DISSERTATION

STUDIES TOWARDS THE TOTAL SYNTHESIS OF SPIROQUINAZOLINE

Submitted by

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In partial fulfillment of the requirements

for the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, CO

Summer, 2007

Dedication

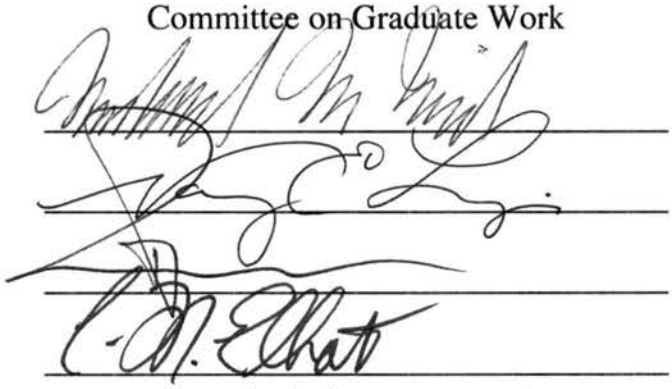
To my dad, for everything he did

COLORADO STATE UNIVERSITY

JUNE, 2007

WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY SIYUAN CHEN ENTITLED STUDIES TOWARDS THE TOTAL SYNTHESIS OF SPIROQUINAZOLINE BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work



Advisor: Robert M. Williams

Department Head: Kathy Reagan

ABSTRACT OF DISSERTATION
STUDIES TOWARD THE TOTAL SYNTHESIS OF
SPIROQUINAZOLINE

Presented herein is the synthesis of a key intermediate in the total synthesis of spiroquinazoline. By using *N*-Boc-serine as starting material, an efficient methodology has been developed to synthesize two types of δ,γ-unsaturated-α-amino acids bearing substitution at either the δ- or γ-position. After this, a novel S_N2' reaction which introduces two quaternary centers has been developed. The quinazolinone core of the molecular has been constructed.

The progress we made in those key steps paves the way to the first total synthesis of spiroquinazoline.

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Ackowledgements

First, I would like to thank Professor Robert M. Williams for giving me the opportunity to study and do research under his guidance and supervision. I also want to thank Professor Williams for granting me the freedom to develop my own ideas. I have been trained to be a good chemist from this research project. I would like to thank all other group members in Williams group for their help and support. Special thanks to Dr. Dan Fishlock, Tenaya Newkirk, O. Andrea Wong, my lab colleagues Hui Li, Carolyn Selenski, Alberto Jimmenez, Ryan Rafferty and Brandon English.

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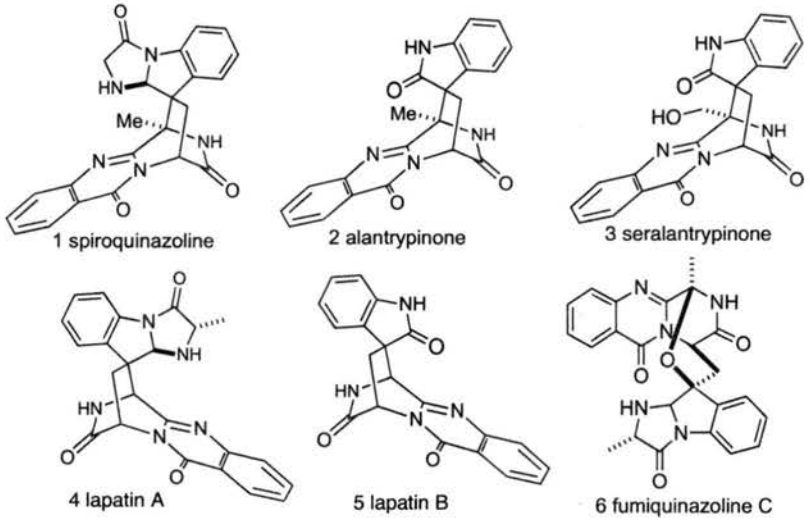
Chapter 1. Introduction

1.1 Isolation and biological studies

Substance P (SP), a member of the neurokinin family and the endogenous ligand for the neurokinin-1 (NK1) receptor, has been implicated in a number of physiological activities and is believed to play an important role in the perception of painful stimuli and inflammatory responses. [1] In 1994, Barrow reported the isolation of a new substance with a new carbon skeleton from *Aspergillus Flavipes.* [2] This natural product showed inhibition of [^{3}H]-SP binding to human astrocytoma cells with an inhibitory concentration (K_I) of 95 μM. This property renders it one of the leading products in the preparation of analgesics. The natural product was named spiroquinazoline. The structures of spiroquinazoline and some close analogues are shown in Scheme 1.

Alantrypinone is a natural product with the same carbon skeleton as spiroquinazoline, but alantrypinone has an oxindole rather than an imidazoleindoline. When alantrypinone was isolated in 1998, no biological activity was reported.[3] Three years later, Yoshihisa Ozoe *et al* performed a series of experiments to determine the potency of alantrypinone and seralantrypinone[4] in terms of their respective abilities to inhibit the specific binding of [^{3}H]EBOB (EBOB= 1-(4-ethylnylphenyl)-4-*n*-propyl-2,6,7-trioxabicyclo[2,2,2]octane) to housefly head and rat brain membranes. [5] As

shown in Figure 1, alantrypinone (PF1198A, IC_{50}=0.34 μM) inhibited [^{3}H]EBOB binding to the housefly GABA (GABA=γ-aminobutyric acid) receptor ca. 6-fold more potently than did seralantrypinone (PF1198B, IC_{50}=2.1 μM). In the rat GABA receptor, alantrypinone (IC_{50}=16 μM) was 8-fold more potent than seralantrypinone (IC_{50}=128 μM). The selectivities that those two natural products showed for housefly *versus* rat GABA receptors were ca. 47-fold and ca. 61-fold respectively (Figure 2).



Scheme 1

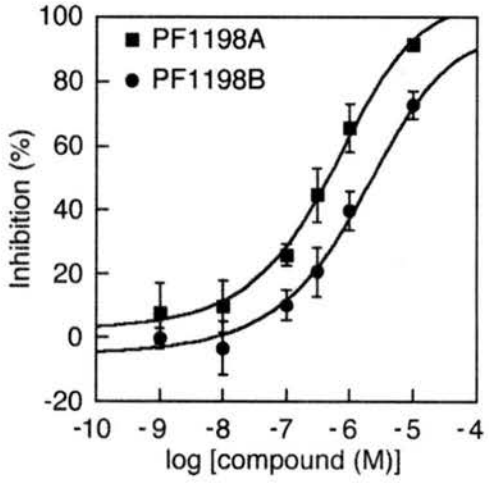


Figure 1 Inhibition of the specific binding of [^{3}H]EBOB to housefly head membranes by PF1198A (alantrypinone) and –B (seralantrypinone). *J. Agric. Food Chem.*, **2004**, *52*, 3884-3887

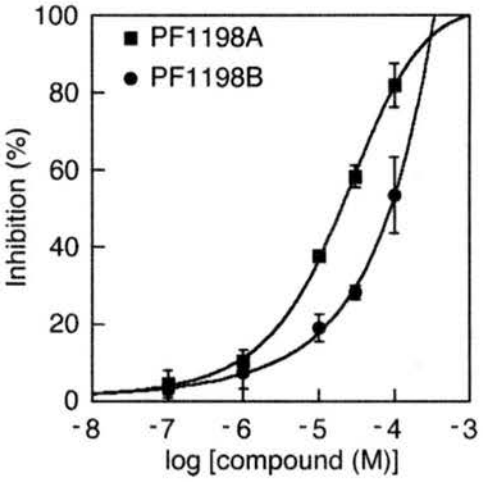


Figure 2 Inhibition of the specific binding of [^{3}H]EBOB to rat brain membranes by PF1198A (alantrypinone) and –B (seralantrypinone). *J. Agric. Food Chem.*, **2004**, *52*, 3884-3887

They then examined the two natural products in terms of their insecticidal activity. In assays using agricultural pest insects, both in the range of 100-500 ppm showed significant insecticidal activity against aphids. Again, alantrypinone was found to be more potent than seralantrypinoe in insecticidal assays using aphids (Figure 3).

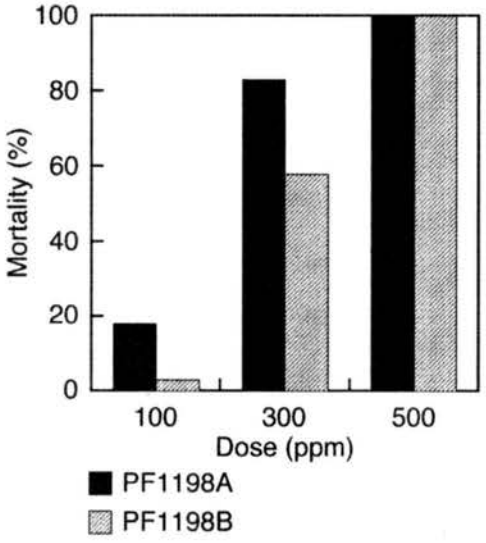


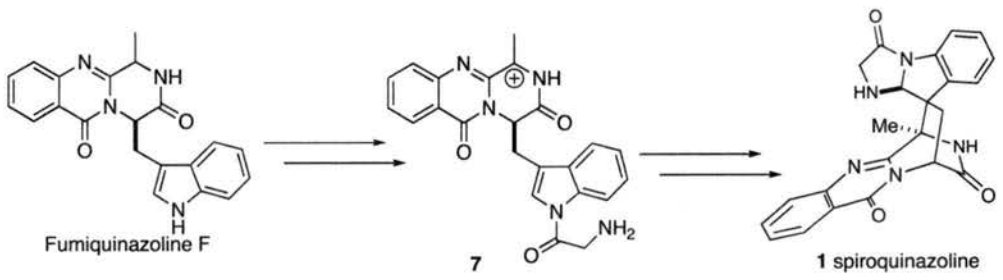
Figure 3 Insecticidal activity of PF1198A (alantrypinone) and -B (seralantrypinone) against aphids. *J. Agric. Food Chem.*, **2004**, *52*, 3884-3887

Lapatin A and B are two natural products recently discovered by Larsen and coworkers. [6] Lapatin A appears to be the enantiomer of spiroquinazoline; however the substituted methyl group is actually in a different position. Lapatin B appears to be the enantiomer of alantrypinone; however it is actually lacking one methyl group. Fumiquinazoline C[7] has a [2,2,3] bridged cycle rather than a [2,2,2] system. With an extra oxygen fumiquinazoline C has a seven-membered ring.

It should be pointed out that reported research on all aspects of spiroquinazoline, such as its biological mechanism, biosynthesis and total synthesis is limited. Until today, nobody has reported the total synthesis of spiroquinazoline. In 1999, Hart reported a total synthesis of (-)-alantrypinone by using an iminium ion generation-indole spirocyclization–intramolecular azomethine trapping cascade. [8,9] Similar chemistry was used by Snider in the total synthesis of fumiquinazoline C, another relative of spiroquinazoline. [10,11]In 2004, Kende reported a total synthesis of (±)-alantrypinone using an intramolecular Diels-Alder reaction. [12,13] First, we will have an overview of the syntheses of those close analogues; then we will discuss some synthetic studies of spiroquinazoline by Hart's research group.

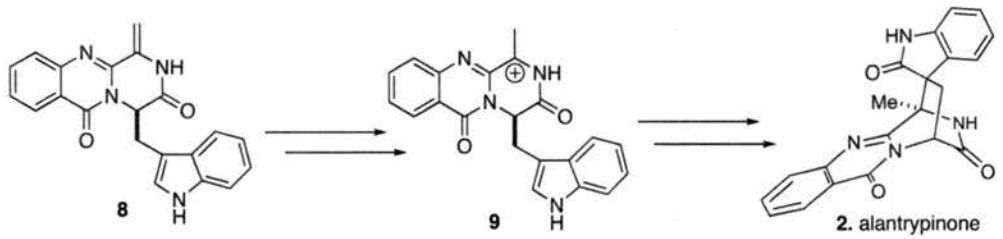
1.2 Hart's Synthesis of (-) Alantrypinone[8,9]

Hart's group spent years on the synthesis of spiroquinazoline. They imagined that nature might produce spiroquinazoline by an oxidative cyclization of fumiquinazoline F *via* the formal equivalent of an *N*-acyliminium ion of type **7** (Scheme 2).



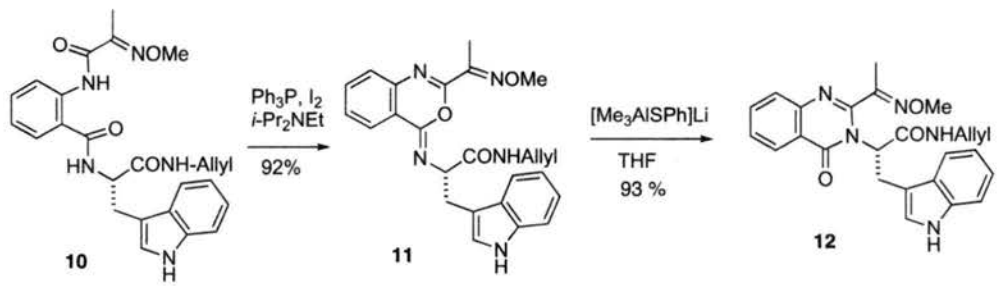
Scheme 2

Alantrypinone is a structurally simpler relative of spiroquinazoline. Hart envisioned that it could be produced *via* a similar oxidative cyclization (Scheme 3).



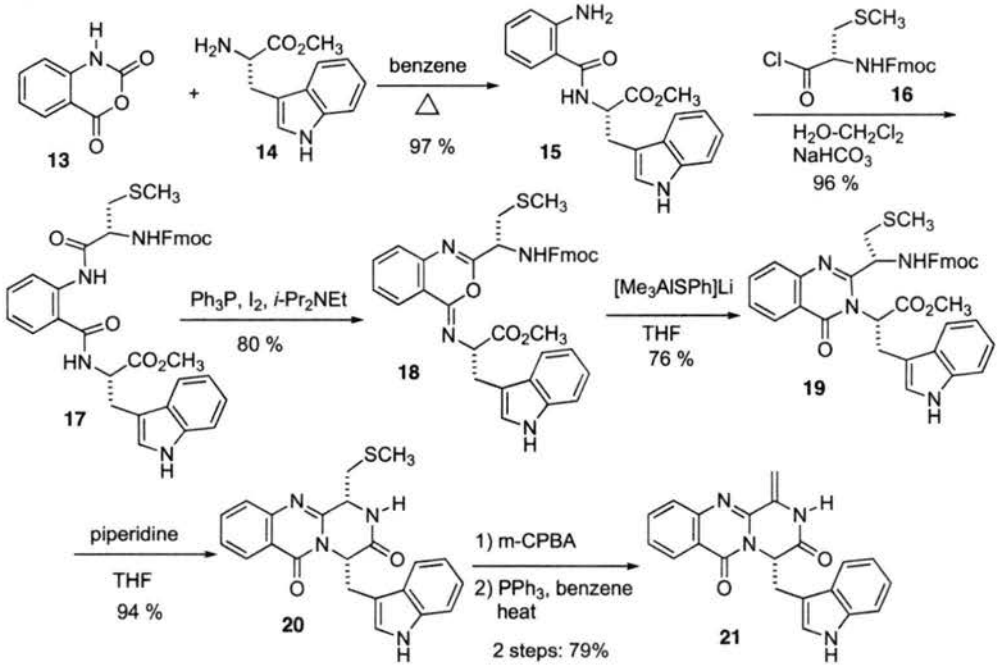
Scheme 3

It seems that the synthesis of alantrypinone is simplified to the synthesis of **9**. In Hart's story, they spent a long time finding a way to synthesize **9**. Although they could make compound **12,** they were unable to achieve cyclization, even under such drastic conditions as reflux in $CHCl_3$-TFA mixture (Scheme 4).



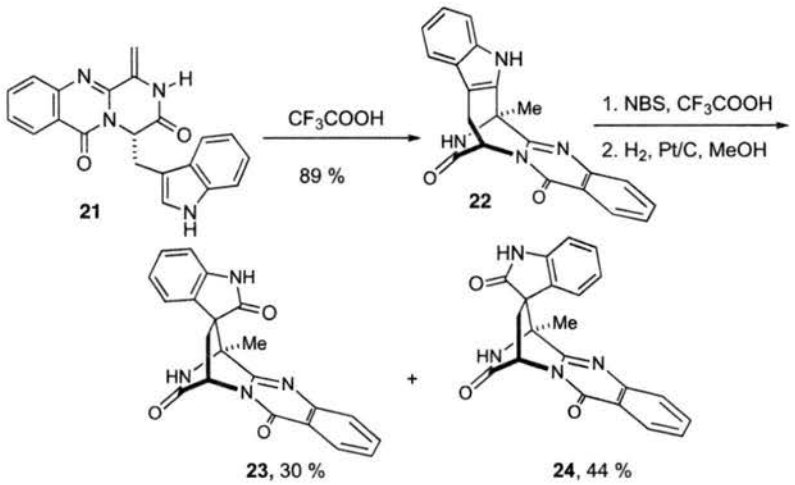
Scheme 4

Their successful synthesis of (-)-alantrypinone is shown in Schemes 5 and 6. Their synthesis started with isatoic anhydride **13**. Coupling between isatoic anhydride **13** and the methyl ester of (*S*)-(-)-tryptophan **14** in benzene gave dipeptide **15** in 97% yield. Reaction of dipeptide **15** with acid chloride **16** derived from *N*-Fmoc-*S*-methylcysteine under Schotten-Baumann conditions gave tripeptide **17** in 96% yield. Cyclization of **17** to benzoxazine **18** was accomplished by treatment with PPh_3-I_2 and Hünig's base in CH_2Cl_2. Treatment of **18** with [Me_3AlSPh]Li in THF gave compound **19** in 76%, which was then converted into quinazolinone **20**. Oxidation of **20** with *m*-CPBA, followed by treatment with PPh_3, gave enamide **21**.



Scheme 5

The next step was the key step. A tertiary carbocation was formed from the terminal alkene in **21** when **21** was treated with TFA. The carbocation was captured by the indole in an intramolecular reaction to afford bridged core **22** in 89% yield. Treatment of **22** with NBS, followed by hydrogenolysis gave a mixture of (-) alantrypinone **23** and 17-epi-alantrypinone **24** in 30% and 44% yields, respectively. We should notice that what they obtained was the enantiomer of (+)-alantyrpinone, the natural product. So we used a different number to denote it. The conversion of **22** to **23+24** was shown to involve rapid formation of a mixture of diastereomeric bromoindoles followed by slower conversion to a mixture of 23-bromo-**23** and **24**. They used hydrogenolysis to remove those aromatic bromine atoms.

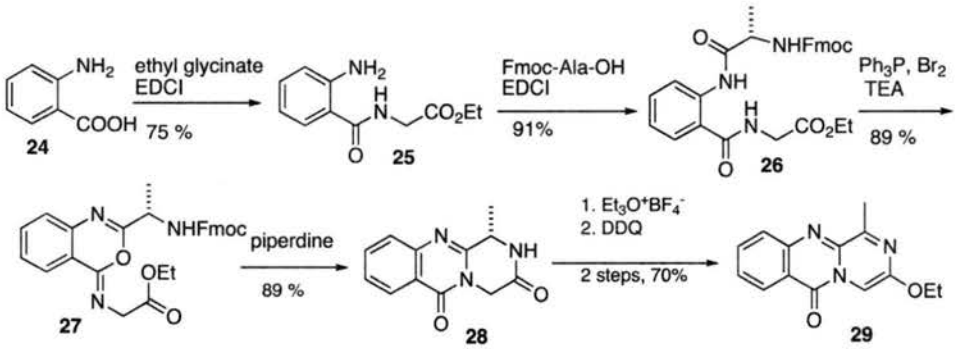


Scheme 6

1.3 Kende's Synthesis of (±) Alantrypinone[12,13]

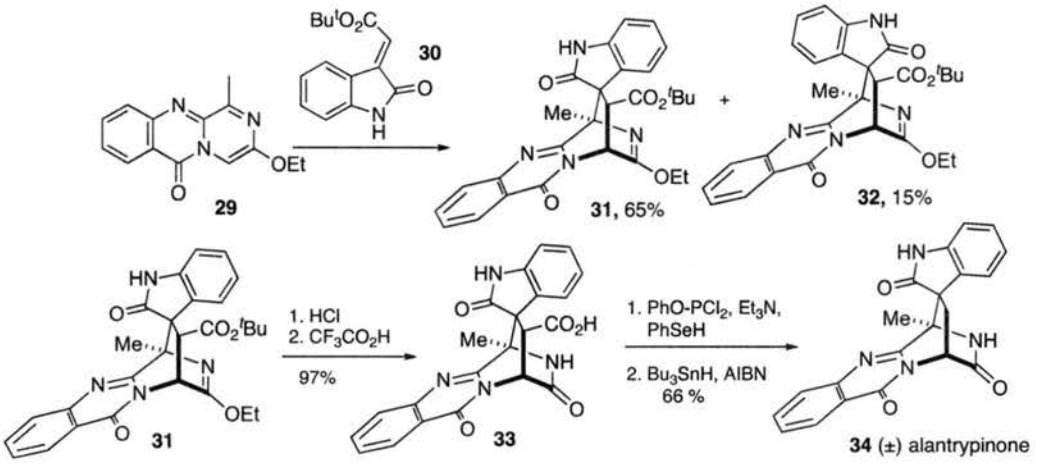
In 2004 Kende and coworkers reported a racemic synthesis of alantrypinone using an intermolecular Diels-Alder reaction. The first part of Kende's synthesis is similar to Hart's synthesis (Scheme 7). Kende's synthesis started with anthranilic

acid, which was coupled with ethyl glycinate using EDCI to provide amide **25**. Compound **25** was then coupled with Fmoc-Ala-OH using EDCI in CH_3CN to produce protected diamide **26** in 68% overall yield. Treatment of compound **26** with Ph_3P and Br_2 and Hünig base led to the corresponding imino benzoxazine **27**. Imino benzoxazine **27** was treated with piperidine to produce the desired tricyclic dione **28** in 79% yield for two steps. Tricylclic dione **28** was treated with triethyloxonium fluoroborate in the presence of sodium carbonate in CH_2Cl_2 to give 85% of an imino ether. A gentle oxidation of the imino ether was accomplished by refluxing with DDQ in benzene to produce azadiene **29** as a stable, crystalline solid.



Scheme 7

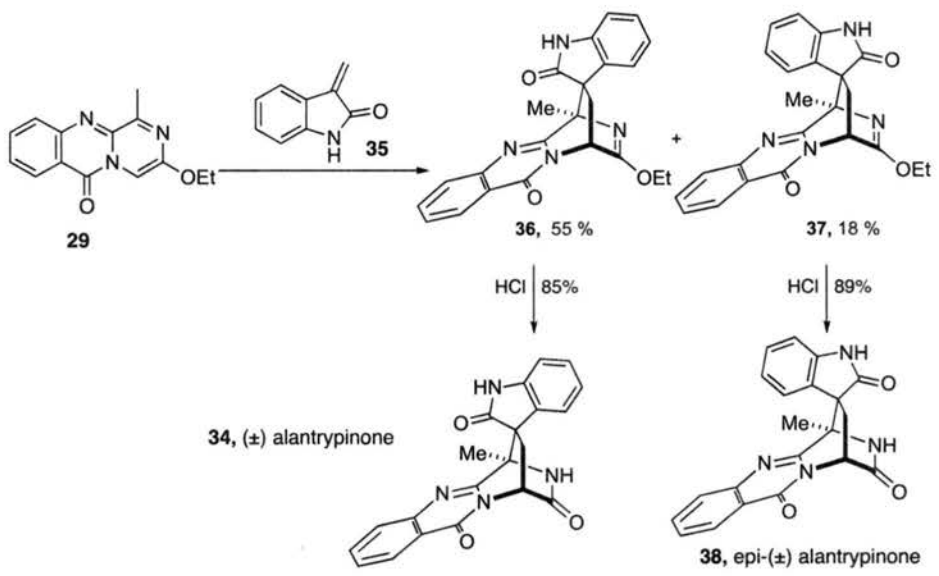
A Diels-Alder reaction between the azadiene **29** and dienophile **30** provided the desired regio chemistry and good *exo* selectivity (Scheme 8). The methyl lactim ether was deprotected by treatment with HCl in ethyl acetate. The *tert*-butyl ester was converted to the acid **33** by treatment with TFA. The acid was then transformed into the corresponding phenylselenyl ester, followed by reduction with *n*-Bu_3SnH and AIBN to produce (±) alantrypinone **34**. We shall notice that what they obtained is a racemic mixture.



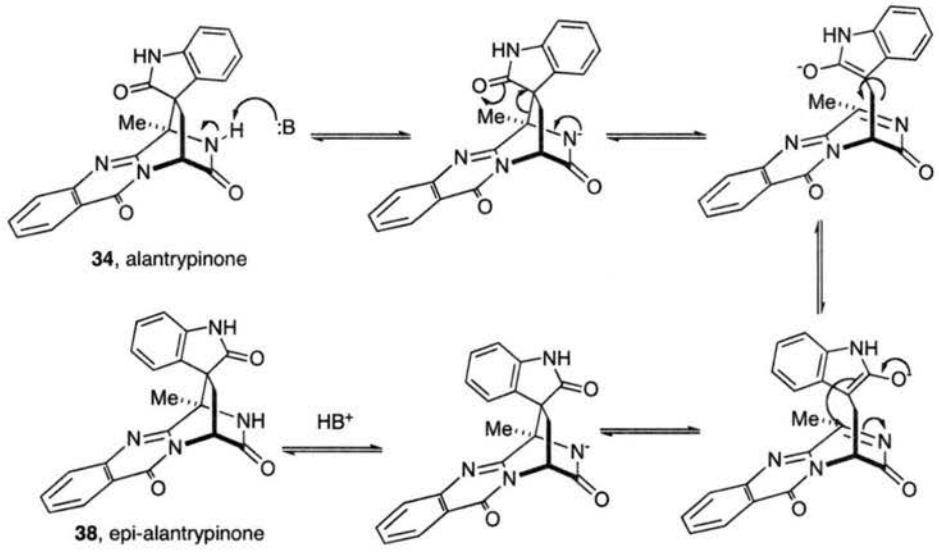
Scheme 8

From these Diels-Alder reactions, it seems that the azadiene **29** is an active diene that might be directly reacted with 3-methyleneoxindole. As expected, an aza Diels-Alder reaction between diene **29** and 3-methyleneoxindole **35** proceeded readily in chloroform at room temperature to produce *exo* isomer **36** in 55% yield and *endo* isomer **37** in 18% yield, as shown in Scheme 9. The *exo* isomer was converted into (±) alantrypinone **34** in good yield.

Kende and coworkers also found a thermal equilibration between (±)-alantrypinone **34** and (±)-epi-alantrypinone **38** under basic condition. When **38** was heated to 100 °C in the presence of a small amount of DBU in DMSO, 75% of **38** was converted to **34**. When **34** was heated to the same temperature at the presence of DBU, the same ratio (3:1) of **34** to **38** was again generated. This interesting epimerization may occur through an anionic retro-Mannich reaction (Scheme 10).



Scheme 9

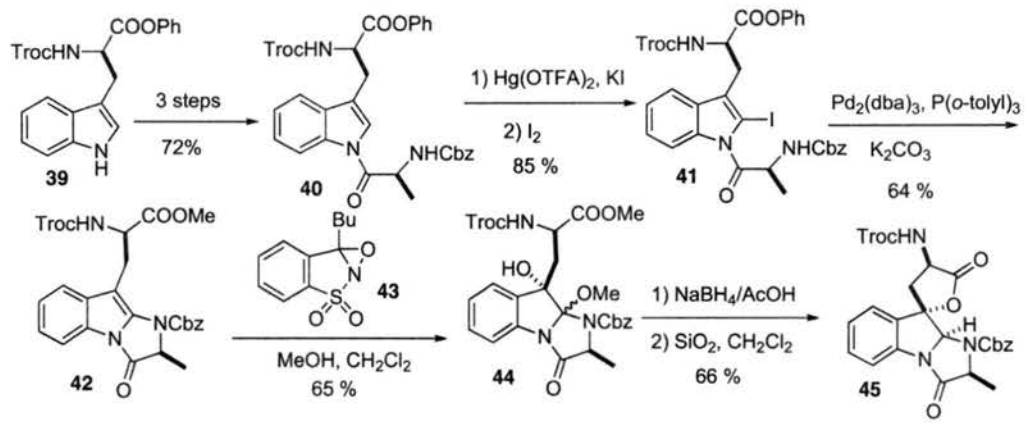


Scheme 10

1.4 Snider's synthesis of fumiquinazoline C[10,11]

Fumiquinazolines A-I are a group of natural products built upon [2, 1-b]-quinazoline-3,6-dione. Among this group of natural products, fumiquinazoline C is the closest analogue of spiroquinazoline. Instead of a [2,2,2] bridged system fumiquinazoline C has a [2,2,3] ring system, which consists of a seven-membered ether ring. That is the major structural difference between spiroquinazoline and fumiquinazoline C. Schemes 11 and 12 show the total synthesis of this natural product by Snider's research group. Snider's synthesis is also based on cation chemistry. In Hart's synthesis of alantrypinone, the cation was captured by the indole ring. In Snider's synthesis of fumiquinazoline C, the cation was captured by a hydroxyl group.

Their synthesis started with *N*-acylindole **40** which could be prepared from D-tryptophan **39** in 3 steps (Scheme 11). Mercuration of **40** with $Hg(OTFA)_2$ followed by iodination gave 85% of iodoindole **41**. Compound **41** then underwent a Buchwald palladium-catalyzed cyclization to afford 64% of **42.** Epoxidation of **42** with the saccharine-derived oxaziridine **43** yielded 65% of **44** as a mixture of diastereomers. Reduction of **44** with $NaBH_4$, followed by lactonization with silica gel in CH_2Cl_2 for 12 h to gave 66% of **45**.

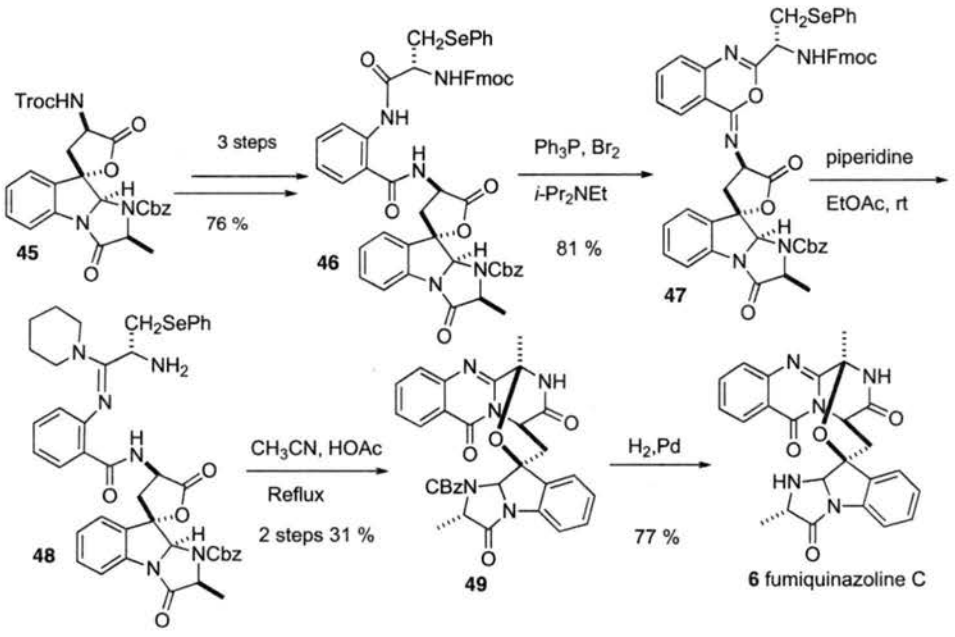


Scheme 11

Reductive deprotection of Troc in **45** with Zn in AcOH afforded an amine, which was coupled with anthranilic acid to yield a dipepetide (Scheme 12). A second coupling of this dipeptide with FmocNHCH(CH_2SePh)CO_2H yielded tripeptide **46**. Treatment of **46** with Ph_3P and Br_2 in the presence of Hünig base provided 76% of iminobenzoxazine **47**. Reaction of **47** with 10 equivalents of piperidine in EtOAc at 25 °C for 10 minutes generated crude amidine amine **48**, which was refluxed in CH_3CN and acetic acid for 2 hours to give 65% of Cbz-fumiquinazoline **49**.

Heating crude **49** in 25:1 CH_3CN/HOAc at reflux for 2 h formed a mixture of Cbz-dehydrofumiquinazoline A (56%) and Cbz-fumiquinazoline C (14%). Further heating in CH_3CN/HOAc converted more of the former product to the latter. Under these reaction conditions, **49** underwent four sequential reactions. First, the amidine amide cyclized to form the quinazolinone. The amine lactone then reacted to give the piperazine ring. At this point, benzeneselenol was eliminated without the need for oxidation to the selenoxide. Finally, under the acidic conditions, the double bond was

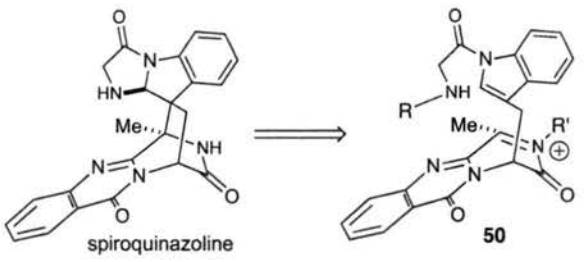
protonated to give a cation that reacted with the alcohol to form the seven-membered ether ring of fumiquinazoline C.



Scheme 12

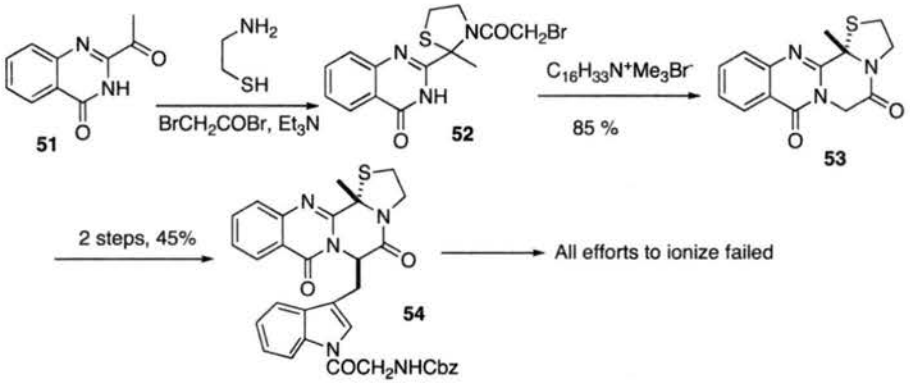
1.5 Hart's studies towards the total synthesis of spiroquinazoline[14,15]

Hart's research group has spent years trying to synthesize spiroquinazoline. They first pursued a biomimetic approach to spiroquinazoline that involved a projected cascade cylization of an N-acryliminium ion as shown in Scheme 13.



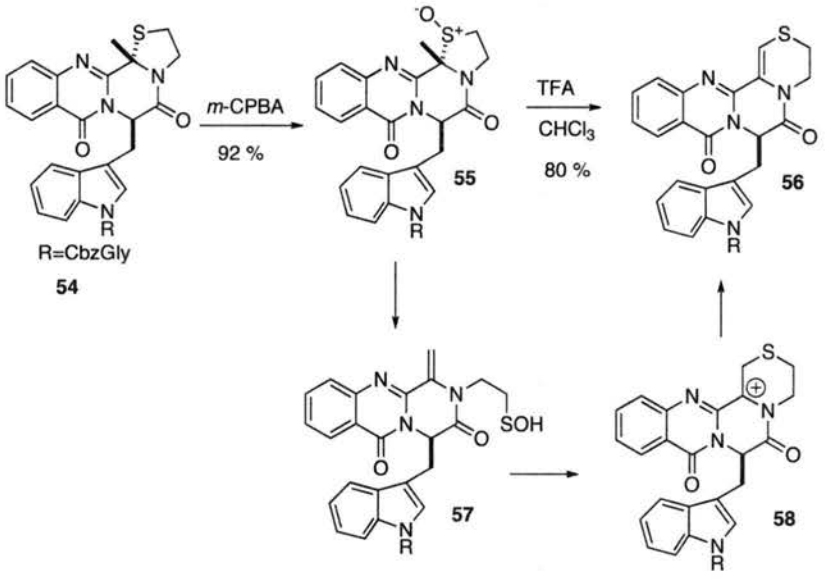
Scheme 13

Their initial target for synthesis was compound **54** (Scheme 14). It was imagined that ionization of the C-S bond would provide an *N*-acyliminium ion of type **50**. Treatment of **51** with 2-aminoethanethiol followed by α-bromoacetyl bromide under basic conditions gave **52**. Addition of hexadecyltrimethylammonium bromide provided **53**. Sequential treatment of **53** with LDA and Li_2CuCl_4 in THF at -78 °C followed by addition of gramine methosulfate provided **54**. All attempts to ionize **54** using a variety of electrophiles such as iodomethane, silver triflate and mercuric triflate have failed.



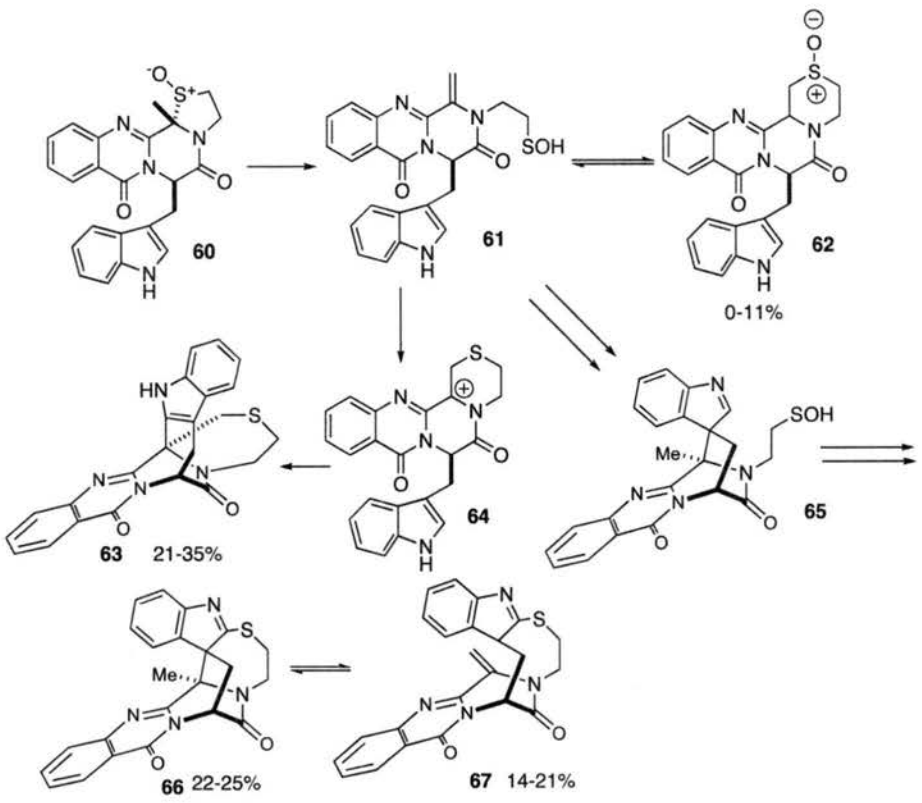
Scheme 14

Compound **54** was then oxidized to sulfoxide **55** by *m*-CPBA (Scheme 15). Compound **56** was formed in 80% when compound **55** was refluxed with TFA in $CHCl_3$. The mechanism of the formation of **56** is also shown in Scheme 15. In this process, compound **55** underwent an elimination reaction to generate compound **57**. Protonation followed by electrophilic addition of the sulfenic acid to the resulting olefin generated an *N*-acyliminium ion **58** which led to compound **56** by a loss of a proton.



Scheme 15

It seems that *N*-acylindole was too electron deficient to participate in an electrophilic aromatic substitution reaction under the sulfoxide rearrangement conditions. The indole sulfoxide **60** without *N*-acryl group was then examined (Scheme 16). The indole sulfoxide was treated with TFA in $CHCl_3$ at reflux to give a complex mixture. This products included sulfoxide **62** (0-11%), bridged indoles **63** (21-35%) and **67** (14-21%), and spiro indoline **66** (22-25%).

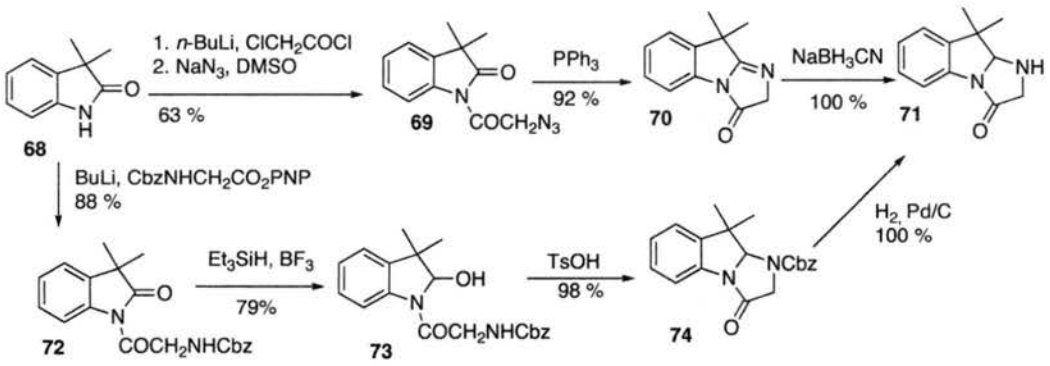


Scheme 16

Sulfenic acid **61** was first generated from **60**. Addition of sulfenic acid **61** to the resulting double bond provided sulfoxide **62**. Addition of the sulfenic acid to the olefin, followed by an electrophilic aromatic substitution reaction provided **63**. The *N*-acryaminium ion formed by addition of the sulfenic acid to the olefin was trapped by C-3 of indole to provide indoline **65**. Addition of the sulfenic acid to the azomethine followed by a Pummerer reaction provided **66**. Fragmentation after protonation of the indoline nitrogen produced **67**. Hart's study demonstrated that an iminium ion generation-indole spirocyclization–intramolecular azomethine trapping cascade was feasible. Indeed, some redesign based on this chemistry had led to the

first synthesis of alantrypinone. However, using this strategy to build the imidazoleindoline ring system is still a big challenge.

It seems hopeless to pursue a total synthesis of spiroquinazoline directly on the basis of iminium cation chemistry mentioned ealier. Another option is to convert alantrypinone to spiroquinazoline by building imidazoloindoline on from the oxindole. To examine the feasibility of this option, Hart's group started with a model study on the transformation of 3,3-dimethyloxindole to imidazoloindoline (Scheme 17).



Scheme 17

Their initial studies focused on the transformation of 3,3-dimethyloxindole to imidazoloindoline and involved an intramolecular Staudinger reaction. Thus, the anion derived from deprotonation of known oxindole **68** was acylated using α-chloroacetyl chloride followed by treatment with sodium azide in DMSO and gave **69** in 63% yield. Treatment of **69** with triphenylphosphine provided the expected intramolecular Staudinger product **70** in 92% yield. Borch reduction of **70** with sodium cyanoborohydride completed the desired four-step annulation and provided **71** in quantitative yield.

An alternative method for converting **68** into **71** involved initial acylation of the anion derived from **68** with *p*-nitrophenyl *N*-Cbz–glycinate to provide imide **72** in 88% yield. Saturation of a dichloromethane solution of **72** with BF_3 gas at –78 °C in the presence of triethylsilane (2 equiv), followed by gradual addition of another 4 equivalents of triethylsilane and an aqueous workup gave carbinol **73** in 79% yield. Treatment of **73** with *p*-toluenesulfonic acid in benzene provided **70**, and hydrogenolysis of the *N*-Cbz group provided **71** in 98% overall yield.

All attempts to apply the annulation methods described above for the conversion of alantrypinone to spiroquinazoline have thus far met with failure. For the first strategy, although they were able to prepare the appropriate acylated substrates from alantrypinone by treatment with α-chloroacetyl chloride followed by treatment with sodium azide, they were not able to accomplish the key aza-Wittig reaction. Instead, the deacylation reaction became the dominant reaction. For the second strategy, the method that relies on the regioselective reduction of imide **72** provided a complex mixture of unidentifiable products when applied to an appropriate alantrypinone derivative. It is not surprising that the amide and C=N bond in quinazolinone core may interfere with the reduction and make the reaction messy.

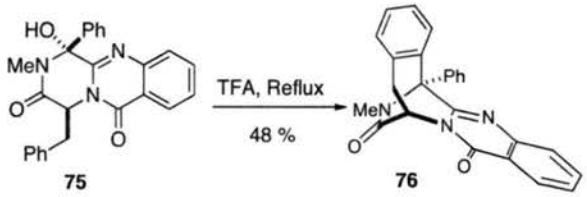
Our goal is to design and implement a total synthesis of spiroquinazoline on the basis of available knowledge of synthetic organic chemistry. From Hart's study we realize that we only have two options: (1) find a strategy to synthesize spiroquinazoline without going through alantrypinone; (2) design a new synthesis of alantrypinone, and a unique method to convert alantrypinone to spiroquinazoline. When we design our synthesis, we must consider a way to construct

bicyclo[2,2,2]diazaoctane and the quinazolinone core. Below is a summary of the options we may have for those two key steps.

1.6 Strategies to construct bicyclo[2,2,2]diazaoctane

(1) Chemistry based on *N*-acyliminium ion

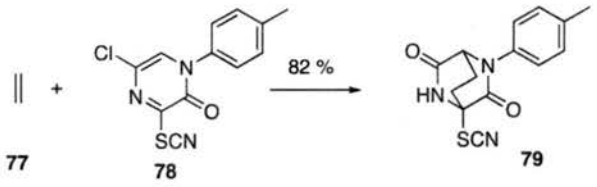
As we discussed above, the *N*-acyliminium ion may be generated by treatment of an olefin with an acid. The cation may be captured by a hydroxyl group, as shown by Snider in the synthesis of fumiquinazoline C. The cation may also be captured by an indole, and this strategy was utilized by Hart to synthesize alantrypinone. However, Hart's study showed that an *N*-acyindole was too electron-deficient to capture the cation. On the other hand, not only the electron-rich indole may capture this cation, but a phenyl without any electron rich subsituent can also capture the cation efficiently (Scheme 18). [16]



Scheme 18

(2) Diels- Alder reaction

The first example of a Diels-Alder reaction of olefin with 2-(1*H*)-pyrazinones was reported in 1991. [17] In the following example, a new and versatile route to 2,5-diazabicyclo[2,2,2]octane-3,6-diones has been developed proceeding through cycloaddition of ethane to 2(1*H*)-pyrazinones (Scheme 19).

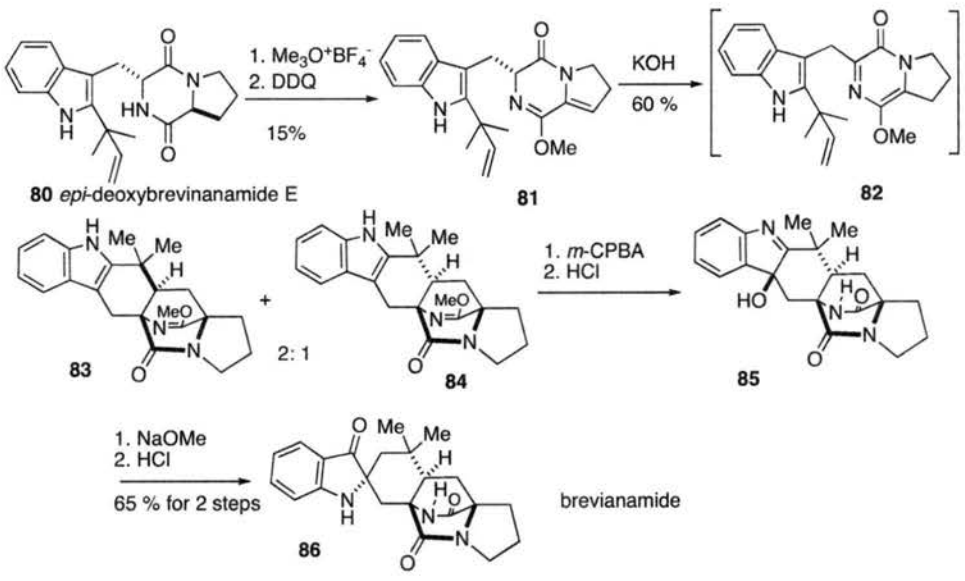


77 78 79

Scheme 19

An intermolecular Diels-Alder reaction of this type has led to a concise total synthesis of alantrypinone by Kende. It should be pointed out that intramolecular Diels-Alder reactions have been used to synthesize paraherquamides, brevianamides and asperparalines by our group. Scheme 20 shows a biomimetic total synthesis of racemic brevianamide. [18]

9-*epi*-Deoxybrevianamide E (**80**) was synthesized according to Kametani's procedure. [19] This substance was converted into a lactim ether, which was then oxidized to unsaturated compound **81** with DDQ. Treatment of this compound with KOH produced labile azadiene **82**, which cyclized to give a mixture of **83** and **84**. Oxidation of **84** by *m*-CPBA followed by Pinacol-type rearrangement produced brevianamide **86** in 65% yield.



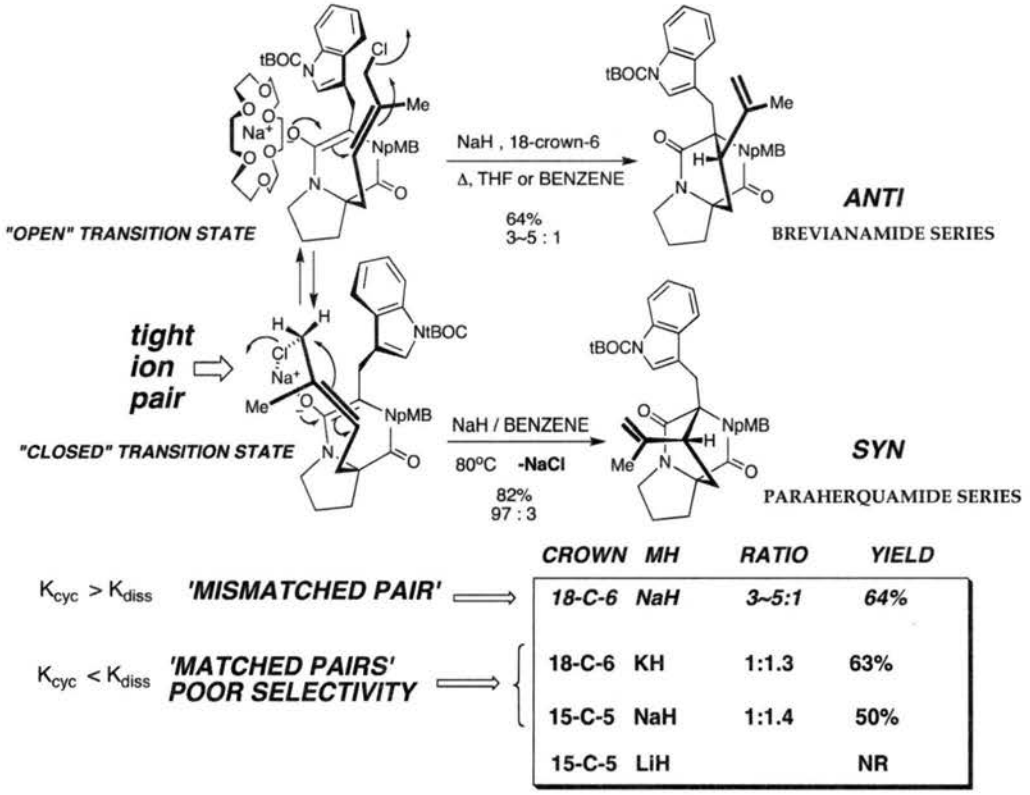
Scheme 20

(3) S_N2'reaction.

Both the Diels-Alder reaction and chemistry based on *N*-acyliminium ion are versatile tools to construct bridged cycles. Both of these two tools also have their limits. The Diels-Alder reaction can only lead to racemic products. Capturing of an *N*-acyliminium ion by another unit intramolecularly usually only leads to [2,2,3] bridged systems, meaning further transformation is required. For example, Hart's group used an NBS promoted rearrangement to convert the [2,2,3] bridge system to the correct [2,2,2] ring system. The selectivity of the rearrangement is not ideal.

To avoid the shortcomings of those two strategies, we are interested in another strategy to build bicyclo[2,2,2]diazaoctane: an S_N2' reaction. The Williams research group has been using this powerful tool in the total synthesis of natural products since 1990.[20]

Different conditions have been examined by Williams' group to observe the affect on the facial selectivity of the S_N2' reaction (Scheme 21). [21] It was found that, in the presence of a polar solvent such as DMF or a metal-complexing ligand such as 18-crown-6, the *anti* product predominated, whereas in a nonpolar solvent such as benzene, the diastereoselectivity was completely reversed to favor the *syn* relative stereochemistry.

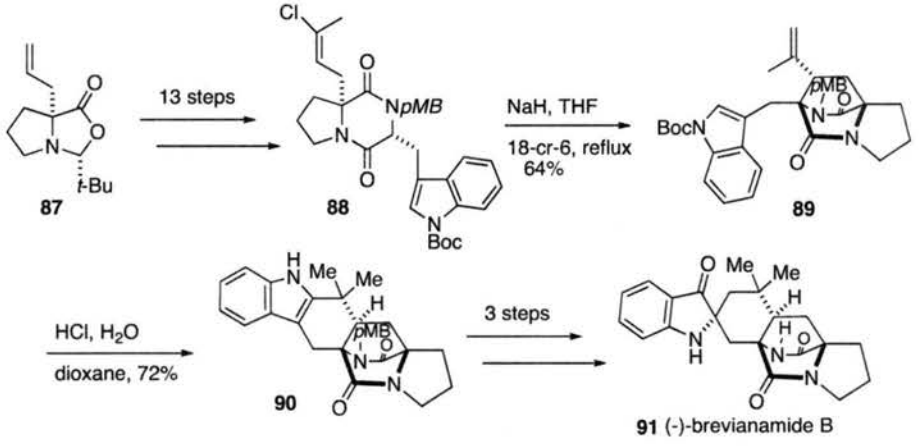


Scheme 21

These results were rationalized in term of "open" and "closed" transition states, as illustrated in Scheme 21. In the presence of a strongly coordinated species, a ligand sphere surrounds the enolate metal counterion and sterically forces the allylic chloride to adopt an "open" transition state, whereas in a nonpolar solvent, the

counter ion and chloride leaving group form a tight, intramolecular contact ion-pair and the reaction takes place through a "closed" transition state. However, better selectivity for the *anti* diastereomer is obtained when the metal ion and the ligand are "mismatched", e.g., Na^+ with 18-crown-6. When the pair is "matched", e.g., Na^+ with 15-crown-5, the metal ion is coordinated so strongly that it is separated from the enolate faster than S_N2' cyclization can take place, and the reaction exhibits poor selectivity.

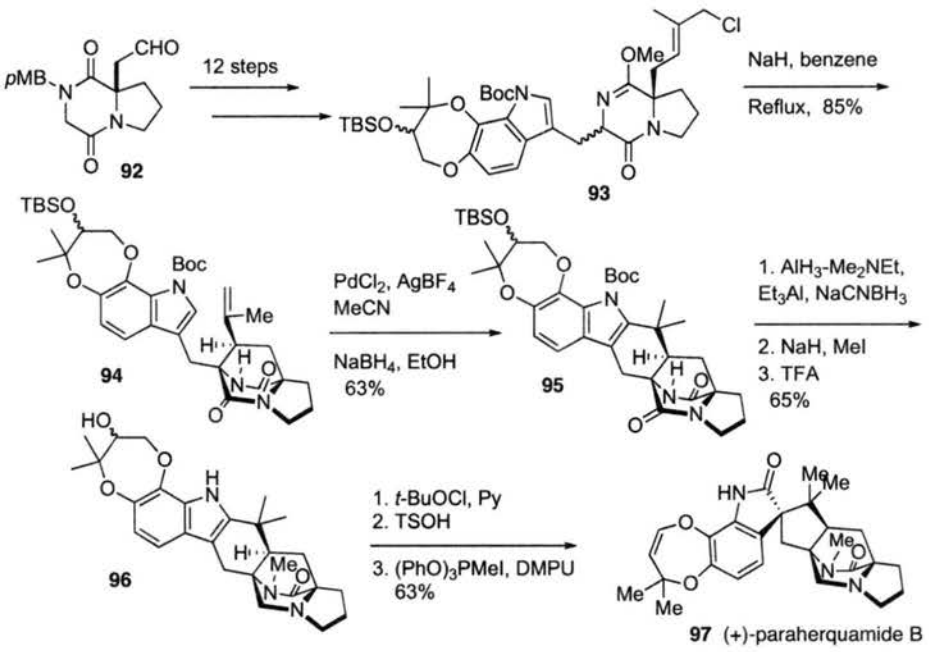
The intramolecular S_N2' cyclization was exploited in the asymmetric total synthesis of (-)-brevianamide B, as illustrated in Scheme 22. Allyl chloride **88** can be synthesized from **87**. The key intramolecular S_N2' cyclization furnished the bicyclo[2,2,2]diazaoctane core **89**. Olefin-cation cyclization with concomitant removal of the Boc protecting group gave the hexacyclic compound **90**. The remaining part of the synthesis followed similar protocols in shown in Scheme 20.



Scheme 22

The intramolecular S_N2' cyclization was also exploited in the asymmetric total synthesis of (+)-paraherquamide B.[22] As illustrated in Scheme 23, allylic chloride **93**

could be prepared from known piperazinedione **92**. The key intramolecular S_N2' cyclization furnished the bicyclo[2,2,2]diazaoctane nucleus **94**. Olefin-cation cyclization with concomitant removal of the Boc protecting group gave the heptacyclic compound **95**. Reduction of the tertiary amide, followed by introduction of the methyl group and deprotection of the Boc group afforded compound **96**. Chlorination by *t*-BuOCl to chloroindolenine followed by rearrangement led to oxindole. Dehydration of oxindole by $(PhO)_3PMeI$ in DMPU yielded paraherquamide B **97**.

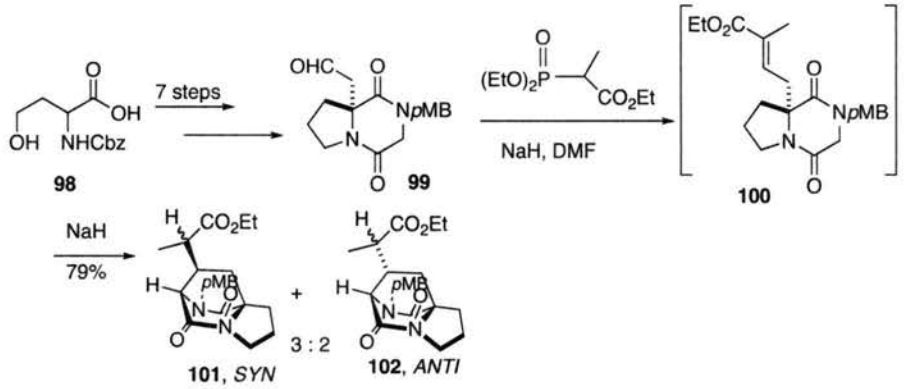


Scheme 23

(4) Intramolecular Michael Addition

This reaction was also reported by Williams' group (Scheme 24). [23] So far it has not been used in any natural product synthesis. Substituted diketopiperazine **99**

was constructed in seven steps from (±)-*N*-Cbz homoserine **98**. A Horner-Wadsworth-Emmons olefination procedure provided unsaturated ester **100**, which cyclized immediately to form a pair of diastereomers **101** and **102**.

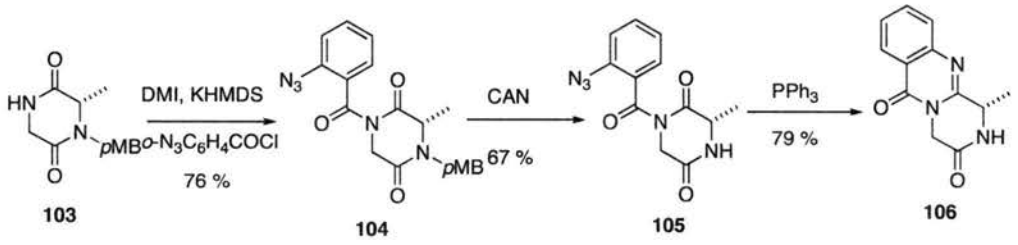


Scheme 24

1.7 Strategies to construct the quinazolinone core

(1) aza –Wittig reaction: [24]

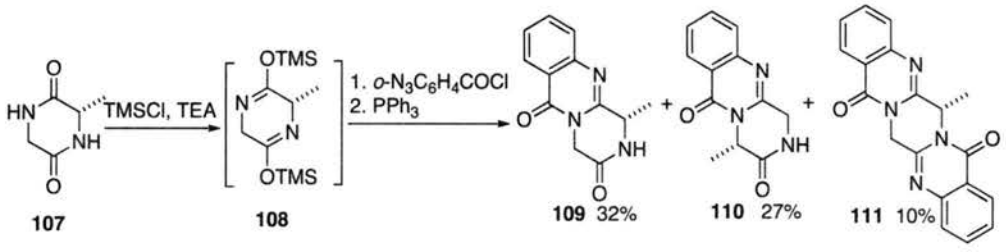
In this case, a simple model **103** was first treated with KHMDS and then with *o*-azidobenzoyl chloride in the presence of DMI (1,3-dimethyl-2-imidazolidinone) to produce compound **104**. Oxidative debenzylation by CAN generated compound **105**. An aza-Wittig reaction on compound **105** produced the quinazolinone core structure **106** (Scheme 25).



Scheme 25

(2) A modified aza-Wittig strategy[24]

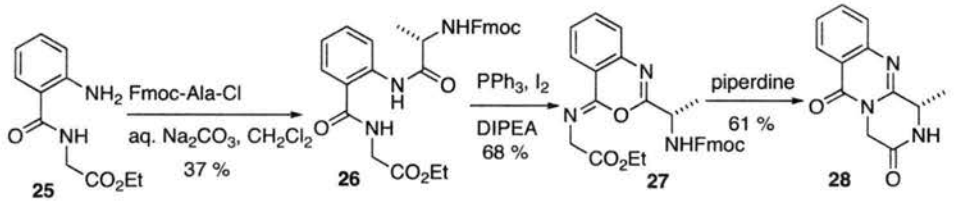
The strategy shown in Scheme 26 is less satisfactory than the one described above. Diketopiperazine **107** was first converted to a labile species: bis(trimethylsilyloxy)-dihydropyrazine **108**. This species was treated with *o*-azidobenzoyl chloride and then with PBu_3 to give a mixture of three compounds. Due to the generation of two unfavorable by-products, the yield was low and purification was troublesome.



Scheme 26

(3) Strategy using benzoxazine

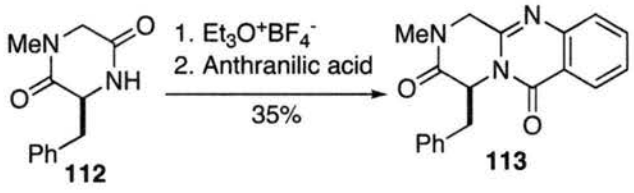
This strategy has been described above in Hart and Kende's syntheis of alantrypinone and Snide's syntheis of fumiquiazoline C. For the purposes of summary and comparision, the strategy is shown in the Scheme 27. As we can see, all three research groups have modified the original strategy to meet their needs



Scheme 27

(4) Strategy using lactim ether

A direct condensation of lactim ether with anthranilic acid may also produce quinazolinone (Scheme 28),[16] but the yield is usually low.



Scheme 28

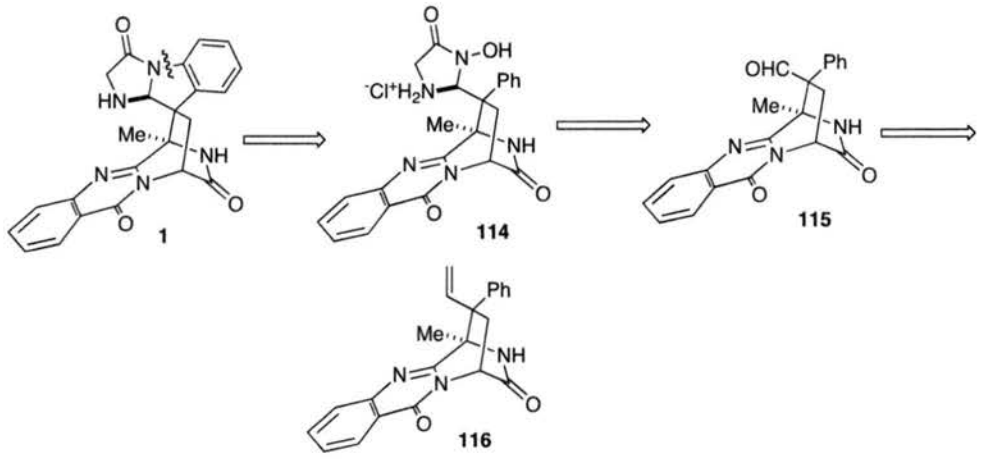
Chapter 2. Results and Discussions

2.1 Synthetic Considerations

We have learned some strategies to build bicyclo[2,2,2]diazaoctane and quinazolinone core. Now we can use the knowledge to do some synthetic analysis of spiroquinazoline.

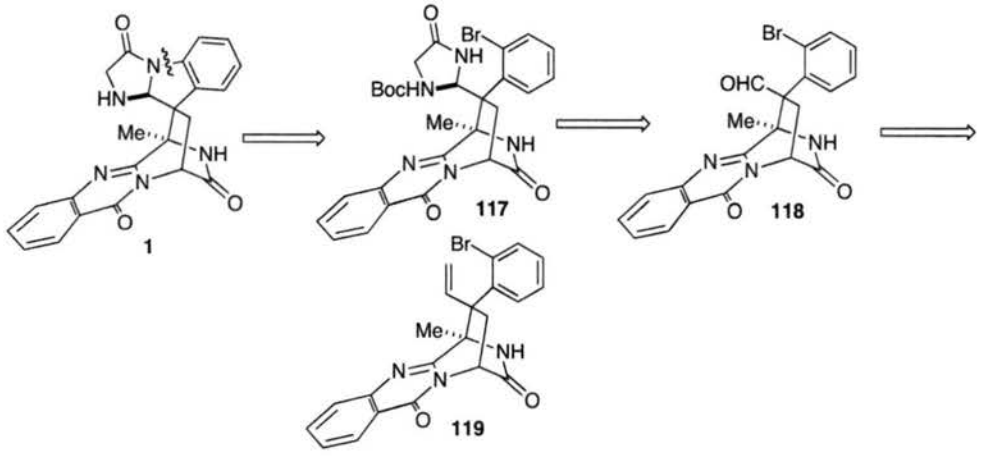
The first disconnection could be on any bond of the imidazoleindoline. There are different possible diconnections depending on the kind of substrate we wish to obtain. The first possiblee disconnection is on the N-C bond in imidazoleindoline (Scheme 29).

In this situation, if there is no *ortho* functional group we should have 3-hydroxyimidazolidin-4-one **114**, which could be condensed with the phenyl to form the imidazoleindoline. [26] The hydroxyl group is necessary for condensation. 3-Hydroxyimidazolidin-4-one **114** could be readily prepared from condensation of 2-amino-*N*-hydroxyethanamide with aldehyde **115**, which itself may be derived from terminal alkene **116** by ozonolysis.



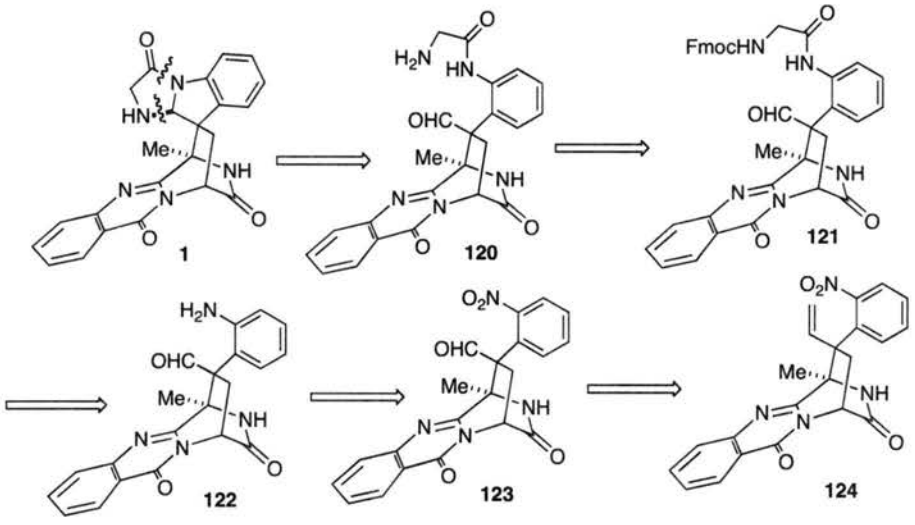
Scheme 29

A appropriate *ortho* functional group will facilitate the synthesis. For example, if the phenyl carries an *ortho* bromine atom, the imidazoleindoline can be formed by a Buchwald palladium catalyzed cyclyzation (Scheme 30). [26] In this case, we shall have imidazolidin-4-one **117** rather than a 3-hydroxyimidazolidin-4-one. Similarly, imidazolidin-4-one **117** can be prepared by condensation of 2-aminoethanamide with aldehyde **118**, which may in turn come from terminal alkene **119**.



Scheme 30

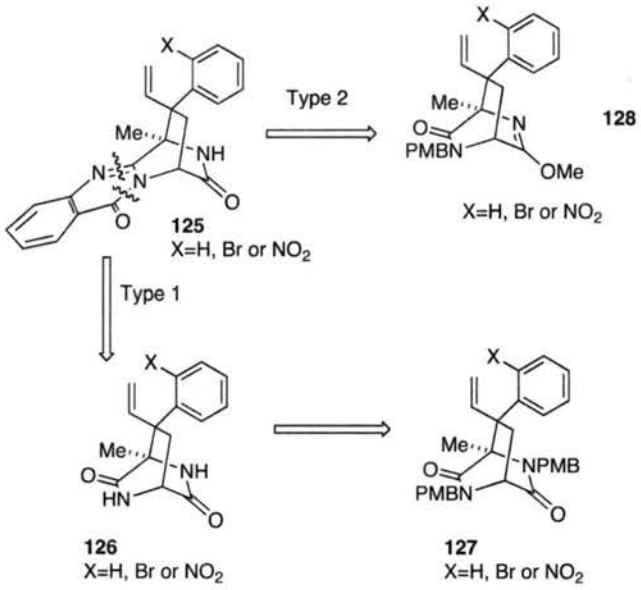
If the phenyl group carries a protected or a latent amino group (for example, a nitro group) the situation is very different. We envision that the imidazoleindoline could be formed by an acid or base promoted condensation of the α-amino amide with aldehyde **120** intramolecularly (Scheme 31). The α-amino amide could come from coupling of Fmoc-glycine with amine **122**. This amine may be formed from a the nitro group in **123**, and the aldehyde from terminal alkene **124**.



