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# Novel Cinchona Alkaloid Derived Ammonium Salts as Phase-Transfer Catalysts for the Asymmetric Synthesis of Beta-Hydroxy Alpha-Amino Acids Via Aldol Reactions and Total Synthesis of Celogentin C.

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NOVEL CINCHONA ALKALOID DERIVED AMMONIUM SALTS AS  
PHASE-TRANSFER CATALYSTS FOR THE ASYMMETRIC SYNTHESIS OF  
BETA-HYDROXY ALPHA-AMINO ACIDS VIA ALDOL REACTIONS  
AND  
TOTAL SYNTHESIS OF CELOGENTIN C

by

Bing Ma

A dissertation submitted to the faculty of

Brigham Young University

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry and Biochemistry

Brigham Young University

August 2009



BRIGHAM YOUNG UNIVERSITY  
GRADUATE COMMITTEE APPROVAL

of a dissertation submitted by

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This dissertation has been read by each member of the following graduate committee  
and by majority vote has been found to be satisfactory.

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## ABSTRACT

NOVEL CINCHONA ALKALOID DERIVED AMMONIUM SALTS AS  
PHASE-TRANSFER CATALYSTS FOR THE ASYMMETRIC SYNTHESIS OF  
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TOTAL SYNTHESIS OF CELOGENTIN C

Bing Ma

Department of Chemistry and Biochemistry

Doctor of Philosophy

**Project I** *Cinchona* alkaloid-derived quaternary ammonium salts have been successfully used as phase-transfer catalysts, particularly in asymmetric alkylations. Our group applied this type of catalyst in the synthesis of  $\beta$ -hydroxy  $\alpha$ -amino acids via aldol reactions and discovered that the Park-Jew catalyst afforded good yields and good enantiomeric excess of the *syn* diastereomers, but negligible diastereoselectivity. This project was therefore focused on the synthesis of novel cinchonidine-derived catalysts with the Park-Jew catalyst as the lead structure. The C3 position of cinchonidine nucleus was modified to achieve dimers and catalysts possessing electron-deficient alkyne and alkene moieties. Synthesized catalysts were tested in the asymmetric aldol reactions, with some of them yielding improvements relative to the Park-Jew catalyst.

**Project II** Celogentin C is a natural product that was isolated from the seeds of *Celosia argentea* by Kobayashi in 2001. It is the most potent inhibitor of the



polymerization of tubulin from among the celogentin family. The novel bicyclic octapeptide structure contains unusual linkages between leucine  $\beta$ -carbon and indole C-6 of tryptophan and between tryptophan indole C-2 and imidazole N-1 of histidine. The project culminated in the first total synthesis of celogentin C. Reaction conditions were developed by synthesizing the left-hand ring and the right-hand ring separately, and the total synthesis was accomplished via a left to right strategy. Key transformations in the construction included intermolecular Knoevenagel condensation, radical conjugate addition, macrolactamization, and oxidative coupling.



## ACKNOWLEDGMENTS

I would like to dedicate my dissertation to my parents. It has been a long time since my first day in school in 1986. Without the altruistic support from them, I would not have gone so far. At this moment, I believe that they are even happier for me than I am for myself. I would also like to ask them to forgive me for not fulfilling my responsibility, for my absence when they need me, and for only staying with them for two weeks during the past five years. I know that they are counting down my returning. I hope I make them proud.

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## List of abbreviations

AcOH	acetic acid
AIBN	2,2'-azobisisobutyronitrile
aq.	aqueous
Arg	arginine
BCB	<i>B</i> -bromocatechol boran
Boc	<i>tert</i> -butoxycarbonyl
Bn	benzyl
Cbz	benzyloxycarbonyl
DBFOX/Bn	( <i>R,R</i> )-4,6-dibenzylfurandiyl-2,2'-bis (4-phenyloxazoline)
DBFOX/Nap	4,6-bis(( <i>R</i> )-4-(naphthalen-2-yl)-4,5-dihydrooxazol -2-yl)
DBFOX/Ph	( <i>R,R</i> )-4,6-dibenzofurandiyl-2,2'-bis(4-phenyloxazoline) dibenzo[ <i>b,d</i> ]furan
DDQ	2,3-dichloro-5,6-dicyano- <i>p</i> -benzoquinone
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzo-triazin-4(3H) -one
DIBAL-H	diisobutylaluminum hydride
DIEA	diisobutylethyl amine
DMF	<i>N,N'</i> -dimethylformamide
DMTMM	4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl

	morpholinium chloride
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EDCI	1-ethyl-3(3'-dimethylaminopropyl)carbodiimide-HCl
g	gram(s)
HBTU	<i>O</i> -(benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
His	histidine
HOBt	1-Hydroxybenzotriazole hydrate
Hz	hertz
<i>J</i>	coupling constant
Leu	leucine
M	mol/liter
mg	milligram(s)
mL	milliliter(s)
μL	microliter(s)
mmol	millimole(s)
mol	mole(s)
MS	molecular sieves
MS	mass spectrometry
NCS	N-chlorosuccinimide
NMM	N-methyl morpholine

Ns	<i>o</i> -nitrobenzo sulfonyl
<i>p</i>	<i>para</i>
Pbf	pentamethyldihydrobenzofuran sulfonyl
Phth	phthaloyl
Pro	proline
PTC	phase-transfer catalyst
sat.	saturated
rt	room temperature
Rf	retention factor
TBAF	tetrabutylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl
<i>t</i> -Bu	<i>tert</i> -butyl
Teoc	2-(trimethylsilyl)ethoxycarbonyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Trp	trptophan
TsOH	toluenesulfonic acid
Val	valine

## CHAPTER I

**Novel *Cinchona* alkaloid derived ammonium salts as phase-transfer catalysts  
for the asymmetric synthesis of  $\beta$ -hydroxy  $\alpha$ -amino acids via aldol reactions**

## 1.1 Introduction

### 1.1.1 Phase-transfer catalysts

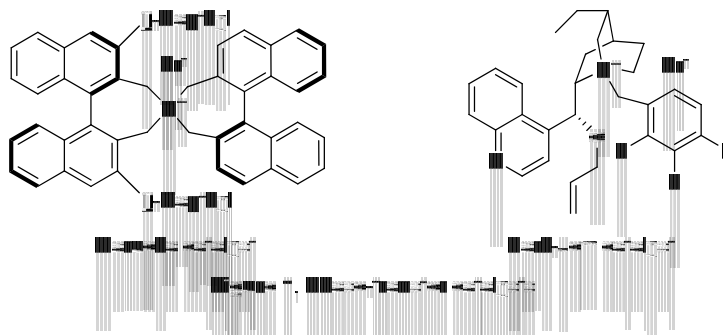
Phase-transfer catalysts (PTC) help to achieve fast heterogeneous reactions by facilitating the migration of certain reactants from one phase to the other. Crown ethers are normally used when cationic reactants are the species to be transferred or solvated; while the corresponding catalysts for anions are typically ammonium salts. Other than fast conversion, phase-transfer catalysts also benefit reactions by improving yields, eliminating byproducts and minimizing waste problems.

Chiral phase-transfer catalysts derived from ammonium salts have shown great utility in modern syntheses due to the ability to generate stereoselective products. Quaternary ammonium salts, based on inexpensive and readily available *cinchona* alkaloids, have been successfully applied in asymmetric reactions, particularly in asymmetric alkylations.<sup>1</sup>

### 1.1.2 Asymmetric synthesis of $\beta$ -hydroxy amino acids

$\beta$ -hydroxy  $\alpha$ -amino acids contain three functional groups making them very useful precursors for a variety of transformations.<sup>2</sup> In addition, these moieties have been found as important components in complex natural bioactive peptides.<sup>3</sup> The asymmetric syntheses of  $\beta$ -hydroxy  $\alpha$ -amino acids usually require stoichiometric amounts of chiral auxiliaries and involve multiple steps.<sup>4</sup> The first catalytic approach by employing a *cinchona* alkaloid derived phase-transfer catalyst in asymmetric aldol reactions was reported by Miller in 1991.<sup>5</sup> However only low enantiomeric excess (ee) values were achieved. Recently, Maruoka developed a particularly

effective phase-transfer catalyst (Figure 1), which produces *anti*  $\beta$ -hydroxy  $\alpha$ -amino acid derivatives with high enantiomeric excess.<sup>6</sup> Unfortunately, the synthesis of the Maruoka catalyst suffers from high cost and a lengthy synthetic route. One of the latest asymmetric syntheses of  $\beta$ -hydroxy  $\alpha$ -amino acid derivatives came out from the Castle group, in which case, simple Park-Jew catalyst (Figure 1)<sup>7</sup> helped to achieve up to 83% ee for *syn* aldol products, although the diastereoselectivity was low (*syn/anti*: 1:1 to 1.3:1).<sup>8</sup>

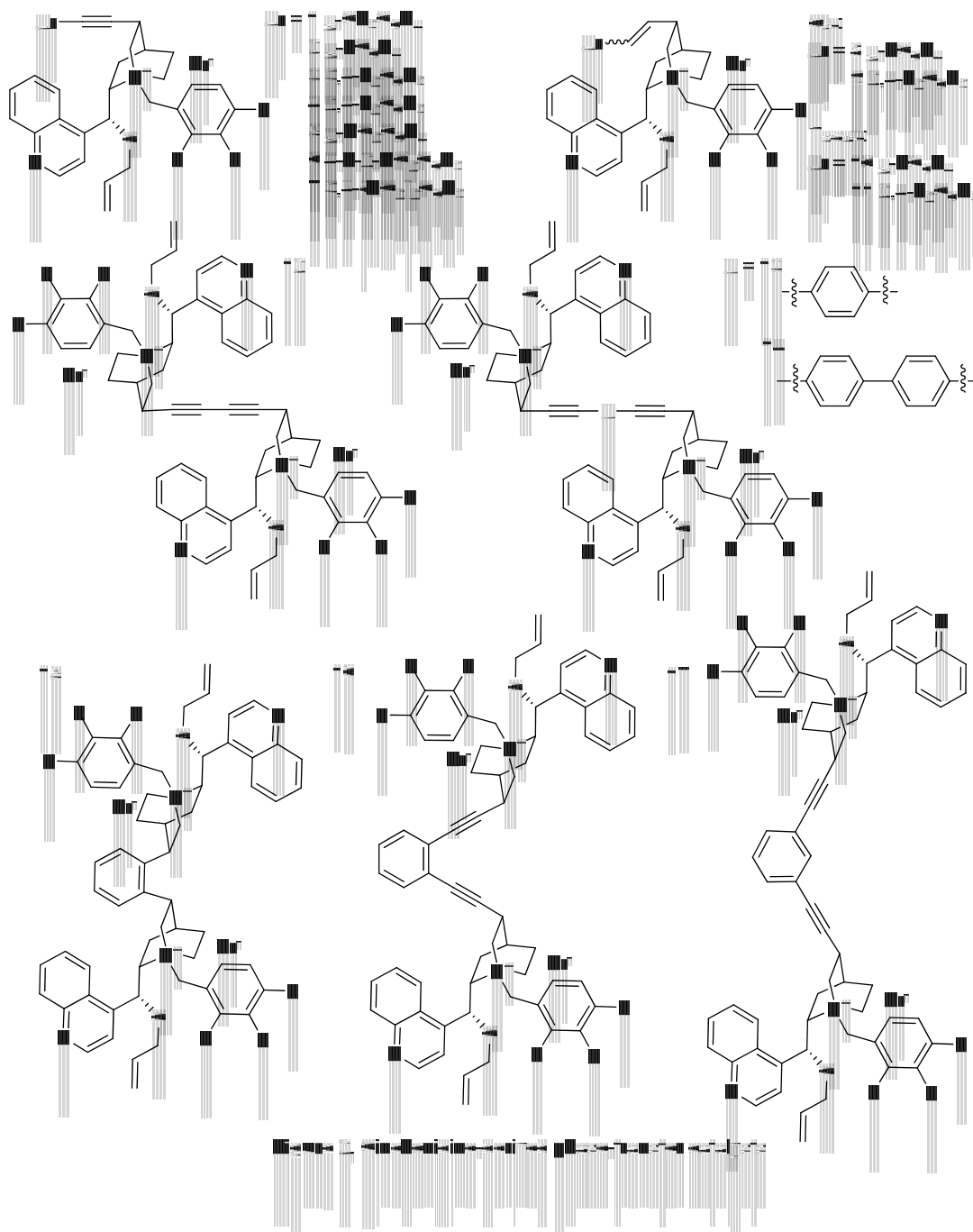


### 1.1.3 Electron deficient and dimerized phase-transfer catalysts

Based on the discovery of aldol reactions mediated by the Park-Jew catalyst, an attempt to improve the stereoselectivity of the reaction was proposed by synthesizing cinchonidine-based electron deficient phase-transfer catalysts, which would retain the 2,3,4-trifluorobenzyl group of the Park-Jew catalyst. The modification of the C3 vinyl group of cinchonidine has a significant influence on the basicity and polarity of the parent molecules.<sup>9</sup> Consequently, it is feasible to achieve tight ion pairs between ammonium salts and enolates, which would eventually realize better stereoselectivity, by installing electron-withdrawing groups onto the C3 position of cinchonidine. In spite of the existence of dimeric cinchonidine-derived phase-transfer catalysts involving dimerization via an *N*-benzyl or *N*-alkyl group,<sup>10</sup> we proposed a novel



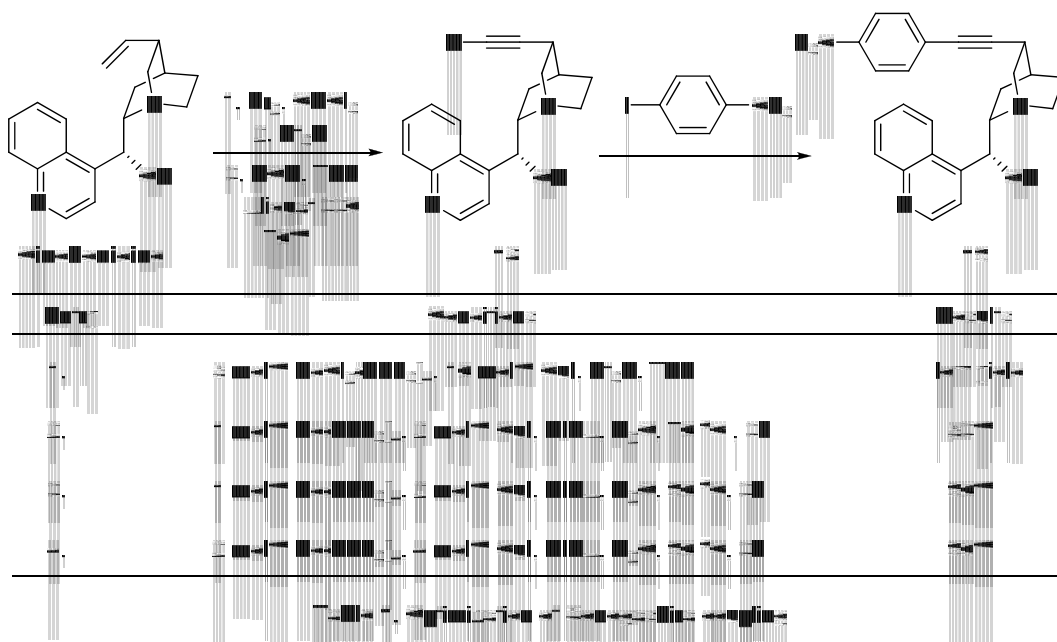
class of dimeric catalysts, which were linked through a C3 alkyne. Initially, seventeen novel cinchonidine-based monomeric and dimeric quaternary ammonium salts (Figure 2, 1-17) were targeted in this project, in order to investigate their efficacy for the synthesis of  $\beta$ -hydroxy  $\alpha$ -amino acids via asymmetric aldol reactions.



## 1.2 Results and discussion

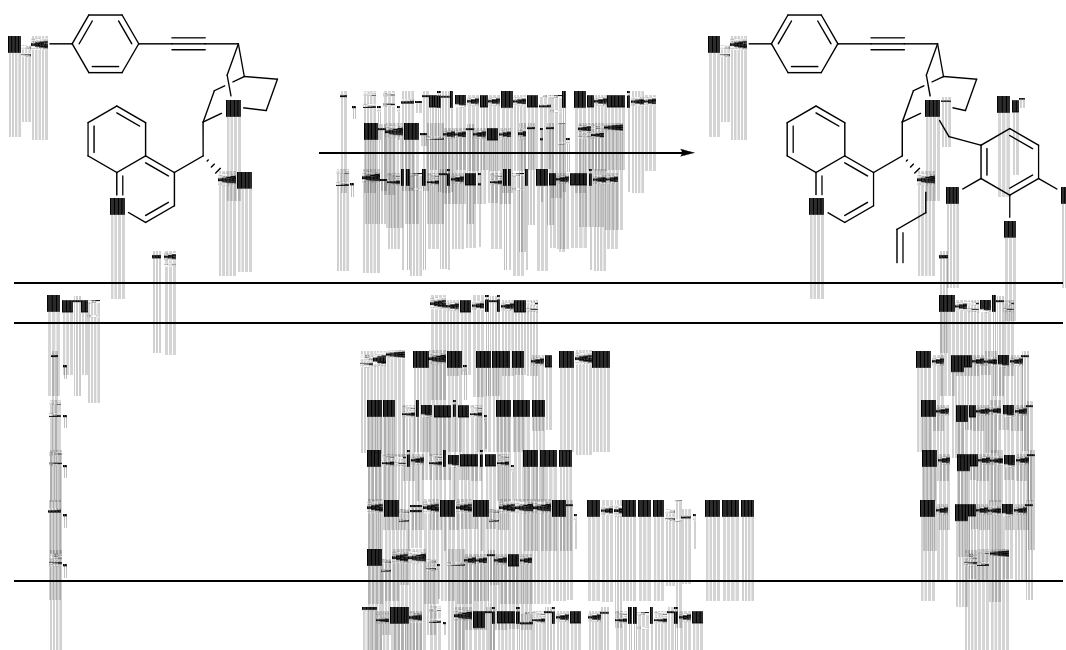
### 1.2.1 Synthesis of phase-transfer catalysts (1 - 7)

The starting material (**18**) for the electron deficient phase-transfer catalysts was obtained from natural cinchonidine by following the Hoffmann procedure.<sup>11</sup> The subsequent Sonogashira coupling was accomplished after considerable experimentation by using *p*-trifluoromethylido benzene as the coupling partner, shown in Table 1. Only a low yield of the arylated product (**19**) was obtained under Hoffmann conditions (Entry 1, Table 1).<sup>12</sup> Fortunately, the coupling in aqueous conditions<sup>13</sup> was optimized to afford **19** with 96% yield (Entry 4, Table 1).

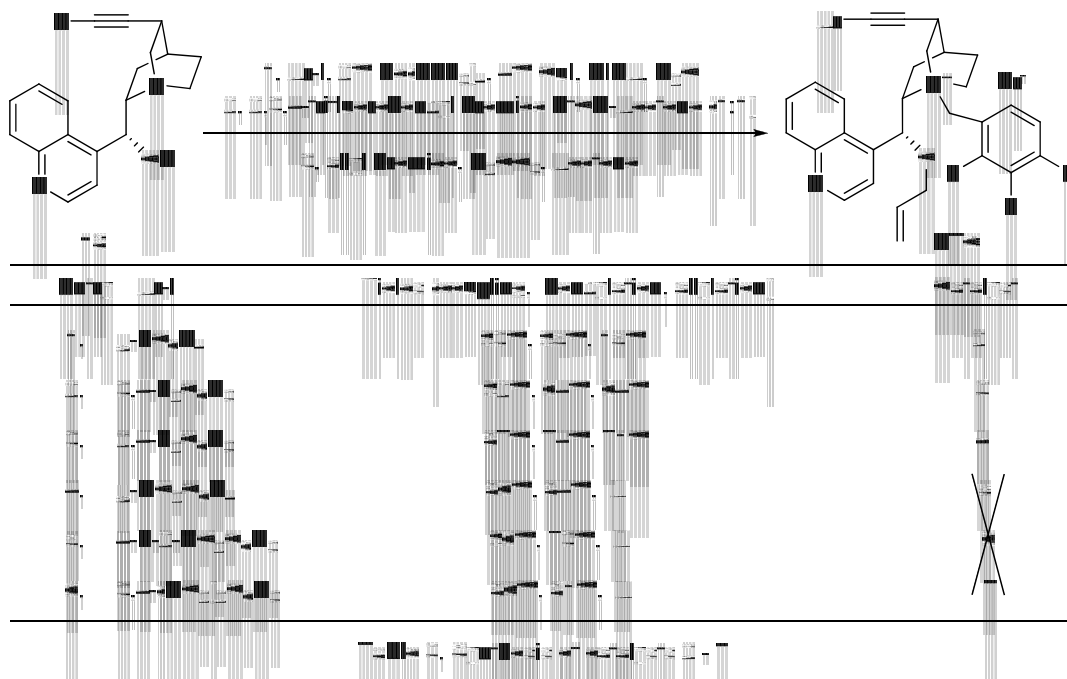


The N-benylation of compound **19** was simply accomplished after stirring with 2,3,4-trifluorobenzyl bromide in EtOH-Acetone at room temperature, which was an improvement to the corresponding conditions developed by Park and Jew.<sup>7</sup> Unfortunately, the O-allylation method used in the Park-Jew catalyst synthesis failed to afford any desired product (Entry 1, Table 2).<sup>7</sup> Weak bases, such as KF alumina<sup>14</sup> and basic alumina<sup>15</sup>, and the catalytic approach<sup>16</sup> did not provide compound **1** either

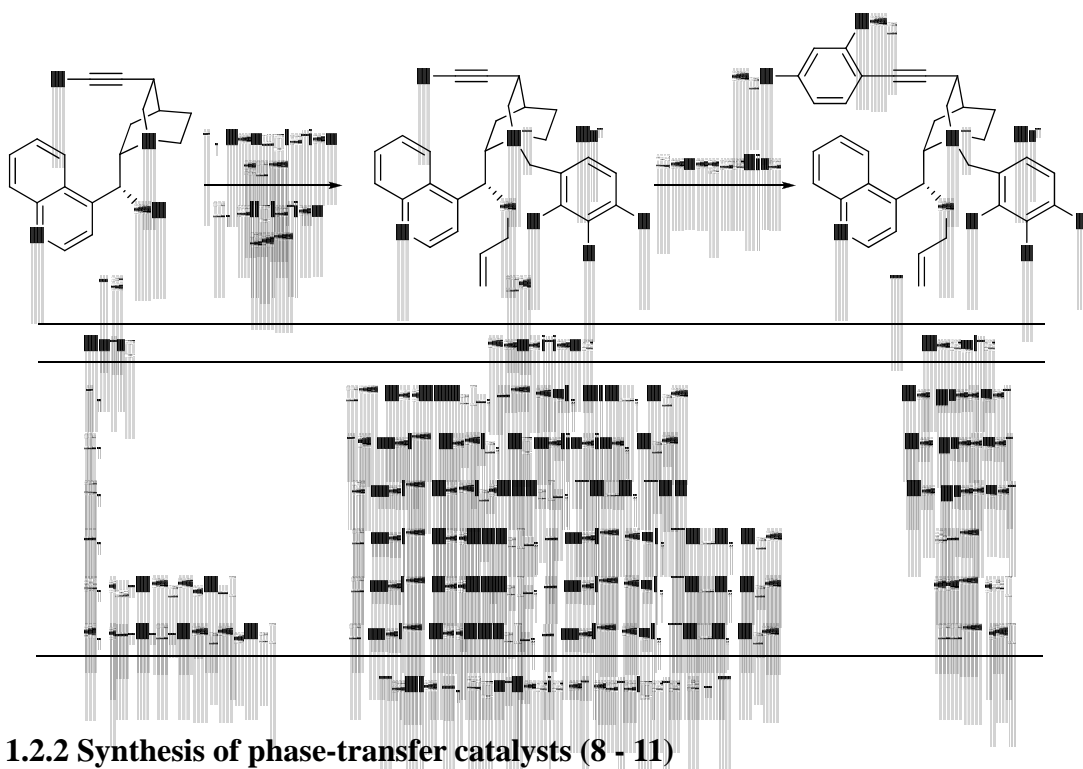
(Entries 2 - 4, Table 2). Interestingly, moderate yield of the allylation product (**1**) was finally achieved by simply employing  $K_2CO_3$  in acetone.



After the successful synthesis of catalyst **1**, the developed method was subsequently applied in the synthesis of other analogous targets **2** - **7** (Table 3). The Sonogashira coupling conditions worked excellently for all the aryl iodides. The following N-benylation afforded the desired intermediates with high yields as well. However, the final O-allylation was problematic in some cases. For the *p*-FC<sub>6</sub>H<sub>4</sub> derived substrate, optimization could only achieve up to 15% yield (Entry 1, Table 3). Despite examining numerous conditions, I was unable to perform the allylation on substrates possessing nitroaryl groups (Entries 4 - 6, Table 3). Eventually, only four phase-transfer catalysts (**1** - **4**) were obtained by following the coupling–benzylation–allylation sequence.

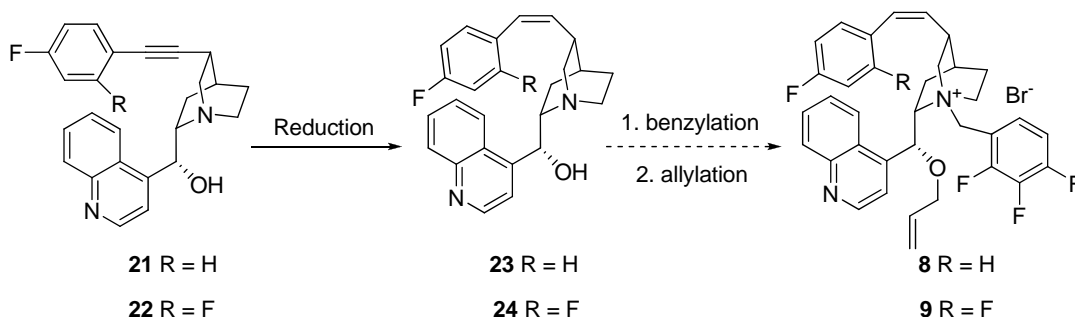


In order to construct the nitroaryl containing catalysts (**5** - **7**), the order of synthetic sequence was modified, and the Sonogashira coupling was performed last. Normal N-benylation and O-allylation conditions were applied on the alkyne (**18**), which afforded the desired intermediate with excellent overall yield. The previous coupling conditions were initially tested with the presence of 2,4-dinitroaryl iodide, which failed to generate the desired final catalyst unfortunately (Entry 1, Table 4). Two more conditions were screened without any promising results (Entries 2 and 3, Table 4). Surprisingly, moderate yield of the conversion was finally realized to produce **7** by switching DIEA to a water soluble base, TBAF,<sup>17</sup> in the traditional method. The modified conditions worked for the other two nitroaryl iodides as well (Entries 5 and 6, Table 4). Even though only a poor yield of catalyst **6** was obtained, enough of this compound was produced to examine its viability as a catalyst.



### 1.2.2 Synthesis of phase-transfer catalysts (8 - 11)

The synthesis of *cis* C3-alkenyl-substituted chiral ammonium salts (**8**, **9**) was



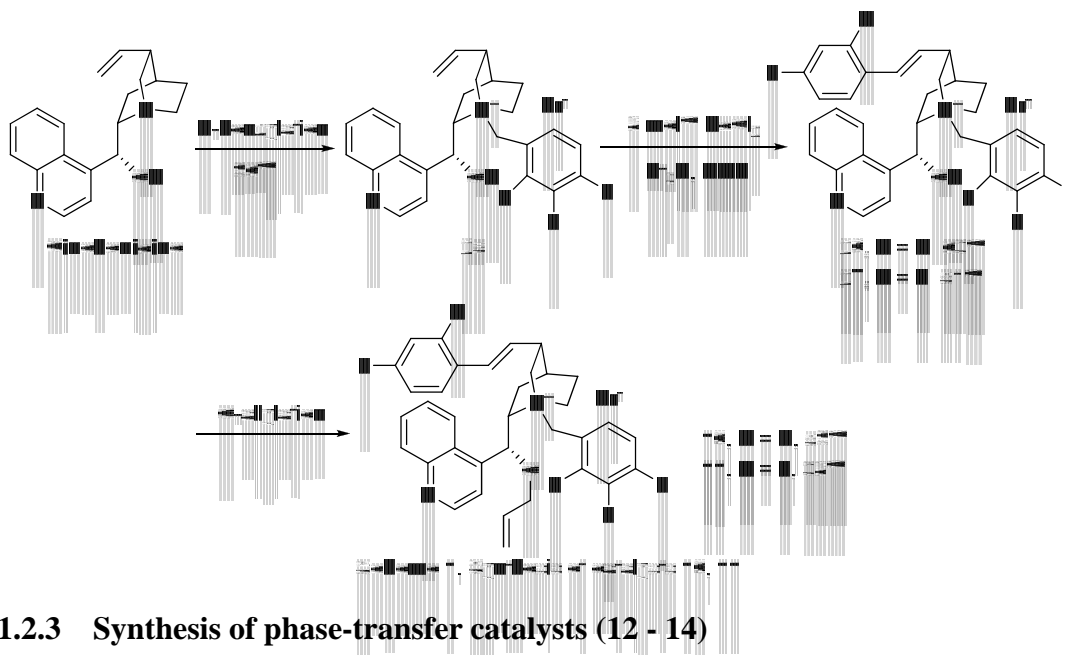
Entry	Conditions	Results
1	H <sub>2</sub> , Lindlar cat., THF, quinoline	No product
2	H <sub>2</sub> , Lindlar cat., MeOH, quinoline, 1000 psi	No product
3	NH <sub>2</sub> NH <sub>2</sub> ·H <sub>2</sub> O, Cu(OAc) <sub>2</sub> , MeOH	No product
4	MeOH, Zn/Cu, reflux	No product

**Table 5.** Synthesis of catalysts **8**, **9**

proposed to be assembled as illustrated in Table 5, with the alkyne reduction as the key step. Unfortunately, Lindlar catalyst as well as other methods failed to generate the desired *cis* reduction products, not to mention the final catalysts.

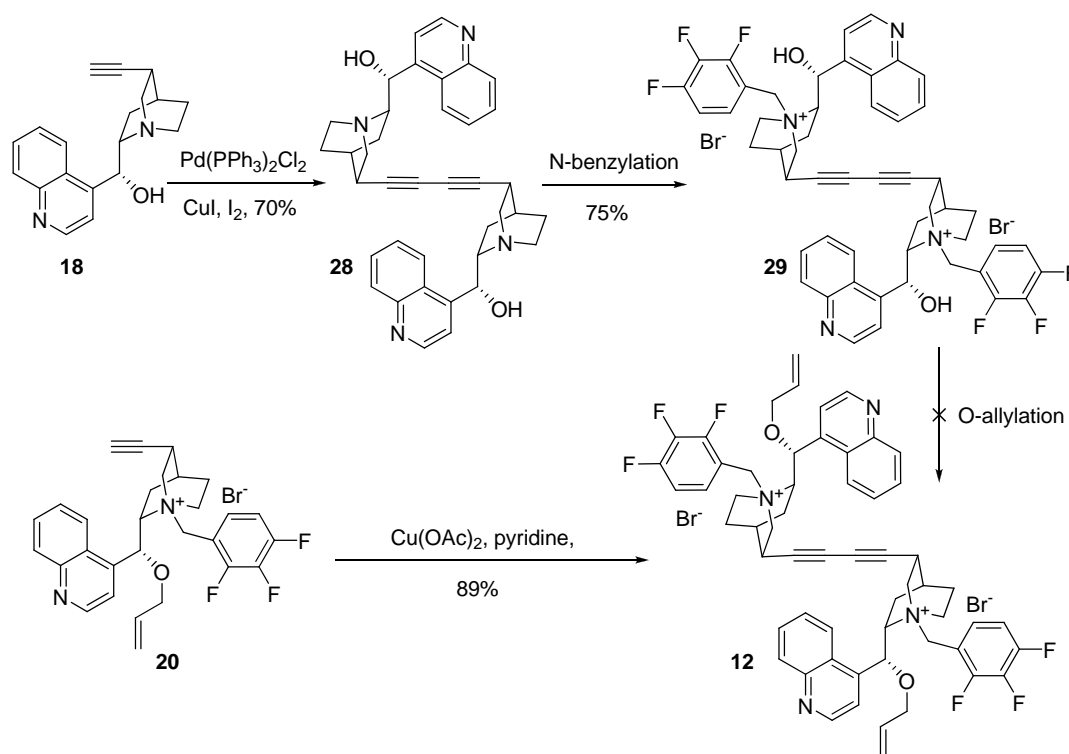
With a Heck reaction as the key transformation, the construction of the *trans*

C3-alkenyl-substituted phase-transfer catalysts (**10**, **11**) was achieved as displayed in Scheme 1. N-benylation product (**25**) was easily obtained by following the traditional conditions. The combination of PdCl<sub>2</sub> and Et<sub>3</sub>N was found to be the best for the Heck coupling in these two cases. At last, regular allylations were performed to achieve the *trans* oriented products (**10**, **11**).



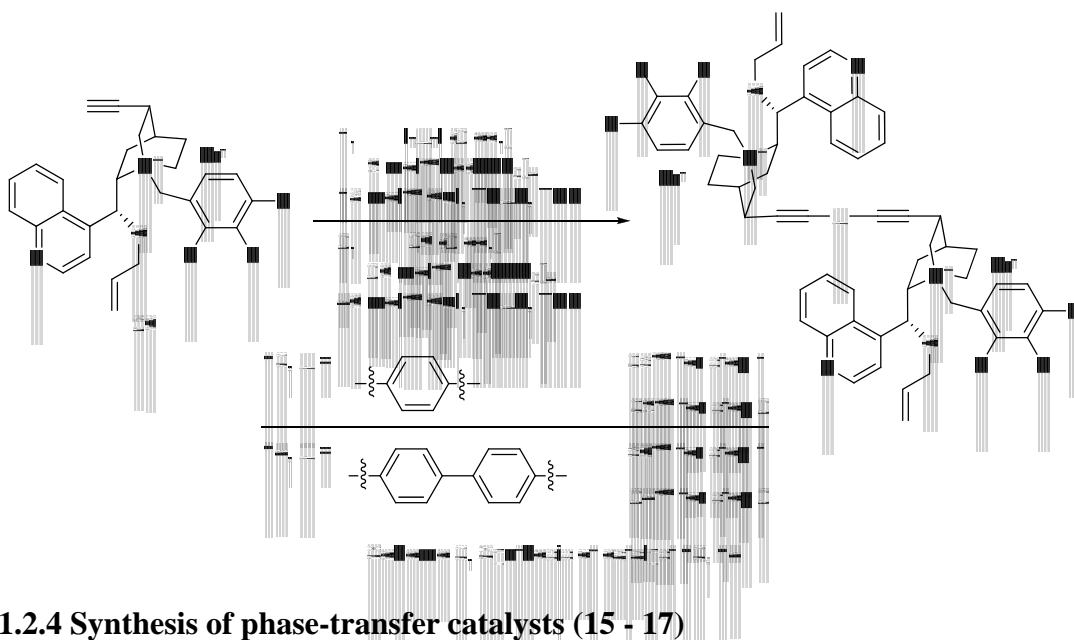
In addition to the catalysts bearing electron-deficient groups at the C3 position, direct dimeric compound (**12**), phenyl and diphenyl linked dimers (**13**, **14**) were constructed to investigate their catalytic activities. The synthesis of **12** is illustrated in Scheme 2. The initial approach was carried out by following a coupling-benylation-allylation route. The alkyne dimerization of compound **18** was simply achieved under a palladium catalyzed condition, which was followed by a successful N-benylation. Unfortunately, the final O-allylation step failed to give the desired compound after several attempts. An alternative route to compound **12** was the direct coupling from the intermediate **20**. Glaser - Hay coupling<sup>18</sup> could not

accomplish the dimerization, while the Eglinton reaction<sup>19</sup> eventually afforded catalyst **12** with high yield.

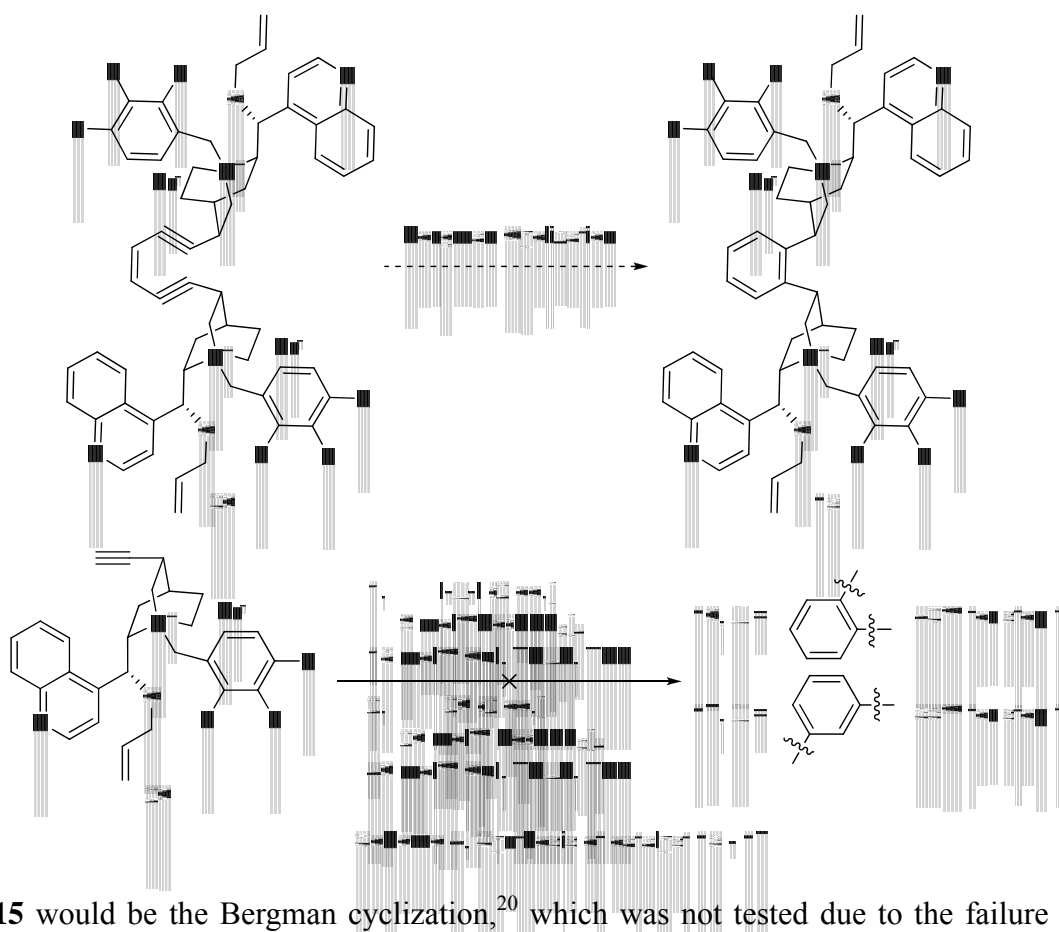


**Scheme 2.** Synthesis of catalyst **12**

The initial attempt to synthesize phenyl and diphenyl-linked dimers (**13**, **14**) was carried out by following a coupling-benylation-allylation sequence. Even though the coupling and N-benylation were very successful, the final O-allylation step was problematic. Another idea of constructing these dimers was to perform the Sonogashira coupling in the late stage. Employing two equivalents of **20** and the appropriate aryl di-iodide only afforded single coupling intermediates, instead of the dimeric catalysts. Thus, the approach toward the targets was split into two sequential couplings (Scheme 3). The second step required increased loading of the Pd catalyst and CuI. Only moderate yields were achieved in both cases. The bis-ammonium salts (**12**, **13**, **14**) were very polar, but still could be purified by using normal silica gel columns.



Among the proposed novel phase-transfer catalysts were some dimers possessing different angles between the units (**15 - 17**) (Scheme 4). The key step in synthesizing

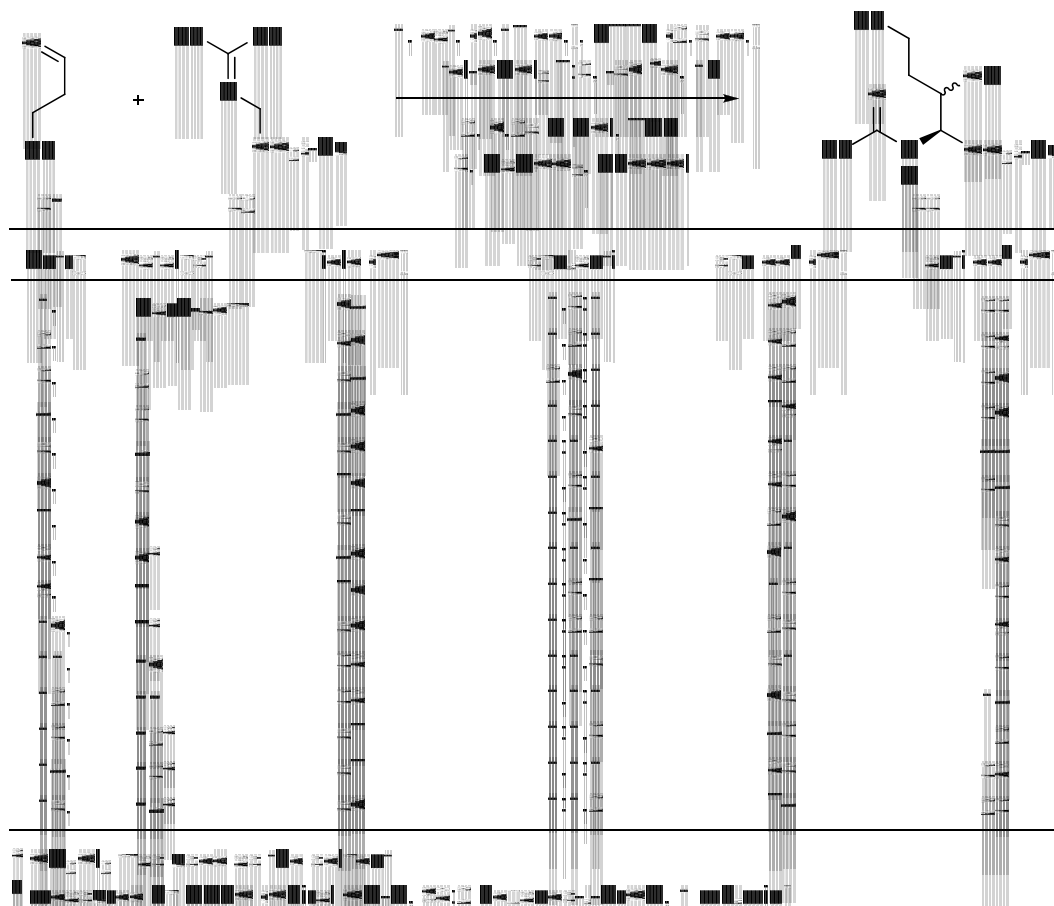




**16** and **17**. Unfortunately, neither of them was produced, even though the first-step couplings afforded moderate yields.

### 1.2.5 Survey of catalysts in asymmetric aldol reactions

The catalytic viability of the synthesized compounds (**1 - 7**, **10 - 14**) were evaluated in the aldol reactions between hydrocinnamaldehyde (**31**) and *tert*-butyl glycinate benzophenone imine (**32**). The results are summarized in Table 6. The Park-Jew catalyst was initially applied in this chemistry, which afforded 64% yield



of **33** with a negligible *syn/anti* ratio of 1.3:1. Even though a reasonable enantiomeric excess (80%) of *syn* products was obtained, the ee value of *anti* isomers was very poor (Entry 1, Table 6). Among these novel catalysts, ammonium salt **4** generated the highest *syn* ee (Entry 5, Table 6). However, no improvement of

the *anti* ee was detected. Interestingly, the diastereoselectivity was moderate and reversed in this case. Catalyst **2** enhanced the diastereoselectivity to 2.6:1, while keeping the *syn* and *anti* ee at the same level (Entry 3, Table 6). Considering the structures of **2** and **4** and the corresponding outcome of the aldol reactions, the *ortho*-fluoro substituent definitely had a significant effect on the conformation of the transition state. The catalyst (**1**), bearing *p*-trifluoromethyl substituted phenyl group, achieved the highest yield in all these cases. *Ortho*-nitro containing compounds (**6**, **7**) typically favored the *anti* isomer, with dropped ee value for both *syn* and *anti* products. Catalysts **10** and **11**, which contained *Z*-alkene moieties, performed more poorly in terms of yields and stereoselectivity. Dimeric catalysts (**12** - **14**) were so polar that they were insoluble in normal toluene-CHCl<sub>3</sub> (7:3) solvent system. Consequently, the asymmetric aldol reactions were performed in dichloromethane in these cases. Unfortunately, none of them showed promising results.

### 1.3 Conclusion

In conclusion, twelve monomeric and dimeric novel cinchonidine-derived phase-transfer catalysts were synthesized. During the synthesis of these compounds, unusual Sonogashira coupling conditions were discovered, consisting of a combination of TBAF and palladium catalyst in aqueous solutions. Meanwhile, the first construction of Z-alkene containing phase-transfer catalysts broadened the research of cinchonidine modification.

The efficiency of these new catalysts was investigated in the asymmetric aldol reactions for the synthesis of  $\beta$ -hydroxy  $\alpha$ -amino acids. Some catalysts improved the reaction in certain aspects. However, none of them substantially improved the low diastereoselectivity of the Park-Jew catalyst.

## 1.4 Experimental

### 1.4.1 General experimental details

Anhydrous diethyl ether, toluene, dimethylformamide, methanol, methylene chloride, and tetrahydrofuran were dried by passage through a Glass Contour solvent drying system containing cylinders of activated alumina. Flash chromatography was carried out using 60–230 mesh silica gel.  $^1\text{H}$  NMR spectra were acquired on 500 MHz spectrometers with tetramethylsilane (0.00 ppm) as internal references. Signals are reported as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), brs (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz).  $^{13}\text{C}$  NMR spectra were acquired on spectrometers operating at 125 MHz with chloroform (77.23 ppm), MeOH (49.87 ppm) and DMSO (49.51 ppm) as internal references. Infrared spectra were obtained on an FT-IR spectrometer. Mass spectral data were obtained using ESI techniques. Optical rotation values were acquired using a polarimeter.

### 1.4.2 General procedure for the synthesis of catalysts 1 - 4

**Sonogashira coupling.** A round-bottomed flask was charged with alkyne **18** (0.72 g, 2.45 mmol), aryl iodide (4.95 mmol),  $\text{Pd}(\text{PPh}_3)_4$  (48.0 mg, 2.5 mol %), CuI (24.0 mg, 5.0 mol %) and *i*-Pr<sub>2</sub>NEt (1.2 mL), followed by H<sub>2</sub>O (40 mL). The resultant mixture was stirred at 90 °C for 3.5 h, then cooled to rt and extracted with CHCl<sub>3</sub> until no more product could be detected in the aqueous layer by TLC (320 mL total). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 10% MeOH in EtOAc elution) afforded the coupling products as yellow solids.

**Benylation.** A solution of the above coupling product (1.0 mmol) in acetone–EtOH (1:1, 8 mL) was treated with 2,3,4-trifluorobenzyl bromide (0.32 mL, 3.0 mmol) and stirred at rt for 16 h. The solid precipitate was filtered and washed with Et<sub>2</sub>O to give a white solid that was used without purification in the next step.

**Allylation.** A suspension of the crude quaternary ammonium salt (1.0 mmol) in acetone (16 mL) was treated with allyl bromide (0.33 mL, 5.0 mmol), followed by K<sub>2</sub>CO<sub>3</sub> (0.69 g, 5.0 mmol). The resultant mixture was stirred at rt for 16 h, concentrated in vacuo, diluted with H<sub>2</sub>O (50 mL), and extracted with CHCl<sub>3</sub> until no more product could be detected in the aqueous layer by TLC (400 mL total). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 5% MeOH in EtOAc elution) afforded the allylation products **1 - 4** as yellow solids.

Catalyst **1**: coupling 96%, benzylation 98%, allylation 52%;  $[\alpha]_D^{25}$  -215.4 (*c* 5.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz)  $\delta$  9.01 (d, *J* = 4.5 Hz, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 4.5 Hz, 1H), 7.82–7.76 (m, 3H), 7.40 (d, *J* = 8.0 Hz, 3H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.49 (s, 1H), 6.25–6.20 (m, 1H), 5.51 (d, *J* = 17.5 Hz, 1H), 5.39 (d, *J* = 10.0 Hz, 1H), 5.31 (d, *J* = 13.0 Hz, 1H), 5.10 (d, *J* = 12.5 Hz, 1H), 4.53–4.51 (m, 1H), 4.38–4.36 (m, 1H), 4.35–4.25 (m, 2H), 4.22–4.16 (m, 1H), 3.80–3.74 (m, 1H), 3.41–3.38 (m, 1H), 2.43–2.37 (m, 1H), 2.36 (m, 1H), 2.22–2.18 (m, 1H), 1.89 (m, 1H), 1.89–1.85 (m, 1H), 1.64–1.54 (m, 1H); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz)  $\delta$  150.0, 148.0, 141.5, 133.2, 131.8 (2C), 130.2, 129.9 (2C), 129.7, 129.3 (2C), 128.5, 126.1, 125.3, 124.9 (2C), 123.3, 120.1, 118.6, 113.6, 113.5,

112.9, 112.8, 90.9, 81.5, 73.6, 70.5, 67.5, 62.2, 56.2, 51.2, 27.3, 26.0, 23.3 (2C); IR (film)  $\nu_{\max}$  2928, 1615, 1515, 1492, 1324, 1165, 1126, 1066, 755  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  621.23854 ( $[\text{M}-\text{Br}]^+$ ,  $\text{C}_{36}\text{H}_{31}\text{F}_6\text{N}_2\text{O}$  requires 621.23351).

Catalyst **2**: coupling 93%, benzylation 95%, allylation 15%;  $[\alpha]_{\text{D}}^{25}$   $-231.9$  ( $c$  4.2,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  9.00 (d,  $J = 5.0$  Hz, 1H), 8.48 (d,  $J = 8.5$  Hz, 1H), 8.14 (d,  $J = 8.5$  Hz, 1H), 7.92–7.75 (m, 4H), 7.41–7.36 (m, 1H), 6.83 (t,  $J = 9.0$  Hz, 2H), 6.76–6.72 (m, 2H), 6.50 (s, 1H), 6.25–6.20 (m, 1H), 5.51 (d,  $J = 18.0$  Hz, 1H), 5.39 (d,  $J = 10.5$  Hz, 1H), 5.37 (d,  $J = 9.0$  Hz, 1H), 5.09 (d,  $J = 13.0$  Hz, 1H), 4.55–4.50 (m, 1H), 4.38–4.34 (m, 1H), 4.33–4.28 (m, 2H), 4.19–4.16 (m, 1H), 3.77–3.73 (m, 1H), 3.41–3.37 (m, 1H), 3.30–3.26 (m, 1H), 2.42–2.35 (m, 1H), 2.33–2.28 (m, 1H), 2.19–2.15 (m, 1H), 1.93–1.90 (m, 1H), 1.61–1.56 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  150.0, 148.0, 141.6, 133.5, 133.3, 133.1, 130.3, 130.0 (2C), 129.4, 128.5, 125.4, 123.3, 120.1, 118.6, 118.2 (2C), 115.3, 115.1, 113.7, 113.5, 112.9, 112.8, 87.8, 81.8, 73.6, 70.5, 67.5, 62.5, 56.2, 51.3, 27.3, 26.1, 23.5 (2C); IR (film)  $\nu_{\max}$  2926, 1600, 1507. 1309, 1232, 1060, 755  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  571.23783 ( $[\text{M}-\text{Br}]^+$ ,  $\text{C}_{35}\text{H}_{31}\text{F}_4\text{N}_2\text{O}$  requires 571.23670).

Catalyst **3**: coupling 87%, benzylation 64%, allylation 64%;  $[\alpha]_{\text{D}}^{25}$   $-254.4$  ( $c$  5.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  9.01 (d,  $J = 4.0$  Hz, 1H), 8.34 (d,  $J = 8.5$  Hz, 1H), 8.17 (d,  $J = 8.0$  Hz, 1H), 7.86 (t,  $J = 7.5$  Hz, 2H), 7.77 (t,  $J = 8.5$  Hz, 1H), 7.72–7.66 (m, 1H), 7.45–7.40 (m, 1H), 7.07–7.00 (m, 1H), 6.68–6.62 (m, 1H), 6.53–6.48 (m, 1H), 6.46 (s, 1H), 6.26–6.19 (m, 1H), 5.53 (d,  $J = 17.5$  Hz, 1H), 5.40 (d,  $J = 11.5$  Hz, 1H), 5.16 (d,  $J = 13.0$  Hz, 1H), 5.08 (d,  $J = 13.0$  Hz, 1H), 4.47–4.42

(m, 1H), 4.56–4.51 (m, 2H), 4.25–4.21 (m, 1H), 4.03–3.99 (m, 1H), 3.72–3.68 (m, 1H), 3.38–3.33 (m, 1H), 3.30–3.24 (m, 1H), 2.42–2.38 (m, 1H), 2.36–2.31 (m, 1H), 2.22–2.17 (m, 1H), 1.88–1.82 (m, 1H), 1.61–1.55 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  150.1, 148.0, 141.4, 133.1, 130.4, 129.7 (2C), 129.6 (2C), 128.4, 128.3, 128.2, 125.3, 122.6, 120.1, 119.9, 118.7, 117.5, 117.3, 113.8, 113.7, 113.5, 113.4, 88.8, 80.8, 73.5, 70.5, 67.7, 62.5, 56.4, 51.2, 27.2, 25.9, 23.3, 23.2; IR (film)  $\nu_{\text{max}}$  2926, 1597, 1514, 1306, 1060, 754  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  589.22966 ( $[\text{M}-\text{Br}]^+$ ,  $\text{C}_{35}\text{H}_{30}\text{F}_5\text{N}_2\text{O}$  requires 589.22728).

Catalyst **4**: coupling 87%, benzylation 74%, allylation 71%;  $[\alpha]_{\text{D}}^{25}$   $-267.0$  ( $c$  5.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  8.99 (d,  $J = 7.5$  Hz, 1H), 8.28 (d,  $J = 14.0$  Hz, 1H), 8.15 (d,  $J = 14.5$  Hz, 1H), 7.84 (d,  $J = 7.5$  Hz, 1H), 7.82–7.77 (m, 1H), 7.72–7.62 (m, 2H), 7.44–7.36 (m, 1H), 6.82–6.66 (m, 3H), 6.43 (s, 1H), 6.22–6.17 (m, 1H), 5.47 (d,  $J = 26.5$  Hz, 1H), 5.37 (d,  $J = 17.5$  Hz, 1H), 5.12 (d,  $J = 22.0$  Hz, 1H), 5.05 (d,  $J = 21.5$  Hz, 1H), 4.40–4.35 (m, 2H), 4.34–4.30 (m, 1H), 4.22–4.17 (m, 1H), 4.00–3.95 (m, 1H), 3.75–3.68 (m, 1H), 3.36–3.32 (m, 1H), 3.31–3.28 (m, 1H), 2.45–2.36 (m, 1H), 2.35–2.30 (m, 1H), 2.20–2.15 (m, 1H), 1.84–1.80 (m, 1H), 1.68–1.64 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  149.9, 148.2, 141.3, 134.2, 134.1, 133.1, 130.2, 129.8 (2C), 129.5, 128.1, 122.6, 120.0, 118.7, 113.8, 113.7, 113.5, 113.4, 111.6, 111.3, 104.1, 103.7, 103.4, 93.4, 85.5, 73.4, 70.4, 67.8, 62.6, 56.4, 51.2, 27.4, 26.0, 23.3, 23.1; IR (film)  $\nu_{\text{max}}$  2926, 1615, 1505, 1265, 1142, 1060, 964, 755  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  589.23732 ( $[\text{M}-\text{Br}]^+$ ,  $\text{C}_{35}\text{H}_{30}\text{F}_5\text{N}_2\text{O}$  requires 589.22728).

### 1.4.3 General procedure for the synthesis of catalysts 5 - 7

**Benzylation.** A solution of **18** (0.20 g, 0.65 mmol) in acetone–EtOH (1:1, 5 mL) was treated with 2,3,4-trifluorobenzyl bromide (0.25 mL, 2.0 mmol) and stirred at rt for 16 h. The solid precipitate was filtered and washed with Et<sub>2</sub>O to give a white solid that was used without purification in the next step.

**Allylation.** A suspension of the crude quaternary ammonium salt (0.15 g, 0.27 mmol) in acetone (7 mL) was treated with allyl bromide (0.040 mL, 0.92 mmol), followed by K<sub>2</sub>CO<sub>3</sub> (0.270 g, 1.95 mmol). The resultant mixture was stirred at rt for 16 h, concentrated in vacuo, diluted with H<sub>2</sub>O (30 mL), and extracted with CHCl<sub>3</sub> until no more product could be detected in the aqueous layer by TLC (150 mL total). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 5% MeOH in EtOAc elution) afforded **20** as a yellow solid.

**Sonogashira coupling.** A round-bottomed flask was charged with **20** (60 mg, 0.105 mmol), aryl iodide (0.21 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (3 mg, 0.0039 mmol), CuI (1.5 mg, 0.0078 mmol), and TBAF·3H<sub>2</sub>O (97 mg, 0.378 mmol), followed by H<sub>2</sub>O (25 mL). The resultant mixture was stirred at 90 °C for 3.5 h. Cooled to rt and extracted with CHCl<sub>3</sub> until no more product could be detected in the aqueous layer by TLC (150 mL total). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. Flash chromatography (5% MeOH in EtOAc elution) afforded the coupling products **5 - 7** as yellow solids.

Catalyst **5**: benzylation 92%, allylation 86%, coupling 60%;  $[\alpha]_D^{25}$  –211.3 (*c* 3.7, DMSO); <sup>1</sup>HNMR (DMSO-*d*<sub>6</sub>, 500 MHz) δ 9.06 (s, 1H), 8.32 (d, *J* = 8.0 Hz, 1H),



8.19 (d,  $J = 8.5$  Hz, 1H), 8.02 (d,  $J = 8.5$  Hz, 2H), 7.89 (t,  $J = 8.0$  Hz, 1H), 7.80–7.76 (m, 1H), 7.74–7.68 (m, 2H), 7.63 (d,  $J = 3.5$  Hz, 1H), 7.00 (d,  $J = 8.0$  Hz, 2H), 6.44 (s, 1H), 6.17–6.12 (m, 1H), 5.48 (d,  $J = 17.0$  Hz, 1H), 5.32 (d,  $J = 10.0$  Hz, 1H), 5.16 (d,  $J = 12.0$  Hz, 1H), 5.05 (d,  $J = 13.5$  Hz, 1H), 4.38–4.33 (m, 1H), 4.31–4.26 (m, 1H), 4.17–4.02 (m, 3H), 3.65–3.60 (m, 1H), 3.17–3.12 (m, 2H), 2.32–2.25 (m, 2H), 2.14–2.08 (m, 1H), 1.79–1.75 (m, 1H), 1.50–1.40 (m, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 125 MHz)  $\delta$  151.2, 148.8, 147.5, 141.2, 134.4, 132.9 (2C), 130.8 (2C), 130.5, 129.1, 128.3, 125.5, 124.3 (2C), 124.1, 120.4, 118.7, 116.0, 114.6, 114.5, 114.2, 114.1, 95.8, 81.2, 73.4, 70.3, 67.5, 61.0, 56.4, 51.1, 27.5, 26.0, 23.9, 23.1; IR (film)  $\nu_{\text{max}}$  2925, 1591, 1341, 1104, 853, 750  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  598.23291 ( $[\text{M}-\text{Br}]^+$ ,  $\text{C}_{35}\text{H}_{31}\text{F}_3\text{N}_3\text{O}_3$  requires 598.23120).

Catalyst **6**: benzylation 92%, allylation 86%, coupling 22%;  $[\alpha]_{\text{D}}^{25}$   $-213.8$  ( $c$  5.0, DMSO);  $^1\text{H}$  NMR (DMSO- $d_6$ , 500 MHz)  $\delta$  9.05 (d,  $J = 4.0$  Hz, 1H), 8.26 (d,  $J = 7.5$  Hz, 1H), 8.15 (d,  $J = 8.5$  Hz, 1H), 7.94 (dd,  $J = 2.5, 8.5$  Hz, 1H), 7.81 (t,  $J = 7.0$  Hz, 1H), 7.72 (d,  $J = 4.0$  Hz, 2H), 7.70–7.57 (m, 2H), 7.53–7.44 (m, 1H), 7.11 (dd,  $J = 5.5, 8.5$  Hz, 1H), 6.42 (s, 1H), 6.18–6.10 (m, 1H), 5.47 (d,  $J = 16.0$  Hz, 1H), 5.31 (d,  $J = 10.0$  Hz, 1H), 5.15 (d,  $J = 13.0$  Hz, 1H), 5.05 (d,  $J = 13.5$  Hz, 1H), 4.45 (t,  $J = 6.5$  Hz, 1H), 4.32–4.23 (m, 1H), 4.14–4.06 (m, 2H), 4.04–4.00 (m, 1H), 3.66–3.62 (m, 1H), 3.57–3.51 (m, 1H), 3.24–3.20 (m, 1H), 2.36–2.27 (m, 2H), 2.12–2.07 (m, 1H), 1.79–1.75 (m, 1H), 1.64–1.55 (m, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 125 MHz)  $\delta$  151.0, 148.8, 141.1, 137.1, 137.0, 134.5, 132.8, 130.8 (2C), 130.3, 129.6, 129.4, 127.9, 124.0, 121.8, 121.5, 118.7, 114.3, 114.2, 114.1, 114.0, 113.4, 113.0, 97.3, 77.0,

73.4, 70.2, 67.6, 61.0, 56.4, 51.3, 27.5, 26.1, 23.8, 23.0; IR (film)  $\nu_{\max}$  2958, 1614, 1514, 1345, 1059, 805, 754  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  616.22208 ( $[\text{M}-\text{Br}]^+$ ,  $\text{C}_{35}\text{H}_{30}\text{F}_4\text{N}_3\text{O}_3$  requires 616.22178).

Catalyst **7**: benzylation 92%, allylation 86%, coupling 54%;  $[\alpha]_{\text{D}}^{25}$   $-214.6$  ( $c$  5.0, DMSO);  $^1\text{H}$  NMR (DMSO- $d_6$ , 500 MHz)  $\delta$  9.04 (d,  $J = 4.5$  Hz, 1H), 8.35 (dd,  $J = 2.5, 8.5$  Hz, 1H), 8.24 (d,  $J = 9.0$  Hz, 1H), 8.12 (d,  $J = 8.5$  Hz, 1H), 7.76 (t,  $J = 7.0$  Hz, 1H), 7.71 (d,  $J = 4.5$  Hz, 2H), 7.66–7.58 (m, 2H), 7.56–7.51 (m, 1H), 7.42 (d,  $J = 8.5$  Hz, 1H), 6.41 (s, 1H), 6.16–6.08 (m, 1H), 5.47 (d,  $J = 17.0$  Hz, 1H), 5.31 (d,  $J = 11.0$  Hz, 1H), 5.13 (d,  $J = 13.5$  Hz, 1H), 5.08 (d,  $J = 13.0$  Hz, 1H), 4.30–4.23 (m, 2H), 4.12–4.00 (m, 3H), 3.70–3.64 (m, 1H), 3.42–3.38 (m, 1H), 3.20–3.16 (m, 1H), 2.37–2.30 (m, 1H), 2.12–2.07 (m, 1H), 1.83–1.77 (m, 1H), 1.62–1.55 (m, 2H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 125 MHz)  $\delta$  151.0, 148.8, 141.2, 136.6, 134.5, 132.7 (2C), 132.3, 132.1, 130.8, 130.3, 129.6, 129.4, 128.1, 128.0, 124.0, 122.8, 120.8, 118.7, 114.5, 114.2, 114.0, 113.8, 103.2, 77.2, 70.3, 67.7, 60.6, 58.3, 56.6, 51.3, 27.9, 26.1, 23.8 (2C); IR (film)  $\nu_{\max}$  2959, 1608, 1514, 1342, 1118, 1058, 721  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  643.21604 ( $[\text{M}-\text{Br}]^+$ ,  $\text{C}_{35}\text{H}_{30}\text{F}_3\text{N}_4\text{O}_5$  requires 643.21628).

#### 1.4.4 General procedure for the synthesis of catalysts **10**, **11**

**Benzylation.** A solution of cinchonidine (0.20 g, 0.68 mmol) in acetone–EtOH (1:1, 10 mL) was treated with 2,3,4-trifluorobenzyl bromide (0.20 mL, 1.56 mmol) and stirred at rt for 16 h, then concentrated in vacuo. Flash chromatography ( $\text{SiO}_2$ , 25% MeOH in EtOAc elution) afforded **25** (0.338 g, 0.65 mmol, 96%) as a white solid.

**Heck reaction.** A solution of **25** (150 mg, 0.30 mmol) in anhydrous DMF (4.0 mL) was treated with aryl iodide (0.60 mmol), PdCl<sub>2</sub> (4.3 mg, 0.024 mmol), and Et<sub>3</sub>N (0.043 mL, 0.308 mmol). The resultant mixture was stirred at 100 °C for 20 h, then concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 5% MeOH in EtOAc elution) afforded the products **26** and **27** as yellow solids.

**Allylation.** A solution of **26** or **27** (0.15 mmol) in acetone (4.0 mL) was treated with allyl bromide (0.064 mL, 0.75 mmol), followed by K<sub>2</sub>CO<sub>3</sub> (0.207 g, 1.50 mmol). The resultant mixture was stirred at rt for 16 h, concentrated in vacuo, diluted with H<sub>2</sub>O (50 mL), and extracted with CHCl<sub>3</sub> until no more product could be detected in the aqueous layer by TLC (200 mL total). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 5% MeOH in EtOAc elution) afforded **10** and **11** as yellow solids.

