**Enantioselective Total Syntheses of Acylfulvene, Irofulven, and the Agelastatins**

by

Dustin S. Siegel

B.S., Chemistry
University of California, San Diego, 2003

Submitted to the Department of Chemistry
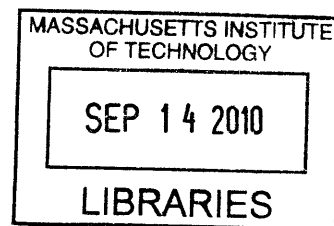In Partial Fulfillment of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY
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at the

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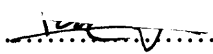
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*To my parents, Phil and Nancy Siegel*

*To my twin sister, Emily Siegel*

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**Preface**

Portions of this work have been adapted from the following articles that were co-written by the author and are reproduced in part with permission from:

Movassaghi, M.; Piizzi, G.; Siegel, D. S.; Piersanti, G. "Enantioselective Total Synthesis of (–)-Acylfulvene and (–)-Irofulven." *Angew. Chem. Int. Ed.* **2006**, *45*, 5859-5863. Copyright 2006 Wiley-VCH Verlag GmbH & Co. KgaA.

Movassaghi, M.; Piizzi, G.; Siegel, D. S.; Piersanti, G. "Observations in the Synthesis of the Core of the Antitumor Illudins via an Enyne Ring Closing Metathesis Cascade." *Tetrahedron Lett.* **2009**, *50*, 5489-5492. Copyright 2009 Elsevier Limited.

Siegel, D. S.; Piizzi, G.; Piersanti, G.; Movassaghi, M. "Enantioselective Total Synthesis of (–)-Acylfulvene and (–)-Irofulven." *J. Org. Chem.* **2009**, *74*, 9292-9304. Copyright 2009 American Chemical Society.

# Enantioselective Total Syntheses of Acylfulvene, Irofulven, and the Agelastatins

by

Dustin S. Siegel

Submitted to the Department of Chemistry
on May 12th, 2010 in Partial Fulfillment of the
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## ABSTRACT

### I. Enantioselective Total Synthesis of (–)-Acylfulvene, and (–)-Irofulven

We report the enantioselective total synthesis of (–)-acylfulvene and (–)-irofulven, which features metathesis reactions for the rapid assembly of the molecular framework of these antitumor agents. We discuss (1) the application of an Evans Cu-catalyzed aldol addition reaction using a strained cyclopropyl ketene thioacetal, (2) an efficient enyne ring-closing metathesis cascade reaction in a challenging setting, (3) the reagent, IPNBSH, for a late stage reductive allylic transposition reaction, and (4) the final ring-closing metathesis/dehydrogenation sequence for the formation of (–)-acylfulvene and (–)-irofulven.

### II. Total Synthesis of the (–)-Agelastatin Alkaloids

The pyrrole-imidazole super-family of marine alkaloids, derived from linear clathrodin-like precursors, constitutes a diverse array of structurally complex natural products. The bioactive agelastatins are members of this family that have a tetracyclic molecular framework incorporating C4–C8 and C7–N12 bond connectivities. We provide a hypothesis for the formation of the unique agelastatin architecture that maximally exploits the intrinsic chemistry of plausible biosynthetic precursors. We report the concise enantioselective total syntheses of the agelastatin alkaloids, including the first total syntheses of agelastatins C and E. Our gram-scale chemical synthesis of agelastatin A was inspired by our hypothesis for the biogenesis of the cyclopentane C-ring and required the development of new transformations including an imidazolone-forming annulation reaction and a carbohydroxylative trapping of imidazolones.

Thesis Supervisor: Professor Mohammad Movassaghi
Title: Associate Professor of Chemistry

# Table of Contents

# Abbreviations

| | |
|---|---|
| Å | angstrom |
| [α] | specific rotation |
| Ac | acetyl |
| Ad-mix α | reagent mixture for Sharpless' asymmetric dihydroxylation |
| Anis | anisaldehyde |
| app | apparent |
| aq | aqueous |
| AQN | anthraquinone |
| atm | atmosphere |
| Boc | *tert*-butyloxycarbonyl |
| Box | bisoxazoline |
| br | broad |
| Bn | benzyl |
| Bu | butyl |
| °C | degree Celsius |
| *c* | cyclo |
| CAM | ceric ammonium molybdate |
| cat. | catalytic |
| CBS | Corey-Bakashi-Shibata |
| cm | centimeter |
| $cm^{-1}$ | wavenumber |
| COSY | correlation spectroscopy |
| d | days |
| d | doublet |
| *d* | deuterium |
| δ | parts per million |
| DART | direct analysis in real time |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DDQ | 2,3-dichloro-5,6-dicyanobenzoquinone |
| DEAD | diethyl azodicarboxylate |
| DET | diethyl tartrate |
| DHQD | dihydroquinidine |
| diam | diameter |
| DIBAL-H | diisobutylaluminium hydride |
| DMAP | 4-dimethylaminopyridine |
| DMDO | dimethyldioxirane |
| DMF | *N,N*-dimethylformamide |
| DMP | Dess-Martin periodinane |
| DMSO | dimethylsulfoxide |
| DNA | deoxyribonucleic acid |
| DTBMP | 2,6-di-*tert*-butyl-4-methylpyridine |
| dr | diastereomeric ratio |
| ee | enantiomeric excess |
| EI | electron ionization |
| equiv | equivalent |

| | |
|---|---|
| ESI | electronspray ionization |
| Et | ethyl |
| EYRCM | enyne ring-closing metathesis |
| FT | Fourier transform |
| g | gram |
| G1 | Grubbs' 1$^{st}$ generation catalyst |
| G2 | Grubbs' 2$^{nd}$ generation catalyst |
| GC | gas chromatography |
| h | hour |
| ht | height |
| HBTU | *O*-benzotriazole-*N*,*N*,*N'*,*N'*-tetramethyl-uronium-hexafluoro-phosphate |
| HMBC | heteronuclear multiple bond correlation |
| HMDS | hexamethyldislylamide |
| HPLC | high performance liquid chromatography |
| HRMS | high resolution mass spectroscopy |
| HSQC | heteronuclear single quantum correlation |
| Hx | hexyl |
| Hz | Hertz |
| *i* | iso |
| IBX | 2-iodoxybenzoic acid |
| IR | infrared |
| IPNBSH | *N*-isopropylidene-*N'*-2-nitrobenzenesulfonyl hydrazine |
| *J* | coupling constant |
| L | liter |
| LDA | lithium diisopropylamide |
| LRMS | low resolution mass spectroscopy |
| m | medium |
| *m* | meta |
| m | multiplet |
| m | milli |
| M | molar |
| μ | micro |
| *m*CPBA | *meta*-chloroperoxybenzoic acid |
| Me | methyl |
| Mes | mesityl |
| MHz | megahertz |
| min | minute |
| mol | mole |
| MS | mass spectrometry |
| *m/z* | mass to charge ratio |
| N | normal |
| NADP | nicotinamide adenine dinucleotide phosphate |
| NaHMDS | sodium hexamethyldislylamide |
| NB | nitrobenzyl |
| NBS | *N*-bromosucinnimide |
| NBSH | *ortho*-nitrobenzenesulfonylhydrazide |

| | |
|---|---|
| NME | *N*-methylephedrin |
| NMM | *N*-methylmorpholine |
| NMP | *N*-methyl-2-pyrrolidone |
| NMR | nuclear magnetic resonance |
| nOe | nuclear Overhauser effect |
| Nuc | nucleophile |
| *o* | ortho |
| *p* | para |
| PCC | pyridinium chlorochromate |
| Ph | phenyl |
| PMA | phosphomolybdic acid |
| ppm | parts per million |
| Pr | propyl |
| PTSA | *para*-toluenesulfonic acid |
| Pybox | 2,6-Bis[(4R)-4-phenyl-2-oxazolinyl]pyridine |
| pyr | pyridine |
| PYR | pyrimidine |
| q | quartet |
| ref | reference |
| RCM | ring-closing metathesis |
| R*f* | retention factor |
| RT | room temperature |
| RuPhos | 2-dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl |
| *s* | sec |
| s | singlet |
| s | strong |
| SES | 2-trimethylsilylethanesulfonyl |
| SPhos | 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl |
| str | stretch |
| *t* | tert |
| t | triplet |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBS | *tert*-butyldimethylsilyl |
| TC | thiophene-2-carboxylate |
| Tf | trifluoromethylsulfonate |
| TFA | trifluoroacetic acid |
| TFE | trifluoroethanol |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMEDA | tetramethylethylenediamine |
| TMS | trimethyl silyl |
| Tris | triphenylmethyl |
| Ts | toluenesulfonic |
| UV | ultraviolet |
| w | weak |
| XPhos | 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl |

# Chapter I.

# Enantioselective Total Synthesis of (–)-Acylfulvene and (–)-Irofulven

## Introduction and Background

The illudins are a family of highly cytotoxic sesquiterpenes isolated from the bioluminescent mushroom *Omphalotus illudens* (Jack O'Lantern mushroom) and other related fungi.[1] The illudins exhibit a unique tricycle core featuring a spiro-cyclopronane A-ring and 6,5-fused BC-ring system. Illudin M (**3**) and illudin S (**4**, Figure 1) are among the most cytotoxic members of this family and have been studied extensively for their promising antitumor activity.[2]
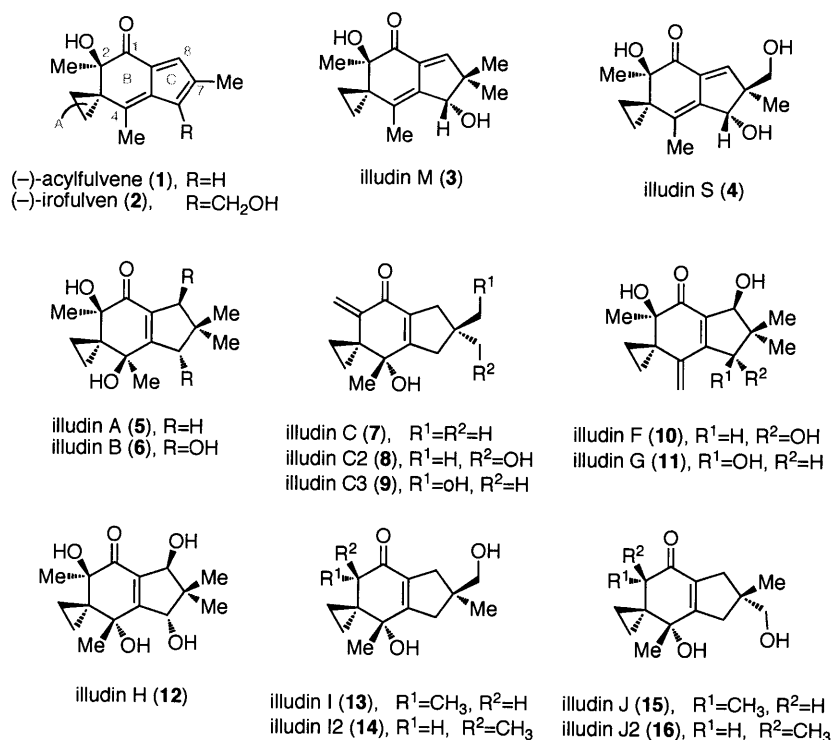


(−)-acylfulvene (**1**), R=H
(−)-irofulven (**2**), R=CH₂OH

illudin M (**3**)

illudin S (**4**)

illudin A (**5**), R=H
illudin B (**6**), R=OH

illudin C (**7**), R¹=R²=H
illudin C2 (**8**), R¹=H, R²=OH
illudin C3 (**9**), R¹=oH, R²=H

illudin F (**10**), R¹=H, R²=OH
illudin G (**11**), R¹=OH, R²=H

illudin H (**12**)

illudin I (**13**), R¹=CH₃, R²=H
illudin I2 (**14**), R¹=H, R²=CH₃

illudin J (**15**), R¹=CH₃, R²=H
illudin J2 (**16**), R¹=H, R²=CH₃

**Figure 1.** The illudin family of sesquiterpenes.

Several studies have been directed at elucidating the biogenesis of the illudin fungal metabolites.[3] Feeding studies involving the addition of carbon-13 and deuterium labeled acetate and mevalonate precursors to cultures of the mushroom *Clitocybe illudens* followed by NMR spectroscopic analysis of the radiolabel enrichment in Illudin M (**3**) and illudin S (**4**) revealed that the biosynthetic sequence likely proceeds according to Scheme 1. The fundamental sesquiterpene precursor farnesyl pyrophosphate (**17**) undergoes ionization followed by cyclization to afford humulyl cation **18**. 1,2-Hydride migration followed by cyclopentane ring formation leads to **20**. Protonation followed by cyclization forms the cyclobutane intermediate

**21**, which then undergoes a 1,2-hydride migration and ring contraction to afford the tricyclic illudin core **22**.
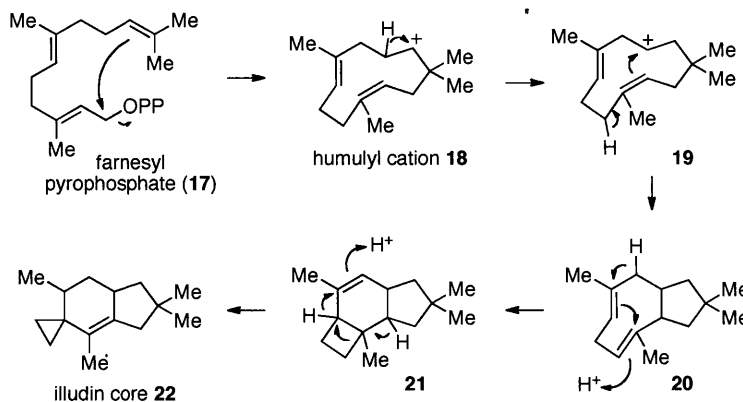


**Scheme 1.** The biosynthesis of the tricyclic illudin core.

Despite their high cytotoxicity, the natural illudins exhibit low therapeutic indices in solid-tumor systems.[4] Consequently, several analogs of the natural illudins have been prepared and evaluated for the treatment of various cancers.[5] Two such semi-synthetic derivatives, (–)-acylfulvene (**1**) and (–)-irofulven (**2**), were prepared from illudin S and have demonstrated greatly enhanced therapeutic potential against several solid tumor systems.[6] The superior pharmacological properties of (–)-acylfulvene (**1**) and (–)-irofulven (**2**) are accompanied by a markedly lower cytotoxicity than that of illudin S (**4**).[7] Several studies have been directed toward elucidating the mechanism of biological activity of the illudins, acylfulvene (**1**), and irofulven (**2**) in order to understand the nature of this selective toxicity.[8] The mechanism is believed to involve an initial activation step by conjugate addition of a hydride (NADPH) or thiol (glutathione or cysteine) nucleophile into the enone moiety followed by nucleophilic addition of DNA to the strained cyclopropane ring to generate a stable aromatic DNA adduct **24** (Scheme 2). The observed onset of apoptosis is believed to be a result of DNA alkylation followed by strand cleavage through this general mechanism. (–)-Irofulven (**2**) is currently undergoing clinical trials for the treatment of various cancers as both a monotherapy and in combination with other chemotherapeutics.[9] The promising antitumor properties and the highly reactive molecular framework of (–)-irofulven (**2**) and other illudins have rendered them interesting synthetic targets.[10]

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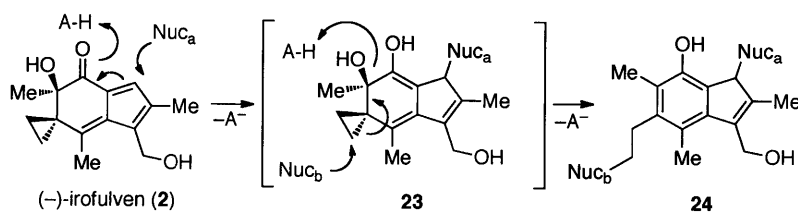
**Scheme 2.** Proposed mechanism of biological activity of (–)-irofulven (**2**). $Nuc_a$ = glutathione, cysteine, or hydride (NADPH). $Nuc_b$ = DNA.

**Review of Prior Enantioselective Syntheses of Acylfulvene and Irofulven.** (–)-Irofulven (**2**) was initially prepared by McMorris in 1996 via a semi-synthesis from illudin S (**4**), which is readily obtained from fermentation of *Omphalotus illudens* (Scheme 3).[6] Treatment of illudin S (**4**) with dilute $H_2SO_4$ in the presence of excess paraformaldehyde afforded (–)-irofulven (**2**) in 38% yield on 353 mg scale along with (–)-acylfulvene (**1**, 17%). Interestingly, (–)-irofulven (**2**) and (–)-acylfulvene (**1**) were shown to be significantly more toxic than their enantiomers, (+)-**2** and (+)-**1** respectively,[10i,10j] which highlights the importance of establishing efficient enantioselective syntheses of these compounds.
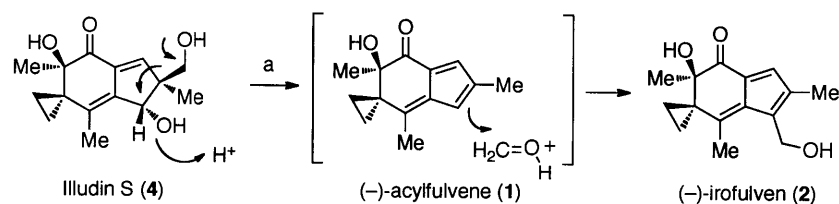


**Scheme 3.** Semi-synthesis of (–)-acylfuvlene (**1**) and (–)-irofulven (**2**). Conditions: a) $(CH_2O)_n$, $H_2SO_4$, $H_2O$, $Me_2CO$, RT, 72 h, 38%.

In a continuation of his studies of these anitcancer agents, McMorris developed the first synthesis of racemic irofulven (**2**) in 1997 via a Padwa carbonyl ylide 1,3-dipolar cycloaddition strategy.[10f] In 2004, McMorris reported a second generation approach for the enantioselective total synthesis of (–)-irofulven (**2**, Scheme 4).[10i] In this approach, the optically active cyclopentenone (+)-**29** was readily prepared from acetylene (**25**) and methacryloyl chloride (**26**). Treatment of **25** and **26** with aluminum trichloride afforded racemic cyclopentenone **27** via a Nazarov cyclization. The enantiomers of cyclopentenone **27** were resolved through a reduction with $BH_3 \cdot THF$ in the presence of catalytic (*S*)-2-methyl-CBS-oxazaborolidine ((*S*)-Me-CBS),

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followed by oxidation to afford (+)-5-chloro-5-methyl-2-cyclopentenone (**29**) in 98% ee. The key cycloaddition reaction of (+)-**29** with diazoketone **30** in the presence of catalytic $Rh_2(OAc)_4$ in refluxing dichloromethane afforded cyclohexane (–)-**31** in 54% yield. Cleavage of the oxo bridge under mild basic conditions followed by acylation and a Grignard addition with methylmagnesium chloride afforded the C2-tertiary alcohol stereocenter (–)-**34**. Ketal formation followed by elimination of the chloride and isomerization of the double bond then afforded the thermodynamically favored cyclopentenone isomer (+)-**36**. After removal of the ketal protecting group, cyclopentenone (+)-**37** was reduced to the fulvene diol (–)-**38** with DIBAL-H in 49% yield. 2-Iodoxybenzoic acid (IBX) oxidation then afforded (–)-acylfulvene (**1**) in 53% yield, which was readily converted to (–)-irofulven (**2**) using their previously reported Prins reaction.[6]
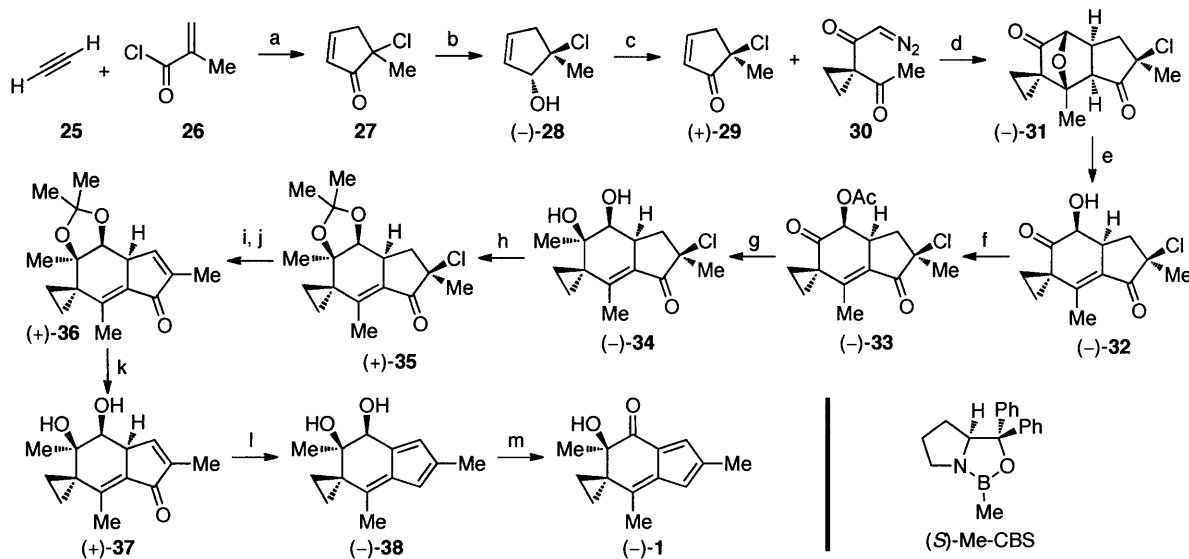


**Scheme 4.** McMorris' enantioselective synthesis of (–)-acylfuvlene (**1**). Conditions: a) $AlCl_3$, $(CH_2Cl)_2$, 35 °C, 8 h, 67%. b) (S)-Me-CBS, $BH_3$, THF, RT, 5 min, 27%, 98% ee. c) PCC, $CH_2Cl_2$, RT, 8 h, 73%. d) $Rh_2(OAc)_4$, $CH_2Cl_2$, Reflux, 1 h, 54%. e) $K_2CO_3$, $^iPrOH$, $H_2O$, RT, 6 h, 70%. f) $Ac_2O$, pyr, RT, 2 h, 90%. g) MeMgCl, THF, –78 °C, 2 h, then 0 °C, 2 h, 87%. h) 2,2-dimethoxypropane, TsOH, DMF, RT, 24 h, 83%. i) DBU, PhH, RT, 1.5 h. j) $RhCl_3 \cdot 3H_2O$, EtOH, Reflux, 20 min, 62% (2 steps). k) AcOH, $H_2O$, 90 °C, 2 h, 78%. l) DIBAL-H, $CH_2Cl_2$, –78 °C, 30 min, 49%. m) IBX, DMSO, RT, 2 h, 53%.

A formal enantioselective synthesis of irofulven (**2**) was reported by Brummond in 2000 employing a key allenic Pauson-Khand reaction to secure the tricyclic core (Scheme 5).[10h] Their synthesis commenced with a Horner-Wadsworth-Emmons reaction involving the treatment of ketone **39**, available in two steps from commercial material, with diethyl 3-trimethylsilylpropynyl phosphate (**40**) to selectively afford the *E*-enyne **41** in 86% yield. The

C2-stereocenter was then genereated via a Sharpless dihydroxylation to afford diol **43** in 49% yield and >95% ee. Selective silylation of the propargylic alcohol afforded **44** in 76% yield and furnished a formal enantioselective synthesis of (–)-irofulven (**2**). Using racemic material, they prepared the key intermediate **47** via acetylide addition to the ketone, acylation, and allene formation. Their key Pauson-Khand reaction was then carried out via treatment of the alkynyl allene **47** with $Mo(CO)_6$ in dimethylsulfoxide (DMSO) and toluene at 110 °C to afford tricycle **48** in 69% yield. Methyllithium addition to the ketone in the presence of cerium trichloride followed by dehydration then afforded **49** in 96% yield. Their synthesis of (–)-irofulven (**2**) was then completed through desilylation, Dess-Martin periodinane (DMP) oxidation, and treatment with formaldehyde in the presence of acid. Notably, this formal enantioselective synthesis was validated by Sturla in 2006, who prepared optically enriched samples of (–)-acylfulvene (**1**) and (–)-irofulven (**2**) via this strategy.[10j]
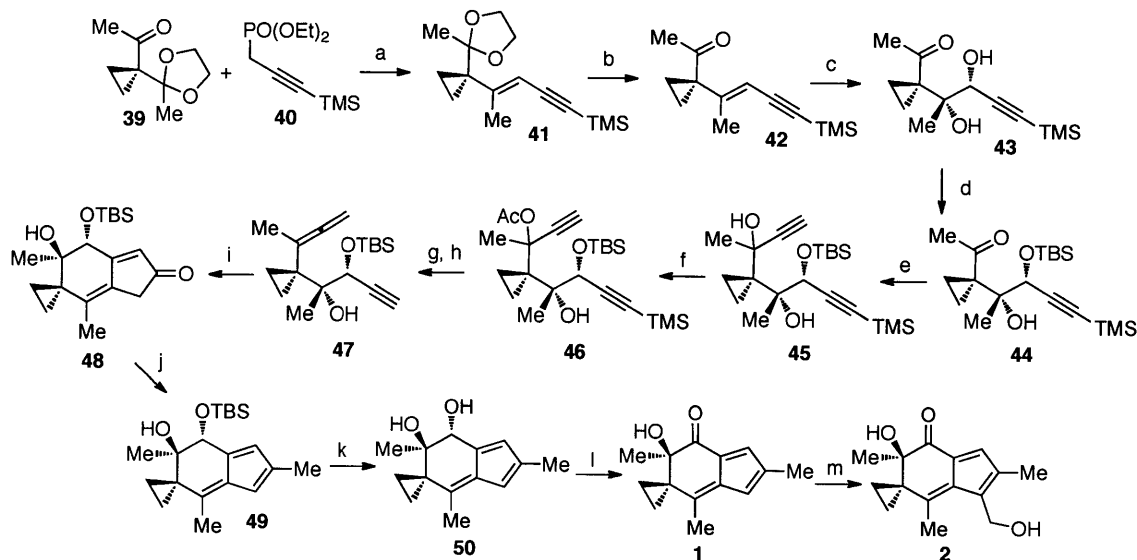


**Scheme 5.** Brummond's formal enantioselective synthesis of (–)-irofulven (**2**) validated by Sturla. Conditions: a) NaHMDS, THF, –78 °C, 86%. b) PTSA, acetone, $H_2O$, 95%. c) $(DHQD)_2PYR$, $K_2OsO_2(OH)_4$, $K_3F_3(CN)_6$, $K_2CO_3$, $CH_3SO_2NH_2$, 'BuOH, $H_2O$, 49%, >95% ee. d) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 76%. e) HCCMgBr, $CeCl_3$, 97% f) $Ac_2O$, DMAP, $Et_3N$, 98%. g) $[(PPh_3)CuH]_6$, 54%. h) $K_2CO_3$, $CH_3OH$, $H_2O$, 95%. i) $Mo(CO)_6$, DMSO, PhMe, 110 °C, 10 min, 69%. j) MeLi (10 eq), $CeCl_3$; 0.1 M HCl, 96%. k) TBAF, 97%. l) DMP, 78%. m) $H_2CO$, $H_2SO_4$, acetone, $H_2O$, 68%.

In addition to validating the formal enantioselective synthesis of (–)-irofulven (**2**) via the strategy reported by Brummond (vide supra, Scheme 5), Sturla also developed a chiral-resolution method for the preparation of these compounds in optically enriched form.[10j] This strategy utilized racemic cyclopentenone (±)-**51**, which was prepared according to Brummond's asymmetric synthesis of **2** (Scheme 6).[10g] Removal of the silyl protecting group furnished *cis*-diol

(±)-**52** that was coupled to chiral acid **53**. The two diastereomers of ester **54** were resolved by preparative HPLC to afford samples of **54** in >98 % ee. Treatment of the optically enriched ester **54** with methyllithium and cerium trichloride in THF then afforded the fulvene diol (–)-**38** in 90%, which was readily converted to (–)-acylfulvene (**1**) through IBX oxidation in 88% yield.
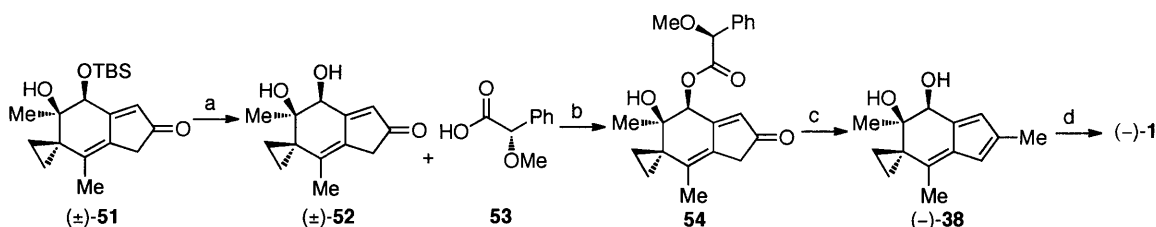


**Scheme 6.** Sturla's chiral resolution strategy. Conditions: a) TBAF, THF, 97%. b) HBTU, DMAP, Et$_3$N, THF, 70%. c) CeCl$_3$, MeLi, THF, 90%. d) IBX, DMSO, 88%.

## Results and Discussion

The promising antitumor properties and the interesting molecular architecture of (–)-acylfulvene (**1**) and (–)-irofulven (**2**) have rendered them interesting synthetic targets to us. We have disclosed the concise enantioselective syntheses of (–)-acylfulvene (**1**) and (–)-irofulven (**2**) and related derivatives.[11] Key features of our approach include a stereoselective aldol addition of a strained ketene hemithioacetal **61**, which secures the C2-stereocenter and enables ready access to aldehyde (+)-**60** (Scheme 7). A key enyne ring-closing metathesis (EYRCM)[12] cascade reaction of trienyne **57** generates the B-ring **56**. A reductive allylic transposition then sets the stage for the final ring-closing olefin metathesis (RCM) to build the C-ring and complete the syntheses of (–)-acylfulvene (**1**) and (–)-irofulven (**2**). Herein, we describe the development of our synthetic strategy to these fascinating molecules.
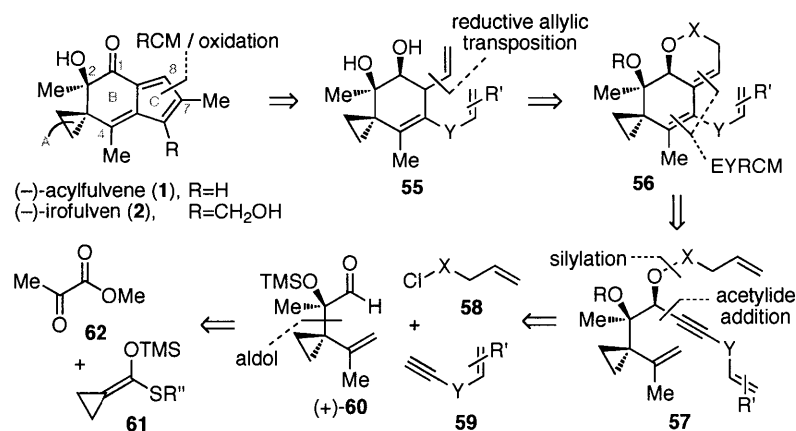


**Scheme 7.** Retrosynthetic analysis of (–)-acylfulvene (**1**) and (–)-irofulven (**2**).

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**Synthesis of the Key Aldehyde Intermediate.** Since aldehyde **60** contains the reactive cyclopropane and tertiary alcohol substructure common to acylfulvene (**1**), irofulven (**2**), and most members of the illudin family, its efficient synthesis was of critical importance.[13] Initially, we developed a synthetic route that enabled us to rapidly generate large quantities of racemic aldehyde **60** for evaluation of our synthetic strategy (Scheme 8). This route involved treatment of pentane-2,4-dione (**63**) with 1,2-dibromoethane and potassium carbonate in DMSO to afford cyclopropyl diketone **64** in 61% yield. Mono-olefination using the Wittig reaction afforded intermediate **65** in 56% yield. Silylcyanation with stoichiometric trimethylsilyl cyanide (TMSCN) in the presence of catalytic InBr$_3$[14] then afforded cyanohydrin **66** in 81% yield, and DIBAL-H reduction afforded racemic aldehyde **60** in multi-gram quantities.
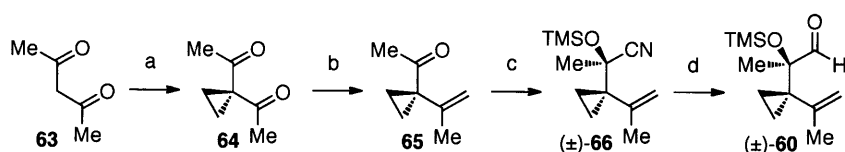


**Scheme 8.** Synthesis of aldehyde (±)-**60**. Conditions: a) (CH$_2$Br)$_2$, K$_2$CO$_3$, DMSO, 61%. b) MePh$_3$PBr, $^t$BuOK, Et$_2$O, 56%. c) TMSCN, InBr$_3$ (5 mol%), CH$_2$Cl$_2$, 81%. d) DIBAL-H, Et$_2$O, –78 °C, 69%.

The enantioselective total synthesis of the target compounds, (–)-**1** and (–)-**2**, required an enantioselective synthesis of aldehyde **60**. Initially, we considered an asymmetric silylcyanation strategy to generate the tertiary alcohol stereocenter (Scheme 9) based on the route to racemic aldehyde **60**. Examination of Jacobsen's thiourea catalyst **67**[15] provided the desired optically enriched cyanohydrin **66**; however, the conversion and level of stereoselection with ketone **65** was non-ideal (50 h, 13%, 53% ee).[16] Furthermore, the selectivity was detrimentally affected by the long reaction times that were required for full conversion of the starting material (8 d, 71%, 34% ee). The use of ketone **65** as a substrate with Hoveyda's catalyst **68**[17] in the presence of Al(O$^i$Pr)$_3$ and Ph$_3$PO afforded the desired compound in good yields (79%), but unfortunately without enantioselection.[16] Likewise, the use of Deng's silylcyanation reaction conditions[18] employing a cinchona alkaloid based catalyst ((DHQD)$_2$AQN) also proved problematic, highlighting the challenge in developing a solution strictly based on the proven route to racemic **60**.

18
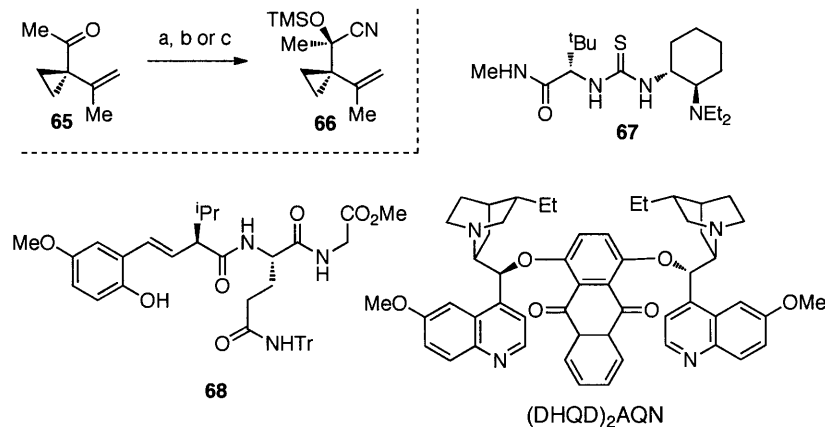
**Scheme 9.** Attempted asymmetric silylcyanation reactions with ketone **65**. Conditions: a) TMSCN, **67**, TFE, CH$_2$Cl$_2$, 50 h, 13%, 53% ee; 8 d, 71%, 34% ee.[16] b) TMSCN, Al(O$^i$Pr)$_3$, **68**, MeOH, PhMe, 3Å MS, 79%, 0% ee.[16] c) TMSCN, (DHQD)$_2$AQN, CH$_2$Cl$_2$, 7 d, 11%, 0% ee.

We investigated several asymmetric oxidation reactions as a means of accessing the tertiary alcohol stereocenter including a Sharpless dihydroxylation, a Sharpless epoxidation, and a substrate directed epoxidation relying on a stereocenter set by a Carreira alkynylation reaction (Scheme 10). Double olefination of diketone **64** afforded the volatile diene **69**, which was subjected to Sharpless' dihydroxylation conditions.[19] While the desired diol **70** was generated in 50% yield, the diene **69** proved to be a poor substrate for enantioselective dihydroxylation.[16] We proceeded to explore the Sharpless asymmetric epoxidation[20] reaction with alcohol **72**, which was prepared from ketone **65** through a Shapiro reaction with dimethylformamide (DMF) followed by a Luche reduction. Unfortunately, the Sharpless epoxidation of diene **72** provided a complex mixture of products likely resulting from the oxidation of the undesired olefin. Also, an alternative synthesis of racemic **73** highlighted its undesired propensity to undergo a Lewis acid catalyzed rearrangement to aldehyde **71**. An approach based on asymmetric alkynylation of aldehyde **71** followed by substrate directed epoxidation also did not provide the desired C2-stereocenter.[21] While Carreira's alkynylation reaction provided the desired product **74** with excellent stereoselectivity (99% ee) using superstoichiometric Zn(OTf)$_2$ and *N*-methylephedrine (NME), the subsequent epoxidation of the allylic alcohol **74** using *meta*-chloroperbenzoic acid (*m*CPBA) resulted in the formation of a complex mixture of products. Since oxidation reactions aimed at forming the stereocenter adjacent to the cyclopropane proved to be problematic, we pursued an alternative route.
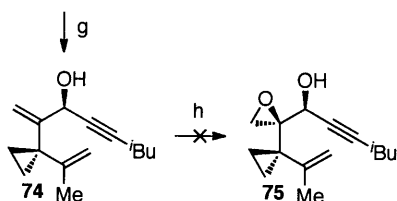
Sharpless' Asymmetric Dihydroxylation
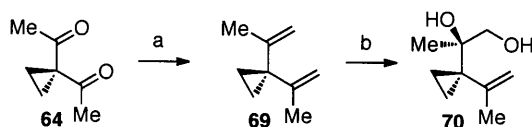


Sharpless' Asymmetric Epoxidation
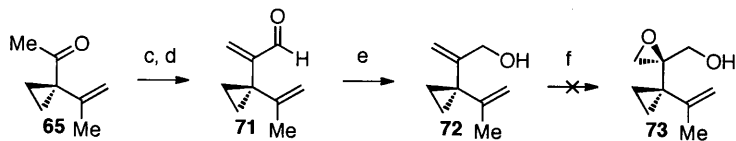


Carreira's Asymmetric
Alkynylation and
directed epoxidation.



**Scheme 10.** Asymmetric oxidation approaches to secure the tertiary alcohol stereocenter. Conditions: a) MePh$_3$PBr, $^t$BuOK, Et$_2$O, 8%. b) AD-mix α, MeSO$_2$NH$_2$, $^t$BuOH, H$_2$O, 50%, 0% ee.[16] c) TrisNHNH$_2$, cat. TsOH, MeCN, 73%. d) $^s$BuLi, TMEDA, hexanes; DMF, 86%. e) NaBH$_4$ CeCl$_3$, CH$_2$Cl$_2$, MeOH, 75%. f) Ti(O$^i$Pr)$_4$, (–)-DET, $^t$BuOOH, CH$_2$Cl$_2$. g) HCC$^t$Bu, Zn(OTf)$_2$, (–)-NME, Et$_3$N, PhMe, 25%, 99% ee. h) $m$CPBA, CH$_2$Cl$_2$.

We sought to use Evans' copper catalyzed aldol reaction for the formation of the desired tertiary alcohol stereocenter,[22] in which we needed to generate a highly strained cyclopropyl ketene hemithioacetal nucleophile **61** (vide supra, Scheme 7). Initial studies by Ainsworth and coworkers aimed at generating the *O*-silylated cyclopropyl ketene acetal **77** revealed that formation of this strained exocyclic double bond was problematic. They reported that the product **77** was generated in at most 10% yield (R = Me, Equation 1).[23] Instead, the *C*-silylated product **78** was formed as the major product (40%, R = Me, Equation 1). Following this report, Pinnick and coworkers observed the formation of trimer **79** in addition to the *C*- and *O*-silylated products **77** and **78** (R = Et, Equation 1).[24] These cyclopropyl ester enolate anions are generally regarded as pyramidalized carbanion centers rather than the *O*-lithiated planar methylene cyclopropane species.[25]



(1)
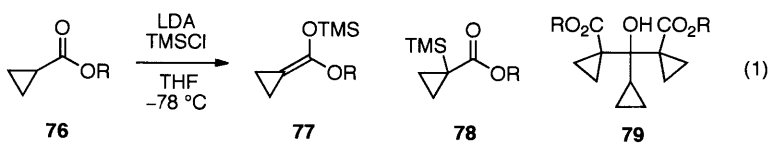
Our studies revealed that enolization of 1-cyclopropylethanone (**80**) at the cyclopropyl carbon is problematic if competing enolization pathways are accessible. Both hard and soft enolization conditions afforded the undesired silyl enol ether **81** exclusively (Scheme 11).[26]
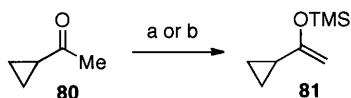


**Scheme 11.** Enolization of 1-cyclopropylethanone (**80**). Conditions: a) LDA, TMSCl, THF, −78 °C, 84%. b) TMSOTf, Et$_3$N, CH$_2$Cl$_2$, −78 °C, 87%.

Interestingly, Seebach and coworkers were able to generate a lithium cyclopropanecarbothioate anion from the corresponding thioester and characterize it through X-Ray crystallographic analysis.[27] This structure exhibited features characteristic of a normal planar *O*-lithiated enolate, as opposed to a pyramidal *C*-lithiated center. Guided by this observation, we reasoned that the enolate of cyclopropyl thioesters might prefer the formation of the *O*-silylated ketene hemithioacetal rather than the *C*-silylated product. To our delight, the *O*-silylated ketene hemithioacetals **61a** and **61b** were generated as the major products through treatment of cyclopropyl thioesters **82a** and **82b** with lithium diisopropylamide (LDA) and trimethylsilyl chloride (TMSCl) in THF at −78 °C (Scheme 12). This reaction afforded an inseparable mixture of *O*- and *C*-silylated products **61** and **83**. The highest selectivity was achieved with ethyl thioester **61b** to generate a 9:1 mixture of **61b** and **83b** in 70% yield; whereas, *tert*-butyl thioester **82a** led to a 3:2 mixture of **61a** and **83a** in 67% yield. Fortunately, the undesired *C*-silylated products **83a** and **83b** did not interfere with the planned aldol reaction. The mixture of compounds **61b/83b** (9:1) could be generated on multi-gram scale and could be stored under an argon atmosphere at −10 °C for greater than a month without any decomposition or *O*- to *C*-silyl transfer. To the best of our knowledge, this is the first example of the formation of a cyclopropyl silylketene hemithioacetal that can be applied in a Mukaiyama aldol reaction.[28]



| **82a**, R = $^t$Bu | 67% | **61a** | (3 : 2) | **83a** |
| **82b**, R = Et | 70% | **61b** | (9 : 1) | **83b** |
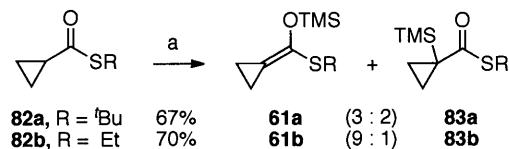
**Scheme 12.** Synthesis of ketene hemithioacetals **61a** and **61b**. Conditions: a) LDA, TMSCl, THF, −78 °C.

**Table 1.** The use of cyclopropyl ketene hemithioacetal in Evans' asymmetric aldol addition reaction.[a]



| Entry | Substrate | Catalyst | Solvent | Temp (°C) | Time (h) | Yield (%) $R^2$ = TMS : H | % ee |
|-------|-----------|----------|---------|-----------|----------|---------------------------|------|
| 1 | 61a | Cu(OTf)$_2$ | CH$_2$Cl$_2$ | −78 | 2 | - : 51 | - |
| 2 | 61a | R,R-CuPybox | CH$_2$Cl$_2$ | −78 | 48 | - : 20 | 0 |
| 3[b] | 61a | R,R-CuPybox | CH$_2$Cl$_2$ | −78 | 18 | - : 19 | 0 |
| 4 | 61a | S,S-CuBox | CH$_2$Cl$_2$ | −78 | 6.5 | - : 73 | −90 |
| 5 | 61a | S,S-CuBox | CH$_2$Cl$_2$ | 23 | 2 | - : 77 | −85 |
| 6 | 61a | S,S-CuBox | THF | −78 | 2 | - : 92 | −95 |
| 7[c] | 61b | S,S-CuBox | THF | −78 | 8 | 71 : 8 | −99 |
| 8[b,c] | 61b | S,S-CuBox | THF | −78 | 1 | 76 : 19 | −95 |
| 9 | 61b | R,R-CuBox | THF | −78 | 12 | - : 93 | 93 |
| **10[c]** | **61b** | **R,R-CuBox** | **THF** | **−78** | **12** | **95 : 0** | **92** |

[a] Reactions were run at [62] = 0.25M, with 10 mol% catalyst loading, and were quenched with TBAF followed by filtration through a plug of silica gel. Enantiomeric excess (ee) was determined by HPLC using a chiralcel AD-H column with the corresponding free alcohol **84** ($R^2$ = H) after desilylation. [b] Reactions were run in the presence of TMSOTf (1 equiv). [c] Reactions were directly filtered through a plug of silica gel without TBAF treatment.

Due to the strain associated with the exocyclic double bond, the cyclopropyl ketene hemithioacetals **61a** and **61b** are highly reactive and are excellent substrates for Evans' copper catalyzed aldol reaction[22] (Table 1). Under optimal conditions, treatment of silylketene hemithioacetal **61b** (1.1 equiv, mixture of **61b:83b** = 9:1) with methyl pyruvate (**62**) in the presence of 10 mol% of (R,R)-CuBox[29] provided the enantiomerically enriched thioester (+)-**84b** ($R^2$ = TMS) in 95% yield and 92% ee (entry 10, Table 1).[30] This reaction was performed on large scale to generate a 19.8 gram batch of the desired product (+)-**84b**, and the (R,R)-Box ligand was recovered in approximately 85% yield from the reaction mixture. As a part of these studies, we also evaluated the (R,R)-CuPybox catalyst, but it proved to be inferior to the CuBox system for this transformation (entries 2 and 3, Table 1). While the tert-butyl substrate **61a** was competent

for this transformation under the optimized conditions (entry 6, Table 1), attempts to derivatize the resulting *tert*-butyl thioester **84a** proved to be ineffective *(vide infra*, Scheme 13).

With esters **84a** and (+)-**84b** in hand, we proceeded to derivatize the thioester moiety selectively. Initially, we investigated methyl cuprate addition into the C4-thioester.[31] Attempts to functionalize *tert*-butyl thioester **84a** proved to be inefficient (Scheme 13). Surprisingly, using a large excess of methyl cuprate (10 equiv), methyl addition occurred exclusively at the C1-methyl ester to afford the lactone **85** in 45% yield. In contrast, addition of one equivalent of methyl cuprate to the more reactive ethyl thioester (+)-**84b** afforded the desired product (+)-**86** in 25% yield. However, this reaction was complicated by significant decomposition of the sensitive cyclopropyl ketone (+)-**86** under the reaction conditions.
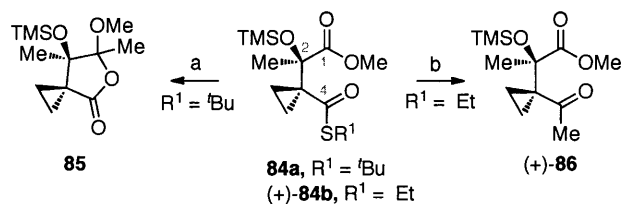


**Scheme 13.** Cuprate addition to the thioesters **84a** and (+)-**84b**. Conditions: a) **84a**, Me$_2$CuLi (10 equiv), Et$_2$O, 0 °C, 2 h, 45%. b) (+)-**84b** Me$_2$CuLi (1 equiv), Et$_2$O, 23 °C, 30 min, 25%.

We found that the ethyl thioester (+)-**84b** could be efficiently derivatized through a modified Fukuyama cross-coupling protocol.[32] Using the reported reaction conditions,[32a] we obtained the desired product (+)-**86** in 42% yield (entry 1, Table 2). Under these conditions, the reaction suffered from incomplete conversion of the starting material (27% recovered (+)-**84b**) and the instability of the catalyst, which was evident from the precipitation of palladium black over the course of the reaction. We developed the optimal conditions for the substrates of interest by evaluating various ligands, reaction temperatures, and solvents (Table 2). Using the optimal conditions, multi-gram quantities of methyl ketone (+)-**86** were efficiently prepared in 83% yield via the cross-coupling of thioester (+)-**84b** with iodomethylzinc using 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (SPhos)[32b] as a supporting ligand in a 1:1.5 THF:NMP[32c] solvent mixture (entry 7, Table 2). SPhos proved to be the ideal ligand for this difficult transformation, providing improved stability for the palladium metal center and high overall efficiency.

**Table 2.** Thioester cross-coupling.[a]



| Entry | Catalyst | Ligand | Solvent[b] | Temp (°C) | Time (h) | Yield (%) |
|-------|----------|--------|-----------|-----------|----------|-----------|
| 1 | $PdCl_2(PPh_3)_2$ | - | PhMe | 23 | 11 | 42 |
| 2 | $PdCl_2(PPh_3)_2$ | - | THF, NMP | 65 | 15 | 66 |
| 3 | $Pd_2(dba)_3$ | SPhos | PhMe | 23 | 11 | 0 |
| 4 | $Pd_2(dba)_3$ | SPhos | THF | 23 | 11 | 0 |
| 5 | $Pd_2(dba)_3$ | SPhos | PhMe | 65 | 11 | 19 |
| 6 | $Pd_2(dba)_3$ | SPhos | THF | 65 | 11 | 42 |
| **7** | **$Pd_2(dba)_3$** | **SPhos** | **THF, NMP** | **65** | **2** | **83** |
| 8 | $Pd_2(dba)_3$ | XPhos | THF, NMP | 65 | 2 | 70 |
| 9 | $Pd_2(dba)_3$ | RuPhos | THF, NMP | 65 | 2 | 66 |

[a] Reactions were run with $PdL_n$ (5 mol%), ligand (20 mol%), MeZnI (5 equiv), [(+)-**84b**] = 0.3M. [b] THF, NMP (1:1.5).

Methylenation of the sensitive and sterically hindered ketone (+)-**86** was achieved through a Takai olefination (Scheme 14).[33] Treatment of ketone (+)-**86** with $CH_2I_2$, Zn dust, $TiCl_4$, and catalytic $PbCl_2$ afforded olefin (+)-**87** in 89% yield.[34] The ester (+)-**87** was then treated with DIBAL-H to afford a mixture of the desired aldehyde (+)-**60** and the corresponding fully reduced primary alcohol (1:2.5 respectively). Without purification, this mixture was immediately oxidized with DMP to give aldehyde (+)-**60** exclusively in 91% yield over the two steps.
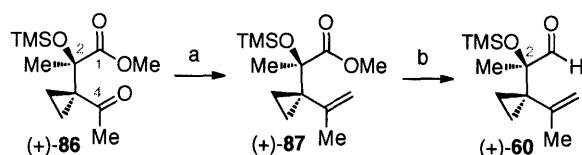


**Scheme 14.** Synthesis of aldehyde (+)-**60**. Conditions: a) $CH_2I_2$, Zn, $TiCl_4$, $PbCl_2$, THF, 89%. b) DIBAL-H, $Et_2O$; DMP, $CH_2Cl_2$, 91%.

The configuration of C2 in aldehyde (+)-**60** was verified through X-ray crystallographic analysis of a corresponding carboxylate derivative **88** with (–)-brucine (Scheme 15).[35] This efficient aldol-based approach for securing the C2-stereochemistry enabled us to generate multi-gram quantities of the key aldehyde (+)-**60**. Notably, aldehyde (+)-**60** possesses a substructure that can be mapped on to most of the illudin sesquiterpenes and provides a platform for the rapid and convergent synthesis of a broad range of derivatives of the functional illudin core structure.[11]
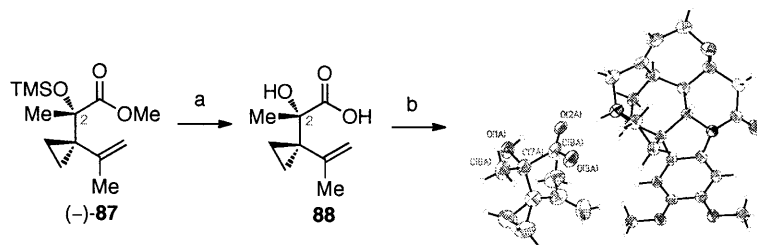


**Scheme 15.** Thermal ellipsoid representation of the carboxylic acid **88** salt with (–)-brucine. Conditions: a) LiOH, THF, 82%. b) (–)-brucine.

**Evaluation of the Enyne Ring-Closing Metathesis Cascade Reaction.** The EYRCM sequence described in Scheme 16 represented our planned approach toward the synthesis of the functional AB-ring system common to the illudins. The enyne metathesis between the tethered olefin and the alkyne of **89** would generate a ruthenium alkylidene **90**[36] that would undergo a ring-closing olefin metathesis to afford a tetrasubstituted alkene on a highly substituted B-ring **92**.[37] We envisioned that elaboration of the functionalized side chain of **92** would potentially allow rapid access to various members of the illudin family.
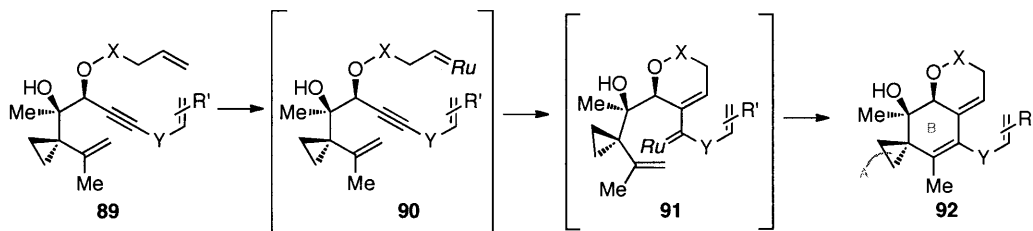


**Scheme 16.** Our planned EYRCM cascade for the formation of the AB-ring system.

We evaluated several olefin tethers for the key EYRCM using model substrate **93** in order to identify optimal tethers that were both stable to the EYRCM reaction conditions and

readily removable (Table 3). Both Grubbs' first- and second-generation metathesis catalysts (**G1** and **G2**, respectively)[38] were evaluated, with **G2** generally providing the desired product **94** with greater efficiency compared to **G1**. Under optimal EYRCM reaction conditions, neither the carbonate nor the carbamate tethers (entries 1 and 2, Table 3) provided the desired EYRCM product **94**. Instead, the carbonate tether fragmented to afford the corresponding propargylic alcohol,[39] and the Lewis basic carbamate likely reduced the activity of the **G2** metathesis catalyst through an unproductive coordination event.
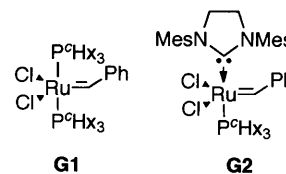
Table 3. Evaluation of olefin tethers for the EYRCM.



| Entry | Tether | Solvent | Temp (°C) | Time | Yield[a] |
|-------|--------|---------|-----------|------|----------|
| 1 | | PhH | 65 | 1.5 h | 0% |
| 2 | | PhMe | 110 | 1.5 h | 0% |
| 3 | | PhMe | 110 | 1.5 h | 47% |
| 4 | | PhH | 80 | 6 h | 15%[b] |
| 5 | | PhH | 65 | 30 min | 91% |
| 6 | | PhH | 65 | 3 h | 92% |

[a] Isolated yields. [b] Isolated yield of free amide after TBS deprotection with TBAF.

Interestingly, when the cyclohexyl ($^{c}$Hx) carbamate (entry 3, Table 3) was submitted to the EYRCM conditions, the product **94** was generated in 47% yield. We attribute this enhanced reactivity to the expected substrate preference to adopt the carbamate rotamer that positions the

allyl substituent trans to the carbonyl. In this conformation the olefin is oriented in close proximity to the alkyne and is poised for the ensuing EYRCM with minimal interference by the Lewis basic carbonyl. In light of this, we also prepared the *tert*-butyldimethylsilyl allylamide (entry 4, Table 3), which would enable access to a more hydrolytically labile cyclic–carbonate by treatment with tetra-*n*-butylammonium fluoride (TBAF). However, the tandem EYRCM–TBAF treatment provided the desired product in only 15% yield, due to the lability of the silylcarbamate under the EYRCM conditions.

None of the carbonate or carbamate based tethers proved superior to silicon based olefin tethers examined for this transformation. When the allylsilane tether, first reported by Grubbs and Yao,[40] was subjected to the EYRCM conditions, the desired product **94** was afforded in 91% yield (entry 5, Table 3) within 30 min. Furthermore, the allyloxysilane tether (entry 6, Table 3)[41] also provided the desired enyne metathesis product in 92% yield, albeit requiring a longer reaction time. Interestingly, in related systems we observed that the diethylallyoxysilane tether (entry 6, Table 3) was optimal as compared to the corresponding dimethyl and diisopropyl variants. The diethylallyloxysilane tether provided the best balance between stability and reactivity. The dimethylallyloxysilane tether was too labile under the EYRCM reactions conditions leading to premature desilylation, while the diisopropylallyloxysilane was both more difficult to prepare due to lower rate of etherification and also gave the desired metathesis products in low yields. Due to the difficulty in elaborating the allylsilane tether to the desired allylic alcohol via oxidation protocols,[42] we focused on applying the allyloxysilane tethers toward the synthesis of (–)-acylfulvene (**1**) and (–)-irofulven (**2**). This tether would allow for direct access to the stable allylic alcohol product from the EYRCM reaction via *in situ* removal of the tether.

The successful synthesis of (–)-acylfulvene (**1**) and (–)-irofulven (**2**) using the EYRCM strategy began with the rapid assembly of key trienynes **98** and **99** via the coupling of readily available aldehyde (+)-**60**, enyne **95**, and allyloxydiethylchlorosilane[43] (**97**, Scheme 17). Addition of the corresponding lithium acetylide of enyne **95** to aldehyde (+)-**60** provided diol **96** (72%) after desilylation of the immediate silyl-migration (C1→C2) product as a mixture of C1-diastereomers ($1S$:$1R$, 5.6:1) favoring the Felkin-Ahn mode of carbonyl addition (Scheme 17). Given the final stage oxidation of the C1-hydroxyl group to the corresponding C1-carbonyl of the target compounds, both diastereomers were moved forward without chromatographic

separation. The diastereomeric mixture of diols **96** were subjected to selective secondary alcohol allyloxydiethylsilylation to afford **98** (65%). Additionally, we developed a one-pot procedure for the formation of the C2-silyl ether substrate **99** in 83% yield directly from **96**, which involved sequential addition of allyloxydiethylchlorosilane (**97**) followed by trimethylsilyl trifluoromethanesulfonate (TMSOTf, Scheme 17).
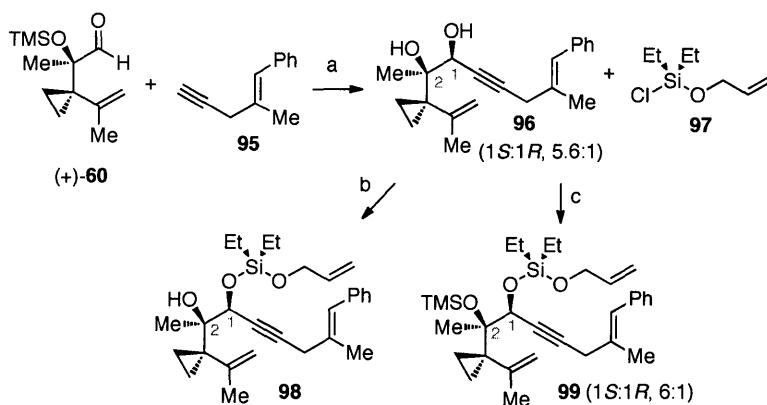


**Scheme 17.** Synthesis of the trienynes **98** and **99**. For clarity, only the major diastereomers are shown. Conditions: a) LiHMDS, THF, −78→40 °C; TBAF, AcOH, 72%. b) (Et)$_2$Si(Cl)OCH$_2$CH=CH$_2$, 2,6-lutidine, CH$_2$Cl$_2$, 65%. c) (Et)$_2$Si(Cl)OCH$_2$CH=CH$_2$, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C; TMSOTf, 83%.

We first evaluated the tandem EYRCM sequence with the C2-hydroxyl substrate **98**; however, this substrate exhibited low efficiency for this transformation. The EYRCM with the C2-hydroxyl trienyne **98** afforded the desired triol in 48% isolated yield, and required a high temperature (110 °C), a long reaction time (2 h), and a high catalyst loading (30 mol%, Scheme 18). We speculated that at high temperature, partial loss of the allyloxydiethylsilyl tether, promoted by the vicinal C2-hydroxyl group, was responsible for the low efficiency of the reaction.
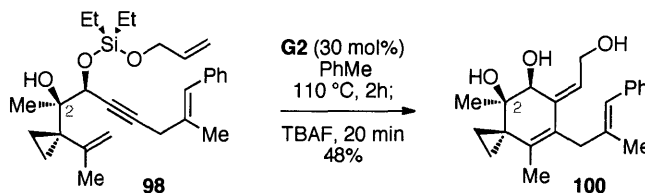


**Scheme 18.** EYRCM with the C2-hydroxyl substrate **98**. For clarity, only the major diastereomers are shown.

Importantly, the reactivity of the C2-silyl ether substrate **99** was significantly enhanced under the EYRCM conditions and required only 15 mol% catalyst loading of **G2** at 90 °C in only

30 min for the reaction to proceed to full conversion (Scheme 19). In the event, the C2-silyl ether substrate **99**, containing the trisubstituted styrenyl alkene, underwent the EYRCM cascade and desilylation reaction smoothly to afford the desired triol **100** in 74% yield (Scheme 19). Interestingly, we observed no byproducts associated with metathesis of the trisubstituted styrenyl olefin under the EYRCM conditions. Both C1-diastereomers of trienyne **99** were equally effective substrates for this key EYRCM cascade to generate triol **100** ($1S{:}1R$, 6:1). Triol **100** contained all the necessary functional groups and the carbon skeleton needed for completion of the synthesis.
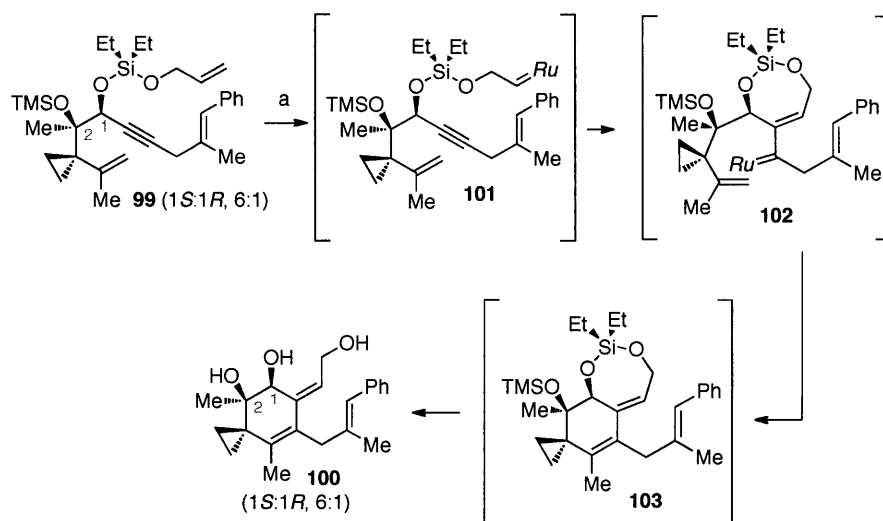


**Scheme 19.** EYRCM cascade. For clarity, only the major diastereomers are shown. Conditions: a) **G2** (15 mol%), PhMe (0.01M), 90 °C, 30 min; TBAF, AcOH, THF, 23 °C, 10 min, 74%.

**Completion of the Synthesis of (–)-Acylfulvene and (–)-Irofulven.** Accordingly, we advanced our synthesis based on a reductive allylic transposition strategy (Scheme 20). Through this strategy, alcohol **105** would be elaborated to the terminal olefin **106**, which would then be converted to tricycle **107** via a RCM reaction. Oxidative dehydrogenation would then provide the fulvene **108**.
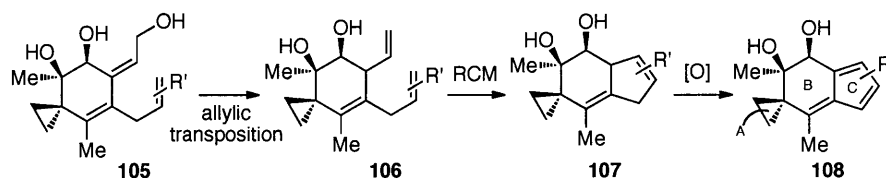


**Scheme 20.** Reductive allylic transposition and C-ring synthesis strategy.

29

With triol **100** in hand, we evaluated the reductive allylic transposition reaction and RCM reaction for the completion of the synthesis of (−)-acylfulvene (**1**) and (−)-irofulven (**2**). We found it necessary to mask the tertiary and secondary alcohols, and developed a tandem process to generate carbonate **109** (Scheme 21). Monosilylation of allylic alcohol **100** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 1 equiv) selectively protected the primary alcohol. Sequential treatment with triphosgene and TBAF afforded the desired carbonate **109** (1*S*:1*R*, 20:1) in 67% yield in a single flask. Enrichment of the major diastereomer was observed as a result of the difficulty in forming the *trans*-fused cyclic carbonate. Substrate **109** was then subjected to Myers' reductive allylic transposition reaction to give the desired triene **111**.[44] In the event, the Mitsunobu displacement of alcohol **109** with 2-nitrobenzene-sulfonylhydrazide (NBSH) in *N*-methylmorpholine (NMM, −30→23 °C) gave triene **111** (9*S*:9*R*, 3:1) via a sigmatropic loss of dinitrogen from the intermediate monoalkyl diazene **110**. Due to the insolubility of the substrate **109** in the optimal reaction media at low temperature and at high concentration, variable yields of the desired product were obtained (35-54%).
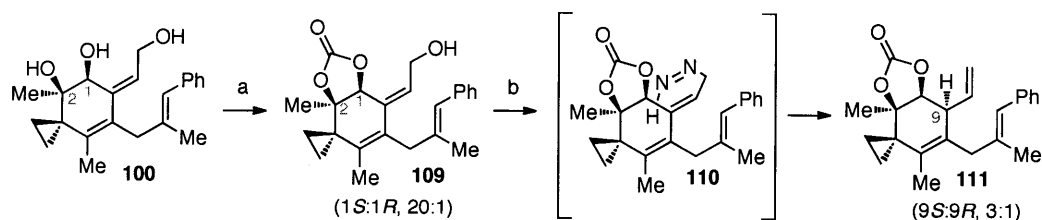


**Scheme 21.** Synthesis of carbonate **109** and the reductive allylic transposition using NBSH. For clarity, only the major diastereomers are shown. Conditions: a) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, −78 °C; triphosgene, 23 °C; TBAF, 67%. b) NBSH, DEAD, $PMe_3$, allylbenzene, NMM, −30 °C, 1 h; 23 °C, 40 min, 47%.

In order to address the complications associated with substrate **109**, we considered the use of a more stable derivative of NBSH that would allow us to carry out the challenging Mitsunobu displacement at higher temperatures and lower solvent concentrations. Thus, the acetone hydrazone derivative, *N*-isopropylidene-*N'*-2-nitrobenzenesulfonyl hydrazine (IPNBSH),[45] was prepared and used for the reductive allylic transposition of alcohol **109** (Scheme 22). We were pleased to find that the Mitsunobu displacement of alcohol **109** with IPNBSH proceeded smoothly at temperatures between 5-23 °C and at lower concentrations to give the stable hydrazone intermediate **112**. Under optimal conditions, the solvolysis of

hydrazone **112** using 2,2,2-trifluoroethanol (TFE) at 0 °C afforded the desired olefin **111** in 71% yield.
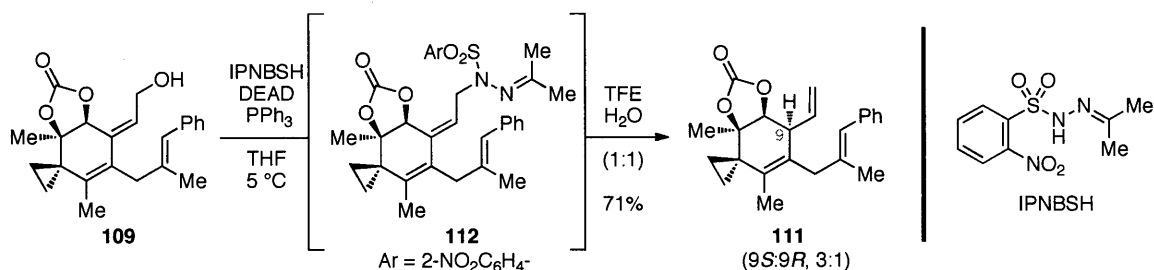


**Scheme 22.** IPNBSH mediated transposition reaction. For clarity, only the major diastereomers are shown.

With triene **111** in hand, we focused on the final stages of the synthesis of (–)-acylfulvene (**1**) and (–)-irofulven (**2**). We established a tandem process to include the RCM, hydrolysis, and dehydrogenation in a single flask. Thus, triene **111** was subjected to a three-step sequence involving the RCM, carbonate hydrolysis, and sequential chloranil oxidation to afford the desired diol fulvene **38** directly in 70% yield (Scheme 23). IBX oxidation then afforded (–)-acylfulvene (**1**) in 80% yield. Interestingly, by replacing chloranil with DDQ, a more potent oxidant, triene **111** could be converted directly to (–)-acylfulvene (**1**) in 30% yield without isolation of any intermediates (Scheme 23). Finally, (–)-acylfulvene (**1**) was then elaborated to (–)-irofulven (**2**) in 35% yield[46] using the protocol described by McMorris and coworkers.[6] All spectroscopic data for (–)-acylfulvene (**1**) and (–)-irofulven (**2**) matched those reported in the literature.
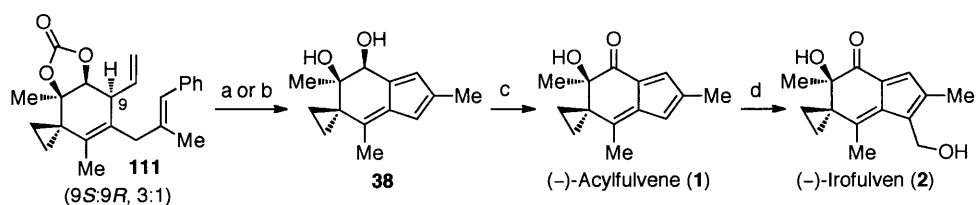


**Scheme 23.** Synthesis of (–)-acylfulvene (**1**) and (–)-irofulven (**2**). For clarity, only the major diastereomers are shown. Conditions: a) **111**→(–)-**1**: G2 (15mol%), PhH, 80 °C, 50 min; NaOMe, MeOH, 23 °C, 18 h; AcOH; DDQ, MeCN, 14 h, 30%. b) **111**→**38**: G2 (15mol%), PhH, 80 °C, 50 min; NaOMe, MeOH, 23 °C, 18 h; AcOH; chloranil, MeCN, 13 h, 70%. c) IBX, DMSO, 80%. d) $H_2SO_4$, $CH_2O$ aq., $Me_2CO$, 4 d, 35%.

# Conclusion

We have described the development of our synthesis of two potent antitumor agents (–)-acylfulvene (**1**) and (–)-irofulven (**2**). The optimal sequence is summarized in Scheme 24. The asymmetric copper catalyzed Evans aldol addition reaction with the strained ketene acetal secured the C2-stereocenter of the target compounds. The powerful EYRCM cascade reaction with the allyloxysilane tether was successfully employed for the B-ring construction. The reagent IPNBSH efficiently provided the necessary reductive transposition of an advanced allylic alcohol. Finally, a tandem RCM/dehydrogenation process was employed for the C-ring construction to complete the syntheses of (–)-acylfulvene (**1**) and (–)-irofulven (**2**).
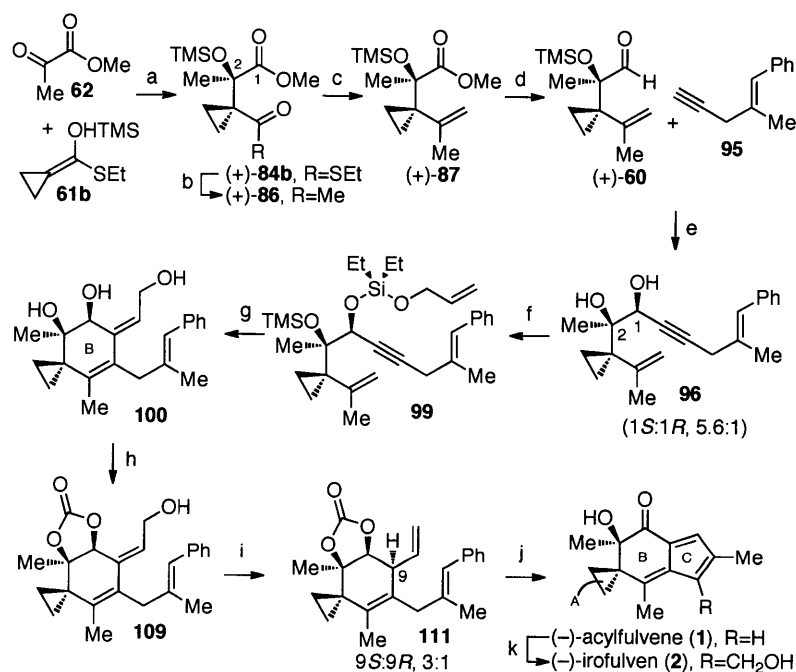


**Scheme 24.** Summary of the enantioselective total synthesis of (–)-acylfulvene (**1**) and (–)-irofulven (**2**). For clarity, only the major diastereomers of intermediates **96-111** are shown. Conditions: a) ($R,R$)-2,2'-isopropylidene-bis(4-$^t$butyl-2-oxazoline), Cu(OTf)$_2$, THF, –78 °C, 12 h, 95%, 92% ee. (b) MeZnI, Pd$_2$(dba)$_3$, SPhos, THF, NMP, 65 °C, 2 h, 83%. (c) CH$_2$I$_2$, TiCl$_4$, Zn, PbCl$_4$, CH$_2$Cl$_2$, THF, 23 °C, 4 h, 89%. (d) DIBAL-H, Et$_2$O, –78 °C; DMP, CH$_2$Cl$_2$, 23 °C, 91%. e) **95**, LiHMDS, THF, –78→–40 °C; TBAF, AcOH, 72%. f) (Et)$_2$Si(Cl)OCH$_2$CH=CH$_2$, 2,6-lutidine, CH$_2$Cl$_2$; TMSOTf, –78 °C, 83%. g) **G2** (15 mol%), PhMe, 90 °C, 30 min; TBAF, AcOH, 74%. h) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, –78 °C; triphosgene; TBAF, 67%. i) IPNBSH, DEAD, Ph$_3$P, THF, 0→23 °C; TFE, H$_2$O, 71%. j) **G2** (15 mol%), PhH, 80 °C; NaOMe; AcOH; DDQ (**111**→(–)-**1**, 30%) - or use chloranil to isolate **38** (70%), then IBX, DMSO, 80%. k) H$_2$SO$_4$, CH$_2$O$_{aq}$, 35%

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42. Our Attempts to cleave allylsilane tethers via oxidation protocols were plagued by low yields. See ref 11c.

43. Allyloxydiethylchlorosilane (**97**) was prepared according to the procedure of Krolevets, A. A.; Antipova, V. V.; Popov, A. G.; Adamov, A. V. *Zh. Obsch. Khim.*, **1988**, *58*, 2274.

44. (a) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841. (b) Myers, A. G.; Movassaghi, M.; Zheng, B. *J. Am. Chem. Soc.* **1997**, *119*, 8572.

45. For an evaluation of the scope of IPNBSH, see: (a) Movassaghi, M.; Ahmad, O. K. *J. Org. Chem.* **2007**, *72*, 1838. For use of IPNBSH in a stereospecific palladium-catalyzed route to monoalkyl diazenes, see: (b) Movassaghi, M.; Ahmad, O. K. *Angew. Chem. Int. Ed.* **2008**, *47*, 8909.

46. (–)-Irofulven (**2**) was obtained in 63% by Dr. Grazia Piizzi via treatment of (–)-acylfulvene (**1**) with acidic formalin for 6 d. See ref 11a.

## Experimental Section

**General Procedures.** All reactions were performed in oven-dried or flame-dried round bottomed flasks or modified Schlenk (Kjeldahl shape) flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon. Gas tight syringes equipped with stainless steel needles or cannulae were used to transfer air- and moisture-sensitive liquids. Flash column chromatography was performed as described by Still et al. using silica gel (60-Å pore size, 32–63 μm, standard grade, Sorbent Technologies) or non-activated alumina gel (80–325 mesh, chromatographic grade, EM Science).[1] Analytical thin–layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel or neutral alumina gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to an ethanolic phosphomolybdic acid (PMA), an acidic solution of p-anisaldehyde (Anis), an aqueous solution of ceric ammonium molybdate (CAM), an aqueous solution of potassium permanganate (KMnO$_4$) or an ethanolic solution of ninhydrin followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on Büchi R-200 rotary evaporators at ~10 Torr (house vacuum) at 25–35 °C, then at ~0.5 Torr (vacuum pump) unless otherwise indicated.

**Materials.** Commercial reagents and solvents were used as received with the following exceptions: dichloromethane, diethyl ether, tetrahydrofuran, acetonitrile, and toluene were purchased from J.T. Baker (Cycletainer™) and were purified by the method of Grubbs et al. under positive argon pressure.[2] Benzene, triethylamine, diisopropylamine, N-methylmorpholine, 1-methyl-2-pyrrolidinone, 2,6-lutidine, and chlorotrimethylsilane were distilled from calcium hydride immediately before use. Methanol was distilled from anhydrous magnesium methoxide. Lithium hexamethyldisilazane was purchased from Aldrich and was stored in a glove box. Sodium hydride was purchased from Aldrich Chemicals as dispersion (60%) in oil and washed four times with hexanes and stored in a glove box. Methanolic sodium methoxide solution (1.0 N) was prepared by addition of sodium hydride to anhydrous methanol at –78 °C. The molarity of n-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).[3] Where necessary (so noted) solutions were degassed by sparging with argon for >10 minutes.

**Instrumentation.** Proton ($^1$H) and carbon ($^{13}$C) nuclear magnetic resonance spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer with a Magnex Scientific superconducting magnet, a Bruker Avance-400 (400 MHz) spectrometer with a SpectroSpin superconducting magnet at 23°C, or a Varian 500 INOVA (500 MHz) as noted. Proton nuclear magnetic resonance ($^1$H NMR) spectra are reported in parts per million from internal tetramethylsilane on the δ scale and are referenced from the residual protium in the NMR solvent (CHCl$_3$: δ 7.27, C$_6$HD$_5$: δ 7.16, CHD$_2$CN: δ 1.94). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, st = sextet, sp = septet, m = multiplet, app = apparent, br = broad), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance spectra are reported in parts per

[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
[2] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.
[3] Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879–1880.

million from internal tetramethylsilane on the δ scale and are referenced from the carbon resonances of the solvent (CDCl$_3$: δ 77.2, C$_6$D$_6$: δ 128.0, CD$_3$CN: δ 118.7 and δ 1.39). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) in Hertz, assignment]. Infrared data were obtained with a Perkin-Elmer 2000 FTIR and are reported as follows: [frequency of absorption (cm$^{-1}$), intensity of absorption (s = strong, m = medium, w = weak, br = broad), assignment]. Gas chromatography was performed on an Agilent Technologies 6890N Network GC System with a HP-5 5% Phenyl Methyl Siloxane column (100 °C, 1 min; 30 °C/min to 250 °C; 250 °C, 2 min). The structure of **88** with (−)-brucine was obtained at the X-ray crystallography laboratory of the Department of Chemistry, Massachusetts Institute of Technology, with the assistance of Dr. Peter Mueller and Mr. Michael A. Schmidt. Gas chromatography low-resolution mass spectra (GC-LRMS) were recorded on an Agilent Technologies 6890N Network GC System with a Restek Rtx-1 100% dimethyl polysiloxane column (100 °C, 5 min; 20 °C/min to 250 °C; 250 °C, 5 min; 30 °C/min to 320 °C; 320 °C, 5 min) with a Agilent 5973*Network* mass selective detector using electron impact ion source (EI). Optical Rotation was recorded on a Jasco P-1010 Polarimeter (Chloroform, Aldrich, Chromosolv Plus 99.9%; Ethanol, Aldrich, Absolute, 200 Proof 99.5%). We are grateful to Dr. Li Li for obtaining the mass spectroscopic data at the Department of Chemistry's Instrumentation Facility, Massachusetts Institute of Technology. High-resolution mass spectra (HRMS) were recorded on a Bruker APEX 4.7 Tesler FTMS spectrometer using electrospray ion source (ESI), unless otherwise noted.
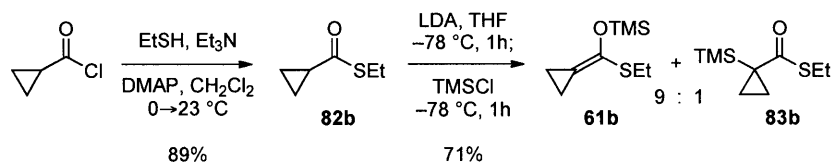
## (Cyclopropylidene(ethylthio)methoxy)trimethylsilane (61b):

Ethanethiol (16.3 mL, 220 mmol, 1.10 equiv) was added slowly to a solution of cyclopropanecarbonyl chloride (18.3 mL, 200 mmol, 1 equiv), triethylamine (33.5 mL, 240 mmol, 1.20 equiv), and 4-dimethylaminopyridine (2.40 g, 20.0 mmol, 0.100 equiv) in dichloromethane (500 mL) at 0 °C, and the resulting mixture was allowed to warm to 23 °C. After 3 h, the reaction mixture was concentrated under reduced pressure, and the residue was partitioned between diethyl ether (400 mL) and water (300 mL). The organic phase was separated and was washed with brine (300 mL), was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by vacuum distillation (50 °C, 5 mmHg) to afford $S$-ethyl cyclopropanecarbothioate (82b, 23.1 g, 89%) as a clear colorless liquid.

$n$-Butyllithium (2.50 M, 33.8 mL, 1.10 equiv) was added to a solution of diisopropylamine (12.9 mL, 92.3 mmol, 1.20 equiv) in THF (192 mL) at 0 °C under argon. The mixture was cooled to −78 °C, and $S$-ethyl cyclopropanecarbothioate (82b, 10.0 g, 76.9 mmol, 1 equiv) was added dropwise via syringe. After 1 h, freshly distilled chlorotrimethylsilane (11.7 mL, 92.3 mmol, 1.20 equiv) was added dropwise. After an additional 1h, the reaction mixture was diluted with pentane (500 mL), and was washed with water (300 mL), phosphate buffer (pH 7, 300 mL), and brine (300 mL). The organic layer was dried over anhydrous sodium sulfate, and was concentrated under reduced pressure. The residue was purified by vacuum distillation (60 °C, 1 mmHg) to afford a mixture (9:1) of (cyclopropylidene(ethylthio)methoxy)trimethylsilane (61b) and 1-(trimethyl-silanyl)-cyclopropanecarbothioic acid $S$-ethyl ester (83b), as clear colorless oil (11.0 g, 71%).

### $S$-ethyl cyclopropanecarbothioate (82b):

| | |
|---|---|
| $^1$H NMR (500 MHz, CDCl$_3$) δ: | 2.87 (q, $J$ = 7.3 Hz, 2H, SCH$_2$), 1.98 (tt, $J$ = 7.7 Hz, 4.6 Hz, 1H, CH), 1.23 (t, $J$ = 7.3, 3H, CH$_3$), 1.15-1.11 (m, 2H, CH$_2$), 0.93-0.89 (m, 2H, CH$_2$). |
| $^{13}$C NMR (125.8 MHz, CDCl$_3$) δ: | 199.5, 23.4, 22.7, 15.0, 10.7. |
| FTIR (neat) cm$^{-1}$: | 2970 (m, C–H), 1681 (s, C=O), 1451 (m), 1419 (m), 1368 (s), 1039 (s), 993 (s). |
| GC-LRMS: | calcd for C$_6$H$_{10}$OS [M]$^+$: 130, found: 130 (7.3 min) |
| GC, $t_R$: | 1.494 min |
| TLC (20% EtOAc in hexanes) R$f$: | 0.55 (UV) |

**(cyclopropylidene(ethylthio)methoxy)trimethylsilane (61b; containing ≤10% 83b):**

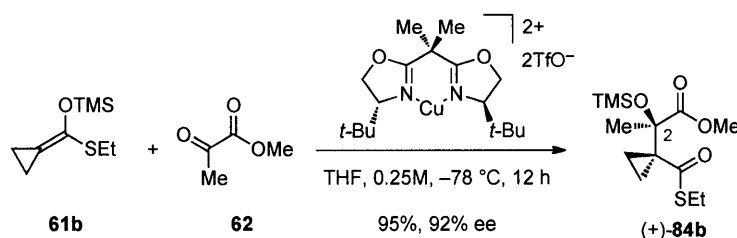| | |
|---|---|
| $^1$H NMR (500 MHz, CDCl$_3$) δ: | 2.78 (q, $J$ = 7.3 Hz, 2H, SCH$_2$), 1.33-1.24 (m, 4H, CH$_2$CH$_2$), 1.27 (t, $J$ = 7.3 Hz, 3H, CH$_3$), 0.24 (s, 9H, Si(CH$_3$)$_3$). |
| $^{13}$C NMR (125.8 MHz, CDCl$_3$) δ: | 135.8, 100.5, 25.5, 15.4, 7.2, 5.1, 0.7. |
| FTIR (neat) cm$^{-1}$: | 2965 (s), 1751 (s), 1449 (w), 1252 (s), 1189 (s), 1071 (m). |
| HRMS (ESI): | calcd for C$_9$H$_{19}$OSSi [M+H]$^+$: 203.0920, found: 203.0926. |
| GC, $t_R$: | 2.499 min |
| TLC (10% EtOAc in hexanes) R$f$: | 0.5 (UV) |

Me  Me ⌉ 2+
O       O     2TfO⁻
N·Cu·N
t-Bu        t-Bu

OTMS
$\diagdown$=SEt   +   O=$\diagdown$O–OMe   $\xrightarrow{\text{THF, 0.25M, –78 °C, 12 h}}$   TMSO Me···$_2$—OMe, SEt

Me

**61b**       **62**       95%, 92% ee       **(+)-84b**

## (+)-(R)-methyl-2-(1-((ethylthio)carbonyl)cyclopropyl)-2-((trimethylsilyl)oxy)propanoate (84b):

A flame-dried flask was charged with (R,R)-2,2'-isopropylidene-bis(4-*tert*-butyl-2-oxazoline) (2.03 g, 6.90 mmol, 0.10 equiv)[4] and copper (II) trifluoromethanesulfonate (2.50 g, 6.90 mmol, 0.10 equiv) in a glove-box under a dinitrogen atmosphere. The flask was sealed with a rubber septum and removed from the glove-box. The flask containing the solids was charged with THF (304 mL) at 23 °C and was flushed with argon. After 1h, the resulting bright green solution was cooled to –78 °C, and methyl pyruvate (**62**, 7.80 g, 76.0 mmol, 1.10 equiv) was added via syringe followed by (cyclopropylidene(ethylthio)methoxy)trimethylsilane (**61b** [mixture of **61b**:**83b** = 9:1], 15.5 g, 69.0 mmol, 1 equiv **61b**) via syringe. After 19 h, the reaction mixture was diluted with diethyl ether (300 mL), and filtered through a plug of silica gel (6 × 6 cm, eluent: 1% triethyamine in diethyl ether). The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatrography (silica gel: diam. 9 cm, ht. 15 cm; eluent: 1% triethylamine in [2% ethyl acetate in hexanes] to 1% triethylamine in [20% ethyl acetate in hexanes]) to afford the desired (+)-(R)-methyl-2-(1-((ethylthio)carbonyl)cyclopropyl)-2-((trimethylsilyl)oxy)propanoate ((+)-**84b**, 19.8 g, 95%, $[\alpha]^{20}_D$ = +30.2 (c 2.22, CHCl₃)) as a colorless liquid. Protodesilylation of the C2-trimethylsilyloxy group of (+)-**84b** afforded samples of the corresponding C2-alcohol (**S1**) that were found to be of 92% ee by chiral HPLC analysis [Chirapak AD-H; 1.5 mL/min; 10% $^i$PrOH in hexanes; $t_R$(minor) = 4.65 min, $t_R$(major) = 5.17 min]. The (R,R)-2,2'-isopropylidene-bis(4-*tert*-butyl-2-oxazoline) ligand was recovered from the reaction mixture (~85%) and purified by flash column chromatography (silica gel: diam. 2.5 cm, ht. 10 cm; eluent: 20% ethyl acetate in dichloromethane).

| ¹H NMR (500 MHz, CDCl₃) δ: | 3.72 (s, 3H, OCH₃), 2.79 (q, J = 7.3 Hz, 2H, SCH₂), 1.58-1.54 (m, 1H, CH₂), 1.53 (s, 3H, CH₃), 1.27-1.19 (m, 2H, CH₂), 1.19 (t, J = 7.3 Hz, 3H, CH₂CH₃), 1.12-1.08 (m, 1H, CH₂), 0.07 (s, 9H, Si(CH₃)₃). |
|---|---|
| ¹³C NMR (125.8 MHz, CDCl₃) δ: | 200.9, 173.4, 75.4, 52.1, 41.8, 24.2, 23.0, 15.3, 14.8, 11.6, 1.5. |
| FTIR (neat) cm⁻¹: | 2954 (m, C–H), 1747 (s, CO₂Me), 1666 (s, COSEt) 1456 (m), 1413 (m), 1372 (m), 1289 (m), 1263 (s). |

[4] For the preparation of (R,R)-2,2'-isopropylidene-bis(4-$^t$butyl-2-oxazoline) see: Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541-4544.

| | |
|---|---|
| HRMS (ESI): | calcd for $C_{13}H_{24}NaO_4SSi$ [M+Na]$^+$: 327.1057, found: 327.1066. |
| GC, $t_R$: | 4.450 min |
| TLC (10% EtOAc in hexanes) R$f$: | 0.4 (UV, CAM) |

The reaction scheme shows compound (+)-84b (TMSO, Me, OMe, SEt, cyclopropyl ketone) reacting with MeZnI, Pd₂dba₃, SPhos in NMP, THF at 65 °C, 2 h (83%) to give (+)-86 (TMSO, Me, OMe, Me).
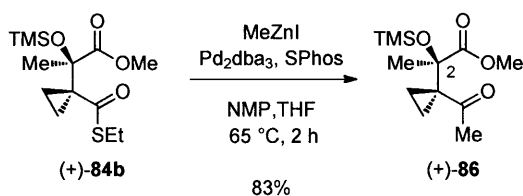
## (+)-(2R)-2-(1-Acetyl-cyclopropyl)-2-(trimethyl-silanyloxy)-propionic acid methyl ester (86):

A Schlenk flask was charged with activated Zn dust (981 mg, 15.0 mmol, 1.50 equiv)[5], placed under reduced pressure (1 Torr), and heated to 65 °C. After 30 min, the flask was backfilled with argon and cooled to 23 °C. Anhydrous $N$-methyl pyrrolidin-2-one (NMP, 10 ml) and iodine (127 mg, 0.500 mmol, 0.050 equiv) were added and the reaction mixture was stirred vigorously for 25 min at which time the red color disappeared. Methyliodide (619 µL, 10.0 mmol, 1 equiv) was added and the reaction mixture was stirred at 23 °C for 14 h to provide a solution of iodomethylzinc in NMP (~1 M).

A solution of iodomethylzinc (~1 M, 8.22 mL, 8.22 mmol, 5.00 equiv), prepared as described above, was added via syringe to a solution of thioester (+)-84b (500 mg, 1.64 mmol, 1 equiv), tris(di-benzylideneacetone)dipalladium (75.3 mg, 0.08 mmol, 0.05 equiv), and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos, 135 mg, 0.33 mmol, 0.20 equiv) in THF (5.5 mL) at 23 °C. The reaction mixture was heated to 65 °C and stirred under an argon atmosphere. After 2 h, the reaction mixture was cooled to 23 °C, diluted with diethyl ether (200 mL), and filtered through a plug of silica gel (diam. 5 cm, ht. 10 cm) to remove most of the NMP. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (silica gel: diam. 5 cm, ht. 12 cm; hexane-EtOAc [95:5]) to afford the desired ketoester (+)-86 as a light yellow oil (353 mg, 83%, $[\alpha]^{20}_D$ = +41.8 ($c$ 2.14, CHCl₃)).

| | |
|---|---|
| $^1$H NMR (500 MHz, CDCl₃) δ: | 3.69 (s, 3H, OCH₃), 1.84 (s, 3H, COCH₃), 1.60-1.54 (m, 1H, CH₂), 1.49 (s, 3H, CH₃), 1.19-1.09 (m, 2H, CH₂), 1.08-1.03 (m, 1H, CH₂), 0.06 (s, 9H, Si(CH₃)₃). |
| $^{13}$C NMR (125.8 MHz, CDCl₃) δ: | 207.7, 173.4, 75.1, 52.1, 41.1, 24.4, 24.2, 13.3, 10.7, 1.6. |
| FTIR (neat) cm$^{-1}$: | 2953 (m, C–H), 1745 (s, CO₂Me), 1685 (s, C=O), 1458 (m), 1434 (m), 1369 (s), 1327 (m), 1253 (s). |
| HRMS (ESI): | calcd for C₁₂H₂₂NaO₄Si [M+Na]$^+$: 281.1180, found: 281.1181. |
| GC, $t_R$: | 3.425 min |
| TLC (20% EtOAc in hexanes) R$f$: | 0.33 (Anis) |

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[5] Activated zinc dust was prepared by sequential washing of Zn dust with 1.2 N HCl in H₂O, H₂O, methanol, and diethyl ether, and drying under vacuum. Also, see: Fieser, L.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967, Vol. 1, p. 1267.

TMSO, O
Me''''̣⟩⟨̣OMe
     ▷⟨
        ⟩=O
        Me
      (+)-86

CH₂I₂, Zn,
TiCl₄, PbCl₂
$\longrightarrow$
CH₂Cl₂, THF
23 °C, 1 h

89%

TMSO, O
Me''''̣⟩⟨̣OMe
     ▷⟨
        ⟩
        Me
      (+)-87
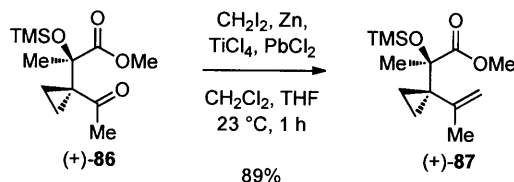
## (+)-(2R)-2-(1-Isopropenyl-cyclopropyl)-2-(trimethyl-silanyloxy)-propionic acid methyl ester (87):

Diiodomethane (3.93 mL, 48.8 mmol, 6.00 equiv) was added to a vigorously stirred suspension of activated zinc dust (5.3 g, 81.0 mmol, 10.8 equiv)[6] and lead (II) chloride (114.0 mg, 0.410 mmol, 0.05 equiv) in THF (60.0 mL) at 23 °C under an argon atmosphere. After 30 min, the reaction mixture was cooled to 0 °C, and titanium tetrachloride (1M in dichloromethane, 9.72 mL, 9.72 mmol, 1.20 equiv) was added dropwise via syringe. The resulting brown reaction mixture was warmed to 23 °C with continued stirring. After 30 min, the reaction mixture was cooled to 0 °C and a solution of ketoester (+)-86 (2.10 mg, 8.10 mmol, 1 equiv) in THF (20.0 mL) was added via cannula. After 1 h, the excess reagent was quenched by the addition of saturated aqueous sodium bicarbonate solution (200 mL). The mixture was extracted with diethyl ether (3 × 200 mL), and the combined organic layers were dried over sodium sulfate, and were concentrated under reduced pressure. Purification by flash column chromatography (silica gel: diam. 4 cm, ht. 8 cm; pentane-diethyl ether [9:1]) afforded the desired (+)-(2R)-2-(1-isopropenyl-cyclopropyl)-2-(trimethyl-silanyloxy)-propionic acid methyl ester (87, 1.86 g, 89%, $[\alpha]^{20}_D$ = +25.4 (c 0.763, CHCl₃)) as a clear colorless liquid.

| | |
|---|---|
| $^1$H NMR (500 MHz, CDCl₃) δ: | 4.92 (s, 1H, C=CH₂), 4.87 (s, 1H, C=CH₂), 3.68 (s, 3H, OCH₃), 1.71 (s, 3H, C=CCH₃), 1.42 (s, 3H, CH₃), 1.05 (ddd, J = 3.9, 5.9, 9.7 Hz, 1H, CH₂), 0.83 (ddd, J = 3.9, 5.9, 9.7 Hz, 1H, CH₂), 0.47 (ddd, J = 3.9, 5.9, 9.7 Hz, 1H, CH₂), 0.38 (ddd, J = 3.9, 5.9, 9.7 Hz, 1H, CH₂), 0.06 (s, 9H, Si(CH₃)₃). |
| $^{13}$C NMR (125.8 MHz, CDCl₃) δ: | 175.6, 146.5, 117.3, 78.0, 51.7, 35.0, 24.6, 22.5, 9.7, 9.5, 1.7. |
| FTIR (neat) cm⁻¹: | 2954 (m, C–H), 1743 (s, CO₂Me), 1639 (w), 1450 (m), 1373 (m), 1252 (s), 1154 (s), 1126 (s), 1019 (m). |
| HRMS (ESI): | calcd for C₁₃H₂₄NaO₃Si [M+Na]⁺: 279.1387, found: 279.1384. |
| GC, $t_R$: | 2.933 min |
| TLC (20% EtOAc in hexanes) R$f$: | 0.60 (Anis) |

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[6] Activated zinc dust was prepared by sequential washing of Zn dust with 1.2 N HCl in H₂O, H₂O, methanol, and diethyl ether, and drying under vacuum. Also, see: Fieser, L.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967, Vol. 1, p. 1267.

TMSO Me••• O OMe (+)-**87**  →  DIBAl-H Et₂O, –78 °C; / Dess-Martin periodinane CH₂Cl₂, 23 °C / 91%  →  TMSO Me••• O H (+)-**60**
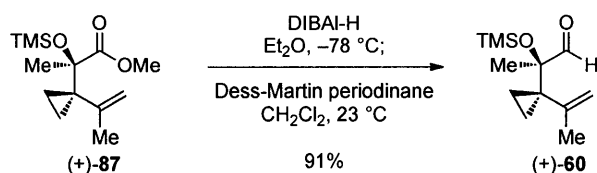
## (+)-(2*R*)-2-(1-Isopropenyl-cyclopropyl)-2-(trimethyl-silanyloxy)-propionaldehyde (60):

Diisobutylaluminum hydride (DIBAl-H, 1.5M in Toluene, 11.7 mL, 17.6 mmol, 3.00 equiv) was added dropwise down the side of the flask into a solution of (+)-(2*R*)-2-(1-isopropenyl-cyclopropyl)-2-(trimethyl-silanyloxy)-propionic acid methyl ester (**87**, 1.5 g, 5.80 mmol, 1 equiv) in diethyl ether (29 mL) at –78 °C under argon. The reaction mixture was stirred and maintained at –78 °C. After 1 h, excess hydride was quenched by the slow addition of methanol (17.6 mmol, 713 µL, 3.00 equiv). The mixture was diluted first with diethyl ether (300 mL), and then with a saturated aqueous solution of Rochelle's salt (200 mL). The mixture was allowed to warm to 23 °C, and the layers were separated. The organic layer was washed with brine (200 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford a mixture of (2*R*)-2-(1-isopropenyl-cyclopropyl)-2-(trimethyl-silanyloxy)-propan-1-ol (**S2**) and (2*R*)-2-(1-isopropenyl-cyclopropyl)-2-(trimethyl-silanyloxy)-propionaldehyde (**60**) as a colorless oil (**S2:60**, 2.5:1). Dess-Martin periodinane (2.71 g, 6.38 mmol, 1.10 equiv) was added to the mixture of (2*R*)-2-(1-isopropenyl-cyclopropyl)-2-(trimethyl-silanyloxy)-propan-1-ol (**S2**) and (2*R*)-2-(1-isopropenyl-cyclopropyl)-2-(trimethyl-silanyloxy)-propionaldehyde (**6 0**) in dichloromethane (29 mL) at 23 °C under argon. After 1 h, the reaction mixture was filtered through a plug of silica gel (diam. 3 cm, ht. 3 cm; eluent: pentane), and was concentrated to afford (2*R*)-2-(1-isopropenyl-cyclopropyl)-2-(trimethyl-silanyloxy)-propionaldehyde (**60**, 1.22 g, 91%, [α]²⁰_D = +63.0 (*c* 0.564, CHCl₃)) as a colorless oil.

## (2*R*)-2-(1-isopropenyl-cyclopropyl)-2-(trimethyl-silanyloxy)-propan-1-ol (S2):

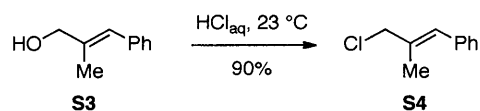| | |
|---|---|
| ¹H NMR (500 MHz, CDCl₃) δ: | 4.99 (m, 2H, C=CH₂), 3.57 (dd, *J* = 7.5, 11.0 Hz, 1H, CH₂OH), 3.46 (dd, *J* = 5.3, 11.0 Hz, 1H, CH₂OH), 1.83 (t, *J* = 1.0 Hz, 3H, CH₃C=CH₂), 1.81 (dd, *J* = 5.3, 7.5 Hz, 1H, OH), 1.27 (s, 3H, CH₃), 0.91-0.88 (m, 1H, CH₂CH₂), 0.65-0.60 (m, 1H, CH₂CH₂), 0.43-0.35 (m, 2H, CH₂), 0.14 (s, 9H, Si(CH₃)₃). |
| ¹³C NMR (125.8 MHz, CDCl₃) δ: | 147.7, 117.6, 69.9, 46.4, 33.2, 23.5, 23.2, 9.2, 8.4, 2.6. |
| FTIR (neat) cm⁻¹: | 3465 (br, O–H), 3078 (w, C–H), 2956 (s, C–H), 1637 (w), 1450 (m), 1413 (m), 1374 (m), 1252 (s). |
| HRMS (ESI): | calcd for C₁₂H₂₄NaO₂Si [M+Na]⁺: 251.1438, found: 251.1442. |
| GC, *t*_R: | 3.013 min. |
| TLC (5% EtOAc in hexanes) R*f*: | 0.19 (Anis). |

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## (+)-(2R)-2-(1-isopropenyl-cyclopropyl)-2-(trimethyl-silanyloxy)-propionaldehyde (60):

| | |
|---|---|
| $^1$H NMR (500 MHz, CDCl$_3$) δ: | 9.50 (s, 1H, CHO), 4.95 (br-s, 1H, C=CH$_2$), 4.87 (br-s, 1H, C=CH$_2$), 1.71 (br-s, 3H, CH$_3$C=CH$_2$), 1.29 (s, 3H, CH$_3$COTMS), 0.97 (ddd, $J$ = 3.8, 5.8, 9.6 Hz, 1H, CH$_2$CH$_2$), 0.78 (ddd, $J$ = 3.9, 5.8, 9.6 Hz, 1H, CH$_2$CH$_2$), 0.48 (ddd, $J$ = 4.0, 5.8, 9.6 Hz, 1H, CH$_2$CH$_2$), 0.41 (ddd, $J$ = 3.8, 5.8, 9.6 Hz, 1H, CH$_2$CH$_2$), 0.09 (s, 9H, Si(CH$_3$)$_3$). |
| $^{13}$C NMR (125.8 MHz, CDCl$_3$) δ: | 203.0, 145.6, 118.0, 79.7, 32.6, 23.2, 20.8, 8.5, 7.5, 2.2. |
| FTIR (neat) cm$^{-1}$: | 2958 (m, C–H), 1735 (s, C=O), 1639 (w), 1448 (w), 1377 (w), 1252 (s). |
| HRMS (ESI): | calcd for C$_{12}$H$_{22}$NaO$_2$Si [M+Na]$^+$: 249.1281, found: 249.1293. |
| TLC (100% hexanes) R$f$: | 0.17 (Anis). |

48

HO⟍⟋Ph  →(HCl_aq, 23 °C, 90%)→  Cl⟍⟋Ph

Me (S3)     Me (S4)

## E-(3-Chloro-2-methyl-prop-1-enyl)-benzene (S4):

Aqueous hydrochloric acid solution (12 N, 51.7 mL, 620 mmol, 3.00 equiv) was slowly added to 2-methyl-3-phenyl-prop-2-en-1-ol (30.6 g, 207 mmol, 1 equiv), and the reaction mixture was stirred and maintained at 23 °C. After 12 h, the reaction mixture was diluted with diethyl ether (50 mL), the layers were separated, and the aqueous layer was further extracted with additional diethyl ether (2 × 50 mL). The combined organic layers were washed with brine (100 mL), were dried over anhydrous sodium sulfate, and were concentrated under reduced pressure (30 °C, 100 mmHg). The residue was purified by vacuum distillation (120 °C, 12 mmHg) to afford 5-chloro-4-methyl-pent-3-enyl)-benzene (S4, 31.0 g, 90%) as a clear colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ:  8.05-8.0 (m, 2H, Ar**H**), 7.98-7.90 (m, 3H, Ar**H**), 7.27 (br-s, 1H, C=C**H**), 4.87 (s, 2H, C**H$_2$**Cl), 2.67 (d, $J$ = 1.5 Hz, 3H, C**H$_3$**).

$^{13}$C NMR (125.8 MHz, CDCl$_3$) δ:  136.9, 134.3, 130.0, 129.1, 128.4, 127.2, 53.1, 16.1.

FTIR (neat) cm$^{-1}$:  2985 (m, C–H), 1950 (w), 1885 (w), 1808 (w), 1599 (m), 1492 (s), 1442 (s), 1261 (s).

HRMS (ESI):  calcd for C$_{10}$H$_{11}$Cl [M]$^+$: 166.0544, found: 166.0538.

TLC (20% EtOAc in hexane) R$f$:  0.70 (KMnO$_4$).

$$\underset{\substack{\text{Cl}\diagdown\diagup\diagdown\text{Ph}\\ \text{Me}\\ \textbf{S4}}}{}\xrightarrow[\substack{\text{THF, 55 °C}\\81\%}]{\substack{\text{HCCMgBr}\\ \text{Li}_2\text{CuCl}_4}}\underset{\substack{\diagdown\diagup\diagdown\text{Ph}\\ \text{Me}\\ \textbf{95b}}}{}$$
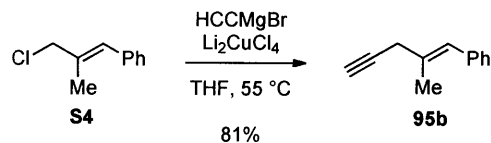
### *E*-(2-Methyl-pent-1-en-4-ynyl)-benzene (95b):

A flame-dried 200-mL round-bottom flask was sequentially charged with a solution of ethynyl magnesium bromide (0.5M in THF, 448 mL, 224 mmol, 2.60 equiv) and a solution of dilithium tetrachlorocuprate (0.1 M in THF, 86.2 mL, 8.62 mmol, 0.10 equiv), and the resulting mixture was stirred at 23 °C. After 15 min, a solution of the allylic chloride **S4** (14.4 g, 86.2 mmol, 1 equiv) in THF (20 mL) was added via cannula and the resulting brown solution was heated to 55 °C. After 50 h, the reaction mixture was cooled to 23 °C and partitioned between diethyl ether (300 mL) and saturated aqueous ammonium chloride solution (150 mL). The aqueous layer was extracted with diethyl ether (2 × 300 mL) and the combined organic layers were washed with brine (150 mL), were dried over anhydrous magnesium sulfate, and were filtered. The dark solution of the crude alkyne **95b** was concentrated (to approximately 300 mL) under reduced pressure (~350 Torr, 28 °C) and was passed through silica gel (diam. 7.5 cm, ht. 30.0 cm; eluent: $^n$pentane) to give the crude alkyne **95b** as a dark yellow oil after removal of volatiles under reduced pressure. Purification of the residue by flash column chromatography (silica gel: diam. 7.5 cm, ht. 32 cm; $^n$pentane:$CH_2Cl_2$, [20:1]) afforded the alkyne **95b** (10.9 g, 81%) as a pale yellow oil.
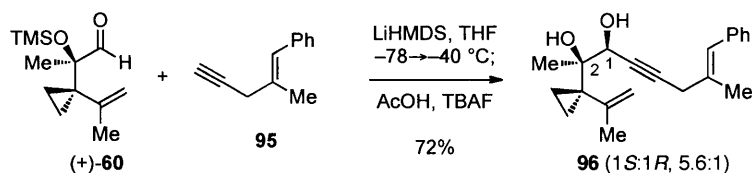
| | |
|---|---|
| $^1$H NMR (500 MHz, CDCl$_3$) δ: | 7.38-7.33 (m, 2H, Ar**H**), 7.30-7.21 (m, 3H, Ar**H**), 6.61 (br-s, 1H, C=C**H**Ph), 3.10 (br-s, 2H, C**H**$_2$), 2.21 (t, $J$ = 2.4 Hz, 1H, C≡C–**H**), 1.94 (br-s, 3H, C**H**$_3$). |
| $^{13}$C NMR (125.8 MHz, CDCl$_3$) δ: | 138.0, 133.1, 129.0, 128.3, 126.5, 81.6, 71.2, 65.7, 29.5, 17.4. |
| FTIR (neat) cm$^{-1}$: | 3298 (s, C≡C–H), 2984 (m, C–H), 2117 (w, C≡C), 1658 (w), 1599 (w), 1490 (m), 1442 (m), 1294 (w), 1155 (w). |
| HRMS (ESI): | calcd for C$_{12}$H$_{12}$Na [M+Na]$^+$: 156.0939, found: 156.0937. |
| TLC (5% CH$_2$Cl$_2$ in hexane) R$f$: | 0.22 (KMnO$_4$). |

TMSO / O / Me / H (+)-60 + Ph / Me 95 → LiHMDS, THF −78→−40 °C; AcOH, TBAF 72% → HO / OH / Me / 2 1 / Me / Ph / Me 96 (1S:1R, 5.6:1)

## E-(2R,3S)-2-(1-Isopropenyl-cyclopropyl)-7-methyl-8-phenyl-oct-7-en-4-yne-2,3-diol (96):

A solution of the alkyne **95** (1.47 g, 9.40 mmol, 1.25 equiv) in THF (50 mL) was added dropwise to a solution of lithium bis(trimethylsilyl)amide (LiHMDS, 1.68 g, 9.77 mmol, 1.30 equiv) in THF (50 mL) at −78 °C. After 5 min, a solution of the aldehyde (+)-**60** (1.70 g, 7.52 mmol, 1 equiv) in THF (12 mL) was added slowly via cannula, and the mixture was warmed to −40 °C. After 40 min, the excess base was quenched by the addition of a saturated aqueous ammonium chloride solution (5 mL) and the resulting mixture was warmed to 23 °C. The reaction mixture was diluted with $H_2O$ (150 mL) and was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried over anhydrous sodium sulfate and were partially concentrated under reduced pressure (to ~10 mL). The flask was charged with additional THF (40 mL) and a mixture of tetrabutylammonium fluoride (TBAF, 1.0 M in THF, 15.0 mL, 15.0 mmol, 2.00 equiv) and acetic acid (0.430 mL, 7.52 mmol, 1.00 equiv) was added to this crude mixture. After 40 min, a saturated aqueous ammonium chloride solution (150 mL) was added, and the mixture was extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were dried over anhydrous sodium sulfate, were filtered, and the volatiles were removed under reduced pressure. The resulting yellow oil was purified by flash column chromatography (silica gel: diam. 5 cm, ht. 30 cm; eluent: hexanes:EtOAc, [4:1]) to give the propargylic alcohol **96** (1.80 g, 72%) as a mixture of C1-diastereomers favoring the anti-isomer (1S:1R, 5.6:1). The C1-stereochemistry of the major diastereomer of **96b** was secured using nOe data for a more advanced intermediate (vide infra, alcohol **109**).

