-4-phenyl-but-2-ynoic acid methyl ester (127). Allyl bromide (485 μL, 5.61 mmol) was added to a solution of alkynoate **36** (213 mg, 1.12 mmol) in CH_2Cl_2 (2.24 mL) at 23 °C in a sealed vial. The vial was then covered in aluminum foil, followed by the addition of Ag_2O (260 mg, 1.12 mmol). The solution was allowed to stir at 23 °C for 45 h then was diluted with Et_2O (3 mL) and filtered through a Celite plug (3 mL). The solution was concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel (7 mL) chromatography (0 → 20% EtOAc in hexanes) to afford enyne **127** (164 mg, 63% yield) as a pale yellow oil. Data for enyne **127**: R_f 0.58 (30% EtOAc in hexanes); IR (film) 2954, 2920, 2859, 2235 (C≡C), 1719 (C=O), 1453, 1434, 1251, 1054, 750, 698 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.50-7.46 (m, 2H), 7.42-7.35 (m, 3H), 6.00-5.87 (m, 1H), 5.39-5.23 (m, 3H), 4.26-4.20 (m, 1H), 4.15-4.08 (m, 1H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 153.6, 136.7, 133.6, 128.9, 128.7, 127.4, 118.3, 85.0, 78.5, 70.2, 69.7, 52.7; HRMS (EI+) calcd for $C_{14}H_{14}O_3$ (M^+) 230.0943; found 230.0942 *m/z*.



128

Preparation of 2-(2-phenyl-2,5-dihydro-furan-3-yl)-acrylic acid methyl ester (128). Grubbs II (6.7 mg, 7.9 μmol) was added to a solution of enyne **127** (36 mg, 0.16 mmol) in toluene (6.4 mL) at 23 °C under a nitrogen atmosphere. The solution was allowed to stir at 23 °C for 3.5 h then was concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel (5 mL) chromatography (0 → 15% EtOAc in hexanes) to afford diene **128** (27 mg, 74% yield) as a brown oil. Data for diene **128**: R_f 0.44 (30% EtOAc in hexanes); IR (film) 2951, 2925, 2854, 1717 (C=O), 1454, 1435, 1268,

1204, 1052, 760, 736, 700 cm^{-1}; ^1H NMR (300 MHz, 293K, C_6D_6) δ 7.24-7.21 (m, 2H), 7.17-7.02 (m, 3H), 6.66-6.65 (m, 1H), 5.94-5.91 (m, 1H), 5.89 (br s, 1H), 5.14 (br s, 1H), 4.72-4.65 (m, 1H), 4.62-4.54 (m, 1H), 3.30 (s, 3H); ^{13}C NMR (75 MHz, 293 K, C_6D_6) δ 166.0, 141.7, 136.7, 133.2, 129.6, 128.7, 127.2, 126.6, 88.6, 75.6, 51.4; HRMS (EI+) calcd for $C_{14}H_{14}O_3$ (M^+) 230.0943; found 230.0934 *m/z*.



132

Preparation of (1*R*,6*R*)-6-benzoyl-3,4-dimethyl-cyclohex-3-enecarboxylic acid methyl ester (132). 2,3-dimethyl-1,3-butadiene (706 μL, 6.24 mmol) was added to a solution of enone **131** (119 mg, 0.624 mmol) in CH_2Cl_2 (6.23 mL) at 23 °C under a nitrogen atmosphere. The solution was cooled to –78 °C followed by the addition $AlCl_3$ (16.6 mg, 0.125 mmol). The solution was allowed to warm to 23 °C over 1.5 h then was quenched with 2M HCl (9 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (9 mL x 1). The combined organic layers were then washed with water (10 mL x1) and brine (10 mL x 1). The solution was then filtered through a silica gel plug (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to a crude oil. The resulting oil was purified by silica gel (7 mL) chromatography (0 → 25% EtOAc in hexanes) to afford enone **132** (111 mg, 65% yield) as a yellow oil. Data for enone **132**: R_f 0.58 (30% EtOAc in hexanes); IR (film) 2917, 1736 (C=O), 1682 (C=O), 1597, 1448, 1386, 1360, 1320, 1294, 1248, 1198, 1176, 1119, 1011, 712, 691 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 8.01-7.97 (m, 2H), 7.59-7.53 (m, 1H), 7.50-7.44 (m, 2H), 3.83 (dt, 1H, J = 11.4, 5.4 Hz), 3.61 (s, 3H), 3.09 (dt, 1H, J = 11.5, 5.9 Hz), 2.43-2.41 (m, 1H), 2.28-2.18 (m, 1H), 2.10-2.03 (m, 1H), 1.67 (br s, 3H), 1.61 (br s, 3H), 1.27-1.26 (m, 1H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 203.1, 175.7, 136.5, 133.0, 128.6,

128.4, 124.3, 51.7, 44.0, 42.2, 35.5, 34.6, 18.7, 18.6; HRMS (EI+) calcd for $C_{17}H_{20}O_3$ (M^+) 272.1412; found 272.1416 *m/z*.

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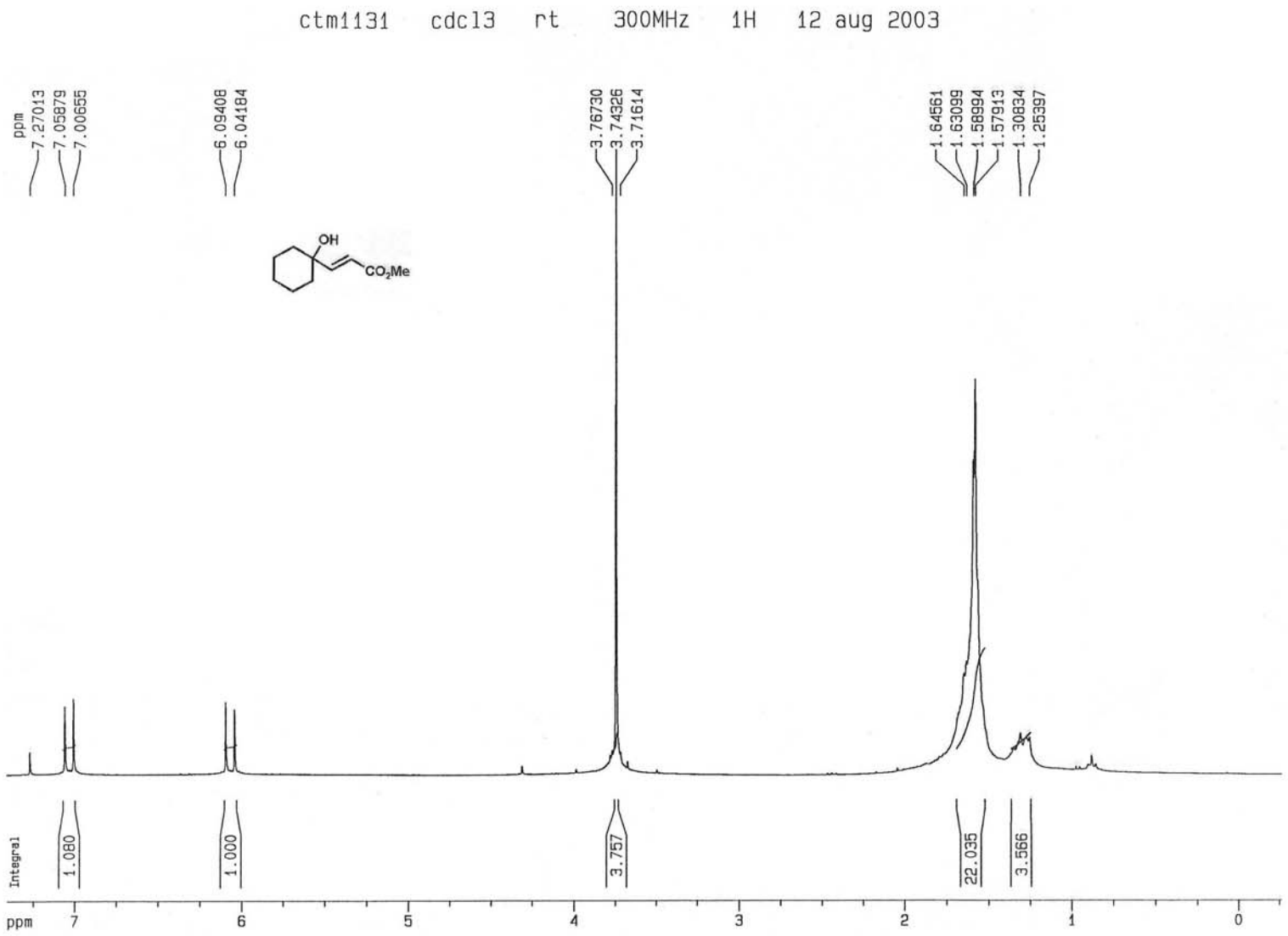
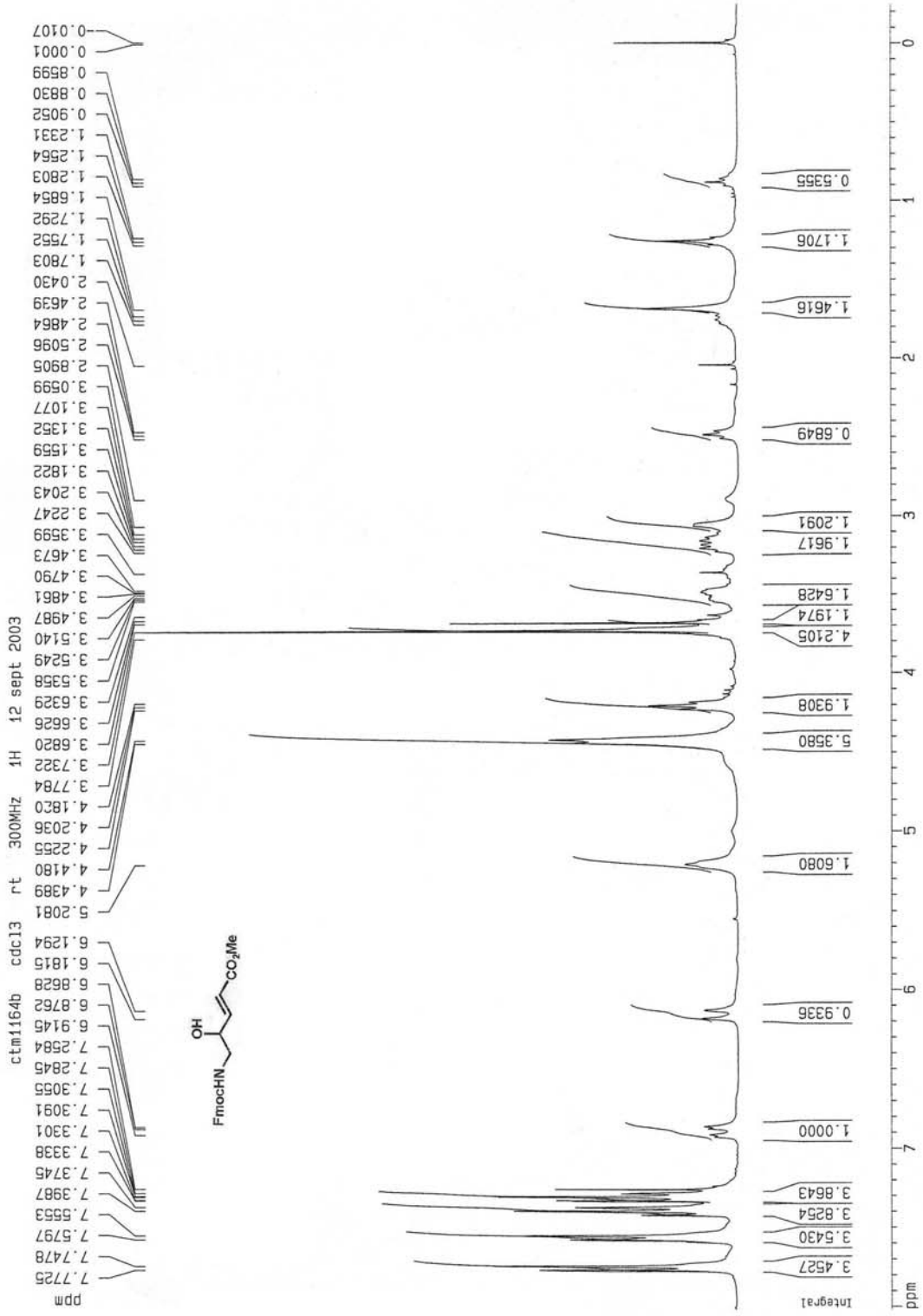
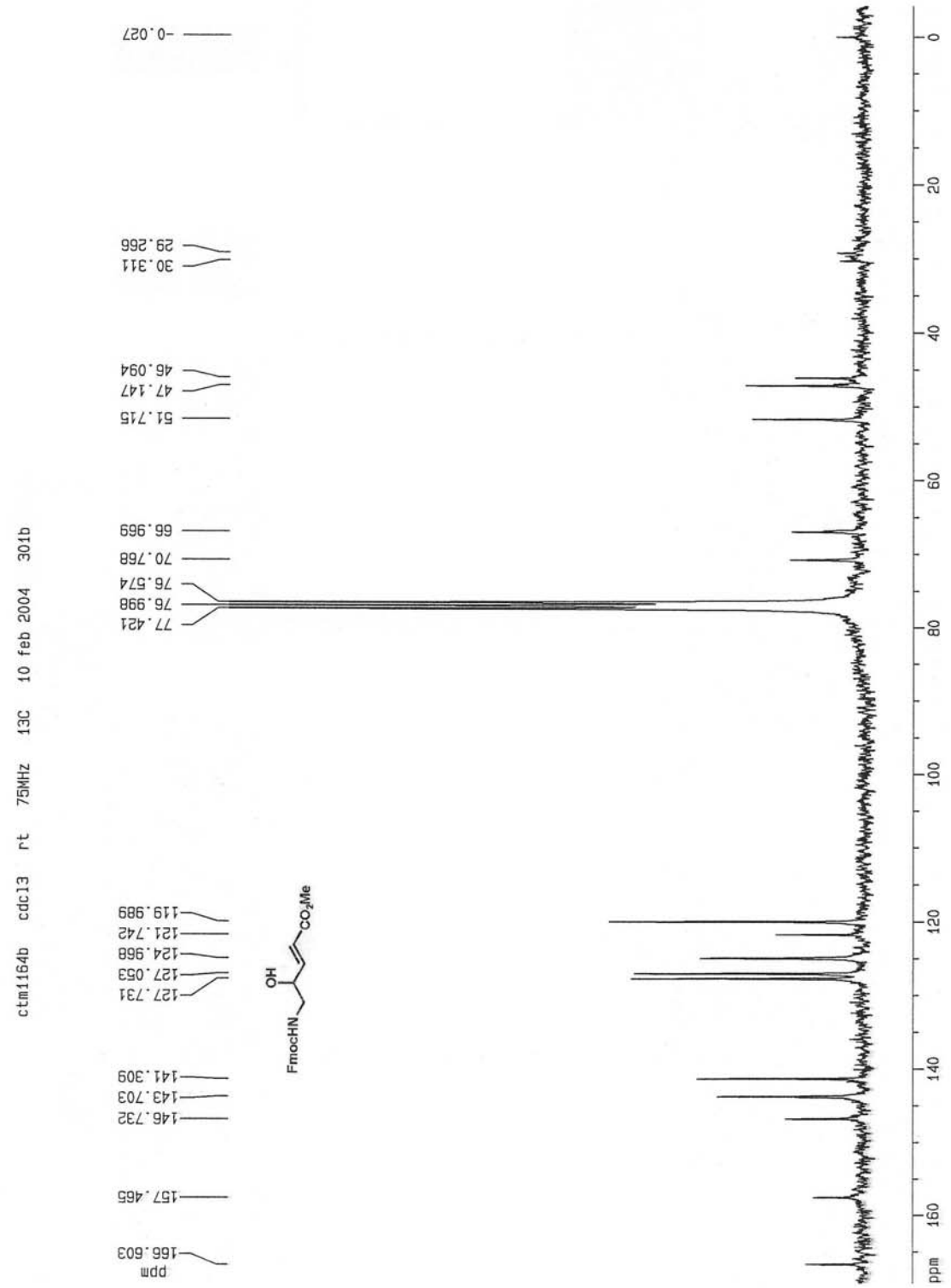
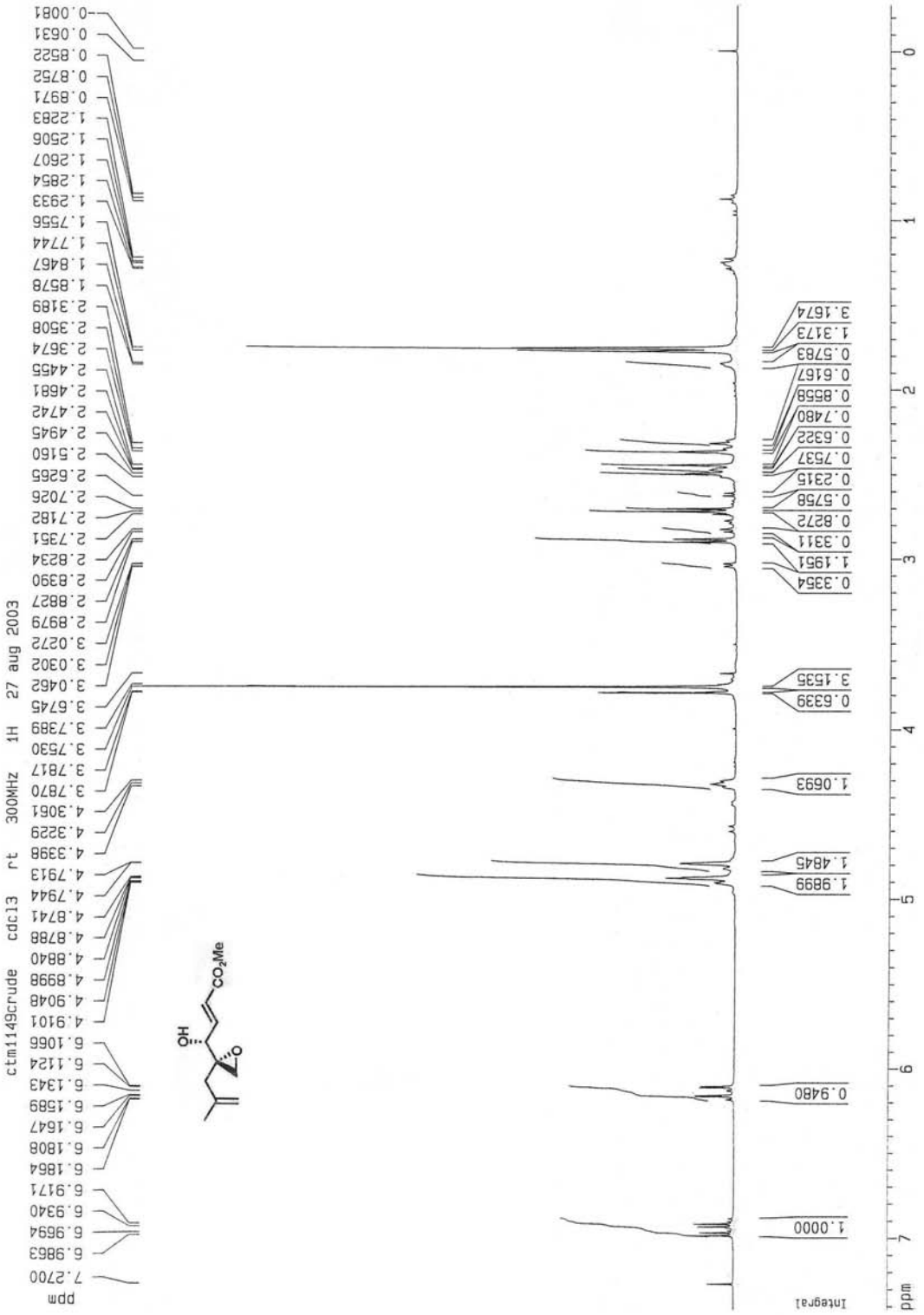
3.95295
3.87162
3.81478
3.78995
3.75304
3.68348
3.63687
3.50603
2.52315
2.49062
2.05018
1.80485
1.79346
1.78074
1.76996
1.66946
1.27939
1.26834
1.25788
1.23675
1.22684
1.21701
1.18712
1.15682
1.14742
1.13330
1.11669
1.10503
1.09456
1.06433
1.05476
1.02473
0.88387
0.07320
OH
CO2Me
Integral
10.952
2.797
13.374
3.625
0.336
1.309
1.000
1.128
ppm