Scheme 31

All of these retrosynthetic analyses led to the same type of compound (**125** in Scheme 32). Our next disconnection will be on the quinazolinone core. We mentioned in Chapter 1 that a useful strategy to make the quinzolinone core is coupling of a diketopiperazine with *o*-azido benzoyl chloride followed by an aza-Wittig reaction. Therefore, the disconnection on the quinazolinone comes very naturally. As shown in Scheme 32, this disconnection may lead to two different types of structures. The first one is **127,** in which the two amides are protected with the

same kind of protecting group. Although this plan seems to be feasible, there is an issue of regioselectivity since the quinazolinone core is attached to only one side of diketopiperazine (DKP). However, it still worths our tentative effort of research. If we take the issue of regio-selectivity into consideration, the two sides of the DKP should be protected with two orthogonal protecting groups. As an example, one amide can be converted into a lactim ether and other one may be protected with an alkyl group such as PMB as seen in **128**. Of course this may lead to a longer synthetic route.



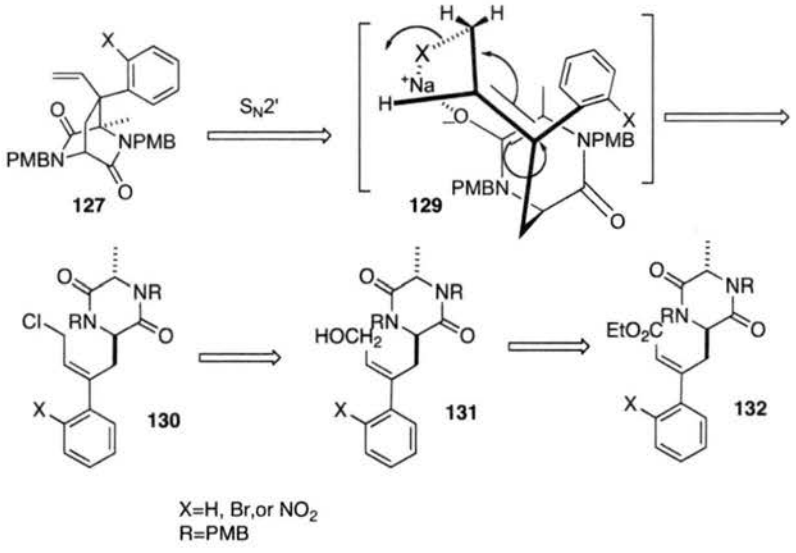
Scheme 32

From these analyses, the second type of disconnection discussed above seems more promising, but compound **127** seems more accessible, and we can do some tentative research on this substrate. The next disconnection will come through an S_N2' reaction (Scheme 33). If we choose reaction conditions which favor closed transition

state **129**, then compound **127** could be derived from **130**. The allyl chloride **130** may be accessible from allyl alcohol **131,** which may arise from conjugated ester **132**.

A similar disconnection may be applied to compound **128** using an S_N2' strategy. Compound **128** may arise from the corresponding protected DKP in which the two amides are protected with orthogonal protecting groups.

It seems that if we can prepare DKP **130**, it could be used to test the S_N2' reaction. Once we develop an efficient S_N2' reaction we can apply this strategy on other more complicated DKPs.

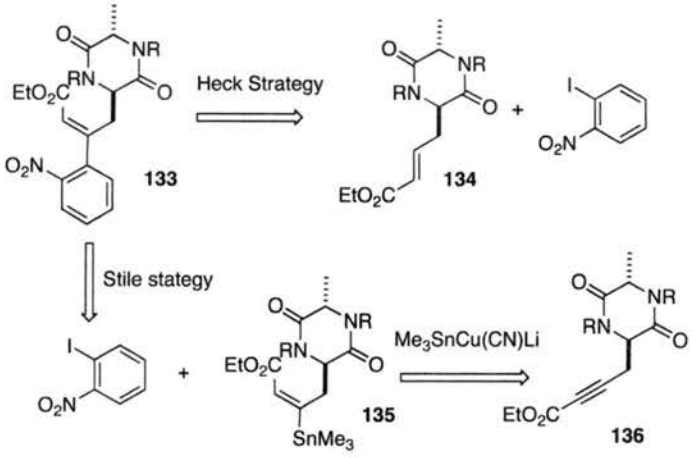


Scheme 33

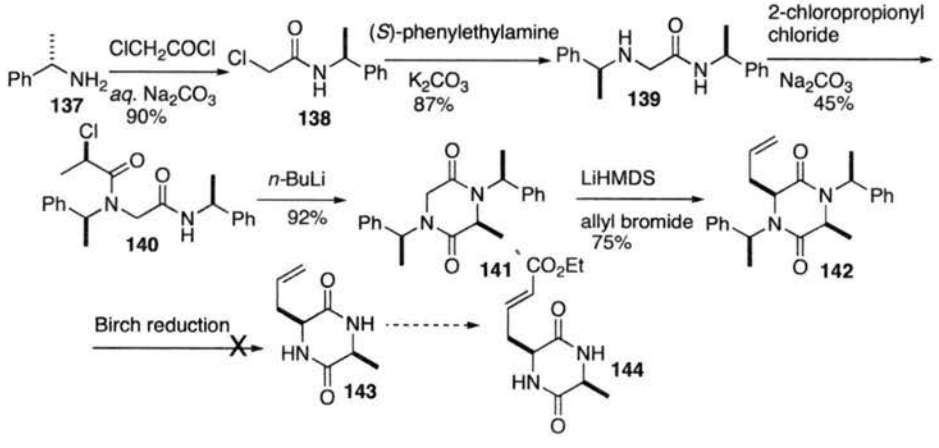
Scheme 34 shows two strategies to prepare the fuctionalized DKP. One is a strategy based on a Heck reaction, and the other is based on a Stille coupling reaction. In DKP **133**, there are chiral centers, but the chiral center from alanine is unimportant. In S_N2' reactions, when the substrate is treated with base, this chiral center will be racemized. The chirality of the S_N2' product therefore depends solely on the other chiral center. The problem is thus simplified to the synthesis of a

functionalized DKP with one chiral center. We can have a brief look at some strategies to do this.

The first strategy is presented and demonstrated by Sandri and coworkers. [27] Scheme 35 shows their method to introduce a chiral center on a DKP using a chiral template. Although no peptide synthesis is needed for this method, the process consumes two equivalents of chiral auxiliary (*R*)-phenylethylamine. Removal of the chiral template by Birch reduction gave inconsistent results. Eventually, we gave up this strategy.

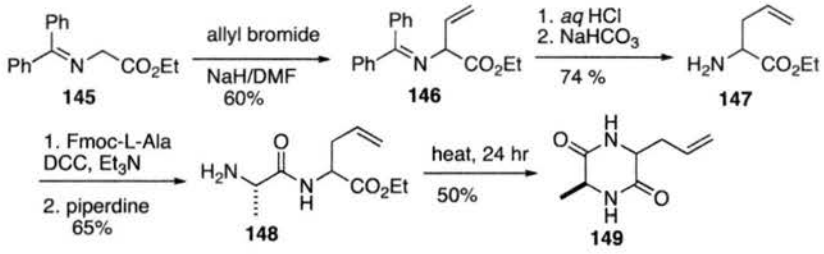


Scheme 34



Scheme 35

Scheme 36 shows a general method to introduce an allyl group on glycine by using *N*-(diphenylmethlene) glycine ethyl ester. [28] The DKP is prepared by peptide coupling followed by intramolecular condensation. Chiral additives must be used to introduce chirality. Our first attempt was to make the racemic product. The yield of the transformation from **145** to **146** was not reproducible. This method is not an economic method to prepare functionalized DKPs due to poor yields and the expensive reagent **145**.

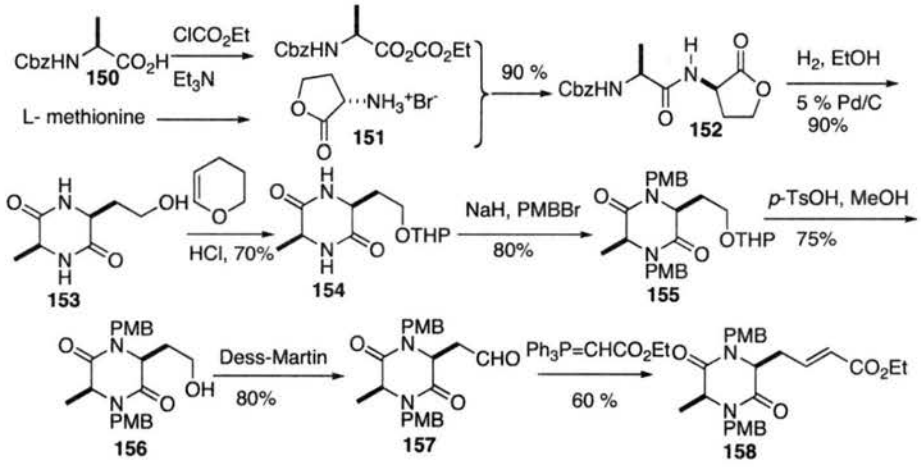


Scheme 36

Sheradky reported a concise synthesis as shown in Scheme 37. [29] In this synthetic route, the starting materials are *N*-Cbz-alanine **150** and α-amino-α-butyrolactone hydro-bromide **151**, which could be prepared by a method previously described. [30] A coupling reaction between these two starting materials gave dipetide **152**. Hydrogenolytic deprotection of Cbz gave a free amine that attacked the lactone to generate compound **153** directly. In spite of this compound's poor solubility in CH_2Cl_2, it can still be oxidized to the corresponding aldehyde by a Dess-Martin reagent. However, the corresponding aldehyde is not separable due to its poor

solubility. To improve solubility, alcohol **153** was first treated with 1,2-dihydrofuran to introduce a THP protecting group. Treatment of **155** with PMBBr and NaH installed two PMB protecting groups on the amides. Deprotection of THP by treatment with TsOH gave the alcohol **156**. This alcohol was readily oxidized to the corresponding aldehyde **157** by Dess-Martin oxidation. A Wittig reaction afforded a conjugate ester **158** which is the substrate for a Heck reaction.

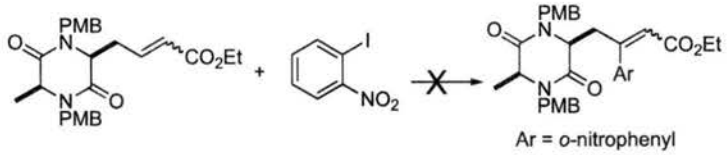
Unfortunately, we were unable to introduce an aryl group into the conjugate ester. All the conditions we tried for the Heck reactions resulted in complex mixtures (Table 1). Since in all conditions base was used, the stability of substrate to base is questionable.



Scheme 37

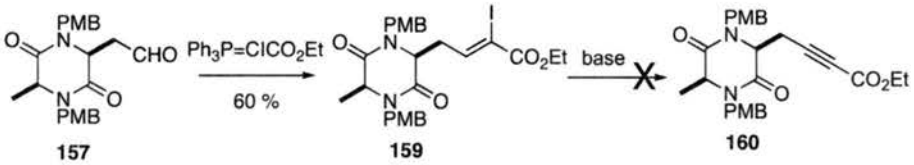
As in our analyses above, an alternative strategy is the Stille strategy. Aldehyde **157** underwent a Wittig reaction to produce vinyl iodide **159**. [31] Different basic conditions were examined to convert vinyl iodide **119** into alkynyl ester **160**, but unfortunately no desired product was observed under all conditions (Scheme 38).

Table 1



Ar = *o*-nitrophenyl

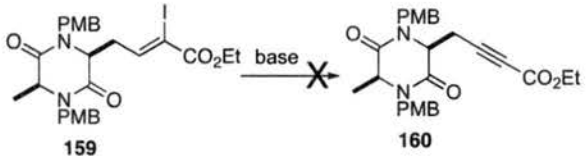
Catalyst	Base	Solvent	T (°C)
$Pd(OAc)_2$	KOAc	DMF	60
$Pd_2(dba)_3$, P(*t*-Bu)$_3$	Cy_2NMe	dioxane	25
$Pd(OAc)_2$	Et_3N	CH_3CN	100
$Pd(OAc)_2$	$Bu_4N^+OAc^-$	Melt salt: $Bu_4N^+OAc^-$ and $Bu_4N^+Br^-$	~100
$Pd(OAc)_2$	$Bu_4N^+Cl^-$	$NaHCO_3$	80
$Pd(OAc)_2$	Cy_2NMe	DMAc+Et_4NBr	85
$Pd(OAc)_2$	Et_3N	DMF	80
$Pd(OAc)_2$	Et_3N	1,2-dchlorobenzene	80



Scheme 38

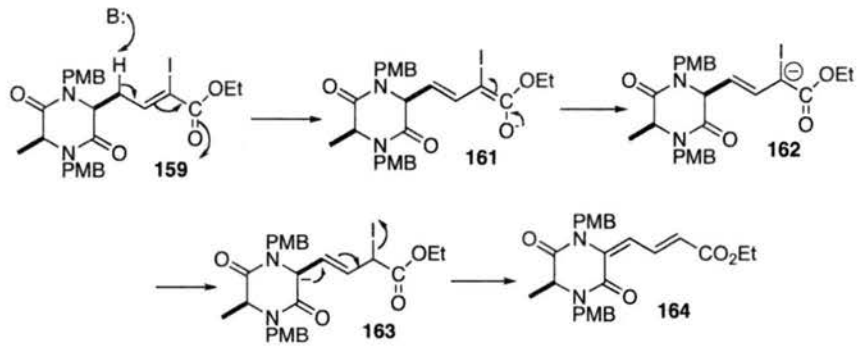
When compound **159** was treated with strong base, only complex mixtures were obtained. Under weak basic conditions, only conjugate diene **164** was obtained (Table 2). The mechanism is shown in Scheme 39.

Table 2



159 160

Entry	Reagents	Solvent	T (°C)	Result
1	K_2CO_3	methanol	25	Messy
2	$KHCO_3$	methanol	25	diene
3	Ag_2O	benzene	25	No reaction
4	Ag_2O	benzene	60	No reaction
5	Ag_2CO_3	benzene	25	No reaction
6	Ag_2CO_3	benzene	60	No reaction
7	NaOAc	ethanol	25	No reaction
8	NaOAc	ethanol	60	diene
9	AgF + Pyr.	pyridine.	25	diene
10	$Ag_2O_2CCF_3$+TEA	benzene	25	diene
11	Quinoline	benzene	25	No reaction
12	Quinoline	benzene	60	No reaction
13	Cy_2NMe	benzene	25	No reaction
14	Cy_2NMe	benzene	25	No reaction



Scheme 39

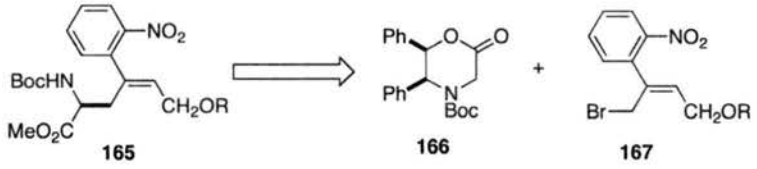
All tentative trials failed. We could not use the Stille strategy above simply because the alkynl ester **160** is not available. However we were sure that the Stille strategy should work after some modifications. Since introduction of an alkynyl ester on a DKP is impossible we must examine the possiblity of introducing it in the stage of amino acid rather than on the DKP. This idea has led to the synthesis of δ-aryl-δ,γ-usaturated-α-amino acids. A new methodology was developed. This will be discussed in the next chapter.

2.2 Synthesis of δ-aryl-δ,γ-usaturated-α-amino acids[32]

Non-proteinogenic α-amino acids are important nitrogenous building blocks, which are useful for the synthesis of natural products as well as a multitude of biologically significant substances.[33,34,35] There has been continuing interest in the development of new methods for the synthesis of enantiomerically pure amino acids with substituents strategically placed at side-chain positions, including the capacity to install unsaturation. Many methods have been developed for the asymmetric synthesis of amino acids. Despite the plethora of extant methodologies, many reactive functionalities remain incompatible with existing templates.

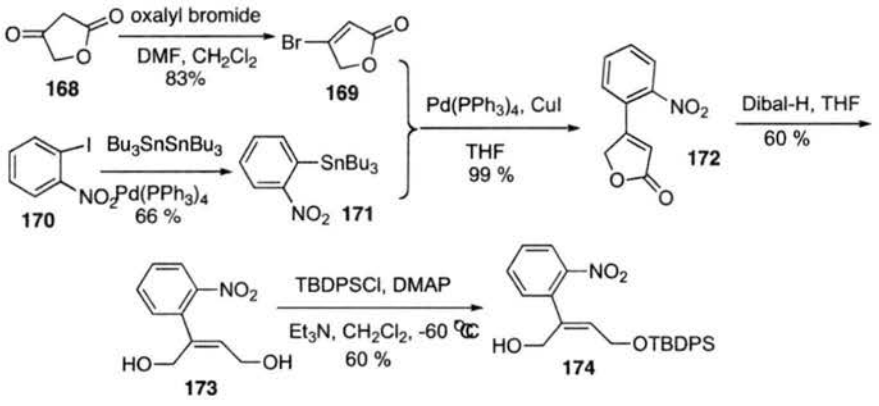
Our tentative trials have demonstrated that introduction of all necessary functionalities in the DKP stage is difficult. We have to seek an alternative option. One option is to introduce those functionalities in the amino acid stage. Access to δ-aryl-δ,γ-usaturated-α-amino acids such as **165** is thus required.

Originally, we envisioned that **165** could be synthesized from Williams lactone template **166** and allyl bromide **167**.[36] The first compound therefore we need to synthesize is the functionalized allyl bromide **167** (Scheme 40).



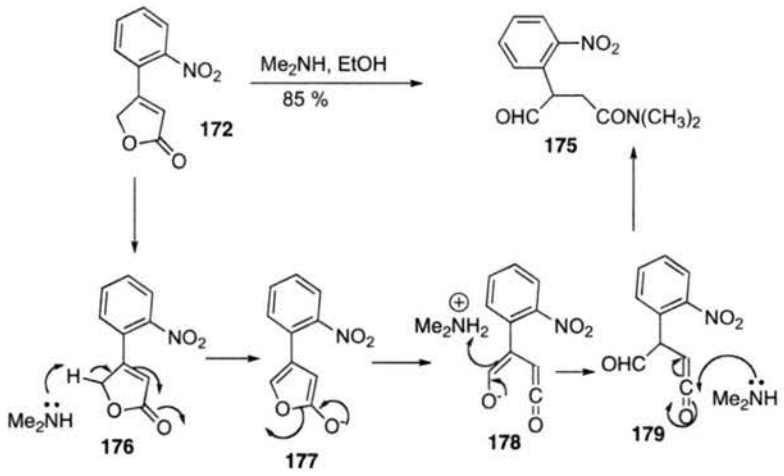
Scheme 40

The synthesis of the allyl bromide started with 4-bromofuran-2(5*H*)-one **169** and tributyl(2-nitrophenyl)stannane **171** (Scheme 41). The former can be prepared from tetronic acid **168** by a Vilsmeier bromination,[37] and the latter can be prepared from *o*-iodonitrobenzene **170** by a Stille reaction[38]. A Stille coupling reaction between **169** and **171** afforded **172** almost quantitatively. Compound **172** was then reduced with DIBAL to afford diol **173**. The two hydroxyl groups can be differentiated by introducing a TBDPS protecting group, which selectively reacted with the less hindered hydroxyl group to give compound **174**.



Scheme 41

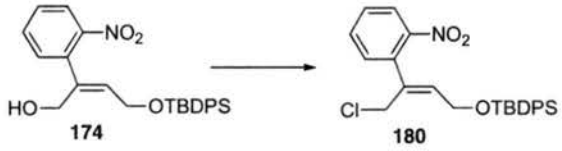
It should be pointed out that another effort to open the lactone led to an interesting result (Scheme 42). When compound **172** was treated with dimethyl amine, aldehyde **175** was produced. This product likely most arises through furan-2-olate anion **177** followed by ketene intermediate **178**. The driving force should be the formation of the aromatic furan ring.[39]



Scheme 42

All efforts to directly convert the allyl alcohol into the corresponding allyl bromide failed. For example, no reaction occurred when allyl alcohol was treated with triphenylphosphine, carbontetrabromide and imidazole. It seems that the allyl alcohol is in a very hindered environment. Fortunately, the allyl alcohol could be converted into allyl chloride **180** (Table 3). [40]

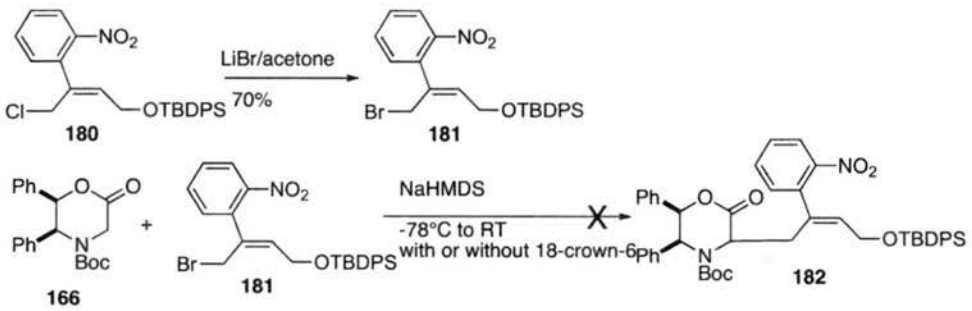
Table 3



Conditions	Yield
MsCl, Collidine, LiCl, DMF, 25 °C	48%
TsCl, Et_3N, DMAP, CH_2Cl_2, 25 °C	No reaction
NCS, Me_2S, CH_2Cl_2, -78 °C to 25°C	60%

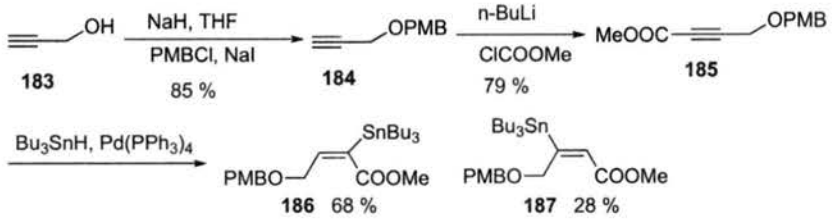
When the TsCl/Et_3N/DMAP system was used, no reaction was observed, probably due to hindrance. Both MsCl/collidine/LiCl and NCS/DMS worked for the reaction; however, both reactions caused partial migration of TBDPS. For the MsCl/collidine/LiCl system, this problem was more serious. We eventually chose NCS/DMS system, which brought us 60% yield.

Allyl chloride **180** obtained above was converted into the corresponding allyl bromide **181** in 70% yield by treatment with LiBr (Scheme 43). Unfortunately, we were unable to couple **181** with the Williams lactone **166**. Different bases such as LiHMDS, NaHMDS and KHMDS have been tried. In all conditions, a small amount of starting materials were recovered. Addition of 18-crown-6 did not change the result. Whenever the base was added to a mixture of Williams lactone and bromide **181**, a dark red solution was obtained. Three factors may influence the reaction: 1) hindrance from the aryl group; 2) hindrance from the TBDPS group; 3) interference from the NO_2. We wer not sure which factor was the real problem, and decided to do some experiments to examine it. First, we decided to change the big TBDPS group to a small protecting group such as PMB. This transformation cannot be performed on compound **181**, because it may undergo cyclization or TBDPS migration.



Scheme 43

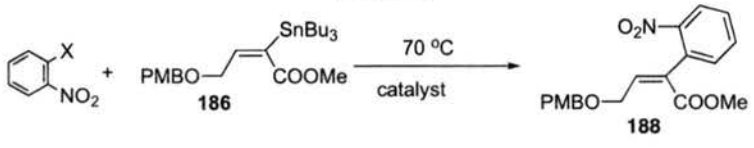
Thus, a new strategy was developed to prepare an allyl chloride with PMB-protected alcohol **184** (Scheme 44). The synthesis started with propargyl alcohol **183** that was treated with NaH and PMBCl to introduce the PMB protecting group. [41] The product **184** thus obtained was treated with *n*-butyl lithium followed by methyl chloroformate to afford compound **185**. [42] A hydrostannation generated two regio-isomers, **186** and **187,** with the desired one (**186**) as the major product. [43]



Scheme 44

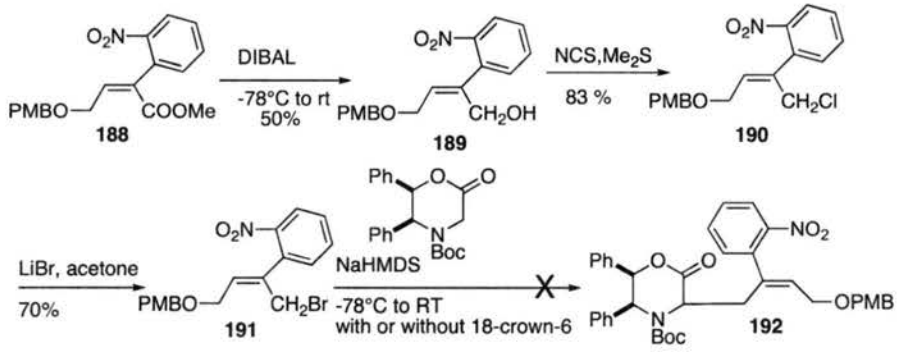
The results of the Stille coupling are listed in Table 4. [44] Both $Pd(PPh_3)_4$ and $PdCl_2(MeCN)_2$ can catalyze this coupling reaction. When $Pd(PPh_3)_4$ was used, co-catalyst CuI was needed. However, when $PdCl_2(MeCN)_2$ was used, a better yield (up to 62% yield) could be obtained.

Table 4



X, NO_2	Catalyst	Cocatalyst	Solvent	Results
X=Br	$Pd(PPh_3)_4$	None	Toluene	No reaction
X=I	$Pd(PPh_3)_4$	None	DMF	No reaction
X=I	$Pd(PPh_3)_4$	CuI	THF	trace
X=I	$Pd(PPh_3)_4$	CuI	DMF	50 %
X=I	$PdCl_2(MeCN)_2$	None	DMF	62 %
X=Br	$PdCl_2(MeCN)_2$	None	DMF	23 %
X=I	$PdCl_2(MeCN)_2$	None	Dioxane	37 %
X=Br	$PdCl_2(MeCN)_2$	None	Dioxane	trace

Compound **188** was then reduced with DIBAL to generate alcohol **189**. Again, we were unable to convert alcohol **189** directly to an allyl bromide by treatment with triphenylphosphine, carbontetrabromide and imidazole (Scheme 45).



Scheme 45

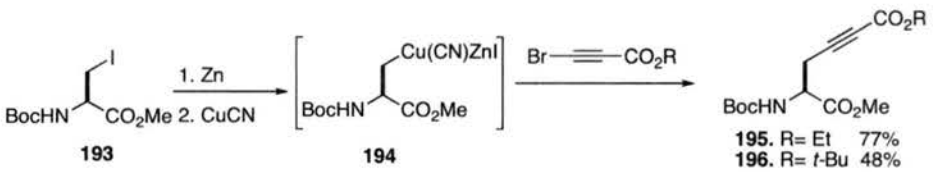
As discussed above, the alcohol was transformed into an allyl chloride, which was then treated with LiBr to afford the allyl bromide **191**. However, we again failed to couple allyl bromide **191** with the Williams lactone template to obtain **192** (Scheme 45).

It seems that the factor of hindrance from the TBDPS protecting group is excluded. We began to realize that the *o*-nitrophenyl group was the problem. The hydrostannation chemistry above gave us a hint. Since *o*-nitrophenyl group was the problem, we would have to introduce the aryl group at a later stage. Namely, we could make an amino acid with a vinyl stannane and introduce the aryl group by a Stille coupling.

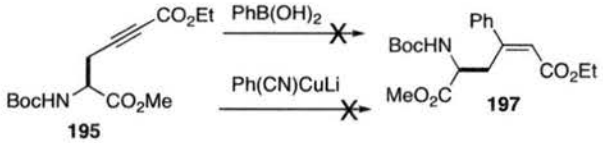
Jackson et al. have reported the synthesis of enantiomerically pure unsaturated α-amino acids *via* coupling to readily available serine-derived β-iodoalanine derivatives using zinc/copper reagents.[45] We have adapted this approach to prepare a variety of δ-aryl-δ,γ-usaturated-α-amino acids.

Our approach commenced with *N-(tert*-butoxycarbonyl)-L-iodoalanine methyl ester **193,** which is commercially available or can be prepared on a large scale by using the reported procedure with serine as the starting material.[46] Iodide **193** was converted into the corresponding Zn/Cu complex **194** and coupled with ethyl 3-bromopropiolate or *tert*-butyl 3-bromopropiolate. [46] The Zn/Cu complex **194** reacted with ethyl-3-bromopropiolate to produce the propargyl species **195** and **196** in 77% and 48% yields, respectively (Scheme 46).

Then we tried to install a phenyl group on compound **195** by treatment with $PhB(OH)_2$ [48] or Ph(CN)CuLi, but no reactions were observed under these conditions (Scheme 47).



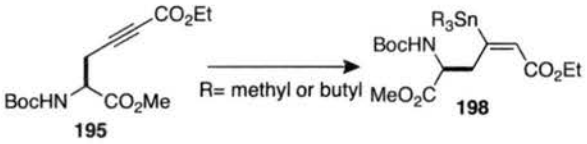
Scheme 46



Scheme 47

Next, we examined the conjugate stannylation of organocopper (I) reagents to the δ,γ-alkynyl residue of **195** (Table 5). The addition of compound **195** to a solution of $Bu_3SnCu•SMe_2$ or $[Bu_3SnCuCN]Li$[49,50] in THF resulted in no reaction, probably due to steric hindrance. When **195** was added to $Me_3SnCu•SMe_2$ in THF, compound **198** was obtained in 23% yield along with 40% recovery of **195**. Piers reported that the (trimethylstannyl)copper(I) dimethylsulfide complex was relatively unreactive towards α,β-unsaturated carbonyl compounds.[48] When a more reactive species, $[Me_3SnCuCN]Li$,[49] was used in place of $Me_3SnCu•SMe_2$ for this reaction, the yield was dramatically improved.

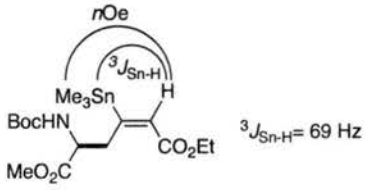
Table 5



X-	Organocopper (II) reagent	Yield
Bu_3Sn-	$[Bu_3SnCuCN]Li$	48%
Me_3Sn-	$Me_3SnCu•SMe_2$	No reaction
Me_3Sn-	$[Me_3SnCuCN]Li$	60%

When **195** was added to $[Me_3SnCuCN]Li$ in dry THF at -78 °C, compound **198** and the corresponding *Z*-isomer were produced in a nearly 1:1 ratio with no recovery of starting material. Separation of the two isomers by flash chromatography proved to be very difficult and synthetically intractable. When $[Me_3SnCuCN]Li$ was treated with EtOH prior to the addition of **195**, the product obtained was exclusively

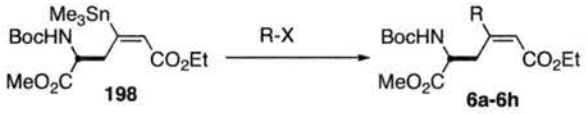
the desired *E*-isomer.[49,50] The geometric configuration of the product was determined by the coupling constant between the α-olefinic proton and the tin atom (^{117}Sn, ^{119}Sn) of the Me_3Sn group (Scheme 48). It is well known that when a trialkylstannyl group and a proton are vicinal on a C=C bond, the $^3J_{Sn\text{-}H}$ values are much larger when these moieties are *trans*- as opposed to *cis*-configured.[51] The $^3J_{Sn\text{-}H}$ value in the present case is 69 Hz, which falls into the expected range for the *E*-stereochemistry. The observation of a significant ^{1}H *n*Oe between the vinyl proton and the Me_3Sn-protons provided corroborating evidence to support the *E*-stereochemistry assigned for **198** (Scheme 49). The optical integrity of **198** was determined by ^{1}H NMR analysis of the derived Mosher's amide[52] which revealed that **198** was obtained in at least 99.5:0.5 er. Compound **198** proved to be a stable substance and can be kept as an oil and exposed to air at ambient temperature for several weeks without detectable decomposition.

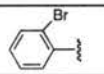
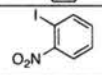
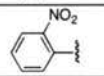
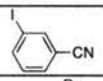
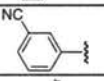
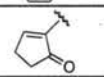
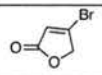
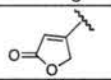
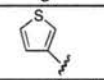
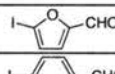
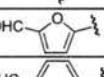
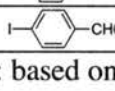
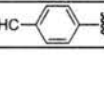


Scheme 48. *E*-Stereochemical assignment for **198**.

Compound **198** was then coupled with a variety of aryl and heterocyclic halides under Stille cross-coupling conditions (Table 6).[53]

Table 6. Stille coupling reactions of stannane **198**



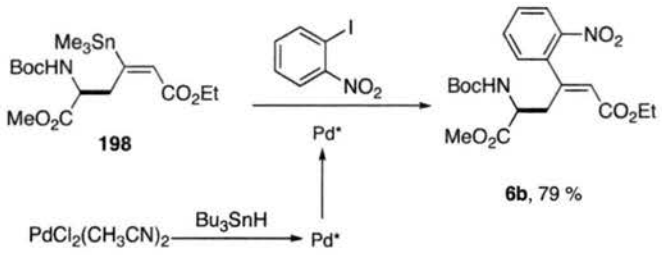
Entry	R-X	conditions	Yield %	R
a		$Pd_2(dba)_3$, CuI, $AsPh_3$, DMF	68	
b		Pd_2Cl_2 $(CH_3CN)_2$, Bu_3SnH	79 (brsm)	
c		$Pd_2(dba)_3$, CuI, $AsPh_3$, DMF	71	
d		$Pd_2(dba)_3$, CuI, $AsPh_3$, DMF	77	
e		$Pd_2(dba)_3$, CuI, $AsPh_3$, DMF	57	
f		$Pd_2(dba)_3$, CuI, $AsPh_3$, DMF	80	
g		$Pd_2(dba)_3$, CuI, $AsPh_3$, DMF	84	
h		$Pd_2Cl_2(CH_3CN)_2$, Bu_3SnH, 45 °C	67	

brsm: based on recovery of starting material.

Our initial efforts examined $Pd(PPh_3)_4$ as the catalyst in the presence of CuI[54] at room temperature. Under these conditions either no product or only trace amounts of product were obtained. Higher temperature only led to decomposition of compound **198**. Amino acid **6a** was successfully prepared by coupling of *o*-bromoiodobenzene with compound **198** using Pd_2dba_3 in the presence of $AsPh_3$ and CuI.[55] Only bromide **6a** was observed as evidenced by ^{13}C NMR spectroscopy and Mass Spectrometry; the corresponding iodide was not observed. The 3-cyanophenyl moiety can be introduced under similar conditions (entry c). Heterocyclic species such as 2-bromocyclopent-2-enone[56] and 4-bromofuran-2(*5H*)-one were also successfully coupled with compound **198** to yield **6d** and **6e** in 77% and 57% yields,

respectively (entries d and e). The coupling of **198** with 3-iodothiophene or 5-iodofuran-2-carboxaldehyde also provided the cross-coupling products in useful yields (entries f and g).

In all cases, the reactions were complete within just two hours with no loss of optical integrity was observed by ^{1}HNMR of Mosher's amides or chiral HPLC analysis. *o*-Iododnitrobenzene coupled with compound **198** to deliver **6b**, albeit in very poor yield. When $PdCl_2(CH_3CN)_2$ was used as the catalyst, an incomplete reaction was observed. We found that the yields could be improved by increasing catalyst loading, but this also caused more homocoupling. Eventually, it was found that treatment of $PdCl_2(CH_3CN)_2$ with *n*-tributyltin hydride followed by addition of compound **198** and *o*-iodonitrobenzene portion-wise resulted in a 79% yield of **6b** (based on a small amount of unreacted starting material, Scheme 49).

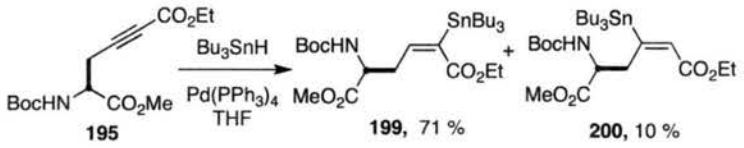


Scheme 49

It was proven unnecessary to employ dry, deoxygenated solvent and the reaction can be manipulated in air at ambient temperature. It should be noted that no reaction occurred when commercially available Pd-black was used. This system also proved effective for the coupling of *p*-iodobenzaldehyde with compound **198** (entry

h). In this case, the catalyst was added in one portion and heating to 45 °C was required. It is known that for aryl iodide substrates, the oxidative addition of Pd(0) in the Stille reaction cycle is accelerated by electron-withdrawing substituents.[57] Strong electron-withdrawing groups, such as aldehydes or nitro groups, consequently accelerate the oxidative addition step so that no ligand is needed (entries b and h). For the other halides examined, which were devoid of strong electron-withdrawing substituents, the ligand has to be added to facilitate the oxidative addition.[58]

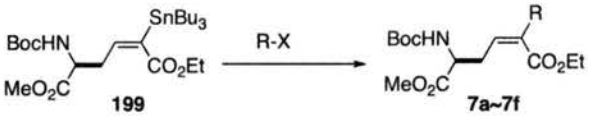
In addition to the copper (I) chemistry described above, compound **195** also underwent a Pd-catalyzed hydrostannylation reaction with *n*-tributyltin hydride providing the alternate regio isomer **199** as the major product in 71% yield along with regioisomer **200** (10%) as shown in Scheme 50.

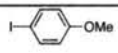
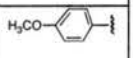
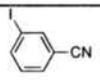
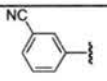
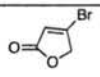
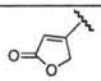
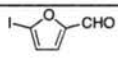
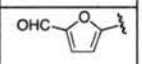


Scheme 50

The two regioisomers **199** and **200** can be separated by flash chromatography and may be stored exposed to air for weeks without significant decomposition. The major isomer **199** can be coupled with a variety of halides to give the amino acids listed in Table 7.

Table 7. Stille coupling reactions of stannane **199**

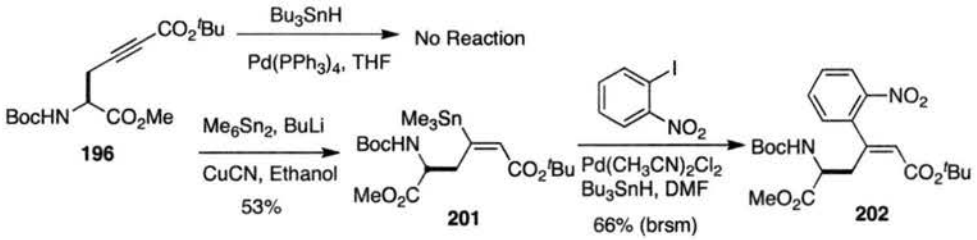


Entry	R-X	conditions	Yield %	R
a		Pd_2dba_3, CuI, $AsPh_3$, DMF	74	
b		Pd_2dba_3, CuI, $AsPh_3$, DMF	79	
c		Pd_2dba_3, CuI, $AsPh_3$, DMF	72	
d		Pd_2dba_3, CuI, $AsPh_3$, DMF	69	
e		Pd_2dba_3, CuI, $AsPh_3$, DMF	84	
f		Pd_2dba_3, CuI, $AsPh_3$, DMF	76	

The catalytic system Pd_2dba_3/CuI/$AsPh_3$ works quite well for the Stille coupling reactions of **199** and the halides listed in Table 7. It does not appear to matter whether the substituent on the phenyl group is an electron-withdrawing group such as cyano, or an electron-donating group such methoxy. 2-Bromocyclopent-2-enone and 4-bromofuran-2(*5H*)-one can couple with compound **199** to yield **7c** and **7d** respectively. The coupling of **199** with 3-iodothiophene or 5-iodofuran-2-carboxaldehye delivered **7e** and **7f** respectively, in good yields.

Compound **195** underwent hydrostannylation with good regioselectivity favoring the γ-stannane **199**. We also examined reaction conditions by using a hindered *tert*-butyl ester that would favor the δ-stannane-type regioisomer **200** (Scheme 51). Compound **196** underwent conjugate addition of [$Me_3SnCuCN$]Li to

yield the δ-substituted stannane **201** in 53% yield (Scheme 3). As a preliminary demonstration of the utility of this species, compound **201** underwent Stille cross-coupling with *o*-iodonitrobenzene to produce the δ-aryl-δ,γ-unsaturated amino acid derivative **202** in which the two ester groups are differentiated.



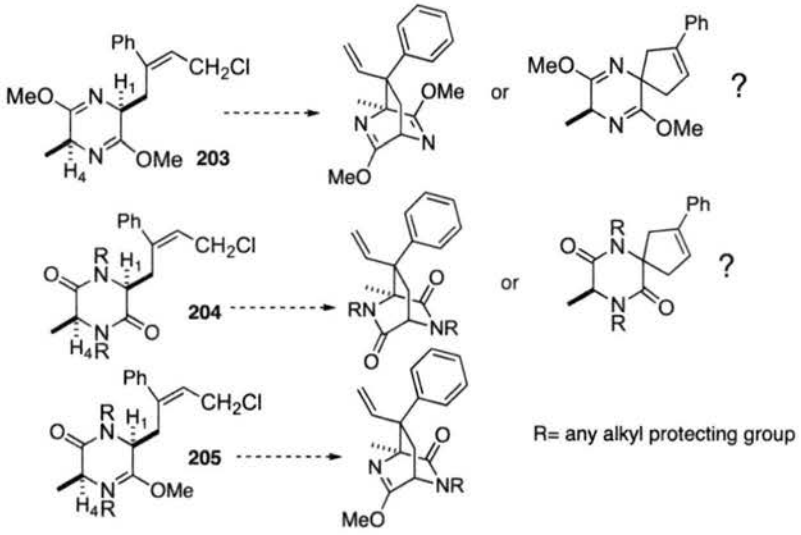
Scheme 51

In summary, we have developed an efficient strategy to synthesize two types of δ, γ-unsaturated-α-amino acids bearing substitution at either the δ- or γ-positions. Those two types of amino acids and related derivatives may be used as important building blocks in natural products.

2.3 A Novel S_N2' Reaction

2.3.1 Introduction of protecting groups

In the first part of this chapter, we mentioned the necessity to differentiate the two amides in the DKP with two orthogonal protecting groups. In the total synthesis of brevianamide B by an S_N2' reaction, a PMB protecting group was used.[21] In the total synthesis of paraherquamide B,[22] the amide was converted into a methyl lactim ether. In our case there is a need to introduce two protecting groups. If we focus on alkyl protecting groups such as PMB and lactim ether, we will have only three options as shown in Scheme 52.



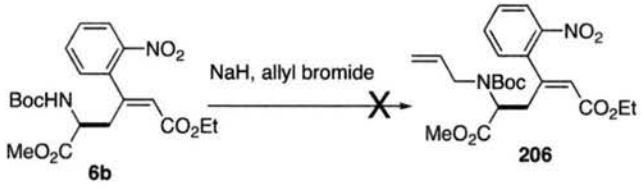
Scheme 52

In the first substrate (**203**), the two amides are present in the form of a bis-lactim ether. A strong base such as BuLi will be required for deprotonation. [59] The acidities of H_1 and H_4 are close, so the substrate may cyclize to form a bridged cycle

or a spirocyclic system. If both sides are protected with the same alkyl group (substrate **204**), the two α-protons H_1 and H_4 are more acidic than those in substate **203**. However, H_1 and H_4 in **204** are still not differentiable so that the substrate may still cyclize to form the undesired spirocyclic system upon treatment with base. In the third case, one amide is protected with an alkyl group and the other is in the form of a lactim ether. It is obvious that H_4 is much more acidic than H_1. The undesired spiro cyclization can be minimized.

Through this analysis, an alkyl protecting group must be introduced at the amino acid stage. At first, we chose an allyl group since it is small and will not cause congestion in the later stages of the synthesis.

We synthesized amino acid **6b** by the Stille coupling reaction, but we found that amino acid **6b** prefers to cyclize to form a six membered lactim after Boc deprotection. Treatment of **6b** with NaH and allyl chloride or PMBBr to introduce an alkyl protecting group only generated a complex mixture (Scheme 53).

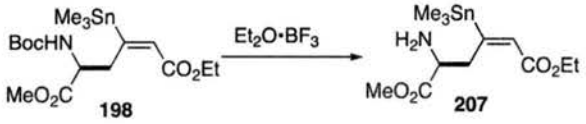


Scheme 53

We chose to start with compound **198**. Introduction of an alkyl protecting group by treatment with NaH and allyl bromide resulted in failure. The Boc deprotection was also troublesome, since the Me_3Sn- group is not compatible with acidic conditions and most Lewis acids. $Et_2O{\bullet}BF_3$ in CH_2Cl_2 is a widely used reagent

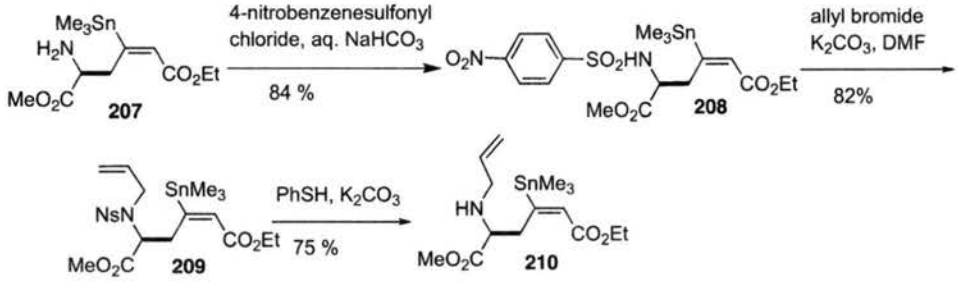
for Boc deprotection. [60] In our case, only 50% yield was obtained when **198** was treated with $Et_2O•BF_3$ in CH_2Cl_2. As we know, BF_3 may complex with weak Lewis bases such as THF, Et_2O, 1,4-dioxane and dimethysulfide. The solvent effect with $Et_2O•BF_3$ is tremendous. Screening several solvents showed that ethyl acetate was the best solvent for Boc deprotection (Table 8).

Table 8



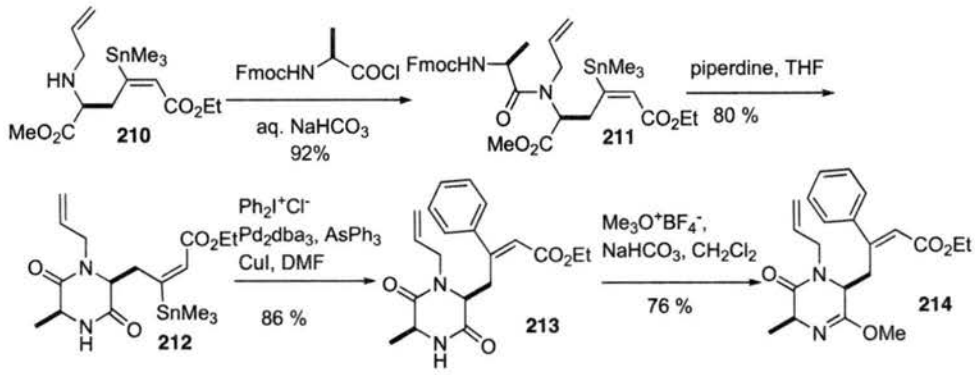
Solvent	Results
CH_2Cl_2	50 %
THF	No reaction
Diethyl ether	66%+20% SM
Ethyl acetate	**95 %**
Dioxane	60 %
CH_3CN	50 %
Acetone	messy

Direct treatment of the free amine with allyl halide under all conditions generated only a complex mixture. Eventually a three-step protocol was used (Scheme 54). The free amine **207** was coupled with *p*-nitrobenzenesulfonyl chloride (NsCl) under Schotten-Bauman conditions to yield sulfonamide **208**. Compound **208** reacted with allyl bromide and K_2CO_3 to produce bisprotected amino acid **209**. Deprotection of the Ns group provided the allyl protected amino acid **210**. [61]



Scheme 54

Compound **210** reacted with the acid chloride derived from Fmoc-alanine under Schotten-Baumann conditions to produce the dipeptide **211** (Scheme 55). Fmoc deprotection gave DKP **212** directly. Stille reaction of **212** with iodobenzene produced **213** in low yield (35%). When diphenyliodolidium chloride ($Ph_2I^+Cl^-$) was used, the yield was dramatically improved. [62] Treatment of compound **213** with $Me_3O^+BF_4^-$ generated lactim ether **214** in which the two amides were differentiated by orthogonal protecting groups: one was protected with a small, electron-rich allyl group, and the other was transformed into a lactim ether. We shall point out that some other weak bases such as $(NH_4)_2CO_3$, Ag_2CO_3 or $CaCO_3$ can also be used in the transformation of **213** to **214** without causing any racememization. Bases such as Li_2CO_3, Na_2CO_3, K_2CO_3, or Cs_2CO_3 caused racemization at C-1 on the DKP.



Scheme 55

2.3.2 First-generation S_N2' reaction

Compound **214** provided an opportunity for an intramolecular Michael reaction to build the bicyclo[2,2,2]diazaoctane. However when compound **214** was treated with NaH, KO^{t}Bu or NaHMDS at various temperatures ranging from -78 °C to 60 °C in THF, it decomposed to some very polar by-products. No desired product of intramolecular Michael addition was observed. Compound **214** was only two steps away from an allyl chloride, which is a precursor of the S_N2' reaction.

Reduction of the conjugate ester in compound **214** was one of the greatest challenges we have met. Compound **214** is not stable to base, and the lactim ether in **214** can be easily reduced. We tried different reducing agents such as DIBAL, $LiBH_4$, $NaBH_4$, $LiAl(O^tBu)_3$ and Red Al without success. $NaBH_4$, or $LiAl(O^tBu)_3$ gave no reaction and all others gave complex mixtures. Then we examined other intermediates in the synthetic route to seek opportunities for reduction. Compounds **209** and **212** were successfully reduced by DIBAL. The conjugate ester in **212** was reduced to the corresponding conjugate aldehyde using DIBAL in 25% yield. The reaction was finished in several minutes. Longer reaction time, more DIBAL or higher temperature

only led to more decomposition. This reaction works only in CH_2Cl_2. In all other solvent such as THF, diethyl ether, toluene or heptane, complex mixtures were obtained. In similar conditions, **213** or **214** could not be reduced to the corresponding aldehyde or alcohol. Another interesting result was that the conjugate ester in compound **208** could be reduced to the corresponding aldehyde in 64% yield. The other ester in this compound is in a hindered environment, and was therefore untouched by the reaction.

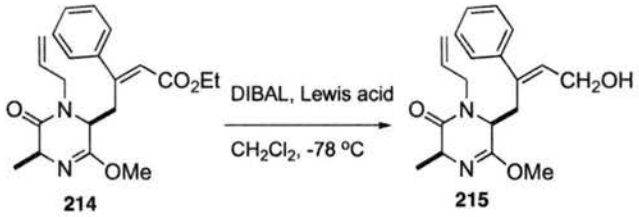
Unfortunately, neither of the corresponding aldehydes obtained from **208** or **212** proved to be useful. The yield for the Stille coupling reaction of the corresponding aldehyde from **212** with diphenyliodonium salt $Ph_2I^+Cl^-$ was too poor for us to push forward (25%). Deprotection of the Ns group from the aldehyde derived from **208** by using thiophenol and K_2CO_3 failed. Though the two products are useless, the two successful reductions gave us a hint: DIBAL should be the right reducing reagent, provided the right solvent is chosen, and perhaps some additive must be used.

The remaining question is: are there any additives that can activate the ester so that it can be selectively reduced?

We found that when one equivalent of Lewis acid $Et_2O{\bullet}BF_3$ was added before the addition of DIBAL, conjugate ester **214** was reduced to the corresponding alcohol in 45% yield (Table 9). When $Me_2O{\bullet}BF_3$ was used instead, the yield was lower. $THF{\bullet}BF_3$ did not work at all, probably because of stronger chelation between BF_3 and the oxygen atom in THF. $^tBu(Me)O{\bullet}BF_3$ didn't work either, probably because it can not chelate with the ester carbonyl efficiently due to hindrance. Those results seem to

demonstrate several points: first, the Lewis acid functions by selectively activating the ester carbonyl; second, the Lewis acid should be neither too strong nor too weak; finally the Lewis acid should not be sterically demanding.

Table 9

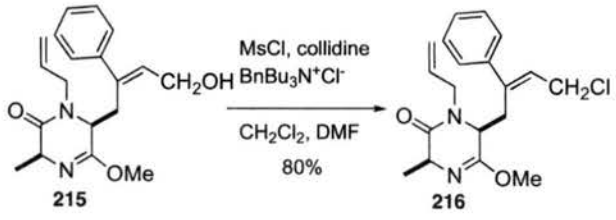


Lewis acid	Results
None	decomposition
$Me_2O•BF_3$	20 %
$Et_2O•BF_3$	45%
$THF•BF_3$	decomposition
$^tBu(Me)O•BF_3$	decomposition
$Me_2S•BF_3$	70 %

Eventually, we found that an ideal yield was obtained when we used one equivalent of $Me_2S•BF_3$ prior to addition of DIBAL. It was found that only one equivalent of Lewis acid can be used. Addition of one equivalent of $Me_2S•BF_3$ plus one equivalent of dimethyl sulfide before addition of DIBAL may also reduce the ester. However, when the reaction was scaled up some by-products were also formed. In all cases over three equivalents of DIBAL have to be used since the Lewis acid consumes one equivalent of DIBAL. Any less than that caused incomplete reduction. In this case, a mixture of alcohol and aldehyde was obtained. Only CH_2Cl_2 can be used as solvent. All other solvents only caused decomposition. A mixed solvent of CH_2Cl_2 with toluene or hexane only led to low yield.

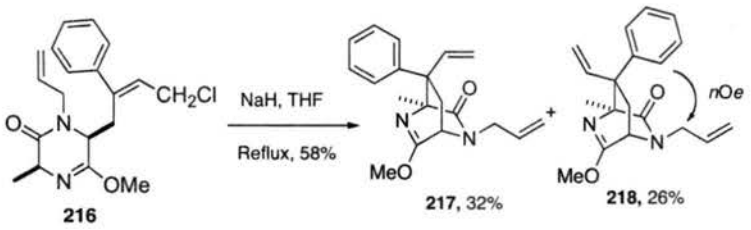
By carefully choosing the reaction solvent and additive, we overcame the difficulties with reduction. We shall point out that using DIBAL and $Me_2S•BF_3$ jointly to reduce a conjugate ester was never reported before.

With ideal yield, we now can access enough of alcohol **215** for our synthesis. Alcohol **215** was first treated with MsCl at the presence of collidine in CH_2Cl_2 to afford a mixture of allyl chloride and mesylate. Then CH_2Cl_2 was removed under vacuum and DMF was added to facilitate the transformation of mesylate to chloride. After several hours, an excess of $BnBu_3N^+ Cl^-$ was added to ensure the reaction was complete. After work-up we obtained allyl chloride **216** in 80% yield (Scheme 56).



Scheme 56

Now we reached the second key step: the S_N2' reaction. Two diastereomers **217** and **218** were obtained when a solution of allyl chloride **216** in THF was refluxed with NaH (Scheme 57). The reaction showed no selectivity. This showed that the tight ion pair mechanism which favors the closed transition state did not apply to this system for some structural reasons. [21]



216 217, 32% 218, 26%

Scheme 57

^{1}H NMR spcetra provided good evidence of the S_N2' reaction. In **216**, there is only three vinyl protons. In **217** or **218** there are six vinyl protons. The methylene group in the allyl chloride had disappeared. The methyl group linked to a methine in the DKP became a singlet, and the methine proton disappeared. The two isomers **217** and **218** showed nearly the same ^{1}H NMR pattern. There were slight differences between the CH_2 protons on the bridges of the two isomers because they are in different magnetic environments. ^{13}C NMR and MS further confirmed the S_N2' products. The R_fs of the two isomers on TLC are close, but they could be separated by PTLC. The desired isomer, compound **218,** is a little more polar than the undesired isomer, compound **217**. The two isomers were identified by NOE experiments. NOE was observed on the allyl methylene when the *o*-phenyl protons in **218** were irradiated.

As we mentioned in Chapter 1, S_N2' reactions have been used in the Williams group to synthesize the families of paraherquamides and brevianamides[20,21,22] since the 1990's. The S_N2' reaction here is unique because two quaternary centers are installed.

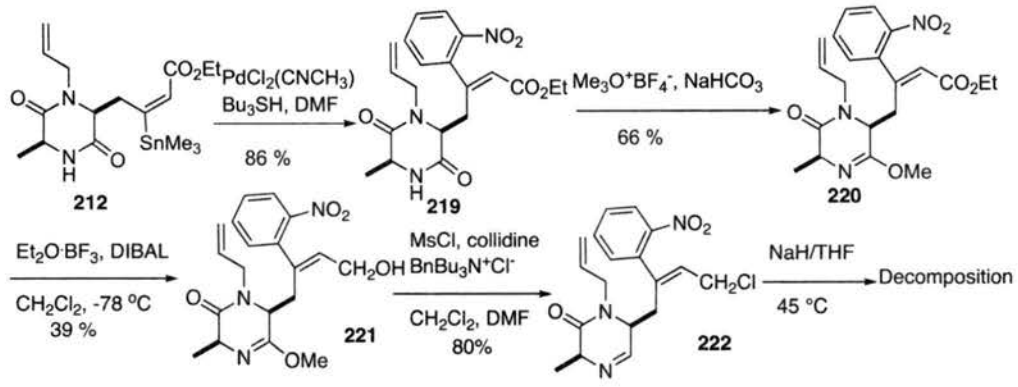
We first tried to optimize the S_N2' reaction. When the reaction temperature was lowered to 45 °C, the reaction was still complete and much cleaner. The reaction was also cleaner when NaH in mineral oil was washed with benzene and then with THF. When benzene was used as solvent, the reaction was very sluggish. When

diethyl ether was used as the solvent, another product was observed, and no S_N2' reaction was observed. When CH_2Cl_2 was used as solvent, the S_N2' reaction was observed; however, with no better yield or better selectivity. In polar solvents such as DMF, the allyl chloride decomposed to a complex mixture. Addition of crown ether also caused decomposition. The S_N2' reaction is a thermal reaction. In the past, we believed that heat was needed to improve the solubility of NaH. When NaHMDS was used to deprotonate the α-H at -78 °C, no reaction was observed by TLC. Even if the reaction mixture was warmed to room temperature, no reaction was observed and only starting material was seen. It seems from this phenomenon that the cyclization also needs heat to overcome the energy barrier. However, when the reaction was warmed up to 45 °C, a very polar by-product was observed on TLC and no S_N2' product was obtained. In summary, refluxing with washed NaH in THF is the best condition for the S_N2' reaction.

2.3.3 Efforts to introduce *ortho* functionality

According to our discussion at the beginning of this chapter, an *ortho* functionality on the phenyl group such as a latent amino group or *ortho*- bromine will greatly facilitate the synthesis of spiroquinazoline or alantrypinone. The most important consideration is that the S_N2' reaction must tolerate those functionalities.

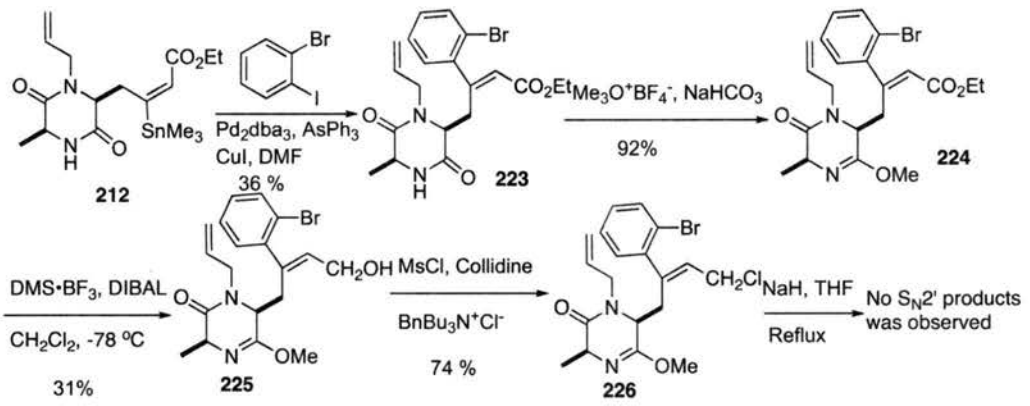
First, we tried to introduce an *ortho*-nitrophenyl by a Stille coupling reaction. By using the same chemistry as we used to synthesize δ,γ-unsaturated amino acid **6b**, we were able to prepare compound **219**. The allyl chloride **222** was prepared by following the same procedure as discussed above (Scheme 58).



Scheme 58

We mixed **222** and NaH in THF and heated it for several hours. All starting material was consumed, but no new spot was observed and substrate **222** decomposed. This demonstrated that NO_2 is not stable to such a basic conditions. In our effort to synthesize δ-aryl-δ,γ-usaturated-α-amino acids, we failed to couple two types of allyl chloride with Williams lactone template. By now we can draw the conclusion that a nitro group is not tolerated in our synthetic route. Therefore, the introduction a nitro group at an early stage is not feasible.

Another synthetic effort was to introduce a bromine atom at the *ortho* position (Scheme 59). Although we could prepare the functionalized allyl chloride **226** by following the same chemistry as before, we were unable to make it cyclize to form any S_N2' product. After refluxing with NaH for several hours, only starting material was observed. Allyl chloride **226** cannot cyclize probably due to hindrance from the bromine atom.



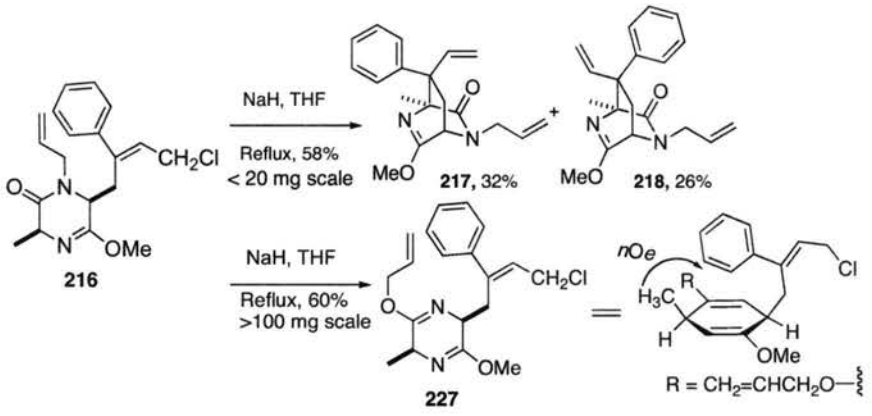
Scheme 59

2.3.4 Unexpected sigmatropic rearrangement

It seems impossible to introduce an *ortho* functional group before the S_N2' reaction. The only remaining choice left is to introduce an *ortho* functional group after S_N2' reaction.

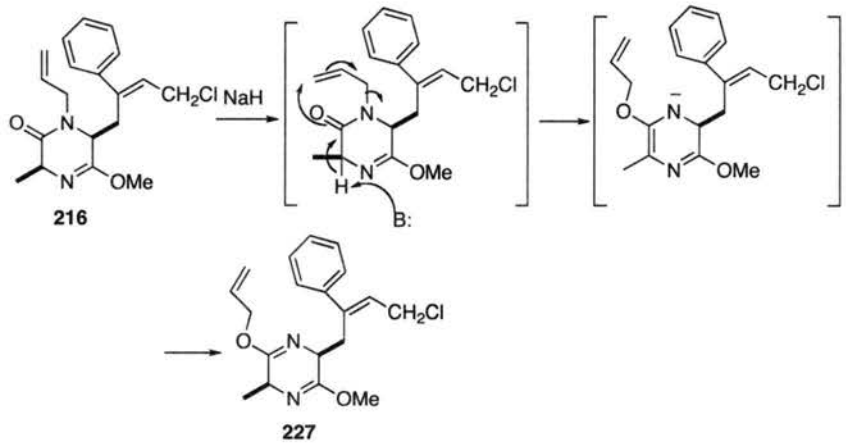
To push forward, we needed to prepare S_N2' products on a gram scale. Unfortunately we met one more technical problem. When the S_N2' reaction was scaled up to 500 mg, a sigmatropic rearrangement product was obtained, and only a trace amount of S_N2' products were observed (Scheme 60). The evidence of the undesired reaction was provided by various spectral analyses. When C_6D_6 was used as the solvent, nearly the same ^1H NMR pattern was obtained for the unexpected by-product as that of allyl chloride **216**, except that the chemical shifts of some protons were slightly different. On ^{13}C NMR, one C=O peak at 180 ppm moved upfield to 169 ppm (C=N). In OR, the absorption at 1695 cm^{-1} for C=O moved to 1685 cm^{-1}, which is typical of C=N. The same exact mass was obtained. The R_f value of the undesired by- product **227** is 0.33 in 33% ethyl acetate/hexanes, in contrast to that of

allyl chloride **216** (Rf=0.2 in 33% ethyl acetate/ hexanes). An *n*Oe was observed between the methyl group and phenyl groups. This result excluded the possibility of an eperimerization product.



Scheme 60

The sigmatropic rearrangement by-product **227** has the same polarity as the the S_N2' product **218**. It was also found that when the starting material was heated without base, no sigmatropic rearrangement was observed. This therefore seems to be a base-promoted sigmatropic rearrangement (Scheme 61).

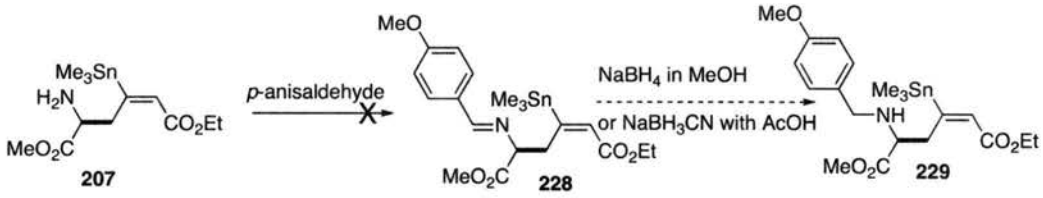


Scheme 61

We mentioned the necessity of an alkyl protecting group to facilitate the S_N2' reaction. We chose the allyl group because it is small and electron rich. It is easy to introduce due to lack of no steric hindrance. We envisioned that the addition of a *tert*-butyl group could suppress the unexpected sigmatropic rearrangement and make the S_N2' reaction favor the desired diastereomer. However, we were unable to introduce it into our substrate due to problems with large steric hindrance. We did not use benzyl type protecting groups initially because we were not sure whetther they could be introduced it efficiently. However, due to the technical problems we met, we needed to try it because we did not have many options with alkyl protecting groups.

2.3.5 Second-generation S_N2' reaction

We must consider using another type of protecting group due to the undesired rearrangement with the allyl protecting group. One option is benzyl-type protecting groups. At first, we avoided this choice for two reasons. First, benzyl type protecting groups on amides, especially in DKPs, are difficult to remove. For example, DDQ and CAN are widely used to remove PMB from protected alcohols, but usually they are not used to remove PMB protecting groups on amides in DKP. Second, benzyl-type protecting groups are hard to introduce. For example, all conditions tried to make **229** by condensation of free amine **207** with *p*-anisaldehyde followed by reduction with $NaCNBH_3$ or $NaBH_4$ failed (Scheme 62). The imine was not observed when we tried to condense the free amine with *p*-anisbenzaldehyde, even in the presence of a dehydrant such as $MgSO_4$ or $(MeO)_3CH$.

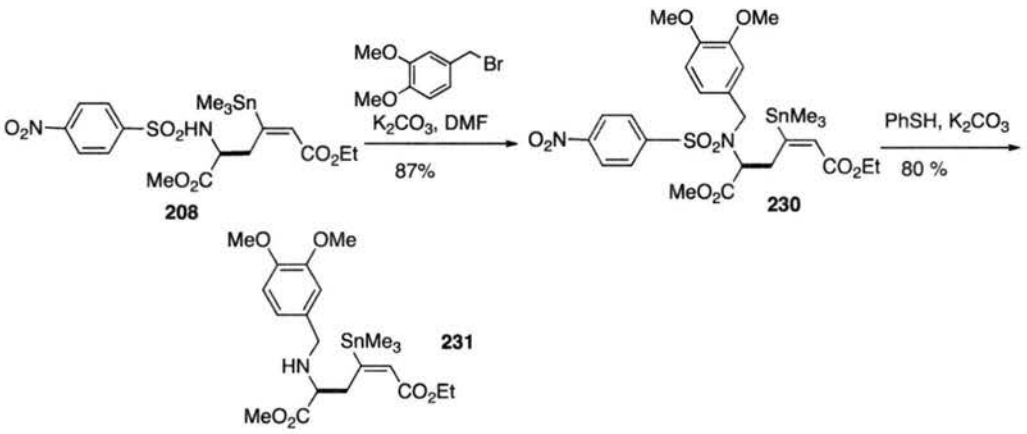


Scheme 62

There are several kinds of benzyl protecting groups and it is well known that removal of 3,4-dimethoxybenzyl group (DMPM) is much easier than with the PMB group. The oxidation potential of DMB is 1.45 V, which is lower than that of PMB

(1.78 V).[63] We chose the 3,4 dimethoxbenzyl group with the hopes that it could be removed by DDQ.