Catalyst **10**: benzylation 96%, Heck reaction 63%, allylation 59%;  $[\alpha]_D^{25} -156.6$  (*c* 5.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz) δ 9.01 (d, *J* = 4.5 Hz, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.87 (t, *J* = 5.5 Hz, 1H), 7.78 (t, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 4.5 Hz, 1H), 7.63–7.58 (m, 1H), 7.32–7.27 (m, 2H), 7.05 (t, *J* = 8.5 Hz, 2H), 6.47 (d, *J* = 4.5 Hz, 1H), 6.45 (s, 1H), 6.19–6.09 (m, 2H), 5.44 (d, *J* = 17.0 Hz, 1H), 5.33 (d, *J* = 12.5 Hz, 1H), 5.29 (d, *J* = 11.0 Hz, 1H), 4.99 (d, *J* = 12.5 Hz, 1H), 4.32–4.28 (m, 1H), 4.19–4.15 (m, 1H), 4.08–4.00 (m, 2H), 3.72–3.69 (m, 1H), 3.59–3.54 (m, 1H), 3.36–3.32 (m, 1H), 2.81–2.78 (m, 1H), 2.31–2.25 (m, 1H), 2.15–2.09 (m, 1H), 2.09–2.05 (m, 1H), 1.88–1.84 (m, 1H), 1.67–1.60 (m, 1H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz) δ 150.2, 148.0, 140.9, 133.9, 132.9, 130.4 (2C), 130.0,

129.9, 129.6, 129.4, 128.0, 127.8, 127.4, 125.0, 123.5, 119.6, 117.9, 117.7, 115.3, 115.0, 113.5, 113.4, 113.3, 113.2, 79.1, 69.3, 67.9, 59.8, 56.3, 51.0, 26.2 (2C), 24.5, 21.0; IR (film)  $\nu_{\max}$  2926, 1600, 1509, 1492, 1309, 1226, 1037, 754  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  573.25388 ( $[\text{M}-\text{Br}]^+$ ,  $\text{C}_{35}\text{H}_{33}\text{F}_4\text{N}_2\text{O}$  requires 573.25235).

Catalyst **11**: benzylation 96%, Heck reaction 51%, allylation 38%;  $[\alpha]_{\text{D}}^{25}$   $-151.6$  ( $c$  5.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 500 MHz)  $\delta$  9.01 (d,  $J = 4.5$  Hz, 1H), 8.26 (d,  $J = 8.5$  Hz, 1H), 8.12 (d,  $J = 8.5$  Hz, 1H), 7.91–7.83 (m, 2H), 7.76 (t,  $J = 8.0$  Hz, 2H), 7.64–7.60 (m, 1H), 7.49–7.45 (m, 1H), 7.15 (t,  $J = 11.5$  Hz, 1H), 6.96 (t,  $J = 8.5$  Hz, 1H), 6.49 (d,  $J = 15.5$  Hz, 1H), 6.45 (s, 1H), 6.28–6.22 (m, 1H), 6.16–6.08 (m, 1H), 5.45 (d,  $J = 17.0$  Hz, 1H), 5.37 (d,  $J = 14.0$  Hz, 1H), 5.32 (d,  $J = 14.0$  Hz, 1H), 4.97 (d,  $J = 13.0$  Hz, 1H), 4.34–4.30 (m, 1H), 4.17–4.13 (m, 1H), 4.10–4.00 (m, 2H), 3.72–3.66 (m, 1H), 3.60–3.55 (m, 1H), 3.19–3.15 (m, 1H), 2.87–2.83 (m, 1H), 2.30–2.26 (m, 1H), 2.16–2.05 (m, 2H), 1.88–1.83 (m, 1H), 1.64–1.60 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 125 MHz)  $\delta$  151.0, 148.7, 141.7, 134.7, 134.5, 131.2 (2C), 130.7, 130.4, 130.3, 129.3, 128.1, 125.7, 124.2, 123.1, 120.3, 118.6, 118.4, 114.2, 114.1, 112.5, 112.3, 104.9, 104.7, 104.5, 79.9, 70.0, 68.6, 60.4, 57.1, 51.7, 26.9 (2C), 25.2, 21.6; IR (film)  $\nu_{\max}$  2928, 1614, 1515, 1273, 1137, 1038, 755  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  591.25235 ( $[\text{M}-\text{Br}]^+$ ,  $\text{C}_{35}\text{H}_{32}\text{F}_5\text{N}_2\text{O}$  requires 591.24293).

#### 1.4.5 Procedure for the synthesis of catalyst 12

A solution of **20** (50 mg, 0.089 mmol) in anhydrous pyridine (2.0 mL) was treated with  $\text{Cu}(\text{OAc})_2$  (160 mg, 0.89 mmol). The resultant mixture was stirred at rt for 4 h, then concentrated in vacuo. Flash chromatography ( $\text{SiO}_2$ , 5–20% MeOH in EtOAc

gradient elution to wash out less polar components, then 100% MeOH elution) afforded **12** (44 mg, 0.039 mmol, 89%) as a yellow solid:  $[\alpha]_D^{25} -81.2$  ( $c$  5.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ , 500 MHz)  $\delta$  9.04 (d,  $J = 4.0$  Hz, 2H), 8.17 (d,  $J = 7.0$  Hz, 2H), 8.05 (d,  $J = 8.0$  Hz, 2H), 7.80 (d,  $J = 7.5$  Hz, 2H), 7.70 (t,  $J = 7.0$  Hz, 2H), 7.68–7.63 (m, 4H), 7.59–7.52 (m, 2H), 6.35 (s, 2H), 6.13–6.04 (m, 2H), 5.42 (d,  $J = 17.0$  Hz, 2H), 5.27 (d,  $J = 10.5$  Hz, 2H), 5.18 (d,  $J = 13.0$  Hz, 2H), 4.96 (d,  $J = 12.0$  Hz, 2H), 4.27–4.23 (m, 2H), 4.12–4.08 (m, 2H), 4.04–3.96 (m, 4H), 3.95–3.92 (m, 2H), 3.78–3.74 (m, 2H), 3.47–3.43 (m, 2H), 3.08–3.04 (m, 2H), 2.25–2.20 (m, 2H), 2.07–2.00 (m, 4H), 1.72–1.68 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{DMSO-}d_6$ , 125 MHz)  $\delta$  150.3 (2C), 148.0 (2C), 140.7 (2C), 133.9 (2C), 130.3 (4C), 130.0 (2C), 129.7 (2C), 127.3 (2C), 124.8 (2C), 123.6 (2C), 119.6 (2C), 117.8 (2C), 113.5 (2C), 113.4 (2C), 113.2 (2C), 113.0 (2C), 78.4 (2C), 69.8 (2C), 69.4 (2C), 67.0 (2C), 65.8 (2C), 59.0 (2C), 56.1 (2C), 50.5 (2C), 26.4 (2C), 25.5 (2C), 22.9 (2C), 21.7 (2C); IR (film)  $\nu_{\text{max}}$  2922, 1614, 1514, 1310, 1037, 753  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  476.20705 ( $[\text{M}-2\text{Br}]^{2+}$ ,  $\text{C}_{58}\text{H}_{54}\text{F}_6\text{N}_4\text{O}_2$  requires 476.20700).

#### 1.4.6 General procedure for the synthesis of catalysts **13**, **14**

**First Sonogashira coupling.** A solution of **20** (100 mg, 0.18 mmol) in THF (8.0 mL) was treated with aryl di-iodide (0.36 mmol),  $\text{Pd}(\text{PPh}_3)_4$  (12 mg, 0.016 mmol),  $\text{CuI}$  (6 mg, 0.032 mmol), and  $\text{TBAF}\cdot 3\text{H}_2\text{O}$  (160 mg, 0.64 mmol). The resultant mixture was stirred at reflux for 30 min and then concentrated in vacuo. Flash chromatography ( $\text{SiO}_2$ , 5% MeOH in EtOAc) afforded the mono-coupling products as yellow solids.

**Second Sonogashira coupling.** A solution of the mono-coupling product (0.12 mmol) and **20** (130 mg, 0.24 mmol) in THF (5 mL) was treated with Pd(PPh<sub>3</sub>)<sub>4</sub> (20 mg, 0.026 mmol), CuI (10 mg, 0.052 mmol), and TBAF·3H<sub>2</sub>O (120 mg, 0.48 mmol). The resultant mixture was stirred at reflux for 30 min and then concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 5–20% MeOH in EtOAc gradient elution to wash out less polar components, then 100% MeOH elution) afforded dimers **10a–b** as yellow solids.

Catalyst **13**: first coupling 35%, second coupling 39%;  $[\alpha]_D^{25}$  -130.2 (*c* 5.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz) δ 9.04 (d, *J* = 4.5 Hz, 2H), 8.33 (d, *J* = 8.5 Hz, 2H), 8.19 (d, *J* = 8.5 Hz, 2H), 7.92 (t, *J* = 7.0 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 2H), 7.71 (d, *J* = 4.5 Hz, 4H), 7.62–7.50 (m, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 6.46 (d, *J* = 7.5 Hz, 2H), 6.44 (s, 2H), 6.16–6.10 (m, 2H), 5.48 (d, *J* = 17.0 Hz, 2H), 5.31 (d, *J* = 10.5 Hz, 2H), 5.18 (d, *J* = 13.0 Hz, 2H), 5.01 (d, *J* = 13.5 Hz, 2H), 4.35–4.24 (m, 4H), 4.16–4.01 (m, 6H), 3.60–3.56 (m, 2H), 3.32–3.29 (m, 2H), 3.23–3.18 (m, 2H), 2.27–2.22 (m, 4H), 2.11–2.03 (m, 2H), 1.77–1.71 (m, 2H), 1.45–1.40 (m, 2H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz) δ 150.4 (2C), 148.0 (2C), 140.4 (2C), 137.2 (2C), 133.7 (2C), 132.6 (4C), 130.0 (4C), 129.7 (2C), 127.5 (2C), 124.6 (2C), 123.3 (2C), 120.9 (2C), 119.6 (2C), 118.0 (2C), 113.5 (2C), 113.4 (2C), 113.3 (2C), 113.2 (2C), 90.8 (2C), 79.1 (2C), 69.5 (2C), 66.6 (2C), 63.4 (2C), 60.6 (2C), 55.5 (2C), 50.4 (2C), 26.5 (2C), 25.2 (2C), 23.0 (2C), 22.4 (2C); IR (film)  $\nu_{\max}$  2929, 1590, 1513, 1492, 1308, 1061, 755 cm<sup>-1</sup>; HRMS (ESI) *m/z* 514.22266 ([M–2Br]<sup>2+</sup>, C<sub>64</sub>H<sub>58</sub>F<sub>6</sub>N<sub>4</sub>O<sub>2</sub> requires 514.22265).

Catalyst **14**: first coupling 56%, second coupling 24%;  $[\alpha]_D^{25}$  -126.6 ( $c$  5.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ , 500 MHz)  $\delta$  9.05 (d,  $J$  = 4.5 Hz, 2H), 8.38 (d,  $J$  = 7.0 Hz, 2H), 8.21 (d,  $J$  = 8.0 Hz, 2H), 7.92 (t,  $J$  = 7.0 Hz, 2H), 7.79 (t,  $J$  = 8.0 Hz, 2H), 7.73 (d,  $J$  = 4.5 Hz, 4H), 7.63–7.59 (m, 2H), 7.41 (d,  $J$  = 8.0 Hz, 4H), 6.79 (d,  $J$  = 8.0 Hz, 4H), 6.46 (s, 2H), 6.19–6.10 (m, 2H), 5.48 (d,  $J$  = 17.0 Hz, 2H), 5.32 (d,  $J$  = 9.5 Hz, 2H), 5.24 (d,  $J$  = 12.5 Hz, 2H), 5.03 (d,  $J$  = 13.0 Hz, 2H), 4.38–4.34 (m, 2H), 4.31–4.26 (m, 2H), 4.16–4.05 (m, 6H), 3.62–3.58 (m, 2H), 3.27–3.24 (m, 4H), 2.30–2.25 (m, 4H), 2.11–2.08 (m, 2H), 1.77–1.74 (m, 2H), 1.49–1.45 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{DMSO-}d_6$ , 125 MHz)  $\delta$  150.4 (2C), 148.1 (2C), 140.6 (2C), 138.7 (2C), 133.8 (2C), 131.7 (4C), 130.2 (4C), 130.0 (2C), 129.8 (2C), 127.6 (2C), 126.4 (4C), 124.8 (2C), 123.7 (2C), 121.0 (2C), 119.6 (2C), 118.0 (2C), 113.6 (2C), 113.5 (2C), 113.4 (2C), 113.2 (2C), 90.6 (2C), 81.7 (2C), 72.9 (2C), 69.5 (2C), 66.5 (2C), 60.6 (2C), 55.3 (2C), 50.4 (2C), 26.6 (2C), 25.4 (2C), 23.0 (2C), 22.5 (2C); IR (film)  $\nu_{\text{max}}$  2926, 1590, 1514, 1492, 1309, 1061, 824, 755  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  552.23873 ( $[\text{M}-2\text{Br}]^{2+}$ ,  $\text{C}_{70}\text{H}_{62}\text{F}_6\text{N}_4\text{O}_2$  requires 552.23830).

## 1.5 Reference

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## **Chapter II**

### **Total synthesis of celogentin C**

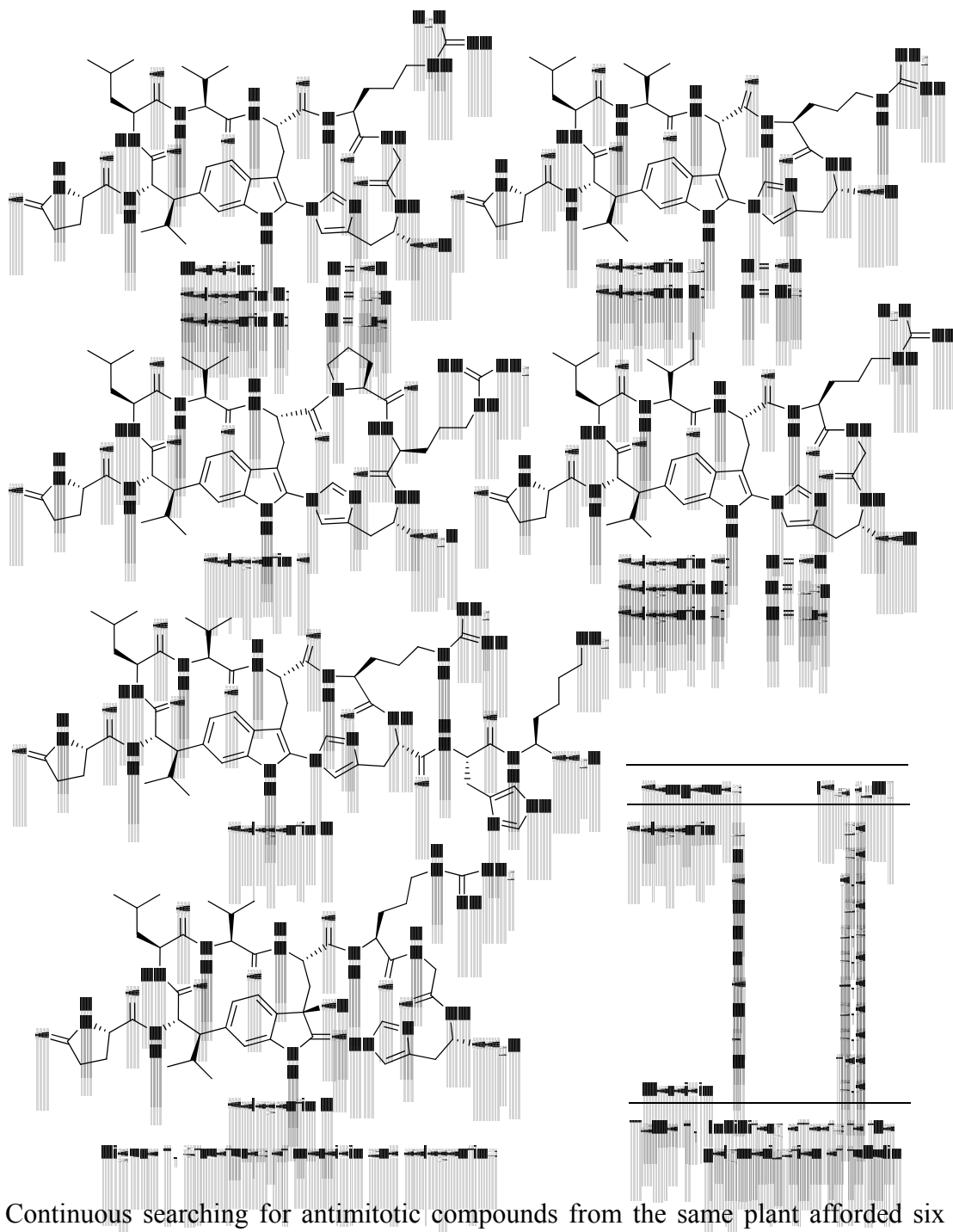
## **2.1 Introduction**

### **2.1.1 Tubulin polymerization**

Microtubules are one of the components of the cytoskeleton. In cell division and mitotic spindle assembly, they play a crucial role.<sup>1</sup> Microtubules are constructed by the self-association of  $\alpha$ ,  $\beta$  tubulin heterodimers. As the main structural element of microtubules, tubulin has significant effects in cell signaling, mitosis and motility in eukaryotes. Meanwhile, tubulin interacts with a variety of natural products, among which, antimicrotubule agents paclitaxel and vinblastine are two typical examples.<sup>2</sup> Paclitaxel and vinblastine bind with tubulin at different sites and afford two opposite effects: paclitaxel facilitates microtubule bundling, while vinblastine disassembles microtubules. Natural compounds containing these notable polymerization and depolymerization properties have potential applications in medicinal chemistry.

### **2.1.2 Separation and bioactivity of moroidin and celogentins**

During the search for bioactive compounds from a Chinese herbal medicine, *Celosia argentea*, which has been used for the treatment of eye and hepatic diseases, Kobayashi isolated moroidin as a natural product. Moroidin, containing a novel bicyclic polypeptide structure, was originally discovered by Williams from *Laportea moroides*.<sup>3</sup> More importantly, moroidin has been found to strongly inhibit the polymerization of tubulin.<sup>4</sup> After further investigation of *Celosia argentea*, three moroidin-type compounds were separated, celogentins A, B and C (Figure 1).<sup>5</sup>



Continuous searching for antimitotic compounds from the same plant afforded six more celogentins, D - H and J.<sup>6</sup> Additionally, in 2004 celogentin K was discovered from the same source.<sup>7</sup> Strong inhibitory effects toward the polymerization of tubulin were detected in most of these celogentins,<sup>6,7</sup> with celogentin C showing the most potent activity (Table 1).

### 2.1.3 Studies toward the total synthesis of moroidin and celogentin C

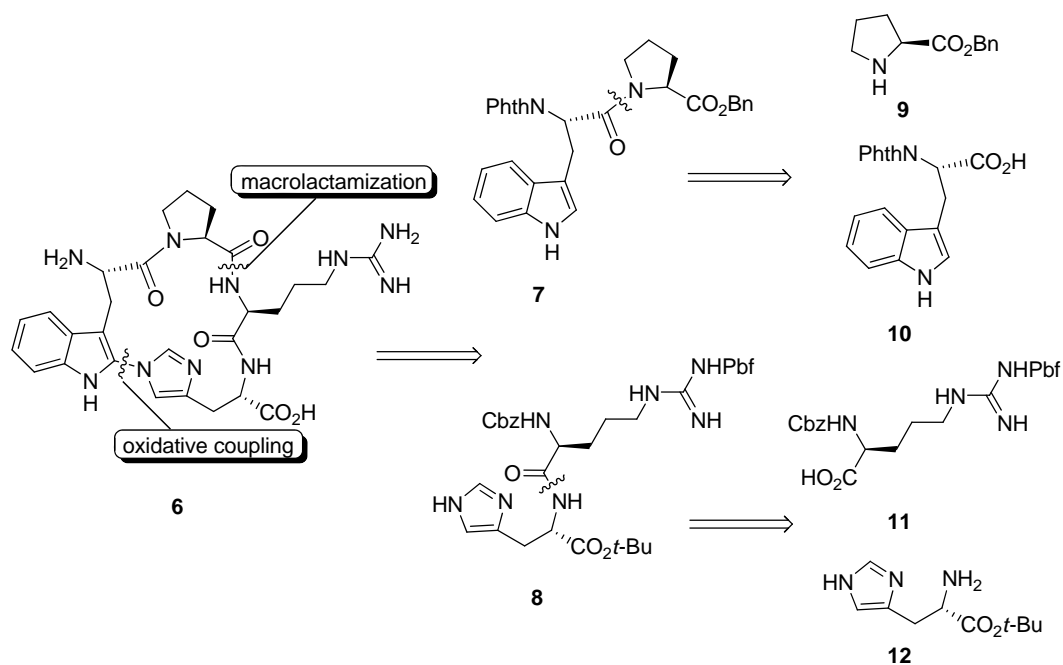
Moroidin and the celogentins share a similar bicyclic architecture, which contains two unusual cross-links: one between the leucine  $\beta$ -C and the indole C-6; the other between indole C-2 and imidazole N-1. All these features make moroidin and the celogentins very challenging targets for total synthesis. Even though it has been more than two decades since the first isolation of moroidin,<sup>3</sup> the studies of this natural product are limited to Moody's construction of the right-hand ring.<sup>8</sup> Because of its potent bioactivity, celogentin C has drawn a significant amount of attention from synthetic chemists. For example, the Hutton group from the University of Melbourne<sup>9</sup> and the Campagne group from France<sup>10</sup> reported their efforts on constructing the tryptophan residue of celogentin C in 2006 and 2008 respectively. Additionally, the Wandless group from Stanford University presented their progress toward celogentin C synthesis at an ACS conference in 2006.<sup>11</sup>

However, the most prominent contributions have come from the Castle group at Brigham Young University. The Castle group reported the first tryptophan residue synthesis in 2003 (Scheme 1),<sup>12</sup> where a Cook-type Pd-catalyzed heteroannulation<sup>13</sup>



from alkyne **2** and iodoaniline **3** was applied as the key transformation. The stereocenter of tryptophan was set early by performing a Park-Jew phase-transfer catalyst promoted alkylation from the glycine derivative **4**.

The synthesis of the celogentin C model right-hand ring, which contained no substituents at the indole C-6 position, was accomplished in 2006.<sup>14</sup> The retrosynthetic analysis is displayed in Scheme 2. Four natural amino acids (**9**, **10**, **11**, **12**) were incorporated into the model right-hand ring, with the early formations of Pro-Trp and His-Arg dipeptides. A very mild and efficient oxidative coupling by using NCS as the oxidant was developed to achieve the new C-N bond between the indole C-2 and the imidazole N-1. The cyclic compound (**6**) was eventually accomplished after a macrolactamization with the presence of HOBT and HBTU in diluted DMF solution.



**Scheme 2.** Retrosynthetic analysis of celogentin C model right-hand ring

Even though promising progress had been made toward the total synthesis of celogentin C by the Castle group, the left-hand ring moiety had not been achieved

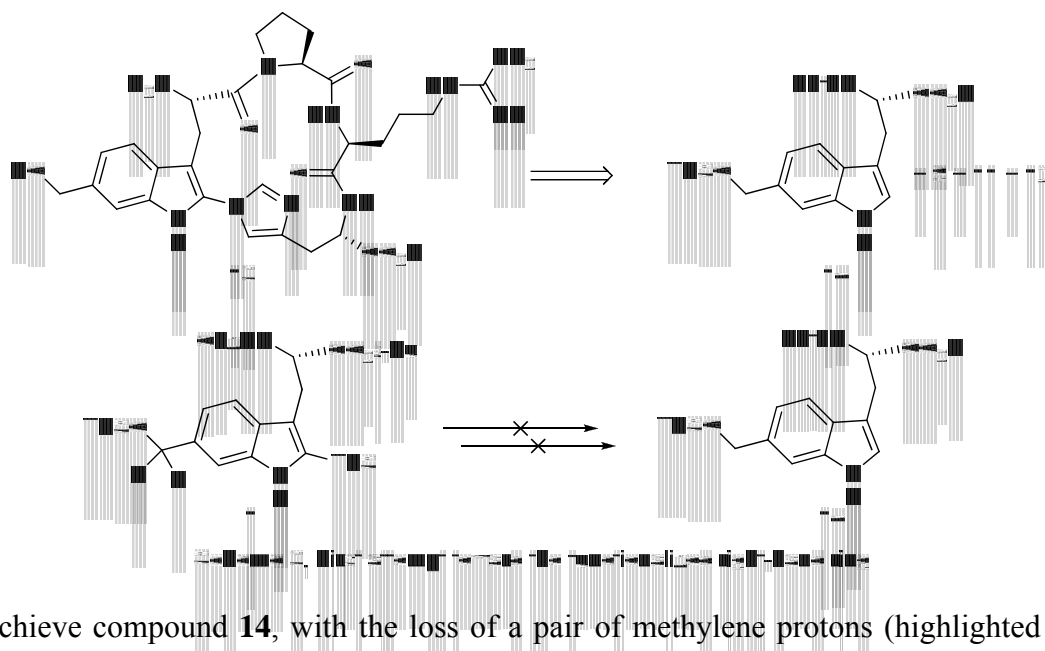
when I joined this project. Also, it is impossible to build the whole molecule from the model right-hand ring compound, due to the absence of the substituents at the indole C-6 position. Consequently, the synthesis of a functionalized right-hand ring of celogentin C is the most urgent task in this project.

## 2.2 Results and discussion

### 2.2.1 Synthesis of the functionalized right-hand ring of celogentin C

#### 2.2.1.1. Hydroxymethyl functionalized right-hand ring of celogentin C

The first attempt toward the functionalized right-hand ring of celogentin C was focused on the synthesis of molecule **13**, with a hydroxymethyl group at the indole C-6 position (Scheme 3). Based on the model studies described previously, the functionalized right-hand ring target would come from a substituted tryptophan and the other three natural amino acids (**9**, **11**, **12**). The methodology for the construction of the substituted tryptophan (**14**) was developed by our group, which afforded compound **1** in its protected version with good yield.<sup>12</sup> The transformation from **1** to **14** only required the cleavage of the *t*-Bu ester and the TES group and the switch of the amine protecting group from Cbz to Phth. Unfortunately, all efforts failed to



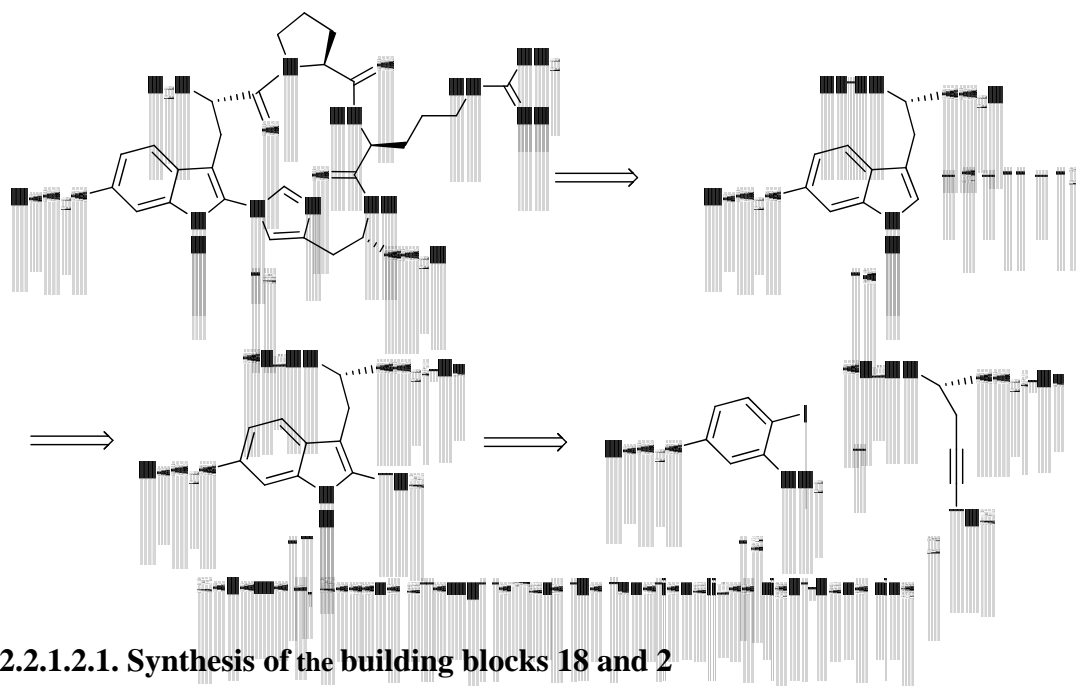
achieve compound **14**, with the loss of a pair of methylene protons (highlighted in compound **1**) in most conditions. Consequently, early struggles in obtaining the tryptophan building block doomed the synthetic route toward the right-hand ring



compound **13**.

### 2.2.1.2. Methyl ester functionalized right-hand ring of celogentin C

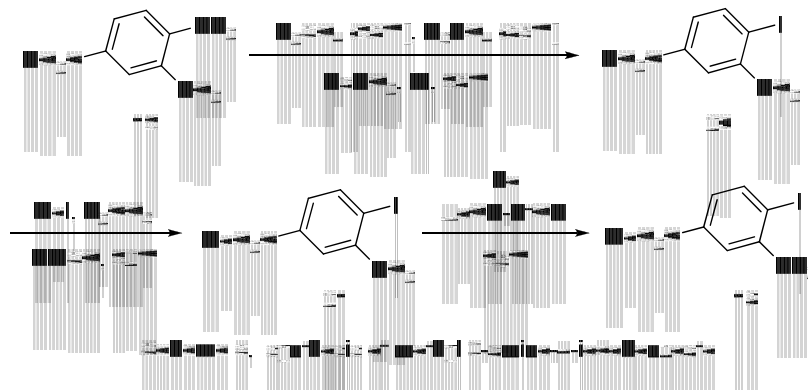
An alternative structure of the functionalized right-hand ring of celogentin C was proposed, which contained a methyl ester group at the indole C-6 position (**15**). Obviously, compound **15** required the substituted tryptophan (**16**) as one of the four building blocks. As proposed, compound **17**, obtained as a heteroannulation product from the iodoaniline (**18**) and the alkyne (**2**), would be applied as the precursor for **16** (Scheme 4).



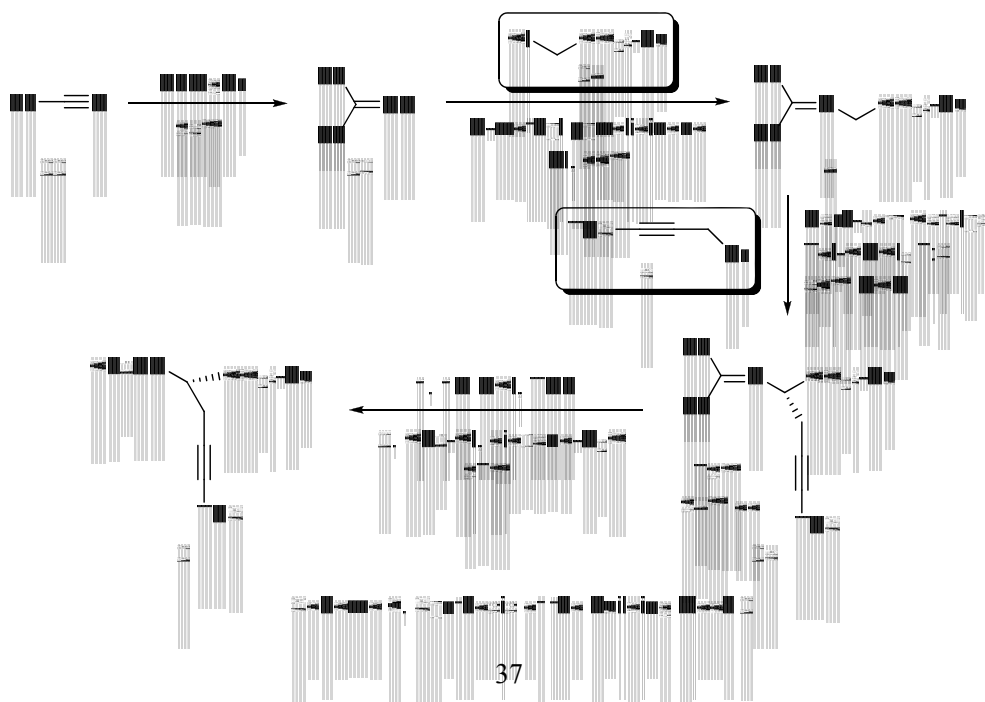
#### 2.2.1.2.1. Synthesis of the building blocks **18** and **2**

The synthesis toward the right-hand ring compound (**15**) started with the iodobenzene (**20**) formation from 4-amino-3-nitrobenzoic acid (**19**). High yield was achieved by following the traditional Sandmeyer conditions.<sup>15</sup> Methyl ester intermediate **21** was initially synthesized by bubbling newly generated  $\text{CH}_2\text{N}_2$  into the solution of **20** in THF.<sup>16</sup> However, considering the potential danger of using  $\text{CH}_2\text{N}_2$ , the reaction condition was switched to a milder one, where the starting

material and methyl iodide was stirred in DMSO with the presence of  $K_2CO_3$  at rt.<sup>17</sup> Excellent yields were obtained in both conditions. The iodoaniline compound (**18**) was easily synthesized after reducing the nitro group.<sup>18</sup>

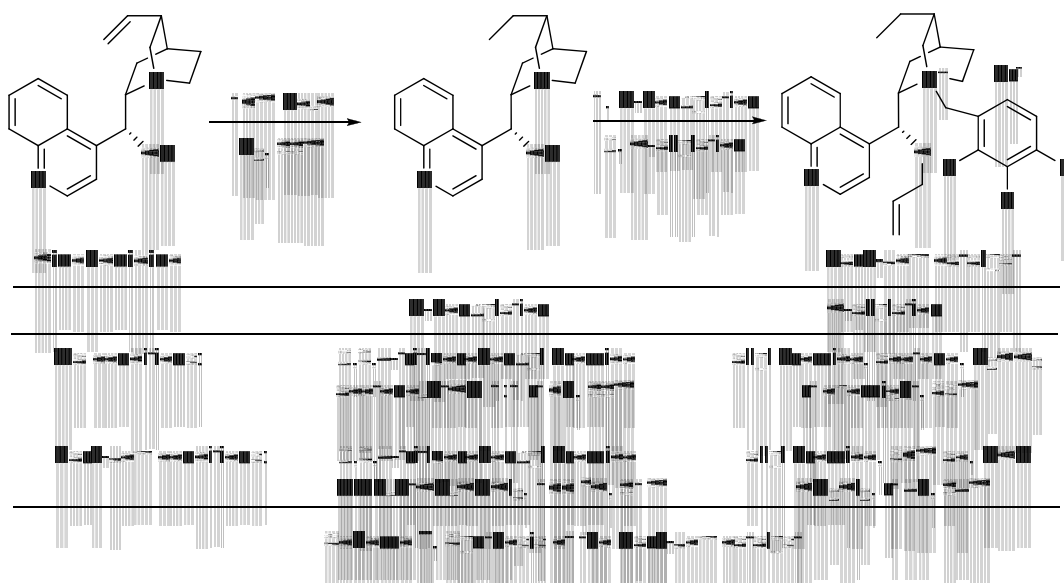


The synthesis of the other coupling partner (**2**) toward the tryptophan moiety was illustrated in Scheme 6. The key intermediate, glycinate Schiff base **4**, was commercially available from Sigma-Aldrich. However, considering the high cost (1 g for \$60) of this early stage intermediate, we decided to synthesize it in the lab. Benzonitrile reacted with phenylmagnesium bromide to afford the diphenylmethanimine (**23**).<sup>19</sup> After heating the imine and the *t*-butyl chloroacetate in *N*-methyl pyrrolidinone, the desired Schiff base was obtained with good yield.<sup>20</sup>



Compared with other methods for synthesizing **4**,<sup>21</sup> this pathway has the shortest sequence and the easiest purification. The Park-Jew phase-transfer catalyst promoted the asymmetric alkylation,<sup>12</sup> and resulted compound **24** with 79% yield and 94% ee. The desired coupling partner **2** was finally achieved after installing the Cbz protecting group.

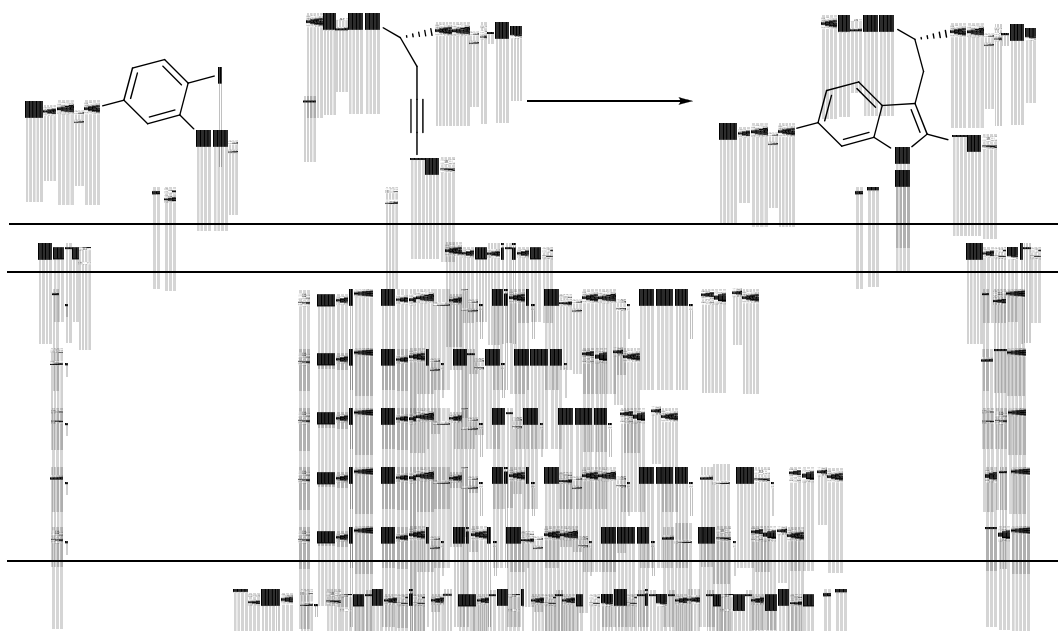
The Park-Jew phase-transfer catalyst was first discovered in 2001.<sup>22</sup> Even though good yields were reported for the first synthesis of this catalyst (91% for N-benylation and 94% for O-allylation, Scheme 7), I encountered challenges in repeating the last two transformations, where harsh conditions, such as high temperature and strong base, were applied. Because of prior experience in the



*cinchona*-derived phase-transfer catalyst syntheses,<sup>23</sup> I introduced the new N-benylation and O-allylation conditions into the synthesis of the Park-Jew catalyst, which turned out to work excellently. No chromatography was necessary, except for the last conversion.

### 2.2.1.2.2 Synthesis of methyl ester substituted tryptophan (17)

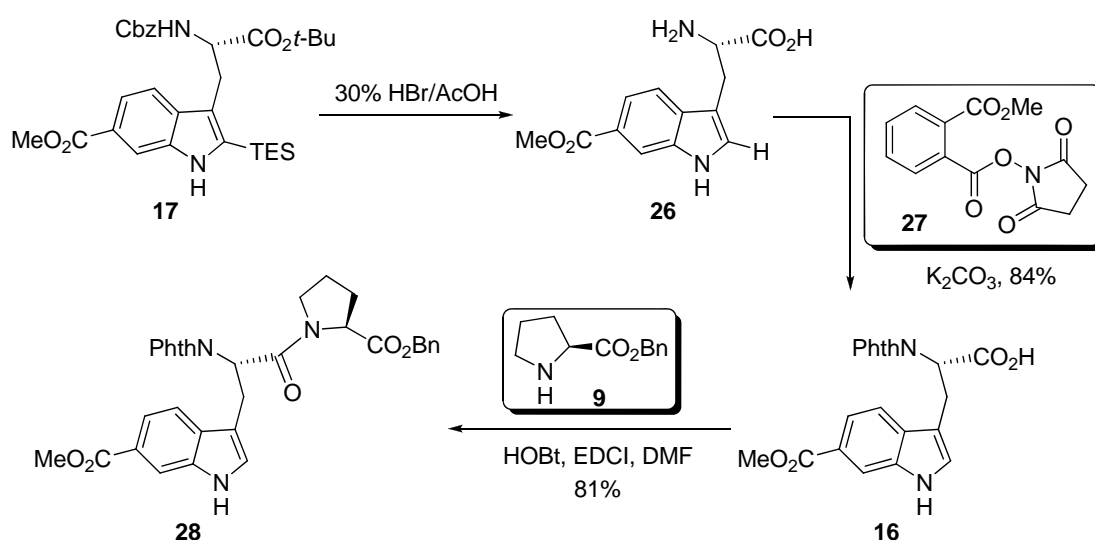
The chemistry for substituted tryptophan construction was previously developed.<sup>12</sup> Nevertheless, it was unclear whether or not the heteroannulation would work for a different iodoaniline precursor. Actually, our suspicions were proved immediately, as the original conditions for the synthesis of compound **1** only generated the desired product (**17**) with 18% yield (Entry 1, Table 2). The yields were improved somewhat by applying Et<sub>3</sub>N as the base (Entries 2 and 3, Table 2). However, a strange impurity always stayed with the product with the same R<sub>f</sub> values. Fortunately, 4Å molecular sieves facilitated the reaction by increasing the yield to 61% (Entry 4, Table 2). An even better result was achieved by switching the catalyst to PdCl<sub>2</sub> (Entry 5). Microwave techniques might be useful for the transformation by improving the yield and shortening the reaction time,<sup>24</sup> but this has not been tested yet.



### 2.2.1.2.3 Synthesis of tryptophan-proline dipeptide

As tryptophan **17** contained no problematic methylene protons such as those in compound **1**, a clean deprotection was envisioned under acidic conditions.

Fortunately, a clean deprotection on substrate **17** was performed by using 30% HBr solution in AcOH, where three groups were removed in one step.<sup>25</sup> Based on the clean NMR spectrum, the crude **26** was protected as a phthalimide without further purification. The methyl ester functionalized tryptophan building block was eventually achieved. Immediately, a traditional peptide coupling procedure was followed to give the Trp-Pro dipeptide (**28**) with good yield. An interesting observation during the process was that the oily compound **9**, benzyl ester protected proline, was not stable at room temperature or even at  $-20\text{ }^{\circ}\text{C}$ . However, **9** could be stored either in THF solution or as its hydrochloric acid salt (Pro-OBn·HCl).

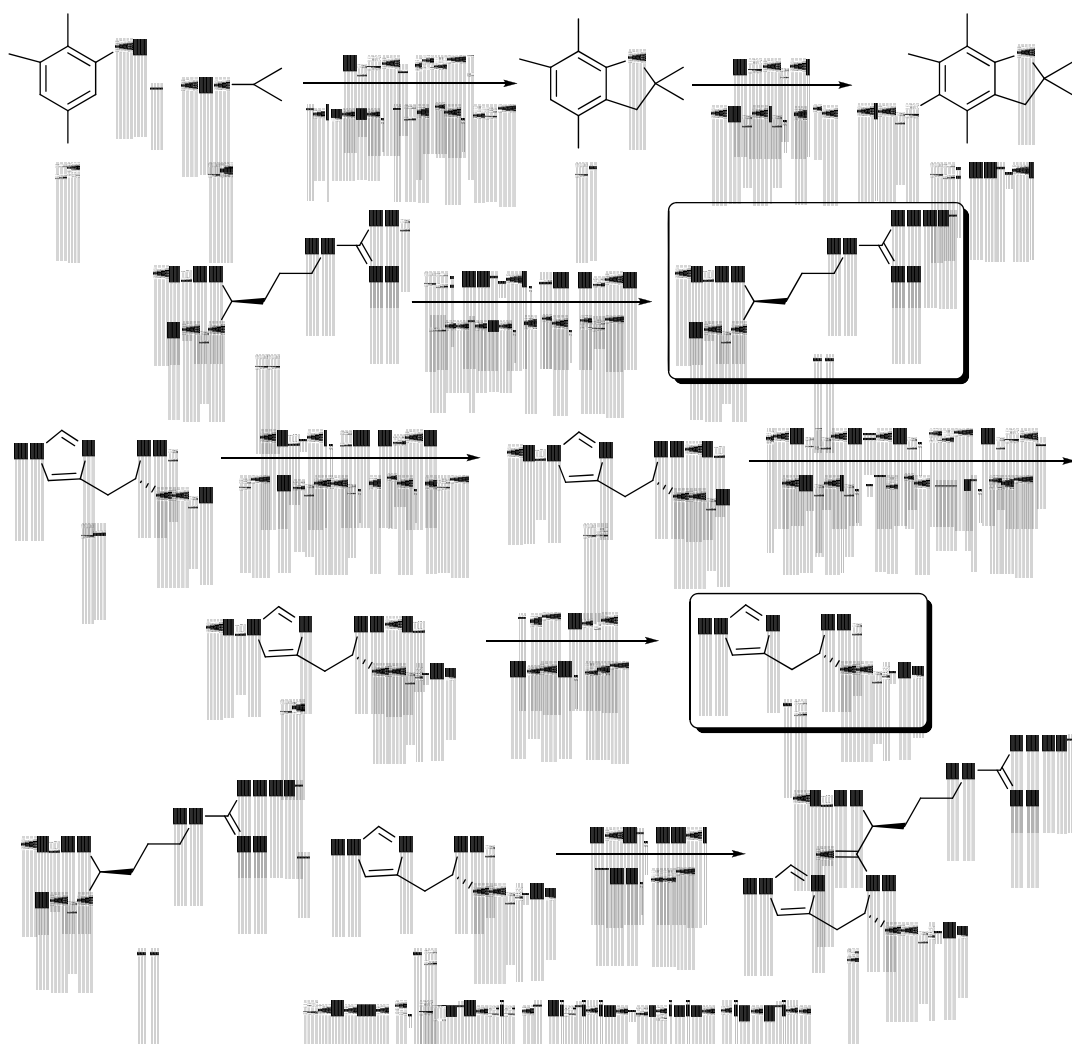


**Scheme 8.** Synthesis of Trp-Pro dipeptide

#### 2.2.1.2.4. Synthesis of histidine-arginine dipeptide

The synthesis of a suitably protected histidine-arginine dipeptide is shown in Scheme 9. The chemistry was initially developed for synthesis of the model right-hand ring of celogentin C. Pentamethyldihydrobenzofuran sulfonyl chloride (Pbf-Cl) was selected for the protection of the guanidine moiety in arginine, which was commercially available from Sigma-Aldrich. In view of the high cost (1 g for

\$80) and easy synthesis,<sup>26</sup> we decided to prepare Pbf-Cl in bulk in the lab. The two-step conversion began with the formation of benzofuran (**31**) from the trimethyl phenol (**29**) and the isobutyl aldehyde (**30**). After treating with chlorosulfonic acid, the desired Pbf-Cl was obtained without too much trouble. Aqueous work-up did provide a clean NMR spectrum of compound **32**, but this material only afforded a low yield of product **11** after reacting with Cbz-Arg-OH (**33**). Surprisingly, crude Pbf-Cl worked much better for the protection. *tert*-Butyl ester protected histidine (**12**)

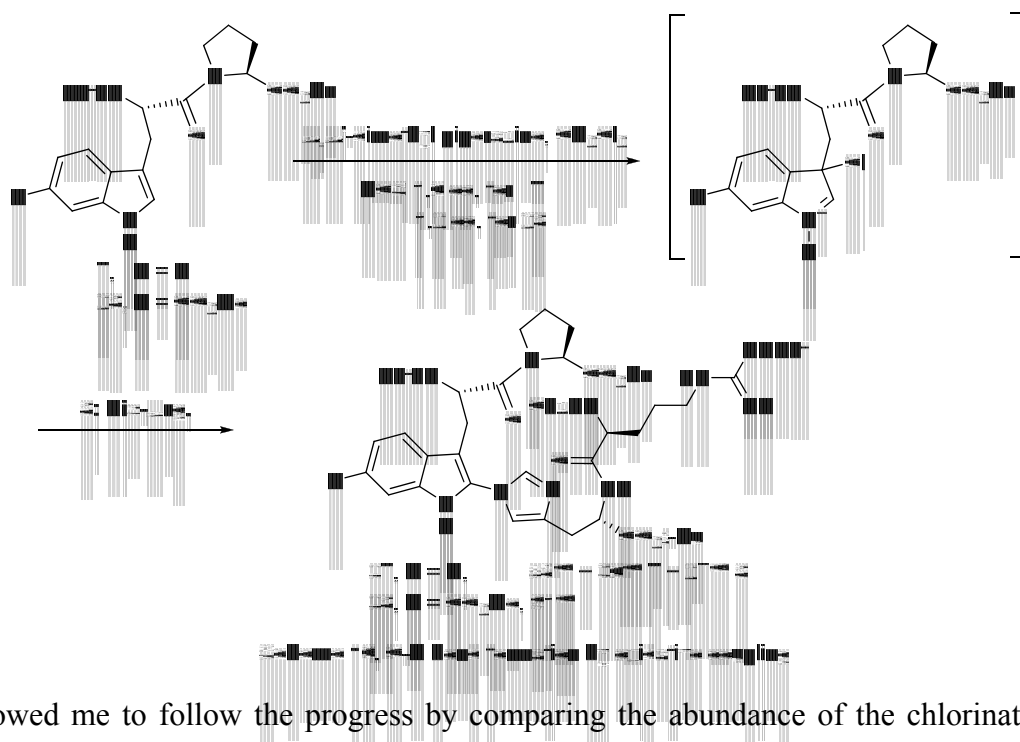


was achieved with an improved *tert*-butylation as the key step (**35** → **36**). Simple isobutene was applied instead of the *N,N*-diisopropyl-*O-tert*-butylisourea, whose synthesis required the strictly anhydrous *t*-BuOH.<sup>27</sup> Finally, normal amide bond

formation procedure afforded the His-Arg dipeptide (**8**) with a good yield.

#### 2.2.1.2.5. Synthesis of the methyl ester functionalized right-hand ring of celogentin C

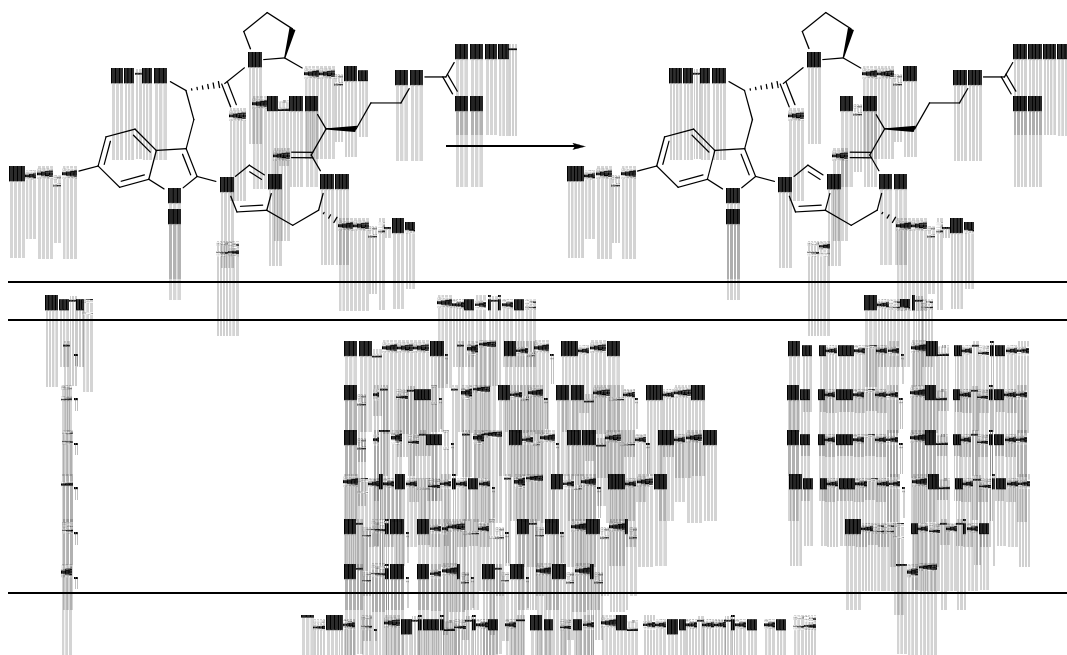
Oxidative coupling was one of the most important transformations toward the construction of the functionalized right-hand ring, which afforded a new carbon-nitrogen bond under extremely mild conditions (Scheme 10). The chemistry was discovered and optimized in the model right-hand ring synthesis,<sup>14</sup> in which case, 58% of the product (**37**) was achieved by using 1.0 equivalent of N-chlorosuccinimide, along with the recovery of 30% of **7** and 27% of **8**. It was also reported that excess amount of NCS resulted in the decline of the yield, presumably due to the propensity of **37** to react with NCS. In the work on substrate **28**, the progress of the oxidation step was monitored by mass spectrometry (MS). NCS was injected into the solution of **28** in CH<sub>2</sub>Cl<sub>2</sub> portionwise, instead of all at once. This



allowed me to follow the progress by comparing the abundance of the chlorinated

intermediate and the starting material by MS. On average, 1.2 equivalents of NCS realized complete conversion from **28** into the intermediate. Then, 91% of the desired product (**38**) was obtained after addition of dipeptide **8** to the reaction mixture.

Unexpectedly, the following cleavage of the benzyl ester and Cbz protecting groups did not proceed smoothly. The original transfer hydrogenation conditions, which worked very well in the model right-hand ring synthesis, only realized the Bn ester deprotection on substrate **38** (Entry 1, Table 3). Normal pressure and high pressure hydrogenation procedures were performed to give the same results. Another transfer catalytic hydrogenation by employing the 1,4-cyclohexadiene as the hydrogen source did not improve anything (Entry 4). The combination of Et<sub>3</sub>SiH and

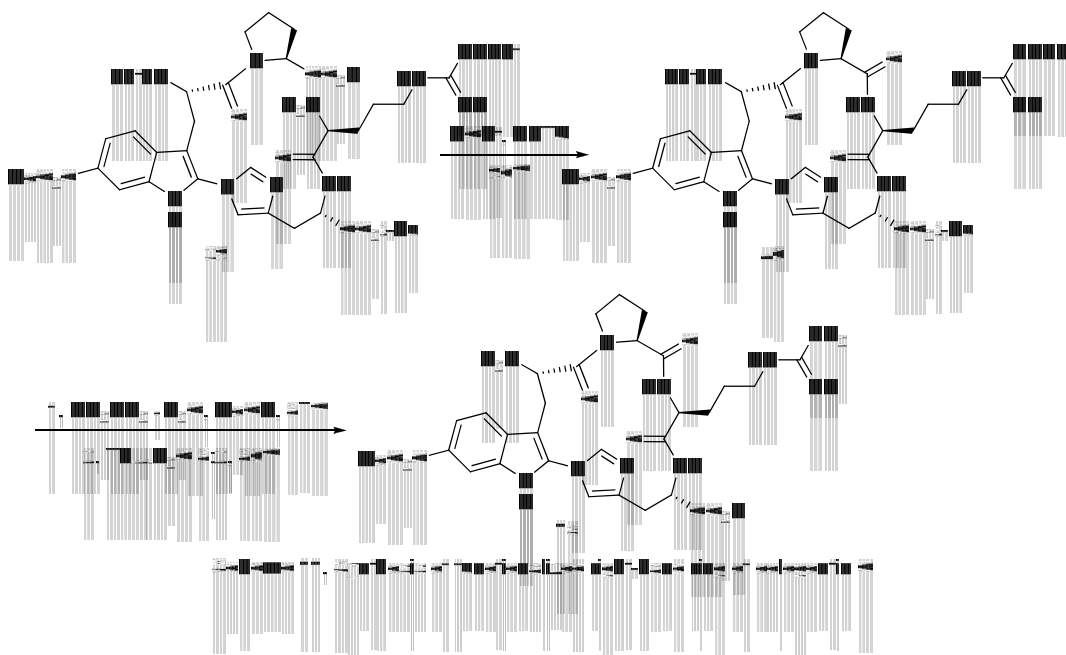


palladium catalyst has shown some applications in late stage reductive deprotections in total synthesis.<sup>29</sup> Thus, these reaction conditions were tested on **38** with Pd(OAc)<sub>2</sub> as the catalyst, which displayed a positive improvement by detecting the desired



product on MS and  $^1\text{H}$  NMR (Entry 5). However, the reaction was messy and hard to purify. Fortunately, a clean deprotection was finally accomplished by simply switching the catalyst to  $\text{PdCl}_2$ . Despite the significant polarity of the product **39**, it was still amenable to purification by flash chromatography. Comparing the structure of **38** and the corresponding intermediate in the model right-hand ring, it was really surprising that an extra substituent ( $-\text{CO}_2\text{Me}$ ), which was far away from the reaction centers, had such a profound effect on the reactivity.

Exposure of the dilute DMF solution of the acyclic precursor **39** to HOBt, HBTU and Hünig's base afforded a smooth macrolactamization, and the cyclic product **40** was isolated in 90% yield as a single isomer. The phthalimide protecting group was subsequently removed by treating **40** with a dilute solution of hydrazine in methanol. The functionalized right-hand ring of celogentin C was ultimately accomplished after the cleavage of the Pbf and *t*-Butyl groups. The reaction conditions ( $\text{TFA}/\text{H}_2\text{O}$  8:2) were previously developed by using simple His-Arg dipeptide **8**.



## 2.2.2 Synthesis of the left-hand ring of celogentin C

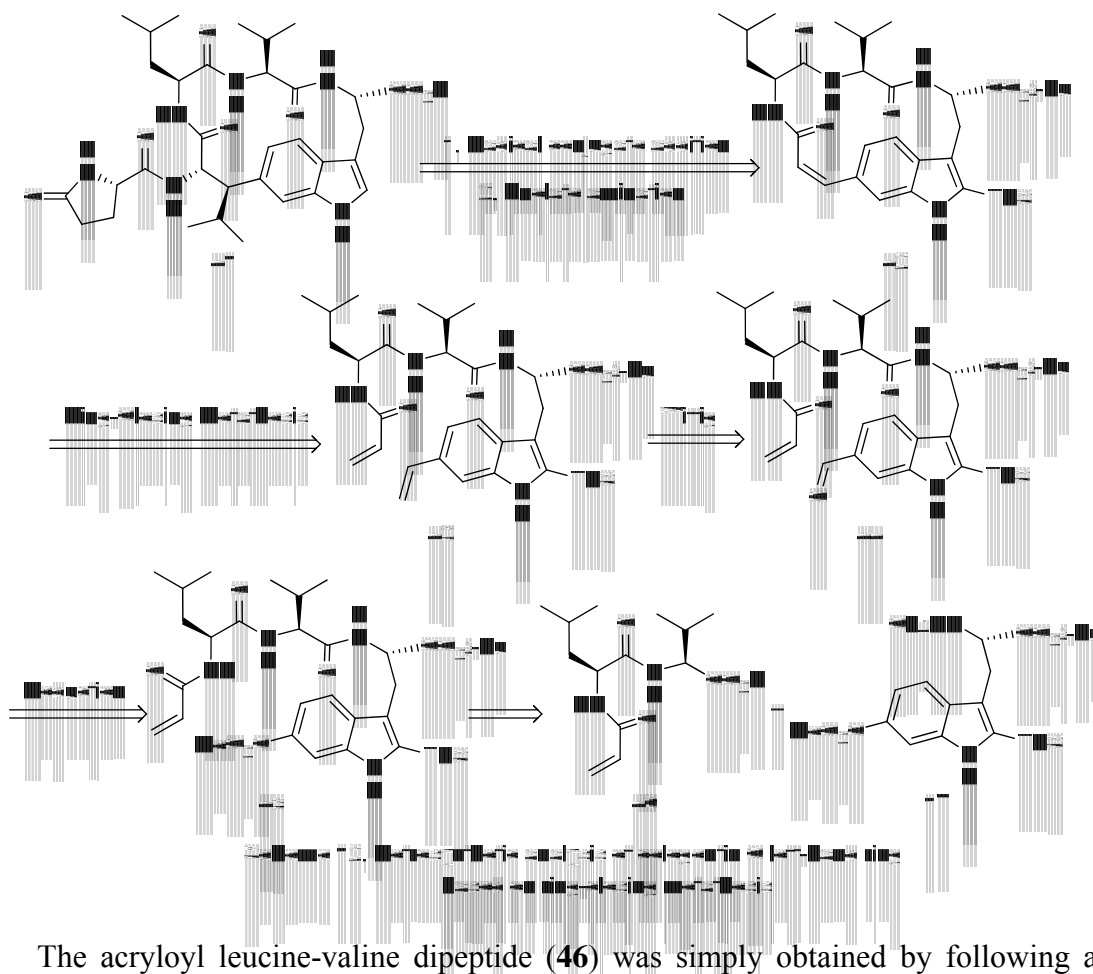
Upon the completion of the functionalized right-hand ring of celogentin C, effort was subsequently focused on the left-hand ring construction. Our initial approach toward the left-hand ring synthesis was developed based on an intramolecular Knoevenagel condensation, which requires a nitro substituted alkane and an aldehyde group at each end of the acyclic precursor.<sup>30</sup> During the process toward the acyclic precursor, we encountered a problematic nitro group installation from the corresponding alkyl halide by S<sub>N</sub>2 fashion<sup>30</sup> and a challenging aldehyde formation. In the end, this method was unsuccessful and a new synthesis was designed toward the left-hand ring of celogentin C.

### 2.2.2.1. Attempted synthesis of the left-hand ring by using ring-closing metathesis

#### 2.2.2.1.1. First generation approach based on ring-closing metathesis

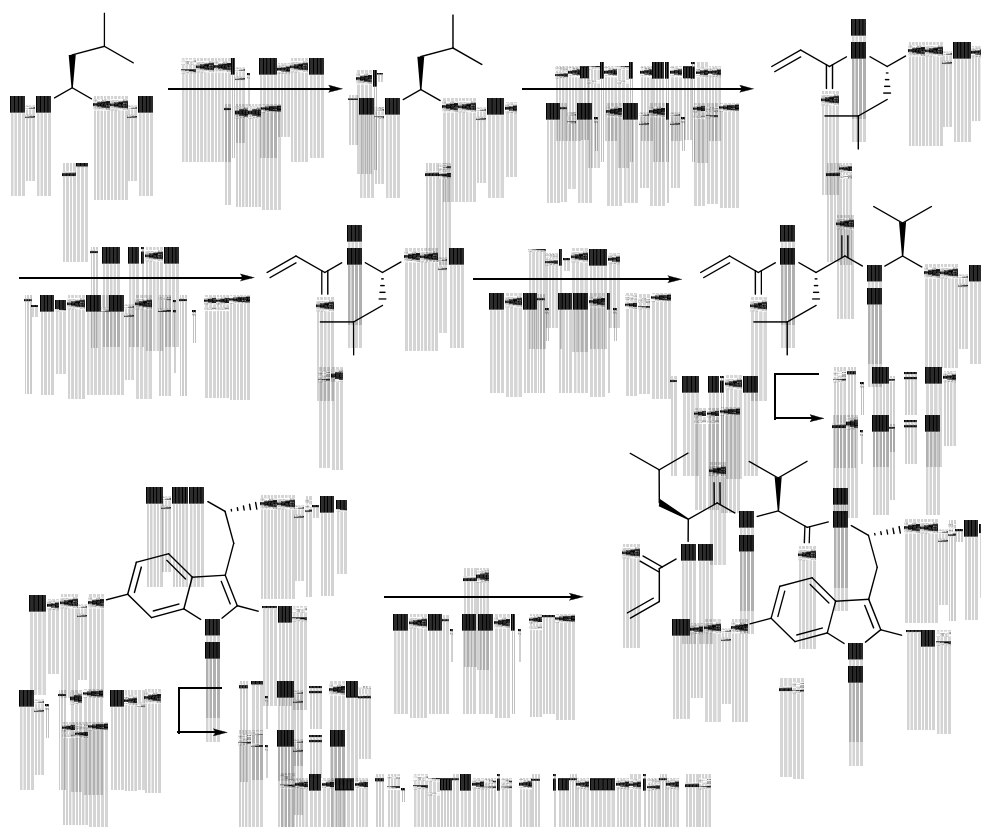
The retrosynthetic analysis is depicted in Scheme 12. The motif of the  $\beta$ -substituted amino acid in compound **41**, which is created by the bond between the indole C-6 of tryptophan and the leucine  $\beta$ -carbon, could be prepared from the  $\alpha$ ,  $\beta$ -unsaturated amide (**42**) by performing a radical conjugate addition,<sup>31</sup> followed by an enolate amination step.<sup>32</sup> The alkene part was proposed to be achieved by employing a ring-closing metathesis reaction on intermediate **43**, which should be available via a straightforward Wittig reaction and a methyl ester reduction from **45**. The left-hand ring molecule can ultimately be derived from two simple coupling partners, **46** and **17**. As discussed above, both methyl ester and hydroxymethyl

functionalized tryptophans (**1**, **17**) have been achieved. We selected **17** as the precursor, because it resembled the corresponding moiety of the functionalized right-hand ring compound (**15**). Thus, the developed conditions for the left-hand ring construction would be applicable to the total synthesis.