ctm1131 cdcl3 rt 300MHz 1H 12 aug 2003
ppm
7.27013
7.05879
7.00655
6.09408
6.04184
3.76730
3.74326
3.71614
1.64561
1.63099
1.58994
1.57913
1.30834
1.25397
OH
CO2Me
Integral
1.080
1.000
3.757
22.035
3.566
ppm
7
6
5
4
3
2
1
0

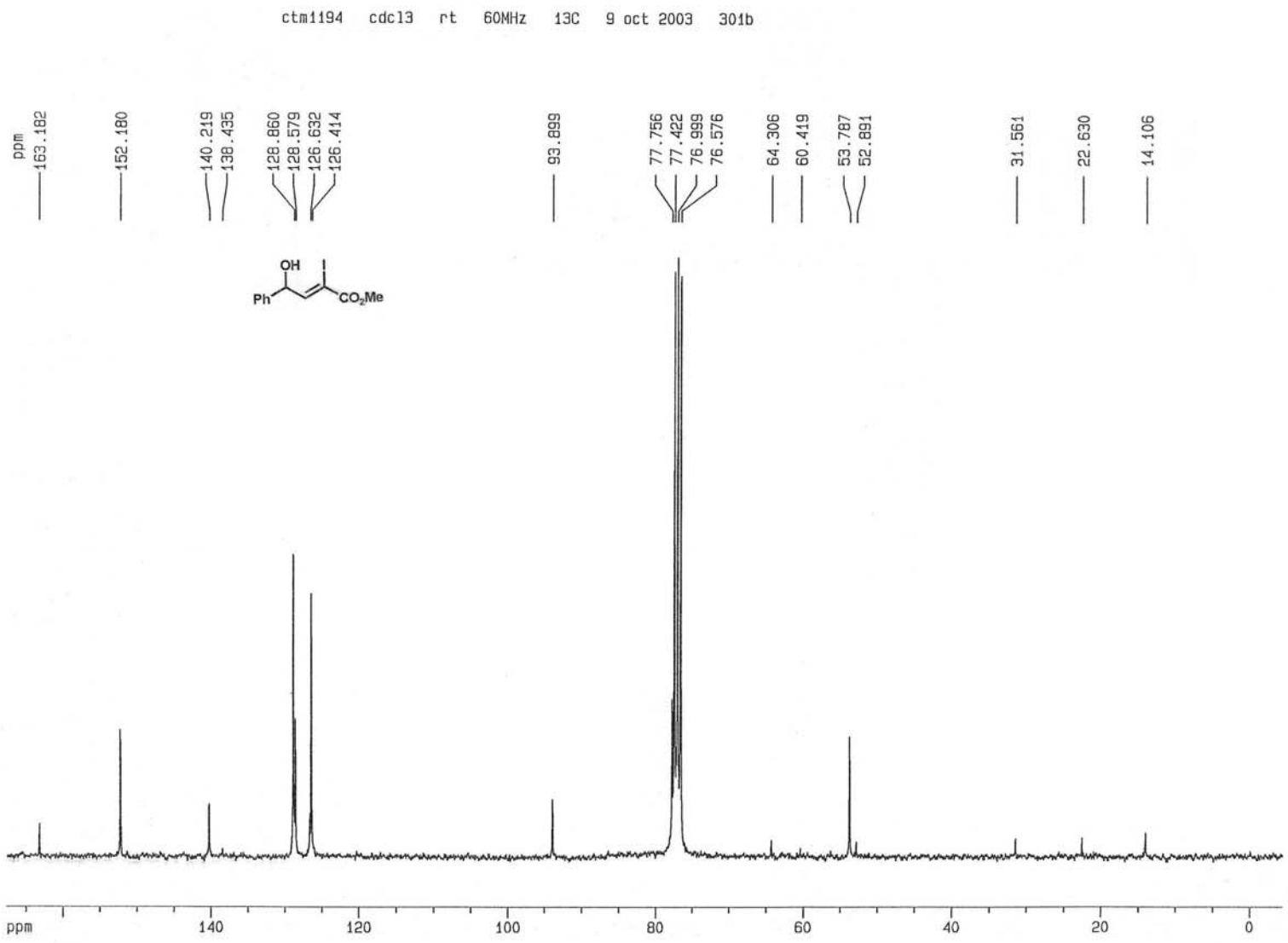

ctm1164b cdcl3 rt 300MHz 1H 12 sept 2003
ppm
7.7725
7.7478
7.5797
7.5553
7.3987
7.3745
7.3338
7.3301
7.3091
7.3055
7.2845
7.2584
6.9145
6.8762
6.8628
6.1815
6.1294
5.2081
4.4389
4.4180
4.2255
4.2036
4.1820
3.7784
3.7322
3.6820
3.6626
3.6329
3.5358
3.5249
3.5140
3.4987
3.4861
3.4790
3.4673
3.3599
3.2247
3.2043
3.1822
3.1559
3.1352
3.1077
3.0599
2.8905
2.5096
2.4864
2.4639
2.0430
1.7803
1.7552
1.7292
1.6854
1.2803
1.2564
1.2331
0.9052
0.8830
0.8599
0.0001
-0.0107
FmocHN
OH
CO2Me
Integral
3.4527
3.5430
3.8254
3.8643
1.0000
0.9336
1.6080
5.3580
1.9308
4.2105
1.1974
1.6428
1.9617
1.2091
0.6849
1.4616
1.1706
0.5355
ppm
0
1
2
3
4
5
6
7


ctm1164b cdcl3 rt 75MHz 13C 10 feb 2004 301b
-0.027
29.266
30.311
46.094
47.147
51.715
66.969
70.768
76.574
76.998
77.421
119.989
121.742
124.968
127.053
127.731
141.309
143.703
146.732
157.465
166.603
ppm
FmocHN
OH
CO2Me
0
20
40
60
80
100
120
140
160
ppm


ctm1149crude cdcl3 rt 300MHz 1H 27 aug 2003
ppm
7.2700
6.9863
6.9694
6.9340
6.9171
6.1864
6.1808
6.1647
6.1589
6.1343
6.1124
6.1066
4.9101
4.9048
4.8998
4.8840
4.8788
4.8741
4.7944
4.7913
4.3398
4.3229
4.3061
3.7870
3.7817
3.7530
3.7389
3.6745
3.0462
3.0302
3.0272
2.8979
2.8827
2.8390
2.8234
2.7351
2.7182
2.7026
2.6265
2.5160
2.4945
2.4742
2.4681
2.4455
2.3674
2.3508
2.3189
1.8578
1.8467
1.7744
1.7556
1.2933
1.2854
1.2607
1.2506
1.2283
0.8971
0.8752
0.8522
0.0631
-0.0081
Integral
1.0000
0.9480
1.4845
1.9899
1.0693
3.1535
0.6339
0.3354
1.1951
0.3311
0.8272
0.5758
0.2315
0.7537
0.6322
0.7480
0.8558
0.6167
0.5783
1.3173
3.1674
ppm
0
1
2
3
4
5
6
7
OH
O
CO2Me

ctm1149 cdcl3 rt 75MHz 13C 2 march 2004 301b
ppm
166.446
145.041
140.581
122.428
114.784
77.421
76.997
76.574
72.023
59.783
51.740
49.481
39.090
23.283
-0.031
ppm
0
20
40
60
80
100
120
140
160
OH
O
CO2Me

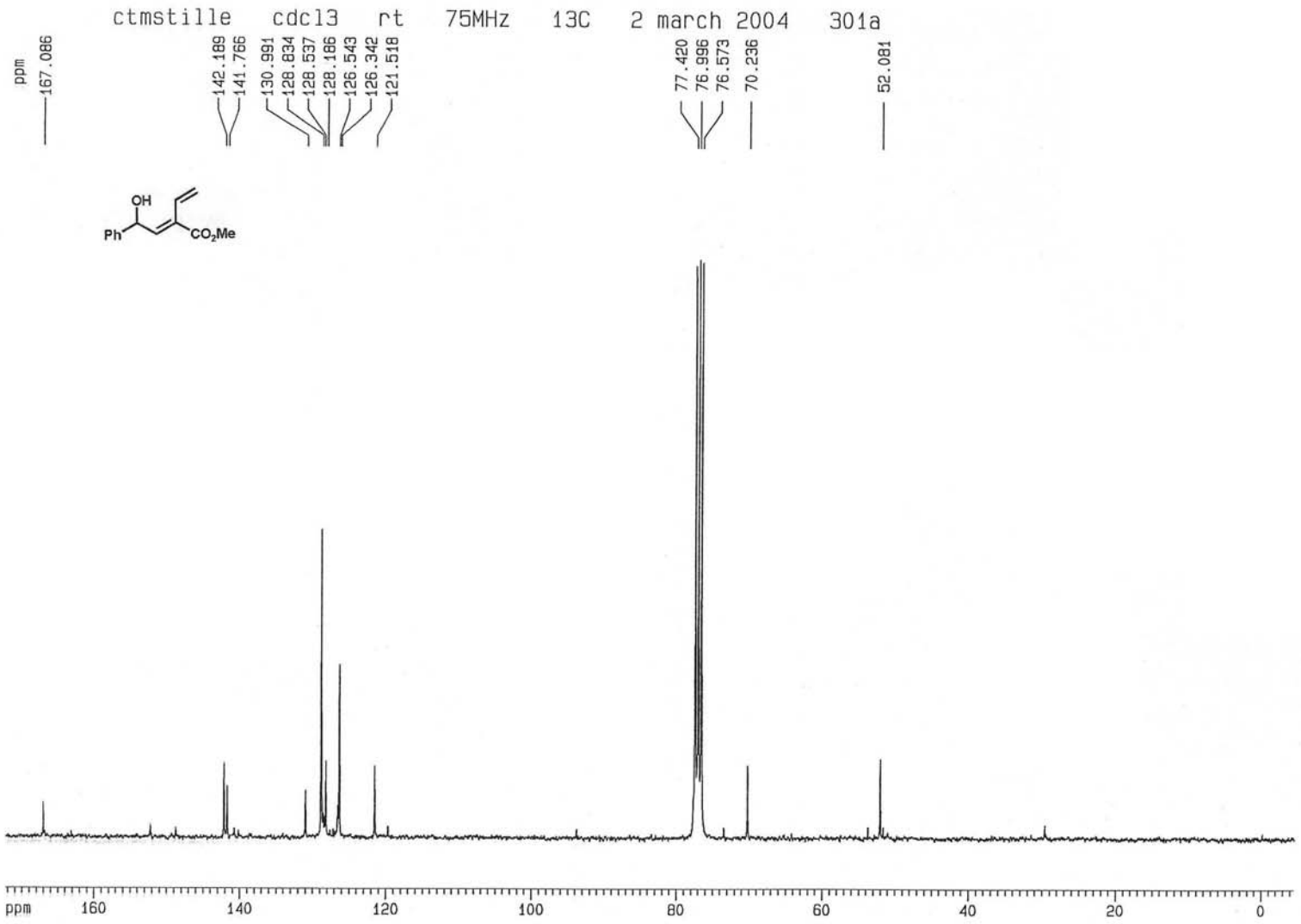
ctm1242a cdcl3 rt 300MHz 1H 25 nov 2003 300
ppm
7.4822
7.4810
7.4769
7.4176
7.3908
7.3873
7.3650
7.3623
7.3593
7.2586
7.1194
6.9075
5.6470
5.5844
5.5576
4.6635
4.6397
4.4882
4.4574
4.1541
4.0612
3.8880
3.8385
3.8348
3.8174
3.8115
3.8078
3.8059
3.8040
3.8020
3.8002
3.7956
3.7915
3.7894
3.7876
3.7620
3.7465
3.5584
2.4284
2.3701
2.3490
2.3288
2.3045
2.2696
2.0410
1.5658
1.2807
1.2568
1.2331
0.8833
0.0701
0.0191
0.0174
0.0108
-0.0001
-0.0111
-0.0155
-0.0172
-0.0191
-0.0209
Integral
3.5001
1.0000
2.2155
4.0287
ppm
0
1
2
3
4
5
6
7
OH
Ph
CO2Me


ctm1194 cdcl3 rt 60MHz 13C 9 oct 2003 301b
ppm
163.182
152.180
140.219
138.435
128.860
128.579
126.632
126.414
93.899
77.756
77.422
76.999
76.576
64.306
60.419
53.787
52.891
31.561
22.630
14.106
OH
Ph
CO2Me
ppm
140
120
100
80
60
40
20
0

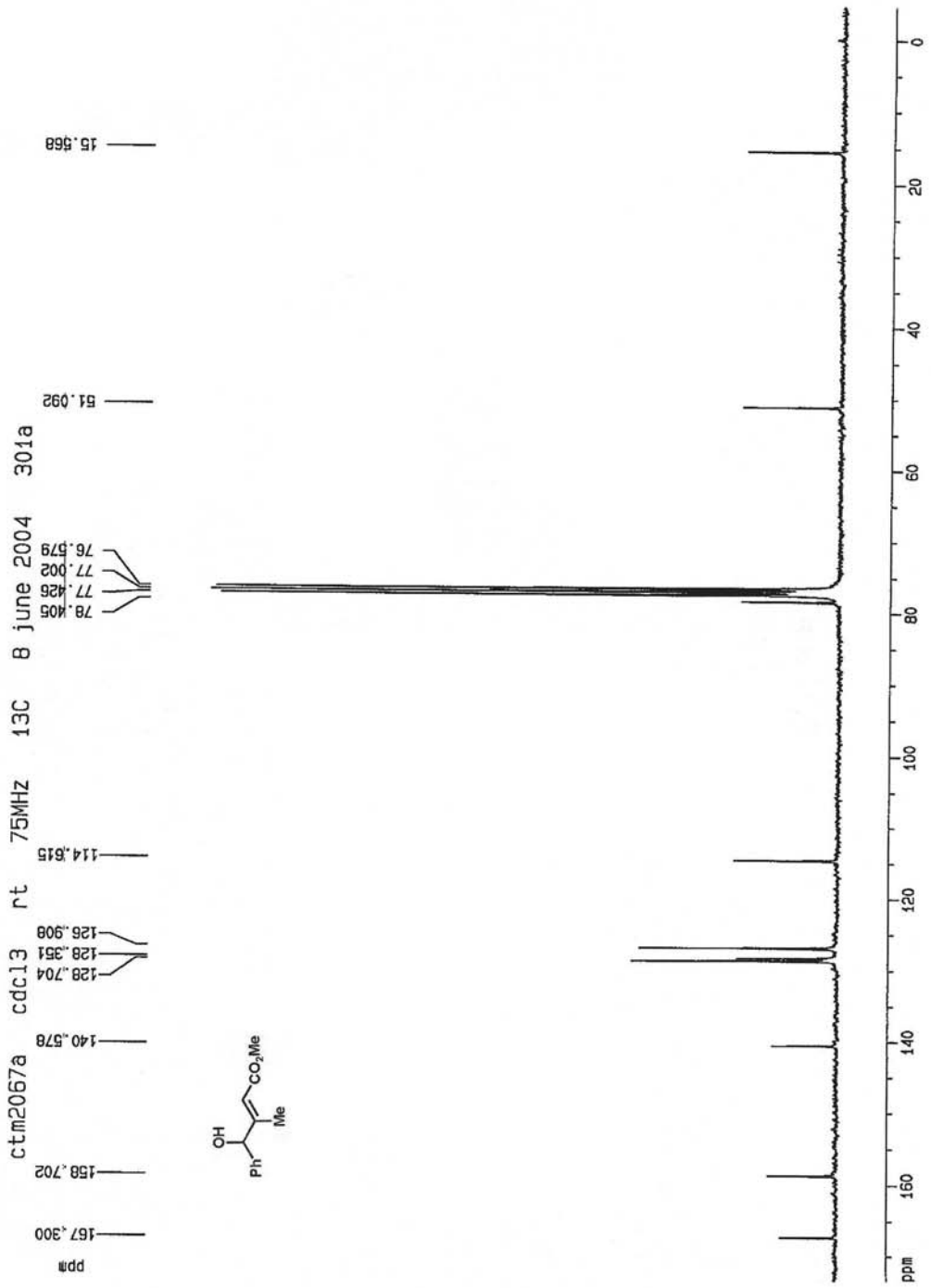
ctm1196 cdcl3 rt 300MHz 1H 10 oct 2003 301b
ppm
7.4547
7.4537
7.4315
7.4286
7.3634
7.3610
7.3365
7.3205
7.2601
7.1889
7.1602
7.1367
6.9094
6.0606
6.0325
5.9403
5.9105
5.8182
5.7895
5.5722
4.2254
4.2020
4.0124
3.8510
3.8428
3.8278
3.7994
3.7902
3.7876
3.7694
3.7285
3.5213
2.9449
2.8742
2.8724
2.4812
2.4582
2.4348
2.4018
1.7706
1.6290
1.6253
1.6054
1.6021
1.5944
1.5785
1.5705
1.5554
1.5070
1.4919
1.4844
1.4827
1.4673
1.4621
1.4563
1.4329
1.2548
0.9667
0.9425
0.9185
0.0001
n-Bu
CO2Me
OH
Ph
Integral
2.2934
1.8503
1.6029
0.9086
1.0000
3.1519
2.4746
3.1025
2.7957
3.2922
ppm

ctm1196 cdc13 rt 60MHz 13C 10 oct 2003 301a
ppm
165.127
150.240
141.195
128.680
128.146
125.992
116.918
99.451
77.421
76.998
76.575
73.685
72.196
52.603
30.503
22.005
19.341
13.568
n-Bu
CO2Me
OH
Ph
ppm
0
20
40
60
80
100
120
140
160