$^1$H NMR (500 MHz, $C_6D_6$, 5.6:1 mixture of (1S)- and (1R)-diastereomers; minor (1R)-isomer denoted by *) δ: 7.40-7.00 (m, 5H, ArH*), 7.24-7.14 (m, 4H, ArH), 7.08-7.03 (m, 1H, ArH), 6.65 (br-s, 1H, C=CHPh), 6.65 (br-s, 1H, C=CHPh*), 5.16 (br-s, 1H, C=CH₂), 5.12 (br-s, 1H, C=CH₂*), 4.95 (br-s, 1H, C=CH₂*), 4.91 (br-s, 1H, C=CH₂), 4.54 (br-s, 1H, CHOH*), 4.48 (br-s, 1H, CHOH), 2.97 (s, 2H, CH₂*), 2.82 (s, 2H, CH₂), 1.93 (s, 1H, CHOH), 1.93 (s, 1H, CHOH*), 1.87 (s, 3H, CH₃*), 1.82 (s, 3H, CH₃*), 1.77 (s, 3H, CH₃), 1.71 (s, 3H, CH₃), 1.64 (s, 1H, OH), 1.64 (s, 1H, OH*), 1.30 (s, 3H, CH₃), 1.29 (s, 3H, CH₃*), 1.26 (ddd, $J$ = 4.6, 6.0, 10.0 Hz, 1H, CH₂CH₂), 1.02 (ddd, $J$ = 10.0, 6.0, 4.6 Hz, 1H, CH₂CH₂*), 0.93 (ddd, $J$ = 4.0, 6.1, 9.8 Hz, 1H, CH₂CH₂), 0.89 (ddd, $J$ = 9.8, 6.1, 4.0 Hz, 1H, CH₂CH₂*), 0.56 (ddd, $J$ = 4.6, 6.1, 10.0 Hz, 1H, CH₂CH₂), 0.52-0.45 (m, 2H, CH₂CH₂*), 0.44 (ddd, $J$ = 4.0, 6.0, 9.8 Hz, 1H, CH₂CH₂).

$^{13}$C NMR (125.8 MHz, C$_6$D$_6$, 5.6:1 mixture of (1$S$)- and (1$R$)-diastereomers; minor (1$R$)-isomer denoted by *) δ: 147.9, 147.9*, 138.7, 138.3*, 133.9*, 133.8, 129.5, 129.3*, 128.9*, 128.8, 127.2*, 127.1, 127.0, 127.0*, 118.4, 118.2*, 84.9, 84.1*, 83.1, 83.0*, 75.6*, 75.1, 69.9, 69.9*, 33.5, 32.6*, 30.2, 30.1*, 23.6*, 23.5, 23.4, 22.4*, 18.1, 18.1*, 11.2, 10.2*, 10.1*, 9.6.

FTIR (neat) cm$^{-1}$:

3440 (br-s, O–H), 2923 (m, C–H), 2227 (w, C≡C), 1635 (w), 1491 (w), 1447 (m), 1375 (m), 1105 (m), 1024 (s).

HRMS (ESI):

calcd for C$_{21}$H$_{26}$NaO$_2$ [M+Na]$^+$: 333.1825, found: 333.1829.

TLC (20% EtOAc in hexanes), R$f$:

0.20 (CAM)
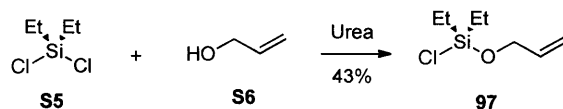
## Allyloxychlorodiethylsilane (97):[7]

Allylalcohol (**S6**, 5.8 g, 100 mmol, 1.00 equiv) was added slowly via syringe over a 6 h period to a stirring mixture of dichlorodiethylsilane (**S5**, 15.8 g, 100 mmol, 1 equiv), and urea (7.2 g, 120 mmol, 1.20 equiv) at 23 °C under argon. The reaction mixture was transferred via cannula to a distillation apparatus, and the residue was purified by vacuum distillation (65 °C, 15 mmHg) to afford allyloxychlorodiethylsilane (**97**, 7.52 g, 43%) as a clear colorless oil.

| | |
|---|---|
| $^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$: | 5.82-5.72 (m, 1H, **CH**), 5.23 (d, $J$ = 17.1 Hz, 1H, **CH**), 4.99 (d, $J$ = 10.4 Hz, 1H, **CH**), 4.12 (br-s, 2H, **CH$_2$**), 0.95 (t, $J$ = 7.6 Hz, 6H, **CH$_3$**), 0.76-0.62 (m, 4H, **CH$_2$**). |
| $^{13}$C NMR (125.8 MHz, C$_6$D$_6$) $\delta$: | 136.7, 115.1, 64.7, 8.9, 6.8. |
| FTIR (neat) cm$^{-1}$: | 3331.2 (br-w), 2959 (s), 1460 (m), 1414 (w), 1243 (m), 1086 (s), 1008 (s). |
| GC-LRMS: | calcd for C$_7$H$_{15}$ClOSi [M]$^+$: 178 found: 178 (6.4 min) |

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[7] Prepared according to the procedure of Krolevets, A. A.; Antipova, V. V.; Popov, A. G.; Adamov, A. V. *Zhurnal Obschchei Khimii*, **1988**, *58*, 2274-2281.
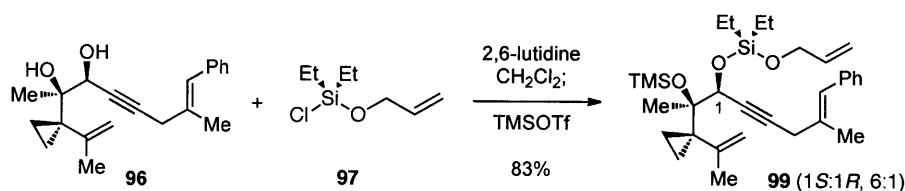
**_E_-(2_R_,3_S_)-2-(1-Isopropenyl-cyclopropyl)-2-(trimethylsilyloxy)-3-(allyloxy-diethyl-silanyloxy)-7-methyl-8-phenyl-oct-7-en-4-yne (99):**

Allyloxychlorodiethylsilane (**97**, 347 mg, 2.00 mmol, 2.00 equiv) was added dropwise to a stirring solution of diol **96** (310 mg, 1.00 mmol, 1 equiv, [1_S_:1_R_, 5.6:1]), and 2,6-lutidine (674 μL, 6.00 mmol, 6.00 equiv) in dichloromethane (5 mL) at 23 °C under argon. After 2 h, the reaction mixture was cooled to –78 °C, and trimethylsilyl trifluoromethanesulfonate (550 μL, 3.00 mmol, 3.00 equiv) was added. After an additional 3 h, excess silylating reagent was quenched by the addition of saturated aqueous sodium bicarbonate solution (5 mL), the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, and were concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel: diam. 2.5 cm, ht. 5 cm; hexanes–EtOAc [98:2]) afforded the sensitive (hydrolysis of alloxydiethylsilyl ether) compound **99** (435 mg, 83%, [1_S_:1_R_, 6:1]) as a light yellow oil containing residual diallyloxydiethylsilane and were used directly in the next step. Samples of metathesis substrate **99** lacking diallyloxydiethylsilane were obtained by further chromatographic purification, at the expense of additional loss of **99**. The presence of residual diallyloxydiethylsilane does not interfere with the following metathesis reaction.

¹H NMR (500 MHz, C₆D₆, 6:1 mixture of (1_S_)- and (1_R_)-diastereomers; minor (1_R_)-isomer denoted by *) δ:7.48-7.1 (m, 5H, ArH*), 7.40-7.36 (m, 2H, ArH), 7.31-7.27 (m, 2H, ArH), 7.18-7.13 (m, 1H, ArH), 6.81 (br-s, 1H, PhCH=CH₂), 6.79 (s, 1H, PhCH=CH₂*), 6.06-5.98 (m, 1H, OCH₂CH=CH₂), 6.06-5.98 (m, 1H, CH₂CH=CH₂*), 5.50 (dq, _J_ = 17.0, 2.0 Hz, 1H, _trans_-OCH₂CH=CH₂), 5.49 (dq, _J_ = 17.0, 2.0 Hz, 1H, _trans_-OCH₂CH=CH₂*), 5.42 (d, _J_ = 2.7 Hz, 1H, C=CH₂), 5.40 (d, _J_ = 2.7 Hz, 1H, C=CH₂*), 5.18-5.13 (m, 2H, _cis_-OCH₂CH=CH₂, C=CH₂), 5.19-5.13 (m, 2H, _cis_-OCH₂CH=CH₂*, C=CH₂*), 4.99 (t, _J_ = 1.8 Hz, 1H, CHOSi), 4.95 (t, _J_ = 1.8 Hz, 1H, CHOSi*), 4.49-3.98 (m, 2H, OCH₂CH=CH₂), 4.49-3.98 (m, 2H, OCH₂CH=CH₂*), 3.10 (s, 2H, CH₂C=C*), 3.02 (s, 2H, CH₂C=C), 2.05 (s, 3H, CH₃*), 2.02 (s, 3H, CH₃), 1.99 (s, 3H, CH₃*), 1.87 (s, 3H, CH₃), 1.53-1.48 (m, 7H, CH₂CH₂, CH₃, CH₃*), 1.30-1.19 (m, 6H, SiCH₂CH₃), 1.05-0.8 (m, 5H, CH₂CH₂, SiCH₂CH₃), 0.76-0.70 (m, 1H,

CH$_2$CH$_2$), 0.66-0.60 (m, 1H, CH$_2$CH$_2$), 0.41 (s, 9H, Si(CH$_3$)$_3$), 0.41 (s, 9H, Si(CH$_3$)$_3$*).

$^{13}$C NMR (125.8 MHz, C$_6$D$_6$, 6:1 mixture of (1$S$)- and (1$R$)-diastereomers) δ:  148.1, 138.9, 137.9, 134.1, 129.5, 128.8, 127.1, 126.9, 118.6, 114.3, 84.0, 83.5, 79.9, 70.1, 64.2, 63.7, 34.2, 30.4, 24.1, 23.1, 18.2, 11.1, 10.3, 7.3, 7.2, 6.5, 5.6, 5.2, 3.4.

FTIR (neat) cm$^{-1}$:    2957 (m, C–H), 2229 (w, C≡C), 1635 (w), 1458 (w), 1415 (w), 1374 (w), 1248 (m), 1133 (m), 1064 (m), 922 (m), 839 (m).

HRMS (ESI):    calcd for C$_{31}$H$_{48}$NaO$_3$Si$_2$ [M+Na]$^+$: 547.3040, found: 547.3028

TLC (5% EtOAc in hexanes) R$f$:    0.62 (UV, CAM, Anis)
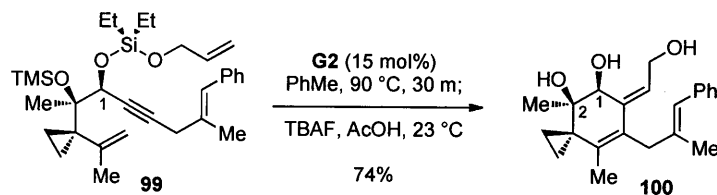
## (6Z)-(4R,5S)-6-(2-Hydroxy-ethylidene)-4,8-dimethyl-7-([2E]-2-methyl-3-phenyl-allyl)-spiro[2.5]oct-7-ene-4,5-diol (100):

Trienyne **99** (435 mg, 0.830 mmol, 1 equiv, [1S:1R, 6:1]) was dried azeotropically by concentration from anhydrous benzene (3 × 1 mL). The residue was dissolved in toluene (83 mL), and the resulting solution deoxygenated by a stream of argon for 5 min. Grubbs' 1,3-dimesityl-4,5-dihydroimidazol-2-ylidenetricyclohexylphosphine benzylidene ruthenium dichloride catalyst (**G2**, 106 mg, 0.124 mmol, 0.15 equiv) was added as a solid at 23 °C, the reaction vessel was purged quickly by a stream of argon, sealed, and the resulting dark-pink solution was stirred until complete dissolution occurred. The reaction mixture was heated to 90 °C by placement in a pre-heated oil bath. After 30 min, the metathesis catalyst was quenched by the addition of ethyl vinyl ether (4 mL). The resulting mixture was cooled to 23 °C, and was filtered through a plug of silica (diam. 4 cm, ht. 1.5 cm; hexanes-EtOAc 95:5). The filtrate was partially concentrated under reduced pressure (to ~5 mL) volume, and a mixture of TBAF (1M in THF, 3.32 mL, 3.32 mmol, 4.00 equiv) and acetic acid (95.0 μL, 1.66 mmol, 2.00 equiv) was slowly added at 23 °C under an argon atmosphere. After 2 h, the reaction mixture was diluted with saturated aqueous sodium bicarbonate solution (10 ml) and extracted with ethyl acetate (4 × 15 ml). The combined organic layers were dried over anhydrous sodium sulfate, and were concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel: diam. 2.5 cm, ht. 2.5 cm; hexanes-EtOAc [1:1] to EtOAc-MeOH [99:1]) afforded the desired triol **100** (209 mg, 74%, [1S:1R, 6:1]) as a light brown oil.

$^1$H NMR (500 MHz, C$_6$D$_6$, 6:1 mixture of (1S)- and (1R)-diastereomers; minor (1R)-isomer denoted by *) δ: 7.27-7.22 (m, 2H, ArH), 7.26-7.00 (m, 5H, ArH*), 7.20-7.15 (m, 2H, ArH), 7.06-7.01 (m, 1H, ArH), 6.39 (s, 1H, PhCH=CH$_2$*), 6.31 (s, 1H, PhCH=CH$_2$), 5.97 (t, J = 7.0 Hz, 1H, C=CH*CH$_2$OH), 5.93 (t, J = 7.0 Hz, 1H, C=CHCH$_2$OH), 4.56 (s, 1H, CHOH*), 4.47 (s, 1H, CHOH), 4.36 (dd, J = 12.5, 7.6 Hz, 1H, CH$_2$OH), 4.22 (dd, J = 12.5, 7.6 Hz, 1H, CH$_2$OH*), 4.06 (dd, J = 12.8, 6.4 Hz, 1H, CH$_2$OH), 3.93 (dd, J = 12.8, 6.4 Hz, 1H, CH$_2$OH*), 3.40-3.28 (m, 3H, CH$_2$*, OH), 3.12 (d, J = 17.7 Hz, 1H, CH$_2$), 3.03 (d, J = 17.7 Hz, 1H, CH$_2$), 2.96 (br-s, 1H, OH), 2.73 (br-s, 1H, OH), 1.72 (s, 3H, CH$_3$*), 1.79 (s, 3H, CH$_3$), 1.35-1.30 (m, 1H, CH$_2$CH$_2$), 1.28 (s, 3H, CH$_3$), 1.25 (s, 3H, CH$_3$), 1.16 (s, 3H, CH$_3$*), 1.13 (s, 3H, CH$_3$*), 0.96-0.90 (m, 1H, CH$_2$CH$_2$*), 0.88-0.83 (m, 1H, CH$_2$CH$_2$), 0.82-0.78 (m, 1H, CH$_2$CH$_2$*), 0.78-

0.73 (m, 1H, CH$_2$CH$_2$), 0.72-0.65 (m, 1H, CH$_2$CH$_2$*), 0.61-0.56 (m, 1H, CH$_2$CH$_2$), 0.56-0.47 (m, 1H, CH$_2$CH$_2$*).

$^{13}$C NMR (125.8 MHz, C$_6$D$_6$, 6:1 mixture of (1*S*)- and (1*R*)-diastereomers) δ: 141.2, 139.4, 138.8, 136.7, 129.6, 128.7, 126.7, 126.6, 126.6, 125.0, 72.9, 70.9, 58.9, 39.8, 28.4, 24.3, 18.9, 15.0, 10.2, 5.4.

FTIR (neat) cm$^{-1}$: 3385 (br-s, O–H), 2930 (m, C–H), 1724 (w), 1626 (w), 1597 (w), 1443 (m), 1377 (m), 1266 (m), 1173 (m).

HRMS (ESI): calcd for C$_{22}$H$_{28}$NaO$_3$ [M+Na]$^+$: 363.1936, found: 363.1936.

TLC (1% MeOH in EtOAc) R$f$: 0.40 (UV, CAM)
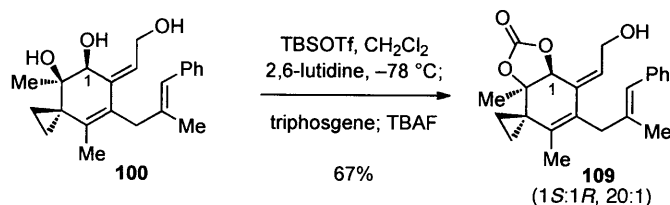
## (6Z)-(4R,5S)-6-(2-Hydroxy-ethylidene)-4,8-dimethyl-7-([2E]-2-methyl-3-phenyl-allyl)-spiro[2.5]oct-7-ene-4,5-diol-carbonate (109):

A solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 91.9 μL, 0.40 mmol, 1.00 equiv) in dichloromethane (1 mL) was added dropwise via cannula transfer (down the side of the flask) to a solution of triol **100** (121 mg, 0.40 mmol, 1 equiv, [1$S$:1$R$, 6:1]), and 2,6-lutidine (269 μL, 2.40 mmol, 6.00 equiv) in dichloromethane (1 mL) at −78 °C under an argon atmosphere. During the addition, the progress of the silylation reaction was monitored by TLC analysis to ensure monosilylation of the starting triol **100**. After completion of the addition of TBSOTf, a solution of triphosgene (178 mg, 0.60 mmol, 1.50 equiv) in dichloromethane (200 μL) was added via cannula and the resulting reaction mixture was allowed to warmed to 23 °C. After 3 h, the resulting dark-red mixture was cooled to 0 °C, treated with TBAF (1M in THF, 4.00 mL, 4.00 mmol, 10.0 equiv), and the resulting mixture was allowed to warm to 23 °C. After 12 h, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (10 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, and were concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel: diam. 3 cm, ht. 15 cm; hexanes-EtOAc [1:1]) afforded the desired carbonate **109** (98.6 mg, 67%, [1$S$:1$R$, 20:1]) as an oil. This step has not yet been optimized for the minor diastereomer, leading to enrichment of the major diastereomer in the product; this procedure has thus far been more practical rather than chromatographic separation of the diastereomers and their independent conversion to the corresponding carbonate.

$^1$H NMR (500 MHz, C$_6$D$_6$, 20:1 mixture of (1$S$)- and (1$R$)-diastereomers; minor (1$R$)-isomer denoted by *) δ: 7.20-7.10 (m, 4H, ArH), 7.19-7.00 (m, 5H, ArH*), 7.03-6.99 (m, 1H, ArH), 6.30 (s, 1H, PhCH=CH$_2$*), 6.08 (s, 1H, PhCH=CH$_2$), 5.95 (t, $J$ = 6.9 Hz, 1H, C=CHCH$_2$OH), 5.67 (t, $J$ = 6.9 Hz, 1H, C=CHCH$_2$OH*), 4.58 (s, 1H, CHO), 4.49 (s, 1H, CHOH*), 4.13-4.02 (m, 2H, CH$_2$OH), 3.99-3.95 (m, 2H, CH$_2$OH*), 3.19 (d, $J$ = 15.8 Hz, 1H, CH$_2$*), 3.09 (d, $J$ = 15.8 Hz, 1H, CH*$_2$), 2.89 (d, $J$ = 17.1 Hz, 1H, CH$_2$), 2.80 (d, $J$ = 17.1 Hz, 1H, CH$_2$), 1.62 (s, 3H, CH$_3$), 1.50 (s, 3H, CH$_3$*), 1.32 (br-s, 1H, OH), 1.15-1.09 (m, 1H, CH$_2$CH$_2$), 1.09 (s, 3H, CH$_3$), 0.99 (s, 3H, CH$_3$*), 0.92 (s, 3H, CH$_3$), 0.86 (s, 3H, CH$_3$*), 0.57-0.51 (m, 1H, CH$_2$CH$_2$), 0.50-0.44 (m, 1H, CH$_2$CH$_2$*), 0.41-35 (m, 1H, CH$_2$CH$_2$), 0.35-0.30 (m, 1H, CH$_2$CH$_2$*), 0.25-0.19 (m, 1H, CH$_2$CH$_2$), 0.18-0.12 (m, 1H, CH$_2$CH$_2$*).

$^{13}$C NMR (125.8 MHz, C$_6$D$_6$, 20:1 mixture of (1*S*)- and (1*R*)-diastereomers) δ: 154.4, 139.0, 138.8, 136.0, 135.9, 133.9, 133.5, 130.1, 129.7, 129.6, 129.5, 128.9, 128.7, 127.4, 127.1, 126.8, 125.6, 81.7, 80.3, 80.2, 59.9, 40.4, 32.9, 32.7, 30.5, 27.6, 23.5, 23.3, 22.9, 22.3, 22.2, 18.6, 16.0, 15.9, 14.7, 10.1, 9.9, 6.8, 6.7.

FTIR (neat) cm$^{-1}$:          3424 (br-m, O–H), 2923 (m, C–H), 1801 (s, C=O), 1653 (w), 1598 (w), 1444 (m), 1381 (m), 1245 (m), 1149 (m), 1024 (m).

HRMS (ESI):          calcd for C$_{23}$H$_{26}$NaO$_4$ [M+Na]$^+$: 389.1723, found: 389.1732.

TLC (50% EtOAc in hexane) R$f$:          0.30 (UV, Anis)

The C1-stereochemistry of the major diastereomer of **109** was secured by the following nOe data:



59
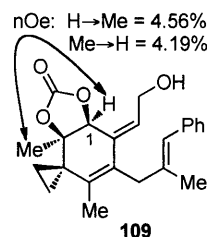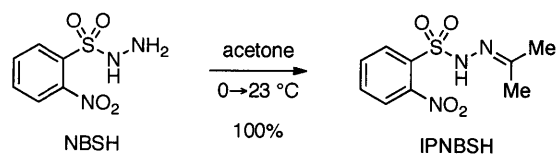
## _N_-Isopropylidene-_N'_-2-nitrobenzenesulfonyl hydrazine (IPNBSH):

NBSH[8] (601 mg, 2.77 mmol, 1 equiv) was dissolved in acetone (3.00 mL, 40.9 mmol, 14.7 equiv) and the mixture was stirred vigorously under argon at 0 °C for 1 h. The mixture was warmed to 23 °C and concentrated under reduced pressure to afford IPNBSH (712 mg, 100%)[9] as a white solid.

| | |
|---|---|
| $^1$H NMR (500 MHz, CD$_3$CN) δ: | 8.25 (br-s, 1H, NH), 8.10-8.06 (m, 1H, ArH), 7.86-7.78 (m, 3H, ArH), 1.87 (s, 3H, CH$_3$), 1.86 (s, 3H, CH$_3$) |
| $^{13}$C NMR (125.8 MHz, CD$_3$CN) δ: | 160.3, 135.7, 133.6, 133.0, 132.1, 125.9, 120.4, 25.2, 17.7. |
| FTIR (neat) cm$^{-1}$: | 3264 (m, N–H), 3093-2916 (w, C–H), 1550 (s, N=C), 1374 (m), 1177 (s). |
| HRMS (ESI): | calcd for C$_9$H$_{12}$N$_3$O$_4$S [M+H]$^+$: 258.0543, found: 258.0546. |
| mp: | 121-123 °C |
| TLC (hexanes:EtOAc 1:1) R$f$: | 0.50 (CAM) |

[8] For synthesis of NBSH see Myers, A. G.; Zheng, B.; Movassaghi, M. _J. Org. Chem._ **1997**, _62_, 7507.
[9] For a prior discussion of IPNBSH, see: (a) Movassaghi, M. Ph.D. Dissertation, Harvard University (2001). For the evaluation of the scope of IPNBSH, and an updated protocol for the synthesis of IPNBSH see: (b) Movassaghi, M.; Ahmad, O. K. _J. Org. Chem._ **2007**, _72_, 1838. For use of IPNBSH in a stereospecific palladium-catalyzed route to monoalkyl diazenes, see: (c) Movassaghi, M.; Ahmad, O. K. _Angew. Chem. Int. Ed._ **2008**, _47_, 8909.
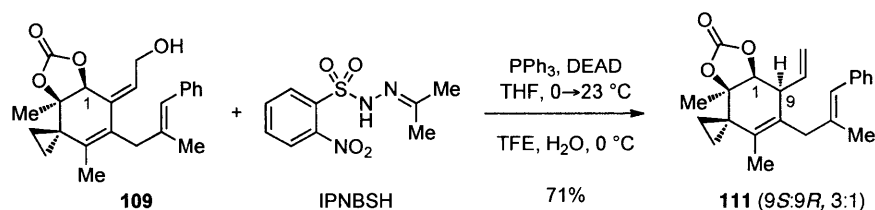
## (4R,5S)-4,8-Dimethyl-7-([2E]-2-methyl-3-phenyl-allyl)-6-vinyl-spiro[2.5]oct-7-ene-4,5-diol-carbonate (111):

The alcohol **109** (20.0 mg, 0.054 mmol, 1 equiv, [1S:1R, 20:1]) was dried azeotropically by concentration from anhydrous benzene (3 × 1 mL). Triphenylphosphine (28.3 mg, 0.108 mmol, 2.00 equiv) and IPNBSH[9] (27.8 mg, 0.108 mmol, 2.00 equiv) were added as solids, and the reaction vessel was sealed under an argon atmosphere. Anhydrous THF (540 μL, purged with a stream of argon for ~5 min) was added and the resulting solution was cooled to 0 °C prior to slow addition of diethyldiazocarboxylate (16.9 μL, 0.108 mmol, 2.00 equiv) via syringe. After 2 h, the reaction mixture was allowed to warm to 23 °C over 15 min. The mixture was then cooled to 0 °C and a mixture of trifluoroethanol and water (1:1, 1.08 mL, purged with a stream of argon for ~5 min) was added. After 14 h at 0 °C, the reaction mixture was warmed to 23 °C, was diluted with brine (10 mL), and the mixture was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel: diam. 1.5 cm, ht 5 cm; eluent: EtOAc:hexane [1:3]) provided triene **111** as a mixture of diastereomers (13.6 mg, 71%; [9S:9R, 3:1]). The C9-stereochemistry of the major diastereomer of **111** was secured using nOe data for a derivative (vide infra, carbonate **S7**).

$^1$H NMR (500 MHz, $C_6D_6$, ~3:1:0.1 mixture of three diastereomers (1S,9S:1S,9R:1R the minor (1S,9R)-diastereomer and the corresponding (1R)-diastereomer are noted as * and **, respectively) δ: 7.40-7.0 (m, 5H, ArH), 6.35 (s, 1H, PhCH**), 6.30 (s, 1H, PhCH*), 6.16 (s, 1H, PhCH), 6.03 (dt, J = 16.9, 9.2 Hz, 1H, CH=CH₂), 5.82 (dt, J = 16.9, 9.2 Hz, 1H, CH**=CH₂), 5.45 (dt, J = 16.9, 9.2 Hz, 1H, CH*=CH₂), 5.07-5.01 (m, 2H, CH=CH₂), 4.93-4.85 (m, 2H, CH=CH*₂), 4.84-4.62 (m, 2H, CH=CH**₂), 3.98 (d, J = 5.3 Hz, 1H, CHO), 3.95 (d, J = 5.3 Hz, 1H, CH*O), 3.86 (d, J = 5.3 Hz, 1H, CH**O), 3.22-3.18 (m, 1H, CH*CH=CH₂), 3.00 (dd, J = 8.7, 6.3 Hz, 1H, CHCH=CH₂), 2.94 (d, J = 15.4 Hz, 1H, CH*₂), 2.82 (d, J = 15.4 Hz, 1H, CH₂), 2.64 (d, J = 15.5 Hz, 1H, CH₂), 2.59 (d, J = 15.5 Hz, 1H, CH*₂), 1.81 (s, 3H, CH*₃), 1.62 (s, 3H, CH₃), 1.56 (s, 3H, CH**₃), 1.21 (s, 3H, CH*₃), 1.20 (s, 3H, CH₃), 1.10 (s, 3H, CH**₃), 0.95-0.90 (m, 1H, CH₂CH₂), 0.77 (s, 3H, CH**₃), 0.75 (s, 3H, CH₃), 0.73-0.66 (m, 2H, CH₂CH*₂), 0.64 (s, 3H,

CH*₃), 0.44-0.38 (m, 2H, CH₂CH₂), 0.35-0.29 (m, 1H, CH₂CH₂), 0.23-0.18 (m, 1H, CH₂CH**₂), 0.10-0.04 (m, 1H, CH₂CH*₂).

$^{13}$C NMR (125.8 MHz, C₆D₆, ~3:1:0.1 mixture of three diastereomers) δ: 154.2, 154.0, 139.0, 136.4, 136.3, 134.5, 134.4, 133.3, 131.4, 130.8, 129.7, 129.6, 128.9, 128.8, 127.8, 126.9, 126.8, 118.9, 118.3, 86.1, 85.0, 83.9, 47.7, 47.5, 43.8, 42.1, 34.5, 28.4, 27.5, 25.3, 24.2, 23.8, 23.3, 18.5, 18.2, 15.7, 15.4, 11.9, 11.8, 10.8, 9.1, 8.8, 8.5.

FTIR (neat) cm$^{-1}$:          3080 (w, C–H), 2934 (w, C–H), 1798 (s, C=O), 1650 (w), 1598 (w), 1444 (w), 1381 (w), 1360 (w), 1238 (m), 1077 (m).

HRMS (ESI):          calcd for C₂₃H₂₆NaO₃ [M+Na]$^{+}$: 373.1780, found: 373.1776.

TLC (hexanes:EtOAc 3:1) R$f$:          0.40 (Anis).
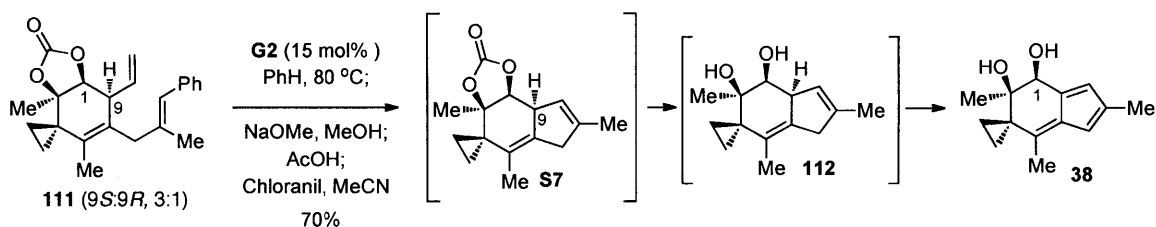
**Fulvenediol 38:**

The triene **111** (5.7 mg, 0.016 mmol, 1 equiv, [(1*S*,9*S*)-**111**:(1*S*,9*R*)-**111**:(1*R*)-**111**, 3:1:0.1]) was dried azeotropically by concentration from anhydrous benzene (3 × 1 mL). Benzene (320 μL) was added followed by **G2** (2.0 mg, 2.4 μmol, 0.15 equiv) at 23 °C, the mixture was sealed under an argon atmosphere, and the resulting dark-pink solution was heated to 80 °C. After 30 min, ethyl vinyl ether (0.1 mL) was introduced via a syringe, and the mixture was cooled to 23 °C. The resulting mixture was charged with a methanolic solution of sodium methoxide (1.0 M in MeOH, 33.0 μL, 0.033 mmol, 2.00 equiv) at 23 °C. After 24 h, conversion to diol **112** was complete by TLC analysis. Acetonitrile (600 μL) was added and the mixture was concentrated under reduced pressure to 30% of the total volume (ca. 300 μL). Acetic acid (1.72 μL, 0.033 mmol, 2.00 equiv) and chloranil (12.5 mg, 0.051 mmol, 3.00 equiv) were added sequentially, and the reaction mixture was stirred at 23 °C. After 13 h, saturated aqueous sodium thiosulfate solution (5 mL) was added and the reaction mixture was extracted with diethyl ether (4 × 5 mL), and the combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (5 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel: diam. 0.5 cm, ht 5 cm; eluent: EtOAc:hexane [1:3]) afforded the fulvenediol **38** (2.4 mg, 70%)[10] as a yellow oil.

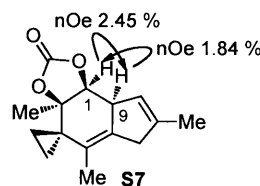| | |
|---|---|
| ¹H NMR (500 MHz, CDCl₃) δ: | 6.34 (br-s, 1H, CH=C), 6.08 (br-s, 1H, CH=C), 4.34 (d, *J* = 6.9 Hz, 1H, CHOH), 2.86 (br-s, 1H, OH), 2.07 (br-s, 3H, CH₃), 1.84 (s, 3H, CH₃), 1.61 (d, *J* = 7.7, 1H, OH), 1.28-1.22 (m, 1H, CH₂CH₂), 1.16 (s, 3H, CH₃), 1.05-1.00 (m, 1H, CH₂CH₂), 0.98-0.92 (m, 1H, CH₂CH₂), 0.87-0.82 (m, 1H, CH₂CH₂). |

The C9-stereochemistry of the major diastereomer of substrates **111** and **112** was secured by the following nOe data with the sensitive intermediate **S7**:[11]



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[10] The C1-diastereomers ((1*R*)-fulvenediol **38**) are chromatographically separable. Crude samples of fulvenediol **38** contain trace amounts of the 1*R*-diastereomer and the oxidation to acylfulvene can be performed on the mixture of these C1-diastereomers.

[11] For full characterization data see: Siegel, D. S.; Piizzi, G.; Piersanti, G.; Movassaghi, M. *J. Org. Chem.* **2009**, *74*, 9292.

| | |
|---|---|
| $^{13}$C NMR (125.8 MHz, CDCl$_3$) δ: | 151.2, 142.1, 138.8, 133.6, 131.4, 114.7, 73.5, 72.8, 30.5, 23.6, 16.6, 16.0, 13.3, 6.8. |
| FTIR (neat) cm$^{-1}$: | 3421 (br-s, O–H), 2916 (s, C–H), 1630 (s), 1443 (m), 1376 (m), 1333 (m), 1114 (m). |
| HRMS (ESI): | calcd for C$_{14}$H$_{18}$NaO$_2$ [M+Na]$^+$: 241.1199, found: 241.1206. |
| TLC (hexanes:EtOAc 1:1) R$f$: | 0.50 (CAM, UV). |
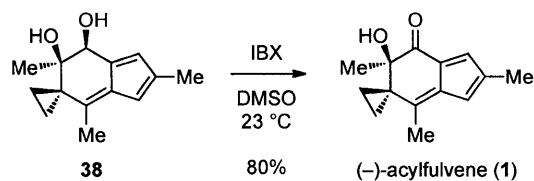
38     80%     (–)-acylfulvene (1)

## (–)-Acylfulvene (1):

The fulvenediol **38** (3.5 mg, 16 μmol, 1 equiv) was dried azeotropically by concentration from anhydrous benzene (3 × 1 mL). Anhydrous DMSO (0.8 mL) was added followed by IBX (9.0 mg, 32 μmol, 2.0 equiv), and the resulting suspension was sealed under an argon atmosphere and stirred at 23 °C. After 4 h, water was added (5 mL) followed by EtOAc (5 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were dried over anhydrous sodium sulfate, and were concentrated under reduced pressure to afford (–)-acylfulvene (**1**, 2.8 mg, 80%, 91% ee, $[\alpha]^{20}_D = -265.5$ ($c$ 0.10, EtOH)) that had spectroscopic data consistent with those reported in the literature.[12] (–)-Acylfulvene (**1**) was determined to be 91% ee by chiral HPLC analysis [Chirapak AD-H; 1.0 mL/min; 10% $^i$PrOH in hexanes; $t_R$(major) = 8.30 min, $t_R$(minor) = 10.21 min].

| | |
|---|---|
| $^1$H NMR (400 MHz, CDCl$_3$) δ: | 7.17 (br-s, 1H, CH=C), 6.43 (br-s, 1H, CH=C), 3.94 (br-s, 1H, OH), 2.16 (s, 3H, CH$_3$), 2.01 (s, 3H, CH$_3$),1.57-1.52 (m, 1H, CH$_2$CH$_2$), 1.39 (s, 3H, CH$_3$), 1.33-1.29 (m, 1H, CH$_2$CH$_2$), 1.10-1.06 (m, 1H, CH$_2$CH$_2$), 0.75-0.71 (m, 1H, CH$_2$CH$_2$). |
| $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ: | 198.3, 159.1, 143.2, 141.2, 136.6, 127.0, 121.2, 77.0, 37.8, 28.3, 17.4, 15.7, 14.8, 10.2. |
| FTIR (neat) cm$^{-1}$: | 3460 (br-m, O–H), 2918 (m, C–H), 1803 (w), 1667 (s, C=O), 1615 (s), 1490 (m), 1445 (m). |
| HRMS (ESI): | calcd for C$_{14}$H$_{16}$NaO$_2$ [M+Na]$^+$: 239.1043, found: 239.1044. |
| TLC (hexanes:EtOAc 1:1) R$f$: | 0.60 (CAM, UV) |

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[12] Our characterization data for acylfulvene was in agreement with those reported in McMorris, T. C.; Staake, M. D.; Kelner, M. J.; *J. Org. Chem.* **2004**, *69*, 619. For optical rotation values reported for (–)-acylfulvene, see: $[\alpha]^{25}_D = -493.4$ ($c$ 2.1 mg/mL, EtOH) in McMorris, T. C.; Staake, M. D.; Kelner, M. J.; *J. Org. Chem.* **2004**, *69*, 619 (please see ref. 12 in this paper) and $[\alpha]^{25}_D$ = –606 ($c$ 0.078, EtOH) in McMorris, T. C.; Kelner, M. J.; Wang, W.; Diaz, M. A.; Estes, L. A.; Taetle, R. *Experientia*, **1996**, *52*, 75. Our measurements were conducted using absolute ethanol (Aldrich, 200 Proof 99.5%) and at 20 °C (pure samples, multiple readings). The enantiomeric excess of our synthetic (–)-acylfulvene was determined by HPLC analysis as described above.

**111** (9*S*:9*R*, 3:1)     G2 (15 mol%)<br>
PhH, 80 °C, 30 min;<br>
NaOMe, MeOH; AcOH;<br>
DDQ, MeCN<br>
30%     (–)-acylfulvene (**1**)
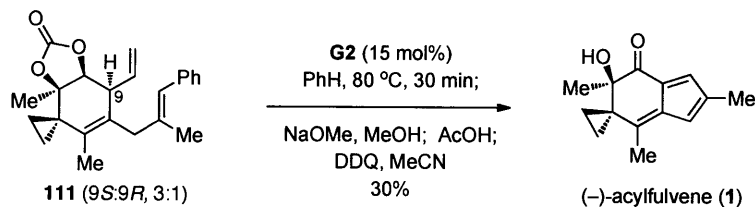
## (–)-Acylfulvene (1):

  The triene **111** ([9*S*:9*R*, 3:1] 6.9 mg, 20 μmol, 1 equiv) was dried azeotropically by concentration from anhydrous benzene (3 × 1 mL). Benzene (400 μL) was added followed by **G2** (2.5 mg, 3.0 μmol, 0.15 equiv) at 23 °C, and the resulting dark-pink solution was sealed under an argon atmosphere and heated to 80 °C. After 30 min, the reaction ethyl vinyl ether (0.1 mL) was added via syringe, and the reaction mixture was cooled to 23 °C. The resulting mixture was charged with a methanolic solution of sodium methoxide (1.0 M in MeOH, 40.0 μL, 0.040 mmol, 2.00 equiv). After 24 h, acetonitrile (800 μL) was added and the mixture was concentrated to 30% of the total volume (ca. 400 μL). Acetic acid (1.72 μL, 0.033 mmol, 2.00 eq) and DDQ (13.6 mg, 0.060 mmol, 3.00 equiv) were added sequentially, and the reaction mixture was sealed under an argon atmosphere. After 13 h, a solution of ascorbic acid (7 mg), citric acid (12.6 mg), and sodium hydroxide (9.4 mg) in $H_2O$ (1 mL) were added to quench the excess oxidant (DDQ). The reaction mixture was diluted with saturated aqueous sodium bicarbonate solution (5 mL), and the resulting mixture was extracted with hexanes (4 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel: diam. 0.5 cm, ht 5 cm; eluent: EtOAc:hexane [1:4]) afforded (–)-acylfulvene (**1**, 1.4 mg, 30%, 91% ee) as a yellow oil. (–)-Acylfulvene (**1**) was determined to be 91% ee by chiral HPLC analysis [Chirapak AD-H; 1.0 mL/min; 10% $^i$PrOH in 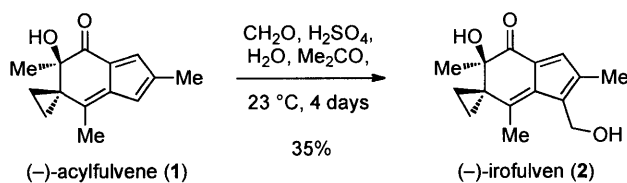hexanes; $t_R$(major) = 8.30 min, $t_R$(minor) = 10.21 min]. For full characterization of (–)-acylfulvene (**1**), see the complete set of data presented above for the two-step procedure.

(−)-acylfulvene (1) → [CH2O, H2SO4, H2O, Me2CO, 23 °C, 4 days, 35%] → (−)-irofulven (2)

## (−)-Irofulven (2):

A solution of (−)-acylfulvene (1, 2.6 mg, 12 μmol, 1 equiv) in acetone (0.5 mL) was added to a solution of formaldehyde (37% wt. in H₂O, 35.0 μL, 0.44 mmol, 67.0 equiv) in a mixture of water (0.5 mL), acetone (1.0 mL), and aqueous hydrosulfuric acid (2.0 N, 0.5 mL) at 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 4 d, the reaction mixture was diluted with dichloromethane (5 mL), and saturated aqueous sodium bicarbonate solution (5 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL), and the combined organic layers were washed sequentially with a saturated aqueous sodium bicarbonate solution (5 mL) and brine (5 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was further diluted by the addition of benzene (5 mL). The volatiles were removed and the total volume reduced (to approximately 1 mL) and the remaining orange solution was immediately[13] purified by flash column chromatography (silica gel: diam. 1 cm, ht 5 cm; EtOAc-hexanes 1:1) to give (−)-irofulven (4, 1.1 mg, 35%, 92% ee, $[\alpha]^{20}_D = -512$ (c 0.03, EtOH)[14]) as an orange oil. Our synthetic (−)-irofulven (4) was determined to be 92% ee by chiral HPLC analysis [Chirapak AD-H; 1.5 mL/min; 20% $^i$PrOH in hexanes; $t_R$(major) = 4.88 min, $t_R$(minor) = 6.51 min].

| | |
|---|---|
| $^1$H NMR (400 MHz, CDCl₃) δ: | 7.11 (br-s, 1H, CH=C), 4.66 (dd, J = 11.6, 8.3 Hz, 2H, CHOH), 3.91 (br-s, 1H, OH), 2.20 (s, 3H, CH₃), 2.16 (s, 3H, CH₃), 1.53-1.49 (m, 1H, CH₂CH₂), 1.39 (s, 3H, CH₃), 1.39-1.33 (m, 1H, CH₂CH₂), 1.11-1.07 (m, 1H, CH₂CH₂), 0.75-0.72 (m, 1H, CH₂CH₂). |
| $^{13}$C NMR (100.6 MHz, CDCl₃) δ: | 198.3, 160.5, 142.4, 138.9, 135.0, 132.5, 127.1, 76.5, 56.6, 38.0, 27.8, 16.5, 14.6, 13.3, 9.8. |
| FTIR (neat) cm$^{-1}$: | 3442 (br-m, O–H), 2920 (m, C–H), 1653 (m, C=O), 1593 (m), 1345 (m), 1280 (m). |
| HRMS (ESI): | calcd for C₁₅H₁₈O₃ [M+]$^+$: 247.1329, found: 247.1331 |
| TLC (hexanes:EtOAc 1:1) Rf: | 0.38 (CAM, UV) |

[13] This is necessary to minimize bisacylfulvene formation; please see: Weinreb, S. M.; McMorris, T. C.; Anchel, M. Tetrahedron Lett. 1971, 38, 3489 and McMorris, T. C.; Kelner, M. J.; Wang W.; Yu, J.; Estes, L. A.; Taetle, R. J. Nat. Prod. 1996, 59, 896.

[14] Our characterization data for irofulven was in agreement with those reported in McMorris, T. C.; Kelner, M. J.; Wang W.; Yu, J.; Estes, L. A.; Taetle, R. J. Nat. Prod. 1996, 59, 896. For an optical rotation value reported for (−)-irofulven, see: $[\alpha]^{25}_D$ = −639 (c 0.096, EtOH) in McMorris, T. C.; Kelner, M. J.; Wang W.; Yu, J.; Estes, L. A.; Taetle, R. J. Nat. Prod. 1996, 59, 896. Our optical rotation measurements were conducted using absolute ethanol (Aldrich, 200 Proof 99.5%) and at 20 °C (pure samples, multiple readings). The enantiomeric excess of our synthetic (−)-irofulven was determined by HPLC analysis as described above.

## Crystal Structure of (2*S*)-2-Hydroxy-2-(1-isopropenyl-cyclopropyl)-propionic acid–(–)-Brucine Complex.[15]
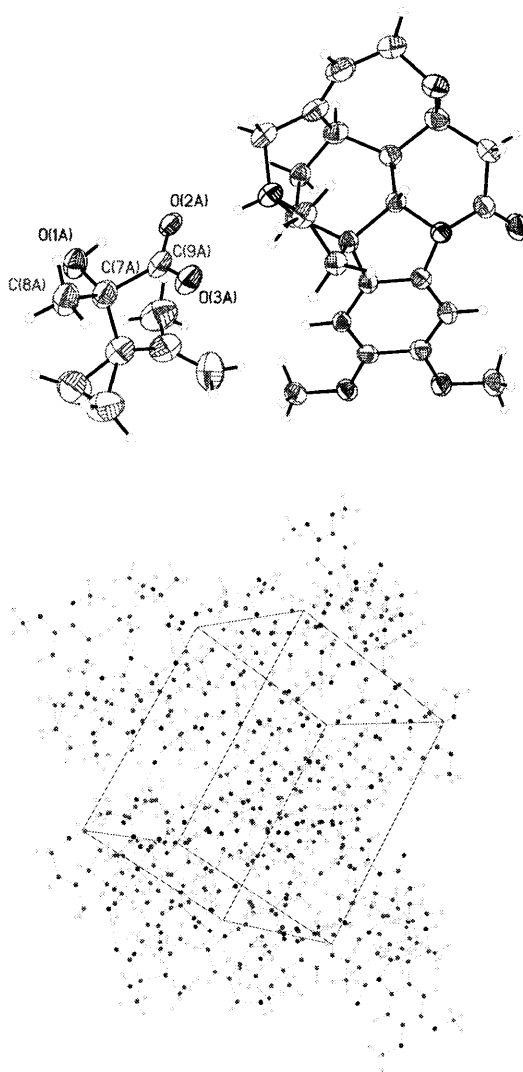




### (2*S*)-2-Hydroxy-2-(1-isopropenyl-cyclopropyl)-propionic acid–(–)-Brucine Complex:

Lithium hydroxide (24 mg, 0.58 mmol, 5.0 equiv) was added to a solution of (–)-**87** (30 mg, 0.12 mmol, 1 equiv) in methanol (0.75 mL) and water (0.25 mL) at 23 °C. After 24 h, the volatiles were removed under reduced pressure and the resulting aqueous solution acidified to pH 3 by addition of aqueous hydrogen chloride solutions (1 N). The mixture was extracted with ethyl acetate (3 × 4 mL), and the combined organic layers were dried over anhydrous sodium sulfate and were concentrated under reduced pressure to afford (2*S*)-2-hydroxy-2-(1-isopropenyl-cyclopropyl)-propionic acid (**88**, 13.0 mg, 66%) as a white solid. (–)-Brucine (30 mg, 0.07 mmol, 1 eq) was added to a solution of (2*S*)-2-hydroxy-2-(1-isopropenyl-cyclopropyl)-propionic acid (**88**, 13.0 mg, 0.07 mmol, 1eq) in ethyl acetate (500 µL). The resulting complex was crystallized by slow diffusion of hexanes into the ethyl acetate solution over 4 days at 23 °C.

[15] Structural parameters for the carboxylic acid, **88**, salt with (–)-brucine are freely available from the Cambridge Crystallographic Data Center under CCDC-622286.

**Table S1. Crystal data and structure refinement.**

| | |
|---|---|
| Identification code | 05204 |
| Empirical formula | C32 H40 N2 O7 |
| Formula weight | 564.66 |
| Temperature | 100(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Orthorhombic |
| Space group | P2(1)2(1)2(1) |
| Unit cell dimensions | a = 12.4406(13) Å     a= 90°. |
| | b = 13.6892(15) Å     b= 90°. |
| | c = 16.1340(17) Å     g = 90°. |
| Volume | 2747.7(5) Å$^3$ |
| Z | 4 |
| Density (calculated) | 1.365 Mg/m$^3$ |
| Absorption coefficient | 0.096 mm$^{-1}$ |
| F(000) | 1208 |
| Crystal size | 0.30 x 0.25 x 0.20 mm$^3$ |
| Theta range for data collection | 1.95 to 25.02°. |
| Index ranges | -14<=h<=14, -16<=k<=16, -19<=l<=19 |
| Reflections collected | 43545 |
| Independent reflections | 2742 [R(int) = 0.0711] |
| Completeness to theta = 25.02° | 100.0 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9810 and 0.9718 |
| Refinement method | Full-matrix least-squares on F$^2$ |
| Data / restraints / parameters | 2742 / 409 / 456 |
| Goodness-of-fit on F$^2$ | 1.085 |
| Final R indices [I>2sigma(I)] | R1 = 0.0580, wR2 = 0.1512 |
| R indices (all data) | R1 = 0.0729, wR2 = 0.1677 |
| Absolute structure parameter | 0(2) |
| Largest diff. peak and hole | 0.315 and -0.305 e.Å$^{-3}$ |

**Table S2. Atomic coordinates (x 10$^4$) and equivalent isotropic displacement parameters (Å$^2$x 10$^3$). U(eq) is defined as one third of the trace of the orthogonalized U$^{ij}$ tensor.**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | 9473(3) | 6082(3) | -2842(2) | 35(1) |
| N(2) | 10377(3) | 6501(3) | -100(2) | 30(1) |
| O(4) | 12864(3) | 5655(3) | -1324(2) | 53(1) |
| O(5) | 11097(3) | 6283(3) | 1188(2) | 52(1) |
| O(6) | 7161(2) | 6624(3) | 1702(2) | 41(1) |
| O(7) | 5981(2) | 6243(2) | 429(2) | 35(1) |
| C(10) | 9832(4) | 7101(3) | -2656(3) | 36(1) |
| C(11) | 9278(4) | 7360(3) | -1851(3) | 31(1) |
| C(12) | 9336(3) | 6396(3) | -1356(2) | 28(1) |
| C(13) | 9040(4) | 5636(3) | -2037(2) | 30(1) |
| C(14) | 9483(4) | 4617(3) | -1903(3) | 37(1) |
| C(15) | 10718(4) | 4687(3) | -1839(3) | 41(1) |
| C(16) | 11164(4) | 5174(4) | -2606(3) | 43(1) |
| C(17) | 10339(4) | 5470(4) | -3243(3) | 41(1) |
| C(18) | 12203(4) | 5326(4) | -2707(4) | 54(1) |

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| | | | | |
|---|---|---|---|---|
| C(19) | 13005(5) | 5051(5) | -2058(4) | 64(2) |
| C(20) | 10961(4) | 5217(3) | -1021(3) | 34(1) |
| C(21) | 12135(4) | 5262(4) | -731(3) | 42(1) |
| C(22) | 12226(3) | 5957(4) | 20(3) | 38(1) |
| C(23) | 11193(3) | 6252(3) | 433(3) | 37(1) |
| C(24) | 10490(3) | 6250(3) | -992(2) | 29(1) |
| C(25) | 9267(3) | 6519(3) | 112(3) | 30(1) |
| C(26) | 8643(3) | 6380(3) | -590(2) | 28(1) |
| C(27) | 7527(3) | 6299(3) | -513(3) | 29(1) |
| C(28) | 7058(3) | 6346(3) | 264(3) | 31(1) |
| C(29) | 7714(4) | 6538(3) | 964(3) | 33(1) |
| C(30) | 8815(4) | 6620(3) | 891(3) | 34(1) |
| C(31) | 5311(3) | 6010(4) | -250(3) | 44(1) |
| C(32) | 7805(4) | 6867(5) | 2409(3) | 55(1) |
| C(1A) | 5708(9) | 5576(7) | -3063(6) | 79(3) |
| C(2A) | 5716(7) | 6631(6) | -3133(5) | 61(2) |
| C(3A) | 5941(11) | 7234(9) | -2519(7) | 72(3) |
| C(5A) | 4474(7) | 7101(8) | -4286(7) | 75(2) |
| C(6A) | 4969(8) | 8037(6) | -4086(6) | 73(2) |
| C(4A) | 5614(7) | 7092(7) | -3969(5) | 57(1) |
| C(7A) | 6528(7) | 6832(6) | -4593(5) | 47(1) |
| O(1A) | 6351(5) | 5865(4) | -4901(3) | 45(1) |
| C(8A) | 6566(7) | 7506(6) | -5339(4) | 52(2) |
| C(9A) | 7602(9) | 6885(6) | -4123(8) | 40(1) |
| O(2A) | 8042(6) | 6065(6) | -3985(4) | 38(1) |
| O(3A) | 7974(11) | 7697(7) | -3939(8) | 46(2) |
| C(1B) | 5740(40) | 6970(20) | -2524(16) | 70(5) |
| C(2B) | 5582(18) | 7480(13) | -3296(11) | 61(2) |
| C(3B) | 5200(20) | 8377(14) | -3388(17) | 71(5) |
| C(5B) | 4474(18) | 6637(17) | -4436(17) | 69(3) |
| C(6B) | 4967(18) | 5866(14) | -3945(15) | 68(3) |
| C(4B) | 5555(16) | 6870(16) | -4052(11) | 57(2) |
| C(7B) | 6546(15) | 6975(13) | -4633(11) | 47(1) |
| O(1B) | 6622(13) | 6180(10) | -5207(9) | 45(1) |
| C(8B) | 6550(20) | 7916(14) | -5138(13) | 52(2) |
| C(9B) | 7570(20) | 7000(18) | -4090(20) | 40(1) |
| O(2B) | 7830(20) | 6166(18) | -3806(14) | 38(1) |
| O(3B) | 7880(30) | 7790(20) | -3800(30) | 46(2) |

**Table S3. Bond lengths [Å] and angles [°].**

| | | | |
|---|---|---|---|
| N(1)-C(10) | 1.496(6) | C(10)-C(11) | 1.513(6) |
| N(1)-C(17) | 1.510(6) | C(11)-C(12) | 1.544(5) |
| N(1)-C(13) | 1.532(5) | C(12)-C(26) | 1.506(6) |
| N(2)-C(23) | 1.373(6) | | |
| N(2)-C(25) | 1.423(5) | | |
| N(2)-C(24) | 1.487(5) | C(12)-C(13) | 1.558(5) |
| O(4)-C(21) | 1.423(6) | C(12)-C(24) | 1.563(6) |
| O(4)-C(19) | 1.456(6) | C(13)-C(14) | 1.515(6) |
| O(5)-C(23) | 1.224(6) | C(14)-C(15) | 1.544(6) |
| O(6)-C(29) | 1.380(5) | C(15)-C(16) | 1.512(7) |
| O(6)-C(32) | 1.433(6) | C(15)-C(20) | 1.536(6) |
| O(7)-C(28) | 1.374(5) | C(16)-C(18) | 1.319(7) |
| O(7)-C(31) | 1.413(5) | C(16)-C(17) | 1.508(7) |
| | | C(18)-C(19) | 1.494(8) |
| | | C(20)-C(24) | 1.532(6) |

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| C(20)-C(21) | 1.535(7) | C(20)-C(15)-C(14) | 106.4(4) |
| C(21)-C(22) | 1.544(7) | C(18)-C(16)-C(17) | 122.8(5) |
| C(22)-C(23) | 1.503(6) | C(18)-C(16)-C(15) | 122.0(5) |
| C(25)-C(30) | 1.384(6) | C(17)-C(16)-C(15) | 115.2(4) |
| C(25)-C(26) | 1.386(6) | C(16)-C(17)-N(1) | 110.0(4) |
| C(26)-C(27) | 1.399(6) | C(16)-C(18)-C(19) | 121.9(6) |
| C(27)-C(28) | 1.383(6) | O(4)-C(19)-C(18) | 110.3(4) |
| C(28)-C(29) | 1.418(6) | C(24)-C(20)-C(21) | 108.5(4) |
| C(29)-C(30) | 1.379(6) | C(24)-C(20)-C(15) | 112.8(4) |
| C(1A)-C(2A) | 1.449(13) | C(21)-C(20)-C(15) | 117.9(4) |
| C(2A)-C(3A) | 1.319(14) | O(4)-C(21)-C(20) | 114.6(4) |
| C(2A)-C(4A) | 1.495(12) | O(4)-C(21)-C(22) | 104.3(4) |
| C(5A)-C(6A) | 1.458(13) | C(20)-C(21)-C(22) | 109.5(4) |
| C(5A)-C(4A) | 1.508(11) | C(23)-C(22)-C(21) | 116.8(4) |
| C(6A)-C(4A) | 1.534(12) | O(5)-C(23)-N(2) | 122.8(4) |
| C(4A)-C(7A) | 1.561(9) | O(5)-C(23)-C(22) | 122.3(4) |
| C(7A)-O(1A) | 1.431(8) | N(2)-C(23)-C(22) | 114.9(4) |
| C(7A)-C(8A) | 1.516(9) | N(2)-C(24)-C(20) | 106.2(3) |
| C(7A)-C(9A) | 1.538(9) | N(2)-C(24)-C(12) | 104.3(3) |
| C(9A)-O(3A) | 1.239(8) | C(20)-C(24)-C(12) | 117.2(3) |
| C(9A)-O(2A) | 1.270(8) | C(30)-C(25)-C(26) | 122.0(4) |
| C(1B)-C(2B) | 1.44(2) | C(30)-C(25)-N(2) | 127.8(4) |
| C(2B)-C(3B) | 1.326(19) | C(26)-C(25)-N(2) | 110.2(4) |
| C(2B)-C(4B) | 1.479(17) | C(25)-C(26)-C(27) | 119.5(4) |
| C(5B)-C(6B) | 1.45(2) | C(25)-C(26)-C(12) | 110.4(3) |
| C(5B)-C(4B) | 1.514(17) | C(27)-C(26)-C(12) | 130.0(4) |
| C(6B)-C(4B) | 1.57(2) | C(28)-C(27)-C(26) | 119.8(4) |
| C(4B)-C(7B) | 1.556(15) | O(7)-C(28)-C(27) | 125.6(4) |
| C(7B)-O(1B) | 1.432(15) | O(7)-C(28)-C(29) | 115.2(4) |
| C(7B)-C(8B) | 1.524(16) | C(27)-C(28)-C(29) | 119.2(4) |
| C(7B)-C(9B) | 1.543(15) | C(30)-C(29)-O(6) | 124.2(4) |
| C(9B)-O(3B) | 1.247(15) | C(30)-C(29)-C(28) | 121.3(4) |
| C(9B)-O(2B) | 1.274(16) | O(6)-C(29)-C(28) | 114.6(4) |
| C(10)-N(1)-C(17) | 113.0(4) | C(29)-C(30)-C(25) | 118.2(4) |
| C(10)-N(1)-C(13) | 107.8(3) | C(3A)-C(2A)-C(1A) | 124.6(9) |
| C(17)-N(1)-C(13) | 113.1(3) | C(3A)-C(2A)-C(4A) | 115.5(8) |
| C(23)-N(2)-C(25) | 124.9(4) | C(1A)-C(2A)-C(4A) | 119.4(8) |
| C(23)-N(2)-C(24) | 118.6(4) | C(6A)-C(5A)-C(4A) | 62.3(6) |
| C(25)-N(2)-C(24) | 109.1(3) | C(5A)-C(6A)-C(4A) | 60.5(5) |
| C(21)-O(4)-C(19) | 114.1(4) | C(2A)-C(4A)-C(5A) | 113.0(7) |
| C(29)-O(6)-C(32) | 115.3(3) | C(2A)-C(4A)-C(6A) | 120.8(7) |
| C(28)-O(7)-C(31) | 116.6(3) | C(5A)-C(4A)-C(6A) | 57.3(6) |
| N(1)-C(10)-C(11) | 104.8(3) | C(2A)-C(4A)-C(7A) | 115.1(7) |
| C(10)-C(11)-C(12) | 102.9(3) | C(5A)-C(4A)-C(7A) | 117.9(7) |
| C(26)-C(12)-C(11) | 114.2(3) | C(6A)-C(4A)-C(7A) | 119.6(7) |
| C(26)-C(12)-C(13) | 115.7(3) | O(1A)-C(7A)-C(8A) | 107.0(6) |
| C(11)-C(12)-C(13) | 101.2(3) | O(1A)-C(7A)-C(9A) | 110.4(6) |
| C(26)-C(12)-C(24) | 102.5(3) | C(8A)-C(7A)-C(9A) | 109.6(7) |
| C(11)-C(12)-C(24) | 110.3(3) | O(1A)-C(7A)-C(4A) | 108.8(6) |
| C(13)-C(12)-C(24) | 113.4(3) | C(8A)-C(7A)-C(4A) | 113.3(7) |
| C(14)-C(13)-N(1) | 111.1(4) | C(9A)-C(7A)-C(4A) | 107.7(7) |
| C(14)-C(13)-C(12) | 115.3(3) | O(3A)-C(9A)-O(2A) | 126.1(8) |
| N(1)-C(13)-C(12) | 104.4(3) | O(3A)-C(9A)-C(7A) | 119.0(8) |
| C(13)-C(14)-C(15) | 108.3(4) | O(2A)-C(9A)-C(7A) | 114.8(6) |
| C(16)-C(15)-C(20) | 115.0(4) | C(3B)-C(2B)-C(1B) | 127(2) |
| C(16)-C(15)-C(14) | 109.7(4) | C(3B)-C(2B)-C(4B) | 115.0(17) |

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| | |
|---|---|
| C(1B)-C(2B)-C(4B) | 116.2(18) |
| C(6B)-C(5B)-C(4B) | 63.7(10) |
| C(5B)-C(6B)-C(4B) | 60.0(9) |
| C(2B)-C(4B)-C(5B) | 118.5(16) |
| C(2B)-C(4B)-C(7B) | 115.3(14) |
| C(5B)-C(4B)-C(7B) | 118.5(16) |
| C(2B)-C(4B)-C(6B) | 114.5(15) |
| C(5B)-C(4B)-C(6B) | 56.3(9) |
| C(7B)-C(4B)-C(6B) | 121.2(16) |
| O(1B)-C(7B)-C(8B) | 107.3(14) |
| O(1B)-C(7B)-C(9B) | 109.3(15) |

| | |
|---|---|
| C(8B)-C(7B)-C(9B) | 106.4(15) |
| O(1B)-C(7B)-C(4B) | 111.8(14) |
| C(8B)-C(7B)-C(4B) | 113.7(16) |
| C(9B)-C(7B)-C(4B) | 108.2(17) |
| O(3B)-C(9B)-O(2B) | 124(2) |
| O(3B)-C(9B)-C(7B) | 120(2) |
| O(2B)-C(9B)-C(7B) | 113.3(17) |

Symmetry transformations used to generate equivalent atom

**Table S4. Anisotropic displacement parameters ($\text{Å}^2$x $10^3$). The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$**

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| N(1) | 45(2) | 30(2) | 31(2) | 1(2) | 4(2) | 0(2) |
| N(2) | 30(2) | 29(2) | 32(2) | -2(2) | -1(2) | 1(1) |
| O(4) | 33(2) | 69(2) | 57(2) | -15(2) | 5(2) | 0(2) |
| O(5) | 40(2) | 82(3) | 33(2) | -2(2) | -7(2) | 3(2) |
| O(6) | 33(2) | 60(2) | 30(2) | -6(1) | 2(1) | 0(2) |
| O(7) | 28(1) | 41(2) | 38(2) | 0(2) | -2(1) | -1(1) |
| C(10) | 47(3) | 28(2) | 32(2) | 1(2) | 0(2) | -2(2) |
| C(11) | 37(2) | 23(2) | 33(2) | 3(2) | -4(2) | -1(2) |
| C(12) | 31(2) | 24(2) | 30(2) | -1(2) | -3(2) | -2(2) |
| C(13) | 35(2) | 26(2) | 29(2) | -1(2) | -2(2) | -2(2) |
| C(14) | 47(3) | 27(2) | 36(2) | -5(2) | -5(2) | -1(2) |
| C(15) | 46(3) | 30(2) | 46(3) | -5(2) | 0(2) | 6(2) |
| C(16) | 50(3) | 38(2) | 41(3) | -12(2) | 7(2) | 4(2) |
| C(17) | 51(3) | 36(2) | 35(2) | -6(2) | 7(2) | -1(2) |
| C(18) | 51(3) | 60(3) | 52(3) | -18(3) | 12(3) | 1(3) |
| C(19) | 43(3) | 90(5) | 58(4) | -25(3) | 8(3) | 9(3) |
| C(20) | 36(2) | 26(2) | 41(2) | -2(2) | -3(2) | 3(2) |
| C(21) | 38(2) | 38(2) | 50(3) | 0(2) | -4(2) | 6(2) |
| C(22) | 29(2) | 41(2) | 42(3) | 5(2) | -4(2) | -1(2) |
| C(23) | 32(2) | 38(2) | 40(3) | 0(2) | -6(2) | 1(2) |
| C(24) | 31(2) | 26(2) | 29(2) | -2(2) | -1(2) | 1(2) |
| C(25) | 29(2) | 26(2) | 36(2) | 0(2) | -3(2) | -2(2) |
| C(26) | 32(2) | 23(2) | 29(2) | 0(2) | -4(2) | 0(2) |
| C(27) | 31(2) | 25(2) | 30(2) | -2(2) | -6(2) | 1(2) |
| C(28) | 27(2) | 27(2) | 39(2) | -2(2) | 2(2) | 1(2) |
| C(29) | 35(2) | 32(2) | 33(2) | 0(2) | 1(2) | 2(2) |
| C(30) | 34(2) | 37(2) | 29(2) | 0(2) | -5(2) | 1(2) |
| C(31) | 26(2) | 59(3) | 45(3) | -6(2) | 0(2) | 0(2) |
| C(32) | 41(3) | 91(4) | 32(2) | -9(3) | -2(2) | 1(3) |
| C(1A) | 99(7) | 66(4) | 71(5) | 5(4) | 24(5) | 3(5) |
| C(2A) | 62(4) | 61(3) | 58(3) | -6(3) | 13(3) | 1(3) |
| C(3A) | 76(7) | 75(5) | 64(4) | -2(4) | -14(5) | -19(5) |
| C(5A) | 66(3) | 80(4) | 79(4) | 2(4) | -3(3) | 7(4) |
| C(6A) | 83(4) | 66(4) | 71(4) | -2(3) | 15(4) | 15(3) |
| C(4A) | 59(3) | 57(3) | 55(3) | -10(2) | 0(2) | 4(3) |
| C(7A) | 61(2) | 40(2) | 38(2) | -5(2) | -6(2) | 5(2) |
| O(1A) | 60(3) | 36(2) | 39(3) | -2(2) | -8(2) | -5(2) |
| C(8A) | 76(4) | 38(3) | 42(3) | -2(3) | -12(3) | 3(4) |

| | | | | | | |
|------|--------|--------|--------|--------|---------|---------|
| C(9A) | 56(2) | 37(2) | 28(2) | -7(2) | 1(2) | 0(2) |
| O(2A) | 48(4) | 36(2) | 28(3) | -10(2) | 2(2) | 5(2) |
| O(3A) | 66(3) | 36(2) | 35(5) | -6(2) | 0(3) | 2(2) |
| C(1B) | 77(11) | 79(11) | 54(5) | 2(7) | 19(9) | -14(10) |
| C(2B) | 66(5) | 59(5) | 59(4) | -9(4) | 7(4) | 3(4) |
| C(3B) | 68(10) | 59(7) | 87(11) | -20(6) | -19(10) | 4(8) |
| C(5B) | 65(4) | 68(7) | 75(6) | -9(6) | -11(5) | 2(6) |
| C(6B) | 65(7) | 65(6) | 72(7) | -5(5) | -12(6) | -8(5) |
| C(4B) | 58(3) | 57(4) | 57(3) | -6(3) | -2(3) | 4(4) |
| C(7B) | 61(2) | 40(2) | 38(2) | -5(2) | -6(2) | 5(2) |
| O(1B) | 60(3) | 36(2) | 39(3) | -2(2) | -8(2) | -5(2) |
| C(8B) | 76(4) | 38(3) | 42(3) | -2(3) | -12(3) | 3(4) |
| C(9B) | 56(2) | 37(2) | 28(2) | -7(2) | 1(2) | 0(2) |
| O(2B) | 48(4) | 36(2) | 28(3) | -10(2) | 2(2) | 5(2) |
| O(3B) | 66(3) | 36(2) | 35(5) | -6(2) | 0(3) | 2(2) |

**Table S5. Hydrogen coordinates (x $10^4$) and isotropic displacement parameters ($\text{Å}^2$x $10^3$) for.**

| | x | y | z | U(eq) |
|--------|-----------|-----------|-----------|-------|
| H(1N) | 8940(30) | 6160(40) | -3190(20) | 42 |
| H(10A) | 9614 | 7554 | -3104 | 43 |
| H(10B) | 10623 | 7130 | -2592 | 43 |
| H(11A) | 8523 | 7559 | -1947 | 37 |
| H(11B) | 9660 | 7893 | -1559 | 37 |
| H(13) | 8239 | 5595 | -2077 | 36 |
| H(14A) | 9279 | 4189 | -2372 | 44 |
| H(14B) | 9183 | 4335 | -1388 | 44 |
| H(15) | 11018 | 4010 | -1804 | 49 |
| H(17A) | 10014 | 4879 | -3493 | 49 |
| H(17B) | 10690 | 5848 | -3690 | 49 |
| H(18) | 12449 | 5619 | -3206 | 65 |
| H(19A) | 12912 | 4354 | -1909 | 77 |
| H(19B) | 13741 | 5138 | -2279 | 77 |
| H(20) | 10570 | 4841 | -583 | 41 |
| H(21) | 12378 | 4593 | -566 | 50 |
| H(22A) | 12688 | 5640 | 440 | 45 |
| H(22B) | 12599 | 6557 | -165 | 45 |
| H(24) | 10998 | 6718 | -1263 | 34 |
| H(27) | 7093 | 6211 | -991 | 35 |
| H(30) | 9251 | 6743 | 1363 | 40 |
| H(31A) | 5337 | 6540 | -658 | 65 |
| H(31B) | 4570 | 5925 | -56 | 65 |
| H(31C) | 5560 | 5402 | -508 | 65 |
| H(32A) | 8312 | 6336 | 2520 | 82 |
| H(32B) | 7339 | 6962 | 2892 | 82 |
| H(32C) | 8204 | 7471 | 2297 | 82 |
| H(1A1) | 6406 | 5316 | -3237 | 118 |
| H(1A2) | 5142 | 5307 | -3419 | 118 |
| H(1A3) | 5570 | 5390 | -2486 | 118 |
| H(3A1) | 6113 | 6983 | -1987 | 86 |
| H(3A2) | 5931 | 7920 | -2610 | 86 |
| H(5A1) | 4360 | 6948 | -4880 | 90 |
| H(5A2) | 3905 | 6858 | -3911 | 90 |

| | | | | |
|---|---|---|---|---|
| H(6A1) | 4716 | 8380 | -3582 | 88 |
| H(6A2) | 5171 | 8470 | -4551 | 88 |
| H(1OA) | 6870(50) | 5620(50) | -4630(40) | 54 |
| H(8A1) | 7166 | 7317 | -5698 | 78 |
| H(8A2) | 6666 | 8181 | -5152 | 78 |
| H(8A3) | 5890 | 7454 | -5648 | 78 |
| H(1B1) | 5490 | 7378 | -2065 | 105 |
| H(1B2) | 6507 | 6827 | -2452 | 105 |
| H(1B3) | 5334 | 6357 | -2532 | 105 |
| H(3B1) | 4998 | 8748 | -2915 | 86 |
| H(3B2) | 5125 | 8649 | -3927 | 86 |
| H(5B1) | 3835 | 6966 | -4200 | 83 |
| H(5B2) | 4450 | 6544 | -5044 | 83 |
| H(6B1) | 5264 | 5294 | -4244 | 81 |
| H(6B2) | 4648 | 5717 | -3397 | 81 |
| H(1OB) | 7210(70) | 6050(160) | -4950(40) | 54 |
| H(8B1) | 5904 | 7942 | -5485 | 78 |
| H(8B2) | 7190 | 7933 | -5491 | 78 |
| H(8B3) | 6557 | 8478 | -4762 | 78 |

# Chapter II.

# Total Synthesis of the (–)-Agelastatin Alkaloids

# Introduction and Background

The agelastatin alkaloids constitute an intriguing subset of the diverse pyrrole-imidazole family of marine alkaloids that are likely derived from the linear biogenetic precursors oroidin[1] (**7**), hymenidin[2] (**8**), and clathrodin[3] (**9**, Figure 1). (–)-Agelastatins A (**1**) and B (**2**) were first isolated in 1993 from the Coral Sea sponge *Agelas dendromorpha* by Pietra, who succesfully identified and chemically examined their unique tetracyclic structures.[4] In 1998, Molinski isolated (–)-agelastatins C (**3**) and D (**4**) from the *Cymbastela* sp. of sponges native to the Indian Ocean.[5] Recently, Al-Mourabit has reported the isolation of (–)-agelastatins E (**5**) and F (**6**) from the New Caledonian sponge *Agelas dendromorpha*.[6] (–)-Agelastatin A (**1**) exhibits significant antitumor activity and inhibits osteopontin-mediated neoplastic transformation and metastasis in addition to slowing cancer cell proliferation by causing cells to accumulate in the $G_2$ phase of the cell cycle.[7] (–)-Agelastatin A (**1**) also exhibits toxicity towards arthropods[5] and selectively inhibits the glycogen synthase kinase-3β, which is a potential target for the treatment of Alzheimer's disease and bipolar disorder.[8,9]
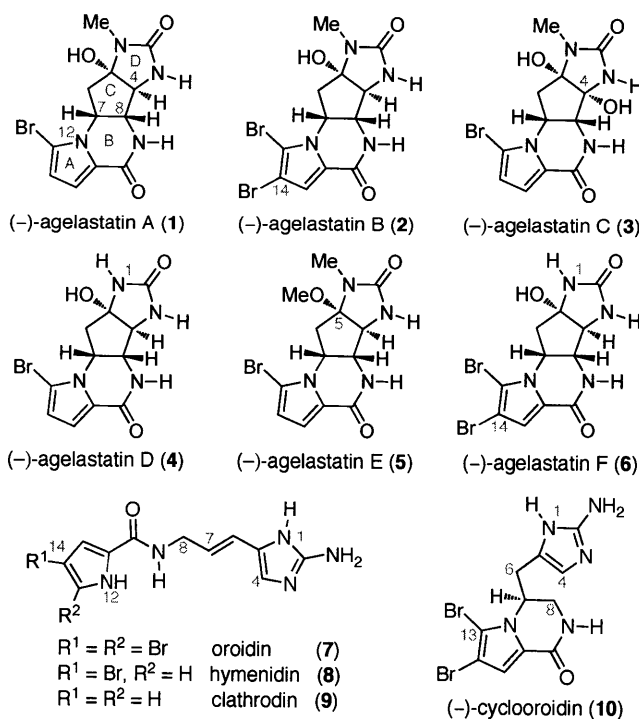


**Figure 1.** The molecular structures of all agelastatin alkaloids (**1-6**) and biogenetically related naturally occurring simple pyrrole-imidazole alkaloids (**7-10**).

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Investigations toward elucidating the metabolic pathways for the biogenesis of the diverse pyrrole-imidazole alkaloids have been limited due to the difficulty of establishing continuous cell lines of the marine invertebrates. However, Kerr has established primary cultures of the marine sponge *Teichaxinella morchella* and through feeding studies has demonstrated that histidine and ornithine (or proline) are the amino acid precursors for the related alkaloid stevensine (**11**, Scheme 1, Path A).[10] This analysis suggests that stevensine (**11**) is derived from cyclization of the linear precursor oroidin (**7**) to afford the C6–C15 linkage. Oroidin (**7**) is likely derived from the condensation of dibromopyrrole **12** and aminoimidazole **13**. The dibromopyrrole **12** is derived from ornithine (**15**) or proline (**16**), and the aminoimidazole **13** is generated from histidine (**16**) through a sequence involving oxidative deamination, carboxylate reduction, and amination reactions. In addition to the feeding studies, this pathway is supported by the co-occurrence of **11**, **12**, and **13** in *Teichaxinella morchella.* Consequently, it is plausible that the marine sponge derived pyrrole-imidazole natural products, including the agelastatin alkaloids (Scheme 1, Path B), are biogenetically linked to similar precursors.[11]
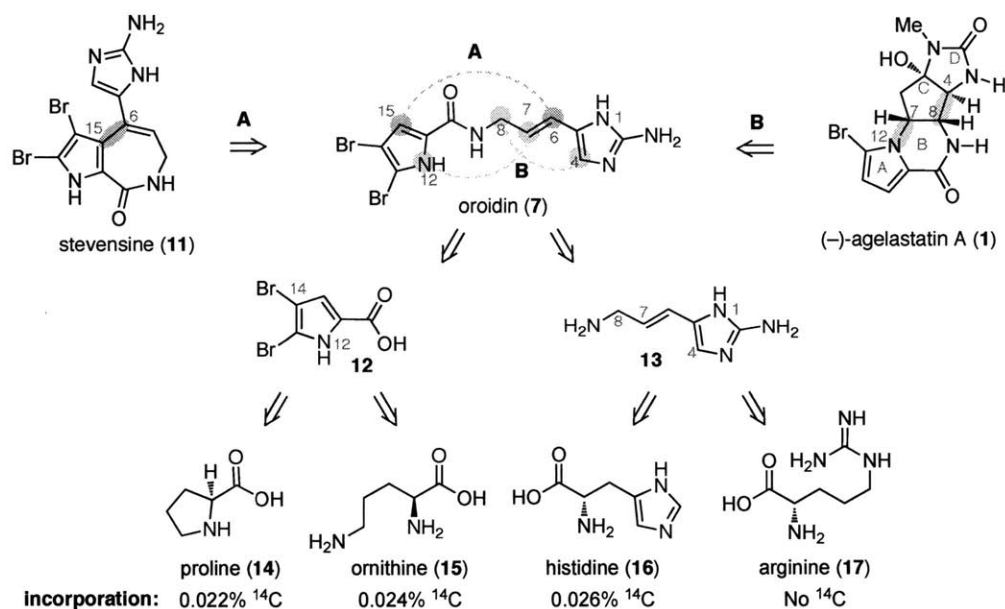


**Scheme 1.** Kerr's feeding studies that elucidate a plausible biosynthetic pathway for stevensine (**11**).

To date, the agelastatins are the only isolated pyrrole-imidazole alkaloids with C4–C8 and C7–N12 connectivities. There are currently two biosynthetic hypotheses for the formation of

the agelastatins (Scheme 2).[4a,11] Pietra has advanced the hypothesis that the linear precursor **18** undergoes an enzyme driven C8-attack of the C4-hydantoin followed by N12-addition to the C7-electrophile to afford the BC-ring system. Refunctionalization at the C4- and C5-centers then provides (–)-agelastatin A (**1**). Alternatively, Al-Mourabit has proposed that the linear aminoimidazole **19** initially undergoes C4-oxidation, which then proceeds through a Nazarov type cyclization to afford the C-ring **21** (Scheme 2). Conjugate addition of the pyrrolyl nitrogen to the C7-electrophile affords the B-ring **22**, which undergoes further elaboration to (–)-agelastatin A (**1**). Notably, both hypotheses suggest that the formation of the all carbon C-ring results from C8-nucleophilic trapping of a C4-electrophile. Furthermore, they suggest the formation of the C-ring prior to the B-ring and attribute stereochemical control to the action of biosynthetic enzymes.

**Pietra's Proposal:**



**Al-Mourabit's Proposal:**
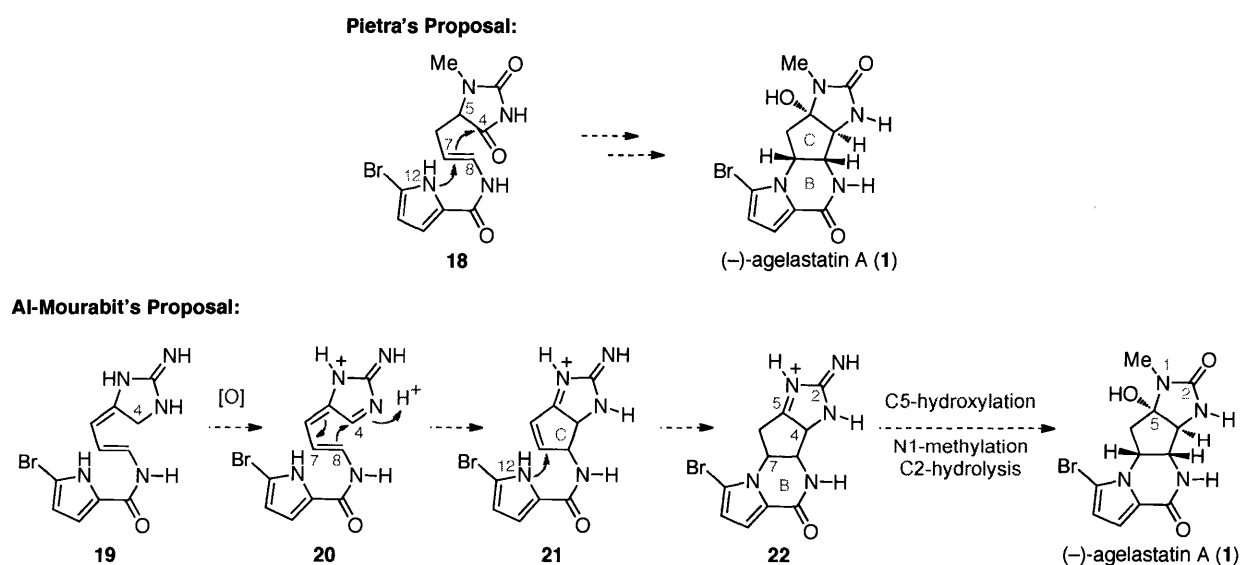


**Scheme 2.** Previously reported biosynthetic pathways for the formation of (–)-agelastatin A (**1**).

**Review of Prior Syntheses of the Agelastatin Alkaloids.** The remarkable biological activity and interesting molecular architecture of the agelastatins have prompted considerable efforts toward their total synthesis from 10 different research groups.[12] In 1999, Weinreb completed the first synthesis of racemic agelastatin A (**1**, Scheme 3).[13] The hetero-Diels-Alder cycloaddition of cyclopentadiene (**23**) with *N*-sulfinyl methyl carbamate **24** afforded the equilibrium mixture **25** and **26**, which was carried on to the bicyclic oxizolidinone **27**. A Sharpless/Kresze allylic amination with sulfodiimide **28** then installed the C8-nitrogen **29**. Elaboration to the pyrrolyl

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cyclopentenone **30** then set the stage for the formation of the N12–C7 bond via a conjugate addition reaction to afford tricycle **31**. A sequence involving bromination, Boc deprotection, and importantly addition of methyl isocyanate afforded the final target (±)-**1**. This first synthesis of racemic agelastatin A (**1**) was completed in 15 steps and approximately 7% overall yield.
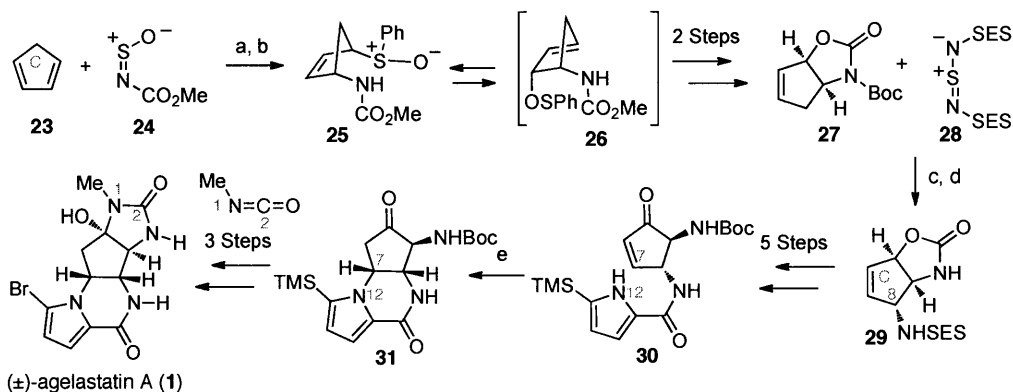


**Scheme 3.** Weinreb's first total synthesis of (±)-agelastatin A (**1**). Conditions: a) PhH, 0 °C. b) PhMgBr THF, –60 °C, 86% (2 steps). c) PhMe, 95 °C, 24 h; NaBH₄, MeOH. d) TFA, CH₂Cl₂, 86% (2 steps). e) CsCO₃, MeOH, 61%.

In 2002, Feldman reported the first enantioselective syntheses of (–)-agelastatin A (**1**) and (–)-agelastatin B (**2**) using a key alkylidenecarbene C–H insertion reaction (Scheme 4).[14] Epoxide **32**, availible in two steps from epichlorohydrin, was used to prepare the key oxazolidinone **33**. Their C–H insertion step involved treatment of **33** with PhI(CN)OTf followed by the addition of TolSO₂Na to afford the C-ring **34** in 34% yield. Elaboration to the cyclopentane **35** then set the stage for the formation of the N12–C7 bond via addition of the pyrrolyl nitrogen to the putative cyclopentenone to afford the B-ring **36** in 67% yield. Deprotection of the *o*-nitrobenzyl protecting groups then afforded des-bromoagelastatin, which was carried on to either (–)-agelastatin A (**1**) or (–)-agelastatin B (**2**) via selective mono- or di-bromination. This first enantioselective synthesis of (–)-agelastatins A (**1**) was completed in 15 steps and approximately 3.6% overall yield with 94% ee.
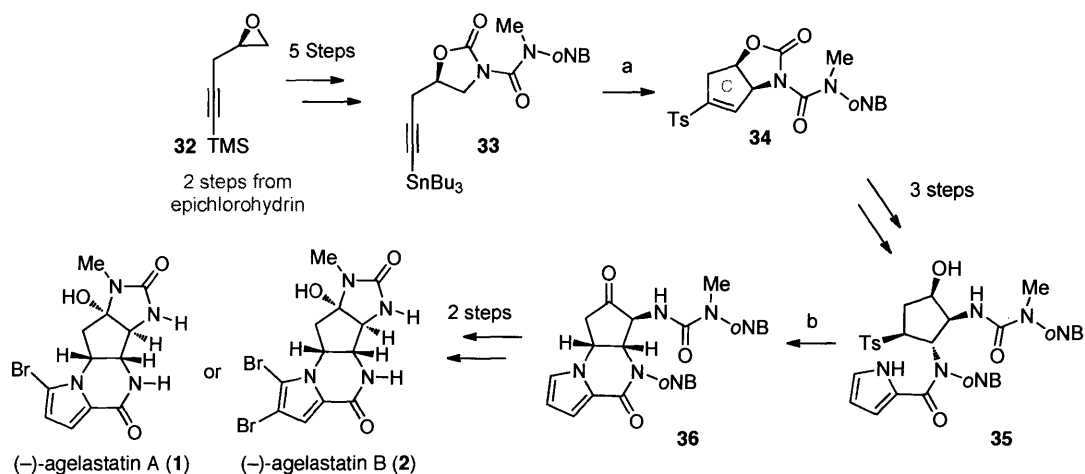
**Scheme 4.** Feldman's first enantioselective total synthesis of (−)-agelastatins A (**1**) and (−)-agelastatins B (**2**). Conditions: a) PhI(CN)OTf, $CH_2Cl_2$, −42 °C, 1h; $TolSO_2Na$, THF, 66 °C, 30 min, 34%. b) $(COCl_2)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, 67%.

In 2003, Hale applied aziridine opening chemistry with the Hough and Richardson aziridine **38** toward the synthesis of (−)-**1** (Scheme 5).[15] From aziridine **38**, carbonate formation followed by treatment with sodium azide selectively generated the aziridine opened product **40**. In 10 additional steps, **40** was converted to the bicyclic carbonate **29** that was an intermediate in Weinreb's synthesis as well (vide supra, Scheme 3). Hale then prepared (−)-agelastatin A (**1**) from **29** to complete their total synthesis in 26 total steps with approximately 0.06% overall yield.
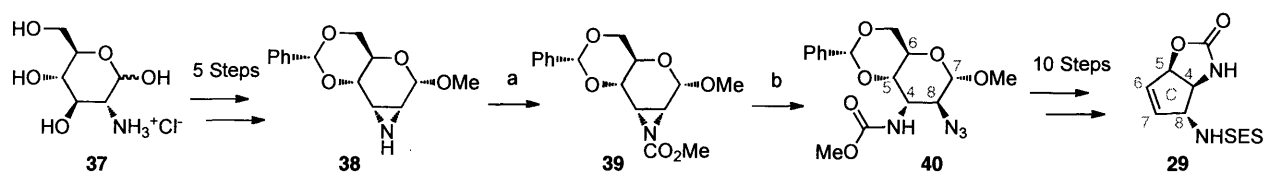


**Scheme 5.** Hale's enantioselective total synthesis of (−)-agelastatins A (**1**). Conditions: a) MeOC(O)Cl, pyr, $CH_2Cl_2$, 86%. b) $NaN_3$, $NH_4Cl$, DMF, 140 °C, 4h, 88%.

Davis' synthesis utilized a $N$-sulfinyl imine based methodology and ring-closing metathesis to efficiently secure (−)-agelastatin A (**1**, Scheme 6).[16] Addition of amino ester **42** to the $N$-sulfinyl imine **41** afforded the diamino ester **43** in 73% yield as a single diastereomer. In five steps, **43** was converted to enone **44**, which was readily advanced to cyclopentenone **45** in 87% yield using the Hoveyda-Grubbs metathesis catalyst. With the C-ring secured, Davis

employed a $Cs_2CO_3$ mediated cyclization reaction to afford tricycle **46** in 66% yield with 22% recovered starting material **45**. Hydrogenative removal of the benzyl protecting groups, followed by in situ treatment with methyl isocyanate then generated des-bromoagelastatin, which was brominated to afford (–)-agelastatin A (**1**) in a total of 11 steps with approximately 15.7% overall yield.
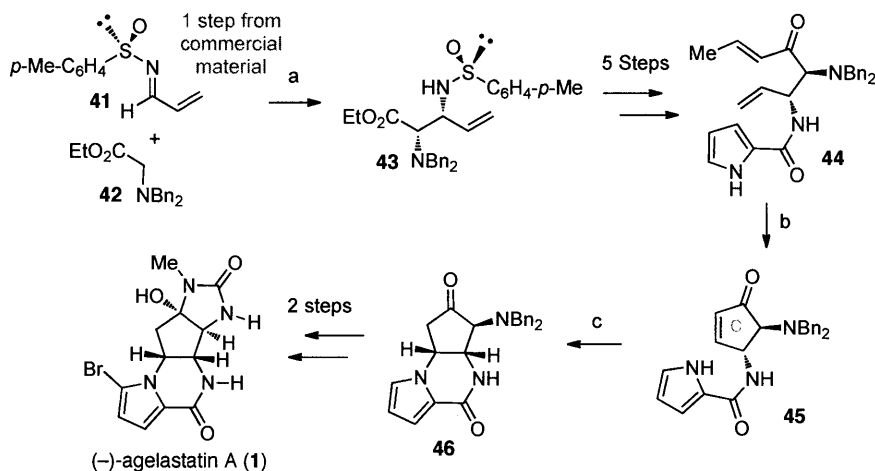


**Scheme 6.** Davis' efficient enantioselective total synthesis of (–)-agelastatin A (**1**). Conditions: a) LDA, $Et_2O$, –78 °C, 30 min, 73%. b) Hoveyda-Grubbs catalyst, $CH_2Cl_2$, 45 °C, 12 h, 87%. c) $Cs_2CO_3$, MeOH, RT, 15 min, 66%.

Sequential palladium-catalyzed asymmetric allylic alkylation reactions were key to Trost's concise total synthesis of (+)-**1** and formal synthesis of (–)-**1** (Scheme 7).[17] The union of cyclopentene **47** and pyrrole **48** was carried out with $[Pd(C_3H_5)Cl]_2$ in the presence of ligand **56** to generate **49** in 83% yield and 92% ee (Scheme 7, Path A). Conversion of the methyl ester **49** to methoxyamide **50** then set the stage for the second asymmetric allylic alkylation with $Pd_2(dba)_3CHCl_3$ and ligand **56** to afford tricycle **51** in 91% yield. An aziridination protocol, mediated by the copper $N$-heterocyclic carbene **57**, then afforded aziridine **52**, which was elaborated to (+)-agelastatin A (**1**) in a total of 9 steps in approximately 6.1% overall yield and 92% ee. Alternatively, Trost also reported the formal synthesis of (–)-**1** starting from pyrrole **53**. In a double asymmetric allylic alkylation process, tricycle **54** was generated directly in 82% yield and 97.5% ee using the same ligand **56** as above with $Pd_2(dba)_3CHCl_3$ (Scheme 7, Path B). A Sharpless/Kresze allylic amination then afforded allylic amine **55** in 43% yield. With only a

single step left to (−)-**1**, this formal synthesis would be completed in 8 steps with approximately 9.6% overall yield and 97.5% ee.
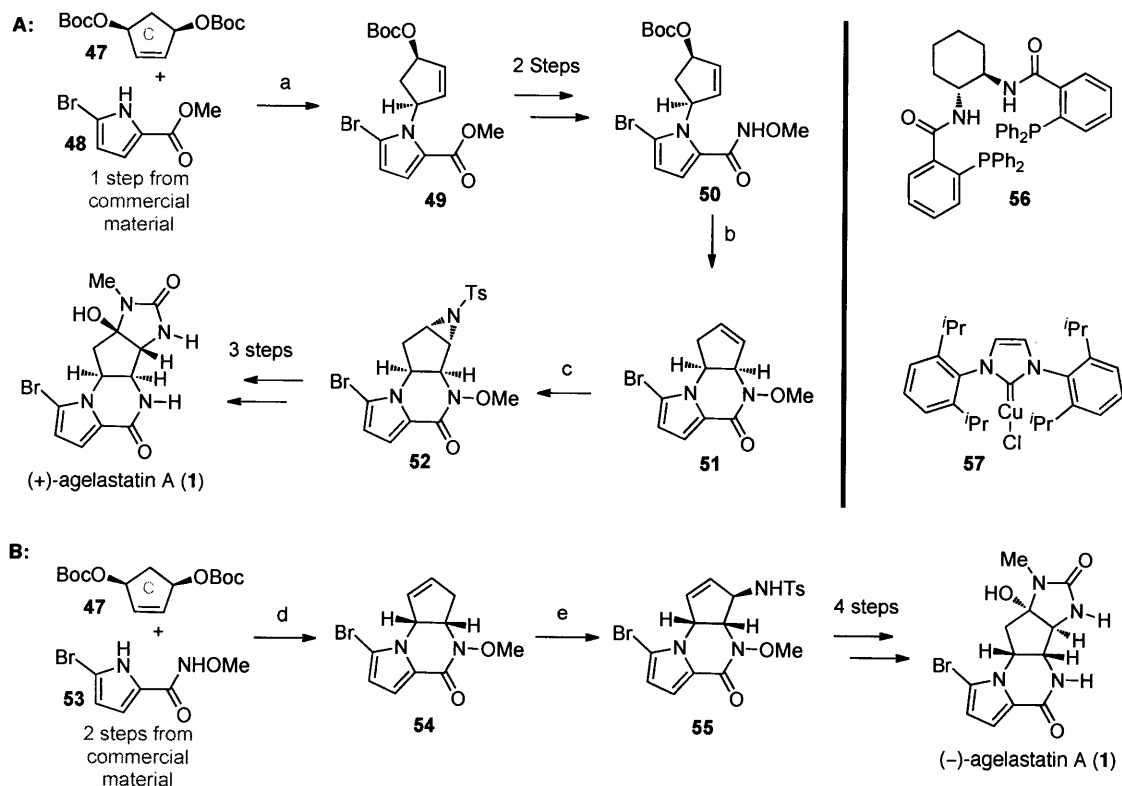


**Scheme 7.** Trost's efficient enantioselective total synthesis of (+)-agelastatin A (**1**, path A) and formal synthesis of (−)-agelastatin A (**1**, Path B). Conditions: a) [Pd(C₃H₅)Cl]₂, **56**, Cs₂CO₃, CH₂Cl₂, RT, 3 h, 83%, 92% ee. b) Pd₂(dba)₃CHCl₃, **56**, Cs₂CO₃, CH₂Cl₂, RT, 12 h, 91%. c) PhI=NTs, **57**, PhH, RT, 4 h, 52%. d) Pd₂(dba)₃CHCl₃, **56**, AcOH, CH₂Cl₂, RT, 6.5 h, 82%, 97.5% ee. e) TsN=S=NTs, PhMe, 100 °C, 40 h; MeOH, (MeO)₃P, 43%.

Ichikawa, Wardrop, and Chida each used sigmatropic rearrangement chemistry to secure the functionalized C-ring core of the agelastatins (Scheme 8). Ichikawa's sigmatropic rearrangement of an allyl cyanate, formed from amide **56**, afforded the amino diol **57** in 85% (Scheme 8, Path A).[18] Removal of the acetonide protecting group followed by ring-closing metathesis with Grubbs' 1st generation metathesis catalyst (**G1**) afforded the cyclopentene **58**, which was carried on to (−)-**1** in 27 steps with approximately 5.1% yield overall. Chida employed sequential Overman and Evans-Mislow rearrangements to afford the diamino alcohol **60** (Scheme 8, Path B).[19] A ring-closing metathesis (RCM) reaction then afforded the C-ring **61**, which was advanced to (−)-agelastatin A (**1**) in a total of 23 steps and approximately 1.2%

overall yield. Finally, Wardrop employed and Overman rearrangment to secure the racemic amino alcohol **63**, which he used to prepare racemic agelastatin A (**1**) in 14 steps and approximately 8% overall yield.[20]
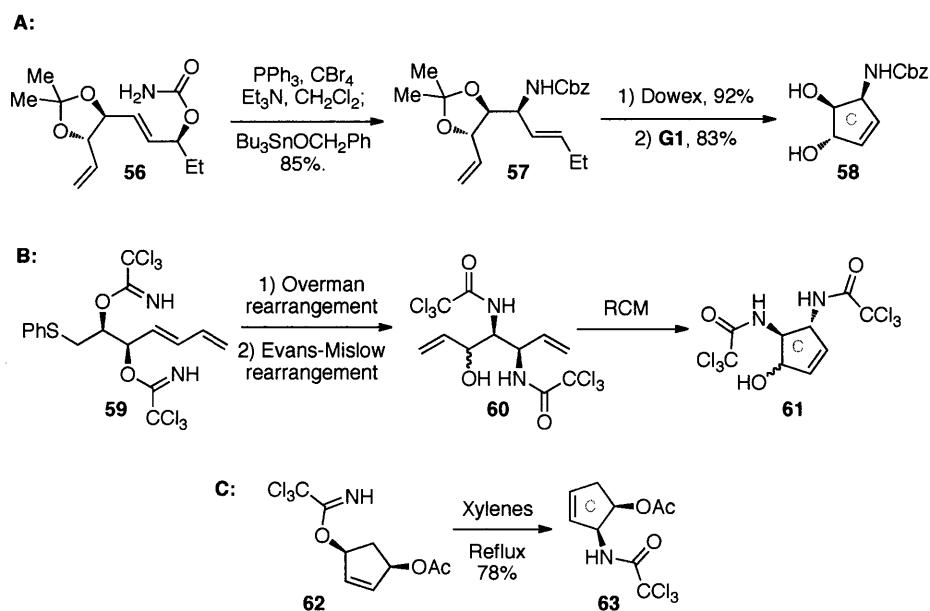


**Scheme 8.** Ichikawa's (Path A), Chida's (Path B), and Wardrops (Path C) total syntheses of agelastatin A (**1**) via sigmatropic rearrangement chemistry.

The interest in the field has continued with application of both aziridination, and radical aminobromination methodologies by Yoshimitsu (Scheme 9).[21] Both nitrile **64** and amide **67** were prepared in >99% ee via a lipase mediated chiral resolution protocol followed by recrystallization. Upon heating at 160 °C in dichloromethane in a high-pressure steel tube, azidoformate **64** underwent aziridination to afford **65** in 92% yield (Scheme 9, Path A). Aziridine **65** was then treated with sodium azide to chemoselectively afford the ring-opened product **66** (63%), which was elaborated to (–)-**1** in 17 steps with approximately 1.4% overall yield. Yoshimitsu also developed a second route to (–)-**1** from amide **67** (Scheme 9, Path B). Subjection of **67** to FeBr₂ and Bu₄NBr afforded the aminobrominated product **68** in 68% yield. The B-ring was then formed through treatment of amide **68** with sodium hydride in dimethylformamide to afford the tetracycle **69** in 91% yield, which was carried on to (–)-**1** in 14 steps overall and approximately 1.8% yield.
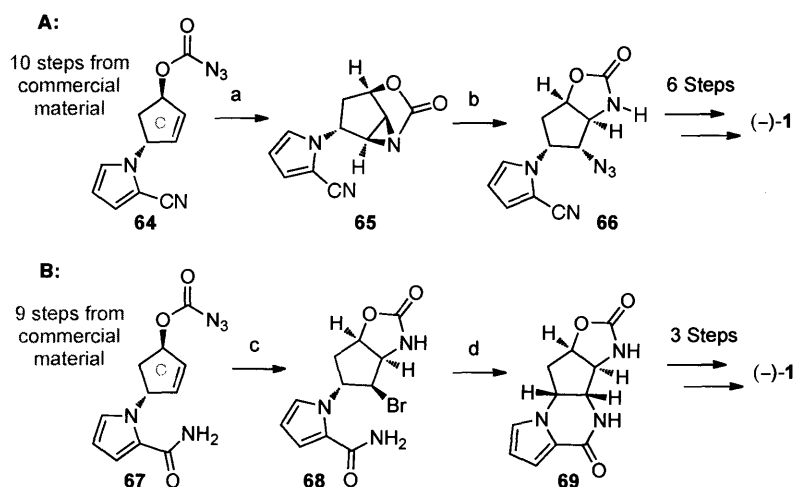
**Scheme 9.** Yoshimitsu's total syntheses of (−)-agelastatin A (1) via aziridination (Path A) and radical aminobromination (Path B) strategies. Conditions: a) 160 °C, CH₂Cl₂, 92%. b) NaN₃, DMF, RT, 61%. c) FeBr₂, Bu₄NBr, EtOH, RT, 19 h, 68%. d) NaH, DMF, RT, 3.3 h, 91%.

Most recently, Du Bois reported an elegant solution to (−)-1 employing his rhodium-catalyzed aziridination methodology.[22] Sulfonamide **70**, readily availible in 99% ee in one step from commercial material, was treated with Rh₂(esp)₂ (0.06 mol%), PhI(OAc)₂, and MgO to afford the aziridine **71** in 95% yield as a single diastereomer. Regioselective aziridine ring-opening with sodium azide afforded the oxathiazepane **72** in 71% yield. Displacement of the oxathiazepane C–O bond with sodium phenylselenide afforded cyclopentane **73**, which was elaborated to (−)-1 in 11 steps and 15% overall yield. Notably, Du Bois prepared (−)-1 on 270 mg scale in a single pass of the material.
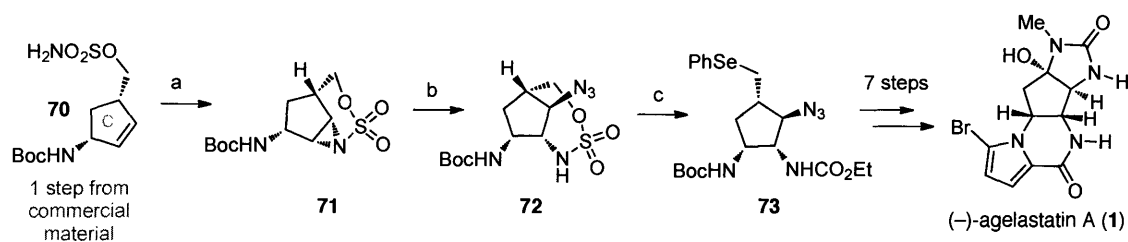


**Scheme 10.** Du Bois' total synthesis of (−)-agelastatin A (1) via a Rhodium-catalyzed aziridination methodology. Conditions: a) Rh₂(esp)₂, PhI(OAc)₂, MgO, CH₂Cl₂, 10 h, 95%. b) NaN₃, ᶦPrOH, H₂O, 5 h, 71%. c) (EtO₂C)₂O, DMAP; Ph₂Se₂, NaBH₄, 15 min, 93%.

Interestingly, all of these syntheses share a common strategy whereby they initially introduce the C-ring followed by its elaboration to afford the desired tetracyclic framework. Additionally, none of the reported total syntheses evaluate existing hypotheses for plausible

biosynthetic steps responsible for the generation of its intriguing molecular architecture, especially with respect to the C-ring formation. Furthermore, there are currently no total syntheses of agelastatins C (**3**), D (**4**), E (**5**), or F (**6**).

## Results and Discussion

Herein, we report a biogenetically inspired and unified approach to the (–)-agelastatins alkaloids using a concise synthetic strategy empowered by the inherent chemistry of potential biosynthetic intermediates.[23] The fascinating molecular architecture of the agelastatins and our interest in evaluating our hypothesis for a biogenetically relevant C-ring formation that permits rapid introduction of three stereocenters motivated these studies. We envisioned an advanced-stage biosynthetic sequence distinct from the existing hypotheses (vide supra, Scheme 2) that relies on: 1) an electrophilic C8 and a nucleophilic C4 involved in C-ring formation, 2) introduction of the C-ring after the B-ring formation, and 3) substrate directed stereochemical control and use of inherent chemistry that is perhaps enhanced by the action of putative biosynthetic enzymes. The development of simplifying transforms[24] guided by our biosynthetic hypothesis is central to our synthetic approach to the agelastatins. This retrobiosynthetic factoring for the rapid generation of molecular complexity is in line with our group's ambitions of delving into the intricate interplay of chemistry and biology in order to explore subtle chemical reactivity in complex settings.[25]

Our retrosynthetic factoring of (–)-agelastatin A (**1**) guided by our retrobiosynthetic analysis of **1** is illustrated in Scheme 11. Ionization of the C5-hydroxyl of **1** followed by the strategic disconnection of C4–C8 reveals the *N*-acyliminium ion **80** and clears three stereocenters and the all carbon C-ring. The mechanistic development of a transform linking **1** to **8 0** highlighted the significance of a versatile precursor pre-agelastatin A (**79**). Our biosynthetic hypothesis asserts that pre-agelastatin A (**79**) may be ionized to the C8-acyliminium ion allowing a 5-*exo*-trig cyclization followed by C5-hydroxylation, securing the C4-, C5-, and C8-stereocenters at the final stage of the biosynthesis (Scheme 11, Path A). We envisioned pre-agelastatin A (**79**) would result from C2-hydrolysis and C8-oxidation of the cyclooroidin analogue **77**, itself formed by C4-protonation of the linear precursor **75**, followed by C7-trapping

by the pyrrolyl-nitrogen (N12) via a 6-*exo*-trig cyclization.[26] Notably, this pathway would suggest a link between the agelastatins and the natural product cyclooroidin (**10**, Fig. 1),[27] and is consistent with Lindel's reported aqueous formic acid promoted conversion of oroidin (**7**) to **10**.[28] Inspired by the potential direct conversion of pre-agelastatin A (**79**) to (–)-agelastatin A (**1**), we targeted the related structure *O*-methyl-pre-agelastatin A (**82**) and envisioned its synthesis from readily available D-aspartic acid derivative **85** (Scheme 11, Path B).
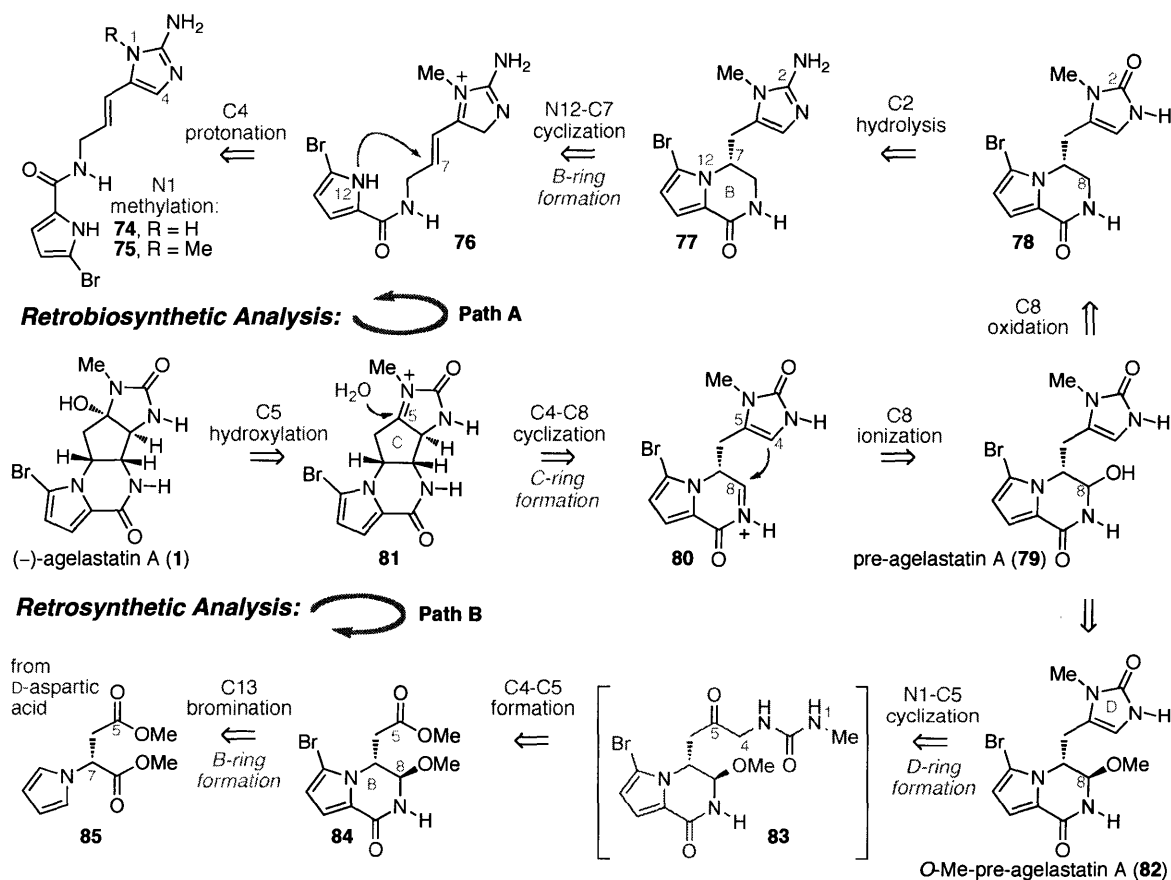


**Scheme 11.** Our retrosynthetic analysis of (–)-agelastatin A (**1**, Path B) inspired by our biosynthetic hypothesis (Path A) that involves intermediacy of pre-agelastatin A (**79**) in a final stage formation of the C-ring and introduction of the C4-, C5-, and C8-stereochemistry (**79**→**1**).