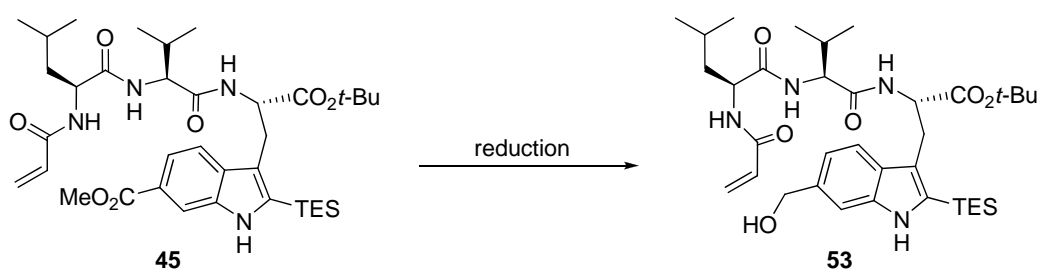


The acryloyl leucine-valine dipeptide (**46**) was simply obtained by following a straightforward route, displayed in Scheme 13. Initial attempts to install the acryloyl group onto the unprotected L-leucine did not afford any product. However, the same condition worked very well for the protected precursor (**48**). After hydrolyzing the methyl ester, valine was installed to generate **51**. At last, the methyl ester was cleaved to afford the carboxylic acid building block (**46**). Meanwhile, the deprotection was performed on substrate **17**, followed by the peptide coupling with

**46** to achieve the important intermediate **45**.



With compound **45** in hand, another crucial transformation would be the reduction of the methyl ester to the corresponding alcohol (**53**), which would be followed by an oxidation to **44**. Considering the direct connection of the methyl ester group to the



Entry	Conditions	Results
1.	1M DIBAL-H in toluene, CH <sub>2</sub> Cl <sub>2</sub> , -78 °C → rt	slow reaction, low yield
2.	NaBH <sub>4</sub> , MeOH/THF 1:1, 0 °C → rt	no reactions
3.	1M LiAlH <sub>4</sub> in Et <sub>2</sub> O, THF, 0 °C → rt	<b>45</b> consumed, no <b>53</b>
4.	LiBH <sub>4</sub> , THF, rt	<b>45</b> consumed, no <b>53</b>

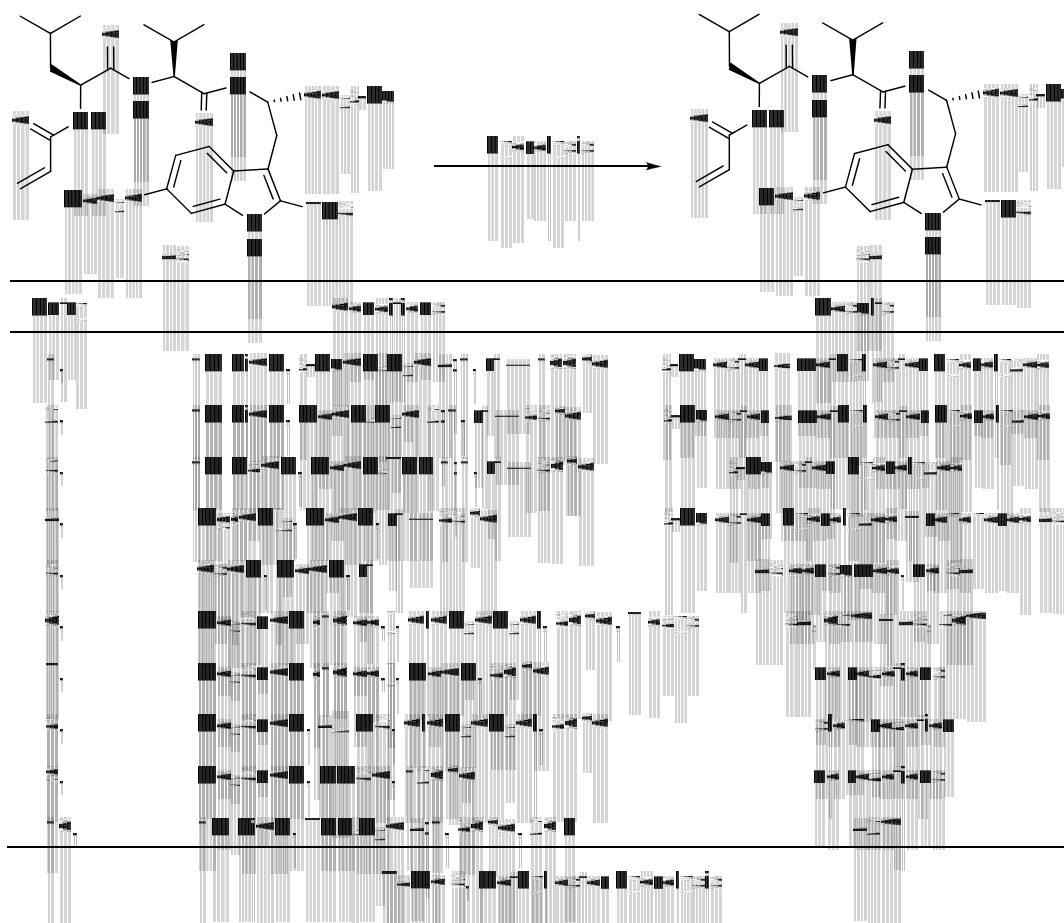
**Table 4.** Methyl ester reduction

electron-rich indole ring, a challenging reduction was anticipated. The DIBAL-H

reduction was initially carried out (Entry 1, Table 4),<sup>33</sup> with the product detected on MS, but not on TLC or NMR, which meant the abundance of the desired alcohol **53** was very low in the crude mixture. Even though most of the starting material retained under the original conditions, extending the reaction time or increasing the equivalents of the reducing agent did not deliver more product. Obviously, the corresponding aldehyde (**44**) was also involved as one of the targeted products. As expected, NaBH<sub>4</sub> was not reactive enough for the substrate **45** (Entry 2). Meanwhile, LiAlH<sub>4</sub> was strong enough to consume the precursor, which, unfortunately, afforded no alcohol or aldehyde (Entry 3). The same result was obtained with the application of LiBH<sub>4</sub> as the reagent. Failure of this transformation was presumably due to the competing side reactions: *t*-Bu ester reduction and acrylamide 1,4-reduction.

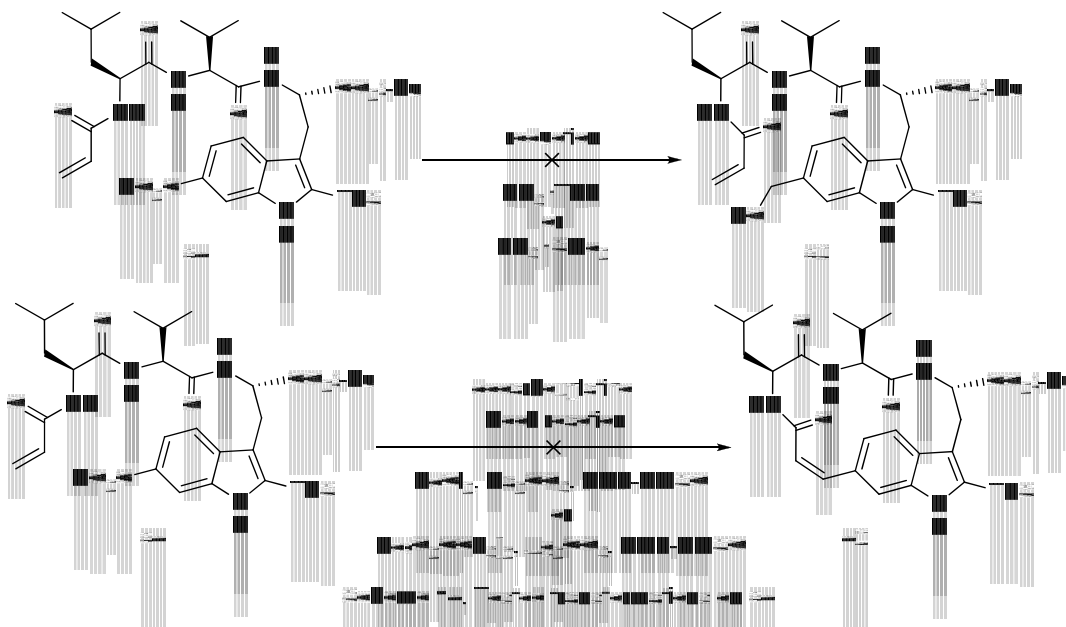
In view of the difficult reduction of the methyl ester in compound **45**, we decided to hydrolyze it to the free carboxylic acid **54** (Table 5), which would be converted to the aldehyde **44** by following an indirect method. Normal aqueous LiOH condition not only hydrolyzed the methyl ester, but cleaved the *tert*-butyl group at the same time (Entries 1 and 2, Table 5). The attempts under lower temperature (Entry 3) or weaker base (Entry 4) afforded the *t*-Bu ester removal only, which suggested a more reactive hindered *t*-Bu ester than an electron-rich methyl ester in this case. However, the strong base, CsOH, ended up with the degradation of the precursor without giving any product (Entry 5). Consequently, we continued to search for mild hydrolysis conditions for **45**, until the Me<sub>3</sub>SnOH reagent, developed by Nicolaou, came to our attention.<sup>34</sup> The desired product was finally detected by following

Nicolaou's conditions, which involved heating of the starting material with  $\text{Me}_3\text{SnOH}$  in 1,2-dichloroethane. However, the hydrolysis proceeded extremely slow. A seven-day reaction only afforded a 63% yield of the product with 36% recovery of the starting material, which demonstrated a very clean transformation with negligible side-reactions (Entry 6, Table 5). Efforts to speed up the hydrolysis failed without any improvement (Entries 7 – 9, Table 5). Surprisingly, the hydrolysis could also be achieved at modest yield by using  $\text{LiOH}$  as the base. However, it only worked in the THF/ $\text{H}_2\text{O}$  solution.



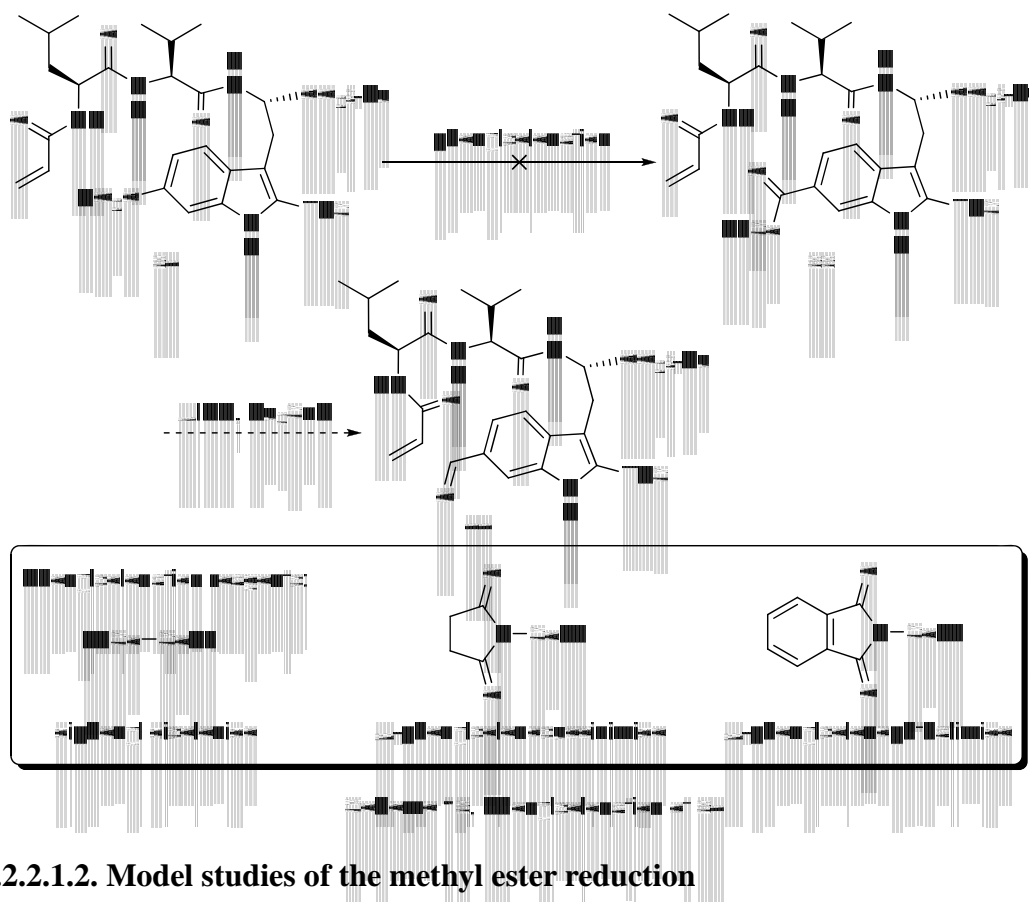
The carboxylic acid intermediate **54** was tested again in reduction conditions by using  $\text{BH}_3$  reagents.<sup>35</sup> No reactions occurred with all the starting material recovered (Scheme 14). After studying the structure of **54** and the cyclized intermediate **42**, we

realized that an elegant decarboxylative Heck reaction might find its application here in transforming **54** to **42** in one step. The intermolecular decarboxylative Heck reaction has been studied deeply by Gooßen<sup>36</sup> and Myers.<sup>37</sup> We envisioned a potential application of this chemistry on our substrate **54** in an intramolecular fashion, which has rarely been touched. Under Gooßen's conditions ( $\text{PdCl}_2 + \text{Na}_2\text{CO}_3$ ), **54** was all consumed without giving any desired product. Unfortunately, Myers' conditions ( $\text{Pd}(\text{O}_2\text{CCF}_3)_2 + \text{Ag}_2\text{CO}_3$ ) delivered the same result.



Another indirect pathway from the carboxylic acid **54** to the aldehyde **44** is shown in Scheme 15, which includes a phenylselenation, followed by a radical reduction.<sup>38</sup> Typically, the phenylselenation reaction requires an organoselenium species and a phosphine reagent. Three commonly used phenylselenation reagents, diphenyl diselenide,<sup>39</sup> *N*-phenylselenosuccinimide,<sup>40</sup> and *N*-phenylselenophthalimide,<sup>41</sup> were employed in the attempted formation of **55** from **54** with the presence of either  $\text{PBu}_3$  or  $\text{PPh}_3$ , which bore different properties in the phosphine  $\pi$  acidity. Unfortunately, the starting material was consumed, and no desired product was detected.

Presumably, the  $\alpha$ ,  $\beta$ -unsaturated amide in **54** had a tendency to react with the organoselenium intermediate.



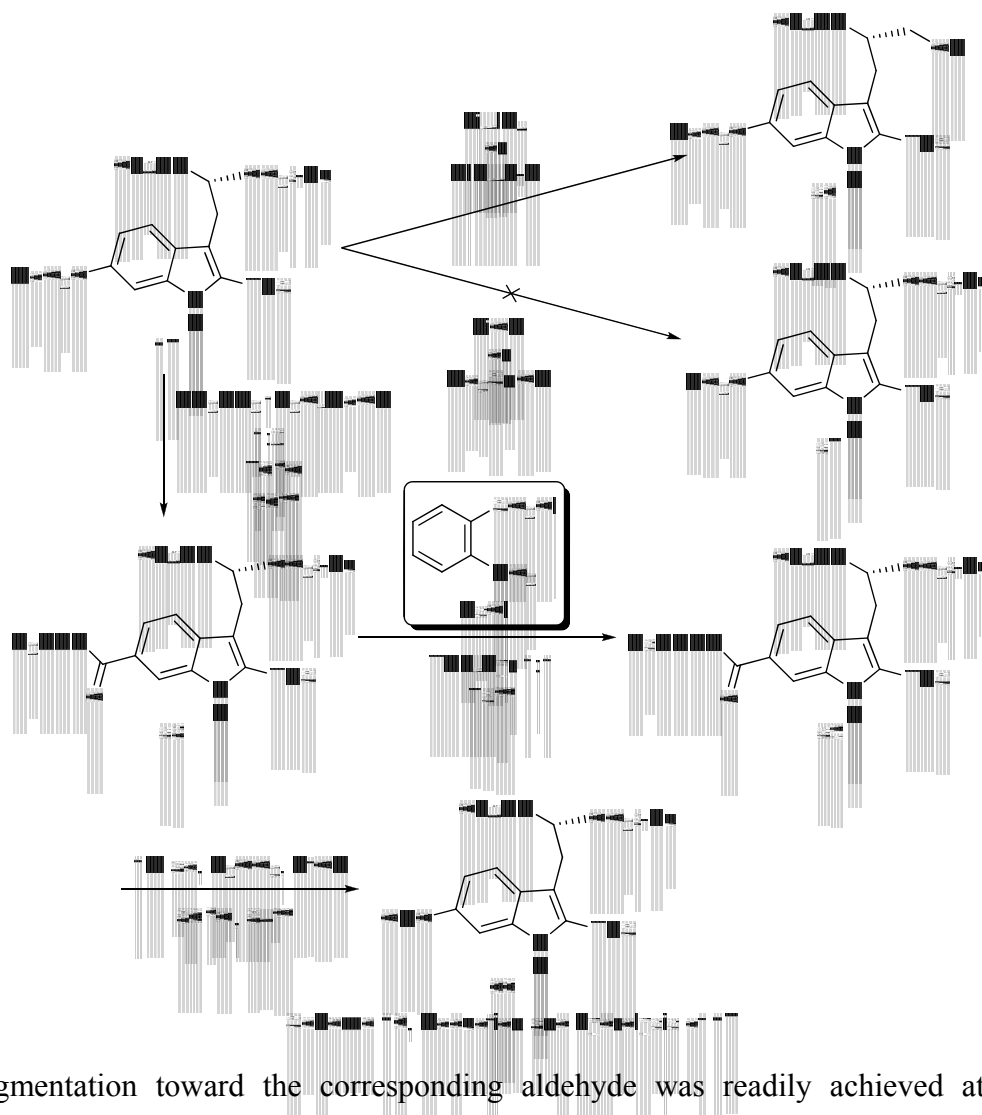
Based on the above results, we concluded that the transformation of the tryptophan C-6 methyl ester was very inert. Instead of using the precious intermediate **45** to investigate reduction conditions, simple tryptophan compound **17** was applied for a model study of the methyl ester reduction.

A direct reduction approach was initially tested on substrate **17**. Unexpectedly, the more hindered *tert*-butyl ester was reduced by using  $\text{LiAlH}_4$  or DIBAL-H, while the methyl ester was retained. Then, hydrolysis conditions were applied in order to obtain the free carboxylic acid product **57**. Aqueous  $\text{LiOH}$  converted the precursor into some unknown products, and  $\text{Me}_3\text{SnOH}$  removed the Cbz protecting group in



**17** without touching the methyl ester.

In 2002, the Braslau group developed modified conditions for the McFadyen-Stevens reaction, where a better leaving group, *ortho*-nitrobenzosulfonyl, was utilized instead of the traditional toluenesulfonyl group. Therefore, the final



fragmentation toward the corresponding aldehyde was readily achieved at low temperature.<sup>42</sup> This chemistry was subsequently tested on compound **17**. The first step of the McFadyen-Stevens reaction was the acyl hydrazine (**58**) formation. The reaction was strongly dependent on the concentration of the hydrazine solution in MeOH. Nothing happened on the substrate in dilute solution by using the conditions which worked for Braslau. However, in pure anhydrous hydrazine solution,<sup>43</sup> di-acyl

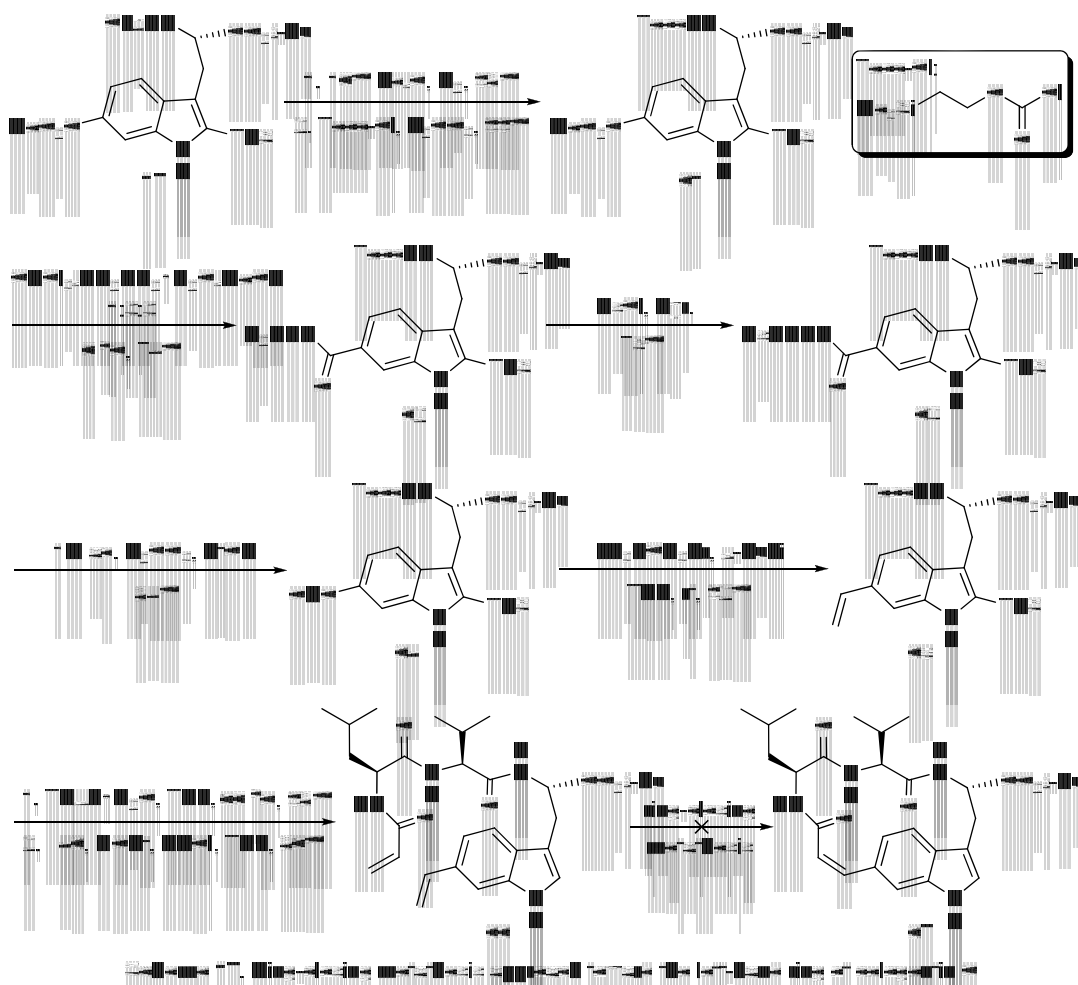
hydrazine was formed with the undesired loss of the *t*-Bu ester. The conditions of nosyl installation were also optimized, with the acyl hydrazine intermediate in THF/Pyridine (1:1) affording the best yield of the product **59**. The final fragmentation was performed in EtOH by using K<sub>2</sub>CO<sub>3</sub> as the base. As described above, with a better leaving group (nosyl) in substrate **59**, the product was achieved readily at a relative low temperature (80 °C vs. 160 °C for standard McFadyen-Stevens reduction). However, the reaction required a strict control of the concentration in order to achieve a good yield. According to my experience, 50 mg of **59** in 10 mL EtOH was the best condition.

#### **2.2.2.1.3. Second generation approach based on ring-closing metathesis**

As described above, the methyl ester reduction was eventually accomplished by applying the McFadyen-Stevens reaction. The overall yield was optimized to 57% over 3 steps (**17** → **60**). However, we envisioned some potential problems when we tried to apply this chemistry into the direct conversion from **45** to **44**. Typically, hydrazine is a strong nucleophile, which has a great possibility to react with the  $\alpha$ ,  $\beta$ -unsaturated amide part in **45**. Consequently, a second generation ring-closing metathesis based approach toward the left-hand ring of celogentin C was proposed (Scheme 17).

The Cbz protecting group was not suitable in the synthesis any more and had to be switched to something different, with 2-(trimethylsilyl)ethoxycarbonyl (Teoc) group as the best candidate. The Cbz cleavage of **17** was simply realized with nearly quantitative yield to afford the free amino intermediate, which was ready for the

installation of the Teoc protecting group. Teoc-Cl is widely used as the precursor for Teoc protection.<sup>44</sup> Nevertheless, Teoc-Cl was not commercially available, due to its poor stability. Thus, it has to be synthesized right before the consumption. An old method of Teoc-Cl synthesis required 2-trimethylsilylethanol as the starting material and phosgene as the reagent.<sup>45</sup> In 2004, Sekine developed a safe method for the



Teoc-Cl formation, where triphosgene was used in place of the dangerous phosgene.<sup>46</sup> Unfortunately, I could not obtain good yield (ca. 30%) and good purity by using triphosgene reagent, while dangerous phosgene afforded the product with 90% yield. Good ventilation and extra care were crucial for the safe performance. Finally, the Teoc protecting group was attached to the free amine intermediate with

99% yield to generate compound **61**. The three-step McFadyen-Stevens reduction was tested on substrate **61** for the synthesis of the aldehyde **64**. Fortunately, previously developed conditions helped to achieve the aldehyde with good overall yield. However, some racemization occurred somewhere during the three-step transformation, as **61** of > 90% ee was converted into **64** of 50% ee. Interestingly the enantiomeric purity was retained during the conversion from the Cbz protected tryptophan (**17**) to its corresponding aldehyde (**60**). Obviously, Teoc protecting group made the  $\alpha$  proton of tryptophan more acidic, so that the  $\alpha$  proton was very sensitive to bases. Three bases, hydrazine, pyridine, and  $K_2CO_3$ , were used respectively in the three-step McFadyen-Stevens reaction. In order to locate the problematic step, elaborate investigations were carried out. In the end, the racemization happened in the first acyl hydrazine formation step, where the solution of the starting material and hydrazine in MeOH was heated at 60 °C. Even room temperature was too high for this reaction. Eventually, the enantiomeric excess was retained at 0 °C without slowing down the reaction too much.

With the aldehyde (**64**) in hand, a Wittig reaction<sup>47</sup> was performed immediately to create a terminal olefin in compound **65**. The releasing of the Teoc protecting group required tetrabutylammonium fluoride as the reagent, which might remove the TES group as well.<sup>48</sup> The reaction at room temperature produced a complex mixture of the desired product and the partially deprotected intermediates. The trouble was readily overcome by increasing the reaction temperature to 60 °C. The side chain (**46**) was installed onto the tryptophan moiety under normal conditions. At this stage, two

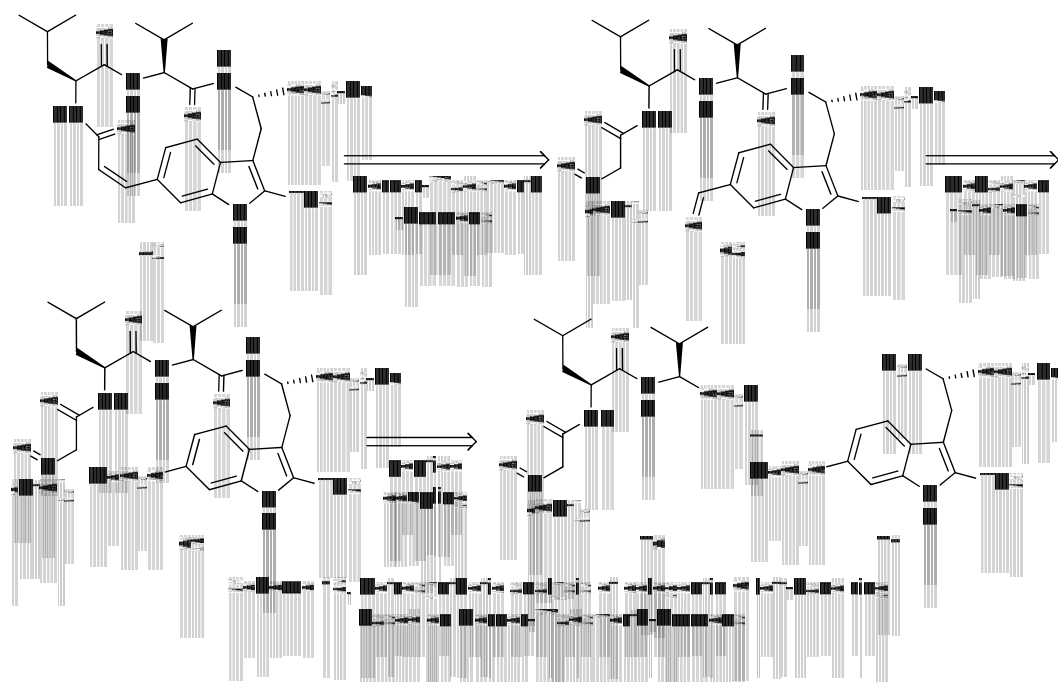
terminal alkenes were arranged on the desired positions. It was finally the time to test the ring-closing metathesis on substrate **66**.

The macrocyclization of **66** was tested by using Grubbs' second generation catalyst in different conditions.<sup>47, 49</sup> Usually, under low loading of the catalyst and low temperature, no reactions happened and the starting material was recovered. However, increased amount of the catalyst or high temperature partially consumed the precursor, in which cases no desired product was detected. Attempts to identify the unknown product failed to give any positive results. The macrocyclic peptide syntheses by using ring-closing metathesis normally generate the desired products in shorter synthetic sequences and higher yields. A wide application of this chemistry has been seen in literature in recent years.<sup>49, 50</sup> This was the reason for us to propose the left-hand ring synthesis by using ring-closing metathesis. However, the substrate we achieved contained an electron-deficient olefin ( $\alpha$ ,  $\beta$ -unsaturated amide), which was likely hard to bind with either the original Ru catalyst or the Ru intermediate. In fact, examples of metathesis on electron-deficient substrates are still rare,<sup>51</sup> not to mention applications in macrocyclic peptide constructions. Consequently, the electron-deficient alkene and the structure itself of **66** are two most likely reasons for the failure of the cyclization.

#### **2.2.2.2. Synthesis of the left-hand ring by using Horner-Wadsworth-Emmons olefination**

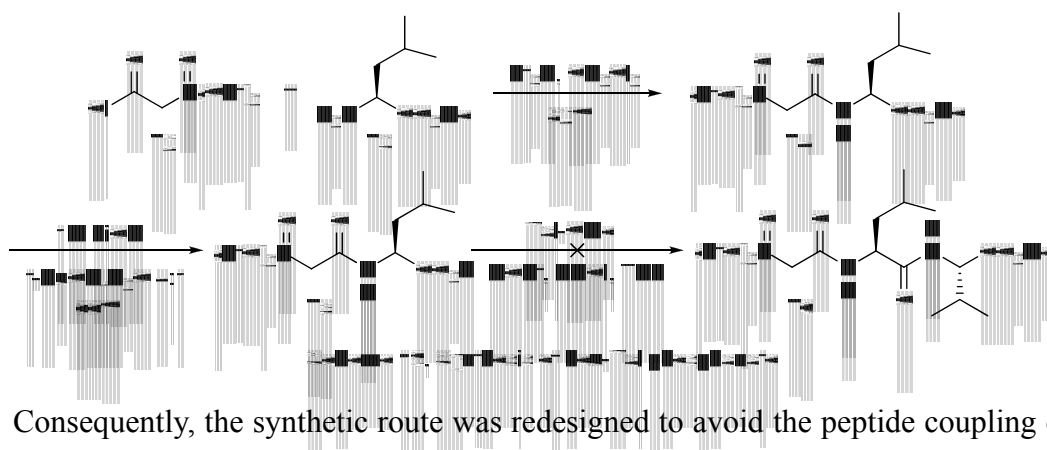
Horner-Wadsworth-Emmons olefination has proven to be highly effective in macrocycle formations.<sup>52</sup> We also envisioned a potential usage of this chemistry in

the left-hand ring synthesis. Based on the reactions we have discovered before, especially, the McFadyen-Stevens reduction, a second approach toward the left-hand ring was proposed in Scheme 18. Instead of using the ring-closing metathesis, the cyclic product **42** was supposed to be obtained by applying an intramolecular Horner-Wadsworth-Emmons olefination, which requires a phosphonate and an aldehyde group at each end of the substrate (**68**). The aldehyde group would be generated from the corresponding methyl ester (**69**) by following the McFadyen-Stevens procedures. At last, compound **69** would be easily synthesized from the Leu-Val phosphonate (**70**) and the tryptophan (**71**) precursors.



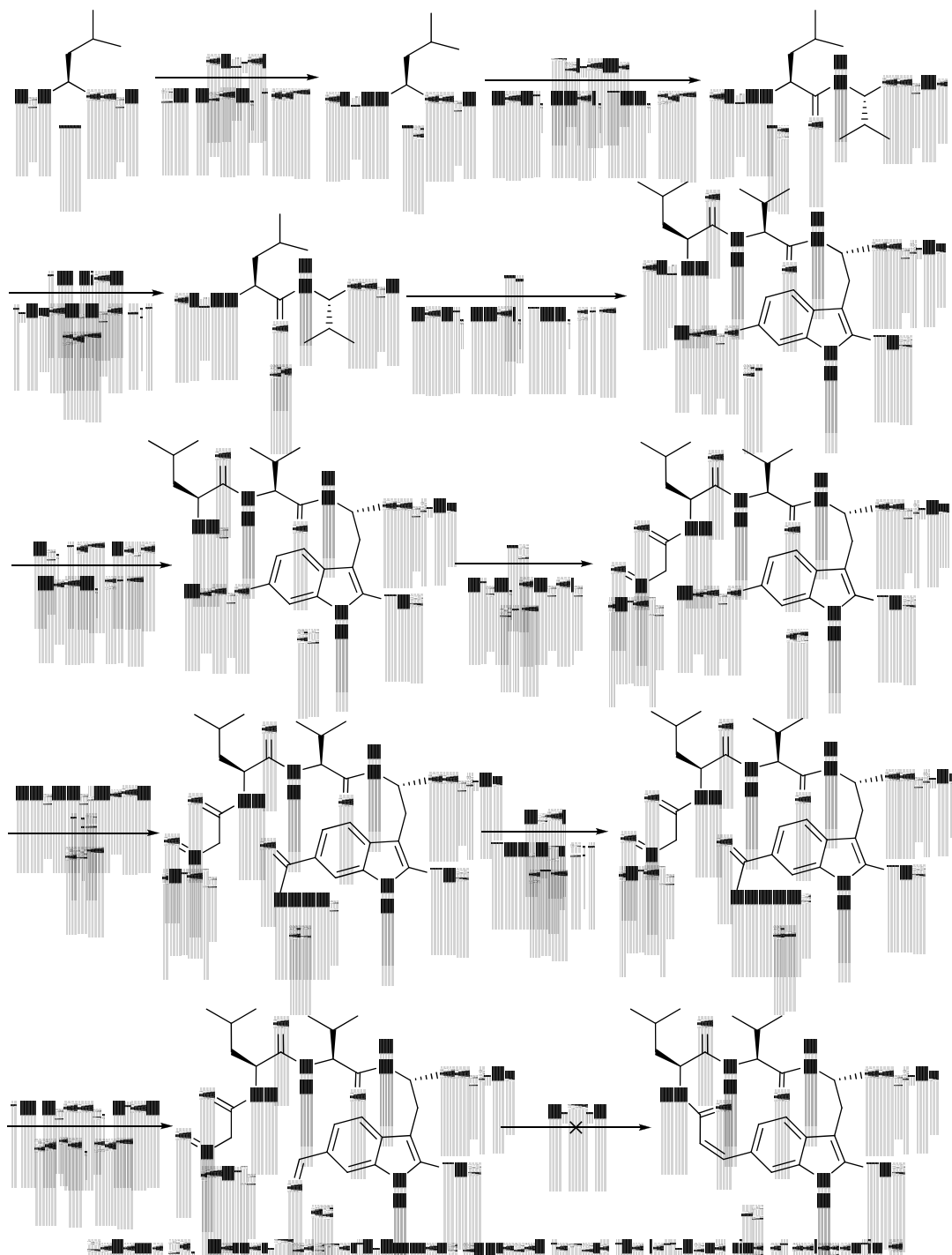
The synthesis of Leu-Val phosphonate began with amide bond formation between compound **72** and Leu-OMe. Traditional conditions<sup>53</sup> afforded the product **74** with good yield, which was hydrolyzed readily to give the carboxylic acid intermediate **75**. Unfortunately, the subsequent peptide coupling with Val-OMe afforded no product at all, with no starting material (**75**) recovered. Even though we had thought about the

problems of peptide coupling in the presence of phosphonate at the beginning of the synthesis, we still performed these reactions, because successful examples did exist in the literature.<sup>54</sup> However, we were not fortunate enough to realize the transformation in this case.



Consequently, the synthetic route was redesigned to avoid the peptide coupling on phosphonate-containing precursors, which required a later stage introduction of the phosphonate group (Scheme 20). The leucine protection was designed as the first step in the synthetic sequence. It (**78**) was accomplished by following a known procedure with quantitative yield.<sup>55</sup> Immediately, the Leu-Val dipeptide was formed after coupling with previously synthesized Val-OMe, which was subsequently submitted to the hydrolysis conditions to afford the corresponding acid (**80**). The tryptophan building block **71** was the product after deprotection of compound **17**, as described in the ring-closing metathesis derived left-hand ring synthesis. The intermediate **71** was coupled with the Cbz protected Leu-Val dipeptide, forming compound **81** with a very good yield. The amino group in **81** was released by catalytic hydrogenation, before coupling with the phosphonate acid chloride (**72**), where only a moderate yield was obtained. With a good amount of the product (**69**) obtained, the optimization of this transformation was not performed immediately.

Acyl hydrazine formation worked excellently on the phosphonate precursor. Fortunately, the other two steps in the McFadyen-Stevens reaction worked as well under previously developed conditions, and achieved the desired aldehyde (**68**) with good overall yield.



Typical intramolecular Horner-Wadsworth Emmons olefination conditions were



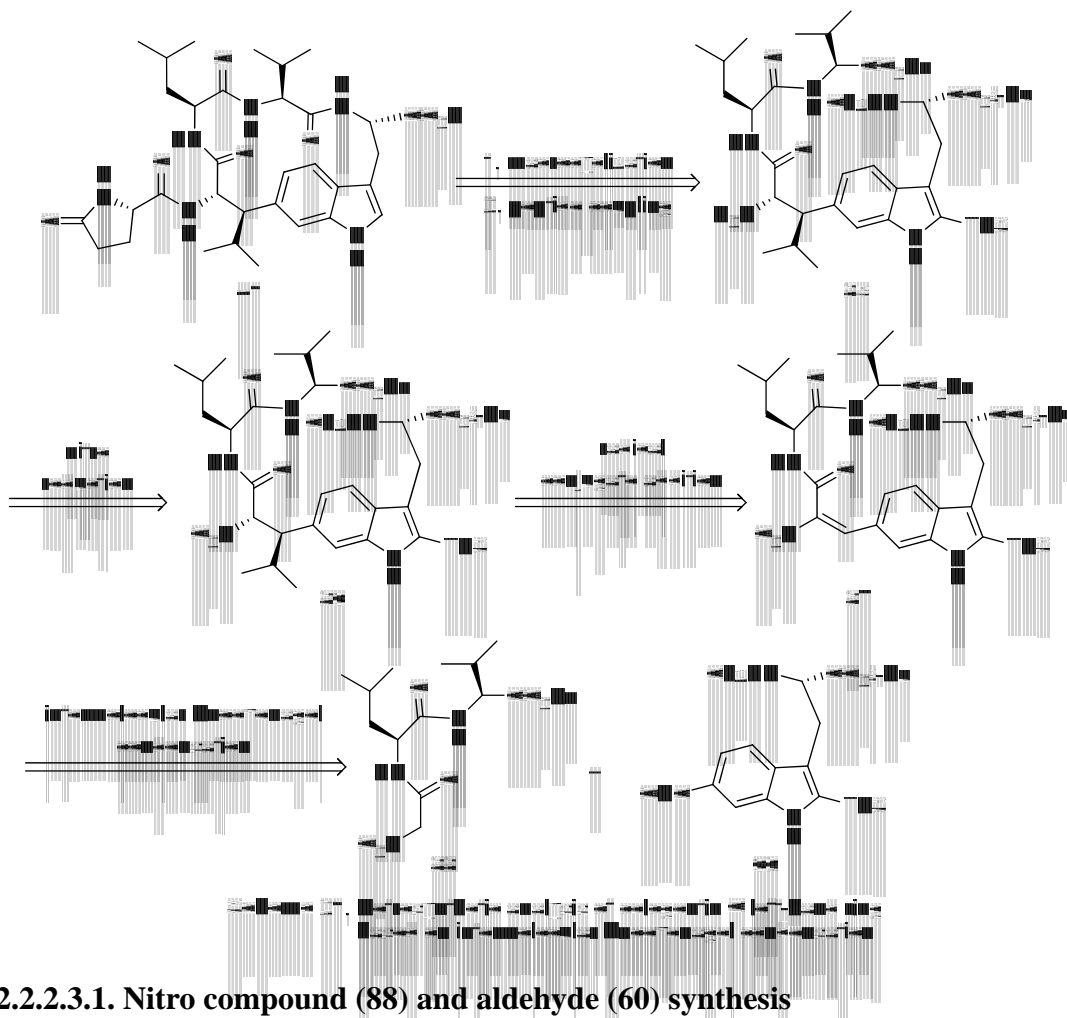
applied to aldehyde **68**, such as (1)  $K_2CO_3$ , 18-crown-6, toluene;<sup>54, 56</sup> and (2) LiCl, organic base, THF.<sup>57</sup> The results were very similar to the ring-closing metathesis chemistry. Under mild conditions, for example, low loading of reagents and low temperature, starting material was consuming slowly without delivering any desired product. Increased amount of the reagents and high temperature achieved nothing different, other than speeding up the consumption the substrate. In most cases, the crude mixture showed a streak upon TLC, instead of multiple spots, which suggested a degradation of the starting material. This assumption was proved from mass spectra, where only very low mass peaks showed up. Crude NMR spectra were messy with the loss of the aldehyde proton. Microwave heating has been introduced to the Horner-Wadsworth-Emmons olefination,<sup>58</sup> which helps to achieve a clean conversion in a short time. This might be a good alternative in the future.

### **2.2.2.3. Synthesis of left-hand ring of celogentin C by using intermolecular**

#### **Knoevenagel condensation**

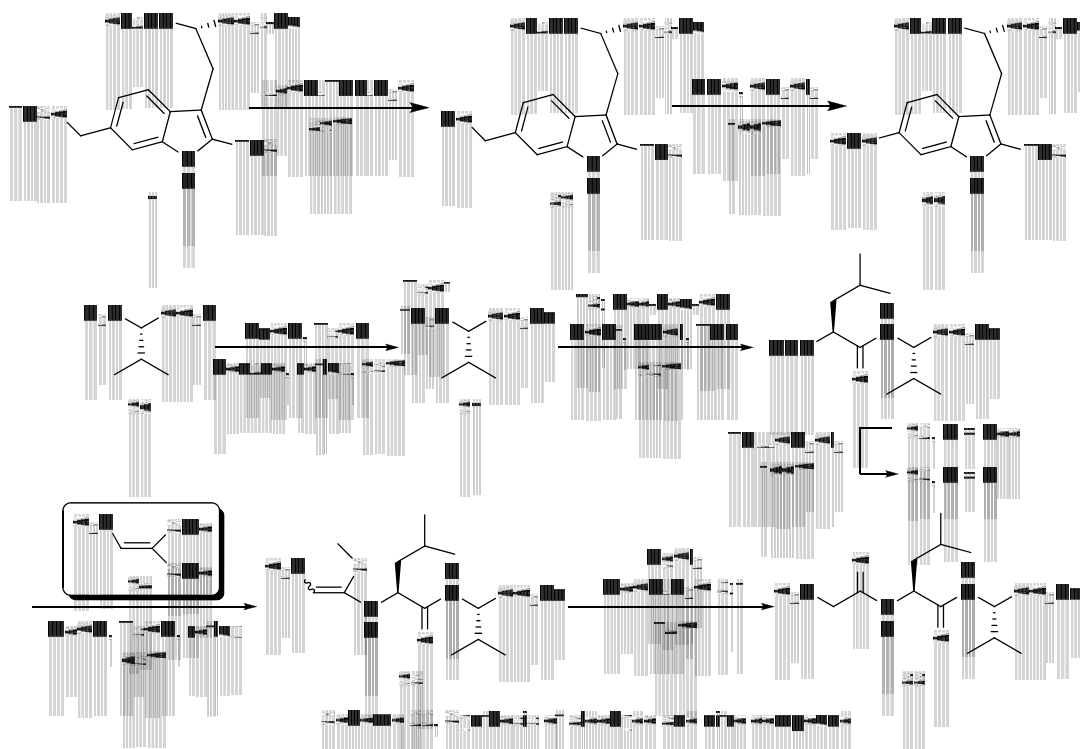
The failure of the left-hand ring constructions by employing decarboxylative Heck reaction, ring-closing metathesis and Horner-Wadsworth-Emmons olefination suggested either a long distance between the two ends of the acyclic precursors or a highly strained ring system with the presence of double bond. Consequently, the macrocyclization step was switched to a different position, and another synthetic route was generated based on the intermolecular Knoevenagel condensation and radical conjugate addition. The retrosynthetic analysis is depicted in Scheme 21. The amide bond between valine-tryptophan in the left-hand ring structure (**41**) would be

formed from the acyclic precursor, and the pyroglutamic moiety would be introduced by a peptide coupling. The amino group in **85** would require the nitro compound **86** as the precursor, in which the isopropyl group could be introduced by applying an asymmetric radical conjugate addition from **87**. At last, the assembly of the left-hand ring would rest on two major building blocks: nitro substituted Leu-Val dipeptide **88** and the aldehyde-functionalized tryptophan **60**.



The aldehyde-substituted tryptophan (**60**) was one of the major starting materials in the synthesis, which was previously obtained after the reduction from the corresponding methyl ester **17** by using McFadyen-Stevens reaction (Scheme 16). However, if we simply focus on achieving a large amount of the aldehyde, there is

another more efficient alternative, which is displayed in Scheme 22. The conversion from compound **1** to **60** only required two high-yielding reactions: the deprotection and the oxidation. The *tert*-butyldimethylsilyl group was selectively removed by applying Paquette conditions,<sup>59</sup> without cleavage of the triethylsilyl moiety. The subsequent oxidation was accomplished under a variety of conditions, with DDQ affording the best yield, mildest conditions and easiest purification.<sup>60</sup> The synthesis



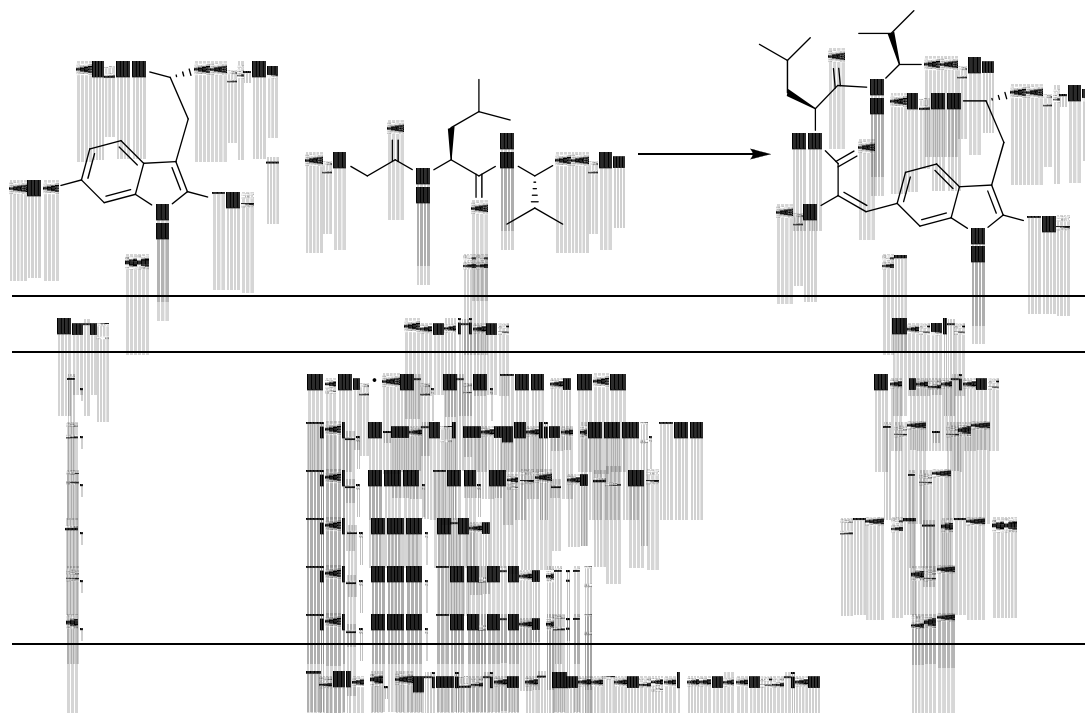
of the nitro substituted Leu-Val dipeptide required compound **93** as the key intermediate, which was synthesized by following the known procedures.<sup>61</sup> Direct S<sub>N</sub>2-type nitro group installation from the corresponding halides was always troublesome, due to the competing nitrite ester formation.<sup>30</sup> Consequently, nitro group introduction was performed based on Rajappa's methodology,<sup>62</sup> with the coupling of the free amine (**93**) and the commercially available dithioacetone acetal (**94**) as the first conversion. Interestingly, only one isomer of the vinyl sulfide **95** was

obtained based on the NMR spectrum. However, we did not try to identify the exact configuration. Eventually, product **88** was obtained after exposing **95** to mercuric chloride with good yield. This reaction was amenable to large scale synthesis (2.5 g).

#### 2.2.2.3.2. Model left-hand ring synthesis

The optimization of the following Knoevenagel condensation is listed in Table 6. In order to achieve a mild transformation from complex starting materials, Lewis acids were selected to facilitate the condensation. Magnesium bromide was initially tested on the substrates in different solvents.<sup>63</sup> Recovered starting materials (**60** and **88**) indicated that MgBr<sub>2</sub> was not a strong enough Lewis acid in this case (Entry 1, Table 6). Consequently, a stronger Lewis acid, TiCl<sub>4</sub>,<sup>64</sup> was introduced to the reaction, which consumed all the starting materials and afforded the desired product fortunately (Entry 2, Table 6). However, the product **96** could not be synthesized with a stable yield by following these conditions, as the yield ranged from 15% to 50%. Efforts were then focused on the optimization of the TiCl<sub>4</sub>-initiated condensation, after negligible improvement by using further purified aldehyde and nitro compound. MgSO<sub>4</sub> and 4Å molecular sieves were firstly applied to facilitate the dehydration step, which only resulted in low yields. A very good yield based on recovery of the starting material was obtained by switching the solvent to diethyl ether, which could not dissolve both starting materials very well and significantly slowed down the reaction (Entry 4, Table 6). Considering the poor solubility and the side reaction suppression in ether, a mixture of THF-ether was proposed to achieve a fast conversion and a high yield at the same time. THF-ether 1:1 mixture

immediately afforded the desired product with 65% yield (Entry 5), while a 2:1 mixture even increased the yield to 80% in small scale reactions (ca. 30 mg of **60**). At 400 mg scale, the reaction could be repeated with 68% yield.



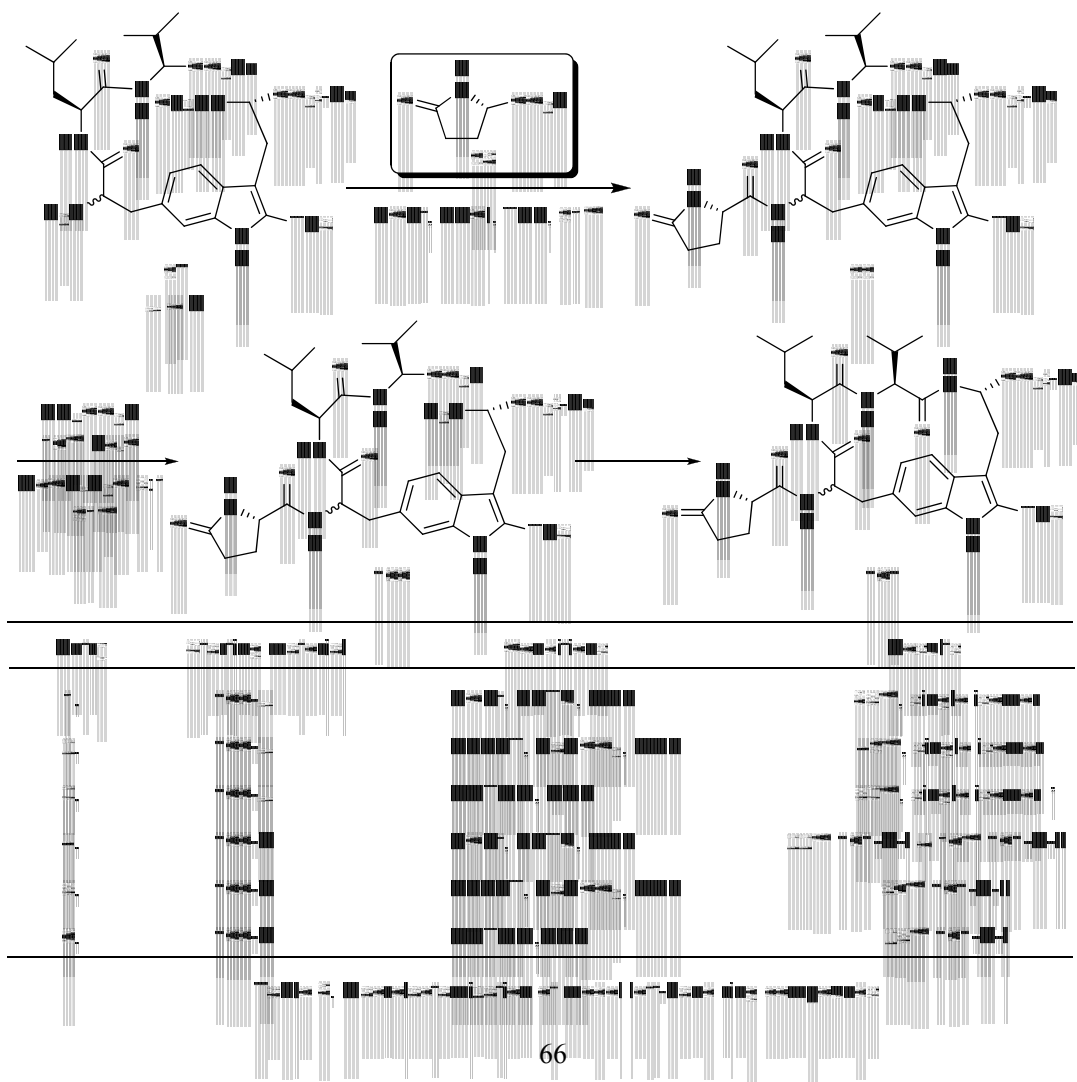
Based on the retrosynthetic analysis in Scheme 21 (**87**  $\rightarrow$  **86**), the following transformation would be the installation of the isopropyl group by using a radical conjugate addition to selectively construct two stereocenters, which would be a very challenging reaction. Due to so many failed attempts toward the left-hand ring of celogentin C, a simple double bond reduction of **87** would be performed to try and synthesize a model left-hand ring first.

The reduction was readily accomplished by using  $\text{NaBH}_4$ ,<sup>65</sup> because of the electron-deficient property of the double bond. However, two isomers (**96**) were generated, which were not separable at this stage. The investigation of the aliphatic nitro group reduction to the free amine (**96**  $\rightarrow$  **97**) is summarized in Table 7. Indium metal was tested under  $\text{HCl}$ <sup>64, 66</sup> or  $\text{AcOH}$  conditions (Entry 1, Table 7), and afforded



$\text{SmI}_2$ ,<sup>70</sup> came to our mind. After treating compound **96** with  $\text{SmI}_2$  in THF-MeOH solvent mixture, the desired product was immediately detected as the major compound. Further optimization afforded the amino compound **97** with 91% yield. Two isomers, named **97-A** and **97-B**, were separable at this stage with nearly equal amounts.

(*S*)-pyroglutamic acid was coupled with both isomers of **97** to form **99** with good yield, which was subsequently subjected to the transfer hydrogenation conditions toward compound **100**. The macrocyclization was initially tested on isomer **100-A** by using HOBt and HBTU in the DMF solution (Entry 1, Table 8), which were successful conditions in the right-hand ring construction. Fortunately, a very good

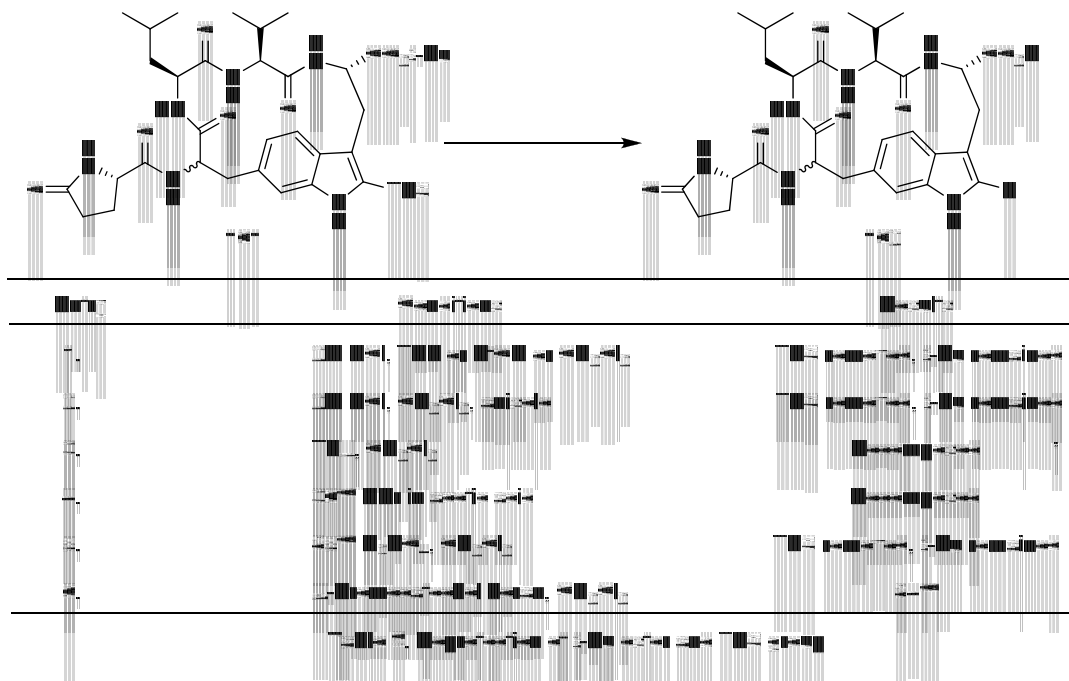


yield of a single isomer was achieved. Some other peptide coupling reagents, such as DEPBT<sup>71</sup> and DMTMM<sup>72</sup>, were investigated and afforded the same isomer with moderate yields. However, the cyclization of the other isomer (**100-B**) was more complicated. After treating with HOBt and HBTU (Entry 3, Table 8), the crude NMR clearly demonstrated a mixture of several isomers, in spite of the clean mass spectrum. The cyclic compounds were detected in two close spots on the TLC plate, which suggested two isomers (**101-B-I** and **101-B-II**) were produced after the macrolactamization. According to the mechanism of peptide coupling, it is likely that the valine  $\alpha$ -stereocenter was racemized to release the hindrance of the ring system. Surprisingly, different major isomers were isolated at moderate to poor yields when DEPBT and DMTMM were employed as the coupling reagents respectively (Entries 5 and 6, Table 8).

The deprotection of the *tert*-butyl ester and the triethylsilyl group to afford the model right-hand ring product was subsequently carried out, which unexpectedly proved to be another big challenge (Table 9). Simple aqueous HCl<sup>73</sup> was initially tested in different solvents, with only the removal of the TES group observed by MS. The retained *t*-Bu group was either not cleaved at all or recaptured by the product, in view of the powerful electrophilicity of the *t*-Bu cation. Thus, anisole was introduced to the reaction as a nucleophilic scavenger (Entry 2). The same deprotection outcome suggested a stable *t*-Bu ester in molecule **101**. On the other hand, stronger acidic conditions, such as TFA<sup>74</sup> and 30% HBr in AcOH<sup>75</sup>, destroyed the starting material. Another mild reagent, *B*-bromocatechol boran (BCB), came to our mind eventually,



which was successfully used in Boger's vancomycin synthesis.<sup>76</sup> Fortunately, a clean cleavage of both protecting groups was finally accomplished after treating with *B*-bromocatechol boran in CH<sub>2</sub>Cl<sub>2</sub> at room temperature (Entry 6).

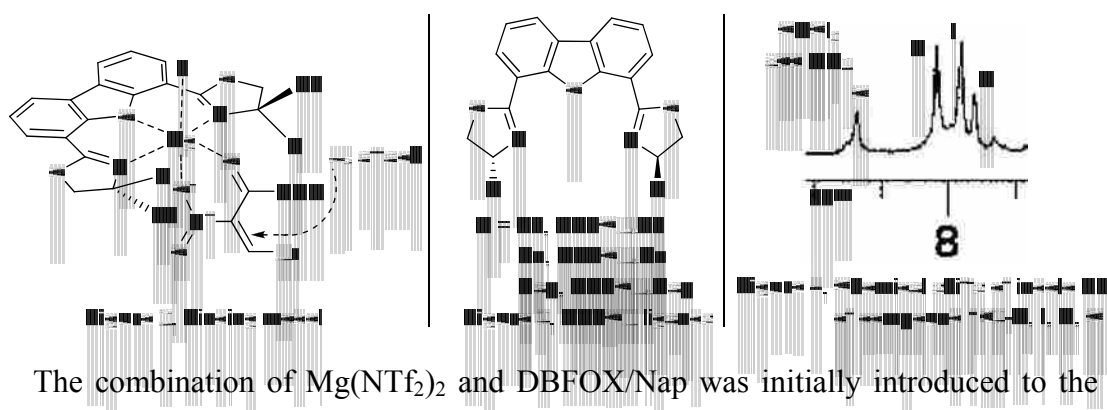


Even though the late stage macrolactamization of isomer **100-B** was still troublesome, we achieved the model left-hand ring synthesis by following the synthetic route based on the intermolecular Knoevenagel condensation. The model studies not only demonstrated a potential approach for the construction of the left-hand ring of celogentin C, but called to our attention the racemization issue during the cyclization.

#### 2.2.2.3.3. Radical conjugate addition and left-hand ring synthesis

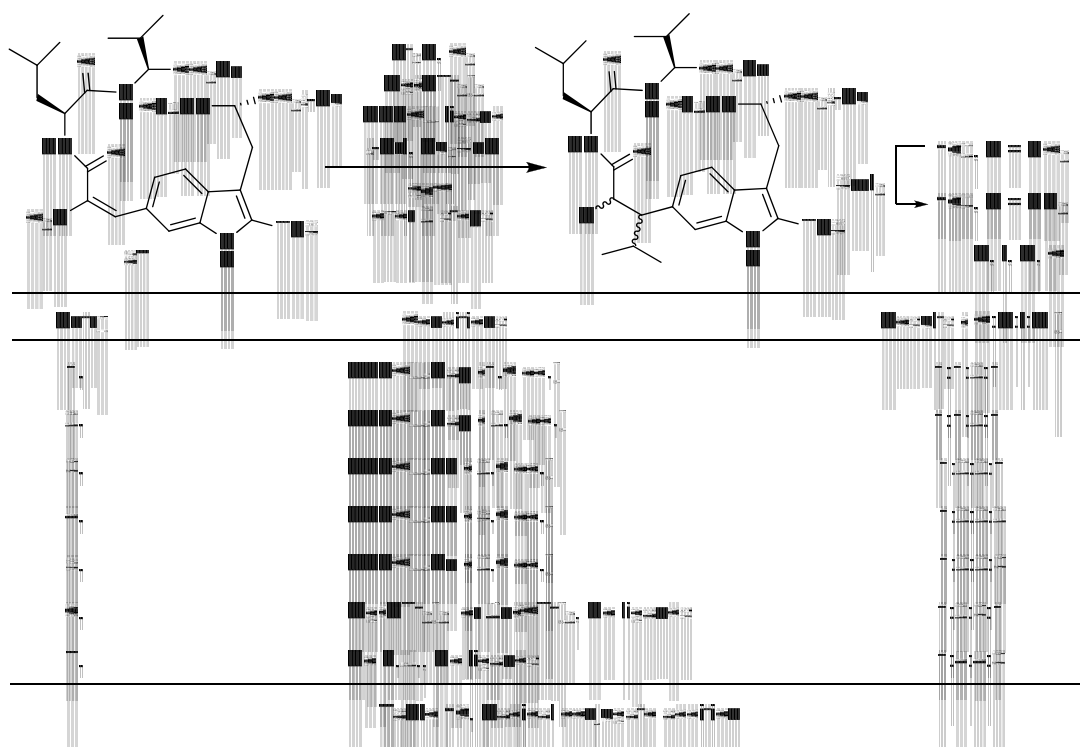
As described before, according to the structure of the left-hand ring of celogentin C, a radical conjugate addition would be carried out to install the *iso*-propyl group onto the Knoevenagel condensation product (**87**), while generating two stereocenters in compound **102** at the same time, as illustrated in Table 10. Considering the

potential racemization of the highly acidic nitro  $\alpha$ -proton in **102**, the intermediate would be immediately reduced to the corresponding amino product **103** by using the previously developed  $\text{SmI}_2$  conditions. The proposed chemistry for delivering the desired stereogenic outcome of the radical conjugate addition is explained in Figure 2. The magnesium Lewis acid binds with the DBFOX ligand and substrate **87**, which directs the radical addition and the subsequent hydrogen atom extraction to the *Si* face, and eventually releases the product with the desired stereochemistry. This binding model was developed based on previous studies of this chemistry using simple and similar precursors in our group, in which cases excellent enantioselectivity and moderate diastereoselectivity were achieved.<sup>64,77</sup> Three ligands, DBFOX/Ph, DBFOX/Bn, and DBFOX/Nap, exhibited the best performance in the model studies, and would be tested in the radical reaction on compound **87**.