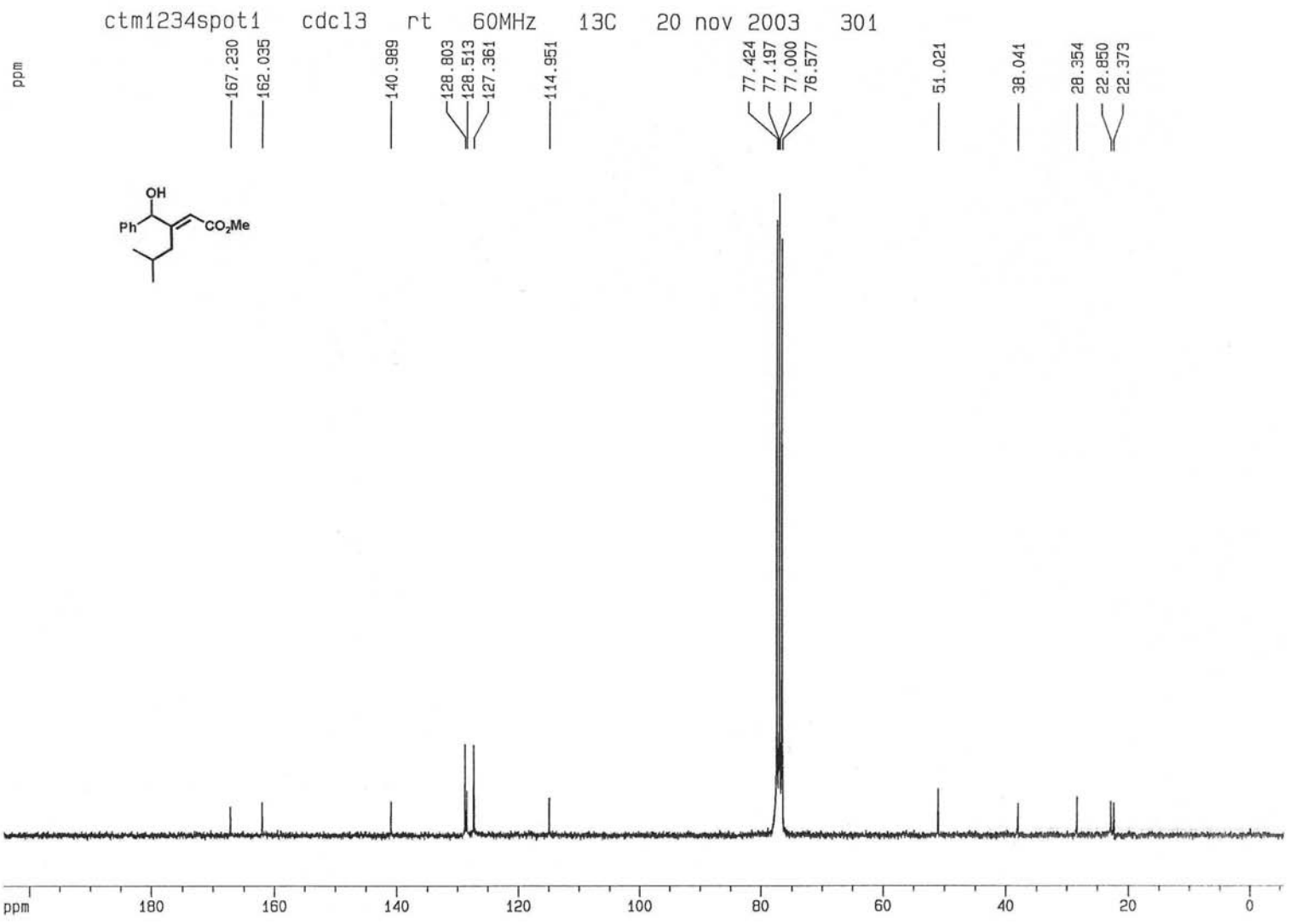
ctm1187 cdc13 rt 300MHz 1H 29 sept 2003 301b
ppm
7.4172
7.4137
7.3958
7.3932
7.3714
7.3480
7.3451
7.3269
7.2595
7.2590
6.8728
6.8429
6.5136
5.6700
5.6531
5.6401
5.6071
5.6018
5.5485
5.5432
5.4846
5.4833
5.4799
5.4452
5.4418
4.5984
4.5934
4.0104
3.8307
3.8115
3.7894
3.7672
3.7340
3.6417
2.4477
2.4359
2.2364
2.2223
2.2089
1.6973
1.6734
1.6423
1.6295
1.5942
1.4184
1.3944
1.3698
1.3447
1.3220
1.3041
1.2947
1.2684
1.2546
0.9463
0.9221
0.9161
0.8978
0.8832
0.8598
0.0003
-0.0004
OH
Ph
CO2Me
Integral
7.4477
1.0000
1.1574
1.4400
1.4607
1.2629
3.5960
1.0562
0.7268
ppm


ctmstille cdcl3 rt 75MHz 13C 2 march 2004 301a
ppm
167.086
142.189
141.766
130.991
128.834
128.537
128.186
126.543
126.342
121.518
77.420
76.996
76.573
70.236
52.081
OH
Ph
CO2Me
ppm
160
140
120
100
80
60
40
20
0

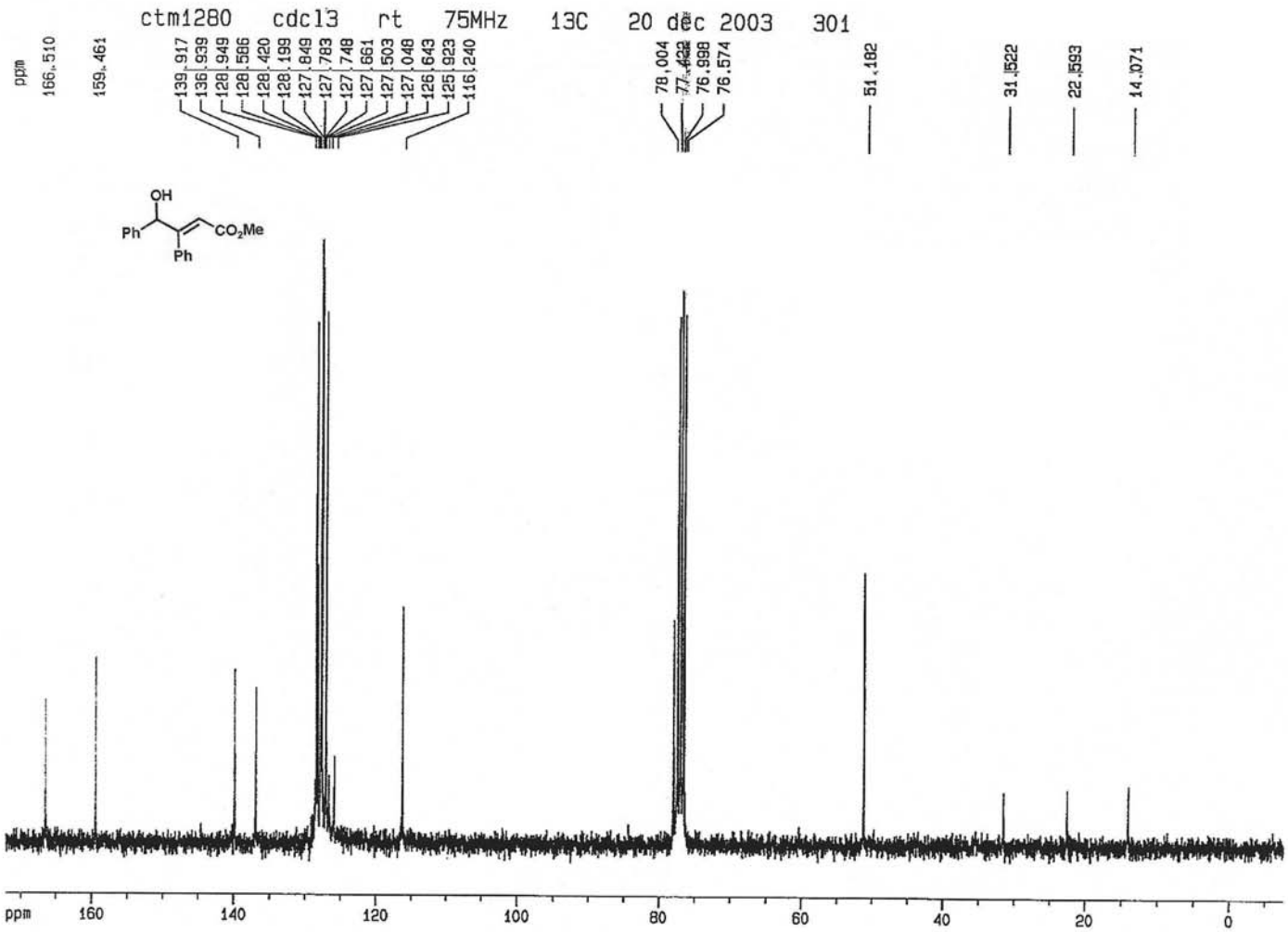
ctm2067a cdcl3 rt 300MHz 1H 1 april 2004 301b
ppm
7.3743
7.3675
7.3628
7.3498
7.3395
7.3345
7.3252
7.3123
7.3104
7.2611
7.1451
6.9101
6.2940
6.2896
6.2854
6.2806
6.2762
6.0136
5.3776
5.3375
5.1375
3.9703
3.9283
3.8265
3.8173
3.8095
3.7973
3.7773
3.7288
3.6619
3.6443
3.6130
3.4823
2.4279
2.1856
2.1475
2.1119
2.0960
2.0533
2.0475
2.0426
1.9916
1.9908
1.9874
1.9865
1.9414
1.9227
1.9199
1.7751
1.7715
1.6733
1.6204
1.5096
1.4695
1.2646
1.2551
0.8802
0.1994
0.0108
-0.0001
-0.0112
OH
Ph
Me
CO2Me
Integral
4.7017
0.8239
0.9932
3.0000
3.2055
ppm


ctm2067a cdcl3 rt 75MHz 13C 8 june 2004 301a
ppm
167.300
158.702
140.578
128.704
128.351
126.908
114.615
78.405
77.426
77.002
76.579
51.092
15.568
OH
Ph
Me
CO2Me
0
20
40
60
80
100
120
140
160
ppm

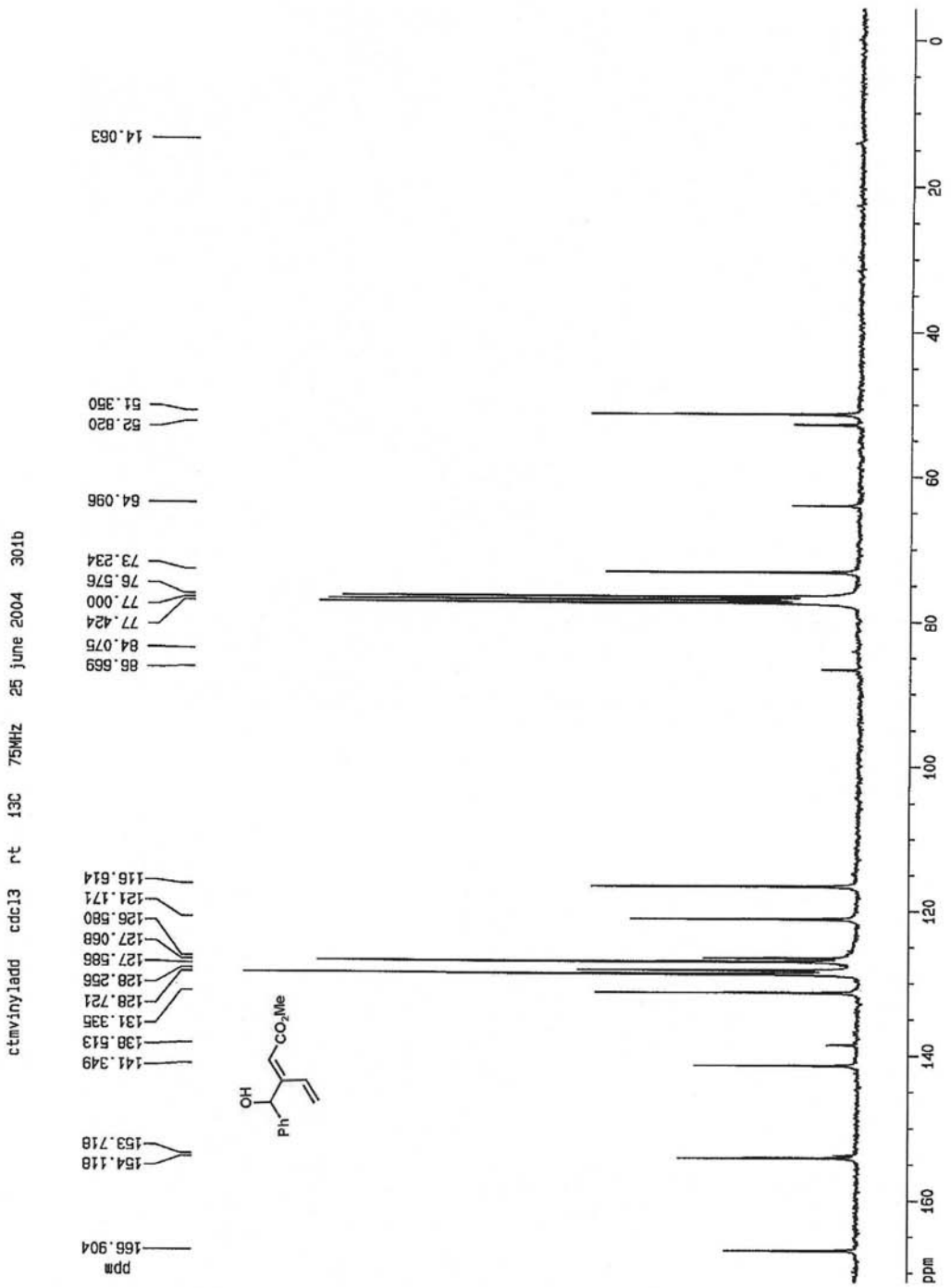
ctm1234spot1 cdcl3 rt 300MHz 1H 19 nov 2003 301b
ppm
7.3617
7.3546
7.3440
7.3410
7.3297
7.3189
7.3133
7.2623
7.2612
7.2173
7.0832
6.3741
6.0421
6.0239
5.2156
3.9607
3.8355
3.7550
3.7468
3.7187
3.6794
3.6449
3.6329
3.4727
3.1668
2.9722
2.9474
2.9305
2.9056
2.1540
2.0176
2.0080
1.9338
1.9110
1.8883
1.8660
1.8430
1.7918
1.7680
1.7500
1.7262
1.5846
1.2550
0.9687
0.9456
0.9398
0.9225
0.9105
0.9008
0.8887
0.8583
0.8526
0.8304
0.0009
0.0003
OH
Ph
CO2Me
Integral
4.4987
0.6739
1.0000
2.8515
1.1223
0.9403
1.7708
1.5744
0.9587
6.9394
ppm