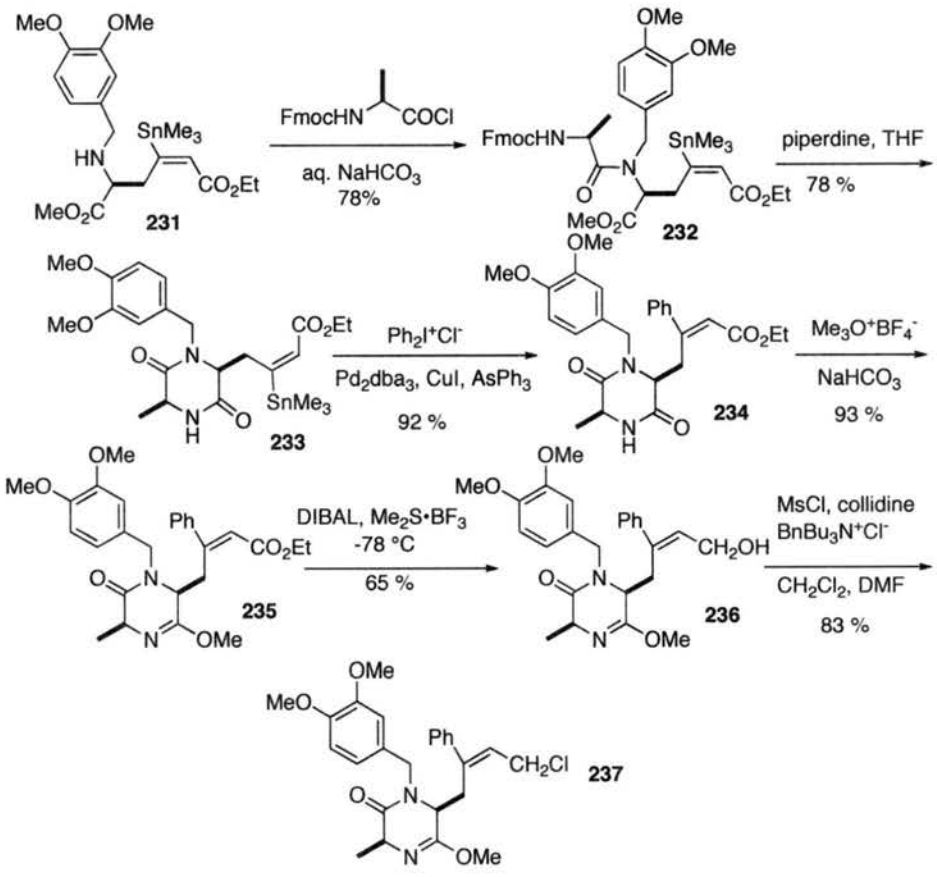
Amide **208** reacted with 3,4-dimethoxybenzyl bromide and K_2CO_3 in DMF to give the bis-protected amino acid **230** in good yield (Scheme 63). Removal of the 4-nitrobenzenesulfonyl group from bisprotected amino acid **230** gave dimethoxybenzyl protected amino acid **231.**



Scheme 63

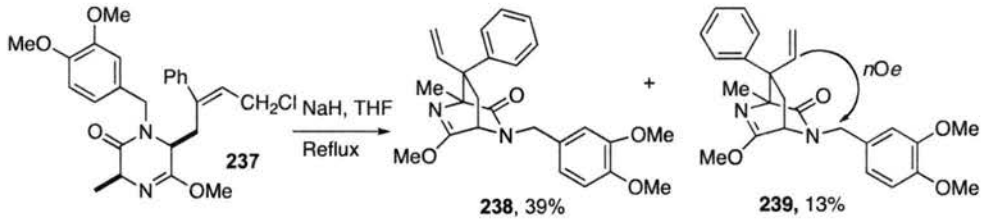
Reaction of **231** with the acid chloride derived from Fmoc-alanine under Schotten-Baumann conditions produced dipeptide **232** (Scheme 64). Deprotection of Fmoc generated DKP **233**. Stille coupling reaction with diphenyliodonium salt $Ph_2I^+Cl^-$ using the same conditions as previously described gave DKP **234**. Compound **234** reacted with trimethyloxonium tetrafluoroborate to give compound **235**. Using the conditions we optimized before, we reduced **235** to alcohol to **236**. So a solution of compound **235** was cooled to -78 °C, and then treated with $Et_2O{\bullet}SMe_2$. Three equivalents of DIBAL in CH_2Cl_2 were then added to the reaction mixture dropwise. Using this method, compound **235** was reduced to alcohol **236**. This alcohol was then

converted into chloride **237** in good yield by treatment with MsCl and collidine followed by $BnBu_3N^+Cl^-$.



Scheme 64

When allyl chloride **237** was refluxed with NaH in THF for several hours, we were happy to find that two S_N2' products, **238** and **239**, were formed (Scheme 65). An NOE was observed between the protons of the benzyl methylene group and one vinyl proton in the desired diastereomer. The reaction is now in favor of the non-desired product. As we demonstrated above, the S_N2' reaction using the allyl protected substrate showed no selectivity for either diastereomer. It seems the protecting group affects the selectivity of the S_N2' reaction.



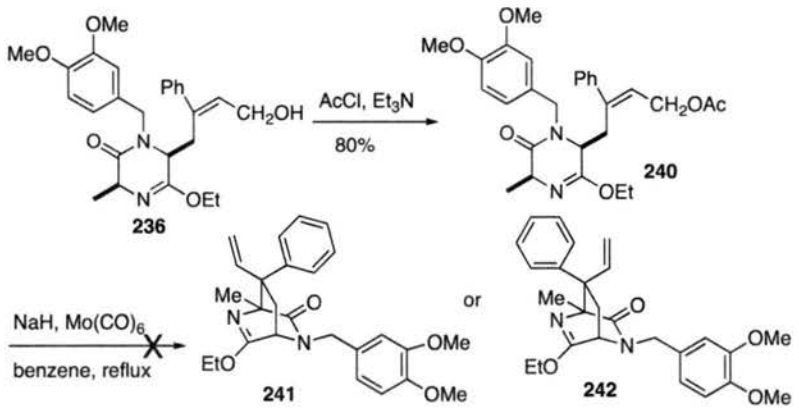
Scheme 65

The S_N2' reaction above was successfully scaled up to several hundred milligrams without any problem. The total yield of the two isomers was nearly 53%. To obtain this yield, NaH should be washed with benzene and THF. Again, the reaction is very slow in benzene. No other solvents worked better than THF. Bases such as NaHMDS and DBU were also tested. When the temperature was below 25 °C, no reacion was observed. When the mixture was heated to 45 °C some very polar by-products were observed on the baseline of TLC.

Although when NaH was used as the base, the S_N2' reaction did work, it is obvious that some of the substrate decomposed. We found that changing of the methyl lactim ether to the ethyl lactim ether did not lead to any improvement of yield.

The ratio of the non-desired diastereomer to the desired one was 3:1. To get better selectivity, we examined transition metal-catalyzed allylic alkylations to build [2,2,2] bridged cycle. Refluxing of substrate in benzene with $Mo(CO)_6$ and NaH only led to decomposition and no bridge cycle was formed (Scheme 66). Perhaps this result is not surprising, given that the α-H on C-4 is not acidic enough. Barry Trost stated in his review: "While the studies [of transition metal-catalyzed allylations with

unstabilized nucleophiles] are limited at present, the results have been disappointing."[64]

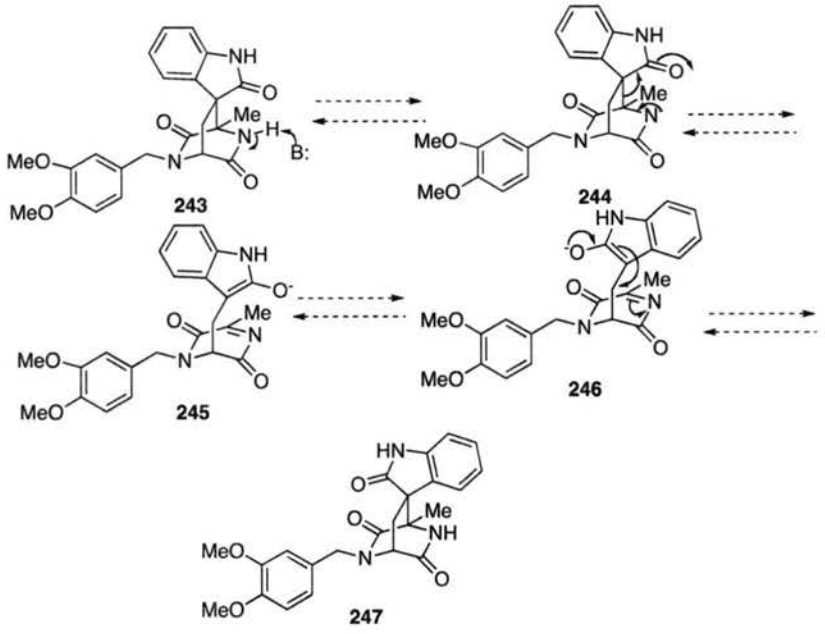


Scheme 66

Although it seems that the alkyl protecting groups affect the selectivity, we did not have many options. The protecting group we chose must meet two requirements: 1) it should be stable enough to survive the synthetic route until we want to remove it; 2) it should be readily introduced. As we mentioned before, we believed that a *tert*-butyl group was a good choice, but we were unable to introduce it due to steric hindrance.

Eventually, we stopped screening different protecting groups. Kende has demonstrated that alantrypinone and *epi*-alnatrypinone can taut with each other when treated with DBU.[13] We believe the undesired diastereomer is still useful. It may lead to the synthesis of *epi*-alantrypinone, which may be converted into alantrypinone. We envisioned that a similar tautomerization may also occur at an earlier stage by the same mechanism as reported (Scheme 67).[13] This requires us to make the oxindole

first, and the methyl lactim ether must be deprotected. The challenge will be how to differentiate the amide of the oxindole and amide of the DKP.



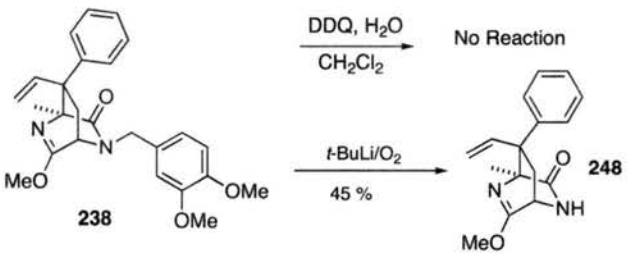
Scheme 67

2.4 Construction of quinazolinone core and future plan

2.4.1 Construction of quinazolinone core

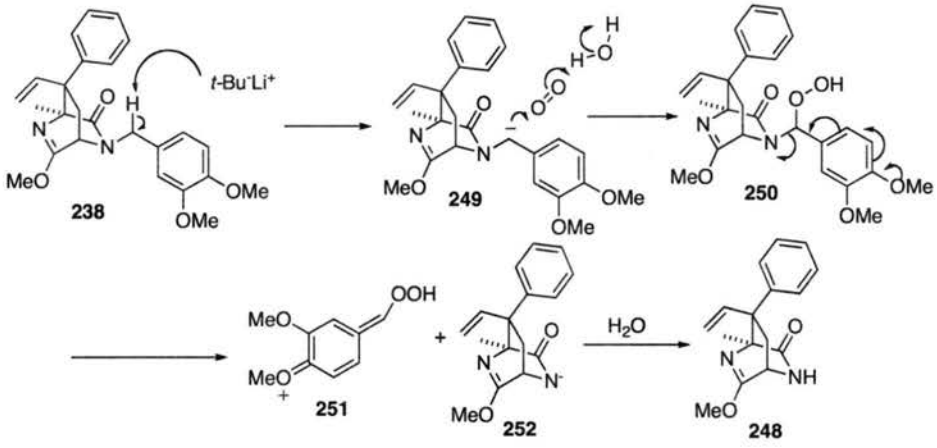
We have developed a novel S_N2'reaction which introduces two quaternary centers in one step. The desired and undesired diastereomers were obtained in 13% and 39% yields respectively. The desired diastereomer may potentially be converted into alantrypinone or spiroquinazoline, but the poor yield makes it very difficult for us to continue this way. The undesired diastereomer may be converted into *epi*-alantrypinone, and Kende has converted *epi*-alantrypinone into alantrypinone. To achieve this conversion, we have to construct the quinazolinone core and the oxindole.

Compound **238** was first treated with DDQ in wet CH_2Cl_2. Surprisingly, the dimethoxybenzyl (DMB) group cannot be removed by DDQ. Harsher conditions were then examined (Scheme 68). We found that the dimethoxybenzyl group could be removed by treatment with *t*-BuLi followed by a stream of oxygen leaving the methyl lactim ether intact. [65]



Scheme 68

Removal of benzyl type protecting groups through a benzyl anion has been reported before.[65] We found that addition of ammonium chloride is unnecessary and damages the lactim ether. We also found that addition of dimethyl sulfide is unnecessary. Addition of dimethyl sulfide did not improve the yield. Usually, dimethyl sulfide is used to break the O-O bond. A mechanism is proposed as shown in Scheme 69. Benzyl anion **249** is formed by deprotonation, and then attacks oxygen to form benzylperoxide **250**. **252** is then formed which gets a proton to deliver the free amide **248**. **251** hydrolyzes to 3,4-dimethoxybenzaldehyde and H_2O_2.

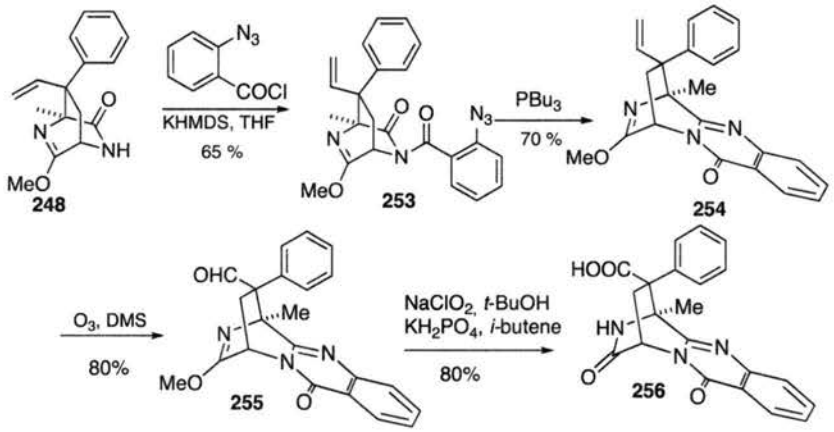


Scheme 69

Product **248** has two amides. One is selectively protected in the form of a methyl lactim ether while the other one is free. Compound **248** was treated with KHMDS followed by *o*-azidobenzyl chloride to produce compound **253**. An intramolecular aza-Wittig reaction generated the quinazolinone core in **254**. We have mentioned the roles of the orthogonal groups on thee DKP. The first role is to facilitate the S_N2' reaction and the second is to differentiate the amides in the DKP.

Thus far, we have demonstrated that our consideration and selection of protecting groups is correct.

The terminal alkene in compound **254** was then oxidized to aldehyde **255** by ozonolysis. We shall point out that the residue remaining after evaporation of solvent should be purified by flash chromatography immediately, otherwise the methyl lactim ether would be deprotected. Some acidic by-product may have been formed after ozonolysis which caused deprotection of the lactim ether. Compound **254** was still contaminated with small amount of a phosphorous by-product generated in aza-Wittig reaction even after purification by flash chromatography. Aldehyde **255** was further oxidized to acid **256** using $NaClO_2$ at the presence of *iso*-butene in a buffered solution (Scheme 70).[66]



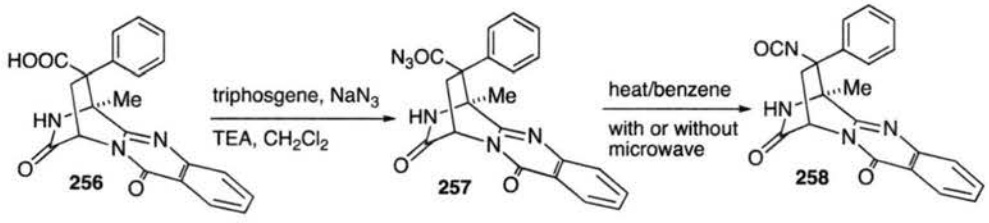
Scheme 70

2.4.2 Efforts to make oxindole

Acid **256** was converted into the corresponding acid azide **257** by treatment with triphosgene and NaN_3 in the presence of triethylamine (Scheme 71).[67] Acid azide **257** was used without further purification following the reported protocol.

Formation of the acid azide was confirmed by IR absorption at 2160 cm^{-1}, and the disappearance of the broad band at 3184 cm^{-1}.

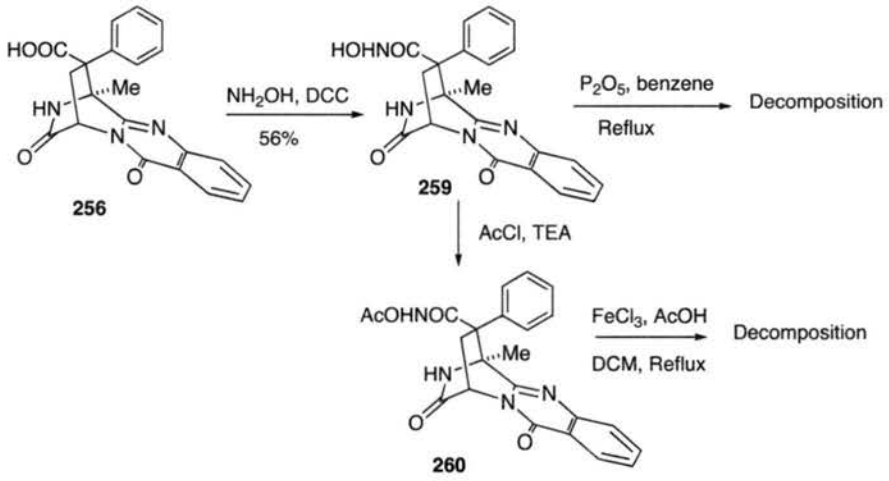
Unfortunately, no oxindole was formed when a solution of **257** in benzene was heated, even when using microwave conditions. Instead, we obtained a by-product (**258**), which is much less polar than *epi*-alantrypinone. An IR absorption at 2280 cm^{-1} was observed, which is a characteristic absorption for the isocyanide group. Indeed cyclization to make five-membered ring by a nitrene insertion into a C-H bond is very uncommon. No precedent has been found in the literature. The problem with this chemistry is probably due to the difficulty for the phenyl group to reach the appropriate angle such that the nitrene can insert into the phenyl C-H bond.



Scheme 71

Compound **256** was treated with hydroxylamine and DCC to yield hydroxamate **259** (Scheme 72). Due to poor solubility, compound **259** has to be used crude. Treatment of **259** with P_2O_5 [68] resulted in decomposition and no oxindole was observed. This demonstrated that substrate **259** is not stable to the condensing reagent P_2O_5. Compound **259** can be further converted into *N*-acetyloxyamide **260**, which had to be used crude, again due to poor solubility. When compound **260** was refluxed with $FeCl_3$ [68] in the presence of acetic acid a complex mixture was obtained.

Eventually, we tried again to introduce an *ortho* funcitionality on **237** by coupling **233** with a different iodide. As we mentioned in **2.3.3,** although we can couple **233** with *o*-idonitrobenzene or *o*-iodobromobenzene, we were unable to make the S_N2' reaction work.



Scheme 72

2.4.3 Conclusion and future plan

As we discussed in this chapter, we have made solid progress toward the first total synthesis of spiroquinazoline. Our progress is represented as follows:

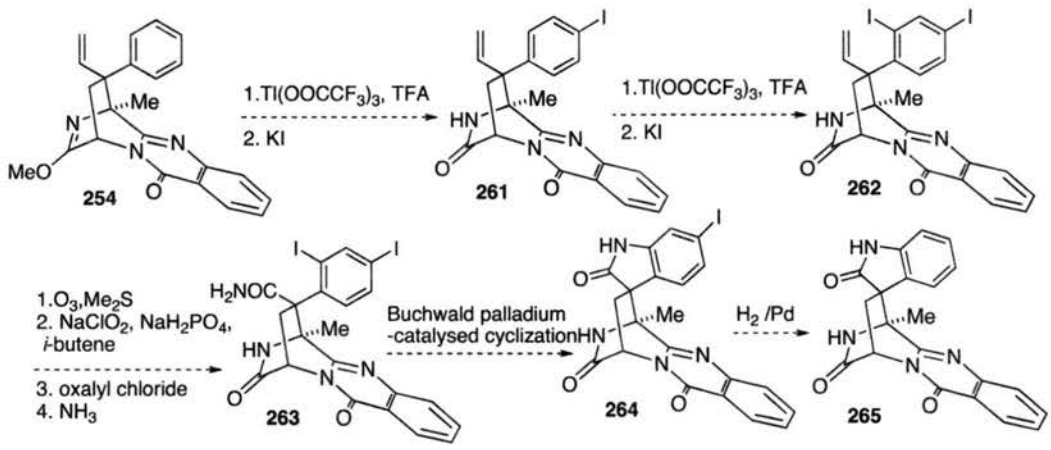
1) We have developed a new methodology to synthesize δ,γ-usaturated-α-amino acids;

2) We have developed an S_N2' reaction to construct a novel bicyclo[2,2,2] diazaoctane which contains two adjacent quaternary centers;

3) We successfully constructed the quinazolinone core on bicyclo[2,2,2]diazaoctane. Unfortunately, we are able to make our natural product due to the lack of an *ortho* functional group.

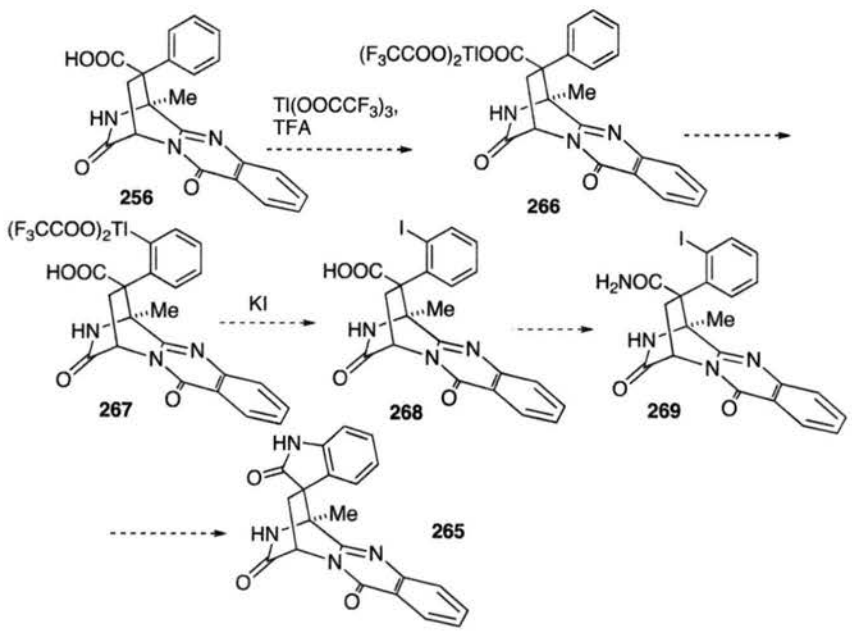
We have demonstrated that it is impossible to introduce an *ortho* functionality before the S_N2' reaction due to the congestion in the S_N2' reaction.

Another option is to introduce an *ortho* functional group after S_N2' reaction. To do that, we would have to block the *para* position of the phenyl. Our new proposal is shown in Scheme 73. We could introduce an *ortho* iodine atom by double thallation[70] followed by treatment with KI. The first thallation and iodination will occur at the *para* position of the phenyl group (**261**). The second time thallation and iodolation will happen at the *ortho* position of the phenyl group due to hinderance caused by the first iodine atom. After Buchward palladium catalyzed-cyclization to make oxindole **264**, the extra iodine atom may be removed by hydrogenolysis.



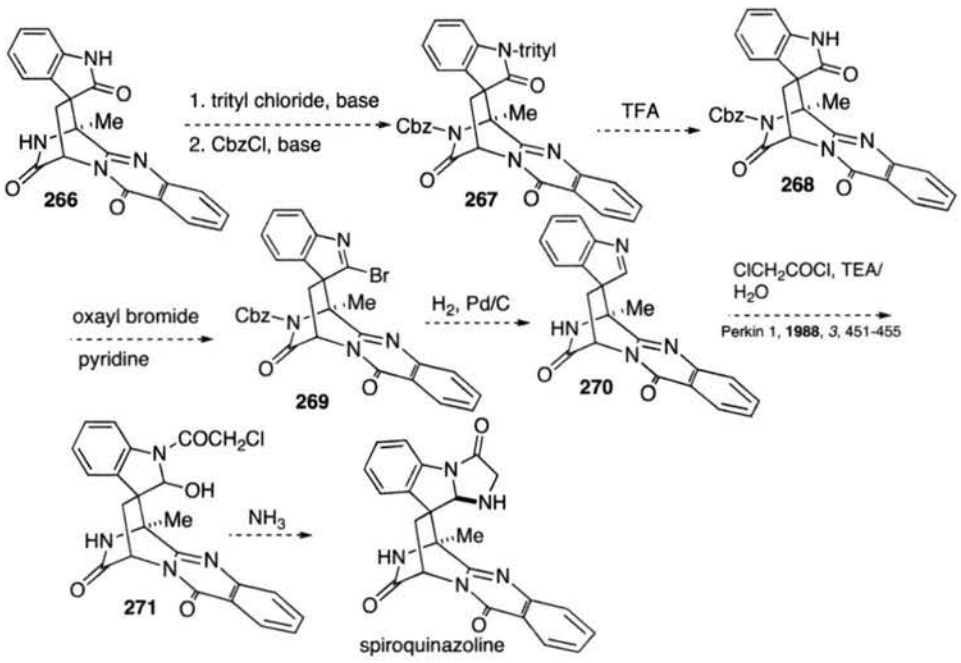
Scheme 73

If we choose to attempt the thallation at a later stage, after the terminal alkene is oxidized to acid **256**, something interesting may happen (Scheme 74). In this case, a mixed thallium (III) salt (**266**) may be formed first. Then, thallium will be delivered to the *ortho* position intramolecularly (**267**). If an *ortho*-directed thallation could happen like this, then double thallation is unnecessary. After treatment with KI, we expect to obtain only the *ortho*-iodo substituted product **268** directly. The acid can be converted into corresponding amide **269**, which can cyclize to form oxindole **265**.



Scheme 74

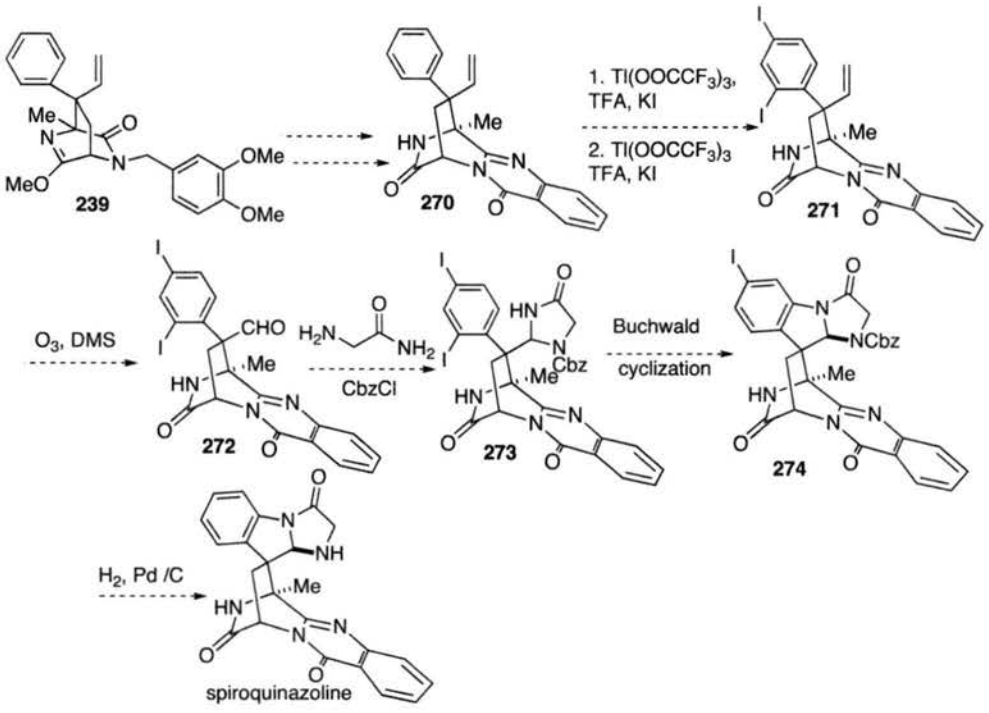
As has been demonstrated by Kende, *epi*-alantrypinone (**265**) can be converted into alantrypinone (**266**) by treatment with DBU in good yield. If we get *epi*-alantrypinone **265,** we can easily form alantrypinone **266**. We also know that Hart failed to convert alantrypinone to spiroquinazoline. Scheme 75 shows our idea to convert alantrypinone into spiroquinazoline. The two amides in alantrypinone are in very different steric environments with different hindrance. The amide on oxindole is in an open environment, which is less hindered. If we introduce a bulky protecting group, for example, trityl, the amide on oxindole will be attacked first. Then, the other amide may be protected with a Cbz protecting group to afford compound **267**. Treatment of compound **267** with TFA will remove trityl protecting group to make compound **268**.



Scheme 75

The oxindole may then undergo a Vilsmeier bromination reaction[71] to produce bromide **269**, which could be reduced to 3*H*-indole **270**. At the same time, the Cbz protecting group will be removed. Following a literature precedent, treatment of 3*H*-indole with α-chloro acetyl chloride will give compound **271**.[72] We envision that this compound could be converted into spiroquinazoline simply by treatment with NH_3 (Scheme 75).

The desired isomer **239** in the S_N2' reaction could be converted into spiroquinazoline more concisely (Scheme 76).



Scheme 76

We have no doubt that the quinazolinone core in **270** could be constructed in a similar fashion to that described. The product obtained could undergo double thallation to introduce two iodine atoms on the phenyl group (**271**). Ozonolysis of the terminal alkene in compound **271** will produce aldehyde **272**, which could then cyclize with 2-aminoethanamide to form an imidazolidin-4-one ring. The amine will then be protected with a Cbz group (**273**). A Buchwald palladium catalyzed cyclization could deliver imidazoindoline ring system **274**. Removal of the Cbz group and the extra iodine atom by hydrogenolysis will produce spiroquinazoline.

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Chapter 3. Experimental Section.

General Procedures

Unless otherwise noted, materials were obtained from commercially available sources and used without further purification. Toluene, diethyl ether, THF and dimethylformamide were degassed with argon and passed through a solvent system (J.C. Meyer of Glass Contour). The molecular sieves were activated by heating at 150 °C at 1 mm Hg for 3 h in a vacuum oven.

All reactions involving hydroscopic substances were conducted with flame- or oven- dried glassware under an inert atmosphere (Ar) dried by passage of atmospheric gases through a column packed with $CaSO_4$.

Chromatographic separations were performed with EM Science TLC plates (silica gel 60, F254, 20 X 20cm X250 μm) or with EM science 230-240-mesh silica gel under positive air pressure. Reactions and chromatographic fractions were monitored and analyzed with EM Science TLC plates. Visualization of TLC was achieved with ultraviolet light or heating of TLC plates submerged in a 5% solution of phosphomolydic acid in 95% ethanol.

Nuclear magnetic resonance (NMR) spectra were acquired using Bruker AC-300, Varian 300 or 400 spectrometers. NMR chemical shifts are given in parts per

million (ppm) relative to internal $CHCl_3$, benzene or methanol. Proton (^1H) NMRs are tabulated in the following order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet) and coupling constant in hertz. When appropriate, the multiplicity of a signal in denoted as "br" to indicate that the signal was broad.

Infrared spectra were recorded on a Perkin-Elmer 1600 series FT-IR as thin films from methylene chloride and were reported as λ_{max} in wave numbers (cm^{-1}),

Mass spectra were obtained on Fisons VG Autospec. Optical rotations were obtained on a Rudolph Research automatic polarimeter Autopol III operating at 589 nm.

4-Bromo-2,5-dihydro-2-oxofuran (169)[36].

168 169

Tetronic acid (0.9 g, 9 mmol) was added to a mixture of 20 mL CH_2Cl_2 and 0.9 mL DMF and cooled to 0 °C. The suspension was stirred for 5 minutes and oxayl bromide (2.23 g, 1 mL, 10.8 mmol) was added over 6 minutes. The color of the mixture turned from yellow to green gradually. The mixture was stirred for 1 h at 0 °C and 2 h at room temperature. 25 mL water was added. The two phases were separated and the aqueous phase was extracted with ether (10 mL X 4). The organic layers were combined and washed with water, saturated aqueous $NaHCO_3$ and saturated NaCl solution. The solvent was removed by rotary evaporation and the residue was recrystallized from diethyl ether to obtain yellow crystals 1.22 g (83 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.82 (2H, d, J = 1 Hz), 6.31 (1H, t, J = 1 Hz).

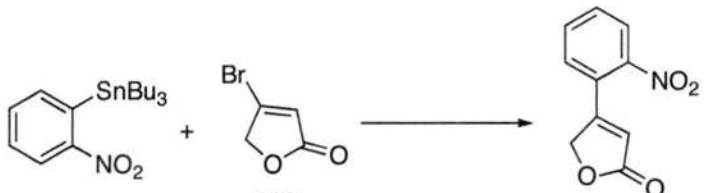
Tributyl(2-nitrophenyl)stannane (171)[37].

170 171

A stirred solution of hexabutylditin (1.4 g, 2.4 mmol), 2-iodo-nitrobenzene (0.5 g, 2 mmol), and $Pd(PPh_3)_4$ (6 mg, 0.006 mmol) in 20 mL toluene was heated at 60 °C for 72 h under argon. After evaporation to remove the solvent, the residue was washed with aqueous KF solution to remove tributyltin iodide. The aqueous layer was

extracted with benzene and dried over anhydrous Na_2SO_4. Purification was performed by flash column chromatography to give 0.66 g of yellow oil (80 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.45-2.05 (27 H, m), 7.35-8.55 (4H, m).

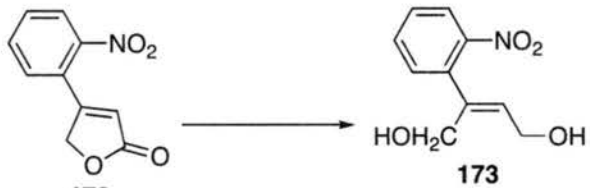
4-(2'-Nitrophenyl)-2,5-dihydro-2-oxofuran (172).



171 **169** **172**

$Pd(PPh_3)_4$ (57 mg, 0.05 mmol) and CuBr (26 mg, 0.13mmol) were added to a solution of **171** (1.565 g, 3.8 mmol) and **169** (0.6192 g, 3.8 mmol) in THF at room temperature. The mixture was refluxed under Ar for 15 h. After cooling, THF was evaporated and 2 mL benzene was added. The mixture was separated through flash column chromatography and 0.7819 g yellow needle crystals were obtained (100 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.08 (2H, d, J = 1.8 Hz), 6.16 (1H, t, J = 1.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.9, 118.7, 125.3, 126.8, 130.4, 131.4, 134.1, 147.3, 163.5, 172.7. IR (NaCl, neat) 1785, 1745, 1648, 1605, 1573, 1522 cm^{-1}. HRMS (FAB+) calc. mass for $C_{10}H_9NO_4$ 206.0453 (M+1), found 206.0444. R_f 0.3 (eluted with 50 % ethyl acetate/ hexane).

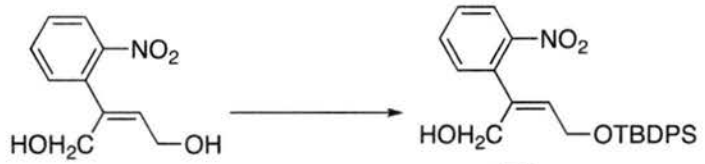
(Z)-(2'-Nitrophenyl)but-2-ene-1,4-diol (173).



172 **173**

102.5 mg of lactone **172** (0.5 mmol) was dissolved in 2.5 mL dry THF and cooled to –76 °C. 2.5 mL 1 N DIBAL solution in THF (2.5 mmol) was added to the solution dropwise over 5 minutes. The mixture was stirred for 30 minutes at –76 °C and then warmed to RT overnight, then quenched with 3 g ice and extracted with ether (10 mL X 3). The extracts were combined and washed with saturated NH_4Cl, water and brine. The solvent was rotovaped and residue was separated by flash chromatography (eluted with 50% ethyl acetate/hexanes) to give 61 mg of orange oil (60 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.49 (1H, br), 2.61 (1H, br), 4.39 (2H, d, J = 6.4 Hz), 4.47 (2H, s), 5.77 (1H, t, J = 6.4 Hz), 7.36-8.1 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 58.9, 61.8, 124.6, 128.7, 131.1, 132.0, 133.5, 137.3, 141.3, 148.1. IR (NaCl, neat) 3336, 2872, 1607, 1570, 1524, 1347 cm^{-1}. HRMS (FAB+) calc. mass for $C_{10}H_9NO_4Na$ 232.0586 (M+Na), found 232.1884. R_f 0.3 (eluted with 100 % ethyl acetate).

(Z)-4-*t*-Butyldiphenylsilyoxy-(2'-nitrophenyl)but-2-ene-1-ol (174).



173 **174**

39.1 mg of compound **173** (0.187 mmol) was dissolved in 2 mL CH_2Cl_2 and cooled to –60 °C. 52 mg (0.187 mmol) of *t*-butyldiphenylsilyl chloride, 0.04 mL triethyl amine (0.29 mmol) and 1 mg of DMAP (4-dimethylamino pyridine) were added. The mixture was stirred and warmed to rt overnight. Removal of the solvent followed by separation through flash chromatography yielded 49 mg of **174** (60 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (9H, s), 2.06 (1H, s), 2.07 (1H, t, J = 6.0 Hz), 4.28 (2H, dd, J = 6.0, 0.9 Hz), 4.31 (2H, d, J = 6.0 Hz), 5.68 (1H, t, J = 6.0 Hz), 7.2-8.0 (14H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 27.0, 60.7, 61.8, 124.5, 128.0, 130.1, 131.2, 132.0, 133.2, 135.8, 137.1, 139.8, 148.5. IR (NaCl, neat) 3422, 3071, 2957, 1608, 1571, 1525 cm^{-1}. HRMS (FAB+) calc. mass for $C_{26}H_{29}NO_4NaSi$ 470.1758 (M+Na), found 470.1757. R_f 0.5 (eluted with 50 % ethyl acetate / hexanes).

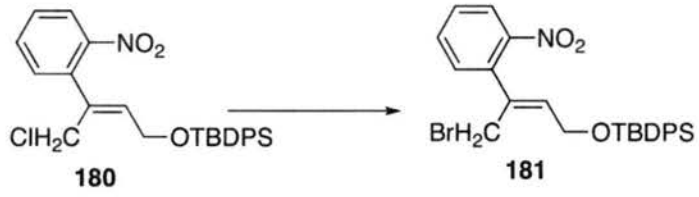
(Z)-1-Chloro-4-*t*-butyldiphenylsilyoxy -(2'-nitrophenyl)but-2-ene (180).

174 **180**

330 mg of compound **174** (0.762 mmol) and *N*-chlorosuccinimide (204 mg, 1.43 mmol) were dissolved in 12 mL CH_2Cl_2 and cooled to -78 °C. 0.224 mL of methyl sulfide (3.05 mmol) was added. The mixture was stirred and warmed to rt

overnight. Removal of the solvent followed by separation through flash chromatography yielded 206 mg of **180** (60 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (9H, s), 4.25 (2H, s), 4.48 (2H, d, J = 6.0 Hz), 5.76 (1H, t, J = 6.0 Hz), 7.2-8.2 (4H, m, 14 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 26.9, 42.4, 60.8, 124.8, 128.1, 129.0, 130.0, 133.3, 133.4, 113.5, 134.5, 135.4,135.8, 136.4. IR (NaCl, neat) 3071, 3050, 1609, 1571, 1526, 1472 cm^{-1}. R_f 0.3 (eluted with 10 % ethyl acetate / hexanes).

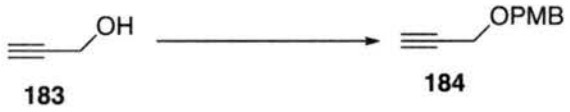
(Z)-1-Bromo-4- *t*-butyldiphenylsilyoxy -(2'-nitrophenyl)but-2-ene (181).



Compound **180** (200 mg, 0.443 mmol) was dissolved in 25 mL anhydrous acetone, and 385 mg of anhydrous LiBr (4.43 mmol) was added. The mixture was stirred at RT under Ar overnight and then concentrated *in vacuo*. 20 mL water and 20 ml ether were added. The layers were separated and the aqueous layers were extracted with ether (20 mL X 3). The extracts were combined and washed with saturated NH_4Cl, water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography (eluted with 25% ether/hexanes) to give 143 mg of **181** as a yellow oil (65 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (9H, s), 4.13 (2H, s), 4.47 (2H, d, J = 6.0 Hz), 5.73 (1H, t, J = 6.0 Hz), 7.2-8.2 (4H, m, 14 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.4, 26.94, 30.4, 42.4, 60.8, 124.8, 128..0, 128.05, 129.1, 130.0, 133.4, 133.5, 134.7, 135.4, 135.7, 135.77, 135.8,

136.5. IR (NaCl, neat) 3070, 3049, 1608, 1525, 1472, 1428 cm^{-1}. R_f 0.3 (eluted with 10 % ethyl acetate / hexanes).

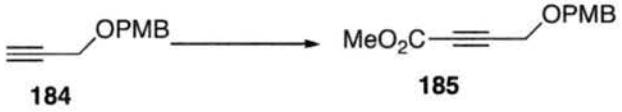
1-Methoxy-4-[(2-propynyloxy)methyl]benzene (184)[40].



183 **184**

To a solution of propargyl alcohol **183** (1.8 mL, 1.73 g, 30.9 mmol) in dry THF (50 mL) at rt was added NaH (1.71 g, 42.8 mmol, 60 % dispersion in mineral oil). After stirring for 30 min, NaI (6.41 g, 42.8 mmol), (dried 24 h at 70 °C at 0.5 Torr) and 4-methoxybenzyl chloride (5.85 mL, 6.75 g, 43.1 mmol) were added. The reaction mixture was heated at reflux for 18 h, cooled to 0 °C and quenched with 80 mL of water. The layers were separated and the aqueous layers were extracted with ether (4 X 75 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography (1:9 ether/hexanes) to give 5.4 g of **184** as a yellow oil (80%). ^1H NMR (300 MHz, $CDCl_3$): δ 2.51 (1H, s), 3.82 (3H, s), 4.17 (2H, s), 4.57 (2H, s), 6.92 (2H, d, J = 8.3 Hz), 7.32 (2H, d, J = 8.3 Hz).

Methyl 4-(*p*-methoxybenzyloxy) -2-butynoate (185)[41].

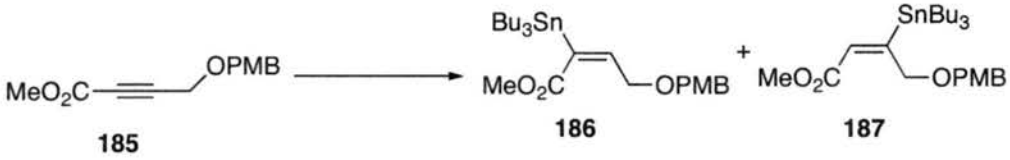


184 **185**

To a solution of **184** (2.28 g, 12.9 mmol) in THF (100 mL) was added *n*-BuLi (1.53 M solution in hexane, 8.5 mL, 13.0 mmol) at -78 °C and the mixture was stirred

at -78 °C for 30 min. To this solution was added methyl chloroformate (1.0 mL, 12.9 mmol) and stirring was continued for 1 h. The mixture was diluted with saturated $NaHCO_3$ (50 mL), and the aqueous layer extracted with ether (30 X 3 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (10% ethyl acetate/hexanes) to afford **185** (2.80 g, 12.0 mmol, 92 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80 (3H, s), 3.81 (3H, s), 4.26 (2H, s), 4.55 (2H, s), 6.86-6.90 (2H, m), 7.25-7.29 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.1, 55.5, 56.5, 71.9, 78.1, 84.0, 114.1, 128.9, 130.2, 153.8, 159.8.

Methyl (*E*)-4-(*p*-methoxybenzyloxy) -3-(tributylstannyl)-2-butenoate (186) and **Methyl (*E*)-4-(*p*-methoxybenzyloxy) -4-(tributylstannyl)-2-butenoate (187)**

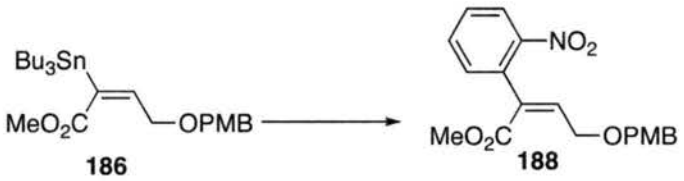


A degassed solution of Bu_3SnH (3.86 mL, 14.4 mmol) in 10 mL THF was added over 10 min to a solution of **185** (3.28 g, 14.4 mmol) and $Pd(PPh_3)_4$ (166 mg, 0.072 mmol) in 30 mL THF, which was stirred at 20 °C under Ar for 5 hrs. THF was removed under reduced pressure. The residue was purified by flash chromatography (10% ethyl acetate/hexanes) to afford 5.0 g of **186** (68 %) and 2.07 g of **187** (28 %) as colorless oils. The first product was **186**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.7-1.6 (27H, m), 3.69 (3H, s), 3.82 (3H, s), 4.48 (2H, s), 4.67 (2H, d, J = 3.0 Hz), 5.92 (1H, t, J = 3.0 Hz), 6.87 (2H, d, J = 8.7 Hz), 7.25 (2H, d, J = 8.7 Hz). ^{13}C NMR (75 MHz ,

$CDCl_3$): δ 11.1, 13.9, 27.5, 29.2, 51.3, 55.4, 72.7, 74.3, 113.8, 123.8, 123.6, 129.9, 130.5, 159.3, 165.0, 177.2. IR (NaCl, neat) 2954, 1713, 1612, 1587, 1514 cm^{-1}. R_f 0.3 (eluted with 10 % ethyl acetate/ hexanes).

The second was product **187**. ^1H NMR (300 MHz, $CDCl_3$): δ 0.7-1.6 (27H, m), 3.68 (3H, s), 3.82 (3H, s), 4.43 (2H, d, J = 4.8 Hz), 4.47 (2H, s), 6.31 (1H, t, J = 4.8 Hz), 6.89 (2H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.4, 13.9, 27.5, 29.1, 51.6, 55.4, 70.4, 72.6, 114.0, 129.7, 130.3, 136.5, 152.7, 159.4, 171.0. IR (NaCl, neat) 2955, 1708, 1612, 1586, 1514 cm^{-1}. R_f 0.3 (eluted with 100 % ethyl acetate).

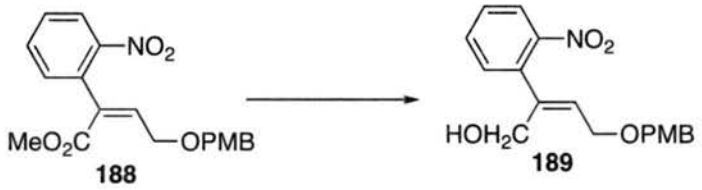
Methyl (E)-4-(*p*-methoxybenzyloxy) -3-(*o*-nitrobenzyl)-2-butenoate (188).



4.932 g of compound **187** (9.4 mmol), 2.34 g of *o*-iodo nitrobenzene (9.4 mmol) and 48 mg of $PdCl_2(MeCN)_2$ (0.188 mmol) were dissolved in 30 mL dry DMF and heated to 70 °C for 12 hrs, and then cooled to rt. 50 mL water and 50 ml ether were added. The layers were separated and the aqueous layers were extracted with ether (3X50 mL). The extracts were combined and washed with saturated NH_4Cl, water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography (1:3 acetate/hexanes) to give 1.87 g of **188** as a yellow oil (55.7%). ^1H NMR (300 MHz, $CDCl_3$): δ 3.64 (3H, s), 3.82 (3H, s), 4.55 (2H, s), 4.76 (2H, d, J = 4.8 Hz), 6.42 (1H, t, J = 4.8 Hz), 6.9 (2H, d, J = 8.7

Hz), 7.32 (2H, d, J = 8.7 Hz), 7.32-8.2 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.1, 55.5, 69.1, 73.0, 114.1, 124.8, 129.2, 129.8, 130.1, 130.7, 132.6, 133.9, 146.7, 159.5, 165.0, 171.4. IR (NaCl, neat) 1723, 1611, 1585, 1525, 1514, 1464 cm^{-1}. R_f 0.3 (eluted with 25 % ethyl acetate/ hexanes).

(*Z*)-4-(*p*-Methoxybenzyloxy) -(2'-nitrophenyl)but-2-ene-1-ol (189).



1.635 g of compound **188** (4.58 mmol) was dissolved in 25 mL dry THF and cooled to –78 °C. 10 mL 1 N DIBAL solution in THF (5.03 mmol) was added to the solution dropwise in 5 minutes. The mixture was stirred for 30 minutes at –78 °C and then warmed to rt overnight, and quenched with 20 g ice and extracted with ether (20 mL X 3). The extracts were combined and washed with saturated NH_4Cl, water and brine. The solvent was rotovaped, and the residue separated by flash chromatography (50% ethyl acetate/hexanes). 0.74 g of a yellow oily liquid was obtained. 0.54 g starting material was recovered (50% based on recovery). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (3H, s), 4.23 (2H, d, J = 6.4 Hz), 4.42 (2H, d, J = 6.3 Hz), 4.42 (2H, s), 4.53 (2H, s), 5.73 (1H, t, J = 6.4 Hz), 6.91 (2H, d, J = 8.0 Hz), 7.29 (2H, d, J = 8.0 Hz), 7.3-8.0 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5, 62.0, 65.7, 72.6, 114.1, 124.6, 128.6, 128.7, 129.9, 132.0, 133.4, 137.3, 142.5, 148.3, 159.6. IR (NaCl, neat) 3425, 1611, 1585, 1570, 1525, 1515 cm^{-1}. R_f 0.3 (eluted with 50% ethyl acetate/ hexanes).

(*Z*)-1-Chloro-4-(*p*-methoxybenzyloxy)-(2'-nitrophenyl)but-2-ene (190).

330 mg of compound **189** (0.52 g, 1.48 mmol) and *N*-chlorosuccinimide (400 mg, 3.0 mmol) was dissolved in 12 mL CH_2Cl_2 and cooled to -78 °C. 0.9 mL of methyl sulfide (5.9 mmol) was added. The mixture was stirred and warmed to rt overnight. Removal of the solvent followed by separation through flash chromatography (eluted with 20% ethyl acetate/ hexanes) yielded 0.458 mg of **190** (83.4 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (3H, s), 4.29 (2H, d, J = 6.3 Hz), 4.39 (2H, s), 4.53 (2H, s), 5.75 (1H, t, J = 6.3 Hz), 6.91 (2H, d, J= 8.7 Hz), 7.33 (2H, d, J = 8.7 Hz), 7.4-8.2 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 42.4, 55.5, 65.6, 72.3,114.1, 124.9, 129.2, 129.8, 130.1, 132.1, 133.2, 136.3, 137.7, 147.6, 159.5. IR (NaCl, neat) 1611, 1585, 1571, 1524, 1514, 1464 cm^{-1}. R_f 0.2 (eluted with 20% ethyl acetate/ hexanes).

(*Z*)-1-Bromo-4-(*p*-methoxybenzyloxy) -(2'-nitrophenyl)but-2-ene (191).

Compound **190** (303 mg, 0.87 mmol) was dissolved in 25 mL anhydrous acetone and 750 mg of anhydrous LiBr (8.6 mmol) was added. The mixture was stirred under Ar overnight and then concentrated *in vacuo*. 20 mL water and 20 ml

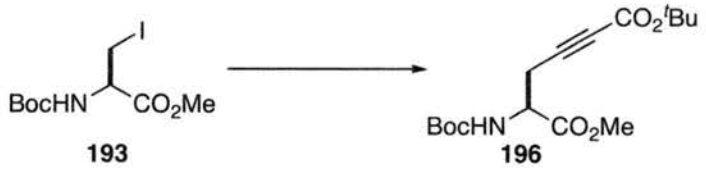
ether were added. The layers were separated, and the aqueous layers were extracted with ether (3 X 20 mL). The extracts were combined and washed with saturated NH_4Cl, water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography (25% ethyl acetate/hexanes) to give 240 mg of **191** as a yellow oil (70 %). ^1H NMR (300 MHz, $CDCl_3$): δ 3.83 (3H, s), 4.27 (2H, s), 4.28 (2H, d, J = 6.4 Hz), 4.54 (2H, s), 5.73 (1H, t, J = 6.4 Hz), 6.92 (2H, d, J = 8.8 Hz), 7.33 (2H, d, J = 8.8 Hz), 7.4-8.2 (4H, m). ^{13}C NMR (100 MHz , $CDCl_3$): δ 30.3, 55.5, 65.7, 72.3, 114.1, 124.9, 129.2, 129.8, 130.1, 132.3, 133.3, 133.7, 136.4, 137.7, 147.5, 159.6. IR (NaCl, neat) 1610, 1584, 1524, 1514, 1343 cm^{-1}. R_f 0.3 (eluted with 100 % ethyl acetate).

4.2. (*S*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)hex-2-ynedioate (195).[45]

A suspention of zinc (9.83 g, 150.4 mmol) in 11.2 mL dry THF and 1,2-dibromoethane (0.65 mL, 7.53 mmol) was heated under Ar to 60 °C for 3 min. After cooling the mixture to 35 °C, trimethylsilyl chloride (0.194 mL, 1.53 mmol) was added and the mixture was vigorously stirred for 30 min. At this point the reaction vessel was kept 35 °C, compound **193** (8.25 g, 25.1 mmol) in 50 mL dry THF was slowly added, and the mixture was stirred for 15-40 min until no starting material remained. The solution of zinc reagent was then converted to the zinc-copper reagent

194 by the following procedure, the solution of zinc reagent was cooled to -10 °C, and a solution prepared from CuCN (2.27 g, 25.1 mmol) and LiCl (2.15 g, 50.2 mmol) in 50 mL dry THF was added. The mixture was stirred at 0 °C for 10 min and then cooled to -55 °C. A solution of ethyl 3-bromoprop-2-ynoate (5.91 g, 33.4 mmol) in 67 mL dry THF was introduced followed by stirring at -55°C for 20 h. After quenching with saturated aqueous NH_4Cl, the mixture was extracted with ethyl acetate (3 X 400 mL), the combined organic layers were washed with 400 mL water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was separated by silica gel flash chromatography (eluted with 20 % ethyl acetate/ hexanes) to give 6.2 g of **195** as a yellow oil (77%). $[\alpha]^{20}_D$ +55.7 (*c* 0.670, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 0.79 (3H, t, *J* = 7.2 Hz), 1.38 (9H, s), 2.39(1H, dd, *J* = 17.4 Hz, 5.4 Hz), 2.54 (1H, dd, *J* = 17.4 Hz, 5.1 Hz), 3.18 (3H, s), 3.81 (2H, q, *J* = 7.2 Hz), 4.34 (1H, ddd, *J* = 7.8 Hz, 5.4 Hz, 5.1 Hz), 5.29 (1H, d, *J* = 7.8 Hz). ^{13}C NMR (75 MHz, C_6D_6): δ 14.3, 23.3, 28.7, 52.5, 52.6, 62.1, 76.6, 80.3, 83.6, 153.5, 155. 4, 170.7. IR (NaCl, neat) 3366, 2980, 2240, 1748, 1712, 1507. HRMS (FAB+) calc. mass for $C_{14}H_{22}NO_6$ 300.1447 (M+1), found: 300.1453. R_f 0.33 (eluted with 20 % ethyl acetate/ hexanes).

(*S*)-1-*tert*-Butyl 6-methyl 5-(*tert*-butoxycarbonylamino)hex-2-ynedioate (196).



193 **196**

A procedure similar to the one described above for the preparation of **195** was used for the synthesis of **196** starting from 2.1 g (6.38 mmol) of compound **3** and 1.44 g (7.02 mmol) of tert-butyl 3-bromoprop-2-ynoate. 1.0 g product was obtained (48%). $[\alpha]^{20}_{D}$ +52.5 (*c* 1.46, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6) : δ 1.24 (9H, s), 1.37 (9H, s), 2.39 (1H, dd, *J* = 17.1 Hz, 5.4 Hz), 2.53 (1H, dd, *J* = 17.1 Hz, 5.1 Hz), 3.15 (3H, s), 4.34 (1H, ddd, *J* = 7.8 Hz, 5.4 Hz, 5.1 Hz), 5.26 (1H, d, *J* = 7.8 Hz). ^{13}C NMR (75 MHz, C_6D_6): δ 23.1, 28.1, 28.6, 52.3, 52.5, 77.8, 80.2, 81.3, 83.0, 152.7, 155.4, 170.8. IR (NaCl, neat) 3366, 2980, 2244, 1750, 1709, 1505. HRMS (FAB+) calc. mass for $C_{16}H_{26}NO_6$ 328.1760 (M+1), found 328.1746. R_f 0.33 (eluted with 20 % ethyl acetate/ hexanes).

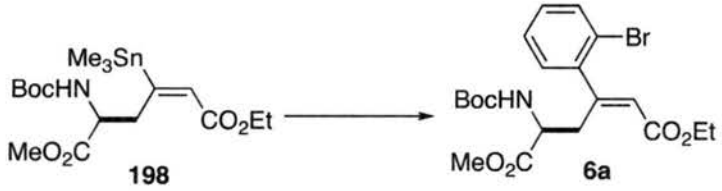
(*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(trimethylstannyl) hex-2-enedioate (198).[49]

195 **198**

To a cold (-20 °C), stirred solution of 5.2 g of hexamethylditin (15.87 mmol) in 150 mL dry THF was added a solution of 10.7 mL (17.12 mmol) of a 1.6M solution of methyl lithium in ether. The mixture was stirred at -20 °C for 15 min to afford a pale yellow solution of Me_3SnLi. This solution was then cooled to -78 °C and 1.66 g (18.52 mmol) of solid CuCN was added in one portion. The mixture was stirred at -78 °C for 5 min and at -48 °C for 15 min to afford a bright orange solution. This solution was then cooled to -78 °C and 0.95 mL (16.0 mmol) of dry ethanol was

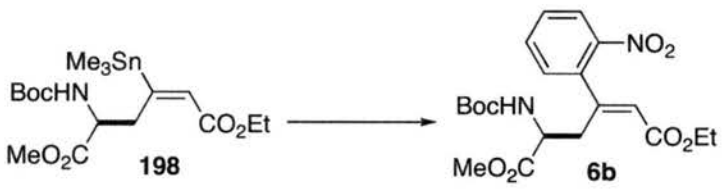
added. After 5 min, a solution of compound **195** in 50 mL dry THF was added dropwise and the mixture was stirred at -78 °C for 4 h. 200 mL NH_4Cl-NH_4OH buffer (consisting of a 9: 1 ratio of saturated aqueous NH_4Cl: 28%~30% NH_4OH, PH=8) was added, the mixture was opened to the atmosphere, and warmed to RT, and was stirred vigorously until the aqueous phase became a deep blue color. The organic phase was separated and the aqueous phase was extracted thoroughly with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel flash column chromatography (eluted with 15 % ethyl acetate/ hexanes) to give 5.0 g of compound **198** as a yellow oil (81%). $[\alpha]^{20}_D$ +60.8 (*c* 2.65, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 0.18 (9H, s), 0.95 (3H, t, *J* = 7.2 Hz), 1.36 (9H, s, $^2J_{Sn\text{-}H}$ = 54.3 Hz), 2.89 (1H, dd, *J* = 12.0 Hz, 3.9 Hz), 3.28 (3H, s), 3.90 (1H, t, *J* = 12.0Hz), 3.95 (2H, q, *J* = 7.2Hz), 4.68 (1H, *J* = 12.0 Hz, 8.1 Hz, 3.9 Hz), 6.09 (1H, d, *J* = 8.1 Hz), 6.22 (1H, s, $^3J_{Sn\text{-}H}$ = 69.0 Hz). ^{13}C NMR (75 MHz, C_6D_6): δ -8.7, 28.7, 28.9, 37.2, 52.3, 54.5, 79.5, 81.0, 133.4, 156.2, 164.9, 165.5, 172.8. IR (NaCl, neat) 3371, 2977, 1751, 1717, 1598, 1507, 1446 cm^{-1}. HRMS (FAB+) calc. mass for $C_{19}H_{36}NO_6Sn$: 494.1565 (M+1), found: 494.1557. R_f 0.33 (eluted with 15 % ethyl acetate/ hexanes).

(*S*,*E*)-1-Ethyl 6-methyl 3-(2-bromophenyl)-5-(*tert*-butoxycarbonylamino) hex-2-enedioate (6a).



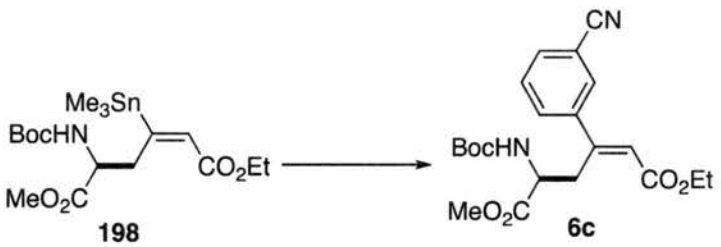
A solution of *o*-iodobromobezene (41.2 mg, 0.146 mmol), CuI (6.67 mg, 35 μmol), $AsPh_3$ (10.7 mg, 35 μmol), and Pd_2dba_3 (9.45 mg, 8.74 μmol) in 1.2 mL dry DMF under Ar was treated with compound **198** (61.3 mg, 0.132 mmol). The reaction mixture was then stirred for 2 h. The solution was then diluted with EtOAc (5 mL) and washed with water. The combined aqueous layers were extracted with EtOAc (2 X 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated to dryness. The resulting oil was purified by silica gel chromatography (eluted with 25% ethyl acatate/hexanes) to yield 41.0 mg of **6a** as a yellow oil (68%). $[\alpha]^{20}_D$ +53.2 (*c* 1.17, CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6): δ 0.91 (3H, t, *J* = 7.2 Hz), 1.41 (9H, s), 3.13 (3H, s), 3.33 (1H, dd, *J* = 12.4 Hz, 4.0 Hz), 3.88 (2H, q, *J* = 7.2 Hz), 4.02 (1H, t = 12.4 Hz), 4.70 (1H, ddd, *J* = 12.4 Hz, 6.6 Hz, 4.0 Hz), 5.89 (1H, s), 5.96 (1H, d, *J* = 6.6 Hz), 6.58-7.25 (4H, m). ^{13}C NMR (75 MHz, C_6D_6): δ 14.4, 28.7, 35.4, 52.1, 53.3, 60.9, 79.6, 121.8, 124.6, 127.9, 128.9, 130.1, 130.9, 133.6, 142.5, 156.2, 167.0, 172.5. IR (NaCl, neat) 3382, 2978, 1748, 1717, 1645, 1507, 1436 cm^{-1}. HRMS (FAB+) calc. mass for $C_{20}H_{27}NO_6Br$: 456.1021 (M+1, ^{80}Br), found: 456.1005. R_f 0.30 (eluted with 25 % ethyl acetate/ hexanes).

(*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(2-nitrophenyl) hex-2-enedioate (6b).



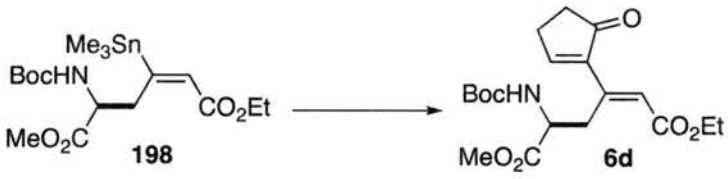
A 25 mL flask equipped with a magnetic stir bar was charged with 80 mg (0.308 mmol) of $PdCl_2(CH_3CN)_2$ and 10 mL of DMF. *n*-Tributyltin hydride (182 μL, 0.339 mmol) was added dropwise and a black precipitate formed immediately. The mixture was stirred for 10 minutes and was added to a solution of 1.98 g compound **198** (4.27 mmol) and 1.12 g (4.49 mmol) of *o*-iodonitrobenzene in 50 mL DMF in three portions (one portion every 5 h). The mixture was stirred overnight. The reaction was then quenched with water and the mixture was extracted with ether (3 X 100 mL). The combined organic extracts were washed with 300 mL water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was separated by silica gel flash column chromatography (eluted with 25 % ethyl acetate/ hexanes) to give 850 mg of **6b** as a yellow oil along with 800 mg of unreacted **198** (47% conversion and 79% yield based on recovered **198**). $[\alpha]^{20}_{D}$ +17.8 (*c* 0.835, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 0.89 (3H, t, *J* = 7.2 Hz), 1.42 (9H, s), 3.11 (3H, s), 3.16 (1H, dd, *J* = 12.9 Hz, 3.6 Hz), 3.85 (2H, q, *J* = 7.2 Hz), 4.03 (1H, t, *J* = 12.9 Hz), 4.64 (1H, ddd, *J* = 12.9 Hz, 9.0 Hz, 3.6 Hz), 5.75 (1H, s), 5.9 (1H, d, *J* = 9.0 Hz), 6.5-7.6 (4H, m). ^{13}C NMR (75 MHz, C_6D_6): δ 14.8, 28.4, 35.6, 52.1, 53.3, 79.6, 81.4, 124.2, 125.3, 128.9, 131.7, 133.6, 137.3, 147.4, 153.4, 156.3, 166.3, 172.4. IR (NaCl, neat) 3389, 2979, 1747, 1716, 1640, 1608, 1528, 1367, 1347 cm^{-1}. HRMS (FAB+) calc. mass for $C_{22}H_{31}N_2O_8$: 451.2080 (M+1), found: 451.2086. R_f 0.30 (eluted with 25 % ethyl acetate/ hexanes).

(*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(3-cyanophenyl) hex-2-enedioate (6c).



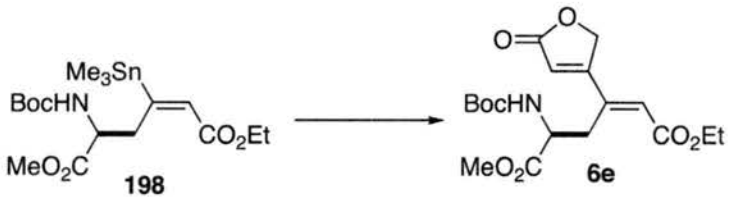
A procedure similar to the one described above for the preparation of **6a** was used for the synthesis of **6c** starting from 19.5 mg (0.0421 mmol) of compound **198** and 10.6 mg (0.0464 mmol) of 3-iodobenzonitrile. Yield: 12.0 mg (71%). $[\alpha]^{20}_{D}$ +46.7 (*c* 0.405, CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6) : δ 0.99 (3H, t, *J*= 7.0 Hz), 1.36 (9H, s), 3.16 (3H, s), 3.20 (1H, dd, *J* = 13.4 Hz, 10.0 Hz), 3.59 (1H, dd, *J* = 13.4 Hz, 9.6 Hz), 3.96 (2H, q, *J* = 7.0 Hz), 4.46 (1H, ddd, *J* = 10.0 Hz, 9.6 Hz, 8.4 Hz), 5.71 (1H, d, *J* = 8.4 Hz), 5.81 (1H, s), 6.40-7.20 (3H, m), 7.21 (1H, s). ^{13}C NMR (100 MHz, C_6D_6): δ 14.5, 28.6, 33.4, 52.1, 53.5, 60.9, 79.8, 113.9, 118.7, 122.8, 129.7, 130.9, 131.1, 132.6, 141.5, 153.0, 155.9, 166.7, 172.2. IR (NaCl, neat) 3371, 2878, 2231, 1744, 1713, 1632, 1510 cm^{-1}. HRMS (FAB+) calc. mass for $C_{21}H_{27}N_2O_6$ 403.1869 (M+1), found 403.1869. R_f 0.30 (eluted with 25 % ethyl acetate/ hexanes).

(*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(5-oxocyclopent-1-enyl)hex-2-enedioate (6d).



A procedure similar to the one described above for the preparation of **6a** was used for the synthesis of **6d** starting from 21.0 mg (0.0454 mmol) of compound **198** and 8.05 mg (0.05 mmol) of 4-bromocyclopent-2-enone. Yield: 13.3 mg (77%). $[\alpha]^{20}_{D}$ +46.5 (*c* 0.550, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6) : δ 0.91 (3H, t, *J* = 6.9 Hz), 1.39 (9H, s), 1.58 (2H, m), 1.78 (2H, t, *J* = 4.5 Hz), 3.07 (1H, dd, *J* = 13.5 H, 5.1 Hz), 3.33 (3H, s), 3.74 (1H, *J* = 13.5 Hz, 10.8 Hz), 3.91(2H, q, *J* = 6.9 Hz), 4.70 (1H, ddd, *J* = 10.8 Hz, 8.1 Hz, 6.9 Hz), 6.37 (1H, d, *J* = 8.1 Hz), 7.41 (1H, t, *J* = 3.0 Hz), 7.66 (1H, s). ^{13}C NMR (100 MHz, C_6D_6): δ 14.7, 26.3, 28.9, 32.6, 36.2, 52.4, 54.5, 61.0, 79.8, 122.5, 140.5, 144.0, 156.4, 163.0, 168.4, 172.8, 205.7. IR (NaCl, neat) 3371, 2978, 1746, 1708, 1625, 1510, 1367 cm^{-1}. HRMS (FAB+) calc. mass for $C_{19}H_{28}NO_7$ 382.1866 (M+1), found 382.1873. R_f 0.30 (eluted with 50 % ethyl acetate/ hexanes).

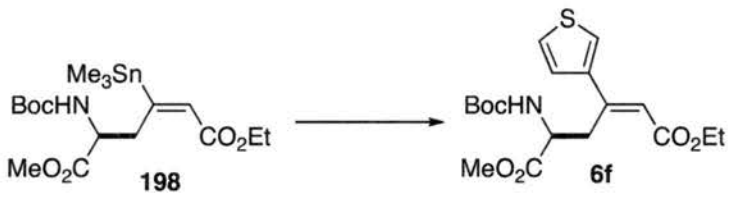
(*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(5-oxo-2,5-dihydrofuran-3-yl)hex-2-enedioate (6e).



A procedure similar to the one described above for the preparation of **6a** was used for the synthesis of **6e** starting from 45.0 mg (0.097 mmol) of compound **198** and 17.4 mg (0.107 mmol) of 4-bromofuran-2(*5H*)-one. Yield: 21. 1 mg (57%). $[\alpha]^{20}_{D}$ +36.0 (*c* 2.19, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 0.93 (3H, t, *J* = 7.2 Hz), 1.35 (9H, s), 2.90 (1H, dd, *J* = 13.2 Hz, 4.8 Hz), 3.21 (1H, dd, *J* = 13.2 Hz, 9.6 Hz), 3.24

(3H, s), 3.87 (2H, q, J = 7.2 Hz), 3.96 (2H, s), 4.69 (1H, ddd, J = 9.6 Hz, 8.1 Hz, 4.8 Hz), 5.34 (1H, s), 5.62 (1H, d, J = 8.1 Hz), 6.15 (1H, s). ^{13}C NMR (75 MHz, C_6D_6): δ 14.4, 28.6, 32.3, 52.4, 53.9, 61.3, 70.0, 80.0, 120.3, 123.2, 143.9, 155.9, 162.1, 166.0, 171.9, 172.2. IR (NaCl, neat) 3376, 2979, 1789, 1752, 1714, 1630, 1599, 1507 cm^{-1}. HRMS (FAB+) calc. mass for $C_{18}H_{26}NO_8$ 384.1658 (M+1), found 384.1673. R_f 0.30 (eluted with 50 % ethyl acetate/ hexanes).

(*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(thiophen-3-yl)hex-2-enedioate (6f).



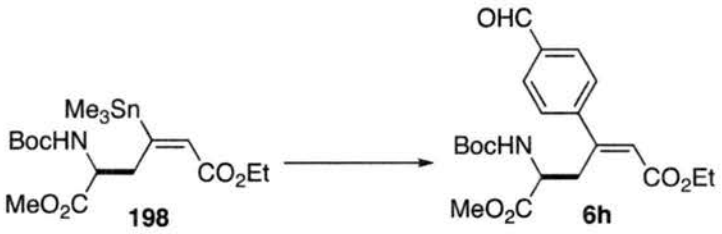
A procedure similar to the one described above for the preparation of **6a** was used for the synthesis of **6f** starting from 19.6 mg (0.0423 mmol) of compound **198** and 9.8 mg (0.0466 mmol) of 3-iodothiophene. Yield: 13.0 mg (80%). $[\alpha]^{20}_D$ +46.1 (*c* 0.460, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6) : δ 0.99 (3H, t, J = 7.1 Hz), 1.38 (9H, s), 3.27 (1H, dd, J = 12.9 Hz, 5.1 Hz), 3.28 (3H, s), 3.76 (1H, dd, J = 12.9 Hz, 9.9 Hz), 3.96 (2H, q, J = 6.9 Hz), 4.77 (1H, ddd, J = 7.8 Hz, 6.9 Hz, 5.1 Hz), 6.22 (1H, d, J = 7.8 Hz), 6.26 (1H, s), 6.65 (1H, dd, J = 5.1 Hz, 3.0 Hz), 6.88 (1H, dd, J = 5.1 Hz, 1.5 Hz), 7.35 (1H, dd, J = 3.0 Hz, 1.5 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ 14.8, 28.9, 33.4, 52.3, 54.9, 60.8, 79.7, 118.5, 125.8, 125.9, 126.9, 141.3, 148.7, 156.1, 167.8, 172.6. IR (NaCl, neat) 3366, 2978, 1745, 1711, 1698, 1619, 1503, 1450 cm^{-1}. HRMS

(FAB+) calc. mass for $C_{18}H_{26}NO_6S$ 384.1481 (M+1), found 384.1489. R_f 0.40 (eluted with 20 % ethyl acetate/ hexanes).

