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FRAGMENTATIONS OF BICYCLIC KETOESTERS AND SYNTHETIC EFFORTS TOWARD ELEUTHEROBIN

By

Qing Xu

A Dissertation Submitted to the Faculty of the

DEPARTMENT OF CHEMISTRY

In Partial Fulfillment of the Requirements
For the Degree of

DOCTOR OF PHILOSOPHY

In the Graduate College

THE UNIVERSITY OF ARIZONA

2002

THE UNIVERSITY OF ARIZONA ®
GRADUATE COLLEGE

As members of the Final Examination Committee, we certify that we have read the dissertation prepared by qing xu

entitled Fragmentations of Bicyclic Keto-esters and Efforts Toward the Synthesis of Eleutherobin

and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy

Jon D Rainier	03/07/02 Date
Michael F. Brown	7 March, 2002 Date
Eugene A. Mash Jr	3-7-02 Date
Robin L Polt	7 March 2002 Date
	3/7/02 Date

Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copy of the dissertation to the Graduate College.

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Jon D Rainier — Dissertation Director

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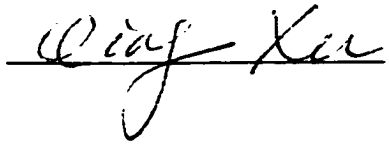
Signed: 

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DEDICATION

To Mom and Dad

for encouragement.

To Yingqing

I love you forever!

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LIST OF ABBREVIATIONS

Ac	Acetyl
acac	Acetylacetonyl
AIBN	2,2'-Azobisisobutyronitrile
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
Boc	tert-Butyloxycarbonyl
t-BuOH	tert-Butyl alcohol
18-C-6	18-Crown-6
Cbz	Benzyloxycarbonyl
COSY	Correlation Spectroscopy
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-4,5-dicyano-1,4-quinone
DET	Diethyl tartrate
DIBAL-H	Diisopropylaluminum hydride
DIPEA	Diisopropylethylamine
DMAD	Dimethylacetylenedicarboxylate
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMF	Dimethylformamide

DMP	Dess-Martin periodinane
DMSO	Methyl sulfoxide
EtOH	Ethanol
HMBC	Heteroatom Multiple Bond Correlation Spectroscopy
HMPA	Hexamethylphosphoramide
IBX	*o*-Iodoxybenzoic acid
LAH	Lithium aluminum hydride
IMDA	Intramolecular Diels-Alder
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
KHMDS	Potassium hexamethyldisilazide
mCPBA	3-Chloroperoxybenzoic acid
MeOH	Methanol
MOM	Methoxymethyl
Ms	Methanesulfonyl
NaHMDS	Sodium hexamethyldisilazide
NBS	N-Bromosuccinamide
NOE	Nuclear Overhauser Effect
NMO	N-Methylmorpholine N-oxide
PCC	Pyridinium chlorochromate
Piv	Pivaloyl
PMB	4-Methoxybenzyl

PPTS	Pyridinium p-toluenesulfonate
Red-Al	Sodium bis(2-methoxyethoxy)aluminum hydride
SAE	Sharpless asymmetric epoxidation
TASF	Tris(dimethylamino)sulfur (trimethylsilyl)difluoride
TBA	Tetrabromoacetone
TBDPS	tert-Butyldiphenylsilyl
TBS	tert-Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TPAP	Tetrapropylammonium perruthenate
TMANO	Trimethylamino N-oxide
TsOH	Toluenesulfonic acid

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ABSTRACT

An unprecedented anionic condensation, fragmentation, and elimination sequence from the coupling of bicyclo[2.2.1]heptenones with aldehydes is described. This reaction leads to the stereoselective formation of disubstituted five-membered rings which are present in a wide array of bioactive molecules. Oxabicyclo[2.2.1]heptenone **106** also undergoes two-carbon ring expansions when subjected to anionic conditions and Michael acceptors. As an outgrowth of this interesting chemistry, we have been able to access the carbon skeleton of oxygenated cembranoids by subjecting bis-activated ene-yne to the enolate from oxabicyclo[2.2.1]heptenone **106**.

In order to demonstrate the synthetic utility of the anionic condensation, fragmentation, and elimination reaction, we have applied it to the synthesis of nortetillapyrone.

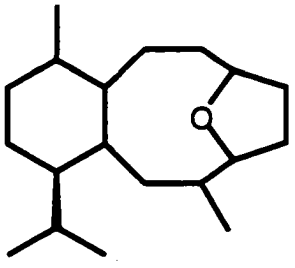
Chapter 1 Introduction

1. 1 Oxygenated Cembranoid Containing Natural Products

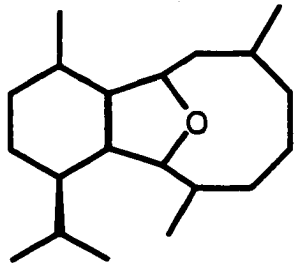
A large number of oxygenated cembranoid containing natural products have been isolated over the last thirty years.[1] As depicted in Figure 1.1, this family includes the sarcodictyins, the cladiellins, the briarellins, and the asbestinins. These marine metabolites have in common a cyclized cembranoid skeleton along with an oxygen bridge. Among the oxygenated cembranoids, the sarcodictyins have received the most attention. This class has the ability to stabilize microtubules and includes eleutherobin,[2-7] sarcodictyin,[8-9] and valdivone.[10] Its members, and especially eleutherobin, show a very similar biological profile to paclitaxel.[3] Another class of molecules within the oxygenated cembranoid family are the cladiellins or eunicellins.[11] These are the most abundant members of this family and show a varied and interesting biological profile. The eunicellins have demonstrated antiflammatory and antitumor properties along with the ability to inhibit the growth of insects.[12] The other two members of the oxygenated cembranoids are the briarellins[13] and the asbestinins[14]. The briarellins have demonstrated moderate toxicity toward HeLa cells.[13] The asbestinins have shown antitumor and antimicrobial activity along with histamine and acetylcholine antagonism.[14] Due to their impressive biological activity and their fascinating structural features, the oxygenated cembranoid family of natural products has received a significant amount of attention from the synthetic chemistry community. To date, this attention has led to the total

synthesis of several members of this family (eleutherobin,[3-5] eleuthosides A and B,[15] sarcodictyin A and B,[16] 7-deacetoxyalcyonin acetate,[17] and sclerophytin A and B[18]), along with a number of approaches to their synthesis.[19-25]

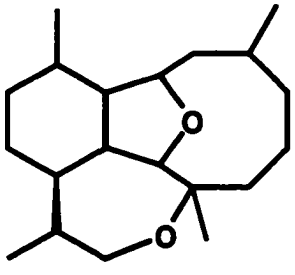
Fig 1.1 Oxygenated Cembranoids



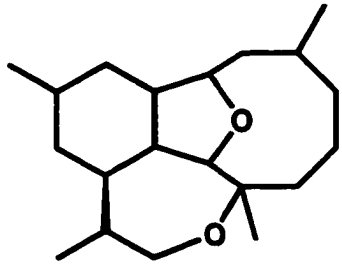
Sarcodictyins



Cladiellins(eunicellins)



Briarellins



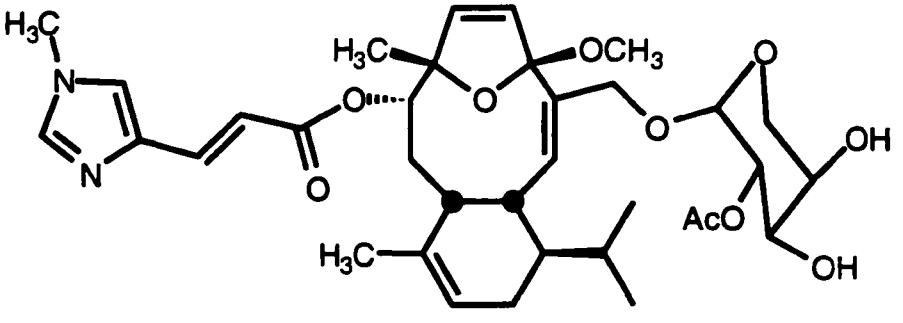
Asbestinins

1.2 Biology and Chemistry of Eleutherobin

1.2.1 The Isolation and Biological Activity of Eleutherobin

In 1995, Fenical et al. disclosed in a patent[26] the isolation and structure of a marine natural product with potent cytotoxicity, which they called eleutherobin (Fig 1.2). Isolated from an Eleutherobia species of soft coral (possibly *E. albiflora* Alcynacea, Alcynacea collected from the Indian Ocean near Bennett's Shoal in Western Australia), Eleutherobin was structurally elucidated by spectroscopic means, even though its absolute stereochemistry remained unknown. In more detailed accounts in 1997, the Fenical group revealed further information about the cytotoxicity of eleutherobin and disclosed its Taxol-like mechanism of action.[3,7] Specifically it has been shown to possess cytotoxic activity with an IC_{50} of 10.7 nM against the HCT116 human colon carcinoma cancer cell line and IC_{50} of 13.8 nM against the A2780 human ovarian carcinoma cell line; its mechanism of its action involves tubulin polymerization and microtubule stabilization.

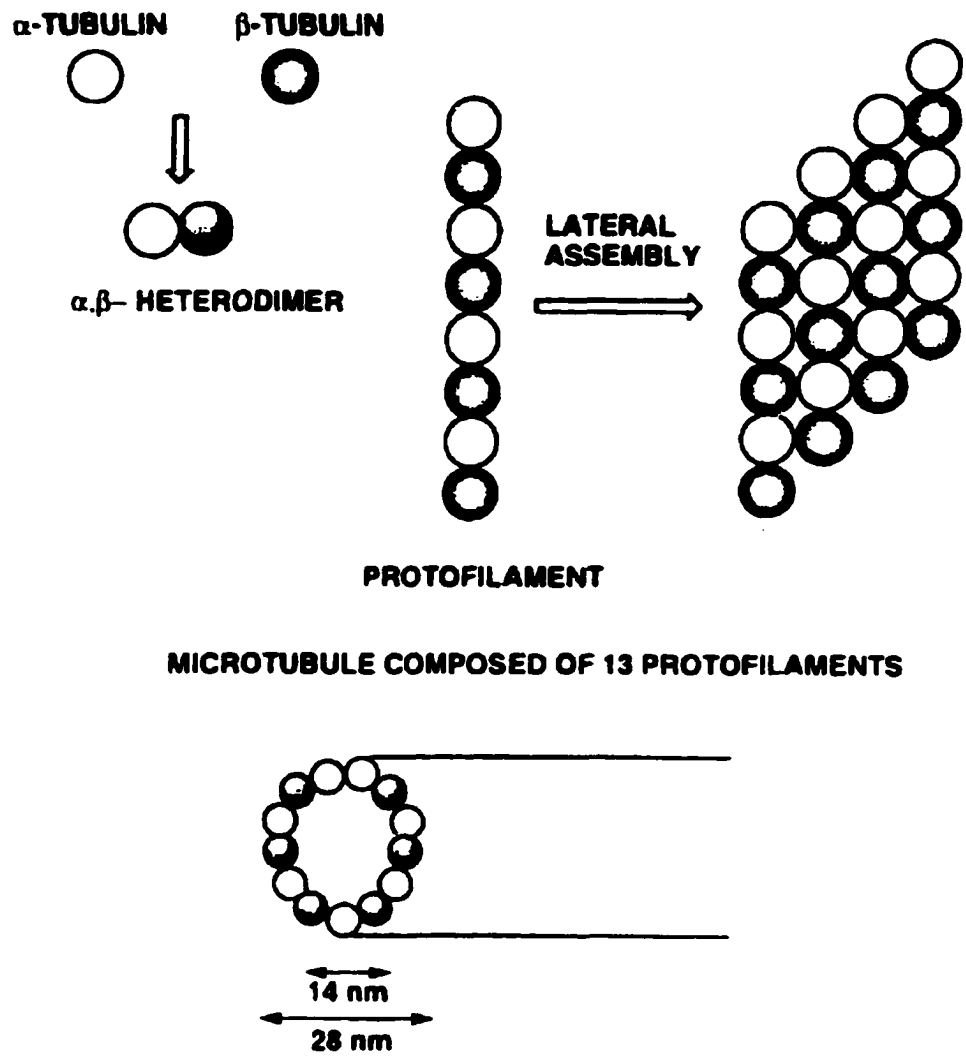
Fig 1.2 Structure of Eleutherobin



Microtubules, like DNA and RNA, are conserved structures in all eukaryotic cells with numerous and diverse functions. By forming a scaffolding network within cells, microtubules maintain cell shape. In neurons, microtubules form a track through the axons along which organelles and proteins are transported. In addition, microtubules are the primary components of the mitotic spindle, which forms during cell division. All eukaryotic cells utilize a spindle, composed of microtubules, to segregate chromosomes during mitosis.[27]

The principal component of microtubules is the protein tubulin, a heterodimer composed of two similar subunits, α and β-tubulin. The ability to reversibly assemble into microtubules (polymer) or disassemble to the tubulin heterodimer (monomer) is an intrinsic property of this protein. Alternating α- and β-tubulin assemble longitudinally into protofilaments which then join laterally with other protofilaments to form the cylindrical microtubule structure. A typical microtubule is composed of 13 protofilaments with an outer diameter of 28 nm and an inner diameter of 14 nm[27] (Fig. 1.3).

Fig 1.3 Structure of Microtubules

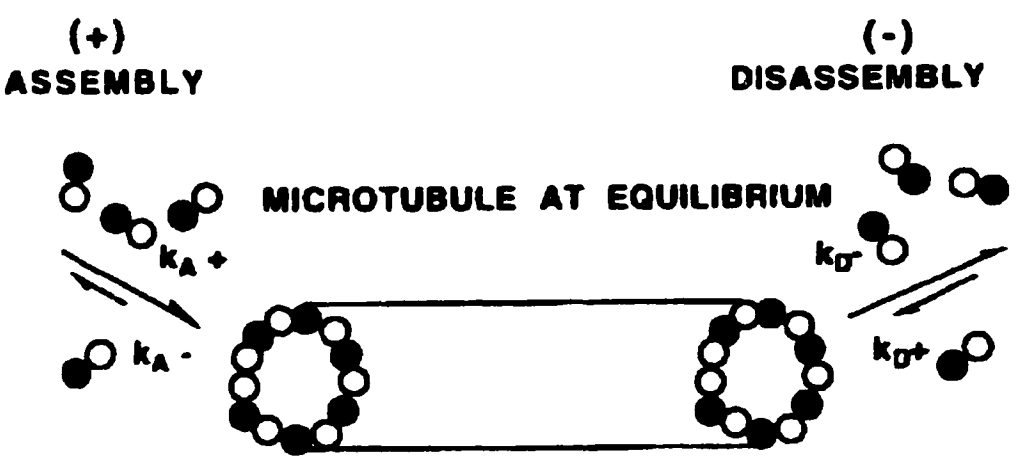


Investigation of the interactions of any tubulin-specific compound with tubulin and microtubules requires an understanding of the dynamic properties of microtubules.[28,29] As a dynamic structure, there is a constant flux between the monomeric and polymeric

forms. If the rates of monomer addition and loss at the microtubule ends are identical, no change in microtubule length at equilibrium is detected. (Figure 1.4)

Eleutherobin, like Taxol, induces tubulin polymerization *in vitro*, stabilizes microtubules and shifts the equilibrium toward the polymerized state. Suppression of the dynamic properties of microtubules by antimitotic agents like Taxol® or eleutherobin has been suggested as a plausible mechanism of cytotoxicity. Additional evidence that eleutherobin acts by a mechanism similar to that of paclitaxel (Taxol®) is provided by the NCI's cytotoxicity panel. Sixty cell lines show a pattern of sensitivity to eleutherobin, with selected breast, renal, ovarian, and lung cancer cell lines similar to those observed for paclitaxel. Evidence that eleutherobin and paclitaxel have common targets is also provided by the fact that A2780/Tax22 cells that are paclitaxel resistant are cross-resistant to eleutherobin.

Fig 1.4 Dynamic Property of Microtubules



1.2.2 Total Synthesis of and Synthetic Efforts Toward Eleutherobin

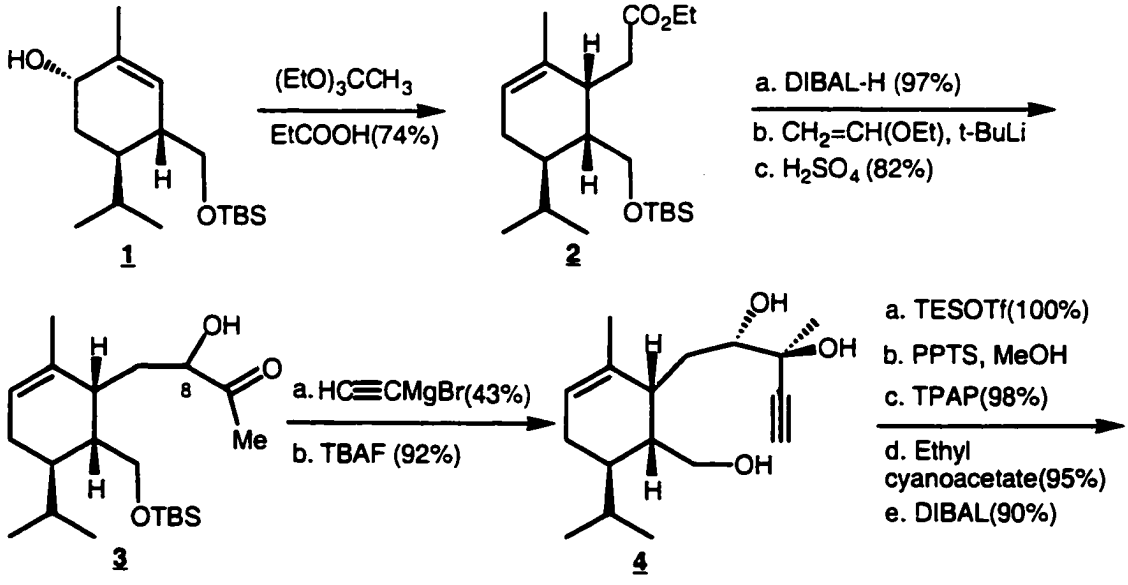
Because of the similar biological activity of eleutherobin with Taxol®, there has been considerable effort devoted to the total synthesis of eleutherobin. To date there have been two-reported total synthesis of eleutherobin from the Nicolaou[2] and Danishefsky[4,5] groups. In addition, Gennari[19,20], Mann[21], Nantz[22,23], Magnus[24], and Jung[25] groups have published approaches to the synthesis of eleutherobin.

1.2.2.1 Nicolaou's Total Synthesis of Eleutherobin

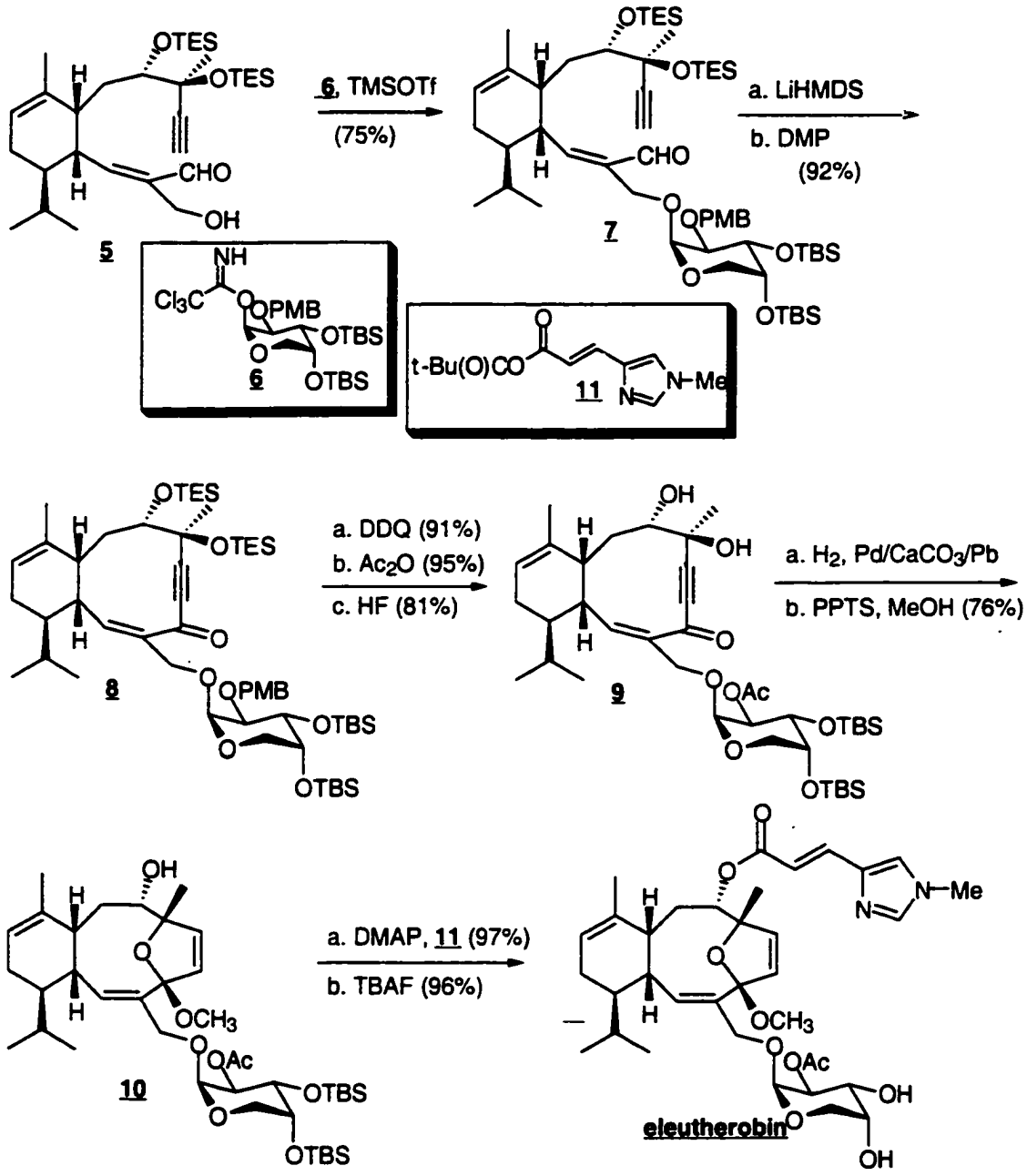
The total synthesis of eleutherobin by Nicolaou's group is shown in Scheme 1.1. Compound **1** was obtained from (+) carvone by a modification of Trost's method[30] and converted to ester **2** via a Claisen rearrangement. DIBAL reduction of **2** gave the corresponding aldehyde, which was reacted with 1-ethoxyvinyllithium and then exposed to acid to afford a 1.25:1 mixture of C-8 epimeric hydroxyketone **3** in 82% overall yield. This mixture was then reacted with excess ethynylmagnesium bromide in a stereoselective manner, affording a chromatographically separable mixture of desired diol (43%) along with its C-7, C-8 diastereoisomer (33%). Removal of the silyl protecting group from the desired diol was accomplished by exposure to TBAF furnishing the pure triol **4** in 92% yield. Global protection of **4** followed by selective deprotection gave the corresponding primary alcohol, which was oxidized to the corresponding aldehyde with TPAP-NMO[31] in DCM. A Knoevenagal condensation between the aldehyde and ethyl cyanoacetate proceeded to give, after reduction with DIBAL, hydroxy aldehyde **5**. In the presence of TMSOTf as a catalyst, **5** reacted with **6** to give the desired β-anomer **7**; the

stage was now set for a crucial macrocyclic ring formation. Treating 7 with LiHMDS in THF caused smooth cyclization via acetylide formation and intramolecular attack on the aldehyde group to afford an intermediate secondary alcohol that was oxidized to 8 with the Dess-Martin reagent[32]. Selective removal of the PMB group from 8 with DDQ led to the formation of the corresponding hydroxy compound; acetylation then led to its acetate (95% yield). Both TES groups were then removed without affecting the TBS group furnishing diol 9. Upon selective hydrogenation of the acetylenic moiety, compound 9 gave rise to the expected lactol, which was converted to methoxy ketal 10 in a straightforward fashion. Finally, the uraconic acid side chain was attached and TBS group removal generated eleutherobin.

Scheme 1.1 Nicolaou's Total Synthesis of Eleutherobin



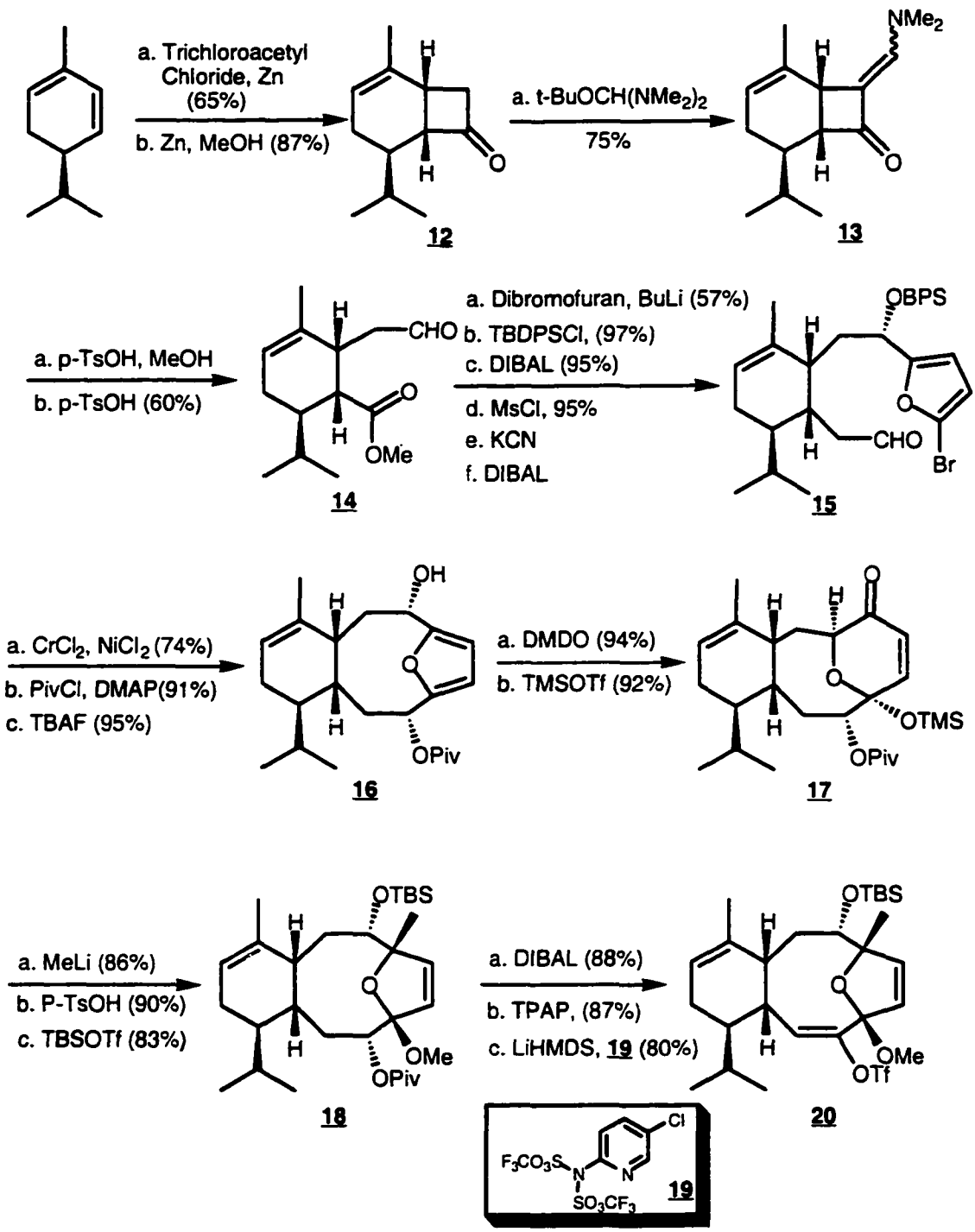
Scheme 1.1 Nicolaou's Total Synthesis of Eleutherobin (continued)



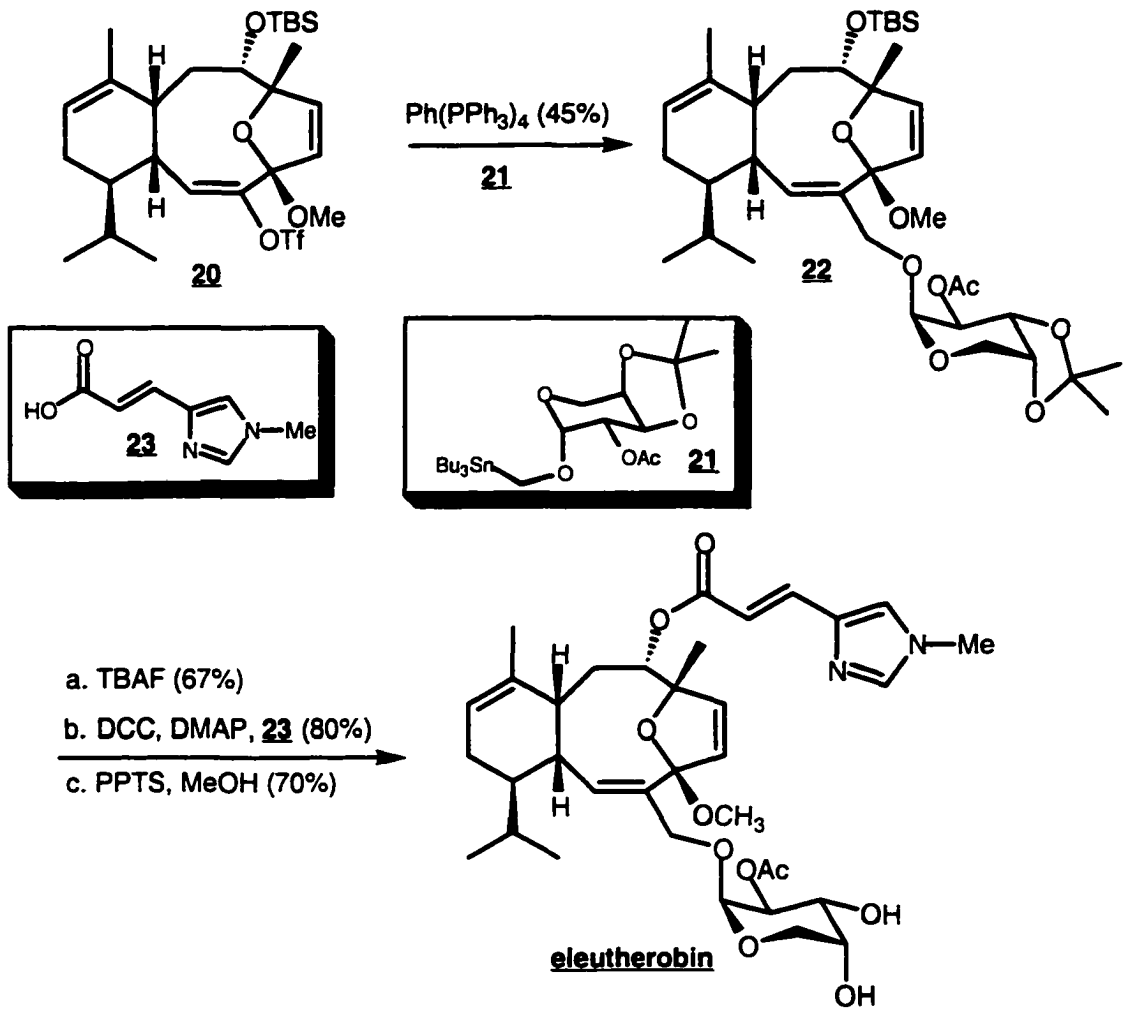
1.2.2.2 Danishefsky's Total Synthesis of Eleutherobin

Danishefsky's eleutherobin synthesis (Scheme 1.2) started with the reaction of dichloroketene with the commercially available (-)-α-phellandrene. Two isomers were generated in an 8:1 ratio, the major one was taken on to eleutherobin. After reductive removal of the chlorines, ketone **12** was reacted with Bredereck's reagent[33] to generate enamine **13**. Acetal formation and hydrolysis then gave aldehyde **14**. Although the coupling of **14** with monolithiated 2,5-dibromofuran gave rise to the desired alcohol in 57% yield, a significant amount of the epimeric compound was also formed. The desired alcohol was converted to the TBDPS ether, and following homologation, aldehyde **15** was achieved. By exposing this aldehyde to Nozaki-Kishi reductive cyclization conditions[34], the macrocyclic ring compound **16** was formed after pivaloyl ester formation and silyl ether hydrolysis with excellent diastereoselection in the formation of the stereogenic center (15:1). Oxidation of **16** with DMDO and TMS ether formation afforded the pyranose compound **17**. Reaction of **17** with methyl lithium provided the corresponding tertiary alcohol. Treatment of this alcohol with methanol in the presence of catalytic p-TsOH afforded the furanose compound **18** after TBS ether formation. DIBAL reduction of the pivaloyl ester, oxidation of the resulting secondary alcohol and enol triflate formation gave **20**. The stage was now set for the attachment of sugar moiety. Thus reaction of triflate **20** with "oxycarbadonor" **21** gave rise to a Stille coupling product **22** in moderate yield. With this critical step accomplished, the alcohol of **22** was unmasked, and the uraconic acid side chain was attached to give eleutherobin.

Scheme 1.2 Danishefsky's Total Synthesis of Eleutherobin



Scheme 1.2 (continued) Danishefsky's Total Synthesis of Eleutherobin

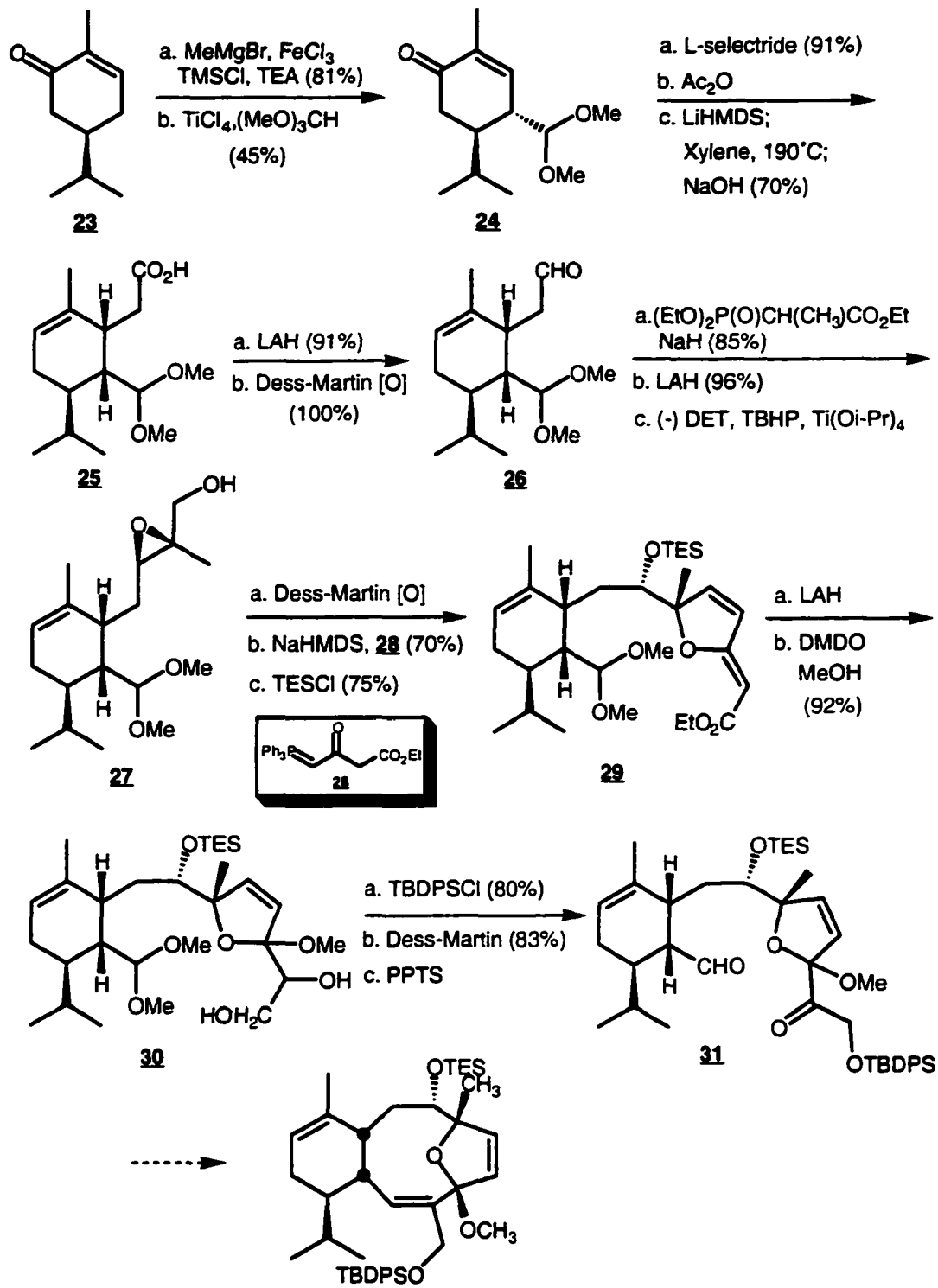


1.2.2.3 Gennari's First Approach toward the Synthesis of Eleutherobin

In a similar fashion to Nicolaou's synthesis, Gennari also starts from the readily available natural product (-) carvone (Scheme 1.3). Selective hydrogenation of (-) carvone provided **23**.[35] Electrophilic formylation occurred form the less hindered face of the intermediate dienoxysilane[36], yielding **24** as the only diastereomer. Diastereoselective

reduction of the ketone from the equatorial direction with L-selectride gave the corresponding alcohol, which was subjected to acetylation followed by an Ireland-Claisen rearrangement to give **25**. The acid appendage was reduced and oxidized to afford aldehyde **26**. Aldehyde **26** was extended through Horner-Wittig reaction with $(EtO)_2P(O)CH(CH_3)CO_2Et$. Reduction of the ester and Sharpless asymmetric epoxidation of the resulting allylic alcohol gave **27**. The epoxy alcohol **27** was then oxidized to the corresponding aldehyde with buffered Dess-Martin periodinane. When this aldehyde was exposed to the anion of **28**, a rapid and *Z*- selective Wittig reaction ensued. The intermediate enolate oxygen performed an intramolecular attack on the epoxide ring at the more substituted carbon, and compound **29** was isolated after protection of the secondary alcohol. The dihydrofuran side chain was further reduced with LAH, and oxidation with DMDO afforded only the exocyclic double bond epoxide, which was smoothly converted to the desired diol **30**. Selective protection of the primary alcohol and oxidation of the secondary alcohol afforded the ketone **31**. Gennari and coworkers are currently studying the cyclization of **31**.

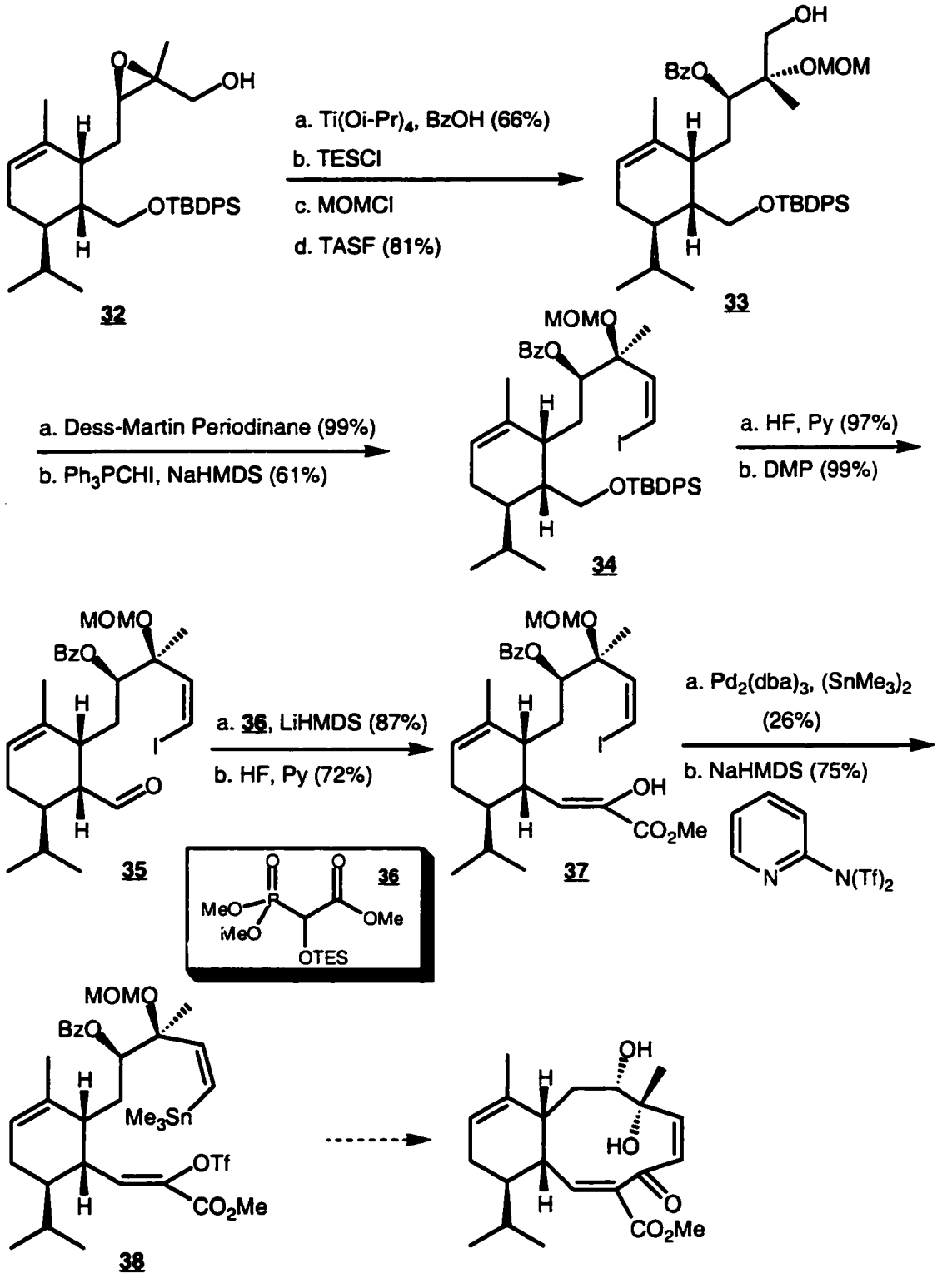
Scheme 1.3 Gennari's First Approach Toward Eleutherobin



1.2.2.4 Gennari's Second Generation Approach Toward the Synthesis of Eleutherobin

Gennari's second generation approach to eleutherobin involved the use of a carbonylative Stille coupling to form the macrocyclic ring system. Toward this goal, Gennari synthesized the precursor for such coupling as shown in Scheme 1.4. Beginning with epoxy alcohol **32**, the epoxide could be opened with benzoic acid in the presence of titanium tetraisopropoxide. Selective protection and deprotection gave alcohol **33**. Alcohol **33** was then oxidized to the corresponding aldehyde; application of Stork's vinyl iodide forming conditions gave *Z*-vinyl iodide **34**. Subsequent treatment with HF and oxidation gave aldehyde **35**. Homologation to the corresponding silyl enol ether was carried out in 87% yield by reacting **35** with the anion of **36**. Removal of the silyl group then gave compound **37**. Treatment of **37** with $Pd_2(dba)_3$ and hexamethylditin gave the corresponding vinylstannane in only 26% yield. The stannane was then converted to enol triflate **38**. Detailed information about the crucial Stille coupling, however, has not been reported to date.

Scheme 1.4 Gennari's Second Approach Toward Eleutherobin



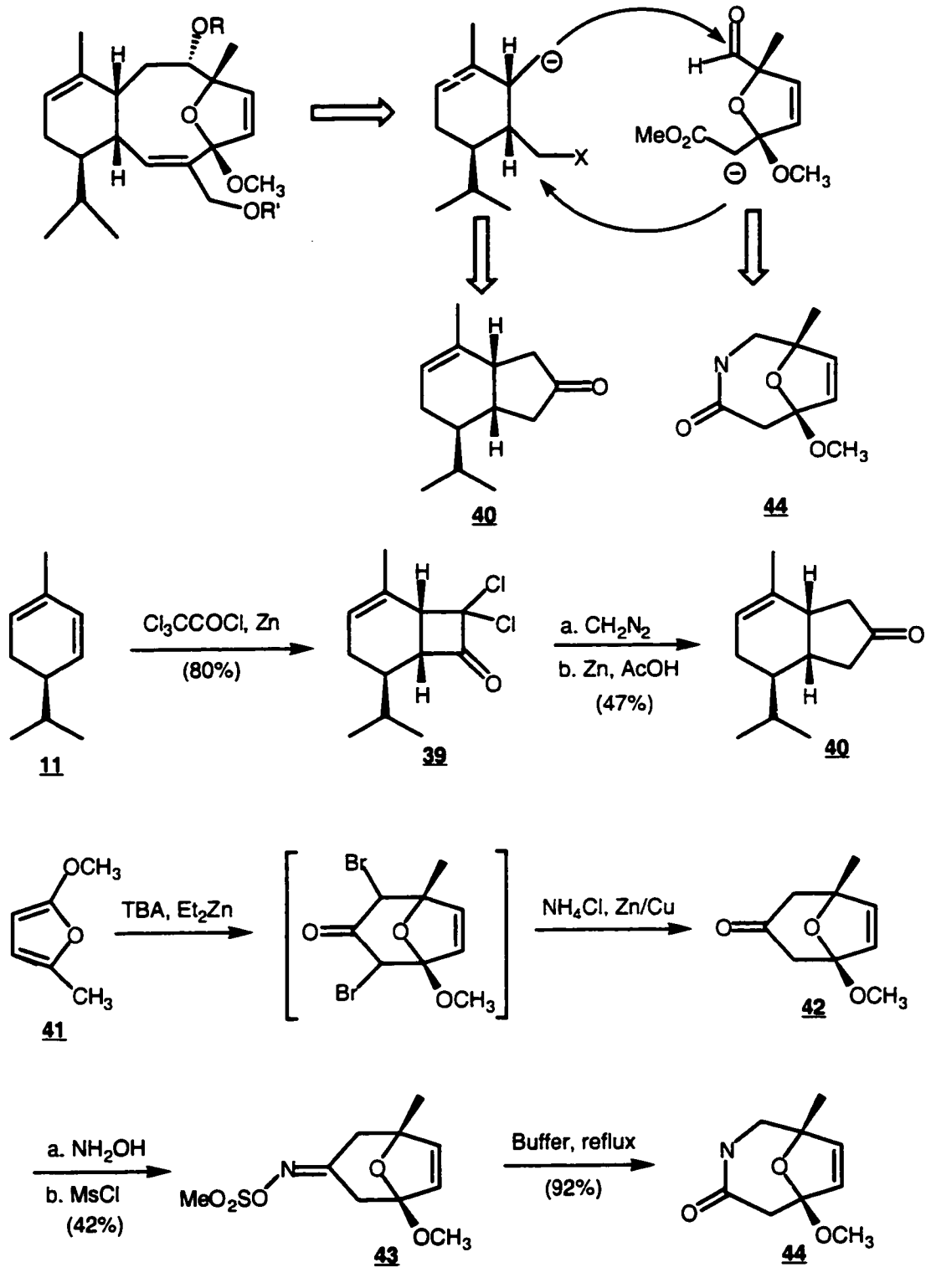
1.2.2.5 Mann's Approach to the Synthesis of Eleutherobin

Mann proposed a concise and highly convergent approach, which would allow the access to not only the skeleton of eleutherobin but also to a range of analogues for biological evaluation. As shown in Scheme 1.5, the retroanalysis leads to two key intermediates **40** and **44**.

The key intermediate **40** was prepared from *rac*-phellandrene via regio-selective addition of dichloroketene to provide dichlorocyclobutanone **39**, followed by ring expansion with diazomethane[37] and dechlorination.

Intermediate **44** was prepared as shown in Scheme 1.5. The key reaction was the cycloaddition of oxyallyl from tetrabromoacetone with 2-methoxy-5-methylfuran.[38] Oxabicycle **42** was obtained in 37% yield. From **42**, two possible oxime mesylates were formed in equal amounts. After chromatographic separation, **43** was isolated in 42% yield. Beckmann rearrangement of **43** then afforded bicyclic lactam **44** efficiently. With both intermediates in hands, their combination is currently being investigated.

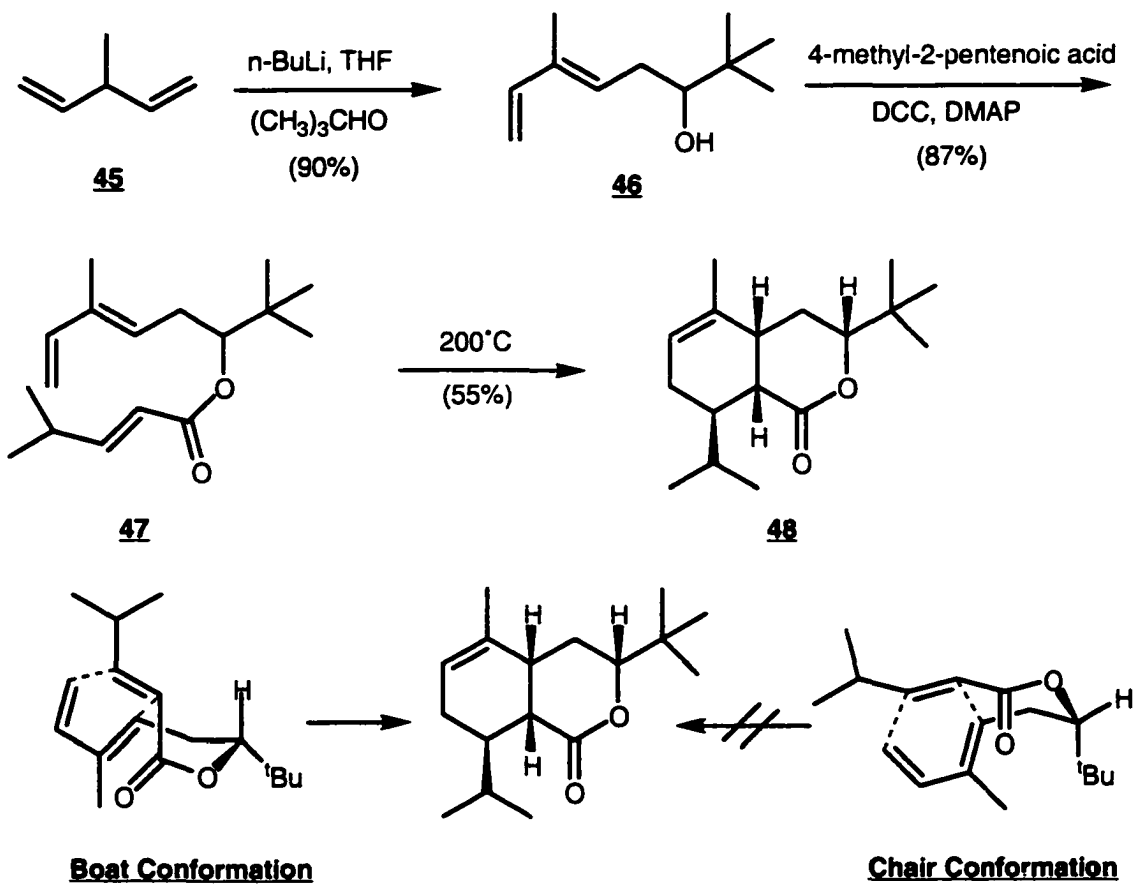
Scheme 1.5 Mann's Approach Toward Eleutherobin



1.2.2.6 Nantz's Approach Toward the Synthesis of Eleutherobin

Nantz selected an IMDA (Intramolecular Diels-Alder) route to synthesize eleutherobin in an effort to accommodate the synthesis of analogues. As shown in Scheme 1.6, they felt that the six membered ring portion could be constructed through a Diels-Alder cycloaddition reaction. Literature precedent had shown that the IMDA would deliver the requisite *cis* ring junction.

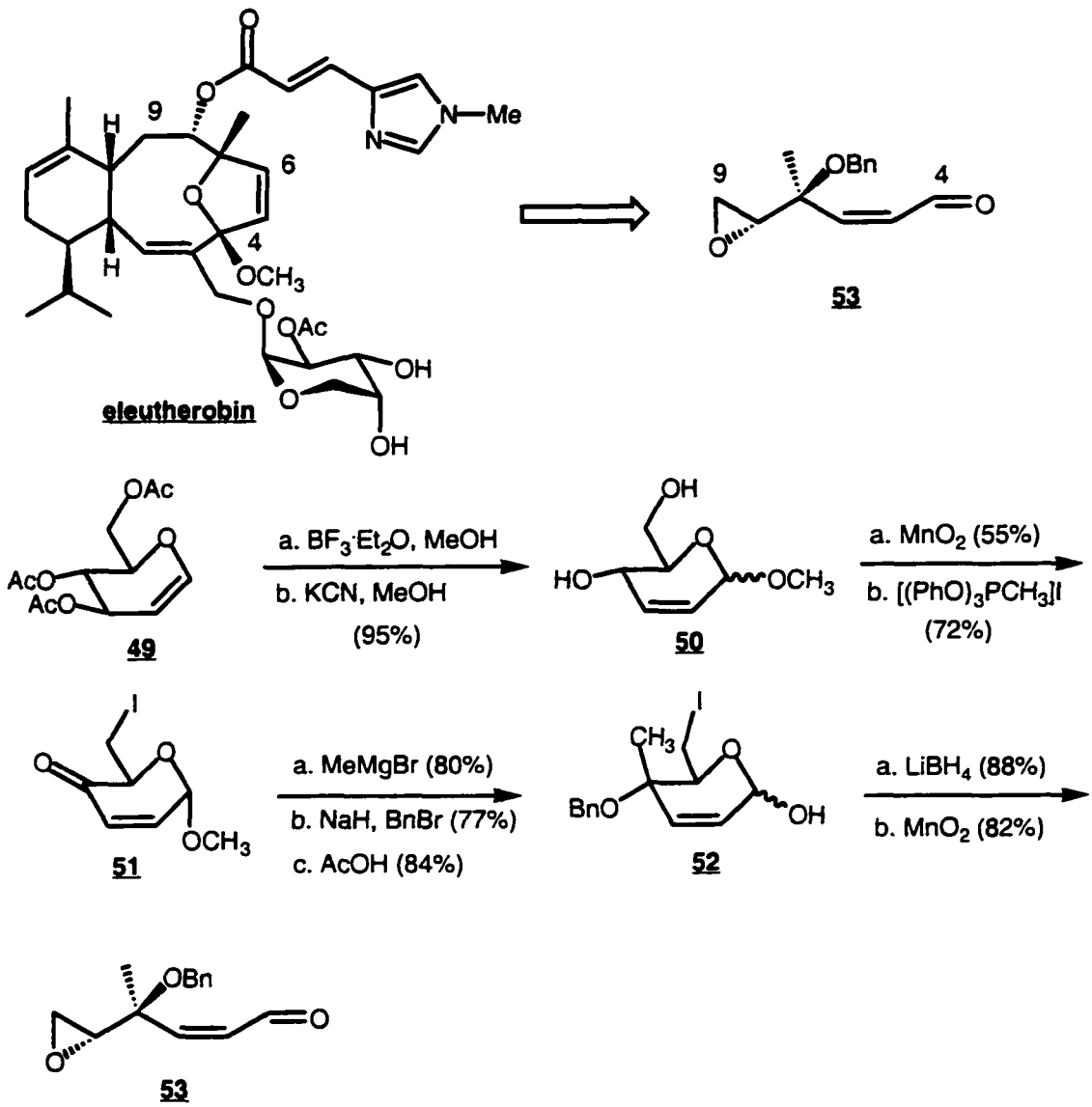
Scheme 1.6 Nantz's Strategy to the Synthesis of Eleutherobin



In order to test the strategy, Nantz selected dienol **46** as a model compound (Scheme 1.6). Dienol **46** was prepared in 90% yield by lithiation of **45** and subsequently addition of trimethylacetaldehyde. Esterification of **46** with trans-4-methyl-2-pentenoic acid delivered **47** in 87% yield. The IMDA was accomplished by heating a solution of **47** in toluene at 200°C for 12 hrs. A single product **48** was obtained in 55% yield. Presumably the stereochemistry was achieved through a boat transition state.

In a separate account, the Nantz group reported their synthesis of the C4-C9 portion of eleutherobin as epoxy alcohol **53**. As shown in Scheme 1.7, tri-acetal-glucal **49** was readily converted to its corresponding methyl pyranoside by exposing it to boron trifluoride etherate[39]. Hydrolysis of the acetate esters gave **50** as an 8:1 ratio of α:β anomers in 95% yield. Manganese dioxide oxidized the α-anomer of **50** to the corresponding α,β-unsaturated ketone. The C(6) alcohol was converted to the iodide **51** by using triphenoxyphosphonium iodide in 72% yield according to the procedure reported by Landauer and Rydon.[40] Treatment of **51** with MeMgBr gave the corresponding methyl adduct in 80% yield. Benzyl protection and acetal hydrolysis led to **52**. Lactol **52** was reduced with lithium borohydride to give the corresponding epoxy alcohol. Oxidation with MnO_2 gave α,β-unsaturated aldehyde **53**.

Scheme 1.7 Nantz's Synthesis of C4-C9 Portion of Eleutherobin

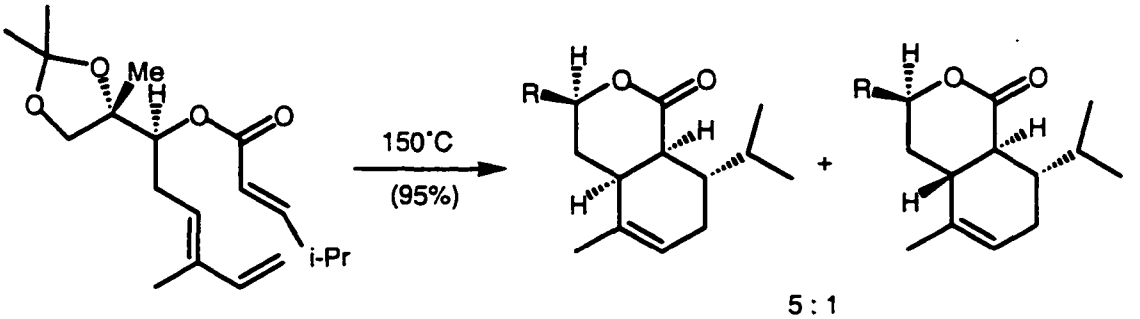


1.2.2.7 Jung's Approach Toward the Synthesis of Eleutherobin

In a similar approach to Nantz, Jung used an intramolecular Diels-Alder reaction to construct the eleutherobin C-ring (Scheme 1.8). As shown in Scheme 1.8, heating **54** in toluene in a sealed tube at 150°C for 10 days gave a 5:1 mixture of the two

diastereomeric lactones **55** and **56** in quantitative yield. Presumably, the major product was formed via a boat transition state.

Scheme 1.8 Jung' s IMDA Strategy



54 **55** **56**

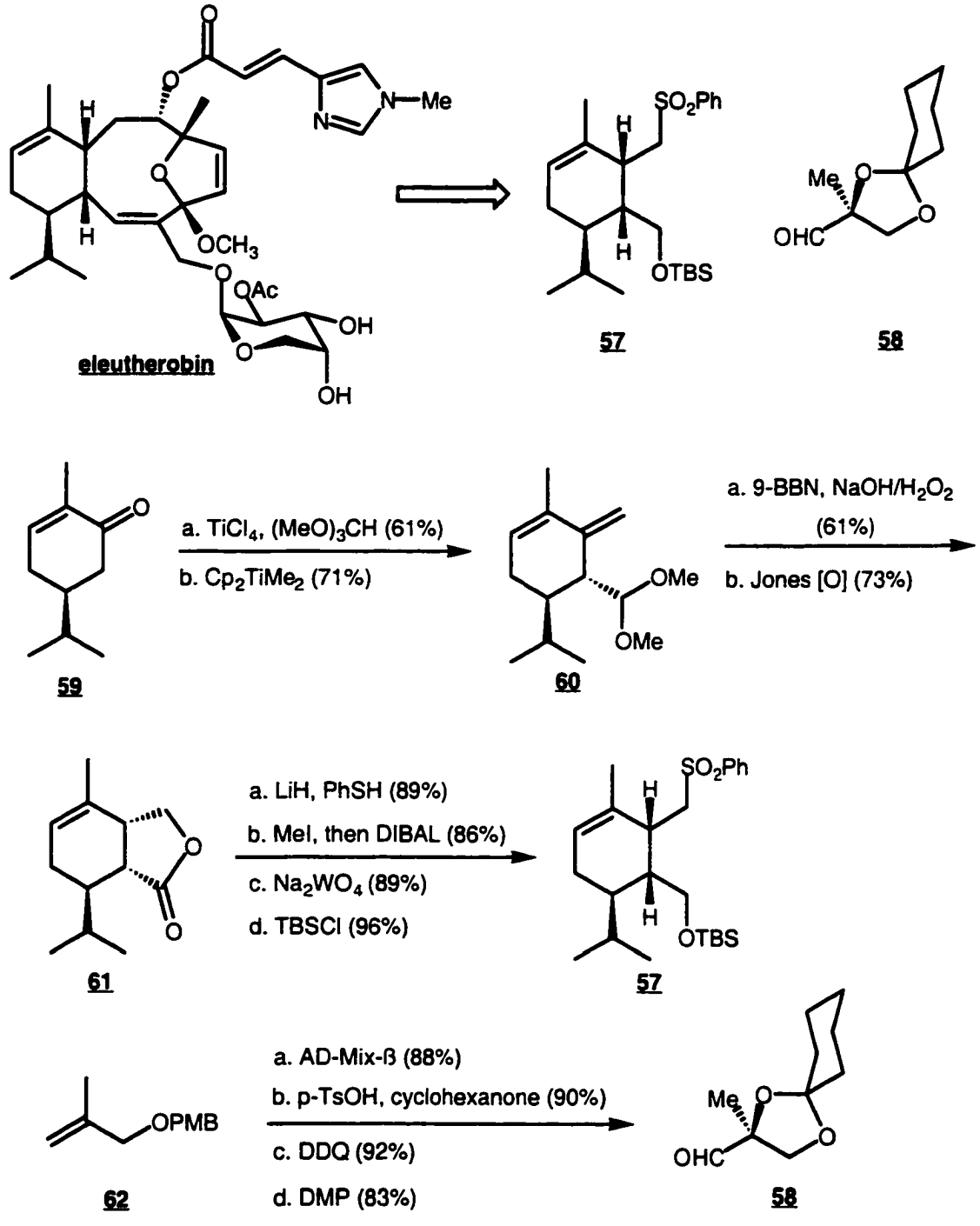
1.2.2.8 Magnus's Approach Toward the Synthesis of Eleutherobin

The strategy that Magnus group has pursued involves the conversion of carvone into *cis*-disubstituted derivative **57** and Julia coupling with **58**. As shown in Scheme 1.9, treatment of **59** with $TiCl_4$/DIPEA followed by trimethylorthoformate afforded the corresponding acetal,[41] methylenation of this compound then provided diene **60**. Hydroboration of **60** using 9-BBN[42] in THF gave, after oxidative work-up, the corresponding alcohol. Jones oxidation[43] then gave lactone **61**. The lactone was opened with lithium phenylthiolate. Esterification and reduction gave the corresponding alcohol. Thioether oxidation using hydrogen peroxide/sodium tungstate dihydrate[44] gave the corresponding sulfone **57** after silyl ether formation.

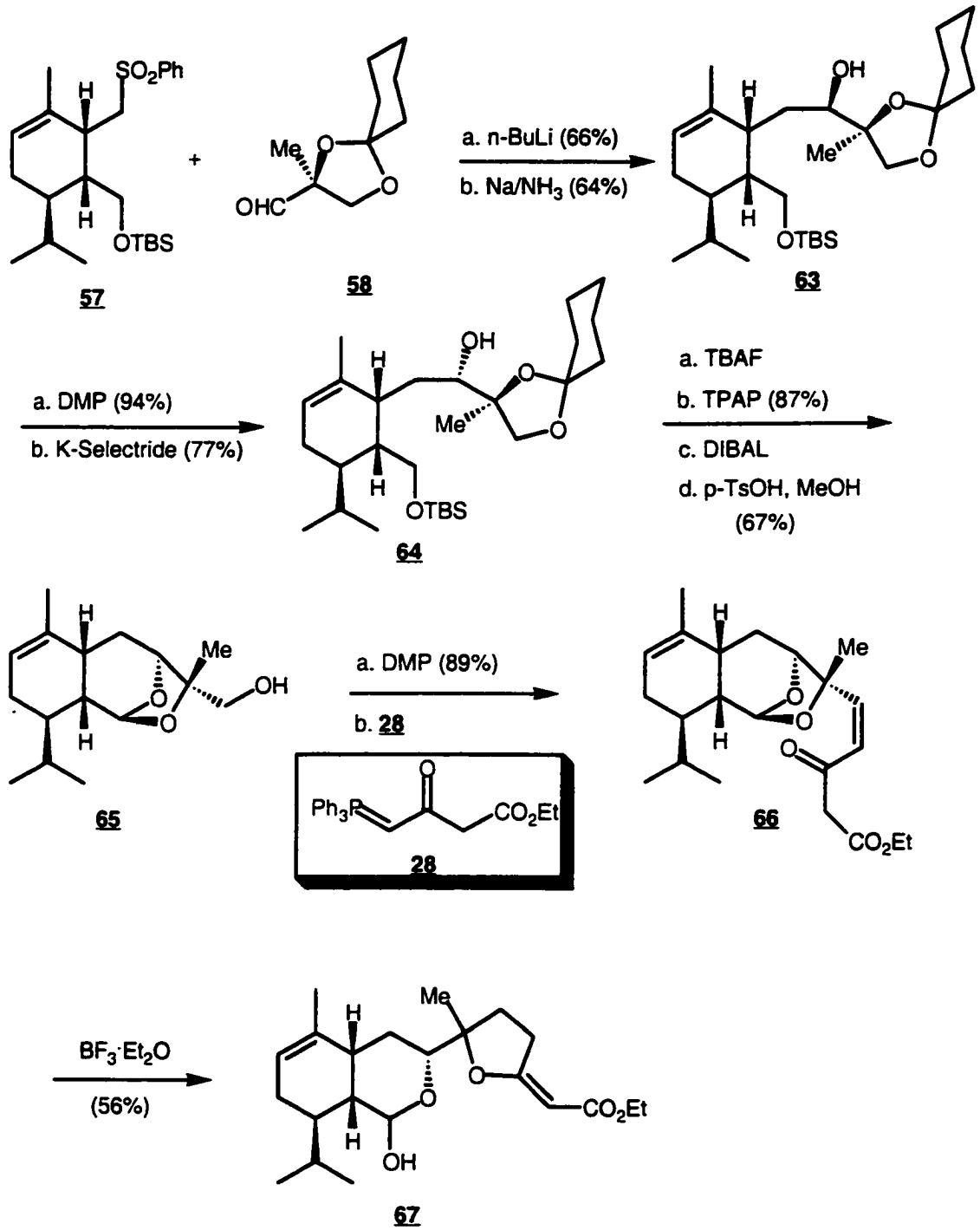
The requisite **58** was synthesized in four steps. Propenyl ether **62** was transformed into the corresponding diol using the Sharpless protocol.[45] Cyclic ketal formation and oxidative hydrolysis of the PMB group gave **58** in an overall yield of 50%.

Treatment of the sulfone **57** with n-BuLi followed by the addition of aldehyde **58** gave the coupled product **63** in 42% yield after reductive removal of the sulfone. Coupled product **63** was converted to the desired **64** via an oxidation-reduction sequence. Hydrolysis of **64** was followed by oxidation of the primary alcohol using TPAP to give the corresponding lactone. Reduction and treatment with methanol and p-TsOH gave **65**. Oxidation of **65** and treatment of the resulting aldehyde with ylide **28** gave ß-keto ester **66** (*Z:E* = 14:1). Treatment of **66** with Lewis acid produced a complex mixture from which **67** was isolated in 56% yield. The desired macrocyclic ring formation is under investigation

Scheme 1.9 Magnus's Approach Toward the Synthesis of Eleutherobin



Scheme 1.9 (continued) Magnus's Approach Toward the Synthesis of Eleutherobin



1.3 Chemistry and Biology of Eunicellin Diterpenes

1.3.1 Isolation and Biology of Eunicellin Diterpenes

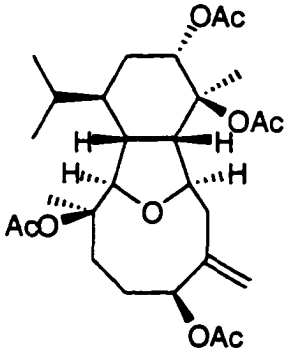
The eunicellin diterpenes are a family of marine metabolites obtained from gorgonian and soft corals. Eunicellin **68**, the first member of this family to be described[11], was isolated in 1968 by Djarassi, Kennard, and coworkers from the coral *Eunicella stricta*. Over 50 other related structures have been reported including: (-)-7-deactoxyalcylonin acetate **69**, which was obtained from a *Cladiella* species of soft coral[46], and sclerophytin A **71** and sclerophytin B **72**. Sclerophytin A was isolated by Sharma and Alam in 1988 from *Sclerophytum capitalis*.[47] Bioassays revealed that this substance exhibits significant *in vitro* toxicity against the L1210 cell line at a concentration of 0.001 μg/ml.

1.3.2 Total Synthesis of Eunicellin Diterpenes

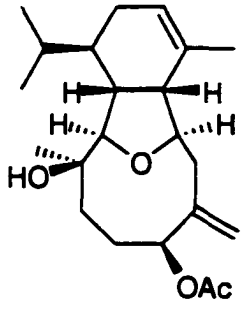
The eunicellin diterpenes are characterized by a unique tricyclic ring system containing hydroisobenzofuran and oxonane subunits. The first total synthesis of a member of the eunicellin diterpene family was disclosed by the Overman group[14a]. This enatioselective total synthesis confirmed the relative and absolute stereochemistry of (-)-7-deacetoxyalcyonin acetate. Through the same strategy, the Overman group also carried out a total synthesis of the alleged structure of sclerophytin A **70**.[14b] At the same time, the Paquette group independently carried out the total synthesis of the alleged structure of sclerophytin A through a different strategy.[15b] Both syntheses established unequivocally that the alleged structure was not sclerophytin A. After reexamining the spectroscopic data, the Paquette group proposed a new structure for sclerophytin A and B, which are

shown in Fig 1.5. These structures were later confirmed by total synthesis by both the Overman and Paquette groups.[18c]

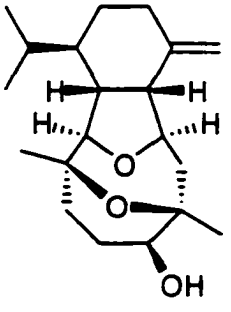
Fig 1.5 Structures of Some Members of Eunicellin Diterpenes



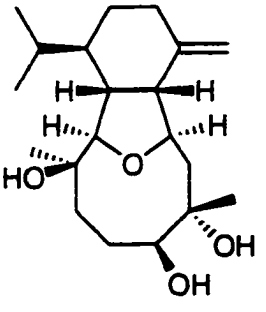
Eunicellin (68)



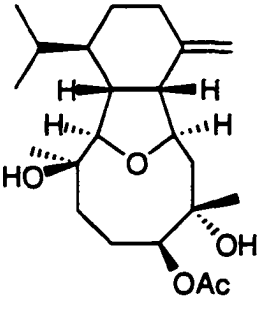
(-) 7-Deacetoxyalcyonin acetate (69)



Alleged Stucture of Sclerophytin A (70)



Sclerophytin A (71)

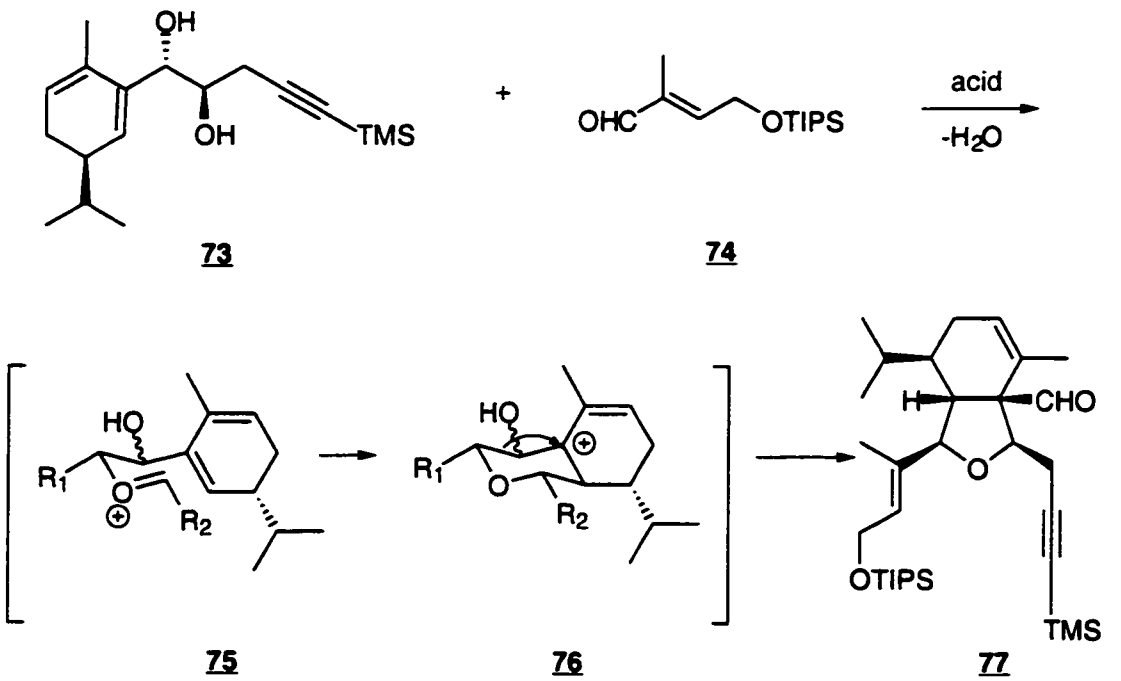


Sclerophytin B (72)

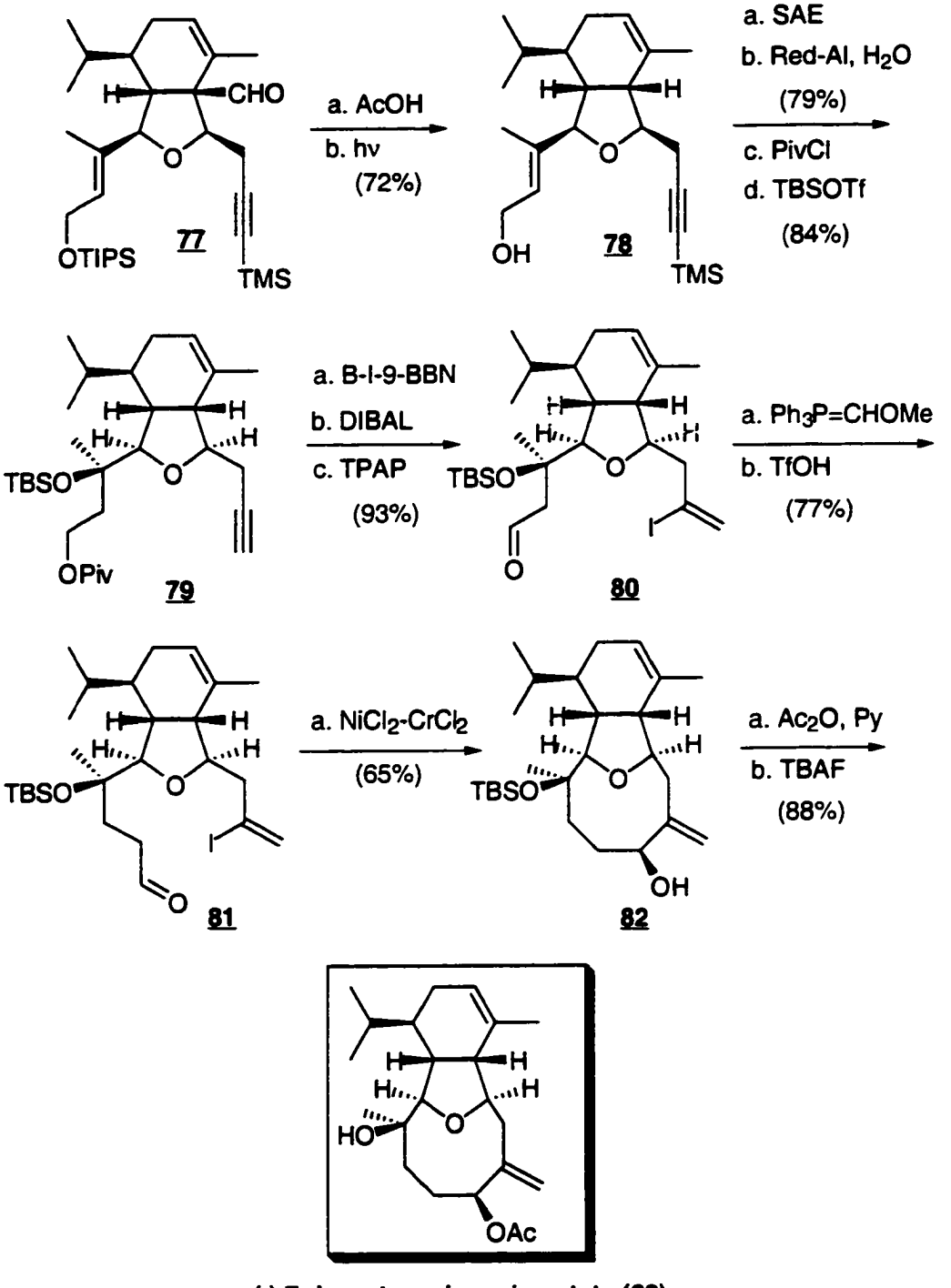
1.3.2.1 Total Synthesis of (-)-7-Deacetoxyalcyonin acetate

The defining reaction of Overman's total synthesis of (-)-7-deacetoxyalcyonin acetate is the stereoselective Prins-pinacol condensation-rearrangement of dienyl diol 73 and aldehyde 74 to assemble the 2-oxabicyclo[4.3.0]non-4-ene 77. The stereochemical outcome of this reaction can be anticipated from the analysis depicted in Scheme 1.10.

Scheme 1.10 Stereochemical Analysis of the Prins-pinacol Reaction



Scheme 1.11 Total Synthesis of (-)-7-Deacetoxyalcyonin Acetate



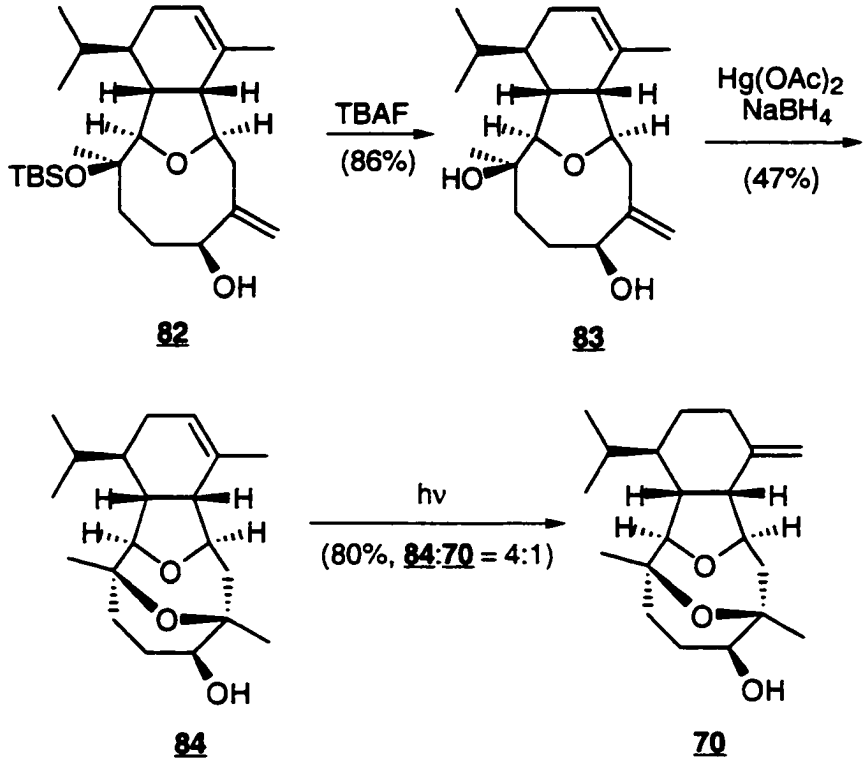
(-) 7-decaetoxyalcyonin actate (69)

The completion of the synthesis of deacetoxyalcyonin acetate is outlined in Scheme 1.11. Hydrolysis of the TIPS ether of compound **77**, followed by stereoselective photolytic deformylation[48] provided **78** in 72% yield. Allylic alcohol **78** was next elaborated by Sharpless asymmetric epoxidation (SAE), reduction of the derived epoxy alcohol and concomitant hydrolysis of the TMS group with aqueous NaOH to provide **79** in 66% yield after selective protection. Iodoboration of the alkyne moiety with *B*-iodo-9-borabicyclo[3.3.1]nonane (*B*-I-9-BBN), followed by reduction of the pivaloyl group with DIBAL, and TPAP oxidation of the resulting alcohol provided aldehyde **80**. Homologation to **81** was accomplished through sequential Wittig reaction and acid hydrolysis. Application of the Nozaki-Kishi reaction conditions provided tricyclic ether **82** in 65% yield. Acetylation of **82** followed by hydrolysis of the silyl ether then gave (-)-7-deacetoxyalcyonin acetate in 88% yield.

1.3.2.2 Overman's Total Synthesis of Alleged Structure of (-)-Sclerophytin A

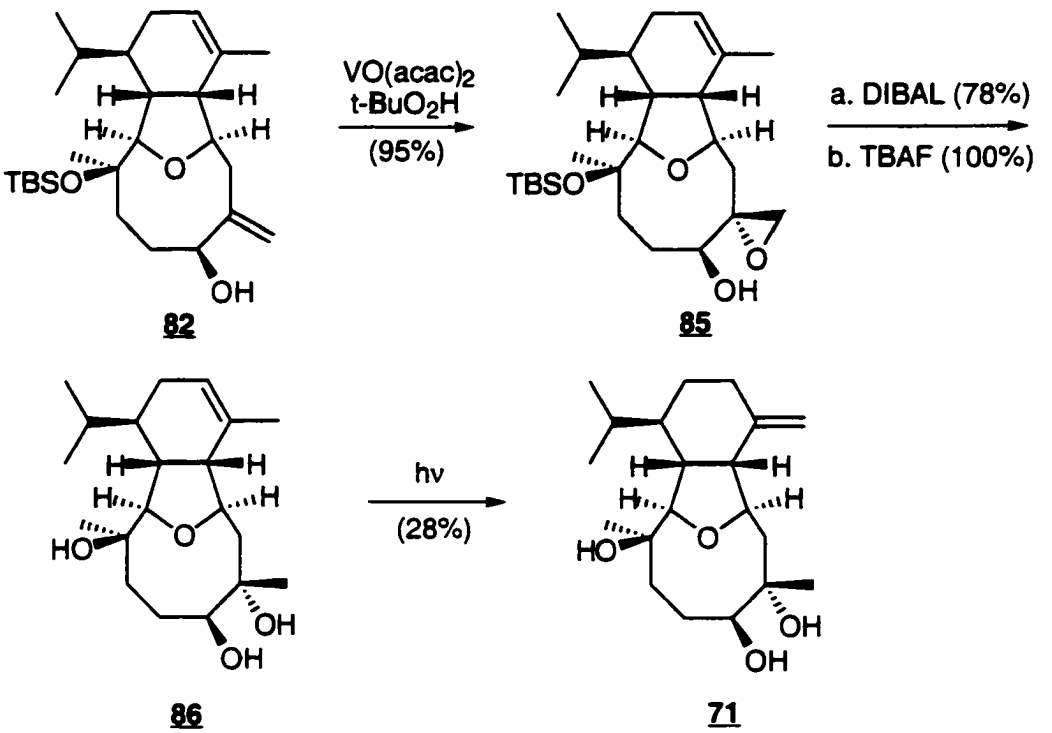
Completion of the synthesis of the presumed structure of sclerophytin A required formation of the bridging tetrahydropyran ring (Scheme 1.12). Desilylation of **82** provided the corresponding diol **83**; sequential treatment of **83** with $Hg(OAc)_2$ and $NaBH_4$ furnished tetracyclic diether **84** in 47% yield. Light-induced olefin isomerization of **84** was realized in high yield through the use of short irradiation in the presence of acetic acid to give **84** and **70** in 4:1 ratio. As discussed above, the spectral data of **70** did not match that reported for sclerophytin A.

Scheme 1.12 Overman's Total Synthesis of Alleged Structure of (-)-Sclerophytin A



By modifying their synthetic strategy, the Overman group synthesized authentic sclerophytin A. As outlined in Scheme 1.13, hydroxy-directed epoxidation of **82** with $VO(acac)_2$/t-BuO_2H occurred with exquisite facial selectivity to deliver the epoxy alcohol **85** in excellent yield. Regioselective reduction of **85** with DIBAL followed by hydrolysis of the TBS silyl ether gave rise to triol **86**. The conversion of **88** to sclerophytin A **71** was accomplished through the use of photochemical isomerization using a medium-pressure Hg lamp.

Scheme 1.13 Overman's Synthesis of Authentic Sclerophytin A

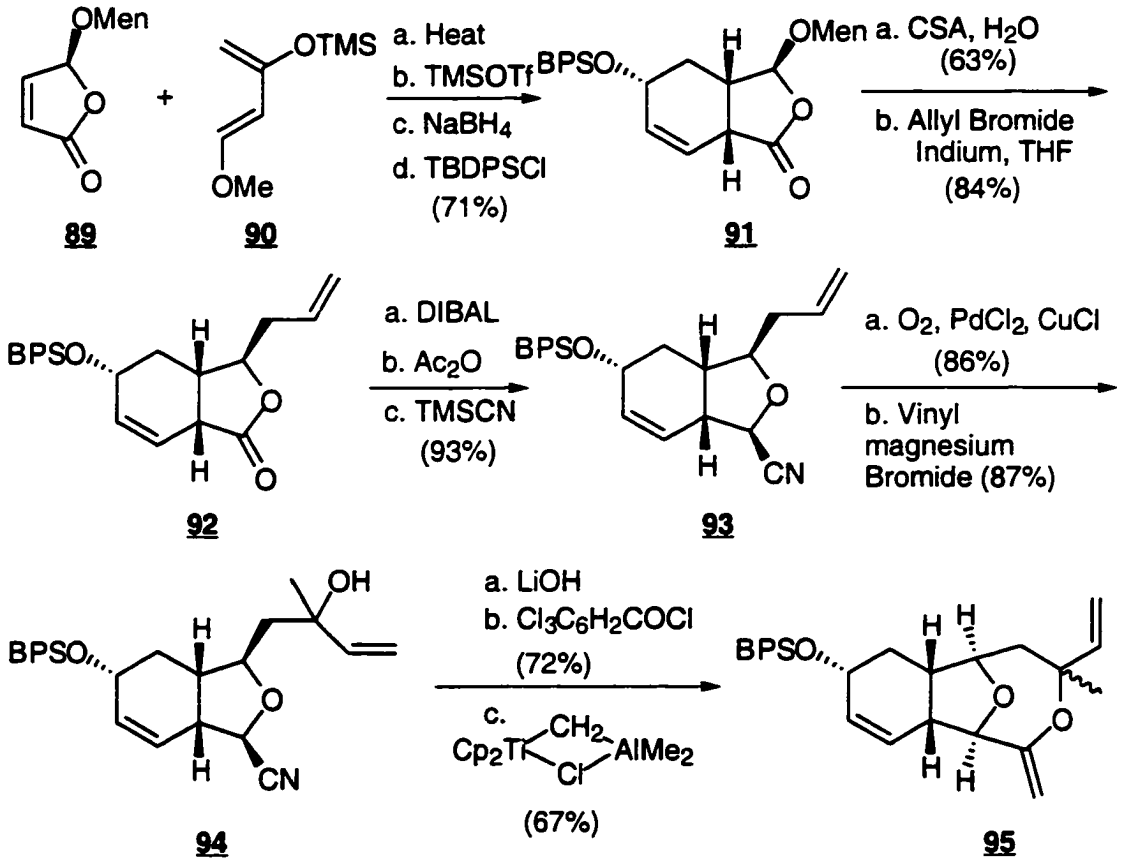


1.3.2.3 Paquette' s Total Synthesis of Alleged Structure of Sclerophytin A

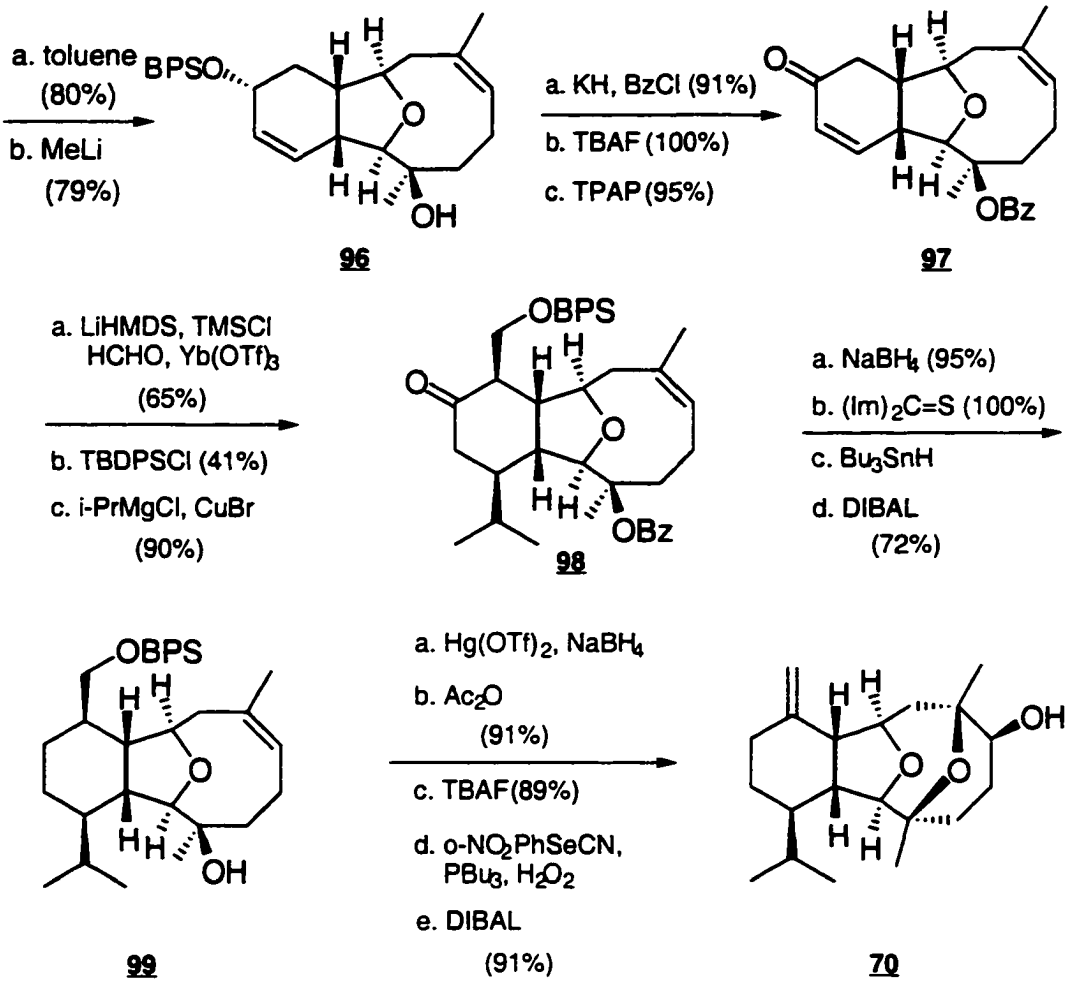
Paquette's synthesis of alleged structure of sclerophytin A is depicted in Scheme 1.14. Hetero Diels-Alder cycloaddition between **89** and Danishefsky's diene **90** gave **91** after Luche Reduction[49] and silyl ether formation. Hydrolysis of **91** and Barbier-type condensation with allylindium gave rise to **92**. Lactone **92** was reduced with DIBAL and the resulting lactol was acetylated followed by treatment of TMSCN in the presence of $BF_3{\cdot}Et_2O$ to give **93**. Wacker oxidation[50] of **93** and vinyl magnesium bromide addition gave **94**. Hydrolysis of the nitrile and application of Yonemitsu modification[51] of the Yamaguchi conditions gave the corresponding lactone, which was transformed into enol

ether **25** in 67% yield. Heating **25** and toluene initiated a [3.3]-sigmatropic rearrangement (80%). MeLi addition to the resulting ketone afforded **26** in 79% yield. Esterification of the tertiary alcohol, hydrolysis of the BPS ether, and oxidation gave α,β-conjugated ketone **27**. Mukayama aldol reaction of the silyl enol ether of **27** with HCHO delivered the β-hydroxy ketone. Conjugate addition using isopropyl cuprate then gave **28**. Deoxygenation of **28** gave **29**. Installation of the exocyclic double bond then gave the alleged structure of sclerophytin A, which, as mentioned above, did not match the spectral data of isolated sclerophytin A.

Scheme 1.14 Paquette' s Total Synthesis of Alleged Structure of Sclerophytin A



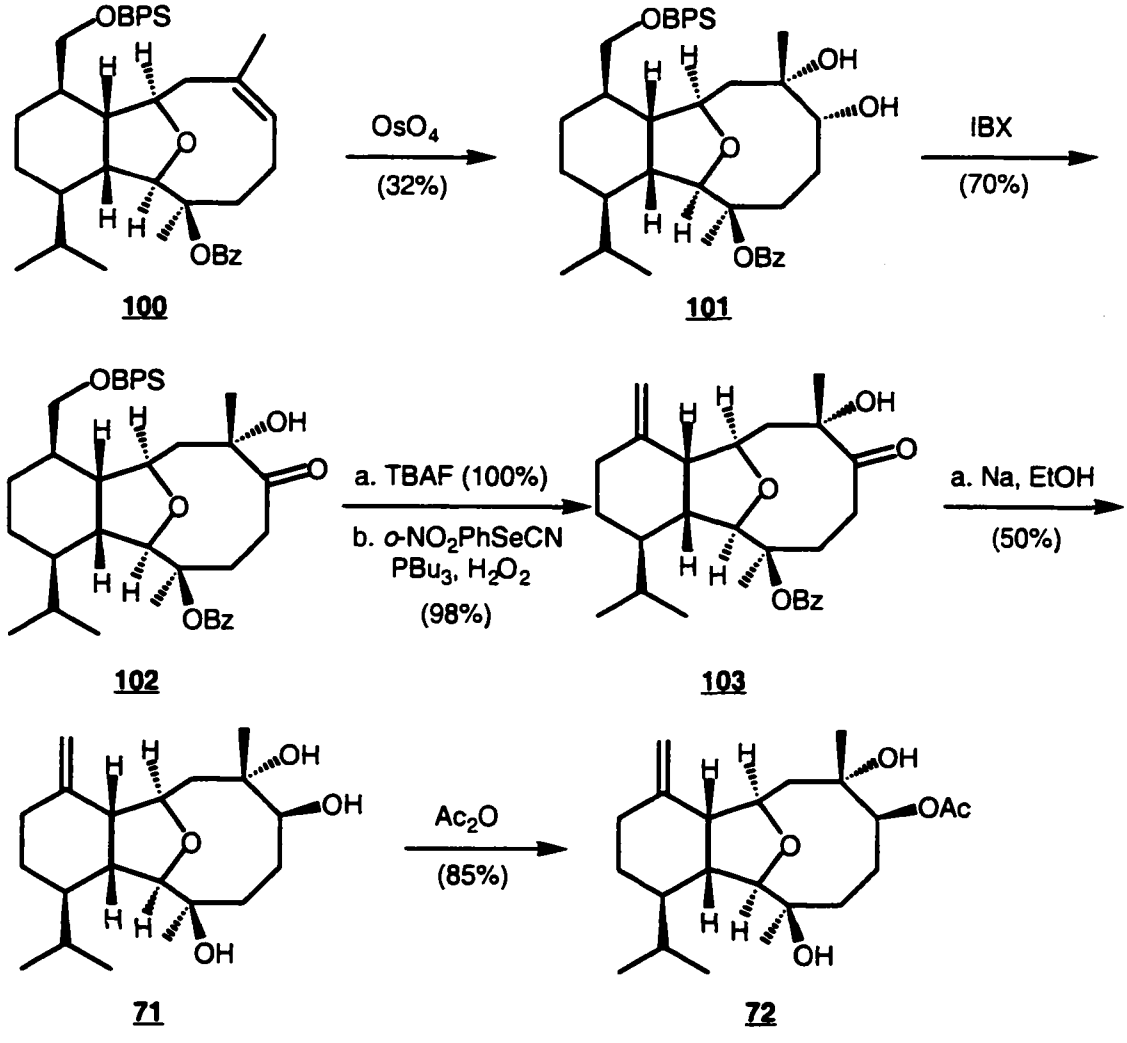
Scheme 1.14 (continued) Paquette' s Total Synthesis of Alleged Structure of Sclerophytin A



Through a slight modification of their synthetic strategy, Paquette's group also successfully generated authentic sclerophytin A and B (Scheme 1.15). Conventional dihydroxylation of **100** proceeded with little facial discrimination, the desired **101** was isolated in 32% yield. The diasteromeric diol was isolated in 48% yield. Oxidation of **101** with *o*-iodoxybenzoic acid (IBX) in DMSO[52] provided **102**. Introduction of the exocyclic

double bond was carried out through sequential desilylation and elimination via the *o*-nitroselenocyanate.[53] Reduction of **103** with sodium in ethanol led cleanly to sclerophytin A. Acylation of the secondary alcohol gave sclerophytin B.

Scheme 1.15 Paquette's Total Sythesis of Sclerophtyin A and B



1.4 Our Strategy Toward the Synthesis of Eleutherobin

The main challenge of constructing eleutherobin is, as can be seen from the literature survey, the formation of the central 10-membered ring. The only successful attempts have involved Nicolaou's intramolecular acetylide addition reaction and Danishefsky's intramolecular Nozaki-Kishi coupling reaction. All the other strategies have essentially failed. In order to circumvent this problem, we considered an addition-fragmentation sequence to construct the eleutherobin ring system. This will be discussed in more detail in the next chapter.

Chapter 2 Synthesis of Oxabicyclo[2.2.1]heptenone 106 and Subsequent Radical Ring Expansion Studies

2.1 Retrosynthetic Analysis

As shown in the retrosynthetic analysis (Figure 2.1), in order to circumvent the unfavorable entropic and enthalpic factors of forming medium-sized rings, our intention was to form the eleutherobin carbon skeleton through an intramolecular cyclization and fragmentation sequence. More Specifically, the eleutherobin skeleton would come from an intramolecular radical or anionic cyclization of **105**. Compound **105** could be traced to oxabicyclo[2.2.1]heptenone **106** and aldehyde **107**.

2.2 Fragmentations in Organic Synthesis

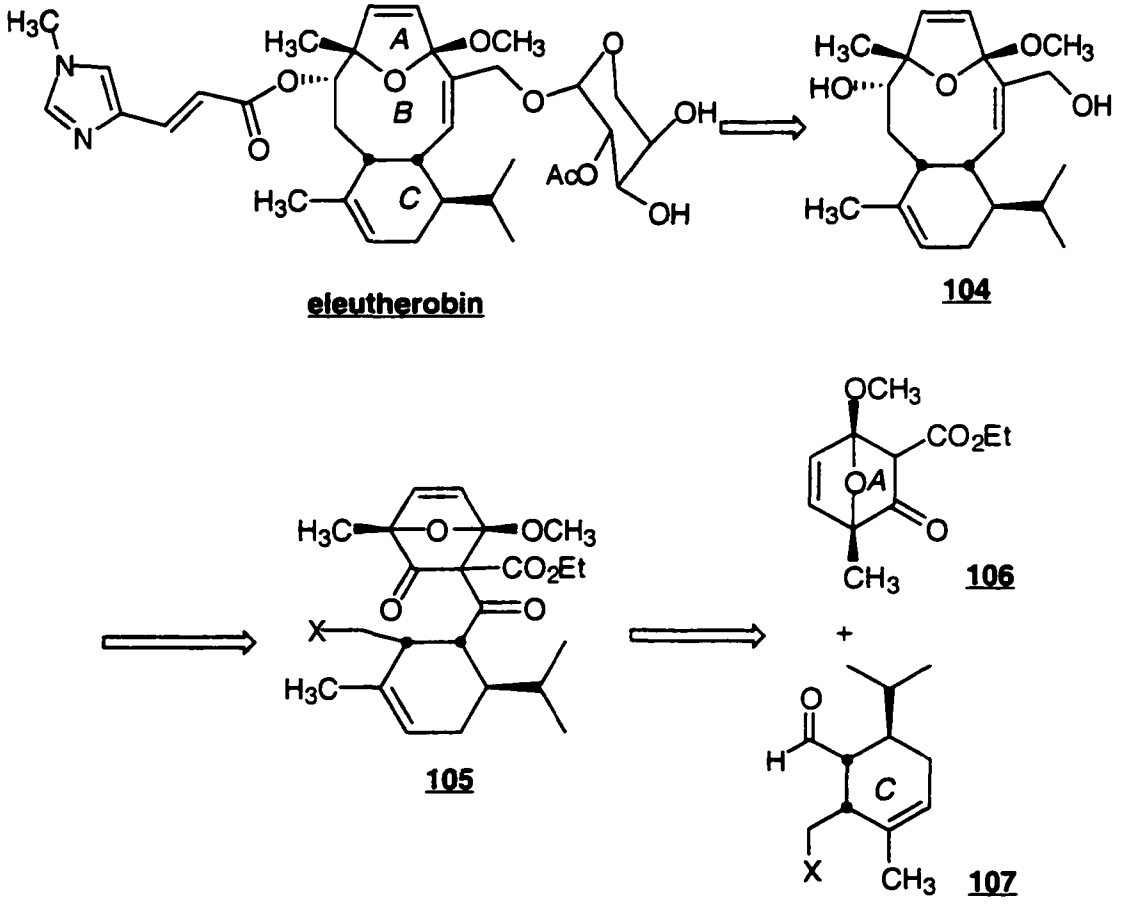
Addition-Fragmentation sequences have been used extensively to form medium ring compounds in organic synthesis. Herein we present a very brief survey of the fragmentation reactions that have been used in organic synthesis.

2.2.1 Radical Fragmentations

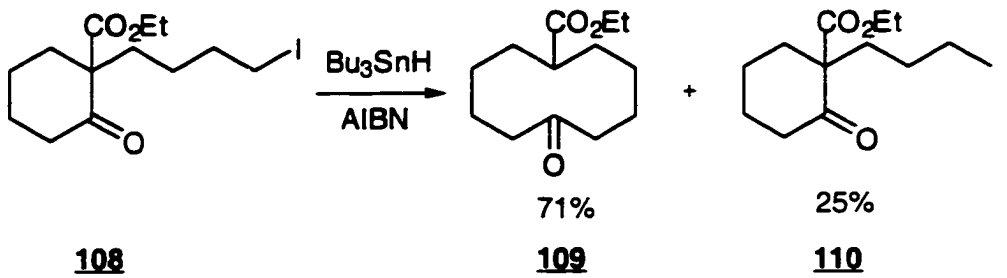
In 1987, Dowd and Choi described a route to medium-sized rings based upon the free radical promoted insertion of a three- or four-carbon chain into a cyclic β-ketoester system.[54] As shown in Scheme 2.1, when iodobutyl derivative **108** was treated with tri-n-

butyltin hydride, smooth ring expansion occurred to yield the enlarged ring product **109** together with reduction product **110**.

Figure 2.1 Retroanalysis of Eleutherobin

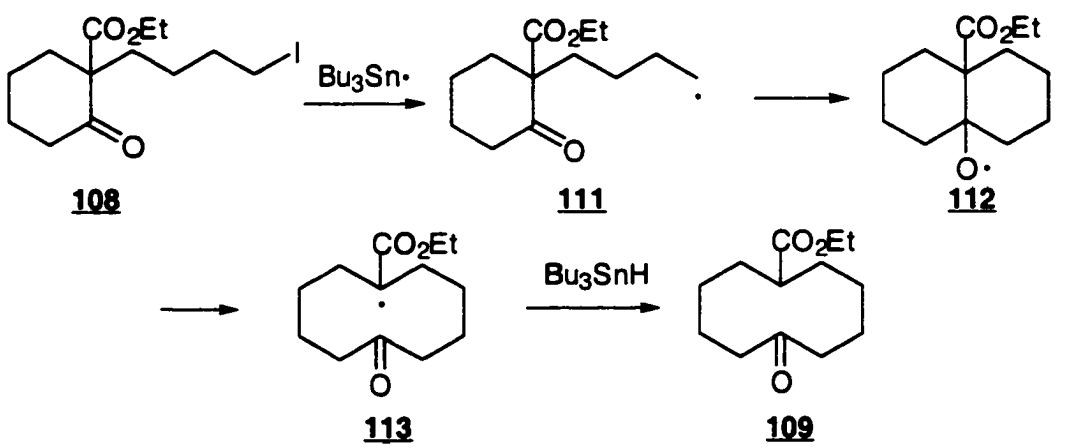


Scheme 2.1 Free Radical Addition/Fragmentation



The reaction proceeded via the addition of the pendant primary radical **111** to the ketone carbonyl followed by a fragmentation-ring expansion of the oxy radical **112** (Scheme 2.2).

Scheme 2.2 Mechanism of Free Radical Addition/Fragmentation

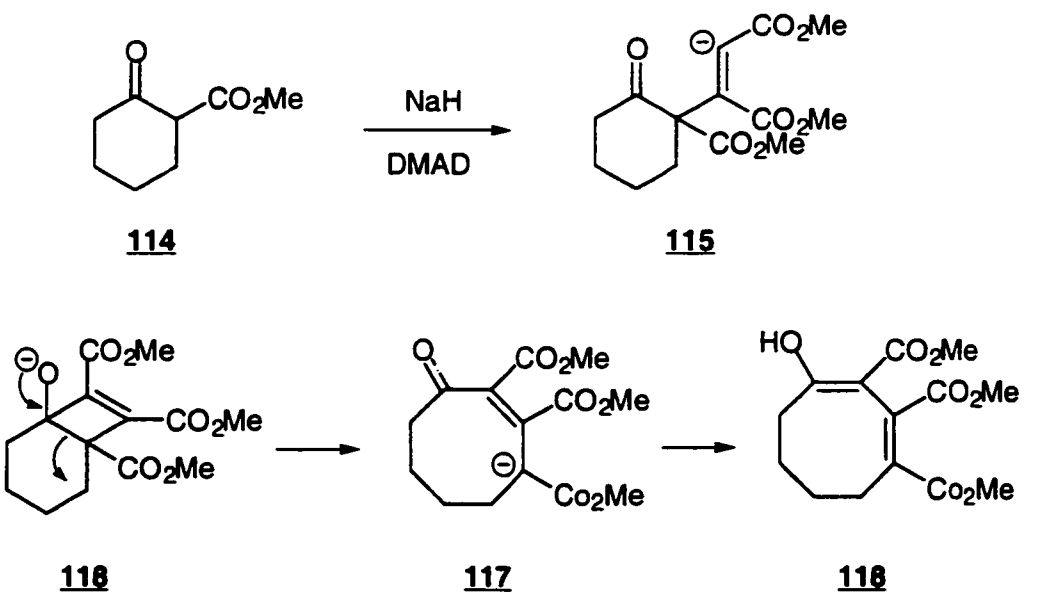


2.2.2 Anionic Fragmentations

2.2.2.1 Fragmentations Involving Activated Alkynes

Proctor and Frew[55] published an addition-retro Dieckmann fragmentation sequence of keto-esters with activated alkynes. As shown in Scheme 2.3, the anion from the deprotonation of **114** was condensed with DMAD to give anion **115** after Michael addition. Anion **115** then attacked the pendant carbonyl. Fragmentation and protonation gave 8-membered enol product **118** after protonation.

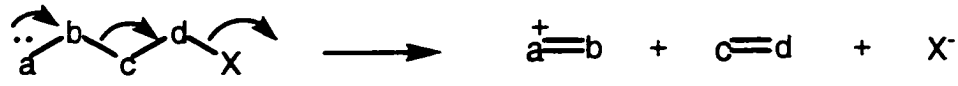
Scheme 2.3 Anionic Fragmentation Involving Activated Alkyne



2.2.2.2 Grob Fragmentations

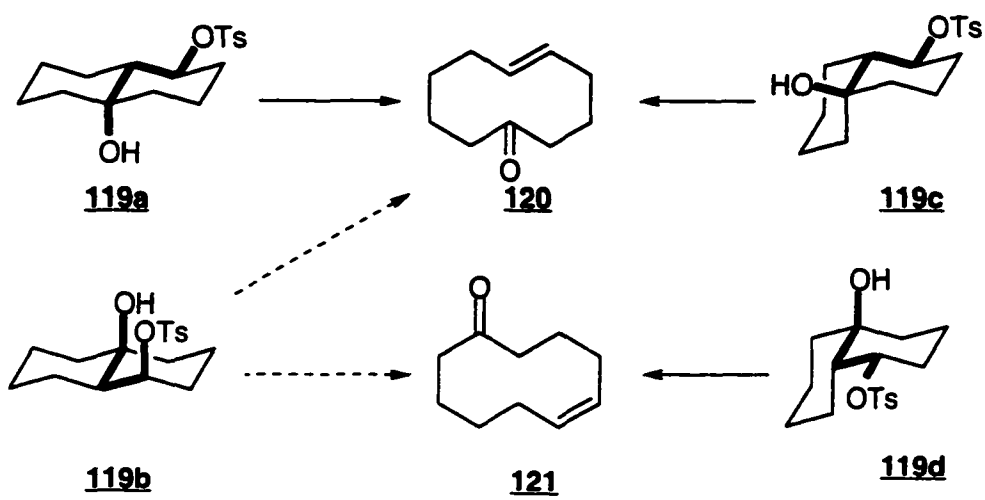
Grob fragmentation is another means of synthesizing medium sized rings involving an anionic fragmentation reaction. By definition, the Grob fragmentation refers to the fragmentation depicted in eq.2.1[56] (Eq 2.1).

Equation 2.1



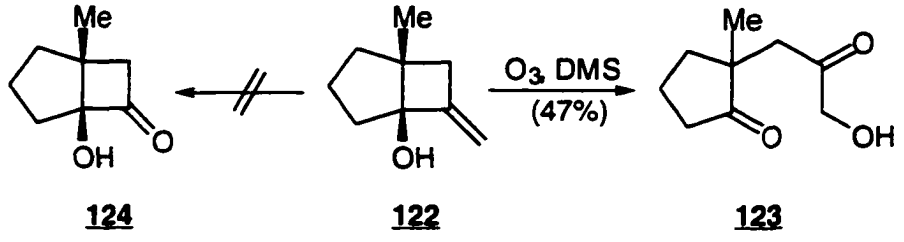
The mechanism of the Grob fragmentation is thought to involve a concerted fragmentation. Therefore the reaction occurs only when the compound can adopt a conformation where the leaving group X as well as the **b-c** bond are antiplanar to the central **c-d** bond.[57] When this stereochemical arrangement cannot be achieved, substitution reactions of the leaving group X or elimination reactions can take place. This requirement was demonstrated by Wharton[58] for the four stereoisomeric tosylates (Scheme 2.4). Tosylates **119a**, **119c** and **119d** have the crucial orientation, in these cases fragmentation to the cyclodecenones occurs in over 90% yield; the isomer **119b**, however, remains largely unchanged.

Scheme 2.4 Fragmentations of Isomeric Tosylates

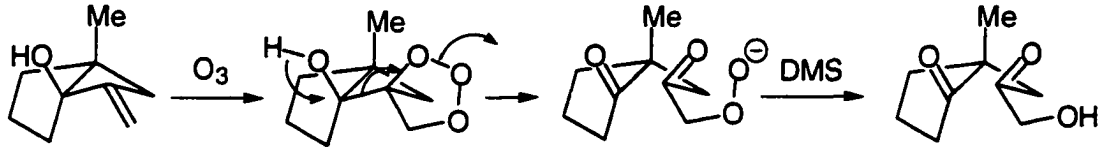


Very recently, Jung and coworkers reported an anomalous ozonolysis sequence that is thought to proceed through a Grob fragmentation.[59] As shown in Scheme 2.5, ozonolysis of **122** did not provide the normal fragmentation product hydroxy ketone **124**. Instead, cyclic hydroxy diketone **123** was isolated in moderate yield. Jung proposed that primary ozonide **125** underwent a Grob-like fragmentation to yield α-hydroperoxyketone **126**. Reductive work-up using dimethyl sulfide gave hydroxy diketone **123**.

Scheme 2.5 Trapping of Primary Ozonide



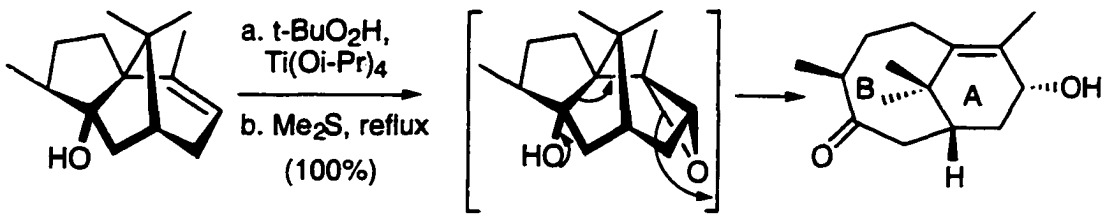
124 **122** **123**



122 **125** **126** **123**

Grob fragmentation has been widely applied to the total synthesis of natural products. Holton and coworkers[60] used a Grob fragmentation for the synthesis of AB ring system of taxane (Scheme 2.6). The synthesis involved the fragmentation of an easily accessible tricyclic compound **127** derived from patchouli alcohol. Hydroxy-directed epoxidation of **127** gave an unstable substance **128** which underwent *in situ* fragmentation to provide the keto alcohol **129**.

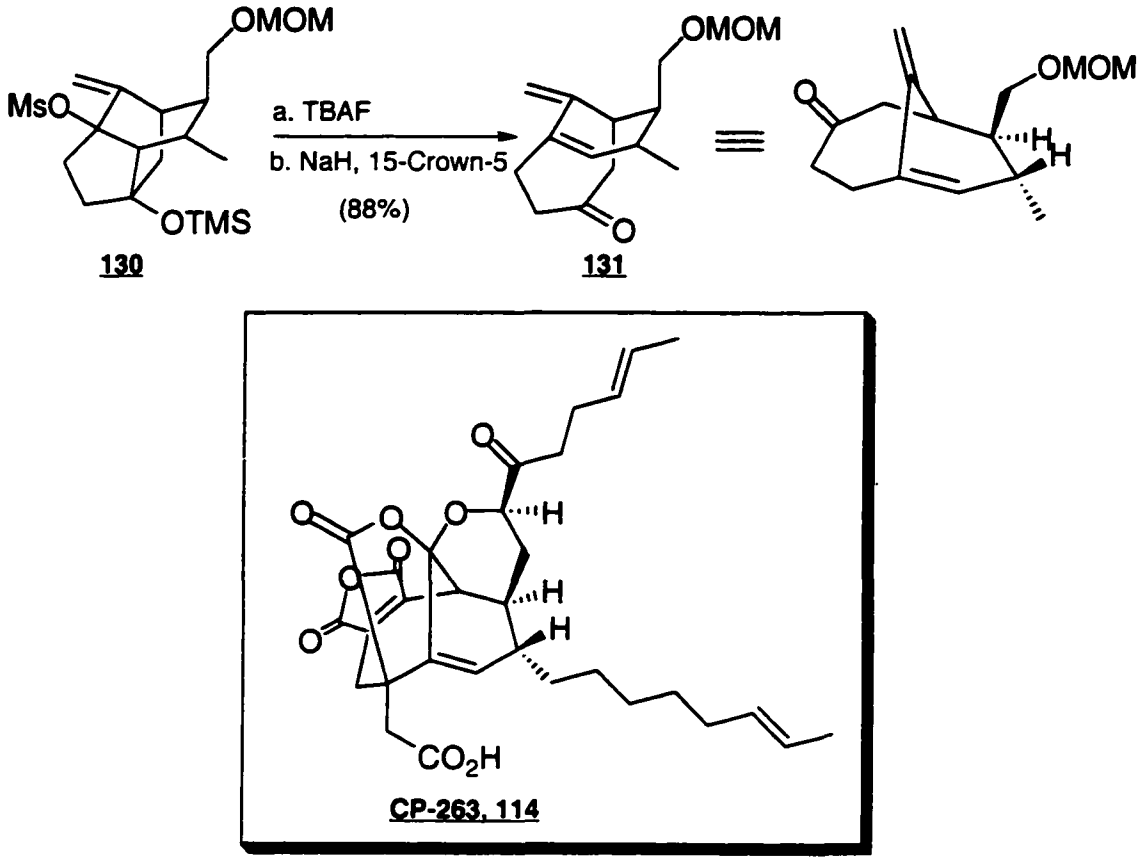
Scheme 2.6 Synthesis of Taxane AB Ring



127 **128** **129**

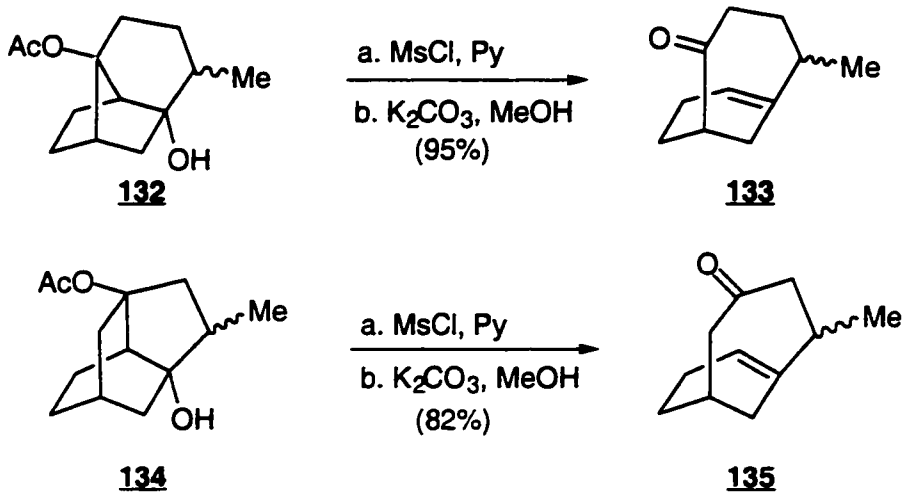
Grob fragmentation has also been successfully used by both the Yoshimitsu[61] and Wood group[62] for the synthesis of the core structure of CP-263,114. As shown in Scheme 2.7, Yoshimitsu's approach involved a Grob fragmentation that was achieved by removal of the TMS group by TBAF, followed by treatment of the resulting alcohol with NaH in the presence of 15-crown-5. This furnished the bicyclic compound **131** in 88% yield. Bicycle **131** contains the core structure of natural product CP-263,114.

Scheme 2.7 Synthesis of Core Structure of CP-263,114



Wood and co-workers also reported a fragmentation approach to the core structure of CP-263,114. As demonstrated in Scheme 2.8, treatment of **132** with MsCl followed by K_2CO_3 afforded the facile fragmentation product **133** in 95% yield. In a similar fashion, model compound **134** gave **135** in 82% yield.

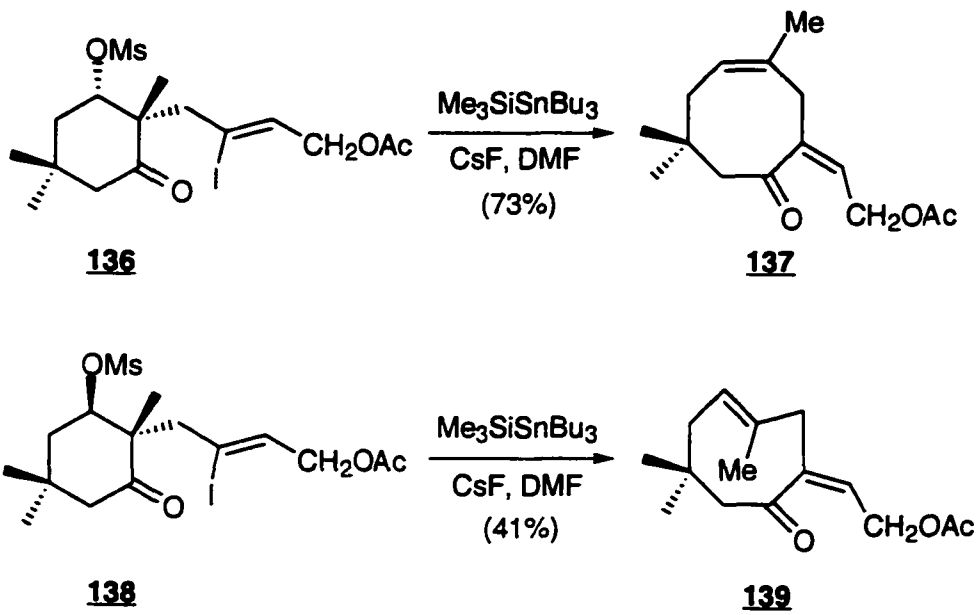
Scheme 2.8 Synthetic Strategies Toward Core Structure of CP-263,114



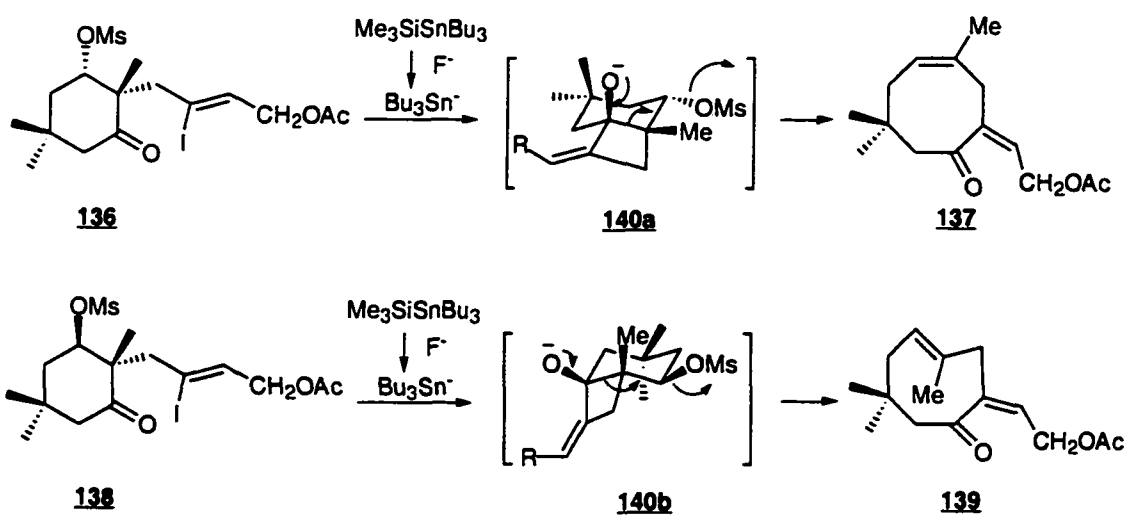
132 133 134 135

Stannyl anions have proven to be useful agent in ring expansion/Grob fragmentations of functionalized cycloalkanones. In 1999, Mori and coworkers[63] reported a novel ring expansion reaction with $Me_3SiSnBu_3$. When a DMF solution of cyclohexanone **136**, $Me_3SiSnBu_3$ (2 eq), and CsF (2 eq) was stirred at room temperature, the expanded cyclooctanone **137** was obtained in 73% yield. In a similar manner, olefin isomer **139** was formed in 41% yield from **138** (Scheme 2.9). The proposed mechanism involved the reaction of $Me_3SiSnBu_3$ with CsF to give stannyl anion via the formation of hypervalent silicate; reaction of the stannyl anion with cyclohexanone derivative **136** or **138** then produced the corresponding vinyl anion, which reacted with the pendant carbonyl group intramolecularly to generate the four-membered ring intermediate **140a** or **140b**. Ring opening of **140a** or **140b** then gave **137** or **139** respectively. The stereochemistry of the mesylate containing center determines the olefin geometry in the final product.