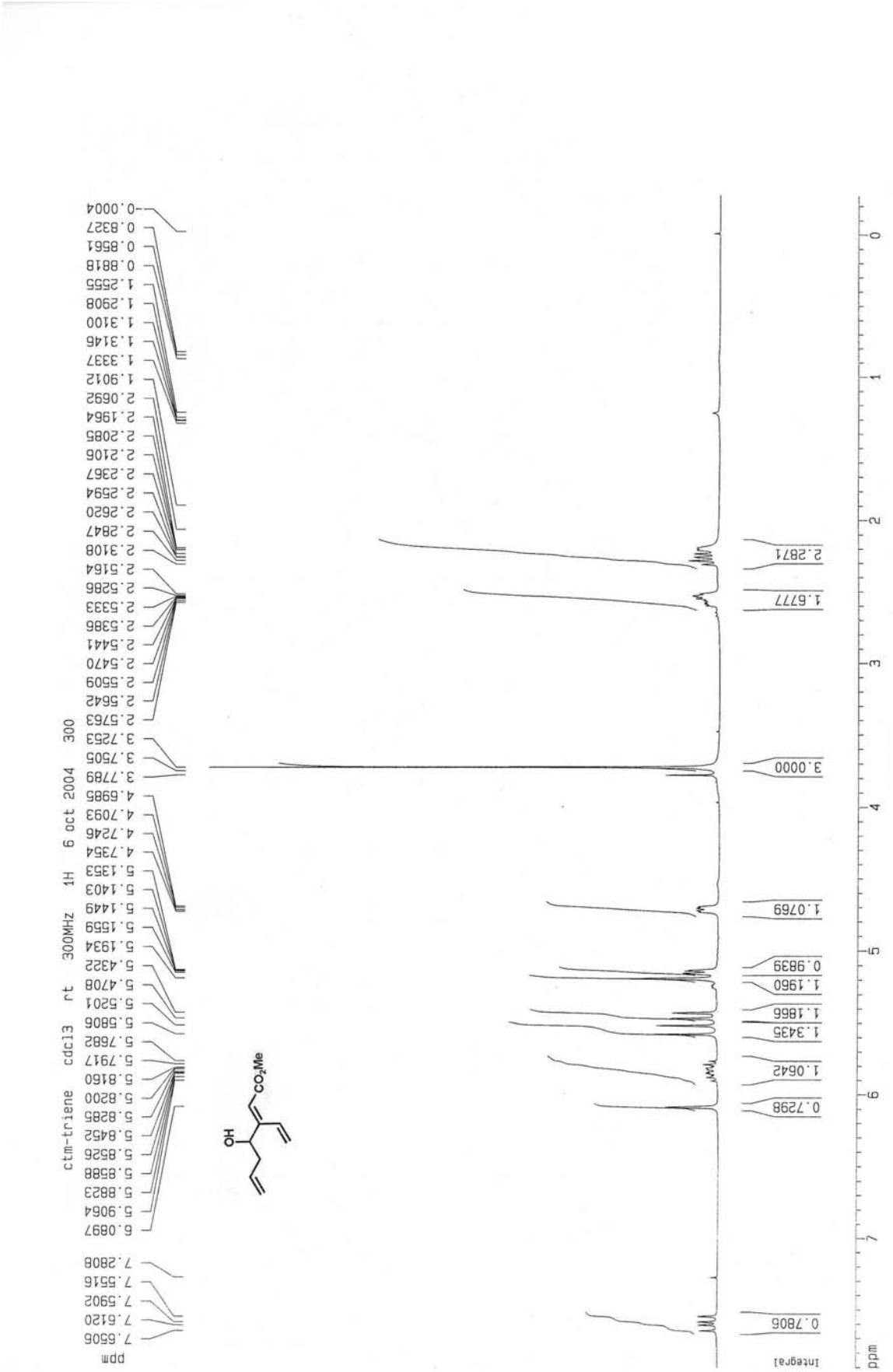

ctm1234spot1 cdcl3 rt 60MHz 13C 20 nov 2003 301
ppm
167.230
162.035
140.989
128.803
128.513
127.361
114.951
77.424
77.197
77.000
76.577
51.021
38.041
28.354
22.850
22.373
OH
Ph
CO2Me
ppm
180
160
140
120
100
80
60
40
20
0

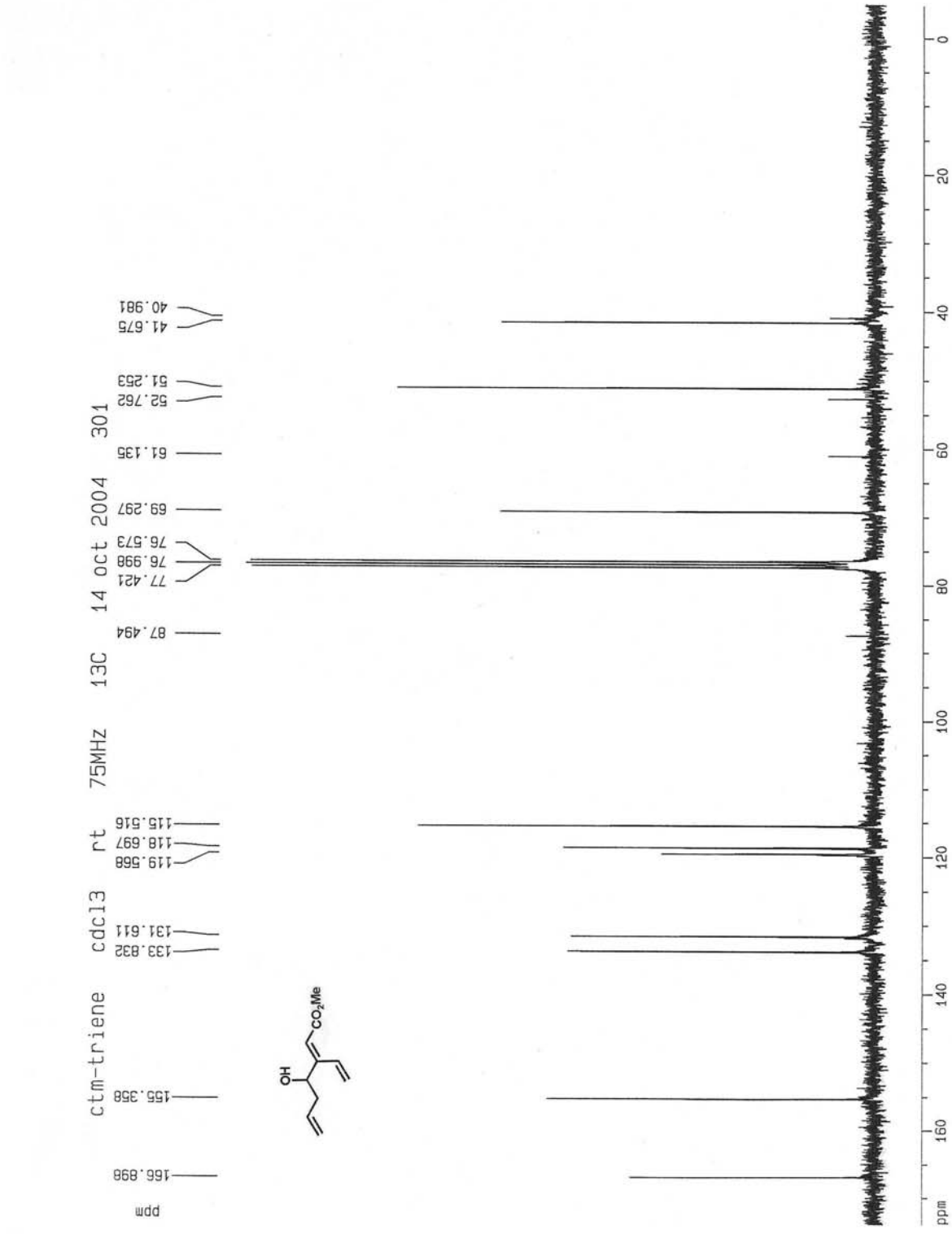
ctm1288 cdc13 rt 300MHz 1H 30 dec 2003 301b
ppm
7.2866
7.2809
7.2703
7.2682
7.2634
7.2564
7.2490
7.2423
7.2319
7.2265
7.2130
6.9265
6.9197
6.9089
6.5460
6.5407
6.4410
6.4362
6.3228
6.1625
5.6745
5.6124
5.4354
3.7945
3.7923
3.7532
3.7358
3.7020
3.6755
3.6419
3.6138
3.6065
3.5843
3.5527
3.4859
3.4690
3.3059
2.8991
2.3337
2.2435
2.2225
2.1668
2.0406
1.9713
1.8858
1.7152
1.5664
1.5109
1.4893
1.4264
1.2547
1.2325
1.2057
0.9771
0.9553
0.9051
0.8833
0.8604
0.0110
0.0001
0.0110
OH
Ph
Ph
CO2Me
Integral
3.0000
1.0249
0.8048
1.9871
8.4775
0.7571
ppm


ctm1280 cdcl3 rt 75MHz 13C 20 dec 2003 301
ppm
166.510
159.461
139.917
136.939
128.949
128.586
128.420
128.199
127.849
127.783
127.748
127.661
127.503
127.048
126.643
125.923
116.240
78.004
76.998
76.574
51.182
31.522
22.593
14.071
OH
Ph
CO2Me
Ph
ppm
160
140
120
100
80
60
40
20
0

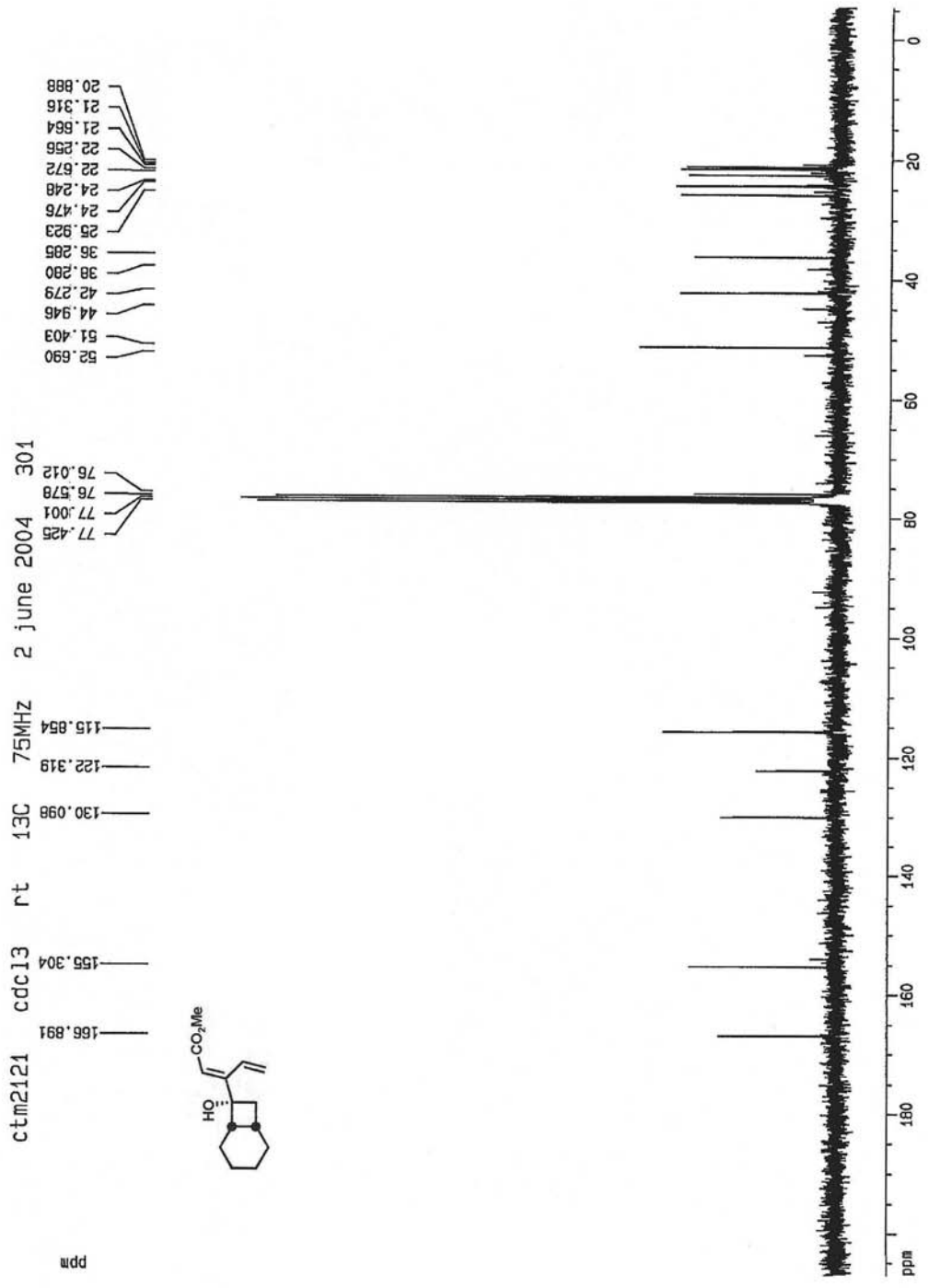
ctmyinyladd cdc13 rt 300MHz 1H 25 june 2004 301b
ppm
7.3833
7.3745
7.3728
7.3700
7.3671
7.3603
7.3562
7.3535
7.3508
7.3311
7.2598
6.3159
6.3142
5.6773
5.4928
5.4904
5.4880
5.4300
5.4276
5.3935
5.3905
5.3886
5.3519
5.3499
5.3470
3.9970
3.8307
3.8012
3.7945
3.7780
3.7551
3.7344
3.7281
3.7210
3.7157
3.6888
3.6783
3.6397
3.5082
3.4644
2.7090
2.4299
2.4091
2.0531
2.0447
1.8410
1.7724
1.5796
1.3948
1.2542
1.2322
1.2055
0.9772
0.9552
0.9057
0.8834
0.8601
0.1542
0.0109
0.0000
-0.0110
OH
Ph
CO2Me
Integral
1.5455
5.3125
0.7894
1.0272
1.2515
1.1632
0.6631
3.0000
ppm


ctmvinyladd cdcl3 rt 13C 75MHz 25 june 2004 301b
14.063
51.350
52.820
64.096
73.234
76.576
77.000
77.424
84.075
86.669
116.614
121.171
126.580
127.068
127.586
128.256
128.721
131.335
138.513
141.349
153.718
154.118
166.904
ppm
OH
Ph
CO2Me
0
20
40
60
80
100
120
140
160
ppm


ctm-triene cdcl3 rt 300MHz 1H 6 oct 2004 300
ppm
7.6506
7.6120
7.5902
7.5516
7.2808
6.0897
5.9064
5.8823
5.8588
5.8526
5.8452
5.8285
5.8200
5.8160
5.7917
5.7682
5.6806
5.5201
5.4708
5.4322
5.1934
5.1559
5.1449
5.1403
5.1353
4.7354
4.7246
4.7093
4.6985
3.7789
3.7505
3.7253
2.5763
2.5642
2.5509
2.5470
2.5441
2.5386
2.5333
2.5286
2.5164
2.3108
2.2847
2.2620
2.2594
2.2367
2.2106
2.2085
2.1964
2.0692
1.9012
1.3337
1.3146
1.3100
1.2908
1.2555
0.8818
0.8561
0.8327
-0.0004
Integral
0.7805
0.7298
1.0642
1.3435
1.1866
1.1960
0.9839
1.0769
3.0000
1.6777
2.2871
ppm
0
1
2
3
4
5
6
7
OH
CO2Me