The combination of  $\text{Mg}(\text{NTf}_2)_2$  and DBFOX/Nap was initially introduced to the reaction toward **102**. Immediately after a nitro group reduction by using  $\text{SmI}_2$ , the corresponding amine (**103**) was obtained with a high yield (90%), which showed as a four-isomer mixture (**103-B, I, N, G**) on the crude NMR spectrum (Entry 1, Table 10). The separation of these four isomers was very challenging, due to the close  $R_f$  values and long elliptical spots on TLC plates. Consequently, the rough ratio of these

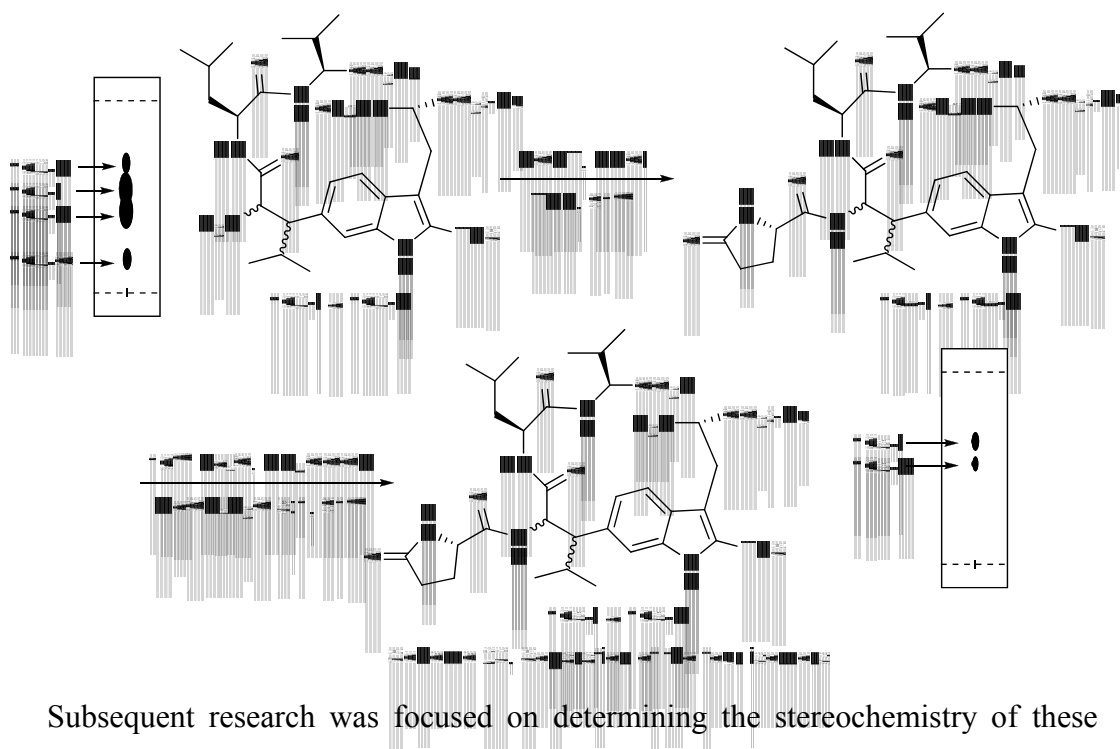
isomers was determined based on the NMR spectra, where indole N-H showed distinct chemical shifts for different compounds (Figure 4), according to which, a ratio of **G/N/I/B** 1:1:2:1 was obtained in Entry 1. Excess DBFOX/Nap ligand and Mg(NTf<sub>2</sub>)<sub>2</sub> failed to improve the ratio (Entry 2, Table 10). Similar ratios were achieved by using DBFOX/Ph ligand at either two or five equivalents of loadings (Entries 3 and 4, Table 10). Interestingly, isomer **B** was produced as the major isomer from the radical reaction with the presence of the DBFOX/Bn ligand. Poor stereoselectivity suggested that the DBFOX–Mg complex might not bind with the substrate (**87**) very well, because of its bulky structure. An easy way to verify the assumption was to carry out the reaction without any ligands, which afforded very similar ratios with increased amount of isomer **I** (Entry 6, Table 10). Eventually, the blank reaction with similar selectivity result (Entry 7, Table 10) cast doubt on the



proposed binding model with our compound (**87**) and determined the simple

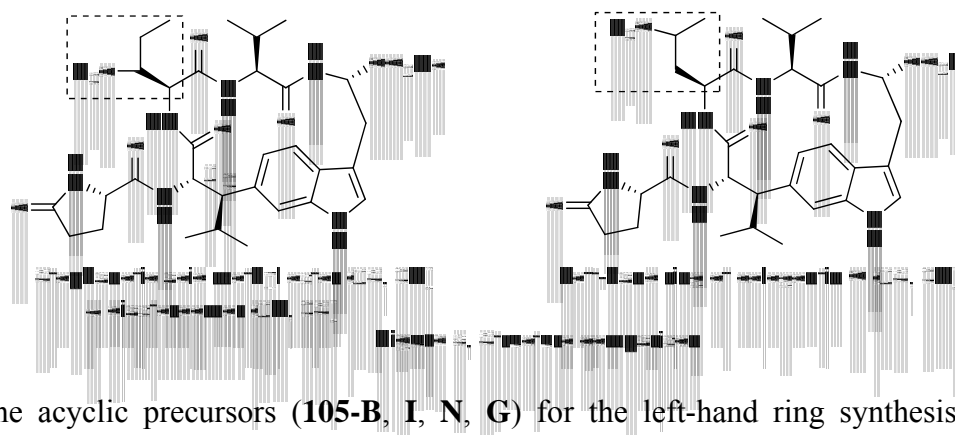
substrate control in the transformation. The most abundant of the four isomers in any reactions is **I** from entry 6.

Despite the poor stereoselectivity in synthesizing compound **103**, further efforts were put into the separation and identification of the desired isomer. Flash chromatography succeeded in isolating **103-B** and **103-G**, while isomers **103-I** and **103-N** were afforded as a mixture (see TLC in Scheme 23). The mixture of **I** and **N** was still too close to be separated after the installation of the pyrrolidinic moiety. Fortunately, after the removal of the protecting groups, compounds **105-I** and **105-N** were both achieved as single isomers.



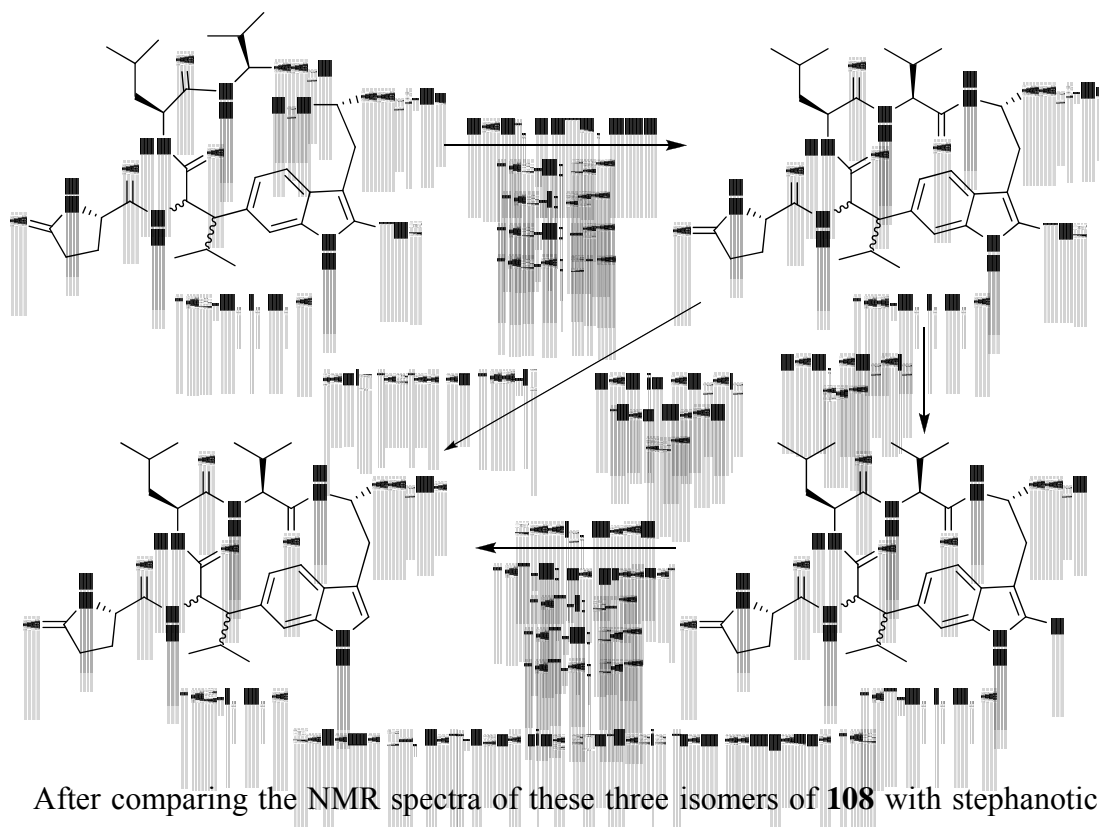
Subsequent research was focused on determining the stereochemistry of these isomers. In 2006, the Moody group accomplished the total synthesis of stephanotic acid methyl ester, in which case the natural product and its diastereomer were synthesized (Figure 5).<sup>78</sup> Considering the similar structures and the same stereochemistry of stephanotic acid methyl ester and the left-hand ring of celogentin

C, we envisioned a straightforward way to figure out the desired isomer. Once the cyclic product was obtained from each isomer of compound **103**, the stereochemistry could be assigned by comparing with Moody's data for the natural product and the diastereomer.

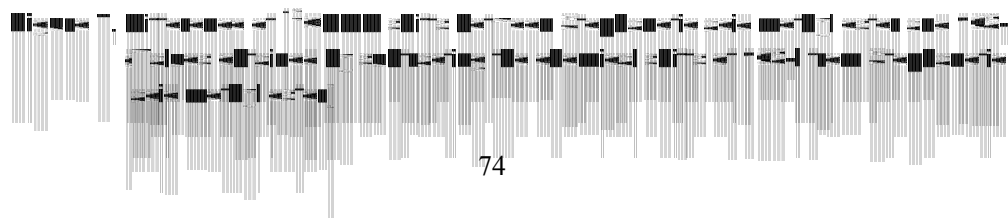
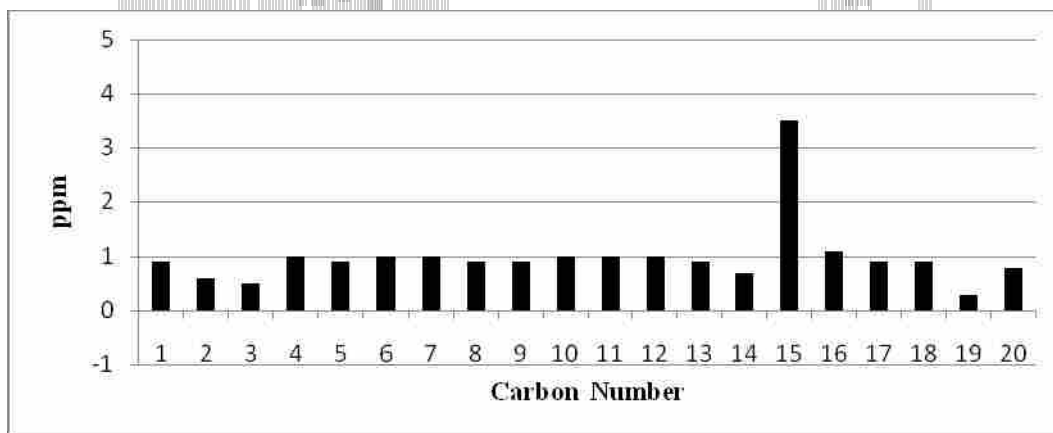
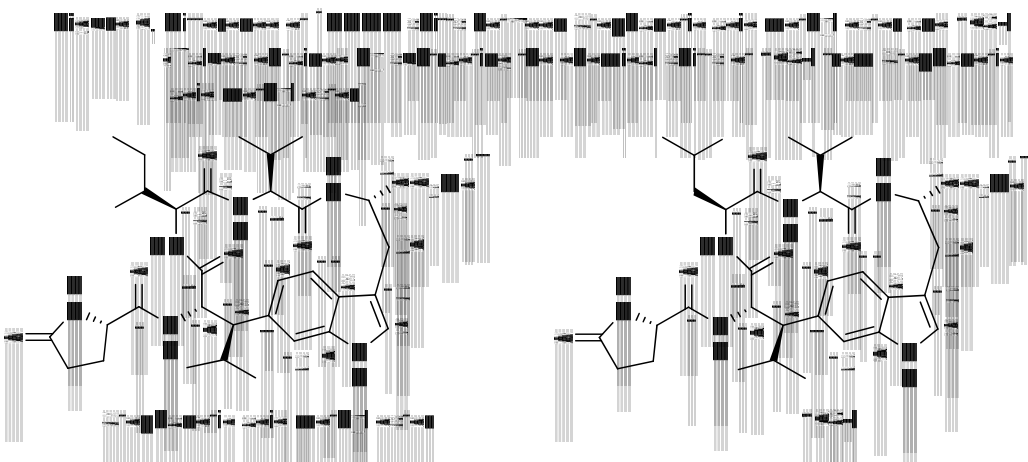
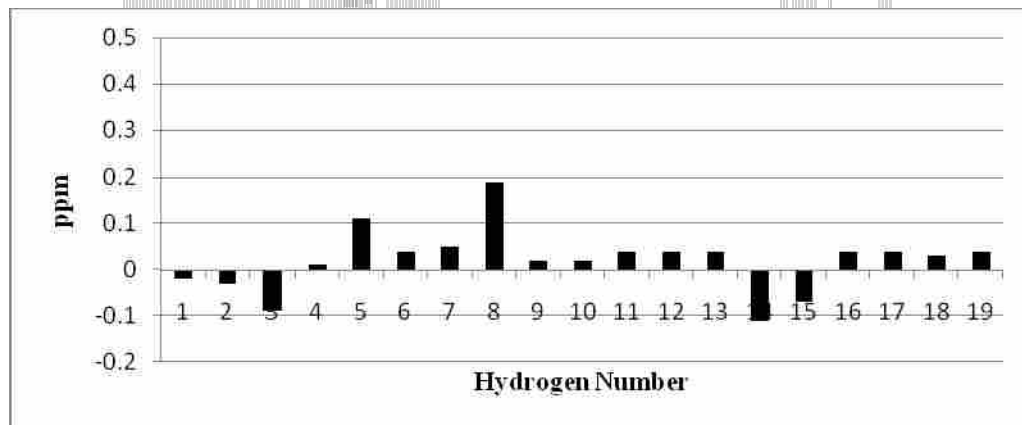
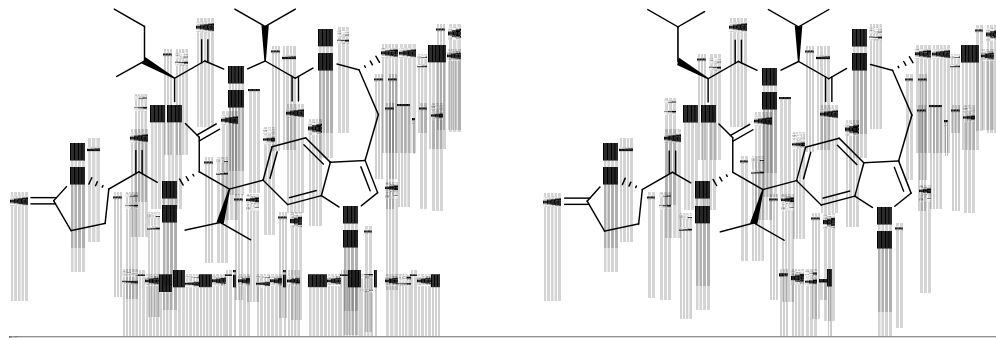


The acyclic precursors (**105-B, I, N, G**) for the left-hand ring synthesis were readily achieved from four isomers of **103** by following the same route illustrated in Scheme 23: a coupling with the pyroglutamic acid, followed by the deprotection. The subsequent ring cyclization was studied by using the combination of HOBt and HBTU in DMF (Scheme 24), which was successfully employed in the right-hand ring and the model left-hand ring synthesis. Moderate to good yields were obtained from each isomer of **105**, with isomer **I** giving the best transformation at 89% yield. Previously developed *t*-Bu ester and TES group deprotection with *B*-bromocatechol boran in dichloromethane afforded the free carboxylic acids (**107-B, I, N, G**) with excellent yields, which were converted to the corresponding methyl esters to match the structure of stephanotic acid methyl ester. Unfortunately, no product from isomer **B** was obtained, presumably because of the small amount of **107-B** and the harsh condition of thionyl chloride in methanol. Meanwhile, three products of **108-I, N, G** were achieved at modest yields under the same conditions. An interesting discovery

of the direct transformation from **106-I** to **108-I** was recently realized by using *B*-bromocatechol borane in MeOH/CH<sub>2</sub>Cl<sub>2</sub>. Even though this condition was not tested on other isomers of compound **106**, it might find potential applications in organic synthesis to achieve the *t*-Bu to methyl ester transesterification in one pot.



After comparing the NMR spectra of these three isomers of **108** with stephanotic acid methyl ester and its diastereomer, we figured out the matches of **108-I** with stephanotic acid methyl ester (Figures 6 and 7), as well as **108-G** with the diastereomer. Consequently, the stereochemistry of **103-I** and **G** was confirmed, with **103-I** as the desired product. Nevertheless, the exact structures of **103-B** and **N** were not clear at this stage. In order to achieve the most amount of **103-I**, the radical conjugate addition would be performed with the presence of Zn(OTf)<sub>2</sub> (Entry 6, Table 10), in which case 36% of the desired isomer would be obtained in two steps, calculated from the ratio (1:2:3:1) and the overall yield (90%). In fact, the desired



compound was separated as a single isomer (**105-I**) with 30% yield over four steps from **87**.

In conclusion, the left-hand ring of celogentin C (**41** or **107-I**) was eventually synthesized based on the intermolecular Knoevenagel condensation, the radical conjugate addition, and the macrolactamization. With the conditions fully developed on left-hand ring and right-hand ring respectively, the total synthesis of celogentin C would be investigated subsequently.

### **2.2.3 Total synthesis of celogentin C**

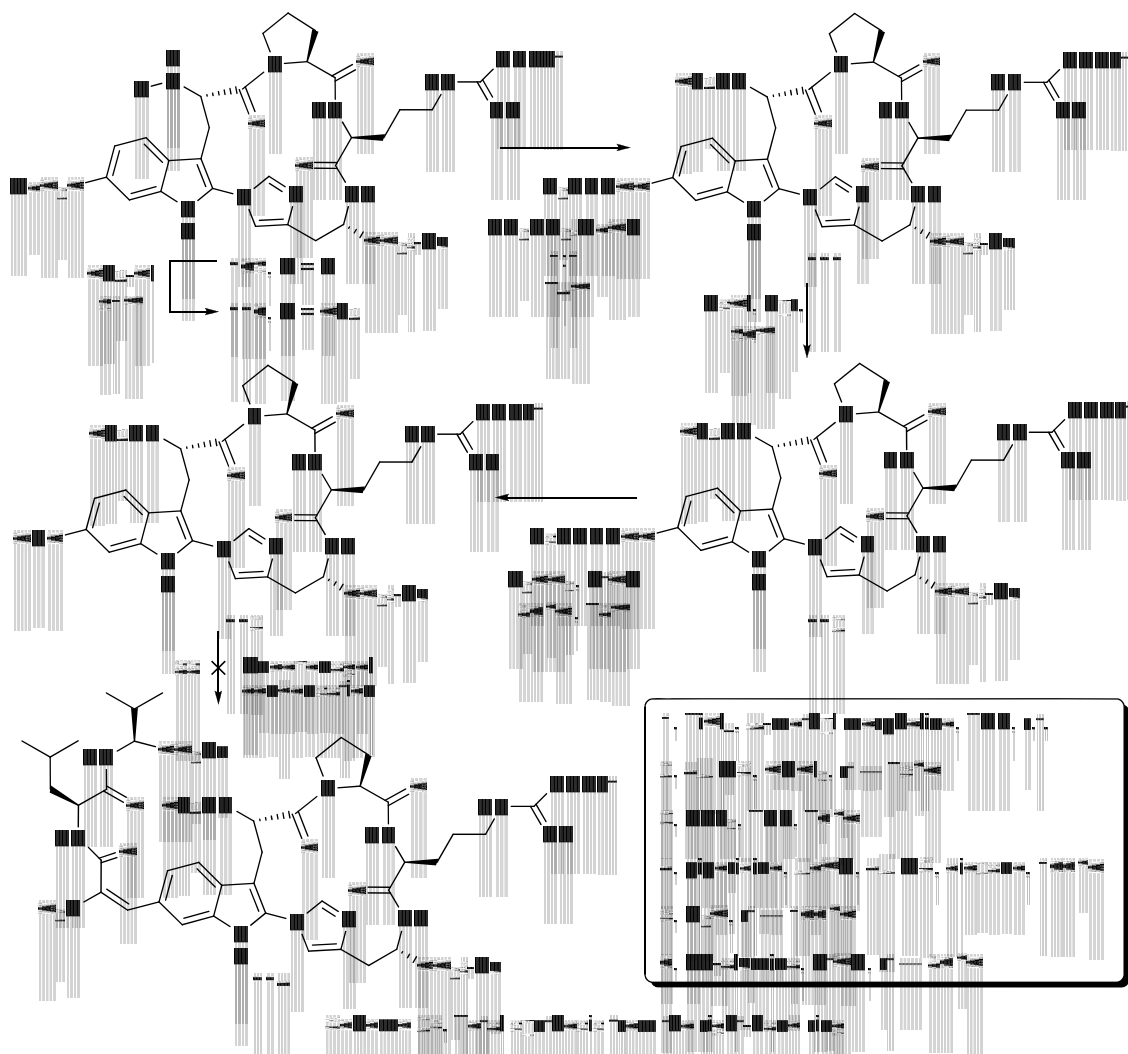
#### **2.2.3.1. Total synthesis of celogentin C from the right-hand ring**

The total synthesis of celogentin C was firstly carried out from the right-hand ring precursor (Scheme 25), which would leave the problematic radical conjugate addition in constructing the left-hand ring to a later stage. The amino intermediate **109**, obtained after deprotection of the methyl ester functionalized right-hand ring compound **40**, was readily protected again as the carboamide (**110**). Direct reduction conditions were explored to convert the methyl ester (**110**) to the corresponding aldehyde (**113**), required as one of the coupling partners for the Knoevenagel condensation. Based on previous studies on the methyl ester reduction, the outcome did not surprise us at all, with the starting material (**110**) consumed and no product isolated. McFadyen-Stevens reduction was tested on this complex substrate (**110**) again. The acyl hydrazine (**111**) formation worked very well as usual. However, extra attention should be paid to the work-up process. With the evaporation of methanol on rotary evaporator, the hydrazine solution became more and more concentrated



and converted the *tert*-butyl ester to the acyl hydrazine in a short time period even at room temperature. Consequently, the crude mixture was concentrated under high vacuum at  $-20\text{ }^{\circ}\text{C}$ , which successfully suppressed the side reaction. The high polarity character of compound **111** made its purification difficult. On the other hand, less pure acyl hydrazine starting material significantly decreased the yields of the following two reactions. Fortunately, an unique solvent system, 10% Et<sub>3</sub>N and 50% MeOH in EtOAc, was developed to accomplish the purification of compound **111** eventually. Nosyl group installation was achieved in pyridine with 90% yield, which was followed by the reduction toward the desired aldehyde (**113**) without too much trouble.

However, further attempts toward the Knoevenagel condensation product (**114**) were futile. TiCl<sub>4</sub> was initially chosen to promote the reaction, which consumed the aldehyde with no product detected (Entry 1, Scheme 25). Activated 4Å molecular sieves were introduced to facilitate the dehydration step.<sup>79</sup> Both starting materials disappeared slowly at 75 °C. However, the unknown product could not be clearly identified. Similar results were observed in the triphenylphosphine catalyzed conditions (Entry 3, Scheme 25).<sup>80</sup> The combination of piperidine and acetic acid (Entry 4, Scheme 25)<sup>81</sup> afforded a very polar compound, bearing the skeleton of the aldehyde **113**, which was presumed to be a deprotection by-product. The heating of both starting materials in H<sub>2</sub>O<sup>82</sup> or with KF-alumina in EtOH<sup>83</sup> both failed to afford the desired product.

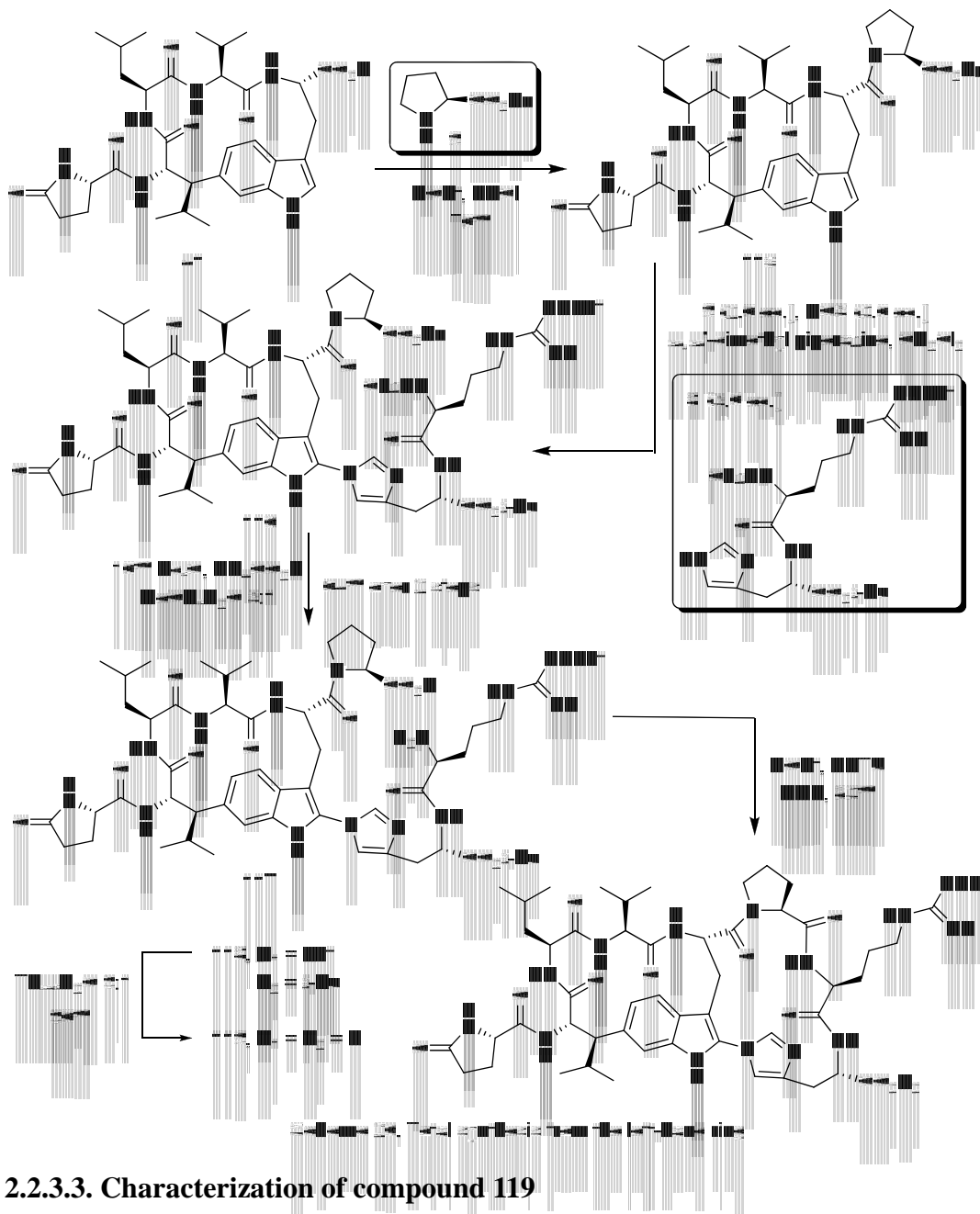


### 2.2.3.2. Total synthesis of celogentin C from the left-hand ring

The total synthesis of celogentin C was subsequently performed from the left-hand ring precursor **41** (Scheme 26). The benzyl protected proline was readily assembled to afford **115** after a peptide coupling procedure. Unfortunately, we could not move any further to obtain the oxidative coupling product **116** by following the traditional reaction conditions, which were 1.2 equivalents of NCS, 2.0 equivalents of *N,N'*-dimethyl piperazine, and one equivalent of Cbz-Arg(Pbf)-His-*t*-Bu dipeptide (**8**) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (see Scheme 10). In order to figure out the problem during this two-step transformation, the chlorinated intermediate, which was generated from the precursor **115** after treating with 0.5 eq. NCS, was carefully studied by

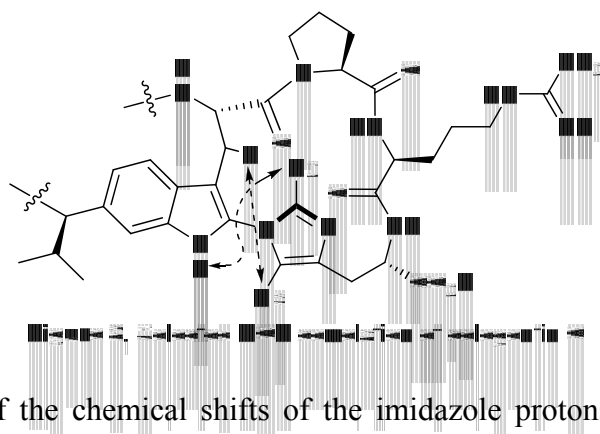
using NMR and MS. To our surprise, a di-chlorinated intermediate was detected on the MS ( $[\text{C}_{45}\text{H}_{57}\text{N}_7\text{O}_8\text{Cl}_2+\text{H}]^+$  894.37310), even with less than one equivalent of NCS. The crude NMR spectrum of the intermediate suggested an oxidation of the proline moiety, in addition to the desired indole oxidation by NCS. Extra benzyl protected proline (2.0 eq.) was introduced to the reaction as a scavenger, which successfully suppressed the unexpected proline oxidation on our substrate. A deep investigation of the mechanism of the by-product elimination with proline benzyl ester is still in progress. We are curious to know whether other amino acids or secondary amines would behave in the same way. The desired mono-chlorinated intermediate finally afforded the coupling product after treatment with five equivalents of His-Arg dipeptide. Excess His-Arg dipeptide was essential to achieve a fast conversion. However, the isolation of compound **116** from the unreacted His-Arg was impossible. So, the crude mixture of **116** was taken to the next reaction without purification. As expected, after the removal of two protecting groups, compound **117** was separated with 64% yield over two steps. The right-hand ring was cyclized excellently to afford a single isomer of **118** with the presence of HOBT and HBTU in very dilute DMF solution (ca. 0.002 M). Finally, the Pbf and the *tert*-butyl group were cleaved in one step after treating with 90% TFA to afford compound **119** as the final product of the proposed total synthesis of celogentin C. A very pure sample was simply achieved by performing a reverse extraction to remove the organic by-products from the aqueous **119** solution. Considering the basic moieties in the molecule, such as guanidine and imidazole, the synthesized

celogentin C was actually formed as a TFA salt.



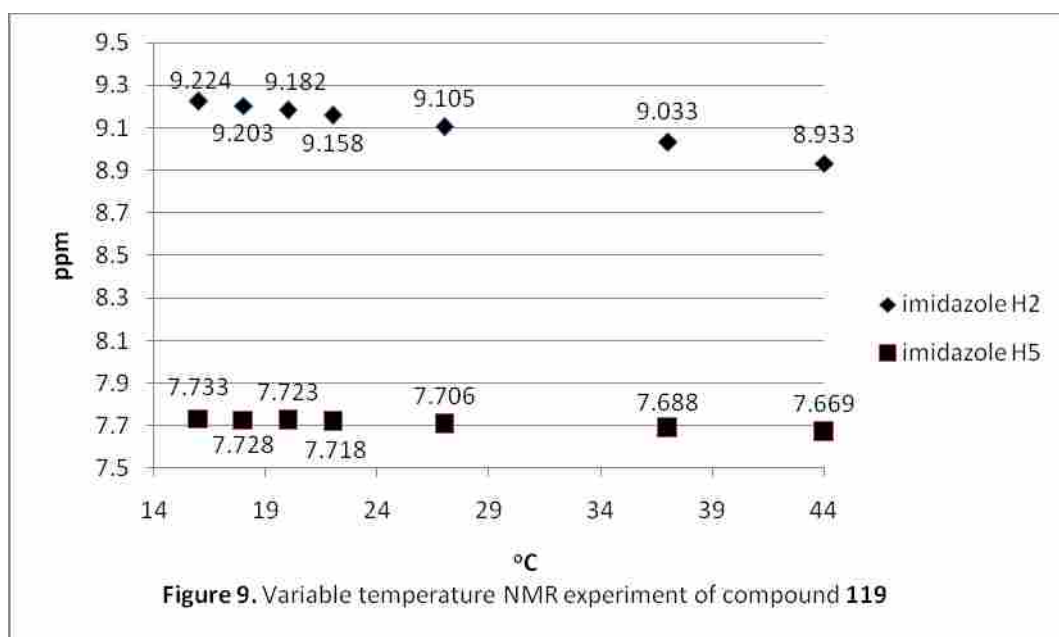
The  $^1\text{H}$  NMR spectrum of the synthesized celogentin C (**119**) demonstrated an exact match with the natural product, except for two imidazole protons H-2 and H-5:  $\delta$  9.16 (H-2) and 7.72 (H-5) for compound **119**,  $\delta$  9.41 (H-2) and 7.79 (H-5) for natural celogentin C. With the confidence of the correct stereochemistry being constructed in the synthesized celogentin C, we hypothesized that the total synthesis

might have achieved an atropisomer of the natural product, which meant the configuration of the indole ring and the imidazole ring was opposite in two compounds. However, the observed NOE effects of the natural and the synthesized celogentin C exhibited the same correlation: indole (N-H)/imidazole (H-2) and imidazole (H-5)/Trp ( $\beta$ -H). We received 0.1 mg of natural celogentin C from the Kobayashi group, which overlapped at the same retention time with compound **119** on reverse phase HPLC. The above observations partially suggested that compound **119** possessed an identical structure with the natural celogentin C. However, further studies must be performed to explain the difference of the  $^1\text{H}$  NMR spectra.

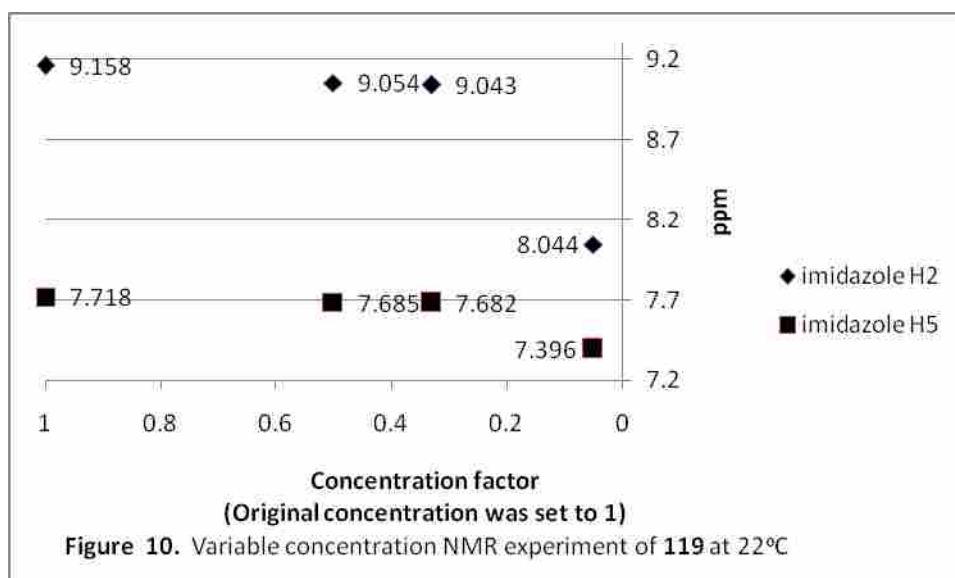


We wondered if the chemical shifts of the imidazole protons were temperature dependent, because, at different temperature, the conformation of the molecule might be different, so that the chemical environment of these two protons would change. Variable-temperature NMR experiments were subsequently executed and the results are displayed in Figure 9. The chemical shift of imidazole H-2 in compound **119** was  $\delta$  9.158 ppm at 22  $^\circ\text{C}$ . Lower temperature brought the chemical shift closer to the corresponding value of natural celogentin C in lower field. Unfortunately, due to the high freezing point of  $\text{DMSO-}d_6$  (ca. 18  $^\circ\text{C}$ ), which was used as the solvent for NMR experiments, we could only drop the temperature to 16  $^\circ\text{C}$ . Meanwhile, higher

temperatures afforded opposite results. More importantly, the difference in chemical shifts of H-2 was as significant as 0.291 ppm at 16 °C and 44 °C. The imidazole H-5 was also temperature dependent in its chemical shift. However, the variation was negligible: only 0.064 ppm over 28 degree temperature range.



The chemical shifts of imidazole protons were also concentration dependent (Figure 10). The concentration factor of the original NMR solution (ca. 6 mg in 0.5 mL DMSO-*d*<sub>6</sub>) was set to 1. When it was diluted with another 0.5 mL DMSO-*d*<sub>6</sub>, the



imidazole H-2 shift moved from  $\delta$  9.158 to 9.054. More remarkably, the chemical shift was even detected at  $\delta$  8.044 in twenty times more diluted solution. The same trend was observed for imidazole H-5 as well.

The natural celogentin C was separated by using reverse phase HPLC with 0.1% aqueous TFA and acetonitrile as the mobile phase. Consequently, it was also collected as a TFA salt, just as our synthesized compound **119**. Concentration and temperature dependent NMR experiments strongly suggested a hydrogen bond effect in the sample, which might have a close correlation with the amount of TFA. Thus, extra TFA (ca. 2  $\mu$ L) was introduced to the solution of the NMR sample. Surprisingly, the chemical shift of imidazole H-2 jumped from  $\delta$  9.158 to 9.529. Consequently, the reported data,  $\delta$  9.41 for H-2, of natural celogentin C was dependent on a precise amount of TFA, concentration and temperature, which was not repeatable.  $^{13}\text{C}$  NMR and some other 2D NMR experiments, such as COSY, TOCSY, NOESY, HMQC and HMBC, supported the successful total synthesis of celogentin C from other aspects.

## 2.3 Conclusion

The first total synthesis of celogentin C was accomplished in this project. The methodology for the right-hand ring moiety was initially developed by synthesizing a model right-hand ring of celogentin C. Considering the possibility to carry out the total synthesis from the right side, the functionalized right-hand ring, which contained a methyl ester group at the indole C-6 position, was proposed and achieved in nine steps with 20% overall yield. Some interesting reactions were further optimized or developed, such as the oxidative coupling and the deprotection of Cbz and benzyl groups by using triethylsilane.

The synthesis of the left-hand ring of celogentin C was firstly developed based on ring-closing metathesis. One of the key steps required a methyl ester reduction toward the corresponding aldehyde, which was eventually realized by employing a three-step McFadyen-Stevens reaction. However, the acyclic precursor could not be closed in the presence of Grubbs' catalyst. Meanwhile, other synthetic routes, developed from intramolecular Horner-Wadsworth-Emmons olefination and intramolecular decarboxylative Heck reaction, afforded negative results unfortunately. At last, the desired left-hand ring was obtained from the protocol based on intermolecular Knoevenagel condensation and macrolactamization.

The total synthesis of celogentin C could not be accomplished from the right-hand ring, due to the problematic intermolecular Knoevenagel condensation on a complex substrate. However, the assembly from the left-hand ring was successful. The crucial transformation, oxidative coupling, was more complicated in the total synthesis,



which required extra Pro-OBn as the scavenger to suppress the side reactions.

The NMR spectrum of the synthesized celogentin C did not match the natural product very well at the first glance, especially the imidazole H-2 and H-5. Further studies revealed that both protons were temperature and concentration dependent and were affected significantly by the amount of TFA in the sample. The interesting discovery not only explained the observation in the NMR spectra, but also would be useful for the total synthesis of moroidin and other celogentins, which also contain imidazole moieties.

## 2.4 Experimental

### 2.4.1. General experimental details

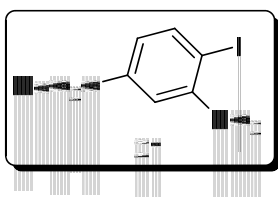
Anhydrous diethyl ether, toluene, dimethylformamide, methanol, methylene chloride, and tetrahydrofuran were dried by passage through a Glass Contour solvent drying system containing cylinders of activated alumina. Flash chromatography was carried out using 60–230 mesh silica gel.  $^1\text{H}$  NMR spectra were acquired on 500 MHz spectrometers with tetramethylsilane (0.00 ppm) as internal references. Signals are reported as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), brs (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz).  $^{13}\text{C}$  NMR spectra were acquired on spectrometers operating at 125 MHz with chloroform (77.23 ppm), MeOH (49.87 ppm) and DMSO (49.51 ppm) as internal references. Infrared spectra were obtained on an FT-IR spectrometer. Mass spectral data were obtained using ESI techniques.

### 2.4.2. Synthesis of the right-hand ring of celogentin C



**4-iodo-3-nitrobenzoic acid (20)**. A 250 mL round bottom flask was charged with 4.2 mL  $\text{H}_2\text{O}$ , followed by  $\text{H}_2\text{SO}_4$  (98%, 3.85 mL) and acetic acid (glacial, 3.85 mL) dropwise at 0 °C. The starting material, 4-amino-3-nitrobenzoic acid (**19**, 1.000 g, 5.490 mmol), was treated while stirring. The solution of  $\text{NaNO}_2$  (418.0 mg, 6.05 mmol) in 1.65 mL  $\text{H}_2\text{O}$  was added over 10 min. The resulting mixture was stirred at 0 °C for 10 min, followed by the solution of KI (1.100g, 6.600 mmol) in 1.65 mL

H<sub>2</sub>O dropwise. The suspension was heated at 60 °C for an hour and cooled to rt. It was then charged with 200 mL EtOAc to dissolve all the residue and treated with 200 mL H<sub>2</sub>O. The solution was extracted with EtOAc (5 × 50 mL). The combined organic layers were dried and concentrated to afford **20** (1.576 g, 5.380 mmol, 98% yield) as a yellow solid: NMR showed a pure product.<sup>84</sup>



**methyl 4-iodo-3-nitrobenzoate (21)**. To a solution of compound **20** (3.200 g, 10.92 mmol) in 90 mL DMSO was treated with K<sub>2</sub>CO<sub>3</sub> (3.000 g, 21.760 mmol), followed by MeI (2.317 g, 1.03 mL, 16.32 mmol). The resulting mixture was stirred at rt for 12 hours. The reaction was treated with 300 mL EtOAc and washed with H<sub>2</sub>O (5 × 80 mL). The organic layer was then dried and concentrated. The crude product was kept under high vacuum overnight to afford product **21** (3.084 g, 10.046 mmol, 92% yield) as a yellow solid: NMR showed a pure product.<sup>85</sup>



**methyl 3-amino-4-iodobenzoate (18)**. To a solution of compound **21** (4.400 g, 14.330 mmol) in EtOH/AcOH (1:1, 100 mL) was treated with Fe (2.000g, 35.54 mmol). The mixture was refluxed at 100 °C for 2 hours and cooled to rt. Excess Fe was removed by using magnetic bar. The resulting mixture was charged with 200 mL H<sub>2</sub>O and 2M HCl until the solution was clear. The solution was extracted with

$\text{CHCl}_3$  (The extraction was monitored by TLC until no product was detected in the organic layer, ca. 500 mL  $\text{CHCl}_3$ ) and the combined organic layers were dried and concentrated in vacuo. The residue was charged with 100 mL  $\text{H}_2\text{O}$  and brought to basic by using 50% KOH. The mixture was extracted with  $\text{CHCl}_3$  ( $5 \times 50$  mL). The combined organic layers were dried and concentrated. Flash chromatography ( $\text{SiO}_2$ ,  $5.5 \times 30$  cm, 10% EtOAc/Hexanes) afforded **18** (3.771 g, 13.613 mmol, 95% yield) as a yellow solid: NMR showed a pure product.<sup>85</sup>

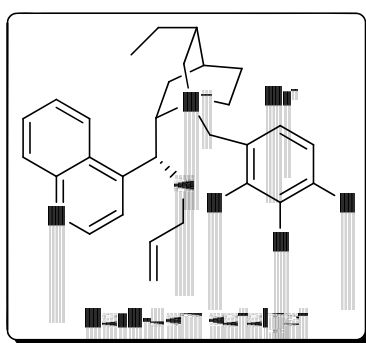


**Dihydrocinchonidine.** To a solution of cinchonidine (8.000 g, 27.200 mmol) in 200 mL anhydrous MeOH was treated with 10% Pd/C (1.600 g). The mixture was stirred under 1 atm  $\text{H}_2$  for 20 hours. It was then filtered through a fine sintered glass pad filter and washed with MeOH ( $5 \times 50$  mL). The solution was concentrated in vacuo to afford dihydrocinchonidine (7.971 g, 26.928 mmol, 99% yield) as a white solid: NMR showed a pure product.<sup>22</sup>

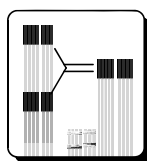


**Benzylated dihydrocinchonidine.** To a solution of dihydrocinchonidine (7.971 g, 26.928 mmol) in Acetone/EtOH (1:1, 200 mL) was treated with 2,3,4-trifluorobenzyl

bromide (6.300 g, 3.600 mL, 28.000 mmol). The resulting mixture was stirred at rt for 20 hours, and concentrated in vacuo. The residue was suspended in a minimum amount of MeOH (ca. 20 mL) and treated with 500 mL Et<sub>2</sub>O. The mixture was filtered and washed with Et<sub>2</sub>O (3 × 50 mL). The compound was dried under vacuum to afford the benzylation product (13.889 g, 26.659 mmol, 99% yield) as a white solid: NMR showed a pure product.<sup>22</sup>

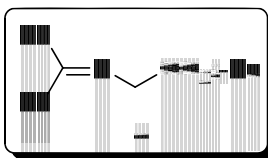


**Park-Jew catalyst.** To a suspension of the above compound (13.889 g, 26.659 mmol) in 300 mL anhydrous acetone was treated with K<sub>2</sub>CO<sub>3</sub> (18.880 g, 136.900 mmol), followed by allyl bromide (16.595 g, 5.93 mL, 136.900 mmol). The mixture was stirred at rt for 24 hours. The resulting mixture was concentrated in vacuo and suspended in 50 mL MeOH. It was then treated with silica gel (50.0 g, 60–200 mesh) and concentrated. Flash chromatography (SiO<sub>2</sub>, 5.5 × 35 cm, 10% → 50% MeOH/EtOAc) afforded Park-Jew catalyst (12.712 g, 22.660 mmol, 85% yield) as a yellow solid.<sup>22</sup>

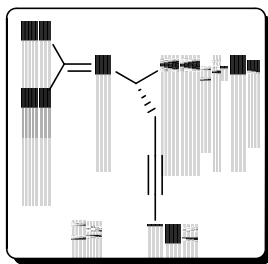


**Diphenylmethanimine.** A 500 mL round bottom flask was degassed with N<sub>2</sub> and charged with a solution of phenylmagnesium bromide in Et<sub>2</sub>O (3.0 M, 84.00 mL,

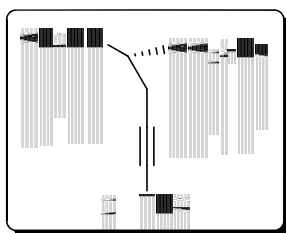
0.252 mol). The mixture was treated with the solution of benzyl nitrile (25.750 g, 25.60 mL, 0.250 mol) in anhydrous Et<sub>2</sub>O (90 mL) over an hour while vigorous stirring. The mixture was refluxed for 10 hours and cooled to 0 °C. The reaction was quenched with 50 mL MeOH dropwise. The mixture was treated with 500 mL H<sub>2</sub>O and extracted with ether (5 × 100 mL). The combined organic layers were dried and concentrated. The crude mixture was distilled under high vacuum to afford the product (110 → 120 °C, ca. 0.5 mmHg, 42.987 g, 0.237 mol, 95% yield) as a slightly yellow oil.<sup>86</sup>



***tert*-butyl 2-(diphenylmethyleneamino)acetate (4)**. To a solution of compound **23** (19.300 g, 0.107 mol) and *tert*-butylchloro acetate (**24**, 16.103 g, 15.30 mL, 0.107 mol) in 90 mL pyrrolidione was treated with KI (2.760 g, 16.600 mmol), followed by K<sub>2</sub>CO<sub>3</sub> (14.800 g, 0.107 mol). The resulting mixture was stirred at 90 °C for 10 hours and cooled to rt. It was treated with 90 mL each of EtOH and H<sub>2</sub>O, followed by 42.8 mL AcOH dropwise while stirring. Added another 22.3 mL EtOH and 160 mL H<sub>2</sub>O. The mixture was filtered and washed with 70% EtOH (2 × 22 mL) and Hexanes (2 × 25 mL). The compound was dried under vacuum to afford the product (18.939 g, 0.0642 mol, 60%) as a white solid.<sup>20</sup>



**(S)-tert-butyl 2-(diphenylmethylenamino)-5-(triethylsilyl)pent-4-ynoate.** A solution of compound **4** (6.750 g, 22.890 mmol) and the Park-Jew catalyst (2.180 g, 3.880 mmol) in Tol-CHCl<sub>3</sub> (7:3, 100 mL) was cooled to -40 °C and treated with (3-bromoprop-1-ynyl) triethylsilane (**5**, 16.000 g, 68.670 mmol). 50% KOH (33.6 mL, 0.296 mmol) was added dropwise and the resulting suspension was stirred at -40 °C for 24 hours. The reaction was quenched with 300 mL H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried and concentrated. Flash chromatography (SiO<sub>2</sub>, 3.5 × 35 cm, 1% → 5% Et<sub>2</sub>O/Hexanes) afforded compound **25** (8.101 g, 18.083 mmol, 79% yield) as a brown oil: 94% ee (measured by HPLC: chiralcel OD-H, 99.8:0.2 hexanes/*i*-PrOH, 1 mL/min).<sup>12</sup>



**(S)-tert-butyl 2-(benzyloxycarbonylamino)-5-(triethylsilyl)pent-4-ynoate.** To a solution of compound **25** (5.100g, 11.320 mmol) in 100 mL THF was treated with 1M HCl (40 mL, 40.000 mmol) dropwise at 0 °C. The resulting mixture was stirred at rt for an hour. It was treated with 100 mL brine and extracted with CHCl<sub>3</sub> (5 × 50 mL). The combined organic layers were dried and concentrated in vacuo.

The residue was dissolved in dioxane/H<sub>2</sub>O (10:1, 120 mL) and treated with

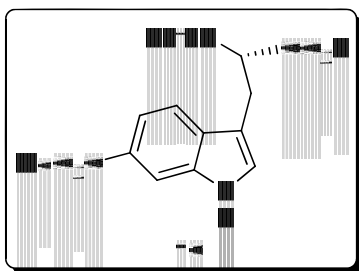
NaHCO<sub>3</sub> (2.460 g, 28.660 mmol), followed by Cbz-Cl (2.897 g, 2.360 mL, 16.980 mmol). The mixture was stirred at rt for 12 hours. It was then treated with 200 mL H<sub>2</sub>O and extracted with CHCl<sub>3</sub> (5 × 50 mL). The combined organic layers were dried and concentrated in vacuo. Dioxane was removed under high vacuum. Flash chromatography (SiO<sub>2</sub>, 5.5 × 25 cm, 0% → 30% Et<sub>2</sub>O/Hexanes) afforded compound **2** (4.579 g, 10.980 mmol, 97% yield) as a brown oil.<sup>12</sup>



**(S)-methyl-3-(2-(benzyloxycarbonylamino)-3-tert-butoxy-3-oxopropyl)-2-(triethyl silyl)-1H-indole-6-carboxylate.** To a solution of the alkyne (**2**, 1.300 g, 3.110 mmol) and the iodo aniline (**18**, 0.860 g, 3.110 mmol) in anhydrous DMF (35 mL) was treated orderly with PdCl<sub>2</sub> (27.0 mg, 0.156 mmol), LiCl (135.0 mg, 3.150 mmol), Na<sub>2</sub>CO<sub>3</sub> (0.760 g, 9.360 mmol) and 0.810 g 4 Å molecular sieves. The resulting mixture was stirred at 100 °C for 10 hours. After cooling to room temperature, the solvent was removed under high vacuum. Flash chromatography (SiO<sub>2</sub>, 2.5 × 30 cm, 10% → 20% EtOAc/Hexanes) afforded **17** (1.234 g, 2.177 mmol, 70% yield) as a yellow solid:  $[\alpha]_D^{25} -5.3$  (*c* 1.00, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.21 (s, 1H), 8.11 (s, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.34–7.26 (m, 3H), 7.26–7.20 (m, 2H), 5.24 (d, *J* = 8.5 Hz, 1H), 4.95 (d, *J* = 12.5 Hz, 1H), 4.91 (d, *J* = 12.0 Hz, 1H), 4.51 (dd, *J* = 14.5, 8.5 Hz, 1H), 3.93 (s, 3H), 3.28 (dd, *J* = 14.0, 5.5 Hz, 1H), 3.16 (dd, *J* = 12.0, 8.5 Hz, 1H), 1.29 (s, 9H),



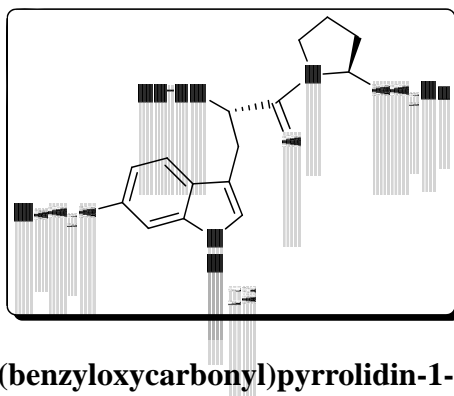
1.05–0.98 (m, 9H), 0.98–0.92 (m, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  171.6, 168.4, 155.8, 137.9, 137.4, 136.4, 132.6, 128.6 (2C), 128.2 (3C), 124.0, 120.6, 118.9, 113.4, 82.2, 66.9, 56.3, 52.2, 30.2, 28.0 (3C), 7.6 (3C), 3.7 (3C); IR (film)  $\nu_{\text{max}}$  3359, 2954, 2875, 1701, 1613, 1509, 1435, 1224, 1154, 1098, 1004, 845, 749  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  567.28706 ( $\text{MH}^+$ ,  $\text{C}_{31}\text{H}_{42}\text{N}_2\text{O}_6\text{SiH}^+$  requires 567.28849); 93% ee (measured by HPLC: chiralcel OD-H, 95:5 hexanes/*i*-PrOH, 1 mL/min).



**(S)-2-(1,3-dioxoisindolin-2-yl)-3-(6-(methoxycarbonyl)-1H-indol-3-yl)propanoic acid.** A solution of compound **17** (5.000 g, 8.810 mmol) in 30% HBr/AcOH (100.0 mL) was stirred at rt for 30 min. The resulting mixture was concentrated at 30 °C by azeotroping with toluene. The crude product of **26** was submitted to the next reaction without purification.

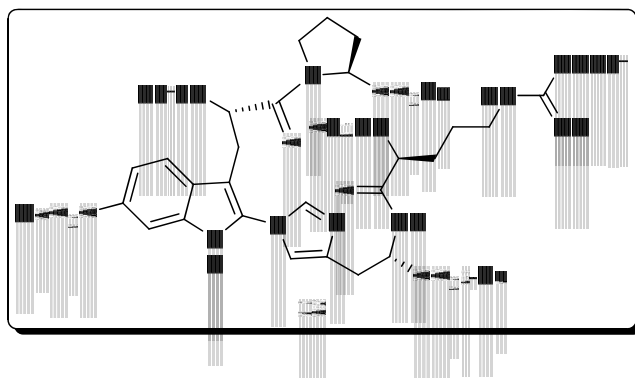
To a solution of the above crude compound **26** and  $\text{Na}_2\text{CO}_3$  (3.660 g, 26.500 mmol) in 35 mL  $\text{H}_2\text{O}$  was treated with methyl 2-(2,5-dioxopyrrolidine-1-carbonyl)benzoate (**27**, 2.950 g, 10.600 mmol) in 65 mL  $\text{CH}_3\text{CN}$ . The resulting mixture was stirred at rt for 9 hours. The solution was acidified with 6M HCl and diluted with 100 mL  $\text{H}_2\text{O}$ . The mixture was extracted with EtOAc ( $5 \times 100$  mL) and concentrated in vacuo. Flash chromatography ( $\text{SiO}_2$ ,  $5.5 \times 30$  cm, 10%  $\rightarrow$  20% MeOH/ $\text{CH}_2\text{Cl}_2$ ) afforded **16** (2.901 g, 7.400 mmol, 84% yield over 2 steps) as a yellow solid:  $[\alpha]_{\text{D}}^{25} +123.6$  ( $c$  1.7, MeOH);  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 500 MHz)  $\delta$  11.22 (s, 1H), 7.94 (s, 1H),

7.76–7.72 (m, 4H), 7.53 (s, 2H), 7.20 (s, 1H), 4.64 (t,  $J = 8.0$  Hz, 1H), 3.82 (s, 3H), 3.65 (d,  $J = 7.5$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  170.4, 168.3 (2C), 167.3, 135.3, 134.1 (2C), 131.7 (2C), 130.7, 126.6, 122.6 (2C), 121.7, 118.8, 117.8, 113.5, 113.4, 56.5, 51.7, 24.7; IR (film)  $\nu_{\text{max}}$  3374, 2947, 1704, 1610, 1393, 1220, 1102, 1021, 724  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  393.10920 ( $\text{MH}^+$ ,  $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}_6\text{H}^+$  requires 393.10884).



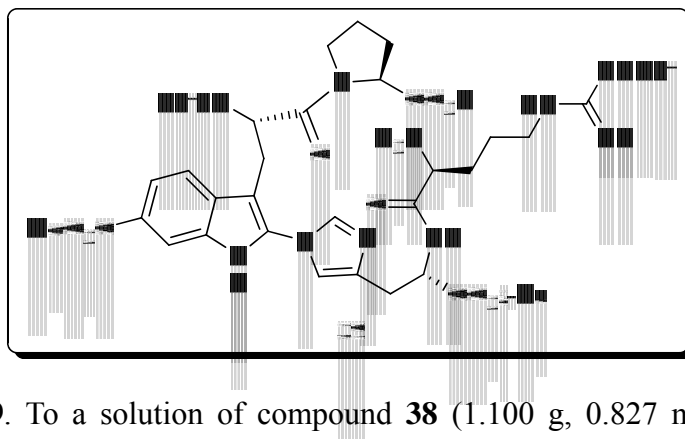
**Methyl-3-((*S*)-3-((*S*)-2-(benzyloxycarbonyl)pyrrolidin-1-yl)-2-(1,3-dioxoisindolin-2-yl)-3-oxopropyl)-1H-indole-6-carboxylate.** To a solution of the carboxylic acid (**16**, 2.800 g, 7.140 mmol) and Pro-OBn (**9**, 1.850 g, 7.700 mmol) in anhydrous DMF (60 mL) was treated with HOBt (1.510 g, 11.520 mmol) at 0 °C, followed by EDCI (2.070 g, 11.520 mmol). The resulting mixture was stirred at 0 °C  $\rightarrow$  rt for 8 hours. The solution was concentrated under high vacuum. The residue was treated with 100 mL sat. aq.  $\text{NaHCO}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$  ( $5 \times 50$  mL). The combined organic layers were concentrated in vacuo. Flash chromatography ( $\text{SiO}_2$ ,  $5.5 \times 23$  cm, 20%  $\rightarrow$  60% EtOAc/Hexanes) afforded **28** (3.348 g, 5.783 mmol, 81% yield) as a yellow solid:  $[\alpha]_{\text{D}}^{25} -74$  ( $c$  1.00,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz, 330 K)  $\delta$  8.15 (brs, 1H), 8.01 (s, 1H), 7.77–7.67 (m, 3H), 7.67–7.59 (m, 2H), 7.55 (d,  $J = 8.0$  Hz, 1H), 7.40–7.28 (m, 5H), 7.20 (s, 1H), 5.28 (brs, 1H), 5.21 (d,  $J = 12.5$  Hz,

1H), 5.13 (d,  $J = 12.5$  Hz, 1H), 4.90 (d,  $J = 7.5$  Hz, 1H), 3.89 (s, 3H), 3.83–3.78 (m, 1H), 3.73–3.67 (m, 1H), 3.50–3.44 (m, 1H), 3.44–3.56 (m, 1H), 2.12–2.04 (m, 1H), 2.01–1.90 (m, 2H), 1.89–1.82 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  172.1, 168.3, 167.9 (2C), 167.7, 135.9, 135.5, 134.4 (2C), 131.6, 131.1, 128.8 (3C), 128.5 (2C), 128.4 (2C), 127.4, 123.8 (2C), 120.7, 118.1, 113.9, 111.5, 67.2, 59.8, 53.3, 52.2, 47.2, 29.0, 25.2, 24.7; IR (film)  $\nu_{\text{max}}$  3338, 2951, 1775, 1714, 1650, 1435, 1383, 1276, 1213, 1087, 750, 719  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  602.18909 ( $\text{MNa}^+$ ,  $\text{C}_{33}\text{H}_{29}\text{N}_3\text{O}_7\text{Na}^+$  requires 602.18977).



**Compound 38.** To a solution of the starting material **28** (0.690 g, 1.200 mmol) in 60 mL anhydrous  $\text{CH}_2\text{Cl}_2$  was treated with  $N,N'$ -dimethylpeperazine (99.2 mg, 135.0 mL, 0.870 mmol), followed by NCS (180.0 mg, 1.440 mmol). The resulting mixture was stirred at rt for 5 hours. It was treated with His-Arg dipeptide (**8**, 900.0 mg, 1.200 mmol) and stirred at rt for 10 hours. The mixture was concentrated in vacuo. Flash chromatography ( $\text{SiO}_2$ ,  $3.5 \times 30$  cm, 2%  $\rightarrow$  10% MeOH/ $\text{CH}_2\text{Cl}_2$ ) afforded **38** (1.453 g, 1.092 mmol, 91% yield) as a yellow solid:  $[\alpha]_{\text{D}}^{25} -186$  ( $c$  0.35,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 500 MHz, mixture of conformational isomers)  $\delta$  8.27 (t,  $J = 7.5$  Hz, 1H), 7.87 and 7.85 (2s, 1H), 7.80–7.76 (m, 1H), 7.76–7.68 (m, 2H), 7.67–7.59 (m, 1H), 7.57 (s, 1H), 7.55–7.43 (m, 1H), 7.41–7.32 (m, 3H), 7.32–7.22 (m, 6H),

7.22–7.16 (m, 2H), 7.04 (d,  $J = 8.0$  Hz, 1H), 6.97 and 6.63 (2d,  $J = 8.5, 8.0$  Hz, 1H), 6.66 (brs, 1H), 6.38 (brs, 2H), 5.18–5.08 and 4.97–4.81 (m, 1H), 5.11 (s, 1H) 5.00 (d,  $J = 12.0$  Hz, 1H), 4.90 (d,  $J = 11.0$  Hz, 1H), 4.82 (t,  $J = 13.0$  Hz, 1H), 4.43–4.38 (m, 1H), 4.38–4.28 (m, 1H), 4.19 and 3.69 (2d,  $J = 12.5, 8.5$  Hz, 1H), 4.04–3.95 (m, 1H), 3.82 and 3.81 (2s, 3H), 3.66–3.42 (m, 2H), 3.40–3.34 (m, 1H), 3.07–2.96 (m, 3H), 2.92 (s, 2H), 2.91–2.78 (m, 2H), 2.47 (s, 3H), 2.41 (s, 3H), 1.98 (s, 3H), 1.85–1.71 (m, 3H), 1.71–1.59 (m, 1H), 1.56–1.42 (m, 3H), 1.39 (s, 9H), 1.36 (s, 6H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 125 MHz, mixture of conformational isomers)  $\delta$  171.8, 171.4, 171.1, 170.3, 166.8, 166.6, 166.3, 165.9, 157.4, 156.1, 155.9, 138.1, 138.0, 137.3, 136.8, 136.0, 134.8, 134.6, 132.7, 132.3, 131.4, 130.5, 130.44, 130.41, 128.5, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 127.57, 127.52, 124.3, 123.4, 123.1, 120.1, 119.9, 118.6, 118.5, 117.7, 117.5, 116.3, 114.5, 113.2, 101.9, 101.8, 86.3, 80.7, 65.9, 65.8, 65.4, 59.4, 58.6, 54.2, 52.5, 51.9, 50.9, 46.8, 46.5, 42.4, 31.0, 29.9, 29.5, 29.3, 28.3, 28.1, 27.7, 27.6, 24.5, 22.4, 21.0, 19.0, 17.6, 12.3; IR (film)  $\nu_{\text{max}}$  3360, 2930, 1715, 1641, 1550, 1437, 1383, 1255, 1159, 1102, 722, 665  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  1331.54949 ( $\text{MH}^+$ ,  $\text{C}_{70}\text{H}_{78}\text{N}_{10}\text{O}_{15}\text{SH}^+$  requires 1331.54416).



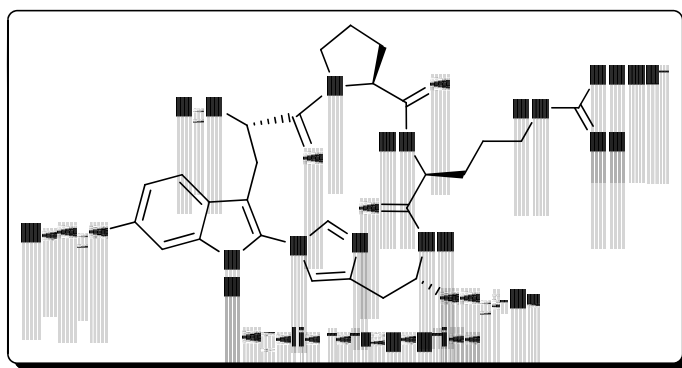
**Compound 39.** To a solution of compound **38** (1.100 g, 0.827 mmol) in 44 mL  $\text{CH}_2\text{Cl}_2$  was treated with  $\text{Et}_3\text{N}$  (0.936 g, 1.76 mL, 9.272 mmol) and  $\text{PdCl}_2$  (88.0 mg,

0.496 mmol), followed by Et<sub>3</sub>SiH (0.919 g, 1.29 mL, 7.92 mmol). The resulting mixture was stirred at rt for 8 hours. It was then treated with silica gel (20.0 g, 60–200 mesh) and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 3.5 × 30 cm, 10% → 50% MeOH/EtOAc) afforded **39** (695.8 g, 0.628 mmol, 76% yield) as a yellow solid:  $[\alpha]_D^{25}$  -138 (*c* 0.60, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz, mixture of conformational isomers) δ 7.98 (s, 1H), 7.85–7.60 (m, 7H), 7.29 (s, 1H), 7.22 and 7.00 (2brs, 1H), 7.11 (brs, 1H), 5.39–5.26 (2m, 1H), 4.38–4.29 (m, 1H), 4.22–4.16 (m, 1H), 3.91 (s, 3H), 3.81–3.72 (m, 1H), 3.71–3.62 (m, 2H), 3.50–3.43 (m, 2H), 2.97 and 2.94 (2s, 3H), 2.57 and 2.52 (2s, 3H), 2.49 and 2.46 (2s, 3H), 2.05 and 2.01 (2s, 3H), 2.00–1.86 (m, 3H), 1.86–1.70 (m, 3H), 1.59 and 1.56 (2s, 9H), 1.44 and 1.42 (2s, 6H), 1.35–1.28 (m, 5H); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz, mixture of conformational isomers) δ 179.4, 170.2, 169.7, 168.2, 167.5, 167.4, 167.2, 158.6, 157.2, 157.0, 138.1, 138.0, 137.9, 136.6, 134.7, 134.3, 133.2, 133.0, 132.5, 132.3, 131.3, 131.1, 130.8, 124.8, 124.2, 123.7, 123.4, 120.9, 118.7, 118.6, 118.4, 117.2, 113.6, 102.1, 86.5, 82.6, 82.4, 78.4, 62.9, 62.1, 57.2, 53.3, 52.9, 52.2, 52.0, 51.4, 51.0, 42.8, 42.4, 29.9, 29.4, 29.1, 24.9, 24.7, 22.6, 22.4, 21.6, 18.5, 17.3, 11.4, 10.5, 8.1; IR (film)  $\nu_{\max}$  3323, 2950, 1712, 1552, 1437, 1384, 1292, 1154, 1090 cm<sup>-1</sup>; HRMS (ESI) *m/z* 1107.46014 (MH<sup>+</sup>, C<sub>55</sub>H<sub>66</sub>N<sub>10</sub>O<sub>13</sub>SH<sup>+</sup> requires 1107.46043).