Our convergent synthesis[29] for the targeted *O*-methyl-pre-agelastatin A (**82**) commenced with pyrrole (+)-**85** (Scheme 12), available in one step from commercially available bismethyl D-aspartic acid.[30] Exposure of pyrrole (+)-**85** to *N*-bromosuccinimide (NBS) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) afforded the bromopyrrole (+)-**86** in 92% yield with 99% ee. Treatment of bromopyrrole (+)-**86** with chlorosulfonyl isocyanate afforded amide

(+)-**87** (82%), which was treated sequentially with sodium borohydride followed by *p*-toluenesulfonic acid (TsOH) in methanol to generate bicycle (+)-**84** as a single diastereomer in 90% yield and 99% ee on greater than 10-gram scale. The conversion of (+)-**87** to bicycle (+)-**84** occured via formation and immediate reduction of the imide intermediate **88**, preventing an undesired C7-epimerization. Interestingly, B-ring formation with the des-bromopyrrole derivative of **87** resulted in significant erosion of enantiomeric excess. This observation was consistent with our postulate that the C7–H bond would be forced to adopt a pseudo-equatorial conformation to minimize allylic strain between the C13-bromine and C6-methylene. In this conformation, deprotonation of the C7-methine is suppressed. The structure and relative stereochemistry of (+)-**84** was secured through X-ray crystallographic analysis, and its thermal ellipsoid representation illustrates that the C6-methylene and C8-methoxy group reside in pseudo-axial conformations (Scheme 12). Importantly, the use of the brominated pyrrole that is present in the final targets provided favorable chemical reactivity beneficial to our synthetic strategy.
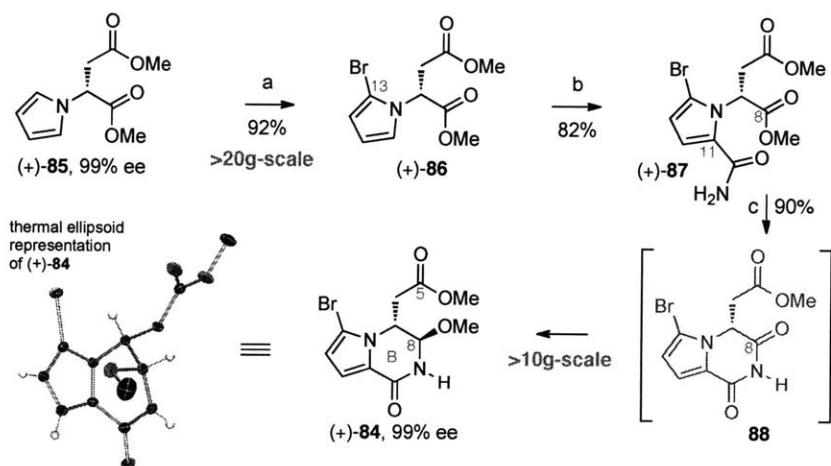


**Scheme 12.** Decagram-scale synthesis of bicycle (+)-**84**. Conditions: a) NBS, DTBMP, THF, 92%. b) $ClSO_2NCO$, MeCN, 0 °C; Na(Hg), $NaH_2PO_4$, 82%. c) $NaBH_4$, MeOH, 0 °C; TsOH•$H_2O$, 23 °C, 90%.

With the C5-ester (+)-**84** in hand, we developed a general approach for the introduction of the imidazolone substructures present in the targeted pre-agelastatin derivatives. Initially, we focused on the direct addition of metallated derivatives of triazone **89**[31,32] to the C5-ester (+)-**84** (Scheme 13). Unfortunately, these strategies were plagued by either lack of reactivity (M = Mg, Cu, Ce, Zn), or the formation of byproducts associated with metal-halogen exchange, double

addition, and competing decomposition pathways (M = Li). Furthermore, these metallated triazone derivatives **89** were unstable at temperatures above 0 °C. Thus, it was necessary for us to develop a method for the C4–C5 bond formation using an activated derivative of the C5-ester (+)-**84** and a stable metallated triazone.
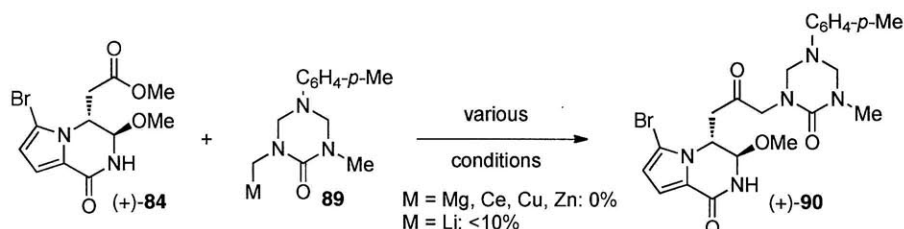


**Scheme 13.** Investigations of metallated triazone addition to the ester (+)-**84**.

We envisioned that the cross-coupling of thioester derivatives[33] with stannyltriazone and stannylurea derivatives would represent a versatile method for the rapid synthesis of substituted imidazolones. The thioester (+)-**91** was readily prepared in 92% yield through treatment of ester (+)-**84** with trimethylaluminum and 4-methylbenzenethiol in dichloromethane (Scheme 14). The structure of (+)-**91** was secured via X-ray crystallographic analysis, revealing the pseudo-equatorial C7–H bond.
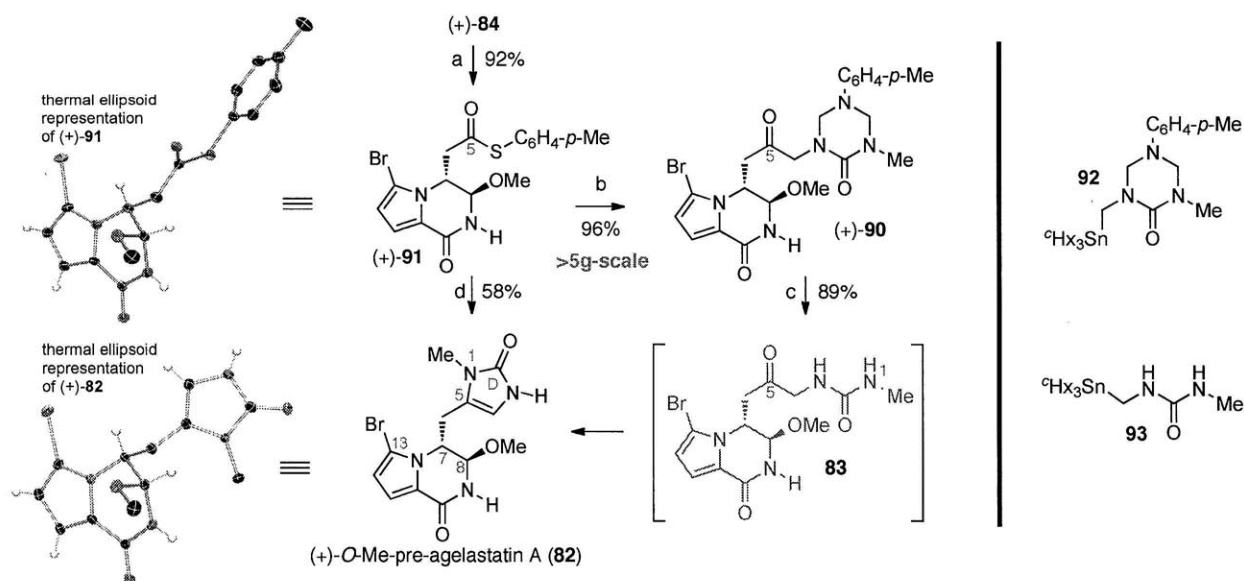


**Scheme 14.** Synthesis of the key intermediate (+)-*O*-methyl-pre-agelastatin A (**82**). Conditions: a) HSC$_6$H$_4$-*p*-Me, AlMe$_3$, CH$_2$Cl$_2$, 0 °C, 92%. b) **92**, CuTC, THF, 50 °C, 96%. c) HCl (0.5 N), MeOH, 23 °C, 89%. d) **93**, CuTC, THF, 50 °C; HCl (0.5 N), MeOH, 23 °C, 58%.

After significant experimentation, we found that the union of thioester (+)-**91** with the readily available stannyltriazone **92**[34] could be achieved in the presence of stoichiometric copper(I)-thiophene-2-carboxylate (CuTC) to efficiently give ketone (+)-**90** in 96% yield on greater than 5-gram scale (Scheme 14). Exposure of triazone (+)-**90** to methanolic hydrogen chloride unraveled the desired keto-urea **83**, which upon condensative cyclization provided the desired (+)-*O*-methyl-pre-agelastatin A (**82**) in 89% yield with 99% ee. The versatility of this new imidazolone annulation was highlighted in the union of thioester (+)-**91** and stannylurea **93** to afford (+)-*O*-methyl-pre-agelastatin A (**82**) without isolation of any intermediates. The structure of (+)-**82** was secured via X-ray crystallographic analysis, and its thermal ellipsoid representation illustrates that the C7-methylimidazolone and C8-methoxy group reside in a pseudo-axial conformations.

With (+)-*O*-methyl-pre-agelastatin A (**82**) in hand we proceeded to evaluate our biosynthetic hypothesis for the chemistry involved in the C-ring formation and rapid introduction of the C4-, C5-, and C8-stereocenters. Gratifyingly, exposure of (+)-**82** to methanesulfonic acid in water at 100 °C indeed provided (–)-agelastatin A (**1**, Scheme 15). Interestingly, (–)-agelastatin A (**1**) is formed as the major product along with (–)-di-*epi*-agelastatin A (not shown) as the minor stereoisomer (~2:1). Monitoring of this reaction by $^1$H NMR revealed that (–)-di-*epi*-agelastatin A is the kinetic product, which equilibrates to the thermodynamically favored product (–)-agelastatin A (**1**). Careful analysis of the rate of solvolysis of each isomer revealed that the C5-hydroxyl of (–)-di-*epi*-agelastatin A ionizes at a significantly faster rate than the corresponding C5-hydroxyl of (–)-agelastatin A (**1**). This observation was key in the development of a simple procedure for preparative separation of (–)-agelastatin A (**1**) from the corresponding minor diastereomer. Upon complete consumption of the pre-agelastatin precursor, treatment with acidic methanol for 5 min efficiently converts (–)-di-*epi*-agelastatin A to (–)-*O*-methyl-di-*epi*-agelastatin A (**96**, Scheme 15). Under preparative conditions, our potentially biomimetic cyclization of (+)-**82** afforded (–)-agelastatin A (**1**) in 49% yield (1.4 g, 99% ee) along with (–)-*O*-methyl-di-*epi*-agelastatin A (**96**) in 22% yield (668 mg). Furthermore, resubmission of (–)-*O*-methyl-di-*epi*-agelastatin A (**96**) to the above protocol afforded a second batch of (–)-agelastatin A (**1**) in 66% yield (421 mg, 99% ee) along with recovered **96** (30%). The structure of (–)-**1** was secured through X-ray crystallographic analysis (Scheme 15). It

should be noted that this 5-(enol*endo*)-*exo*-trig[35] type of C-ring cyclization with an acyliminium ion is a rare and challenging reaction as evidenced by the paucity of relevant examples in the literature.[36]
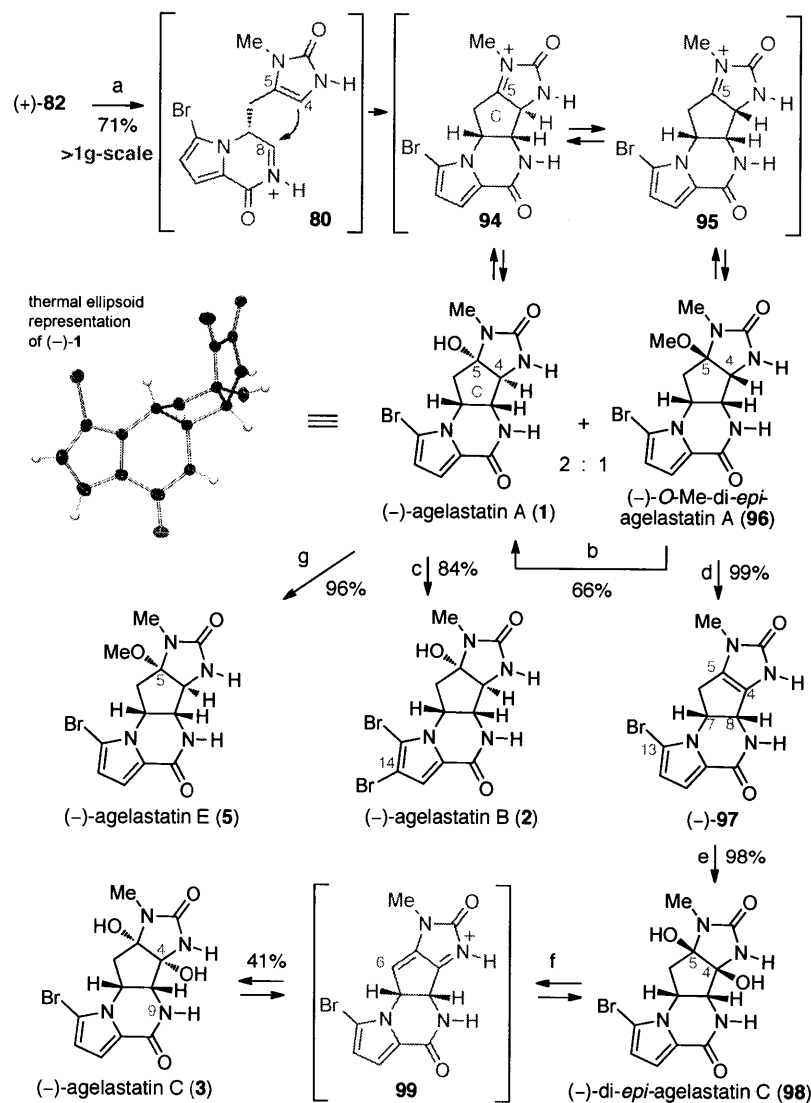


**Scheme 15.** Gram-scale synthesis of (–)-agelastatin A (**1**), and syntheses of (–)-agelastatin B (**2**), (–)-agelastatin C (**3**), and (–)-agelastatin E (**5**). Conditions: a) MeSO₃H, H₂O, 100 °C; MeOH, 49% (–)-**1**, 22% (–)-**96**. b) MeSO₃H, H₂O, 100 °C; MeOH, 66% (30% recovered (–)-**96**). c) NBS, DTBMP, THF, H₂O, 0 °C, 84%. d) pyr, 115 °C, 99%. e) DMDO, acetone, H₂O, 98%. f) Amberlyst® 15, H₂O, 100 °C, 5 d, 41% (42% recovered (–)-**98**). g) Amberlyst® 15, MeOH, 65 °C, 96%.

We then moved to address the synthesis of (–)-agelastatins B (**2**), C (**3**), and E (**5**, Scheme 15). Under optimal conditions treatment of (–)-agelastatin A (**1**) with NBS and DTBMP in a water–tetrahydrofuran solvent mixture afforded the natural product (–)-agelastatin B (**2**) in 84%

yield. We next turned our focus toward the installation of the C4-hydroxyl group present in (–)-agelastatin C (**3**). Importantly, (–)-*O*-methyl-di-*epi*-agelastatin A (**96**) served as a versatile precursor for the synthesis of (–)-agelastatin C (**3**, Scheme 15). Heating a solution of (–)-*O*-methyl-di-*epi*-agelastatin A (**96**) in pyridine afforded (–)-dehydroagelastatin A (**97**) in 99% yield.[37] As anticipated, treatment of (–)-**97** with dimethyldioxirane (DMDO) gave (–)-di-*epi*-agelastatin C (**98**, 98%) via oxidation on the convex face. Significantly, exposure of (–)-di-*epi*-agelastatin C (**98**) to acid (Amberlyst® 15) in water at 100 °C slowly afforded (–)-agelastatin C (**3**, 41%, along with 42% recovered **98**). We propose that this equilibration occurs via the intermediate **99**, which is consistent with our observations of deuterium incorporation at the C6-methylene using $D_2O$ as solvent.[38] The newly isolated (–)-agelastatin E (**5**) was then prepared directly from (–)-agelastatin A (**1**, Scheme 15). According to a protocol previously described by Pietra,[4b] (–)-agelastatin A (**1**) was treated with Amberlyst® 15 in methanol at 65 °C for 2 h to afford (–)-agelastatin E (**5**) in 96% yield.

Our unified strategy for the C-ring formation utilizes the inherent chemistry of the pre-agelastatin intermediates for the generation of chemical complexity and stereochemical control to address the synthesis of the agelastatin alkaloids. Collectively, our observations hint at a plausible biosynthetic sequence for the formation of the agelastatins. For example, the stereochemical outcome for the key C-ring cyclization is controlled by the C7-methine to secure the desired thermodynamically favored C4-, C5-, and C8-stereocenters. Specifically, the C5-stereocenter is controlled by the C4-stereochemistry to give a *cis*-fused CD-ring system upon hydroxylation. It is feasible that the innate selectivity for this stereochemical outcome may perhaps be enhanced by the action of putative biosynthetic enzymes.

Furthermore, the C13-bromine that is present in all agelastatins is critical for the key C-ring cyclization. Treatment of the des-bromo derivative **100** under the cyclization conditions did not result in the desired C-ring formation, but rather gave the pyrrolopyrazinone **101** (Scheme 16). Thus, the allylic strain between the C13-bromine and C6-methylene that restricts the C7–H to a pseudo-equatorial conformation is essential for the formation of the agelastatins. Consequently, the C13-bromine is likely incorporated prior to C-ring formation in this plausible biosynthetic sequence. While our total syntheses do not in any way confirm our hypothesis for their biogenesis, it is gratifying to have chemical validation for our proposed mode and timing of bond and ring formations in this alkaloid family.
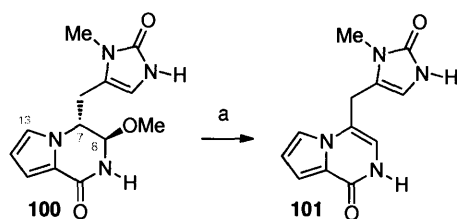
**Scheme 16.** Key observation concerning the biogenetically inspired C-ring synthesis. Conditions: a) MeSO₃H, H₂O, 100 °C, 20 min, 57%.

# Conclusion
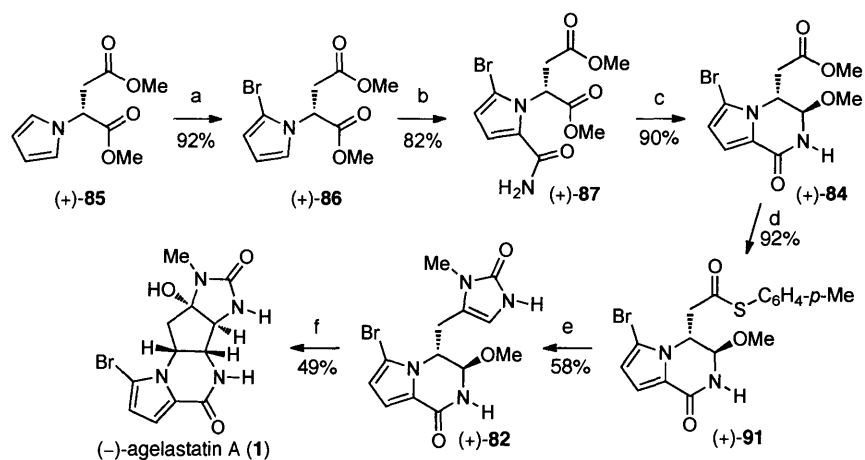


**Scheme 17.** Summary of our concise synthesis of (–)-agelastatin A (**1**). Conditions: a) NBS, DTBMP, THF, 92%. b) ClSO₂NCO, MeCN, 0 °C; Na(Hg), NaH₂PO₄, 82%. c) NaBH₄ MeOH, 0 °C; TsOH•H₂O, 23 °C, 90%. d) HSC₆H₄-*p*-Me, AlMe₃, CH₂Cl₂, 0 °C, 92%. e) **93**, CuTC, THF, 50 °C; HCl (0.5 N), MeOH, 23 °C, 58%. f) MeSO₃H, H₂O, 100 °C; MeOH, 49%.

We have completed the total syntheses of the agelastatin alkaloids through a highly concise and unifying strategy inspired by our biosynthetic hypothesis. Key features of our synthesis of the agelastatin alkaloids include: 1) the concise large scale enantioselective total synthesis of our proposed "pre-agelastatin" derivatives using a route from simple readily available starting materials, 2) the use of the bromopyrrole allylic strain, to prevent C7-epimerization, enabling access to key intermediates with >99% ee, 3) the rapid and versatile synthesis of imidazolone derivatives via a new [4+1] annulation strategy, 4) the validation of our planned 5-*exo*-trig advanced stage C-ring formation consistent with our hypothesis for their biogenesis, and 5) the verification of our plausible biogenetically relevant hypothesis for the

formation of (–)-agelastatin C (**3**) through oxidation of (–)-dehydroagelastatin A (**97**) followed by its equilibration. Our synthesis of (–)-agelastatin A (**1**) is summarized in Scheme 19 (7 steps, longest linear sequence). The overall efficiency of our strategy is evidenced by our preparation of a 1.4 gram batch of (–)-agelastatin A (**1**) in eight steps from commercial material in 22% overall yield through isolation of keto triazone (+)-**90**. With efficient access to the natural agelastatin alkaloids and related derivatives, mechanistic studies aimed at unlocking their chemical and biological mode of action are ongoing.

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38. Treatment of either (–)-di-*epi*-agelastatin C (**98**) or (–)-agelastatin C (**3**) with MeSO₃H (10 equiv) in $D_2O$ at 100 °C for 3 d, afforded a 1:1 equilibrium mixture of (–)-di-*epi*-agelastatin C (**98**) and (–)-agelastatin C (**3**) with quantitative deuterium incorporation at the C6-methylene as indicated by $^1H$ NMR analysis.

## Experimental Section

**General Procedures.** All reactions were performed in oven-dried or flame-dried round bottomed flasks or modified Schlenk (Kjeldahl shape) flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon. Gas tight syringes equipped with stainless steel needles or cannulae were used to transfer air- and moisture-sensitive liquids. Where necessary (so noted), solutions were deoxygenated by argon purging for a minimum of 10 min. Flash column chromatography was performed as described by Still et al. using silica gel (60-Å pore size, 40–63 μm, 4-6% $H_2O$ content, Zeochem).[1] Analytical thin–layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to an ethanolic phosphomolybdic acid (PMA), an acidic solution of *p*-anisaldehyde (Anis), an aqueous solution of ceric ammonium molybdate (CAM), an aqueous solution of potassium permanganate ($KMnO_4$) or an ethanolic solution of ninhydrin followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on Büchi R-200 rotary evaporators at ~10 torr (house vacuum) at 25–35 °C, then at ~0.5 torr (vacuum pump) unless otherwise indicated.

**Materials.** Commercial reagents and solvents were used as received with the following exceptions: dichloromethane, diethyl ether, tetrahydrofuran, acetonitrile, toluene, methanol, triethylamine, and pyridine were purchased from J.T. Baker (Cycletainer™) and were purified by the method of Grubbs et al. under positive argon pressure.[2] Copper thiophene 2-carboxylate (CuTC), a tan colored solid, was purchased from Matrix Inc. and was used as received. Chlorosulfonyl isocyanate was purchased from TCI and was used as received. Sodium Amalgam was freshly prepared before use.[3] The molarity of *sec*-butyllithium solutions were determined by titration using diphenylacetic acid as an indicator (average of three determinations).[4] The molarity of DMDO[5] solutions were determined by titration using triphenylphosphine with ^{31}P NMR analysis.

**Instrumentation.** Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance spectra were recorded with Varian inverse probe 500 INOVA and Varian 500 INOVA spectrometers. Proton nuclear magnetic resonance (^{1}H NMR) spectra are reported in parts per million on the δ scale and are referenced from the residual protium in the NMR solvent ($CDCl_3$: δ 7.24, Toluene-$d_8$: δ 7.09, 7.00, 6.98, 2.09; $CHD_2OD$: δ 3.31). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, st = sextet, sp = septet, m = multiplet, app = apparent, br = broad), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million on the δ scale and are referenced from the carbon resonances of the solvent ($CDCl_3$: δ 77.23, Toluene-$d_8$: δ 137.86, 129.24, 128.33, 125.49, 20.40, $CD_3OD$: δ 49.15, Pyridine-$d_5$: δ 150.35, 135.91, 123.87, DMSO-$d_6$: δ 39.51). Data is reported as

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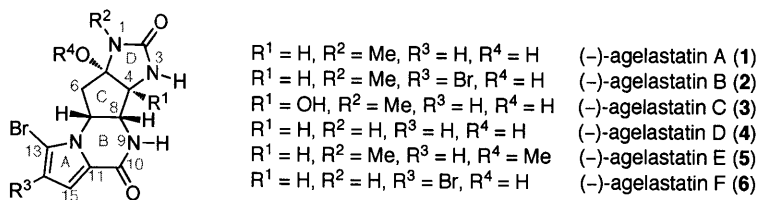[3] Sodium amalgam (5% wt) was prepared according to: Brasen, W. R.; Hauser, C. R. *Org. Synth.* **1954**, *34*, 56-57.
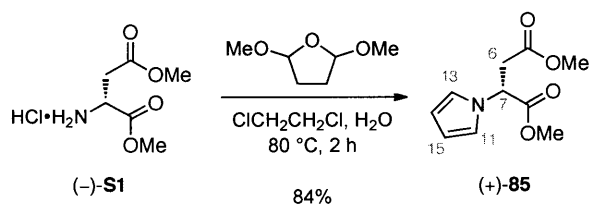[4] Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879–1880.
[5] For the preparation of DMDO see: Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91-96.

follows: chemical shift. Infrared data (IR) were obtained with a Perkin-Elmer 2000 FTIR and are reported as follows: [frequency of absorption (cm$^{-1}$), intensity of absorption (s = strong, m = medium, w = weak, br = broad)]. Optical Rotation was recorded on a Jasco P-1010 Polarimeter (chloroform, Aldrich, Chromosolv Plus 99.9%; methanol, Aldrich, Chromosolv Plus 99.9%; pyridine, purified by the method of Grubbs et al.[2]). Chiral HPLC analysis was performed on an Agilent Technologies 1100 Series system. Semi-preparative HPLC was performed on a Waters system with the 1525 Binary HPLC Pump, 2489 UV/Vis Detector, SFO System Fluidics Organizer, and 2767 Sample Manager components. The structures of (–)-**1**, (+)-**82**, (+)-**84**, and (+)-**91** were obtained at the X-ray crystallography laboratory of the Department of Chemistry, Massachusetts Institute of Technology, with the assistance of Mr. Justin Kim. We are grateful to Dr. Li Li for obtaining the mass spectrometric data at the Department of Chemistry's Instrumentation Facility, Massachusetts Institute of Technology. High-resolution mass spectrometric data (HRMS) were recorded on a Bruker Daltonics APEXIV 4.7 Tesla FT-ICR-MS spectrometer using electronspray ion source (ESI) or direct analysis in real time (DART) ionization source.

**Positional Numbering System.** In assigning the $^1$H and $^{13}$C NMR data of all intermediates en route to our total synthesis of (–)-**1** through (–)-**6** we have employed a uniform numbering system consistent with that of the final targets.



| | |
|---|---|
| R$^1$ = H, R$^2$ = Me, R$^3$ = H, R$^4$ = H | (–)-agelastatin A (**1**) |
| R$^1$ = H, R$^2$ = Me, R$^3$ = Br, R$^4$ = H | (–)-agelastatin B (**2**) |
| R$^1$ = OH, R$^2$ = Me, R$^3$ = H, R$^4$ = H | (–)-agelastatin C (**3**) |
| R$^1$ = H, R$^2$ = H, R$^3$ = H, R$^4$ = H | (–)-agelastatin D (**4**) |
| R$^1$ = H, R$^2$ = Me, R$^3$ = H, R$^4$ = Me | (–)-agelastatin E (**5**) |
| R$^1$ = H, R$^2$ = H, R$^3$ = Br, R$^4$ = H | (–)-agelastatin F (**6**) |

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## (+)-(R)-Dimethyl-2-(1H-pyrrol-1-yl)succinate (85):[6]

To a solution of (–)-dimethyl D-aspartate hydrogenchloride[7] (S1, 20.0 g, 101 mmol, 1 equiv) in water (153 ml) at 23 °C was added 1,2-dichloroethane (153 mL) via syringe followed by 2,5-dimethoxytetrahydrofuran (13.1 mL, 101 mmol, 1.00 equiv), and the resulting mixture was heated to 80 °C. After 2 h, the brown reaction mixture was cooled to 23 °C, and the aqueous layer was separated and was extracted with dichloromethane (3 × 150 mL). The combined organic layers were dried over anhydrous sodium sulfate and were concentrated under reduced pressure. The brown residue was purified by flash column chromatography (silica gel: diam. 6 cm, ht. 15 cm; eluent: 50% diethyl ether in hexanes) to afford pyrrole (+)-85 (17.9 g, 84%) as colorless oil that was found to be 99% ee by chiral HPLC analysis [Welk-O (S,S); 3 mL/min; 2% isopropanol in hexanes; $t_R$(major) = 4.5 min, $t_R$(minor) = 5.2 min]. (+)-85 could be stored for greater than a month as a solution frozen in benzene at –8 °C without any erosion of enantiomeric excess.

| | |
|---|---|
| $^1$H NMR (500 MHz, CDCl$_3$, 21 °C): | δ 6.69 (t, $J$ = 2.2 Hz, 2H, C$_{11}$**H**, C$_{13}$**H**), 6.15 (t, $J$ = 2.1 Hz, 2H, C$_{14}$**H**, C$_{15}$**H**), 5.11 (dd, $J$ = 7.9, 6.8 Hz, 1H, C$_7$**H**), 3.71 (s, 3H, OC**H$_3$**), 3.66 (s, 3H, OC**H$_3$**), 3.26 (dd, $J$ = 16.8, 8.0 Hz, 1H, C$_6$**H$_a$**), 2.92 (dd, $J$ = 16.7, 6.8 Hz, 1H, C$_6$**H$_b$**). |
| $^{13}$C NMR (125.8 MHz, CDCl$_3$, 21 °C): | δ 170.4, 170.0, 120.1, 109.2, 57.8, 53.0, 52.2, 37.5. |
| FTIR (neat) cm$^{-1}$: | 3643 (m), 3466 (m), 3103 (m), 2956 (s), 1739 (br-s), 1557 (w), 1490 (s), 729 (s). |
| HRMS (DART) ($m/z$): | calc'd for C$_{10}$H$_{14}$NNaO$_4$, [M+Na]$^+$: 212.0917 found: 212.0911. |
| $[\alpha]_D^{22}$: | +71.3 ($c$ 0.37, CHCl$_3$). |
| TLC (25% ethyl acetate in hexanes), R$f$: | 0.50 (CAM, UV). |

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[6] For a previous report of the synthesis of (–)-85 in 99% ee see: Jefford, C. W.; de Villedone de Naide, F.; Sienkiewicz, K. *Tetrahedron: Asymmetry* **1996**, *7*, 1069-1076.

[7] (–)-Dimethyl D-aspartate hydrochloride (S1) can be purchased from commercial sources. Alternatively, we prepared S1 from (–)-D-aspartic acid in 99% yield on greater than 35 gram scale according to the following procedure: Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068-3074.

(+)-85 → NBS, DTBMP, THF, 0 °C, 1 h, 92% → (+)-86
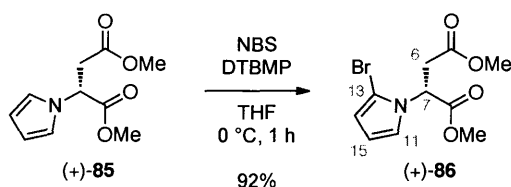
## (+)-(R)-Dimethyl 2-(2-bromo-1H-pyrrol-1-yl)succinate (86):

N-Bromosuccinimide (NBS, 13.7 g, 77.0 mmol, 1.00 equiv) was added as solid in one portion to a solution of pyrrole (+)-85 (16.2 g, 77.0 mmol, 1 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 17.3 g, 84.0 mmol, 1.10 equiv) in tetrahydrofuran (385 mL) at 0 °C. After 1 h, the clear colorless reaction mixture was quenched with a mixture of saturated aqueous sodium thiosulfate solution and saturated aqueous sodium bicarbonate solution (1:1, 200 mL). The solution was diluted with ethyl acetate (800 mL) and water (800 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 800 mL), and the combined organic layers were dried over anhydrous sodium sulfate and were concentrated under reduced pressure. The sample of the crude colorless residue was purified by flash column chromatography (silica gel: diam. 9 cm, ht. 17 cm; eluent: 10% ethyl acetate in hexanes) to afford (+)-86 (20.6 g, 92%) as a colorless oil that was found to be 99% ee by chiral HPLC analysis [Welk-O (R,R); 3 mL/min; 2% isopropanol in hexanes; $t_R$(major) = 3.5 min, $t_R$(minor) = 4.1 min]. While neat (+)-86 is sensitive toward long term storage, it could be stored for greater than a month as a solution frozen in benzene at −8 °C without any $C_{13} \rightarrow C_{14}$ bromine migration.

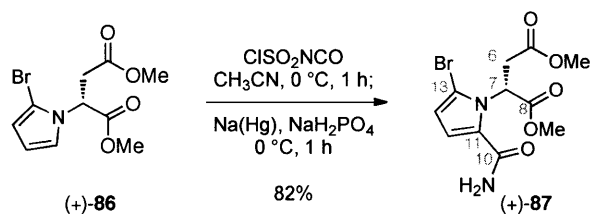| | |
|---|---|
| $^1$H NMR (500 MHz, CDCl$_3$, 21 °C): | δ 6.74 (ddd, $J$ = 3.1, 1.9, 0.2 Hz, 1H, C$_{11}$**H**), 6.18-6.16 (m, 2H, C$_{14}$**H**, C$_{15}$**H**), 5.38 (t, $J$ = 7.2 Hz, 1H, C$_7$**H**), 3.73 (s, 3H, OC**H$_3$**), 3.67 (s, 3H, OC**H$_3$**), 3.27 (dd, $J$ = 16.8, 7.5 Hz, 1H, C$_6$**H$_a$**), 2.92 (dd, $J$ = 16.8, 7.0 Hz, 1H, C$_6$**H$_b$**). |
| $^{13}$C NMR (125.8 MHz, CDCl$_3$, 21 °C): | δ 170.3, 169.8, 120.6, 111.7, 110.6, 102.1, 56.2, 53.3, 52.4, 37.2. |
| FTIR (neat) cm$^{-1}$: | 3654 (w), 3468 (w), 3130 (m), 2954 (s), 1739 (br-s), 1437 (s), 1010 (s), 709 (s). |
| HRMS (ESI) (m/z): | calc'd for C$_{10}$H$_{12}$BrNNaO$_4$, [M+Na]$^+$: 311.9842 found: 313.9847. |
| [α]$_D$$^{22}$: | +65.9 (c 1.06, CHCl$_3$). |
| TLC (25% ethyl acetate in hexanes) R$f$: | 0.42 (CAM, UV). |

## (+)-(R)-Dimethyl 2-(2-bromo-5-carbamoyl-1H-pyrrol-1-yl)succinate (87):

Chlorosulfonyl isocyanate (4.28 mL, 49.0 mmol, 1.05 equiv) was added slowly via syringe to a solution of bromopyrrole (+)-86 (13.6 g, 46.8 mmol, 1 equiv) in acetonitrile (235 mL) at 0 °C. After 1 h, anhydrous powdered sodium phosphate monobasic (28.2 g, 235 mmol, 5.00 equiv) followed by freshly prepared sodium amalgam (5%-Na, 110 g, 239 mmol, 5.11 equiv) were added as solids to the reaction mixture. After 1h, the reaction mixture was diluted with ethyl acetate (800 mL), and silica gel (400 mL) was added to the reaction mixture. The resulting slurry was filtered through a plug of silica gel (diam. 9 cm, ht. 8 cm; eluent: ethyl acetate). The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel: diam. 9 cm, ht. 15 cm; eluent: 50% ethyl acetate in hexanes) to afford (+)-87 (12.7 g, 82%) as white solid. Pyrrole (+)-87 could be stored for greater than a month as a solution frozen in benzene at –8 °C. Exposure of (+)-87 to alcoholic solvents, namely methanol, or base results in rapid lactamization and erosion of enantiomeric excess.

| | |
|---|---|
| $^1$H NMR (500 MHz, CDCl$_3$, 21 °C)[8]: | δ 6.69 (br-d, $J$ = 3.9 Hz, 1H, C$_{15}$H), 6.23 (d, $J$ = 4.1 Hz, 1H, C$_{14}$H), 5.78 (br-s, 2H, N$_9$H$_2$), 5.78 (br-s, 1H, C$_7$H)[9], 3.69 (s, 3H, OCH$_3$), 3.65 (s, 3H, OCH$_3$), 3.59 (br-d, $J$ = 14.4 Hz, 1H, C$_6$H$_a$), 2.89 (br-dd, $J$ = 16.4, 6.3 Hz, 1H, C$_6$H$_b$). |
| $^{13}$C NMR (125.8 MHz, CDCl$_3$, 21 °C)[8]: | δ 171.2, 169.5, 162.5, 125.2, 115.1, 111.7, 111.7[9], 56.8, 53.0, 52.3, 37.3. |
| FTIR (neat) cm$^{-1}$: | 3359 (m), 3191 (m), 2953 (m), 1740 (s), 1660 (m), 1602 (m), 1534 (w), 1438 (s), 1413 (m), 1272 (m), 1011 (m) 751 (m). |
| HRMS (DART) ($m/z$): | calc'd for C$_{11}$H$_{14}$BrN$_2$O$_5$, [M+H]$^+$: 333.0081 found: 333.0074. |
| [α]$_D$$^{22}$: | +74.0 ($c$ 1.25, CHCl$_3$). |
| M.p.: | 45–49 °C. |
| TLC (33% in hexanes in ethyl acetate) R$f$: | 0.44 (CAM, UV). |

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[8] Resonances at 21 °C are broadened due to rotamers.

[9] Resonance is obscured due to line broadening. At higher temperature in toluene-d$_8$ the signals are resolved; however, rotamers persist for $^{13}$C NMR. $^1$H NMR (500 MHz, Toluene-d$_8$, 80 °C) δ 6.30 (br-s, 1H, C$_7$H), 6.27 (dd, $J$ = 4.1, 1.1 Hz, 1H, C$_{15}$H), 6.01 (dd, $J$ = 4.1 0.6 Hz, 1H, C$_{14}$H), 5.40 (br-s, 2H, N$_9$H$_2$), 3.66 (dd, $J$ = 16.5, 6.7 Hz, 1H, C$_6$H$_a$), 3.37 (s, 3H, OCH$_3$), 3.36 (s, 3H, OCH$_3$), 2.86 (dd, $J$ = 16.6, 6.5 Hz, 1H, C$_6$H$_b$). $^{13}$C NMR (125.8 MHz, Toluene-d$_8$, 80 °C; Minor rotamer resonances denoted by *) δ 170.7, 169.2, 162.9, 126.8, 115.1*, 114.9*, 114.8, 114.6*, 112.2*, 112.0*, 111.6, 111.4*, 110.9 (br), 57.1 (br), 52.3, 52.1*, 51.7*, 51.5, 51.3*, 37.9*, 37.7, 37.5*.

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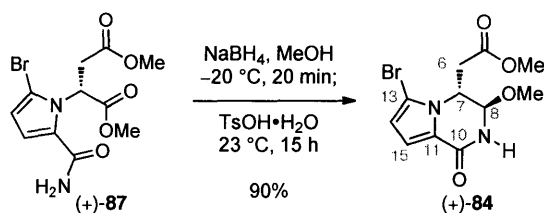
## (+)-Methyl-2-((3R,4R)-6-bromo-3-methoxy-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)-acetate (84):

Anhydrous methanol (377 mL, precooled to –20 °C) was added to a 2L flask charged with (+)-**87** (12.5 g, 37.7 mmol, 1 equiv) at –20 °C followed immediately by sodium borohydride (7.12 g, 188 mmol, 5.00 equiv) as a solid in one portion (Note: Significant gas evolution was observed. The internal temperature remained below –10 °C). After 20 minutes, acetone (41.0 mL, 566 mmol, 15.0 equiv) was added slowly via syringe to the reaction mixture. After 10 min, the reaction mixture was diluted with methanol (1L, –20 °C), and a solution of p-toluenesulfonic acid hydrate (TsOH•H₂O, 43.0 g, 226 mmol, 6.00 equiv) in methanol (100 mL) was added slowly via cannula over a 10 min period, while maintaining an internal temperature of –20 °C. The resulting mixture (pH = 3) was allowed to slowly warm to 23 °C. After 15 h, the reaction mixture was basified with saturated aqueous sodium bicarbonate solution (pH = 7) and was concentrated under reduced pressure to a volume of approximately 200 mL. The resulting mixture was partitioned between dichloromethane (750 mL) and saturated aqueous sodium bicarbonate solution (750 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (4 × 750 mL). The combined organic layers were dried over anhydrous sodium sulfate, and were concentrated under reduced pressure to provide a white solid residue. This solid was purified by flash column chromatography (silica gel: diam. 5 cm, ht. 12 cm; eluent: 25% hexanes in ethyl acetate) to afford the bicycle (+)-**84** (10.8 g, 90%) as white crystalline solid that was found to be 99% ee by chiral HPLC analysis [Chiralpak AD-H; 0.54 mL/min; 21% isopropanol in hexanes; $t_R$(major) = 16.2 min, $t_R$(minor) = 11.6 min]. Crystals of the bicycle (+)-**84** suitable for X-ray diffraction were obtained from methanol. For a thermal ellipsoid representation of the bicycle (+)-**84** see page 123.

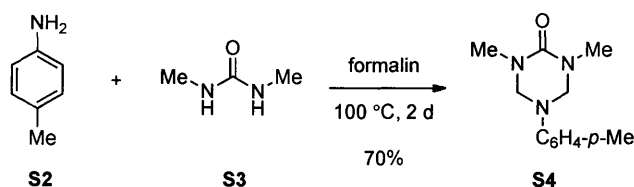| | |
|---|---|
| ¹H NMR (500 MHz, CDCl₃, 21 °C): | δ 7.73 (br-d, J = 4.4 Hz, 1H, N₉**H**), 6.94 (d, J = 4.1 Hz, 1H, C₁₅**H**), 6.29 (d, J = 4.1 Hz, 1H, C₁₄**H**), 4.84 (dd, J = 9.8, 3.5 Hz, 1H, C₇**H**), 4.80 (dd, J = 4.8, 1.5 Hz, 1H, C₈**H**), 3.73 (s, 3H, OC**H₃**), 3.37 (s, 3H, OC**H₃**), 2.75 (dd, J = 17.0, 10.8 Hz, 1H, C₆**H**ₐ), 2.65 (dd, J = 17.0, 3.6 Hz, 1H, C₆**H**ᵦ). |
| ¹³C NMR (125.8 MHz, CDCl₃, 21 °C): | δ 170.2, 159.7, 123.5, 115.3, 113.2, 106.3, 84.7, 55.2, 53.6, 52.5, 36.6. |
| FTIR (neat) cm⁻¹: | 3226 (br-m), 2952 (m), 1736 (s), 1669 (s), 1553 (m), 1423 (s), 1384 (w), 1319 (m), 1088 (m). |
| HRMS (ESI) (m/z): | calc'd for C₁₁H₁₃BrN₂NaO₄, [M+Na]⁺: 317.0131, found: 317.0135. |
| [α]_D²²: | +128.1 (c 0.61, CHCl₃). |
| M.p.: | 156–157 °C. |
| TLC (25% hexanes in ethyl acetate), Rf: | 0.31 (CAM, UV). |
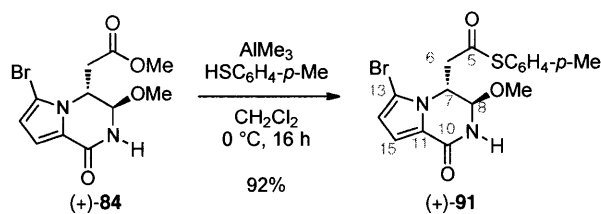
## (+)-S-p-Tolyl-2-((3R,4R)-6-bromo-3-methoxy-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)ethanethioate (91):

Trimethyl aluminum (2 M in toluene, 30.7 mL, 61.5 mmol, 5.00 equiv) was added slowly via syringe to a solution of 4-methylbenzenethiol (7.80 g, 61.5 mmol, 5.00 equiv) in dichloromethane (123 mL) at 0 °C. After 40 min, a pre-cooled solution (0 °C) of bicycle (+)-**84** (3.90 g, 12.3 mmol, 1 equiv) in dichloromethane (90 mL) was added via cannula. After 16 h, the light yellow reaction mixture was diluted with saturated aqueous potassium sodium tartrate solution (360 mL) and saturated aqueous sodium bicarbonate solution (250 mL). After 1h, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 250 mL). The combined organic layers were dried over anhydrous sodium sulfate and were concentrated under reduced pressure to afford an opaque white oil. The residue was purified by flash column chromatography (silica gel: diam. 5 cm, ht. 14 cm; eluent: 50% ethyl acetate in hexanes) to afford thioester (+)-**91** (4.8 g, 92%) as white crystalline solid. Crystals of the thioester (+)-**91** suitable for X-ray diffraction were obtained from isopropanol. For a thermal ellipsoid representation of the thioester (+)-**91** see page 127.

| | |
|---|---|
| $^1$H NMR (500 MHz, CDCl$_3$, 21 °C): | δ 8.01 (br-d, $J$ = 4.6 Hz, 1H, N$_9$**H**), 7.30 (app-d, $J$ = 8.1 Hz, 2H, SAr-$o$-**H**), 7.24 (d, $J$ = 7.9 Hz, 2H, SAr-$m$-**H**), 6.95 (d, $J$ = 4.1 Hz, 1H, C$_{15}$**H**), 6.30 (d, $J$ = 4.1 Hz, 1H, C$_{14}$**H**), 4.89 (app-dd, $J$ = 10.4, 3.5 Hz, 1H, C$_7$**H**), 4.79 (dd, $J$ = 4.8, 1.5 Hz, 1H, C$_8$**H**), 3.33 (s, 3H, OC**H$_3$**), 3.09 (dd, $J$ = 16.6, 10.5 Hz, 1H, C$_6$**H**$_a$), 2.98 (dd, $J$ = 16.6, 3.5 Hz, 1H, C$_6$**H**$_b$), 2.37 (s, 3H, SArC**H$_3$**). |
| $^{13}$C NMR (125.8 MHz, CDCl$_3$, 21 °C): | δ 194.9, 159.9, 140.6, 134.6, 130.5, 123.5, 123.0, 115.4, 113.2, 106.4, 83.6, 55.3, 53.7, 45.1, 21.6. |
| FTIR (neat) cm$^{-1}$: | 3216 (s), 3094 (m), 2931 (s), 2248 (w), 1670 (br-s), 1553 (s), 1423 (s), 1318 (s), 1087 (s), 733 (s). |
| HRMS (DART) ($m/z$): | calc'd for C$_{17}$H$_{18}$BrN$_2$O$_3$S, [M+H]$^+$: 409.0216, found: 409.0212. |
| $[\alpha]_D^{22}$: | +97.8 ($c$ 0.3, CHCl$_3$). |
| M.p.: | 133–135 °C (dec.). |
| TLC (25% hexanes in ethyl acetate), R$f$: | 0.42 (CAM, UV). |

## 1,3-Dimethyl-5-(*p*-tolyl)-1,3,5-triazinan-2-one (S4):

*p*-Toluidine (**S2**, 12.2 g, 113 mmol, 1.00 equiv) was added as a solid to a solution of *N*,*N*'-dimethylurea (**S3**, 10.0 g, 113 mmol, 1 equiv) in formalin (37% wt in water, 18.4 ml, 227 mmol, 2.00 equiv) at 23 °C, and the resulting suspension was heated to 100 °C. After 2 d, the reaction mixture was allowed to cool to 23 °C, and was partitioned between dichloromethane (500 mL) and water (500 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, and were concentrated under reduced pressure. The solid residue was purified by crystallization from hot hexanes to afford triazone **S4** (17.4 g, 70%) as a tan crystalline solid.

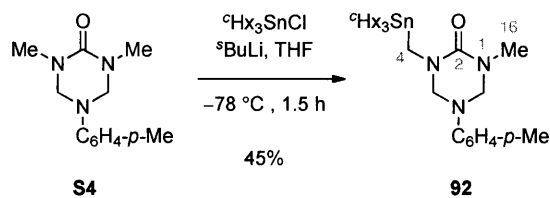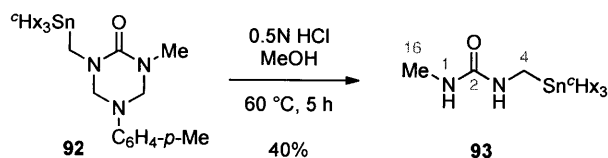| | |
|---|---|
| $^1$H NMR (500 MHz, CDCl$_3$, 21 °C): | δ 7.06 (d, $J$ = 8.5 Hz, 2H, NAr-*o*-**H**), 6.89 (d, $J$ = 8.5 Hz, 2H, NAr-*m*-**H**), 4.60 (s, 4H, NC**H$_2$**N, NC**H$_2$**N), 2.85 (s, 6H, NC**H$_3$**, NC**H$_3$**), 2.27 (s, 3H, NArC**H$_3$**). |
| $^{13}$C NMR (125.8 MHz, CDCl$_3$, 21 °C): | 155.9, 145.6, 132.0, 129.7, 119.2, 67.1, 32.1, 20.4. |
| FTIR (neat) cm$^{-1}$: | 3029 (s), 2872 (s), 1638 (s), 1513 (s), 1451 (m), 1403 (m), 1294 (m), 1197 (m), 1093 (w). |
| HRMS (ESI) (*m/z*): | calc'd for C$_{12}$H$_{17}$N$_3$NaO, [M+Na]$^+$: 242.1264, found: 242.1275. |
| M.p.: | 79–82 °C. |
| TLC (10% ethyl acetate in hexanes), R*f*: | 0.80 (CAM, UV). |

## 1-Methyl-5-(*p*-tolyl)-3-((tricyclohexylstannyl)methyl)-1,3,5-triazinan-2-one (92):

To a solution of triazone **S4** (10.0 g, 46.0 mmol, 1 equiv) in tetrahydrofuran (400 mL) at –78 °C was added *sec*-butyllithium (1.4 M in cyclohexane, 34.5 mL, 48.0 mmol, 1.05 equiv) rapidly via cannula. After 10 min, the resulting bright orange mixture was added via cannula over a 15 min period to a solution of tricyclohexyltin chloride (20.3 g, 50.0 mmol, 1.10 equiv) in tetrahydrofuran (400 mL) at –78 °C. After 1.5 h, saturated aqueous ammonium chloride solution (100 mL) was added via syringe, and the resulting mixture was concentrated under reduced pressure. The residue was partitioned between dichloromethane (800 mL) and water (800 mL). The layers were separated, and the organic layer was washed with brine (800 mL), was dried over anhydrous sodium sulfate, and was concentrated under reduced pressure. The crude residue adsorbed onto silica gel was purified by flash column chromatography (silica gel: diam. 6 cm, ht. 15 cm; eluent: hexanes then 10% ethyl acetate in hexanes) to afford stannyltriazone **92** (12.1 g, 45%) as a white solid.

| | |
|---|---|
| $^1$H NMR (500 MHz, CDCl$_3$, 21 °C): | δ 7.07 (dd, $J$ = 8.7, 0.7 Hz, 2H, NAr-*o*-**H**), 6.89 (d, $J$ = 8.5 Hz, 2H, NAr-*m*-**H**), 4.60 (s, 2H, NC**H**$_2$N), 4.58 (s, 2H, NC**H**$_2$N), 2.85 (s, 3H, NC**H**$_3$), 2.78 (t, $J$ = 12.2 Hz, 2H, NC**H**$_2$Sn), 2.27 (s, 3H, NArC**H**$_3$), 1.82-1.74 (m, 6H, $^c$Hx), 1.65-1.56 (m, 9H, $^c$Hx), 1.52-1.13 (m, 18H, $^c$Hx). |
| $^{13}$C NMR (125.8 MHz, CDCl$_3$, 21 °C): | δ 156.3, 146.1, 132.2, 130.0, 119.5, 69.2, 67.3, 32.7, 32.3, 29.5, 28.7, 27.9, 27.4, 20.8. |
| FTIR (neat) cm$^{-1}$: | 2915 (s), 2844 (s), 1636 (s), 1515 (s), 1444 (s), 1407 (m), 1299 (s), 1201 (m), 991 (m). |
| HRMS (DART) (*m/z*): | calc'd for C$_{30}$H$_{50}$N$_3$OSn, [M+H]$^+$: 588.2987, found: 588.2982. |
| M.p.: | 59–62 °C. |
| TLC (15% ethyl acetate in hexanes), R$f$: | 0.20 (CAM, UV). |

## Reaction Scheme

Reaction of **92** (cHx₃Sn-substituted triazinone with C₆H₄-p-Me) with 0.5N HCl, MeOH at 60 °C, 5 h, 40% to give **93** ($Me-N_1^{16}...N_4-Sn^cHx_3$ urea).

(cHx₃Sn … O … N–Me; 92; C₆H₄-p-Me) →(0.5N HCl, MeOH, 60 °C, 5 h, 40%)→ (Me–N(H)–C(O)–N(H)–CH₂–Sn cHx₃; 93)

## 1-Methyl-3-((tricyclohexylstannyl)methyl)urea (93):

Aqueous hydrochloric acid solution (0.5 N, 2.30 mL, 1.15 mmol, 2.00 equiv) was added via syringe to a solution of stannyltriazone **92** (338 mg, 0.576 mmol, 1 equiv) in methanol (11.5 mL) at 23 °C, and the resulting mixture was heated to 60 °C. After 5 h, the reaction mixture was allowed to cool to 23 °C, and was neutralized with saturated aqueous sodium bicarbonate solution (4 mL). The resulting mixture was concentrated under reduced pressure, and the residue was partitioned between dichloromethane (50 mL) and water (50 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and were concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel: diam. 2.5 cm, ht. 15 cm; eluent: 15% ethyl acetate in dichloromethane) to afford stannylurea **93** (104 mg, 40%) as a white crystalline solid.

| | |
|---|---|
| $^1$H NMR (500 MHz, CDCl₃, 21 °C): | δ 4.63 (br-s, 1H, NH), 4.33 (br-s, 1H, NH), 2.77 (br-d, $J$ = 4.6 Hz, C₁₆H₃), 2.75-2.65 (m, 2H, C₄H₂), 1.85-1.74 (m, 6H, $^c$Hx), 1.70-1.44 (m, 18H, $^c$Hx), 1.36-1.16 (m, 9H, $^c$Hx). |
| $^{13}$C NMR (125.8 MHz, CDCl₃, 21 °C): | δ 160.7, 32.5, 29.3, 27.5, 27.2, 26.9. 22.3. |
| FTIR (neat) cm$^{-1}$: | 3357 (br-m), 2912 (s), 2842 (s), 1628 (s), 1580 (s), 1442 (m), 1279 (m), 1167 (w). |
| HRMS (ESI) ($m/z$): | calc'd for C₂₁H₄₀N₂NaOSn, [M+Na]$^+$: 479.2068, found: 479.2056. |
| M.p.: | 144–148 °C. |

TLC (15% ethyl acetate in dichloromethane), R$f$: 0.25 (CAM, UV).

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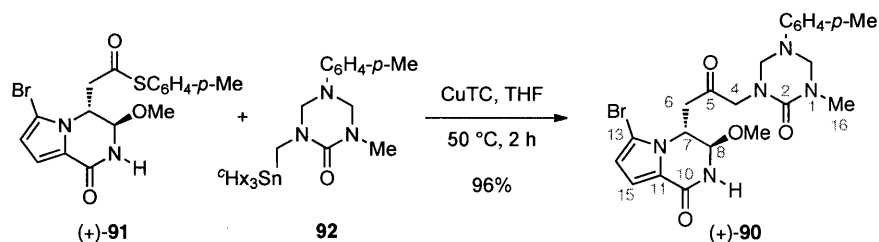
## (+)-(3*R*,4*R*)-6-Bromo-3-methoxy-4-(3-(3-methyl-2-oxo-5-(*p*-tolyl)-1,3,5-triazinan-1-yl)-2-oxopropyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2*H*)-one (90):

A flask was charged with thioester (+)-**91** (5.70 g, 13.9 mmol, 1 equiv), stannyltriazone **92** (9.80 g, 16.8 mmol, 1.20 equiv), and copper thiophene 2-carboxylate (CuTC, 4.00 g, 21.0 mmol 1.50 equiv) at 23 °C and placed under an argon atmosphere. Anhydrous tetrahydrofuran (140 mL) was added via syringe, and the entire reaction mixture was degassed thoroughly by passage of a stream of argon. After the reaction mixture was heated to 50 °C for 2 h, the resulting brown reaction mixture was allowed to cool to 23 °C, was diluted with ethyl acetate (500 mL), and was filtered through a plug of celite with ethyl acetate as eluent (3 × 200 mL). The resulting green filtrate was washed with ~5% aqueous ammonium hydroxide solution (4 × 600 mL), and brine (400 mL). The resulting light yellow organic layer was dried over anhydrous sodium sulfate and was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel: diam. 5 cm, ht. 14 cm; eluent: 5% methanol in ethyl acetate then 10% methanol in ethyl acetate) and was lyophilized from benzene to afford ketone (+)-**90** (6.7 g, 96%) as a light tan solid.

| | |
|---|---|
| $^1$H NMR (500 MHz, CDCl$_3$, 21 °C): | δ 7.04 (dd, $J$ = 8.6, 0.6 Hz, 2H, NAr-*o*-**H**), 6.93 (d, $J$ = 4.0 Hz, 1H, C$_{15}$**H**), 6.89 (d, $J$ = 8.5 Hz, 2H, NAr-*m*-**H**), 6.55 (d, $J$ = 4.6 Hz, 1H, N$_9$**H**), 6.26 (d, $J$ = 4.1 Hz, 1H, C$_{14}$**H**), 4.85 (ddd, $J$ = 11.2, 2.8, 1.4 Hz, 1H, C$_7$**H**), 4.81 (d, $J$ = 11.6 Hz, 1H, NC**H$_2$**N), 4.71 (d, $J$ = 12.0, Hz, 1H, NC**H$_2$**N), 4.66 (dd, $J$ = 11.7, 1.3 Hz, 1H, NC**H$_2$**N), 4.63-4.60 (m, 2H, C$_8$**H**, NC**H$_2$**N), 3.92 (d, $J$ = 17.7 Hz, 1H, C$_4$**H$_a$**), 3.85 (d, $J$ = 17.7 Hz, 1H, C$_4$**H$_b$**) 3.33 (s, 3H, OC**H$_3$**), 2.92 (s, 3H, C$_{16}$**H$_3$**), 2.79 (dd, $J$ = 17.9, 11.2, Hz, 1H, C$_6$**H$_a$**), 2.39 (dd, $J$ = 17.9, 2.9 Hz, 1H, C$_6$**H$_b$**), 2.23 (s, 3H, NArC**H$_3$**). |
| $^{13}$C NMR (125.8 MHz, CDCl$_3$, 21 °C): | δ 204.4, 159.5, 155.8, 145.4, 132.7, 130.1, 123.6, 119.4, 114.7, 112.7, 105.7, 83.4, 67.8, 66.8, 55.6, 55.0, 52.7, 41.1, 32.2, 20.7. |
| FTIR (neat) cm$^{-1}$: | 3248 (m), 2921 (m), 1724, (m), 1667 (s), 1640 (s), 1514 (s), 1422 (s), 1316 (s), 1087 (m). |
| HRMS (ESI) (*m/z*): | calc'd for C$_{22}$H$_{26}$BrN$_5$NaO$_4$, [M+Na]$^+$: 526.1060, found: 526.1063. |
| [α]$_D$$^{22}$: | +81.1 (c 0.62, CHCl$_3$). |
| M.p.: | 101–105 °C. |
| TLC (5% methanol in ethyl acetate), R*f*: | 0.20 (CAM, UV). |

(+)-90 → (+)-O-Me-pre-agelastatin A (82)

0.5N HCl, MeOH, 65 °C, 4 h, 89%

## (+)-O-Methyl-pre-agelastatin A (82):

Aqueous hydrochloric acid solution (0.5 N, 23.8 mL, 11.9 mmol, 2.00 equiv) was added via syringe to a solution of ketone (+)-90 (3.00 g, 5.90 mmol, 1 equiv) in methanol (1.18 L) at 23 °C, and the entire reaction mixture was degassed thoroughly by passage of a stream of argon. After the reaction mixture was heated to 65 °C for 4 h, the light pink reaction mixture was allowed to cool to 23 °C, and was concentrated to approximately 250 mL volume under reduced pressure. The resulting solution was basified to pH = 8 by the addition of a 5% aqueous ammonium hydroxide in methanol solution and the reaction mixture became a clear light orange color. A silica gel (50 mL) slurry in a 1% aqueous ammonium hydroxide in methanol solution (75 mL) was added and the resulting mixture was concentrated to dryness under reduced pressure. The crude residue adsorbed onto silica gel was purified by flash column chromatography (silica gel: diam. 5 cm, ht. 15 cm; eluent: 9% methanol, 1% ammonium hydroxide in chloroform to 13.5% methanol, 1.5% ammonium hydroxide in chloroform) to afford (+)-O-methyl-pre-agelastatin A (82, 1.87 g, 89%) as a light tan solid that was found to be 99% ee by chiral HPLC analysis [Chiralcel OD-H; 0.8 mL/min; 35% isopropanol in hexanes; $t_R$(major) = 14.9 min, $t_R$(minor) = 12.1 min]. Crystals of (+)-O-methyl-pre-agelastatin A (82) suitable for X-ray diffraction were obtained from methanol. For a thermal ellipsoid representation of (+)-O-methyl-pre-agelastatin A (82) see page 132. (+)-O-Methyl-pre-agelastatin A (82) is best used immediately in the following step; however, it could be stored as a dry solid at –8 °C under an argon atmosphere, or as a suspension frozen in benzene at –8 °C under an argon atmosphere for greater than a month. (+)-O-Methyl-pre-agelastatin A (82) is sparingly soluble in organic solvents, methanol, and water.

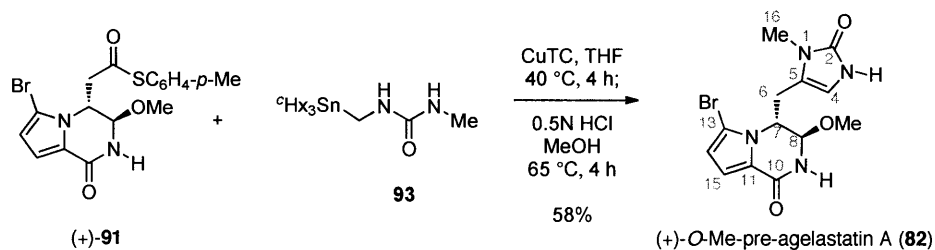| | |
|---|---|
| $^1$H NMR (500 MHz, CD$_3$OD, 21 °C): | δ 6.90 (dd, $J$ = 4.1, 0.4 Hz, 1H, C$_{15}$H), 6.27 (d, $J$ = 4.1 Hz, 1H, C$_{14}$H), 5.97 (t, $J$ = 0.7 Hz, 1H, C$_4$H), 4.76 (d, $J$ = 1.6 Hz, 1H, C$_8$H), 4.54 (ddd, $J$ = 8.4, 6.1, 1.5 Hz, 1H, C$_7$H), 3.35 (s, 3H, OCH$_3$), 3.14 (s, 3H, C$_{16}$H$_3$), 2.95 (ddd, $J$ = 15.4, 6.0, 0.8 Hz, 1H, C$_6$H$_a$), 2.78 (ddd, $J$ = 15.4, 8.5, 0.8 Hz, 1H, C$_6$H$_b$). |
| $^{13}$C NMR (125.8 MHz, CD$_3$OD, 21 °C): | δ 161.2, 156.1, 124.5, 120.2, 116.1, 113.5, 108.8, 108.5, 84.9, 58.0, 55.2, 29.5, 27.7. |
| FTIR (neat) cm$^{-1}$: | 3227 (br-m), 2936 (w), 1666 (s), 1552 (m), 1460 (w), 1421 (m), 1386 (w), 1319 (m), 1085 (m). |
| HRMS (ESI) (m/z): | calcd for C$_{13}$H$_{15}$BrN$_4$NaO$_3$, [M+Na]$^+$: 377.0220, found: 377.0221. |
| $[\alpha]_D^{22}$: | +248.7 (c 0.032, methanol). |
| M.p.: | 157-161 °C (dec.). |

TLC (18% methanol, 2% ammonium hydroxide in chloroform), $R_f$: 0.40 (CAM, UV).

## Direct synthesis of (+)-*O*-methyl-pre-agelastatin A (19):

Anhydrous tetrahydrofuran (1 mL) was added via syringe to a flask charged with (+)-**91** (20.0 mg, 49.0 μmol, 1 equiv), urea **93** (67.0 mg, 147 μmol, 3.00 equiv), and copper thiophene 2-carboxylate (CuTC, 23.3 mg, 123 μmol, 2.50 equiv) at 23 °C and under an argon atmosphere. The entire reaction mixture was degassed thoroughly by passage of a stream of argon, and the mixture was heated to 40 °C. After 4 h, the reaction mixture was allowed to cool to 23 °C, was diluted with methanol (7 mL), and was filtered through a plug of celite with methanol washings (3 × 1 mL). Aqueous hydrochloric acid solution (0.5 N, 196 μL, 98.0 μmol, 2.00 equiv) was added to the filtrate, and the resulting mixture was heated to 65 °C. After 4 h, the reaction mixture was allowed to cool to 23 °C and was basified to pH = 8 by the addition of a 5% aqueous ammonium hydroxide in methanol solution. The resulting mixture was concentrated under reduced pressure, and the crude residue adsorbed onto silica gel was purified by flash column chromatography (silica gel: diam. 1.5 cm, ht. 10 cm; eluent: 10% methanol in dichloromethane to 15% methanol in dichloromethane) to afford (+)-*O*-methyl-pre-agelastatin A (**82**, 10.0 mg, 58%) as a tan solid that was found to be 99% ee by chiral HPLC analysis [Chiralcel OD-H; 0.8 mL/min; 35% isopropanol in hexanes; $t_R$(major) = 14.9 min, $t_R$(minor) = 12.1 min]. See page 108 for full characterization data.

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(+)-O-Me-pre-agelastatin A (**82**)  (−)-agelastatin A (**1**)  (−)-O-Me-di-*epi*-agelastatin A (**96**)

49%  22%

MeSO₃H, H₂O
100 °C, 15 h;

MeSO₃H,
MeOH
23 °C, 5 min

## (−)-Agelastatin A (1) and (−)-O-methyl-di-*epi*-agelastatin A (96):

A solution of methanesulfonic acid (10.9 mL, 168 mmol, 20.0 equiv) in water (100 mL) was added slowly via syringe to a solution of (+)-O-methyl-pre-agelastatin A (**82**, 2.97 g, 8.39 mmol, 1 equiv) in water (1.68 L) at 23 °C. The entire reaction mixture was degassed thoroughly by passage of a stream of argon, and the mixture was heated to 100 °C. After 15 h, the reaction mixture was allowed to cool to 23 °C and was basified to pH = 8 by addition of 5% aqueous ammonium hydroxide solution. The resulting mixture was concentrated under reduced pressure. The crude residue was dissolved in methanol (839 mL) and the resulting mixture was acidified to pH = 2 by the addition of a solution of 5% methanesulfonic acid in methanol (20 mL). After 5 min, the reaction mixture was basified to pH = 8 by addition of by addition of 5% aqueous ammonium hydroxide solution. The resulting mixture was concentrated under reduced pressure, and the crude residue adsorbed onto silica gel was purified by flash column chromatography (silica gel: diam. 7 cm, ht. 14 cm; eluent: 9% methanol, 1.0% ammonium hydroxide in chloroform to 13.5% methanol, 1.5% ammonium hydroxide in chloroform) to afford (−)-agelastatin A (**1**, 1.40 g, 49%) as a tan solid that was found to be 99% ee by chiral HPLC analysis [Chiralpak AD-H; 0.53 mL/min; 10% isopropanol in hexanes; $t_R$(major) = 40.0 min, $t_R$(minor) = 24.5 min]. (−)-O-Methyl-di-*epi*-agelastatin A (**96**, 668 mg, 22%) was also isolated as light tan solid. (−)-Agelastatin A (**1**) is sparingly soluble in organic solvents, methanol, and water. Crystals of (−)-agelastatin A (**1**) suitable for X-ray diffraction were obtained from methanol. For a thermal ellipsoid representation of (−)-agelastatin A (**1**) see page 137.

### (−)-agelastatin A (1):

| | |
|---|---|
| ¹H NMR (500 MHz, CD₃OD, 21 °C): | δ 6.92 (d, $J$ = 4.0 Hz, 1H, C₁₅**H**), 6.33 (d, $J$ = 4.1 Hz, 1H, C₁₄**H**), 4.60 (app-dt, $J$ = 11.9, 6.0 Hz, 1H, C₇**H**), 4.09 (d, $J$ = 5.4 Hz, 1H, C₈**H**), 3.88 (s, 1H, C₄**H**), 2.81 (s, 3H, C₁₆**H₃**), 2.65 (dd, $J$ = 13.1, 6.3 Hz, 1H, C₆**H**), 2.10 (app-t, $J$ = 12.7 Hz, 1H, C₆**H**). |
| ¹³C NMR (125.8 MHz, CD₃OD, 21 °C): | δ 161.6, 161.2, 124.3, 116.2, 113.9, 107.4, 95.8, 67.5, 62.3, 54.5, 40.1, 24.4. |
| FTIR (neat) cm⁻¹: | 3269 (m), 2921 (w), 1651 (s), 1552 (w), 1423 (m), 1378 (w), 1090 (w), 746 (w). |
| HRMS (ESI) (*m/z*): | calc'd for C₁₂H₁₃BrN₄NaO₃, [M+Na]⁺: 363.0063, found: 363.0073. |
| $[\alpha]_D^{22}$: | −87.6 (c 0.10, methanol).[10] |

[10] Optical rotations from naturally occuring samples of (−)-agelastatin A (**1**). $[\alpha]_D$ = −59.3 (c 0.13, methanol), Hong, T. W.; Jímenez, D. R.; Molinski, T. F. *J. Nat. Prod.* **1998**, *61*, 158–161. $[\alpha]_D^{26}$ = −88.9 (c 0.09, chloroform), Pettit, G. R.; Ducki, S.; Herald, D. L.; Doubek, D. L.; Schmidt, J. M.; Chapuis, J.-C. *Oncol. Res.* **2005**, *15*, 11-20. $[\alpha]_D^{25}$ = −58.5 (c 0.21, methanol), Tilvi, S.; Moriou, C.; Martin, M.-T.; Gallard, J.-F.; Sorres, J.; Patel, K.; Petek, S.; Debitus, C.; Ermolenko, L.; Al-Mourabit, A. *J. Nat. Prod.* Article ASAP,

M.p.: 213–215 °C (dec.).

TLC (18% methanol, 2% ammonium hydroxide in chloroform), R*f*: 0.34 (CAM, UV).

## (–)-*O*-methyl-di-*epi*-agelastatin A (96):

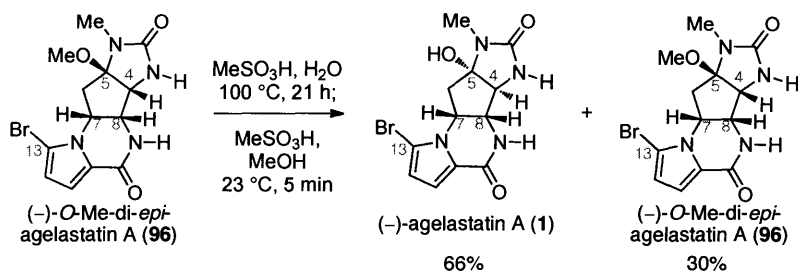| | |
|---|---|
| $^1$H NMR (500 MHz, CD$_3$OD, 21 °C): | δ 6.90 (d, $J$ = 4.1 Hz, 1H, C$_{15}$**H**), 6.33 (d, $J$ = 4.1 Hz, 1H, C$_{14}$**H**), 4.95 (ddd, $J$ = 10.4, 7.2, 5.1 Hz, 1H, C$_7$**H**), 4.42 (app-t, $J$ = 5.4 Hz, 1H, C$_8$**H**), 4.22 (d, $J$ = 5.9 Hz, 1H, C$_4$**H**), 3.13 (s, 3H, OC**H$_3$**), 2.69 (s, 3H, NC**H$_3$**), 2.53 (dd, $J$ = 13.4, 7.1 Hz, 1H, C$_6$**H**), 2.32 (dd, $J$ = 13.5 10.5 Hz, 1H, C$_6$**H**). |
| $^{13}$C NMR (125.8 MHz, CD$_3$OD, 21 °C): | δ 162.4, 161.6, 124.9, 116.3, 114.3, 107.2, 100.1, 59.3, 58.6, 55.1, 49.9, 42.2, 24.9. |
| FTIR (neat) cm$^{-1}$: | 3374 (m), 2951 (w), 1703 (s), 1659 (s), 1552 (m), 1424 (m), 1346 (w). |
| HRMS (ESI) (*m/z*): | calc'd for C$_{13}$H$_{15}$BrN$_4$NaO$_3$, [M+Na]$^+$: 377.0220, found: 377.0220. |
| [α]$_D$$^{22}$: | –70.0 (c 0.042, methanol). |
| M.p.: | 205–208 °C. |

TLC (18% methanol, 2% ammonium hydroxide in chloroform), R*f*: 0.60 (CAM, UV).

(−)-O-Me-di-epi-
agelastatin A (96)

MeSO$_3$H, H$_2$O
100 °C, 21 h;

MeSO$_3$H,
MeOH
23 °C, 5 min

(−)-agelastatin A (1)

66%

+

(−)-O-Me-di-epi-
agelastatin A (96)

30%

## Equilibration of (−)-*O*-methyl-di-*epi*-agelastatin A (96) to (−)-agelastatin A (1):

A solution of methanesulfonic acid (613 μL, 9.44 mmol, 5.00 equiv) in water (10 mL) was added slowly via syringe to a solution of (−)-*O*-methyl-di-*epi*-agelastatin A (**96**, 668 mg, 1.89 mmol, 1 equiv) in water (378 mL) at 23 °C. The entire reaction mixture was degassed thoroughly by passage of a stream of argon and was heated to 100 °C. After 21 h, the reaction mixture was allowed to cool to 23 °C and was basified to pH = 8 by addition of 5% aqueous ammonium hydroxide solution. The resulting mixture was concentrated under reduced pressure. The crude residue was dissolved in methanol (378 mL) and the resulting mixture was acidified to pH = 2 by the addition of a solution of 5% methanesulfonic acid in methanol (20 mL). After 5 min, the reaction mixture was basified to pH = 8 by addition of by addition of 5% aqueous ammonium hydroxide solution. The resulting mixture was concentrated under reduced pressure, and the crude residue adsorbed onto silica gel was purified by flash column chromatography (silica gel: diam. 4 cm, ht. 14 cm; eluent: 9% methanol, 1.0% ammonium hydroxide in chloroform to 13.5% methanol, 1.5% ammonium hydroxide in chloroform) to afford (−)-agelastatin A (**1**, 421 mg, 66%) as a tan solid. (−)-*O*-Methyl-di-*epi*-agelastatin A (**96**, 200 mg, 30%) was also isolated as a light tan solid. See pages 110 and 111 for full characterization data.

(–)-agelastatin A (**1**) → NBS, DTBMP, THF, H$_2$O, 0 °C, 3 h, 84% → (–)-agelastatin B (**2**)
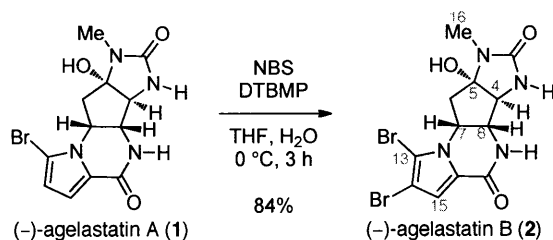
## (–)-Agelastatin B (2):

$N$-Bromosuccinimide (NBS, 5.0 mg, 28 μmol, 1.1 equiv) was added as a solid in one portion to a solution of (–)-agelastatin A (**1**, 9.1 mg, 27 μmol, 1 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 8.3 mg, 41 μmol, 1.5 equiv) in water (500 μL) and tetrahydrofuran (1.00 mL) at 0 °C. After 2 h, a mixture of saturated aqueous sodium thiosulfate solution and saturated aqueous sodium bicarbonate solution (1:1, 100 μL,) was added, and the resulting mixture was purified directly by flash column chromatography (silica gel: diam. 1.5 cm, ht. 9 cm; eluent: 9% methanol, 1.0% ammonium hydroxide in chloroform to 13.5% methanol, 1.3% ammonium hydroxide in chloroform) to afford (–)-agelastatin B (**2**, 9.4 mg, 84%) as a white crystalline solid that was found to be 99% ee by chiral HPLC analysis [Chiralpak AD-H; 0.53 mL/min; 10% isopropanol in hexanes; $t_R$(major) = 27.7 min, $t_R$(minor) = 21.1 min]. (–)-Agelastatin B (**2**) is sparingly soluble in organic solvents, methanol, and water.

| | |
|---|---|
| $^1$H NMR (500 MHz, CD$_3$OD, 21 °C): | δ 6.97 (s, 1H, C$_{15}$**H**), 4.60 (app-dt, $J$ = 12.0, 6.0 Hz, 1H, C$_7$**H**), 4.11 (d, $J$ = 5.4 Hz, 1H, C$_8$**H**), 3.88 (s, 1H, C$_4$**H**), 2.81 (s, 3H, C$_{16}$**H**$_3$), 2.68 (dd, $J$ = 13.1, 6.5 Hz, 1H, C$_6$**H**$_a$), 2.12 (app-t, $J$ = 12.6 Hz, 1H, C$_6$**H**$_b$). |
| $^{13}$C NMR (125.8 MHz, CD$_3$OD, 21 °C): | δ 161.5, 160.2, 124.9, 117.1, 108.9, 101.8, 95.7, 67.5, 62.2, 55.5, 40.0, 24.4. |
| FTIR (neat) cm$^{-1}$: | 3219 (m), 2919 (m), 1639 (s), 1548 (m), 1497 (m), 1403 (m), 1360 (m). |
| HRMS (ESI) (*m/z*): | calc'd for C$_{12}$H$_{13}$Br$_2$N$_4$O$_3$, [M+H]$^+$: 418.9349, found: 418.9343. |
| $[\alpha]_D^{22}$: | –60.6 (c 0.018, methanol).[11] |
| M.p.: | 211–214 °C (dec.). |

TLC (18% methanol, 2% ammonium hydroxide in chloroform), R*f*: 0.25 (CAM, UV).

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[11] $[\alpha]_D^{20}$ = –60.3 (c 0.50, methanol), Feldman, K. S.; Saunders, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 9060-9061.

(-)-O-Me-di-*epi*-agelastatin A (**96**) → (-)-dehydro-agelastatin A (**97**)

Pyridine
115 °C, 24 h
99%
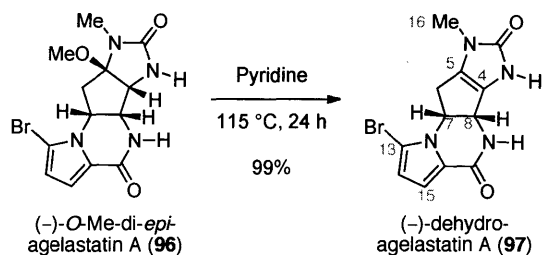
## (–)-Dehydroagelastatin A (97):[12]

A solution of (–)-*O*-methyl-di-*epi*-agelastatin A (**96**, 11.6 mg, 32.8 μmol, 1 equiv) in pyridine (3.28 mL) sealed under an argon atmosphere was heated to 115 °C. After 24 h, the resulting mixture was allowed to cool to 23 °C, and was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel: diam. 1.5 cm, ht. 8 cm; eluent: 9% methanol, 1% ammonium hydroxide in chloroform) to afford (–)-dehydroagelastatin A (**97**, 10.9 mg, 99%) as a light tan solid that was found to be 99% ee by chiral HPLC analysis [Chiralcel OD-H; 0.8 mL/min; 35% isopropanol in hexanes; $t_R$(major) = 53.8 min, $t_R$(minor) = 62.8 min]. (–)-dehydroagelastatin A (**97**) is sparingly soluble in organic solvents, methanol, and water.

| | |
|---|---|
| $^1$H NMR (500 MHz, CD$_3$OD, 21 °C): | δ 6.91 (d, $J$ = 4.0 Hz, 1H, C$_{15}$**H**), 6.39 (d, $J$ = 4.1 Hz, 1H, C$_{14}$**H**), 5.34 (app-q, $J$ = 7.1 Hz, 1H, C$_7$**H**), 5.10 (dd, $J$ = 6.7, 1.6 Hz, 1H, C$_8$**H**), 3.48 (dd, $J$ = 14.4, 7.4 Hz, 1H, C$_6$**H**$_a$), 3.22 (s, 3H, C$_{16}$**H**$_3$), 2.63 (ddd, $J$ = 14.4, 7.2, 1.8 Hz, 1H, C$_6$**H**$_b$). |
| $^{13}$C NMR (125.8 MHz, CD$_3$OD, 21 °C): | δ 160.0, 158.5, 127.5, 124.0, 120.3, 116.0, 114.2, 107.2, 57.1, 53.1, 32.4, 29.1. |
| FTIR (neat) cm$^{-1}$: | 3209 (br-m), 2924 (w), 1691 (s), 1657 (s), 1555 (m), 1427 (m), 1375 (w), 1323 (w). |
| HRMS (ESI) (*m/z*): | calc'd for C$_{12}$H$_{12}$BrN$_4$O$_2$, [M+H]$^+$: 323.0138, found: 323.0144. |
| $[\alpha]_D^{22}$: | –765.9 (c 0.07, methanol). |
| M.p.: | 219-222 °C (dec.). |

TLC (18% methanol, 2% ammonium hydroxide in chloroform), R$f$: 0.30 (CAM, UV).

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[12] For a previous report of the synthesis of (–)-dehydroagelastatin A (**97**) see: D'Ambrosio, M.; Guerriero, A.; Ripamonti, M.; Debitus, C.; Waikedre, J.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 727-735.

(–)-agelastatin A (1) → (–)-dehydro-agelastatin A (97)

MsCl
Et$_3$N, Pyr.

0 °C, 15 h

53%
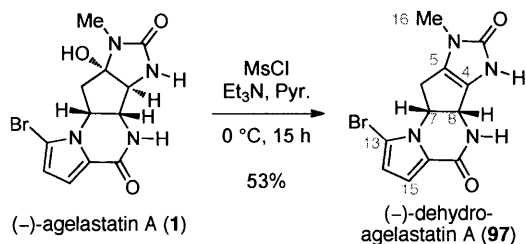
## Alternate synthesis of (–)-dehydroagelastatin A (97):

Methanesulfonyl chloride (MsCl, 45.5 μL, 588 μmol, 1.00 equiv) was added to a solution of (–)-agelastatin A (1, 200 mg, 588 μmol, 1 equiv) and triethylamine (164 μL, 1.18 mmol, 2.00 equiv) in pyridine (2.94 mL) at 0 °C under an argon atmosphere. After 15 h, the dark orange reaction mixture was purified directly by flash column chromatography (silica gel: diam. 2.5 cm, ht. 10 cm; eluent: 9% methanol, 1% ammonium hydroxide in chloroform to 13.5% methanol, 1.5% ammonium hydroxide in chloroform) to afford (–)-dehydroagelastatin A (97, 100 mg, 53%) as a light tan solid that was found to be 99% ee by chiral HPLC analysis [Chiralcel OD-H; 0.8 mL/min; 35% isopropanol in hexanes; $t_R$(major) = 53.8 min, $t_R$(minor) = 62.8 min]. See page 114 for full characterization data. (–)-Agelastatin A (1, 80 mg, 40%) was also recovered from the reaction mixture.

115

(-)-dehydro-
agelastatin A (97)

DMDO
acetone

H₂O
0 °C, 30 min

98 %

(-)-di-*epi*-agelastatin C (98)
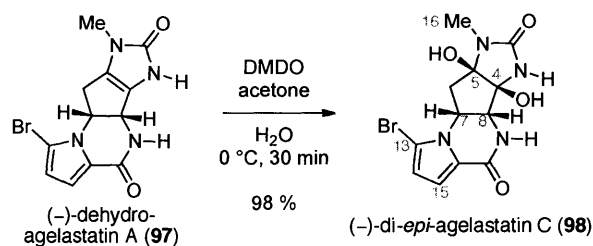
## (-)-Di-*epi*-agelastatin C (98):

Freshly prepared dimethyldioxirane (DMDO, 0.108 M in acetone, 2.16 mL, 233 μmol, 1.00 equiv) was added via syringe to a solution of (–)-dehydroagelastatin A (97, 75.0 mg, 233 μmol, 1 equiv) in acetone (2.3 mL) and water (2.3 mL) at 0 °C. After 30 min, the reaction mixture was concentrated under reduced pressure to afford (–)-di-*epi*-agelastatin C (98, 81.5 mg, 98%) as a white solid. (–)-di-*epi*-agelastatin C (98) is sparingly soluble in organic, methanol, and water, and is sensitive to base.

| | |
|---|---|
| ¹H NMR (500 MHz, CD₃OD, 21 °C): | δ 6.89 (d, $J$ = 4.1 Hz, 1H, C₁₅**H**), 6.33 (d, $J$ = 4.0 Hz, 1H, C₁₄**H**), 5.05-5.00 (m, 1H, C₇**H**), 4.23 (d, $J$ = 5.8 Hz, 1H, C₈**H**), 2.72 (s, 3H, C₁₆**H₃**), 2.56 (ddd, $J$ = 13.6, 6.8, 1.0 Hz, 1H, C₆**H**ₐ), 2.40 (dd, $J$ = 13.7, 10.0 Hz, 1H, C₆**H**ᵦ). |
| ¹³C NMR (125.8 MHz, CD₃OD, 21 °C): | δ 161.2, 159.9, 124.6, 116.3, 114.4, 107.1, 94.0, 92.5, 64.3, 54.2, 42.7, 25.0. |
| FTIR (neat) cm⁻¹: | 3335 (br-s), 2922 (m), 2851 (m), 1691 (s), 1658 (s), 1553 (m), 1424 (m), 1337 (w), 1127 (w). |
| HRMS (ESI) (*m/z*): | calc'd for C₁₂H₁₃BrN₄NaO₄, [M+Na]⁺: 379.0012, found: 379.0024. |
| [α]ᴅ²²: | –89.1 (c 0.011, methanol). |
| M.p.: | 190-194 °C (dec.). |

TLC (18% methanol, 2% ammonium hydroxide in chloroform), R*f*: 0.21 (CAM, UV).

(–)-di-*epi*-agelastatin C (**98**)                    (–)-agelastatin C (**3**)
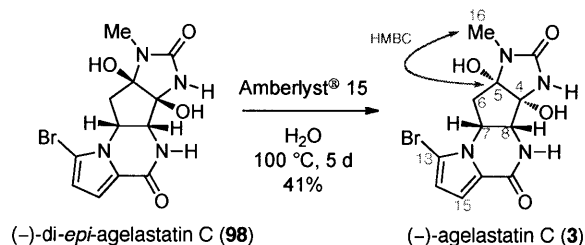
## (–)-Agelastatin C (3):

Amberlyst® 15 (400 mg) was added to a solution of (–)-di-*epi*-agelastatin C (**98**, 10.0 mg, 28.0 μmol, 1 equiv) in water (14 mL) at 23 °C. The entire reaction mixture was degassed thoroughly by passage of a stream of argon and the reaction mixture was heated to 100 °C. After 5 d, the light yellow hot reaction mixture was filtered through a plug of cotton, and the filtered resin beads were washed with hot water (3 × 1 mL). The filtrate was allowed to cool to 23 °C and was concentrated under reduced pressure to approximately 1 mL volume. The resulting mixture was purified directly by semi-preparative HPLC [Grace Vydac semi-preparative HPLC column, C18, monomeric 120Å; 10.0 mL/min; 15% acetonitrile and 0.1% trifluoroacetic acid in water; $t_R$(**98**) = 4.3 min, $t_R$(**3**) = 5.2 min] to afford (–)-agelastatin C (**3**, 4.1 mg, 41%) as a white solid. (–)-Agelastatin C (**3**) is sparingly soluble in organic solvents, methanol, and water, and is sensitive to base. (–)-Di-*epi*-agelastatin C (**98**, 4.2 mg, 42%) was also isolated from the reaction mixture. Treatment of either (–)-di-*epi*-agelastatin C (**31**) or (–)-agelastatin C (**3**) with methanesulfonic acid (10 equiv) in $D_2O$ at 100 °C for 3 d afforded a 1:1 equilibrium mixture of (–)-**3** and (–)-**98** with quantitative deuterium incorporation at the C6-, C14-, and C15-centers as indicated by $^1H$ NMR analysis.

| | |
|---|---|
| $^1H$ NMR (500 MHz, CD$_3$OD, 21 °C): | δ 6.92 (d, $J$ = 4.1 Hz, 1H, C$_{15}$**H**), 6.34 (d, $J$ = 4.1 Hz, 1H, C$_{14}$**H**), 4.57 (ddd, J = 11.9, 6.8, 5.2 Hz, 1H, C$_7$**H**), 4.19 (d, $J$ = 5.2 Hz, 1H, C$_8$**H**), 2.79 (s, 3H, C$_{16}$**H$_3$**), 2.68 (dd, $J$ = 13.3, 6.9 Hz, 1H, C$_6$**H$_a$**), 2.05 (dd, $J$ = 13.3, 11.9 Hz, 1H, C$_6$**H$_b$**). |
| $^{13}C$ NMR (125.8 MHz, CD$_3$OD, 21 °C): | δ 160.4, 159.8, 124.1, 116.3, 114.1, 107.5, 93.9, 90.0, 62.1, 52.1, 41.1, 24.6. |
| FTIR (neat) cm$^{-1}$: | 3311 (br-s), 2921 (w), 1679 (s), 1642 (s), 1554 (m), 1425 (s), 1335 (w), 1273 (w), 1206 (m), 1184 (m), 1129 (m), 742 (w). |
| HRMS (ESI) (*m/z*): | calc'd for C$_{12}$H$_{14}$BrN$_4$O$_4$, [M+H]$^+$: 357.0193, found: 357.0199. |
| $[\alpha]_D{}^{22}$: | –26.9 (c 0.125, methanol).[13] |

TLC (18% methanol, 2% ammonium hydroxide in chloroform), R*f*: 0.21 (CAM, UV).

HMBC correlations (500 MHz, CD$_3$OD, 21 °C) additional data: C2-H16, C4-H6$_a$, C4-H8, C5-H6$_a$, C5-H6$_b$, C5-H8, **C5-H16**, C6-H7, C6-H8, C7-H6$_a$, C7-H6$_b$, C7-H8, C7-H14, C7-H15, C8-H6$_a$, C8-H7, C10-H14, C10-H15, C11-H7, C11-H14, C11-H15, C13-H7, C13-H14, C13-H15, C14-H15, C15-H14. Key correlations are shown in bold.

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[13] $[\alpha]_D$ = –5 (c 0.06, methanol), Hong, T. W.; Jímenez, D. R.; Molinski, T. F. *J. Nat. Prod.* **1998**, *61*, 158–161.

(–)-agelastatin A (1) → Amberlyst® 15, MeOH, 65 °C, 2 h, 96% → (–)-agelastatin E (5)
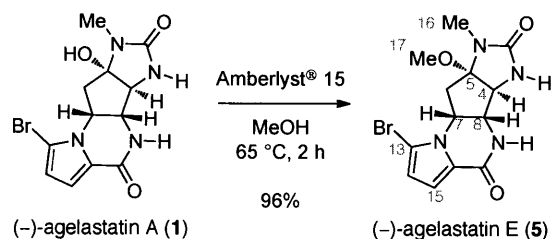
## (–)-Agelastatin E (5):[14]

Amberlyst® 15 (25.0 mg) was added to a solution of (–)-agelastatin A (**1**, 10.0 mg, 29.4 μmol, 1 equiv) in methanol (5.8 mL) at 23 °C, and the resulting mixture was heated to 65 °C. After 2 h, the reaction mixture was filtered through a plug of cotton, and the filtrate was concentrated to afford (–)-agelastatin E (**5**, 10.0 mg, 96%) as a light tan solid. (–)-Agelastatin E (**5**) was sparingly soluble in organic solvents, methanol, and water.

| | |
|---|---|
| $^1$H NMR (500 MHz, CD$_3$OD, 21 °C): | δ 6.91 (d, $J$ = 4.0 Hz, 1H, C$_{15}$**H**), 6.33 (d, $J$ = 4.1 Hz, 1H, C$_{14}$**H**), 4.62 (app-dt, $J$ = 11.9, 6.1 Hz, 1H, C$_7$**H**), 4.12 (d, $J$ = 5.6 Hz, 1H, C$_8$**H**), 4.09 (s, 1H, C$_4$**H**), 3.18 (s, 1H, C$_{17}$**H$_3$**), 2.79 (s, 3H, C$_{16}$**H$_3$**), 2.66 (dd, $J$ = 13.2, 6.5 Hz, 1H, C$_6$**H$_a$**), 2.14 (app-t, $J$ = 12.7 Hz, 1H, C$_6$**H$_b$**). |
| $^{13}$C NMR (125.8 MHz, CD$_3$OD, 21 °C): | δ 161.9, 161.1, 124.2, 116.2, 114.0, 107.5, 100.2, 62.1, 61.2, 53.9, 50.8, 39.3, 24.7. |
| FTIR (neat) cm$^{-1}$: | 3239 (br-m), 2927 (m), 1703 (s), 1659 (s), 1552 (m), 1425 (s), 1377 (w), 1302 (w), 1198 (w), 1103 (m). |
| HRMS (DART) ($m/z$): | calc'd for C$_{13}$H$_{14}$BrN$_4$O$_3$, [M–H]$^-$: 353.0255, found: 353.0254. |
| [α]$_D$$^{22}$: | –63.4 (c 0.054, methanol).[15] |
| M.p.: | 186–190 °C (dec.). |

TLC (18% methanol, 2% ammonium hydroxide in chloroform), R$f$: 0.60 (CAM, UV).

[14] For a previous report of the semi-synthesis of (–)-agelastatin E (**5**) see: D'Ambrosio, M.; Guerriero, A.; Chiasera, G.; Pietra, F. *Helv. Chim. Acta* **1994**, *77*, 1895-1902.

[15] [α]$_D$$^{25}$ = –28 (c 0.09, methanol), Tilvi, S.; Moriou, C.; Martin, M.-T.; Gallard, J.-F.; Sorres, J.; Patel, K.; Petek, S.; Debitus, C.; Ermolenko, L.; Al-Mourabit, A. *J. Nat. Prod.* Article ASAP, Publication Date (Web): February 17, 2010. **DOI:** 10.1021/np900539j.

# Table S1. Comparison of our data for (–)-agelastatin A (1) with literature:
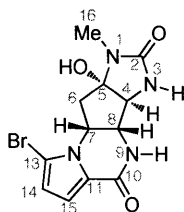


(–)-agelastatin A (**1**)

| Assignment | Pietra's Report[16]<br>$^1$H NMR, 300 MHz, CD$_3$OD | Du Bois' Report[17]<br>$^1$H NMR, 400 MHz, CD$_3$OD | This Work[18]<br>$^1$H NMR, 500 MHz, CD$_3$OD |
|---|---|---|---|
| C4 | 3.89 (br-s, 1H) | 3.87 (br-s, 1H) | 3.88 (s, 1H) |
| C6′ | 2.65 (br-dd, $J$ = 12.9, 6.6 Hz, 1H) | 2.64 (dd, $J$ = 12.8, 6.4 Hz, 1H) | 2.65 (dd, $J$ = 13.1, 6.3 Hz, 1H) |
| C6″ | 2.10 (br-t, $J$ = 12.3, 12.9, Hz, 1H) | 2.09 (dd, $J$ = 12.8, 12.4 Hz, 1H) | 2.10 (app-t, $J$ = 12.7 Hz, 1H) |
| C7 | 4.60 (m, $J$ = 12.3, 6.6, 5.4 Hz, 1H) | 4.59 (dt, $J$ = 12.0, 6.0 Hz, 1H) | 4.60 (app-dt, $J$ = 11.9, 6.0 Hz, 1H) |
| C8 | 4.09 (br-d, $J$ = 5.4 Hz, 1H) | 4.08 (d, $J$ = 5.6 Hz, 1H) | 4.09 (d, $J$ = 5.4 Hz, 1H) |
| C14 | 6.33 (d, $J$ = 4.2 Hz, 1H) | 6.32 (d, $J$ = 4.0 Hz, 1H) | 6.33 (d, $J$ = 4.1 Hz, 1H) |
| C15 | 6.92 (br-d, $J$ = 4.2 Hz, 1H) | 6.90 (d, $J$ = 4.0 Hz, 1H) | 6.92 (d, $J$ = 4.0 Hz, 1H) |
| C16 | 2.81 (s, 3H) | 2.80 (s, 3H) | 2.81 (s, 3H) |

| Assignment | Pietra's Report[16]<br>$^{13}$C NMR, 75 MHz, CD$_3$OD | Du Bois' Report[17]<br>$^{13}$C NMR, 125 MHz, CD$_3$OD | This Work[18]<br>$^{13}$C NMR, 125.8 MHz, CD$_3$OD |
|---|---|---|---|
| C2 | 163.00 | 161.4 | 161.6 |
| C4 | 68.98 | 67.4 | 67.5 |
| C5 | 97.24 | 95.6 | 95.8 |
| C6 | 41.58 | 40.0 | 40.1 |
| C7 | 55.96 | 54.4 | 54.5 |
| C8 | 63.76 | 62.2 | 62.3 |
| C10 | 162.65 | 161.1 | 161.2 |
| C11 | 125.71 | 124.1 | 124.3 |
| C13 | 108.80 | 107.3 | 107.4 |
| C14 | 115.37 | 113.8 | 113.9 |
| C15 | 117.59 | 116.0 | 116.2 |
| C16 | 25.79 | 24.2 | 24.4 |

---

[16] The reference points for the residual protium and carbon resonances of the NMR solvent were not provided. D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Ribes, O.; Pusset, J.; Leroy, S.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1305-1306.
[17] The reference points for the residual protium and carbon resonances of the NMR solvent were not provided. When, P. M.: Du Bois, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 3802-3805.
[18] In this report, the NMR spectra are referenced from the residual protium resonance, CHD$_2$OD: δ 3.31, and carbon resonance, CD$_3$OD: δ 49.15.

# Table S2. Comparison of our data for (–)-Agelastatin B (2) with literature:



(–)-agelastatin B (2)
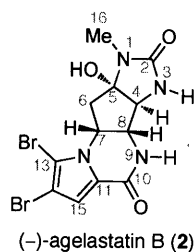
| Assignment | Feldman's Report[19] \n ¹H NMR, 300 MHz, CD₃OD | This Work[18] \n ¹H NMR, 500 MHz, CD₃OD |
|---|---|---|
| C4 | 3.88 (s, 1H) | 3.88 (s, 1H) |
| C6′ | 2.68 (dd, $J$ = 13.1, 6.5 Hz, 1H) | 2.68 (dd, $J$ = 13.1, 6.5 Hz, 1H) |
| C6″ | 2.12 (t, $J$ = 12.6 Hz, 1H) | 2.12 (app-t, $J$ = 12.6 Hz, 1H) |
| C7 | 4.60 (dt, $J$ = 11.8, 6.0 Hz, 1H) | 4.60 (app-dt, $J$ = 12.0, 6.0 Hz, 1H) |
| C8 | 4.11 (d, $J$ = 5.5 Hz, 1H) | 4.11 (d, $J$ = 5.4 Hz, 1H) |
| C15 | 6.96 (s, 1H) | 6.97 (s, 1H) |
| C16 | 2.81 (s, 3H) | 2.81 (s, 3H) |

| Assignment | Feldman's Report[19] \n ¹³C NMR, 75 MHz, CD₃OD | This Work[18] \n ¹³C NMR, 125.8 MHz, CD₃OD |
|---|---|---|
| C2 | 161.4 | 161.5 |
| C4 | 67.6 | 67.5 |
| C5 | 95.6 | 95.7 |
| C6 | 40.0 | 40.0 |
| C7 | 55.5 | 55.5 |
| C8 | 62.1 | 62.2 |
| C10 | 159.6 | 160.2 |
| C11 | 111.0 | 124.9[20] |
| C13 | 108.6 | 108.9 |
| C14 | 101.8 | 101.8 |
| C15 | 117.0 | 117.1 |
| C16 | 24.2 | 24.4 |

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[19] The reference point for the residual protium of the NMR solvent was not provided. The ¹³C NMR spectrum is referenced from the carbon resonance, CD₃OD: δ 49.00. Feldman, K. S.; Saunders, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 9060-9061.
[20] The C11 ¹³C NMR resonance is reassigned to δ 124.9.

# Table S3. Comparison of our data for (–)-Agelastatin C (3) with literature:
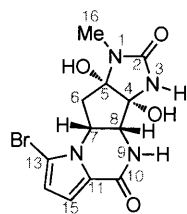


(–)-agelastatin C (3)

| Assignment | Molinski's Report[21] <br> $^1$H NMR, CD$_3$OD | This Work[18] <br> $^1$H NMR, 500 MHz, CD$_3$OD |
|---|---|---|
| C6a | 2.68 (dd, $J$ = 13.3, 6.7 Hz, 1H) | 2.68 (dd, $J$ = 13.3, 6.9 Hz, 1H) |
| C6b | 2.05 (dd, $J$ = 13.3, 11.9 Hz, 1H) | 2.05 (dd, $J$ = 13.3, 11.9 Hz, 1H) |
| C7 | 4.56 (m, $J$ = 11.9, 6.7, 5.1 Hz, 1H) | 4.57 (ddd, $J$ = 11.9, 6.8, 5.2 Hz, 1H) |
| C8 | 4.19 (d, $J$ = 5.1 Hz, 1H) | 4.19 (d, $J$ = 5.2 Hz, 1H) |
| C14 | 6.33 (d, $J$ = 4.1 Hz, 1H) | 6.34 (d, $J$ = 4.1 Hz, 1H) |
| C15 | 6.92 (d, $J$ = 4.1 Hz, 1H) | 6.92 (d, $J$ = 4.1 Hz, 1H) |
| C16 | 2.78 (s, 3H) | 2.79 (s, 3H) |

| Assignment | Molinski's Report[21] <br> $^{13}$C NMR, CD$_3$OD | This Work[18] <br> $^{13}$C NMR, 125.8 MHz, CD$_3$OD |
|---|---|---|
| C2 | 160.26 | 160.4 |
| C4 | 89.85 | 90.0 |
| C5 | 93.78 | 93.9 |
| C6 | 40.96 | 41.1 |
| C7 | 51.97 | 52.1 |
| C8 | 61.91 | 62.1 |
| C10 | 159.61 | 159.8 |
| C11 | 124.00 | 124.1 |
| C13 | 107.29 | 107.5 |
| C14 | 113.90 | 114.1 |
| C15 | 116.11 | 116.3 |
| C16 | 24.47 | 24.6 |

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[21] The reference points for the residual protium and carbon resonances of the NMR solvent and the magnetic field strength were not provided. Hong. T. W.; Jimenez, D. R.; Molinski, T. F. *J. Nat. Prod.* **1998**, *61*, 158-161.

# Table S4. Comparison of our data for (–)-agelastatin E (5) with literature:
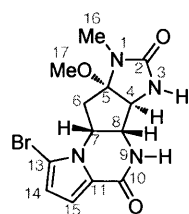


(–)-agelastatin E (5)

| Assignment | Al-Mourabit's Report[22]<br>¹H NMR, 600 MHz, CD₃OD | This Work[18]<br>¹H NMR, 500 MHz, CD₃OD |
|---|---|---|
| C4 | 4.08 (br-s, 1H) | 4.09 (s, 1H) |
| C6′ | 2.66 (dd, $J$ = 12.9, 6.6 Hz, 1H) | 2.66 (dd, $J$ = 13.2, 6.5 Hz, 1H) |
| C6″ | 2.14 (br-t, $J$ = 12.9, Hz, 1H) | 2.14 (app-t, $J$ = 12.7 Hz, 1H) |
| C7 | 4.62 (m, $J$ = 12.6, 6.6 Hz, 1H) | 4.62 (app-dt, $J$ = 11.9, 6.1 Hz, 1H) |
| C8 | 4.11 (d, $J$ = 5.4 Hz, 1H) | 4.12 (d, $J$ = 5.6 Hz, 1H) |
| C14 | 6.32 (d, $J$ = 4.1 Hz, 1H) | 6.33 (d, $J$ = 4.1 Hz, 1H) |
| C15 | 6.91 (d, $J$ = 4.1 Hz, 1H) | 6.91 (d, $J$ = 4.0 Hz, 1H) |
| C16 | 2.78 (s, 3H) | 2.79 (s, 3H) |
| C17 | 3.18 (s, 3H) | 3.18 (s, 3H) |

| Assignment | Al-Mourabit's Report[22]<br>¹³C NMR, 150.8 MHz, CD₃OD | This Work[18]<br>¹³C NMR, 125.8 MHz, CD₃OD |
|---|---|---|
| C2 | 162.2 | 161.9 |
| C4 | 61.2 | 61.2 |
| C5 | 101.0 | 100.2 |
| C6 | 39.3 | 39.3 |
| C7 | 53.9 | 53.9 |
| C8 | 62.2 | 62.1 |
| C10 | 161.2 | 161.1 |
| C11 | 124.2 | 124.2 |
| C13 | 107.4 | 107.5 |
| C14 | 114.0 | 114.0 |
| C15 | 116.2 | 116.2 |
| C16 | 24.7 | 24.7 |
| C17 | 50.8 | 50.8 |

[22] The NMR spectra are referenced from the residual protium resonance, CHD₂OD: δ 3.32, and carbon resonance, CD₃OD: δ 49.0. Tilvi, S.; Moriou, C.; Martin, M.-T.; Gallard, J.-F.; Sorres, J.; Patel, K.; Petek, S.; Debitus, C.; Ermolenko, L.; Al-Mourabit, A. *J. Nat. Prod.* Article ASAP, Publication Date (Web): February 17, 2010. **DOI:** 10.1021/np900539j.