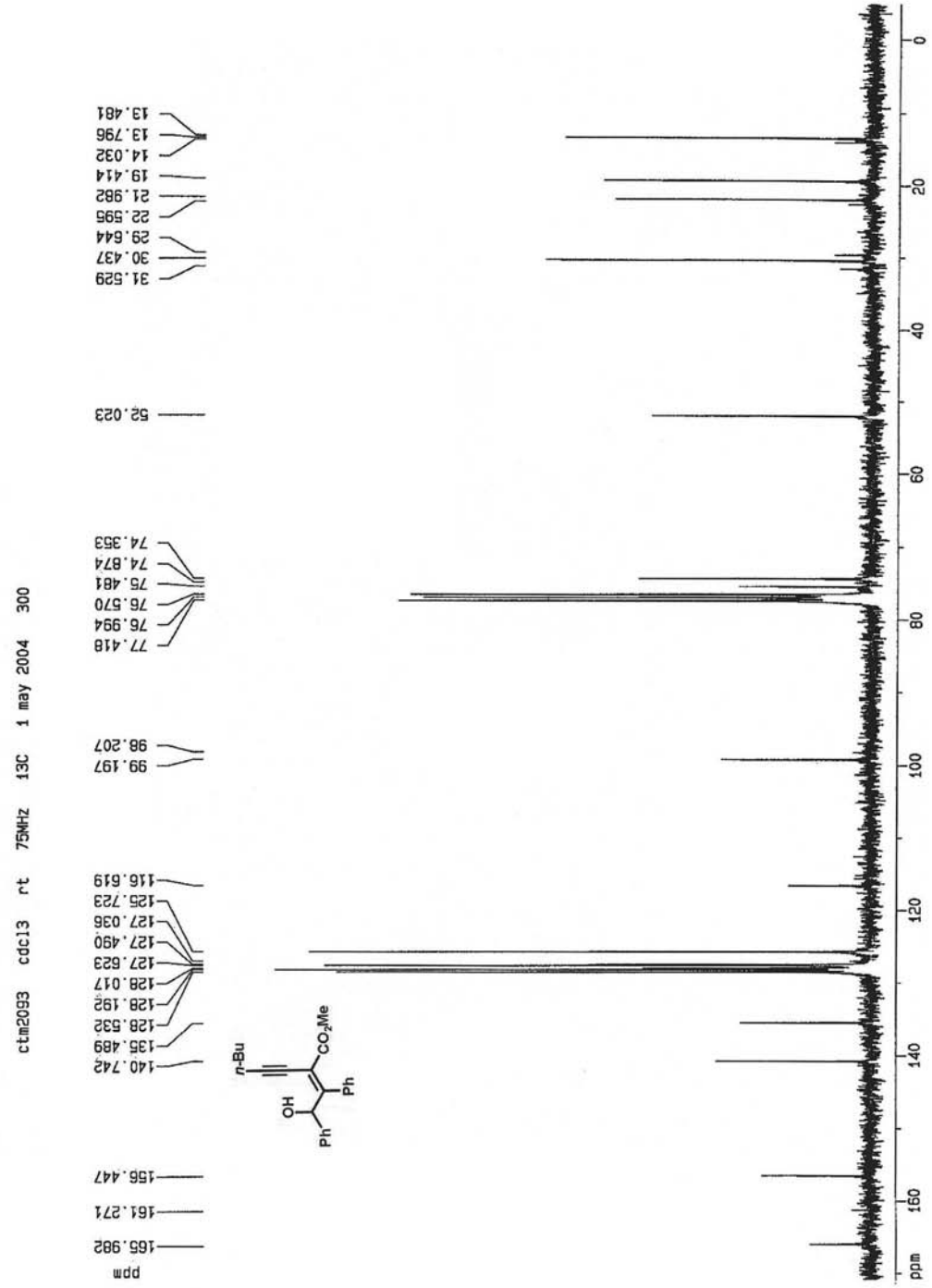

ctm-triene cdcl3 rt 75MHz 13C 14 oct 2004 301
ppm
166.898
155.358
133.832
131.611
119.568
118.697
115.516
87.494
77.421
76.998
76.573
69.297
61.135
52.762
51.253
41.675
40.981
OH
CO2Me
ppm
0
20
40
60
80
100
120
140
160

ctm2121 cdcl3 rt 300MHz 1H 2 june 2004 301b
ppm
7.4884
7.4860
7.4494
7.4469
7.4278
7.4252
7.3887
7.3863
7.2669
5.9761
5.9608
5.7006
5.6963
5.6897
5.6848
5.6294
5.6242
5.5640
5.5592
5.5542
5.5250
5.5201
5.5152
3.9848
3.8228
3.7853
3.7694
3.7425
3.7070
3.7034
3.6960
2.6230
2.5117
2.3611
2.3474
2.3358
2.2857
2.1909
2.1518
2.1006
1.7447
1.7284
1.7150
1.6851
1.6765
1.5414
1.5294
1.5190
1.5105
1.5017
1.4937
1.4812
1.4696
1.4653
1.4541
1.2543
1.1468
1.0723
0.8804
0.0002
CO2Me
HO
Integral
0.8546
1.1037
1.2784
1.1608
0.6664
3.0000
1.4515
2.2212
1.9638
0.9867
1.9156
1.4738
5.2543
7.0461
1.3339
2.3089
ppm

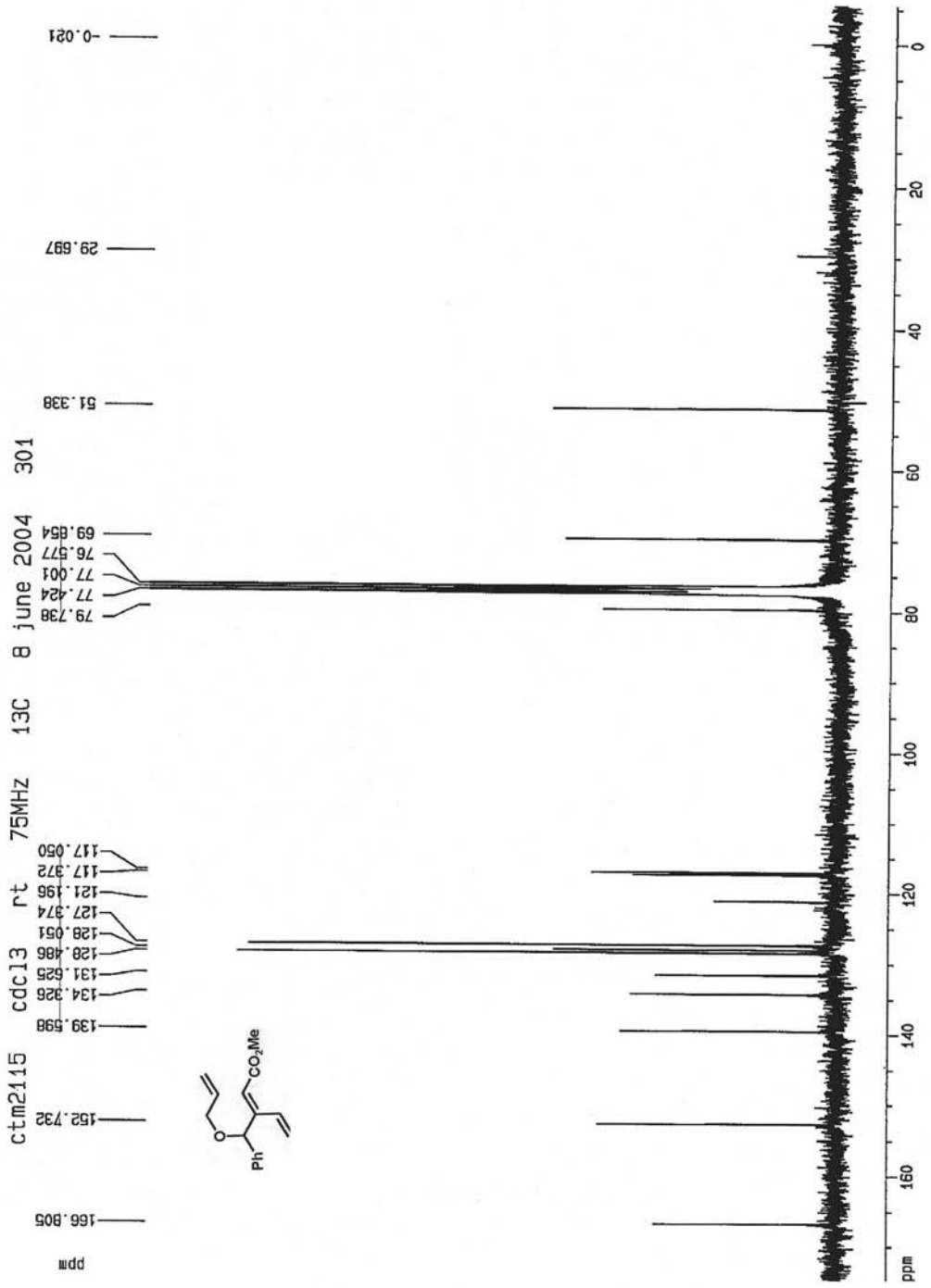

ctm2121 cdc13 rt 13C 75MHz 2 june 2004 301
166.891
155.304
130.098
122.319
115.854
77.425
77.001
76.578
76.012
52.690
51.403
44.946
42.279
38.280
36.285
25.923
24.476
24.248
22.672
22.256
21.664
21.316
20.888
CO2Me
HO
ppm
0
20
40
60
80
100
120
140
160
180

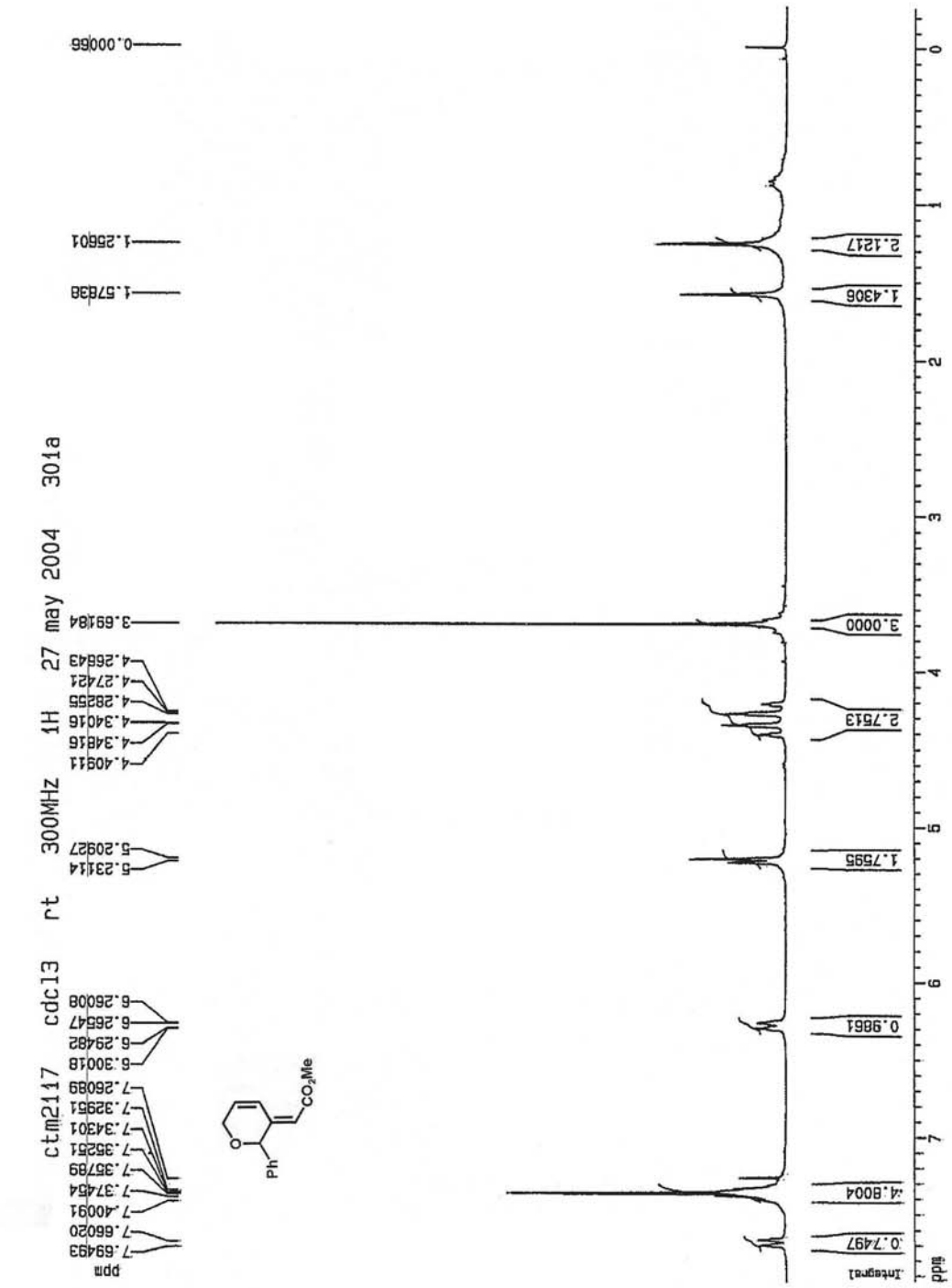
ctm2100 cdc13 rt 300MHz 1H 8 may 2004 301
ppm
7.4162
7.3282
7.3037
7.2697
7.2194
6.8815
6.8589
6.8536
6.3058
6.1223
6.0989
4.7318
3.4539
3.4387
3.4170
2.0804
2.0569
1.5595
0.1584
0.0100
0.0004
0.0112
Integral
0.7961
6.0431
5.7132
2.0527
1.0970
0.6318
3.0000
1.0623
2.1693
OH
Ph
Ph
CO2Me

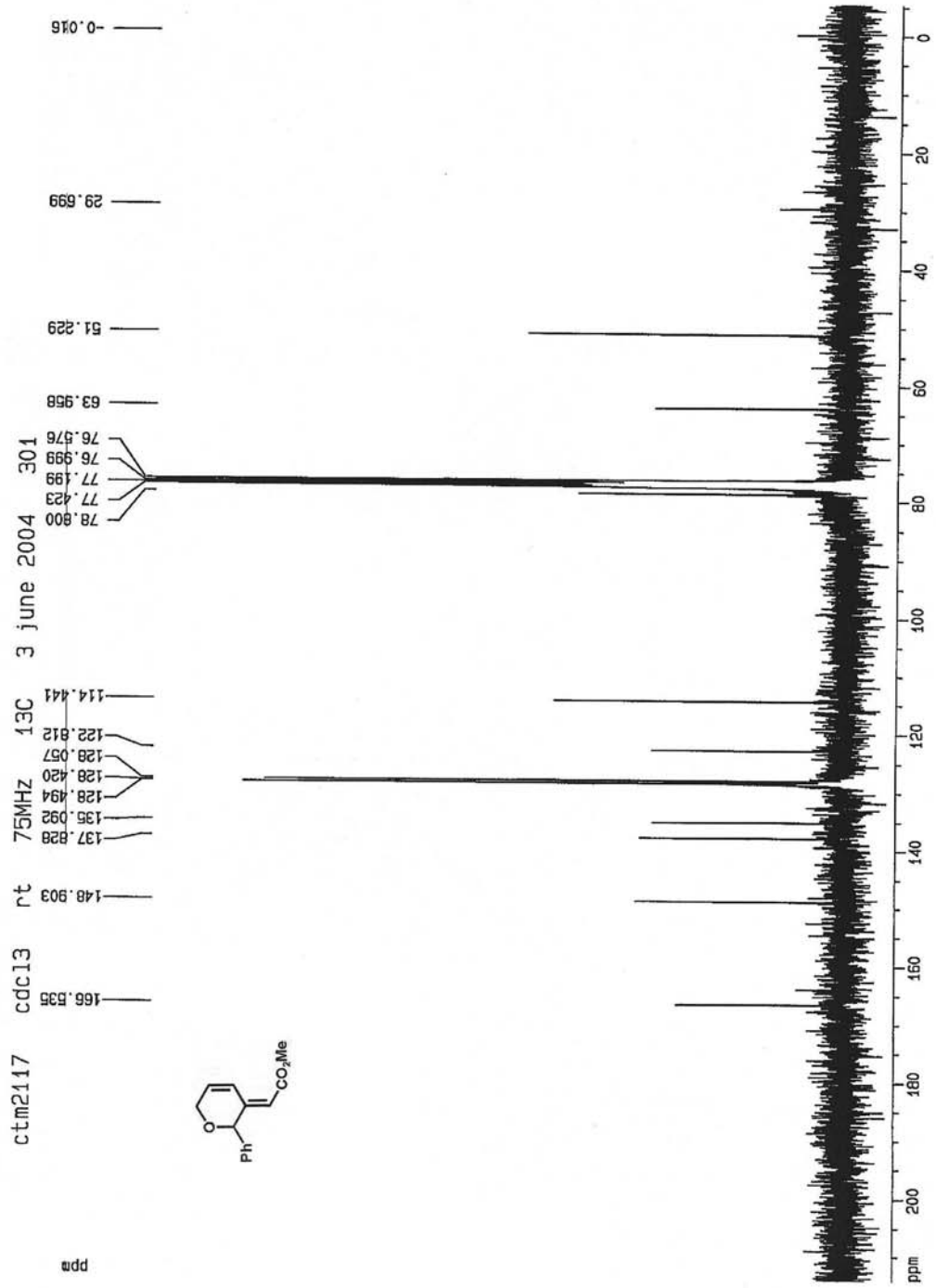
ctm2093 cdc13 rt 300MHz 1H 1 may 2004 301b
ppm
7.3600
7.3574
7.3553
7.3161
7.2903
7.2868
7.2596
7.2405
7.2350
7.2112
7.2092
6.8773
6.8726
6.8455
6.7300
6.5576
6.3489
6.3241
6.2544
6.0970
3.8783
3.8003
3.7692
3.7257
3.6826
3.5205
3.5035
3.4827
3.4163
3.3651
3.2346
2.4866
2.4636
2.4400
2.2200
2.1947
1.7761
1.6126
1.6092
1.5894
1.5859
1.5786
1.5600
1.5392
1.4763
1.4607
1.4520
1.4361
1.4254
1.4020
1.2680
1.2581
0.9366
0.9124
0.8882
0.8834
0.8600
0.1571
0.0002
n-Bu
CO2Me
Ph
OH
Ph
Integral
10.491
2.023
0.970
3.000
2.304
0.889
3.978
3.142
2.418
4.193
ppm