Scheme 2.9 Fragmentations of Cyclohexanone Derivatives

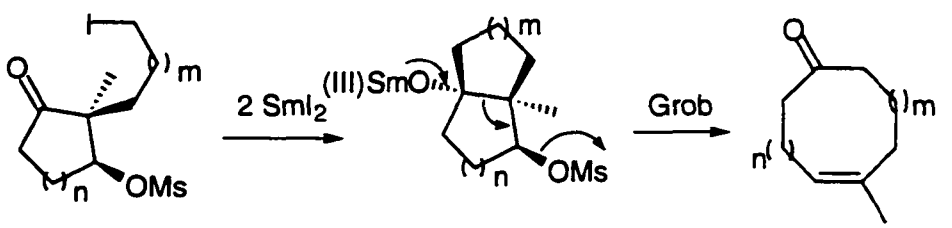


Scheme 2.10 Mechanism of Fragmentation of Cyclohexadione Derivative



SmI_2 has also been used for addition-fragmentation reactions, Molander and co-workers[64] have demonstrated that iodoketone **141** gives the ring expanded product **143** after being subjected to SmI_2 (Table 2.1).

Table 2. 1 Barbier Type Addition/Grob Fragmentation



141 **142** **143**

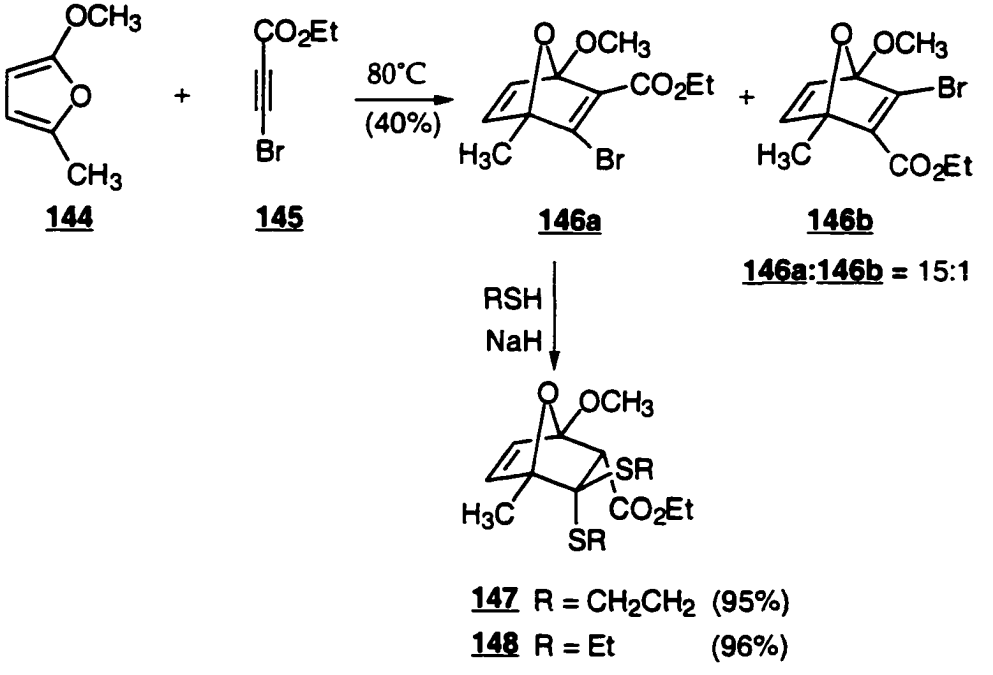
substrate	product	yield
n=1, m=1	**143a**	69
n=1, m=2	**143b**	42
n=2, m=1	**143c**	86
n=2, m=2	**143d**	51

2.3 Synthesis of Oxabicyclo[2.2.1]heptenone 106

2.3.1 First Generation Synthesis of 106

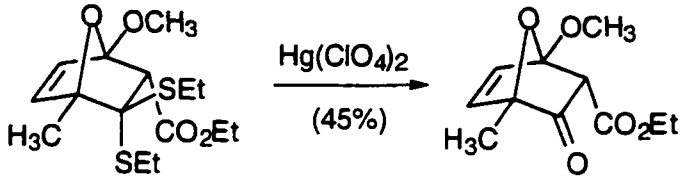
As was shown in the analysis given in Fig 2.1 (vide supra), our initial goal was to devise a strategy for the synthesis of oxabicyclo[2.2.1]heptenone **106**. It was synthesized in a three- step sequence following Leroy's conditions for the related 2,5-dihydroderivative of **106**. Dithioketal precursors to **106** came from the condensation of bromopropynoate **145** with 2-methoxy-5-methyl furan[65] **144** followed by dithioketal formation using anionic conditions[66] (Scheme 2.11).

Scheme 2.11 Synthesis of Dithioketal Derivative



As Leroy had been unsuccessful in his attempts to hydrolyze the cyclic dithiane, it was not surprising that our attempts to hydrolyze the more sensitive **147** were equally unsuccessful. Fortunately, we were able to overcome these problems by turning to the corresponding acyclic dithiane **148**. Hydrolysis of **148** using $Hg(ClO_4)_2$ provided a 45% yield of **106** (Scheme 2.12)[67].

Scheme 2.12 Synthesis of 106

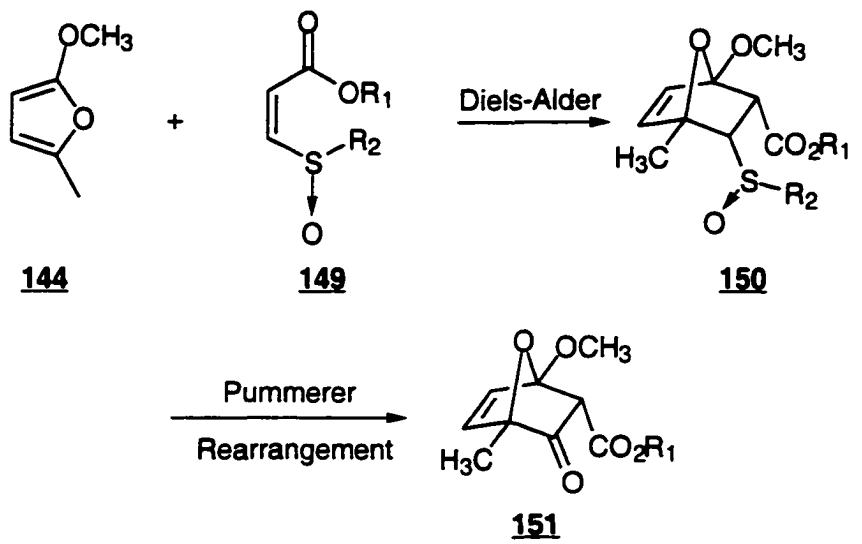


148 **106**

2.3.2 Second Generation Synthesis of Oxabicyclo[2.2.1] heptenone 106

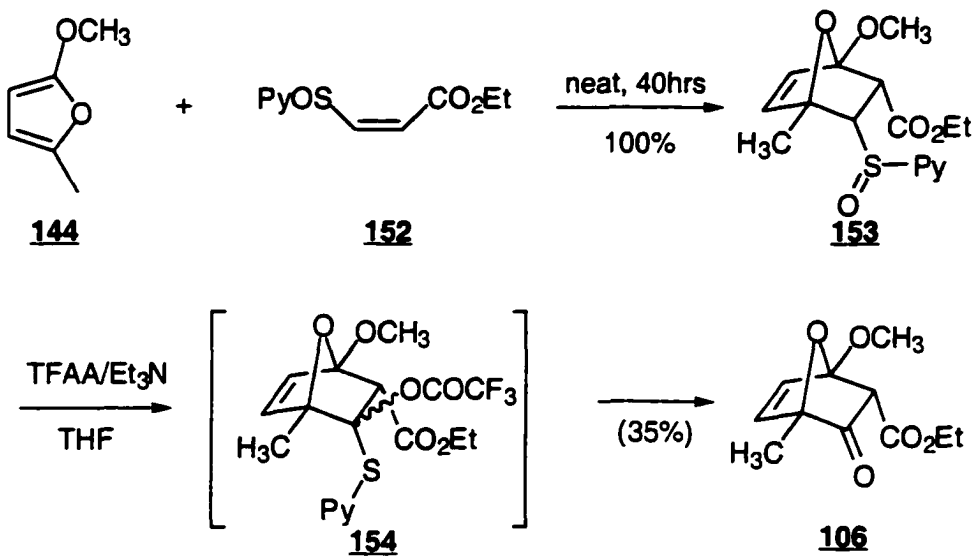
While the above sequence provided the desired ß-keto-ester **106** in a relatively efficient manner, it was not suitable for synthesis of oxabicyclo[2.2.1]heptenone in enantiomeric pure form. For this reason, we set out to find a second approach to **106**, and settled upon the use of a sulfoxide as a dienophile in a Diels-Alder reaction with 2-methoxy-5-methyl furan. In theory, the resulting bicyclic sulfoxide could be transformed into the corresponding bicyclic ketoester through a Pummerer rearrangement[68]. We were hopeful that the use of a chiral sulfoxide would provide enantiomerically enriched ketoester (Figure 2.2).

Figure 2.2 Second Generation Approach to 106



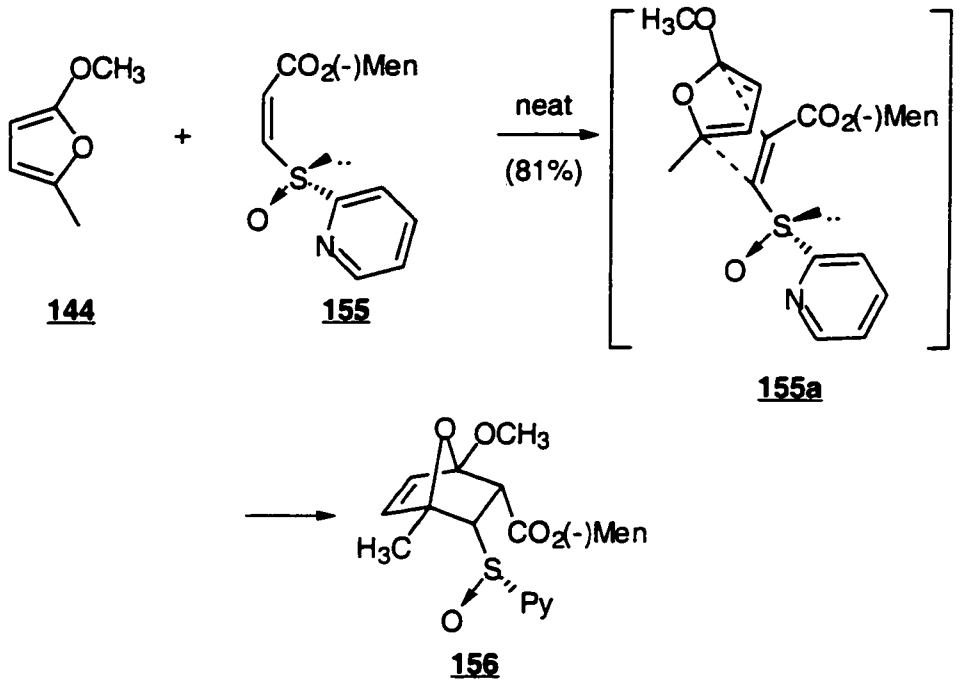
To test the feasibility of this strategy, racemic sulfoxide **152**[69] was condensed in a Diels-Alder reaction with 2-methoxy-5-methyl furan. This provided bicyclic sulfoxide **153** in quantitative yield. Treating **153** with triethylamine and TFAA gave oxabicyclo[2.2.1]heptenone **106** in 35% yield. Presumably, this reaction proceeds through mixed ketal **154**.

Scheme 2.13 Second Generation Synthesis of Oxabicyclo[2.2.1]heptenone 106



Having successfully demonstrated the applicability of this two-step sequence, we investigated its asymmetric version. From the studies carried out by Koizumi and coworkers[70], the chirality of the sulfoxide controls the facial selectivity in the Diels-Alder reaction (please refer to Scheme 5.2 for the Diels-Alder reaction between 3-methoxyfuran and diasteromeric mixture of (*S*) and (*R*) menthyl 3-(2-pyridylsulfinyl) acrylate). As shown in Scheme 2.14, (*S*) menthyl 3-(2-pyridylsulfinyl) acrylate **155** was dissolved in 5 equivalents of 2-methoxy-5-methyl furan, and stirred at rt for 40 h. This gave diasteromerically pure sulfoxide **156** in 81% yield. The product comes from the approach of the diene from the face of sulfur lone pair (or in other words, opposite to the face of pyridinyl group).

Scheme 2.14 Asymmetric Diels-Alder Reaction



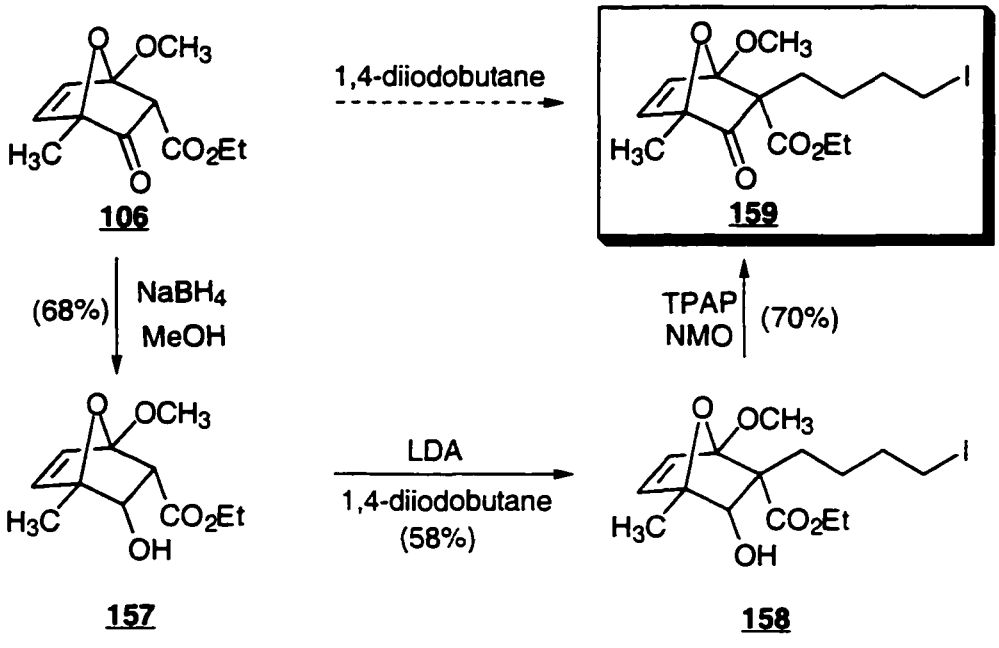
2.4 Reactions of oxabicyclo[2.2.1]heptenone 106 with iodides and subsequent fragmentation study

2.4.1 Reaction with Iodides and Synthesis of Model Compound 159

In order to test the strategy depicted in Fig 2.1, we synthesized model compound **159** and studied its addition-fragmentation chemistry. The most direct method of synthesizing **156** would involve the treatment of **106** with 1,4-diiodobutane. Unfortunately the coupling of **106** with 1,4-diiodobutane was unsuccessful using the conditions employed for the coupling of **106** with methyl iodide. In fact, prolonged exposure of **106** to the reaction conditions led to its decomposition. This problem was circumwented by reducing **106** to ß-hydroxy ester **157**. β-hydroxy ester **157** served as a much better

substrate for alkylation and hydroxyiodide **158** was formed in 58% yield. TPAP oxidation of **155** then gave model compound **159** (Scheme 2.15).

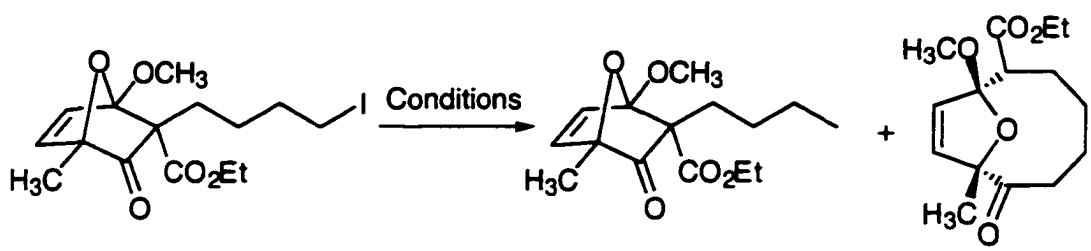
Scheme 2.15 Synthesis of Model Compound 159



2.4.2 Fragmentation Studies of 159

With **159** in hand, we studied its cyclization/fragmentation chemistry. Dowd's condition[55] (slow addition of n-Bu_3SnH and AIBN to **159**) gave only the reduced product **160**, no addition-fragmentation product **161** was found (Table 2.2).

Table 2.2 Fragmentation Studies of 159



159 160 161

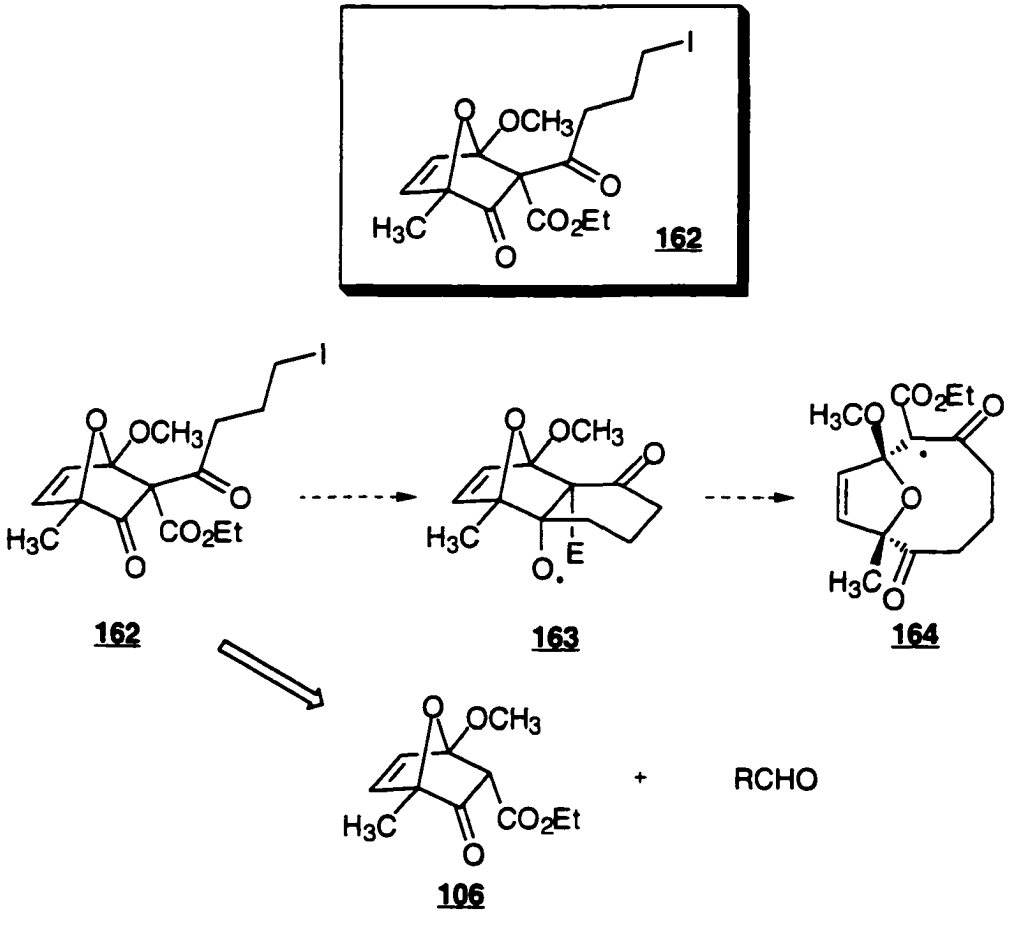
Entry	Conditions	Results
1	AIBN(10%), Bu_3SnH(1.5 eq)	exclusively 160
2	AIBN(10%),Bu_3SnH(1.5 eq)	exclusively 160
3	AIBN(10%),Bu_3SnH(1.5 eq) slowly addition(over 48hrs)	exclusively 160

2.4.3 Rationale of Failure to Effect a Fragmentation

From our studies, we suspect that the reason for the failed fragmentation could be either that the initially formed radical was not able to add to ketone moiety intramolecularly due to unfavorable entropics, or that the addition process was reversible. Keeping these factors in mind, we decided to incorporate a ketone group into the tether. The hope was that this group would facilitate the radical addition due to a favorable entropic component to the reaction energetics. Furthermore, the fragmented radical of 164 would be stabilized by two electron withdrawing groups. The synthesis of 162 was

envisioned coming from condensation of bicyclic ketoester **106** with an aldehyde followed by oxidation. However, much to our surprise, when the anion of **106** was treated with benzaldehyde, no aldol addition product was formed; instead, a rearranged dihydrofuran product was formed. This reaction will be addressed in more detail in the next chapter.

Scheme 2.16 Modification of Model Compound



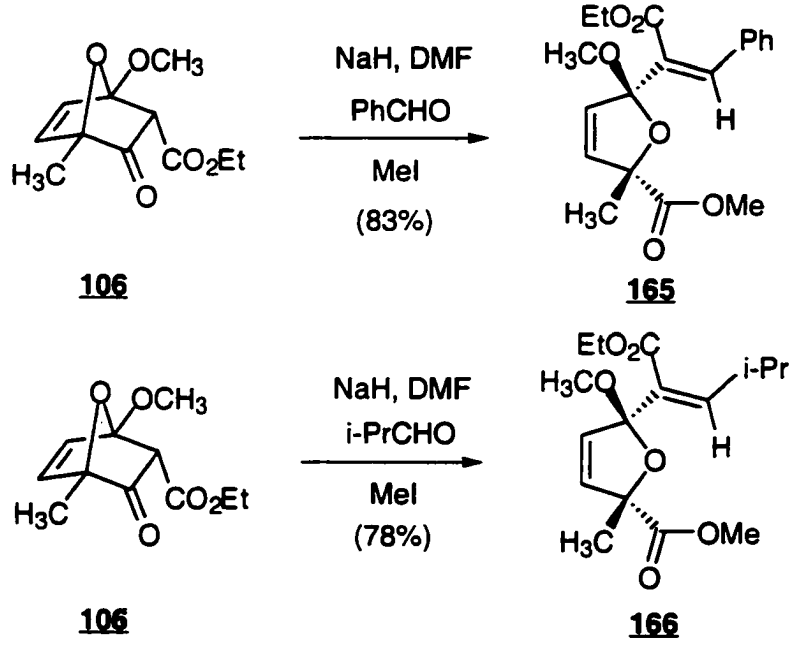
Chapter 3 Fragmentation Chemistry of Oxabicyclo[2.2.1]heptenone 106

3.1 Reactions of Oxabicyclo[2.2.1]heptenone 106 with Aldehydes

3.1.1 An Unexpected Rearrangement

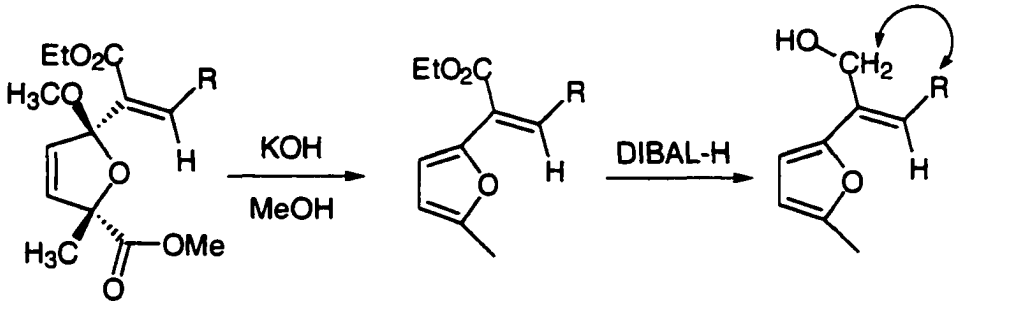
As discussed in the previous chapter, when the anion of oxabicyclo[2.2.1]heptenone **106** was exposed to benzaldehyde at 0°C, dihydrofuran product **165** was formed in good yield after quenching the reaction with methyl iodide. The condensation with isobutyraldehyde proceeded in a similar manner (Scheme 3.1).[71]

Scheme 3.1 An Unexpected Rearrangement



Much effort was devoted to determining the olefin geometry of **165** and **166**. NOESY spectra did not provide useful information; there were no NOE enhancements observed between the ethyl ester hydrogens and any other hydrogens. Efforts were also made to reduce the ester group to the corresponding hydroxymethyl group with the hope that we might observe NOE enhancements between the methylene hydrogens of the hydroxymethyl group and nearby hydrogens. However, the reduction did not give alcohol product, instead the starting material decomposed during the reaction condition. After much experimentation, we were finally able to determine the olefin geometry by converting the dihydrofuran product to substituted furans **169** and **170** (Scheme 3.2). Treatment of **165** and **166** with methanolic KOH resulted in hydrolysis, decarboxylation, and aromatization to give **167** and **168** respectively. DIBAL reduction then gave allyl alcohols **169** and **170**. As depicted, NOESY cross-peaks were observed between the isopropyl/phenyl hydrogens and the methylene hydrogens of the hydroxymethyl group, thereby establishing the trisubstituted olefin geometry.

Scheme 3.2 Determination of the Olefin Geometry



165 R = Ph
166 R = *i*-Pr

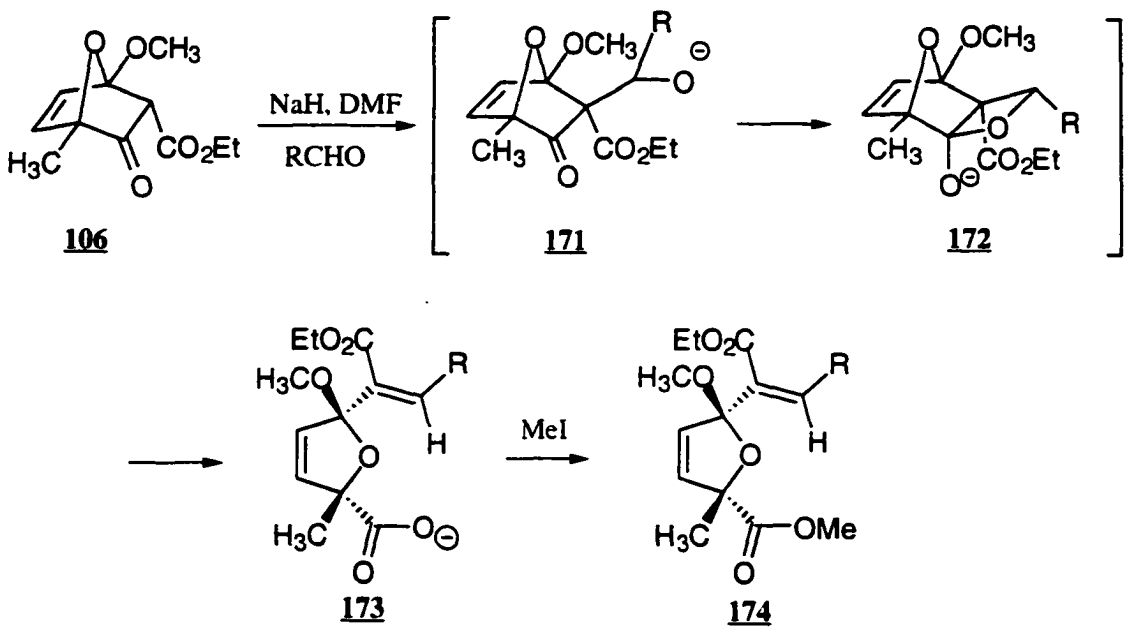
167 R = Ph (87%)
168 R = *i*-Pr (90%)

169 R = Ph (78%)
170 R = *i*-Pr (30%)

3.1.2 Mechanism of the Addition-Fragmentation-Elimination Sequence

While any detailed mechanistic discussion requires further experimentation, a reasonable working hypothesis is depicted in Scheme 3.3. It is highly likely that aldol condensation to give **171** precedes fragmentation. We believe that alkoxide **171** undergoes cyclization to **172**. Fragmentation then generates furan **173**. Trapping with MeI provides the final isolable product. The nature of the selectivity in the formation of the olefin is not readily apparent.

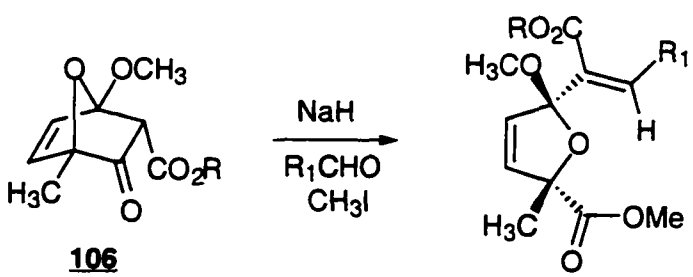
Scheme 3.3 Mechanism of the Addition-Fragmentation-Elimination Sequence



3.1.3 Addition-Fragmentation-Elimination Reactions of 106 with Aldehydes

We were pleased to find that the condensation/fragmentation was general. In addition to benzaldehyde and isobutyraldehyde, 4-benzyloxybutanal, 3-benzyloxycarbonyl-aminopropanal and ethyl glyoxylate also underwent the condensation and fragmentation sequence to give furans **175a**, **175b** and **175c** in 68%, 61% and 91% yields respectively. Each of the products existed either predominantly or exclusively as its *Z*-olefin isomer. In an effort to examine whether the ester was playing a role, replacement of the ethyl ester group of the starting ß-ketoester with a *t*-butyl ester did not have a significant influence on the reaction. As illustrated in Table 3.1, reaction of **106** with isobutyraldehyde and benzaldehyde gave **176a** and **176b** in 83% and 74% yield respectively. In both instances the *Z*-olefin product was still favored.

Table 3.1 Reactions of 106 with Aldehydes



106

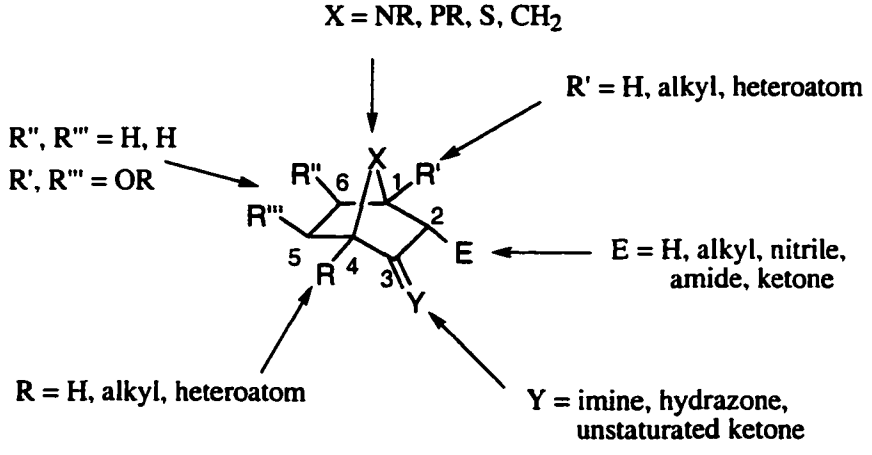
Entry	R	R_1	Furan	Yield	*E:Z*
1	Et	$(CH_2)_3OBn$	**175a**	68%	0:1
2	Et	$(CH_2)_2NHCbz$	**175b**	61%	0:1
3	Et	CO_2Me	**175c**	91%	1:3
4	t-Bu	i-Pr	**176a**	83%	0:1
5	t-Bu	Ph	**176b**	74%	1:9

3. 2 Scope of the Addition-Fragmentation-Elimination Sequence

3.2.1 Synthesis of Various Bicyclic Ring Systems

In an effort to further determine its scope, we also subjected other bicyclic substrates to the reaction conditions. Fig 3.1 lists the possible bicyclic ring manipulations. These include: (a) the effect of saturation and heteroatoms at C-5 and C-6; (b) substitutions on the bridge; (c) the bridgehead substitution; (d) the effect of anion stabilizing groups other than β-ketoester on the reaction. Each of these studies will provide us with information concerning the condensation-fragmentation sequence as well as providing us with interesting products.

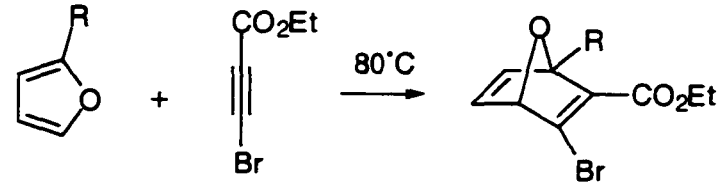
Fig 3.1 Manipulations of Bicyclic Ring System



We have not studied all of the above variations yet, shown below are our results thus far. The oxabicyclo[2.2.1] ring systems used in this study are readily accessible using the

same sequence as before (Diels-Alder cycloaddition reaction between bromopropynoate and the appropriate diene followed by a two-step hydrolysis of the bicyclo[2.2.1]heptenone ring system). In this manner, we were able to synthesize the two oxabicyclo[2.2.1] ring systems shown in Scheme 3.4. These substrates were generated in an effort to determine the effect of bridgehead substitution on the reaction.

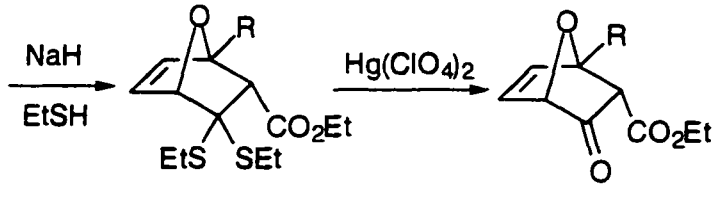
Scheme 3.4 Syntheses of Various Oxabicyclic Ring Systems



145

177 R= CH_3, (55%)

178 R= H, (25%)



179 R= CH_3, (96%)

180 R= H, (89%)

(Endo:Exo=3:1)

181 R=CH_3, (66%)

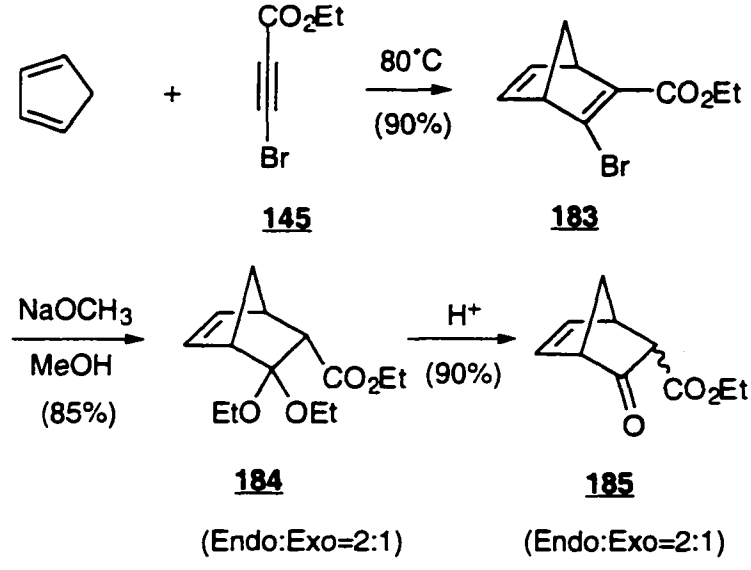
182 R=H, (55%)

(Endo:Exo=2:1)

We have also examined bicyclo[2.2.1]heptenone **185**. As depicted, its synthesis involved the Diels-Alder cycloaddition between cyclopentadiene and bromopropiolate

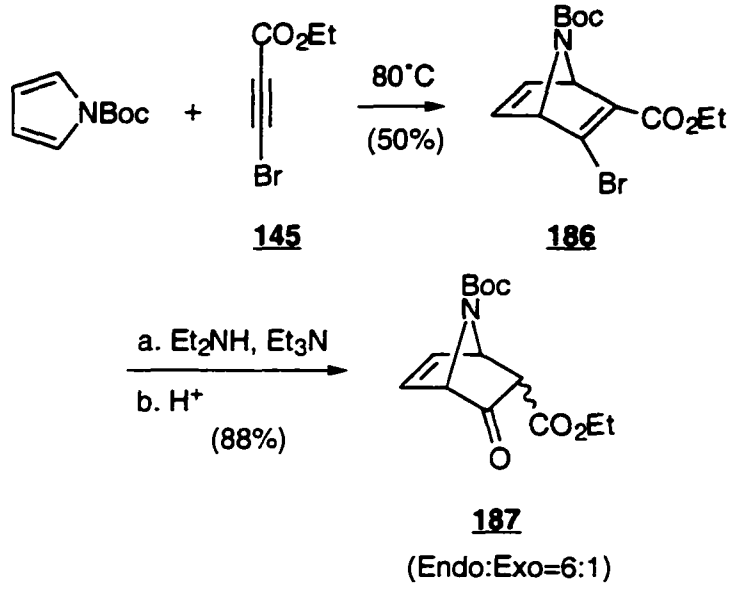
145. Conversion of cycloadduct **183** into diethyl ketal **184**, acidic hydrolysis of **184** then gave β-ketoester **185** in excellent yield (Scheme 3.5).

Scheme 3.5 Synthesis of Bicyclo[2.2.1]heptenone 185



We have also examined the corresponding azabicyclic ring system. By following Trudell and coworker's two-step sequence[72] we were able to synthesize azabicyclio[2.2.1]heptenone **187**.

Scheme 3.6 Synthesis of Azabicyclo[2.2.1]heptenone 187



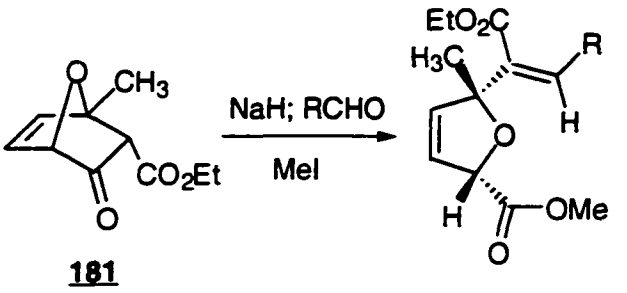
145 186 187

(Endo:Exo=6:1)

3.2.2 Addition-Fragmentation-Elimination Reactions of 181

As was mentioned above, we do not currently have an explanation for the predominance of the *Z*-olefin from the coupling reactions of **106**. However, we do know that bridgehead substitution is important in the selectivity. The condensation of **181** with isobutyraldehyde and benzaldehyde led to the exclusive formation of *Z*-olefin product **188** and **189** in 65% and 80% yield respectively (Table 3.2), the olefin geometry was confirmed through NOESY spectra of the corresponding reduction products.

Table 3.2 Addition-Fragmentation-Elimination Reactions of 181



181

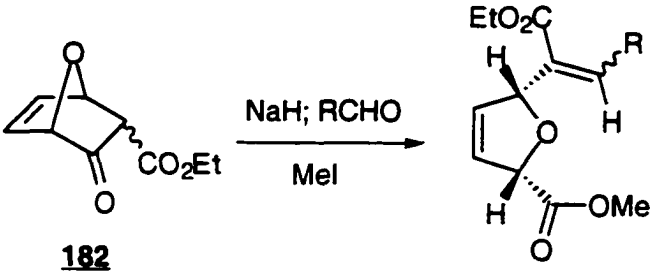
Entry	R	Furan	Yield	Z:E[a]
1	i-Pr	**188**	65%	1:0
2	Ph	**189**	80%	1:0

a. determined through ^{1}HNMR

3.2.3 Addition-Fragmentation-Elimination Reactions of 182

In contrast to the condensation of **181** and **106**, the condensation of 2.5-unsubstituted oxabicyclo[2.2.1]heptenone **182** with isobutyraldehyde and benzaldehyde led to mixtures of the *E*- and *Z*- alkenes of **190** and **191** in 45% and 56% yield respectively (see Table 3.3).

Table 3.3 Addition-Fragmentation-Elimination Reactions of 182



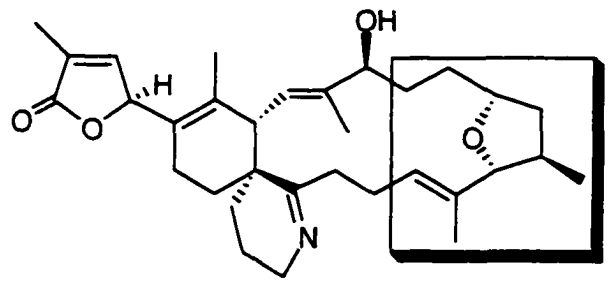
182

Entry	R	Furan	Yield	Z:E[a]
1	i-Pr	**190**	45%	2:1
2	Ph	**191**	56%	1:3

a. determined through ^{1}HNMR

After its optimization, this particular reaction might be useful for the synthesis of gymnodimine. Gymnodimine is a potent marine toxin produced by the dinoflagellate *G.* cf. *Mikimotoi* that is responsible for the neurotoxic shellfish-poisoning incident that occurred on the North Island of New Zealand in 1993[73]. Its interesting biological property and structural features have inspired several approaches toward its total synthesis[74]. As shown in Fig 3.2, gymnodimine contains a substituted tetrahydrofuran moiety; we believe that the elaboration of our addition-fragmentation sequence could lead to the synthesis of this portion of the molecule.

Fig 3.2 Structure of Gymnodimine

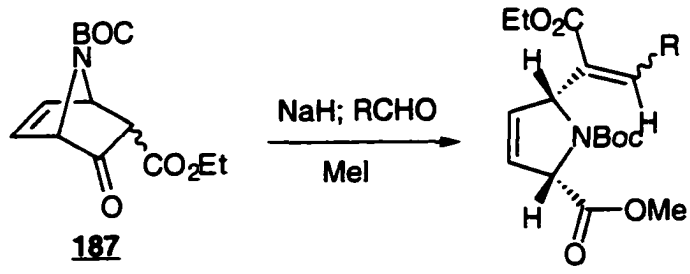


Gymnodimine

3.2.4 Addition-Fragmentation-Elimination Reactions of 187

The azabicyclo[2.2.1]heptenone **187** also undergoes the condensation, fragmentation and elimination sequence. As illustrated in Table 3.4, the condensation of **187** with isobutyraldehyde, benzaldehyde, propanal, ethyl glyoxylate, fufural, 4-methoxybenzaldehyde gave dihydropyrroles **192**, **193**, **194**, **195**, **196** and **197** in 60%, 76%, 84%, 83%, 87% and 70% yields respectively. These results are provided by Dr. Mahika Weerasakare.

Table 3.4 Addition-Fragmentation-Elimination Reactions of 187



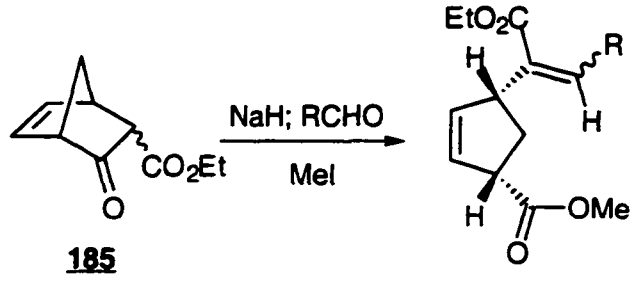
Entry	R	Products	Yield	Z:E[a]
1	i-Pr	192	60%	1:0
2	Ph	193	76%	3:1
3	Et	194	84%	3:1
4	CO_2Et	195	83%	4:1
5	C_4H_3O	196	87%	3:1
6	$CH_3OC_6H_4$	197	70%	5:1

a. determined through ^{1}HNMR

3.2.5 Addition-Fragmentation-Elimination Reactions of 185

In contrast to the above reactions, which predominantly form *Z*-olefins, the all carbon bicyclo[2.2.1] heptenone **185** gave predominantly or exclusively *E*-olefins. As shown in Table 3.5, **185** reacted with isobutyraldehyde and benzaldehyde to give substituted cyclopentenes **198** and **199** in 94% and 91% yields respectively. In both instances, the *E*-olefin was produced as the major product.

Table 3.5 Addition-Fragmentation-Elimination Reactions of 185



185

Entry	R	Products	Yield	Z:E[a]
1	i-Pr	198	94%	1:3
2	Ph	199	91%	0:1

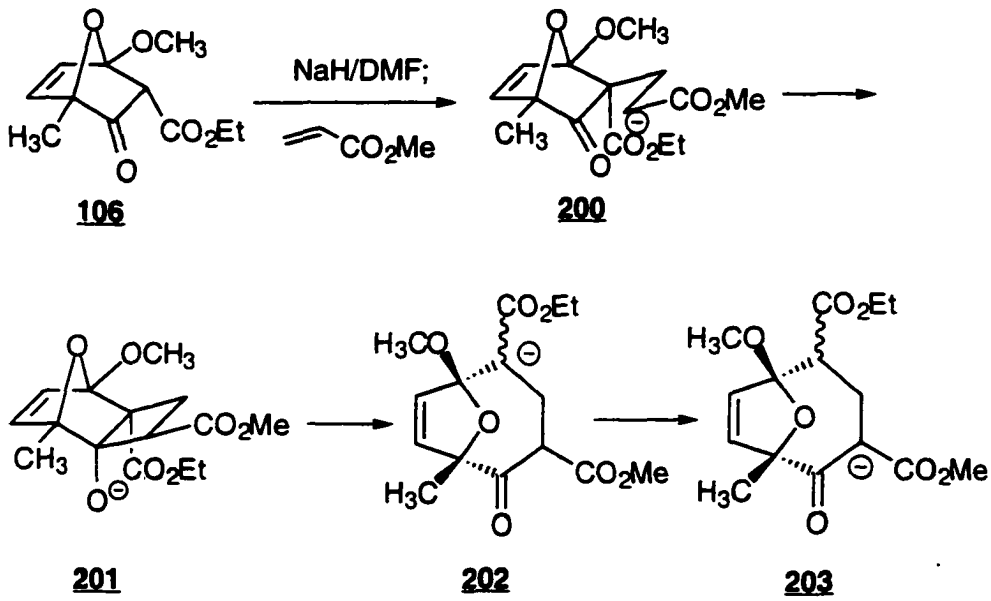
a. determined through ^{1}HNMR

3.3 Two and Four-Carbon Ring Expansions

3.3.1 Two-Carbon Ring Expansions of Oxabicyclo[2.2.1]heptenone 106

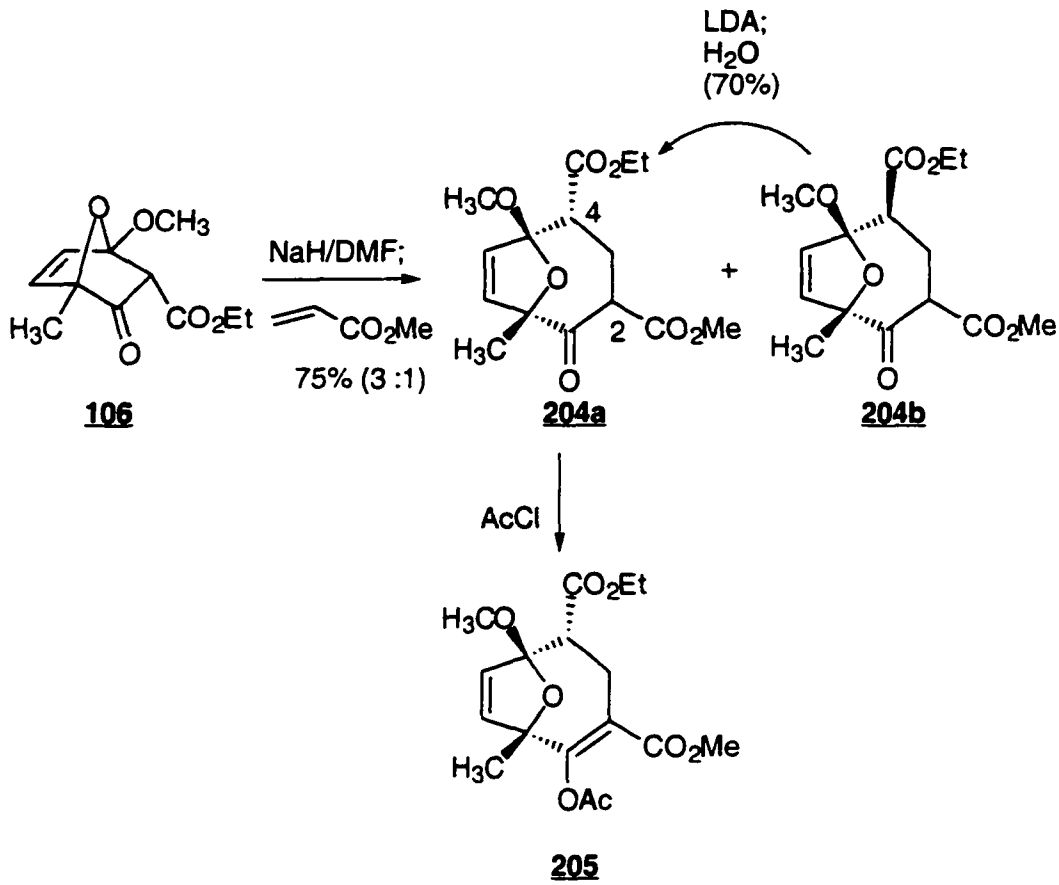
Having discovered the interesting reactions of aldehydes with various bicyclo[2.2.1]heptenones, a program was initiated to examine the hypothesis presented in Scheme 3.7. If **106** could be induced to undergo a Michael addition onto an activated alkene and if the aldehyde mechanism (Scheme 3.3) were operative, the Michael adduct would undergo cyclization onto the pendant ketone to generate two-carbon ring expanded products[75].

Scheme 3.7 Hypothesis for Two-Carbon Ring Expansion



With this in mind, **106** was subjected to NaH followed by addition of methyl acrylate. As was the hope, products from this reaction were expanded bicycles **204a** and **204b** as a 2.5:1 mixture of readily separable diastereomers at C-4. When combined with our aldehyde condensation studies, this experiment demonstrated that the formation of four-membered rings is facile in oxabicyclo[2.2.1]heptenone condensations. The major product **204a** was shown to be a 1:1 mixture at C-2; upon treating **204a** with KO*t*-Bu followed by AcCl, enol acetate **205** was formed. The minor diastereomer **204b**, when deprotonated with LDA followed by quenching with water, can be converted into the major diastereomer in 70% yield (Scheme 3.8).

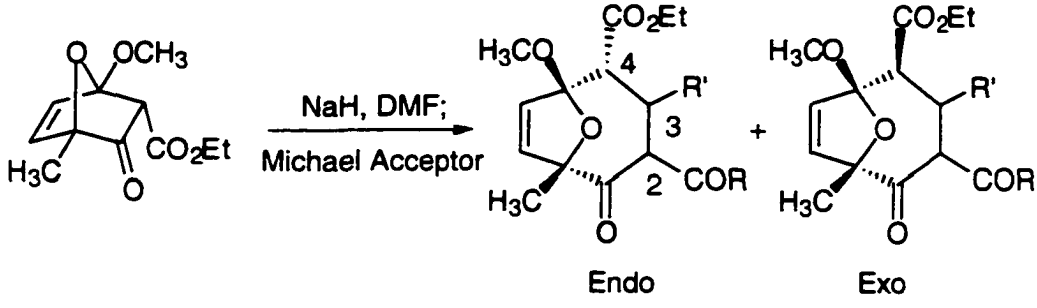
Scheme 3.8 Reactions of 106 with Methyl Acrylate



As presented in Table 3.6, other Michael acceptors also underwent the two-carbon ring expansion cascade with **106**. Thus dimethyl fumarate gave ring expanded product **206** in 69% yield, 4-pentenyl acrylate gave **207** in 70% yield. In addition, α,β-unsaturated conjugated ketone also underwent the ring expansion reaction; methyl vinyl ketone and 4- pentenylvinyl ketone gave the corresponding ring expanded products **208** and **209** in 60% and 70% yields respectively. However, the use of methyl methacrylate led to the recovery of starting material. From the mechanism of the expansion (Scheme

3.7), hydrogen transfer to the final β-ketoester **199** from **198** occurred in the course of the reaction. We believe that the presence of the methyl group in methyl methacrylate blocks this hydrogen transfer process, and thus the expansion was not able to proceed.

Table 3.6 Reactions of 106 with Other Michael Acceptors



Michael Acceptor	R	R'	Product	Yield	Endo:Exo
Dimethyl Maleate	OCH_3	CO_2CH_3	**206**	69%	3.3:1[a]
4-Pentenyl Acrylate	$O(CH_2)_2CHCH_2$	H	**207**	70%	3.4:1
Methyl Vinyl Ketone	CH_3	H	**208**	60%	3:1
4-Pentenylvinyl Ketone	$(CH_2)_3CHCH_2$	H	**209**	70%	3:1
Methyl Methacrylate	OCH_3	H	**210**	----[b]	----

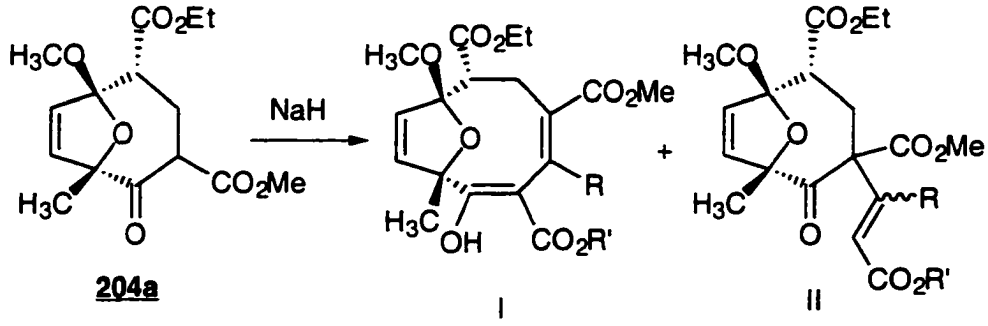
[a] Mixture of three diastereomers at C-3 and C-4

[b] Reaction led to the recovery of starting material

3.3.2 Ring Expansions of Oxabicyclo[4.2.1]nonene 204a

Having demonstrated the two-carbon ring expansions of **106**, we turned our attention back to the synthesis of oxygenated cembranoids. We became intrigued with the possibility of generating their oxygen-bridged 10-membered ring through an anionic two-carbon ring expansion reaction of oxabicyclo[4.2.1]nonene **204a**. Using the protocol of Proctor and Frew[55], treatment of **204a** with NaH followed by addition of DMAD resulted in the formation of oxygen bridged cyclodecatriene **211** in 92% yield (Table 3.7). Unfortunately, other activated alkynes were not as reactive as DMAD. For example, when **204a** was exposed to NaH followed by ethyl propiolate we isolate in 60% yield of a 1:1 mixture of ring expanded product **212** and Michael adducts **213** respectively.

Table 3.7 Ring Expansions of Oxabicyclo[4.2.1]nonene 204a

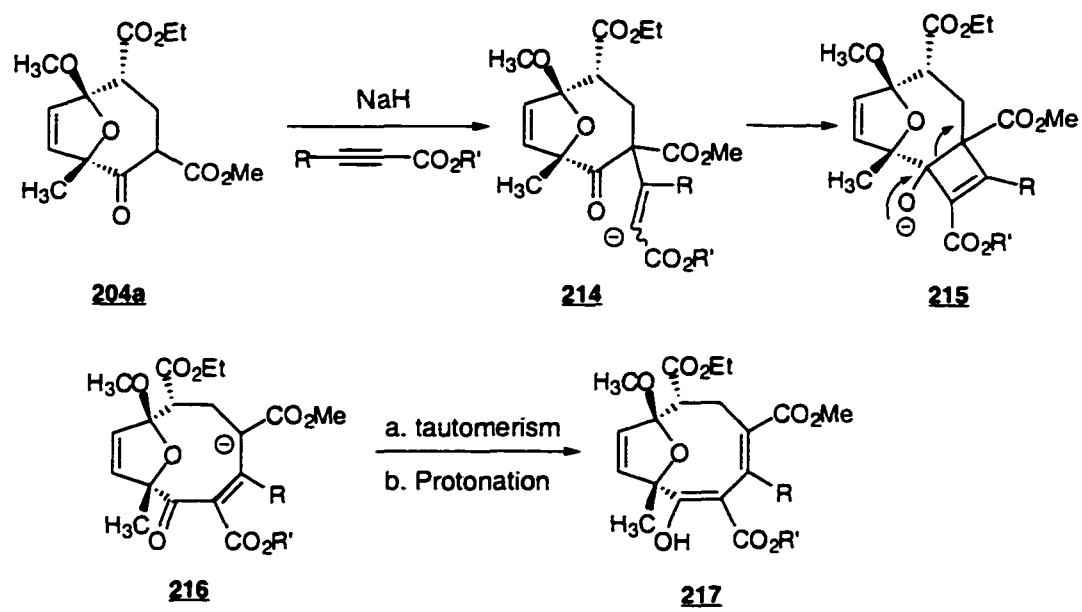


204a I II

alkyne	R	R'	Product	Yield	I:II
MeO_2C—≡—CO_2Me	CO_2CH_3	Me	**211**	92%	1:0
≡—CO_2Et	H	Et	**212, 213**	60%	1:1

As has been discussed by Proctor[55], the reaction leading to **211** and **212** most likely proceeds through the formation of a cyclobutene intermediate followed by a subsequent fragmentation reaction (Scheme 3.9).

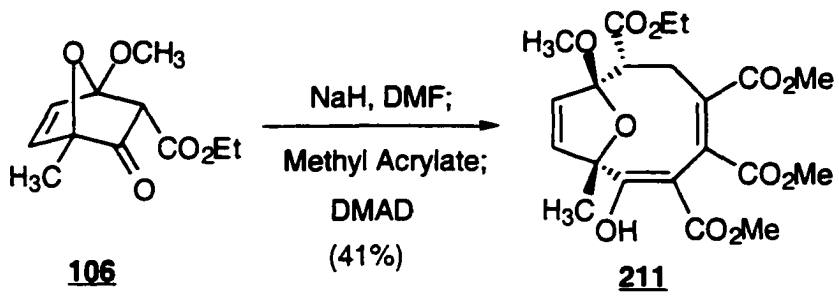
Scheme 3.9 Mechanism for the Ring Expansion of 204a



3.3.3 Single Flask Four-Carbon Ring Expansion

By taking advantage of the proton transfer that was observed in the initial two-carbon ring expansion reaction (Scheme 3.10), we were able to carry out a single flask, four-carbon ring expansion of **106**. That is, by exposing **106** to NaH and DMF followed by methyl acrylate and then DMAD in THF we were able to isolate oxygen bridged cyclodecatriene **211** in 42% overall yield.

Scheme 3.10 Single-Flask Four-Carbon Ring Expansions



106 211

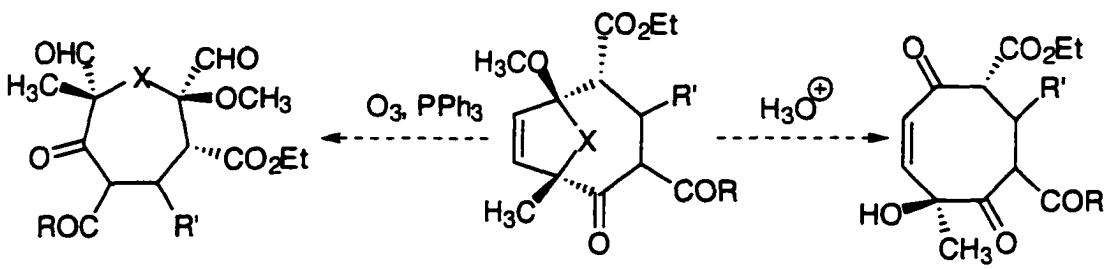
- FOUR BONDS BEING FORMED, 2 BROKEN

3.4 Utility of Bicyclo[4.2.1] Ring Systems-the Synthesis of 7,8-Membered Rings

We are confident that the tandem anionic ring expansion reactions described above will allow us to generate a variety of highly functionalized medium rings. For example, from bicyclo[4.2.1] systems **218**, the oxidative fragmentation of the olefin will provide functionalized 7-membered rings **219**. Alternatively, hydrolysis of **218** will allow us to access functionalized cyclooctenones **220**. As seven-and eight- membered carbacycles and oxacycles are key components in a number of biologically active molecules, we are confident that this chemistry will have an impact on the synthesis of these systems and thus on the study of the biological processes that these agents might effect. An added benefit to the use of bridged structures will be the conformational constraints inherent to bicyclic systems that are not present in the corresponding medium ring compounds. By

taking advantage of these constraints, the stereoselective functionalization of a number of ring systems should be possible.

Scheme 3.11 Elaboration of Bicyclo[4.2.1] Ring System



3.5 Conclusion

We have identified an unprecedented anionic condensation, fragmentation, and elimination sequence from the coupling of bicyclo[2.2.1]heptenones with aldehydes. This reaction leads to the stereoselective formation of disubstituted five-membered rings, which are present in a wide array of bioactive molecules. In addition, oxabicyclo[2.21]heptenones and oxabicyclo[4.2.1]nonenes undergo anionic two-carbon ring expansions with various Michael acceptors. These reactions result in the efficient formation of oxabicyclo[4.2.1]nonenes and oxygen-bridged cyclodecene skeletons, respectively. The efficiency of these ring expansion reactions bodes favorably for their use in the synthesis of bioactive targets, which contain medium-sized rings.

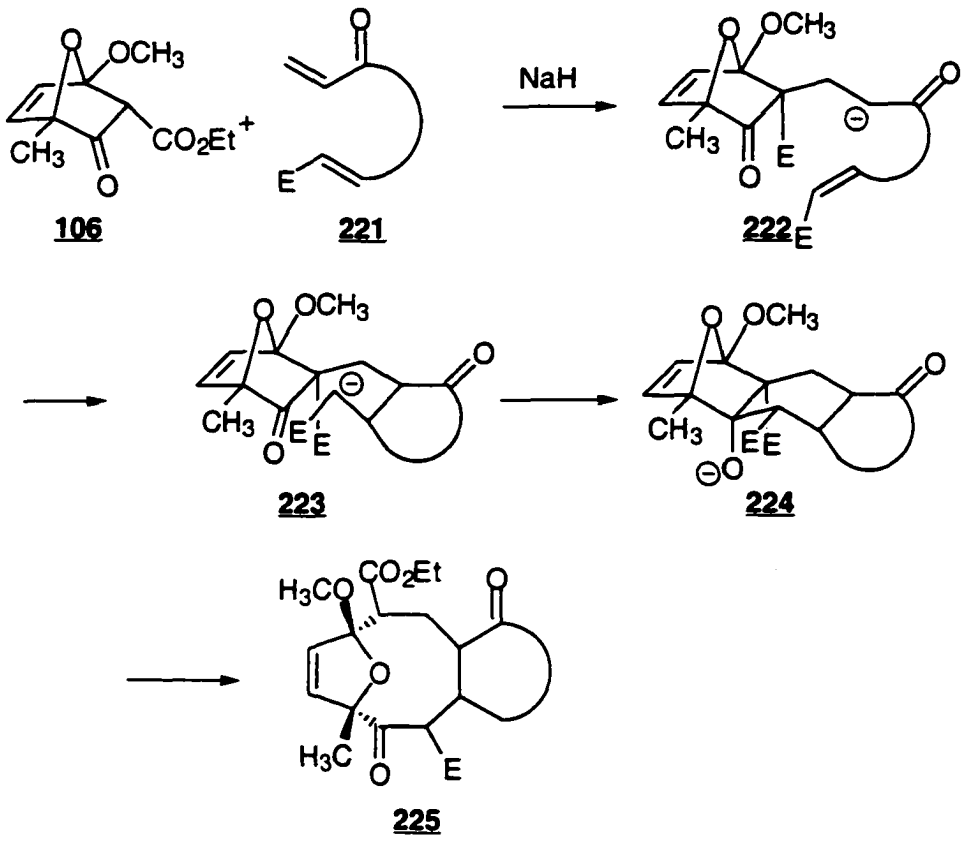
Chapter 4 Tandem Anionic Fragmentation

4.1 Introduction

Having demonstrated the formation of **211** from **106** through two sequential two-carbon ring expansion reactions, we became curious about the possibility of using a similar protocol to generate the oxygenated cembranoids carbon skeleton. That is, we believed that the oxygenated cembranoids might come from the anionic coupling of **106** with a molecule containing two Michael acceptors linking one another through an alkyl chain (e.g. **221**) As demonstrated in Scheme 4.1, we initially envisioned a 'round trip' mechanistic pathway for the conversion of **106** to **225**. Immediately after Michael addition, the anion of **222** was expected to undergo a 6-exo-trig cyclization onto the pendant activated alkene. Anionic cyclization onto the pendant ketone would then afford **224**. Following oxyanionic fragmentation of the bicyclic ring system, compound **225** would result. If this endeavor were successful, we would be nicely positioned to efficiently generate a wide variety of oxygenated cembranoids from relatively simple substrates.

With this goal in mind, we synthesized a series of molecules containing two Michael acceptor functionalities and studied their reactions with **106**. Shown below are the results.

Scheme 4.1 Tandem Fragmentation Reaction

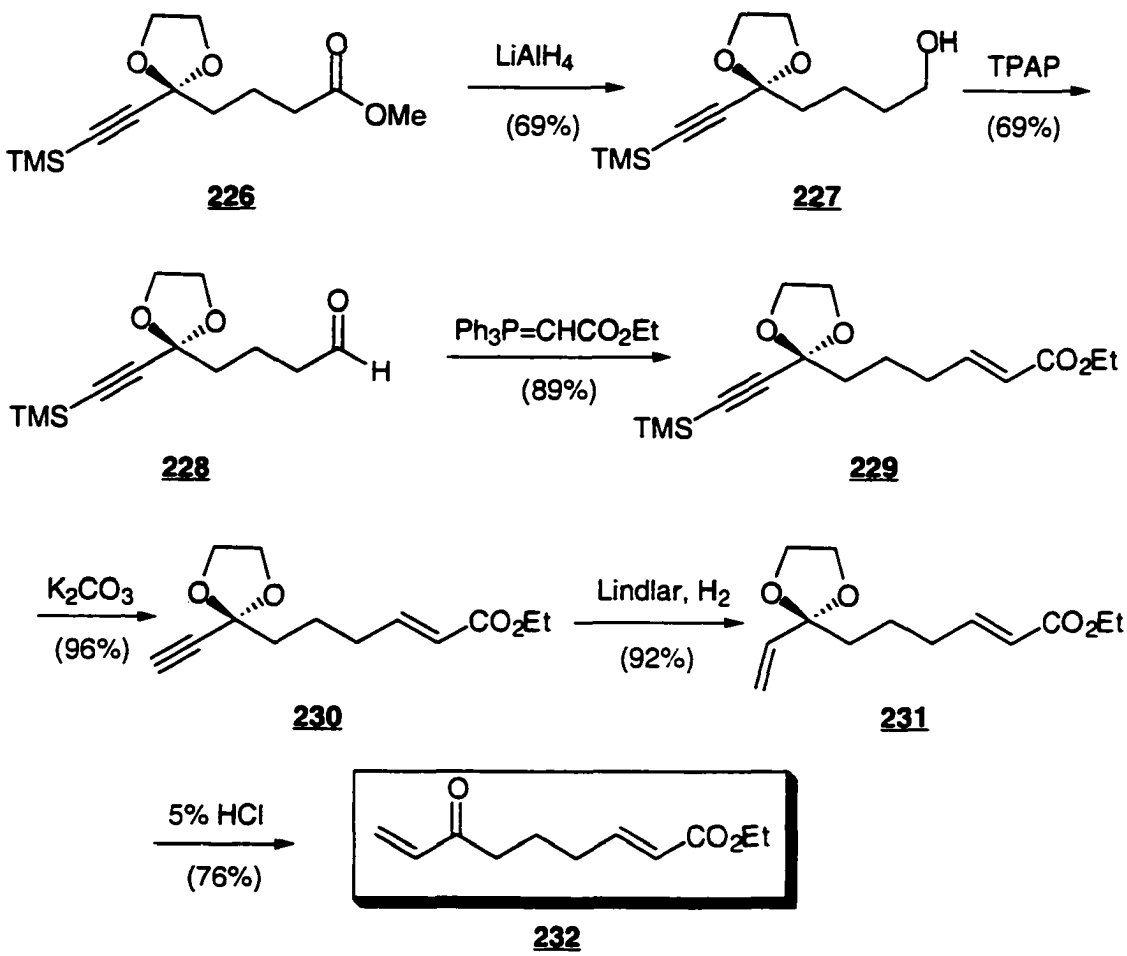


4.2 Tandem Fragmentation Reactions of Coupling Precursor Containing Double Michael Acceptors

The first coupling precursor that we examined was compound **232**. The synthesis of **232** is shown in Scheme 4.2. Reduction of methyl 5,5-diethylenoxy-7-trimethylsilyl-6-heptynoate **226**[76] by $LiAlH_4$ and subsequent TPAP oxidation afforded aldehyde **228** with an overall yield of 49%. Under Wittig reaction conditions, aldehyde **228** was converted to α,β-unsaturated ester **229** in 89% yield. Treatment of **229** with K_2CO_3 in ethanol removed the TMS group providing **230** in 96% yield, partial hydrogenation using Lindlar

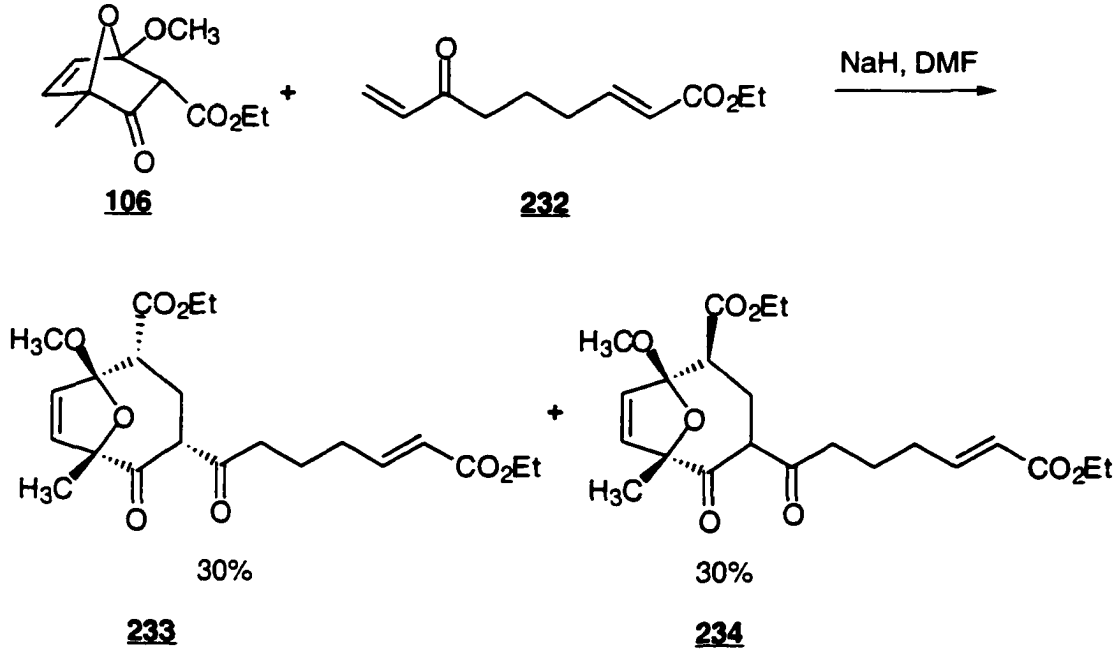
catalyst converted the alkyne moiety into alkene **231** in 92% yield, and finally, acidic hydrolysis gave substrate **232** in 76% yield.

Scheme 4.2 Synthesis of Coupling Precursor 232



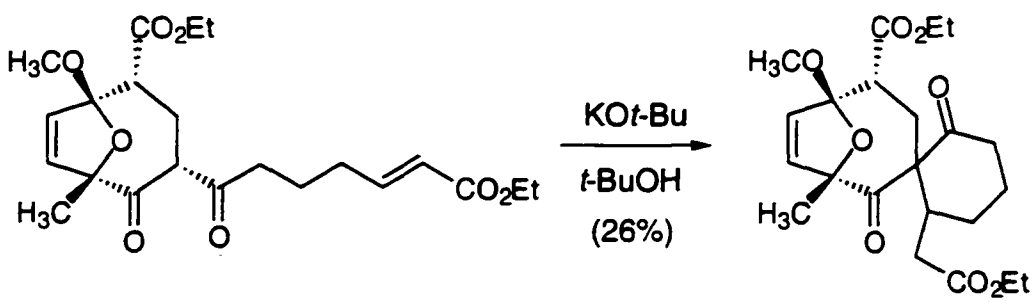
With coupling precursor **232** in hand, we investigated the feasibility of the 'round-trip' fragmentation reaction. By subjecting the anion of **106** to substrate **232**, we were surprised to isolate only the oxabicyclo[4.2.1] ring systems **233** and **234** in approximately 60% overall yield. The expected tricyclic compound was not detected (Scheme 4.3). Apparently, the anion from **106** reacted preferentially with the conjugated ketone, the resulting adduct then reacted selectively with the pendant ketone. These results point to the ease with which oxabicyclo[2.2.1]heptenone **106** undergoes four-membered ring formation. Cyclobutane formation occurs in spite of the possibility of generating a six-membered ring through cyclization onto the unsaturated ester.

Scheme 4.3 Fragmentation Reaction of 232



We also briefly examined the intramolecular ring expansion of oxabicyclo[4.2.1]nonene **233**. Thus treatment of **233** with KO*t*-Bu in *t*-BuOH afforded a 26% yield of spirofused compound **235**. However, heating the anion from **235** in DMSO at 80°C for 12h did not induce a ring expansion process; it led only to the recovery of starting material **235** (Scheme 4.4).

Scheme 4.4 Ring Expansions of 233



233 **235**

4.3 Fragmentations of Coupling Precursors Containing Double Michael Acceptors with gem-Dimethyl group

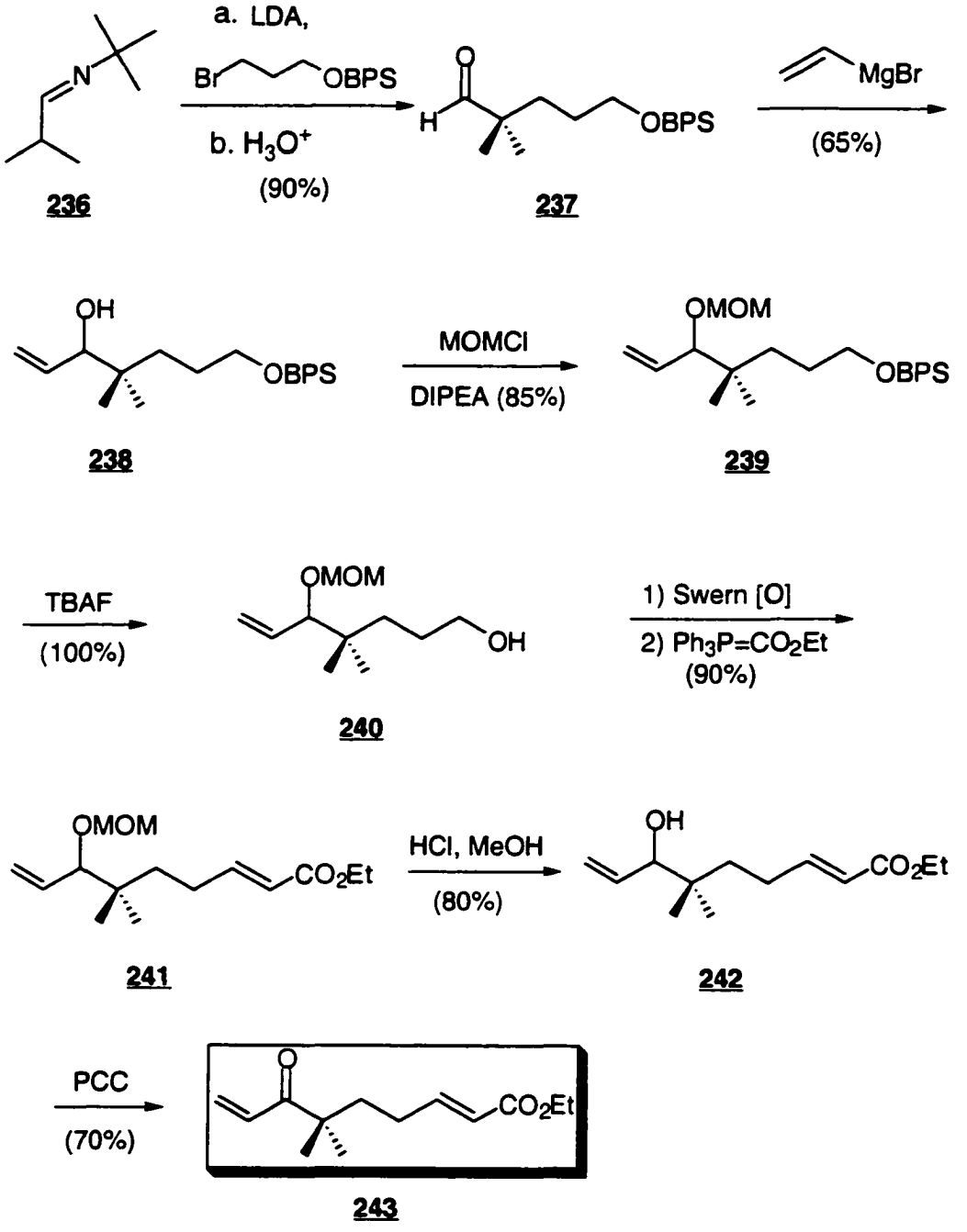
In order to further explore the working hypothesis of Scheme 4.1, we decided to modify the structure of the tether. The substitution of a gem-dimethyl group on the tether would presumably facilitate the fragmentation process.

The Thorpe-Ingold effect[77] was initially proposed to explain the ease of ring closure as a function of substitution. In the formation of small rings *via* cyclization reactions, a

substantial reduction in the C-C-C bond angle must occur. This situation changes when the fragment that cyclizes, $-CH_2CR_2CH_2-$ or $-CH_2CR_2CH_2CH_2-$, bears geminal methyl (R $=CH_3$) or other non-hydrogen substitution. Here the carbon that is geminally substituted resembles the central carbon of neopentane at which the bond angle is reduced to the tetrahedral angle, 109°28'. This decreases the angle deformation (i.e., strain) incurred upon cyclization; in other words, the formation of rings bearing gem-dialkyl groups should be easier than it would be in the absence of such groups.

The effect has been shown to be present in six and five-membered rings. For example, the ratio of rates of lactone formation from $Br-(CH_2)_{-n-3}CR_2CH_2-CO_2^-$, $R=CH_3$, to the rates when R = H (K_{Gem}/K_H) is 38.5 for n=6, 6.62 for n=9, 1.13 for n= 10, 0.61 for n = 11, and 1.22 for n = 16.[78] The sizeable effect in the formation of the six-membered rings seems at first surprising, considering that there is virtually no change of bond angle. Allinger and Zalkow have proposed a different explanation of the gem-dialkyl effect in such rings[79]. The gem-dialkyl groups in open chains substantially increase the number of gauche interactions, thus increasing the overall enthalpy of the molecule. When rings are formed, some of the gauche interactions become intraannular, and therefore attenuated, the unfavorable enthalpy effect of gem disubstitution is diminished. At the same time, branching diminishes the mobility, and hence the entropy of the chains, Because of this, the entropy change upon ring closure is made more favorable (less negative) by alkyl substitution.

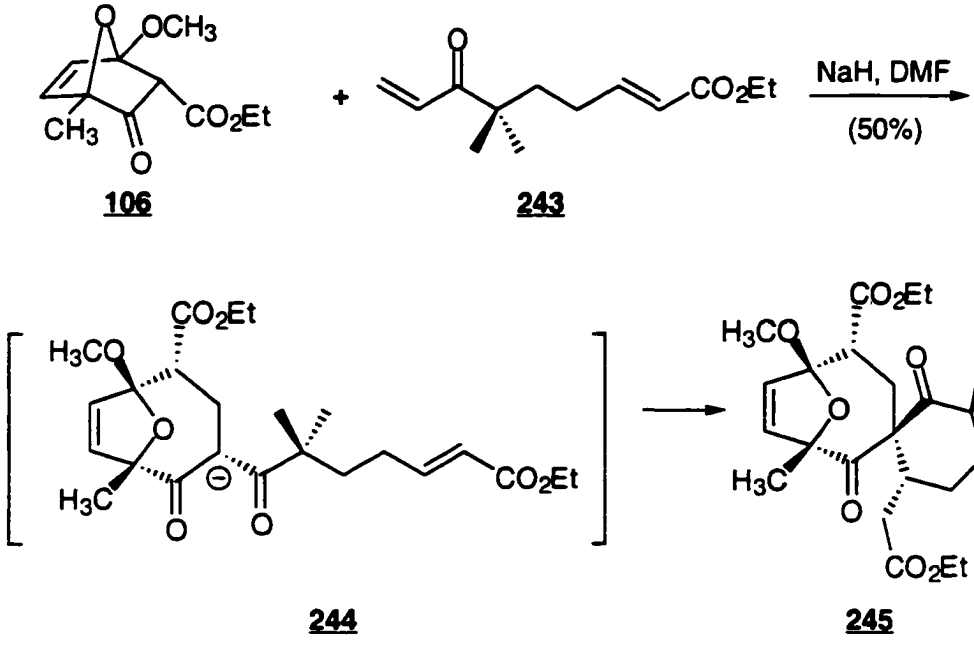
Scheme 4.5 Synthesis of Coupling Precursor 243



Keeping the gem-dialkyl effect in mind, we set out to synthesize coupling precursor **243** (Scheme 4.5). The anionic coupling of t-butyl imine **236** with the TBDPS ether of bromopropanol gave aldehyde **237** after acidic hydrolysis of the imine functionality[80], vinyl magnesium bromide addition then provided **238** in 65% yield. MOM ether formation and TBAF hydrolysis of the TBDPS group gave alcohol **240** in 85% yield over the two steps. Oxidation of **240** by Swern oxidation was followed by a Wittig reaction to give **241** in an overall 90% yield. Methanolysis of the MOM ether and PCC oxidation gave coupling precursor **243** in 56% overall yield.

We subjected **243** to the anion from **106** and isolated a crystalline product, which after careful characterization, turned out to be tricyclic spiral compound **245** (Scheme 4.6). X-ray analysis confirmed the relative stereochemistry of this compound. Clearly the reaction initially went through a two-carbon ring expansion to generate intermediate **244**. Due to the gem-alkyl effect, the anion of **244** added to the second Michael acceptor to generate **245**. Similar to the fragmentation reaction between oxabicyclo[2.2.1]heptenone **106** and **232**, **106** still undergoes four-membered ring formation in spite of the presence of gem-dimethyl group on the tether.

Scheme 4.6 Fragmentation Reactions of 243



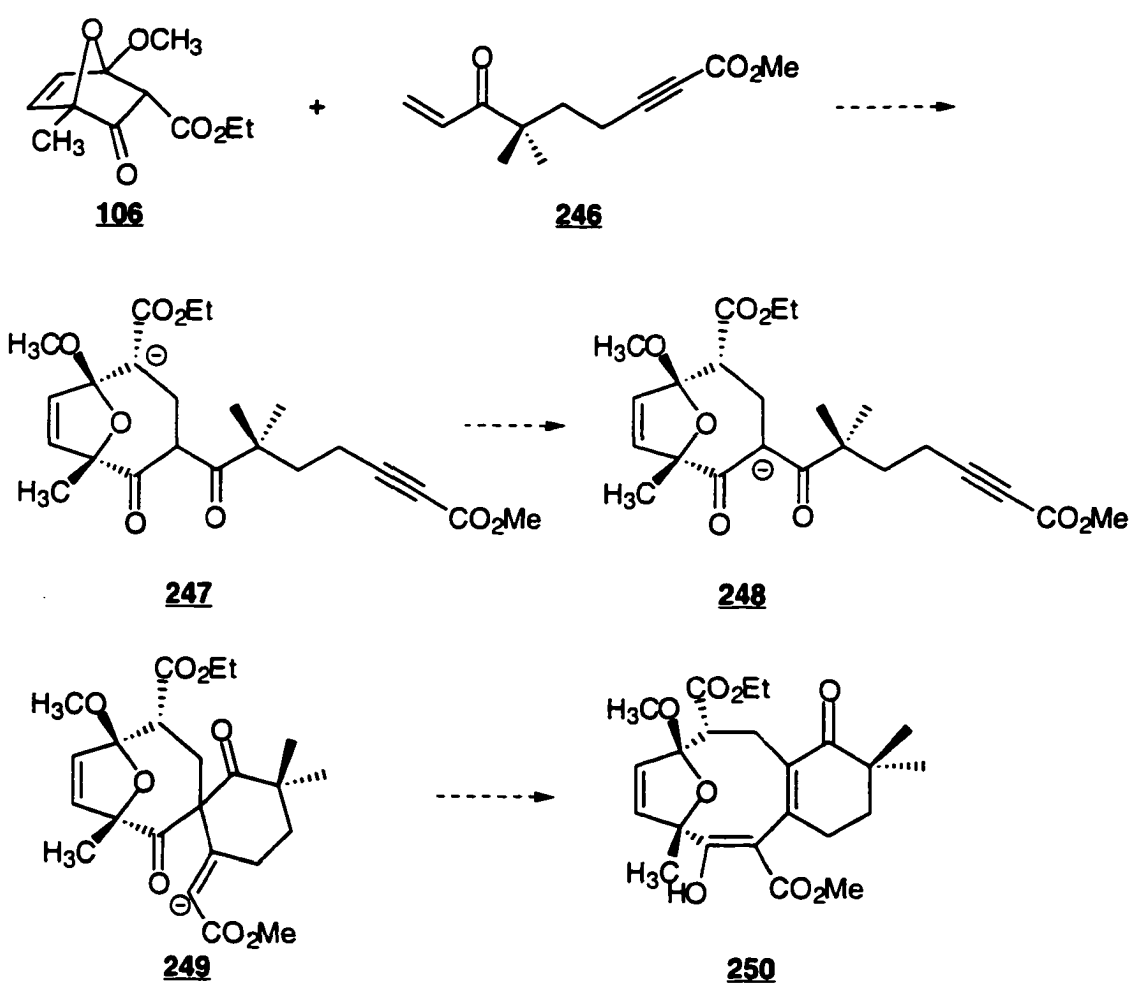
4.4 Fragmentation of Compounds Containing Double Michael Acceptors

4.4.1 Introduction

The above studies suggested that the two-carbon fragmentation is a highly favorable process, the resulting anion could add to a second Michael acceptor with gem-dimethyl substitution. However the subsequent fragmentation had not occurred with ene-enes. In Chapter 3, we demonstrated that the bicyclo[4.2.1] ring system underwent addition-fragmentation reactions with activated alkynes. Thus we decided to replace one of the Michael Acceptors with an activated alkyne.

Scheme 4.7 outlines a possible mechanism for this reaction. Based on our previous studies, the 'round-trip' mechanism depicted in Scheme 4.1 seemed unlikely. Thus we propose a sequential two-carbon ring expansion mechanism. The first two-carbon ring expansion reaction gives **247**. Proton transfer and intramolecular cyclization to the activated alkyne moiety should give **248**. Ring expansion of **248** should give the cembranoid carbon skeleton.

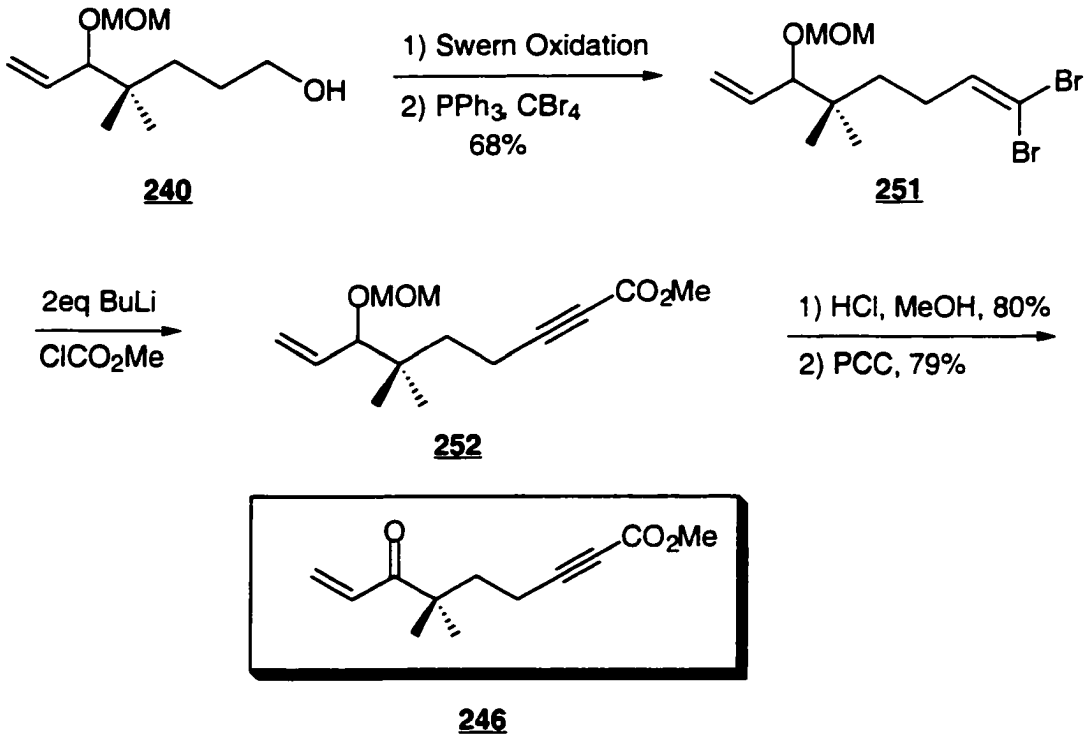
Scheme 4.7 Working Mechanisms



4.4.2 Stepwise Fragmentation

Scheme 4.8 outlines the synthesis of coupling precursor **246**. Swern oxidation of alcohol **240** and alkyne formation via a Corey-Fuchs reaction[81] gave **251** in 68% overall yield. Compound **251** was treated with 2 equivalents of BuLi to generate an alkynyl anion that was trapped with methylchloroformate to give **252**. Methanolysis of the MOM ether and PCC oxidation then gave coupling precursor **246**.

Scheme 4.8 Synthesis of Coupling Precursor 246

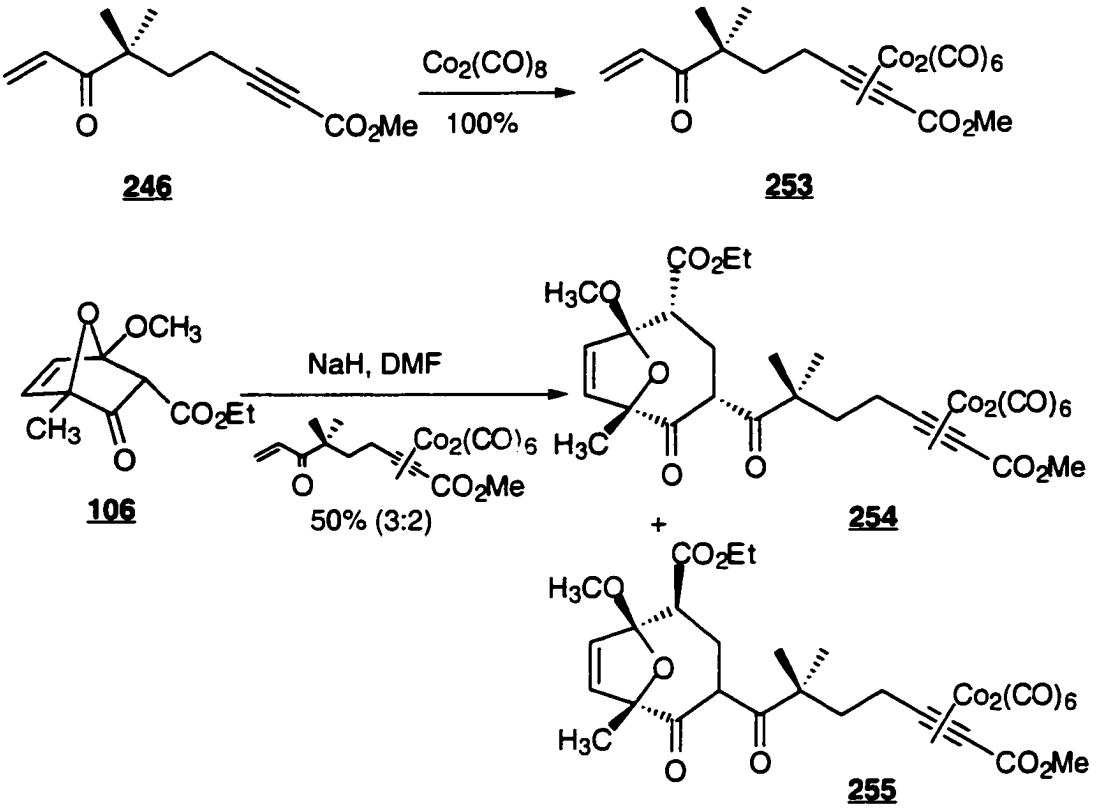


240 **251** **252** **246**

In an effort to determine the feasibility of the sequential two-carbon ring expansion for the synthesis of the cembranoid carbon skeleton, we decided to initially proceed in a

stepwise fashion *via* the formation of oxabicyclo[4.2.1]nonene **254** and **255**. With this in mind, the alkyne in **246** was masked as the corresponding $Co_2(CO)_6$ complex **253**. The anionic coupling of **106** with **253** gave a 55% yield of readily separable diasteromeric oxabicyclo[4.2.1]nonenes **254** and **255** (Scheme 4.9).

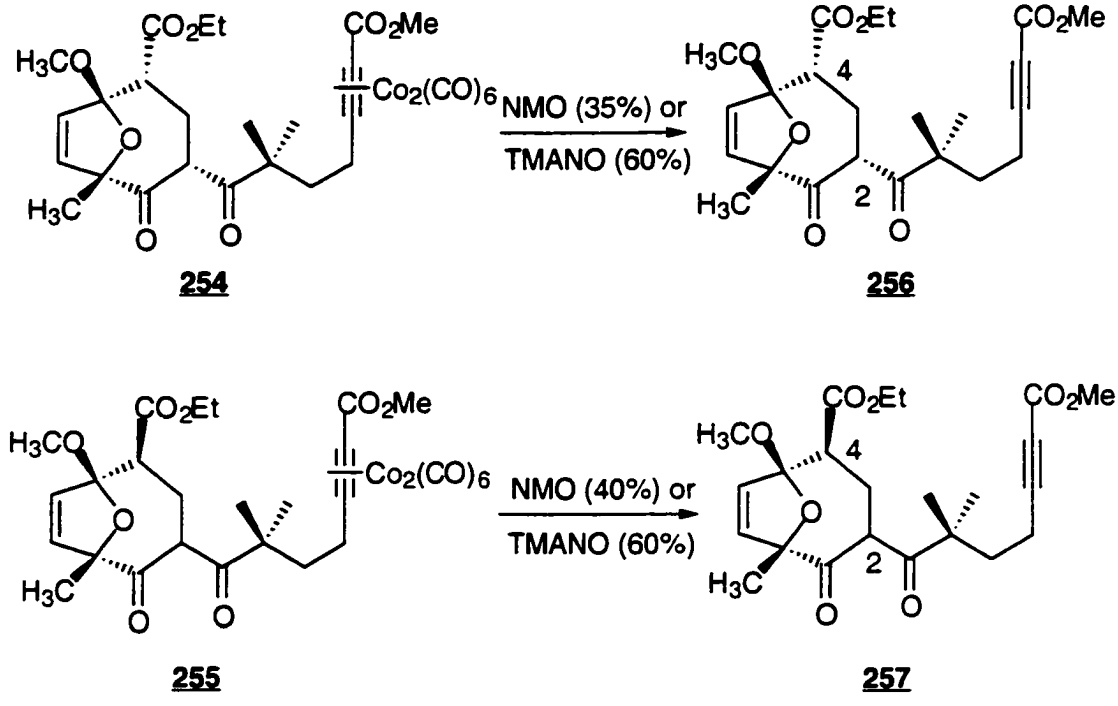
Scheme 4.9 Stepwise Fragmentation



Compounds **254** and **255** were subsequently decomplexed using either N-methyl morpholine N-Oxide (NMO) or trimethylamine-N-Oxide (TMANO). NMO gave 40% of

the decomplexed product **256** and **257**, TMANO worked slightly better, decomplexed product was formed in 60% yield.

Scheme 4.10 Decomplexation Reactions



254 **256**

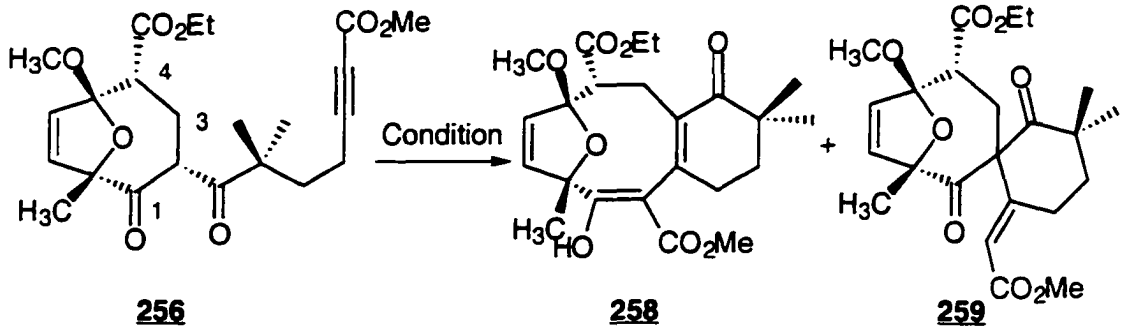
255 **257**

Following the oxidative decomplexation of cobalt from the alkyne, each of the C-4 diastereomers was subjected individually to the anionic two-carbon ring expansion reaction. When **256** was treated with NaH at rt for 12 h, we isolated a 40% yield of the desired ring expansion product **258** along with a 40% yield of product **259** as a single diastereomer (we have not been able to determine the relative stereochemistry of the spiro unit in **259**). The gross structure of **259** was determined by the similarities of its ^{1}H

NMR spectra with the spirofused compound obtained from the attempted ring expansion reaction of a bis-activated diene analogous to **246**. When the reaction was carried out at 50°C for 12 h, a 40% yield of **258** was isolated. Under these conditions, formation of **259** was not observed. We also examined the effectiveness of KH as the base in the **256** to **258** conversion. When **256** was subjected to KH at 0°C and allowed to warm to RT over 1 h we isolated a 50% yield of the enol acetate of **258** after acylation of the crude reaction mixture (ring expanded product **258** was unstable to chromatography, while enol acetate was much more stable). As in the NaH at elevated temperature experiment, we did not isolate **259** using KH (Table 4.1)[82].

Interestingly, in an analogous fashion to what we had observed in the intermolecular ring expansion reaction of **204b**, C-4 diastereomer **257** decomposed to unrecognizable products when exposed to the anionic fragmentation conditions. The reason for the divergent reactivity profiles of uncomplexed **257** is unclear at the present time but may be due to the facial approach of the activated alkyne onto the intermediate enolate. If this is true and the C-4 ester is directing the attack, approach form the α-face does not appear to be productive.

Table 4.1 Intramolecular Addition-Fragmentation Sequences



256 **258** **259**

Condition	Yield	**258**: **259**
NaH, DMF, 25°C	80%	1 : 1
NaH, DMF, 50°C	40%	1 : 0
KH/DMF, then Ac_2O, DMAP	50% (yield for enol acetate of **258**)	1 : 0

4.4.3 Single Flask Entry into the Oxygenated Cembranoid Skeleton 258

Having established that **256** could be transformed into the corresponding tricycle in a stepwise fashion, we began investigations into the single step conversion of **106** into the oxygenated cembranoid skeleton through its reaction with **246** (Scheme 4.11). The results are given in Table 4.2. Subjecting the anion from **106** in THF to **246** resulted only in the formation of oxabicyclo[4.2.1]nonenes **256** and **257** in 14% and 6% respectively. Changing the solvent from THF to DMF provided the desired product **258** in 17% yield, together with 17% yield of compound **259**. Finally, we isolated **258** in 20% yield by

subjecting **246** to **106** and KH at rt followed by *in situ* acylation of the doubly ring expanded enolate. The main by-product (22% yield) was spirofused substrate **259** as a mixture of diastereomers. Although formed in a modest yield, the conversion of **106** into **258** represents the coupling and fragmentation of six C-C bonds in a single flask and forms an almost direct entry into the oxygenated cembranoid skeleton.

Scheme 4.11 Single Flask Tandem Fragmentation

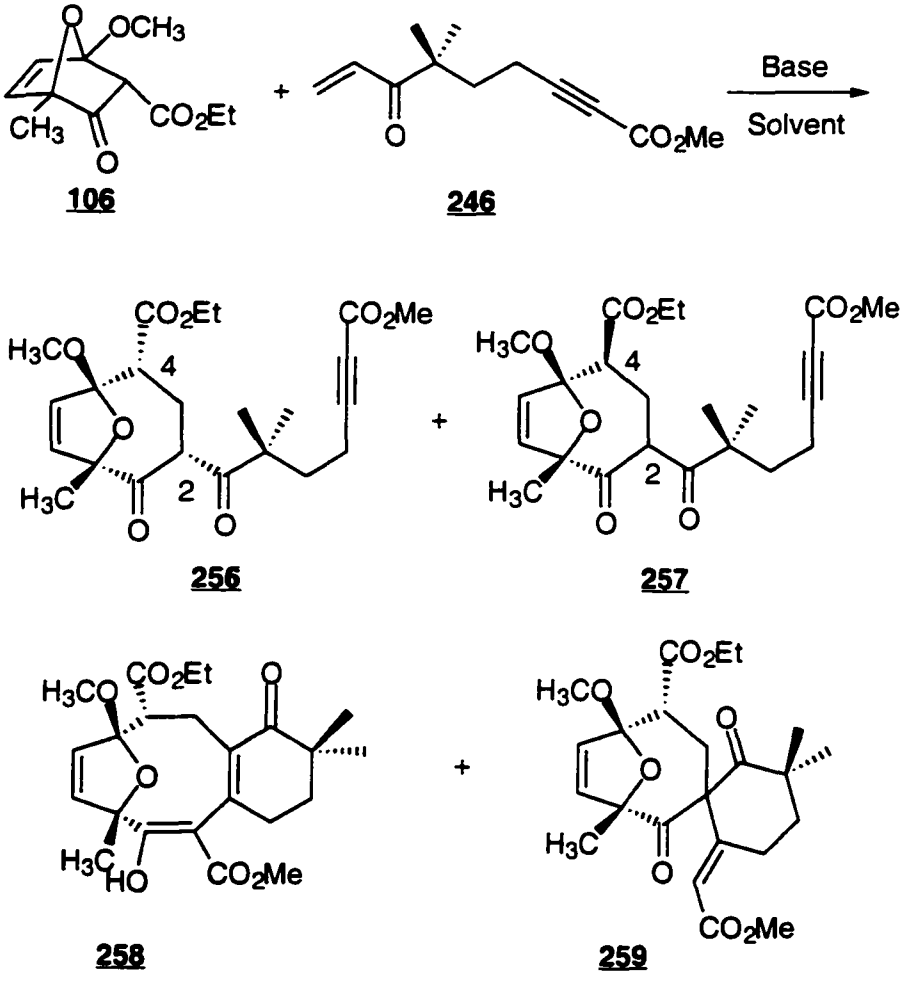


Table 4.2 Single Flask Tandem Fragmentations

Conditions	256	257	258	259
NaH/THF	14%	6%	0	0
NaH/DMF	0	0	17%	17%
KH/DMF, Ac_2O, DMAP	0	0	20% (yield for the enol acetate)	22%

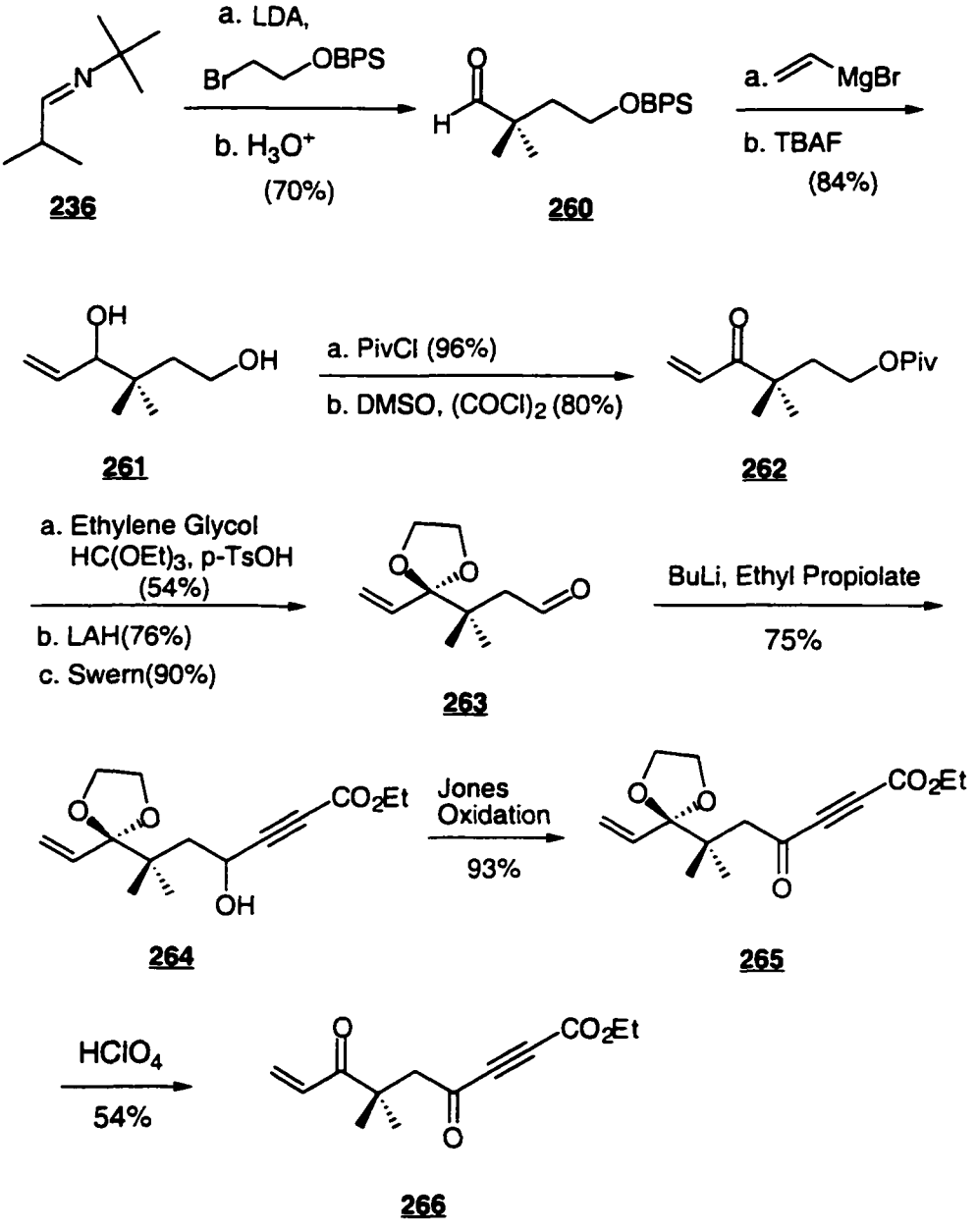
4.5 Fragmentation of Coupling Precursor 266

In order to further improve the efficiency of this tandem process, we decided to slightly modify the structure of coupling precursor. In Chapter 3, we demonstrated that oxabicyclo[4.2.1]nonene gave a better yield upon reacting with DMAD (doubly activated alkyne). Keeping this mind, we decided to put a ketone group in the coupling precursor to further activate the alkyne. The synthesis of **266** is shown in Scheme 4.12.

The anionic coupling of **236** with TBDPS ether of bromoethanol gave aldehyde **260** after acidic hydrolysis of the imine functionality, vinyl magnesium bromide addition and TBAF hydrolysis of the TBDPS group provided diol **261** in 84% yield over the two steps. Sequential protection of the diol afforded compound **262**. Ketone protection, reduction, and Swern oxidation then provided aldehyde **263** in good yield. The aldehyde was then reacted with the anion from the deprotonation of ethyl propiolate by BuLi to afford **264**

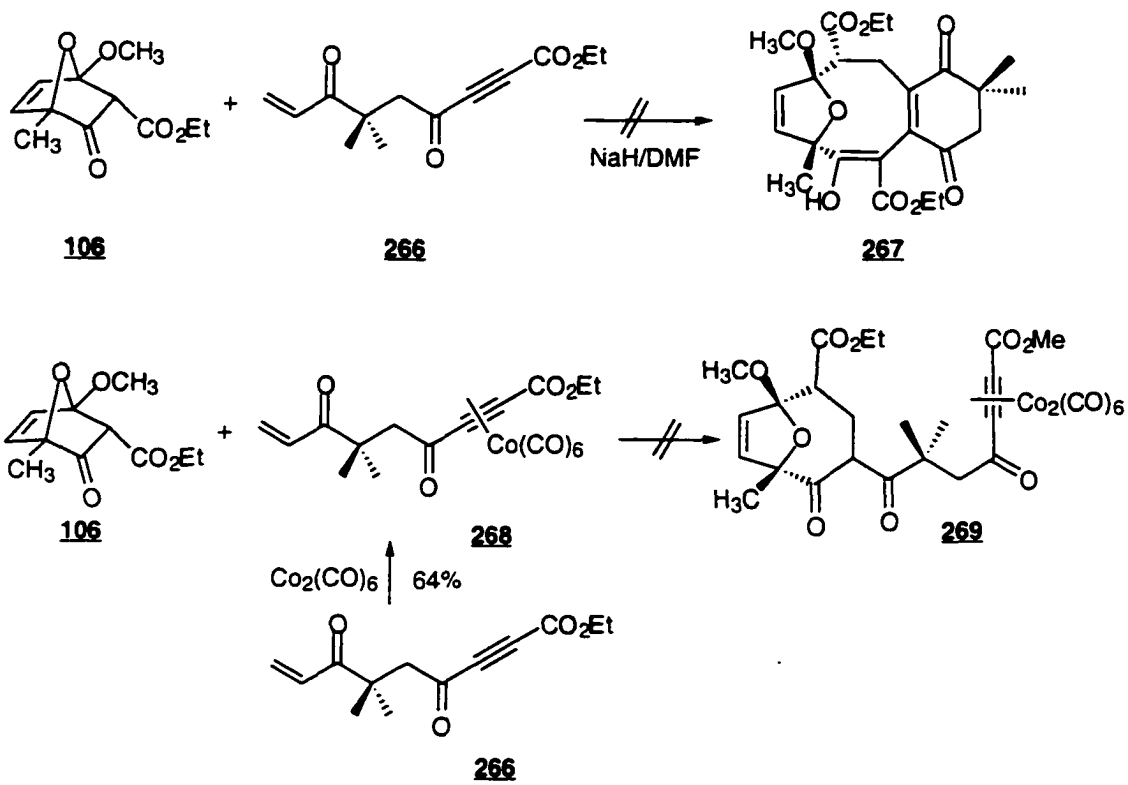
in 75% yield. Jones oxidation and perchloric acid hydrolysis then provided coupling precursor **266**.

Scheme 4.12 Synthesis of Coupling Precursor 266



Unfortunately, the coupling of **266** with **106** proved fruitless. By subjecting **266** to the anion from **106** did not provide tricyclic **267**. In addition, there were no identifiable product between the anionic coupling of **106** and masked alkyne **268**.

Scheme 4.13 Fragmentation of 266



4.6 Conclusion

In conclusion, we have demonstrated that oxabicyclo[2.2.1]heptenones undergo anionic coupling and fragmentation sequence with compounds containing two Michael acceptors. These reactions lead to ring expanded products impressively by using the

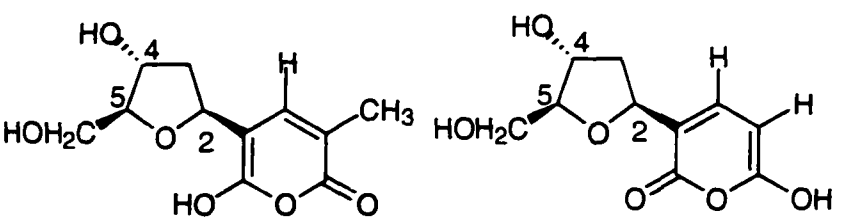
reactions that we have discovered. We have been able to generate the entire oxygenated cembranoid skeleton in a single flsk from the coupling of **106** with **246**.

Chapter 5 Synthetic Efforts Toward Nortetillapyrone

5.1 Introduction

Tetillapyrone **270** and nortetillapyrone **271** were isolated from *Tetilla japonica* by Herz and coworkers[83] from the Gulf of Thailand. The structures were established by NMR spectrometry and X-ray analysis, and are shown in Fig 5.1. Both nortetillapyrone and tetillapyrone contain a 2-substituted-4-hydroxy-5-hydroxymethyltetrahydrofuran moiety; we felt these two natural products could serve as targets to show the synthetic utility of our addition-fragmentation reaction discussed in Chapter 3. Our initial efforts have been devoted to the synthesis of nortetillapyrone.

Fig 5.1 Structures of Tetillapyrone and Nortetillapyrone

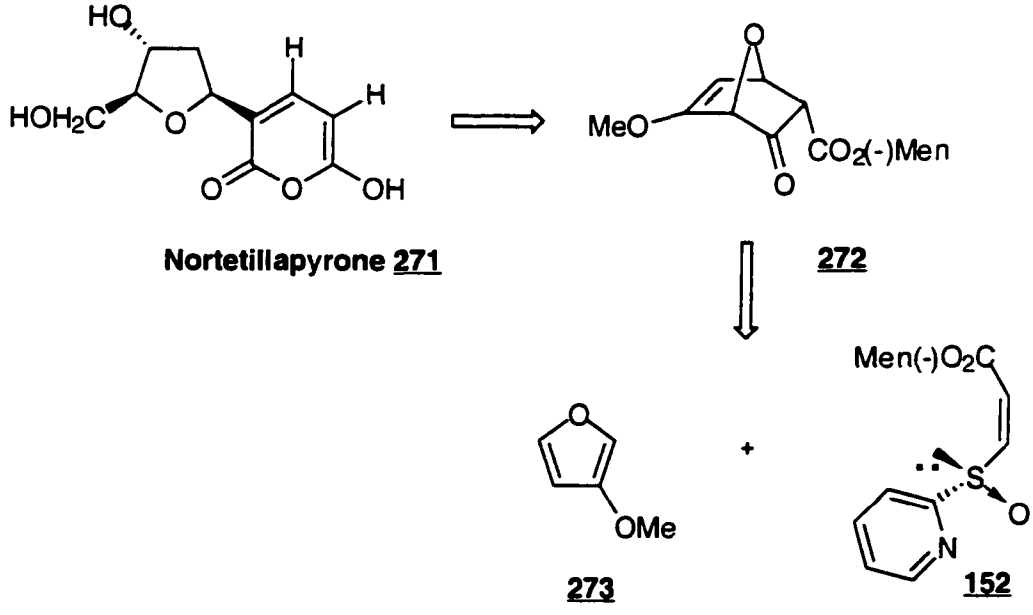


Tetillapyrone 270 **Nortetillapyrone 271**

We believed that nortetillapyrone could be derived from the condensation-fragmentation-elimination reaction of keto-ester **272** with the appropriate aldehyde. Keto-ester **272**, similar to that discussed in the Chapter 2, can be synthesized through an

asymmetric Diels-Alder reaction of 3-methoxyfuran **273** and **152** followed by a Pummerer rearrangement (Fig 5.2).

Fig 5.2 Retroanalysis of Nortetillapyrone

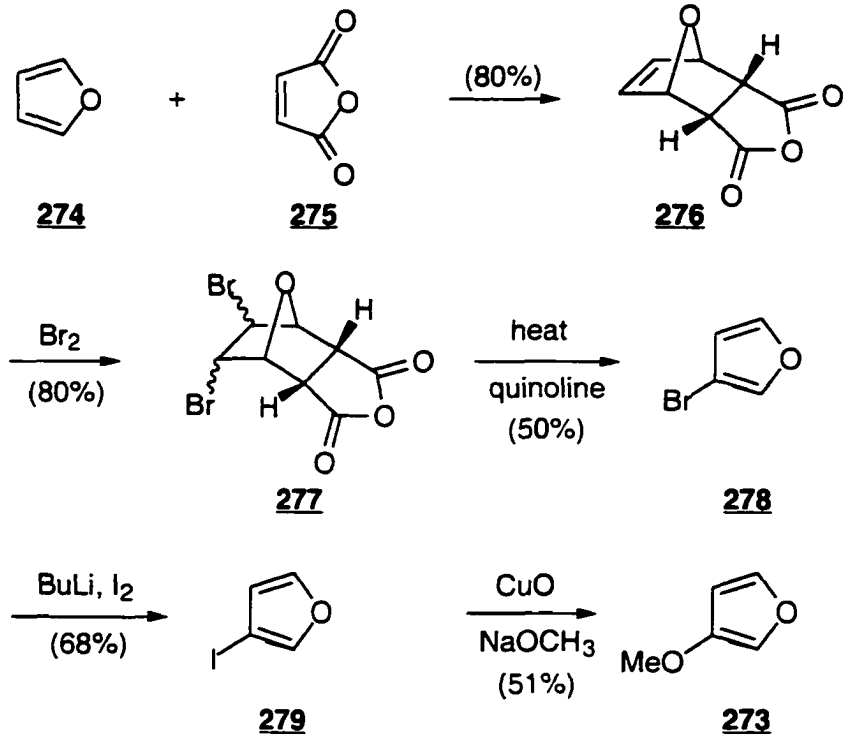


5.2 Synthesis of 3-Methoxyfuran

The synthesis of 3-methoxyfuran started with the Diels-Alder cycloaddition reaction between furan and maleic anhydride. The resulting adduct **276** was treated with Br_2 in DCM to generate diasteromeric dibromo compounds **277** in 90% overall yield[84]. Heating **277** with quinoline initiated a tandem HBr elimination and retro-Diels-Alder reaction to give 3-bromofuran **278**.[85] Treatment of 3-bromofuran with *t*-BuLi, followed by trapping

with I_2, gave rise to 3-iodofuran[86] reaction of 3-iodofuran with sodium methoxide in the presence of CuO then provided 3-methoxyfuran **273** in 50% yield.[87]

Scheme 5.1 Synthesis of 3-Methoxyfuran



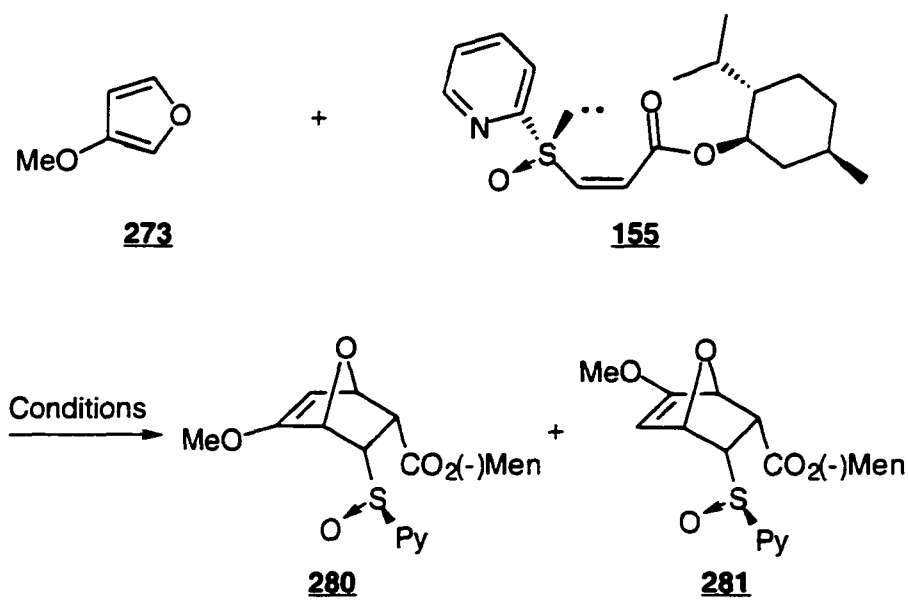
274 275 276 277 278 279 273

5.3 Synthesis of Keto-ester 272

With 3-methoxyfuran in hand, we investigated its asymmetric Diels-Alder reaction with **155**. As demonstrated in Table 5.1, when the reaction was mediated by Et_2AlCl it gave a 1:1 mixture of readily separable products in equal amounts. NMR experiments confirmed that these two products were regioisomers. The major regioisomer contained a

• mixture of endo and exo diastereomers (endo:exo = 10:1). The minor regioisomer consisted of the endo isomer only. Interestingly, when the cycloaddition was run neat in the absence of Lewis acid, a 95% yield was achieved, and the ratio of the two regioisomers was improved to 2:1.

Table 5.1 Asymmetric Diels-Alder Reaction



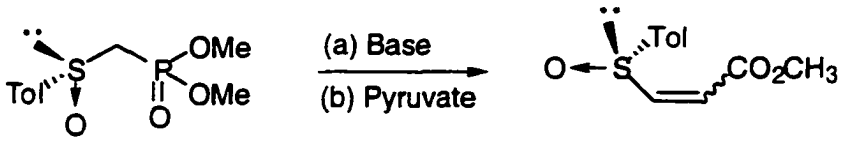
Condition	Results	280:281
Et_2AlCl	60%	1:1
Neat	95%	2:1

While the yield for this reaction is satisfactory, the selectivity is disappointing. We suspect that this is mainly due to electronic reasons. The pyridinyl group, while

enhancing the reactivity of the dienophile, increases the electron-withdrawing ability of the sulfinyl group. Because of this, there is little difference between the sulfinyl group and the ester group in terms of electron-withdrawing ability. Hence the Diels-Alder reaction becomes less regioselective.

Based on this, the reaction could be improved through the use of dienophile **283**. Replacing the pyridinyl group with a more electron-donating tolyl group will, in theory, lead to increased selectivity in the Diels-Alder reaction. Although the replacement of **155** with **283** will effect the reactivity of the dienophile to some extent, the relatively reactive diene (3-methoxyfuran) will still enable the reaction to proceed. Sulfoxide **283** is a well-known compound; its synthesis by Cardellichio and coworkers[88] is shown in Table 5.2. Treatment of Dimethylphosphorylmethyl p-tolyl sulfoxide with base followed by Pyruvate resulted in the formation of activated alkene **283**. Several base/solvent systems were used and the results were found to be the best in the case in which anhydrous K_2CO_3 was used.