# Crystal Structure of Bicycle (+)-84

**View 1:**
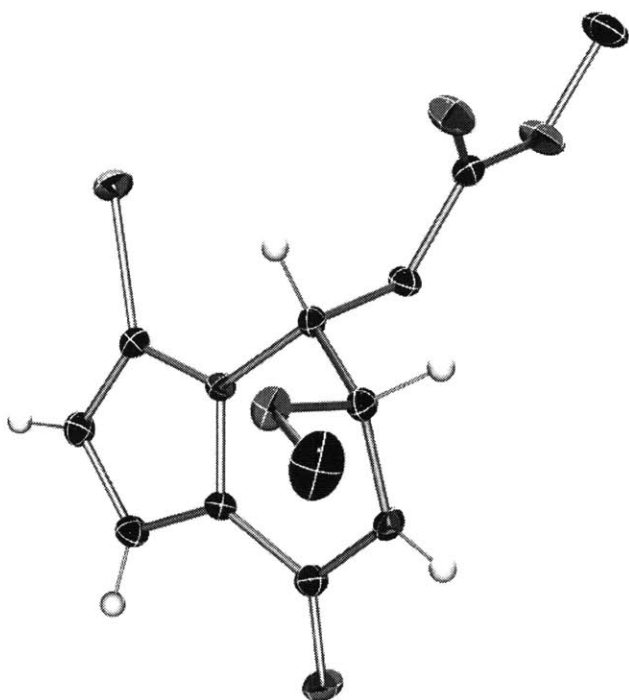


**View 2:**
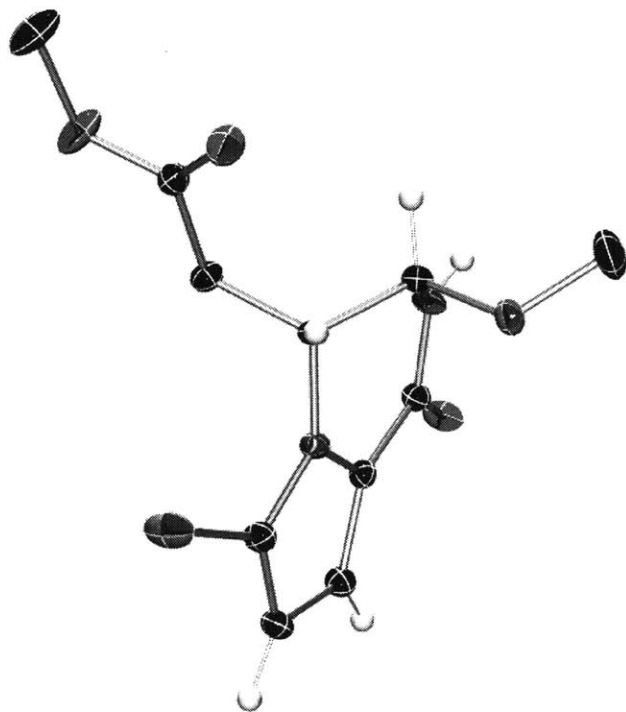


**View 3:**
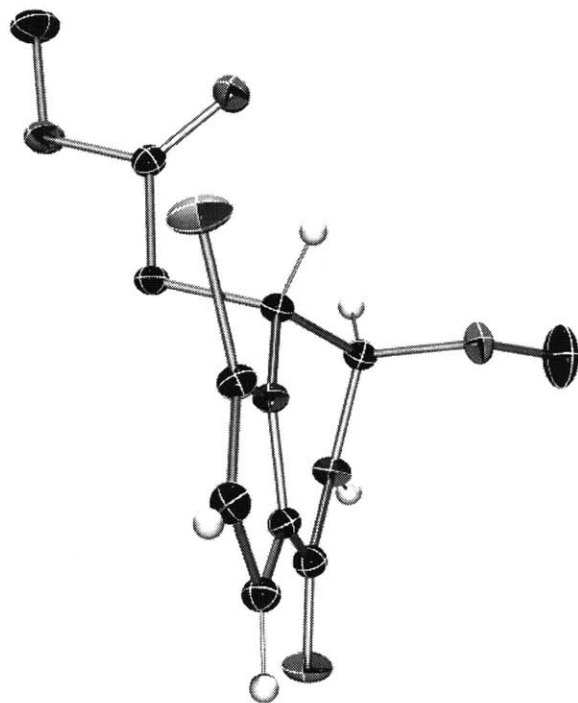
**Table S5.** Crystal data and structure refinement for bicycle (+)-**84.**

| | |
|---|---|
| Identification code | 10011 |
| Empirical formula | C11 H13 Br N2 O4 |
| Formula weight | 317.14 |
| Temperature | 100(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Orthorhombic |
| Space group | P2(1)2(1)2(1) |
| Unit cell dimensions | a = 8.4061(9) Å     a= 90°. |
| | b = 9.2037(10) Å     b= 90°. |
| | c = 17.3522(18) Å     g = 90°. |
| Volume | 1342.5(2) Å³ |
| Z | 4 |
| Density (calculated) | 1.569 Mg/m³ |
| Absorption coefficient | 3.070 mm⁻¹ |
| F(000) | 640 |
| Crystal size | 0.35 x 0.20 x 0.15 mm³ |
| Theta range for data collection | 2.35 to 29.56°. |
| Index ranges | -11<=h<=11, -12<=k<=12, -24<=l<=24 |
| Reflections collected | 35594 |
| Independent reflections | 3764 [R(int) = 0.0403] |
| Completeness to theta = 29.56° | 100.0 % |
| Absorption correction | None |
| Max. and min. transmission | 0.6559 and 0.4129 |
| Refinement method | Full-matrix least-squares on F² |
| Data / restraints / parameters | 3764 / 155 / 168 |
| Goodness-of-fit on F² | 1.030 |
| Final R indices [I>2sigma(I)] | R1 = 0.0224, wR2 = 0.0556 |
| R indices (all data) | R1 = 0.0241, wR2 = 0.0561 |
| Absolute structure parameter | 0.009(6) |
| Largest diff. peak and hole | 0.646 and -0.476 e.Å⁻³ |

**Table S6.** Atomic coordinates ( x 10⁴) and equivalent isotropic displacement parameters (Å²x 10³) for bicycle (+)-**84.** U(eq) is defined as one third of the trace of the orthogonalized U$^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Br(1) | 4530(1) | 12344(1) | 7612(1) | 25(1) |
| O(3) | -588(2) | 11005(1) | 7596(1) | 22(1) |
| O(1) | 3784(1) | 7512(2) | 5030(1) | 21(1) |
| C(11) | 4314(2) | 9440(2) | 5895(1) | 13(1) |
| C(8) | 1060(2) | 10016(2) | 5919(1) | 13(1) |
| C(13) | 4913(2) | 11063(2) | 6798(1) | 15(1) |
| O(2) | 1136(2) | 11236(1) | 5425(1) | 18(1) |
| C(6) | 1639(2) | 9434(2) | 7331(1) | 15(1) |
| N(9) | 1681(2) | 8707(2) | 5561(1) | 15(1) |
| C(7) | 1994(2) | 10421(2) | 6642(1) | 12(1) |
| C(10) | 3270(2) | 8482(2) | 5451(1) | 14(1) |

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| N(12) | 3685(2) | 10368(2) | 6443(1) | 13(1) |
| C(5) | 194(2) | 9954(2) | 7768(1) | 15(1) |
| O(4) | -98(2) | 9125(1) | 8382(1) | 26(1) |
| C(14) | 6335(2) | 10625(2) | 6477(1) | 16(1) |
| C(16) | -1439(3) | 9579(2) | 8850(1) | 30(1) |
| C(15) | 5961(2) | 9584(2) | 5907(1) | 15(1) |
| C(17) | 16(3) | 11172(3) | 4806(1) | 35(1) |

**Table S7.** Bond lengths [Å] and angles [°] for bicycle (+)-**84**.

| | | | |
|---|---|---|---|
| Br(1)-C(13) | 1.8667(16) | O(2)-C(8)-C(7) | 106.33(13) |
| O(3)-C(5) | 1.2064(19) | N(9)-C(8)-C(7) | 111.66(13) |
| O(1)-C(10) | 1.232(2) | N(12)-C(13)-C(14) | 109.66(14) |
| C(11)-N(12) | 1.384(2) | N(12)-C(13)-Br(1) | 120.57(12) |
| C(11)-C(15) | 1.390(2) | C(14)-C(13)-Br(1) | 129.74(12) |
| C(11)-C(10) | 1.463(2) | C(8)-O(2)-C(17) | 113.14(14) |
| C(8)-O(2) | 1.4135(19) | C(5)-C(6)-C(7) | 111.19(13) |
| C(8)-N(9) | 1.452(2) | C(10)-N(9)-C(8) | 122.51(14) |
| C(8)-C(7) | 1.525(2) | N(12)-C(7)-C(8) | 107.35(13) |
| C(13)-N(12) | 1.362(2) | N(12)-C(7)-C(6) | 110.72(13) |
| C(13)-C(14) | 1.379(2) | C(8)-C(7)-C(6) | 113.40(13) |
| O(2)-C(17) | 1.430(2) | O(1)-C(10)-N(9) | 122.42(15) |
| C(6)-C(5) | 1.510(2) | O(1)-C(10)-C(11) | 122.61(15) |
| C(6)-C(7) | 1.532(2) | N(9)-C(10)-C(11) | 114.93(14) |
| N(9)-C(10) | 1.366(2) | C(13)-N(12)-C(11) | 108.15(13) |
| C(7)-N(12) | 1.463(2) | C(13)-N(12)-C(7) | 127.87(14) |
| C(5)-O(4) | 1.3321(19) | C(11)-N(12)-C(7) | 123.63(13) |
| O(4)-C(16) | 1.452(2) | O(3)-C(5)-O(4) | 123.83(16) |
| C(14)-C(15) | 1.413(2) | O(3)-C(5)-C(6) | 124.62(15) |
| | | O(4)-C(5)-C(6) | 111.54(14) |
| N(12)-C(11)-C(15) | 108.14(14) | C(5)-O(4)-C(16) | 115.14(14) |
| N(12)-C(11)-C(10) | 120.30(14) | C(13)-C(14)-C(15) | 106.74(15) |
| C(15)-C(11)-C(10) | 131.49(15) | C(11)-C(15)-C(14) | 107.28(14) |
| O(2)-C(8)-N(9) | 112.54(14) | | |

Symmetry transformations used to generate equivalent atoms:

**Table S8.** Anisotropic displacement parameters (Å$^2$x 10$^3$) for bicycle (+)-**84**. The anisotropic displacement factor exponent takes the form: $-2p^2[ h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12} ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Br(1) | 21(1) | 28(1) | 27(1) | -16(1) | 3(1) | -7(1) |
| O(3) | 21(1) | 25(1) | 21(1) | 4(1) | 4(1) | 8(1) |
| O(1) | 16(1) | 22(1) | 25(1) | -11(1) | 1(1) | 1(1) |
| C(11) | 13(1) | 14(1) | 12(1) | -1(1) | 1(1) | 1(1) |
| C(8) | 12(1) | 13(1) | 15(1) | -1(1) | 0(1) | 0(1) |
| C(13) | 15(1) | 15(1) | 15(1) | -3(1) | 0(1) | -2(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| O(2) | 20(1) | 17(1) | 17(1) | 4(1) | -5(1) | 0(1) |
| C(6) | 15(1) | 14(1) | 16(1) | 0(1) | 3(1) | 2(1) |
| N(9) | 11(1) | 15(1) | 19(1) | -5(1) | -1(1) | -1(1) |
| C(7) | 10(1) | 12(1) | 14(1) | -1(1) | 1(1) | -1(1) |
| C(10) | 14(1) | 15(1) | 14(1) | -1(1) | 0(1) | 0(1) |
| N(12) | 11(1) | 14(1) | 14(1) | -2(1) | 1(1) | 0(1) |
| C(5) | 16(1) | 14(1) | 14(1) | -2(1) | 0(1) | -2(1) |
| O(4) | 33(1) | 20(1) | 24(1) | 6(1) | 16(1) | 8(1) |
| C(14) | 13(1) | 18(1) | 17(1) | -1(1) | -2(1) | -2(1) |
| C(16) | 36(1) | 23(1) | 29(1) | 2(1) | 20(1) | 3(1) |
| C(15) | 13(1) | 17(1) | 16(1) | -1(1) | 1(1) | 1(1) |
| C(17) | 38(1) | 37(1) | 28(1) | 12(1) | -18(1) | -7(1) |

**Table S9.** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($\text{Å}^2$x $10^3$) for bicycle (+)-**84**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(8) | -75 | 9846 | 6065 | 16 |
| H(6A) | 1454 | 8430 | 7148 | 18 |
| H(6B) | 2569 | 9420 | 7681 | 18 |
| H(9) | 1070(20) | 8200(20) | 5292(12) | 18 |
| H(7) | 1718 | 11442 | 6786 | 14 |
| H(14) | 7367 | 10959 | 6613 | 20 |
| H(16A) | -1233 | 10550 | 9060 | 44 |
| H(16B) | -1588 | 8890 | 9275 | 44 |
| H(16C) | -2402 | 9605 | 8532 | 44 |
| H(15) | 6697 | 9077 | 5590 | 18 |
| H(17A) | 261 | 10338 | 4475 | 52 |
| H(17B) | 79 | 12068 | 4503 | 52 |
| H(17C) | -1060 | 11065 | 5016 | 52 |

# Crystal Structure of Thioester (+)-91

**View 1:**
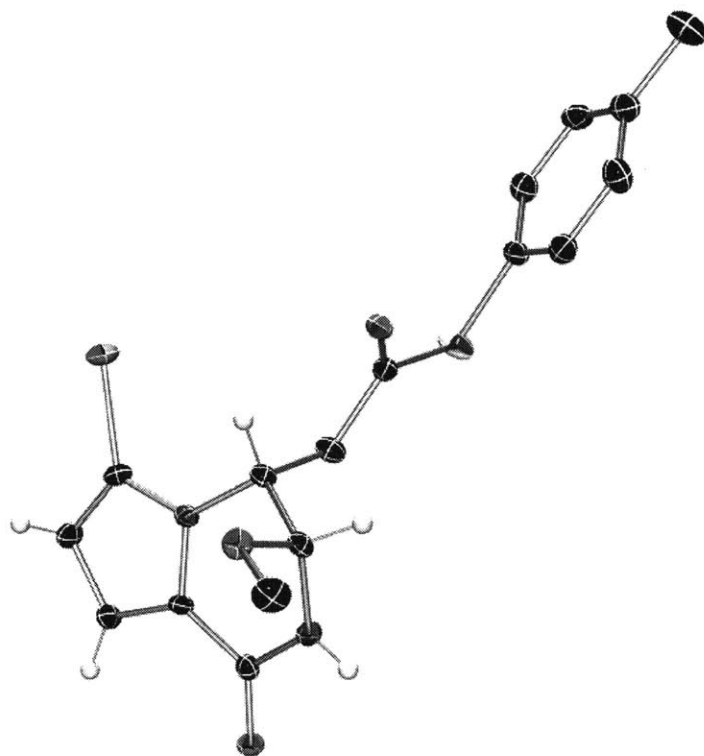


**View 2:**
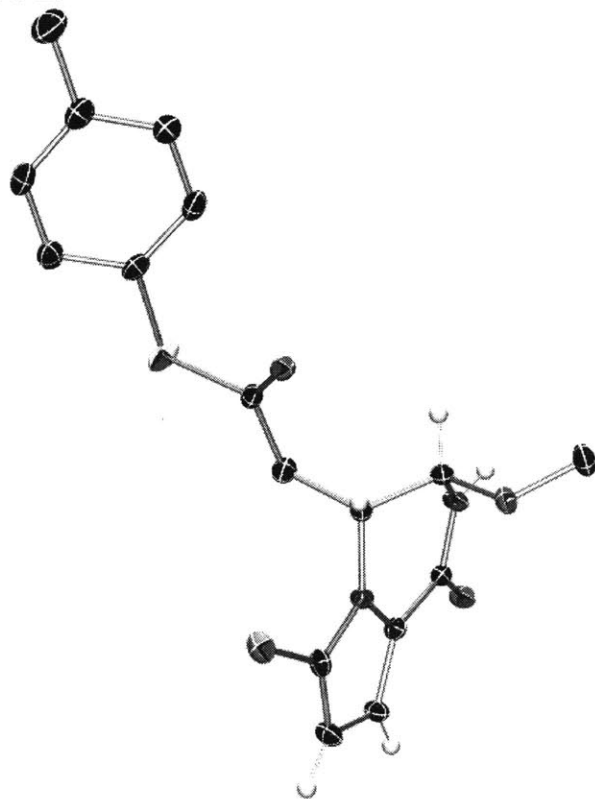


**View 3:**
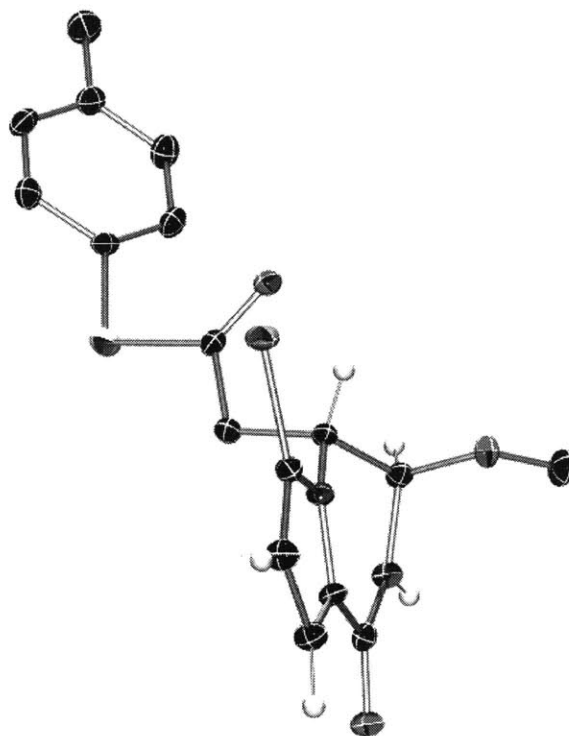
**Table S10.** Crystal data and structure refinement for thioester (+)-**91**.

| | |
|---|---|
| Identification code | 10013 |
| Empirical formula | C17 H17 Br N2 O3 S |
| Formula weight | 409.30 |
| Temperature | 100(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Monoclinic |
| Space group | P2(1) |

Unit cell dimensions
$a = 9.2556(9)$ Å $\quad \alpha = 90°$.
$b = 8.0917(8)$ Å $\quad \beta = 91.799(2)°$.
$c = 11.7613(12)$ Å $\quad \gamma = 90°$.

| | |
|---|---|
| Volume | 880.41(15) Å$^3$ |
| Z | 2 |
| Density (calculated) | 1.544 Mg/m$^3$ |
| Absorption coefficient | 2.470 mm$^{-1}$ |
| F(000) | 416 |
| Crystal size | 0.35 x 0.35 x 0.15 mm$^3$ |
| Theta range for data collection | 1.73 to 29.13°. |
| Index ranges | -12<=h<=12, -10<=k<=11, -16<=l<=16 |
| Reflections collected | 19103 |
| Independent reflections | 4583 [R(int) = 0.0383] |
| Completeness to theta = 29.13° | 99.9 % |
| Absorption correction | None |
| Max. and min. transmission | 0.7082 and 0.4785 |
| Refinement method | Full-matrix least-squares on F$^2$ |
| Data / restraints / parameters | 4583 / 203 / 222 |
| Goodness-of-fit on F$^2$ | 1.008 |
| Final R indices [I>2sigma(I)] | R1 = 0.0251, wR2 = 0.0560 |
| R indices (all data) | R1 = 0.0282, wR2 = 0.0570 |
| Absolute structure parameter | 0.014(5) |
| Largest diff. peak and hole | 0.519 and -0.232 e.Å$^{-3}$ |

**Table S11.** Atomic coordinates ( x 10$^4$) and equivalent isotropic displacement parameters (Å$^2$x 10$^3$) for thioester (+)-**91**. U(eq) is defined as one third of the trace of the orthogonalized U$^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Br(1) | 135(1) | 9493(1) | 3768(1) | 20(1) |
| S(1) | 3998(1) | 4712(1) | 5370(1) | 26(1) |
| O(3) | 1618(1) | 4293(2) | 4073(1) | 17(1) |
| C(5) | 2720(2) | 5054(2) | 4221(2) | 15(1) |
| C(7) | 2125(2) | 6816(2) | 2470(2) | 14(1) |
| C(19) | 2830(2) | 1758(3) | 7926(2) | 22(1) |
| C(17) | 3282(2) | 3004(3) | 6116(2) | 18(1) |
| C(22) | 2870(2) | 1547(3) | 5576(2) | 21(1) |
| C(18) | 3263(2) | 3118(3) | 7301(2) | 21(1) |
| C(6) | 3212(2) | 6452(3) | 3461(2) | 18(1) |
| C(20) | 2403(2) | 297(3) | 7410(2) | 22(1) |

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| | | | | |
|---|---|---|---|---|
| C(23) | 1951(3) | -1187(3) | 8091(2) | 33(1) |
| C(21) | 2420(2) | 214(3) | 6216(2) | 25(1) |
| O(1) | 4980(2) | 8576(2) | 117(1) | 18(1) |
| O(2) | 1148(2) | 5943(2) | 706(1) | 19(1) |
| C(11) | 3137(2) | 9187(2) | 1394(2) | 14(1) |
| N(12) | 2177(2) | 8549(2) | 2165(1) | 14(1) |
| C(13) | 1509(2) | 9849(2) | 2670(2) | 16(1) |
| C(16) | 1114(2) | 4835(3) | -239(2) | 26(1) |
| N(9) | 3697(2) | 6443(2) | 833(2) | 16(1) |
| C(10) | 4007(2) | 8076(2) | 723(2) | 15(1) |
| C(8) | 2425(2) | 5821(2) | 1393(2) | 15(1) |
| C(15) | 3040(2) | 10894(3) | 1419(2) | 17(1) |
| C(14) | 2000(2) | 11308(3) | 2229(2) | 18(1) |

**Table S12.** Bond lengths [Å] and angles [°] for thioester (+)-**91**.

| | | | |
|---|---|---|---|
| Br(1)-C(13) | 1.8635(17) | N(12)-C(7)-C(6) | 110.21(16) |
| S(1)-C(17) | 1.776(2) | C(8)-C(7)-C(6) | 113.14(17) |
| S(1)-C(5) | 1.789(2) | C(20)-C(19)-C(18) | 121.9(2) |
| O(3)-C(5) | 1.199(2) | C(22)-C(17)-C(18) | 120.05(19) |
| C(5)-C(6) | 1.521(3) | C(22)-C(17)-S(1) | 122.48(16) |
| C(7)-N(12) | 1.448(3) | C(18)-C(17)-S(1) | 117.23(17) |
| C(7)-C(8) | 1.533(3) | C(17)-C(22)-C(21) | 119.72(19) |
| C(7)-C(6) | 1.544(3) | C(19)-C(18)-C(17) | 119.3(2) |
| C(19)-C(20) | 1.381(3) | C(5)-C(6)-C(7) | 112.71(16) |
| C(19)-C(18) | 1.390(3) | C(19)-C(20)-C(21) | 117.9(2) |
| C(17)-C(22) | 1.387(3) | C(19)-C(20)-C(23) | 121.89(19) |
| C(17)-C(18) | 1.397(3) | C(21)-C(20)-C(23) | 120.2(2) |
| C(22)-C(21) | 1.387(3) | C(22)-C(21)-C(20) | 121.2(2) |
| C(20)-C(21) | 1.406(3) | C(8)-O(2)-C(16) | 113.47(15) |
| C(20)-C(23) | 1.510(3) | C(15)-C(11)-N(12) | 108.31(16) |
| O(1)-C(10) | 1.235(2) | C(15)-C(11)-C(10) | 131.64(17) |
| O(2)-C(8) | 1.414(2) | N(12)-C(11)-C(10) | 120.04(17) |
| O(2)-C(16) | 1.427(2) | C(13)-N(12)-C(11) | 107.77(15) |
| C(11)-C(15) | 1.385(3) | C(13)-N(12)-C(7) | 128.29(16) |
| C(11)-N(12) | 1.389(2) | C(11)-N(12)-C(7) | 123.21(16) |
| C(11)-C(10) | 1.456(2) | N(12)-C(13)-C(14) | 109.77(16) |
| N(12)-C(13) | 1.365(2) | N(12)-C(13)-Br(1) | 120.69(14) |
| C(13)-C(14) | 1.373(3) | C(14)-C(13)-Br(1) | 129.53(15) |
| N(9)-C(10) | 1.358(3) | C(10)-N(9)-C(8) | 123.69(17) |
| N(9)-C(8) | 1.457(2) | O(1)-C(10)-N(9) | 122.22(18) |
| C(15)-C(14) | 1.416(3) | O(1)-C(10)-C(11) | 122.47(18) |
| | | N(9)-C(10)-C(11) | 115.29(17) |
| C(17)-S(1)-C(5) | 104.18(9) | O(2)-C(8)-N(9) | 112.99(15) |
| O(3)-C(5)-C(6) | 124.42(18) | O(2)-C(8)-C(7) | 105.37(15) |
| O(3)-C(5)-S(1) | 124.72(15) | N(9)-C(8)-C(7) | 111.24(16) |
| C(6)-C(5)-S(1) | 110.86(14) | C(11)-C(15)-C(14) | 107.20(18) |
| N(12)-C(7)-C(8) | 107.21(15) | C(13)-C(14)-C(15) | 106.95(19) |

Symmetry transformations used to generate equivalent atoms:

**Table S13.** Anisotropic displacement parameters ($Å^2$x $10^3$) for thioester (+)-**91**. The anisotropic displacement factor exponent takes the form: $-2p^2[ h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12} ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Br(1) | 18(1) | 24(1) | 19(1) | -3(1) | 8(1) | -4(1) |
| S(1) | 20(1) | 35(1) | 24(1) | 13(1) | -7(1) | -8(1) |
| O(3) | 19(1) | 16(1) | 15(1) | 2(1) | 2(1) | 0(1) |
| C(5) | 17(1) | 18(1) | 12(1) | 1(1) | 1(1) | 2(1) |
| C(7) | 16(1) | 12(1) | 13(1) | 1(1) | 1(1) | -3(1) |
| C(19) | 21(1) | 30(1) | 13(1) | 3(1) | 2(1) | 2(1) |
| C(17) | 12(1) | 23(1) | 17(1) | 8(1) | -1(1) | 1(1) |
| C(22) | 22(1) | 27(1) | 14(1) | 2(1) | -1(1) | 6(1) |
| C(18) | 20(1) | 23(1) | 18(1) | 0(1) | -4(1) | 2(1) |
| C(6) | 19(1) | 18(1) | 17(1) | 2(1) | -1(1) | -6(1) |
| C(20) | 19(1) | 28(1) | 19(1) | 6(1) | -1(1) | 3(1) |
| C(23) | 38(1) | 32(1) | 27(1) | 10(1) | -2(1) | -8(1) |
| C(21) | 31(1) | 21(1) | 21(1) | 1(1) | -4(1) | 2(1) |
| O(1) | 20(1) | 15(1) | 19(1) | 1(1) | 7(1) | -1(1) |
| O(2) | 21(1) | 19(1) | 16(1) | -4(1) | -3(1) | 0(1) |
| C(11) | 16(1) | 14(1) | 12(1) | 2(1) | 3(1) | -1(1) |
| N(12) | 15(1) | 12(1) | 15(1) | 1(1) | 2(1) | -2(1) |
| C(13) | 14(1) | 20(1) | 13(1) | -3(1) | 3(1) | -2(1) |
| C(16) | 33(1) | 26(2) | 18(1) | -7(1) | -2(1) | -3(1) |
| N(9) | 19(1) | 12(1) | 18(1) | -1(1) | 5(1) | 0(1) |
| C(10) | 17(1) | 14(1) | 13(1) | 0(1) | -1(1) | 2(1) |
| C(8) | 19(1) | 12(1) | 15(1) | 2(1) | 1(1) | -2(1) |
| C(15) | 22(1) | 11(1) | 18(1) | 0(1) | 4(1) | 0(1) |
| C(14) | 20(1) | 14(1) | 20(1) | -3(1) | 5(1) | 1(1) |

**Table S14.** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for thioester (+)-**91**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(7) | 1129 | 6547 | 2719 | 17 |
| H(19) | 2827 | 1836 | 8732 | 26 |
| H(22) | 2896 | 1463 | 4772 | 25 |
| H(18) | 3544 | 4114 | 7674 | 25 |
| H(6A) | 4158 | 6159 | 3146 | 22 |
| H(6B) | 3347 | 7464 | 3925 | 22 |
| H(23A) | 2805 | -1851 | 8298 | 49 |
| H(23B) | 1270 | -1858 | 7633 | 49 |
| H(23C) | 1485 | -817 | 8783 | 49 |

| | | | | |
|---|---|---|---|---|
| H(21) | 2118 | -773 | 5842 | 30 |
| H(16A) | 1943 | 5053 | -715 | 38 |
| H(16B) | 216 | 4999 | -688 | 38 |
| H(16C) | 1159 | 3694 | 38 | 38 |
| H(9) | 4120(20) | 5750(30) | 416(17) | 19 |
| H(8) | 2588 | 4638 | 1605 | 18 |
| H(15) | 3573 | 11647 | 975 | 20 |
| H(14) | 1699 | 12389 | 2428 | 21 |

# Crystal Structure of (+)-*O*-Methyl-pre-agelastatin A (82)

**View 1:**
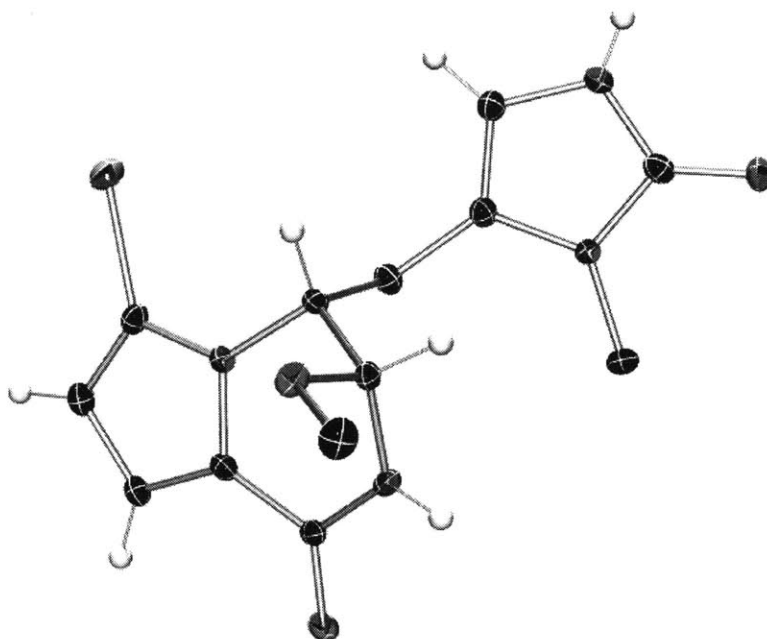


**View 2:**
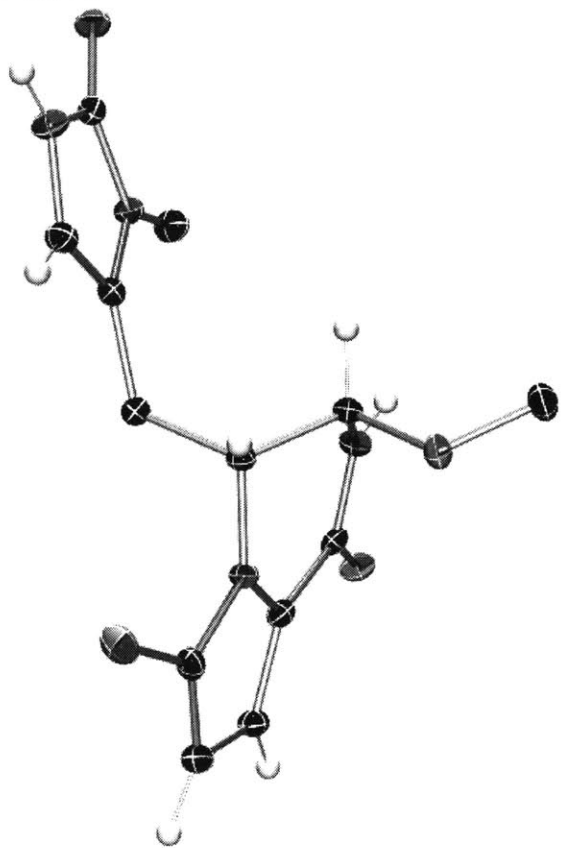


**View 3:**
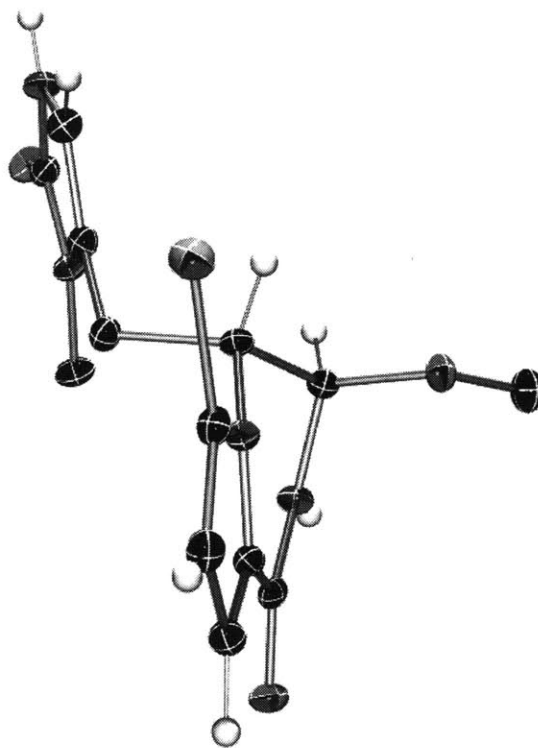
**Table S15.** Crystal data and structure refinement for (+)-*O*-methyl-pre-agelastatin A (**82**).

| | |
|---|---|
| Identification code | 10012 |
| Empirical formula | C14 H19 Br N4 O4 |
| Formula weight | 387.24 |
| Temperature | 100(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Orthorhombic |
| Space group | P2(1)2(1)2(1) |
| Unit cell dimensions | a = 10.3843(11) Å   a= 90°. |
| | b = 10.7461(11) Å   b= 90°. |
| | c = 14.0947(15) Å   g = 90°. |
| Volume | 1572.8(3) Å$^3$ |
| Z | 4 |
| Density (calculated) | 1.635 Mg/m$^3$ |
| Absorption coefficient | 2.640 mm$^{-1}$ |
| F(000) | 792 |
| Crystal size | 0.49 x 0.20 x 0.18 mm$^3$ |
| Theta range for data collection | 2.38 to 29.56°. |
| Index ranges | -14<=h<=14, -14<=k<=14, -19<=l<=19 |
| Reflections collected | 31959 |
| Independent reflections | 4413 [R(int) = 0.0524] |
| Completeness to theta = 29.56° | 100.0 % |
| Absorption correction | None |
| Max. and min. transmission | 0.6479 and 0.3578 |
| Refinement method | Full-matrix least-squares on F$^2$ |
| Data / restraints / parameters | 4413 / 199 / 220 |
| Goodness-of-fit on F$^2$ | 1.016 |
| Final R indices [I>2sigma(I)] | R1 = 0.0276, wR2 = 0.0618 |
| R indices (all data) | R1 = 0.0327, wR2 = 0.0635 |
| Absolute structure parameter | -0.007(6) |
| Largest diff. peak and hole | 0.598 and -0.372 e.Å$^{-3}$ |

**Table S16.** Atomic coordinates ( x 10$^4$) and equivalent isotropic displacement parameters (Å$^2$x 10$^3$) for (+)-*O*-methyl-pre-agelastatin A (**82**). U(eq) is defined as one third of the trace of the orthogonalized U$^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Br(1) | 159(1) | 5727(1) | 8694(1) | 19(1) |
| C(7) | 299(2) | 8579(2) | 9501(1) | 12(1) |
| O(1) | 3736(1) | 10457(1) | 9284(1) | 17(1) |
| N(9) | 1768(2) | 10252(2) | 9958(1) | 14(1) |
| C(13) | 1556(2) | 6821(2) | 8716(2) | 14(1) |
| C(4) | -2779(2) | 9358(2) | 8879(1) | 16(1) |
| N(1) | -1764(2) | 11168(2) | 8930(1) | 13(1) |
| O(2) | -3553(2) | 12482(1) | 9115(1) | 18(1) |
| O(3) | 1132(1) | 8682(1) | 11052(1) | 16(1) |
| C(17) | 1400(2) | 9361(2) | 11909(1) | 20(1) |

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| N(3) | -3662(2) | 10316(2) | 8998(1) | 16(1) |
| C(15) | 3436(2) | 7809(2) | 8539(1) | 15(1) |
| C(8) | 740(2) | 9455(2) | 10295(1) | 12(1) |
| N(12) | 1452(2) | 7949(2) | 9159(1) | 12(1) |
| C(6) | -325(2) | 9256(2) | 8651(1) | 15(1) |
| C(10) | 2770(2) | 9819(2) | 9433(1) | 12(1) |
| C(2) | -3051(2) | 11429(2) | 9029(1) | 15(1) |
| C(16) | -794(2) | 12148(2) | 8888(2) | 18(1) |
| C(11) | 2611(2) | 8564(2) | 9047(1) | 13(1) |
| C(5) | -1592(2) | 9867(2) | 8832(1) | 14(1) |
| C(14) | 2771(2) | 6692(2) | 8339(1) | 16(1) |
| O(1S) | 9175(2) | 1656(2) | 1844(1) | 27(1) |
| C(1S) | 7951(2) | 1693(2) | 1404(2) | 24(1) |

**Table S17.** Bond lengths [Å] and angles [°] for (+)-$O$-methyl-pre-agelastatin A (**82**).

| Br(1)-C(13) | 1.8678(19) | N(12)-C(13)-Br(1) | 120.24(15) |
|---|---|---|---|
| C(7)-N(12) | 1.457(2) | C(14)-C(13)-Br(1) | 129.98(16) |
| C(7)-C(8) | 1.532(3) | C(5)-C(4)-N(3) | 107.96(19) |
| C(7)-C(6) | 1.545(3) | C(2)-N(1)-C(5) | 109.55(17) |
| O(1)-C(10) | 1.234(2) | C(2)-N(1)-C(16) | 121.94(17) |
| N(9)-C(10) | 1.359(3) | C(5)-N(1)-C(16) | 128.43(17) |
| N(9)-C(8) | 1.448(3) | C(8)-O(3)-C(17) | 113.06(15) |
| C(13)-N(12) | 1.368(2) | C(2)-N(3)-C(4) | 110.46(17) |
| C(13)-C(14) | 1.375(3) | C(11)-C(15)-C(14) | 107.40(18) |
| C(4)-C(5) | 1.350(3) | O(3)-C(8)-N(9) | 112.48(16) |
| C(4)-N(3) | 1.388(3) | O(3)-C(8)-C(7) | 106.02(15) |
| N(1)-C(2) | 1.372(3) | N(9)-C(8)-C(7) | 110.20(15) |
| N(1)-C(5) | 1.416(3) | C(13)-N(12)-C(11) | 107.54(17) |
| N(1)-C(16) | 1.459(3) | C(13)-N(12)-C(7) | 128.87(17) |
| O(2)-C(2) | 1.252(3) | C(11)-N(12)-C(7) | 122.15(16) |
| O(3)-C(8) | 1.413(2) | C(5)-C(6)-C(7) | 116.37(16) |
| O(3)-C(17) | 1.439(2) | O(1)-C(10)-N(9) | 121.63(19) |
| N(3)-C(2) | 1.355(3) | O(1)-C(10)-C(11) | 122.74(19) |
| C(15)-C(11) | 1.380(3) | N(9)-C(10)-C(11) | 115.62(18) |
| C(15)-C(14) | 1.413(3) | O(2)-C(2)-N(3) | 127.34(19) |
| N(12)-C(11) | 1.382(3) | O(2)-C(2)-N(1) | 126.9(2) |
| C(6)-C(5) | 1.492(3) | N(3)-C(2)-N(1) | 105.78(17) |
| C(10)-C(11) | 1.464(3) | C(15)-C(11)-N(12) | 108.65(18) |
| O(1S)-C(1S) | 1.415(3) | C(15)-C(11)-C(10) | 131.65(19) |
| | | N(12)-C(11)-C(10) | 119.69(18) |
| N(12)-C(7)-C(8) | 106.31(16) | C(4)-C(5)-N(1) | 106.24(18) |
| N(12)-C(7)-C(6) | 107.86(14) | C(4)-C(5)-C(6) | 129.41(19) |
| C(8)-C(7)-C(6) | 113.71(16) | N(1)-C(5)-C(6) | 124.23(18) |
| C(10)-N(9)-C(8) | 122.66(17) | C(13)-C(14)-C(15) | 106.60(18) |
| N(12)-C(13)-C(14) | 109.78(18) | | |

Symmetry transformations used to generate equivalent atoms:

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**Table S18.** Anisotropic displacement parameters ($Å^2$x $10^3$) for (+)-$O$-methyl-pre-agelastatin A (**82**). The anisotropic displacement factor exponent takes the form: $-2p^2[\,h^2\,a*^2U^{11} + ... + 2\,h\,k\,a*\,b*\,U^{12}\,]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Br(1) | 22(1) | 15(1) | 20(1) | -4(1) | 1(1) | -4(1) |
| C(7) | 10(1) | 12(1) | 14(1) | -2(1) | 1(1) | 0(1) |
| O(1) | 11(1) | 18(1) | 23(1) | 2(1) | 2(1) | 0(1) |
| N(9) | 14(1) | 10(1) | 17(1) | -2(1) | 2(1) | -2(1) |
| C(13) | 18(1) | 12(1) | 14(1) | -2(1) | -2(1) | 0(1) |
| C(4) | 16(1) | 14(1) | 17(1) | -2(1) | 0(1) | 1(1) |
| N(1) | 11(1) | 11(1) | 17(1) | -2(1) | -1(1) | 0(1) |
| O(2) | 17(1) | 14(1) | 24(1) | -4(1) | -1(1) | 4(1) |
| O(3) | 20(1) | 15(1) | 12(1) | 0(1) | -2(1) | -1(1) |
| C(17) | 27(1) | 21(1) | 14(1) | -2(1) | -3(1) | 1(1) |
| N(3) | 11(1) | 16(1) | 21(1) | 1(1) | 2(1) | 0(1) |
| C(15) | 13(1) | 16(1) | 15(1) | 0(1) | 2(1) | 3(1) |
| C(8) | 12(1) | 11(1) | 13(1) | -1(1) | 1(1) | 1(1) |
| N(12) | 11(1) | 12(1) | 14(1) | -1(1) | 1(1) | 1(1) |
| C(6) | 14(1) | 16(1) | 14(1) | -1(1) | -1(1) | 2(1) |
| C(10) | 11(1) | 12(1) | 15(1) | 4(1) | -3(1) | 0(1) |
| C(2) | 12(1) | 19(1) | 13(1) | -2(1) | -1(1) | 1(1) |
| C(16) | 14(1) | 16(1) | 25(1) | -3(1) | -1(1) | -3(1) |
| C(11) | 11(1) | 15(1) | 13(1) | 2(1) | 0(1) | 1(1) |
| C(5) | 14(1) | 14(1) | 13(1) | -2(1) | -1(1) | 1(1) |
| C(14) | 17(1) | 16(1) | 16(1) | -1(1) | 0(1) | 4(1) |
| O(1S) | 19(1) | 29(1) | 32(1) | 6(1) | 5(1) | -2(1) |
| C(1S) | 27(1) | 19(1) | 25(1) | 4(1) | -2(1) | -2(1) |

**Table S19.** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for (+)-$O$-methyl-pre-agelastatin A (**82**).

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(7) | -318 | 7952 | 9764 | 14 |
| H(9) | 1820(20) | 10950(16) | 10199(16) | 16 |
| H(4) | -2976 | 8497 | 8837 | 19 |
| H(17A) | 2117 | 9936 | 11799 | 31 |
| H(17B) | 1631 | 8777 | 12415 | 31 |
| H(17C) | 634 | 9834 | 12097 | 31 |
| H(3) | -4461(16) | 10210(20) | 9060(17) | 19 |
| H(15) | 4294 | 8004 | 8358 | 18 |
| H(8) | -3 | 9980 | 10504 | 15 |
| H(6A) | 284 | 9898 | 8423 | 17 |
| H(6B) | -440 | 8646 | 8131 | 17 |

| | | | | |
|---|---|---|---|---|
| H(16A) | -1189 | 12947 | 9057 | 27 |
| H(16B) | -443 | 12197 | 8244 | 27 |
| H(16C) | -99 | 11960 | 9336 | 27 |
| H(14) | 3098 | 5989 | 8009 | 20 |
| H(1O1) | 9730(20) | 1980(20) | 1516(16) | 32 |
| H(1S1) | 7284 | 1498 | 1873 | 36 |
| H(1S2) | 7921 | 1080 | 890 | 36 |
| H(1S3) | 7799 | 2526 | 1145 | 36 |

## Crystal Structure of (–)-Agelastatin A (1)

**View 1:**
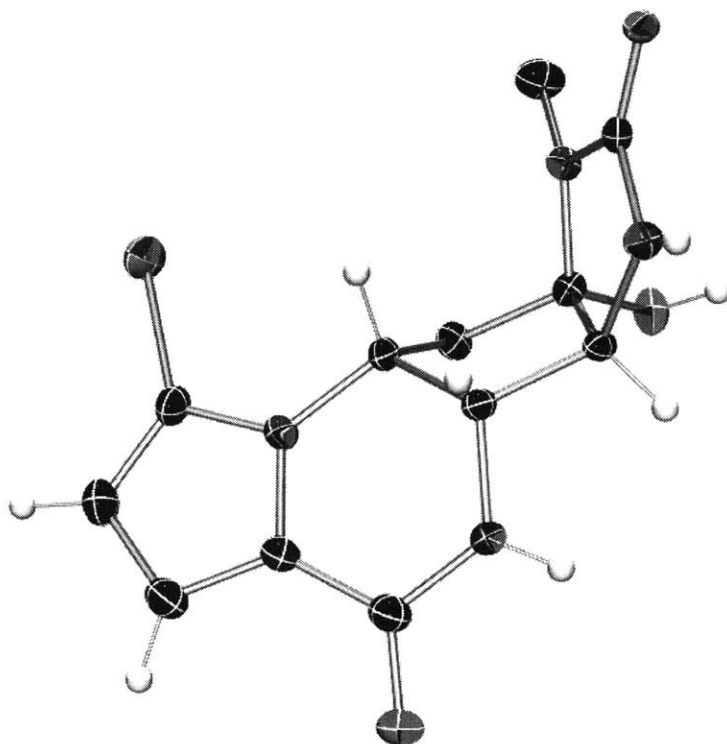


**View 2:**
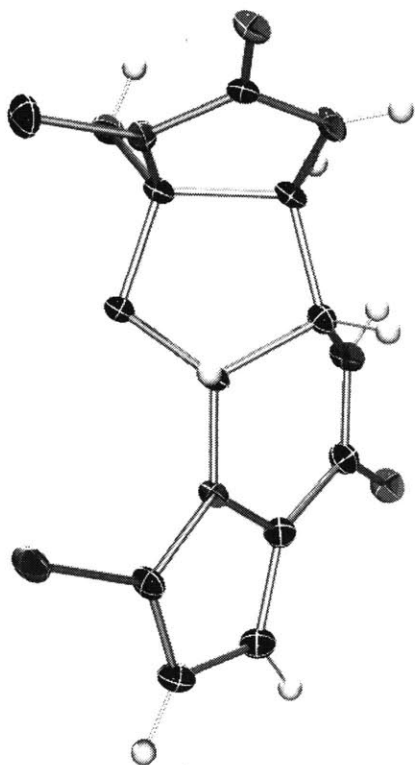
**View 3:**
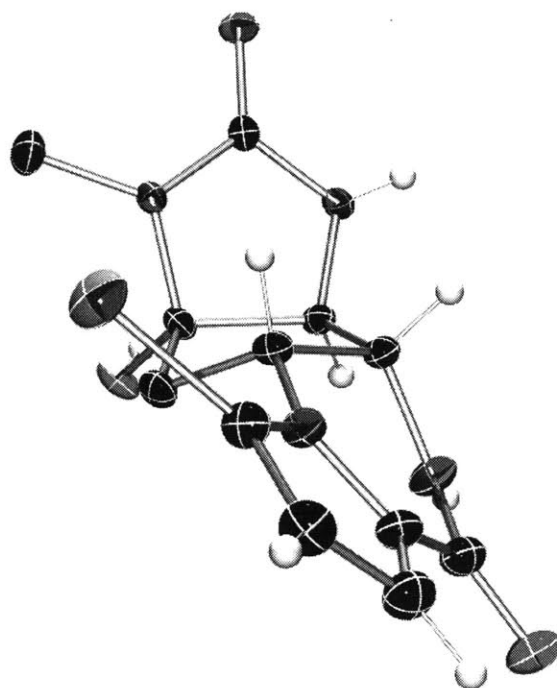
**Table S20.** Crystal data and structure refinement for (–)-agelastatin A (**1**).

| | |
|---|---|
| Identification code | 10026 |
| Empirical formula | C12 H16 Br N4 O4.50 |
| Formula weight | 368.20 |
| Temperature | 100(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Monoclinic |
| Space group | P2(1) |
| Unit cell dimensions | a = 13.5873(14) Å    a= 90°. |
| | b = 6.9161(7) Å    b= 98.786(2)°. |
| | c = 15.7114(17) Å    g = 90°. |
| Volume | 1459.1(3) Å³ |
| Z | 4 |
| Density (calculated) | 1.676 Mg/m³ |
| Absorption coefficient | 2.844 mm⁻¹ |
| F(000) | 748 |
| Crystal size | 0.48 x 0.25 x 0.04 mm³ |
| Theta range for data collection | 1.31 to 30.03°. |
| Index ranges | -19<=h<=19, -9<=k<=9, -22<=l<=21 |
| Reflections collected | 39133 |
| Independent reflections | 8508 [R(int) = 0.0524] |
| Completeness to theta = 30.03° | 99.9 % |
| Absorption correction | None |
| Max. and min. transmission | 0.8947 and 0.3422 |
| Refinement method | Full-matrix least-squares on F² |
| Data / restraints / parameters | 8508 / 402 / 426 |
| Goodness-of-fit on F² | 1.017 |
| Final R indices [I>2sigma(I)] | R1 = 0.0346, wR2 = 0.0795 |
| R indices (all data) | R1 = 0.0437, wR2 = 0.0829 |
| Absolute structure parameter | 0.015(5) |
| Largest diff. peak and hole | 0.875 and -0.490 e.Å⁻³ |

**Table S22.** Atomic coordinates ( x 10⁴) and equivalent isotropic displacement parameters (Å²x 10³) for (–)-agelastatin A (**1**). U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Br(1A) | 10024(1) | 9800(1) | 4181(1) | 20(1) |
| O(1A) | 7655(1) | 2032(3) | 3166(1) | 19(1) |
| O(2A) | 5380(1) | 12339(3) | 4193(1) | 15(1) |
| O(3A) | 6575(1) | 7489(3) | 5834(1) | 16(1) |
| N(1A) | 6544(2) | 10312(3) | 4960(1) | 13(1) |
| N(3A) | 5476(2) | 9051(3) | 3910(2) | 16(1) |
| N(9A) | 6925(1) | 4729(4) | 3601(1) | 16(1) |
| N(12A) | 8666(1) | 6765(3) | 3693(1) | 13(1) |
| C(2A) | 5761(2) | 10700(4) | 4338(2) | 13(1) |
| C(4A) | 6100(2) | 7438(4) | 4214(2) | 13(1) |
| C(5A) | 6771(2) | 8256(4) | 5039(2) | 13(1) |

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| | | | | |
|---|---|---|---|---|
| C(6A) | 7840(2) | 7741(4) | 4947(2) | 14(1) |
| C(7A) | 7830(2) | 7787(4) | 3976(2) | 12(1) |
| C(8A) | 6834(2) | 6839(3) | 3592(2) | 13(1) |
| C(10A) | 7700(2) | 3773(4) | 3354(2) | 15(1) |
| C(11A) | 8604(2) | 4898(4) | 3361(2) | 14(1) |
| C(13A) | 9618(2) | 7390(4) | 3713(2) | 15(1) |
| C(14A) | 10170(2) | 5986(4) | 3382(2) | 16(1) |
| C(15A) | 9532(2) | 4414(3) | 3163(2) | 16(1) |
| C(16A) | 7030(2) | 11771(4) | 5551(2) | 20(1) |
| Br(1B) | 677(1) | 1059(1) | -861(1) | 30(1) |
| O(1B) | 3160(2) | 8724(3) | 175(1) | 28(1) |
| O(2B) | 3843(1) | -1576(3) | 2515(1) | 17(1) |
| O(3B) | 1898(1) | 3202(3) | 2824(1) | 22(1) |
| N(1B) | 2475(2) | 446(3) | 2140(1) | 15(1) |
| N(3B) | 3984(2) | 1698(3) | 2274(2) | 16(1) |
| N(9B) | 3293(2) | 6008(4) | 988(2) | 21(1) |
| N(12B) | 1965(2) | 4066(3) | -199(2) | 18(1) |
| C(2B) | 3473(2) | 41(4) | 2325(2) | 14(1) |
| C(4B) | 3345(2) | 3314(4) | 2009(2) | 14(1) |
| C(5B) | 2286(2) | 2529(4) | 2096(2) | 15(1) |
| C(6B) | 1615(2) | 3162(4) | 1279(2) | 18(1) |
| C(7B) | 2307(2) | 3044(4) | 598(2) | 16(1) |
| C(8B) | 3300(2) | 3896(4) | 1057(2) | 15(1) |
| C(10B) | 2944(2) | 6983(4) | 254(2) | 22(1) |
| C(11B) | 2275(2) | 5912(4) | -382(2) | 20(1) |
| C(13B) | 1303(2) | 3459(4) | -886(2) | 20(1) |
| C(14B) | 1190(2) | 4839(5) | -1516(2) | 25(1) |
| C(15B) | 1809(2) | 6408(4) | -1198(2) | 25(1) |
| C(16B) | 1704(2) | -950(4) | 2232(2) | 26(1) |
| O(1W) | 5937(1) | 1920(3) | 1936(2) | 27(1) |
| O(2W) | 3590(2) | 477(4) | 8668(2) | 47(1) |
| O(3W) | 4605(2) | 3913(5) | 9290(2) | 59(1) |

**Table S23.** Bond lengths [Å] and angles [°] for (−)-agelastatin A (1).

| | | | |
|---|---|---|---|
| Br(1A)-C(13A) | 1.870(3) | N(12A)-C(7A) | 1.464(3) |
| O(1A)-C(10A) | 1.239(3) | C(4A)-C(8A) | 1.556(3) |
| O(2A)-C(2A) | 1.252(3) | C(4A)-C(5A) | 1.571(3) |
| O(3A)-C(5A) | 1.419(3) | C(5A)-C(6A) | 1.524(3) |
| N(1A)-C(2A) | 1.357(3) | C(6A)-C(7A) | 1.523(3) |
| N(1A)-C(5A) | 1.456(3) | C(7A)-C(8A) | 1.541(3) |
| N(1A)-C(16A) | 1.459(3) | C(10A)-C(11A) | 1.453(3) |
| N(3A)-C(2A) | 1.350(3) | C(11A)-C(15A) | 1.385(3) |
| N(3A)-C(4A) | 1.438(3) | C(13A)-C(14A) | 1.376(4) |
| N(9A)-C(10A) | 1.350(3) | C(14A)-C(15A) | 1.401(4) |
| N(9A)-C(8A) | 1.465(3) | Br(1B)-C(13B) | 1.868(3) |
| N(12A)-C(13A) | 1.360(3) | O(1B)-C(10B) | 1.251(3) |
| N(12A)-C(11A) | 1.391(3) | O(2B)-C(2B) | 1.244(3) |

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| | | | |
|---|---|---|---|
| O(3B)-C(5B) | 1.410(3) | O(1A)-C(10A)-C(11A) | 122.2(2) |
| N(1B)-C(2B) | 1.372(3) | N(9A)-C(10A)-C(11A) | 115.5(2) |
| N(1B)-C(16B) | 1.447(3) | C(15A)-C(11A)-N(12A) | 107.7(2) |
| N(1B)-C(5B) | 1.463(3) | C(15A)-C(11A)-C(10A) | 131.8(3) |
| N(3B)-C(2B) | 1.349(3) | N(12A)-C(11A)-C(10A) | 120.2(2) |
| N(3B)-C(4B) | 1.437(3) | N(12A)-C(13A)-C(14A) | 109.8(2) |
| N(9B)-C(10B) | 1.357(4) | N(12A)-C(13A)-Br(1A) | 120.95(18) |
| N(9B)-C(8B) | 1.465(3) | C(14A)-C(13A)-Br(1A) | 129.24(18) |
| N(12B)-C(13B) | 1.361(3) | C(13A)-C(14A)-C(15A) | 106.8(2) |
| N(12B)-C(11B) | 1.388(4) | C(11A)-C(15A)-C(14A) | 107.9(2) |
| N(12B)-C(7B) | 1.452(3) | C(2B)-N(1B)-C(16B) | 123.3(2) |
| C(4B)-C(8B) | 1.541(4) | C(2B)-N(1B)-C(5B) | 111.8(2) |
| C(4B)-C(5B) | 1.563(3) | C(16B)-N(1B)-C(5B) | 122.5(2) |
| C(5B)-C(6B) | 1.521(4) | C(2B)-N(3B)-C(4B) | 112.60(19) |
| C(6B)-C(7B) | 1.530(3) | C(10B)-N(9B)-C(8B) | 123.8(2) |
| C(7B)-C(8B) | 1.546(3) | C(13B)-N(12B)-C(11B) | 107.7(2) |
| C(10B)-C(11B) | 1.448(4) | C(13B)-N(12B)-C(7B) | 128.2(2) |
| C(11B)-C(15B) | 1.384(4) | C(11B)-N(12B)-C(7B) | 124.0(2) |
| C(13B)-C(14B) | 1.367(4) | O(2B)-C(2B)-N(3B) | 125.8(2) |
| C(14B)-C(15B) | 1.416(4) | O(2B)-C(2B)-N(1B) | 125.8(2) |
| | | N(3B)-C(2B)-N(1B) | 108.4(2) |
| C(2A)-N(1A)-C(5A) | 112.7(2) | N(3B)-C(4B)-C(8B) | 114.7(2) |
| C(2A)-N(1A)-C(16A) | 123.4(2) | N(3B)-C(4B)-C(5B) | 103.2(2) |
| C(5A)-N(1A)-C(16A) | 123.5(2) | C(8B)-C(4B)-C(5B) | 106.0(2) |
| C(2A)-N(3A)-C(4A) | 112.4(2) | O(3B)-C(5B)-N(1B) | 111.8(2) |
| C(10A)-N(9A)-C(8A) | 123.6(2) | O(3B)-C(5B)-C(6B) | 109.9(2) |
| C(13A)-N(12A)-C(11A) | 107.9(2) | N(1B)-C(5B)-C(6B) | 113.7(2) |
| C(13A)-N(12A)-C(7A) | 128.3(2) | O(3B)-C(5B)-C(4B) | 114.8(2) |
| C(11A)-N(12A)-C(7A) | 123.82(19) | N(1B)-C(5B)-C(4B) | 100.89(19) |
| O(2A)-C(2A)-N(3A) | 126.5(2) | C(6B)-C(5B)-C(4B) | 105.5(2) |
| O(2A)-C(2A)-N(1A) | 124.5(2) | C(5B)-C(6B)-C(7B) | 102.81(19) |
| N(3A)-C(2A)-N(1A) | 109.0(2) | N(12B)-C(7B)-C(6B) | 115.4(2) |
| N(3A)-C(4A)-C(8A) | 113.5(2) | N(12B)-C(7B)-C(8B) | 111.0(2) |
| N(3A)-C(4A)-C(5A) | 103.5(2) | C(6B)-C(7B)-C(8B) | 103.9(2) |
| C(8A)-C(4A)-C(5A) | 105.46(18) | N(9B)-C(8B)-C(4B) | 109.3(2) |
| O(3A)-C(5A)-N(1A) | 111.9(2) | N(9B)-C(8B)-C(7B) | 110.5(2) |
| O(3A)-C(5A)-C(6A) | 107.80(19) | C(4B)-C(8B)-C(7B) | 104.8(2) |
| N(1A)-C(5A)-C(6A) | 114.4(2) | O(1B)-C(10B)-N(9B) | 120.4(3) |
| O(3A)-C(5A)-C(4A) | 115.33(19) | O(1B)-C(10B)-C(11B) | 123.8(3) |
| N(1A)-C(5A)-C(4A) | 101.15(19) | N(9B)-C(10B)-C(11B) | 115.7(3) |
| C(6A)-C(5A)-C(4A) | 106.22(19) | C(15B)-C(11B)-N(12B) | 108.0(2) |
| C(7A)-C(6A)-C(5A) | 103.11(19) | C(15B)-C(11B)-C(10B) | 131.6(3) |
| N(12A)-C(7A)-C(6A) | 113.87(19) | N(12B)-C(11B)-C(10B) | 120.4(2) |
| N(12A)-C(7A)-C(8A) | 110.6(2) | N(12B)-C(13B)-C(14B) | 110.2(3) |
| C(6A)-C(7A)-C(8A) | 104.85(19) | N(12B)-C(13B)-Br(1B) | 120.4(2) |
| N(9A)-C(8A)-C(7A) | 110.6(2) | C(14B)-C(13B)-Br(1B) | 129.4(2) |
| N(9A)-C(8A)-C(4A) | 108.67(19) | C(13B)-C(14B)-C(15B) | 106.6(2) |
| C(7A)-C(8A)-C(4A) | 104.47(19) | C(11B)-C(15B)-C(14B) | 107.4(3) |
| O(1A)-C(10A)-N(9A) | 122.2(2) | | |

Symmetry transformations used to generate equivalent atoms:

**Table S24.** Anisotropic displacement parameters ($\text{Å}^2$x $10^3$) for (–)-agelastatin A (**1**). The anisotropic displacement factor exponent takes the form: $-2p^2[\,h^2\,a^{*2}U^{11} + ... + 2\,h\,k\,a^*\,b^*\,U^{12}\,]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Br(1A) | 13(1) | 17(1) | 30(1) | -5(1) | 4(1) | -5(1) |
| O(1A) | 20(1) | 12(1) | 25(1) | -2(1) | 2(1) | 0(1) |
| O(2A) | 10(1) | 13(1) | 21(1) | 2(1) | 2(1) | 1(1) |
| O(3A) | 12(1) | 22(1) | 14(1) | 4(1) | 2(1) | 0(1) |
| N(1A) | 12(1) | 13(1) | 14(1) | -2(1) | 1(1) | 0(1) |
| N(3A) | 11(1) | 13(1) | 22(1) | -1(1) | -4(1) | 2(1) |
| N(9A) | 12(1) | 10(1) | 25(1) | -1(1) | 4(1) | -4(1) |
| N(12A) | 10(1) | 12(1) | 16(1) | 0(1) | 2(1) | 0(1) |
| C(2A) | 8(1) | 17(1) | 14(1) | -1(1) | 4(1) | 0(1) |
| C(4A) | 8(1) | 14(1) | 17(1) | 2(1) | 1(1) | 1(1) |
| C(5A) | 9(1) | 13(1) | 17(1) | 0(1) | 2(1) | 1(1) |
| C(6A) | 9(1) | 16(1) | 15(1) | -1(1) | 2(1) | 1(1) |
| C(7A) | 9(1) | 10(1) | 18(1) | 0(1) | 2(1) | 0(1) |
| C(8A) | 11(1) | 11(1) | 16(1) | 0(1) | 1(1) | 0(1) |
| C(10A) | 14(1) | 15(1) | 16(1) | 2(1) | 0(1) | 1(1) |
| C(11A) | 15(1) | 12(1) | 16(1) | 0(1) | 3(1) | 2(1) |
| C(13A) | 12(1) | 14(1) | 20(1) | 0(1) | 2(1) | -4(1) |
| C(14A) | 13(1) | 17(1) | 20(1) | 3(1) | 5(1) | 3(1) |
| C(15A) | 16(1) | 13(1) | 19(1) | 1(1) | 5(1) | 2(1) |
| C(16A) | 19(1) | 16(1) | 24(1) | -5(1) | -3(1) | -2(1) |
| Br(1B) | 29(1) | 26(1) | 29(1) | -1(1) | -9(1) | -9(1) |
| O(1B) | 38(1) | 17(1) | 29(1) | 3(1) | 1(1) | -3(1) |
| O(2B) | 17(1) | 14(1) | 20(1) | 0(1) | -2(1) | 2(1) |
| O(3B) | 16(1) | 32(1) | 18(1) | -3(1) | 2(1) | 8(1) |
| N(1B) | 10(1) | 16(1) | 18(1) | 2(1) | 1(1) | 1(1) |
| N(3B) | 10(1) | 17(1) | 22(1) | 0(1) | 0(1) | 1(1) |
| N(9B) | 28(1) | 14(1) | 18(1) | 0(1) | -2(1) | -4(1) |
| N(12B) | 19(1) | 17(1) | 17(1) | 2(1) | -2(1) | 0(1) |
| C(2B) | 13(1) | 18(1) | 11(1) | -1(1) | 2(1) | -1(1) |
| C(4B) | 13(1) | 12(1) | 17(1) | 0(1) | 0(1) | 0(1) |
| C(5B) | 11(1) | 16(1) | 17(1) | -3(1) | 2(1) | 2(1) |
| C(6B) | 12(1) | 21(1) | 20(1) | 2(1) | -1(1) | 3(1) |
| C(7B) | 16(1) | 14(1) | 15(1) | 0(1) | -2(1) | 1(1) |
| C(8B) | 15(1) | 12(1) | 17(1) | 0(1) | 0(1) | 0(1) |
| C(10B) | 25(1) | 18(1) | 22(1) | 2(1) | 4(1) | 2(1) |
| C(11B) | 23(1) | 16(1) | 20(1) | 2(1) | 2(1) | 2(1) |
| C(13B) | 20(1) | 21(1) | 19(1) | -3(1) | -2(1) | -1(1) |
| C(14B) | 26(1) | 30(1) | 18(1) | 0(1) | -2(1) | 0(1) |
| C(15B) | 29(1) | 23(2) | 22(1) | 4(1) | 4(1) | 2(1) |
| C(16B) | 17(1) | 23(1) | 38(2) | 5(1) | 4(1) | -5(1) |
| O(1W) | 16(1) | 29(1) | 36(1) | -3(1) | 4(1) | -4(1) |

| | | x | y | z | | |
|---|---|---|---|---|---|---|
| O(2W) | 68(2) | 37(1) | 39(2) | 1(1) | 17(1) | -4(1) |
| O(3W) | 58(2) | 52(2) | 70(2) | 14(2) | 17(2) | 4(2) |

**Table S25.** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x 10 $^3$) for (–)-agelastatin A (**1**).

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(3A) | 5979(14) | 7400(50) | 5910(20) | 24 |
| H(3C) | 5030(18) | 8970(50) | 3485(14) | 19 |
| H(9A) | 6394(16) | 4140(40) | 3660(20) | 19 |
| H(4A) | 5695 | 6311 | 4359 | 16 |
| H(6A1) | 8314 | 8702 | 5242 | 16 |
| H(6A2) | 8020 | 6441 | 5184 | 16 |
| H(7A) | 7831 | 9163 | 3780 | 15 |
| H(8A) | 6601 | 7324 | 2996 | 15 |
| H(14A) | 10852 | 6068 | 3316 | 20 |
| H(15A) | 9704 | 3226 | 2921 | 19 |
| H(16A) | 6673 | 13002 | 5450 | 31 |
| H(16B) | 7720 | 11939 | 5453 | 31 |
| H(16C) | 7023 | 11354 | 6146 | 31 |
| H(3B) | 2340(20) | 2970(50) | 3263(17) | 33 |
| H(3D) | 4624(13) | 1690(40) | 2343(19) | 20 |
| H(9B) | 3540(20) | 6620(40) | 1443(15) | 25 |
| H(4B) | 3520 | 4449 | 2396 | 17 |
| H(6B1) | 1369 | 4497 | 1334 | 22 |
| H(6B2) | 1039 | 2280 | 1140 | 22 |
| H(7B) | 2412 | 1653 | 463 | 19 |
| H(8B) | 3876 | 3338 | 813 | 18 |
| H(14B) | 776 | 4761 | -2060 | 30 |
| H(15B) | 1889 | 7585 | -1492 | 30 |
| H(16D) | 2007 | -2223 | 2361 | 39 |
| H(16E) | 1234 | -1018 | 1694 | 39 |
| H(16F) | 1351 | -553 | 2702 | 39 |
| H(1WB) | 5980(30) | 3100(30) | 1780(20) | 40 |
| H(1WA) | 6400(20) | 1660(50) | 2325(18) | 40 |
| H(2WA) | 3980(30) | 1650(50) | 8790(30) | 70 |
| H(2WB) | 3620(30) | 90(60) | 9199(16) | 70 |
| H(3WA) | 4290(30) | 4630(70) | 8840(30) | 89 |
| H(3WB) | 5240(15) | 4070(80) | 9230(30) | 89 |

# Appendix A.

## Spectra for Chapter I

DEC. & VT
dfrq        125.674
dn              C13
dpwr             34
dof          1498.1
dm              nnn
dmm               w
dmf           10000
dseq
dres            1.0
homo              n

ACQUISITION
sfrq       499.749
tn              H1
at           3.277
np           65536
sw          9998.8
fb        not used
bs               1
tpwr            56
pw             8.2
d1           5.000
tof         1498.1
nt              16
ct              16
alock            n
gain      not used

PROCESSING
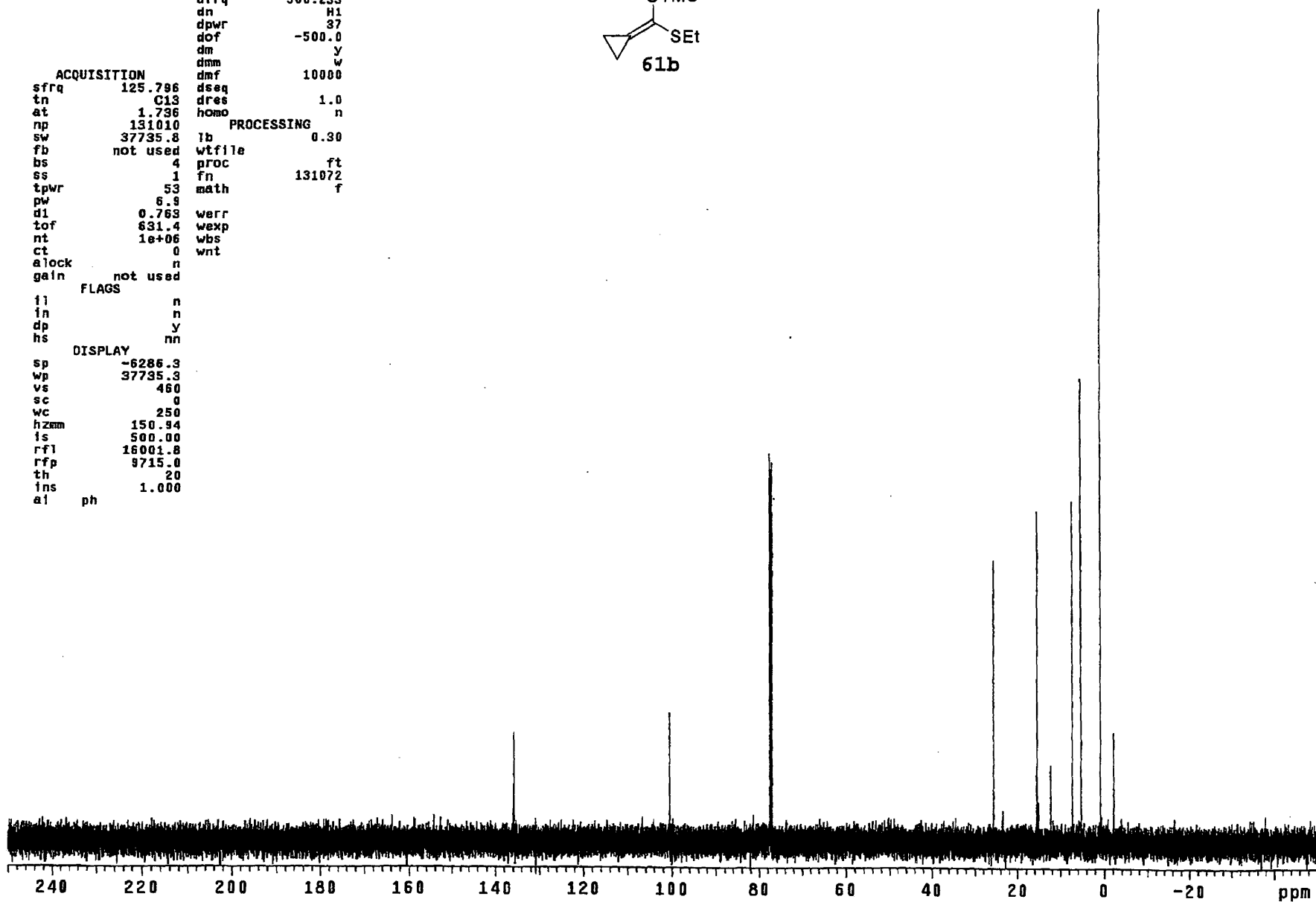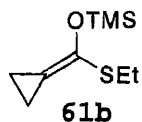wtfile
proc             ft
fn           65536
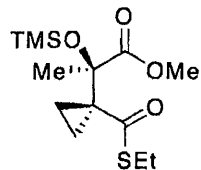math             f

werr
wexp
wbs
wnt

FLAGS
11               n
1n               n
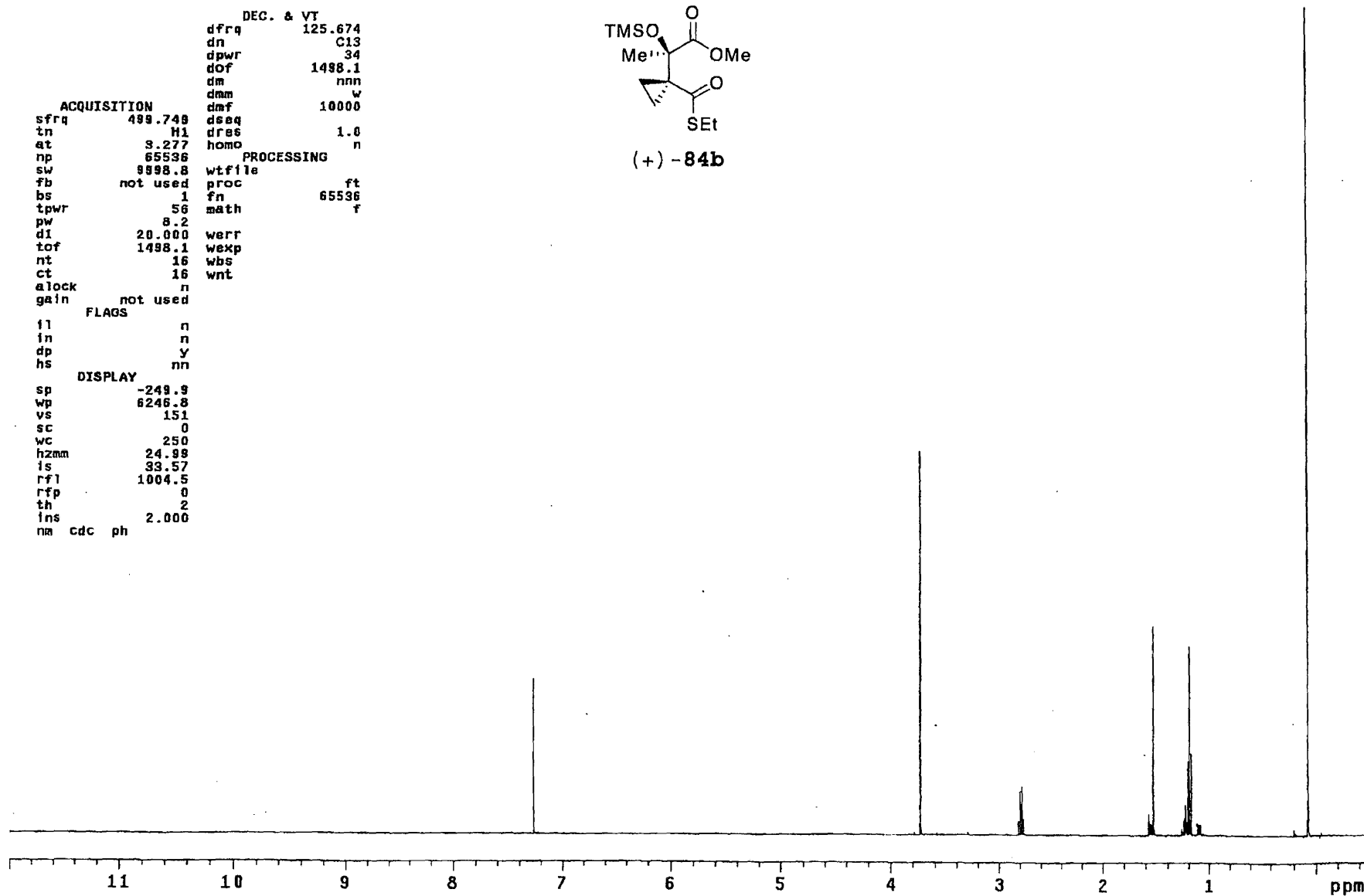dp               y
hs              nn

DISPLAY
sp          -249.9
wp          6246.8
vs              84
sc               0
wc             250
hzmm         24.98
1s           99.57
rfl         4638.2
rfp         3633.1
th               5
1ns          1.000
nm  cdc  ph
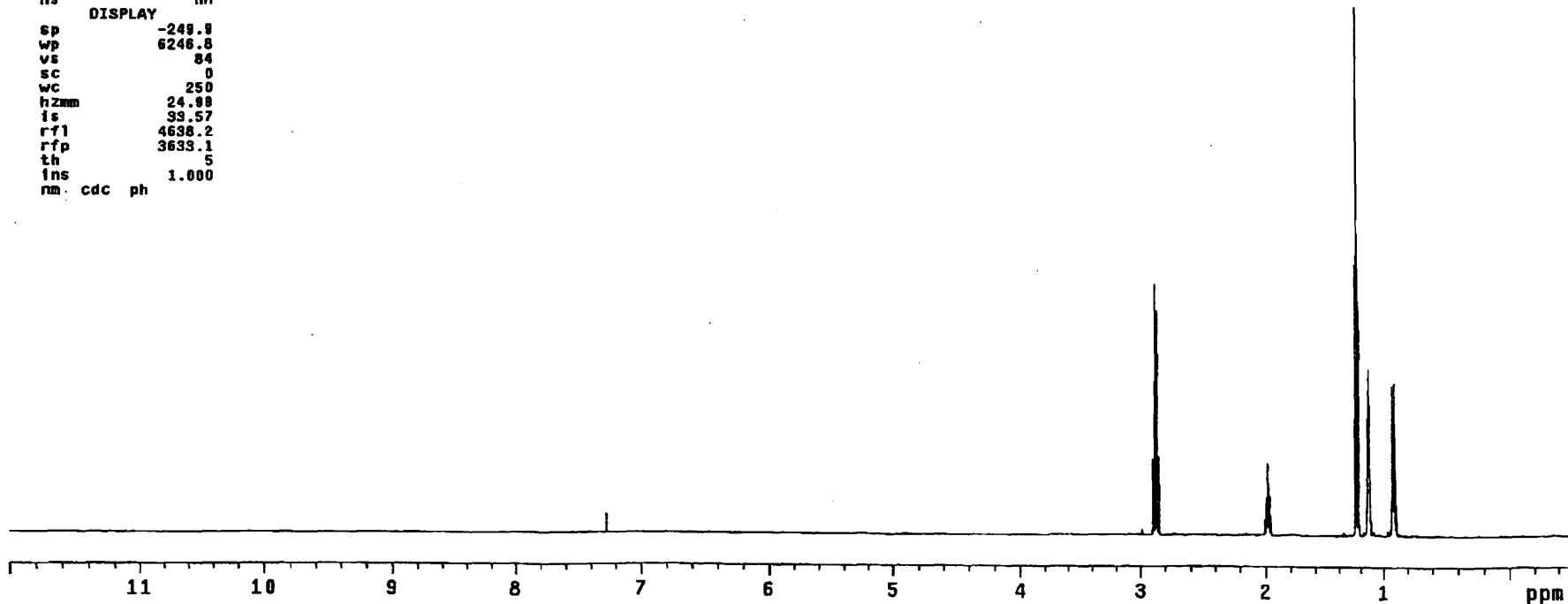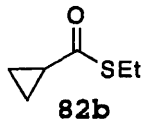
**82b**



         11        10         9         8         7         6         5         4         3         2         1      ppm

exp1 s2pul

```
                              DEC. & VT
                         dfrq      500.233
                         dn           H1
                         dpwr         37
                         dof       -500.0
                         dm            y
                         dmm           w
         ACQUISITION     dmf        10000
sfrq      125.796        dseq
tn           C13         dres        1.0
at         1.736         homo          n
np        131010            PROCESSING
sw        37735.8        lb          0.30
fb       not used        wtfile
bs            4          proc         ft
ss            1          fn       131072
tpwr         53          math          f
pw          6.9
d1        0.763          werr
tof        631.4         wexp
nt         1e+06         wbs
ct          224          wnt
alock         n
gain     not used
         FLAGS
il            n
in            n
dp            y
hs           nn
         DISPLAY
sp       -6291.4
wp       37735.3
vs          280
sc            0
wc          250
hzmm      150.94
is      11464.55
rfl      16007.0
rfp       9715.0
th           20
ins       1.000
ai    ph
```
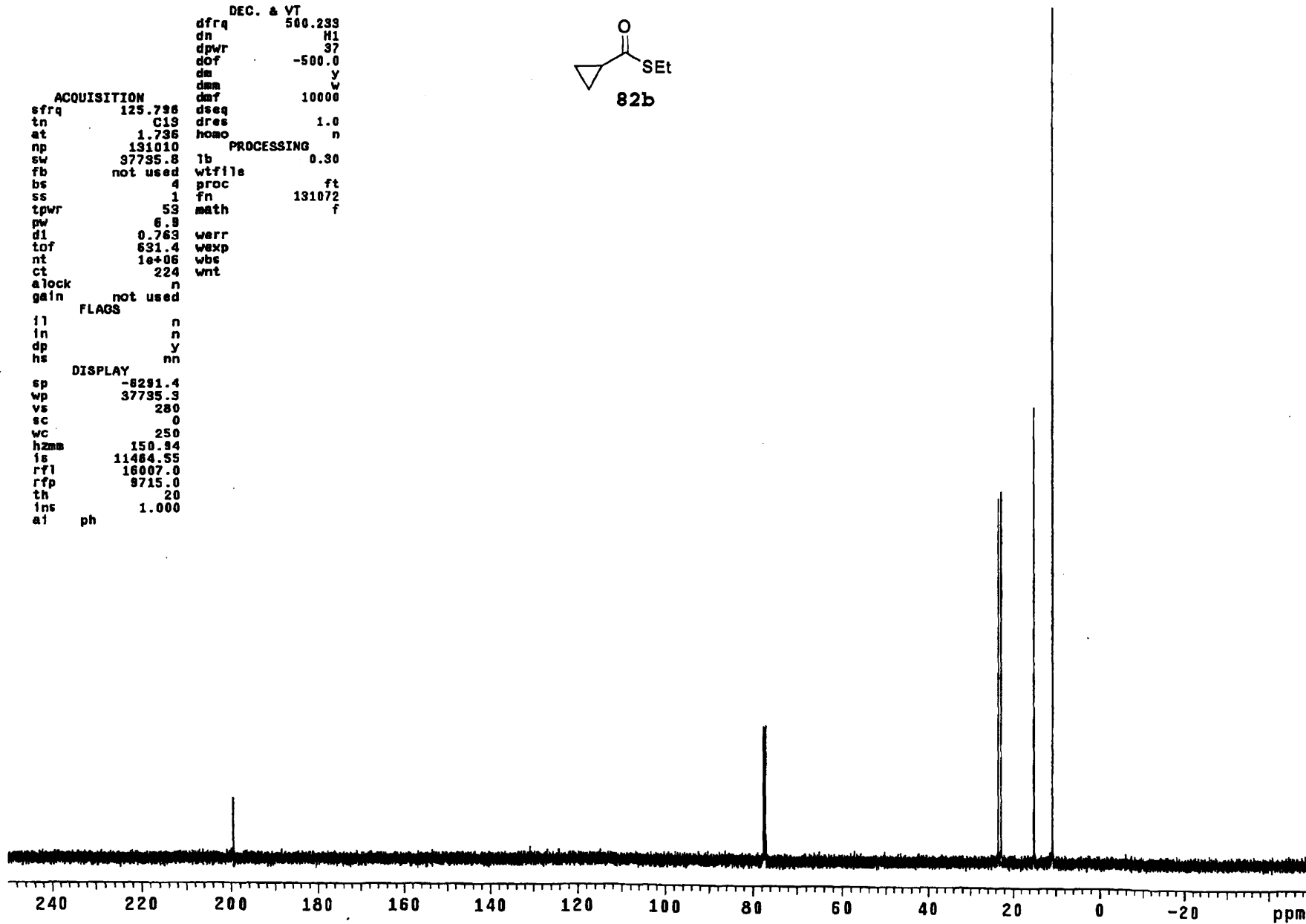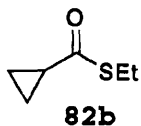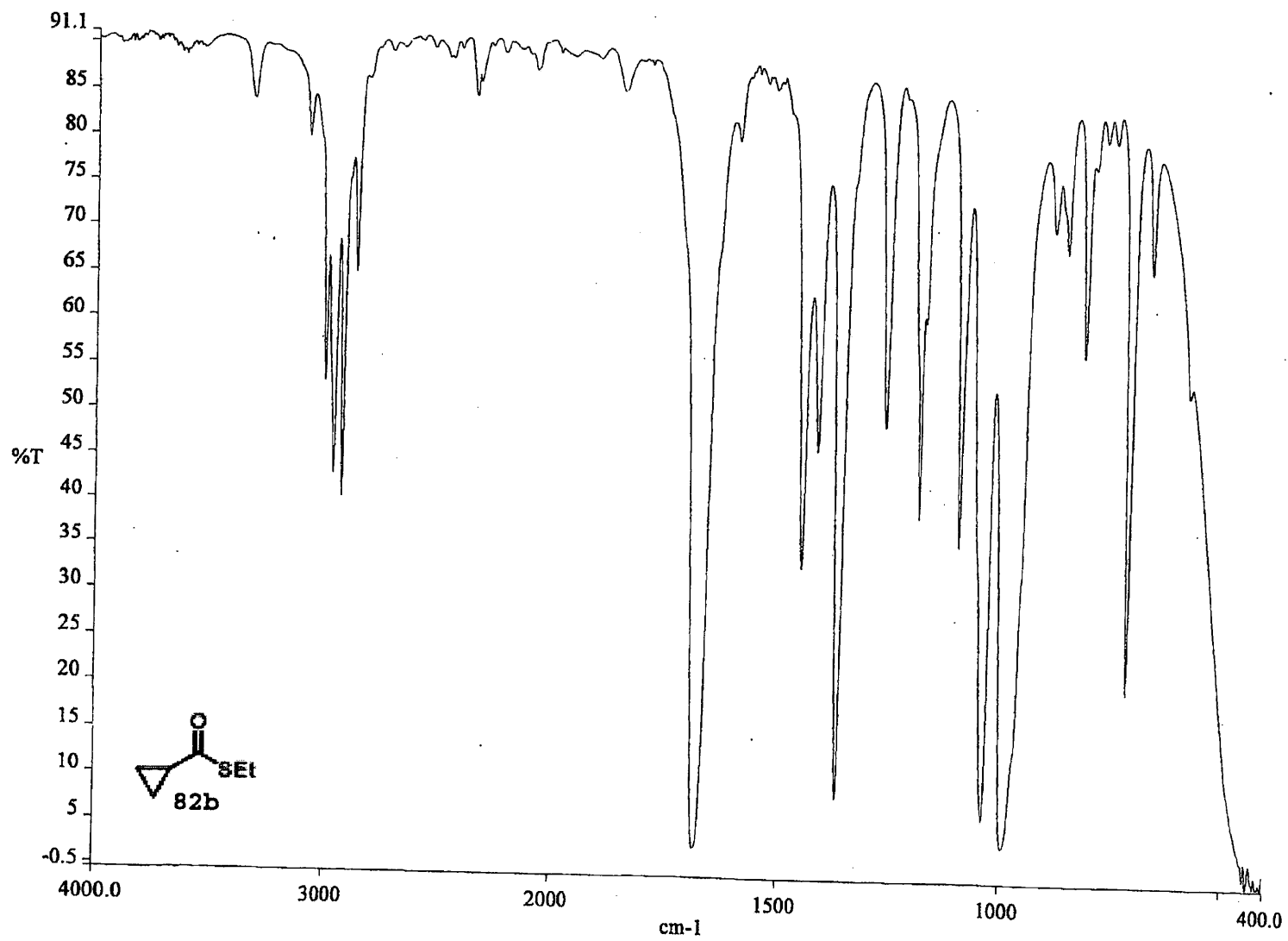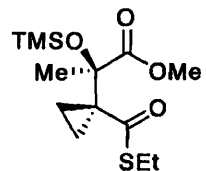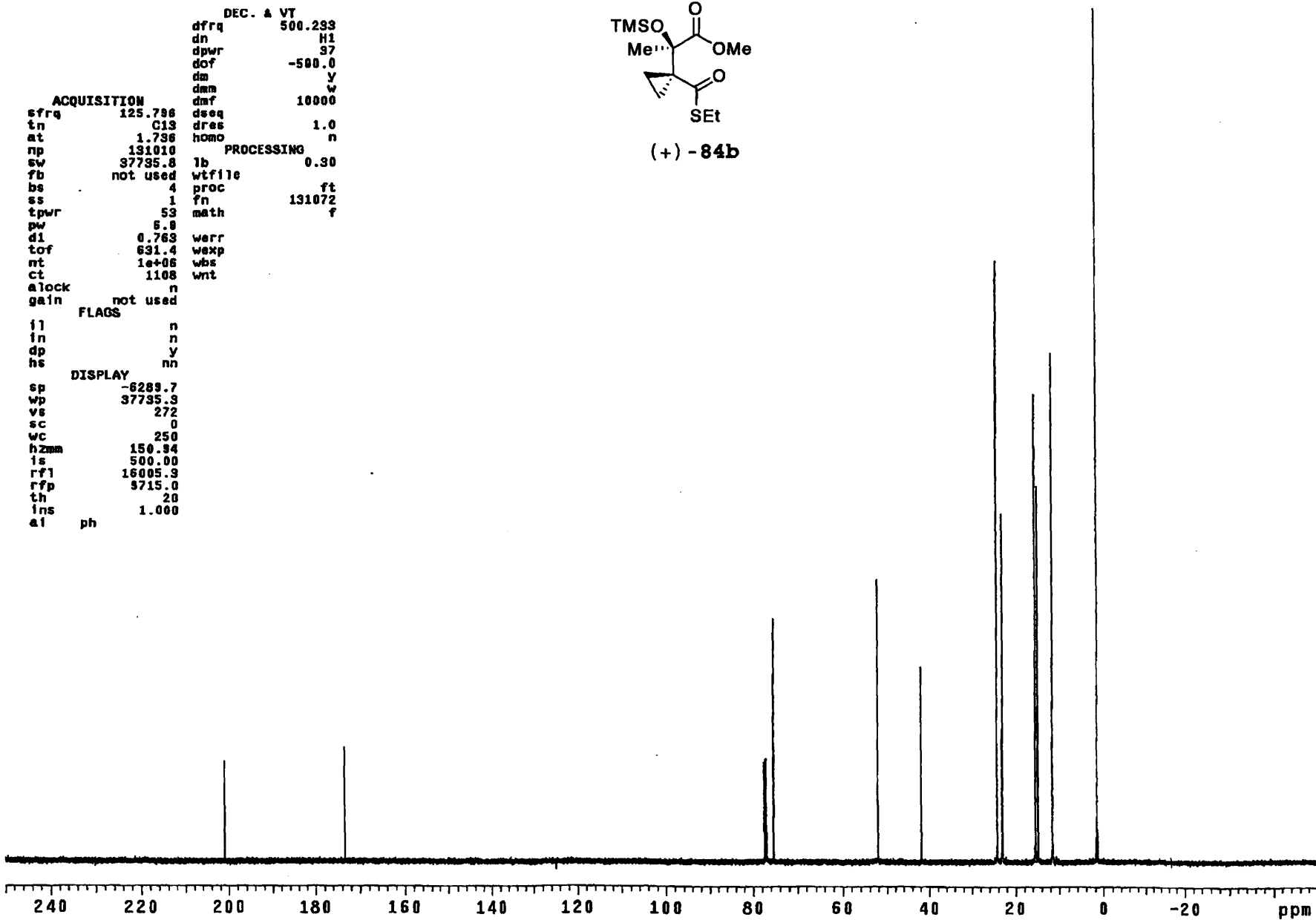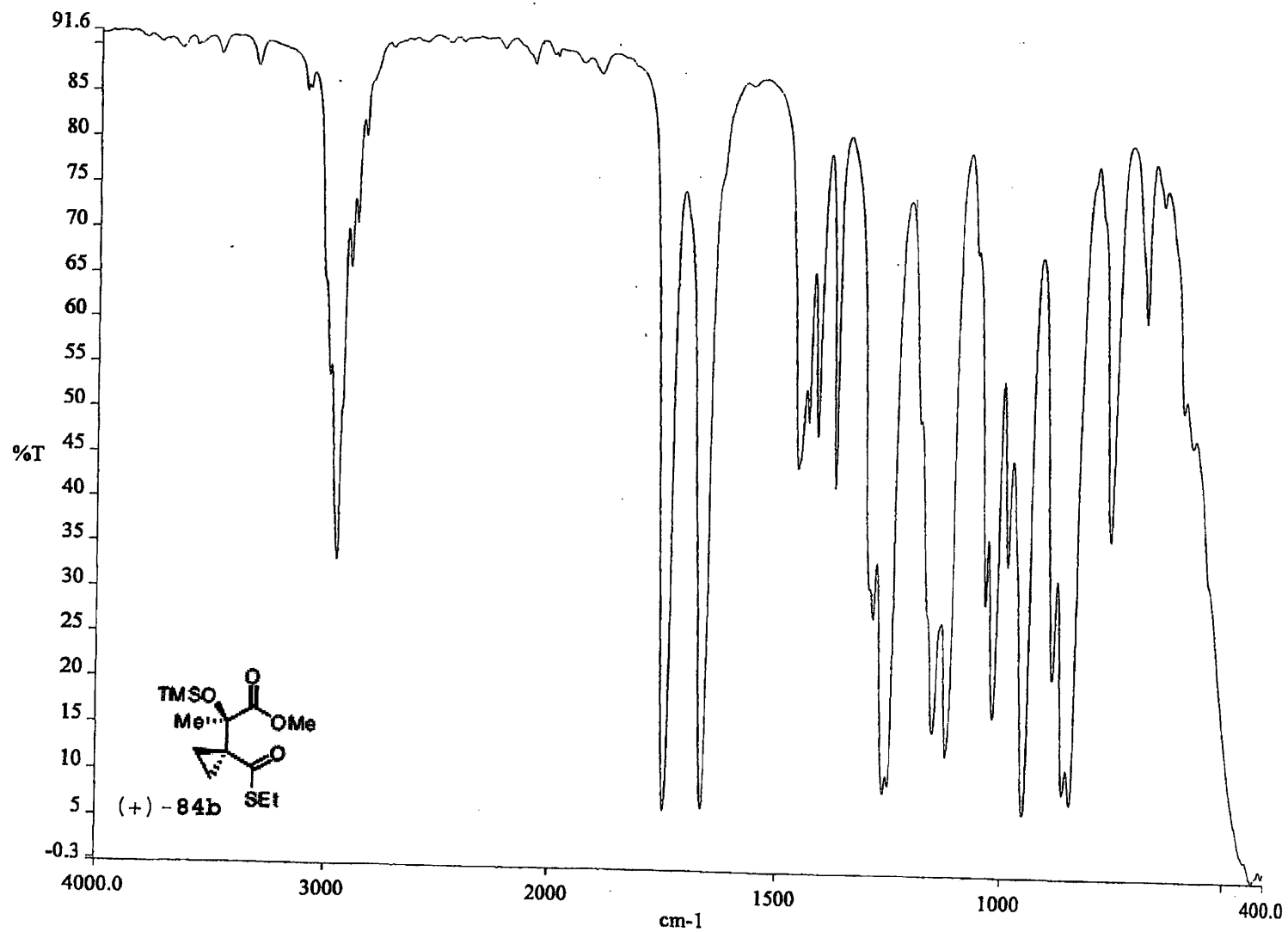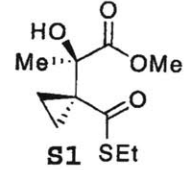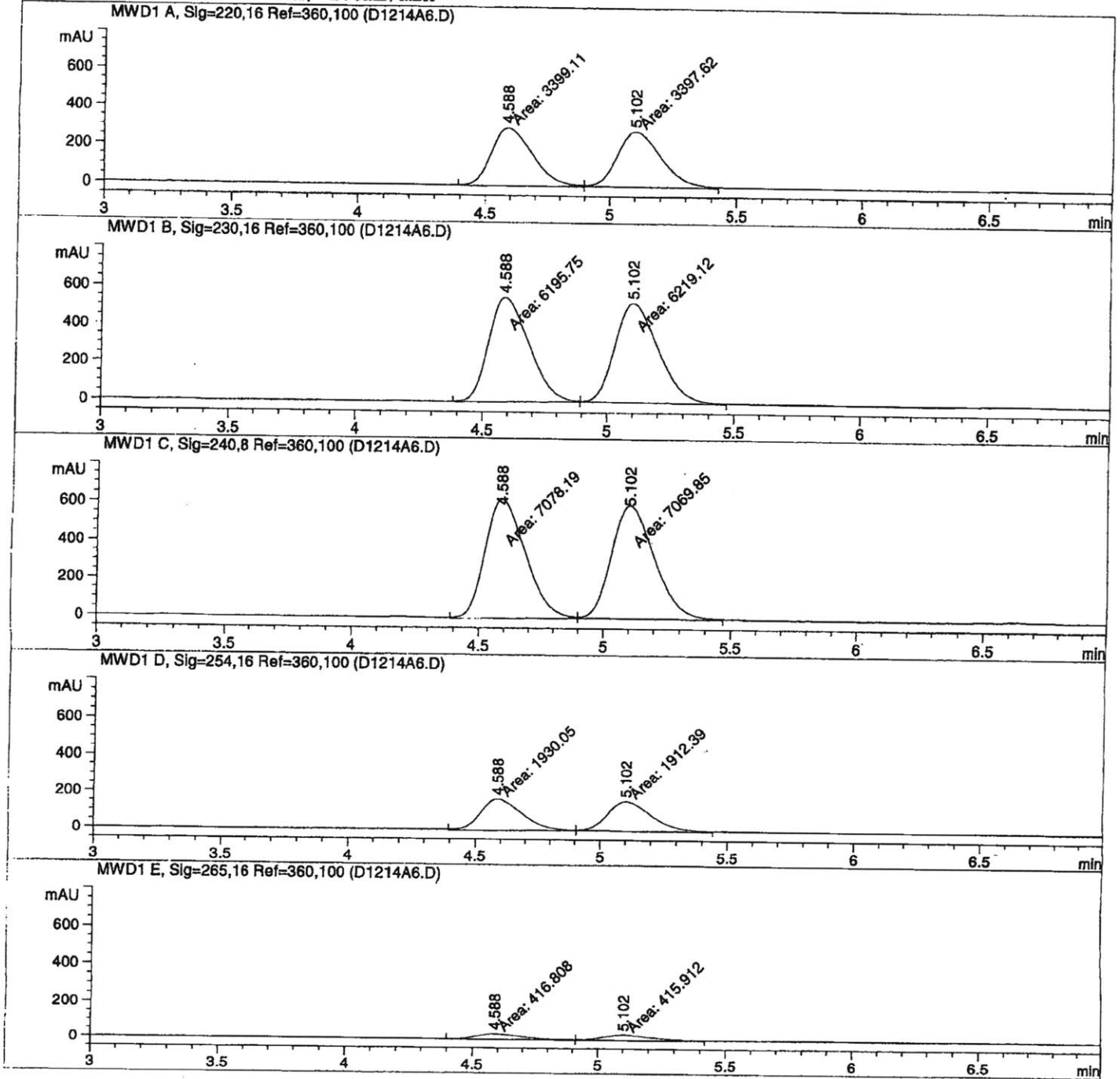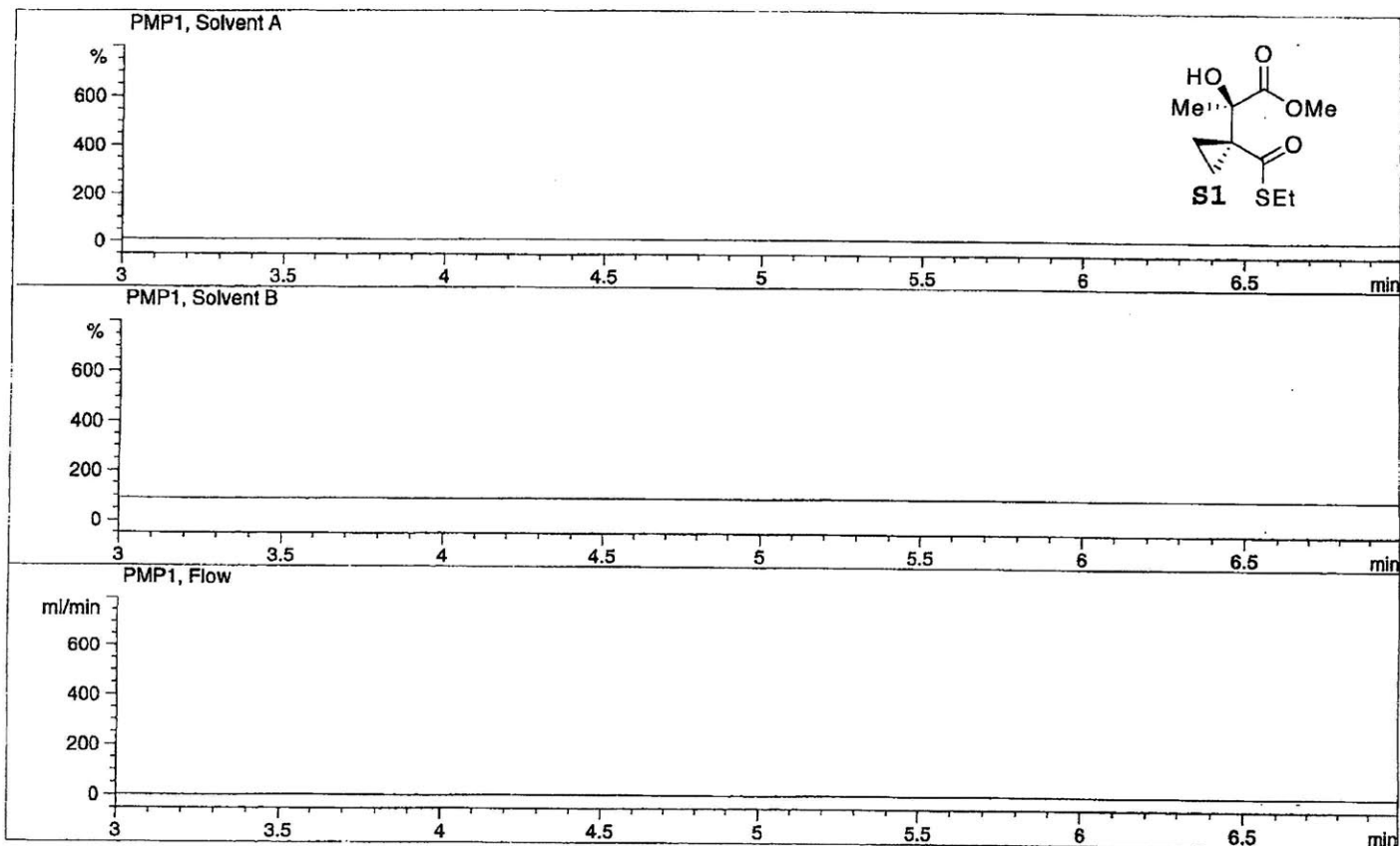
82b

expl s2pul

DEC. & VT
dfrq        125.674
dn            C13
dpwr           34
dof         1498.1
dm            nnn
dmm            w
dmf          10000

        ACQUISITION
sfrq      499.749    dseq
tn           H1      dres         1.0
at         3.277     homo          n
np         65536        PROCESSING
sw        9998.8     wtfile
fb        not used   proc          ft
bs            1      fn         65536
tpwr          56     math          f
pw           8.2
d1        10.000     werr
tof       1498.1     wexp
nt            16     wbs
ct            16     wnt
alock          n
gain      not used
        FLAGS
il             n
in             n
dp             y
hs            nn
        DISPLAY
sp         -250.2
wp        6246.5
vs           151
sc             0
wc           250
hzmm       24.99
is         33.57
rfl       4637.9
rfp       3633.1.
th             7
ins        9.000
nm   cdc  ph
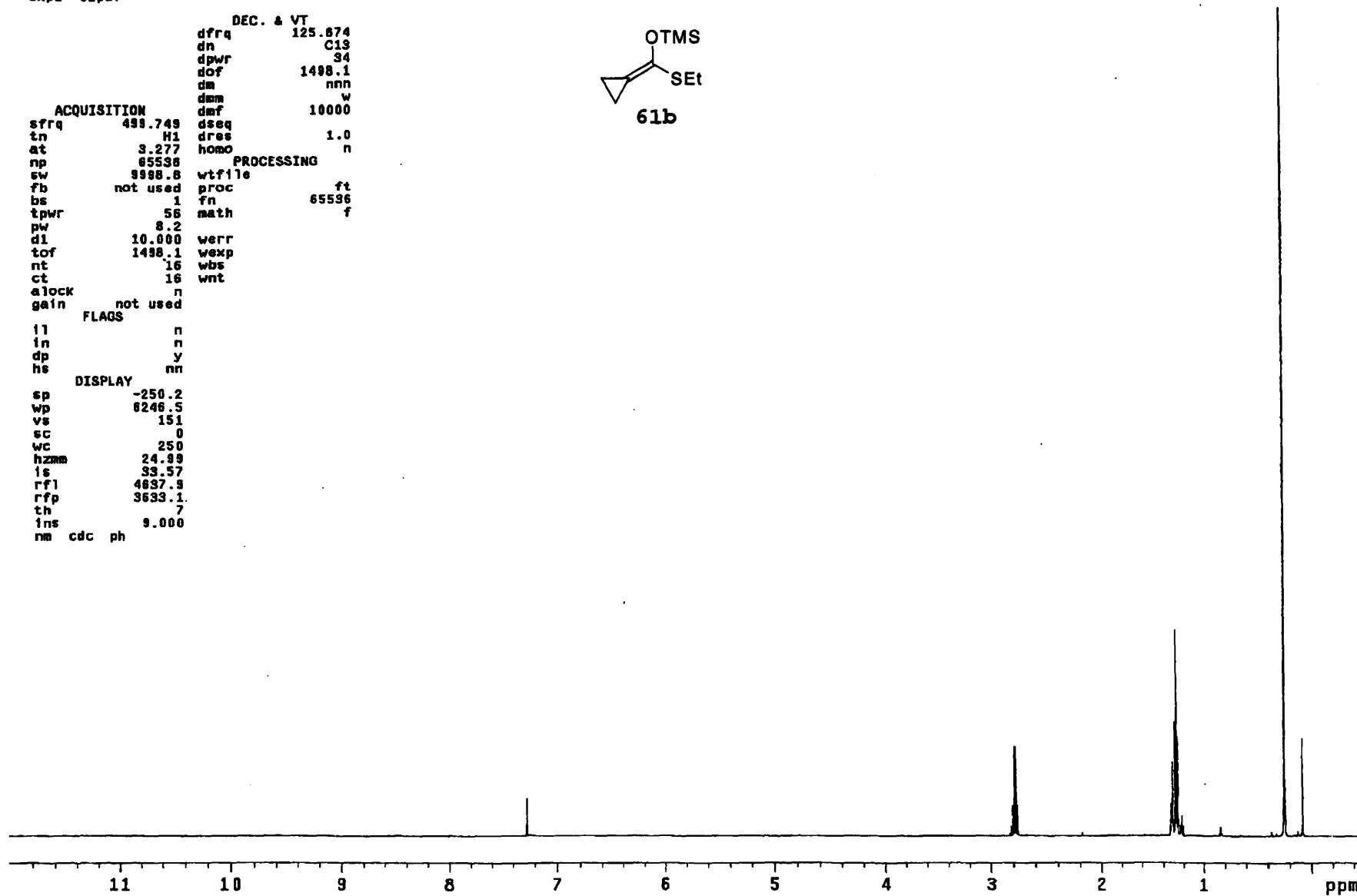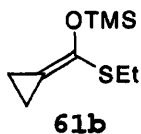
OTMS

SEt

**61b**

11   10   9   8   7   6   5   4   3   2   1   ppm

exp1 s2pul

DEC. & VT
dfrq        500.233
dn               H1
dpwr             37
dof          -500.0
dm                y
dmm               w
dmf           10000
dseq
dres            1.0
homo              n
     PROCESSING
lb             0.30
wtfile
proc             ft
fn           131072
math              f

werr
wexp
wbs
wnt

    ACQUISITION
sfrq       125.796
tn             C13
at           1.736
np          131010
sw         37735.8
fb        not used
bs               4
ss               1
tpwr            53
pw             6.9
d1           0.763
tof          631.4
nt           1e+06
ct               0
alock            n
gain      not used
     FLAGS
il               n
in               n
dp               y
hs              nn
    DISPLAY
sp         -6286.3
wp         37735.3
vs             460
sc               0
wc             250
hzmm        150.94
is         500.00
rfl        16001.8
rfp         9715.0
th              20
ins          1.000
ai    ph
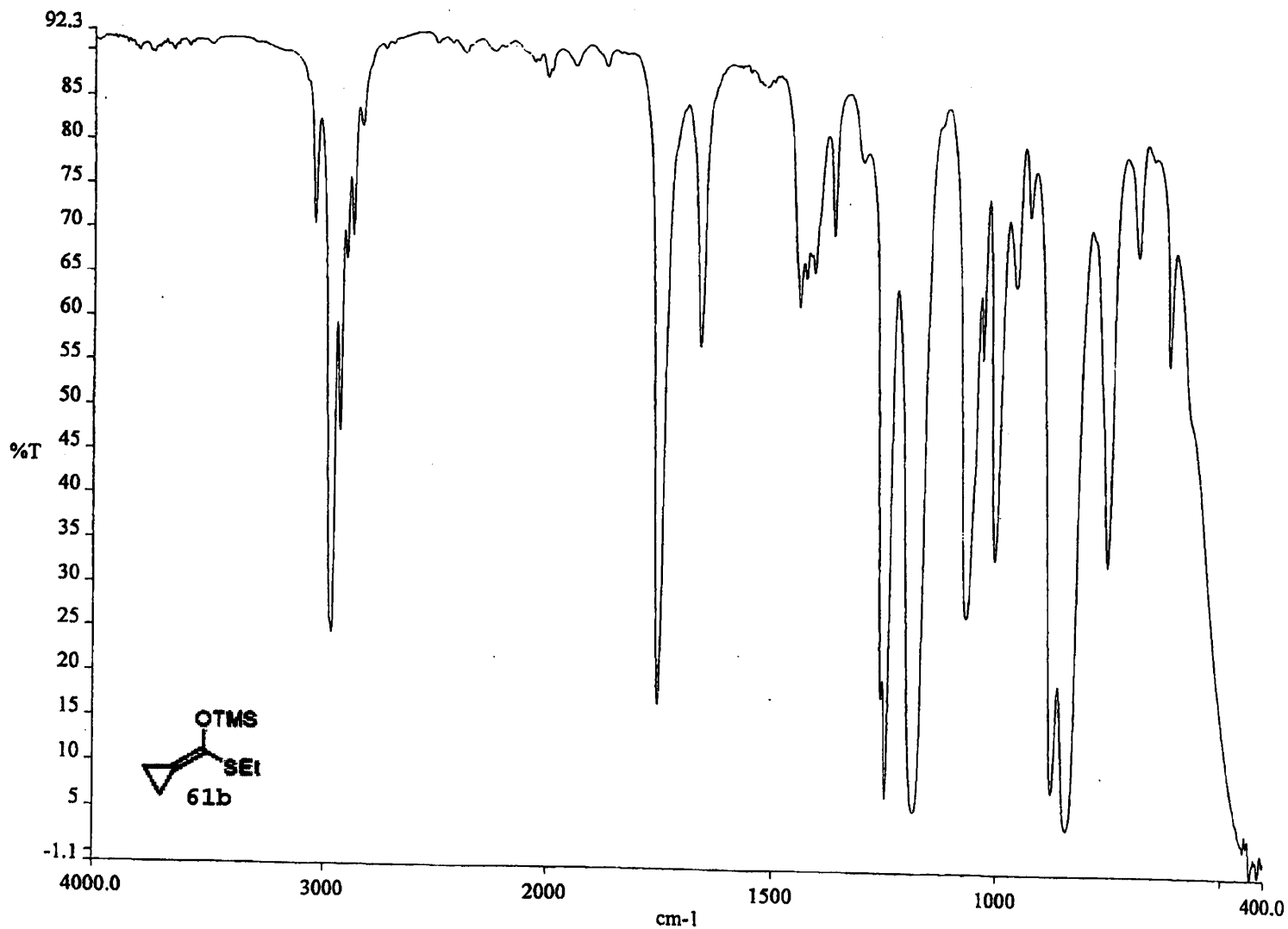
OTMS

SEt

61b

240   220   200   180   160   140   120   100   80   60   40   20   0   -20   ppm

expl s2pul

DEC. & VT
dfrq        125.674
dn          C13
dpwr        34
dof         1498.1
dm          nnn
dmm         w
dmf         10000

ACQUISITION
sfrq        499.748
tn          H1
at          3.277
np          65536
sw          9998.8
fb          not used
bs          1
tpwr        56
pw          8.2
d1          20.000
tof         1498.1
nt          16
ct          16
alock       n
gain        not used

dseq
dres        1.0
homo        n
PROCESSING
wtfile
proc        ft
fn          65536
math        f

werr
wexp
wbs
wnt

FLAGS
il          n
in          n
dp          y
hs          nn

DISPLAY
sp          -249.9
wp          6246.8
vs          151
sc          0
wc          250
hzmm        24.98
is          33.57
rfl         1004.5
rfp         0
th          2
ins         2.000
nm  cdc  ph

(+)-**84b**

expl s2pul

DEC. & VT
dfrq        500.233
dn              H1
dpwr            37
dof         -500.0
dm               y
dmm              w
dmf          10000
dseq
dres           1.0
homo             n
PROCESSING
lb            0.30
wtfile
proc            ft
fn          131072
math             f
werr
wexp
wbs
wnt

ACQUISITION
sfrq       125.796
tn             C13
at           1.796
np          131010
sw         37735.8
fb        not used
bs               4
ss               1
tpwr            53
pw             6.8
d1           0.763
tof          631.4
nt           1e+06
ct            1108
alock            n
gain      not used
FLAGS
il               n
in               n
dp               y
hs              nn
DISPLAY
sp         -6289.7
wp         37735.3
vs             272
sc               0
wc             250
hzmm        150.94
is          500.00
rfl        16005.3
rfp         5715.0
th              20
ins          1.000
ai       ph

(+)-**84b**

Zorbax CN; 1.0%iPrOH-hex; 1.0mL/min

MWD1 A, Sig=220,16 Ref=360,100 (D1214A6.D)

mAU
4.588 Area: 3399.11
5.102 Area: 3397.62

MWD1 B, Sig=230,16 Ref=360,100 (D1214A6.D)

mAU
4.588 Area: 6195.75
5.102 Area: 6219.12

MWD1 C, Sig=240,8 Ref=360,100 (D1214A6.D)

mAU
4.588 Area: 7078.19
5.102 Area: 7069.85

MWD1 D, Sig=254,16 Ref=360,100 (D1214A6.D)

mAU
4.588 Area: 1930.05
5.102 Area: 1912.39

MWD1 E, Sig=265,16 Ref=360,100 (D1214A6.D)

mAU
4.588 Area: 416.808
5.102 Area: 415.912

```
===================================================================
                      Area Percent Report
===================================================================

Sorted By            :        Signal
Multiplier           :        1.0000
Dilution             :        1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 A, Sig=220,16 Ref=360,100

Peak RetTime Type   Width      Area        Height      Area
  #   [min]         [min]    [mAU*s]       [mAU]        %
----|-------|----|-------|-----------|-----------|--------|
  1   4.588  MM   0.1896 3399.11206   298.79694   50.0110
  2   5.102  MM   0.1992 3397.62256   284.23749   49.9890

Totals :                  6796.73462   583.03442

 Results obtained with enhanced integrator!

Signal 2: MWD1 B, Sig=230,16 Ref=360,100

Peak RetTime Type   Width      Area        Height      Area
  #   [min]         [min]    [mAU*s]       [mAU]        %
----|-------|----|-------|-----------|-----------|--------|
  1   4.588  MM   0.1867 6195.75098   553.00427   49.9059
  2   5.102  MM   0.1972 6219.11719   525.51385   50.0941

Totals :                  1.24149e4   1078.51813

 Results obtained with enhanced integrator!
```

Signal 3: MWD1 C, Sig=240,8 Ref=360,100

```
Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   4.588 MM    0.1882 7078.19482  626.99695  50.0295
  2   5.102 MM    0.1979 7069.85059  595.39844  49.9705

Totals :                 1.41480e4   1222.39539
```

Results obtained with enhanced integrator!

