

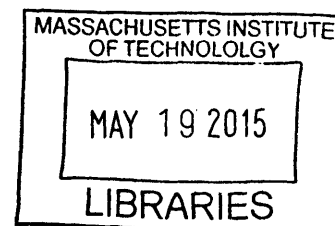
Development of Epipolythiodiketopiperazine Syntheses and the Total Synthesis of  
Diketopiperazine Alkaloids

**ARCHIVES**

by

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*To my family*

## Acknowledgements

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## Preface

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# Development of Epipolythiodiketopiperazine Syntheses and the Total Synthesis of Diketopiperazine Alkaloids

By

Timothy Adams

Submitted to the Department of Chemistry  
on February 15, 2015 in Partial Fulfillment of the  
Requirements for the Degree of Doctor of Philosophy in  
Organic Chemistry

## ABSTRACT

### **I. The Development of Epipolythiodiketopiperazine (ETP) Syntheses**

Epipolythiodiketopiperazine (ETP) alkaloids represent a structurally complex and biologically potent class of secondary fungal metabolites and these molecules have been known since the 1930s. The biological activity of these molecules is quite potent and the modes of toxicity possessed by these agents involve the generation of reactive oxygen species (ROS) and direct manipulation of target proteins. The biosynthesis of these compounds has been the subject of active study and we have presented our own hypothesis how these molecules are synthesized by fungi. Efforts to synthesize these alkaloids have been known since the late 1960 to early 1970s and all have highlighted the need to install the requisite disulfide bridge at a late-stage. The ETP motif is known to be notoriously sensitive as it is reactive towards bases and Lewis acids, and in photochemical and redox reactions.

### **II. Development of ETP Syntheses for the Application of the Total Synthesis of (+)-Bionectin A**

The concise and efficient total synthesis of (+)-bionectin A is described. Our approach to these natural products features a new and scalable method for *erythro*- $\beta$ -hydroxytryptophan amino acid synthesis and a new mercaptan reagent for the epipolythiodiketopiperazine (ETP) synthesis that can be unraveled under very mild conditions. The development of this new reagent was accomplished after exploring the acid promoted incorporation of different alkyl thiols into diketopiperazine diol substrates.

### **III. Concise Total Synthesis of (+)-Luteoalbusin A**

The first total synthesis of (+)-luteoalbusin A is described. Our concise and enantioselective synthesis began from the simple starting materials L-alanine and L-tryptophan. Transformations central to our route include a highly regioselective Friedel-Crafts indolization that can be performed on multi-gram scale, as well as a highly diastereoselective oxidation and thiolation. Moreover, this divergent synthesis features a

common aminothioisobutyryl intermediate that can be utilized to construct (+)-luteoalbusin A. The spectral data obtained from the synthetic samples confirmed the assigned structure for this natural product.

Thesis Supervisor: Professor Mohammad Movassaghi  
Title: Professor of Chemistry



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## abbreviations

Å	angstrom
[ $\alpha$ ]	specific rotation
Ac	acetyl
app	apparent
aq	aqueous
atm	atmosphere
Boc	<i>tert</i> -butoxycarbonyl
br	broad
Bu	butyl
Bz	benzoyl
°C	degree Celsius
<i>c</i>	concentration
c	centi
CAM	ceric ammonium molybdate
cat.	Catalytic
cm	centimeter
cm <sup>-1</sup>	wavenumber
cod	cyclooctadiene
d	days
d	doublet
<i>d</i>	deuterium
$\delta$	parts per million
DART	direct analysis in real time
dba	dibenzylideneacetone
diam	diameter
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
DTBMP	2,6-di- <i>tert</i> -butyl-4-methylpyridine
dr	diastereomeric ratio
EC <sub>50</sub>	half maximal effective concentration
ee	enantiomeric excess
EI	electronic ionization
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
ETP	epidithiodiketopiperazine
FT	fourier transform
g	gram
gCOSY	gradient-selected correlation spectroscopy
h	hour
ht	height
HMBC	heteronuclear multiple bond correlation
HPLC	high performance liquid chromatography

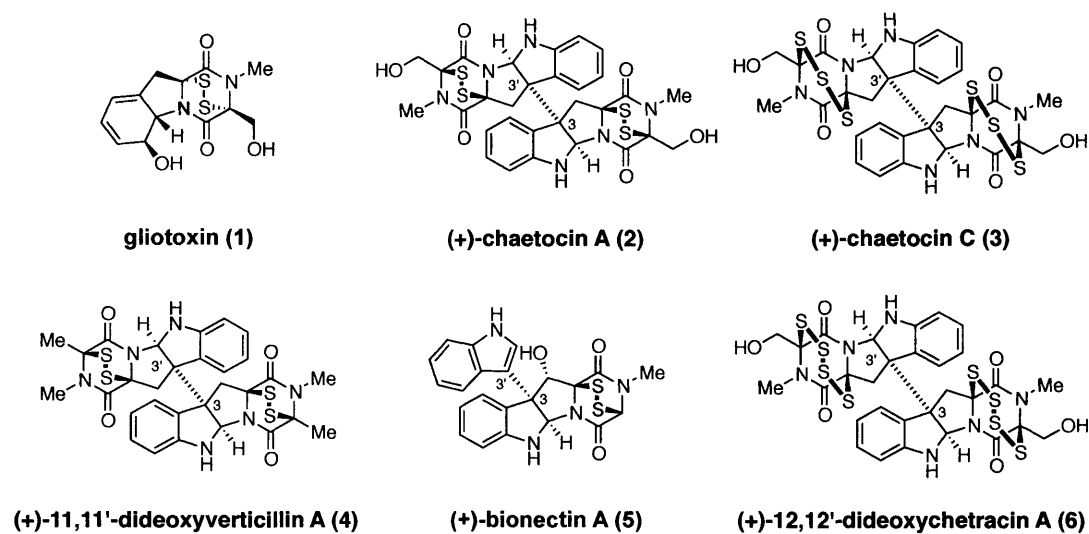
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum correlation
Hz	Hertz
<i>i</i>	<i>iso</i>
IC <sub>50</sub>	half maximal inhibitory concentration
IR	infrared
<i>J</i>	coupling constant
L	liter
m	medium
<i>m</i>	<i>meta</i>
m	meter
m	mili
M	molar
M	molecular mass
μ	micro
<i>m</i> CPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
Mhz	megahertz
min	minute
mol	mole
MOM	methoxymethyl
M.p.	melting point
MPLC	medium performance liquid chromatography
MS	mass spectrometry
<i>m/z</i>	mass to charge ratio
N	Normal
NBS	<i>N</i> -bromosuccinimide
NMP	<i>N</i> -methylpyrrolidine
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
Ph	phenyl
piv	pivaloyl
PMA	phosphomolybdic acid
PMP	<i>para</i> -methoxyphenyl
ppm	parts per million
PPTS	pyridinium <i>para</i> -toluenesulfonate
Pr	propyl
py	pyridine
q	quartet
ref	reference
R <sub>f</sub>	retention factor
ROESY	rotating frame nuclear Overhauser effect spectroscopy

rt	room temperature
s	sec
s	singlet
s	strong
SAR	structure activity relationship
SEM	2-(trimethylsilyl)ethoxymethyl
SRB	sulforhadoamine B
str	stretch
<i>t</i>	<i>tert</i>
t	triplet
TBA	tetrabutylammonium
TBS	<i>tert</i> -butyldimethylsilyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	<i>para</i> -toluenesulfonyl
UV	ultraviolet
Vis	visible
w	weak

## **Chapter I.**

### **I. The Development of Epipolythiodiketopiperazine (ETP) Syntheses**

## Introduction and Background



**Figure 1.** Representative epipolythiodiketopiperazine alkaloids.

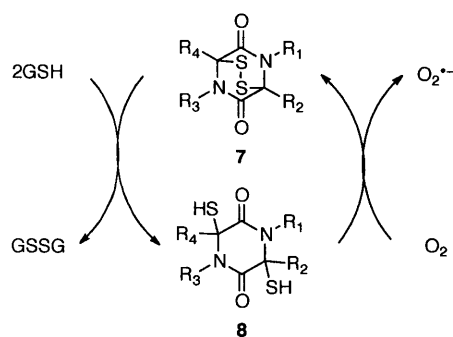
Epipolythiodiketopiperazine (ETP) alkaloids represent a structurally complex and biologically potent class of secondary fungal metabolites (Figure 1).<sup>1,2,3</sup> This class of compounds can be arranged in different categories, including monomeric, dimeric C3,C3' ( $sp^3-sp^3$ ) linked homo- and heterodimers, as well as C3-(3'-indolyl) derivatives (Figure 1). These molecules are all known to contain reactive bicyclic disulfide bonds that exhibit reactivity towards oxidants, reductants, UV light, as well as strong acids and bases.<sup>4</sup> Gliotoxin (1), a natural product that was first reported by Weindling in 1936 and was later synthesized by Kishi and coworkers in 1970, represents one of the earliest naturally occurring epidthiodiketopiperazines known.<sup>5,6</sup> The dimeric subset of these alkaloids have been known since the 1970s, with the discovery of (+)-chaetocin A (2), (+)-chaetocin C (3), and (+)-11,11'-dideoxyverticillin A (4).<sup>7,8</sup> The C3-(3'-indolyl) alkaloids such as (+)-bionectin A (5) exhibit significant cytotoxic activity against the murine P388 lymphocytic leukemia cell line.<sup>9-11</sup>

## Biological Activity of ETPs

Structure activity relationships (SAR) studies have shown the importance of the ETP motif in these molecules.<sup>12,13</sup> There are several known ways in which epidithiodiketopiperazines alkaloids are known to induce cytotoxicity. These methods include direct sulfidation of cysteine residues of proteins resulting in covalent deactivation of the protein, by the evolution of reactive oxygen species through redox cycling, and by the sequestration of zinc cations from proteins through the zinc-ejection mechanism.

Evidence that advances the hypothesis for the deactivation of enzymes through direct incorporation of the ETPs into proteins stems from toxicity studies of gliotoxin in thymocyte cells.<sup>12</sup> With concentrations of gliotoxin greater than 50  $\mu\text{M}$ , calcium influx in these cells had been observed and this was directly implicated in the toxicity of gliotoxin. The increase in calcium flux is known to be due to the interaction of gliotoxin with a thiol residue in the redox-sensitive plasma membrane calcium channel. The addition of glutathione or dithiothreitol was found to inhibit this activity since the reduced ETP is unable to oxidatively modify the thiol residues of proteins. This study provided evidence for mixed disulfide formation as a possible means for the necrotic effects of gliotoxin. Furthermore, gliotoxin was found to deactivate proteins such as alcohol dehydrogenase by forming a 1:1 covalent complex with cysteine residue 281 or 282.<sup>12</sup>

Redox cycling is another way in which these molecules can exhibit virulence towards bacterial cells (Figure 1).<sup>13-15</sup> This process was implicated as part of the toxic biological activity of sporidesmin and of other ETPs on erythrocytes, where the toxic



**Scheme 1.** ETP-catalyzed autoxidation of glutathione.

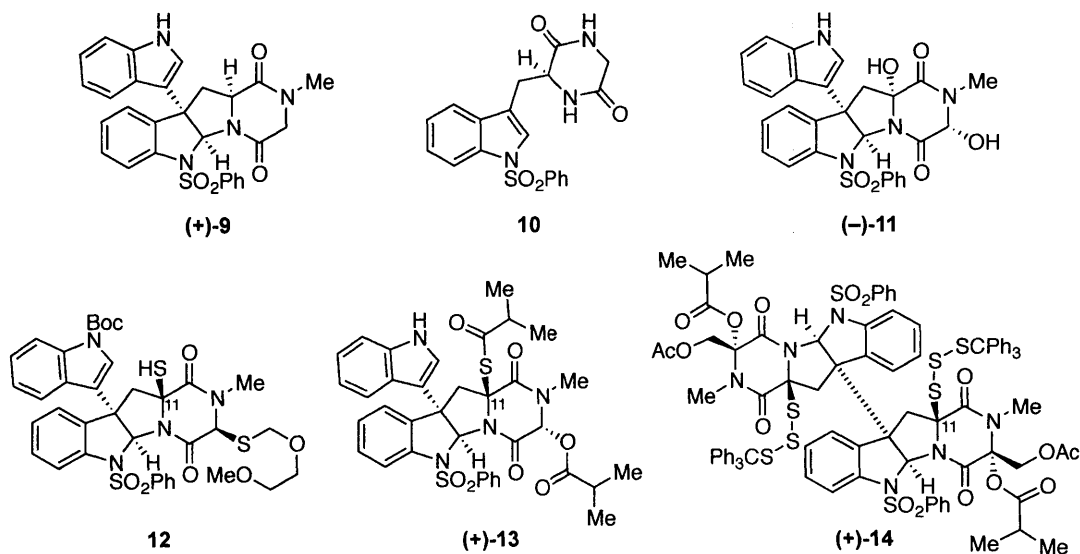
effects appear to be due the generation of reactive oxygen species.<sup>12</sup> The process involves the cycling between two alternative states of the ETP, from the oxidized, bicyclic form to the reduced, dithiol state. In biological environments, the disulfide bond of ETPs such as in **7**, is known to break when exposed to cofactors such as glutathione.<sup>16</sup> As the thiols of **8** cyclize to the closed form (**7**), an equivalent of the dimeric glutathione is reduced to two equivalents of glutathione, and reactive oxygen species (ROS) such as hydrogen peroxide and super oxide are generated by the ETP. These reactive oxygen species are thought to promote cell death through oxidative damage or cell signaling.<sup>17</sup>

Beyond the generation of harmful reactive oxygen species or the direct incorporation of ETPs to proteins, the third known mechanism of ETP-related toxicity has been linked to the sequestration of key cationic metals from critical proteins such as p300 in thymocyte cells.<sup>15</sup> These proteins are critical to the preservation of cells during episodes of hypoxia-related stress. ETPs were found to reversibly bind to the CH1 domain of these p300 proteins when reducing additives such as dithiothreitol (DDT) were added. The CH1 domain contains three key zinc cations, and when these active sites were exposed to ETPs such as gliotoxin (**1**), Zn ejection from the domain was observed. This observation suggested that the ETP can bind to the CH1 domain and coordinate to the



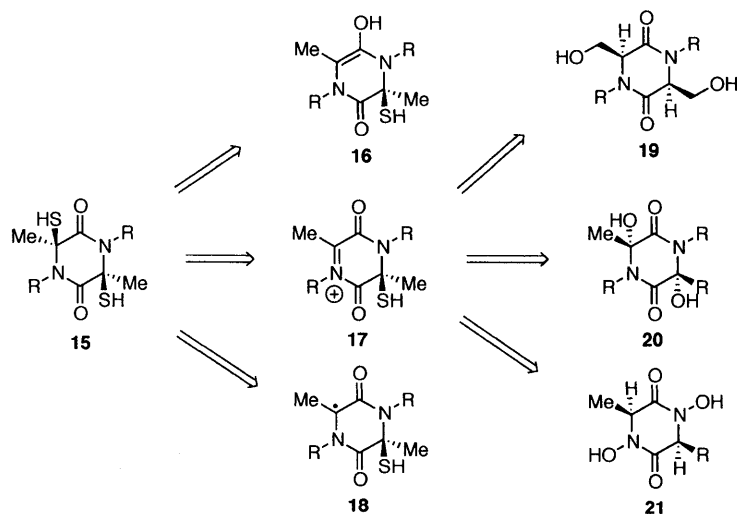
zinc cations, and in high enough concentrations, the ETP may form a stable complex with the zinc atoms; thereby disrupting the tertiary structure of the domain. This interaction has been found to severely impede the activity of these proteins.

**Figure 2.** ETP derivatives that lack cytotoxic effects.



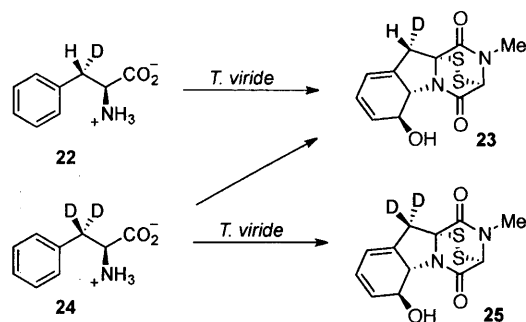
According to our own SAR studies, the ETP motif in these molecules is imperative for the anticancer biological activity against U-937 and HeLa cell lines.<sup>3a</sup> Based on the SAR studies of our prepared synthetic intermediates used in the preparation of ETP alkaloids, those intermediates possessing non-oxidized  $\alpha$ -positions such as diketopiperazine (+)-9, open diketopiperazines including 10, and  $\alpha$ -hydroxylated analogues such as (-)-11 result in a complete loss of biological activity against U-937 and HeLa cell lines (Figure 2).<sup>3</sup> Furthermore, the study demonstrated that sulfuration at only the tryptophan C- $\alpha$  position is not sufficient for potent activity as in the case of C11 monothiols 12, C11 thioester (+)-13, and open chain polysulfane derivatives (+)-14. This study, consistent with other reports on the activity of these compounds, suggests the need for the disulfide bond for anticancer activity.

## Biosynthesis of these compounds



**Scheme 2.** Three common modes for the synthesis of ETPs

When considering the mechanism of the sulfidation of these diketopiperazines, the introduction of sulfur at the *C*- $\alpha$ -positions of these diketopiperazines is believed to proceed through the generation of reactive acyl iminiums.<sup>18</sup> There are three pathways that are described for the biosynthetic formation of the disulfide functional group of ETPs. The biosynthetic routes for the incorporation of sulfur may be achieved through the protonation of the enamide derived from  $\beta$ -elimination (19),  $\alpha$ -elimination of the  $\alpha$ -hydroxyamino acid (20), or by elimination of the *N*-Hydroxylated amino acid (21) (Scheme 2).<sup>18</sup>

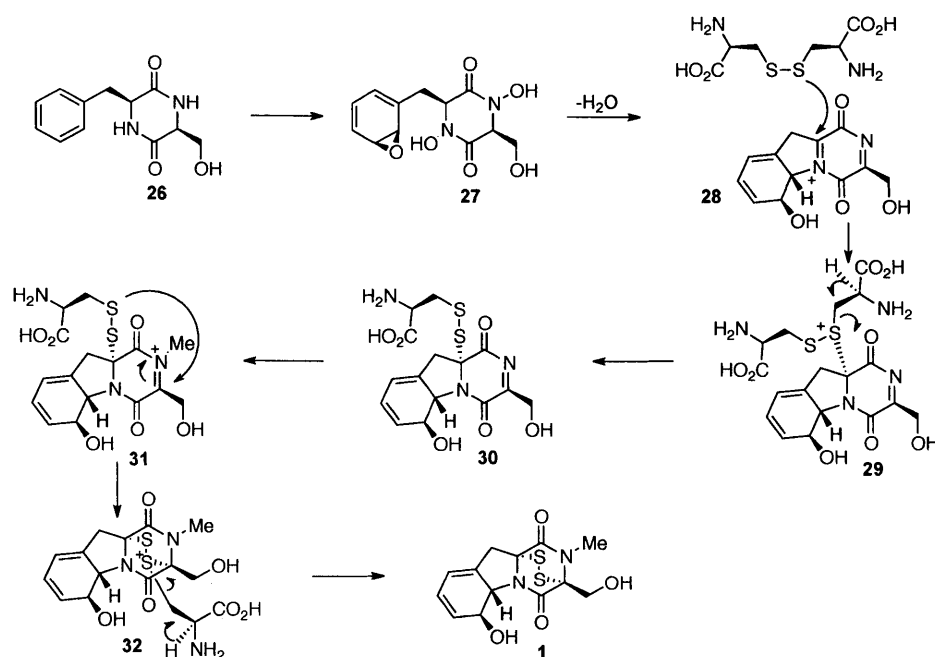


**Scheme 3.** Kirby's studies on the incorporation of *B*-deuterated phenylalanine into gliotoxin.

The possibility of acyl iminium formation resulting from protonation of the enamide is certainly possible given the existence of these intermediates in biological processes.<sup>19</sup> These enamide intermediates may arise by  $\beta$ -elimination of heteroatom linked amino acid residues such as cysteine, threonine, serine, etc. Despite the existence of these intermediates, feeding studies conducted by Kirby and coworkers suggests that the intermediate involved in the formation of the ETP may not involve the enamine (Scheme 3).<sup>20</sup> Exposing monodeutero- and dideuterophenyl alanine (**22** and **24**) to *T. viride* species of fungus resulted in the formation of monodeutero- (**23**) and dideuterogliotoxin (**25**) derivatives. Kirby had postulated that the benzylic proton exchange of **23** should be faster than its rate of incorporation into gliotoxin. The cofactor, pyridoxal, was implicated in proton/deuteron exchange at the methylene position. Furthermore, although the exchange of the isotopic label could be enzymatically driven, the process would not be necessary for the biosynthesis of gliotoxin. The formation of the dideuterogliotoxin (**25**) derivative among the reaction products greatly diminished the likelihood of the acyl iminium cation forming as a result of enamide protonation.

Having considered the enamide alternative, the acyl iminum could be hypothetically generated from elimination of the *C*-hydroxylated species (**20**) or the *N*-Hydroxylated intermediate (**21**). Ottenheijm and coworkers championed the hypothesis involving the elimination of the *N*-Hydroxyl group.<sup>18,21</sup> *N*-Hydroxylated natural compounds are also known as in the case of mycelianamide<sup>22</sup> and astechrome.<sup>23</sup>

Ottenheijm's biosynthetic proposal for the formation of gliotoxin begins with the L-phenylalanine/L-serine diketopiperazine **26** (Scheme 4).<sup>18</sup> The substrate subsequently



**Scheme 4.** Ottenheim's biosynthetic hypothesis for gliotoxin.

undergoes enzymatic oxidation to form the bis-*N,N*-dihydroxylated epoxide **27**. Dehydrative elimination of the *N*-Hydroxyl group, followed by cyclization generates iminium cation **28**. This electrophile is trapped by an equivalent of cystine, forming the intermediary sulfonium **29**.  $\beta$ -elimination from one of the cysteine residues would lead to mixed disulfide **30**. *N*-methylation of **30** leads to the formation of another acyl iminium cation, **31**, that undergoes nucleophilic trapping of the mixed disulfide to generate bicyclic sulfonium **32**. A final  $\beta$ -elimination of the sulfonium of **32** leads to the desired product, gliotoxin **1**.

Despite the precedence of *N*-Hydroxylated natural products, a closer examination of the dimeric and C3-(3'-indolyl) ETP alkaloids reveals that many of these compounds possess an *N*-methyl group.<sup>18</sup> Given the widespread presence of the *N*-alkylated variations of these natural products and of those which lack the disulfide bridge, it is plausible that the installation of sulfur at the  $\alpha$ -positions takes place after *N*-methylation.

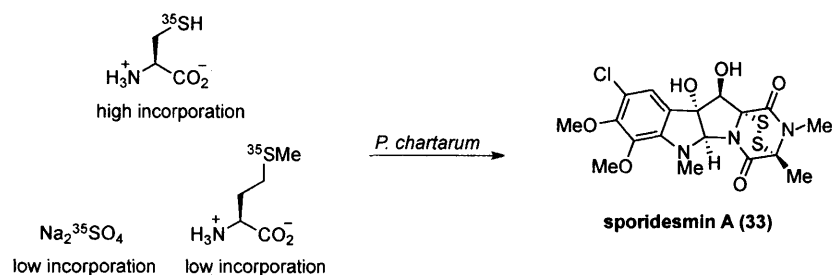
Such a hypothesis is inconsistent with Ottenheijm's biosynthetic proposal, which would require the involvement of non *N*-alkylated substrates.

Support for our proposal involving *C*- $\alpha$ -hydroxylated intermediates (such as **20**) as biosynthetic precursors for the ETP is further substantiated by the existence of natural products such as (+)-WIN 64821<sup>24</sup> and (-)-ditryptophenaline.<sup>25</sup> Although a biosynthetic lineage of these compounds to related ETPs has yet to be proven, it is possible for the installation of sulfur to be late stage. If indeed the ETP were formed at a late stage, such a transformation would rely on the *C*- $\alpha$ -hydroxylated intermediate for accessing the acyl iminium cation. Further support for the late stage installation of sulfur can be gathered when considering the biosynthetic mechanism involved in the dimerization of cyclotryptamine compounds. For natural products such as (-)-chimonanthine, single electron oxidation of the indole substructure in tryptamine is necessary for the dimerization of these molecules; a process that may be incompatible with the presence of the redox sensitive disulfide bond.<sup>18</sup>

The *C*- $\alpha$ -hydroxylated precursor to the acyl iminium cation seemed the most likely intermediate, and such reactive intermediates are known as in the biosynthesis of ergotamine.<sup>18,26</sup> We have conjectured in our biosynthetic proposal for these ETPs that the oxidation of the *C*- $\alpha$ -centers can be accomplished by oxidative enzymes such as P450 monooxygenases. Evidence supporting this hypothesis can be found from experiments conducted by Howlett and coworkers, whose biogenetic studies elucidated the genes involved in the synthesis of these of sporidesmin PL and gliotoxin.<sup>27</sup> In her gene knockout and mutation studies, Howlett had identified biosynthetic gene clusters that were critical to the production of proteins responsible for the modification of the side

chains in the epidithiodiketopiperazine substructure. Furthermore, he had determined that a number of gene products involved in the biosynthetic pathways of sporidesmin PL and gliotoxin bore sequence homology to key enzymes such as P450 monooxygenase, zinc finger transcriptional regulator, dipeptidase, etc.<sup>18,27</sup>

When considering other structural elements of sporidesmin A, components such as the sulfur bridge and the *N*-methyl group were found to be traced to isotopically labeled feedstocks.<sup>28</sup> The metabolic processing of *S*-<sup>14</sup>CH<sub>3</sub> methionine by *P. chartarum* led to formation of *N*-<sup>14</sup>CH<sub>3</sub> sporidesmin A. Furthermore, experiments conducted by Towers and Wright suggests that the source of sulfur may be cysteine.<sup>18, 28</sup> Although isotopic labeling studies had shown inorganic sulfur and methionine to be competent contributors of <sup>14</sup>S labeled sulfur atoms, L-cysteine-<sup>35</sup>S was shown to contribute the highest levels of <sup>35</sup>S incorporated sporidesmin A (**33**) (Scheme 5).<sup>18</sup> The cofactor, pyridoxal, was implicated in the transfer of sulfur. For the formation of the disulfide bond, the presumption is that the bond formation takes place spontaneously in the presence of oxygen.

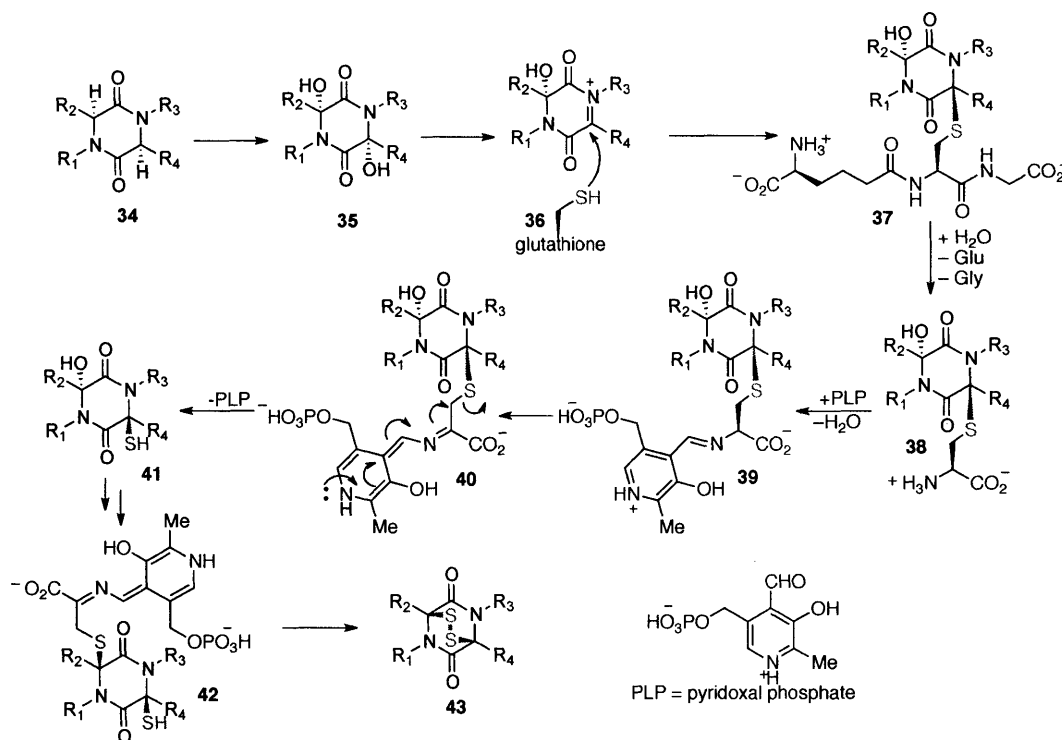


**Scheme 5.** Kirby's studies on the incorporation of b-deuterated phenylalanine into gliotoxin.

## Our Hypothesis for ETP Biogenesis

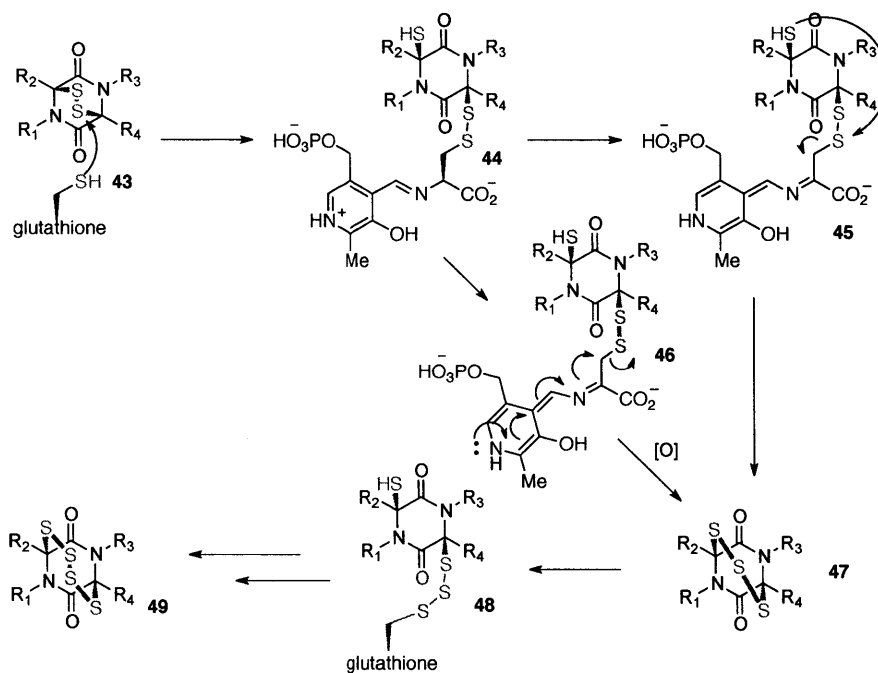
Based on our own biosynthetic hypothesis, which was later corroborated by Hertweck and coworkers in 2014,<sup>27c</sup> it is believed that the installation of sulfur of the

ETPs involves the addition of nucleophilic sulfur onto an acyl iminum species (Scheme 6).<sup>3d</sup> Diketopiperazine **34** may undergo dihydroxylation at the  $\alpha$ -positions to form diketopiperazine diol **35**. Ionization of the  $\alpha$ -hydroxylated species forms the acyl iminum **36**, which may undergo nucleophilic attack from the thiol of glutathione to form



**Scheme 6.** Our unifying biosynthetic proposal for the incorporation of sulfur in ETP alkaloids. The glutathione-linked intermediate **37**. Subsequent hydrolysis of the L-glutamine and L-glycine residues of the glutathione-ETP intermediate leads to the formation of the cysteine-linked diketopiperazine **38**. The removal of the bound cysteine residue could be achieved by its interaction with the cofactor, pyridoxal phosphate (PLP). The free amine of the cysteine-bound ETP adds to the aldehyde functional group of the PLP cofactor, resulting in condensation and formation of the corresponding imine **39**. The protonated pyridinium acts as an electron sink, which allows for the tautomerization of the imine to generate exocyclic enamine **40**. Enamine **40** can expel the bound diketopiperazine-

thiolate leading to form hydroxythiol **41**. After a second round of these transformations at the other  $\alpha$ -position to produce iminothiol **42**, a transient dithiol is formed and undergoes oxidative cyclization to form epidithiodiketopiperazine **43**.



**Scheme 7.** Our unifying biosynthetic proposal for the incorporation of sulfur in higher order ETP alkaloids.

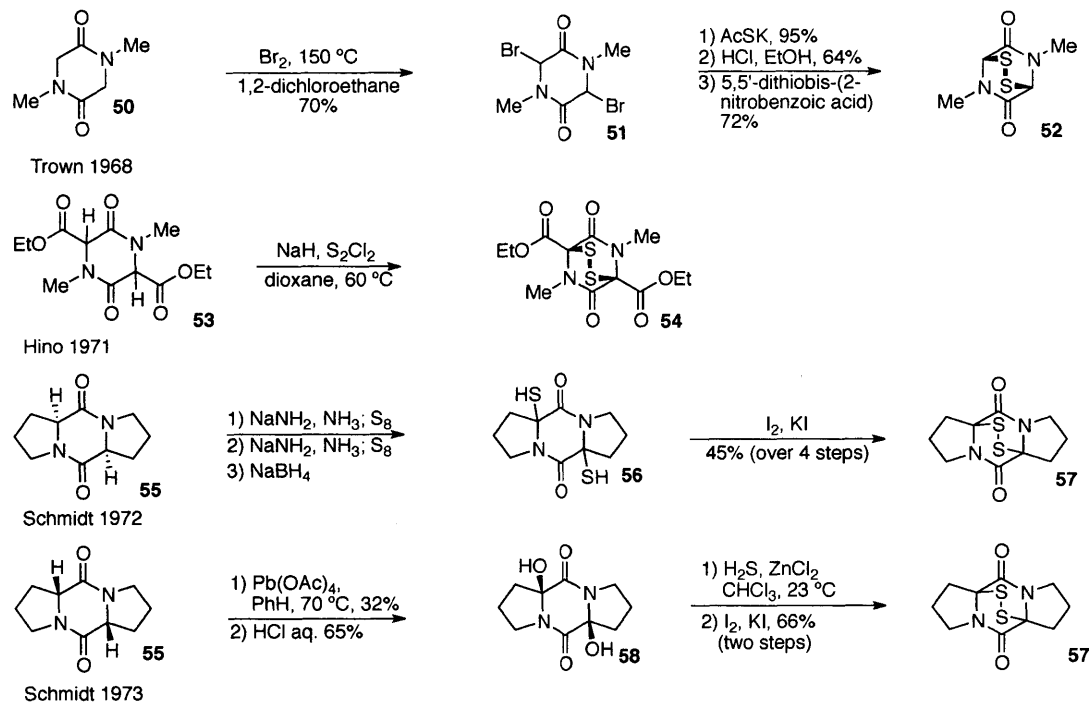
Furthermore, higher order polysulfane derivatives can be produced in a similar fashion, starting from the epidithiodiketopiperazine (**43**) (Scheme 7).<sup>3d,4</sup> Our proposed biosynthetic pathway involves the addition of a second equivalent of a glutathione nucleophile to the diketopiperazine disulfide bond of **43** to form intermediate thiol **44**. The epitritiodiketopiperazine substrate (**47**) can be accessed in two different ways. One of which involves the imine tautomerization of the PLP-linked thiol (**46**) to form the enamine functionality needed to expel the disulfide of **46** that leads to epitritiodiektopiperazine **47** after oxidation. The second mechanism can be described as an intramolecular nucleophilic attack of the disulfide by the free C- $\alpha$  thiol in **45** to



directly lead to **47**. Further sulfurations of the polysulfide bridge would be achieved through this iterative process, thus leading to epitetrathiodiketopiperazine **49**.

### Methods for Accessing ETPs

**Scheme 8.** Prior synthetic approaches to the epidithiodiketopiperazine substructure



Scheme 8 shows representative methods for accessing the epidithiodiketopiperazine functional group.<sup>27c,28</sup> One of the earliest methods for the synthesis of ETPs originates from Trown and coworkers in 1968.<sup>29</sup> After bromination of the  $\alpha$ -positions of sarcosine anhydride **50** with bromine and heating in dichloroethane to 150 °C, direct displacement of the secondary bromide of  $\alpha$ -positions of **51** with thioacetate led to the formation of the bis-thioacetic ester intermediate in 95% yield. Following this step, the acetyl groups of the thioesters were cleaved with a solution of hydrochloric acid in ethanol, and the intermediate dithiol was treated with 5,5'-dithiobis-(2-nitrobenzoic acid). This oxidation led to the formation of the desired bis-sarcosine

ETP **52** in 72% yield. The *syn* substitution for these thiols is required in order for successful oxidation to the disulfide.

Furthermore, other methods for accessing these ETPs have included deprotonation of the *C*- $\alpha$ -positions of **53** with sodium hydride and trapping the enolate with an electrophilic sulfur source as demonstrated by Hino in 1971.<sup>30</sup> The intramolecular trapping of the sulfenyl chloride to produce ETP **54** precludes the use of oxidants for forming the disulfide bond. This method also helped to enhance the *syn* diastereoselectivity of the sulfidation of the *C*- $\alpha$  positions. Use of elemental/monoclinic sulfur to synthesize ETPs was first reported by Schmidt in 1972.<sup>31</sup> Repeated treatments to these sulfidation conditions were necessary for the double incorporation of sulfur at the *C*- $\alpha$  positions. A separate oxidation step, with *in situ* generated potassium triiodide from iodine and potassium iodide, was necessary to form the desired bicycle **57** in 45% over 4 steps.

One of the earliest examples of forming ETPs through the use of Lewis Acids and hydrogen sulfide was executed by Schmidt in 1973.<sup>31</sup> Radical oxidation of the *C*- $\alpha$  positions of **55** with lead tetraacetate in benzene at 70 °C, followed by hydrolysis of the corresponding *C*- $\alpha$  acetate esters led to the formation of diol **58**. Ionization of these tertiary alcohols was achieved by using zinc dichloride, and the resulting acyl iminium cations were trapped by a hydrogen sulfide. Potassium triiodide oxidation of the bithiols led to the formation of **57** in 66% yield. Furthermore, future advances in the synthesis of ETPs centered on the trapping of acyl iminium cations generated by non-alcohol leaving groups as shown by Matsunari in 1975 (Scheme 9).<sup>32</sup> Treatment of diketopiperazine **59** with NBS and AIBN



led to radical bromination of the *C*- $\alpha$  centers. This was followed by exposure to sodium acetate in methanol produced the *C*- $\alpha$  bisdimethoxy intermediate **60** in 66% yield. After reduction of the bromides with tributyltin hydride and AIBN, the dimethoxydiketopiperazine was sequentially treated with zinc dichloride and hydrogen sulfide and was followed by oxidation with potassium triiodide to afford the desired ETP **61** in 18% yield over three steps. In the same year, Ottenheim had reported a case where activation of the *C*- $\alpha$  centers could be achieved by the synthesis of diketopiperazine substrates through the use of  $\alpha$ -ketoacid chlorides.<sup>33</sup> Exposure of indoline amide **62** to 2-oxo-propanoyl chloride afforded chloro-hydroxy diketopiperazine **63**. Treatment of **63** with zinc dichloride and hydrogen sulfide, followed by molecular oxygen generated the desired indoline ETP **64** in 37% yield over three steps. Overman's 2007 report for the synthesis of ETP **67** illustrates another method that involves oxidation of the  $\alpha$ -positions through esterification.<sup>34</sup> Radical oxidation of intermediate **65** with copper diacetate and AIBN afforded silyl ether **67** in 73% yield. After converting the TMS silyl ether to the acetate in high yield, scandium triflate promoted ionization of the acetate groups and trapping with hydrogen sulfide produced the corresponding bithiol, which was exposed to molecular oxygen to afford **67** in 37% over two steps.

Use of thiol nucleophiles to trap acyl iminium cations was shown to be possible in more advanced systems as demonstrated by Movassaghi and coworkers in 2009. The report had shown the utility of trithiocarbonate diketopiperazine adducts as precursors to the ETP in the total synthesis of 11,11'-dideoxyverticillin A.<sup>4</sup> Use of this dithiol nucleophile was intended to maximize the diastereoselectivity of the sulfidation step. Treatment diol **68** with potassium trithiocarbonate with TFA led to the formation of the

bistrithiocarbonate adduct **69** in 56% yield. Mild aminolysis of the trithiocarbonates was executed with the addition of ethanolamine, and the subsequent titration of the reaction mixture with potassium triiodide gave (+)-11,11'-dideoxyverticillin (**70**) in 62% yield.

In the synthesis of (+)-chaetocin A (**72**), a different set of synthetic challenges related to differences in ionization potential of the analogous tertiary alcohols prompted the search for other complimentary sulfidation methods. These differences in ionizing ability of these tertiary alcohols stemmed from the presence of neighboring heteroatoms, thus slowing the rate of ionization due to inductive effects. As a result, a new systematic approach was developed to address the syntheses of ETPs such as (+)-chaetocin A (**72**).<sup>3d</sup> The dimeric bisdisulfide **71** was found to cyclize upon exposure to Lewis acids such as  $\text{BF}_3 \cdot \text{OEt}_2$  with dichloromethane in 82%. Methanolysis of the alcohols was achieved using Otera's catalyst in methanol and toluene at 85 °C, which afforded the natural product (**72**) in 92% yield. The utility of this method was further revealed in its application to the syntheses of higher order ETPs such as (+)-chaetocin C and (+)-12,12'-dideoxytetracin A.<sup>3d</sup>

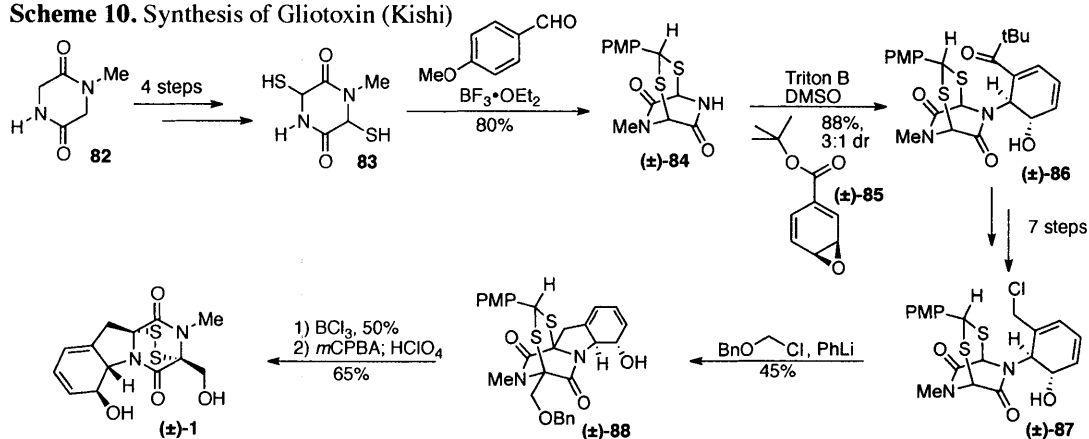
In 2012, Nicolaou had applied Schmidt's method of using monoclinic sulfur and strong bases such as sodium bis(trimethylsilyl)amide (NaHMDS) to convert bis-L-phenylalanine diketopiperazine **73** to tetrasulfide **74**.<sup>35</sup> Reduction of this higher order polysulfane (**74**) with sodium borohydride, followed by treatment with potassium triiodide produced the desired ETP **75** in 72%. Furthermore, acyclic ETP precursors such as **76** may undergo cyclization and thiolation in a one pot procedure as delineated by Hilton in 2013.<sup>36</sup> Treatment of diacetate **76** with benzylamine and 4-methoxy- $\alpha$ -toluenethiol (PMBSH) and 4-*N,N*-dimethylaminopyridine (DMAP) was shown to

produce bis-*para*-methoxybenzyl disulfide **77** in 68% yield. Cleavage of the two thioethers with boron tribromide at  $-78\text{ }^{\circ}\text{C}$ , followed by exposure to iodine at  $23\text{ }^{\circ}\text{C}$  produced the desired ETP **78** in 85% yield.

Furthermore, Movassaghi and coworkers had developed another method of synthesizing ETPs through a highly diastereoselective bissulfidation strategy.<sup>3e</sup> In the synthesis of (+)-bionectin A, advanced intermediate (+)-**79** was found to undergo a diastereoselective double sulfidation when treated with 4-mercapto-2-butanone and TFA, with concomitant loss of the BOC protecting groups on the N'1 and C12 positions. This produced the desired bithioether major product **80** in 80% yield as a 3:1 mixture of diastereomers. The desired adduct was isolated after the photoinduced deprotection of the benzenesulfonyl protecting group, which afforded the penultimate bithioether intermediate (**80**) in 56% yield. Mild unraveling of these thioethers with pyrrolidine in the presence of ethanethiol produced (+)-bionectin A (**81**) in 81% yield.

### Representative Synthesis of ETP natural products

**Scheme 10.** Synthesis of Gliotoxin (Kishi)

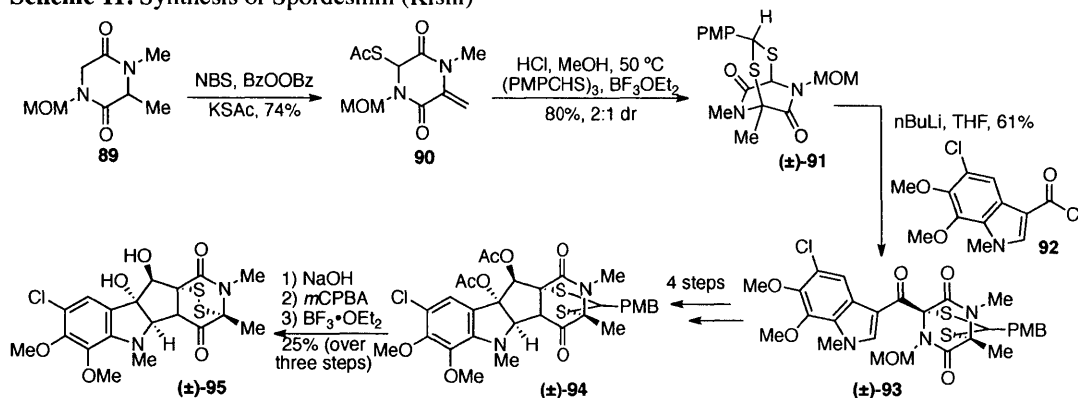


Over the course of the early 1970s, Kishi and coworkers were able to complete the total syntheses of a number of epidithiodiketopiperazine alkaloids.<sup>28</sup> Example

syntheses include gliotoxin, sporodesmin<sup>37</sup> and hyalodendrin.<sup>38</sup> For the total syntheses of these natural products, Kishi's strategy involved the early installation of sulfur at the C- $\alpha$ -positions as a protected thiol ketal, followed by subsequent alkylation steps for further elaboration at the bridgehead carbons. This thioketal protecting group effectively enabled the sulfur functionality to be carried over many steps. The thiols were deprotected at a late stage and were oxidized to form the desired disulfide bond.

For Kishi's gliotoxin synthesis, the sarcosine-glycine derived diketopiperazine **82** was elaborated using the method first developed by Trown and coworkers (Scheme 10).<sup>28</sup> After accessing the dithioacetal ( $\pm$ )-**84** through the thioketalization of **83** with anisaldehyde and  $\text{BF}_3 \cdot \text{OEt}_2$ , the compound was treated with Triton B and epoxide ( $\pm$ )-**85** in DMSO, which resulted in the formation of *N*-alkylated intermediate ( $\pm$ )-**86**. Further synthetic steps led to the formation of benzylic chloride ( $\pm$ )-**87**, which was cyclized via bridgehead deprotonation with phenyl lithium, followed by intramolecular displacement of the benzylic chloride and bridgehead alkylation with benzyl chloromethyl ether (BOMCl) to form intermediate ( $\pm$ )-**88** in 45% yield. Deprotection of the benzyl ether of ( $\pm$ )-**88** with boron trichloride, followed oxidative deprotection of the *para*-methoxyphenyl (PMP) group with *m*CPBA in perchloric acid furnished ( $\pm$ )-gliotoxin (**1**)

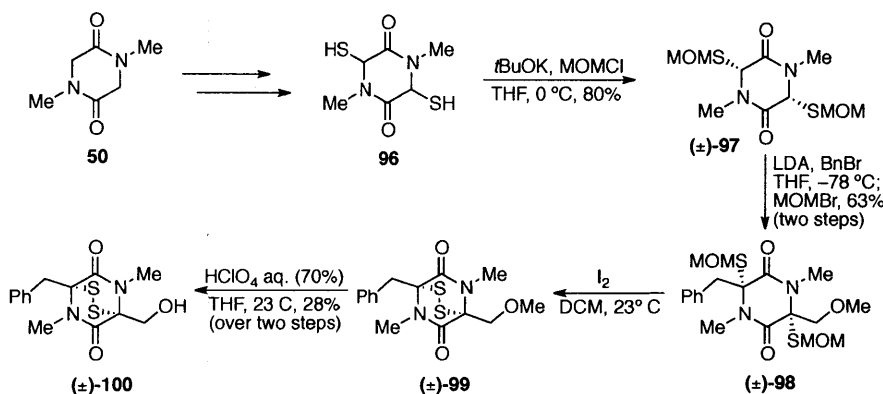
**Scheme 11.** Synthesis of Sporodesmin (Kishi)



in 65% yield.

For the synthesis of sporodesmin, Kishi's synthesis commenced with the thiolation of diketopiperazine **89** (Scheme 11).<sup>37</sup> Radical bromination of the  $\alpha$ -centers with NBS was followed by elimination and  $S_N2$  displacement with potassium thioacetate to afford intermediate **90** in 74% yield. Methanolysis of the thioester with catalytic hydrochloric acid, followed by treatment with boron trifluoride diethyletherate and trapping of the acyl iminium with anisaldehyde dithioacetal trimer led to the formation of PMP protected disulfide ( $\pm$ )-**91** in 80% yield as a 2:1 mixture of diastereomers. After the installation of the  $C$ - $\alpha$ -sulfur groups, intermediate ( $\pm$ )-**91** was treated with *n*BuLi and acid chloride **92**. This coupling reaction led to the formation of ( $\pm$ )-**93** in 61% yield. After further elaborations, tetracyclic diacetate ( $\pm$ )-**94** was treated with sodium hydroxide to hydrolyze the acetyl groups. The protected thiols were released upon addition of *m*CPBA and  $BF_3 \cdot OEt_2$ , which ultimately afforded sporodesmin ( $\pm$ )-**95** in 25% yield over three steps.