Table 5.2 Literature Synthesis of Sulfoxide 283

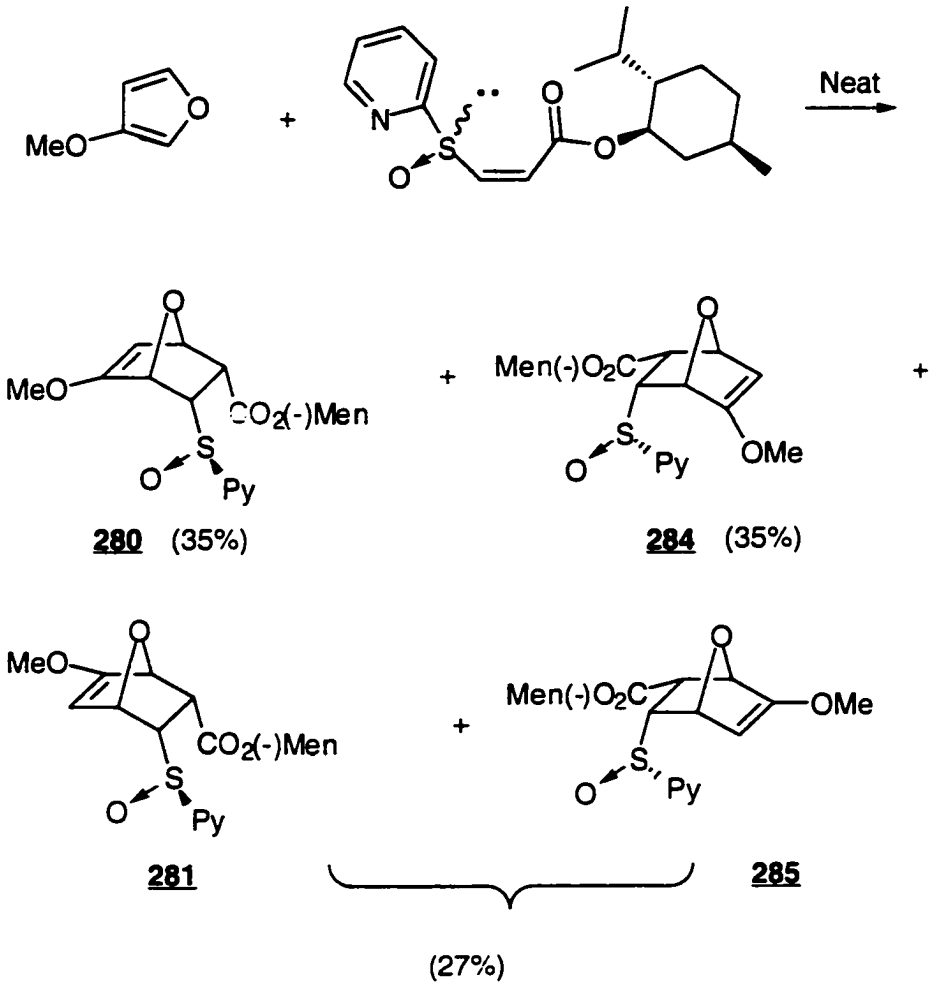


282 **283**

Base	Solvent	(E)-isomer		(Z)-isomer	
		Yield	e.e	Yield	e.e
K_2CO_3	MeCN	51%	>98%	5%	>98%

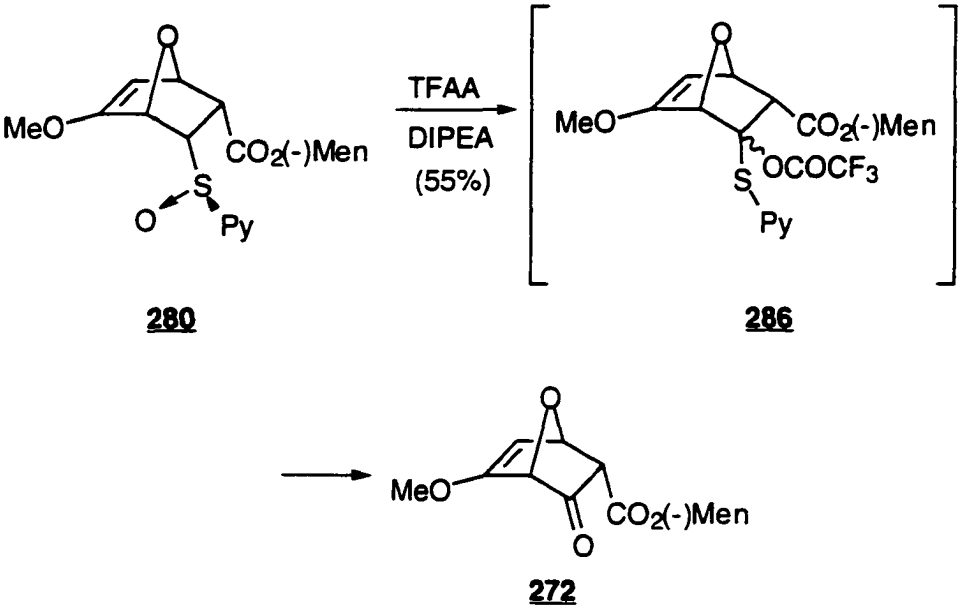
We have examined the Diels-Alder reaction between 3-methoxyfuran and an mixture of $(\underline{S})_S$ menthyl 3-(2-pyridylsulfinyl) acrylate and $(\underline{S})_R$ menthyl 3-(2-pyridylsufinyl) acrylate. As shown in scheme 5.2, the reaction proceeded with excellent overall yield: three fractions were isolated from the reaction mixture. The first fraction corresponded to compound **280**, the second portion was shown to be the Diels-Alder reaction adduct of 3-methoxyfuran and $(\underline{S})_R$ menthyl 3-(2-pyridylsulfinyl) acrylate, the final portion contained mixtures of **281** and **285**, which are the regioisomers of **280** and **284** respectively.

Scheme 5.2 Diels-Alder Reaction



In order to utilize chiral sulfoxide, we needed to convert the Diels-Alder adduct to the bicyclic ketoester. This was accomplished with **280** through treatment with TFAA and DIPEA; a Pummerer rearrangement product **272** was isolated in 55% yield (Scheme 5.3). The rearrangement presumably went through mixed O,S- ketal intermediate **286**.

Scheme 5.3 Pummerer Rearrangement

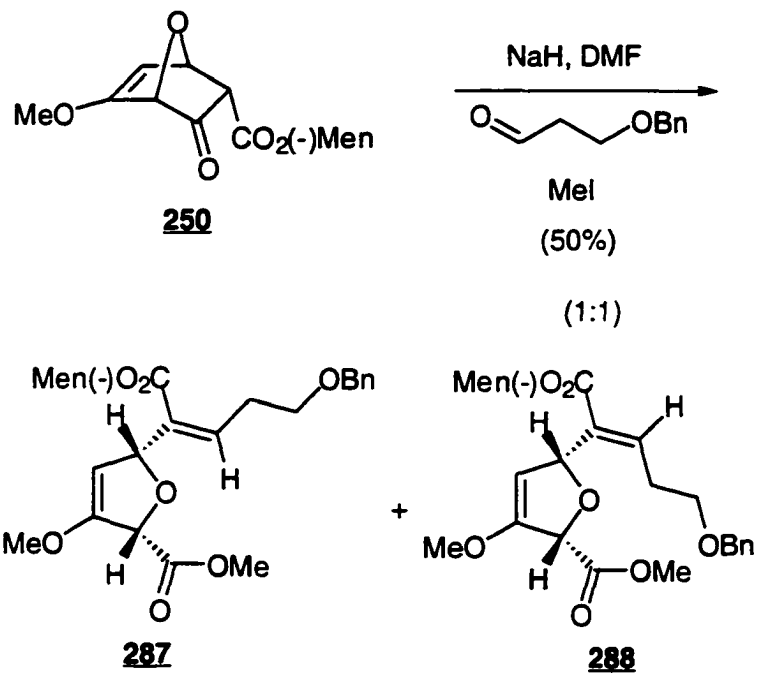


280 286 272

5.4 Addition-Fragmentation-Elimination Reaction of 272

With the enantiomerically pure bicyclic ketoester **272** in hand, we investigated its addition-fragmentation-elimination reaction with 3-benzyloxypropanal. By subjecting the anion of the keto-ester **250** with 3-benzyloxypropanal, a 1:1 mixture of *E* and *Z* olefin products **287** and **288** were isolated in 50% overall yield.

Scheme 5.4 Addition-Fragmentation-Elimination Reactions



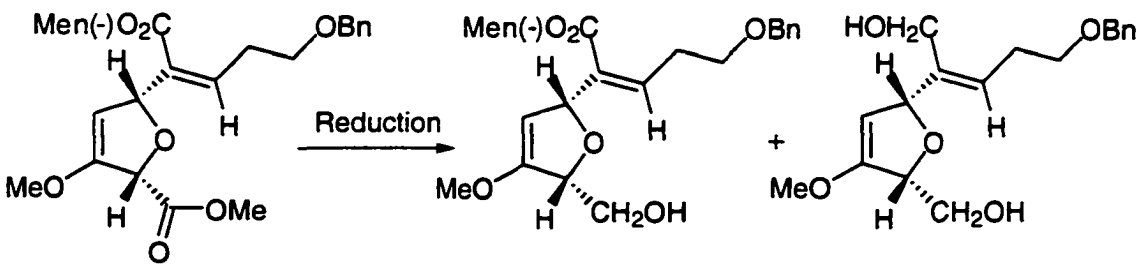
Although the selectivity in the reaction was disappointing, it was not surprising based upon our results with 2,5-unsubstituted furan (see Table 3.3). We decided to move forward from *Z*-alkene isomer **287**.

5.5 Reduction of 287

With adduct **287** in hand, the next transformation to nortetillapyrone involved the selective reduction of the isolated ester in the presence of the conjugated ester. The reduction proved to be somewhat problematic. Both $LiAlH_4$ and Red-Al gave no identifiable product; DIBAL reduced both esters leading to diol **290**; $LiBH_4$ was more selective, but the desired alcohol **289** was isolated in very low yield; ultimately, the best

result was achieved by treating **287** with $LiBEt_3H$; the desired alcohol **289** was isolated in 56% yield.

Table 5.3 Reduction of Fragmentation product 287



287 **289** **290**

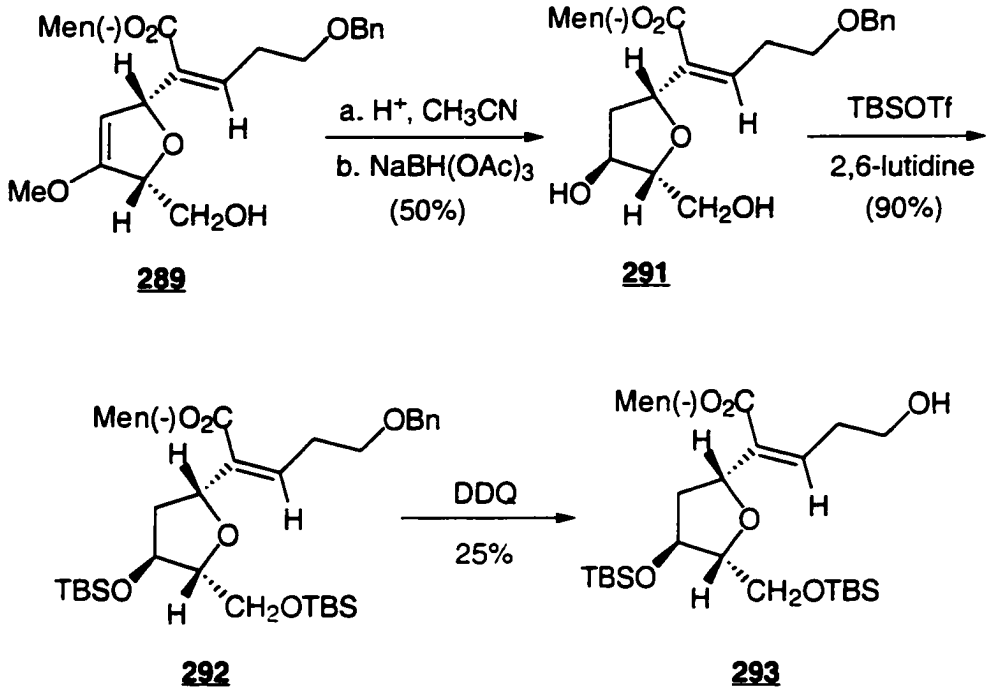
Reduction	**289** (%)	**290** (%)
DIBAL	0	25
$LiBH_4$	30	0
$LiBEt_3H$	**56**	**0**
$LiAlH_4$	0	0
Red-Al	0	0

5.6 Synthesis Toward Nortetillapyrone

Further efforts toward the synthesis of nortetillapyrone are shown in Scheme 5.5. Treatment of alcohol **289** with aqueous HCl in acetonitrile gave the corresponding ketone. Directed reduction of the ketone by the pendant hydroxyl with $NaBH(OAc)_3$ gave

1,3-diol **291** in an overall yield of 50% for the two steps. TBS ether formation and treatment with DDQ provided alcohol **293**. Unfortunately, the oxidative hydrolysis reaction was very capricious, stirring the reaction for longer period of time resulted in decreased yield. For this reason, the reaction was stopped after ca. 50% conversion and the product was isolated in ca. 50% yield based on recovered starting material.

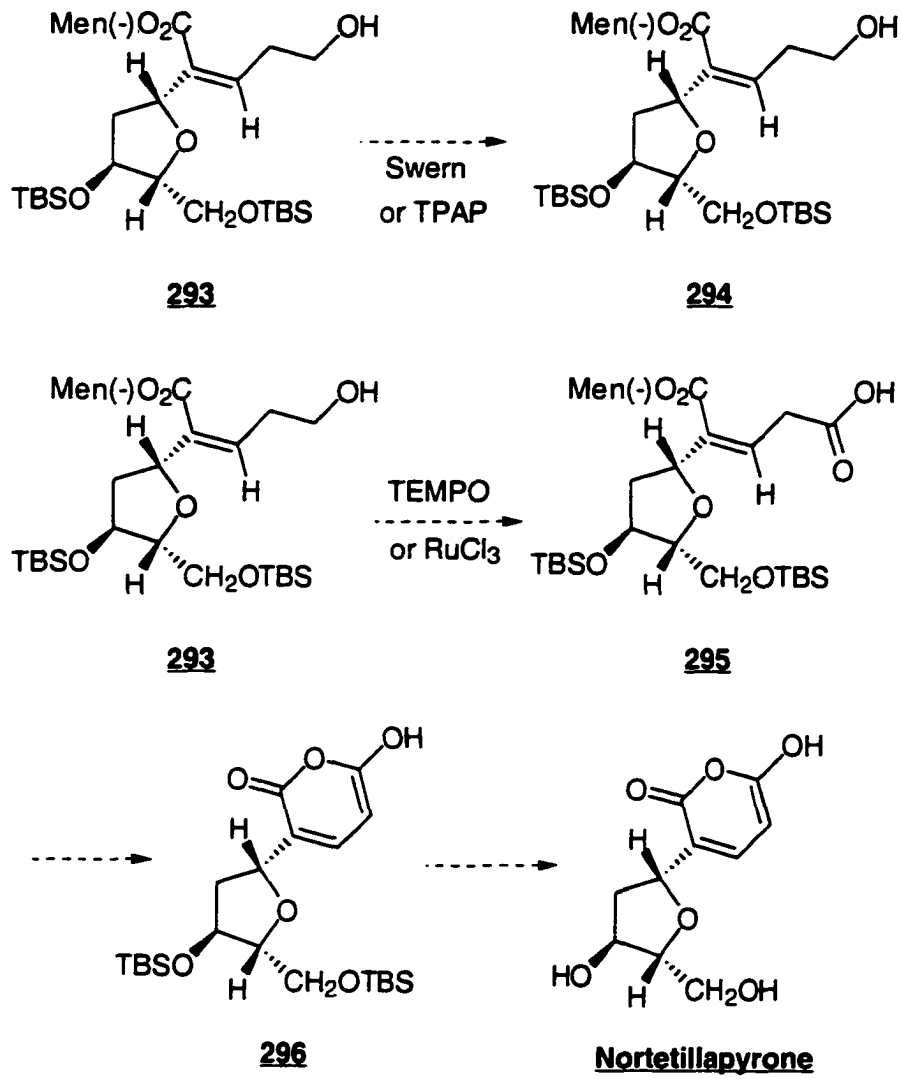
Scheme 5.5 Syntheses Toward Nortetillapyrone



289 **291** **292** **293**

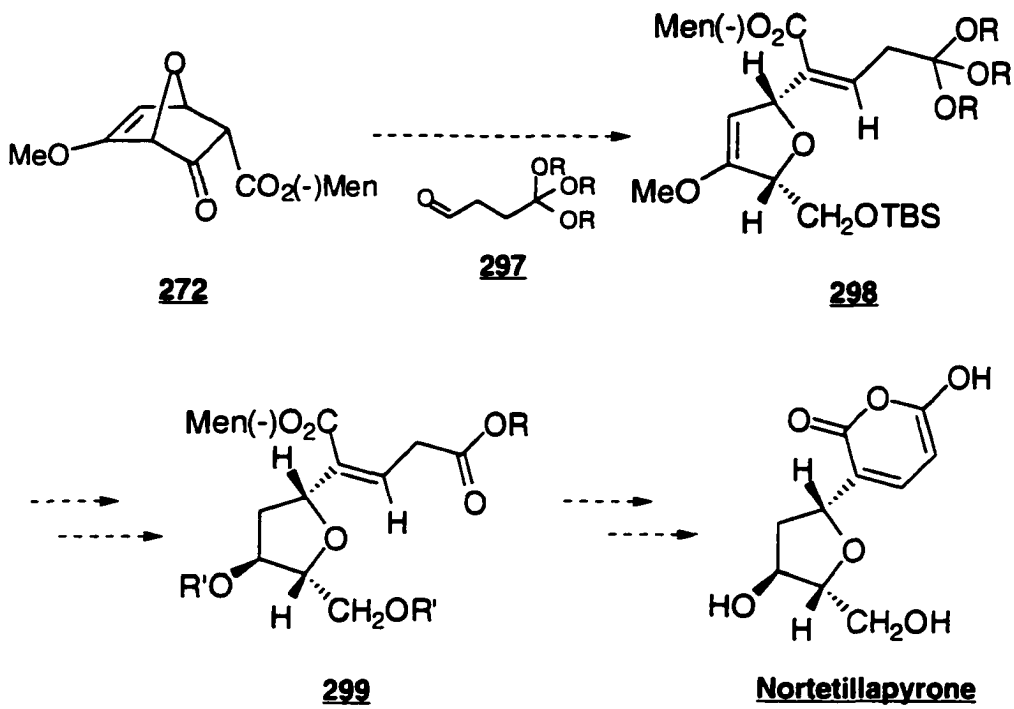
Unfortunately, the attempted oxidation of the primary alcohol in **293** reactions with either TPAP or under Swern oxidation conditions did not provide aldehyde **294**. Efforts to convert the alcohol into the corresponding carboxylic acid also failed.

Scheme 5.6 Unsuccessful Oxidation Reactions



In order to circumvent the oxidation problem, our future plan is to use an aldehyde with an orthoester functionality, after the fragmentation reaction, the orthoester can be hydrolyzed directly to an ester; thus avoiding the oxidation step. The anhydride formation should be secured soon thereafter.

Scheme 5.7 Future Plans



272 **297** **298**

299 **Nortetillapyrone**

Chapter 6. Conclusions

In an attempt to devise a strategy for the synthesis of oxygenated cembranoid containing natural products, we discovered an interesting anionic coupling and fragmentation reaction of oxabicyclo[2.2.1]heptenones. This reaction is general and leads to a wide variety of functionalized five-membered ring products. We recently started to apply this methodology for the total synthesis of natural products. Our initial efforts have been devoted to the synthesis of nortetillapyrone. The furan portion of the molecule has been synthesized using the coupling/condensation sequence.

In addition, oxabicyclo[2.2.1]heptenone **106** undergoes an anionic two-carbon ring expansion reactions with activated alkenes to generate oxabicyclo[4.2.1] ring systems. The resulting oxabicyclo[4.2.1] system can undergo two-carbon ring expansion to generate oxabicyclo[6.2.1]nonenes.

Lastly, we demonstrated that oxabicyclo[2.2.1]heptenone **106** undergo anionic coupling and fragmentation sequences with compounds containing two Michael acceptors. These reactions lead to the efficient synthesis of the carbon skeleton of eleutherobin.

Chapter 7. Experimental

7.1 General Methods

NMR spectra were recorded on a Bruker EM-600, Bruker EM-500, Bruker AM-250, or a Varian 300 spectrometer. Chemical shifts were reported in δ, parts per million (ppm), relative to chloroform (δ=7.24 ppm) as an internal standard. Coupling constants, *J*, were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Arizona on a Jeol HX-110A and are reported as % relative intensity to the molecular base peak. IR spectra were recorded on a Nicolet Impact 410. Ether, THF, hexanes, benzene, and toluene were distilled from sodium/benzophenone. CH_2Cl_2, $CHCl_3$, TMEDA, $(i\text{-Pr})_2NEt$, Et_3N, and Et_2NH were distilled from CaH_2. All other reagents were used without purification. Unless otherwise stated, all reactions were run under an atmosphere of argon in flame-dried glassware. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20 mmHg) with a Büchi Rotavapor.

7.2 Experimental Procedures

Preparation of (±)-ethyl-1-methoxy-3-bromo-4-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2-carboxylate 146a and (±)-ethyl-1-methyl-3-bromo-4-methoxyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2-carboxylate 146b. A solution of ethyl 3-bromopropiolate **145** (0.25 g, 1.4 mmol), 2-methoxy-5-methyl furan **144** (0.39 g, 3.5 mmol), and benzene (4 mL) was heated to 80°C for 8 hr. After cooling to rt, the mixture was concentrated. Flash column chromatography (7:1 hexanes/ethyl acetate) gave 0.18 g of **146a** and 18mg (5%) of **146b**.

146a: ^{1}H NMR (250MHz, $CDCl_3$) δ 6.89 (d, J = 5.3 Hz, 1H), 6.82 (d, J = 5.2 Hz, 1H), 4.19 (m, 2H), 3.46 (s, 3H), 1.61 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 162.2, 153.7, 146.5, 142.9, 141.6, 116.5, 88.6, 60.6, 54.4, 15.5, 14.0; IR (CCl_4) 1715, 1320 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_{13}O_4Br$ (MH^+) 289.0075, found 289.0081.

Preparation of (±)-ethyl-1-methoxy-3,3-diethylmercapto-4-methyl-7-oxabicyclo-[2.2.1]hepta-5-ene-2-carboxylate 148. A solution of **146a** (0.78 g, 2.7 mmol) and THF (20 mL) was added over 2 h to a solution of EtSNa (20 mL of a 0.27 M solution in THF, 5.4 mmol) at 0°C. After the addition was completed, the reaction was immediately quenched with $NaHCO_3$ (sat., 20 mL), extracted with ether, dried ($MgSO_4$), and concentrated. Flash chromatography (5:1 hexanes/ethyl acetate) afforded 0.86 g (96%) of **148** as a single diastereomer. ^{1}H NMR (250MHz, $CDCl_3$) δ 6.63 (d, J = 5.6 Hz, 1H), 6.39 (d, J = 5.6 Hz, 1H), 4.12 (m, 2H), 3.47 (s, 3H), 3.40 (s, 3H), 2.76 (m, 4H), 1.60 (s, 3H),

1.24 (m, 6H), 1.12 (t, J = 7.5 Hz, 3H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 168.8, 140.2, 134.6, 113.1, 88.5, 73.7, 63.3, 61.0, 53.9, 25.8, 24.8, 16.3, 14.0, 13.8, 13.3; IR (CCl_4) 1749 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{24}O_4S_2Cs$ (MCs^+) 465.0170, found 465.0165.

Preparation of (±)-ethyl-1-methoxy-4-methyl-7-oxabicyclo[2.2.1]hepta-5-ene-3-one-2-carboxylate 106. Procedure A (Recommended): To a solution of **148** (1.60 g, 4.82 mmol) and THF (15mL) at 0°C was added water (1.5 mL, 88 mmol) and $CaCO_3$ (0.80 g, 80 mmol) followed by a solution of $Hg(ClO_4)_2$ (3.47 g, 8.67 mmol) and water (1.5 mL, 88 mmol). The reaction mixture was diluted with 5:1 hexanes/ethyl acetate (100 mL), filtered, and concentrated. Flash column chromatography (5:1 hexanes/ethyl acetate) gave 0.52 g (47%) of **106** and 0.28 g (17%) of **106a**. Procedure B: To a solution of **148** (0.20 g, 0.88 mmol) and THF (4mL) at 0°C was added water (0.8 mL, 44 mmol) and $CaCO_3$ (0.12 g, 1.2 mmol) followed by $Hg(ClO_4)_2$ (0.54 g, 1.3 mmol). The reaction mixture was immediately diluted with ether (25 mL) and phosphate buffer (pH 7.0, 25 mL). The aqueous phase was extracted with ether (3×25 mL); the extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (5:1 hexanes/ethyl acetate) gave 82 mg (61%) of **106** as thick oil.

106: ^{1}H NMR (250MHz, $CDCl_3$) δ 6.84 (d, J = 5.6 Hz, 1H), 6.19 (d, J = 5.6 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.55 (s, 3H), 3.40 (s, 1H), 1.55 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 198.1, 166.7, 140.0, 133.9, 111.3, 88.1, 61.6, 53.9, 53.3, 14.0, 12.5; IR (CCl_4): 1734, 1777 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_{15}O_5$ (MH^+) 227.0919, found 227.0915.

106a: ^{1}H NMR (600MHz, $CDCl_3$) δ 6.50 (d, *J* = 15.4 Hz, 1H), 5.36 (d, *J* = 15.4 Hz, 1H), 4.12-4.05 (m, 2H), 3.61 (s, 1H), 3.24 (s, 3H), 2.7-2.64 (m, 2H), 2.51-2.43 (m, 2H), 2.02 (s, 3H), 1.27 (t, *J* = 7.4 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (150MHz, $CDCl_3$) δ 170.0, 160.3, 131.4, 119.5, 109.1, 99.6, 63.7, 61.0, 50.4, 28.1, 25.8, 14.9, 14.3, 14.2, 12.4.

Representative Procedure for the Condensation, Fragmentation, and Elimination Reaction. Preparation of (±)-5-methoxycarbonyl-5-methyl-2-methoxy-2-Z-[ethyl-3-phenylprop-2-enoate]-2,5-dihydrofuran 165. A solution of **106** (0.05 g, 0.20 mmol) and DMF (1 mL) was added dropwise to a slurry of NaH (0.006 g, 0.20 mmol) and DMF (0.5 mL) at 0°C. After stirring for 1 h at 0°C, benzaldehyde (0.04 mL, 0.4 mmol) was added. The mixture was allowed to slowly warm to rt, stirred for 1 h, and quenched with methyl iodide (0.3 mL, 5 mmol). $NaHCO_3$ (sat., 10 mL) was added, the mixture was separated and the aqueous phase was extracted with ether (3×15 mL). The extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (5:1 hexanes/ethyl acetate) provided 0.06 g (83%) of furan **165** as a colorless oil. ^{1}H NMR (250MHz, $CDCl_3$) δ 7.31 (s, 1H), 7.18 (s, 5H), 6.16 (d, *J* = 5.8 Hz, 1H), 6.04 (d, *J* = 5.7 Hz, 1H), 4.11 (m, 2H), 3.61 (s, 3H), 3.22 (s, 3H), 1.59 (s, 3H), 1.04 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 172.0, 168.1, 135.1, 133.9, 133.8, 132.7, 130.4, 128.3, 128.2, 128.1, 113.6, 90.0, 60.9, 52.4, 50.4, 24.9, 13.6; IR (CCl_4) 1758, 1727, 1258, 1215 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{22}O_6Cs$ (MCs^+) 479.0471, found 479.0483.

Preparation of (+)-5-methoxycarbonyl-5-methyl-2-methoxy-2-Z-[ethyl-4-methylpent-2-enoate]-2,5-dihydrofuran 166. Prepared according to the representative

•procedure using **106** (0.08 g, 0.4 mmol), NaH (0.01 g, 0.4 mmol), isobutyraldehyde (0.07 mL, 0.8 mmol), DMF (3 mL), and methyl iodide (0.3 mL, 5 mmol) to give 0.091 g (78%) of **166** as a colorless oil. ^{1}H NMR (250MHz, $CDCl_3$) δ 6.37 (d, J = 10.2 Hz, 1H), 6.21 (d, J = 5.8 Hz, 1H), 6.05 (d, J = 5.7 Hz, 1H), 4.18 (m, 2H), 3.70 (s, 3H), 3.20 (s, 3H), 2.85 (m, 1H), 1.62 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 172.2, 167.2, 146.7, 132.6, 130.7, 130.4, 113.6, 89.5, 60.5, 52.2, 50.3, 28.7, 24.8, 22.6, 22.5, 14.2; IR (CCl_4) 1764, 1721, 1449 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{24}O_6Cs$ (MCs^+) 445.0627, found 445.0614.

Preparation of dihydrofuran 175a. To a slurry of NaH (2.4 mg, 0.097 mmol) and DMF (0.3 mL) at 0°C was added a solution of **106** (22 mg, 0.097 mmol) and DMF (0.3 mL). After stirring for 1 h, 4-benzyloxybutanal (87 mg, 0.486 mmol) was added slowly. After stirring for an additional 1 h, MeI (0.3 mL, 0.5 mmol) was added and the reaction mixture was stirred for another 1 h. After quenching with $NaHCO_3$ ((aq, sat) 8 mL), the mixture was extracted with ethyl acetate (3×15 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (6:1 hexanes/ethyl acetate) provided 27 mg (68%) of furan **175a** as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 7.26 (m, 1H), 6.61 (t, J=7.7 Hz, 1H), 6.25 (d, J=6.0 Hz, 1H), 6.08 (d, J=6.0 Hz, 1H), 4.49 (s, 2H), 4.24 (m, 2H), 3.71 (s, 3H), 3.48 (t, J=6.5 Hz, 2H), 3.24 (s, 3H), 2.39 (m, 2H), 1.77 (m, 2H), 1.65 (s, 3H), 1.28 (t, J=7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3, 167.0, 140.3, 138.7, 133.1, 132.7, 130.9, 128.4, 127.7, 127.5, 123.4, 113.6, 89.6, 73.0, 69.8, 60.6, 52.1, 50.4, 29.3, 26.2, 25.0, 14.3; IR (CCl_4) 2999, 2851, 1785, 1746, 1696 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{30}O_7$ (MCs^+) 551.1042, found 551.1050.

Preparation of dihydrofuran 175c. To a slurry of NaH (2.0 mg, 0.084 mmol) and DMF (0.3 mL) at 0°C was added a solution of **106** (22 mg, 0.097 mmol) and DMF (0.3 mL). After stirring for 1 h, ethyl glyoxylate (43 mg, 0.42 mmol) was then added slowly to the reaction mixture. After an additional 1 h, MeI (0.3 mL, 0.5 mmol) was added and the reaction mixture was stirred for another 1.5 h. After quenching with $NaHCO_3$ (aq, sat. 8 mL), the mixture was extracted with ethyl acetate (3×15 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (3:1 hexanes/ethyl acetate) provided 30 mg (91%) of furan **175c** as a 5.4:1 mixture of olefins as a colorless oil. *Z*-isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.15 (d, *J*=5.8 Hz, 1H), 6.09 (d, *J*=5.8 Hz, 1H), 4.30 (dq, *J*=10.8, 7.1 Hz, 2H), 4.18 (dq, *J*=10.8, 7.1 Hz, 2H), 3.75 (s, 3H), 3.31 (s, 3H), 1.67 (s, 3H), 1.32 (t, *J*=7.1 Hz, 3H), 1.28 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 166.3, 164.9, 147.2, 133.9, 129.2, 123.4, 112.6, 90.5, 61.5, 60.9, 52.5, 50.7, 24.8, 14.0, 13.8; IR (CCl_4) 2981, 1752, 1739, 1023 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{23}O_8$ (MH^+) 343.1393, found 343.1396.

Preparation of (±)-ethyl-3-bromo-7-oxabicyclo[2.2.1]hepta-2,5-diene-2-carboxylate 178. A solution of ethyl 3-bromopropiolate (1.5 g, 8.0 mmol) and furan (6 mL, 82 mmol) was heated at 80°C in a pressure tube for 24 h. After cooling and concentrating, the resulting oil was purified by flash chromatography (5:1 hexanes/ethyl acetate) to give 0.47 g (24%) of **178** as a colorless oil. ^{1}H NMR (250MHz, $CDCl_3$) δ 7.20 (dd, *J* = 5.4, 1.8 Hz, 1H), 7.14 (dd, *J* = 5.3, 1.8 Hz, 1H), 5.65 (t, *J* = 1.6 Hz, 1H), 5.28 (t, *J* = 1.6 Hz, 1H), 4.20 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 162.3, 148.7, 144.2, 143.1, 141.2, 89.5, 84.5, 60.8, 14.1; IR (CCl_4): 1703, 1314 cm^{-1};

Preparation of (±)-ethyl-3,3-diethylmercapto-7-oxabicyclo-[2.2.1]hepta-5-ene-2-carboxylate 180. Prepared according to the procedure for **148** using **178** (0.47 g, 1.9 mmol), THF (15 mL), and EtSNa (15 mL of a 0.25 M solution in THF, 3.8 mmol) to give 0.49 (89%) of **180** as a 3:1 mixture of endo:exo isomers.

180 (endo isomer) ^{1}H NMR (250MHz, $CDCl_3$) δ 6.60 (dd, J = 5.7, 1.7 Hz, 1H), 6.40 (dd, J = 5.8, 1.8 Hz, 1H), 5.04 (d, J = 4.3 Hz, 1H), 4.74 (s, 1H), 4.02 (m, 2H), 3.34 (d, J = 4.3 Hz, 1H), 2.74 (m, 3H), 2.54 (m, 1H), 1.18 (q, J = 7.1 Hz, 6H), 1.09 (t, J = 7.5 Hz, 3H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 168.8, 136.0, 133.9, 86.6, 80.3, 66.6, 60.8, 58.9, 25.0, 24.6, 13.8, 13.4, 13.3; IR (CCl_4) 1734, 1172 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{21}O_3S_2$ (MH^+) 289.0932, found 289.0942.

180 (exo isomer) ^{1}H NMR (250MHz, $CDCl_3$) δ 6.43 (s, 2H), 5.21 (s, 1H), 4.90 (s, 1H), 4.20 (dq, J = 7.2, 1.8 Hz, 2H), 2.84-2.66 (m, 5H), 1.30-1.13 (m, 9H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 170.3, 135.7, 135.5, 85.3, 81.1, 65.2, 61.1, 58.2, 25.4, 25.2, 14.0, 13.7, 13.3; IR (CCl_4) 1734, 1178 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{21}O_3S_2$ (MH^+) 289.0932, found 289.0942.

Preparation of (±)-ethyl-7-oxabicyclo[2.2.1]hepta-5-ene-3-one-2-carboxylate 182. Prepared according to the procedure outlined for the formation of **106** using **180** (0.23 g, 0.8 mmol), $Hg(ClO_4)_2$ (0.64 g, 1.6 mmol), $CaCO_3$ (0.3 g, 3.0 mmol), H_2O (0.8 mL, 44 mmol), and THF (4mL) to afford 0.8 g (55%) of **182** as a colorless oil and a 2:1 mixture of endo:exo isomers. **182 (endo isomer)** ^{1}H NMR (250MHz, $CDCl_3$) δ 6.94 (dd, J = 5.8, 1.7 Hz, 1H), 6.40 (dd, J = 5.8, 2.0 Hz, 1H), 5.32 (d, J = 4.0 Hz, 1H), 4.73 (d, J = 1.8 Hz, 1H), 4.12 (q, J = 7.3 Hz, 2H), 3.35 (d, J = 4.0 Hz, 1H), 1.24 (t, J = 7.3 Hz, 3H); **(endo**

isomer) ^{1}H NMR (250MHz, $CDCl_3$) δ 6.72 (dd, *J* = 5.8, 1.6 Hz, 1H), 6.54 (dd, *J* = 5.8, 1.9 Hz, 1H), 5.54 (s, 1H), 4.66 (s, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.87 (s, 1H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 199.3, 198.1, 166.9, 166.5, 141.7, 141.2, 132.6, 127.8, 82.7, 81.5, 81.5, 79.5, 61.8, 61.6, 50.0, 48.0, 14.0; IR (CCl_4) 1777, 1734 cm^{-1}; HRMS (FAB) calcd for $C_9H_{11}O_4$ (MH^+) 183.0657, found 183.0656.

Preparation of (±)-ethyl-3-bromo-bicyclo[2.2.1]hepta-2,5-diene-2-carboxylate 183. Prepared according to the procedure outlined for the formation of **146a** using cyclopetadiene (0.84 g, 12.7 mmol), ethyl 3-bromopropiolate (1.84 g, 10.4 mmol), and benzene (20 mL) to afford 2.06 g (90%) of **183** as a colorless oil. ^{1}H NMR (250MHz, $CDCl_3$) δ 6.85 (m, 1H), 6.79 (m, 1H), 4.17 (m, 2H), 3.94 (m, 1H), 3.62 (s, 1H), 2.26 (d, *J* = 6.6 Hz, 1H), 2.07 (d, *J* = 6.6 Hz, 1H), 1.26 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 163.7, 148.3, 142.9, 142.0, 140.3, 71.6, 61.6, 60.4, 52.0, 14.1; HRMS (FAB) calcd for $C_{10}H_{12}O_2Br$ (MH^+) 243.0021, found 243.0029.

Preparation of (±)-ethyl-3,3-diethylmercapto-bicyclo-[2.2.1]hepta-5-ene-2-carboxylate 184. A solution of **183** (0.6 g, 2.7 mmol) and ethanol (2 mL) was added to a solution of sodium ethoxide (1 mL of a 5.4 M solution in ethanol, 5.4 mmol) at rt. The resulting mixture was heated to 85°C for 0.2 h. After cooling to rt, the reaction was quenched with $NaHCO_3$ (sat., 40 mL), extracted with ether (3×50 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (5:1 hexanes/ethyl acetate) gave 0.4 g (63%) of **184** as yellow oil. ^{1}H NMR (250MHz, $CDCl_3$) δ (endo isomer) 6.55 (m, 1H), 5.95 (m, 1H), 4.15 (m, 1H), 3.97 (m, 1H), 3.79-3.43 (m, 3H), 3.25 (m, 1H), 2.98 (d, *J* = 3.3 Hz, 1H), 2.88 (m, 2H), 1.67 (m, 1H), 1.55 (m, 1H), 1.24-1.02 (m, 9H); (exo isomer) 6.15 (m,

1H), 6.12 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 4.15 (m, 1H), 3.97 (m, 1H), 3.79-3.43 (m, 3H), 3.25 (m, 1H), 2.42 (d, J = 2.6 Hz, 1H), 2.14 (d, J = 8.2 Hz, 1H), 1.55 (m, 1H), 1.24-1.02 (m, 9H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 172.3, 171.3, 138.7, 137.4, 136.2, 130.1, 128.2, 112.4, 112.1, 59.9, 59.8, 58.3, 57.7, 56.5, 55.0, 53.1, 50.9, 47.2, 47.1, 46.0, 44.6, 43.8, 15.3, 15.2, 14.8, 14.2, 14.1; IR (CCl_4): 1740, 1178, 1060 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{23}O_4$ (MH^+) 255.1596, found 255.1602.

Preparation of (±)-ethyl-bicyclo[2.2.1]hepta-5-ene-3-one-2-carboxylate 185. A solution of **184** (0.35 g, 1.4 mmol) and THF (2 mL) was added dropwise to a solution of HCl (2 mL of a 2 M aqueous solution) and THF (2 mL). After 0.2 h the reaction mixture was extracted with ether (3×25 mL), the extracts were dried ($MgSO_4$), and concentrated to give 0.24 g (95%) of **185** as a colorless oil. ^{1}H NMR (250MHz, $CDCl_3$) δ (endo isomer) 6.67 (m, 1H), 5.97 (m, 1H), 4.07 (m, 2H), 3.25 (s, 1H), 3.10 (s, 1H), 3.06 (d, J = 3.0 Hz, 1H), 2.04 (d, J = 9.7 Hz, 1H), 1.84 (d, J = 9.5 Hz, 1H), 1.19 (m, 3H); (exo isomer) δ 6.51 (m, 1H), 6.14 (m, 1H), 4.07 (m, 2H), 3.28 (s, 1H), 3.03 (s, 1H), 2.78 (d, J = 3.8 Hz, 1H), 2.42 (d, J = 9.8 Hz, 1H), 2.12 (s, 1H), 1.19 (m, 3H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 207.1, 204.5, 168.7, 168.3, 142.4, 142.0, 133.0, 128.2, 61.2, 61.0, 55.7, 54.8, 52.9, 50.4, 47.9, 47.8, 44.0, 42.6, 14.0; IR (CCl_4) 1764, 1721, 1313 cm^{-1}; HRMS (FAB) calcd for $C_{10}H_{13}O_3$ (MH^+) 181.0865, found 181.0856.

Preparation of (±)-5-methoxycarbonyl-2-[ethyl-4-methylpent-2-enoate]-2,5-dihydrofuran 190. Prepared according to the procedure outlined for the formation of **162** using **182** (0.16 g, 0.89 mmol), NaH (0.02 g, 0.9 mmol), isobutyraldehyde (0.14 mL, 1.8

mmol), DMF (6 mL), and methyl iodide (0.6 mL, 10 mmol) to give 0.11 g (45%) of **190** as a 1:2 mixture of *E*- and *Z*-alkenes.

190 (*Z*-alkene isomer): ^{1}H NMR (250MHz, $CDCl_3$) δ 6.37 (d, J = 9.9 Hz, 1H), 6.02 (m, 1H), 5.83 (m, 1H), 5.57 (br. s, 1H), 5.25 (m, 1H), 4.17 (dq, J = 7.2, 2.6 Hz, 2H), 3.70 (s, 3H), 3.23 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 6.5 Hz, 6H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 170.9, 166.4, 150.8, 132.1, 128.4, 124.2, 87.1, 84.3, 60.2, 51.9, 28.1, 22.4, 22.3, 14.1; IR (CCl_4) 1762, 1719 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{20}O_5Cs$ (MCs^+) 401.0365, found 401.0374.

190 (E-alkene isomer): ^{1}H NMR (300MHz, $CDCl_3$) δ 6.67 (d, J = 10.5 Hz, 1H), 5.99 (m, 1H), 5.92 (m, 1H), 5.83 (m, 1H), 5.24 (m, 1H), 4.11 (m, 2H), 3.72 (s, 3H), 2.90 (m, 1H), 1.20 (t, J = 6.9 Hz, 3H), 1.00 (dd, J = 6.0, 4.2 Hz, 6H); ^{13}C NMR (75MHz, $CDCl_3$) δ 170.6, 166.6, 153.8, 131.2, 127.7, 125.0, 84.1, 82.5, 60.4, 52.0, 27.1, 22.5, 22.4, 14.0; IR (CCl_4): 1765, 1721, 1258 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{20}O_5Cs$ (MCs^+) 401.0365, found 401.0357.

Preparation of (+)-5-methoxycarbonyl-2-[ethyl-3-phenylprop-2-enoate]-2,5-dihydrofuran 191. Prepared according to the procedure outlined for the formation of **162** using **182** (0.14 g, 0.77 mmol), NaH (0.02 g, 0.8 mmol), benzaldehyde (0.17 mL, 1.6 mmol), DMF (6 mL), and methyl iodide (0.6 mL, 10 mmol) to give 0.13 g (56%) of **191** as a 3:1 mixture of *E*- and *Z*-alkenes.

191 (*E*-alkene isomer): ^{1}H NMR (250MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.38-7.32 (m, 5H), 5.90 (m, 2H), 5.83 (m, 1H), 5.28 (m, 1H), 4.19 (m, 2H), 3.74 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 170.7, 166.5, 143.5, 134.3, 130.7, 129.4, 128.9,

128.4, 128.3, 124.8, 84.3, 82.7, 60.6, 52.0, 14.0; IR (CCl_4) 1767, 1720, 1243 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{19}O_5$ (MH^+) 303.1232, found 303.1235.

191 (*Z*-alkene isomer): ^1H NMR (250MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.27 (s, 5H), 6.13 (m, 1H), 5.94 (m, 1H), 5.70 (m, 1H), 5.34 (m, 1H), 4.11 (dq, J = 7.2, 2.1 Hz, 2H), 3.74 (s, 3H), 1.08 (t, J = 7.2 Hz, 3H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 170.7, 167.5, 135.8, 135.7, 132.6, 131.4, 128.6, 128.1, 127.9, 124.8, 88.2, 84.6, 60.8, 52.2, 13.7; IR (CCl_4) 1765, 1703, 1216 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{19}O_5$ (MH^+) 303.1232, found 303.1228.

Preparation of (±)-2-methoxycarbonyl-4-[ethyl-4-methylpent-2-enoate]-1-cyclopentene 198. Prepared according to the procedure outlined for the formation of **162** using **185** (0.22 g, 1.2 mmol), NaH (0.043 g, 1.8 mmol), isobutyraldehyde (0.22 mL, 2.4 mmol), DMF (6 mL), and methyl iodide (0.6 mL, 10 mmol) to give 0.28 g (94%) of **198** as a 1:3 mixture of *Z*- and *E*-alkenes.

198 (*Z*-alkene isomer): ^1H NMR (300MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.71 (m, 1H), 5.56 (d, J = 9.6 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.65 (s, 3H), 3.53 (m, 1H), 3.07 (m, 1H), 2.53 (m, 1H), 1.80 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.95 (d, J = 6.0 Hz, 3H), 0.93 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 174.6, 168.2, 146.9, 135.5, 132.7, 129.8, 60.2, 51.8, 50.2, 47.8, 35.0, 28.4, 22.7, 22.6, 14.2; IR (CCl_4) 1740, 1715, 1215 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{22}O_4Cs$ (MCs^+) 399.0572, found 399.0566.

198 (*E*-alkene isomer): ^1H NMR (300MHz, $CDCl_3$) δ 6.54 (d, J = 10.5 Hz, 1H), 5.75 (s, 2H), 4.11 (q, J = 7.2 Hz, 2H), 3.89 (m, 1H), 3.67 (s, 3H), 3.57 (m, 1H), 2.83 (m, 1H), 2.44 (m, 1H), 2.03 (m, 1H), 1.22 (t, J = 6.9 Hz, 1H), 0.97 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75MHz, $CDCl_3$) δ 174.6, 167.9, 150.6, 136.6, 130.9, 127.8, 60.4, 51.8, 50.4, 43.7, 34.2,

27.2, 22.5, 22.2, 14.1; IR (CCl_4): 1740, 1709, 1246 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{22}O_4Cs$ (MCs^+) 399.0572, found 399.0566.

Preparation of (±)-2-methoxycarbonyl-4-E-[ethyl-3-phenylprop-2-enoate]-1-cyclopentene 199. Prepared according to the procedure outlined for the formation of **162** using **185** (0.09 g, 0.50 mmol), KOt-Bu (0.083 g, 0.75 mmol), benzaldehyde (0.06 mL, 0.6 mmol), DMF (3 mL), and methyl iodide (0.3 mL, 5 mmol) to give 0.13 g (91%) of **199**. ^1H NMR (300MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.40-7.33 (m, 5H), 5.81 (m, 1H), 5.70 (m, 1H), 4.21 (q, J = 6.9 Hz, 2H), 4.05 (m, 1H), 3.72 (s, 3H), 3.61 (m, 1H), 2.41 (m, 2H), 1.27 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 174.3, 167.4, 139.9, 135.6, 135.4, 134.2, 128.9, 128.3, 128.2, 128.0, 60.5, 51.8, 50.4, 44.0, 33.0, 14.0; IR (CCl_4) 1740, 1715, 1233 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{20}O_4Cs$ (MCs^+) 433.0416, found 433.0400.

Representative Procedure for the Tandem Michael Addition-Anionic Fragmentation Reaction. Generation of Oxabicyclo[4.2.1]nonenes 204a and 204b. A solution of Keto-ester **106**(0.11g, 0.50 mmol), NaH (0.012g, 0.50mmol) in 1.8ml DMF was allowed to stir at 0°C for 0.7h. To this was added a solution of methyl acrylate (0.07ml, 0.75mmol) and 0.7ml DMF over 1hr via syringe pump. After stirring for an additional 2h while warming to rt, the reaction mixture was poured into PH=7.5 phosphate buffer. The mixture was extracted with ether (25ml×3), ether layer was combined, dried over $MgSO_4$, and concentrated. Flash column chromatography (3:1 hexanes/ethyl acetate) provided 85mg of **204a** (55%) along with 26 mg of **204b** (15%).

To simplify its characterization, **204a** (1:1 mixture at C-2 isomers) was converted into the corresponding enol acetate. To a solution of **204a** (0.085g, 0.27mmol), THF (1.5ml)

and KO*t*-Bu (0.032g, 0.29mmol) at 0°C was added AcCl (0.023 g, 0.30 mmol). After 0.5h the mixture was poured into aqueous saturated $NaHCO_3$ solution, extracted with ether (25ml×3), ether was combined, dried ($MgSO_4$), and concentrated. Flash column chromatography (3:1 hexanes/ethyl acetate) gave 62 mg (65%) of enol acetate **205**. ^1H NMR (300MHz, $CDCl_3$) δ 6.23 (d, *J* = 5.7Hz, 1H), 6.09 (d, *J* = 5.4Hz, 1H), 4.15 (q, *J* = 5.4Hz, 2H), 3.70 (s,3H), 3.26 (s, 3H), 3.01 (dd, *J*=12.6, 3.6Hz, 1H), 2.84 (dd, *J*=16.2, 3.6Hz, 1H), 2.51 (dd, *J*=16.2, 12.6Hz, 1H), 2.18 (s, 3H), 1.44 (s, 3H), 1.27 (t, *J* = 5.4 Hz, 3H).; ^{13}C NMR (75MHz, $CDCl_3$) δ 171.4, 169.2, 167.0, 155.1, 134.4, 127.9, 119.7, 115.4, 86.0, 60.7, 55.8, 52.2, 51.6, 27.3, 21.2, 20.4, 14.1; IR(CCl_4) 1765, 1758cm^{-1}; HRMS calcd for $C_{17}H_{23}O_8$ (MH^+) 355.1393, found 355.1404.

204b: ^1H NMR (300MHz, $CDCl_3$) δ 6.11 (d, *J* = 5.7Hz, 1H), 5.75 (d, *J* = 5.7Hz, 1H), 5.14 (dd, *J* = 11.6, 2.4 Hz, 1H), 4.21 (m, 2H), 3.72 (s, 3H), 3.30 (s, 3H), 3.04 (dd, *J* = 4.5, 2.4 Hz, 1H), 2.08 (m, 2H), 1.57 (s, 3H), 1.29 (t, *J* = 6.9 Hz, 3H), ^{13}C NMR (75MHz, $CDCl_3$) δ 210.5, 171.6, 171.5, 137.4, 133.1, 116.1, 92.8, 60.9, 53.9, 52.1, 51.2, 49.0, 26.9, 20.8, 14.2; IR (CCl_4) 1734 cm^{-1}; HRMS calcd for $C_{15}H_{21}O_7$ (MH^+) 313.1287, found 313.1288.

Oxabicyclo[4.2.1]nonenes 206. According to the general procedure, **106** (0.117 g, 0.52mmol), NaH (0.013 g, 0.52mmol), dimethyl fumarate (0.088 g, 0.61mmol) and DMF (2ml) gave 0.11g (55%) of **206 (endo)** and 0.026 g (15%) of **206 (exo)**.

To simplify its characterization, **206 (endo)** (1:1 micture of C-2 isomers) was converted into the corresponding enol acetate. To a solution of **206 (endo)** (0.017 g, 0.29 mmol), THF (2ml), and KO*t*-Bu (0.038 g, 0.34 mmol) at 0°C was added AcCl (0.023 ml,

0.44 mmol). After 0.5 h the reaction mixture was poured into aqueous saturated $NaHCO_3$ (15ml), extracted with ether (3 × 25 ml), dried ($MgSO_4$), and concentrated. Flash chromatography (3:1 hexanes/ethyl acetate) provided 70mg (59%) of enol acetate as a colorless oil: ^1H NMR (250MHz, $CDCl_3$) δ 6.17 (s, 2H), 4.62 (d, J = 5.4Hz, 1H), 4.14 (q, J = 7.1Hz, 2H), 3.71 (s, 3H), 3.54 (s, 3H), 3.40 (d, J = 5.4Hz, 1H), 3.26 (s, 3H), 2.17 (s, 3H), 1.39 (s, 3H), 1.23 (t, J = 7.1Hz, 3H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 170.2, 169.2, 168.6, 166.2, 159.5, 137.2, 128.9, 118.8, 114.3, 85.5, 60.7, 57.2, 52.5, 52.3, 51.1, 44.0, 21.4, 20.5, 13.9;IR: 1746.1, 1721.4 cm^{-1}; HRMS calcd for $C_{19}H_{25}O_{10}$ (MH^+) 413.1448, found 413.1444.

206 (exo): ^1H NMR (300MHz, $CDCl_3$) δ (1:1 mixture of isomers) 6.25 (d, J = 6.0 Hz, 1H), 6.01(d, J = 6.0 Hz, 1H), 6.0(d, J = 6Hz, 1H), 5.90(d, J =6.0 Hz, 1H), 4.47 (d, J = 10.5 Hz, 1H), 4.24-4.11 (m, 5H), 3.80 (d, J = 10.5 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.60 (s, 3H), 3.30-3.14 (m, 3H), 3.25 (s, 3H), 3.23 (s, 3H), 1.55 (s, 3H), 1.53 (s, 3H), 1.29 (t, J = 6.9 Hz, 3H), 1.24 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 205.5, 204.5, 172.3, 171.7, 170.6, 170.2, 169.6, 167.3, 135.7, 130.4, 130.2, 115.8, 115.2, 93.1, 92.1, 61.4, 61.1, 60.3, 58.9, 58.5, 53.0, 52.8, 52.7, 52.4, 50.9, 50.5, 45.0, 43.5, 21.1, 20.6, 14.1, 14.0; IR (CCl_4) 1740.0 cm^{-1}; HRMS calcd for $C_{17}H_{23}O_9$ (MH^+) 371.1342, found 371.1335.

Oxabicyclo[4.2.1]nonenes 207. According to the general procedure, **106** (0.13 g, 0.57mmol), NaH (0.014 g, 0.57mmol), 3-butenyl acrylate (excess), and DMF (2ml) gave 0.12 g of **207 (endo)** (61%) and 0.036 g of **207 (exo)** (18%) after flash chromatography (3:1 hexanes/ethyl acetate).

207 (endo): (1:1 mixture of C-2 isomers) ^{1}H NMR (300MHz, $CDCl_3$) δ 6.14 (d, *J* = 6.0 Hz, 1H), 6.10 (d, *J* = 5.7Hz, 1H), 6.04 (d, *J* = 6.0 Hz, 1H), 5.98 (d, *J* =6.0 Hz, 1H), 6.0-5.7 (m, 2H), 5.12-5.02 (m, 4H), 4.25-4.04 (m, 8H), 3.60 (dd, *J* = 12.6, 4.2 Hz, 1H), 3.50 (dd, *J* = 12.6, 4.2 Hz, 1H), 3.44 (dd, *J* = 5.7, 2.1 Hz, 1H), 3.27 (s, 3H), 3.21 (s, 3H), 3.13 (dd, *J* = 12.6, 4.2 Hz, 1H), 2.41-2.28 (m, 4H), 2.10-1.83 (m, 4H), 1.54 (s, 3H), 1.50 (s, 3H), 1.25 (t, *J* = 5.7 Hz, 6H); ^{13}C NMR (75MHz, $CDCl_3$) δ 207.2, 207.0, 172.7, 172.0, 171.2, 170.3, 169.9, 167.7, 136.6, 136.2, 136.0, 133.9, 133.7, 133.4, 129.7, 129.2, 117.6, 117.2, 116.8, 116.5, 116.0, 92.5, 92.2, 91.9, 64.6, 64.3, 63.5, 61.0, 60.8, 59.6, 57.4, 54.8, 51.4, 51.0, 50.8, 32.9, 32.6, 31.5, 29.4, 27.8, 26.6, 22.1, 21.4, 20.9, 14.1; IR (CCl_4): 1721 cm^{-1}.HRMS calcd for $C_{18}H_{25}O_7$ (MH^+) 353.1600, found 353.1600.

207 (exo): ^{1}H NMR (300MHz, $CDCl_3$) δ 6.10 (d, *J* = 5.7 Hz, 1H), 5.75 (d, *J* = 5.7 Hz, 1H), 5.77-5.74 (m, 1H), 5.11-5.02 (m, 2H), 4.29-4.10 (m, 4H), 3.29 (s, 3H), 3.02 (dd, *J* = 4.8, 2.4 Hz, 1H), 2.39 (tq, *J* = 6.9, 1.5 Hz, 2H), 2.10-2.00 (m, 2H), 1.56 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 208.1, 171.4, 171.0, 137.4, 133.8, 130.1, 117.2, 116.1, 92.8, 64.1, 60.8, 54.0, 51.1, 49.0, 32.9, 26.8, 20.8, 14.2; IR (CCl_4) 1746.1, 1721.4 cm^{-1}; HRMS calcd for $C_{18}H_{25}O_7$ (MH^+) 353.1600, found 353.1604.

Oxabicyclo[4.2.1]nonenes 208. According to the general procedure, **106** (0.12 g, 0.52 mmol), NaH (0.013 g, 0.5 mmol), methyl vinyl ketone (0.052 ml, 0.63 mmol), and DMF (2ml) gave 0.062 g of **208 (endo)** (40%) along with 0.020 g of **208 (exo)** (13%) after flash chromatography (3:1 hexanes/ethyl acetate).

208 (endo) (1:1 mixture of C-2 isomers): ^{1}H NMR (500MHz, $CDCl_3$) δ 6.15 (d, *J* = 5.8 Hz, 1H), 6.14 (d, *J* = 5.8 Hz, 1H), 6.03 (d, *J* = 5.8 Hz, 1H), 5.98 (d, *J* = 5.8 Hz, 1H),

4.14 (m, 4H), 3.43 (dd, J = 12.8, 4.0 Hz, 1H), 3.37 (dd, J = 5.2, 2.6 Hz, 1H) 3.27 (s, 3H), 3.22 (s, 3H), 3.09(dd, J = 12.7, 3.7 Hz, 1H), 2.38 (dd, J = 4.6, 4.0Hz, 1H), 2.35 (dd, J = 5.1, 4.0 Hz, 1H), 2.14 (s, 3H), 2.13 (s, 3H), 2.10 (dd, J = 3.6, 1.8Hz, 1H), 1.84 (m, 2H), 1.57 (s, 3H), 1.49 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 209.8, 209.5, 205.7, 200.7, 172.0, 171.3, 136.2, 135.2, 130.2, 129.7, 117.3, 116.9, 92.4, 92.1, 66.5, 62.9, 61.0, 60.8, 54.9, 51.1, 51.0, 50.9, 30.0, 29.2, 26.9, 26.3, 21.8, 20.9, 14.1, 14.0 ; IR (CCl_4) 1740, 1709 cm^{-1}; HRMS calcd for $C_{15}H_{21}O_6$ (MH^+) 297.1338, found 297.1331.

208 (exo): ^{1}H NMR (500MHz, $CDCl_3$) δ 6.07 (d, J = 5.5 Hz, 1H), 5.72 (d, J = 5.5 Hz, 1H), 5.28 (dd, J =11.5, 1.5 Hz, 1H), 4.16 (m, 1H), 4.12 (m, 1H), 3.30 (s, 3H), 3.00 (dd, J = 5.0, 2.5 Hz, 1H), 2.15 (s, 3H), 2.10 (partially obscured ddd, J = 15.8, 2.1, 2.1 Hz, 1H), 1.82 (ddd, J = 15.8, 11.4, 4.9 Hz, 2H), 1.57 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 210.6, 206.6, 171.7, 137.3, 130.1, 116.4, 93.0, 60.9, 59.4, 51.1, 48.7, 30.8, 25.7, 20.9, 14.1; IR (CCl_4) 1727, 1709.1 cm^{-1}; HRMS calcd for $C_{15}H_{21}O_6$ (MH^+) 297.1338, found 297.1346.

Representative Procedure for the Tandem Michael Addition-Anionic Fragmentation Reaction. The Generation of Oxabicyclo[6.2.1]dodecene 211. A solution of **204a** (0.043 g, 0.14 mmol), NaH (0.003 g, 0.14 mmol) and THF (0.7ml) at 0°C was added DMAD (0.024 mL, 0.15 mmol). After stirring for 2h the reaction mixture was poured into pH = 7.5 phosphate buffer. The mixture was extracted with ethyl acetate (3×25ml), organic layer was combined, dried over $MgSO_4$, and concentrated. Flash column chromatography (3:1 hexanes/ethyl acetate) provided 58mg (92%) of **211** as a

colorless oil. ^{1}H NMR (250MHz, $CDCl_3$) δ 13.6 (s, 1H), 6.54 (d, *J* = 5.8 Hz, 1H), 5.79 (d, *J* = 5.8 Hz, 1H), 4.12 (q, *J* = 7.3 Hz, 2H), 3.84 (s, 3H), 3.69 (s, 3H), 3.67 (s, 3H), 3.15 (s, 3H), 3.03 (dd, *J* = 3.9, 9.7 Hz, 1H), 2.53 (m, 2H), 1.68 (s, 3H), 1.23 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 176.5, 173.3, 171.5, 169.7, 167.1, 143.8, 138.2, 125.9, 117.6, 94.9, 91.6, 77.2, 61.1, 52.6, 52.5, 50.6, 49.6, 31.5, 25.2, 14.1 IR (CCl_4) 3403, 1733 cm^{-1}; HRMS calcd for $C_{21}H_{27}O_{11}$ (MH^+) 455.1553, found 455.1555.

211 was converted to the corresponding enol acetate: To a solution of **211** (0.063 g, 0.14 mmol), THF (1.0ml), and NaH (0.004 g, 0.14 mmol) at 0°C was added acetyl chloride (0.011 mL, 0.15 mmol) after 2h the reaction was poured into aqueous saturated $NaHCO_3$, extracted with ether (25×3ml), ether layer was combined, dried, and concentrated. Flash column chromatography (1:1 hexanes/ethyl acetate) provided 35 mg of **211 acetate** (51%) as a colorless oil: ^{1}H NMR (300MHz, $CDCl_3$) δ 6.23 (d, J = 6.0 Hz, 1H), 5.92 (d, *J* = 6.0 Hz, 1H), 4.11 (q, *J* = 6.9 Hz, 2H), 3.85 (s, 3H), 3.68 (s, 3H), 3.60 (s, 3H), 3.15 (s, 3H), 3.11 (partially obscured d, *J* = 11.7 Hz, 1H), 2.78 (dd, *J* = 14.1, 11.7 Hz, 1H), 2.78-2.58(dd, *J* = 14.1, 1.5 Hz, 1H), 2.26 (s, 3H), 1.62 (s, 3H), 1.22 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 171.1, 169.4, 167.7, 165.6, 164.6, 158.6, 145.6, 136.4, 127.4, 125.2, 118.1, 114.1, 91.1, 61.1, 52.8, 52.5, 52.4, 50.7, 49.4, 31.4, 24.7, 21.4, 14.1; IR (CCl_4) 1783, 1738 cm^{-1}; HRMS calcd for $C_{23}H_{29}O_{12}$ (MH^+) 497.1659, found 497.1662.

Oxabicyclo[6.2.1]dodecene 212 and Oxabicyclo[4.2.1]nonene 213. According to the general procedure, **204a** (0.090g, 0.29mmol), THF (1.5ml), NaH (0.007 g, 0.29

mmol) and ethyl propiolate (0.031 g, 0.32 mmol) gave 52 mg (60%) of an inseparable mixture of **212** and **213** after flash chromatography (3:1 hexanes/ethyl acetate).

To effect separation, the mixture of **212** and **213** was converted to the corresponding enol acetate. To a solution of the mixture and THF (1ml) at 0°C was added KOt-Bu (0.014 g, 0.13 mmol). After stirring for 0.5 h, acetyl chloride (0.01 ml, 0.14 mmol) was added. The reaction mixture was stirred for an additional 0.5 h, diluted with ether (10 ml), washed with aqueous saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated. Flash chromatography (2:1 hexanes/ethyl acetate) provided 0.010 g (17% from **204a**) of **212 acetate** along with 0.030 g (25% from **204a**) of **213**.

212 acetate: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.31 (s, 1H), 6.26 (d, J = 6.0 Hz, 1H), 5.95 (d, J = 6.0 Hz, 1H), 4.17 (m, 4H), 3.76 (s, 3H), 3.14 (s, 3H), 3.06 (d, J = 10.2 Hz, 1H), 2.56 (br d, J = 7.2 Hz, 3H), 2.46 (dd, J = 14.1, 10.5 Hz, 1H), 2.24 (s, 3H), 1.54 (s, 3H), 1.28(t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C NMR (300MHz, $CDCl_3$) δ 172.3, 168.0, 166.8, 164.6, 155.7, 136.3, 134.4, 132.4, 126.7, 118.3, 116.3, 90.9, 61.5, 60.8, 52.1, 50.7, 50.5, 27.6, 24.9, 21.3, 14.2, 14.1; IR (CCl_4) 1728, 1635 cm^{-1}; HRMS calcd for $C_{22}H_{28}O_{10}Cs$ (MCs^+) 585.0737, found 585.0727.

213 (1:1 mixture of C-2 isomers): ^{1}H NMR (500MHz, $CDCl_3$) δ 7.13 (d, J = 16.2 Hz, 1H), 6.15 (d, J = 5.8Hz, 1H), 6.08 (d, J = 5.8 Hz, 1H), 6.07 (d, J = 5.9 Hz, 1H), 6.01 (d, J = 5.8 Hz, 1H), 5.98 (d, J = 12.4 Hz, 1H), 5.90 (d, J = 12.4 Hz, 1H), 5.78(d, J = 16.2 Hz, 1H), 4.15 (m, 8H), 3.77 (s, 3H), 3.75 (s, 3H), 3.67 (dd, J = 12.5, 4.3 Hz, 1H), 3.53 (dd, J = 12.6, 4.0Hz, 1H), 3.22 (s, 3H), 3.21 (s, 3H), 2.71 (dd, J = 14.9, 12.7 Hz, 1H), 2.23 (dd, J = 14.9, 4.1 Hz, 1H), 2.20 (dd, J = 14.9, 4.4 Hz, 1H), 1.85 (dd, J =14.9, 12.6 Hz, 1H),

1.56 (s, 3H), 1.53 (s, 3H), 1.25 (t, J = 7.1 Hz, 6H), 1.24(t, J = 7.2Hz, 6H); ^{13}C NMR(75MHz, $CDCl_3$) δ 205.2, 202.4, 171.5 171.4, 170.4, 167.9, 165.4, 164.9.144.5, 140.9, 136.3, 136.2, 129.5, 128.9, 123.8, 122.5, 116.5, 116.1, 92.6, 92.4, 63.8, 62.8, 61.0, 60.7, 60.4, 53.0, 52.8, 51.6, 50.9, 33.3, 32.6, 22.3, 22.1, 14.2, 14.1. IR (CCl_4) 1734, 1221 cm^{-1}; HRMS calcd for $C_{20}H_{27}O_9$ (MH^+) 411.1655, found 411.1659.

5,5-diethyleneoxy-7-trimethylsilyl-6-heptyn-1-ol 227. A solution of methyl 5,5-diethlenoxy-7-trimethylsilyl-6-heptynoate (1.15 g, 4.25 mmol) and THF (40 ml) at 0°C was added $LiAlH_4$ (0.16 g, 4.25 mmol). After stirring for 0.2 h, the mixture was poured into 0.5M HCl solution, extracted with ether (80×3ml), ether was combined, dried, and concentrated. Flash column chromatography (1:1 hexanes/ethyl acetate) gave 1.0 g (100%) of **227**. ^{1}H NMR (600MHz, $CDCl_3$) δ 4.06-4.00 (m, 2H), 3.94-3.88 (m, 2H), 3.60 (t, J = 5.8Hz, 2H), 1.85 (m, 2H), 1.76 (s, 1H), 1.60-1.54 (m, 4H), 0.12 (s, 9H); ^{13}C NMR (150MHz, $CDCl_3$) δ 102.9, 102.5, 88.6, 64.7, 64.6, 64.6, 62.6, 38.6, 32.4, 20.0, -0.2. IR (CCl_4): 3376, 2968, 2900, 2166, 1252 cm^{-1}; HRMS calcd for $C_{12}H_{23}O_3Si$ (MH^+) 243.1416, found 243.1416.

5,5-diethyleneoxy-7-trimethylsilyl-6-heptyn-1-aldehyde 228. A solution of **227** (0.54g, 2.23 mmol), DCM (2 mL) and NMO (0.39g, 3.34 mmol) was added TPAP (0.04 g, 0.112 mmol) at rt. After stirring for 0.2 h, the mixture was concentrated. Flash column chromatography (3:1 hexanes/ethyl acetate) provided 0.37 g (69%) of **228**. ^{1}H NMR (600MHz, $CDCl_3$) δ 9.73 (t, J = 1.8Hz, 1H), 4.05-4.00 (m, 2H), 3.96-3.91 (m, 2H), 2.48 (dt, J = 8.9, 1.7 Hz, 2H), 1.90-1.82 (m, 4H), 0.13 (s, 9H); ^{13}C NMR (150MHz, $CDCl_3$) δ

202.1, 155.2, 102.6, 102.2, 88.9, 64.6, 43.3, 38.0, 16.5, -0.3; IR (CCl_4) 2963, 2895, 2166, 1715, 1258, 851 cm^{-1}; HRMS calcd for $C_{12}H_{21}O_3Si(MH^+)$ 241.1260, found 241.1258.

Ethyl 7,7-diethyleneoxy-9-trimethylsilyl-8-nonyn-(E)-2-enoate 229. A solution of **228** (0.37 g, 1.56 mmol) and DCM (5 ml) was added carbethoxymethylenetriphenylphosphorane (0.82 g, 2.3 mmol) at rt. After stirring for 3 h, the mixture was concentrated. Flash column chromatography (4:1 hexanes/ethyl acetate) gave 0.42g (89%) of **229**. ^1H NMR (600MHz, $CDCl_3$) δ 6.91 (dt, J = 18.7, 8.3Hz, 1H), 5.79 (d, J = 18.8 Hz, 1H), 4.14 (q, J = 8.6 Hz, 2H), 4.05-4.00 (m, 2H), 3.95-3.90 (m, 2H), 2.23 (q, J = 9.0 Hz, 2H), 1.87-1.83 (m, 2H), 1.72-1.65 (m, 2H), 1.24 (t, J = 8.6 Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (150MHz, $CDCl_3$) δ 166.6, 148.5, 121.6, 102.7, 102.4, 88.7, 64.5, 60.0, 38.27, 31.7, 22.2, 14.2, -0.3; IR (CCl_4) 2969, 2895, 2166, 1721, 1258 cm^{-1}; HRMS calcd for $C_{16}H_{27}O_4Si(MH^+)$ 311.1679, found 311.1679.

Ethyl 7,7-diethyleneoxy-8-nonyn-(E)-2-nonenoate 230. A solution of **229** (0.71 g, 2.29 mmol) and EtOH (5 ml) at rt was added K_2CO_3 (0.32 g, 2.29 mmol). After stirring for 2 hrs, the mixture was concentrated. Flash column chromatography (5:1 hexanes/ethyl acetate) provided 0.52 g (96%) of **230**. ^1H NMR (500MHz, $CDCl_3$) δ 6.92 (dt, J = 18.5, 8.3 Hz, 1H), 5.80 (d, J = 18.8Hz, 1H), 4.14 (q, J = 8.6Hz, 2H), 4.07-4.04 (m, 2H), 3.98-3.92 (m, 2H), 2.47 (s, 1H), 2.23 (q, J = 8.7 Hz, 2H), 1.89-1.86 (m, 2H), 1.73-1.67 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 166.6, 148.4, 121.7, 102.6, 81.3, 72.0, 64.6, 60.1, 38.2, 31.7, 22.1, 14.2; IR (CCl_4): 3308, 2969, 2895, 2166, 1721, 1660, 1376 cm^{-1}. HRMS calcd for $C_{13}H_{19}O_4(MH^+)$ 239.1283, found 239.1286.

Ethyl 7,7-diethyleneoxy-2,8-nonadienoate 231. To a solution of **230** (0.52 g, 2.18 mmol) and EtOH (16 mL) was added Lindlar catalyst (20 mg), and the mixture was mounted with a H_2 balloon. After stirring for overnight, the mixture was concentrated, flash column chromatography (5:1 hexanes/ethyl acetate) gave 0.48g (92%) of **231**. ^{1}H NMR (500MHz, $CDCl_3$) δ 6.83 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.79 (dt, *J* = 15.6, 1.4 Hz, 1H), 5.60 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.24 (dd, *J* = 17.2, 1.8 Hz, 1H), 5.05 (dd, *J* = 10.6, 1.8 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.85-3.78 (m, 2H), 3.78-3.72 (m, 2H), 2.11 (dq, *J* = 7.4, 1.4 Hz, 2H), 1.62-1.55 (m, 2H), 1.49-1.43 (m, 2H), 1.16 (t, *J* = 7.1Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 166.4, 148.6, 137.5, 121.4, 115.4, 108.6, 64.4, 59.9, 37.2, 32.0, 21.7, 14.1; IR (CCl_4) 2987, 2956, 2888, 1728, 1660, 1271 cm^{-1}; HRMS calcd for $C_{13}H_{21}O_4$(MH^+) 241.1440, found 241.1441

Ethyl 7-oxo-2,8-nonadienoate 232. To a solution of **231** (0.48 g, 2.03 mmol) and THF (3 ml) was added 5% HCl solution (1.5 mL) at rt. After stirring for 3 h, the mixture was poured into aqueous saturated NH_4Cl solution, extracted with ether (40×3ml), ether was combined, dried, concentrated. Flash column chromatography (5:1 hexanes/ethyl acetate) gave 0.30 g (76%) of **232**. ^{1}H NMR (500MHz, $CDCl_3$) δ 6.87 (dt, *J* = 7.0, 16.0 Hz, 1H), 6.29 (dd, *J* = 18.0, 10.5 Hz, 1H), 6.16 (dd, *J* = 18.0, 1.0 Hz, 1H), 5.79 (dd, *J* = 3.5, 1.5 Hz, 1H), 5.76 (dd, *J* = 3.5, 1.5 Hz, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 2.56 (t, J = 7.5 Hz, 2H), 2.19 (dq, *J* = 7.0, 1.5 Hz, 2H), 1.76 (p, *J* = 7.0 Hz, 2H), 1.23 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 199.9, 166.4, 147.9, 136.4, 128.1, 122.0, 60.1, 38.4, 31.3, 22.0, 14.2. IR (CCl_4): 2987, 2944, 1721, 1654, 1271 cm^{-1}; HRMS calcd for $C_{11}H_{17}O_3$ (MH^+) 197.1178, found 197.1178.

Oxabicyclo[4.2.1]nonenes 233 and 234. To a solution of **106** (0.071 g, 0.314 mmol), NaH (0.007 g, 0.314 mmol) and DMF (0.7 mL) at 0°C was added a solution of **232** (0.068 g, 0.34 mmol) and DMF (0.6 mL). After stirring for 0.5h the reaction mixture was poured into aqueous saturated NH_4Cl solution, extracted with ether (30×3ml), dried, concentrated. Organic extracts were combined, dried over $MgSO_4$, and concentrated. Flash column chromatography (3:2 hexanes/ethyl acetate) gave 42mg (32%) of **233** and 36mg (27%) of **234**.

233: (mixture of C-2 isomers) ^{1}H NMR (600MHz, $CDCl_3$) δ 6.88 (dt, *J* = 15.7, 6.9 Hz, 1H), 6.86 (dt, *J* = 15.7, 7.0 Hz, 1H), 6.15 (d, *J* = 5.8 Hz, 1H), 6.14 (d, *J* = 5.7 Hz, 1H), 6.02 (d, *J* = 5.7 Hz, 1H), 5.98 (d, *J* = 5.8 Hz, 1H), 5.80 (dt, *J* = 15.7, 1.3 Hz, 1H), 5.79(dt, *J* = 15.7, 1.4 Hz, 1H), 4.18-4.10 (m, 4H), 3.43 (dd, *J* = 7.7, 3.9 Hz, 1H), 3.36 (dd, *J* = 5.1, 2.7 Hz, 1H), 3.23 (s, 3H), 3.28 (s, 3H), 3.08 (dd, *J* = 12.7, 3.7 Hz, 1H), 2.51(ddd, *J* = 17.6, 8.1, 6.8 Hz, 1H), 2.39 (ddd, *J* = 15.1, 4.2, 4.2 Hz, 1H), 2.06 (ddd, *J* = 15.1, 3.7, 2.1 Hz, 1H), 1.55 (s, 3H), 1.51 (s, 3H).); ^{13}C NMR (125MHz, $CDCl_3$) δ 209.8, 209.7, 207.3, 201.9, 172.0, 171.3, 166.6, 166.4, 148.1, 147.8, 136.1, 135.2, 130.2, 129.8, 122.2, 121.9, 117.4, 116.9, 92.4, 92.1, 77.2, 66.1, 62.2, 61.0, 60.8, 60.2, 54.9, 51.0, 51.0, 42.0, 40.7, 31.2, 31.1, 26.9, 26.2, 21.9, 21.5, 21.3, 20.9, 14.1, 14.1, 14.1; IR (CCl_4) 2981, 1938, 1728, 1620, 1370, 1184 cm^{-1}; HRMS calcd for $C_{22}H_{31}O_8$ (MH^+) 423.2019, found 423.2021.

234: ^{1}H NMR (500MHz, $CDCl_3$) δ 6.89 (dt, *J* = 15.4, 6.9 Hz, 1H), 6.07 (d, *J* = 5.6 Hz, 1H), 5.80 (d, *J* = 15.6 Hz, 1H), 5.72 (d, *J* = 5.6 Hz, 1H), 5.27 (dd, *J* = 11.3, 1.5 Hz, 1H), 4.27-4.09 (m, 4H), 3.29 (s, 3H), 3.00 (dd, *J* = 4.6, 2.2 Hz, 1H), 2.55 (dt, *J* = 17.5,

7.5 Hz, 1H), 2.32 (ddd, J = 17.5, 7.8, 6.0Hz, 1H), 2.26-2.13 (m, 2H), 2.07 (d, J = 15.8 Hz, 1H), 1.88 (ddd, J = 15.8, 11.4H, 4.8 Hz, 1H), 1.82-1.65 (m, 2H), 1.56 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 210.9, 208.2, 171.7, 166.6, 148.2, 137.3, 130.2, 121.8, 116.2, 93.0, 60.8, 60.1, 58.6, 51.1.

4,4-dimethyl-7-t-butyldiphenylsilanyloxy-1-heptene-3-ol 238. To a solution of vinylmagnesium bromide (1M in THF, 20.3 mmol) at 0°C was added a solution of 5-t-butyldiphenylsilanyloxy-2,2-dimethylpentanal (5.0 g, 13.5 mmol) and THF (15ml) dropwise over 1h. After stirring for 0.5h, the mixture was quenched with saturated NH_4Cl solution. The aqueous phase was extracted with ether (200 mL×3). The organic extracts were dried over $MgSO_4$, and concentrated. Flash column chromatography (5:1 hexane/ethyl acetate) gave 4.0 g (74%) of 4,4-dimethyl-7-t-butyldiphenylsilanyloxy-1-heptene-3-ol **238** as a colorless oil. ^{1}H NMR (600MHz, $CDCl_3$) δ 7.65 (dd, J= 7.8, 1.2 Hz, 4H), 7.42-7.34 (m, 6H), 5.90 (ddd, J = 17.3, 10.5, 6.8 Hz, 1H), 5.20 (dt, J= 17.2, 1.2 Hz, 1H), 5.15 (dt, J= 10.4, 1.2 Hz, 1H), 3.78 (d, J = 6.6 Hz, 1H), 3.62 (t, J = 6.6 Hz, 2H), 1.58-1.48 (m, 2H), 1.33 (ddd, J= 13.2, 6.0, 2.4 Hz, 1H), 1.23 (ddd, J= 16.2, 12.0, 6.0 Hz, 1H), 1.04 (s, 9H), 0.86 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (150MHz, $CDCl_3$) δ 137.9, 135.6, 134.1, 129.5, 127.6, 127.5, 116.4, 79.9, 64.7, 36.9, 34.6, 27.0, 26.9, 22.8, 22.7, 19.2. IR (CCl_4) 2969, 1548 cm^{-1}; HRMS calcd for $C_{25}H_{35}OSi$ (MH^+) 379.2457, found 379.2466.

4,4-dimethyl-5-methoxymethoxy-6-heptene-1-ol 240. To a solution of 4,4-dimethyl-7-t-butyldiphenylsilanyloxy-1-heptene-3-ol **238** (4.0 g, 10.1 mmol) and DCM (10ml) was added MOMCl (1.62 g, 20.2 mmol) at ambient temperature followed by a solution of DIPEA (3.52 mL, 20.2 mmol) and DCM (10 mL). After stirring for 12 h, the

mixture was quenched by saturated $NaHCO_3$ solution. The aqueous phase was extracted with ether (200 mL×3), dried, and concentrated to provide the MOM ether. The MOM ether was taken on to the formation of **240** without further purification.

To a solution of the crude MOM ether from above and THF (30 mL), was added TBAF (17 mL of a 1 M solution in THF, 17.2 mmol). After stirring for 2.5 h, the reaction was quenched through the addition of H_2O (50 mL). The aqueous phase was extracted with ethyl acetate (3x200 mL). The organic extracts were dried and concentrated. Flash chromatography (hexanes/ethyl acetate 3:2) gave 1.8 g (85%) of **240** as a colorless oil. 1H NMR (600 MHz, $CDCl_3$) δ 5.64 (ddd, *J* = 17.4, 10.2, 8.4 Hz, 1H), 5.22 (dd, *J*= 10.2, 1.8 Hz, 1H), 5.13 (dd, *J*=17.4, 1.2 Hz, 1H), 4.61 (d, *J*=8.1 Hz, 1H), 4.42 (d, *J*=8.1 Hz, 1H), 3.63 (d, *J*=8.4 Hz, 1H), 3.54 (t, *J*=6.6 Hz, 2H), 3.30 (s, 3H), 2.20 (bs, 1H), 1.56-1.45 (m, 2H), 1.34 (dt, *J*=13.2, 4.8 Hz, 1H), 1.22 (ddd, *J*=12.6, 12.6, 4.8 Hz, 1H), 0.85 (s, 3H), 0.82 (s, 3H); 13C NMR (150 MHz, CDCl3) δ 134.9, 119.1, 93.8, 84.3, 63.6, 55.6, 36.4, 34.5, 26.9, 23.3, 23.2; IR (CCl4) 3376, 2944, 2888, 1036 cm^{-1}. HRMS calcd for C11H23O3 (M+H) 203.1647, found 203.1644.

4,4-dimethyl-5-methoxymethoxy-6-heptenal. To a solution of oxalyl chloride (0.87 mL, 9.95 mmol) and CH_2Cl_2 (5 mL) at -60°C was added a solution of DMSO (0.94 mL, 13.3 mmol) and CH2Cl2 (5 mL) dropwise. After the resulting solution had stirred for 10 min, a solution of **240** (1.34 g, 6.63 mmol) and CH_2Cl_2 (10 mL) was added. The mixture was stirred for 10 min and a solution of NEt_3 (3.71 mL, 26.5 mmol) and CH_2Cl_2 (10 mL) was added. After warming to rt, the reaction mixture was stirred for 1 h and then quenched with NH_4Cl ((sat, aq.) 30 mL). The aqueous phase was extracted with

ether (100x3 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (hexanes/ethyl acetate 3:1) gave 1.30 g (97%) of 4,4-dimethyl-5-methoxymethoxy-6-heptenal as a colorless oil. ^1H NMR (250 MHz, $CDCl_3$) δ 9.75 (t, *J*=1.8 Hz, 1H), 5.66 (ddd, *J*=17.0, 10.4, 8.3 Hz, 1H), 5.28 (ddd, *J*=10.0, 1.9, 0.5 Hz, 1H), 5.17 (ddd, *J*=17.2, 1.8, 0.6 Hz, 1H), 4.64 (d, *J*=6.9 Hz, 1H), 4.45 (d, *J*=6.7 Hz, 1H), 3.64 (d, *J*=8.3 Hz, 1H), 3.34 (s, 3H), 2.48-2.38 (m, 2H), 1.71 (ddd, *J*=13.9, 10.1, 6.2 Hz, 1H), 1.54 (ddd, *J*=13.9, 10.5, 6.1 Hz, 1H), 0.88 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 202.9, 134.6, 119.7, 93.8, 84.1, 55.8, 39.0, 36.3, 30.4, 23.3, 23.2; IR (CCl_4) 2956, 2888, 1709, 1042 cm^{-1}.

6,6-dimethyl-7-methoxymethoxy-2,8-nonadienoate 241. To a solution of 4,4-dimethyl-5-methoxymethoxy-6-heptenal (1.8 g, 8.9 mmol) and DCM (18ml) was added (carbethoxymethylene) triphenylphosphorane (4.65 g, 13.35 mmol) at rt. After stirring for 12 hs, the mixture was concentrated, flash column chromatography (hexane: ethyl acetate 5:1) gave 2.0 g (88%) of **241**. ^1H NMR (600MHz, $CDCl_3$) δ 6.92 (dt, *J* = 15.6, 6.6 Hz, 1H), 5.77 (d, *J* = 15.6 Hz, 1H), 5.64 (ddd, *J* = 17.4, 10.8, 8.4 Hz, 1H), 5.24 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.14 (d, *J* = 17.4 Hz, 1H), 4.64 (d, *J* = 6.6 Hz, 1H), 4.44 (d, *J* = 6.6 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.64 (d, *J* = 8.4 Hz, 1H), 3.32 (s, 3H), 2.22-2.10 (m, 2H), 1.49 (ddd, *J* = 12.6, 12.6, 5.4 Hz, 1H), 1.33 (ddd, *J* = 12.6, 12.6, 4.8 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 3H), 0.85 (s, 3H). ^{13}C NMR (150MHz, $CDCl_3$) δ 166.7, 149.8, 134.8, 120.9, 119.5, 93.8, 84.0, 60.1, 55.8, 36.9, 36.7, 26,7, 23.2, 23.2, 14.2. IR (CCl_4) 2956, 2888, 1721, 1654, 1153, 1042 cm : HRMS calcd for $C_{15}H_{27}O_4(MH^+)$ 271.1909, found 271.1912.

6,6-dimethyl-7-hydroxy-2,8-nonadienoate 242. To a solution of **241** (1.92 g, 7.11 mmol) and THF (14 mL) was added a few drops of 6M HCl solution, the mixture was then heated up to reflux. After stirring for 5 h, the mixture was quenched with saturated $NaHCO_3$ solution, the aqueous phase was extracted with ether (80X3ml), dried, and concentrated. Flash column chromatography (hexanes:ethyl acetate 3:1) gave 1.0 g (62%) of **242**. ^1H NMR (500MHz, $CDCl_3$) δ 6.92 (dt, J = 15.5, 6.5 Hz, 1H), 5.87 (ddd, J = 17.5, 10.5, 7.0 Hz, 1H), 5.77 (d, J = 16.0 Hz, 1H), 5.18 (d, J = 17.5 Hz, 1H), 5.14 (d, J = 10.5 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.76 (d, J = 6.7 Hz, 1H), 2.21-2.09 (m, 2H), 1.75 (s, 1H), 1.46 (ddd, J = 13.5, 12.0, 5.5 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H), 0.85 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$) δ 166.7, 148.8, 137.8, 120.9, 116.6, 79.9, 60.0, 37.0, 36.8, 26.8, 22.7, 22.6, 14.2; IR (CCl_4) 3518, 2969, 2876, 1728, 1660, 1376 cm^{-1}; HRMS calcd for $C_{13}H_{23}O_3$ (MH^+) 227.1647, found 227.1652.

6,6-dimethyl-7-oxo-2,8-nonadienoate 243. To a solution of **242** (1.0 g, 4 mmol) and DCM (20 mL) was added PCC (1.6 g, 12 mmol) at rt. After stirring for 3 h, the mixture was diluted with ether, filtered, and concentrated. Flash column chromatography (hexanes/ethyl acetate 5:1) gave 0.91 g (91%) of **243**. ^1H NMR (250MHz, $CDCl_3$) δ 6.76 (dt, J = 15.6, 6.8 Hz, 1H), 6.66 (dd, J = 16.9, 10.3 Hz, 1H), 6.21 (dd, J = 16.9, 2.2 Hz, 1H), 5.65 (dt, J = 15.6, 1.5 Hz, 1H), 5.53 (dd, J = 10.3, 2.2 Hz, 1H), 4.02 (q, J = 7.2 Hz, 2H), 2.16-1.88 (m, 2H), 1.59-1.52 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H), 1.02 (s, 6H); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 202.8, 166.1, 148.1, 130.3, 128.5, 121.2, 59.8, 45.8, 37.2, 27.2, 23.6, 14.0; IR (CCl_4) 2975, 1728, 1697, 1197 cm^{-1}; HRMS calcd for $C_{13}H_{21}O_3$ (MH^+) 225.1491, found 225.1491.

Oxabicyclo[4.2.1]nonene 245. A solution of keto-ester **106** (0.059 g, 0.26 mmol), NaH (0.006 g, 0.26 mmol) and DMF (1.8 mL) was allowed to stir at 0°C for 0.5 h. To this was added a solution of **243** (0.064 g, 0.287 mmol) and 0.5 mL DMF over 1h *via* syringe pump. The reaction mixture was then poured into saturated NH_4Cl solution, extracted with ether (25mlx3), dried over $MgSO_4$, and concentrated. Flash column chromatography (hexanes/ethyl acetate 3:1) provided 56 mg of **245** (50%). ^1H NMR (600MHz, $CDCl_3$) δ 6.06 (d, J = 6.0 Hz, 1H), 6.04 (d, J = 6.0 Hz, 1H), 4.14 (m, 2H), 4.09 (q, J = 6.6 Hz, 2H), 3.24 (s, 3H), 3.11 (dd, J = 12.6, 2.4 Hz, 1H), 2.90 (ddd, J = 17.4, 9.0, 4.8 Hz, 1H), 2.31 (dd, J = 15.6, 2.4 Hz, 1H), 2.02 (dd, J = 15.6, 9.6 Hz, 1H), 1.99 (dd, J = 15.6, 4.2 Hz, 1H), 1.82-1.77 (m, 2H), 1.73-1.67 (m, 2H), 1.62 (s, 3H), 1.53 (ddd, ?), 1.35 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR (150MHz, $CDCl_3$) δ 214.3, 209.3, 171.8, 171.5, 137.5, 130.1, 115.9, 93.3, 70.8, 60.9, 60.6, 54.0, 51.0, 47.3, 41.6, 41.4, 36.8, 28.9, 27.3, 23.8, 23.4, 21.4, 14.2, 14.1; IR (CCl_4) 2987, 2938, 1734, 1700, 1190 cm^{-1}; HRMS calcd for $C_{24}H_{35}O_8$ (MH^+), found.

3-methoxymethoxy-4,4-dimethyl-8,8-dibromo-1,7-octadiene 251. To a solution of CBr_4 (4.0 g, 12.0 mmol), PPh_3 (6.3 g, 24.0 mmol), and CH_2Cl_2 (20 mL) at 0°C was added a solution of 4,4-dimethyl-5-methoxymethoxy-6-heptenal (1.2 g, 6.0 mmol) and CH_2Cl_2 (20 mL) over 0.5 h. The reaction mixture was diluted with hexanes (160 mL), filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate 20:1) gave 1.60 g (75%) of 3-methoxymethoxy-4,4-dimethyl-8,8-dibromo-1,7-octadiene **251** as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 6.33 (t, J=7.5 Hz, 1H), 5.66 (ddd, J=17.2, 10.3, 8.4 Hz, 1H), 5.26 (dd, J=10.4, 0.5 Hz, 1H), 5.16 (dd, J=17.5, 1.0 Hz, 1H), 4.66 (d, J=6.8 Hz, 1H), 4.47

(d, *J*=6.8 Hz, 1H), 3.64 (d, *J*=8.3 Hz, 1H), 3.36 (s, 3H), 2.10-2.00 (m, 2H), 1.43 (ddd, *J*=13.5, 11.0, 5.5 Hz, 1H), 1.31 (ddd, *J*=13.5, 11.5, 6.0 Hz, 1H), 0.91 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 134.8, 119.5, 93.9, 88.3, 84.1, 55.8, 36.7, 36.4, 27.9, 23.2, 23.0; IR (CCl_4): 2963, 2888, 1481, 1153, 1042 cm^{-1}.

Methyl 6,6-dimethyl-7-methoxymethoxy-8-nonene-2-ynoate 252. To a solution of 3-methoxymethoxy-4,4-dimethyl-8,8-dibromo-1,7-octadiene **251** (1.49 g, 4.18 mmol) and THF (20 mL) at -78°C was added BuLi (5.58 mL of a 1.5 M solution in hexane, 8.37 mmol). After warming to rt and stirring for 1 h, the reaction mixture was cooled to -78°C and methyl chloroformate (0.97 mL, 12.5 mmol) was added. After stirring for 1 h at rt, the reaction was quenched with NH_4Cl ((sat, aq.) 30 mL). The aqueous phase was extracted with ether (100×3 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (hexanes/ethyl acetate 5:1) gave 0.87 g (82%) of **252** as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.58 (ddd, *J*=17.2, 10.4, 8.2 Hz, 1H), 5.21 (dd, *J*=10.4, 1.9 Hz, 1H), 5.10 (dd, *J*=17.1, 2.0 Hz, 1H), 4.58 (d, *J*=6.9 Hz, 1H), 4.38 (d, *J*=6.9 Hz, 1H), 3.67 (s, 3H), 3.57 (d, *J*=8.2 Hz, 1H), 3.30 (s, 3H), 2.30 (ddd, *J*=17.0, 10.4, 6.1 Hz, 1H), 2.21 (ddd, *J*=17.0, 10.0, 6.1 Hz, 1H), 1.65 (ddd, *J*=13.6, 10.0, 6.5 Hz, 1H), 1.47 (ddd, *J*=13.7, 10.8, 6.1 Hz, 1H), 0.84 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 154.0, 134.4, 127.1, 119.6, 93.6, 90.2, 83.6, 72.4, 55.6, 52.3, 36.5, 36.5, 23.0, 13.4; IR (CCl_4) 2963, 2895, 2240, 1721, 1437, 1266 cm^{-1}; HRMS calcd for $C_{14}H_{23}O_4$ (M+H) 255.1598, found 255.1596.

Methyl 6,6-dimethyl-7-hydroxy-8-nonene-2-ynoate. To a solution of **252** (0.82 g, 3.2 mmol) and MeOH (16 mL) was added six drops of HCl (conc.). The reaction mixture

was then heated to reflux for 3 h. After cooling to rt, the reaction was quenched with NH_4Cl ((sat, aq.) 15 mL), and extracted with ether (80 mLx3). The extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (hexanes/ethyl acetate 3:1) gave 0.55 g (82%) of methyl 6,6-dimethyl-7-hydroxy-8-nonene-2-ynoate as a colorless oil. ^1H NMR (600 MHz, $CDCl_3$) δ 5.84 (ddd, *J*=16.7, 10.4, 6.8 Hz, 1H), 5.21 (d, *J*=16.8 Hz, 1H), 5.17 (d, *J*=10.2 Hz, 1H), 3.72 (d, *J*=6.5 Hz, 1H), 3.68 (s, 3H), 2.33 (ddd, *J*=16.8, 10.2, 6.0 Hz, 1H), 2.30 (ddd, *J*=16.8, 10.2, 6.0 Hz, 1H), 1.69 (ddd, *J*=13.8, 10.2, 6.6 Hz, 1H), 1.56 (d, *J*=3.6 Hz, 1H), 1.53 (ddd, *J*=13.8, 10.2, 6.2 Hz, 1H), (m, 1H), 0.82 (s, 6H): ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.2, 137.4, 116.9, 90.5, 79.4, 72.5, 52.4, 37.0, 36.4, 22.6, 22.3, 13.7; IR (CCl_4) 3537, 2963, 2882, 2246, 1721 cm^{-1}; HRMS calcd for $C_{12}H_{19}O_3$ (M+H) 211.1339, found 211.133.

Preparation of methyl 6,6-dimethyl-7-oxo-8-nonene-2-ynoate 246. To a solution of methyl 6,6-dimethyl-7-hydroxy-8-nonene-2-ynoate (1.2 g, 5.71 mmol) and CH_2Cl_2 (20 mL) was added PCC (2.46 g, 10.4 mmol). After 3 h, ether (20 mL) was added to the reaction and the mixture was filtered. Concentration and flash chromatography (hexanes/ethyl acetate 3:1) gave 1.0 g (80%) of **246** as a colorless oil. ^1H NMR (600 MHz, $CDCl_3$) δ 6.72 (dd, *J*=16.8, 10.2 Hz, 1H), 6.30 (dd, *J*=16.9, 2.1 Hz, 1H), 5.63 (dd, *J*=10.3, 2.1 Hz, 1H), 3.68 (s, 3H), 2.19 (m, 2H), 1.84 (m, 2H), 1.12 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.5, 154.0, 130.2, 129.2, 89.0, 72.9, 52.4, 45.8, 36.8, 23.6, 14.3; HRMS calcd for $C_{12}H_{17}O_3$ (MH^+) 209.1178, found 209.1169.

Preparation of [methyl 6,6-dimethyl-7-oxo-8-nonene-2-ynoate] dicobalt hexacarbonyl complex 253. A solution of **246** (0.212 g, 1.02 mmol) and ether (1 mL)

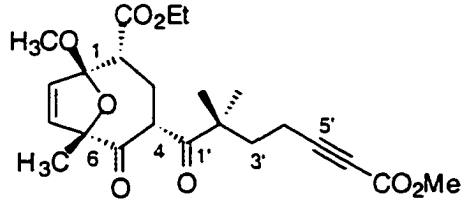
• was added to a solution of dicobalt octacarbonyl (0.348 g, 1.02 mmol) and ether (6 mL) at rt. After 2 h the mixture was concentrated. Flash chromatography (hexanes/ethyl acetate 7:1) gave 0.46 g (92%) of **253** as a dark-red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (bs, 1H), 6.36 (d, *J*=15.6 Hz, 1H), 5.68 (bs, 1H), 3.82 (s, 3H), 2.68 (s, 2H), 1.90 (s, 2H), 1.20 (s, 6H); IR (CCl_4): 2925, 2104, 2073, 2042, 1709, 1234 cm^{-1}; HRMS calcd for $C_{18}H_{17}O_9Co_2$ (M+H) 494.9537, found 494.9536.

Preparation of [1-methoxy-2-ethyloxycarbonyl-4-(7'-ethyloxycarbonyl-5'-heptyn-2',2'-dimethyl-1'-carbonyl)-5-oxo-6-methyl-[4.2.1]-9-oxabicyclic-7-nonene] dicobalt hexacarbonyl complex 254 and 255. A solution of **106** (0.02 g, 0.088 mmol) and DMF (0.4 mL) was added to a slurry of NaH (0.0026 g, 0.088 mmol) DMF (0.1 mL) at 0°C. After stirring for 0.5 h, a solution of [methyl 6,6-dimethyl-7-oxo-8-nonene-2-ynoate] dicobalt hexacarbonyl complex **253** (0.054 g, 0.11 mmol) and DMF (0.2 mL) was added. The reaction mixture was quenched with $NaHCO_3$ ((sat, aq.) 0.5 mL) after 1 h. The mixture was extracted with ethyl acetate (3×10 mL), the extracts were dried ($MgSO_4$), and concentrated. Flash chromatography (hexanes/ethyl acetate 3:1) gave 0.02 g (32%) of **254** and 0.012 g (19%) of **255** as red oils. **254**: IR (CCl_4) 2938, 2098, 2067, 2036, 1709, 1227 cm^{-1}; HRMS calcd for $C_{29}H_{31}O_{14}Co_2$ (MH^+) 721.0378, found 721.0369. **255**: IR (CCl_4) 2956, 2104, 2067, 2042, 1715, 1234 cm^{-1}. HRMS calcd for $C_{29}H_{31}O_{14}Co_2$ (MH^+) 721.0378, found 721.0369.

Preparation of 1-methoxy-2-ethyloxycarbonyl-4-(7'-ethyloxycarbonyl-5'-heptyn-2',2'-dimethyl-1'-carbonyl)-5-oxo-6-methyl-[4.2.1]-9-oxabicyclic-7-nonene 256. To a solution of **254** (13 mg, 0.018 mmol) and CH_2Cl_2 was added TMANO (13 mg,

0.18 mmol). The mixture was concentrated after 1 h. Flash chromatography (hexanes/ethyl acetate 5:1) gave 5 mg (64%) of 1-methoxy-2-ethyloxycarbonyl-4-(7'-ethyloxycarbonyl-5'-heptyn-2',2'-dimethyl-1'-carbonyl)-5-oxo-6-methyl-[4.2.1]-9-oxabicyclic-7-nonene **256** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (d, *J*=5.8 Hz, 1H), 6.02 (d, *J*=5.8 Hz, 1H), 4.58 (dd, *J*=11.5, 1.5 Hz, 1H), 4.13 (m, 2H), 3.73 (s, 3H), 3.28 (s, 3H), 3.13 (dd, *J*=13.0, 4.0 Hz, 1H), 2.33 (ddd, *J*=17.0, 10.0, 5.5 Hz, 1H), 2.27 (ddd, *J*=17.0, 10.0, 5.5 Hz, 1H), 2.04 (ddd, *J*=15.5, 12.5, 12.5 Hz, 1H), 1.95 (ddd, *J*=14.0, 10.0, 6.0 Hz, 1H), 1.82 (ddd, *J*=13.5, 3.5, 1.5 Hz, 1H), 1.63 (ddd, *J*=14.0, 10.5, 6.0 Hz, 1H), 1.54 (s, 3H), 1.25 (t, *J*=7.1 Hz, 3H), 1.11 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.8, 209.2, 171.1, 154.2, 136.3, 129.6, 116.8, 91.9, 89.6, 72.8, 61.0, 56.3, 55.1, 52.5, 51.0, 47.8, 36.6, 28.6, 24.8, 22.5, 21.0, 14.3, 14.1; HRMS calcd for $C_{23}H_{31}O_8$ (M+H) 435.2019, found 435.2018.

Summary of NOE Difference Experiments for



(1) Irradiation at 3.13ppm (C-2) resulted in enhancements at 1.90ppm (C-3) and 4.58ppm (C-4).

Summary of ^{1}H-COSY experiment:

1 Correlation was found between 1.63ppm (C-3') and 1.95ppm (C-3').

2 Correlation was found between 1.63ppm (C-3') and 2.30ppm (C-4').

3 Correlation was found between 1.82ppm (C-3) and 2.04ppm (C-3).

4 Correlation was found between 1.82ppm (C-3) and 3.13ppm (C-2).

5 Correlation was found between 1.82ppm (C-3) and 4.58ppm (C-4).

6 Correlation was found between 1.95ppm (C-3') and 2.30ppm (C-4').

7 Correlation was found between 2.04ppm (C-3) and 3.13ppm (C-2).

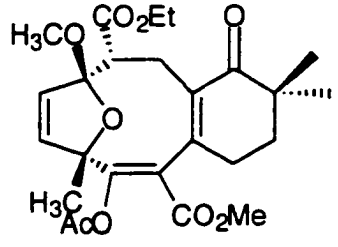
8 Correlation was found between 2.04ppm (C-3) and 4.58ppm (C-4).

Preparation of 1-methoxy-2-ethyloxycarbonyl-4-(7'-ethyloxycarbonyl-5'-heptyn-2',2'-dimethyl-1'-carbonyl)-5-oxo-6-methyl-[4.2.1]-9-oxabicyclic-7-nonene 257. To a solution of **255** (9 mg, 0.0125 mmol) and CH_2Cl_2 was added TMANO (9 mg, 0.125 mmol). After 1 h the reaction mixture was concentrated. Flash chromatography (hexanes/ethyl acetate 2:1) gave 3.5 mg (65%) of **257** as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.08 (d, *J*=5.7 Hz, 1H), 5.74 (d, *J*=5.7 Hz, 1H), 5.72 (dd, *J*=11.2, 1.9 Hz, 1H), 4.29-4.10 (m, 2H), 3.72 (s, 3H), 3.29 (s, 3H), 2.99 (dd, *J*=4.7, 2.2 Hz, 1H), 2.26 (ddd, *J*=9.4, 6.7, 2.7 Hz, 2H), 2.05 (ddd, *J*=15.9, 11.2, 4.8 Hz, 1H), 1.97 (ddd, *J*=13.9, 9.3, 6.7 Hz, 1H), 1.76 (dt, *J*=15.9, 2.2 Hz, 1H), 1.63 (partially obscured ddd, *J*=13.6, 9.8, 6.2 Hz, 1H), 1.54 (s, 3H), 1.27 (t, *J*=7.1 Hz, 3H), 1.11 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 213.0, 210.1, 171.8, 155.0, 137.4, 130.1, 116.2, 92.8, 89.8, 73.0, 60.9, 53.0, 52.5, 51.2, 49.0, 48.0, 36.5, 28.0, 24.6, 22.3, 21.0, 14.4, 14.2; IR (CCl_4) 2963, 2240, 1728, 1264 cm^{-1}; HRMS calcd for $C_{23}H_{31}O_8$ (M+H) 435.2019, found 435.2018.

Preparation of enol acetate 258. A solution of 1-methoxy-2-ethyloxycarbonyl-4-(7'-ethyloxycarbonyl-5'-heptyn-2',2'-dimethyl-1'-carbonyl)-5-oxo-6-methyl-[4.2.1]-9-

oxabicyclic-7-nonene **256** (16 mg, 0.037 mmol) and DMF (1.2 mL) was added to a slurry of KH (4.4 mg, 0.11 mmol) and DMF (0.3 mL) at 0°C. The reaction mixture was immediately warmed to rt. After 1 h, DMAP (4.5 mg, 0.037 mmol) and Ac_2O (11 mg, 0.074 mmol) were added. After another 1 h, the reaction mixture was poured into phosphate buffer (pH 7.5). The aqueous phase was extracted with CH_2Cl_2, the extracts were dried (Na_2SO_4), and concentrated. Flash chromatography (hexanes/ethyl acetate 2:1) gave 8.5 mg (50%) of enol acetate of **258** as a red oil. ^1H NMR (500 MHz, $CDCl_3$) δ 6.28 (d, *J*=6.0 Hz, 1H), 5.96 (d, *J*=6.0 Hz, 1H), 4.20 (q, *J*=7.0 Hz, 2H), 3.67 (s, 3H), 3.13 (s, 3H), 2.90 (dd, *J*=11.3, 1.2 Hz, 1H), 2.71 (dd, *J*=13.5, 1.5 Hz, 1H), 2.43-2.39 (m, 2H), 2.29 (s, 3H), 2.27 (dd, *J*=13.5, 11.5 Hz, 1H), 1.91-1.88 (m, 2H), 1.57 (s, 3H), 1.31 (t, *J*=7.1 Hz, 3H), 1.19 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 172.8, 167.9, 164.8, 155.5, 147.3, 135.8, 135.4, 127.9, 118.7, 118.1, 90.5, 60.7, 52.3, 50.4, 50.3, 40.7, 35.8, 28.8, 27.1, 24.2, 24.1, 23.5, 21.3, 14.2; IR (CCl_4) 2938, 1789, 1734, 1672, 1073 cm^{-1}; HRMS calcd for $C_{25}H_{33}O_9$ (MH^+) 477.2125, found 477.2132.

Summary of HMBC Experiment for



(1) Correlation was found between ^1H (1.15ppm) and ^{13}C (202.6ppm).

(2) Correlation was found between ^1H (1.15ppm) and ^{13}C (40.6ppm).

(3) Correlation was found between ^1H (1.15ppm) and ^{13}C (35.8ppm).

(4) Correlation was found between ^{1}H (1.19ppm) and ^{13}C (202.6ppm).

(5) Correlation was found between ^{1}H (1.19ppm) and ^{13}C (40.6ppm).

(6) Correlation was found between ^{1}H (1.19ppm) and ^{13}C (35.8ppm).

(7) Correlation was found between ^{1}H (1.25ppm) and ^{13}C (60.7ppm).

(8) Correlation was found between ^{1}H (1.57ppm) and ^{13}C (155.5ppm).

(9) Correlation was found between ^{1}H (1.57ppm) and ^{13}C (135.8ppm).

(10) Correlation was found between ^{1}H (1.57ppm) and ^{13}C (90.5ppm).

(11) Correlation was found between ^{1}H (1.89ppm) and ^{13}C (147.2ppm).

(12) Correlation was found between ^{1}H (2.27ppm) and ^{13}C (147.2ppm).

(13) Correlation was found between ^{1}H (2.27ppm) and ^{13}C (135.4ppm).

(14) Correlation was found between ^{1}H (2.27ppm) and ^{13}C (118.1ppm).

(15) Correlation was found between ^{1}H (2.28ppm) and ^{13}C (167.9ppm).

(16) Correlation was found between ^{1}H (2.28ppm) and ^{13}C (118.1ppm).

(17) Correlation was found between ^{1}H (2.71ppm) and ^{13}C (147.2ppm).

(18) Correlation was found between ^{1}H (2.71ppm) and ^{13}C (135.4ppm).

(19) Correlation was found between ^{1}H (2.71ppm) and ^{13}C (118.1ppm).

(20) Correlation was found between ^{1}H (2.90ppm) and ^{13}C (202.6ppm).

(21) Correlation was found between ^{1}H (2.90ppm) and ^{13}C (135.4ppm).

(22) Correlation was found between ^{1}H (2.90ppm) and ^{13}C (118.1ppm).

(23) Correlation was found between ^{1}H (3.13ppm) and ^{13}C (118.1ppm).

(24) Correlation was found between ^{1}H (3.67ppm) and ^{13}C (164.8ppm).

(25) Correlation was found between ^{1}H (4.20ppm) and ^{13}C (172.8ppm).

(26) Correlation was found between ^{1}H (5.96ppm) and ^{13}C (135.8ppm).

(27) Correlation was found between ^{1}H (5.96ppm) and ^{13}C (118.7ppm).

(28) Correlation was found between ^{1}H (5.96ppm) and ^{13}C (90.5ppm).

(29) Correlation was found between ^{1}H (6.27ppm) and ^{13}C (127.9ppm).

(30) Correlation was found between ^{1}H (6.27ppm) and ^{13}C (118.7ppm).

(31) Correlation was found between ^{1}H (6.27ppm) and ^{13}C (90.5ppm).

Preparation of enol acetate of 258 and 259 from the coupling of 106 with 246. A solution of **106** (22 mg, 0.097 mmol) and DMF (0.4 mL) was added to a slurry of KH (3.9 mg, 0.097 mmol) and DMF (0.4 mL) at 0°C. After 0.5 h, a solution of **246** (22 mg, 0.107 mmol) and DMF (0.5 mL) was added over 1 h. The resulting mixture was warmed to rt and stirred for an additional 0.5 h. To the mixture was added DMAP (11.8 mg, 0.097 mmol) and Ac_2O (0.02 mL, 0.2 mmol). After 0.5 h, the reaction was poured into phosphate buffer (pH 7.5). The aqueous phase was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated. Flash chromatography (hexanes/ethyl acetate 2:1) gave 10 mg (22%) of **259** and 9 mg (20%) of enol acetate of **258** as colorless oils. **259** (mixture of diastereomers) major isomer. ^{1}H NMR (600 MHz, CD_2Cl_2) δ 6.22 (d, *J*=5.8 Hz, 1H), 6.16 (d, *J*=5.8 Hz, 1H), 5.79 (s, 1H), 4.17-4.10 (m, 2H), 3.73-3.70 (m, 1H), 3.69 (s, 3H), 3.29 (s, 3H), 3.20 (dd, *J*=13.1, 2.8 Hz, 1H), 2.65 (ddt, *J*=17.8, 6.7, 2.2 Hz, 1H), 2.39 (dd, *J*=15.3, 13.1 Hz, 1H), 1.75 (?), 1.48 (s, 3H), 1.25 (t, *J*=7.2 Hz, 3H), 1.14 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.3, 209.0, 171.0, 166.3, 157.9, 135.4, 130.7, 120.2, 117.5, 92.4, 74.4, 61.0, 51.9, 51.3, 51.2, 44.4, 34.0,

•32.5, 26.1, 24.2, 22.5, 21.1, 14.1; IR (CCl_4) 2987, 2944, 1734, 1709, 1178 cm^{-1}; HRMS calcd for $C_{23}H_{30}O_8$ (M+H) 435.2019, found 435.2027.

Minor isomer: ^1H NMR (600 MHz, $CDCl_3$) δ 6.14 (d, *J*=5.8 Hz, 1H), 6.04 (d, *J*=5.8 Hz, 1H), 5.52 (s, 1H), 4.13 (m, 2H), 3.68 (s, 3H), 3.35 (m, 1H), 3.27 (s, 3H), 2.88 (m, 1H), 2.33-2.30 (m, 2H), 2.25 (dd, *J*=15.0, 4.2 Hz, 1H), 1.92 (dd, *J*=15.0, 12.6 Hz, 1H), 1.67 (dd, *J*=6.6, 4.8 Hz, 1H), 1.45 (s, 3H), 1.27 (t, *J*=7.2 Hz, 3H), 1.16 (s, 3H), 1.12 (s, 3H).

Preparation of (-) 2-(-) Menthoxycarbonyl-3-pyridinylsulfinyl-5-methoxy-9-oxabicyclo-5-hexene 280 and (+) 2-(-) Menthoxycarbonyl-3-pyridinylsulfinyl-6-methoxy-9-oxabicyclo-5-hexene 281. To a solution of (Ss)-menthyl-3-(2-pyridylsulfinyl) arylate (0.54 g, 1.60 mmol) and DCM (0.35 mL) was added 3-methoxyfuran (0.28 g, 2.88 mmol). After stirring for 8 h, the mixture was concentrated, flash column chromatography (first ether, then ether/*i*-propanol 5:1) afforded 0.51g (74%) of (-) 2-(-) Menthoxycarbonyl-3-pyridinylsulfinyl-5-methoxy-9-oxabicyclo-5-hexene **280** as a 10:1 isomeric mixture and 0.17g (24%) of (+) 2-(-) Menthoxycarbonyl-3-pyridinylsulfinyl-6-methoxy-9-oxabicyclo-5-hexene **281**.

280: $[\alpha]^{22}_D$ = -113.3° ($CHCl_3$, c=1.0); ^{1}HNMR (600MHz, $CDCl_3$) δ 8.56 (d, *J*=4.6 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.83 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.32 (dd, *J* = 7.2, 4.8 Hz, 1H), 5.11 (m, 1H), 5.02 (d, *J* = 1.8 Hz, 1H), 4.69 (d, *J* = 4.2 Hz, 1H), 4.55 (dt, J = 10.8, 4.2Hz, 1H), 4.11 (dd, *J* = 9.6, 4.2 Hz, 1H), 3.70 (s, 3H), 3.59 (dd, *J* = 9.0, 3.6 Hz, 1H), 1.80 (dquin, *J* = 7.2, 3.0 Hz, 1H), 1.74 (d, *J* = 12.0 Hz, 1H), 1.64-1.60 (m, 2H), 1.38-1.31(m, 2H), 1.25-1.21 (m, 1H), 1.04-0.88 (m, 2H), 0.86 (d, *J*=7.2 Hz, 3H), 0.81 (d, *J* =

6.6 Hz, 3H), 0.71(d, *J*=7.2 Hz, 3H); ^{13}CNMR (75MHz, $CDCl_3$) δ 169.6, 165.9, 164.2, 149.3, 137.5, 124.7, 122.6, 97.8, 81.6, 79.2, 75.2, 62.3, 57.8, 50.2, 46.7, 40.3, 34.1, 31.2, 26.1, 23.2, 21.9, 20.6, 16.1; IR (CCl_4) 2956, 2931, 1734, 1641, 1042 cm^{-1}; HRMS (FAB) calculated for $C_{23}H_{32}O_5SN$ (MH^+) 434.2001, found 434.1995.

281: $[\alpha]^{22}_D$ = +122.5° ($CHCl_3$, c=0.9); ^{1}HNMR (300MHz, $CDCl_3$) δ (ppm) 8.51(ddd, *J* = 4.8, 1.8, 1.2 Hz, 1H), 7.79 (m, 2H), 7.31 (ddd, *J* = 6.6, 4.8, 1.8 Hz, 1H), 5.47 (d, *J* = 2.1 Hz, 1H), 5.28 (ddd, *J* = 3.9, 1.8, 1.2 Hz, 1H), 4.84 (dd, *J* = 4.5, 0.6 Hz, 1H), 4.49 (dt, *J* = 11.1, 4.5 Hz, 1H), 4.06 (dd, *J* = 8.7, 3.9 Hz, 1H), 3.60 (s, 3H), 3.43 (dd, *J* = 8.4, 4.2 Hz, 1H), 1.84 (dquin, *J* = 6.9, 2.4 Hz, 1H), 1.69-1.58 (m, 3H), 1.36-1.26 (m, 2H), 0.89-0.71 (m, 3H), 0.85 (d, *J*=6.9 Hz, 3H), 0.80 (d, *J* = 6.3 Hz, 3H), 0.68 (d, *J* = 6.9 Hz, 3H); ^{13}CNMR(75MHz, $CDCl_3$) δ 168.9, 166.0, 165.0, 149.2, 137.6, 124.7, 122.1, 97.0, 81.8, 81.1, 75.0, 67.2, 57.6, 48.0, 46.5, 40.6, 33.9, 31.1, 25.9, 23.0, 21.9, 20.6, 15.9; IR (CCl_4) 2974, 1746, 1635, 1184, 1042 cm^{-1}; HRMS (FAB) calculated for $C_{23}H_{32}O_5SN$ (MH^+) 434.2001, found 434.2006.

Preparation of (-) 2-(-) Menthoxycarbonyl-3-oxo-5-methoxy-9-oxabicyclo-5-hexene 272. A solution of 2-(-) Menthoxycarbonyl-3-pyridinylsulfinyl-5-methoxy-9-oxabicyclo-5-hexene **280** (0.48g, 1.10mmol) and toluene (10 mL) was added DIPEA (0.76 mL, 4.24 mmol), TFAA (0.30mL, 2.12 mmol) at 0°C. After stirring for 0.7 h, the mixture was poured into saturated $NaHCO_3$ solution, extracted with ether (3×30ml), dried over $MgSO_4$, and concentrated. Flash column chromatography (hexanes/ethyl acetate 5:1) gave 0.19 g (54%) of (-) 2-(-)Menthoxycarbonyl-3-oxo-5-methoxy-9-oxabicyclo-5-hexene **272**. $[\alpha]^{22}_D$ = -264.7° ($CHCl_3$, c=1.25); ^{1}HNMR(600MHz, $CDCl_3$) δ 5.42 (d, *J* =

1.8Hz, 1H), 5.30 (ddd, J = 3.6, 1.8, 1.2 Hz, 1H), 4.68 (dt, J = 10.8, 4.2 Hz, 1H), 4.44 (d, J = 1.2 Hz, 1H), 3.68 (s, 3H), 3.42 (d, J = 9.6 Hz, 1H), 1.94-1.90 (m, 1H), 1.82 (dquin, J = 6.6, 2.2 Hz, 1H), 1.68-1.64 (m, 2H), 1.47-1.39 (m, 2H), 1.26-1.23 (m, 1H), 1.05-0.98 (m, 2H), 0.88 (d, J = 7.2 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 7.2 Hz, 3H); ^{13}CNMR(150MHz, $CDCl_3$) δ 198.5, 166.8, 162.2, 102.4, 82.2, 80.5, 75.6, 58.4, 51.1, 46.7, 40.7, 34.0, 31.4, 26.0, 23.2, 21.9, 20.7, 16.1; IR (CCl_4) 3105, 3037, 1820, 1555, 1489, 1042 cm^{-1}; HRMS (FAB) calculated for $C_{18}H_{27}O_5$ (MH^+) 323.1858, found 323.1864.

Preparation of (-) 5-methoxycarbonyl-3-methoxy-2-*Z*-[(-) menthyl-5-benzyoxypent-2-enoate]-2,5-dihydrofuran 287 and (-) 5-methoxycarbonyl-3-methoxy-2-*E*-[(-)menthyl-5-benzyoxypent-2-enoate]-2,5-dihydrofuran 288. A solution of (-) 2-(-)Menthoxycarbonyl-3-oxo-5-methoxy-9-oxabicyclo-5-hexene **272** (0.12 g, 0.37 mmol) and DMF (0.8 mL) was added dropwise to a slurry of NaH(0.008g, 0.9mmol) and DMF (0.2 mL) at 0°C. After stirring for 0.5h, a solution of 3-benzyloxypropylaldehyde (0.06g, 0.37mmol) and DMF (0.5ml) was added, 10 mins later, excess methyl iodide was added to quench the reaction. After stirring for an additional 1 h, the mixture was poured into saturated $NaHCO_3$ solution and the aqueous phase was extracted with ether (3×30ml), dried over $MgSO_4$, and concentrated. Flash column chromatography (hexanes/ethyl acetate 5:1) gave 0.048 g (26%) of (-) 5-methoxycarbonyl-3-methoxy-2-*Z*-[menthyl-5-benzyoxypent-2-enoate]-2,5-dihydrofuran **287** and 0.046 g (25%) of (-) 5-methoxycarbonyl-3-methoxy-2-*E*-[menthyl-5-benzyoxypent-2-enoate]-2,5-dihydrofuran **288**.

287: $[\alpha]^{22}_D$ = -82.8° ($CHCl_3$, c=0.35); ^{1}HNMR(300MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 6.87 (t, *J* = 6.6 Hz, 1H), 5.64 (t, *J* = 1.5 Hz, 1H), 5.07 (dd, *J* = 2.7, 2.1 Hz, 1H), 4.93 (t, *J* = 1.5 Hz, 1H), 4.81 (dt, *J* = 11.1, 4.2 Hz, 1H), 4.54 (s, 2H), 3.72 (s, 3H), 3.67 (s, 3H), 3.60 (t, *J* = 6.9 Hz, 2H), 2.88 (n, *J* = 6.9 Hz, 2H), 2.04 (m, 1H), 1.89 (dquin, *J* = 7.2, 2.4 Hz, 1H), 1.71-1.65 (m, 2H), 1.56-1.38 (m, 2H), 1.13-0.98 (m, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 7.2 Hz, 3H), 0.75 (d, *J* = 7.2 Hz, 3H); ^{13}CNMR(75MHz, $CDCl_3$) δ 170.3, 166.0, 153.4, 140.0, 138.5, 133.3, 128.3, 127.6, 127.5, 96.6, 83.9, 80.2, 74.3, 72.8, 69.4, 58.0, 52.3, 47.1, 41.0, 34.2, 31.4, 30.2, 26.2, 23.1, 22.0, 20.9, 16.1; IR (CCl_4) 2969, 2876, 1765, 1697, 1666, 1203 cm^{-1}; HRMS (FAB) calculated for $C_{29}H_{41}O_7$ (MH^+) 501.2852, found 501.2849.