**Compound 40.** To a solution of compound **39** (0.965 g, 0.872 mmol) in anhydrous DMF (35 mL) was treated with HOBT (183.7 mg, 1.308 mmol) and HBTU (505.7 mg, 1.308 mmol) at 0 °C. The resulting mixture was stirred at 0 °C → rt for 12 hours. The solution was treated with 50 mL sat. aq. NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 × 30 mL). The combined organic layers were dried and concentrated in vacuo. DMF was removed under high vacuum. Flash chromatography (SiO<sub>2</sub>, 3.5 × 30 cm, 5% → 20% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) afforded **40** (854.6 g, 0.785 mmol, 90% yield) as a yellow solid:  $[\alpha]_D^{25} -30$  (*c* 0.48, MeOH); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz) δ 12.23 (brs, 1H), 8.01 (s, 1H), 7.90–7.82 (m, 5H), 7.80 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 6.5 Hz, 1H), 7.45 (s, 1H), 7.16 (d, *J* = 9.0 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.71 (brs, 1H), 6.37 (brs, 2H), 5.18 (dd, *J* = 9.5, 3.0 Hz, 1H), 4.68–4.63 (m, 1H), 4.33–4.26 (m, 1H), 4.19 (d, *J* = 9.5 Hz, 1H), 4.16–4.08 (m, 1H), 3.79 (s, 3H), 3.46–3.39 (m, 1H), 3.22 (dd, *J* = 15.5, 9.5 Hz, 1H), 3.13 (dd, *J* = 15.5, 6.5 Hz, 1H), 3.08–3.04 (m, 1H), 3.05–2.97 (m, 3H), 2.94 (s, 2H), 2.88–2.80 (m, 1H), 2.45 (s, 3H), 2.39 (s, 3H), 1.98 (s, 3H), 1.97–1.88 (m, 1H), 1.76–1.67 (m, 2H), 1.67–1.56 (m, 1H), 1.50–1.42 (m, 3H), 1.38 (s, 9H), 1.34 (s, 6H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz) δ 171.8, 170.9, 169.2, 167.0, 166.8, 166.0, 157.4, 156.0, 138.1, 137.3, 136.3 (2C), 135.1 (3C), 131.4 (2C), 131.0, 130.6 (3C), 124.3 (2C), 123.7 (2C), 119.5, 117.4,

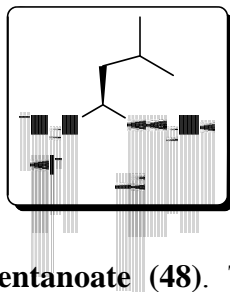
116.3, 116.0, 113.4, 101.6, 86.3, 81.2, 79.2, 61.9, 54.9, 53.1, 52.2 (2C), 51.8, 46.7, 42.4, 30.7, 29.0, 28.3 (2C), 27.6, 27.4 (3C), 24.6, 22.9, 18.9, 17.6, 12.3; IR (film)  $\nu_{\max}$  3340, 2974, 1774, 1713, 1636, 1484, 1290, 1156, 1091, 1029, 749, 721  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  1089.44986 ( $\text{MH}^+$ ,  $\text{C}_{55}\text{H}_{64}\text{N}_{10}\text{O}_{12}\text{SH}^+$  requires 1089.45138).



**Cyclic tetrapeptide.** To a solution of compound **40** (0.490 g, 0.450 mmol) in 30 mL MeOH was treated with hydrazine monohydrate (0.30 mL, 6.000 mmol). The mixture was stirred at rt for 10 hours, then concentrated in vacuo. Excess hydrazine monohydrate was removed under high vacuum. Flash chromatography ( $\text{SiO}_2$ ,  $2.5 \times 22$  cm, 10%  $\rightarrow$  50% MeOH/ $\text{CH}_2\text{Cl}_2$ ) afforded **40** (375.0 mg, 0.391 mmol, 87% yield) as a yellow solid:  $[\alpha]_{\text{D}}^{25} -18$  (c 0.67,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 500 MHz, mixture of conformational isomers)  $\delta$  12.34 and 12.16 (2brs, 1H), 8.46 and 7.99 (2d,  $J = 9.0$  Hz, 1H), 8.01 and 7.89 (2s, 1H), 7.97 and 7.87 (2d,  $J = 7.0$  Hz, 1H), 7.86 (s, 1H), 7.72 and 7.65 (2d,  $J = 8.5$  Hz, 1H), 7.62 and 7.42 (2d,  $J = 8.0$  Hz, 1H), 7.37 and 7.23 (2s, 1H), 6.69 (brs, 1H), 6.37 (brs, 1H), 4.49 (dt,  $J = 10.0, 3.0$  Hz, 1H), 4.36 (dt,  $J = 11.5, 2.0$  Hz, 1H), 4.26 (dd,  $J = 16.0, 8.0$  Hz, 1H), 4.17 (dd,  $J = 8.0, 5.0$  Hz, 1H), 4.15–4.08 (m, 1H), 4.03 (t,  $J = 7.5$  Hz, 1H), 3.86 (s, 3H), 3.76–3.69 (m, 1H), 3.56–3.46 (m, 1H), 3.41 and 3.17 (2d,  $J = 5.0$  Hz, 1H), 3.12–3.03 (m, 3H), 3.03–2.96 (m, 3H), 2.94 (s, 2H), 2.89–2.80 (m, 1H), 2.77–2.69 (m, 1H), 2.68–2.61

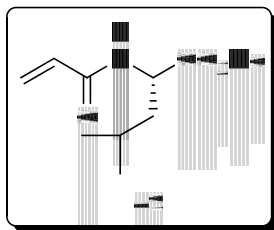
(m, 1H), 2.48 and 2.45 (2s, 3H), 2.41 and 2.40 (2s, 3H), 1.99 and 1.98 (2s, 3H), 1.78–1.63 (m, 1H), 1.68–1.53 (m, 2H), 1.42 (s, 6H), 1.39 (s, 9H), 1.33–1.22 (m, 2H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 125 MHz, mixture of conformational isomers)  $\delta$  176.0, 173.4, 173.8, 171.8, 171.7, 171.3, 170.6, 170.2, 169.9, 167.0, 166.9, 157.4, 156.0, 138.3, 137.4, 137.3, 136.9, 136.5, 134.1, 132.9, 132.5, 132.0, 131.4, 130.9, 129.8, 124.3, 123.3, 122.8, 120.1, 119.2, 119.1, 118.7, 118.3, 116.2, 113.3, 113.1, 106.2, 102.8, 86.3, 81.1, 80.9, 69.8, 60.4, 59.8, 53.8, 53.6, 52.9, 52.7, 52.2, 51.9, 46.9, 46.4, 42.4, 31.0, 30.1, 29.4, 28.3, 27.6, 24.3, 21.9, 19.0, 17.6, 12.3; IR (film)  $\nu_{\text{max}}$  3312, 2960, 1714, 1632, 1552, 1435, 1368, 1292, 1154, 1091  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  959.44517 ( $\text{MH}^+$ ,  $\text{C}_{47}\text{H}_{62}\text{N}_{10}\text{O}_{10}\text{SH}^+$  requires 959.44439).

#### 2.4.3. Synthesis of the left-hand ring of celogentin C

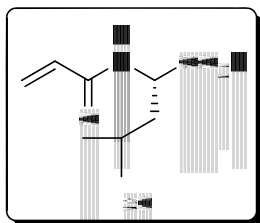


**(S)-methyl 2-amino-4-methylpentanoate (48)**. To a solution of L-leucine (**47**, 5.000 g, 38.150 mmol) in 65 mL anhydrous MeOH was treated with thionyl chloride (9.466 g, 5.80 mL, 79.550 mmol) dropwise at 0 °C. The resulting mixture was stirred at 0 °C  $\rightarrow$  rt for 12 hours. The solution was concentrated in vacuo and kept under high vacuum to afford the product **48** (6.924 g, 38.150 mmol, 100%) as a white solid.<sup>87</sup>





**(S)-methyl 2-acrylamido-4-methylpentanoate (49).** To a suspension of the leucine methyl ester (**48**, 3.000 g, 16.529 mmol) in 160 mL anhydrous CH<sub>2</sub>Cl<sub>2</sub> was treated with Et<sub>3</sub>N at 0 °C. The resulting mixture was stirred at 0 °C → rt for 6 hours. It was then concentrated in vacuo. The residue was treated with 100 mL sat. aq. NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 mL). The combined organic layers were dried and concentrated. Flash chromatography (SiO<sub>2</sub>, 3.0 × 30 cm, 1% → 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) afforded **49** (3.125 g, 15.702 mmol, 95% yield) as a brown oil:  $[\alpha]_D^{25} -4.3$  (*c* 2.67, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 6.32 (dd, *J* = 17.0, 1.5 Hz, 1H), 6.14 (dd, *J* = 17.0, 10.5 Hz, 1H), 5.96 (d, *J* = 8.0 Hz, 1H), 5.69 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.78–4.72 (m, 1H), 3.75 (s, 3H), 1.73–1.63 (m, 2H), 1.63–1.54 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 173.8, 165.3, 130.5, 127.5, 52.6, 50.8, 42.0, 25.1, 23.0, 22.2; IR (film)  $\nu_{\max}$  3277, 2957, 2871, 1747, 1659, 1628, 1542, 1437, 1205, 1155, 985 cm<sup>-1</sup>; HRMS (ESI) *m/z* 200.12920 (MH<sup>+</sup>, C<sub>10</sub>H<sub>17</sub>NO<sub>3</sub>H<sup>+</sup> requires 200.12812).



**(S)-2-acrylamido-4-methylpentanoic acid (50).** To a solution of the methyl ester (**49**, 3.460 g, 17.380 mmol) in *t*-BuOH/H<sub>2</sub>O (4:1, 158 mL) was treated with the

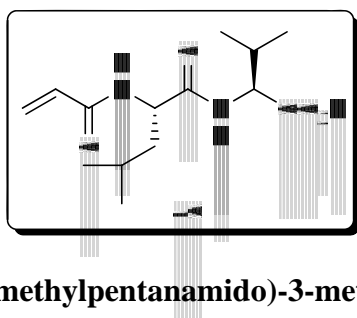
solution of LiOH (1.460 g, 34.830 mmol) in 35 mL H<sub>2</sub>O. The resulting mixture was stirred at rt for 2 hours. The solution was diluted with 150 mL H<sub>2</sub>O and acidified with 6 M HCl (ca. 6.5 mL). The mixture was extracted with CHCl<sub>3</sub> (5 × 50 mL). The combined organic layers were dried and concentrated in vacuo. The residue was kept under high vacuum for 8 hours to afford the product (3.183 g, 17.206 mmol, 99%) as a yellow solid:  $[\alpha]_D^{25}$  31.6 (*c* 1.95, MeOH); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 11.50 (brs, 1H), 7.13 (d, *J* = 6.5 Hz, 1H), 6.30 (d, *J* = 17.0 Hz, 1H), 6.21 (dd, *J* = 16.0, 10.5, 1H), 5.67 (d, *J* = 10.0 Hz, 1H), 4.75–4.67 (m, 1H), 1.77–1.67 (m, 2H), 1.67–1.58 (m, 1H), 0.94 (s, 3H), 0.93 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 176.2, 166.5, 130.1, 127.9, 51.1, 41.2, 24.9, 22.9, 21.9; IR (film)  $\nu_{\max}$  3301, 2960, 1722, 1657, 1625, 1544, 1231, 985 cm<sup>-1</sup>; HRMS (ESI) *m/z* 186.11262 (MH<sup>+</sup>, C<sub>9</sub>H<sub>15</sub>NO<sub>3</sub>H<sup>+</sup> requires 186.11247).



**(*S*)-methyl 2-((*S*)-2-acrylamido-4-methylpentanamido)-3-methylbutanoate (51).**

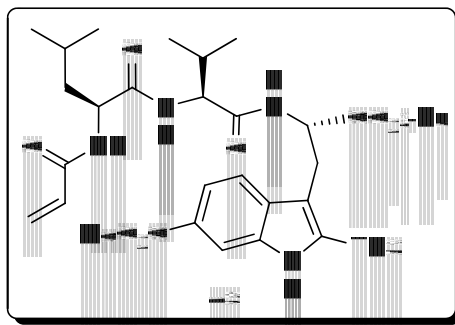
To a solution of compound **50** (212.0 mg, 1.140 mmol) and Val-OMe (150.0 mg, 1.140 mmol) in 3.0 mL anhydrous THF was treated with HOBt (198.0 mg, 1.490 mmol) at °C, followed by EDCI (276.0 mg, 1.49 mmol). The resulting mixture was stirred at 0 °C → rt for 12 hours. The solution was treated with 100 mL sat. aq. NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 mL). The combined organic layers were dried and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 2.5 × 20 cm, 1% →

5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) afforded **51** (288.8 mg, 0.969 mmol, 85% yield) as a yellow solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 6.91 (d, *J* = 8.5 Hz, 1H), 6.52 (d, *J* = 8.5 Hz, 1H), 6.34 (d, *J* = 15.0 Hz, 1H), 6.19 (d, *J* = 9.0 Hz, 1H), 5.65 (d, *J* = 8.5 Hz, 1H), 4.79–4.62 (m, 1H), 4.58–4.42 (m, 1H), 4.73 (s, 3H), 2.25–2.08 (m, 1H), 1.78–1.42 (m, 3H), 1.10–0.79 (m, 12H); HRMS (ESI) *m/z* 299.19553 (MH<sup>+</sup>, C<sub>15</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>H<sup>+</sup> requires 299.19653).



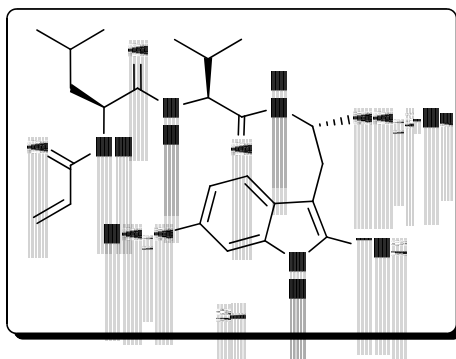
**(S)-2-((S)-2-acrylamido-4-methylpentanamido)-3-methylbutanoic acid (46)**. To a solution of compound **51** (130.0 mg, 0.436 mmol) in *t*-BuOH/H<sub>2</sub>O (4:1, 5 mL) was treated with 1M LiOH (87.2 μL, 0.872 mmol). The resulting mixture was stirred at rt for 2 hours. The reaction was diluted with 50 mL H<sub>2</sub>O and acidified with 1M HCl (ca. 1.5 mL). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 × 30mL). The combined organic layers were dried and concentrated in vacuo. The residue was kept under high vacuum for 8 hours to afford the product **46** (122.6 mg, 0.432 mmol, 99%) as a white solid: [α]<sub>D</sub><sup>25</sup> −41.1 (*c* 1.93, MeOH); <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz) δ 6.31 (dd, *J* = 19.5, 12.5 Hz, 1H), 6.23 (dd, *J* = 17.5, 2.5 Hz, 1H), 5.67 (dd, *J* = 10.5, 2.0 Hz, 1H), 4.56 (dd, *J* = 9.0, 6.0 Hz, 1H), 4.28–4.23 (m, 1H), 2.20–2.12 (m, 1H), 1.72–1.58 (m, 3H), 1.02–0.88 (m, 12H); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz) δ 174.5, 168.1 (2C), 131.8, 127.4, 60.2, 53.4, 41.8, 32.5, 26.1, 23.6, 22.1, 19.9, 18.4; IR (film) ν<sub>max</sub> 3281, 2960, 1652, 1543, 1468, 1409, 1236, 1159, 1034, 986 cm<sup>−1</sup>; HRMS (ESI)





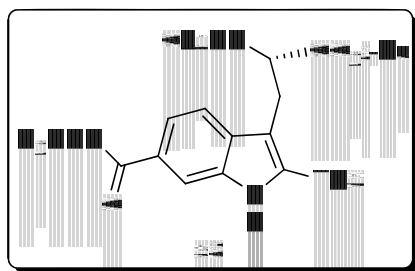
**Compound 45.** To a solution of the amine (**52**, 590.0 mg, 1.370 mmol) and the acid (**46**, 388.0 mg, 1.370 mmol) in 25 mL anhydrous THF was treated with HOBT (240.0 mg, 1.78 mmol) at 0 °C, followed by EDCI (334.0 mg, 1.78 mmol). The resulting mixture was stirred at 0 °C → rt for 12 hours. It was then treated with 100 mL sat. aq. NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4×50mL). The combined organic layers were dried and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 2.5×21 cm, 1% → 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) afforded **45** (927.6 mg, 1.329 mmol, 97% yield) as a yellow solid:  $[\alpha]_D^{25} -7.9$  (*c* 0.85, MeOH); <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz, mixture of conformational isomers) δ 8.10 (s, 1H), 7.72 and 7.66 (2d, *J* = 8.0 Hz, 1H), 7.65 and 7.35 (2d, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 6.37–6.27 (m, 1H), 6.27–6.20 (m, 1H), 5.70–5.64 (m, 1H), 4.66–4.56 (m, 1H), 4.56–4.45 (m, 1H), 4.26–4.15 (m, 1H), 3.90 (s, 3H), 3.43–3.31 (m, 1H), 3.23–3.10 (m, 1H), 2.16–1.97 (m, 1H), 1.70–1.56 (m, 1H), 1.56–1.42 (m, 1H), 1.36–1.25 (m, 1H), 1.11 (s, 9H), 1.04–0.80 (m, 27H); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz, mixture of conformational isomers) δ 174.5, 173.2, 172.6, 170.3, 168.1, 139.8, 138.8, 134.0, 131.8, 127.5, 124.1, 121.4, 120.8, 120.7, 120.0, 114.6, 82.6, 60.0, 56.8, 54.1, 53.2, 52.5, 41.7, 32.6, 31.0, 29.8, 28.1 (3C), 26.1, 23.6, 22.1, 19.8, 18.8, 7.8 (3C), 4.5 (3C); IR (film)  $\nu_{\max}$  3280, 2956, 1716, 1645, 1554, 1436, 1367, 1295, 1223, 1156, 1099, 738 cm<sup>-1</sup>; HRMS (ESI) *m/z*

699.41475 (MNa<sup>+</sup>, C<sub>37</sub>H<sub>58</sub>N<sub>4</sub>O<sub>7</sub>SiH<sup>+</sup> requires 699.41581).



**Compound 54.** To a solution of the methyl ester (**45**, 825.0 mg, 1.180 mmol) in 5.0 mL 1,2-dichloroethane was treated with Me<sub>3</sub>SnOH (3.360 g, 18.88 mmol). The resulting suspension was stirred at 80 °C for 7 days. The reaction was treated with 100 mL brine and acidified with 6M HCl (ca. 4.0 mL). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 × 30 mL). The combined organic layers were dried and concentrated. Flash chromatography (SiO<sub>2</sub>, 3.0 × 30 cm, 1% → 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) afforded the recovered starting material (**45**, 296.5 mg, 0.425 mmol, 36%) and the product (**54**, 508.5 mg, 0.743 mmol, 63% yield) as a white solid: [α]<sub>D</sub><sup>25</sup> -24 (c 0.80, MeOH); <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz) δ 8.05 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 6.35 (dd, *J* = 17.0, 10.0, 1H), 6.25 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.68 (dd, *J* = 10.5, 2.0 Hz, 1H), 4.61 (dd, *J* = 8.5, 8.0 Hz, 1H), 4.52 (dd, *J* = 9.0, 6.0 Hz, 1H), 4.20 (d, *J* = 7.5 Hz, 1H), 3.33 (dd, *J* = 14.5, 9.5 Hz, 1H), 3.12 (dd, *J* = 14.5, 7.5 Hz, 1H), 2.03–1.97 (m, 1H), 1.68–1.58 (m, 1H), 1.55–1.49 (m, 2H), 1.09 (s, 9H), 1.05–0.97 (m, 15H), 0.97–0.85 (m, 12H); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz) δ 175.7, 174.6, 173.2, 172.8, 168.2, 140.1, 136.7, 132.6, 131.8, 130.3, 127.4, 121.4, 120.9, 119.1, 114.2, 82.5, 60.2, 56.9, 53.2, 41.7, 32.4, 29.9, 28.1 (3C), 26.1, 23.7, 22.0, 19.8, 18.9, 8.1 (3C), 4.6 (3C); IR (film) ν<sub>max</sub> 3275, 2957, 1734, 1643, 1541, 1387, 1234,

1155  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  685.39989 ( $\text{MNa}^+$ ,  $\text{C}_{36}\text{H}_{56}\text{N}_4\text{O}_7\text{SiH}^+$  requires 685.39910).

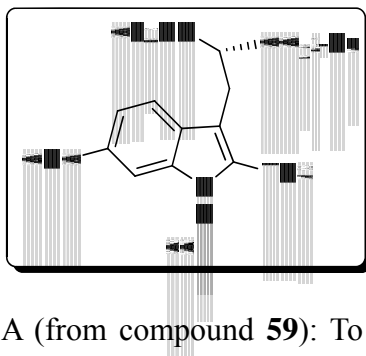


**Compound 58.** To a solution of the methyl ester (**17**, 200.0 mg, 0.353 mmol) in 10 mL MeOH was treated with hydrazine monohydrate at rt. The resulting mixture was stirred at 70 °C for 3 hours. The reaction was cooled to rt and concentrated in vacuo. Excess hydrazine monohydrate was removed under high vacuum. Flash chromatography ( $\text{SiO}_2$ ,  $2.5 \times 30$  cm, 0%  $\rightarrow$  5% MeOH/EtOAc) afforded the product (**58**, 180.0 mg, 0.318 mmol, 90% yield) as a white solid:  $[\alpha]_D^{25} +4.1$  ( $c$  1.89 MeOH);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  7.91 (s, 1H), 7.67 (d,  $J = 8.0$  Hz, 1H), 7.40 (d,  $J = 9.0$  Hz, 1H), 7.29–7.19 (m, 5H), 4.93 (s, 2H), 4.36 (t,  $J = 7.5$  Hz, 1H), 3.38–3.30 (m, 1H), 3.12 (dd,  $J = 14.0, 8.5$  Hz, 1H), 1.24 (s, 9H), 1.06–0.92 (m, 15H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  173.3, 171.3, 158.3, 139.9, 138.2, 137.4, 133.0, 129.5 (2C), 129.0, 128.8 (2C), 127.2, 121.7, 120.1, 118.3, 112.1, 82.7, 67.6, 58.8, 29.9, 28.3 (3C), 7.9 (3C), 4.5 (3C); IR (film)  $\nu_{\text{max}}$  3324, 2955, 2875, 1711, 1634, 1528, 1368, 1236, 1154, 739  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  567.29789 ( $\text{MH}^+$ ,  $\text{C}_{30}\text{H}_{42}\text{N}_4\text{O}_5\text{SiH}^+$  requires 567.29972).



**Compound 59.** To a solution of the acylhydrazine (**58**, 50.0 mg, 0.0883 mmol) in anhydrous THF/Pyridine (1:1, 20 mL) was treated with 2-nitrobenzene-1-sulfonyl chloride (**NSCl**, 23.0 mg, 0.104 mmol). The resulting mixture was stirred at rt for 17 hours. The reaction was concentrated in vacuo. Pyridine was removed under high vacuum. Flash chromatography (SiO<sub>2</sub>, 2.5 × 30 cm, 10% → 50% EtOAc/Hexanes) afforded the product (**59**, 49.7 mg, 0.0662 mmol, 75% yield) as a yellow solid:  $[\alpha]_D^{25}$  -1.4 (*c* 1.0 CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.71 (d, *J* = 12.0 Hz, 2H), 8.57 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.78 (s, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.32–7.24 (m, 4H), 7.24–7.15 (m, 2H), 5.31 (d, *J* = 8.0 Hz, 1H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.84 (d, *J* = 12.0 Hz, 1H), 4.54–4.46 (m, 1H), 3.30 (dd, *J* = 14.5, 5.0 Hz, 1H), 3.09 (dd, *J* = 14.5, 10.0 Hz, 1H), 1.33 (s, 9H), 1.02–0.96 (m, 9H), 0.96–0.89 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 171.7, 167.6, 155.9, 147.9, 138.0, 137.8, 134.7, 133.1, 132.4, 132.1, 131.9, 128.6, 128.3, 128.1, 126.4, 123.7, 120.5, 119.3, 118.0, 114.9, 111.3, 82.4, 66.9, 60.6, 56.3, 30.1, 28.0 (3C), 14.4, 7.5 (3C), 3.7 (3C); IR (film)  $\nu_{\max}$  3348, 2956, 2875, 1709, 1543, 1395, 1355, 1235, 1176, 1005, 738 cm<sup>-1</sup>; HRMS (ESI) *m/z* 774.25982 (MNa<sup>+</sup>, C<sub>36</sub>H<sub>45</sub>N<sub>5</sub>O<sub>9</sub>SiNa<sup>+</sup> requires 774.25995).

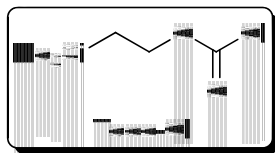




**Compound 60.** Procedure A (from compound **59**): To a solution of compound **59** (20.0 mg, 0.0266 mmol) in 2.0 mL EtOH was treated with 1M K<sub>2</sub>CO<sub>3</sub> (50.0 μL, 0.0500 mmol). The resulting mixture was stirred at 80 °C for 2 hours. The reaction was cooled to rt and diluted with 2 mL H<sub>2</sub>O. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 × 3 mL). The combined organic layers were dried and concentrated. Flash chromatography (SiO<sub>2</sub>, 1.5 × 10 cm, 10% → 30% EtOAc/Hexanes) afforded **60** (12.0 mg, 0.0223 mmol, 84% yield) as a yellow solid.

Procedure B (from compound **89**): To a solution of the alcohol (**89**, 3.990 g, 7.410 mmol) in 100 mL absolute CH<sub>2</sub>Cl<sub>2</sub> was treated with the suspension of DDQ (1.690 g, 7.410 mmol) in 40 mL CH<sub>2</sub>Cl<sub>2</sub> at 0 °C dropwise over 10 min. The resulting mixture was treated with 20 g silica gel (60–200 mesh) and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 3.5 × 30 cm, 10% → 30% EtOAc/Hexanes) afforded **60** (3.970 g, 7.410 mmol, 100% yield) as a yellow solid:  $[\alpha]_D^{25} +4.2$  (*c* 1.38, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 10.02 (s, 1H), 8.48 (brs, 1H), 7.88 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.32–7.28 (m, 3H), 7.22–7.18 (m, 2H), 5.30 (d, *J* = 8.0 Hz, 1H), 4.93 (d, *J* = 12.0 Hz, 1H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.55–4.49 (m, 1H), 3.30 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.16 (dd, *J* = 14.5, 9.0 Hz, 1H), 1.30 (s, 9H), 1.20–0.94 (m, 15H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 192.8, 171.5, 155.8, 139.2, 138.0, 136.4, 133.9, 131.4, 128.6 (2C), 128.3, 128.2 (2C), 121.0, 120.6,

119.6, 114.1, 82.3, 66.9, 56.3, 30.2, 28.0 (3C), 7.6 (3C), 3.7 (3C); IR (film)  $\nu_{\max}$  3346, 2955, 2875, 1701, 1606, 1508, 1368, 1224, 1153, 740  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  537.27470 ( $\text{MH}^+$ ,  $\text{C}_{30}\text{H}_{40}\text{N}_2\text{O}_5\text{SiH}^+$  requires 537.27793).

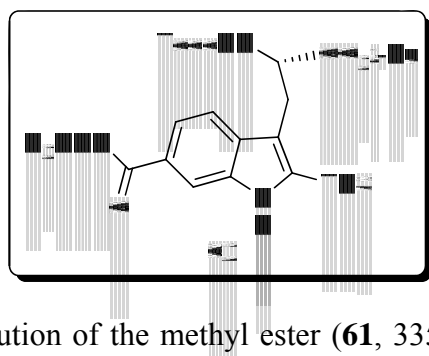


**2-(trimethylsilyl)ethyl carbonochloridate (Teoc-Cl).** A 50 mL flask was charged with  $\text{K}_2\text{CO}_3$  (1.000 g, 7.240 mmol) and degassed with  $\text{N}_2$ . Injected 5.0 mL anhydrous toluene and 2-(trimethylsilyl)ethanol (821.3 mg, 1.00 mL, 6.96 mmol). The resulting mixture was cooled to  $-10\text{ }^\circ\text{C}$ . The suspension was treated with the solution of phosgene in toluene (20%, 5.10 mL) over 30 min while vigorous stirring. The reaction was stirred at rt for an hour.  $\text{N}_2$  was bubbled through the mixture for an hour to get rid of the excess phosgene. The solution was filtered through a pad of anhydrous  $\text{MgSO}_4$ , and washed with dry ether ( $5 \times 5$  mL). The filtration was concentrated in vacuo. Toluene was then removed under high vacuum to afford the product (704.4 mg, 3.902 mmol, 56% yield) as a colorless oil.<sup>45</sup>



**Compound 61.** To a solution of the amine (**52**, 400.0 mg, 0.930 mmol) in anhydrous THF was treated with  $\text{K}_2\text{CO}_3$  (1.270 g, 9.300 mmol), followed by 2-(trimethylsilyl)ethyl carbonochloridate (260.0 mg, 1.440 mmol). The resulting mixture was stirred at rt for 12 hours. The reaction was treated with 20 mL  $\text{H}_2\text{O}$  and

extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The combined organic layers were dried and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 3.5 × 30 cm, 10% EtOAc/Hexanes) afforded **61** (530.3 mg, 0.921 mmol, 99% yield) as a yellow solid:  $[\alpha]_D^{25} +5.9$  (c 3.2, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.45 (brs, 1H), 8.13 (s, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 5.14 (d, *J* = 8.0 Hz, 1H), 4.48 (dd, *J* = 14.5, 8.0 Hz, 1H), 4.03–3.93 (m, 2H), 3.93 (s, 3H), 3.28 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.14 (dd, *J* = 14.0, 9.5 Hz, 1H), 1.30 (s, 9H), 1.01 (d, *J* = 6.0 Hz, 9H), 0.97 (t, *J* = 6.0 Hz, 6H), 0.88–0.78 (m, 2H), –0.04 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 171.8, 168.4, 156.1, 137.9, 137.3, 132.5, 123.8, 120.6, 120.4, 118.8, 113.4, 82.0, 63.3, 56.1, 52.1, 30.1, 28.0 (3C), 17.7, 7.6 (3C), 3.7 (3C), –1.4 (3C); IR (film)  $\nu_{\max}$  3357, 2954, 1698, 1509, 1435, 1367, 1295, 1224, 1156, 1099, 838, 749 cm<sup>-1</sup>; HRMS (ESI) *m/z* 577.31269 (MH<sup>+</sup>, C<sub>29</sub>H<sub>48</sub>N<sub>2</sub>O<sub>6</sub>Si<sub>2</sub>H<sup>+</sup> requires 577.31237).



**Compound 62.** To a solution of the methyl ester (**61**, 335.0 mg, 0.581 mmol) in 5 mL CHCl<sub>3</sub> was treated with 15 mL MeOH and 15 mL hydrazine monohydrate at 0 °C. The mixture was stirred at 0 °C for 48 hours and concentrated under high vacuum at 0 °C. Flash chromatography (SiO<sub>2</sub>, 2.5 × 20 cm, 1% → 10% MeOH/EtOAc) afforded **62** (250.0 mg, 0.430 mmol, 74% yield) as a yellow solid:  $[\alpha]_D^{25} +9.0$  (c 1.63, MeOH); <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz) δ 7.87 (s, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 4.30 (t, *J* = 8.0 Hz, 1H), 3.97 (t, *J* = 8.5 Hz,

1H), 3.30 (dd,  $J = 15.0, 6.5$  Hz, 1H), 3.08 (dd,  $J = 14.0, 9.0$  Hz, 1H), 1.21 (s, 9H), 1.03–0.93 (m, 16H), 0.88–0.80 (m, 2H), –0.04 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  173.5, 171.3, 158.7, 140.0, 137.4, 133.0, 127.1, 121.7, 120.1, 118.2, 112.1, 82.6, 64.2, 58.6, 29.9, 28.3 (3C), 18.7, 7.9 (3C), 4.5 (3C), –1.3 (3C); IR (film)  $\nu_{\text{max}}$  3320, 2954, 2875, 1705, 1630, 1526, 1330, 1250, 1155, 1062, 860, 838, 738  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  577.32320 ( $\text{MH}^+$ ,  $\text{C}_{28}\text{H}_{48}\text{N}_4\text{O}_5\text{Si}_2\text{H}^+$  requires 577.32360).

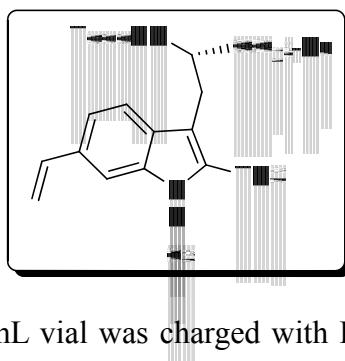


**Compound 63.** To a solution of the acyl hydrazine (**62**, 610.0 mg, 1.060 mmol) in anhydrous pyridine (30.0 mL) was treated with  $\text{NsCl}$  (281.0 mg, 1.290 mmol). The solution was stirred at rt for 20 hours. Pyridine was removed under high vacuum. Flash chromatography ( $\text{SiO}_2$ ,  $2.5 \times 20$  cm, 20%  $\rightarrow$  50% EtOAc/Hexanes) afforded product **63** (605.0 mg, 0.795 mmol, 75% yield) as a yellow solid:  $[\alpha]_{\text{D}}^{25} -4.3$  ( $c$  0.77,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.71 (dd,  $J = 19.0, 5.0$  Hz, 2H), 8.52 (s, 1H), 8.12 (dd,  $J = 8.0$  Hz, 1H), 8.01 (d,  $J = 8.0$  Hz, 1H), 7.78 (s, 1H), 7.72 (t,  $J = 8.0$  Hz, 1H), 7.62 (d,  $J = 8.5$  Hz, 1H), 7.60 (t,  $J = 6.5$  Hz, 1H), 7.33 (d,  $J = 8.5$  Hz, 1H), 5.11 (d,  $J = 8.5$  Hz, 1H), 4.54–4.45 (m, 1H), 4.06–3.98 (m, 1H), 3.98–3.81 (m, 1H), 3.28 (dd,  $J = 14.0, 5.0$  Hz, 1H), 3.08 (dd,  $J = 14.0, 9.0$  Hz, 1H), 1.33 (s, 9H), 1.05–0.90 (m, 15H), 0.86 (t,  $J = 9.0$  Hz, 2H), –0.04 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  171.9, 167.5, 156.3, 148.0, 138.0, 137.8, 134.7, 133.1, 132.4, 132.2, 131.9, 126.4, 123.8, 120.6, 119.4, 118.0, 111.2, 82.3, 63.5, 56.0, 30.0, 28.0 (3C), 17.7, 7.5

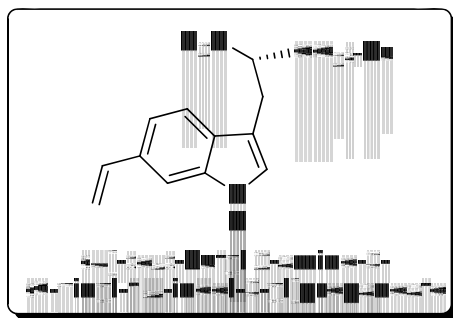
(3C), 3.7 (3C), -1.4 (3C); IR (film)  $\nu_{\max}$  3324, 2955, 1701, 1543, 1356, 1250, 1177, 839, 738  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  762.30114 ( $\text{MH}^+$ ,  $\text{C}_{34}\text{H}_{51}\text{N}_5\text{O}_9\text{SSi}_2\text{H}^+$  requires 762.30188).



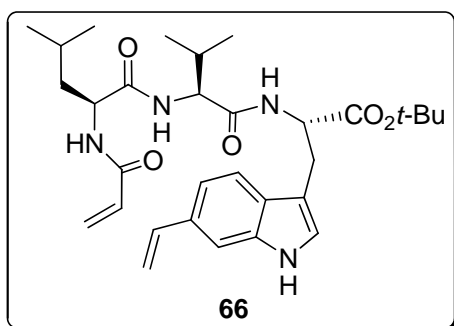
**Compound 64.** To a solution of compound **63** (530.0 mg, 0.696 mmol) in 105 mL EtOH was treated with 1M  $\text{K}_2\text{CO}_3$  (1.37 mL, 1.370 mmol). The resulting mixture was refluxed for 3 hours. The reaction was cooled to rt and concentrated in vacuo. Flash chromatography ( $\text{SiO}_2$ ,  $2.5 \times 18$  cm, 10%  $\rightarrow$  20% EtOAc/Hexanes) afforded product **64** (319.2 mg, 0.585 mmol, 84% yield) as a yellow solid:  $[\alpha]_{\text{D}}^{25} -5.3$  ( $c$  0.73,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  10.0 (s, 1H), 8.39 (s, 1H), 7.88 (s, 1H), 7.72 (d,  $J = 8.5$  Hz, 1H), 7.62 (d,  $J = 9.0$  Hz, 1H), 5.12 (d,  $J = 8.0$  Hz, 1H), 4.56–4.46 (m, 1H), 4.04–3.86 (m, 2H), 3.28 (dd,  $J = 14.5, 6.5$  Hz, 1H), 3.14 (dd,  $J = 14.5, 9.0$  Hz, 1H), 1.30 (s, 9H), 1.06–0.92 (m, 15H), 0.87–0.81 (m, 2H), -0.04 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  192.8, 171.7, 156.1, 139.1, 138.0, 133.9, 131.4, 121.1, 120.6, 119.6, 114.0, 82.2, 63.4, 56.1, 30.2, 28.0 (3C), 17.7, 7.6 (3C), 3.7 (3C), -1.3 (3C); IR (film)  $\nu_{\max}$  3346, 2955, 2876, 1690, 1607, 1508, 1368, 1250, 1153, 1090, 1062, 1005, 838, 739  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  547.30134 ( $\text{MH}^+$ ,  $\text{C}_{28}\text{H}_{46}\text{N}_2\text{O}_5\text{Si}_2\text{H}^+$  requires 547.30180).



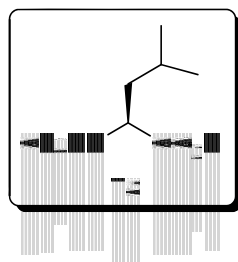
**Compound 65.** To the 20 mL vial was charged with  $\text{Ph}_3\text{PCH}_2\text{Br}$  (820.0 mg, 2.340 mmol) under Ar. Injected 8 mL absolute THF to the vial. *n*-BuLi solution (1.6 M in Hexanes, ca. 1.5 mL, 2.400 mmol) was then injected dropwise, until the yellow color of the solution did not fade away. The resulting mixture was stirred at rt for one hour. The clean solution of the Wittig reagent was then transferred to another 20 mL vial, which was charged with the aldehyde (**64**, 256.0 mg, 0.469 mmol). The mixture was stirred at rt for an hour. The reaction was concentrated in vacuo. Flash chromatography ( $\text{SiO}_2$ ,  $2.5 \times 25$  cm, 5%  $\rightarrow$  10% EtOAc/Hexanes) afforded product **65** (234.7 mg, 0.431 mmol, 84% yield) as a white solid:  $[\alpha]_{\text{D}}^{25} -1.0$  ( $c$  3.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.98 (s, 1H), 7.55 (d,  $J = 8.0$  Hz, 1H), 7.34 (s, 1H), 7.22 (d,  $J = 8.5$  Hz, 1H), 6.80 (dd,  $J = 18.0, 11.0$  Hz, 1H), 5.73 (d,  $J = 17.5$  Hz, 1H), 5.17 (d,  $J = 11.0$  Hz, 1H), 5.04 (d,  $J = 8.0$  Hz, 1H), 4.49–4.41 (m, 1H), 4.06–3.93 (m, 2H), 3.27 (dd,  $J = 14.5, 5.5$  Hz, 1H), 3.09 (dd,  $J = 14.5, 10.0$  Hz, 1H), 1.34 (s, 9H), 1.04–0.97 (m, 9H), 0.97–0.89 (m, 6H), 0.89–0.82 (m, 2H),  $-0.04$  (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  172.0, 156.2, 138.9, 138.0, 133.7, 132.4, 129.1, 120.6, 119.2, 118.0, 112.0, 109.0, 81.8, 63.3, 56.1, 29.9, 28.0 (3C), 17.7, 7.6 (3C), 3.8 (3C),  $-1.3$  (3C); IR (film)  $\nu_{\text{max}}$  3358, 2954, 1702, 1508, 1250, 1156, 1063, 838, 738  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  545.32254 ( $\text{MH}^+$ ,  $\text{C}_{29}\text{H}_{48}\text{N}_2\text{O}_4\text{Si}_2\text{H}^+$  requires 545.32372).



**(S)-tert-butyl 2-amino-3-(6-vinyl-1H-indol-3-yl)propanoate.** To a solution of compound **65** (200.0 mg, 0.368 mmol) in 20 mL THF was treated with tetrabutylammonium fluoride hydrate (480.0 mg, 1.838 mmol) at rt. The resulting mixture was stirred at 60 °C for 2 hours. The reaction was concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 2.5×20 cm, 20% MeOH/EtOAc) afforded product (103.1 mg, 0.361 mmol, 98% yield) as a yellow oil:  $[\alpha]_D^{25} +10.9$  (*c* 1.2, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.25 (brs, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.34 (s, 1H), 7.28–7.24 (m, 1H), 7.03 (s, 1H), 6.81 (dd, *J* = 17.0, 10.5 Hz, 1H), 5.73 (d, *J* = 17.5 Hz, 1H), 5.18 (d, *J* = 10.5 Hz, 1H), 3.71 (t, *J* = 7.5 Hz, 1H), 3.23 (dd, *J* = 14.0, 4.5 Hz, 1H), 2.96 (dd, *J* = 14.5, 7.5 Hz, 1H), 1.90–1.60 (brs, 2H), 1.43 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 174.8, 137.9, 136.7, 132.3, 127.8, 123.8, 119.1, 118.1, 112.1, 111.9, 109.5, 81.3, 55.7, 31.0, 28.2 (3C); IR (film)  $\nu_{\max}$  3366, 2977, 2923, 1724, 1622, 1455, 1361, 1245, 1156, 899, 813 cm<sup>-1</sup>; HRMS (ESI) *m/z* 287.17543 (MH<sup>+</sup>, C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>H<sup>+</sup> requires 287.17540).



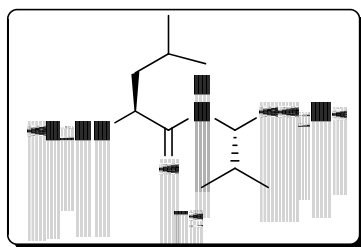
**Compound 66.** To a solution of the amino compound ((*S*)-tert-butyl 2-amino-3-(6-vinyl-1H-indol-3-yl)propanoate, 105.2 mg, 0.368 mmol) and the carboxylic acid (**46**, 105.0 mg, 0.368 mmol) in anhydrous THF was treated with HOBt (70.0 mg, 0.515 mmol) at 0 °C, followed by EDCI (95.0 mg, 0.515 mmol). The resulting mixture was stirred at 0 °C → rt for 12 hours. The solution was treated with 30 mL sat. aq. NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×30mL). The combined organic layers were dried and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 2.5×21 cm, 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) afforded **66** (175.0 mg, 0.317 mmol, 86% yield) as a yellow solid:  $[\alpha]_D^{25} -32.4$  (*c* 1.43, MeOH); <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz) δ 7.48 (d, *J* = 8.0 Hz, 1H), 7.33 (s, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.08 (s, 1H), 6.78 (dd, *J* = 18.0, 11.0 Hz, 1H), 6.35–6.20 (m, 2H), 5.74–5.64 (m, 2H), 5.09 (d, *J* = 11.0 Hz, 1H), 4.67–4.58 (m, 1H), 4.56–4.47 (m, 1H), 4.27–4.16 (m, 1H), 3.23 (dd, *J* = 14.5, 7.5 Hz, 1H), 3.12 (dd, *J* = 14.5, 7.5 Hz, 1H), 2.14–2.01 (m, 1H), 1.69–1.54 (m, 3H), 1.31 (s, 9H), 1.02–0.77 (m, 12H); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz) δ 174.7, 173.4, 172.6, 168.1, 139.6, 138.3, 132.9, 131.7, 128.9, 127.5, 125.6, 119.5, 118.4, 111.3, 111.1, 110.7, 82.8, 79.6, 60.0, 55.4, 53.3, 41.8, 32.4, 28.3 (3C), 26.1, 23.6, 22.1, 19.9, 18.8; IR (film)  $\nu_{\max}$  3281, 2961, 1726, 1643, 1542, 1368, 1233, 1156 cm<sup>-1</sup>; HRMS (ESI) *m/z* 575.32021 (MNa<sup>+</sup>, C<sub>31</sub>H<sub>44</sub>N<sub>4</sub>O<sub>5</sub>Na<sup>+</sup> requires 575.32039).



**(*S*)-2-(benzyloxycarbonylamino)-4-methylpentanoic acid (78).** To a solution of



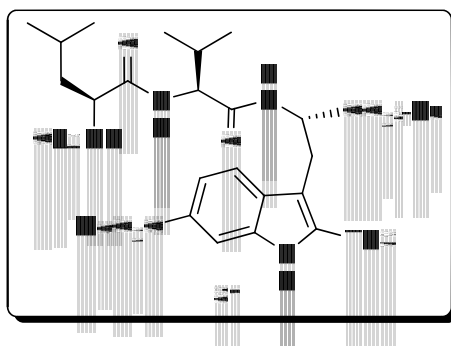
L-leucine (**77**, 535.0 mg, 4.084 mmol) in aq. NaOH (2M, 5.0 mL, 10.000 mmol) was treated with benzyl chloroformate (805.6 mg, 0.70 mL, 4.725 mmol) dropwise at 0 °C over 30 min. The resulting mixture was stirred at rt for 4 hours. The reaction was diluted with 20 mL H<sub>2</sub>O and acidified with 6M HCl (ca. 2.5 mL). The mixture was extracted with EtOAc (5×20 mL). The combined organic layers were dried and concentrated in vacuo, then kept under high vacuum overnight to afford the product (**78**, 1.082 g, 4.084 mmol) as a colorless oil.<sup>55</sup>



**(S)-methyl 2-((S)-2-(benzyloxycarbonylamino)-4-methylpentanamido)-3-methylbutanoate (79)**. To a solution of Cbz-Leu-OH (**78**, 1.078 g, 4.070 mmol) and Val-OMe (0.690 g, 4.07 mmol) in anhydrous THF (30 mL) was treated with HOBT (690.0 mg, 5.290 mmol) at 0 °C, followed by EDCI (990.0 mg, 5.290 mmol). The resulting mixture was stirred at 0 °C → rt for 12 hours. The reaction was treated with 100 mL sat. aq. NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (5×30mL). The combined organic layers were dried and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 2.5×25 cm, 10% → 40% EtOAc/Hexanes) afforded **79** (1.385 g, 3.663 mmol, 90% yield) as a yellow oil.



**(S)-2-((S)-2-(benzyloxycarbonylamino)-4-methylpentanamido)-3-methylbutanoic acid (80).** To a solution of the methyl ester (**79**, 1.000 g, 2.645 mmol) in *t*-BuOH/H<sub>2</sub>O (4:1, 25 mL) was treated with 1M LiOH (5.3 mL, 5.300 mmol). The resulting mixture was stirred at rt for 12 hours. The reaction was diluted with 50 mL H<sub>2</sub>O and acidified with 6M HCl (ca. 2.0 mL). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5×30mL). The combined organic layers were dried and concentrated in vacuo. The residue was kept under high vacuum overnight to afford the product (**80**, 0.866 g, 2.380 mmol, 90% yield) as a yellow oil.



**Compound 81.** To a solution of the amino compound (**52**, 1.145 g, 2.650 mmol) and Cbz-Leu-Val-OH (**80**, 0.965 g, 2.650 mmol) in anhydrous THF (40 mL) was treated with HOBT (460.0 mg, 3.440 mmol) at 0 °C, followed by EDCI (640.0 mg, 3.440 mmol). The resulting mixture was stirred at 0 °C → rt for 12 hours. The reaction was treated with 100 mL sat. aq. NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (5×30mL). The combined organic layers were dried and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 3.5×30 cm, 10% → 40% EtOAc/Hexanes) afforded **81**

(1.876 g, 2.411 mmol, 91% yield) as a yellow solid:  $[\alpha]_D^{25} -11.0$  (*c* 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.27 (s, 1H), 8.12 (s, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.39–7.27 (m, 5H), 6.46 (d, *J* = 9.0 Hz, 1H), 6.43 (d, *J* = 8.5 Hz, 1H), 5.27 (d, *J* = 7.5 Hz, 1H), 5.10 (s, 2H), 4.69 (dd, *J* = 16.5, 8.5 Hz, 1H), 4.23 (t, *J* = 6.5 Hz, 1H), 4.20–4.14 (m, 1H), 3.91 (s, 3H), 3.25 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.17 (dd, *J* = 14.0, 9.0 Hz, 1H), 2.10–2.02 (m, 1H), 1.70–1.59 (m, 1H), 1.59–1.43 (m, 2H), 1.18 (s, 9H), 1.10–0.97 (m, 27H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 172.2, 171.2, 170.5, 168.3, 156.5, 137.9, 137.6, 136.4, 132.6, 128.7 (2C), 128.4, 128.3 (2C), 124.1, 120.7, 120.1, 118.7, 113.5, 82.2, 67.3, 58.3, 54.8, 53.9, 52.2, 41.4, 31.6, 29.6, 27.9 (3C), 24.9, 23.2, 22.1, 19.2, 17.9, 7.7 (3C), 3.7 (3C); IR (film)  $\nu_{\max}$  3325, 2956, 1645, 1531, 1436, 1368, 1295, 1219, 1154, 1099, 1044, 737, 698 cm<sup>-1</sup>; HRMS (ESI) *m/z* 779.44168 (MH<sup>+</sup>, C<sub>42</sub>H<sub>62</sub>N<sub>4</sub>O<sub>8</sub>SiH<sup>+</sup> requires 779.44097).



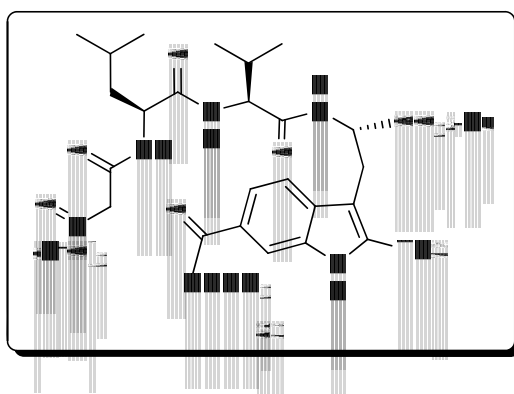
**Compound 82.** To a solution of the starting material (**81**, 750.0 mg, 0.964 mmol) in MeOH (60 mL) was treated with NH<sub>4</sub>OAc (79.4 mg, 0.964 mmol), followed by 10% Pd/C (227.0 mg). The resulting mixture was stirred under H<sub>2</sub> (1 atm) at rt for 24 hours. The reaction was filtered through a fine sintered glass pad filter and washed with MeOH (5 × 50 mL). The solution was concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 2.5 × 30 cm, 10% MeOH/EtOAc) afforded the amino

product (**82**, 564.9 mg, 0.877 mmol, 91% yield) as a white solid:  $[\alpha]_D^{25} -0.3$  (c 0.67, MeOH);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.54 (s, 1H), 8.16 (s, 1H), 7.74 (d,  $J = 8.5$  Hz, 1H), 7.64 (t,  $J = 7.0$  Hz, 2H), 6.48 (d,  $J = 7.0$  Hz, 1H), 4.70 (dd,  $J = 17.0, 7.5$  Hz, 1H), 4.20 (dd,  $J = 9.5, 6.5$  Hz, 1H), 3.92 (s, 3H), 3.35–3.26 (m, 2H), 3.17 (dd,  $J = 14.0, 9.5$  Hz, 1H), 2.13–2.04 (m, 1H), 1.74–1.60 (m, 2H), 1.40–1.23 (m, 3H), 1.27 (s, 9H), 1.06–0.99 (m, 9H), 0.98 (t,  $J = 5.5$  Hz, 6H), 0.94 (d,  $J = 6.5$  Hz, 3H), 0.92 (d,  $J = 6.5$  Hz, 3H), 0.87 (d,  $J = 6.5$  Hz, 3H), 0.77 (d,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  175.8, 171.2, 170.9, 168.4, 137.9, 137.7, 132.7, 123.7, 120.4 (2C), 118.8, 113.5, 82.0, 57.9, 54.8, 53.7, 52.2, 44.1, 31.2, 29.5, 27.9 (3C), 25.0, 23.7, 21.2, 19.4, 17.8, 7.6 (3C), 3.7 (3C); IR (film)  $\nu_{\text{max}}$  3321, 2956, 1652, 1511, 1367, 1295, 1222, 1155, 1098, 738  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  677.38356 ( $\text{MNa}^+$ ,  $\text{C}_{34}\text{H}_{56}\text{N}_4\text{O}_6\text{SiNa}^+$  requires 667.38613).



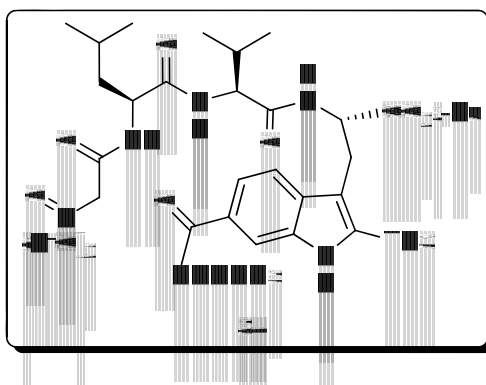
**Compound 69.** To a solution of the amino compound (**82**, 250.0 mg, 0.388 mmol) in 30 mL anhydrous  $\text{CH}_2\text{Cl}_2$  was treated with  $\text{Et}_3\text{N}$  (1.05 mL, 7.76 mmol), followed by the solution of the phosphonate (**72**, 266.8 mg, 1.244 mmol) in 10 mL anhydrous  $\text{CH}_2\text{Cl}_2$ . The resulting mixture was stirred at rt for 18 hours. The reaction was concentrated in vacuo. Flash chromatography ( $\text{SiO}_2$ ,  $3.5 \times 25$  cm, 50% EtOAc/Hexanes to 100% EtOAc, then 10% MeOH/EtOAc) afforded the product (**69**,

162.6 mg, 0.198 mmol, 51% yield) as a yellow solid:  $[\alpha]_D^{25} -11.4$  ( $c$  2.67,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.65 (s, 1H), 8.15 (s, 1H), 7.74 (d,  $J = 8.5$  Hz, 1H), 7.62 (d,  $J = 8.5$  Hz, 1H), 7.12 (d,  $J = 8.0$  Hz, 1H), 6.65–6.59 (m, 2H), 4.67 (dd,  $J = 16.0, 8.0$  Hz, 1H), 4.46–4.40 (m, 1H), 4.23–4.12 (m, 4H), 3.92 (s, 3H), 3.27 (dd,  $J = 14.5, 8.0$  Hz, 1H), 3.17 (dd,  $J = 14.0, 8.5$  Hz, 1H), 2.95 (d,  $J = 4.5$  Hz, 1H), 2.91 (d,  $J = 4.0$  Hz, 1H), 2.11–2.04 (m, 1H), 1.70–1.59 (m, 1H), 1.54–1.47 (m, 1H), 1.46–1.41 (m, 1H), 1.40–1.26 (m, 7H), 1.18 (s, 9H), 1.06–0.94 (m, 15H), 0.90–0.83 (m, 12H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  171.7, 171.2, 170.5, 168.4, 164.4, 137.9, 137.8, 132.4, 123.8, 120.4, 119.9, 118.7, 113.5, 81.9, 63.0 (d,  $J = 6.1$  Hz, 1C), 62.8 (d,  $J = 6.1$  Hz, 1C), 58.6, 54.7, 52.3, 52.1, 41.1, 35.8 (d,  $J = 130.5$  Hz, 1C), 31.1, 29.3, 27.8 (3C), 24.7, 23.2, 21.7, 19.2, 18.1, 16.51, 16.47, 7.6 (3C), 3.7 (3C); IR (film)  $\nu_{\text{max}}$  3284, 2957, 2874, 1714, 1642, 1542, 1367, 1295, 1222, 1158, 1099, 1026, 975, 750  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  823.45231 ( $\text{MH}^+$ ,  $\text{C}_{40}\text{H}_{67}\text{N}_4\text{O}_{10}\text{PSiH}^+$  requires 823.44368).



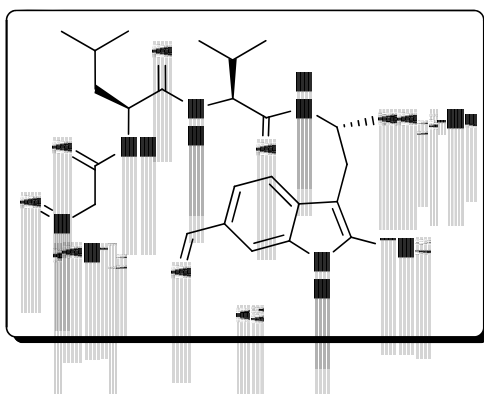
**Compound 83.** To a solution of the methyl ester (69, 65.0 mg, 0.0791 mmol) in 1.0 mL MeOH was treated with hydrazine monohydrate (0.50 mL). The resulting mixture was stirred at rt for 36 hours. The reaction was concentrated in vacuo. Excess hydrazine was removed under high vacuum. Preparation TLC (50%

MeOH/EtOAc) afforded the product (**83**, 55.3 mg, 0.0672 mmol, 85% yield) as a white solid:  $[\alpha]_D^{25} -20.0$  (*c* 0.50, MeOH);  $^1\text{H NMR}$  ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  7.87 (d,  $J = 1.5$  Hz, 1H), 7.64 (d,  $J = 8.5$  Hz, 1H), 7.40 (dd,  $J = 8.0, 1.5$  Hz, 1H), 4.61 (t,  $J = 8.5$  Hz, 1H), 4.41 (dd,  $J = 9.5, 6.0$  Hz, 1H), 4.20–4.10 (m, 4H), 3.34 (dd,  $J = 14.5, 8.5$  Hz, 1H), 3.13 (dd,  $J = 14.0, 8.0$  Hz, 1H), 2.07–1.97 (m, 1H), 1.70–1.61 (m, 1H), 1.50–1.41 (m, 2H), 1.32 (t,  $J = 3.0$  Hz, 6H), 1.18–1.15 (m, 1H), 1.14 (s, 9H), 1.05–0.98 (m, 15H), 0.94–0.86 (m, 12H);  $^{13}\text{C NMR}$  ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  174.3, 173.1, 172.6, 171.3, 166.9, 166.8, 139.9, 137.5, 132.9, 127.2, 121.3, 120.1, 118.4, 112.1, 82.6, 64.4, 64.2, 60.1, 56.9, 53.5, 41.8, 32.5, 29.8, 28.2 (3C), 25.8, 23.7, 21.9, 19.8, 18.9, 16.83, 16.78, 8.0 (3C), 4.5 (3C); IR (film)  $\nu_{\text{max}}$  3289, 2957, 1653, 1540, 1368, 1242, 1157, 1026, 974  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  823.46282 ( $\text{MH}^+$ ,  $\text{C}_{39}\text{H}_{67}\text{N}_6\text{O}_9\text{PSiH}^+$  requires 823.45492).



**Compound 84.** To a solution of the acyl hydrazine (**83**, 17.6 mg, 0.0214 mmol) in THF/Pyridine (2:1, 5.3 mL) was treated with NsCl (22.2 mg, 0.106 mmol). The resulting mixture was stirred at rt for 20 hours. The reaction was concentrated in vacuo. Pyridine was then removed under high vacuum. Preparation TLC (30% MeOH/EtOAc) afforded the product (**84**, 21.0 mg, 0.0208 mmol, 97% yield) as a yellow solid:  $[\alpha]_D^{25} -13.8$  (*c* 0.47, MeOH);  $^1\text{H NMR}$  ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  8.19 (d,

$J = 7.5$  Hz, 1H), 7.89 (d,  $J = 8.0$  Hz, 1H), 7.81–7.75 (m, 2H), 7.70 (t,  $J = 8.0$  Hz, 1H), 7.62 (d,  $J = 9.0$  Hz, 1H), 7.35 (dd,  $J = 8.5, 1.5$  Hz, 1H), 7.01 (d,  $J = 9.0$  Hz, 1H), 6.65 (d,  $J = 8.5$  Hz, 1H), 4.59 (t,  $J = 8.5$  Hz, 1H), 4.39 (dd,  $J = 9.0, 6.0$  Hz, 1H), 4.20–4.10 (m, 4H), 3.34 (t,  $J = 4.0$  Hz, 1H), 3.10 (dd,  $J = 14.0, 8.0$  Hz, 1H), 3.02 (dd,  $J = 34.0, 15.0$  Hz, 1H), 2.99 (dd,  $J = 34.0, 15.0$  Hz, 1H); 2.05–1.95 (m, 1H), 1.67–1.57 (m, 1H), 1.45–1.38 (m, 2H), 1.35–1.27 (m, 7H), 1.15 (s, 9H), 1.05–0.96 (m, 15H), 0.92–0.83 (m, 12H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  174.3, 173.2, 172.6, 170.4, 166.9, 139.7, 138.2, 135.6, 133.6, 133.4, 132.8, 128.9, 126.5, 125.9, 121.5, 120.1, 118.8, 115.7, 112.6, 82.6, 64.31, 64.26, 60.2, 56.9, 53.5, 41.9, 32.4, 31.5 (d,  $J = 113.1$  Hz, 1C), 29.7, 28.2 (3C), 25.8, 23.7, 22.0, 19.8, 18.9, 16.85, 16.80, 8.0 (3C), 4.5 (3C); IR (film)  $\nu_{\text{max}}$  3259, 2923, 1645, 1541, 1366, 1230, 1154, 1022  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  1008.43341 ( $\text{MH}^+$ ,  $\text{C}_{45}\text{H}_{70}\text{N}_7\text{O}_{13}\text{PSSiH}^+$  requires 1008.43320).



**Compound 68.** To a solution of compound **84** (21.0 mg, 0.0208 mmol) in 5.0 mL ethanol was treated with 1M  $\text{K}_2\text{CO}_3$  (41.6  $\mu\text{L}$ , 0.0416 mmol). The resulting mixture was stirred at 80  $^\circ\text{C}$  for 2 hours. The reaction was concentrated in vacuo. Preparation TLC (50% MeOH/EtOAc) afforded the product (**68**, 14.8 mg, 0.0187 mmol, 90% yield) as a yellow solid:  $[\alpha]_{\text{D}}^{25} -14.0$  (c 0.20, MeOH);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz, mixture of conformational isomers)  $\delta$  9.94 (s, 1H), 8.14 (dd,  $J = 8.0, 2.0$  Hz, 1H),

7.93 (s, 1H), 7.84 (dd,  $J = 7.5, 1.5$  Hz, 1H), 7.76 (dd,  $J = 7.5$  Hz, 1.5 Hz, 1H), 7.75 (dd,  $J = 7.0, 1.5$  Hz, 1H), 7.74 (d,  $J = 8.5$  Hz, 1H), 7.53 (dd,  $J = 8.0, 1.0$  Hz, 1H), 4.62 (t,  $J = 8.5$  Hz, 1H), 4.40 (dd,  $J = 10.5, 5.0$  Hz, 1H), 4.19–4.10 (m, 4H), 3.39–3.31 (m, 2H), 3.14 (dd,  $J = 15.0, 8.5$  Hz, 1H), 2.06–1.96 (m, 2H), 1.72–1.64 (m, 1H), 1.64–1.56 (m, 1H), 1.54–1.44 (m, 2H), 1.36–1.27 (m, 6H), 1.13 (s, 9H), 1.05–1.01 (m, 15H), 0.94–0.84 (m, 12H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz, mixture of conformational isomers)  $\delta$  194.9, 174.3, 173.1, 172.3, 166.8, 140.6, 140.0, 135.3, 134.1, 133.8, 132.2, 140.0, 130.9, 130.6, 125.8, 121.9, 120.7, 120.1, 116.4, 82.6, 64.3, 64.2, 60.2, 56.8, 53.4, 41.9, 36.7, 33.2, 32.5, 31.0, 30.8, 30.7, 30.5, 30.4, 29.7, 28.2, 28.1, 27.1, 25.9, 23.7, 22.0, 19.8, 19.0, 16.8, 16.7, 7.9, 4.4; IR (film)  $\nu_{\text{max}}$  3290, 2957, 2928, 1650, 1541, 1367, 1244, 1156, 1026  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  793.43063 ( $\text{MH}^+$ ,  $\text{C}_{39}\text{H}_{65}\text{N}_4\text{O}_9\text{PSiH}^+$  requires 793.43312).