Signal 4: MWD1 D, Sig=254,16 Ref=360,100

```
Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   4.588 MM    0.1918 1930.04724  167.68768  50.2297
  2   5.102 MM    0.2014 1912.39209  158.27319  49.7703

Totals :                 3842.43933   325.96088
```

Results obtained with enhanced integrator!

Signal 5: MWD1 E, Sig=265,16 Ref=360,100

```
Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   4.588 MM    0.2159  416.80847   32.17342  50.0538
  2   5.102 MM    0.2246  415.91214   30.85807  49.9462

Totals :                  832.72061    63.03149
```

Results obtained with enhanced integrator!
================================================================
                    *** End of Report ***

Zorbax CN; 1.0%iPrOH-hex; 1.0mL/min

MWD1 A, Sig=220,16 Ref=360,100 (D239F20.D)

mAU
600
400
200
0

4.587 Area: 181.121
5.095 Area: 4735.19

3    3.5    4    4.5    5    5.5    6    6.5    min

MWD1 B, Sig=230,16 Ref=360,100 (D239F20.D)

mAU
600
400
200
0

4.587 Area: 336.084
5.095 Area: 8768.99

3    3.5    4    4.5    5    5.5    6    6.5    min

MWD1 C, Sig=240,8 Ref=360,100 (D239F20.D)

mAU
600
400
200
0

4.587 Area: 381.785
5.095 Area: 9955.82

3    3.5    4    4.5    5    5.5    6    6.5    min

MWD1 D, Sig=254,16 Ref=360,100 (D239F20.D)

mAU
600
400
200
0

4.587 Area: 102.105
5.095 Area: 2672.1

3    3.5    4    4.5    5    5.5    6    6.5    min

MWD1 E, Sig=265,16 Ref=360,100 (D239F20.D)

mAU
600
400
200
0

4.587 Area: 19.3189
5.095 Area: 511.64

3    3.5    4    4.5    5    5.5    6    6.5    min

156

PMP1, Solvent A

PMP1, Solvent B

PMP1, Flow

===========================================================================
                          Area Percent Report
===========================================================================
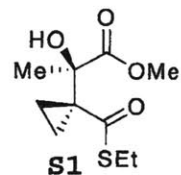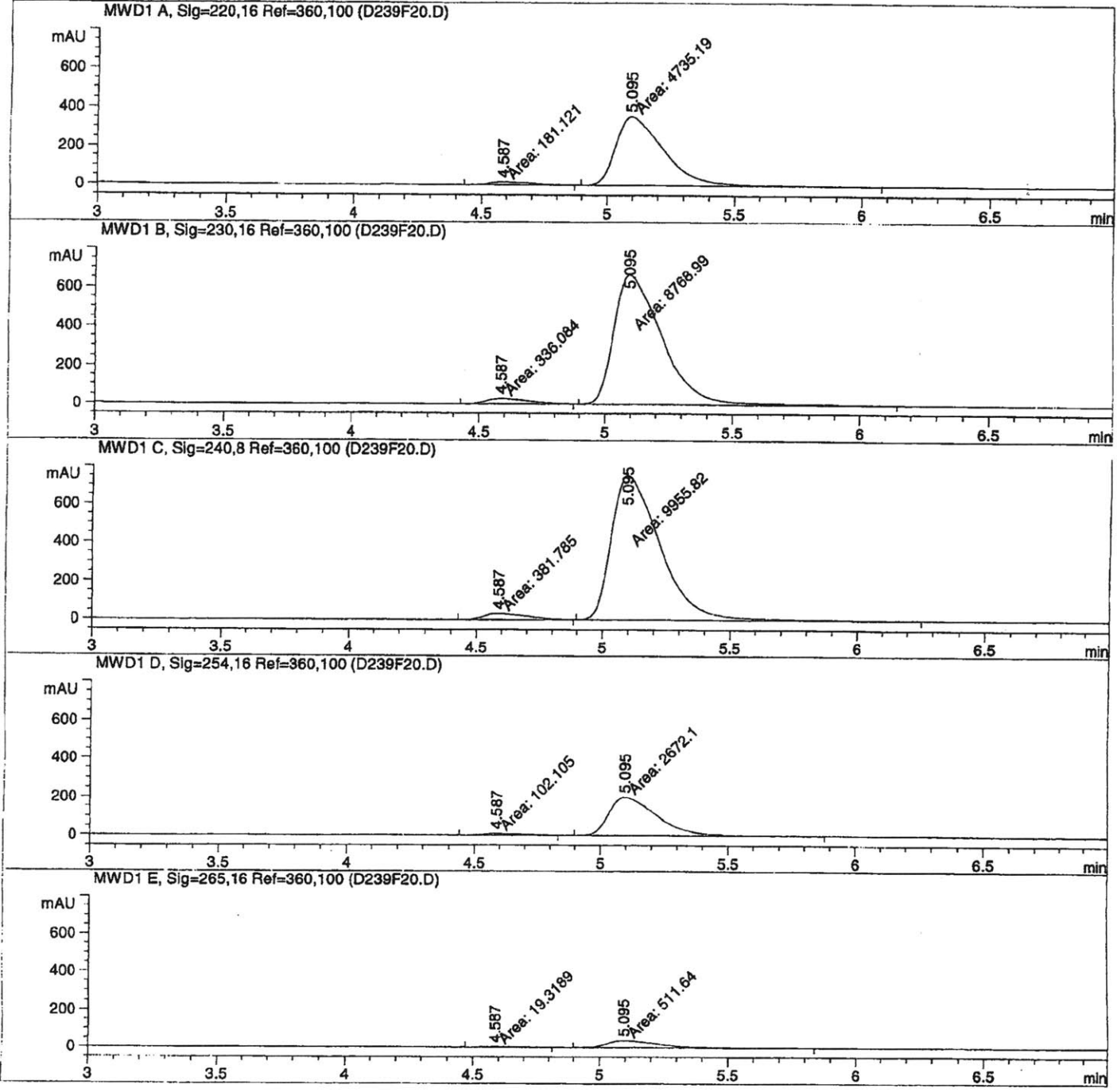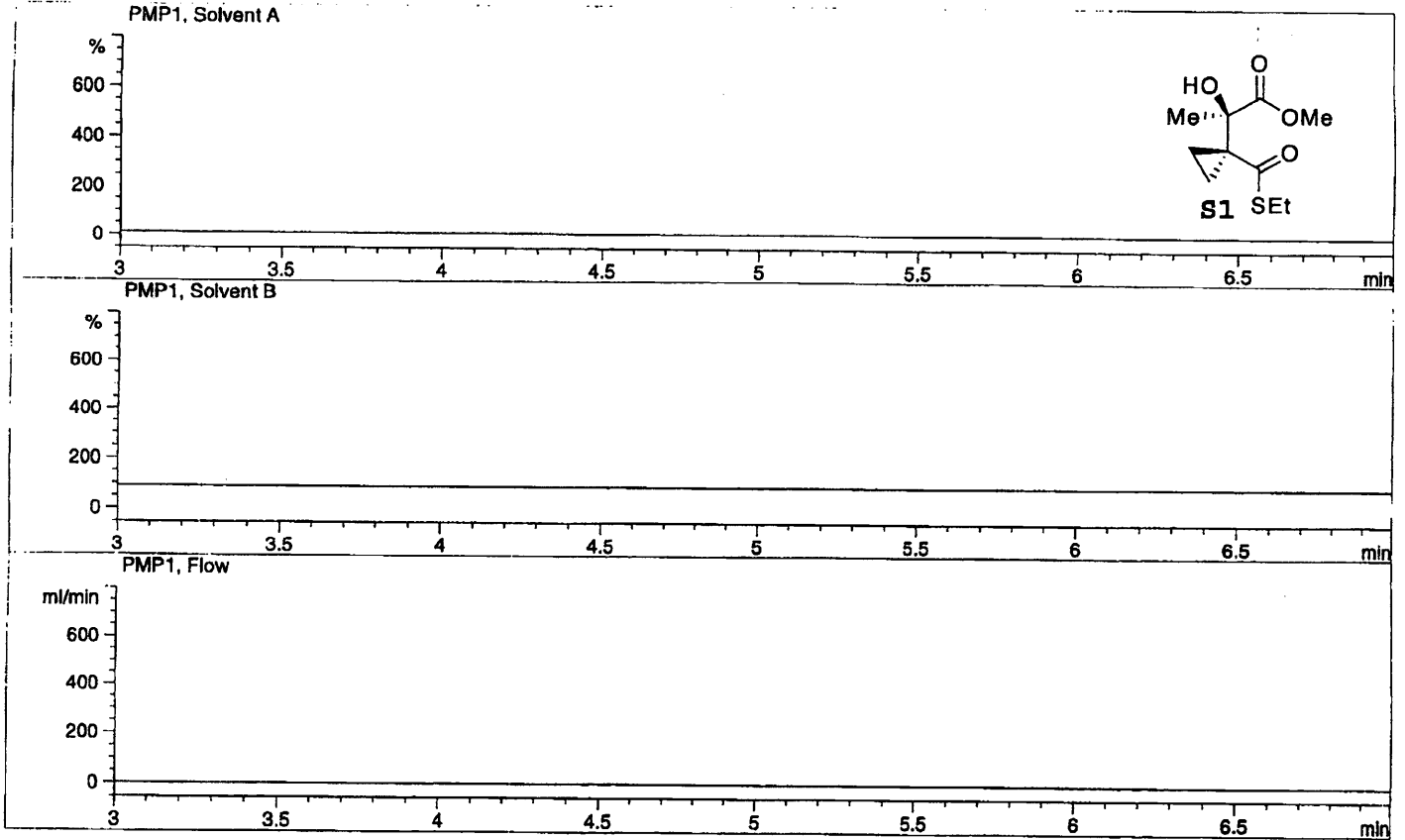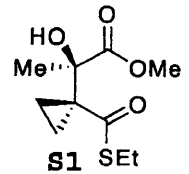
Sorted By              :      Signal
Multiplier             :      1.0000
Dilution               :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 A, Sig=220,16 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|------|---------|------|--------|-------------|------------|----------|
| 1 | 4.587 | MM | 0.1984 | 181.12068 | 15.21405 | 3.6841 |
| 2 | 5.095 | MM | 0.2209 | 4735.18701 | 357.24994 | 96.3159 |

Totals :                        4916.30769   372.46399

 Results obtained with enhanced integrator!

Signal 2: MWD1 B, Sig=230,16 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|------|---------|------|--------|-------------|------------|----------|
| 1 | 4.587 | MM | 0.1964 | 336.08368 | 28.51702 | 3.6912 |
| 2 | 5.095 | MM | 0.2197 | 8768.99316 | 665.32880 | 96.3088 |

Totals :                        9105.07684   693.84582

 Results obtained with enhanced integrator!

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Signal 3: MWD1 C, Sig=240,8 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 4.587 | MM | 0.1971 | 381.78519 | 32.28540 | 3.6932 |
| 2 | 5.095 | MM | 0.2201 | 9955.81836 | 753.86084 | 96.3068 |

Totals :                    1.03376e4    786.14624

Results obtained with enhanced integrator!

Signal 4: MWD1 D, Sig=254,16 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 4.587 | MM | 0.1951 | 102.10541 | 8.72269 | 3.6805 |
| 2 | 5.095 | MM | 0.2212 | 2672.10400 | 201.31873 | 96.3195 |

Totals :                    2774.20941   210.04141

Results obtained with enhanced integrator!

Signal 5: MWD1 E, Sig=265,16 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 4.587 | MM | 0.1958 | 19.31890 | 1.64459 | 3.6385 |
| 2 | 5.095 | MM | 0.2330 | 511.64023 | 36.59689 | 96.3615 |

Totals :                    530.95913    38.24148

Results obtained with enhanced integrator!
===============================================================
*** End of Report ***

158

exp1 s2pul

DEC. & VT
dfrq        125.795
dn              C13
dpwr             37
dof               0
dm              nnn
dmm               c
dmf           10000
dseq
dres            1.0
homo              n
PROCESSING
wtfile
proc             ft
fn           131072
math              f

werr
wexp
wbs
wnt

ACQUISITION
sfrq        500.235
tn               H1
at            3.200
np            64000
sw          10000.0
fb         not used
bs                1
ss                1
tpwr             59
pw              9.8
d1                0
tof           1498.2
nt               16
ct               16
alock             n
gain       not used
FLAGS
il                n
in                n
dp                y
hs               nn
DISPLAY
sp          -250.2
wp          6252.7
vs             151
sc               0
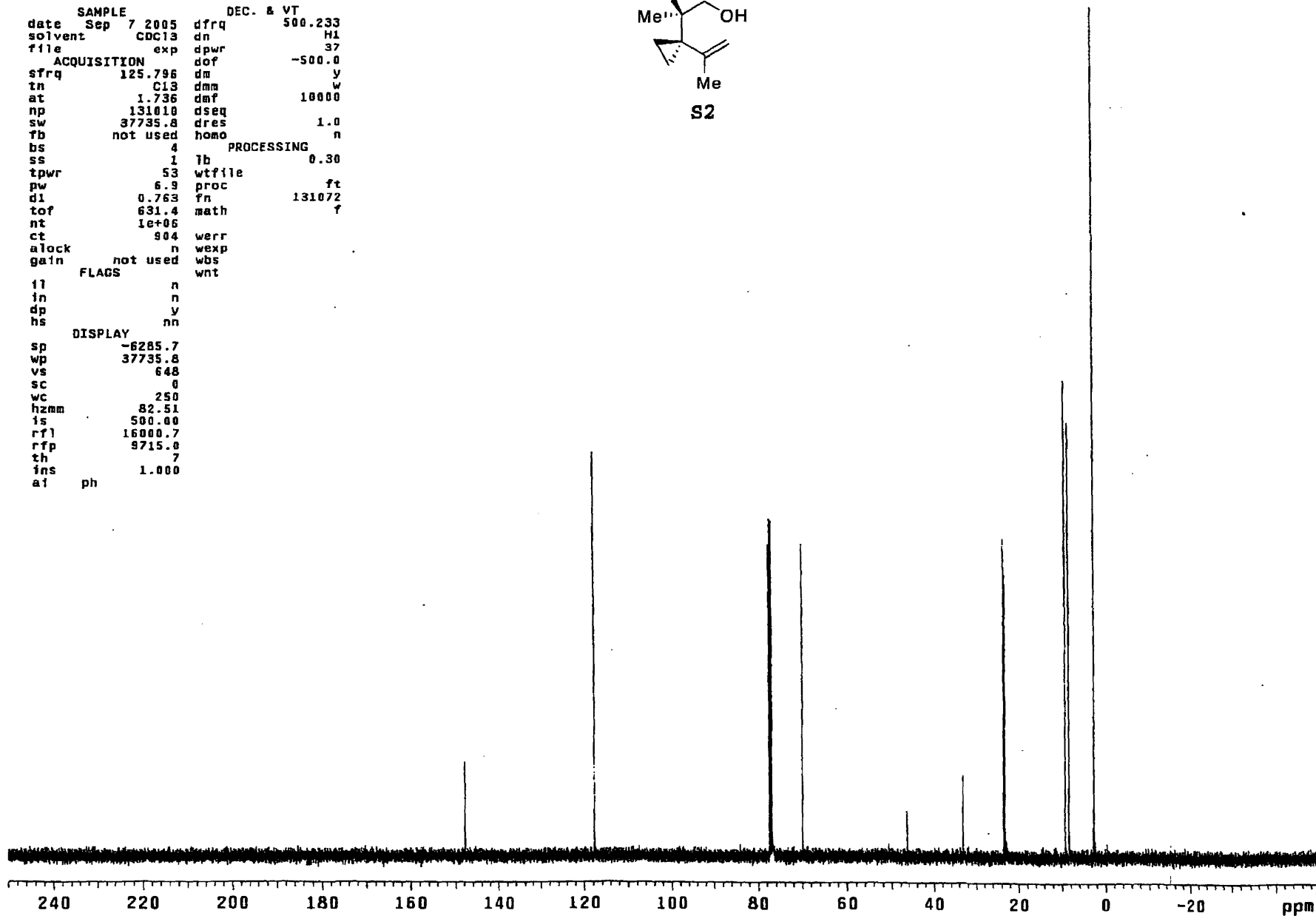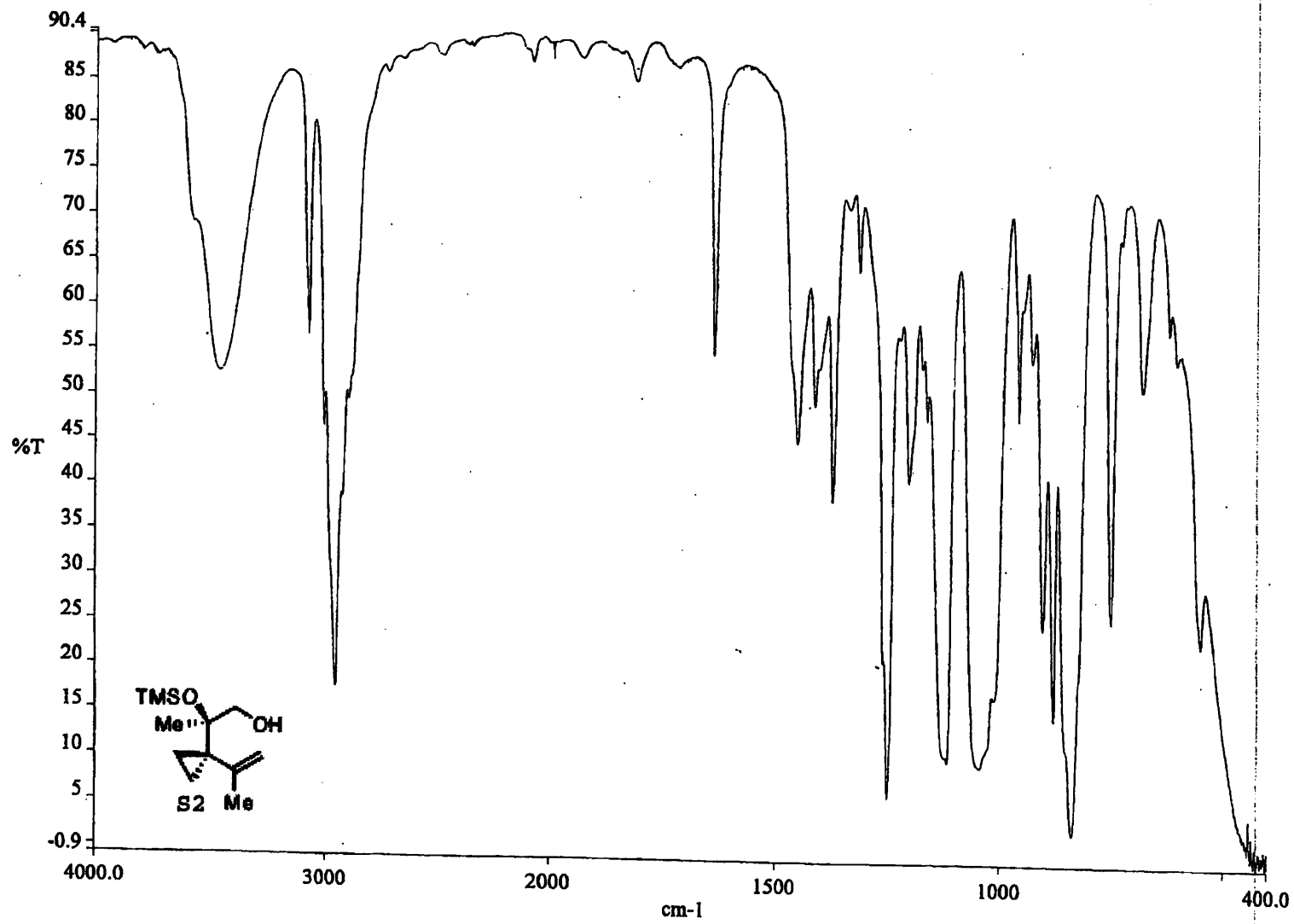wc             250
hzmm         25.01
is          100.00
rfl         4632.6
rfp         3636.7
th               7
ins          1.000
nm    ph

(+)-86

exp1  s2pul

DEC. & VT
| | |
|---|---|
| dfrq | 500.233 |
| dn | H1 |
| dpwr | 37 |
| dof | -500.0 |
| dm | y |
| dmm | w |
| dmf | 10000 |
| dseq | |
| dres | 1.0 |
| homo | n |

ACQUISITION
| | |
|---|---|
| sfrq | 125.756 |
| tn | C13 |
| at | 1.736 |
| np | 131010 |
| sw | 37735.8 |
| fb | not used |
| bs | 4 |
| ss | 1 |
| tpwr | 53 |
| pw | 6.9 |
| d1 | 0.763 |
| tof | 631.4 |
| nt | 1e+06 |
| ct | 900 |
| alock | n |
| gain | not used |

PROCESSING
| | |
|---|---|
| lb | 0.30 |
| wtfile | |
| proc | ft |
| fn | 131072 |
| math | f |
| werr | |
| wexp | |
| wbs | |
| wnt | |

FLAGS
| | |
|---|---|
| il | n |
| in | n |
| dp | y |
| hs | nn |

DISPLAY
| | |
|---|---|
| sp | -6287.4 |
| wp | 37735.3 |
| vs | 1279 |
| sc | 0 |
| wc | 250 |
| hzmm | 150.94 |
| is | 500.00 |
| rfl | 16003.0 |
| rfp | 9715.0 |
| th | 10 |
| ins | 1.000 |
| ai    ph | |



(+)-86

exp1  s2pul

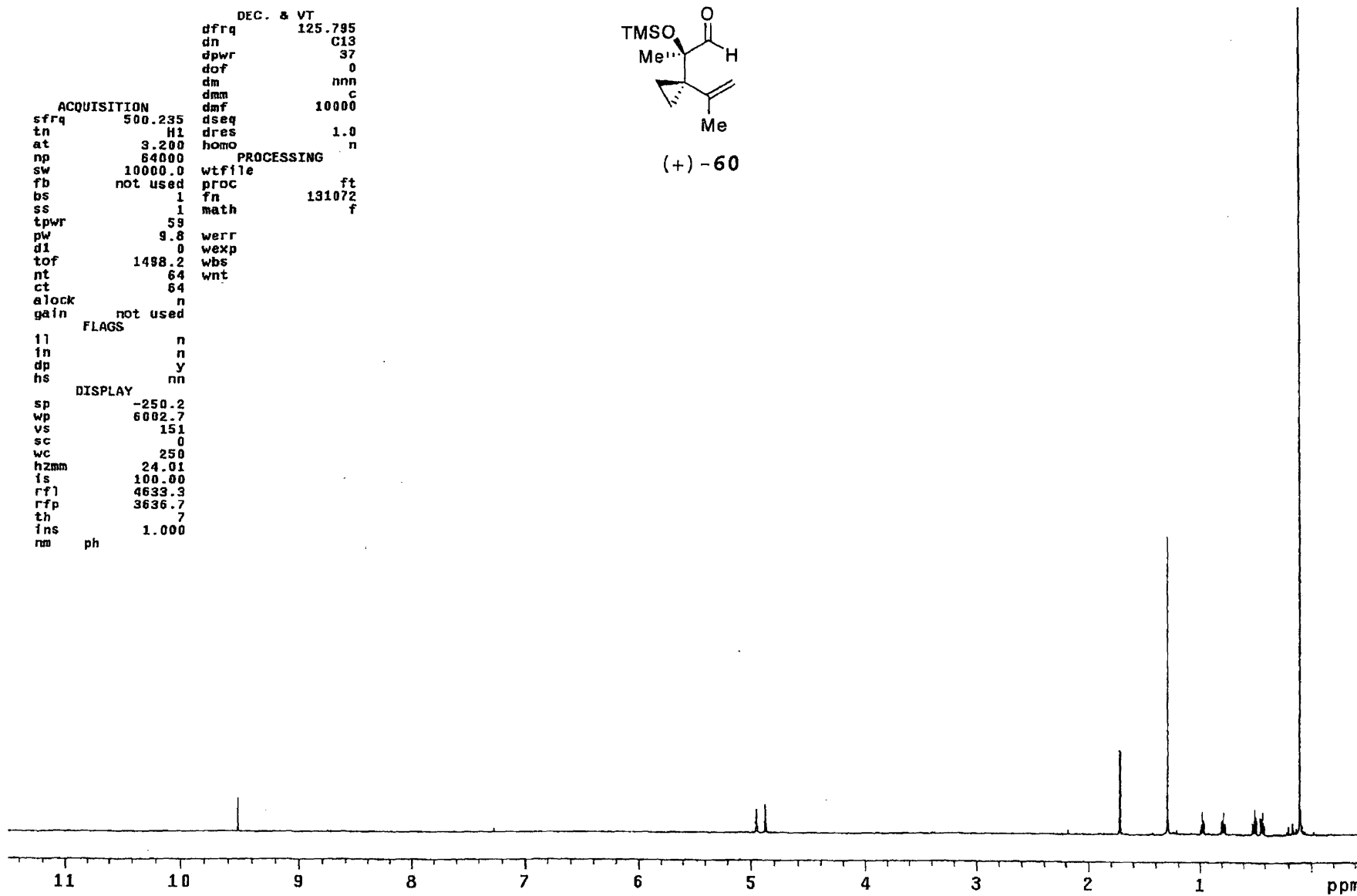                                    DEC. & VT
                              dfrq        125.795
                              dn              C13
                              dpwr             37
                              dof               0
                              dm              nnn
                              dmm               c
         ACQUISITION          dmf           10000
sfrq       500.235            dseq
tn              H1            dres            1.0
at           3.200            homo              n
np           64000              PROCESSING
sw         10000.0            wtfile
fb        not used            proc             ft
bs               1            fn           131072
ss               1            math              f
tpwr            59
pw             9.8            werr
d1               0            wexp
tof         1498.2            wbs
nt              16            wnt
ct              16
alock            n
gain      not used
         FLAGS
il               n
in               n
dp               y
hs              nn
         DISPLAY
sp          -250.2
wp          6252.9
vs             151
sc               0
wc             250
h2mm         25.01
is          100.00
rfl         4631.0
rfp         3636.7
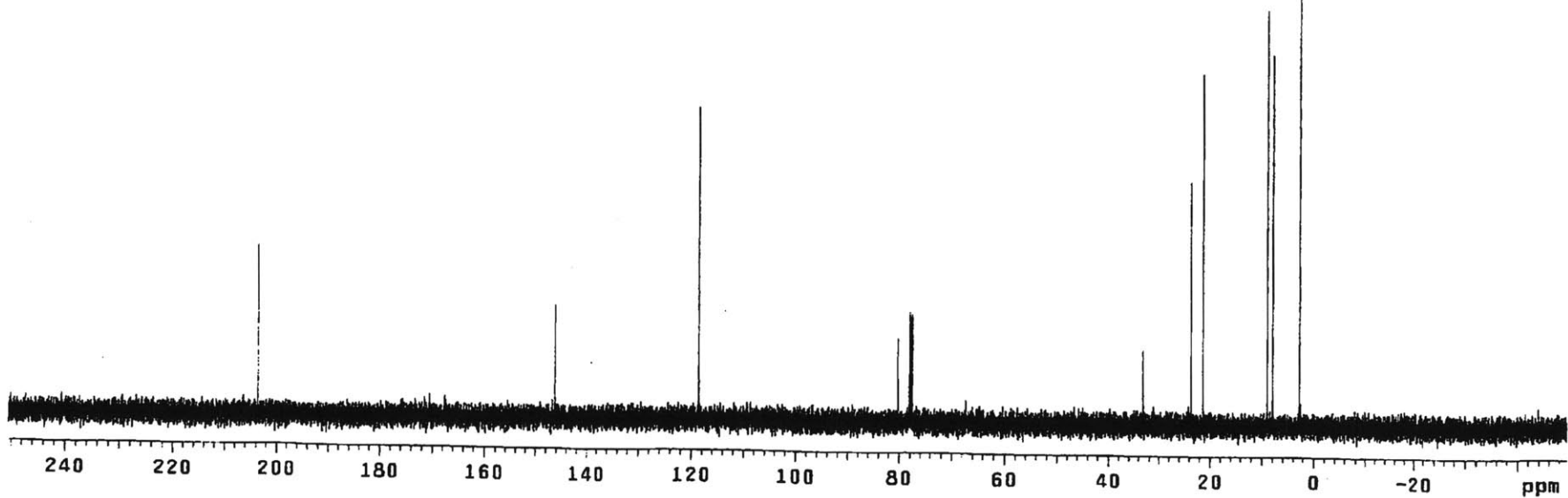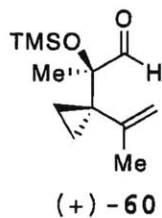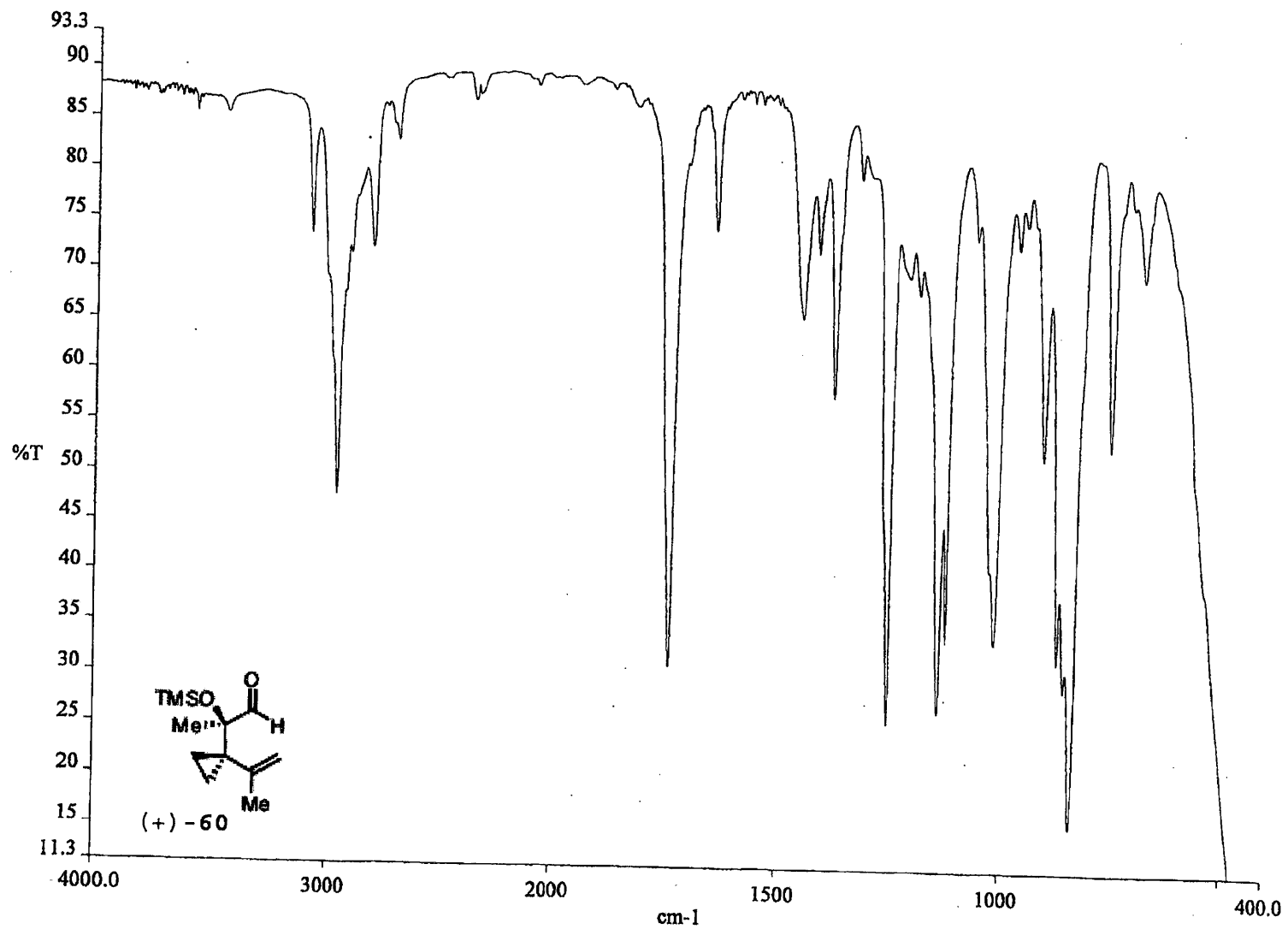th               2
ins          3.000
nm      ph

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(+)-87
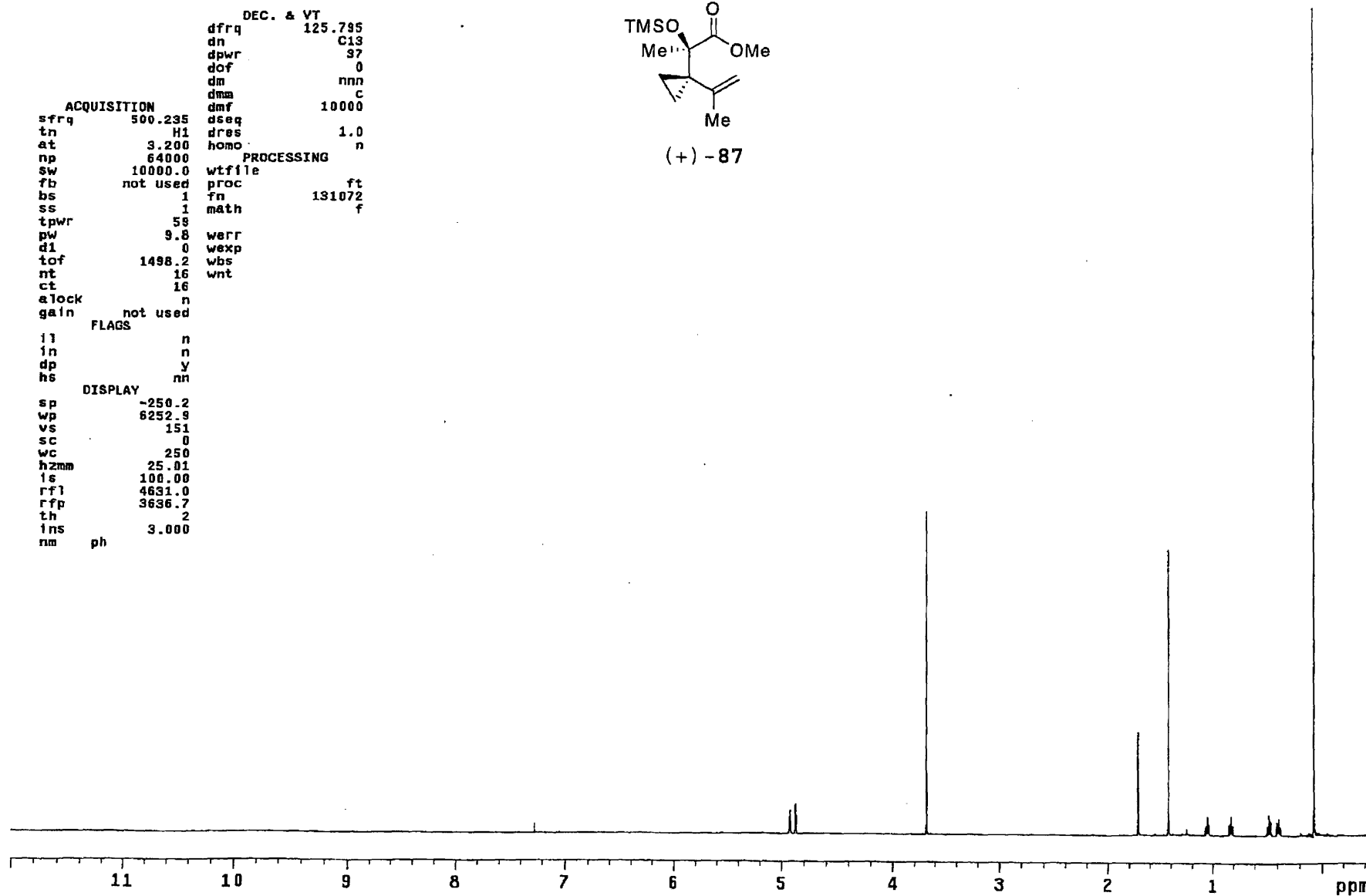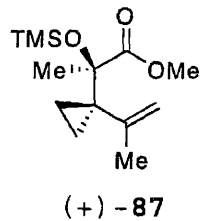
DEC. & VT
dfrq        500.233
dn              H1
dpwr            37
dof         -500.0
da               y
dmm              w
dmf          10000
dseq
dres           1.0
homo             n
PROCESSING
lb            0.30
wtfile
proc            ft
fn          131072
math             f

werr
wexp
wbs
wnt

ACQUISITION
sfrq        125.796
tn             C13
at           1.796
np          131010
sw         37735.8
fb        not used
bs               4
ss               1
tpwr            53
pw             6.9
d1           0.763
tof          631.4
nt           1e+06
ct             200
alock            n
gain      not used
FLAGS
il               n
in               n
dp               y
hs              nn
DISPLAY
sp         -8285.1
wp         37735.3
vs             170
sc               0
wc             250
hzmm        150.94
is          500.00
rfl        16000.7
rfp         9715.0
th              14
ins          1.000
ai      ph
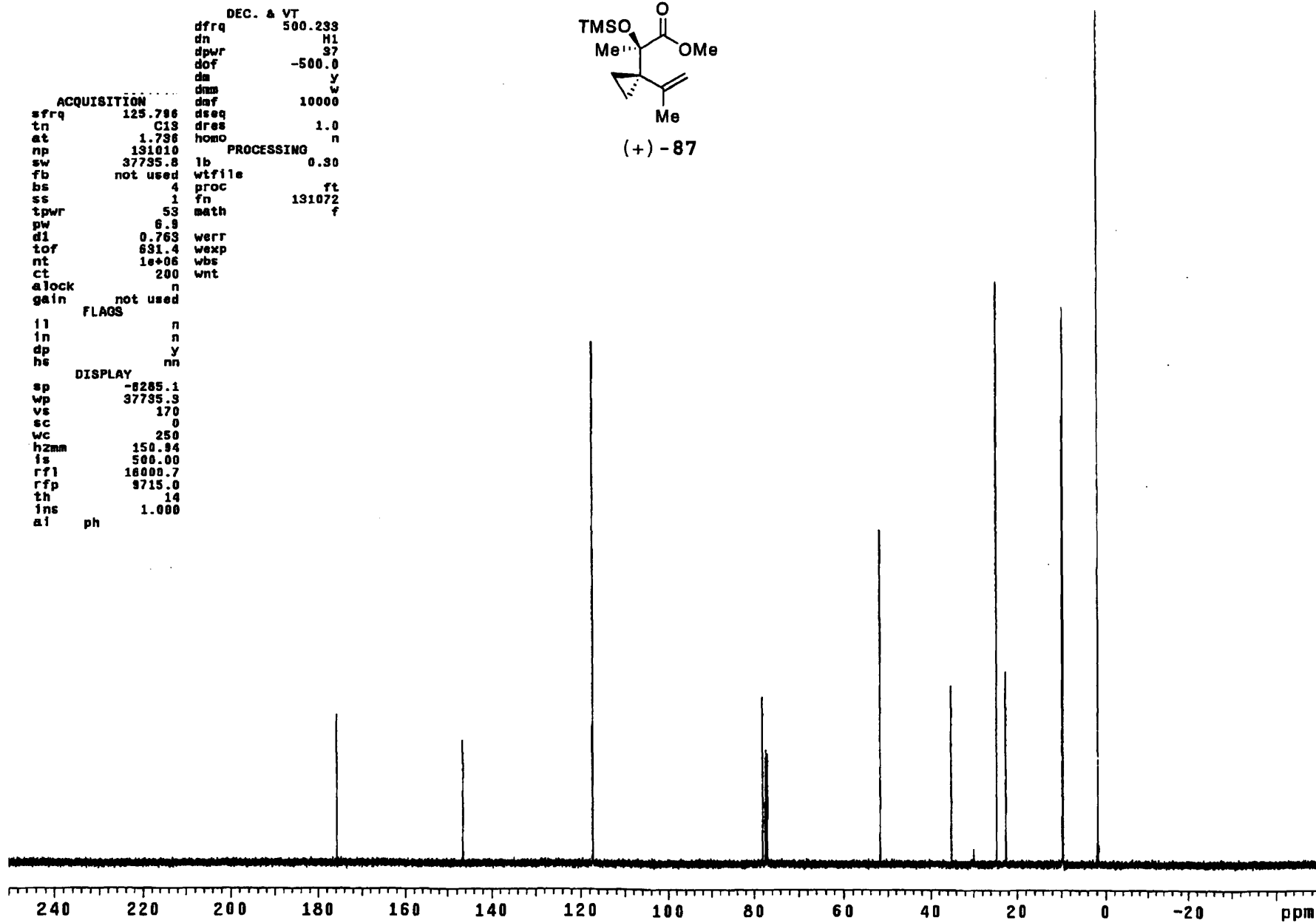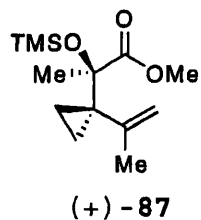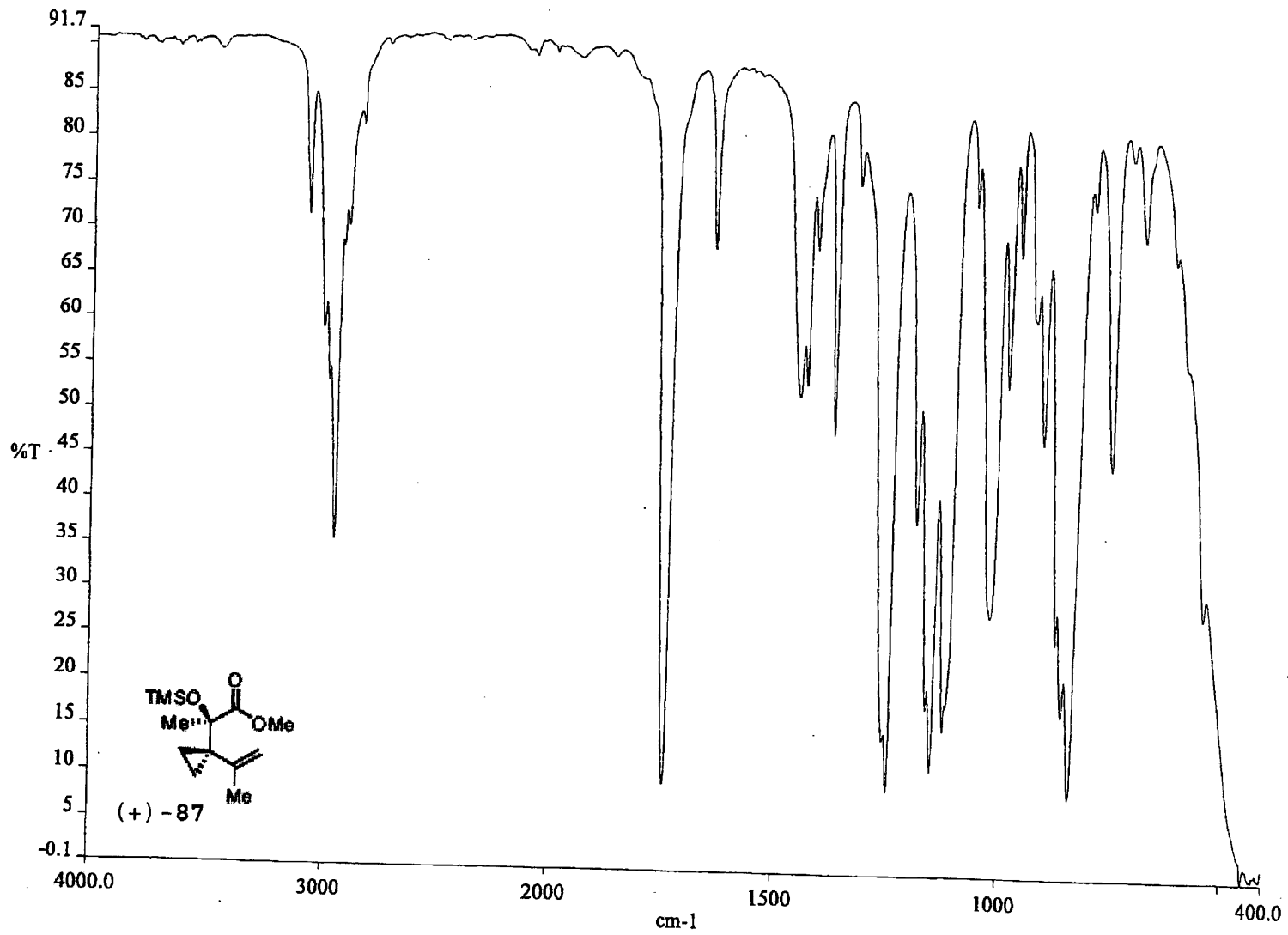
(+)-87

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exp903  s2pul

ACQUISITION
sfrq       500.235
tn              H1
at           3.200
np           64000
sw         10000.0
fb        not used
bs              4
ss              1
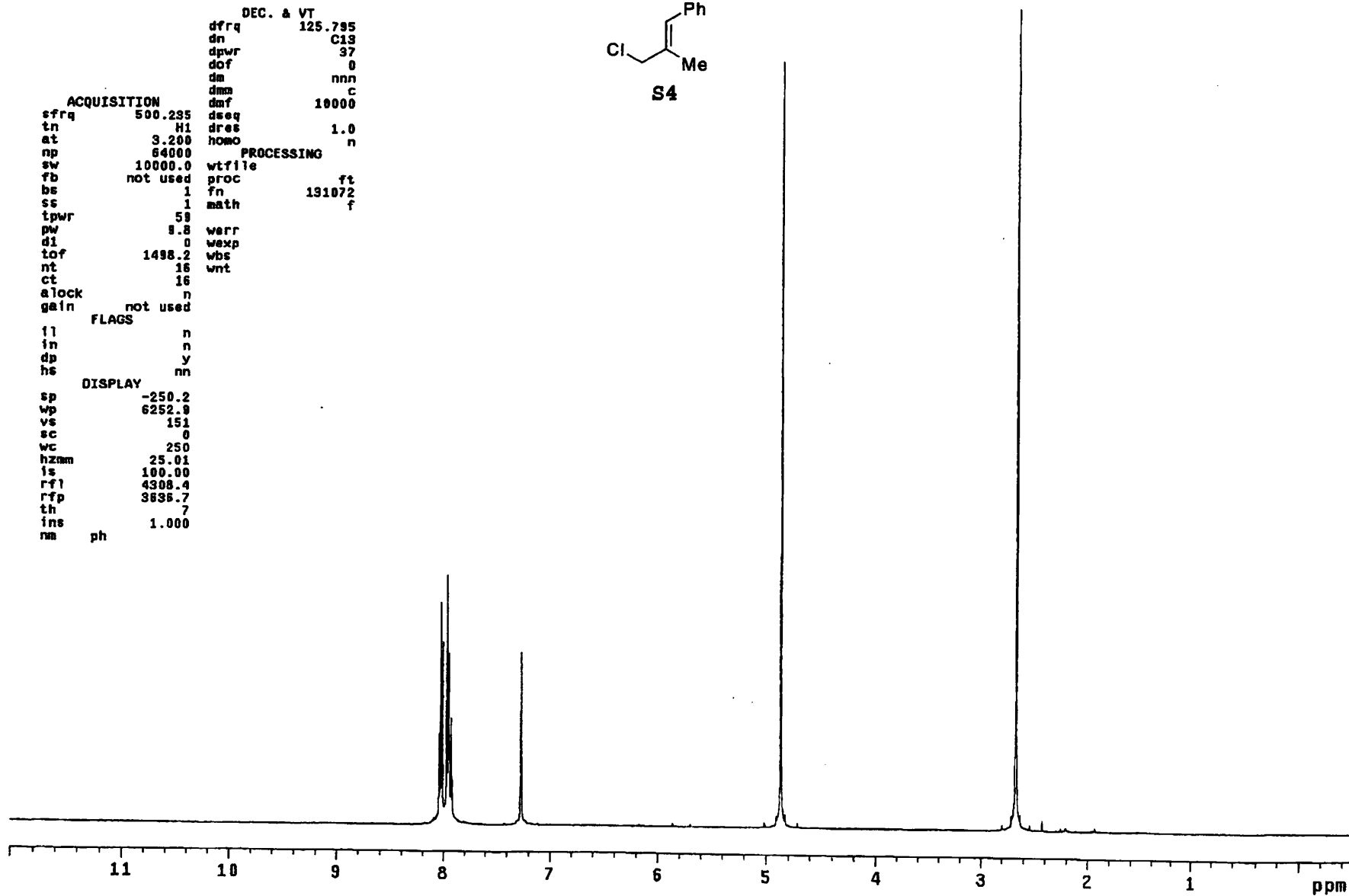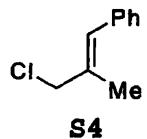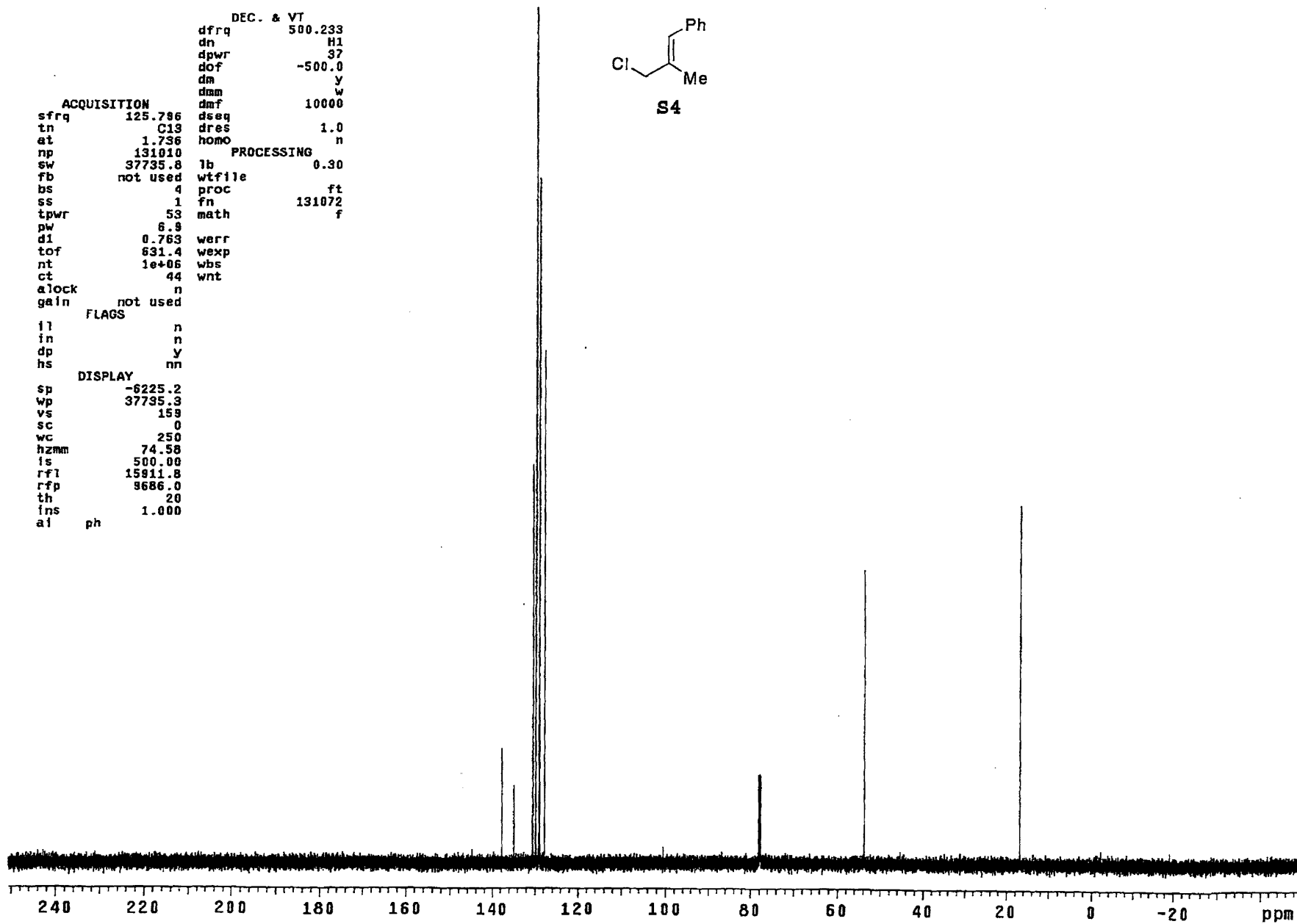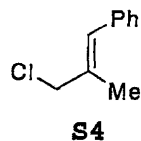tpwr           59
pw            9.8
d1         15.000
tof        1498.2
nt             32
ct             32
alock           n
gain      not used
FLAGS
ll              n
in              n
dp              y
hs             nn
DISPLAY
sp         -250.2
wp         6252.7
vs            151
sc              0
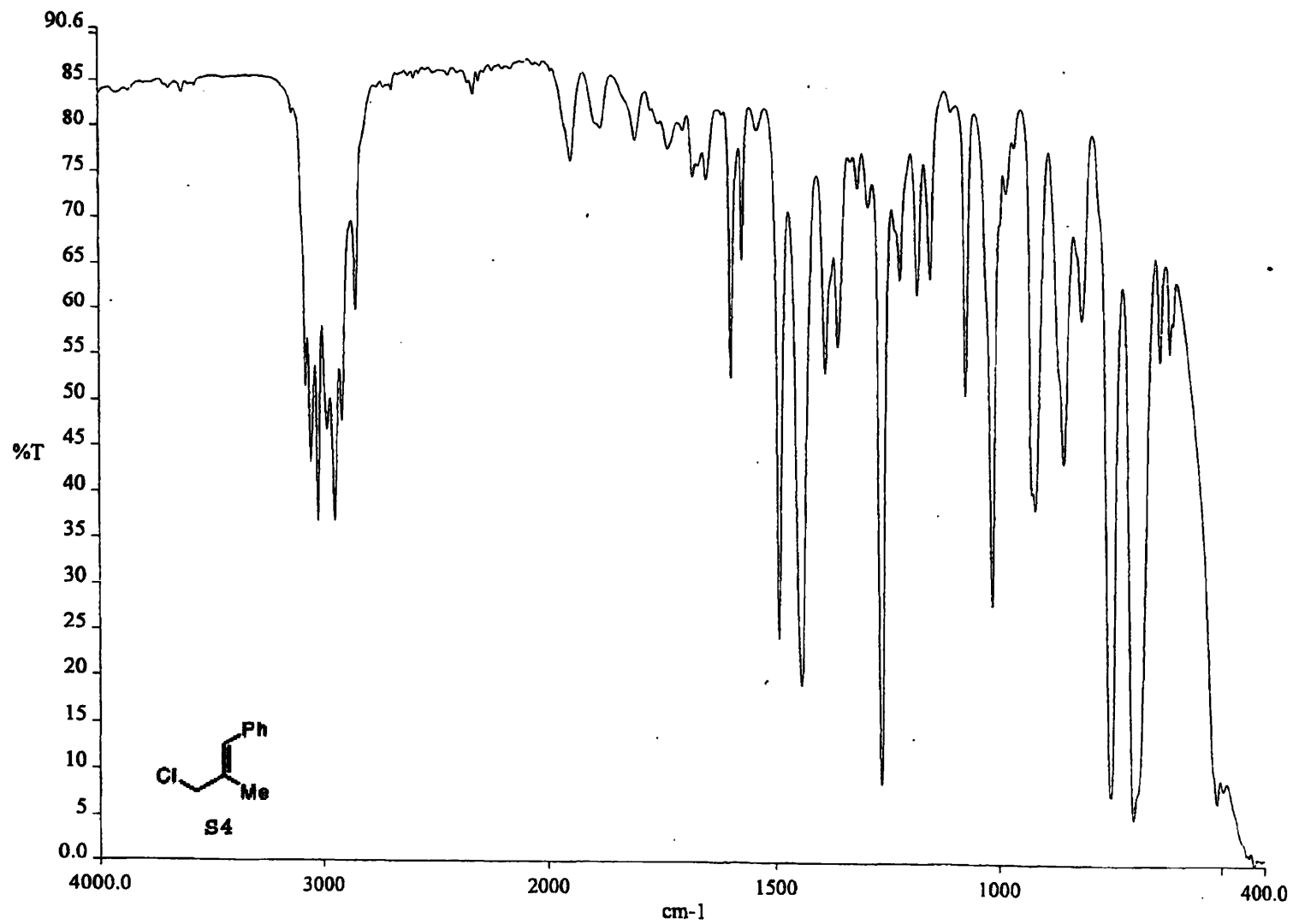wc            250
hzmm        25.01
is         100.00
rfl        4632.5
rfp        3636.7
th              7
ins         3.000
nm      ph
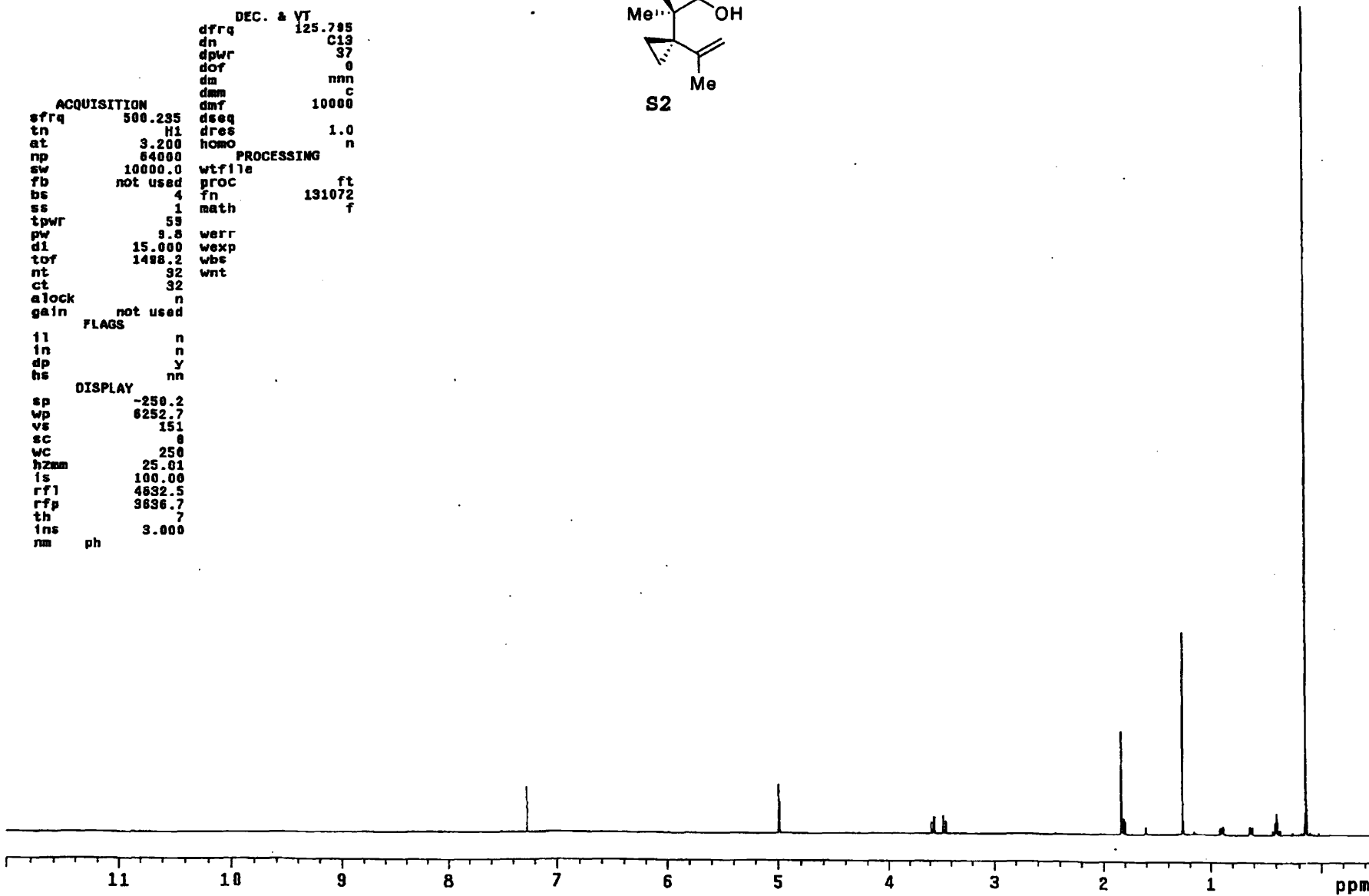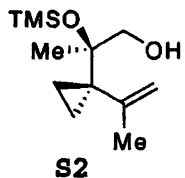
DEC. & VT
dfrq       125.795
dn             C13
dpwr            37
dof              0
dm             nnn
dmm              c
dmf          10000
dseq
dres           1.0
homo             n
PROCESSING
wtfile
proc            ft
fn          131072
math             f
werr
wexp
wbs
wnt

TMSO
Me''
OH
Me

S2

expl s2pul

SAMPLE
date    Sep  7 2005
solvent        CDC13
file           exp
    ACQUISITION
sfrq        125.796
tn             C13
at           1.736
np          131010
sw         37735.8
tb        not used
bs             4
ss             1
tpwr          53
pw           6.9
d1         0.763
tof        631.4
nt         1e+06
ct           904
alock          n
gain     not used
    FLAGS
ll             n
in             n
dp             y
hs            nn
    DISPLAY
sp        -6285.7
wp         37735.8
vs           648
sc             0
wc           250
hzmm        82.51
is         500.00
rfl       16000.7
rfp        9715.8
th             7
ins        1.000
ai    ph
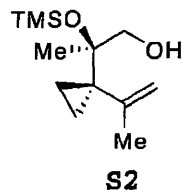
DEC. & VT
dfrq       500.233
dn             H1
dpwr           37
dof        -500.0
dm             y
dmm            w
dmf         10000
dseq
dres          1.0
homo           n
    PROCESSING
lb          0.30
wtfile
proc           ft
fn         131072
math            f

werr
wexp
wbs
wnt



TMSO
Me''
Me
OH
Me

S2

240    220    200    180    160    140    120    100    80    60    40    20    0    -20    ppm

exp1 s2pul

DEC. & VT
dfrq        125.795
dn              C13
dpwr             37
dof               0
dm              nnn
dmm               c
dmf           10000
dseq
dres            1.0
homo              n
    PROCESSING
wtfile
proc             ft
fn           131072
math              f

werr
wexp
wbs
wnt

ACQUISITION
sfrq       500.235
tn             H1
at          3.200
np          64000
sw        10000.0
fb       not used
bs              1
ss              1
tpwr           59
pw            9.8
d1              0
tof        1498.2
nt             64
ct             64
alock           n
gain     not used
    FLAGS
11              n
in              n
dp              y
hs             nn
    DISPLAY
sp         -250.2
wp         6002.7
vs            151
sc              0
wc            250
hzmm        24.01
is         100.00
rfl        4633.3
rfp        3636.7
th              7
ins         1.000
nm      ph

(+)-60

exp2 s2pul

SAMPLE
date     Nov 1 2005
solvent       CDCl3
file           exp
   ACQUISITION
sfrq      125.796
tn            C13
at          1.736
np         131010
sw        37735.8
fb       not used
bs              4
ss              1
tpwr           53
pw            6.9
d1          0.763
tof         631.4
nt          1e+07
ct             12
alock           n
gain     not used
      FLAGS
il              n
in              n
dp              y
hs             nn
      DISPLAY
sp        -6225.8
wp        37735.8
vs            121
sc              0
wc            250
hzmm        10.91
is         500.00
rfl        15911.8
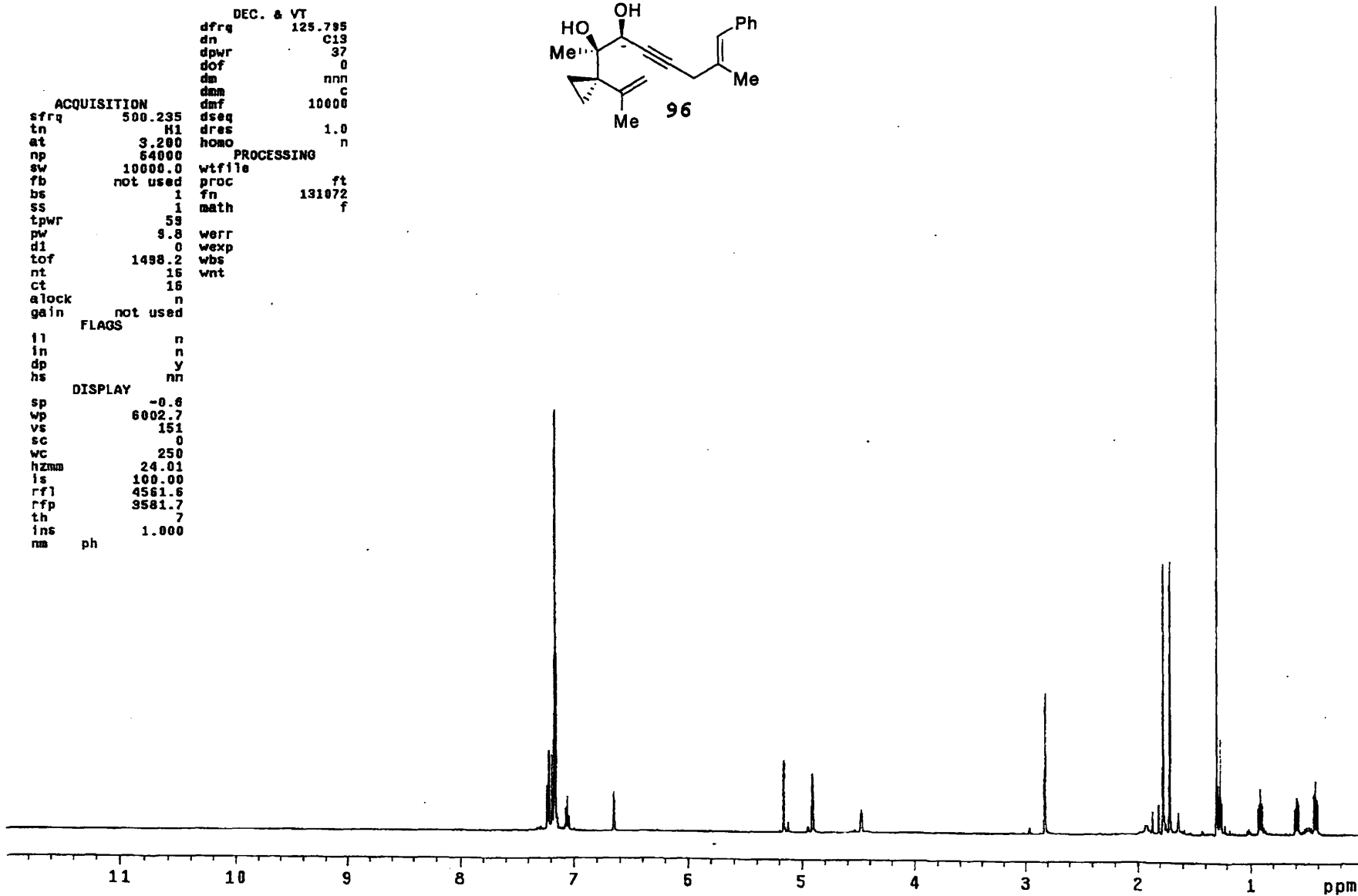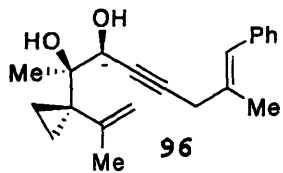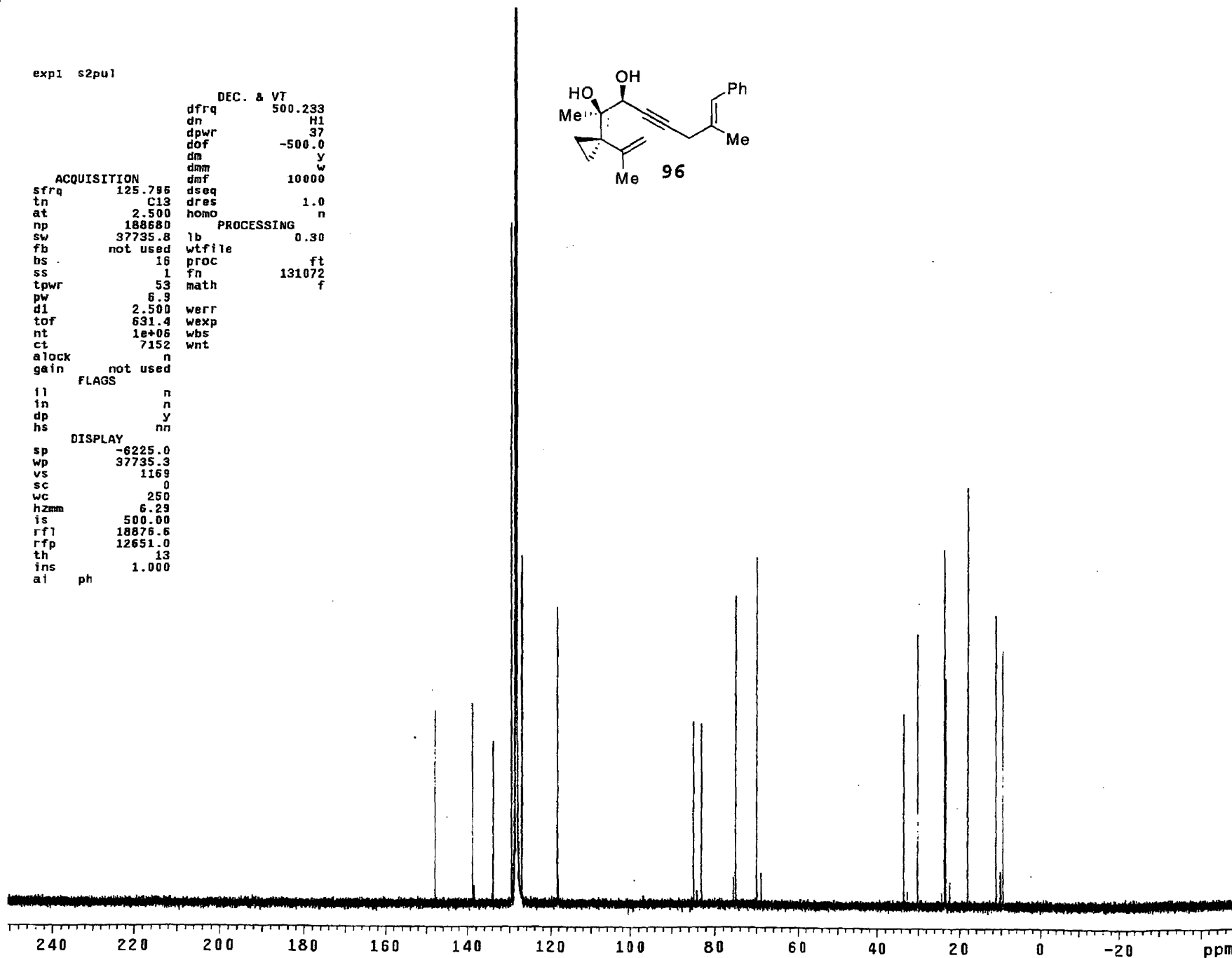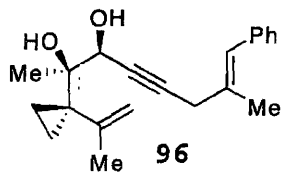rfp        9686.0
th             20
ins         1.000
ai      ph

        DEC. & VT
dfrq      500.233
dn             H1
dpwr           37
dof        -500.0
dm              y
dmm             w
dmf         10000
dseq
dres          1.0
homo            n
      PROCESSING
lb           0.30
wtfile
proc           ft
fn         131072
math            f

werr
wexp
wbs
wnt

(+) - 60

exp60 s2pul

DEC. & VT
dfrq          125.795
dn               C13
dpwr              37
dof                0
dm               nnn
dmm                c
dmf            10000
dseq
dres             1.0
homo               n
PROCESSING
wtfile
proc              ft
fn            191072
math               f

werr
wexp
wbs
wnt

ACQUISITION
sfrq        500.235
tn               H1
at            3.200
np            64000
sw          10000.0
fb         not used
bs                1
ss                1
tpwr             59
pw              9.8
d1                0
tof          1498.2
nt               16
ct               16
alock             n
gain       not used
FLAGS
il                n
in                n
dp                y
hs               nn
DISPLAY
sp           -250.2
wp           6252.9
vs              151
sc                0
wc              250
hzmm          25.01
is           100.00
rfl          4308.4
rfp          3635.7
th                7
ins           1.000
nm     ph

S4



ppm scale: 11 10 9 8 7 6 5 4 3 2 1

DEC. & VT

| | |
|---|---|
| dfrq | 500.233 |
| dn | H1 |
| dpwr | 37 |
| dof | -500.0 |
| dm | y |
| dmm | w |
| dmf | 10000 |
| dseq | |
| dres | 1.0 |
| homo | n |

ACQUISITION

| | |
|---|---|
| sfrq | 125.796 |
| tn | C13 |
| at | 1.736 |
| np | 131010 |
| sw | 37735.8 |
| fb | not used |
| bs | 4 |
| ss | 1 |
| tpwr | 53 |
| pw | 6.9 |
| d1 | 0.763 |
| tof | 631.4 |
| nt | 1e+06 |
| ct | 44 |
| alock | n |
| gain | not used |

PROCESSING

| | |
|---|---|
| lb | 0.30 |
| wtfile | |
| proc | ft |
| fn | 131072 |
| math | f |
| werr | |
| wexp | |
| wbs | |
| wnt | |

FLAGS

| | |
|---|---|
| il | n |
| in | n |
| dp | y |
| hs | nn |

DISPLAY

| | |
|---|---|
| sp | -6225.2 |
| wp | 37735.3 |
| vs | 159 |
| sc | 0 |
| wc | 250 |
| hzmm | 74.58 |
| is | 500.00 |
| rfl | 15911.8 |
| rfp | 9686.0 |
| th | 20 |
| ins | 1.000 |
| ai | ph |

S4

240  220  200  180  160  140  120  100  80  60  40  20  0  -20  ppm

exp2  s2pul

SAMPLE
date    Jan 21 2006
solvent        CDCl3
file           exp
    ACQUISITION
sfrq       500.235
tn              H1
at           3.200
np           64000
sw         10000.0
fb        not used
bs               1
ss               1
tpwr            59
pw             9.8
d1               0
tof         1498.2
nt              16
ct              16
alock            n
gain      not used
    FLAGS
il               n
in               n
dp               y
hs              nn
    DISPLAY
sp          -250.2
wp          6252.8
vs             151
sc               0
wc             250
hzmm         25.01
is          100.00
rfl         4622.3
rfp         3621.7
th               7
ins          1.000
nm      ph

     DEC. & VT
dfrq       125.795
dn             C13
dpwr            37
dof              0
dm             nnn
dmm              c
dmf          10000
dseq
dres           1.0
homo             n
   PROCESSING
wtfile
proc            ft
fn          131072
math             f

werr
wexp
wbs
wnt

95

exp2  s2pul

SAMPLE
date      Jan 21 2006
solvent          COCl3
file              exp
ACQUISITION
sfrq        125.796
tn              C13
at            1.736
np          131010
sw         37735.8
fb       not used
bs                4
ss                1
tpwr             53
pw              6.9
d1            0.763
tof           631.4
nt            1e+07
ct              592
alock             n
gain     not used
FLAGS
il                n
in                n
dp                y
hs               nn
DISPLAY
sp         -6225.8
wp         37735.8
vs              414
sc                0
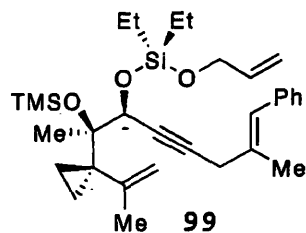wc              250
hzmm         150.94
is           500.00
rfl         15911.8
rfp          9686.0
th               20
ins           1.000
ai       ph
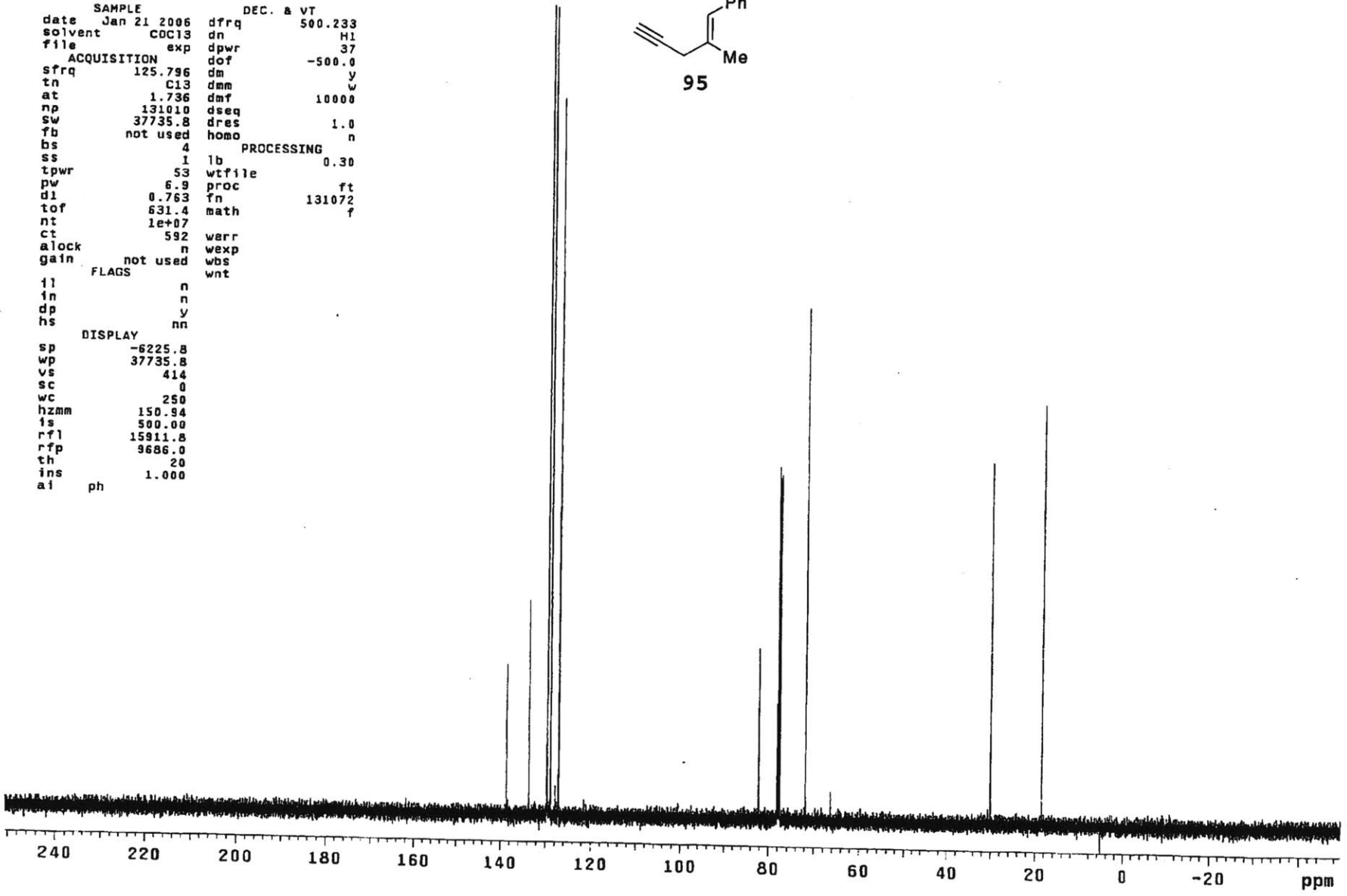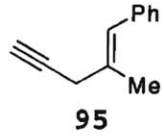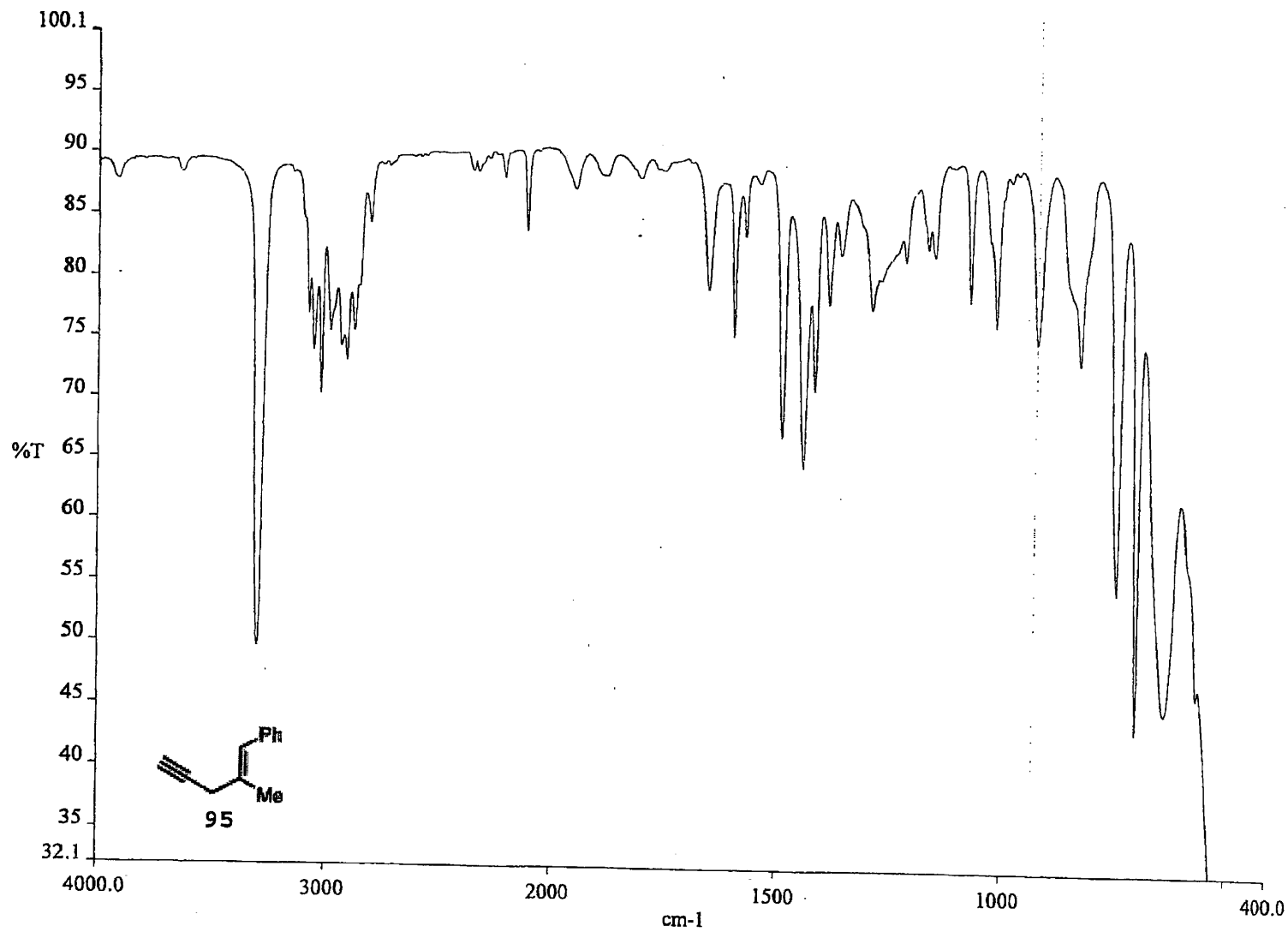
DEC. & VT
dfrq        500.233
dn               H1
dpwr             37
dof          -500.0
dm                y
dmm               w
dmf           10000
dseq
dres            1.0
homo              n
PROCESSING
lb             0.30
wtfile
proc             ft
fn           131072
math              f

werr
wexp
wbs
wnt

**95**

Ph / Me structure with alkyne

expl s2pul

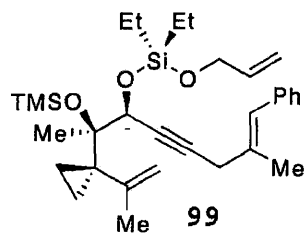DEC. & VT
dfrq        125.795
dn             C13
dpwr            37
dof              0
dm             nnn
dmm              c
dmf          10000
dseq
dres           1.0
homo             n
    PROCESSING
wtfile
proc            ft
fn          131072
math             f

werr
wexp
wbs
wnt

ACQUISITION
sfrq       500.235
tn             H1
at           3.200
np           64000
sw         10000.0
fb        not used
bs               1
ss               1
tpwr            59
pw             9.8
d1               0
tof         1498.2
nt              16
ct              16
alock            n
gain      not used
    FLAGS
il               n
in               n
dp               y
hs              nn
    DISPLAY
sp            -0.6
wp          6002.7
vs             151
sc               0
wc             250
hzmm         24.01
is          100.00
rfl         4561.6
rfp         3581.7
th               7
ins          1.000
nm       ph

96

expl  s2pul

DEC. & VT
dfrq        500.233
dn              H1
dpwr            37
dof         -500.0
dm               y
dmm              w
dmf          10000
dseq
dres           1.0
homo             n
    PROCESSING
lb            0.30
wtfile
proc            ft
fn          131072
math             f

werr
wexp
wbs
wnt

    ACQUISITION
sfrq       125.796
tn             C13
at           2.500
np          188680
sw         37735.8
fb        not used
bs              16
ss               1
tpwr            53
pw             6.9
d1           2.500
tof          631.4
nt           1e+06
ct            7152
alock            n
gain      not used
    FLAGS
il               n
in               n
dp               y
hs              nn
    DISPLAY
sp         -6225.0
wp         37735.3
vs            1169
sc               0
wc             250
hzmm          6.29
is          500.00
rfl        18876.6
rfp        12651.0
th              13
ins          1.000
ai      ph

exp10 s2pul

SAMPLE
date     Oct 30 2005
solvent     Benzene
file          exp
    ACQUISITION
sfrq        499.749
tn             H1
at          3.277
np          65536
sw         9998.8
fb       not used
bs              1
tpwr           56
pw            8.2
d1              0
tof        1498.1
nt             16
ct             16
alock           n
gain     not used
    FLAGS
ll              n
in              n
dp              y
hs             nn
    DISPLAY
sp        -1002.6
wp         9998.8
vs            132
sc              0
wc            250
hzmm        40.00
is          33.57
rfl        1002.6
rfp             0
th              7
ins         1.000
nm   cdc  ph

DEC. & VT
dfrq        125.674
dn             C13
dpwr            34
dof         1498.1
dm             nnn
dmm              w
dmf          10000
dseq
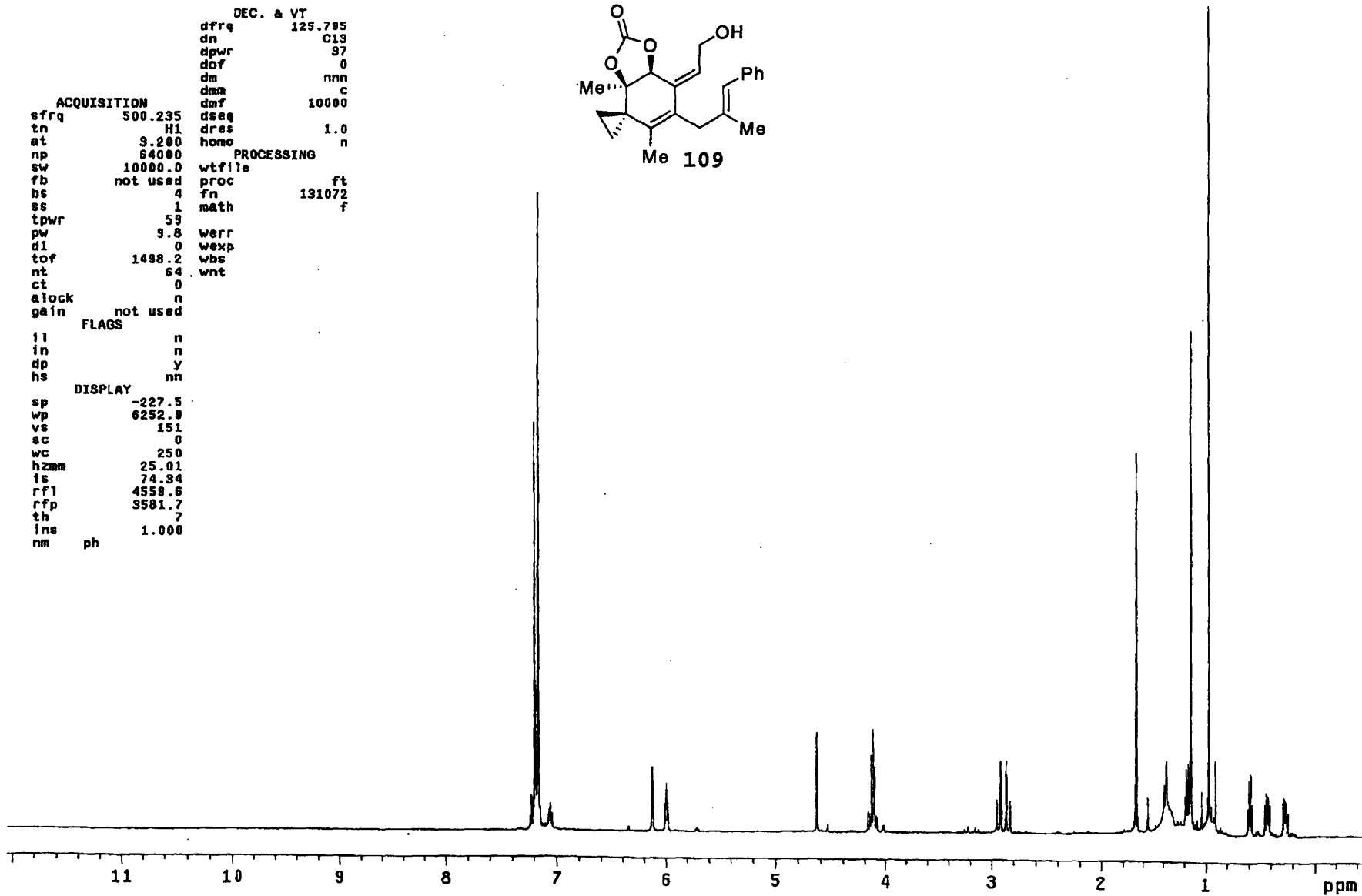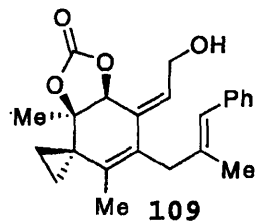dres           1.0
homo             n
    DEC2
dfrq2            0
dn2
dpwr2            1
dof2             0
dm2              n
dmm2             c
dmf2           200
dseq2
dres2          1.0
homo2            n
    DEC3
dfrq3            0
dn3
dpwr3            1
dof3             0
dm3              n
dmm3             c
dmf3           200
dseq3
dres3          1.0
homo3            n
    PROCESSING
wtfile
proc            ft
fn           65536
math             f

werr
wexp
wbs
wnt

97

exp2   s2pul

| SAMPLE | | DEC. & VT | |
|---|---|---|---|
| date | Jan 20 2006 | dfrq | 500.233 |
| solvent | Benzene | dn | H1 |
| file | .exp | dpwr | 37 |
| ACQUISITION | | dof | -500.0 |
| sfrq | 125.796 | dm | y |
| tn | C13 | dmm | w |
| at | 1.736 | dmf | 10000 |
| np | 131010 | dseq | |
| sw | 37735.8 | dres | 1.0 |
| fb | not used | homo | n |
| bs | 4 | PROCESSING | |
| ss | 1 | lb | 0.30 |
| tpwr | 53 | wtfile | |
| pw | 6.9 | proc | ft |
| d1 | 0.763 | fn | 131072 |
| tof | 631.4 | math | f |
| nt | 10000 | | |
| ct | 20 | werr | |
| alock | n | wexp | |
| gain | not used | wbs | |
| FLAGS | | wnt | |
| il | n | | |
| in | n | | |
| dp | y | | |
| hs | nn | | |
| DISPLAY | | | |
| sp | -6218.9 | | |
| wp | 37735.8 | | |
| vs | 172 | | |
| sc | 0 | | |
| wc | 250 | | |
| hzmm | 150.94 | | |
| is | 500.00 | | |
| rfl | 22370.3 | | |
| rfp | 16151.4 | | |
| th | 20 | | |
| ins | 1.000 | | |
| ai | ph | | |
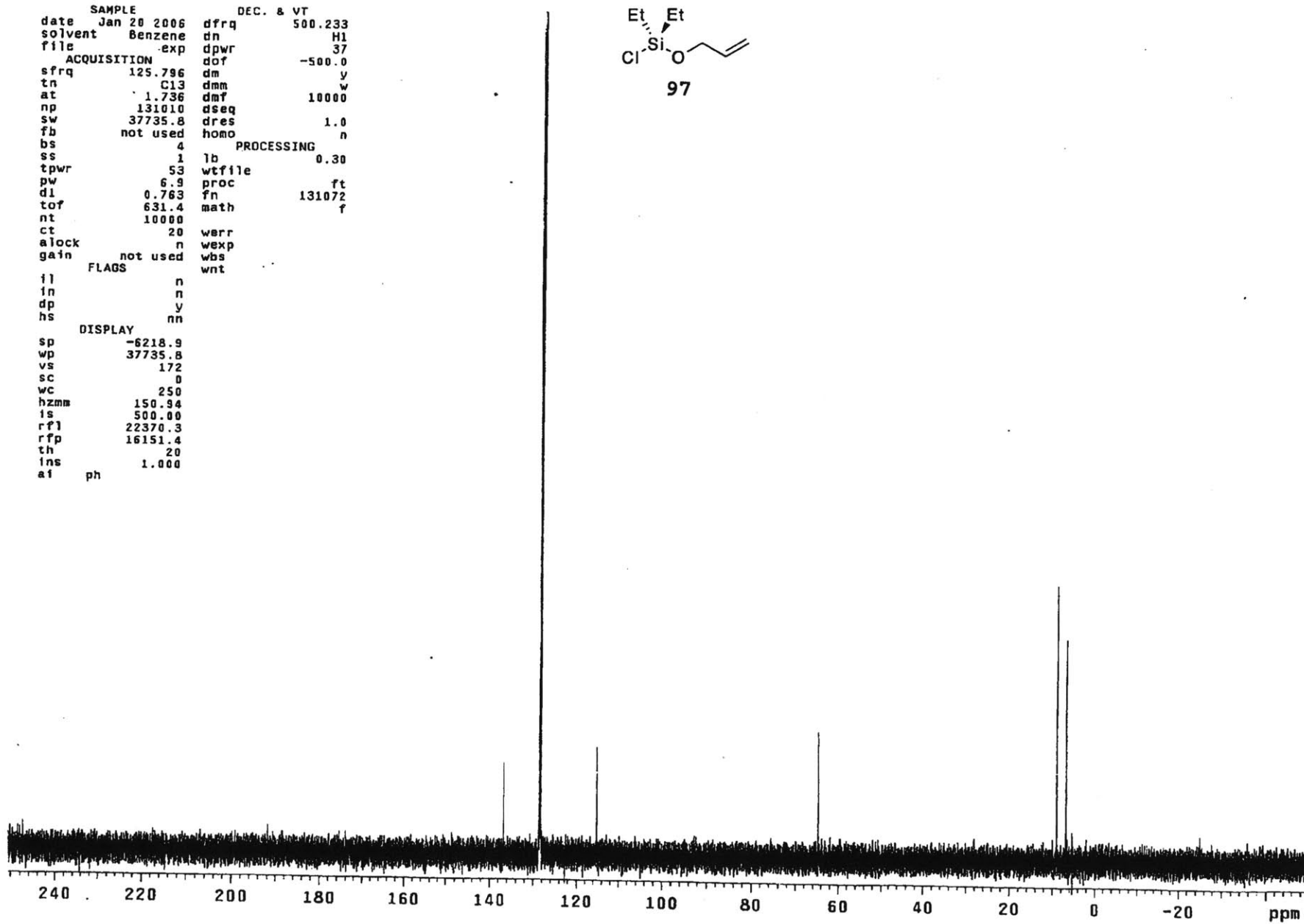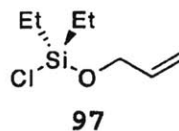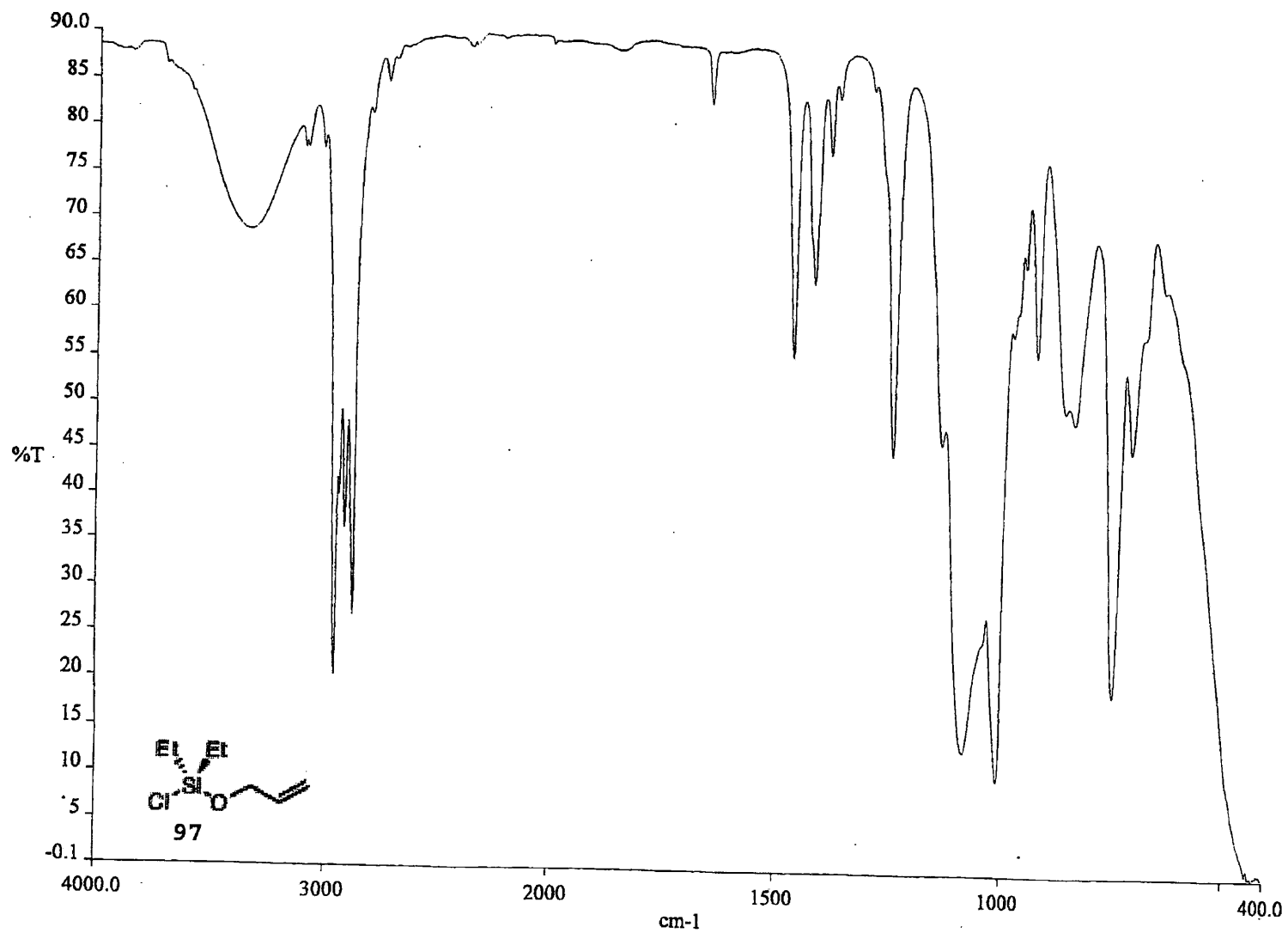
97

expl s2pul

DEC. & VT
dfrq        125.674
dn              C13
dpwr             34
dof          1498.1
dm              nnn
dmm               w
dmf           10000
dseq
dres            1.0
homo              n
PROCESSING
wtfile
proc             ft
fn            65536
math              f

werr
wexp
wbs
wnt

ACQUISITION
sfrq      499.749
tn             H1
at          3.277
np          65536
sw         9998.8
fb       not used
bs              4
tpwr           56
pw            8.2
d1              0
tof        1498.1
nt             64
ct             64
alock           n
gain     not used
FLAGS
il              n
in              n
dp              y
hs             nn

DISPLAY
sp         -250.0
wp         6246.8
vs            151
sc              0
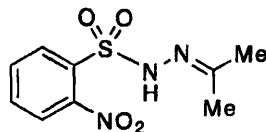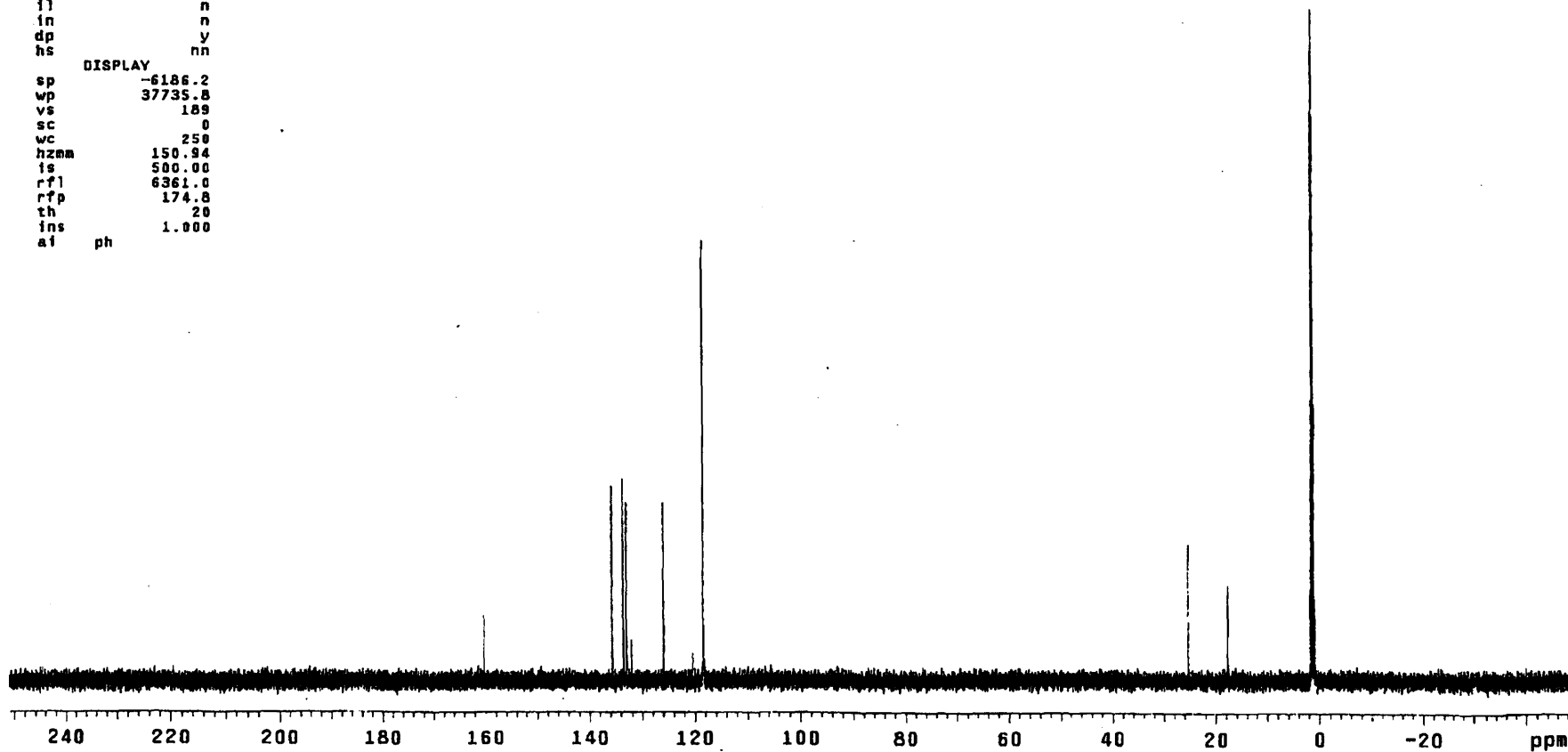wc            250
hzmm        24.99
is          16.79
rfl        4566.2
rfp        3628.1
th              7
ins         1.000
nm  cdc  ph
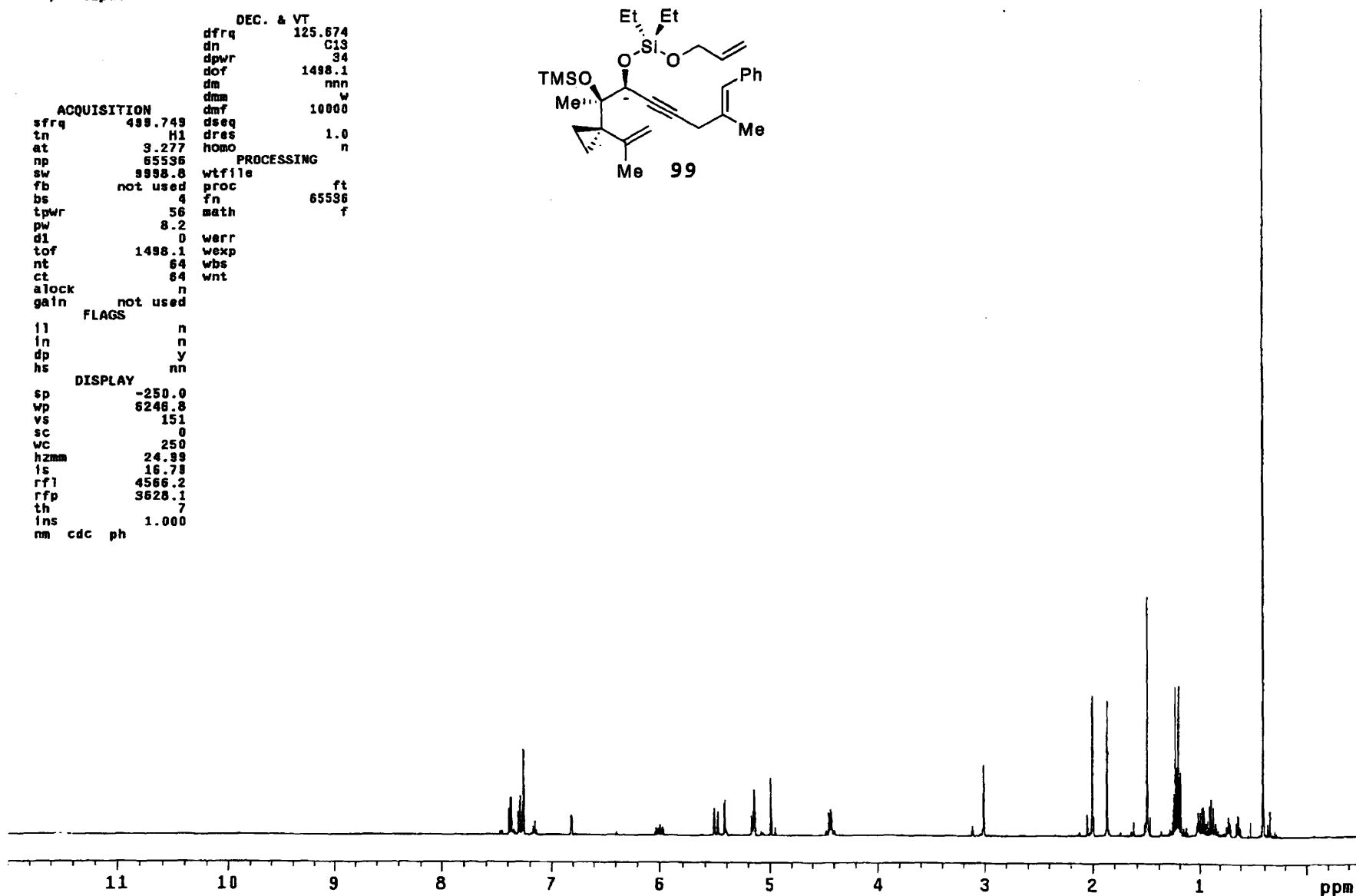
expl  s2pul