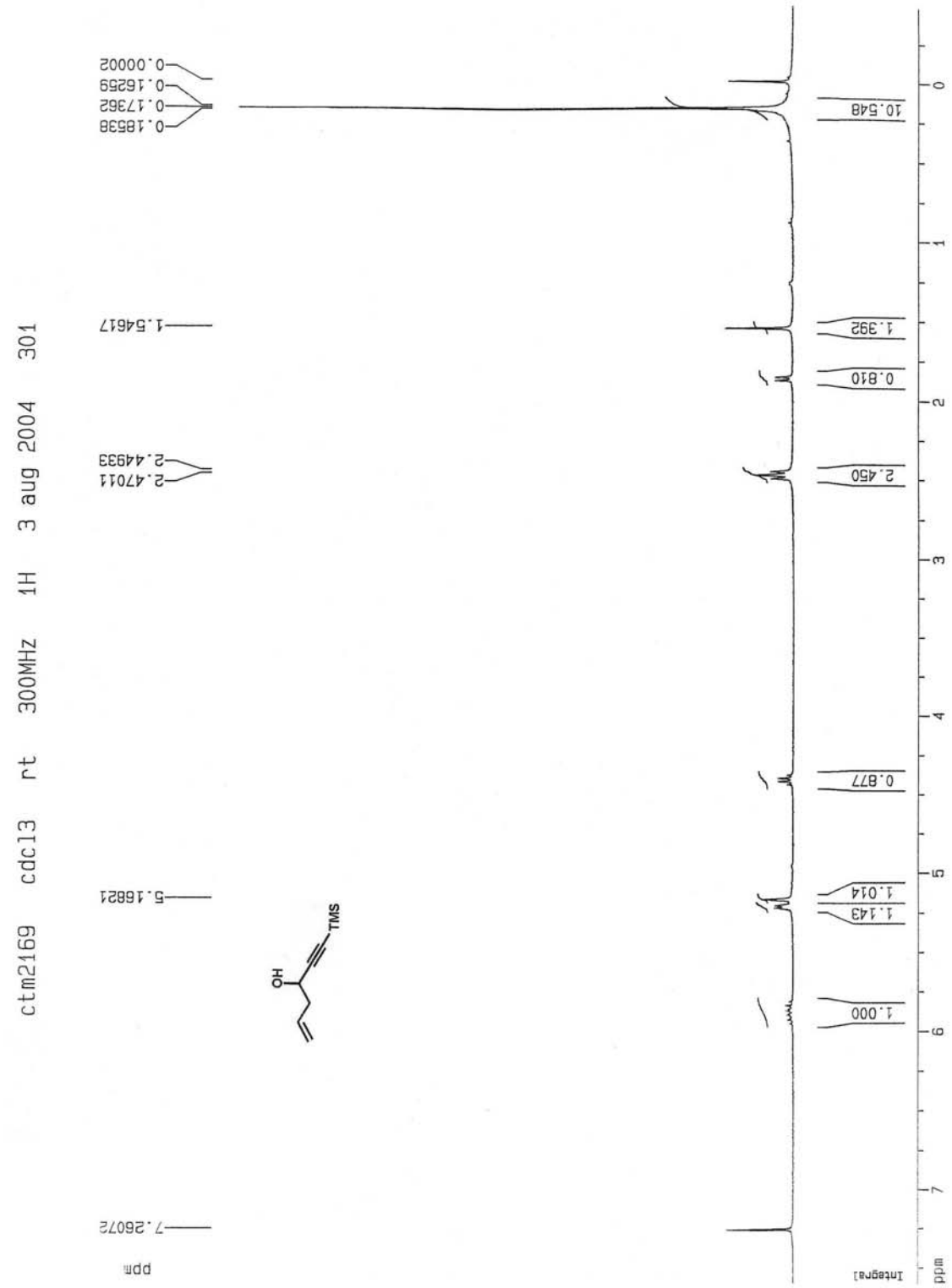

ctm2093 cdcl3 rt 75MHz 13C 1 may 2004 300
ppm
165.982
161.271
156.447
140.742
135.489
128.532
128.192
128.017
127.623
127.490
127.036
125.723
116.619
99.197
98.207
77.418
76.994
76.570
75.481
74.874
74.353
52.023
31.529
30.437
29.644
22.595
21.982
19.414
14.032
13.796
13.481
n-Bu
CO2Me
Ph
OH
Ph
ppm

ctm2115 cdc13 rt 300MHz 1H 26 may 2004 301
ppm
7.5397
7.3435
7.3366
7.3265
7.2587
6.2574
5.9416
5.9223
5.5927
5.5324
5.3909
5.3526
5.2599
5.2233
4.0220
4.0040
3.9806
3.9619
3.7477
1.5533
1.2565
0.0000
Integral
4.1172
4.3562
0.6760
0.8516
1.4723
1.5122
2.2127
1.1620
2.6242
3.0000
1.1442
Ph
CO2Me

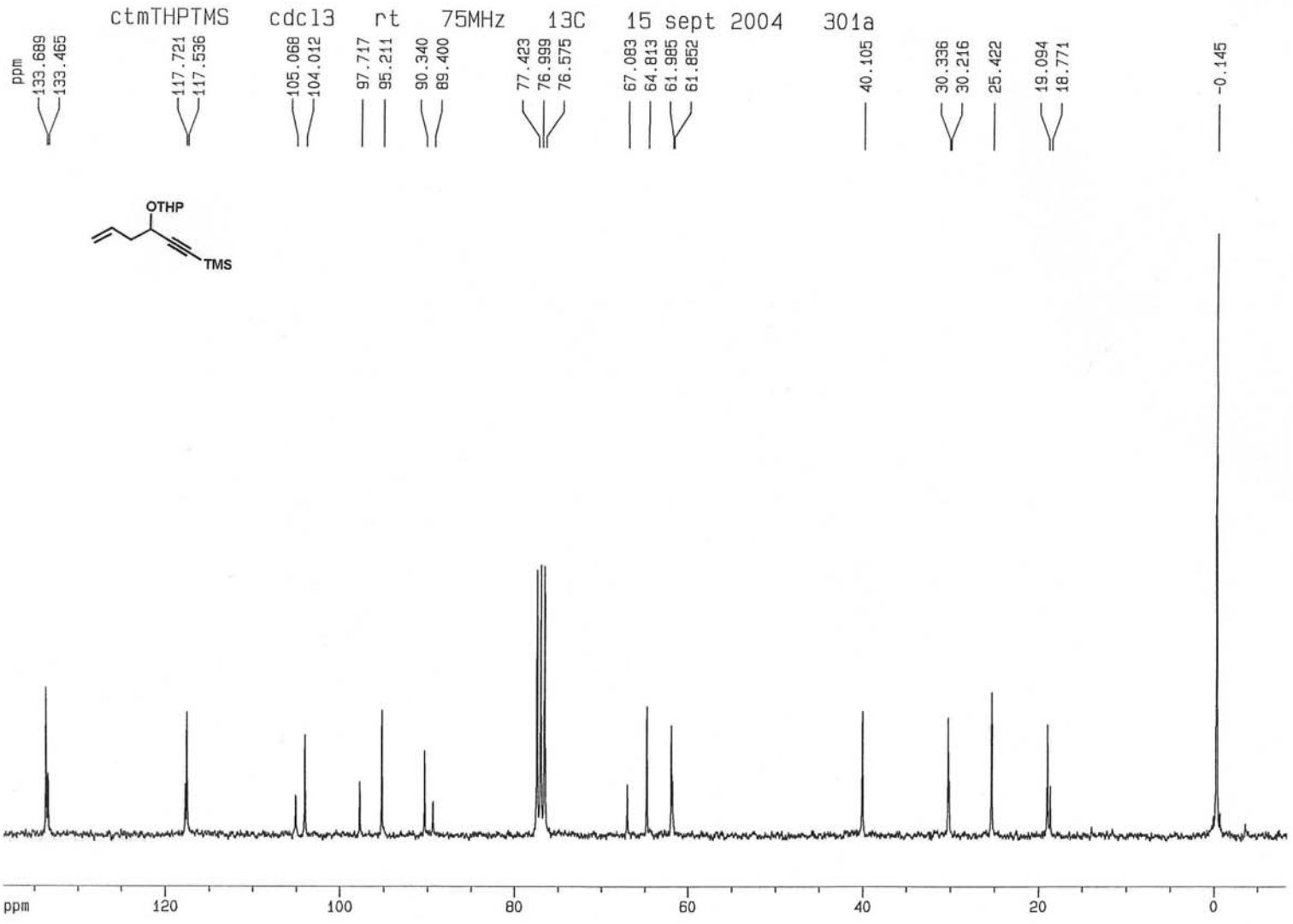

ctm2115 cdcl3 rt 75MHz 13C 8 june 2004 301
166.805
152.732
139.598
134.326
131.625
128.486
128.051
127.374
121.196
117.372
117.050
79.738
77.424
77.001
76.577
69.854
51.338
29.697
-0.021
ppm
0
20
40
60
80
100
120
140
160
ppm
Ph
CO2Me


ctm2117 cdc13 rt 300MHz 1H 27 may 2004 301a
ppm
7.69493
7.66020
7.40091
7.37454
7.35789
7.35251
7.34301
7.32951
7.26089
6.30018
6.29482
6.26547
6.26008
5.23114
5.20927
4.40911
4.34816
4.34016
4.28255
4.27421
4.26643
3.69184
1.57838
1.25601
0.00066
Integral
0.7497
4.8004
0.9861
1.7595
2.7513
3.0000
1.4306
2.1217
Ph
CO2Me

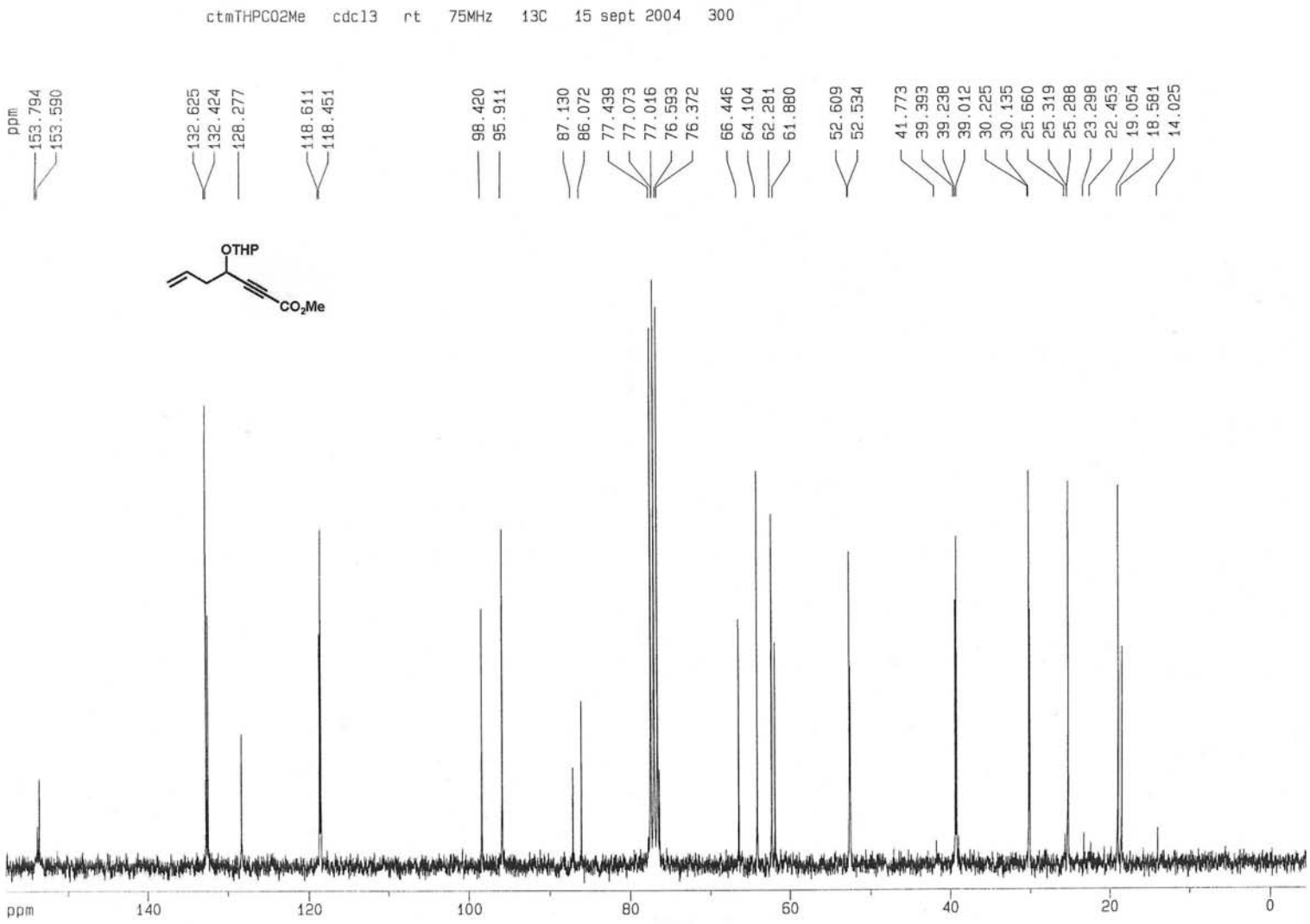

ctm2117 cdc13 rt 75MHz 13C 3 june 2004 301
166.535
148.903
137.828
135.092
128.494
128.420
128.057
122.812
114.441
78.800
77.423
77.199
76.999
76.576
63.958
51.229
29.699
-0.046
ppm
0
20
40
60
80
100
120
140
160
180
200
Ph
CO2Me

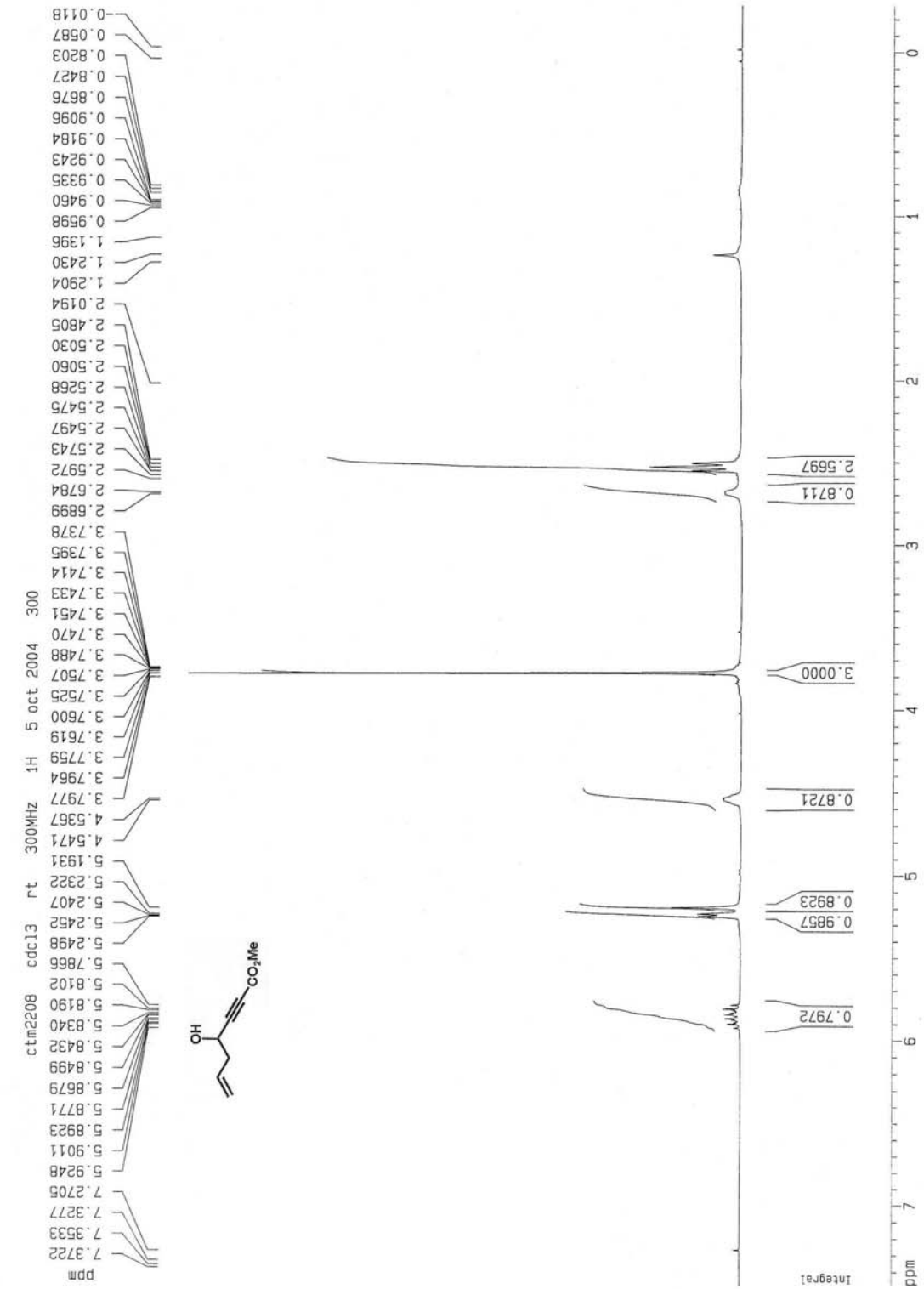

ctm2169 cdc13 rt 300MHz 1H 3 aug 2004 301
ppm
7.26072
5.16821
1.54617
2.49393
2.47011
0.18538
0.17362
0.16259
0.00002
Integral
10.548
2.450
1.392
0.810
0.877
1.014
1.143
1.000
OH
TMS