(*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(5-formylfuran-2-yl)hex-2-enedioate (6g).

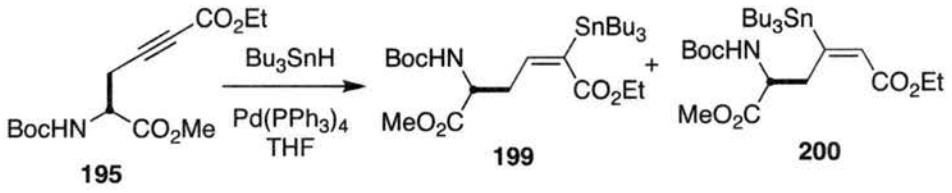
A procedure similar to the one described above for the preparation of **6a** was used for the synthesis of **6g** starting from 53.5 mg (0.116 mmol) of compound **198** and 28.2 mg (0.127 mmol) of 5-iodofuran-2-carbaldehyde. Yield: 38.4 mg (84%). $[\alpha]^{20}_D$ +27.2 (*c* 1.13, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 0.94 (3H, t, *J* = 7.1 Hz), 1.36 (9H, s), 3.17 (1H, dd, *J* = 13.2 Hz, 5.7 Hz), 3.29 (3H, s), 3.50 (1H, dd, *J* = 13.2 Hz, 9.9 Hz), 3.90 (2H, q, *J* = 7.1 Hz), 4.69 (1H, ddd, *J* = 9.9 Hz, 8.1 Hz, 5.7 Hz), 6.02 (1H, d, *J* = 8.1 Hz), 6.37 (1H, d, 4.2 Hz), 6.55 (1H, d, 4.2Hz), 6.67 (1H, s), 9.13 (1H, s). ^{13}C NMR (75 MHz, C_6D_6): δ 14.4, 28.6, 31.1, 52.3, 54.7, 61.0, 79.9, 113.9, 119.6, 121.1, 140.6, 153.4, 156.2, 156.7, 167.2, 172.2, 177.7. IR (NaCl, neat) 3366, 2978, 1746, 1713, 1683, 1623, 1500, 1447 cm^{-1}. HRMS (FAB+) calc. mass for $C_{19}H_{26}NO_8$ 396.1658 (M+1), found 396.1649. R_f 0.25 (eluted with 25 % ethyl acetate/ hexanes).

(*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(4-formylphenyl) hex-2-enedioate (6h).



A procedure similar to the one described above for the preparation of **6b** was used for the synthesis of **6h** starting from 45.0 mg (0.0972 mmol) of compound **198** and 21.6 mg (0.117 mmol) of 4-iodobenzaldehyde. Yield: 26.4 mg (67%). $[\alpha]^{20}_{D}$ +66.8 (*c* 0.467, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 0.99 (3H, t, *J* = 6.9 Hz), 1.37 (9H, s), 3.19 (3H, s), 3.28 (1H, dd, *J* = 13.2 Hz, 5.1 Hz), 3.75 (1H, dd, *J* = 13.2 Hz, 9.9 Hz), 3.87 (2H, q, *J* = 6.9 Hz), 4.55 (1H, ddd, *J* = 9.9 Hz, 8.4 Hz, 5.1 Hz), 5.80 (1H, d, *J* = 8.4 Hz), 6.03 (1H, s), 7.12 (2H, d, *J* = 4.8 Hz), 7.39 (2H, d, *J* = 4.8 Hz), 9.59 (1H, s). ^{13}C NMR (100 MHz, C_6D_6): δ 14.5, 28.7, 33.4, 52.1, 53.7, 60.9, 79.7, 122.7, 130.0, 130.2, 137.4, 145.7, 154.2, 155.9, 166.9, 172.4, 191.0. IR (NaCl, neat) 3371, 2979, 1745, 1704, 1604, 1511 cm^{-1}. HRMS (FAB+) calc. mass for $C_{21}H_{28}NO_7$ 406.1866 (M+1), found 406.1874. R_f 0.30 (eluted with 33 % ethyl acetate/ hexanes).

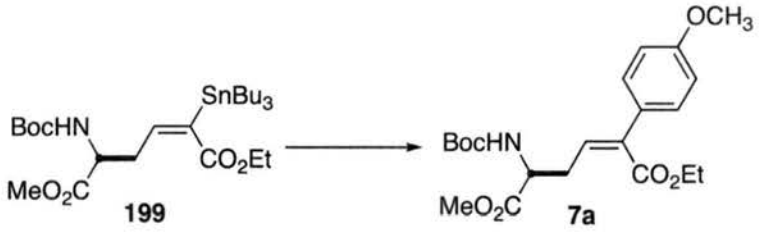
(*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-2-(tri-*n*-butyl stannyl)hex-2-enedioate (199) and **(*S*,*E*)-1-ethyl 6-methyl 5-(*tert*-butoxycarbonyl amino)-3-(tri-*n*-butylstannyl)hex-2-enedioate (200).**



A solution of compound **195** (347.8 mg, 022 mmol) and $Pd(PPh_3)_4$ (5 mg, 4.3 mmol) in dry THF (10 mL) under Ar was treated with *n*-tributyltin hydride (343 mL, 0.24 mmol). The reaction mixture was then stirred for 2 h and the solvent was evaporated to dryness. The resulting oil was purified by silica gel chromatography (eluted with 5% ethyl acetate/hexanes). The first eluting compound was **200** (66 mg, 10%) and the slower eluting substance was **199** (487 mg, yield 71%). Data for **199**: $[\alpha]^{20}_D$ +33.5 (*c* 1.10, CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6): δ 0.96 (9H, t, *J* = 7.6 Hz), 1.01 (3H, t, *J* = 7.2 Hz), 1.02 (6H, t, *J* = 8.8 Hz), 1.37 (6H, m), 1.42 (9H, s), 1.59 (6H, m), 2.90 (2H, m), 3.28 (3H, s), 3.95 (2H, q, *J* = 7.2 Hz), 4.58 (1H, ddd, *J* = 13.2 Hz, 7.2 Hz, 0.4Hz), 5.76 (1H, d, *J* = 7.2 Hz), 6.09 (1H, t, *J* = 7.4 Hz, $^3J_{Sn\text{-}H}$ = 45.0 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ 11.0, 14.3, 14.7, 28.0, 28.7, 29.6, 35.2, 52.1, 54.0, 60.8, 79.6, 141.1, 146.9, 156.1, 171.1, 172.8. IR (NaCl, neat) 3364, 2957, 2928, 2872, 2854, 1754, 1719, 1607, 1500 cm^{-1}. HRMS (FAB+) calc. mass for $C_{26}H_{50}NO_6Sn$: 591.2671 (M+1), found: 591.2647. R_f 0.33 (eluted with 10 % ethyl acetate/ hexanes). Data for **200**: $[\alpha]^{20}_D$ +54.3 (*c* 3.30, CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6): δ 0.93 (9H, t, *J* = 7.4 Hz), 0.94 (3H, t, *J* = 7.0 Hz), 1.02 (6H, t, *J* = 8.2 Hz), 1.36 (6H, m), 1.41 (9H, s), 1.58 (6H, m), 2.97 (1H, dd, *J* = 12.4 Hz, 3.6 Hz), 3.31 (3H, s), 3.92 (2H, q, *J* = 7.0

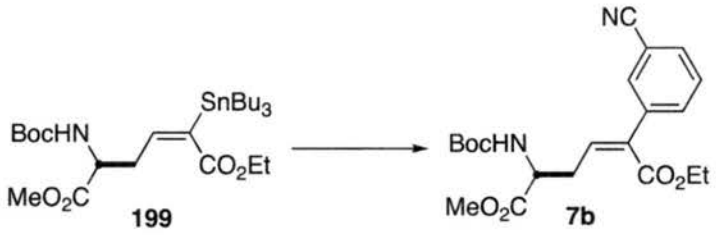
Hz), 4.02 (2H, t, J = 12.4 Hz), 4.71 (1H, ddd, J = 12.4 Hz, 12.4 Hz, 8.4 Hz), 6.23 (1H, d, J = 8.4 Hz), 6.34 (1H, s, $^{3}J_{Sn\text{-}H}$ = 60.0 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ 10.7, 14.2, 14.5, 28.1, 28.8, 29.7, 37.6, 52.2, 54.6, 60.6, 79.5, 132.1, 156.5, 165.3, 168.1, 173.0. IR (NaCl, neat) 3364, 2957, 2929, 2872, 2854, 1754, 1719, 1607, 1503 cm^{-1}. HRMS (FAB+) calc. mass for $C_{26}H_{50}NO_6Sn$: 591.2671 (M+1), found: 591.2671. R_f 0.30 (eluted with 15 % ethyl acetate / hexanes).

(*S*,*Z*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-2-(4-methoxy phenyl) hex-2-enedioate (7a).



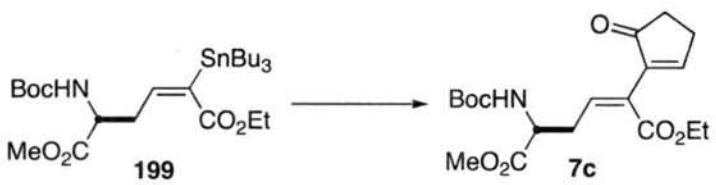
A procedure similar to the one described above for the preparation of **6a** was used for the synthesis of **7a** starting from 40.0 mg (0.0678 mmol) of compound **199** and 17.4 mg (0.0745 mmol) of 1-iodo-4-methoxybenzene. Yield: 20.4 mg (74%). $[\alpha]^{20}_{D}$ +20.9 (*c* 0.675, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6) : δ 0.94 (3H, t, J = 7.1 Hz), 1.42 (9H, s), 2.81 (2H, t, J = 7.2 Hz), 3.25 (3H, s), 3.28 (3H, s), 4.01 (2H, q, J = 7.1 Hz), 4.61 (1H, q, J = 7.5 Hz), 5.71 (1H, d, J=7.5 Hz), 5.89 (1H, t, J = 7.5 Hz), 6.72 (2H, d, J = 8.7 Hz), 7.23 (2H, d, J = 8.7 Hz). ^{13}C NMR (75 MHz, C_6D_6): δ 14.4, 28.7, 33.5, 52.1, 54.1, 55.1, 61.2, 79.8, 114.4, 129.3, 130.6, 131.6, 138.5, 156.1, 160.4, 168.6, 172.8. IR (NaCl, neat) 3371, 2978, 1745, 1715, 1608, 1513 cm^{-1}. HRMS (FAB+) calc. mass for $C_{21}H_{30}NO_7$ 408.2022 (M+1), found 408.2003. R_f 0.33 (eluted with 33 % ethyl acetate/ hexanes).

(*S*,*Z*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-2-(3-cyanophenyl) hex-2-enedioate (7b).



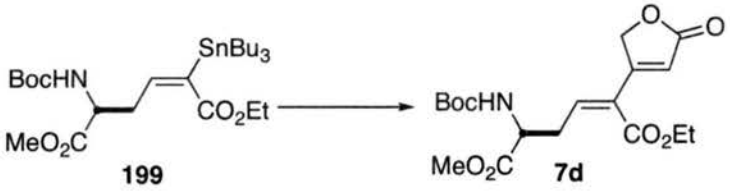
A procedure similar to the one described above for the preparation of **6a** was used for the synthesis of **7b** starting from 41.3 mg (0.070 mmol) of compound **199** and 17.6 mg (0.077 mmol) of 3-iodobenzonitrile. Yield: 22.0 mg (79%). $[\alpha]^{20}_{D}$ +27.4(*c* 0.625, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 0.84 (3H, t, *J* = 6.9 Hz), 1.41 (9H, s), 2.82 (1H, t, *J* = 7.5 Hz), 3.25 (3H, s), 3.88 (2H, q, *J* = 6.9 Hz), 4.57 (1H, q, *J* = 7.5 Hz), 5.53 (1H, d, *J* = 7.2 Hz), 5.75 (1H, t, *J* = 7.8 Hz), 6.61 (1H, t, *J* = 7.5 Hz), 6.8-7.4 (4H, m). ^{13}C NMR (100 MHz, C_6D_6): δ 14.3, 28.7, 33.7, 52.3, 53.8, 61.5, 80.1, 113.5, 118.9, 129.2, 131.5, 131.8, 132.1, 136.1, 138.1, 139.5, 156.0, 166.8, 172.5. IR (NaCl, neat) 3373, 2979, 2231, 1745, 1716, 1511, 1438 cm^{-1}. HRMS (FAB+) calc. mass for $C_{21}H_{27}N_2O_6$ 403.1869 (M+1), found 403.1864. R_f 0.30 (eluted with 25 % ethyl acetate/ hexanes).

(*S*,*Z*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-2-(5-oxocyclopent-1-enyl)hex-2-enedioate (7c).



A procedure similar to the one described above for the preparation of **6a** was used for the synthesis of **7c** starting from 42.4 mg (0.0718 mmol) of compound **199** and 12.7 mg (0.079 mmol) of 4-bromocyclopent-2-enone. Yield: 19.7 mg (72%). $[\alpha]^{20}_{D}$ +20.2 (*c* 0.130, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 1.01 (3H, t, *J* = 7.2 Hz), 1.66 (9H, s), 1.68 (2H, m), 1.85 (2H, m), 2.83(2H, m), 3.30 (3H, s), 4.05 (2H, q, *J* = 7.2 Hz), 4.59 (1H, m), 5.64 (1H, d, *J* = 6.9 Hz), 6.82 (1H, t, *J* = 7.8 Hz), 6.96 (1H, t, *J* = 2.9 Hz). ^{13}C NMR (75 MHz, C_6D_6) : δ 14.5, 26.3, 28.7, 33.2, 35.3, 52.2, 53.9, 61.4, 79.7, 130.0, 135.6, 140.5, 156.0, 160.0, 167.0, 172.6, 205.6. IR (NaCl, neat) 3367, 2978, 1745, 1709, 1509, 1367 cm^{-1}. HRMS (FAB+) calc. mass for $C_{19}H_{28}NO_7$ 382.1866 (M+1), found 382.1874. R_f 0.33 (eluted with 50 % ethyl acetate/ hexanes).

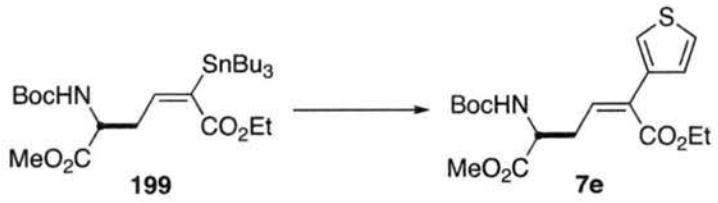
(*S*,*Z*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-2-(5-oxo-2,5-dihydrofuran-3-yl)hex-2-enedioate (7d).



A procedure similar to the one described above for the preparation of **6a** was used for the synthesis of **7d** starting from 36.0 mg (0.061 mmol) of compound **199** and 10.93 mg (0.0671 mmol) of 4-bromofuran-2(*5H*)-one. Yield: 16.0 mg (69%). $[\alpha]^{20}_{D}$ +20.8 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 0.82 (3H, t, *J* = 7.2 Hz), 1.37 (9H, s), 2.65 (1H, m), 2.66 (1H, t, *J* = 8.1 Hz), 3.21 (3H, s), 3.81 (2H, q, *J* = 7.2 Hz), 4.11 (2H, s), 4.40 (1H, dd, *J* = 14.1 Hz, 8.1 Hz), 5.36 (1H, d, *J* = 8.1 Hz), 5.54 (1H, t, *J* = 7.8 Hz), 5.98 (1H, s). ^{13}C NMR (75 MHz, C_6D_6): δ 14.2, 28.6, 33.7, 52.4,

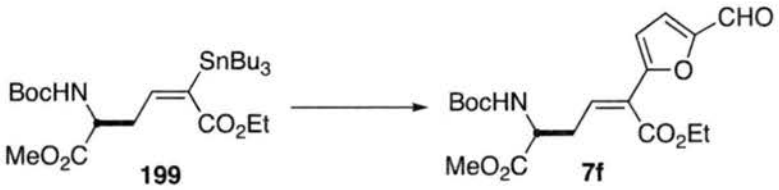
53.5, 61.8, 70.5, 80.3, 117.5, 129.5, 140.4, 155.9, 158.7, 164.9, 172.1, 172.9. IR (NaCl, neat) 3364, 2979, 1785, 1750,1716, 1634, 1516 cm^{-1}. HRMS (FAB+) calc. mass for $C_{18}H_{26}NO_8$ 384.1658 (M+1), found 384.1649. R_f 0.30 (eluted with 50 % ethyl acetate/ hexanes).

(*S*,*Z*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-2-(thiophen-3-yl)hex-2-enedioate (7e).



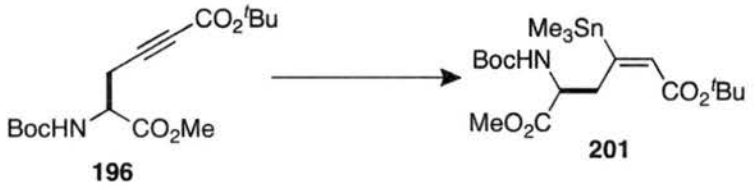
A procedure similar to the one described above for the preparation of **6a** was used for the synthesis of **7e** starting from 35.6 mg (0.0603 mmol) of compound **199** and 13.9 mg (0.0633 mmol) of 3-iodothiophene. Yield: 19.4 mg (84%). $[\alpha]^{20}_D$ +17.0 (*c* 0.635, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 0.91 (3H, t, *J* = 7.1 Hz), 1.40 (9H, s), 2.76 (2H, t, *J* = 7.5 Hz), 3.25 (3H, s), 3.96 (2H, q, *J* = 7.1 Hz), 4.57 (1H, q, *J* = 7.5 Hz), 5.64 (1H, d, *J* = 7.5 Hz), 5.95 (1H, t, *J* = 8.1 Hz), 6.77 (1H, dd, *J* = 5.1 Hz, 3.3 Hz), 6.94 (1H, dd, *J* = 5.1 Hz, 1.2 Hz), 7.08 (1H, dd, *J* = 3.3 Hz, 1.2 Hz). ^{13}C NMR (75 MHz, C_6D_6): δ 14.6, 28.9, 33.5, 52.3, 54.2, 61.5, 79.9, 123.2, 125.9, 127.2, 132.3, 133.4, 138.6, 156.0, 168.5, 172.6. IR (NaCl, neat) 3372, 2978, 1743, 1717, 1506, 1436, 1366 cm^{-1}. HRMS (FAB+) calc. mass for $C_{18}H_{26}NO_6S$ 384.1481 (M+1), found 384.1486. R_f 0.30 (eluted with 25 % ethyl acetate/ hexanes).

(*S*,*Z*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-2-(5-formylfuran-2-yl)hex-2-enedioate (7f).



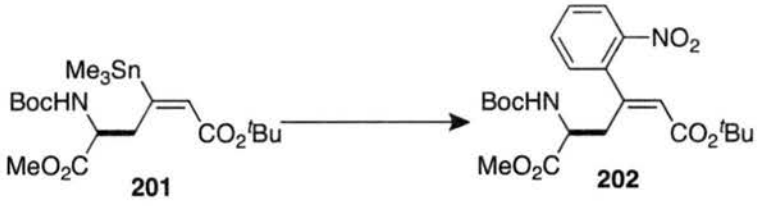
A procedure similar to the one described above for the preparation of **6a** was used for the synthesis of **7f** starting from 40.3 mg (0.0683 mmol) of compound **199** and 16.7 mg (0.0751 mmol) of 5-iodofuran-2-carbaldehyde. Yield: 20.5 mg (76%). $[\alpha]^{20}_{D}$ -1.3 (*c* 0.555, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 0.92 (3H, t, *J* = 7.2 Hz), 1.39 (9H, s), 2.78 (2H, m), 3.23 (3H, s), 3.93 (2H, q, *J* = 7.2 Hz), 4.50 (1H, m), 5.42 (1H, d, *J* = 7.8 Hz), 6.36 (1H, d, *J* = 3.6 Hz), 6.46 (1H, d, *J* = 3.6 Hz), 6.66 (1H, t, *J* = 7.95 Hz), 9.22 (1H, s). ^{13}C NMR (75 MHz, C_6D_6): δ 14.3, 28.6, 33.2, 52.2, 53.7, 61.8, 80.0, 111.8, 121.8, 127.0, 137.5, 152.8, 154.9, 155.9, 165.0, 172.4, 177.0. IR (NaCl, neat) 3365, 2979, 1742, 1716, 1678, 1500, 1439 cm^{-1}. HRMS (FAB+) calc. mass for $C_{19}H_{26}NO_8$ 396.1658 (M+1), found 396.1640. R_f 0.30 (eluted with 33 % ethyl acetate/ hexanes).

(*S*,*E*)-1-*tert*-Butyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(trimethylstannyl)hex-2-enedioate (201).



A procedure similar to the one described above for the preparation of **198** was used for the synthesis of **201** starting from 0.91 mg (2.78 mmol) of compound **196** and 1.09 g (3.34 mmol) of hexamethylditin. Yield: 729 mg (53%). $[\alpha]^{20}_{D}$ +60.8 (*c* 2.65, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 0.13 (9H, s, $^2J_{Sn\text{-}H}$ = 54.3 Hz), 1.36 (9H, s), 1.42 (9H, s), 2.89(1H, dd, *J* = 12.0 Hz, 3.9 Hz), 3.28 (3H, s), 3.95 (1H, t, *J* = 12.0 Hz), 4.68 (1H, ddd, *J* = 12.0 Hz, 8.1 Hz, 3.9 Hz), 6.09 (1H, d, *J* = 8.1 Hz), 6.22 (1H, s, $^3J_{Sn\text{-}H}$ = 69.0 Hz). ^{13}C NMR (75 MHz, C_6D_6): δ -8.7, 28.7, 28.9, 37.2, 52.3, 54.5, 79.5, 81.0, 133.4, 156.2, 164.9, 165.5, 172.8. IR (NaCl, neat) 3371, 2977, 1751, 1717, 1598, 1507, 1446 cm^{-1}. HRMS (FAB+) calc. mass for $C_{19}H_{36}NO_6Sn$ 494.1565 (M+1), found 494.1557. R_f 0.33 (eluted with 15 % ethyl acetate/ hexanes).

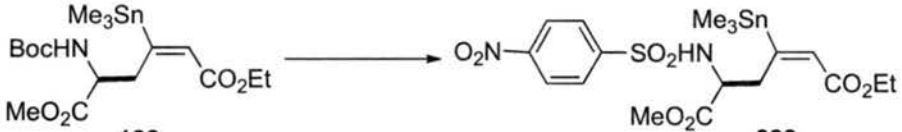
(*S*,*E*)-1-*tert*-Butyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(2-nitro phenyl)hex-2-enedioate (202).



A procedure similar to the one described above for the preparation of **6b** was used for the synthesis of **202** starting from 404 mg (1.03 mmol) of compound **201** and 284 mg (1.14 mmol) of *o*-iododnitrobenzene. 94.9 mg product was obtained along with the recovery of 246 mg compound **201** (25% conversion and 66% yield based on recovered **201**). $[\alpha]^{20}_{D}$ +17.8 (*c* 0.835, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 1.36 (9H, s), 1.42 (9H, s), 3.11 (3H, s), 3.16 (1H, dd, *J* = 12.9 Hz, 3.6 Hz), 4.03 (1H, t, *J* = 12.9 Hz), 4.64 (1H, ddd, *J* = 12.9 Hz, 9.0 Hz, 3.6 Hz), 5.75 (1H, s), 6.02 (1H, d, *J* =

9.0 Hz), 6.5-7.6 (4H, m). ^{13}C NMR (75 MHz, C_6D_6) : δ 28.4, 28.8, 35.6, 52.1, 53.3, 79.6, 81.4, 124.2, 125.3, 128.9, 131.7, 133.6, 137.3, 147.4, 153.4, 156.3, 166.3, 172.4. IR (NaCl, neat) 3389, 2979, 1747, 1716, 1640, 1608, 1528, 1367, 1347 cm^{-1}. HRMS (FAB+) calc. mass for $C_{22}H_{31}N_2O_8$ 451.2080 (M+1), found 451.2086. R_f 0.30 (eluted with 25 % ethyl acetate/ hexanes).

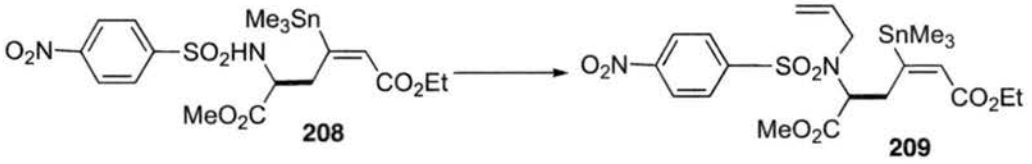
5-(4-Nitro-benzenesulfonylamino)-3-(trimethyl-stannanyl)-hex-2-enedioic acid 1-ethyl ester 6-methyl ester (208).



932 mg (2.013 mmol) of amino acid **198** was deprotected by the same procedure as reported before. The residue thus obtained was dissolved in 15 mL CH_2Cl_2 and 20 mL 5% aqueous $NaHCO_3$ was added. A solution of 446.1 mg (2.013 mmol) of 4-nitobenzenesulfonyl chloride in 15 mL CH_2Cl_2 was added over a period of 5 min at room temperature. The resulting mixture was stirred overnight. The organic layer was separated and the aqueous layer was extracted with 10 mL of CH_2Cl_2. The solvent was evaporated *in vacuo* and the residue was separated through flash chromatography (25% ethyl acetate/hexanes). 894 mg (1.63 mmol) of product **208** was obtained as yellow oil (81 %). $[\alpha]^{20}_D$ +39.9 (*c* 2.63, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 0.15 (9H, s, $^3J_{Sn\text{-}H}$ = 54 Hz), 0.95 (3H, t, *J* = 7.2 Hz), 2.76 (2H, ddd, *J* = 12.3 Hz, 4.2 Hz, 1.2 Hz), 2.96 (3H, s), 3.66 (1H, dt, *J* = 12.3 Hz, 1.2 Hz), 3.94 (2H, qd, *J* = 7.2 Hz, 1.2 Hz), 4.37 (1H, m), 6.27 (1H, t, *J* = 0.9 Hz, $^3J_{Sn\text{-}H}$ = 65Hz), 6.90 (1H, d, *J* = 8.1 Hz), 7.55 (4H, s). ^{13}C NMR (100 MHz, C_6D_6): δ -9.0, 14.4, 37.1, 52.2,

56.5, 61.2, 124.2, 128.5, 132.9, 147.3, 150.1, 166.0, 166.2, 171.4. IR (NaCl, neat) 3268, 3107, 1744, 1709, 1693, 1606, 1532, 1435 cm^{-1}. HRMS (FAB+) calc. mass for $C_{18}H_{26}N_2O_8SSn$: 550.0432 (M+1), found: 550.0440. R_f 0.25 (eluted with 20 % ethyl acetate / hexanes).

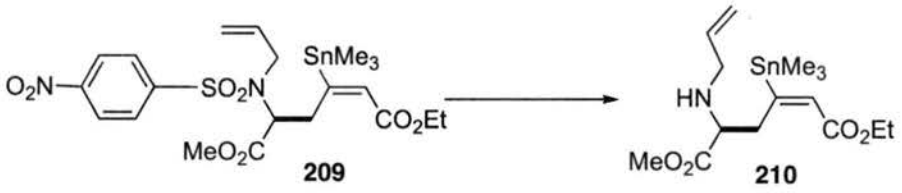
5-[Allyl-(4-nitro-benzenesulfonyl)-amino]-3-(trimethyl-stannanyl)-hex-2-enedioic acid 1-ethyl ester 6-methyl ester (209).



To a solution of compound **208** 894 mg (1.63 mmol) and 676 mg K_2CO_3 (4.89 mmol) in dry DMF 10 mL, allyl bromide 211 μL (2.443 mmol) was added. After stirring for 16 h, the reaction mixture was poured into water (40 mL). The aqueous layer was extracted with Et_2O (3 × 40 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in *vacuo* to give product **209** (1.33 mmol, 786 mg) as an yellow oil in 82% yield. $[\alpha]^{20}_D$ -22.8 (*c* 2.77, CH_2Cl_2). ^1H NMR (300MHz, C_6D_6): 0.27 (9H, s, $^3J_{Sn\text{-}H}$ = 55 Hz), 0.96 (3H, t, *J* = 7.2 Hz), 3.07 (3H, s), 3.40-3.70 (2H, m), 3.95 (2H, q, *J* = 7.2 Hz), 3.98 (1H, ddt, *J* = 15.0 Hz, 6.0 Hz, 1.5 Hz), 4.10 (1H, ddt, *J* = 15.0 Hz, 6.9 Hz, 1.2 Hz), 4.95 (1H, t, *J* = 7.5 Hz), 4.98 (1H, t, *J* = 1.5 Hz), 5.22 (1H, dq, *J* = 17.1 Hz, 1.5 Hz), 5.79 (1H, m), 6.29 (1H, t, *J* = 1.5 Hz, $^3J_{Sn\text{-}H}$ = 68Hz), 7.60 (2H, d, *J* = 9.0Hz), 7.68 (2H, d, *J* = 9.0 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ -7.8, 14.6, 35.7, 49.7, 52.1, 60.3, 61.1, 119.1, 124.2, 131.5, 134.8, 146.7, 150.2, 164.3, 170.3, 171.2. IR (NaCl, neat) 2982, 1742, 1708, 1684,

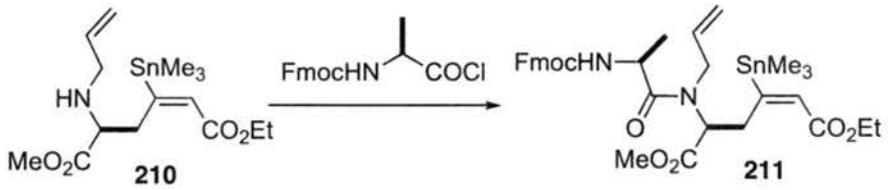
1606, 1532, 1507, 1456 cm^{-1}. HRMS (FAB+) calc. mass for $C_{21}H_{31}N_2O_8SSn$: 591.0823 (M+1), found: 591.0811. R_f 0.30 (eluted with 20 % ethyl acetate / hexanes).

5-Allylamino-3-(trimethyl-stannanyl)-hex-2-enedioic acid 1-ethyl ester 6-methyl ester (210)).



To a solution of compound **209** (1.34 mmol, 786 mg) and K_2CO_3 (6.7 mmol, 926mg) in dry DMF (10 mL) was added PhSH (4.02 mmol, 442 μL). After stirring for 1 h, the reaction mixture was poured into water (20 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organic layers were washed with 1 N $NaHCO_3$ (3 × 15 mL), brine, dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (eluted with 20% ethyl acatate/hexanes) afforded compound **210** (3.16 mmol, 407 mg) as a yellow oil in 75% yield. $[\alpha]^{20}_D$ -12.6 (*c* 1.41, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 0.14 (9H, s, $^3J_{Sn\text{-}H}$ = 54 Hz), 1.0 (3H, t, *J* = 7.2 Hz), 1.58 (1H, b), 2.93 (1H, ddt, *J* = 13.5Hz, 5.7Hz, 1.2Hz), 3.12 (1H, ddt, *J* = 13.5 Hz, 6.3 Hz, 1.2 Hz), 3.20 (1H, ddd, *J* = 13.5 Hz, 9.9 Hz, 1.5Hz), 3.34 (3H, s), 3.41 (1H, dd, *J* = 9.9Hz, 4.5 Hz), 3.74 (1H, ddd, *J* = 13.8 Hz, 4.5 Hz, 1.5 Hz), 5.70 (1H, m), 6.36 (1H, t, *J*= 1.5 Hz, $^3J_{Sn\text{-}H}$ = 74 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ -7.2, 14.7, 38.1, 51.6, 51.7, 60.0, 62.0, 116.7, 130.5, 136.8, 164.5, 169.9, 175.2. IR (NaCl, neat) 3314, 3078, 1738, 1713, 1595, 1435 cm^{-1}. HRMS (FAB+) calc. mass for $C_{15}H_{28}N_1O_4Sn$: 405.1051 (M+1), found: 405.1071. R_f 0.30 (eluted with 20 % ethyl acetate / hexanes).

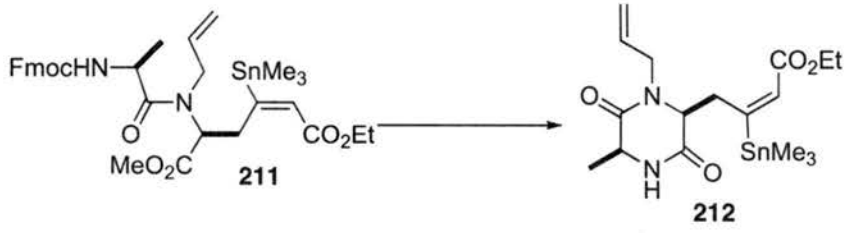
5-{Allyl-[2-(9H-fluoren-9-ylmethoxycarbonylamino)-propionyl]-amino}-3-(trimethyl-stannanyl)-hex-2-enedioic acid 1-ethyl ester 6-methyl ester (211)



To a vigorously stirred two-phase system consisting of a solution of the compound **210** (400 mg, 0.99 mmoL) in 10 mL CH_2Cl_2 and 10 mL 2% aqueous $NaHCO_3$ was added dropwise a solution of Fmoc-Ala acid chloride in 5 mL CH_2Cl_2 over a period of 5 min prepared from 324 mg Fmoc-Ala at 0 °C. The resulting mixture was stirred for 15 min. The organic layer was separated and the aqueous layer was extracted with 10 mL of CH_2Cl_2. The solvent was evaporated *in vacuo* and the residue was separated through flash chromatography (25% ethyl acetate/hexanes). 634 mg (0.91 mmol) of product **211** was obtained as a white solid (92 %). $[\alpha]^{20}_D$ -12.8 (*c*3.62, CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6): 0.34 (9H, s, $^3J_{Sn\text{-}H}$ = 54 Hz), 0.99 (3H, t, J = 7.2 Hz), 1.16 (3H, d, J =7.2 Hz), 3.26 (3H, s), 3.65 (2H, m), 3.91 (1H, m), 3.97 (2H, q, J = 7.2 Hz), 4.08 (1H, J = 7.2 Hz), 4.55 (1H, dd, J = 8.8 Hz, 2.4 Hz), 4.70 (1H, m), 5.08 (1H, dd, J = 10.4 Hz, 0.8 Hz), 5.38 (1H, dd, J = 13.6 Hz, 0.8 Hz), 6.0 (1H, d, J = 8.4 Hz), 5.9 (1H, m), 6.3 (1H, $^3J_{Sn\text{-}H}$ = 68Hz), 7.14 (2H, m), 7.22 (2H, t, J = 7.6 Hz), 7.52 (2H, dd, J = 16.8 Hz, 7.2 Hz), 7.56 (2H, d, J = 8.0 Hz). . ^{13}C NMR (100 MHz, C_6D_6) δ -0.73, 14.7, 19.3, 34.3, 47.7, 48.0, 50.3, 52.2, 60.1, 61.4, 67.4, 118.4, 120.6, 125.8, 126.0, 130.2, 134.6, 142.06, 142.12, 144.8, 145.0, 156.0, 164.5, 171.7, 173.4, 173.5. IR (NaCl, neat) 3415, 3317, 3066, 3040, 1739, 1708, 1652, 1593,

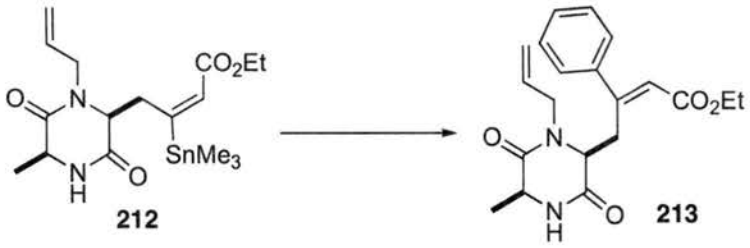
1506, 1450 cm^{-1}. HRMS (FAB+) calc. mass for $C_{33}H_{43}N_2O_7Sn$: 699.2092 (M+1), found: 699.2083. R_f 0.30 (eluted with 25% ethyl acetate /hexanes).

4-(1-Allyl-5-methyl-3,6-dioxo-piperazin-2-yl)-3-(trimethyl-stannanyl)-but-2-enoic acid ethyl ester (212)



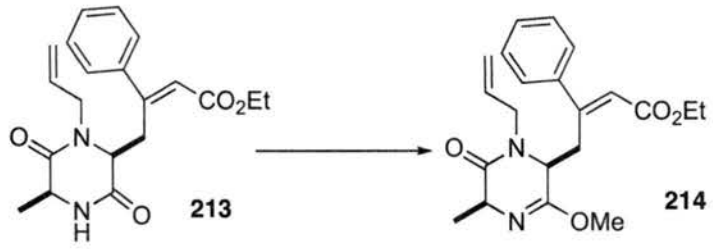
To a solution of compound **211** (634 mg, 0.91 mmol) in 20 mL THF, cooled to 0 °C, was added 175 μL piperidine (2.07 mmol) in one portion. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuo* and residue separated through flash chromatography (75% acetate/ hexanes). 370 mg of product **212** was obtained (0.417 mmol, 92%) as a yellow oil. $[\alpha]^{20}_D$ +43.6 (*c* 1.77, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): 0.18 (s, 9H, $^3J_{Sn\text{-}H}$ = 54 Hz), 0.98 (3H, t, *J* = 7.2 Hz), 1.30 (2H, d, *J* = 7.2 Hz), 3.02 (dd, 1H, *J* = 10.5 Hz, 12 Hz), 3.53 (1H, m), 3.69 (ddd, 1H, *J* = 1.5 Hz, 4.8 Hz, 12 Hz), 3.85 (1H, dd, 1H, *J* = 6.9, Hz, 15.0 Hz), 3.88 (1H. m), 3.94 (2H, q, ^3J = 7.2 Hz), 4.09 (1H, q, *J* = 4.8 Hz), 4.76 (1H, ddt, *J* = 16.5 Hz, 4.8 Hz, 1.5 Hz), 5.02 (1H, dd, *J* = 10.2 Hz, 1.5 Hz), 5.28 (dd, 1H, *J* =17.1 Hz, 1.5 Hz), 5.55 (1H, br), 5.79 (1H, m), 6.30 (s, 1H, $^3J_{Sn\text{-}H}$ = 69 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ -7.61, 14.6, 22.5, 38.4, 47.1, 52.2, 60.2, 60.6, 118.4, 130.5, 133.6, 164.3, 166.5, 167.8, 169.9. IR (NaCl, neat) 3230, 1707, 1678, 1594, 1461, 1368 cm^{-1}. HRMS (FAB+) calc. mass for $C_{17}H_{29}N_2O_4Sn$: 445.1149 (M+1), found: 445.1150. R_f 0.30 (eluted with 100% ethyl acetate).

4-(1-Allyl-5-methyl-3,6-dioxo-piperazin-2-yl)-3-phenyl-but-2-enoic acid ethyl ester (213)



A solution of diphenyliodonium chloride (82.6 mg, 0.261 mmol), CuI (5.43 mg, 0.0285 mmol), $AsPh_3$ (8.72 mg, 0.0285 mmol) and Pd_2dba_3 (6.52 mg, 7.12 μmol) in 3 mL dry DMF under Ar was treated with compound **212** (105.15 mg, 0.2373 mmol). The reaction mixture was then stirred for 4 hours. The solution was then diluted with EtOAc (6 mL) and washed with water. The combined aqueous layers were extracted with 3 mL EtOAc. The combined organic were dried (Na_2SO_4), filtered, and evaporated to dryness. The resulting oil was purified by silica gel chromatography (75% ethyl acetate/ hexanes) to yield **213** as a yellow oil 54.8 mg (65%). $[\alpha]^{20}_D$ +54.7 (*c* 32.1, CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6): δ 0.99 (3H, t, *J* = 7.2 Hz), 1.42 (3H, d, *J* = 7.2Hz), 3.32 (1H, q, *J* = 7.2 Hz), 3.43 (1H, q, *J* = 3.6 Hz), 3.70 (1H, qd, *J* = 6.9 Hz, 0.9 Hz), 3.81 (1H, m), 3.95 (1H, dd, *J* = 7.2 Hz, 0.6 Hz), 4.0 (2H, q, *J* = 7.2 Hz), 4.59 (1H, ddt, *J* = 15Hz, 4.5Hz, 1.5Hz), 4.76 (1H, m), 4.79 (1H, m), 4.83 (1H, m), 5.5 (1H, m), 6.20 (s, 1H), 6.5-7.5 (5H, m). ^{13}C NMR (100 MHz, C_6D_6): δ 14.8, 22.3, 35.6, 47.7, 52.6, 58.7, 60.6, 118.7, 121.0, 127.9, 129.3, 129.7, 133.0, 155.5, 166.5, 167.1, 167.4. IR (NaCl, neat) 324, 1709, 1689, 1667, 1597, 1452 cm^{-1}. HRMS (FAB+) calc. mass for $C_{20}H_{25}N_2O_4$: 357.1814 (M+1), found: 357.1822. R_f 0.30 (eluted with 100% ethyl acetate).

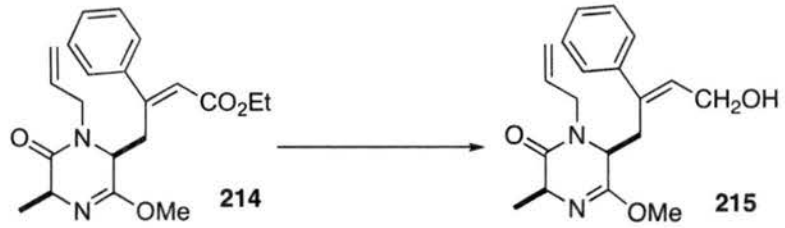
4-(1-Allyl-3-methoxy-5-methyl-6-oxo-1,2,5,6-tetrahydro-pyrazin-2-yl)-3-phenyl-but-2-enoic acid ethyl ester (214).



To a one-necked 5 mL round-bottomed flask, equipped with a magnetic stirrer bar, was added 94 mg (0.264 mmol) of compound **213**, and 3 mL of dry CH_2Cl_2. Then 43 mg (0.29 mmol) trimethyloxonium tetrafluoroborate and 66.5 mg (0.792 mmol) of $NaHCO_3$ was added. The reaction mixture was stirred at 0 °C for 4 h and then poured into 5 mL of ice. The aqueous layer was extracted twice with 10 mL of CH_2Cl_2, and the combined organic layers were washed twice with 10 mL of brine, dried over Na_2SO_4 and concentrated by rotary evaporation. The residue was separated by flash chromatography to give **214** as a pale yellow oil 72.1 mg (74%). $[\alpha]^{20}_D$ +133.3 (*c* 1.67, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 1.01 (3H, t, ^3J = 7.2 Hz), 1.69 (3H, d, ^3J = 7.2 Hz), 3.18 (3H, s), 3.32 (1H, dd, J = 12.9 Hz, 9.3 Hz), 3.65 (1H, q, J = 7.5 Hz), 3.75 (1H, ddd, J = 12.9 Hz, 5.4 Hz, 0.9 Hz), 3.99 (2H, qd, J =7.2 Hz, 1.8 Hz), 4.10 (1H, ddd, J = 9.3 Hz, 5.4 Hz, 0.9Hz), 4.49 (1H, dd, J = 7.5 Hz, 1.2 Hz). 4.80 (1H, ddt, J = 14.7 Hz, 4.8 Hz, 1.5 Hz), 4.92 (1H, dd, J =10.2 Hz, 1.5 Hz), 5.09 (1H, qd, J = 17.1 Hz, 1.5 Hz), 5.73 (1H, m), 6.17 (1H, s), 7.0-7.3 (5H, m). ^{13}C NMR (75 MHz, C_6D_6): δ 14.8, 22.1, 36.2, 46.9, 52.8, 55.9, 57.0, 60.6, 118.3, 120.3, 127.5, 129.1, 129.6, 133.7, 141.2, 155.3, 160.4, 166.4, 170.1. IR (NaCl, neat) 2981, 1700, 1659,

1624, 1576, 1558, 1742, 1457 cm^{-1}. HRMS (FAB+) calc. mass for $C_{21}H_{27}N_2O_4$: 371.1971 (M+1), found: 371.1968. R_f 0.35 (eluted with 75 % ethyl acetate / hexanes).

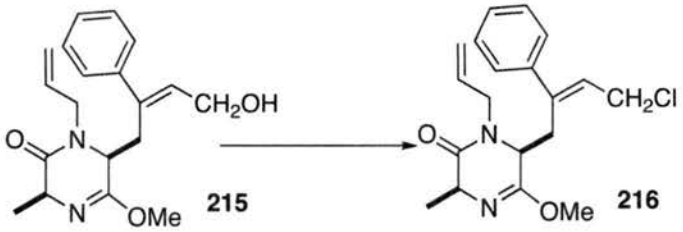
(3*S*,6*R*,*E*)-1-Allyl-6-(4-hydroxy-2-phenyl-but-2-enyl)-5-methoxy-3-methyl-1,6-dihydropyrazin-2(3*H*)-one (215).



179 mg (0.483 mmol) of compound **214** was dissolved in 6 mL CH_2Cl_2 and cooled to -78 °C under Ar. 50.8 μL (0.483 mmol) of $Me_2S{\bullet}BF_3$ was added dropwise. The reaction mixture was stirred for 30 minutes. 1.93 mL 1M DIBAL (1.93 mol) in CH_2Cl_2 was added dropwise. The reaction mixture was stirred for 10 min and was then quenched with 5 mL saturated aqueous solutiuon of sodium potassium tartrate, The reaction mixture was stirred vigorously overnight at rt. The mixture was extracted with CH_2Cl_2. The organic phase was combined and concentrated. Flash column (5% methanol/ethyl acetate) gave 136.3 mg product **215** as a yellow oil (86%). $[\alpha]^{20}_D$ +68.0 (*c* 0.65, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): 1.63 (3H, d, *J* = 7.2 Hz), 1.75 (1H, br), 2.78 (H, m), 2.80 (1H, m), 3.10 (1H, ddd, *J*= 15.3 Hz, 7.5 Hz, 0.9 Hz), 3.33 (3H, s), 3.86 (1H, dt, *J* = 6.9 Hz, 1.2 Hz), 4.10 (1H, m), 4.43 (1H, qd, *J*= 7.5 Hz, 1.5 Hz), 4.75 (2H, m), 5.44 (1H, m), 5.95 (1H, t, *J*= 3.3 Hz), 6.0 (1H, m), 7.0-7.4 (5H, m). ^{13}C NMR (75 MHz, C_6D_6): δ 22.6, 35.5, 47.2, 53.1, 55.2, 56.9, 60.1, 118.5, 127.2, 128.9, 129.1, 132.6, 132.9, 137.4, 160.4, 170.4. IR (NaCl, neat) 3408 (br), 1694, 1651, 1639, 1493, 1470, 1442 cm^{-1}. HRMS (FAB+) calc. mass for

$C_{19}H_{25}N_2O_3$: 329.1865 (M+1), found: 329.1869. R_f 0.25 (eluted with 5 % methanol/ ethyl acetate).

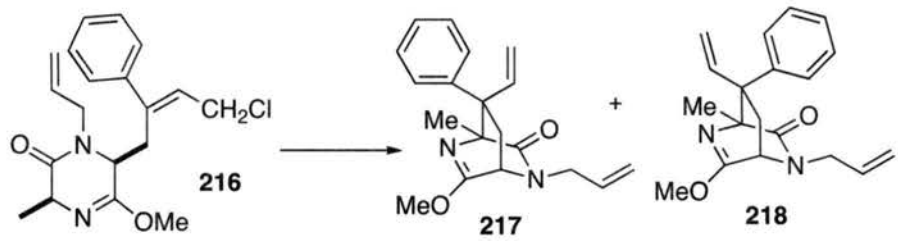
(3*S*,6*R*,*E*)-1-Allyl-6-(4-chloro-2-phenyl-but-2-enyl)-5-methoxy-3-methyl-1,6-dihydropyrazin-2(3*H*)-one (216)



To a solution of 13 mg (0.0332 mmol) of **215** in 2mL CH_2Cl_2 at 0 °C was added collidine 43.8 μL (0.33 mmol) followed by dropwise addition of MsCl 2.83 μL (0.0365 mmol). The reaction mixture was stirred at 0 °C for 3.5 h and 23 °C for 14 h. At this time, the reaction mixture was concentrated and 2mL DMF was added. After the reaction mixture was stirred at rt for 24 h, 58 mg (0.166 mmol) $BnBu_3NCl$ was added, and the mixture was stirred at rt for additional 6 h. The reaction mixture was concentrated in high vacuum and extracted with (67% ethyl acetate/ hexanes). The combined extracts were washed with 0.005 N HCl in water, washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography (33% ethyl acetate/ hexanes) gave 13 mg (88%) of the product as an oil. $[\alpha]^{20}_D$ +66.0 (*c* 0.65, CH_2Cl_2). ^{1}HNMR (300 MHz, C_6D_6): δ 1.56 (3H, d, *J* = 7.5Hz), 2.65 (1H, ddd, *J* = 14.7 Hz, 6.9 Hz, 0.6 Hz), 2.73 (1H, ddd, *J* = 14.7 Hz, 8.1 Hz, 0.6 Hz), 3.02 (1H, ddt, *J* = 15.0 Hz, 7.2 Hz, 1.2 Hz), 3.30 (3H, s), 3.78 (1H, m), 3.83 (1H, dd, *J* = 8.1Hz, 6.3 Hz), 4.42 (1H, qd, *J* =7.5 Hz, 1.2 Hz), 4.58 (1H,dt, *J* = 4.5 Hz, 1.5 Hz), 4.63 (1H, *J* = 3.0 Hz, 1.5 Hz), 4.69 (1H, ddd, *J* =17.1 Hz, 2.7 Hz, 1.5 Hz), 4.75 (1H, ddd, *J* = 10.2 Hz, 2.4 Hz, 1.5

Hz), 5.50 (1H, m), 5.73 (1H, t, J = 8.1 Hz), 6.9-7.4 (5H, m). ^{13}C NMR (100 MHz, C_6D_6): δ 22.4, 35.1, 40.6, 47.0, 52.9, 54.9, 56.7, 118.5, 127.2, 127.3, 128.9, 129.1, 133.0, 141.0, 141.3, 160.1, 169.9, 176.3. IR (NaCl, neat) 2977, 1695, 1658, 1465, 1440, 1417 cm^{-1}. HRMS (FAB+) calc. mass for $C_{19}H_{24}N_2O_2Cl$: 347.1526 (M+1), found: 347.1527. R_f 0.33 (eluted with 75 % ethyl acetate / hexanes).

2-Allyl-6-methoxy-4-methyl-8-phenyl-8-vinyl-2,5-diaza-bicyclo[2.2.2]oct-5-en-3-one (217) (218)

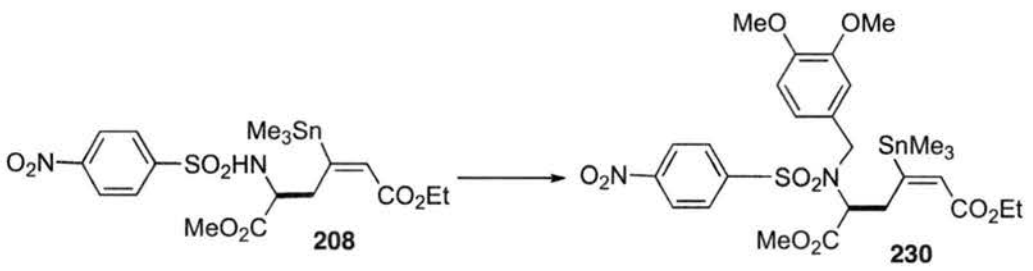


A solution of compound **216** (13 mg, 0.0375 mmol), 60% NaH (1.52 mg, 0.375 mmol) in 2 mL dry THF was reluxed under Ar for 6 hours. The solution was then diluted with 5 mL EtOAc and washed with water. The combined aqueous layers were extracted with EtOAc (5 mL X 2). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. The resulting oil was purified by silica gel chromatography (40% ethyl acetate/ hexanes). The first compound was **217** (3 mg, 26%). $[\alpha]^{20}_D$ +66.4 (c 0.25, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 1.875 (1H, dd, J = 13.8 Hz, 1.8 Hz), 1.878 (3H, s), 2.28 (1H, dd, J = 14.1 Hz, 3.6 Hz), 3.52 (3H, s), 3.57 (1H, ddt, J = 15.3 Hz, 6.3 Hz, 1.5 Hz), 3.69 (2H, dd, J = 3.6 Hz, 1.8 Hz), 3.89 (1H, ddt, J = 15.3 Hz, 5.7 Hz, 1.5 Hz), 4.87 (1H, m), 4.91 (1H, m), 5.01 (1H, dd, J = 15.3 Hz, 0.6 Hz), 5.17 (1H, dd, J = 11.1 Hz, 0.6 Hz), 5.51 (1H, m), 6.28 (1H, dd, J =

15.3 Hz, 11.1 Hz). 6.9~7.3 (m, 5H). ^{13}C NMR (100 MHz, C_6D_6): δ 15.4, 18.3, 40.9, 47.3, 53.3, 54.3, 54.6, 70.6, 116.7, 118.3, 127.0, 128.3, 129.8, 133.8, 143.8, 144.9, 171.8, 172.6. IR (NaCl, neat) 1682, 1650, 1599, 1493, 1444 cm^{-1}. HRMS (FAB+) calc. mass for $C_{19}H_{23}N_2O_2$: 311.1760 (M+1), found: 311.1761. R_f 0.35 (eluted with 40% ethyl acetate / hexanes).

The second one was **218** (3.7 mg, 32%). $[\alpha]^{20}_D$ +35.4 (*c* 0.308, CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6): 1.85 (3H, s), 2.17 (1H, dd, *J* = 13.6 Hz, 2.8 Hz), 2.27 (1H, dd, *J* = 13.6 Hz, 3.2 Hz), 3.50 (3H, s), 3.51 (1H, ddt, *J* = 15.2 Hz, 6.4 Hz, 1.2 Hz), 3.68 (1H, t, *J* = 2.4 Hz), 4.09 (1H, ddt, *J* = 15.2 Hz, 5.6 Hz, 1.6 Hz), 4.88 (1H, t, *J* = 1.2 Hz,), 4.91 (1H, dd, *J* = 6.4 Hz, 1.2 Hz), 4.96 (1H, dd, *J* = 17.6 Hz, 0.4 Hz), 5.17 (1H, dd, *J* = 10.8 Hz, 0.4 Hz), 5.52 (1H, m), 6.10 (1H, dd, *J* = 17.6, 10.8 Hz), 6.9~7.4 (5H, m). ^{13}C NMR (100 MHz, C_6D_6): 18.3, 42.2, 47.3, 54.2 54.4, 70.7, 116.2, 118.5, 127.1, 128.2, 128.5, 129.3, 133.6, 143.7, 144.8, 172.5, 173.1. IR (NaCl, neat) 2924, 1683, 1648, 1557, 1496, 1444 cm^{-1}. HRMS (FAB+) calc. mass for $C_{19}H_{23}N_2O_2$: 311.1760 (M+1), found: 311.1758. R_f 0.33 (eluted with 40 % ethyl acetate / hexanes).

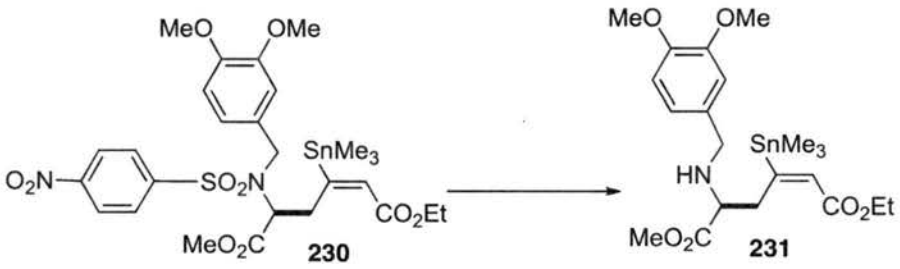
(*S*,*E*)-1-Ethyl 6-methyl 5-((3,4-dimethoxybenzyl)(4-nitrophenyl thioperoxy) amino)-3-(trimethyl stannyl)hex-2-enedioate (230)



To a solution of compound **208** (1.90 g, 3.46 mmol) and 5.0 g K_2CO_3

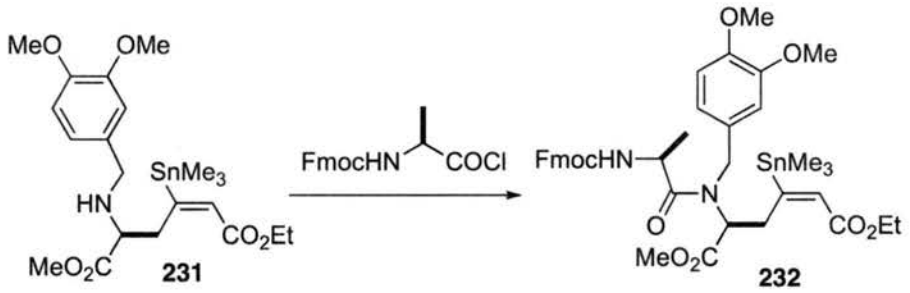
(36.2 mmol) in 40 mL dry DMF, 3,4-dimethoxybenzyl bromide (1.1 g, 4.76 mmol) was added. After stirring for 16 h, the reaction mixture was poured into water (100 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column gave 2.1 g product **230** (3.0 mmol) as an yellow oil in 87% yield. $[\alpha]^{20}_D$ -11.8 (*c*4.08, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): 0.26 (9H, s, $^3J_{Sn-H}$ = 54 Hz), 0.98 (t, *J* = 7.2 Hz), 3.05 (3H, s), 3.36 (3H, s), 3.44 (1H, ddd, *J* = 12.3 Hz, 4.8 Hz, 1.5 Hz), 3.53 (s, 3H), 3.64 (1H, t, *J* = 11.4 Hz), 3.96 (2H, q, *J* = 7.2 Hz), 4.64 (1H, d, *J* = 2.1 Hz), 4.91 (1H, dd, *J* = 10.5 Hz, 4.8 Hz), 6.25 (1H, dd, *J* = 1.2 Hz, 0.3 Hz, $^3J_{Sn-H}$ = 51 Hz), 6.53 (d, 1H, *J* = 8.1 Hz), 7.05 (1H, dd, *J* = 8.1 Hz, 1.8 Hz), 7.06 (1H, d, *J* = 2.1 Hz), 7.66 (4H, q, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ -7.7, 14.6, 35.7, 50.8, 52.2, 55.8, 55.9, 60.3, 61.4, 66.0, 112.0, 113.3, 122.0, 124.3, 129.1, 131.2, 146.9, 150.17, 150.27, 150.40, 164.3, 170.7, 171.3. IR (NaCl, neat) 3105, 1739, 1706, 1606, 1594, 1532, 1517, 1464, 1441, 1422 cm^{-1}. HRMS (FAB+) calc. mass for $C_{27}H_{36}N_2O_{10}SSn$: 700.1112 (M+1), found: 700.1127. R_f 0.30 (eluted with 20 % ethyl acetate / hexanes).

(*S*,*E*)-1-Ethyl 6-methyl 5-(3,4-dimethoxybenzylamino)-3-(trimethyl stannyl)hex-2-enedioate (231)



To a solution of 2.1 g compound **230** (3.00 mmol) and 4.14 g K_2CO_3 (30 mmol) in dry 50 mL DMF was added 1.01 mL PhSH (9.91 mmol). After stirring for 1 h, the reaction mixture was poured into 100 mL water. The aqueous layer was extracted with Et_2O (50 mL X 3) and the combined organic layers were washed with 1 N $NaHCO_3$ (50 mL X 3), brine, and dried (Na_2SO_4), then concentrated *in vacuo*. Flash column chromatography (33% ethyl acetate/ hexanes) afforded 1.23 g compound **231** as a yellow oil in 79.7% yield. $[\alpha]^{20}_D$ -12.7 (*c* 3.47, CH_2Cl_2). R*f* = 0.30 (eluted with 33% ethyl acetate/ hexanes). ^{1}H NMR (300 MHz, C_6D_6): δ 0.12 (s, 9H, $^3J_{Sn\text{-}H}$ = 54 Hz), 1.0 (t, *J* = 7.2 Hz), 1.9 (1H, br), 3.38 (3H, s), 3.40 (3H, s), 3.43 (1H, dd, *J* = 8.1 Hz, 1.2 Hz), 3.50 (3H, s), 3.555 (1H, m), 3.56 (1H, d, *J* = 12.6 Hz), 3.66 (1H, ddd, *J* = 12.9 Hz, 4.8 Hz, 1.2 Hz), 3.73 (d, 1H, *J* = 12.6 Hz), 4.02 (2H, q, *J* = 7.2 Hz), 6.36 (1H, t, *J* = 1.5 Hz, $^3J_{Sn\text{-}H}$ = 72 Hz), 6.58 (d, 1H, *J* = 8.1 Hz), 6.8-6.9 (2H, m). ^{13}C NMR (75 MHz, C_6D_6): δ -7.6, 14.7, 38.1, 51.8, 52.8, 55.9, 56.0,60.1, 61.8, 112.5,113.2, 121.2, 130.8, 132.9, 149.8, 150.6, 164.5, 169.4, 175.3. IR (NaCl, neat) 2979, 2953, 1734, 1713, 1593, 1516, 1464 cm^{-1}. HRMS (FAB+) calc. mass for $C_{21}H_{34}N_1O_6Sn$: 515.1419 (M+1), found: 515.1418. R_f 0.30 (eluted with 15 % ethyl acetate / hexanes).

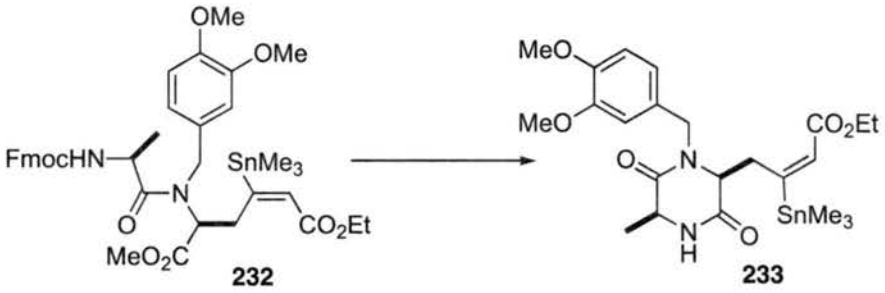
(*S*,*E*)-1-Ethyl 6-methyl 5-((*S*)-2-(((9*H*-fluoren-9-yl)methoxy) carbonyl amino)-*N*-(3,4-dimethoxy benzyl)propanamido)-3-(trimethylstannyl) hex-2-enedioate (232)



To a vigorously stirred two-phase system consisting of a solution of 1.23 g compound **231** (2.39 mmoL) in 100 mL CH_2Cl_2 and 100 mL 2% aqueous $NaHCO_3$ was added dropwise a solution of acid chloride prepared from 0.819 g Fmoc-Ala (2.63 mmol) in 40 mL CH_2Cl_2 at 0 °C. The resulting mixture was stirred for 15 min. The organic layer was separated and the aqueous layer was extracted with 100 mL of CH_2Cl_2. The solvent was evaporated *in vacuo* and the residue was separated through flash chromatography (eluted with 25% ethyl acetate/hexanes). 1.50 g of product **232** (1.86 mmol) was obtained as a yellow oil (78%). $[\alpha]^{20}_D$ -12.1 (*c* 7.03, CH_2Cl_2). ^{1}HNMR (300 MHz, C_6D_6): δ 0.36 (9H, s), 1.0 (3H, d, *J* = 7.2 Hz), 1.01 (3H, t, *J* = 7.2 Hz), 3.14 (3H, s), 3.2 (1H, m), 3.37 (1H, ddd, *J* = 12.9 Hz, 6.9 Hz, 0.6 Hz), 3.42 (3H, s), 3.57 (1H, m), 3.68 (1H, t, *J* = 5.4 Hz), 3.76 (3H, s), 4.02 (2H, q, *J* = 7.2 Hz), 4.10 (1H, t, *J* = 7.2 Hz), 4.24 (1H, t, *J* = 11.3 Hz), 4.26 (1H, d, *J* = 6.9 Hz), 4.36 (1H, dd, *J* = 10.5 Hz, 6.9 Hz), 4.54 (1H, d, *J* = 16.8 Hz), 4.76 (1H, d, *J* = 6.9 Hz), 4.79 (1H, d, *J* = 16.8 Hz), 5.44 (1H, d, *J* = 8.4 Hz), 6.6-7.6 (8H, m). ^{13}C NMR (75 MHz, C_6D_6): δ -7.1, 14.7, 18.6, 33.9, 47.9, 50.7, 52.0, 55.9, 56.2, 60.0, 61.8, 67.5, 112.1, 113.1, 120.6, 121.2, 125.8, 126.0, 127.8, 129.5, 129.9, 142.0, 144.7, 145.0, 150.3, 150.8, 156.5,

164.5, 171.6, 173.7. IR (NaCl, neat) 3355, 3065, 1739, 1732, 1600, 1652, 1593, 1516, 1464, 1451 cm^{-1}. HRMS (FAB+) calc. mass for $C_{39}H_{49}N_2O_9Sn$: 809.246 (M+1), found: 809.2457. R_f 0.30 (eluted with 33 % ethyl acetate / hexanes).

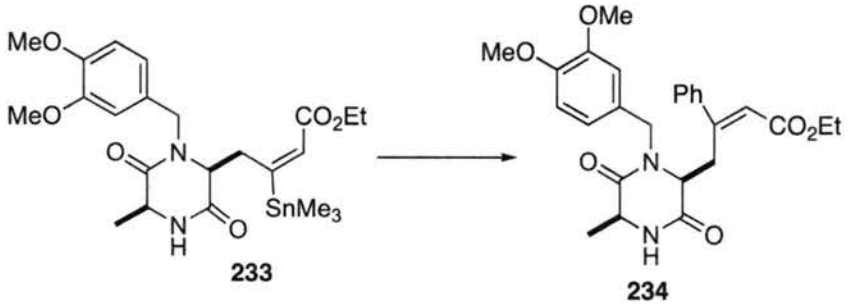
(*E*)-Ethyl 4-((2*S*,5*S*)-1-(3,4-dimethoxybenzyl)-5-methyl-3,6-dioxopiperazin -2-yl)-3-(trimethyl stannyl)but-2-enoate (233)



To a solution of 1.50 g compound **232** (1.86 mmol) in 60 mL THF, cooled to 0 °C, was added 0.9 mL piperidine (9.29 mmol) in one portion. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuo* and residue separated through flash chromatography. 800 mg of product **233** was obtained as a yellow oil (1.45 mmol, 78%). $[\alpha]^{20}_D$ +41.1 (*c* 0.37, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 0.20 (9H, s, $^3J_{Sn\text{-}H}$ = 81 Hz), 1.0 (3H, t, *J* = 7.2 Hz), 1.43 (3H, d, *J* = 7.2Hz), 3.1 (1H, dd, *J* = 12.3 Hz, 11.1 Hz), 3.36 (3H, s), 3.49 (3H, s), 3.73 (1H, m), 3.78 (1H, dd, *J* = 4.8 Hz, 1.5 Hz), 3.82 (1H, dd, *J* = 4.8 Hz, 1.5 Hz), 3.91(2H, q, ^3J = 7.2Hz), 4.0 (2H, q, *J* = 7.2Hz), 4.28 (1H, dd, *J* = 4.8, 10.5 Hz), 4.39 (1H, d, *J* = 14.4 Hz), 5.53 (1H, d, *J* = 14 Hz), 6.34 (1H, s, $^3J_{Sn\text{-}H}$ = 69 Hz), 6.57 (1H, d, *J* = 8.4 Hz), 7.1-7.2 (2H, m). ^{13}C NMR (75 MHz, C_6D_6): δ -7.54, 14.6, 22.6, 38.4, 47.4, 52.3, 55.9, 60.3, 112.7, 113.7, 121.5, 130.5, 130.6, 150.1, 150.6, 164.4, 167.32, 167.35, 168.37, 168.38, 170.2. IR (NaCl, neat) 3233, 3062, 1704, 1682, 1662, 1593, 1516, 1463 cm^{-1}.

HRMS (FAB+) calc. mass for $C_{23}H_{35}N_2O_6Sn$: 554.1528 (M+1), found: 554.1528. R_f 0.35 (eluted with 100 % ethyl acetate).

(*E*)-Ethyl 4-((2*S*,5*S*)-1-(3,4-dimethoxybenzyl)-5-methyl-3,6-dioxopiperazin -2-yl)-3-phenylbut-2-enoate (234)

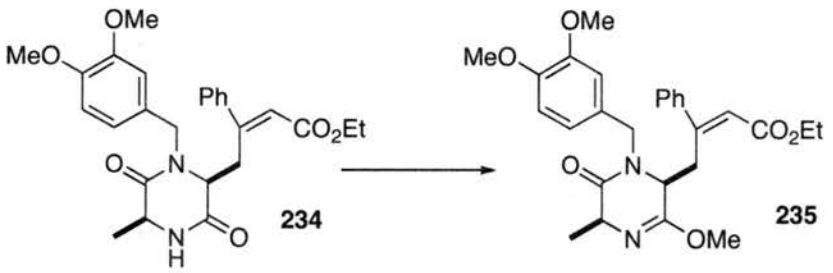


233 234

A solution of diphenyliodonium chloride (403 mg, 1.27mmol), CuI (58.1 mg, 0.305 mmol), $AsPh_3$ (93.3 mg, 0.305 mmol) and Pd_2dba_3 (69.8 mg, 0.0762 mmol) in 3 mL dry DMF was treated under Ar with compound **233** (705.5 mg, 1.27 mmol). The reaction mixture was then stirred for 4 hours. The solution was then diluted with EtOAc (60 mL) and washed with water. The combined aqueous layers were back extracted with EtOAc (30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. The resulting oil was purified by silica gel chromatography (eluted with 100% ethyl acetate) to yield 545 mg of **234** as a yellow oil (92%). $[\alpha]^{20}_D$ +20.6 (*c* 2.27, CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6): δ 1.01 (3H, t, *J* = 6.9 Hz), 1.48 (3H, d, *J* = 7.2 Hz), 3.30 (3H, s), 3.34 (1H, m), 3.38 (3H, s), 3.82 (1H, dd, *J* = 6.0 Hz, 0.6 Hz), 3.89 (1H, d, *J* = 14.7 Hz), 4.02 (2H, q, *J* = 6.9 Hz), 4.13 (1H, t, *J* = 8.1 Hz), 5.10 (1H, m), 5.31 (1H, d, *J* = 14.7 Hz), 6.21 (1H, s), 6.43 (1H, d, *J* = 8.7 Hz), 6.3-7.5 (7H, m). ^{13}C NMR (75 MHz, C_6D_6): δ 14.6, 22.1, 35.4, 48.1, 52.5,

55.8,55.9, 58.5, 60.6, 112.5, 113.1, 121.0,121.3, 127.9, 129.3, 129.8,130.1, 140.5, 150.0, 150.4, 155.4, 166.6, 167.9. IR (NaCl, neat) 3302, 3059, 1706, 1688, 1662, 1593, 1576, 1516, 1448 cm^{-1}. HRMS (FAB+) calc. mass for $C_{26}H_{31}N_2O_6$: 467.2182 (M+1), found: 467.2165. R_f 0.35 (eluted with 100 % ethyl acetate).