288: $[\alpha]^{22}_D$ = -90.4° ($CHCl_3$, c=0.64); ^{1}HNMR(600MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 7.00 (t, *J* = 7.2 Hz, 1H), 5.89 (dd, *J* = 4.8, 1.8 Hz, 1H), 5.03 (dd, *J* = 4.2, 1.8Hz, 1H), 4.87 (m, 1H), 4.74 (dt, *J* = 10.8, 4.8Hz, 1H), 4.53 (s, 2H), 3.76 (s, 3H), 3.68 (s, 3H), 3.58 (t, *J* = 6.0 Hz, 1H), 2.90 (ddd, *J* = 16.2, 13.8, 6.6 Hz, 1H), 2.81 (ddd, *J* = 15.6, 13.8, 6.6 Hz, 1H), 2.03 (m, 1H), 1.88 (dquin, *J* = 7.2, 2.4 Hz, 1H), 1.68 (m, 2H), 1.45 (m, 2H), 1.06 (m, 1H), 1.02 (q, *J* = 11.4 Hz, 2H), 0.92 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 7.2 Hz, 3H), 0.76 (d, *J* = 6.6 Hz, 3H); ^{13}CNMR (150MHz, $CDCl_3$) δ 169.6, 166.2, 153.7, 143.7, 138.4, 132.1, 128.4, 127.6, 96.2, 80.7, 79.8, 75.1, 74.4, 72.9, 69.1, 58.2, 52.3, 47.1, 40.9, 34.3, 31.5, 28.7, 26.3, 23.4, 22.1, 21.0, 16.3; IR (CCl_4) 2969, 2876, 1765, 1697, 1666, 1203 cm^{-1}; HRMS (FAB) calculated for $C_{29}H_{41}O_7$ (MH^+) 501.2852, found 501.2875.

Preparation of (-) 5-hydroxymethyl-3-methoxy-2-*Z*-[(-) menthyl-5-benzyoxypent-2-enoate]-2,5-dihydrofuran 289. A solution of (-) 5-methoxycarbonyl-3-methoxy-2-*Z*-[menthyl-5-benzyoxypent-2-enoate]-2,5-dihydrofuran (0.22 g, 0.45 mmol) **287** and THF (4 mL) was added $LiBHEt_3$ (1M solution in THF, 0.895 mmol) at -70°C, the mixture was warmed up to rt over 15 mins, and stirred at rt for an additional 10 mins. After quenching with saturated NH_4Cl, the mixture was separated and the aqueous phase was extracted with ethyl acetate (3×30ml), dried over $MgSO_4$, and concentrated. Flash column chromatography (hexanes/ethyl acetate 3:1) gave 0.117g (56%) of (-) 5-hydroxymethyl-3-methoxy-2-Z-[(-) menthyl-5-benzyoxypent-2-enoate]-2,5-dihydrofuran **289**. $[\alpha]^{22}_D$ = -36.6° ($CHCl_3$, c=0.2); ^{1}HNMR(500MHz, $CDCl_3$) δ 7.34-7.25 (m, 5H), 6.23 (t, *J* = 7.0 Hz, 1H), 5.43 (d, *J* = 3.0Hz, 1H), 4.81 (dt, *J* = 7.0, 4.5 Hz, 1H), 4.68 (s, 1H), 4.63 (m, 1H), 4.50 (s, 2H), 3.73 (dt, *J* = 12.0, 3.0 Hz, 1H), 3.67 (m, 1H), 3.66 (s, 3H), 3.54 (t, *J* = 6.5 Hz, 2H), 2.73-2.63 (m, 3H), 2.05 (m, 1H), 1.86 (dquin, *J* = 7.0, 2.5 Hz, 1H), 1.66 (m, 2H), 1.51-1.48 (m, 2H), 1.39 (tt, *J* = 11.5, 3.0 Hz, 1H), 1.10-0.98 (m, 2H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.75(d, *J* = 7.0 Hz, 3H); ^{13}CNMR(125MHz, $CDCl_3$) δ 167.0, 157.0, 138.3, 137.9, 135.4, 128.4, 127.7, 127.6, 93.8, 83.8, 82.5, 74.9, 72.9, 69.1, 62.4, 57.7, 47.0, 41.0, 34.2, 31.4, 30.0, 26.3, 23.3, 22.0, 20.8, 16.2; IR(CCl_4) 3537, 2963, 2938, 2876, 1721, 1672, 1567, 1221 cm^{-1}; HRMS (FAB) calculated for $C_{28}H_{41}O_6$ (M+H) 473.2903, found 473.2892.

Preparation of (-) 5-tert-butyldimethylsilyloxymethyl-3-tert-butyldimethylsilyloxy-2-Z-[(-) menthyl-5-benzyoxypent-2-enoate]-2,5-dihydrofuran 292. To a solution of (-) 5-hydroxymethyl-3-methoxy-2-Z-[(-) menthyl-5-benzyoxypent-

'2-enoate]-2,5-dihydrofuran **289** (0.117 g, 0.25 mmol) and CH_3CN (2 mL) was added 1mL 1M HCl at rt. After stirring for 15 h, the mixture was poured into saturated NH_4Cl solution and the aqueous phase was extracted with ethyl acetate (3×30ml), dried over $MgSO_4$, and concentrated to give crude mixture. The crude mixture was added $NaBH(OAc)_3$ solution [made by adding $NaBH_4$ (38mg, 1mmol) to a solution of 0.4ml AcOH in 1.5ml DCM] at 0°C, after stirring for 0.5 h, the mixture was poured into saturated $NaHCO_3$ solution, the aqueous phase was extracted with ethyl acetate (3×30ml), dried over $MgSO_4$, and concentrated. Flash column chromatography (hexane:ethyl acetate 1:2) gave 0.05g (50%) of (-) 5-hydroxymethyl-3-hydroxy -2-Z-[(-) menthyl-5-benzyoxypent-2-enoate]-2,5-dihydrofuran **291**.

To a solution of (-) 5-hydroxymethyl-3-hydroxy -2-Z-[(-) menthyl-5-benzyoxypent-2-enoate]-2.5-dihydrofuran **291** (0.05 g, 0.11 mmol) and DCM (1mL) was added 2,6-lutidine (0.036 ml, 0.33 mmol), TBSOTf (0.06 ml, 0.27 mmol) successively at 0°C. After stirring for 0.5h, the mixture was poured into saturated $NaHCO_3$ solution, extracted with ether (3×30ml), dried over $MgSO_4$, and concentrated. Flash column chromatography (hexanes:ethyl acetate 5:1) gave 0.067g (90%) of (-) 5-tert-butyldimethylsilyloxymethyl-3-tert-butyldimethylsilyloxy-2-Z-[(-) menthyl-5-benzyoxypent-2-enoate]-2,5-dihydrofuran **292**. $[\alpha]^{22}_D$ = -41.2° ($CHCl_3$, c=0.9); ^{1}HNMR(600MHz, $CDCl_3$) δ 7.37-7.20 (m, 5H), 6.38 (t, *J* = 7.2 Hz, 1H), 4.86 (dd, *J* = 9.0, 6.0 Hz, 1H), 4.80 (dt, *J* = 10.8, 4.2 Hz, 1H), 4.53 (s, 2H), 4.30 (m, 1H), 3.86 (m, 1H), 3.69 (dd, *J* = 10.8, 4.0 Hz , 1H), 3.56 (t, *J* = 6.6 Hz, 2H), 3.51 (dd, *J* = 10.8, 6.6 Hz, 1H), 2.85 (ddd, *J* = 14.6, 14.6, 7.2 Hz, 1H), 2.77 (ddd, *J* = 14.6, 14.6, 7.2 Hz, 1H), 2.11 (ddd, *J* = 12.6, 5.4, 1.8 Hz, 1H), 2.04 (m,

1H), 1.92 (dquin, J = 6.6, 2.2 Hz, 1H), 1.75 (ddd, J = 11.4, 9.9, 0.4 Hz, 1H), 1.70 (m, 2H), 1.51 (m, 1H), 1.42 (m, 1H), 1.07 (m, 1H), 1.10 (q, J = 11.4 Hz, 2H), 0.91 (s, 9H), 0.90 (s, 9H), 0.91 (d, 6H), 0.77 (d, J = 6.6 Hz, 3H), 0.09 (s, 6H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}CNMR(150MHz, $CDCl_3$) δ 166.2, 147.9, 138.5, 136.2, 134.5, 128.3, 127.7, 127.6, 87.3,77.4, 74.2, 73.9, 72.8, 69.4, 63.6, 47.0, 42.2, 41.0, 34.2, 31.4, 29.8, 26.0, 25.9, 25.8, 23.0, 22.0, 20.9, 18.3, 18.0, 15.9, -4.7, -5.2; IR (CCl_4) 2950, 2932, 2864, 1721, 1271, 1104 cm^{-1}. HRMS (FAB) calculated for $C_{39}H_{69}O_6Si_2$ 689.4633, found 689.4631.

Preparation of (-) 5-tert-butyldimethylsilyloxymethyl-3-tert-butyldimethylsilyloxy-2-*Z*-[(-) menthyl-5-hydroxypent-2-enoate]-2,5-dihydrofuran 293. To a solution of (-) 5-tert-butyldimethylsilyloxymethyl-3-tert-butyldimethylsilyloxy-2-*Z*-[(-) menthyl-5-benzyoxypent-2-enoate]-2,5-dihydrofuran **292** (0.017 g, 0.025 mmol), DCM (0.6 mL) and H_2O (0.03mL) was added DDQ (excess). Afetr stirring for 8 h, the mixture was diluted with ether and washed with saturated $NaHCO_3$ solution, ether was dried over $MgSO_4$ and concentrated. Flash column chromatography (hexanes:ethyl acetate 5:1) gave 0.006 g (40%) of (-) 5-tert-butyldimethylsilyloxymethyl-3-tert-butyldimethylsilyloxy-2-*Z*-[(-) menthyl-5-hydroxypent-2-enoate]-2,5-dihydrofuran **293** and 0.006g (35%) of recovered **292**. $[\alpha]^{22}_D$ = -46.5° ($CHCl_3$, c=0.2); ^{1}HNMR(500MHz, $CDCl_3$) δ 6.30 (dt, J = 8.0, 1.0 Hz, 1H), 4.84(dd, J = 10.0, 5.5 Hz, 1H), 4.77 (dt, J = 4.5, 12.0 Hz, 1H), 4.26 (m, 1H), 3.83 (ddd, = 6.5, 4.5, 2.0 Hz, 1H), 3.71 (n, J = 5.0 Hz, 2H), 3.64 (dd, J = 10.5, 4.0 Hz, 1H), 3.47 (dd, J = 6.5, 3.0 Hz, 1H), 2.65 (m, 2H), 2.04 (ddd, J = 12.5, 5.5, 1.5 Hz, 1H), 1.99 (m, 2H), 1.86 (dquin, J = 7.5, 2.5 Hz, 1H), 1.73 (ddd, J = 12.5, 10.0, 6.0 Hz, 1H), 1.70-1.65 (m, 2H),

1.52-1.45 (m, 1H), 1.41-1.35 (m, 1H), 1.05 (dq, J = 12.5, 2.5 Hz, 1H), 0.98 (q, J = 11.0 Hz, 2H), 0.89 (d, J = 6.5 Hz, 3H), 0.87 (s, 18H), 0.86 (d, J = 6.5 Hz, 3H), 0.74 (d, J = 6.5 Hz, 3H), 0.054 (s, 3H), 0.049 (s, 3H), 0.042 (s, 3H), 0.038 (s, 3H); ^{13}CNMR(125MHz, $CDCl_3$) δ 166.6, 135.8, 135.2, 87.5, 77.5, .74.6, 74.0, 65.8, 63.6, 61.9, 47.1, 42.0, 41.0, 34.2, 32.4, 31.4, 26.2, 25.9, 25.8, 23.3, 22.0, 20.8, 18.3, 18.0, 16.2, 15.3, -4.7, -5.37, -5.39; IR (CCl_4) 3503, 2956, 2932, 2857, 1715, 1561, 1258 cm^{-1}; HRMS (FAB) calculated for $C_{32}H_{63}O_6Si_2$ 599.4163, found 599.4186.

APPENDIX 1

PERMISSIONS

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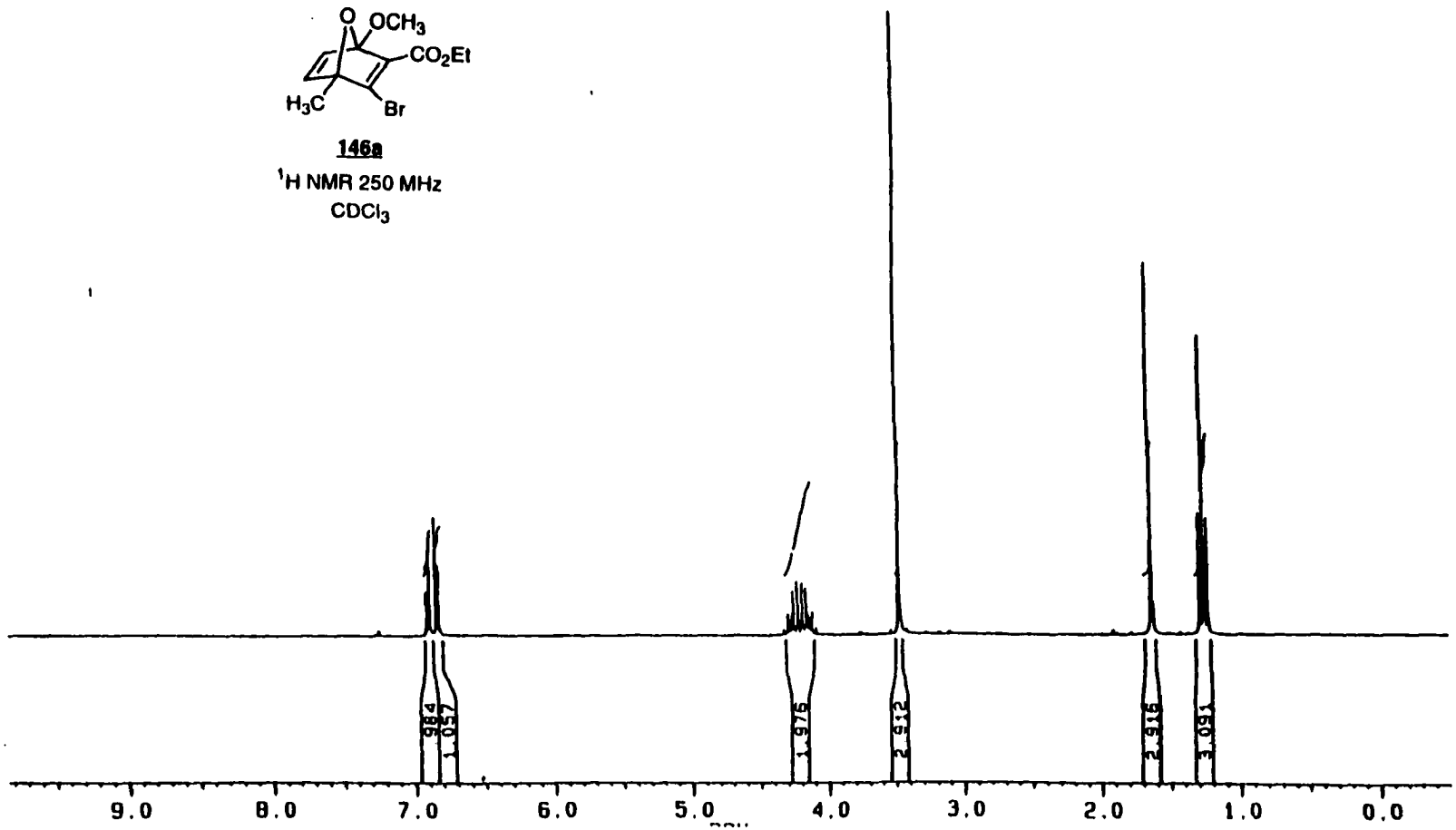
(1) "A Novel Anionic Condensation, Fragmentation, and Elimination Reaction of Bicyclo[2.2.1]heptenone Ring Systems," by Jon D. Rainier and Qing Xu published in *Organic Letters* **1999**, *1*, 27-29. Copyright 1999, American Chemical Society.

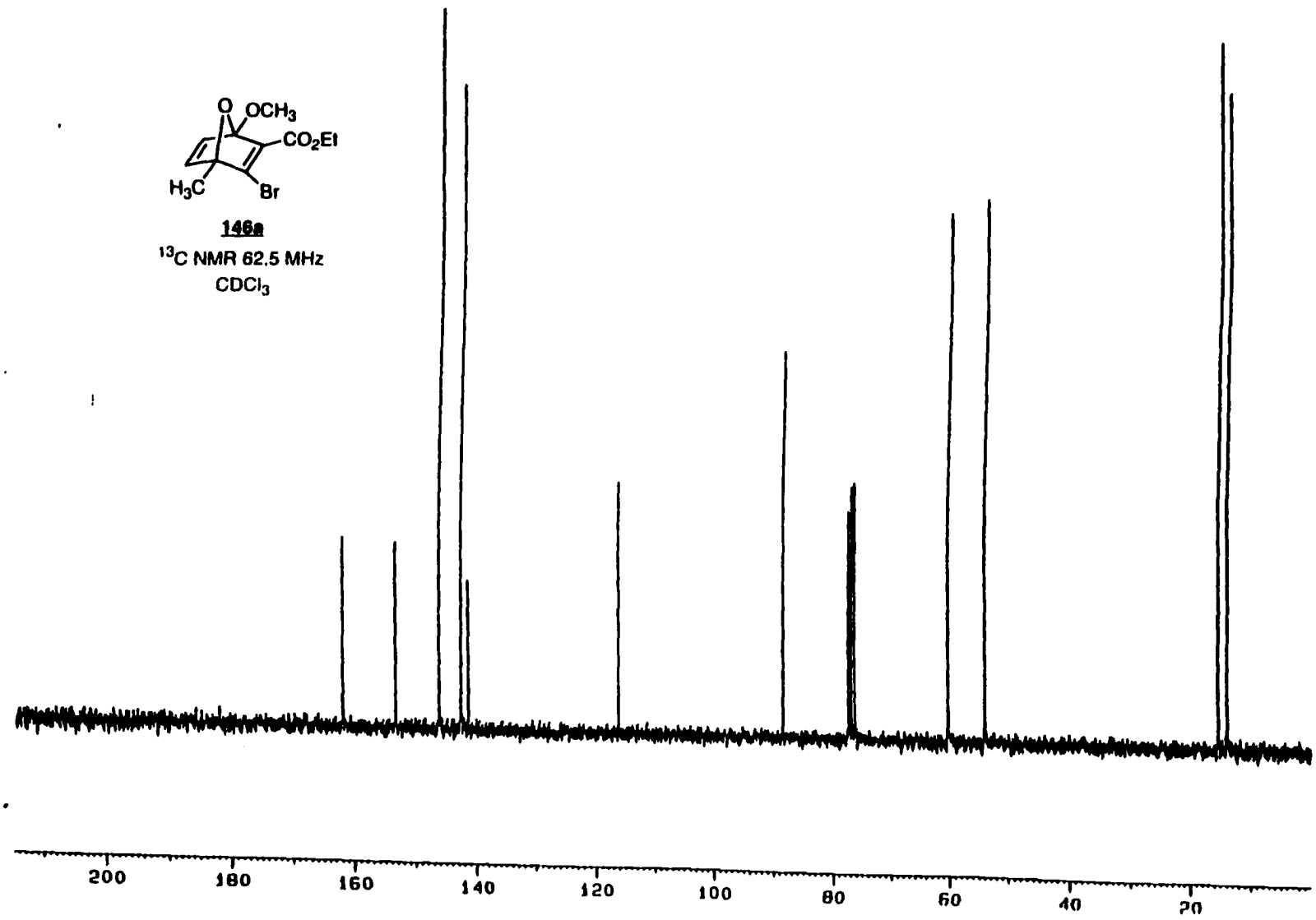
(2) "Anionic Two-Carbon Ring Expansions of Oxabicyclo[2.2.1]-heptenes and Oxabicyclo[4.2.1]nonenes," by Jon D. Rainier and Qing Xu published in *Organic Letters* **1999**, *1*, 1161-1163. Copyright 1999, American Chemical Society.

(3) "Anionic Ring Expansion Reactions of Oxabicyclo[4.2.1]heptenones. An Efficient Entry into the Carbon Framework of Oxygenated Cembranoids," by Qing Xu, Mahika Weeresakare and Jon D. Rainier published in *Tetrahedron* **2001**, *57*, 8029. Copyright 2001, Elsevier Science Ltd.

APPENDIX 2

SPECTRA

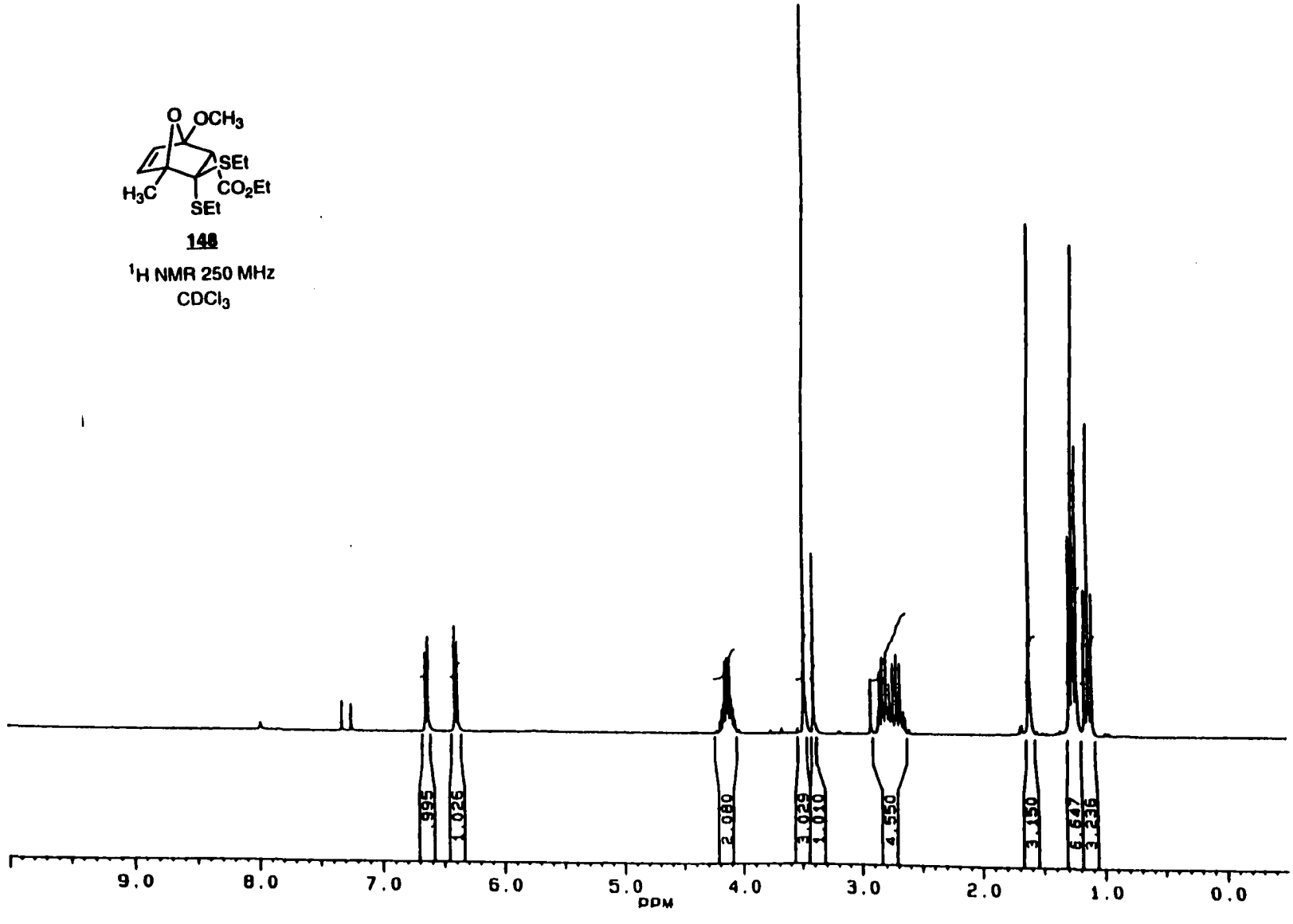

O
OCH3
CO2Et
H3C
Br
146a
1H NMR 250 MHz
CDCl3
9.84
1.057
1.976
2.912
2.916
3.091
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

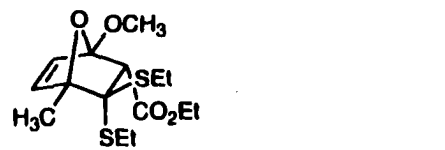

O
OCH3
CO2Et
H3C
Br
146a
13C NMR 62.5 MHz
CDCl3
200
180
160
140
120
100
80
60
40
20

148

^{1}H NMR 250 MHz

$CDCl_3$

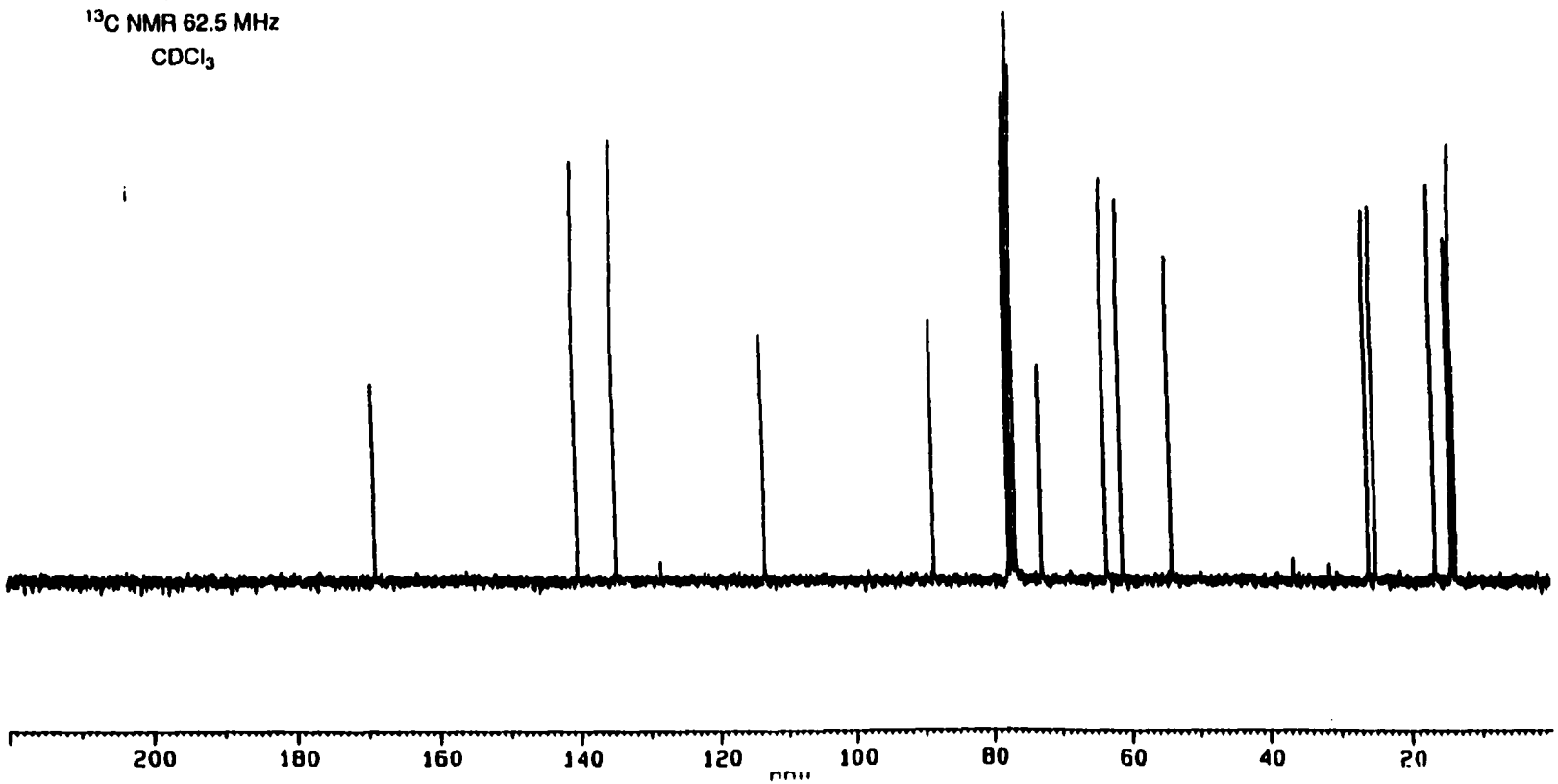


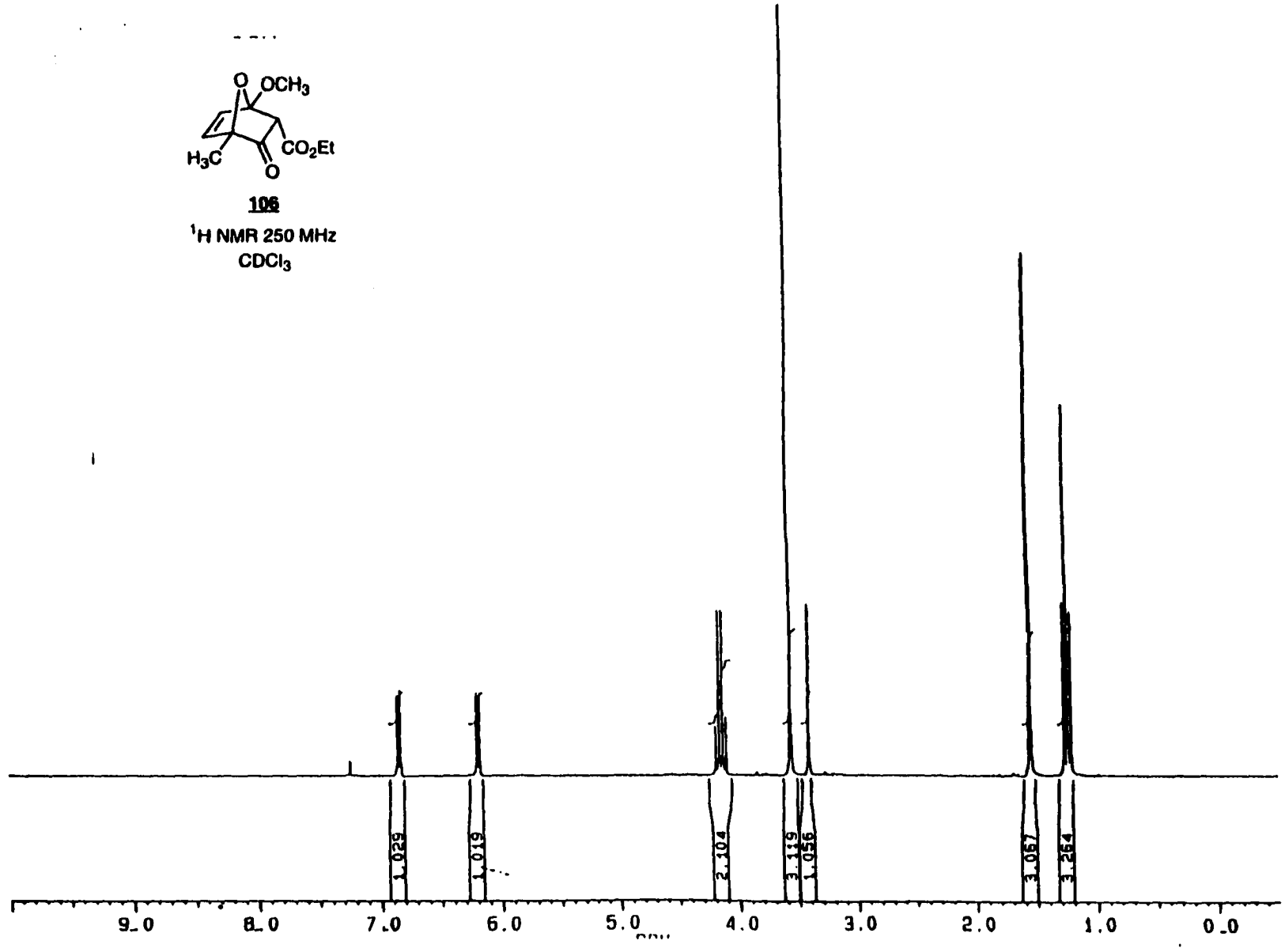


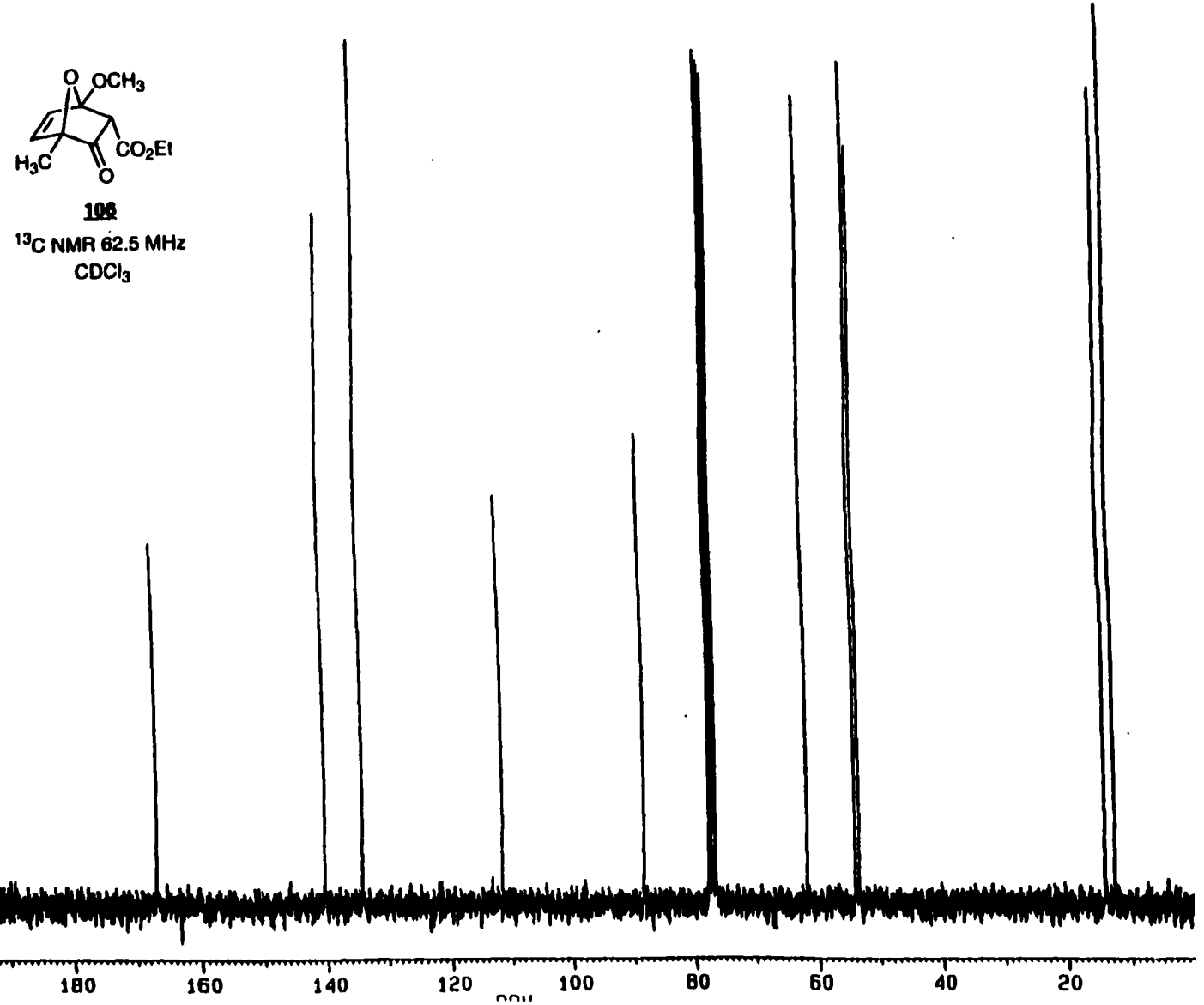
148

^{13}C NMR 62.5 MHz

$CDCl_3$



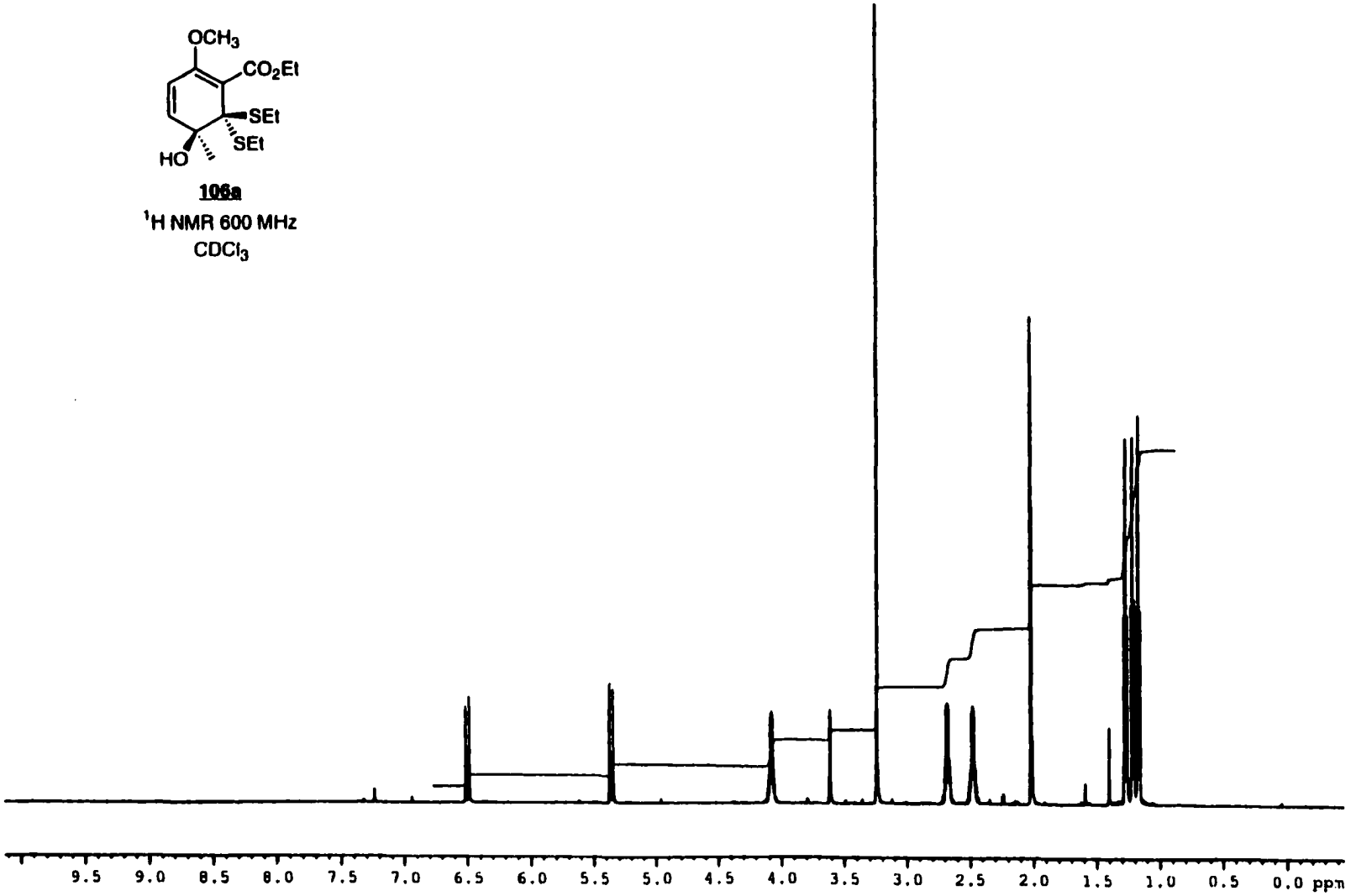

O
OCH3
H3C
CO2Et
O
106
1H NMR 250 MHz
CDCl3
1.029
1.019
2.104
3.119
1.056
3.057
3.264
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0



106

^{13}C NMR 62.5 MHz

$CDCl_3$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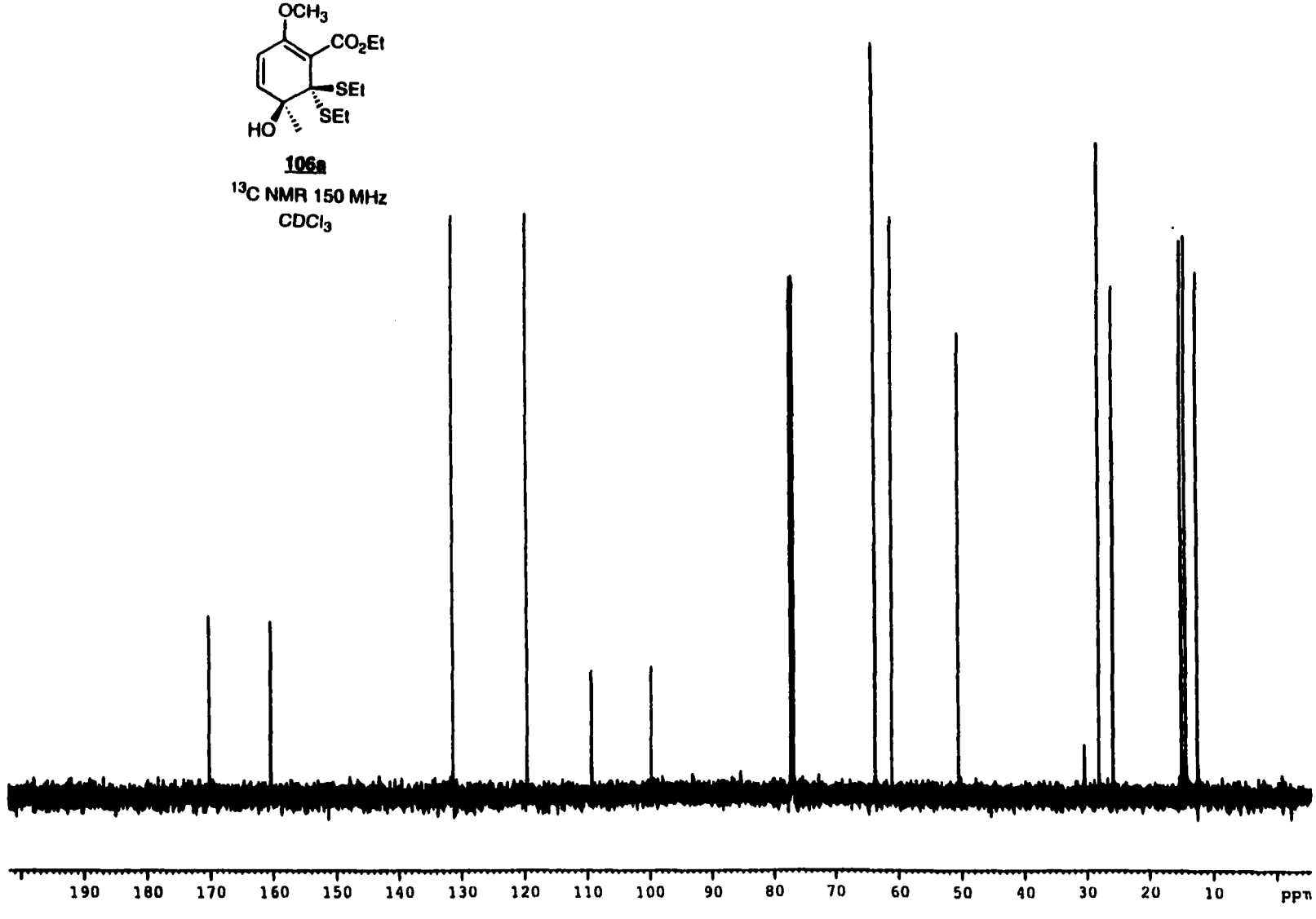
SEt
SEt
HO
106a
1H NMR 600 MHz
CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm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CO2Et
SEt
SEt
HO
106a
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CDCl3
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180
170
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150
140
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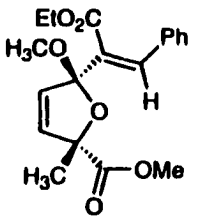
100
90
80
70
60
50
40
30
20
10
ppm



162

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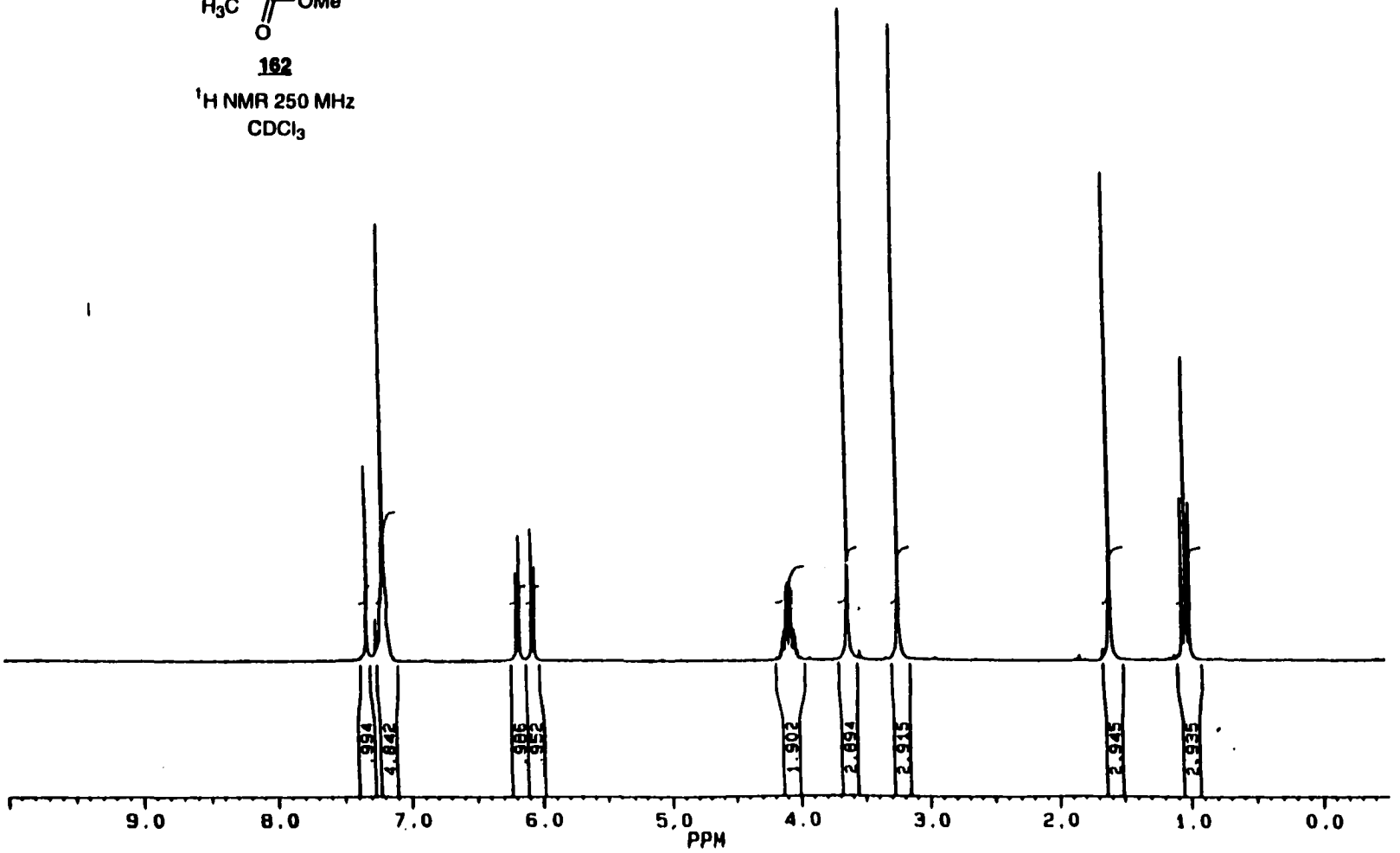
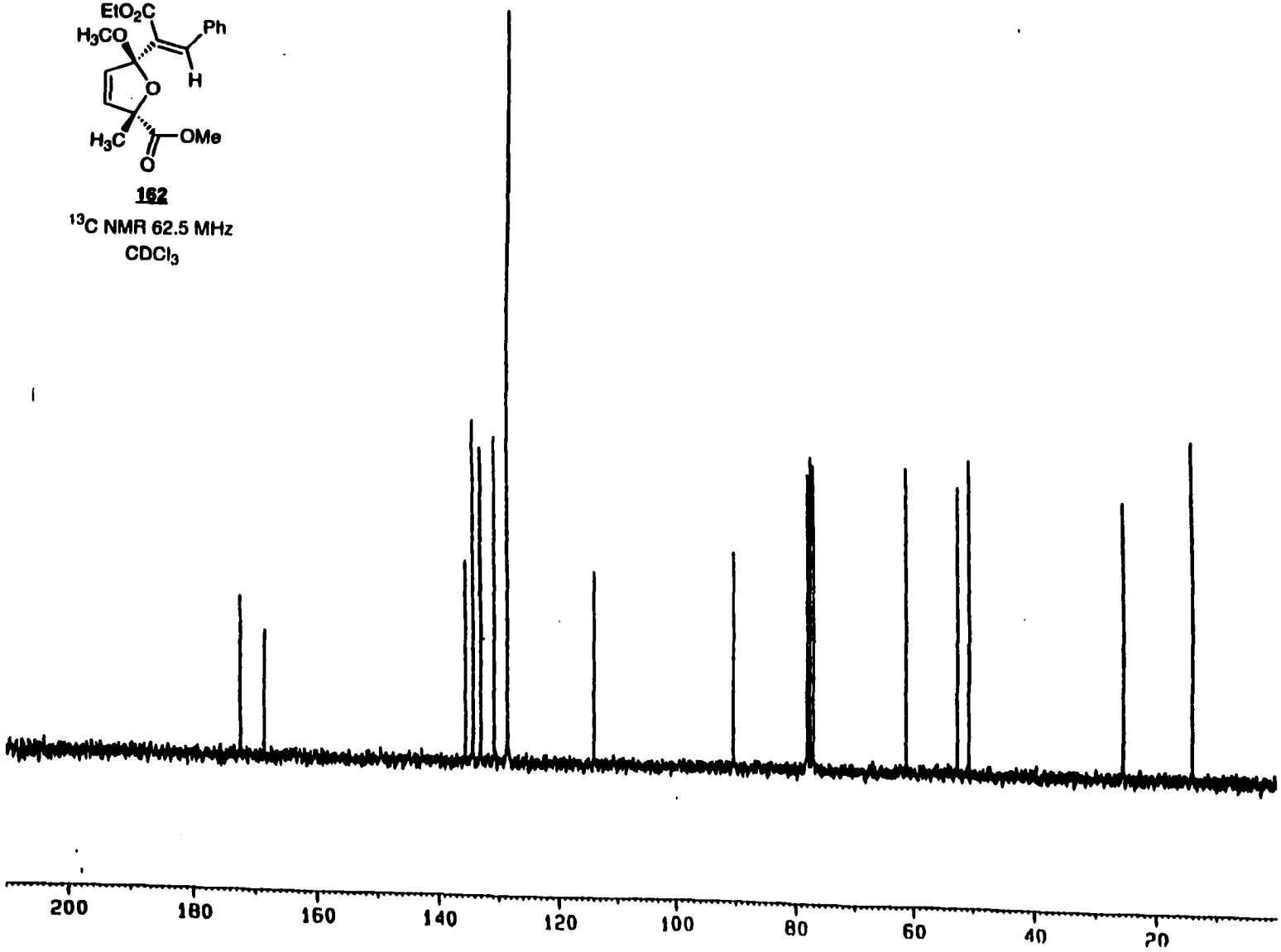
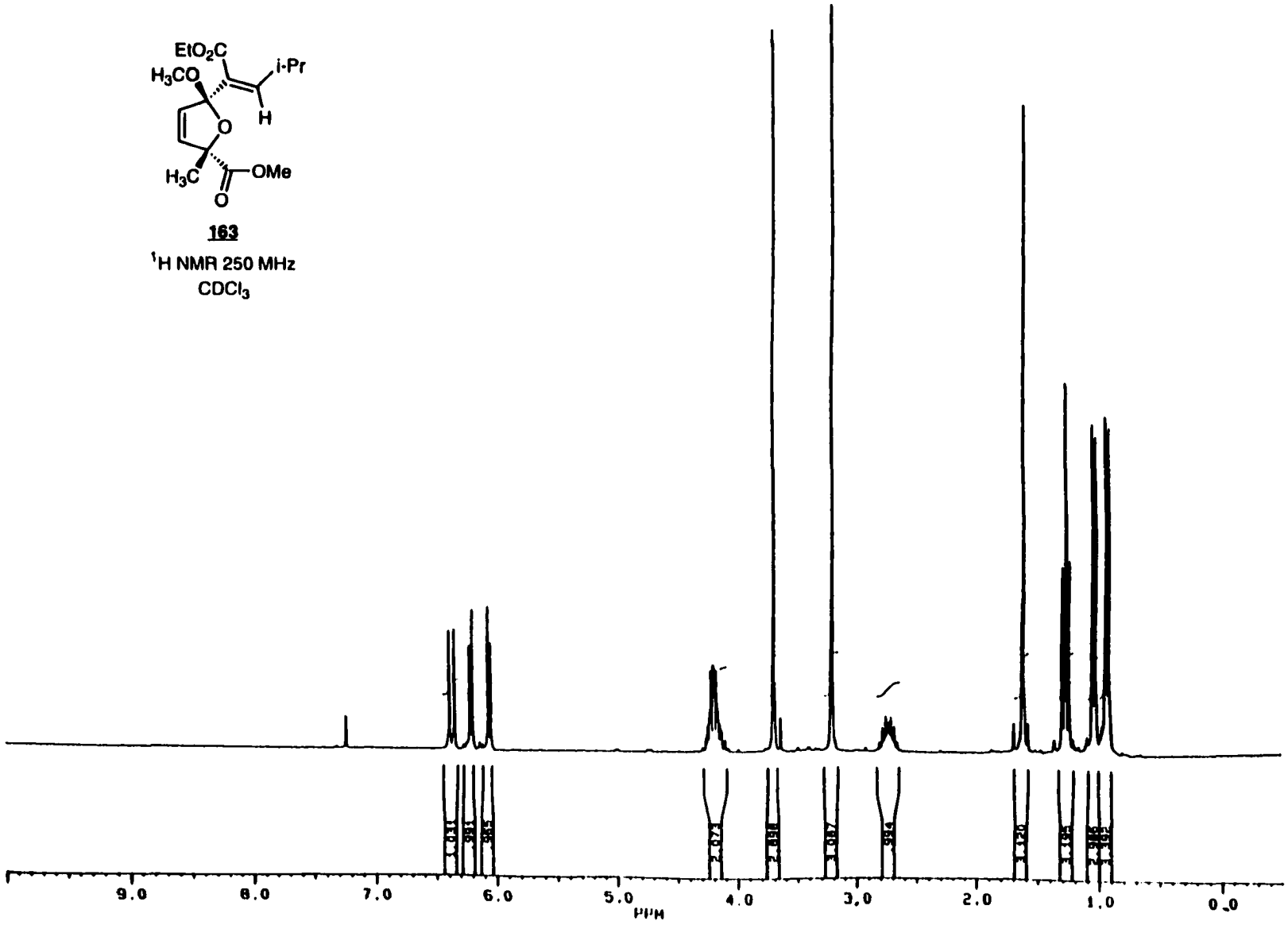
$CDCl_3$



162

^{13}C NMR 62.5 MHz
$CDCl_3$

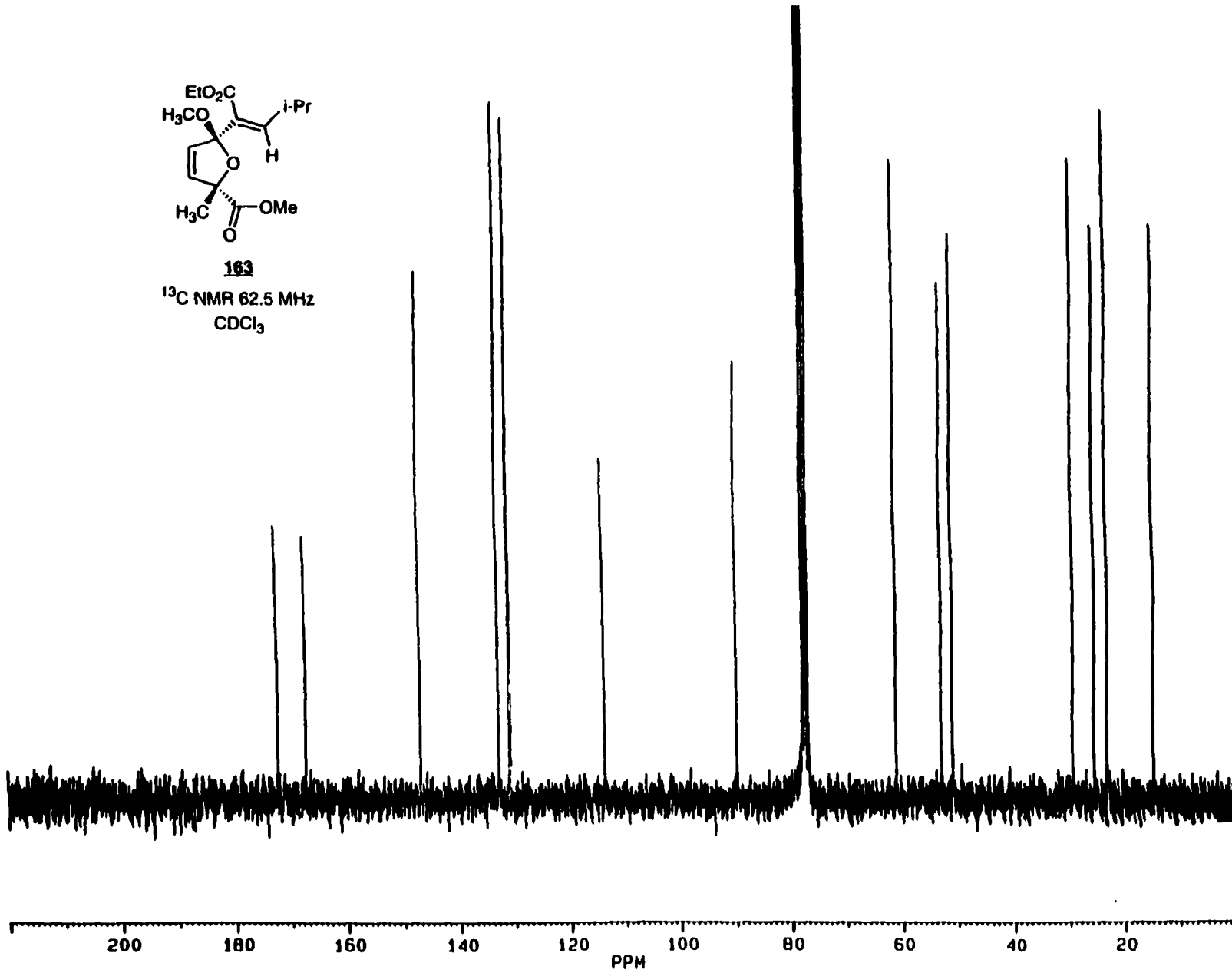


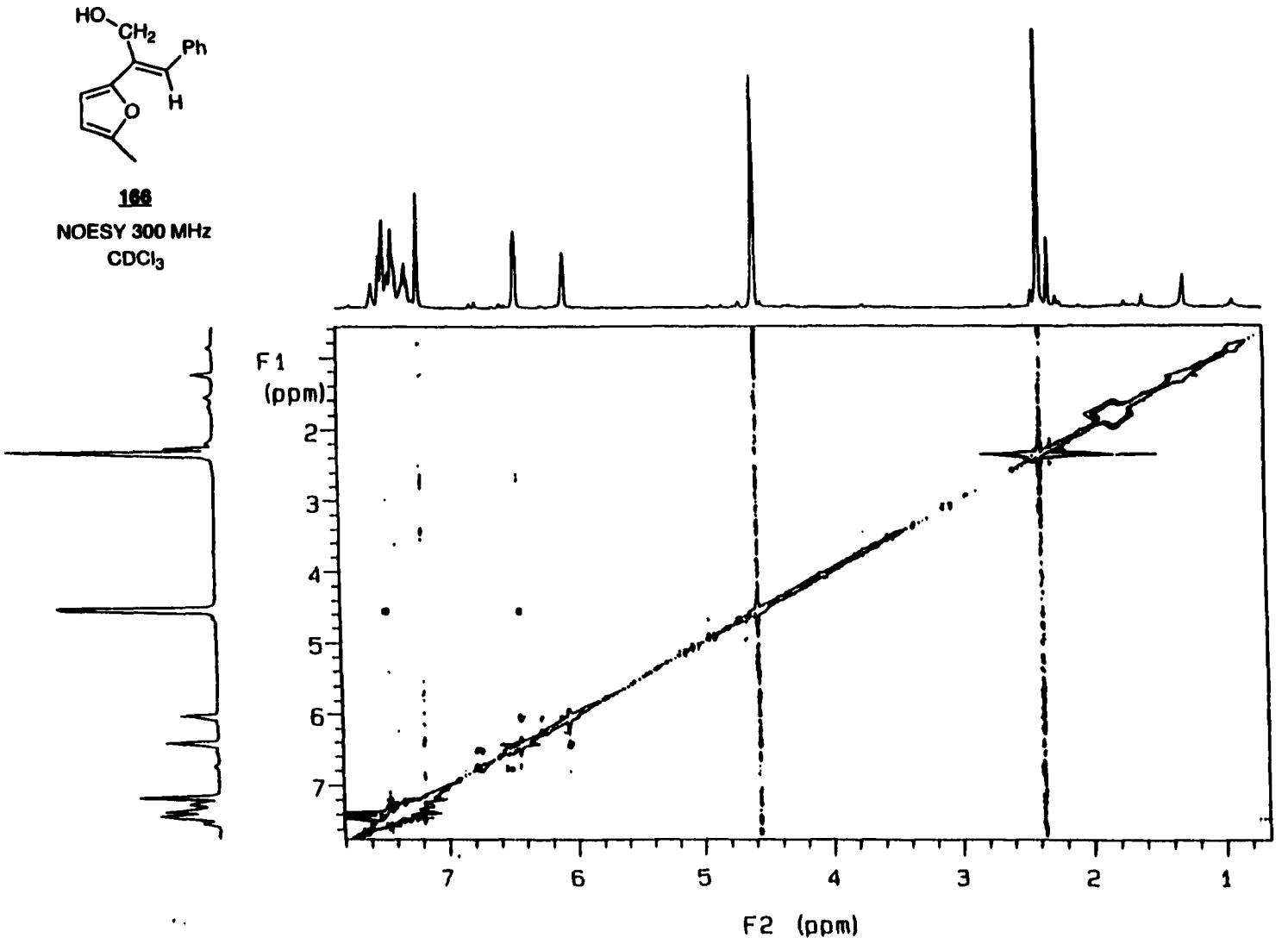


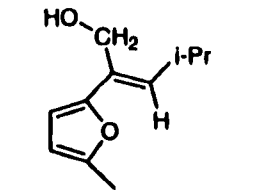
163

^{1}H NMR 250 MHz

$CDCl_3$

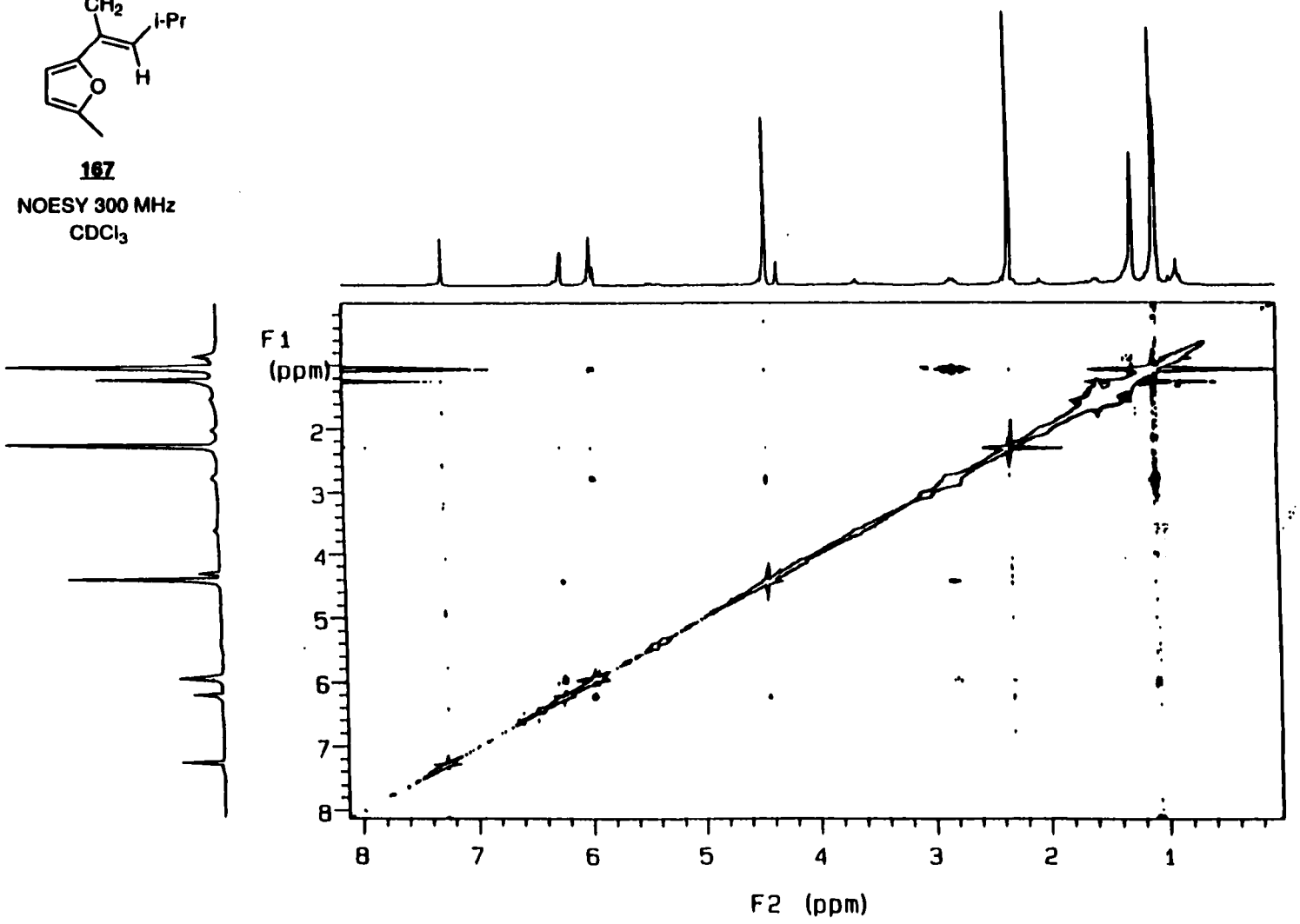

EtO2C
H3CO
i-Pr
H
O
H3C
OMe
O
163
13C NMR 62.5 MHz
CDCl3
200
180
160
140
120
100
80
60
40
20
PPM


HO
CH2
Ph
H
O
166
NOESY 300 MHz
CDCl3
F1
(ppm)
2
3
4
5
6
7
7
6
5
4
3
2
1
F2 (ppm)



167

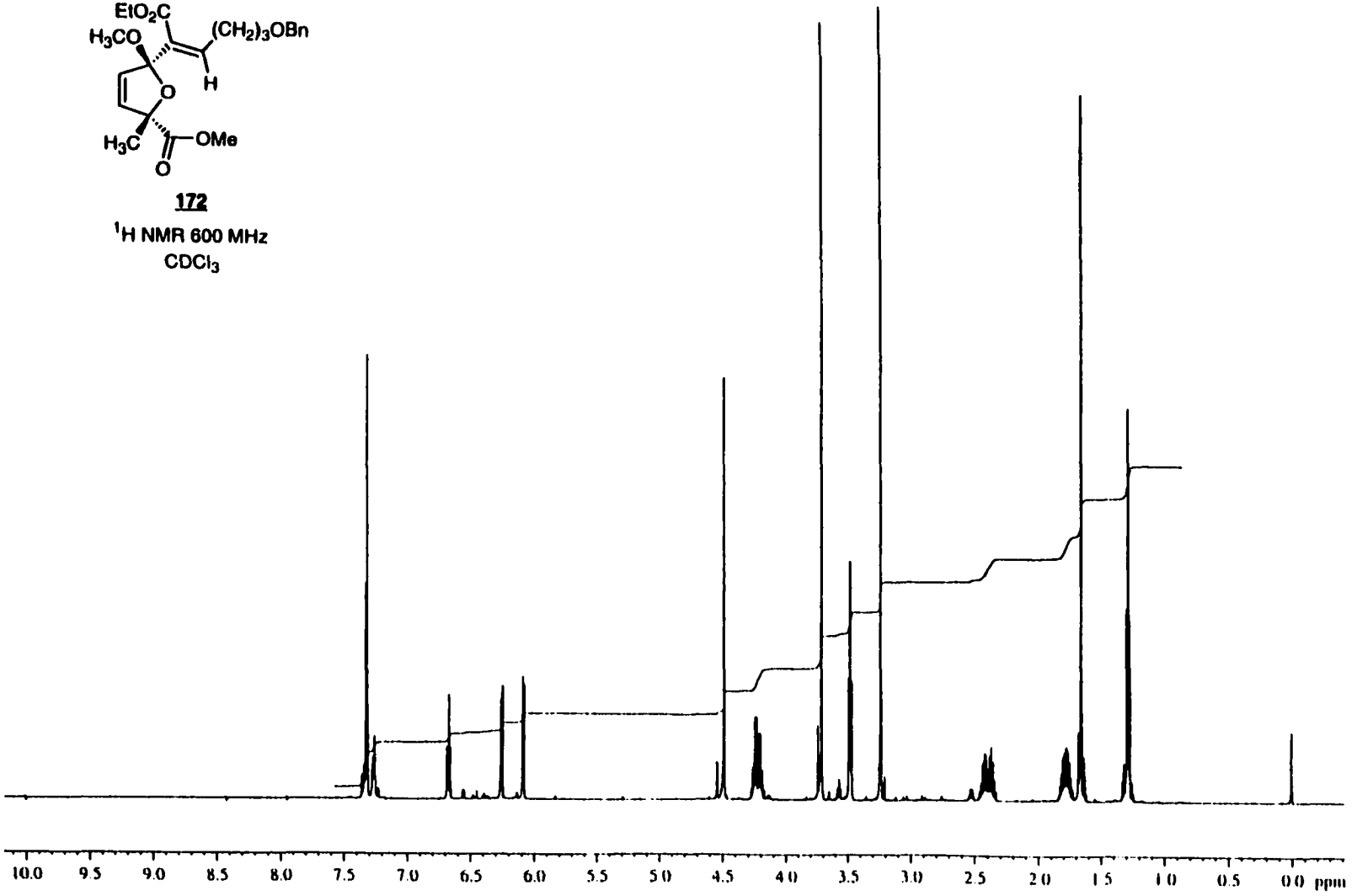
NOESY 300 MHz
$CDCl_3$

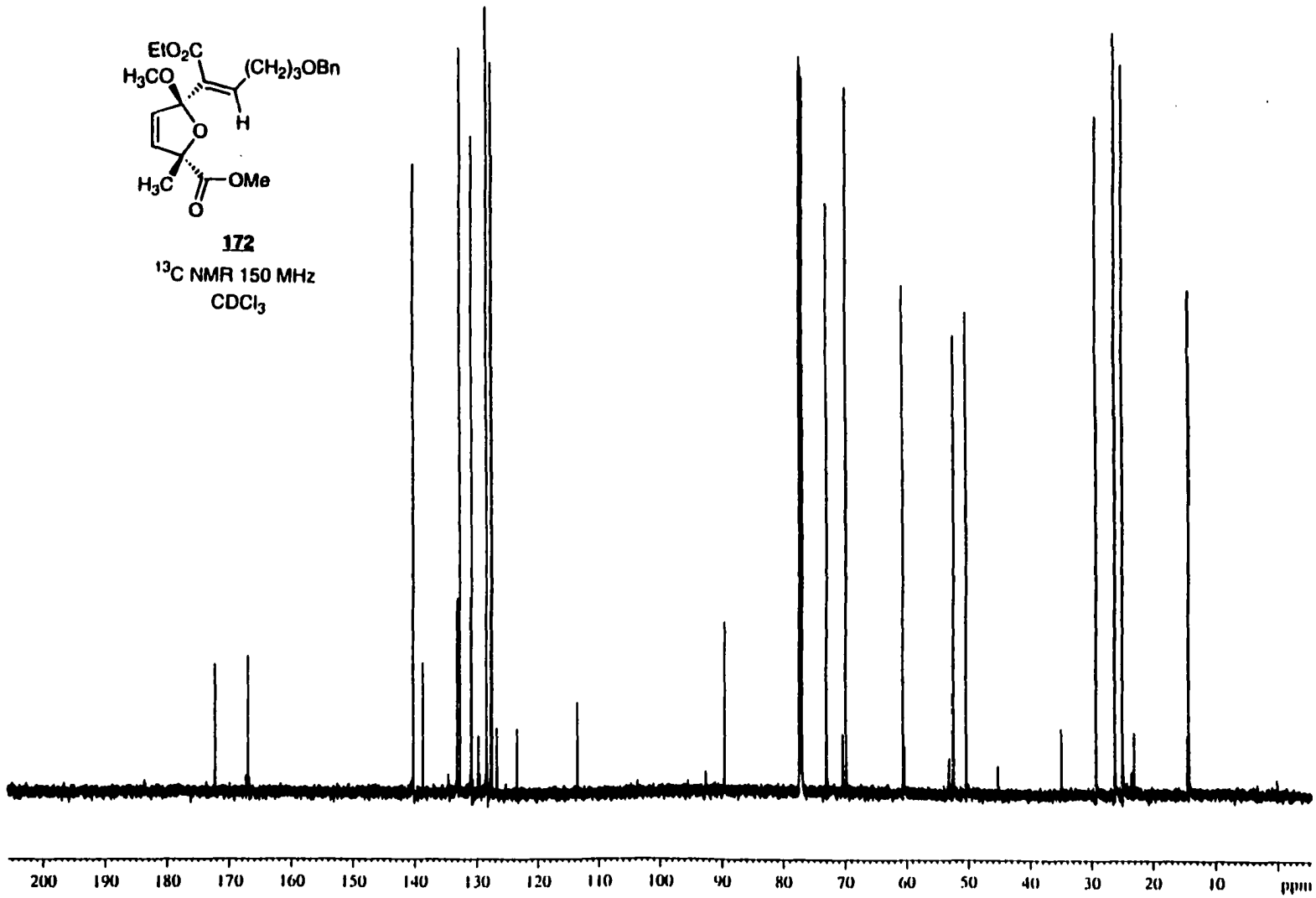


172

^{1}H NMR 600 MHz

$CDCl_3$

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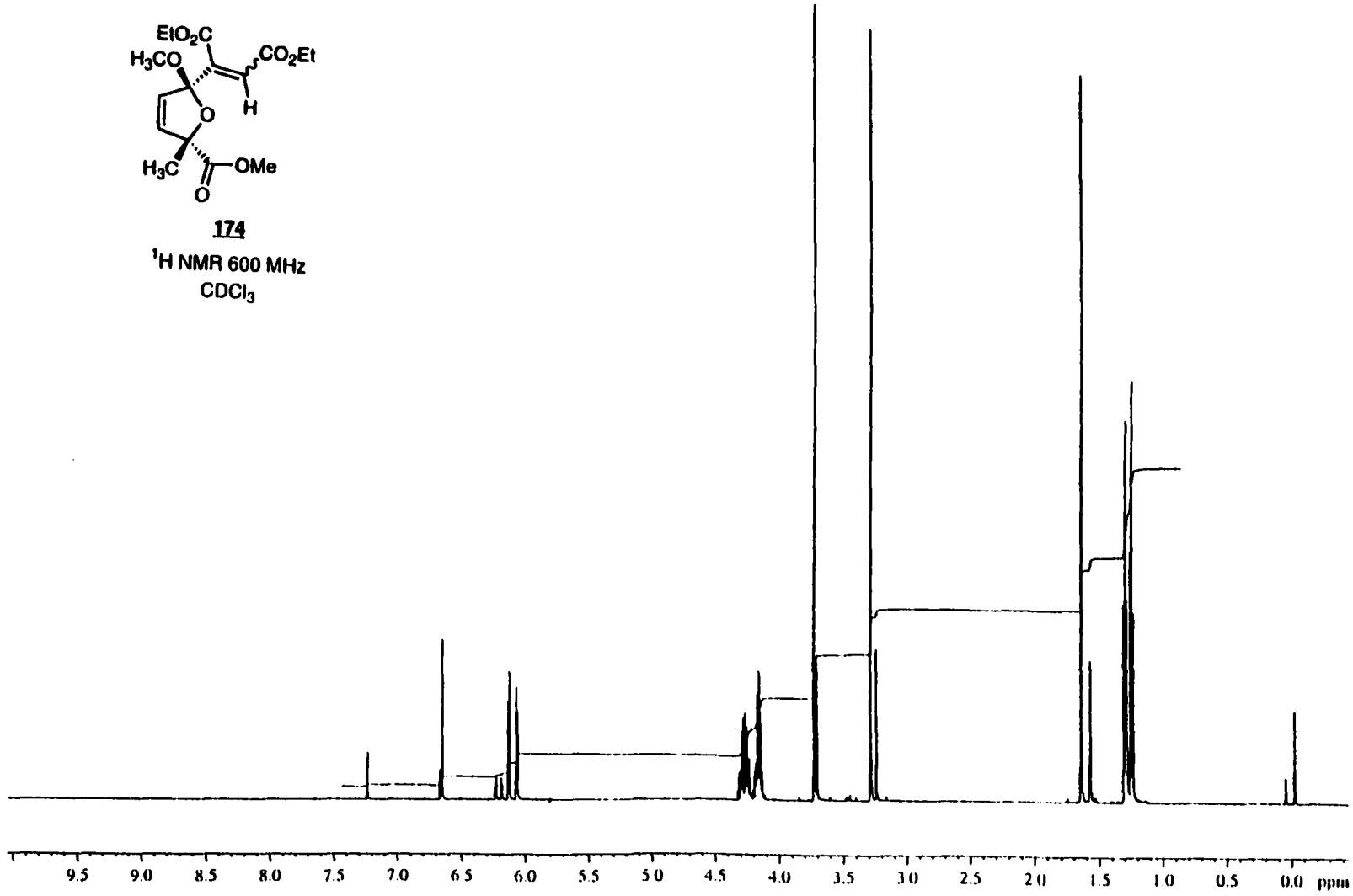
H3CO
(CH2)3OBn
H
O
H3C
OMe
O
172
13C NMR 150 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



174

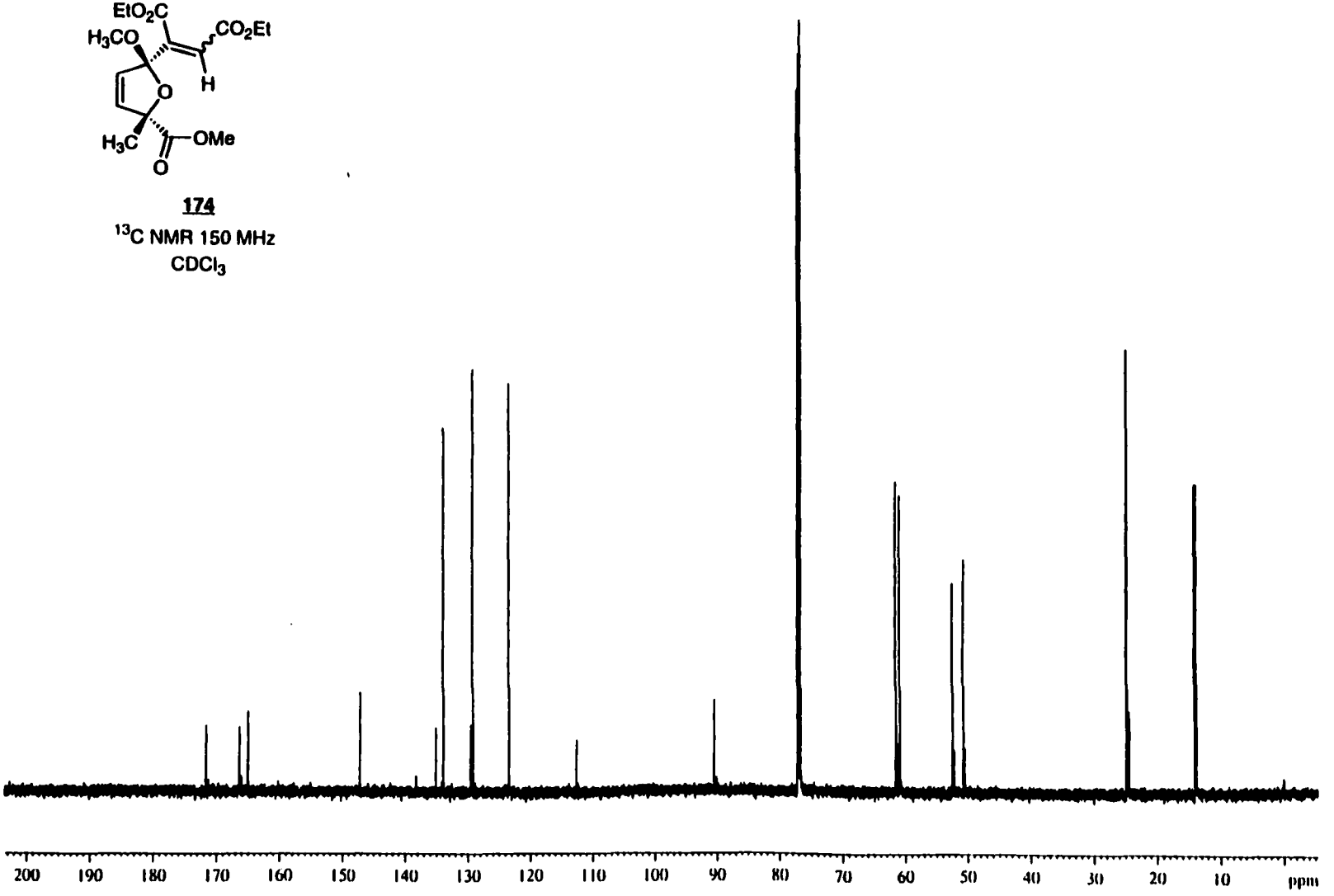
^{1}H NMR 600 MHz

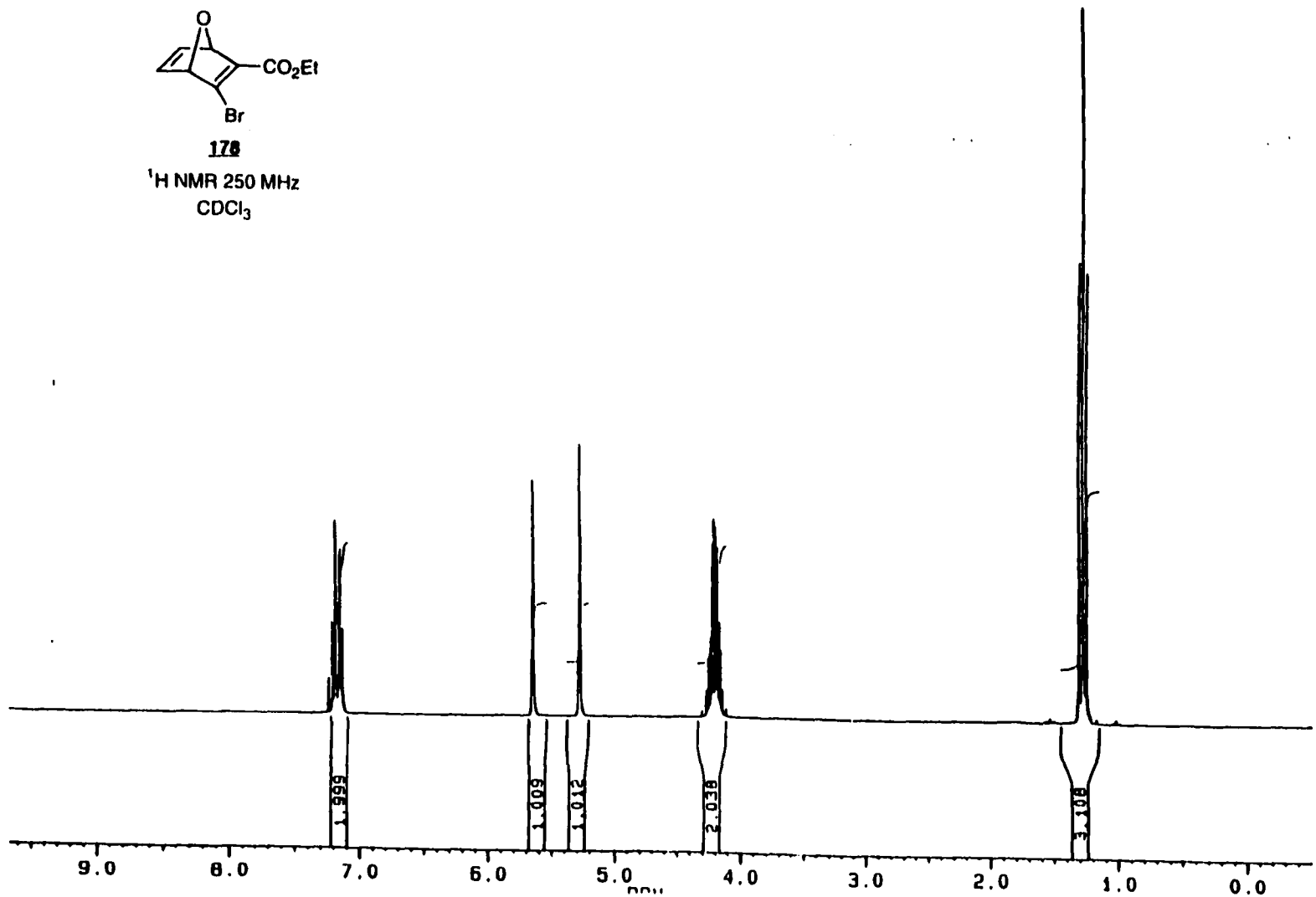
$CDCl_3$

174

^{13}C NMR 150 MHz

$CDCl_3$

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Br
178
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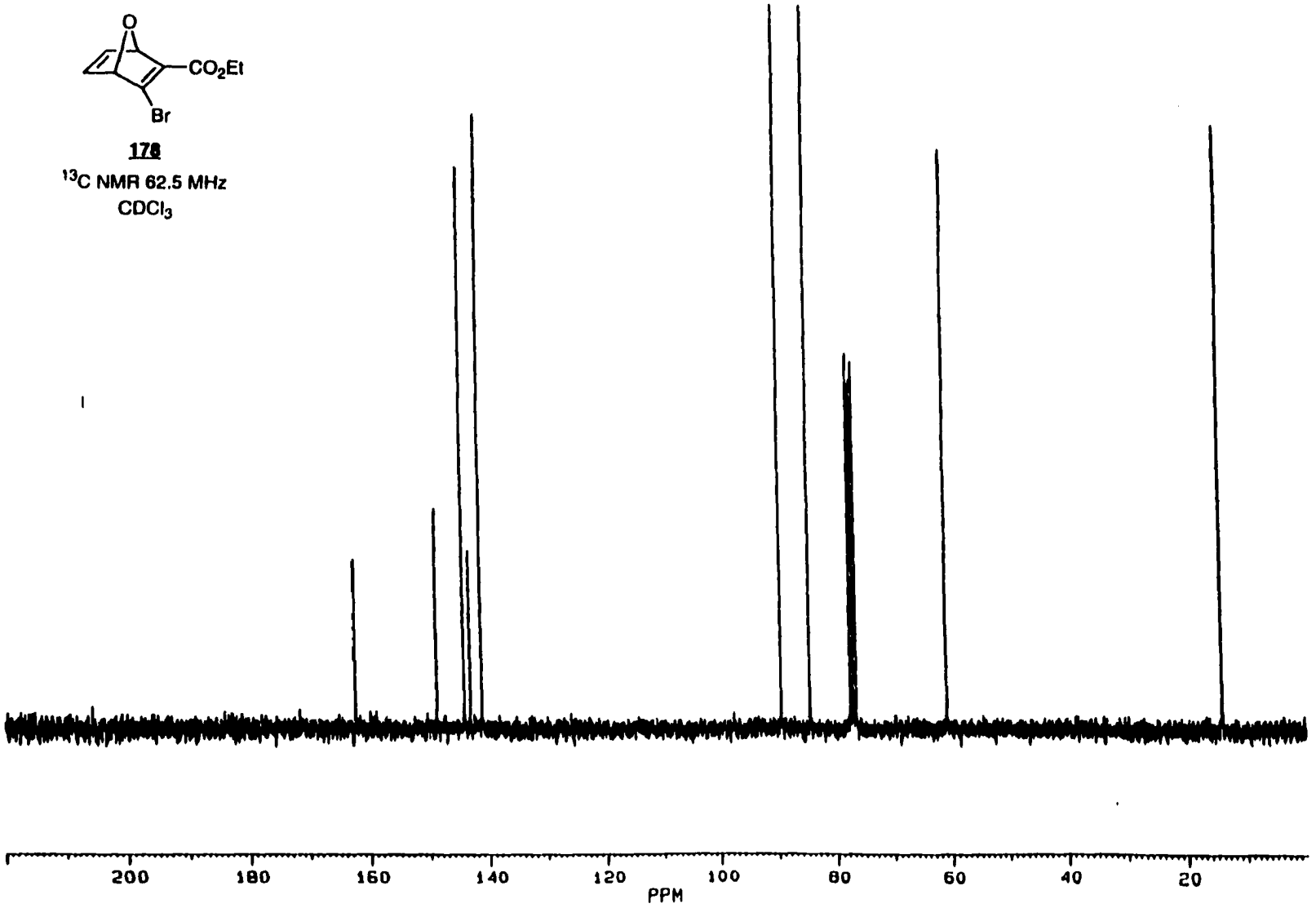
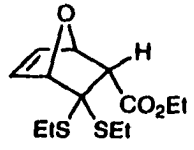
CDCl3
1.999
1.009
1.012
2.038
3.108
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

178

^{13}C NMR 62.5 MHz
$CDCl_3$

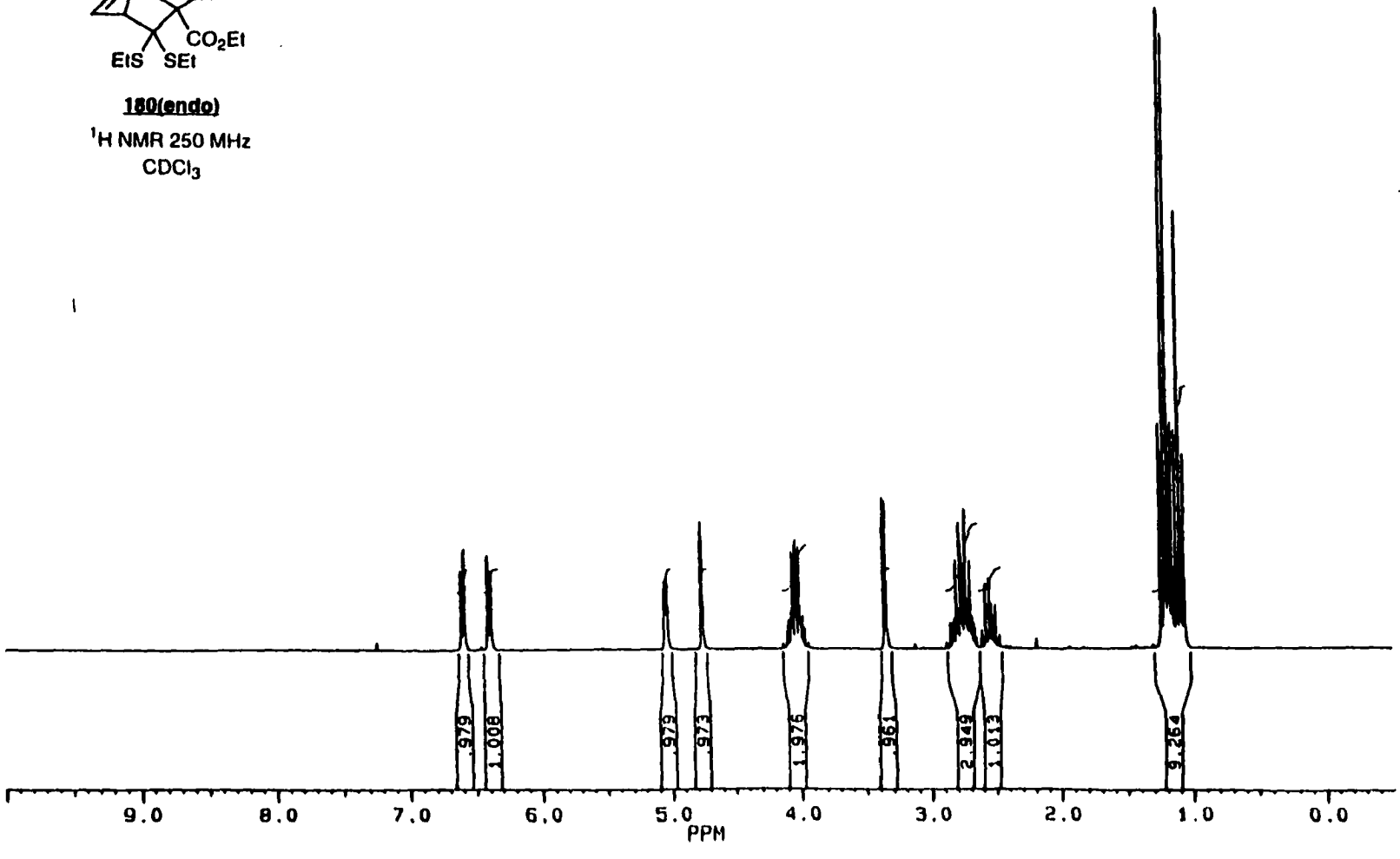


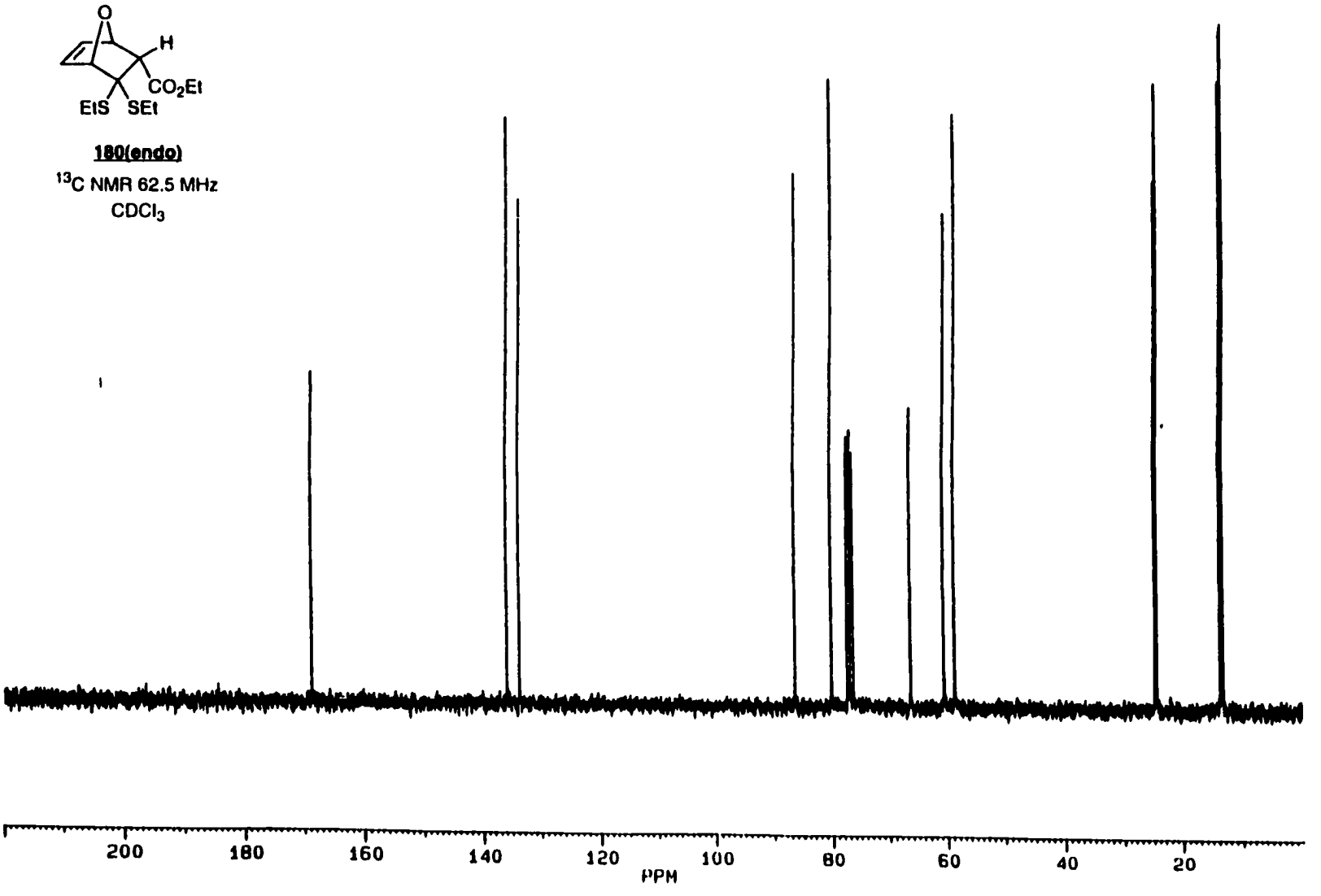


180(endo)

^{1}H NMR 250 MHz

$CDCl_3$

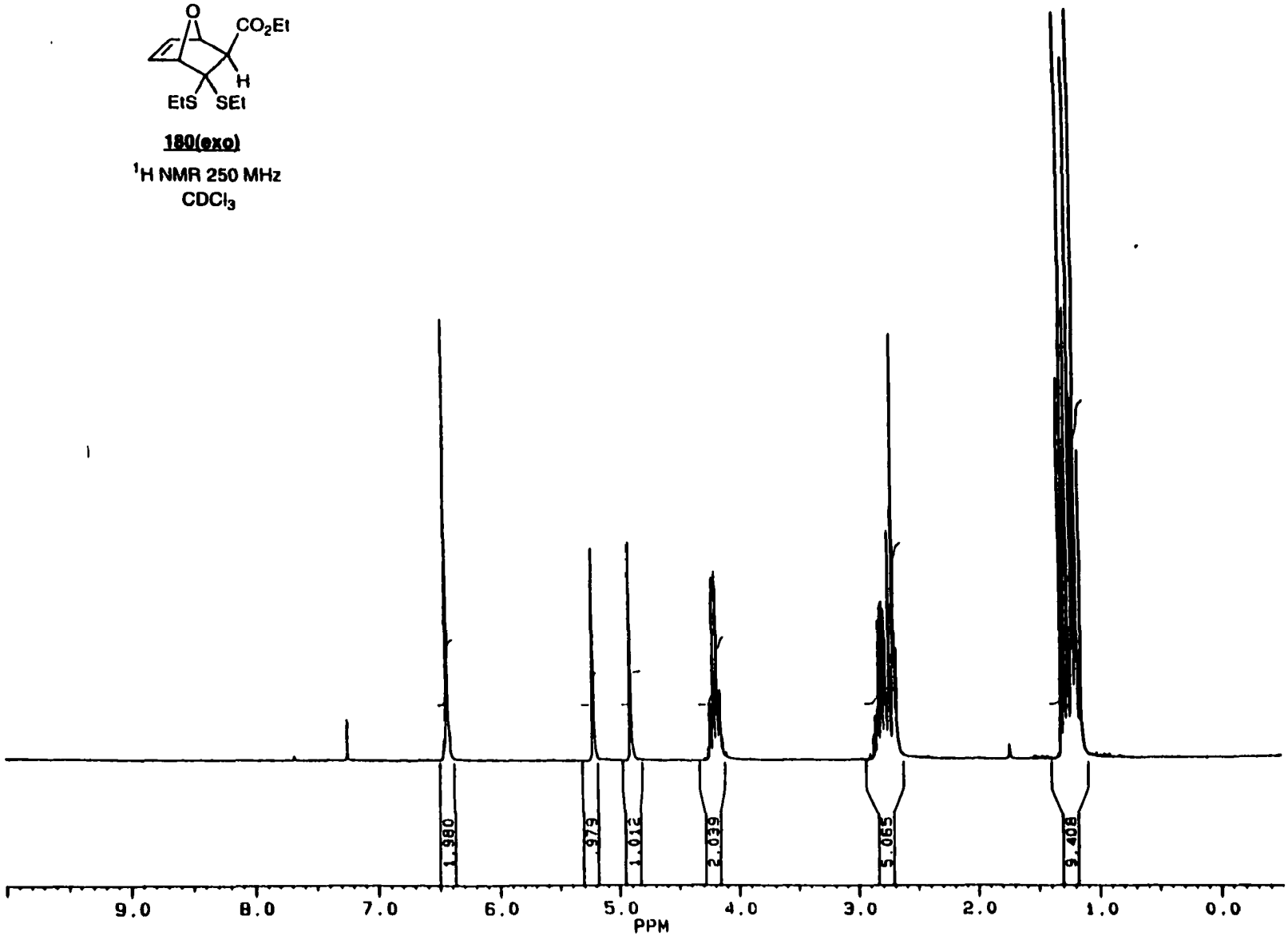


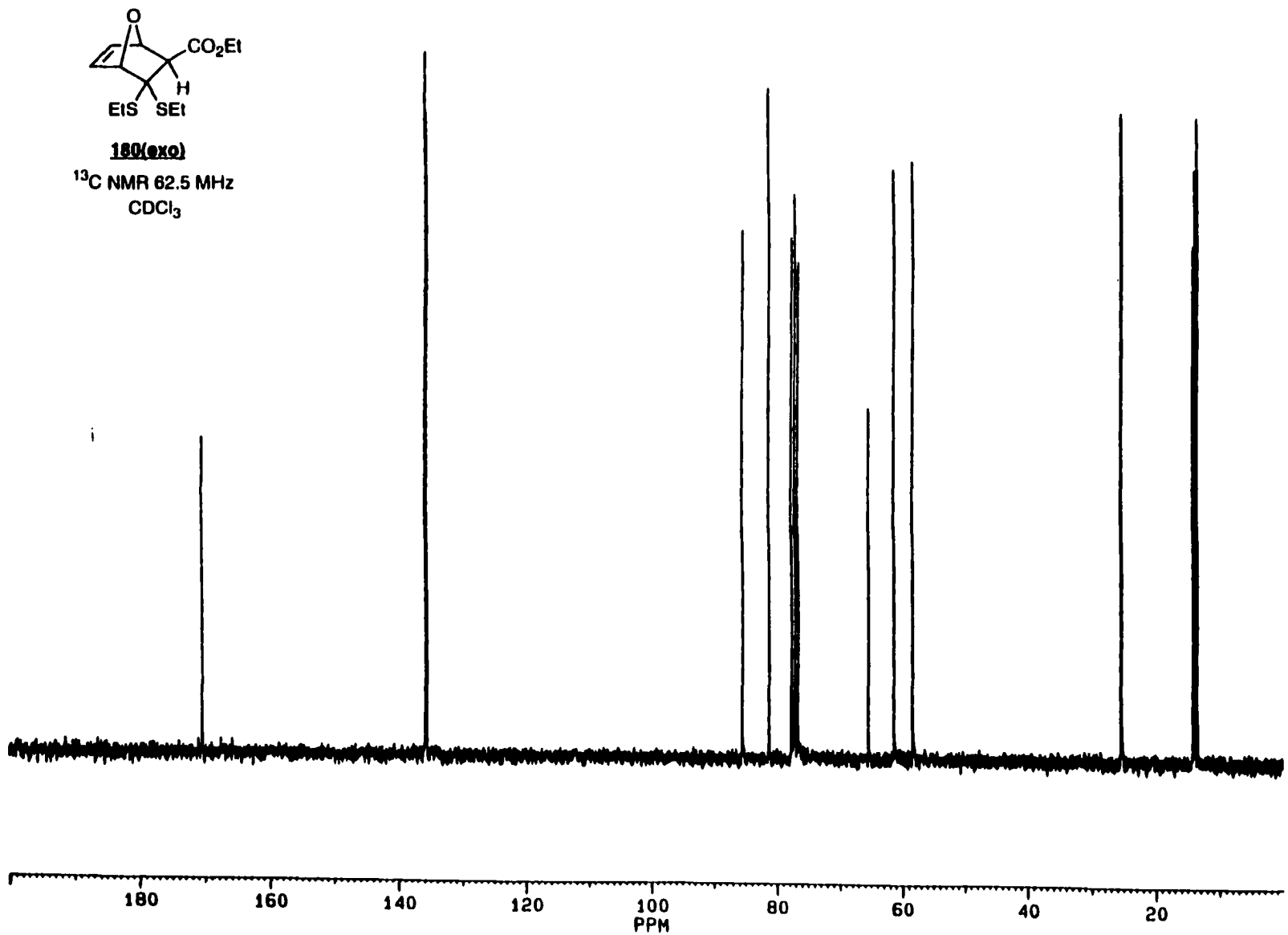

O
H
CO2Et
EtS SEt
180(endo)
13C NMR 62.5 MHz
CDCl3
200
180
160
140
120
100
80
60
40
20
PPM

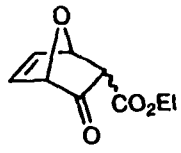
180(exo)

^{1}H NMR 250 MHz

$CDCl_3$



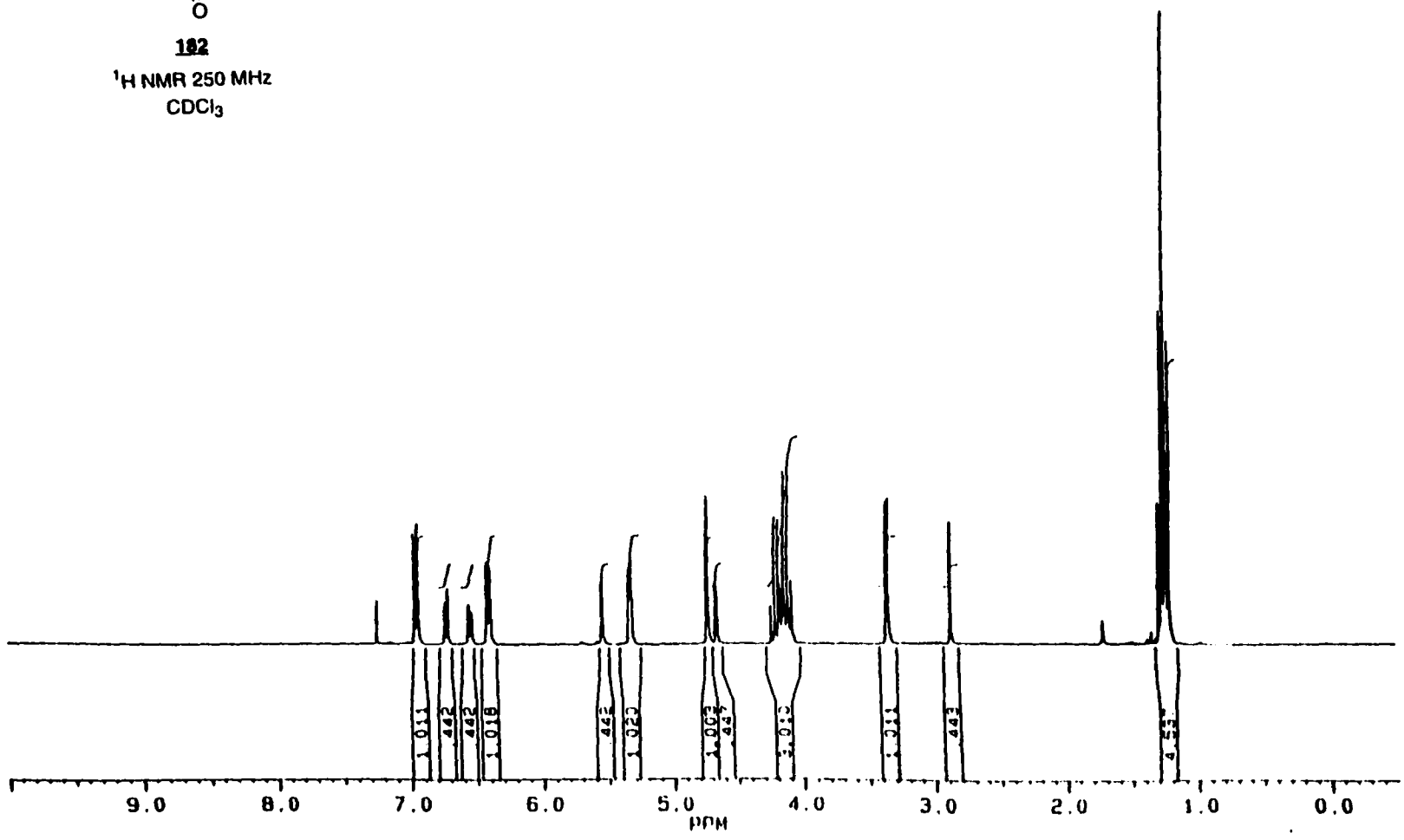

O
CO2Et
H
EtS SEt
180(exo)
13C NMR 62.5 MHz
CDCl3
180
160
140
120
100
PPM
80
60
40
20

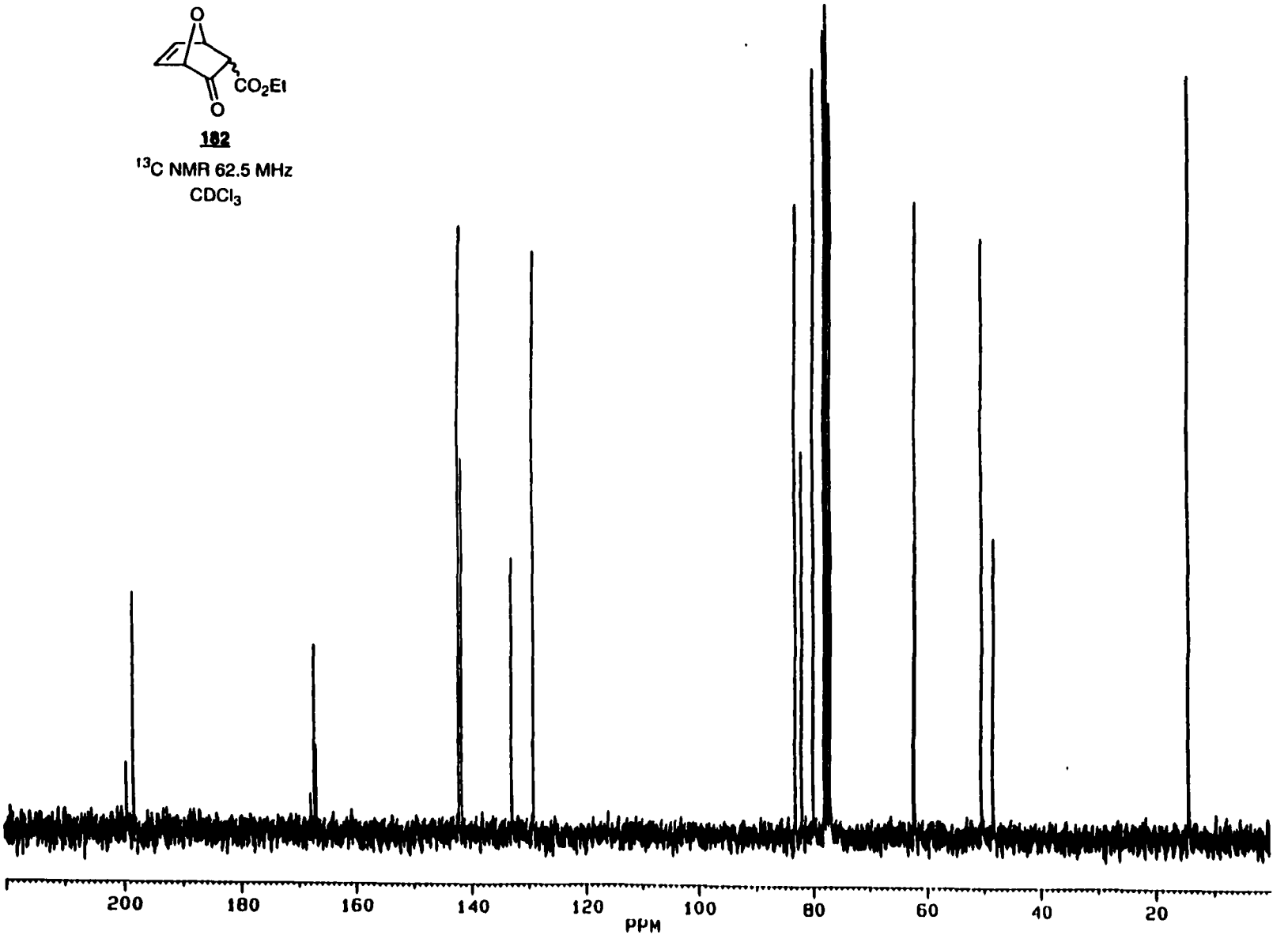


182

^{1}H NMR 250 MHz

$CDCl_3$

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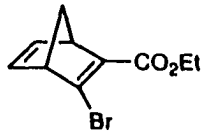
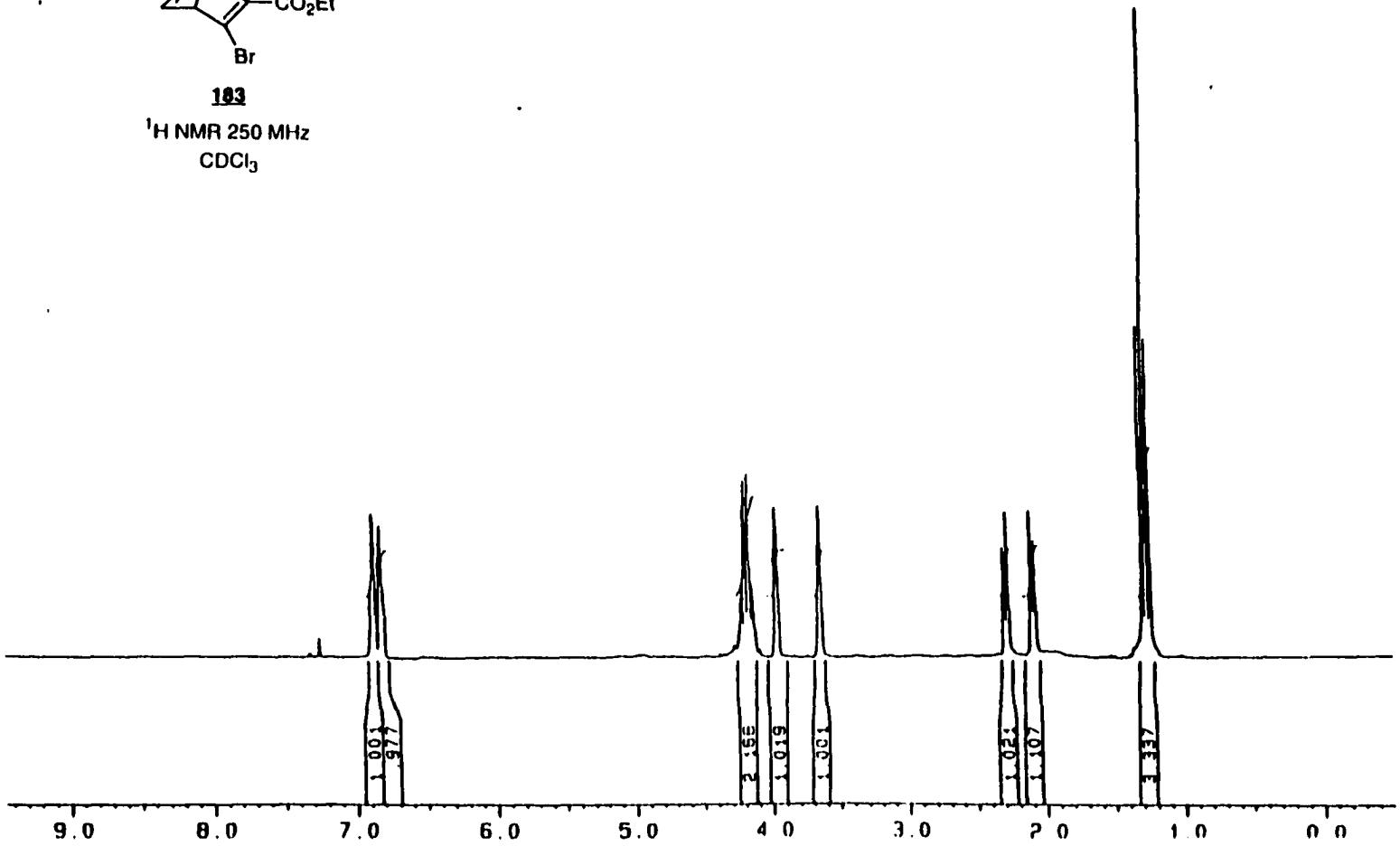
CO2Et
O
182
13C NMR 62.5 MHz
CDCl3
200
180
160
140
120
100
80
60
40
20
PPM