DEC. & VT
dfrq        500.233
dn              H1
dpwr            37
dof          -500.0
dm               y
dmm              w
dmf          10000
dseq
dres           1.0
homo             n
PROCESSING
lb            0.30
wtfile
proc            ft
fn          131072
math             f

werr
wexp
wbs
wnt

ACQUISITION
sfrq       125.796
tn             C13
at           1.736
np          131010
sw         37735.8
fb        not used
bs               4
ss               1
tpwr            53
pw             6.9
d1           0.763
tof          631.4
nt           1e+06
ct              92
alock            n
gain      not used
FLAGS
il               n
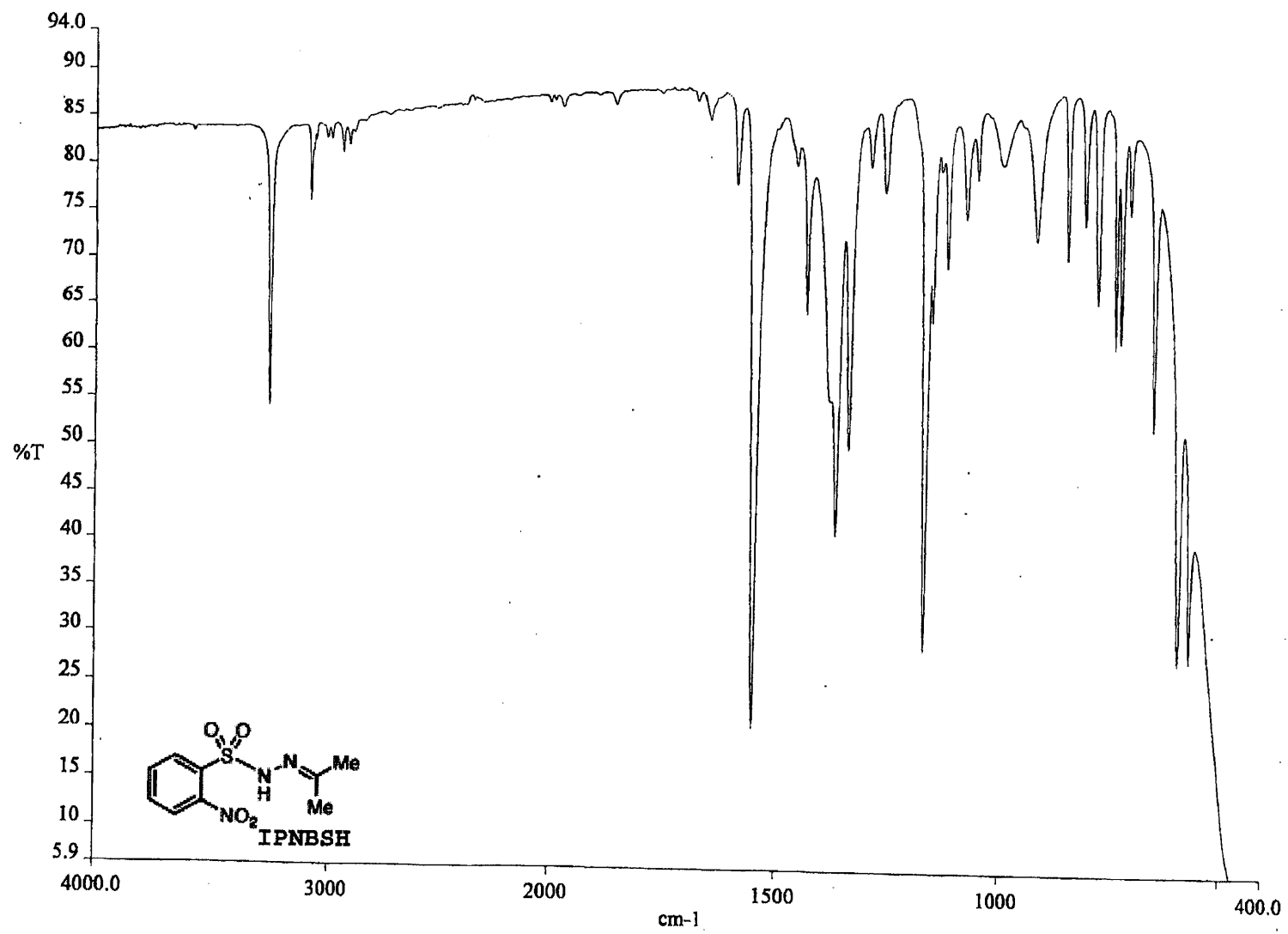in               n
dp               y
hs              nn
DISPLAY
sp         -6221.2
wp         37735.3
vs             200
sc               0
wc             250
hzmm        150.94
is          500.00
rfl        22373.2
rfp        16151.4
th              20
ins          1.000
ai      ph
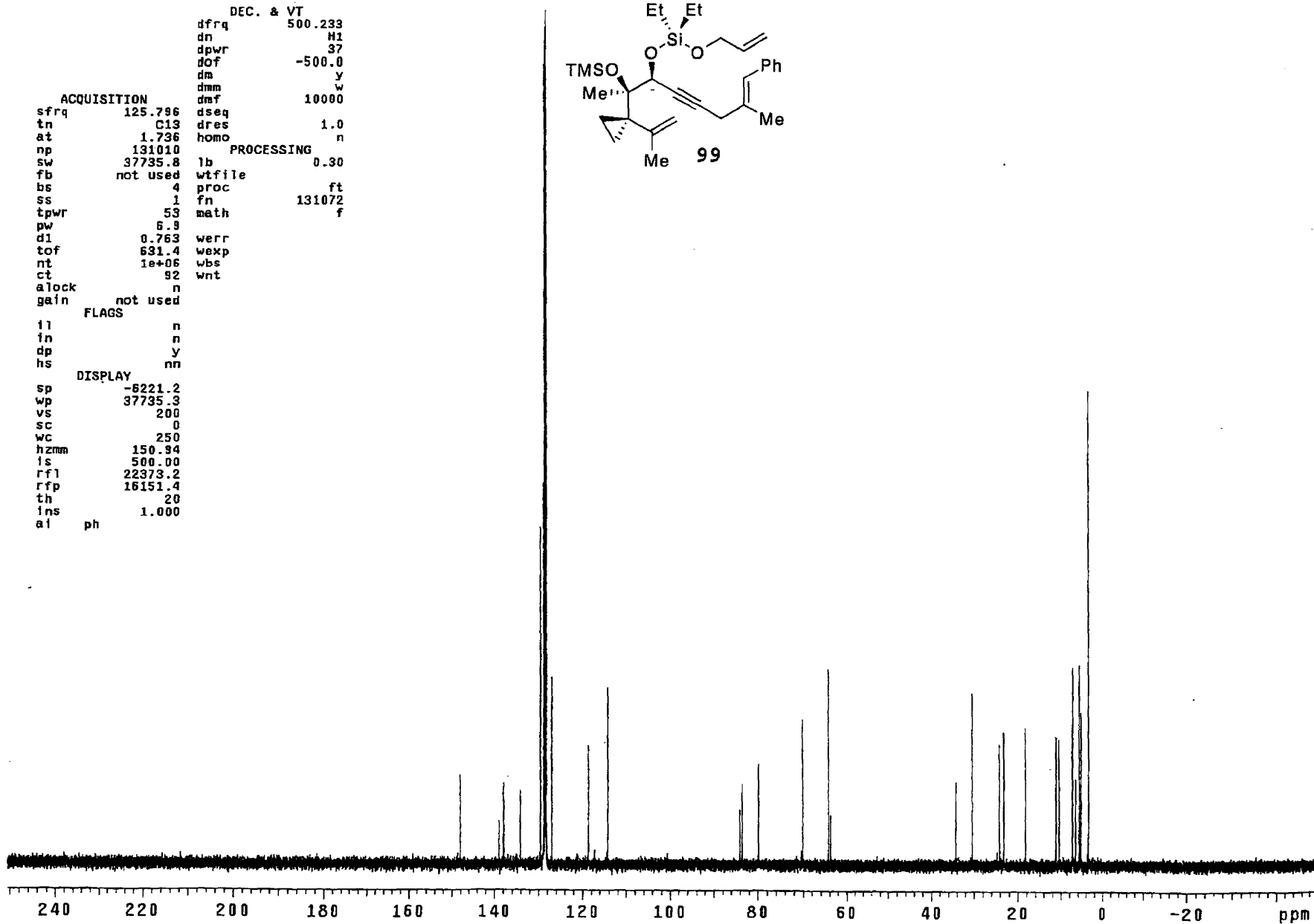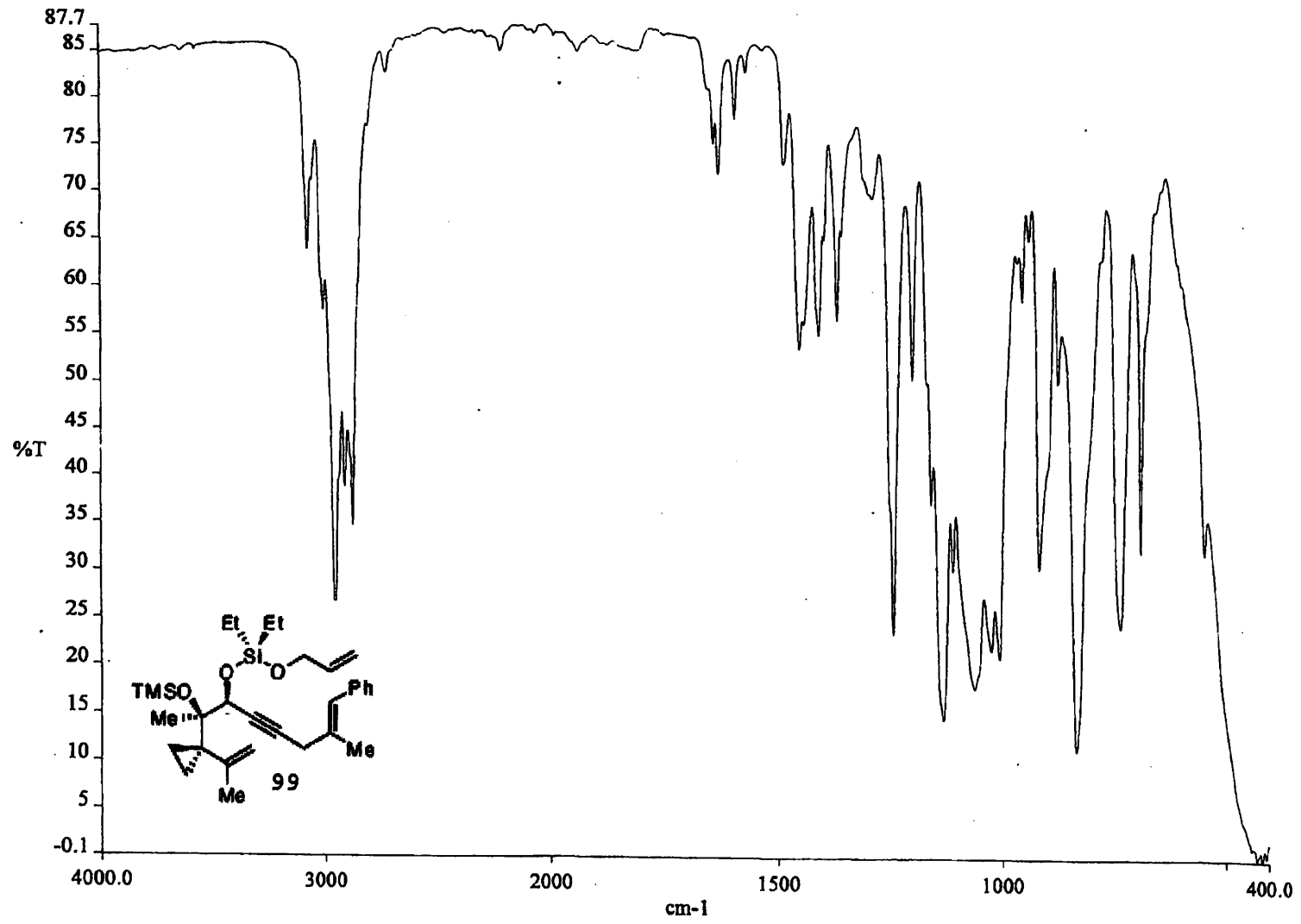
exp1  s2pul

```
                              DEC. & VT
                         dfrq      125.674
                         dn           C13
                         dpwr          34
                         dof       1498.1
                         dm           nnn
                         dmm            W
        ACQUISITION      dmf        10000
sfrq      499.749        dseq
tn            H1         dres         1.0
at         3.277         homo           n
np         65536          PROCESSING
sw         9998.8        wtfile
fb       not used        proc          ft
bs             4         fn         65536
tpwr          56         math           f
pw           8.2
d1             0         werr
tof       1498.1         wexp
nt            64         wbs
ct            64         wnt
alock          n
gain     not used
        FLAGS
il             n
in             n
dp             y
hs            nn
        DISPLAY
sp        -250.1
wp        5996.9
vs           151
sc             0
wc           250
hzmm       23.99
is        537.18
rfl       4566.4
rfp       3578.2
th             7
ins        1.000
nm   cdc  ph
```
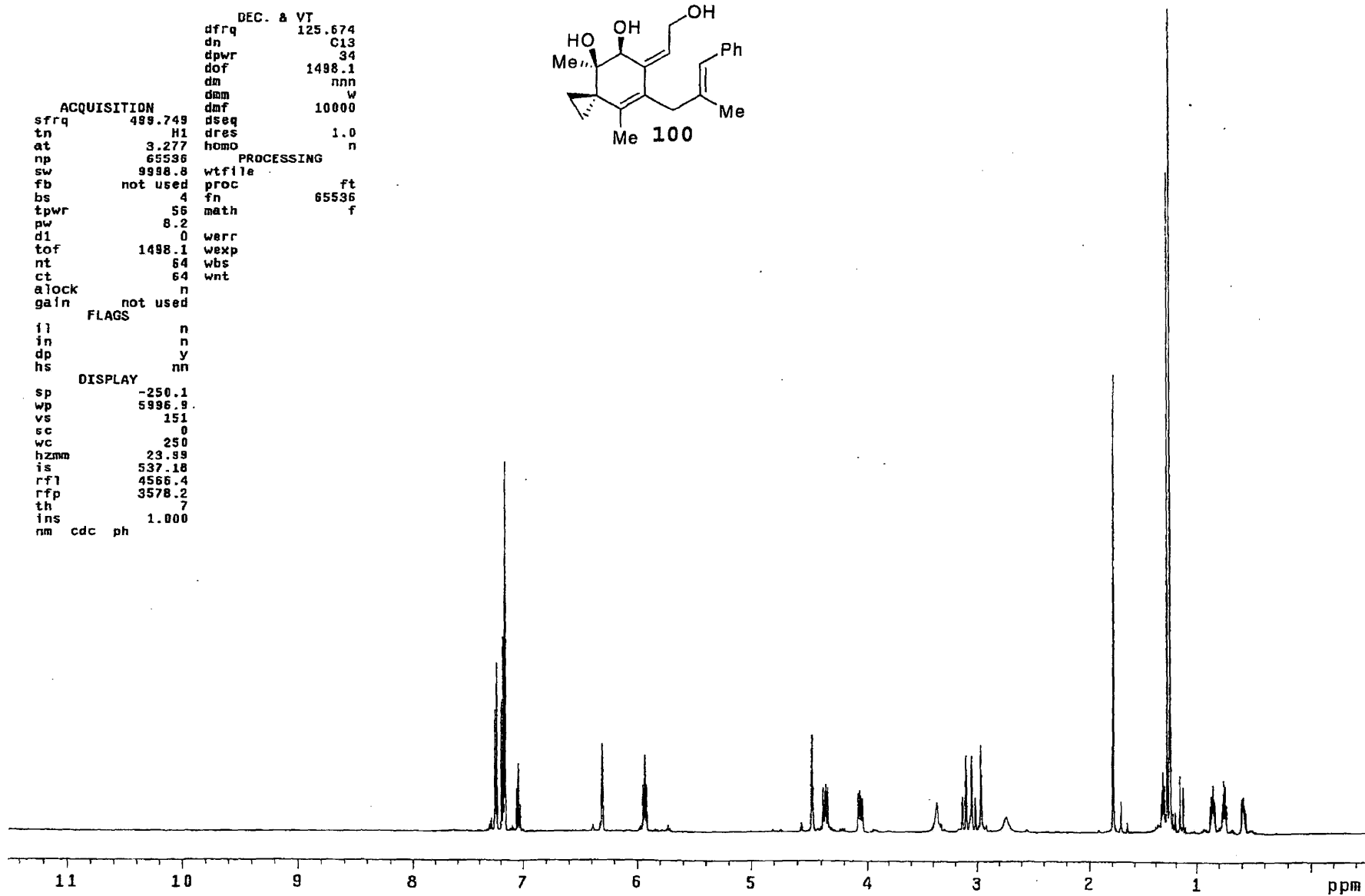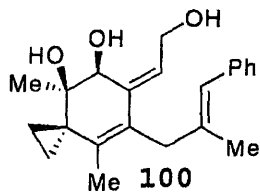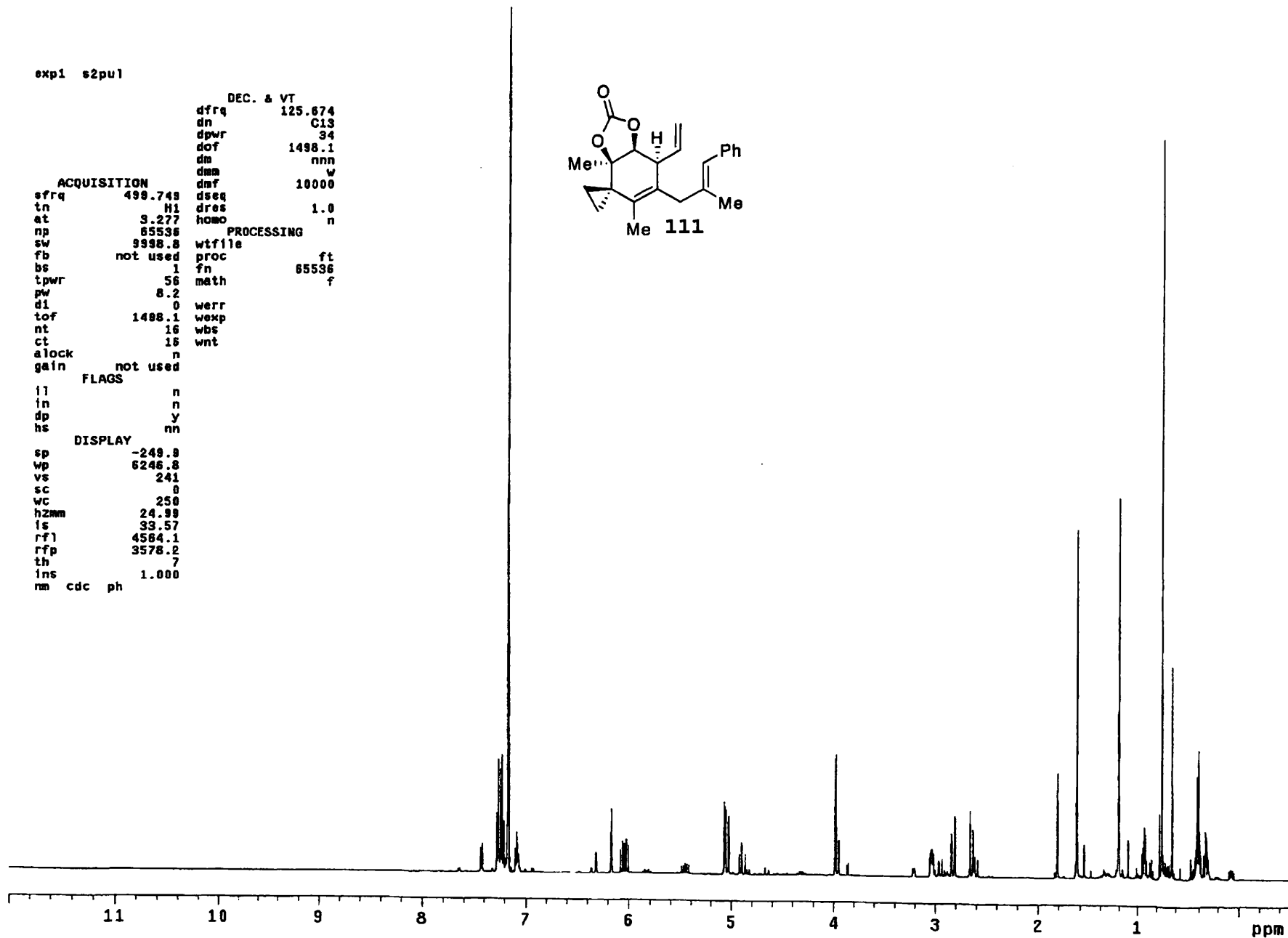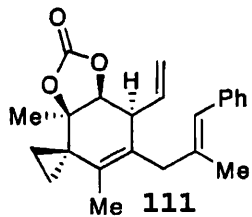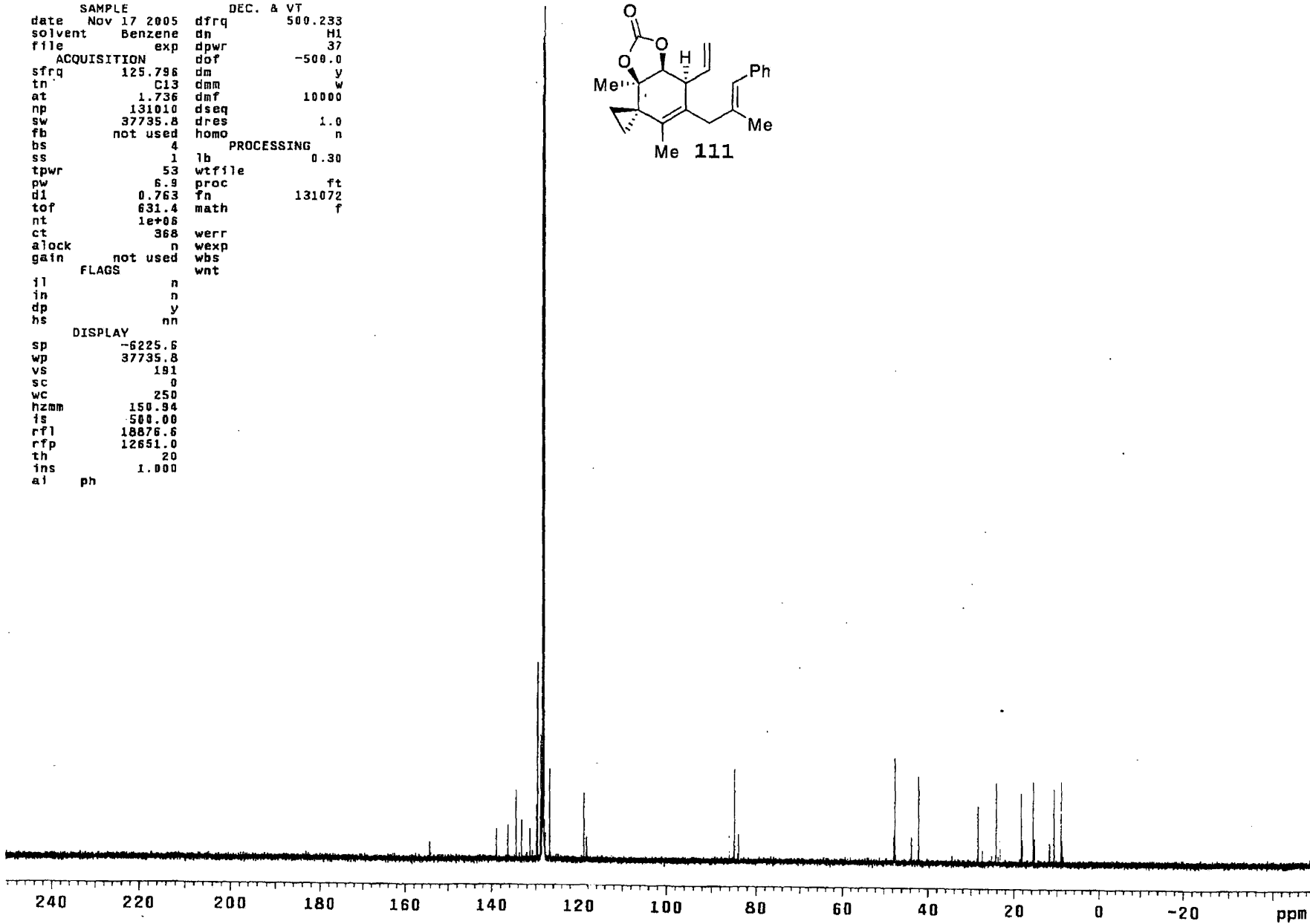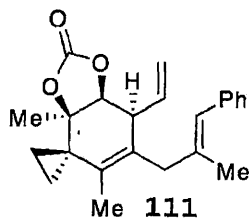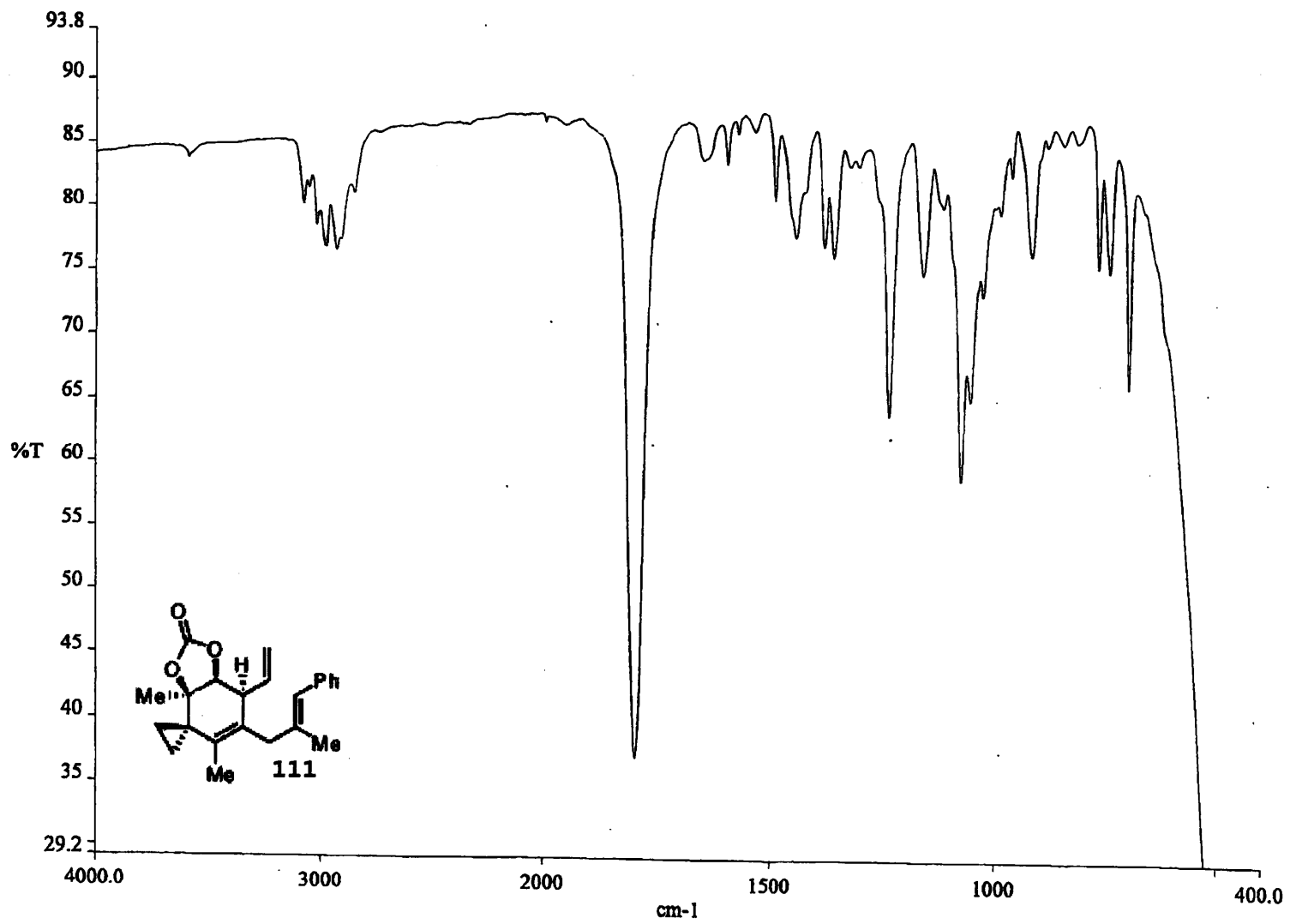
Structure labeled **100** with HO, OH, OH, Me, Ph, Me, Me substituents.

ppm axis: 11  10  9  8  7  6  5  4  3  2  1  ppm

expl s2pul

DEC. & VT
dfrq        500.233
dn              H1
dpwr            37
dof          -500.0
dm              y
dmm             w
dmf           10000
dseq
dres           1.0
homo            n

PROCESSING
lb            0.30
wtfile
proc           ft
fn          131072
math            f

werr
wexp
wbs
wnt

ACQUISITION
sfrq       125.796
tn             C13
at           1.736
np          131010
sw         37735.8
fb        not used
bs               4
ss               1
tpwr            53
pw             6.9
d1           0.763
tof          631.4
nt           1e+06
ct             372
alock            n
gain      not used

FLAGS
il               n
in               n
dp               y
hs              nn

DISPLAY
sp         -6224.7
wp         37735.3
vs             337
sc               0
wc             250
hzmm         40.69
is          500.00
rfl        22374.6
rfp        16149.3
th              20
ins          1.000
ai      ph

Me 100

expl s2pul
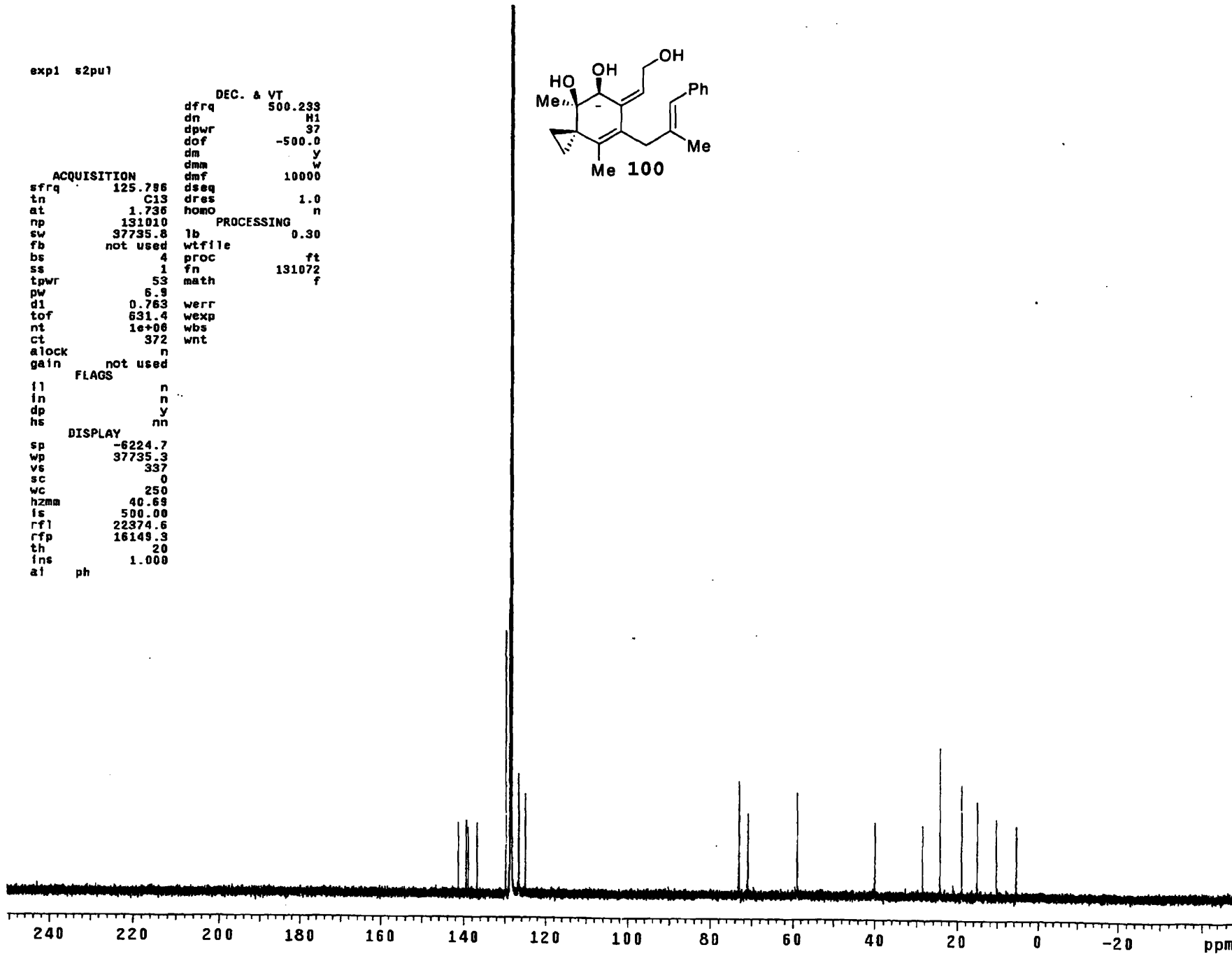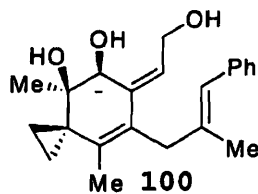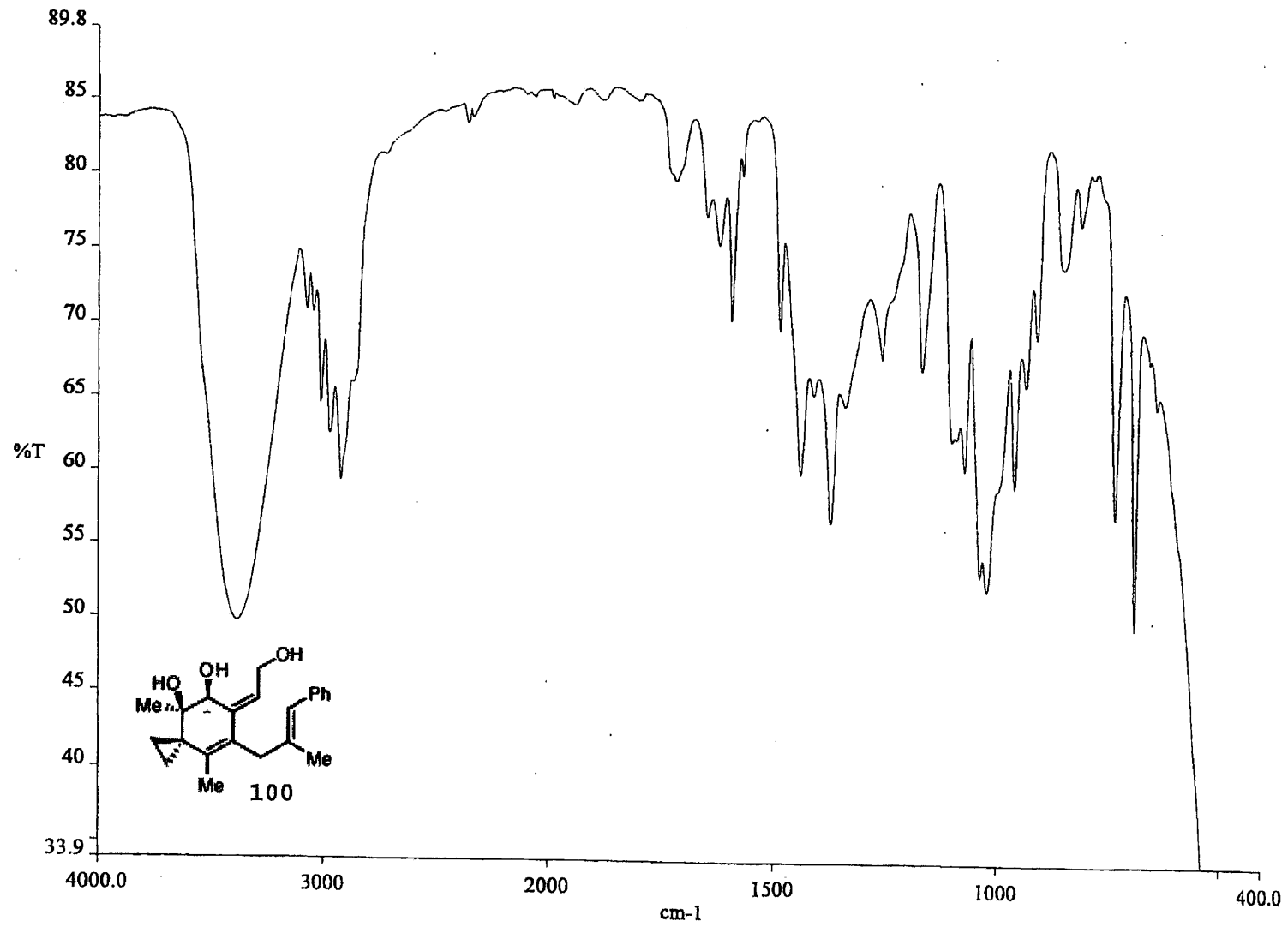
DEC. & VT
dfrq        125.795
dn              C13
dpwr             97
dof               0
dm              nnn
dmm               c
dmf           10000
dseq
dres            1.0
homo              n
PROCESSING
wtfile
proc             ft
fn           131072
math              f

ACQUISITION
sfrq        500.235
tn               H1
at            3.200
np            64000
sw          10000.0
fb         not used
bs                4
ss                1
tpwr             59
pw              9.8
d1                0
tof          1498.2
nt               64
ct                0
alock             n
gain       not used
FLAGS
il                n
in                n
dp                y
hs               nn
DISPLAY
sp           -227.5
wp           6252.9
vs              151
sc                0
wc              250
hzmm          25.01
is            74.34
rfl          4559.6
rfp          3581.7
th                7
ins           1.000
nm       ph

werr
wexp
wbs
wnt

189

exp1  s2pul

DEC. & VT
dfrq        500.233
dn              H1
dpwr            37
dof          -500.0
dm               y
dmm              w
dmf           10000
dseq
dres           1.0
homo             n

ACQUISITION
sfrq        125.795
tn              C13
at            1.736
np           131010
sw          37735.8
fb        not used
bs               4
ss               1
tpwr            53
pw             6.9
d1           0.763
tof          631.4
nt           1e+06
ct               0
alock            n
gain      not used

PROCESSING
lb            0.30
wtfile
proc            ft
fn          131072
math             f

werr
wexp
wbs
wnt

FLAGS
il               n
in               n
dp               y
hs              nn

DISPLAY
sp         -6225.0
wp         37735.3
vs             654
sc               0
wc             250
hzmm         20.24
is          500.00
rfl        18876.6
rfp        12651.0
th               7
ins          1.000
ai    ph

240  220  200  180  160  140  120  100  80  60  40  20  0  -20  ppm
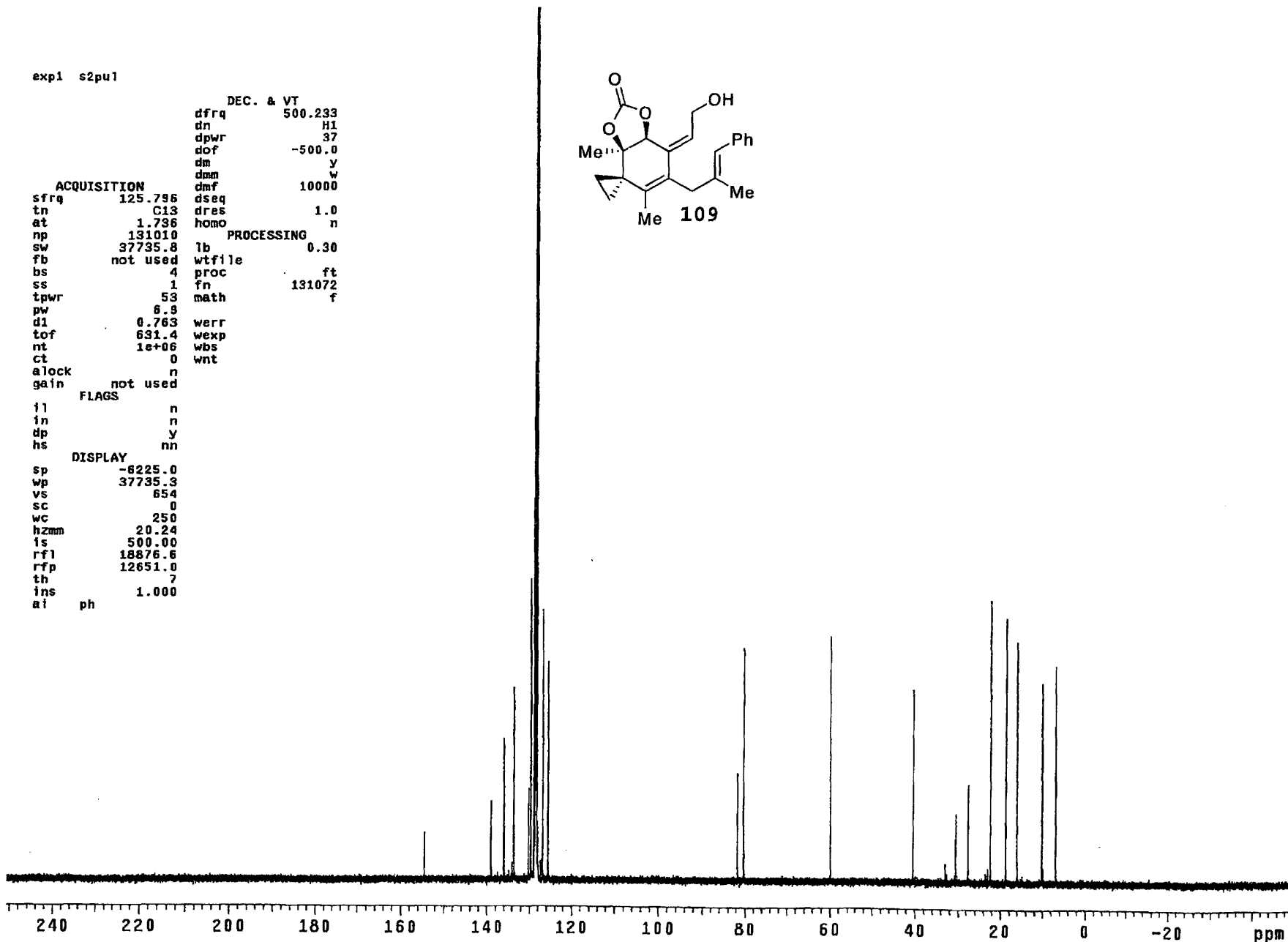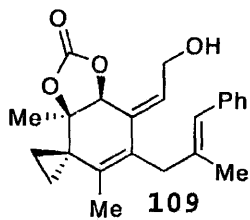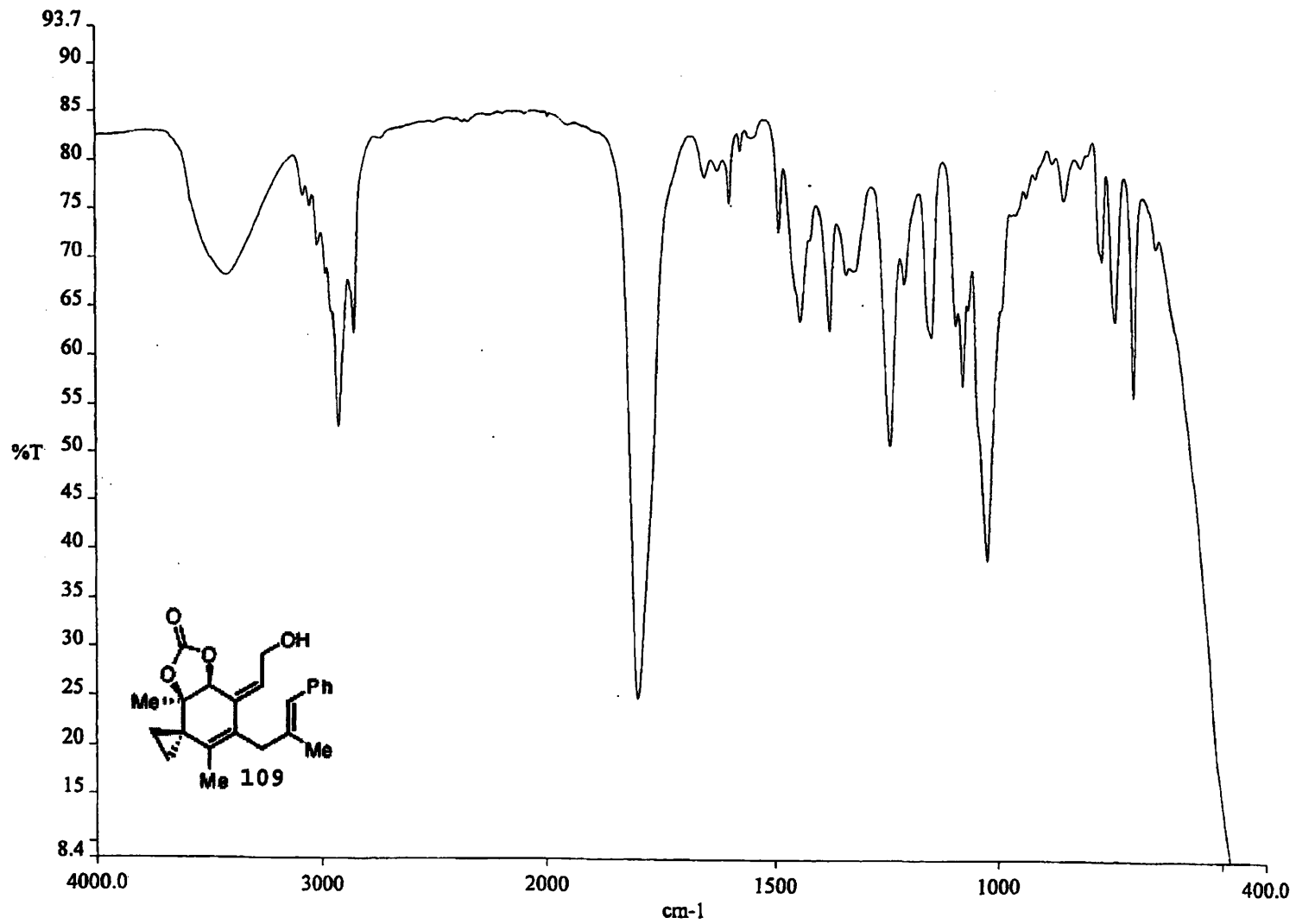
exp1 s2pul

DEC. & VT
dfrq          125.673
dn               C13
dpwr              30
dof                0
dm               nnn
dmm                w
dmf            10000
dseq
dres             1.0
homo               n
PROCESSING
wtfile
proc              ft
fn            131072
math               f

werr
wexp
wbs
wnt              wft

ACQUISITION
sfrq      499.750
tn             H1
at          3.001
np          63050
sw        10504.2
fb       not used
bs              1
tpwr           56
pw            8.9
d1          2.000
tof        1519.5
nt             16
ct             16
alock           n
gain     not used
FLAGS
il              n
in              n
dp              y
hs             nn
DISPLAY
sp         -249.9
wp         6246.8
vs            151
sc              0
wc            250
hzmm        24.99
is          33.57
rfl        3746.9
rfp         969.5
th              1
ins         6.000
nm  cdc  ph
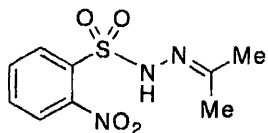
IPNBSH
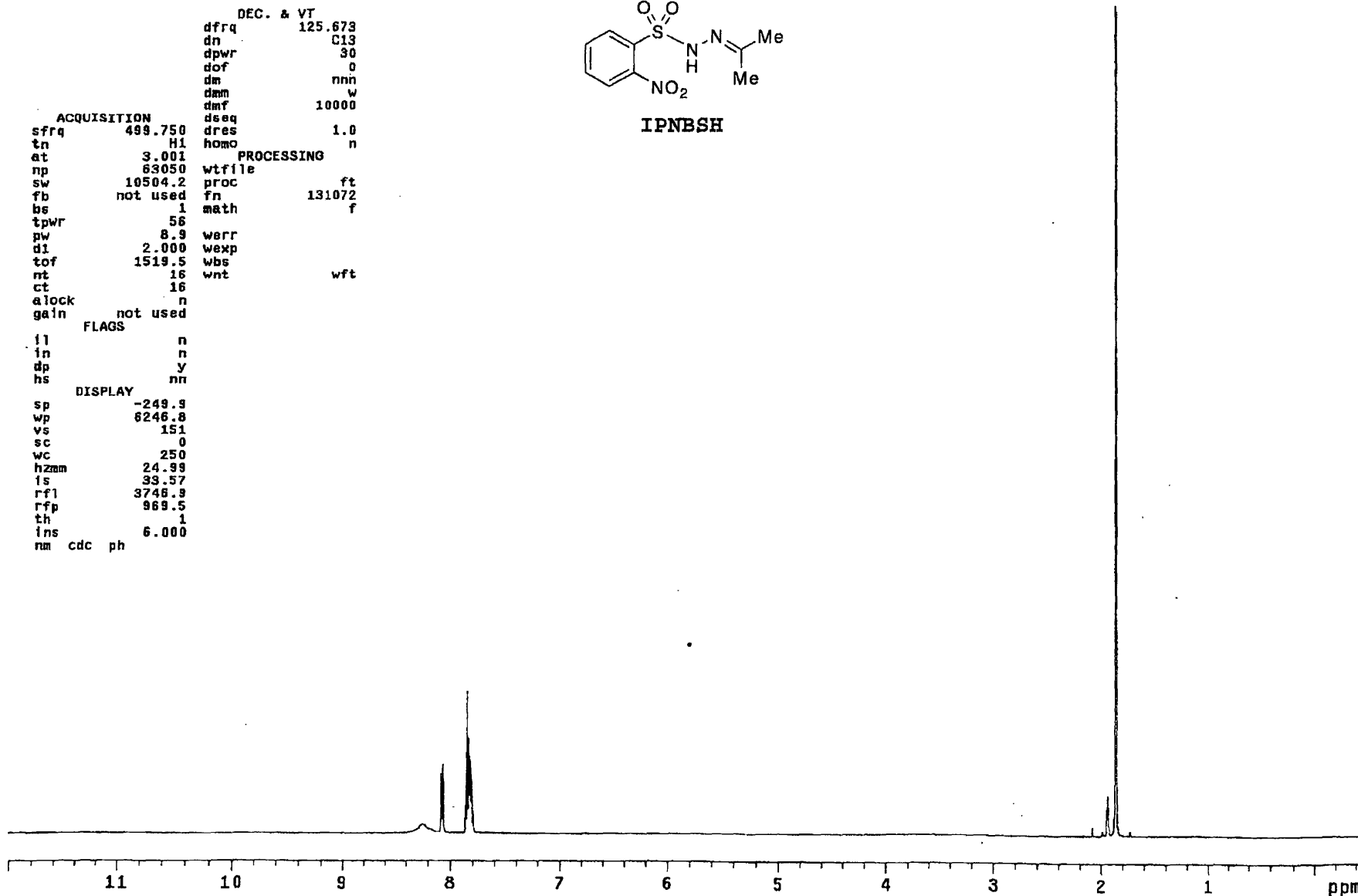
exp2    s2pul

         SAMPLE                  DEC. & VT
date    Jan 20 2006    dfrq        500.236
solvent acetonitri~    dn              H1
            le         dpwr            37
file           exp     dof          -500.0
    ACQUISITION        dm               y
sfrq      125.796      dmm              w
tn            C13      dmf           10000
at          1.736      dseq
np         131010      dres           1.0
sw        37735.8      homo             n
fb       not used      PROCESSING
bs              4      lb            0.30
ss              1      wtfile
tpwr           53      proc            ft
pw            6.9      fn          131072
d1          0.763      math             f
tof         631.4
nt          1e+06      werr
ct             84      wexp
alock           n      wbs
gain     not used      wnt
       FLAGS
il              n
in              n
dp              y
hs             nn
     DISPLAY
sp         -6186.2
wp        37735.8
vs            189
sc              0
wc            250
hzmm       150.94
is         500.00
rfl        6361.0
rfp         174.8
th             20
ins         1.000
al      ph

**IPNBSH**



240   220   200   180   160   140   120   100   80   60   40   20   0   -20   ppm

expl s2pul

DEC. & VT
dfrq        125.674
dn            C13
dpwr           34
dof         1498.1
dm            nnn
dmm             w
dmf          10000
dseq
dres          1.0
homo            n

PROCESSING
wtfile
proc           ft
fn           65536
math            f

werr
wexp
wbs
wnt

ACQUISITION
sfrq       499.749
tn            H1
at          3.277
np           65536
sw          9998.8
fb        not used
bs             1
tpwr          56
pw           8.2
d1             0
tof         1498.1
nt            16
ct            16
alock          n
gain      not used

FLAGS
il             n
in             n
dp             y
hs            nn

DISPLAY
sp          -249.8
wp          6246.8
vs            241
sc             0
wc            250
hzmm         24.99
is          33.57
rfl         4564.1
rfp         3578.2
th             7
ins         1.000
nm   cdc   ph

111

11  10  9  8  7  6  5  4  3  2  1  ppm

exp2  s2pul

| SAMPLE | | DEC. & VT | |
|---|---|---|---|
| date | Nov 17 2005 | dfrq | 500.233 |
| solvent | Benzene | dn | H1 |
| file | exp | dpwr | 37 |
| ACQUISITION | | dof | -500.0 |
| sfrq | 125.796 | dm | y |
| tn | C13 | dmm | w |
| at | 1.736 | dmf | 10000 |
| np | 131010 | dseq | |
| sw | 37735.8 | dres | 1.0 |
| fb | not used | homo | n |
| bs | 4 | PROCESSING | |
| ss | 1 | lb | 0.30 |
| tpwr | 53 | wtfile | |
| pw | 6.9 | proc | ft |
| d1 | 0.763 | fn | 131072 |
| tof | 631.4 | math | f |
| nt | 1e+06 | | |
| ct | 368 | werr | |
| alock | n | wexp | |
| gain | not used | wbs | |
| FLAGS | | wnt | |
| il | n | | |
| in | n | | |
| dp | y | | |
| hs | nn | | |
| DISPLAY | | | |
| sp | -6225.6 | | |
| wp | 37735.8 | | |
| vs | 191 | | |
| sc | 0 | | |
| wc | 250 | | |
| hzmm | 150.94 | | |
| is | 500.00 | | |
| rfl | 18876.6 | | |
| rfp | 12651.0 | | |
| th | 20 | | |
| ins | 1.000 | | |
| ai | ph | | |
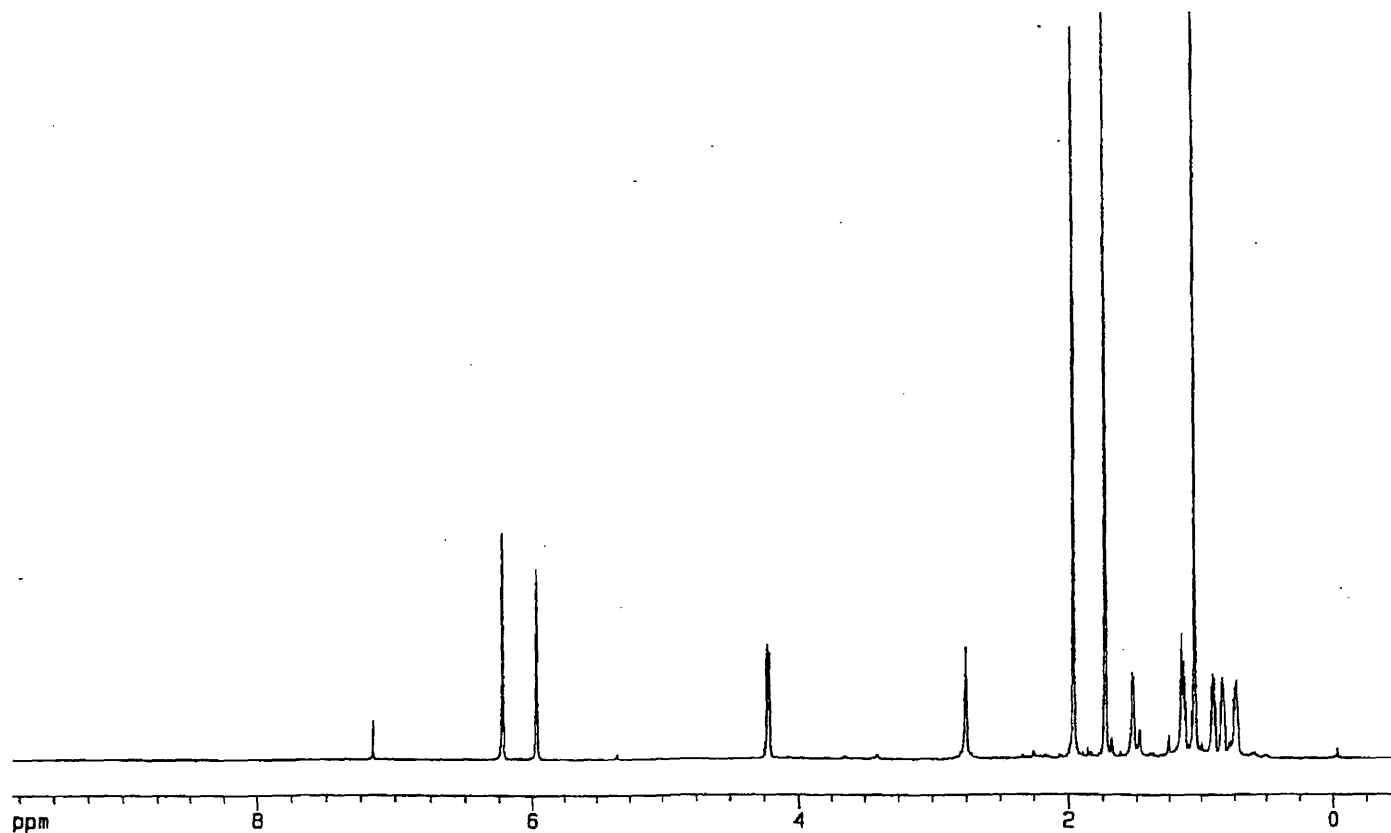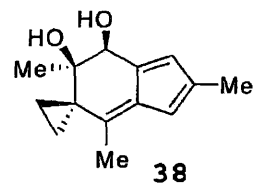


Me 111

240  220  200  180  160  140  120  100  80  60  40  20  0  -20  ppm

Me''' HO HO Me Me

**38**

Current Data Parameters
NAME
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_            20060206
Time                12.05
INSTRUM             spect
PROBHD    5 mm CPTCI 1H/
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                      8
DS                      0
SWH           8992.806 Hz
FIDRES        0.137219 Hz
AQ          3.6439073 sec
RG                   22.6
DW            55.600 usec
DE             6.00 usec
TE              298.0 K
D1          1.00000000 sec
MCREST      0.00000000 sec
MCWRK       0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1             10.00 usec
PL1             0.60 dB
SFO1      600.1314635 MHz

F2 - Processing parameters
SI                  32768
SF        600.1300773 MHz
WDW                    EM
SSB                     0
LB              0.30 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX               20.00 cm
CY               13.02 cm
F1P             10.000 ppm
F1             6001.30 Hz
F2P             -0.500 ppm
F2             -300.07 Hz
PPMCM       0.52500 ppm/cm
HZCM        315.06830 Hz/cm

ppm    8    6    4    2    0

199

HO O
Me''' 
Me
Me  (−)-1

Current Data Parameters
NAME
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_            20060206
Time               19.53
INSTRUM            spect
PROBHD       5mm BBO BB-1
PULPROG             zg30
TD                 65536
SOLVENT             C6D6
NS                    16
DS                     2
SWH          8278.146 Hz
FIDRES       0.126314 Hz
AQ          3.9584243 sec
RG                 287.4
DW            60.400 usec
DE             6.00 usec
TE             300.0 K
D1          1.00000000 sec

============ CHANNEL f1 ==========
NUC1                  1H
P1             7.90 usec
PL1            0.00 dB
SFO1      400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF       400.1300000 MHz
WDW                   EM
SSB                    0
LB              0.30 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX             20.00 cm
F1P           12.012 ppm
F1           4806.17 Hz
F2P           -0.503 ppm
F2           -201.07 Hz
PPMCM       0.62570 ppm/cm
HZCM      250.36191 Hz/cm

(−)-1
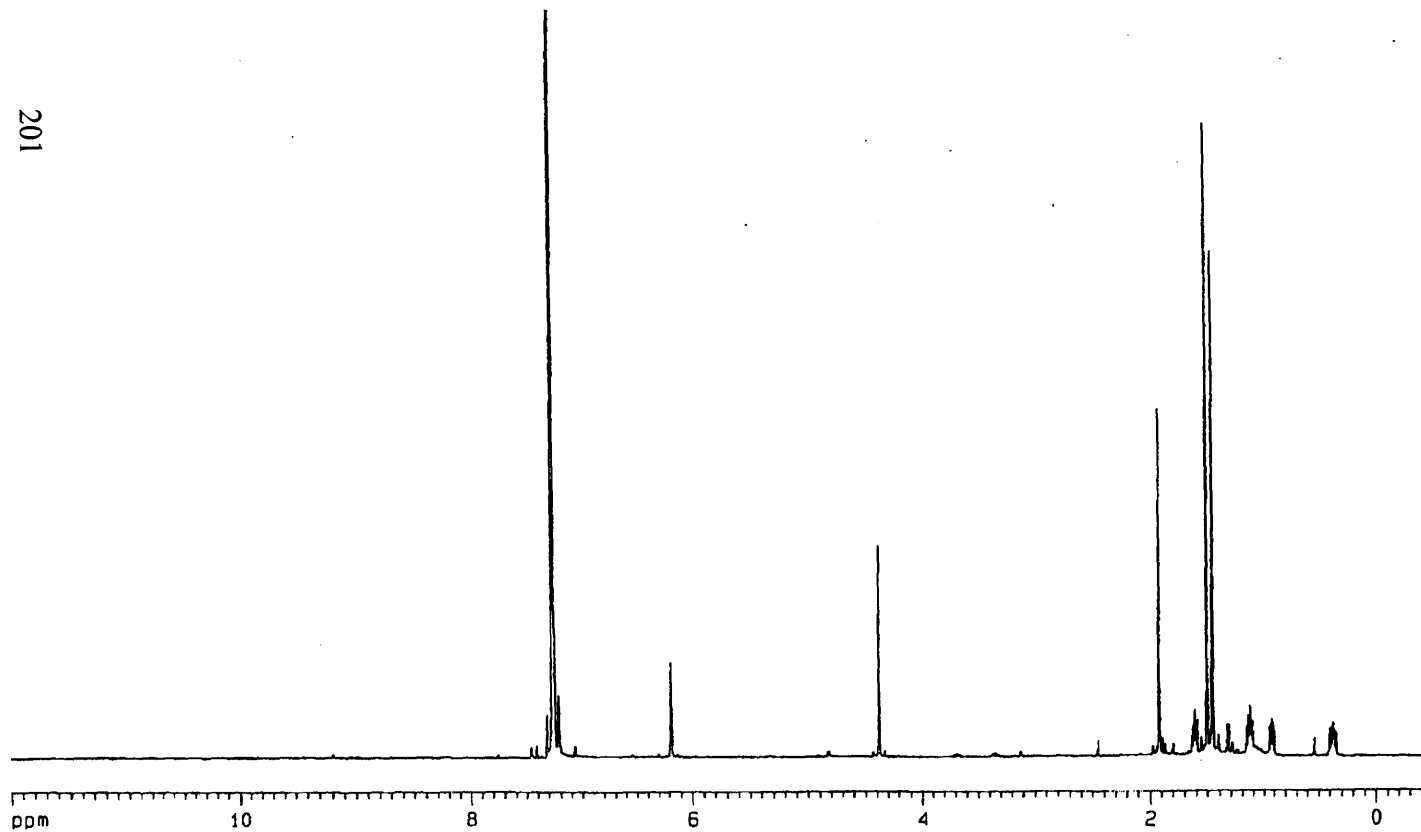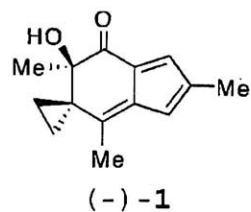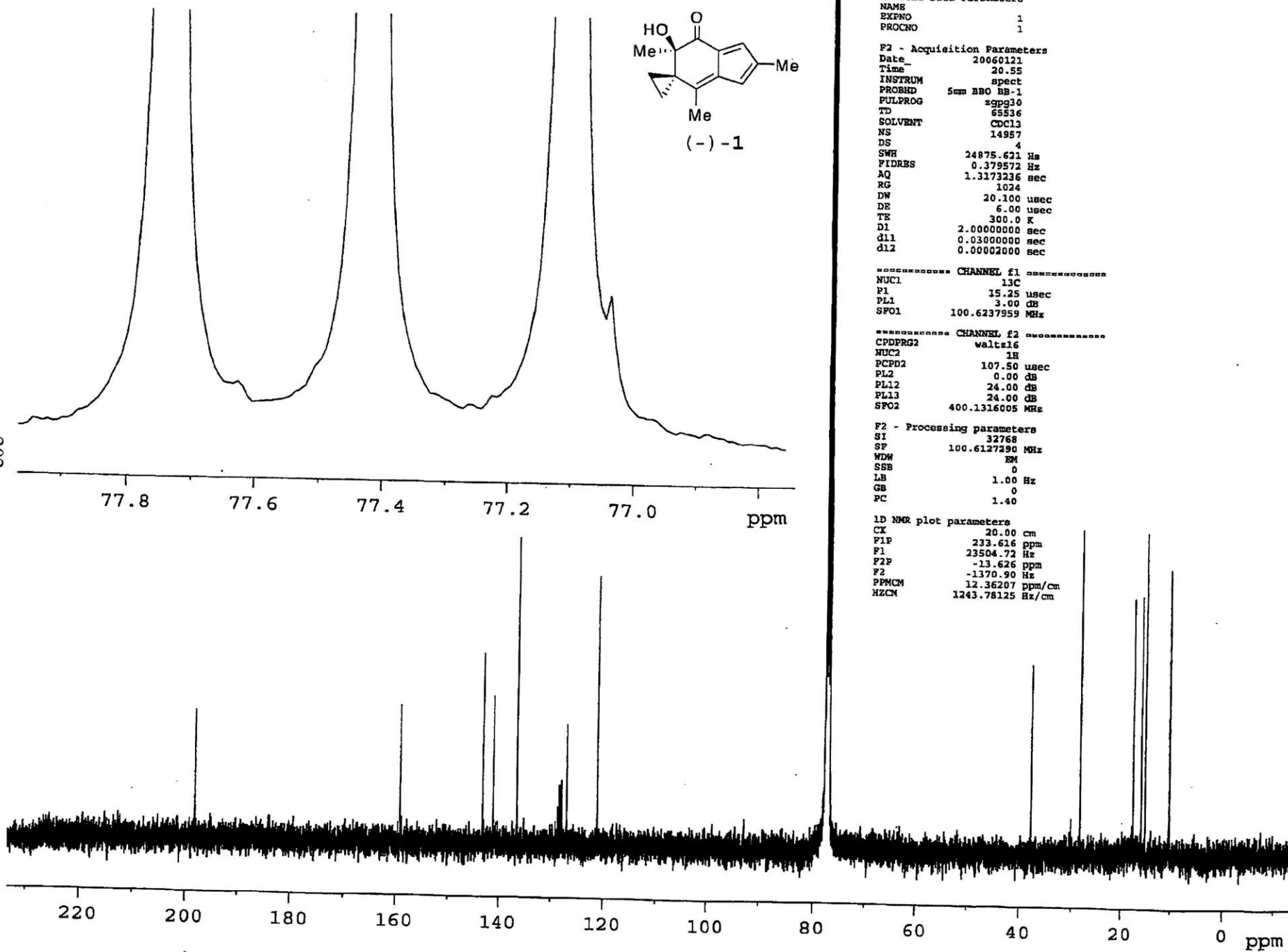
Current Data Parameters
NAME
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20060121
Time                     20.55
INSTRUM                  spect
PROBHD          5mm BBO BB-1
PULPROG                 zgpg30
TD                       65536
SOLVENT                  CDCl3
NS                       14957
DS                           4
SWH               24875.621 Hz
FIDRES             0.379572 Hz
AQ                1.3173236 sec
RG                        1024
DW                   20.100 usec
DE                    6.00 usec
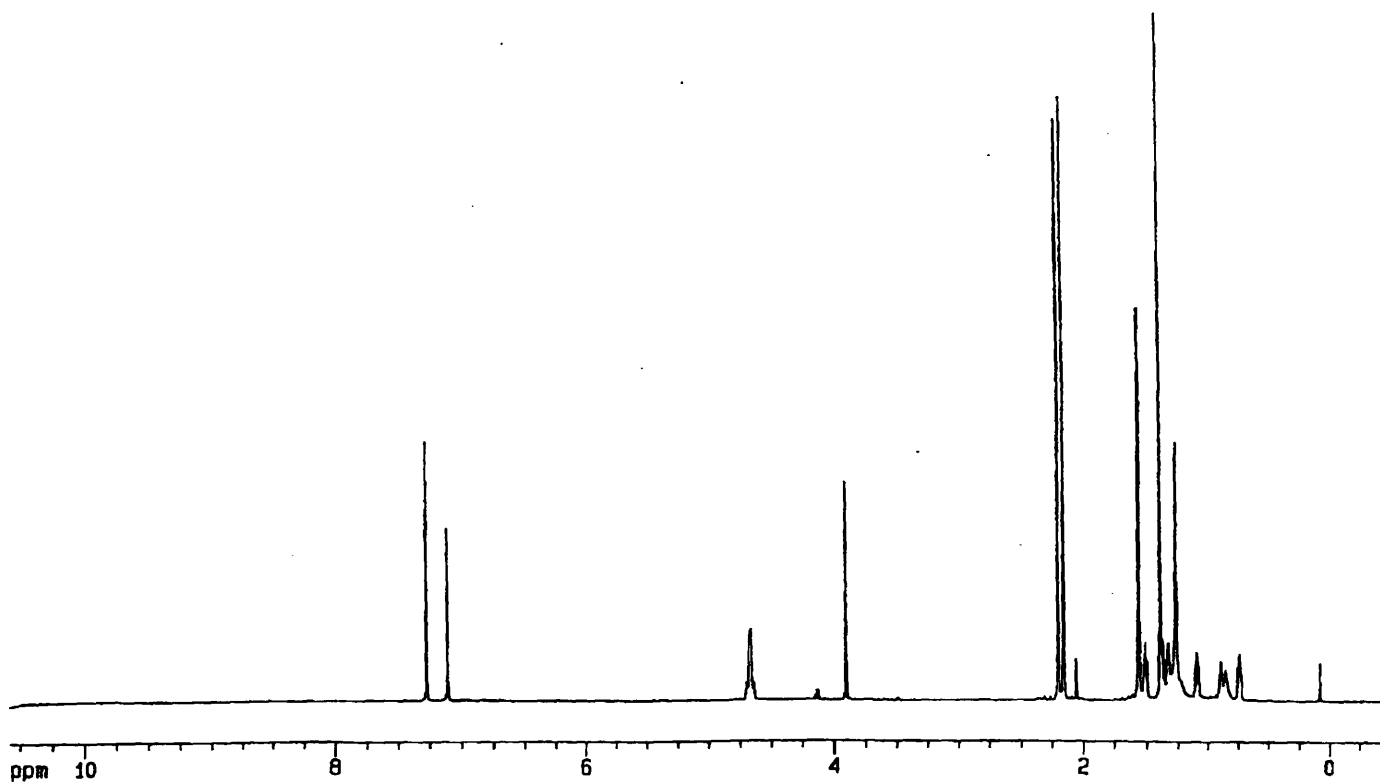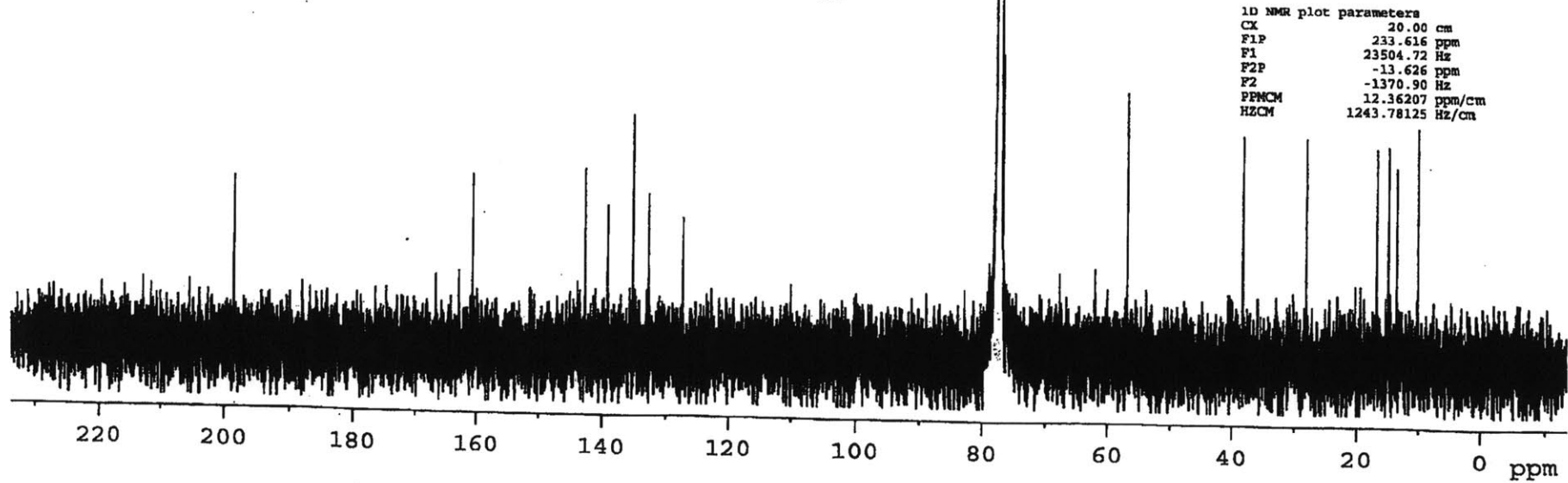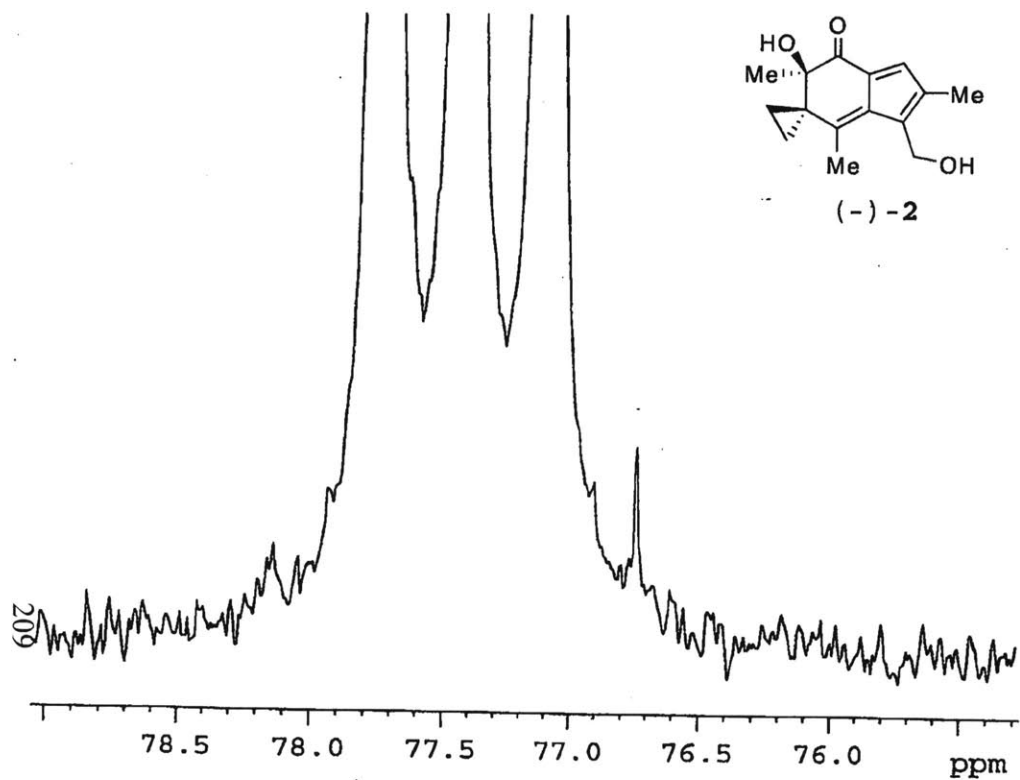TE                       300.0 K
D1               2.00000000 sec
d11              0.03000000 sec
d12              0.00002000 sec


========== CHANNEL f1 ==========
NUC1                       13C
P1                   15.25 usec
PL1                    3.00 dB
SFO1            100.6237959 MHz

========== CHANNEL f2 ==========
CPDPRG2               waltz16
NUC2                        1H
PCPD2               107.50 usec
PL2                    0.00 dB
PL12                  24.00 dB
PL13                  24.00 dB
SFO2            400.1316005 MHz

F2 - Processing parameters
SI                       32768
SF              100.6127290 MHz
WDW                         EM
SSB                          0
LB                     1.00 Hz
GB                           0
PC                        1.40

1D NMR plot parameters
CX                    20.00 cm
F1P                 233.616 ppm
F1                23504.72 Hz
F2P                 -13.626 ppm
F2                -1370.90 Hz
PPMCM            12.36207 ppm/cm
HZCM            1243.78125 Hz/cm

Zorbax CN; 1.0%iPrOH-hex; 1.0mL/min

MWD1 A, Sig=220,16 Ref=360,100 (D2176RAC.D)

mAU

8.294  Area: 911.219

10.232  Area: 898.297

MWD1 B, Sig=230,16 Ref=360,100 (D2176RAC.D)

mAU

8.295  Area: 1503.81

10.232  Area: 1513.19

MWD1 C, Sig=240,16 Ref=360,100 (D2176RAC.D)

mAU

8.291  Area: 1606.83

10.232  Area: 1579.44

MWD1 D, Sig=254,16 Ref=360,100 (D2176RAC.D)

mAU

8.288  Area: 1001.91

10.232  Area: 970.258

MWD1 E, Sig=270,16 Ref=360,100 (D2176RAC.D)

mAU

8.296  Area: 181.006

10.232  Area: 183.13

```
=====================================================================
                         Area Percent Report
=====================================================================

Sorted By            :      Signal
Multiplier           :      1.0000
Dilution             :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 A, Sig=220,16 Ref=360,100

Peak RetTime Type  Width      Area       Height      Area
  #   [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   8.294 MM    0.3635  911.21899   41.78366  50.3570
  2  10.232 MM    0.4289  898.29730   34.90594  49.6430

Totals :                 1809.51630   76.68960


Results obtained with enhanced integrator!

Signal 2: MWD1 B, Sig=230,16 Ref=360,100

Peak RetTime Type  Width      Area       Height      Area
  #   [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   8.295 MM    0.3657 1503.81494   68.54411  49.8446
  2  10.232 MM    0.4320 1513.18909   58.38517  50.1554

Totals :                 3017.00403  126.92929


Results obtained with enhanced integrator!

Signal 3: MWD1 C, Sig=240,16 Ref=360,100

Peak RetTime Type  Width      Area       Height      Area
  #   [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   8.291 MM    0.3521 1606.82849   76.06040  50.4298
  2  10.232 MM    0.4278 1579.44067   61.52729  49.5702

Totals :                 3186.26917  137.58769


Results obtained with enhanced integrator!

Signal 4: MWD1 D, Sig=254,16 Ref=360,100

Peak RetTime Type  Width      Area       Height      Area
  #   [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   8.288 MM    0.3491 1001.91046   47.83171  50.8025
  2  10.232 MM    0.4357  970.25781   37.11912  49.1975

Totals :                 1972.16827   84.95083


Results obtained with enhanced integrator!

Signal 5: MWD1 E, Sig=270,16 Ref=360,100

Peak RetTime Type  Width      Area       Height      Area
  #   [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   8.296 MM    0.4375  181.00645    6.89578  49.7084
  2  10.232 MM    0.4941  183.12990    6.17725  50.2916

Totals :                  364.13635   13.07303
```

HO    O

Me''    Me

Me    (-)-1

Zorbax CN; 1.0%iPrOH-hex; 1.0mL/min

MWD1 A, Sig=220,16 Ref=360,100 (D2176F7.D)

mAU

100
75
50
25
0

8.302
Area: 1327.35

10.209
Area: 57.1813

7    8    9    10    11    min

MWD1 B, Sig=230,16 Ref=360,100 (D2176F7.D)

mAU

100
75
50
25
0

8.302
Area: 2166.57

10.209
Area: 107.444

7    8    9    10    11    min

MWD1 C, Sig=240,16 Ref=360,100 (D2176F7.D)

mAU

100
75
50
25
0

8.300
Area: 2408.78

10.209
Area: 125.988

7    8    9    10    11    min

MWD1 D, Sig=254,16 Ref=360,100 (D2176F7.D)

mAU

100
75
50
25
0

8.298
Area: 1490.56

10.209
Area: 72.1906

7    8    9    10    11    min

MWD1 E, Sig=270,16 Ref=360,100 (D2176F7.D)

mAU

100
75
50
25
0

8.304
Area: 203.788

10.203
Area: 9.53781

7    8    9    10    11    min

206

```
=================================================================
                      Area Percent Report
=================================================================

Sorted By          :      Signal
Multiplier         :      1.0000
Dilution           :      1.0000
Use Multiplier & Dilution Factor with ISTDs
```



(-)-1
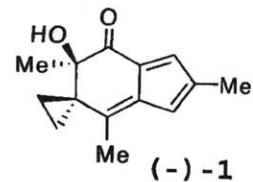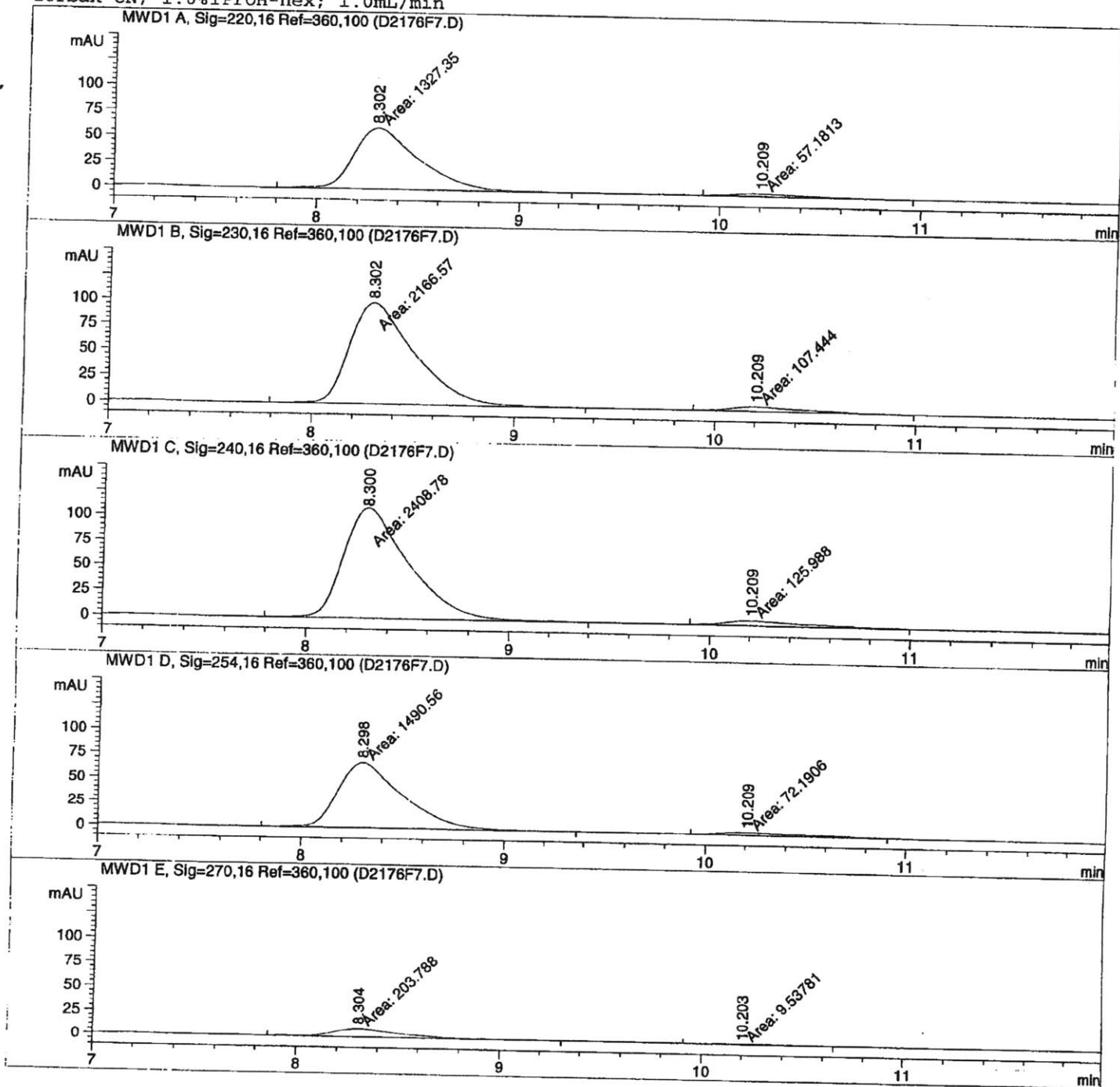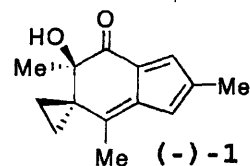
```
Signal 1: MWD1 A, Sig=220,16 Ref=360,100

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   8.302 MM    0.3690 1327.35315   59.95131  95.8700
  2  10.209 MM    0.3880   57.18126    2.45643   4.1300

Totals :                  1384.53440   62.40774

 Results obtained with enhanced integrator!

Signal 2: MWD1 B, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   8.302 MM    0.3658 2166.57349   98.70364  95.2752
  2  10.209 MM    0.4169  107.44352    4.29493   4.7248

Totals :                  2274.01701  102.99857

 Results obtained with enhanced integrator!

Signal 3: MWD1 C, Sig=240,16 Ref=360,100

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   8.300 MM    0.3678 2408.77856  109.15147  95.0296
  2  10.209 MM    0.4560  125.98849    4.60503   4.9704

Totals :                  2534.76705  113.75651

 Results obtained with enhanced integrator!

Signal 4: MWD1 D, Sig=254,16 Ref=360,100

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   8.298 MM    0.3686 1490.56372   67.39674  95.3806
  2  10.209 MM    0.4593   72.19061    2.61948   4.6194

Totals :                  1562.75433   70.01622

 Results obtained with enhanced integrator!

Signal 5: MWD1 E, Sig=270,16 Ref=360,100

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   8.304 MM    0.3836  203.78841    8.85333  95.5290
  2  10.203 MM    0.3813    9.53781 4.16884e-1   4.4710

Totals :                   213.32622    9.27021
```

(-)-2
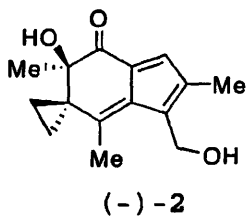
Current Data Parameters
NAME
EXPNO              1
PROCNO             1

F2 - Acquisition Parameters
Date_          20060123
Time              13.01
INSTRUM           spect
PROBHD   5 mm CPTCI 1H/
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    0
SWH          7936.508 Hz
FIDRES       0.121102 Hz
AQ         4.1288805 sec
RG                 28.5
DW          63.000 usec
DE           6.00 usec
TE              298.0 K
D1        1.00000000 sec
MCREST    0.00000000 sec
MCWRK     0.01500000 sec

======= CHANNEL f1 =======
NUC1                 1H
P1           8.00 usec
PL1            -4.00 dB
SFO1     600.1323934 MHz

F2 - Processing parameters
SI                32768
SF       600.1300114 MHz
WDW                  EM
SSB                   0
LB             0.30 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX             20.00 cm
CY              9.86 cm
F1P           10.800 ppm
F1           6481.40 Hz
F2P           -0.500 ppm
F2           -300.07 Hz
PPMCM       0.56500 ppm/cm
HZCM        339.07346 Hz/cm

ppm   10        8        6        4        2        0

(−)-2

Inset expansion axis (ppm): 78.5  78.0  77.5  77.0  76.5  76.0  ppm

Main spectrum axis (ppm): 220  200  180  160  140  120  100  80  60  40  20  0  ppm
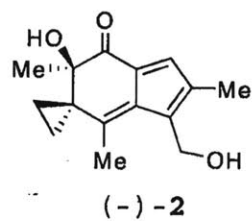
Current Data Parameters
NAME
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20060124
Time                   8.53
INSTRUM               spect
PROBHD        5mm BBO BB-1
PULPROG             zgpg30
TD                    65536
SOLVENT              CDCl3
NS                    13967
DS                        4
SWH           24875.621 Hz
FIDRES         0.379572 Hz
AQ            1.3173236 sec
RG                    16384
DW              20.100 usec
DE               6.00 usec
TE                 300.0 K
D1           2.00000000 sec
d11          0.03000000 sec
d12          0.00002000 sec

============ CHANNEL f1 ============
NUC1                   13C
P1              15.25 usec
PL1              3.00 dB
SFO1        100.6237959 MHz

============ CHANNEL f2 ============
CPDPRG2            waltz16
NUC2                    1H
PCPD2          107.50 usec
PL2              0.00 dB
PL12            24.00 dB
PL13            24.00 dB
SFO2        400.1316005 MHz

F2 - Processing parameters
SI                    32768
SF          100.6127290 MHz
WDW                      EM
SSB                       0
LB               1.00 Hz
GB                        0
PC                     1.40

1D NMR plot parameters
CX               20.00 cm
F1P            233.616 ppm
F1            23504.72 Hz
F2P            -13.626 ppm
F2            -1370.90 Hz
PPMCM       12.36207 ppm/cm
HZCM        1243.78125 Hz/cm

Zorbax CN; 1.0%iPrOH-hex; 1.0mL/min

MWD1 A, Sig=220,16 Ref=360,100 (D2IRORAC.D)

mAU

4.881  Area: 255.954

6.508  Area: 270.032

MWD1 B, Sig=230,16 Ref=360,100 (D2IRORAC.D)

mAU

4.881  Area: 444.233

6.508  Area: 456.632

MWD1 C, Sig=240,16 Ref=360,100 (D2IRORAC.D)

mAU

4.881  Area: 479.681

6.508  Area: 505.273

MWD1 D, Sig=254,16 Ref=360,100 (D2IRORAC.D)

mAU

4.881  Area: 353.306

6.508  Area: 374.115

MWD1 E, Sig=270,16 Ref=360,100 (D2IRORAC.D)

mAU

4.881  Area: 141.929

6.508  Area: 135.897

```
================================================================
                      Area Percent Report
================================================================

Sorted By          :        Signal
Multiplier         :        1.0000
Dilution           :        1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 A, Sig=220,16 Ref=360,100

Peak RetTime Type  Width     Area       Height    Area
  #   [min]        [min]   [mAU*s]       [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   4.881 MM    0.1691  255.95450   25.22759  48.6618
  2   6.508 MM    0.2286  270.03177   19.68349  51.3382

Totals :                  525.98627   44.91107


Results obtained with enhanced integrator!

Signal 2: MWD1 B, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area       Height    Area
  #   [min]        [min]   [mAU*s]       [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   4.881 MM    0.1724  444.23315   42.93738  49.3118
  2   6.508 MM    0.2301  456.63242   33.07205  50.6882

Totals :                  900.86557   76.00943


Results obtained with enhanced integrator!

Signal 3: MWD1 C, Sig=240,16 Ref=360,100

Peak RetTime Type  Width     Area       Height    Area
  #   [min]        [min]   [mAU*s]       [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   4.881 MM    0.1700  479.68124   47.03773  48.7008
  2   6.508 MM    0.2305  505.27335   36.53200  51.2992

Totals :                  984.95459   83.56973


Results obtained with enhanced integrator!

Signal 4: MWD1 D, Sig=254,16 Ref=360,100

Peak RetTime Type  Width     Area       Height    Area
  #   [min]        [min]   [mAU*s]       [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   4.881 MM    0.1703  353.30612   34.58545  48.5697
  2   6.508 MM    0.2314  374.11542   26.94118  51.4303

Totals :                  727.42154   61.52663


Results obtained with enhanced integrator!

Signal 5: MWD1 E, Sig=270,16 Ref=360,100

Peak RetTime Type  Width     Area       Height    Area
  #   [min]        [min]   [mAU*s]       [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   4.881 MM    0.1827  141.92921   12.94412  51.0856
  2   6.508 MM    0.2336  135.89722    9.69631  48.9144

Totals :                  277.82643   22.64043
```

Zorbax CN; 1.0%iPrOH-hex; 1.0mL/min

MWD1 A, Sig=220,16 Ref=360,100 (D2178IRO.D)

mAU

4.856
Area: 395.197

6.483
Area: 17.1663

MWD1 B, Sig=230,16 Ref=360,100 (D2178IRO.D)

mAU

4.856
Area: 658.599

6.483
Area: 25.6802

MWD1 C, Sig=240,16 Ref=360,100 (D2178IRO.D)

mAU

4.856
Area: 711.18

6.483
Area: 27.7622

MWD1 D, Sig=254,16 Ref=360,100 (D2178IRO.D)

mAU

4.856
Area: 526.386

6.483
Area: 21.4113

MWD1 E, Sig=270,16 Ref=360,100 (D2178IRO.D)

mAU

4.856
Area: 201.683

6.483
Area: 7.12811

(-)-2
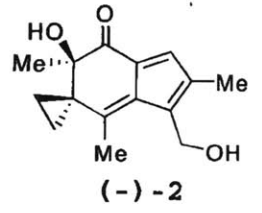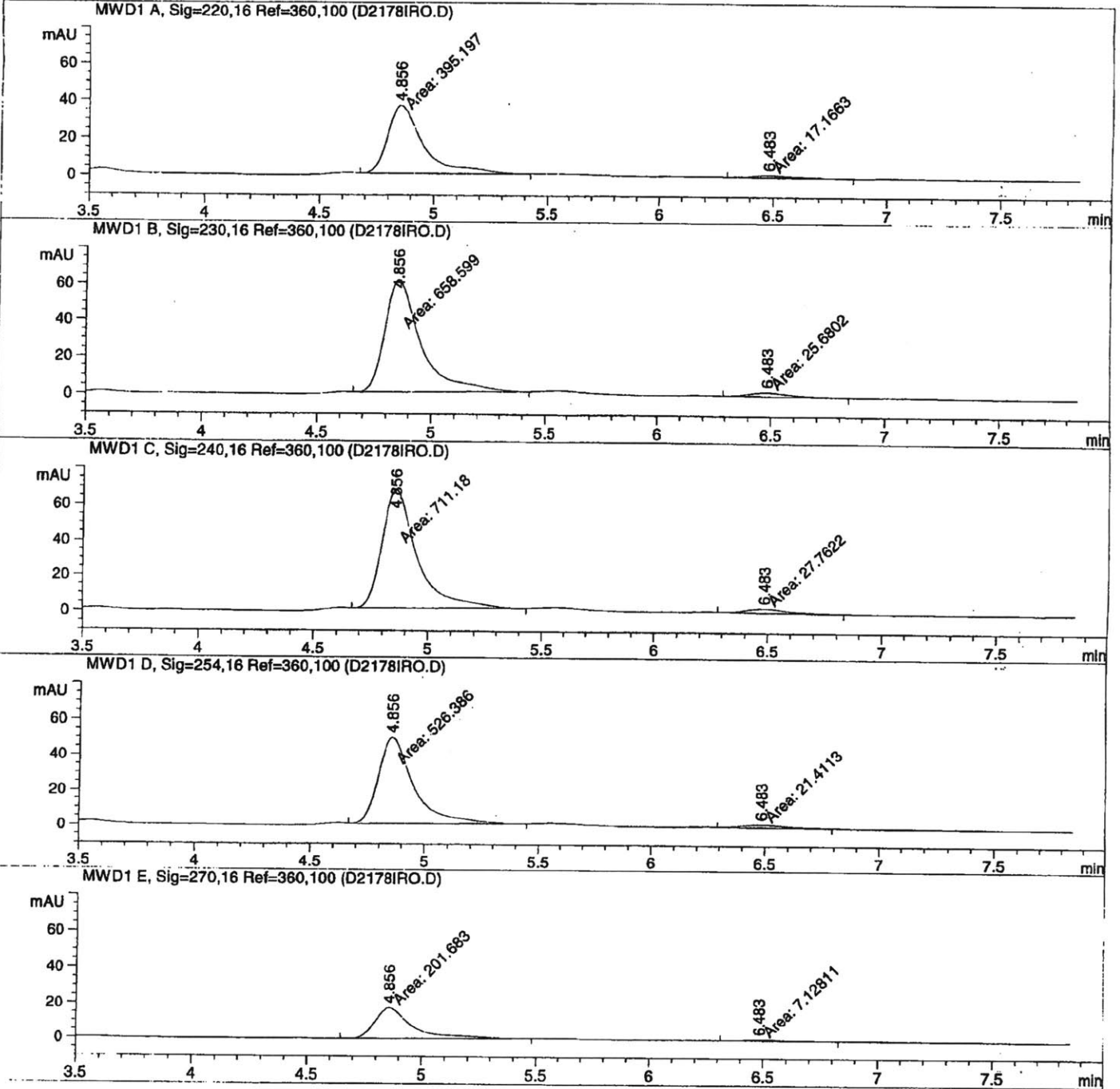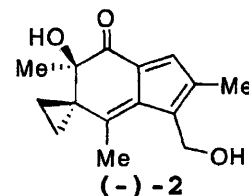
```
===============================================================
                      Area Percent Report
===============================================================

Sorted By              :      Signal
Multiplier             :      1.0000
Dilution               :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 A, Sig=220,16 Ref=360,100

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]       %
----|-------|----|-------|----------|-----------|--------|
  1   4.856 MM    0.1823  395.19705    36.14056  95.8371
  2   6.483 MM    0.2388   17.16626     1.19831   4.1629

Totals :                  412.36331    37.33887

 Results obtained with enhanced integrator!

Signal 2: MWD1 B, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]       %
----|-------|----|-------|----------|-----------|--------|
  1   4.856 MM    0.1798  658.59857    61.06145  96.2471
  2   6.483 MM    0.2199   25.68021     1.94622   3.7529

Totals :                  684.27878    63.00767

 Results obtained with enhanced integrator!

Signal 3: MWD1 C, Sig=240,16 Ref=360,100

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]       %
----|-------|----|-------|----------|-----------|--------|
  1   4.856 MM    0.1770  711.18018    66.97616  96.2430
  2   6.483 MM    0.2160   27.76224     2.14248   3.7570

Totals :                  738.94242    69.11864

 Results obtained with enhanced integrator!

Signal 4: MWD1 D, Sig=254,16 Ref=360,100

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]       %
----|-------|----|-------|----------|-----------|--------|
  1   4.856 MM    0.1777  526.38641    49.36498  96.0914
  2   6.483 MM    0.2169   21.41133     1.64554   3.9086

Totals :                  547.79775    51.01052

 Results obtained with enhanced integrator!

Signal 5: MWD1 E, Sig=270,16 Ref=360,100

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]       %
----|-------|----|-------|----------|-----------|--------|
  1   4.856 MM    0.1871  201.68265    17.96253  96.5863
  2   6.483 MM    0.2061    7.12811  5.76507e-1   3.4137

Totals :                  208.81076    18.53904
```



(-)-2

# Appendix B.

## Spectra for Chapter II

DEC. & VT
dfrq        125.845
dn             C13
dpwr            30
dof              0
dm             nnn
dmm              c
dmf            200
dseq
dres           1.0
homo             n
     PROCESSING
wtfile
proc            ft
fn          262144
math             f

werr
wexp
wbs
wnt            wft

ACQUISITION
sfrq      500.435
tn             H1
at          4.999
np         120102
sw        12012.0
fb       not used
bs              2
tpwr           56
pw            8.0
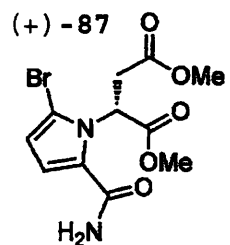d1          0.100
tof        3003.2
nt             32
ct             10
alock           n
gain     not used
     FLAGS
il              n
in              n
dp              y
hs             nn
     DISPLAY
sp         -250.2
wp         6255.3
vs              8
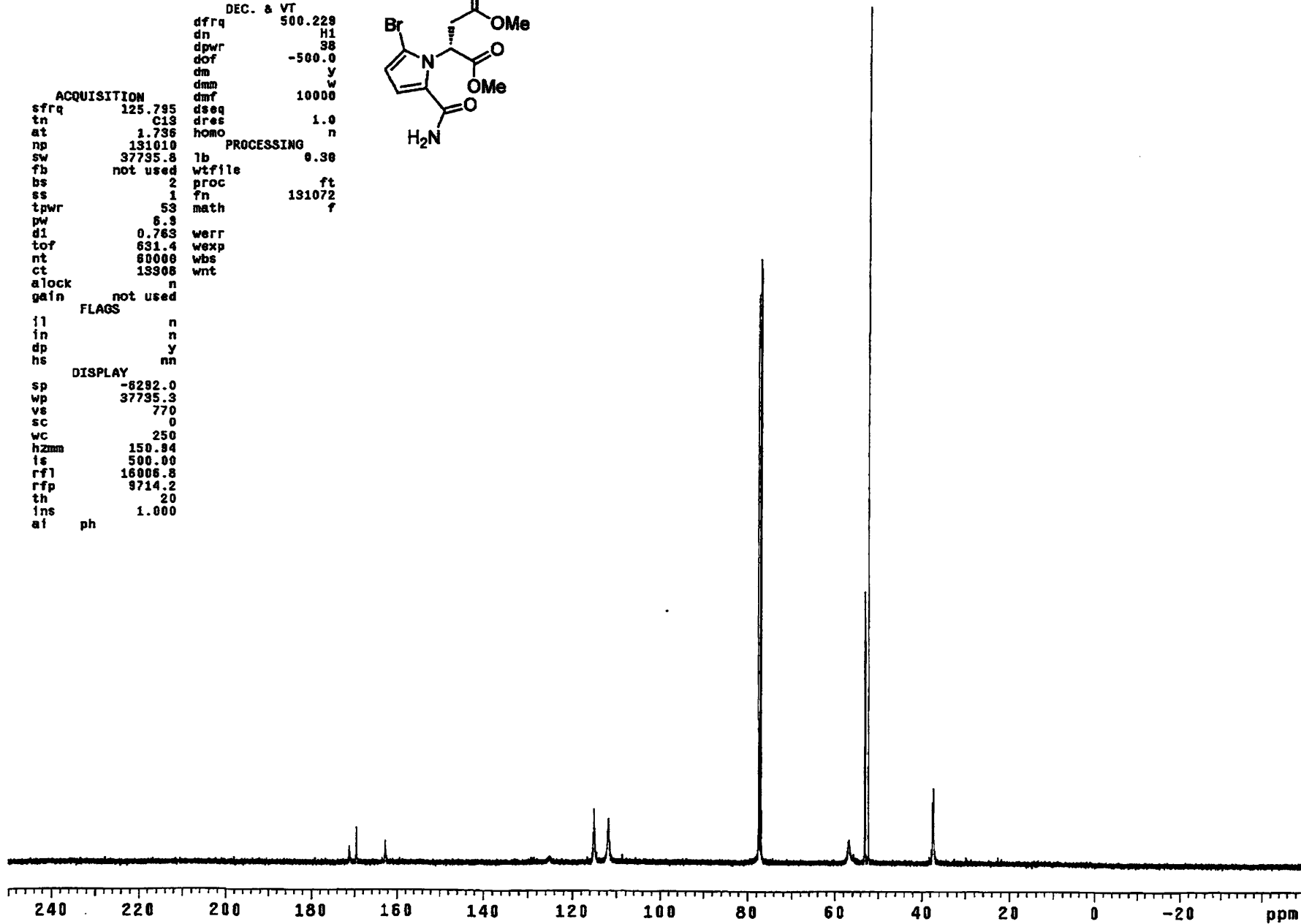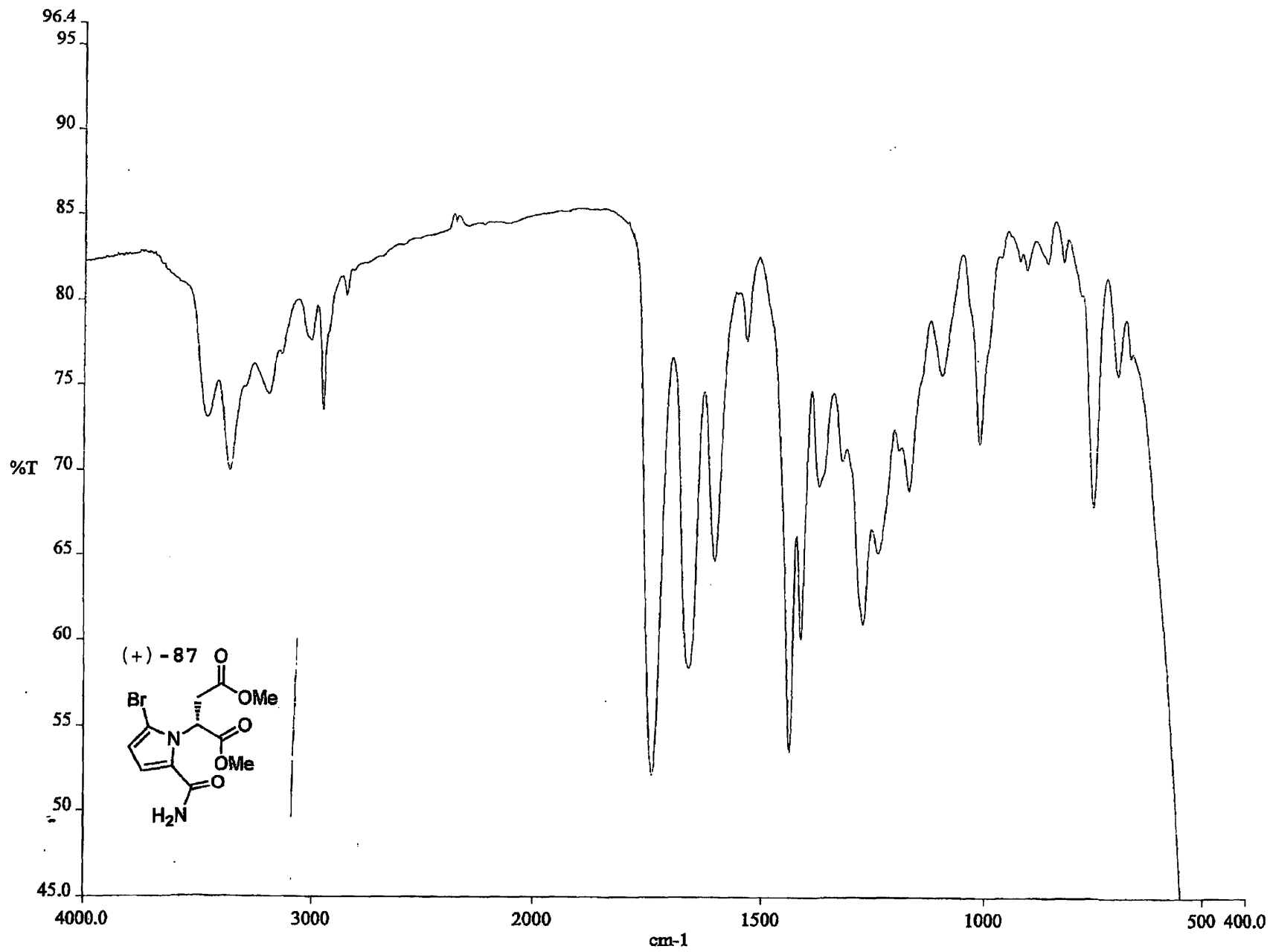sc              0
wc            250
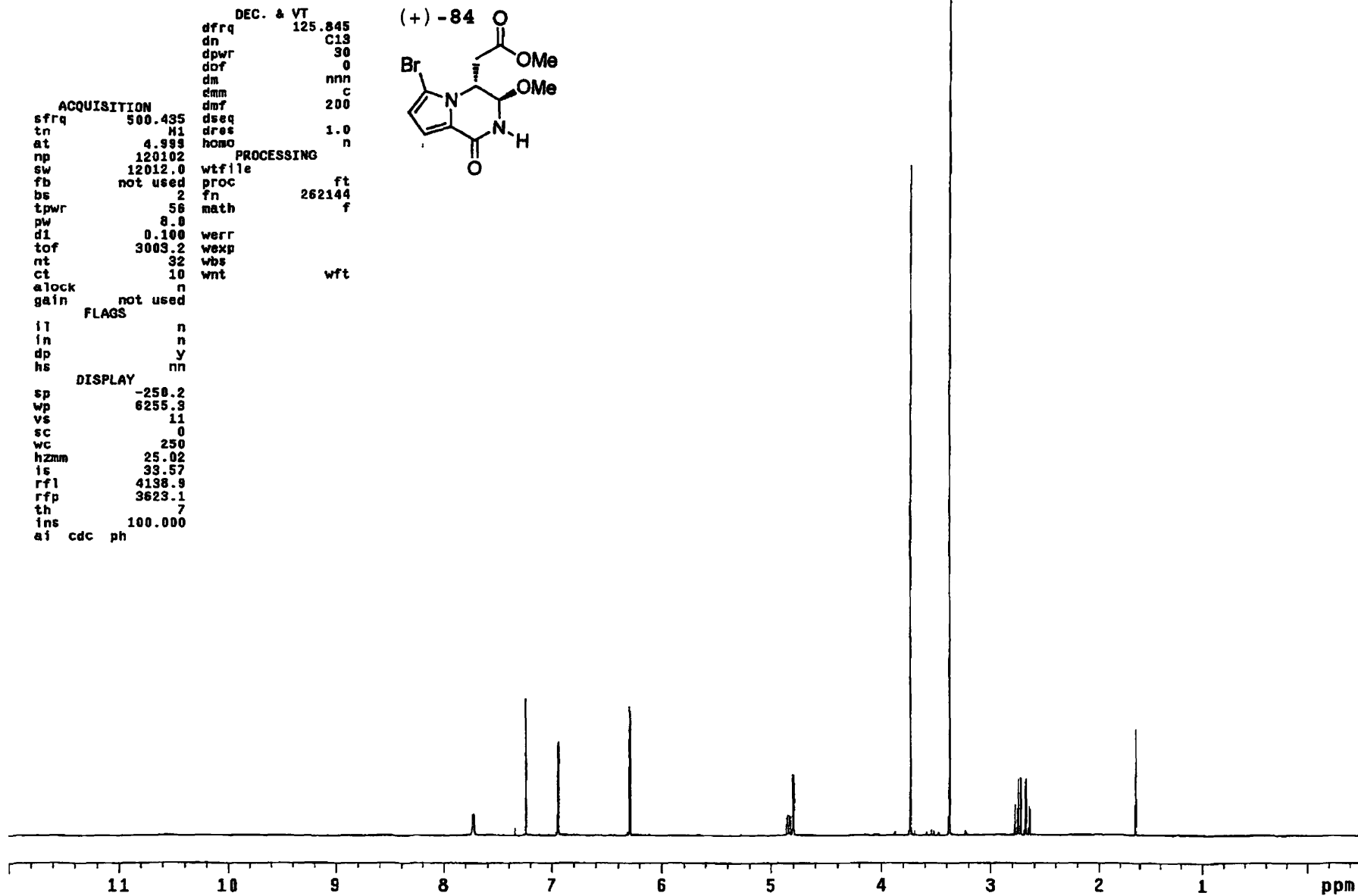hzmm        25.02
is          39.57
rfl        4138.4
rfp        9623.1
th              7
ins       100.000
ai   cdc  ph
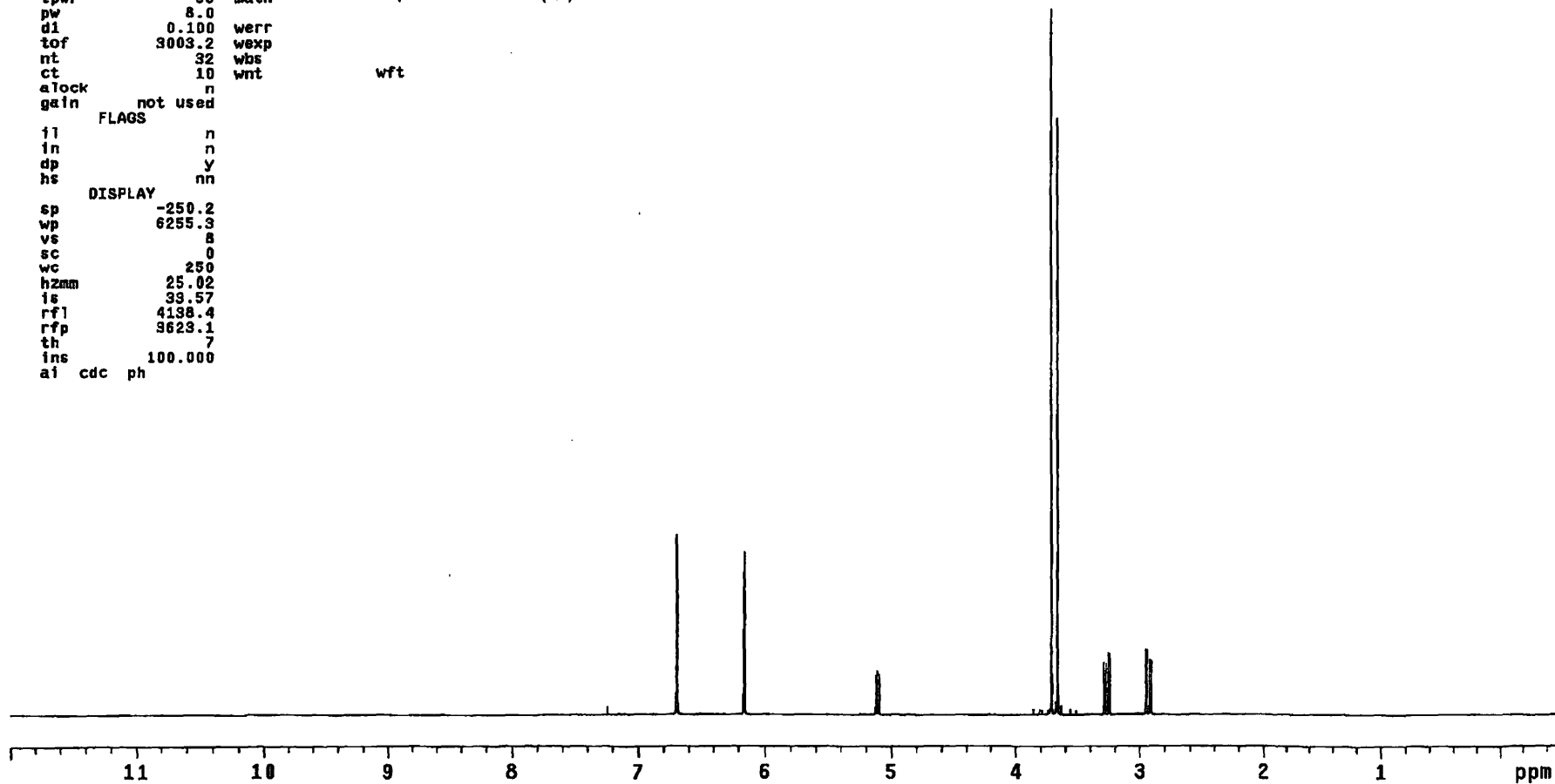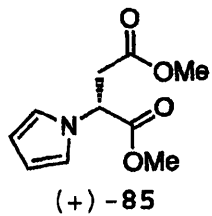
(+)-85