**Scheme 12.** Synthesis of Hyalodendrin (Kishi)

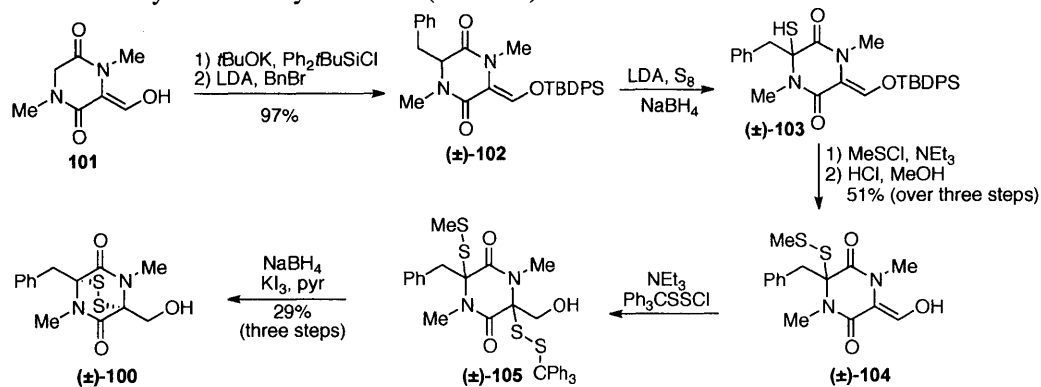


In Kishi's hyalodendrin synthesis, a similar early stage installation of the sulfur functionality at the  $C$ - $\alpha$  positions was adopted, with the thiols protected as bithioethers (Scheme 12).<sup>38</sup> Dithiol **96** was prepared from sarcosine anhydride **50** using Trown's



methodology.<sup>29</sup> The thiols of **96** were protected as the bishioethers through treatment with potassium *tert*-butoxide and chloromethyl methyl ether to form the Bis-MOM protected dithioether ( $\pm$ )-**97** in 80% yield. Subsequent alkylation steps were performed with exposure of ( $\pm$ )-**97** to 2 equivalents of LDA, which was followed by treatment with benzyl bromide and bromomethyl methyl ether to produce the *syn*-dialkylated intermediate ( $\pm$ )-**98**. Deprotection of the bishioether group of ( $\pm$ )-**98** involved oxidative unraveling with iodine, followed by exposure to perchloric acid to hydrolyze the methoxy group. These steps afforded the desired natural product ( $\pm$ )-**100** in 28% over two steps.

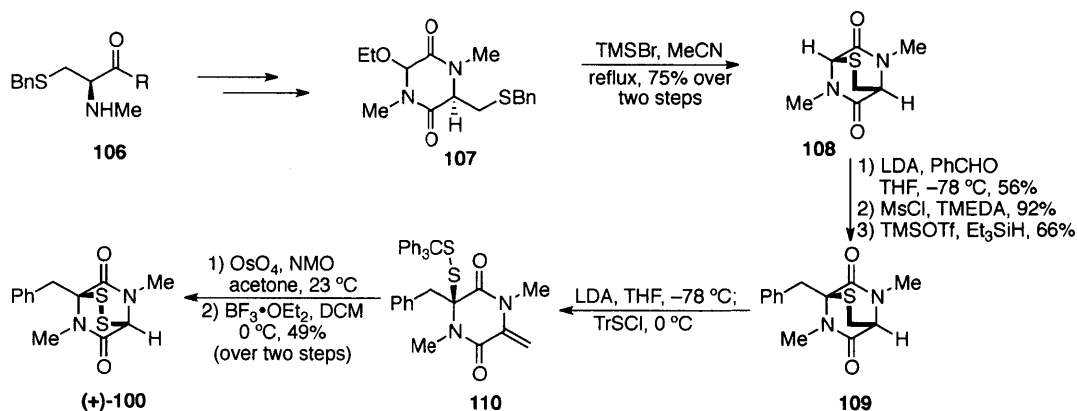
**Scheme 13.** Synthesis of Hyalodendrin (Rastetter)



Furthermore, Rastetter and coworkers had made contributions to ETP total synthesis (Scheme 13). The synthesis of ( $\pm$ )-hyalodendrin by Rastetter in 1980, as opposed to the syntheses conducted by Kishi and coworkers, features a late stage installation of sulfur at the  $\alpha$ -positions that was followed by diketopiperazine alkylation.<sup>39</sup> This total synthesis was one of the first to employ acyclic disulfides as precursors to the ETP. Starting with enol **101**, protection of the enol alcohol with *tert*-butyldiphenylchlorosilane (TBDPSCI), followed by benzylation of the other  $\alpha$ -center with benzyl bromide and LDA produced silyl ether ( $\pm$ )-**102** in 97% yield. After sulfur incorporation to produce thiol ( $\pm$ )-**103** in a manner akin to Schmidt's sulfidation

methodology, further elaborations to construct the mixed disulfide of ( $\pm$ )-**104** involved treating ( $\pm$ )-**103** with triethylamine, followed by the addition of methyl sulfonyl chloride. Methanolysis of the silylenol ether of this intermediate afforded ( $\pm$ )-**104** in 51% yield over the three-step process. The formation of the mixed trityl disulfide ( $\pm$ )-**105** was achieved in a similar fashion, with exposure of ( $\pm$ )-**104** to triethylamine and trityldisulfonyl chloride. Both disulfides were reductively cleaved with sodium borohydride to generate the *in situ* unprotected dithiols, which were oxidized to afford ( $\pm$ )-hyalodendrin (**100**) in 29% yield over the three steps.

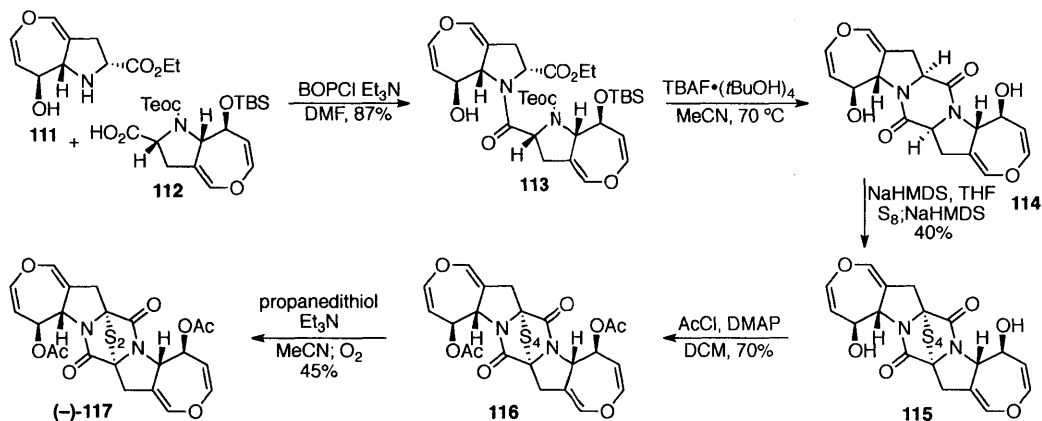
**Scheme 14.** Synthesis of (+)-hyalodendrin (Fukuyama)



In 2014, Fukuyama and coworkers had reported a synthesis of (+)-hyalodendrin that was similar to Kishi's total synthesis in that it relies on the incorporation of sulfur at an early stage (Scheme 14).<sup>40</sup> Critical to this synthesis was the polysulfane cyclization methodology developed in our laboratory for the synthesis of more complex ETPs.<sup>3d</sup> In this route, L-cysteine derivative **106** was further elaborated into diketopiperazine **107**. Treatment of **107** with trimethylsilyl bromide (TMSBr) in refluxing acetonitrile generated the cyclized, monoprotected C- $\alpha$  sulfide **108**. Alkylation of intermediate **108** was conducted using benzaldehyde and LDA at  $-78$  °C in 56% yield. The resulting secondary

benzylic alcohol was efficiently mesylated and was reduced using trimethylsilyl triflate (TMSOTf) and triethyl silane as the reductant, which led to the formation of bicycle **109** in 66% yield. The exocyclic olefin in **110** was produced through elimination of the sulfide with LDA and the resulting thiolate was treated with tritylsulfenyl chloride to generate the mixed trityldisulfide **110**. This enamide double bond underwent dihydroxylation with Upjohn's conditions and the resulting trityl disulfide was cyclized with  $\text{BF}_3 \cdot \text{OEt}_2$  at 0 °C to afford the desired (+)-hyalodendrin (**100**) in 49% over two steps.

**Scheme 15.** Synthesis of (–)-Acetylaranotin (Reisman)



Reisman's synthesis of (–)-acetylaranotin represents the utility of installing sulfur groups at the *C*- $\alpha$  positions with the use of diketopiperazine enolates and trapping with electrophilic sulfur (Scheme 15).<sup>41</sup> Few synthetic strategies involve late stage sulfur incorporation with harsh basic conditions in complex molecular settings as in this case. The synthesis involved the coupling of amine **111** and carboxylic acid **112** with *N,N'*-bis(2-oxo-3-oxazolidinyl) phosphinic chloride (BOPCl) to produce amide **113** in 87% yield. Cleavage of the TBS silyl ether and of the Teoc group with TBAF in acetonitrile, followed by heating to 70 °C led to the formation of diketopiperazine diol **114**. Exposure of diol **114** to NaHMDS and monoclinic sulfur, followed by the addition of more

NaHMDS led to the formation of tetrasulfide **115** in moderate yield. The remaining steps involved acetylation of the secondary allylic alcohols with acetyl chloride and DMAP in 70% yield, followed by sequential treatment with propanedithiol and molecular oxygen under basic conditions. These last steps afforded the natural product (–)-**117** in 45% yield.

## Conclusion

The characterization of epipolythiodiketopiperazines has had a rich history that extends back to the early 20<sup>th</sup> century.<sup>5</sup> ETPs display cytotoxic activity in ways that involve the direct sulfidation of protein residues, the formation of reactive oxygen species, and through the sequestration of metals from enzymes. Such activity is thought to be possessed in higher order ETP containing natural products as well. These compounds display a wide variety of biological activity, including antibacterial, anticancer, antiviral, and antiparasitic activity. The earliest syntheses to be completed for these compounds were completed in the 1970s and 1980s from Kishi, Rastetter and others. The early methods of the syntheses of ETPs involved the use of strongly basic conditions and electrophilic sulfur sources to generate the ETP. This approach to the synthesis of ETPs could best be achieved using simple diketopiperazine scaffolds, although there are known syntheses that have been able to use this strategy in complex systems, as in the case of Reisman's synthesis of (–)-Acetylaranotin. More developments have highlighted the biomimetic approach of using acidic conditions and nucleophilic thiols to install the sulfur functional groups that would serve as precursors to the ETP. When addressing complex syntheses of these compounds, careful retrosynthetic planning

is necessary to access these molecules given their inherent sensitivity to a number of reaction conditions.

#### References for the first chapter:

1. **For reviews on cyclotryptophan and cyclotryptamine alkaloids**, see: Anthoni, U.; Christophersen, C.; Nielsen, P. H. in *Alkaloids: Chemical and Biological Perspectives*, ed. S. W. Pelletier, Pergamon Press, London, 1999, vol. 13, ch. 2, pp. 163–236; T. Hino and M. Nakagawa, in *The Alkaloids: Chemistry and Pharmacology*, ed. A. Brossi, Academic Press, New York, 1989, vol. 34, ch. 1, pp. 1–75.
2. **For select reports on epipolythiodiketopiperazines**, see: (a) Jordan, T. W.; Cordiner, S. J. *Trends Pharmacol. Sci.*, **1987**, *8*, 144. (b) Waring, P.; Eichner, R. D.; Mullbacher, A. *Med. Res. Rev.* **1988**, *8*, 499. (c) Gardiner, D. M.; Waring, P.; Howlett, B. J. *Microbiology*, **2005**, *151*, 1021. (d) Patron, N. J.; Waller, R. F.; Cozijnsen, A. J.; Straney, D. C.; Gardiner, D. M.; Nierman, W. C.; Howlett, B. J. *BMC Evol. Biol.*, **2007**, *7*, 174. (e) Huang, R.; Zhou, X.; Xu, T.; Yang, X.; Liu, Y. *Chem. Biodiversity*, **2010**, *7*, 2809. (f) Iwasa, E.; Hamashima Y.; Sodeoka, M. *Isr. J. Chem.*, **2011**, *51*, 420.
3. (a) Boyer, N.; Morrison, K. C.; Kim, J.; Hergenrother, P. J.; Movassaghi M. *Chem. Sci.*, **2013**, *4*, 1646. (b) DeLorbe, J. E.; Horne, D.; Jove, R.; Mennen, S. M.; Nam, S.; Zhang, F.L.; Overman, L. E. *J. Am. Chem. Soc.* **2013**, *135*, 4117. (c) Kim, J.; Ashenurst, J. A.; Movassaghi, M. *Science*, **2009**, *324*, 238. (d) Kim, K.; Movassaghi, M. *J. Am. Chem. Soc.* **2010**, *132*, 14376. (e) Coste, A.; Kim, J.; Adams, T. C.; Movassaghi, M. *Chem. Sci.* **2013**, *4*, 3191; (f) Boyer, N.; Movassaghi, M. *Chem. Sci.* **2012**, *3*, 1798; and references cited in these reports.
4. Kim, J.; Ashenurst, J. A.; Movassaghi, M. *Science*, **2009**, *324*, 238.

5. Weindling, R.; Emerson, O. H. *Phytopathology*, **1936**, 26, 1068.
6. Fukuyama, T.; Kishi, Y. *J. Am. Chem. Soc.* **1976**, 98, 6723.
7. Hauser, D.; Weber, H. P.; Sigg, H. P. *Helv. Chim. Acta* **1979**, 53, 1061.
8. Katagiri, K.; Sato, K.; Hayakawa, S.; Matsushima, T.; Minato, H. *J. Antibiot.* (Tokyo) **1970**, 23, 420.
9. Zheng, C. J.; Kim, C. J.; Bae, K. S.; Kim, Y. H.; Kim, W. G. *J. Nat. Prod.* **2006**, 69, 1816.
10. Dong, J. Y.; He, H. P.; Shen, Y. M.; Zhang, K. Q. *J. Nat. Prod.* **2005**, 68, 1510.
11. Usami, Y.; Yamaguchi, J.; Numata, A. *Heterocycles*, **2004**, 63, 1123.
12. Gardiner, D. M.; Waring, P.; Howlett, B. J. *Microbiology*, **2005**, 151, 1021.
13. Kwon-Chung, K. J.; Sugui, J. A.; *Med. Mycol.* **2009**, 47, S97.
14. (a) Munday, R. *Chem.-Biol. Interact.* **1982**, 41, 361. (b) Munday, R. *J. Appl. Toxicol.* **1987**, 7, 17. (c) Chai, C. L. L.; Heath, G. A.; Buleatt, P. B.; O'Shea, G. A. *J. Chem. Soc. Perkin Trans. 2*, **1999**, 389. (d) Chai, C. L. L.; Waring, P. *Redox Rep.* **2000**, 5, 257. (e) Scharf, D. H.; Remme, N.; Heinekamp, T.; Hortschansky, P.; Brakhage, A. A.; Hertweck, C. *J. Am. Chem. Soc.* **2010**, 132, 10136.
15. Iwasa, E.; Hamashima, Y.; Sodeoka, M. *Isr. J. Chem.* **2011**, 51, 420.
16. (a) Jordan, T. W.; Pederson, J. S. *J. Cell Sci.* **1986**, 85, 33 (b) Bernardo, P. H.; Brasch, N.; Chai, C. L. L.; Waring, P. *J. Biol. Chem.* **2003**, 278, 46549.
17. Waring, P.; Mamchak, A.; Khan, T.; Sjaarda, A.; Sutton, P. *Cell Death Differ.* **1995**, 2, 201.
18. Kim, J.; Movassaghi, M. *Chem. Soc. Rev.* **2009**, 38, 3035.
19. Bycroft, B. W. *Nature* **1969**, 224, 595.

20. Johns, N.; Kirby, G. W.; Bu'Lock, J. D.; Ryles, A. P. *J. Chem. Soc., Perkin Trans. I* **1975**, 383.
21. Hercheid, J. D. M.; Nivad, R. J. F.; Tijhuis, M. W.; Ottenheijm, H. C. J. *J. Org. Chem.* **1980**, *45*, 1885.
22. Oxford, A. E.; Raistrick H. *Biochemical Journal* **1947**, *42*, 323.
23. Arai, K.; Sato, S.; Shimizu, S.; Keiicki, N.; Yamamoto, Y. *Chem. Pharm. Bull.* **1981**, *29*, 1510.
24. Barrow, C. J.; Cai, P.; Snyder, J. K.; Sedlock, D. M.; Sun, H. H.; Cooper, R. *J. Org. Chem.* **1993**, *58*, 6016.
25. Nakagawa, M.; Sugumi, H.; Kodato, S.; Hino, T. *Tetrahedron Letters*, **1981**, *22*, 5323.
26. Quigley, F. R.; Floss, H. G. *J. Org. Chem.* **1981**, *46*, 464.
27. (a) Fox, E. M.; Howlett, B. J.; *Mycol. Res.* **2008**, *112*, 162. (b) Gardiner, D. M.; Howlett, B. J. *FEMS Microbiol. Lett.* **2005**, *248*, 241. (c) Scharf, D. H.; Habel, A.; Heinekamp, T.; Brakhage, A. A.; Hertweck, C. *J. Am. Chem. Soc.* **2014**, *136*, 11674.
28. Towers, N. R.; Wright, D. E. *N. Z. J. Agric. Res.* **1969**, *12*, 275.
28. Kim, J. PhD. Dissertation, Massachusetts Institute of Technology, 2013.
29. Trown, P. W. *Biochem. Biophys. Res. Commun.* **1968**, *33*, 402.
30. Hino, T.; Sato, T. *Tetrahedron Lett.* **1971**, *12*, 3127.
31. (a) Poisel, H.; Schmidt, U. *Chem. Ber.* **1972**, *105*, 625. (b) Ohler, E.; Tataruch, F.; Schmidt, U. *Chem. Ber.* **1973**, *106*, 396.
32. Yoshimura, J.; Nakamura, H.; Matsunari, K.; Sugiuama Y. *Chem. Lett.* **1974**, 559.
33. Ottenheijm, H. C. J.; Kerkoff, G. P. C.; Bijen, J. W. H. A. *J. Chem. Soc. Chem.*

*Comm.* **1975**, 768.

34. Overman, L. E.; Sato, T. *Org. Lett.* **2007**, 9, 5267.

35. Nicolaou, K. C.; Giguere, D.; Totokotsopoulos, S.; Sun, Y. P. *Angew. Chem. Int. Ed.* **2012**, 51, 728.

36. Sil, B. C.; Hilton, S. T. *Synlett*, **2014**, 24, 2563.

37. Fukuyama, T.; Kishi, Y. *J. Am. Chem. Soc.* **1976**, 98, 6723.

38. Fukuyama T.; Nakatsuka, S.; Kishi, Y. *Tetrahedron* **1981**, 37, 2045.

39. Williams, R. M.; Rastetter, W. H. *J. Org. Chem.* **1980**, 45, 2625.

40. Takeuchi, R.; Shimokawa, J.; Fukuyama, T. *Chem. Sci.* **2014**, 5, 2003.

41. Codelli, J.; Puchlopek, A. L.; Reisman, S. E. *J. Am. Chem. Soc.* **2012**, 134, 1930.

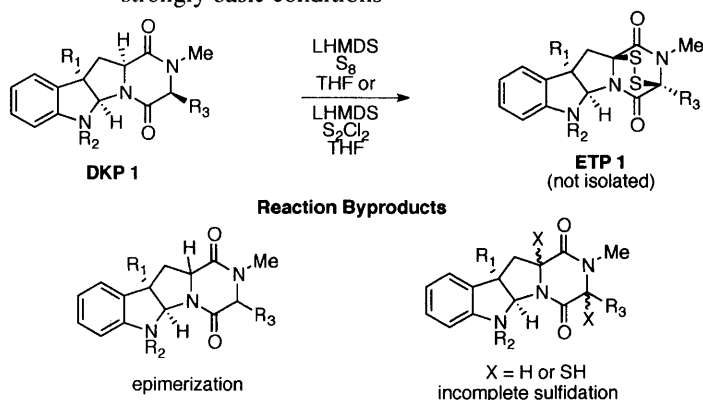


## **II. Development of ETP Syntheses for the Application of the Total Synthesis of (+)-Bionectin A**

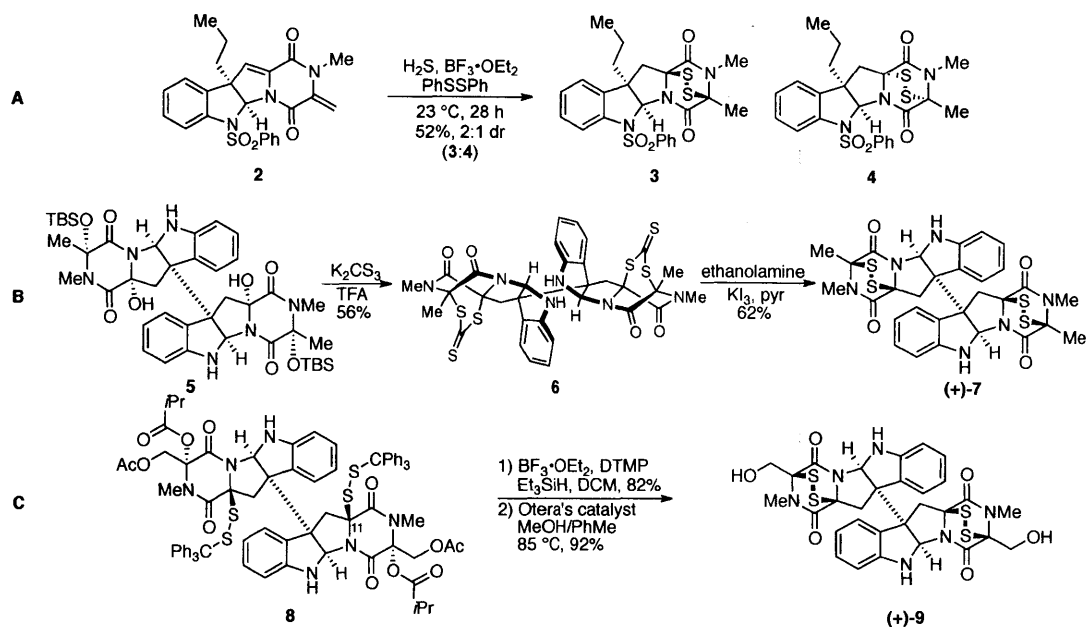
## Introduction and Background

The development of more technologies for the syntheses of epipolythiodiketopiperazines has been an area of active research.<sup>1</sup> Beginning in the late 1970s, the early methods for synthesizing ETPs called for the use of radical intermediates and strong bases. Although these methods can indeed produce the desired ETP moiety, they may prove too harsh with respect to late-stage incorporation of sulfur for certain natural products. The ETP motif is known to be quite sensitive to bases and UV light, possess mild stability to acids, and are known to be redox active.<sup>2</sup> Functional group incompatibility issues may certainly arise due to the sensitivity of this group; and therefore, we had sought to develop more robust, complimentary methods for accessing these structures at the late stage. Preliminary studies in our group had shown the direct conversion of the complex diketopiperazine **1-DKP** (Scheme 1) to the corresponding epidithiodiketopiperazine **1-ETP** to be challenging (Scheme 1). Eventually, greater success in accessing the ETP natural products would involve the use of acidic conditions.

**Scheme 1.** Previous attempts at forming ETPs through strongly basic conditions



Scheme 2 shows the final steps of our previous methods for the construction of complex epidithiodiketopiperazines. Diene **2**, reaction **A**, a model substrate used to test



**Scheme 2.** Our group's strategies for the sulfidation of diketopiperazines.

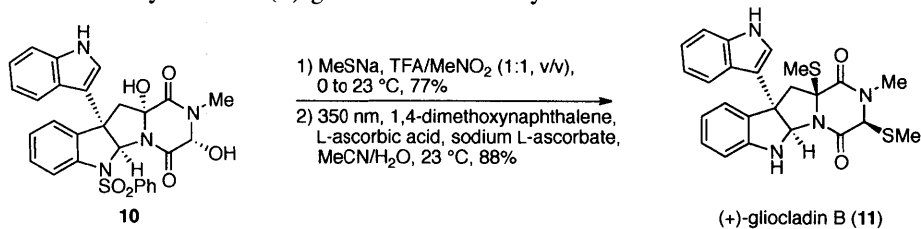
the effectiveness of a direct sulfidation, was converted to the ETP with exposure to hydrogen sulfide and boron trifluoride diethyl etherate ( $\text{BF}_3 \cdot \text{OEt}_2$ ) in moderate yield.<sup>2</sup> A 2:1 mixture of diastereomers was obtained, with the desired diastereomer **3** being the major component. We have developed other ETP synthetic methodologies, such as the use of a trithiocarbonate in order to maximize the diastereoselectivity of the thiolation step.<sup>2</sup> Final elaboration to ETP (+)-**7**, reaction **B**, involved cleavage of the trithiocarbonate with ethanolamine and titration of the reaction mixture with a  $\text{KI}_3$ -pyridine solution. This produced the desired (+)-11,11'-dideoxyverticillin A (+)-**7** in 62% yield. Furthermore, a robust method for accessing higher order polysulfane ETPs (such as epitriethiodiketopiperazines and epitetrathiodiketopiperazines) was developed.<sup>2</sup> An example of this methodology was delineated in the synthesis of (+)-chaetocin A (**9**), reaction **C**, where the dimeric disulfide **8** was obtained using a highly diastereoselective monothiolation reaction of the C11 position, followed by sulfidation of this monothiol with trityl sulfenyl chloride.<sup>2b,3</sup> Ionization of the isobutyrate leaving group of **8** with

boron trifluoride diethyl etherate ( $\text{BF}_3 \cdot \text{OEt}_2$ ) followed by methanolysis of the acetate using Otera's catalyst in toluene at 90 °C led to the cyclization of the mixed disulfide to form the (+)-chaetocin A (**9**).

### Development of Alkyl Mercaptan Reagents for the Synthesis of ETPs

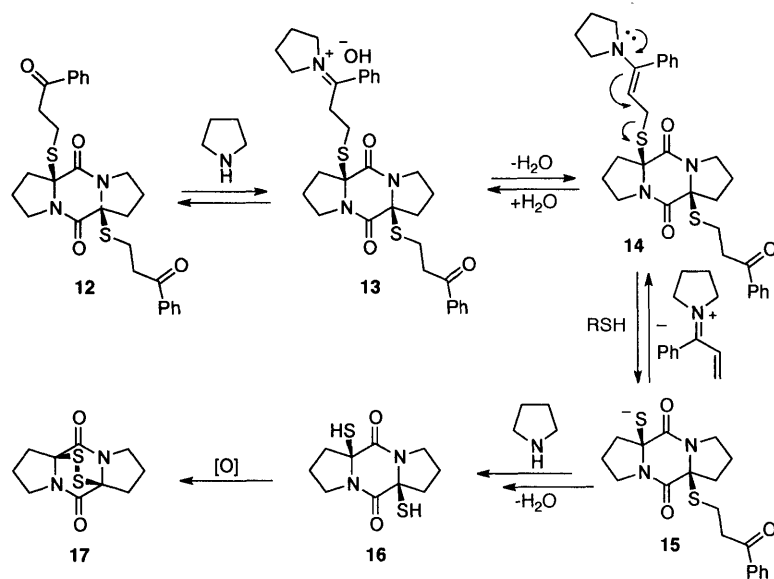
The previous ETP synthetic methods outlined above were quite successful in their application of the total synthesis of certain natural products. However, when addressing the syntheses of other related ETPs, such as in (+)-bionectin A, limitations to the scope of these methods became apparent.<sup>4</sup> Differences in ionizing potential of either tertiary alcohol of the C- $\alpha$ -positions resulted in either incomplete or poorly diastereoselective sulfidations in the presence of Bronsted or Lewis acids and hydrogen sulfide. Thus, a complementary method was sought to aid in the preparation (+)-bionectin A and of other related systems.

**Scheme 3.** Synthesis of (+)-gliocladin B with alkyl thiols



From our previous study of (+)-gliocladin B, we had observed that direct conversion of diketopiperazine diol (+)-**10** to (+)-gliocladin B (**11**) was possible with TFA and alkyl thiols such as sodium methane thiolate (Scheme 3).<sup>3</sup> The desired benzene sulfonyl protected natural product was obtained in 77% as a single diastereomer.<sup>3</sup> The high diastereoselectivity of this reaction prompted us to seek an analogous transformation with other alkyl thiols to essentially serve as hydrogen sulfide surrogates, where removal of the alkyl group could be conducted at a late stage and under mild conditions to afford the

ETP. We conjectured that the process by which the alkyl group could be removed would involve a  $\beta$ -elimination of the thiol. After investigating different electron withdrawing groups, we determined that ketones were the optimal functional group for this elimination. Since ETPs are known to possess sensitivity to a basic conditions, we sought the use of milder reaction conditions such as secondary amines. Through a mechanism analogous to our biosynthetic proposal of ETPs, we hypothesized that the secondary amine, such as pyrrolidine, could condense with the diketone **12** to form iminium **13** (Scheme 4). Tautomerization to form the enamine **14** and expulsion of the thiol via  $\beta$ -elimination would lead to intermediate **15**. After a second round of this pyrrolidine-catalyzed  $\beta$ -elimination at the other sulfide, dithiol **16** would be liberated and in the presence of molecular oxygen, would ultimately lead to the formation of ETP **17**.



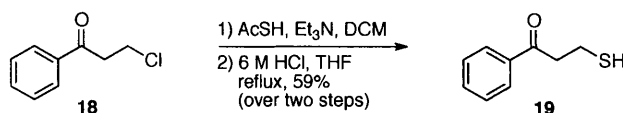
**Scheme 4.** New biogenetically inspired route to ETPs

In the development of this chemistry, two concerns had to be addressed. One of which involved the reversibility of the thiol expulsion. To drive the equilibrium towards product formation, a sacrificial thiol (or excess pyrrolidine) was necessary to sequester

the reactive unsaturated iminium-leaving group. The second concern pertained to the final oxidation step leading to product formation. Although molecular oxygen appeared to be suitable for the disulfide bond formation in select model systems, the addition of KI<sub>3</sub>-pyridine solutions was sometimes necessary to effect the final S-S bond formation.

## Results and Discussion

### Development of Alkylthiol Nucleophiles

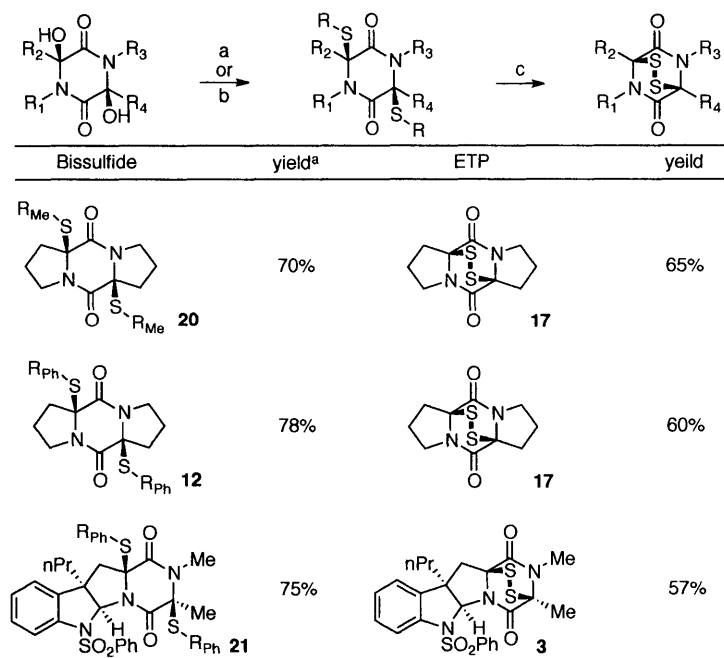


**Scheme 5.** Synthesis of 3-mercaptopropiophenone

The thiol nucleophiles could be readily prepared from the conjugate addition of the corresponding enone with a thioacid or through the direct displacement of the alkyl halide, followed by hydrolysis.<sup>4</sup> *In situ* generation of the enone from the alkyl halide upon exposure to bases such as triethylamine may also be involved. For preparation of the 3-mercapto-propiophenone, chloride **18** was exposed to thioacetic acid and triethylamine to produce the intermediate thioester, which was subjected to 6 N aqueous hydrochloric acid and heated to reflux (Scheme 5). This hydrolysis produced the desired mercaptan **19** in 59% over two steps, which was one of two main thiols that were explored in the acid promoted thiolation and in the sulfide deprotection steps.

Table 1 (font) shows the select substrates that were utilized in the development of this methodology. Subjection of the bisproline diketopiperazine diol to trifluoroacetic acid and commercially available 4-mercapto-2-butanone in acetonitrile produced diketopiperazine bissulfide **20** as a 4:1 mixture of diastereomers, where the major (syn) product was isolated in 70% yield. Unraveling the protected thiols of **20** with pyrrolidine

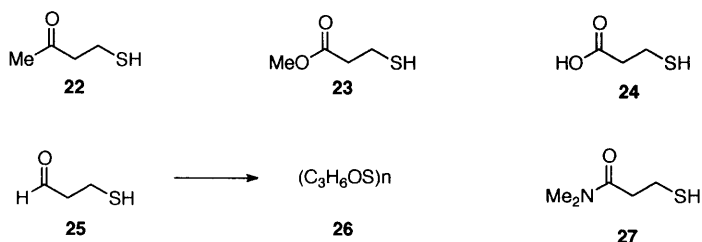
in acetonitrile under an oxygen atmosphere provided the desired ETP **17** in 65% yield. Employment of other thiols for this substitution was successful, with 3-mercaptopropiophenone providing high levels of diastereoselectivity and comparable yields. Treatment of the bisproline diol with 3-mercaptopropiophenone (**19**) and TFA in acetonitrile produced bithioether **12** as 9:1 mixture of diastereomers, where the desired syn product was isolated in 78% yield. This bithioether adduct was mildly cleaved upon treatment with pyrrolidine while under an oxygen atmosphere and this produced ETP **17** in 60% yield. When testing this methodology on the more advanced tetracyclic model substrates, bithioether **21** was synthesized from its corresponding diol as an 8:1 mixture of diastereomers, with the desired syn product being isolated in 75% yield. Cleavage of the thioethers with pyrrolidine in acetonitrile gave the desired ETP **3** in 57% yield.



**Table 1.** Stereoselective sulfidation of diketopiperazines. *Conditions:* (a) 4-mercapto-2-butanone, TFA, MeCN, 23 °C; (b) 3-mercaptopropiophenone, TFA, MeCN, 23 °C. (c) pyrrolidine, O<sub>2</sub>, MeCN, 23 °C.

One advantage of the use of the 4-mercapto-2-butanone reagent is that its corresponding bissulfide adduct underwent the pyrrolidine-catalyzed deprotection at a faster rate and was thus more suitable when applied to more sensitive systems.<sup>4</sup>

**Scheme 6.** Other explored thiols for the sulfidation diketopiperazines.

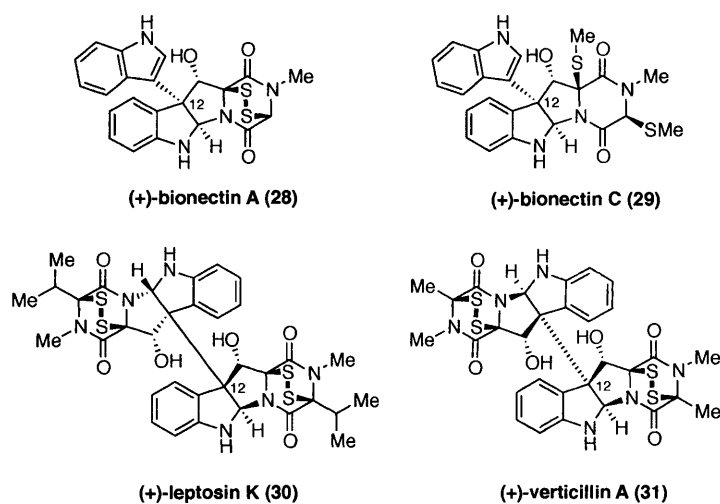


As seen previously, other thiols such as hydrogen sulfide, and thiols such as **19** and **22**, are able to trap the *C*- $\alpha$  acyl iminium of the diketopiperazines under acidic conditions. Commercially available reagent **22** was a thiol that was utilized in our total synthesis of (+)-bionectin A and C (Scheme 6). In light of these thiols, other reagents were found to be less applicable to ETP synthesis. After initial consideration of aldehyde **25**, we decided that this thiol would not be an optimal reagent for sulfidation of diketopiperazines due to its known propensity to spontaneously oligomerize to **26**.<sup>5</sup> Other reagents such as the methyl ester **23**<sup>6</sup>, the commercially available carboxylic acid **24**, and the amide **27**<sup>7</sup> were found to be competent nucleophiles in the thiolation of the *C*- $\alpha$  acyl iminium. However, the alkyl groups of these sulfides could not be removed using the mild pyrrolidine conditions. These sulfide adducts were unreactive towards amine and alkoxide bases in protic or aprotic solvent. Ultimately, ketone thiols were shown to be the most reliable reagent with respect to the thiolation and removal of the ketoalkyl groups.



## Total Synthesis of (+)-Bionectin A

(+)-Bionectins A and C belong to the subclass of  $\beta$ -Hydroxytryptophan derived natural products, and they were first isolated in 2006 by Zheng *et al.* from the fungus *Bionectra byssicola* species (Figure 1).<sup>8</sup> These compounds are known to be cytotoxic towards methicillin-resistant and quinolone-resistant staphylococcus aureus Gram-positive eubacteria with MICs as low as  $10 \mu\text{g mL}^{-1}$ . These molecules possess a C3-(3'-indolyl) substructure and belong to the  $\beta$ -hydroxy subclass of ETP natural products (Figure 1).

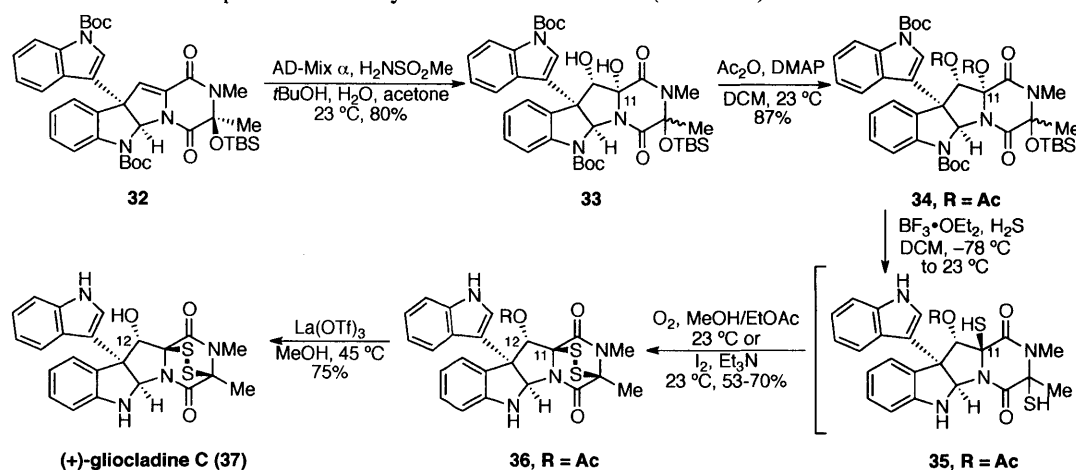


**Figure 1.** Representative C12-hydroxylated ETPs

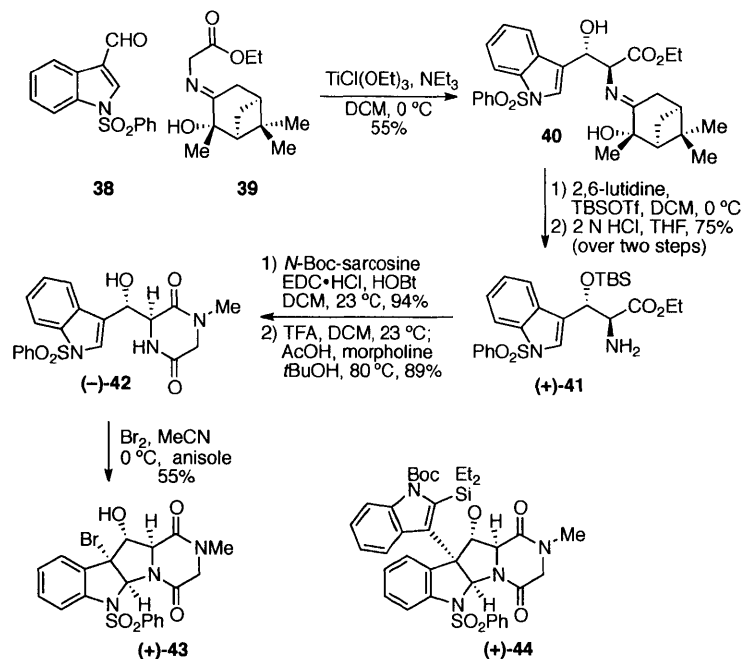
Overman has previously reported the synthesis of several bionectin natural products and of other related derivatives such as (+)-gliocladiene C (Scheme 7).<sup>9</sup> His synthesis involved the preparation of the advanced C3-(3'-indolyl) intermediate **32**, which was oxidized using the Sharpless dihydroxylation protocol to generate the desired diol **33** in 80% yield. The diols were acetylated with acetic anhydride and DMAP to afford intermediate **34** in high yield. The C11 tertiary alcohol and the C15 silyl ether of **34** were treated with boron trifluoride diethyl etherate and hydrogen sulfide to produce

bisthiol **35**. The generated bisthiol **35** was oxidized in the same pot with molecular oxygen to produce the desired ETP **36**. Alternatively, iodine and triethylamine were found to be suitable conditions for this disulfide formation and the reaction yield ranged from 53% to 70% yield. A final methanolysis of the C12 secondary acetate with lanthanum triflate in methanol at 45 °C was found to produce (+)-glioclidine C (**37**) in 75% yield.

**Scheme 7.** Final steps in the Total Synthesis of Glioclidine C (Overman)



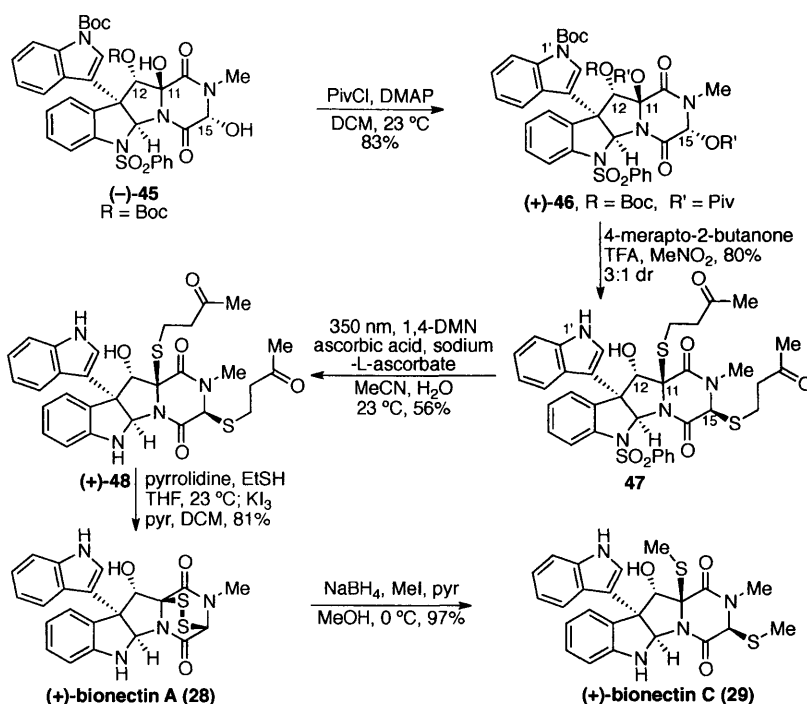
The synthetic strategy used in our synthesis of (+)-bionectin A relied on our bis-thiolation/deprotection methodology for the installation of the disulfide bridge (Scheme 8). Our synthesis of (+)-bionectin A and C commenced with a diastereoselective aldol coupling of indole-3-carboxaldehyde **38** and (–)-pinanone-derived ethyl iminoglycinate **39**<sup>11</sup> to produce  $\beta$ -hydroxytryptophan derivative **40** in 58% yield in 14:1 diastereomeric ratio. Silyl protection of the benzylic secondary alcohol was achieved with TBSOTf and 2,6-lutidine at 0 °C. Subsequent hydrolysis of the imine with 2 N hydrochloric acid afforded the amine (+)-**41** in 75% yield over two steps. Compounds of this type were previously accessed using methods of Feldman.<sup>12</sup> The efficient EDC promoted amino acid coupling of amine (+)-**41** with *N*-Boc-sarcosine afforded the intermediate peptide in



**Scheme 8.** Asymmetric synthesis of b-hydroxy intermediate (+)-46

94% yield, which was subjected to trifluoroacetic acid in dichloromethane. The reaction was concentrated and treated with acetic acid, morpholine and *tert*-butanol at 80 °C to generate diketopiperazine (–)-42 in 89% yield. Exposure of (–)-42 to bromine in acetonitrile at 0 °C cleanly produced the desilylated tetracycle intermediate (+)-43 as a 9:1 mixture of endo:exo products, favoring the desired endo diastereomer in 55% yield. The above synthetic sequence was contemporaneously executed and refined by Dr. Justin Kim and Dr. Alexis Coste, my collaborators on this project.<sup>10</sup> They proceeded to advance diketopiperazine (+)-43 to silacycle (+)-44 and verified its absolute stereochemistry.

For the remaining steps leading towards (+)-bionectin (28), Dr. Kim demonstrated the esterification of the C11 and C15 alcohols of intermediate (–)-45 using pivaloyl chloride and DMAP at 23 °C to produce diester (+)-46 in 83% yield (Scheme 9). Treatment of a solution of dipivaloate (+)-46 with 4-mercapto-2-butanone with TFA in nitromethane at 23 °C produced bithioether 47 in 80% yield as a 3:1 diastereomeric



**Scheme 9.** Final steps for the synthesis of (+)-bionectins A and C  
(Executed by Justin Kim)

mixture with concomitant loss of the *tert*-butoxycarbonyl groups at the N1' amine and C12 alcohol. The major diastereomer possessed the desired C11,C15-stereochemistry and could be isolated in 56% yield upon photoinduced electron transfer-mediated removal of the benzenesulfonyl group to form (+)-48.<sup>13</sup> The bithioethers were removed with a mild enamine-mediated transthioetherification protocol employing pyrrolidine in tetrahydrofuran at 23 °C. As opposed to the model substrates that were explored in Table 1, a sacrificial thiol additive was found to optimize the unveiling of the C- $\alpha$  thiols: exposure to an atmosphere of oxygen was insufficient in oxidizing the dithiol to the disulfide. Mild oxidation of the generated dithiol with KI<sub>3</sub> in pyridine afforded the target natural product (+)-bionectin A (28) in 81% yield over two steps. Consistent with the biosynthesis of (+)-bionectin C, the bis-*S*-methyl derivative (+)-29 was produced in 97%

yield by reduction of disulfide (+)-**28** with sodium borohydride, followed by the addition of methyl iodide.

### **Conclusion**

Using a biomimetic protocol for the cleavage of  $\beta$ -mercaptan-linked ketones, we were able to access (+)-bionectin A and C. The use of this method was advantageous in that the previous methods used to synthesize other complex ETPs weren't not applicable to these natural products. This lack of applicability is due to the incomplete ionization of the C11 alcohol and the lack of stereocontrol for the C15 sulfidation. Although different thiols were able to diastereoselectively add to diketopiperazine substructures, only ketone thiols were found to undergo mild cleavage to reveal the thiol. This procedure is robust for the synthesis of ETPs and the method obviates the need for noxious hydrogen sulfide. This method of synthesizing ETPs compliments our growing repertoire of strategies that can be used to access a broad range of alkaloids.

## References for chapter 2

1. For select methods of ETP synthesis, see (a) Trown, P. W. *Biochem. Biophys. Res. Commun.* **1968**, *33*, 402. (b) Hino, T.; Sato, T. *Tetrahedron Lett.* **1971**, *12*, 3127. (c) Ohler, E.; Tataruch, F.; Schmidt, U. *Chem. Ber.* **1973**, *106*, 396. (d) Yoshimura, J.; Nakamura, H.; Matsunari, K.; Sugiama Y. *Chem. Lett.* **1974**, 559.
2. (a) Kim, J.; Ashenurst, J. A.; Movassaghi, M. *Science*, **2009**, *324*, 238. (b) Kim, K.; Movassaghi, M. *J. Am. Chem. Soc.* **2010**, *132*, 14376.
3. Boyer, N.; Movassaghi, M. *Chem. Sci.* **2012**, *3*, 1798.
4. Coste, A.; Kim, J.; Adams, T. C.; Movassaghi, M. *Chem. Sci.* **2013**, *4*, 3191.
5. Carlsen, L.; Egsgaard, H. *J. Chem. Soc. Perkin Trans. II* **1984**, 609.
6. Kumar, I.; Jolly, R. S. *Org. Lett.* **2001**, *3*, 283.
7. Casuso, P.; Loinaz, I.; Moller, M.; Carrasco, P.; Pomposo, J. A.; Grande, H. J.; Odriozola, I. *Supramolecular Chemistry*, **2009**, *21*, 581.
8. Zheng, C. J.; Kim, C. J.; Bai, Y. H.; Kim, Y. H.; Kim, W. G. *J. Nat. Prod.* **2006**, **69**, 1816.
9. Delorbe, J. E.; Horne, D.; Jove, R.; Mennen, S. M.; Nam, S.; Zhang, F. L.; Overman, L. E.; *J. Am. Chem. Soc.* **2013**, *135*, 4117.
10. see supporting information in: Coste, A.; Kim, J.; Adams, T. C.; Movassaghi, M. *Chem. Sci.* **2013**, *4*, 3191.
11. Oguri, T.; Kawai, N.; Shiori, T.; Yamada, S. I.; *Chem. Pharm. Bull.* **1978**, *26*, 803.
12. (a) Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc.* **1994**, *116*, 8544. (b) Feldman, K. S.; Karatjas, A. G. *Org. Lett.* **2004**, *6*, 8544. (c) Feldman, K. S.;

Vidulova, D. B.; Karatjas A. G. *J. Org. Chem.* **2005**, *70*, 6429. (d) Koketsu, K.;

Oguri, H.; Watanabe, K.; Oikawa, H. *Org. Lett.* **2006**, *8*, 4719.