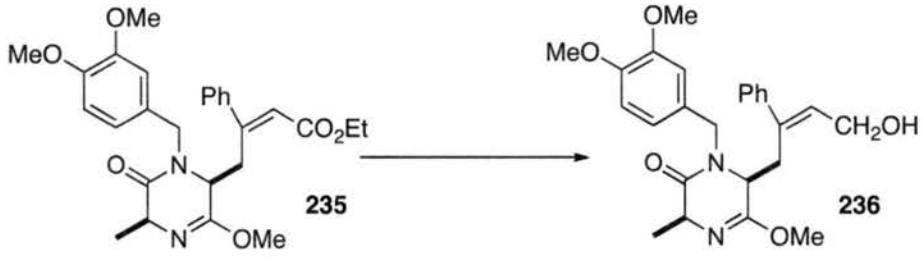
(*E*)-Ethyl 4-((2*S*,5*S*)-1-(3,4-dimethoxybenzyl)-3-ethoxy-5-methyl-6-oxo-1,2,5,6-tetrahydro pyrazin-2-yl)-3-phenylbut-2-enoate (235)



To a one-necked 100 mL round-bottomed flask, equipped with a magnetic stirrer bar, were added 480 mg (1.03 mmol) of compound **234**, and 50 mL of dry CH_2Cl_2 and 865 mg (10.3 mmol) of $NaHCO_3$. Then 304.4 mg (2.06 mmol) of trimethyloxonium tetrafluoroborate was added. The reaction mixture was stirred at 0 °C for 4 h and then poured into 50 g of ice. The aqueous layer was extracted twice with 50 mL of CH_2Cl_2, and the combined organic layers were washed twice with 50 mL of brine, dried over Na_2SO_4 and concentrated by rotary evaporation. The residue was separated by flash chromatography to give 461 mg of **235** as a pale yellow oil (0.96 mmol, 93.2%). $[\alpha]^{20}_D$ +70.6 (*c* 4.63, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 1.02 (3H, t, *J* = 7.2 Hz), 1.76 (3H, d, *J* = 7.2 Hz), 3.09 (3H, s), 3.32 (3H, s), 3.37 (1H, m), 3.43 (3H, s), 3.85 (1H, t, *J* = 7.2 Hz), 4.02 (1H, m), 4.14 (1H, d, *J* = 14.4 Hz), 4.26 (1H, m), 4.61 (1H, q, *J* = 7.2 Hz), 5.62 (1H, d, *J* = 14.4 Hz), 6.19 (1H, s), 6.49

(1H, d, J = 9.0 Hz), 7.0~7.3 (m, 5H). ^{13}C NMR (75 MHz, C_6D_6): δ 14.7, 21.9, 35.9, 47..1,52.6,55.4, 55.78, 55.83, 57.0, 60.5, 112.5,113.5, 120.4, 121.6, 127.6, 128.9, 129.1, 129.7, 130.9, 141.2, 150.0, 150.6, 155.4, 160.5, 166.6, 170.8. IR (NaCl, neat) 1699, 1652, 1593, 1516, 1446, 1420 cm^{-1}. HRMS (FAB+) calc. mass for $C_{23}H_{22}N_3O_2$: 481.2339 (M+1), found: 481.2335. R_f 0.30 (eluted with 75 % ethyl acetate / hexanes).

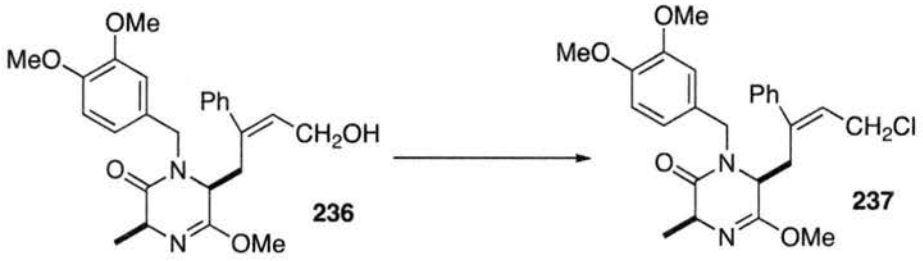
(3*S*, 6*S*)-1-(3,4-Dimethoxybenzyl)-5-ethoxy-6-((*E*)-4-hydroxy-2-phenylbut-2-enyl)-3-methyl-1,6-dihydropyrazin-2(3*H*)-one (236)



461 mg (0.959 mmol) of compound **235** was dissolved in 30 mL CH_2Cl_2 and cooled to -78 °C under Ar. 101 μL (0.959 mmol) of $Et_2O{\bullet}SMe_2$ was added dropwise. The reaction mixture was stirred for 30 minutes. 3.84 mL 1M DIBAL in CH_2Cl_2 was added dropwise. The reaction mixture was stirred for 10 min and was then quenched with 50 mL saturated aqueous solutiuon of sodium potassium tartrate. The reaction mixture was stirred vigorously overnight at rt. The mixture was extracted with CH_2Cl_2. The organic phases were combined and concentrated. Flash chromatography (eluted with 5% MeOH/acetate) gave 273.4 mg of product **236** as a yellow oil (0.623 mmol, 65%). $[\alpha]^{20}_D$ +26.4 (*c* 2.60, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 1.68 (3H, d, J = 7.2 Hz), 2.85 (2H, d, J = 6.3Hz), 3.32 (3H, s), 3.29 (3H,s), 3.30 (1H, m), 3.33 (3H, s), 3.40 (1H, d, J = 11.7 Hz), 3.64 (1H, d, J = 14.4 Hz), 3.99 (1H, dt, J = 6.6 Hz,

0.9 Hz), 4.07 (1H, t, J = 6.0 Hz), 4.57 (2H, qd, J = 7.2 Hz, 0.9 Hz), 5.52 (1H, J = 14.4 Hz), 5.93 (1H, t, J = 6.6 Hz), 6.35-7.4 (8H, m). ^{13}C NMR (75 MHz, C_6D_6): δ 22.4, 35.6, 53.0, 54.6, 55.8, 55.9, 57.0, 60.1, 112.6, 113.0, 121.4, 127.3, 129.9, 133.2, 137.1, 141.6, 150.1, 150.6, 160.9, 171.4. IR (NaCl, neat) 3415, 1694, 1656, 1640, 1593, 1516, 1494, 1463 cm^{-1}. HRMS (FAB+) calc. mass for $C_{25}H_{31}N_2O_5$: 439.2233 (M+1), found: 439.2230. R_f 0.30 (eluted with 5 % methanol / ethyl acetate).

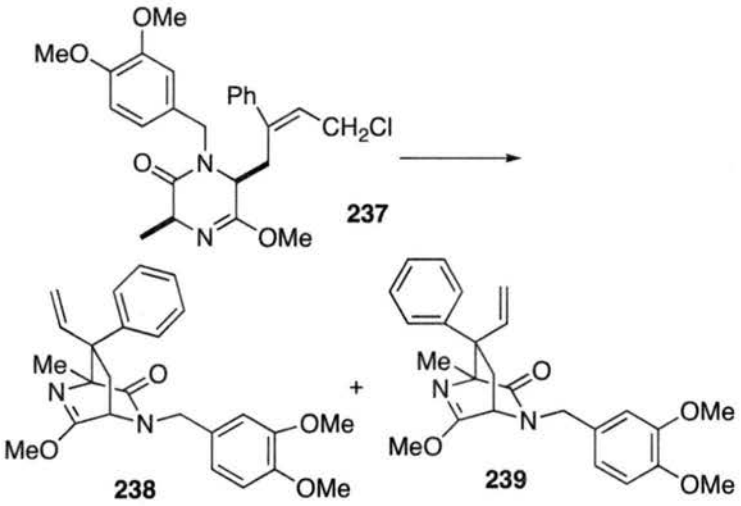
(3*S*,6*S*)-6-((*E*)-4-Chloro-2-phenylbut-2-enyl)-1-(3,4-dimethoxybenzyl)-5-ethoxy-3-methyl-1,6-dihydropyrazin-2(3*H*)-one (237)



To a solution of 220 mg (0.502 mmol) of **236** in 20 mL CH_2Cl_2 at 0 °C was added collidine 528 μL (0.502 mmol) followed by dropwise addition of MsCl 37.7 μL (0.552 mmol). The reaction mixture was stirred at 0 °C for 3.5 h and 23 °C for 14 h. At this time, the reaction mixture was concentrated and 20 mL DMF was added. After the reaction mixture was stirred at rt for 24 h, 783 mg (251 mmol) $BnBu_3NCl$ was added, and the mixture was stirred at rt for additional 6 h. The reaction mixture was concentrated in high vacuum and extracted and with EtOAc/Et_2O (2/1). The combined extracts were washed with 100 mL X 3 0.005 N HCl in water, washed with brine, dried over Na_2SO_4 and concentrated. Flash column (75% ethyl acetate/ hexanes) gave 190 mg of product **237** as an oil (83%). $[\alpha]^{20}_D$ +25.1 (*c* 3.92, CH_2Cl_2).

^{1}H NMR (300 MHz, C_6D_6): δ 1.64 (3H, d, J = 6.9 Hz), 2.81 (1H, t, J = 5.1 Hz), 3.24 (3H, s), 3.29 (3H, s), 3.34 (3H, s), 3.38 (1H, m), 3.60 (1H, d, J = 14.4 Hz), 3.67 (1H, m), 3.87 (1H, t, J = 7.2 Hz), 3.93 (1H, t, J = 7.2 Hz), 4.54 (1H, qd, J = 6.9, 0.9 Hz), 5.44 (1H, d, J = 14.4 Hz), 5.78 (1H, t, J = 8.1 Hz). ^{13}C NMR (75 MHz, C_6D_6): δ 22.5, 35.2, 40.6, 47.5, 52.9, 54.6, 55.8, 55.8, 55.9, 56.9, 112.5, 113.0, 121.3, 127.3, 127.4, 129.9, 140.9, 141.3, 150.2, 150.7, 160.4, 170.5. IR (NaCl, neat) 1736, 1699, 1695, 1656, 1652, 1607, 1592, 1516, 1494, 1464, 1444 cm^{-1}. HRMS (FAB+) calc. mass for $C_{25}H_{30}N_2O_4Cl$: 457.1894 (M+1), found: 458.1878. R_f 0.30 (eluted with 75 % ethyl acetate /hexanes).

S_N2' Reaction

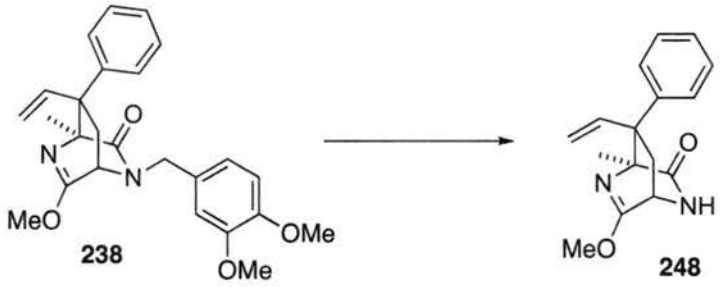


60% NaH (9.5 mg, 0.234 mmol) was first washed with benzene and then with THF under Ar. A solution of compound **237** (420 mg, 0.919 mmol) in 50 mL dry THF was added. The mixture was heated to 60 °C under Ar for 6 hours. The reaction was then cooled to rt and 30 mL hexane was added to quench the reaction. The solution was then diluted with 50 mL EtOAc and washed with water. The combined

aqueous layers were back extracted with EtOAc (50 mL X 2). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. The resulting oil was purified by silica gel chromatography (eluted with 50 % ethyl acetate/ hexanes). The first compound is **238**: 151 mg, 39.1%. $[\alpha]^{20}_D$ +28.4 (*c* 1.84, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 1.88 (1H, dd, *J* = 13.5 Hz, 0.6 Hz), 1.93 (3H, s), 2.23 (1H, dd, *J* = 13.5 Hz, 3.6 Hz), 3.37 (3H, s), 3.42 (3H, s), 3.47 (3H, s), 3.83 (1H, m), 4.26 (1H, d, *J* = 15.6 Hz), 4.48 (1H, d, *J* = 15.6 Hz), 4.99 (1H, d, *J* = 17.4 Hz), 5.18 (1H, d, *J* = 11.1 Hz), 6.32 (1H, dd, *J* = 17.4, 11.1 Hz), 6.5-7.5 (8H, m). ^{13}C NMR (75 MHz, C_6D_6): δ 18.4, 41.1, 48.6, 53.5, 54.2,54.8, 55.9, 70.6, 112.3, 112.7, 116.8, 121.2, 126.9, 129.8, 143.8, 144.8, 150.2, 150.8, 172.0,173.1. IR (NaCl, neat) 2944, 1679, 1649, 1593, 1516, 1493, 1445 cm^{-1}. HRMS (FAB+) calc. mass for $C_{25}H_{29}N_2O_4$: 421.2127 (M+1), found: 421.2136. R_f 0.33 (eluted with 50 % ethyl acetate / hexanes).

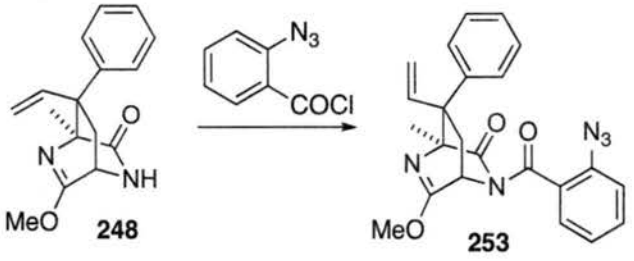
The second compound is **239**: 50.5mg, 13.1%. $[\alpha]^{20}_D$ +98 (*c* 0.5, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 1.85 (1H, dd, *J* = 15.9 Hz, 1.2 Hz), 1.94 (3H, s), 2.18 (1H, dd, *J* = 15.9 Hz, 3.6 Hz), 3.36 (3H, s), 3.41 (3H, s), 3.47 (3H, s), 3.82 (1H, m), 4.26 (1H, d, *J* = 13.5 Hz), 4.48 (1H, d, *J* = 13.5 Hz), 4.99 (1H, d, *J* = 17.7 Hz), 5.18 (1H, d, *J* = 11.1 Hz), 6.32 (1H, dd, *J* = 17.7, 11.1 Hz), 6.5-7.5 (8H, m). ^{13}C NMR (75 MHz, C_6D_6): δ 18.4, 41.0, 48.5, 53.5, 54.3, 55.8, 55.9, 70.5, 112.3, 112.7, 116.8, 126.9, 130.1, 143.8, 144.8, 150.1,150.8, 172.0,173.1. IR (NaCl, neat) 2944, 1676, 1647, 1592, 1516, 1496, 1444 cm^{-1}. HRMS (FAB+) calc. mass for $C_{23}H_{22}N_3O_2$: 421.2127 (M+1), found: 421.2110. R_f 0.30 (eluted with 50 % ethyl acetate / hexanes).

(4*S*)-6-Eethoxy-4-methyl-8-phenyl-8-vinyl-2,5-diazabicyclo[2.2.2]oct-5-en-3-one (248)



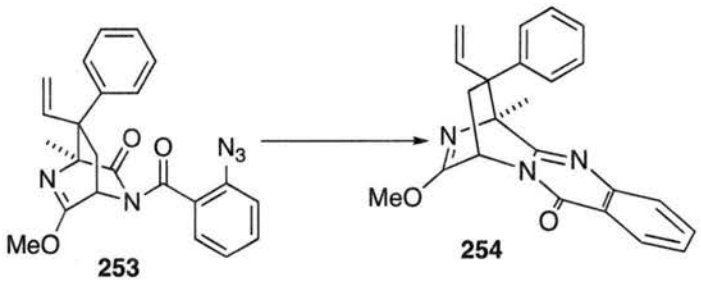
A stirred solution of compound **238** (55 mg, 0.131 mmol) in 3 mL dry THF under Ar was cooled to -78 °C and 0.77 mL of *t*-BuLi was added. After 10 min of stirring at -78 °C, a stream of oxygen was passed through the brown solution for 15 min. 10 mL CH_2Cl_2 and several drops of water were added. The mixture was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to yield 16 mg of **248** (45%). $[\alpha]^{20}_D$ +88 (*c* 0.55, CH_2Cl_2). ^{1}H NMR (300MHz, C_6D_6): δ 1.74 (dd, 1H, *J* = 13.5 Hz, 1.8 Hz), 1.82 (s, 3 H), 2.16 (dd, 1H, *J* = 13.5 Hz, 3.6 Hz), 3.39 (dd, 1H, *J* = 3.6 Hz, 1.8 Hz), 3.45 (3H, s), 5.09 (dd, 1H, *J* = 17.4 Hz, 0.6 Hz), 5.20 (dd, 1H, *J* = 10.8 Hz, 0.6 Hz), 6.26 (dd, 1H, *J* = 10.8 Hz, 17.4 Hz), 6.97 (1H, br), 7.0-7.4 (5H, m). ^{13}C NMR (100 MHz, C_6D_6): δ 17.7, 41.8, 50.7, 53.0, 54.2, 70.3, 116.9, 126.9, 128.9, 129.8, 143.8, 144.9, 172.5, 176.9. IR (NaCl, neat) 3218, 3084, 1690, 1649, 1598, 1516, 1493, 1447 cm^{-1}. HRMS (FAB+) calc. mass for $C_{16}H_{19}N_2O_2$: 271.1447 (M+1), found: 271.1443. R_f 0.30 (eluted with 75 % ethyl acetate / hexanes).

(4*S*)-2-(2-Azidophenylcarbonyl)-6-methoxy-4-methyl-8-phenyl-8-vinyl-2,5-diazabicyclo[2.2.2]oct-5-en-3-one (253)



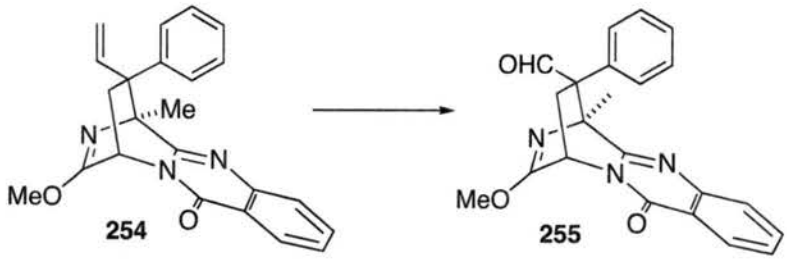
To a cooled (-78 °C) solution of compound **248** (16 mg, 0.0593 mmol) in dry THF was added dropwise 0.154 mL of 0.5 M KHMDS in toluene under Ar. The solution was stirred at -78 °C for 15 min and was then was treated with a solution of *o*-azidobenzoyl chloride (0.0711 mmol) in 1 mL THF and was left to warm to rt over 24 h while protected from light. The solvent was evaporated and the residue was chromatographed on silica gel (eluted with 25% ethyl acetate/hexanes) to give 16 mg compound **253** (65%). $[\alpha]^{20}_{D}$ +75.7 (*c* 0.667, CH_2Cl_2). ^{1}H NMR (300MHz, C_6D_6): δ 1.62 (s, 3H), 1.91 (dd, 1H, *J* = 14.4 Hz, 1.8 Hz), 1.96 (1H, dd, *J* = 14.4, 3.6 Hz), 3.45 (3H, s), 5.06 (d, 1H, *J* = 17.4 Hz), 5.17 (d, 1H, *J* = 11.4 Hz,) 5.76 (1H, dd, *J* = 1.8, 3.6 Hz), 6.14 (dd, 1H, *J* = 11.4 Hz, 17.4 Hz), 6.58 (1H, dd, *J* = 8.1 Hz, 0.9 Hz), 6.74 (1H, dt, *J* = 7.8 Hz, 0.9 Hz), 6.86 (1H, dt, *J* = 7.8 Hz, 1.5 Hz), 7.0-7.4 (6H, m). ^{13}C NMR (75 MHz, C_6D_6): δ 17.9, 39.2, 51.1, 52.2, 54.4, 71.8, 117.2, 118.8, 125.0, 127.2, 127.9, 128.2, 128.9, 129.5, 131.5, 137.6, 142.5, 144.3, 166.8, 171.0, 171.5. IR (NaCl, neat) 2128, 2100, 1737, 1686, 1649, 1598, 1580, 1488, 1447 cm^{-1}. HRMS (FAB+) calc. mass for $C_{23}H_{22}N_5O_3$: 416.1723 (M+1), found: 416.1728. R_f 0.50 (eluted with 25 % ethyl acetate / hexanes).

Compound (254)



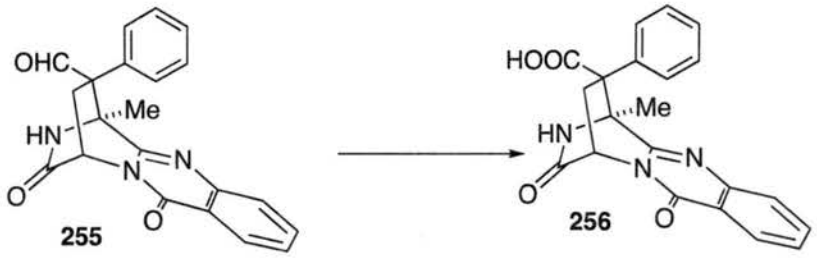
A solution of 16 mg of compound **253** (0.0383 mmol) and 10.4 μL tributylphosphine (0.0422 mmol) in dry toluene was stirred at RT for 3h under Ar. The solution was evaporated under reduced pressure and the residue was chromatographed on silica gel (eluted with 25% ethyl acetate/ hexanes) yielding 9.9 mg of compound **254** (70%). $[\alpha]^{20}_{D}$ +80.5 (*c* 0.41, CH_2Cl_2). ^{1}H NMR (300MHz, C_6D_6): δ 1.87 (1H, dd, *J* = 14.4 Hz, 2.1 Hz), 2.07 (s, 3H), 2.33 (dd, 1H, *J* = 14.4 Hz, 3.6 Hz), 3.44 (3H, s), 4.59 (d, 1H, *J* = 17.1 Hz,) 4.68 (1H, d, *J* = 11.1 Hz), 6.05 (dd, *J* = 2.1 Hz, 3.6 Hz), 7.0-7.4 (7H, m), 7.78 (1H, ddd, *J* = 8.1 Hz, 1.2Hz, 0.6 Hz), 8.48 (1H, ddd, *J*= 8.1 Hz, 1.8 Hz, 0.6 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ 18.6, 38.9, 48.7, 52.7, 54.3, 69.6, 116.5, 121.2, 127.0, 127.1, 127.5, 128.5,128.9, 129.5, 134.5, 142.3, 144.6, 148.5, 157.1, 159.6, 171.7. IR (NaCl, neat) 3061, 1681, 1647, 1608, 1564, 1493, 1469, 1445 cm^{-1}. HRMS (FAB+) calc. mass for $C_{23}H_{22}N_3O_2$: 372.1712 (M+1), found: 372.1711. R_f 0.30 (eluted with 25 % ethyl acetate / hexanes).

Compound (255)



8.0 mg of compound **254** was dissolved in CH_2Cl_2 and cooled to -78 °C. A stream of ozone was passed through until the solution turned blue. The solution was bubbled with air until the blue color disappeared. Several drops of dimethyl sulfide were added. The mixture was concentrated under reduced pressure and separated by flash chromatography to give 6.4 mg of compound **255** (80%). $[\alpha]^{20}_{D}$ +100.7 (*c* 0.407, CH_2Cl_2). ^{1}H NMR (400MHz, C_6D_6): δ 1.38 (1H, dd, *J* = 10.5Hz, 1.5 Hz), 2.11 (s, 3H), 2.86 (1H, dd, *J* = 10.5 Hz, 2.7 Hz), 3.36 (3H, s), 5.98 (1H, dd, *J* = 1.5 Hz, 2.7 Hz), 6.9-7.4 (7H, m), 7.65 (1H, ddd, 1H, *J* = 6.0 Hz, 0.9 Hz, 0.3 Hz), 8.35 (1H, ddd, *J* = 6.0 Hz, 0.9 Hz, 0.3 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ 18.9, 35.4, 48.0, 54.4, 61.9, 67.4, 121.2,127.4, 127.6, 127.9, 128.9, 129.3, 129.5, 134.6, 139.3, 155.4, 159.3,172.3, 198.5. IR (NaCl, neat) 2946, 1722, 1682, 1643, 1608, 1565, 1495, 1469, 1448 cm^{-1}. HRMS (FAB+) calc. mass for $C_{22}H_{20}N_3O_3$: 374.1499 (M+1), found: 374.1500. R_f 0.35 (eluted with 25 % ethyl acetate / hexanes).

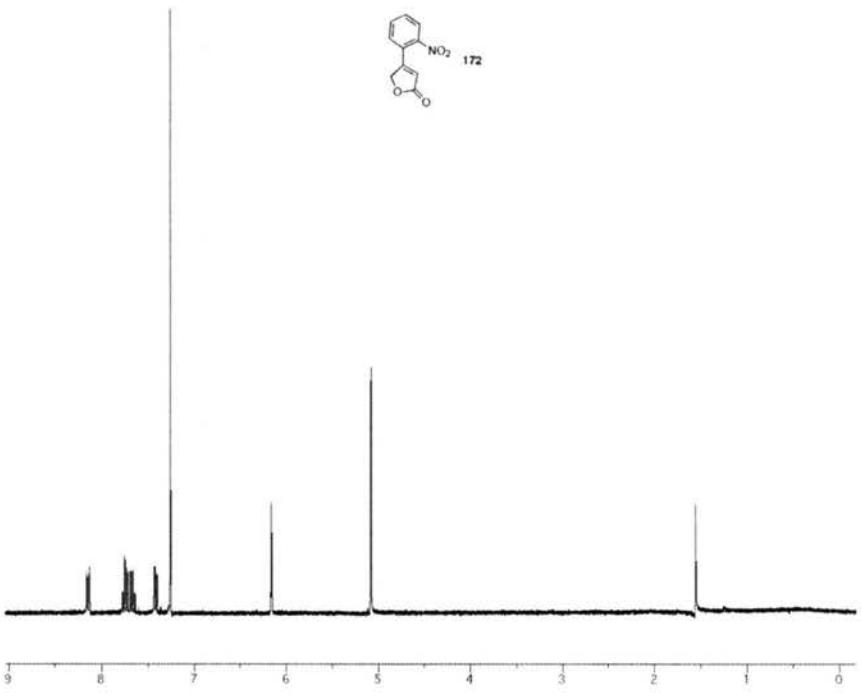
Compound (256)



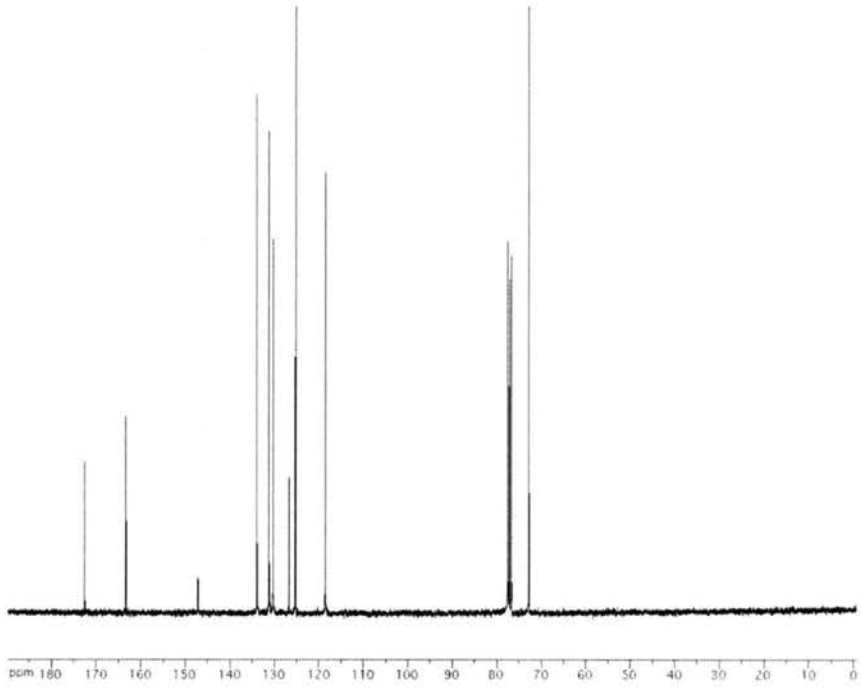
A solution of $NaClO_2$ (7.4 mg, 0.082 mmol) and KH_2PO_4 (12.2 mg, 0.090 mmol) in 0.2 mL water was added to a stirred solution of 6.0 mg (0.0214 mmol) of compound **255** in 1.2 mL *tert*-butanol and 0.3 mL 2-methyl-2-butene at rt. The mixture was diluted with EtOAc and water. The organic layers were dried over Na_2SO_4, filtered and concentrated to afford a residue. Purification of the crude residue by silica gel chromatography afforded 5.0 mg of **256** as a white solid (80%). $[\alpha]^{20}_D$ -143 (*c* 0.143, CH_3OH). ^1H NMR (400MHz, CD_3OD): δ 1.65 (3H, s), 2.90 (d, 1H, J = 10.8 Hz), 3.05 (1H, dd, J = 10.8 Hz, 2.7 Hz), 5.70 (1H, bs), 7.0-8.4 (9H, m). ^{13}C NMR (100 MHz, CD_3OD): δ 14.3, 28.4, 36.6, 52.3, 61.0, 119.3, 123.6, 124.8, 125.1, 125.6, 126.2, 126.4, 127.5, 132.2, 135.8, 138.3, 146.6, 157.0, 166.0, 167.7. IR (NaCl, neat) 3184, 1705, 1620, 1609, 1469, 1443 cm^{-1}. HRMS (FAB+) calc. mass for $C_{21}H_{17}N_3O_4$: 376.1297 (M+1), found: 376.1299. R_f 0.20 (eluted with 5 % methanol / ethyl acetate).

Appendix

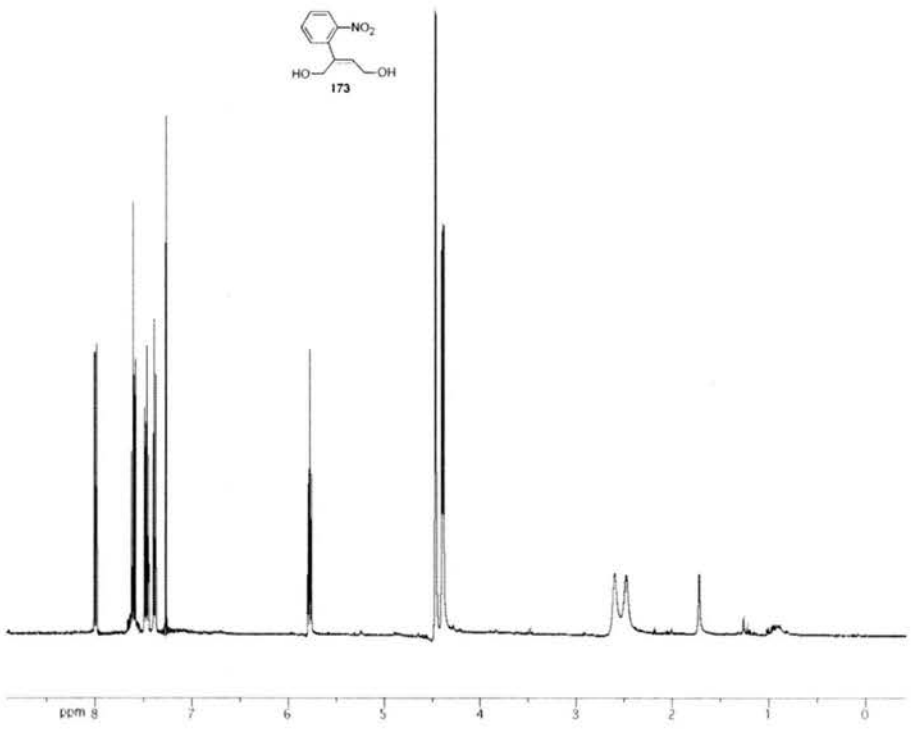
^{1}H NMR and ^{13}C NMR Spectrums



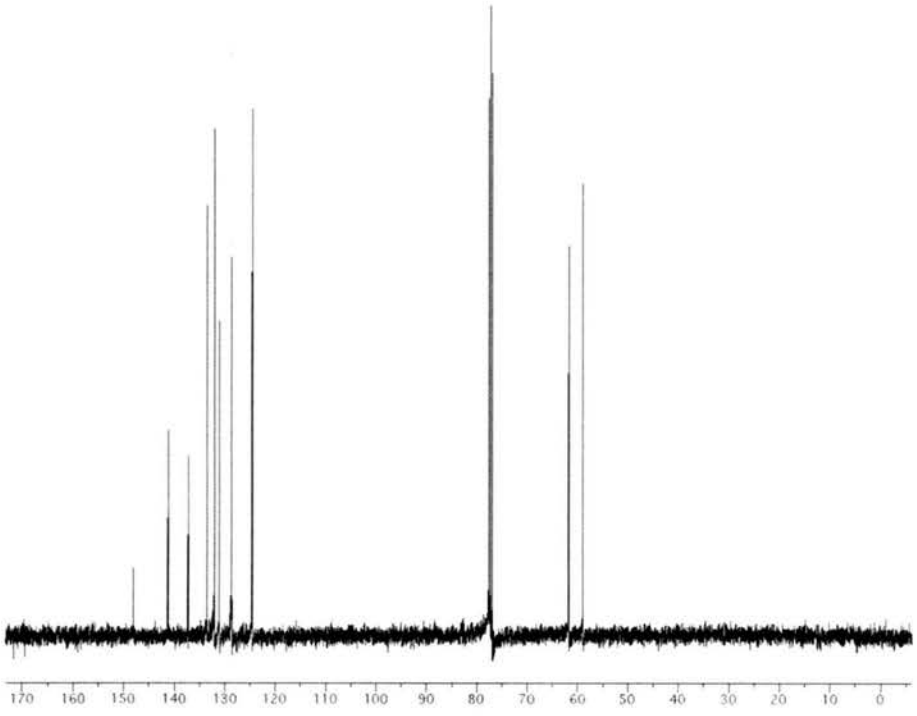
^{1}HNMR, $CDCl_3$, 300 MHz, filename: csy110-1



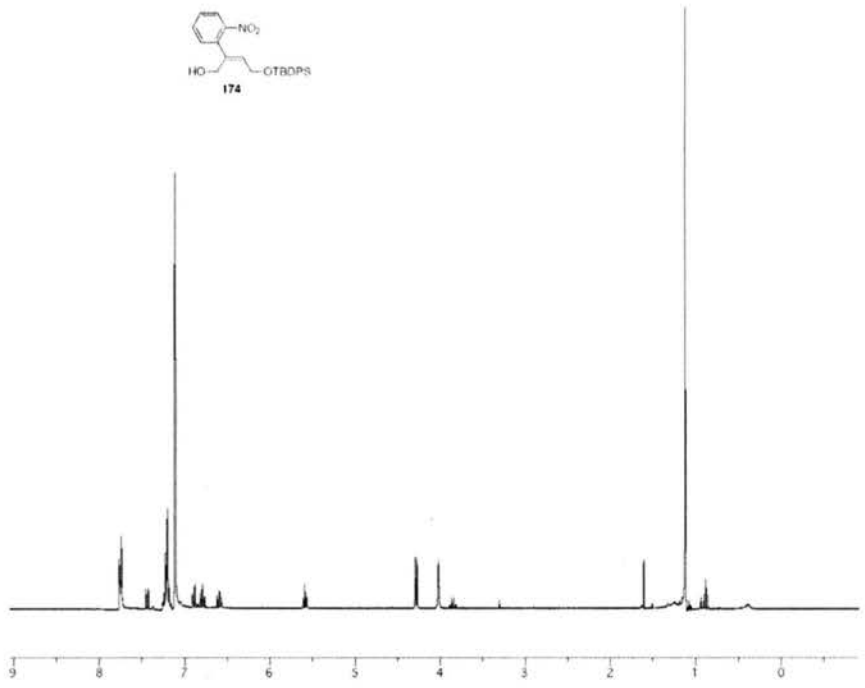
^{13}CNMR, $CDCl_3$, 75 MHz, filename: csy110-1-c13



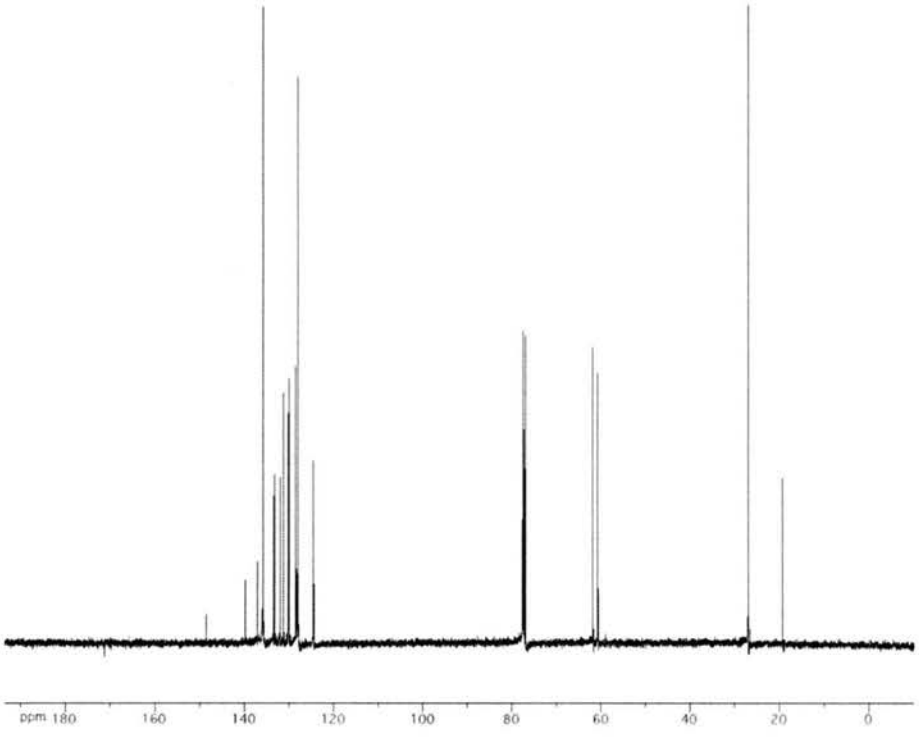
^{1}HNMR, $CDCl_3$, 300 MHz, filename: csy132-1



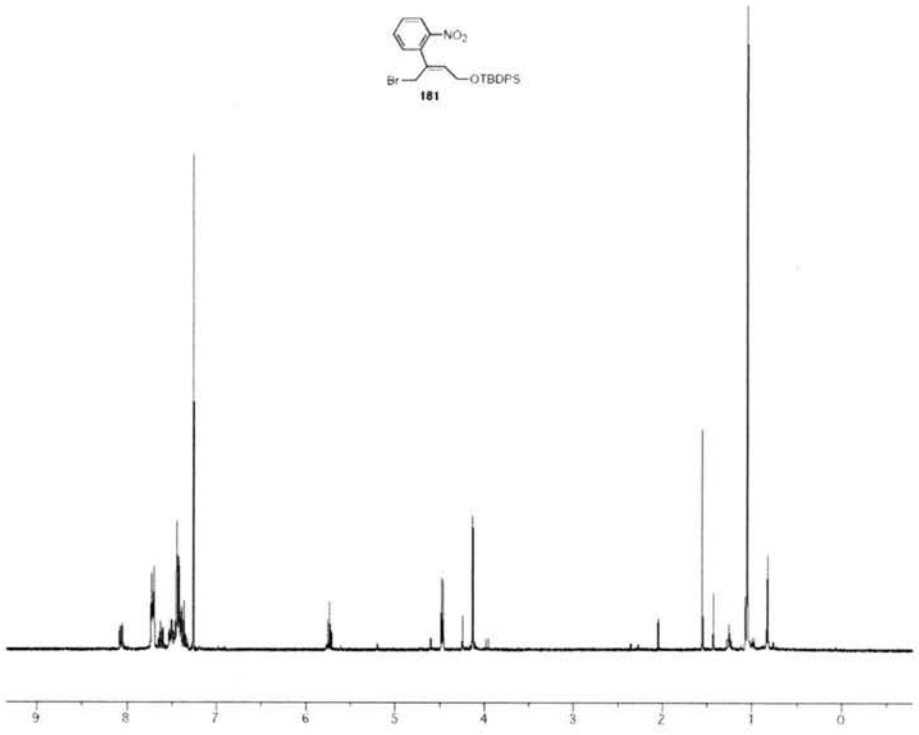
^{13}CNMR, $CDCl_3$, 100 MHz, filename: csy132-1-c13



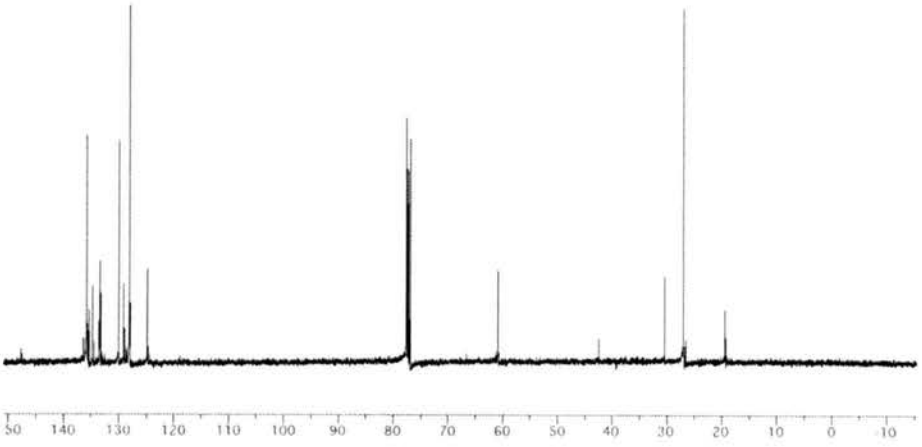
^{1}HNMR, $CDCl_3$, 300 MHz, filename: csy132-1



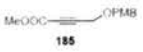
^{13}CNMR, $CDCl_3$, 100 MHz, filename: csy132-1



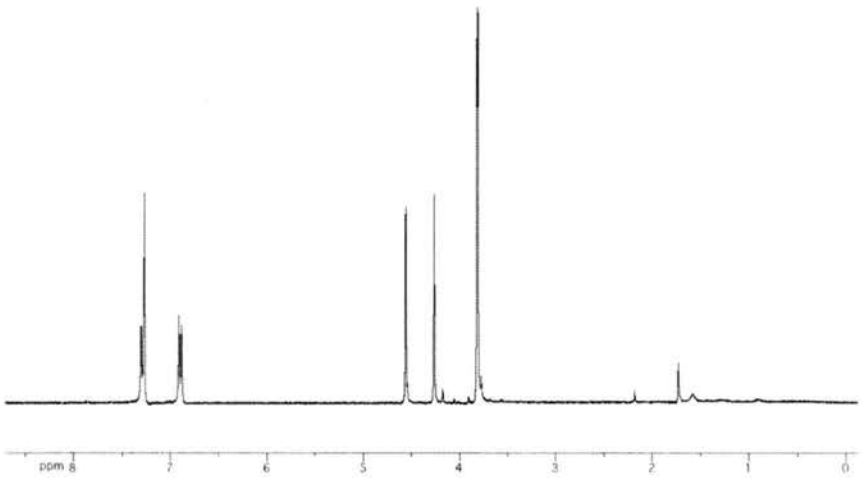
^{1}HNMR, $CDCl_3$, 300 MHz, filename: csy170-2



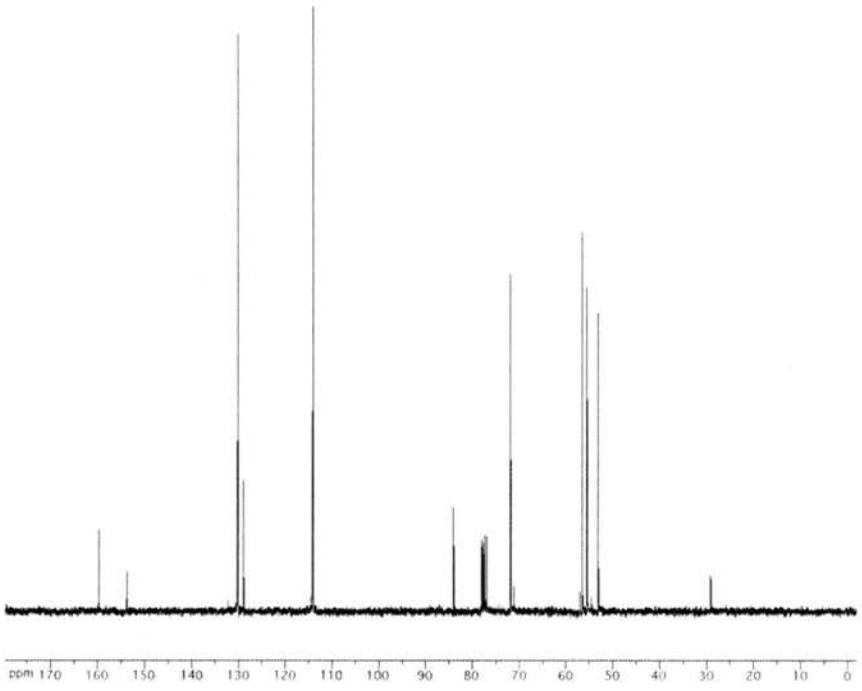
^{13}CNMR, $CDCl_3$, 100 MHz, filename: csy170-2-c13



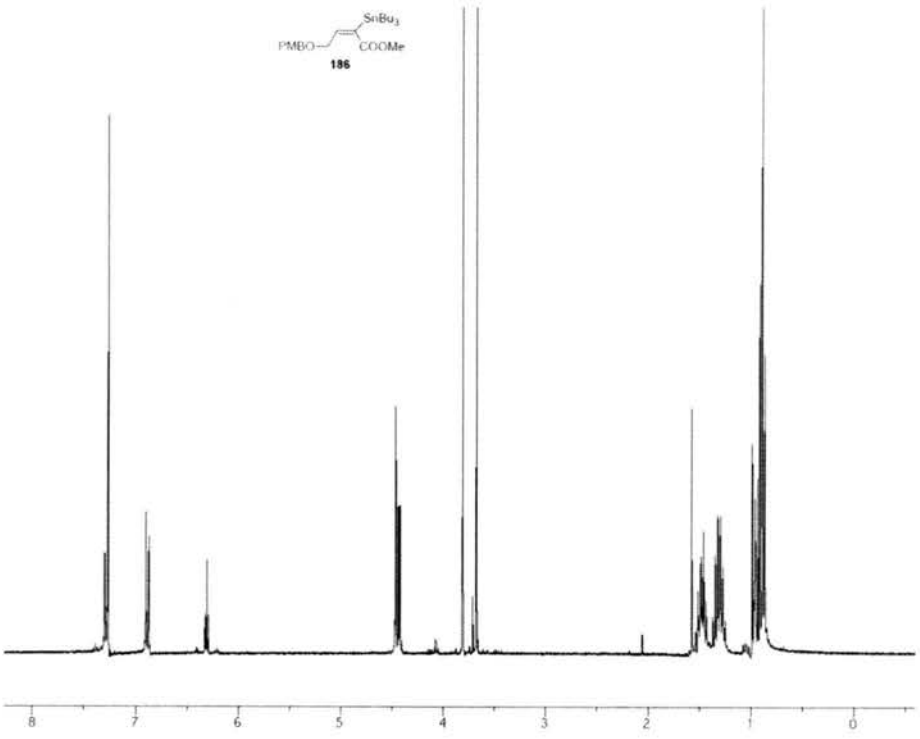
185



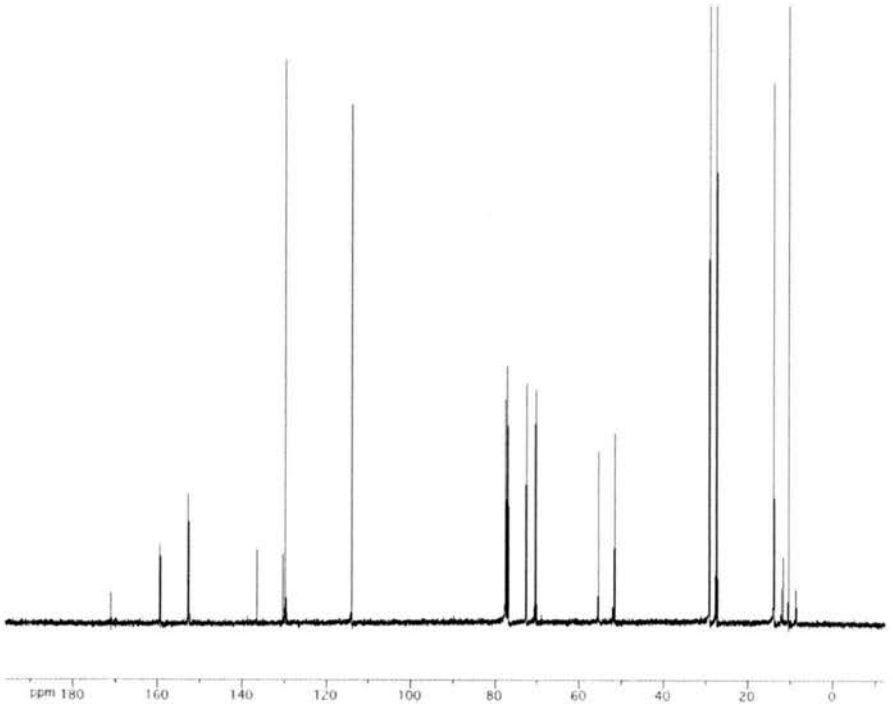
^{1}HNMR, $CDCl_3$, 300 MHz, filename: csy191-1



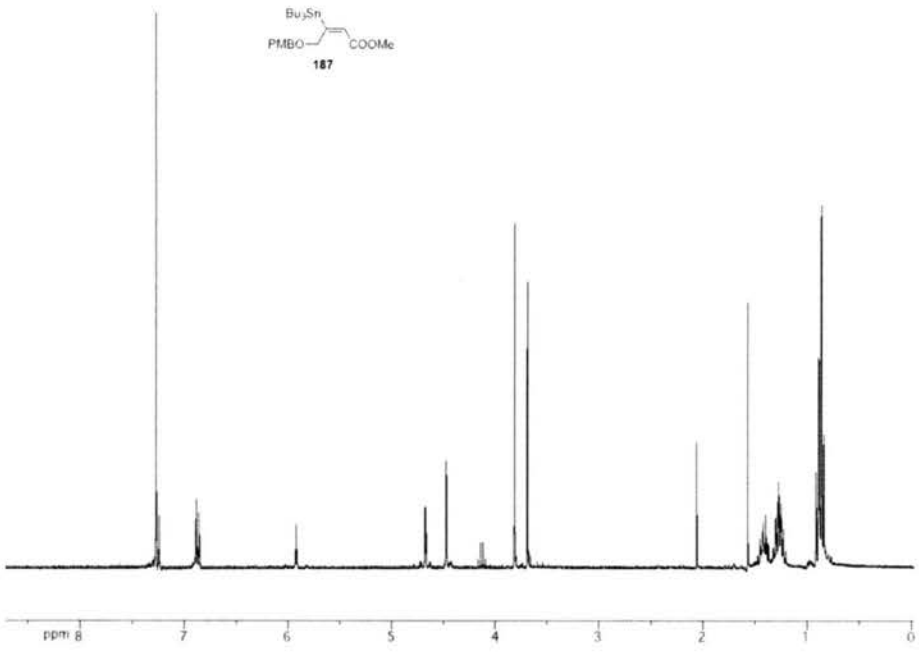
^{13}CNMR, $CDCl_3$, 75 MHz, filename: csy191-1-c13



^{1}HNMR, $CDCl_3$, 300 MHz, filename: csy192-2



^{13}CNMR, $CDCl_3$, 75 MHz, filename: csy192-2-c13



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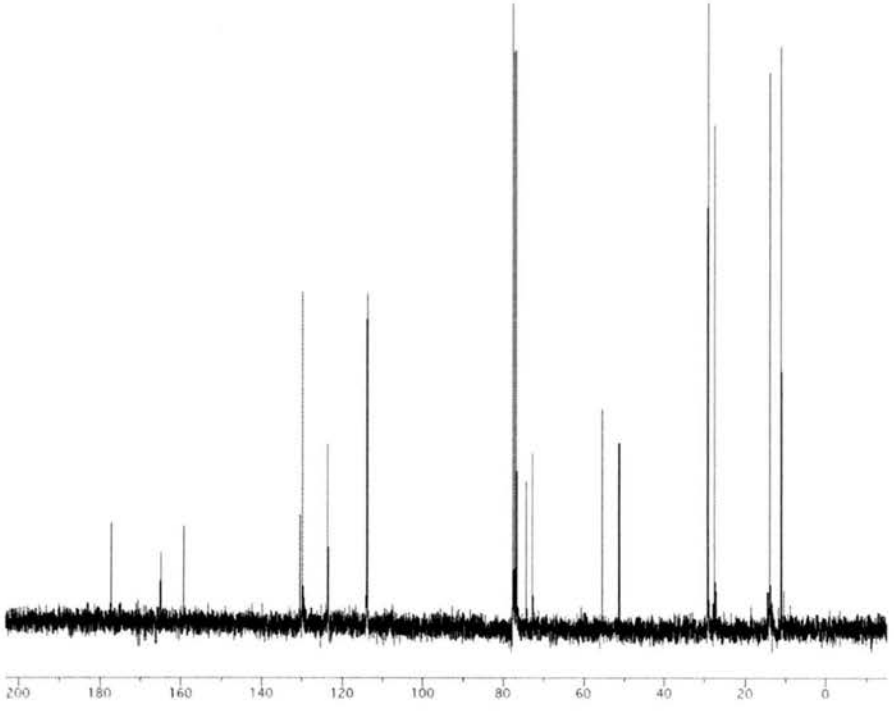
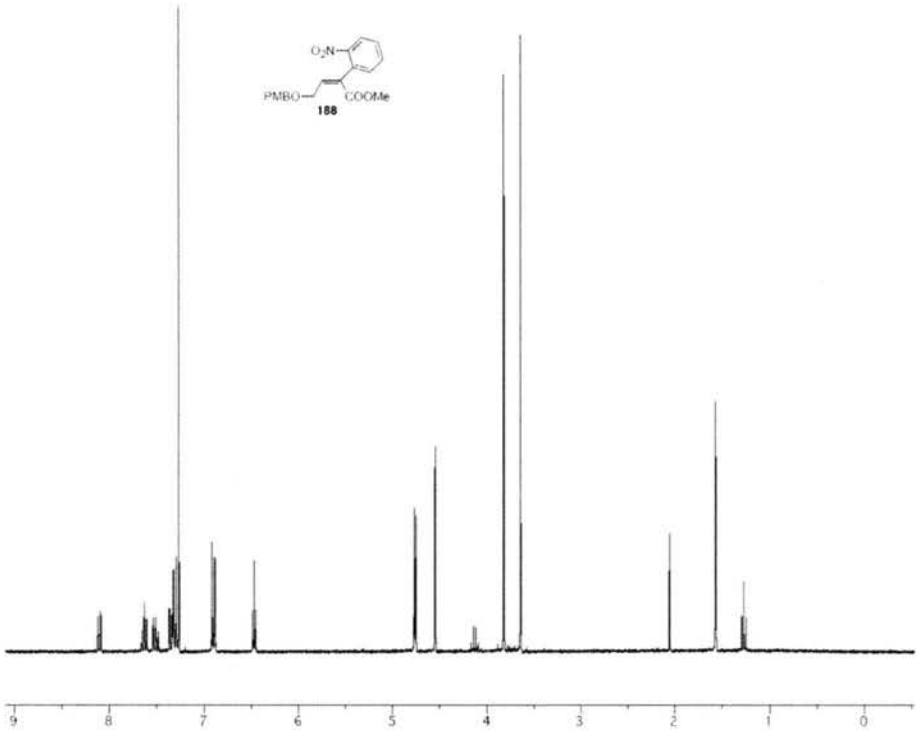
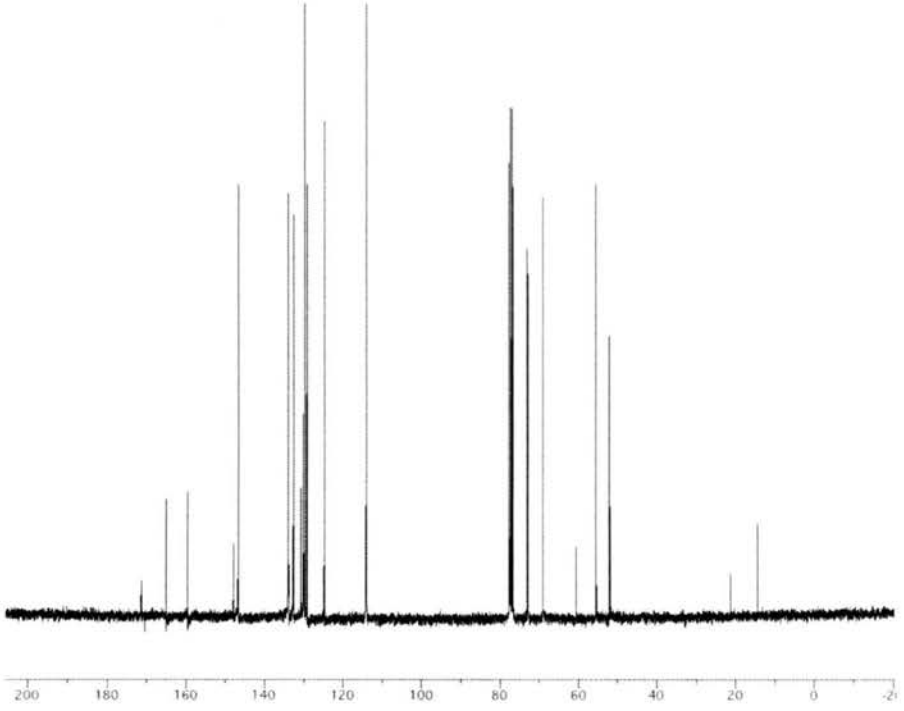


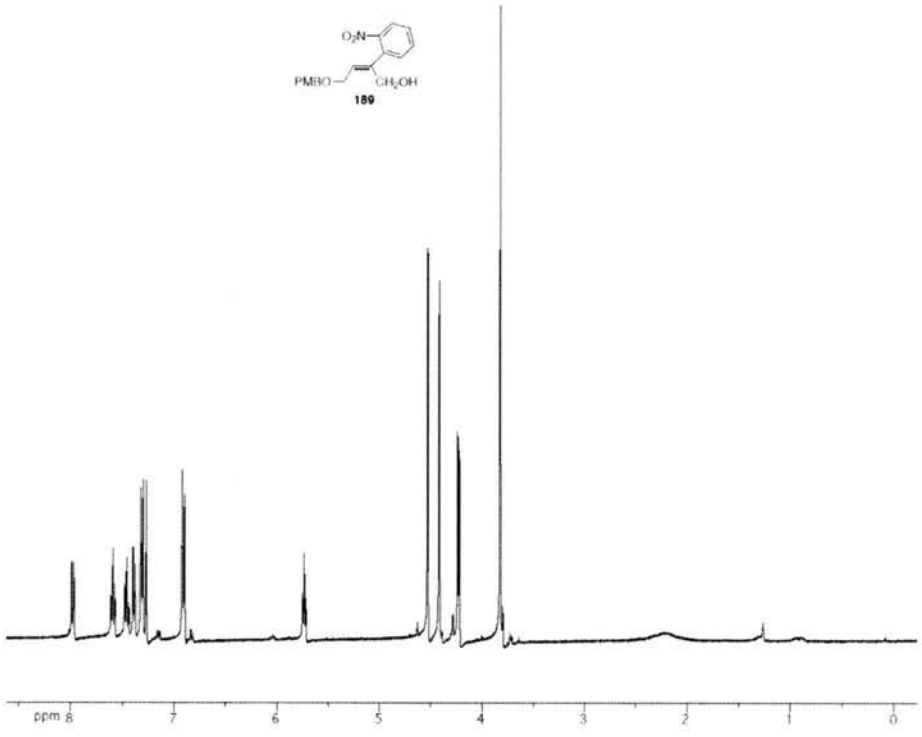
^{13}CNMR, $CDCl_3$, 75 MHz, filename: csy192-1-c13



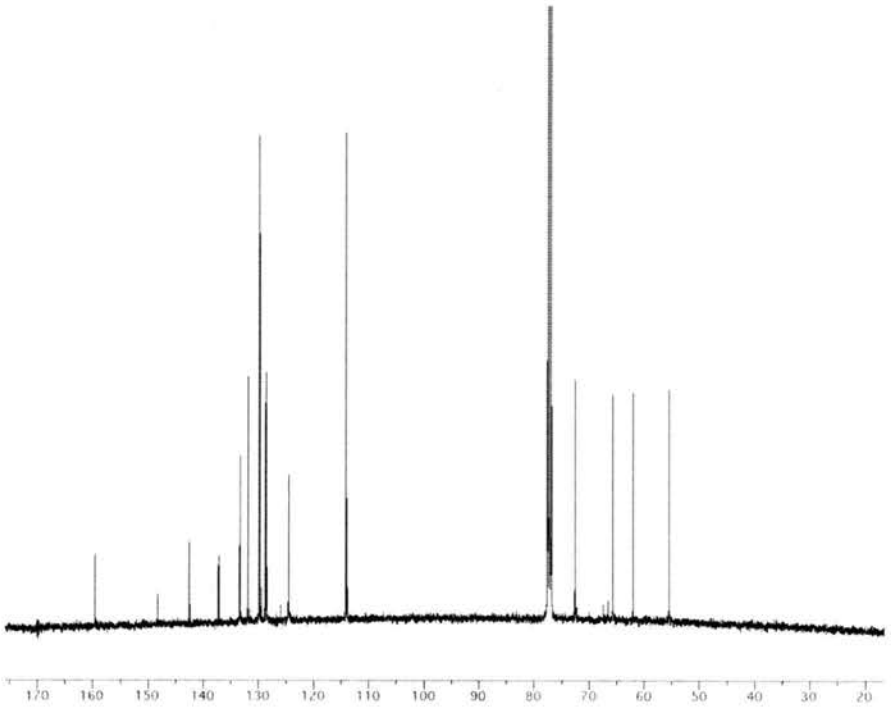
^{1}HNMR, $CDCl_3$, 300 MHz, filename: csy195-1



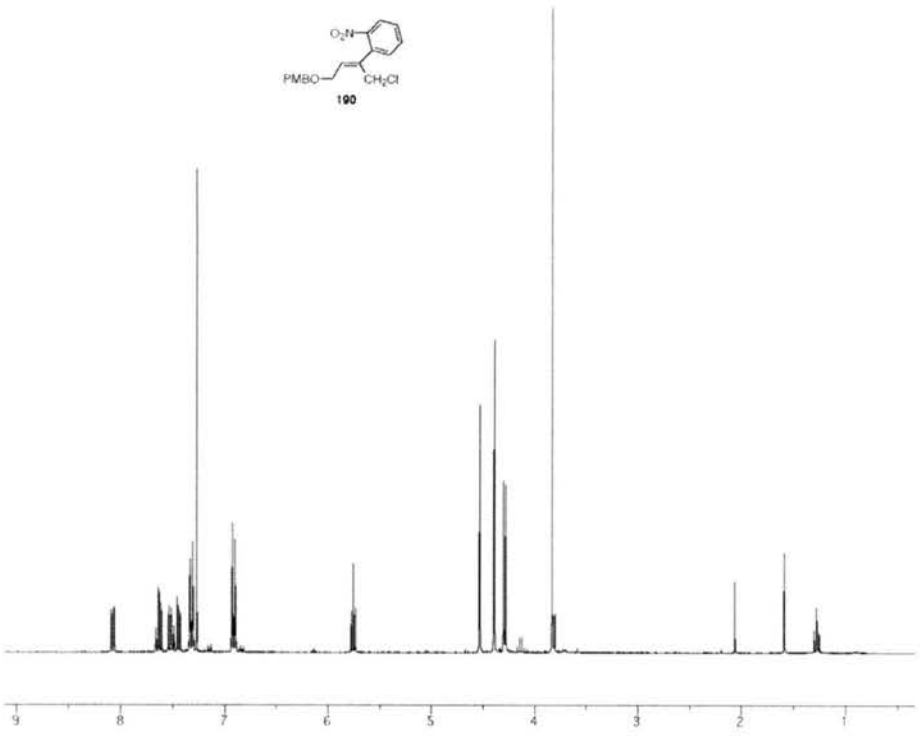
^{13}CNMR, $CDCl_3$, 75 MHz, filename: csy195-1



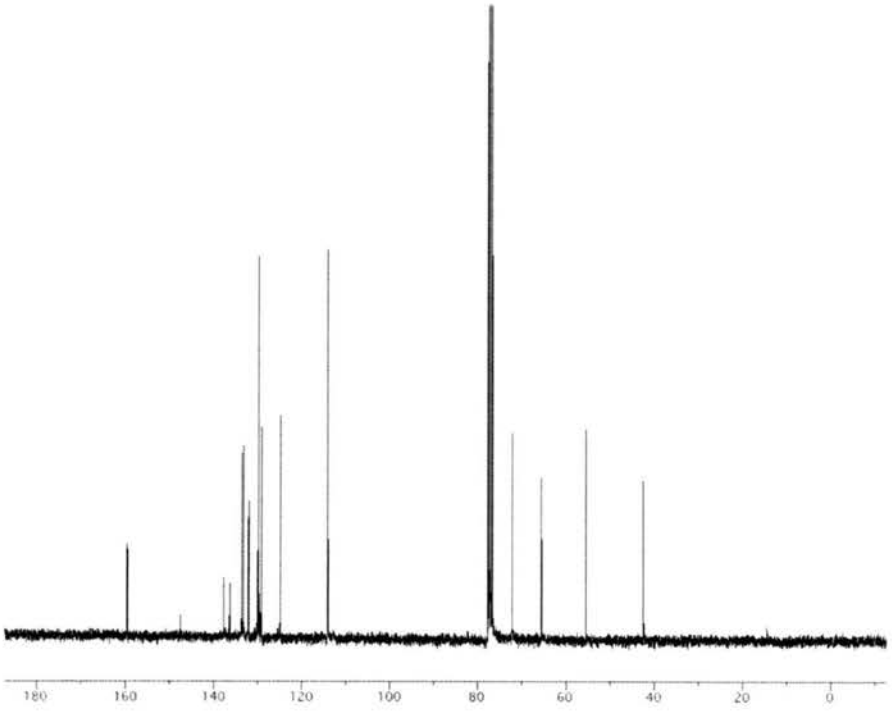
^{1}HNMR, $CDCl_3$, 300 MHz, filename: csy200-1



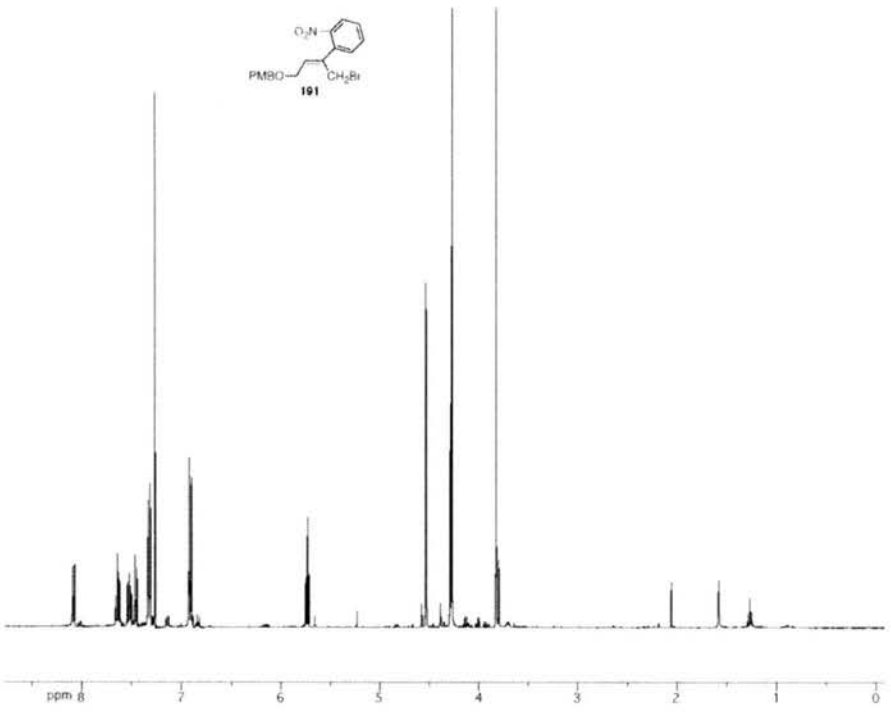
^{13}CNMR, $CDCl_3$, 100 MHz, filename: csy200-1-c13



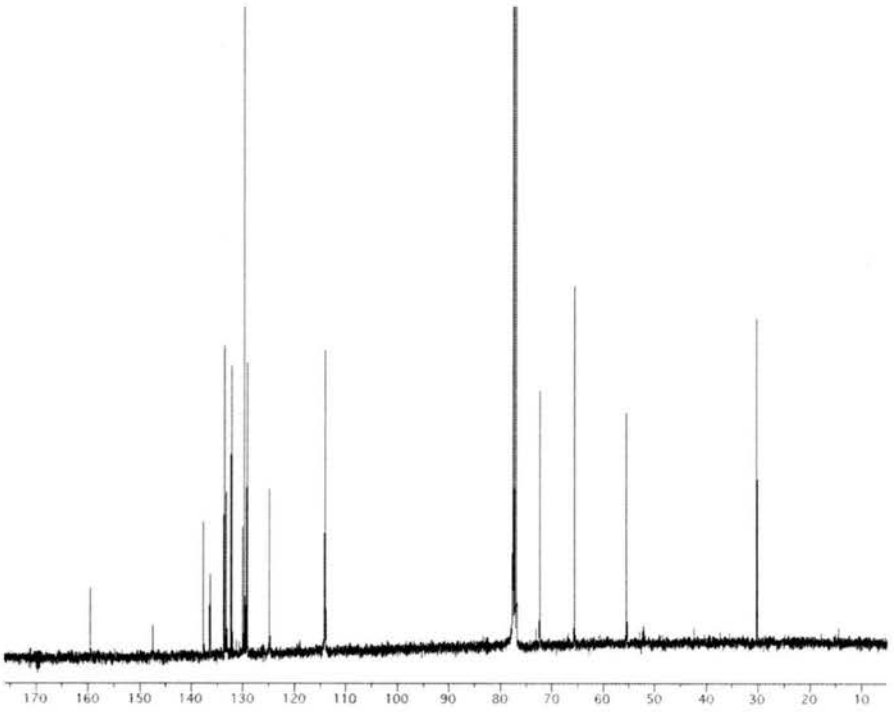
^{1}HNMR, $CDCl_3$, 300 MHz, filename: csy202-1