ACQUISITION
sfrq        125.795
tn              C13
at            1.736
np          131010
sw          37735.8
fb        not used
bs                2
ss                1
tpwr             53
pw              6.9
d1            0.763
tof           631.4
nt             1000
ct               32
alock             n
gain       not used

FLAGS
il                n
in                n
dp                y
hs               nn

DISPLAY
sp          -6308.1
wp          37735.8
vs               21
sc                0
wc              250
hzmm           5.75
is           500.00
rfl         16024.3
rfp          9716.2
th                7
ins           1.000
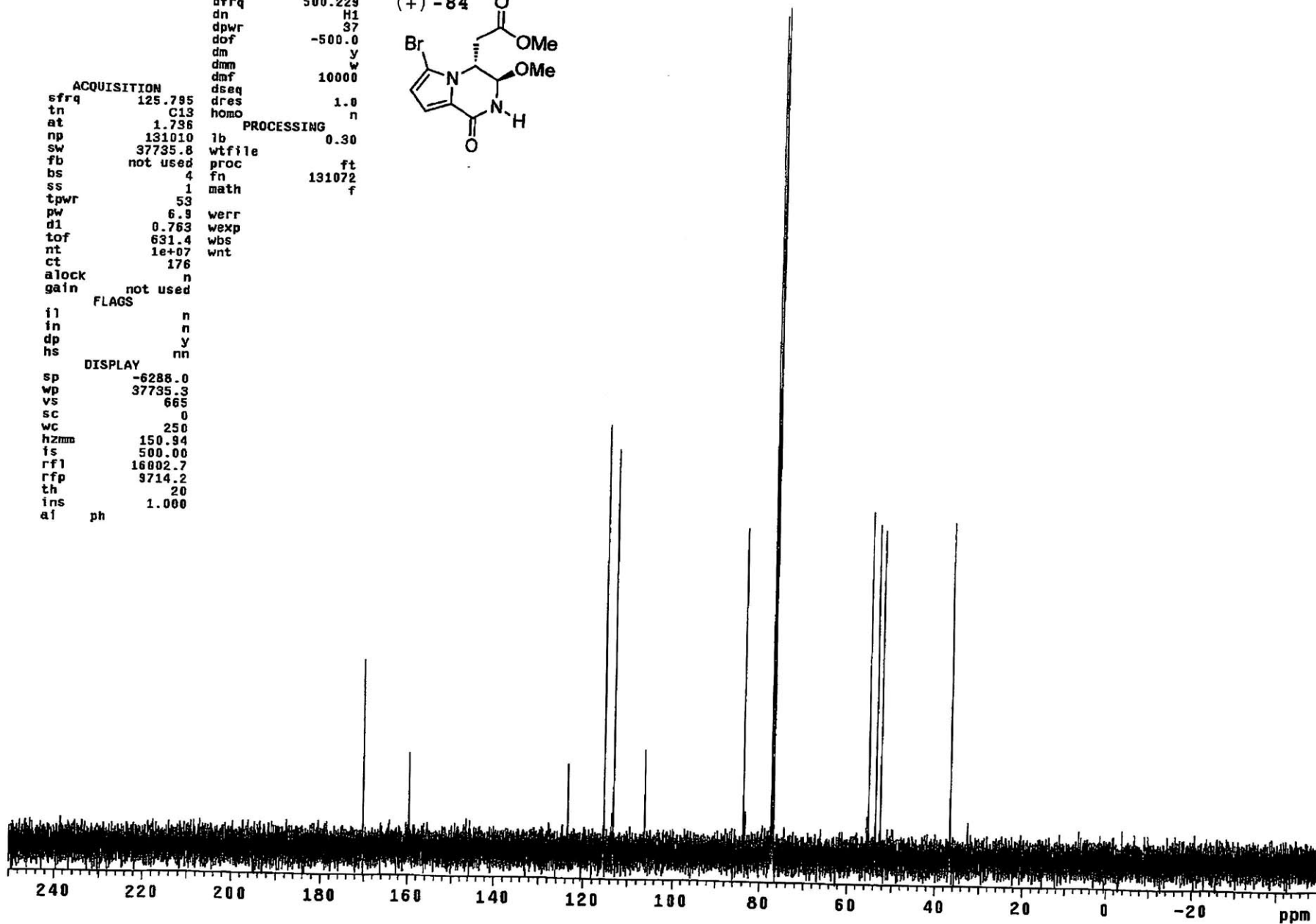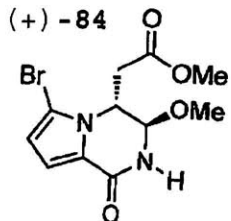ai       ph

DEC. & VT
dfrq        500.229
dn               H1
dpwr             38
dof          -500.0
dm                y
dmm               w
dmf           10000
dseq
dres            1.0
homo              n

PROCESSING
lb             0.30
wtfile
proc             ft
fn           131072
math              f

werr
wexp
wbs
wnt

(+)-85

MWD1 C, Sig=240,16 Ref=360,100

(+)-85

```
==========================================================================
                          Area Percent Report
==========================================================================

  Sorted By              :      Signal
  Multiplier             :      1.0000
  Dilution               :      1.0000
  Use Multiplier & Dilution Factor with ISTDs


  Signal 1: MWD1 C, Sig=240,16 Ref=360,100
```
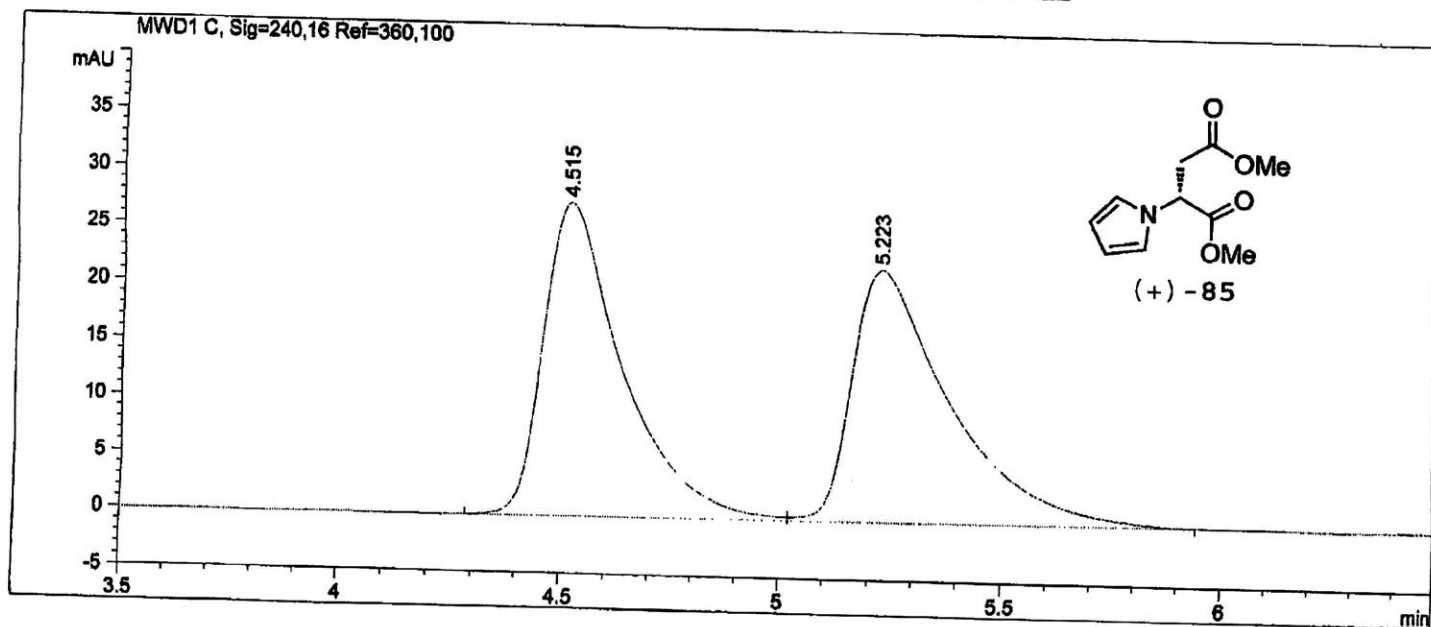
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 4.515 | BV | 0.1810 | 342.47797 | 27.56392 | 50.0382 |
| 2 | 5.223 | VB | 0.2221 | 341.95474 | 22.15433 | 49.9618 |

```
  Totals :                      684.43271   49.71825

  Results obtained with enhanced integrator!
==========================================================================
                          *** End of Report ***
```

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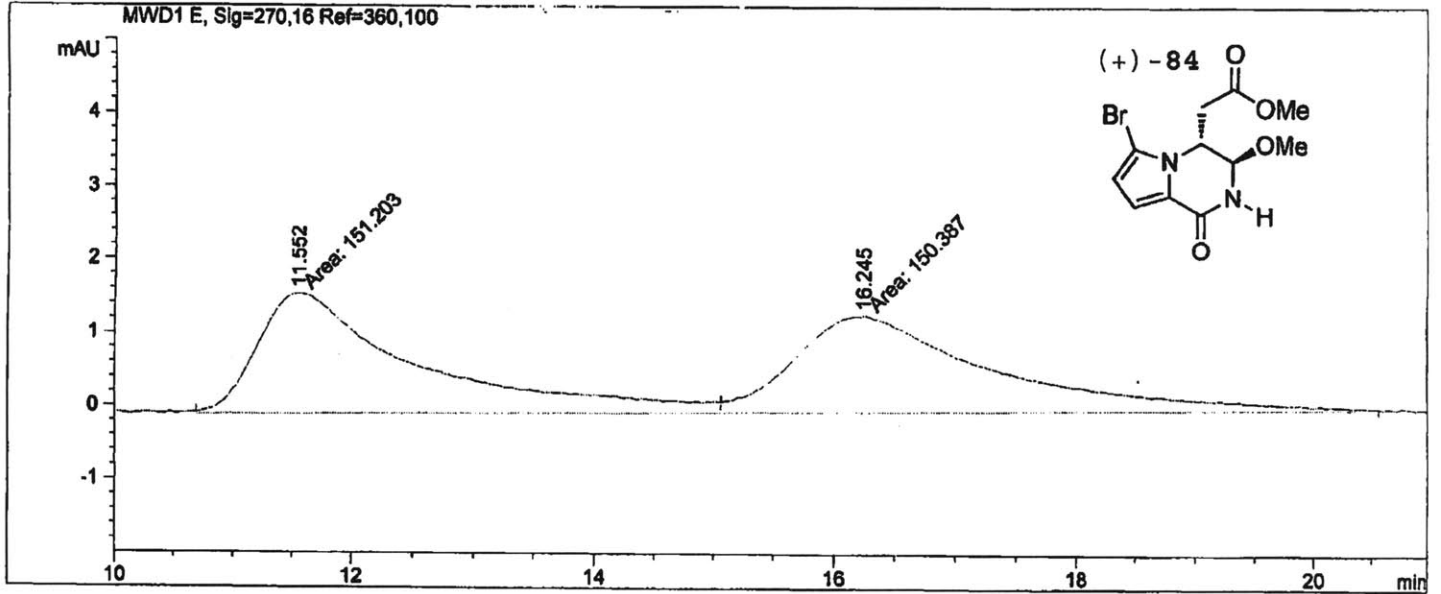Injection Date   :                          Seq. Line :    1
Sample Name      :                           Location : Vial 91
Acq. Operator    :                                Inj :    1
                                         Inj Volume : 1 µl

Acq. Method      :
Last changed     :
Analysis Method  :
Last changed     :

MWD1 C, Sig=240,16 Ref=360,100

4.591
Area: 549.214

(+)-85
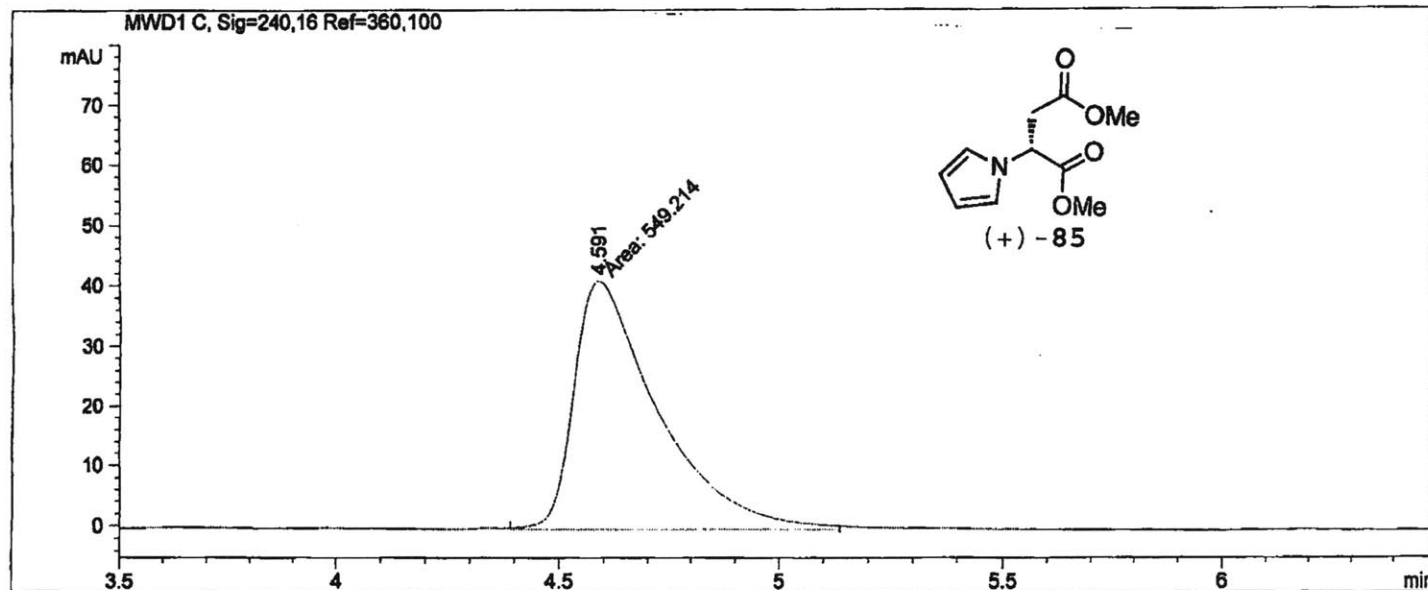
## Area Percent Report

Sorted By           :      Signal
Multiplier          :      1.0000
Dilution            :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 C, Sig=240,16 Ref=360,100

| Peak | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|------|---------------|------|-------------|--------------|--------------|--------|
| 1 | 4.591 | MM | 0.2209 | 549.21417 | 41.44402 | 100.0000 |

Totals :                       549.21417    41.44402

Results obtained with enhanced integrator!
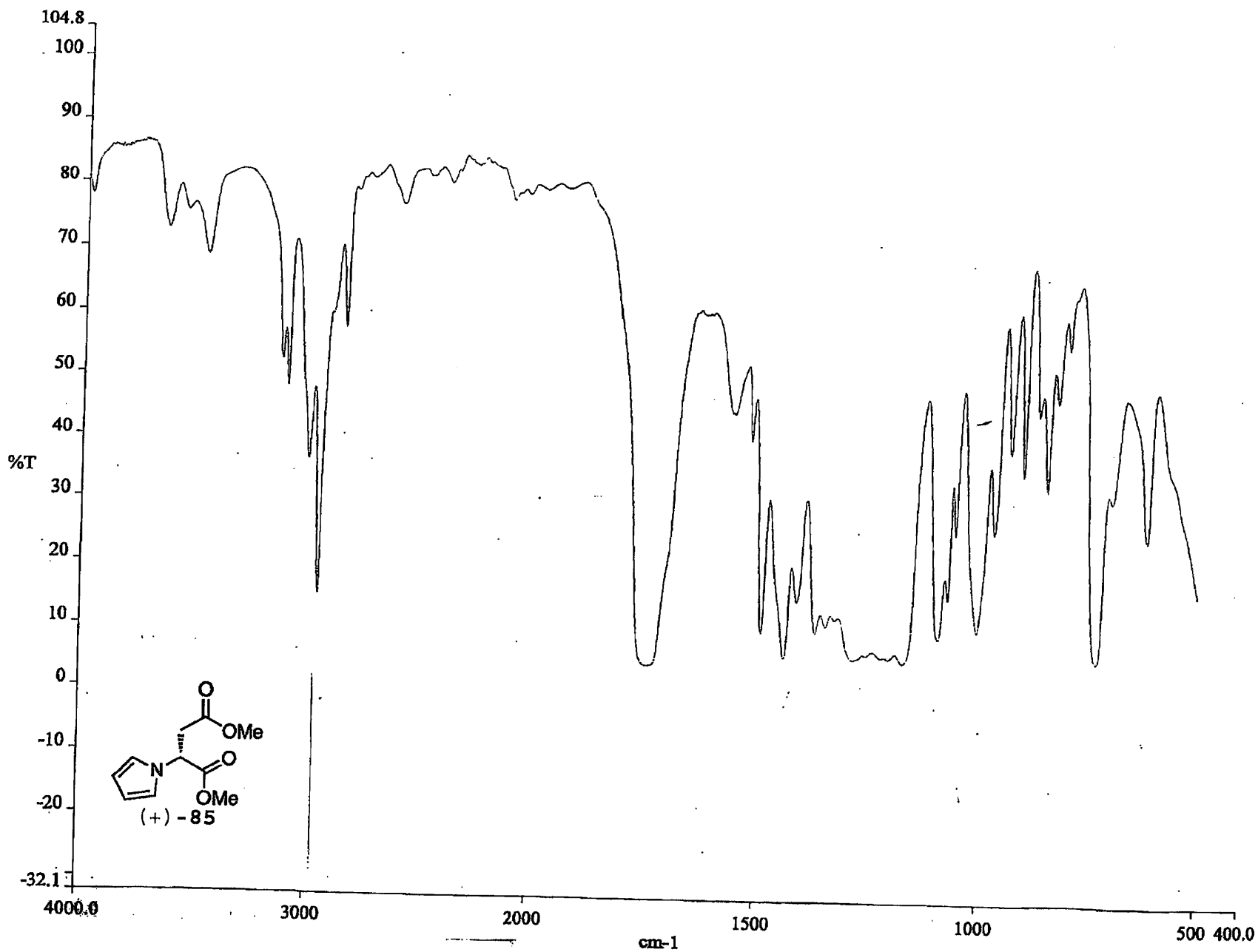
*** End of Report ***

(+)-85

DEC. & VT
dfrq        125.845
dn             C13
dpwr            30
dof              0
dm             nnn
dmm              c
dmf            200
dseq
dres           1.0
homo             n
PROCESSING
wtfile
proc            ft
fn          262144
math             f

werr
wexp
wbs
wnt            wft

ACQUISITION
sfrq      500.435
tn             H1
at          4.999
np         120102
sw        12012.0
fb       not used
bs              2
tpwr           56
pw            8.0
d1          0.100
tof        3003.2
nt             32
ct             22
alock           n
gain     not used
FLAGS
il              n
in              n
dp              y
hs             nn
DISPLAY
sp         -250.2
wp         6255.3
vs              7
sc              0
wc            250
hzmm        25.02
is          33.57
rfl        4137.5
rfp        3623.1
th              7
ins         1.000
ai  cdc  ph

(+) -86

DEC. & VT
dfrq        500.229
dn              H1
dpwr            38
dof         -500.0
dm              y
dmm             w
dmf          10000
dseq
dres           1.0
homo            n
PROCESSING
lb            0.30
wtfile
proc            ft
fn          131072
math            f

werr
wexp
wbs
wnt
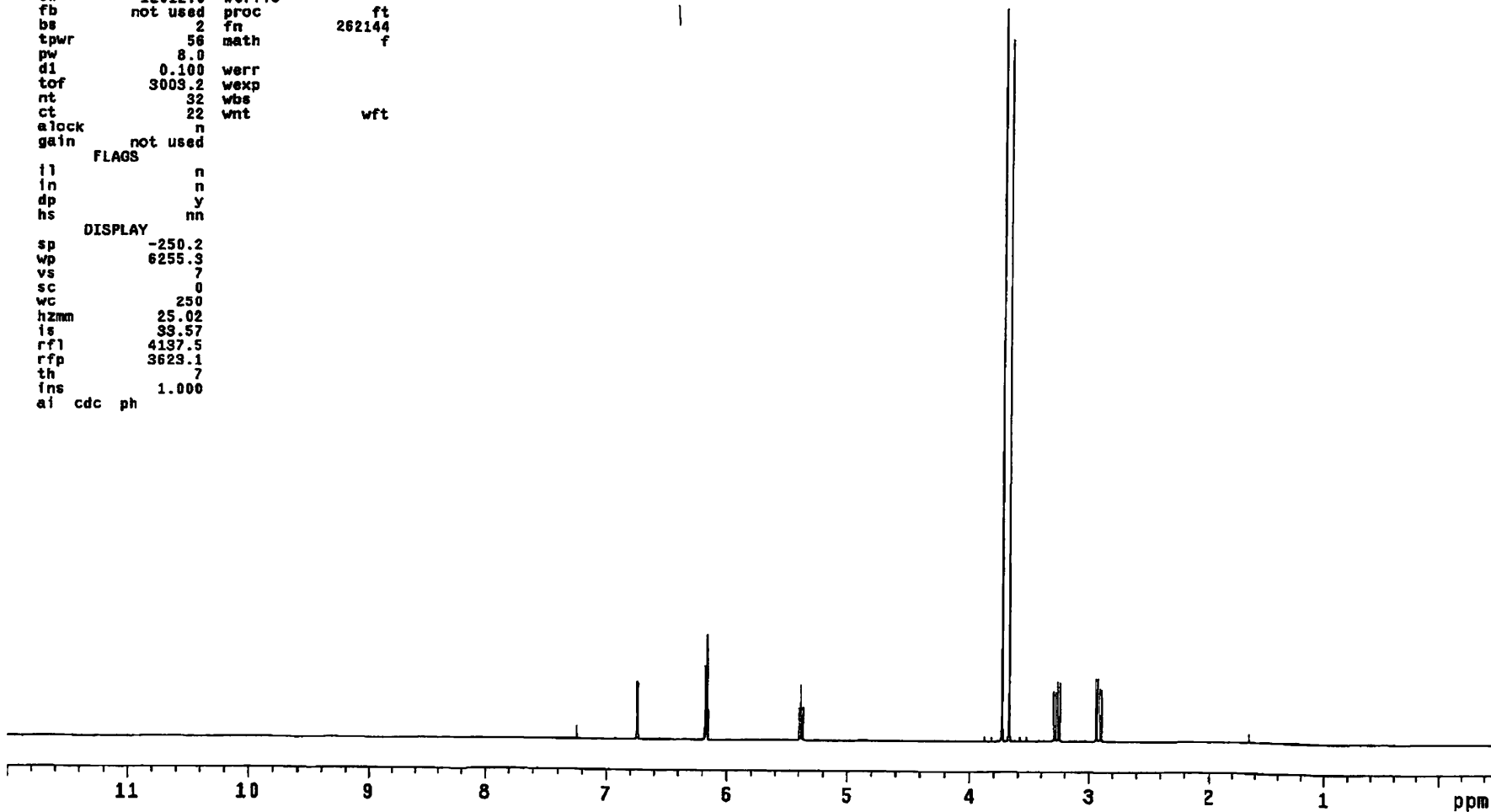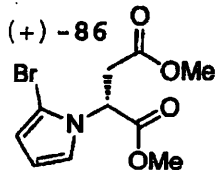
ACQUISITION
sfrq     125.795
tn           C13
at         1.736
np        131010
sw       37735.8
fb      not used
bs             4
ss             1
tpwr          53
pw           6.9
d1         0.763
tof        531.4
nt         1e+06
ct           100
alock          n
gain    not used
     FLAGS
il             n
in             n
dp             y
hs            nn
     DISPLAY
sp       -6320.4
wp       37735.3
vs           193
sc             0
wc           250
hzmm      150.94
is        500.00
rfl       16006.2
rfp        9685.2
th             9
ins        1.000
ai      ph

(+) -86



240    220    200    180    160    140    120    100    80    60    40    20    0    -20    ppm

```
MWD1 D, Sig=254,16 Ref=360,100
```
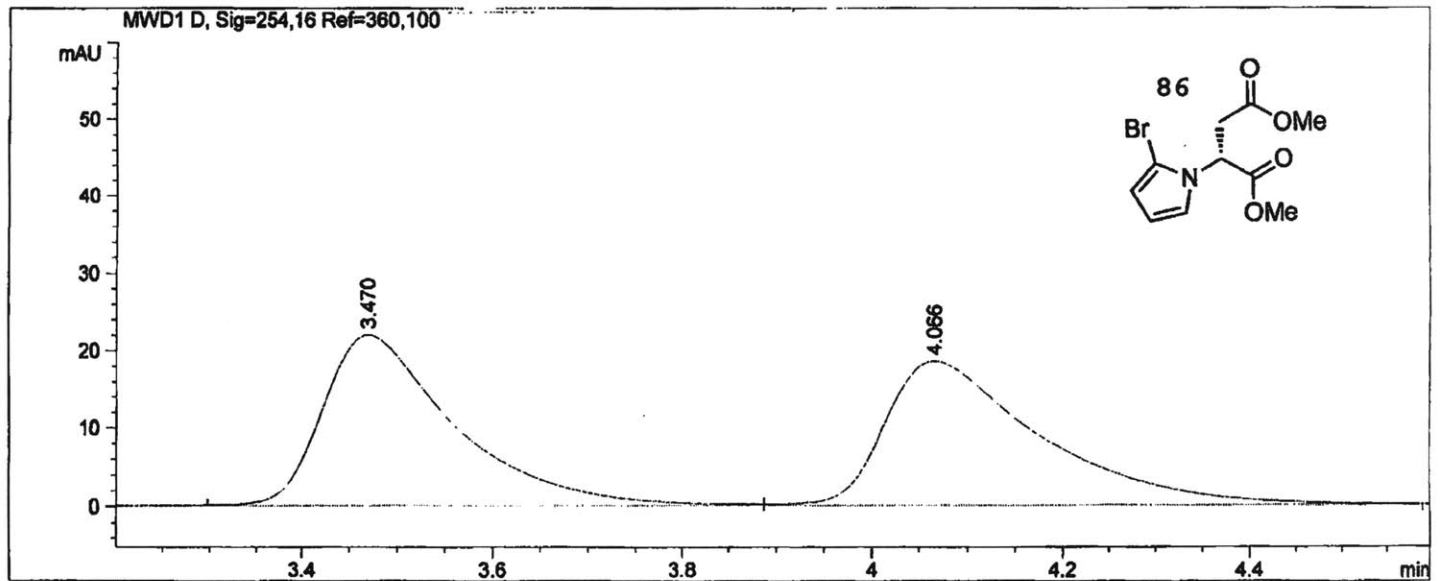
Area Percent Report

Sorted By          :      Signal
Multiplier         :      1.0000
Dilution           :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 D, Sig=254,16 Ref=360,100

| Peak<br># | RetTime<br>[min] | Type | Width<br>[min] | Area<br>[mAU*s] | Height<br>[mAU] | Area<br>% |
|------|---------|------|--------|-----------|----------|---------|
| 1 | 3.470 | BV | 0.1392 | 209.35068 | 21.96089 | 49.9378 |
| 2 | 4.066 | VB | 0.1622 | 209.87196 | 18.52020 | 50.0622 |

Totals :                      419.22264    40.48109

Results obtained with enhanced integrator!

*** End of Report ***

MWD1 D, Sig=254,16 Ref=360,100 (

(+)-86

3.604

====================================================================

Area Percent Report

====================================================================
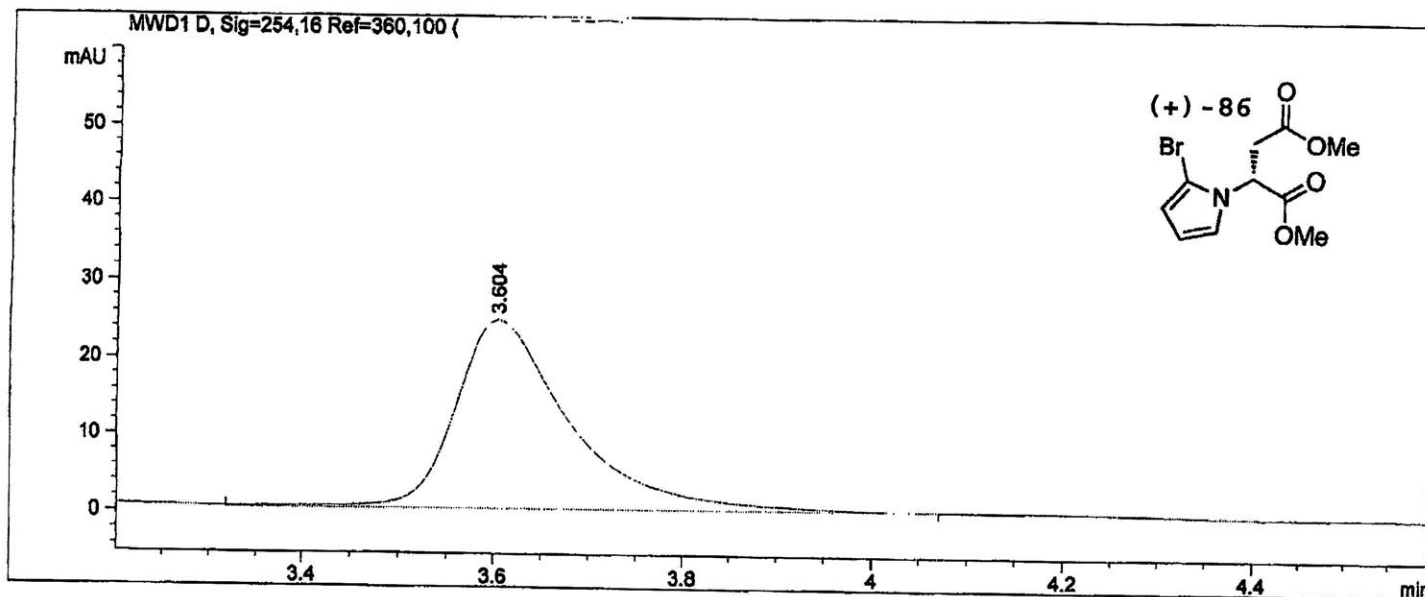
Sorted By              :          Signal
Multiplier             :          1.0000
Dilution               :          1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 D, Sig=254,16 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|------|---------|------|--------|-----------|-----------|-----------|
| 1 | 3.604 | VP | 0.1247 | 207.81982 | 24.56680 | 100.0000 |

Totals :                      207.81982     24.56680

Results obtained with enhanced integrator!
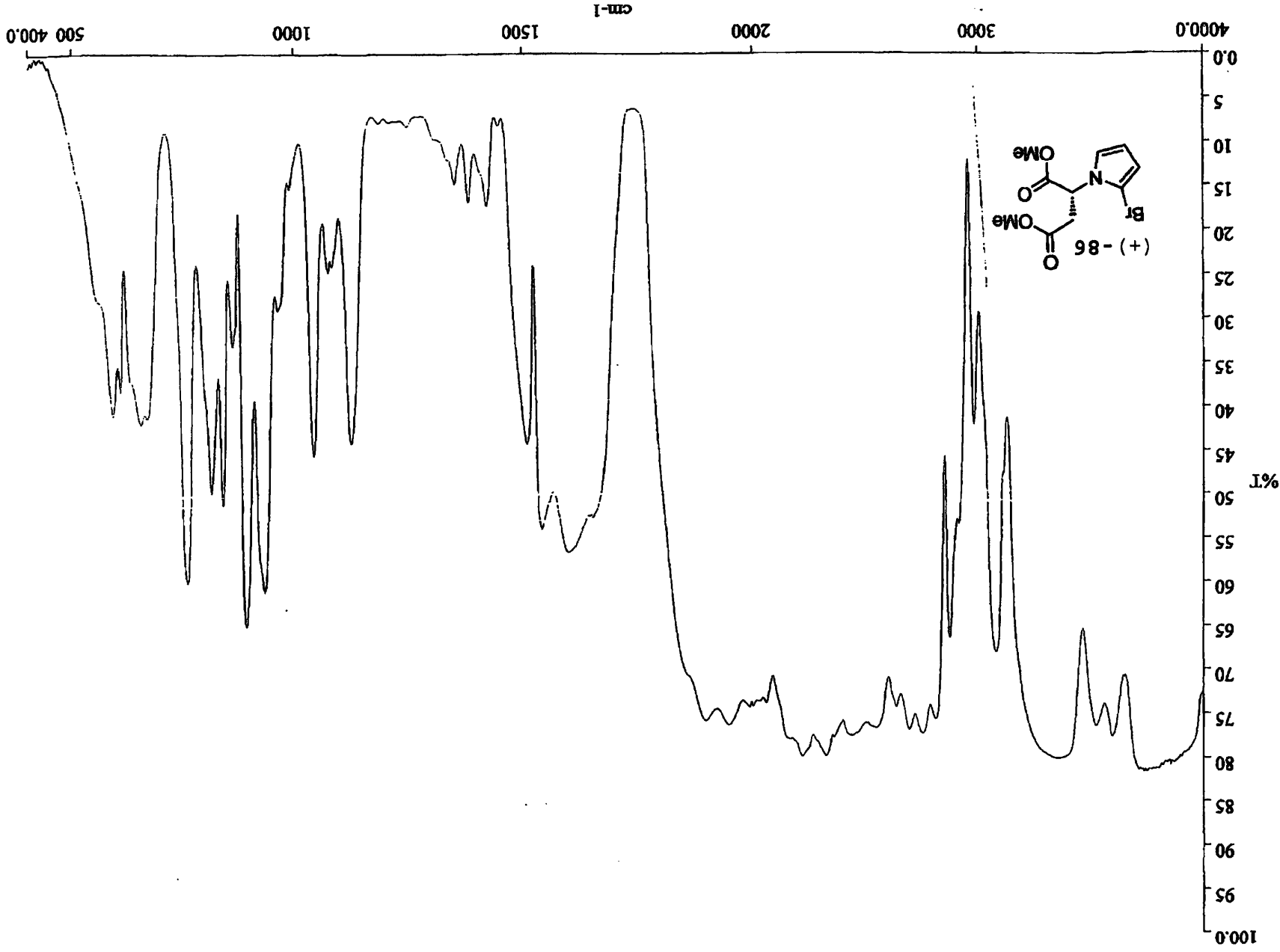
====================================================================

*** End of Report ***

(+)-86

225
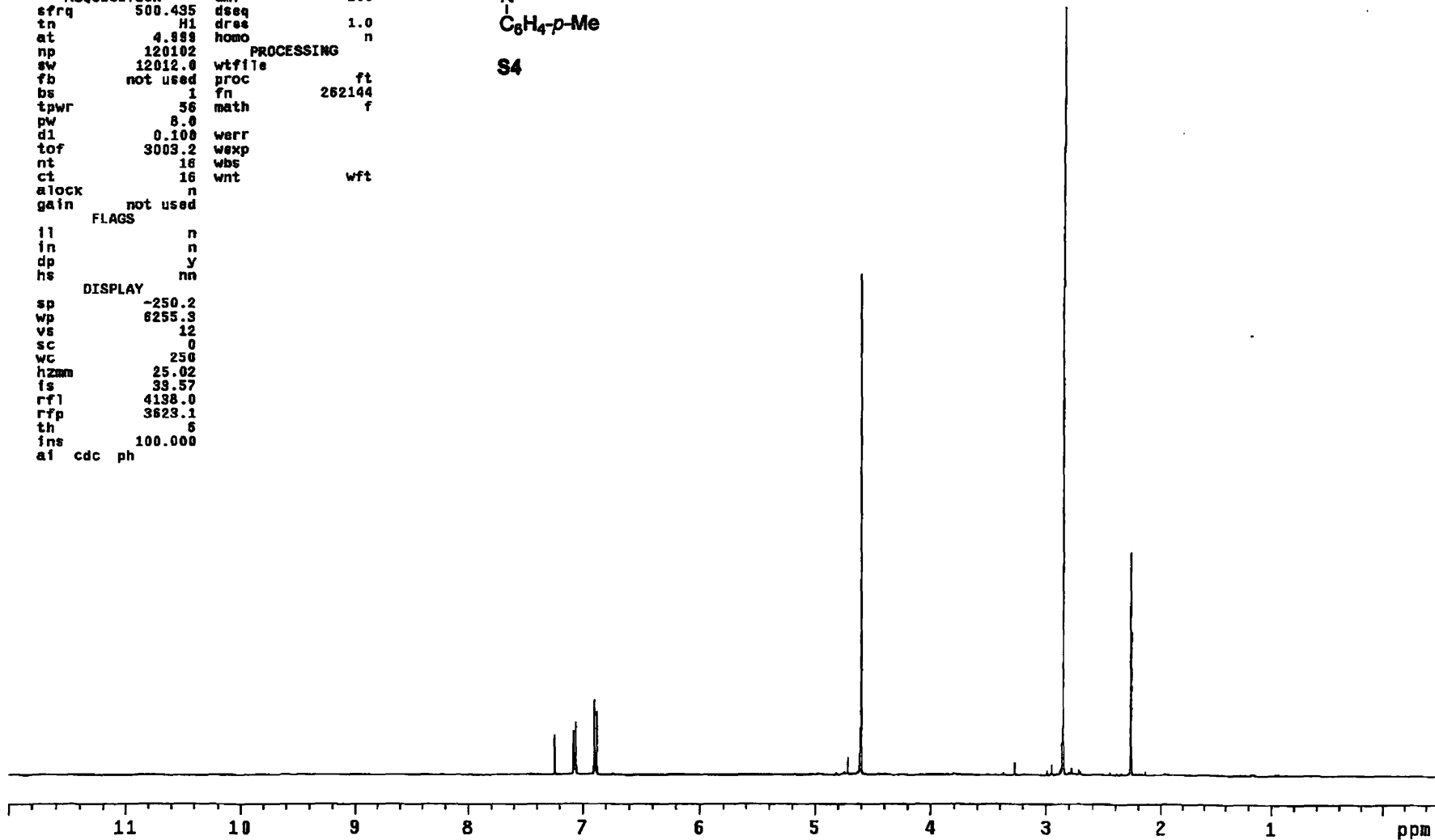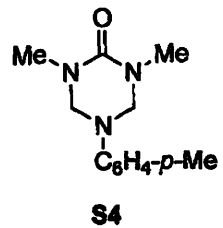
ACQUISITION
sfrq        500.435
tn              H1
at           4.999
np         120102
sw         12012.0
fb       not used
bs              2
tpwr           56
pw            8.0
d1          0.100
tof         3003.2
nt             32
ct             18
alock           n
gain     not used
       FLAGS
il              n
in              n
dp              y
hs             nn
       DISPLAY
sp         -250.2
wp         6255.3
vs             19
sc              0
wc            250
h2mm        25.02
is          33.57
rfl        4139.7
rfp        3623.1
th              7
ins       100.000
ai   cdc  ph

       DEC. & VT
dfrq       125.845
dn             C13
dpwr            30
dof              0
dm             nnn
dmm              c
dmf            200
dseq
dres           1.0
homo             n
       PROCESSING
wtfile
proc            ft
fn          262144
math             f

werr
wexp
wbs
wnt            wft

(+)-87

DEC. & VT
dfrq        500.229
dn              H1
dpwr            38
dof          -500.0
dm              y
dmm             w
dmf          10000
dseq
dres          1.0
homo            n
PROCESSING
lb           0.30
wtfile
proc           ft
fn          131072
math            f
werr
wexp
wbs
wnt

ACQUISITION
sfrq        125.795
tn             C13
at            1.736
np          131010
sw          37735.8
fb         not used
bs              2
ss              1
tpwr            53
pw            6.9
d1           0.763
tof          631.4
nt          60000
ct          13306
alock           n
gain       not used
FLAGS
il              n
in              n
dp              y
hs             nn
DISPLAY
sp          -6292.0
wp          37735.3
vs             770
sc              0
wc             250
hzmm         150.94
is           500.00
rfl         16006.8
rfp          9714.2
th              20
ins           1.000
ai     ph

(+)-87
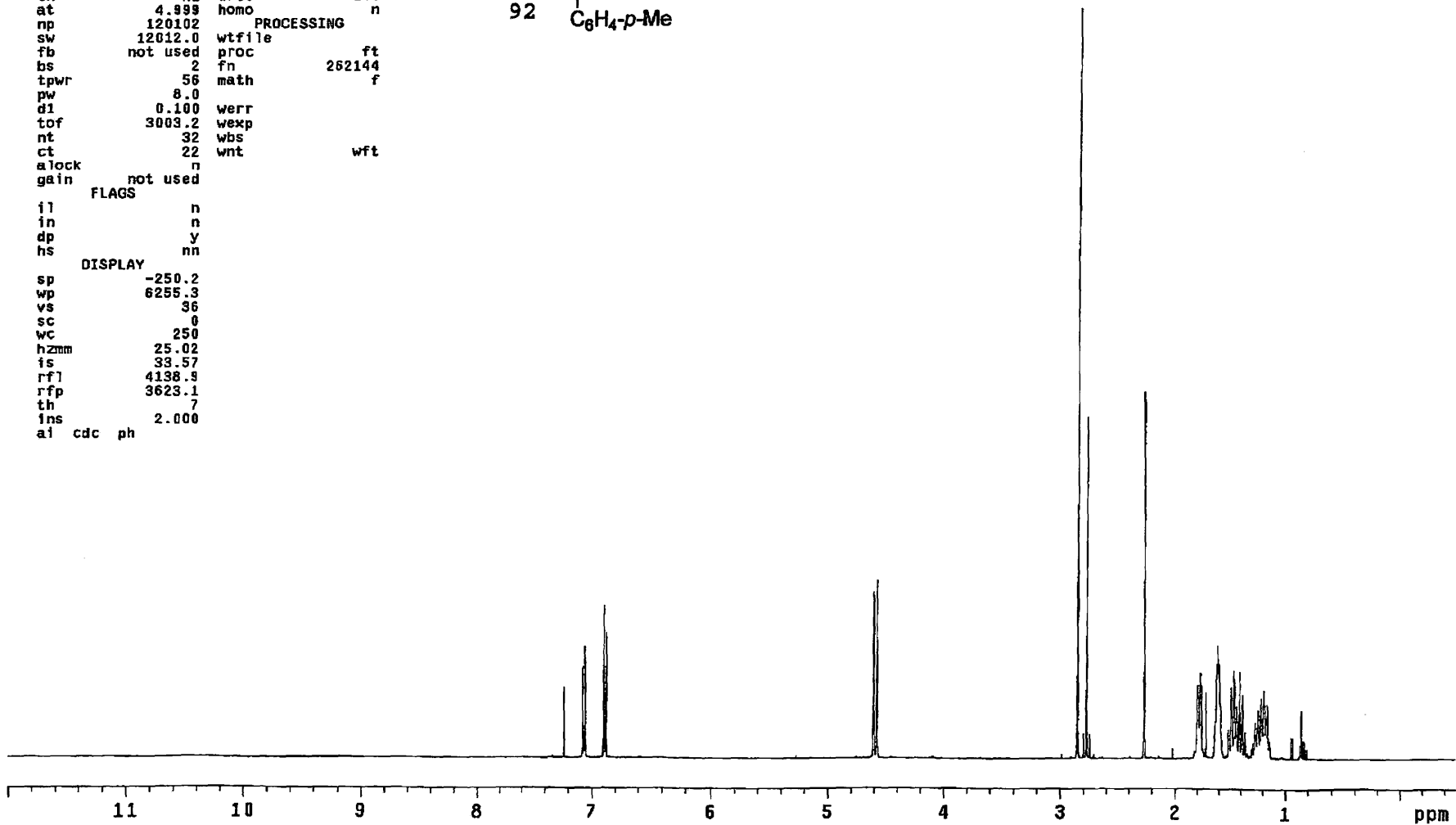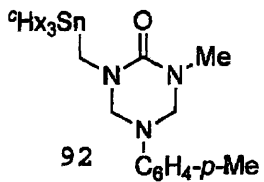
(+)-87

ACQUISITION
sfrq        500.435
tn              H1
at           4.999
np          120102
sw          12012.0
fb         not used
bs              2
tpwr            56
pw             8.0
d1           0.100
tof          3003.2
nt              32
ct              10
alock           n
gain       not used
        FLAGS
il              n
in              n
dp              y
hs             nn
        DISPLAY
sp          -250.2
wp          6255.9
vs              11
sc              0
wc             250
hzmm         25.02
is           33.57
rfl         4138.9
rfp         3623.1
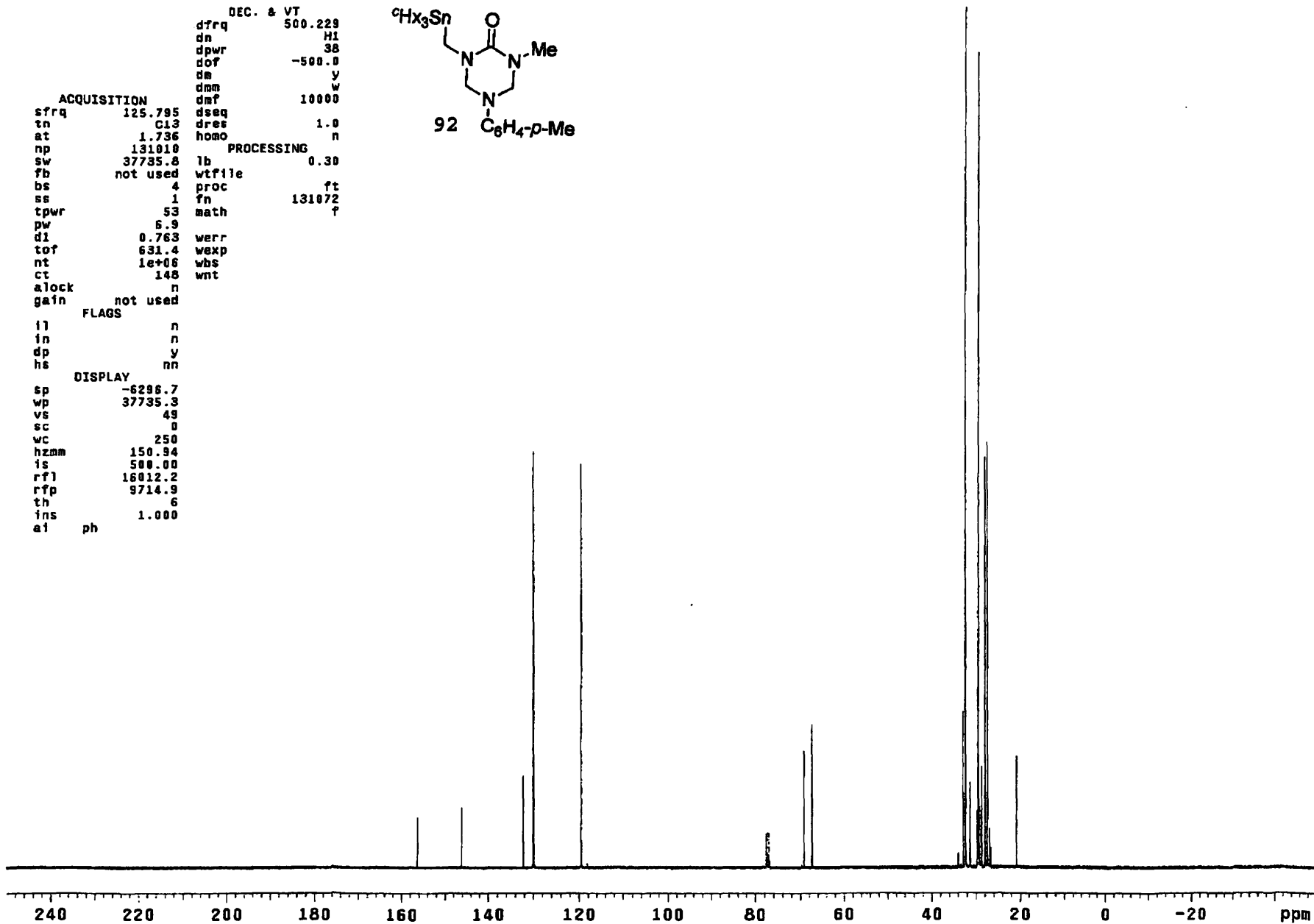th              7
ins        100.000
ai   cdc  ph

DEC. & VT
dfrq        125.845
dn             C13
dpwr            30
dof             0
dm             nnn
dmm             c
dmf            200
dseq
dres           1.0
homo            n
     PROCESSING
wtfile
proc            ft
fn          262144
math            f

werr
wexp
wbs
wnt          wft

(+)-84

DEC. & VT
dfrq    500.229
dn          H1
dpwr        37
dof      -500.0
dm           y
dmm          w
dmf       10000
dseq
dres        1.0
homo          n
    PROCESSING
lb         0.30
wtfile
proc         ft
fn       131072
math          f

werr
wexp
wbs
wnt

ACQUISITION
sfrq    125.795
tn          C13
at        1.736
np       131010
sw      37735.8
fb     not used
bs            4
ss            1
tpwr         53
pw          6.9
d1        0.763
tof       631.4
nt        1e+07
ct          176
alock         n
gain   not used
    FLAGS
il            n
in            n
dp            y
hs           nn
    DISPLAY
sp      -6288.0
wp      37735.3
vs          665
sc            0
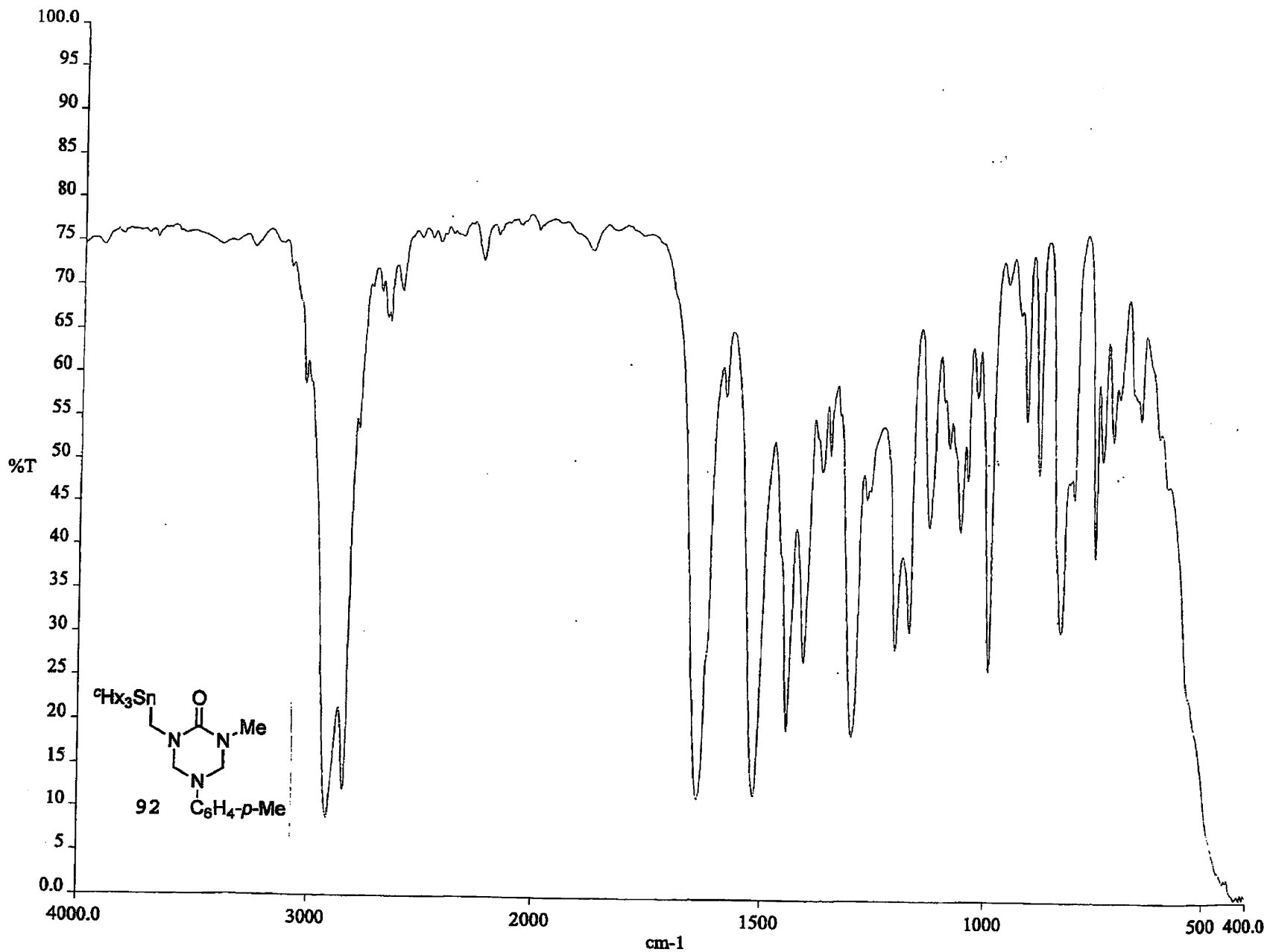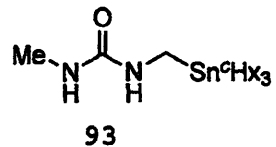wc          250
hzmm     150.94
is       500.00
rfl     16002.7
rfp      9714.2
th           20
ins       1.000
ai      ph

(+)-84

MWD1 E, Sig=270,16 Ref=360,100

(+)-84

Peak 1: 11.552, Area: 151.203
Peak 2: 16.245, Area: 150.387

MWD1 E, Sig=270,16 Ref=360,100

(+)-84

Area Percent Report

```
Sorted By               :        Signal
Multiplier              :        1.0000
Dilution                :        1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Signal 1: MWD1 E, Sig=270,16 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|--------|
| 1 | 16.523 | MM | 1.8067 | 483.25354 | 4.45788 | 100.0000 |

Totals :                        483.25354    4.45788

Results obtained with enhanced integrator!
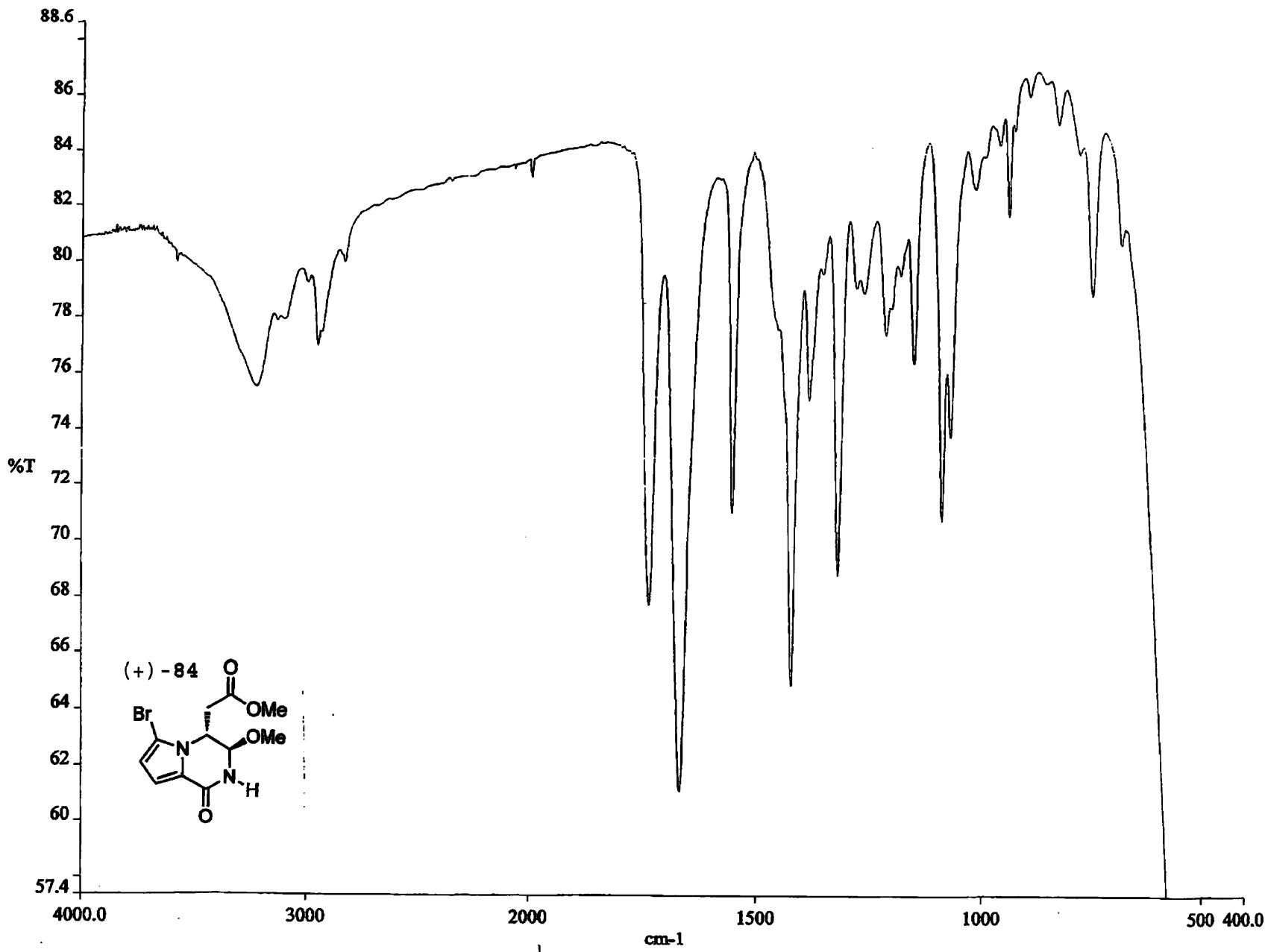
*** End of Report ***

ACQUISITION
sfrq        500.435
tn              H1
at           4.998
np         120102
sw        12012.0
fb        not used
bs              2
tpwr           56
pw            8.0
d1           0.100
tof         3003.2
nt             32
ct             20
alock           n
gain       not used
        FLAGS
il              n
in              n
dp              y
hs             nn
        DISPLAY
sp          -250.2
wp         6255.3
vs             14
sc              0
wc            250
hzmm        25.02
is          33.57
rfl        4138.0
rfp        3623.1
th              7
ins       100.000
ai   cdc  ph

DEC. & VT
dfrq        125.845
dn             C13
dpwr            30
dof              0
dm             nnn
dmm              c
dmf            200
dseq
dres           1.0
homo             n
        PROCESSING
wtfile
proc            ft
fn          262144
math             f

werr
wexp
wbs
wnt            wft

(+)-91

DEC. & VT
dfrq        499.744
dn              H1
dpwr            34
dof              0
dm             yyy
dmm              w
dmf          10400
dseq
dres           1.0
homo             n

PROCESSING
lb            1.00
wtfile
proc            ft
fn          131072
math             f

werr
wexp
wbs
wnt

ACQUISITION
sfrq        125.672
tn             C13
at           2.000
np          125588
sw         31397.2
fb        not used
bs               2
tpwr            59
pw             6.7
d1           3.000
tof              0
nt            5000
ct             710
alock            n
gain      not used

FLAGS
il               n
in               n
dp               y
hs              nn

DISPLAY
sp         -3766.1
wp         31396.7
vs            1340
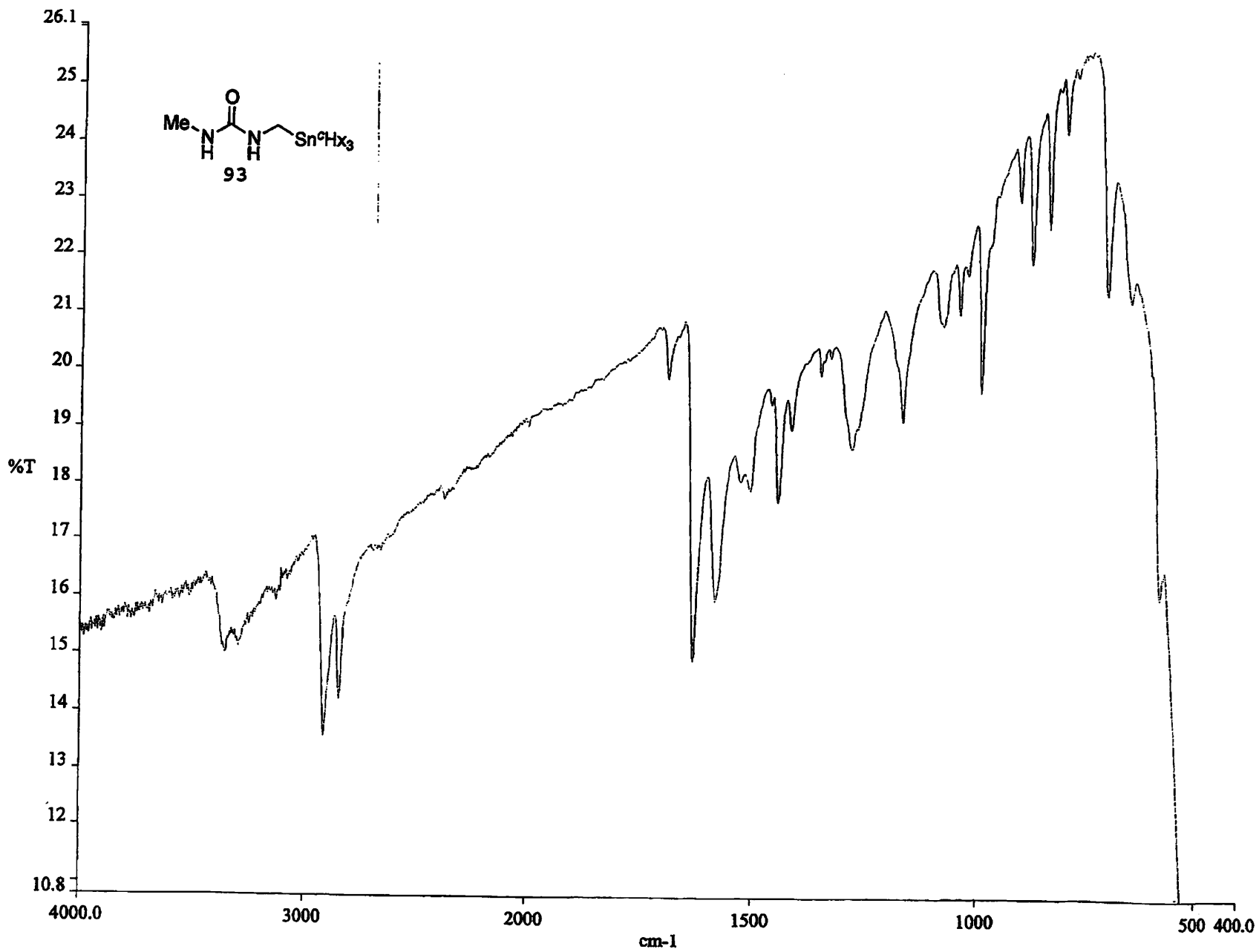sc               0
wc             250
hzmm        125.59
is          500.00
rfl        13471.3
rfp         9704.7
th              10
ins        100.000
ai   cdc  ph

(+)-91

DEC. & VT
dfrq        125.845
dn           C13
dpwr          30
dof            0
dm           nnn
dmm            c
dmf          200
dseq
dres         1.0
homo           n

PROCESSING
wtfile
proc          ft
fn        262144
math           f

werr
wexp
wbs
wnt          wft
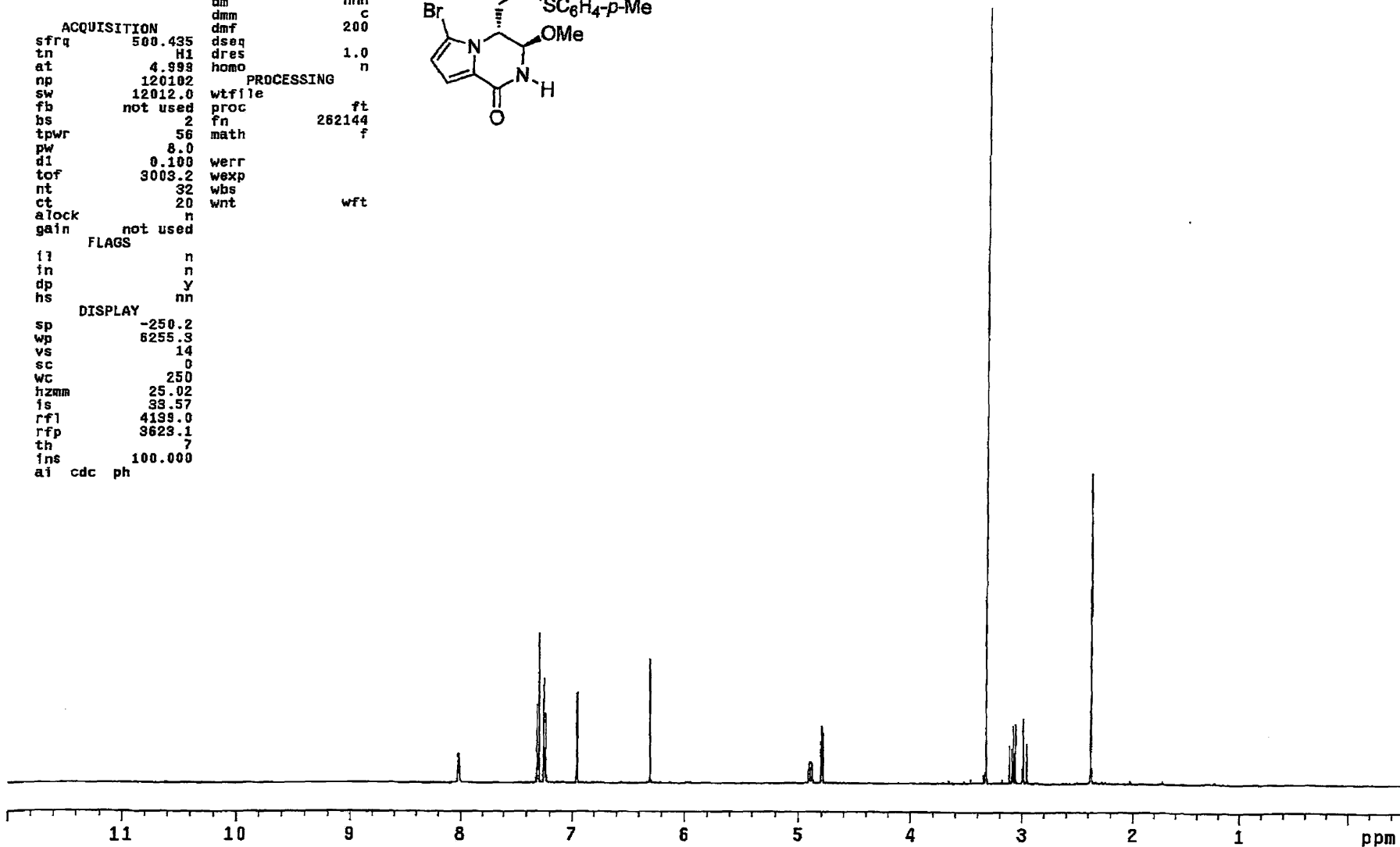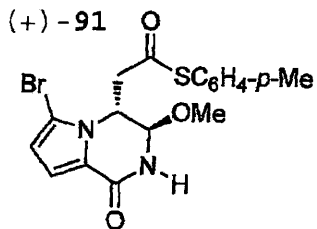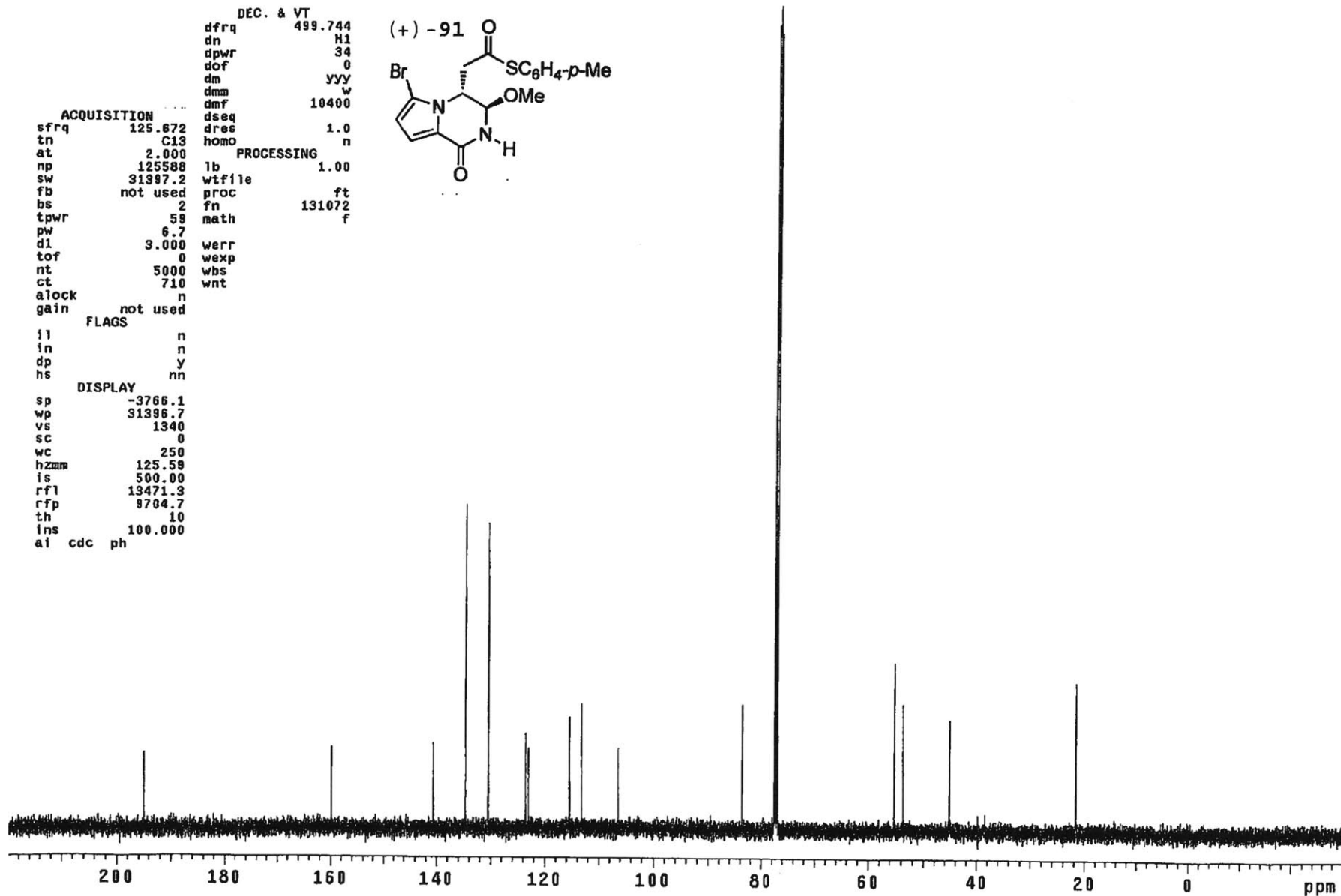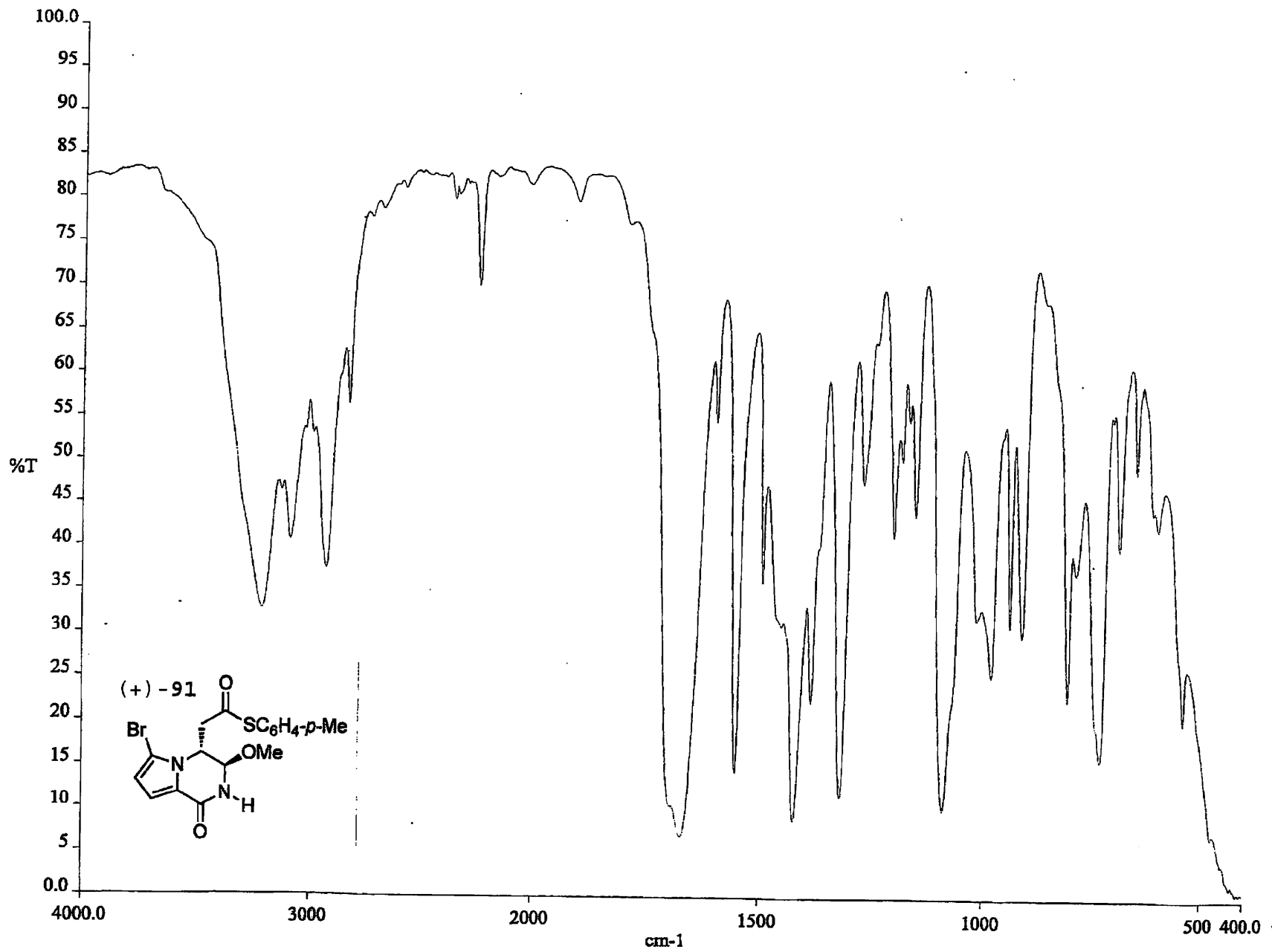
ACQUISITION
sfrq      500.435
tn            H1
at         4.999
np        120102
sw       12012.0
fb      not used
bs             1
tpwr          56
pw           8.0
d1         0.108
tof       3003.2
nt            16
ct            16
alock          n
gain    not used
      FLAGS
il             n
in             n
dp             y
hs            nn
      DISPLAY
sp        -250.2
wp        6255.3
vs            12
sc             0
wc           250
hzmm       25.02
is         33.57
rfl       4138.0
rfp       3623.1
th             6
ins      100.000
ai   cdc  ph

S4

DEC. & VT
dfrq        500.229
dn              H1
dpwr            38
dof          -500.0
dm               y
dmm              w
dmf          10000
dseq
dres           1.0
homo             n
PROCESSING
lb            0.30
wtfile
proc            ft
fn          131072
math             f

werr
wexp
wbs
wnt

ACQUISITION
sfrq      125.795
tn            C13
at          1.736
np         131010
sw        37735.8
fb       not used
bs              4
ss              1
tpwr           53
pw            6.9
d1          0.763
tof         631.4
nt         1e+09
ct             12
alock           n
gain     not used
        FLAGS
il              n
in              n
dp              y
hs             nn
        DISPLAY
sp        -6332.3
wp        37735.3
vs             25
sc              0
wc            250
hzmm       150.94
is         500.00
rfl       16047.1
rfp        9714.2
th             20
ins         1.000
al      ph

**S4**
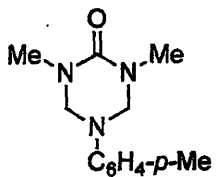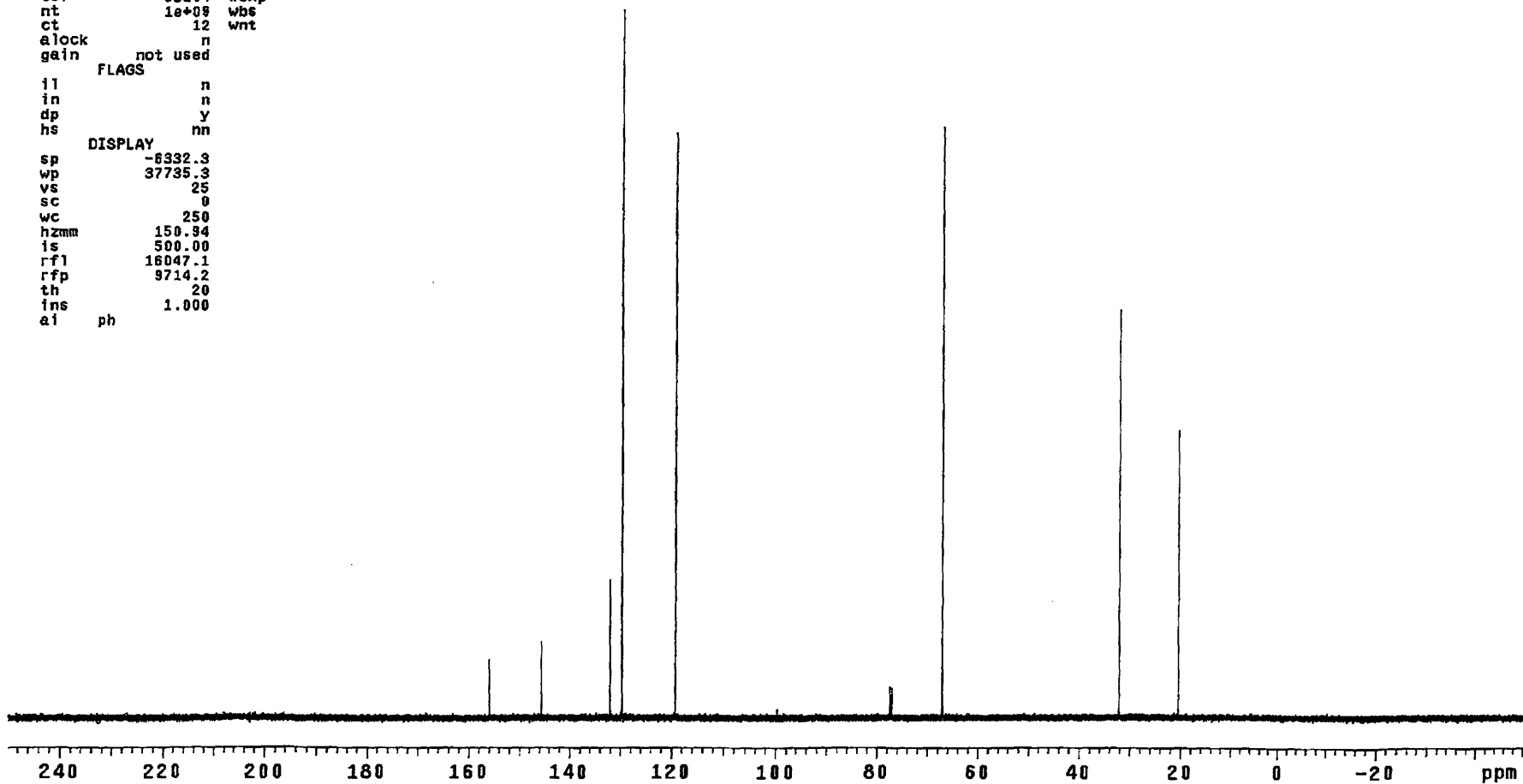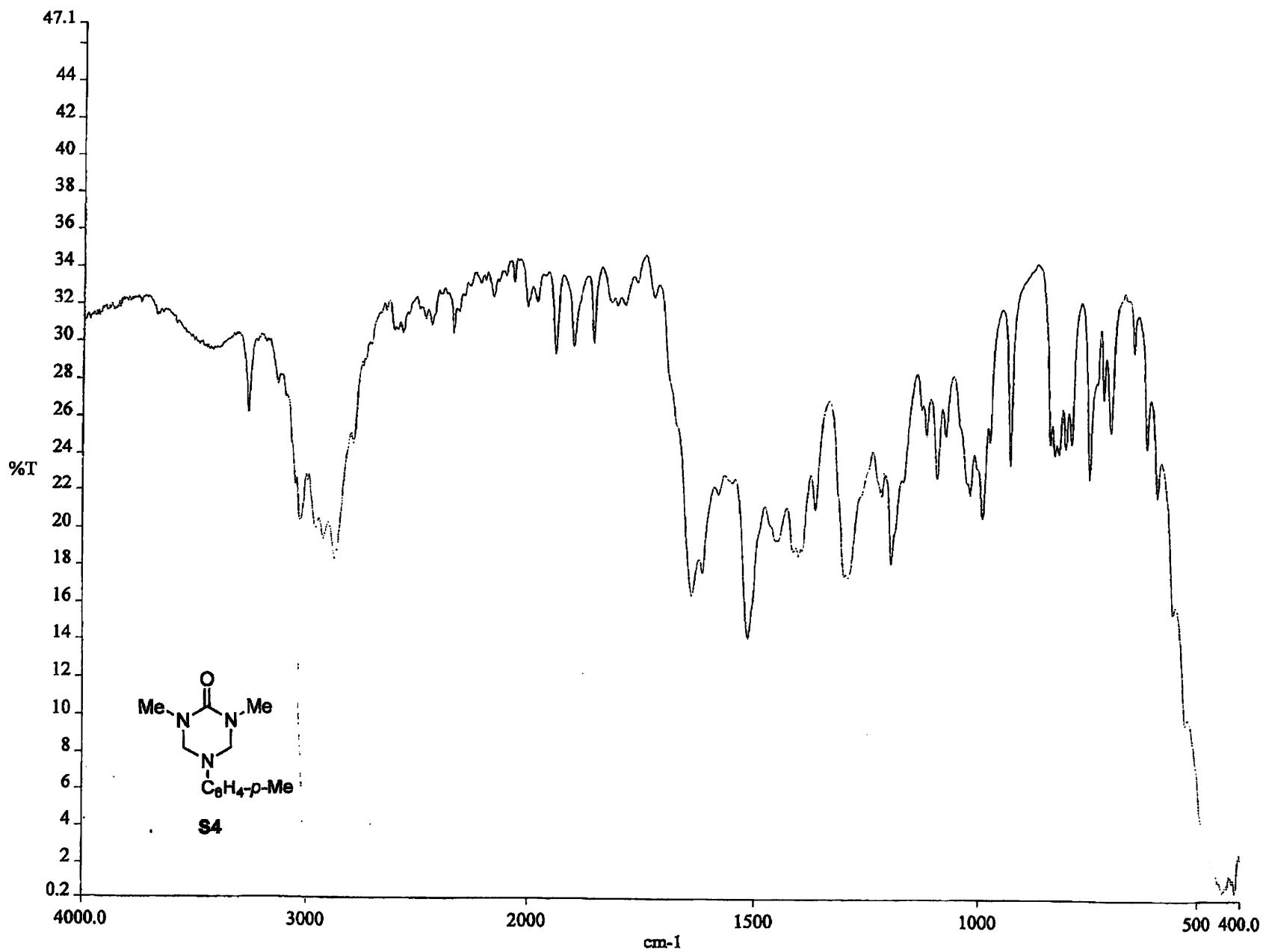
ACQUISITION
sfrq        500.435
tn              H1
at           4.999
np          120102
sw         12012.0
fb        not used
bs               2
tpwr            56
pw             8.0
d1           0.100
tof         3003.2
nt              32
ct              22
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
hs              nn
      DISPLAY
sp          -250.2
wp          6255.3
vs              36
sc               0
wc             250
hzmm         25.02
is           33.57
rfl         4138.9
rfp         3623.1
th               7
ins          2.000
ai   cdc  ph

      DEC. & VT
dfrq       125.845
dn             C13
dpwr            30
dof              0
dm             nnn
dmm              c
dmf            200
dseq
dres           1.0
homo             n
     PROCESSING
wtfile
proc            ft
fn          262144
math             f

werr
wexp
wbs
wnt            wft

$^{c}Hx_3Sn$

92   $C_6H_4$-p-Me

DEC. & VT
dfrq      500.229
dn             H1
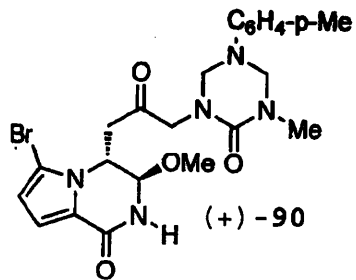dpwr           38
dof        -500.0
dm              y
dmm             w
dmf         10000
dseq
dres          1.0
homo            n
PROCESSING
lb           0.30
wtfile
proc           ft
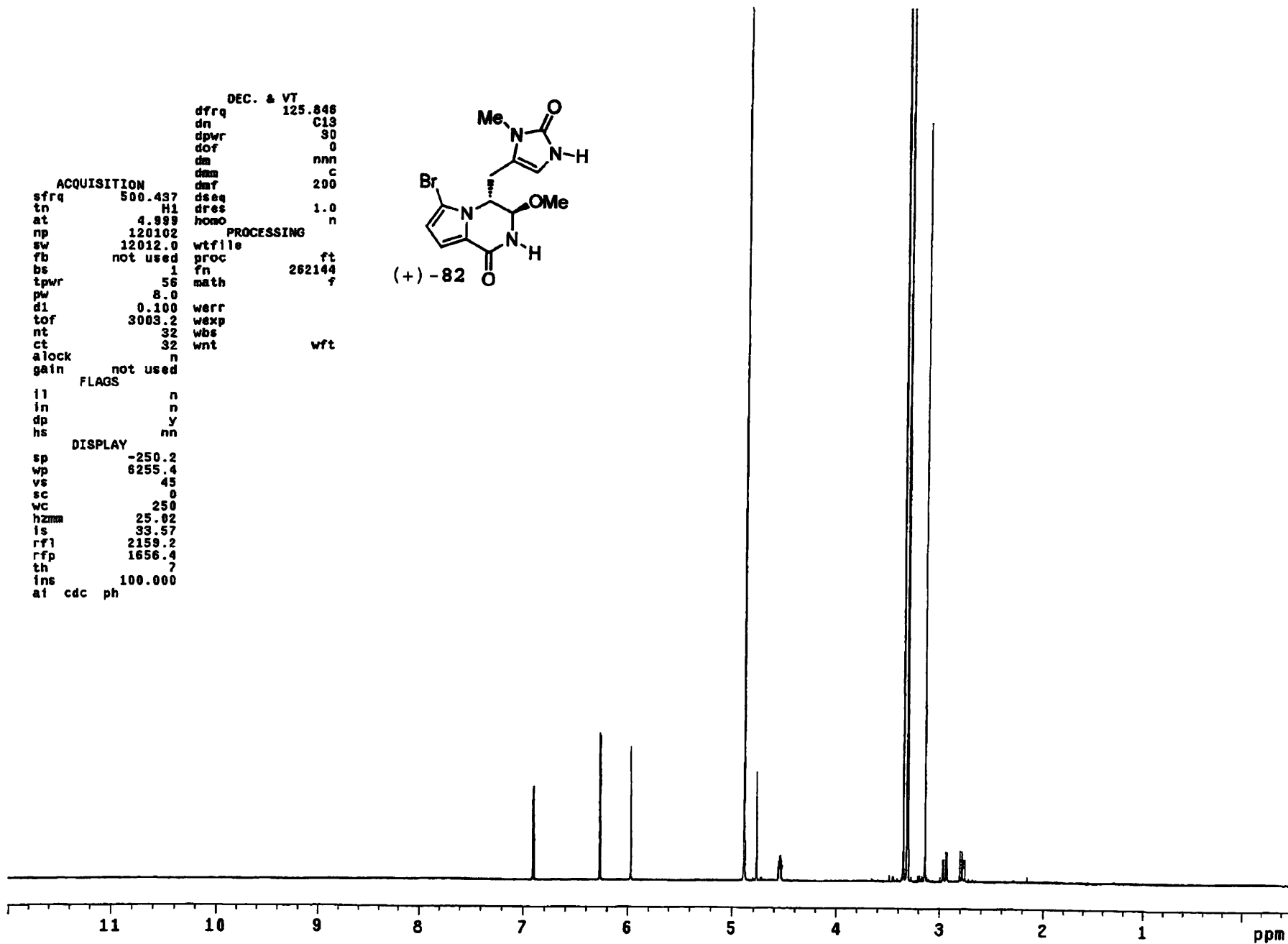fn         131072
math            f

werr
wexp
wbs
wnt

ACQUISITION
sfrq       125.795
tn             C13
at           1.736
np          131010
sw         37735.8
fb        not used
bs               4
ss               1
tpwr            53
pw             6.9
d1           0.763
tof          631.4
nt          1e+06
ct             148
alock            n
gain      not used
FLAGS
il               n
in               n
dp               y
hs              nn
DISPLAY
sp         -6296.7
wp         37735.3
vs              49
sc               0
wc             250
hzmm        150.94
is          500.00
rfl        16012.2
rfp         9714.9
th               6
ins          1.000
ai       ph
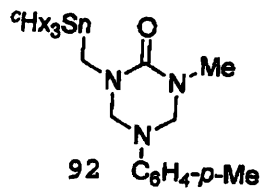
92

The spectrum is plotted with %T on the y-axis (0.0 to 100.0) and cm-1 on the x-axis (4000.0 to 400.0).

Structure label: $^cHx_3Sn$, O, Me, N, N, N, **92** $C_6H_4$-*p*-Me

DEC. & VT
dfrq        125.845
dn             C13
dpwr            30
dof              0
dm             nnn
dmm              c
dmf            200
dseq
dres           1.0
homo             n
    PROCESSING
wtfile
proc            ft
fn          262144
math             f

werr
wexp
wbs
wnt            wft

ACQUISITION
sfrq      500.435
tn             H1
at          4.999
np         120102
sw        12012.0
fb       not used
bs              1
tpwr           56
pw            8.0
d1          0.100
tof        3009.2
nt             16
ct             16
alock           n
gain     not used
    FLAGS
il              n
in              n
dp              y
hs             nn
    DISPLAY
sp         -250.2
wp         6255.3
vs            111
sc              0
wc            250
hzmm        25.02
is          33.57
rfl        4139.2
rfp        3623.1
th             10
ins         1.000
ai  cdc  ph
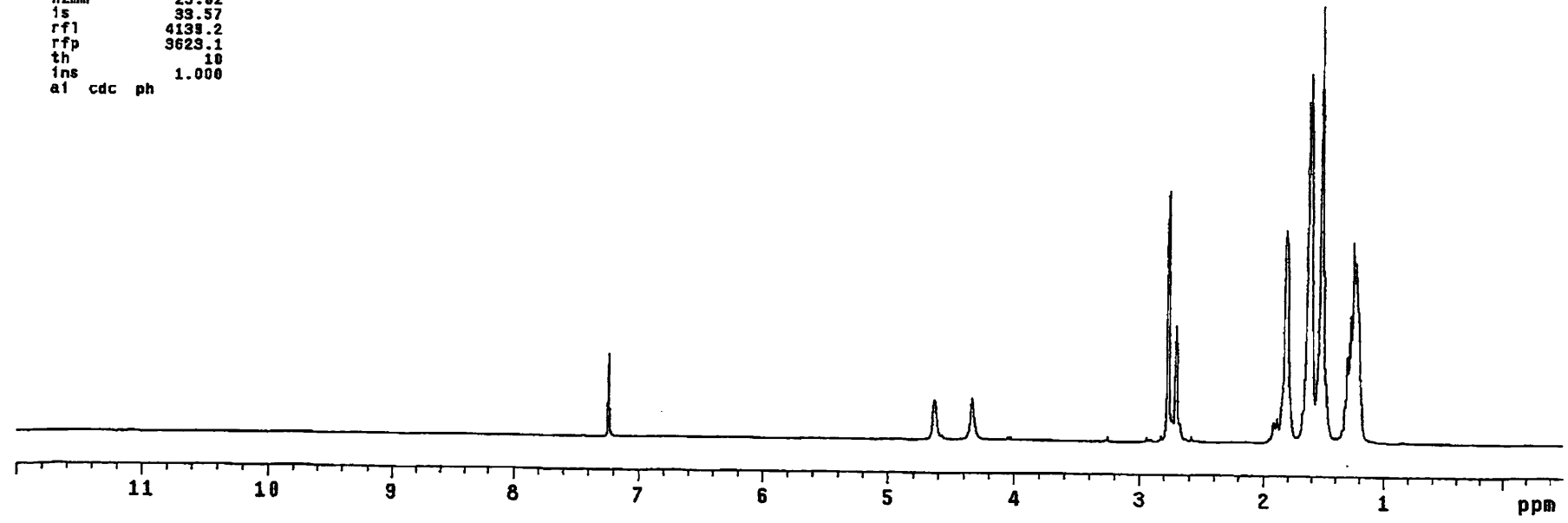
93

DEC. & VT
dfrq        500.229
dn              H1
dpwr            38
dof          -500.0
dm               y
dmm              w
dmf           10000
dseq
dres           1.0
homo             n
    PROCESSING
lb            0.30
wtfile
proc            ft
fn          131072
math             f

werr
wexp
wbs
wnt

ACQUISITION
sfrq      125.795
tn            C13
at          1.736
np         131010
sw        37735.8
fb       not used
bs              4
ss              1
tpwr           53
pw            6.9
d1          0.763
tof         681.4
nt          1e+09
ct            536
alock           n
gain     not used
     FLAGS
il              n
in              n
dp              y
hs             nn
   DISPLAY
sp        -6290.3
wp        37735.3
vs            236
sc              0
wc            250
hzmm       150.94
is         500.00
rfl        16005.0
rfp         9714.2
th              3
ins         1.000
ai    ph

Me
N
H

O

N
H

Sn$^c$Hx$_3$

93

DEC. & VT
dfrq 125.845
dn C13
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n

PROCESSING
wtfile
proc ft
fn 262144
math f

werr
wexp
wbs
wnt wft

ACQUISITION
sfrq 500.435
tn H1
at 4.999
np 120102
sw 12012.0
fb not used
bs 1
tpwr 56
pw 8.0
d1 0.100
tof 3003.2
nt 16
ct 16
alock n
gain not used

FLAGS
il n
in n
dp y
hs nn

DISPLAY
sp -250.2
wp 6255.3
vs 24
sc 0
wc 250
hzmm 25.02
is 33.57
rfl 4139.6
rfp 3623.1
th 6
ins 100.000
ai cdc ph
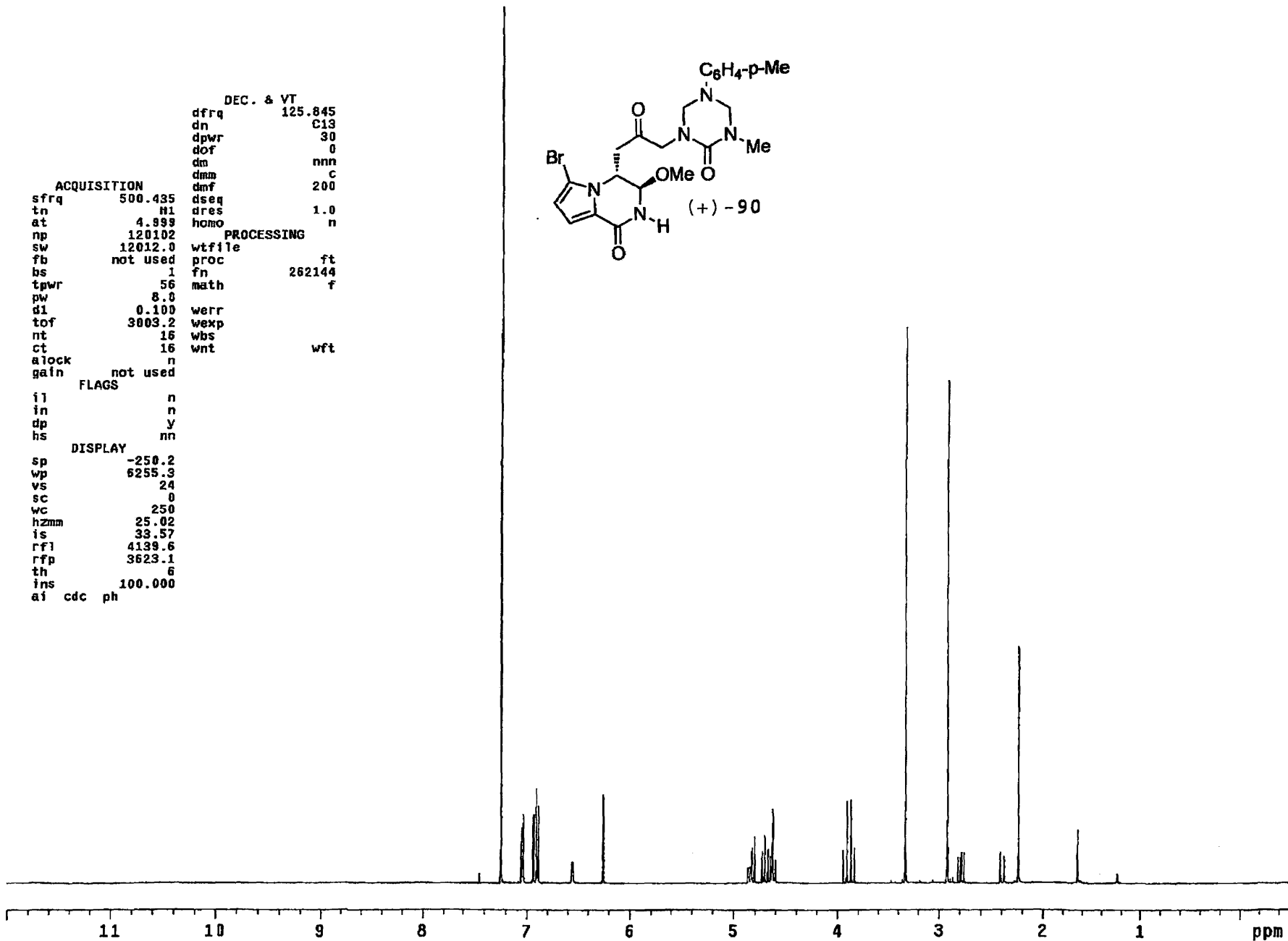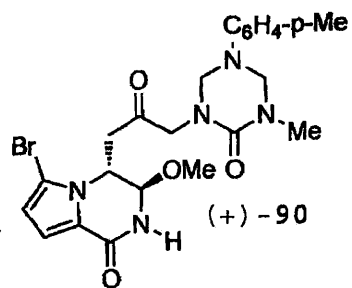
C$_6$H$_4$-p-Me

Br

OMe

Me

(+)-90

DEC. & VT
dfrq       500.229
dn              H1
dpwr            38
dof         -500.0
dm               y
dmm              w
dmf          10000
dseq
dres           1.0
homo             n
      PROCESSING
lb            0.30
wtfile
proc            ft
fn          131072
math             f
werr
wexp
wbs
wnt

ACQUISITION
sfrq       125.795
tn             C13
at           1.736
np          131010
sw         37735.8
fb        not used
bs               4
ss               1
tpwr            53
pw             6.9
d1           0.763
tof          631.4
nt           1e+09
ct              60
alock            n
gain            60
      FLAGS
il               n
in               n
dp               y
hs              nn
      DISPLAY
sp         -6389.4
wp         37735.3
vs             132
sc               0
wc             250
hzmm          3.17
is          500.00
rfl        16024.9
rfp         9714.9
th              15
ins          1.000
ai     ph
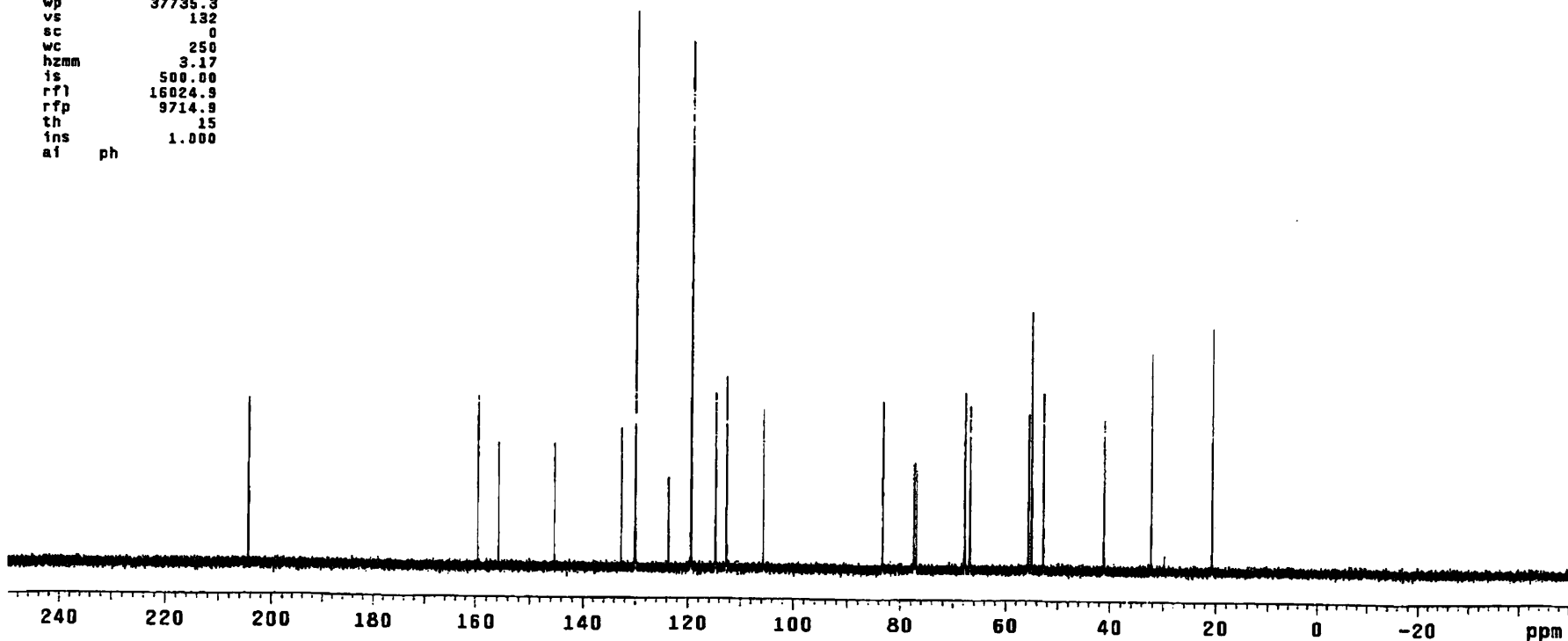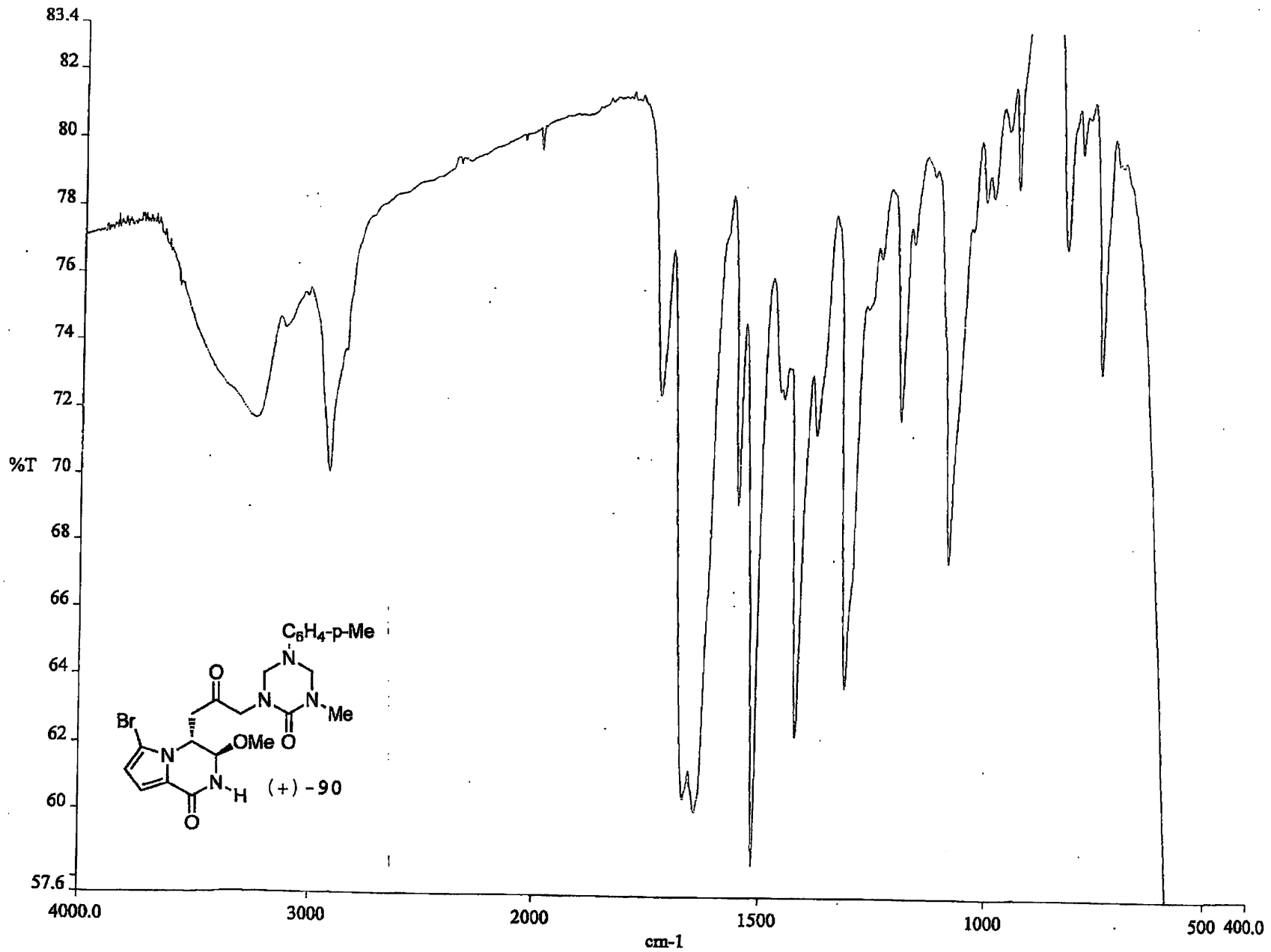
C6H4-p-Me

(+)-90

ACQUISITION
sfrq    500.437
tn    H1
at    4.999
np    120102
sw    12012.0
fb    not used
bs    1
tpwr    56
pw    8.0
d1    0.100
tof    3003.2
nt    32
ct    32
alock    n
gain    not used

FLAGS
il    n
in    n
dp    y
hs    nn

DISPLAY
sp    -250.2
wp    6255.4
vs    45
sc    0
wc    250
hzmm    25.02
is    33.57
rfl    2159.2
rfp    1656.4
th    7
ins    100.000
ai  cdc  ph

DEC. & VT
dfrq    125.846
dn    C13
dpwr    30
dof    0
dm    nnn
dmm    c
dmf    200
dseq    
dres    1.0
homo    n

PROCESSING
wtfile
proc    ft
fn    262144
math    f

werr
wexp
wbs
wnt    wft

(+)-82
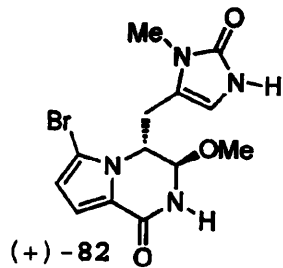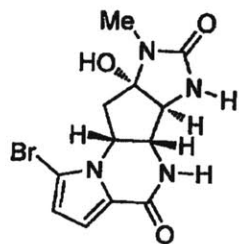
ACQUISITION
sfrq        125.795
tn            C13
at          1.736
np          131010
sw          37735.8
fb         not used
bs              4
ss              1
tpwr           53
pw            6.9
d1          0.763
tof         631.4
nt          1e+09
ct          8268
alock           n
gain           60
         FLAGS
il              n
in              n
dp              y
hs             nn
        DISPLAY
sp         -6115.7
wp         37735.3
vs           4867
sc              0
wc            250
h2mm        150.94
is          500.00
rfl        12298.8
rfp         6182.5
th              5
ins         1.000
ai     ph

DEC. & VT
dfrq        500.231
dn             H1
dpwr           38
dof         -500.0
dm              y
dmm             w
dmf         10000
dseq
dres          1.0
homo            n
      PROCESSING
lb           0.30
wtfile
proc           ft
fn         131072
math            f
werr
wexp
wbs
wnt

(+)-82
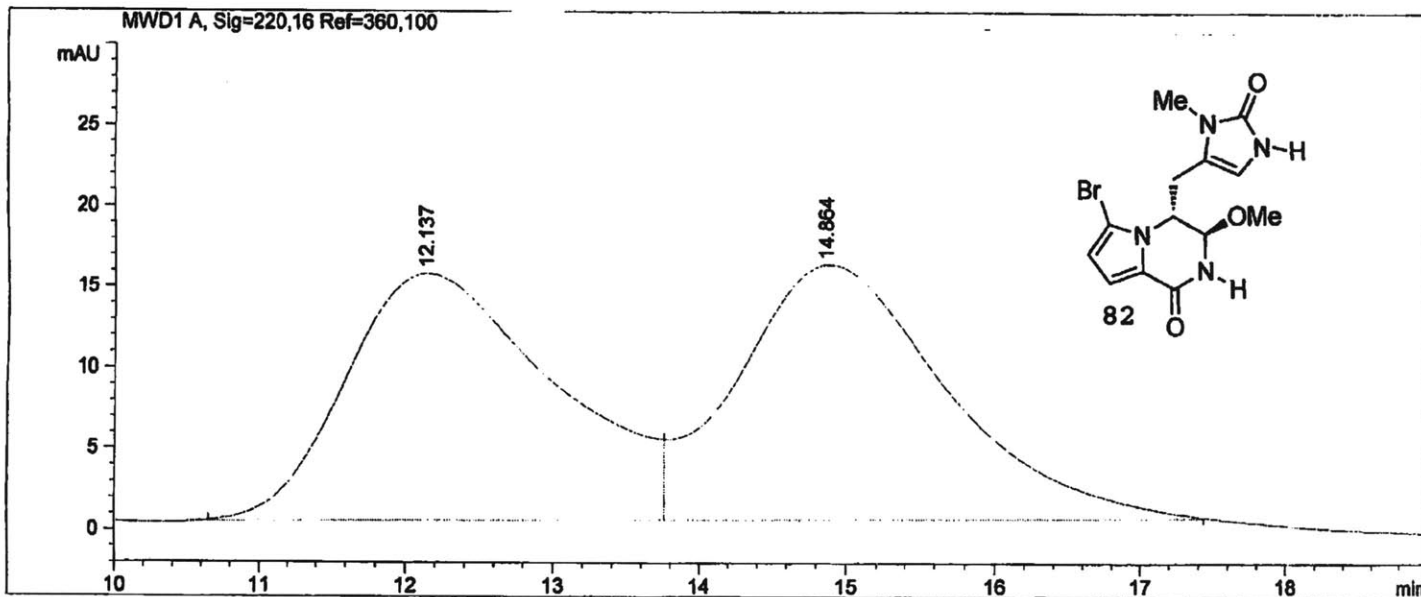
MWD1 A, Sig=220,16 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 12.137 | BV | 1.1608 | 1499.41431 | 15.28030 | 49.0828 |
| 2 | 14.864 | VB | 1.1626 | 1555.45105 | 15.82612 | 50.9172 |

Totals :                              3054.86536    31.10642

Results obtained with enhanced integrator!

*** End of Report ***