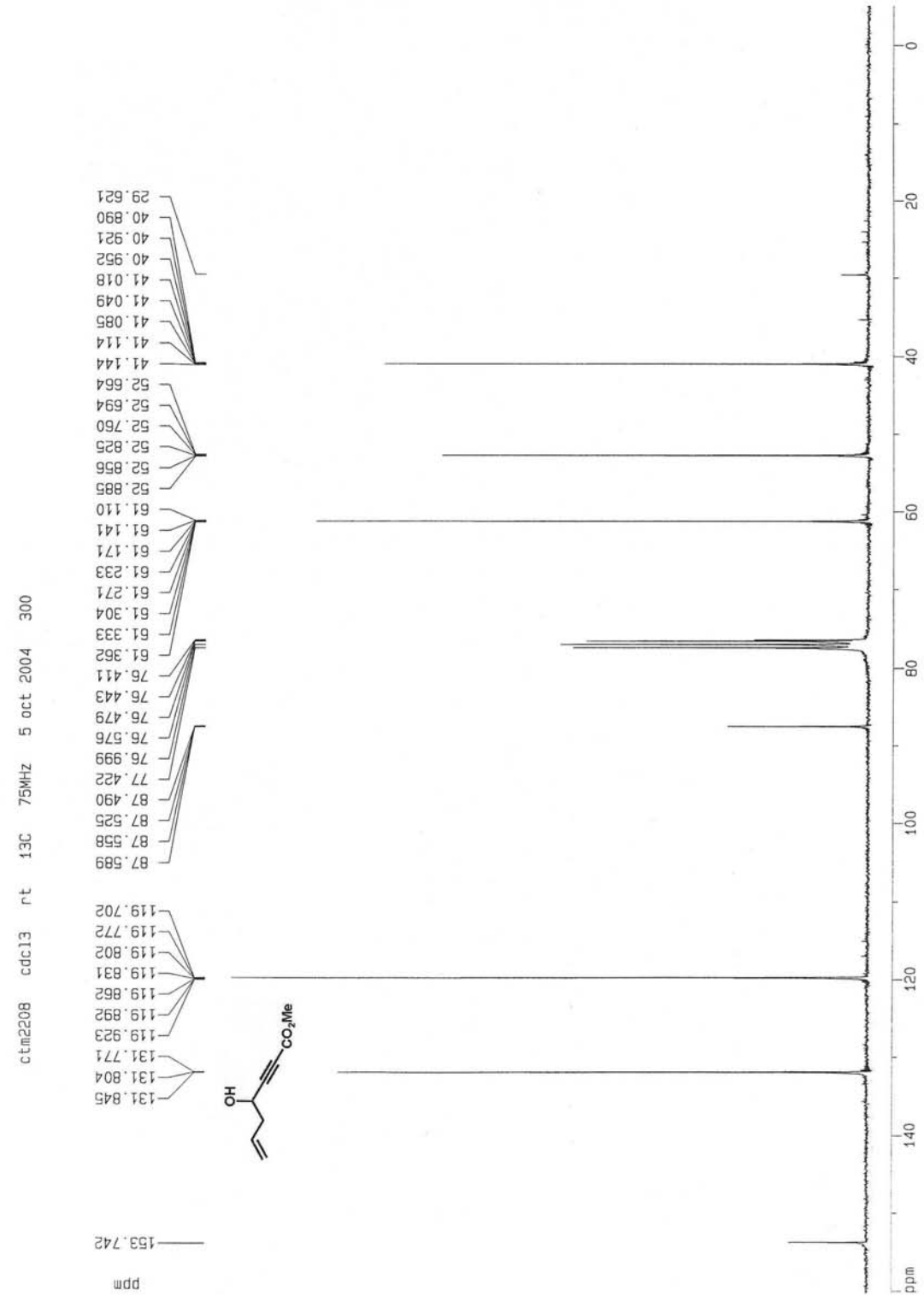
ctm2172 cdc13 rt 300MHz 1H 7 aug 2004 301
ppm
7.26265
4.42173
5.12536
5.12204
2.49335
2.47050
1.74097
1.64159
1.62723
1.61086
1.56688
1.26728
1.25918
0.90255
0.88374
0.86060
0.16170
0.13300
0.12259
0.09725
0.00016
OTHP
TMS
Integral
1.000
2.609
0.921
0.335
0.718
0.310
0.427
1.096
1.485
2.959
16.414
5.754
0.712
3.577
10.852
ppm


ctmTHPTMS cdcl3 rt 75MHz 13C 15 sept 2004 301a
ppm
133.689
133.465
117.721
117.536
105.068
104.012
97.717
95.211
90.340
89.400
77.423
76.999
76.575
67.083
64.813
61.985
61.852
40.105
30.336
30.216
25.422
19.094
18.771
-0.145
OTHP
TMS
ppm
120
100
80
60
40
20
0

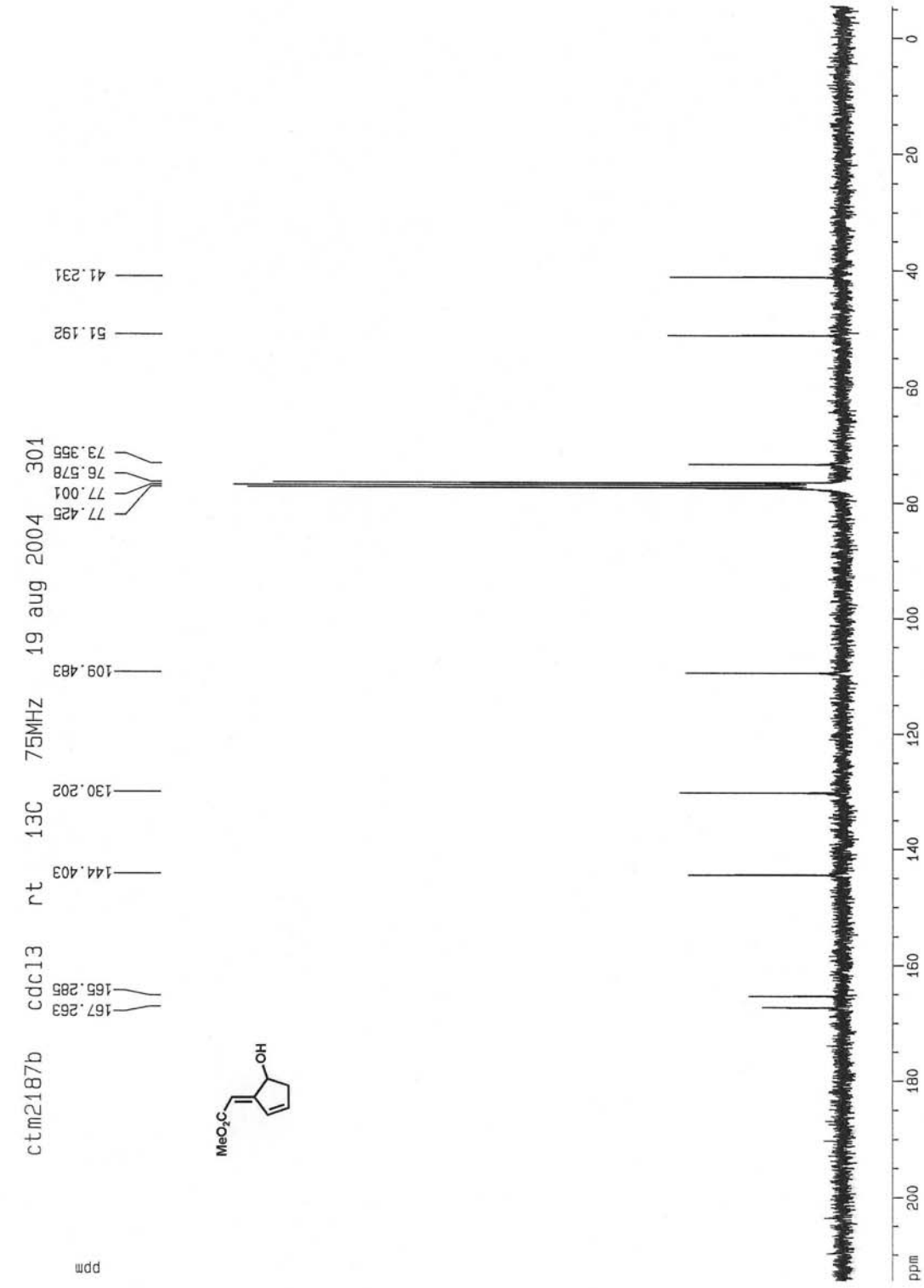
ctm2181 cdcl3 rt 300MHz 1H 12 aug 2004 301b
ppm
7.3817
7.2621
6.9114
5.9518
5.8947
5.8713
5.8475
5.8377
5.8240
5.2288
5.2238
5.2007
5.1761
5.1706
5.1669
5.1620
5.1425
5.1391
5.1366
5.1336
4.9383
4.9281
4.7770
4.6020
4.5798
4.5576
4.4050
4.3831
3.7880
3.7773
3.7716
3.7502
3.5456
2.5798
2.5567
2.5285
2.5055
1.7881
1.7829
1.7410
1.6924
1.6803
1.6652
1.6539
1.6481
1.6361
1.6246
1.6148
1.5991
1.5946
1.5819
1.5619
1.5297
1.2703
1.2538
0.9363
0.9143
0.8906
-0.0001
-0.0111
OTHP
CO2Me
Integral
1.0000
0.7176
1.7332
0.7244
0.4688
0.6497
0.4207
0.6397
4.2326
1.5098
2.7656
2.7242
9.4568
ppm

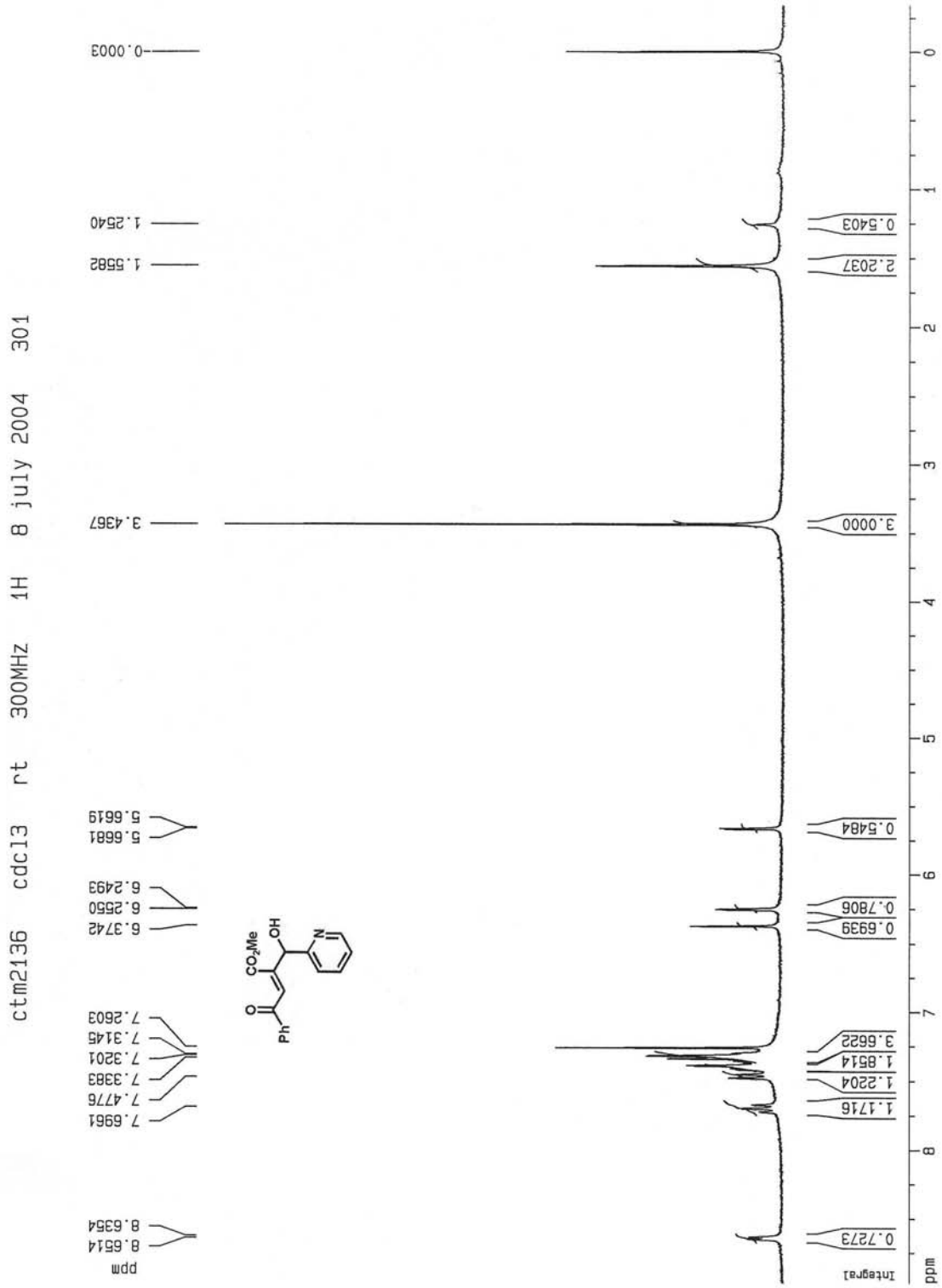

ctmTHPCO2Me cdcl3 rt 75MHz 13C 15 sept 2004 300
ppm
153.794
153.590
132.625
132.424
128.277
118.611
118.451
98.420
95.911
87.130
86.072
77.439
77.073
77.016
76.593
76.372
66.446
64.104
62.281
61.880
52.609
52.534
41.773
39.393
39.238
39.012
30.225
30.135
25.660
25.319
25.288
23.298
22.453
19.054
18.581
14.025
OTHP
CO2Me
ppm
140
120
100
80
60
40
20
0

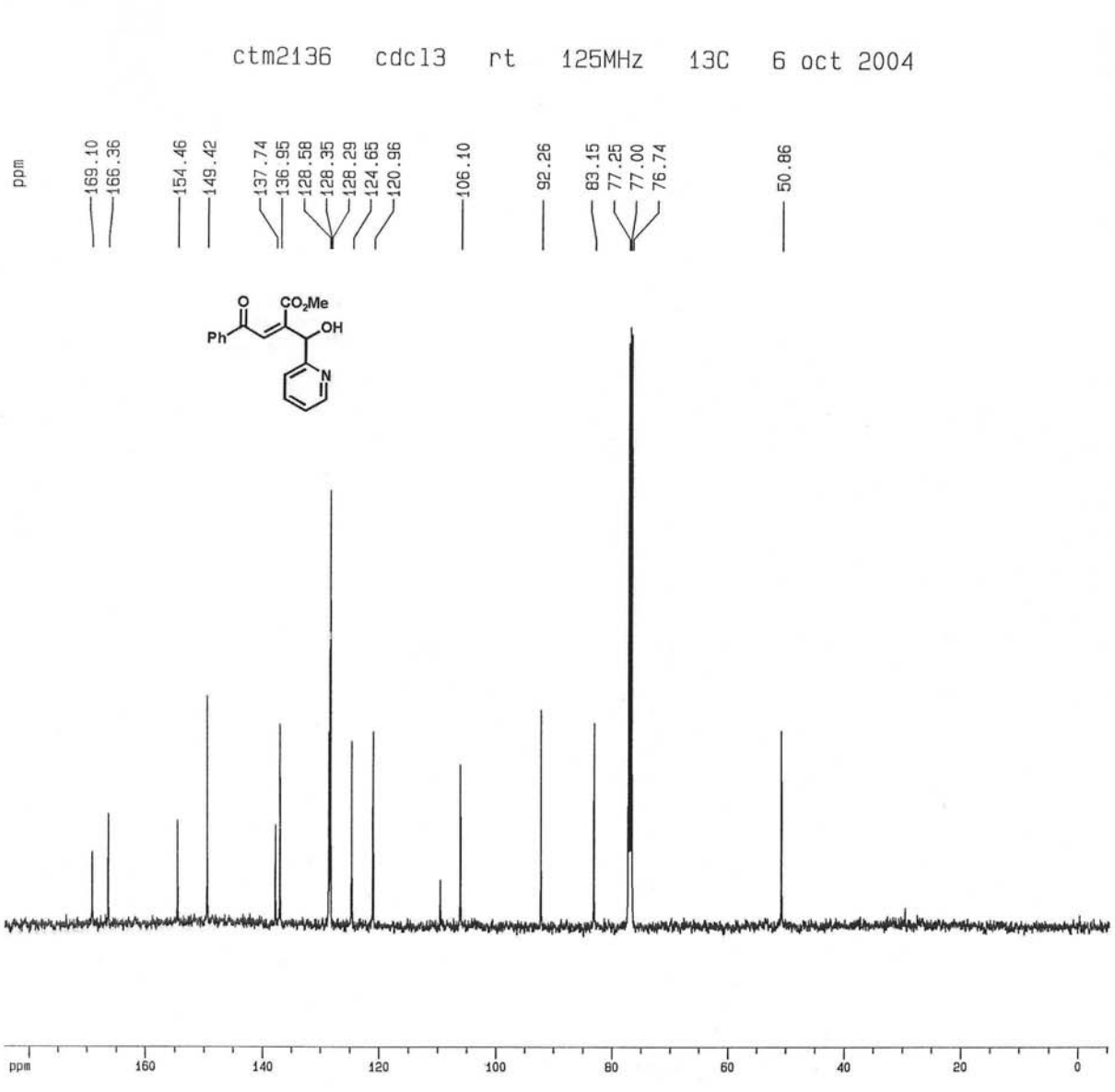

ctm2208 cdcl3 rt 300MHz 1H 5 oct 2004 300
ppm
7.3722
7.3533
7.3277
7.2705
5.9248
5.9011
5.8923
5.8771
5.8679
5.8499
5.8432
5.8340
5.8190
5.8102
5.7866
5.2498
5.2452
5.2407
5.2322
5.1931
4.5471
4.5367
3.7977
3.7964
3.7759
3.7619
3.7600
3.7525
3.7507
3.7488
3.7470
3.7451
3.7433
3.7414
3.7395
3.7378
2.6899
2.6784
2.5972
2.5743
2.5497
2.5475
2.5268
2.5060
2.5030
2.4805
2.0194
1.2904
1.2430
1.1396
0.9598
0.9460
0.9335
0.9243
0.9184
0.9096
0.8676
0.8427
0.8203
0.0587
-0.0118
Integral
0.7972
0.9857
0.8923
0.8721
3.0000
0.8711
2.5697
ppm
0
1
2
3
4
5
6
7
OH
CO2Me


ctm2208 cdc13 rt 13C 75MHz 5 oct 2004 300
ppm
153.742
131.845
131.804
131.771
119.923
119.892
119.862
119.831
119.802
119.772
119.702
87.589
87.558
87.525
87.490
77.422
76.999
76.576
76.479
76.443
76.411
61.362
61.333
61.304
61.271
61.233
61.171
61.141
61.110
52.885
52.856
52.825
52.760
52.694
52.664
41.144
41.114
41.085
41.049
41.018
40.952
40.921
40.890
29.621
OH
CO2Me
0
20
40
60
80
100
120
140
ppm

ctm2187b cdc13 rt 300MHz 1H 19 aug 2004 301b
ppm
7.3796
7.2721
7.2616
7.2449
7.2418
6.9103
6.5144
6.5091
6.4986
6.4946
6.4891
6.4803
5.8248
4.8022
4.7854
3.9808
3.8571
3.8137
3.7392
3.6504
3.6252
3.4926
2.9524
2.9434
2.9360
2.9303
2.9213
2.9141
2.8891
2.8819
2.8747
2.8688
2.8598
2.8527
2.4736
2.4658
2.4573
2.4121
2.4045
2.3958
2.0979
2.0457
1.7714
1.5642
1.2592
0.9767
0.9556
0.9045
0.8835
0.8603
0.1175
0.0690
0.0107
-0.0004
-0.0113
MeO2C
OH
Integral
4.5411
0.5388
0.6950
0.5055
0.6385
3.0000
0.8989
0.7675
0.8655
ppm


ctm2187b cdc13 rt 13C 75MHz 19 aug 2004 301
167.263
165.285
144.403
130.202
109.483
77.425
77.001
76.578
73.355
51.192
41.231
MeO2C
OH
ppm
0
20
40
60
80
100
120
140
160
180
200


ctm2136 cdcl3 rt 300MHz 1H 8 july 2004 301
ppm
8.6514
8.6354
7.6961
7.4776
7.3383
7.3201
7.3145
7.2603
6.3742
6.2550
6.2493
5.6681
5.6619
3.4367
1.5582
1.2540
0.0003
Integral
0.7273
1.4716
1.2204
1.8514
3.6622
0.6939
0.7806
0.5484
3.0000
2.2037
0.5403
ppm