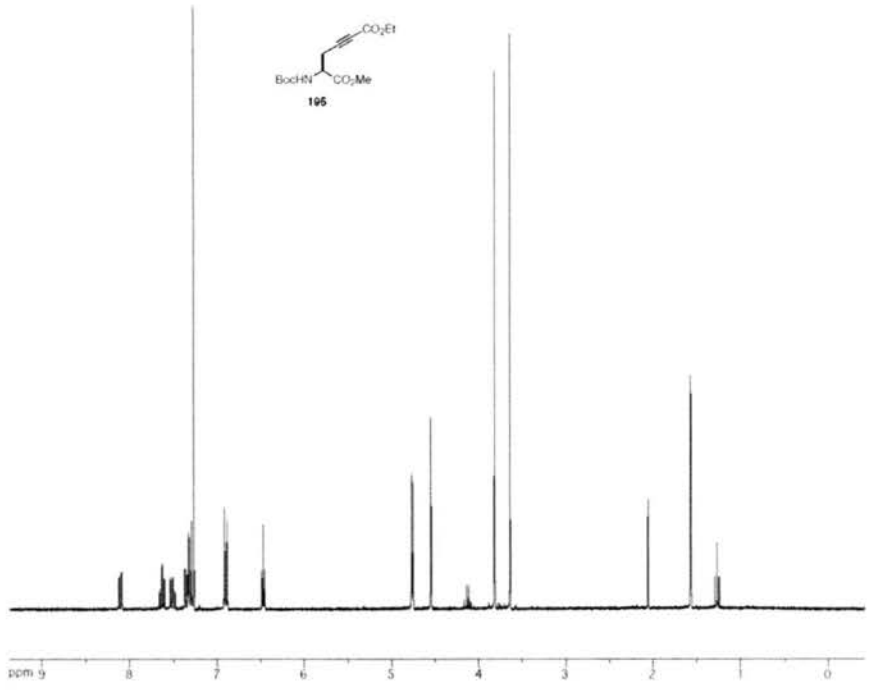
^{13}CNMR, $CDCl_3$, 75 MHz, filename: csy202-1-c13



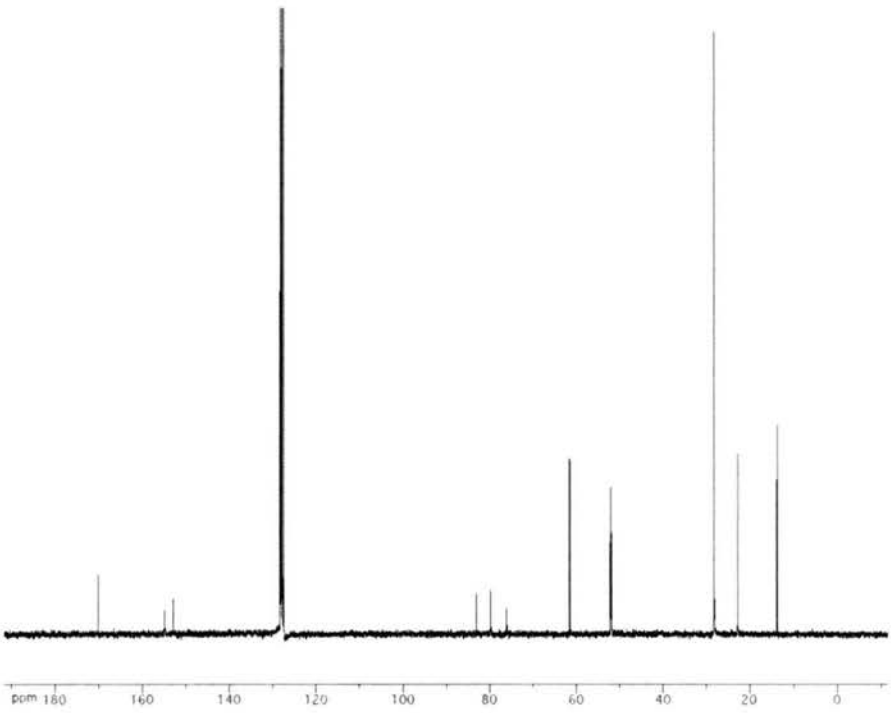
^{1}HNMR, $CDCl_3$, 300 MHz, filename: csy203-1



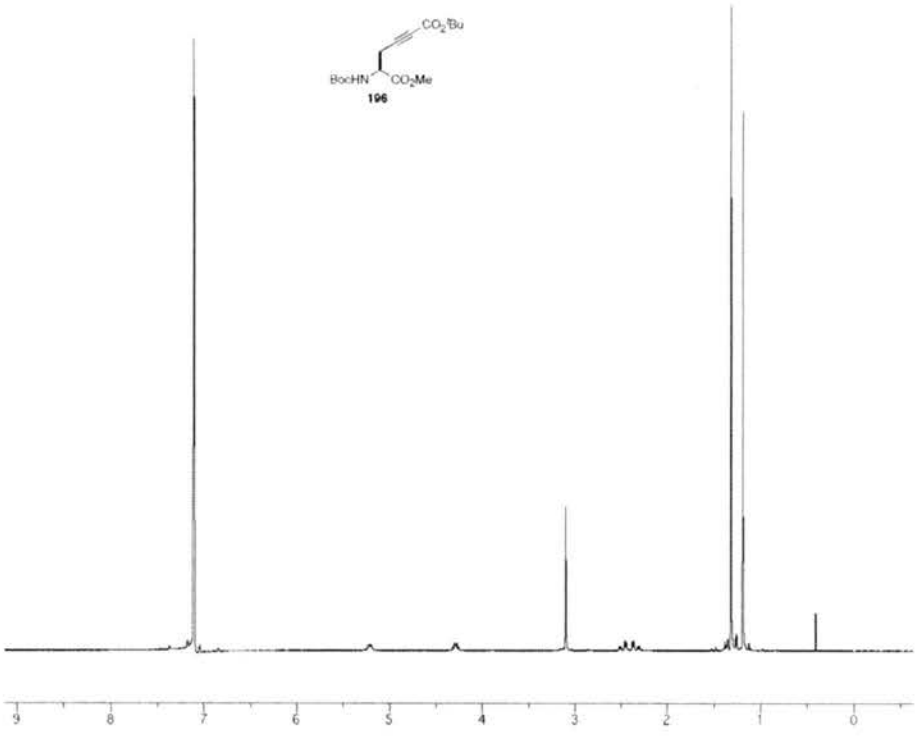
^{13}CNMR, $CDCl_3$, 100 MHz, filename: csy203-1-c13



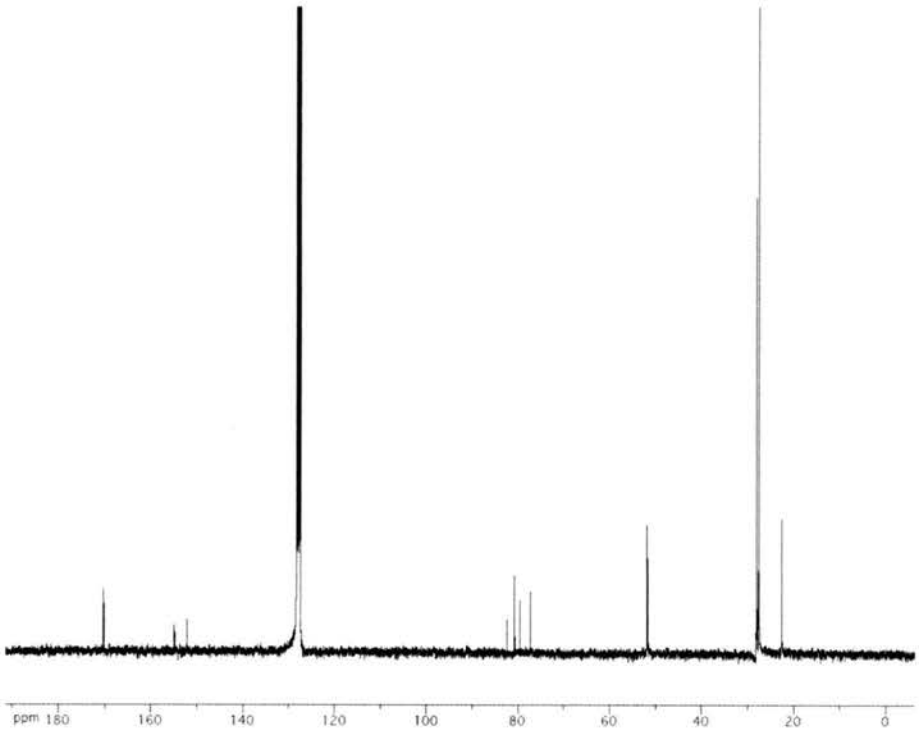
^{1}HNMR, C_6D_6, 300 MHz, filename: csy288-1



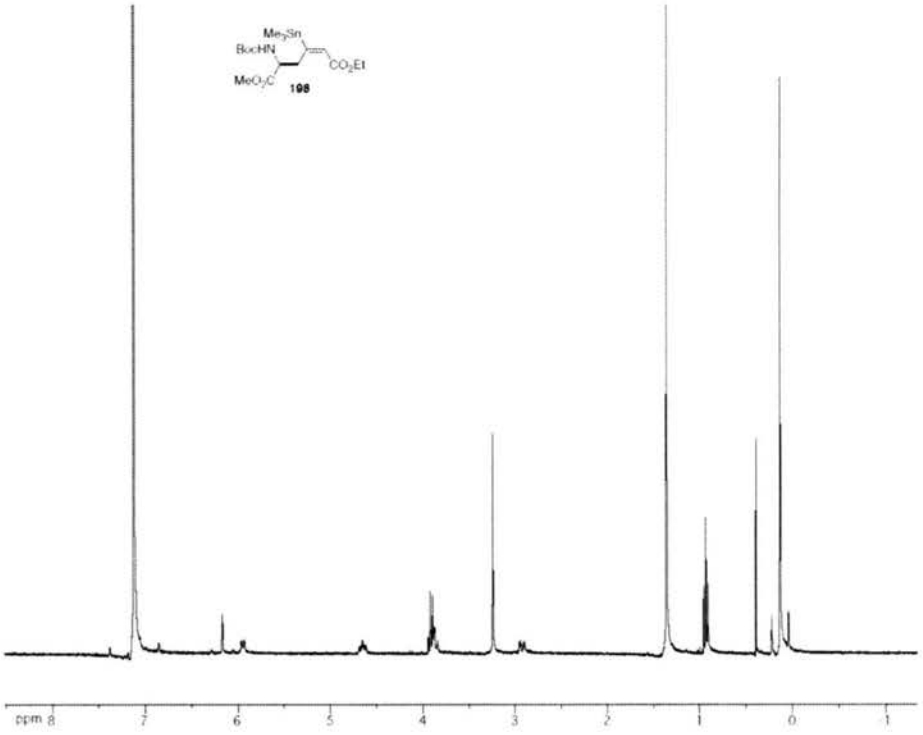
^{13}CNMR, C_6D_6, 75 MHz, filename: csy288-1-c13



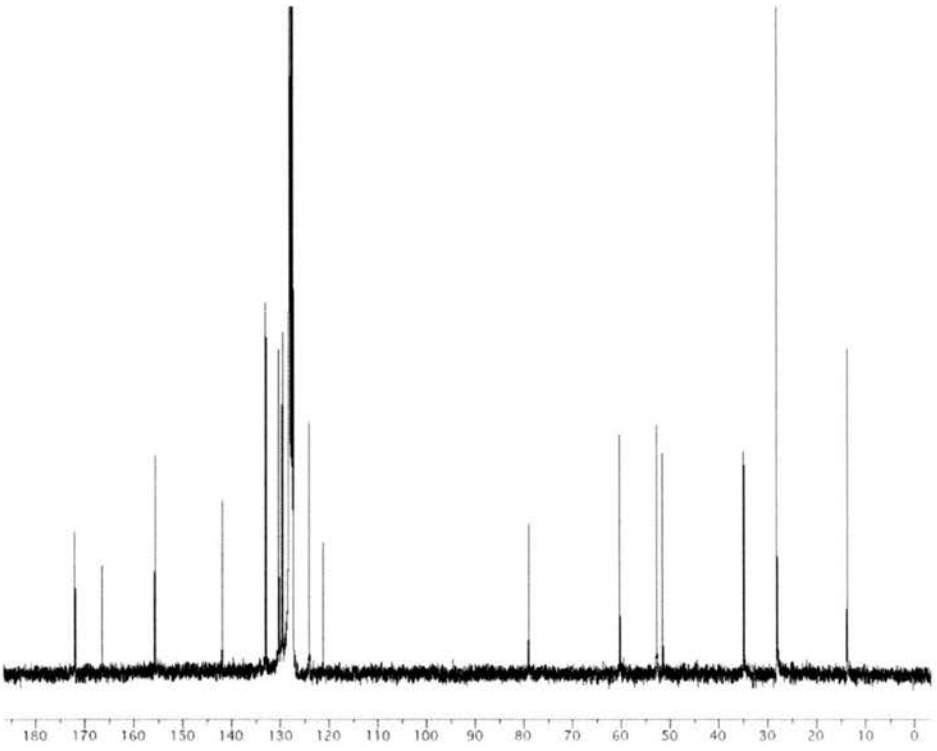
^{1}HNMR, C_6D_6, 300 MHz, filename: csy556-1



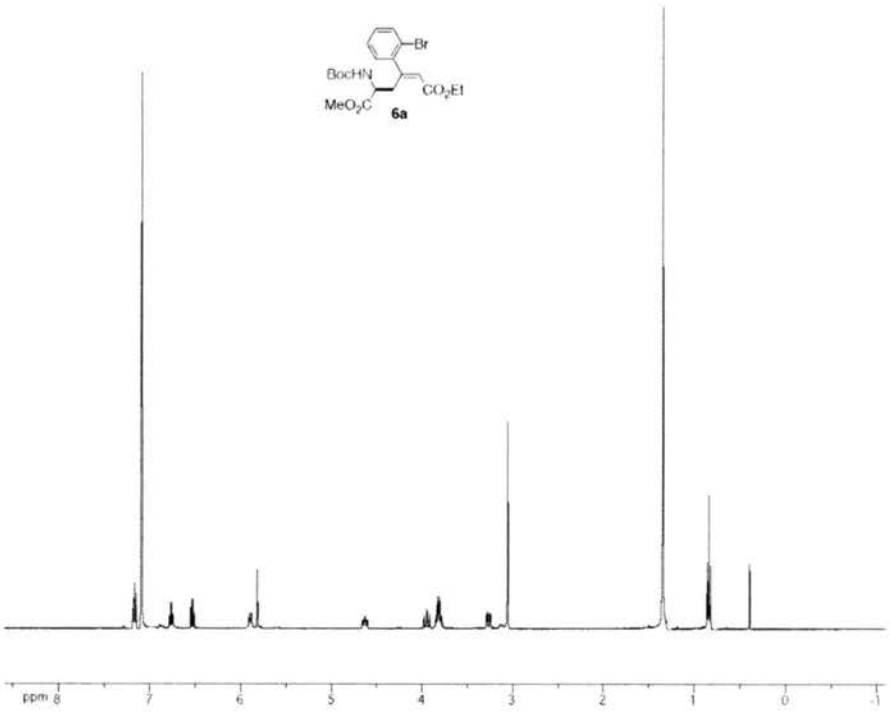
^{13}CNMR, C_6D_6, 75 MHz, filename: csy556-1-c13



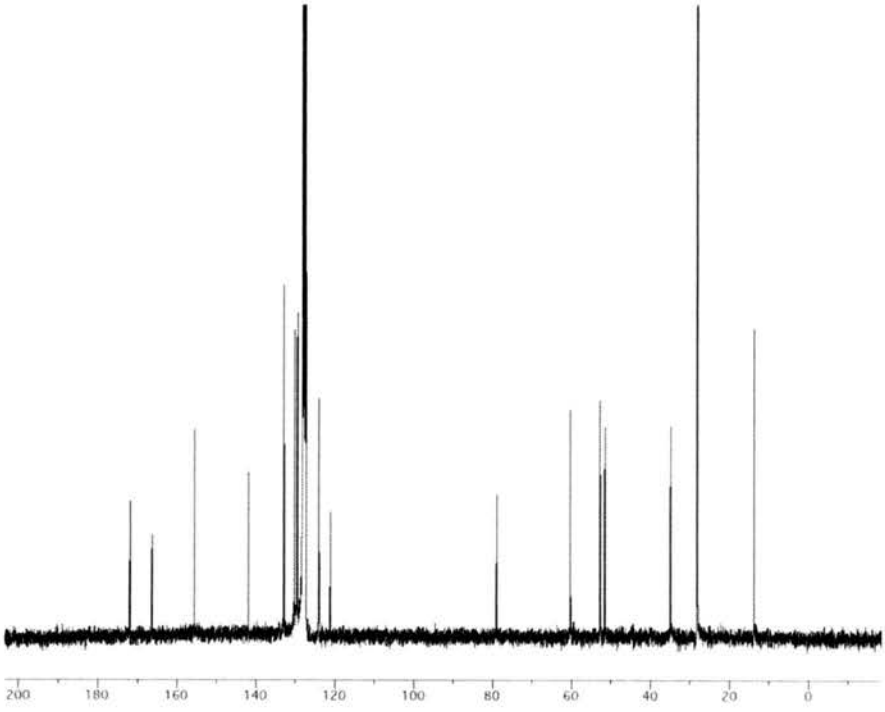
^{1}HNMR, C_6D_6, 300 MHz, filename: csy306-1



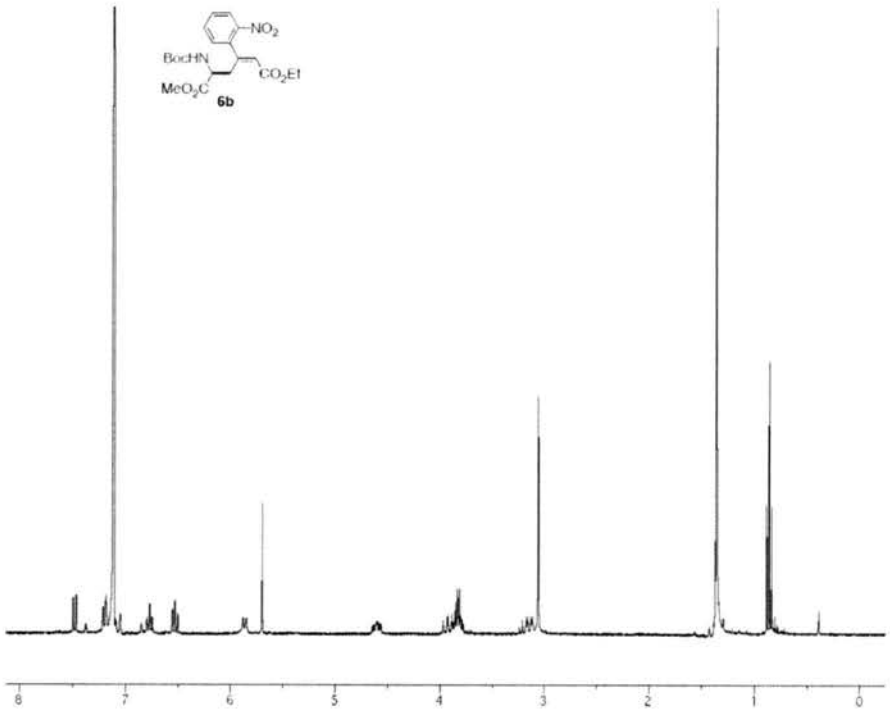
^{13}CNMR, C_6D_6, 75 MHz, filename: csy306-1-c13



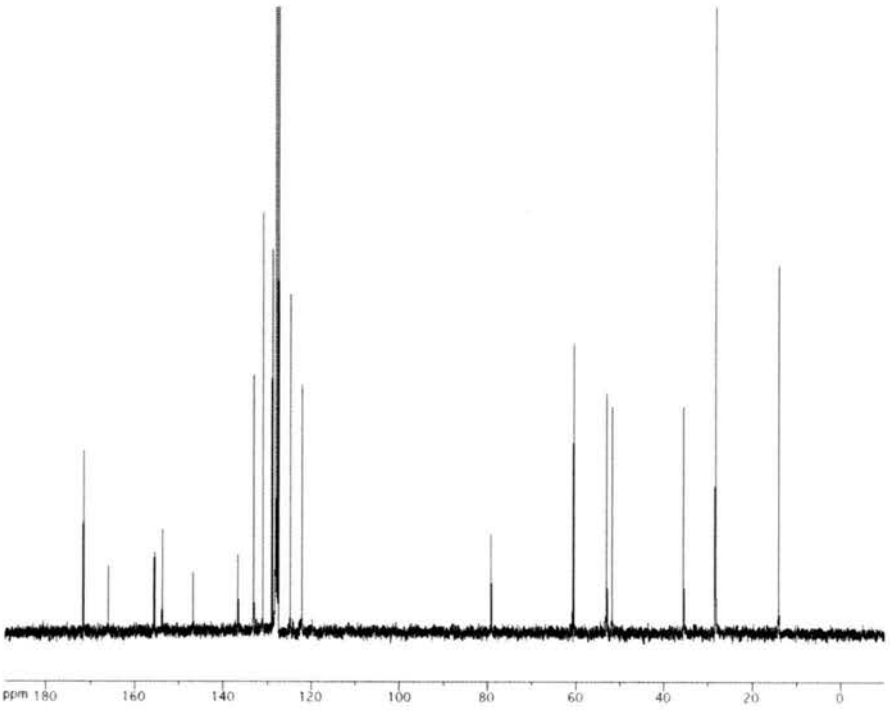
^{1}HNMR, C_6D_6, 400 MHz, filename: csy612-1



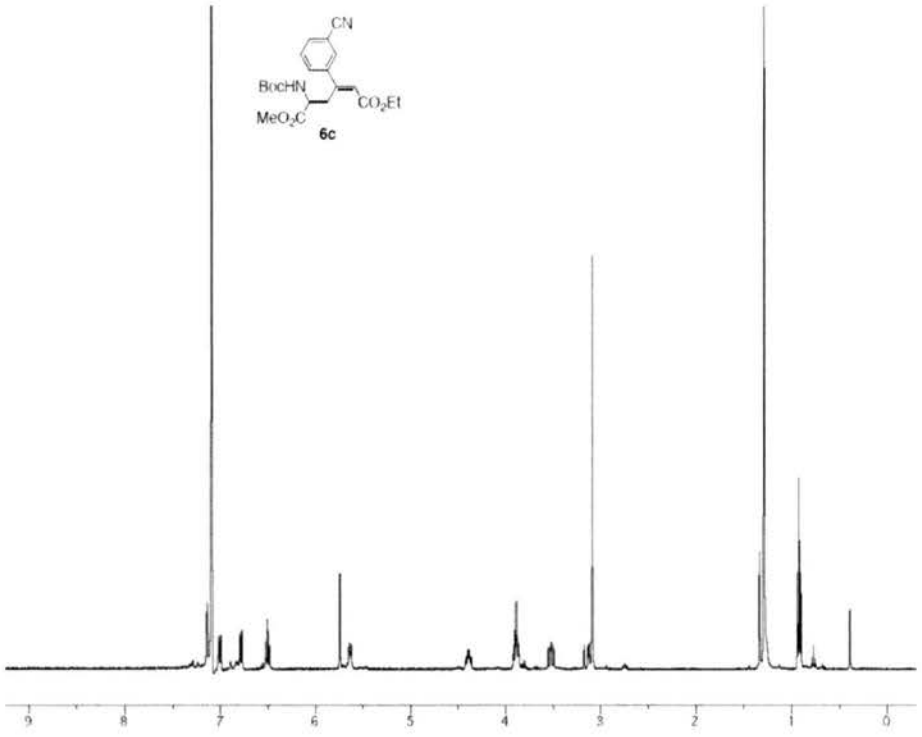
^{13}CNMR, C_6D_6, 100 MHz, filename: csy612-1-c13



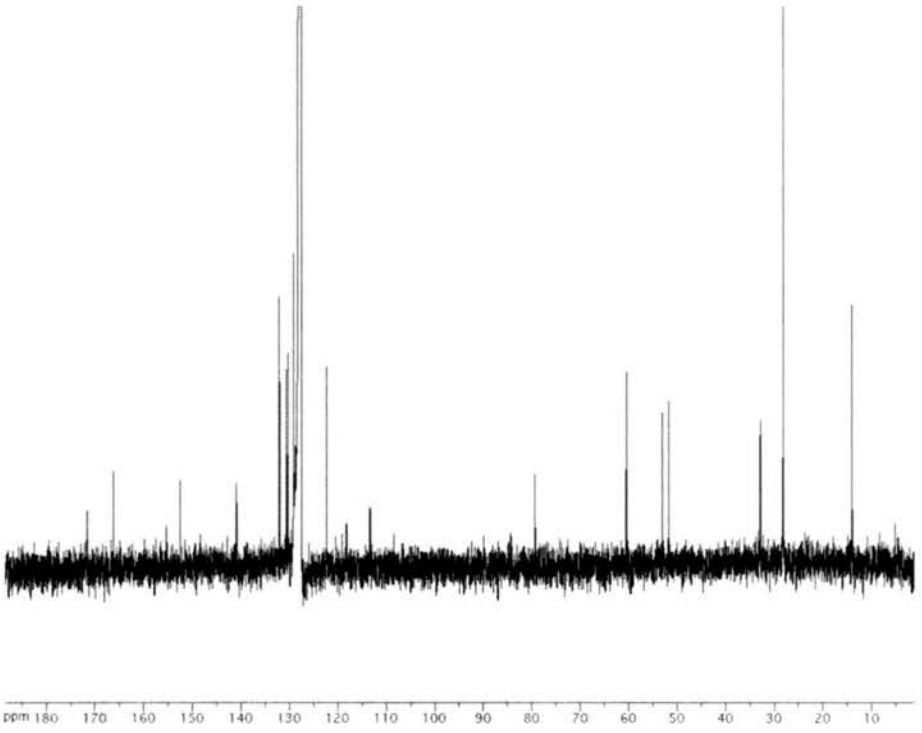
^{1}HNMR, C_6D_6, 300 MHz, filename: csy391-1



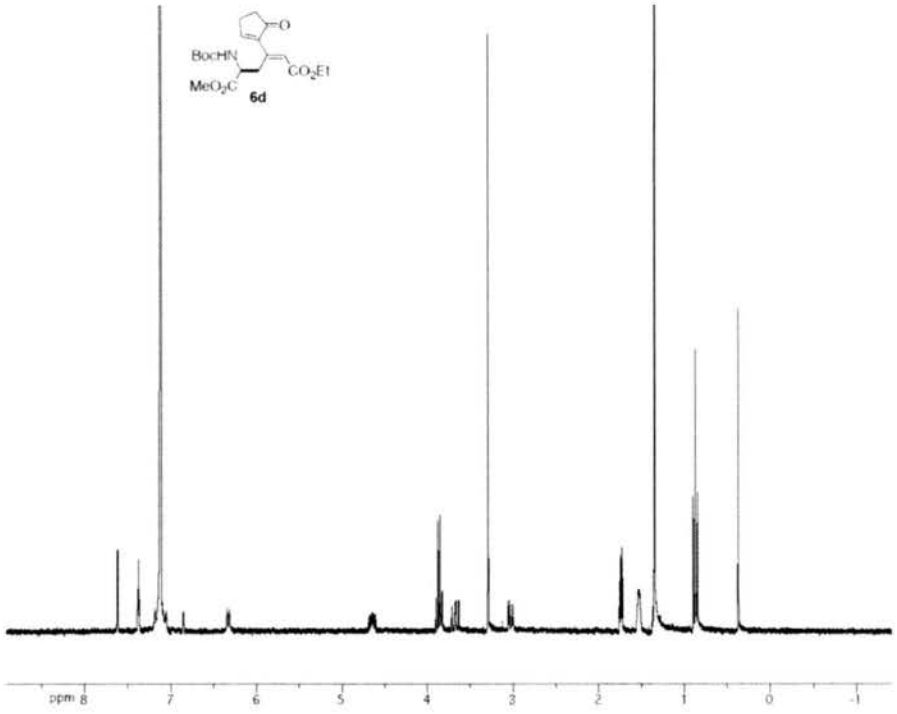
^{13}CNMR, C_6D_6, 75 MHz, filename: csy391-1-c13



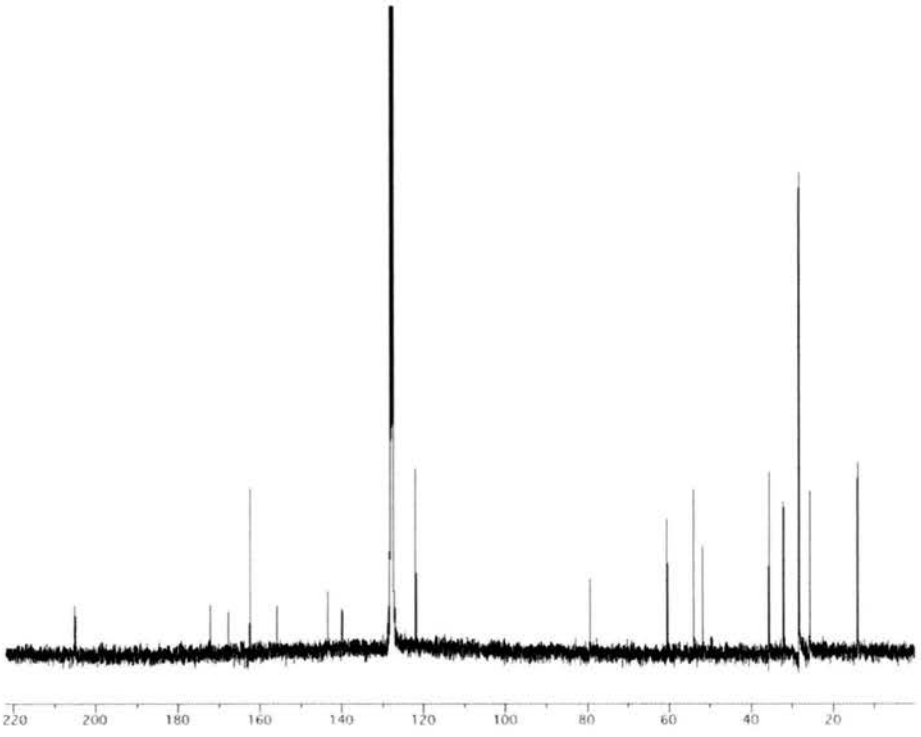
^{1}HNMR, C_6D_6, 400 MHz, filename: csy594-1



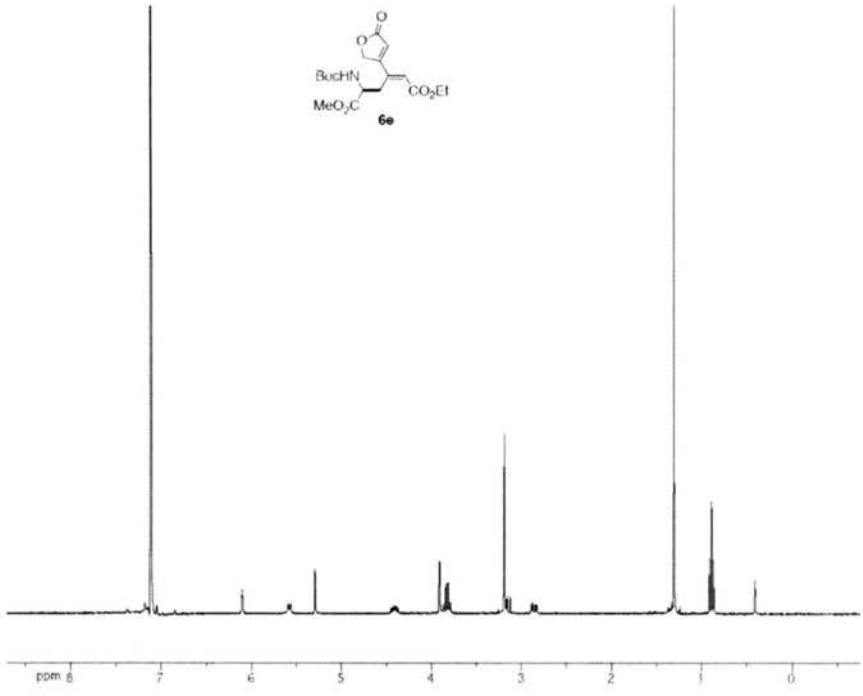
^{13}CNMR, C_6D_6, 100 MHz, filename: csy594-1-c13



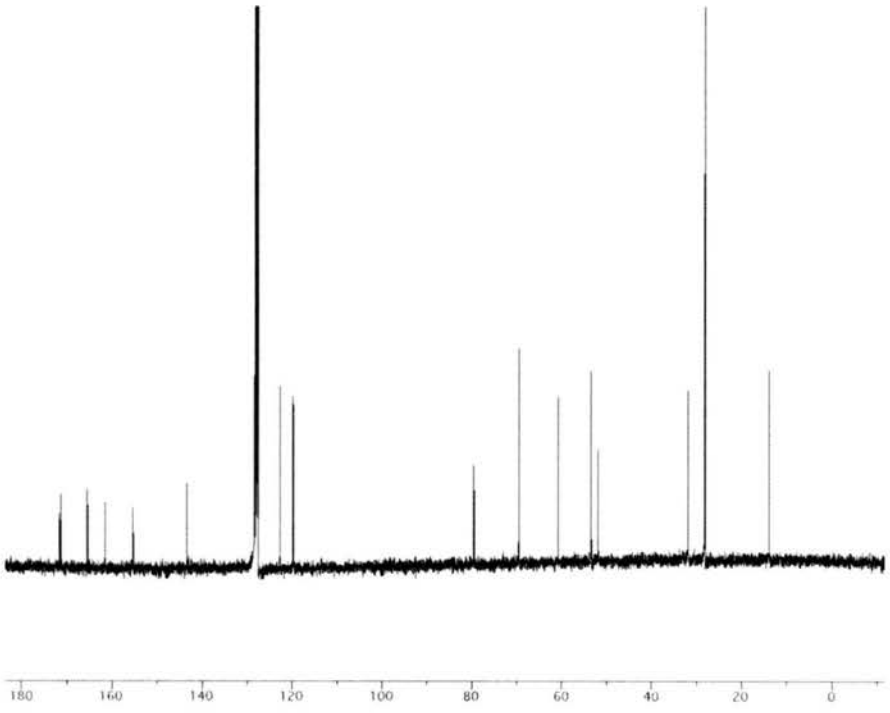
^{1}HNMR, C_6D_6, 300 MHz, filename: csy610-1



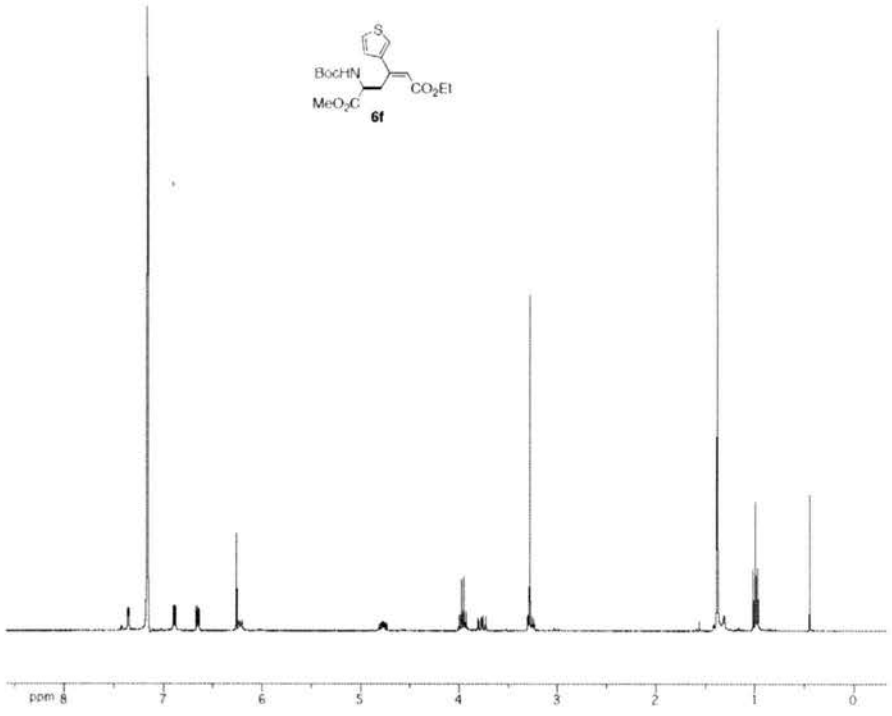
^{13}CNMR, C_6D_6, 100 MHz, filename: csy610-1-c13



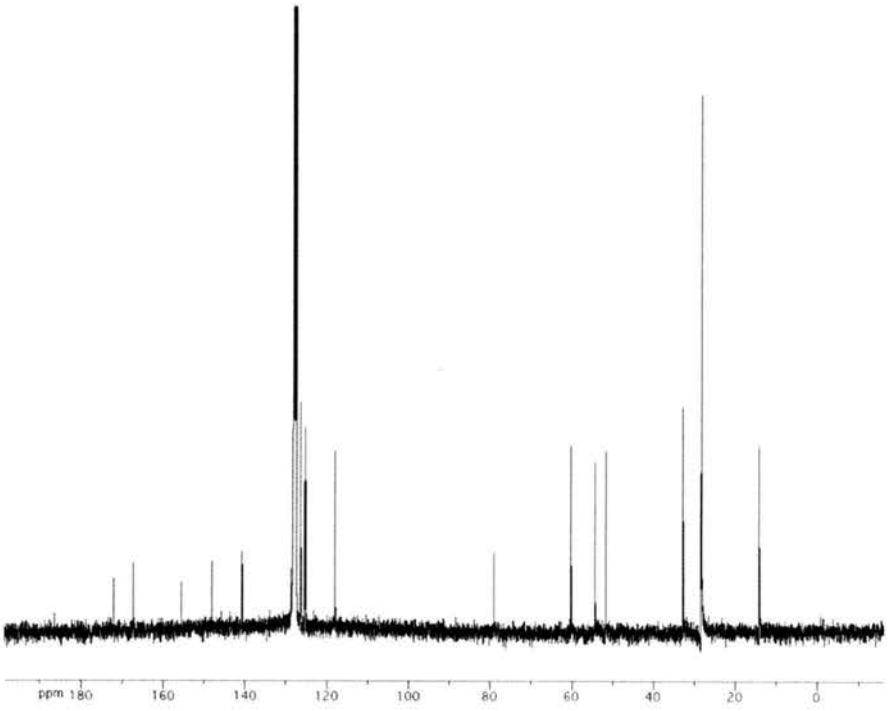
^{1}HNMR, C_6D_6, 300 MHz, filename: csy614-1



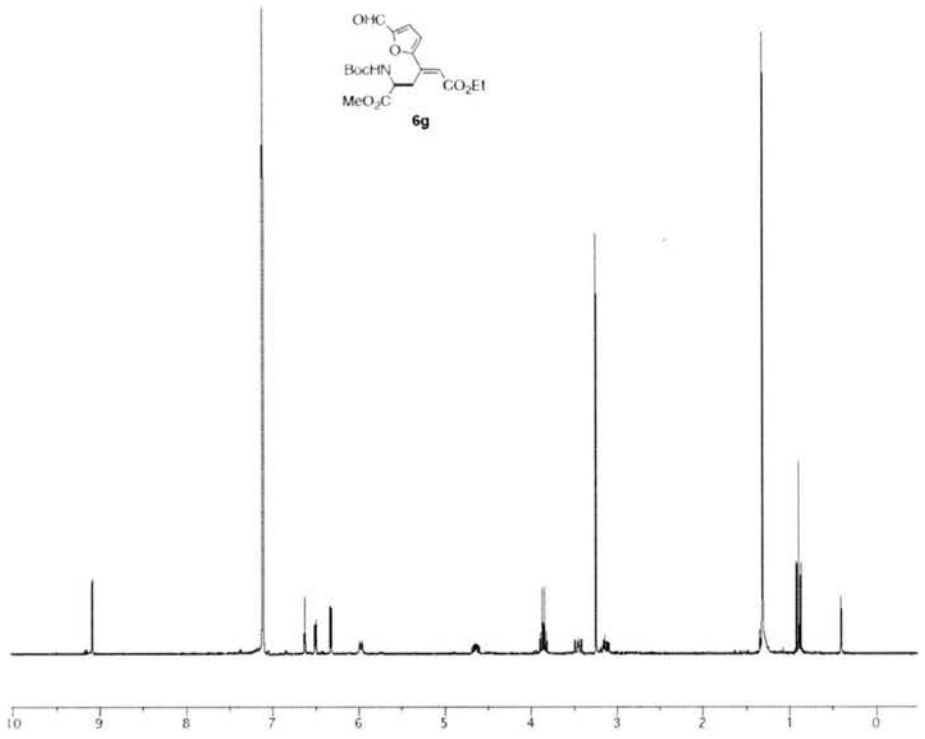
^{13}CNMR, C_6D_6, 75 MHz, filename: csy614-1-c13



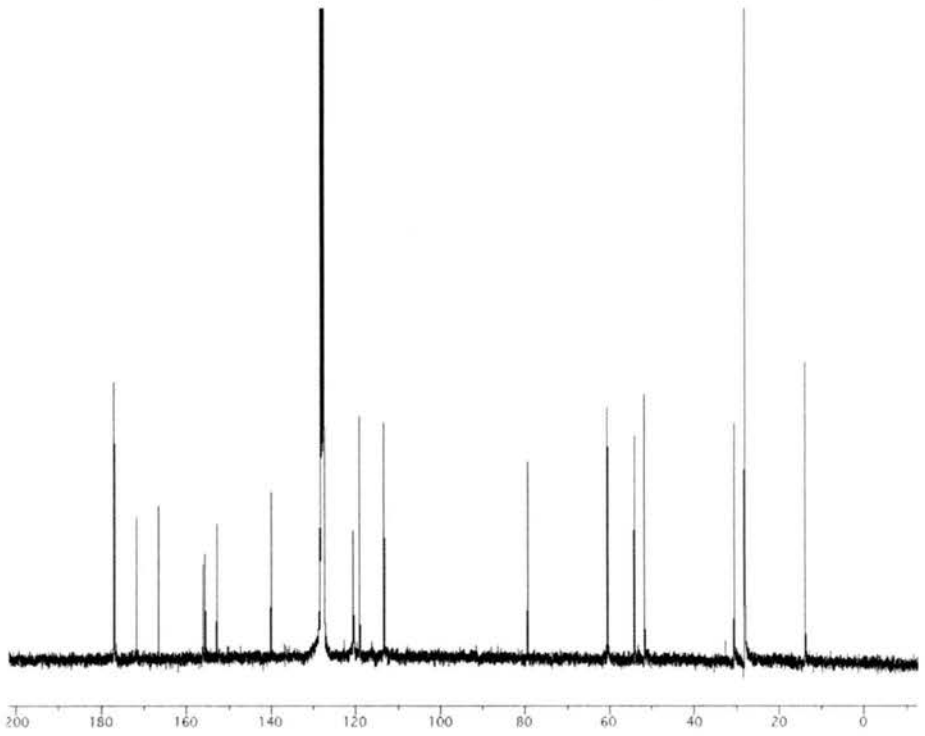
^{1}HNMR, C_6D_6, 300 MHz, filename: csy609-1



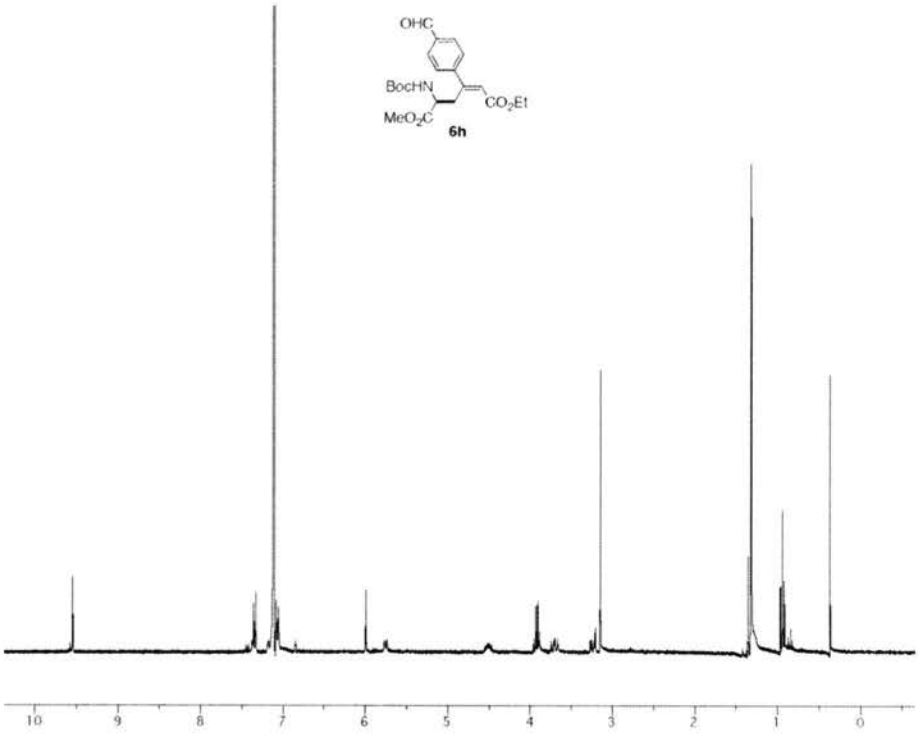
^{13}CNMR, C_6D_6, 100 MHz, filename: csy609-1-1



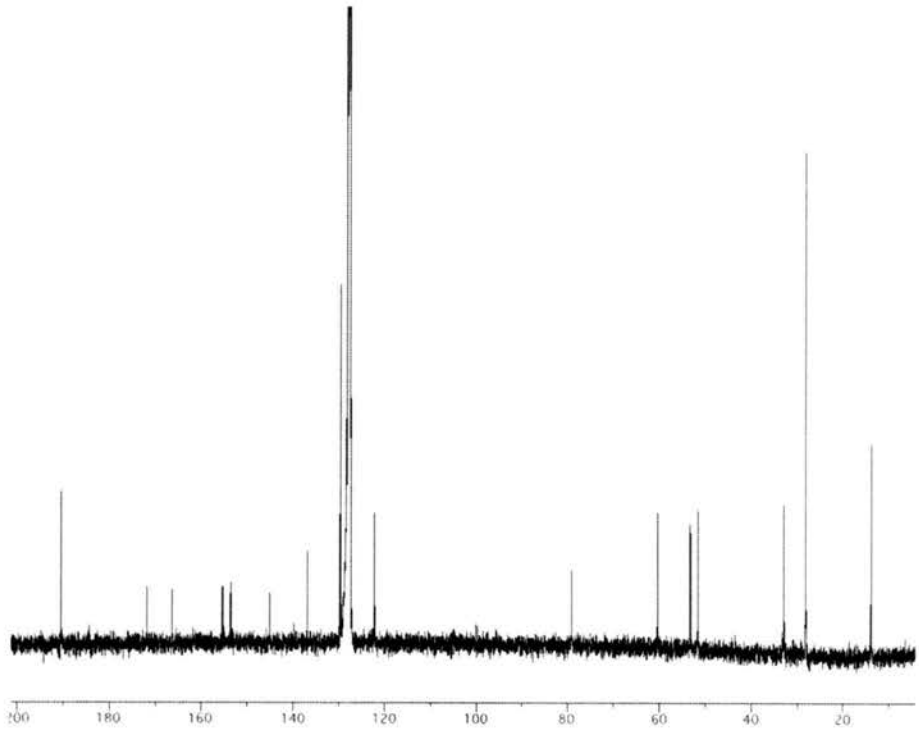
^{1}HNMR, C_6D_6, 300 MHz, filename: csy613-1



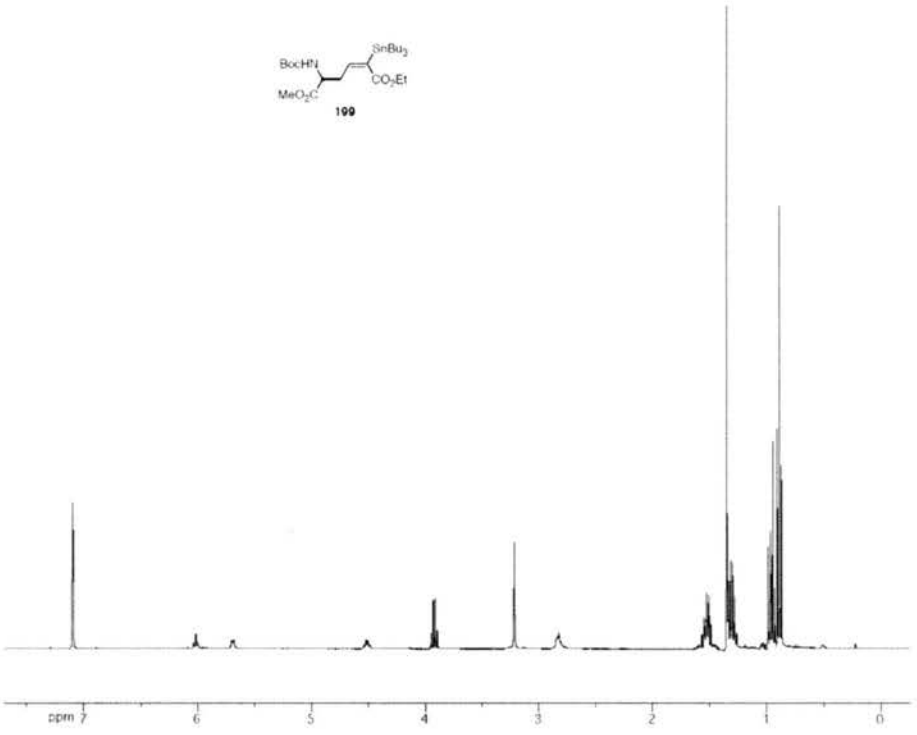
^{13}CNMR, C_6D_6, 75 MHz, filename: csy613-1-c13



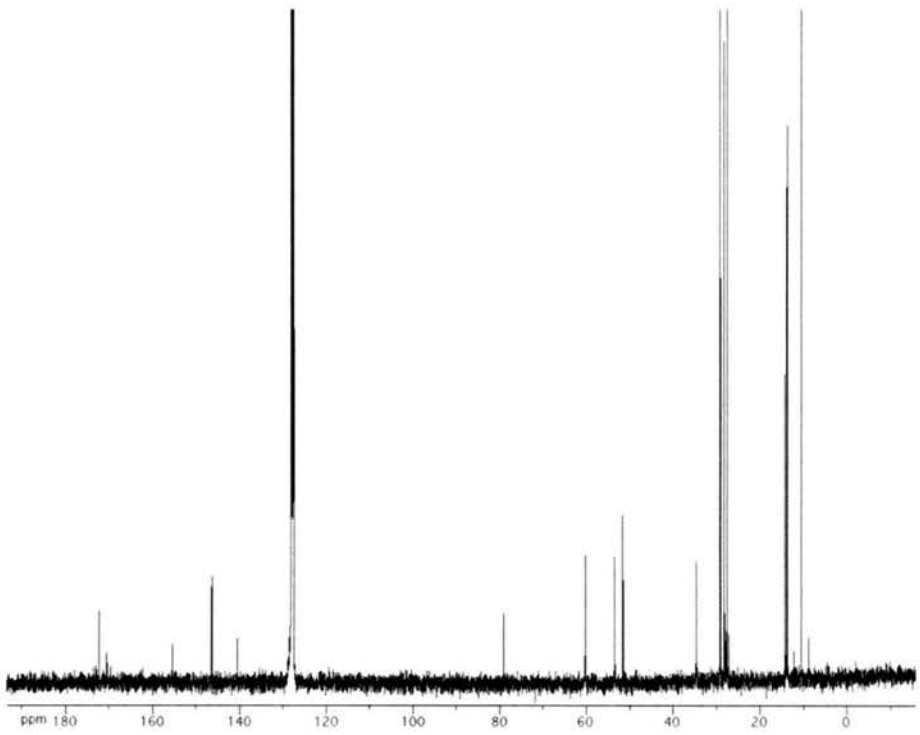
^{1}HNMR, C_6D_6, 300 MHz, filename: csy611-1



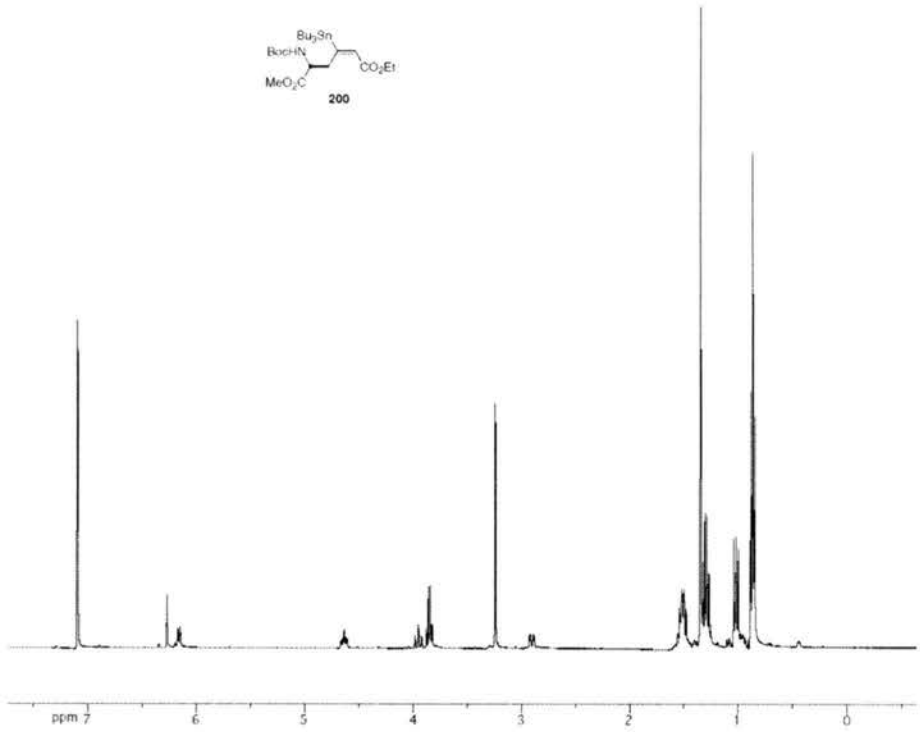
^{13}CNMR, C_6D_6, 100 MHz, filename: csy611-1-c13



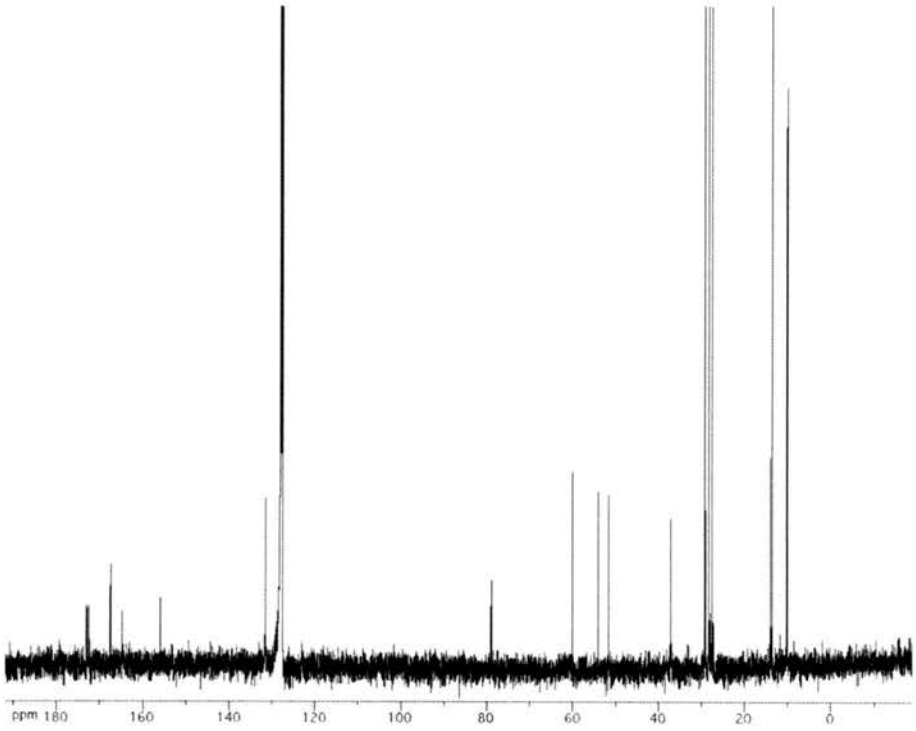
^{1}HNMR, C_6D_6, 400 MHz, filename: csy588-1



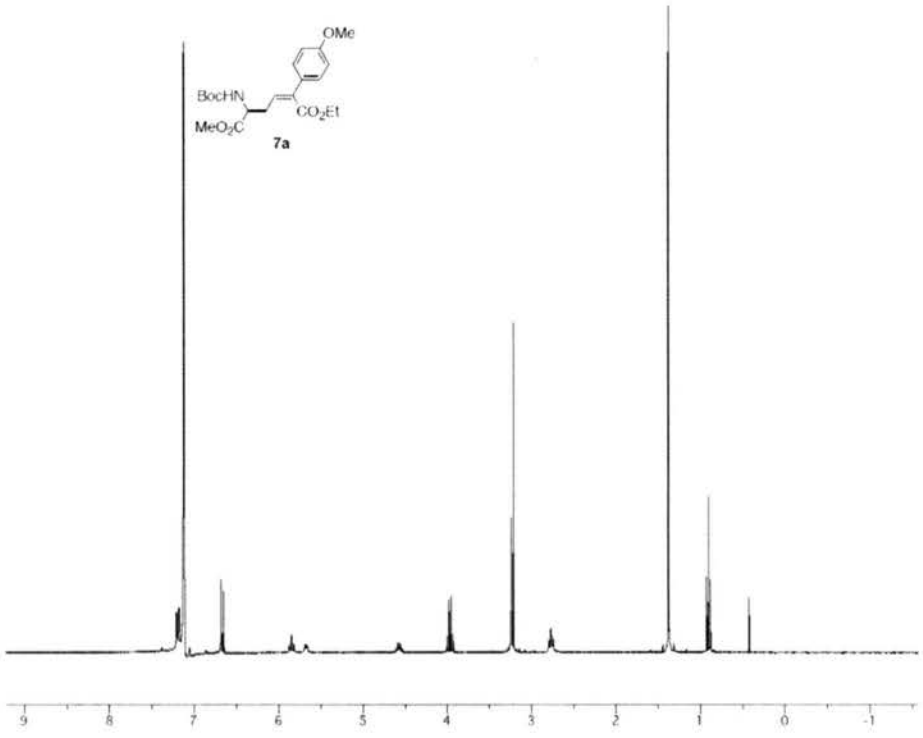
^{13}CNMR, C_6D_6, 100 MHz, filename: csy588-1-c13



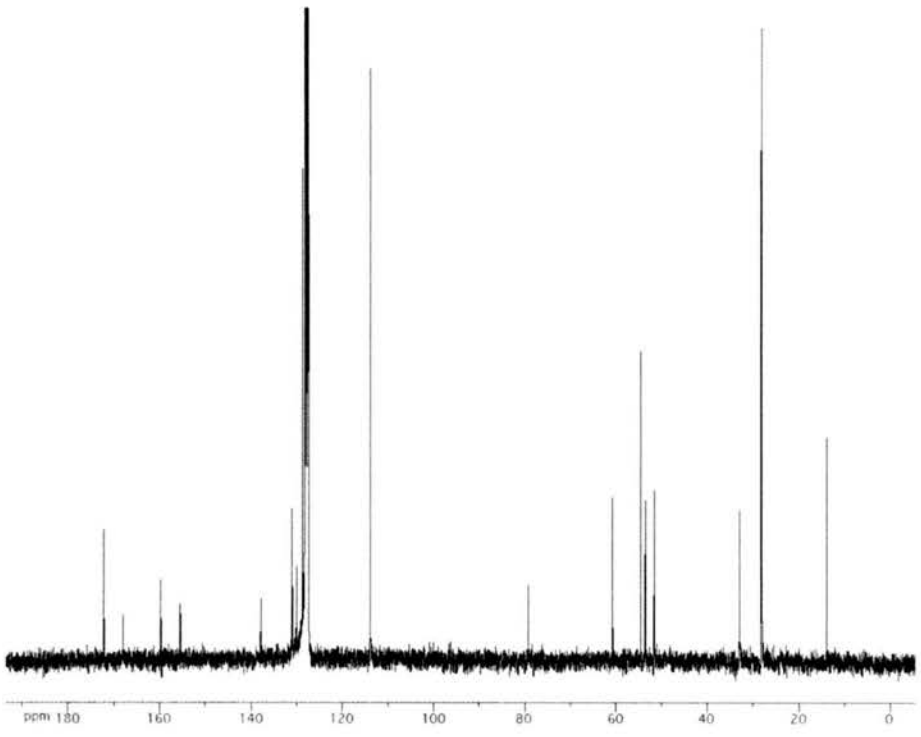
^{1}HNMR, C_6D_6, 400 MHz, filename: csy588-2



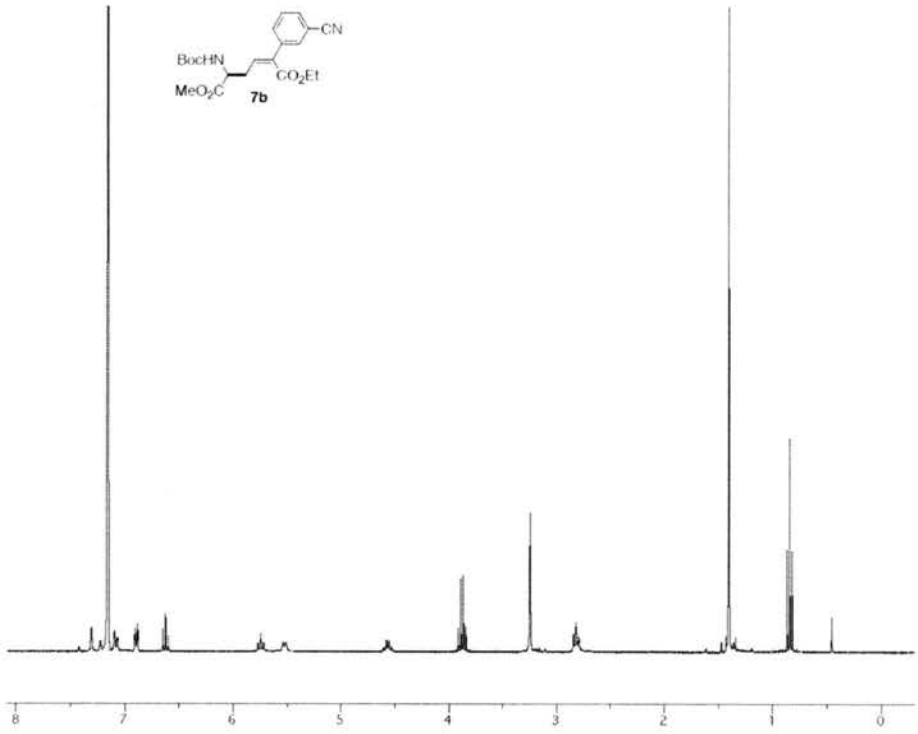
^{13}CNMR, C_6D_6, 100 MHz, filename: csy588-2-c13



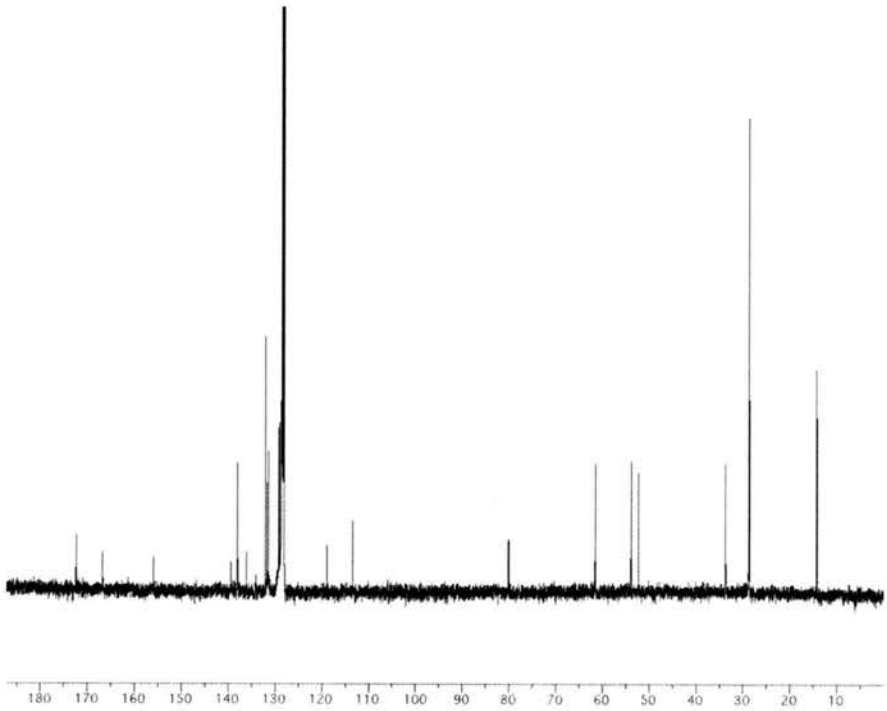
^{1}HNMR, C_6D_6, 300 MHz, filename: csy620-1



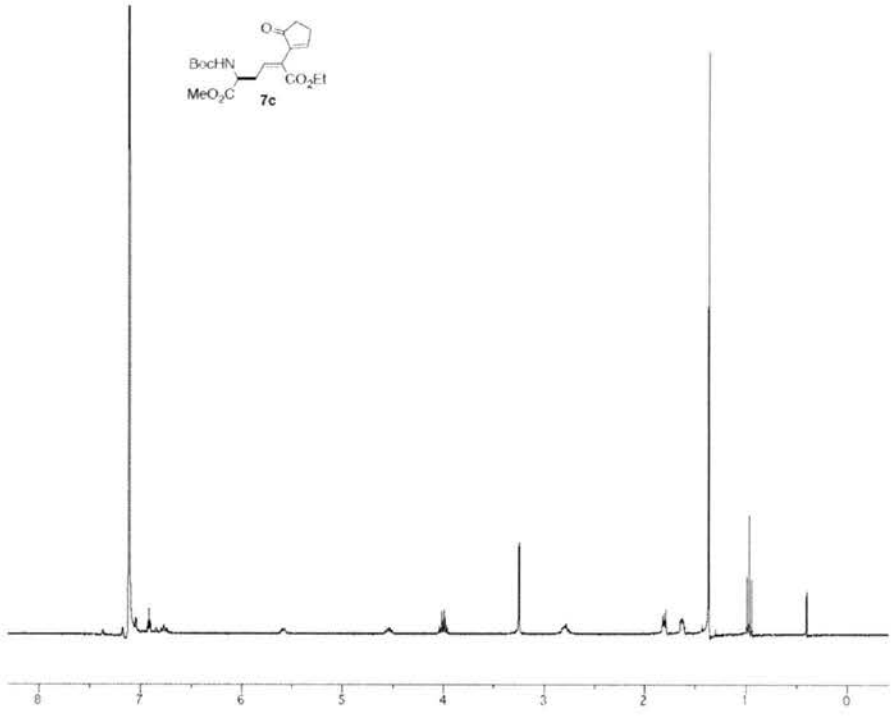
^{13}CNMR, C_6D_6, 75 MHz, filename: csy620-1-c13



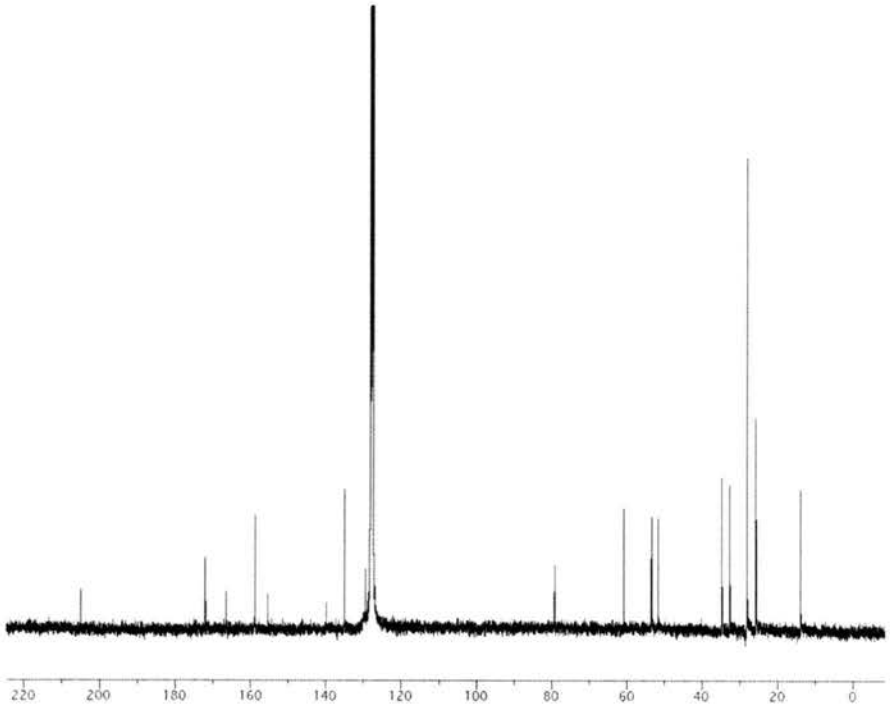
^{1}HNMR, C_6D_6, 300 MHz, filename: csy618-1



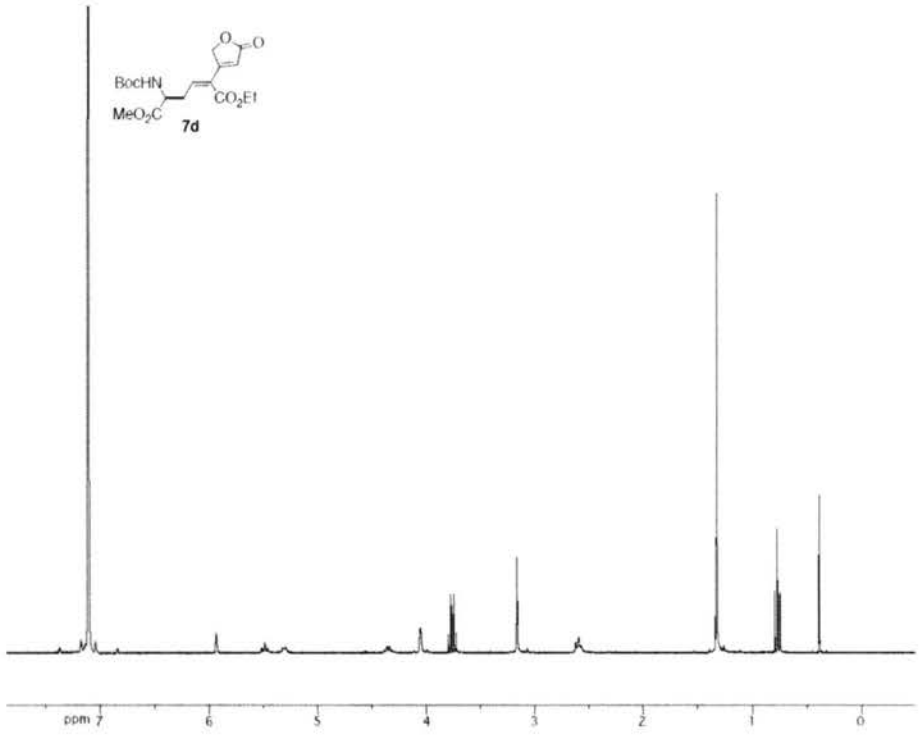
^{13}CNMR, C_6D_6, 100 MHz, filename: csy618-1-c13