```
================================================================
Injection Date   :                        Seq. Line :    1
Sample Name      :                        Location : Vial 91
Acq. Operator    :                            Inj :    1
                                        Inj Volume : 1 µl
Acq. Method      :
Last changed     :
Analysis Method  :
Last changed     :

================================================================
```
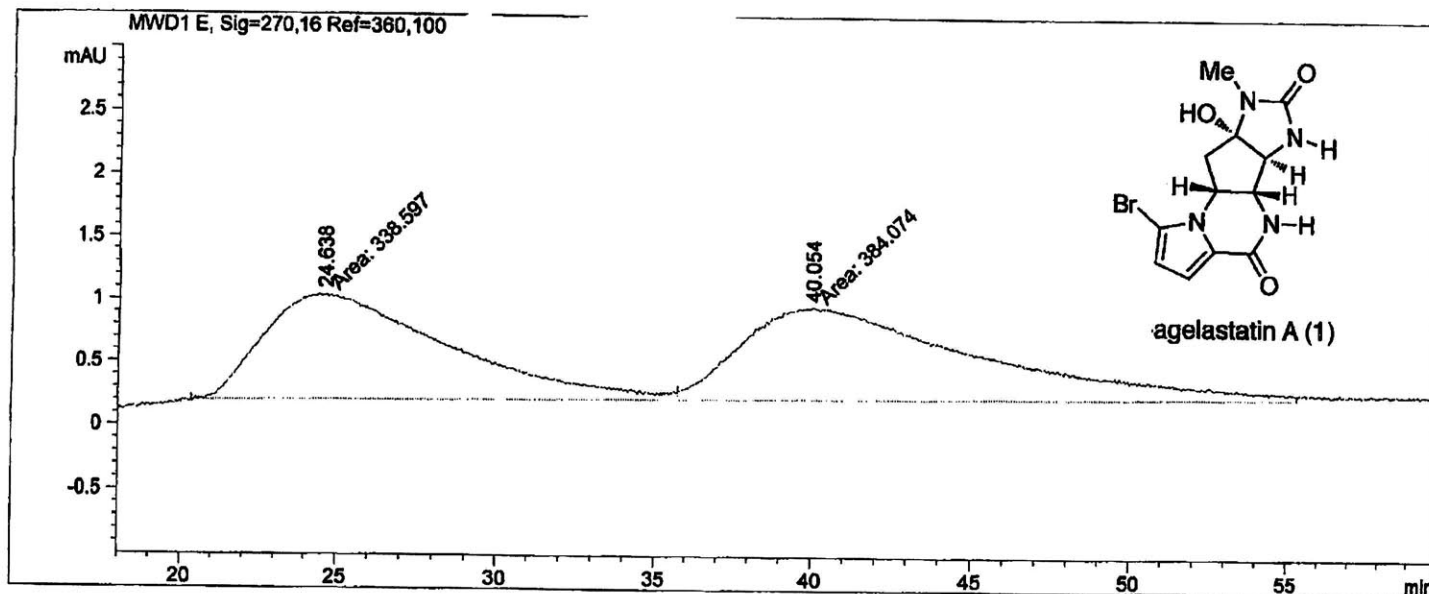
MWD1 A, Sig=220,16 Ref=360,100



(+)-82
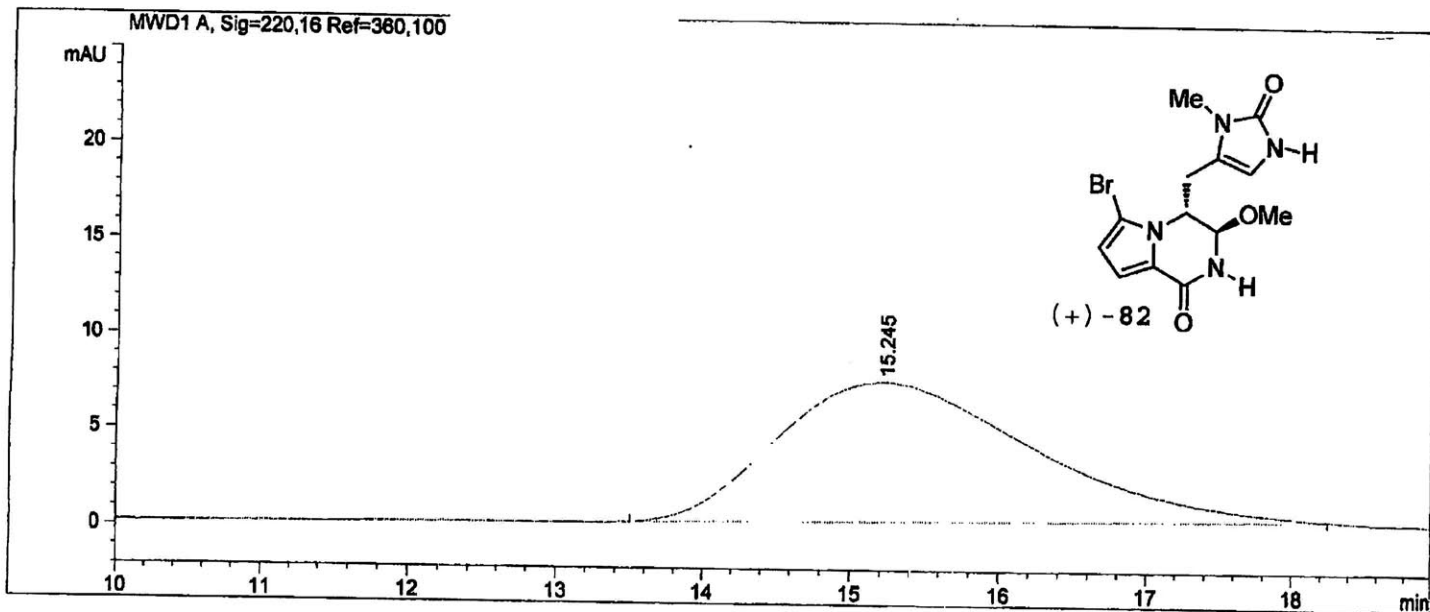
```
================================================================
                    Area Percent Report
================================================================

Sorted By          :       Signal
Multiplier         :       1.0000
Dilution           :       1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 A, Sig=220,16 Ref=360,100

Peak RetTime Type  Width     Area      Height    Area
 #   [min]        [min]   [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
  1  15.245 PB   1.4033  875.68500   7.33223 100.0000

Totals :                  875.68500   7.33223

Results obtained with enhanced integrator!
================================================================
              *** End of Report ***
```
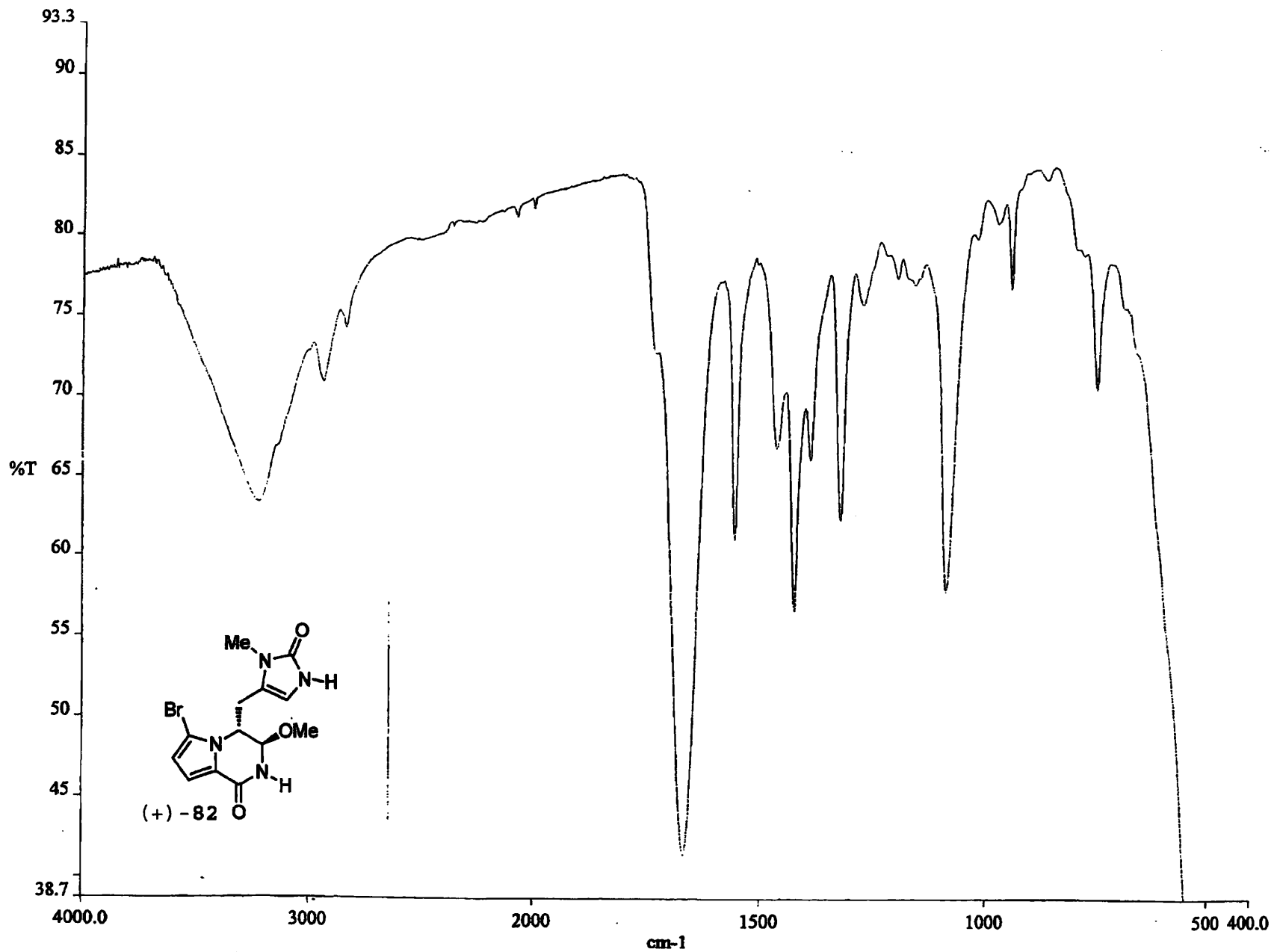
DEC. & VT
dfrq        125.846
dn             C13
dpwr            30
dof              0
dm             nnn
dmm              c
dmf            200
dseq
dres           1.0
homo             n

ACQUISITION
sfrq      500.437
tn             H1
at          4.999
np        120102
sw        12012.0
fb      not used        PROCESSING
bs              1     wtfile
tpwr           56     proc           ft
pw            8.0     fn         262144
d1          0.100     math            f
tof        3003.2
nt             16     werr
ct             16     wexp
alock           n     wbs
gain     not used     wnt           wft
        FLAGS
il              n
in              n
dp              y
hs             nn
        DISPLAY
sp         -250.2
wp         6255.4
vs             68
sc              0
wc            250
hzmm        25.02
is          33.57
rfl        2159.4
rfp        1656.4
th              7
ins       100.000
al  cdc  ph

(−)-agelastatin A (1)



11   10   9   8   7   6   5   4   3   2   1   ppm

DEC. & VT
dfrq      500.231
dn            H1
dpwr          38
dof       -500.0
dm             y
dmm            w
dmf        10000
dseq
dres         1.0
homo           n
PROCESSING
lb          0.30
wtfile
proc          ft
fn        131072
math           ¥
werr
wexp
wbs
wnt
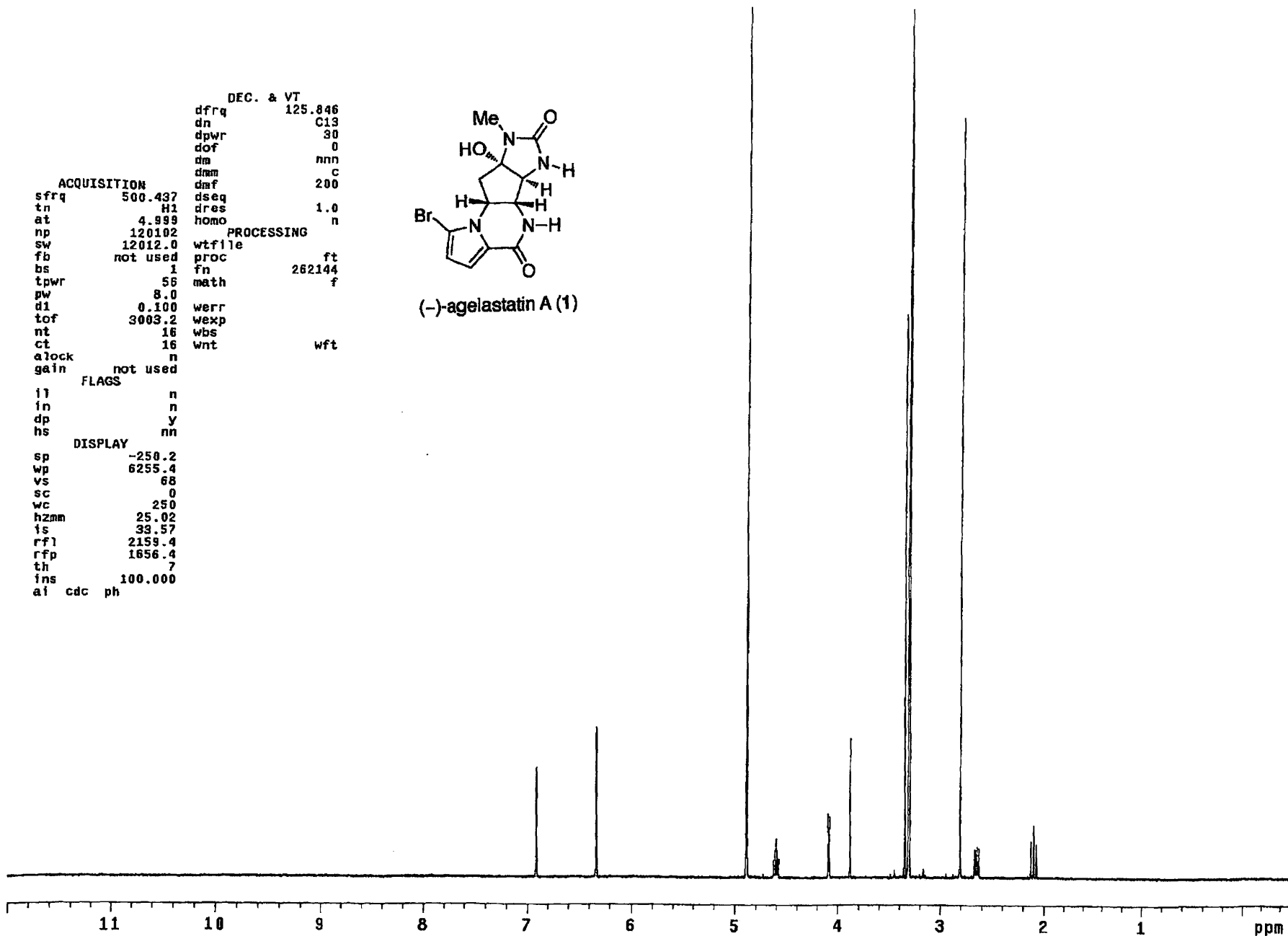
ACQUISITION
sfrq      125.795
tn            C13
at          1.736
np         131010
sw        37735.8
fb       not used
bs             4
ss             1
tpwr          53
pw           6.9
d1         0.763
tof        631.4
nt         1e+09
ct         21180
alock          n
gain          60
      FLAGS
il             n
in             n
dp             y
hs            nn
      DISPLAY
sp        -6115.7
wp        37735.3
vs          7283
sc             0
wc           250
hzmm        5.16
is        500.00
rfl      12298.8
rfp       6182.5
th            10
ins        1.000
a1    ph

(–)-agelastatin A (1)

MWD1 E, Sig=270,16 Ref=360,100



agelastatin A (1)

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 24.638 | MF | 6.6959 | 338.59686 | 8.42801e-1 | 46.8535 |
| 2 | 40.054 | FM | 8.6223 | 384.07428 | 7.42408e-1 | 53.1465 |

Totals :                   722.67114     1.58521

Results obtained with enhanced integrator!

```
==================================================================================
                       *** End of Report ***
```

256

(–)-agelastatin A (1)
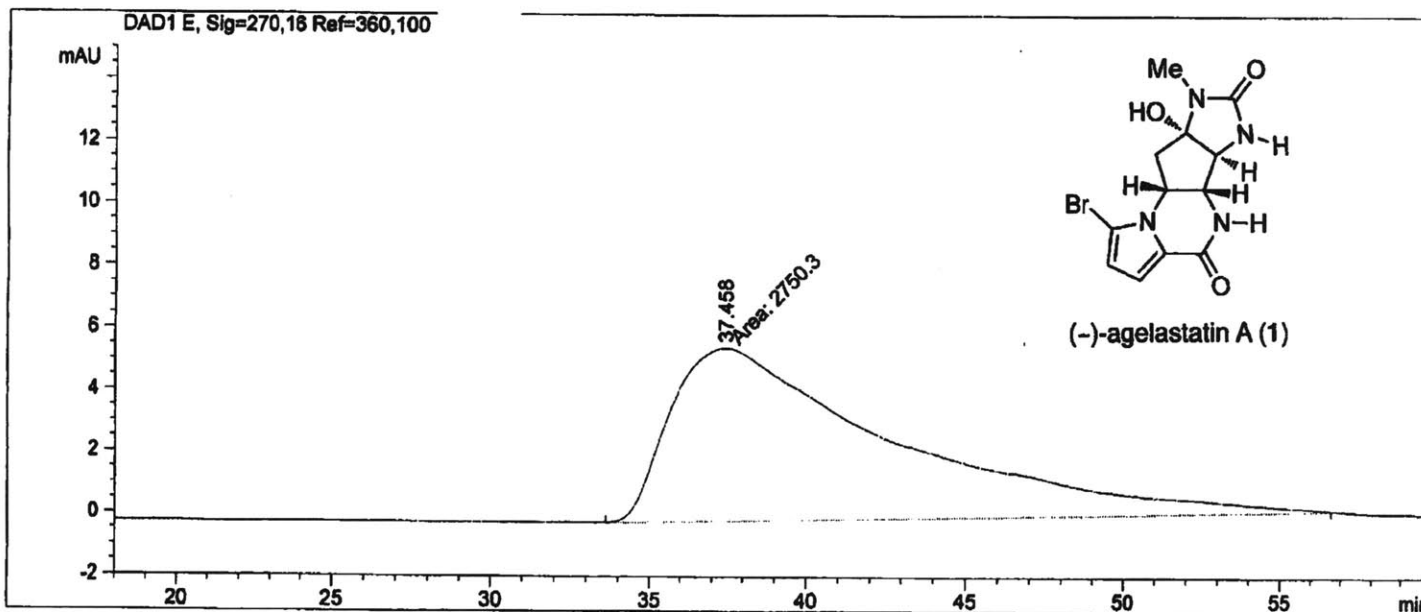
```
================================================================
                    Area Percent Report
================================================================

Sorted By            :       Signal
Multiplier           :       1.0000
Dilution             :       1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 E, Sig=270,16 Ref=360,100

Peak RetTime Type  Width     Area      Height      Area
 #    [min]        [min]    [mAU*s]     [mAU]        %
----|-------|----|-------|-----------|-----------|--------|
 1   37.458 MM    8.1336 2750.29980    5.63566 100.0000

Totals :                   2750.29980   5.63566

Results obtained with enhanced integrator!
================================================================
                  *** End of Report ***
```

257

(–)-agelastatin A (1)

ACQUISITION
sfrq        500.437
tn               H1
at            4.989
np           120102
sw          12012.0
fb         not used
bs                1
tpwr             56
pw              8.0
d1            0.100
tof          3003.2
nt               32
ct               32
alock             n
gain       not used
      FLAGS
11                n
in                n
dp                y
hs               nn
      DISPLAY
sp           -250.2
wp           6255.4
vs              136
sc                0
wc              250
hzmm          25.02
is            33.57
rfl          2159.0
rfp          1656.4
th                7
ins         100.000
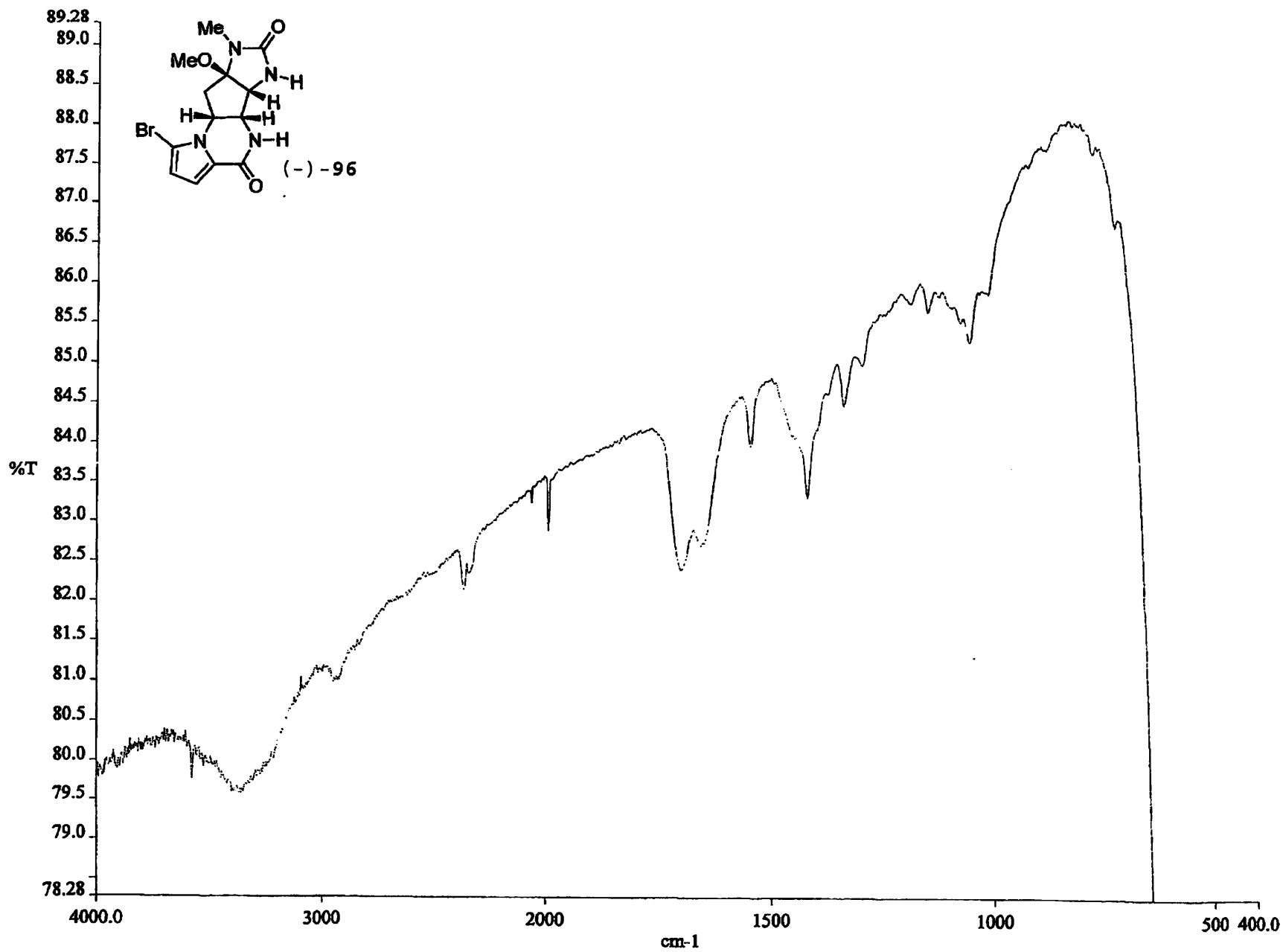ai   cdc  ph

DEC. & VT
dfrq        125.846
dn              C13
dpwr             30
dof               0
dm              nnn
dmm               c
dmf             200
dseq
dres            1.0
homo              n
    PROCESSING
wtfile
proc             ft
fn           262144
math              f

werr
wexp
wbs
wnt             wft

(−)-96

ACQUISITION
sfrq        125.795
tn             C13
at            1.736
np           131010
sw          37735.8
fb        not used
bs               4
ss               1
tpwr            53
pw             6.9
d1           0.763
tof          631.4
nt           1e+09
ct             356
alock            n
gain      not used
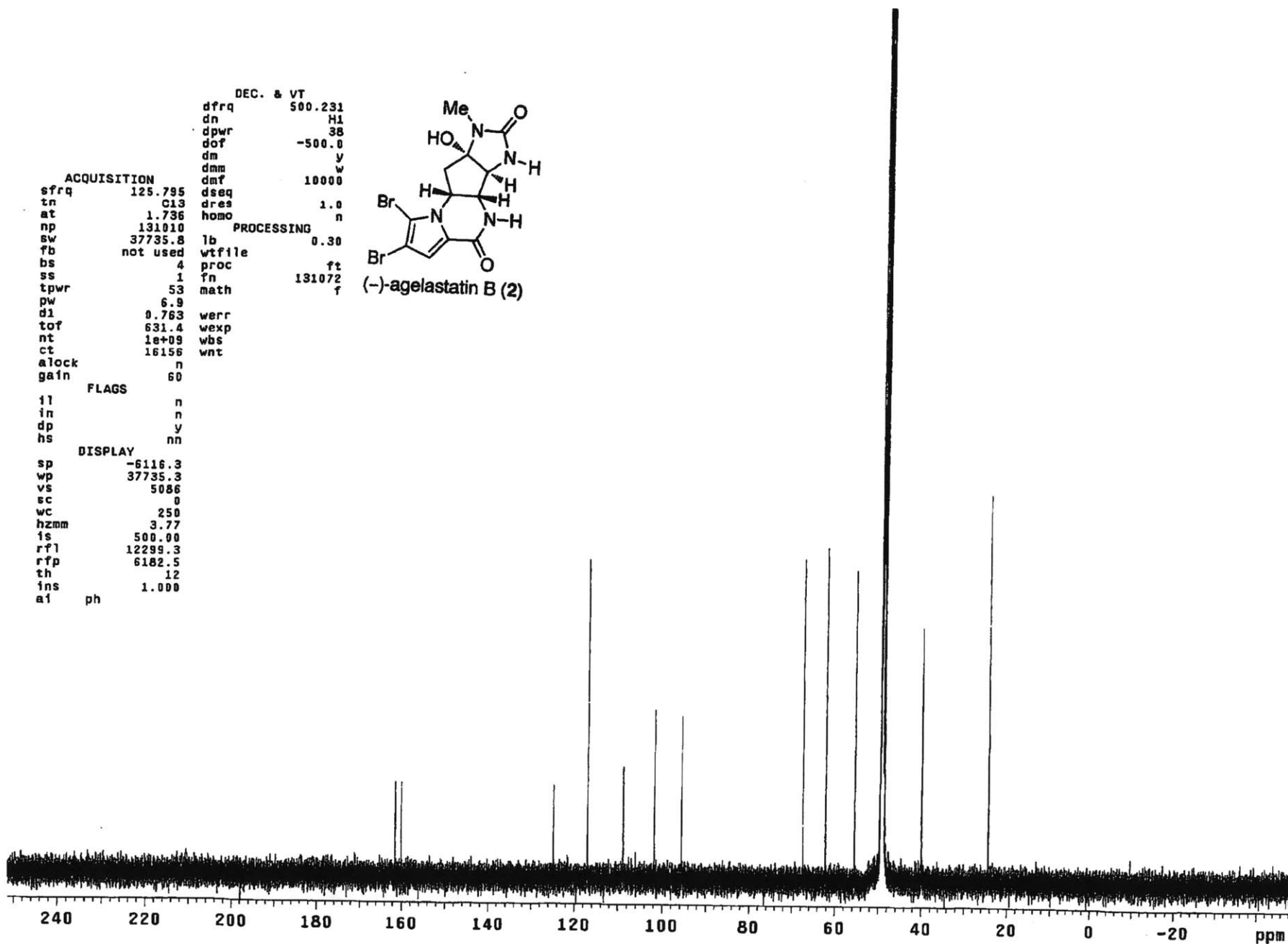       FLAGS
il               n
in               n
dp               y
hs              nn
       DISPLAY
sp         -6117.5
wp         37735.3
vs             920
sc               0
wc             250
hzmm        150.94
is          500.00
rfl        12300.3
rfp         6182.2
th               7
ins          1.000
ai     ph
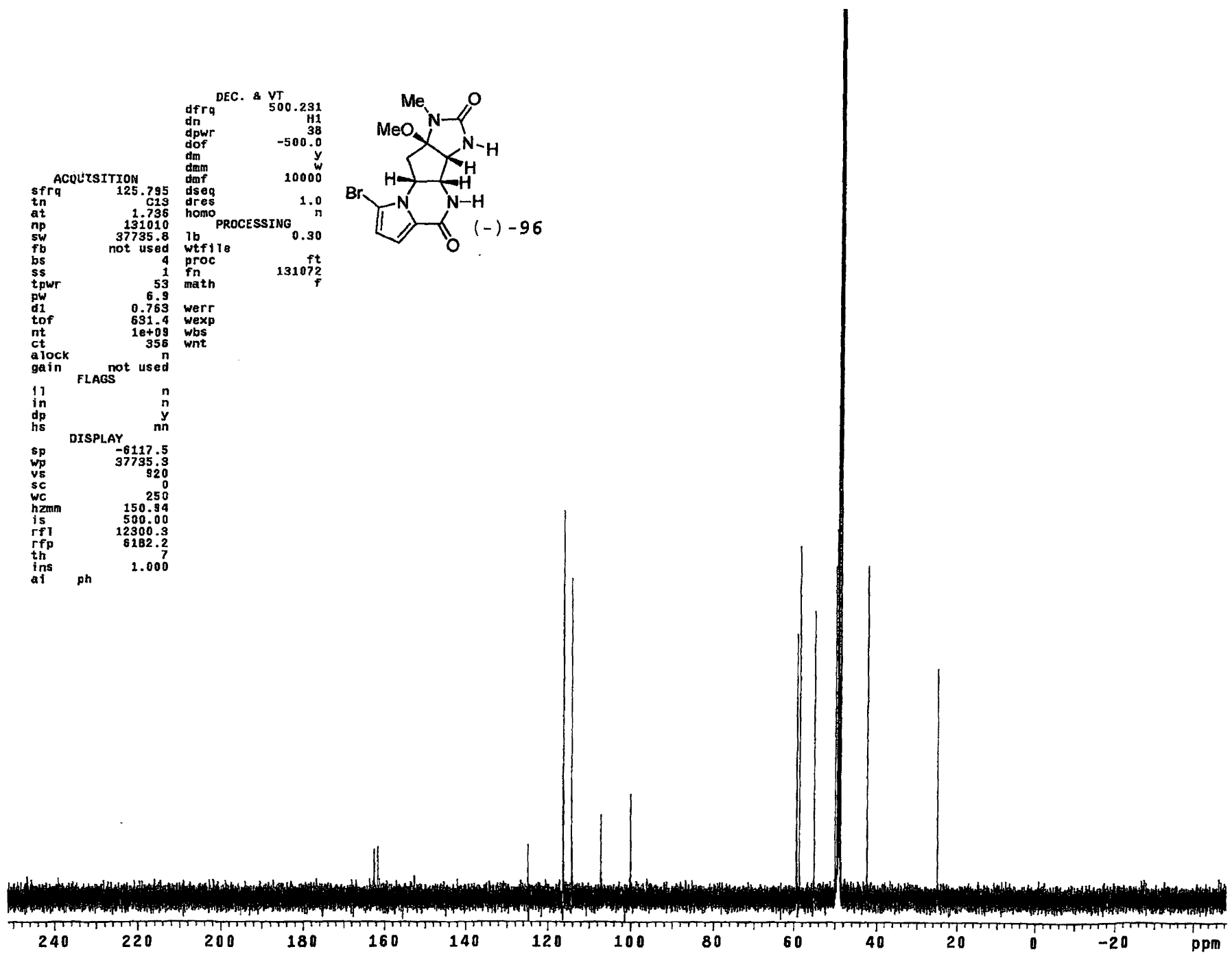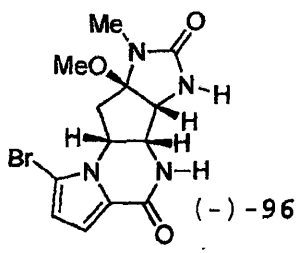
DEC. & VT
dfrq        500.231
dn              H1
dpwr            38
dof         -500.0
dm               y
dmm              w
dmf          10000
dseq
dres           1.0
homo             n
   PROCESSING
lb            0.30
wtfile
proc            ft
fn          131072
math             f

werr
wexp
wbs
wnt

(-)-96

(−)−96

DEC. & VT
dfrq 125.846
dn C13
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n
PROCESSING
wtfile
proc ft
fn 262144
math f

werr
wexp
wbs
wnt wft

ACQUISITION
sfrq 500.437
tn H1
at 4.999
np 120102
sw 12012.0
fb not used
bs 1
tpwr 56
pw 8.0
d1 0.100
tof 3003.2
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -250.2
wp 6255.4
vs 63
sc 0
wc 250
hzmm 25.02
is 33.57
rfl 2159.4
rfp 1656.4
th 4
ins 100.000
ai cdc ph
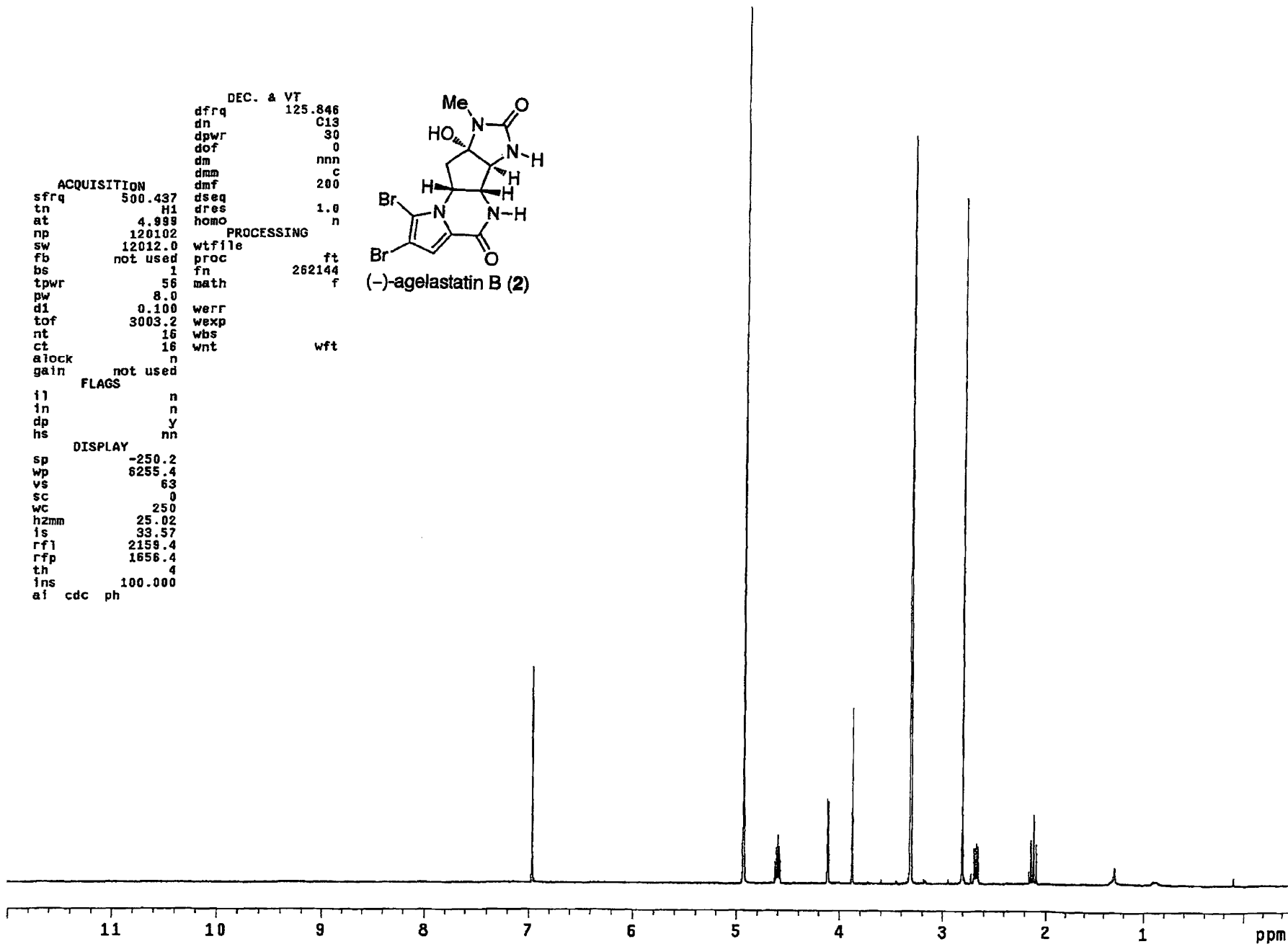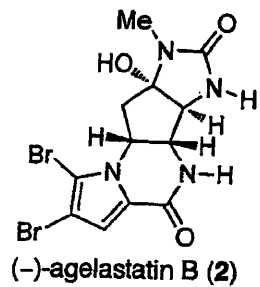


(–)-agelastatin B (2)

DEC. & VT
dfrq    500.231
dn         H1
dpwr       38
dof     -500.0
dm          y
dmm         w
dmf     10000
dseq
dres      1.0
homo        n

PROCESSING
lb       0.30
wtfile
proc       ft
fn     131072
math        f

ACQUISITION
sfrq    125.795
tn         C13
at       1.736
np      131010
sw     37735.8
fb     not used
bs          4
ss          1
tpwr       53
pw        6.9
d1       0.763
tof      631.4
nt      1e+09
ct      16156
alock       n
gain       60

FLAGS
il          n
in          n
dp          y
hs         nn

DISPLAY
sp     -6116.3
wp     37735.3
vs       5086
sc          0
wc        250
hzmm     3.77
is     500.00
rfl    12299.3
rfp     6182.5
th         12
ins     1.000
al      ph

(–)-agelastatin B (2)

MWD1 E, Sig=270,16 Ref=360,100

mAU

8 —

6 —

4 —

2 —

0 —

21.048  Area: 1230.72

27.637  Area: 1585.95

15    20    25    30    35    min

agelastatin B (2)
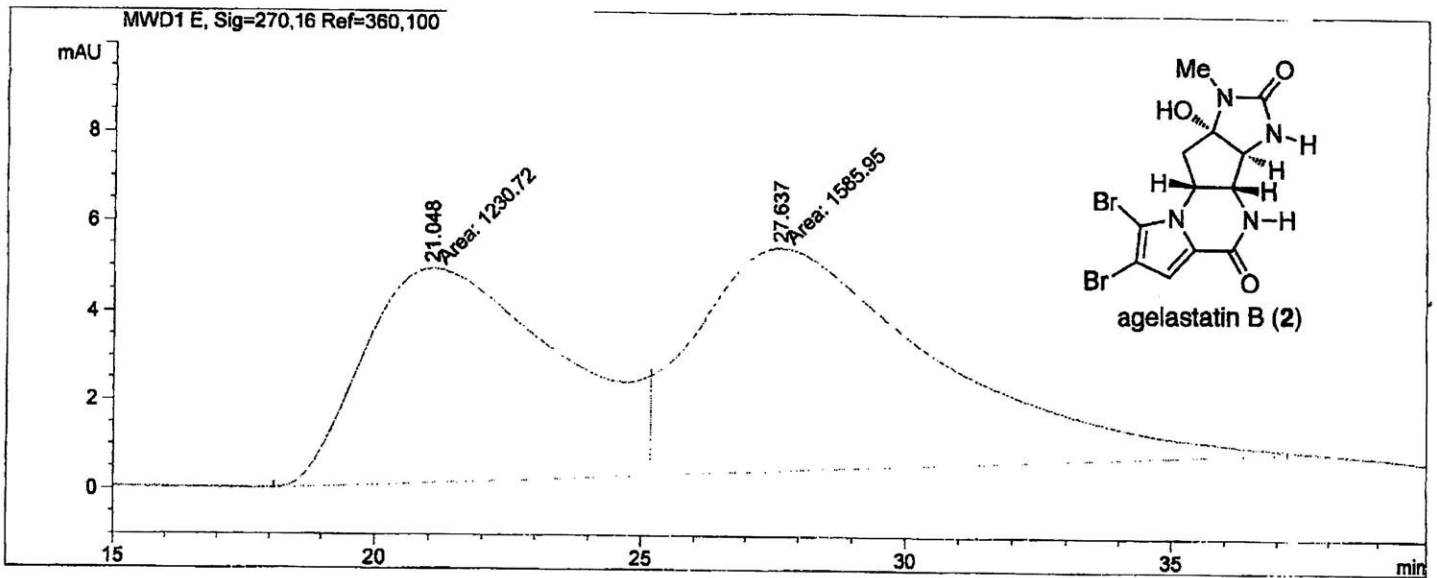
```
================================================================
                    Area Percent Report
================================================================

Sorted By          :       Signal
Multiplier         :       1.0000
Dilution           :       1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 E, Sig=270,16 Ref=360,100

Peak RetTime Type  Width     Area       Height      Area
 #   [min]        [min]    [mAU*s]      [mAU]         %
----|-------|----|-------|-----------|----------|--------|
  1  21.048 MF   4.2737 1230.71851     4.79959  43.6941
  2  27.637 FM   5.2827 1585.95435     5.00365  56.3059

Totals :                 2816.67285     9.80324

Results obtained with enhanced integrator!
================================================================
                  *** End of Report ***
```

MWD1 E, Sig=270,16 Ref=360,100

(−)-agelastatin B (2)
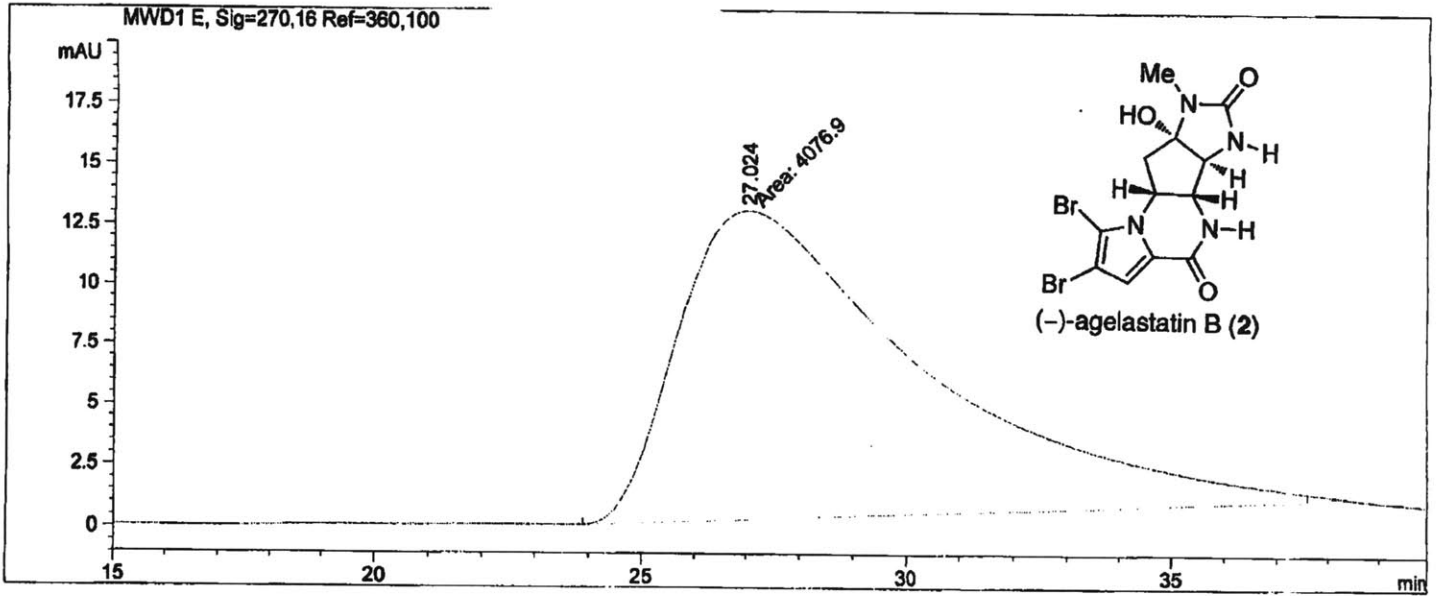
```
==================================================================================
                           Area Percent Report
==================================================================================

  Sorted By          :       Signal
  Multiplier         :       1.0000
  Dilution           :       1.0000
  Use Multiplier & Dilution Factor with ISTDs


  Signal 1: MWD1 E, Sig=270,16 Ref=360,100

  Peak RetTime Type  Width     Area      Height     Area
   #   [min]        [min]   [mAU*s]     [mAU]        %
  ---|-------|----|-------|----------|----------|--------|
   1  27.024  MM   5.3130 4076.89722  12.78911 100.0000

  Totals :                 4076.89722  12.78911
```

Results obtained with enhanced integrator!
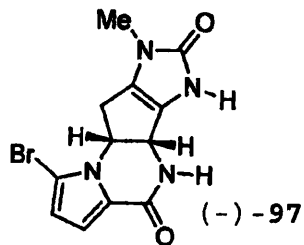```
==================================================================================
                          *** End of Report ***
```

83.4
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
51.1

%T

Me
N
O
HO
N—H
H
Br
H
H
N
N—H
Br
O
(–)-agelastatin B (2)

4000.0    3000    2000    1500    1000    500  400.0

cm-1

DEC. & VT
dfrq    500.231
dn          H1
lpwr        38
_of     -500.0
dm           y
dmm          w
dmf      10000
dseq
dres       1.0
homo         n
PROCESSING
lb         0.30
wtfile
proc        ft
fn      131072
math         f

werr
wexp
wbs
wnt

ACQUISITION
sfrq    125.795
tn          C13
at        1.736
np       131010
sw      37735.8
fb     not used
bs            4
ss            1
tpwr         53
pw          6.9
d1        0.763
tof       631.4
nt        1e+09
ct          576
alock         n
gain         60
       FLAGS
il            n
in            n
dp            y
hs           nn
     DISPLAY
sp      -6116.9
wp      37735.3
vs         1100
sc            0
wc          250
hzmm     150.94
is       500.00
rfl     12299.7
rfp      6182.2
th            7
ins       1.000
ai    ph

(-)-97



240   220   200   180   160   140   120   100   80   60   40   20   0   -20   ppm
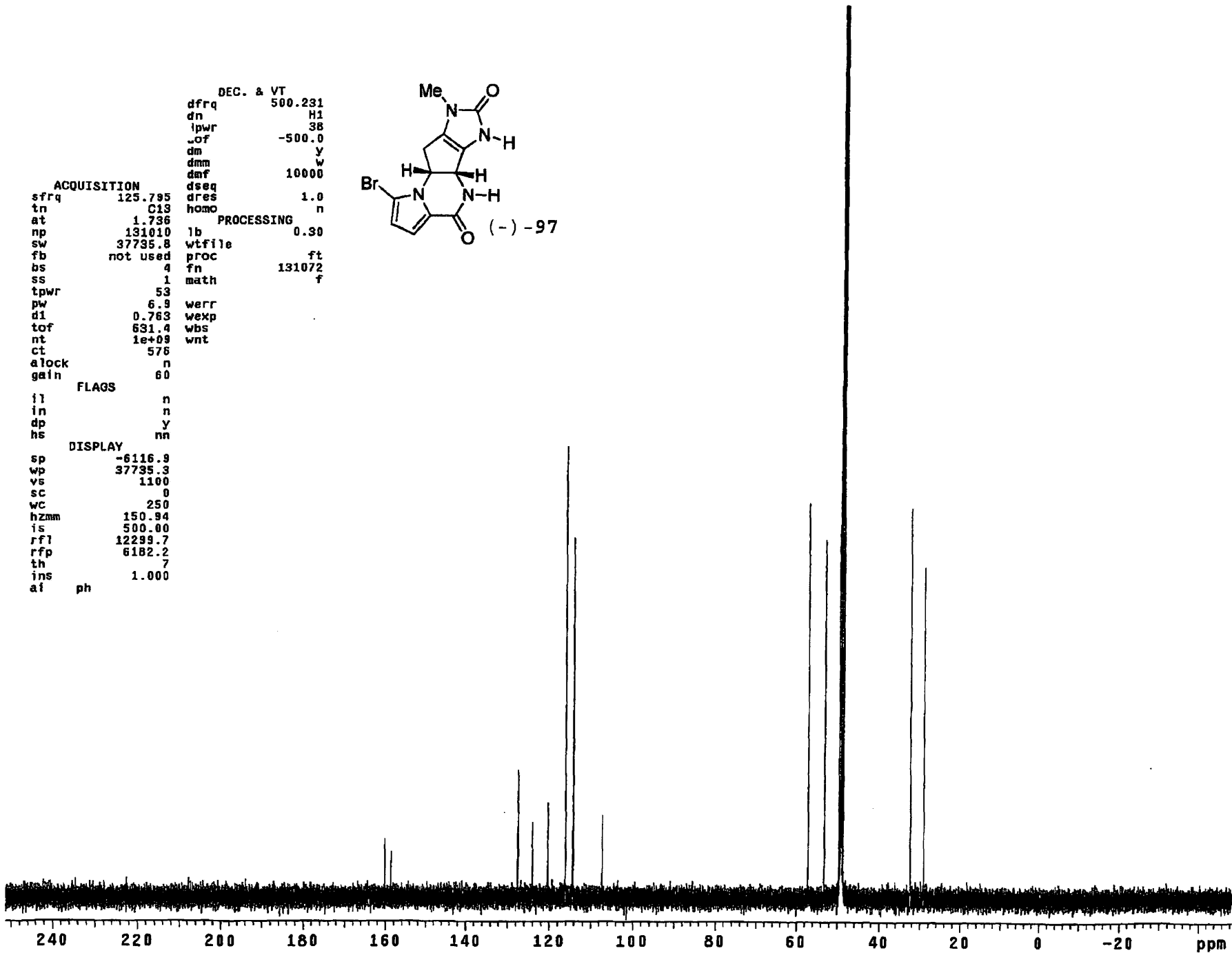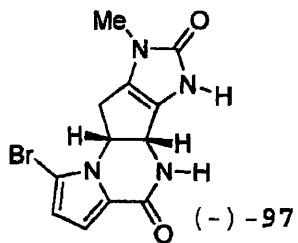
```
===================================================================================
Injection Date   :                              Seq. Line :   1
Sample Name      :                               Location : Vial 91
Acq. Operator    :                                    Inj :   1
                                             Inj Volume : 1 µl
Acq. Method      :
Last changed     :
Analysis Method  :
Last changed     :
===================================================================================
```
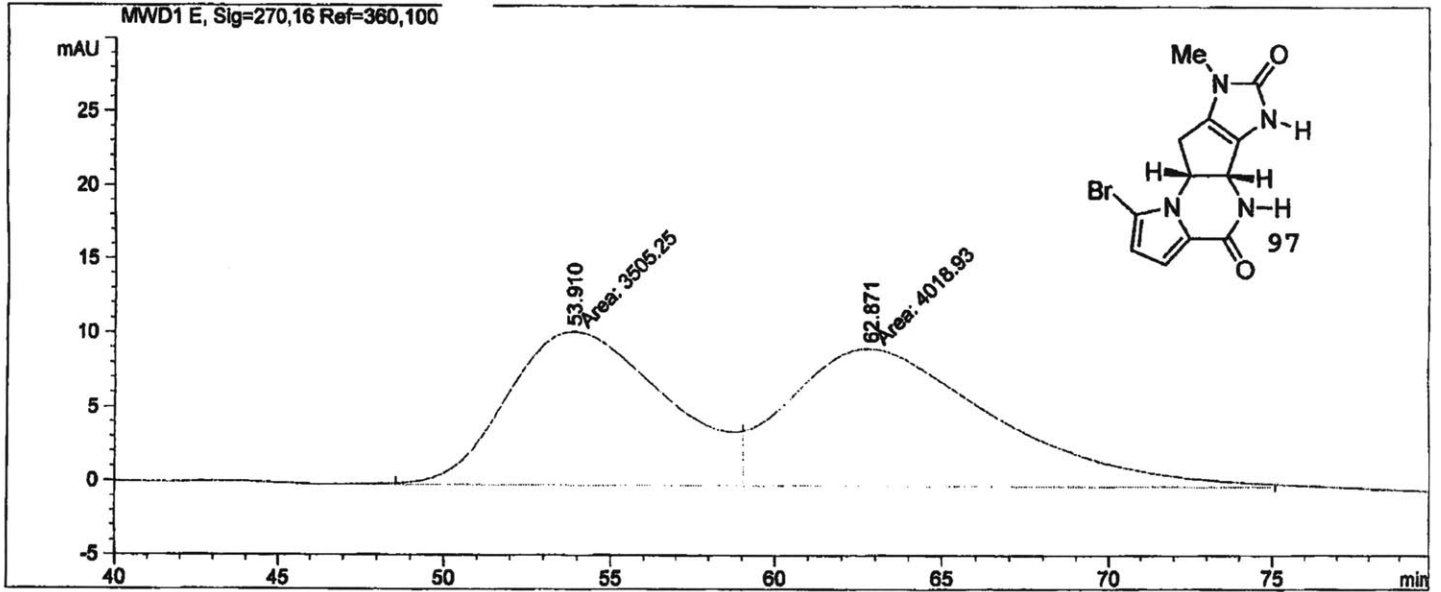


```
===================================================================================
                              Area Percent Report
===================================================================================

Sorted By            :        Signal
Multiplier           :        1.0000
Dilution             :        1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 E, Sig=270,16 Ref=360,100

Peak RetTime Type  Width     Area         Height      Area
  #   [min]        [min]    [mAU*s]       [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1  53.910 MF   5.6060  3505.24609   10.42107   46.5865
  2  62.871 FM   7.1602  4018.92529    9.35472   53.4135

Totals :                 7524.17139   19.77579

Results obtained with enhanced integrator!
===================================================================================
                           *** End of Report ***
```
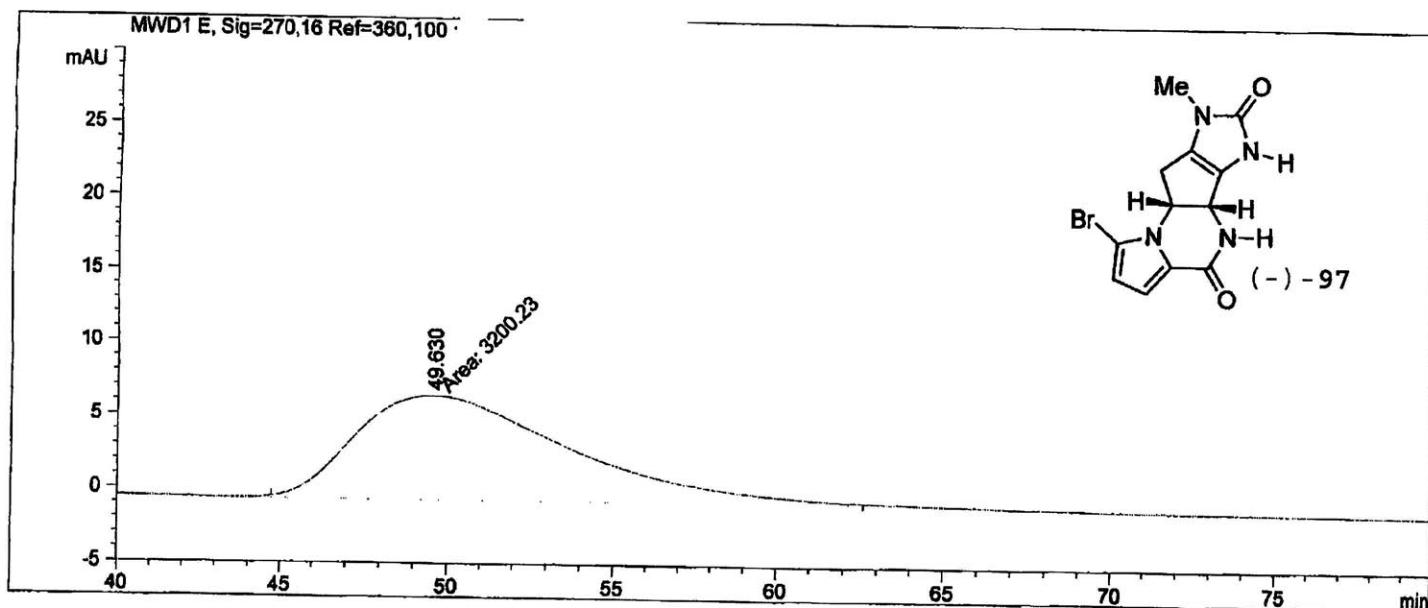
```
================================================================
Injection Date  :                        Seq. Line :    1
Sample Name     :                        Location  : Vial 91
Acq. Operator   :                             Inj  :    1
                                       Inj Volume  : 1 µl
Acq. Method     :
Last changed    :
Analysis Method :
Last changed    :
================================================================
```

MWD1 E, Sig=270,16 Ref=360,100



```
================================================================
                      Area Percent Report
================================================================

Sorted By             :        Signal
Multiplier            :        1.0000
Dilution              :        1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 E, Sig=270,16 Ref=360,100

Peak RetTime Type  Width    Area       Height     Area
 #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
 1   49.630 MM   7.4872 3200.22583   7.12375 100.0000

Totals :                  3200.22583   7.12375

Results obtained with enhanced integrator!
================================================================
                  *** End of Report ***
```
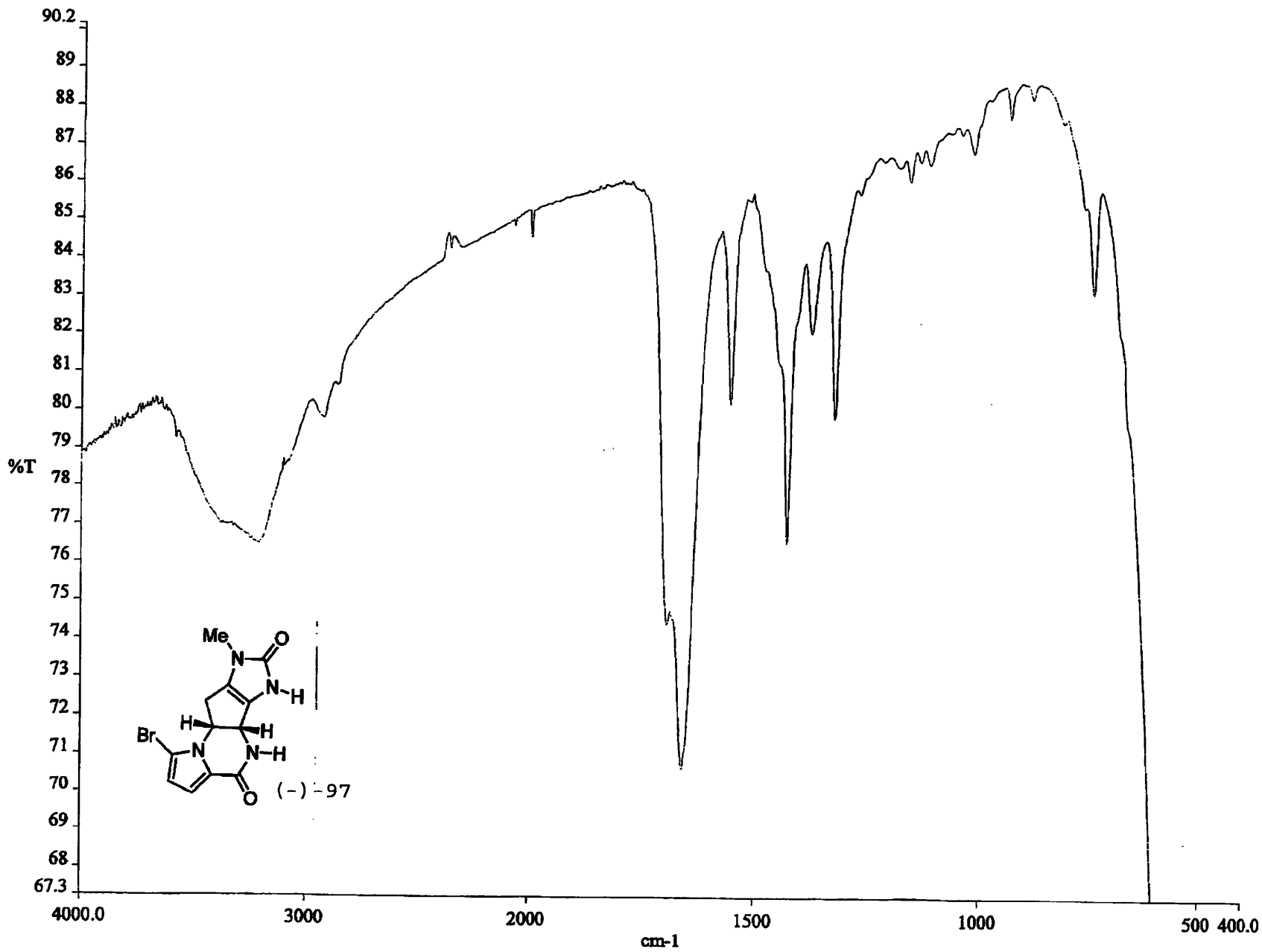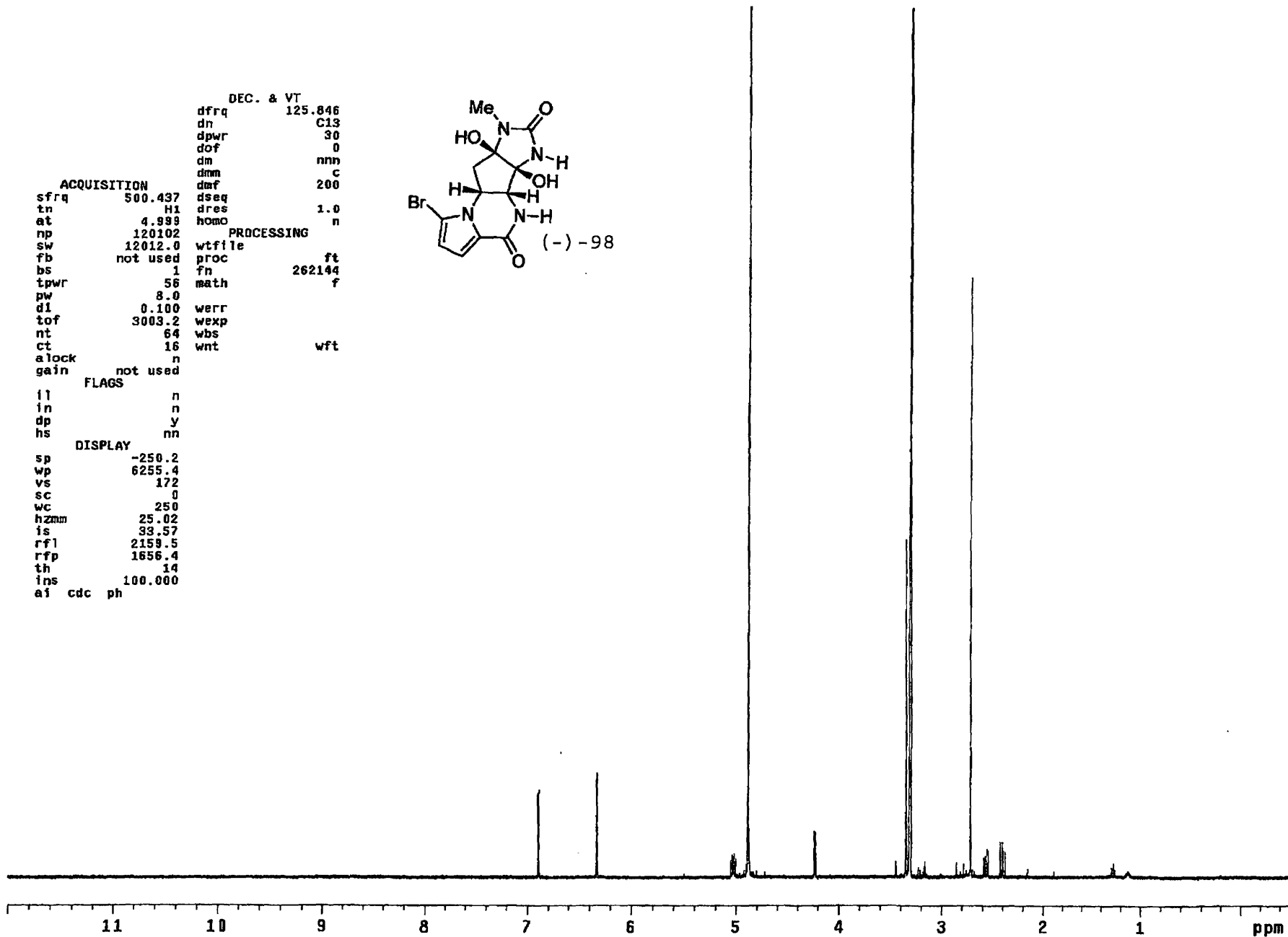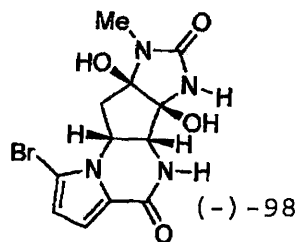
DEC. & VT
dfrq        125.846
dn              C13
dpwr             30
dof               0
dm              nnn
dmm               c
dmf             200
dseq
dres            1.0
homo              n
PROCESSING
wtfile
proc             ft
fn           262144
math              f

werr
wexp
wbs
wnt             wft

ACQUISITION
sfrq        500.437
tn               H1
at            4.999
np           120102
sw          12012.0
fb         not used
bs                1
tpwr             56
pw              8.0
d1            0.100
tof          3003.2
nt               64
ct               16
alock             n
gain       not used
FLAGS
il                n
in                n
dp                y
hs               nn
DISPLAY
sp           -250.2
wp           6255.4
vs              172
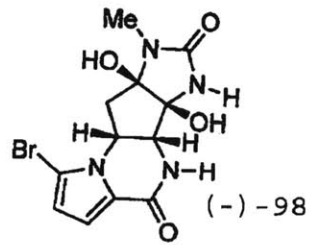sc                0
wc              250
hzmm          25.02
is            33.57
rfl          2159.5
rfp          1656.4
th               14
ins         100.000
ai   cdc   ph
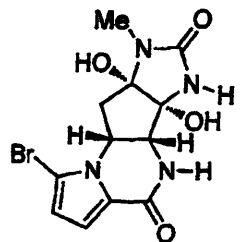
(-)-98

ACQUISITION
sfrq        500.437
tn              H1
at           4.999
np          120102
sw         12012.0
fb        not used
bs               1
tpwr            56
pw             8.0
d1           0.100
tof         3003.2
nt              64
ct              33
alock            n
gain      not used
        FLAGS
ll               n
in               n
dp               y
hs              nn
        DISPLAY
sp          -250.2
wp          6255.4
vs              51
sc               0
wc             250
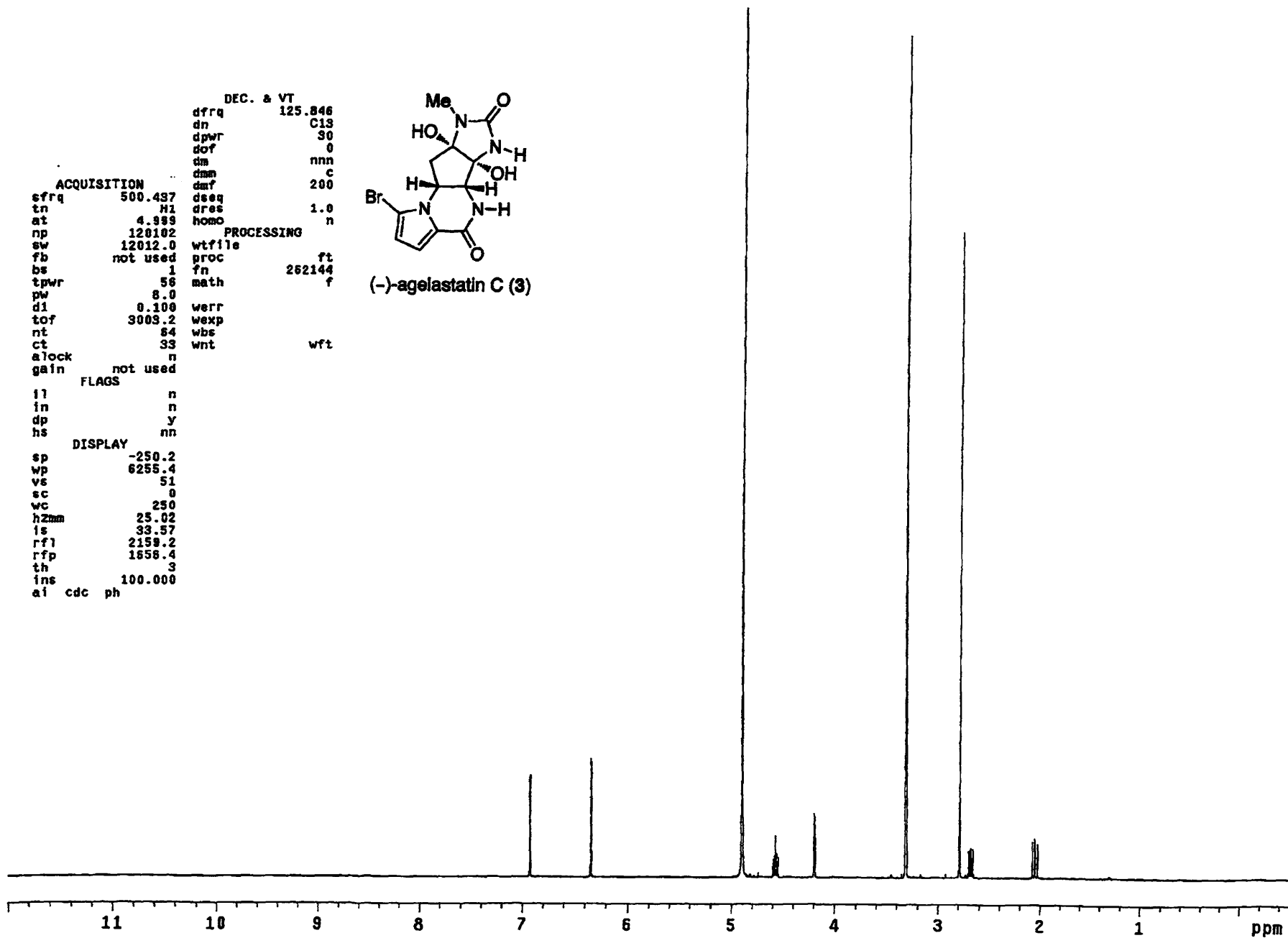hzmm         25.02
is           33.57
rfl         2159.2
rfp         1558.4
th               3
ins        100.000
ai   cdc  ph

        DEC. & VT
dfrq        125.846
dn              C13
dpwr             30
dof               0
dm              nnn
dmm               c
dmf             200
dseq
dres            1.0
homo              n
      PROCESSING
wtfile
proc             ft
fn           262144
math              f

werr
wexp
wbs
wnt             wft

(–)-agelastatin C (3)

DEC. & VT
dfrq        500.231
dn              H1
dpwr            38
dof          -500.0
dm               y
dmm              w
dmf           10000
dseq
dres           1.0
homo             n
      PROCESSING
lb            0.30
wtfile
proc            ft
fn          131072
math             f

werr
wexp
wbs
wnt

ACQUISITION
sfrq       125.795
tn             C13
at           1.736
np          131010
sw         37735.8
fb       not used
bs               4
ss               1
tpwr            53
pw             6.9
d1           0.763
tof          631.4
nt          1e+09
ct           20820
alock            n
gain            60
      FLAGS
il               n
in               n
dp               y
hs              nn
      DISPLAY
sp         -6116.4
wp         37735.3
vs            5122
sc               0
wc             250
hzmm        150.94
is          500.00
rfl        12299.2
rfp         6182.2
th               7
ins          1.000
ai     ph
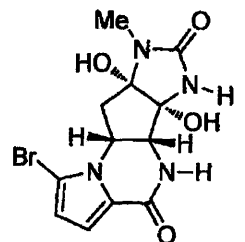
(−)-agelastatin C (3)

(–)-agelastatin C (3)
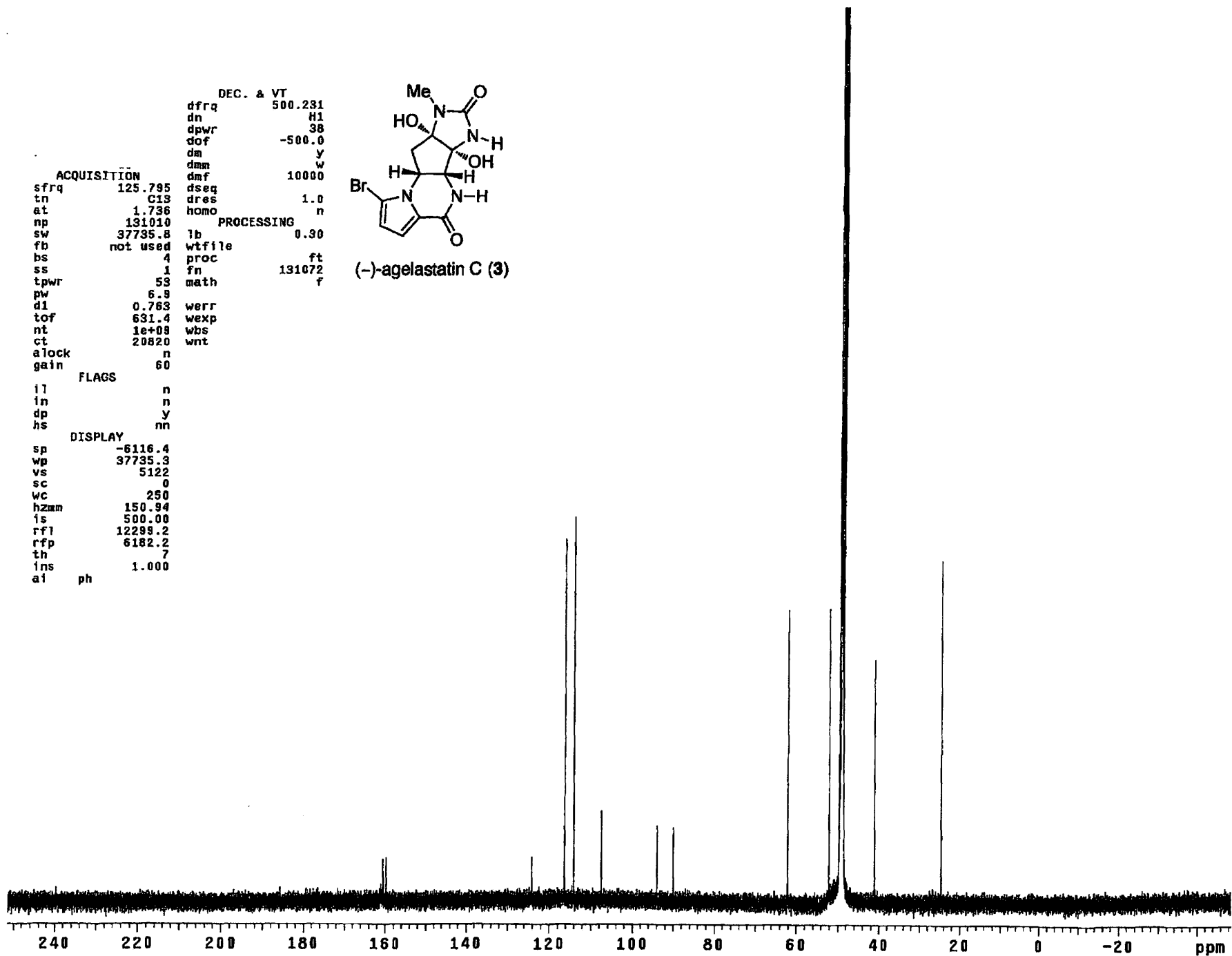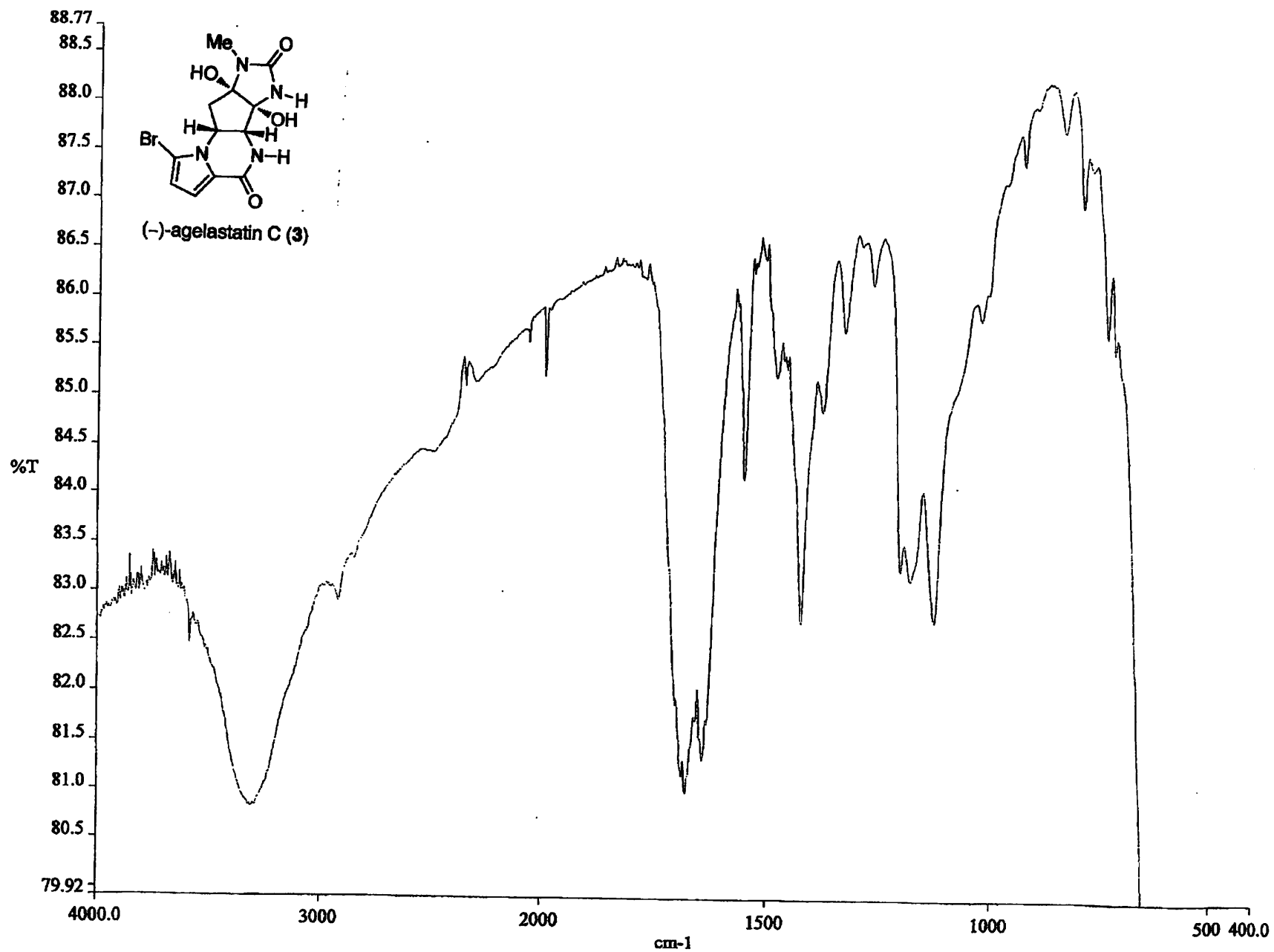
exp3   gCOSY

FLAGS
hs                    nn
solvent      CD3OD    sspul            n
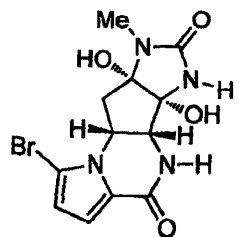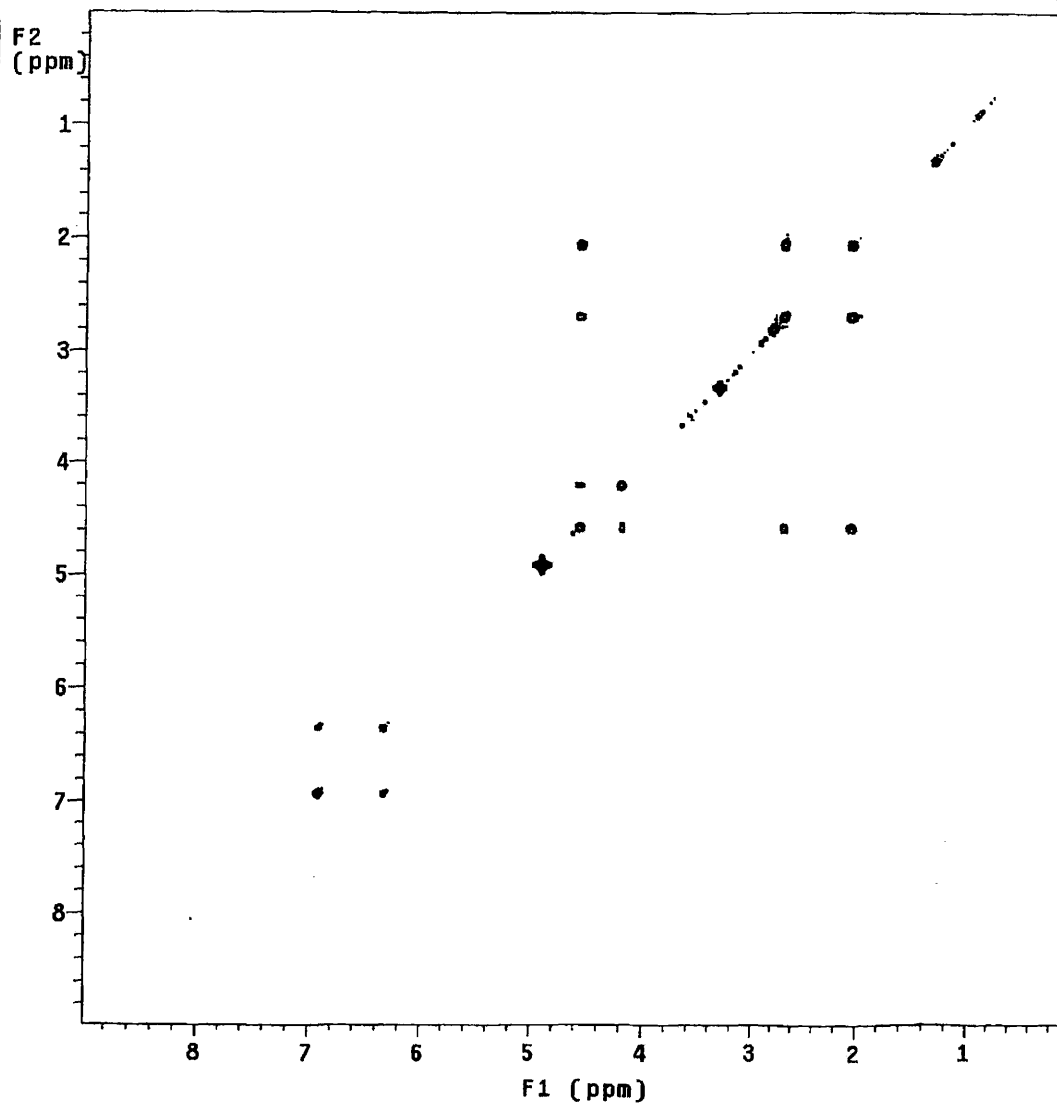sample   undefined    hsglvl        2000
     ACQUISITION           SPECIAL
sw         4490.3    temp      not used
at          0.228    gain            58
np           2048    spin             0
fb       not used    F2 PROCESSING
ss             16    sb          -0.114
d1          1.000    sbs       not used
nt             23    fn            2048
   2D ACQUISITION     F1 PROCESSING
sw1        4490.3    sb1         -0.057
ni            128    sbs1      not used
   TRANSMITTER        proc1           1p
tn             H1    fn1           2048
sfrq      499.746         DISPLAY
tof        -252.5    sp             4.6
tpwr           56    wp          4486.0
pw          9.200    sp1            0.6
    GRADIENTS         wp1         4486.0
gzlvl1       2000    rf1           -0.2
gt1       0.001000   rfp              0
gstab     0.000500   rfl1           3.8
    DECOUPLER         rfp1             0
dn            C13         PLOT
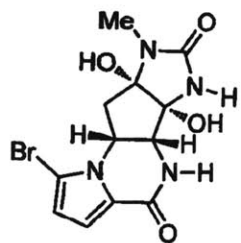dm            nnn    wc           138.9
                     sc               0
                     wc2          138.9
                     sc2              0
                     vs             322
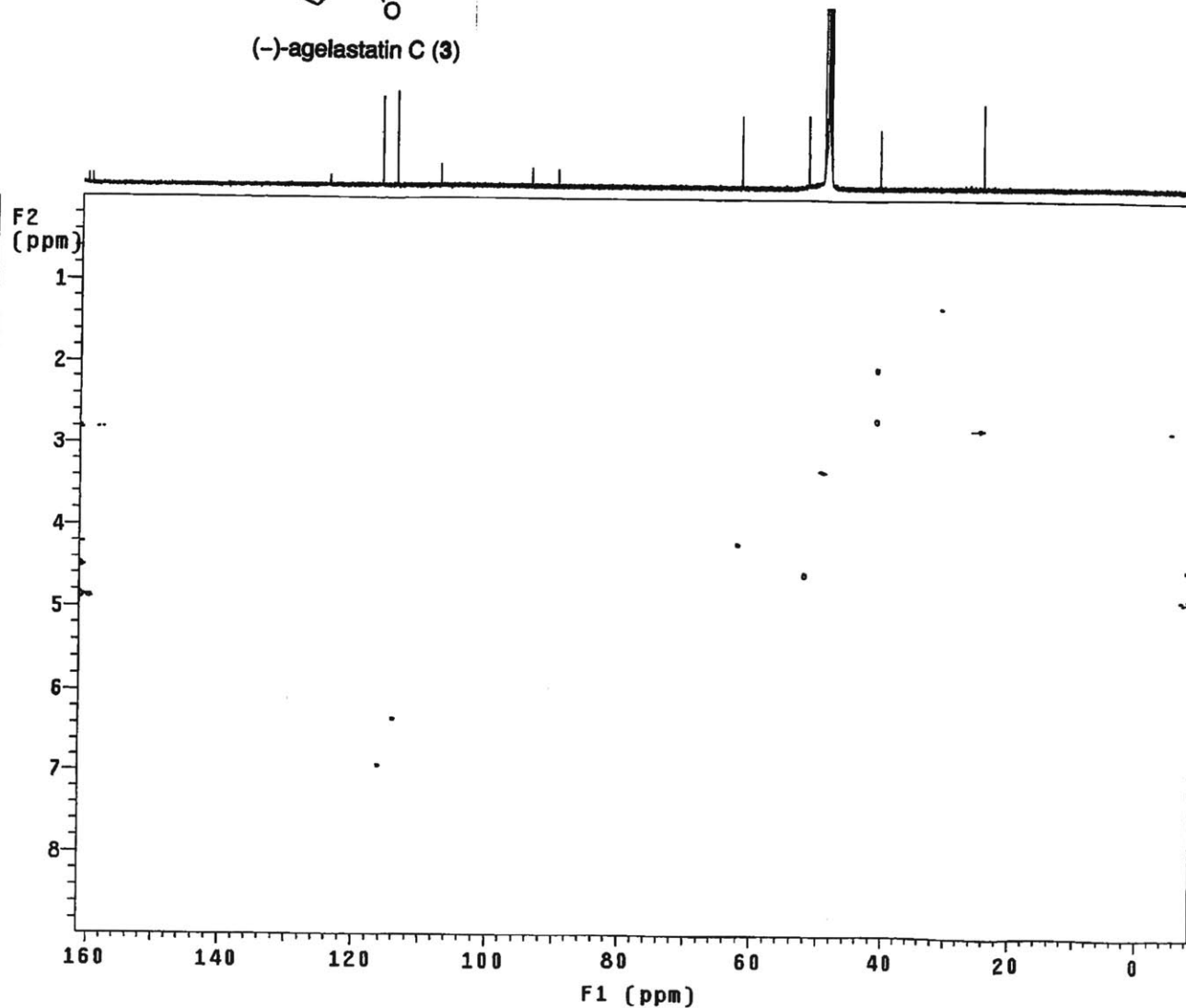                     th               2
                     al   cdc   av

(−)-agelastatin C (3)

exp4 HSQC

FLAGS
hs                    n
solvent      CD3OD    sspul              n
sample    undefined   PFGflg             y
     ACQUISITION      hsglvl          2000
sw          4490.3       SPECIAL
at           0.150    temp      not used
np            1348    gain            52
fb        not used    spin             0
ss             256       PRESATURATION
d1           1.000    satmode            n
nt              37    satpwr             0
   2D ACQUISITION     satdly             0
sw1        21361.8    satfrq             0
n1             256      F2 PROCESSING
phase      arrayed    gf           0.105
    TRANSMITTER       gfs       not used
tn              H1    fn            2048
sfrq       499.746      F1 PROCESSING
tof         -252.5    sb1        -0.024
tpwr            56    sbs1       -0.024
pw           9.200    proc1           lp
    DECOUPLER         fn1           2048
dn             C13       DISPLAY
dof        -2514.8    sp             5.1
dm             nny    wp          4486.0
dmm            ccg    sp1        -1064.1
dmf          32200    wp1        21341.0
dpwr            53    rf1         3167.7
pwxlvl          59    rfp         3168.4
pwx         18.000    rfl1       15417.0
    HSQC              rfp1       14332.1
j1xh         140.0       PLOT
null         0.350    wc           170.0
nullflg          n    sc               0
mult             2    wc2          110.0
                      sc2              0
                      vs             322
                      th               2
                      ai   cdc   ph

ACQUISITION ARRAYS
array         phase
arraydim        512

1             phase
1                 1
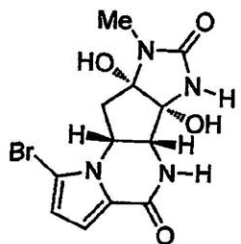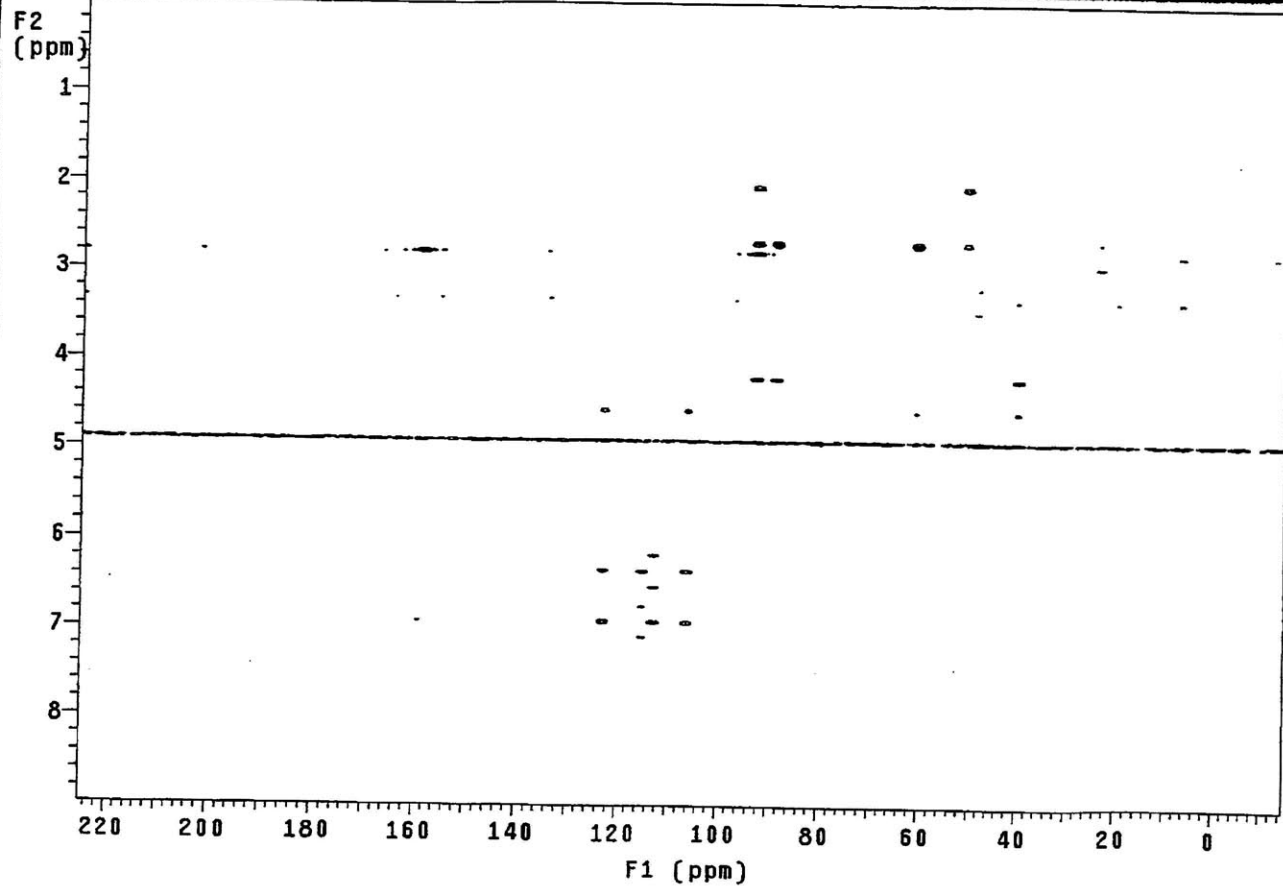2                 2

(–)-agelastatin C (3)

exp5  HMBC

FLAGS                    ACQUISITION ARRAYS
solvent    CD3OD     hs            n    array        phase
sample  undefined    sspul         n    arraydim       512
   ACQUISITION       PFGflg        n    i
sw        4490.3     hsglvl     2000    1            phase
at         0.228        SPECIAL         1              1
np          2048     temp    not used   2              2
fb      not used     gain         52
ss            32     spin          0
d1         1.000     PRESATURATION
nt            40     satmode       n
   2D ACQUISITION    satpwr        0
sw1      30154.5     satdly        0
ni           256     satfrq        0
phase    arrayed     F2 PROCESSING
   TRANSMITTER       sb        0.114
tn            H1     sbs     not used
sfrq     499.746     fn         2048
tof       -252.5     F1 PROCESSING
tpwr          56     sb1       0.004
pw         9.200     sbs1    not used
   DECOUPLER         fn1        2048
dn           C13     sp            4.6
dof       1255.1     wp         4486.0
dm           nnn     sp1       -1853.5
dmm          ccc     wp1       30125.1
dmf        32200     rfl          -0.2
dpwr          53     rfp           0
pwx[v]        59     rfl1       1882.9
pwx       18.000     rfp1          0
   HMBC                 PLOT
j1xh       140.0     wc          170.0
jnxh         8.0     sc            0
                     wc2         110.0
                     sc2           0
                     vs          322
                     th            2
                     ai  cdc  av

(−)-agelastatin C (**3**)

(−)-agelastatin E (5)

DEC. & VT
dfrq    500.231
dn          H1
dpwr        38
dof      -500.0
dm           y
dmm          w
dmf      10000
dseq
dres       1.0
homo         n
PROCESSING
lb        0.30
wtfile
proc       ft
fn      131072
math         f

werr
wexp
wbs
wnt

ACQUISITION
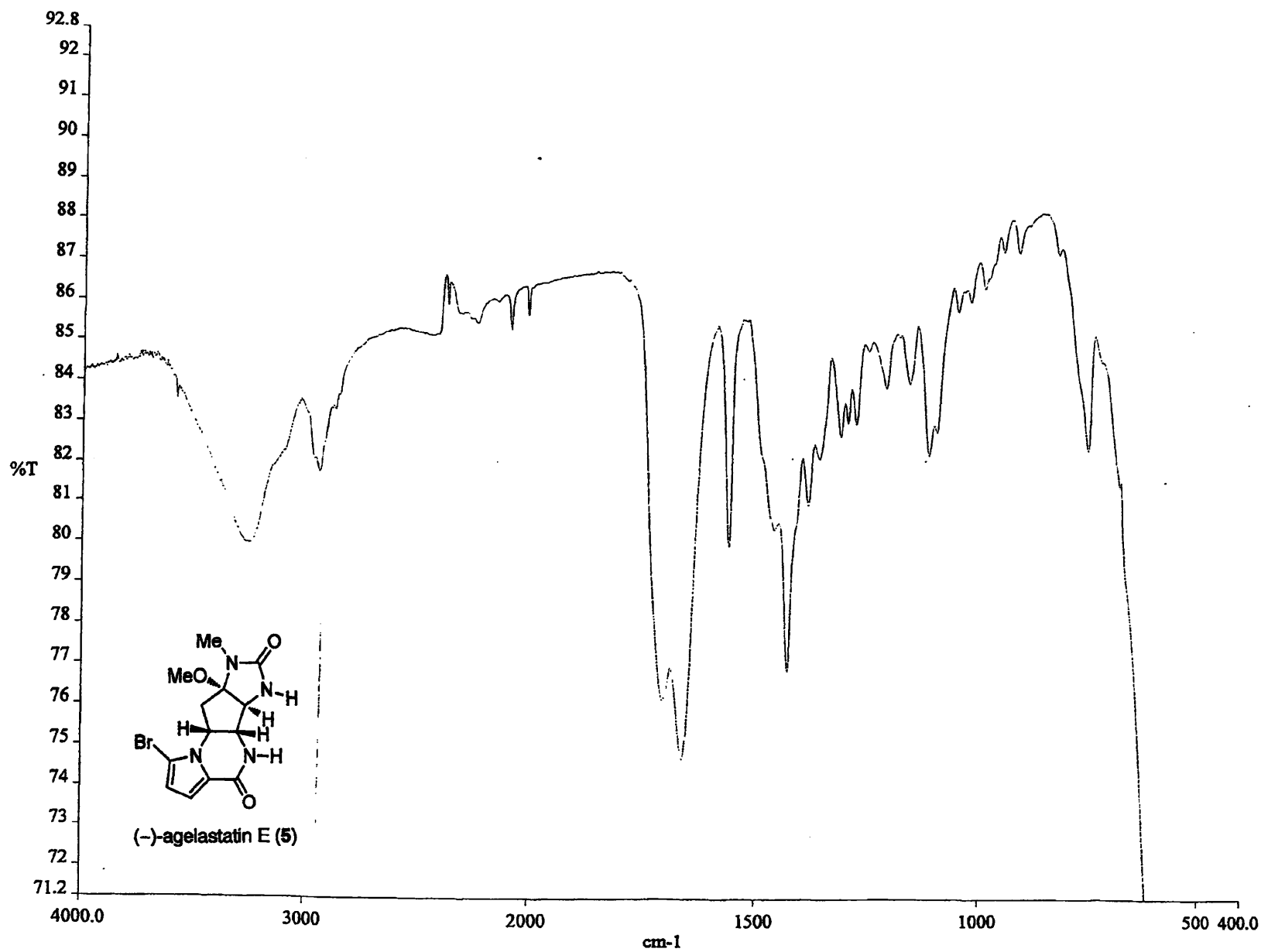sfrq    125.795
tn          C13
at        1.736
np       131010
sw      37735.8
fb     not used
bs           4
ss           1
tpwr        53
pw         6.9
d1       0.763
tof      631.4
nt       1e+09
ct         448
alock        n
gain   not used
FLAGS
il           n
in           n
dp           y
hs          nn
DISPLAY
sp      -6118.1
wp      37735.3
vs        1265
sc           0
wc         250
hzmm    150.94
is    23000.00
rfl    12300.9
rfp     6182.2
th          11
ins      1.000
ai    ph

(–)-agelastatin E (5)

(−)-agelastatin E (5)
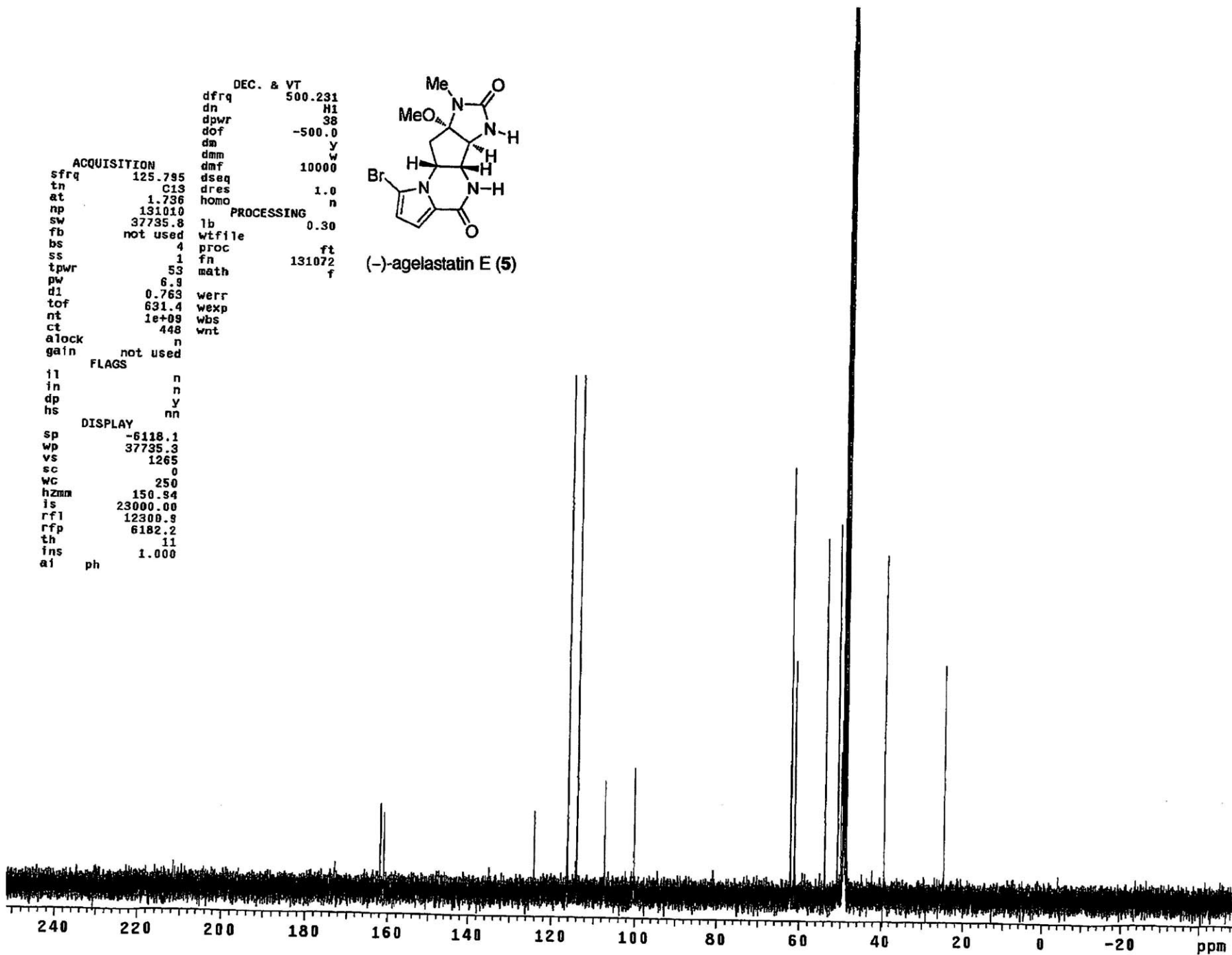
# Dustin S. Siegel

Massachusetts Institute of Technology, Department of Chemistry
77 Massachusetts Avenue, 18-243, Cambridge, MA 02139
Lab: (617) 324-0394, dsiegel@mit.edu

**PERSONAL:**    Born December 16, 1980.

**EDUCATION:**

| | |
|---|---|
| 2004-Present | **Massachusetts Institute of Technology**, Cambridge, MA |
| | Ph.D. candidate, Organic Chemistry |
| | *Cumulative Graduate GPA*: 4.9 / 5.0 |
| | *Advisor*: Associate Professor Mohammad Movassaghi |

| | |
|---|---|
| 1999-2003 | **University of California, San Diego**, San Diego, CA |
| | *Degree:* B.S. Chemistry, *Cum Laude* / Departmental Honors with High Distinction |
| | *Major GPA*: 3.77/4.00    *Cumulative GPA*: 3.61/4.00 |
| | *Advisor*: Professor Clifford P. Kubiak |

**PROFESSIONAL EXPERIENCE:**

| | |
|---|---|
| 2004-Present | **Massachusetts Institute of Technology**, Cambridge, MA |
| | Department of Chemistry, Advisor: Associate Professor Mohammad Movassaghi |
| | *Graduate Research Assistant* |

- The total synthesis of the (–)-agelastatin alkaloids.
- The enantioselective total synthesis of (–)-acylfulvene and (–)-irofulven.

| | |
|---|---|
| 2003-2004 | **ChemBridge Research Laboratories**, Rancho Bernardo, CA |
| | *Research Associate* |

- Development of small molecules for medicinial chemistry.

| | |
|---|---|
| 2002-2003 | **University of California, San Diego**, San Diego, CA |
| | Department of Chemistry, Advisor: Professor Clifford P. Kubiak |
| | *Undergraduate Research Assistant* |

- Development of charge transfer complexes for application in molecular electronics.

**HONORS AND ACTIVITIES:**

| | |
|---|---|
| 2009 | Award for Outstanding Teaching at MIT. |
| 2009 | Guest lecturer for two lectures of an advanced organic chemistry class at MIT. |
| 2006 | Sigma-Aldrich Graduate Student Innovation Award. |
| 2006 | Gordon Research Conference Travel Grant. |
| 2006 | *SYNLETT* Star Journal Award, for academic excellence. |
| 2006 | Guest lecturer for one lecture of a graduate synthetic organic chemistry class at MIT. |
| 2003 | President of the American Chemical Society Student Affiliates at UCSD. |
| 2002 | California Institute for Telecommunications and Information Technology Fellowship. |
| 2002 | American Chemical Society Student Affiliates Undergraduate Summer Research Fellowship. |

## PUBLICATIONS:

- Movassaghi, M.; Siegel, D. S.; Sunkyu, H. "Total Synthesis of All (–)-Agelastatin Alkaloids." **2010,** *Manuscript in Preparation.*

- Siegel, D. S.; Piizzi, G.; Piersanti, G.; Movassaghi, M. "Enantioselective Total Synthesis of (–)-Acylfulvene and (–)-Irofulven." *J. Org. Chem.* **2009,** *74,* 9292-9304.

- Movassaghi, M.; Piizzi, G.; Siegel, D. S.; Piersanti, G. "Observations in the Synthesis of the Core of the Antitumor Illudins via an Enyne Ring Closing Metathesis Cascade." *Tetrahedron Lett.* **2009,** *50,* 5489-5492.

- Movassaghi, M.; Piizzi, G.; Siegel, D. S.; Piersanti, G. "Enantioselective Total Synthesis of (–)-Acylfulvene and (–)-Irofulven." *Angew. Chem. Int. Ed.* **2006,** *45,* 5859-5863.

- Stires, J. C.; Kasibhatla, B. S.; Siegel, D.; Kwong, J. C.; Caballero, J. B.; Labonte, A. P.; Reifenberger, R. G.; Datta, S.; Kubiak, C. P. "Conducting molecular nanostructures assembled from charge-transfer complexes grafted onto silicon surfaces." *Proc. SPIE Int. Soc. Opt. Eng.* **2003,** *5223,* 85-90.

## PRESENTATIONS:

- "Enantioselective Total Synthesis of (–)-Acylfulvene and (–)-Irofulven." MIT Graduate Student Research Symposium (Boston, MA, May 2008)
- "Enantioselective Total Synthesis of (–)-Acylfulvene and (–)-Irofulven." ACS National Meeting Boston (Boston, MA, August 2007)
- "Enantioselective Total Synthesis of (–)-Acylfulvene and (–)-Irofulven." Aldrich Graduate Student Innovation Award Symposium (Milwaukee, WI, August 2006)
- "Enantioselective Total Synthesis of (–)-Acylfulvene and (–)-Irofulven." Gordon Research Conference; Stereochemistry (Newport, RI, June 2006)

## TEACHING EXPERIENCE:

| | |
|---|---|
| 2008 | One semester of teaching assistantship as head TA for an advanced organic chemistry class at MIT (Professors M. Movassaghi, and S. L. Buchwald). |
| 2007 | One semester of teaching assistantship for an advanced organic chemistry class at MIT (Professors M. Movassaghi, and S. L. Buchwald). |
| 2005 | One semester of teaching assistantship for an advanced synthetic organic chemistry graduate level class at MIT (Professor M. Movassaghi). |
| 2005 | One semester of teaching assistantship as head TA for an organic chemistry graduate class at MIT (Professor S. O'Connor, and Dr. K. Berkowski). |
| 2004 | One semester of teaching assistantship for a laboratory chemistry class at MIT (Dr. J. Schrenk). |

## REFERENCES:

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**Rick L. Danheiser, Ph.D.**
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