Current Data Parameters

NAME	ctm2136
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

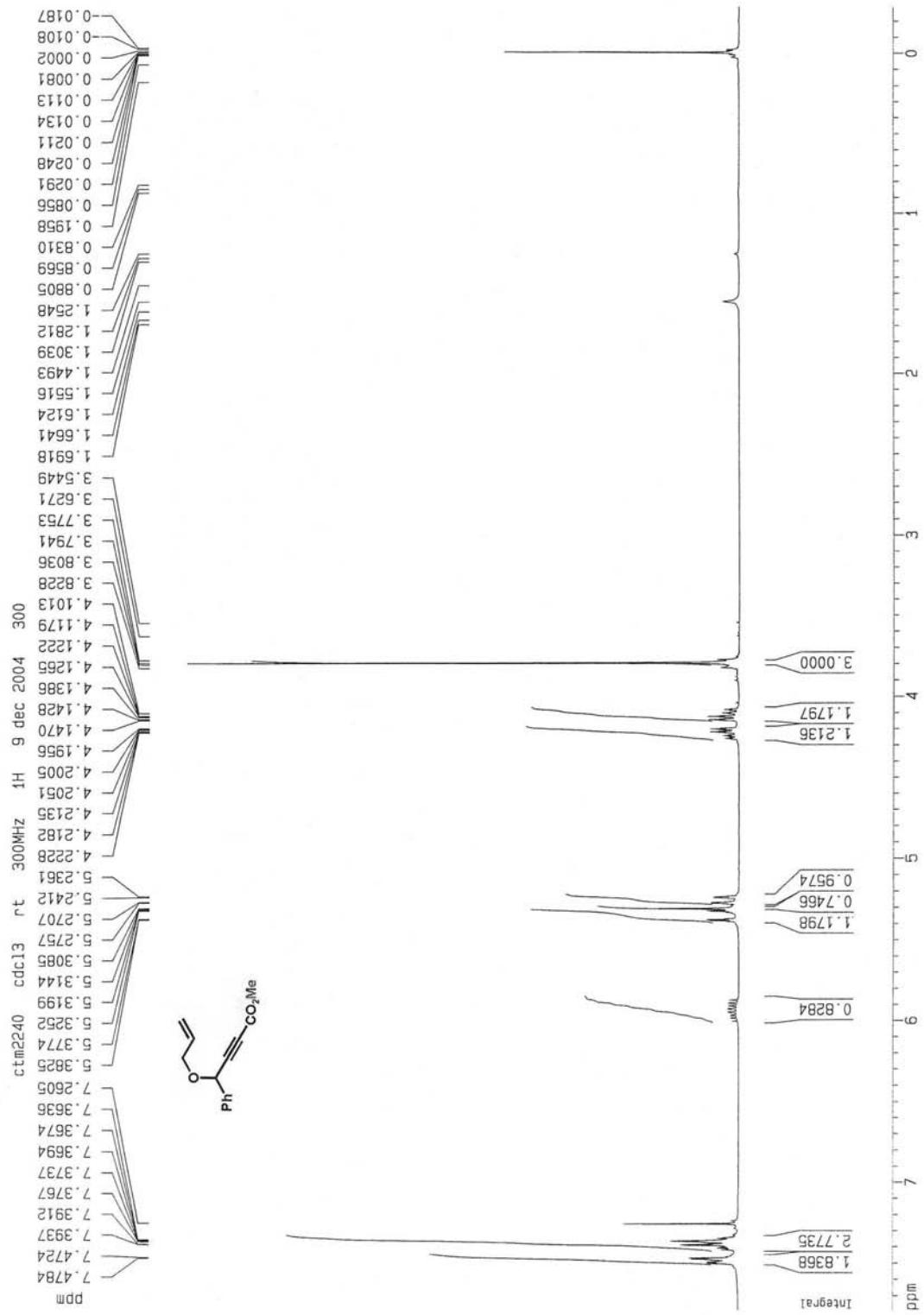
Date_	500000
Time	8.16
INSTRUM	spect
PROBHD	5 mm TXI 13C
PULPROG	c13wonoe
TD	32768
SOLVENT	CDCl3
NS	2879
DS	0
SWH	32679.738 Hz
FIDRES	0.997306 Hz
AQ	0.5014004 sec
RG	32768
DW	15.300 usec
DE	6.00 usec
TE	290.0 K
D3	0.00100000 sec
PL12	6.00 dB
D1	6.00000000 sec
CPDPRG2	waltz16
PCPD2	100.00 usec
SFO2	500.1330008 MHz
NUC2	1H
PL2	120.00 dB
P1	21.60 usec
DE	6.00 usec
SFO1	125.7715724 MHz
NUC1	13C
PL1	0.00 dB

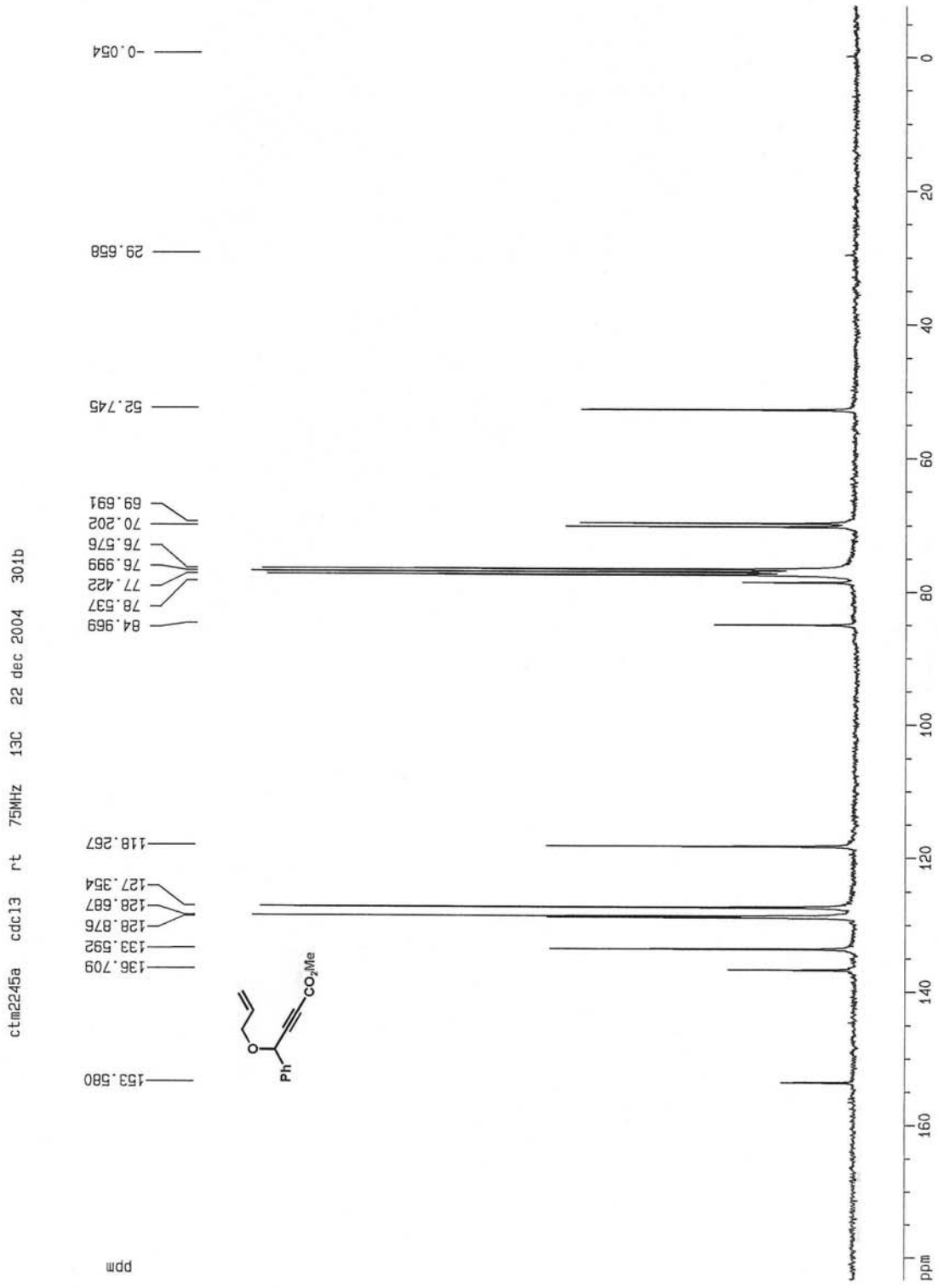
F2 - Processing parameters

SI	8192
SF	125.7578000 MHz
WDW	EM
SSB	0
LB	4.00 Hz
GB	0
PC	1.00

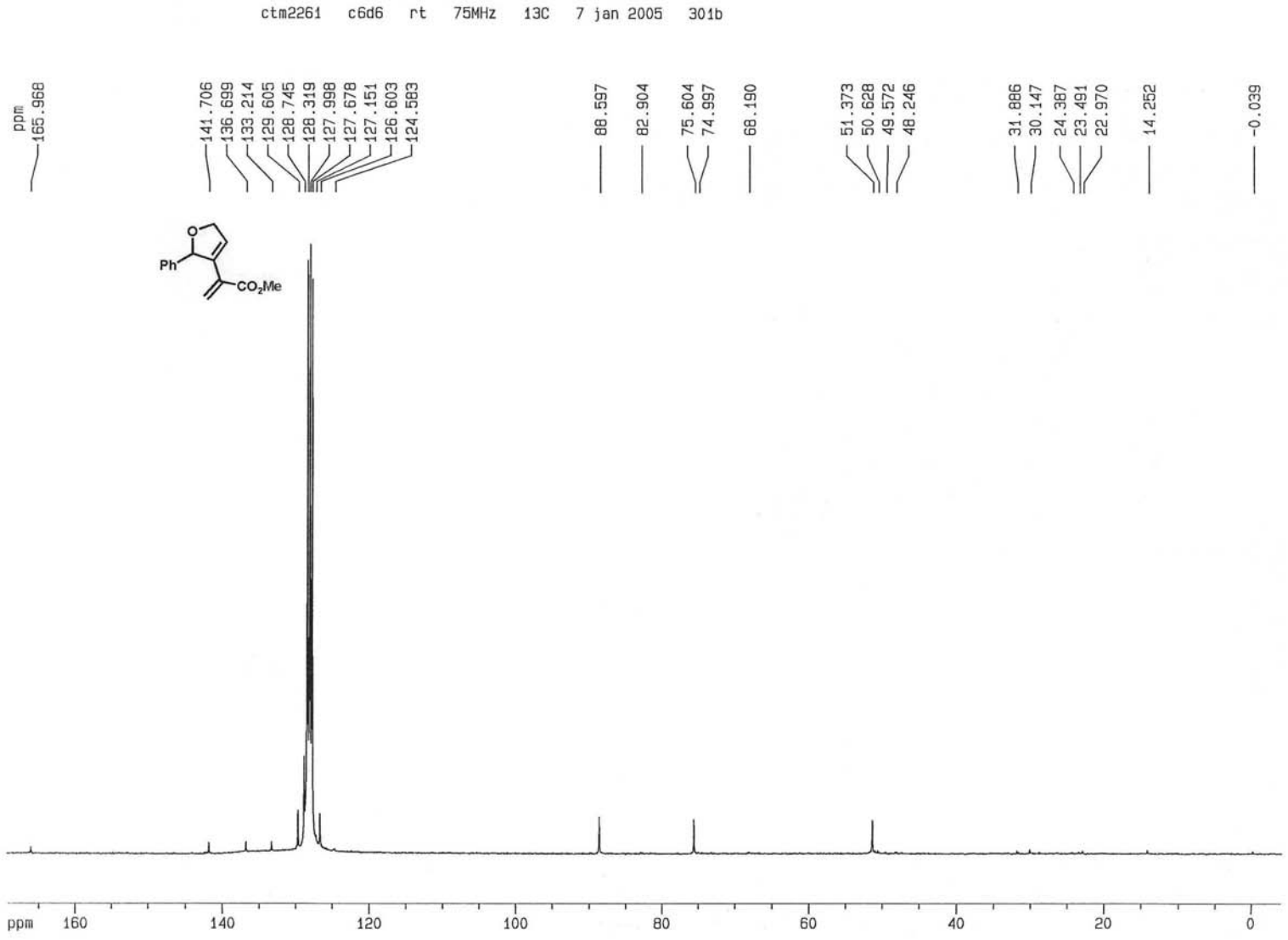
1D NMR plot parameters

CX	20.00 cm
F1P	184.225 ppm
F1	23167.73 Hz
F2P	-5.150 ppm
F2	-647.63 Hz
PPMCM	9.46874 ppm/cm
HZCM	1190.76794 Hz/cm


ctm2240 cdcl3 rt 300MHz 1H 9 dec 2004 300
ppm
7.4784
7.4724
7.3937
7.3912
7.3767
7.3737
7.3694
7.3674
7.3636
7.2605
5.3825
5.3774
5.3252
5.3199
5.3144
5.3085
5.2757
5.2707
5.2412
5.2361
4.2228
4.2182
4.2135
4.2051
4.2005
4.1956
4.1470
4.1428
4.1386
4.1265
4.1222
4.1179
4.1013
3.8228
3.8036
3.7941
3.7753
3.6271
3.5449
1.6918
1.6641
1.6124
1.5516
1.4493
1.3039
1.2812
1.2548
0.8805
0.8569
0.8310
0.1958
0.0856
0.0291
0.0248
0.0211
0.0134
0.0113
0.0081
0.0002
-0.0108
-0.0187
Integral
1.8368
2.7735
0.8284
1.1798
0.7466
0.9574
1.2136
1.1797
3.0000
Ph
O
CO2Me
ppm


ctm2245a cdcl3 rt 75MHz 13C 22 dec 2004 301b
153.580
136.709
133.592
128.876
128.687
127.354
118.267
84.969
78.537
77.422
76.999
76.576
70.202
69.691
52.745
29.658
-0.054
Ph
O
CO2Me
ppm
0
20
40
60
80
100
120
140
160

ctm2261 c6d6 rt 300MHz 1H 7 jan 2005 301b
ppm
7.2491
7.2436
7.2214
7.2173
7.1452
7.1396
7.1171
7.1114
7.0914
7.0717
7.0483
6.6602
6.6540
5.9226
5.9160
5.9114
5.8887
5.1450
4.6736
4.6708
4.6676
4.6557
4.6527
4.6495
4.6167
4.6129
4.6083
4.6063
4.6022
4.5993
4.5572
3.3671
3.3328
3.3015
3.2669
3.2596
3.2484
3.2331
3.1494
3.1028
3.0954
3.0544
3.0371
2.8283
1.4364
1.4221
1.4124
1.3598
1.2598
1.2317
1.2139
1.1998
0.9668
0.9620
0.9456
0.9353
0.9144
0.9057
0.8842
0.8607
-0.0002
Ph
CO2Me
Integral
2.0356
4.0834
0.6268
0.9514
1.2745
1.4459
1.5284
1.6444
3.0000
ppm
7
6
5
4
3
2
1
0


ctm2261 c6d6 rt 75MHz 13C 7 jan 2005 301b
ppm
165.968
141.706
136.699
133.214
129.605
128.745
128.319
127.998
127.678
127.151
126.603
124.583
88.597
82.904
75.604
74.997
68.190
51.373
50.628
49.572
48.246
31.886
30.147
24.387
23.491
22.970
14.252
-0.039
Ph
CO2Me
ppm
160
140
120
100
80
60
40
20
0

ctm2256 cdcl3 rt 300MHz 1H 3 jan 2005 301b
ppm
Integral
Ph
CO2Me
O
8.0067
8.0026
7.9975
7.9792
7.9742
7.5641
7.5395
7.4950
7.4928
7.4723
7.4674
7.4439
7.2599
7.1912
7.0783
6.9091
3.9268
3.8767
3.8587
3.8385
3.8213
3.8012
3.7829
3.6101
3.1404
3.1207
3.1019
3.0829
3.0648
3.0453
2.3668
2.3501
2.2756
2.2652
2.2274
2.1006
2.0931
2.0279
1.7357
1.6681
1.6125
1.5498
1.3065
1.2692
1.2592
0.9772
0.9553
0.9055
0.8837
0.8606
0.8328
0.0110
0.0001
0.0110
1.957
1.106
2.045
1.320
3.000
1.018
1.749
3.350
3.503
11.140
2.972
4.138
2.739

ctm2256 cdcl3 rt 75MHz 13C 3 jan 2005 300
ppm
203.144
175.733
136.508
132.970
128.611
128.430
124.272
77.421
76.999
76.576
51.723
44.048
42.169
35.521
34.617
31.574
22.633
18.659
18.622
18.143
14.075
-0.028
Ph
CO2Me
ppm

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