183

^{1}H NMR 250 MHz

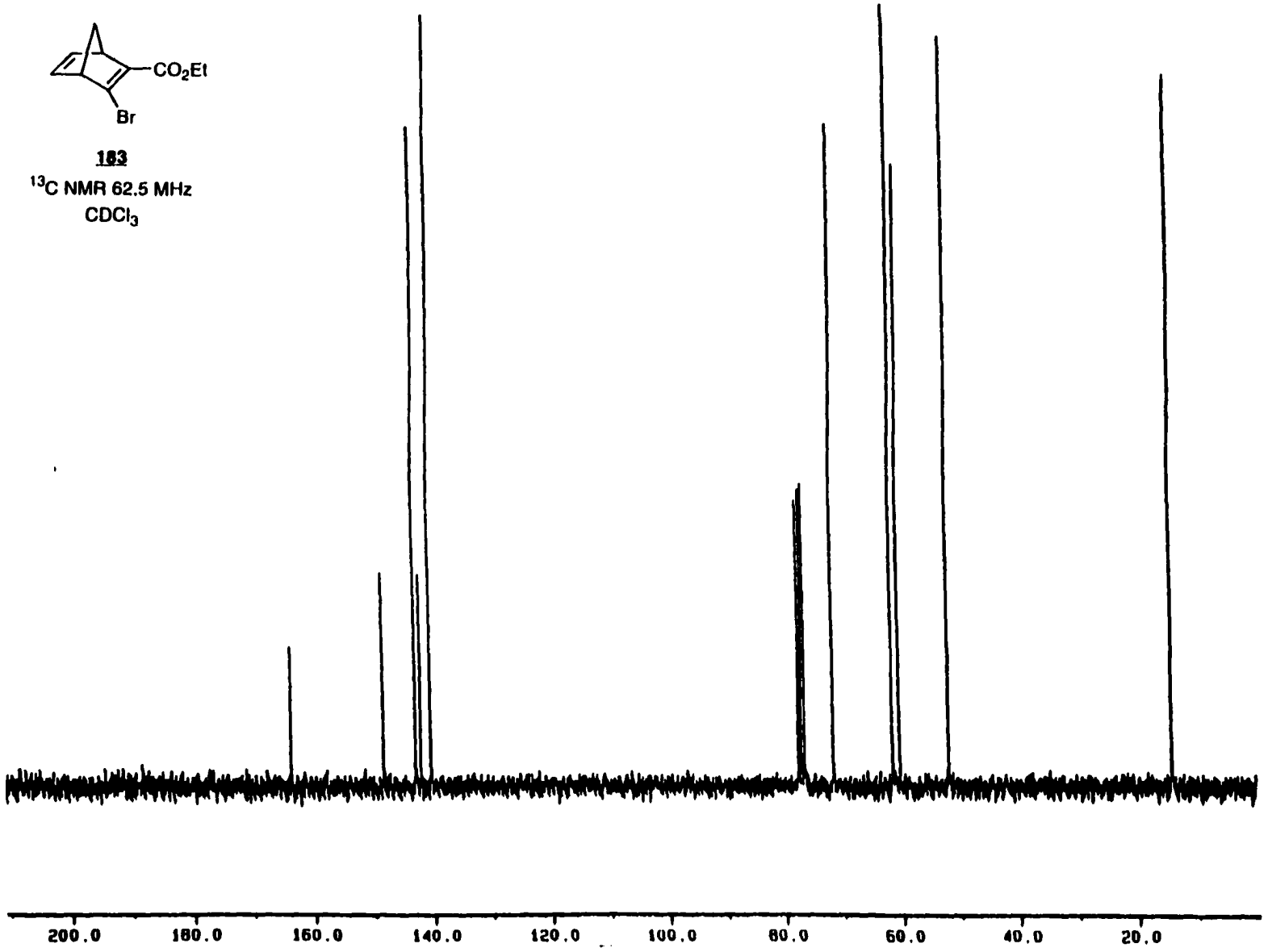
$CDCl_3$



183

^{13}C NMR 62.5 MHz

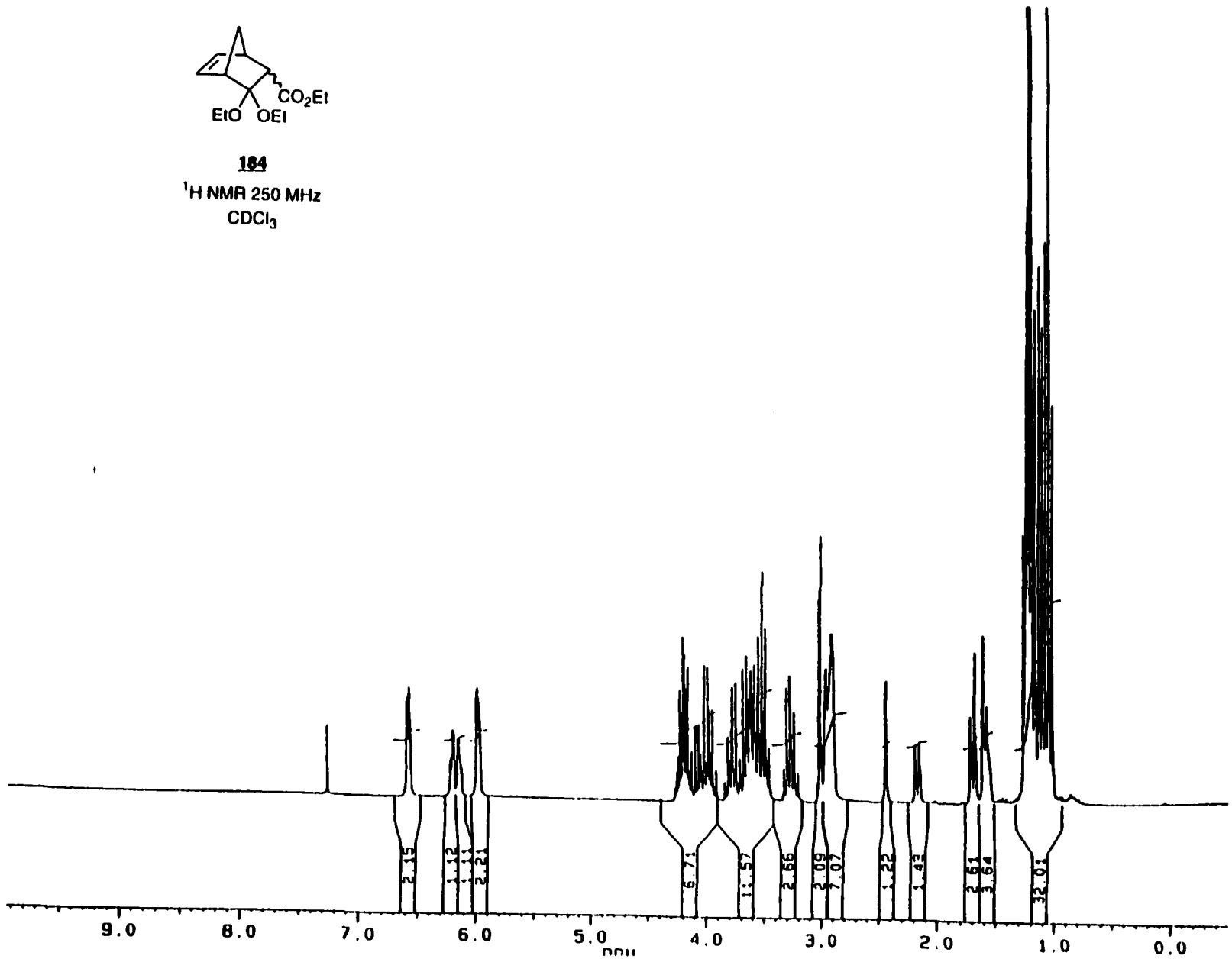
$CDCl_3$

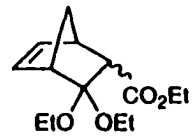


184

^{1}H NMR 250 MHz

$CDCl_3$

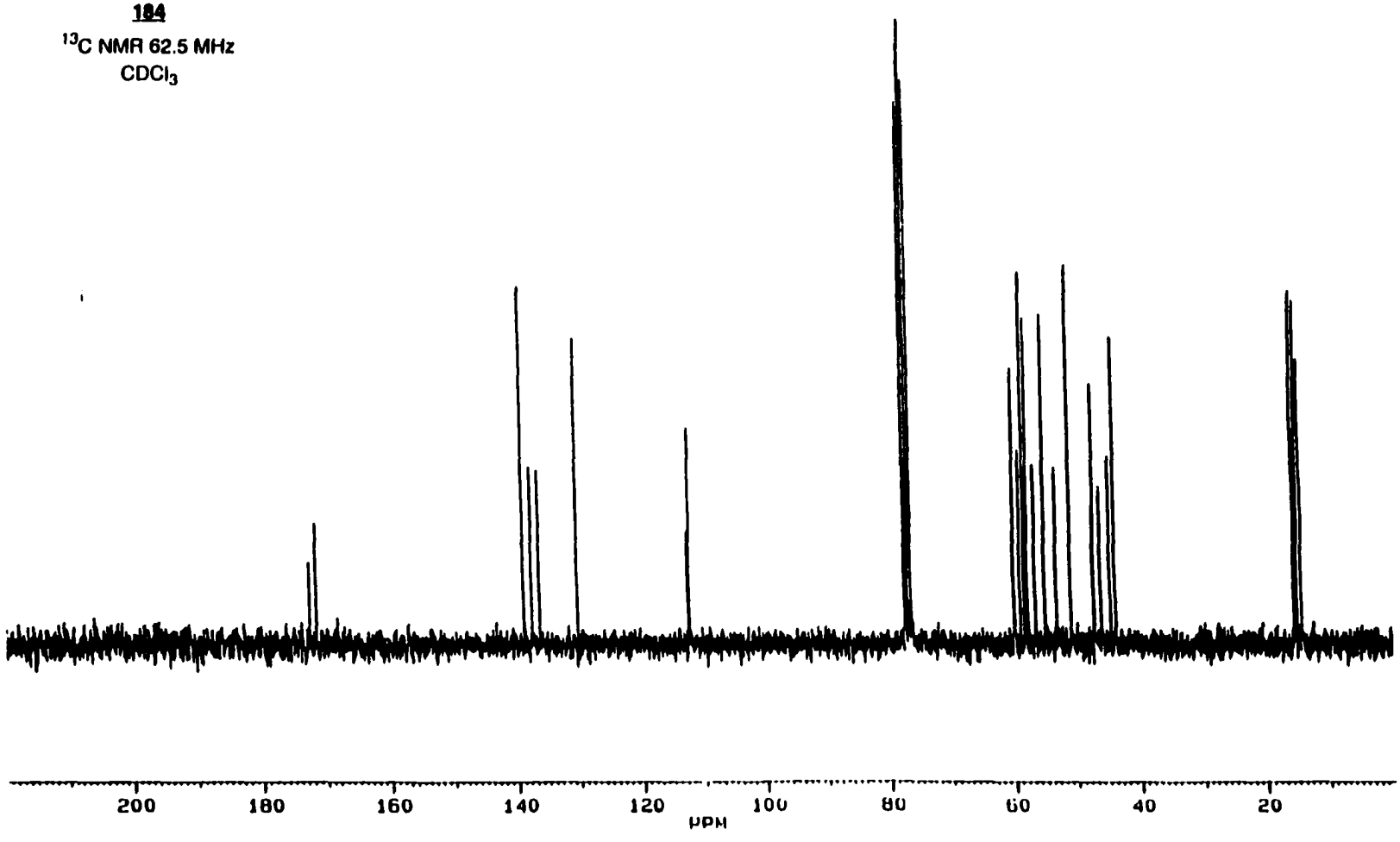




184

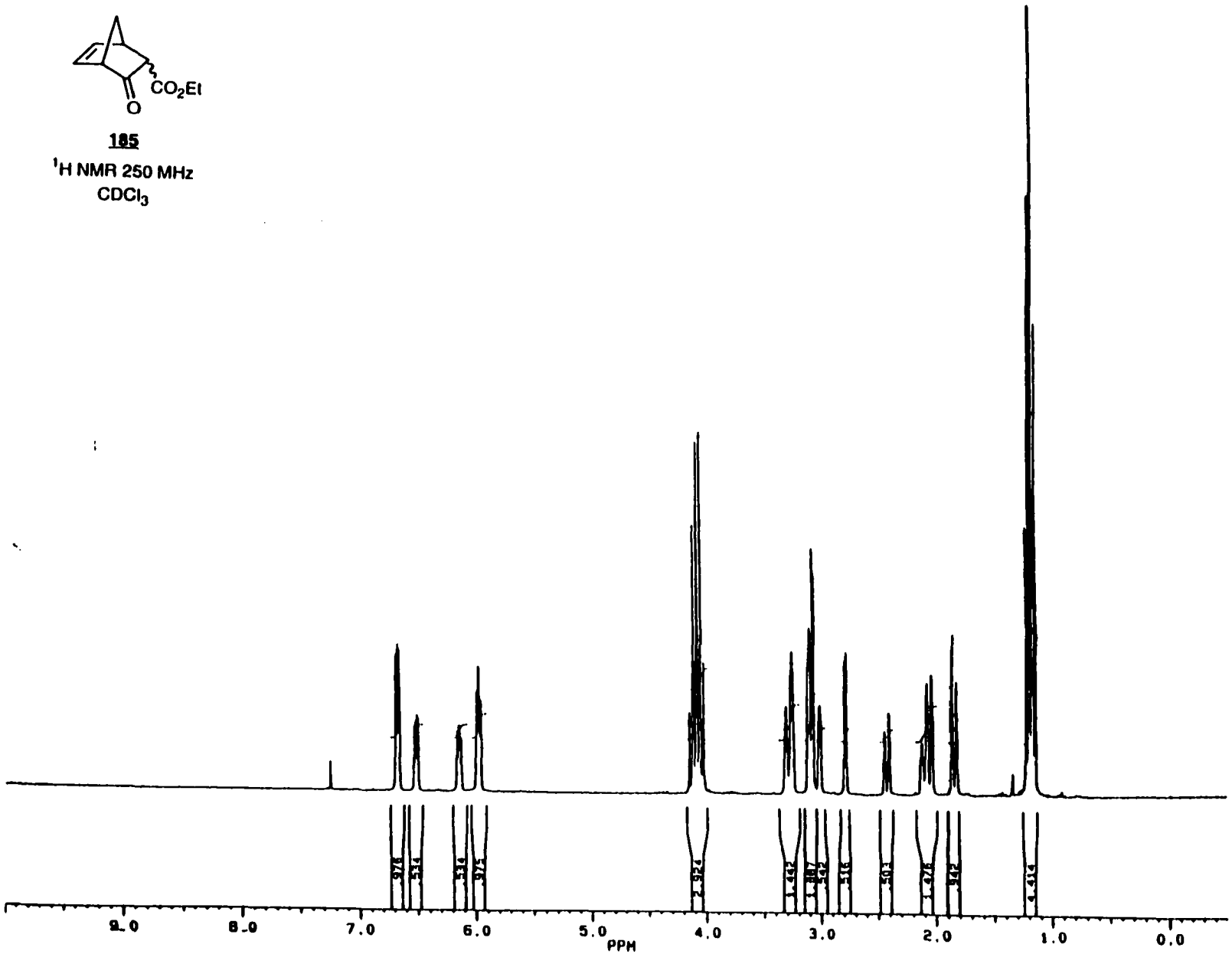
^{13}C NMR 62.5 MHz

$CDCl_3$



185

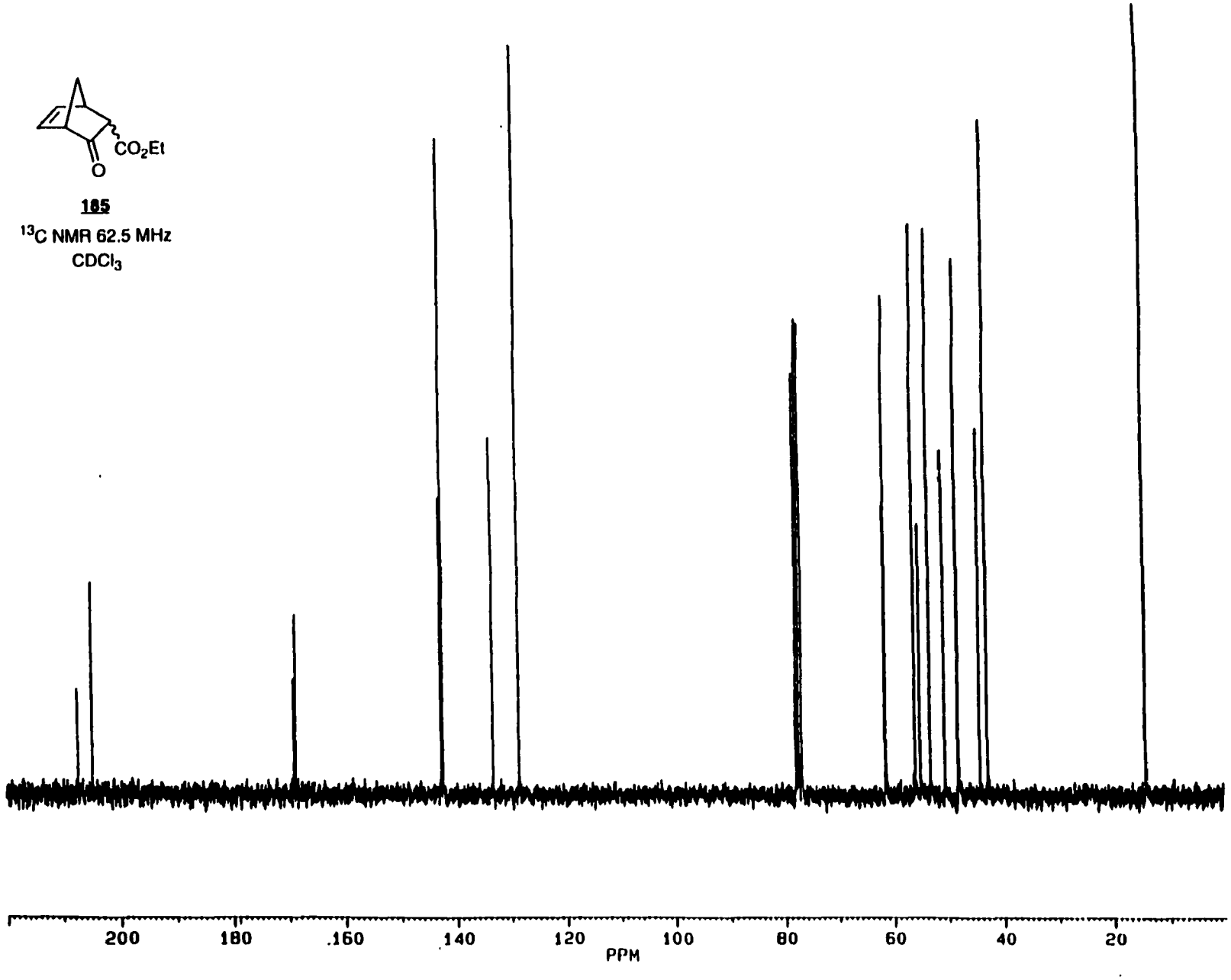
^{1}H NMR 250 MHz
$CDCl_3$

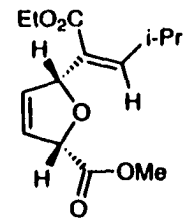


185

^{13}C NMR 62.5 MHz

$CDCl_3$

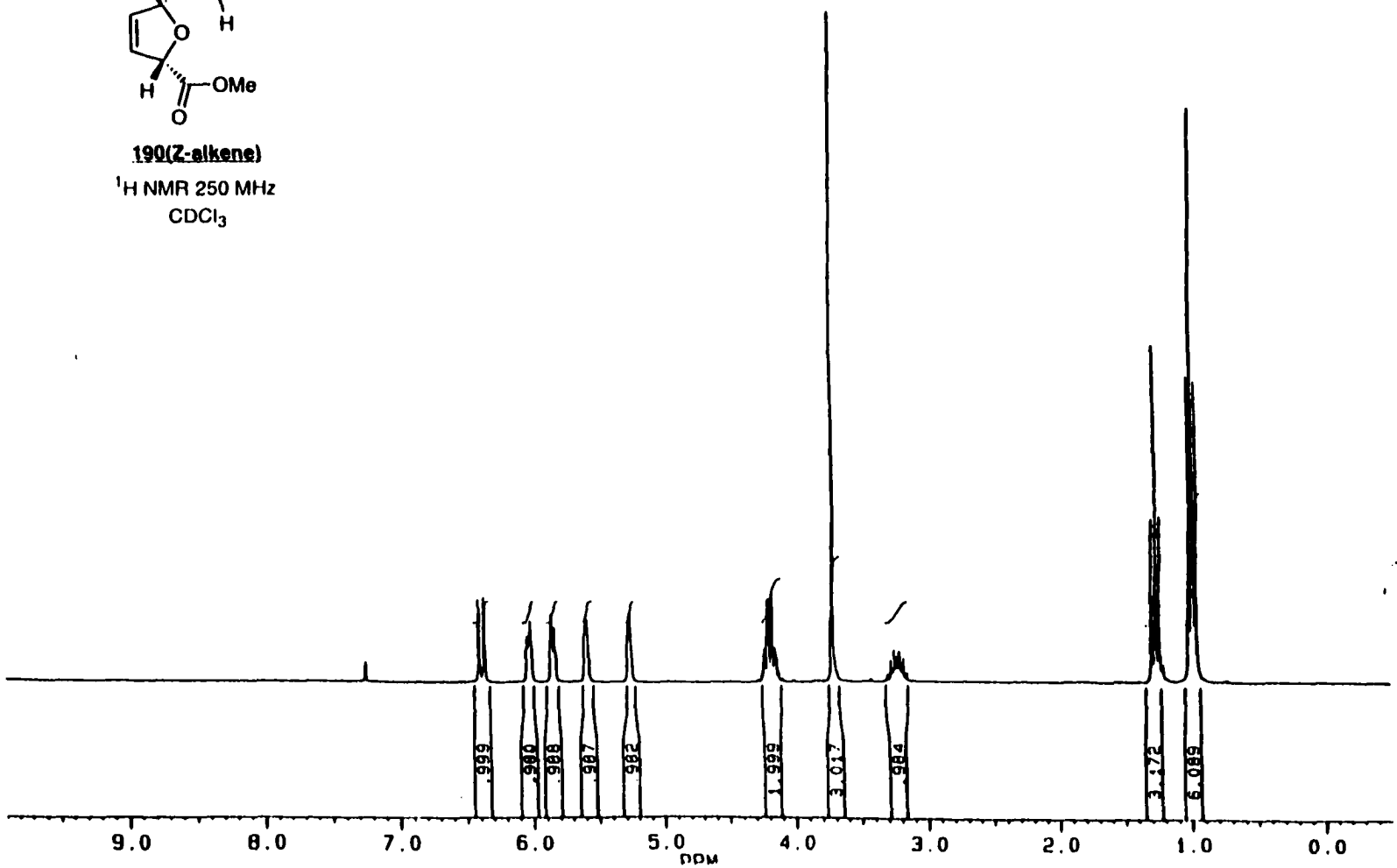


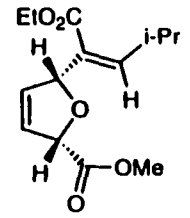


190(Z-alkene)

^{1}H NMR 250 MHz

$CDCl_3$

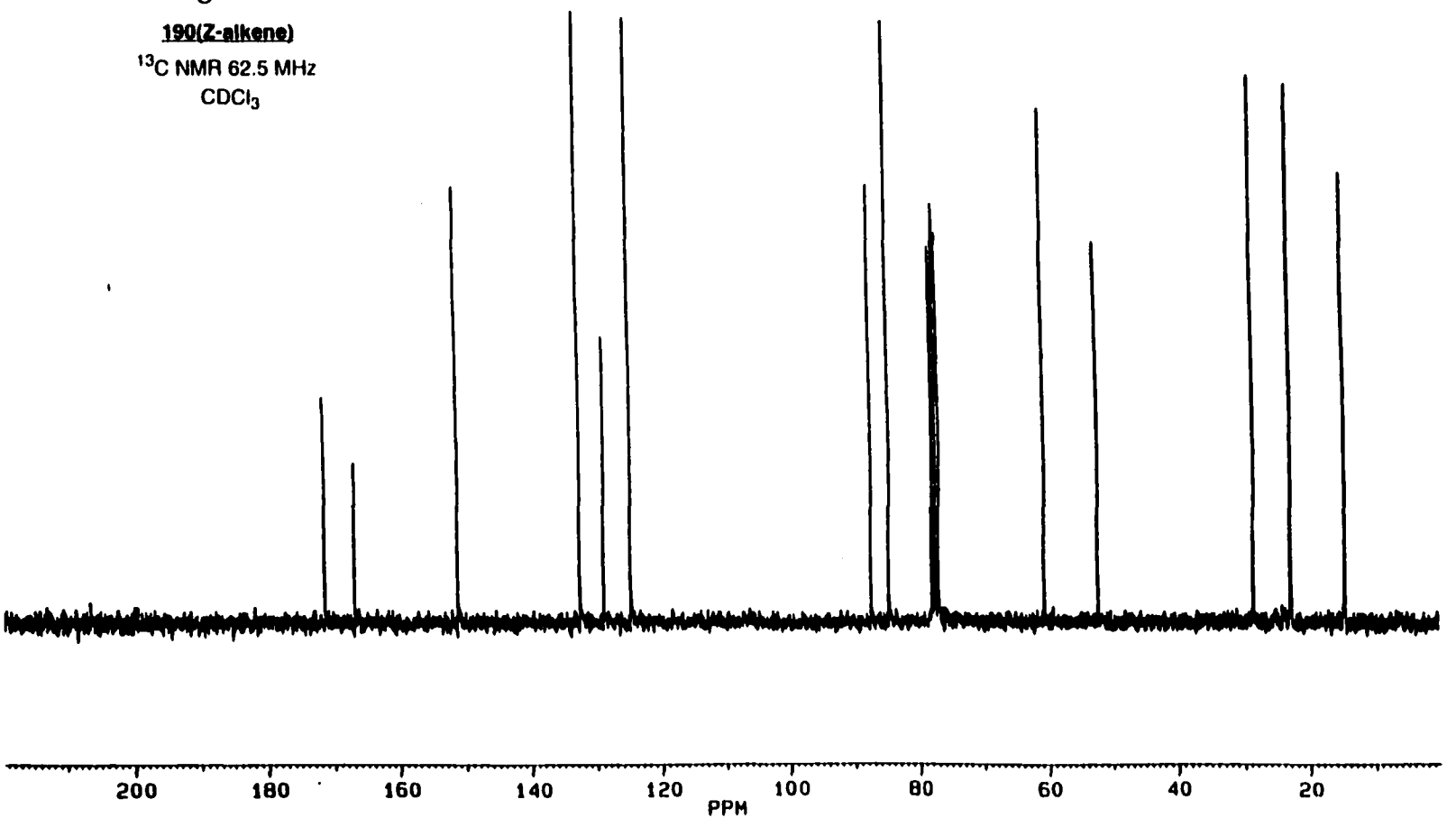


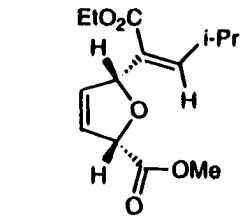


190(Z-alkene)

^{13}C NMR 62.5 MHz

$CDCl_3$

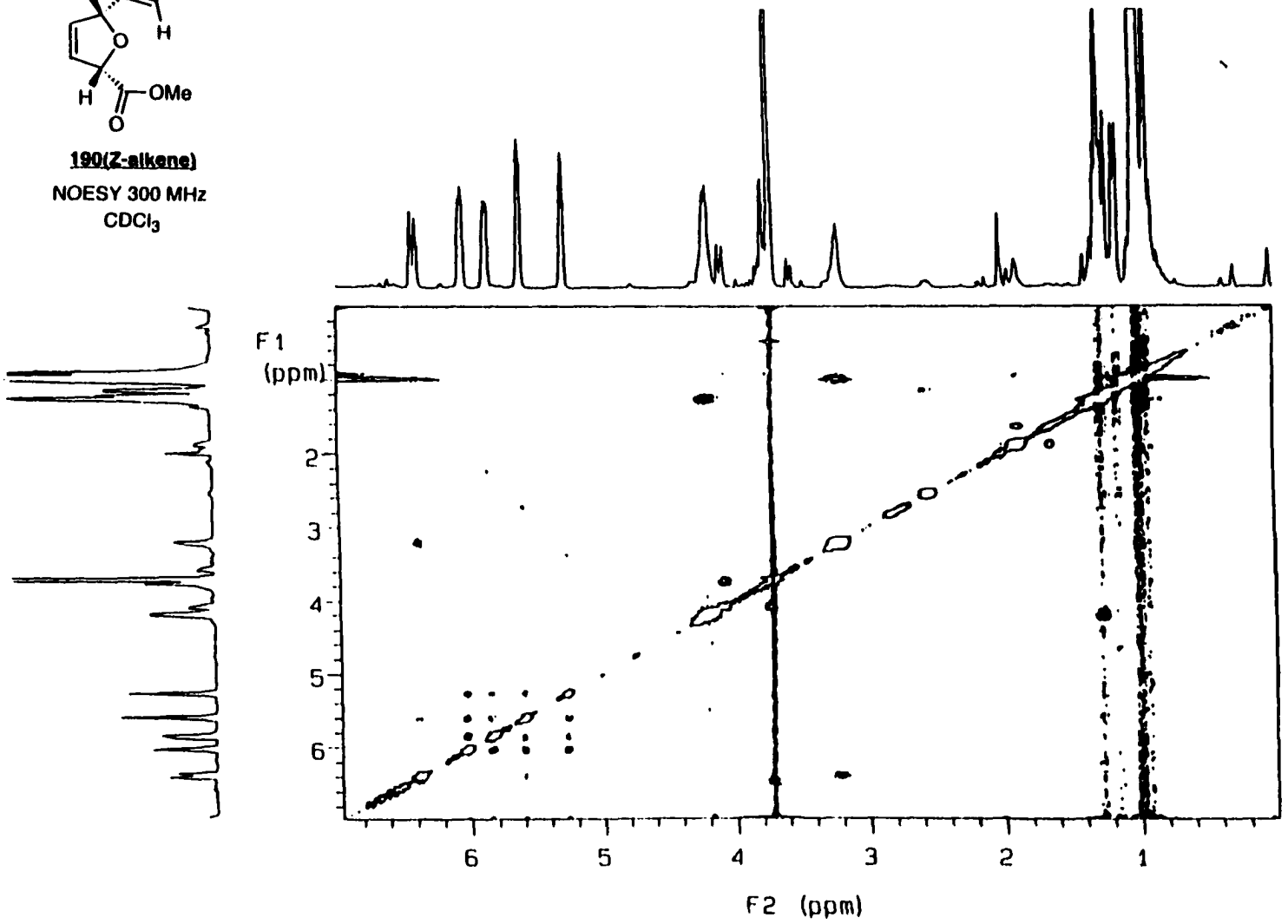


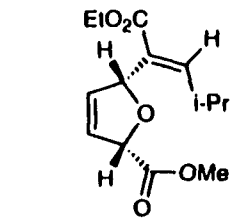


190(Z-alkene)

NOESY 300 MHz

$CDCl_3$

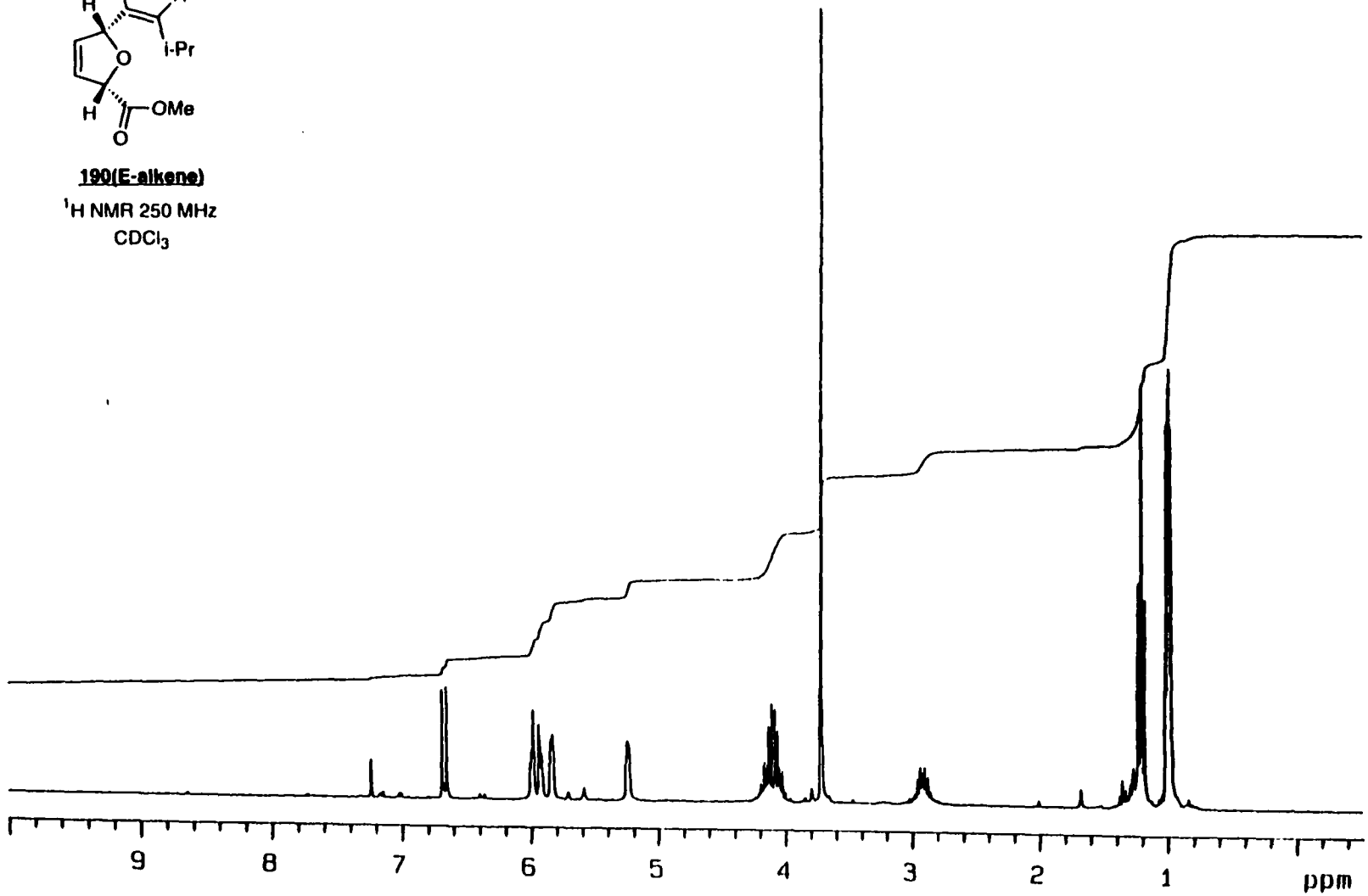


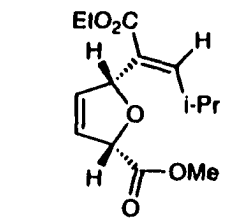


190(E-alkene)

^{1}H NMR 250 MHz

$CDCl_3$

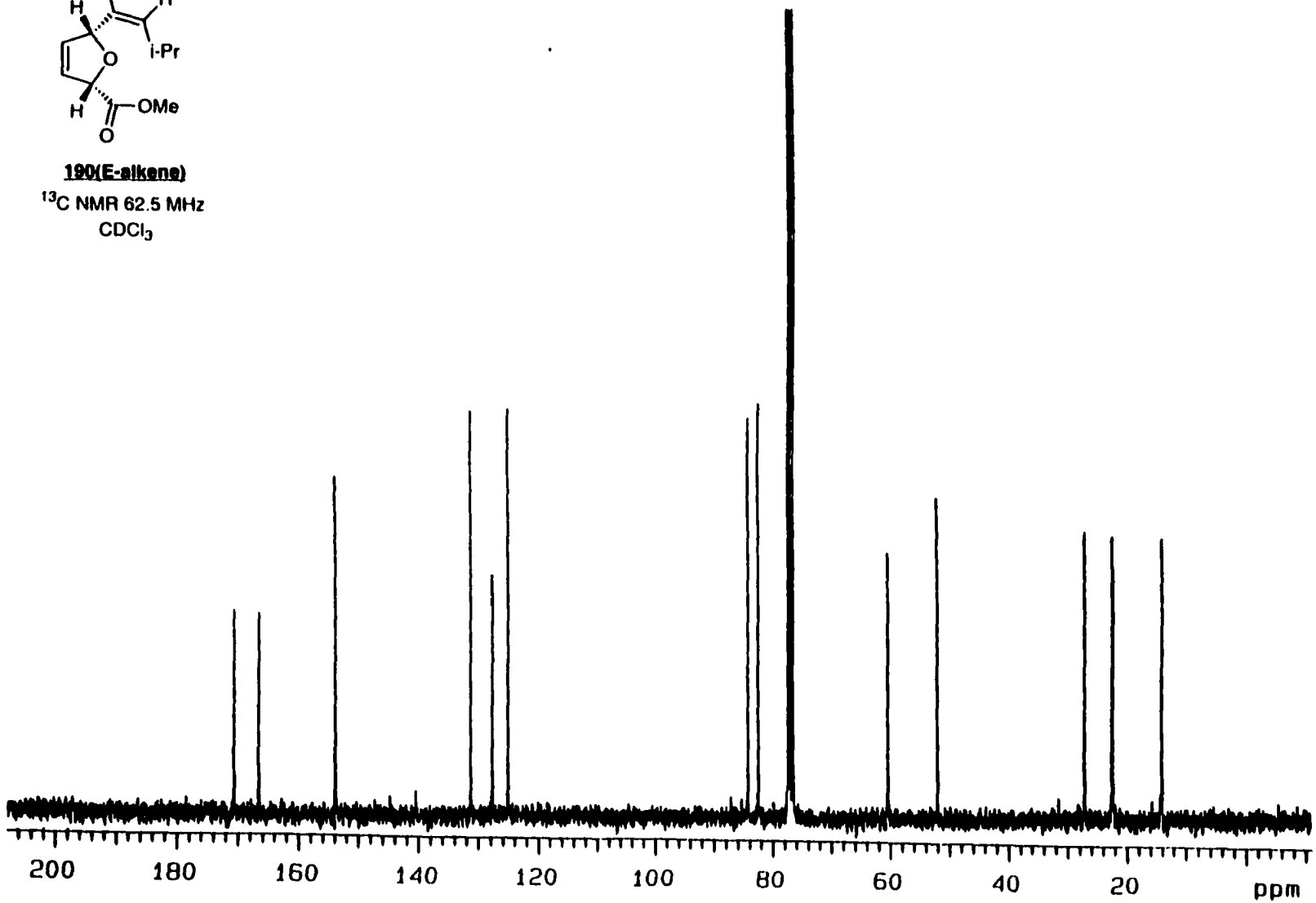


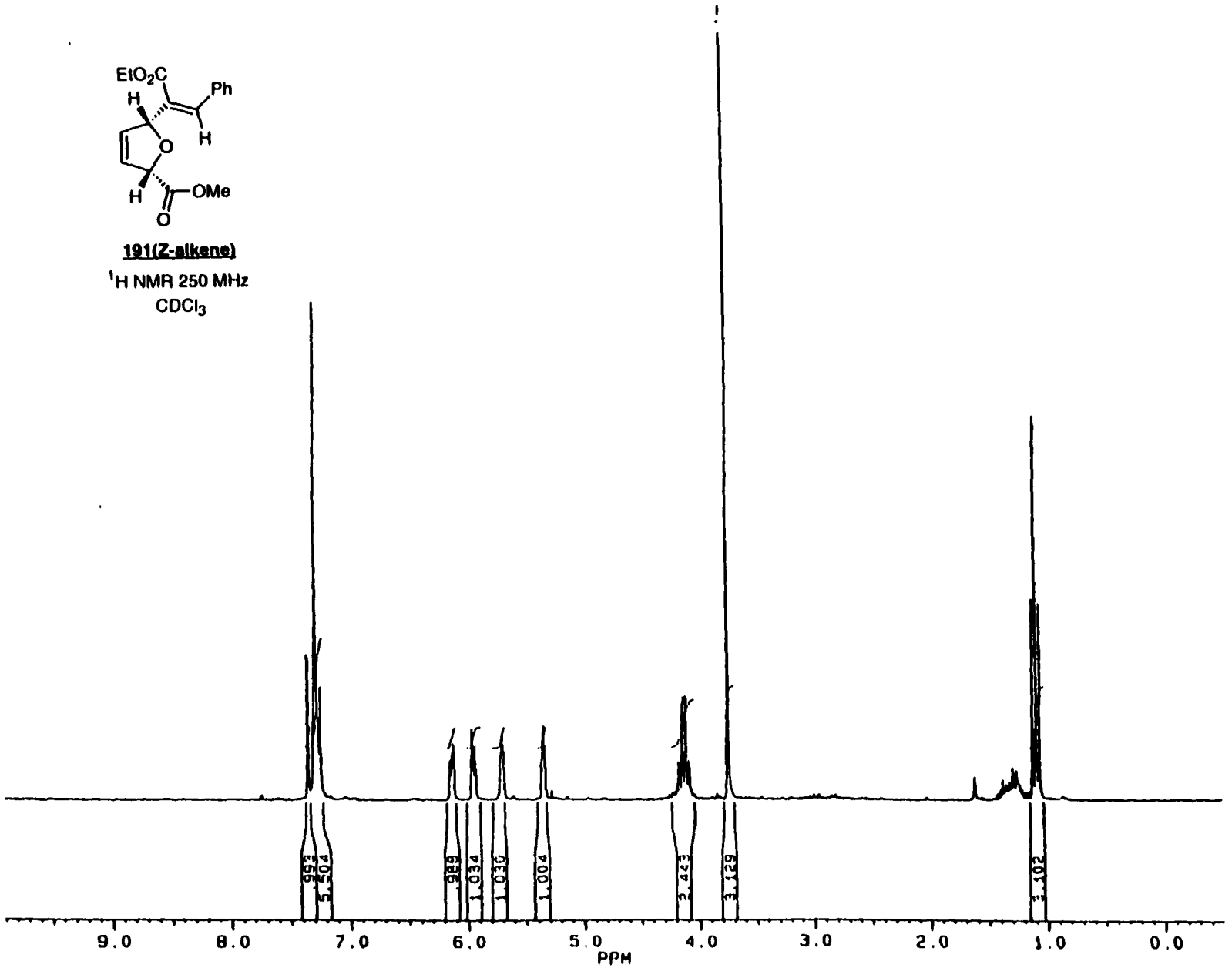


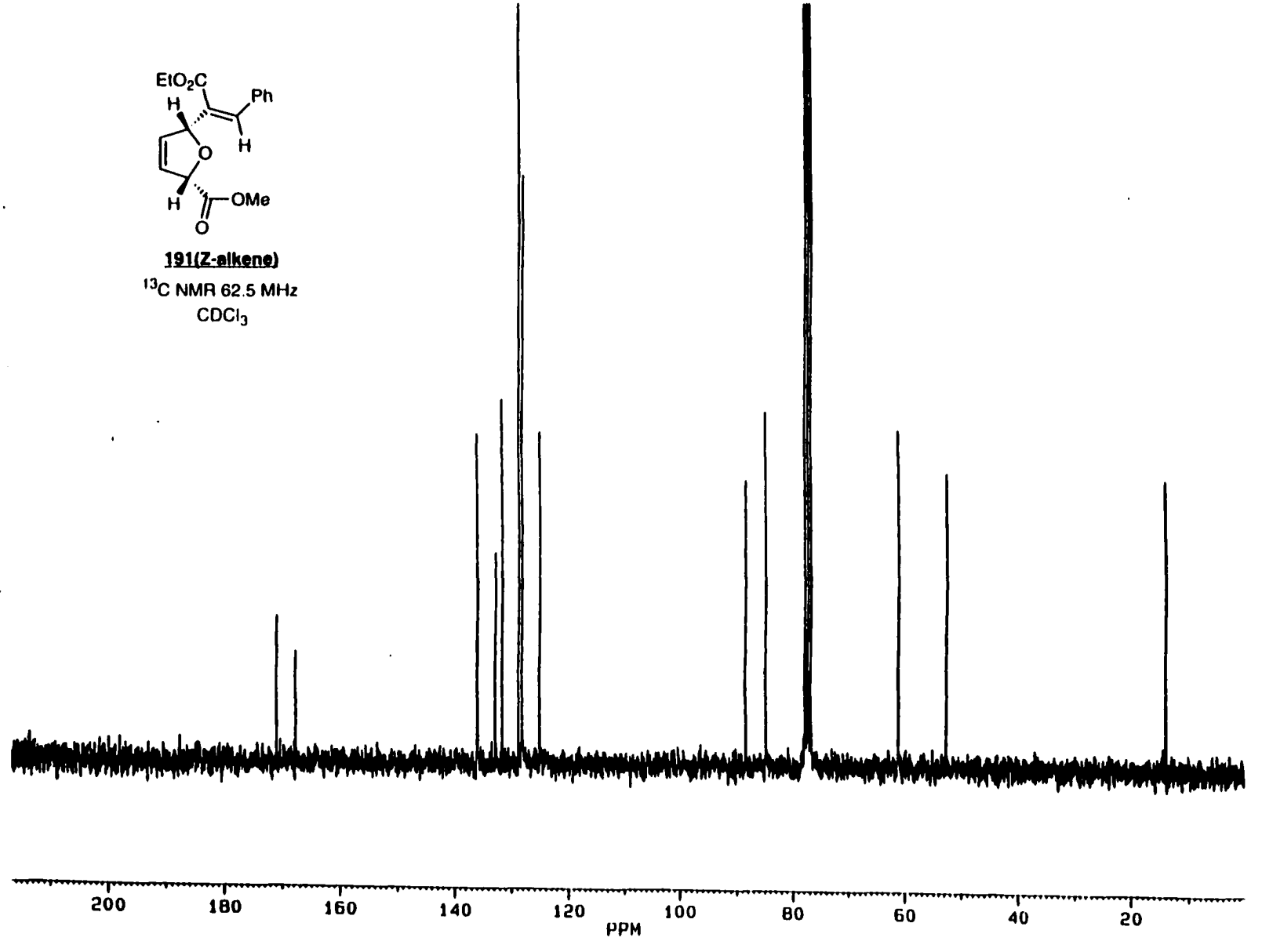
190(E-alkene)

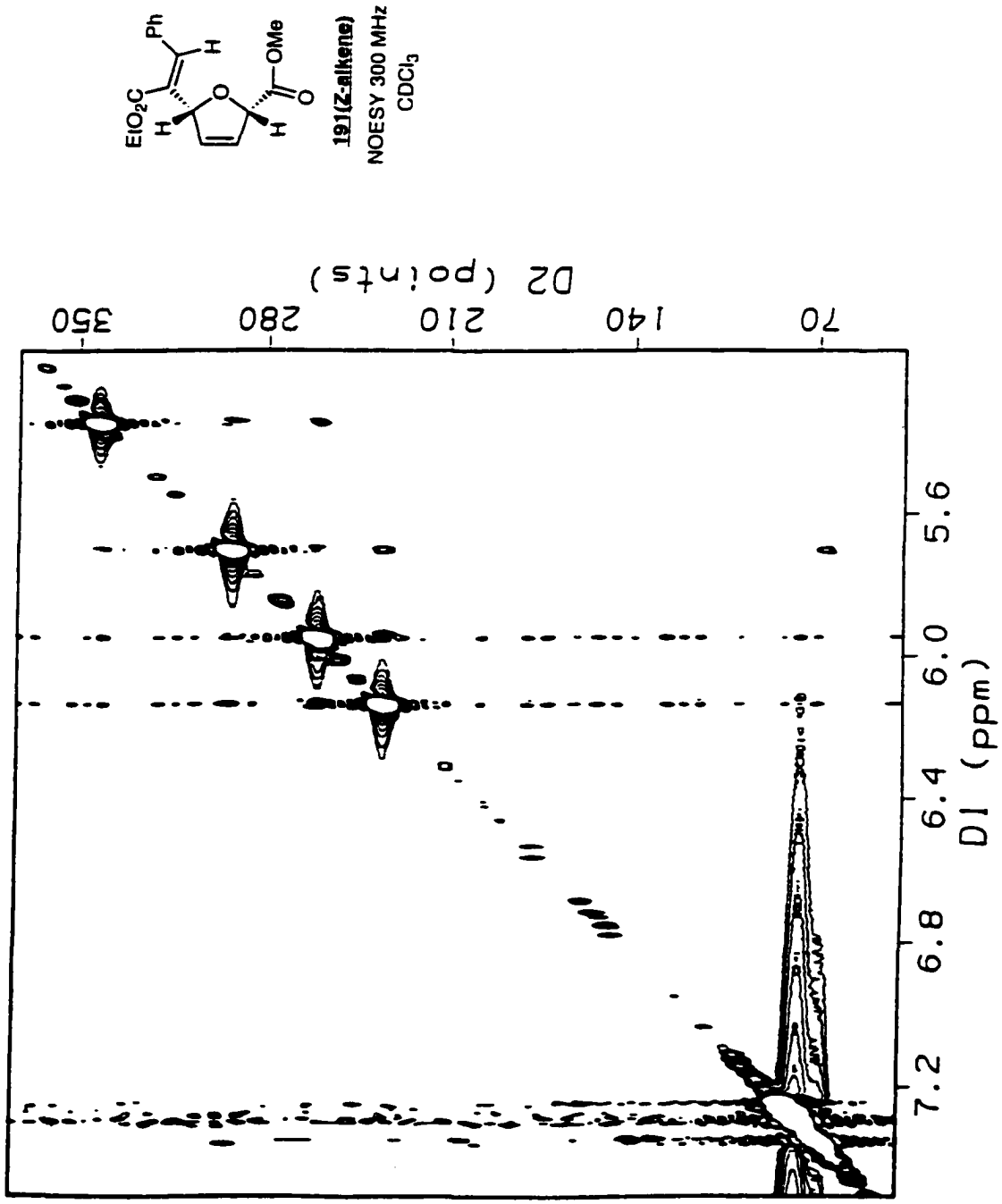
^{13}C NMR 62.5 MHz

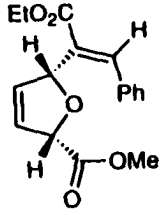
$CDCl_3$




EtO2C
H
Ph
O
H
H
OMe
O
191(Z-alkene)
1H NMR 250 MHz
CDCl3
9.92
5.504
.999
1.034
1.030
1.004
2.443
3.129
3.102
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM


EtO2C
H
Ph
H
O
H
OMe
O
191(Z-alkene)
13C NMR 62.5 MHz
CDCl3
200
180
160
140
120
100
80
60
40
20
PPM

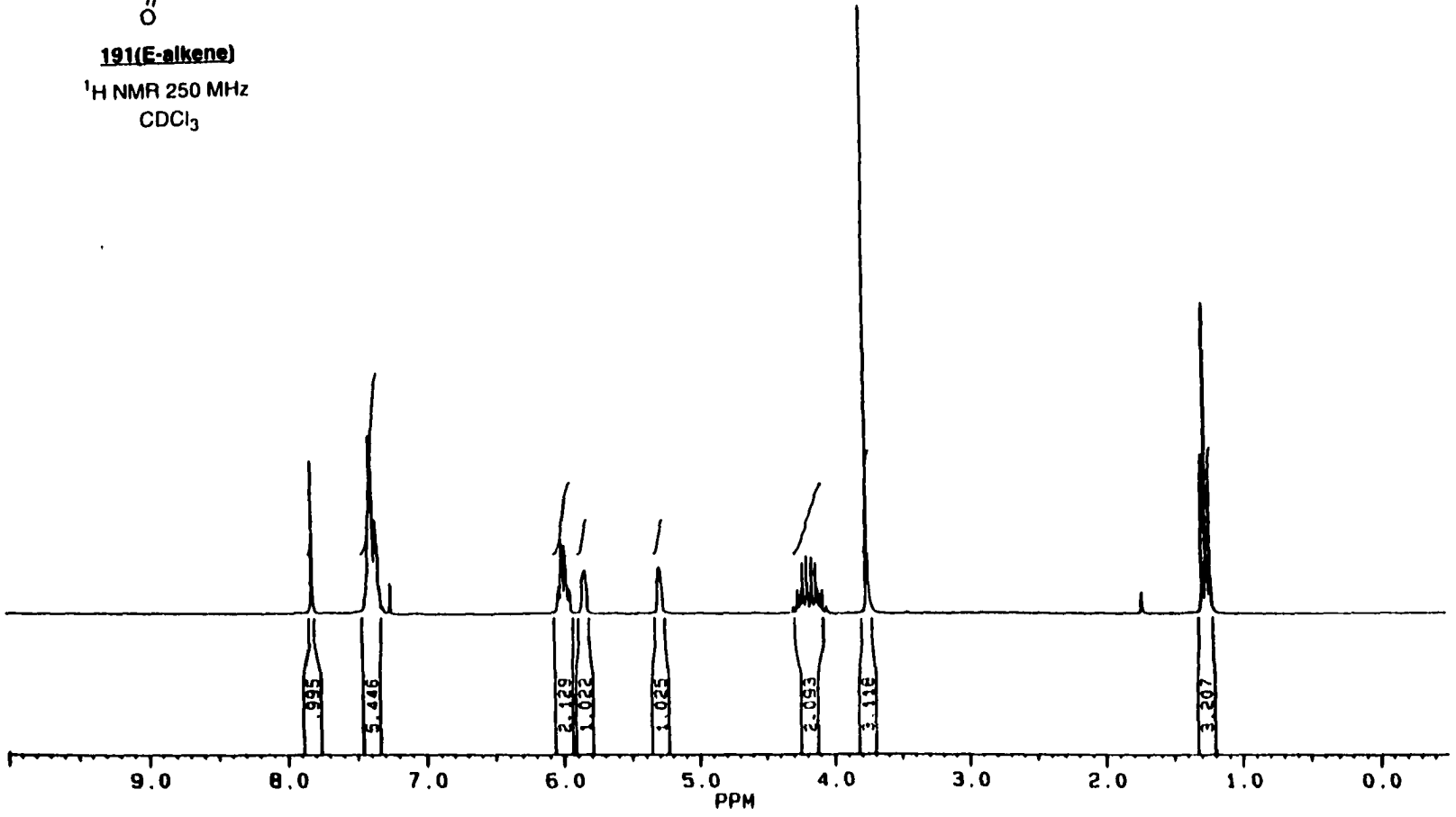

Ph
H
OMe
O
EtO2C
H
H
19j(Z-alkene)
NOESY 300 MHz
CDCl3
D2 (points)
70
140
210
280
350
D1 (ppm)
5.6
6.0
6.4
6.8
7.2

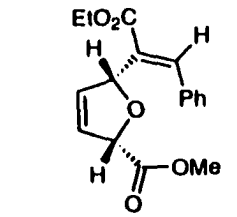


191(E-alkene)

^{1}H NMR 250 MHz

$CDCl_3$

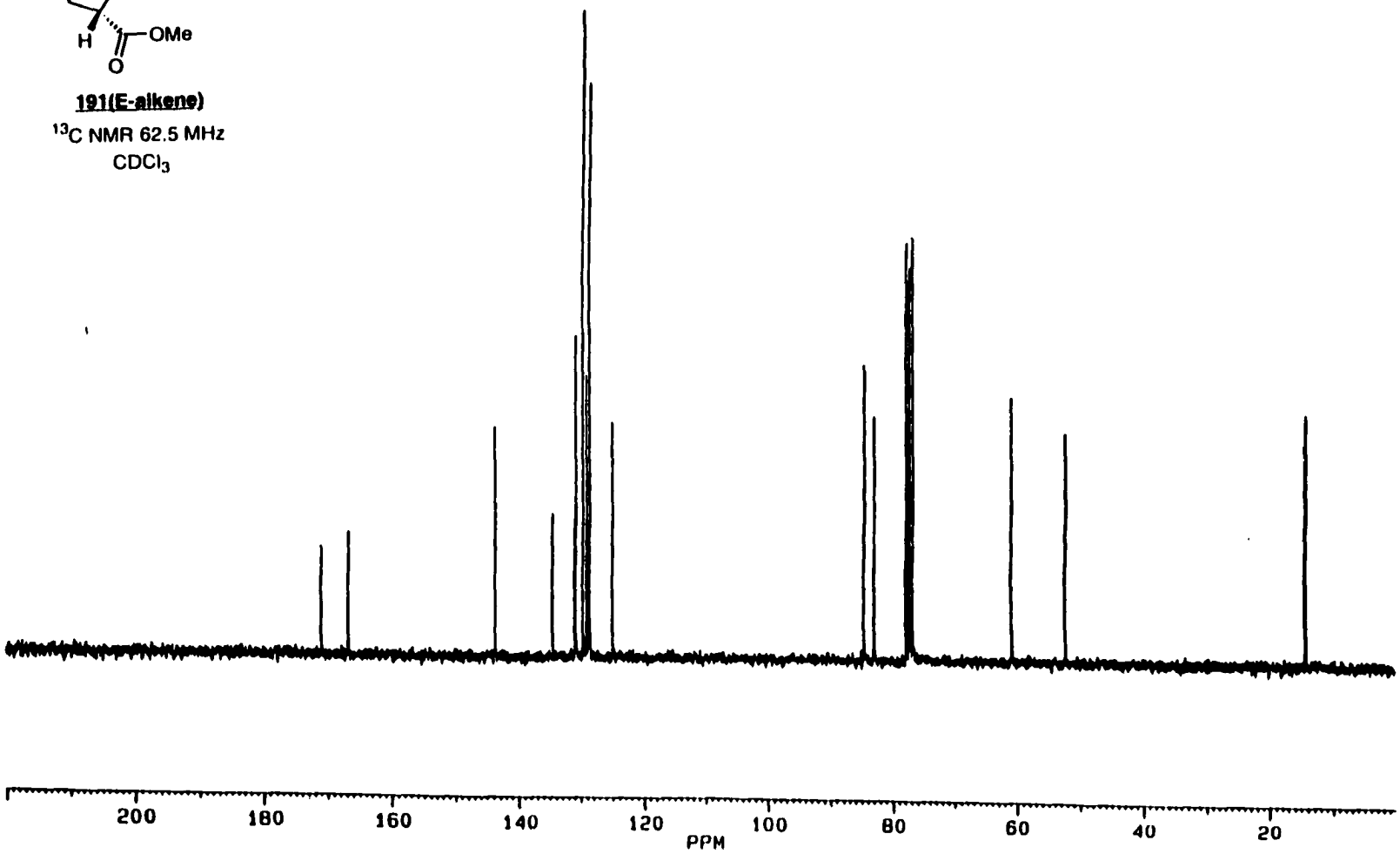


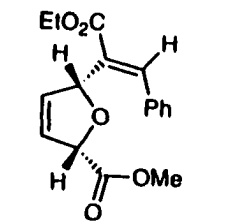


191(E-alkene)

^{13}C NMR 62.5 MHz

$CDCl_3$

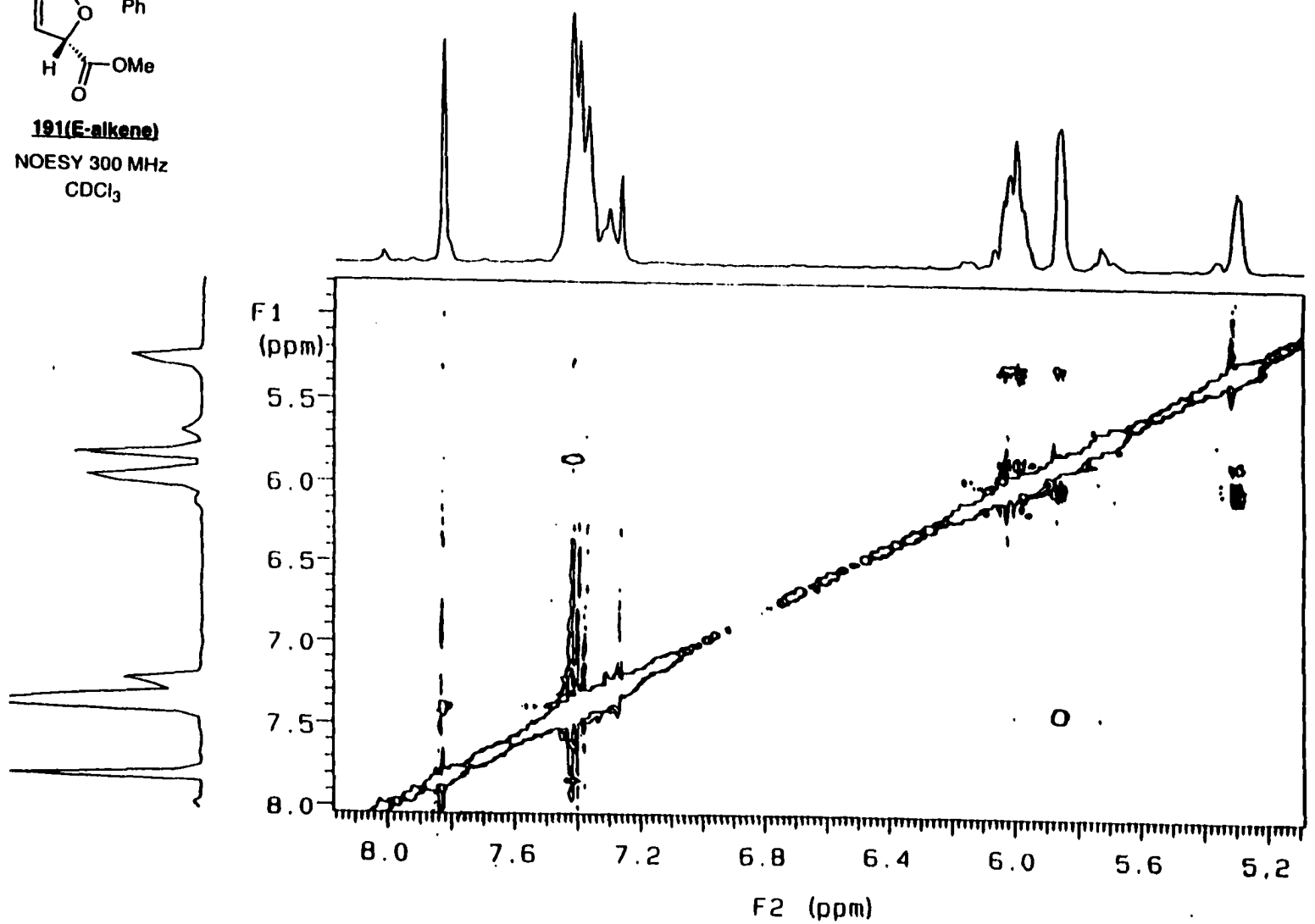


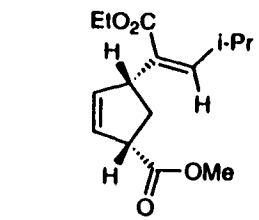


191(E-alkene)

NOESY 300 MHz

$CDCl_3$

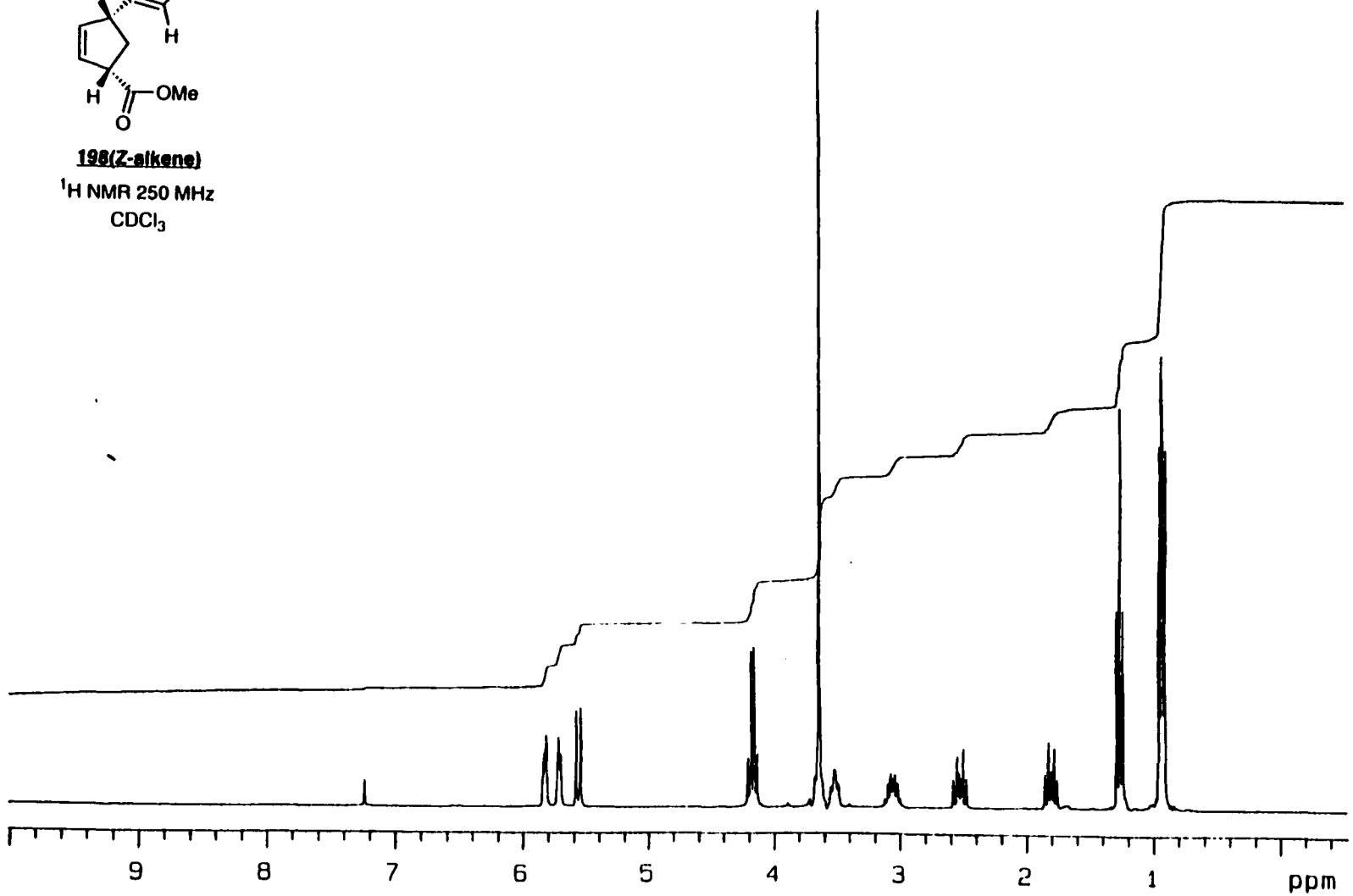


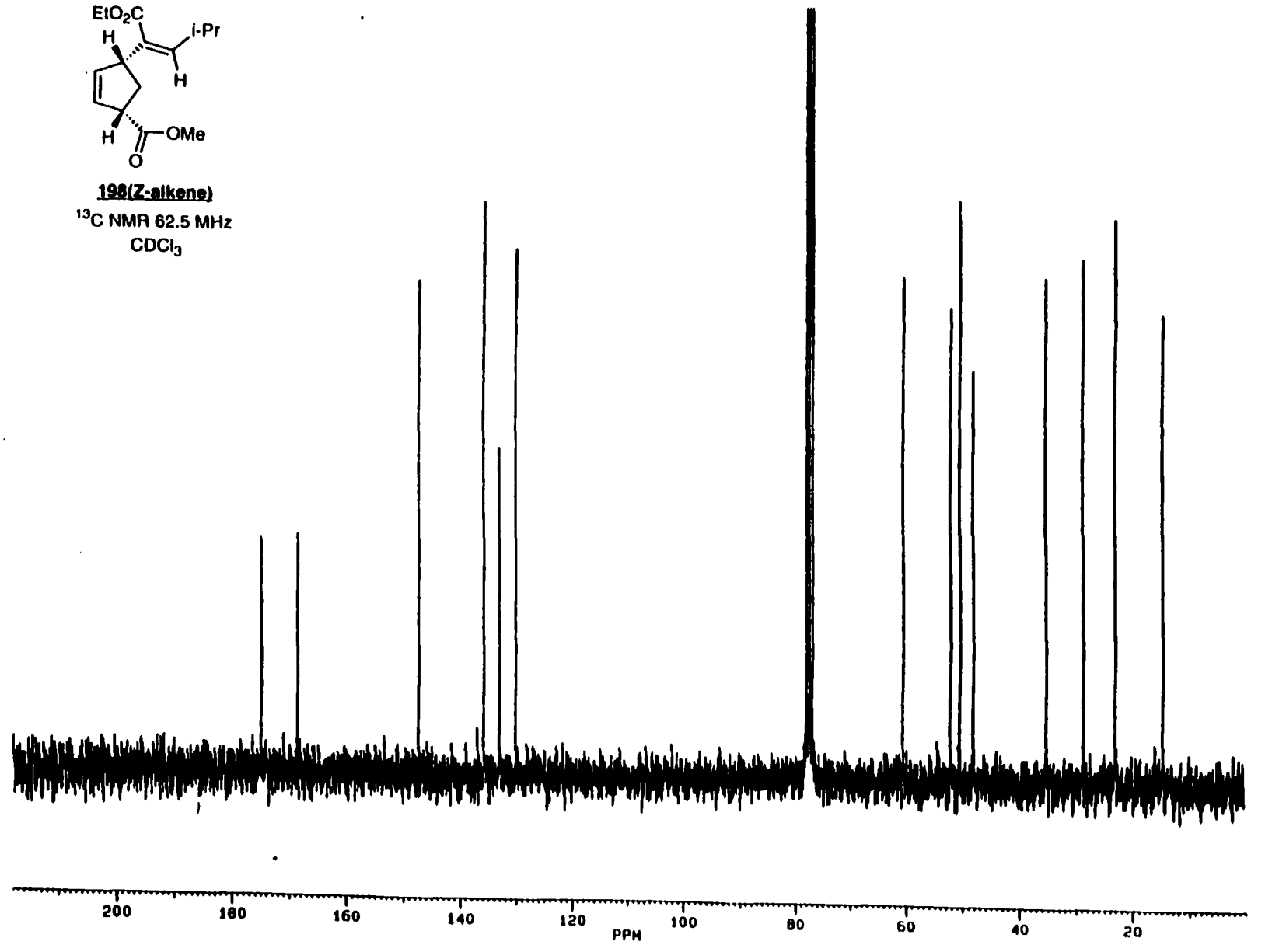


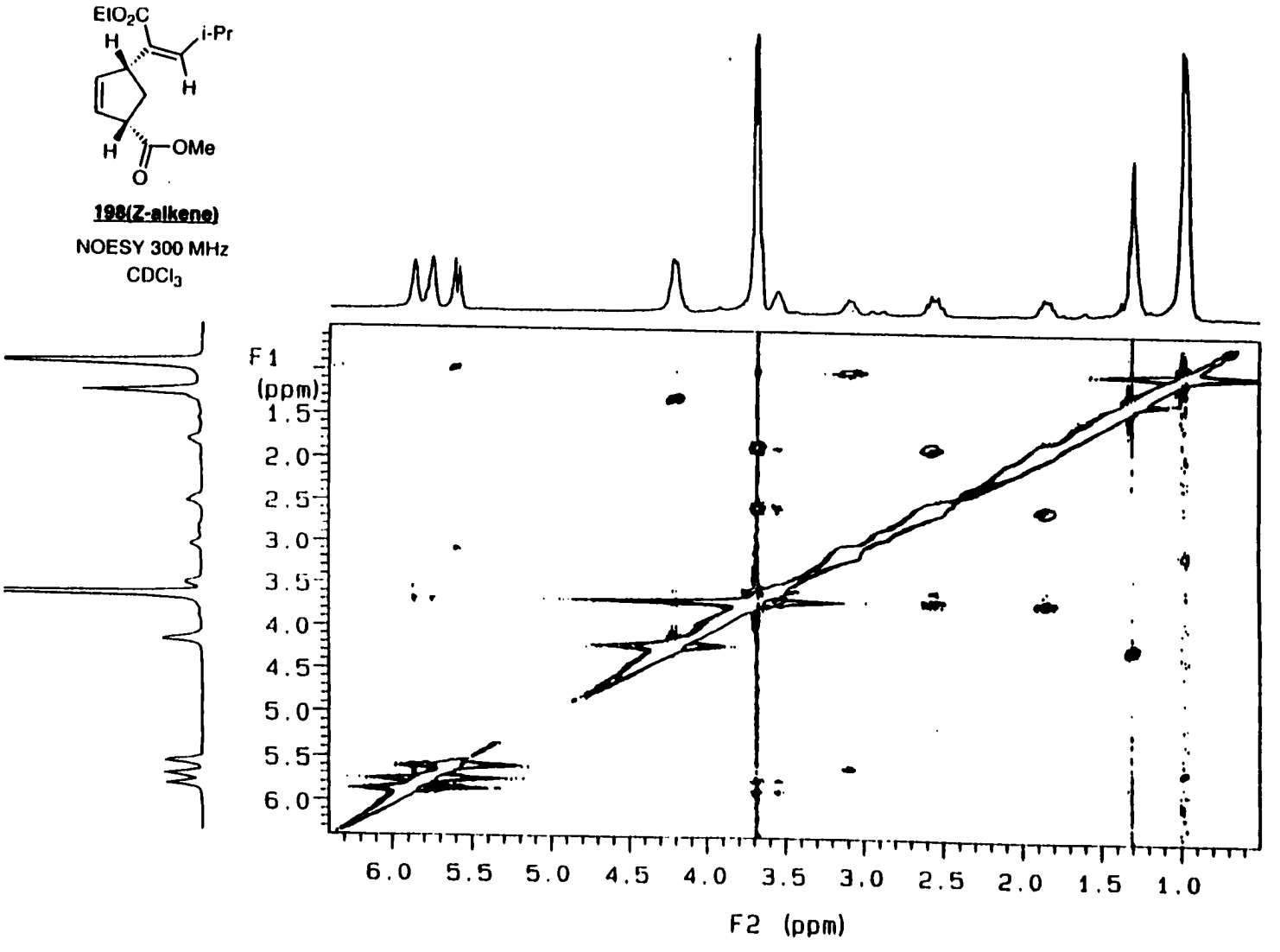
198(Z-alkene)

^{1}H NMR 250 MHz

$CDCl_3$



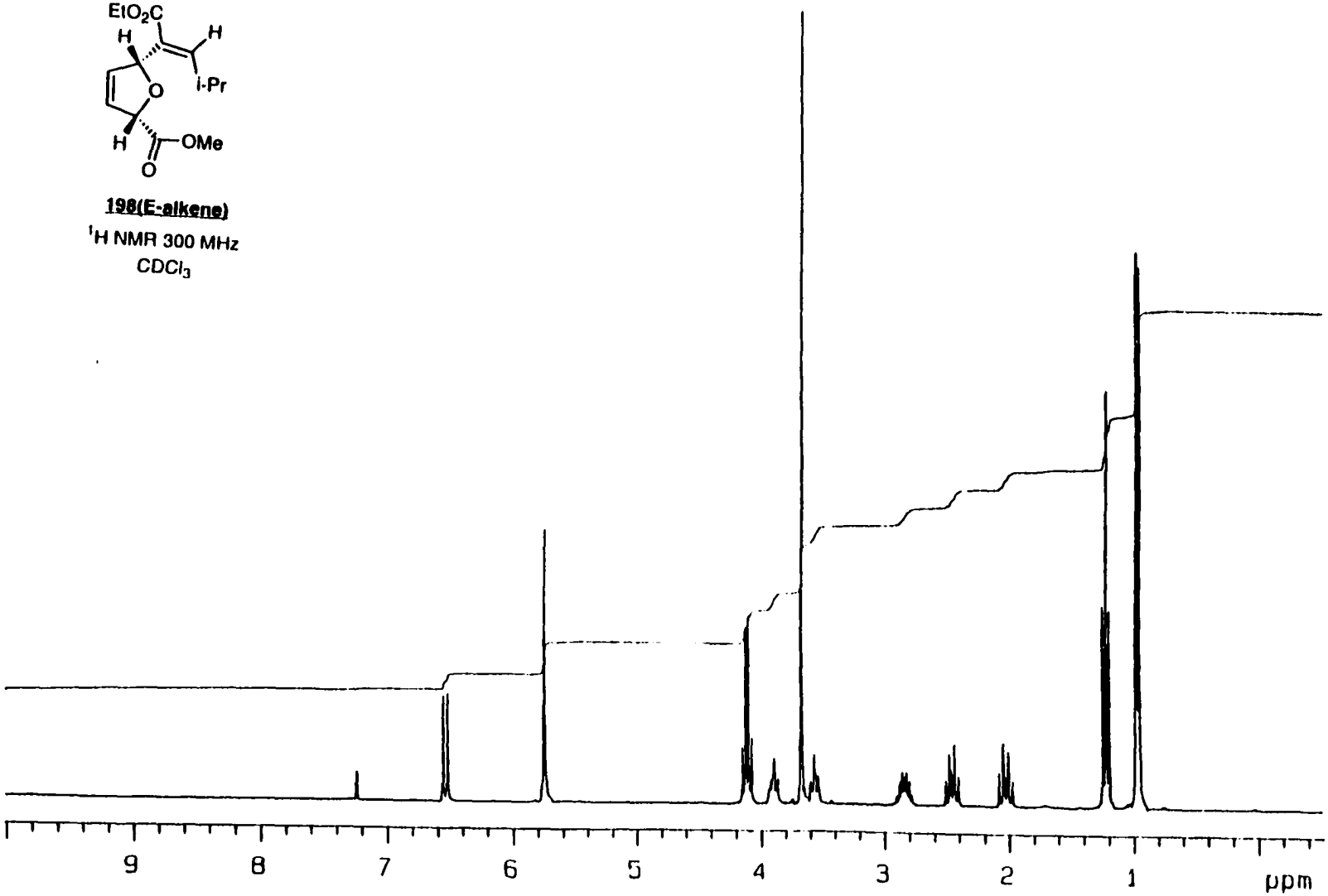

EtO2C
H
i-Pr
H
H
OMe
O
198(Z-alkene)
13C NMR 62.5 MHz
CDCl3
200
180
160
140
120
100
80
60
40
20
PPM


EtO2C
H
i-Pr
H
H
OMe
O
198(Z-alkene)
NOESY 300 MHz
CDCl3
F1
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
F2 (ppm)

198(E-alkene)

^{1}H NMR 300 MHz

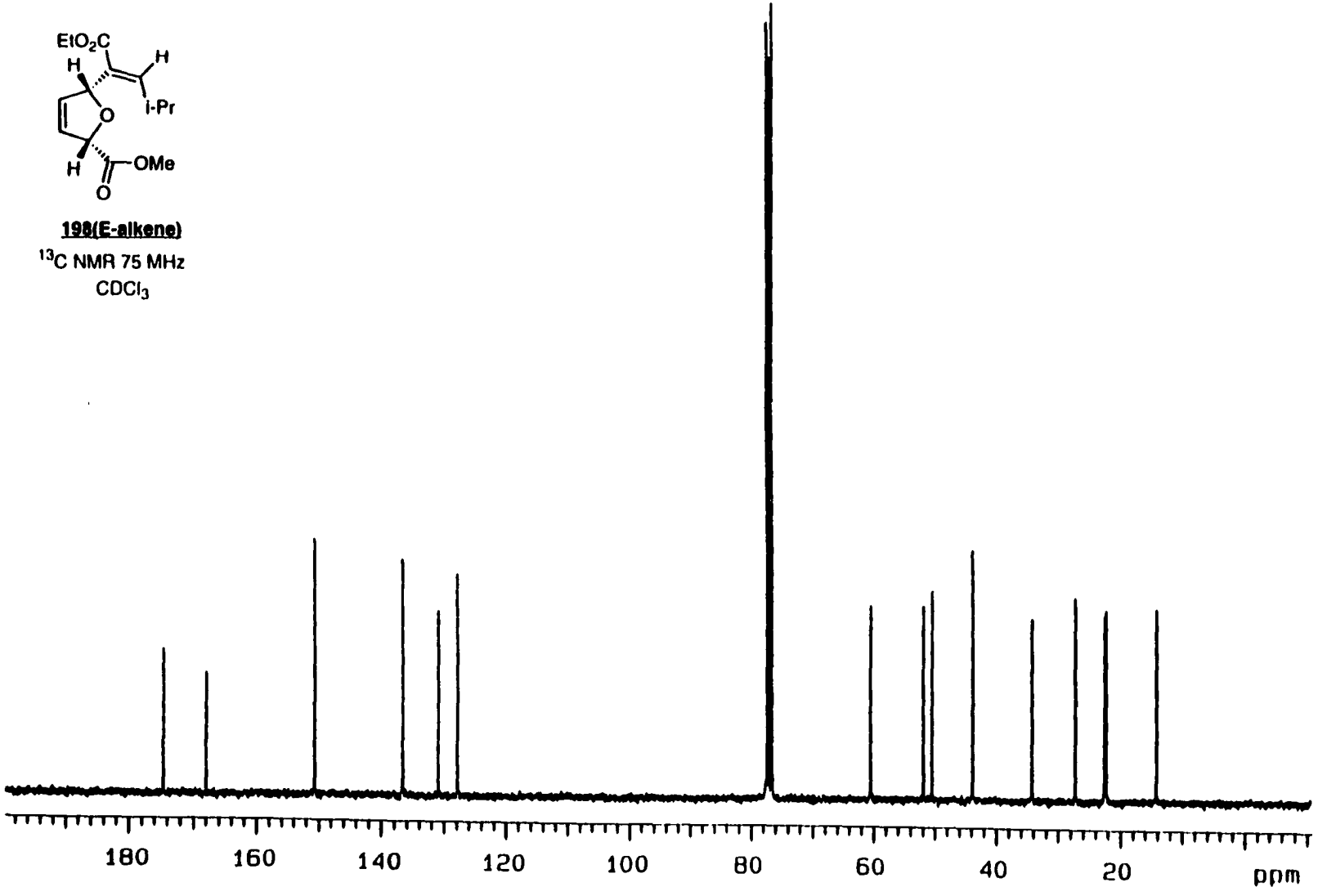
$CDCl_3$

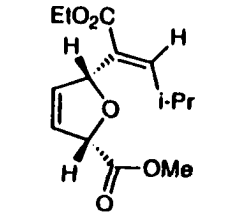


198(E-alkene)

^{13}C NMR 75 MHz

$CDCl_3$

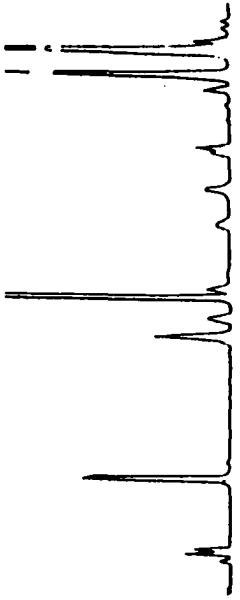


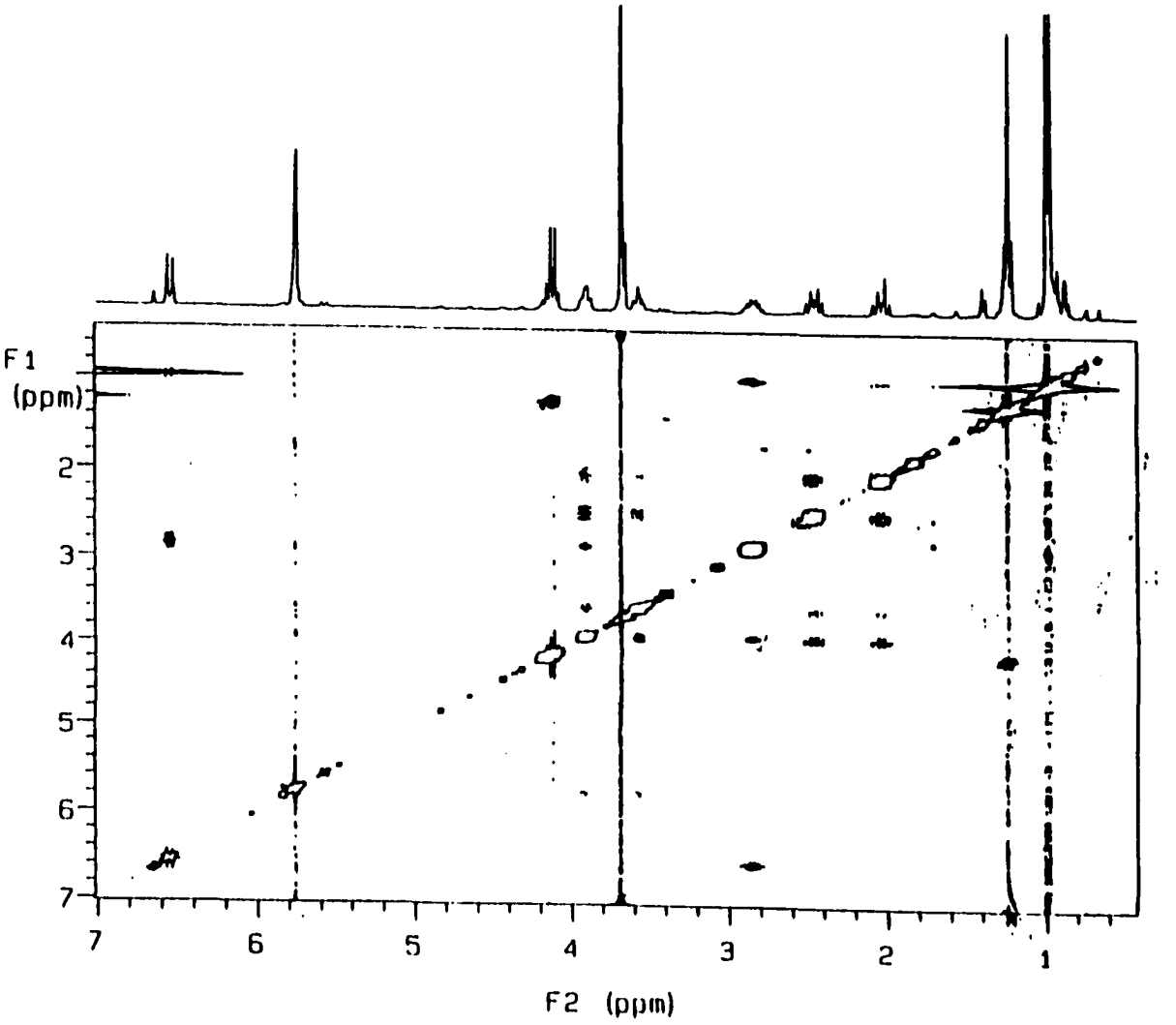


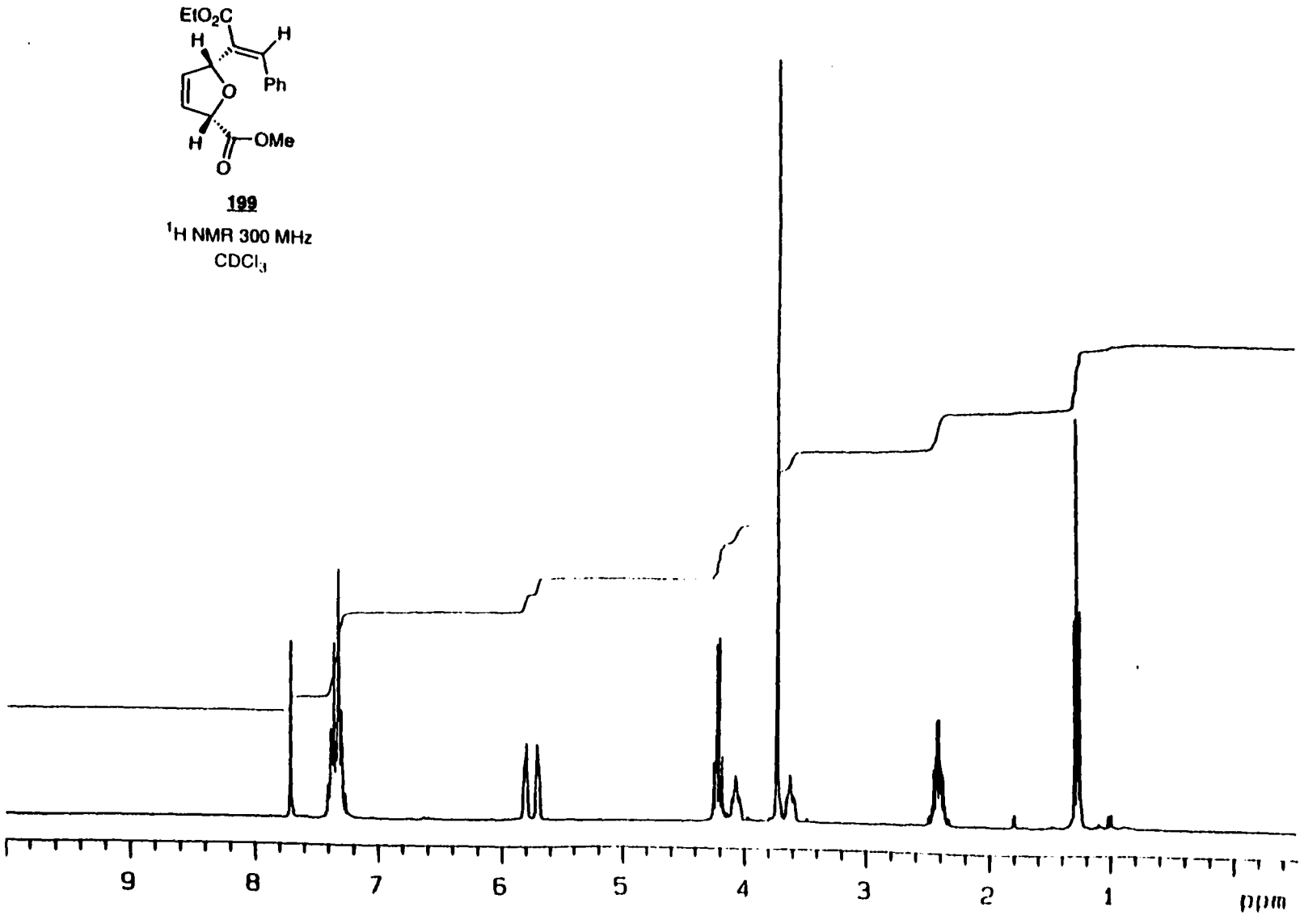
198(E-alkene)

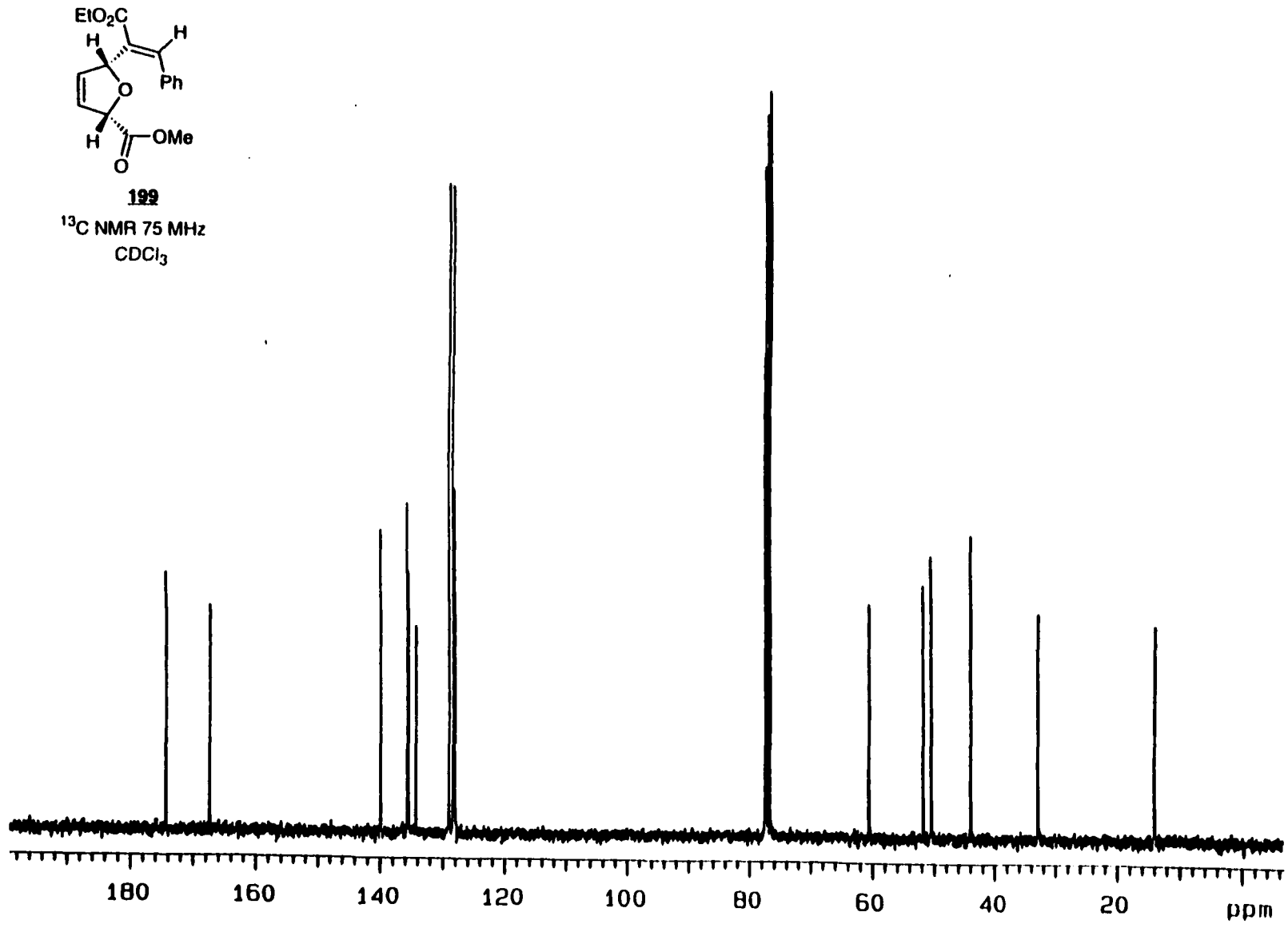
NOESY 300 MHz

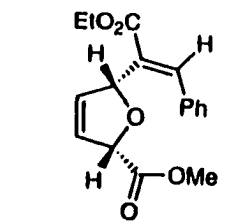
$CDCl_3$






EtO2C
H
H
Ph
O
H
OMe
O
199
1H NMR 300 MHz
CDCl3
9
8
7
6
5
4
3
2
1
ppm

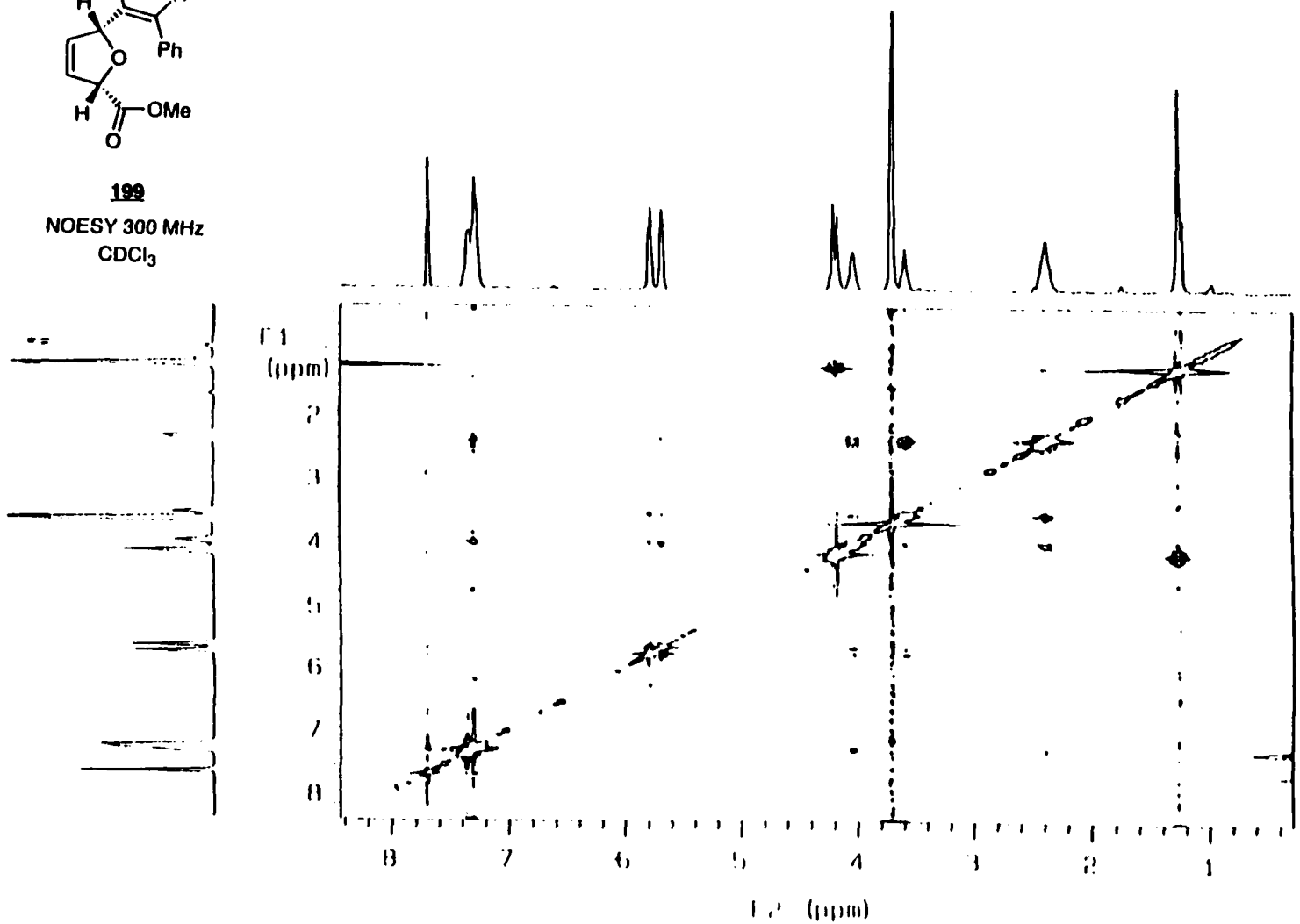

EtO2C
H
H
Ph
O
H
OMe
O
199
13C NMR 75 MHz
CDCl3
180
160
140
120
100
80
60
40
20
ppm



199

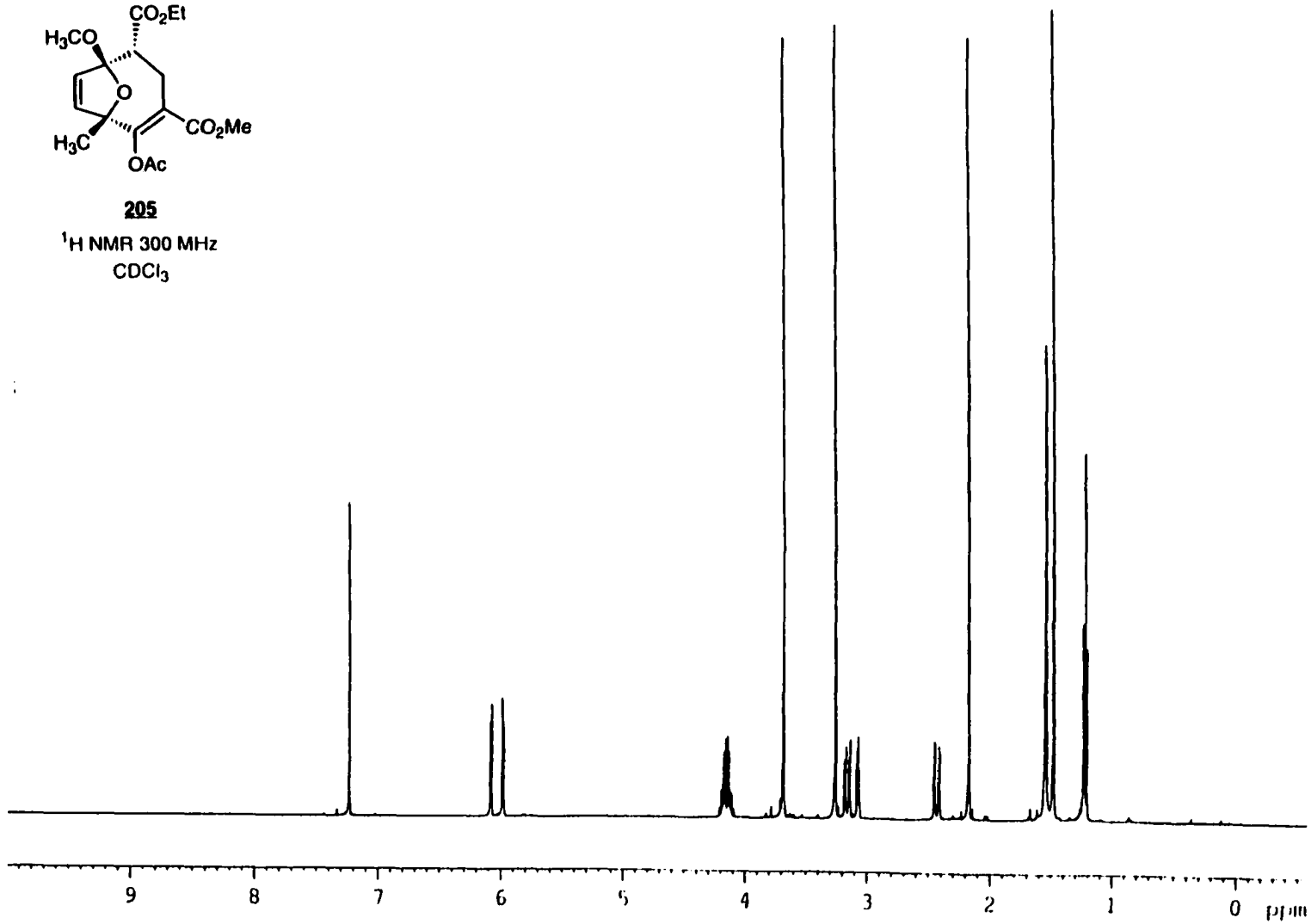
NOESY 300 MHz

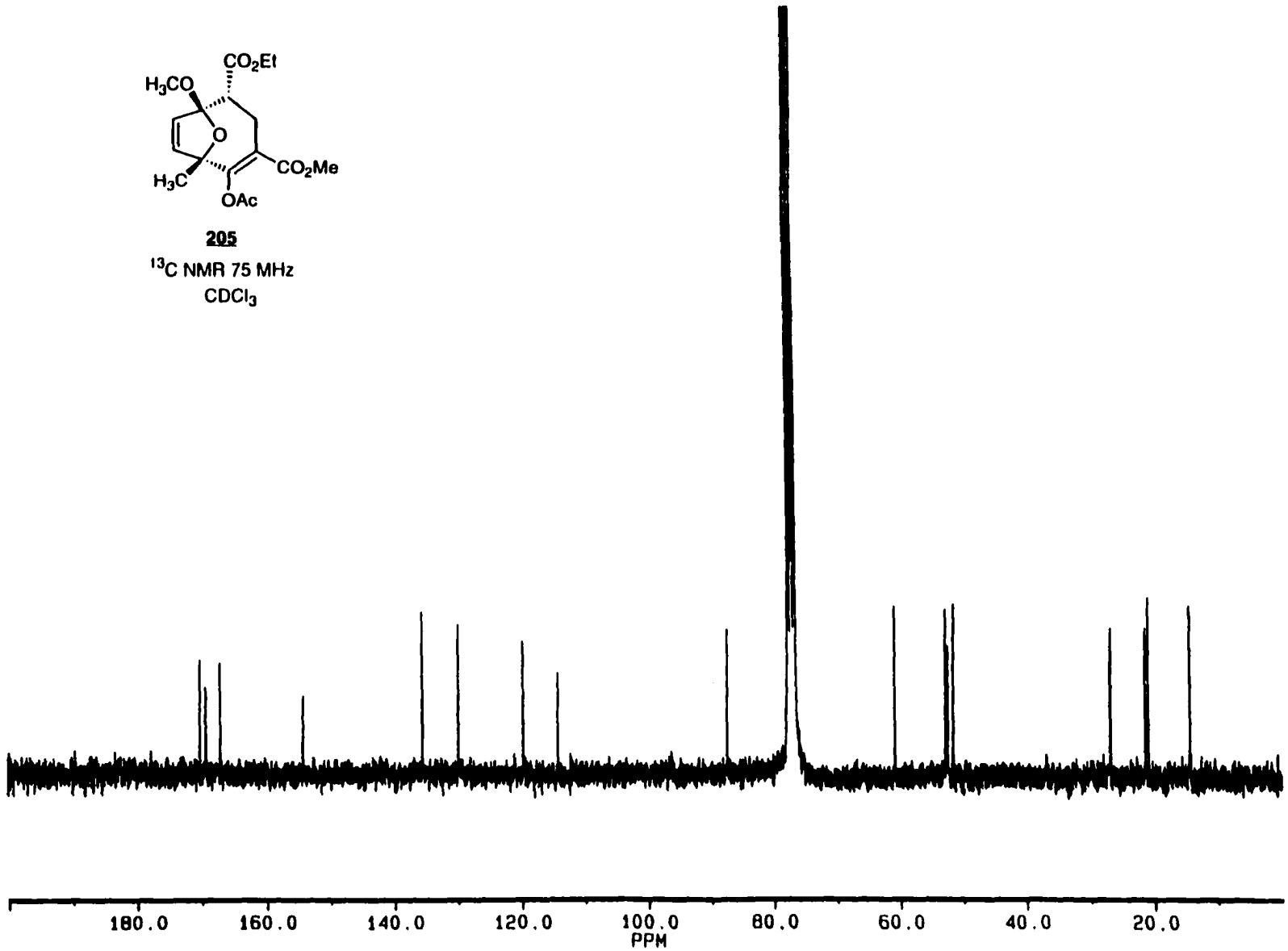
$CDCl_3$

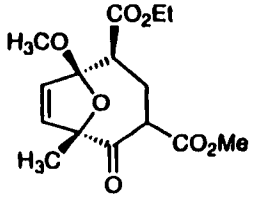


205

^{1}H NMR 300 MHz
$CDCl_3$



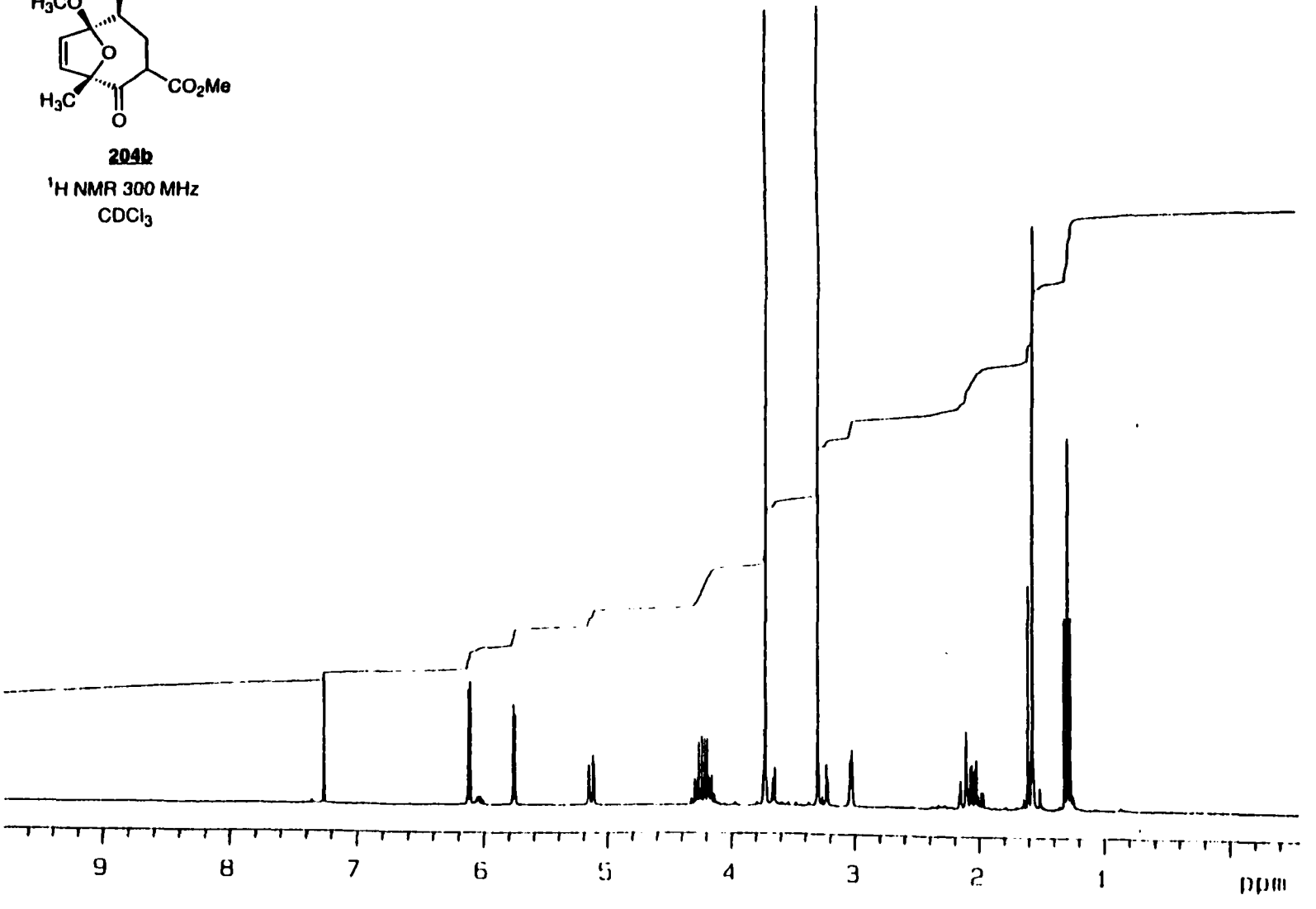

CO2Et
H3CO
O
CO2Me
H3C
OAc
205
13C NMR 75 MHz
CDCl3
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
PPM



204b

^{1}H NMR 300 MHz

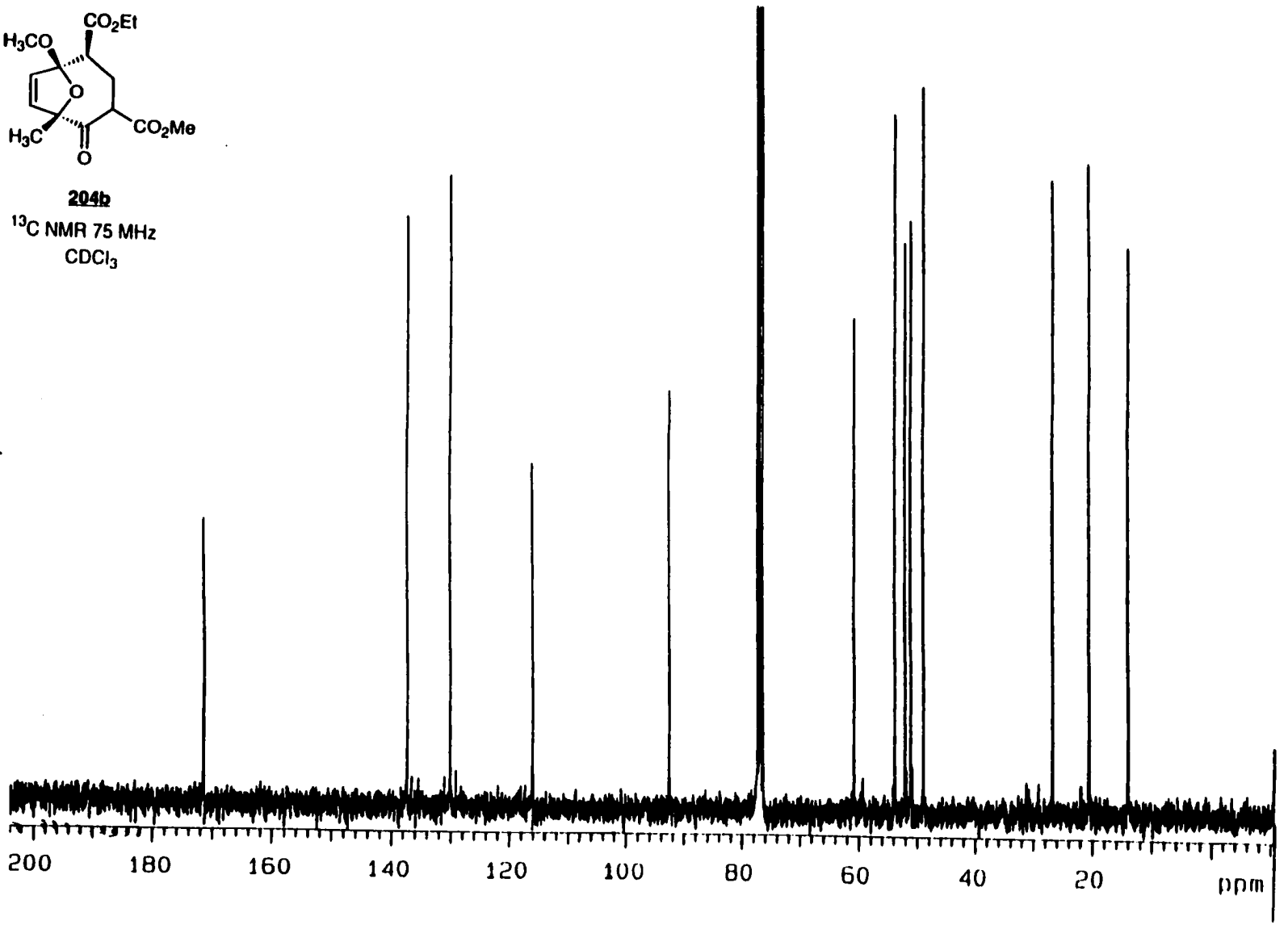
$CDCl_3$

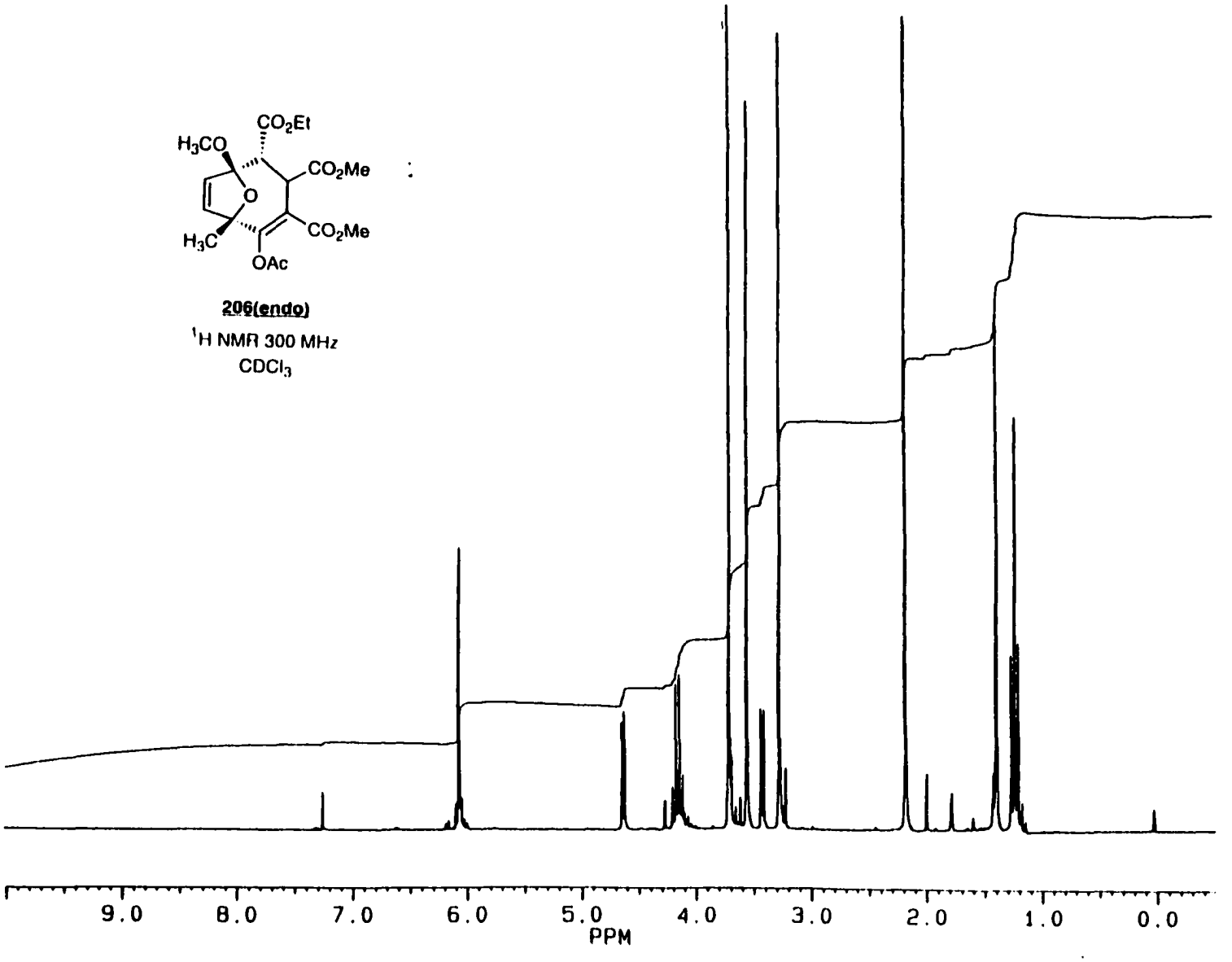


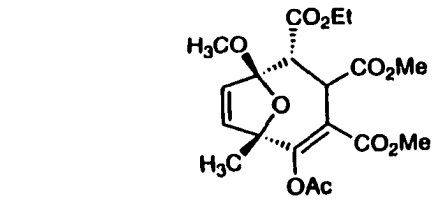
204b

^{13}C NMR 75 MHz

$CDCl_3$



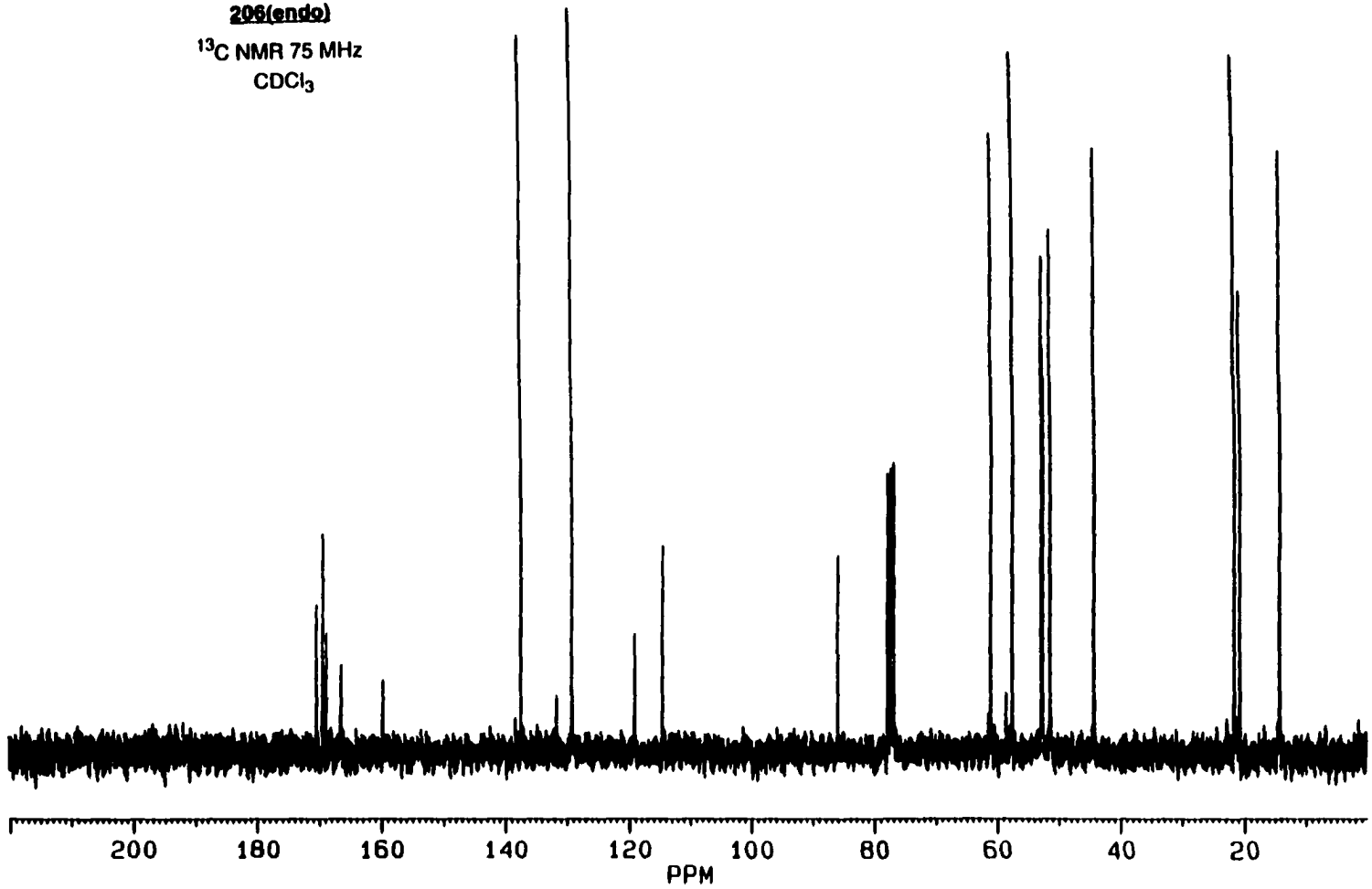

CO2Et
H3CO
CO2Me
O
CO2Me
H3C
OAc
206(endo)
1H NMR 300 MHz
CDCl3
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

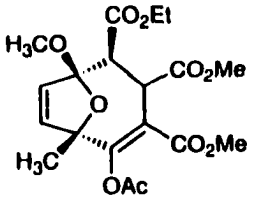


206(endo)

^{13}C NMR 75 MHz

$CDCl_3$

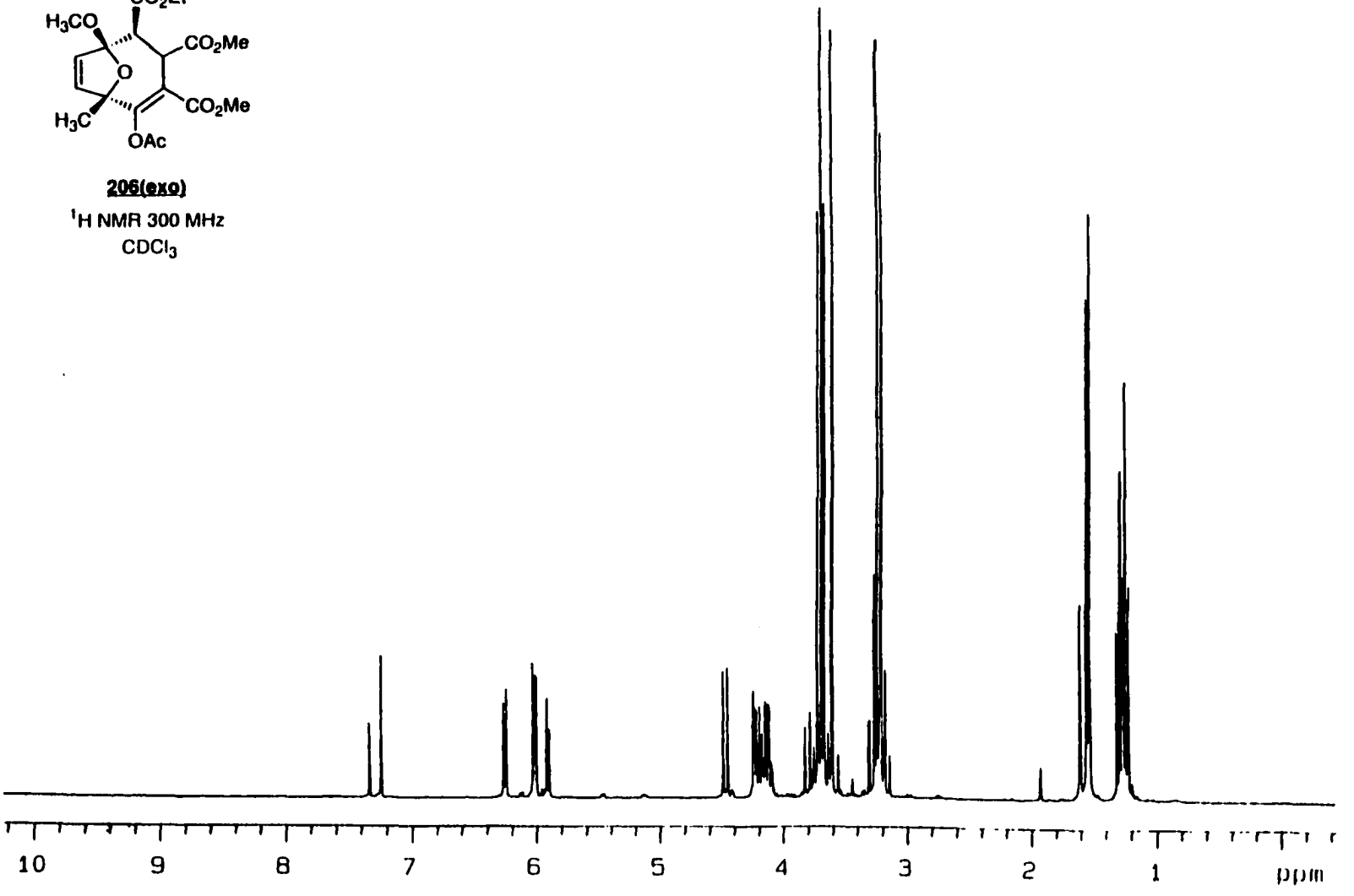




206(exo)

^{1}H NMR 300 MHz

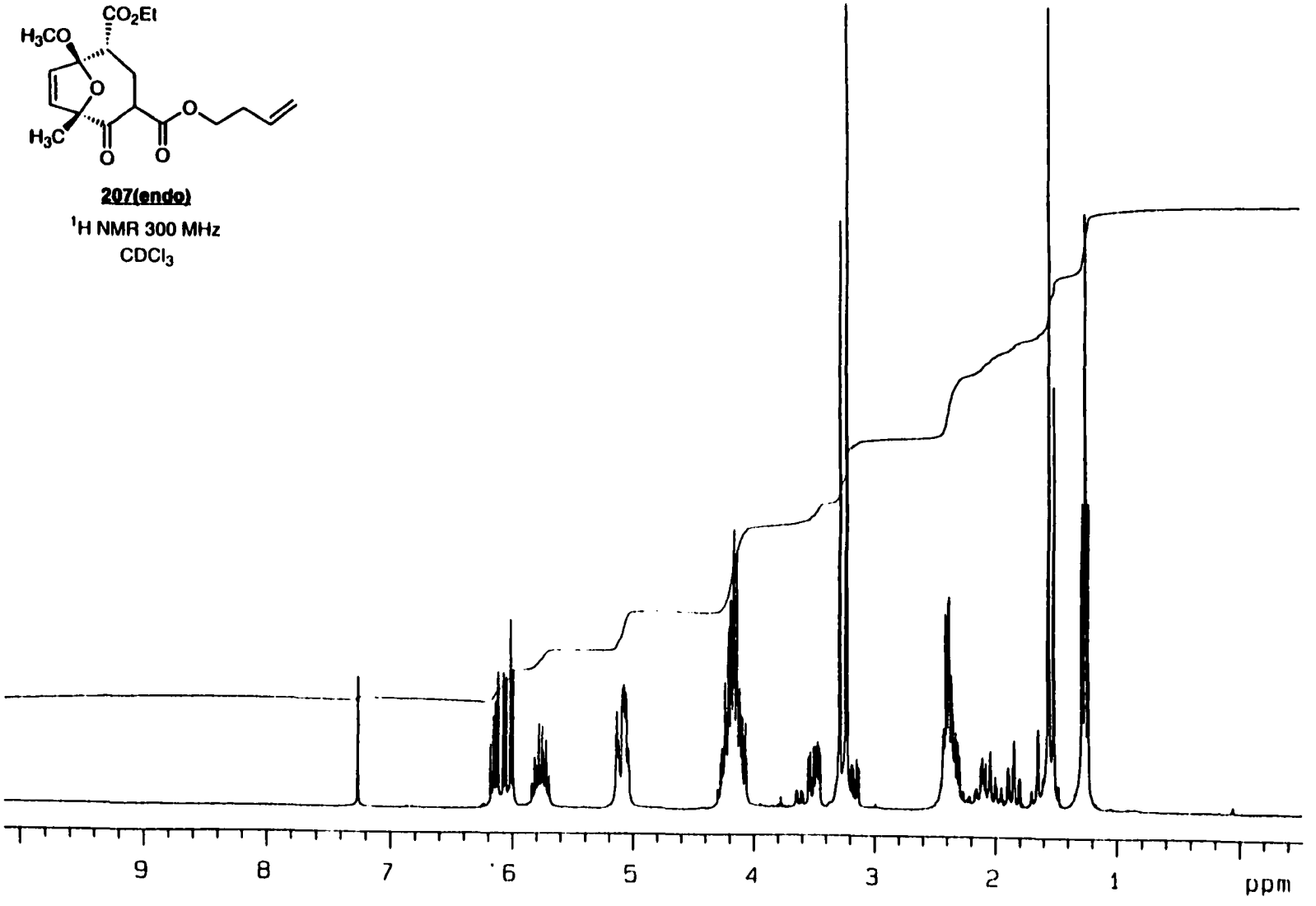
$CDCl_3$



207(endo)