13. Hamada, T.; Nishida, A.; and Yonemitsu, O.; *J. Am. Chem. Soc.* **1986**, *108*, 140.

## Experimental Section

**General Procedures.** All reactions were performed in oven-dried or flame-dried round-bottom flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon. Cannulae or gas-tight syringes with stainless steel needles were used to transfer air- or moisture-sensitive liquids. Where necessary (so noted), solutions were deoxygenated by sparging with argon for a minimum of 10 min. Flash column chromatography was performed as described by Still et al. using granular silica gel (60-Å pore size, 40–63  $\mu\text{m}$ , 4–6%  $\text{H}_2\text{O}$  content, Zeochem).<sup>1</sup> Analytical thin layer chromatography (TLC) was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to short wave ultraviolet light (254 nm) and an aqueous solution of ceric ammonium molybdate (CAM) followed by heating on a hot plate (~ 250 °C). Organic solutions were concentrated at 29–30 °C on rotary evaporators capable of achieving a minimum pressure of ~2 torr. The benzenesulfonyl photodeprotection was accomplished by irradiation in a Rayonet RMR-200 photochemical reactor (Southern New England Ultraviolet Company, Branford, CT, USA) equipped with 16 lamps (RPR-3500, 24 W,  $\lambda_{\text{max}} = 350 \text{ nm}$ , bandwidth ~ 20 nm).

**Materials.** Commercial reagents and solvents were used as received with the following exceptions: dichloromethane, acetonitrile, tetrahydrofuran, methanol, pyridine, toluene, and triethylamine were purchased from J.T. Baker (Cycletainer<sup>TM</sup>) and were purified by the method of Grubbs *et al.* under positive argon pressure.<sup>2</sup> Nitromethane and nitroethane (from Sigma–Aldrich) were purified by fractional distillation over calcium

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<sup>1</sup> Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, 43, 2923..

<sup>2</sup> Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* 1996, 15, 1518.



hydride and were stored over Linde 4Å molecular sieves in Schlenk flasks sealed with septa and teflon tape under argon atmosphere.<sup>3</sup> Titanium (IV) ethoxide (99.99%-Ti) PURATREM and bromine were purchased from Strem Chemicals, Inc.; *N*-Boc-L-sarcosine, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, *N*-Hydroxybenzotriazole, *tert*-butyldimethylsilyl trifluoromethanesulfonate, trifluoroacetic acid, 4-(dimethylamino)pyridine, silver nitrate were purchased from Chem-Impex; 1,4-dimethoxynaphthalene was purchased from Alfa Aesar; di-*tert*-butyl dicarbonate was purchased from Oakwood Products, Inc.; 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) was purchased from OChem Incorporation. All other solvents and chemicals were purchased from Sigma–Aldrich. 1,4-Dimethoxynaphthalene was purified by crystallization from absolute ethanol.

**Instrumentation.** Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded with a Bruker AVANCE-600 NMR spectrometer (with a Magnex Scientific superconducting actively-shielded magnet) or with a Varian inverse probe 500 INOVA spectrometer, are reported in parts per million on the δ scale, and are referenced from the residual protium in the NMR solvent (CDCl<sub>3</sub>: δ 7.26 (CHCl<sub>3</sub>), or acetone-**d**<sub>6</sub>: δ 2.05 (acetone-**d**<sub>6</sub>).<sup>4</sup> Data are reported as follows: chemical shift [multiplicity (br = broad, s = singlet, d = doublet, t = triplet, sp = septet, m = multiplet), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance (<sup>13</sup>C NMR) spectra were recorded with a Bruker AVANCE-600 NMR Spectrometer (with a Magnex Scientific superconducting actively-shielded magnet) or a Bruker AVANCE-400 NMR

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<sup>3</sup> Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 5<sup>th</sup> ed.; Butterworth–Heinemann: London, 2003.

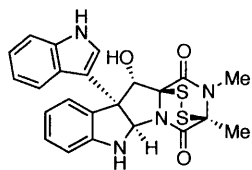
<sup>4</sup> Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* 2010, 29, 2176.

Spectrometer (with a Magnex Scientific superconducting magnet) or with a Varian 500 INOVA spectrometer, are reported in parts per million on the  $\delta$  scale, and are referenced from the carbon resonances of the solvent ( $\text{CDCl}_3$ :  $\delta$  77.23, acetone- $d_6$ : 29.84). Data are reported as follows: chemical shift (multiplicity, coupling constant(s) in Hertz, assignment). Infrared data (IR) were obtained with a Perkin-Elmer 2000 FTIR and are reported as follows: frequency of absorption ( $\text{cm}^{-1}$ ), intensity of absorption (s = strong, m = medium, w = weak, br = broad). Optical rotations were measured on a Jasco-1010 polarimeter with a sodium lamp and are reported as follows:  $[\alpha]_D^{25}$  ( $c$  = g/100 mL, solvent). We are grateful to Dr. Li Li and Deborah Bass for obtaining the mass spectrometric data at the Department of Chemistry's Instrumentation Facility, Massachusetts Institute of Technology. High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics APEXIV 4.7 Tesla FT-ICR-MS using an electrospray (ESI) ionization source.

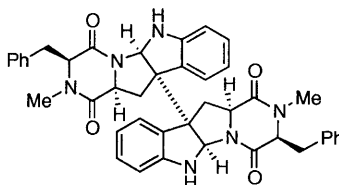
**Positional Numbering System.** At least three numbering systems for dimeric diketopiperazine alkaloids exist in the literature.<sup>5</sup> In assigning the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of all intermediates en route to our total syntheses of (+)-bionectins A (1) and C (2), we wished to employ a uniform numbering scheme. For ease of direct comparison, particularly between early intermediates, non-thiolated diketopiperazines, and advanced compounds, the numbering system used by Barrow for (+)-WIN-64821 (using positional numbers 1–21) is optimal and used throughout this report. In key instances, the products are accompanied by the numbering system as shown below.

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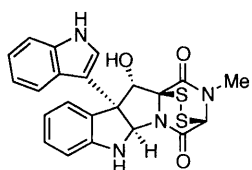
<sup>5</sup> (a) Von Hauser, D.; Weber, H. P.; Sigg, H. P. *Helv. Chim. Acta* **1970**, *53*, 1061. (b) Barrow, C. J.; Cai, P.; Snyder, J. K.; Sedlock, D. M.; Sun, H. H.; Cooper, R. *J. Org. Chem.* **1993**, *58*, 6016. (c) Springer, J. P.; Büchi, G.; Kobbe, B.; Demain, A. L.; Clardy, J. *Tetrahedron Lett.* **1977**, *28*, 2403. (d) Zheng, C.-J.; Kim, C.-J.; Bae, K. S.; Kim, Y.-H.; Kim, W.-G. *J. Nat. Prod.* **2006**, *69*, 1816. (e) DeLorbe, J. E.; Jabri, S. Y.; Mennen, S. M.; Overman, L. E.; Zhang, F.-L. *J. Am. Chem. Soc.* **2011**, *133*, 6549.



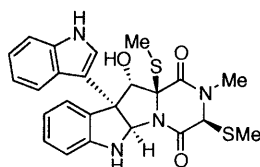
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Kim's isolation report  
Overman's report



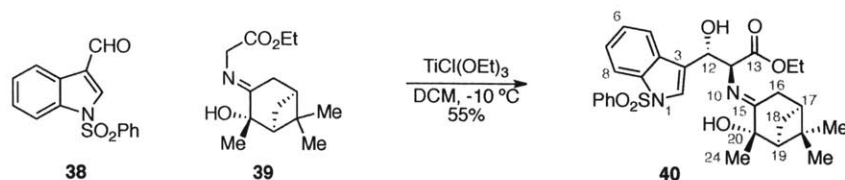
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Barrow's numbering for the  
simpler diketopiperazine  
framework



(+)-bionectin A (1)  
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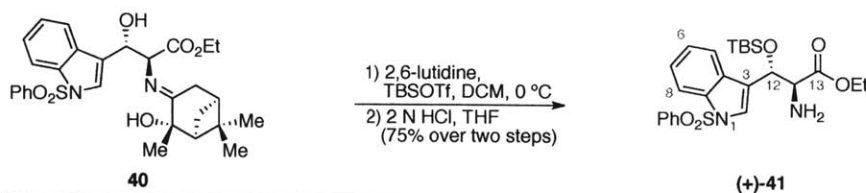


(+)-bionectin C (2)  
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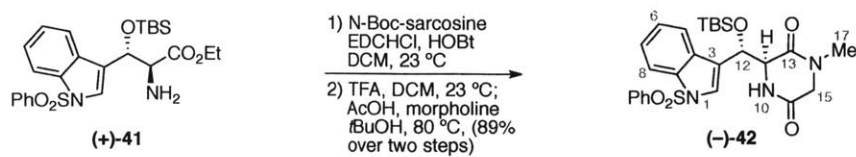
### **12-Hydroxytryptophan Alcohol 40:**

A solution of chlorotitanium (IV) triethoxide (11.2 g, 51.5 mmol, 1.05 equiv) in dichloromethane (69 mL) was added via cannula to a solution of ethyl 2-((1*S*,2*S*,5*S*)-2-hydroxypinan-3-imino)glycinate (**39**, 12.4 g, 48.9 mmol, 1 equiv) in dichloromethane (300 mL) at  $-10\text{ }^{\circ}\text{C}$ . A fine powder of 1-(phenylsulfonyl)-1*H*-indole-3-carbaldehyde (10, 14.7 g, 51.5 mmol, 1.05 equiv) was then added to the reaction mixture. Triethylamine (13.6 mL, 98.0 mmol, 2.00 equiv) was added dropwise via syringe and the reaction mixture was stirred at  $0\text{ }^{\circ}\text{C}$ . After 7 h, brine (1 L) at  $0\text{ }^{\circ}\text{C}$  was added to the reaction mixture and the resulting bilayer suspension was filtered through Celite. The organic layer was separated, and the aqueous layer was extracted with dichloromethane ( $2 \times 100\text{ mL}$ ). The combined organic layers were dried with anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting orange foam was purified by flash column chromatography on silica gel (eluent: gradient, 30 $\rightarrow$ 50% ethyl acetate in hexanes) to provide an inseparable mixture of diastereomeric aldol products (15.2 g, 55%) as a foam. For the full characterization data of **40**, please see Coste, A.; Kim, J.; Adams, T. C.; Movassaghi, M. *Chem. Sci.* **2013**, *4*, 3191.



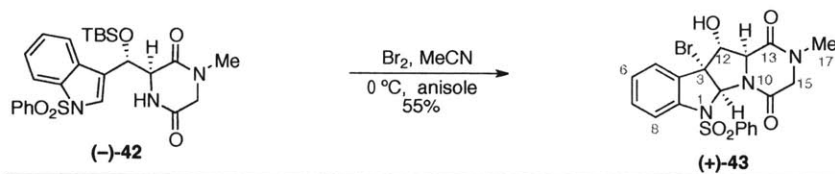
### **12-Hydroxytryptophan Amine (+)-41:**

*t*-Butyldimethylsilyl trifluoromethanesulfonate (7.26 mL, 31.5 mmol, 1.20 equiv) was added via syringe to a solution of 12-hydroxytryptophan alcohol **40** (14.1 g, 26.3 mmol, 1 equiv) and 2,6-lutidine (6.23 mL, 53.7 mmol, 2.04 equiv) in dichloromethane (500 mL) at 0 °C. After 2 h, saturated aqueous ammonium chloride solution (750 mL) was added to the reaction mixture and the resulting solution was allowed to warm to 23 °C. After 10 min, the layers were separated and the aqueous layer was further extracted with dichloromethane (2 × 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting orange foam was advanced to the amine hydrolysis step. Aqueous hydrogen chloride solution (2 N, 300 mL) was added to a solution of the crude 12-hydroxytryptophan silyl ether in tetrahydrofuran (300 mL) at 23 °C. After 2.0 h, the mixture was concentrated to remove the organic solvent. The resulting mixture was extracted with ethyl acetate (3 × 300 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting orange foam was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes) to provide 12-hydroxytryptophan amine (+)-**41** (11.8 g, 75%) as a yellow foam. For the full characterization data of (+)-**41**, please see Coste, A.; Kim, J.; Adams, T. C.; Movassaghi, M. *Chem. Sci.* **2013**, *4*, 3191.



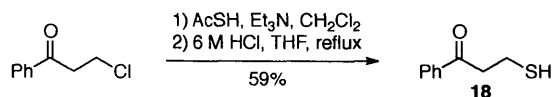
### Diketopiperazine (–)-42:

A round-bottom flask was charged sequentially with 12-hydroxytryptophan amine (+)-41 (7.05 g, 14.0 mmol, 1 equiv), *N*-Boc-sarcosine (2.57 g, 13.6 mmol, 1.30 equiv), *N*-hydroxybenzotriazole (2.13 g, 15.7 mmol, 1.50 equiv), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrogen chloride (4.03 g, 21.0 mmol, 2.00 equiv), and powdered 4 Å molecular sieves (3.00 g), and the contents were placed under an atmosphere of argon. Dichloromethane (70 mL) was introduced via cannula and the resulting solution was cooled to 0 °C. Triethylamine (4.40 mL, 31.5 mmol, 3.00 equiv) was subsequently added dropwise via syringe and the reaction mixture was allowed to warm slowly to 23 °C. After 8 h, saturated aqueous sodium bicarbonate solution (200 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 250 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting orange foam was advanced to the diketopiperazine formation stage. Trifluoroacetic acid (27 mL) was introduced dropwise to a solution of the crude dipeptide in dichloromethane (140 mL) at 23 °C. After 1 h, the reaction mixture was concentrated to dryness under reduced pressure. The crude residue was dissolved in tert-butanol (210 mL). Acetic acid (32 mL) and morpholine (32 mL) were successively added to the solution, and the resulting reaction mixture was warmed to 80 °C. After 1.5 h, the reaction mixture was concentrated under reduced pressure and the solids were removed by vacuum filtration over a sintered funnel. The solids were extracted with ethyl acetate and the combined organic filtrates were concentrated under reduced pressure. The resulting orange oil was purified by flash column chromatography on silica gel (eluent: 50% ethyl acetate in hexanes) to provide diketopiperazine (–)-42 (5.0 g, 89% over two steps) as a yellow foam. For the full characterization data of (–)-42, please see Coste, A.; Kim, J.; Adams, T. C.; Movassaghi, M. *Chem. Sci.* **2013**, *4*, 3191.



### **Tetracyclic Bromide (+)-43:**

A solution of bromine (2 M, 20.3 mL, 40.0 mmol, 4.00 equiv) in acetonitrile that was precooled to 0 °C was poured in one portion into a solution of diketopiperazine (–)-15 (5.36 g, 10.1 mmol, 1 equiv) in acetonitrile (200 mL) at 0 °C. After 10 min, anisole (6.63 mL, 61.0 mmol, 6.00 equiv) was poured into the reaction mixture. After 10 min, a mixture of saturated aqueous sodium thiosulfate solution and saturated aqueous sodium bicarbonate solution (1:1, 300 mL) was added to the red solution. The reaction mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 30% acetone in dichloromethane) to afford the endo-tetracyclic bromide (+)-43 (5.50 g, 55%) as a white foam. For the full characterization data of (+)-43, please see Coste, A.; Kim, J.; Adams, T. C.; Movassaghi, M. *Chem. Sci.* **2013**, *4*, 3191.

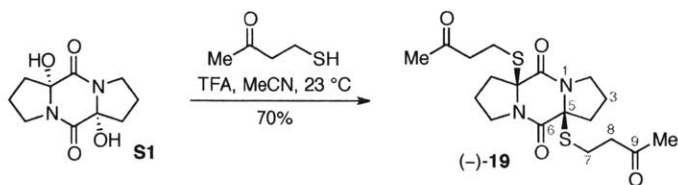


### **3-Mercaptopropiophenone (18):**

Triethylamine (1.49 mL, 10.7 mmol, 1.50 equiv) was added to a solution of 3-chloropropiophenone (1.20 g, 7.12 mmol, 1 equiv) in dichloromethane (100 mL) at 23 °C. Thioacetic acid (602  $\mu$ L, 8.54 mmol, 1.20 equiv) was then added dropwise to the solution. After 1 h, the reaction mixture was concentrated in vacuo. The crude residue was dissolved in tetrahydrofuran (50 mL) and aqueous hydrochloric acid (6 N, 50 mL) was added to the solution. The reaction mixture was then heated to reflux. After 36 h, the reaction was diluted with ethyl acetate (200 mL) and washed with saturated aqueous sodium bicarbonate solution (400 mL). The aqueous layer was extracted with ethyl acetate (3  $\times$  200 mL), and the combined organic layers were dried over sodium sulfate, were filtered, and were concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica gel (eluent: 20% ethyl acetate in hexanes) to afford 3-mercaptopropiophenone (**18**, 703 mg, 59.4%) as a colorless oil.

$^1\text{H NMR}$ (500 MHz, $\text{CDCl}_3$ , 20 °C):	$\delta$ 7.93 (d, $J = 7.5$ , 2H, CPh- <i>o</i> -H), 7.55 (t, $J = 7.5$ , 1H, CPh- <i>p</i> -H), 7.45 (app-t, $J = 7.5$ , 2H, CPh- <i>m</i> -H), 3.31 (t, $J = 7$ , 2H, $\text{CH}_2\text{CH}_2\text{SH}$ ), 2.89 (dt, $J = 8.5$ , 6.0, 2H, $\text{CH}_2\text{CH}_2\text{SH}$ ), 1.74 (t, $J = 8.5$ , 1H, SH).
$^{13}\text{C NMR}$ (125.8 MHz, $\text{CDCl}_3$ , 20 °C):	$\delta$ 198.2 (C=O), 136.8 (CPh- <i>ipso</i> -C), 133.6 (CPh- <i>p</i> -C), 128.9 (CPh- <i>m</i> -C), 128.2 (CPh- <i>o</i> -C), 42.7 ( $\text{CH}_2\text{CH}_2\text{SH}$ ), 19.1 ( $\text{CH}_2\text{CH}_2\text{SH}$ ).
FTIR (thin film) $\text{cm}^{-1}$ :	3061 (w), 2941 (w), 1683 (s), 1597 (m), 1580 (m) 1448 (m).
HRMS (ESI) ( $m/z$ ):	calc'd for $\text{C}_9\text{H}_{11}\text{OS}$ [ $\text{M}+\text{H}$ ] $^+$ : 167.0525, found 167.0526
TLC (20% ethyl acetate in hexanes), $R_f$ :	0.28 (UV, CAM).

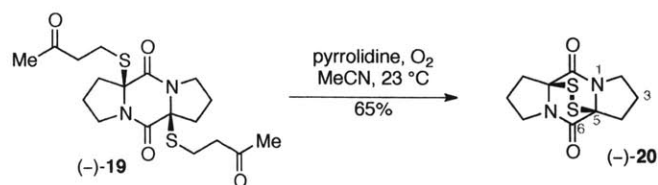




**Bisproline Bis(ethylmethylketone thioether) (-)-19:**

Trifluoroacetic acid (15 mL) was added via syringe to a solution of bisproline diol **S1** (397 mg, 1.76 mmol, 1 equiv) and 3-mercaptoputan-2-one (**18**, 928  $\mu$ L, 8.77 mmol, 5.00 equiv) in acetonitrile (15 mL) at 23 °C. The clear solution immediately turned yellow. After 30 min, the reaction was diluted with ethyl acetate (50 mL) and washed with saturated aqueous sodium bicarbonate solution (50 mL). The aqueous layer was extracted with ethyl acetate (3  $\times$  20 mL), and the combined organic layers were dried over sodium sulfate, were filtered, and were concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica gel (eluent: 3% acetone in dichloromethane) to afford the bisproline bis(ethylmethylketone thioether) (-)-**19** (490 mg, 70.2%) as a white solid.

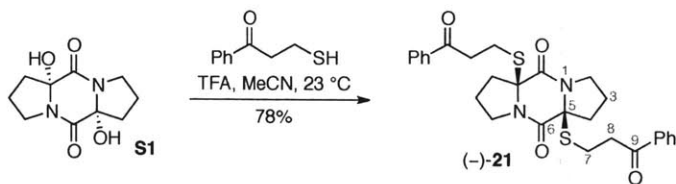
$^1\text{H NMR}$ (500 MHz, $\text{CDCl}_3$ , 20 °C):	$\delta$ 3.68–3.62 (m, 2H, $\text{C}_2\text{H}$ ), 3.56–3.51 (m, 2H, $\text{C}_2\text{H}$ ), 2.90–2.87 (m, 4H, $\text{C}_8\text{H}$ ), 2.75–2.61 (m, 4H, $\text{C}_7\text{H}$ ), 2.46–2.42 (m, 2H, $\text{C}_4\text{H}_a$ ), 2.33–2.22 (m, 2H, $\text{C}_3\text{H}_a$ ), 2.12–2.04 (m, 2H, $\text{C}_4\text{H}_b$ ), 2.10 (s, 6H, $\text{COCH}_3$ ), 2.01–1.95 (m, 2H, $\text{C}_3\text{H}_b$ ).
$^{13}\text{C NMR}$ (125.8 MHz, $\text{CDCl}_3$ , 20 °C):	$\delta$ 206.4 ( $\text{C}_9$ ), 165.3 ( $\text{C}_6$ ), 71.7 ( $\text{C}_5$ ), 45.4 ( $\text{C}_2$ ), 43.2 ( $\text{C}_7$ ), 35.4 ( $\text{C}_4$ ), 30.0 ( $\text{COCH}_3$ ), 25.2 ( $\text{C}_8$ ), 20.0 ( $\text{C}_3$ ).
FTIR (thin film) $\text{cm}^{-1}$ :	1715 (m), 1660 (s), 1409 (s), 1363 (w), 1158 (w)
HRMS (ESI) ( $m/z$ ):	calc'd for $\text{C}_{18}\text{H}_{30}\text{N}_3\text{O}_4\text{S}_2$ $[\text{M}+\text{NH}_4]^+$ : 416.1672, found: 416.1679.
$[\alpha]_D^{24}$ :	-33 ( $c = 0.28$ , $\text{CH}_2\text{Cl}_2$ ).
TLC (10% acetone in dichloromethane), $R_f$ :	0.39 (UV, CAM).



### **Bisproline Epidithiodiketopiperazine (-)-20:**

Pyrrolidine (70.0  $\mu\text{L}$ , 852  $\mu\text{mol}$ , 4.07 equiv) was added to a solution of bis(ethylmethylketone thioether) (-)-19 (83.5 mg, 210  $\mu\text{mol}$ , 1 equiv) in acetonitrile (250  $\mu\text{L}$ ) at 23 °C, and the reaction was placed under a balloon of oxygen. The clear solution immediately turned orange. After 1 h, the reaction was diluted with dichloromethane (5 mL) and washed with saturated aqueous ammonium chloride solution (5 mL). The aqueous layer was extracted with ethyl acetate (3  $\times$  3 mL), and the combined organic layers were dried over sodium sulfate, were filtered, and were concentrated under reduced pressure. The orange residue was purified by flash column chromatography on silica gel (eluent: 3% acetone in dichloromethane) to afford the bisproline epidithiodiketopiperazine (-)-20 (34.8 mg, 64.8%) as a white solid.

<sup>1</sup> H NMR (500 MHz, CDCl <sub>3</sub> , 20 °C):	$\delta$ 3.88–3.84 (m, 2H, C <sub>2</sub> H <sub>a</sub> ), 3.58–3.52 (m, 2H, C <sub>2</sub> H <sub>b</sub> ), 3.02–2.94 (m, 2H, C <sub>4</sub> H <sub>a</sub> ), 2.35–2.27 (m, 2H, C <sub>4</sub> H <sub>b</sub> ), 2.35–2.27 (m, 2H, C <sub>3</sub> H <sub>a</sub> ), 2.25–2.18 (m, 2H, C <sub>3</sub> H <sub>b</sub> ).
<sup>13</sup> C NMR (125.8 MHz, CDCl <sub>3</sub> , 20 °C):	$\delta$ 164.1 (C <sub>6</sub> ), $\delta$ 78.1 (C <sub>5</sub> ), $\delta$ 46.6 (C <sub>2</sub> ), $\delta$ 32.9 (C <sub>4</sub> ), $\delta$ 24.4 (C <sub>3</sub> ).
FTIR (thin film) cm <sup>-1</sup> :	2921 (m), 1660 (s), 1405 (m), 1338 (w), 1097 (m)
HRMS (ESI) ( <i>m/z</i> ):	calc'd for C <sub>10</sub> H <sub>12</sub> N <sub>2</sub> NaO <sub>2</sub> S <sub>2</sub> [M+Na] <sup>+</sup> : 279.0323, found: 279.0314.
[ $\alpha$ ] <sub>D</sub> <sup>24</sup> :	-144 (c = 0.11, CH <sub>2</sub> Cl <sub>2</sub> ).
TLC (10% acetone in dichloromethane), R <sub>f</sub> :	0.44 (UV, CAM).



**Bisproline bis(ethylphenylketone thioether) (-)-21:**

Trifluoroacetic acid (1 mL) was added via syringe to a solution of bisproline diol **S1** (36.6 mg, 0.162 mmol, 1 equiv) and 3-mercaptopropiophenone (**18**, 76.2  $\mu$ L, 801  $\mu$ mol, 5.00 equiv) in acetonitrile (1 mL) at 23 °C. The clear solution immediately turned yellow. After 30 min, the reaction was diluted with ethyl acetate (5 mL) and washed with saturated aqueous sodium bicarbonate solution (5 mL). The aqueous layer was extracted with ethyl acetate (3  $\times$  5 mL), and the combined organic layers were dried over sodium sulfate, were filtered, and were concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica gel (eluent: 3% acetone in dichloromethane) to afford the bisproline bis(ethylmethylketone thioether) (-)-**21** (65.9 mg, 77.5%) as a white solid.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 20 °C):

$\delta$  7.89 (d,  $J$  = 7.5, 4H, C<sub>OPh-*o*</sub>-H), 7.53 (t,  $J$  = 7.5, 2H, C<sub>OPh-*p*</sub>-H), 7.42 (app-t,  $J$  = 8.0, 4H, C<sub>OPh-*m*</sub>-H), 3.73–3.67 (m, 2H, C<sub>2</sub>H<sub>a</sub>), 3.61–3.56 (m, 2H, C<sub>2</sub>H<sub>b</sub>), 3.33–3.27 (m, 2H, C<sub>7</sub>H<sub>a</sub>), 3.23–3.26 (m, 2H, C<sub>7</sub>H<sub>b</sub>), 3.12–3.09 (m, 4H, C<sub>8</sub>H), 2.55–2.51 (m, 2H, C<sub>4</sub>H<sub>a</sub>), 2.38–2.28 (m, 2H, C<sub>3</sub>H<sub>a</sub>), 2.17–2.10 (m, 2H, C<sub>4</sub>H<sub>b</sub>), 2.05–1.99 (m, 2H, C<sub>3</sub>H<sub>b</sub>).

$^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ , 20 °C):

$\delta$  198.7 (C<sub>9</sub>), 166.2 (C<sub>6</sub>), 137.2 (C<sub>OPh-*ipso*</sub>-C), 133.6 (C<sub>OPh-*p*</sub>-C), 128.9 (C<sub>OPh-*m*</sub>-C), 128.2 (C<sub>OPh-*o*</sub>-C), 72.5 (C<sub>5</sub>), 45.7 (C<sub>2</sub>), 38.9 (C<sub>7</sub>), 35.7 (C<sub>4</sub>), 25.7 (C<sub>8</sub>), 20.1 (C<sub>3</sub>).

FTIR (thin film)  $\text{cm}^{-1}$ :

2956 (w), 1683 (m), 1660 (m), 1597 (w), 1448 (w), 1406 (m), 1350 (w).

HRMS (ESI) ( $m/z$ ):

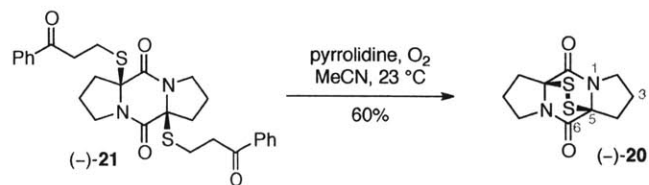
calc'd for C<sub>28</sub>H<sub>34</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub> [M+NH<sub>4</sub>]<sup>+</sup>: 540.1925, found: 540.1925.

$[\alpha]_{\text{D}}^{24}$ :

-54 ( $c$  = 0.17, CH<sub>2</sub>Cl<sub>2</sub>).

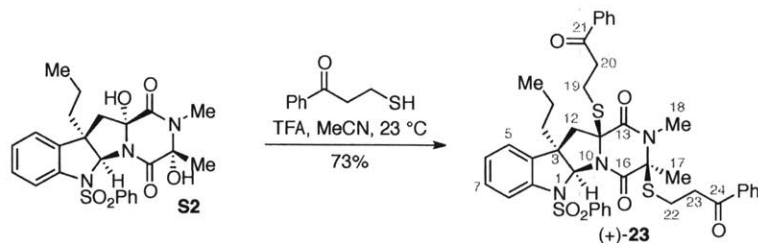
TLC (10% acetone in dichloromethane), R<sub>f</sub>:

0.43 (UV, CAM).



**Bisproline Epidithiodiketopiperazine (-)-20:**

Pyrrolidine (24.3  $\mu$ L, 284  $\mu$ mol, 3.79 equiv) was added to a solution of bis(ethylmethylketone thioether) (-)-**21** (39.2 mg, 75.0  $\mu$ mol, 1 equiv) in acetonitrile (250  $\mu$ L) at 23 °C, and the reaction was placed under a balloon of oxygen. The clear solution immediately turned orange. After 1 h, the reaction was diluted with dichloromethane (5 mL) and washed with saturated aqueous ammonium chloride solution (5 mL). The aqueous layer was extracted with dichloromethane (3  $\times$  3 mL), and the combined organic layers were dried over sodium sulfate, were filtered, and were concentrated under reduced pressure. The orange residue was purified by flash column chromatography on silica gel (eluent: 3% acetone in dichloromethane) to afford the bisproline epidithiodiketopiperazine (-)-**20** (11.5 mg, 59.8%) as a white solid. Please see page 61 for the full characterization data for bisproline epidithiodiketopiperazine (-)-**20**.



### **3-Propyl Tetracyclic Bis(ethylphenylketone thioether) (+)-23:**

Trifluoroacetic acid (1 mL) was added via syringe to a solution of 3-propyl tetracyclic diol **S2** (46.3 mg, 95.4  $\mu\text{mol}$ , 1 equiv) and 3-mercaptopropiophenone (**18**, 72.3  $\mu\text{L}$ , 477  $\mu\text{mol}$ , 5.00 equiv) in acetonitrile (1 mL) at 23 °C. The clear solution immediately turned yellow. After 30 min, the reaction was diluted with ethyl acetate (5 mL) and washed with saturated aqueous sodium bicarbonate solution (2 mL). The aqueous layer was extracted with ethyl acetate ( $3 \times 5$  mL), and the combined organic layers were dried over sodium sulfate, were filtered, and were concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica gel (eluent: 3% acetone in dichloromethane) to afford the 3-propyl tetracyclic bis(ethylphenylketone thioether) (+)-**23** (54.5 mg, 73.1%) as a white solid.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 20 °C):

$\delta$  8.00–7.97 (m, 4H, C<sub>OPh-*m*-H</sub>), 7.81 (d,  $J = 8.5$ , 2H, SO<sub>2</sub>Ph-*o*-H), 7.67 (d, 1H, C<sub>8</sub>H), (7.53–7.48, (m, 1H, SO<sub>2</sub>Ph-*p*-H), 7.53–7.48 (m, 2H, SO<sub>2</sub>Ph-*m*-H), 7.47–7.53 (m, 4H, C<sub>OPh-*o*-H</sub>), 7.47–7.35 (m, 2H, C<sub>OPh-*p*-H</sub>), 7.53–7.48 (m, 1H, SO<sub>2</sub>Ph-*p*-H), 7.17 (app-dt,  $J = 1.3$ , 7.0, 1H, C<sub>7</sub>H), 7.06 (d,  $J = 7.5$ , 1H, C<sub>5</sub>H), 7.00 (app-t,  $J = 7.5$ , 1H, C<sub>6</sub>H), 6.26 (s, 1H, C<sub>2</sub>H), 3.45–3.38 (m, 1H, C<sub>19</sub>H<sub>a</sub>), 3.30–3.23 (m, 1H, C<sub>19</sub>H<sub>b</sub>), 3.12–3.02 (m, 2H, C<sub>20</sub>H), 3.07 (s, 3H, C<sub>18</sub>H), 2.99–2.92 (m, 2H, C<sub>22</sub>H), 2.81 (d,  $J = 14$ , 1H, C<sub>12</sub>H<sub>a</sub>), 2.61–2.68 (m, 2H, C<sub>23</sub>H), 2.30 (d,  $J = 14$ , 1H, C<sub>12</sub>H<sub>b</sub>), 1.92 (s, 3H, C<sub>17</sub>H), 1.44–1.37 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.31–1.22 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.56–0.52 (m, 3H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 20 °C):

$\delta$  199.1 (C<sub>21</sub>), 198.4 (C<sub>24</sub>), 166.7 (C<sub>16</sub>), 164.8 (C<sub>13</sub>), 143.6 (C<sub>9</sub>), 138.9 (SO<sub>2</sub>Ph-*ipso*-C), 137.2 (C<sub>OPh-*ipso*-C</sub>), 137.1 (C<sub>OPh-*ipso*-C</sub>), 136.3 (C<sub>4</sub>), 133.9 (SO<sub>2</sub>Ph-*p*-C), 133.9 (C<sub>OPh-*p*-C</sub>), 133.8 (C<sub>OPh-*p*-C</sub>), 129.9 (C<sub>7</sub>), 129.4

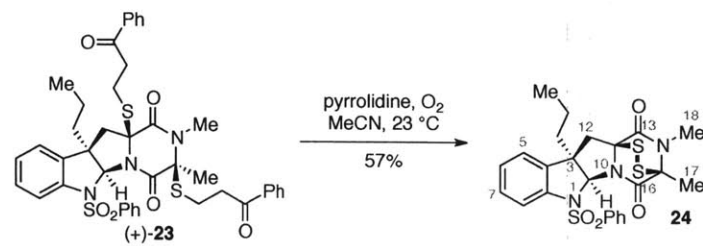
(SO<sub>2</sub>Ph-*o*-C), 129.3 (SO<sub>2</sub>Ph-*m*-C), 129.2 (COPh-*o*-C), 129.0 (COPh-*o*-C), 128.8 (COPh-*m*-C), 128.1 (COPh-*m*-C), 125.3 (C<sub>6</sub>), 123.5 (C<sub>5</sub>), 116.6 (C<sub>8</sub>), 83.0 (C<sub>2</sub>), 71.7 (C<sub>11</sub>), 68.8 (C<sub>15</sub>), 54.1 (C<sub>3</sub>), 50.0 (C<sub>12</sub>), 42.5 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 39.6 (C<sub>20</sub>), 38.8 (C<sub>23</sub>), 30.1 (C<sub>18</sub>), 27.1 (C<sub>17</sub>), 25.9 (C<sub>19</sub>), 25.3 (C<sub>22</sub>), 38.4 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 14.7 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>).

FTIR (thin film) cm<sup>-1</sup>: 2924 (m), 2851 (m), 1682 (s), 1597 (w), 1448 (m), 1372 (m).

HRMS (ESI) (*m/z*): calc'd for C<sub>42</sub>H<sub>47</sub>N<sub>4</sub>O<sub>6</sub>S<sub>3</sub> [M+NH<sub>4</sub>]<sup>+</sup>: 799.2652, found: 799.2658

[α]<sub>D</sub><sup>24</sup>: +124 (c = 0.075)

TLC (5% acetone in dichloromethane), R<sub>f</sub>: 0.25 (UV, CAM)



### **3-Propyl Pentacyclic Epidithiodiketopiperazine (24):**

Pyrrolidine (6.8  $\mu\text{L}$ , 82.8  $\mu\text{mol}$ , 4.16 equiv) was added to a solution of 3-propyl tetracyclic bis(ethylphenylketone thioether) (+)-**23** (15.6 mg, 19.9  $\mu\text{mol}$ , 1 equiv) in acetonitrile (150  $\mu\text{L}$ ) at 23  $^{\circ}\text{C}$ , and the reaction was placed under a balloon of oxygen. The clear solution immediately turned orange. After 1 h, the reaction was diluted with dichloromethane (3 mL) and washed with saturated aqueous ammonium chloride solution (3 mL). The aqueous layer was extracted with ethyl acetate ( $3 \times 2$  mL), and the combined organic layers were dried over sodium sulfate, were filtered, and were concentrated under reduced pressure. The orange residue was purified by flash column chromatography on silica gel (eluent: 3% acetone in dichloromethane) to afford the 3-propyl pentacyclic epidithiodiketopiperazine **24** (5.9 mg, 57.4%) as a white solid.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 20  $^{\circ}\text{C}$ ):

$\delta$  7.80 (d,  $J = 7.0$ , 2H,  $\text{SO}_2\text{Ph-}o\text{-H}$ ), 7.53 (app-t,  $J = 7.0$ , 1H,  $\text{SO}_2\text{Ph-}p\text{-H}$ ), 7.46–7.37 (m, 1H,  $\text{C}_8\text{H}$ ), 7.46–7.37 (m, 2H,  $\text{SO}_2\text{Ph-}m\text{-H}$ ), 7.29, (app-dt,  $J = 1.1$ , 7.7, 1H,  $\text{C}_7\text{H}$ ), 7.16 (app-t,  $J = 7.7$ , 1H,  $\text{C}_6\text{H}$ ), 7.12 (d,  $J = 7.6$ , 1H,  $\text{C}_5\text{H}$ ), 6.09 (s, 1H,  $\text{C}_2\text{H}$ ), 3.19 (d,  $J = 15.2$ , 1H,  $\text{C}_{12}\text{H}_a$ ), 2.98 (s, 2H,  $\text{C}_{18}\text{H}$ ), 2.57 (d,  $J = 15.2$ , 1H,  $\text{C}_{12}\text{H}_b$ ), 1.87 (s, 3H,  $\text{C}_{17}\text{H}$ ), 1.43–1.30 (m, 1H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.22–1.04 (m, 2H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.77–0.68 (m, 2H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ).

$^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ , 20  $^{\circ}\text{C}$ ):

$\delta$  165.9 ( $\text{C}_{13}$ ), 161.6 ( $\text{C}_{16}$ ), 142.1 ( $\text{C}_9$ ), 139.8 ( $\text{SO}_2\text{Ph-}ipso\text{-C}$ ), 137.6 ( $\text{C}_4$ ), 133.4 ( $\text{SO}_2\text{Ph-}p\text{-C}$ ), 129.3 ( $\text{C}_7$ ), 129.2 ( $\text{SO}_2\text{Ph-}m\text{-C}$ ), 127.4 ( $\text{SO}_2\text{Ph-}o\text{-C}$ ), 125.9 ( $\text{C}_6$ ), 123.6 ( $\text{C}_5$ ), 118.4 ( $\text{C}_8$ ), 83.7 ( $\text{C}_2$ ), 73.7 ( $\text{C}_{11}$ ), 73.5 ( $\text{C}_{15}$ ), 55.9 ( $\text{C}_3$ ), 41.8 ( $\text{C}_{12}$ ), 40.0 ( $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 27.7 ( $\text{C}_{18}$ ), 18.3 ( $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 18.0 ( $\text{C}_{17}$ ), 14.3 ( $\text{CH}_2\text{CH}_2\text{CH}_3$ ).

FTIR (thin film)  $\text{cm}^{-1}$ :

2960 (w), 1713 (s), 1688 (s), 1478 (w), 1460 (w), 1341 (m), 1172 (m), 1092 (w).

HRMS (ESI) ( $m/z$ ):

calc'd for  $C_{24}H_{25}NaN_3O_4S_3$   $[M+Na]^+$ :  
538.0899, found: 538.0923.

TLC (1% acetone in dichloromethane),  $R_f$ :

0.21 (UV, CAM).

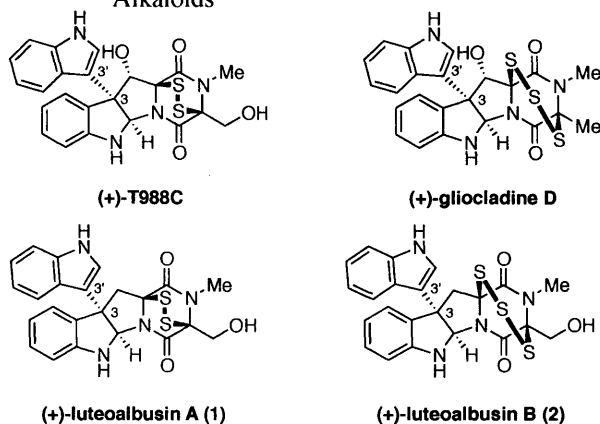


### **Chapter III.**

#### **Concise Total Synthesis of (+)-Luteoalbusin A**

## Introduction and Background

**Figure 1.** Representative C3-(3'-indolyl) Diketopiperazine Alkaloids



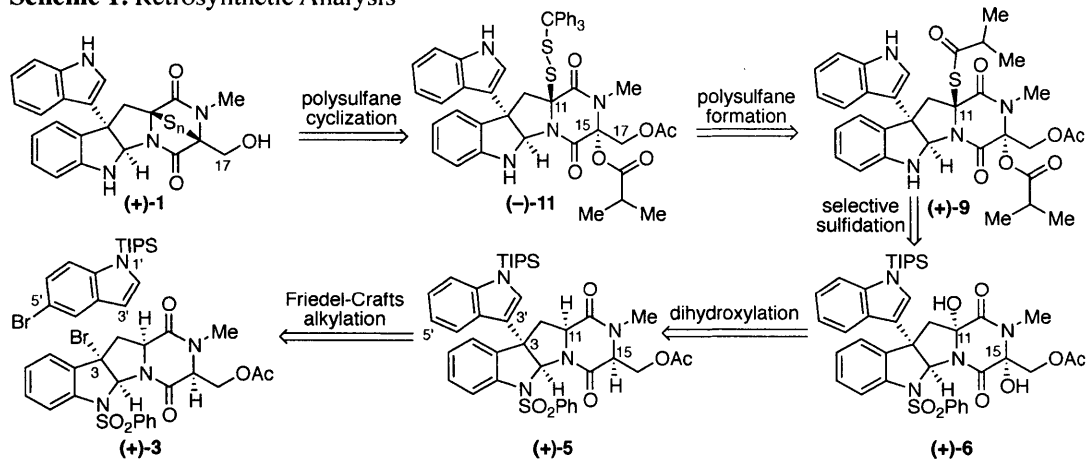
Marine natural products, such as epipolythiodiketopiperazine (ETP) alkaloids, represent a structurally complex and biologically potent class of secondary fungal metabolites.<sup>1-3</sup> The nature of the substituent at the C3 position of these ETPs can give rise to different varieties of these compounds.<sup>4-7</sup> Dimeric ETPs such as (+)-dideoxyverticillin, (+)-chaetocin A and other structurally related derivatives have been synthesized by our laboratory.<sup>8</sup> In addition, the C3-(3'-indolyl) substitution establishes an interesting subset of these diketopiperazine alkaloids and representative examples are shown in Figure 1.<sup>9,10</sup> These molecules possess a hexahydropyrroloindole substructure, as well as an epipolythiodiketopiperazine moiety. In 2012, the synthesis of two C3-(3'-indolyl) ETPs, (+)-12-deoxybionectin and (+)-bionectin A, were reported by our laboratory.<sup>8c,9c</sup> As part of our expanding program to access new C3-(3'-indolyl) alkaloids, we took interest in the synthesis of a recently discovered molecule: (+)-luteoalbusin A (1). This natural product was first isolated from the marine fungi *Acrostalagmus luteoalbus* SCSIO F457 by Wang and coworkers in 2012.<sup>10</sup> This mycotoxin is derived from L-tryptophan and L-serine. It has been found in related systems that these molecules possess increased virulence

activity with an increased degree of sulfuration of the ETP moiety.<sup>11</sup> The biological targets of these natural products includes a range of ailments such as antitumor, antiviral, antibacterial, anti-inflammatory, and various psychiatric disorders.<sup>10</sup> Howlett and coworkers had reported that the cytotoxic activity characteristic of these molecules involves the generation of reactive oxygen species from the epipolysulfane bridge.<sup>12</sup> Given the intriguing biological activity and structural complexity of these compounds, we sought the development of their efficient syntheses. Herein, we report the first concise total synthesis of and the synthetic challenges associated with the preparation of (+)-luteoalbusin A (**1**).

## Results and Discussion

### Retrosynthetic Analysis

**Scheme 1.** Retrosynthetic Analysis

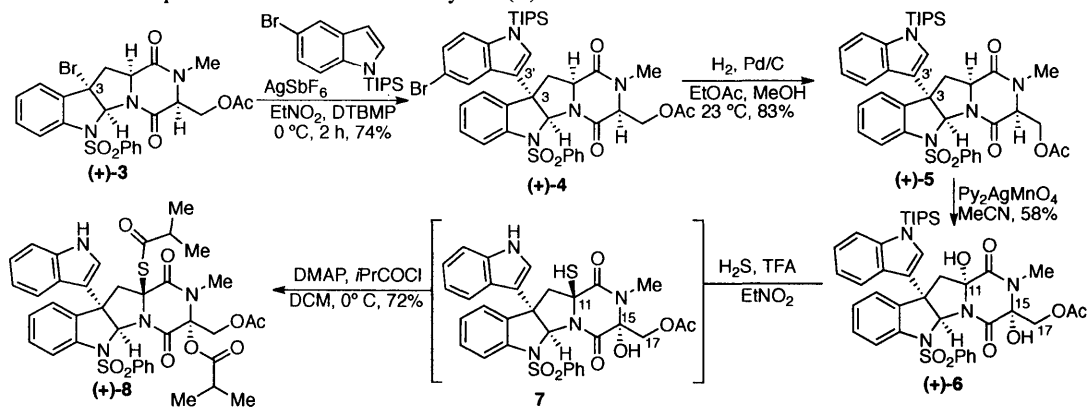


The retrosynthesis of (**1**) involved a late stage deacetylation of the C17 alcohol and Lewis acid promoted cyclization of the corresponding disulfide (-)-**11** (Scheme 1). Introduction of the mixed sulfides was achieved through the formation of key intermediate (+)-**9**. We envisioned that the requisite substrate for the introduction of sulfur at the C11 position to be diol (+)-**6**. Diketopiperazinediol (+)-**6** was readily

obtained by utilizing a highly diastereoselective double C-H oxidation at the C11 and C15 positions of (+)-**5** with bispyridinesilver(I) permanganate. Diketopiperazinediol precursor (+)-**5** was produced by utilizing a highly regioselective Friedel-Crafts indolization of (+)-**3** and C5'-bromo-N1'-TIPS indole. Tetracyclic diketopiperazine bromide (+)-**3** was quickly accessed in 3 steps according to our previously reported procedure.<sup>8b</sup>

## Synthetic Approach

**Scheme 2.** Preparation of aminothioisobutyrate (+)-**9**

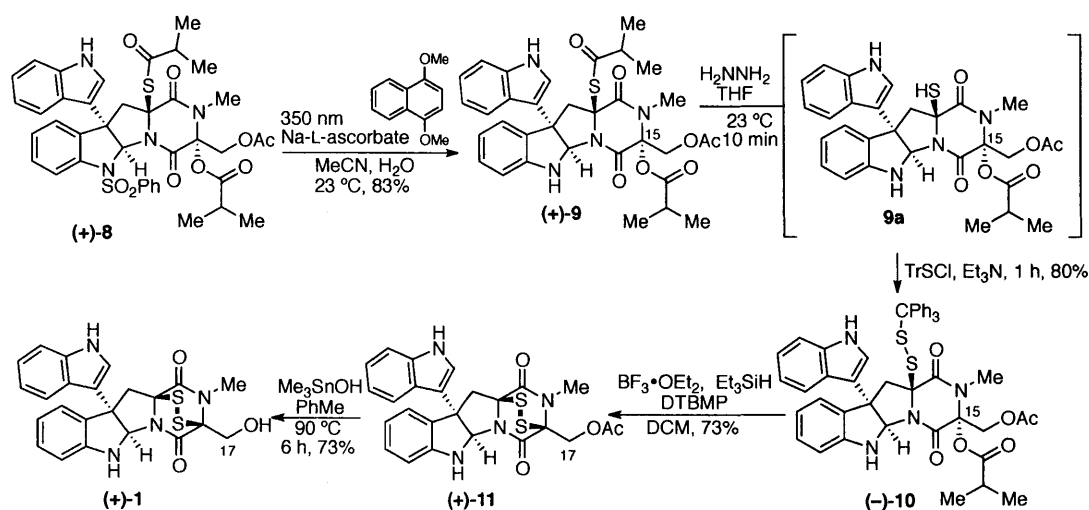


Our synthesis of (+)-luteoalbusin A (+)-**1** began with the silver-mediated Friedel-Crafts indolization of (+)-**3** (Scheme 2). From our preliminary studies on the regioselectivity of the indolization, Friedel-Crafts reactions involving an indole nucleophile typically result in a mixture of constitutional isomers, with the C3-N1' linked product as the major product. Because of this lack of selectivity, protecting groups were required on the N1' position, as well as the C5' position, to maximize the formation of the desired C3-C3' regioisomer.<sup>9c</sup> Therefore, we had designed the nucleophilic indole fragment to contain a removable bromide at the C5' position and a triisopropyl silyl (TIPS) group at the N1' position. Treatment of (+)-**3** with 5-bromo-1-(triisopropylsilyl)-

1*H*-indole and silver(I) tetrafluoroborate in nitroethane at 0 °C afforded the desired C3-indolyhexacyclic bromide (+)-**4** as the sole regioisomer in 74% yield. With the desired product in hand, the C5' bromide of (+)-**4** was removed through hydrogenolysis under one atmosphere of hydrogen gas in a 2:3 mixture of ethyl acetate and methanol at 23 °C to produce hexahydropyrroloindole (+)-**5** in 83% yield. After construction of the hexacyclic core, further functionalization of the diketopiperazine moiety was addressed. Oxidation of the C11 and C15 alpha centers of the diketopiperazine would be necessary to install the requisite polysulfide bridge in both natural products. A diastereoselective dihydroxylation of the C11 and C15 alpha centers of (+)-**5** with bis(pyridine)silver(I) permanganate (Py<sub>2</sub>AgMnO<sub>4</sub>) in acetonitrile at 23 °C provided hexacyclic diol (+)-**6** as a single diastereomer in 58% yield, which represents an approximate yield of 80% for each oxidation event.<sup>13,14</sup> The mechanism is believed to go through a stereoretentive radical rebound mechanism with initial hydrogen atom abstraction, followed by trapping of the generated carbon centered radical.<sup>15</sup> The shown configurations for the C11 and C15 tertiary alcohols in (+)-**6** are consistent with our previous observations for this oxidation on similar systems by NMR analysis.<sup>8</sup> For the subsequent sulfidation of the C11 position, it has been observed in our earlier studies of related systems that nonnucleophilic solvents are necessary for the selective ionization of the C11 alcohol and trapping with an alkyl mercaptan.<sup>8c,9c</sup> Furthermore, due to the inductive effect of the neighboring heteroatom at C17, the rate of ionization at the C15 position is greatly decreased.<sup>8b</sup> Thus, exposure of diol (+)-**6** to trifluoroacetic acid (TFA) in hydrogen sulfide (H<sub>2</sub>S) saturated nitroethane at 0 °C produced monothiol **7** with concomitant loss of the TIPS protecting group at the N1' position.<sup>16</sup> After concentrating the reaction, the residue was treated with

4-dimethylaminopyridine (DMAP) and isobutyryl chloride in dichloromethane at 0 °C to generate the desired isobutyrylthioester (+)-**8** in 72% yield over two steps. The isobutyrate groups at C11 and C15 served two purposes. Activation of the tertiary alcohol at C15 through esterification with isobutyryl chloride was required for the polysulfane cyclization step. Moreover, the acylation of the C11 thiol was necessary to enhance the stability of the molecule for the photoinduced electron transfer-promoted removal of the N1-benzenesulfonyl group.<sup>17</sup> Other sulfur containing functional groups at the C11 position were observed to be incompatible with the photochemical reaction conditions and would often lead to decomposition of the substrate. Thus treatment of (+)-**9** with 1,4-dimethoxynaphthalene (1,4-DMN) in buffered aqueous ascorbic acid/acetonitrile solution in 350 nm light produced the desired common intermediate (+)-**9** in 83% yield.