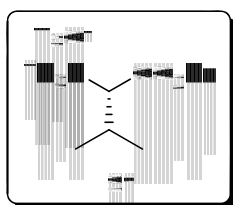
**(S)-tert-butyl**

**2-(benzyloxycarbonylamino)-3-(6-(hydroxymethyl)-2-(triethylsilyl)**

**-1H-indol-3-yl)propanoate (2).** A solution of the (S)-tert-butyl 2-(benzyloxycarbonylamino)-3-(6-((tert-butyldimethylsilyloxy)methyl)-2-(triethylsilyl)-1H-indol-3-yl)propanoate (**1**, 3.400 g, 5.210 mmol) in 160 mL AcOH-THF- $\text{H}_2\text{O}$  (3:2:2) was stirred at rt for 4 hours. The reaction was diluted with 200 mL  $\text{H}_2\text{O}$  and extracted with  $\text{CHCl}_3$  ( $3 \times 50$  mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ )

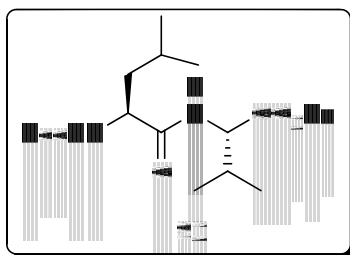


and concentrated in vacuo. Acetic acid was removed under high vacuum. Flash chromatography (SiO<sub>2</sub>, 3.5×30 cm, EtOAc/Hexanes 1:2 → 1:1) afforded **89** (2.500 g, 4.640 mmol, 89% yield) as a white solid:  $[\alpha]_D^{25} -2.2$  (*c* 2.3, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.06 (br s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.35 (s, 1H), 7.30–7.21 (m, 5H), 7.05 (d, *J* = 7.5 Hz, 1H), 5.02 (d, *J* = 8.5 Hz, 1H), 4.96 (d, *J* = 12.0 Hz, 1H), 4.91 (d, *J* = 12.0 Hz, 1H), 4.75 (d, *J* = 5.5 Hz, 2H), 4.53–4.48 (m, 1H), 3.29 (dd, *J* = 5.5, 14.5 Hz, 1H), 3.12 (dd, *J* = 10, 15 Hz, 1H), 1.72 (t, *J* = 5.5 Hz, 1H), 1.34 (s, 9H), 0.99 (m, 6H), 0.93 (m, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 171.8, 155.8, 138.8, 136.5, 135.5, 133.4, 128.7, 128.6 (2C), 119.2 (3C), 120.2, 119.4, 119.2, 109.7, 82.0, 66.8, 66.2, 56.2, 29.9, 28.0 (3C), 7.6 (3C), 3.8 (3C); IR (film)  $\nu_{\max}$  3353, 2954, 2874, 1705, 1499, 1393, 1240, 1153, 1005, 738 cm<sup>-1</sup>; HRMS (ESI) *m/z* 539.29369 (MH<sup>+</sup>, C<sub>30</sub>H<sub>42</sub>N<sub>2</sub>O<sub>5</sub>SiH<sup>+</sup> requires 539.29358).

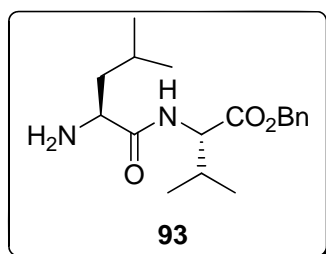


**Compound 91.** To a suspension of the L-valine (4.000 g, 34.180 mmol) in 200 mL benzene was treated with benzyl alcohol (11.135 g, 10.66 mL, 103.1 mmol), followed by *p*-toluenesulfonic acid (7.860 g, 41.38 mmol). The resulting mixture was refluxed for 6 hours. Generated water was removed by using a Barret trap. The reaction was cooled to rt and concentrated in vacuo. The residue was treated with 150 mL ether and cooled to 0 °C. The mixture was filtered and washed with ether (5 × 50 mL). The residue was kept under high vacuum over night to afford the product

(**91**, 12.306 g, 32.471 mmol, 95%) as a white solid.<sup>88</sup>

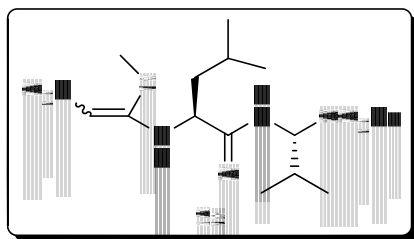


**Compound 92.** To a solution of Val-OBn (**91**, 11.000 g, 29.000 mmol) and Boc-Leu-OH (6.720 g, 29.000 mmol) in anhydrous THF (150 mL) was treated with *N*-methyl morpholine (14.685 g, 15.50 mL, 145.400 mmol) and HOBt (4.540 g, 34.900 mmol) at 0 °C, followed by EDCI (6.540 g, 34.900 mmol). The resulting mixture was stirred at 0 °C → rt for 12 hours. The reaction was treated with 100 mL sat. aq. NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 × 30 mL). The organic layers were dried and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 3.5 × 25 cm, 30% EtOAc/Hexanes) afforded **92** (11.327 g, 26.970 mmol, 93% yield) as a white solid.<sup>88</sup>

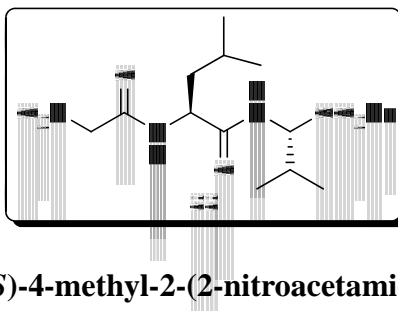


**Compound 93.** To a solution of Boc-Leu-Val-OBn (**92**, 5.680 g, 13.520 mmol) in 19.0 mL anhydrous CH<sub>2</sub>Cl<sub>2</sub> was treated with trifluoroacetic acid (17.760g, 12.0 mL, 155.789 mmol) dropwise at 0 °C. The resulting mixture was stirred at rt for 1 hour. The reaction was concentrated in vacuo. The residue was dissolved in 100 mL CH<sub>2</sub>Cl<sub>2</sub> and basicified with 2M NaOH (ca. 80 mL). Separated the organic layer. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 30 mL). Combined organic layers

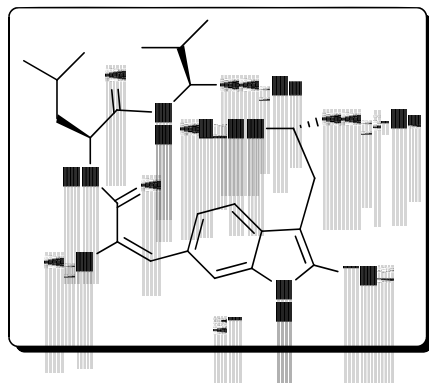
were dried and concentrated to afford the product (**93**, 4.326 g, 13.520 mmol, 100%) as a yellow oil.<sup>88</sup>



**(S)-benzyl 3-methyl-2-((S)-4-methyl-2-(1-(methylthio)-2-nitrovinylamino)pentan-2-amido)butanoate (95).** To a solution of (*S*)-benzyl 2-((*S*)-2-amino-4-methylpentan-2-amido)-3-methylbutanoate (**93**, 4.300 g, 13.440 mmol) in 77 mL MeCN was treated with (2-nitroethene-1,1-diyl)bis(methylsulfane) (**94**, 2.200 g, 13.440 mmol), followed by *p*-toluenesulfonic acid (254.0 mg, 1.340 mmol). The resulting mixture was refluxed for 18 h. The reaction was cooled to rt and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 3.5 × 35 cm, EtOAc/Hexanes 1:10 → 1:1, then pure EtOAc) afforded **95** (3.810 g, 8.720 mmol, 65% yield) as a yellow solid:  $[\alpha]_D^{25} +165.7$  ( $c$  0.77, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  10.39 (d,  $J$  = 7.0 Hz, 1H), 7.40–7.32 (m, 5H), 6.55 (s, 1H), 6.36 (d,  $J$  = 8.5 Hz, 1H), 5.20 (d,  $J$  = 12.5 Hz, 1H), 5.11 (d,  $J$  = 12.5 Hz, 1H), 4.60 (dd,  $J$  = 9.0, 5.0 Hz, 1H), 4.27–4.23 (m, 1H), 2.36 (s, 3H), 2.25–2.18 (m, 1H), 1.86–1.74 (m, 3H), 0.98 (d,  $J$  = 6.5 Hz, 3H), 0.93 (t,  $J$  = 6.5 Hz, 6H), 0.86 (d,  $J$  = 7.0 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  171.5, 170.3, 164.4, 135.3, 128.9 (2C), 128.8, 128.6 (2C), 108.2, 67.4, 58.0, 57.3, 42.3, 31.6, 25.1, 23.1, 21.6, 19.2, 17.8, 14.8; IR (film)  $\nu_{\max}$  3303, 2961, 1741, 1663, 1560, 1467, 1332, 1223, 1153, 1077, 1003, 763 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  438.20560 (MH<sup>+</sup>, C<sub>21</sub>H<sub>31</sub>N<sub>3</sub>O<sub>5</sub>SH<sup>+</sup> requires 438.20572).

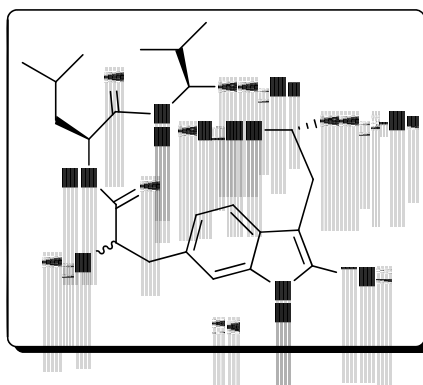


**(S)-benzyl-3-methyl-2-((S)-4-methyl-2-(2-nitroacetamido)pentanamido)butanoate (88).** To a suspension of **95** (3.810 g, 8.720 mmol) in 60 mL MeCN/H<sub>2</sub>O (3:1) was treated with mercuric chloride (2.710 g, 10.000 mmol). The reaction was stirred at 45 °C for 40 hours. The mixture was concentrated in vacuo. H<sub>2</sub>O was removed under high vacuum. The residue was treated with 100 mL CH<sub>2</sub>Cl<sub>2</sub> and 20 g silica gel (60–200 mesh), which was then concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 3.5×35 cm, EtOAc/Hexanes 1:10 → 1:3, then pure EtOAc) afforded **88** (2.230 g, 5.480 mmol, 74% yield) as a white solid:  $[\alpha]_D^{25} -40.9$  (*c* 0.44, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.78 (d, *J* = 8.5 Hz, 1H), 7.38–7.33 (m, 5H), 6.68 (d, *J* = 9.0 Hz, 1H), 5.21 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 5.10 (s, 2H), 4.62–4.57 (m, 1H), 4.48 (dd, *J* = 8.5, 5.0 Hz, 1H), 2.18 (m, 1H), 1.68–1.55 (m, 3H), 0.92–0.85 (m, 12H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 172.1, 171.3, 160.7, 135.3, 128.8 (2C), 128.8, 128.7 (2C), 77.8, 67.4, 57.8, 52.5, 41.5, 31.2, 24.9, 22.9, 22.3, 19.0, 17.8; IR (film)  $\nu_{\max}$  3277, 2963, 1741, 1651, 1564, 1375, 1263, 1003, 751, 697 cm<sup>-1</sup>; HRMS (ESI) *m/z* 408.21250 (MH<sup>+</sup>, C<sub>20</sub>H<sub>29</sub>N<sub>3</sub>O<sub>6</sub>H<sup>+</sup> requires 408.21291).



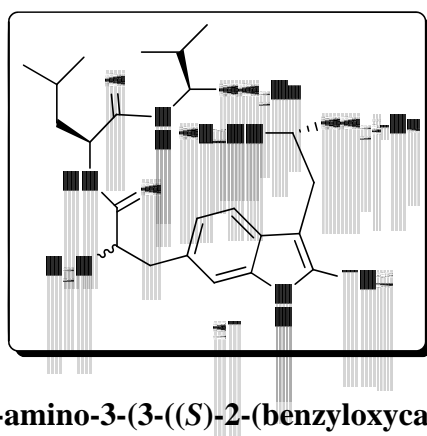
**(S)-benzyl 2-((S)-2-((E)-3-(3-((S)-2-(benzyloxycarbonylamino)-3-*tert*-butoxy-3-oxopropyl)-2-(triethylsilyl)-1H-indol-6-yl)-2-nitroacrylamido)-4-methylpentanamide)-3-methylbutanoate (**87**). A solution of the aldehyde (**60**, 774.0 mg, 1.440 mmol) and the nitro compound (**88**, 877.0 mg, 2.150 mmol) in THF-Et<sub>2</sub>O (10.0 mL, 2:1) was cooled to 0 °C. The mixture was treated with 1 M TiCl<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> (3.03 mL, 3.030 mmol) dropwise under Ar, followed by *N*-methyl morpholine (583.8 mg, 0.63 mL, 5.780 mmol). The resulting mixture was then stirred at 40 °C for 6 hours. The reaction was cooled to rt, quenched with 1 mL H<sub>2</sub>O and diluted with 50 mL CH<sub>2</sub>Cl<sub>2</sub>. The mixture was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 3.5 × 30 cm, EtOAc/Hexanes 1:6 → 1:3) afforded **87** (922.0 mg, 0.979 mmol, 68% yield) as a yellow solid:  $[\alpha]_D^{25} -44.8$  (*c* 1.2, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.72 (s, 1H), 8.20 (s, 1H), 7.86 (s, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.36–7.33 (m, 6H), 7.31–7.27 (m, 2H), 7.23–7.21 (m, 2H), 7.13 (d, *J* = 8.5 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.65 (d, *J* = 6.0 Hz, 1H), 5.23 (d, *J* = 12.0 Hz, 1H), 5.22 (d, *J* = 4.5 Hz, 1H), 5.15 (d, *J* = 11.5 Hz, 1H), 4.93 (dd, *J* = 22.0, 12.0, Hz, 2H), 4.63–4.57 (m, 2H), 4.52–4.48 (m, 1H), 3.26 (dd, *J* = 15.0, 6.0 Hz, 1H), 3.10 (dd, *J* = 14.0, 9.0 Hz, 1H), 2.18 (m, 1H), 1.71–1.65 (m, 1H), 1.64–1.55 (m, 2H), 1.30 (s, 9H), 1.01–0.92 (m, 14H), 0.92–0.83 (m, 13H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125**

MHz)  $\delta$  171.6, 171.5, 171.2, 162.0, 155.8, 141.1, 139.6, 139.5, 138.8, 136.4, 135.4, 132.6, 128.8 (2C), 128.7, 128.63 (2C), 128.60 (3C), 128.3, 128.2, 123.9, 122.2, 120.8, 119.7, 114.3, 82.3, 67.3, 66.9, 57.8, 56.1, 53.4, 40.6, 31.4, 30.1, 28.0 (3C), 24.7, 22.9, 22.0, 19.1, 17.8, 7.5 (3C), 3.7 (3C); IR (film)  $\nu_{\max}$  3323, 2957, 2874, 1729, 1651, 1519, 1301, 1153, 1093, 1003, 751, 697  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  943.49920 ( $\text{MH}^+$ ,  $\text{C}_{50}\text{H}_{67}\text{N}_5\text{O}_{10}\text{SiH}^+$  requires 943.49955).



**(S)-benzyl 2-((S)-2-(3-(3-((S)-2-(benzyloxycarbonylamino)-3-*tert*-butoxy-3-oxo propyl)-2-(triethylsilyl)-1H-indol-6-yl)-2-nitropropanamido)-4-methylpentanamido)-3-methylbutanoate (**96: A & B**):** To a solution of compound **87** (120.0 mg, 0.130 mmol) in *i*-PrOH/ $\text{CHCl}_3$  (4:1, 15.0 mL) was treated with 300 mg  $\text{SiO}_2$ , followed by  $\text{NaBH}_4$  (24.6 mg, 0.065 mmol). The resulting mixture was stirred at rt for 30 min. The reaction was concentrated in vacuo. Flash chromatography ( $\text{SiO}_2$ ,  $2.5 \times 20$  cm, EtOAc/Hexanes 1:3) afforded **96 (A and B)**, 117.0 mg, 0.126 mmol, 97% yield) as a yellow solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz, mixture of two isomers)  $\delta$  8.14 and 8.11 (2s, 1H), 7.53 (d,  $J = 8.0$  Hz, 1H), 7.40–7.22 (m, 10H), 7.16 and 7.13 (2s, 1H), 7.12–7.04 and 7.04–6.96 (2m, 1H), 6.89 and 6.86 (2d,  $J = 8.0$  Hz, 1H), 6.48 and 6.42 (2d,  $J = 8.5$  Hz, 1H), 5.39–5.31 (m, 1H), 5.25–5.17 (m, 2H), 5.16–5.56 (m, 1H), 5.00–4.89 (m, 2H), 4.56–4.50 (m, 1H), 4.50–4.44 (m, 1H),

4.44–4.38 (m, 1H), 3.66–3.56 (m, 1H), 3.55–3.45 (m, 1H), 3.28–3.21 (m, 1H), 3.14–3.06 (m, 1H), 2.20–2.11 (m, 1H), 1.66–1.46 (m, 2H), 1.45–1.34 (m, 1H), 1.29 and 1.27 (2s, 9H), 1.04–0.96 (m, 9H), 0.96–0.88 (m, 6H), 0.88–0.80 (m, 9H), 0.74–0.65 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz, mixture of two isomers)  $\delta$  171.8, 171.5, 171.3, 171.2, 163.6, 163.2, 155.8, 138.9, 138.8, 136.5, 135.3, 135.2, 133.6, 128.83, 128.80, 128.77, 128.71, 128.62, 128.59, 128.16, 128.12, 120.32, 120.28, 120.14, 119.80, 111.55, 111.49, 91.1, 90.6, 82.0, 67.4, 67.3, 66.8, 57.6, 57.5, 56.2, 56.1, 52.7, 52.4, 41.2, 40.6, 37.4, 37.1, 31.30, 31.28, 29.9, 27.97, 27.96, 24.8, 24.5, 22.9, 22.8, 22.2, 21.9, 19.1, 19.0, 17.72, 17.66, 7.6, 3.8; IR (film)  $\nu_{\text{max}}$  3316, 2957, 2917, 1721, 1654, 1557, 1456, 1368, 1245, 1154, 1062, 1004, 737, 698; HRMS (ESI)  $m/z$  928.48892 ( $\text{MH}^+$ ,  $\text{C}_{50}\text{H}_{69}\text{N}_5\text{O}_{10}\text{SiH}^+$  requires 928.48865).



**(2*S*)-benzyl 2-((2*S*)-2-(2-amino-3-(3-((*S*)-2-(benzyloxycarbonylamino)-3-*tert*-butoxy-3-oxopropyl)-2-(triethylsilyl)-1*H*-indol-6-yl)propanamido)-4-methylpentanamido)-3-methylbutanoate (97: A & B).** To a solution of **96** (**A** and **B**, 117.0 mg, 0.126 mmol) in 3.0 mL absolute MeOH was treated with 0.1 M  $\text{SmI}_2$  in THF (18.0 mL, 1.800 mmol) dropwise under Ar. The resulting mixture was stirred at rt for 30 min. The reaction was quenched with 30 mL sat. aq.  $\text{NaHCO}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$  ( $5 \times 20$  mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and

concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 3.5×20 cm, EtOAc → 5% Et<sub>3</sub>N in EtOAc) afforded **97** (**A**: 45.0 mg, 0.0502 mmol, 39.8%; **B**: 56.8 mg, 0.0633 mmol, 50.2%) as a yellow solid: **A**: [ $\alpha$ ]<sub>D</sub><sup>25</sup> -40.9 ( *c* 1.3, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.98 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.38–7.33 (m, 4H), 7.30–7.23 (m, 6H), 7.19 (s, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 5.24 (d, *J* = 59.0 Hz, 1H), 5.21 (d, *J* = 12.0 Hz, 1H), 5.13 (d, *J* = 12.5 Hz, 1H), 4.98 (d, *J* = 12.5 Hz, 1H), 4.92 (d, *J* = 12.0 Hz, 1H), 4.55 (dd, *J* = 9.0, 5.0 Hz, 1H), 4.51–4.45 (m, 1H), 4.45–4.40 (m, 1H), 3.66–3.61 (m, 1H), 3.38–3.32 (m, 1H), 3.28 (dd, *J* = 14.5, 5.5 Hz, 1H), 3.12 (dd, *J* = 14.5, 9.5 Hz 1H), 2.77 (dd, *J* = 13.5, 9.5 Hz, 1H), 2.24–2.17 (m, 1H), 1.72–1.64 (m, 1H), 1.60–1.52 (m, 3H), 1.52–1.42 (m, 1H), 1.33 (s, 9H), 1.03–0.96 (m, 9H), 0.96–0.87 (m, 18H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  175.2, 172.2, 171.8, 171.7, 155.8, 139.1, 136.5, 135.5, 133.1, 131.8, 128.8 (2C), 128.64, 128.60, 128.58 (3C), 128.2 (2C), 128.1, 121.1, 120.2, 119.5, 111.5, 82.0, 67.2, 66.8, 57.4, 56.7, 56.2, 51.8, 45.9, 41.1, 40.4, 31.3, 29.9, 28.0 (3C), 24.9, 23.1, 22.2, 19.2, 17.8, 7.6 (3C), 3.8 (3C); IR (film)  $\nu_{\max}$  3318, 2959, 1732, 1654, 1512, 1355, 1154, 1012, 748 cm<sup>-1</sup>; HRMS (ESI) *m/z* 898.51408 (MH<sup>+</sup>, C<sub>50</sub>H<sub>71</sub>N<sub>5</sub>O<sub>8</sub>SiH<sup>+</sup> requires 898.51447). **B**: [ $\alpha$ ]<sub>D</sub><sup>25</sup> +5.1 ( *c* 2.7, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.13 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.37–7.33 (m, 4H), 7.30–7.22 (m, 6H), 7.16 (s, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 5.26 (d, *J* = 23.0 Hz, 1H), 5.21 (d, *J* = 12.5 Hz, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 4.97 (d, *J* = 12.5 Hz, 1H), 4.92 (d, *J* = 12.5 Hz, 1H), 4.57 (dd, *J* = 8.5, 5.0 Hz, 1H), 4.51–4.43 (m, 2H), 3.65 (dd, *J* = 10.0, 3.5 Hz, 1H),



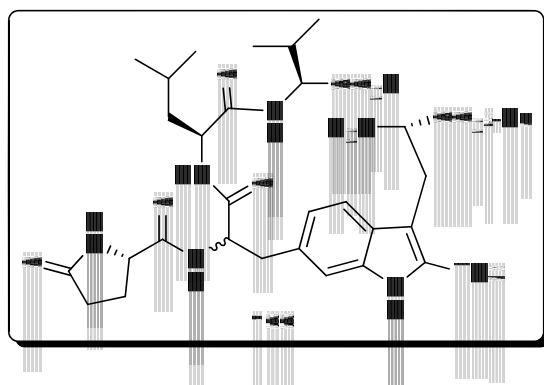
3.38 (dd,  $J = 14.0, 4.0$  Hz, 1H), 3.29 (dd,  $J = 14.5, 6.0$  Hz, 1H), 3.11 (dd,  $J = 14.5, 9.5$  Hz, 1H), 2.61 (dd,  $J = 13.0, 10.5$  Hz, 1H), 2.24–2.16 (m, 1H), 1.74–1.70 (m, 1H), 1.62–1.52 (m, 4H), 1.34 (s, 9H), 1.03–0.96 (m, 9H), 0.96–0.87 (m, 18H);  $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  175.4, 172.0, 171.8, 171.7, 155.8, 139.0, 136.5, 135.5, 133.0, 131.9, 128.7 (2C), 128.60, 128.57, 128.53 (3C), 128.2, 128.1 (2C), 120.8, 120.2, 119.6, 111.5, 81.9, 67.2, 66.8, 57.4, 56.9, 56.2, 51.8, 45.8, 41.3, 40.2, 31.3, 29.8, 28.0 (3C), 24.9, 23.1, 22.2, 19.2, 17.8, 7.6 (3C), 3.8 (3C); IR (film)  $\nu_{\text{max}}$  3307, 2957, 1724, 1653, 1515, 1368, 1154, 1004, 753  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  898.51408 ( $\text{MH}^+$ ,  $\text{C}_{50}\text{H}_{71}\text{N}_5\text{O}_8\text{SiH}^+$  requires 898.51447).



**(*S*)-benzyl 2-((*S*)-2-(3-(3-((*S*)-2-(benzyloxycarbonylamino)-3-*tert*-butoxy-3-oxopropyl)-2-(triethylsilyl)-1H-indol-6-yl)-2-((*S*)-5-oxopyrrolidine-2-carboxamido)propanamido)-4-methylpentanamido)-3-methylbutanoate (99: A & B).** To a solution of compound **97** (**A** or **B**, 200.0 mg, 0.223 mmol) in 10 mL THF was treated with (*S*)-pyroglutamic acid (57.8 mg, 0.446 mmol) and HOBt (59.3 mg, 0.446 mmol), followed by EDCI (82.8 mg, 0.446 mmol) at 0 °C. The mixture was stirred at 0 °C  $\rightarrow$  rt for 8 hours. The resulting mixture was treated with 30 mL sat. aq.  $\text{NaHCO}_3$  and extracted with  $\text{CHCl}_3$  ( $3 \times 20$  mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. Flash chromatography ( $\text{SiO}_2$ ,  $2.5 \times 15$

mL cm, 1% → 3% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) afforded **99** (205.0 mg, 0.203 mmol, 91% yield) as a yellow solid: **A**: [ $\alpha$ ]<sub>D</sub><sup>25</sup> +8.9 ( *c* 0.93, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  9.01 (brs, 1H), 7.86 (brs, 1H), 7.66 (brs, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.38–7.20 (m, 11H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.02 (s, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 5.23 (d, *J* = 12.5 Hz, 1H), 5.17 (d, *J* = 7.0 Hz, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 4.91 (d, *J* = 12.5 Hz, 1H), 4.79 (d, *J* = 12.5 Hz, 1H), 4.76–4.68 (m, 3H), 4.45–4.40 (m, 1H), 3.90–3.86 (m, 1H), 3.25 (dd, *J* = 4.5, 14.0 Hz, 1H), 3.17–3.10 (m, 1H), 3.04–2.94 (m, 2H), 2.23–2.15 (m, 1H), 2.15–2.06 (m, 1H), 2.06–1.97 (m, 1H), 1.97–1.86 (m, 1H), 1.65–1.53 (m, 3H), 1.53–1.43 (m, 1H), 1.35 (s, 9H), 0.98–0.82 (m, 21H), 0.81–0.73 (m, 6H) ; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  179.3, 172.4, 171.9, 171.8, 171.6 (2C), 155.6, 138.8, 136.4, 135.2, 133.4, 128.6 (3C), 128.5, 128.36 (2C), 128.32 (3C), 127.93, 127.89, 120.3, 119.5, 118.8, 112.4, 81.8, 67.1, 66.6, 57.4, 56.7, 56.2, 55.0, 52.0, 41.4 (2C), 38.3, 31.3, 29.7, 28.9, 27.9 (3C), 24.8, 24.6, 22.5, 22.4, 19.1, 17.9, 7.4 (3C), 3.6 (3C); IR (film)  $\nu_{\max}$  3293, 2958, 1723, 1651, 1541, 1246, 1154, 737 cm<sup>-1</sup>; HRMS (ESI) *m/z* 1009.54965 (MH<sup>+</sup>, C<sub>55</sub>H<sub>76</sub>N<sub>6</sub>O<sub>10</sub>SiH<sup>+</sup> requires 1009.54650). **B**: [ $\alpha$ ]<sub>D</sub><sup>25</sup> -1.6 ( *c* 1.47, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  9.08 (brs, 1H), 7.61 (brs, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.36–7.21 (m, 11H), 7.18 (s, 1H), 7.06–6.98 (m, 1H), 6.98–6.90 (m, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.18 (d, *J* = 7.0 Hz, 1H), 5.14 (d, *J* = 12.0 Hz, 1H), 5.03 (d, *J* = 12.5 Hz, 1H), 4.98 (d, *J* = 12.0 Hz, 1H), 4.90 (d, *J* = 12.0 Hz, 1H), 4.80–4.72 (m, 1H), 4.56–4.49 (m, 1H), 4.48–4.42 (m, 1H), 4.42–4.37 (m, 1H), 4.00–3.93 (m, 1H), 3.28 (dd, *J* = 5.0, 14.0 Hz, 1H), 3.19 (dd, *J* = 7.0, 13.0 Hz, 1H), 3.10–3.00 (m, 2H), 2.36–2.25 (m, 2H), 2.24–2.18 (m,

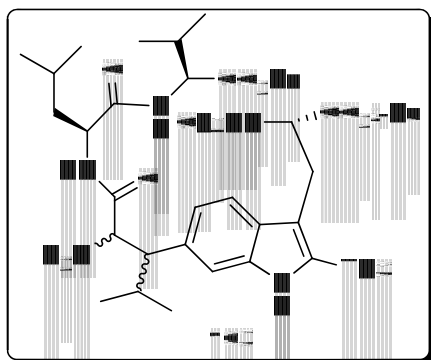
1H), 2.16–2.08 (m, 1H), 2.08–2.02 (m, 1H), 1.56–1.46 (m, 1H), 1.46–1.32 (m, 2H), 1.34 (s, 9H), 1.00–0.87 (m, 15H), 0.85–0.76 (m, 6H), 0.72–0.62 (m, 3H), 0.58–0.48 (m, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 179.4, 173.2, 172.3, 172.2, 172.1, 172.0, 155.9, 139.3, 136.6, 135.3, 133.4, 130.0, 128.8 (3C), 128.63, 128.59, 128.4 (2C), 128.2, 128.1 (2C), 120.2, 119.6, 119.3, 112.2, 81.9, 67.3, 66.8, 57.4, 56.9, 56.1, 56.0, 52.5, 41.0 (2C), 38.0, 31.3, 29.7, 29.6, 28.1 (3C), 25.7, 24.6, 23.0, 21.3, 19.2, 18.0, 7,6 (3C), 3.9 (3C); IR (film) ν<sub>max</sub> 3292, 2956, 2874, 1701, 1654, 1540, 1248, 1152, 736, 696 cm<sup>-1</sup>; HRMS (ESI) *m/z* 1009.54965 (MH<sup>+</sup>, C<sub>55</sub>H<sub>76</sub>N<sub>6</sub>O<sub>10</sub>SiH<sup>+</sup> requires 1009.54650).



**(S)-2-((S)-2-(3-(3-((S)-2-amino-3-*tert*-butoxy-3-oxopropyl)-2-(triethylsilyl)-1H-indol-6-yl)-2-((S)-5-oxopyrrolidine-2-carboxamido)propanamido)-4-methylpentanamido)-3-methylbutanoic acid (100: A & B).** To a solution of compound **99** (A or **B**: 96.0 mg, 0.0952 mmol) in MeOH-H<sub>2</sub>O (10 mL, 5:1) was treated with NH<sub>4</sub>CO<sub>2</sub>H (120.0 mg, 1.911 mmol), followed by 10% Pd/C (75.0 mg). The reaction was stirred at rt for 12 hours. The resulting mixture was filtered through a fine sintered glass pad filter and washed with MeOH (5 × 10 mL). The filtration was concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 1.5 × 25 cm, MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1:5 → 1:1) afforded **100** (67.9 mg, 0.0866 mmol, 91% yield) as a yellow solid: **A**: [α]<sub>D</sub><sup>25</sup> +5.3 ( *c* 1.0 ,

CH<sub>3</sub>OH); <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz) δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.29 (s, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 4.78 (dd, *J* = 10.0, 5.0 Hz, 1H), 4.45 (dd, *J* = 9.0, 6.5 Hz, 1H), 4.20–4.16 (m, 1H), 4.05 (dd, *J* = 8.5, 4.0 Hz, 1H), 3.65–3.62 (m, 1H), 3.34 (dd, *J* = 14.5, 5.0 Hz, 1H), 3.31–3.26 (m, 1H), 3.00 (dd, *J* = 13.5, 10.5 Hz, 1H), 2.95 (dd, *J* = 14.5, 9.5 Hz, 1H), 2.30–2.22 (m, 1H), 2.18–2.11 (m, 1H), 2.11–2.01 (m, 2H), 1.71–1.60 (m, 4H), 1.33 (s, 9H), 1.02–0.97 (m, 13H), 0.97–0.93 (m, 7H), 0.93–0.89 (m, 7H); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz) δ 181.6, 178.2, 174.9, 174.8, 173.8, 173.7, 141.0, 133.6, 132.1, 129.3, 121.6, 121.3, 119.7, 113.1, 82.6, 61.4, 58.5, 58.1, 56.1, 53.9, 42.1, 39.3, 33.1, 32.9, 30.2, 28.2 (3C), 26.8, 26.0, 23.7, 22.1, 20.4, 18.6, 8.0 (3C), 4.7 (3C); IR (film)  $\nu_{\max}$  3288, 2957, 1735, 1647, 1514, 1369, 1255, 1156, 1026, 739 cm<sup>-1</sup>; HRMS (ESI) *m/z* 785.46199 (MH<sup>+</sup>, C<sub>40</sub>H<sub>64</sub>N<sub>6</sub>O<sub>8</sub>SiH<sup>+</sup> requires 785.46277). **B**: [ $\alpha$ ]<sub>D</sub><sup>25</sup> +13.2 (*c* 0.67, CH<sub>3</sub>OH); <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz) δ 7.51 (d, *J* = 8.5 Hz, 1H), 7.23 (s, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 4.75 (t, *J* = 7.5 Hz, 1H), 4.24–4.19 (m, 2H), 4.19–4.16 (m, 1H), 4.12–4.09 (m, 1H), 3.61 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.27 (dd, *J* = 14.0, 5.5 Hz, 1H), 3.14 (dd, *J* = 13.5, 9.0 Hz, 1H), 3.04 (dd, *J* = 13.0, 6.5 Hz, 1H), 2.94 (dd, *J* = 14.0, 9.5 Hz, 1H), 2.35–2.27 (m, 1H), 2.27–2.18 (m, 2H), 2.15–2.08 (m, 1H), 1.85–1.78 (m, 1H), 1.46–1.38 (m, 1H), 1.34–1.26 (m, 2H), 1.33 (s, 9H), 1.03–0.93 (m, 15H), 0.92–0.87 (m, 6H), 0.59 (d, *J* = 6.0 Hz, 3H), 0.49 (d, *J* = 6.5 Hz, 3H); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz) δ 181.2, 178.2, 175.2, 175.0, 173.9, 173.3, 141.0, 133.5, 131.7, 129.4, 121.6, 121.4, 119.9, 113.2, 82.5, 61.5, 58.6, 58.1, 56.9, 53.6, 41.6, 39.5, 33.1, 33.0, 30.8, 28.4 (3C), 26.8, 25.4, 23.7, 21.4, 20.3, 18.7, 8.0 (3C), 4.8 (3C); IR (film)  $\nu_{\max}$  3369, 2957, 1735, 1655, 1590, 1396, 1256,

1156, 739  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  785.46058 ( $\text{MH}^+$ ,  $\text{C}_{50}\text{H}_{71}\text{N}_5\text{O}_8\text{SiH}^+$  requires 785.46277).



**(S)-benzyl-2-((S)-2-(2-amino-3-(3-((S)-2-(benzyloxycarbonylamino)-3-*tert*-butoxy-3-oxopropyl)-2-(triethylsilyl)-1H-indol-6-yl)-4-methylpentanamido)-4-methylpentanamido)-3-methylbutanoate (103)**. A suspension of compound **87** (370.0 mg, 0.399 mmol) and  $\text{Zn}(\text{OTf})_2$  (283.0 mg, 0.790 mmol) in 6.0 mL dry  $\text{CH}_2\text{Cl}_2$  was stirred at rt until it was homogeneous (ca. 1 hour). The resulting solution was cooled to  $-78$  °C under Ar. Then treated it with *i*-PrI (32.5 mg, 37.6  $\mu\text{L}$ , 0.191 mmol) and  $\text{Bu}_3\text{SnH}$  (88.0 mg, 50.3  $\mu\text{L}$ , 0.191 mmol), followed by the solution of  $\text{Et}_3\text{B}$  in  $\text{CH}_2\text{Cl}_2$  (3.45 M, 109.0  $\mu\text{L}$ , 0.376 mmol) and 4 mL  $\text{O}_2$ . The addition of the *i*-PrI,  $\text{Bu}_3\text{SnH}$ ,  $\text{Et}_3\text{B}$  in  $\text{CH}_2\text{Cl}_2$  and  $\text{O}_2$  (Same amounts as above) was repeated three more times at 30 min interval. The solution was quenched with 5 mL 1M HCl and extracted with  $\text{CH}_2\text{Cl}_2$  ( $5 \times 10$  mL). The organic layers were dried and concentrated in vacuo.

The above crude product was dissolved in 5.0 mL dry MeOH, which was treated with the solution of  $\text{SmI}_2$  in THF (0.1 M, 36.0 mL, 3.600 mmol) under Ar. The resulting mixture was stirred at rt for 30 min before quenching with 100 mL sat. aq.  $\text{NaHCO}_3$ . The solution was extracted with  $\text{CH}_2\text{Cl}_2$  ( $5 \times 20$  mL). The combined

organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The majority of the tin compounds were removed by using a small column (10% KF in silica gel, 15.0 g, CH<sub>2</sub>Cl<sub>2</sub> to 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub>). Flash chromatography (SiO<sub>2</sub>, 3.5 × 30 cm, EtOAc/Hex 1:3 → 4:1, then pure EtOAc) afforded four isomers of **103** (**B**: 55.0 mg, 0.0586 mmol, 15% yield, **I+N**: 222.2 mg, 0.237 mmol, 59% yield; **G**: 60.0 mg, 0.0639 mmol, 16% yield) as white solids: **103-B**:  $[\alpha]_D^{25} -38.5$  (*c* 0.8, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.91 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.37–7.26 (m, 11H), 7.13 (s, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.5 Hz, 1H), 5.19 (d, *J* = 6.0 Hz, 1H), 5.18 (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 5.02 (d, *J* = 12.5 Hz, 1H), 4.96 (d, *J* = 12.5 Hz, 1H), 4.48 (dd, *J* = 9.0, 5.0 Hz, 1H), 4.45 (dd, *J* = 15.0, 8.0 Hz, 1H), 4.12–4.06 (m, 1H), 3.85 (d, *J* = 4.5 Hz, 1H), 3.25 (dd, *J* = 15.0, 6.5 Hz, 1H), 3.12 (dd, *J* = 14.0, 8.5 Hz, 1H), 3.06 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.20–2.10 (m, 2H), 1.69–1.36 (m, 3H), 1.33–1.22 (m, 2H), 1.26 (s, 9H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.04–0.96 (m, 9H), 0.95–0.89 (m, 6H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.77 (d, *J* = 6.5 Hz, 3H), 0.47 (d, *J* = 6.0 Hz, 3H), 0.34 (d, *J* = 6.5 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 175.0, 172.2, 171.9, 171.7, 155.8, 138.9, 136.5, 135.5, 133.2, 132.7, 128.8 (3C), 128.63, 128.61 (2C), 128.56 (3C), 128.2, 128.1, 120.1, 119.8, 118.9, 112.4, 81.9, 67.1, 66.9, 57.3, 57.0, 56.2, 55.1, 51.3, 39.8, 31.3, 29.9, 28.6, 28.0 (3C), 24.2, 22.9, 21.53, 21.49, 21.2, 19.2, 17.8, 7.6 (3C), 3.9 (3C); IR (film)  $\nu_{\max}$  3322, 2959, 1723, 1657, 1514, 1156, 1012, 743, 699 cm<sup>-1</sup>; HRMS (ESI) *m/z* 940.55947 (MH<sup>+</sup>, C<sub>53</sub>H<sub>77</sub>N<sub>5</sub>O<sub>8</sub>SiH<sup>+</sup> requires 940.56142). **103-I & N**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.05 and 7.95 (2s, 1H), 7.69 and 7.39 (2d, *J* = 7.5 Hz, 1H), 7.51

(t,  $J = 8.0$  Hz, 1H), 7.36–7.27 (m, 10H), 7.20 and 7.14 (2s, 1H), 6.94 and 6.56 (2d,  $J = 9.5$  and  $8.5$  Hz, 1H), 6.90 (m, 1H), 5.21 and 5.19 (2d,  $J = 9.0$  Hz, 1H), 5.03 (dd,  $J = 12.5$ ,  $6.0$ , 1H), 4.96 (dd,  $J = 12.0$ ,  $4.0$  Hz, 1H), 4.51–4.41 (m, 2H), 4.33 (dd,  $J = 15.0$ ,  $9.0$  Hz, 1H), 3.87 and 3.67 (2d,  $J = 6.5$  and  $3.5$  Hz, 1H), 3.29–3.20 (m, 1H), 3.19–3.10 (m, 1H), 3.00 and 2.81 (t and dd,  $J = 7.5$ ,  $11.0$  and  $4.0$  Hz, 1H), 2.54–2.47 and 2.08–1.98 (m, 1H), 2.20–2.10 (m, 1H), 1.72–1.67 and 1.62–1.57 (2m, 1H), 1.57–1.36 (m, 5H), 1.27 and 1.25 (2s, 10H), 1.12 (d,  $J = 6.0$  Hz, 3H), 1.04–0.97 (m, 6H), 0.93 (t,  $J = 6.0$  Hz, 6H), 0.91–0.87 (m, 6H), 0.85 (d,  $J = 6.0$  Hz, 3H), 0.83–0.77 (m, 6H), 0.70 (d,  $J = 6.0$  Hz, 3H); HRMS (ESI)  $m/z$  940.55950 ( $MH^+$ ,  $C_{53}H_{77}N_5O_8SiH^+$  requires 940.56142). **103-G**:  $[\alpha]_D^{25} -16.9$  ( $c$  0.95,  $CHCl_3$ );  $^1H$  NMR ( $CDCl_3$ , 500 MHz)  $\delta$  8.29 (s, 1H), 7.48 (d,  $J = 8.0$  Hz, 1H), 7.38–7.26 (m, 11H), 7.07 (s, 1H), 6.85 (d,  $J = 8.0$  Hz, 1H), 6.60 (d,  $J = 6.0$  Hz, 1H), 5.23 (d,  $J = 8.0$  Hz, 1H), 5.22 (d,  $J = 12.5$  Hz, 1H), 5.12 (d,  $J = 12.5$  Hz, 1H), 5.02 (d,  $J = 12.0$  Hz, 1H), 4.96 (d,  $J = 12.5$  Hz, 1H), 4.55–4.51 (m, 1H), 4.47 (dd,  $J = 15.0$ ,  $8.0$  Hz, 1H), 4.27–4.20 (m, 1H), 3.73–3.65 (m, 1H), 3.24 (dd,  $J = 14.0$ ,  $6.5$  Hz, 1H), 3.14 (dd,  $J = 14.0$ ,  $8.5$  Hz, 1H), 2.86 (dd,  $J = 8.5$ ,  $6.5$  Hz, 1H), 2.39–2.31 (m, 1H), 2.21–2.13 (m, 1H), 1.96–1.50 (m, 3H), 1.49–1.41 (m, 1H), 1.30–1.20 (m, 1H), 1.25 (s, 9H), 1.05–0.97 (m, 12H), 0.96–0.84 (m, 15H), 0.78–0.63 (m, 6H);  $^{13}C$  NMR ( $CDCl_3$ , 125 MHz)  $\delta$  172.0 (2C), 171.9, 171.7, 155.8, 139.2, 136.5, 135.5, 133.0 (2C), 128.8 (3C), 128.66, 128.62 (2C), 128.57 (3C), 128.21, 128.17, 121.5, 119.7, 118.8, 111.0, 81.8, 67.2, 66.9, 57.69, 57.51, 56.2, 52.1, 45.9, 40.4, 31.3, 29.9, 28.9, 28.0 (3C), 24.5, 22.9, 21.9 (2C), 19.2 (2C), 18.1, 7.6 (3C), 3.9 (3C); IR (film)  $\nu_{max}$  3288, 2959, 1727,

1651, 1535, 1457, 1356, 1253, 1155, 1011, 739  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  940.55947 ( $\text{MH}^+$ ,  $\text{C}_{53}\text{H}_{77}\text{N}_5\text{O}_8\text{SiH}^+$  requires 940.56142).



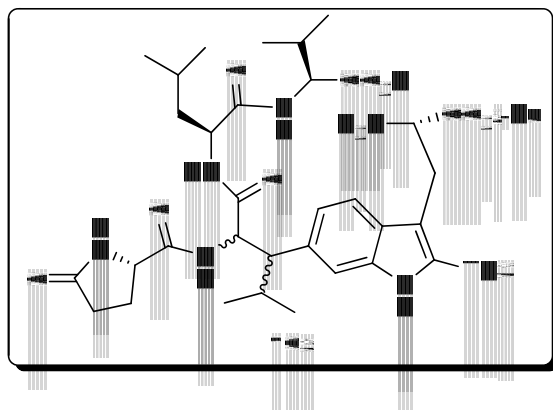
**(S)-benzyl 2-((S)-2-(3-(3-((S)-2-(benzyloxycarbonylamino)-3-tert-butoxy-3-oxopropyl)-2-(triethylsilyl)-1H-indol-6-yl)-4-methyl-2-((S)-5-oxopyrrolidine-2-carboxamido)pentanamido)-4-methylpentanamido)-3-methylbutanoate** (**104**;

isomer **B**, **I** & **N** and **G**). To a solution of compound **103** (isomer **B**, or **I** & **N**, or **G**: 105.0 mg, 0.112 mmol) and (*S*)-pyroglutamic acid (21.9 mg, 0.169 mmol) in 6 mL THF was treated with HOBt (22.1 mg, 0.169 mmol), followed by EDCI (31.4 mg, 0.169 mmol) at 0 °C. The reaction was stirred at 0 °C → rt for 10 hours. The resulting mixture was treated with 5 mL aq.  $\text{NaHCO}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$  (3 × 20 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. Flash chromatography ( $\text{SiO}_2$ , 2.5 × 20 cm, 2% → 5% MeOH in  $\text{CH}_2\text{Cl}_2$ ) afforded **104** (111.0 mg, 0.106 mmol, 94% yield) as yellow solids: **104-B**:  $[\alpha]_D^{25} +1.3$  ( $c$  0.53,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  7.52 (d,  $J = 8.5$  Hz, 1H), 7.39–7.25 (m, 10H), 7.15 (s, 1H), 6.79 (d,  $J = 8.0$  Hz, 1H), 5.20 (d,  $J = 12.5$  Hz, 1H), 5.11 (d,  $J = 12.0$  Hz, 1H), 5.03–4.96 (m, 3H), 4.52 (dd,  $J = 8.5, 6.0$  Hz, 1H), 4.35–4.30 (m, 2H), 3.89 (dd,  $J = 9.5, 4.0$  Hz, 1H), 3.13–3.04 (m, 2H), 2.19–2.05



(m, 2H), 1.98–1.90 (m, 1H), 1.89–1.80 (m, 1H), 1.63–1.55 (m, 1H), 1.54–1.36 (m, 5H), 1.25 (s, 9H), 1.03–0.93 (m, 15H), 0.93–0.87 (m, 9H), 0.87–0.79 (m, 9H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  181.6, 174.7, 174.5, 173.55, 173.48, 172.8, 158.4, 140.6, 138.2, 137.3, 133.8, 132.2, 129.7 (5C), 129.6 (5C), 129.1, 129.0, 121.3, 119.8, 115.6, 82.6, 68.0, 67.7, 59.5, 58.7, 58.1, 56.7, 55.6, 52.9, 42.1, 31.9, 30.3, 29.77, 29.76, 28.3 (3C), 26.7, 25.8, 23.5, 22.6, 22.3, 19.6, 19.1, 18.7, 8.0 (3C), 4.6 (3C); IR (film)  $\nu_{\text{max}}$  3292, 2962, 2479, 1733, 1646, 1546, 1456, 1225, 1155, 1011, 754  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  1051.59291 ( $\text{MH}^+$ ,  $\text{C}_{58}\text{H}_{82}\text{N}_6\text{O}_{10}\text{SiH}^+$  requires 1051.59345). **104-I** & N:  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 500 MHz)  $\delta$  10.26 (s, 1H), 8.32 and 7.87 (d and s,  $J = 8.5$  Hz, 1H), 7.78 and 7.72 (2d,  $J = 8.0$  Hz, 1H), 7.64 and 7.16 (2d,  $J = 8.0$  Hz, 1H), 7.47 (d,  $J = 8.0$  Hz, 1H), 7.40–7.23 (m, 12H), 7.08 (s, 1H), 6.79 (d,  $J = 8.0$  Hz, 1H), 5.08 (d,  $J = 12.5$  Hz, 1H), 4.99 (d,  $J = 12.5$  Hz, 1H), 4.98 (d,  $J = 12.5$  Hz, 1H), 4.93–4.87 (m, 2H), 4.23–4.17 (m, 1H), 4.16–4.07 (m, 2H), 4.02–3.98 (m, 1H), 3.17 (dd,  $J = 14.0, 6.0$  Hz, 1H), 3.05–2.98 (m, 2H), 2.29–2.20 (m, 1H), 2.18–2.06 (m, 3H), 1.91–1.80 (m, 2H), 1.26–1.20 (m, 3H), 1.15 and 1.04 (2s, 9H), 0.98–0.83 (m, 15H), 0.79 (d,  $J = 6.5$  Hz, 3H), 0.73–0.64 (m, 12H), 0.59 (d,  $J = 2.5$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 125 MHz)  $\delta$  177.4 and 177.3 (1C), 172.2 and 172.1 (1C), 171.7 and 171.6 (1C), 171.3, 170.81 and 170.79 (1C), 170.0 and 169.9 (1C), 155.83 and 155.78 (1C), 138.6 and 138.4 (1C), 136.9, 135.8, 130.9 and 130.7 (1C), 130.6, 128.3 and 128.2 (5C), 128.0 and 127.9 (5C), 127.7, 127.5, 120.0 and 119.9 (1C), 118.0, 112.4, 80.1, 65.7, 65.3, 57.3 and 57.2 (1C), 56.8 and 56.7 (1C), 55.40 and 55.38 (1C), 55.29 and 55.26 (1C), 52.3, 50.53 and 50.51 (1C), 50.45 and 50.42 (1C), 41.17,

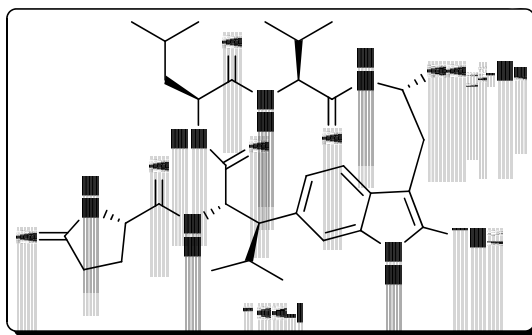
29.54 and 29.52 (1C), 29.0, 28.1, 27.4 and 27.3 (3C), 25.33 and 25.29 (1C), 23.6, 22.8, 21.7, 21.4, 18.6, 18.1, 17.6, 7.4 (3C), 3.1 (3C); HRMS (ESI)  $m/z$  1051.59935 ( $MH^+$ ,  $C_{58}H_{82}N_6O_{10}SiH^+$  requires 1051.59345). **104-G**:  $[\alpha]_D^{25} +4.3$  ( $c$  0.88,  $CHCl_3$ );  $^1H$  NMR ( $CD_3OD$ , 500 MHz) (two isomers 2:1, NMR reported for the major isomer)  $\delta$  10.02 (s, 1H), 8.22 (d,  $J = 15.0$  Hz, 1H), 7.73 (d,  $J = 10.0$  Hz, 1H), 7.50 (d,  $J = 12.0$  Hz, 1H), 7.39–7.23 (m, 10H), 7.19 (s, 1H), 6.94 (d,  $J = 10.0$  Hz, 1H), 5.19 (d,  $J = 15.0$  Hz, 1H), 5.10 (d,  $J = 15.0$  Hz, 1H), 5.03 (d,  $J = 15.0$  Hz, 1H), 4.99 (d,  $J = 15.0$  Hz, 1H), 4.93 (d,  $J = 15.0$  Hz, 1H), 4.34 (dd,  $J = 10.0, 5.0$  Hz, 1H), 4.30–4.24 (m, 2H), 4.02 (d,  $J = 10.0$  Hz, 1H), 4.01–3.95 (m, 1H), 3.18–3.06 (m, 2H), 2.53–2.46 (m, 1H), 2.42–2.31 (m, 4H), 2.29–2.22 (m, 1H), 2.22–2.13 (m, 1H), 2.13–2.04 (m, 1H), 1.68–1.62 (m, 2H), 1.40–1.32 (m, 2H), 1.18 (s, 9H), 1.06–0.84 (m, 24H), 0.76 (d,  $J = 10.0$  Hz, 3H), 0.38 (d,  $J = 10.0$  Hz, 3H), –0.07 (d,  $J = 10.0$  Hz, 3H);  $^{13}C$  NMR ( $CDCl_3$ , 125 MHz)  $\delta$  178.8, 173.2, 172.3, 172.1 (2C), 171.9, 155.9, 139.0, 136.5, 135.2, 133.3, 131.1, 128.8 (3C), 128.6 (3C), 128.5, 128.4 (3C), 128.2, 128.1, 119.7, 119.0, 115.0, 81.9, 67.4, 66.9, 57.2, 56.9, 56.5, 56.2, 52.9, 52.2, 40.4, 31.4, 29.9, 29.7, 28.4, 28.0 (3C), 26.1, 23.9, 22.9, 21.8, 20.4, 19.2, 17.9, 17.6, 7.6 (3C), 3.9 (3C); IR (film)  $\nu_{max}$  3293, 2958, 1701, 1664, 1541, 1258, 1153, 1004, 736, 698  $cm^{-1}$ ; HRMS (ESI)  $m/z$  1051.59291 ( $MH^+$ ,  $C_{58}H_{82}N_6O_{10}SiH^+$  requires 1051.59345).



**(S)-2-((S)-2-(3-(3-((S)-2-amino-3-*tert*-butoxy-3-oxopropyl)-2-(triethylsilyl)-1H-indol-6-yl)-4-methyl-2-((S)-5-oxopyrrolidine-2-carboxamido)pentanamido)-4-methylpentanamido)-3-methylbutanoic acid (105: B, I, N and G).** To a solution of compound **104** (isomer **B**, or **I** & **N**, or **G**: 110.0 mg, 0.105 mmol) in MeOH/H<sub>2</sub>O (5:1, 10.0 mL) was treated with NH<sub>4</sub>COOH (132.0 mg, 2.09 mmol), followed by 100 mg 10% Pd/C. The resulting mixture was stirred at rt for 8 hours. The crude mixture was filtered through a column (SiO<sub>2</sub>, 2.5 × 20 cm, MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1:2) to remove Pd/C and most of the NH<sub>4</sub>COOH. The filtration was concentrated in vacuo and water was removed under high vacuum. Flash chromatography (SiO<sub>2</sub>, 2.5 × 20 cm, 10% → 25% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) afforded **105** (78.9 mg, 0.0955 mmol, 94% yield) as yellow solids: **105-B**:  $[\alpha]_D^{25} +3.2$  (*c* 0.41, MeOH); <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.19 (s, 1H), 7.01 (d, *J* = 9.0 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 5.20 (d, *J* = 9.5 Hz, 1H), 4.50 (dd, *J* = 8.5, 6.0 Hz, 1H), 4.18 (d, *J* = 5.0 Hz, 1H), 3.96 (dd, *J* = 9.5, 4.0, Hz, 1H), 3.66–3.64 (m, 2H), 3.25 (dd, *J* = 11.0, 4.5 Hz, 1H), 3.17 (dd, *J* = 9.5, 5.5 Hz, 1H), 2.96 (dd, *J* = 14.5, 10.0 Hz, 1H), 2.21–2.02 (m, 2H), 2.03–1.96 (m, 1H), 1.93–1.86 (m, 1H), 1.70–1.59 (m, 1H), 1.59–1.51 (m, 2H), 1.51–1.42 (m, 1H), 1.28 (s, 9H), 1.04–0.96 (m, 15H),

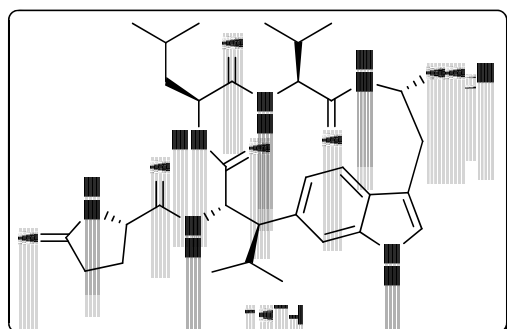
0.96–0.84 (m, 18H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  181.5, 178.2, 175.3, 174.5, 173.55, 173.46, 140.7, 133.8, 132.3, 129.6, 128.9, 121.4, 119.5, 115.6, 82.3, 61.5, 58.5, 58.1, 56.8, 55.5, 53.6, 41.9, 33.2, 33.0, 30.3, 29.8, 28.4 (3C), 26.7, 25.8, 23.7, 22.6, 22.1, 20.3, 18.9, 18.6, 8.0 (3C), 4.7 (3C); IR (film)  $\nu_{\text{max}}$  3303, 2958, 2874, 1654, 1592, 1404, 1252, 1155, 737  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  827.50930 ( $\text{MH}^+$ ,  $\text{C}_{43}\text{H}_{70}\text{N}_6\text{O}_8\text{SiH}^+$  requires 827.50972); **105-I**:  $[\alpha]_{\text{D}}^{25}$   $-18.8$  ( $c$  0.43, MeOH);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  10.13 (s, 1H), 7.50 (d,  $J = 8.5$  Hz, 1H), 7.23 (s, 1H), 6.89 (d,  $J = 8.0$  Hz, 1H), 5.10 (d,  $J = 11.5$  Hz, 1H), 4.29 (dd,  $J = 8.5, 4.0$  Hz, 1H), 4.04 (dd,  $J = 10.5, 4.5$  Hz, 1H), 3.98 (d,  $J = 5.0$  Hz, 1H), 3.75 (t,  $J = 8.5$  Hz, 1H), 3.67–3.63 (m, 1H), 3.28 (dd,  $J = 14.0, 6.5$  Hz, 1H), 3.18 (dd,  $J = 13.5, 4.0$  Hz, 1H), 3.05 (dd,  $J = 14.0, 9.0$  Hz, 1H), 2.56–2.46 (m, 1H), 2.44–2.36 (m, 1H), 2.36 (m, 1H), 2.36–2.29 (m, 1H), 2.20–2.12 (m, 1H), 2.11–2.02 (m, 1H), 2.01–1.93 (m, 1H), 1.44–1.36 (m, 1H), 1.35–1.28 (m, 1H), 1.26 (s, 9H), 1.04–0.98 (m, 15H), 0.87 (d,  $J = 7.0$  Hz, 3H), 0.83 (d,  $J = 7.0$  Hz, 3H), 0.72 (t,  $J = 7.5$  Hz, 6H), 0.64 (d,  $J = 7.0$  Hz, 3H), 0.52 (d,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  181.7, 178.1, 175.6, 175.2, 173.6, 172.7, 140.7, 133.7, 131.9, 129.8, 128.9, 121.5, 119.4, 113.7, 82.3, 61.4, 58.5, 58.4, 57.1, 54.1, 53.7, 41.7, 33.5, 32.9, 30.7, 29.6, 28.4 (3C), 27.1, 25.3, 23.7, 22.4, 21.5, 20.2, 18.6, 17.9, 8.0 (3C), 4.8 (3C); IR (film)  $\nu_{\text{max}}$  3290, 2957, 2874, 1667, 1594, 1404, 1368, 1255, 1156, 736  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  827.51514 ( $\text{MH}^+$ ,  $\text{C}_{43}\text{H}_{70}\text{N}_6\text{O}_8\text{SiH}^+$  requires 827.50972). **105-N**:  $[\alpha]_{\text{D}}^{25}$   $-18.8$  ( $c$  0.43, MeOH);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  7.47 (d,  $J = 8.5$  Hz, 1H), 7.20 (s, 1H), 6.83 (d,  $J = 8.5$  Hz, 1H), 5.08 (d,  $J = 11.5$  Hz, 1H), 4.42 (dd,  $J = 9.5, 8.5$  Hz, 1H),

4.13 (d,  $J = 5.0$  Hz, 1H), 3.85 (dd,  $J = 9.0, 3.5$  Hz, 1H), 3.66–3.56 (m, 2H), 3.30–3.22 (m, 2H), 2.97 (dd,  $J = 14.0, 8.5$  Hz, 1H), 2.15–2.07 (m, 1H), 1.95–1.87 (m, 1H), 1.80–1.74 (m, 2H), 1.73–1.67 (m, 2H), 1.27 (s, 9H), 1.04–0.93 (m, 21H), 0.93–0.84 (m, 14H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  181.4, 178.0, 175.2, 174.5, 173.7, 173.5, 140.7, 133.6, 132.0, 129.5, 128.9, 121.2, 118.9, 115.6, 82.4, 64.5, 61.3, 58.6, 57.6, 56.2, 54.4, 53.7, 41.6, 33.1, 30.8, 30.3, 28.3 (3C), 26.3, 26.1, 23.9, 22.7, 21.4, 20.3, 18.7, 17.9, 8.0 (3C), 4.7 (3C); IR (film)  $\nu_{\text{max}}$  3288, 2957, 2874, 1658, 1589, 1402, 1368, 1249, 1155, 1098, 1030, 737  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  827.50930 ( $\text{MH}^+$ ,  $\text{C}_{43}\text{H}_{70}\text{N}_6\text{O}_8\text{SiH}^+$  requires 827.50972). **105-G**:  $[\alpha]_{\text{D}}^{25} +23.1$  ( $c$  1.33, MeOH);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  7.48 (d,  $J = 8.0$  Hz, 1H), 7.18 (s, 1H), 6.97–6.92 (m, 1H), 5.07 (d,  $J = 11.5$  Hz, 1H), 4.31 (dd,  $J = 8.5, 5.0$  Hz, 1H), 4.06 (d,  $J = 5.5$  Hz, 1H), 3.90 (dd,  $J = 12.0, 4.0$  Hz, 1H), 3.68–3.61 (m, 2H), 3.24 (dd,  $J = 14.5, 7.0$  Hz, 1H), 3.21–3.15 (m, 1H), 2.98 (dd,  $J = 14.0, 13.5$  Hz, 1H), 2.53–2.46 (m, 1H), 2.46–2.38 (m, 1H), 2.36–2.28 (m, 1H), 2.23–2.15 (m, 1H), 2.13–2.00 (m, 2H), 1.28–1.19 (m, 12H), 1.08–1.00 (m, 12H), 1.00–0.93 (m, 6H), 0.91 (d,  $J = 7.0$  Hz, 3H), 0.88 (d,  $J = 7.0$  Hz, 6H), 0.77 (d,  $J = 7.0$  Hz, 3H), 0.46 (d,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  181.3, 178.0, 175.3, 174.0, 173.6, 171.8, 140.7, 134.1, 132.2, 129.7, 128.8, 120.1, 119.2 (2C), 83.7, 61.0, 58.2 (2C), 57.0 (2C), 53.5, 53.2, 41.5, 32.9, 31.0, 29.2, 28.2 (3C), 26.9, 24.9, 23.9, 22.3, 20.4, 20.3, 18.7, 17.6, 8.0 (3C), 4.7 (3C); IR (film)  $\nu_{\text{max}}$  3263, 2956, 1654, 1589, 1367, 1257, 1155  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  827.50889 ( $\text{MH}^+$ ,  $\text{C}_{43}\text{H}_{70}\text{N}_6\text{O}_8\text{SiH}^+$  requires 827.50972).



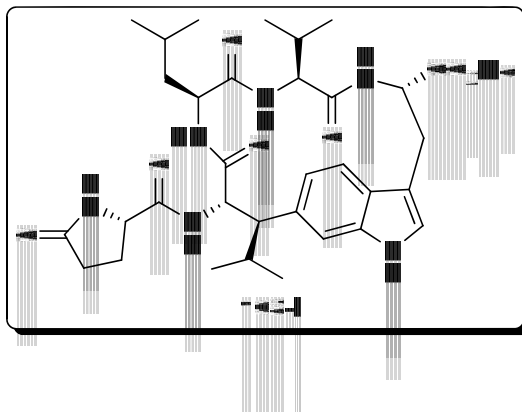
**Compound 106-I.** To a solution of compound **105-I** (40.0 mg, 0.0484 mmol) in 10.0 mL DMF was treated with HOBT (9.8 mg, 0.0726 mmol), followed by HBTU (27.6 mg, 0.0726 mmol) at 0 °C. The resulting mixture was stirred at 0 °C → rt for 8 hours. DMF was removed under high vacuum. The residue was dissolved in 5 mL CH<sub>2</sub>Cl<sub>2</sub> and treated with 5 mL sat. aq. NaHCO<sub>3</sub>. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 2.5 × 20 cm, 1% → 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) afforded **106-I** (35.6 mg, 0.0440 mmol, 91% yield) as a yellow solid:  $[\alpha]_D^{25} -81.1$  (*c* 0.83, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) (two isomers 2:1, data reported for the major isomer) δ 9.15 (brs, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 6.0 Hz, 1H), 7.39 (s, 1H), 7.22 (s, 1H), 7.06 (d, *J* = 7.0 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 1H), 5.77 (brs, 1H), 5.35–5.26 (m, 1H), 5.20–5.02 (m, 1H), 4.65–4.39 (m, 1H), 4.38–4.08 (m, 1H), 3.75–3.50 (m, 2H), 3.46–3.18 (m, 1H), 3.16–3.03 (m, 1H), 2.60–2.40 (m, 1H), 2.46–2.28 (m, 3H), 2.28–2.15 (m, 1H), 2.15–2.04 (m, 1H), 1.53 (s, 9H), 1.50–1.25 (m, 3H), 1.10–0.68 (m, 33H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 178.8, 173.0, 172.4, 171.5, 171.2, 170.2, 139.9, 133.5, 131.8, 129.1, 126.7, 119.2, 118.2, 114.8, 81.8, 59.1, 57.3, 57.0, 56.6, 56.1, 53.4, 53.2, 50.7, 40.4, 30.0, 29.5, 28.8, 28.1 (3C), 26.0, 24.9, 22.7, 22.1, 21.8, 19.1, 18.2, 7.5 (3C), 3.9 (3C); IR (film)

$\nu_{\max}$  3307, 2958, 2875, 1651, 1515, 1464, 1369, 1258, 1154, 736  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  809.49509 ( $\text{MH}^+$ ,  $\text{C}_{43}\text{H}_{68}\text{N}_6\text{O}_7\text{SiH}^+$  requires 809.49915).