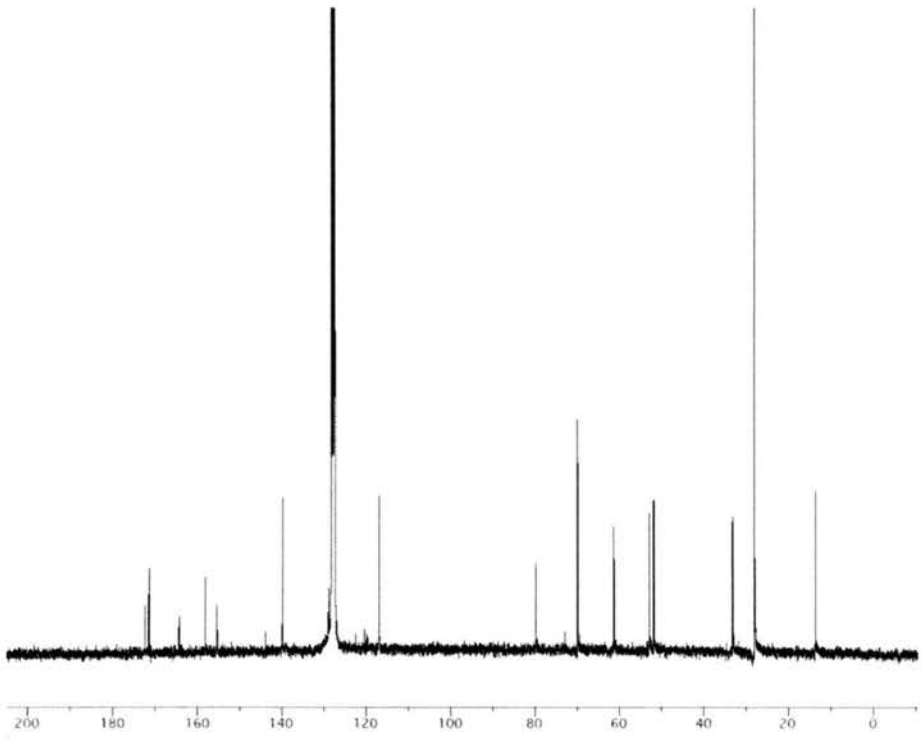
^{1}HNMR, C_6D_6, 300 MHz, filename: csy619-1



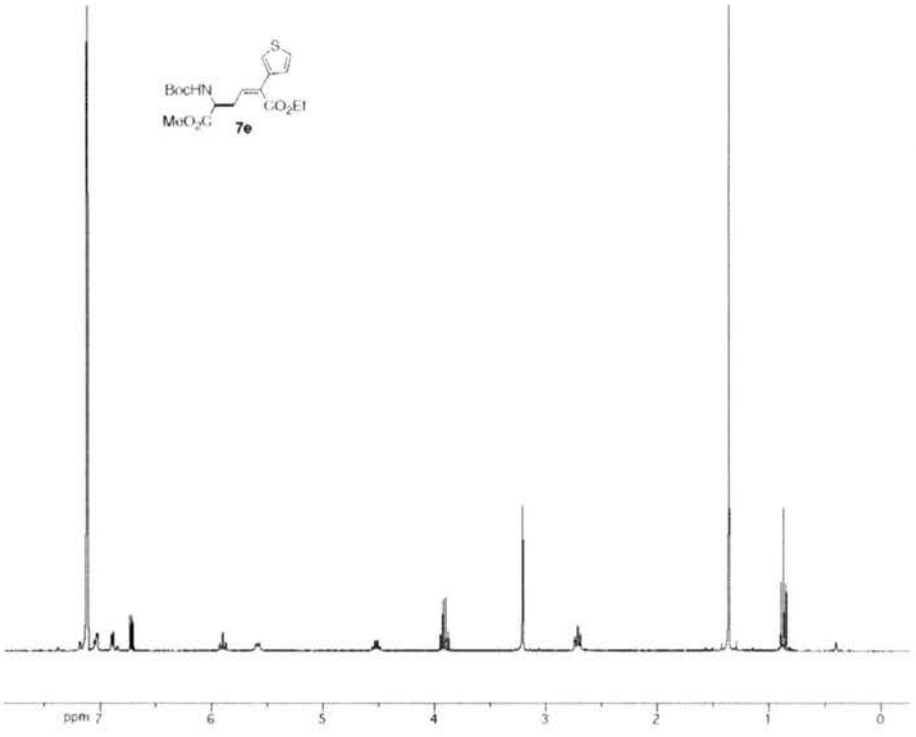
^{13}CNMR, C_6D_6, 75 MHz, filename: csy619-1-1



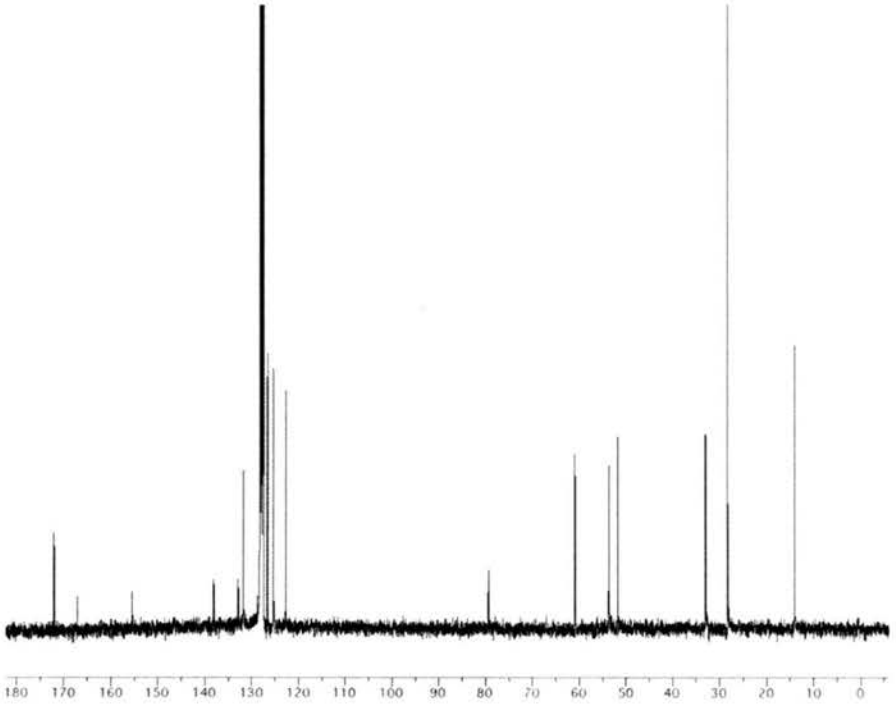
^{1}HNMR, C_6D_6, 300 MHz, filename: csy615-1



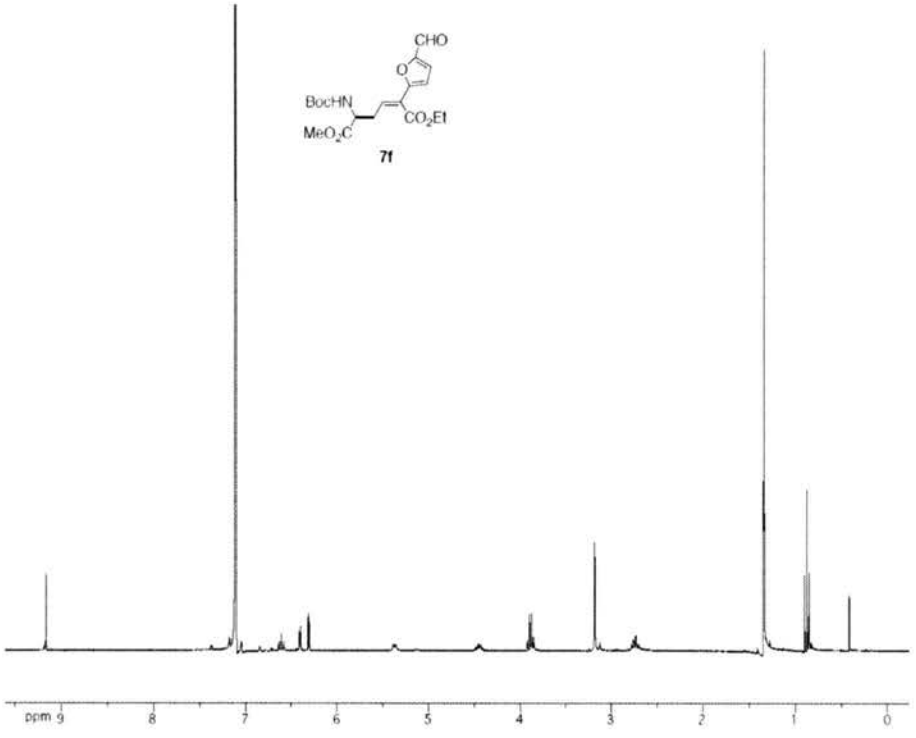
^{13}CNMR, C_6D_6, 75 MHz, filename: csy615-1-c13



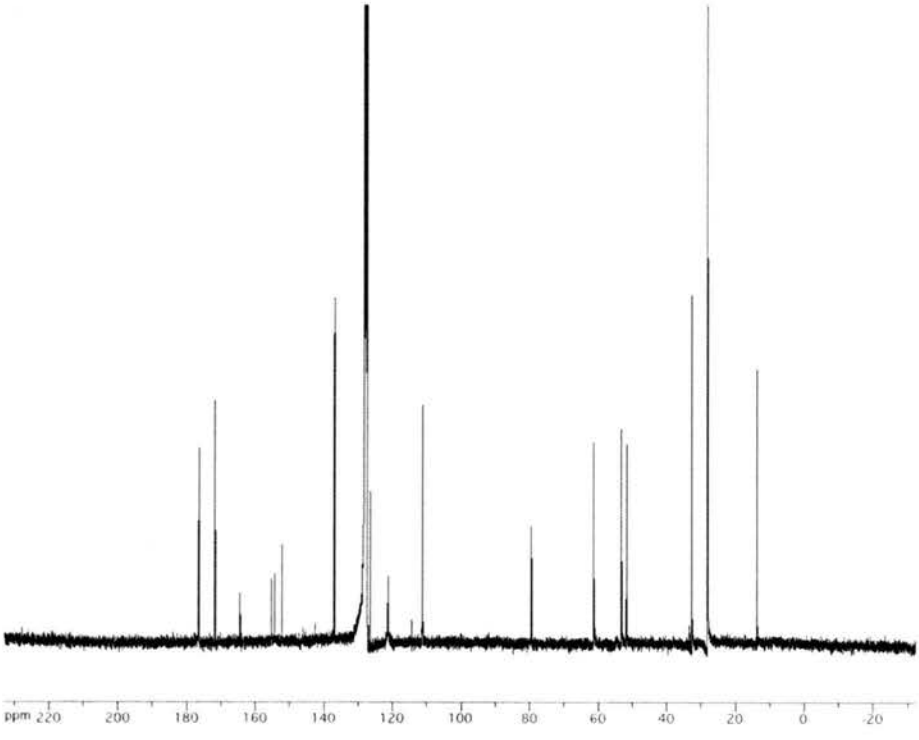
^{1}HNMR, C_6D_6, 300 MHz, filename: csy616-1



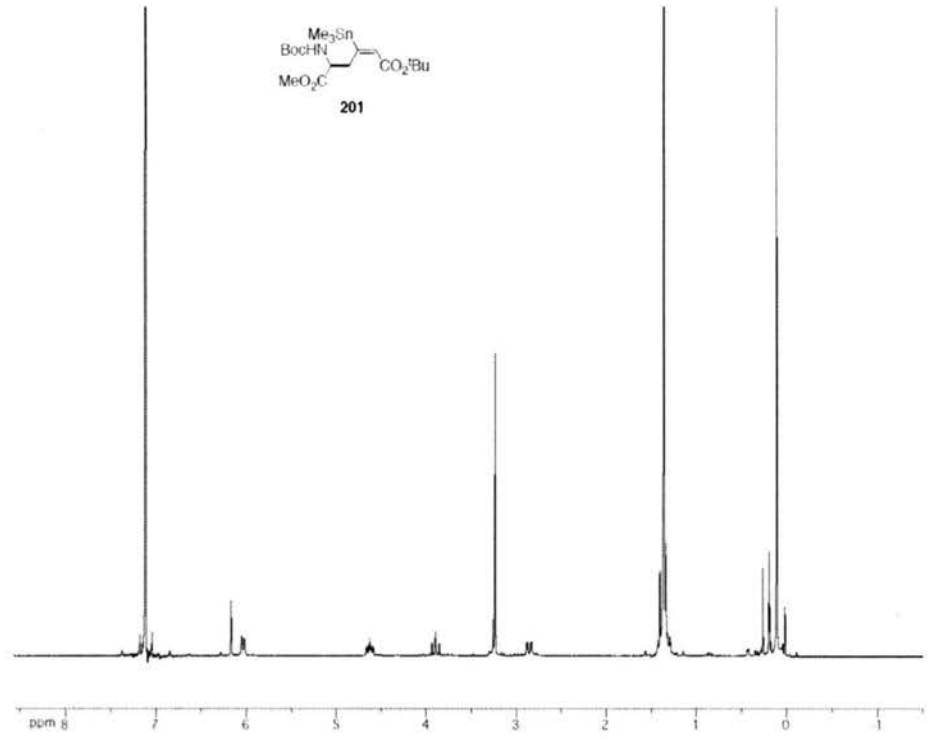
^{13}CNMR, C_6D_6, 75 MHz, filename: csy616-1-c13



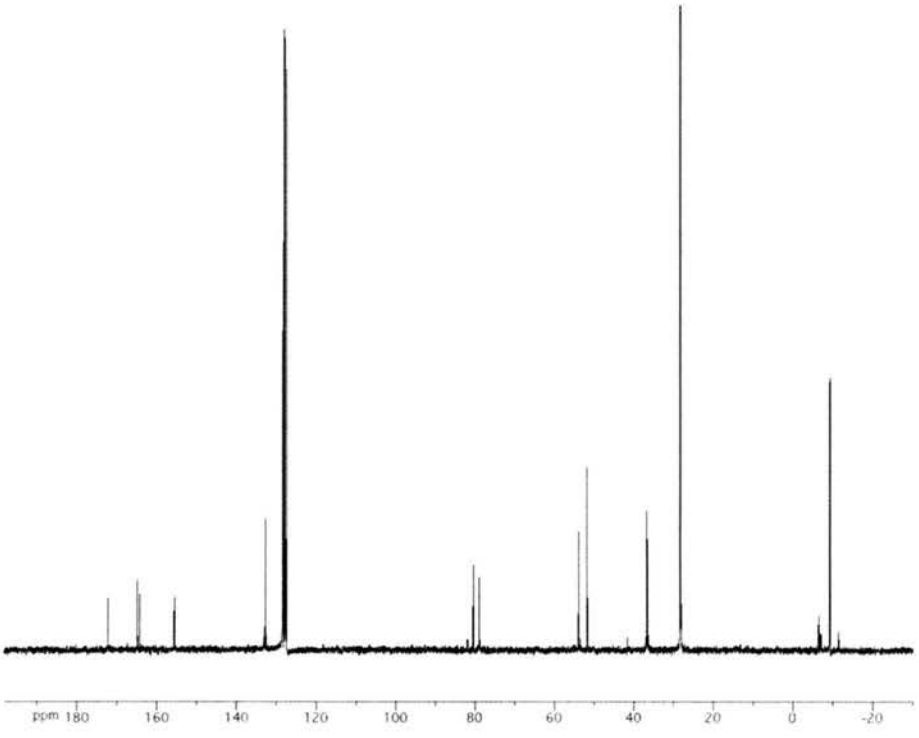
^{1}HNMR, C_6D_6, 300 MHz, filename: csy617-1



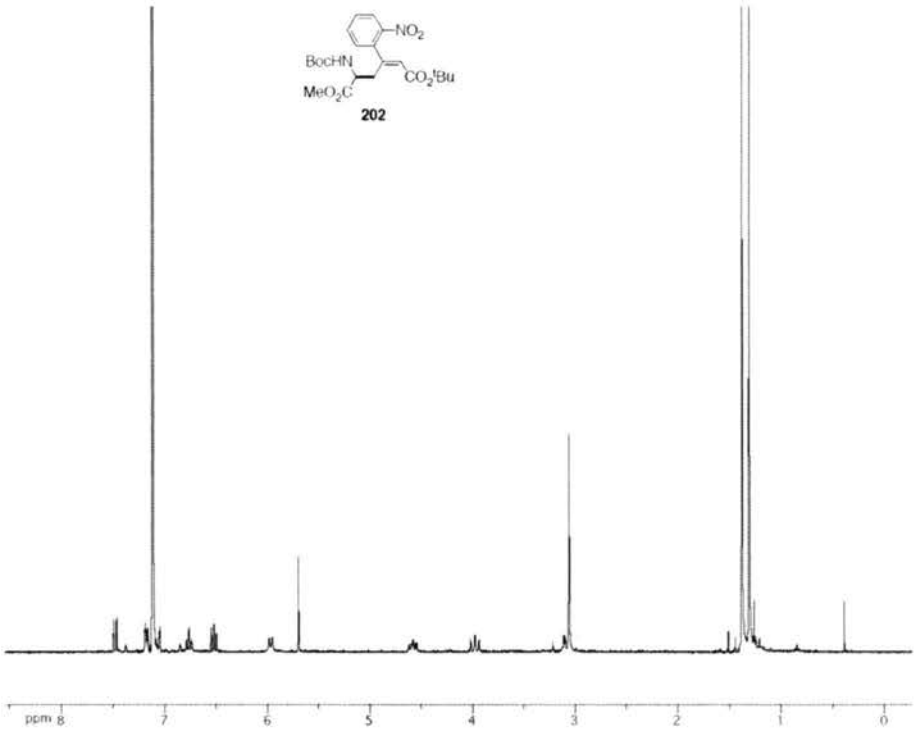
^{13}CNMR, C_6D_6, 75 MHz, filename: csy617-1-c13



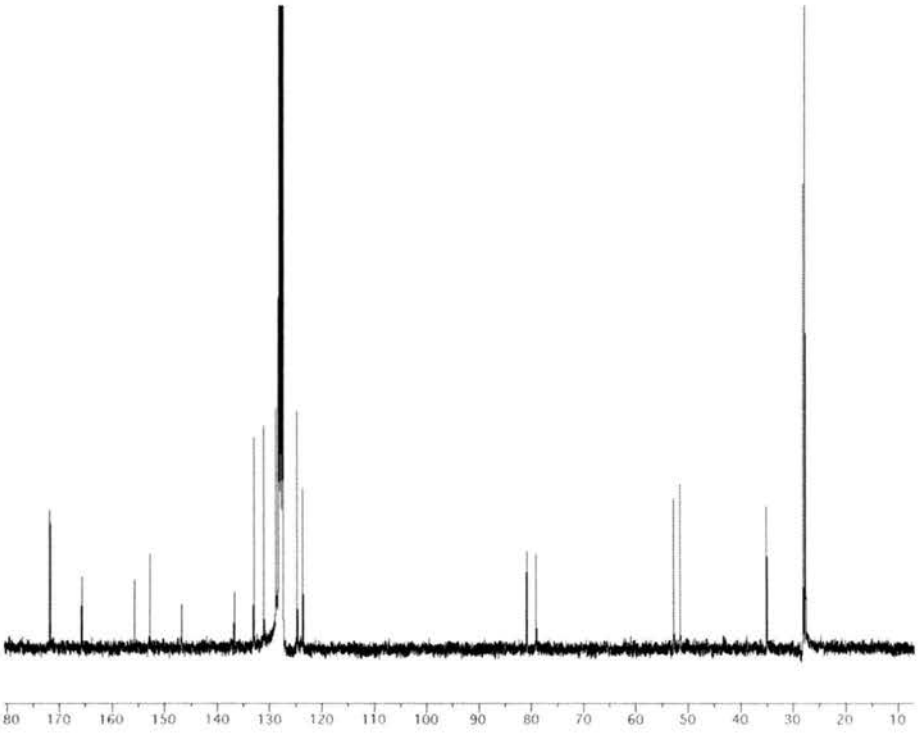
^{1}HNMR, C_6D_6, 300 MHz, filename: csy562-1



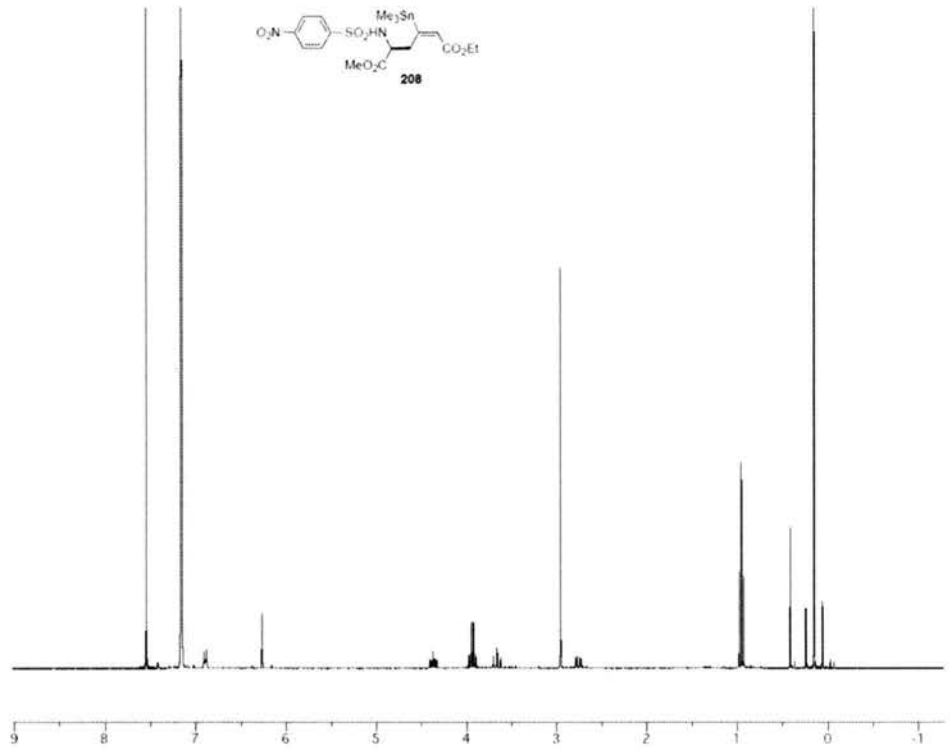
^{13}CNMR, C_6D_6, 75 MHz, filename: csy562-1-c13



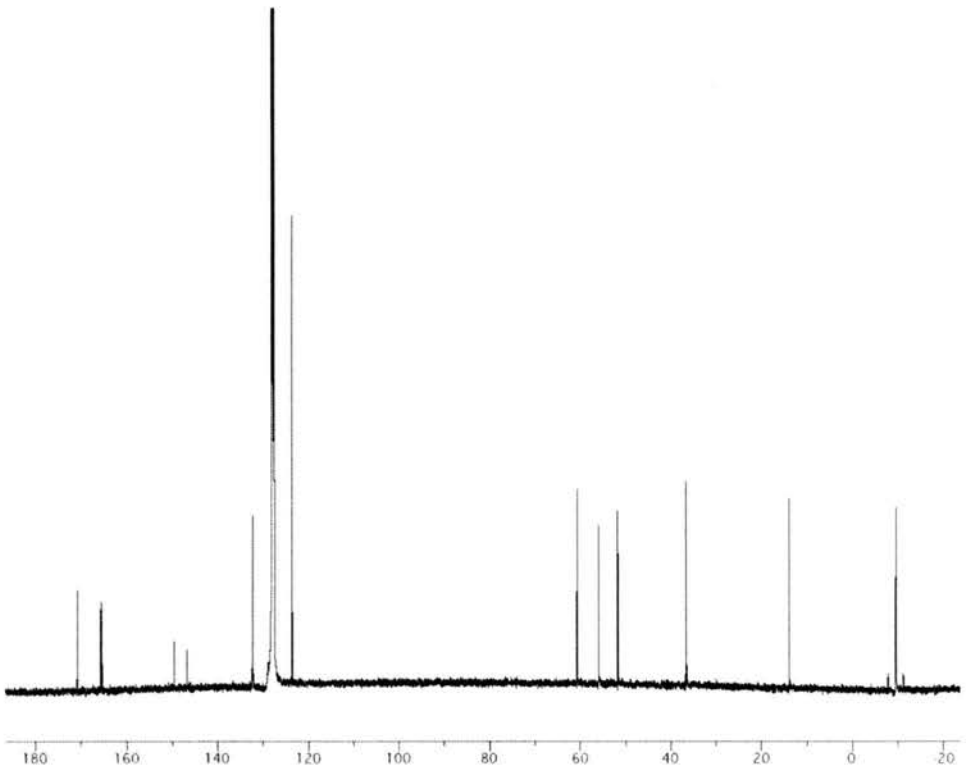
^{1}HNMR, C_6D_6, 300 MHz, filename: csy564-1



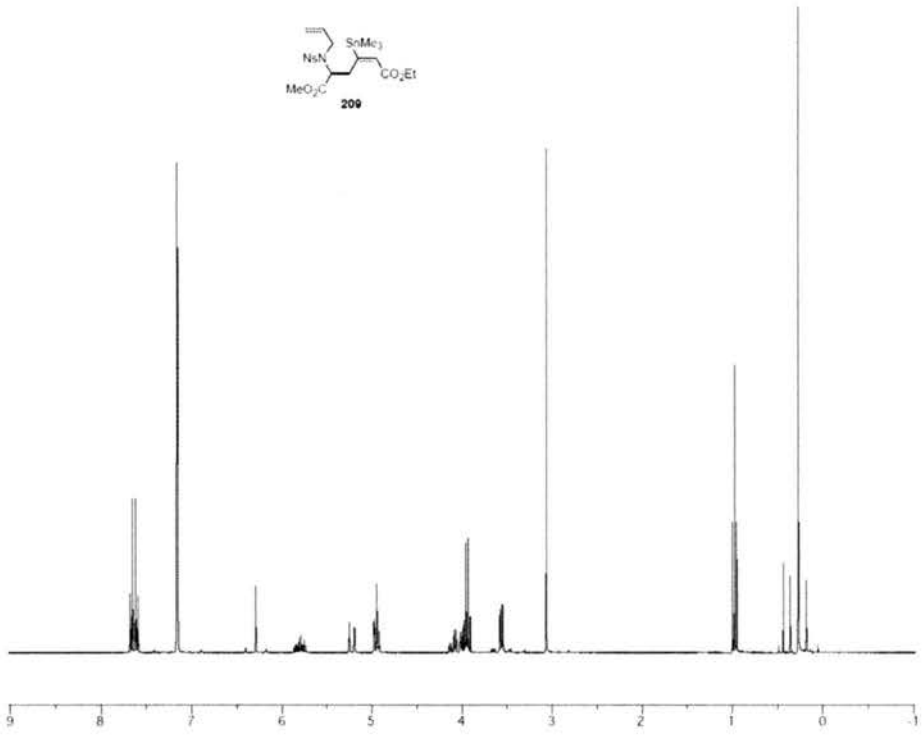
^{13}CNMR, C_6D_6, 75 MHz, filename: csy564-1-c13



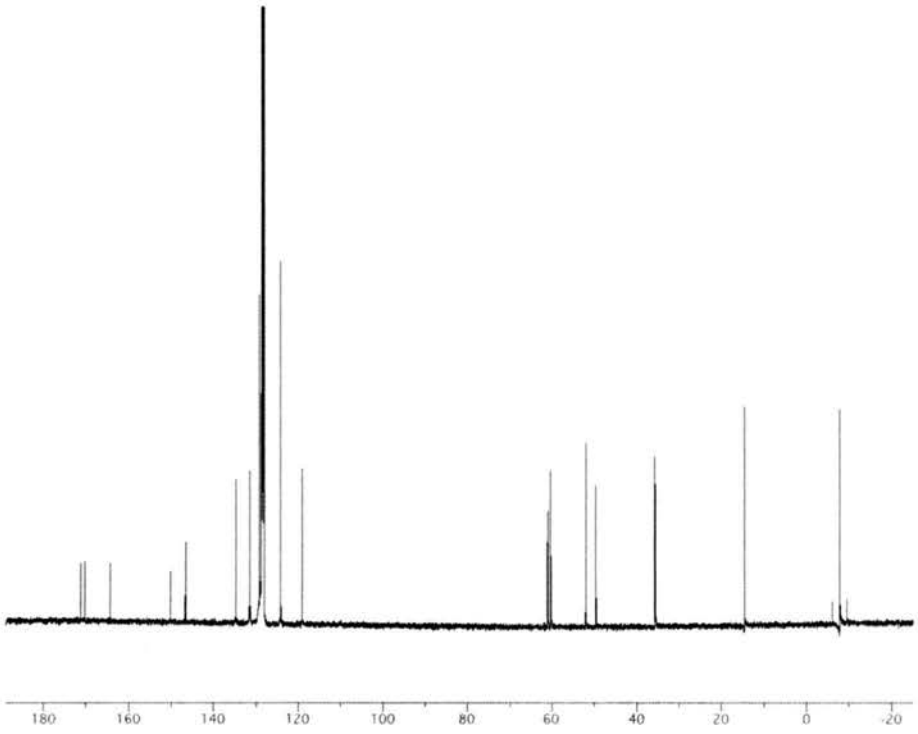
^{1}HNMR, C_6D_6, 300 MHz, filename: csy643-1



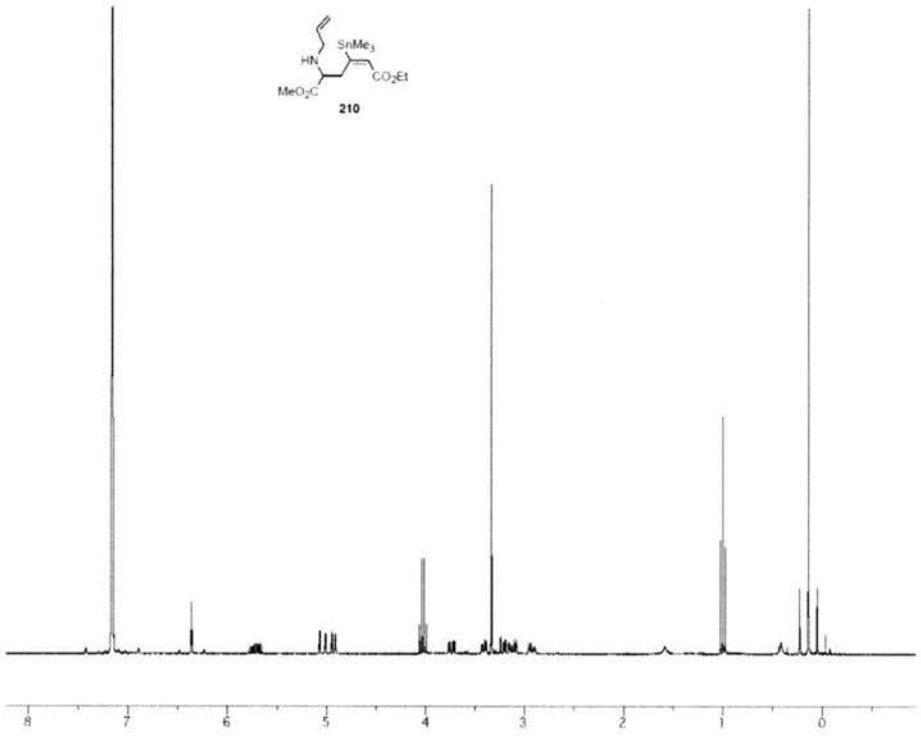
^{13}CNMR, C_6D_6, 100 MHz, filename: csy643-1-c13



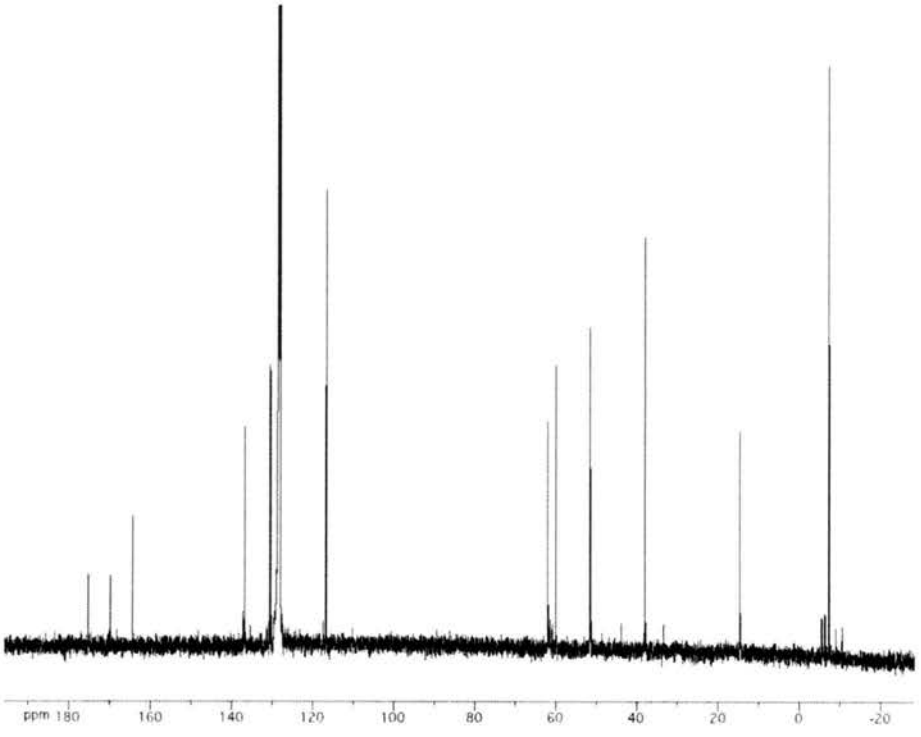
^{1}HNMR, C_6D_6, 300 MHz, filename: csy644-1



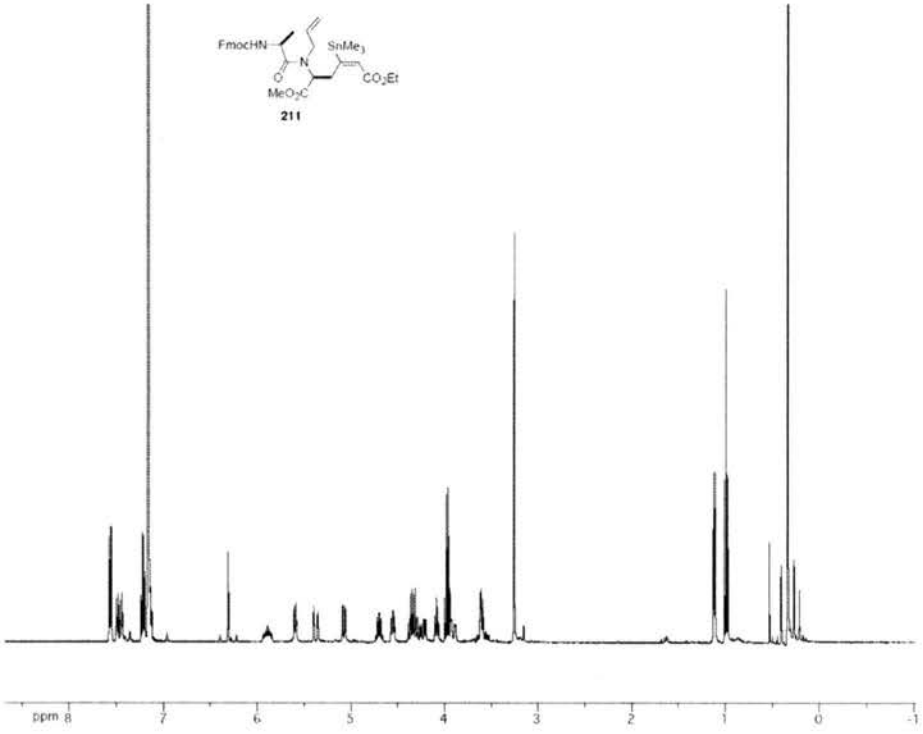
^{13}CNMR, C_6D_6, 100 MHz, filename: csy644-1-c13



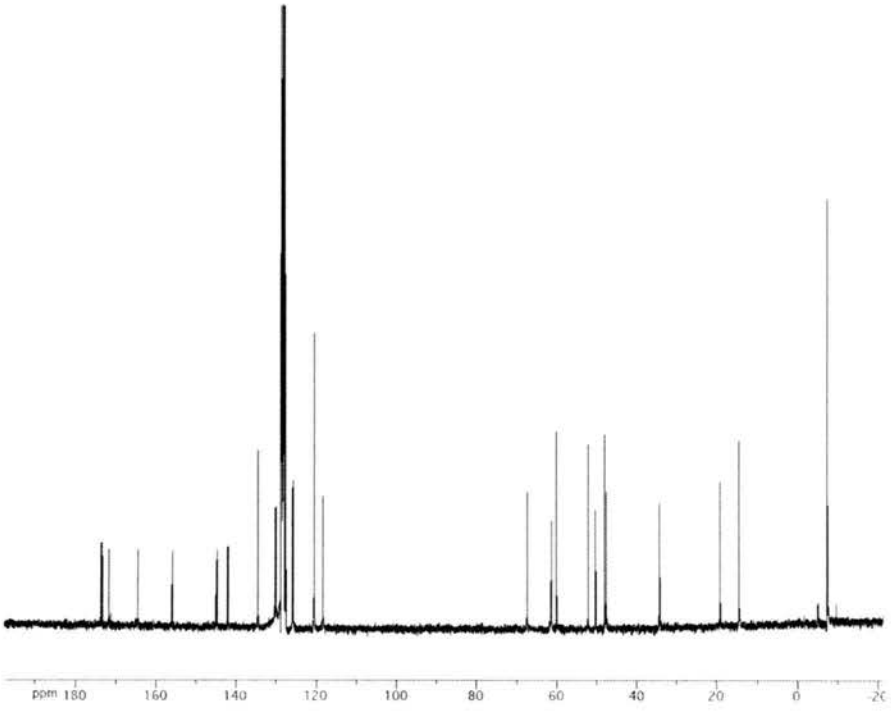
^{1}HNMR, C_6D_6, 300 MHz, filename: csy645-1



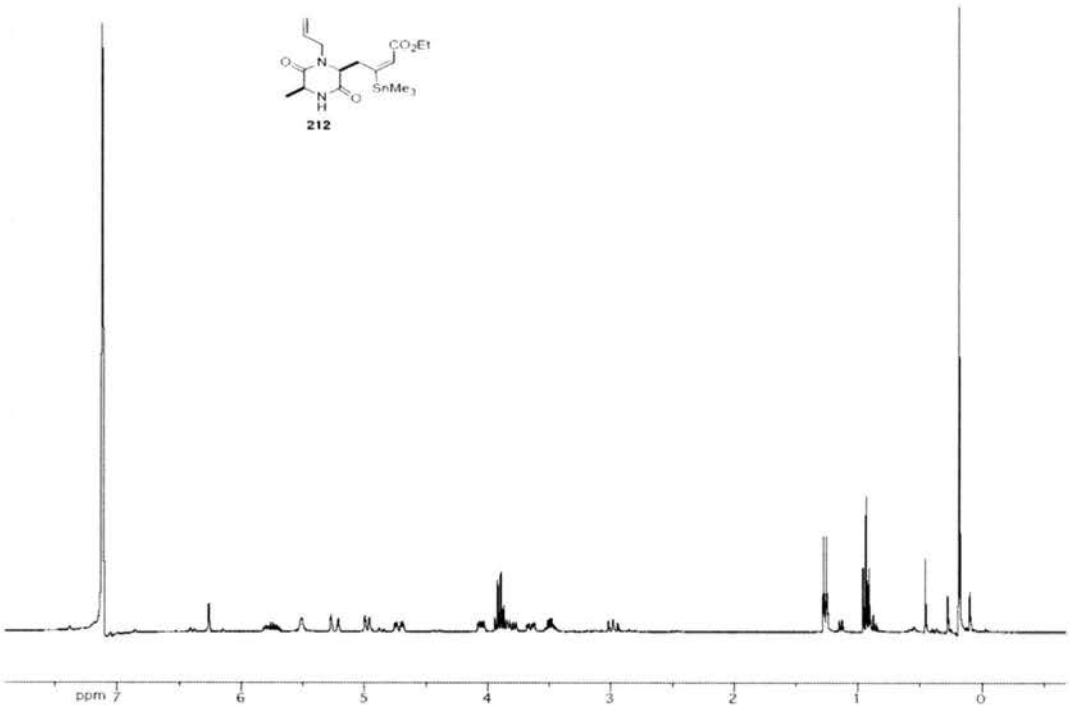
^{13}CNMR, C_6D_6, 100 MHz, filename: csy645-1-c13



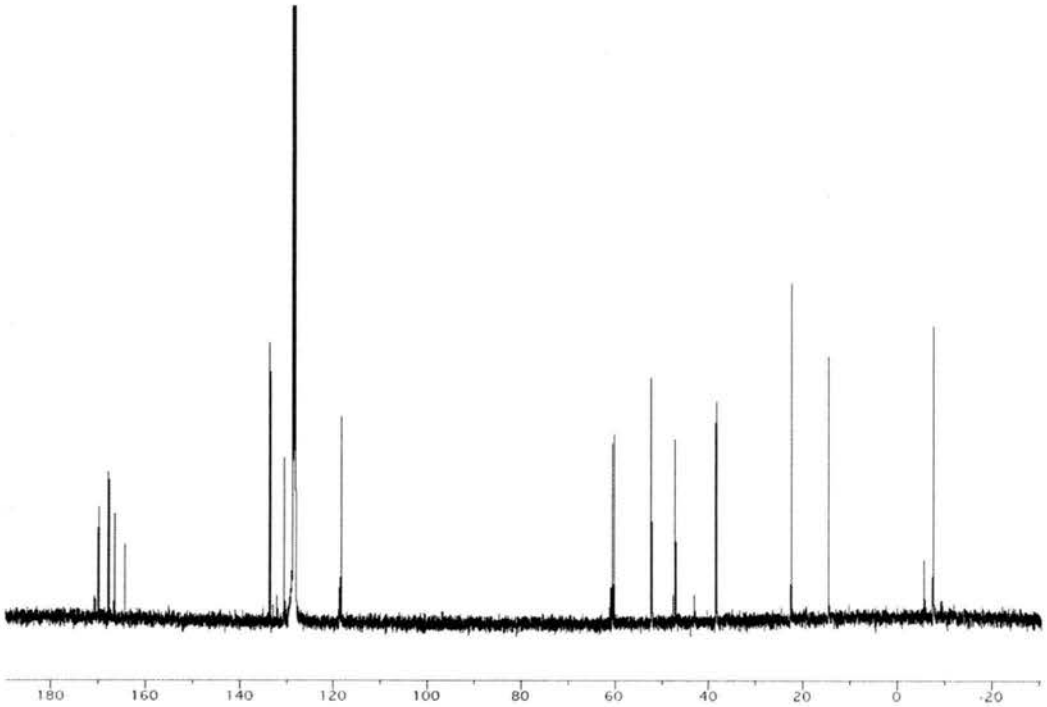
^{1}HNMR, C_6D_6, 400 MHz, filename: csy515-1



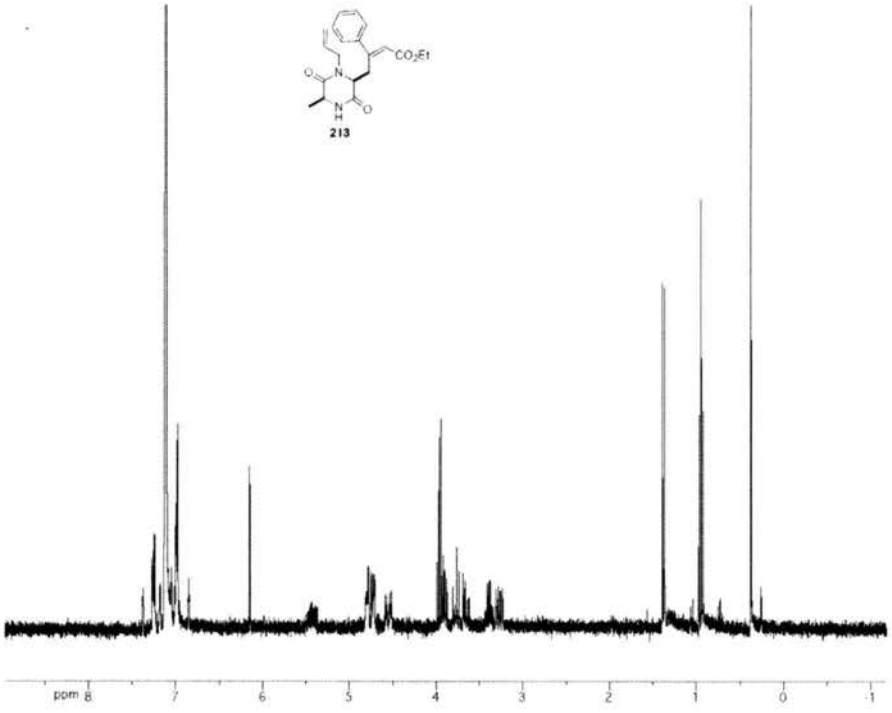
^{13}CNMR, C_6D_6, 100 MHz, filename: csy515-1-c13



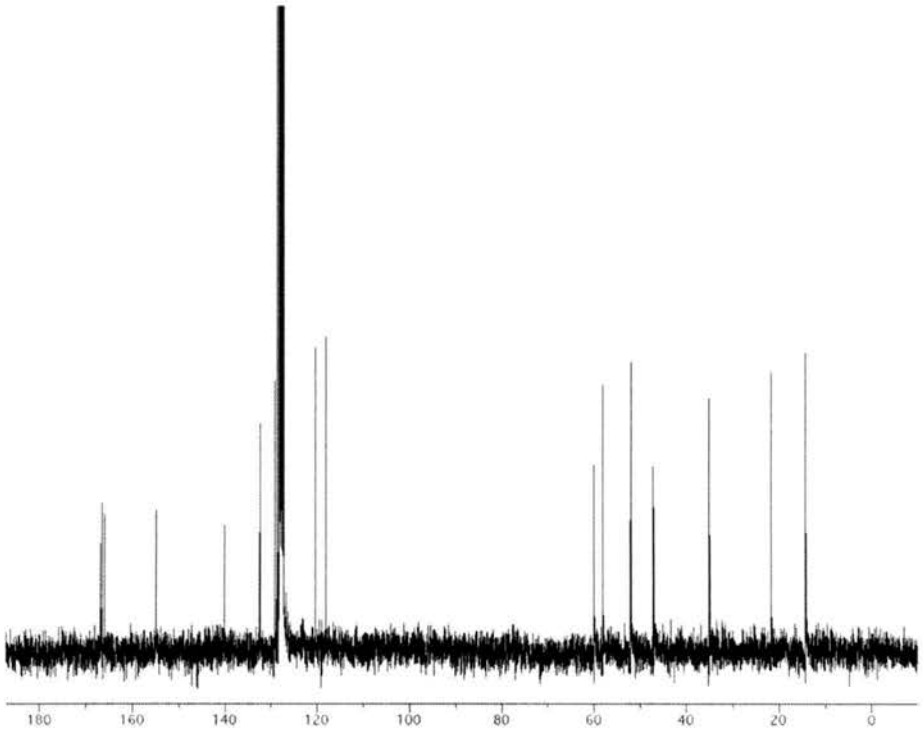
^{1}HNMR, C_6D_6, 300 MHz, filename: csy516-1



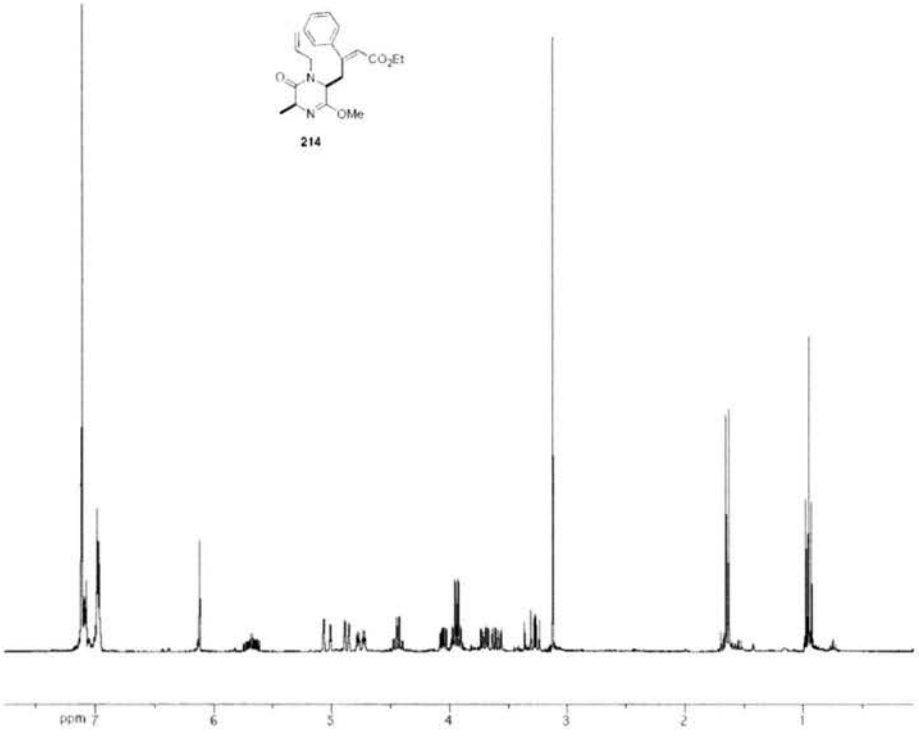
^{13}CNMR, C_6D_6, 100 MHz, filename: csy516-1-c13



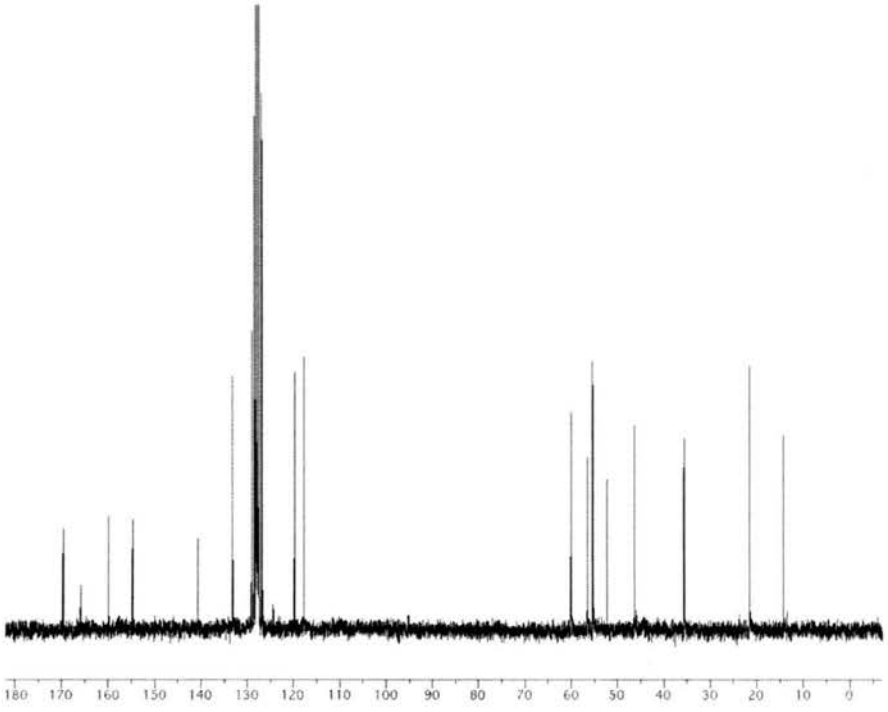
^{1}HNMR, C_6D_6, 400 MHz, filename: csy599-1



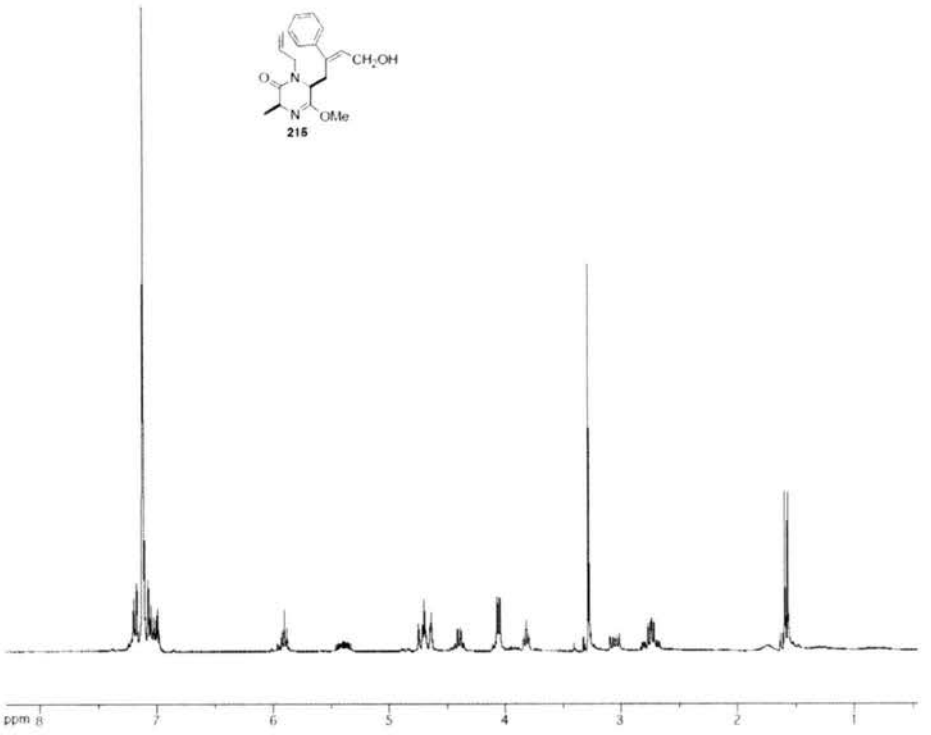
^{13}CNMR, C_6D_6, 100 MHz, filename: csy599-1-c13



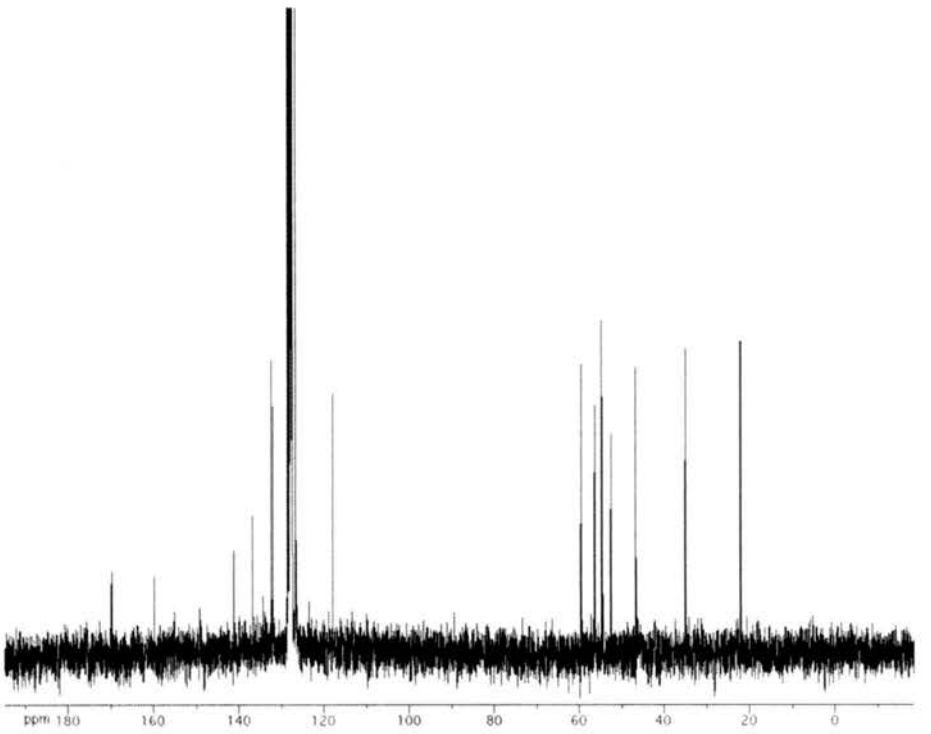
^{1}HNMR, C_6D_6, 300 MHz, filename: csy603-1



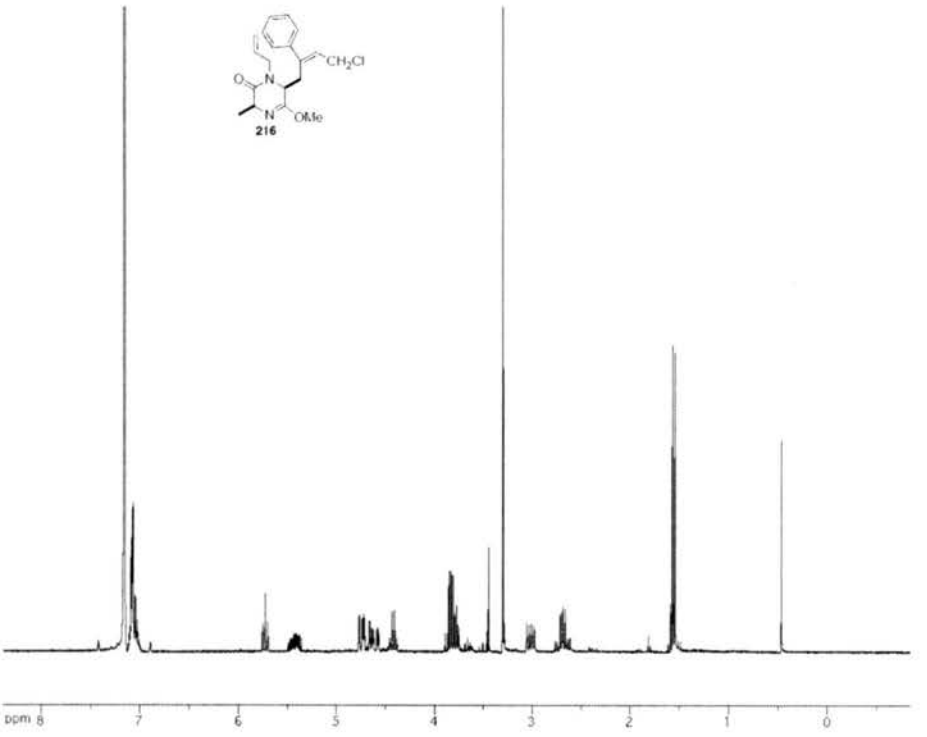
^{13}CNMR, C_6D_6, 75 MHz, filename: csy603-1-c13



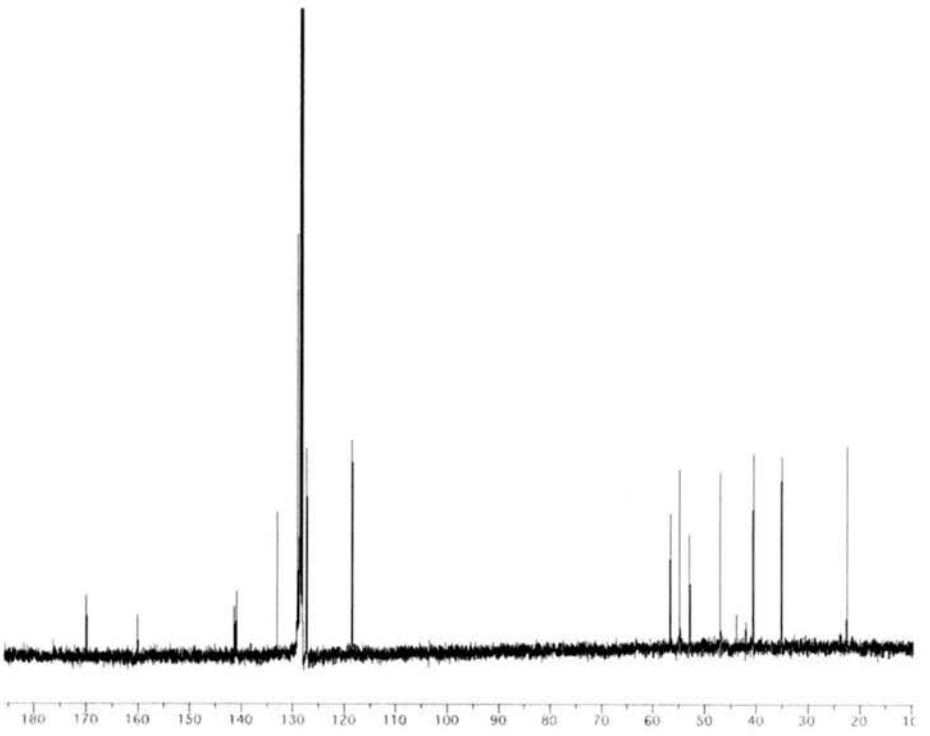
^{1}HNMR, C_6D_6, 300 MHz, filename: csy604-1



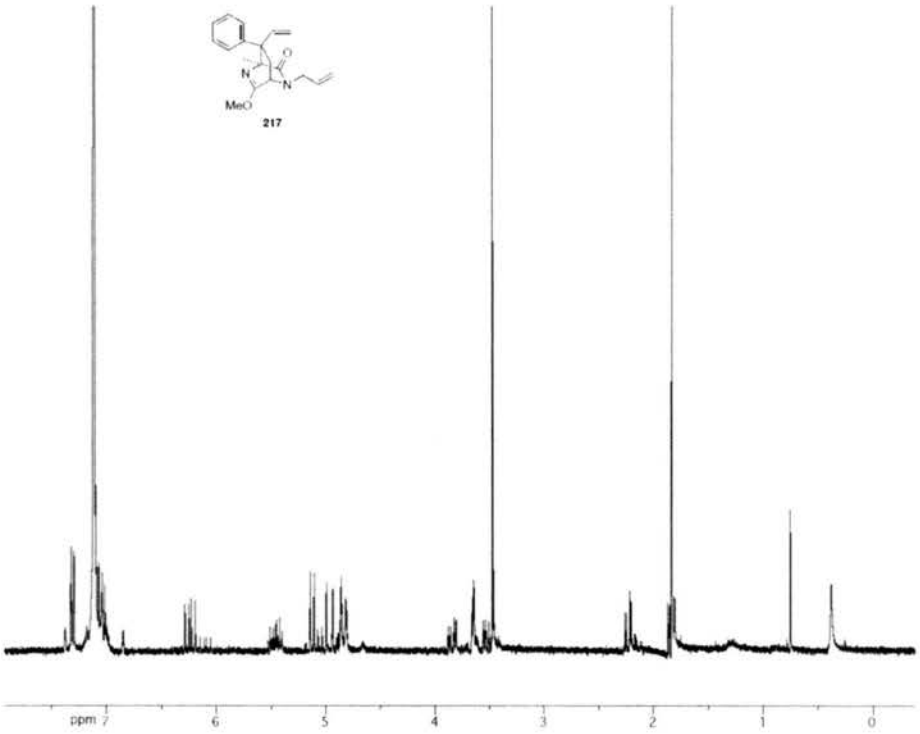
^{13}CNMR, C_6D_6, 75 MHz, filename: csy604-1-c13



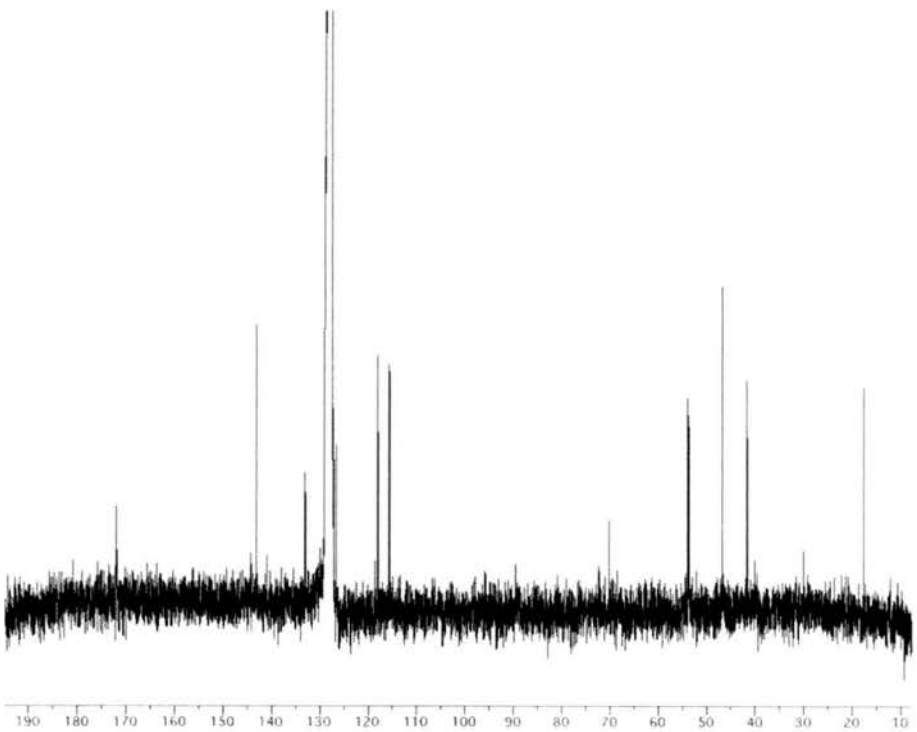
^{1}HNMR, C_6D_6, 300 MHz, filename: csy605-1



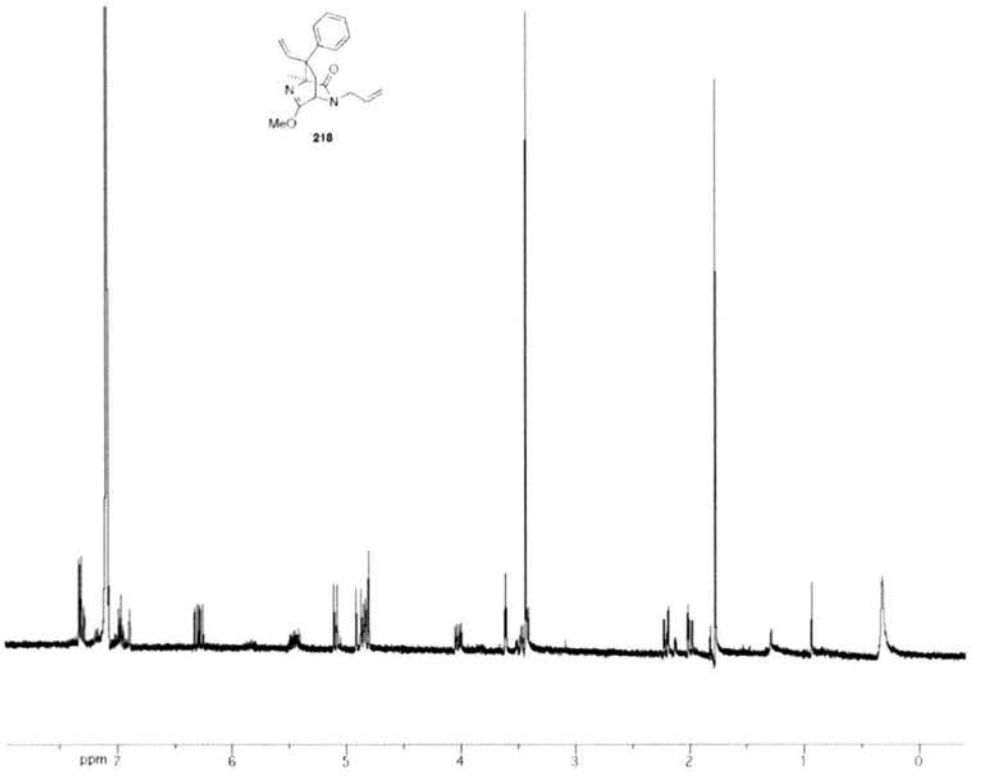
^{13}CNMR, C_6D_6, 100 MHz, filename: csy605-1-c13



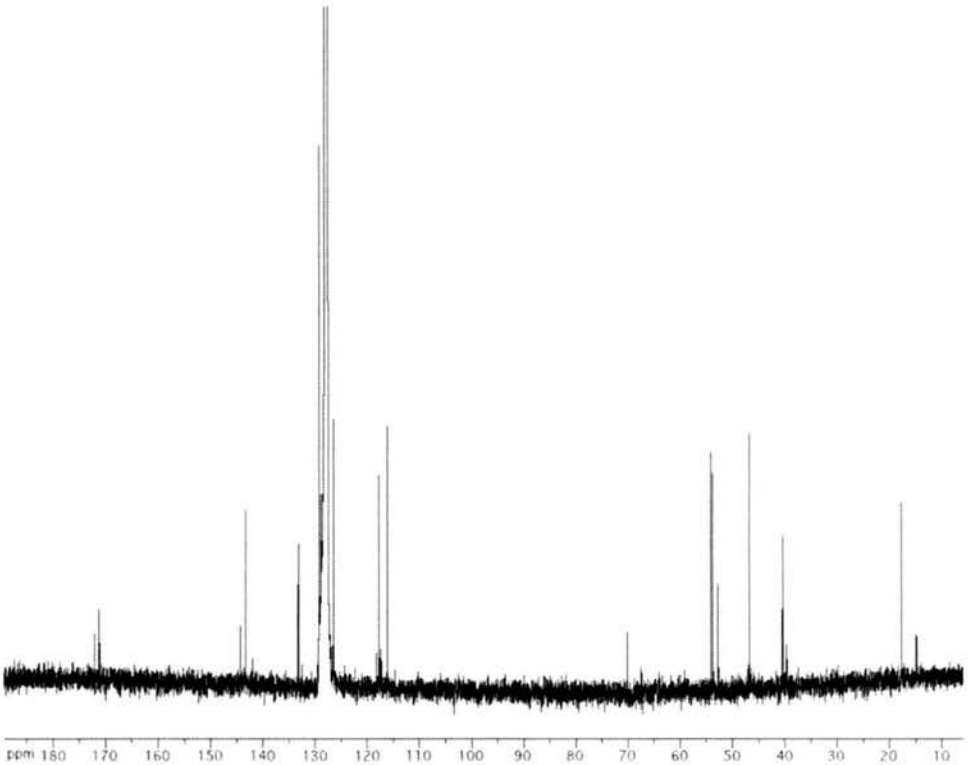
^{1}HNMR, C_6D_6, 300 MHz, filename: csy607-2