**Scheme 3.** Final Steps Towards (+)-lutealbusin A (**1**)



Selective hydrazinolysis of the thioisobutyryl group at C11 over the C15 isobutyrate was achieved with one equivalent of hydrazine in THF at 23 °C (Scheme 3). Subsequent exposure of the regenerated hemithioaminal **9a** to triphenylmethane sulfenyl chloride (TrSCl) and triethyl amine provided the desired mixed disulfide (-)-**10** in 80%

yield.<sup>18,19</sup> Ionization of the C15 isobutyrate group and subsequent cyclization of the disulfide with concomitant loss of the triphenylmethyl cation was accomplished through the treatment of (-)-**10** with boron trifluoride diethyletherate and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in dichloromethane. This furnished the penultimate luteoalbusin A acetate (+)-**11** in 73% yield. Late-stage deprotection of the C17 alcohol of (+)-**11** was achieved by utilizing trimethyltin hydroxide in toluene at 90 °C.<sup>20</sup> This deprotection afforded (+)-luteoalbusin A (**1**) in 73% yield. The data obtained from our synthetic samples matched the known characterization data from the isolation report.<sup>10</sup> Furthermore, consistent with our earlier synthesis of epipolythiodiektopiperazines,<sup>8b</sup> a similar strategy has been applied to the first total synthesis of (+)-luteoalbusin B and efforts towards the optimization of this synthesis are presently ongoing.

## Conclusion

Epipolythiodiektopiperazine alkaloids represent a structurally fascinating and biologically potent class of natural products. Using commercially available starting materials, (+)-luteoalbusin A have been synthesized from the tetracyclic bromide (+)-**3**. Friedel-Crafts arylation of the C3 position generated the desired hexacyclic bromide (+)-**3**. The C5'-bromide and N1'-TIPS groups were instrumental for maximizing regioselectivity in the addition. Two highly diastereoselective functionalizations were critical to the synthesis: a dihydroxylation of the C11 and C15 positions and the sulfidation of the C11 position with hydrogen sulfide. Furthermore, studies conducted by our laboratory and by our collaborators have provided evidence for the translational applicability of the biological activity of these compounds in cancer cell lines.

## References

1. **For reviews on cyclotryptophan and cyclotryptamine alkaloids**, see: Anthoni U., Christophersen C. and Nielsen P. H. in *Alkaloids: Chemical and Biological Perspectives*, ed. S. W. Pelletier, Pergamon Press, London, 1999, vol. 13, ch. 2, pp. 163–236; T. Hino and M. Nakagawa, in *The Alkaloids: Chemistry and Pharmacology*, ed. A. Brossi, Academic Press, New York, 1989, vol. 34, ch. 1, pp. 1–75.
2. **For reviews on epipolythiodiketopiperazines**, see: (a) Jordan, T. W.; Cordiner, S. J. *Trends Pharmacol. Sci.*, **1987**, *8*, 144. (b) Waring, P.; Eichner, R. D.; Mullbacher, A. *Med. Res. Rev.* **1988**, *8*, 499. (c) Gardiner, D. M.; Waring, P.; Howlett, B. J. *Microbiology*, **2005**, *151*, 1021. (d) Patron, N. J.; Waller, R. F.; Cozijnsen, A. J.; Straney, D. C.; Gardiner, D. M.; Nierman, W. C.; Howlett, B. J. *BMC Evol. Biol.*, **2007**, *7*, 174. (e) Huang, R.; Zhou, X.; Xu, T.; Yang, X.; Liu, Y. *Chem. Biodiversity*, **2010**, *7*, 2809. (f) Iwasa, E.; Hamashima Y.; Sodeoka, M. *Isr. J. Chem.*, **2011**, *51*, 420.
3. (a) Boyer, N.; Morrison, K. C.; Kim, J.; Hergenrother, P. J.; Movassaghi M. *Chem. Sci.*, **2013**, *4*, 1646. (b) DeLorbe, J. E.; Horne, D.; Jove, R.; Mennen, S. M.; Nam, S.; Zhang, F.L.; Overman, L. E. *J. Am. Chem. Soc.* **2013**, *135*, 4117; and references cited in these reports.
4. **For approaches to the C3sp<sup>3</sup>–C7'sp<sup>2</sup> linkage in total synthesis**, see: (a) Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488. (b) Overman, L. E.; Peterson, E. A. *Tetrahedron*, **2003**, *59*, 6905. (c) Govek, S. P.; Overman, L.



- E. *Tetrahedron* **2007**, *63*, 8499; (d) Kodanko, J. J.; Hiebert, S.; Peterson, E. A.; Sung, L.; Overman, L. E.; de Moura Linck, V.; Goerck, G. C.; Amador, T. A.; Leal, M. B.; Elisabetsky, E. *J. Org. Chem.* **2007**, *72*, 7909. (e) Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw T.; Garg, N. K. *Tetrahedron* **2010**, *66*, 4687. (f) Snell, R. H.; Woodward, R. L.; Willis, M. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 9116. (g) Zhu, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 10815. (h) Kieffer, M. E.; Chuang K. V.; Reisman, S. E. *Chem. Sci.* **2012**, *3*, 3170. (i) Kieffer, M. E.; Chuang, K. V.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 5557.
5. **For approaches to the C3sp<sup>3</sup>–C3' sp<sup>3</sup> linkage**, see: (a) Hendrickson, J. B.; Rees, R.; Goschke, R. *Proc. Chem. Soc. Lond.* **1962**, 383. (b) Hino, T.; Yamada, S. I. *Tetrahedron Lett.* **1963**, *4*, 1757. (c) Scott, A. I.; McCapra F.; Hall, E. S. *J. Am. Chem. Soc.* **1964**, *86*, 302. (d) Nakagawa, M.; Sugumi, H.; Kodato S.; Hino, T. *Tetrahedron Lett.*, **1981**, *22*, 5323. (e) Fang, C. L.; Horne, S.; Taylor, N.; Rodrigo, R. *J. Am. Chem. Soc.* **1994**, *116*, 9480. (f) Link, J. T.; Overman, L. E. *J. Am. Chem. Soc.* **1996**, *118*, 8166. (g) Overman, L. E.; Paone D.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702. (h) Somei, M.; Oshikiri, N.; Hasegawa, M.; Yamada, F. *Heterocycles*, **1999**, *51*, 1237. (i) Overman, L. E.; Larrow, J. F.; Stearns, B. A.; Vance, J. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 213. (j) Ishikawa, H.; Takayama, H.; Aimi, N. *Tetrahedron Lett.* **2002**, *43*, 5637. (k) Matsuda, Y.; Kitajima, M.; Takayama, H. *Heterocycles*, **2005**, *65*, 1031.
6. **For approaches to the C3sp<sup>3</sup>–N1' linkages**, see: (a) Matsuda, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 125. (b) Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886. (c) Espejo, V. R.; Rainier, J. D. *J. Am. Chem. Soc.*

- 2008, 130, 12894. (d) Newhouse, T.; Lewis, C. A.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, 131, 6360. (e) Espejo, V. R.; Li, X. B.; Rainier, J. D. *J. Am. Chem. Soc.* **2010**, 132, 8282. (f) Espejo, V. R.; Rainier, J. D. *Org. Lett.* **2010**, 12, 2154. (g) Perez-Balado, C.; de Lera, A. R. *Org. Biomol. Chem.* **2010**, 8, 5179. (h) Villanueva-Margalef, I.; Thurston, D. E.; Zinzalla, G. *Org. Biomol. Chem.* **2010**, 8, 5294. (i) Rainier, J. D.; Espejo, V. R. *Isr. J. Chem.* **2011**, 51, 473.
7. **For approaches to epipolythiodiketopiperazines**, see: (a) Trown, P. W. *Biochem. Biophys. Res. Commun.* **1968**, 33, 402. (b) Hino, T.; Sato, T. *Tetrahedron Lett.* **1971**, 12, 3127. (c) Poisel, H.; Schmidt, U. *Chem. Ber.* **1971**, 104, 1714. (d) Poisel, H.; Schmidt, U. *Chem. Ber.* **1972**, 105, 625. (e) Ohler, E.; Tataruch, F.; Schmidt, U. *Chem. Ber.* **1973**, 106, 396. (f) Ottenheijm, H. C. J.; Herscheid, J. D. M.; Kerkhoff, G. P. C.; Spande, T. F. *J. Org. Chem.* **1976**, 41, 3433. (g) Coffen, D. L.; Katonak, D. A.; Nelson, N. R.; Sancilio, F. D. *J. Org. Chem.* **1977**, 42, 948. (h) Herscheid, J. D. M.; Nivard, R. J. F.; Tijhuis, M. W.; Scholten, H. P. H.; Ottenheijm, H. C. J. *J. Org. Chem.* **1980**, 45, 1885. (i) Williams, R. M.; Armstrong, R. W.; Maruyama, L. K.; Dung, J.-S.; Anderson, O. P. *J. Am. Chem. Soc.* **1985**, 107, 3246. (j) Moody, C. J.; Slawin, A. M. Z.; Willows, D.; *Org. Biomol. Chem.* **2003**, 1, 2716. (k) Aliev, A. E.; Hilton, S. T.; Motherwell, W. B.; Selwood, D. L. *Tetrahedron Lett.* **2006**, 47, 2387. (l) Overman, L. E.; Sato, T. *Org. Lett.* **2007**, 9, 5267. (m) Polaske, N. W.; Dubey, R.; Nichol, G. S.; Olenyuk, B. *Tetrahedron: Asymmetry*, **2009**, 20, 2742. (n) Ruff, B. M.; Zhong, S.; Nieger, M.; Brase, S. *Org. Biomol. Chem.* **2012**, 10, 935. (o) Nicolaou, K. C.; Giguere, D.; Totokotsopoulos, S.; Sun, Y. P. *Angew. Chem., Int.*

- Ed.* **2012**, *51*, 728. (p) Williams, R. M.; Rastetter, W. H. *J. Org. Chem.*, **1980**, *45*, 2625. (q) Iwasa, E.; Hamashima, Y.; Fujishira, S.; Higuchi, E.; Ito, A.; Yoshida, M.; Sodeoka, M. *J. Am. Chem. Soc.* **2010**, *132*, 4078.
8. **For our synthetic strategies relevant to epipolythiodiketopiperazines**, see: (a) Kim, J.; Ashenhurst, J. A.; Movassaghi, M. *Science*, **2009**, 324, 238. (b) Kim, J.; Movassaghi, M. *J. Am. Chem. Soc.* **2012**, *132*, 14376. (c) Coste, A.; Kim, J.; Adams, T. C.; Movassaghi, M. *Chem. Sci.* **2012**, *4*, 3191.
9. (a) Feng, Y.; Blunt, J. W.; Cole, A. L. J.; Munro, M. H. G. *J. Nat. Prod.* **2004**, *67*, 2090. (b) Dong, J. Y.; He, H. P.; Shen, Y.-M.; Zhang, K. Q. *J. Nat. Prod.* **2005**, *68*, 1510. (c) Boyer, N.; Movassaghi, M. *Chem. Sci.* **2012**, *3*, 1789.
10. Wang, F. Z.; Huang, Z.; Shi, X. F.; Chen, Y. C.; Zhang, W. M.; Tian, X. P.; Li, J.; Zhang, S. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7265.
11. Saito, T.; Suzuki, Y.; Koyama, K.; Natori, S.; Iitaka, Y.; Kinoshita, T. *Chem. Pharm. Bull.* **1942**, *36*, 1942.
12. Gardiner, D. M.; Waring, P.; Howlett, B. J. *Microbiology*, **2005**, *151*, 1021.
13. Gardner, K.; Mayer, J. M. *Science*, **1995**, *269*, 1849.
14. Firouzabadi, H.; Vessal, B.; Naderi, M.; *Tetrahedron Lett.* **1978**, *23*, 1847.
15. Strassner, T.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 7821.
16. High degrees of diastereoselectivity was achieved in the thiolation with H<sub>2</sub>S due to the C3 stereocenter.
17. Hamada, T.; Nishida, A.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 140.
18. For epidithiodiketopiperazine synthesis using sulfenyl chlorides such as chloro(triphenylmethane)disulfane for thiol protection, see 15. For preparation of

this reagent, see: Williams, C. R.; Britten, J. F.; Harpp, D. N. *J. Org. Chem.* **1994**, *59*, 806.

19. The efficiency of the thiol sulfenylation in the presence of the C17 alcohol was inefficient and led to decomposition of the material.

20. Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 1378.

## Experimental Section

**General Procedures.** All reactions were performed in oven-dried or flame-dried round-bottom flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon. Cannulae or gas-tight syringes with stainless steel needles were used to transfer air- or moisture-sensitive liquids. Where necessary (so noted), solutions were deoxygenated by sparging with argon for a minimum of 10 min. Flash column chromatography was performed as described by Still et al. using granular silica gel (60-Å pore size, 40–63  $\mu\text{m}$ , 4–6%  $\text{H}_2\text{O}$  content, Zeochem).<sup>6</sup> Analytical thin layer chromatography (TLC) was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to short wave ultraviolet light (254 nm) and an aqueous solution of ceric ammonium molybdate (CAM) followed by heating on a hot plate ( $\sim 250$  °C). Organic solutions were concentrated at 29–30 °C on rotary evaporators capable of achieving a minimum pressure of  $\sim 2$  torr. The benzenesulfonyl photodeprotection was accomplished by irradiation in a Rayonet RMR-200 photochemical reactor (Southern New England Ultraviolet Company, Branford, CT, USA) equipped with 16 lamps (RPR-3500, 24 W,  $\lambda_{\text{max}} = 350$  nm, bandwidth  $\sim 20$  nm).

**Materials.** Commercial reagents and solvents were used as received with the following exceptions: dichloromethane, acetonitrile, tetrahydrofuran, methanol, pyridine, toluene, and triethylamine were purchased from J.T. Baker (Cycletainer<sup>TM</sup>) and were purified by the method of Grubbs *et al.* under positive argon pressure.<sup>7</sup> Nitromethane and nitroethane (from Sigma–Aldrich) were purified by fractional distillation over calcium

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<sup>6</sup> Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, 43, 2923.

<sup>7</sup> Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* 1996, 15, 1518.

hydride and were stored over Linde 4Å molecular sieves in Schlenk flasks sealed with septa and teflon tape under argon atmosphere.<sup>8</sup> Titanium (IV) ethoxide (99.99%-Ti) PURATREM and bromine were purchased from Strem Chemicals, Inc.; *N*-Boc-L-sarcosine, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, *N*-Hydroxybenzotriazole, *tert*-butyldimethylsilyl trifluoromethanesulfonate, trifluoroacetic acid, 4-(dimethylamino)pyridine, silver nitrate were purchased from Chem-Impex; 1,4-dimethoxynaphthalene was purchased from Alfa Aesar; di-*tert*-butyl dicarbonate was purchased from Oakwood Products, Inc.; 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) was purchased from OChem Incorporation. All other solvents and chemicals were purchased from Sigma–Aldrich. 1,4-Dimethoxynaphthalene was purified by crystallization from absolute ethanol.

**Instrumentation.** Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded with a Bruker AVANCE-600 NMR spectrometer (with a Magnex Scientific superconducting actively-shielded magnet) or with a Varian inverse probe 500 INOVA spectrometer, are reported in parts per million on the δ scale, and are referenced from the residual protium in the NMR solvent (CDCl<sub>3</sub>: δ 7.26 (CHCl<sub>3</sub>), or acetone-**d**<sub>6</sub>: δ 2.05 (acetone-**d**<sub>6</sub>).<sup>9</sup> Data are reported as follows: chemical shift [multiplicity (br = broad, s = singlet, d = doublet, t = triplet, sp = septet, m = multiplet), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance (<sup>13</sup>C NMR) spectra were recorded with a Bruker AVANCE-600 NMR Spectrometer (with a Magnex Scientific superconducting actively-shielded magnet) or a Bruker AVANCE-400 NMR

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<sup>8</sup> Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 5<sup>th</sup> ed.; Butterworth–Heinemann: London, 2003.

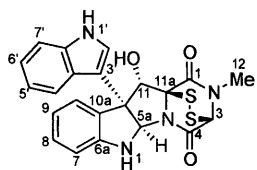
<sup>9</sup> Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* 2010, 29, 2176.

Spectrometer (with a Magnex Scientific superconducting magnet) or with a Varian 500 INOVA spectrometer, are reported in parts per million on the  $\delta$  scale, and are referenced from the carbon resonances of the solvent ( $\text{CDCl}_3$ ;  $\delta$  77.23, acetone- $\text{d}_6$ : 29.84). Data are reported as follows: chemical shift (multiplicity, coupling constant(s) in Hertz, assignment). Infrared data (IR) were obtained with a Perkin-Elmer 2000 FTIR and are reported as follows: frequency of absorption ( $\text{cm}^{-1}$ ), intensity of absorption (s = strong, m = medium, w = weak, br = broad). Optical rotations were measured on a Jasco-1010 polarimeter with a sodium lamp and are reported as follows:  $[\alpha]_{\lambda}^T$  °C (c = g/100 mL, solvent). We are grateful to Dr. Li Li and Deborah Bass for obtaining the mass spectrometric data at the Department of Chemistry's Instrumentation Facility, Massachusetts Institute of Technology. High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics APEXIV 4.7 Tesla FT-ICR-MS using an electrospray (ESI) ionization source.

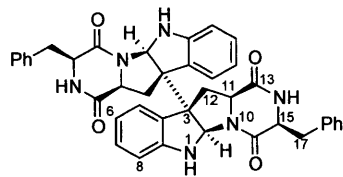
**Positional Numbering System.** At least three numbering systems for dimeric diketopiperazine alkaloids exist in the literature.<sup>10</sup> In assigning the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of all intermediates en route to our total syntheses of (+)-luteoalbusin A (**1**) and B (**2**), we wished to employ a uniform numbering scheme. For ease of direct comparison, particularly between early intermediates, non-thiolated diketopiperazines, and advanced compounds, the numbering system used by Barrow for (+)-WIN-64821 (using positional numbers 1–21) is optimal and used throughout this report. In key instances, the products are accompanied by the numbering system as shown below.

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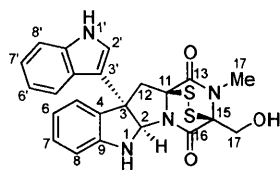
<sup>10</sup> (a) Von Hauser, D.; Weber, H. P.; Sigg, H. P. *Helv. Chim. Acta* 1970, 53, 1061. (b) Barrow, C. J.; Cai, P.; Snyder, J. K.; Sedlock, D. M.; Sun, H. H.; Cooper, R. *J. Org. Chem.* 1993, 58, 6016. (c) Springer, J. P.; Büchi, G.; Kobbe, B.; Demain, A. L.; Clardy, J. *Tetrahedron Lett.* 1977, 28, 2403. (d) Zheng, C.-J.; Kim, C.-J.; Bae, K. S.; Kim, Y.-H.; Kim, W.-G. *J. Nat. Prod.* 2006, 69, 1816. (e) DeLorbe, J. E.; Jabri, S. Y.; Mennen, S. M.; Overman, L. E.; Zhang, F.-L. *J. Am. Chem. Soc.* 2011, 133, 6549.



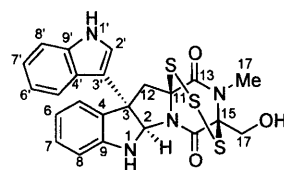
(+)-bionectin A  
Kim's isolation report  
Overman's reports



(+)-WIN-64821  
Barrow's numbering for the  
simpler diketopiperazine  
framework

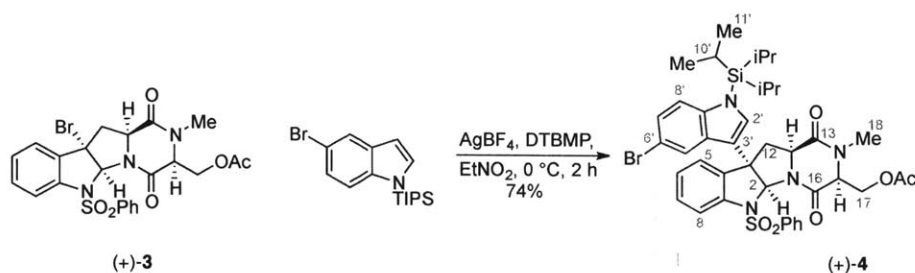


(+)-luteoalbusin A (1)  
*This document*



(+)-luteoalbusin B (2)  
*This document*





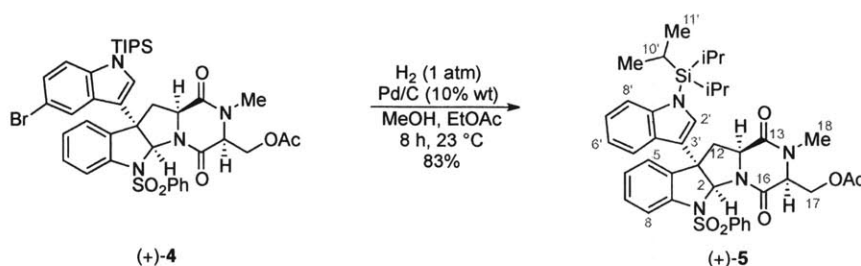
### C3-(5-Bromo-1-TIPS-indol-3-yl)-pyrrolidinoindoline (+)-6:

A round-bottom flask was charged with endo-tetracyclic bromide (+)-3 (348 mg, 630  $\mu\text{mol}$ , 1 equiv), 2,6-di-tert-butyl-4-methylpyridine (DTBMP, 155 mg, 760  $\mu\text{mol}$ , 1.20 equiv), and 5-bromo-1-triisopropylsilyl-1H-indole (889 mg, 2.52 mmol, 4.00 equiv), and the mixture was dried azeotropically (concentration of a benzene solution, 2  $\times$  15 mL) under reduced pressure and placed under an argon atmosphere. Anhydrous nitroethane (10 mL) was introduced via syringe, and the mixture was cooled to 0  $^{\circ}\text{C}$  in an ice-water bath. A solution of silver (I) tetrafluoroborate (491 mg, 2.52 mmol, 4.00 equiv) in anhydrous nitroethane (5 mL) at 0  $^{\circ}\text{C}$  was introduced via cannula to the solution containing the tetracyclic bromide (+)-17. After 5 min, a black precipitate was observed in the clear yellow reaction solution. The reaction flask was covered in aluminum foil, and the suspension was maintained at 0  $^{\circ}\text{C}$ . After 1 hour, saturated aqueous sodium chloride solution (25 mL) was introduced, and the resulting biphasic mixture was vigorously stirred for 30 min at 0  $^{\circ}\text{C}$ . The reaction mixture was diluted with ethyl acetate (10 mL), was filtered through a Celite pad, and the solid was washed with ethyl acetate (3  $\times$  20 mL). The combined filtrates were washed with 5% aqueous citric acid solution (2  $\times$  50 mL), water (3  $\times$  50 mL), and saturated aqueous sodium chloride solution (25 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The resulting orange residue was purified by flash column chromatography (eluent: gradient, 2  $\rightarrow$  10% acetone in dichloromethane) to afford the indole adduct (+)-6 (421 mg, 81.0%) as a white solid. Structural assignments were made with additional information from gCOSY, HSQC, and HMBC data.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 20  $^{\circ}\text{C}$ ):

$\delta$  7.97 (d,  $J = 8.5$ , 2H,  $\text{SO}_2\text{Ph-}o\text{-H}$ ), 7.71 (d,  $J = 8.5$ , 1H,  $\text{C}_8\text{H}$ ), 7.51 (t,  $J = 7.5$ , 1H,  $\text{SO}_2\text{Ph-}p\text{-H}$ ), 7.36 (t,  $J = 7.5$ , 2H,  $\text{SO}_2\text{Ph-}m\text{-H}$ ), 7.29-7.25 (m, (2H,  $\text{C}_7\text{H}$ ,  $\text{C}_8\text{H}$ ), 7.13 (dd,  $J = 9.0$ , 2.0, 1H,  $\text{C}_7\text{H}$ ), 6.96 (apt-t,  $J = 7.5$ , 1H,  $\text{C}_6\text{H}$ ), 6.89 (s, 1H,  $\text{C}_2\text{H}$ ), 6.84 (d,  $J = 7.5$ , 1H,  $\text{C}_5\text{H}$ ), 6.51 (d,  $J = 1.8$ , 1H,  $\text{C}_5\text{H}$ ), 6.27 (s, 1H,  $\text{C}_2\text{H}$ ), 4.86 (dd,  $J = 12.5$ , 2.5, 1H,  $\text{C}_{17}\text{H}_a$ ), 4.60 (dd,  $J = 12.5$ , 2.5, 1H,  $\text{C}_{17}\text{H}_b$ ), 4.47 (dd,  $J = 10.5$ , 7.5, 1H,  $\text{C}_{15}\text{H}$ ), 4.05 (app-t,  $J = 2.5$ , 1H,  $\text{C}_{15}\text{H}$ ), 3.05 (dd,  $J = 14.5$ , 10.5, 1H,  $\text{C}_{12}\text{H}_a$ ), 3.03 (s, 3H,  $\text{C}_{18}\text{H}$ ), 2.80 (dd,  $J = 14.5$ ,

	10.5, 1H, C <sub>12</sub> H <sub>b</sub> ), 1.96 (s, 3H, CH <sub>3</sub> acetate), 1.56 (app-sp, <i>J</i> = 7.5, 3H, C <sub>10</sub> H), 1.37 (app-d, <i>J</i> = 18.0, 18H, C <sub>11</sub> H).
<sup>13</sup> C NMR (150 MHz, CDCl <sub>3</sub> , 20 °C):	δ 170.9 (C=O <sub>acetate</sub> ), 168.5 (C <sub>13</sub> ), 166.0 (C <sub>16</sub> ), 141.3 (C <sub>9</sub> ), 139.8 (C <sub>9</sub> ), 137.3 (SO <sub>2</sub> Ph- <i>i</i> -C), 134.6 (C <sub>4</sub> ), 134.2 (SO <sub>2</sub> Ph- <i>p</i> -C), 130.9 (C <sub>2</sub> ), 130.3 (C <sub>4</sub> ), 129.6 (C <sub>7</sub> ), 129.3, (SO <sub>2</sub> Ph- <i>m</i> -C (C <sub>9</sub> ), 127.9 (SO <sub>2</sub> Ph- <i>o</i> -C), 125.4 (C <sub>7</sub> ) 124.7 (C <sub>6</sub> ), 124.1, (C <sub>5</sub> ), 121.8 (C <sub>5</sub> ), 116.1 (C <sub>8</sub> ), 115.7 (C <sub>8</sub> ), 115.4 (C <sub>3</sub> ), 113.6 (C <sub>6</sub> ), 83.1, (C <sub>2</sub> ), 61.1 (C <sub>11</sub> ), 60.8 (C <sub>17</sub> ), 59.1 (C <sub>15</sub> ), 55.0 (C <sub>3</sub> ), 38.5 (C <sub>12</sub> ), 30.0 (C <sub>14</sub> ), 20.9 (CH <sub>3</sub> acetate) 18.3 (C <sub>11</sub> ) 12.9 (C <sub>10</sub> )
FTIR (thin film) cm <sup>-1</sup> :	3061 (s), 2950 (s), 1675 (m), 1451 (m), 1385 (m).
HRMS (ESI) ( <i>m/z</i> ):	calc'd for C <sub>40</sub> H <sub>48</sub> BrN <sub>4</sub> O <sub>6</sub> S [M+H] <sup>+</sup> : 819.2242, found: 819.2262.
[α] <sub>D</sub> <sup>24</sup> :	+139.9 ( <i>c</i> = 0.34, CHCl <sub>3</sub> ).
TLC (5% acetone in dichloromethane), R <sub>f</sub> :	0.26 (UV, CAM, KMnO <sub>4</sub> ).



### C3-(1-TIPS-indol-3-yl)-pyrrolidinoindoline (+)-7:

A mixture of anhydrous methanol and ethyl acetate (3:2 v/v, 5 mL) was introduced into around-bottom flask charged with the indole adduct (+)-6 (108 mg, 130  $\mu\text{mol}$ , 1 equiv) and palladium on activated charcoal (10% w/w, 27.7 mg, 301  $\mu\text{mol}$ , 0.200 equiv). The flask was purged with argon for 5 minutes. The flask was then sealed under an atmosphere of hydrogen after being purged with hydrogen gas for 10 minutes. The solution was vigorously stirred at room temperature for 8 hours. The reaction was diluted with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (2  $\times$  10 mL). The organic layers were combined, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting orange residue was purified by flash column chromatography (eluent: gradient, 2  $\rightarrow$  10% acetone in dichloromethane) to afford the indole adduct (+)-7 (80.7 mg, quantitative yield) as a white solid.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 20  $^\circ\text{C}$ ):

$\delta$  8.05 (d,  $J = 7.0$ , 2H,  $\text{SO}_2\text{Ph-}o\text{-H}$ ), 7.82 (d,  $J = 8.5$ , 1H,  $\text{C}_8\text{H}$ ), 7.57 (app-t,  $J = 7.0$ , 1H,  $\text{SO}_2\text{Ph-}p\text{-H}$ ), 7.41-7.38 (m, 3H,  $\text{C}_8\text{H}$ ,  $\text{SO}_2\text{Ph-}m\text{-H}$ ), 7.25 (t,  $J = 8.0$ , 1H,  $\text{C}_7\text{H}$ ), 7.01 (t,  $J = 7.5$ , 1H,  $\text{C}_7\text{H}$ ), 6.97 (s, 1H,  $\text{C}_2\text{H}$ ), 6.93 (t,  $J = 7.5$ , 1H,  $\text{C}_6\text{H}$ ), 6.76 (d,  $J = 7.5$ , 1H,  $\text{C}_5\text{H}$ ), 6.55 (t,  $J = 7.5$ , 1H,  $\text{C}_6\text{H}$ ), 6.32 (s, 1H,  $\text{C}_2\text{H}$ ), 6.02 (d, 2H,  $J = 8.5$ , 1H,  $\text{C}_5\text{H}$ ), 4.90 (dd,  $J = 11.5$ , 3.0, 1H,  $\text{C}_{17}\text{H}_a$ ), 4.60 (dd,  $J = 11.5$ , 3.0, 1H,  $\text{C}_{17}\text{H}_b$ ), 4.46 (dd,  $J = 10.5$ , 6.5, 1H,  $\text{C}_{15}\text{H}$ ), 4.03 (app-t,  $J = 2.7$ , 1H,  $\text{C}_{11}\text{H}$ ), 3.09 (dd,  $J = 14.0$ , 10.5, 1H,  $\text{C}_{12}\text{H}_a$ ), 3.05 (s, 3H,  $\text{C}_{18}\text{H}$ ), 2.69 (dd,  $J = 14.5$ , 10.0, 1H,  $\text{C}_{12}\text{H}_b$ ), 2.04 (s, 3H,  $\text{CH}_3_{\text{acetate}}$ ), 1.61 (app-sp,  $J = 7.5$ , 3H,  $\text{C}_{10}\text{H}$ ), 1.07 (app-d,  $J = 18.0$ , 18H,  $\text{C}_{11}\text{H}$ ).

$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , 20  $^\circ\text{C}$ ):

$\delta$  171.0 ( $\text{C}=\text{O}_{\text{acetate}}$ ), 168.9 ( $\text{C}_{13}$ ), 166.5 ( $\text{C}_{16}$ ), 142.7 ( $\text{C}_9$ ), 139.7 ( $\text{C}_9$ ), 137.0 ( $\text{SO}_2\text{Ph-}i\text{-C}$ ), 135.0 ( $\text{C}_4$ ), 133.7 ( $\text{SO}_2\text{Ph-}p\text{-C}$ ), 129.4 ( $\text{C}_2$ ), 129.3

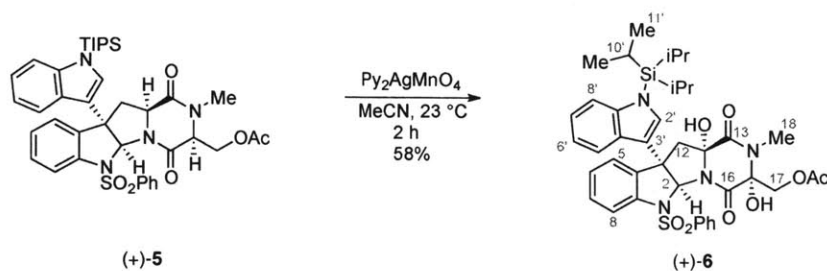
(SO<sub>2</sub>Ph-*m*-C), 129.1 (SO<sub>2</sub>Ph-*o*-C),  
128.5 (C<sub>4</sub>), 128.3 (C<sub>7</sub>), 124.6 (C<sub>7</sub>),  
123.8 (C<sub>6</sub>), 122.3 (C<sub>5</sub>), 120.2 (C<sub>5</sub>),  
119.3 (C<sub>8</sub>), 115.7 (C<sub>8</sub>) 115.3 (C<sub>3</sub>),  
114.6 (C<sub>6</sub>), 82.9 (C<sub>2</sub>), 61.1 (C<sub>11</sub>), 60.9  
(C<sub>17</sub>), 59.5 (C<sub>15</sub>), 55.3 (C<sub>3</sub>), 38.6 (C<sub>12</sub>),  
29.9 (C<sub>17</sub>), 21.0 (CH<sub>3</sub><sub>acetate</sub>), (18.4 (C<sub>11'</sub>),  
13.0 (C<sub>10'</sub>).

FTIR (thin film) cm<sup>-1</sup>: 2950 (br-s), 1734 (m), 1675 (m), 1384  
(m), 1150 (m),

HRMS (ESI) (*m/z*): calc'd for C<sub>40</sub>H<sub>52</sub>N<sub>5</sub>O<sub>6</sub>SSi [M+NH<sub>4</sub>]<sup>+</sup>:  
758.3402,  
found: 758.3391.

[α]<sub>D</sub><sup>24</sup>: +137.1 (*c* = 1.12, CHCl<sub>3</sub>).

TLC (5% acetone in dichloromethane), R<sub>f</sub>: 0.34 (UV, CAM, KMnO<sub>4</sub>).



### C3-(1-TIPS-indol-3-yl)-pyrrolidinoindoline diol (+)-8:

Bis(pyridine)silver permanganate (581 mg, 1.51 mmol, 5.00 equiv) was added as a solid to a solution of C3-(1-TIPS-indol-3-yl)-pyrrolidinoindoline (+)-7 (224 mg, 303  $\mu$ mol, 1 equiv) in acetonitrile (10 mL) at 23 °C. After 2 hours, the reaction mixture was diluted with ethyl acetate (10 mL) and washed with aqueous sodium bisulfite solution (1 M, 20 mL). The resulting aqueous layer was extracted with ethyl acetate (2  $\times$  20 mL) and the combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica gel (eluent: 5% acetone in dichloromethane) to afford pyrrolidinoindoline diol (+)-8 (136 mg, 58%) as a colorless solid. Structural assignments were made using additional information from gCOSY, HSQC, and HMBC experiments.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 20 °C):

$\delta$  7.81 (d,  $J$  = 8.3, 2H, SO<sub>2</sub>Ph-*o*-H), 7.68 (d,  $J$  = 8.0, 1H, C<sub>8</sub>H), 7.46 (t,  $J$  = 8.0, 1H, SO<sub>2</sub>Ph-*p*-H), 7.41 (d,  $J$  = 8.0, 1H, C<sub>8</sub>H), 7.28-7.23 (m, 3H, SO<sub>2</sub>Ph-*m*-H, C<sub>7</sub>H), 7.05 (t,  $J$  = 8.0, 1H, C<sub>7</sub>H), 7.02 (t,  $J$  = 8.0, 1H, C<sub>6</sub>H), 6.95 (d,  $J$  = 7.0, 1H, C<sub>5</sub>H), 6.92 (s, 1H, C<sub>2</sub>H), 6.67 (t,  $J$  = 7.0, 1H, C<sub>6</sub>H), 6.53 (br-d,  $J$  = 7.0, 1H, C<sub>5</sub>H), 5.04 (br-s, 1H, OH), 5.02 (br-s, OH), 4.85 (d,  $J$  = 11.0, 1H, C<sub>17</sub>H<sub>a</sub>), 4.25 (d,  $J$  = 11.0, 1H, C<sub>17</sub>H<sub>b</sub>), 3.21 (d,  $J$  = 14.5, 1H, C<sub>12</sub>H<sub>a</sub>), 3.15 (d,  $J$  = 14.5, 1H, C<sub>12</sub>H<sub>b</sub>), 2.98 (s, 3H, C<sub>17</sub>H), 1.88 (s, 3H, CH<sub>3</sub><sub>acetate</sub>), 1.59 (h, 3H, C<sub>10</sub>H), 1.05 (app-d, 18H, C<sub>11</sub>H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, 20 °C):

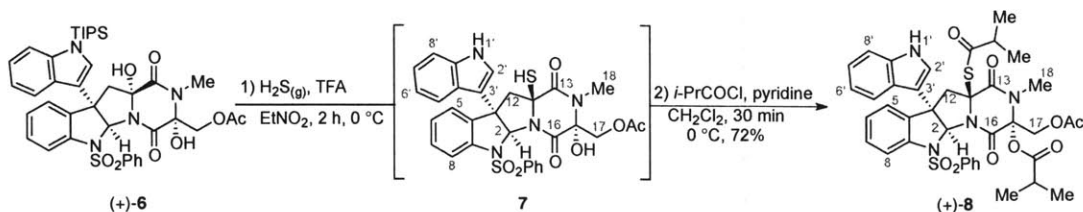
$\delta$  170.4 (C=O<sub>acetate</sub>), 167.3 (C<sub>13</sub>), 167.0 (C<sub>16</sub>), 142.6 (C<sub>9</sub>), 139.7 (C<sub>9</sub>), 137.5 (C<sub>4</sub>), 135.4 (C<sub>4</sub>), 133.7 (SO<sub>2</sub>Ph-*p*-C), 131.0 (C<sub>6</sub>), 129.4 (C<sub>7</sub>), 129.2 (SO<sub>2</sub>Ph-*m*-C), 128.4 (SO<sub>2</sub>Ph-*i*-C), 128.1 (SO<sub>2</sub>Ph-*o*-C), 125.0 (C<sub>2</sub>), 124.6 (C<sub>5</sub>), 122.3 (C<sub>7</sub>), 120.6 (C<sub>6</sub>), 119.4 (C<sub>5</sub>), 116.7 (C<sub>3</sub>), 115.9 (C<sub>8</sub>), 114.6 (C<sub>8</sub>), 88.3 (C<sub>11</sub>), 86.3 (C<sub>15</sub>), 83.7 (C<sub>2</sub>), 63.8

FTIR (thin film)  $\text{cm}^{-1}$ : (C<sub>17</sub>), 54.3 (C<sub>3</sub>), 46.4 (C<sub>12</sub>), 27.7 (C<sub>18</sub>), 20.9 (CH<sub>3</sub><sub>acetate</sub>), 18.4 (C<sub>11'</sub>), 13.0 (C<sub>10</sub>).  
3374 (s), 2949 (s), 2869 (m), 1749 (m), 1697 (s), 1450 (m), 1374 (s), 1229 (m), 1170 (s),

HRMS (ESI) (*m/z*): calc'd for C<sub>40</sub>H<sub>49</sub>N<sub>4</sub>O<sub>8</sub>SSi [M+H]<sup>+</sup>: 773.3035, found: 773.3016.

[ $\alpha$ ]<sub>D</sub><sup>24</sup>: +9.0 (*c* = 0.91, CHCl<sub>3</sub>).

TLC (10% acetone in dichloromethane), R<sub>f</sub>: 0.23 (UV, CAM).



### Hexacyclic thioisobutyrate (+)-10:

A slow stream of hydrogen sulfide gas was introduced into a solution of diol (+)-8 (507 mg, 660  $\mu\text{mol}$ , 1 equiv) in anhydrous nitroethane (10.0 mL) at 0 °C, providing a saturated hydrogensulfide solution. After 15 min, trifluoroacetic acid (1 mL) was added via syringe, and the slow introduction of hydrogen sulfide into the mixture was maintained for another 10 min. The reaction mixture was left under an atmosphere of hydrogen sulfide for an additional 2 h at 0 °C. The resulting mixture was concentrated under reduced pressure to afford the hexacyclic aminothiolsulfide **9** that was used in the next step without further purification. The orange residue was dissolved in anhydrous dichloromethane (10 mL) and cooled to 0 °C in an ice–water bath. 4-dimethylaminopyridine (DMAP) (802, 6.56 mmol, 10.0 equiv) was added to the solution of the hexacyclic aminothiolsulfide **9** followed by addition of isobutyryl chloride (344  $\mu\text{L}$ , 3.28 mmol, 5.00 equiv). After 30 minutes, the ice–water bath was removed, and the yellow solution was allowed to warm to 23 °C. Methanol (1 mL) was added to the solution. After 5 min, the reaction mixture was diluted with dichloromethane (10 mL). The resulting mixture was sequentially washed with aqueous hydrogen chloride solution (1 N, 2  $\times$  20 mL), water (2  $\times$  20 mL), and saturated aqueous sodium chloride solution (20 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The yellow residue was purified by flash column chromatography on silica gel (eluent: gradient, 15  $\rightarrow$  30% acetone in hexanes) to afford the thioisobutyrate (+)-10 (368 mg, 72.1%) as a colorless gel.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 20 °C):

$\delta$  7.88 (br-s, 1H,  $\text{N}_1\text{H}$ ), 7.75 (d,  $J = 8.0$ , 1H,  $\text{C}_8\text{H}$ ), 7.52 (app-d,  $J = 8.5$ , 2H,  $\text{SO}_2\text{Ph-}o\text{-H}$ ), 7.35-7.26 (m, 3H,  $\text{C}_6\text{H}$ ,  $\text{C}_7\text{H}$ ,  $\text{SO}_2\text{Ph-}p\text{-H}$ ), 7.23 (d,  $J = 8.5$ , 1H,  $\text{C}_5\text{H}$ ) 7.11 (app-d,  $J = 7.5$ , 1H,  $\text{C}_8\text{H}$ ), 7.07 (app-d,  $J = 7.5$ , 1H,  $\text{C}_5\text{H}$ ), 7.06-7.01 (m, 3H,  $\text{SO}_2\text{Ph-}m\text{-H}$ ,  $\text{C}_6\text{H}$ ), 6.75 (app-t,  $J = 7.5$ , 1H,  $\text{C}_7\text{H}$ ), 6.74 (s, 1H,  $\text{C}_2\text{H}$ ), 6.36 (d,  $J = 2.5$ , 1H,  $\text{C}_2\text{H}$ ), 4.81 (d,  $J = 11.5$ , 1H,  $\text{C}_{17}\text{H}_a$ ), 4.47 (d,  $J = 11.5$ , 1H,  $\text{C}_{17}\text{H}_b$ ), 3.91 (d,  $J = 14.5$ , 1H,  $\text{C}_{12}\text{H}_a$ ), 3.50 (d,  $J = 14.5$ , 1H,  $\text{C}_{12}\text{H}_b$ ), 2.89 (s, 3H,  $\text{C}_{18}\text{H}$ ), 2.63 (app-sp,  $J = 7.0$ , 1H,  $\text{CH}_{\text{isobutyrate}}$ ), 2.18 (app-sp,  $J = 7.0$ , 1H,  $\text{CH}_{\text{thioisobutyrate}}$ ), 2.14 (s, 3H,  $\text{CH}_{3\text{acetate}}$ ), 1.25-1.19 (m, 6H,  $\text{CH}_{3\text{isobutyrate}}$ ), 0.92 (d,  $J = 7.5$ , 3H,

$\text{CH}_{3\text{thioisobutyrate}}$ , 0.82 (d,  $J = 7.5$ , 3H,  $\text{CH}_{3\text{thioisobutyrate}}$ ).

$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , 20 °C):

$\delta$  200.7 ( $\text{C}=\text{O}_{\text{thioisobutyrate}}$ ), 175.7 ( $\text{C}=\text{O}_{\text{isobutyrate}}$ ), 170.5 ( $\text{C}=\text{O}_{\text{acetate}}$ ), 166.7 ( $\text{C}_{13}$ ), 161.6 ( $\text{C}_{16}$ ), 143.1 ( $\text{C}_9$ ), 138.6 ( $\text{SO}_2\text{Ph-}i\text{-C}$ ), 137.6 ( $\text{C}_9$ ), 136.7 ( $\text{C}_4$ ), 133.7 ( $\text{SO}_2\text{Ph-}p\text{-C}$ ), 129.8 ( $\text{C}_7$ ), 129.1 ( $\text{SO}_2\text{Ph-}m\text{-C}$ ), 127.8 ( $\text{SO}_2\text{Ph-}o\text{-C}$ ), 125.8 ( $\text{C}_6$ ), 125.5 ( $\text{C}_5$ ), 125.1 ( $\text{C}_4$ ), 123.9 ( $\text{C}_2$ ), 122.9 ( $\text{C}_7$ ), 120.6 ( $\text{C}_6$ ), 120.2 ( $\text{C}_5$ ), 117.4 ( $\text{C}_8$ ), 116.7 ( $\text{C}_3$ ), 111.9 ( $\text{C}_8$ ), 87.4 ( $\text{C}_{15}$ ), 85.1 ( $\text{C}_2$ ), 74.8 ( $\text{C}_{11}$ ), 63.9 ( $\text{C}_{17}$ ), 54.3 ( $\text{C}_3$ ), 44.5 ( $\text{C}_{12}$ ), 43.9 ( $\text{CH}_{\text{thioisobutyrate}}$ ), 34.5 ( $\text{CH}_{\text{isobutyrate}}$ ), 29.1 ( $\text{C}_{18}$ ), 21.8 ( $\text{CH}_{3\text{acetate}}$ ), 19.8 ( $\text{CH}_{3\text{isobutyrate}}$ ), 19.6 ( $\text{CH}_{3\text{isobutyrate}}$ ), 19.6 ( $\text{CH}_{3\text{thioisobutrate}}$ ), 19.0 ( $\text{CH}_{3\text{thioisobutyrate}}$ ).

FTIR (thin film)  $\text{cm}^{-1}$ :

3398 (s), 2974 (m), 1745 (s), 1698 (s), 1461 (m), 1448 (m), 1369 (s), 1266 (w), 1220 (m), 1171 (m), 1092 (m), 1054 (m), 950 (m).

HRMS (ESI) ( $m/z$ ):

calc'd for  $\text{C}_{39}\text{H}_{40}\text{N}_4\text{NaO}_9\text{S}_2$  [ $\text{M}+\text{Na}$ ] $^+$ : 795.2129, found: 795.2161.