**Compound 107-I.** To a solution of compound **106-I** (30.0 mg, 0.0371 mmol) in 10 mL anhydrous  $\text{CH}_2\text{Cl}_2$  was treated with the solution of *B*-bromocatechol boran (58.1 mg, 0.298 mmol) in 0.76 mL  $\text{CH}_2\text{Cl}_2$ . The mixture was stirred at rt in dark for 4 hours. The reaction was quenched with 1 mL MeOH and concentrated in vacuo. Flash chromatography ( $\text{SiO}_2$ ,  $1.5 \times 20$  cm, MeOH/ $\text{CH}_2\text{Cl}_2$  1:10  $\rightarrow$  2:1) afforded **107-I** (21.9 mg, 0.0343 mmol, 92% yield) as a yellow solid:  $[\alpha]_{\text{D}}^{25} -102.2$  ( $c$  0.93, MeOH);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  7.50 (d,  $J = 8.0$  Hz, 1H), 7.00 (s, 1H), 6.98 (s, 1H), 6.95 (d,  $J = 8.5$  Hz, 1H), 4.93 (d,  $J = 11.5$  Hz, 1H), 4.68 (t,  $J = 5.5$  Hz, 1H), 4.30–4.24 (m, 2H), 4.03 (d,  $J = 7.0$  Hz, 1H), 3.67–3.59 (m, 2H), 3.31–3.27 (m, 1H), 3.07 (dd,  $J = 12.0, 4.0$  Hz, 1H), 2.50–2.42 (m, 1H), 2.42–2.28 (m, 2H), 2.28–2.17 (m, 2H), 1.99–1.81 (m, 1H), 1.52–1.40 (m, 3H), 0.95 (d,  $J = 5.5$  Hz, 6H), 0.90 (d,  $J = 6.5$  Hz, 3H), 0.89–0.84 (m, 6H), 0.80 (d,  $J = 6.0$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  181.7, 178.1, 174.7, 174.3, 173.1, 170.9, 137.7, 130.8, 128.9, 124.6, 119.6, 119.2, 116.0, 111.5, 59.9, 57.8, 57.7, 56.9, 54.0, 53.8, 44.6, 31.9, 30.5, 29.3, 18.1, 27.1, 25.6, 23.8, 22.4, 21.7, 19.6, 18.6, 18.1; IR (film)  $\nu_{\max}$  3277, 2959, 1656, 1523, 1400, 1271, 1152, 1096, 806  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  639.34300

(MH<sup>+</sup>, C<sub>33</sub>H<sub>46</sub>N<sub>6</sub>O<sub>7</sub>H<sup>+</sup> requires 639.35007).



### Compound 108-I.

Procedure A. To a solution of the acid (**107-I**, 5.0 mg, 0.00784 mmol) in 0.50 mL absolute MeOH was treated with SOCl<sub>2</sub> (15 uL, 25.1 mg, 0.211 mmol) at 0 °C. The reaction was stirred at 0 °C for 2 h. The resulting mixture was treated with 2 mL sat. aq. NaHCO<sub>3</sub> and extracted with CHCl<sub>3</sub> (3 × 3 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 1.5 × 5 cm, MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1% → 5%) afforded the product **108-I** (2.7 mg, 0.00423 mmol, 54% yield) as a white solid.

Procedure B. To a solution of the *t*-butyl ester (**106-I**, 20.0 mg, 0.0314 mmol) in 2 mL absolute CH<sub>2</sub>Cl<sub>2</sub> was treated with the solution of *B*-bromocatechol boran (62.3 mg, 0.314 mmol) at rt. The resulting mixture was stirred at rt for 2 hours and treated with 2 mL anhydrous MeOH. The reaction was stirred at rt for 2 hours and concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 2.5 × 15 cm, pure CH<sub>2</sub>Cl<sub>2</sub> to 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) afforded the product (**108-I**, 17.4 mg, 0.0267 mmol, 85% yield) as a white solid: [α]<sub>D</sub><sup>25</sup> −95.3 (c 0.56, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz) δ 10.7 (s, 1H), 8.59 (d, *J* = 9.0 Hz, 1H), 8.43 (d, *J* = 10.0 Hz, 1H), 7.90 (s, 1H), 7.37 (d, *J* = 9.0 Hz, 2H), 7.01 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.90 (s, 1H), 6.84 (d, *J* = 7.5 Hz,



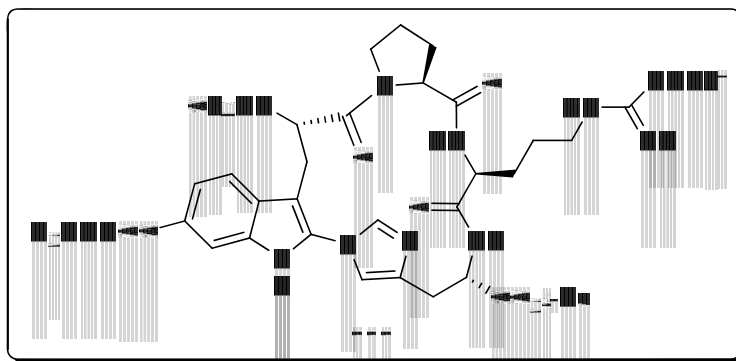
1H), 5.24 (m, 1H), 4.86 (t,  $J = 11.0$  Hz, 1H), 4.12 (dd,  $J = 8.5, 3.0$  Hz, 1H), 4.04 (dt,  $J = 11.5, 3.5$  Hz, 1H), 3.89 (dd,  $J = 7.5, 6.0$  Hz, 1H), 3.66 (s, 3H), 3.28 (dd,  $J = 15.0, 6.0$  Hz, 1H), 3.16 (dd,  $J = 15.0, 8.5$  Hz, 1H), 3.00 (dd,  $J = 11.5, 3.0$  Hz, 1H), 2.27–2.20 (m, 1H), 2.16–2.10 (m, 1H), 2.10–2.04 (m, 2H), 1.72–1.65 (m, 1H), 1.43–1.33 (m, 2H), 1.26–1.19 (m, 2H), 0.91 (d,  $J = 7.5$  Hz, 3H), 0.87 (t,  $J = 8.5$  Hz, 6H), 0.78 (t,  $J = 6.5$  Hz, 6H), 0.70 (d,  $J = 6.0$  Hz, 3H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 125 MHz)  $\delta$  177.4, 172.3, 172.1, 171.7, 169.6, 169.8, 136.0, 129.8, 125.6, 123.5, 119.0, 117.7, 114.5, 108.4, 58.2, 55.1, 55.0, 52.0, 51.9, 51.7, 51.2, 42.8, 30.6, 29.0, 27.0, 26.7, 25.5, 23.7, 23.2, 21.8, 20.8, 18.6, 17.6, 17.3; IR (film)  $\nu_{\text{max}}$  3269, 2959, 1744, 1650, 1515, 1437, 1261, 1025, 803  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  653.36426 ( $\text{MH}^+$ ,  $\text{C}_{34}\text{H}_{48}\text{N}_6\text{O}_7\text{H}^+$  requires 653.36572)

#### 2.4.4. Total synthesis of celogentin C



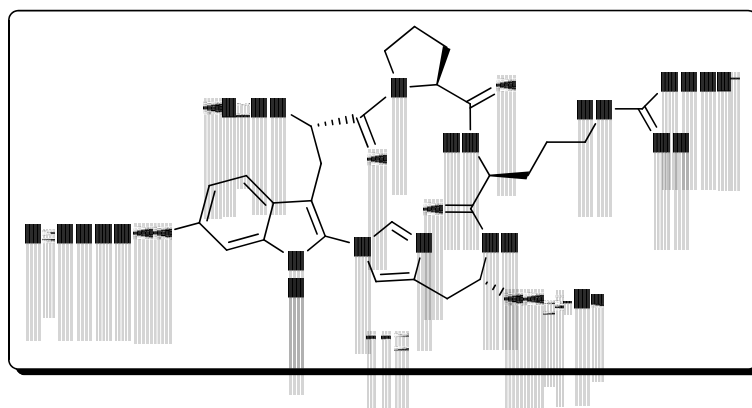
**Compound 110.** To a solution of the amino compound (**109**, 148.0 mg, 0.154 mmol) in dioxane/ $\text{H}_2\text{O}$  (10:1, 7.4 mL) was treated with  $\text{Et}_3\text{N}$  (222.0  $\mu\text{L}$ , 1.540 mmol), followed by benzyl chloroformate (26.2 mg, 22.2  $\mu\text{L}$ , 0.154 mmol). The resulting solution was stirred at rt for 23 hours. The reaction was concentrated under high vacuum. Flash chromatography ( $\text{SiO}_2$ ,  $2.5 \times 25$  cm, 2%  $\rightarrow$  8% MeOH/EtOAc)

afforded the product (**110**, 153.0 mg, 0.140 mmol, 91% yield) as a yellow solid:  $[\alpha]_D^{25} -14.2$  (*c* 0.60, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz, mixture of conformational isomers)  $\delta$  8.14 and 7.83 (2s, 1H), 8.07 (d, *J* = 6.0 Hz, 1H), 7.83 (s, 1H), 7.78 and 7.50 (2d, *J* = 8.0, 8.5 Hz, 1H), 7.40–7.33 (m, 2H), 7.32–7.24 (m, 3H), 7.29 and 7.09 (2s, 1H), 5.13 (d, *J* = 12.5 Hz, 1H), 5.09 (d, *J* = 12.5 Hz, 1H), 5.06–4.93 (m, 4H), 4.62 (dd, *J* = 11.5, 3.0 Hz, 1H), 4.45 (dd, *J* = 12.0, 2.0 Hz, 1H), 4.33 (dd, *J* = 8.0, 3.5 Hz, 1H), 4.23 (t, *J* = 8.0 Hz, 1H), 3.92 and 3.91 (2s, 3H), 3.66–3.59 and 3.57–3.50 (2m, 1H), 3.30–3.22 (m, 2H), 3.22–3.13 (m, 2H), 3.12–3.00 (m, 3H), 2.95 and 2.93 (2s, 2H), 2.62–2.55 (m, 1H), 2.52 and 2.51 (2s, 3H), 2.46 (s, 3H), 2.03 and 2.02 (2s, 3H), 1.96–1.88 and 1.86–1.74 (2m, 1H), 1.72–1.58 (m, 1H), 1.50 and 1.49 (2s, 9H), 1.42 and 1.41 (2d, *J* = 2.0 Hz, 6H), 1.33–1.23 (m, 1H); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz, mixture of conformational isomers)  $\delta$  175.2, 173.7, 173.5, 173.4, 173.3, 172.6, 172.4, 171.7, 169.6, 169.2, 159.9, 158.9, 158.4, 140.2, 139.5, 139.4, 138.7, 138.4, 138.3, 138.2, 137.6, 134.5, 134.5, 134.4, 134.3, 133.9, 133.6, 132.6, 131.4, 129.6, 129.5, 129.2, 129.0, 128.8, 126.3, 126.1, 125.4, 122.4, 121.4, 120.6, 119.7, 118.6, 115.3, 115.1, 105.2, 102.6, 87.8, 83.3, 68.0, 67.9, 62.0, 61.4, 56.1, 55.7, 55.1, 54.9, 54.5, 53.4, 52.8, 52.7, 44.1, 32.3, 31.7, 31.5, 30.5, 28.9, 28.5, 28.4, 26.0, 25.3, 23.2, 19.7, 18.5, 12.6; IR (film)  $\nu_{\max}$  3324, 2974, 1714, 1633, 1552, 1447, 1291, 1253, 1155, 1092, 752 cm<sup>-1</sup>; HRMS (ESI) *m/z* 1093.48064 (MH<sup>+</sup>, C<sub>55</sub>H<sub>68</sub>N<sub>10</sub>O<sub>12</sub>SH<sup>+</sup> requires 1093.48116).



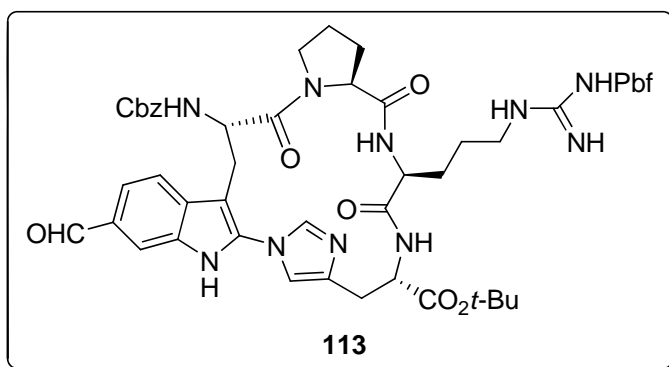
**Compound 111.** To a solution of the methyl ester (**110**, 66.0 mg, 0.0600 mmol) in 3.0 mL MeOH was treated with hydrazine monohydrate (3.0 mL). The resulting mixture was stirred at rt for 24 hours. The reaction was concentrated under high vacuum at 0 °C. Preparation TLC (10% Et<sub>3</sub>N, 50% MeOH in EtOAc) afforded the product (**111**, 48.8 mg, 0.0187 mmol, 74% yield) as a white solid:  $[\alpha]_D^{25} -6.9$  (*c* 1.0, MeOH); <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz, mixture of conformational isomers) δ 8.05 and 7.81 (2s, 1H), 7.95 and 7.88 (2s, 1H), 7.86 and 7.61 (2d, *J* = 8.5 Hz, 1H), 7.56 and 7.49 (2d, *J* = 8.5 Hz, 1H), 7.40–7.32 (m, 2H), 7.32–7.20 (m, 3H), 7.27 and 7.09 (2s, 1H), 5.11 (d, *J* = 4.0 Hz, 2H), 5.08–5.00 (m, 2H), 4.96 (t, *J* = 13.0 Hz, 2H), 4.61 (d, *J* = 8.0 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.33 (dd, *J* = 8.0, 3.5 Hz, 1H), 4.23 (t, *J* = 8.0 Hz, 1H), 3.68–3.59 and 3.58–3.49 (m, 1H), 3.30–3.21 (m, 2H), 3.20–3.11 (m, 3H), 3.11–3.00 (m, 2H), 2.96 and 2.94 (2s, 2H), 2.62–2.54 (m, 1H), 2.52 and 2.51 (2s, 3H), 2.46 (s, 3H), 2.03 and 2.02 (2s, 3H), 1.96–1.89 and 1.85–1.76 (2m, 1H), 1.74–1.57 (m, 1H), 1.50 (s, 9H), 1.46–1.35 (m, 6H), 1.35–1.23 (m, 1H); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz, mixture of conformational isomers) δ 175.3, 173.7, 173.5, 173.3, 172.6, 172.5, 171.7, 170.6, 170.1, 160.0, 159.0, 158.4, 158.1, 140.2, 139.5, 138.8, 138.3, 138.2, 134.7, 134.5, 134.4, 133.6, 132.9, 131.4, 130.2, 129.7, 129.5, 129.2, 129.0, 128.8, 128.5, 126.1, 121.5, 120.6, 120.2, 120.0, 119.9, 118.6, 112.8,

112.7, 105.2, 102.6, 87.8, 83.3, 67.9, 61.9, 61.3, 56.1, 55.7, 55.2, 54.9, 54.6, 53.4, 47.8, 44.1, 32.3, 31.7, 31.5, 30.9, 30.5, 28.8, 28.5, 28.4, 27.9, 26.0, 25.3, 23.2, 19.7, 18.5, 12.6, 9.47; IR (film)  $\nu_{\max}$  3298, 2974, 1637, 1551, 1453, 1255, 1155, 1108, 698  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  1093.49154 ( $\text{MH}^+$ ,  $\text{C}_{54}\text{H}_{68}\text{N}_{12}\text{O}_{11}\text{SH}^+$  requires 1093.49240).



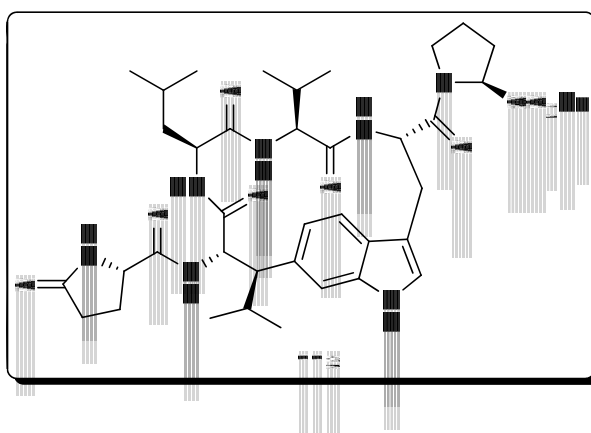
**Compound 112.** To a solution of the acyl hydrazine (**111**, 15.0 mg, 0.0137 mmol) in THF/Pyridine (2:1, 4.5 mL) was treated with  $\text{NsCl}$  (6.0 mg, 0.0274 mmol). The resulting mixture was stirred at rt for 12 hours. The reaction was concentrated in vacuo. Pyridine was removed under high vacuum. Preparation TLC (50% MeOH in EtOAc) afforded the product (**112**, 15.7 mg, 0.0123 mmol, 90% yield) as a yellow solid:  $[\alpha]_{\text{D}}^{25} +6.0$  ( $c$  1.67, MeOH);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz, mixture of conformational isomers)  $\delta$  8.19–8.13 (m, 2H), 8.04 and 7.82 (2s, 1H), 7.90–7.72 (m, 3H), 7.68 and 7.54 (2d,  $J = 9.0$  Hz, 1H), 7.50 and 7.46 (2d,  $J = 9.0$  Hz, 1H), 7.40–7.32 (m, 2H), 7.32–7.22 (m, 3H), 7.27 and 7.07 (2s, 1H), 5.10 (d,  $J = 4.0$  Hz, 2H), 5.05–4.95 (m, 4H), 4.65–4.58 (m, 1H), 4.47–4.41 (m, 1H), 4.36–4.30 (m, 1H), 4.23 (t,  $J = 7.5$  Hz, 1H), 3.66–3.60 and 3.59–3.49 (m, 1H), 3.29–3.20 (m, 2H), 3.20–3.11 (m, 2H), 3.11–3.00 (m, 3H), 2.96 and 2.93 (2s, 2H), 2.60–2.53 (m, 1H), 2.52 and 2.51 (2s, 3H), 2.46 (s, 3H), 2.02 (s, 3H), 1.97–1.86 and 1.84–1.64 (2m,

1H), 1.82–1.55 (m, 1H), 1.49 (s, 9H), 1.42 and 1.41 (2s, 6H), 1.36–1.26 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz, mixture of conformational isomers)  $\delta$  175.2, 173.7, 173.5, 173.3, 172.6, 172.4, 171.7, 169.7, 169.2, 159.9, 158.9, 158.3, 158.1, 149.8, 140.2, 139.5, 138.7, 138.3, 138.2, 137.6, 134.7, 134.5, 134.2, 134.0, 133.6, 133.4, 132.7, 130.8, 129.7, 129.5, 129.2, 129.0, 128.9, 128.8, 126.1, 126.0, 121.4, 120.6, 119.8, 118.6, 115.6, 113.1, 105.3, 102.6, 87.8, 83.3, 68.0, 67.9, 62.0, 61.3, 56.1, 55.7, 55.1, 54.9, 54.6, 53.4, 44.1, 36.7, 32.3, 31.7, 31.5, 30.9, 30.5, 28.9, 28.5, 28.4, 25.3, 23.2, 19.7, 18.5, 12.7; IR (film)  $\nu_{\text{max}}$  3360, 2928, 1637, 1541, 1369, 1239, 1145, 1081, 847  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  1278.46970 ( $\text{MH}^+$ ,  $\text{C}_{60}\text{H}_{71}\text{N}_{13}\text{O}_{15}\text{S}_2\text{H}^+$  requires 1278.47068).



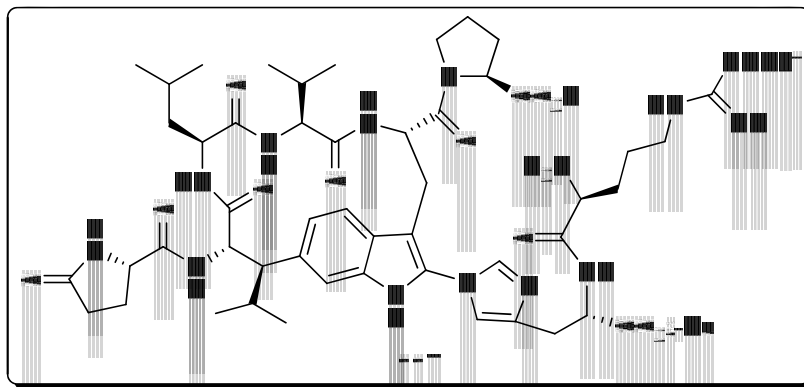
**Compound 113.** To a solution of compound **112** (22.5 mg, 0.0176 mmol) in 3.0 mL EtOH was treated with 1M  $\text{K}_2\text{CO}_3$  (36.0  $\mu\text{L}$ , 0.0360 mmol). The resulting mixture was stirred at 80  $^\circ\text{C}$  for 2 hours. The reaction was concentrated in vacuo. Preparation TLC (20% MeOH/EtOAc) afforded the product (**113**, 14.6 mg, 0.0137 mmol, 78% yield) as a yellow solid:  $[\alpha]_{\text{D}}^{25} +3.0$  ( $c$  0.53, MeOH);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz, mixture of conformational isomers)  $\delta$  10.00 (s, 1H), 8.09 and 8.02 (2s, 1H), 7.97 and 7.96 (2s, 1H), 7.86 and 7.58 (2d,  $J = 8.0$  Hz, 1H), 7.73 and 7.68 (2d,  $J = 8.5$  Hz, 1H),

7.42–7.34 (m, 2H), 7.34–7.23 (m, 3H), 7.32 and 7.12 (2s, 1H), 5.12 (d,  $J = 5.0$  Hz, 2H), 5.07–4.95 (m, 4H), 4.64 (dd,  $J = 11.0, 2.0$  Hz, 1H), 4.46 (dd,  $J = 12.5, 2.5$  Hz, 1H), 4.34 (dd,  $J = 7.5, 3.0$  Hz, 1H), 4.24 (t,  $J = 8.0$  Hz, 1H), 3.68–3.60 and 3.60–3.53 (2m, 1H), 3.31–3.23 (m, 2H), 3.23–3.14 (m, 2H), 3.14–3.00 (m, 3H), 2.97 and 2.95 (2s, 2H), 2.63–2.56 (m, 1H), 2.53 and 2.52 (2s, 3H), 2.45 (s, 3H), 2.04 and 2.03 (2s, 3H), 1.98–1.87 and 1.87–1.76 (m, 1H), 1.74–1.60 (m, 1H), 1.51 (s, 9H), 1.47–1.36 (m, 6H), 1.35–1.26 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz, mixture of conformational isomers)  $\delta$  194.4, 194.3, 175.2, 173.8, 173.5, 173.3, 172.6, 172.5, 171.7, 160.0, 159.0, 158.4, 158.2, 140.2, 139.5, 138.7, 138.5, 138.3, 138.2, 137.6, 135.4, 134.9, 134.5, 134.1, 133.7, 133.6, 133.5, 133.2, 133.0, 130.0, 129.7, 129.5, 129.2, 129.0, 128.8, 126.1, 122.0, 121.7, 121.3, 120.6, 120.4, 120.2, 118.6, 117.0, 116.4, 105.4, 103.0, 87.8, 83.3, 68.0, 67.9, 62.0, 61.4, 56.1, 55.7, 55.1, 54.9, 54.5, 53.5, 44.1, 32.3, 31.7, 31.5, 30.5, 28.9, 28.5, 28.4, 27.7, 26.0, 25.3, 19.7, 18.5, 12.6; IR (film)  $\nu_{\text{max}}$  3327, 2929, 1635, 1554, 1453, 1368, 1252, 1154, 1028  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  1063.47122 ( $\text{MH}^+$ ,  $\text{C}_{54}\text{H}_{66}\text{N}_{10}\text{O}_{11}\text{SH}^+$  requires 1063.47060).



**Compound 115.** To a solution of compound **41** (15.0 mg, 0.0235 mmol) and (*S*)-benzyl pyrrolidine-2-carboxylate (4.55 mg, 0.0230 mmol) in 2.0 mL THF was

treated with HOBt ( 4.50 mg, 0.0345 mmol), followed by EDCI (6.38 mg, 0.0345 mmol) at 0 °C. The resulting mixture was stirred at 0 °C → rt for 8 hours. The reaction was treated with 5 mL sat. aq. NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 × 5 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Preparation TLC (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1:10) afforded **compound 115** (13.5 mg, 0.0164 mmol, 70% yield) as a white solid: [ $\alpha$ ]<sub>D</sub><sup>25</sup> -102.5 (c 0.90, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz)  $\delta$  10.6 (s, 1H), 8.51 (d, *J* = 9.0 Hz, 1H), 8.33 (d, *J* = 9.0 Hz, 1H), 7.85 (s, 1H), 7.45–7.28 (m, 6H), 6.98 (s, 1H), 6.93 (d, *J* = 7.0 Hz, 1H), 6.87 (s, 1H), 6.74 (brs, 1H), 5.36–5.27 (m, 1H), 5.18 (d, *J* = 12.5 Hz, 1H), 5.12 (d, *J* = 12.5 Hz, 1H), 4.90–4.82 (m, 1H), 4.44–4.37 (m, 1H), 4.15–4.07 (m, 1H), 4.06–3.98 (m, 1H), 3.92–3.81 (m, 2H), 3.81–3.73 (m, 1H), 3.59–3.48 (m, 1H), 3.28–3.19 (m, 1H), 3.08–3.00 (m, 1H), 3.00–2.94 (m, 1H), 2.29–2.18 (m, 2H), 2.18–2.03 (m, 2H), 2.03–1.92 (m, 2H), 1.92–1.78 (m, 2H), 1.74–1.65 (m, 1H), 1.43–1.32 (m, 2H), 1.32–1.18 (m, 2H), 0.90–0.60 (m, 18H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz)  $\delta$  177.4, 172.2, 171.8, 171.7, 169.9, 169.5, 169.1, 135.8 (2C), 129.5, 128.4 (2C), 128.3, 128.1, 127.9 (2C), 127.6, 126.0, 124.1, 117.9, 107.9, 69.7, 65.9, 58.6, 57.5, 55.0, 52.0, 51.6, 49.9, 46.7, 42.7, 30.2, 28.9, 28.5, 26.8, 26.1, 25.5, 24.8, 23.7, 23.1, 21.8, 20.9, 18.7, 17.7, 17.3; IR (film)  $\nu_{\max}$  3269, 2958, 1741, 1654, 1541, 1439, 1265, 1171, 1026, 699 cm<sup>-1</sup>; HRMS (ESI) *m/z* 826.4478 (MH<sup>+</sup>, C<sub>45</sub>H<sub>59</sub>N<sub>7</sub>O<sub>8</sub>H<sup>+</sup> requires 826.4498).



**Compound 117.** To a solution of compound **115** (7.0 mg, 0.00848 mmol) and (*S*)-benzyl pyrrolidine-2-carboxylate (3.5 mg, 0.0170 mmol) in 2.0 mL anhydrous CH<sub>2</sub>Cl<sub>2</sub> was treated with one drop of *N,N'*-dimethyl piperazine, followed by NCS (3.3 mg, 0.0254 mmol). The resulting solution was stirred at rt for 6 hours. The reaction was treated with Cbz-Arg(Pbf)-His-*t*-Bu (**8**, 31.9 mg, 0.0424 mmol). The mixture was stirred at rt for 24 hours and concentrated in vacuo to afford the crude compound **116**.

The above crude compound **116** was dissolved in MeOH/H<sub>2</sub>O (5:1, 2.0 mL), which was treated with NH<sub>4</sub>COOH (18.0 mg, 0.252 mmol), followed by 10% Pd/C (25.0 mg). The reaction was stirred at rt for 4 hours. The crude mixture was filtered through a fine sintered glass pad filter and washed with MeOH (5 × 5 mL). The mixture was concentrated in vacuo. Preparation TLC (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1:2) afforded compound **117** (7.3 mg, 0.00540 mmol, 64% over 2 steps) as a white solid:  $[\alpha]^{25}_{\text{D}}$  -42.4 (*c* 0.45, CH<sub>3</sub>OH); <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz, mixture of conformational isomers) δ 7.91 and 7.89 (2s, 1H), 7.68 and 7.58 (2d, *J* = 8.5 Hz, 1H), 7.53 and 7.40 (2s, 1H), 7.37 and 7.25 (s, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 7.00 (s, 1H), 5.92 (dd, *J* = 12.0, 5.0 Hz, 1H), 4.65–4.58 (m, 2H), 4.35 (dd, *J* = 8.0, 3.5 Hz, 1H), 4.30–4.22 (m,



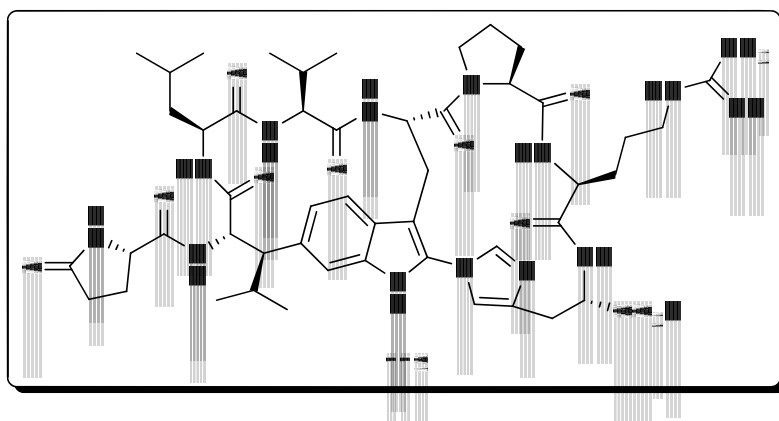
3H), 4.20–4.15 (m, 1H), 3.99–3.91 (m, 1H), 3.59–3.55 (m, 2H), 3.22–3.11 (m, 6H), 3.00 and 2.97 (2s, 2H), 2.58 and 2.56 (2s, 3H), 2.51 and 2.49 (s, 3H), 2.39–2.30 (m, 3H), 2.26–2.10 (m, 2H), 2.08 and 2.05 (2s, 3H), 2.04–1.93 (m, 2H), 1.85–1.37 (m, 22H), 1.37–1.28 (m, 3H), 0.97 (d,  $J = 6.5$  Hz, 3H), 0.94–0.84 (m, 6H), 0.84–0.74 (m, 9H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz, mixture of conformational isomers)  $\delta$  181.67 and 181.65 (1C), 174.7, 171.8 and 171.7 (1C), 172.5, 172.3, 171.9, 171.7, 160.0 and 159.9 (1C), 158.4, 139.5, 139.3, 138.7 and 138.6 (1C), 135.21 and 135.20 (1C), 134.7 and 134.6 (1C), 133.6, 132.81 and 132.79 (1C), 130.8, 130.4, 128.8, 126.8, 126.2 and 126.1 (1C), 121.4, 120.8 and 120.6 (1C), 118.6 and 118.5 (1C), 115.8, 103.3, 87.8 and 87.7 (1C), 83.33 and 83.27 (1C), 74.0 and 73.6 (1C), 73.54 and 73.49 (1C), 71.3, 71.0, 64.6, 63.5, 62.15 and 62.13 (1C), 62.10 and 62.05 (1C), 59.3, 57.8, 55.6 and 55.4 (1C), 54.5 and 54.3 (1C), 53.7 and 53.4 (1C), 47.1, 44.1, 43.9, 41.6, 33.5, 33.2, 31.2, 30.9, 30.5, 29.1, 28.9 (2C), 28.5 and 28.3 (3C), 27.1, 26.1 and 25.8 (1C), 23.6, 22.3, 21.8, 19.7, 19.3, 19.1, 18.5, 18.0, 12.6; IR (film)  $\nu_{\text{max}}$  3287, 2961, 1644, 1551, 1455, 1376, 1253, 1155, 1104  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  1353.70220 ( $\text{MH}^+$ ,  $\text{C}_{67}\text{H}_{96}\text{N}_{14}\text{O}_{14}\text{SH}^+$  requires 1353.70311).



**Compound 118.** To a solution of Compound **117** (7.3 mg, 0.00540 mmol) in 2.0 mL

DMF was treated with HOBt (1.1 mg, 0.0081 mmol) and HBTU (3.0 mg, 0.0081 mmol). The resulting solution was stirred at rt for 8 hours. The mixture was treated with 2 mL sat. aq. NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (5×5 mL). The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. DMF was then removed under high vacuum. Preparation TLC (MeOH/EtOAc 1:2) afforded compound **118** (6.0 mg, 0.0045 mmol, 83% yield) as a yellow solid:  $[\alpha]_D^{25} -28.3$  (*c* 0.067, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz)  $\delta$  11.45 (s, 1H), 8.82 (d, *J* = 9.5 Hz, 1H), 8.56 (d, *J* = 9.0 Hz, 1H), 8.43 (d, *J* = 9.0 Hz, 1H), 8.34 (d, *J* = 9.5 Hz, 1H), 7.89 (s, 1H), 7.88 (s, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.34 (s, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.89 (brd, *J* = 9.5 Hz, 1H), 6.86 (s, 1H), 6.64 (brs, 1H), 6.61 (brd, *J* = 4.5 Hz, 1H), 6.51 (brs, 1H), 5.74–5.66 (m, 1H), 4.89–4.79 (m, 2H), 4.17–4.07 (m, 4H), 4.07–4.00 (m, 1H), 4.00–3.93 (m, 1H), 3.92–3.84 (m, 1H), 3.56 (t, *J* = 8.0 Hz, 1H), 3.22–1.98 (m, 1H), 3.07 (brd, *J* = 3.0 Hz, 1H), 3.05–2.98 (m, 2H), 2.96 (s, 2H), 2.78 (dd, *J* = 16.0, 12.5 Hz, 1H), 2.60 (t, *J* = 13.0 Hz, 1H), 2.48 (s, 3H), 2.43 (s, 3H), 2.30–2.19 (m, 2H), 2.17–2.10 (m, 1H), 2.10–2.01 (m, 4H), 2.00 (s, 3H), 1.89–1.81 (m, 1H), 1.81–1.66 (m, 3H), 1.66–1.58 (m, 1H), 1.54–1.40 (m, 3H), 1.41 (s, 9H), 1.40 (s, 3H), 1.39 (s, 3H), 1.32–1.26 (m, 1H), 1.19–1.11 (m, 1H), 0.82 (d, *J* = 6.5 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H), 0.73 (d, *J* = 7.0 Hz, 3H), 0.68 (dd, *J* = 14.0, 7.0 Hz, 9H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz)  $\delta$  177.3, 172.1, 171.5, 171.3, 171.1, 170.8, 170.0, 169.3, 169.1, 157.4, 156.0, 138.2, 137.3, 137.2, 132.6, 131.4, 130.5, 129.6, 129.4, 128.9, 125.0, 124.2, 119.3, 116.6, 116.2, 113.8, 99.9, 86.2, 81.5, 61.6, 57.2, 55.1, 54.7, 52.2, 52.1, 51.2, 50.4, 48.5, 47.2, 46.8, 42.4, 41.4, 35.1, 31.5, 31.2, 29.9,

28.9 (2C), 28.2 (2C), 27.5 (3C), 26.5, 26.1, 25.5, 25.0, 23.9, 23.0, 21.8, 20.8, 18.9, 18.6, 18.1, 17.5, 16.9, 12.2; IR (film)  $\nu_{\max}$  3311, 2923, 1660, 1552, 1514, 1260, 1100, 845, 802  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  1335.69063 ( $\text{MH}^+$ ,  $\text{C}_{67}\text{H}_{94}\text{N}_{14}\text{O}_{13}\text{SH}^+$  requires 1335.69183).



**Compound 119.** Compound **118** (8.0 mg, 0.00599 mmol) was dissolved in TFA/ $\text{H}_2\text{O}$  (9:1, 1.0 mL) at 0 °C. The resulting mixture was stirred at rt for 2 hours. The reaction was diluted with 3.0 mL distilled water and extracted with  $\text{CH}_2\text{Cl}_2$  ( $5 \times 3$  mL). The water layer was concentrated under high vacuum to afford compound **119** as a white TFA salt (6.0 mg, ca. 0.00539 mmol, ca. 90% yield):  $[\alpha]_{\text{D}}^{25} -57.8$  ( $c$  0.083, MeOH/ $\text{H}_2\text{O}$  1:1);  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 500 MHz)  $\delta$  11.81 (s, 1H), 9.16 (brs, 1H), 8.84 (d,  $J = 9.5$  Hz, 1H), 8.56 (d,  $J = 8.5$  Hz, 1H), 8.35 (d,  $J = 8.5$  Hz, 1H), 8.20 (d,  $J = 9.0$  Hz, 1H), 7.89 (s, 1H), 7.72 (s, 1H), 7.61 (brs, 1H), 7.57 (d,  $J = 8.0$  Hz, 1H), 7.02 (d,  $J = 8.5$  Hz, 1H), 6.98 (d,  $J = 8.0$  Hz, 1H), 6.94 (s, 1H), 6.80 (d,  $J = 6.5$  Hz, 1H), 5.69–5.61 (m, 1H), 4.92 (t,  $J = 10.5$  Hz, 1H), 4.84 (t,  $J = 10.5$  Hz, 1H), 4.24–4.18 (m, 1H), 4.14 (t,  $J = 6.0$  Hz, 1H), 4.11 (dd,  $J = 8.0, 2.5$  Hz, 1H), 4.06–3.94 (m, 2H), 3.83–3.78 (m, 1H), 3.61 (t,  $J = 7.5$  Hz, 1H), 3.40 (d,  $J = 15.0$  Hz, 1H), 3.32 (dd,  $J = 15.0, 5.5$  Hz, 1H), 3.13–3.03 (m, 3H), 2.93 (t,  $J = 12.5$  Hz,

1H), 2.60 (t,  $J = 15.5$  Hz, 1H), 2.30–2.20 (m, 2H), 2.20–2.13 (m, 1H), 2.13–2.07 (m, 2H), 2.07–1.96 (m, 2H), 1.92–1.74 (m, 3H), 1.74–1.66 (m, 1H), 1.66–1.58 (m, 1H), 1.42–1.36 (m, 3H), 1.22–1.13 (m, 1H), 0.84 (d,  $J = 7.0$  Hz, 3H), 0.78 (d,  $J = 6.5$  Hz, 3H), 0.76–0.70 (m, 9H), 0.68 (d,  $J = 6.0$  Hz, 3H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 125 MHz)  $\delta$  177.4, 172.1, 171.6, 171.4, 171.1 (3C), 169.3, 169.0, 156.7, 136.8, 132.9, 131.9, 127.1, 124.8, 119.81, 119.80, 119.3, 114.1, 102.6, 61.5, 57.2, 55.1, 54.8, 52.1, 51.9, 51.4, 50.0, 47.1, 46.9, 41.5, 40.5, 31.0, 29.8, 29.0 (2C), 28.2, 28.8, 26.6, 25.5 (2C), 24.9, 24.0, 23.9, 23.0, 21.7, 20.9, 18.5, 18.2, 17.0; IR (film)  $\nu_{\text{max}}$  3278, 2964, 1673, 1535, 1434, 1198, 1135, 801  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  1027.54819 ( $\text{MH}^+$ ,  $\text{C}_{50}\text{H}_{70}\text{N}_{14}\text{O}_{10}\text{H}^+$  requires 1027.54721).

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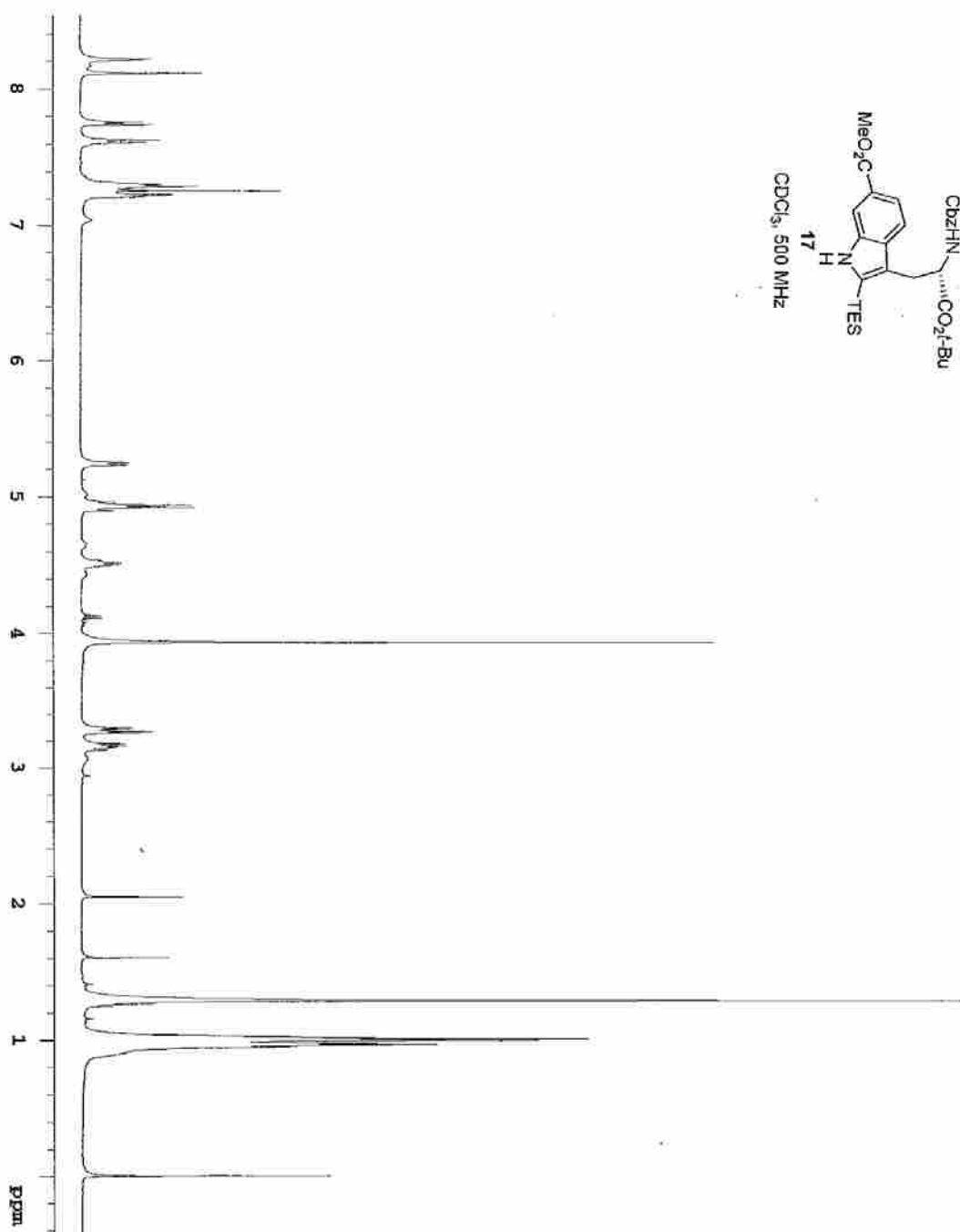
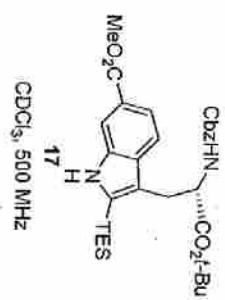
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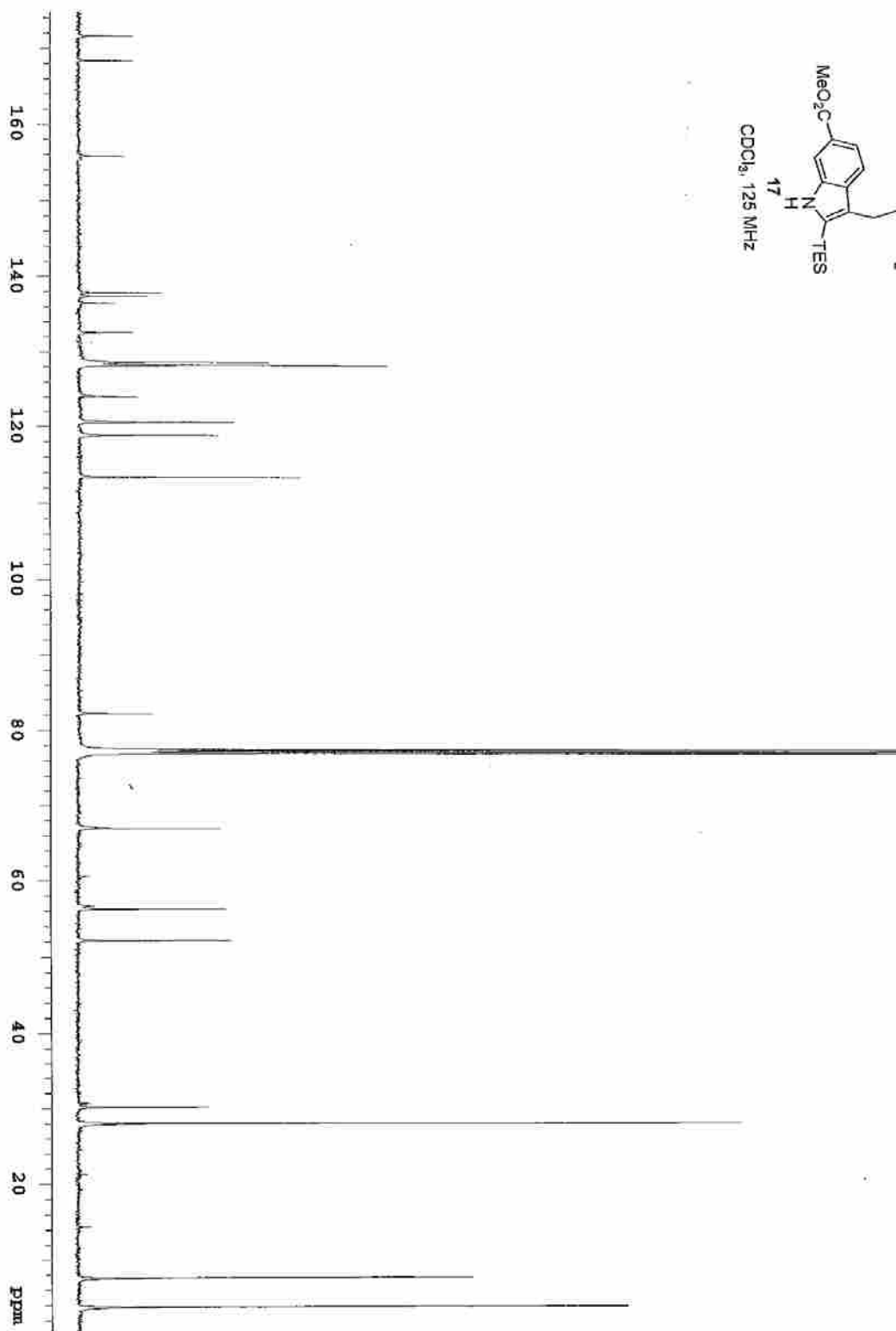
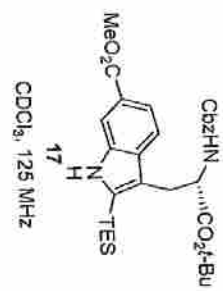


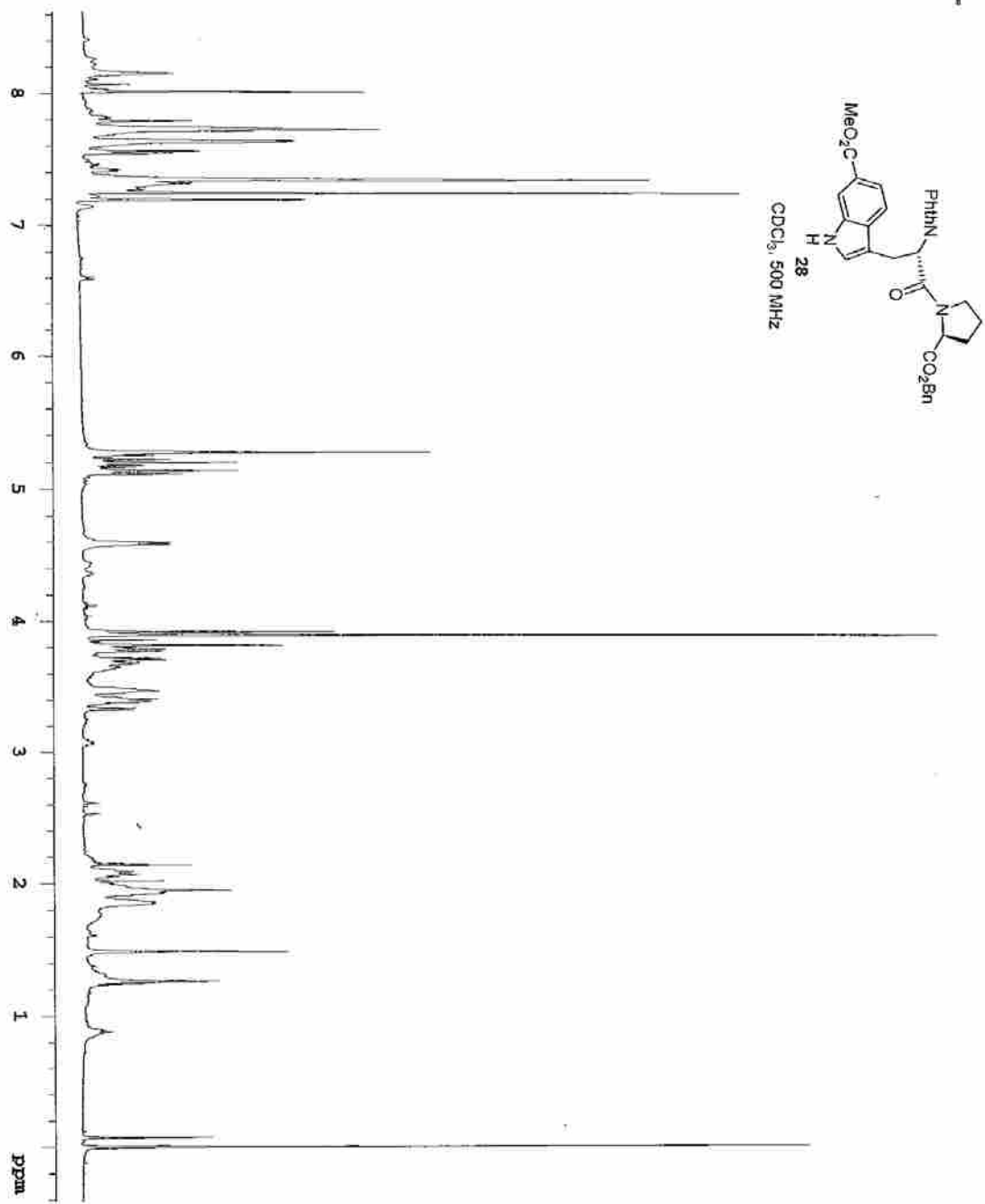
**Appendix: NMR and HPLC for Chapter II compounds**

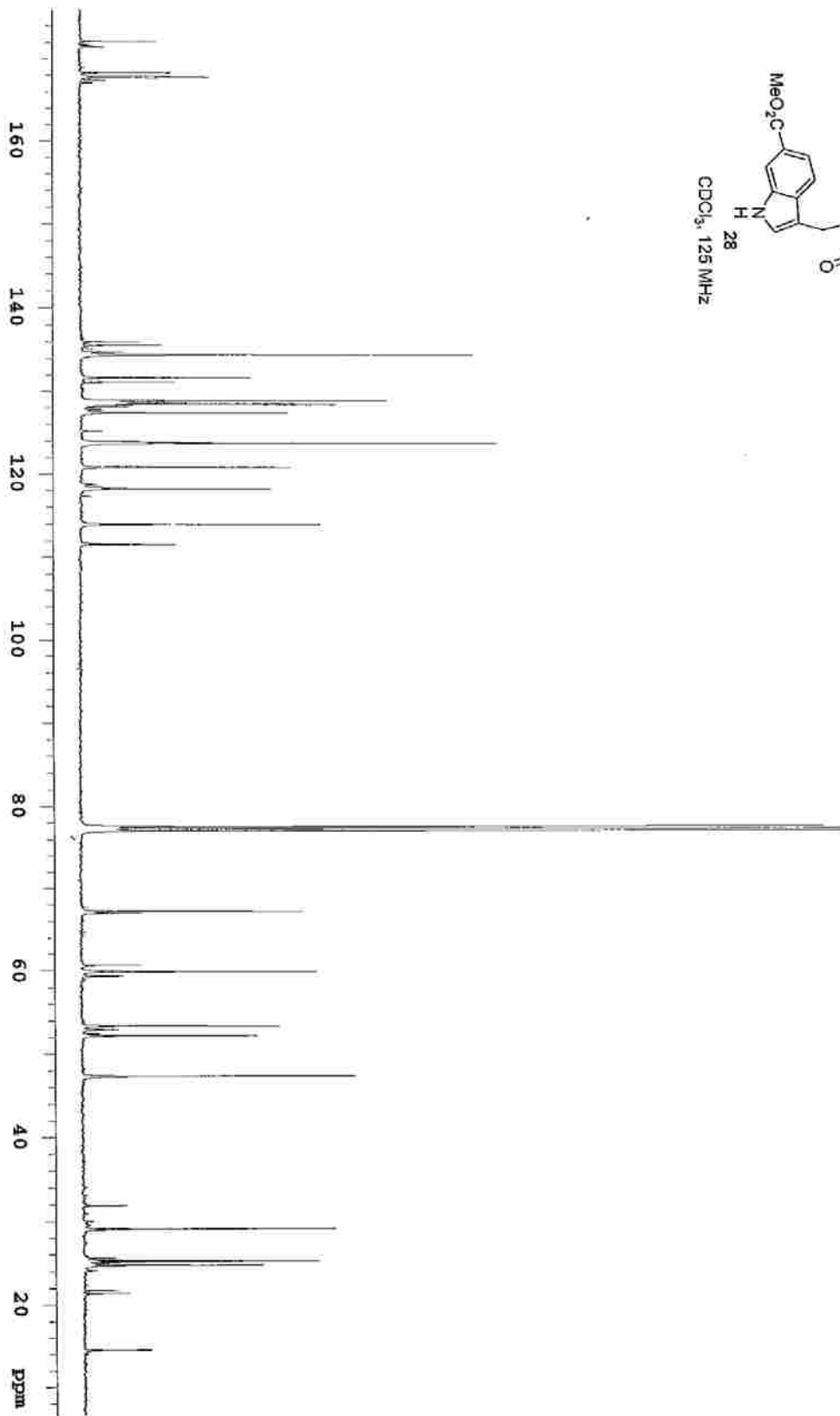
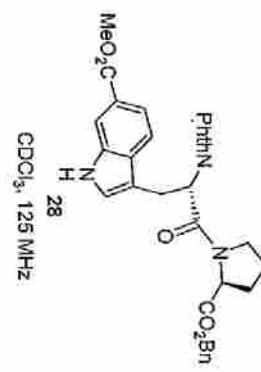


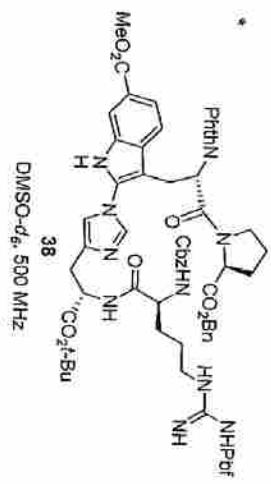






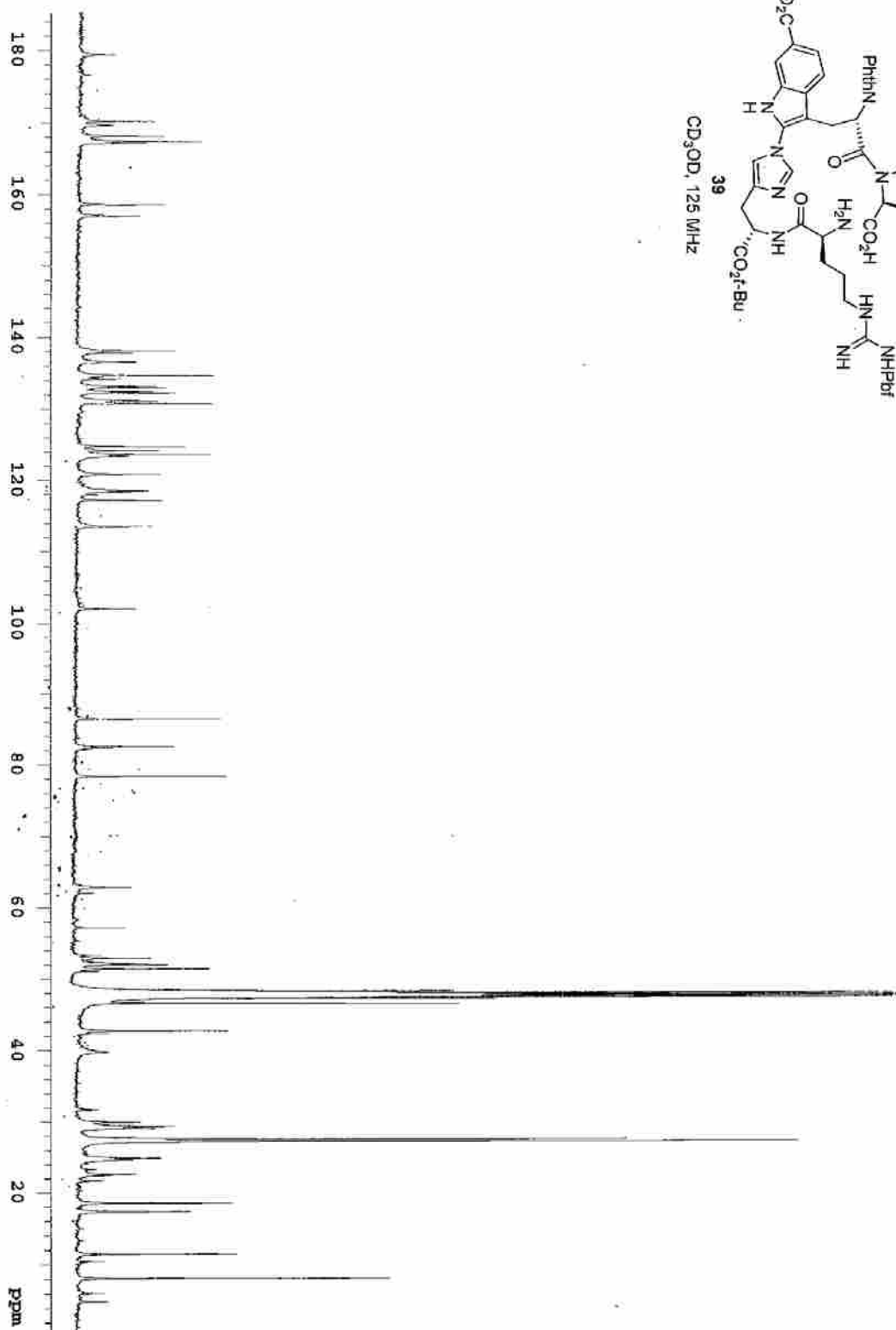
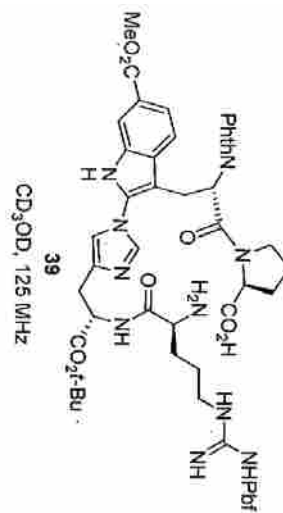


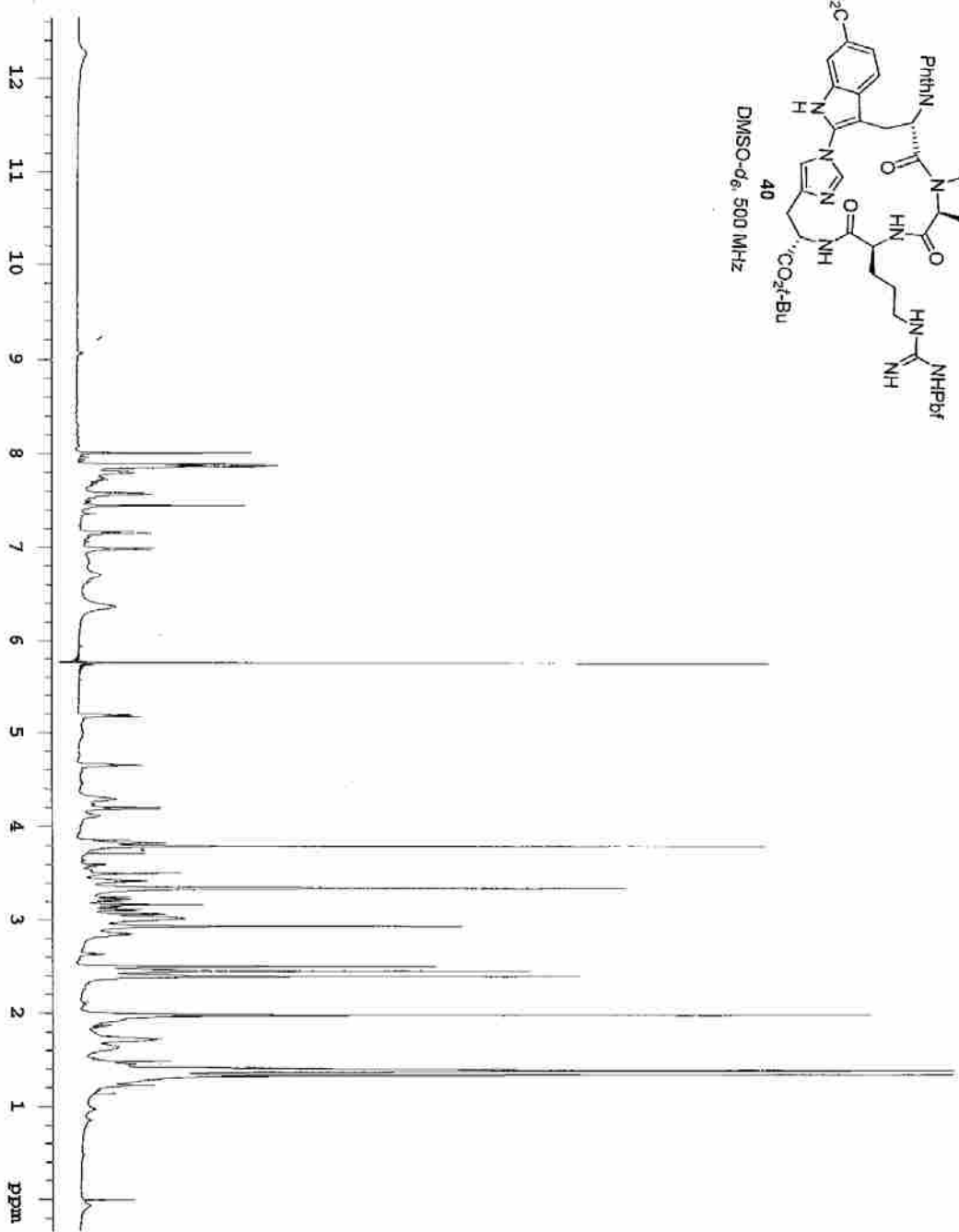
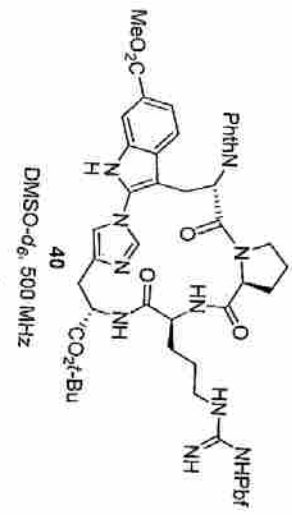




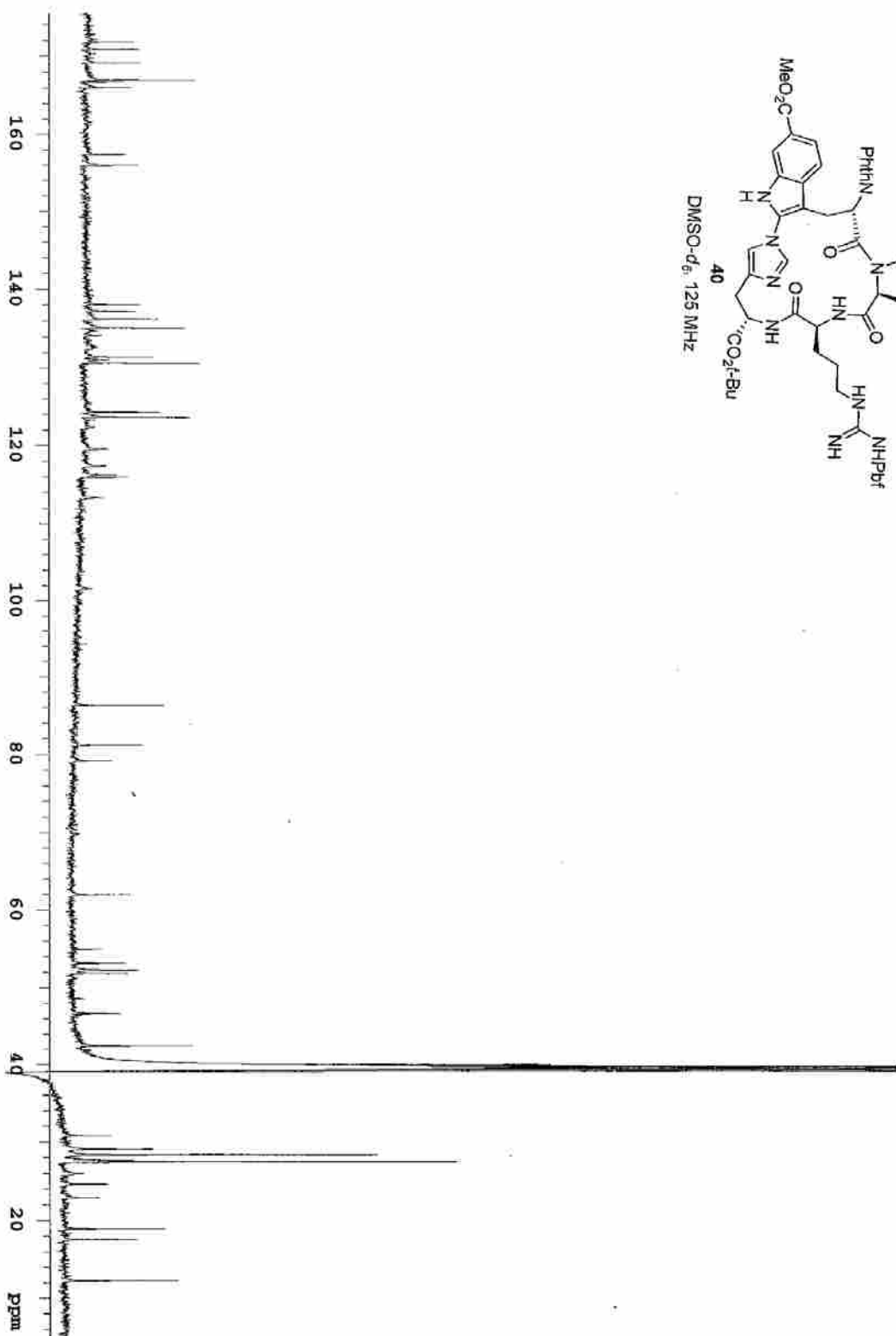
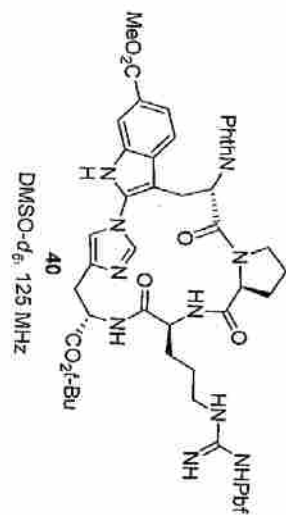