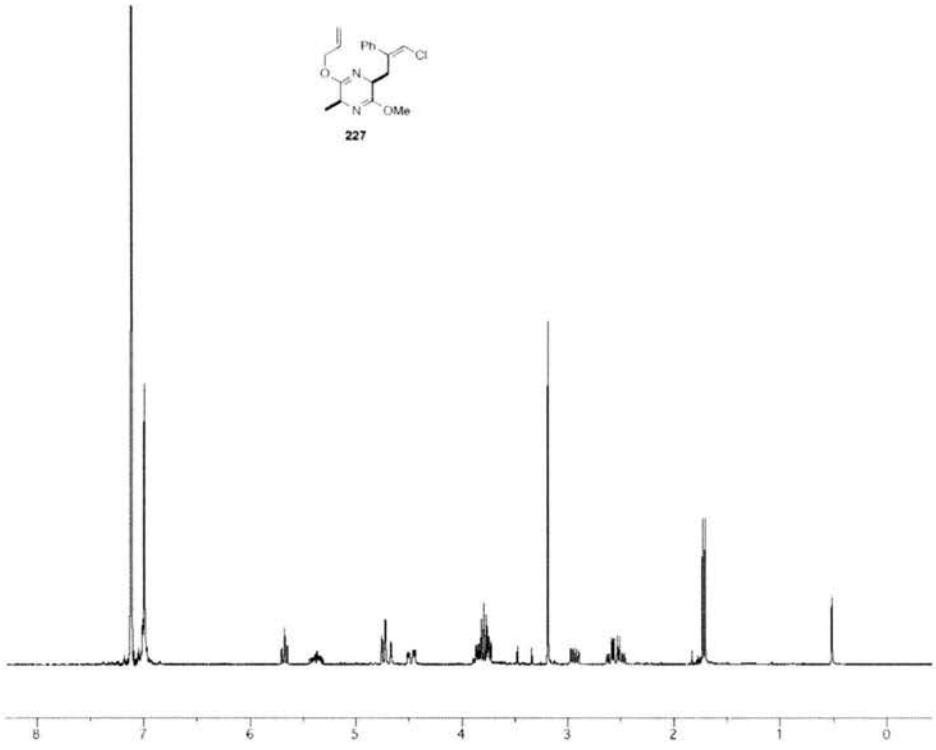
^{13}CNMR, C_6D_6, 100 MHz, filename: csy607-2-c13



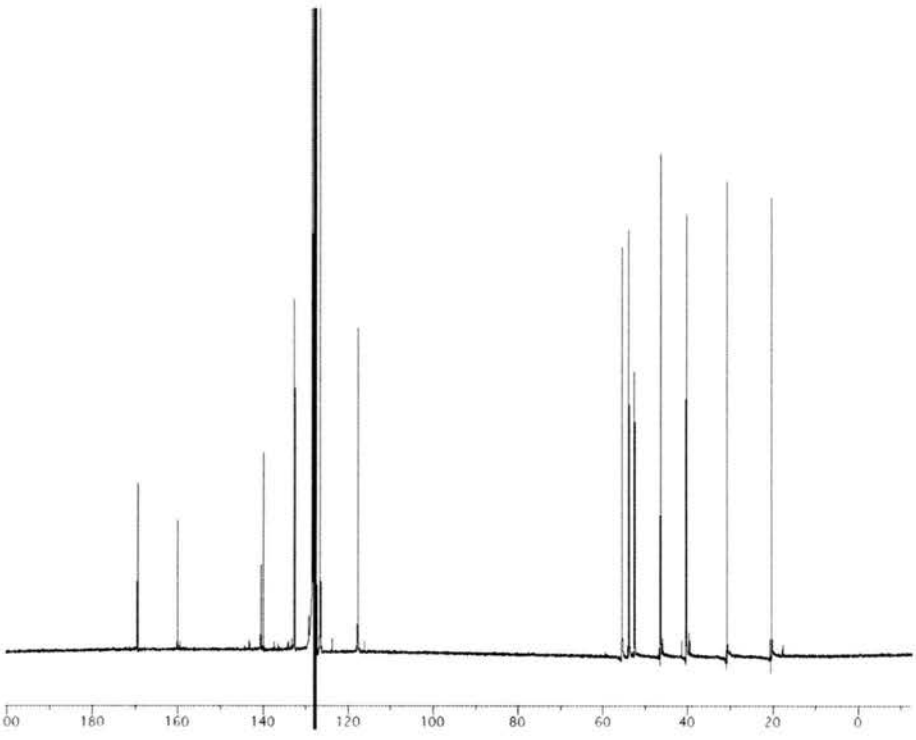
^{1}HNMR, C_6D_6, 400 MHz, filename: csy607-1



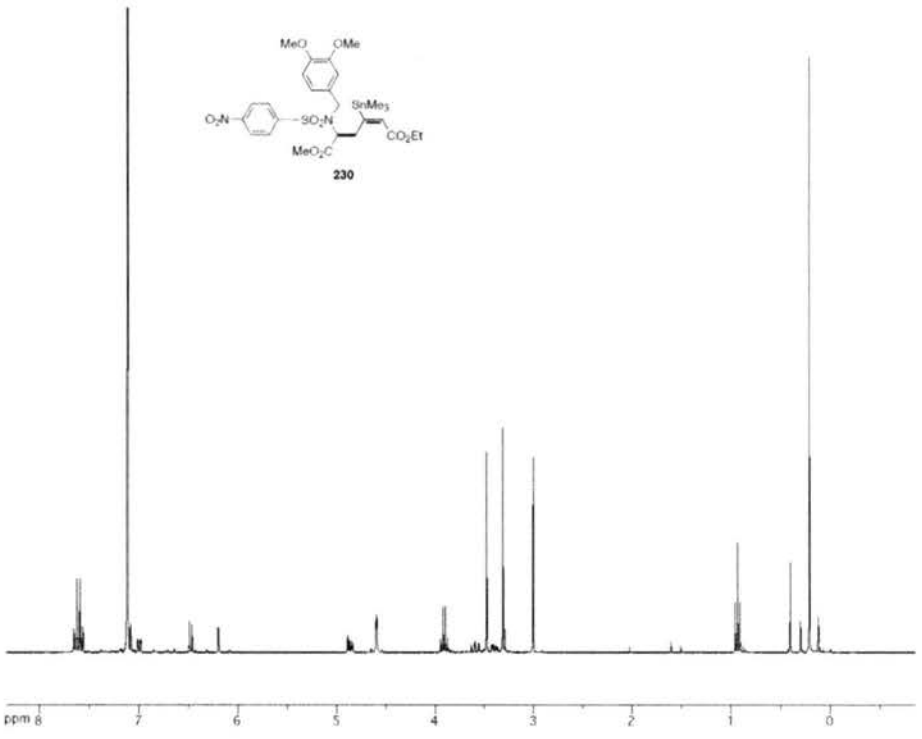
^{13}CNMR, C_6D_6, 100 MHz, filename: csy607-1-c13



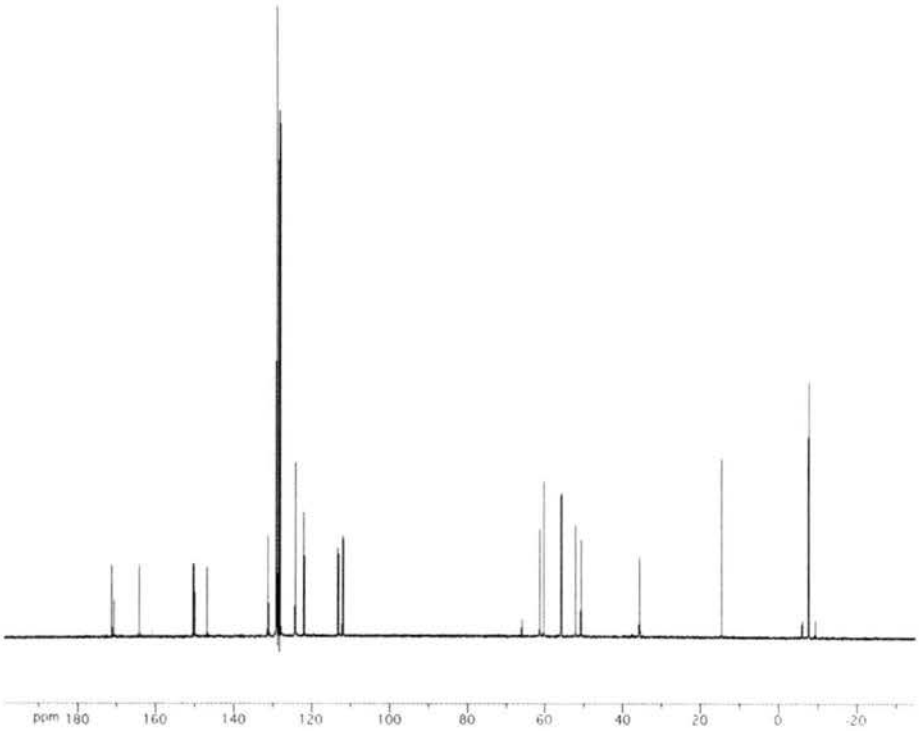
^{1}HNMR, C_6D_6, 300 MHz, filename: csy681-2



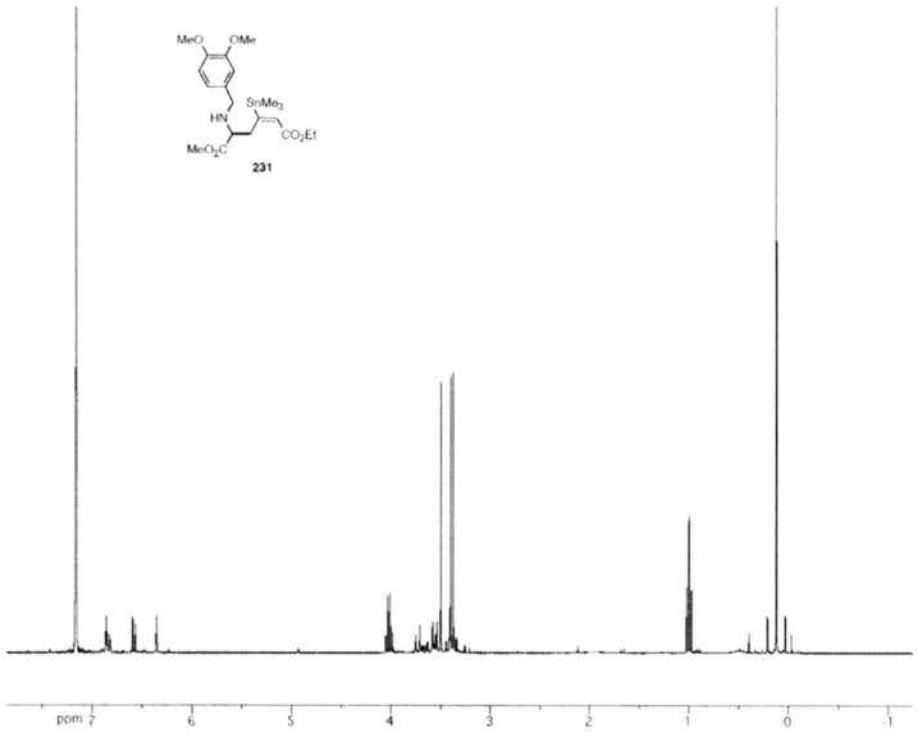
^{13}CNMR, C_6D_6, 75 MHz, filename: csy681-2-c13



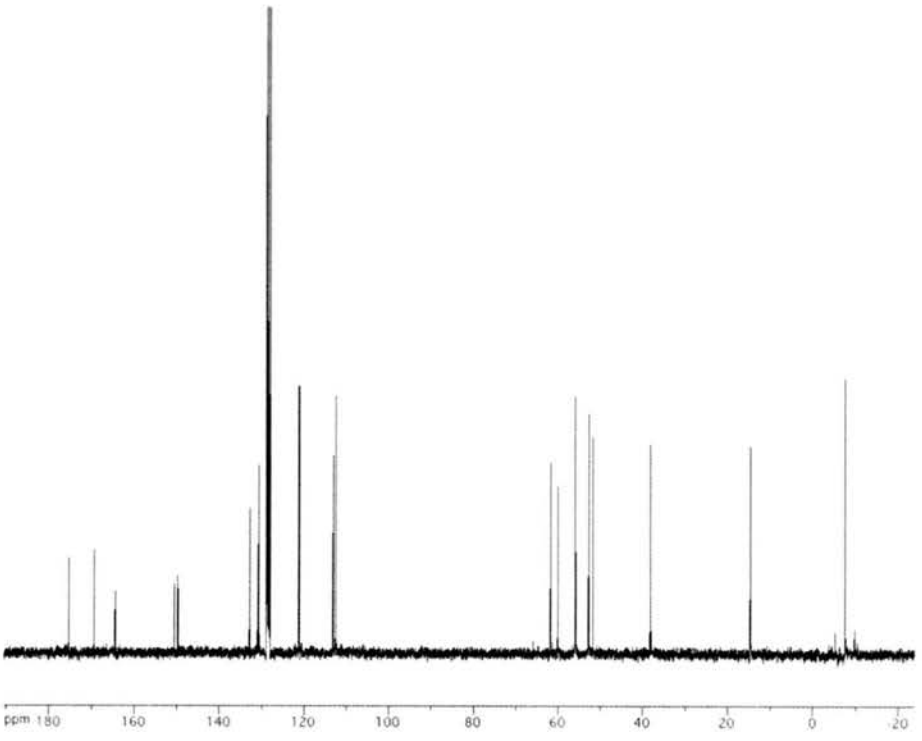
^{1}HNMR, C_6D_6, 300 MHz, filename: csy684-1



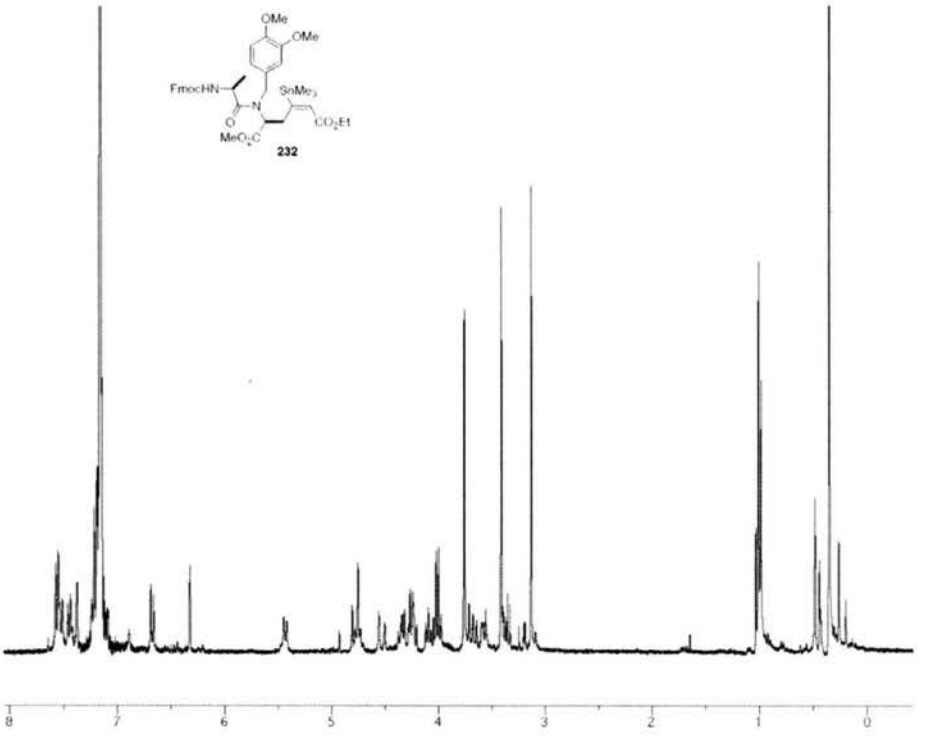
^{13}CNMR, C_6D_6, 100 MHz, filename: csy684-1-c13



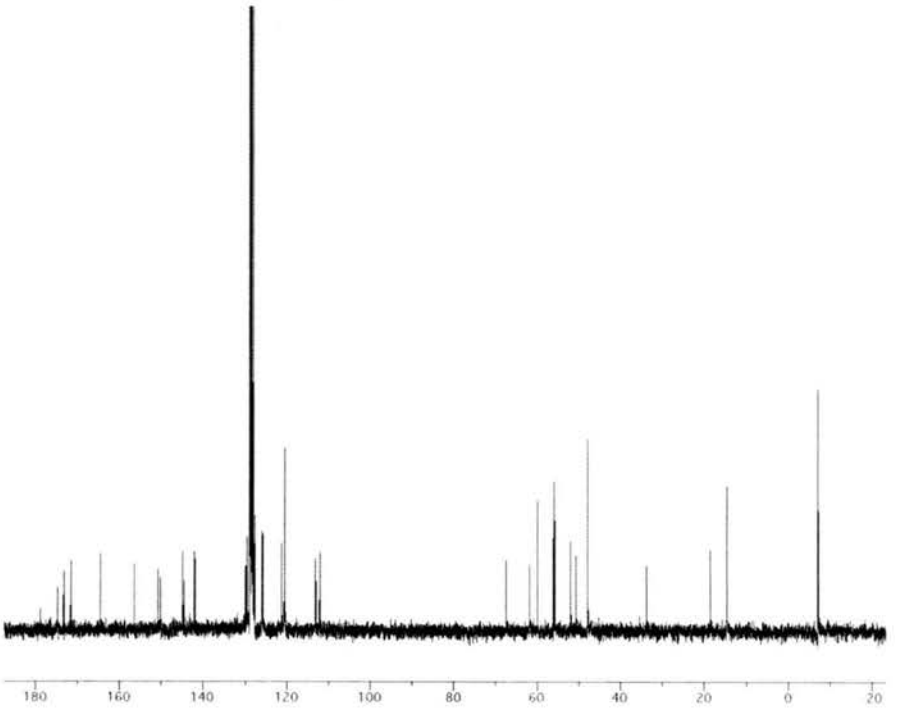
^{1}HNMR, C_6D_6, 300 MHz, filename: csy685-1



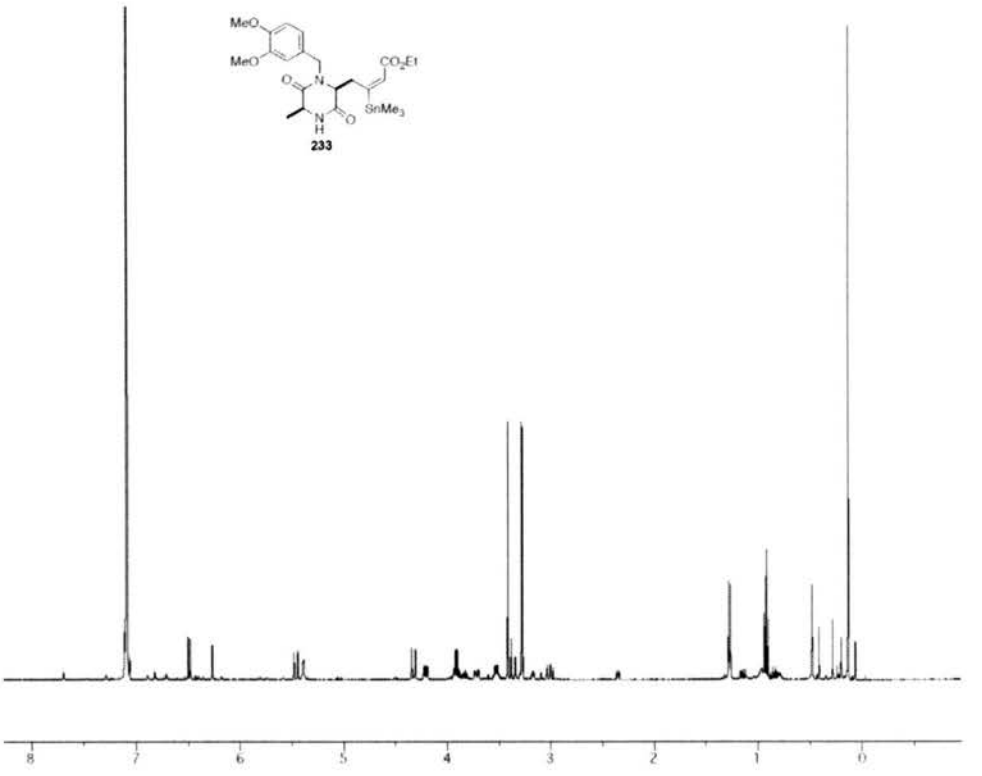
^{13}CNMR, C_6D_6, 100 MHz, filename: csy685-1-c13



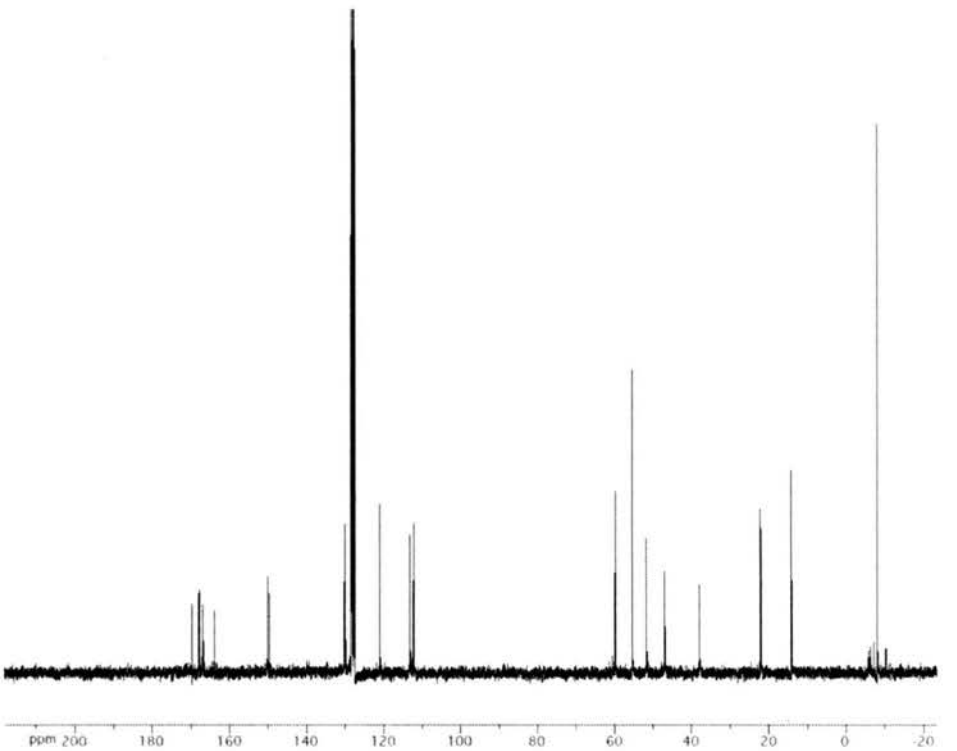
^{1}HNMR, C_6D_6, 300 MHz, filename: csy686-1



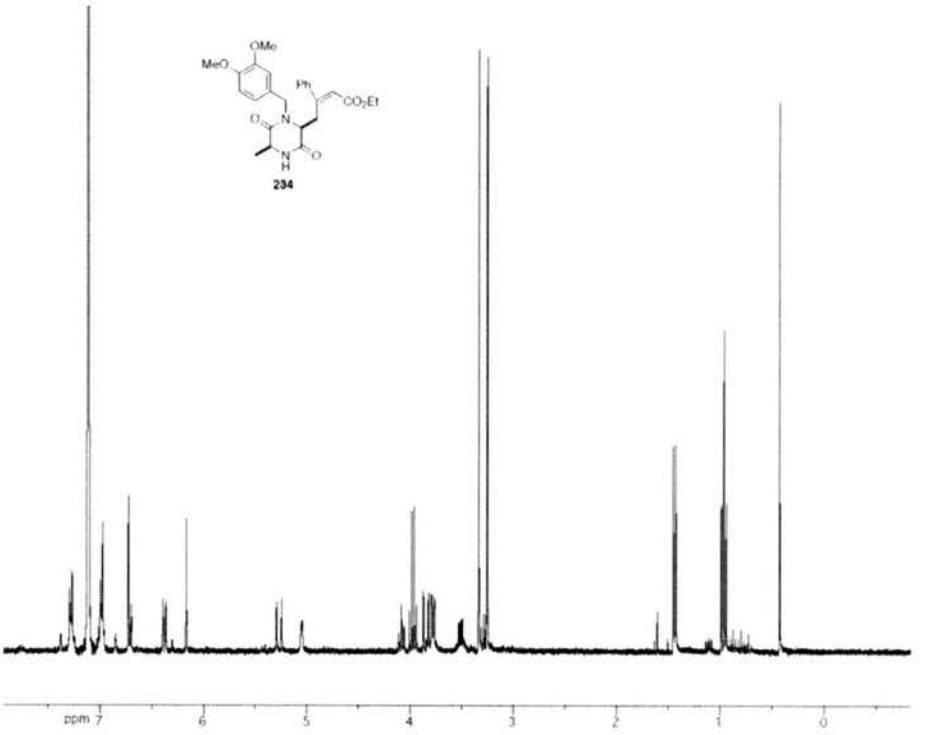
^{13}CNMR, C_6D_6, 75 MHz, filename: csy686-1-c13



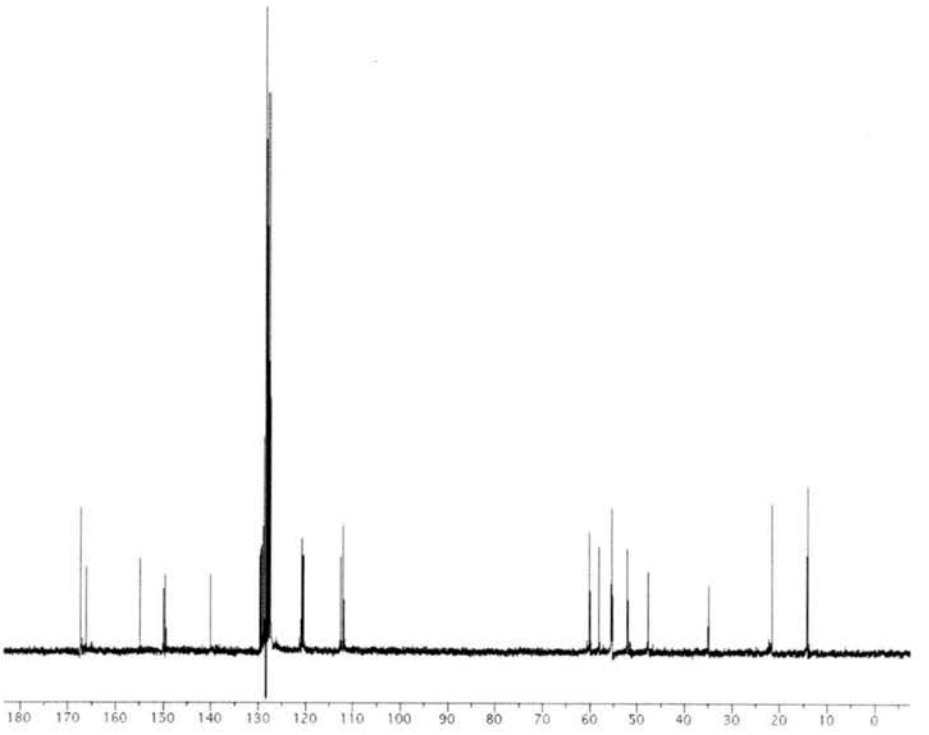
^{1}HNMR, C_6D_6, 300 MHz, filename: csy687-1-1



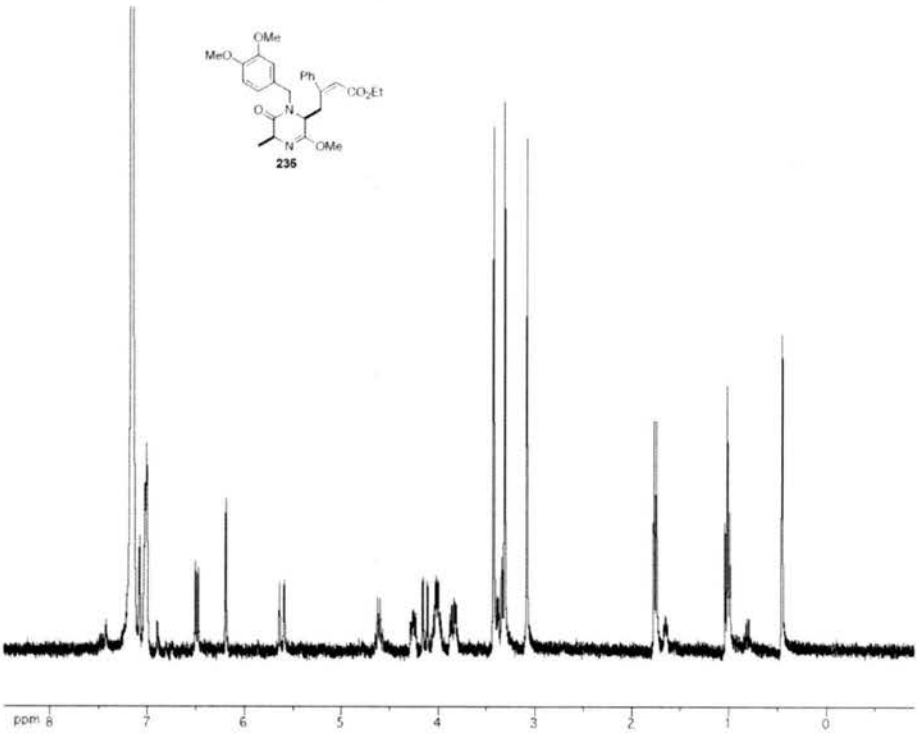
^{13}CNMR, C_6D_6, 75 MHz, filename: csy687-1



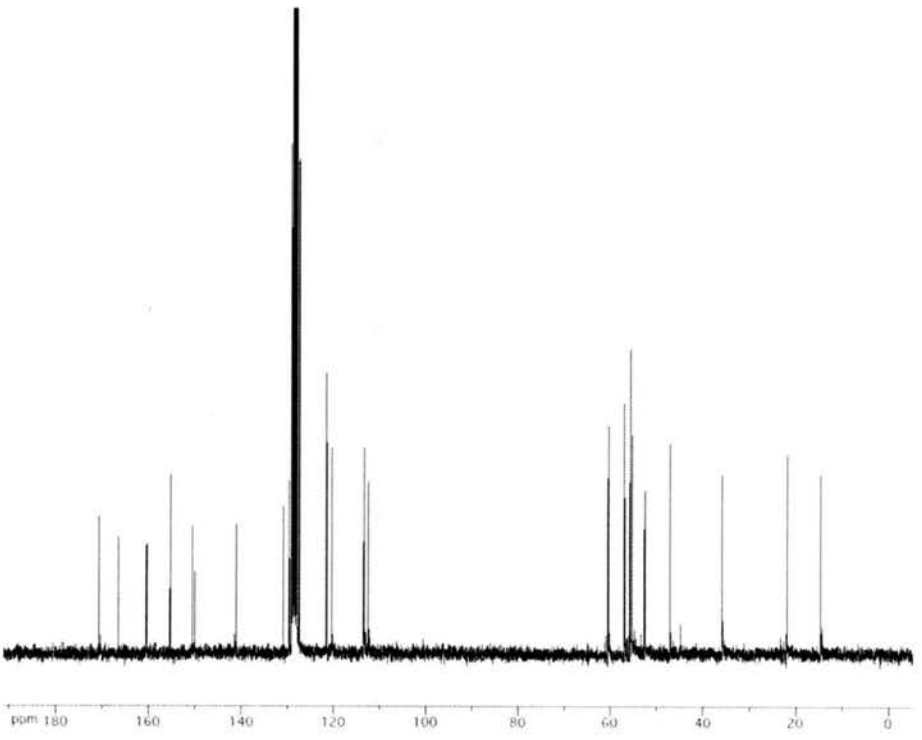
^{1}HNMR, C_6D_6, 400 MHz, filename: csy693-1



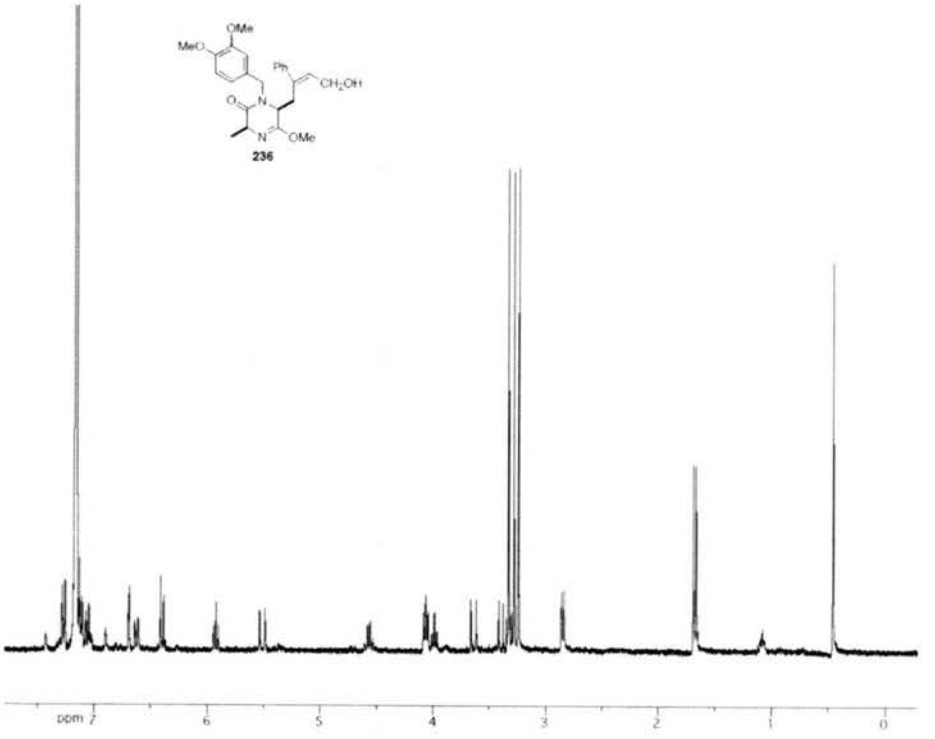
^{13}CNMR, C_6D_6, 75 MHz, filename: csy693-1-c13



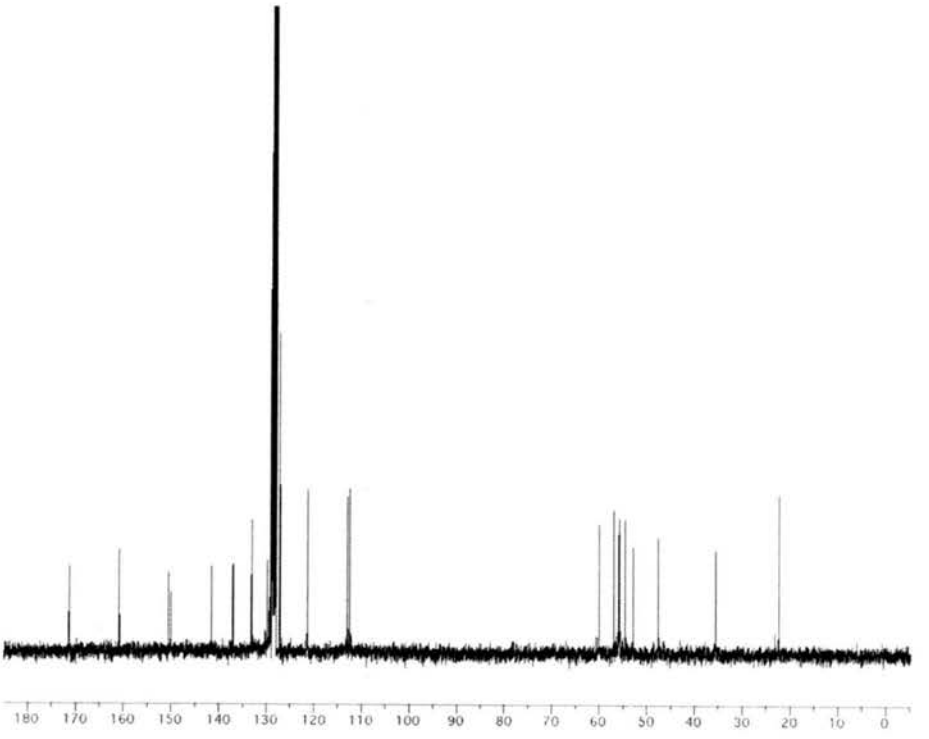
^{1}HNMR, C_6D_6, 300 MHz, filename: csy694-1



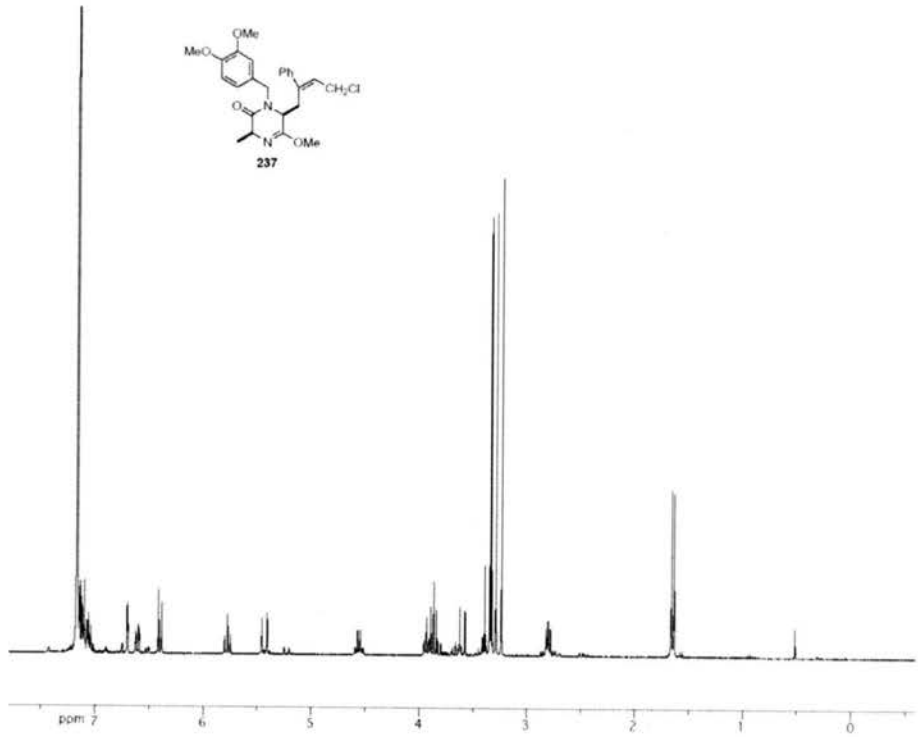
^{1}HNMR, C_6D_6, 75 MHz, filename: csy694-1-c13



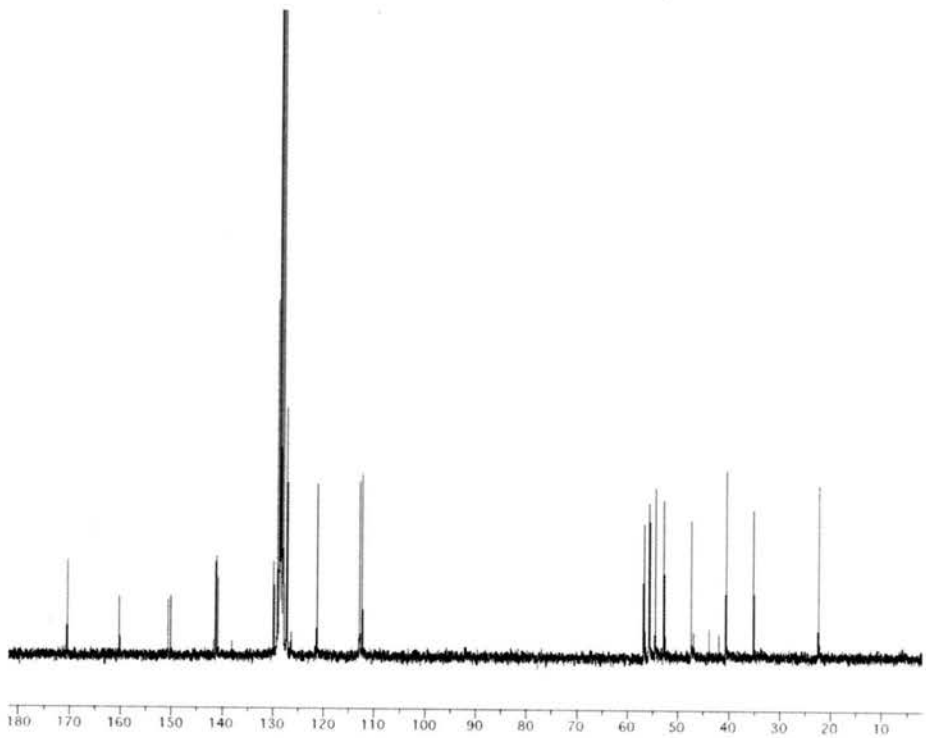
^{1}HNMR, C_6D_6, 300 MHz, filename: csy695-1



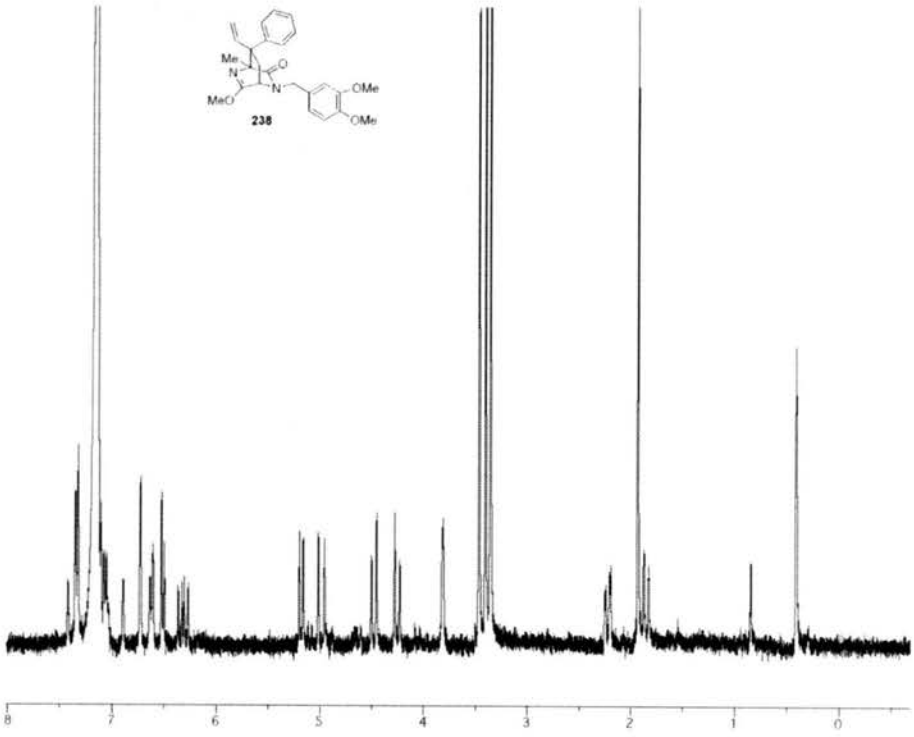
^{13}CNMR, C_6D_6, 75 MHz, filename: csy695-1-c13



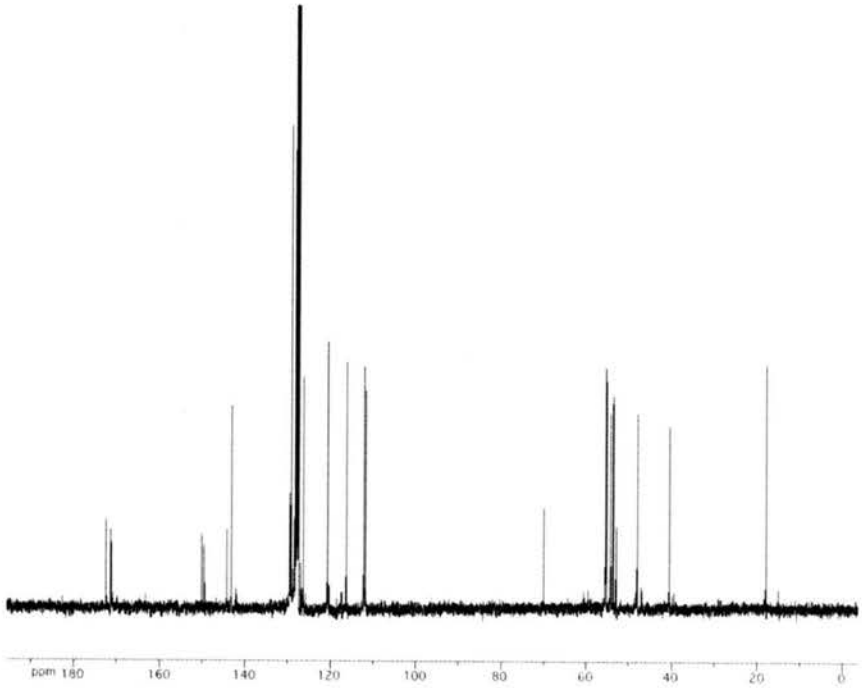
^{1}HNMR, C_6D_6, 300 MHz, filename: csy696-1



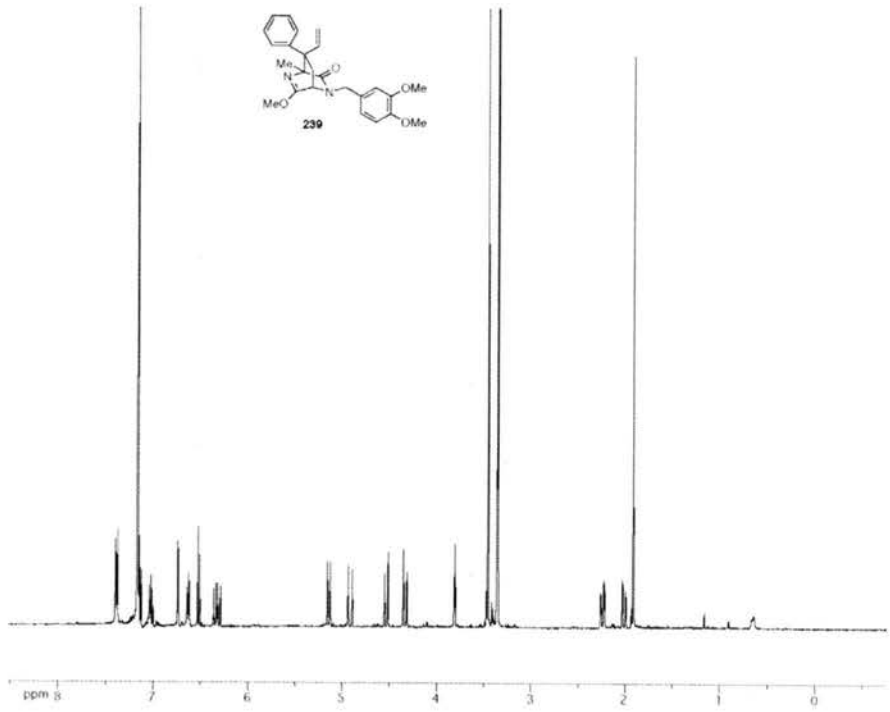
^{13}CNMR, C_6D_6, 75 MHz, filename: csy696-1-c13



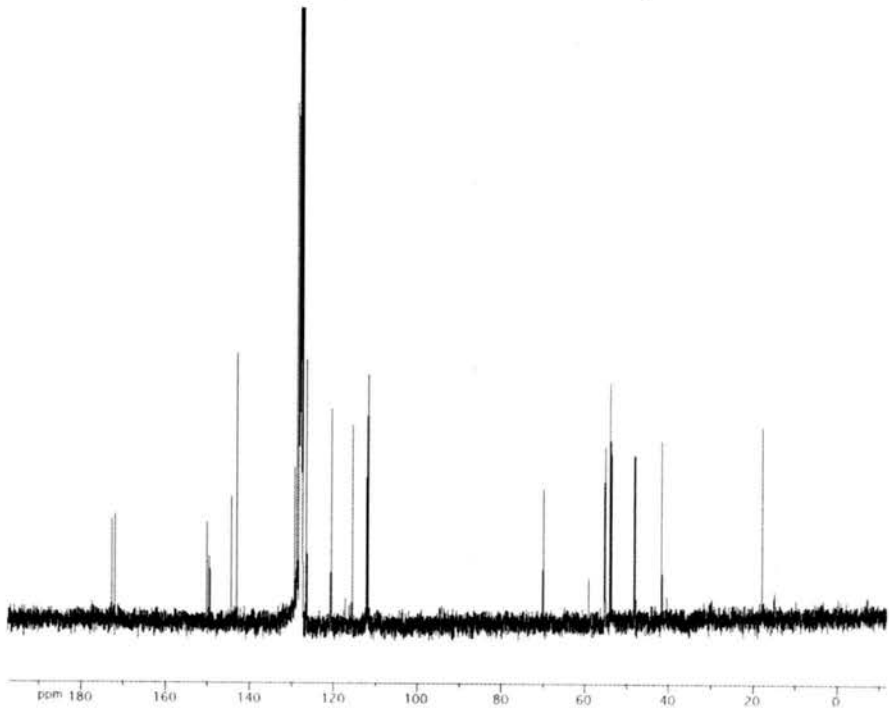
^{1}HNMR, C_6D_6, 300 MHz, filename: csy697-2



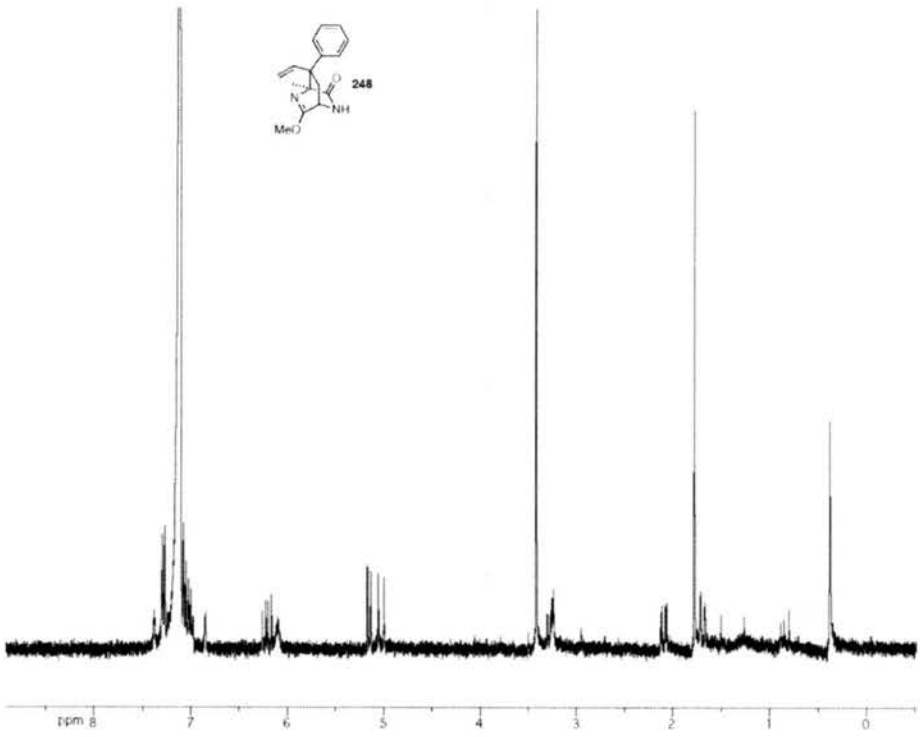
^{1}HNMR, C_6D_6, 75 MHz, filename: csy697-2-c13



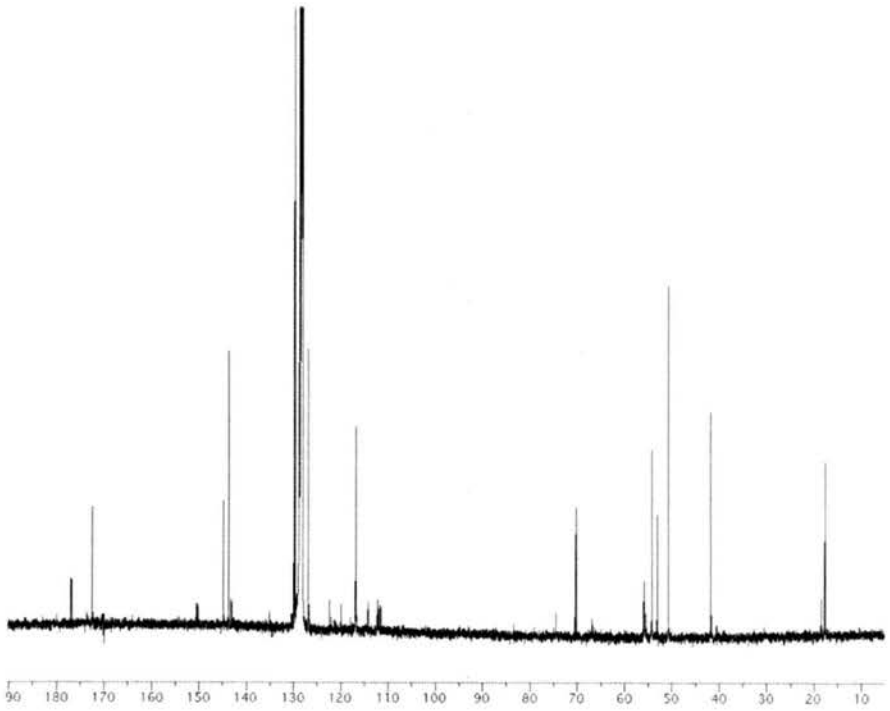
^{1}HNMR, C_6D_6, 300 MHz, filename: csy697-3



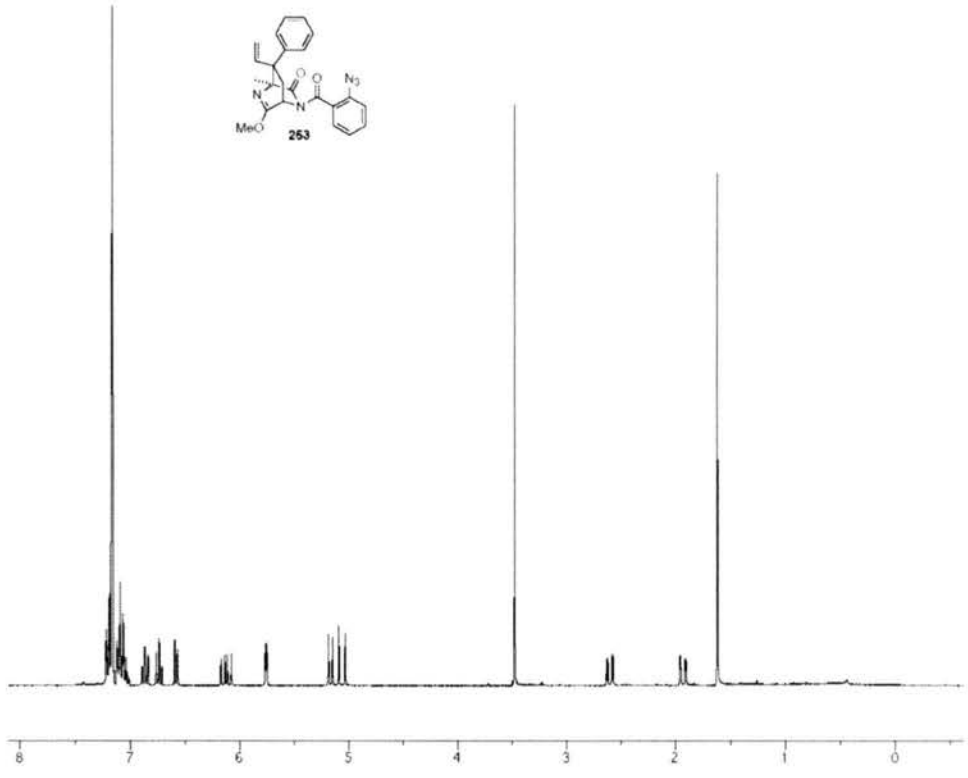
^{13}CNMR, C_6D_6, 75 MHz, filename: csy697-3-c13



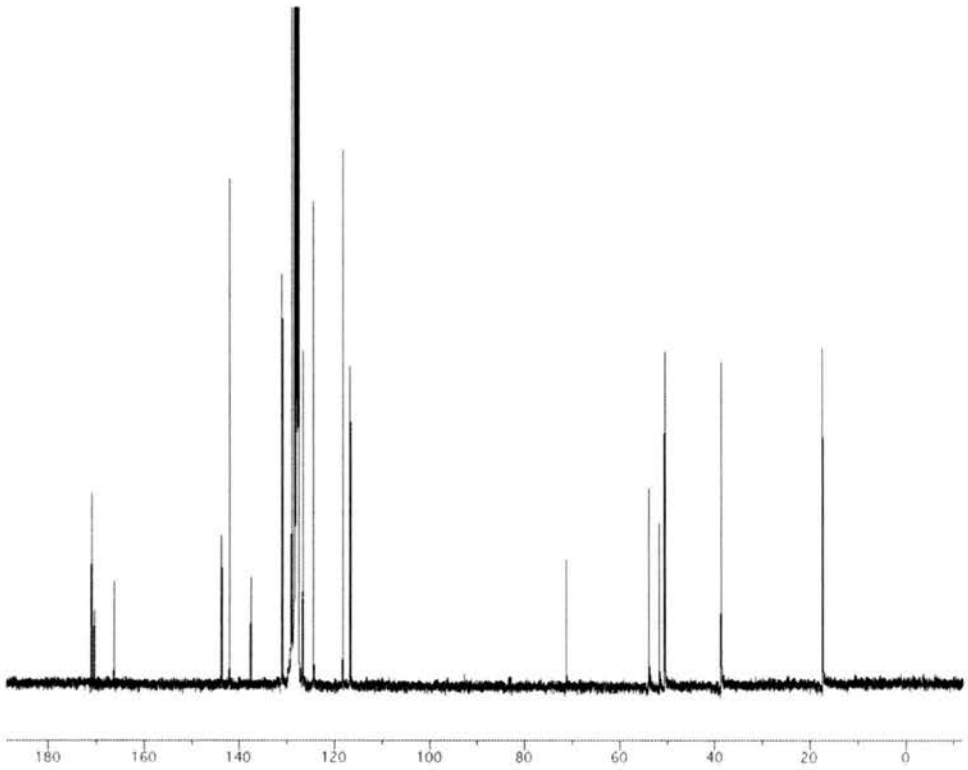
^{1}HNMR, C_6D_6, 300 MHz, filename: csy703-1



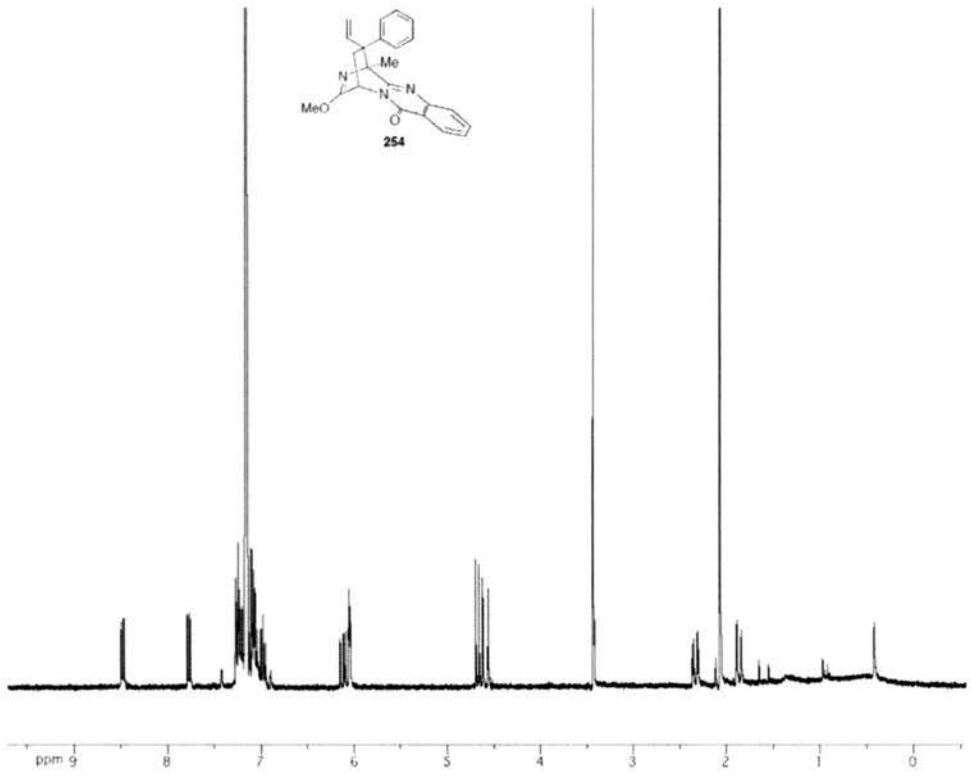
^{13}CNMR, C_6D_6, 100 MHz, filename: csy703-1-c13



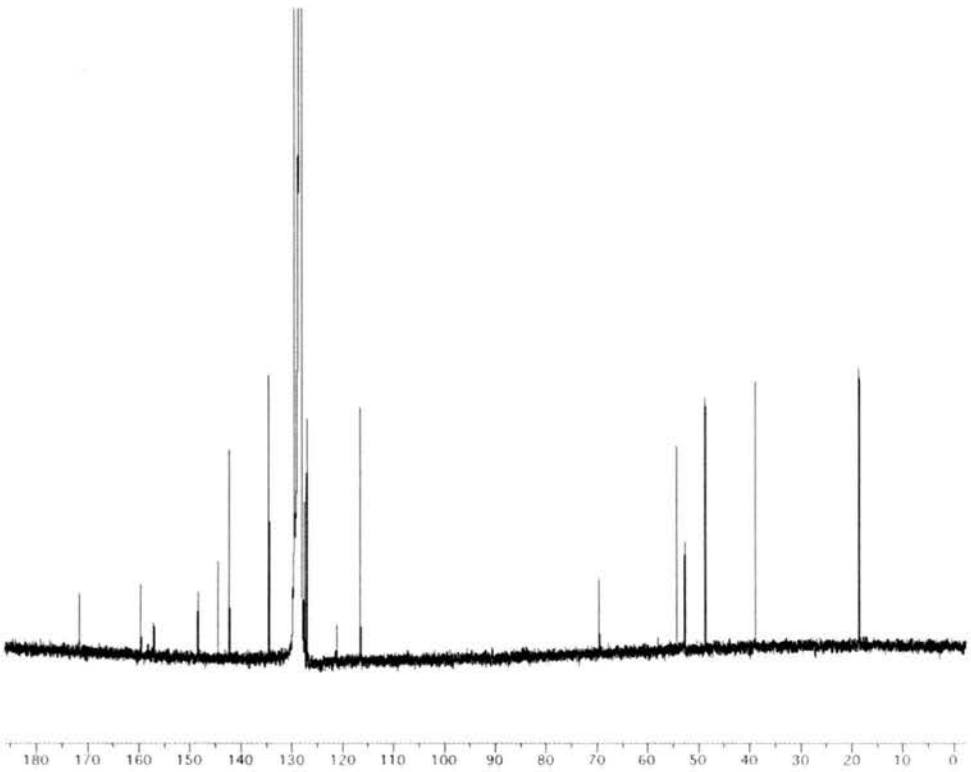
^{1}HNMR, C_6D_6, 300 MHz, filename: csy704-1



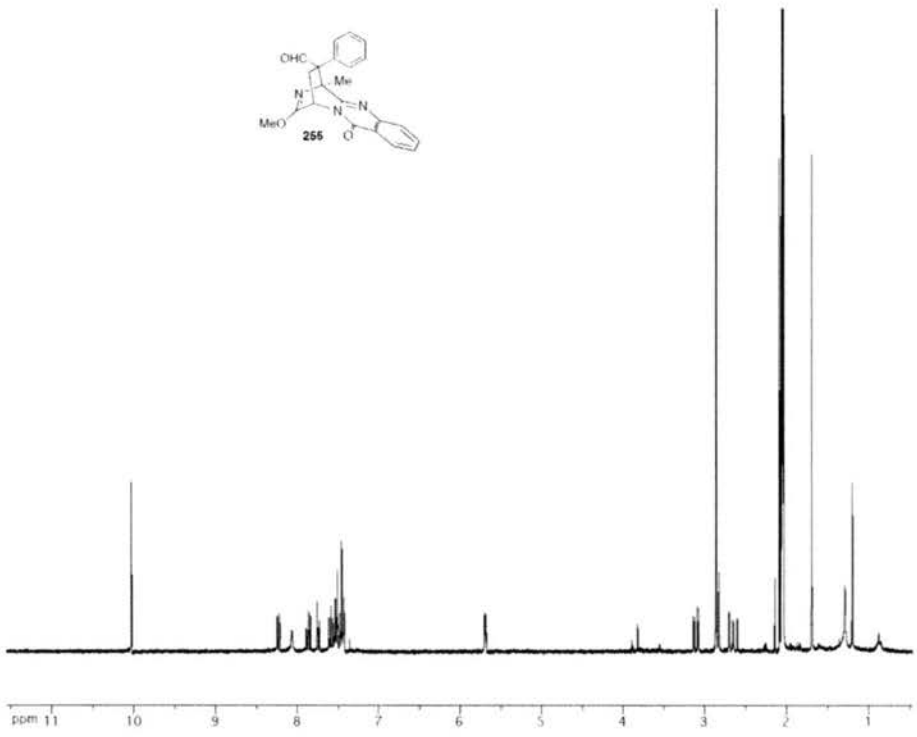
^{13}CNMR, C_6D_6, 75 MHz, filename: csy704-1-c13



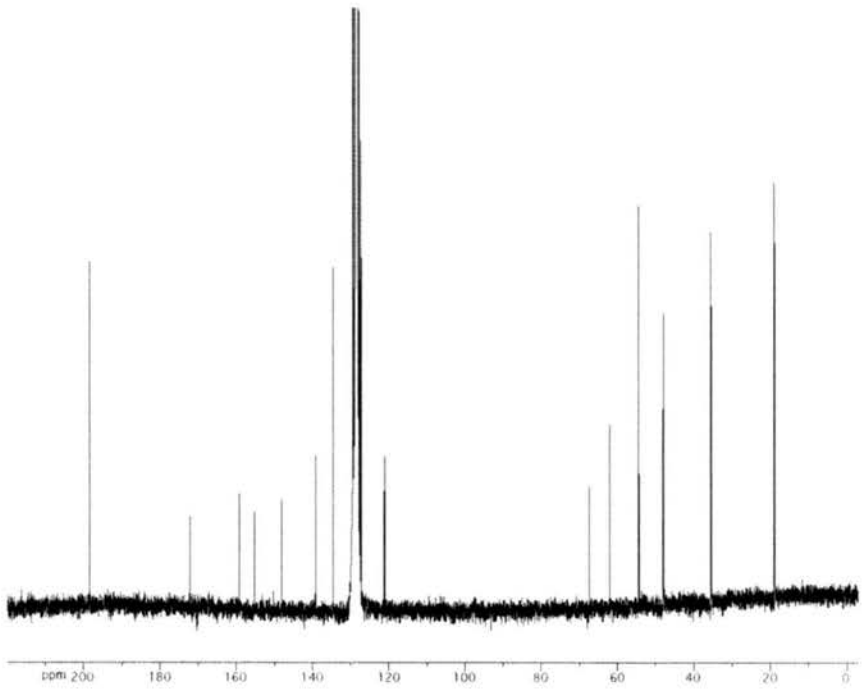
^{1}HNMR, C_6D_6, 300 MHz, filename: csy705-1



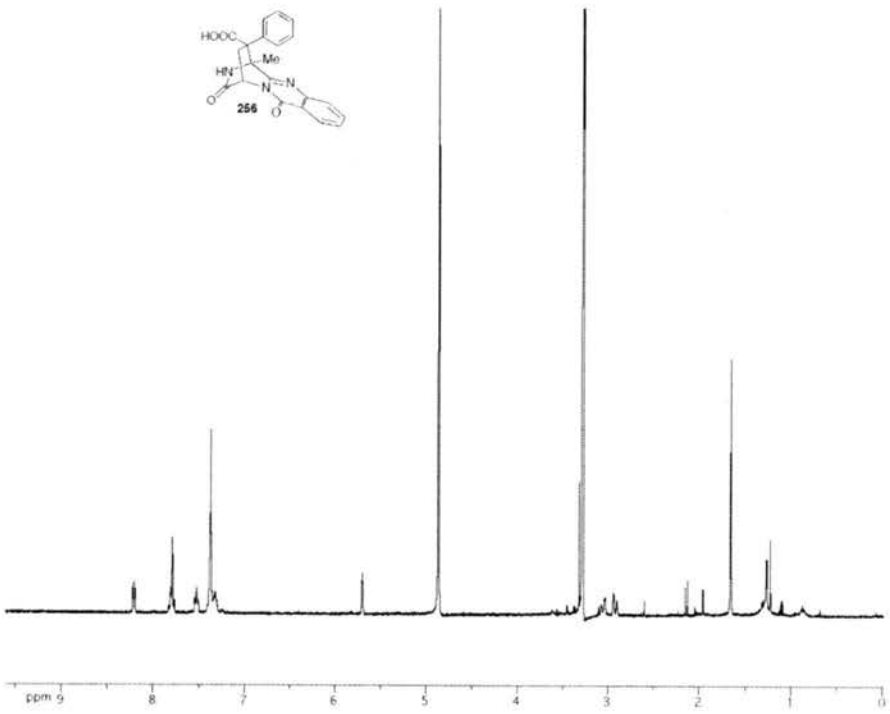
^{13}CNMR, C_6D_6, 100 MHz, filename: csy705-1-c13



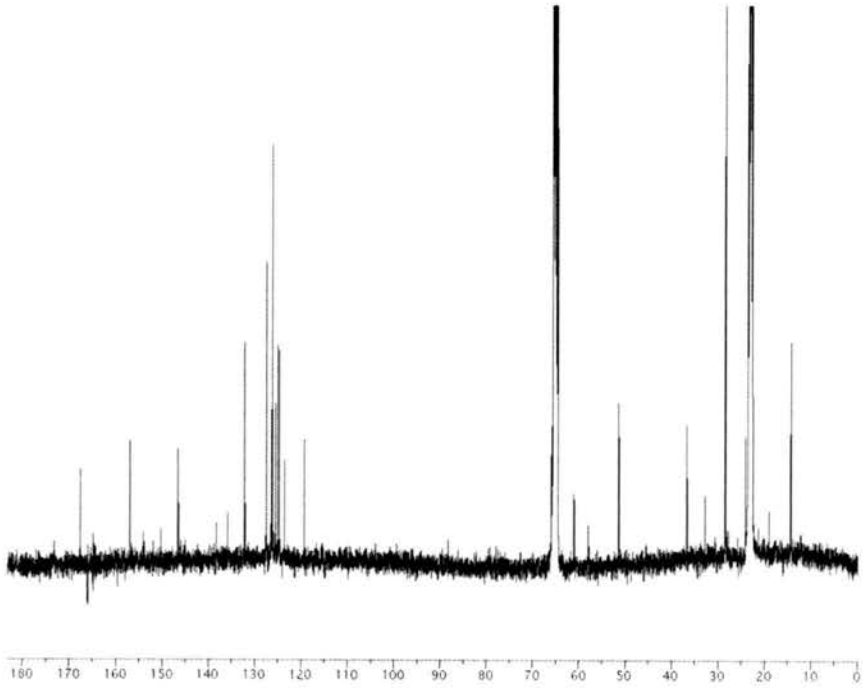
^{1}HNMR, C_6D_6, 400 MHz, filename: csy706-1



^{13}CNMR, C_6D_6, 100 MHz, filename: csy706-1-c13



^{1}HNMR, CD_3OD, 400 MHz, filename: csy714-1



^{13}CNMR, CD_3OD, 100 MHz, filename: csy714-1-c1