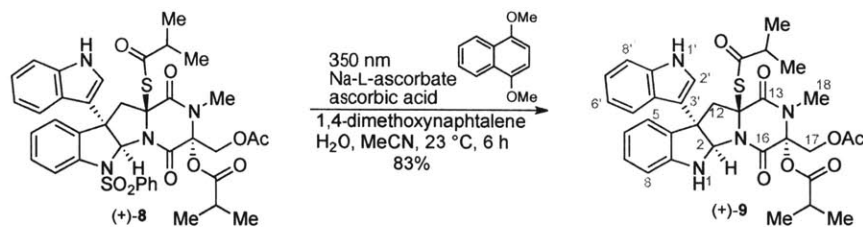
$[\alpha]_{\text{D}}^{24}$ :

+31 ( $c = 0.45$ ,  $\text{CHCl}_3$ ).

TLC (5% ethyl acetate in dichloromethane),  $R_f$ :

0.26 (UV, CAM,  $\text{KMnO}_4$ ).





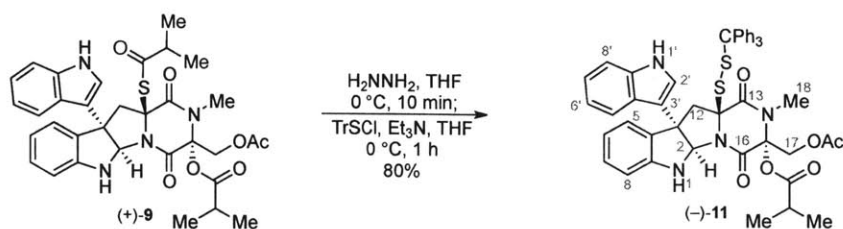
### Hexacyclic aminothioisobutyrate (+)-9:

A 125-mL Pyrex round-bottom flask was sequentially charged with hexacyclicthioisobutyrate (+)-8 (524 mg, 565  $\mu\text{mol}$ , 1 equiv), L-ascorbic acid (966 mg, 5.65 mmol, 10.0 equiv), sodium L-ascorbate (1.11 g, 5.65 mmol, 10.0 equiv), and 1,4-dimethoxynaphthalene (2.12 g, 11.3 mmol, 20.0 equiv), and the mixture was placed under an argon atmosphere. A solution of water in acetonitrile (20% v/v, 20 mL) that was purged with argon for 15 min at 23  $^{\circ}\text{C}$  was transferred to the flask via cannula. The system was vigorously stirred under an argon atmosphere and irradiated with a Rayonet photoreactor equipped with 16 lamps emitting at 350 nm at 23  $^{\circ}\text{C}$ . After 6 hours, the lamps were turned off, and the reaction mixture was diluted with ethyl acetate (30 mL). The resulting solution was sequentially washed with saturated aqueous sodium bicarbonate solution (30 mL), water ( $2 \times 30$  mL), and saturated aqueous sodium chloride solution (30 mL). The aqueous layer was extracted with ethyl acetate ( $2 \times 20$  mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: gradient, 5 $\rightarrow$ 20% acetone in hexanes) to afford the aminothioisobutyrate (+)-9 (297 mg, 83.0%) as a colorless oil.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 20  $^{\circ}\text{C}$ ):

$\delta$  8.36 (br-s, 1H,  $\text{N}_1\text{H}$ ), 7.82 (d,  $J = 8.5$ , 1H,  $\text{C}_5\text{H}$ ), 7.30 (d,  $J = 8.5$ , 1H,  $\text{C}_8\text{H}$ ), 7.16-7.13 (m, 2H,  $\text{C}_7\text{H}$ ,  $\text{C}_5\text{H}$ ), 7.09 (app-t,  $J = 7.5$ , 1H,  $\text{C}_7\text{H}$ ), 7.02 (app-t,  $J = 7.5$ , 1H,  $\text{C}_6\text{H}$ ), 6.82 (d,  $J = 2.6$ , 1H,  $\text{C}_2\text{H}$ ), 6.71 (app-t,  $J = 7.5$ , 1H,  $\text{C}_6\text{H}$ ), 6.66 (d,  $J = 7.5$ , 1H,  $\text{C}_8\text{H}$ ), 6.11 (s, 1H,  $\text{C}_2\text{H}$ ), 4.81 (d,  $J = 13.5$ , 1H,  $\text{C}_{17}\text{H}_a$ ), 4.46 (d,  $J = 13.5$ , 1H,  $\text{C}_{12}\text{H}_b$ ), 4.18 (d,  $J = 14.5$ , 1H,  $\text{C}_{12a}\text{H}$ ), 3.57 (d,  $J = 14.5$ , 1H,  $\text{C}_{12}\text{H}_b$ ), 2.94 (s, 3H,  $\text{C}_{18}\text{H}$ ), 2.62 (app-sp,  $J = 7.0$  1H,  $\text{CH}_{\text{isobutyrate}}$ ), 2.19 (app-sp,  $J = 7.0$  1H,  $\text{CH}_{\text{thioisobutyrate}}$ ), 2.12 (s, 3H,  $\text{CH}_{3\text{acetate}}$ ), 1.21 (d,  $J = 7.0$ , 3H,  $\text{CH}_{3\text{isobutyrate}}$ ), 1.18 (d,  $J = 7.0$ , 3H,  $\text{CH}_{3\text{isobutyrate}}$ ), 0.92 (d,  $J = 7.0$ , 3H,  $\text{CH}_{3\text{thioisobutyrate}}$ ), 0.83 (d,  $J = 7.0$ , 3H,  $\text{CH}_{3\text{thioisobutyrate}}$ ).

$^{13}\text{C}$ NMR (150 MHz, $\text{CDCl}_3$ , 20 °C):	$\delta$ 201.2 ( $\text{C}=\text{O}_{\text{thioisobutyrate}}$ ), 175.5 ( $\text{C}=\text{O}_{\text{isobutyrate}}$ ), 170.5 ( $\text{C}=\text{O}_{\text{acetate}}$ ), 166.5 ( $\text{C}_{13}$ ), 162.7 ( $\text{C}_{16}$ ), 149.5 ( $\text{C}_9$ ), 137.9 ( $\text{C}_9$ ), 133.1 ( $\text{C}_4$ ), 129.4 ( $\text{C}_7$ ), 125.7 ( $\text{C}_4$ ), 125.1 ( $\text{C}_5$ ), 123.5 ( $\text{C}_2$ ), 122.9 ( $\text{C}_7$ ), 120.9 ( $\text{C}_6$ ), 120.4 ( $\text{C}_5$ ), 120.1 ( $\text{C}_6$ ), 118.2 ( $\text{C}_3$ ), 112.2 ( $\text{C}_8$ ), 110.1 ( $\text{C}_8$ ), 87.1 ( $\text{C}_{15}$ ), 84.0 ( $\text{C}_2$ ), 73.9 ( $\text{C}_{11}$ ), 63.7 ( $\text{C}_{17}$ ), 54.7 ( $\text{C}_3$ ), 44.0 ( $\text{C}_{12}$ ), 43.8 ( $\text{CH}_{\text{thioisobutyrate}}$ ), 34.5 ( $\text{CH}_{\text{isobutyrate}}$ ), 29.0 ( $\text{C}_{18}$ ), 21.8 ( $\text{CH}_{3\text{acetate}}$ ), 19.9 ( $\text{CH}_{3\text{isobutyrate}}$ ), 19.7 ( $\text{CH}_{3\text{isobutyrate}}$ ), 19.5 ( $\text{CH}_{3\text{thioisobutyrate}}$ ), 19.1 ( $\text{CH}_{3\text{thioisobutyrate}}$ ).
FTIR (thin film) $\text{cm}^{-1}$ :	3385 (br), 2975 (m), 2360 (m), 1748 (s), 1686 (s), 1609 (w), 1484 (w), 1423 (w), 1379 (m), 1223 (m), 1067 (w), 747 (m).
HRMS (ESI) ( $m/z$ ):	calc'd for $\text{C}_{33}\text{H}_{36}\text{N}_4\text{NaO}_7\text{S}$ $[\text{M}+\text{Na}]^+$ : 655.2197, found: 655.2183.
$[\alpha]_{\text{D}}^{24}$ :	+26 ( $c = 0.085$ , $\text{CHCl}_3$ ).
TLC (50% ethyl acetate in hexanes), $R_f$ :	0.38 (UV, CAM).



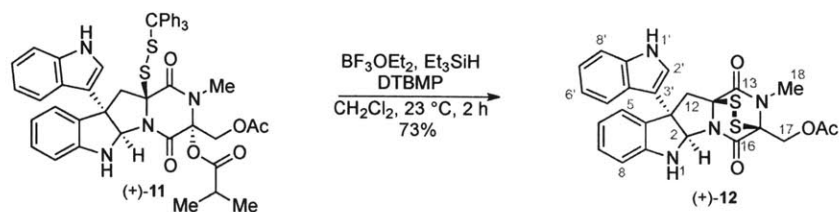
### Triphenylmethanedisulfide (–)-11:

Anhydrous hydrazine in tetrahydrofuran (1 M, 800  $\mu\text{L}$ , 800  $\mu\text{mol}$ , 1.00 equiv) was added via syringe to a solution of aminothiobutyrate (+)-**9** (50.3 mg, 800  $\mu\text{mol}$ , 1 equiv) in anhydrous tetrahydrofuran (2 mL) at 0  $^{\circ}\text{C}$ . After 10 min, the reaction mixture was diluted sequentially with saturated aqueous ammonium chloride solution (5 mL) and ethyl acetate (5 mL). The organic layer was sequentially washed with saturated aqueous ammonium chloride solution (10 mL), water ( $2 \times 10$  mL), and saturated aqueous sodium chloride solution (10 mL). The aqueous layer was extracted with ethyl acetate ( $2 \times 10$  mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to afford the hexacyclic aminothiol that was used in the next step without further purification. Triethylamine (111  $\mu\text{L}$ , 8.00 mmol, 10.0 equiv) and solid triphenylmethanesulfonyl chloride (124 mg, 4.00 mmol, 5.00 equiv) were sequentially added to a solution of aminothiol in anhydrous tetrahydrofuran (2 mL) at 0  $^{\circ}\text{C}$  under an argon atmosphere. After 1 h, the solution was partitioned between saturated aqueous ammonium chloride (5 mL) and ethyl acetate (5 mL). The aqueous layer was extracted with ethyl acetate ( $2 \times 10$  mL), and the combined organic layers were washed sequentially with water ( $2 \times 20$  mL) and saturated aqueous sodium chloride solution (20 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: gradient, 10  $\rightarrow$  50% ethyl acetate in hexanes) to afford triphenylmethanedisulfide (–)-**11** (53.6 mg, 80.1 %) as a white solid.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 20  $^{\circ}\text{C}$ ):

$\delta$  8.01 (br-s, 1H,  $\text{N}_1\text{H}$ ), 7.82 (d,  $J = 8.0$ , 1H,  $\text{C}_5\text{H}$ ), 7.32 (d,  $J = 8.0$ , 1H,  $\text{C}_8\text{H}$ ), 7.27-7.23 (m, 9H,  $\text{C}(\text{Ph-}o\text{-H})_3$ ,  $\text{C}(\text{Ph-}p\text{-H})_3$ ), 7.22-7.19 (m, 2H,  $\text{C}_7\text{H}$ ,  $\text{C}_7\text{H}$ ), 7.17-7.14 (m, 6H,  $\text{C}(\text{Ph-}m\text{-H})_3$ ), 7.06 (app-t,  $J = 7.5$ , 1H,  $\text{C}_6\text{H}$ ), 6.82 (d,  $J = 7.5$ , 1H,  $\text{C}_8\text{H}$ ), 6.73-6.69 (m, 3H,  $\text{C}_2\text{H}$ ,  $\text{C}_6\text{H}$ ,  $\text{C}_5\text{H}$ ), 5.93 (s, 1H,  $\text{C}_2\text{H}$ ), 4.93 (s, 1H,  $\text{N}_1\text{H}$ ), 4.66 (d,  $J = 12.5$ , 1H,  $\text{C}_{17}\text{H}_a$ ), 4.40 (d,  $J = 12.5$ , 1H,  $\text{C}_{17}\text{H}_b$ ), 3.55 (d,  $J = 15.0$ , 1H,  $\text{C}_{12}\text{H}_a$ ), 2.92 (d,  $J = 15.0$ , 1H,  $\text{C}_{12}\text{H}_b$ ), 2.80 (s, 3H,  $\text{C}_{18}\text{H}$ ), 2.61 (app-sp,  $J = 7.5$ , 1H,  $\text{CH}_{\text{isobutyrate}}$ ), 1.98 (s, 3H,  $\text{CH}_{\text{acetate}}$ ), 1.21-1.18 (m, 6H,  $\text{CH}_{\text{isobutyrate}}$ ).

$^{13}\text{C}$ NMR (125 MHz, $\text{CDCl}_3$ , 20 °C):	$\delta$ 175.5 ( $\text{C}=\text{O}_{\text{isobutyrate}}$ ), 170.8 ( $\text{C}=\text{O}_{\text{acetate}}$ ), 164.7 ( $\text{C}_{13}$ ), 163.1 ( $\text{C}_{16}$ ), 148.7 ( $\text{C}_9$ ), 144.8 ( $\text{C}(\text{Ph-}i\text{-C})_3$ ), 137.9 ( $\text{C}_9$ ), 131.9 ( $\text{C}_4$ ), 131.4 ( $\text{C}(\text{Ph-}m\text{-C})_3$ ), 129.6 ( $\text{C}_7$ ), 128.3 ( $\text{C}(\text{Ph-}o\text{-C})_3$ ), 127.8 ( $\text{C}(\text{Ph-}p\text{-C})_3$ ), 125.9 ( $\text{C}_4$ ), 126.0 ( $\text{C}_5$ ), 123.5 ( $\text{C}_2$ ), 122.9 ( $\text{C}_7$ ), 121.1 ( $\text{C}_6$ ), 120.5 ( $\text{C}_5$ ), 120.3 ( $\text{C}_6$ ), 118.3 ( $\text{C}_3$ ), 112.0 ( $\text{C}_8$ ), 110.3 ( $\text{C}_8$ ), 87.5 ( $\text{C}_2$ ), 84.1 ( $\text{C}_{15}$ ), 73.7 ( $\text{C}_{11}$ ), 63.4 ( $\text{C}_{17}$ ), 54.2 ( $\text{C}_3$ ), 47.2 ( $\text{C}_{12}$ ), 34.4 ( $\text{CH}_{\text{isobutyrate}}$ ), 28.7 ( $\text{C}_{18}$ ), 21.7 ( $\text{CH}_{\text{acetate}}$ ), 19.5 ( $\text{CH}_{\text{isobutyrate}}$ ), 19.1 ( $\text{CH}_{\text{isobutyrate}}$ ).
FTIR (thin film) $\text{cm}^{-1}$ :	3402 (br-m), 3056 (w), 2975 (w), 2360 (w), 1747(m), 1684 (s), 1609 (w), 1485 (w), 1459 (w), 1446 (w), 1377 (m), 1223 (w), 1067 (m)
HRMS (ESI) ( $m/z$ ):	calc'd for $\text{C}_{48}\text{H}_{44}\text{N}_4\text{NaO}_6\text{S}_2$ $[\text{M}+\text{Na}]^+$ : 859.2594, found: 859.2569.
$[\alpha]_{\text{D}}^{24}$ :	-50 ( $c = 0.38$ , $\text{CHCl}_3$ ).
TLC (50% ethyl acetate in hexanes), $R_f$ :	0.58 (UV, CAM).



**(+)-Luteoalbusin A Acetate (12):**

Dichloromethane (1 mL) was added via syringe to a flask charged with bis(triphenylmethanedisulfide) (–)-11 (37.4 mg, 400  $\mu\text{mol}$ , 1 equiv) and 2,6-di-tert-butyl-4-methylpyridine (118 mg, 570  $\mu\text{mol}$ , 15.0 equiv) under an argon atmosphere. Triethylsilane (60.2  $\mu\text{L}$ , 400  $\mu\text{mol}$ , 10.0 equiv) was then added to the solution at 23  $^\circ\text{C}$  via syringe followed by borontrifluoride-etherate (45.9  $\mu\text{L}$ , 0.40 mmol, 10.0 equiv). After 2 hours, a saturated aqueous ammonium chloride solution (2 mL) was added to the solution. The reaction mixture was diluted with dichloromethane (10 mL) and washed with saturated aqueous ammonium chloride solution (5 mL). The aqueous layer was extracted with dichloromethane ( $2 \times 5$  mL), and the combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 50% ethyl acetate in hexanes) to afford (+)-luteoalbusin A acetate (**12**) (14.0 mg, 73.0%) as a white solid.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 20  $^\circ\text{C}$ ):

$\delta$  8.07 (br-s, 1H,  $\text{N}_1\text{H}$ ), 7.51 (d,  $J = 7.5$ , 1H,  $\text{C}_5\text{H}$ ), 7.38 (d,  $J = 8.0$ , 1H,  $\text{C}_8\text{H}$ ), 7.24–7.18 (m, 3H,  $\text{C}_7\text{H}$ ,  $\text{C}_7\text{H}$ ,  $\text{C}_5\text{H}$ ), 7.10 (app-t,  $J = 8.5$ , 1H,  $\text{C}_6\text{H}$ ), 6.96 (d,  $J = 2.6$ , 1H,  $\text{C}_2\text{H}$ ), 6.88 (app-t,  $J = 7.5$ , 1H,  $\text{C}_6\text{H}$ ), 6.75 (d,  $J = 7.5$ , 1H,  $\text{C}_8\text{H}$ ), 5.99 (s, 1H,  $\text{C}_2\text{H}$ ), 5.32 (s, 1H,  $\text{N}_1\text{H}$ ), 4.99 (d,  $J = 13.5$ , 1H,  $\text{C}_{17}\text{H}_a$ ), 4.71 (d,  $J = 13.5$ , 1H,  $\text{C}_{17}\text{H}_b$ ), 4.15 (d,  $J = 15.0$ , 1H,  $\text{C}_{12}\text{H}_a$ ), 3.14 (s, 3H,  $\text{C}_{18}\text{H}$ ), 3.00 (d,  $J = 15.0$ , 1H,  $\text{C}_{12}\text{H}_b$ ), 2.18 (s, 3H,  $\text{CH}_{3\text{acetate}}$ ).

$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , 20  $^\circ\text{C}$ ):

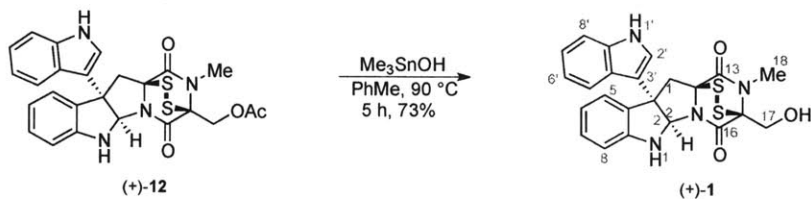
$\delta$  170.3 ( $\text{C}=\text{O}_{\text{acetate}}$ ), 166.6 ( $\text{C}_{13}$ ), 161.9 ( $\text{C}_{16}$ ), 148.7 ( $\text{C}_9$ ), 138.0 ( $\text{C}_9$ ), 132.3 ( $\text{C}_4$ ), 129.9 ( $\text{C}_7$ ), 125.6 ( $\text{C}_4$ ), 124.7 ( $\text{C}_5$ ), 123.4 ( $\text{C}_2$ ), 123.3 ( $\text{C}_7$ ), 120.9 ( $\text{C}_6$ ), 120.6 ( $\text{C}_5$ ), 120.1 ( $\text{C}_6$ ), 117.0 ( $\text{C}_3$ ), 112.4 ( $\text{C}_8$ ), 110.8 ( $\text{C}_8$ ), 83.8 ( $\text{C}_2$ ), 75.5 ( $\text{C}_{15}$ ), 75.0 ( $\text{C}_{11}$ ), 60.6 ( $\text{C}_{17}$ ), 56.2 ( $\text{C}_3$ ), 44.3 ( $\text{C}_{12}$ ), 28.8 ( $\text{C}_{18}$ ), 21.4 ( $\text{CH}_{3\text{acetate}}$ ).

FTIR (thin film)  $\text{cm}^{-1}$ : 3380 (br m), 2921 (m), 2850 (s), 1750 (m), 1689 (m), 1459 (s), 1377 (m), 1223 (w), 1048 (w), 744 (w), 666 (w).

HRMS (ESI) ( $m/z$ ): calc'd for  $\text{C}_{25}\text{H}_{23}\text{N}_4\text{O}_4\text{S}_2$   $[\text{M}+\text{H}]^+$ : 507.1155, found: 507.1146.

$[\alpha]_{\text{D}}^{24}$ : +42.0 ( $c = 0.095$ ,  $\text{CHCl}_3$ ).

TLC (50% ethyl acetate in hexanes),  $R_f$ : 0.36 (UV, CAM).



**(+)-Luteoalbusin A (1):**

Trimethyltin hydroxide (3.9 mg, 200  $\mu\text{mol}$ , 1.00 equiv) was added as a solid to a sealed tube reaction vessel containing a solution of (+)-luteoalbusin A acetate (**12**) (11.0 mg, 200  $\mu\text{mol}$ , 1 equiv) in toluene (2 mL) under an argon atmosphere. The resulting reaction mixture was heated to 90  $^{\circ}\text{C}$ . After 5 h, the solution was diluted with dichloromethane (10 mL) and loaded onto a silica gel column and purified by flash column chromatography (eluent: 50% ethyl acetate in hexanes) to afford (+)-luteoalbusin A (**1**, 7.4 mg, 73%) as a colorless gel.

$^1\text{H}$  NMR (500 MHz, acetone- $d_6$ , 20  $^{\circ}\text{C}$ ):

$\delta$  10.25 (br-s, 1H,  $\text{N}_1\text{H}$ ), 7.56 (d,  $J = 8.0$ , 1H,  $\text{C}_5\text{H}$ ), 7.43 (d,  $J = 8.0$ , 1H,  $\text{C}_8\text{H}$ ), 7.33 (d,  $J = 8.0$ , 1H,  $\text{C}_5\text{H}$ ), 7.12 (dd,  $J = 8.0, 7.5$ , 1H,  $\text{C}_7\text{H}$ ), 7.12 (dd,  $J = 8.0, 7.5$ , 1H,  $\text{C}_7\text{H}$ ), 6.99 (dd,  $J = 8.0, 7.5$ , 1H,  $\text{C}_6\text{H}$ ), 6.79 (d,  $J = 8.0$ , 1H,  $\text{C}_8\text{H}$ ), 6.78 (dd,  $J = 8.0, 7.5$ , 1H,  $\text{C}_6\text{H}$ ), 6.22 (br-s, 1H,  $\text{N}_1\text{H}$ ), 5.98 (d,  $J = 1.0$ , 1H,  $\text{C}_2\text{H}$ ), 4.66 (dd,  $J = 7.5, 6.0$ , 1H, OH), 4.34 (d,  $J = 12.7$ , 1H,  $\text{C}_{17}\text{H}_a$ ), 4.41 (d,  $J = 12.7$ , 1H,  $\text{C}_{17}\text{H}_b$ ), 4.05 (d,  $J = 15.0$ , 1H,  $\text{C}_{12}\text{H}_a$ ), 3.18 (s, 3H,  $\text{C}_{18}\text{H}$ ), 3.10 (d,  $J = 15.0$ , 1H,  $\text{C}_{12}\text{H}_b$ ).

$^{13}\text{C}$  NMR (150 MHz, acetone- $d_6$ , 20  $^{\circ}\text{C}$ ):

$\delta$  168.1 ( $\text{C}_{13}$ ), 164.2 ( $\text{C}_{16}$ ), 150.7 ( $\text{C}_9$ ), 139.7 ( $\text{C}_9$ ), 134.4 ( $\text{C}_4$ ), 130.6 ( $\text{C}_7$ ), 127.1 ( $\text{C}_4$ ), 125.9 ( $\text{C}_5$ ), 125.0 ( $\text{C}_2$ ), 123.7 ( $\text{C}_7$ ), 121.1 ( $\text{C}_6$ ), 120.8 ( $\text{C}_5$ ), 120.8 ( $\text{C}_6$ ), 118.5 ( $\text{C}_3$ ), 113.9 ( $\text{C}_8$ ), 111.6 ( $\text{C}_8$ ), 85.1 ( $\text{C}_2$ ), 79.0 ( $\text{C}_{15}$ ), 76.1 ( $\text{C}_{11}$ ), 61.4 ( $\text{C}_{17}$ ), 57.5 ( $\text{C}_3$ ), 45.5 ( $\text{C}_{12}$ ), 28.8 ( $\text{C}_{18}$ ).

FTIR (thin film)  $\text{cm}^{-1}$ :

3380 (br-s), 2920 (s), 2850 (s), 1750 (m), 1689 (m), 1483 (w), 1459 (w), 1378 (w), 1223 (m), 1100 (w), 1048 (w).

HRMS (ESI) ( $m/z$ ):

calc'd for  $\text{C}_{23}\text{H}_{21}\text{N}_4\text{O}_3\text{S}_2$  [ $\text{M}+\text{H}$ ] $^+$ : 465.1050, found: 465.1045.

$[\alpha]_D^{24}$ :

+290 ( $c = 0.085$ ,  $\text{CHCl}_3$ ).

TLC (50% ethyl acetate in hexanes),  $R_f$ : 0.36 (UV, CAM).



**Table S1. Comparison of our data for (+)-Luteoalbusin A with literature:**

Assignment	This Work (+)-Luteoalbusin A <sup>1</sup> H NMR, 500 MHz, acetone- <i>d</i> <sub>6</sub> , 20 °C	Wang's Report (+)-Luteoalbusin A <sup>1</sup> H NMR, 500 MHz, acetone- <i>d</i> <sub>6</sub> , 20 °C	Δδ (ppm)
N1	6.22 (s)	6.22 (s)	0
C2	5.98 (d, <i>J</i> = 1.0)	5.98 (d, <i>J</i> = 0.9)	0
C3	–	–	–
C4	–	–	–
C5	7.32 (d, <i>J</i> = 8.0)	7.33 (d, <i>J</i> = 8.0)	–0.01
C6	6.77 (dd, <i>J</i> = 8.0, 7.5)	6.78 (dd, <i>J</i> = 8.0, 7.5)	–0.01
C7	7.11 (dd, <i>J</i> = 8.0, 7.5)	7.12 (dd, <i>J</i> = 7.9, 7.6)	–0.01
C8	6.78 (d, <i>J</i> = 8.0)	6.79 (d, <i>J</i> = 8.0)	–0.01
C9	–	–	–
N10	–	–	–
C11	–	–	–
C12	3.09 (d, <i>J</i> = 15.0), 4.06 (d, <i>J</i> = 15.0)	3.10 (d, <i>J</i> = 15.0), 4.05 (d, <i>J</i> = 15.0)	0.01, –0.01
C13	–	–	–
C14	3.17 (s)	3.18 (s)	–0.01
C15	–	–	–
C16	–	–	–
C17	4.34 (d, <i>J</i> = 12.7), 4.41 (d, <i>J</i> = 12.7)	4.34 (d, <i>J</i> = 12.8), 4.41 (d, <i>J</i> = 12.8)	0
OH	–	4.67 (dd, <i>J</i> = 7.5, 6.0)	–
N1'	10.27 (s)	10.25 (s)	0.02
C2'	7.13 (d, <i>J</i> = 2.5)	7.15 (d, <i>J</i> = 2.5)	–0.02
C3'	–	–	–
C4'	–	–	–
C5'	7.55 (d, <i>J</i> = 8.0)	7.56 (d, <i>J</i> = 7.9)	–0.01
C6'	6.99 (dd, <i>J</i> = 8.0, 7.5)	6.99 (dd, <i>J</i> = 8.0, 7.4)	0
C7'	7.11 (dd, <i>J</i> = 8.0, 7.5)	7.12 (dd, <i>J</i> = 8.0, 7.5)	–0.01
C8'	7.42 (d, <i>J</i> = 8.0)	7.43 (d, <i>J</i> = 8.0)	0.01
C9'	–	–	–

**Table S2. Comparison of our data for (+)-Luteoalbusin A with literature:**

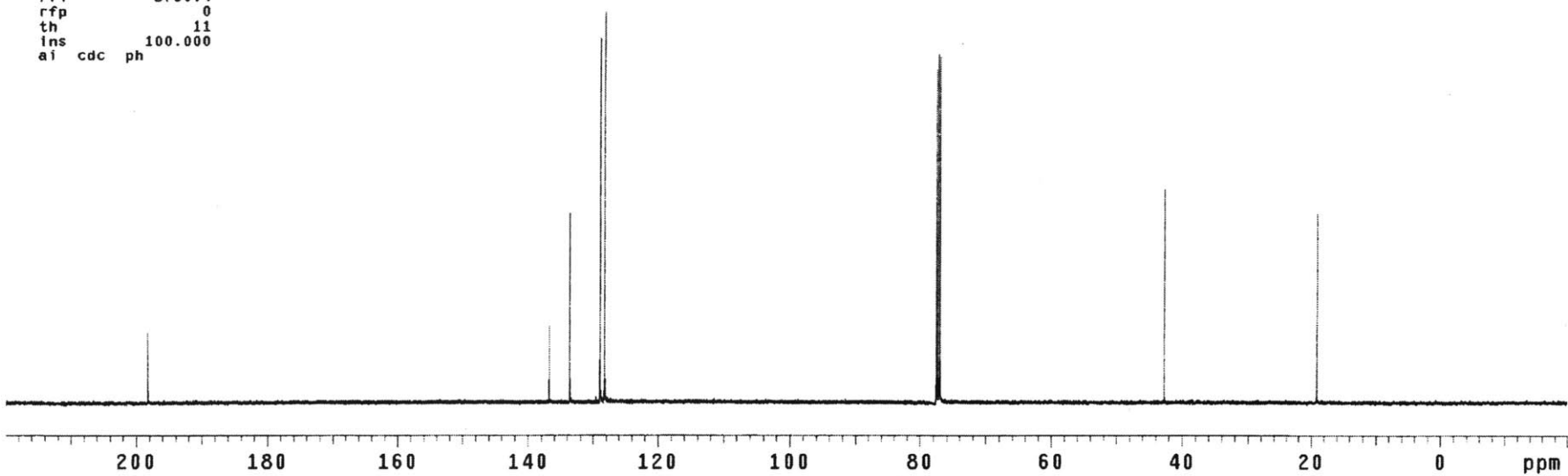
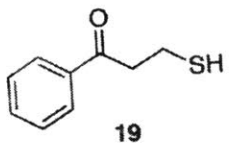
<b>Assignment</b>	<b>This Work</b> (+)-Luteoalbusin A <sup>13</sup> C NMR, 125 MHz, acetone- <i>d</i> <sub>6</sub> , 20 °C	<b>Wang's Report</b> (+)-Luteoalbusin A <sup>13</sup> C NMR, 125 MHz, acetone- <i>d</i> <sub>6</sub> , 20 °C	<b>Δδ</b> (ppm)
N1	–	–	–
C2	85.1	85.1	0
C3	57.5	57.5	0
C4	134.4	134.4	0
C5	125.9	125.9	0
C6	120.7	120.8	–0.1
C7	130.5	130.6	–0.1
C8	111.5	111.6	–0.1
C9	150.7	150.7	0
N10	–	–	–
C11	76.0	76.1	–0.1
C12	45.5	45.5	0
C13	168.1	168.1	0
C14	28.7	28.8	–0.1
C15	79.1	79.0	0.1
C16	164.2	164.3	–0.1
C17	61.1	61.4	–0.3
OH	–	–	–
N1'	–	–	–
C2'	124.9	125.0	–0.1
C3'	118.4	118.5	–0.1
C4'	127.1	127.1	0
C5'	121.1	120.8	0.3
C6'	121.1	121.1	0
C7'	123.6	123.7	–0.1
C8'	113.8	113.9	–0.1
C9'	139.7	139.7	0

**Appendix A.**  
**Spectra for Chapter 2**

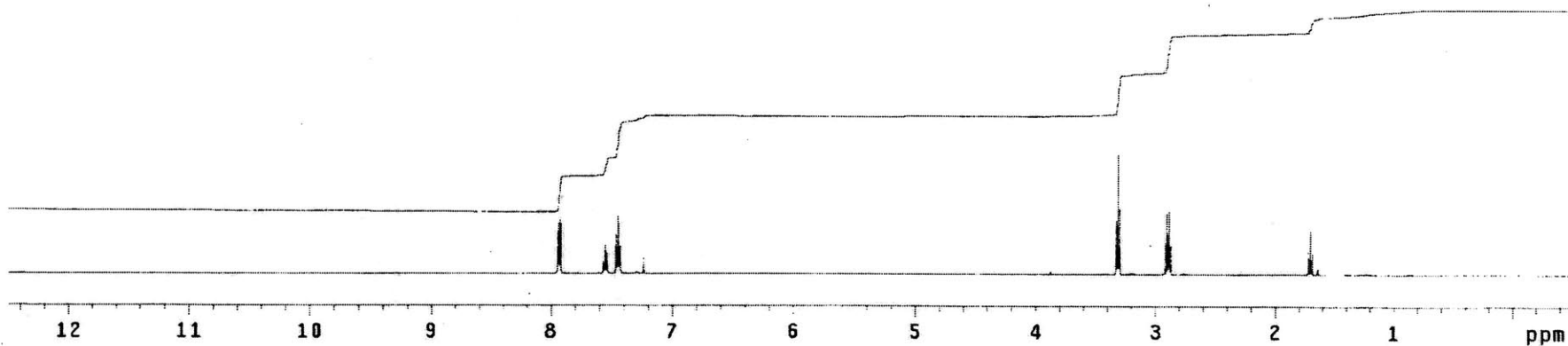
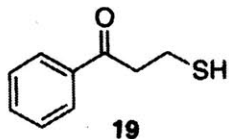
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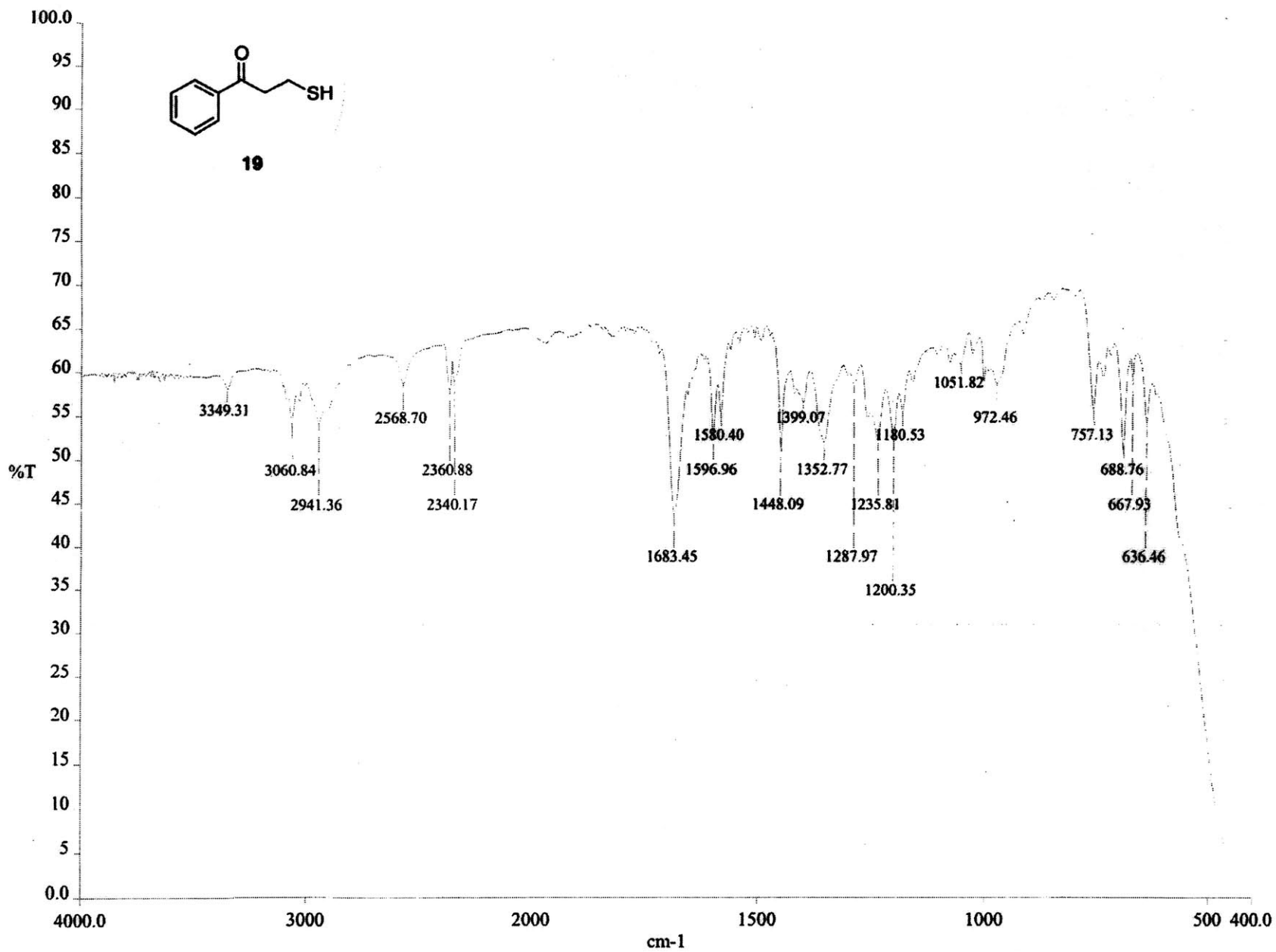
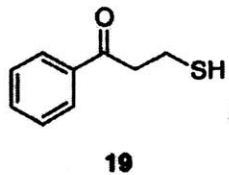
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np         125588
sw         31397.2
fb         not used
bs         8
tpwr       58
pw         6.7
d1         3.000
tof        0
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ct         1392
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gain      not used
          FLAGS
il        n
in        n
dp        y
hs        nn
          DISPLAY
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vs        378
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ai cdc ph

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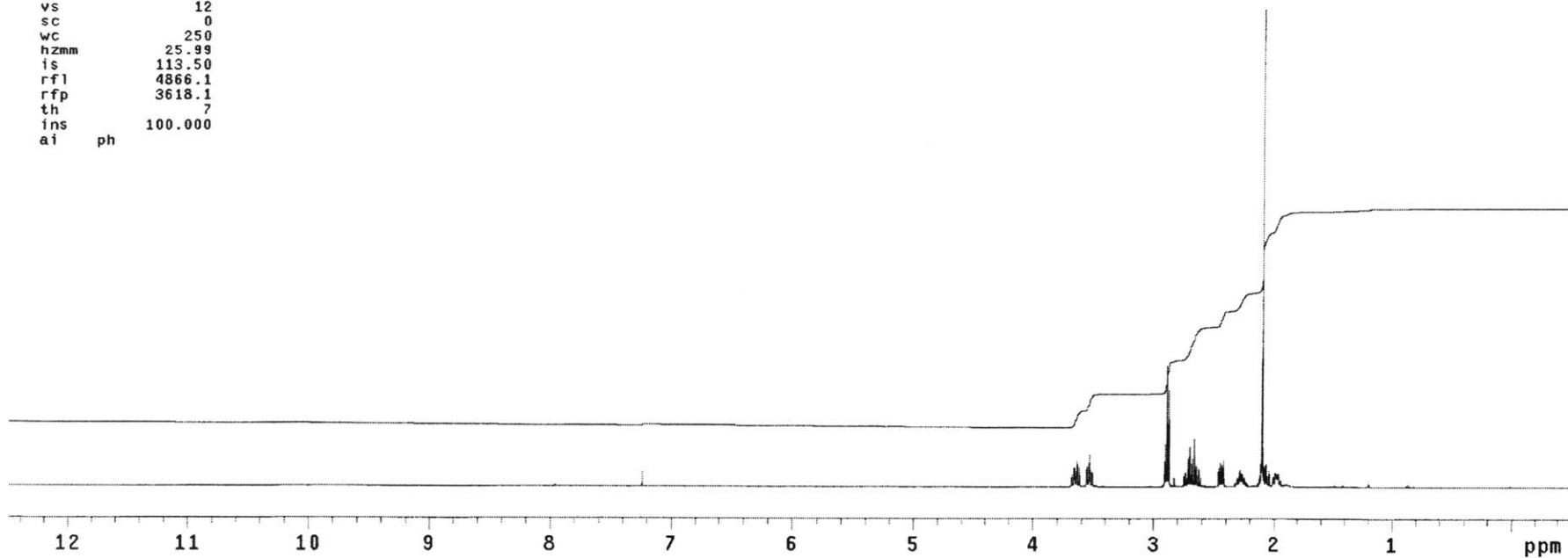
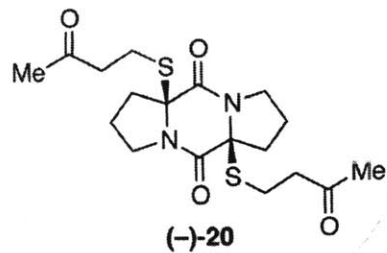
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ln	H1	dmm	w
at	3.001	dmf	10000
np	63050	dseq	
sw	10504.2	dres	1.0
fb	not used	homo	n
bs	3	DEC2	
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d1	2.000	dpwr2	1
tof	1519.5	dof2	0
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gain	not used	dseq2	
	FLAGS	dres2	1.0
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dp	y	dfrq3	0
hs	nn	dn3	
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rfp	3618.1	wfile	
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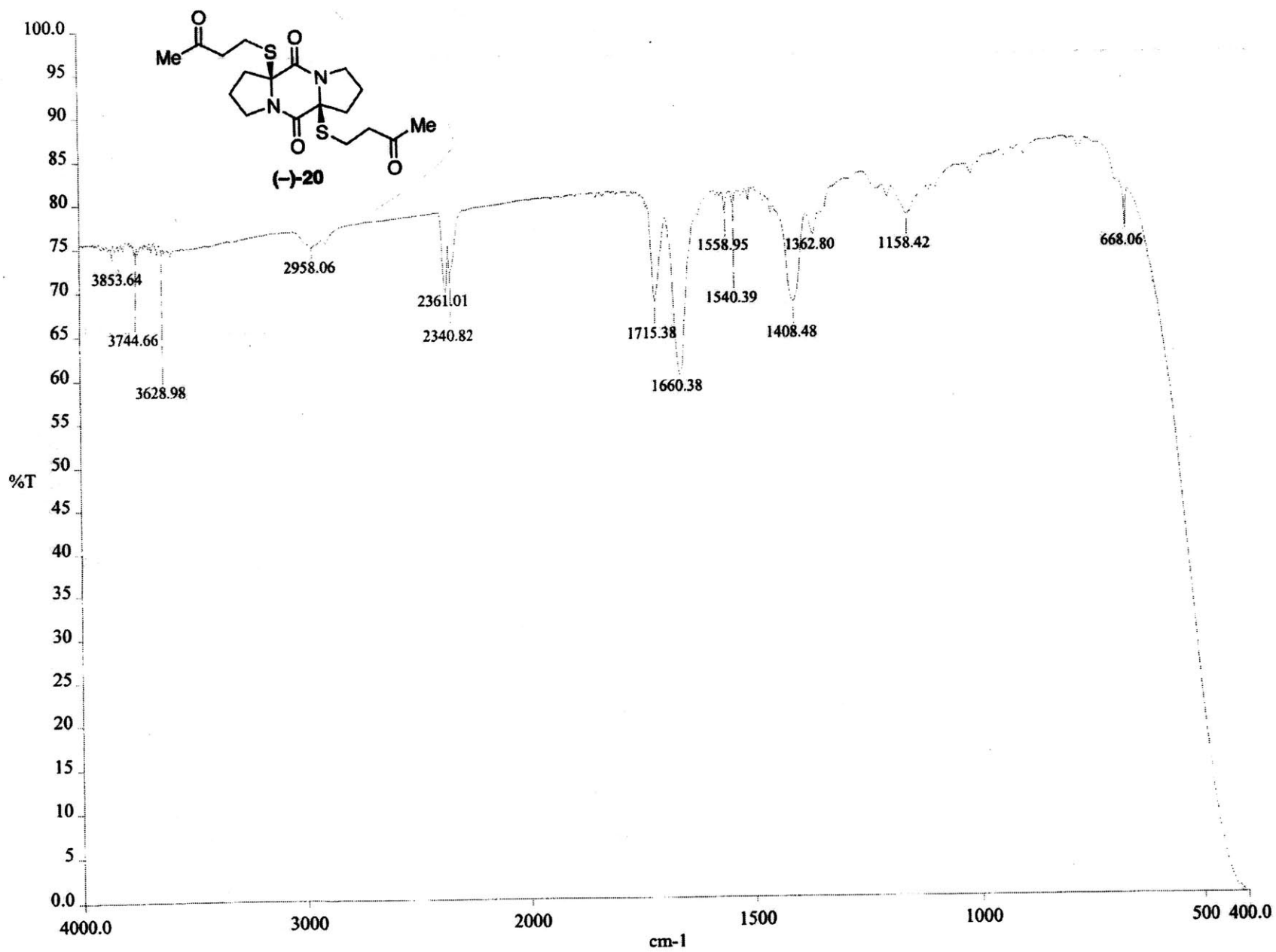