^{1}H NMR 300 MHz

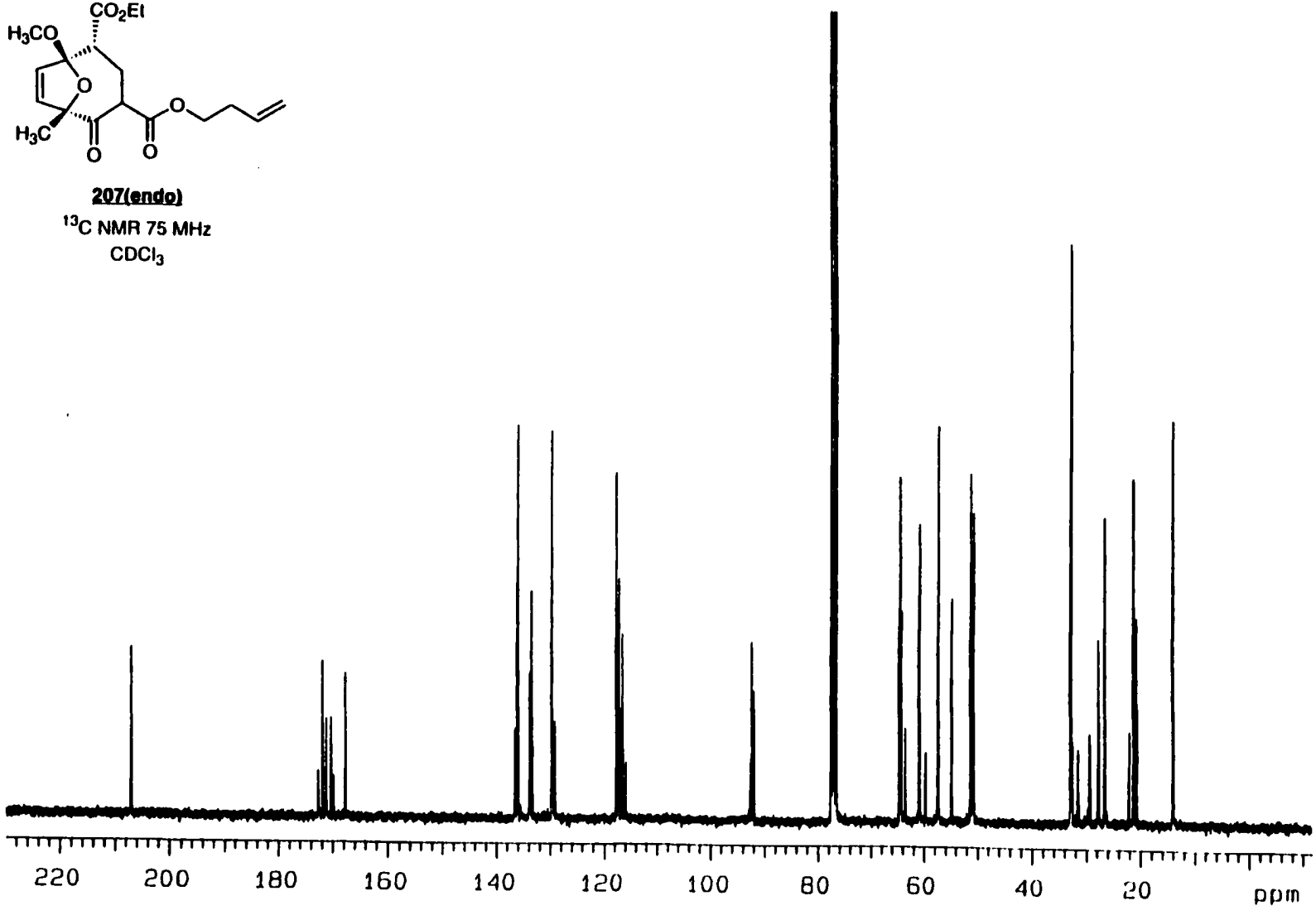
$CDCl_3$

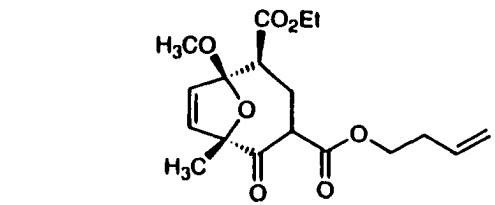


207(endo)

^{13}C NMR 75 MHz

$CDCl_3$

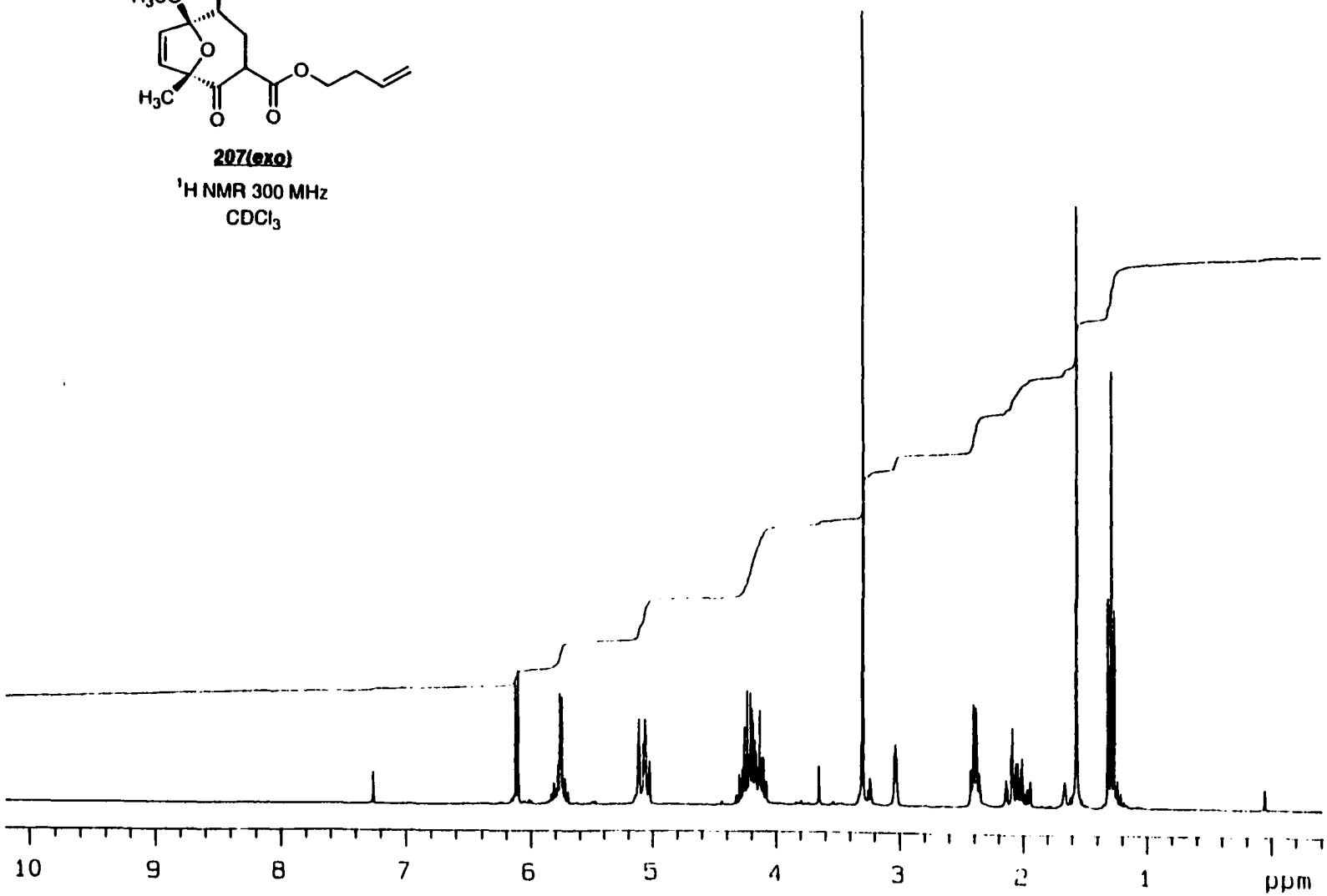


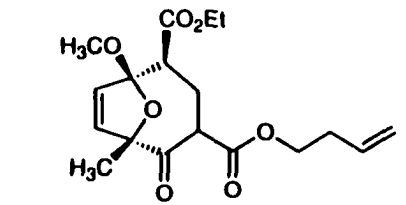


207(exo)

^{1}H NMR 300 MHz

$CDCl_3$

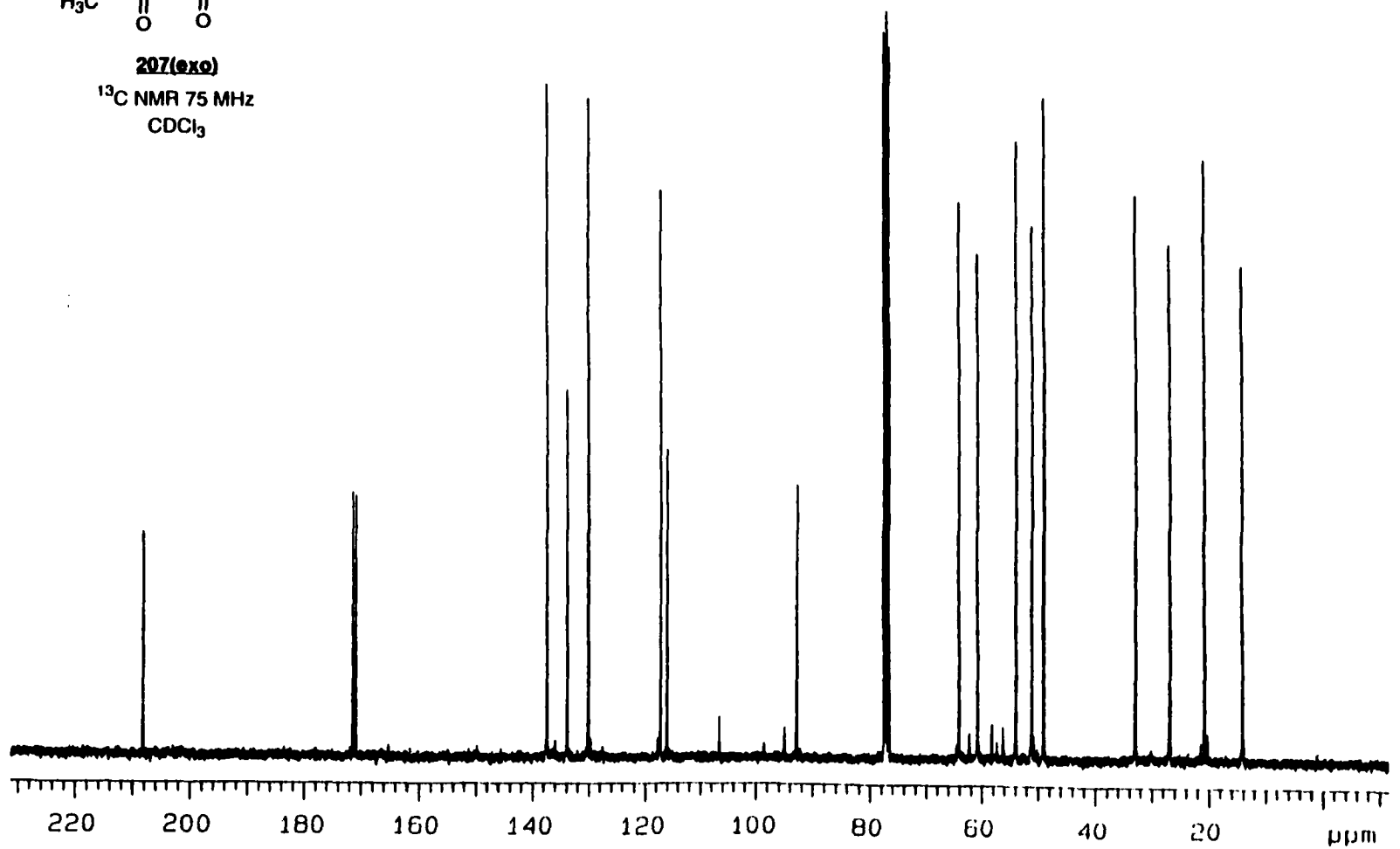




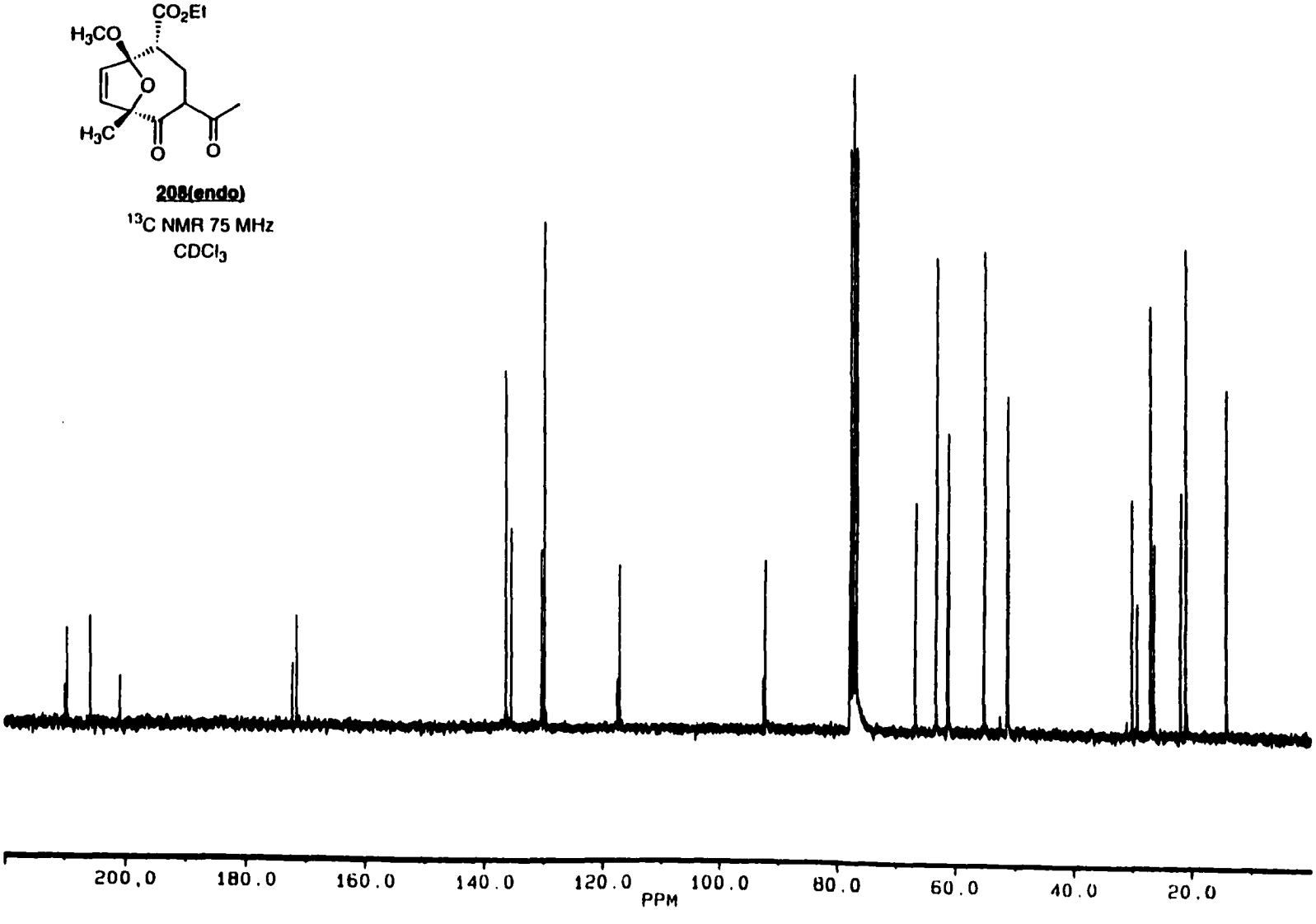
207(exo)

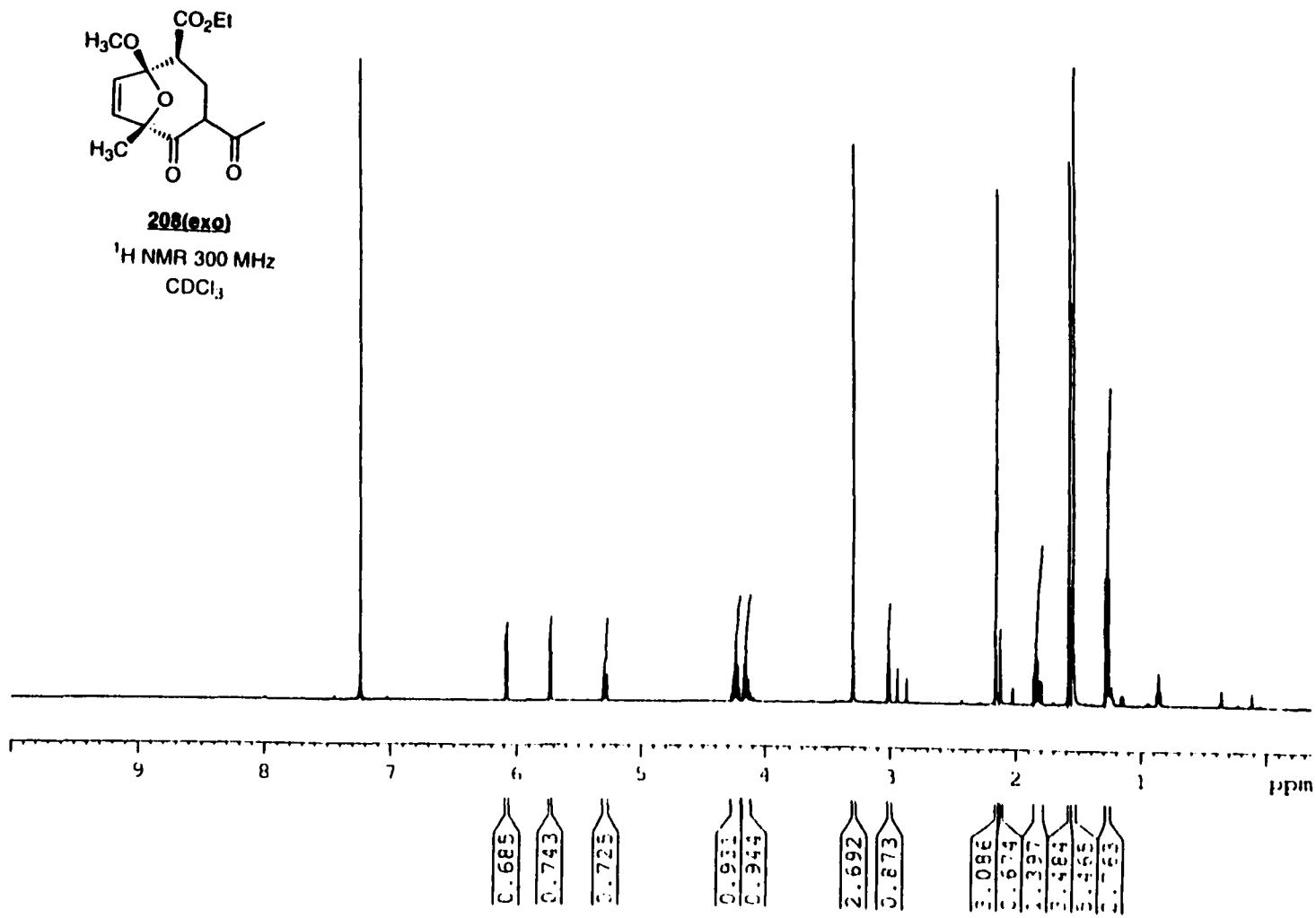
^{13}C NMR 75 MHz

$CDCl_3$



208(endo)
^{1}H NMR 300 MHz
$CDCl_3$
H_3C
H_3CO
CO_2Et
O
O
O
1.012
0.713
0.329
3.343
0.322
0.400
2.847
1.306
0.768
0.269
0.288
1.389
0.783
1.626
0.727
1.604
3.440
3.917
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

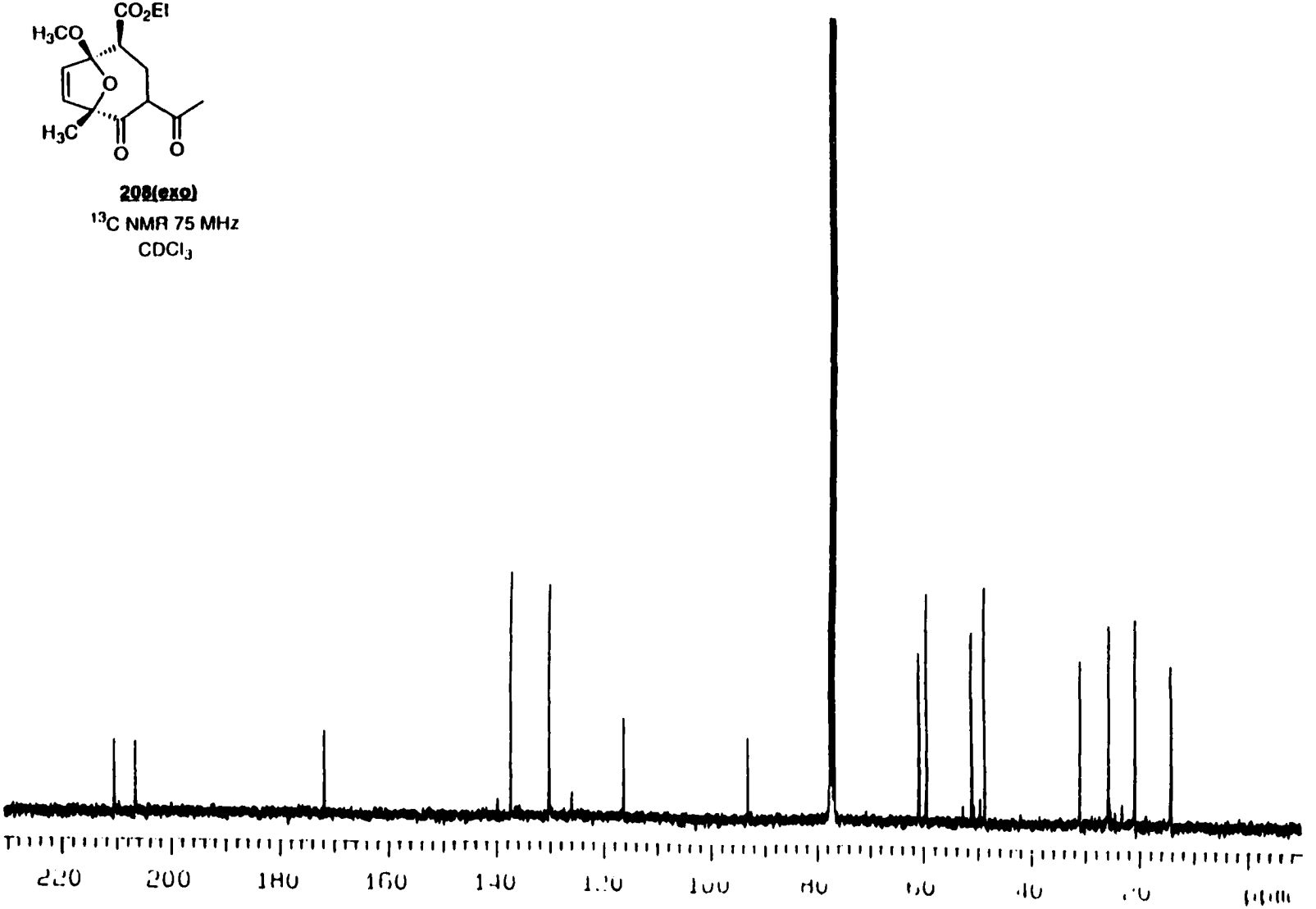

CO2Et
H3CO
O
H3C
O
O
208(endo)
13C NMR 75 MHz
CDCl3
200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
PPM

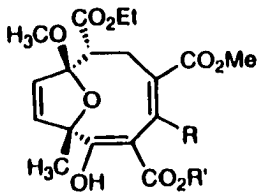

CO2Et
H3CO
O
H3C
O
O
208(exo)
1H NMR 300 MHz
CDCl3
9
8
7
6
5
4
3
2
1
ppm
0.685
0.743
0.725
0.933
0.344
2.692
0.873
3.085
2.674
1.397
3.484
3.465
2.463

208(exo)

^{13}C NMR 75 MHz

$CDCl_3$

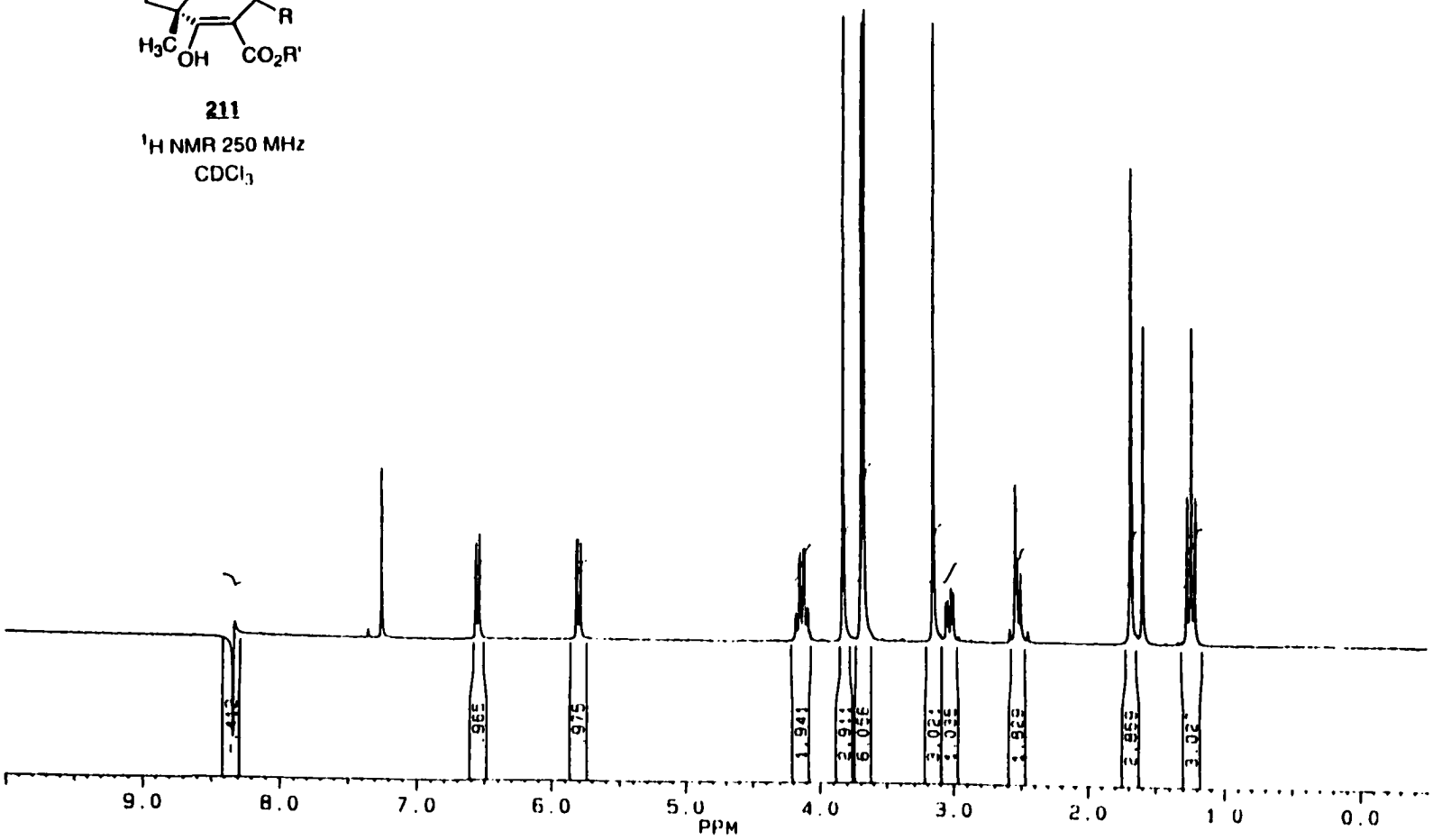




211

^{1}H NMR 250 MHz

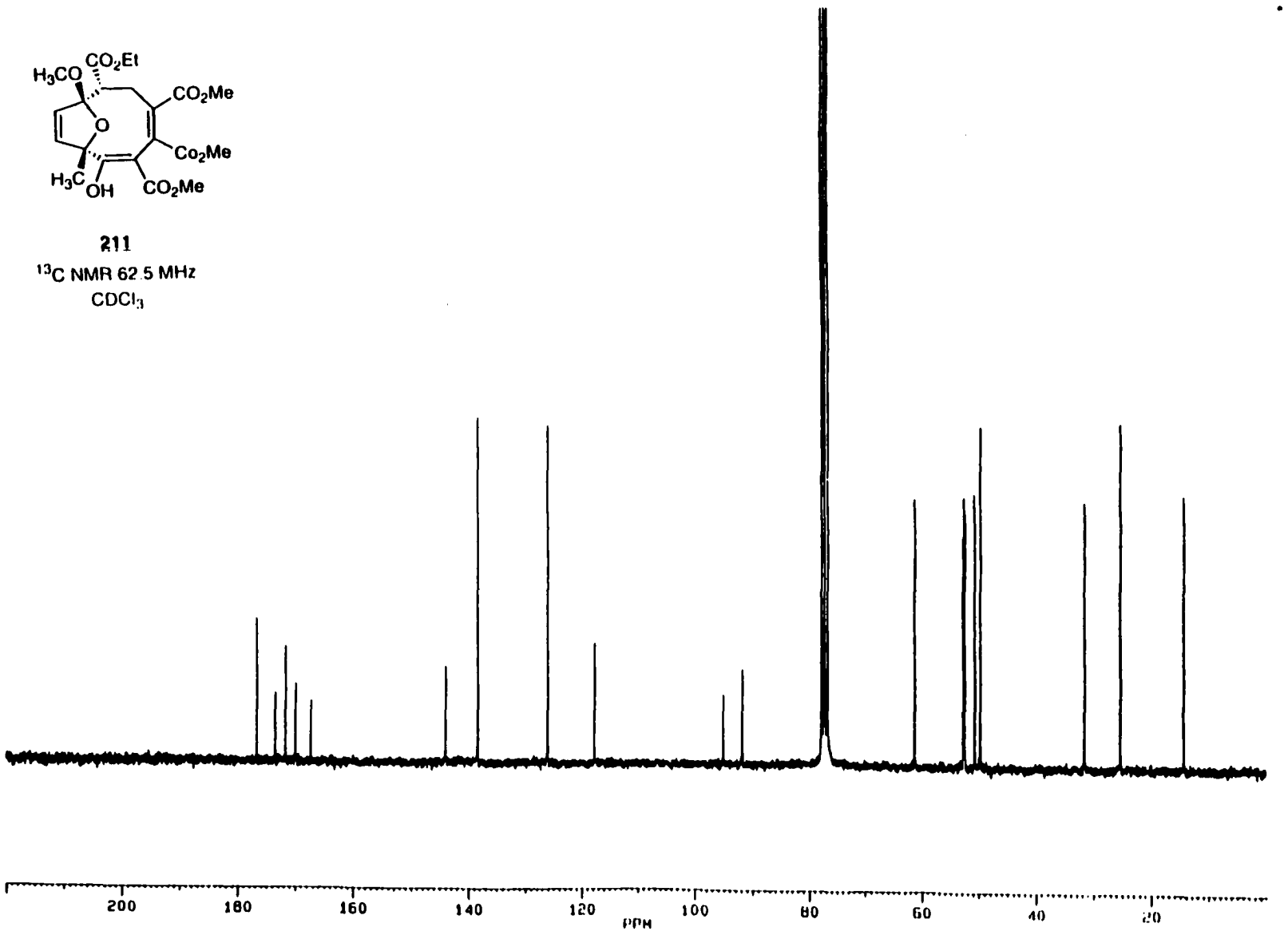
$CDCl_3$



211

^{13}C NMR 62.5 MHz

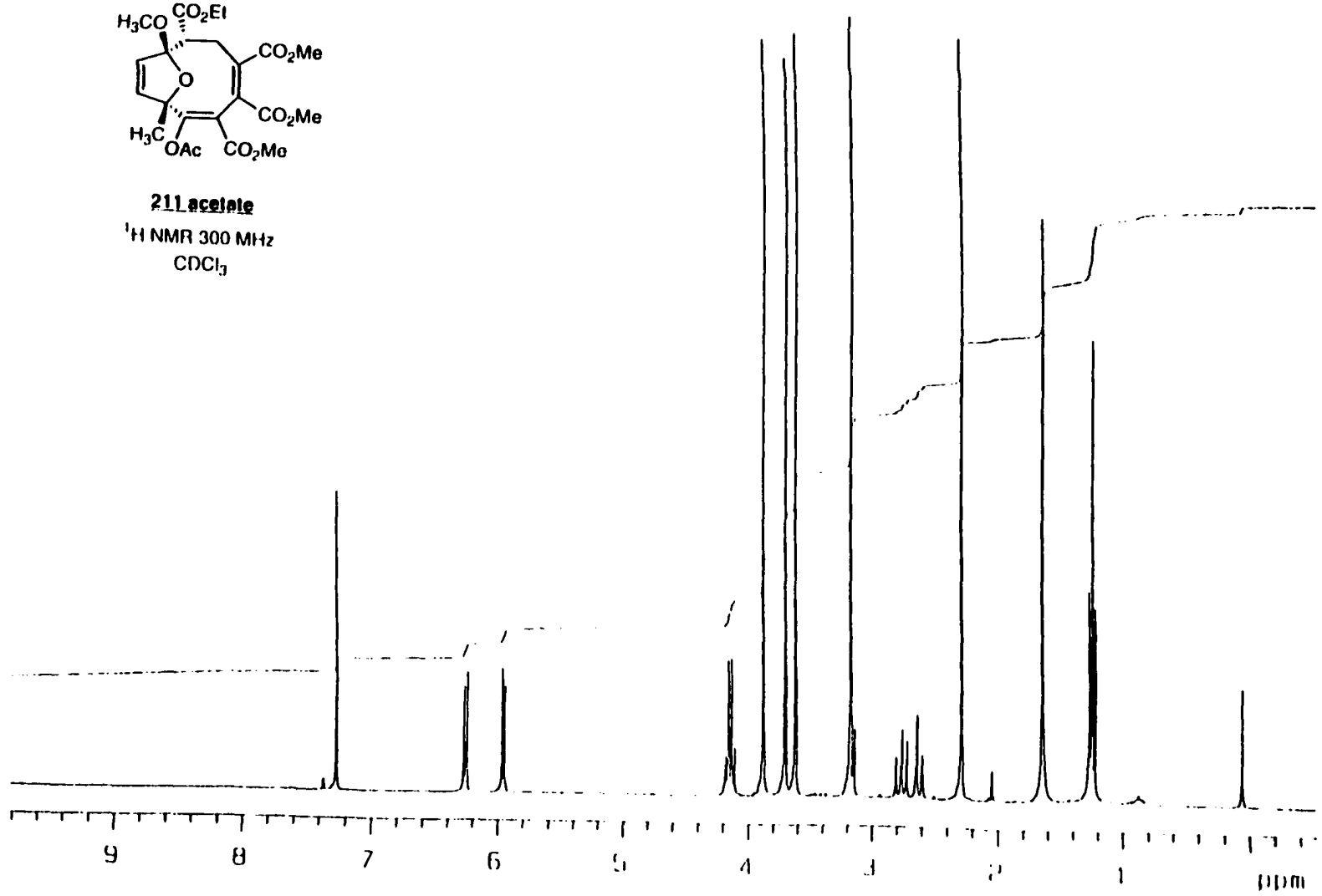
$CDCl_3$

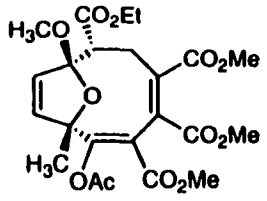


211 acetate

^{1}H NMR 300 MHz

$CDCl_3$

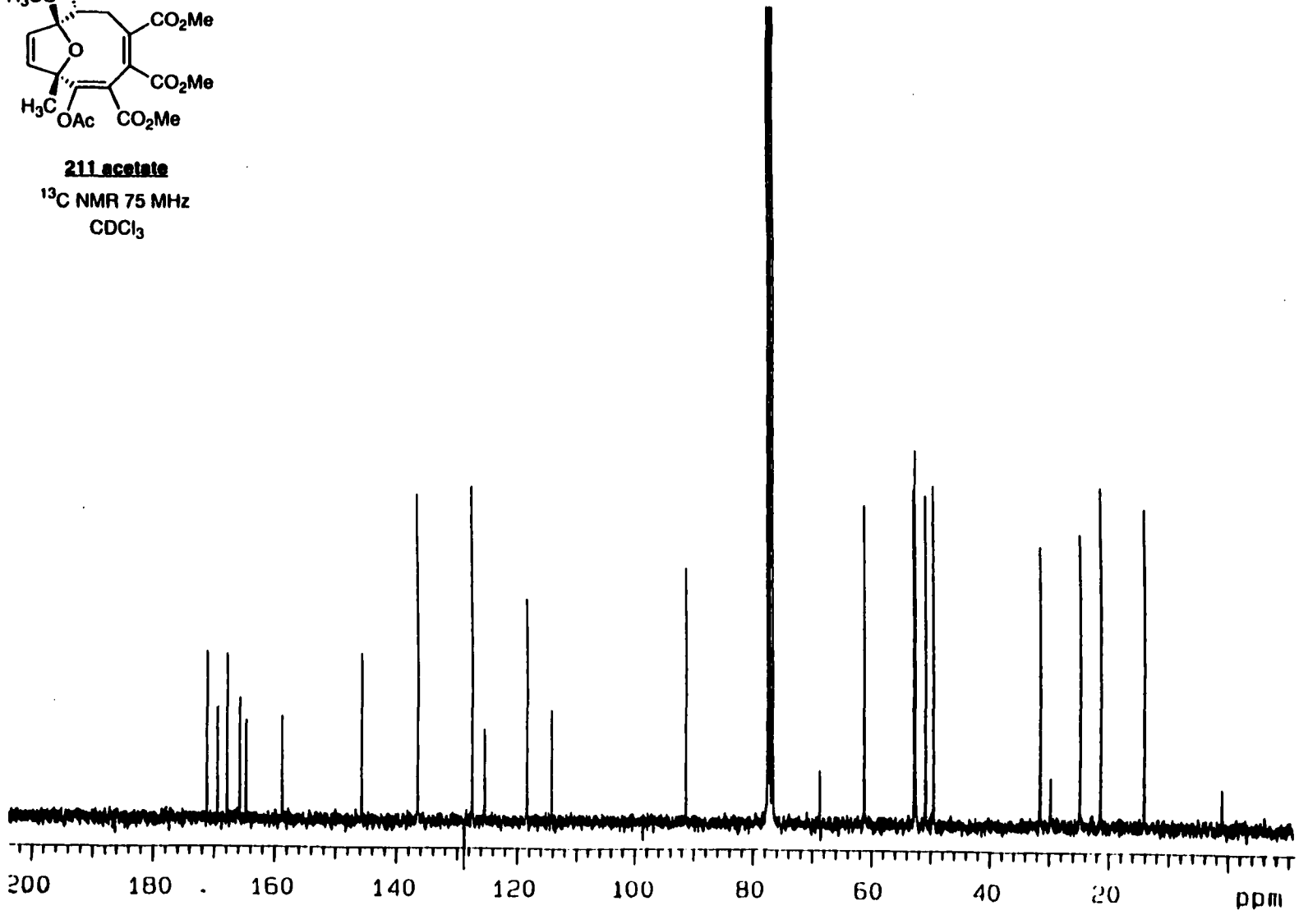


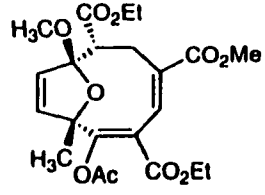


211 acetate

^{13}C NMR 75 MHz

$CDCl_3$

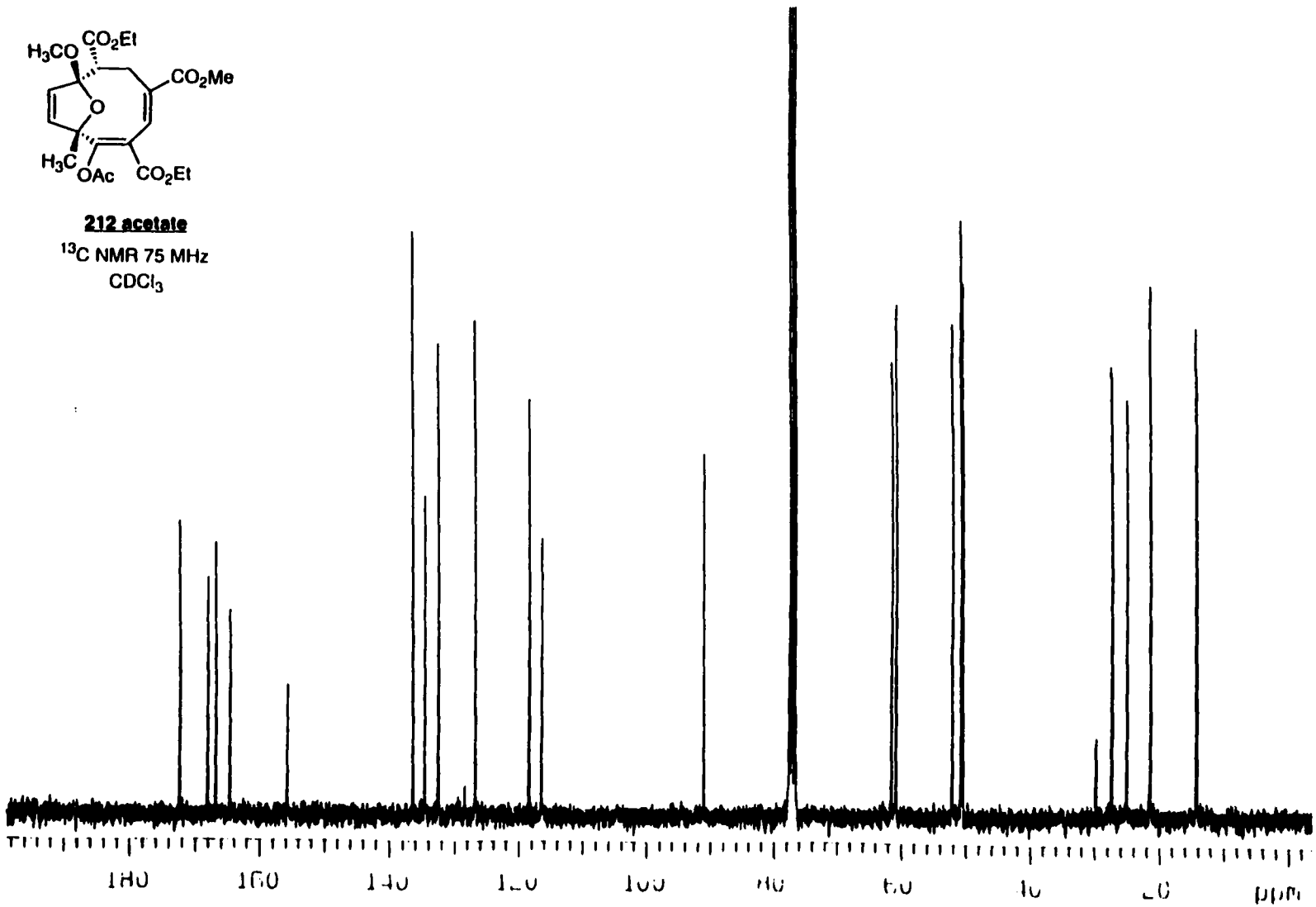


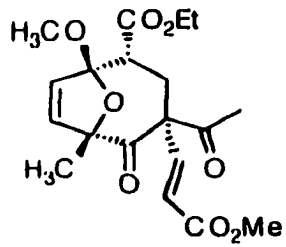


212 acetate

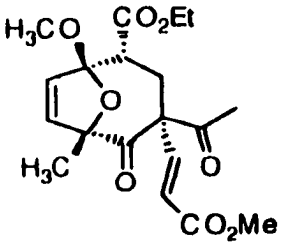
^{1}H NMR 300 MHz

$CDCl_3$

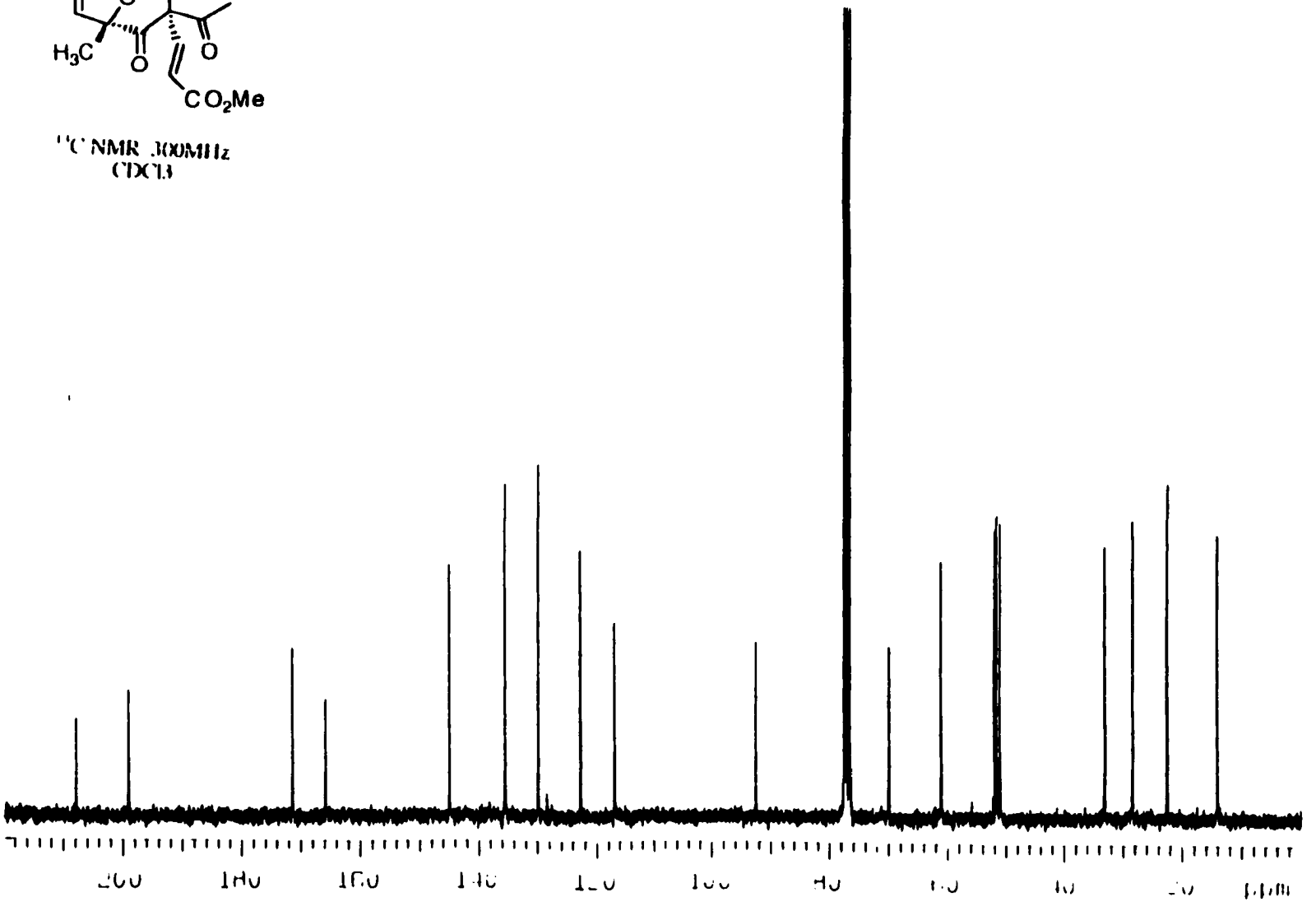

H3CO
CO2Et
CO2Me
O
H3C
OAc
CO2Et
212 acetate
13C NMR 75 MHz
CDCl3
180
160
140
120
100
80
60
40
20
ppm



^{1}H NMR 300MHz
$CDCl_3$

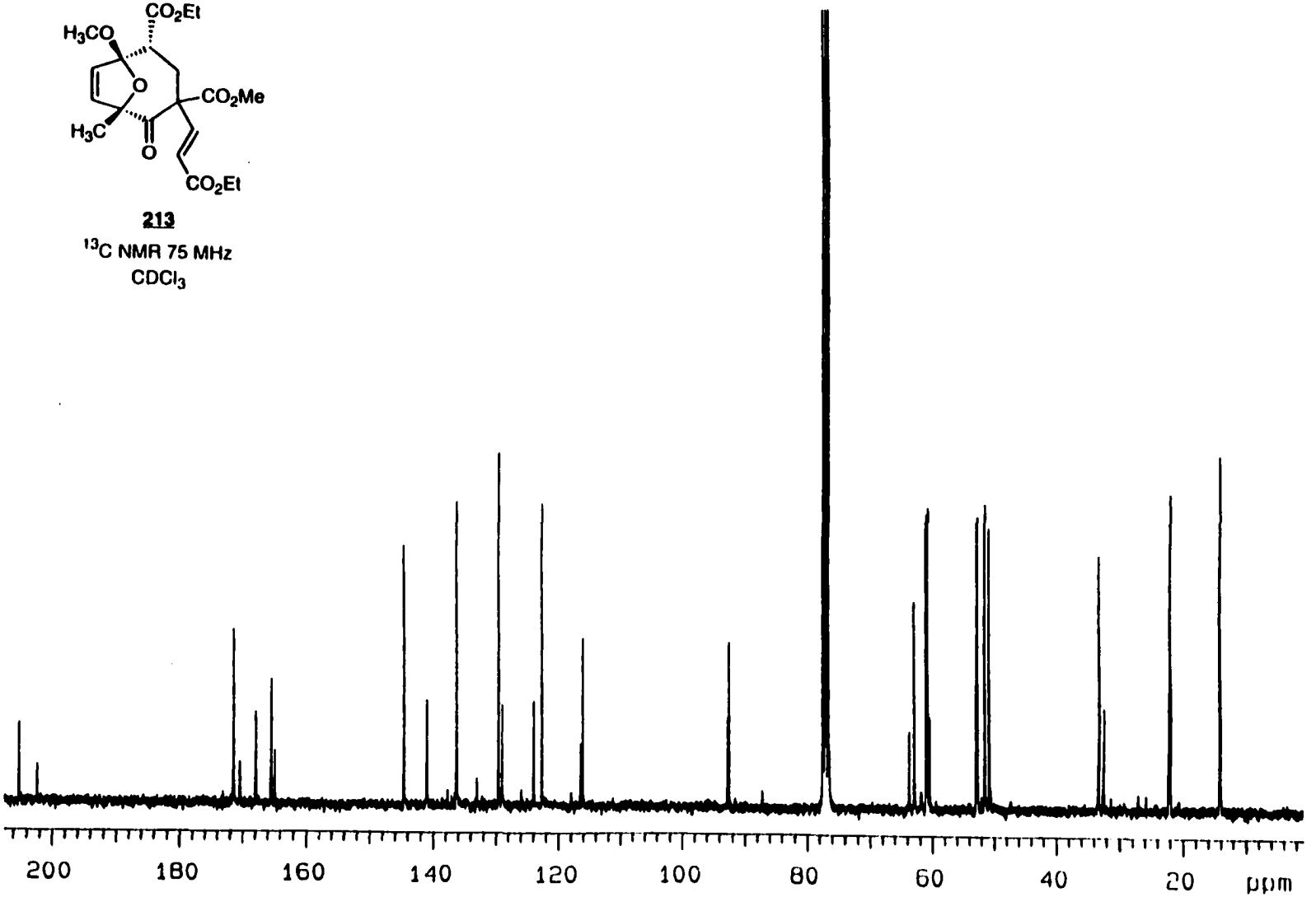


^{13}C NMR 300MHz
$CDCl_3$



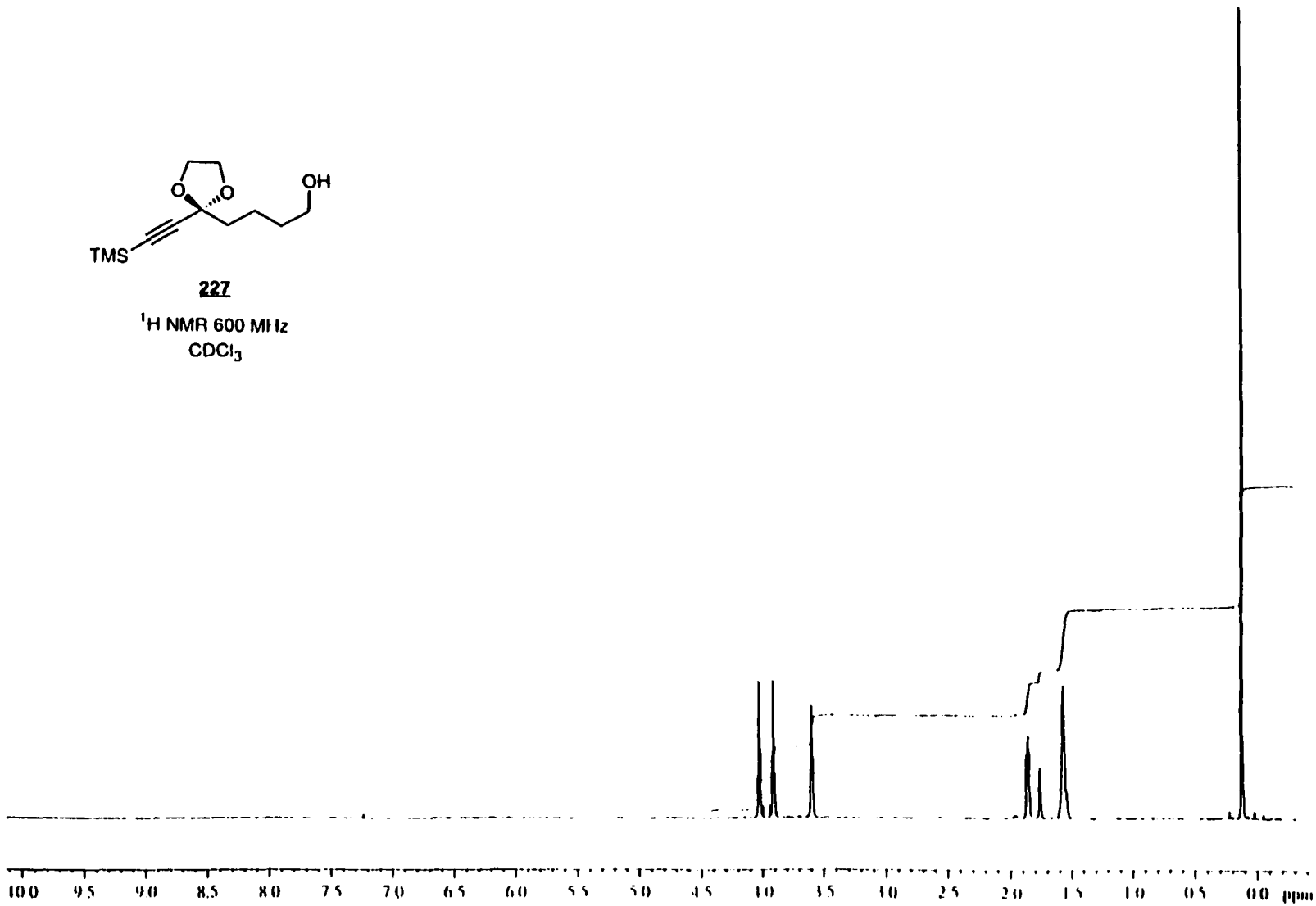
213

^{13}C NMR 75 MHz
$CDCl_3$



227

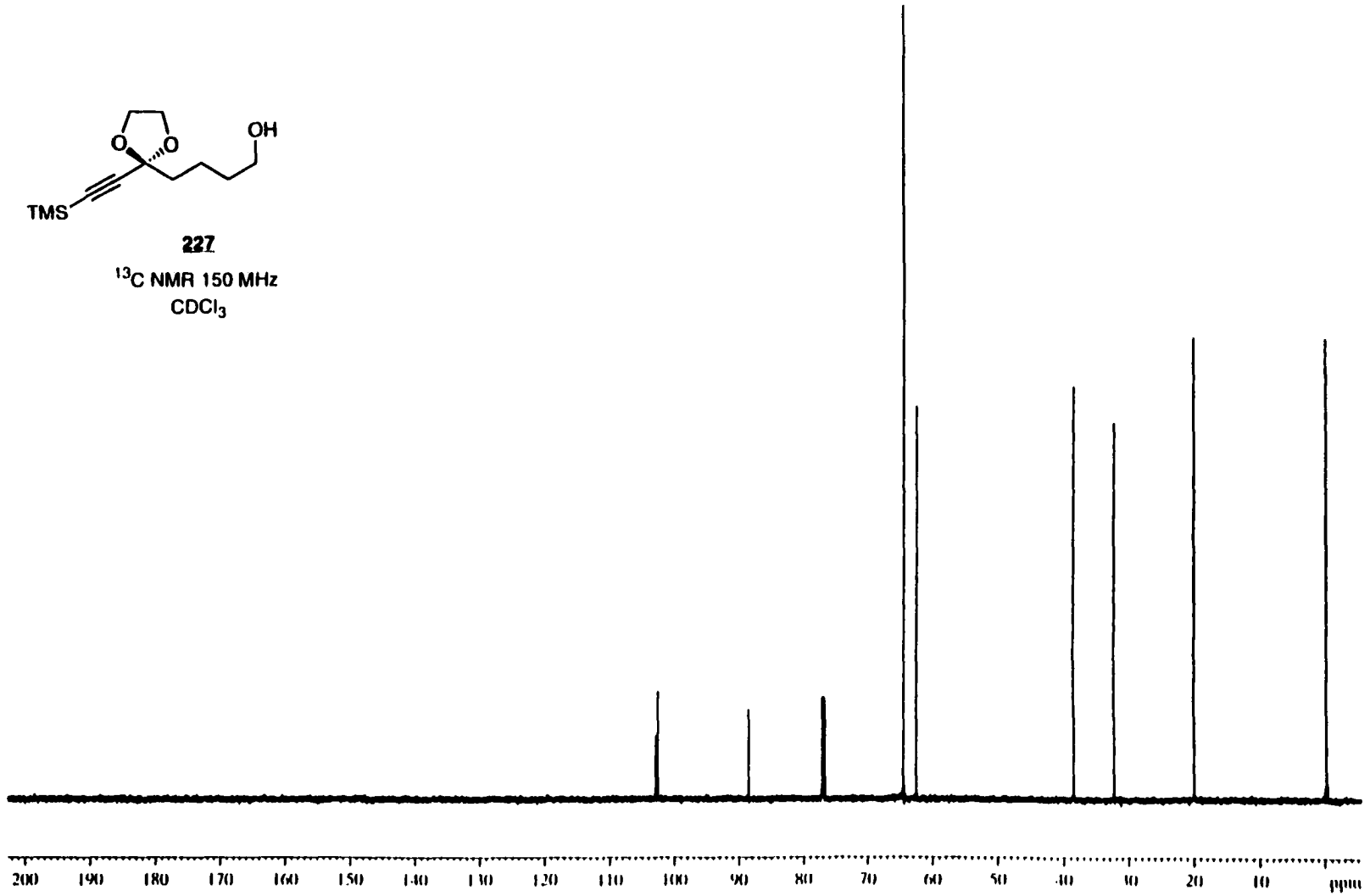
^{1}H NMR 600 MHz
$CDCl_3$



227

^{13}C NMR 150 MHz

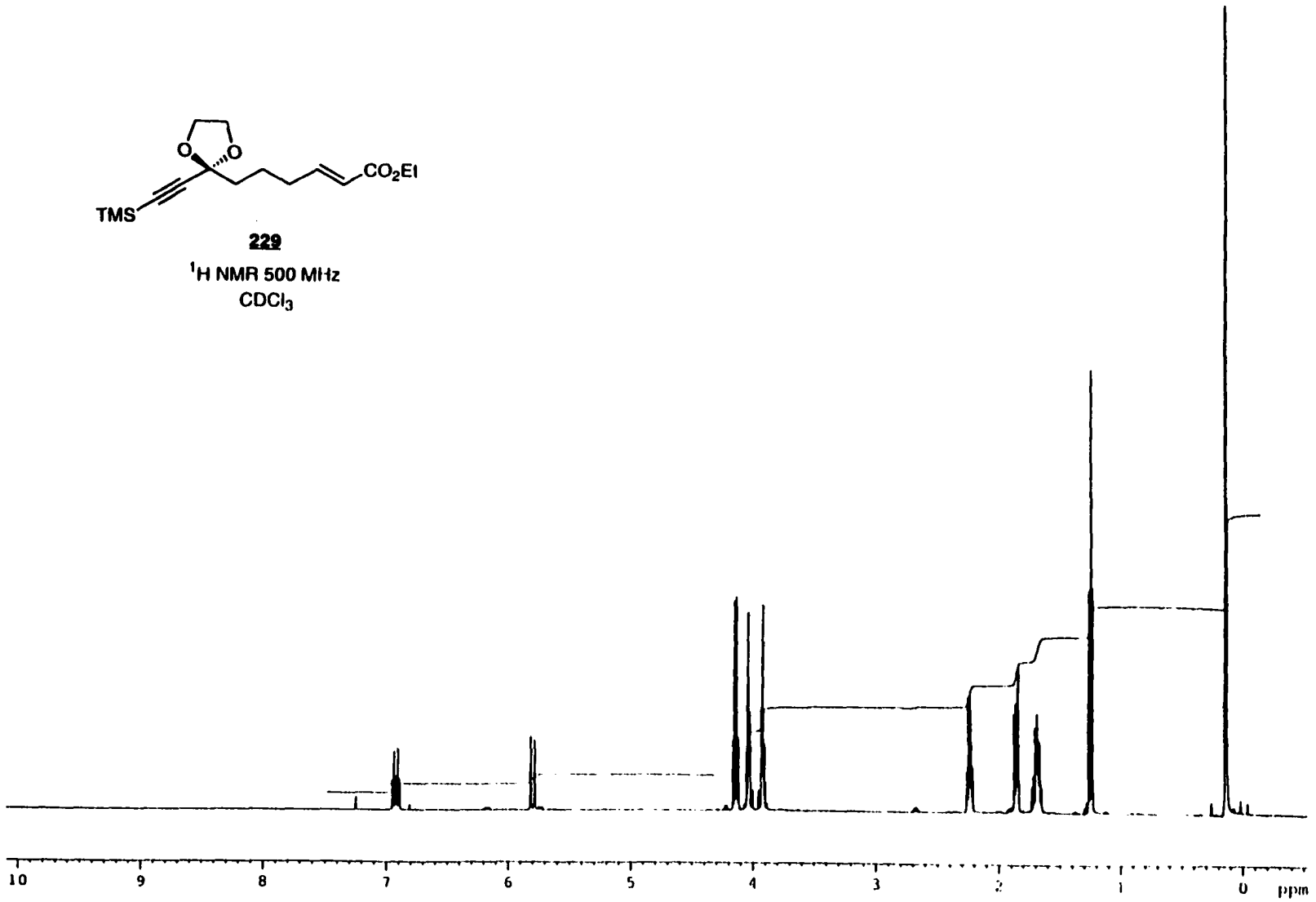
$CDCl_3$



229

^{1}H NMR 500 MHz

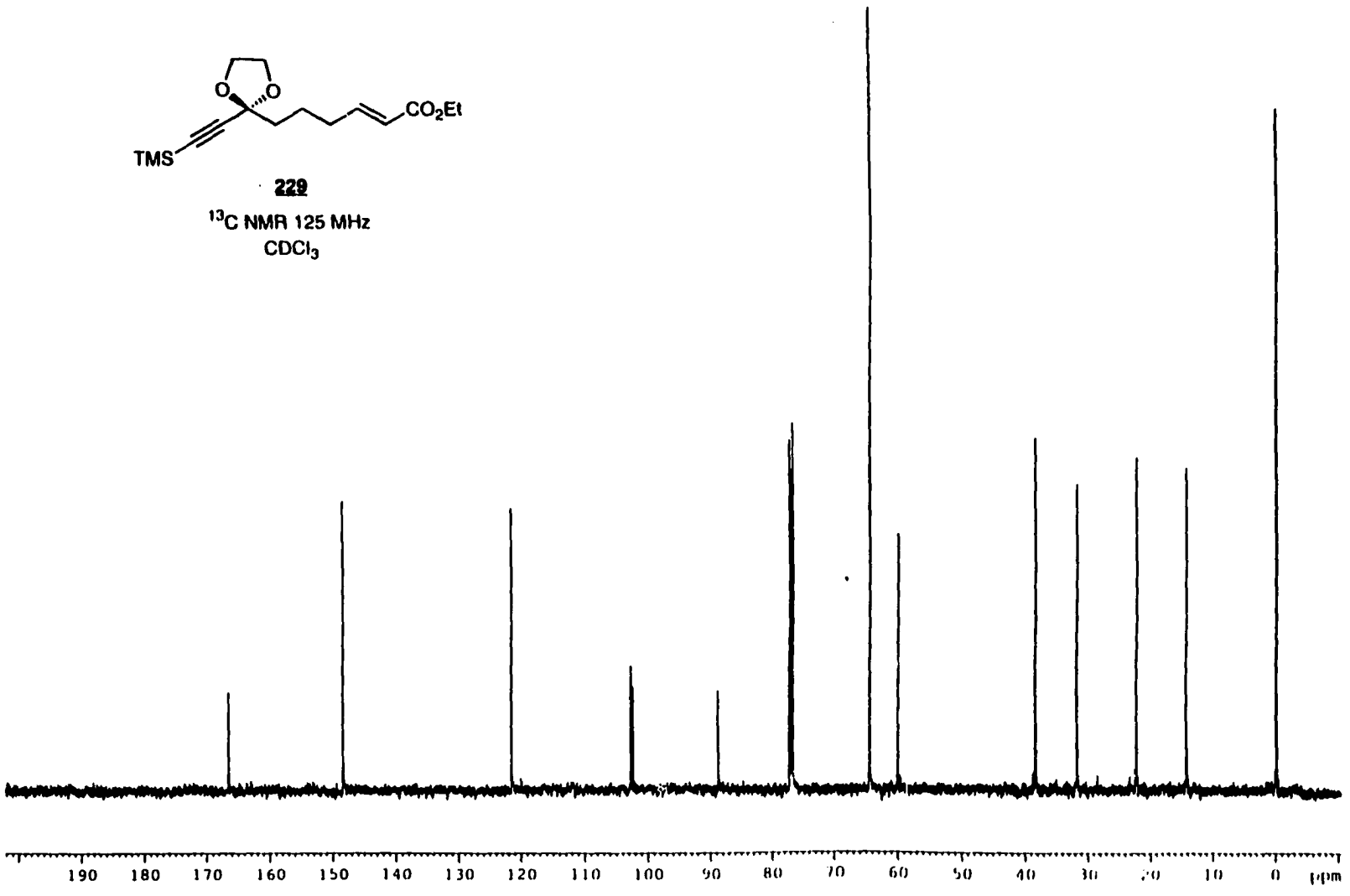
$CDCl_3$



229

^{13}C NMR 125 MHz

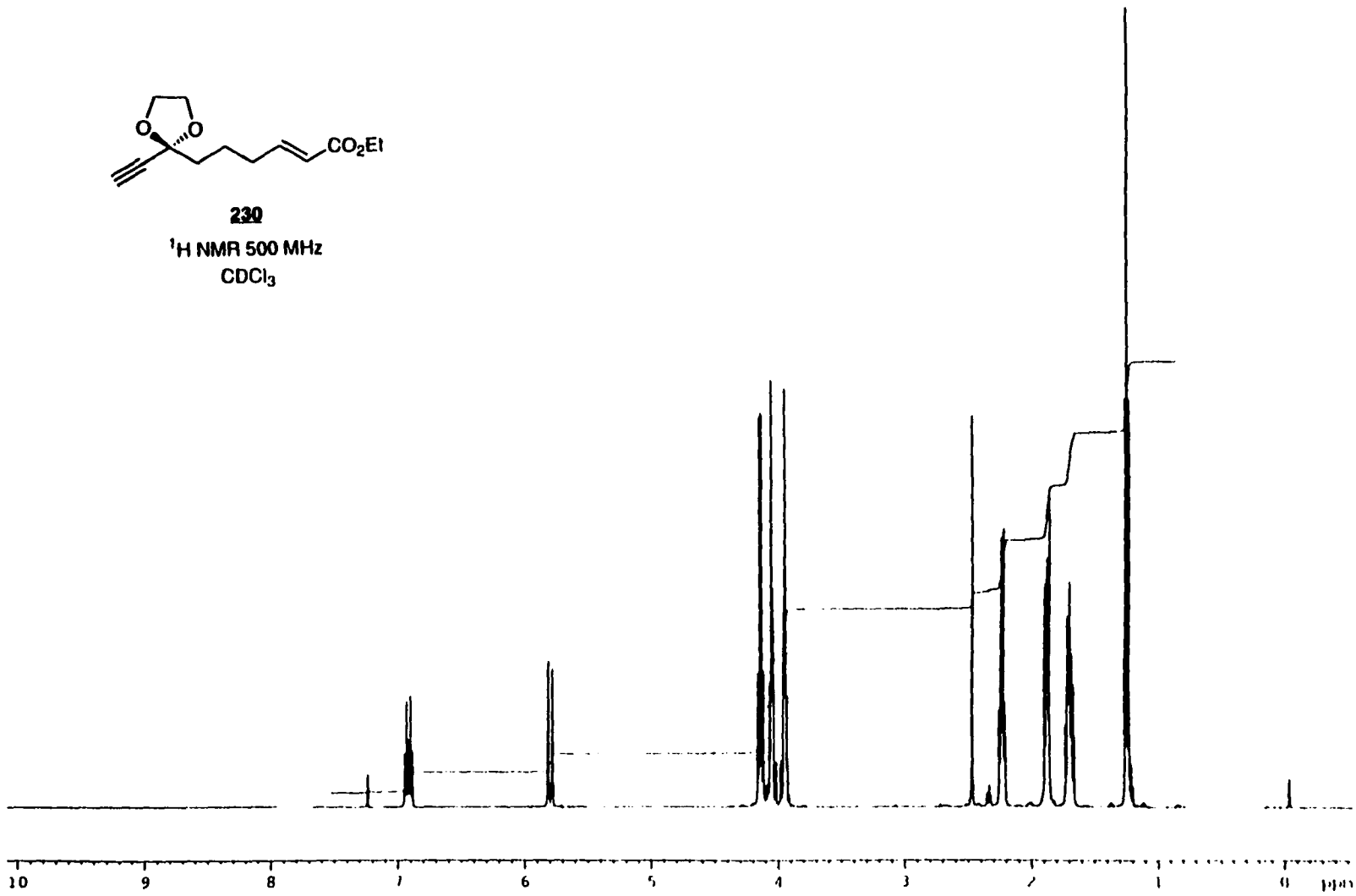
$CDCl_3$

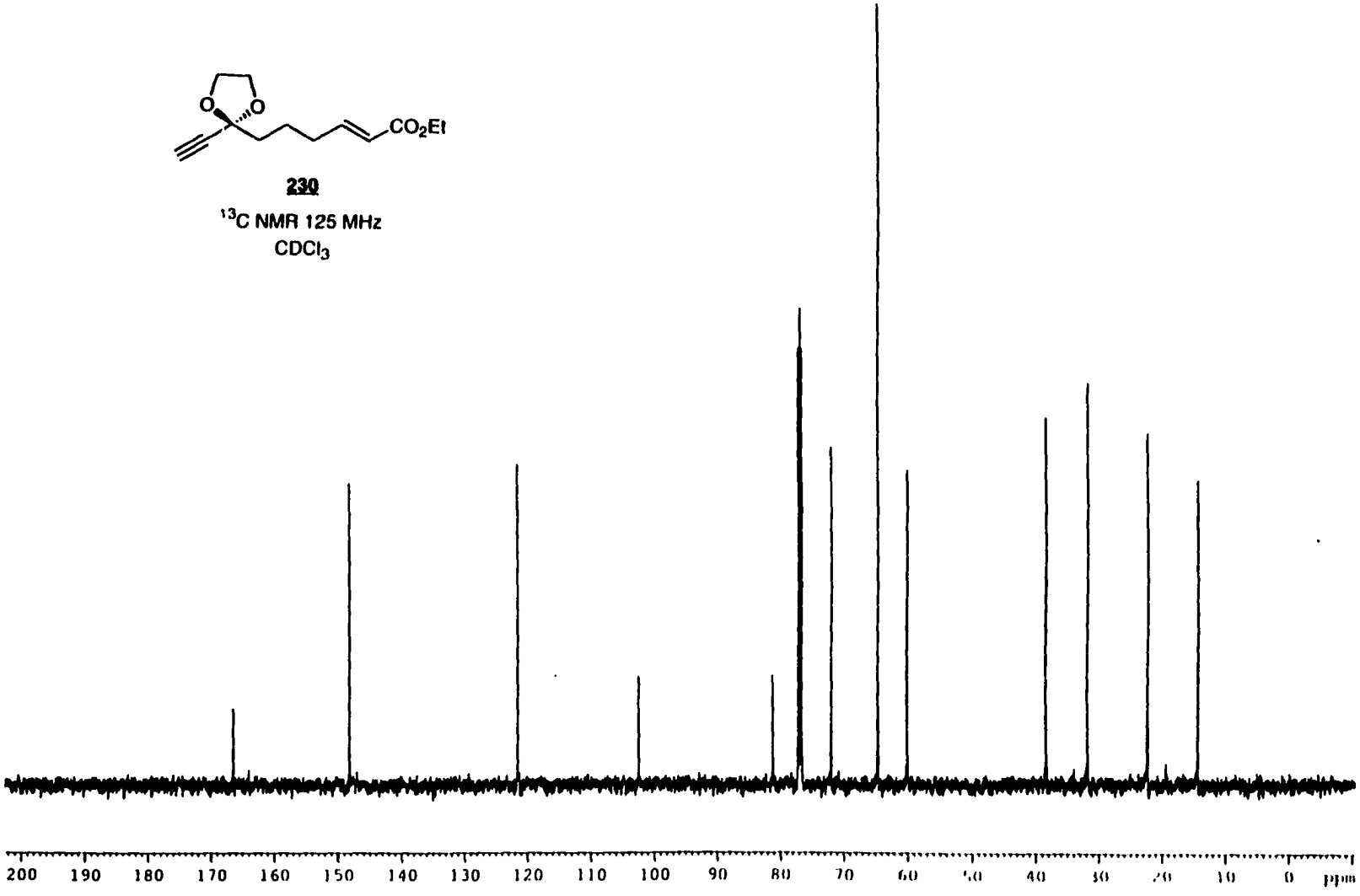


230

^{1}H NMR 500 MHz

$CDCl_3$

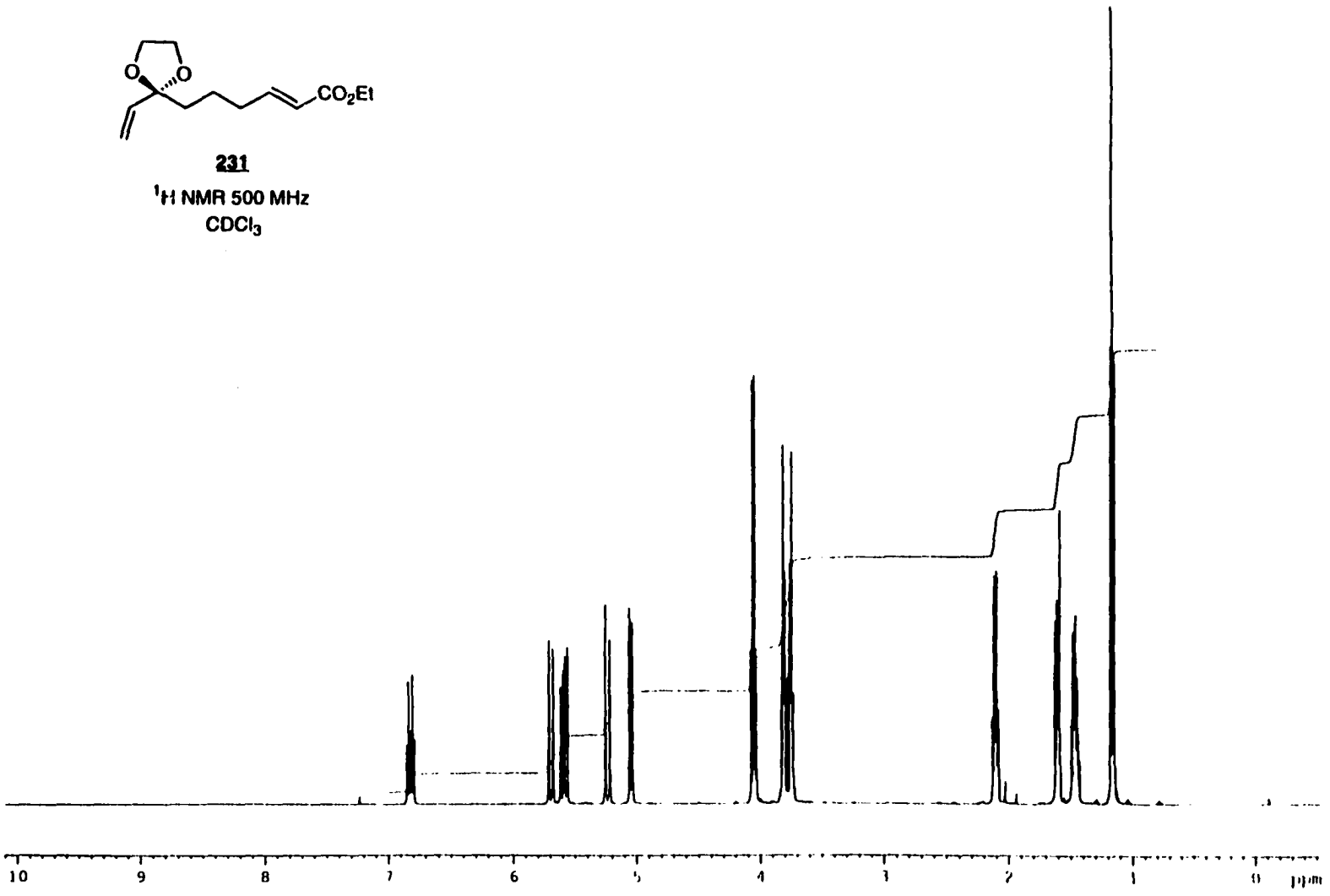


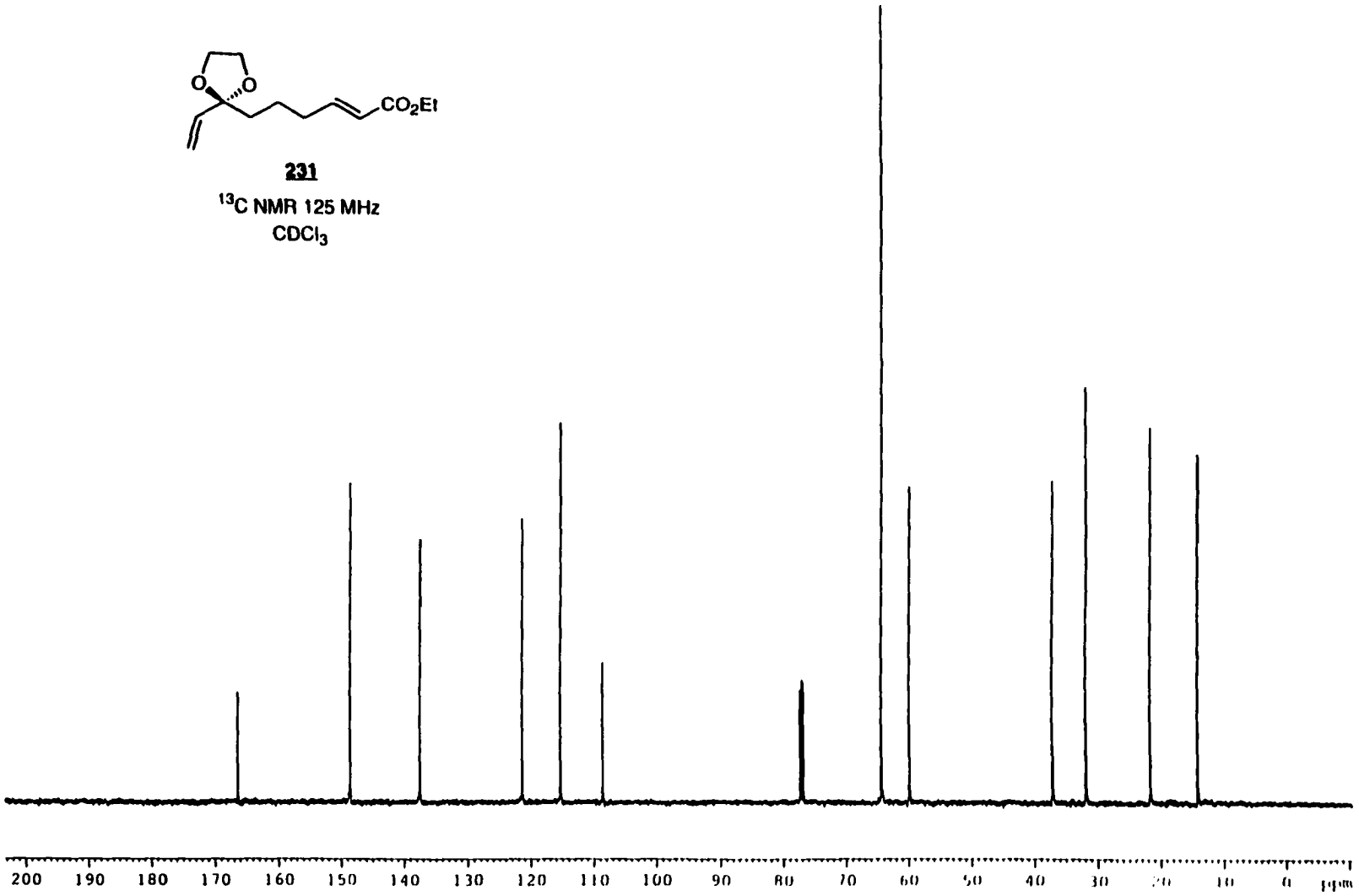

CO2Et
230
13C NMR 125 MHz
CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

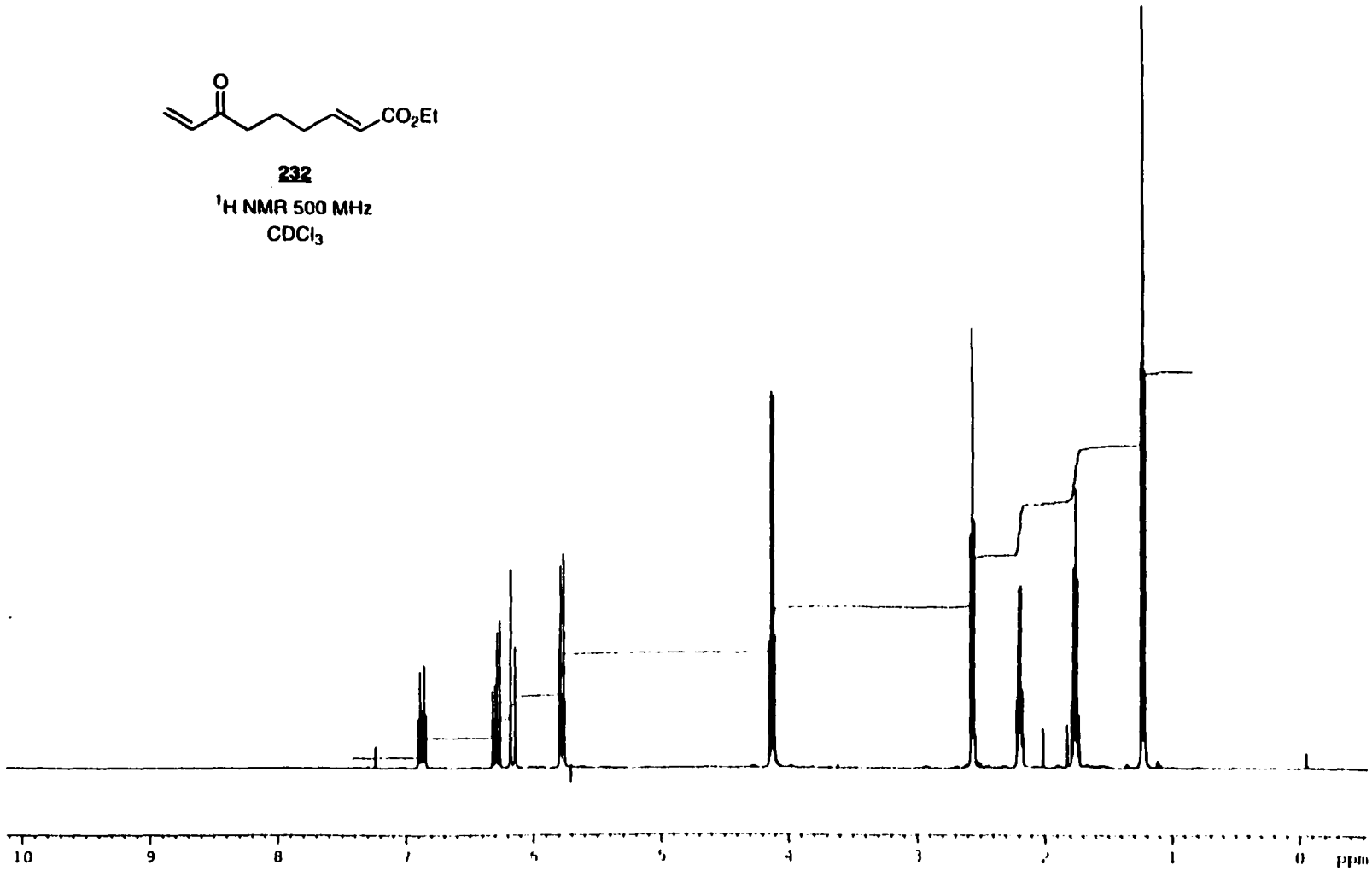
231

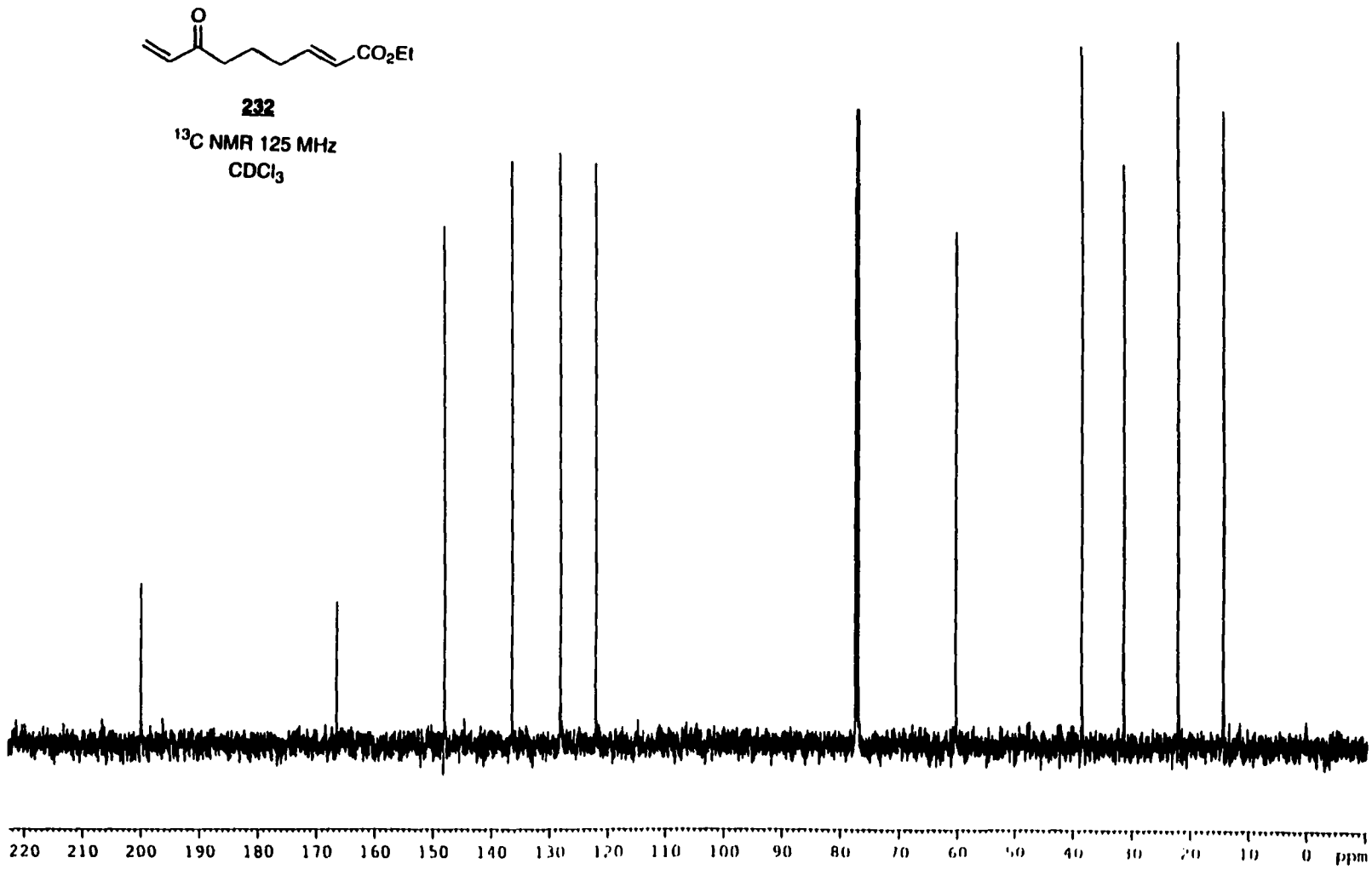
^{1}H NMR 500 MHz

$CDCl_3$



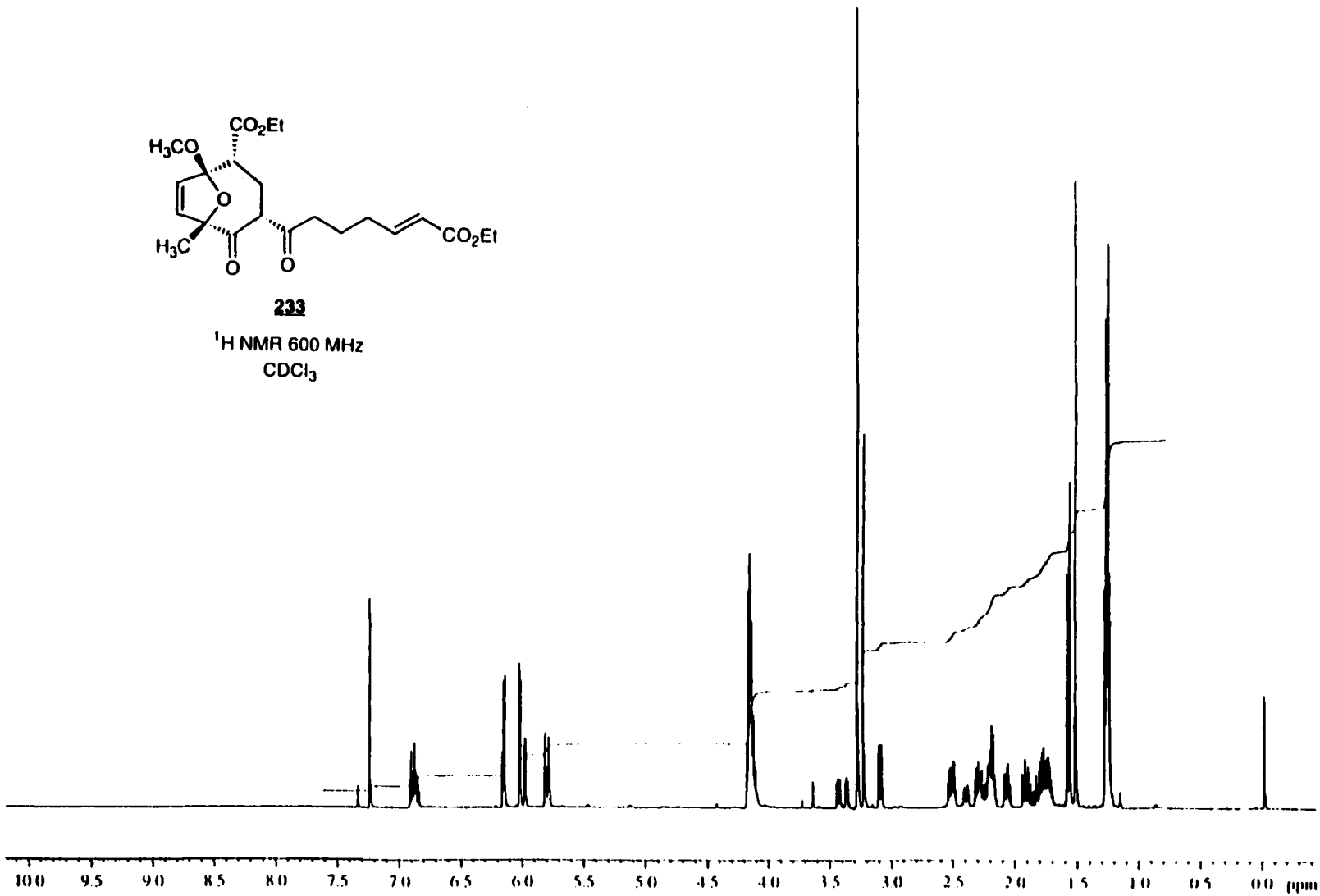

O
O
CO2Et
231
13C NMR 125 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


O
CO2Et
232
1H NMR 500 MHz
CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm


O
CO2Et
232
13C NMR 125 MHz
CDCl3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

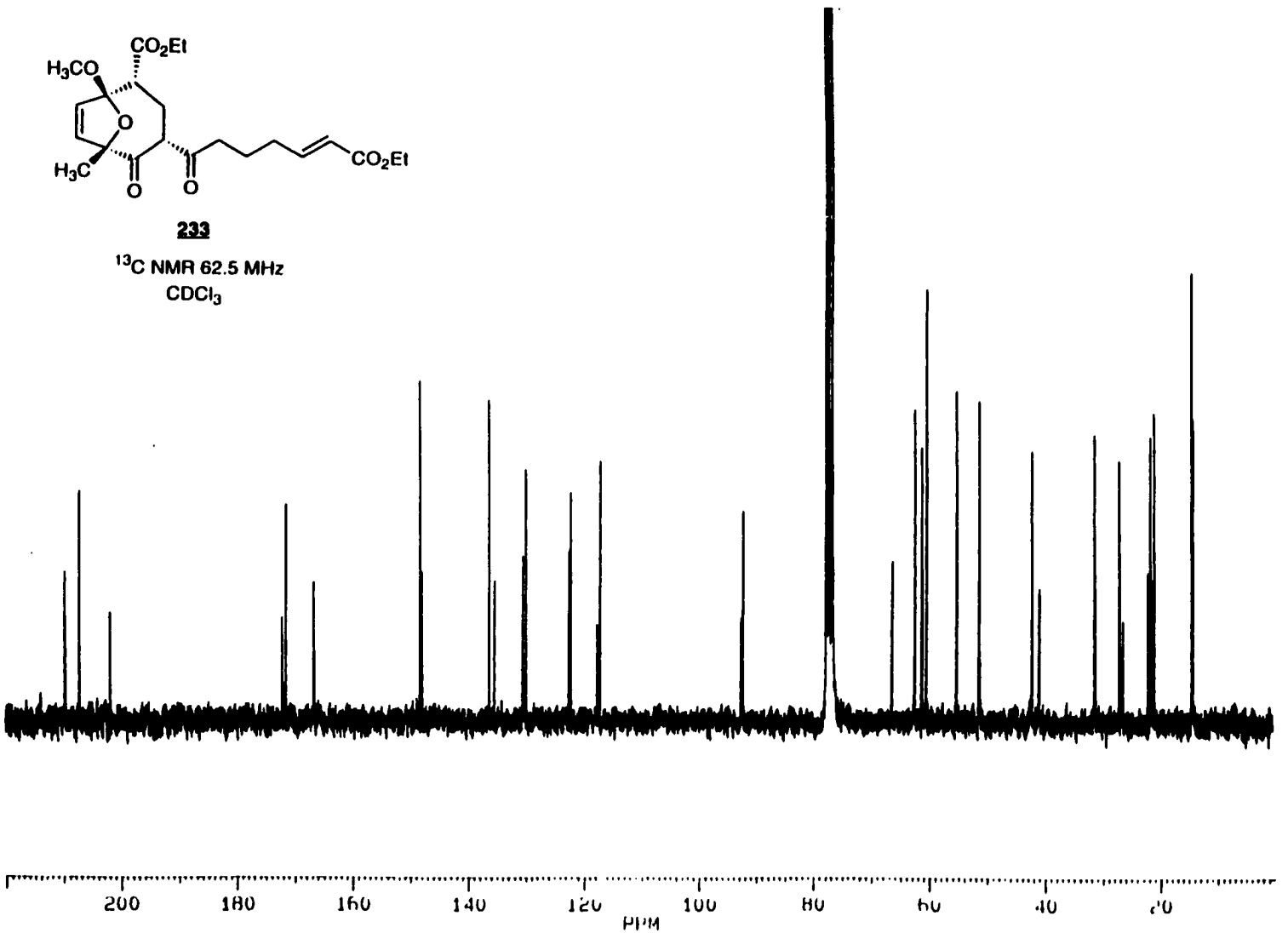
233

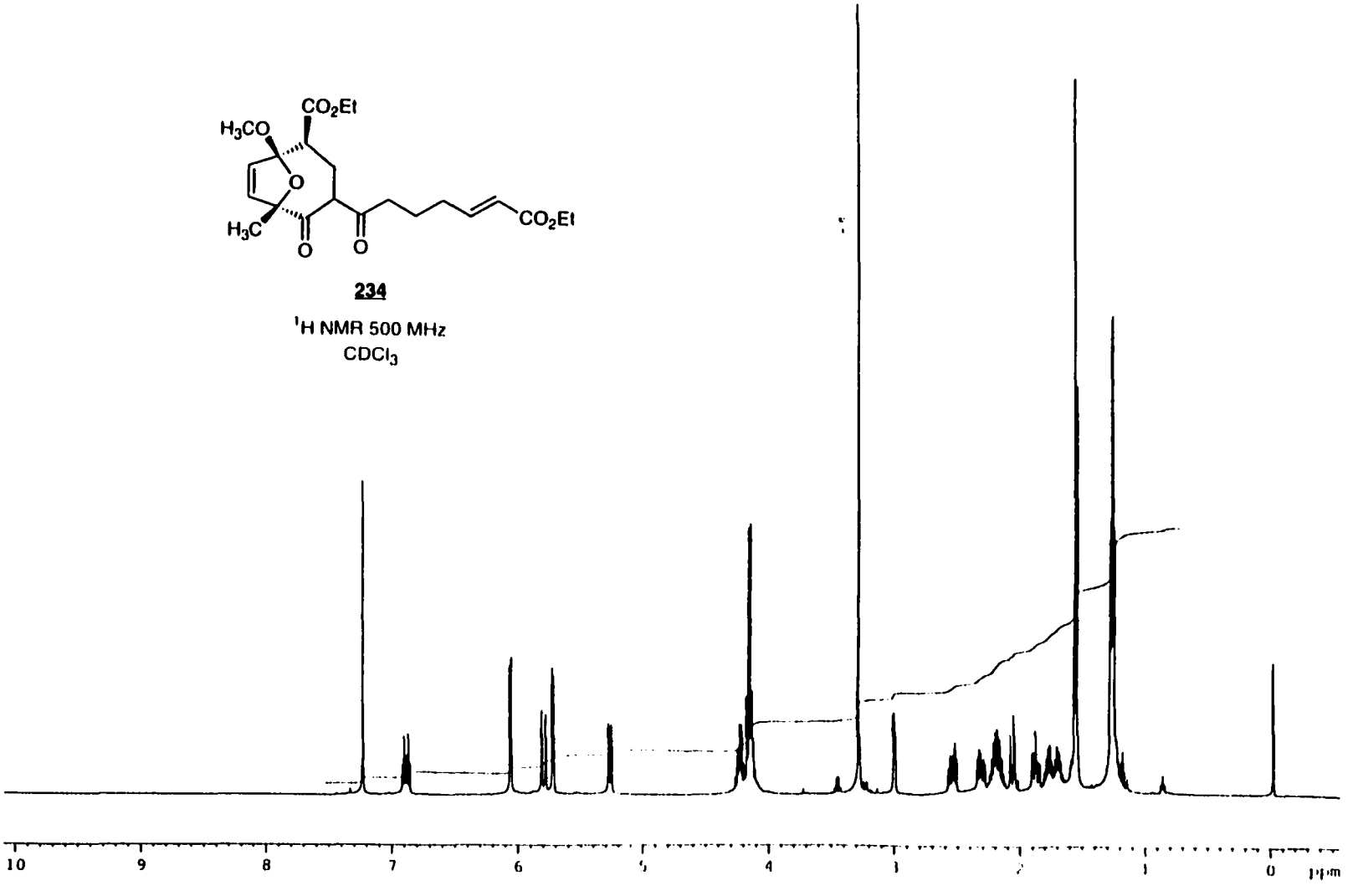
^{1}H NMR 600 MHz
$CDCl_3$



233

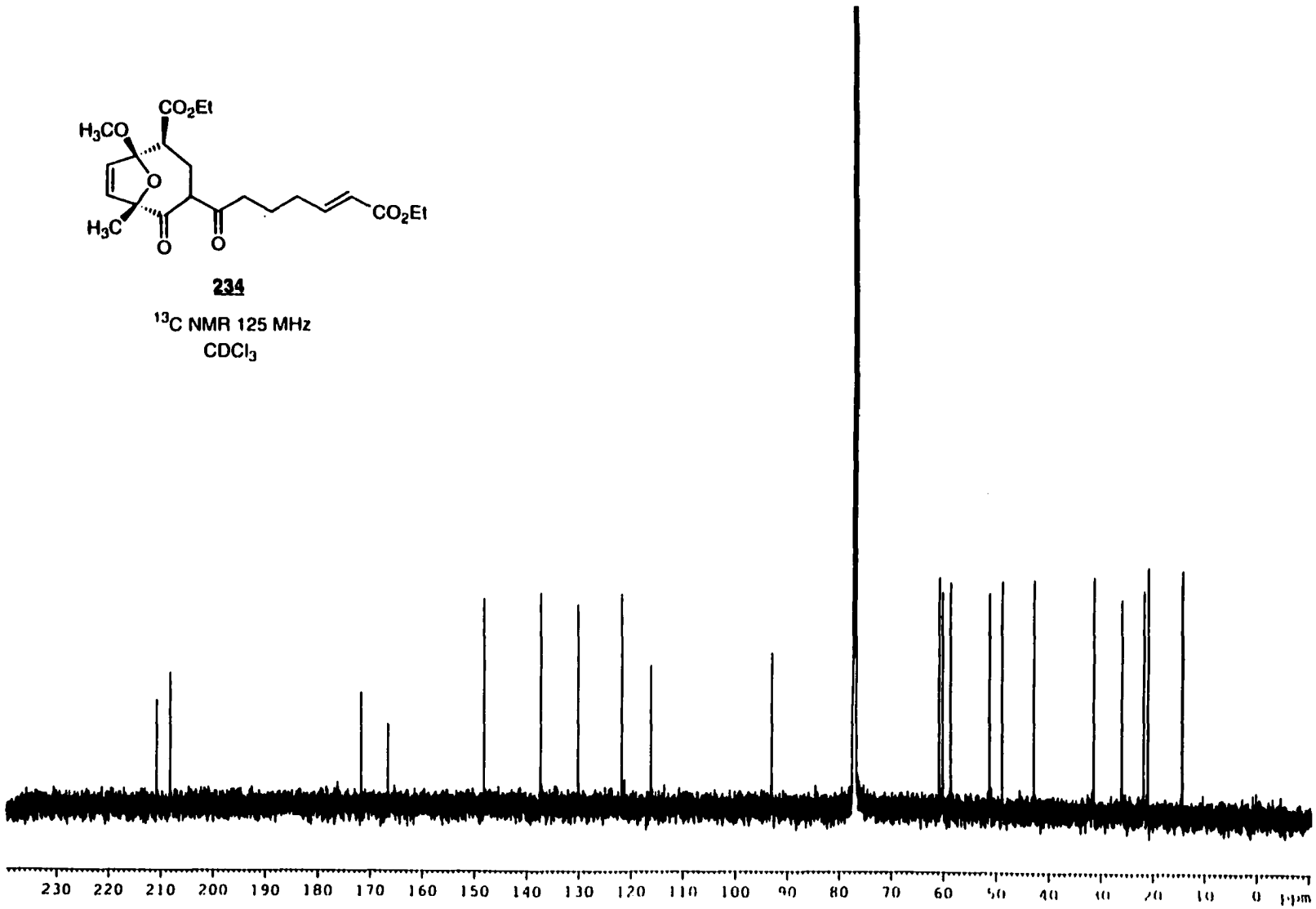
^{13}C NMR 62.5 MHz
$CDCl_3$




CO2Et
H3CO
O
H3C
O
O
CO2Et
234
1H NMR 500 MHz
CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm

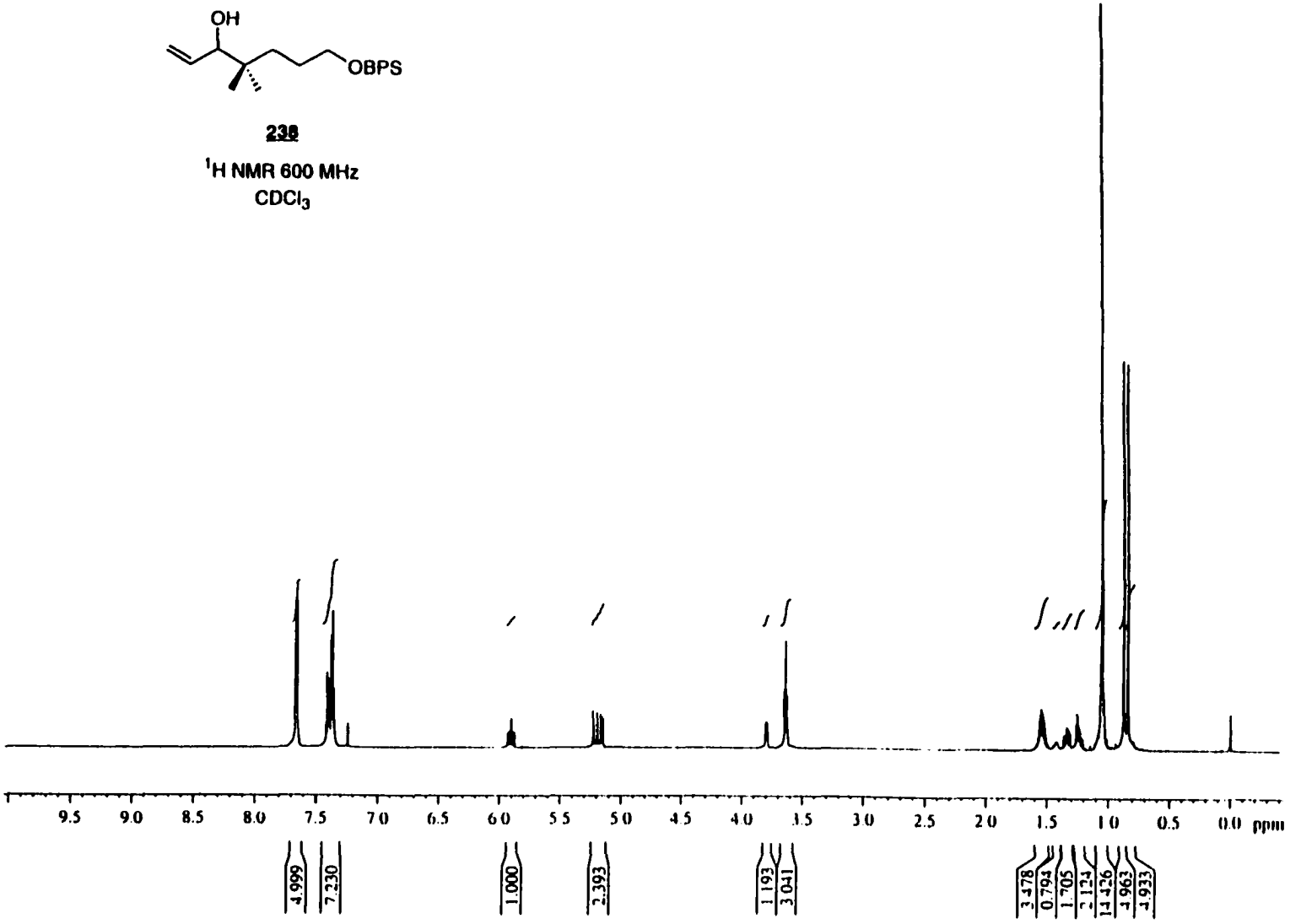
234

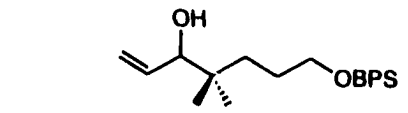
^{13}C NMR 125 MHz
$CDCl_3$



238

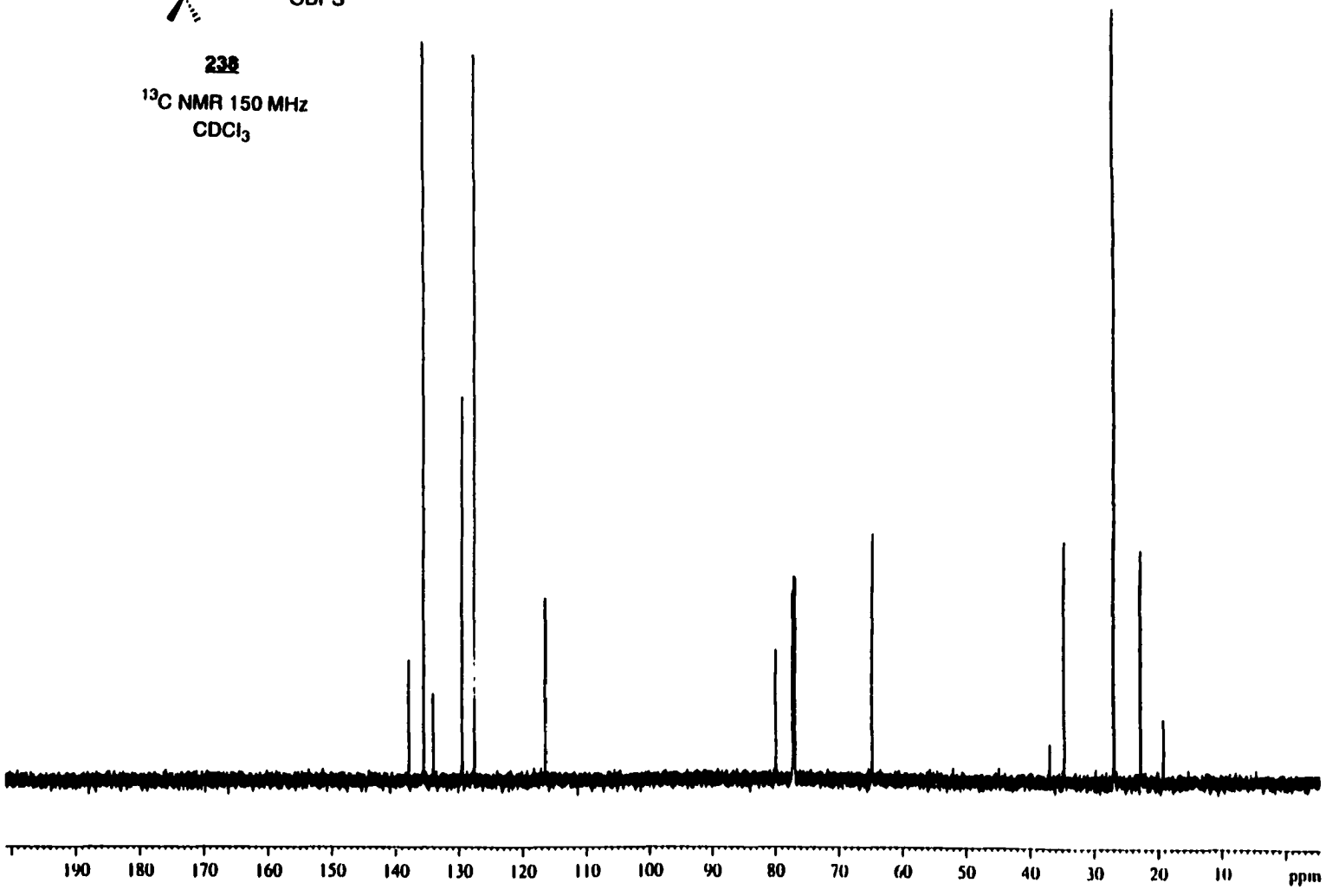
^{1}H NMR 600 MHz
$CDCl_3$





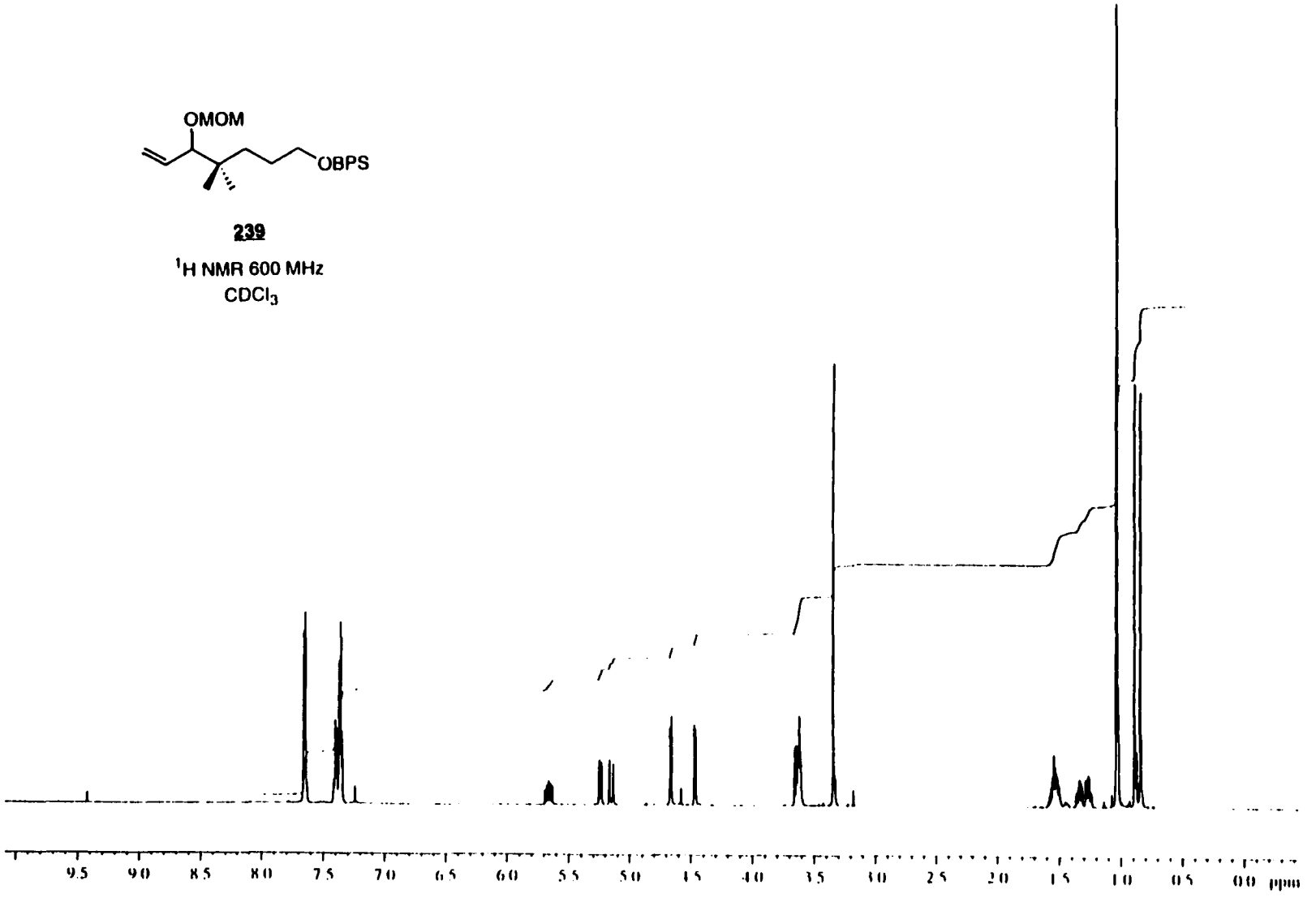
238

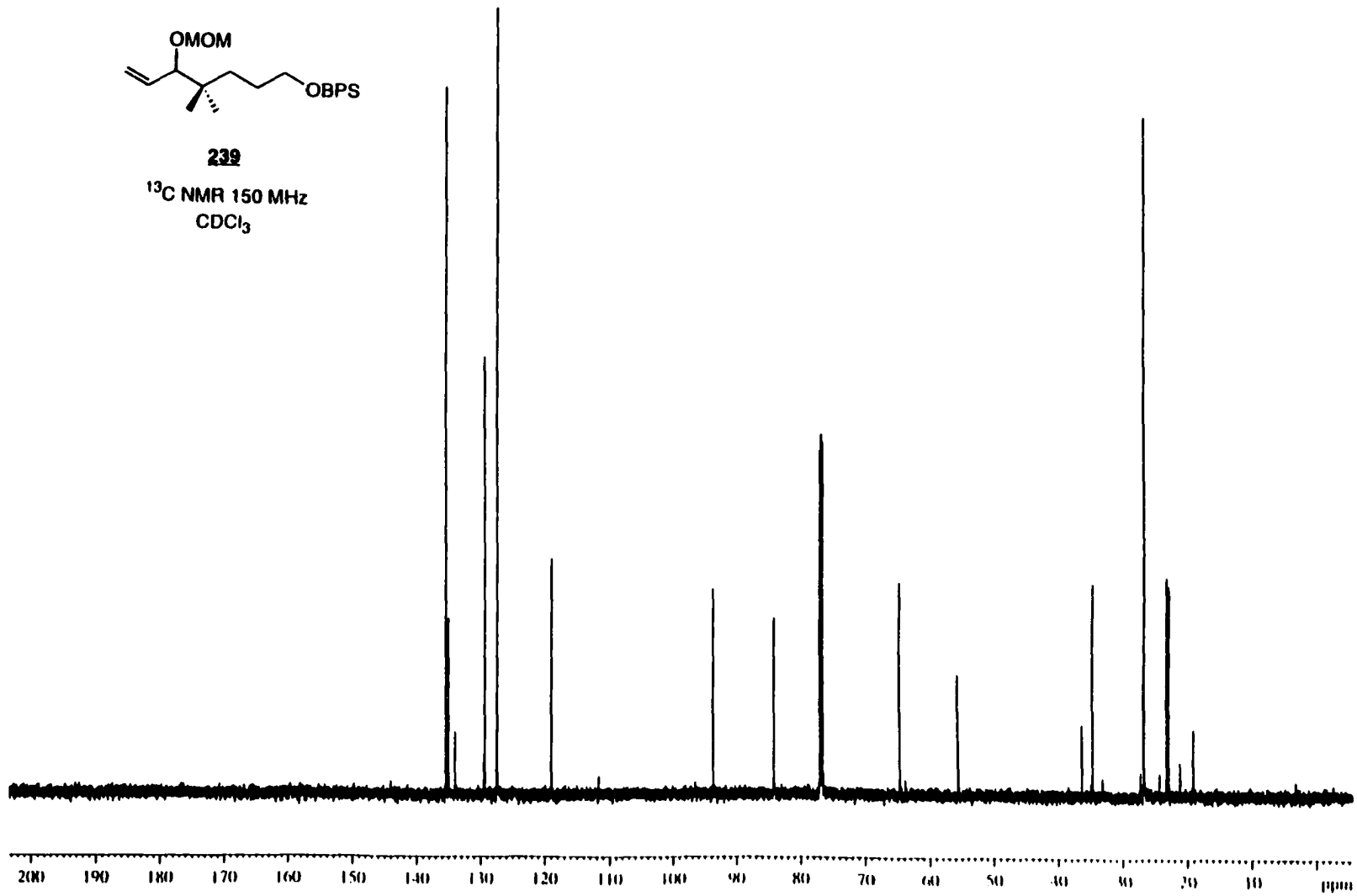
^{13}C NMR 150 MHz
$CDCl_3$



239

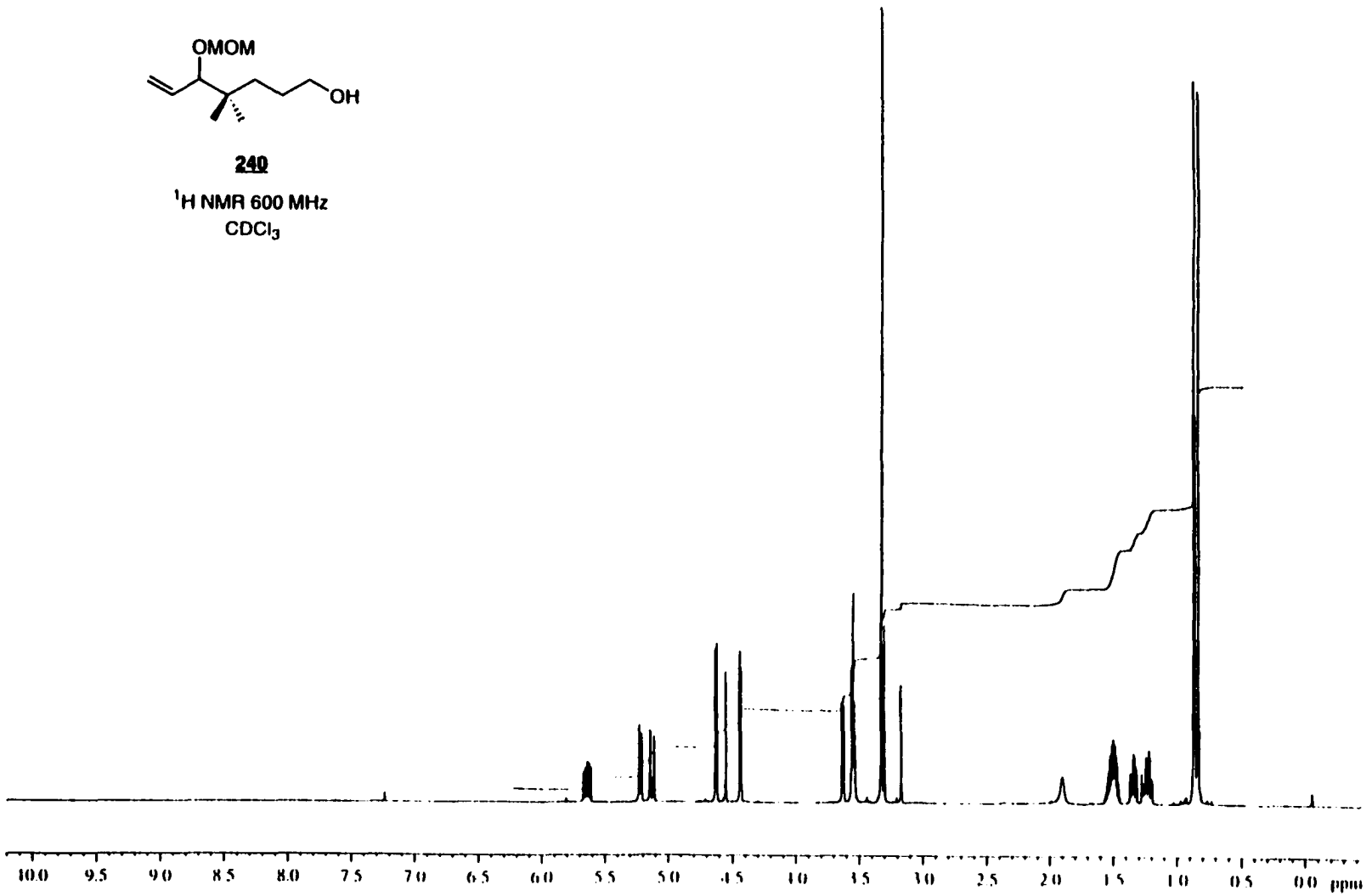
^{1}H NMR 600 MHz
$CDCl_3$

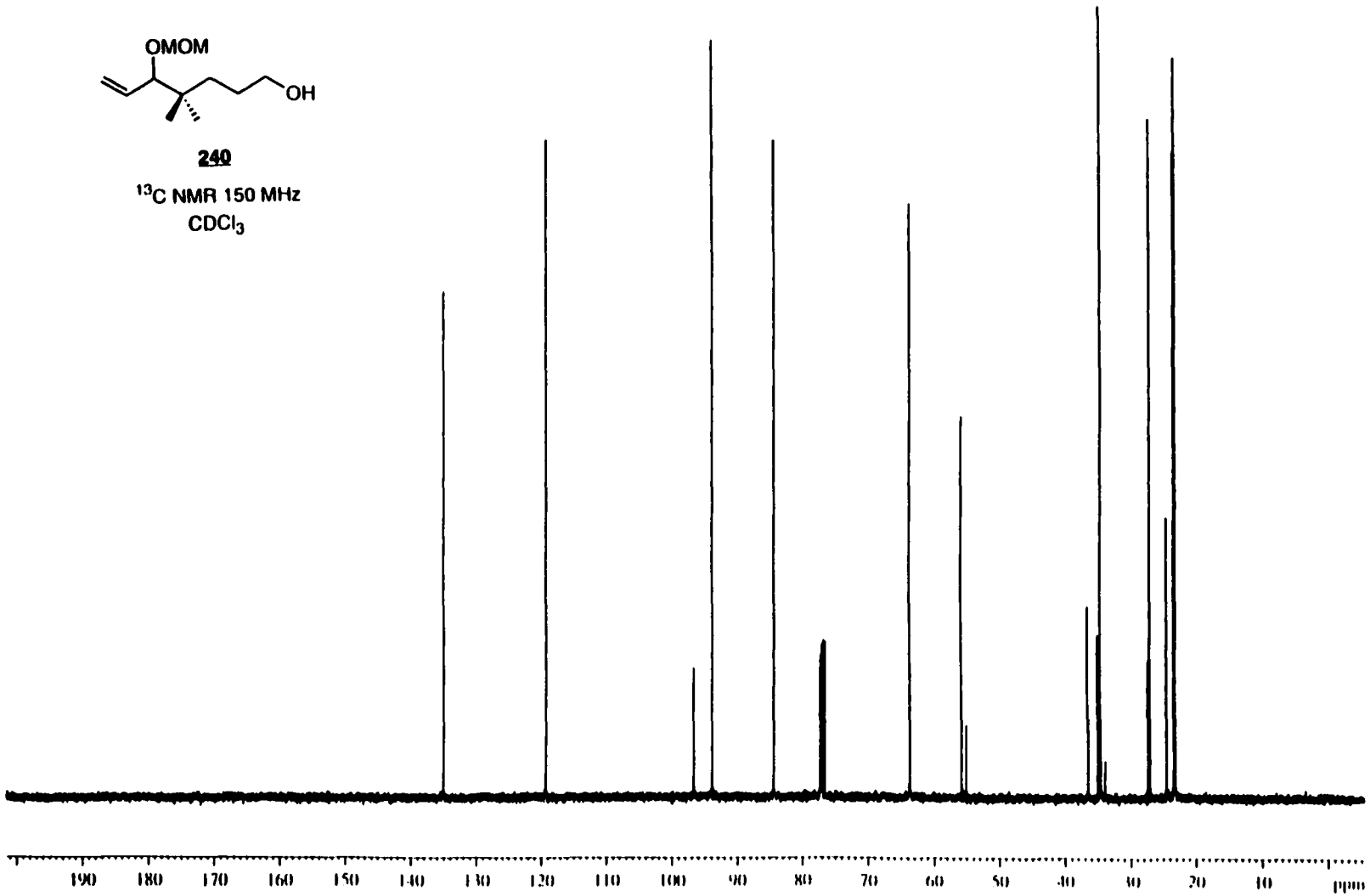


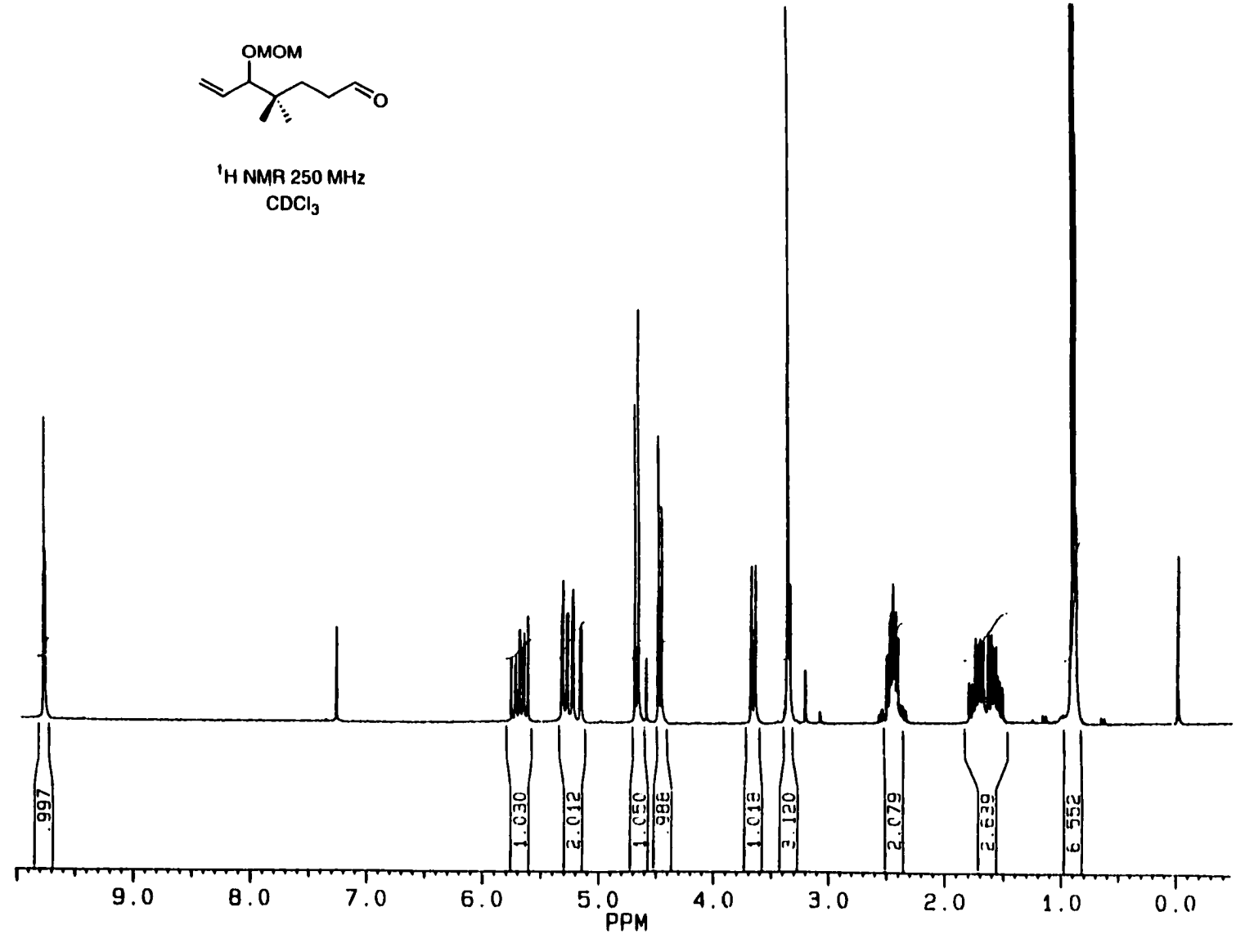

OMOM
OBPS
239
^{13}C NMR 150 MHz
$CDCl_3$
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