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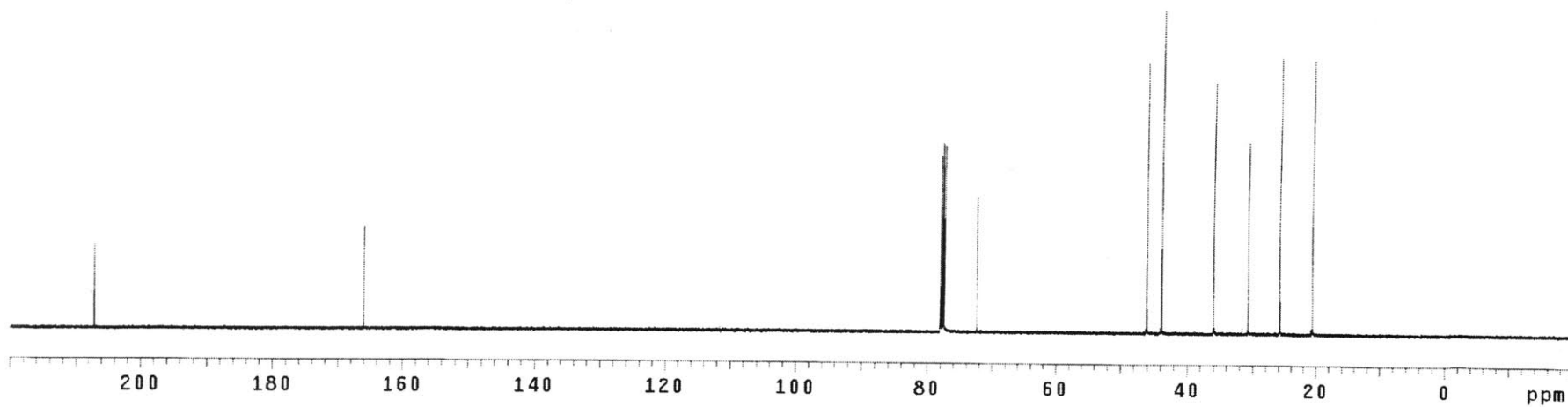
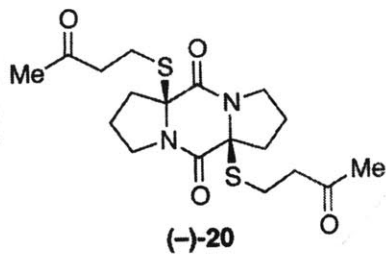
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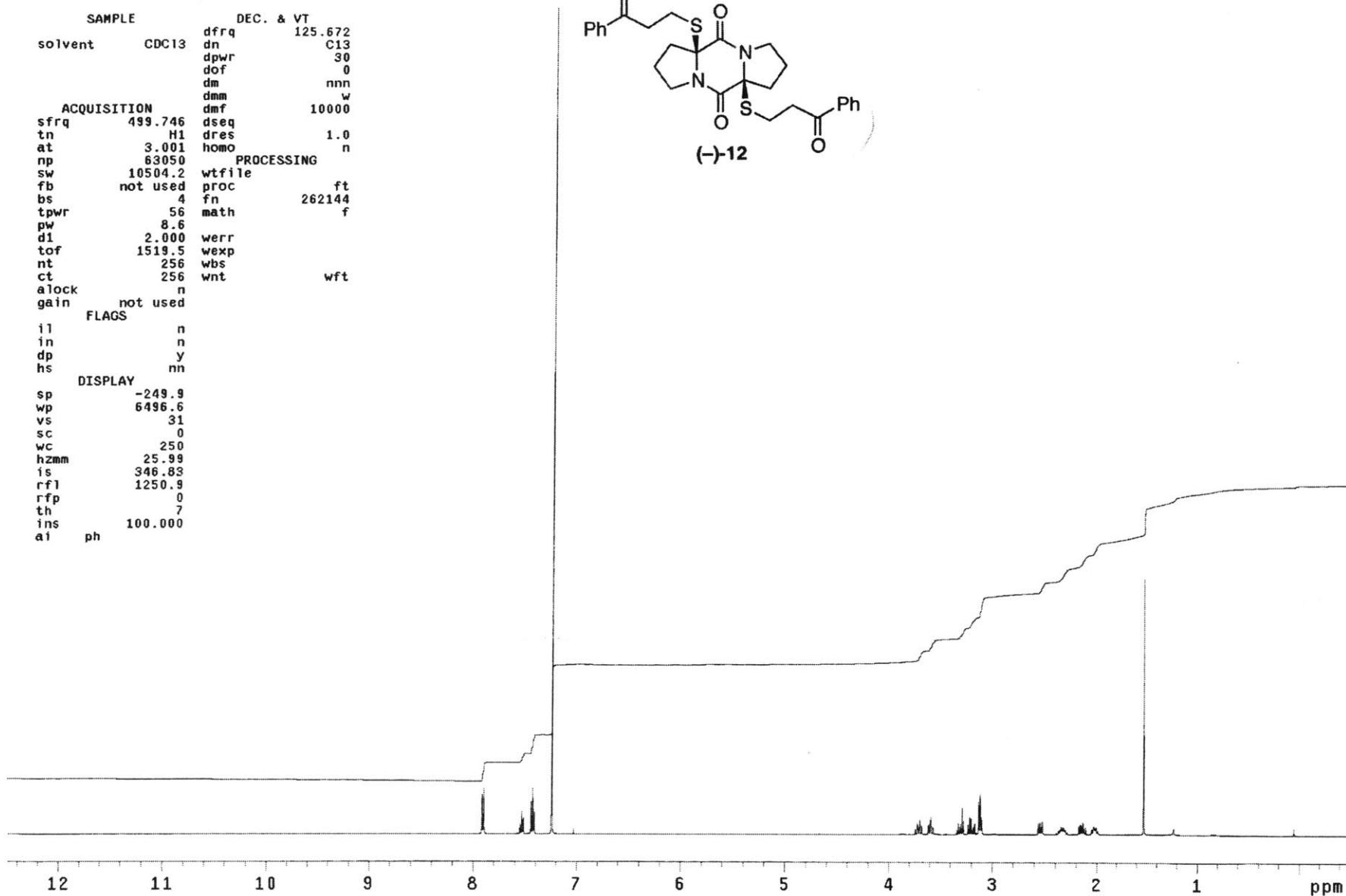
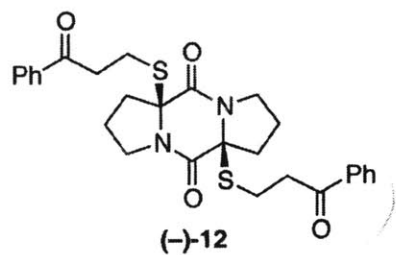
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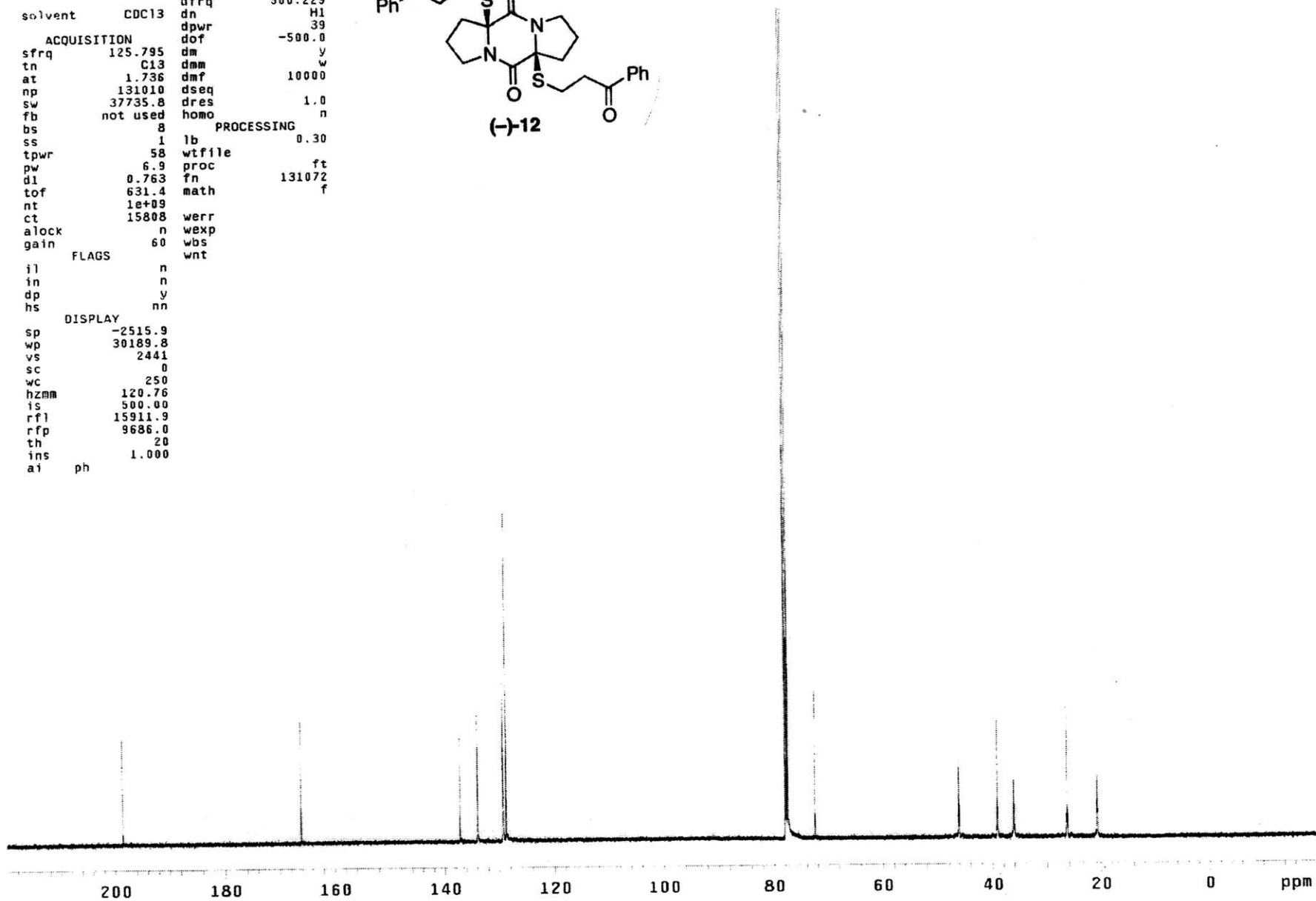
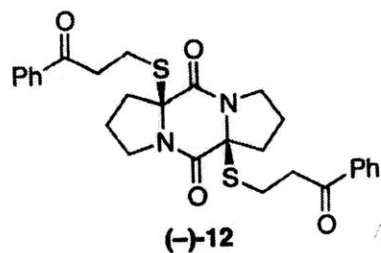
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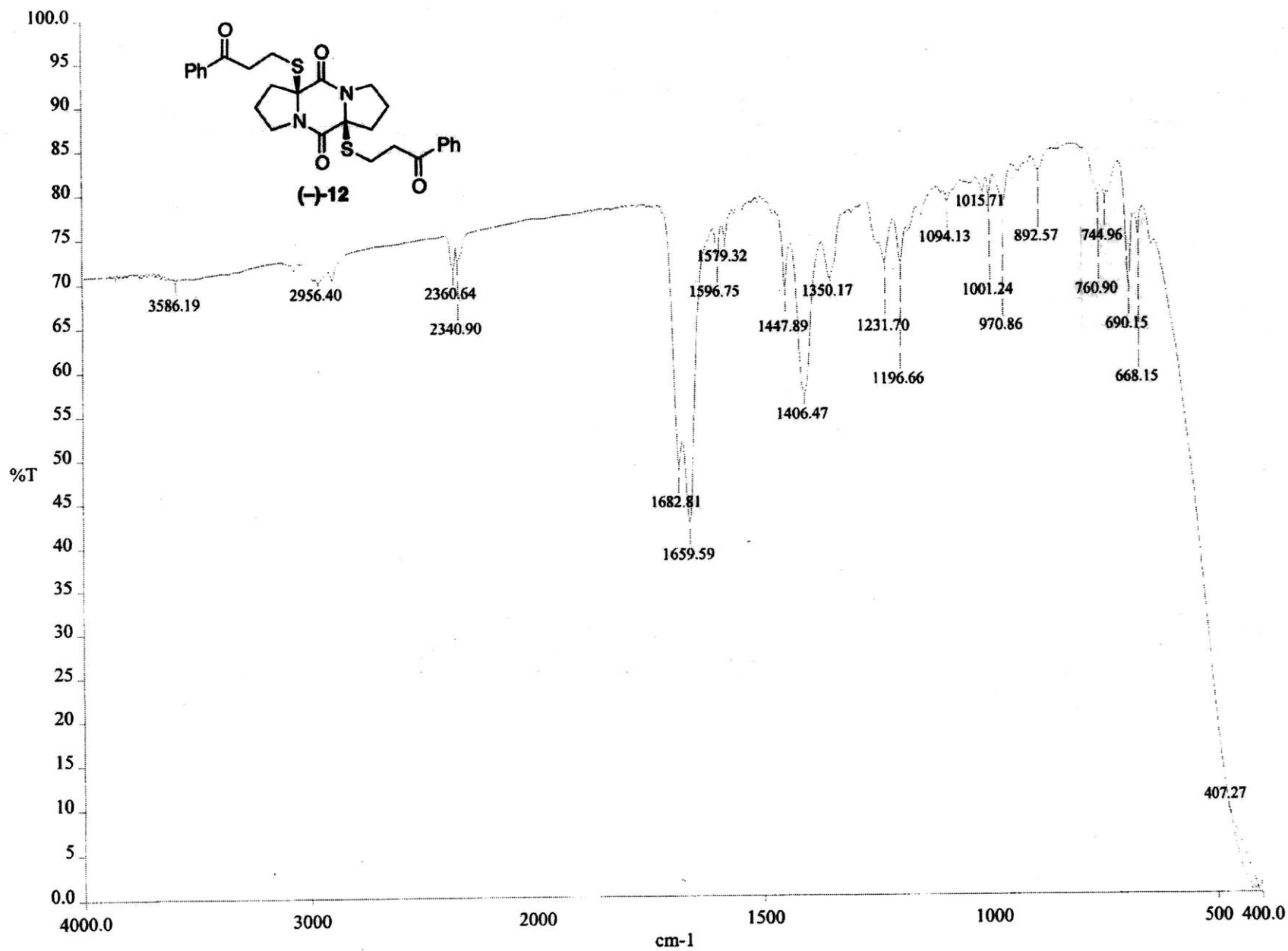


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tn	H1	homo	n
at	3.001	PROCESSING	
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dp	y		
hs	nn		
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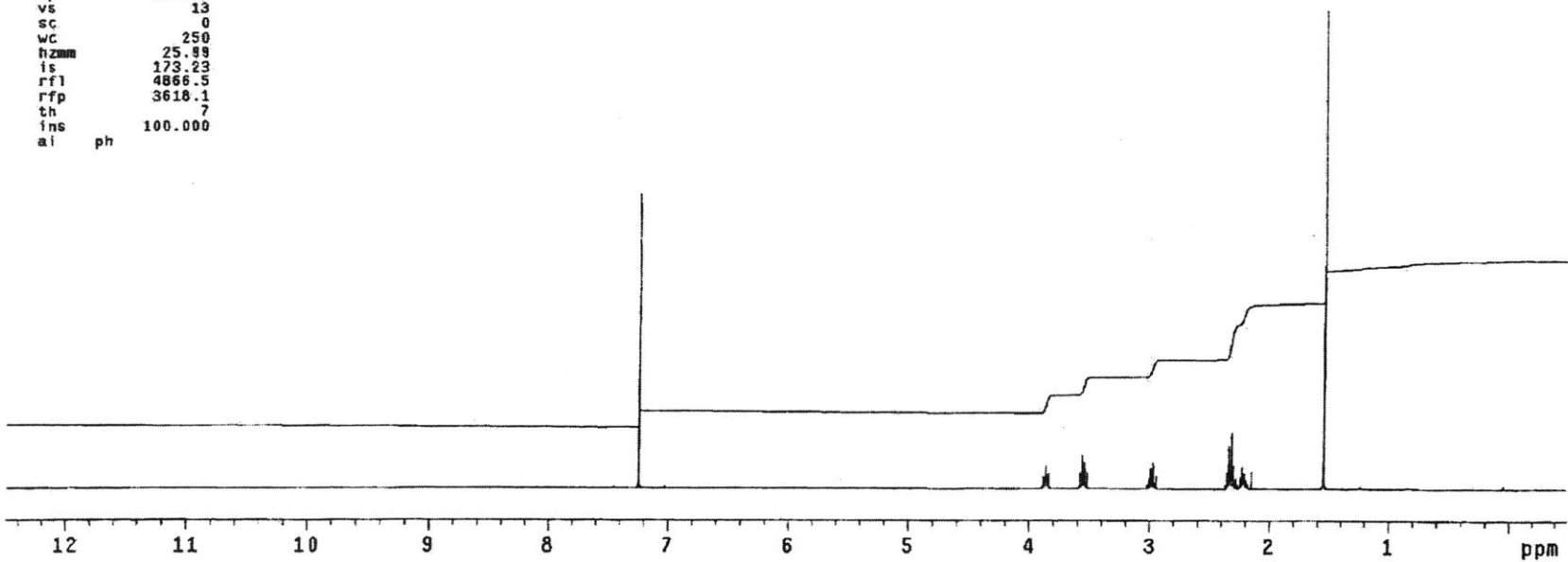
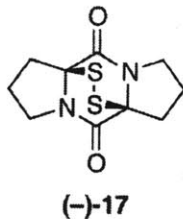
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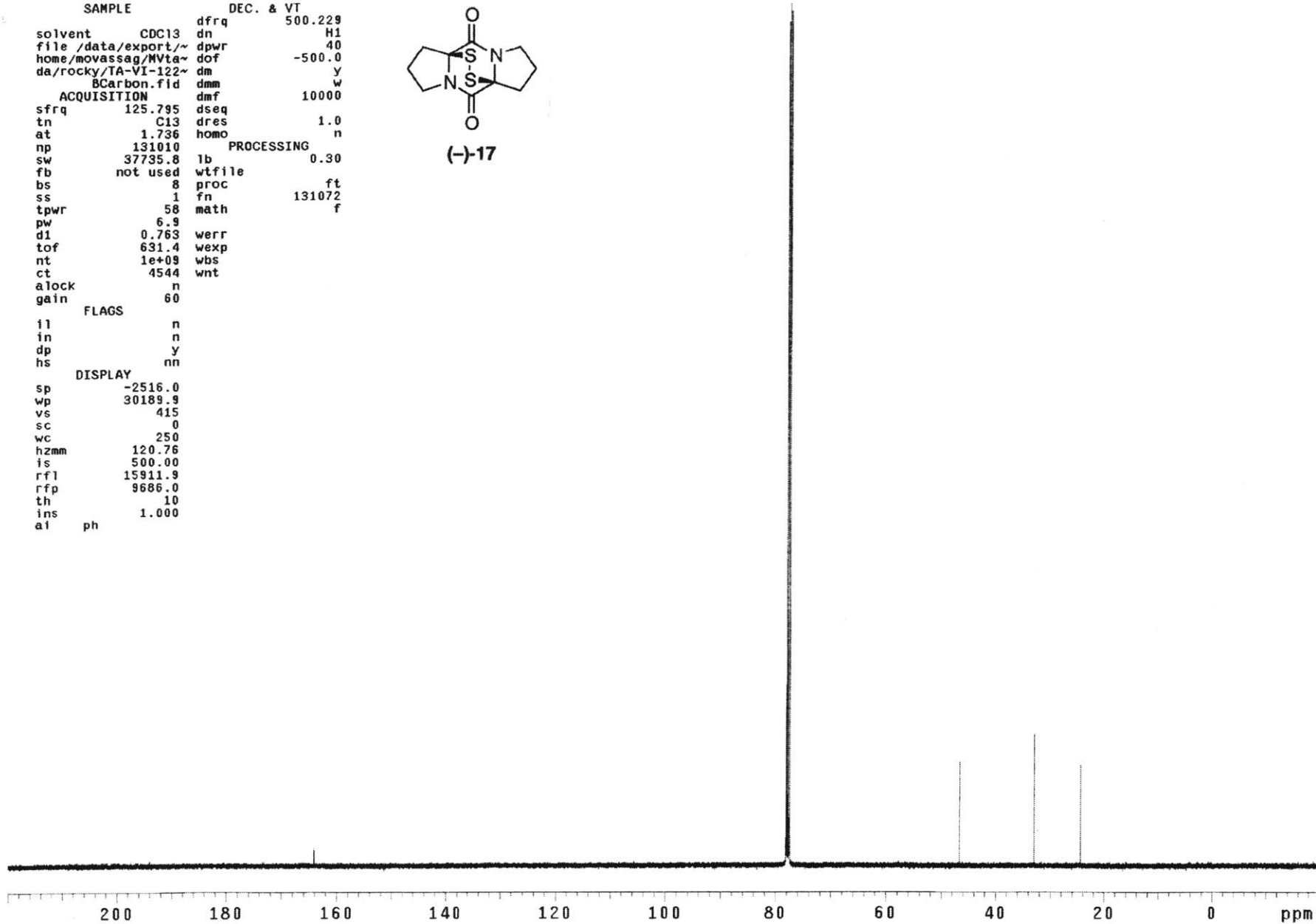
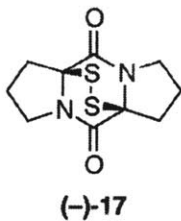
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in	n		
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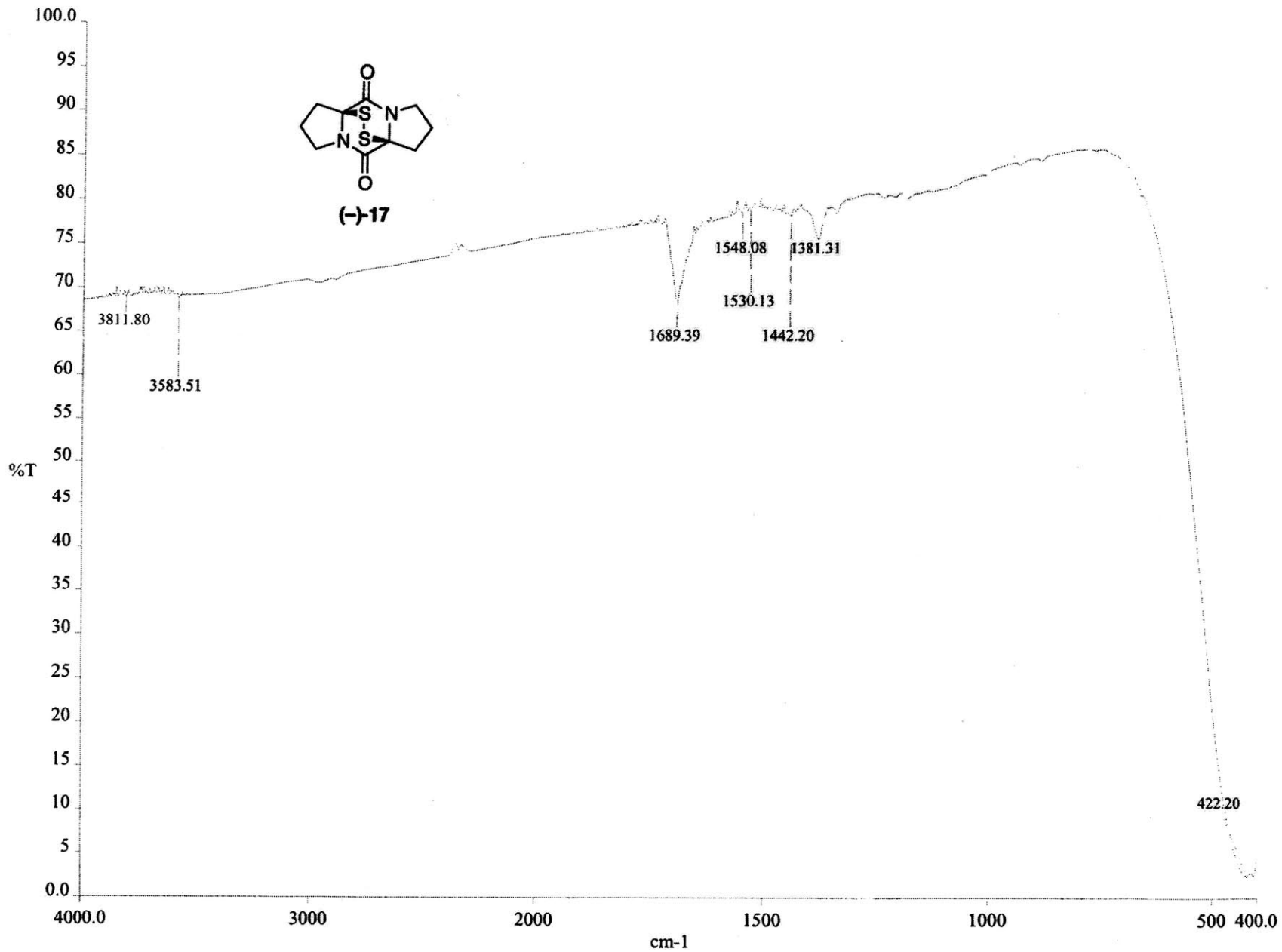


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d1            0.763   werr
tof           631.4   wexp
nt            1e+09   wbs
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gain          60
  FLAGS
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  in          n
  dp          y
  hs         nn
  DISPLAY
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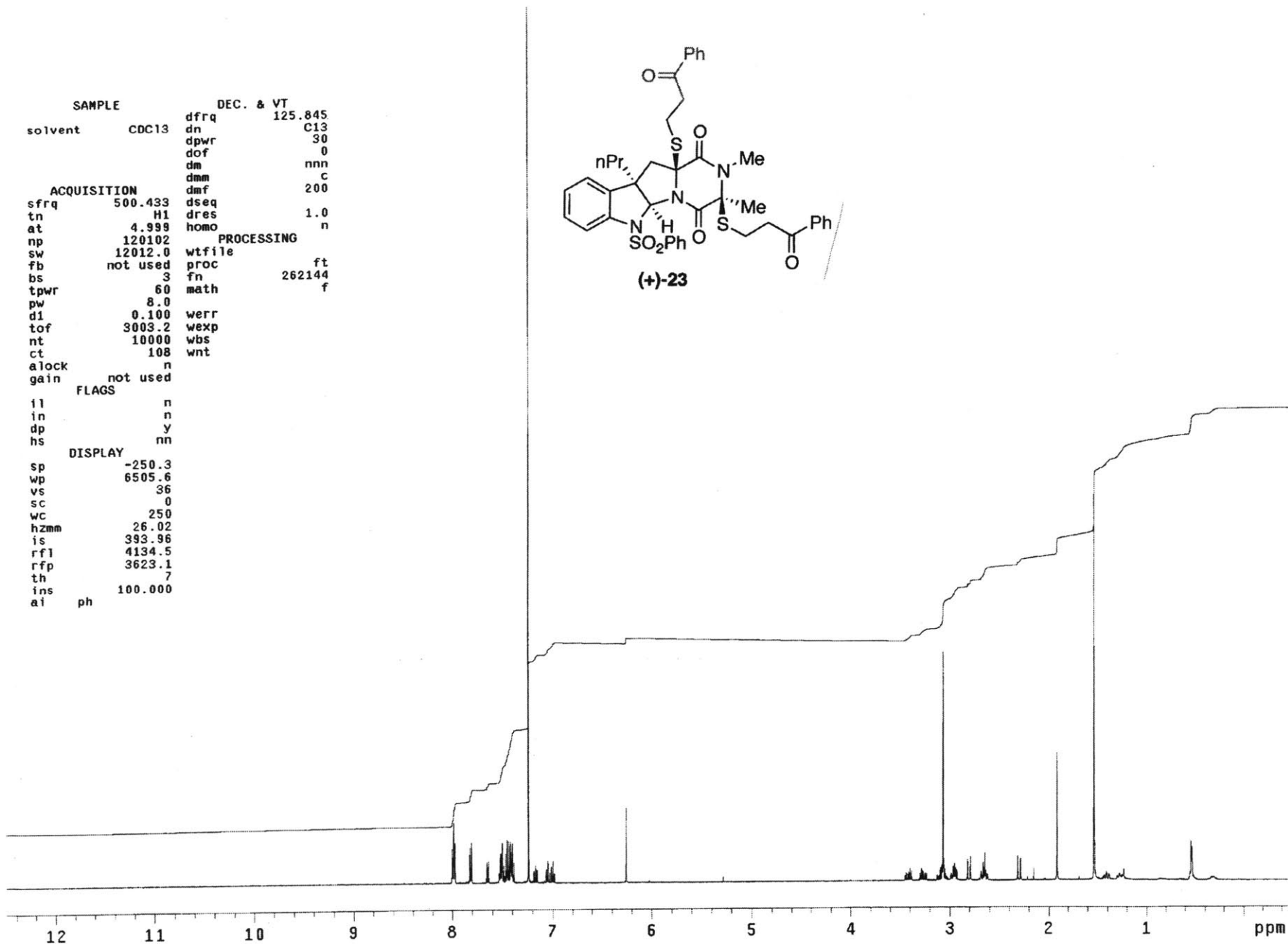
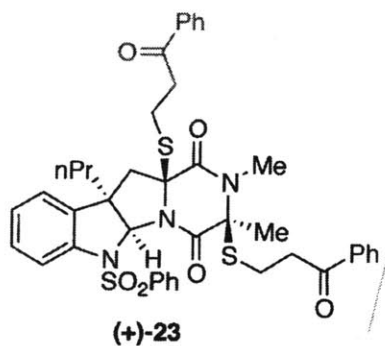
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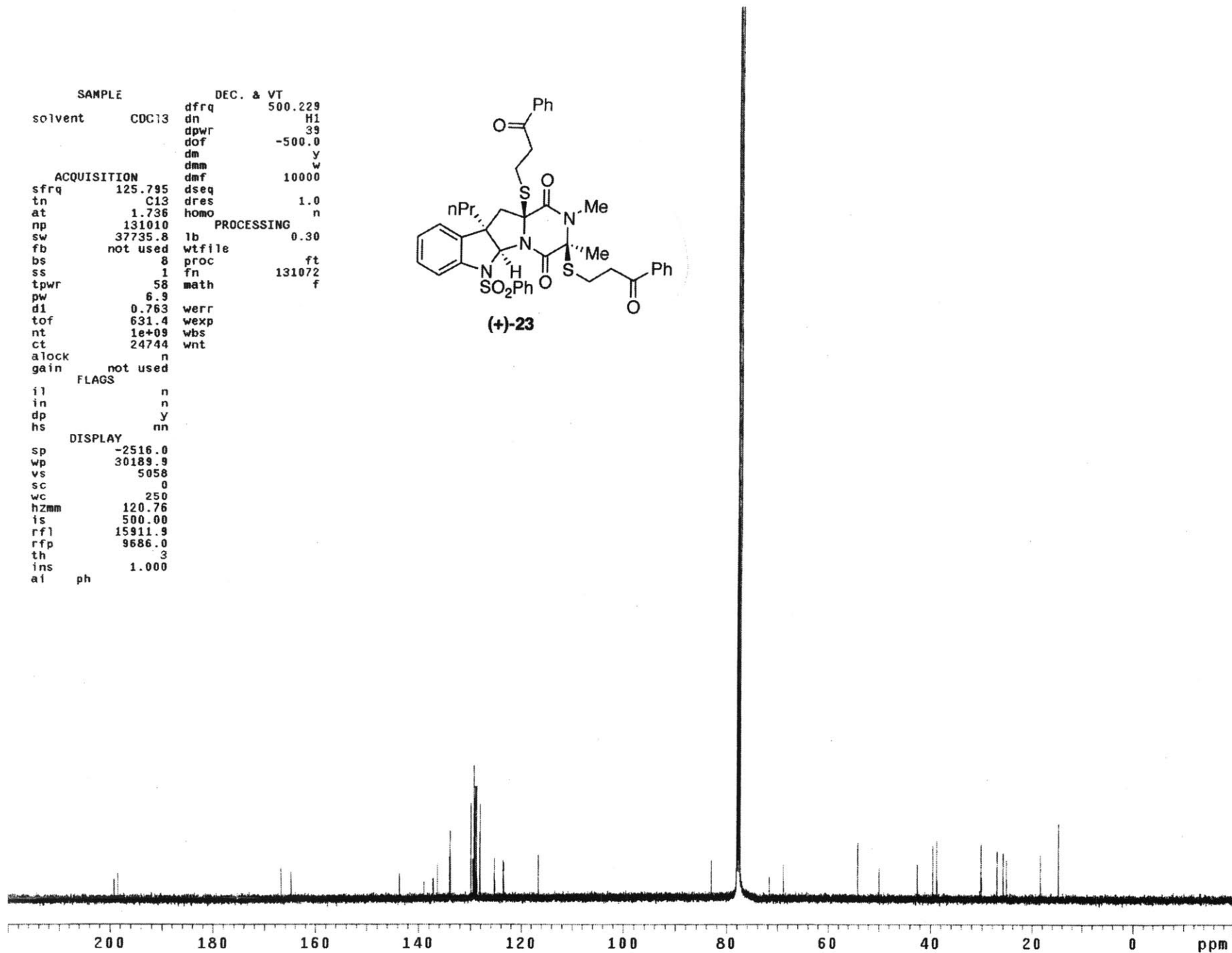
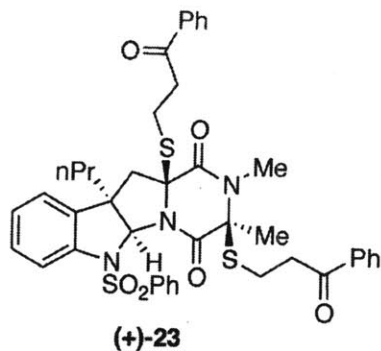
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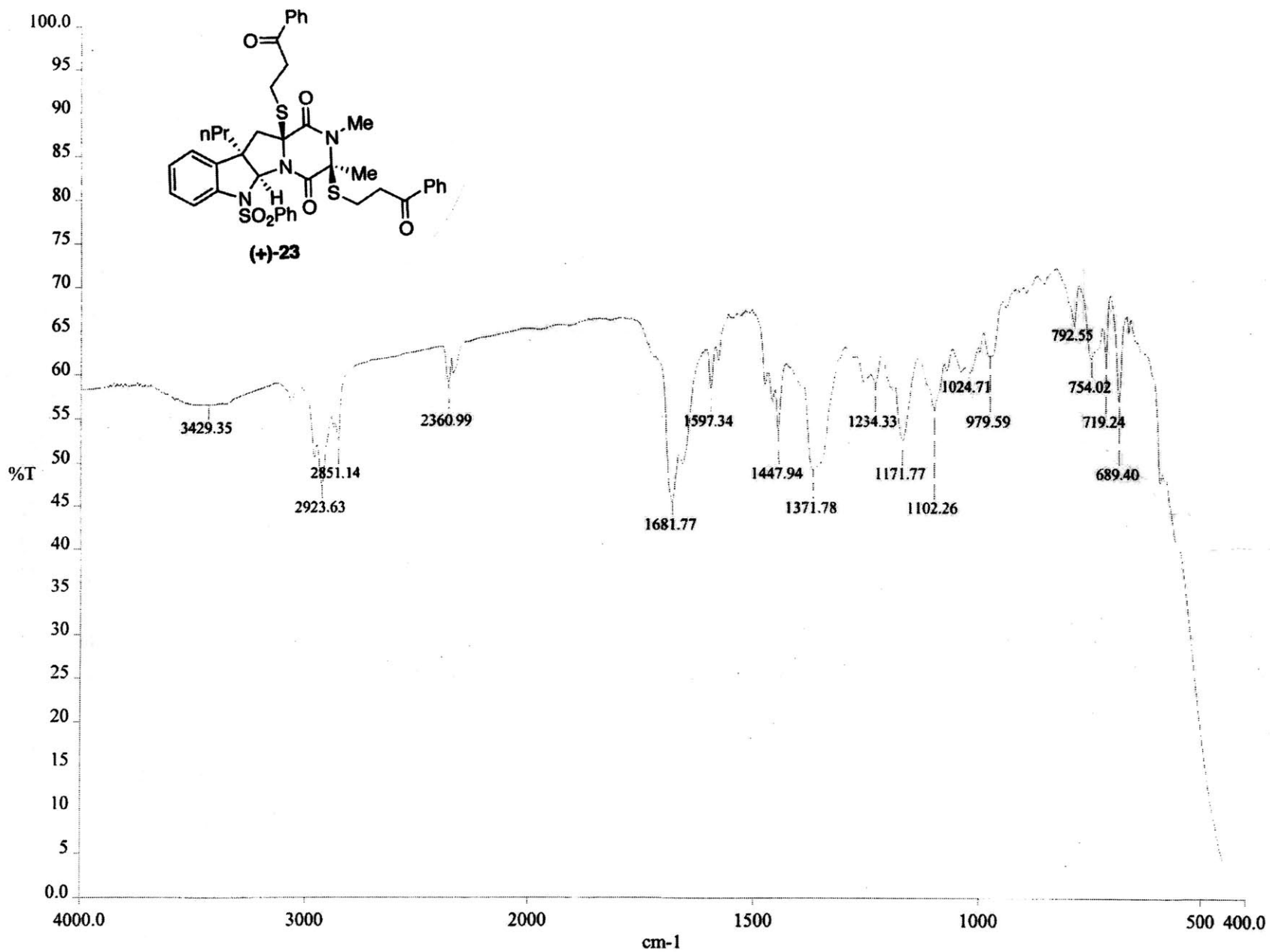
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solvent	CDC13	dfrq	125.845
		dn	C13
		dpwr	30
		dof	0
		dm	nnn
		dmm	c
		dmf	200
ACQUISITION		dseq	1.0
sfrq	500.433	dres	n
tn	H1	homo	
at	4.999	PROCESSING	
np	120102	wtfile	ft
sw	12012.0	proc	262144
fb	not used	fn	f
bs	3	math	
tpwr	60		
pw	8.0		
d1	0.100	werr	
tof	3003.2	wexp	
nt	10000	wbs	
ct	108	wnt	
alock	n		
gain	not used		
FLAGS			
fl	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-250.3		
wp	6505.6		
vs	36		
sc	0		
wc	250		
hzmm	26.02		
is	393.96		
rfl	4134.5		
rff	3623.1		
th	7		
ins	100.000		
ai	ph		





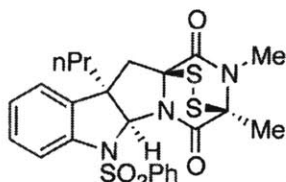
SAMPLE		DEC. & VT	
solvent	CDC13	dfrq	500.229
		dn	H1
		dpwr	39
		dof	-500.0
		dm	y
		dmm	w
ACQUISITION		dmf	10000
sfrq	125.795	dseq	
tn	C13	dres	1.0
at	1.736	homo	n
np	131010	PROCESSING	
sw	37735.8	lb	0.30
fb	not used	wtfile	
bs	8	proc	ft
ss	1	fn	131072
tpwr	58	math	f
pw	6.9		
d1	0.763	werr	
tof	631.4	wexp	
nt	1e+09	wbs	
ct	24744	wnt	
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-2516.0		
wp	30189.9		
vs	5058		
sc	0		
wc	250		
hzmm	120.76		
is	500.00		
rfl	15911.9		
rfp	9686.0		
th	3		
ins	1.000		
al	ph		



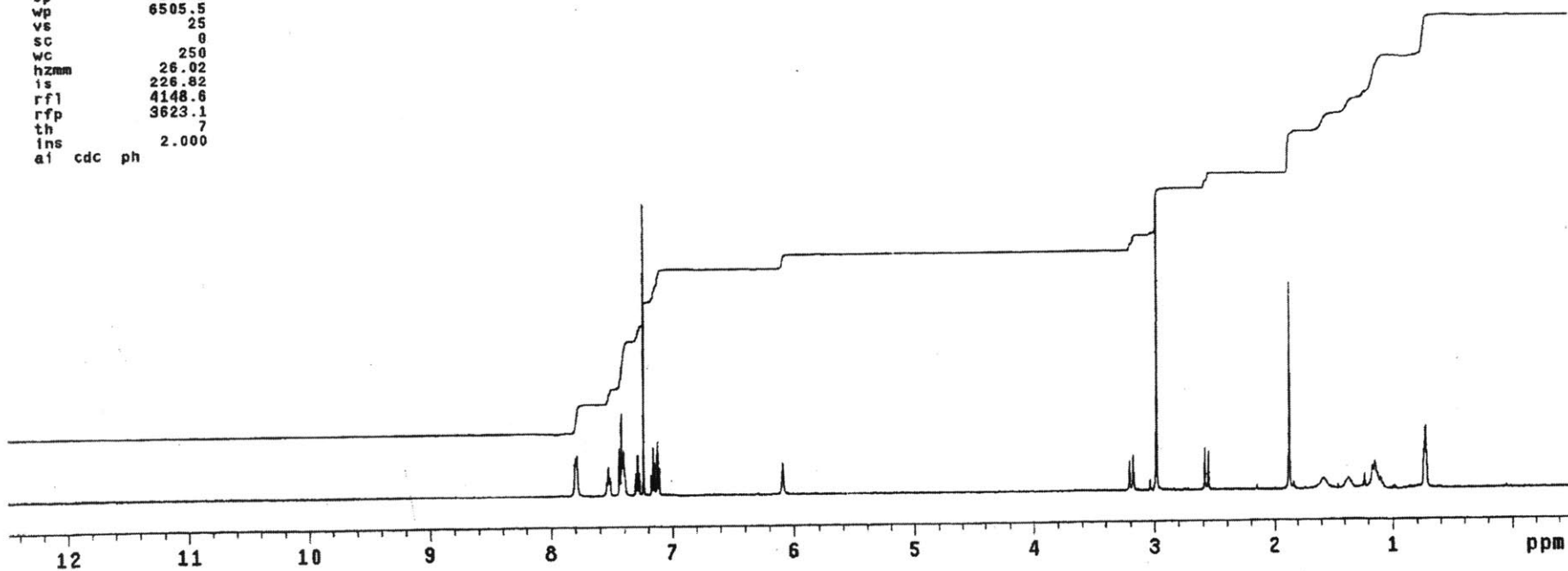


c:\pel\_data\spectra\groups\movass-1\mvtada\ta-7-135.sp - DO NOT CHANGE THE FILE NAME!!!

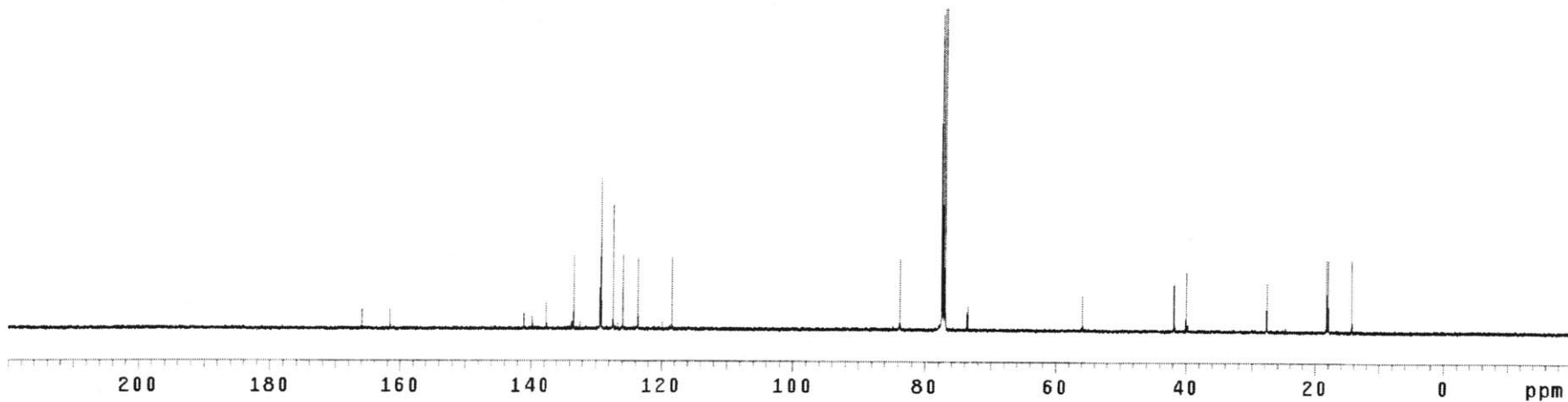
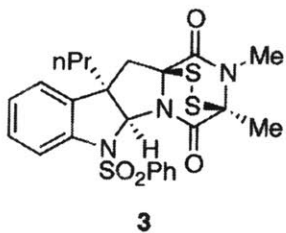
SAMPLE		DEC. & VT	
date		dfrq	125.844
solvent	CDC13	dn	C13
		dpwr	30
		dof	0
		dm	nnn
		dmm	c
		dmf	200
ACQUISITION		PROCESSING	
sfrq	500.431	dseq	1.0
tn	H1	dres	n
at	4.999	homo	
np	120102	wtfile	
sw	12012.0	proc	ft
fb	not used	fn	262144
bs	1	math	f
tpwr	60		
pw	8.0	werr	
d1	0.100	wexp	
tof	3003.2	wbs	
nt	11111	wnt	wft
ct	8		
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-250.3		
wp	6505.5		
vs	25		
sc	0		
wc	250		
hzmm	26.02		
is	226.82		
rfl	4148.6		
rfp	3623.1		
th	7		
ins	2.000		
a1	cdc ph		

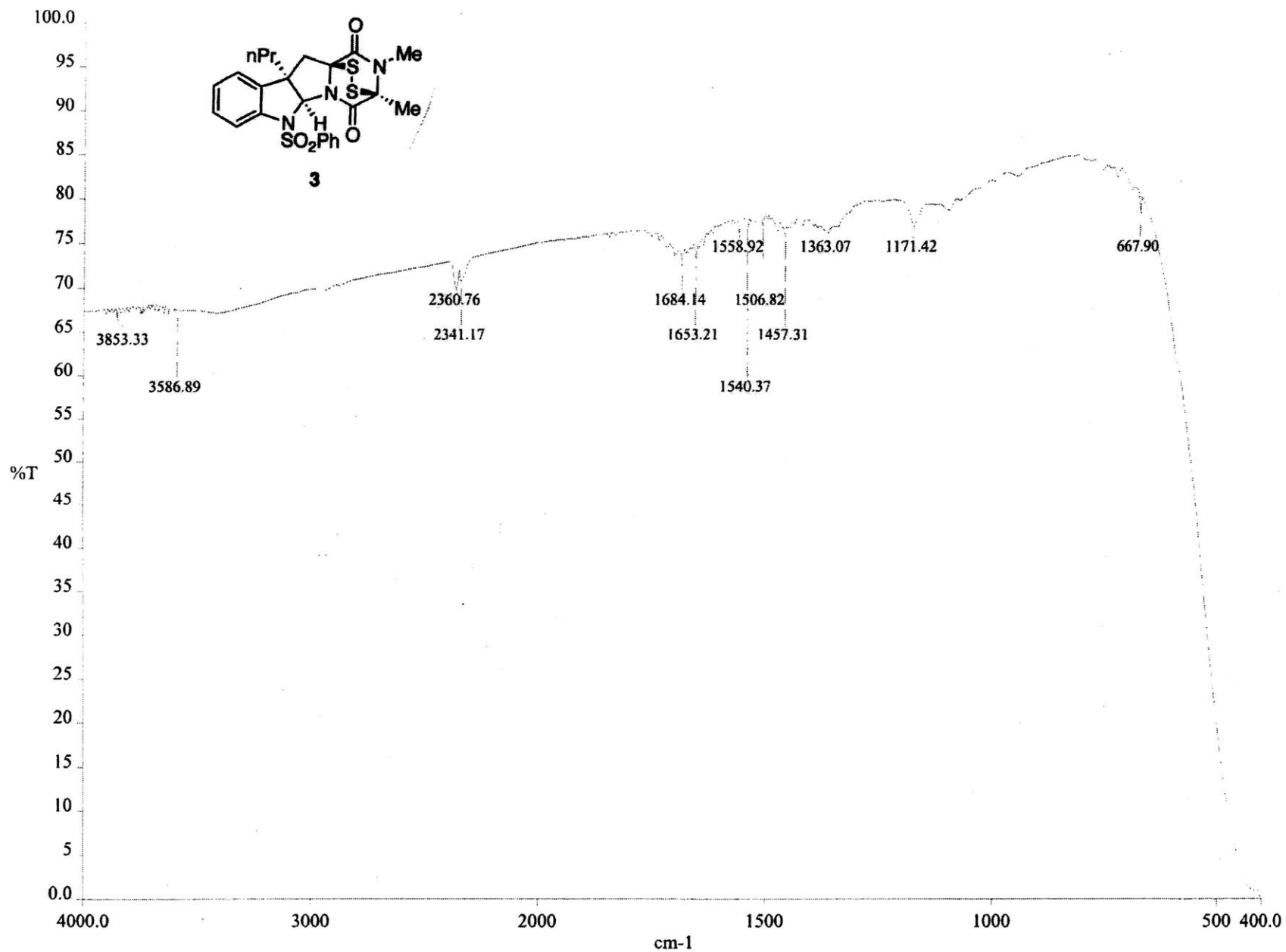
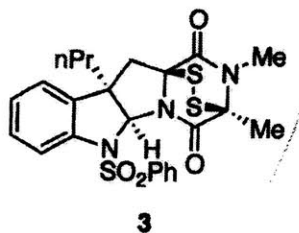


3



SAMPLE		DEC. & VT	
solvent	CDC13	dfrq	500.229
		dn	H1
		dpwr	40
		dof	-500.0
		dm	y
		dmm	w
		dmf	10000
ACQUISITION		dseq	
sfrq	125.795	dres	1.0
tn	C13	homo	n
at	1.736	PROCESSING	
np	131010	lb	1.00
sw	37735.8	wfile	
fb	not used	proc	ft
bs	8	fn	131072
ss	1	math	f
tpwr	58		
pw	6.9		
d1	0.763	werr	
tof	631.4	wexp	
nt	1.11111e+06	wbs	
ct	4112	wnt	
alock	n		
gain	60		
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-2515.9		
wp	30187.6		
vs	354		
sc	0		
wc	250		
hzmm	120.75		
is	500.00		
rfl	16002.7		
rfp	9714.2		
th	20		
ins	1.000		
ai	ph		

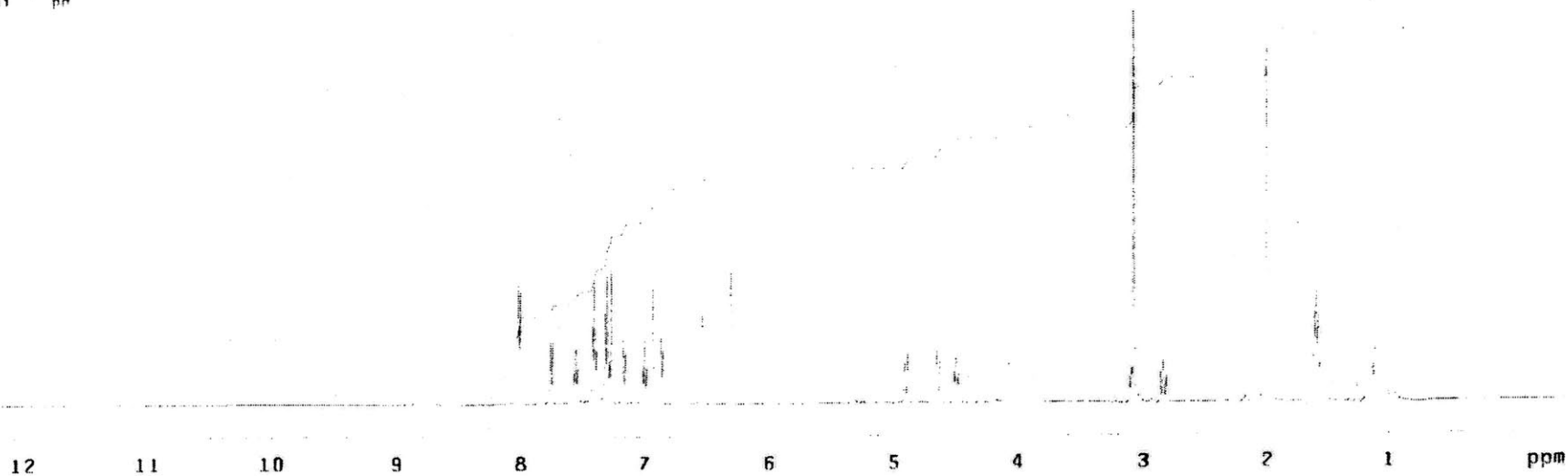
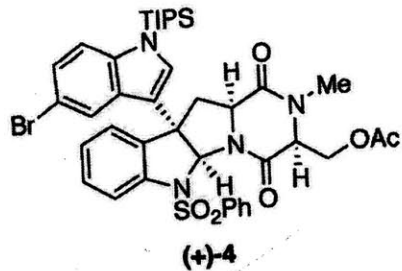




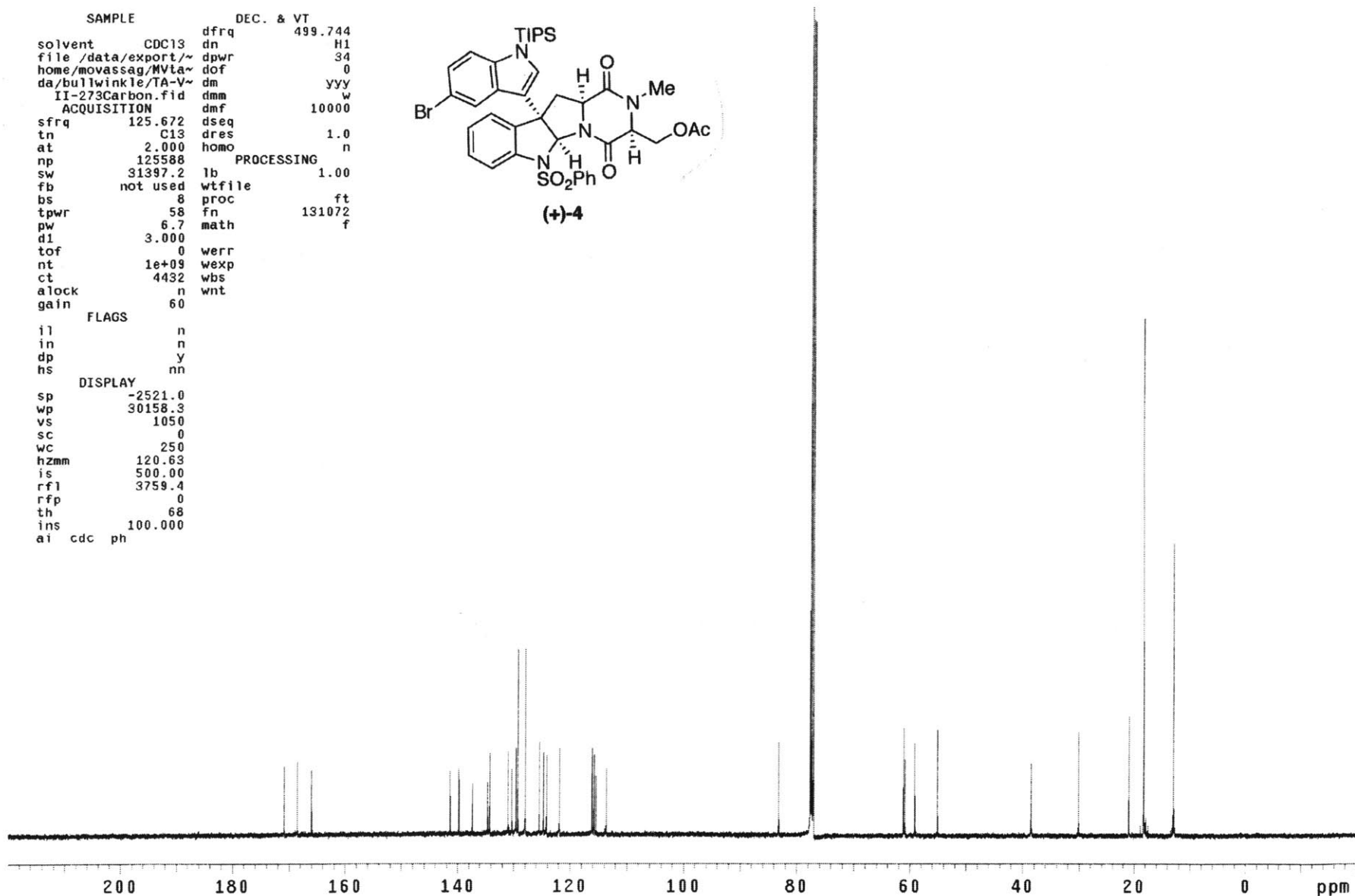
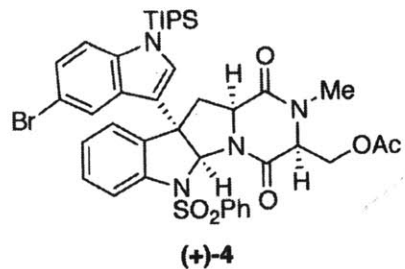
c:\pel\_data\spectra\scan\_rto.sp - DO NOT CHANGE THE FILE NAME!!!

**Appendix B.**  
**Spectra for Chapter 3**

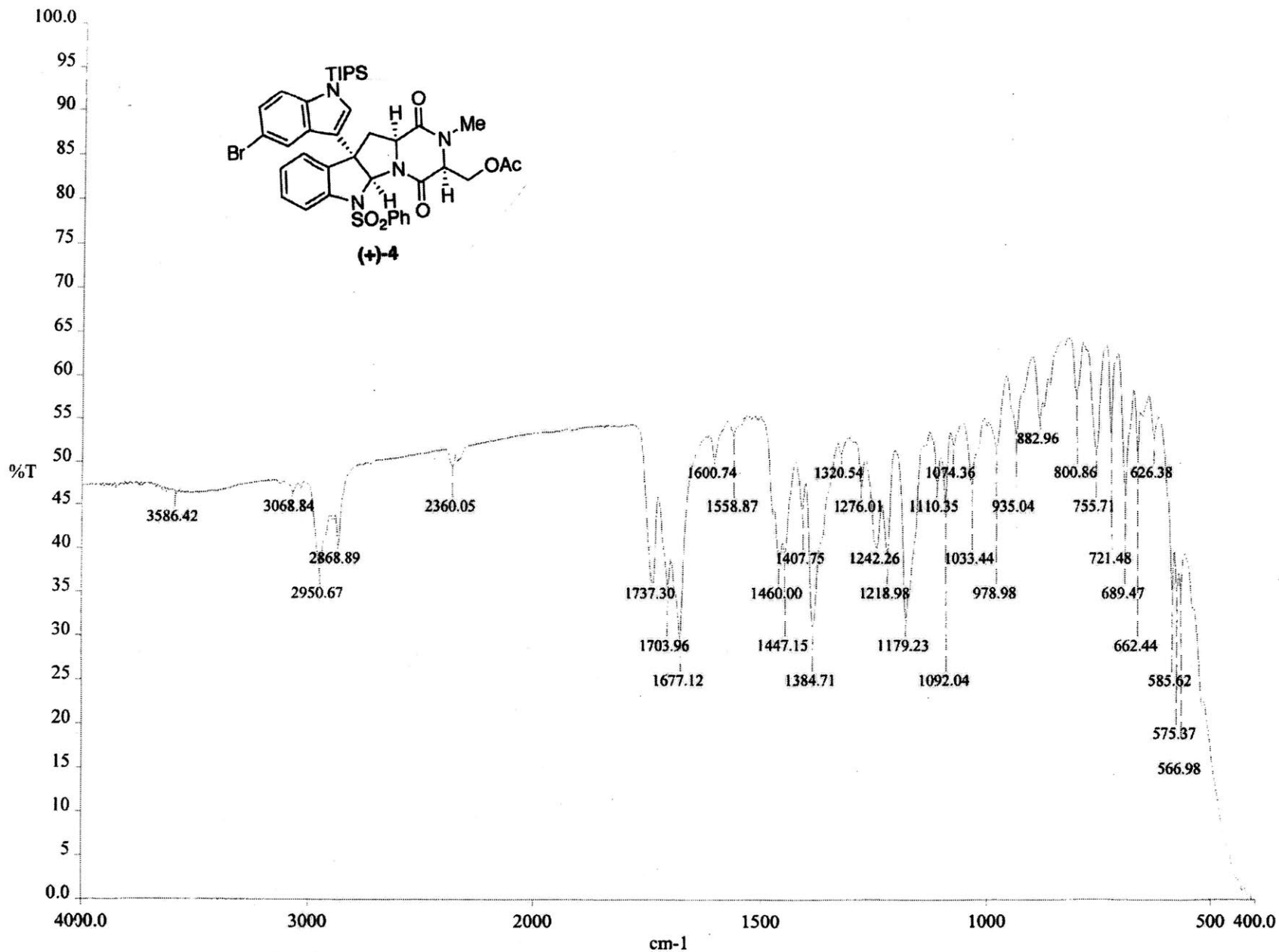
SAMPLE	DEC. & VT	dfrq	125.845
solvent	CDCl3	dn	C13
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	500.433	dm	nan
tn	H1	dmm	c
at	4.999	dof	200
np	120102	dseq	
sw	12012.0	dres	-1.0
fb	not used	homo	n
bs	3	PROCESSING	
tpwr	57	wtfile	
pw	8.0	proc	ft
d1	0.100	fn	262144
tof	3003.2	math	†
nt	1000		
ct	36	werr	
alock	n	wexp	
gain	not used	wbs	
FLAGS	wnt		
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-250.3		
wp	6505.6		
vs	162		
sc	0		
wc	750		
hzmm	26.02		
is	172.84		
rfl	500.6		
rfp	0		
th	7		
ins	100.000		
ai	ph		



SAMPLE		DEC. & VT	
solvent	CDC13	dfrq	499.744
file	/data/export/~	dn	H1
home	/movassag/MVta~	dpwr	34
da	/bullwinkle/TA-V~	dof	0
	II-273Carbon.fid	dm	yyy
	ACQUISITION	dmm	w
sfrq	125.672	dmf	10000
tn	C13	dseq	
at	2.000	dres	1.0
np	125588	homo	n
sw	31397.2	PROCESSING	
fb	not used	lb	1.00
bs	8	wtfile	
tpwr	58	proc	ft
pw	6.7	fn	131072
d1	3.000	math	f
tof	0	werr	
nt	1e+09	wexp	
ct	4432	wbs	
alock	n	wnt	
gain	60		
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-2521.0		
wp	30158.3		
vs	1050		
sc	0		
wc	250		
hzmm	120.63		
is	500.00		
rfl	3759.4		
rfp	0		
th	68		
ins	100.000		
ai	cdc ph		







c:\pel\_data\spectra\groups\movass~1\mvtada\ta-7-273.sp - DO NOT CHANGE THE FILE NAME!!!

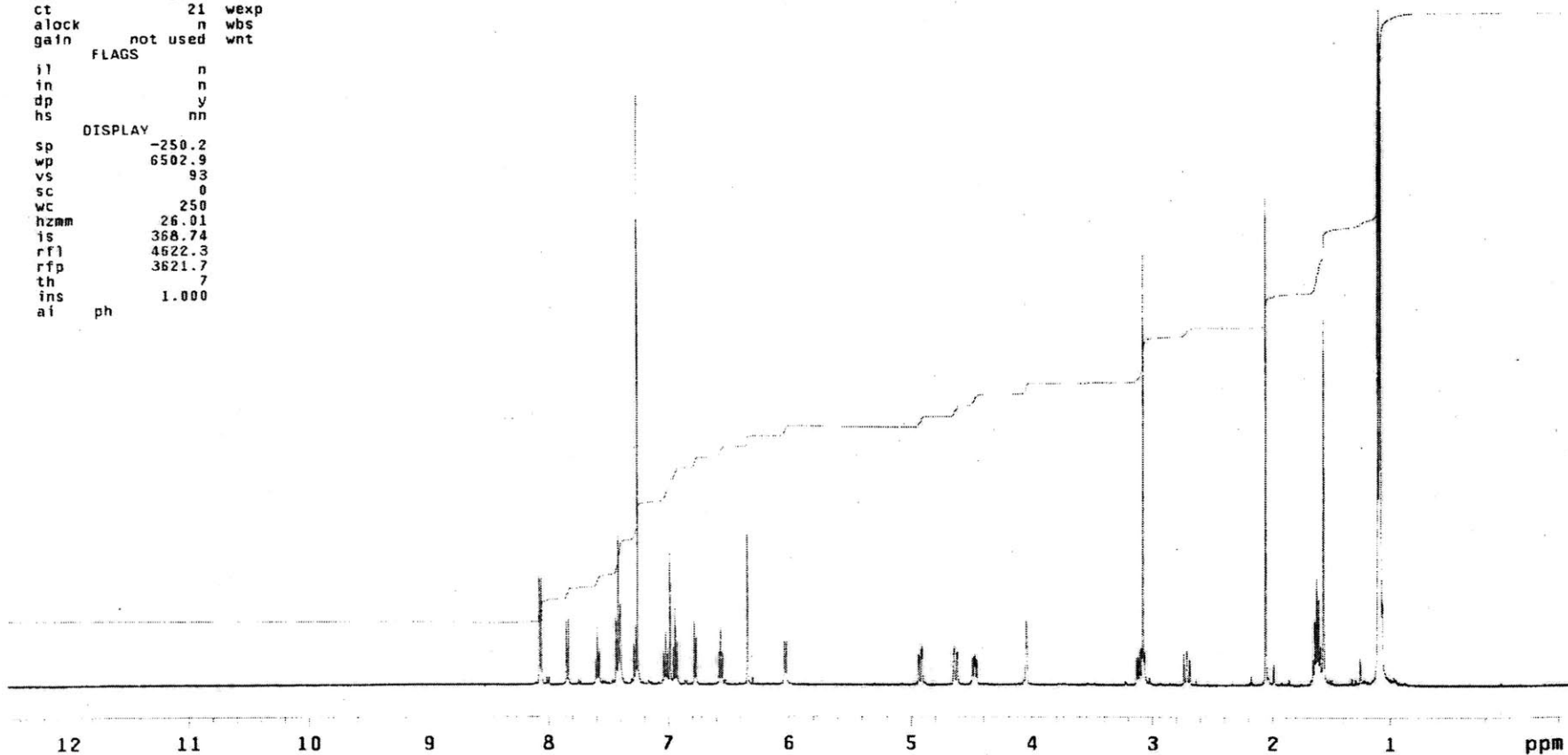
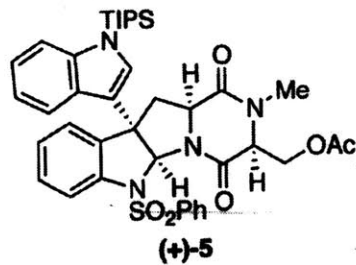
```

s2pu1
SAMPLE          DEC. & VT
solvent         CDC13      dfrq      125.794
file            exp        dn           C13
ACQUISITION    dof        dpwr      38
sfrq           500.231    dm         0
tn             H1         dmm        nnn
at            3.200      dmf        10700
np            64000      dseq
sw           10000.0     dres       1.0
fb            not used   homo        n
bs            3
ss            1          wtfile
tpwr          59         proc        ft
pw            9.0        fn          131072
dl            1.800      math        f
tof           1498.2
nt            1000      werr
ct            21         wexp
alock         not used   wbs
gain          not used   wnt

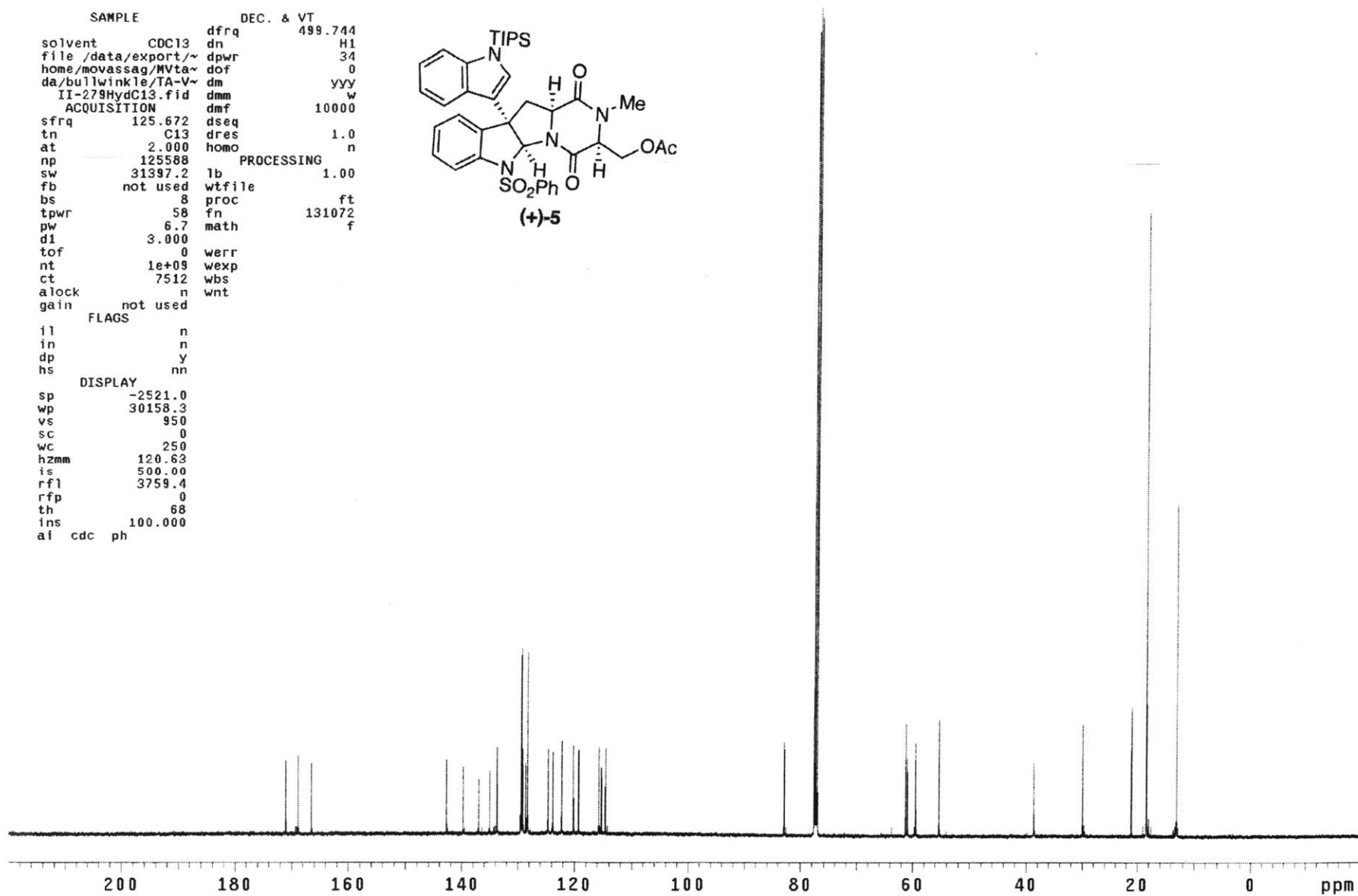
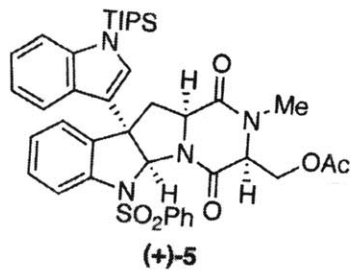
  FLAGS
  j1          n
  in          n
  dp          y
  hs          nn

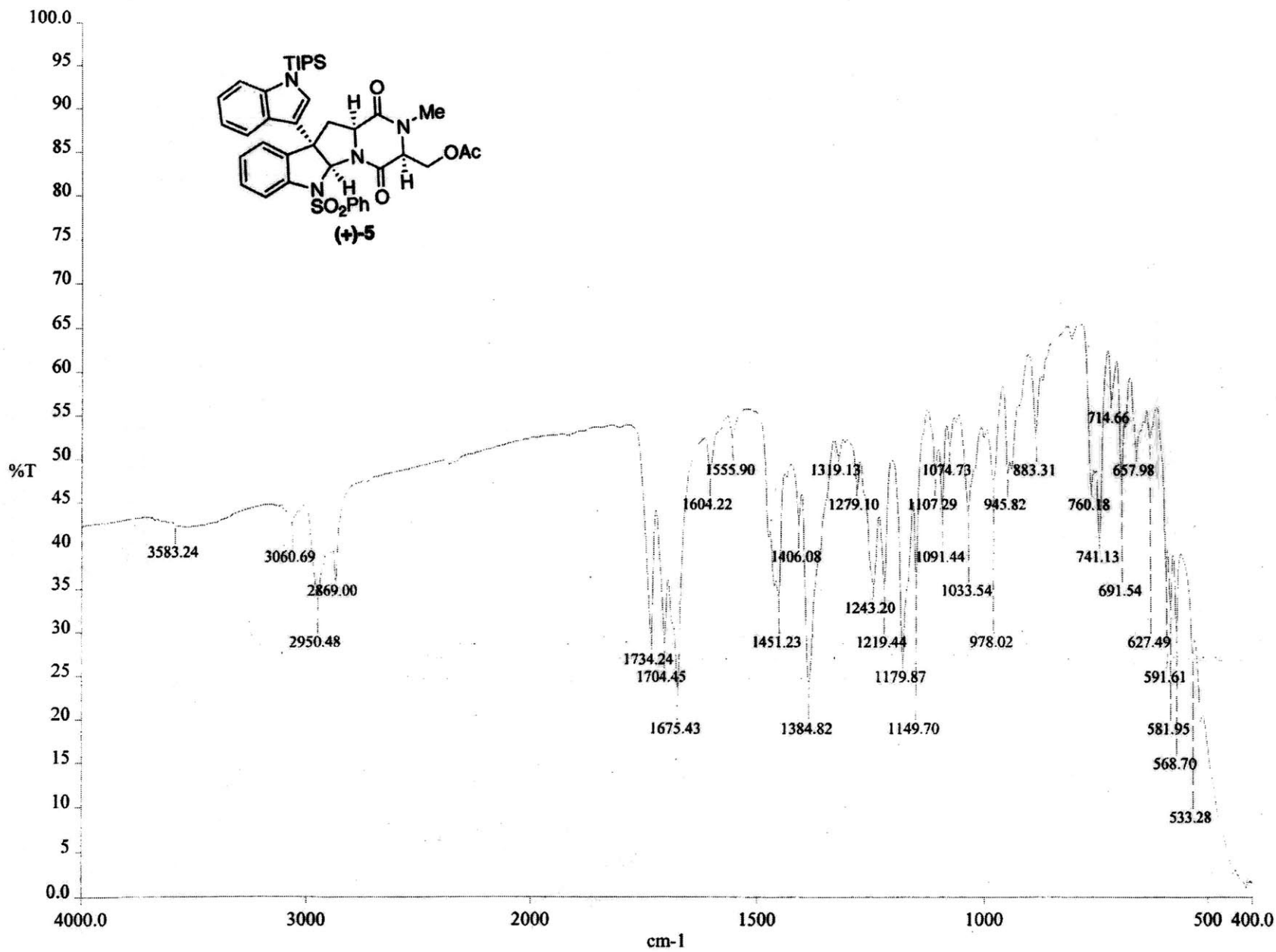
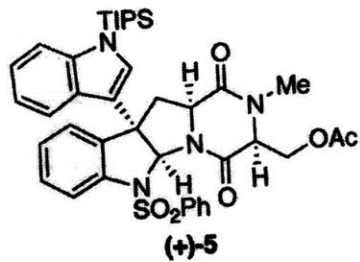
  DISPLAY
  sp          -250.2
  wp          6502.9
  vs          93
  sc          0
  wc          250
  hzmm        26.01
  is          368.74
  rfl         4622.3
  rfp         3621.7
  th          7
  ins         1.000
  ai          ph

```



SAMPLE		DEC. & VT	
solvent	CDC13	dfrq	499.744
file	/data/export/~	dn	H1
home	/movassag/MVta~	dpwr	34
da	/bullwinkle/TA-V~	dof	0
II-279HydC13.fid		dm	yyy
ACQUISITION		dmm	w
sfrq	125.672	dmf	10000
tn	C13	dseq	
at	2.000	dres	1.0
np	125588	homo	n
sw	31397.2	PROCESSING	
fb	not used	lb	1.00
bs	8	wfile	
tpwr	58	proc	ft
pw	6.7	fn	131072
d1	3.000	math	f
tof	0	werr	
nt	1e+09	wexp	
ct	7512	wbs	
alock	n	wnt	
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-2521.0		
wp	30158.3		
vs	950		
sc	0		
wc	250		
hzmm	120.62		
is	500.00		
rfl	3759.4		
rfp	0		
th	68		
ins	100.000		
ai	cdc ph		



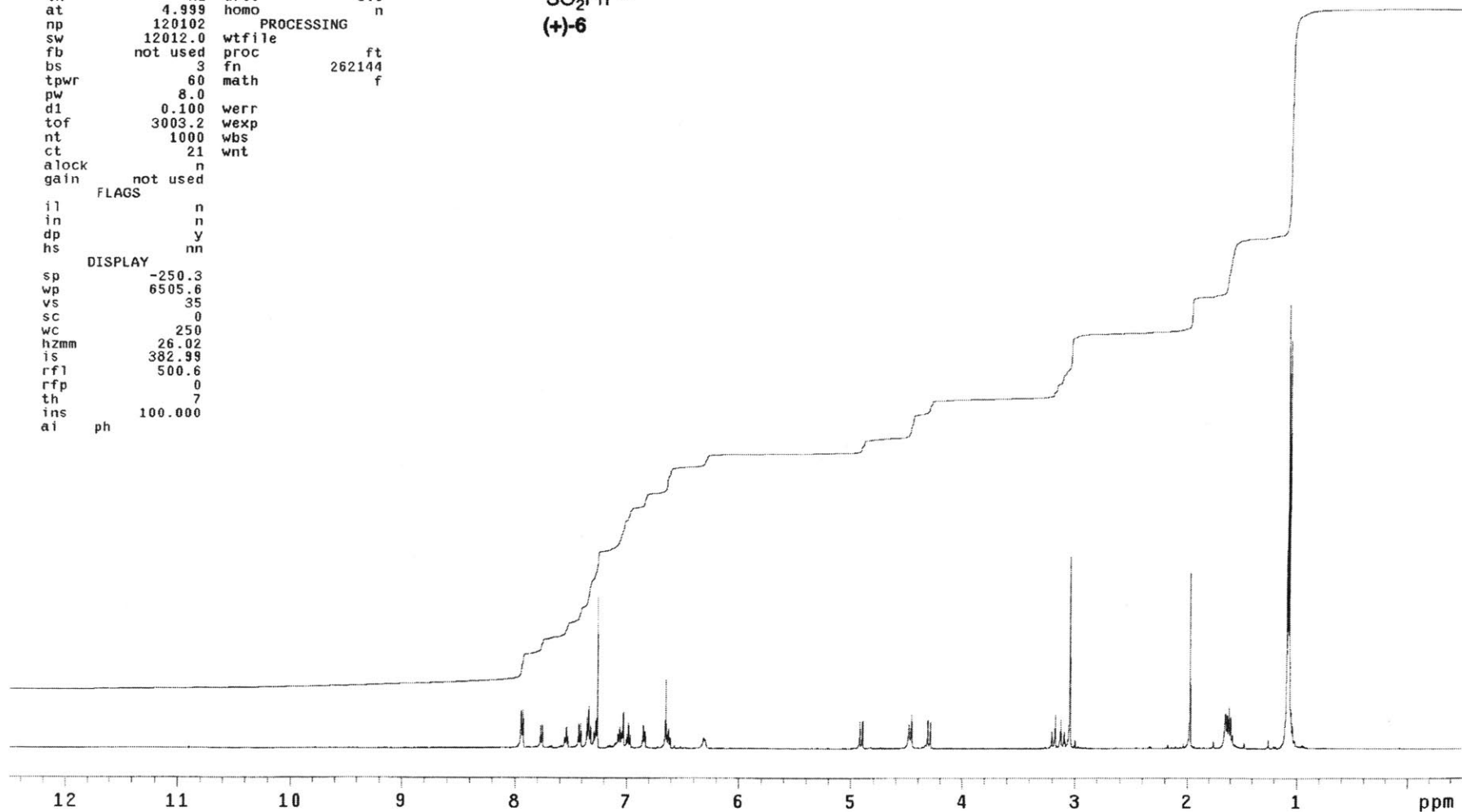
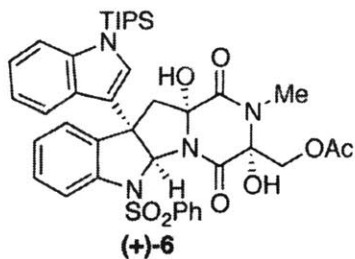


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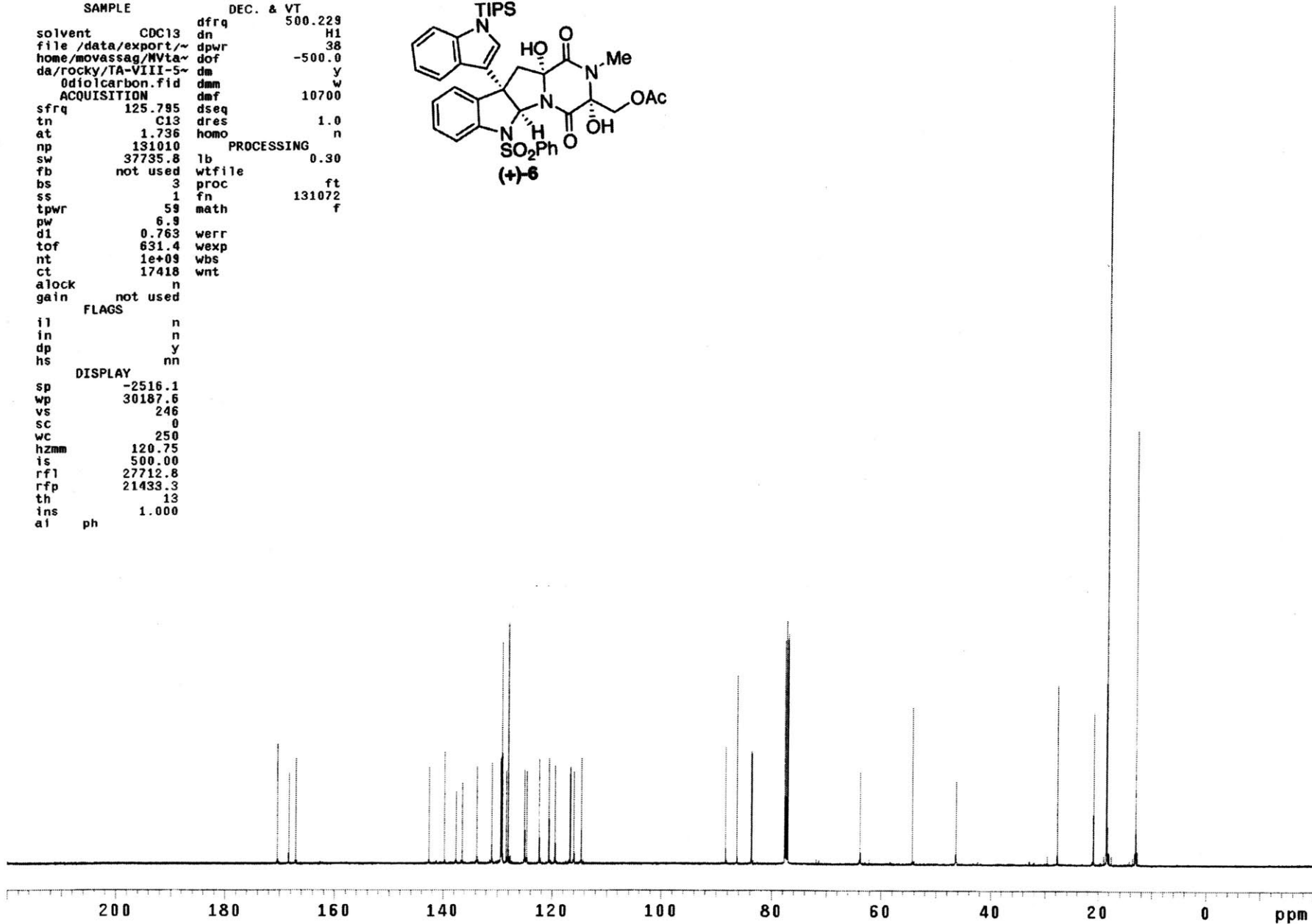
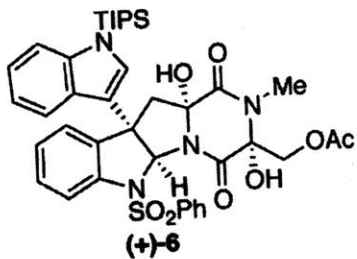
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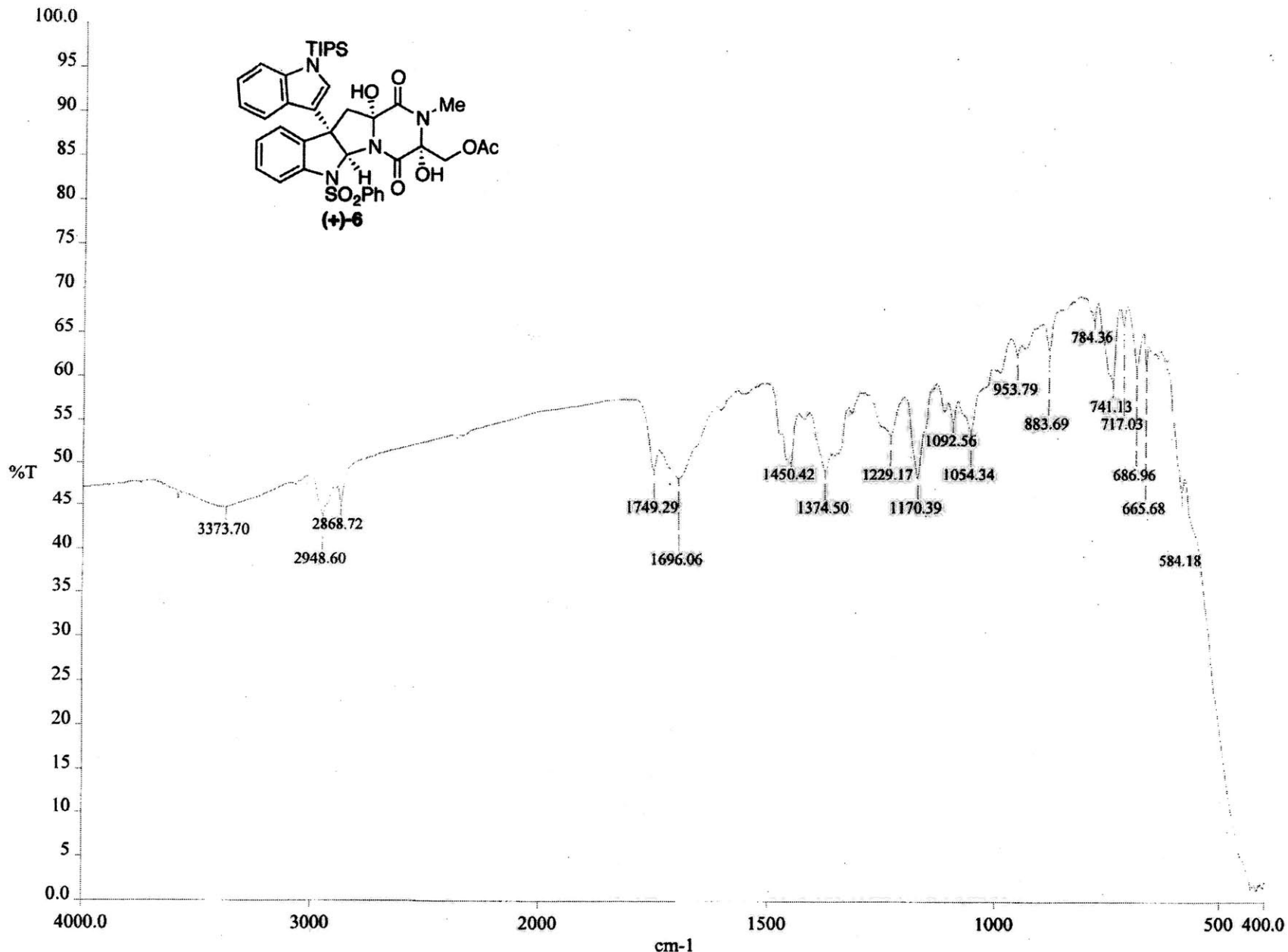
s2pu1
SAMPLE          DEC. & VT
solvent         CDC13      dfrq      125.845
file            /data/export/~      dn        C13
home/movassag/MVta~      dpwr      30
da/casper/TA-VIII~      dof        0
50-1.fid       dmm        nnn
ACQUISITION    dmf        200
sfrq           500.433     dseq
tn             H1         dres      1.0
at            4.999      homo      n
np            120102     wtfile
sw            12012.0    proc
fb            not used  fn        262144
bs            3         math
tpwr          60        f
pw            8.0
d1            0.100     werr
tof           3003.2    wexp
nt            1000     wbs
ct            21       wnt
alock         n
gain          not used
FLAGS
il            n
in            n
dp            y
hs            nn
DISPLAY
sp            -250.3
wp            6505.6
vs            35
sc            0
wc            250
hzmm          26.02
is            382.99
rf1           500.6
rfp           0
th            7
ins           100.000
ai            ph

```



SAMPLE		DEC. & VT	
solvent	CDC13	dfrq	500.229
file	/data/export/~	dn	H1
home	/movassag/MVta~	dpwr	38
da/rocky/TA-VIII-5~		dof	-500.0
OdioIcarbon.fid		dm	y
ACQUISITION		dmm	w
sfrq	125.795	dmf	10700
tn	C13	dseq	
at	1.736	dres	1.0
np	131010	homo	n
sw	37735.8	PROCESSING	
fb	not used	lb	0.30
bs	3	wtfile	
ss	1	proc	ft
tpwr	59	fn	131072
pw	6.9	math	f
d1	0.763	werr	
tof	631.4	wexp	
nt	1e+09	wbs	
ct	17418	wnt	
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-2516.1		
wp	30187.6		
vs	246		
sc	0		
wc	250		
hzmm	120.75		
is	500.00		
rf1	27712.8		
rfp	21433.3		
th	13		
ins	1.000		
af	ph		





c:\pel\_data\spectra\groups\movass-1\mvtadata-7-277.sp - DO NOT CHANGE THE FILE NAME!!!

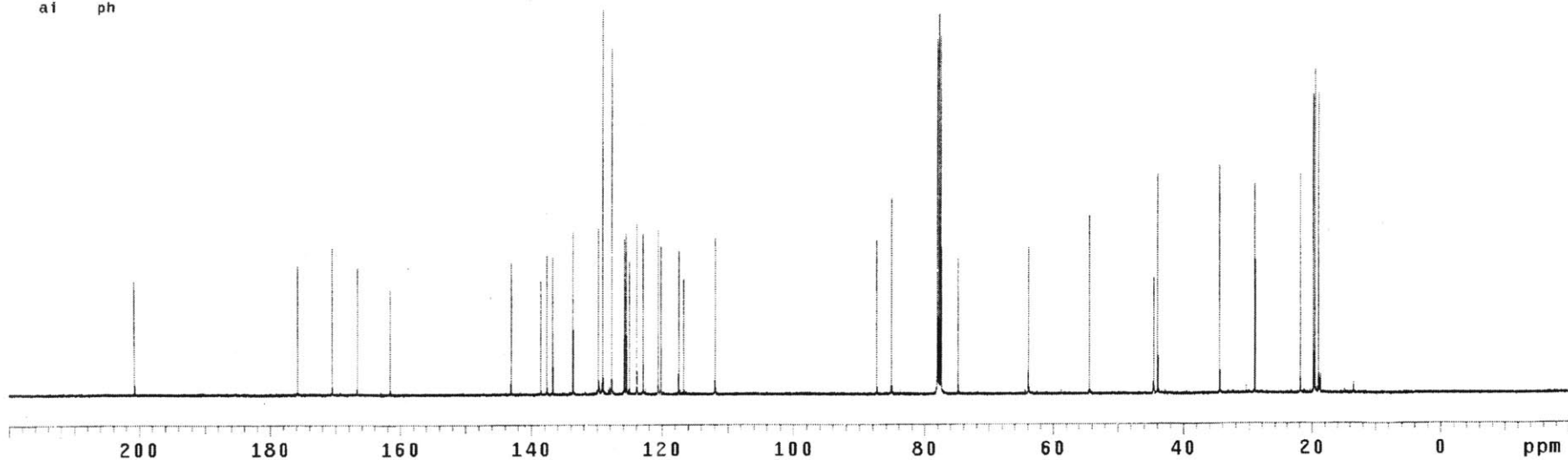
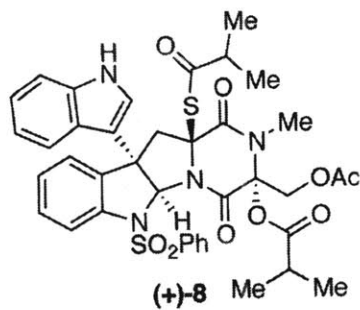


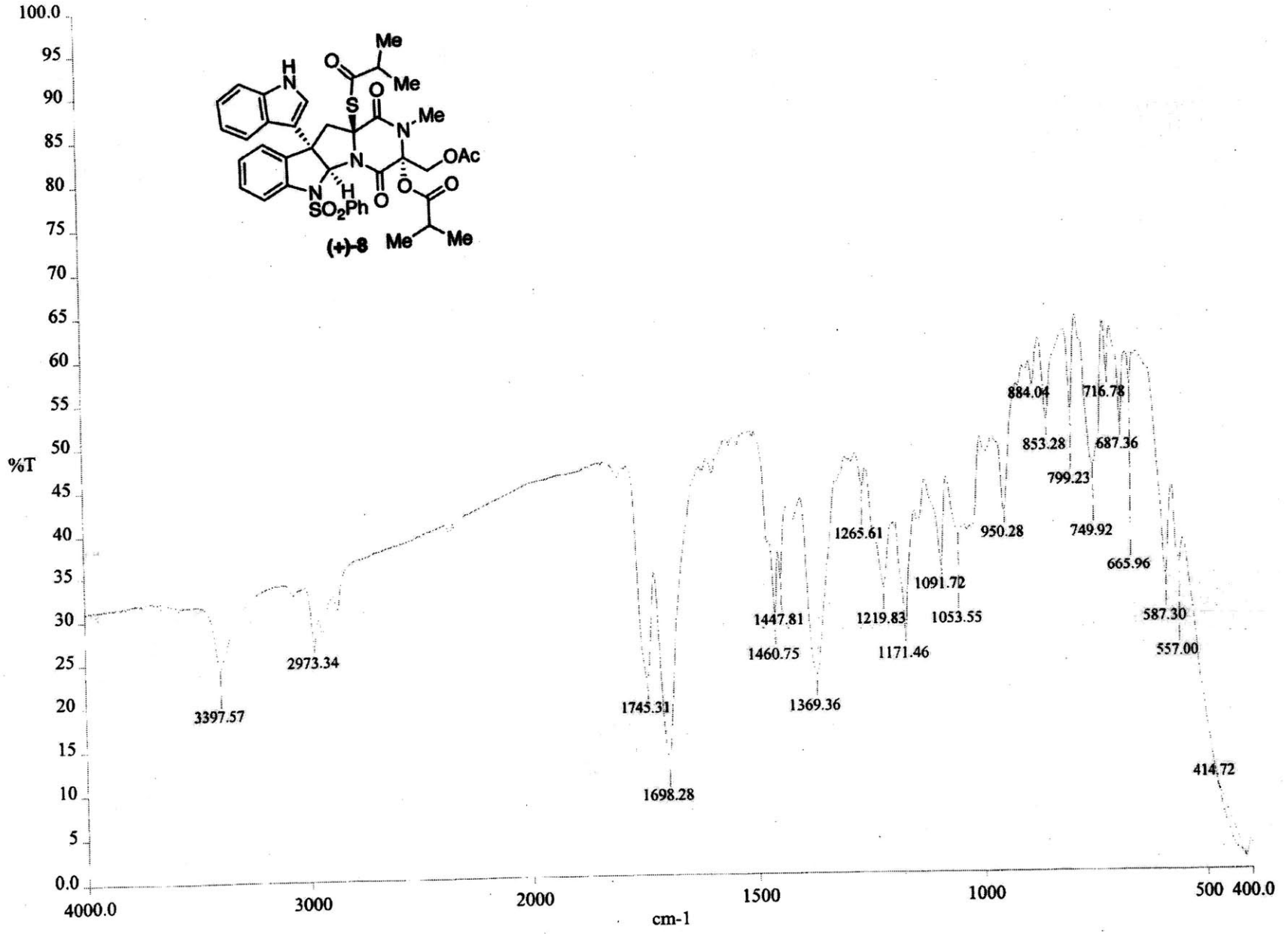


```

SAMPLE          DEC. & VT
solvent         CDC13  dfrq 500.229
file            /data/export/~  dn  H1
home/movassag/MVta~  dpwr 38
da/rocky/TA-VIII-5~  dof  -500.0
0thioestercarbon.f~  dm  y
id              dmm  w
                dmf  10700
ACQUISITION    dseq
sfrq           125.795  dres 1.0
tn             C13      homo  n
at            1.736
np            131010  1b  0.30
sw            37735.8  wtfile
fb            not used  proc
bs            8       fn  131072
ss            1       math  f
tpwr          59
pw            6.9    werr
d1            0.763  wexp
tof           631.4  wbs
nt            1e+09  wnt
ct            16800
alock         n
gain          not used
FLAGS
il            n
in            n
dp            y
hs            nn
DISPLAY
sp            -2516.0
wp            30189.9
vs            328
sc            0
wc            250
hzmm          120.76
is            500.00
rfl           15911.9
rfp           9686.0
th            20
ins           1.000
ai            ph

```



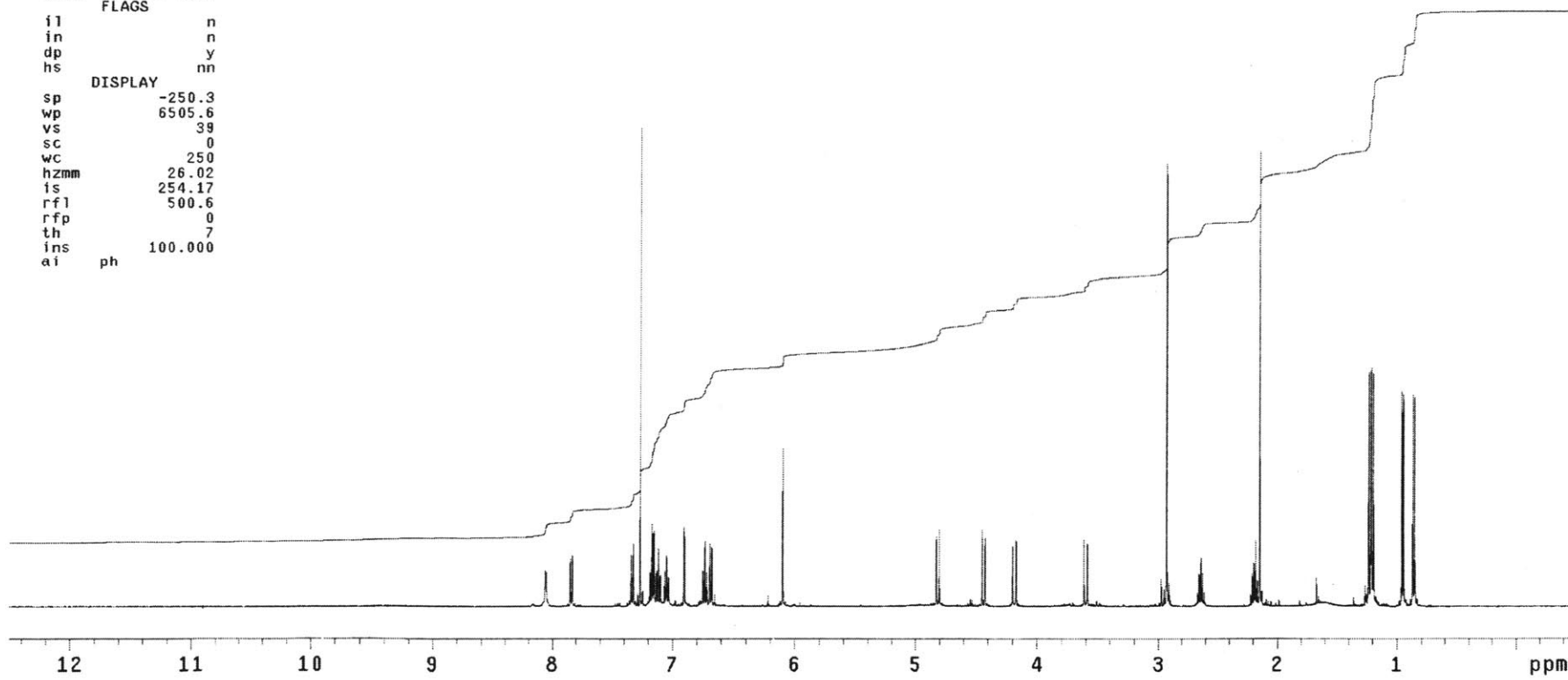
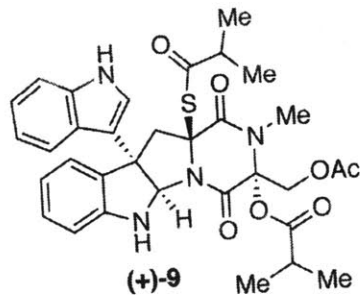


c:\pel\_data\spectra\groups\movass~1\mvtda\ta-7-303.sp - DO NOT CHANGE THE FILE NAME!!!