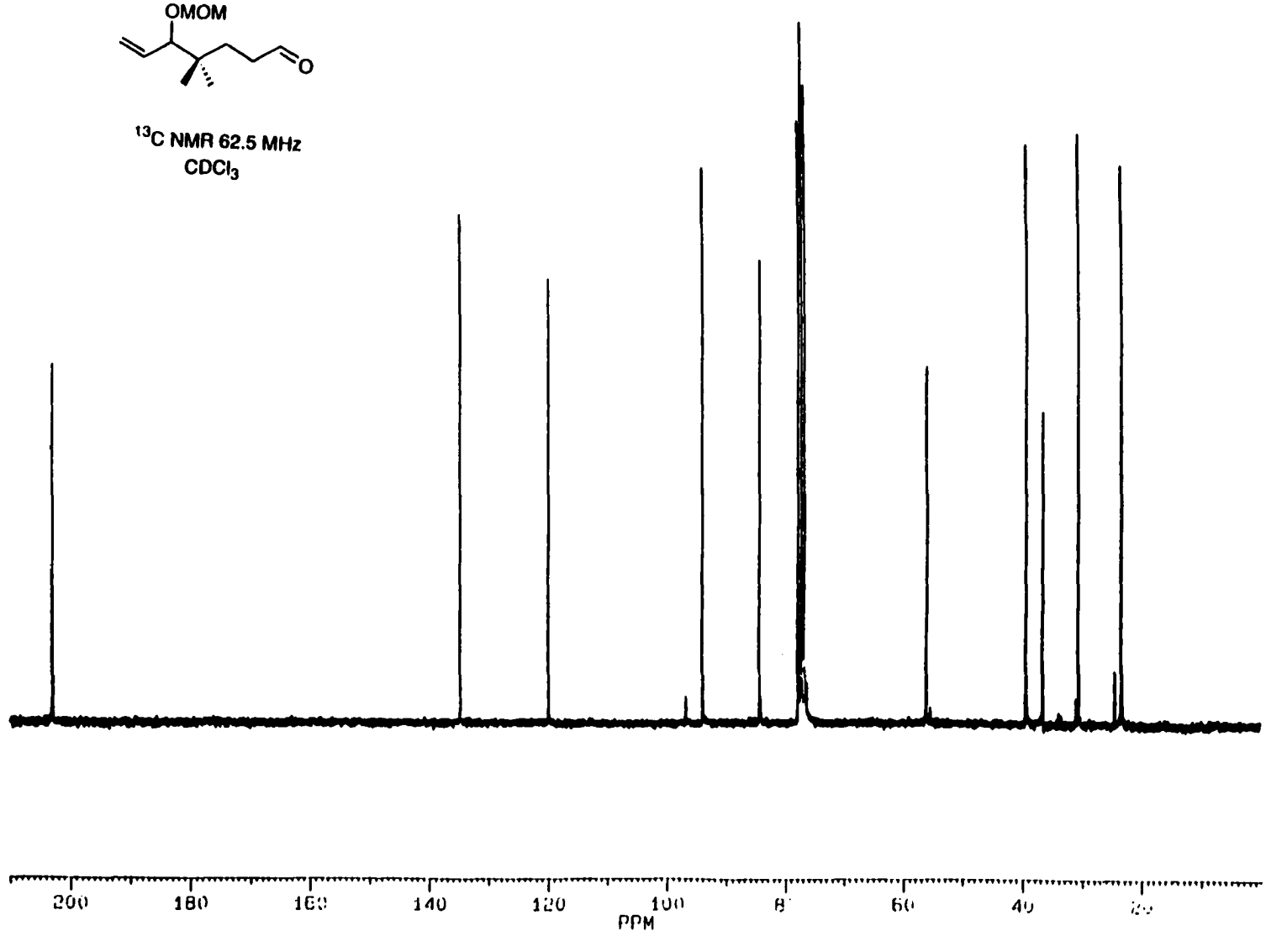
240

^{1}H NMR 600 MHz
$CDCl_3$



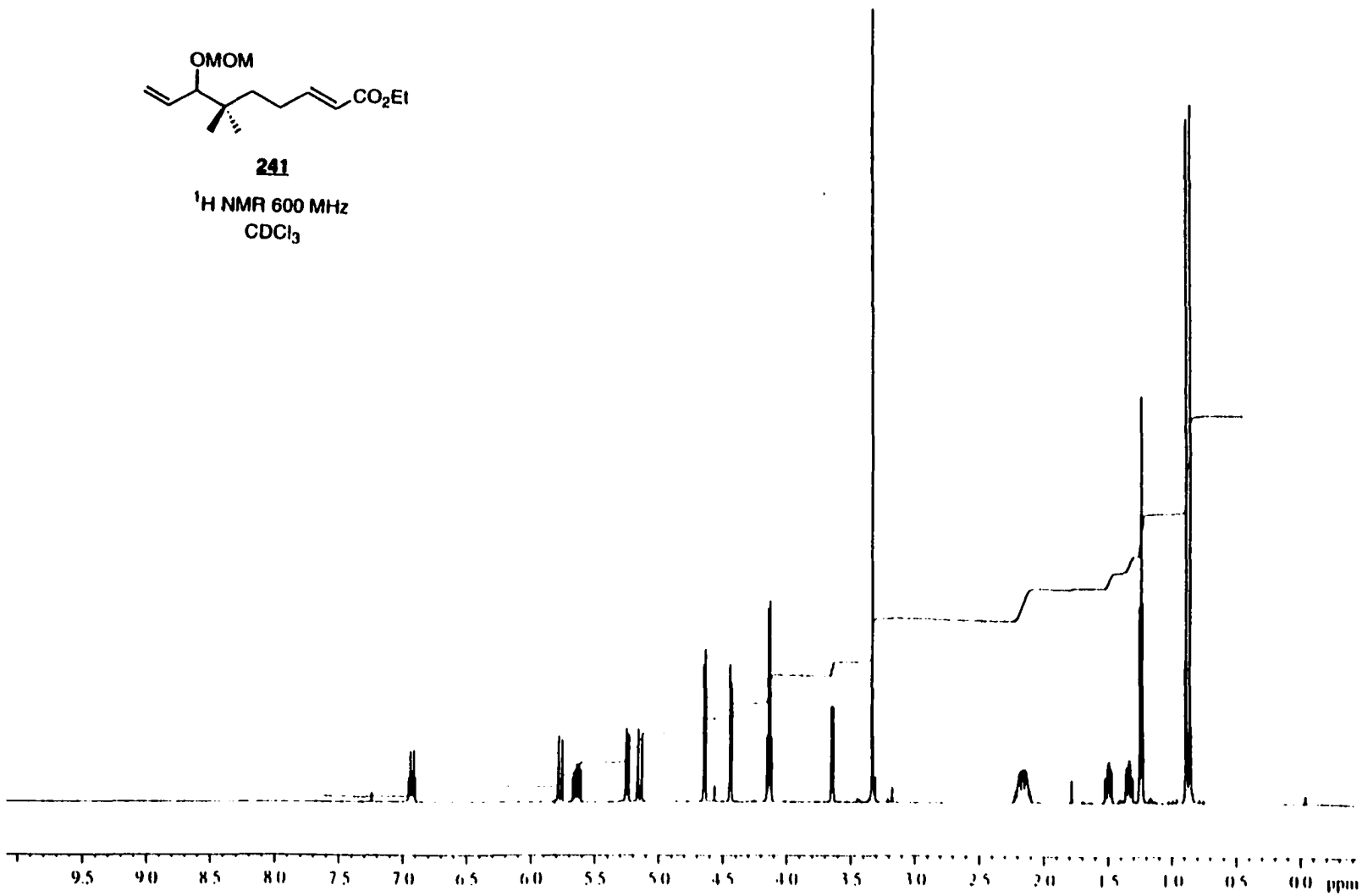

OMOM
OH
240
^{13}C NMR 150 MHz
$CDCl_3$
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

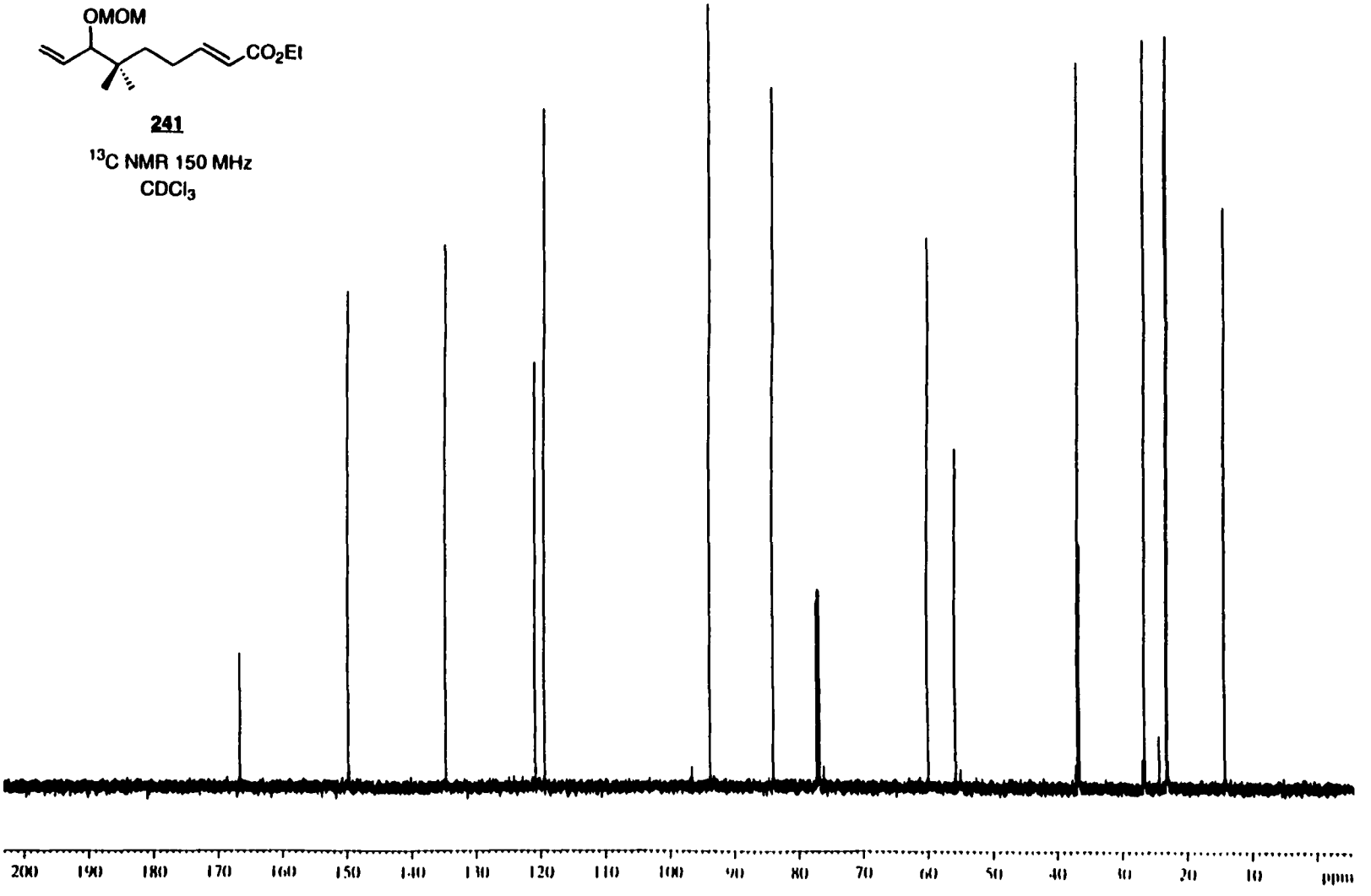

OMOM
O
^{1}H NMR 250 MHz
$CDCl_3$
.997
1.030
2.012
1.050
.986
1.018
3.120
2.079
2.639
6.552
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM


OMOM
O
^{13}C NMR 62.5 MHz
$CDCl_3$
200
180
160
140
120
100
60
40
PPM

241

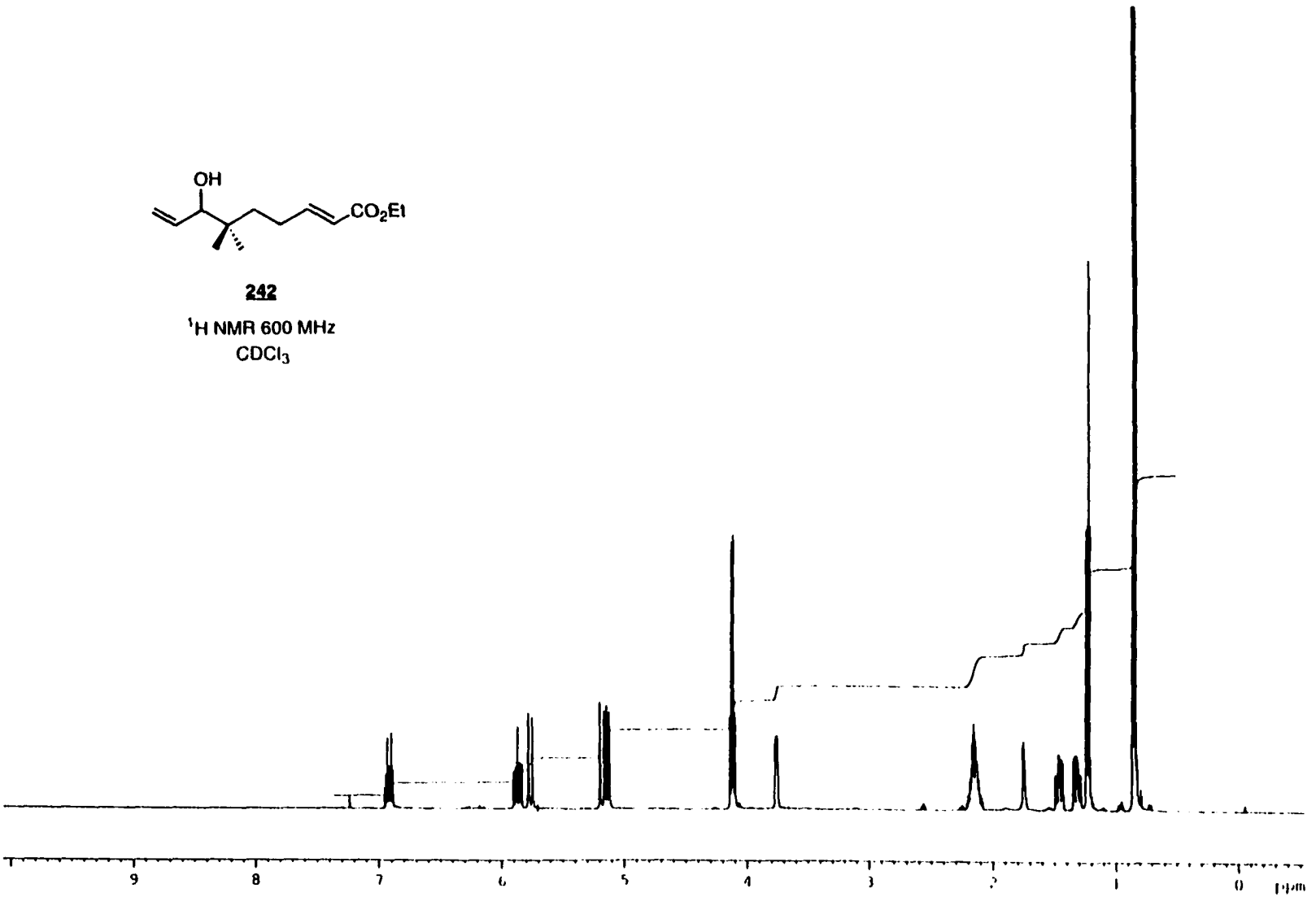
^1H NMR 600 MHz
$CDCl_3$

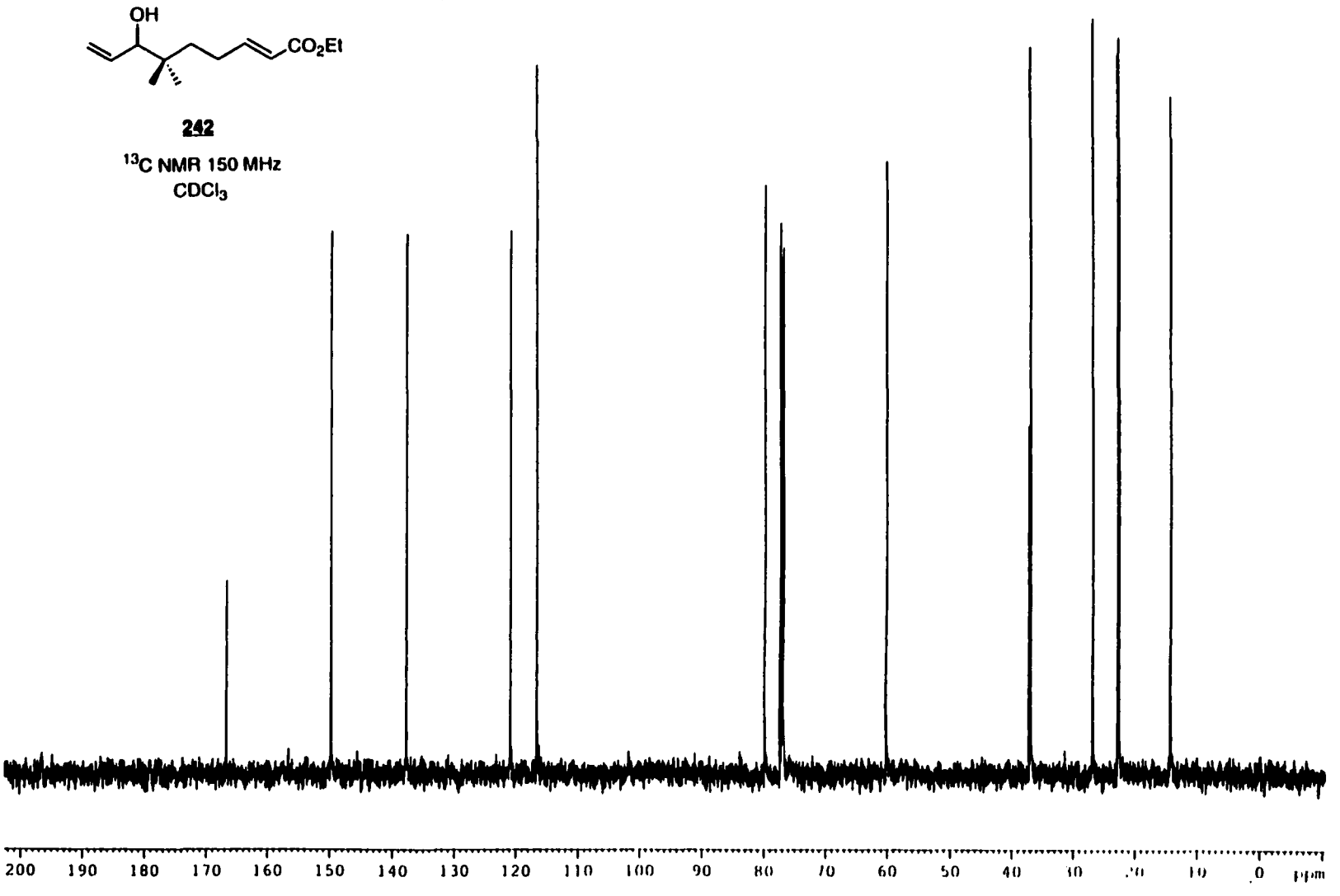



OMOM
CO2Et
241
13C NMR 150 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

242

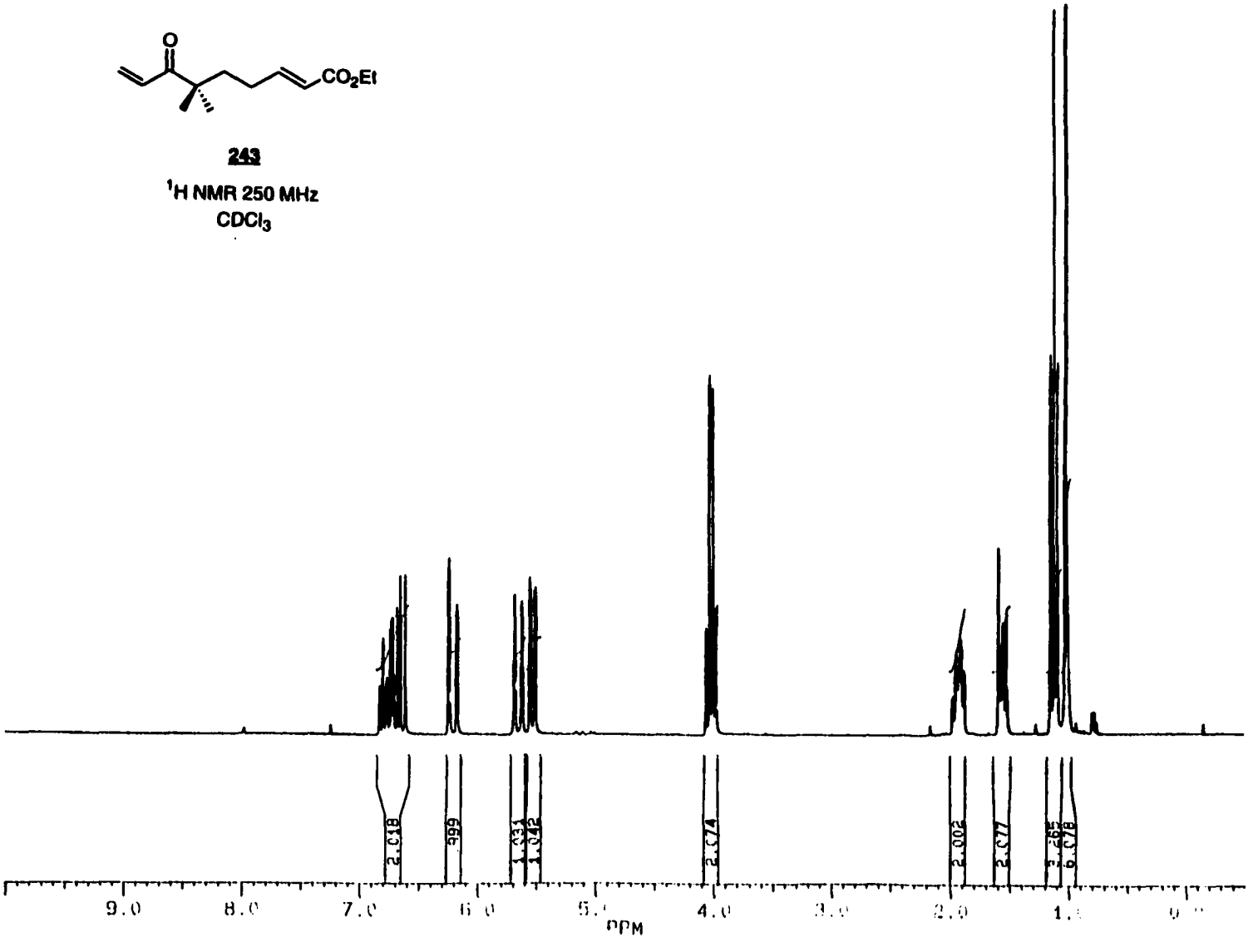
^{1}H NMR 600 MHz
$CDCl_3$

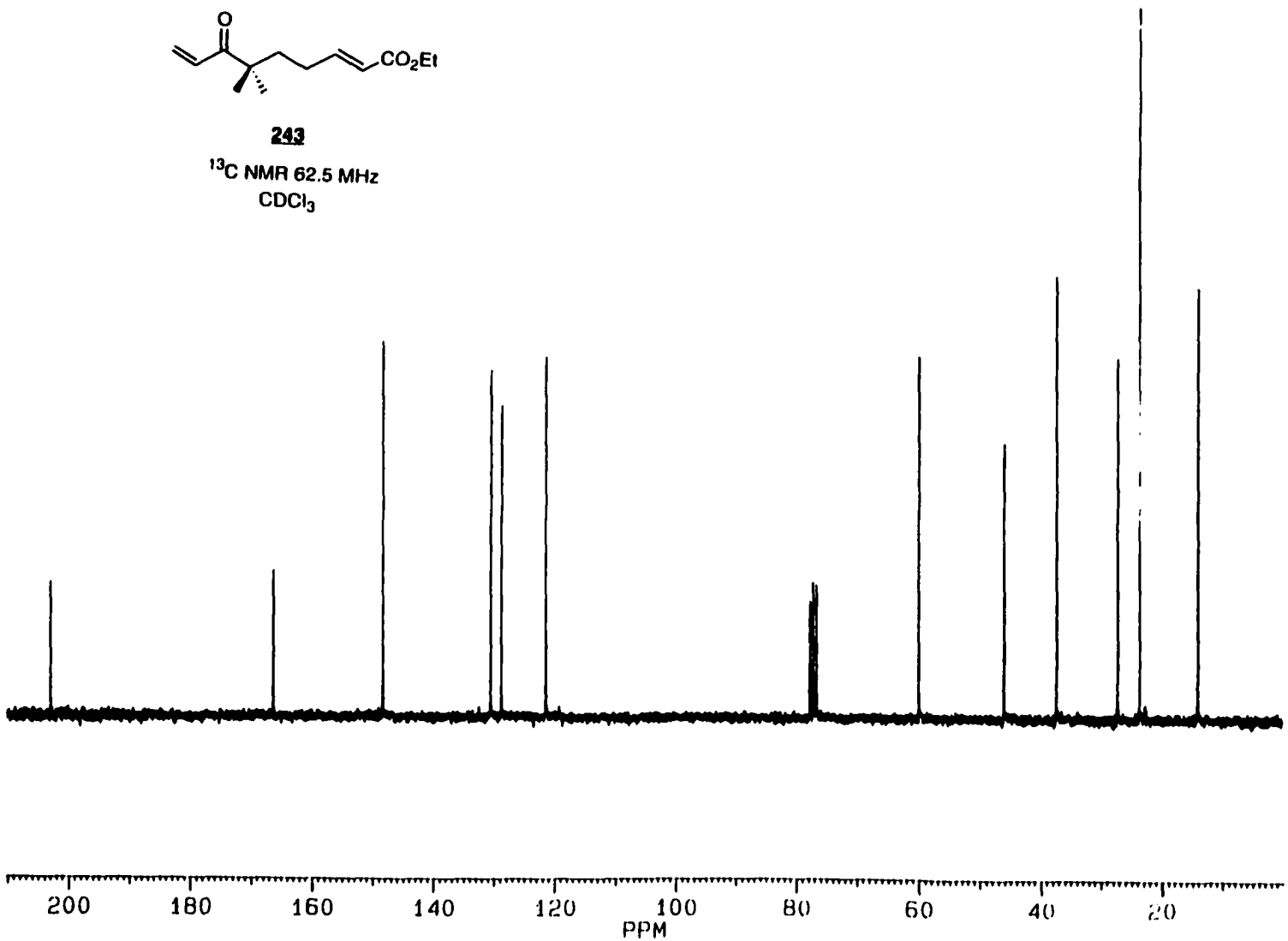



OH
CO2Et
242
13C NMR 150 MHz
CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

243

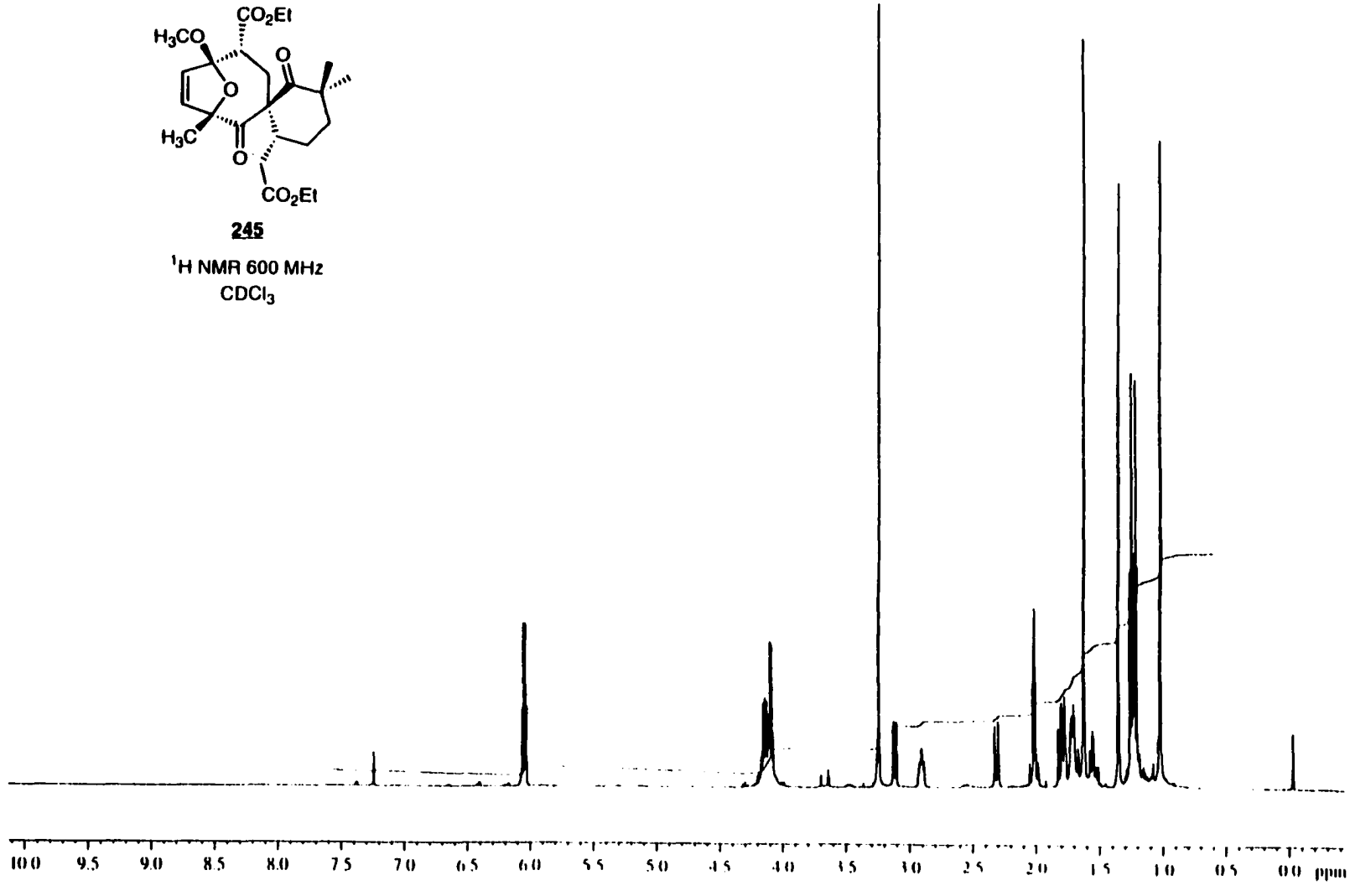
^{1}H NMR 250 MHz
$CDCl_3$

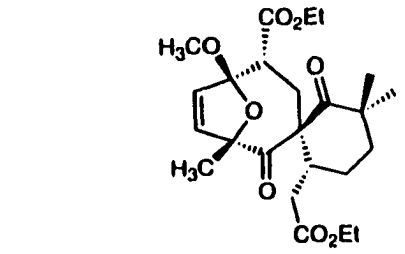



O
CO2Et
243
13C NMR 62.5 MHz
CDCl3
200
180
160
140
120
100
80
60
40
20
PPM

245

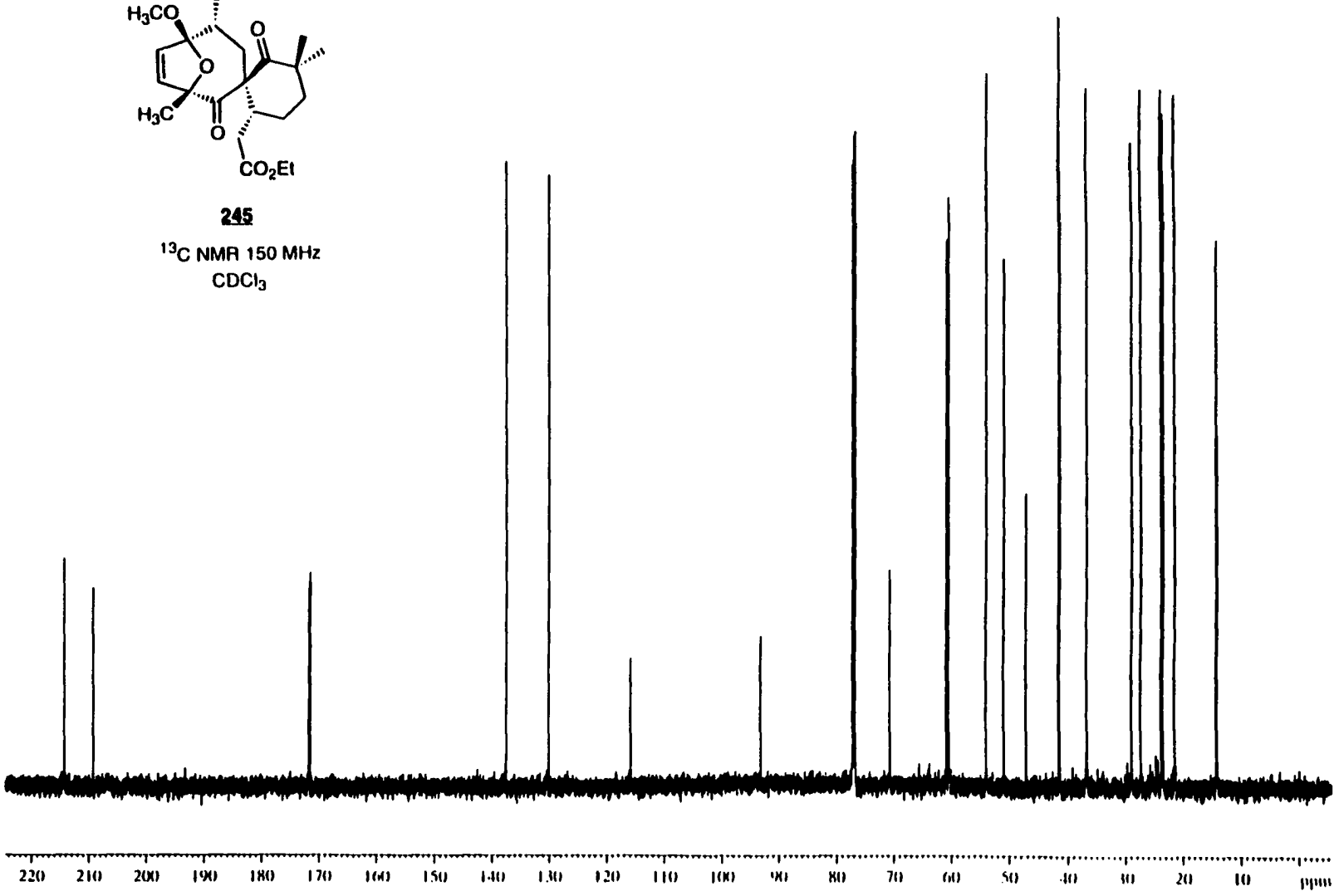
^{1}H NMR 600 MHz
$CDCl_3$

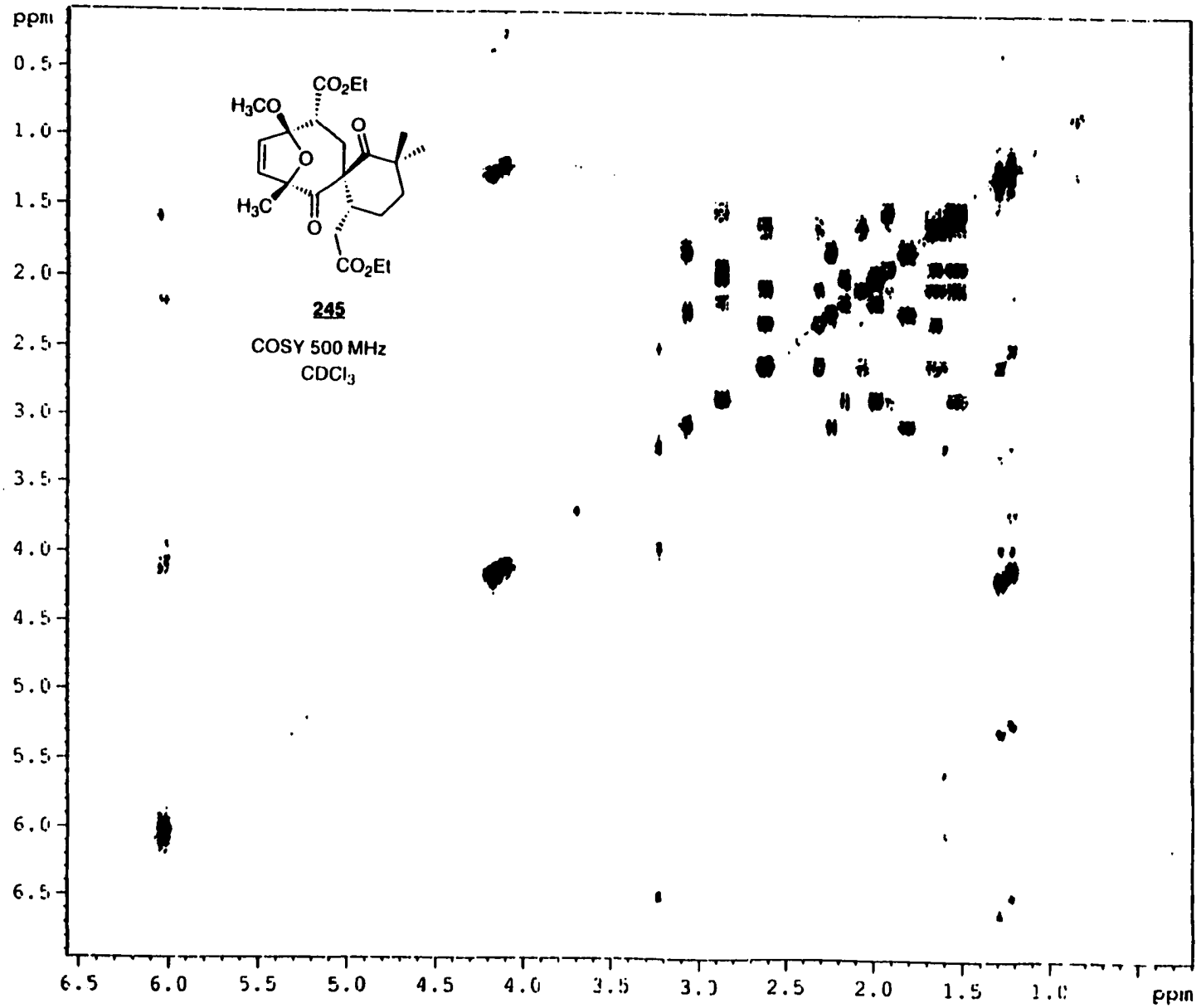


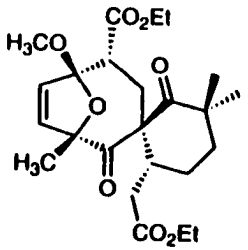


245

^{13}C NMR 150 MHz
$CDCl_3$

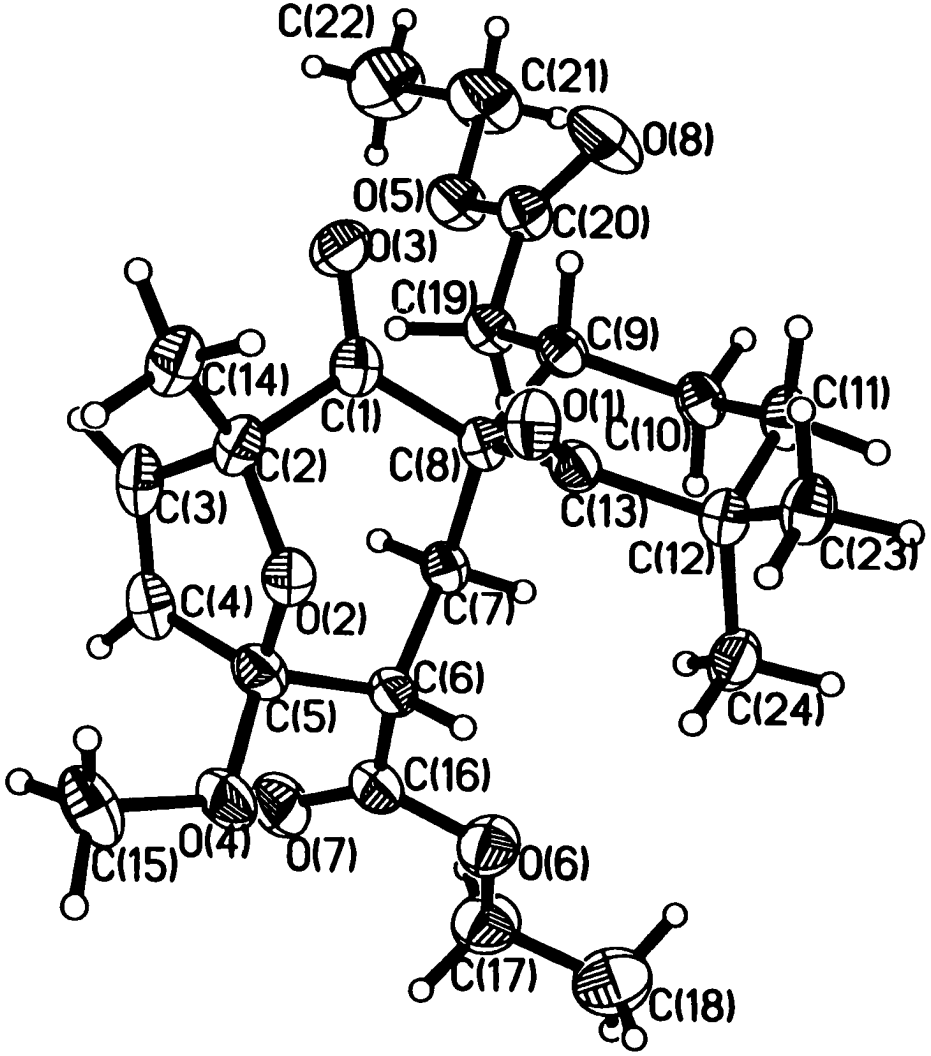



ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
CO_2Et
H_3CO
O
O
H_3C
O
CO_2Et
245
COSY 500 MHz
$CDCl_3$
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm



245

X-ray Structure
$CDCl_3$



NOTES

This written report is accompanied by an electronic Crystallographic Information File (CIF) which should be supplied to any journal publishing these results. It contains calculated distances and angles beyond those in the attached tables and all needed crystallographic information for generating other needed results. With modifications it is suitable for electronic submission to Acta Crystallographica Section C as a structure report. Observed and calculated structure factors are in the file qx01m.fcf and fofc.txt. Publications arising from this report must either 1) include the preparer(s) as coauthors when significant contributions were made and/or 2) acknowledge the Molecular Structure Laboratory and NSF grant CHE9610374 which provided the diffractometer. A copy of any paper reporting these results should be provided to MSL after publication.

EXPERIMENTAL

A colorless plate of C_{24} H_{34} O_8 having approximate dimensions of 0.05 x 0.20 x 0.30 mm was mounted on a glass fiber in a random orientation. Examination of the crystal on a Bruker SMART 1000 CCD detector X-ray diffractometer at 170(2)K and a power setting of 50KV, 40mA showed measurable diffraction to at least theta = 27.0165 deg. Data were collected on the SMART1000 system using graphite monochromated Mo Kα radiation (λ=0.71073).

Cell constants and an orientation matrix for integration were determined from reflections obtained in three orthogonal 5 deg. wedges of reciprocal space. A total of 3736 frames at 1 detector setting covering 0 < 2θ < 60 deg were collected, having an ω scan width of 0.3 and an exposure time of 20 seconds. The frames were integrated using the Bruker SAINT software package's narrow frame algorithm. A total of 29326 reflections were integrated and retained of which 5740 were unique (<redundancy> = 5.12, R_{int} = 5.8%, R_{sig} = 6.6%). Of the unique reflections, 3809 (66.36%) were observed I>2σ(I). The final Orthorhombic cell parameters of a = 12.7684(11), b = 13.2230(12), c = 14.3605(13), α = 90, β = 90, γ = 90, volume = 2424.6(4) $Å^3$ are based on the refinement of the XYZ-centroids of 971 reflections with I > 10σ(I) covering the range of 2.6325 < θ < 27.0165. No empirical absorption corrections were applied. Systematic absences and intensity statistics indicate the space group to be P2(1)2(1)2(1) (#19) which was consistent with refinement.

The structure was solved using SHELXS in the Bruker SHELXTL (Version 5.0) software package[1]. Refinements were performed using the freely available SHELXL and illustrations were made using XP. Solution was achieved utilizing direct methods followed by Fourier synthesis. Hydrogen atoms were added at idealized positions, constrained to ride on the atom to which they are bonded and given thermal parameters equal to 1.2 or 1.5 times U_{iso} of that bonded atom. The final anisotropic full-matrix least squares refinement based on F^2 of all reflections converged (maximum shift/esd = 0.001) at R1 = 0.0752, wR2 = 0.0894 and goodness-of-fit = 0.912. "Conventional" refinement indices using the 3809 reflections with F > 4 σ(F) are R1 = 0.0405, wR2 =

0.0806. The model consisted of 289 variable parameters, 0 constraints and 0 restraints. There were no correlation coefficients greater than 0.50. The highest peak on the final difference map was 0.186 e/Å^3 located 1.01 Å from O6. The lowest peak on the final difference map was -0.166 e/Å^3 located 0.47 Å from H22C. Scattering Factors and anomalous dispersion were taken from International Tables Vol C Tables 4.2.6.8 and 6.1.1.4.

This compound crystalizes in a *chiral* space group. The crystal contained only one enantiomer of the title compound. The absolute configuration was *not* determined by refinement of the Flack x parameter. Flack x parameter = -0.8(8). Expected values are 0 (within 3 esd's) for correct and +1 for inverted absolute structure. The large esd precludes reliable determination of the absolute configuration. However, the reported configuration was chosen as refinement of the inverted structure yielded a Flack x parameter of 1.6(9).

STRUCTURE

The structure of the title compound was determined to be that expected by the sample's preparer. It is a tricyclic compound, with an eight-membered ring featuring a double bond between C3 and C4. The eight-membered ring is bound to a second six-membered ring through a *spiro*- junction at C8. The third ring is a five-membered cyclic ether incorporating the C3-C4 double bond and bridgehead centers C2 and C5. The bridging atom is O2. The molecule is a discrete species in the crystal, with no intermolecular hydrogen bonding found. The unit cell contains four molecules, all the same enantiomer. .

FIGURES

Fig. (1). An thermal ellipsoid rendering of the molecule with 50% probability ellipsoids.

EQUATIONS

$R_{int} = \sum|Fo^2-\langle Fo^2\rangle|/\sum[Fo^2]$

$R_{sig} = \sum[\sigma(Fo^2)]/\sum[Fo^2]$

$R_1 = \Sigma||Fo|-|Fc||/\sum|Fo|$

$wR_2 = \{\sum[w(Fo^2-Fc^2)^2]/\sum[w(Fo^2)^2]\}^{1/2}$

$w=1/[\sigma^2(Fo^2)+(0.0425P)^2+0.00P]$ where $P=(Fo^2+2Fc^2)/3$

$GOF = S = \{\sum[w(Fo^2-Fc^2)^2]/(n-p)\}^{1/2}$

REFERENCES

Bruker (1997) SAINT Reference Manual Version 5.0, Bruker AXS Inc., Madison, Wisconsin, USA.

Bruker (1997) SHELXTL Reference Manual Version 5.0, Bruker AXS Inc., Madison, Wisconsin, USA.

Bruker (1997) SMART Reference Manual Version 5.0, Bruker AXS Inc., Madison, Wisconsin, USA.

FLACK X-PARAMETER - (a) Flack, H.D. (1983) Acta Cryst. A39, 876-881. (b) Bernardinelli, G. & Flack, H. D. (1985) Acta Cryst. A41, 500-511.

Table 1. Crystal data and structure refinement for qx01m.

Identification code	qx01m	
Empirical formula	C24 H34 O8	
Formula weight	450.51	
Temperature	170(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 12.7684(11) Å	a= 90°.
	b = 13.2230(12) Å	b= 90°.
	c = 14.3605(13) Å	g = 90°.
Volume	2424.6(4) $Å^3$	
Z	4	
Density (calculated)	1.234 Mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	968	
Crystal size	0.30 x 0.20 x 0.05 mm^3	
Theta range for utilized data	2.09 to 28.30°.	
Limiting Indices	-16<=h<=16, -17<=k<=16, -18<=l<=19	
Reflections utilized	29326	
Independent reflections	5740 [R(int) = 0.0577]	
Completeness to theta = 28.30°	97.4 %	
Absorption correction	None	
Max. and min. transmission	0.9954 and 0.9729	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5740 / 0 / 289	
Goodness-of-fit on F^2	0.912	
Final R indices [I>2sigma(I)]	R1 = 0.0405, wR2 = 0.0806	
R indices (all data)	R1 = 0.0752, wR2 = 0.0894	
Absolute structure parameter	-0.8(8)	
Largest diff. peak and hole	0.186 and -0.166 $e.Å^{-3}$	
RMS difference density	0.036$e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for qx01m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	7921(1)	8081(1)	326(1)	32(1)
O(2)	8525(1)	7104(1)	-1345(1)	29(1)
O(3)	9374(1)	9602(1)	-889(1)	37(1)
C(13)	8782(1)	7835(1)	609(1)	25(1)
O(4)	8933(1)	5498(1)	-1851(1)	39(1)
O(5)	12719(1)	10384(1)	-48(1)	39(1)
C(3)	9612(2)	7949(2)	-2367(1)	35(1)
C(9)	10413(1)	8853(1)	619(1)	27(1)
C(8)	9745(1)	8107(1)	13(1)	24(1)
C(19)	11434(1)	9155(1)	131(1)	28(1)
O(6)	11122(1)	5022(1)	-94(1)	43(1)
O(7)	11347(1)	5421(1)	-1591(1)	46(1)
C(7)	10459(1)	7216(1)	-298(1)	26(1)
C(5)	9357(2)	6434(2)	-1601(1)	31(1)
C(23)	7841(2)	7383(2)	2075(1)	35(1)
O(8)	11515(1)	10671(1)	1058(1)	56(1)
C(14)	7800(2)	8643(2)	-1974(1)	38(1)
C(6)	9983(2)	6243(1)	-710(1)	28(1)
C(12)	8914(1)	7415(1)	1599(1)	27(1)
C(1)	9293(1)	8692(2)	-830(1)	28(1)
C(20)	11865(2)	10145(2)	450(1)	33(1)
C(2)	8776(1)	8109(1)	-1637(1)	29(1)
C(24)	9385(2)	6354(2)	1635(1)	37(1)
C(16)	10878(2)	5524(2)	-876(1)	34(1)
C(11)	9614(1)	8186(2)	2111(1)	33(1)
C(10)	10621(1)	8437(2)	1591(1)	30(1)
C(4)	9922(2)	7005(2)	-2356(1)	36(1)
C(17)	12063(2)	4397(2)	-142(2)	49(1)
C(15)	8363(2)	5497(2)	-2707(1)	49(1)
C(22)	13931(2)	11625(2)	-547(2)	72(1)
C(21)	13238(2)	11317(2)	215(2)	62(1)
C(18)	12174(2)	3878(2)	765(2)	65(1)

Table 3. Bond lengths [Å] and angles [°] for qx01m.

O(1)-C(13)	1.216(2)	C(4)-H(4A)	0.9500
O(2)-C(2)	1.431(2)	C(17)-C(18)	1.479(3)
O(2)-C(5)	1.431(2)	C(17)-H(17A)	0.9900
O(3)-C(1)	1.210(2)	C(17)-H(17B)	0.9900
C(13)-C(12)	1.536(2)	C(15)-H(15A)	0.9800
C(13)-C(8)	1.541(2)	C(15)-H(15B)	0.9800
O(4)-C(5)	1.398(2)	C(15)-H(15C)	0.9800
O(4)-C(15)	1.430(2)	C(22)-C(21)	1.465(3)
O(5)-C(20)	1.342(2)	C(22)-H(22A)	0.9800
O(5)-C(21)	1.450(2)	C(22)-H(22B)	0.9800
C(3)-C(4)	1.310(3)	C(22)-H(22C)	0.9800
C(3)-C(2)	1.511(3)	C(21)-H(21A)	0.9900
C(3)-H(3A)	0.9500	C(21)-H(21B)	0.9900
C(9)-C(10)	1.524(2)	C(18)-H(18A)	0.9800
C(9)-C(19)	1.532(2)	C(18)-H(18B)	0.9800
C(9)-C(8)	1.568(2)	C(18)-H(18C)	0.9800
C(9)-H(9A)	1.0000		
C(8)-C(1)	1.547(3)	C(2)-O(2)-C(5)	109.42(13)
C(8)-C(7)	1.555(2)	O(1)-C(13)-C(12)	120.36(16)
C(19)-C(20)	1.493(3)	O(1)-C(13)-C(8)	118.24(15)
C(19)-H(19A)	0.9900	C(12)-C(13)-C(8)	120.74(15)
C(19)-H(19B)	0.9900	C(5)-O(4)-C(15)	114.75(16)
O(6)-C(16)	1.341(2)	C(20)-O(5)-C(21)	115.64(15)
O(6)-C(17)	1.460(2)	C(4)-C(3)-C(2)	109.81(18)
O(7)-C(16)	1.197(2)	C(4)-C(3)-H(3A)	125.1
C(7)-C(6)	1.541(2)	C(2)-C(3)-H(3A)	125.1
C(7)-H(7A)	0.9900	C(10)-C(9)-C(19)	111.38(15)
C(7)-H(7B)	0.9900	C(10)-C(9)-C(8)	112.10(15)
C(5)-C(4)	1.504(3)	C(19)-C(9)-C(8)	111.86(14)
C(5)-C(6)	1.530(3)	C(10)-C(9)-H(9A)	107.0
C(23)-C(12)	1.532(3)	C(19)-C(9)-H(9A)	107.0
C(23)-H(23A)	0.9800	C(8)-C(9)-H(9A)	107.0
C(23)-H(23B)	0.9800	C(13)-C(8)-C(1)	104.69(13)
C(23)-H(23C)	0.9800	C(13)-C(8)-C(7)	116.77(14)
O(8)-C(20)	1.202(2)	C(1)-C(8)-C(7)	111.89(14)
C(14)-C(2)	1.512(3)	C(13)-C(8)-C(9)	105.80(13)
C(14)-H(14A)	0.9800	C(1)-C(8)-C(9)	108.81(14)
C(14)-H(14B)	0.9800	C(7)-C(8)-C(9)	108.49(13)
C(14)-H(14C)	0.9800	C(20)-C(19)-C(9)	113.69(16)
C(6)-C(16)	1.505(3)	C(20)-C(19)-H(19A)	108.8
C(6)-H(6A)	1.0000	C(9)-C(19)-H(19A)	108.8
C(12)-C(24)	1.527(3)	C(20)-C(19)-H(19B)	108.8
C(12)-C(11)	1.543(3)	C(9)-C(19)-H(19B)	108.8
C(1)-C(2)	1.541(3)	H(19A)-C(19)-H(19B)	107.7
C(24)-H(24A)	0.9800	C(16)-O(6)-C(17)	115.62(15)
C(24)-H(24B)	0.9800	C(6)-C(7)-C(8)	120.80(14)
C(24)-H(24C)	0.9800	C(6)-C(7)-H(7A)	107.1
C(11)-C(10)	1.524(2)	C(8)-C(7)-H(7A)	107.1
C(11)-H(11A)	0.9900	C(6)-C(7)-H(7B)	107.1
C(11)-H(11B)	0.9900	C(8)-C(7)-H(7B)	107.1
C(10)-H(10A)	0.9900	H(7A)-C(7)-H(7B)	106.8
C(10)-H(10B)	0.9900	O(4)-C(5)-O(2)	108.99(14)

O(4)-C(5)-C(4)	116.43(15)	O(7)-C(16)-C(6)	125.99(18)
O(2)-C(5)-C(4)	103.39(16)	O(6)-C(16)-C(6)	110.91(16)
O(4)-C(5)-C(6)	105.67(15)	C(10)-C(11)-C(12)	113.49(15)
O(2)-C(5)-C(6)	105.97(14)	C(10)-C(11)-H(11A)	108.9
C(4)-C(5)-C(6)	115.80(15)	C(12)-C(11)-H(11A)	108.9
C(12)-C(23)-H(23A)	109.5	C(10)-C(11)-H(11B)	108.9
C(12)-C(23)-H(23B)	109.5	C(12)-C(11)-H(11B)	108.9
H(23A)-C(23)-H(23B)	109.5	H(11A)-C(11)-H(11B)	107.7
C(12)-C(23)-H(23C)	109.5	C(11)-C(10)-C(9)	112.35(15)
H(23A)-C(23)-H(23C)	109.5	C(11)-C(10)-H(10A)	109.1
H(23B)-C(23)-H(23C)	109.5	C(9)-C(10)-H(10A)	109.1
C(2)-C(14)-H(14A)	109.5	C(11)-C(10)-H(10B)	109.1
C(2)-C(14)-H(14B)	109.5	C(9)-C(10)-H(10B)	109.1
H(14A)-C(14)-H(14B)	109.5	H(10A)-C(10)-H(10B)	107.9
C(2)-C(14)-H(14C)	109.5	C(3)-C(4)-C(5)	109.98(18)
H(14A)-C(14)-H(14C)	109.5	C(3)-C(4)-H(4A)	125.0
H(14B)-C(14)-H(14C)	109.5	C(5)-C(4)-H(4A)	125.0
C(16)-C(6)-C(5)	111.66(15)	O(6)-C(17)-C(18)	107.51(17)
C(16)-C(6)-C(7)	106.79(15)	O(6)-C(17)-H(17A)	110.2
C(5)-C(6)-C(7)	112.88(15)	C(18)-C(17)-H(17A)	110.2
C(16)-C(6)-H(6A)	108.5	O(6)-C(17)-H(17B)	110.2
C(5)-C(6)-H(6A)	108.5	C(18)-C(17)-H(17B)	110.2
C(7)-C(6)-H(6A)	108.5	H(17A)-C(17)-H(17B)	108.5
C(24)-C(12)-C(23)	108.16(15)	O(4)-C(15)-H(15A)	109.5
C(24)-C(12)-C(13)	114.02(15)	O(4)-C(15)-H(15B)	109.5
C(23)-C(12)-C(13)	108.99(15)	H(15A)-C(15)-H(15B)	109.5
C(24)-C(12)-C(11)	111.30(15)	O(4)-C(15)-H(15C)	109.5
C(23)-C(12)-C(11)	108.84(15)	H(15A)-C(15)-H(15C)	109.5
C(13)-C(12)-C(11)	105.42(14)	H(15B)-C(15)-H(15C)	109.5
O(3)-C(1)-C(2)	118.75(16)	C(21)-C(22)-H(22A)	109.5
O(3)-C(1)-C(8)	121.36(16)	C(21)-C(22)-H(22B)	109.5
C(2)-C(1)-C(8)	119.82(16)	H(22A)-C(22)-H(22B)	109.5
O(8)-C(20)-O(5)	123.61(18)	C(21)-C(22)-H(22C)	109.5
O(8)-C(20)-C(19)	126.35(18)	H(22A)-C(22)-H(22C)	109.5
O(5)-C(20)-C(19)	110.04(16)	H(22B)-C(22)-H(22C)	109.5
O(2)-C(2)-C(3)	103.36(16)	O(5)-C(21)-C(22)	108.53(19)
O(2)-C(2)-C(14)	110.05(15)	O(5)-C(21)-H(21A)	110.0
C(3)-C(2)-C(14)	115.15(15)	C(22)-C(21)-H(21A)	110.0
O(2)-C(2)-C(1)	109.94(14)	O(5)-C(21)-H(21B)	110.0
C(3)-C(2)-C(1)	106.85(14)	C(22)-C(21)-H(21B)	110.0
C(14)-C(2)-C(1)	111.14(16)	H(21A)-C(21)-H(21B)	108.4
C(12)-C(24)-H(24A)	109.5	C(17)-C(18)-H(18A)	109.5
C(12)-C(24)-H(24B)	109.5	C(17)-C(18)-H(18B)	109.5
H(24A)-C(24)-H(24B)	109.5	H(18A)-C(18)-H(18B)	109.5
C(12)-C(24)-H(24C)	109.5	C(17)-C(18)-H(18C)	109.5
H(24A)-C(24)-H(24C)	109.5	H(18A)-C(18)-H(18C)	109.5
H(24B)-C(24)-H(24C)	109.5	H(18B)-C(18)-H(18C)	109.5
O(7)-C(16)-O(6)	123.05(19)		

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for qx01m. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	24(1)	45(1)	28(1)	2(1)	-2(1)	-1(1)
O(2)	28(1)	34(1)	26(1)	1(1)	0(1)	-5(1)
O(3)	42(1)	31(1)	39(1)	6(1)	-7(1)	-2(1)
C(13)	26(1)	26(1)	24(1)	-2(1)	-2(1)	1(1)
O(4)	47(1)	38(1)	33(1)	-10(1)	-7(1)	-11(1)
O(5)	38(1)	36(1)	43(1)	-5(1)	12(1)	-14(1)
C(3)	33(1)	52(1)	21(1)	3(1)	0(1)	-9(1)
C(9)	25(1)	28(1)	27(1)	-4(1)	0(1)	-1(1)
C(8)	21(1)	28(1)	22(1)	-2(1)	1(1)	-3(1)
C(19)	26(1)	29(1)	29(1)	-2(1)	1(1)	-3(1)
O(6)	46(1)	40(1)	42(1)	4(1)	6(1)	14(1)
O(7)	55(1)	48(1)	36(1)	-9(1)	10(1)	11(1)
C(7)	25(1)	31(1)	24(1)	-3(1)	0(1)	-2(1)
C(5)	31(1)	33(1)	29(1)	-7(1)	0(1)	-5(1)
C(23)	31(1)	45(1)	28(1)	6(1)	4(1)	-5(1)
O(8)	58(1)	49(1)	60(1)	-28(1)	25(1)	-19(1)
C(14)	38(1)	44(1)	32(1)	9(1)	-6(1)	-6(1)
C(6)	32(1)	27(1)	24(1)	-4(1)	3(1)	-1(1)
C(12)	24(1)	33(1)	24(1)	2(1)	0(1)	-1(1)
C(1)	21(1)	36(1)	26(1)	2(1)	4(1)	-2(1)
C(20)	31(1)	35(1)	33(1)	-4(1)	2(1)	-5(1)
C(2)	30(1)	33(1)	25(1)	7(1)	-2(1)	-4(1)
C(24)	44(1)	39(1)	28(1)	9(1)	0(1)	2(1)
C(16)	41(1)	31(1)	30(1)	-6(1)	-1(1)	-4(1)
C(11)	32(1)	42(1)	25(1)	0(1)	-2(1)	-6(1)
C(10)	27(1)	35(1)	26(1)	-4(1)	-3(1)	-2(1)
C(4)	33(1)	51(1)	23(1)	-5(1)	1(1)	-5(1)
C(17)	52(1)	41(1)	55(1)	1(1)	7(1)	14(1)
C(15)	47(1)	63(2)	38(1)	-19(1)	-9(1)	-9(1)
C(22)	80(2)	59(2)	78(2)	3(1)	18(2)	-35(2)
C(21)	73(2)	44(1)	70(2)	-13(1)	19(1)	-33(1)
C(18)	70(2)	53(2)	71(2)	5(1)	-4(2)	16(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for qx01m.

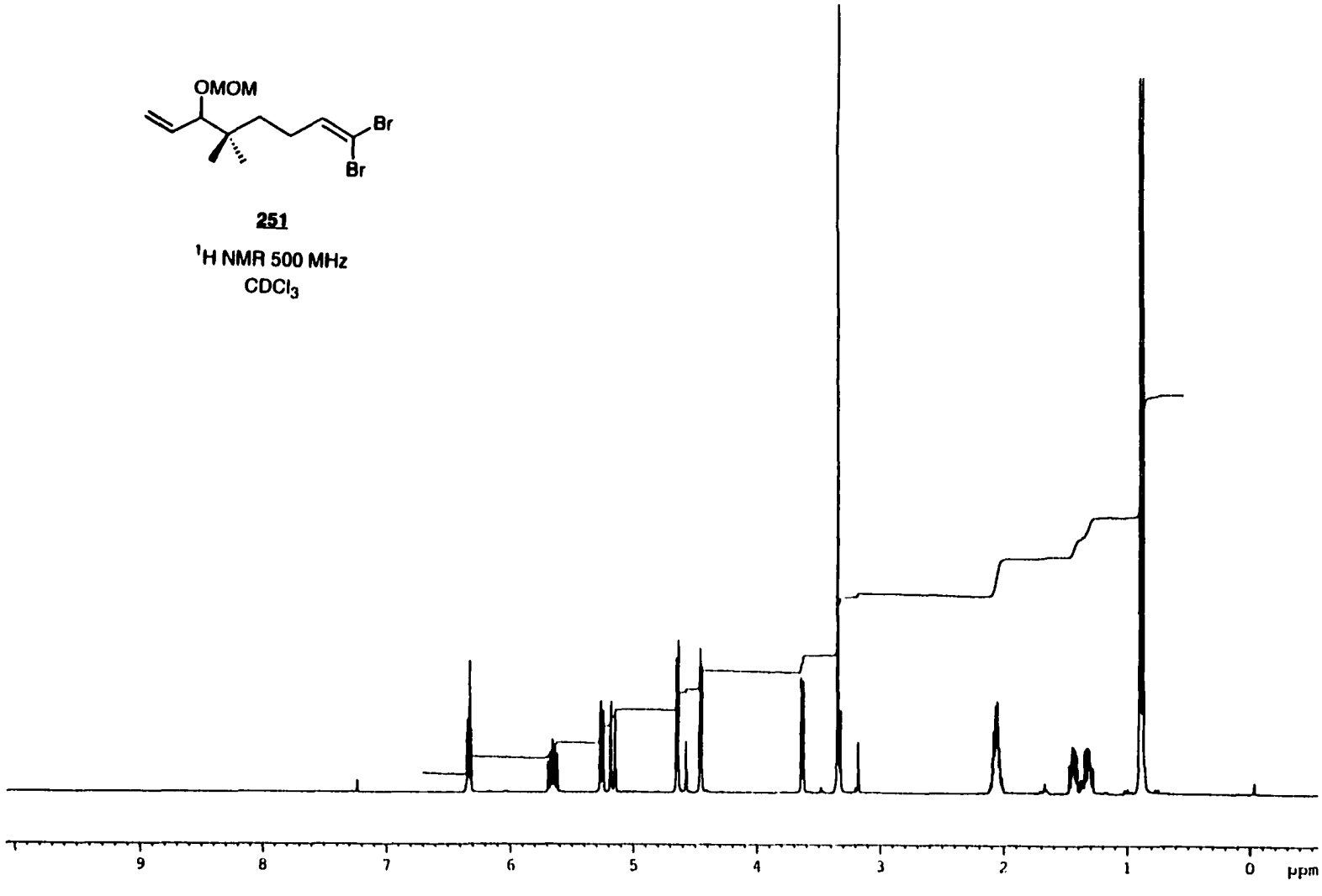
	x	y	z	U(eq)
H(3A)	9873	8456	-2774	42
H(9A)	9990	9484	697	32
H(19A)	11964	8622	243	33
H(19B)	11306	9189	-548	33
H(7A)	10954	7488	-766	32
H(7B)	10880	7014	250	32
H(23A)	7392	6891	1758	52
H(23B)	7517	8054	2045	52
H(23C)	7928	7184	2728	52
H(14A)	7488	8258	-2487	56
H(14B)	7983	9322	-2192	56
H(14C)	7296	8695	-1462	56
H(6A)	9504	5938	-236	33
H(24A)	8926	5882	1301	55
H(24B)	9452	6139	2285	55
H(24C)	10077	6360	1341	55
H(11A)	9211	8817	2208	39
H(11B)	9795	7912	2732	39
H(10A)	11053	7818	1540	35
H(10B)	11024	8941	1953	35
H(4A)	10428	6722	-2764	43
H(17A)	12684	4824	-266	59
H(17B)	11997	3895	-650	59
H(15A)	8093	4816	-2829	74
H(15B)	8828	5701	-3217	74
H(15C)	7776	5973	-2664	74
H(22A)	14294	12251	-376	108
H(22B)	13515	11739	-1111	108
H(22C)	14447	11092	-664	108
H(21A)	13651	11213	791	74
H(21B)	12712	11851	335	74
H(18A)	12802	3451	755	97
H(18B)	11556	3456	879	97
H(18C)	12239	4382	1262	97

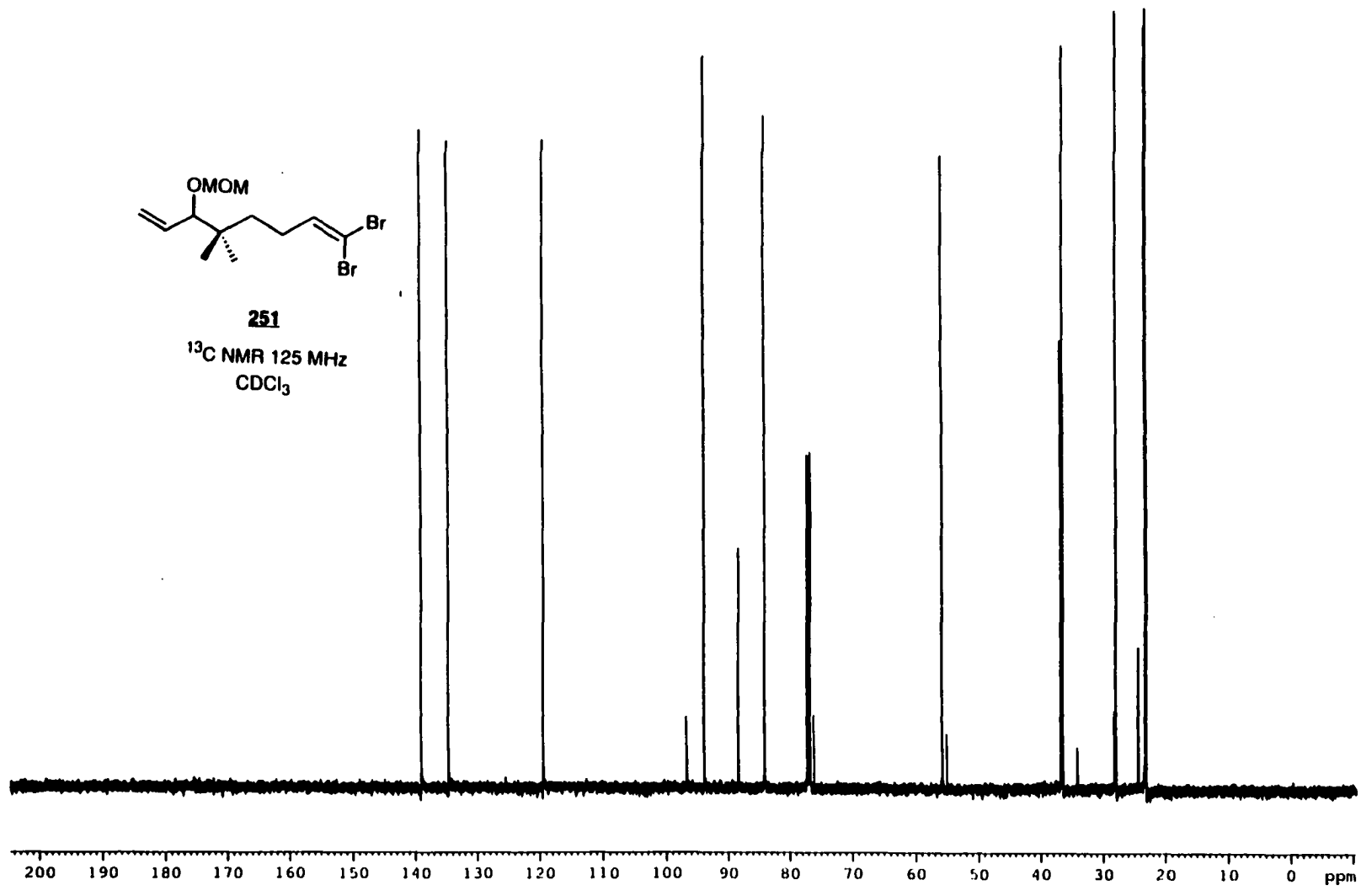
Table 6. Torsion angles [°] for qx01m.

O(1)-C(13)-C(8)-C(1)	1.8(2)	C(9)-C(8)-C(1)-O(3)	-8.2(2)
C(12)-C(13)-C(8)-C(1)	-168.93(15)	C(13)-C(8)-C(1)-C(2)	-78.52(18)
O(1)-C(13)-C(8)-C(7)	-122.54(18)	C(7)-C(8)-C(1)-C(2)	48.9(2)
C(12)-C(13)-C(8)-C(7)	66.7(2)	C(9)-C(8)-C(1)-C(2)	168.73(15)
O(1)-C(13)-C(8)-C(9)	116.67(17)	C(21)-O(5)-C(20)-O(8)	2.3(3)
C(12)-C(13)-C(8)-C(9)	-54.1(2)	C(21)-O(5)-C(20)-C(19)	-177.94(18)
C(10)-C(9)-C(8)-C(13)	51.37(18)	C(9)-C(19)-C(20)-O(8)	3.5(3)
C(19)-C(9)-C(8)-C(13)	177.30(15)	C(9)-C(19)-C(20)-O(5)	-176.23(15)
C(10)-C(9)-C(8)-C(1)	163.38(14)	C(5)-O(2)-C(2)-C(3)	19.16(17)
C(19)-C(9)-C(8)-C(1)	-70.69(18)	C(5)-O(2)-C(2)-C(14)	142.65(15)
C(10)-C(9)-C(8)-C(7)	-74.67(18)	C(5)-O(2)-C(2)-C(1)	-94.62(16)
C(19)-C(9)-C(8)-C(7)	51.27(19)	C(4)-C(3)-C(2)-O(2)	-10.5(2)
C(10)-C(9)-C(19)-C(20)	-78.2(2)	C(4)-C(3)-C(2)-C(14)	-130.59(18)
C(8)-C(9)-C(19)-C(20)	155.48(16)	C(4)-C(3)-C(2)-C(1)	105.46(19)
C(13)-C(8)-C(7)-C(6)	46.6(2)	O(3)-C(1)-C(2)-O(2)	-165.93(16)
C(1)-C(8)-C(7)-C(6)	-73.96(19)	C(8)-C(1)-C(2)-O(2)	17.0(2)
C(9)-C(8)-C(7)-C(6)	165.99(15)	O(3)-C(1)-C(2)-C(3)	82.6(2)
C(15)-O(4)-C(5)-O(2)	70.11(19)	C(8)-C(1)-C(2)-C(3)	-94.49(18)
C(15)-O(4)-C(5)-C(4)	-46.3(2)	O(3)-C(1)-C(2)-C(14)	-43.8(2)
C(15)-O(4)-C(5)-C(6)	-176.40(15)	C(8)-C(1)-C(2)-C(14)	139.12(16)
C(2)-O(2)-C(5)-O(4)	-144.59(14)	C(17)-O(6)-C(16)-O(7)	5.1(3)
C(2)-O(2)-C(5)-C(4)	-20.13(17)	C(17)-O(6)-C(16)-C(6)	-172.65(17)
C(2)-O(2)-C(5)-C(6)	102.12(15)	C(5)-C(6)-C(16)-O(7)	29.5(3)
O(4)-C(5)-C(6)-C(16)	63.08(19)	C(7)-C(6)-C(16)-O(7)	-94.3(2)
O(2)-C(5)-C(6)-C(16)	178.66(15)	C(5)-C(6)-C(16)-O(6)	-152.77(16)
C(4)-C(5)-C(6)-C(16)	-67.4(2)	C(7)-C(6)-C(16)-O(6)	83.40(18)
O(4)-C(5)-C(6)-C(7)	-176.59(14)	C(24)-C(12)-C(11)-C(10)	72.2(2)
O(2)-C(5)-C(6)-C(7)	-61.01(18)	C(23)-C(12)-C(11)-C(10)	-168.67(16)
C(4)-C(5)-C(6)-C(7)	52.9(2)	C(13)-C(12)-C(11)-C(10)	-51.9(2)
C(8)-C(7)-C(6)-C(16)	-176.49(16)	C(12)-C(11)-C(10)-C(9)	57.9(2)
C(8)-C(7)-C(6)-C(5)	60.4(2)	C(19)-C(9)-C(10)-C(11)	176.80(16)
O(1)-C(13)-C(12)-C(24)	121.07(19)	C(8)-C(9)-C(10)-C(11)	-57.0(2)
C(8)-C(13)-C(12)-C(24)	-68.4(2)	C(2)-C(3)-C(4)-C(5)	-1.7(2)
O(1)-C(13)-C(12)-C(23)	0.1(2)	O(4)-C(5)-C(4)-C(3)	132.78(18)
C(8)-C(13)-C(12)-C(23)	170.66(16)	O(2)-C(5)-C(4)-C(3)	13.3(2)
O(1)-C(13)-C(12)-C(11)	-116.56(19)	C(6)-C(5)-C(4)-C(3)	-102.1(2)
C(8)-C(13)-C(12)-C(11)	54.0(2)	C(16)-O(6)-C(17)-C(18)	-177.74(18)
C(13)-C(8)-C(1)-O(3)	104.52(19)	C(20)-O(5)-C(21)-C(22)	-162.8(2)
C(7)-C(8)-C(1)-O(3)	-128.10(18)		

251

^{1}H NMR 500 MHz
$CDCl_3$





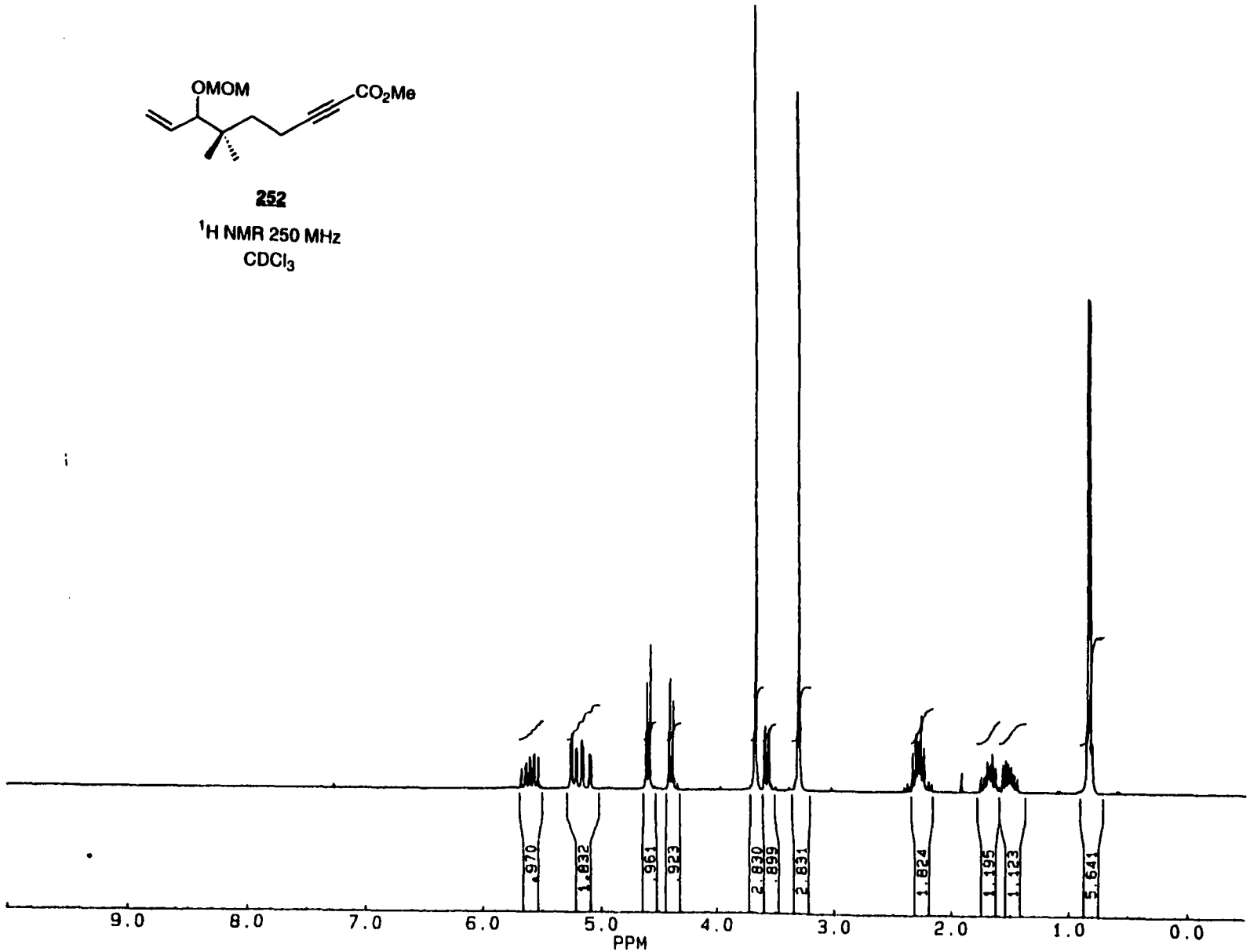
251

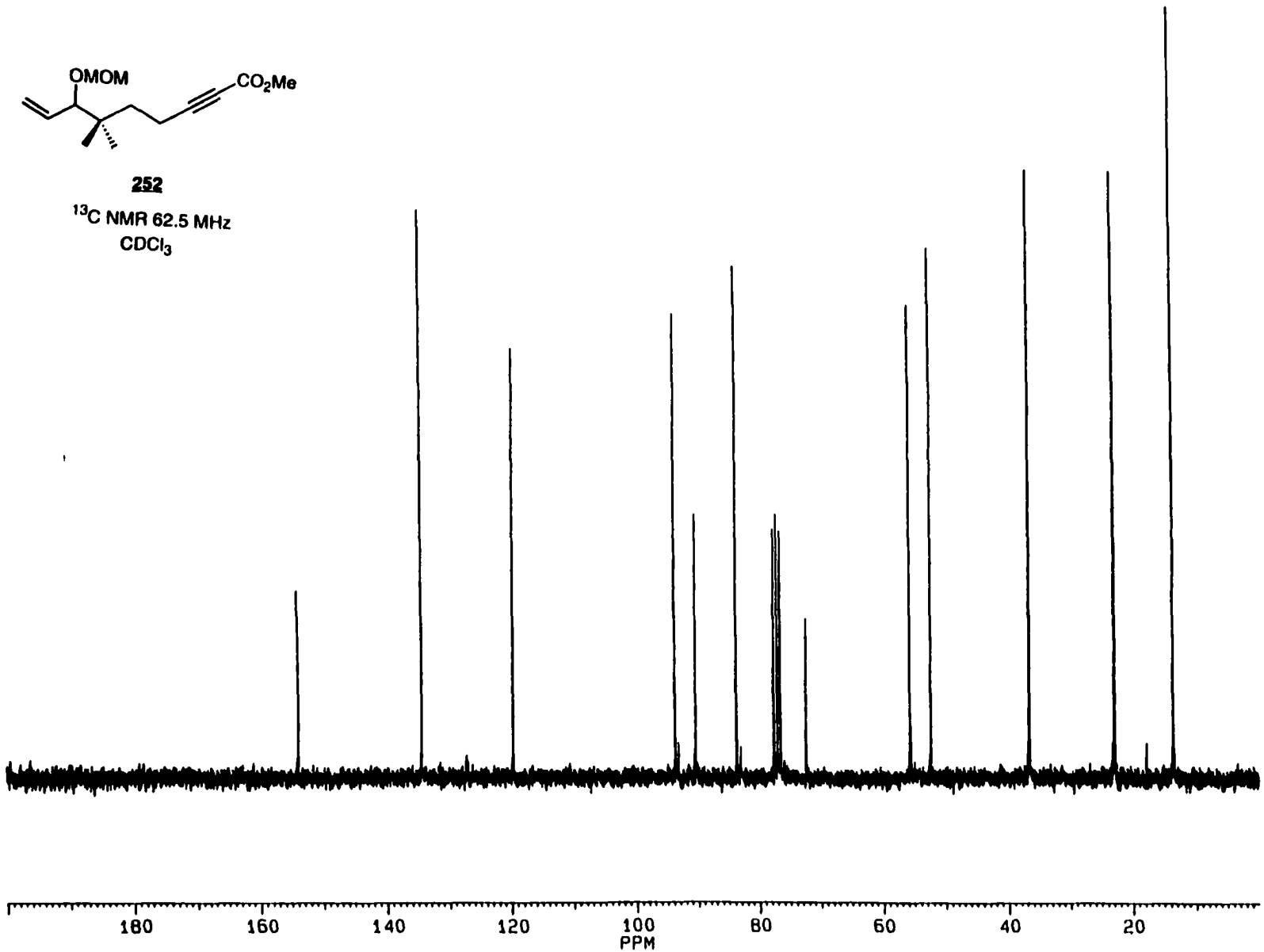
^{13}C NMR 125 MHz

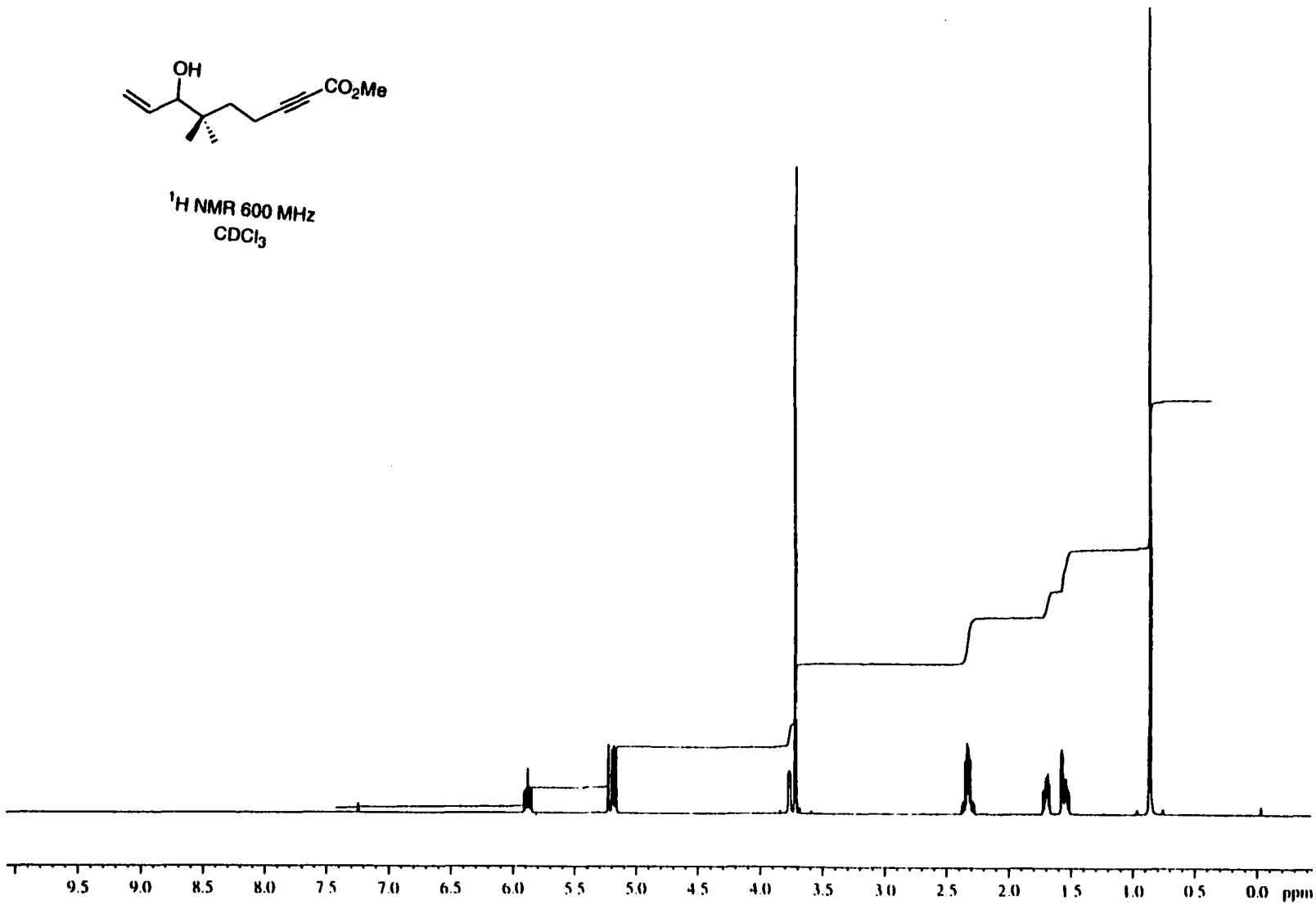
$CDCl_3$

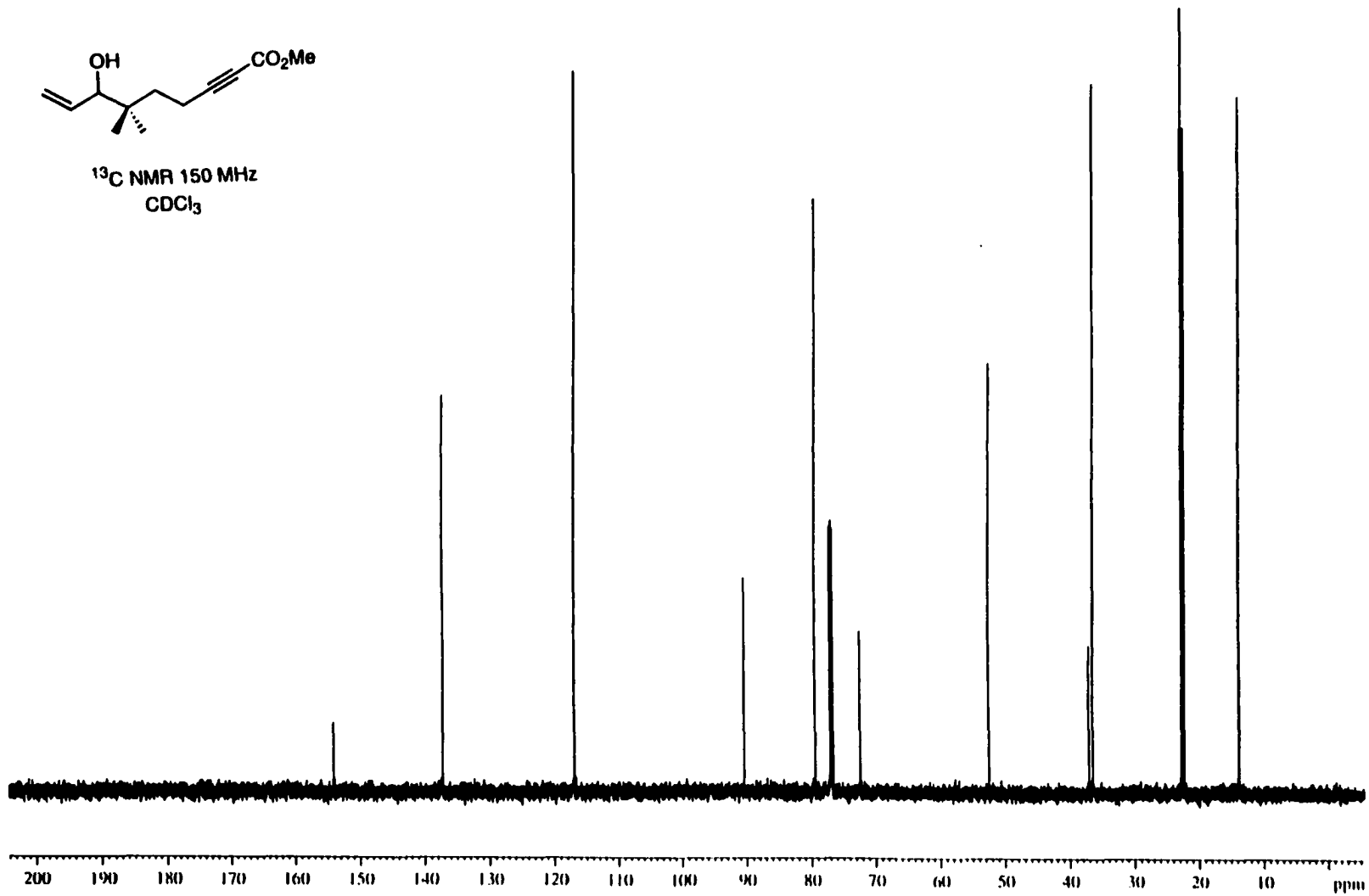
252

^{1}H NMR 250 MHz
$CDCl_3$



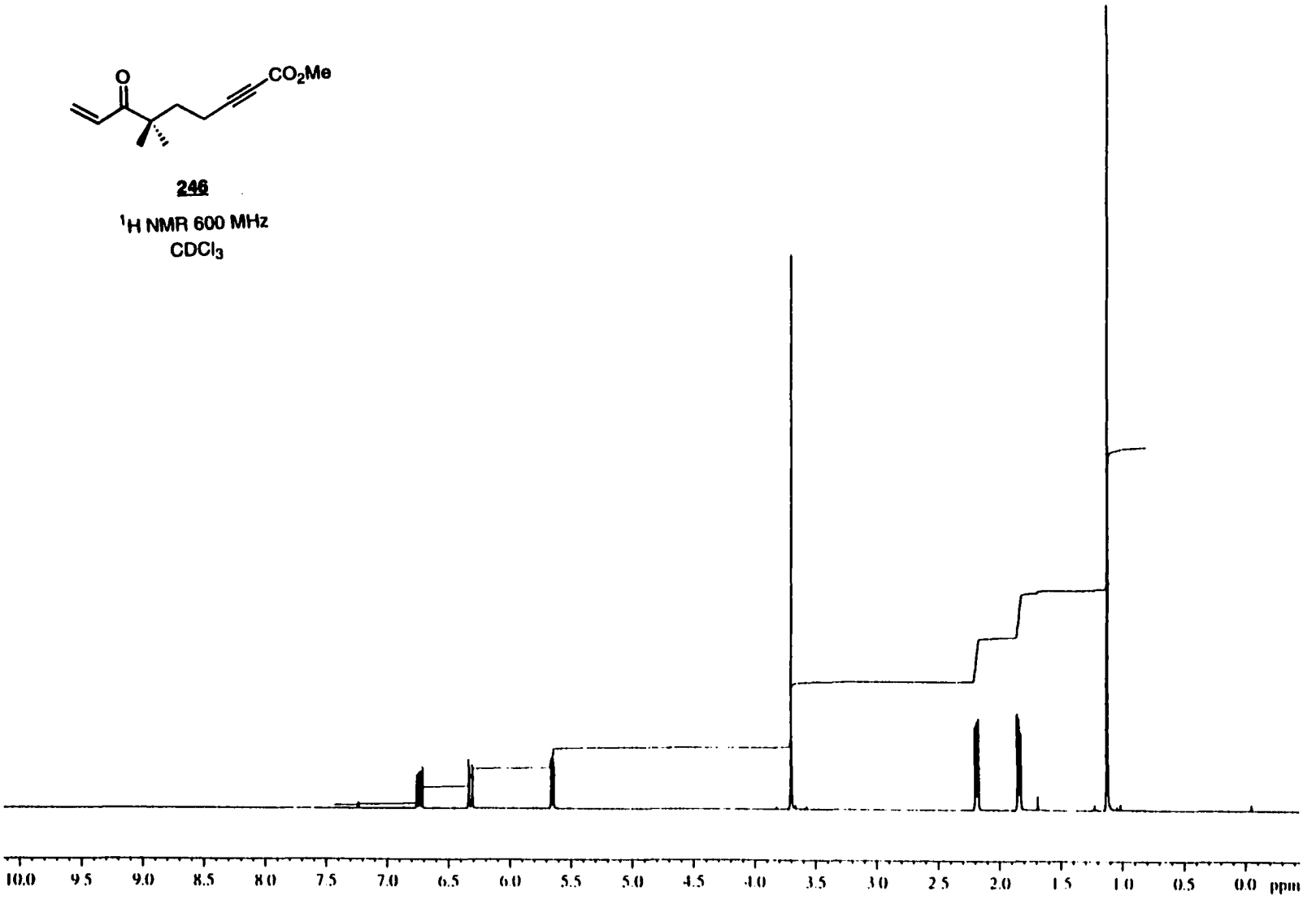

OMOM
CO2Me
252
13C NMR 62.5 MHz
CDCl3
180
160
140
120
100
80
60
40
20
PPM


OH
CO2Me
1H NMR 600 MHz
CDCl3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


OH
CO2Me
13C NMR 150 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

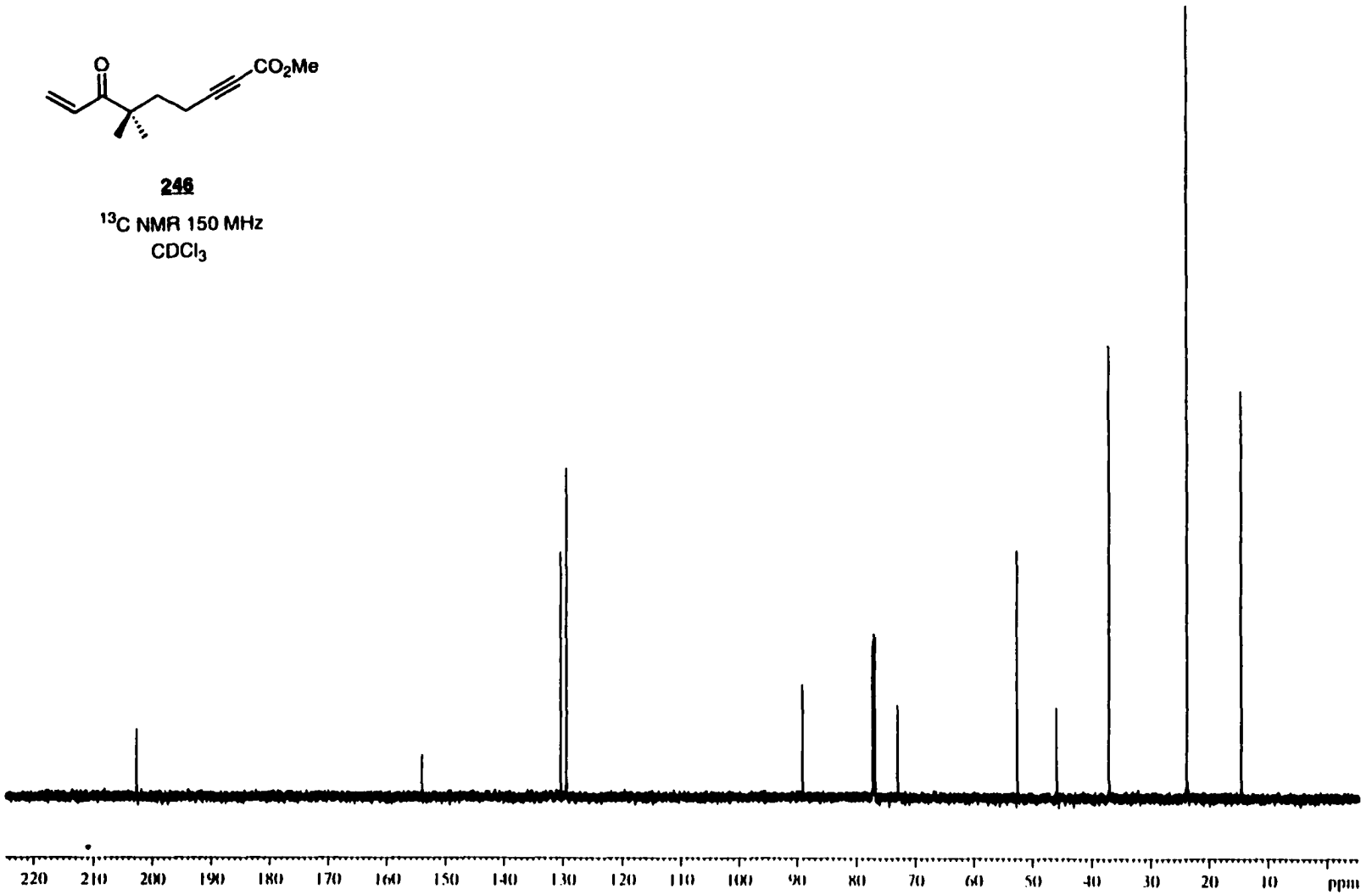
246

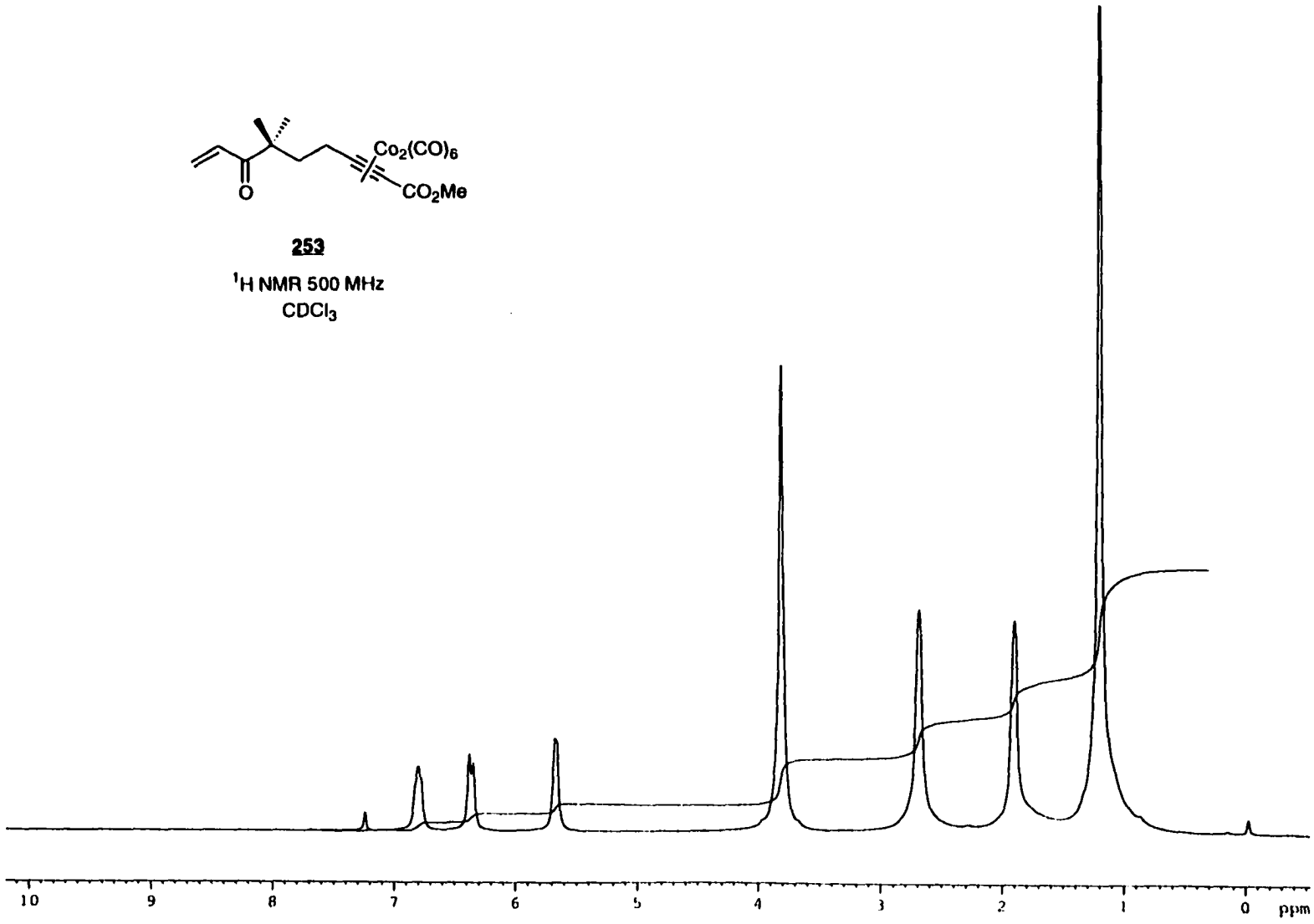
^{1}H NMR 600 MHz
$CDCl_3$



246

^{13}C NMR 150 MHz
$CDCl_3$

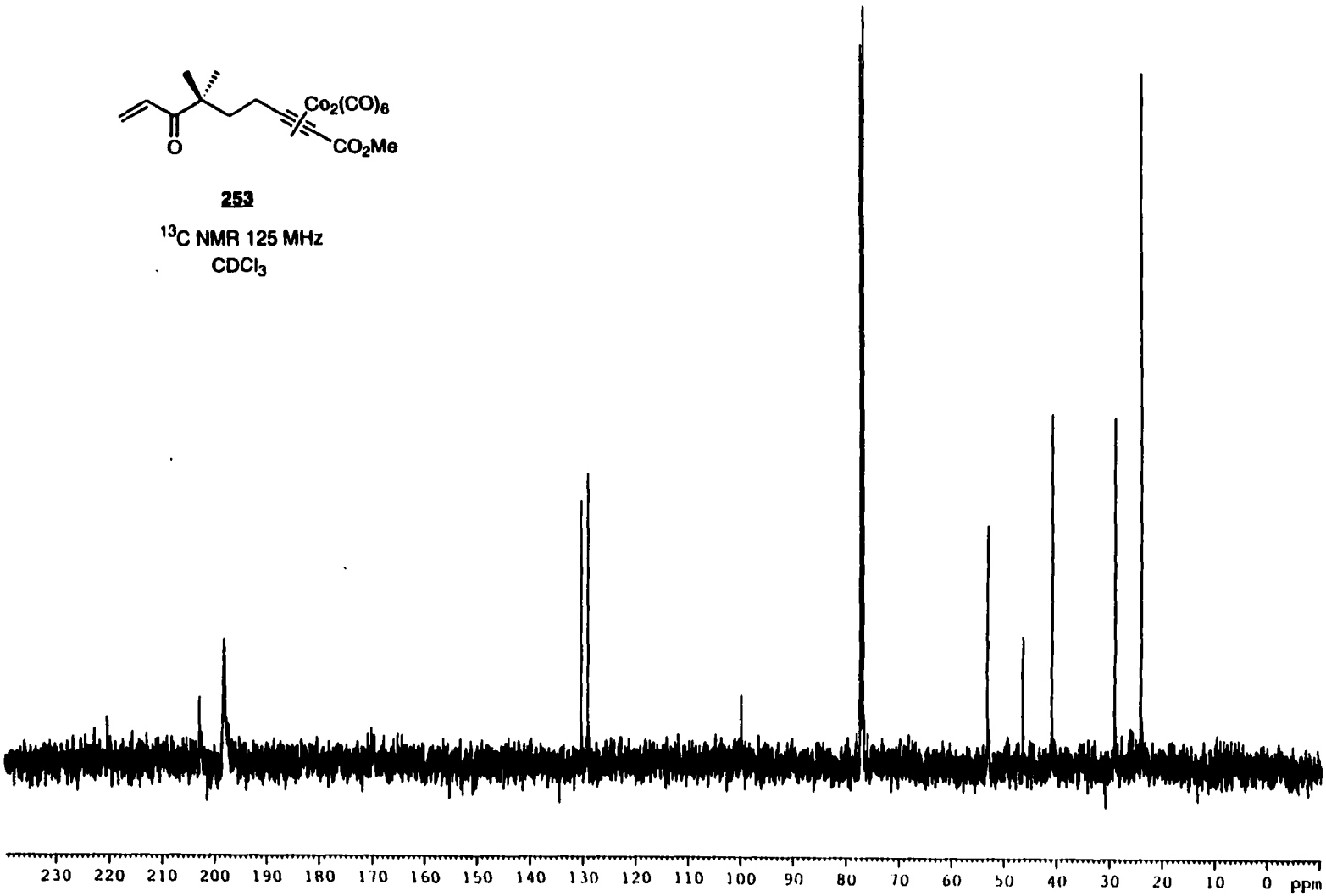


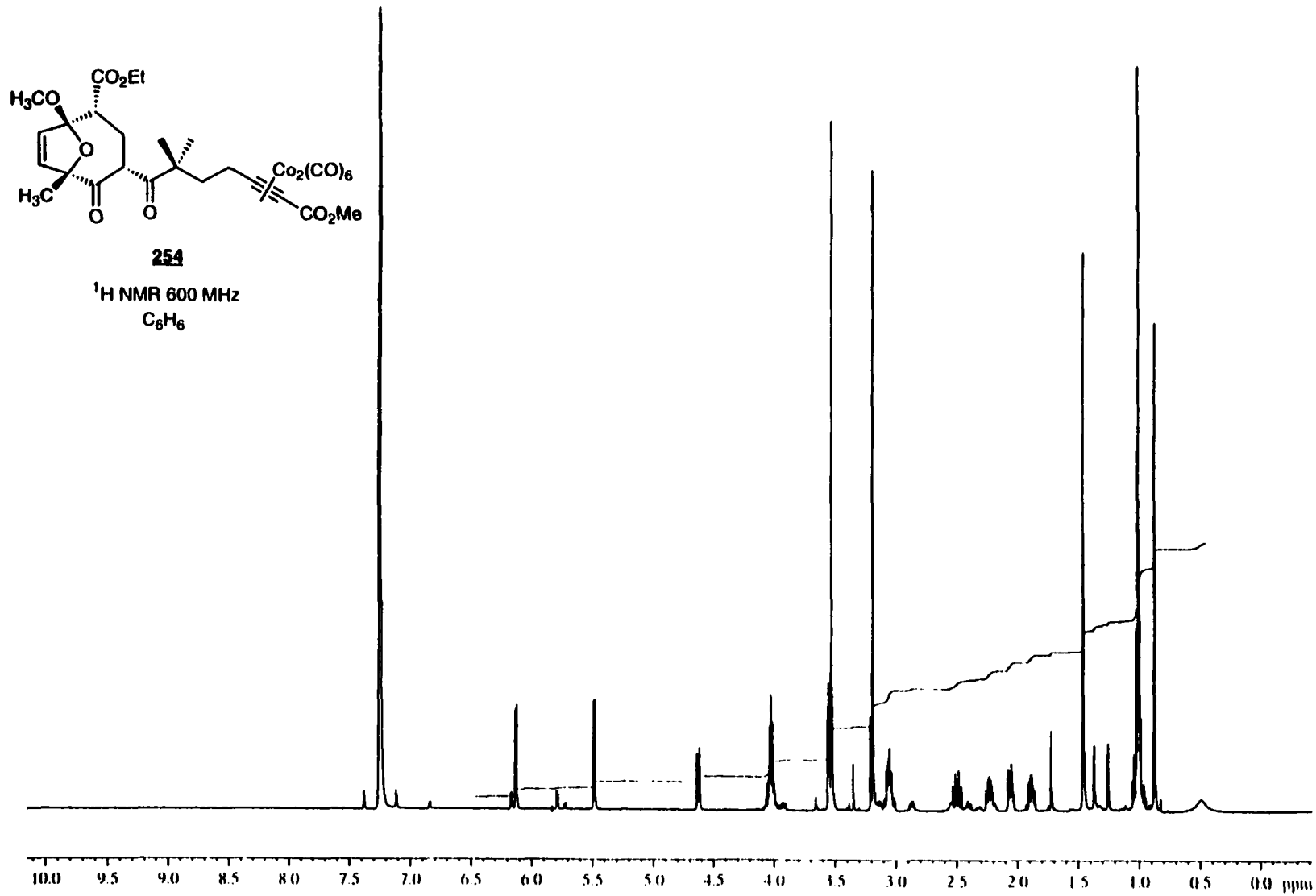

Co2(CO)6
CO2Me
O
253
1H NMR 500 MHz
CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm

253

^{13}C NMR 125 MHz

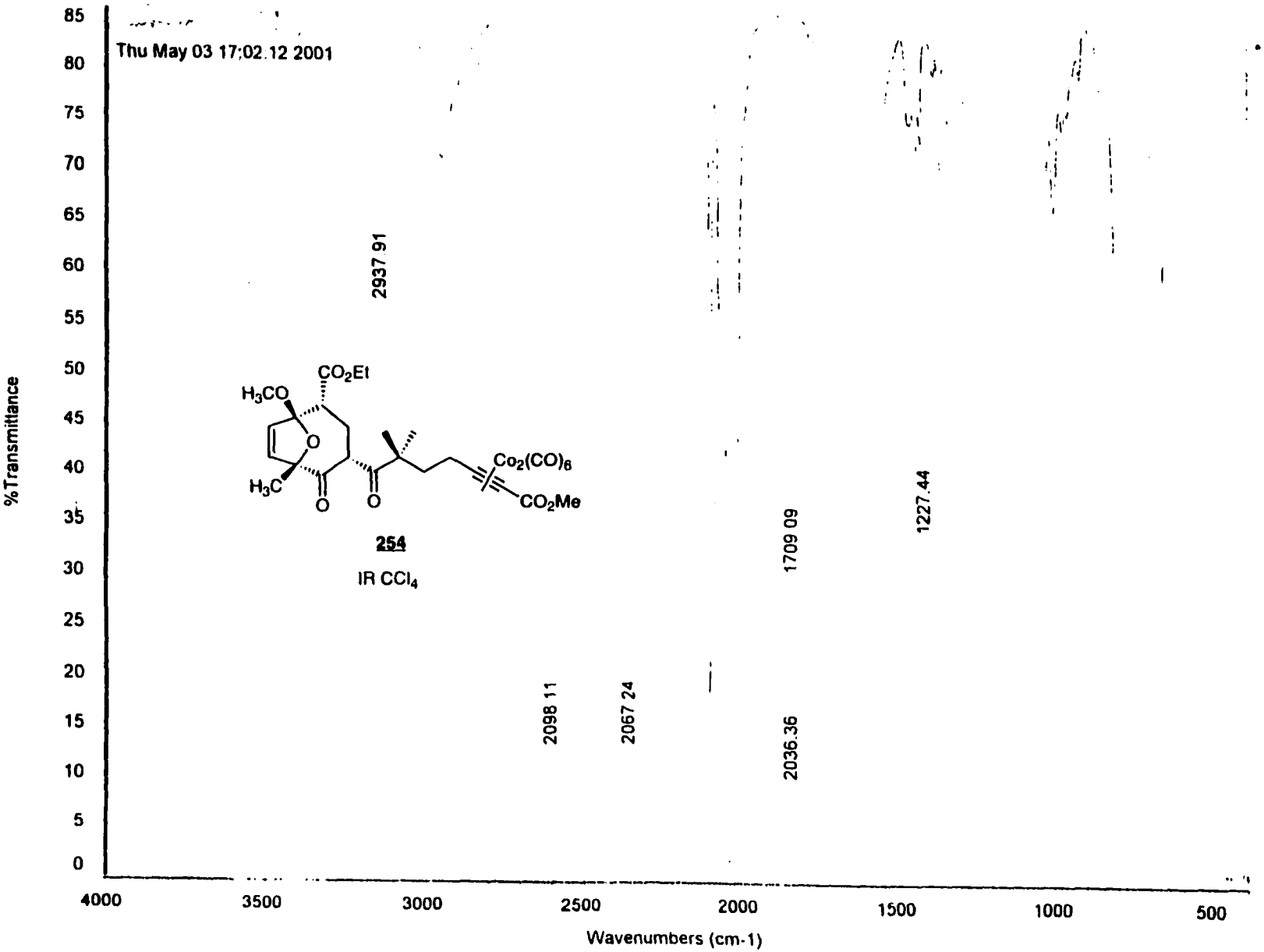
$CDCl_3$





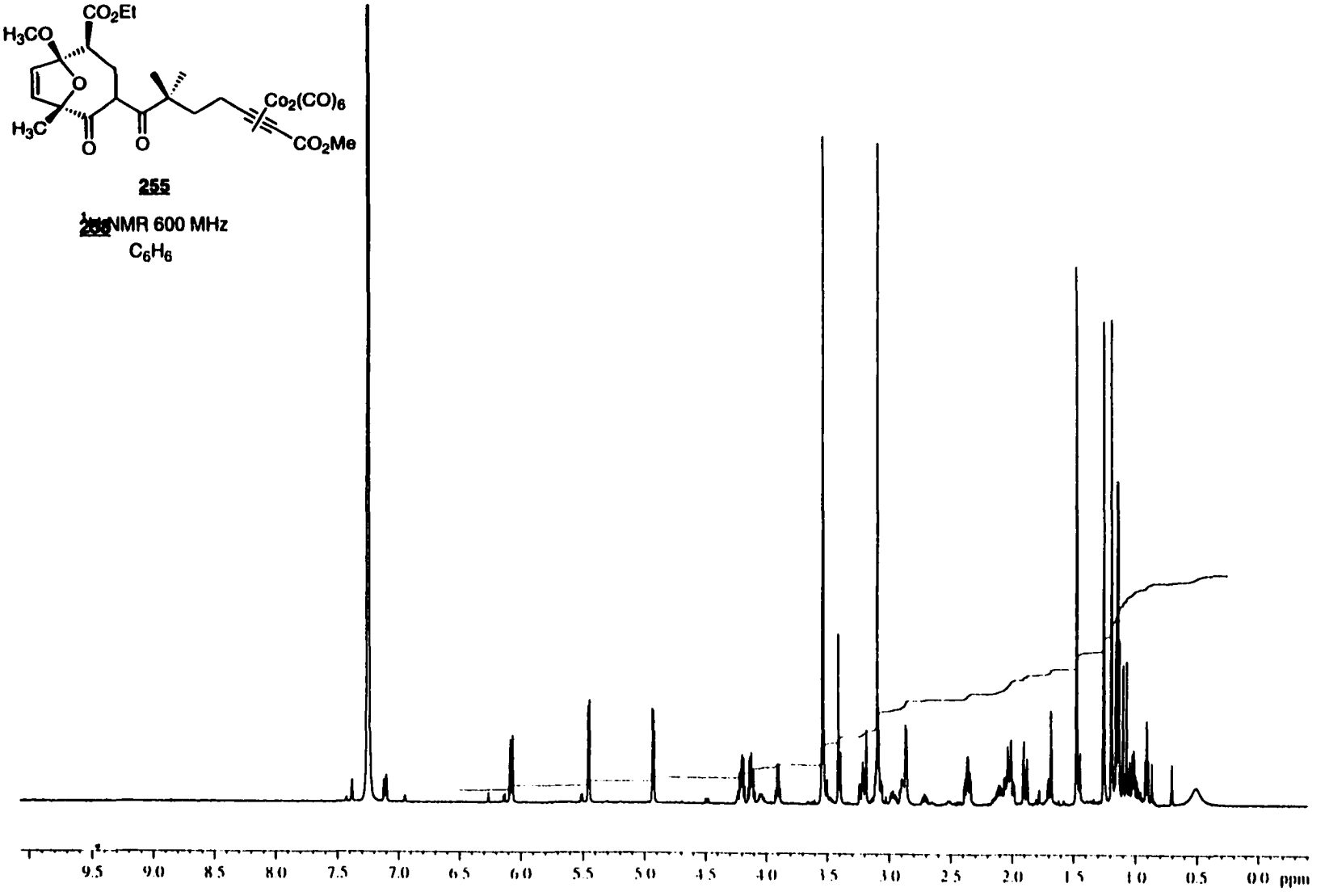
254

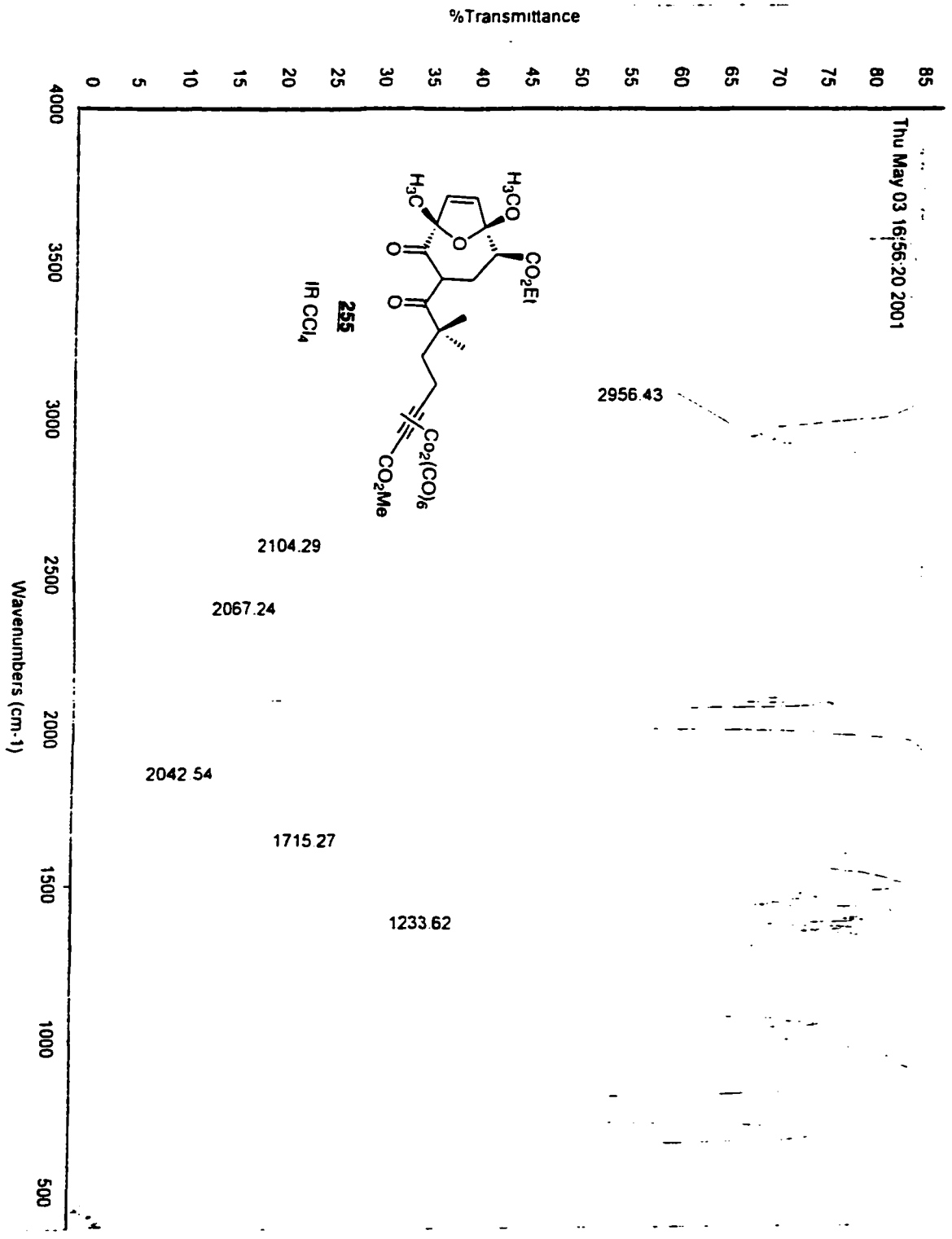
^{1}H NMR 600 MHz
C_6H_6

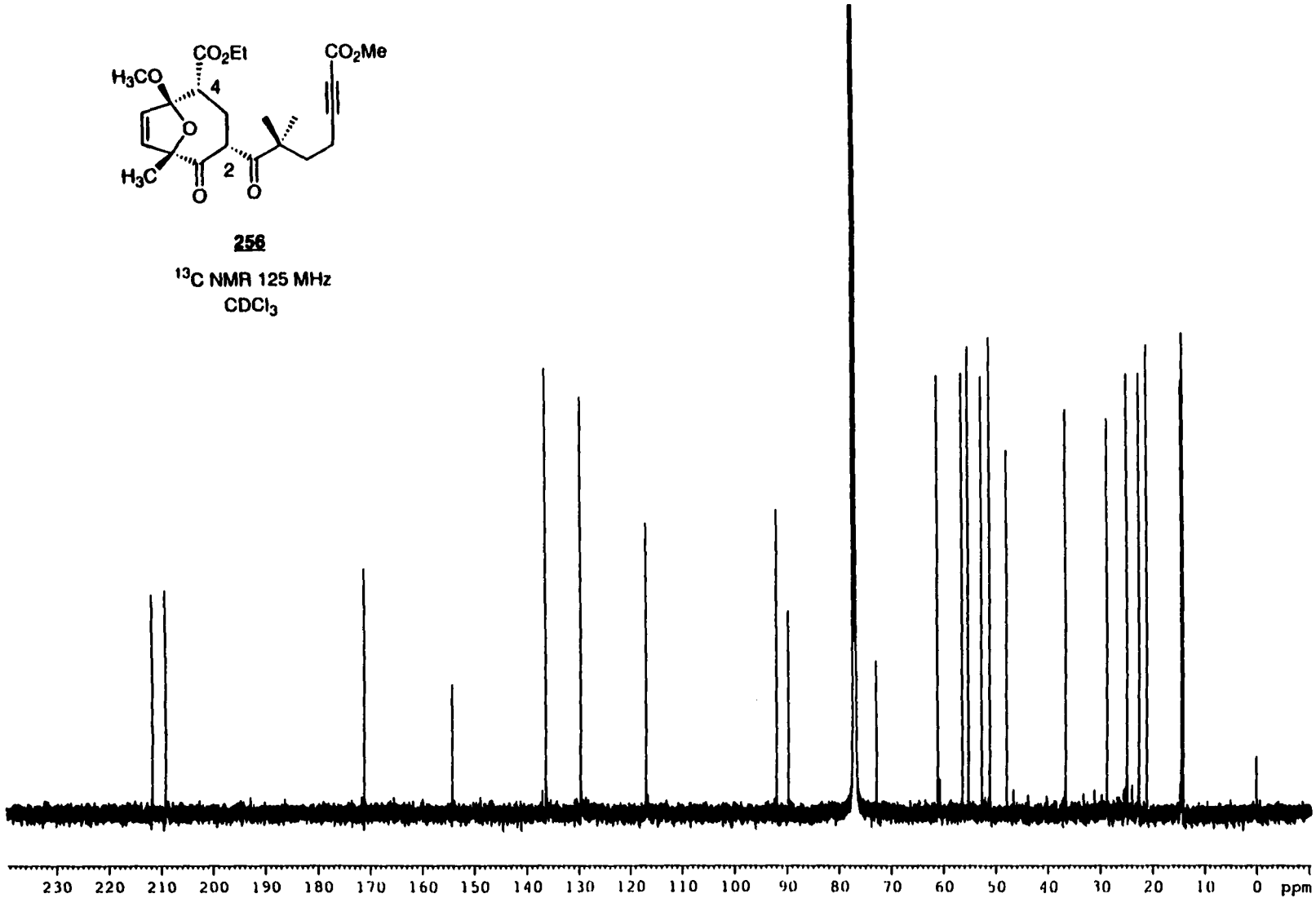

Thu May 03 17:02:12 2001
%Transmittance
Wavenumbers (cm-1)
2937.91
2098.11
2067.24
2036.36
1709.09
1227.44
CO2Et
H3CO
H3C
O
O
O
Co2(CO)6
CO2Me
254
IR CCl4

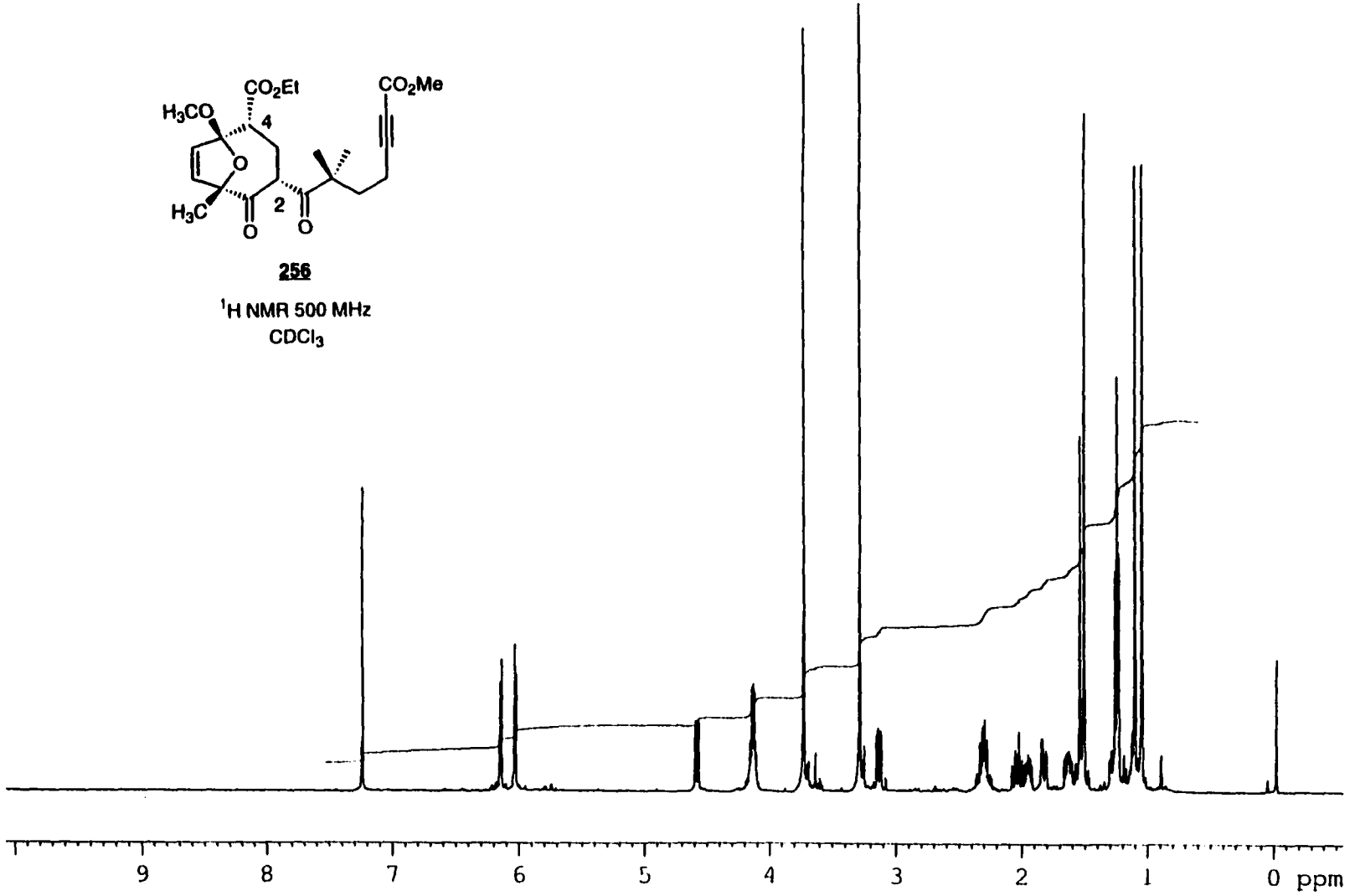
255

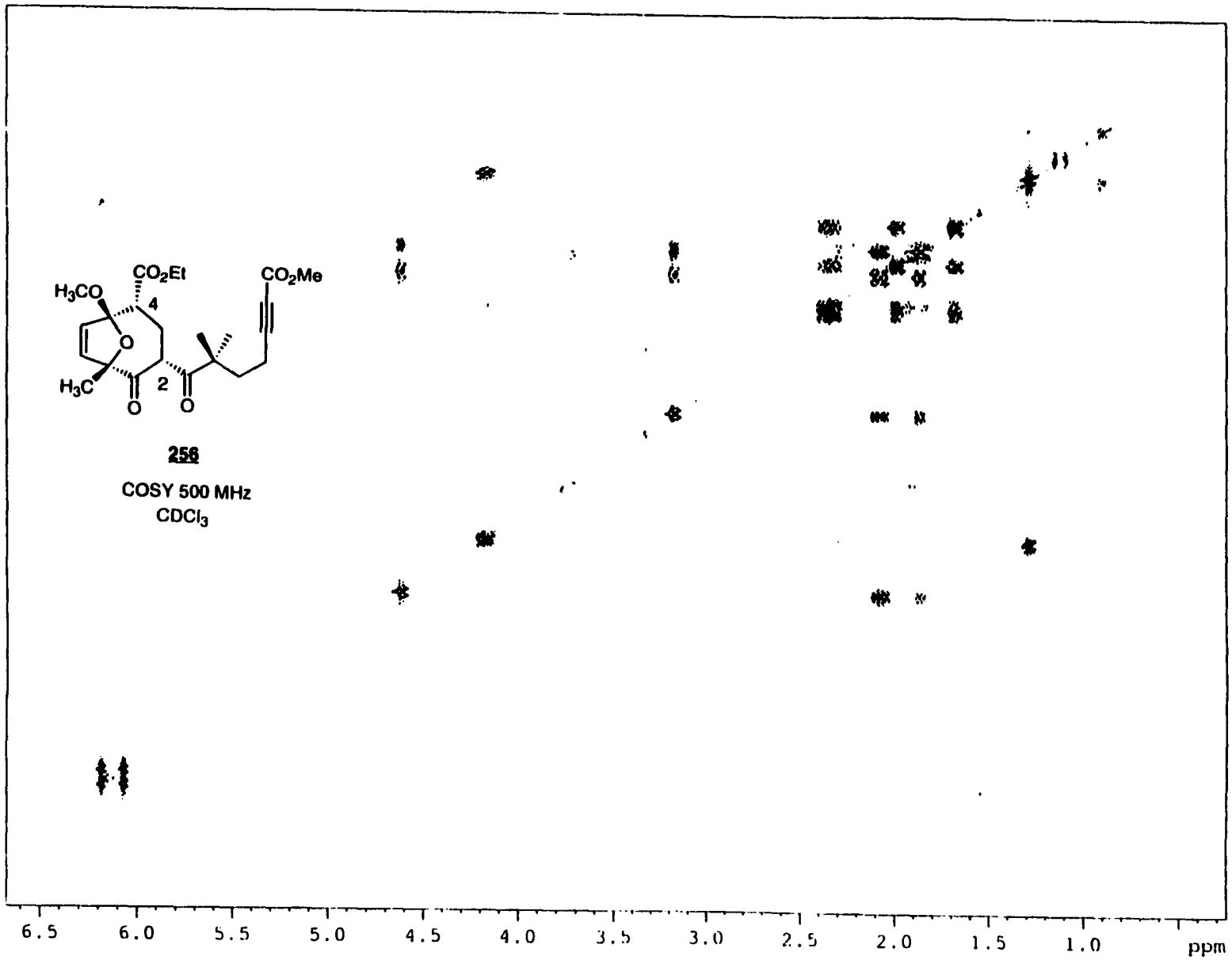
^{1}H NMR 600 MHz
C_6H_6

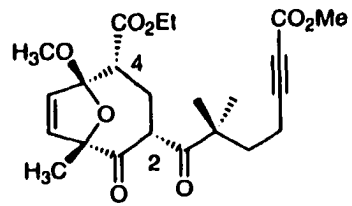



%Transmittance
Wavenumbers (cm-1)
Thu May 03 16:56:20 2001
255
IR CCl_4
2956.43
2104.29
2067.24
2042.54
1715.27
1233.62
H_3C
H_3CO
CO_2Et
$Co_2(CO)_6$
CO_2Me


CO2Et
CO2Me
H3CO
4
O
H3C
2
O
O
256
13C NMR 125 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

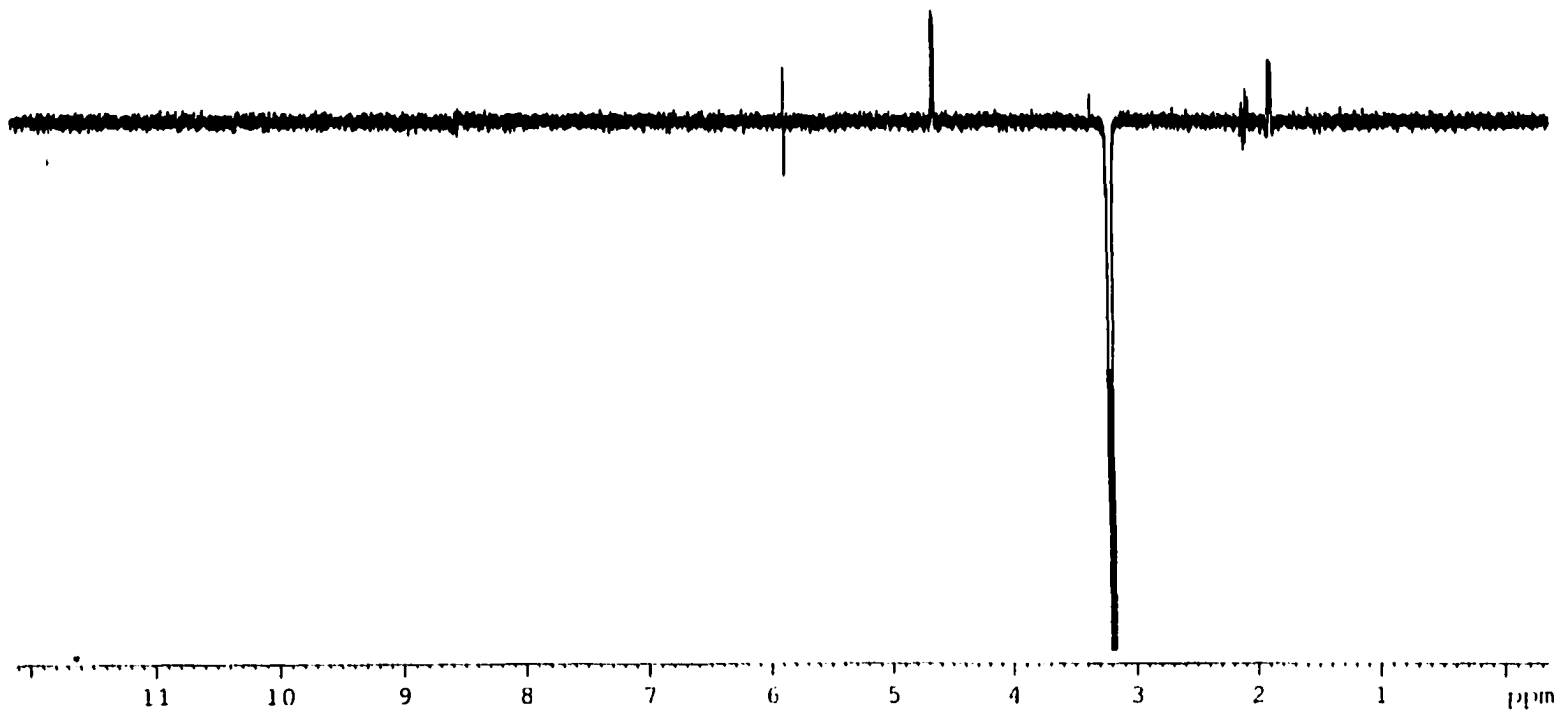

CO2Et
CO2Me
H3CO
4
O
2
H3C
O
O
256
1H NMR 500 MHz
CDCl3
9
8
7
6
5
4
3
2
1
0 ppm

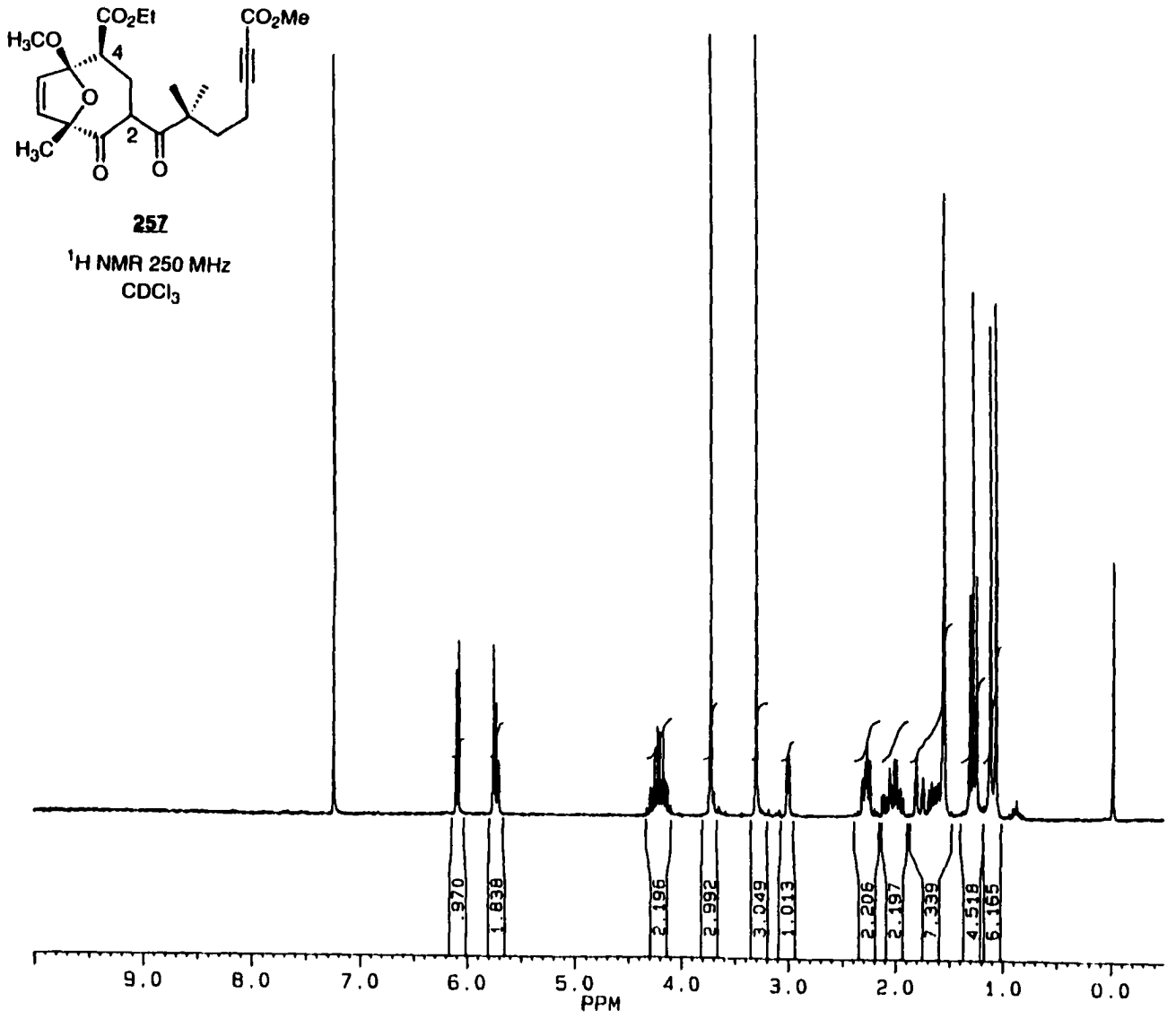

CO2Et
CO2Me
H3CO
4
O
H3C
2
O
O
256
COSY 500 MHz
CDCl3
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm



256

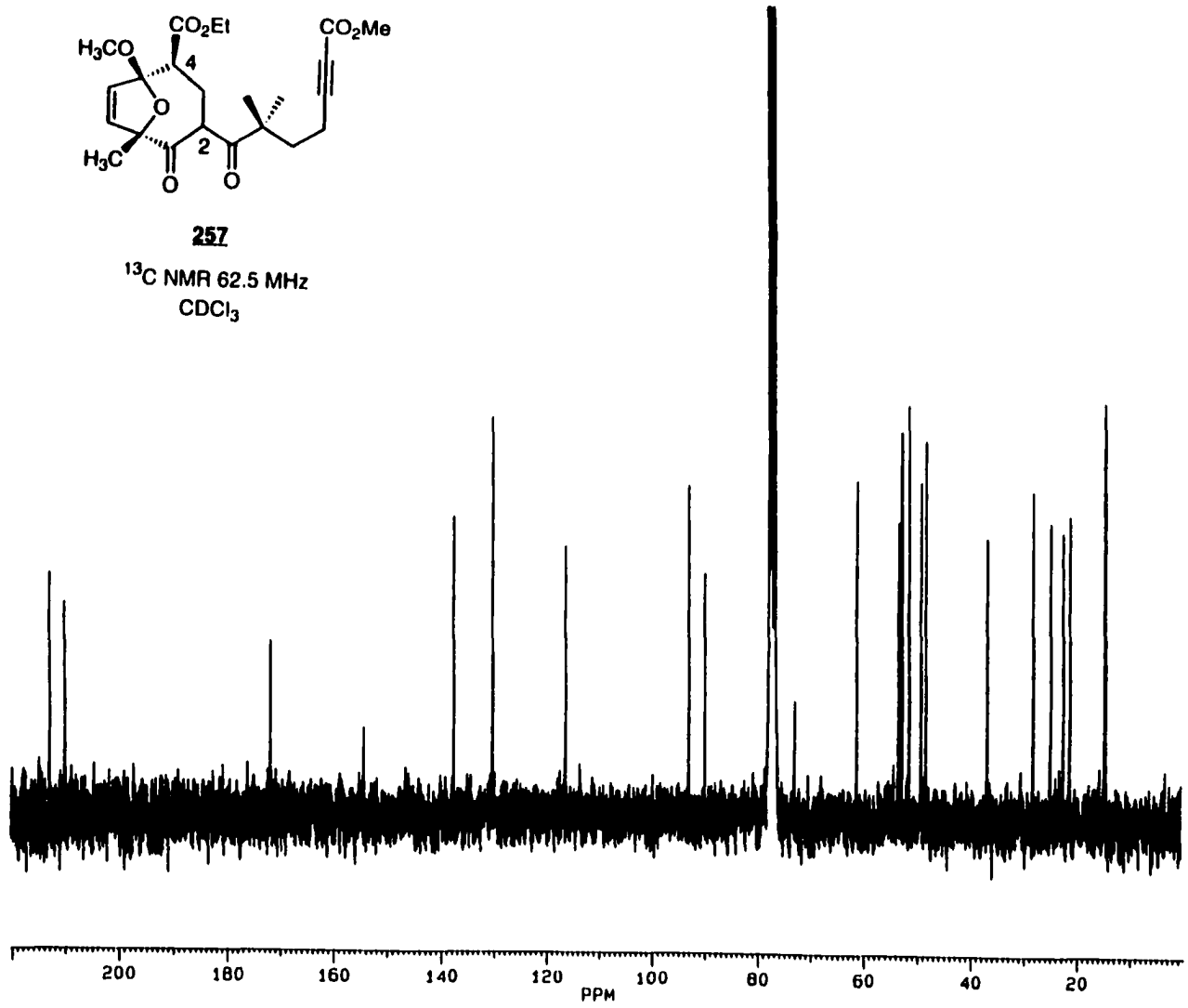
1D NOE 500 MHz
$CDCl_3$

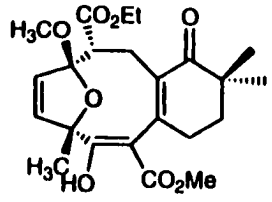



CO2Et
CO2Me
H3CO
4
O
2
H3C
O
O
257
1H NMR 250 MHz
CDCl3
.970
1.838
2.196
2.992
3.049
1.013
2.206
2.197
7.339
4.518
6.165
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

257

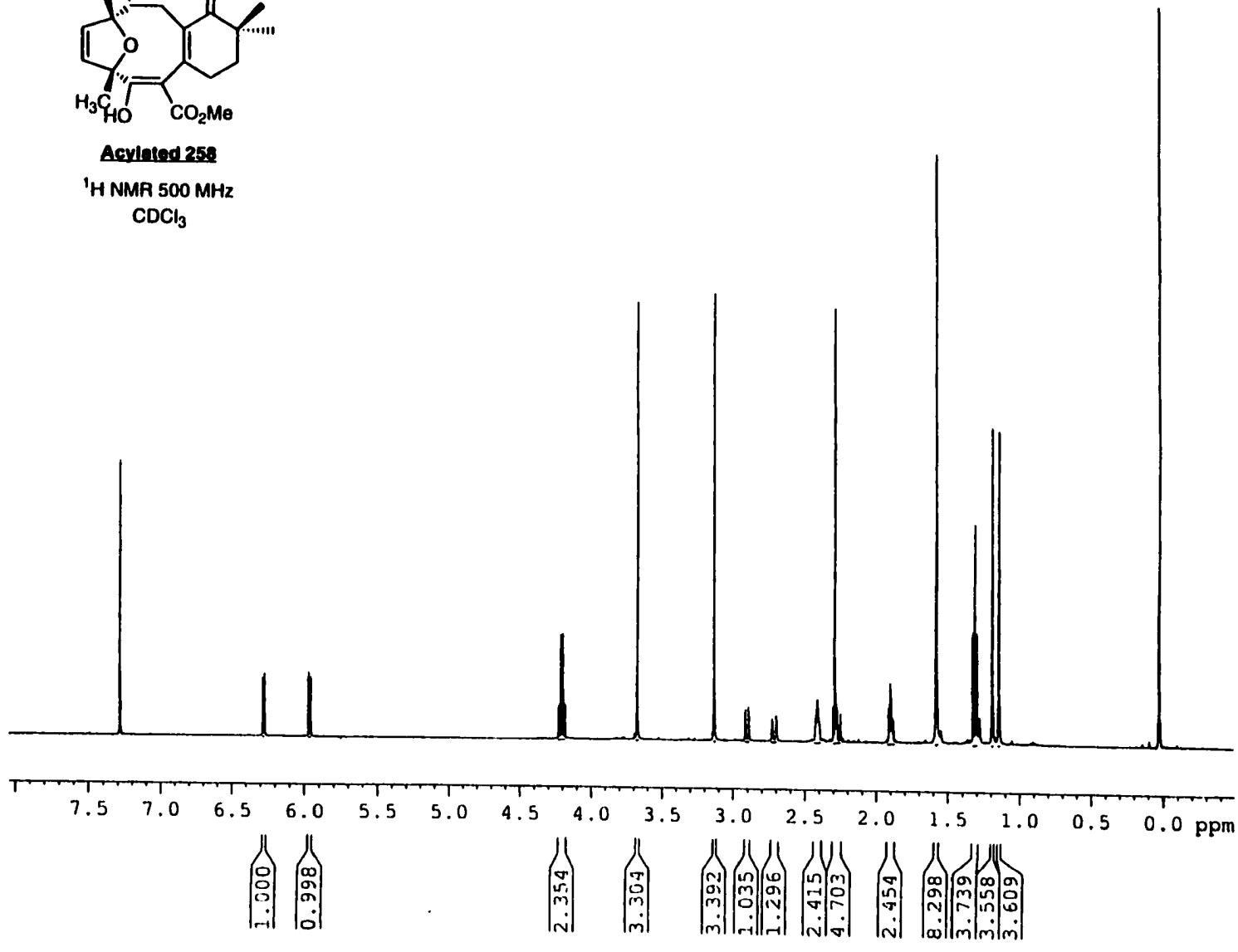
^{13}C NMR 62.5 MHz
$CDCl_3$





Acylated 258

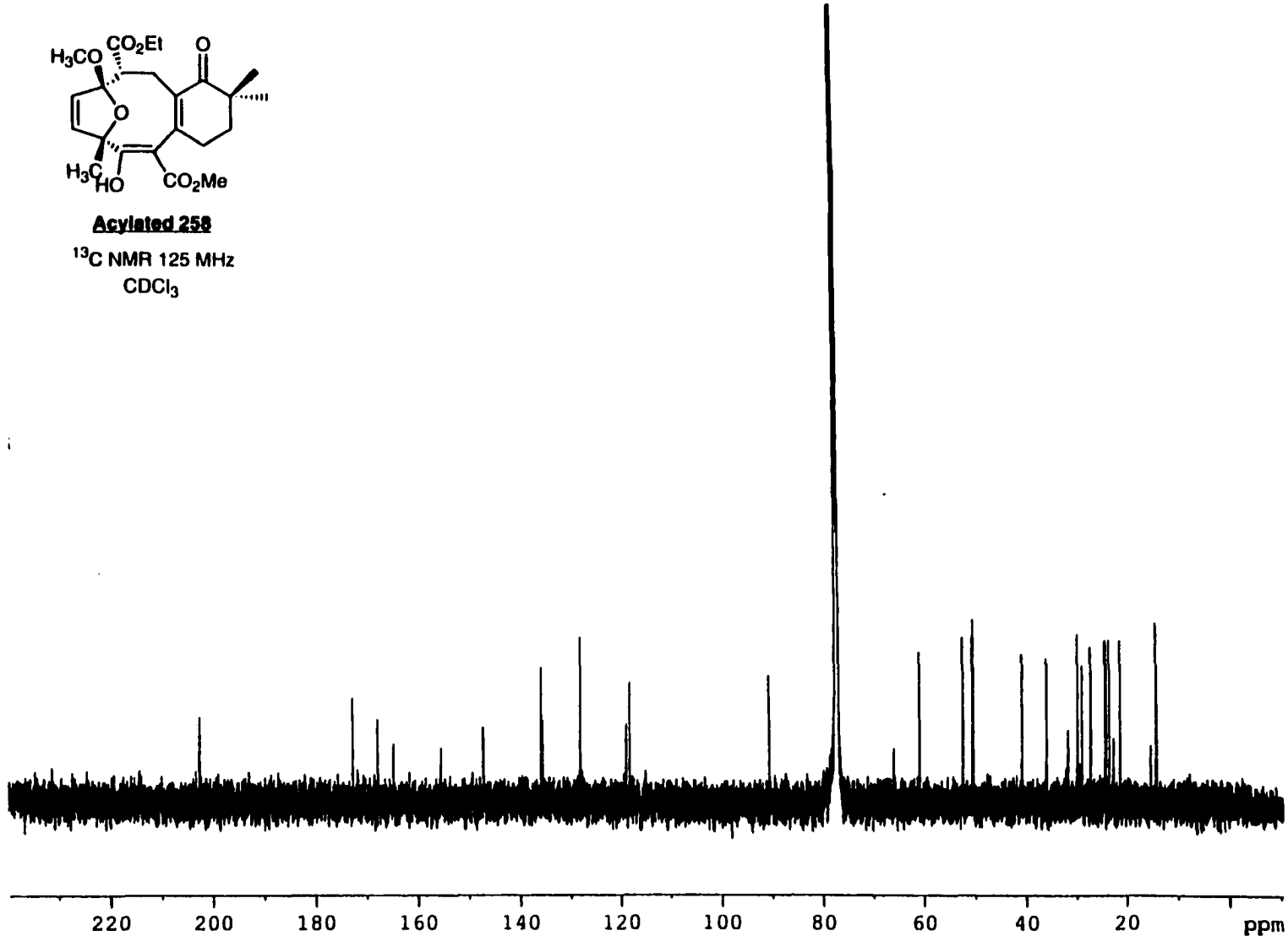
^{1}H NMR 500 MHz
$CDCl_3$

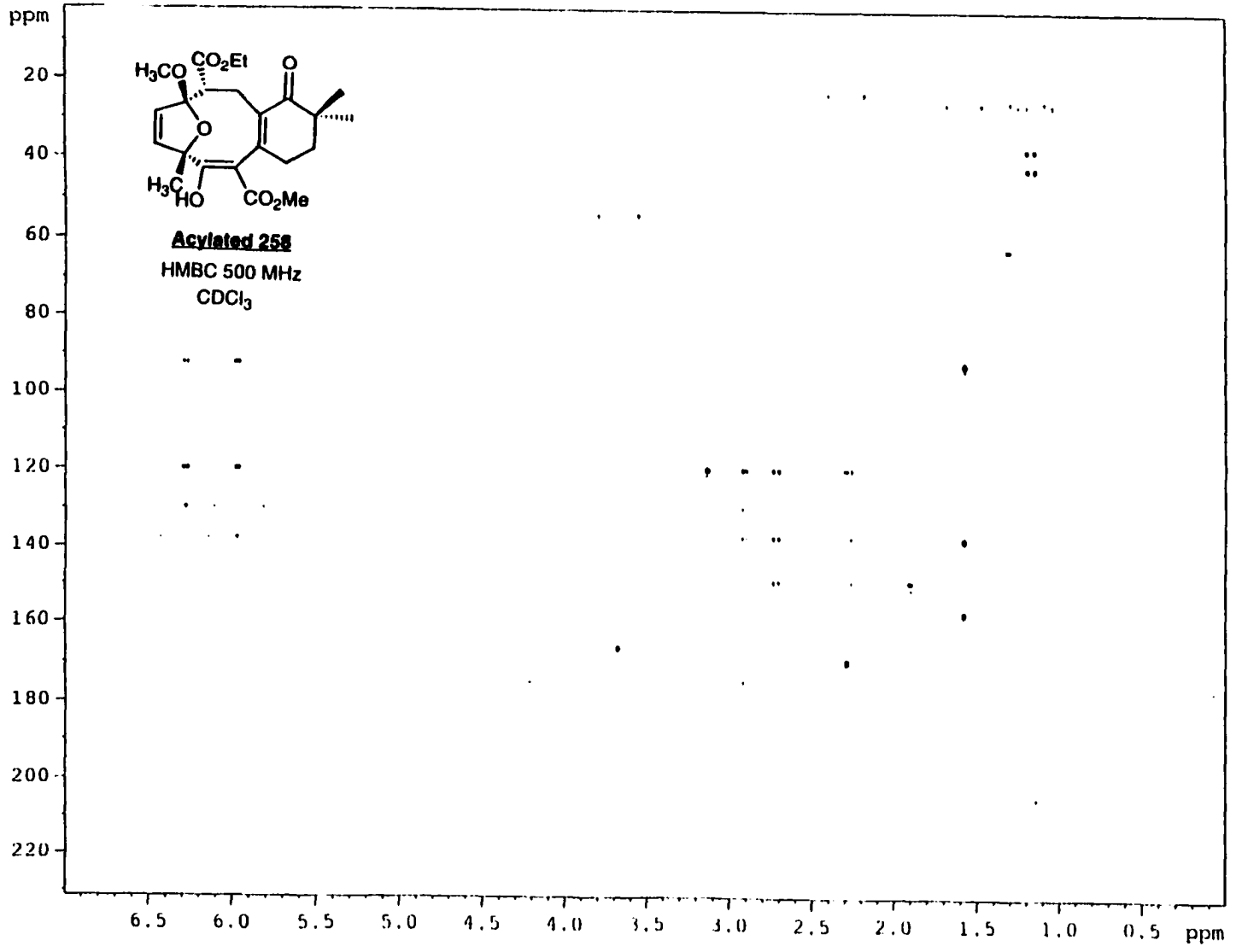


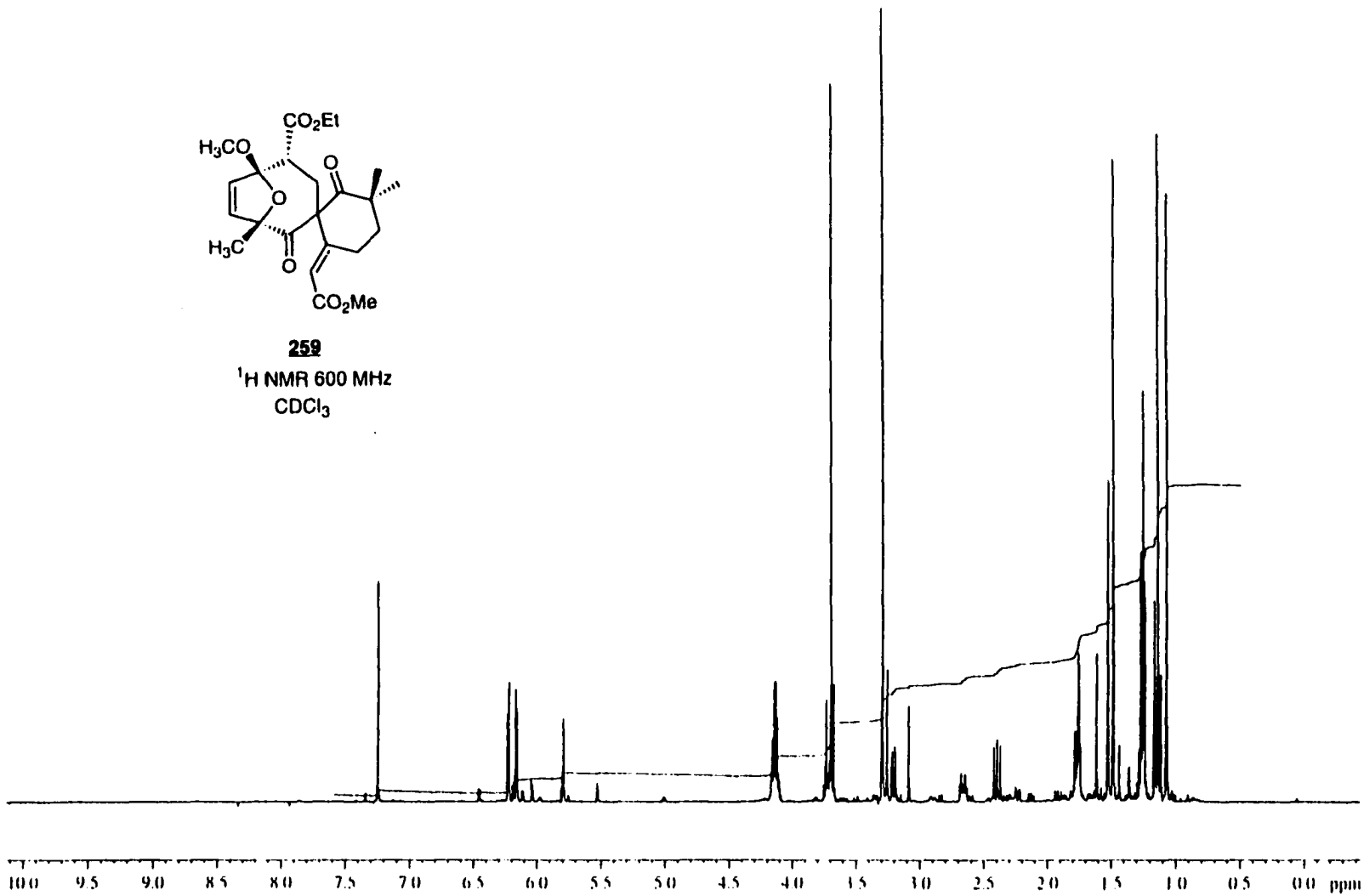
Acylated 258

^{13}C NMR 125 MHz

$CDCl_3$



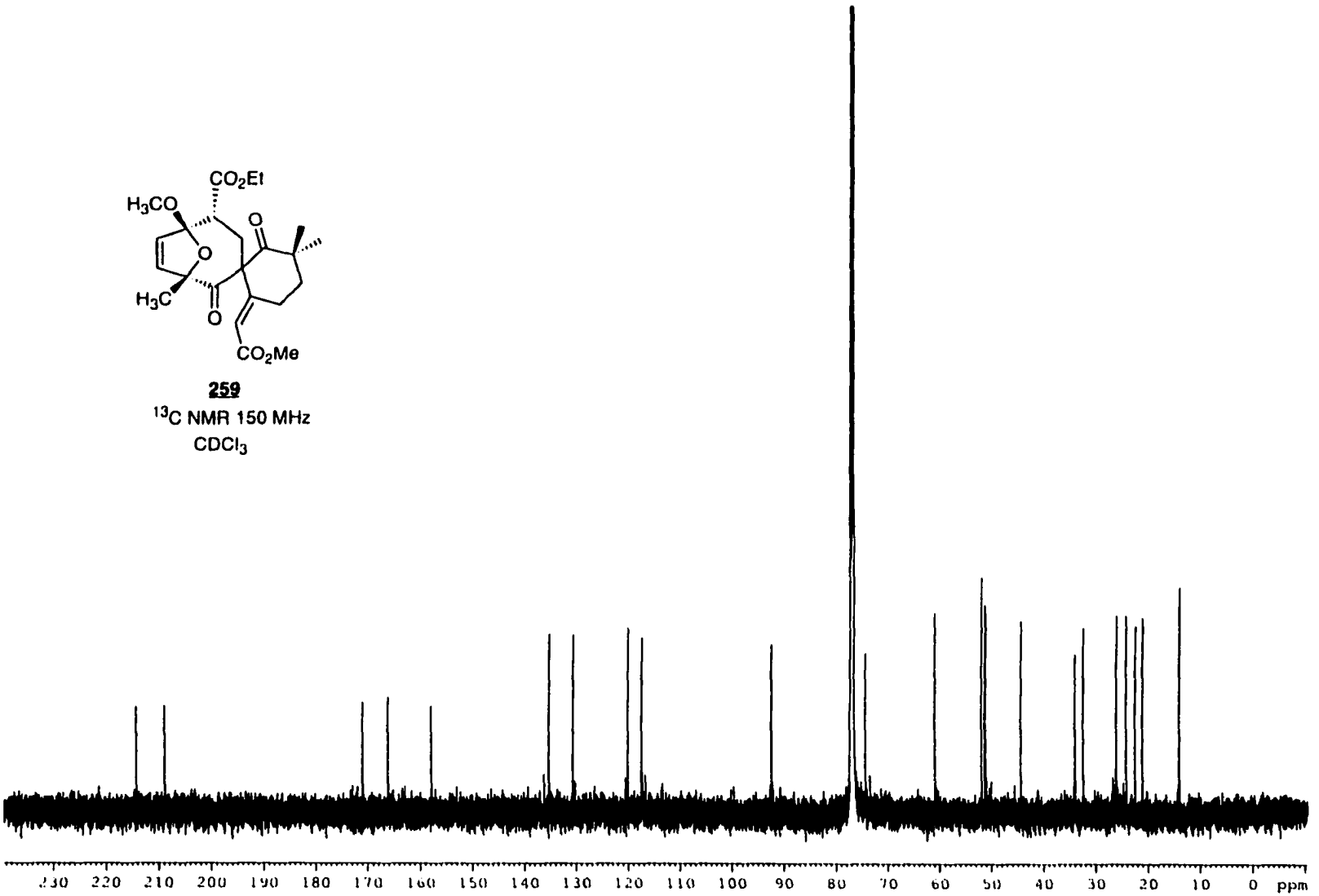

ppm
20
40
60
80
100
120
140
160
180
200
220
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
H3CO
CO2Et
O
O
H3C
HO
CO2Me
Acylated 258
HMBC 500 MHz
CDCl3

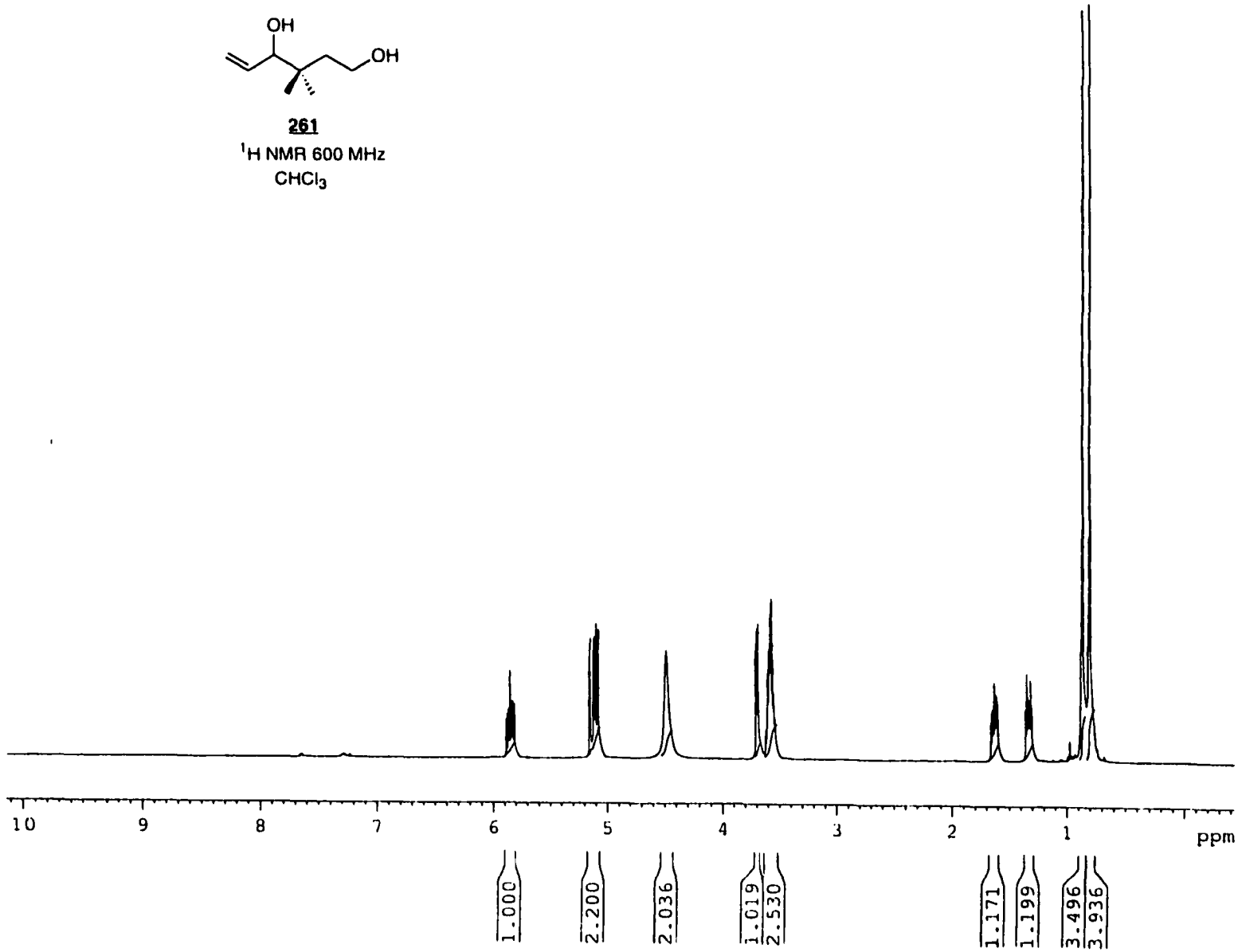

CO2Et
H3CO
O
O
H3C
O
CO2Me
259
1H NMR 600 MHz
CDCl3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

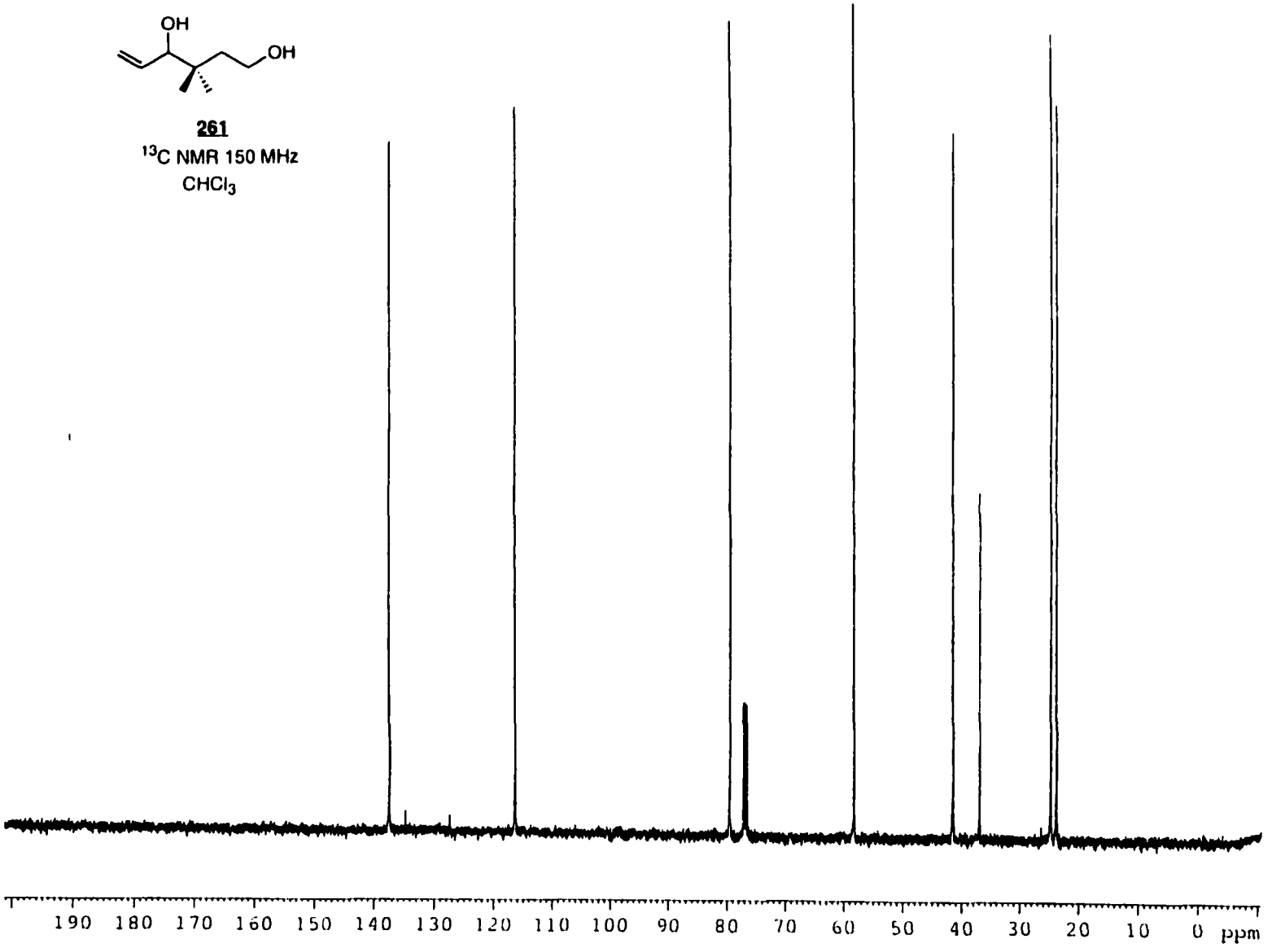
259

^{13}C NMR 150 MHz

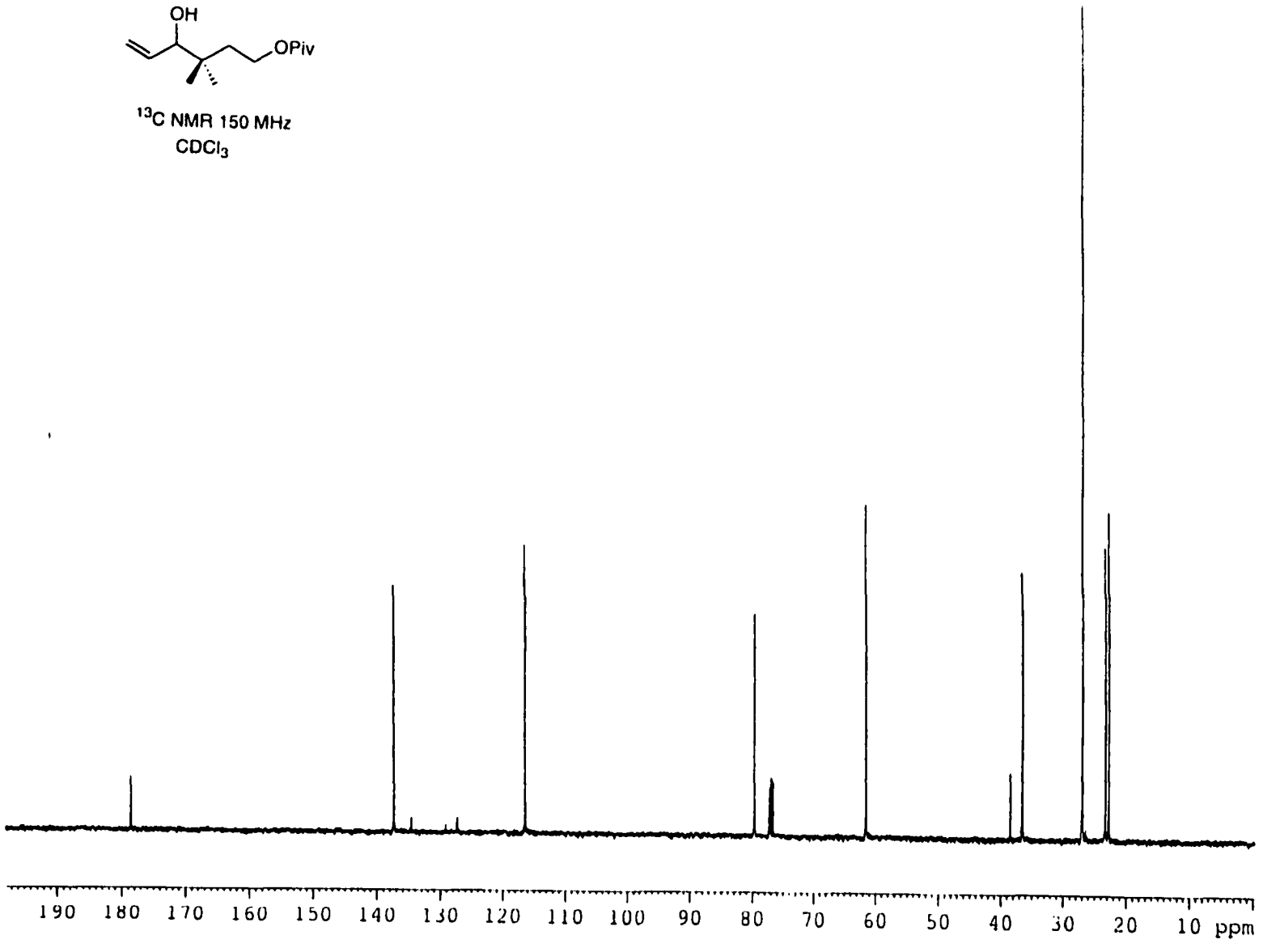
$CDCl_3$




OH
OH
261
^{1}H NMR 600 MHz
$CHCl_3$
10
9
8
7
6
5
4
3
2
1
ppm
1.000
2.200
2.036
1.019
2.530
1.171
1.199
3.496
3.936


OH
OH
261
^{13}C NMR 150 MHz
$CHCl_3$
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

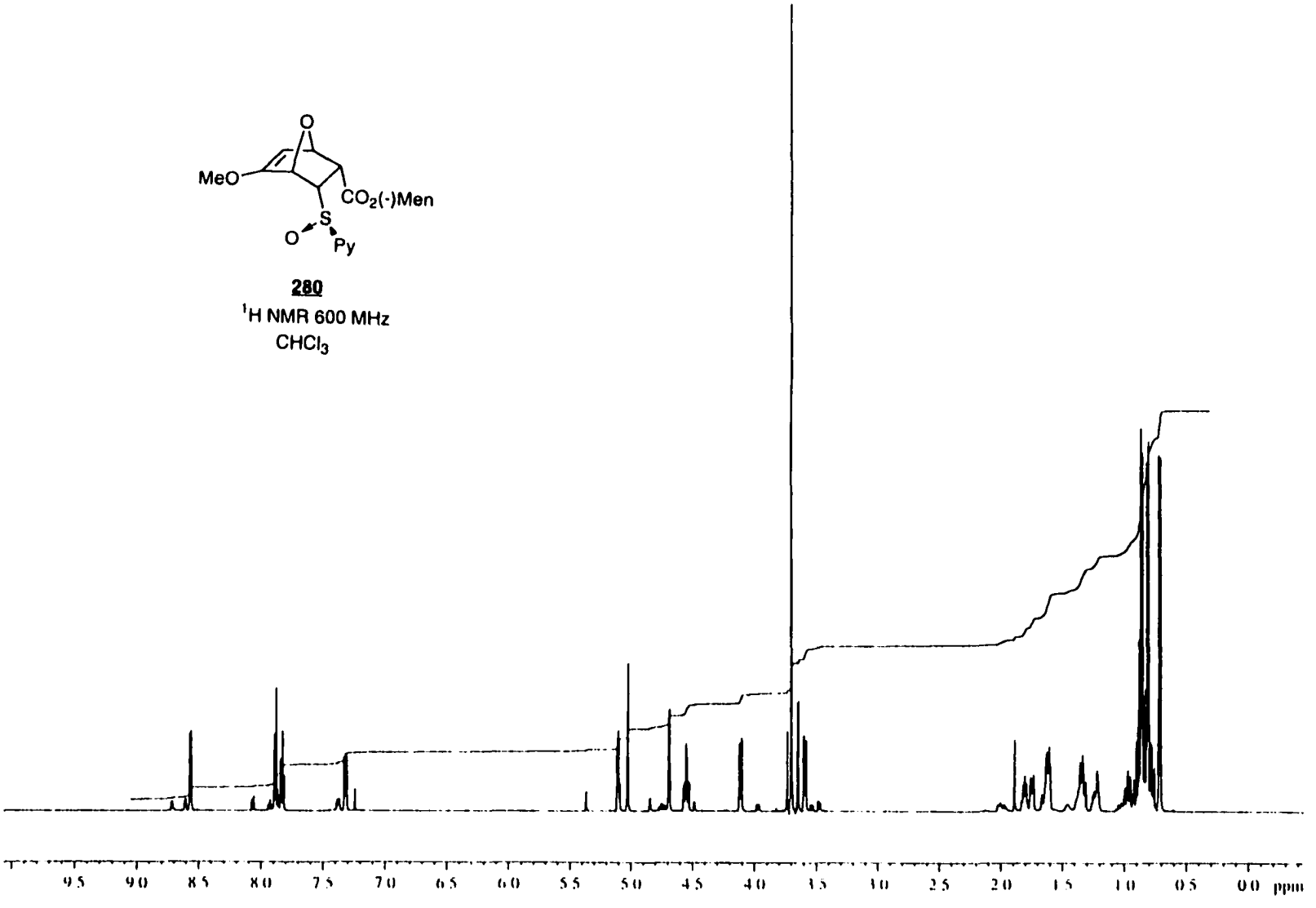
OH
OPiv
^{1}H NMR 600 MHz
$CDCl_3$
1.000
2.243
2.415
1.122
1.139
1.242
1.235
10.679
7.389
ppm

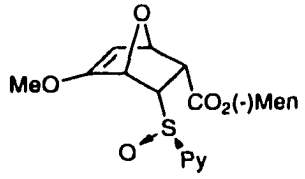

OH
OPiv
^{13}C NMR 150 MHz
$CDCl_3$
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

280

^{1}H NMR 600 MHz

$CHCl_3$

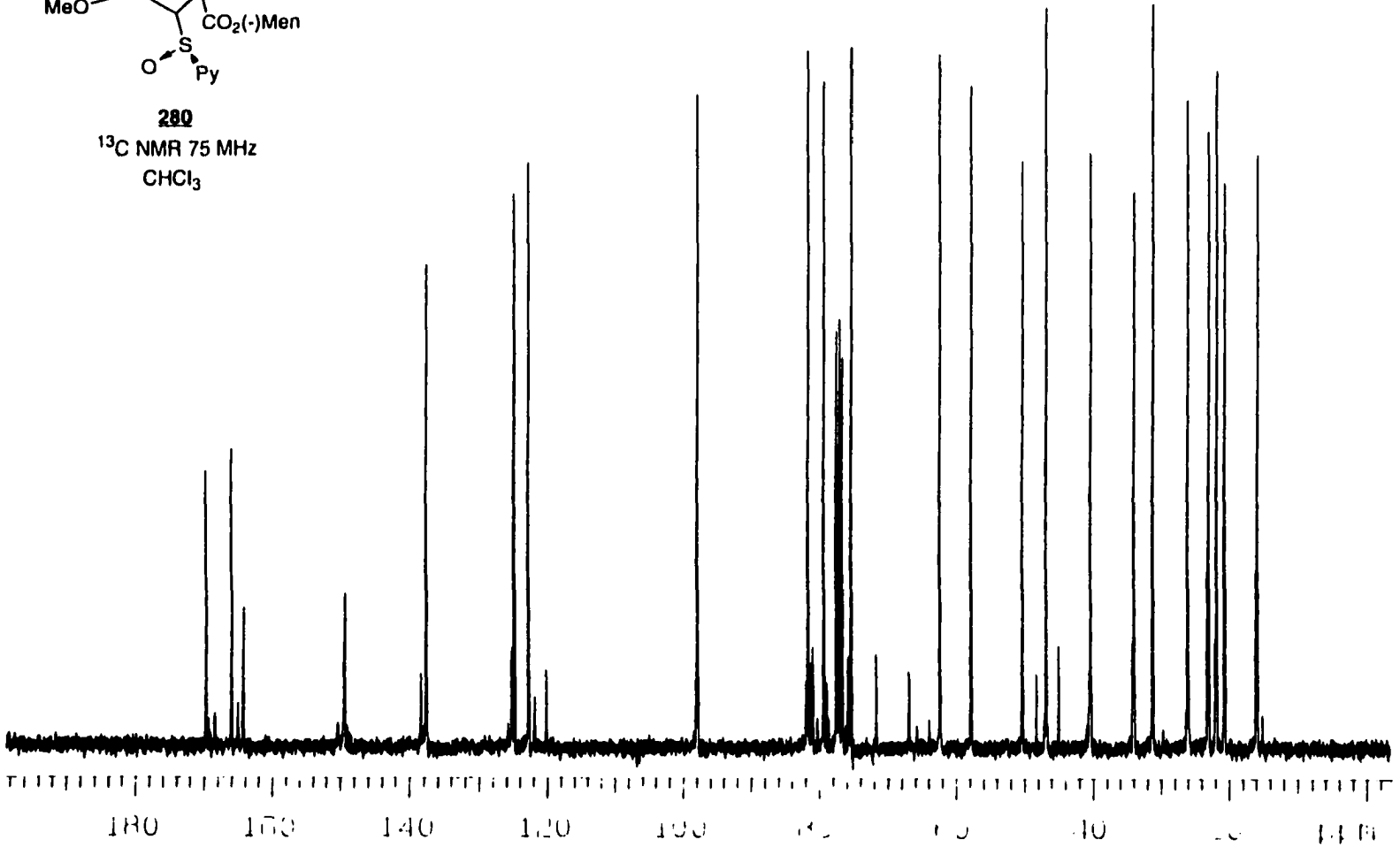




280

^{13}C NMR 75 MHz

$CHCl_3$



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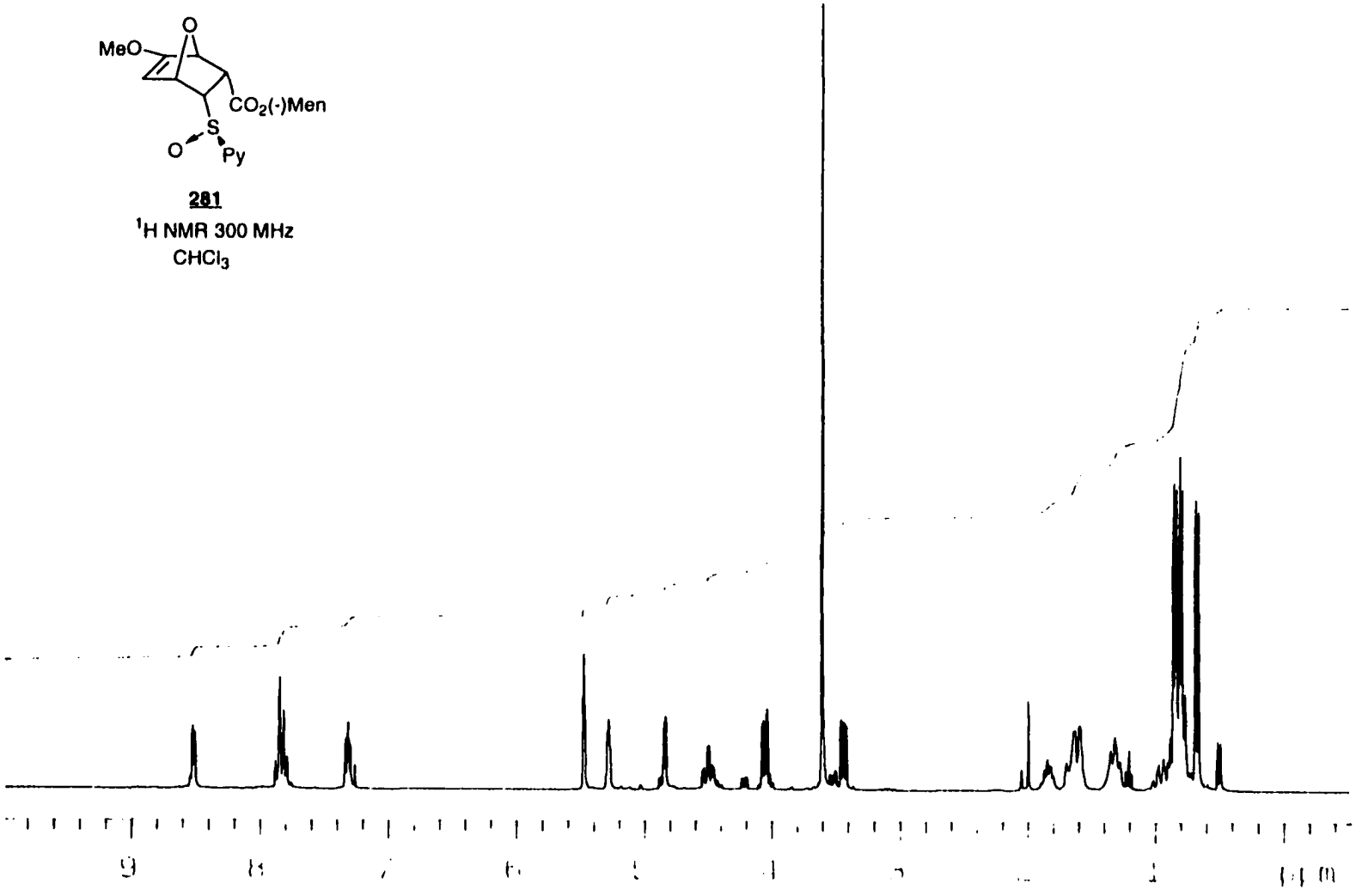
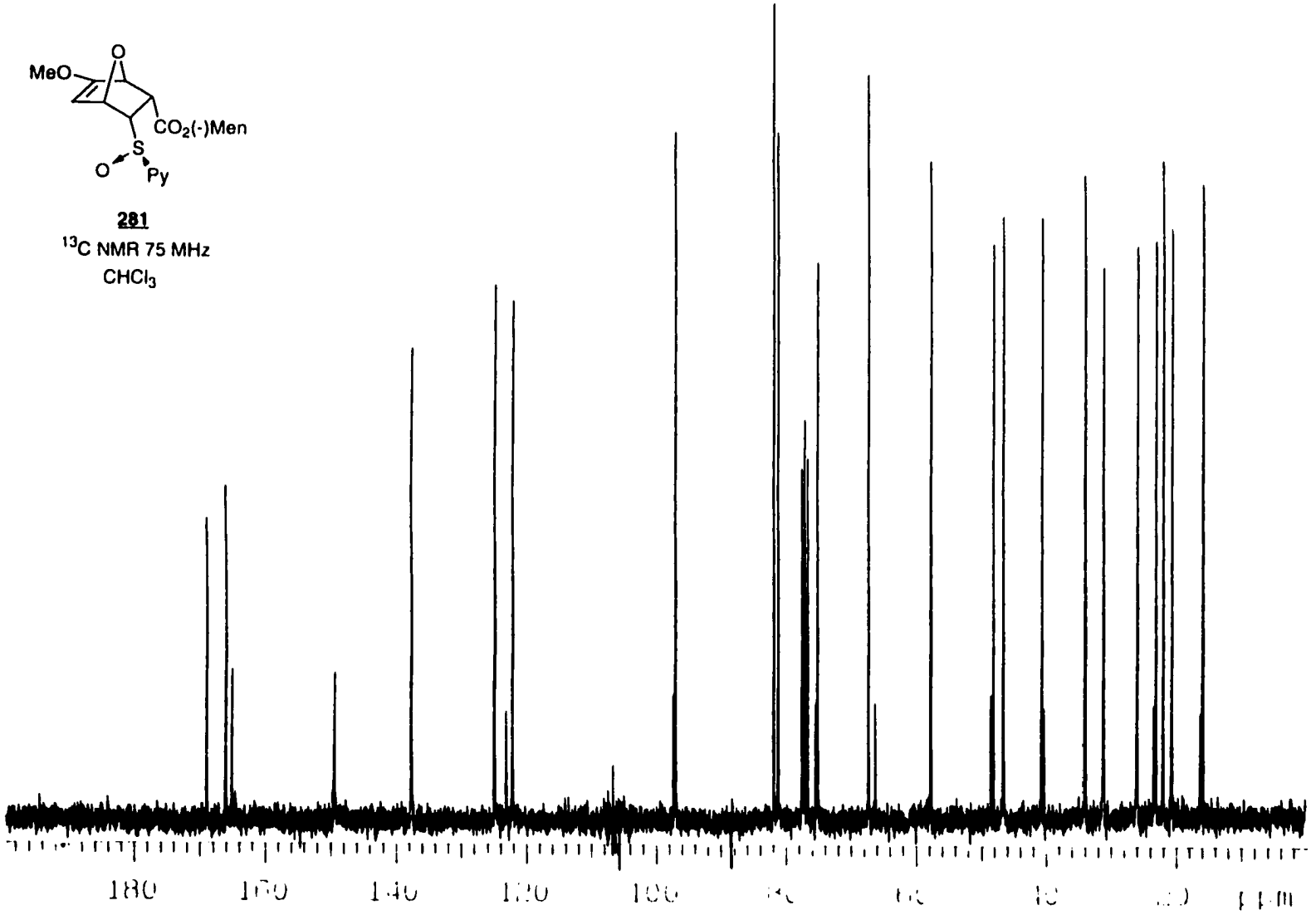
^{1}H NMR 300 MHz

$CHCl_3$

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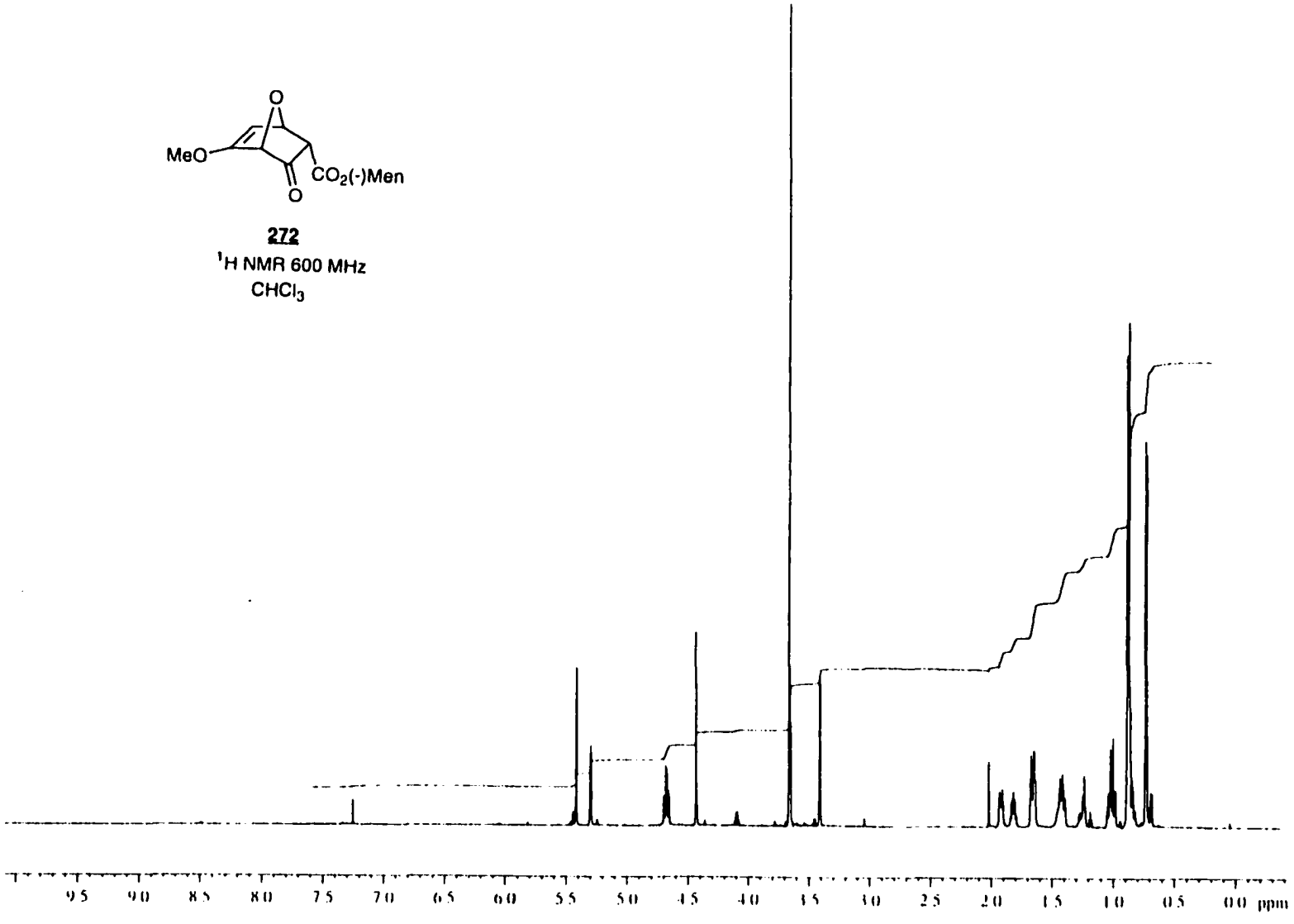
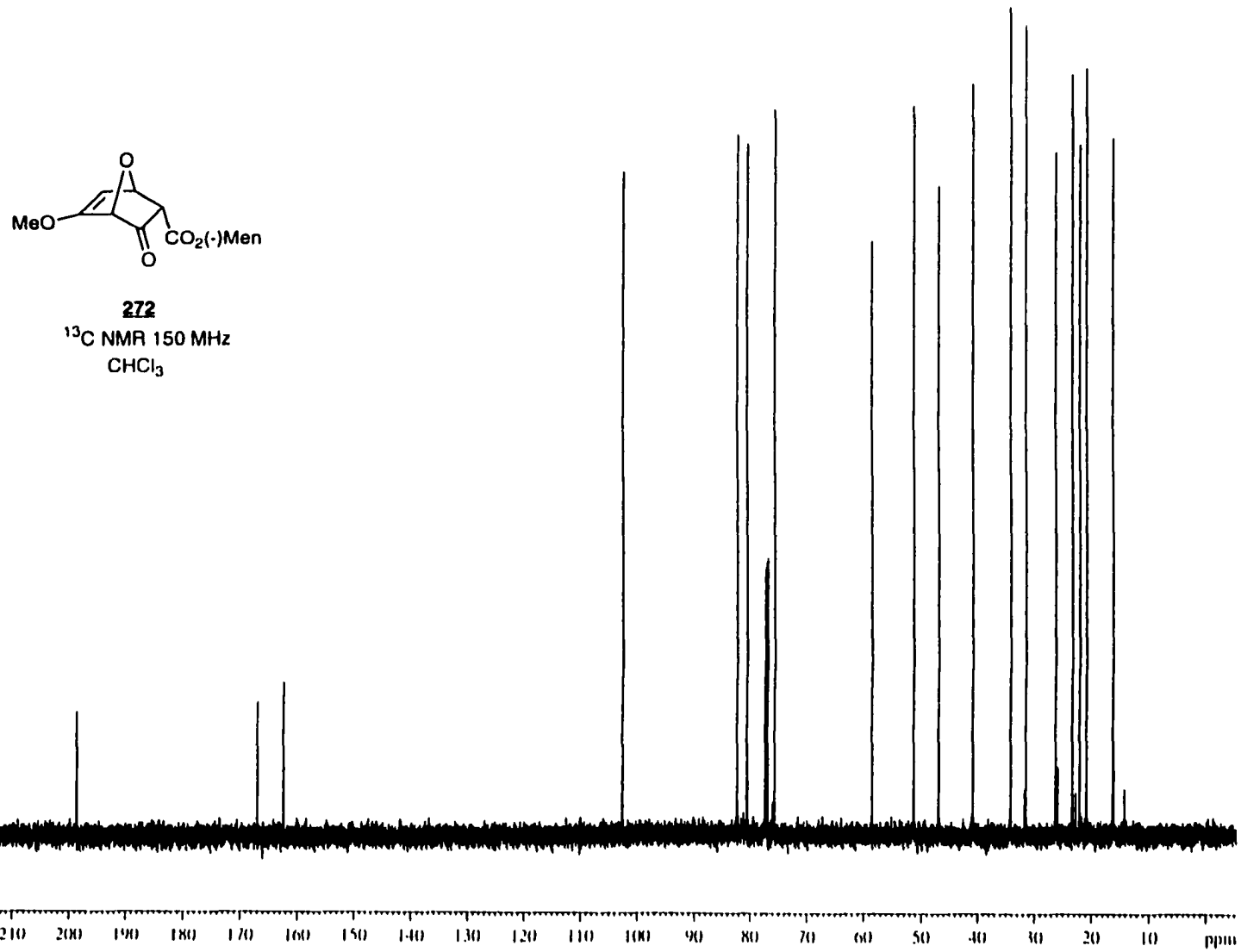
S
O
Py
281
13C NMR 75 MHz
CHCl3
180
160
140
120
100

272

^{1}H NMR 600 MHz

$CHCl_3$





272

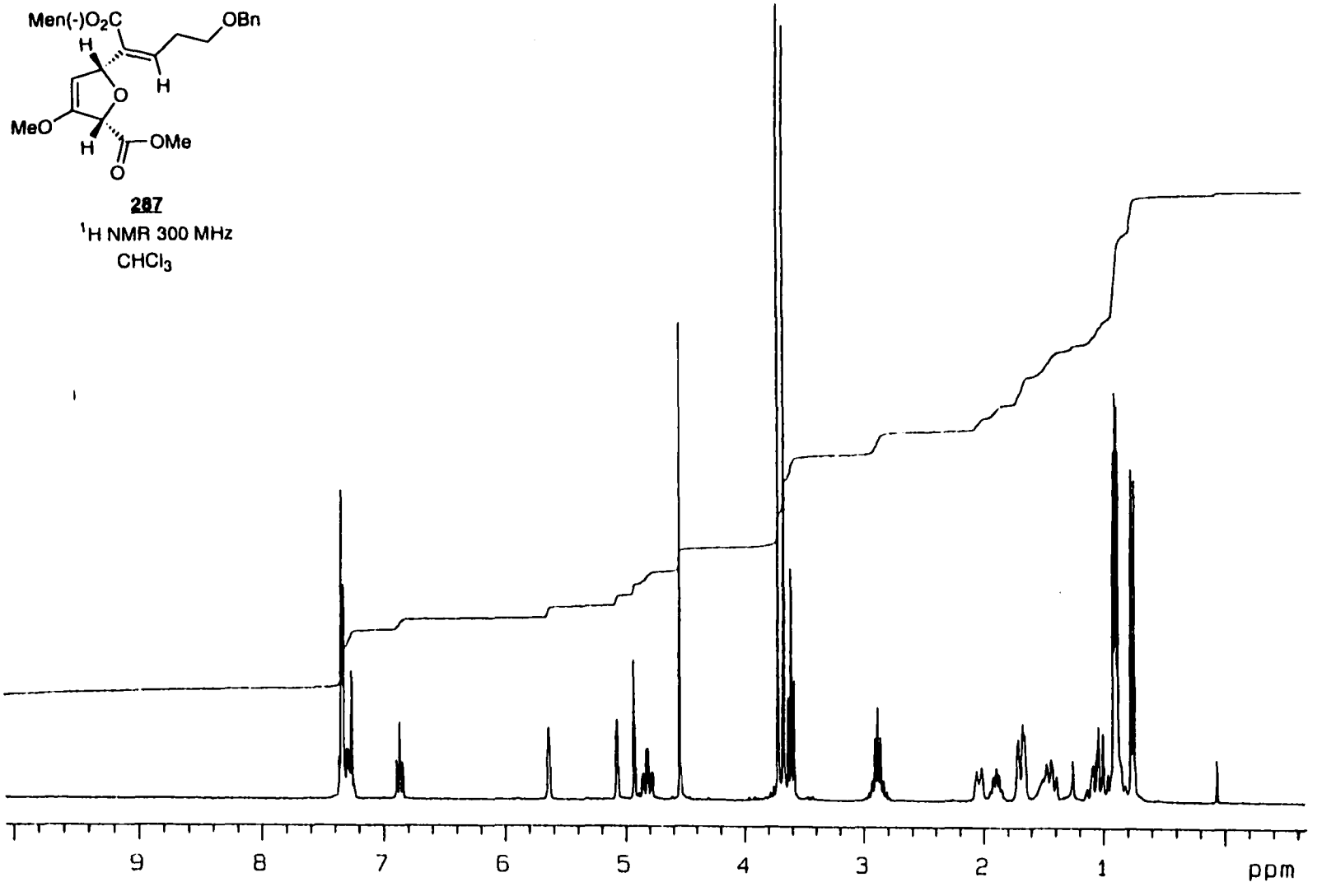
^{13}C NMR 150 MHz

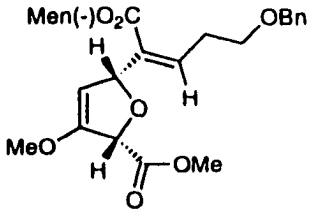
$CHCl_3$

287

^{1}H NMR 300 MHz

$CHCl_3$





287

^{13}C NMR 75 MHz

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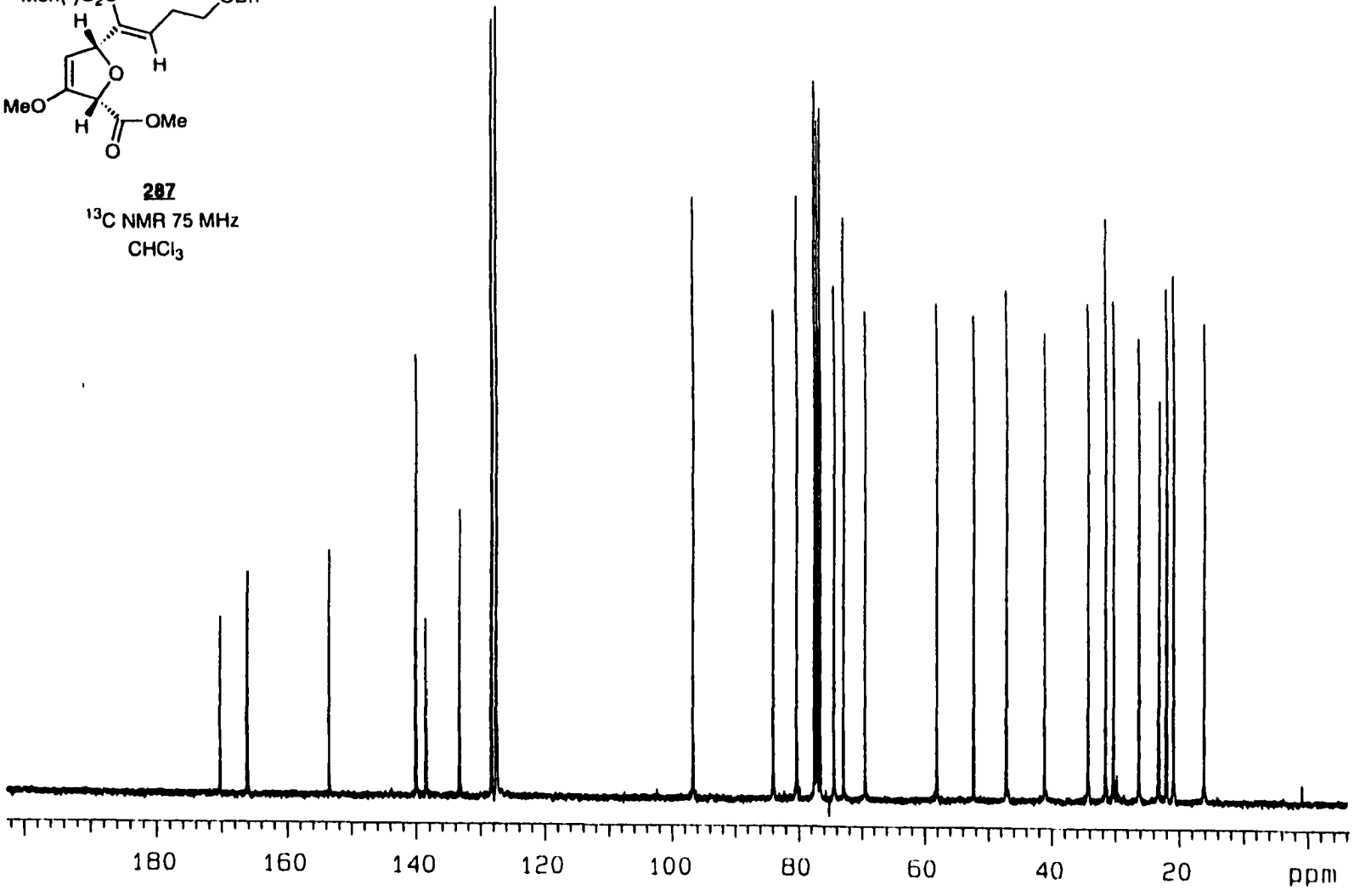

288

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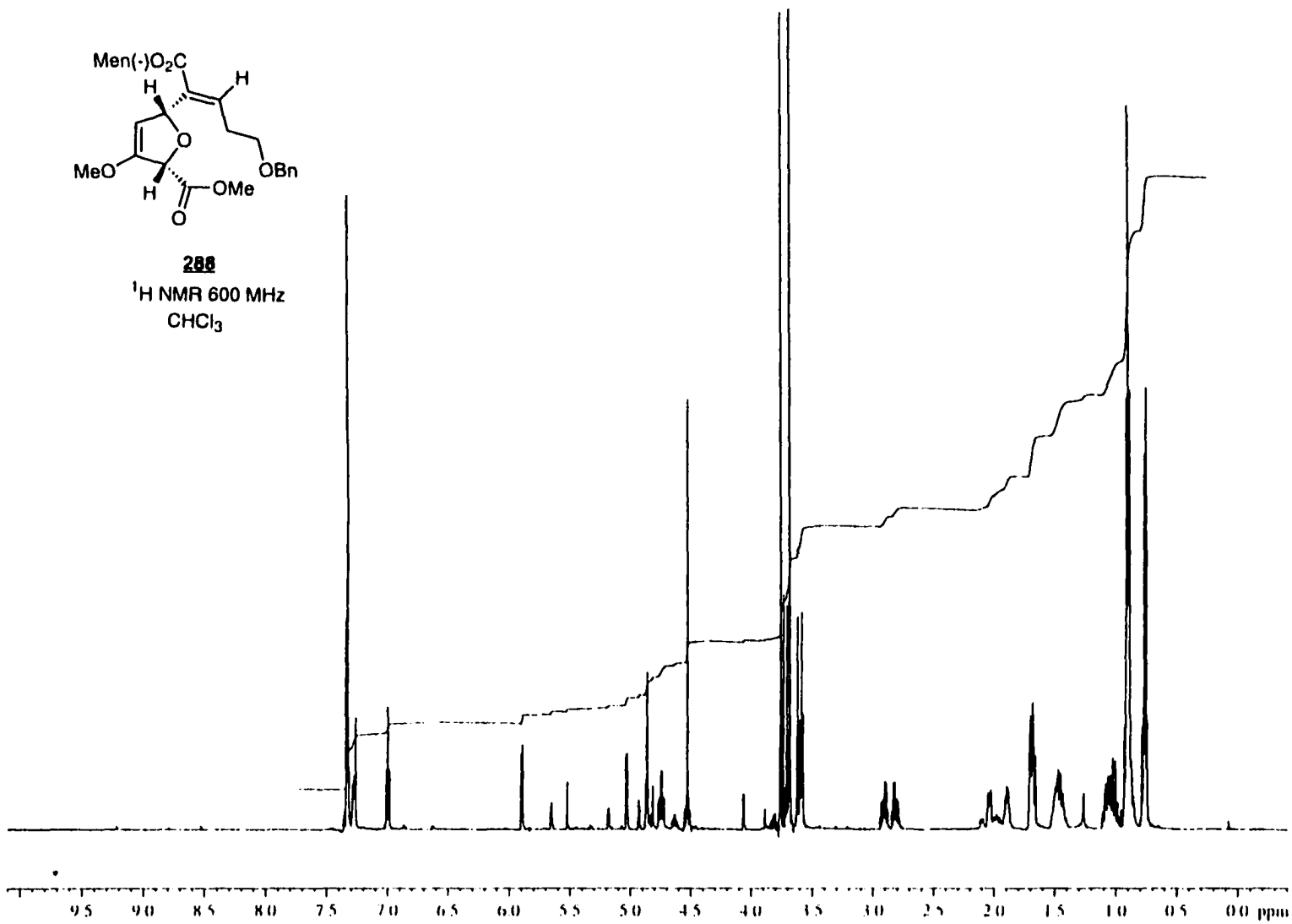

288

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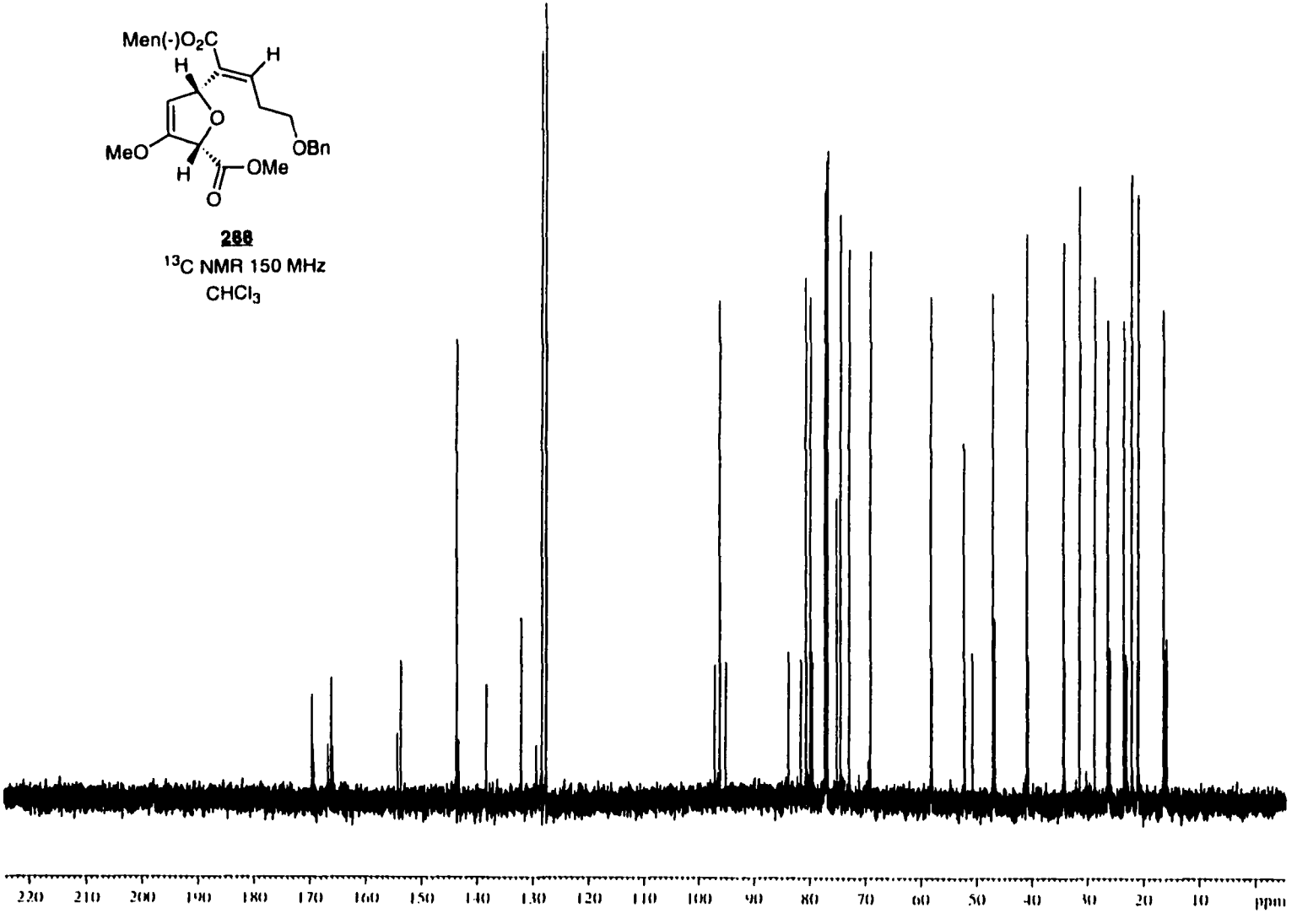
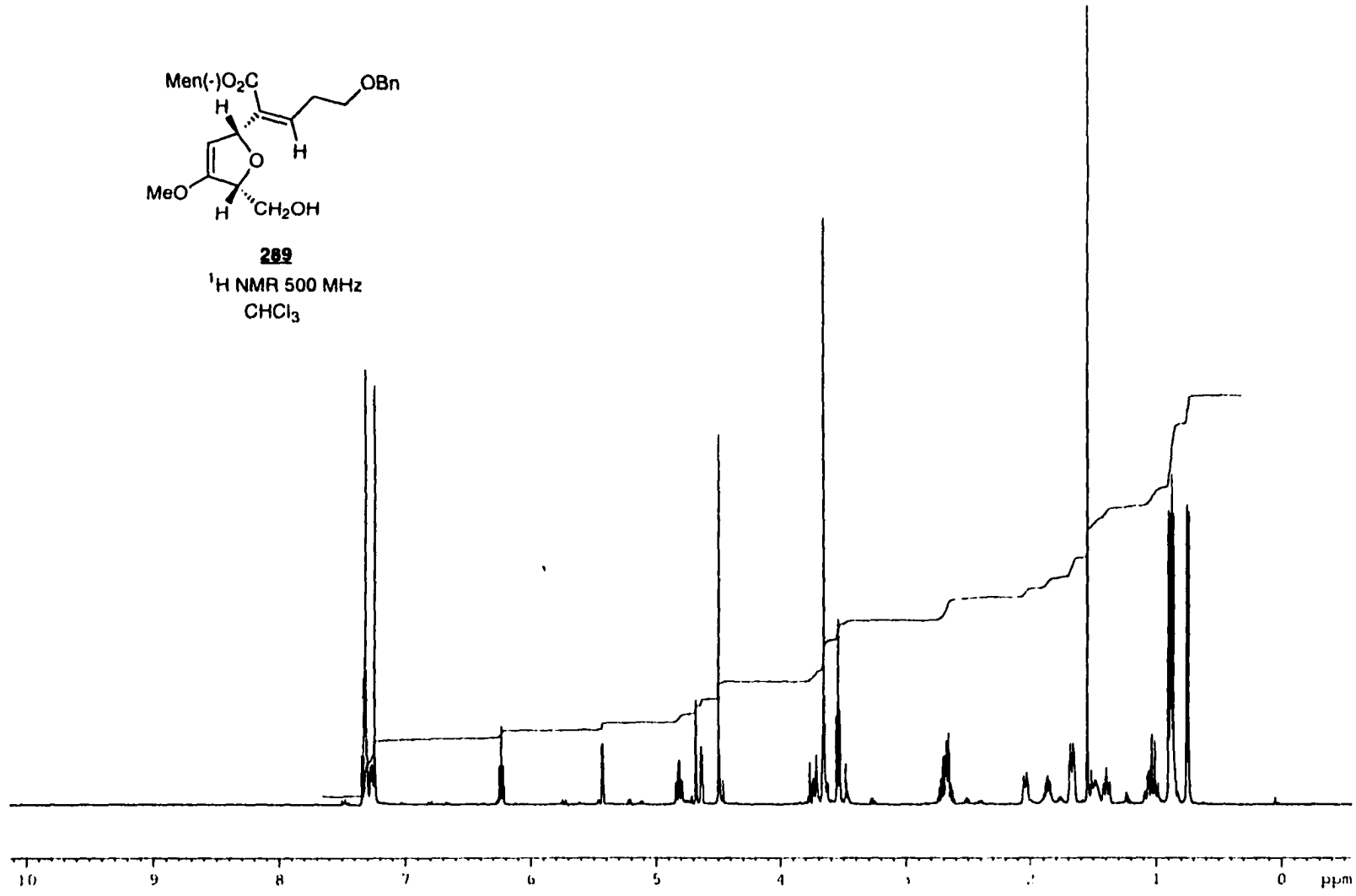
$CHCl_3$

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H
H
O
MeO
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269
1H NMR 500 MHz
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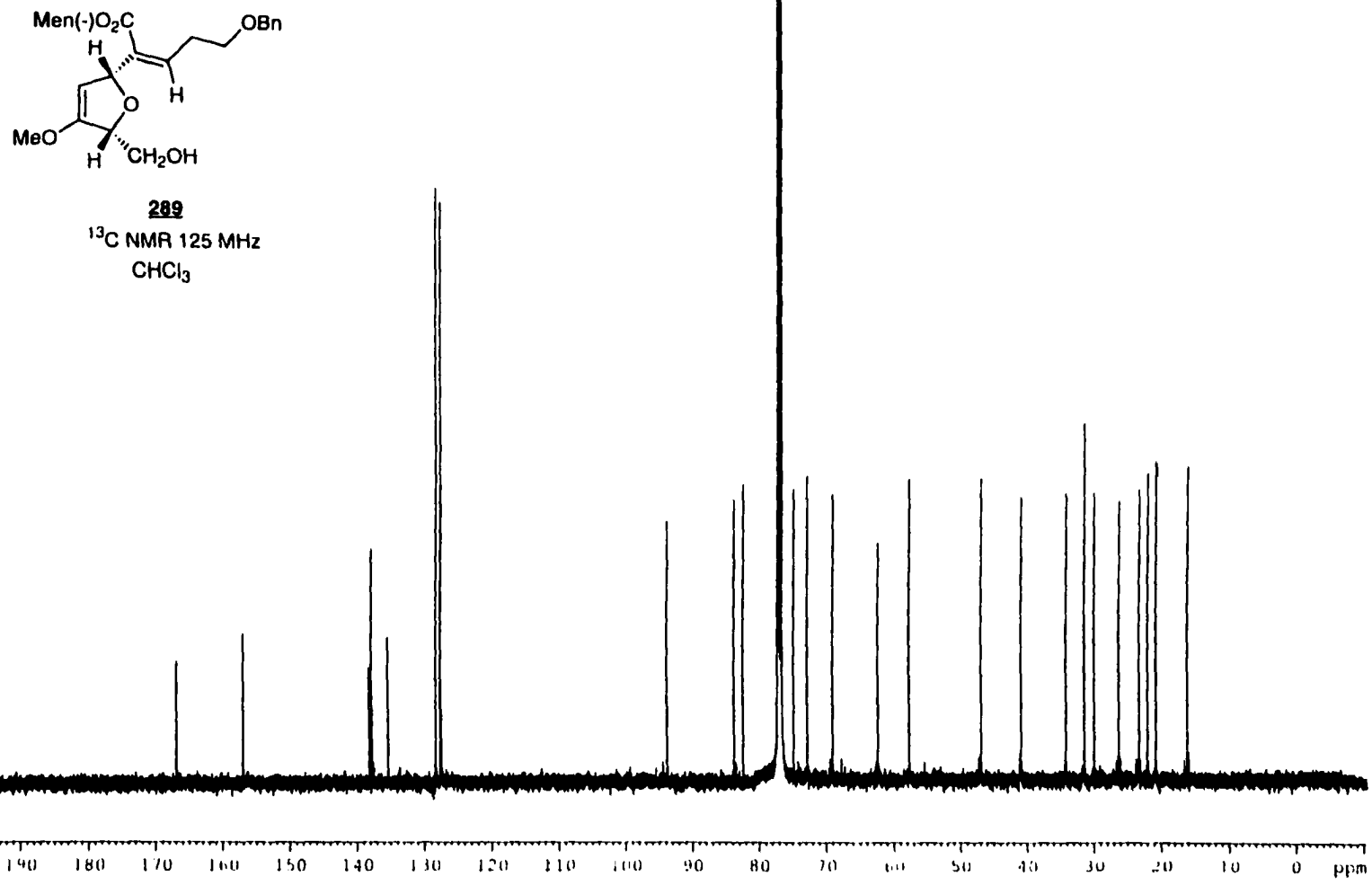
8
7
6
5
4
3
2
1
0
ppm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H
H
O
MeO
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289
13C NMR 125 MHz
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200
190
180
170
160
150
140
130
120
110
100
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80
70
60
50
40
30
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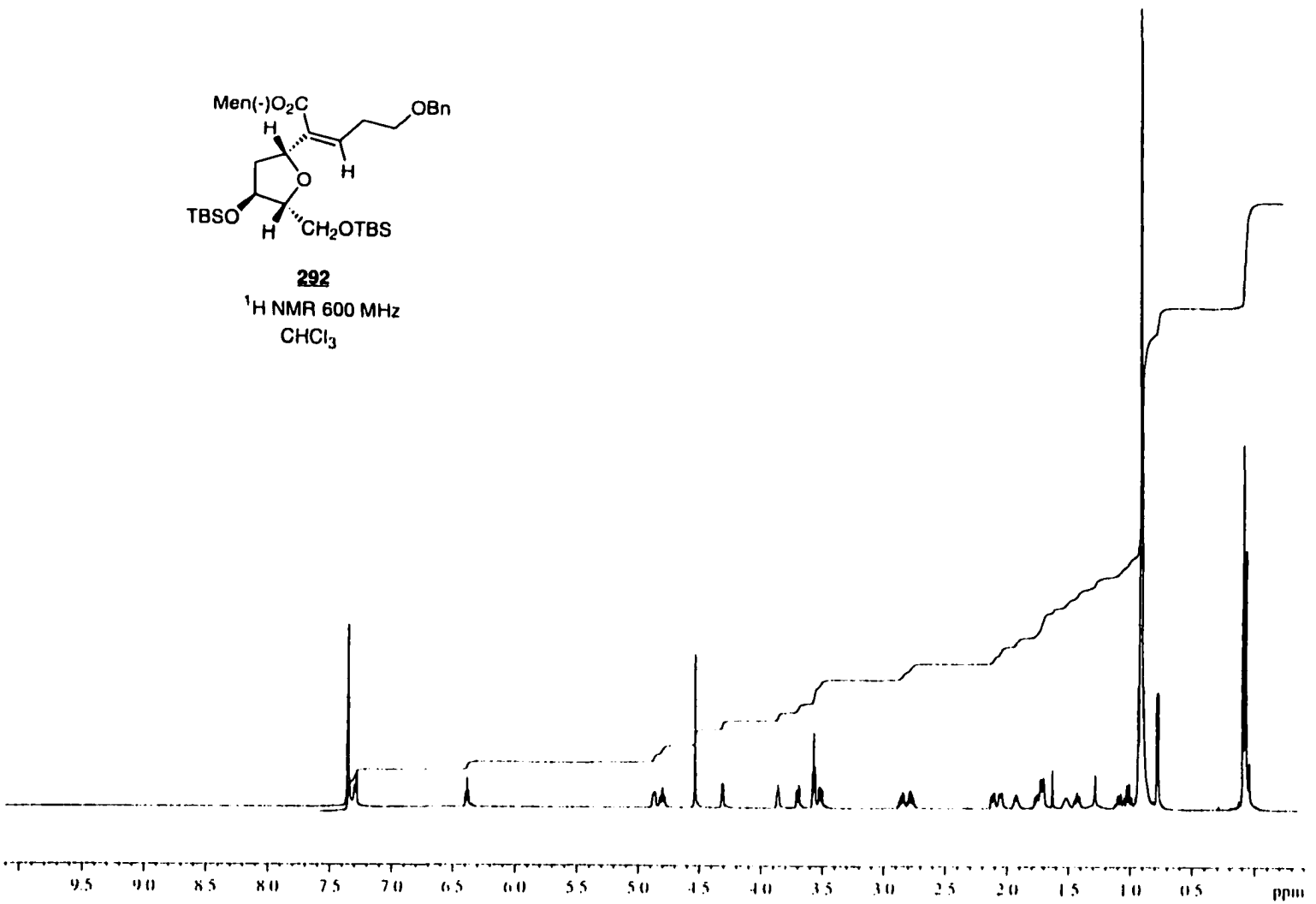
ppm

292

^{1}H NMR 600 MHz

$CHCl_3$



292

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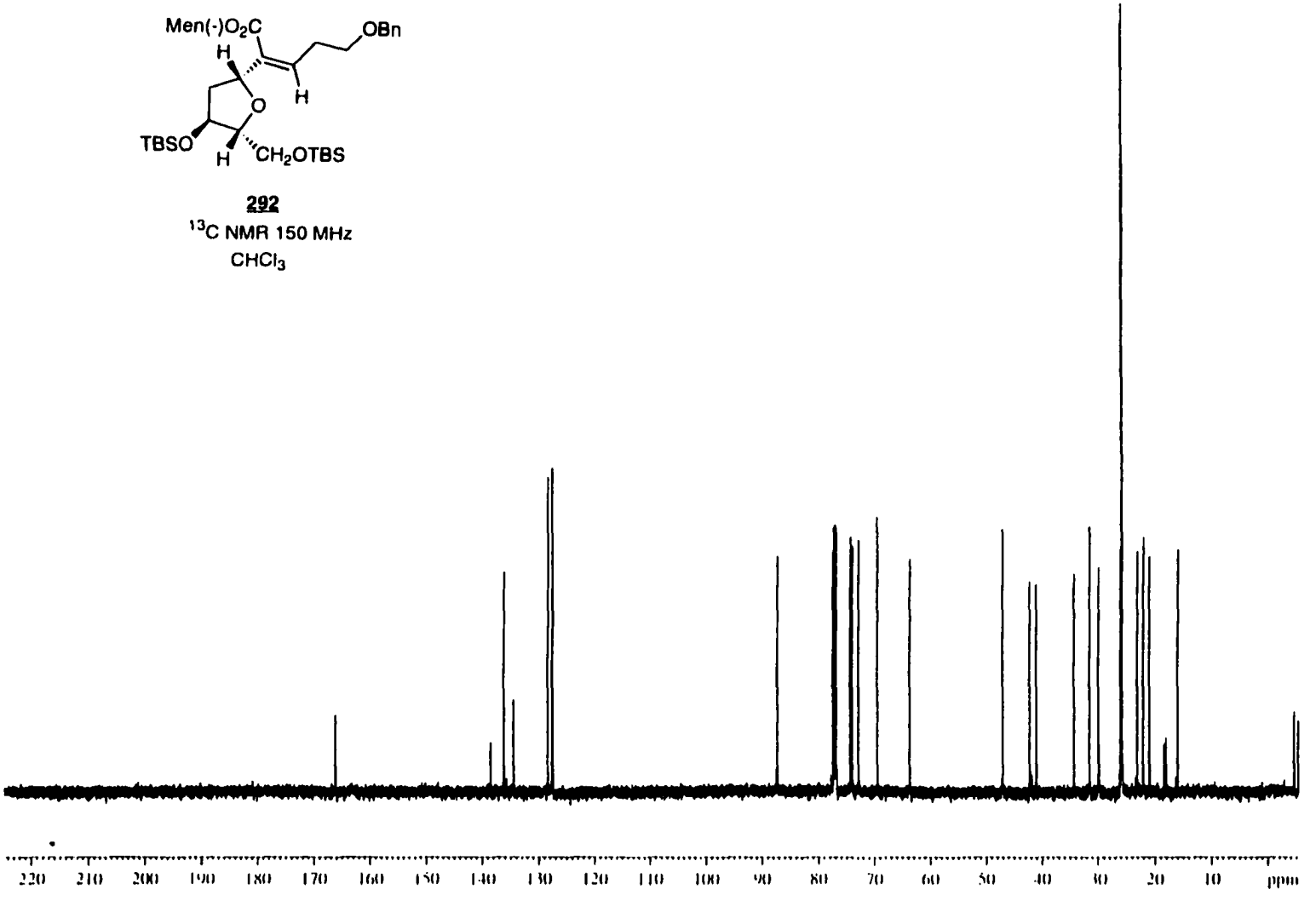
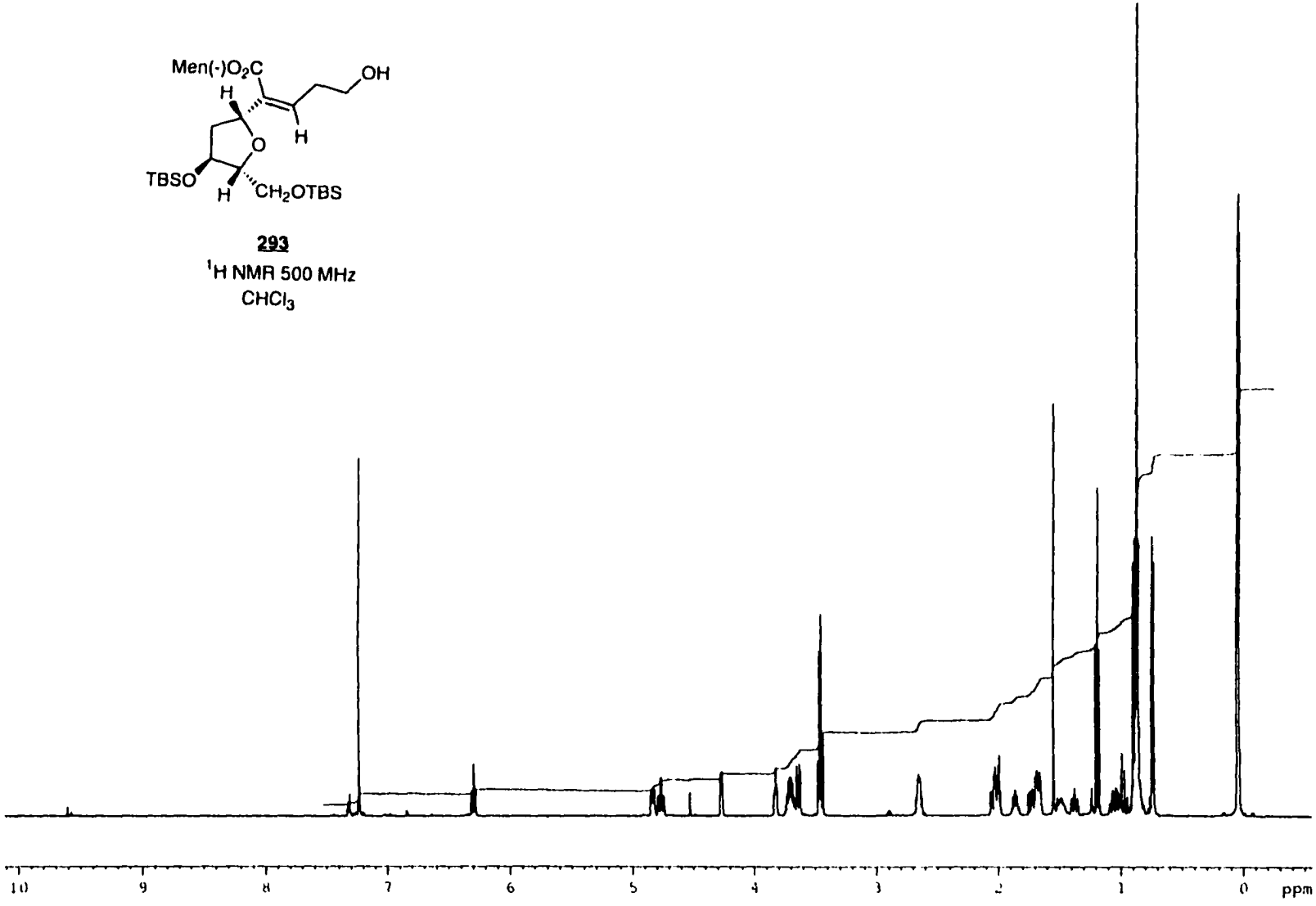
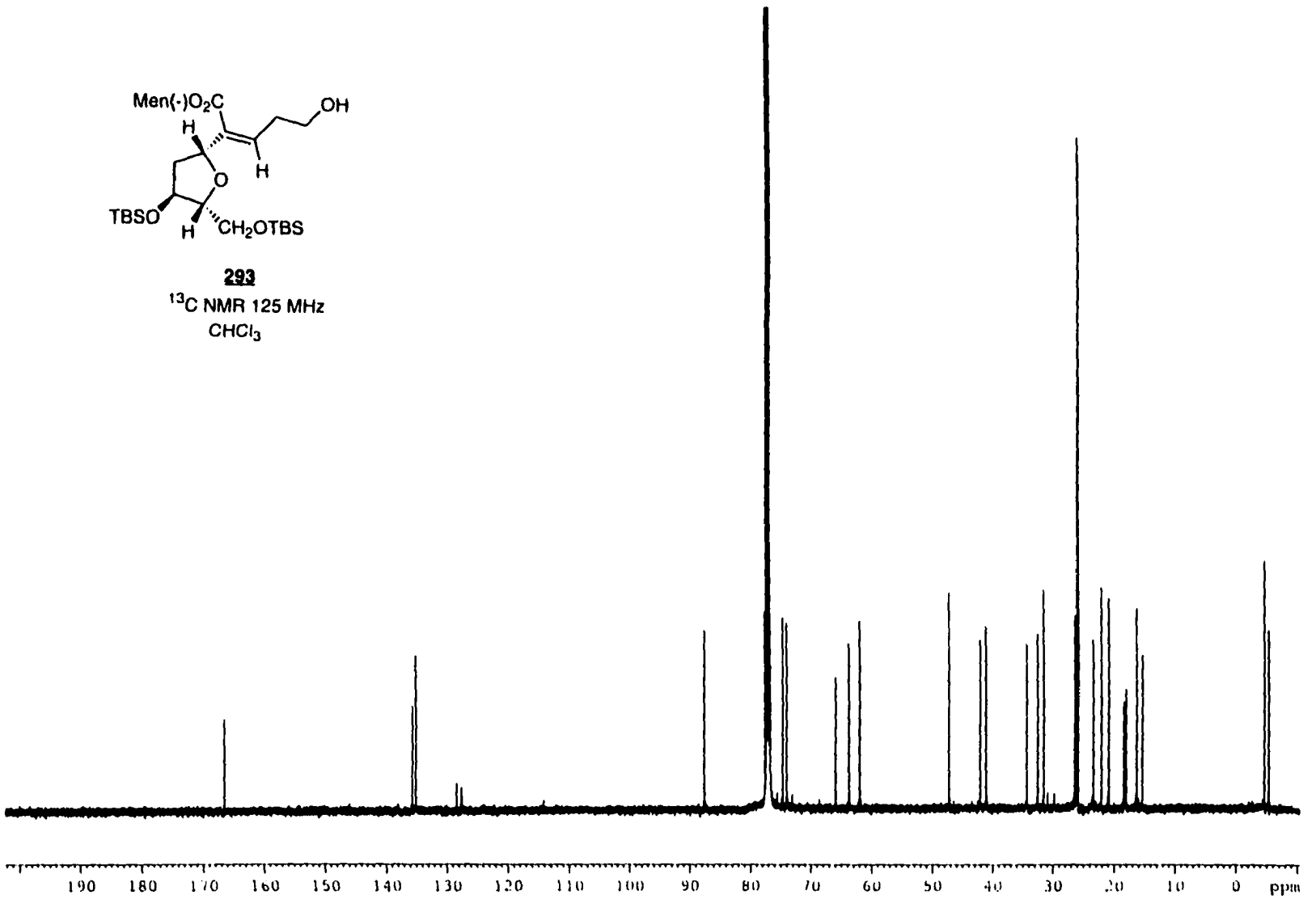


293

^{1}H NMR 500 MHz

$CHCl_3$




Men(-)O2C
OH
H
H
O
TBSO
H
CH2OTBS
293
13C NMR 125 MHz
CHCl3
190
180
170
160
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140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

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