```

s2pu1
SAMPLE      DEC. & VT
solvent     CDC13      dfrq      125.845
file /data/export/~  dn         C13
home/movassag/MVta~ dpwr        30
da/casper/TA-VIII~  dof         0
255-2.fid    dm         nnn
ACQUISITION  dmm         c
sfrq       500.433    dmf        200
tn          H1        dseq
at          4.999     dres       1.0
np          120102    homo
sw          12012.0   wtfile
fb          not used  proc
bs          3         fn          262144
tpwr        60       math
pw          8.0
d1          0.100    werr
tof         3003.2   wexp
nt          1000     wbs
ct          0        wnt
alock       n
gain        not used
          FLAGS
il          n
in          n
dp          y
hs          nn
          DISPLAY
sp          -250.3
wp          6505.6
vs          39
sc          0
wc          250
hzmm        26.02
is          254.17
rfl         500.6
rfp         0
th          7
ins         100.000
ai          ph

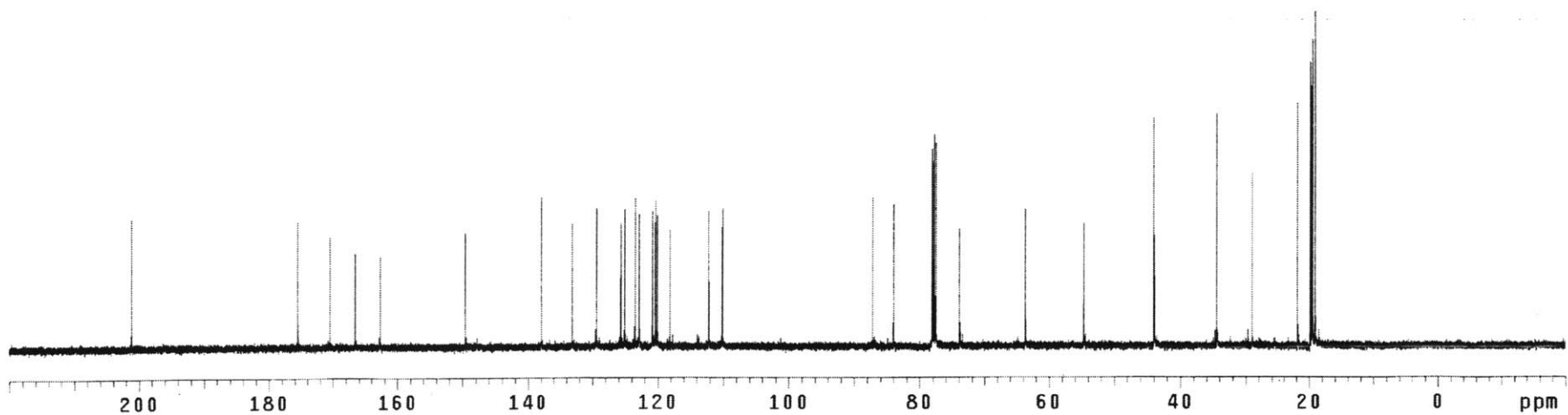
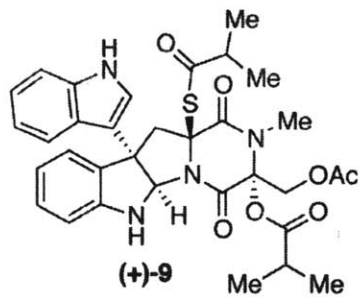
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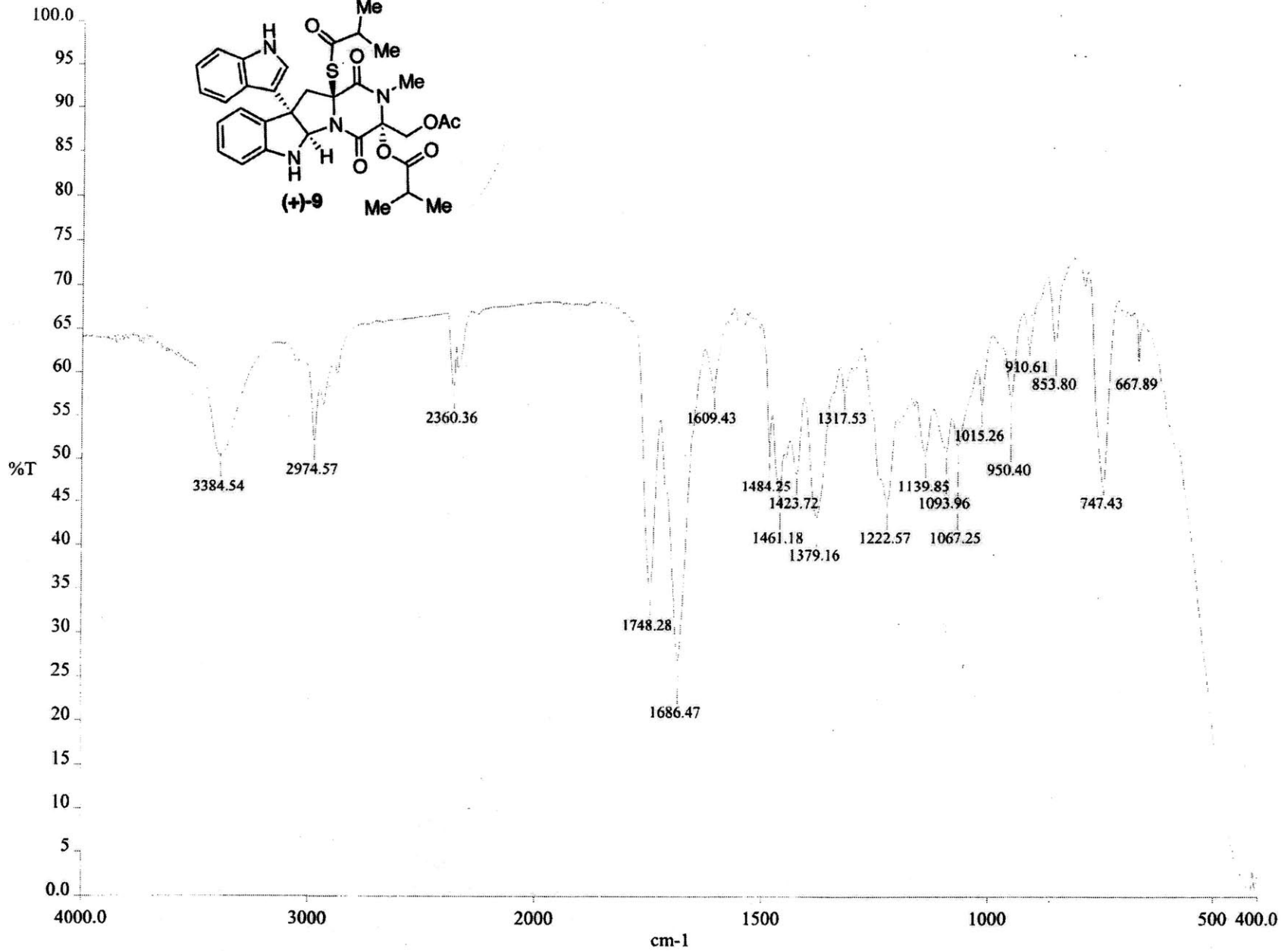
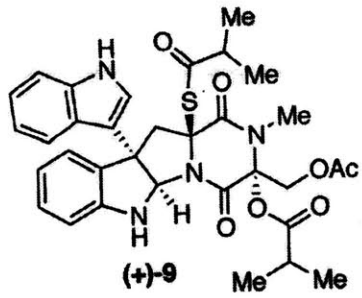


```

s2pu1
SAMPLE
solvent CDC13
file /data/export/~
home/movassag/MVta~
da/rocky/TA-VIII-6~
6carbon.fid
ACQUISITION
sfrq 125.795
tn C13
at 1.736
np 131010
sw 37735.8
fb not used
bs 8
ss 1
tpwr 59
pw 6.9
d1 0.763
tof 631.4
nt 1e+09
ct 552
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -2516.0
wp 30189.9
vs 224
sc 0
wc 250
hzmm 120.76
is 500.00
rf1 15911.9
rfp 9686.0
th 20
ins 1.000
ai ph
DEC. & VT
dfrq 500.229
dn H1
dpwr 38
dof -500.0
dm y
dmm w
dmf 10700
dseq
dres 1.0
homo n
PROCESSING
lb 0.30
wtfile
proc ft
fn 131072
math f
werr
wexp
wbs
wnt

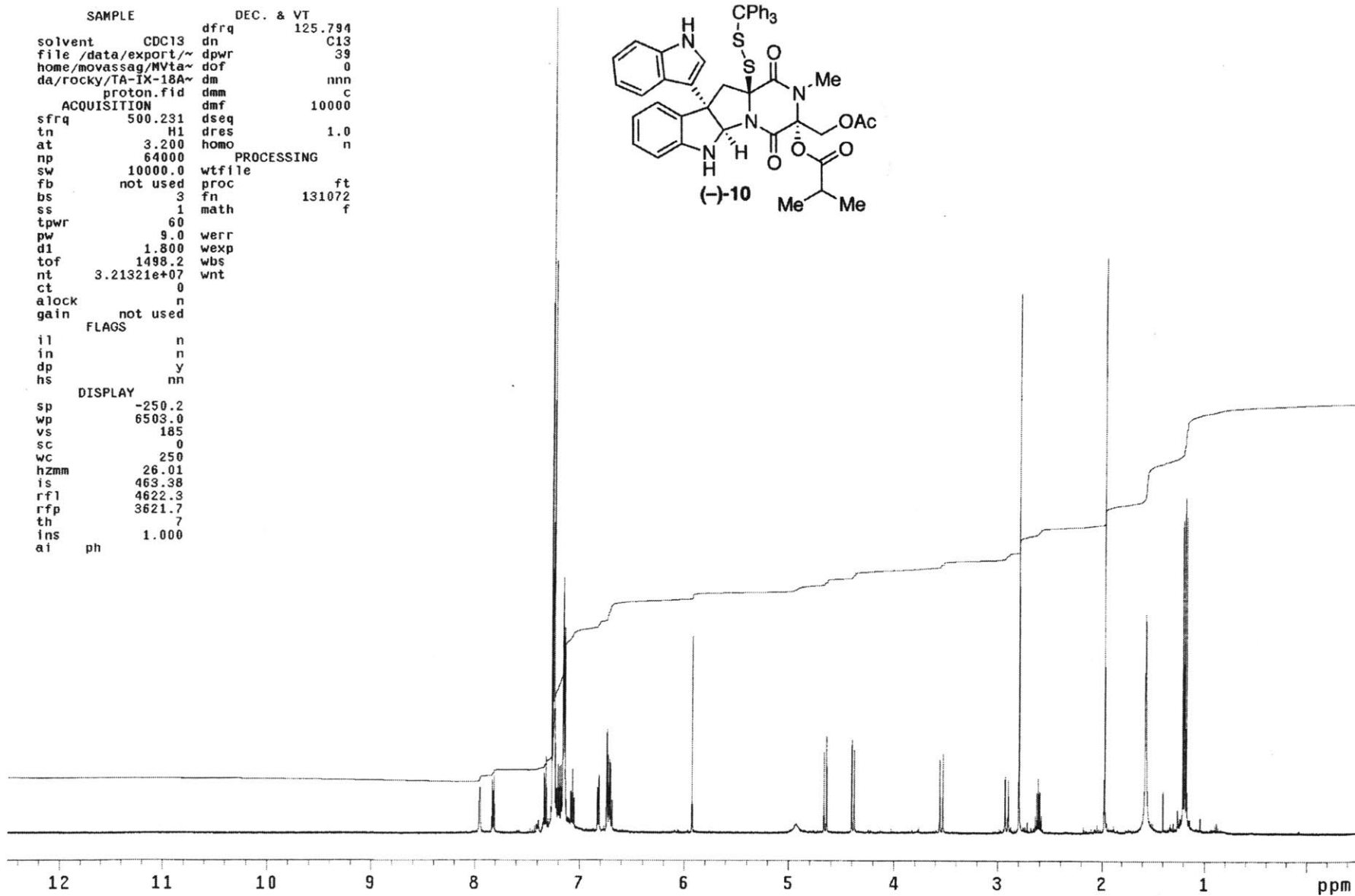
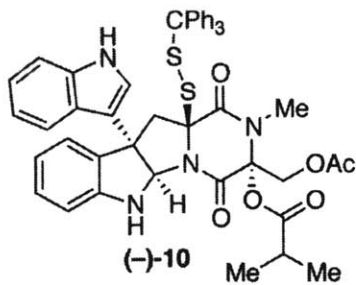
```





c:\pel\_data\spectra\groups\movass-1\ta-7-260.sp - DO NOT CHANGE THE FILE NAME!!!

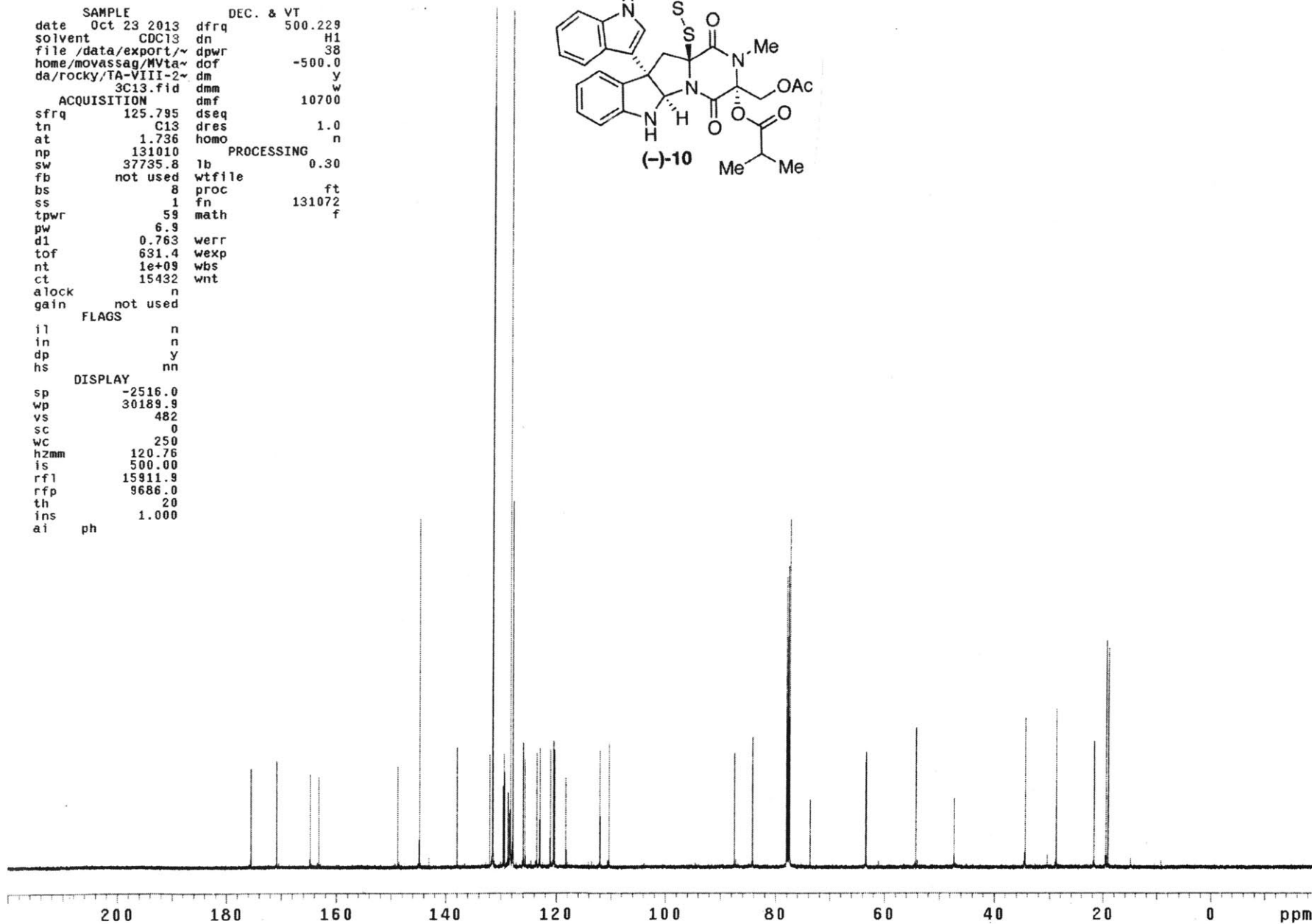
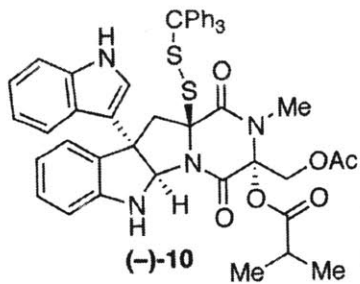
SAMPLE	DEC. & VT
solvent CDC13	dfrq 125.794
file /data/export/~	dn C13
home/movassag/MVta~	dpwr 39
da/rocky/TA-IX-18A~	dof 0
proton.fid	dm nnn
ACQUISITION	dmm c
sfrq 500.231	dmf 10000
tn H1	dseq
at 3.200	dres 1.0
np 64000	homo n
sw 10000.0	PROCESSING
fb not used	wtfile
bs 3	proc ft
ss 1	fn 131072
tpwr 60	math f
pw 9.0	werr
d1 1.800	wexp
tof 1498.2	wbs
nt 3.21321e+07	wnt
ct 0	
alock n	
gain not used	
FLAGS	
il n	
in n	
dp y	
hs nn	
DISPLAY	
sp -250.2	
wp 6503.0	
vs 185	
sc 0	
wc 250	
hzmm 26.01	
is 463.38	
rfl 4622.3	
rfp 3621.7	
th 7	
ins 1.000	
ai ph	

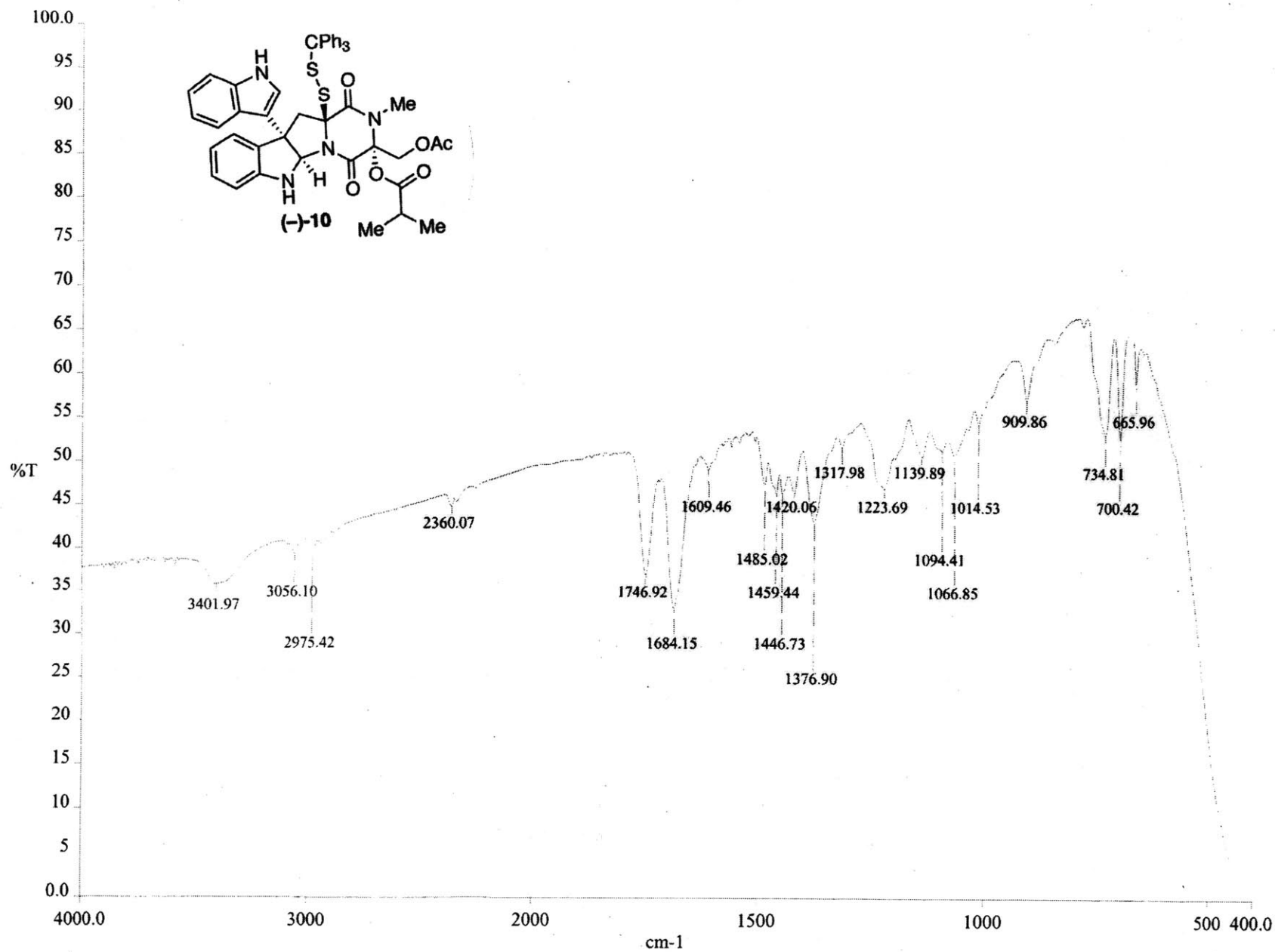
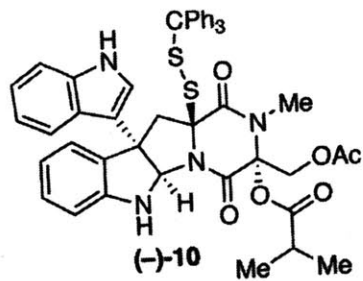


TA-VIII-23C13

exp1 s2pu1

SAMPLE		DEC. & VT	
date	Oct 23 2013	dfrq	500.229
solvent	CDCl3	dn	H1
file	/data/expo1/~	dpwr	38
home	/movassag/MVta~	dof	-500.0
da/rocky/TA-VIII-2~		dm	y
	3C13.fid	dmm	w
ACQUISITION		dmf	10700
sfrq	125.795	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	8	proc	ft
ss	1	fn	131072
tpwr	59	math	f
pw	6.9		
d1	0.763	werr	
tof	631.4	wexp	
nt	1e+09	wbs	
ct	15432	wnt	
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-2516.0		
wp	30189.9		
vs	482		
sc	0		
wc	250		
hzmm	120.76		
is	500.00		
rfl	15911.9		
rfp	9686.0		
th	20		
ins	1.000		
ai	ph		





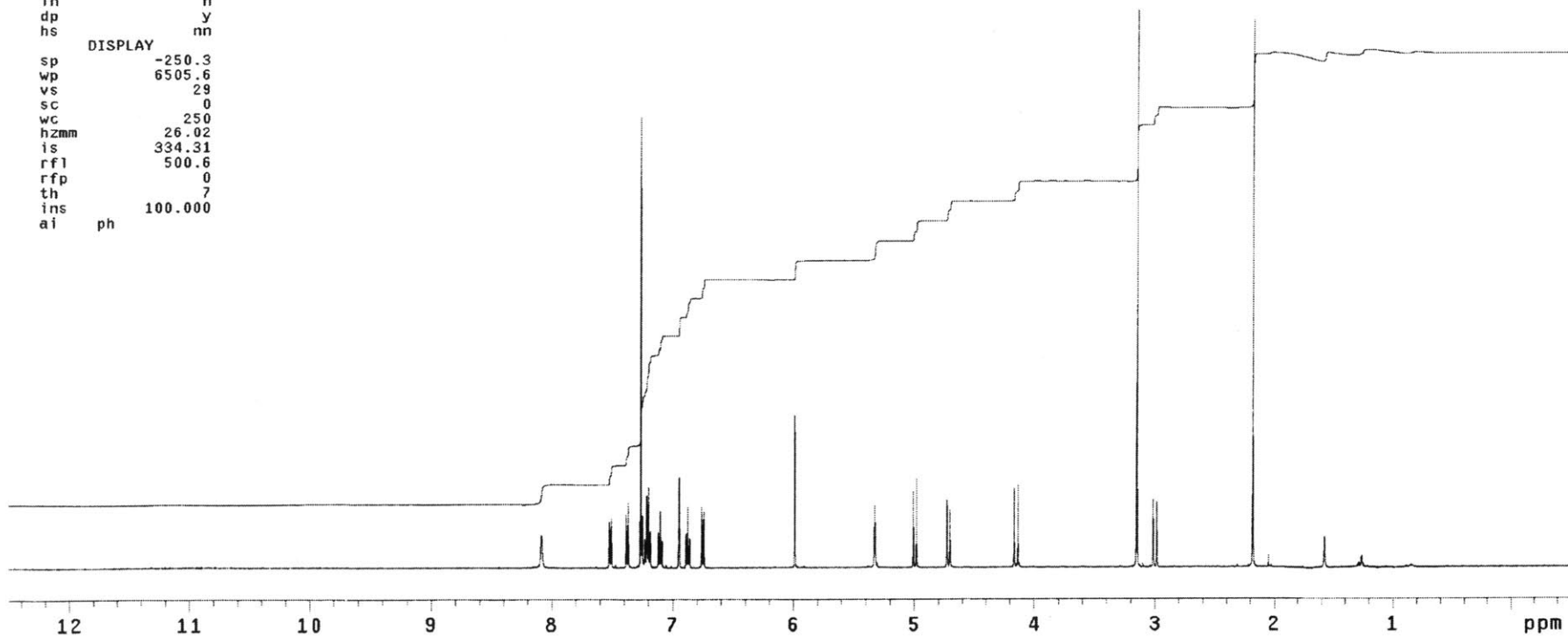
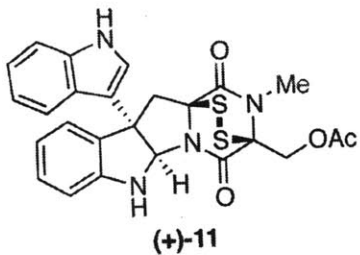
c:\pel\_data\spectra\groups\movass-1\mvtada\ta-8-6.sp - DO NOT CHANGE THE FILE NAME!!!



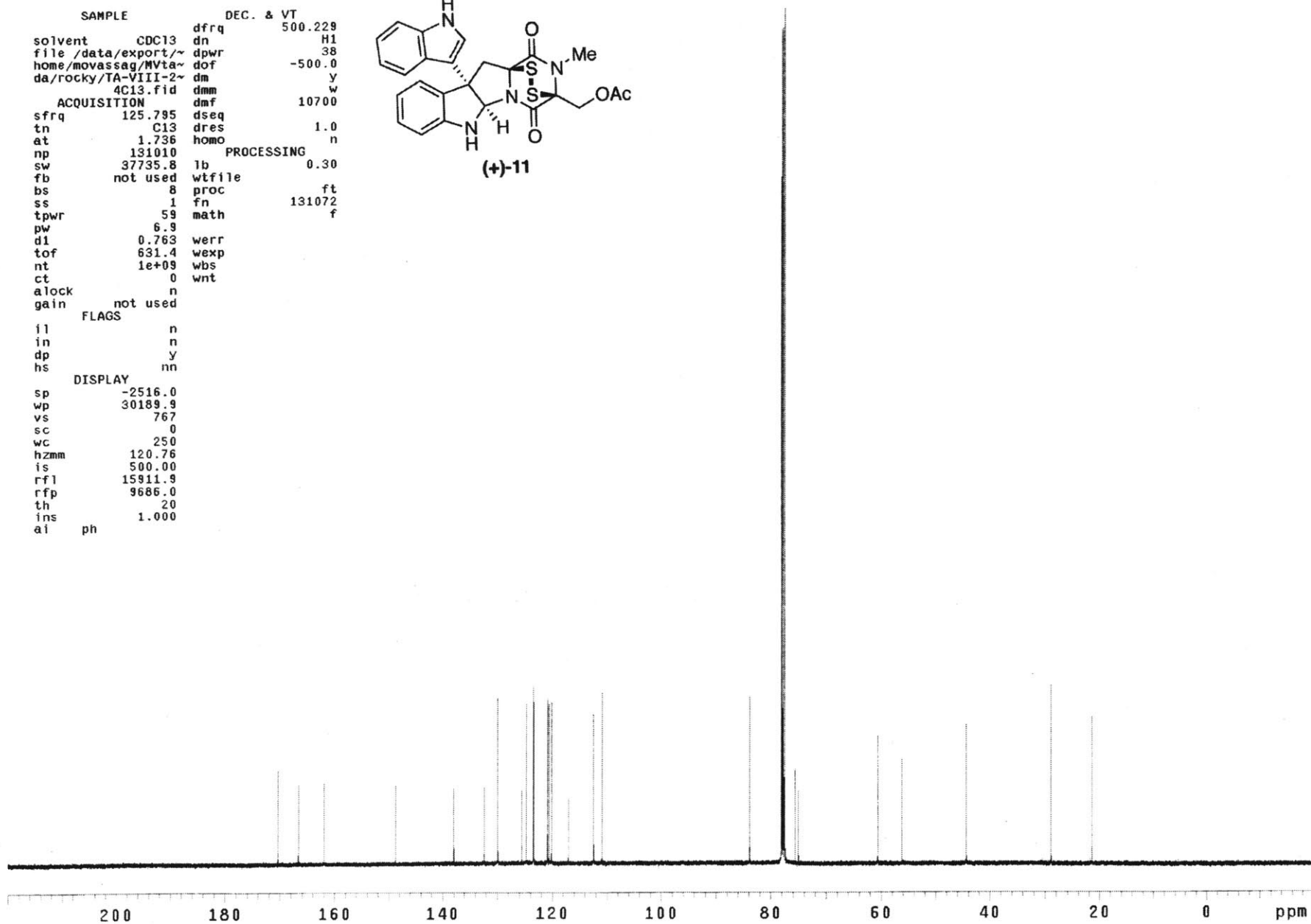
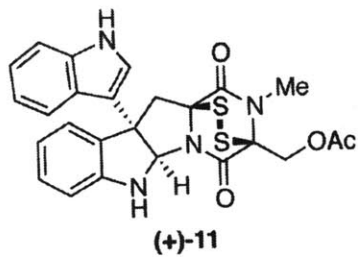
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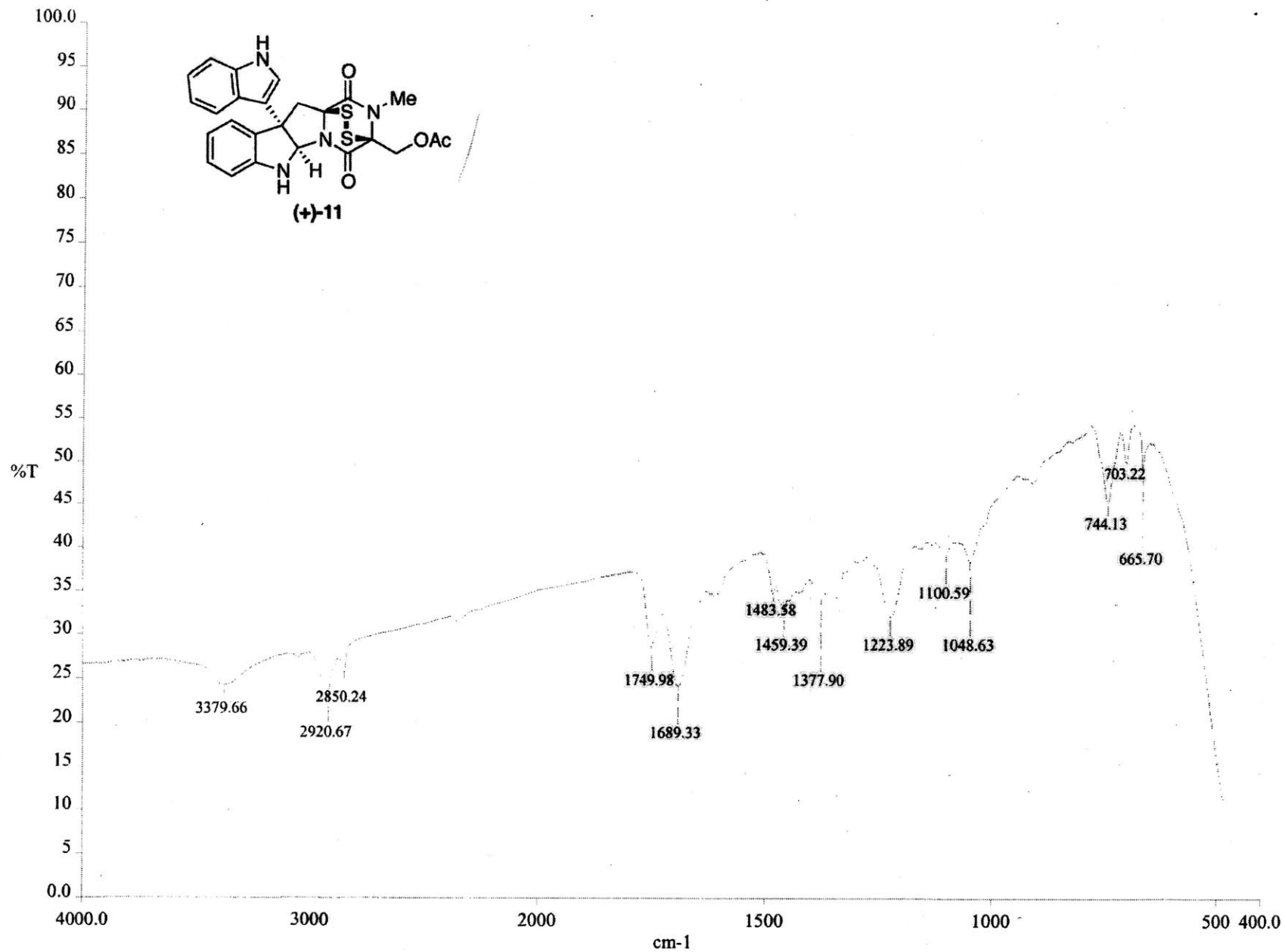
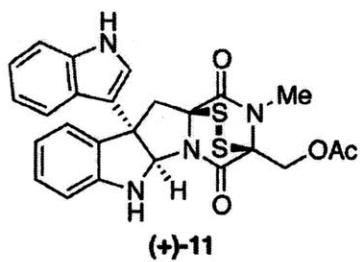
SAMPLE          DEC. & VT
solvent         CDC13      dfrq      125.845
file            /data/export/~ dn          C13
home/movassag/MVta~ dpwr       30
da/casper/TA-VIII-- dof          0
24proton.fid   dm           nnn
ACQUISITION    dmm           c
sfrq           500.433    dmf          200
tn             H1         dseq
at             4.999      dres        1.0
np            120102     homo        n
sw            12012.0    wtfile
fb            not used   proc         ft
bs            3         fn           262144
tpwr          60        math          f
pw            8.0
d1            0.100     werr
tof           3003.2    wexp
nt            1000     wbs
ct            9         wnt
alock         not used
gain          not used
FLAGS
il            n
in            n
dp            y
hs            nn
DISPLAY
sp            -250.3
wp            6505.6
vs            29
sc            0
wc            250
hzmm         26.02
is            334.31
rfl          500.6
rfp          0
th            7
ins          100.000
ai           ph

```



SAMPLE		DEC. & VT
solvent	CDC13	dfrq 500.229
file	/data/export/~	dn H1
home	/movassag/MVta~	dpwr 38
da	/rocky/TA-VIII-2~	dof -500.0
	4C13.fid	dm y
ACQUISITION		dmm w
sfrq	125.795	dmf 10700
tn	C13	dseq 1.0
at	1.736	dres 1.0
np	131010	homo n
sw	37735.8	PROCESSING
fb	not used	lb 0.30
bs	8	wfile
ss	1	proc ft
tpwr	59	fn 131072
pw	6.9	math f
d1	0.763	werr
tof	631.4	wexp
nt	1e+09	wbs
ct	0	wnt
alock	n	
gain	not used	
FLAGS		
il	n	
in	n	
dp	y	
hs	nn	
DISPLAY		
sp	-2516.0	
wp	30189.9	
vs	767	
sc	0	
wc	250	
hzmm	120.76	
is	500.00	
rfl	15911.9	
rfp	9686.0	
th	20	
ins	1.000	
ai	ph	



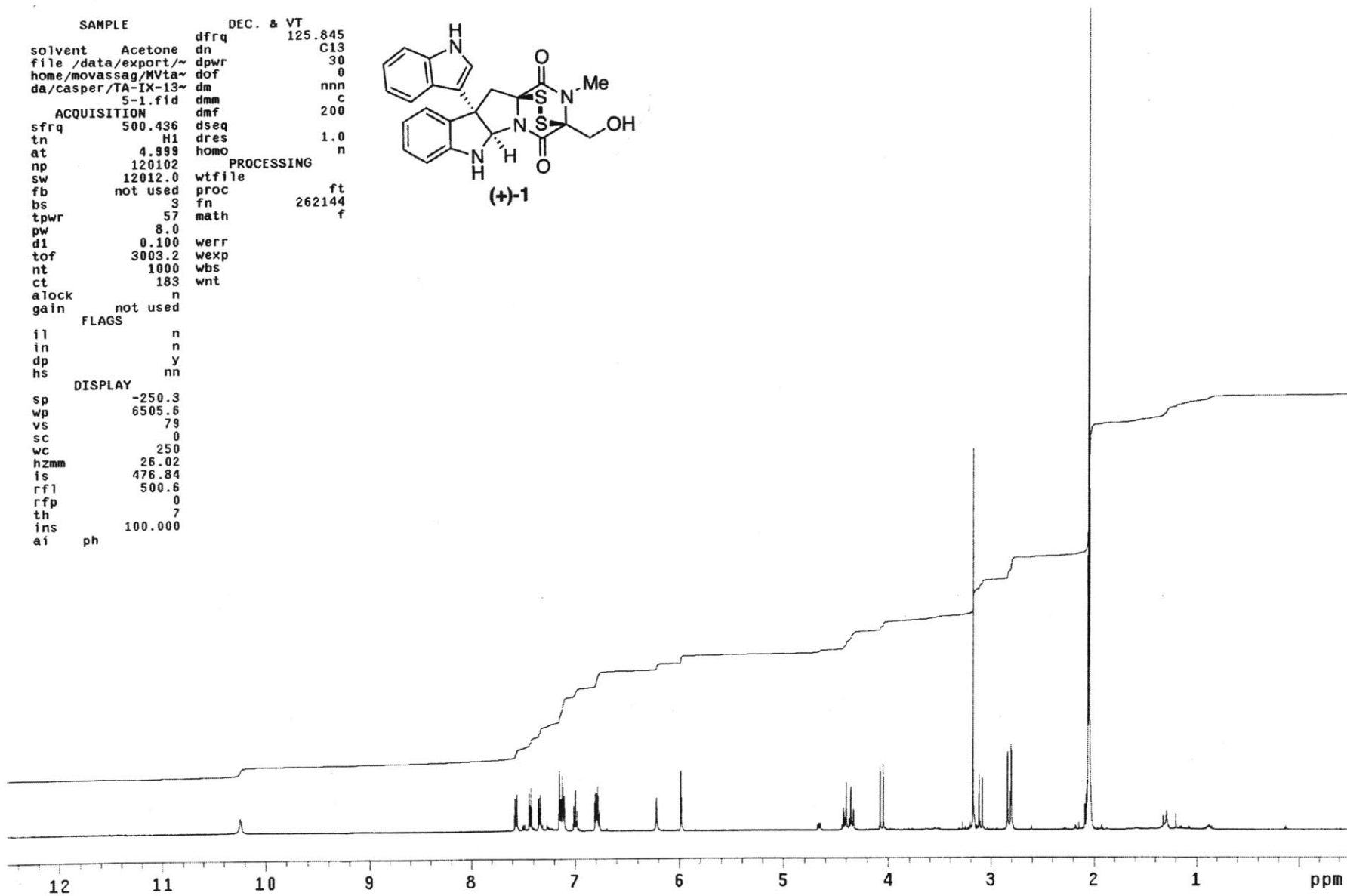
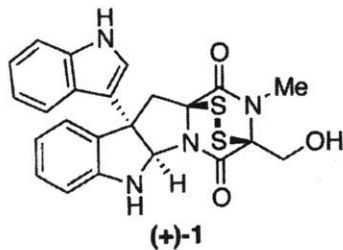


c:\pel\_data\spectra\groups\movass~1\mvtada\ta-8-7.sp - DO NOT CHANGE THE FILE NAME!!!

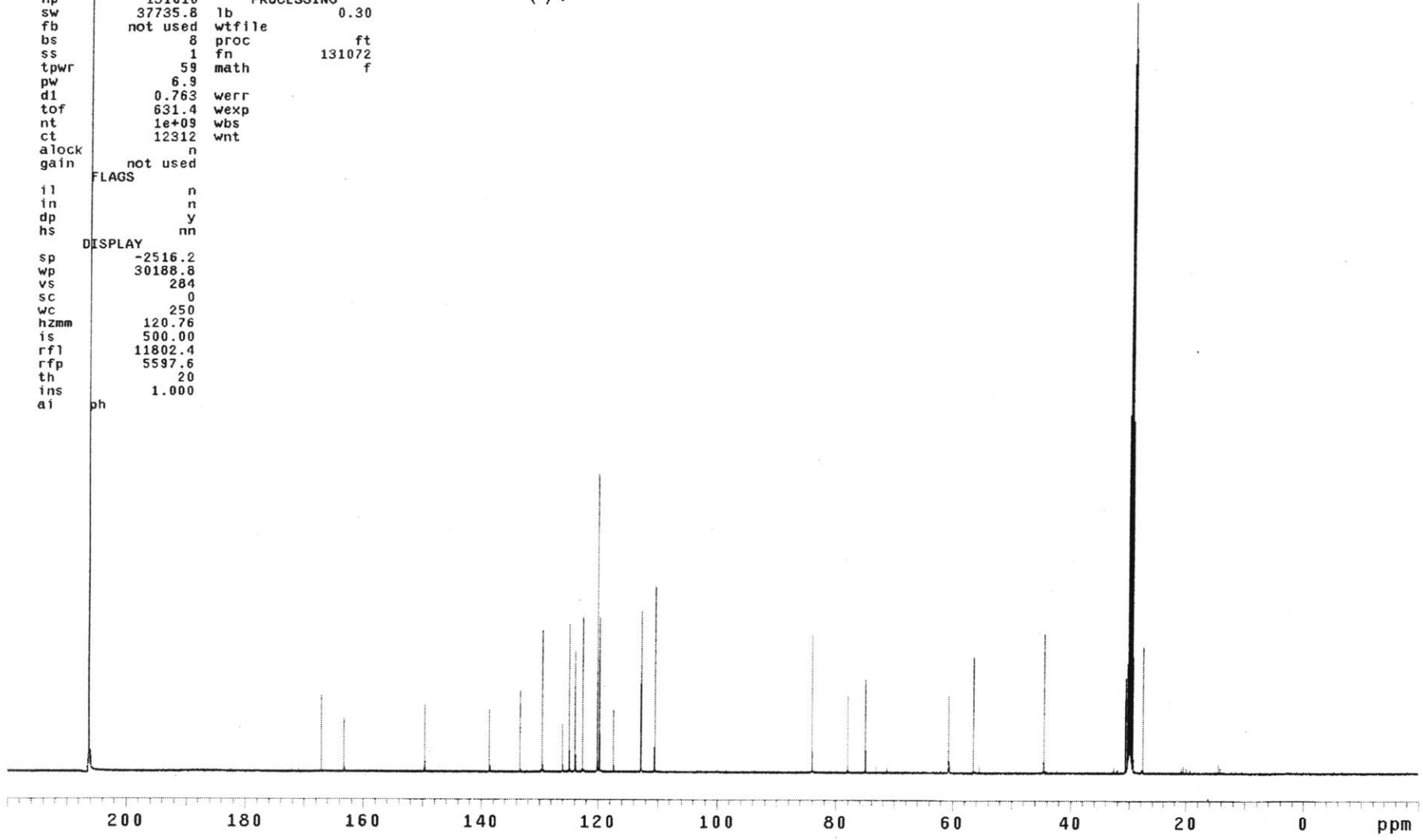
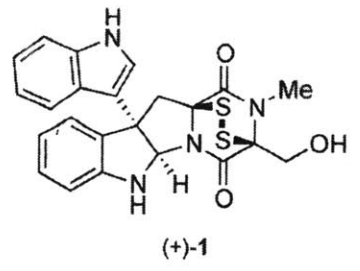
SAMPLE DEC. & VT

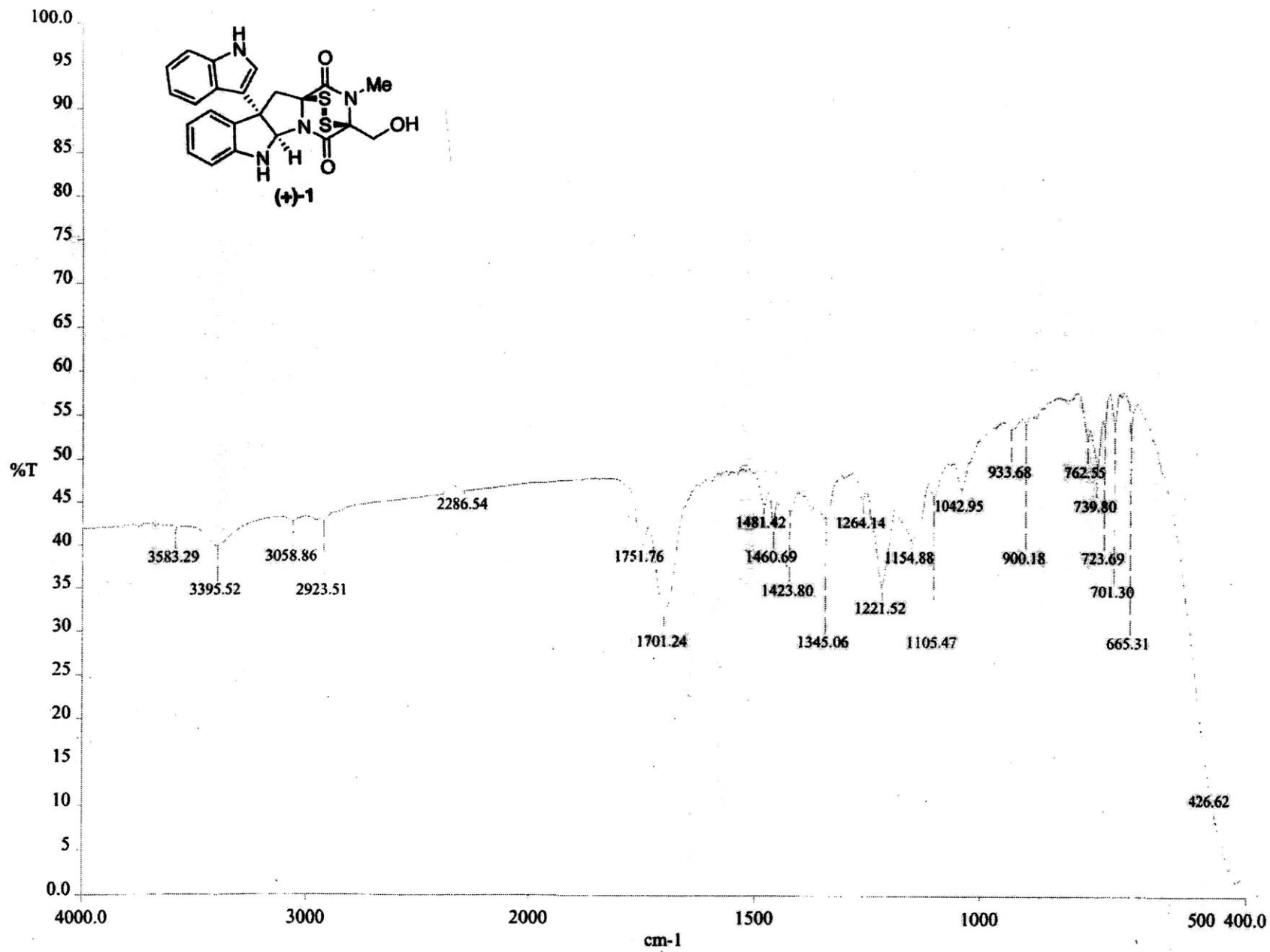
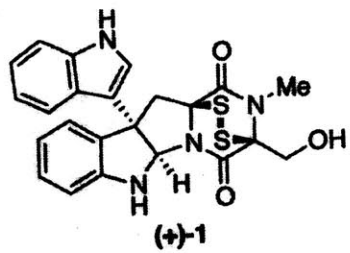
solvent Acetone dfrq 125.845  
file /data/export/~ dn C13  
home/movassag/MVta~ dpwr 30  
da/casper/TA-IX-13~ dof 0  
5-1.fid dm nnn  
ACQUISITION dmm c  
dmf 200  
sfrq 500.436 dseq  
tn H1 dres 1.0  
at 4.999 homo n  
np 120102 PROCESSING  
sw 12012.0 wtfile  
fb not used proc ft  
bs 3 fn 262144  
tpwr 57 math f  
pw 8.0  
d1 0.100 werr  
tof 3003.2 wexp  
nt 1000 wbs  
ct 183 wnt  
alock n  
gain not used  
FLAGS  
il n  
in n  
dp y  
hs nn

DISPLAY  
sp -250.3  
wp 6505.6  
vs 79  
sc 0  
wc 250  
hzmm 26.02  
is 476.84  
rfl 500.6  
rfp 0  
th 7  
ins 100.000  
ai ph



SAMPLE DEC. & VT  
 solvent Acetone dfrq 500.232  
 file /data/export/~ dn H1  
 home/mbvassag/MVta~ dpwr 38  
 da/rocky/TA-VIII-5~ dof -500.0  
 2carbon.fid dm y  
 ACQUISITION dmm w  
 sfrq 125.795 dmf 10700  
 tn C13 dseq 1.0  
 at 1.736 homo n  
 np 131010 PROCESSING  
 sw 37735.8 lb 0.30  
 fb not used wtfile  
 bs 8 proc ft  
 ss 1 fn 131072  
 tpwr 59 math f  
 pw 6.9  
 dl 0.763 werr  
 tof 631.4 wexp  
 nt 1e+09 wbs  
 ct 12312 wnt  
 alock n  
 gain not used  
 FLAGS  
 il n  
 in n  
 dp y  
 hs nn  
 DISPLAY  
 sp -2516.2  
 wp 30188.8  
 vs 284  
 sc 0  
 wc 250  
 hzmm 120.76  
 is 500.00  
 rfl 11802.4  
 rfp 5597.6  
 th 20  
 ins 1.000  
 ai ph





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## Curriculum Vitae

### Timothy C. Adams

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Boston, MA 02125

tadams@mit.edu  
Phone: 321.759.9115

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### Education

Massachusetts Institute of Technology, Cambridge, MA  
*Ph.D. in Organic Chemistry, expected Jan 2015*  
Graduate Research Advisor: Professor Mohammad Movassaghi  
Focus: Multi-step chemical synthesis

University of Florida, Gainesville, FL  
*B.S. in Chemistry, 2009*  
Undergraduate Research Advisor: Professor Sukwon Hong  
Focus: Organocopper chemistry

### Professional and Research Experience

Graduate Research Assistant  
*Massachusetts Institute of Technology, Mohammad Movassaghi, Cambridge, MA, 2009-present*

- Conducted methodology studies for the synthesis of densely functionalized sulfur-containing diketopiperazine molecules. The project involved the design and synthesis of a new mercaptan reagent for use as a hydrogen sulfide surrogate. This discovery led to the completion of several natural products, including (+)-bionectins A and C.
- Conducted the first known total synthesis of (+)-luteoalbusins A. A novel, intramolecular thiolation strategy was developed to access the higher order polysulfane congeners for this family of alkaloids.

Undergraduate Research Assistant  
*University of Florida, Sukwon Hong, Gainesville, FL, 2007-2009*

- Designed and synthesized chiral, acyclic diaminocarbene ligands for Cu (I) catalyzed Michael addition reaction. Studies were also conducted to elucidate the mechanism for this transformation.

### Academic Honors and Awards

2012-2014	National Science Foundation Graduate Research Fellowship
2010-2011	Walter L. Hughes Memorial Graduate Fellowship
2009-2010	Graduate Institute Fellowship-MIT
2008-2009	REU Research Fellowship-University of Florida
2008-2009	ACS Petroleum Research Fellowship-University of Florida
2007-2009	American Chemical Society Scholar

### Teaching Experience

Grader in Synthetic Organic Chemistry II (graduate)  
*Massachusetts Institute of Technology, Cambridge, MA, 2014*

Teaching Assistant in Organic Chemistry I (undergraduate)

*Massachusetts Institute of Technology, Cambridge, MA, 2010*

- Led multiple discussion sections centered on molecular structure and chemical reactivity.

Teaching Assistant in Organic Chemistry II (undergraduate)

*Massachusetts Institute of Technology, Cambridge, MA, 2009*

- Led multiple discussion sections focused on rudimentary organic synthesis.

Tutor in Organic Chemistry I and II (undergraduate)

*Brevard Community College, Palm Bay, FL, 2007*

- Held one on one tutoring sessions in basic organic chemistry.

### **Publications**

2013 "Concise Total Synthesis of (+)-Bionectins A and C" Coste, A.; Kim, J.; Adams, T. C.; Movassaghi, M. *Chem. Sci.* **2013**, *4*, 3191-3197.

### **Conferences**

2013 Boston Symposium on Organic and Bioorganic Chemistry  
Poster presenter: "The Concise Total Synthesis of (+)-Bionectin A and C"