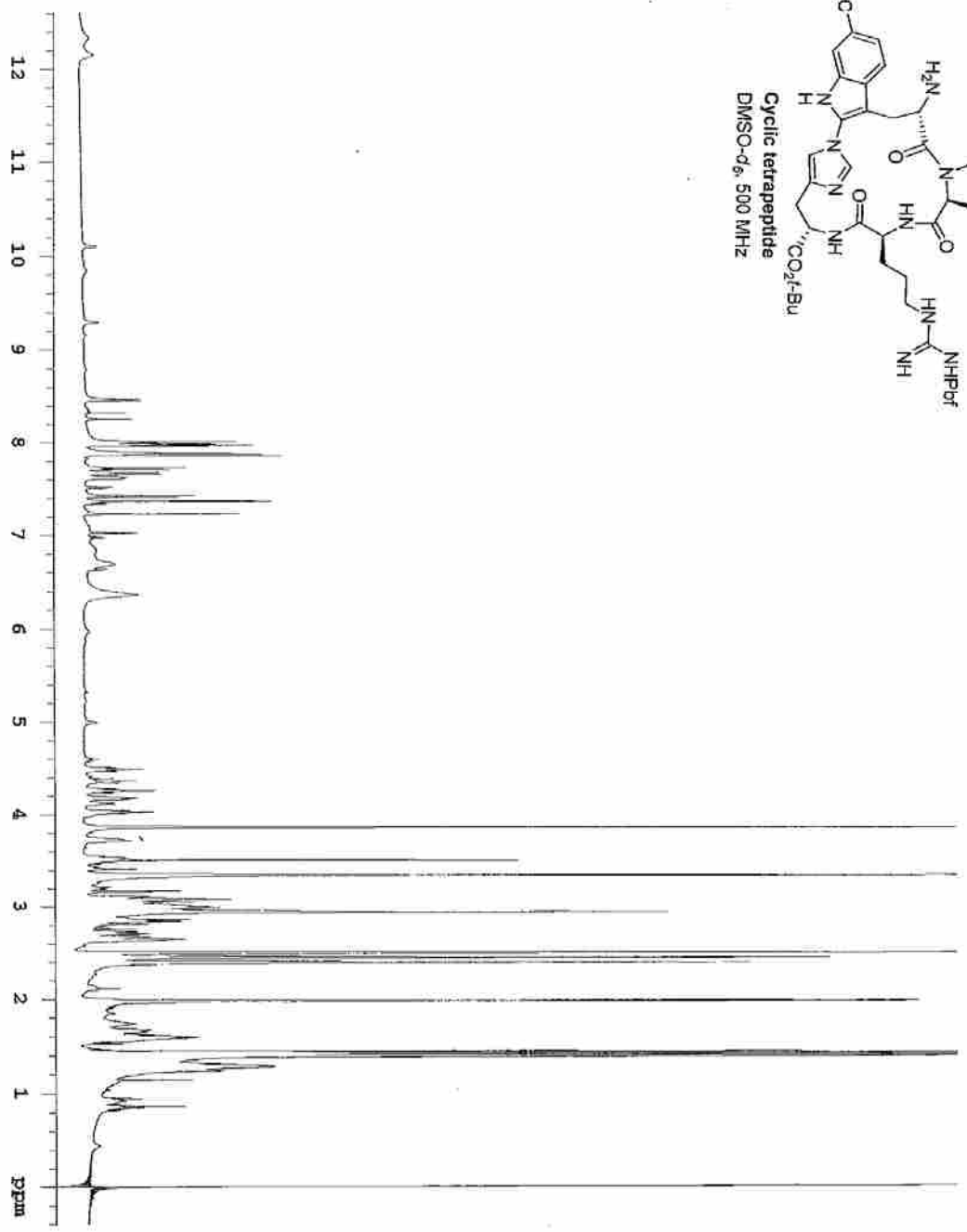
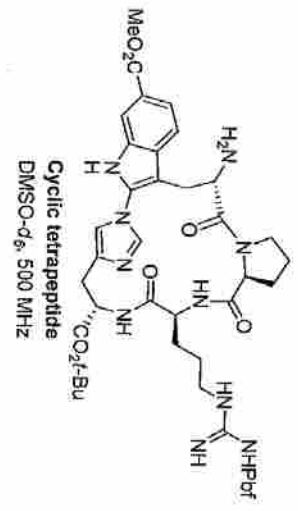


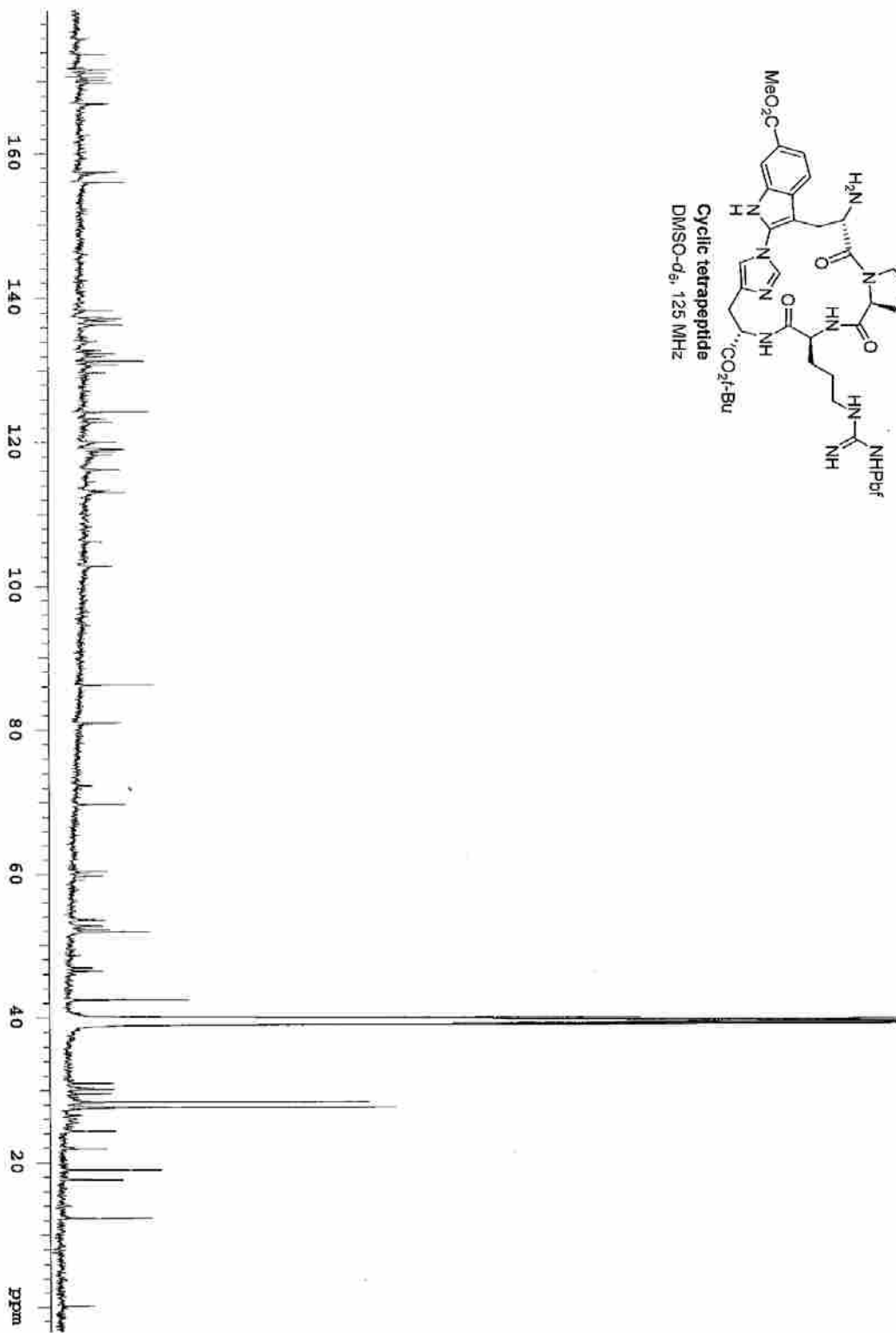
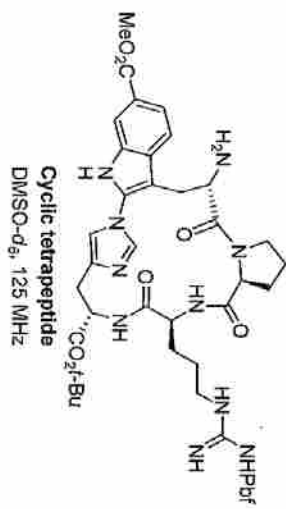


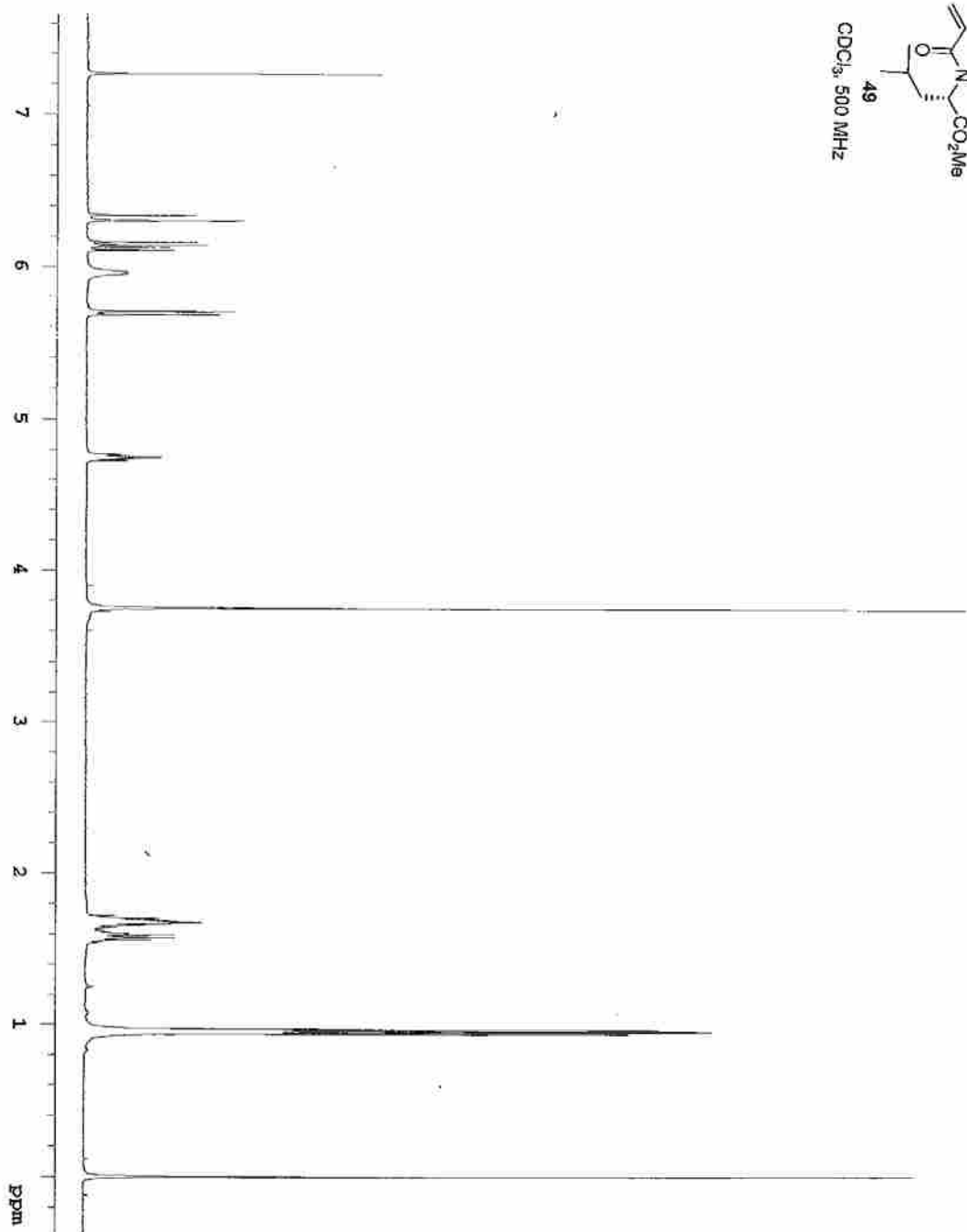
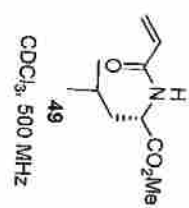


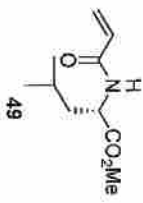




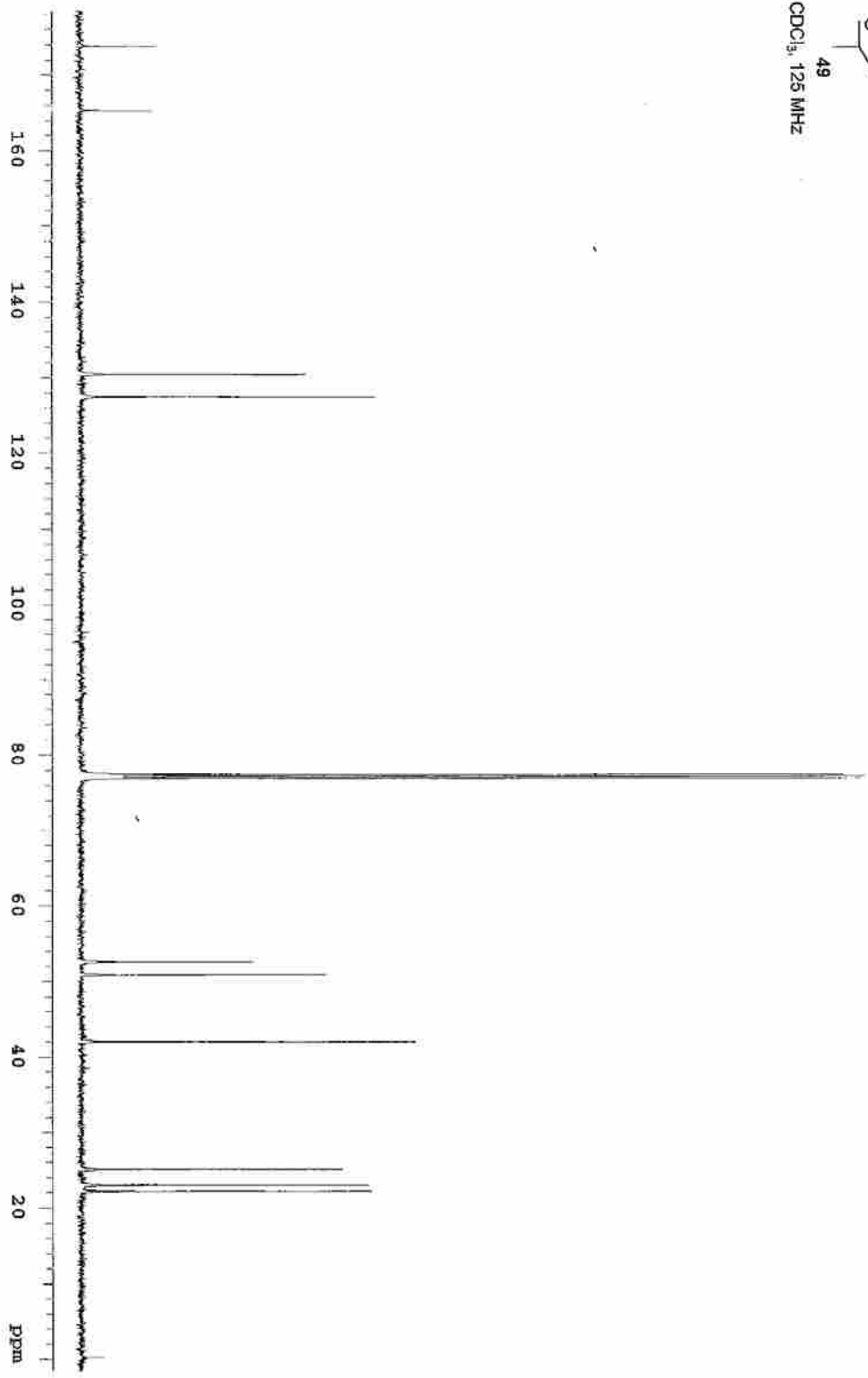


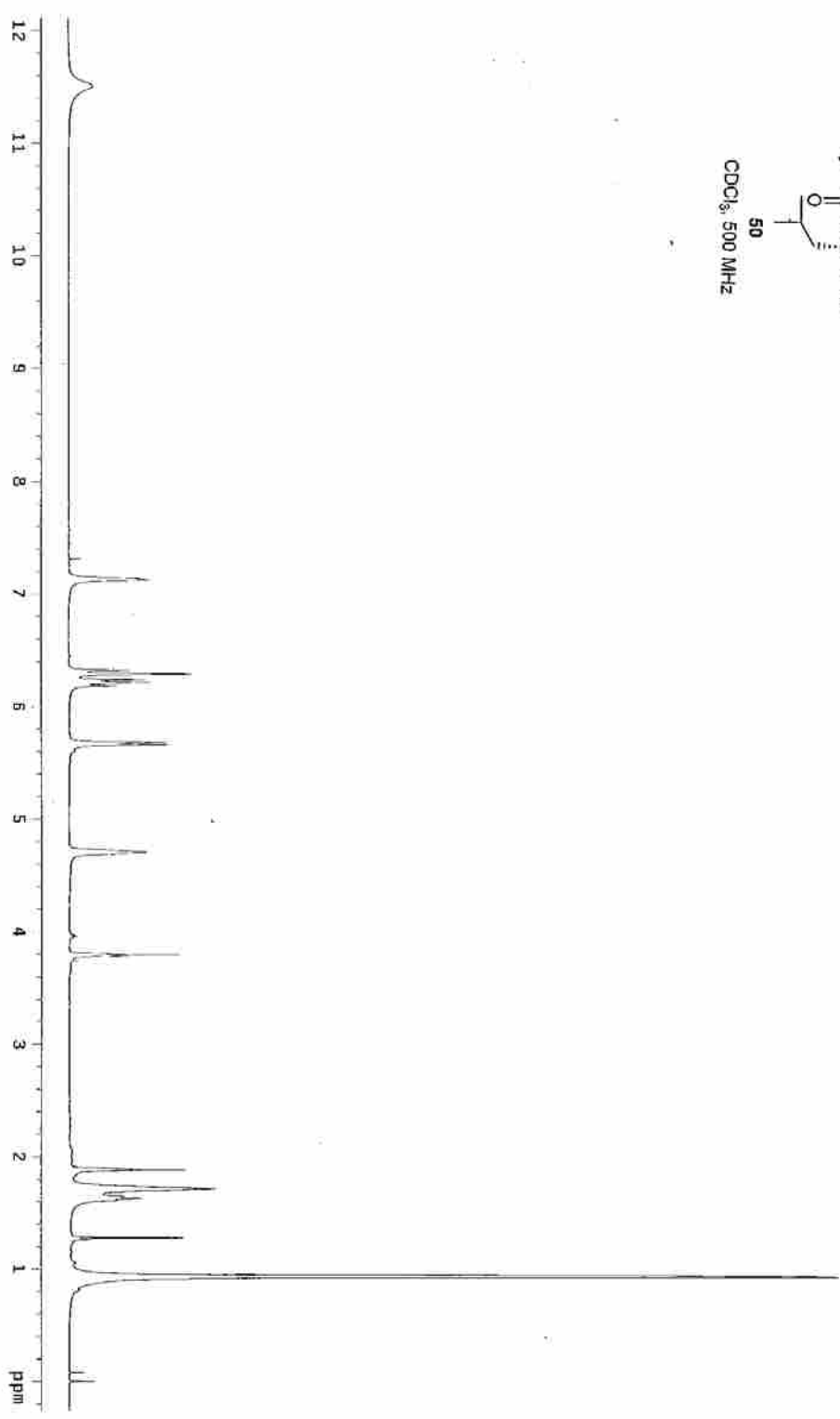
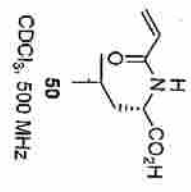


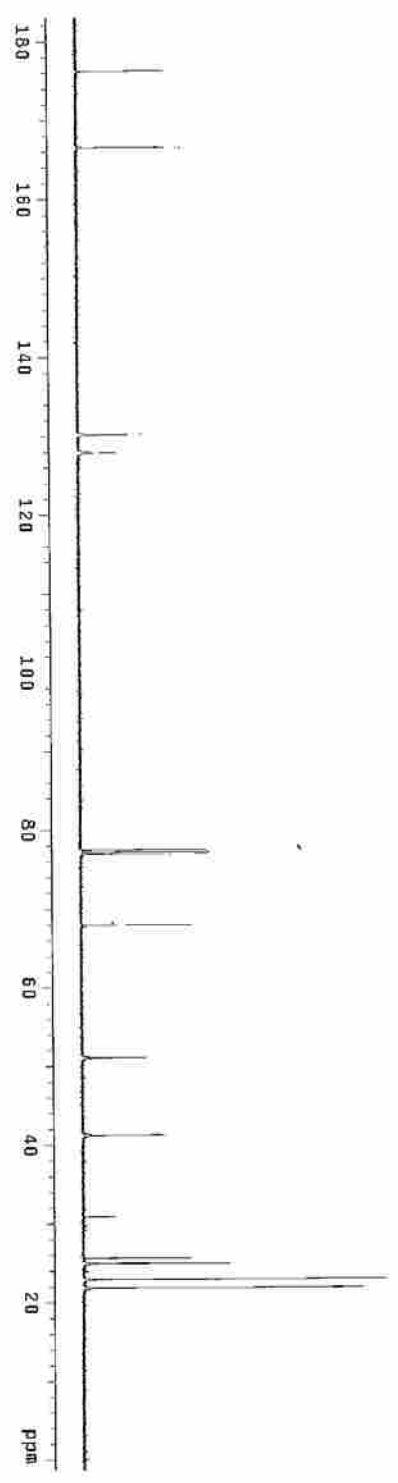
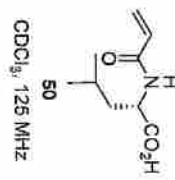


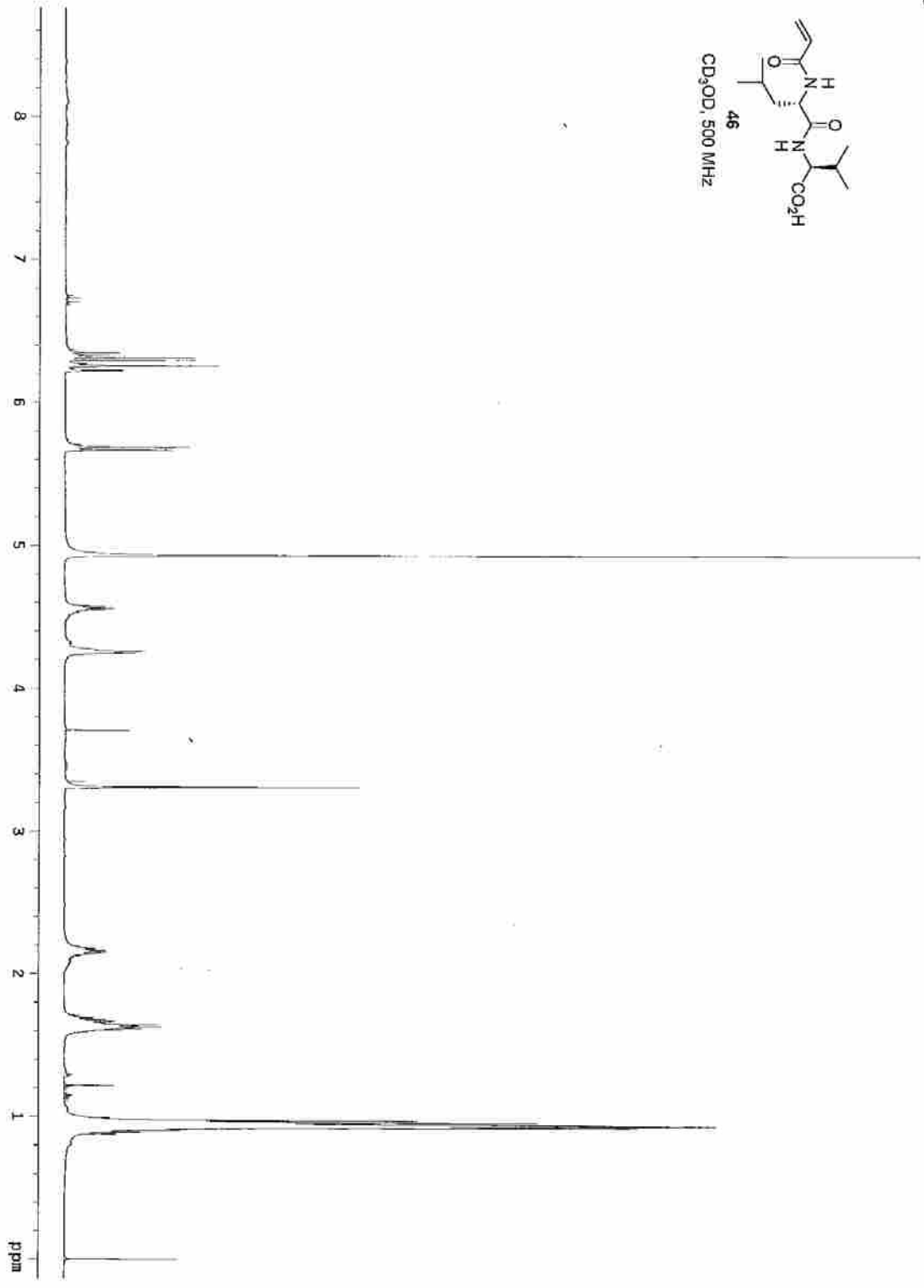
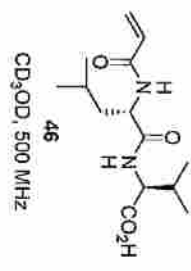


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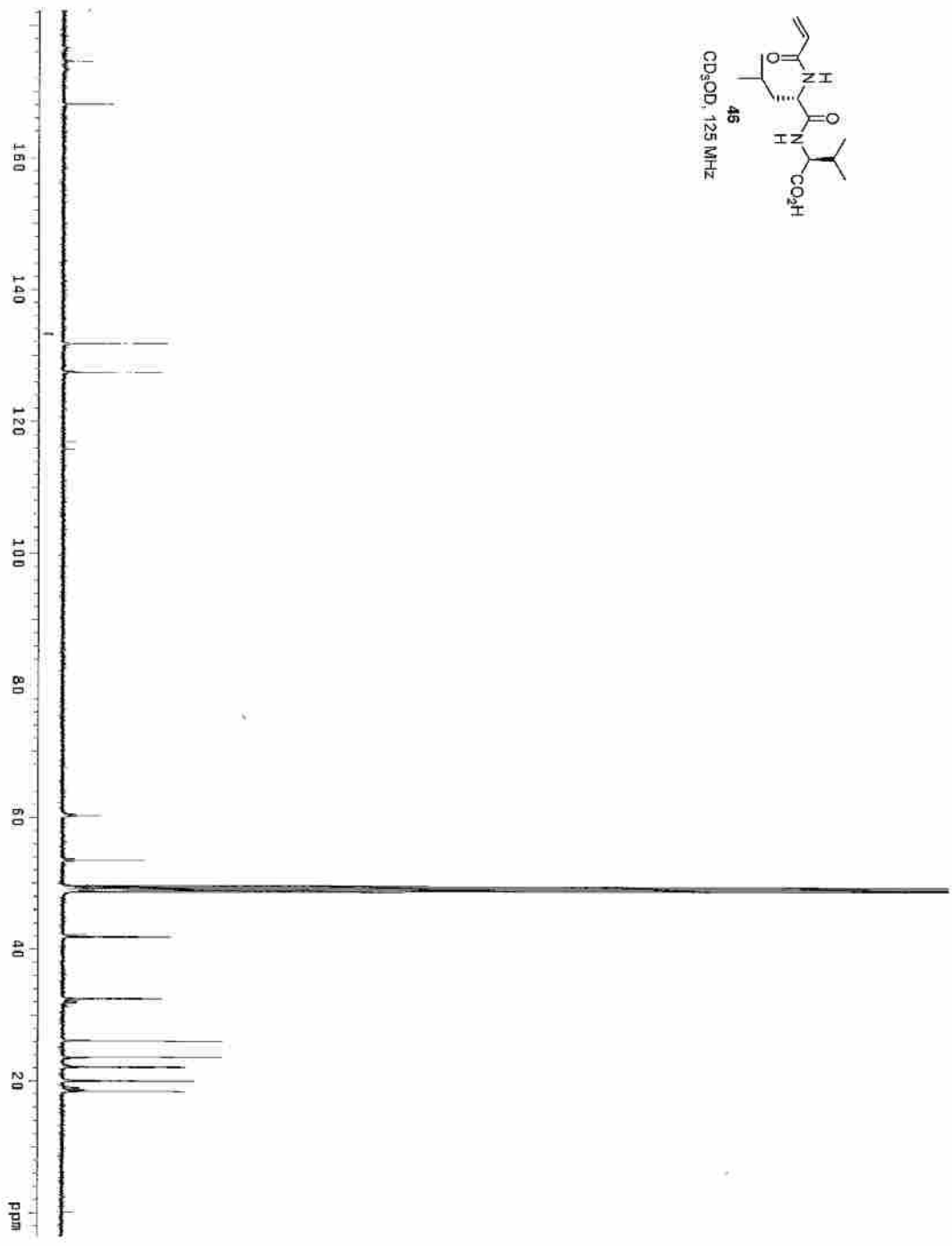
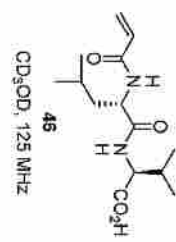


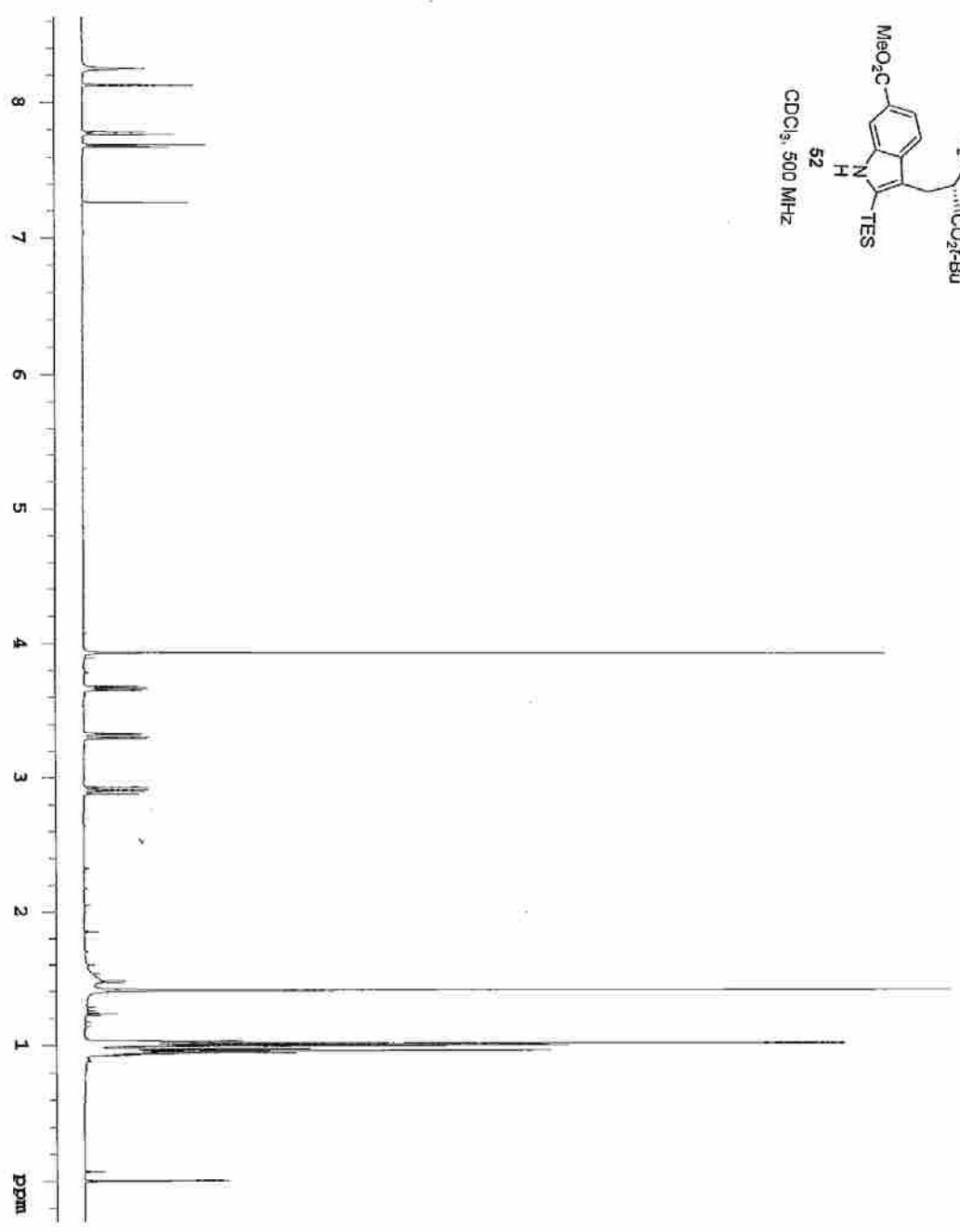
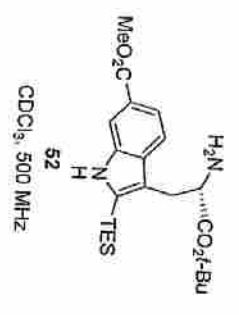


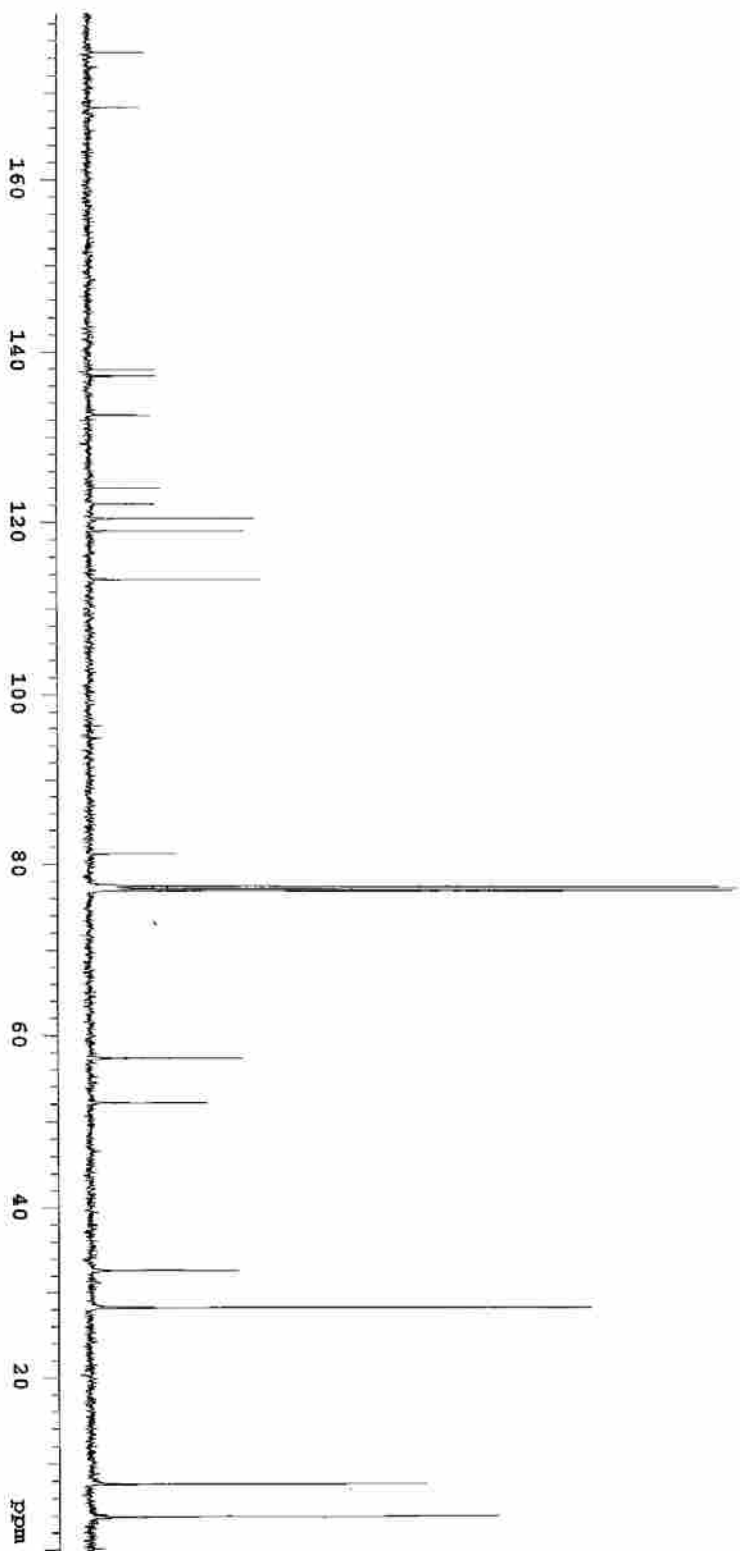
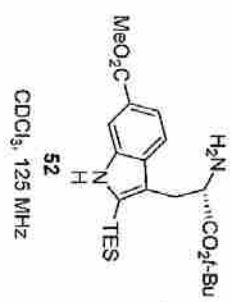




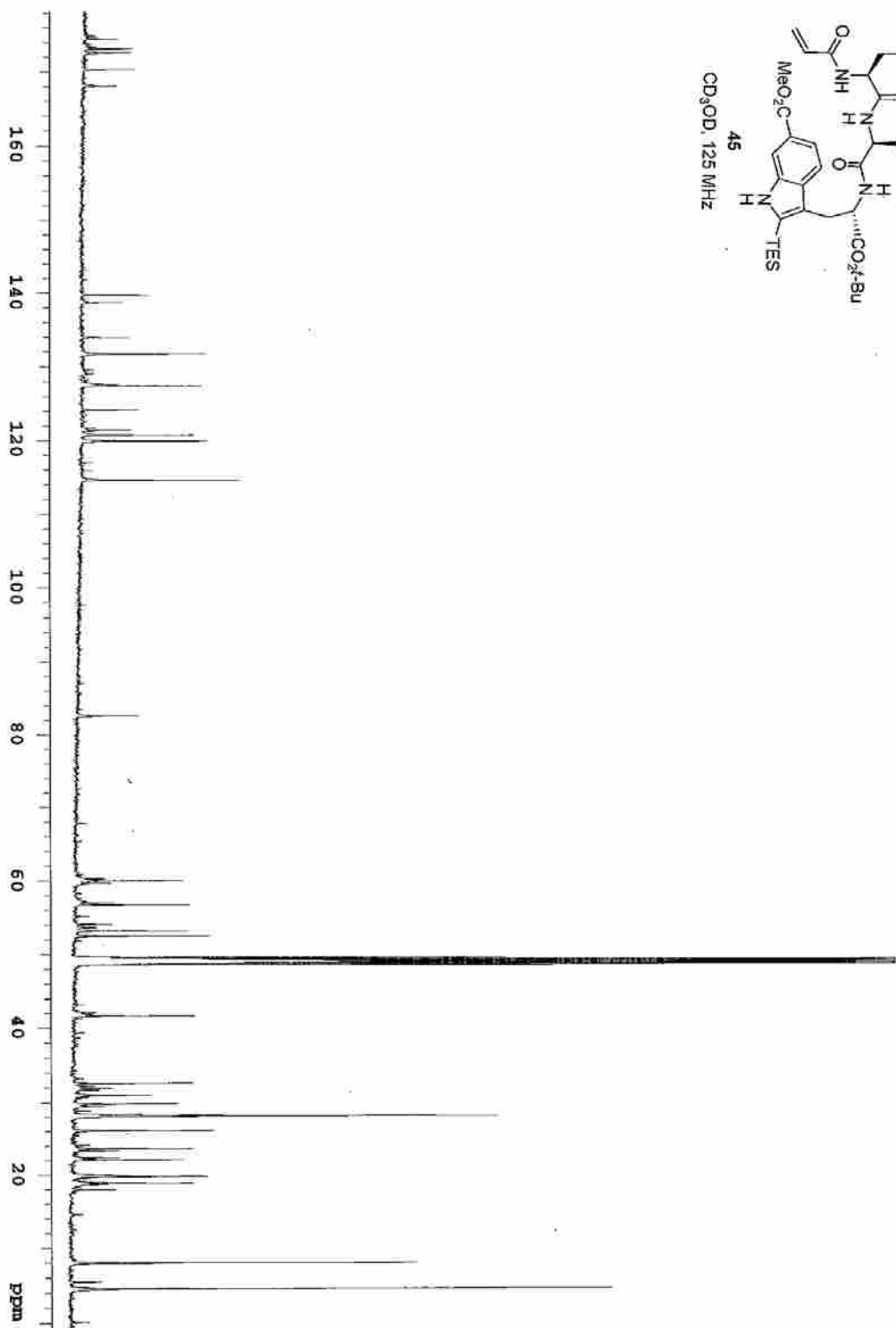
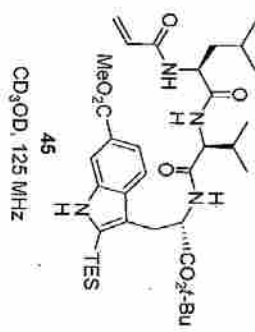


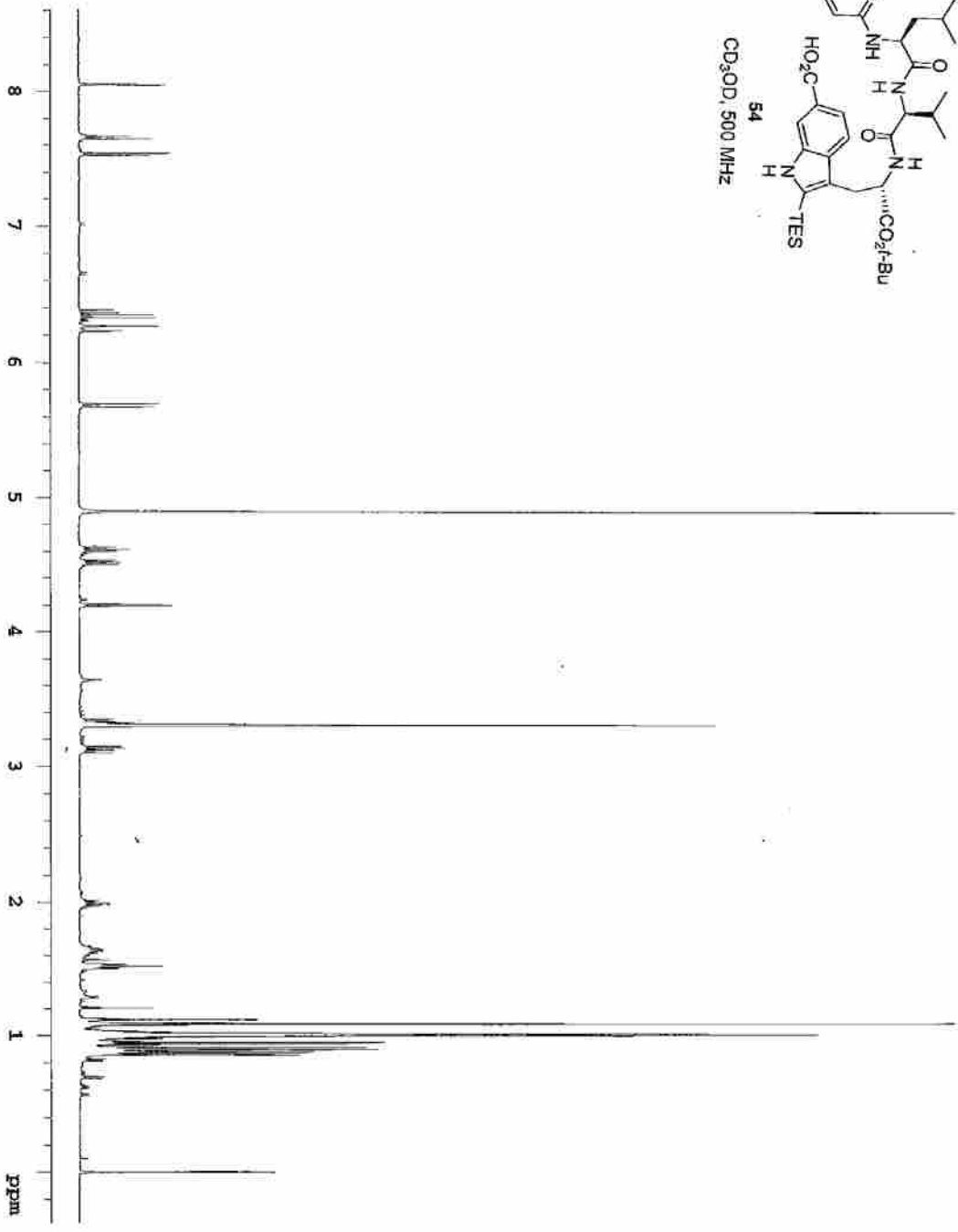
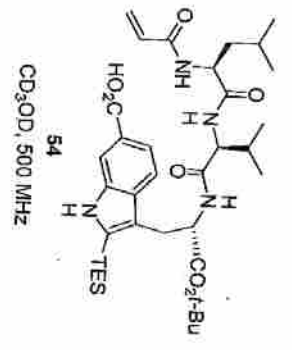


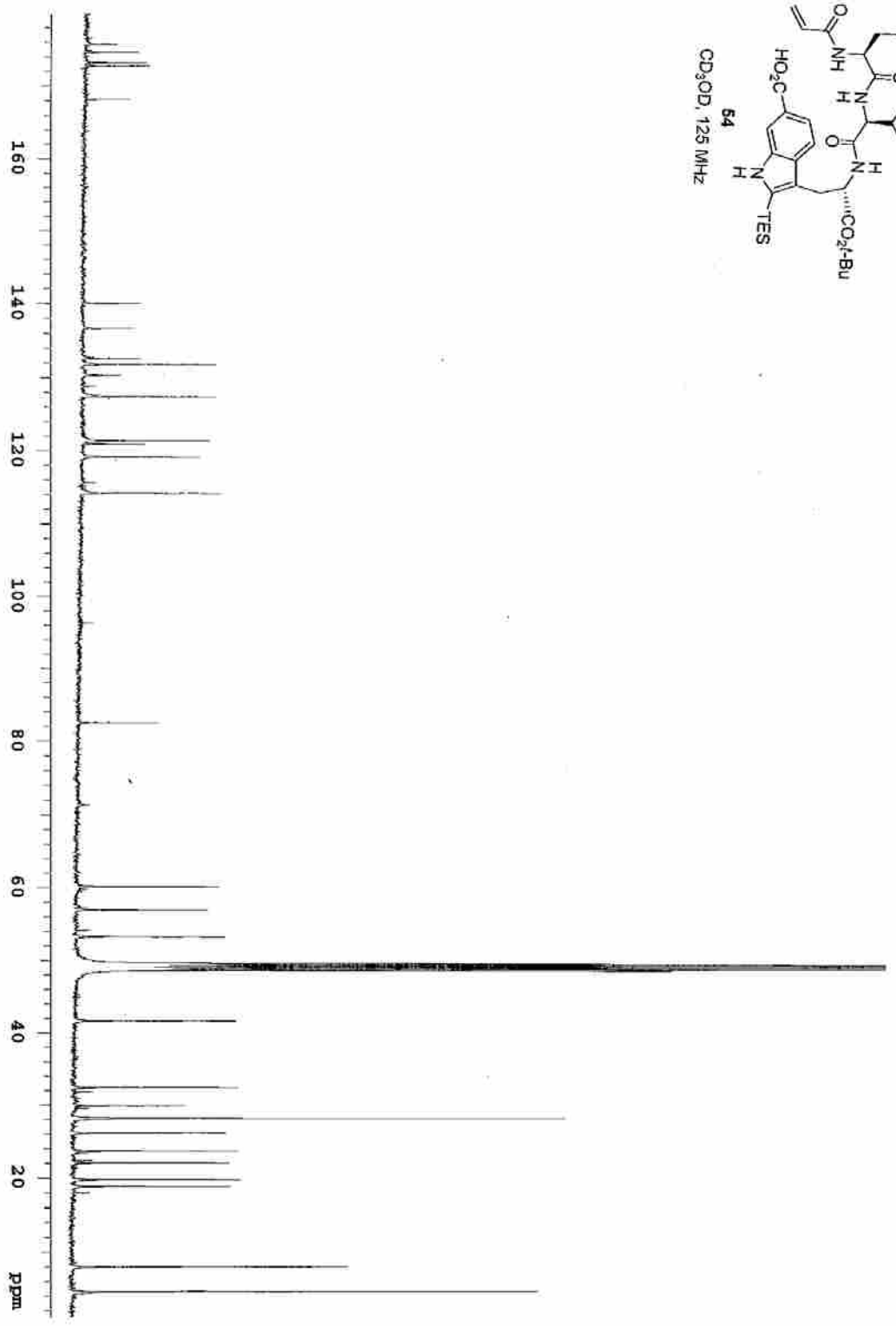
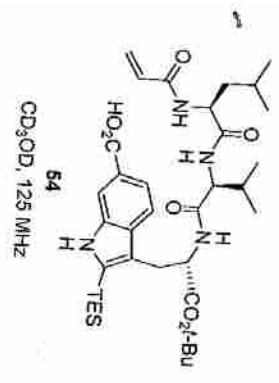


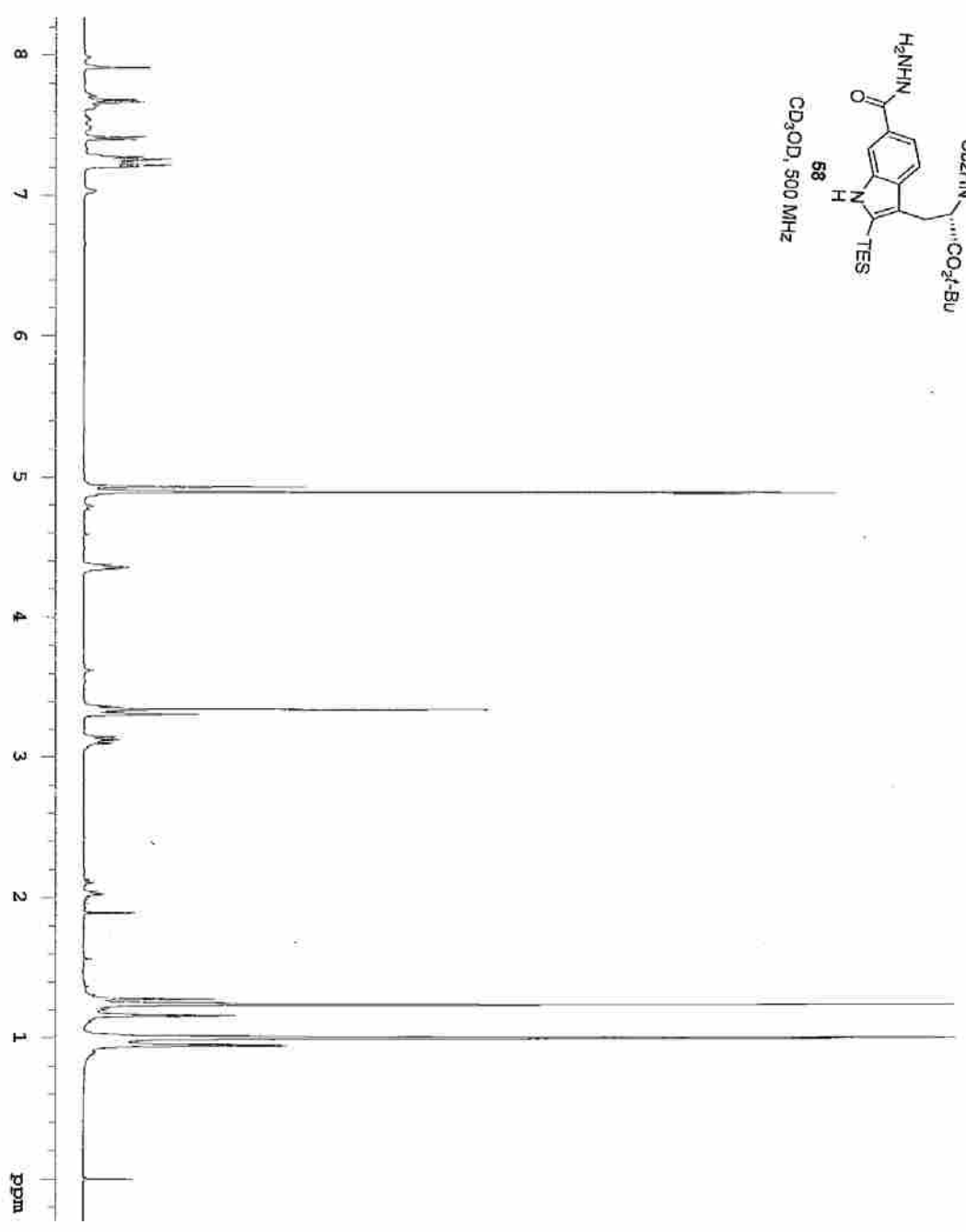
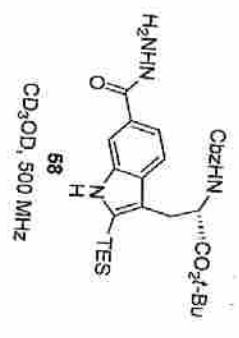




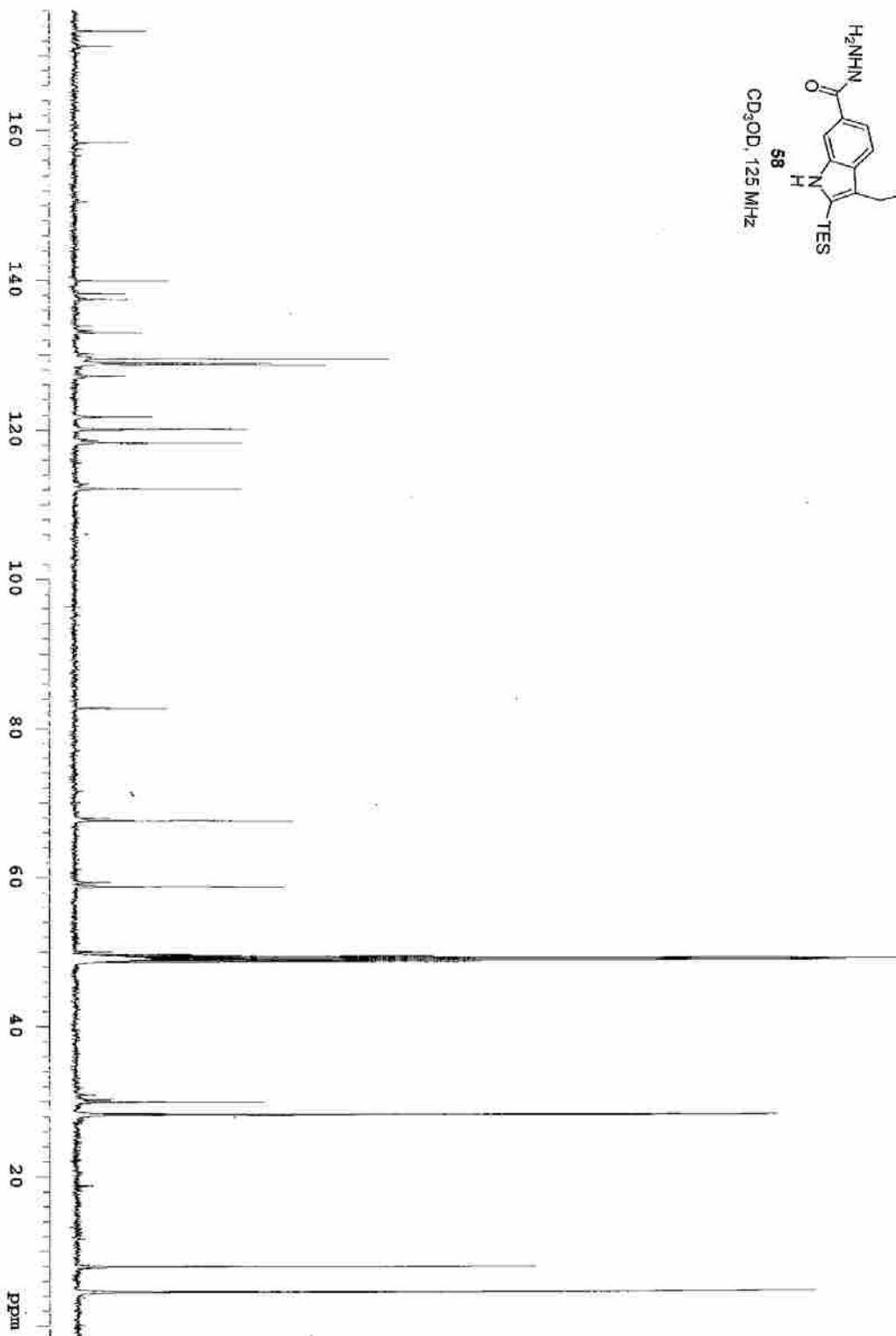
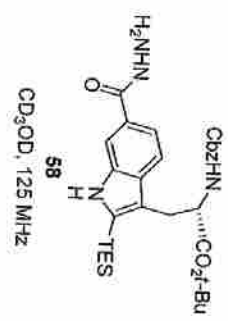


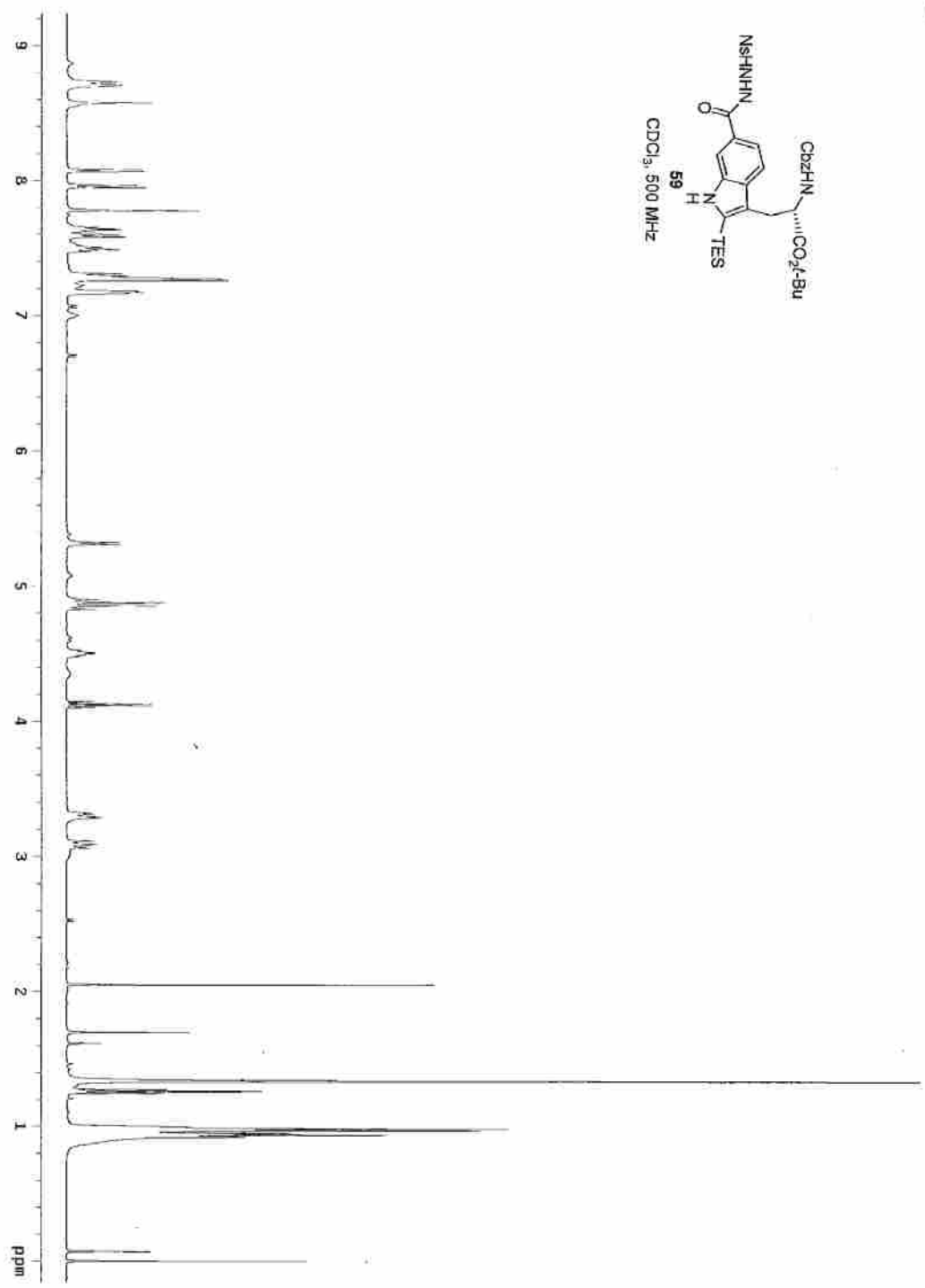
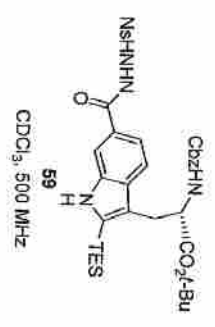


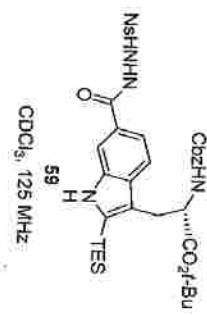




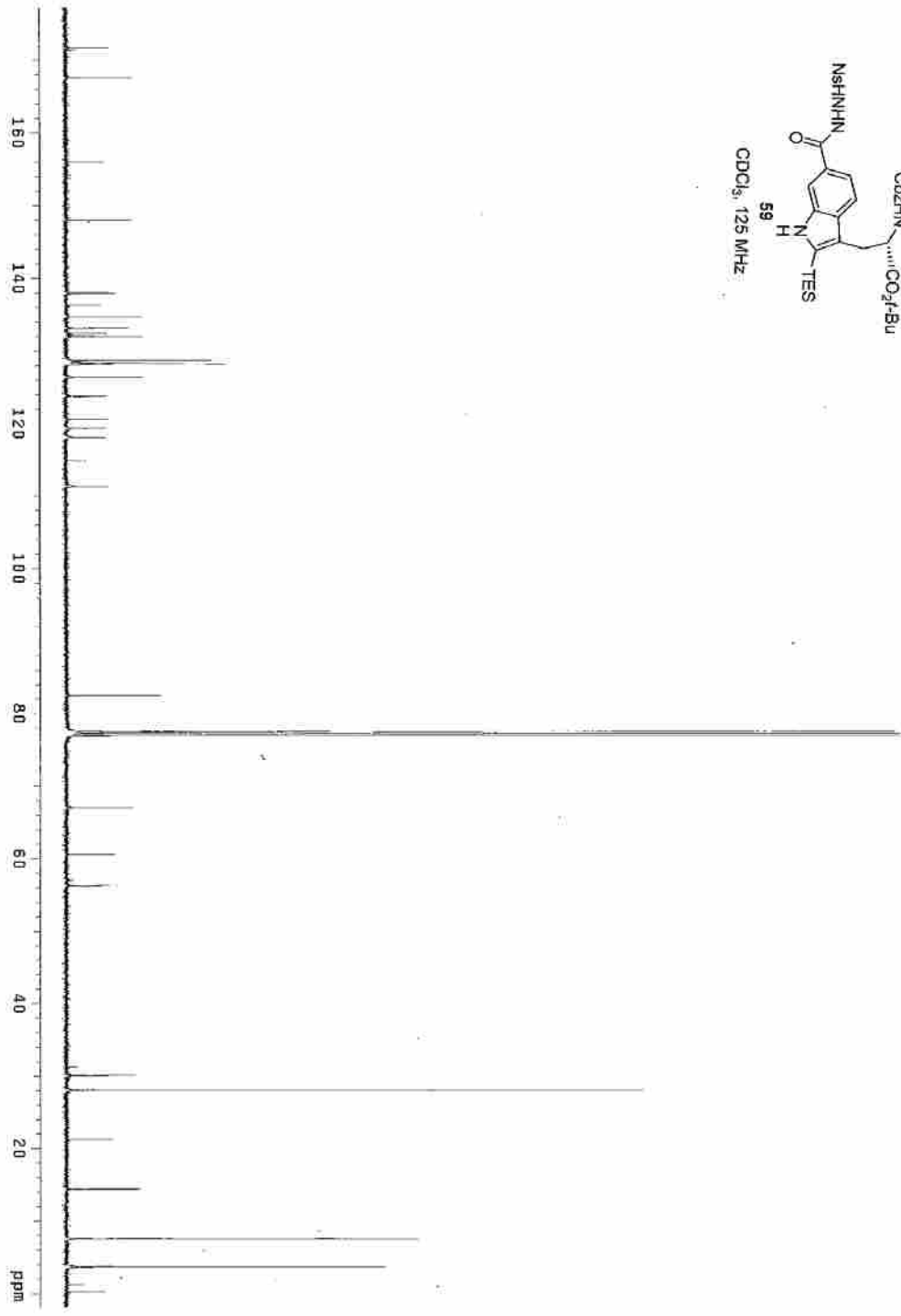


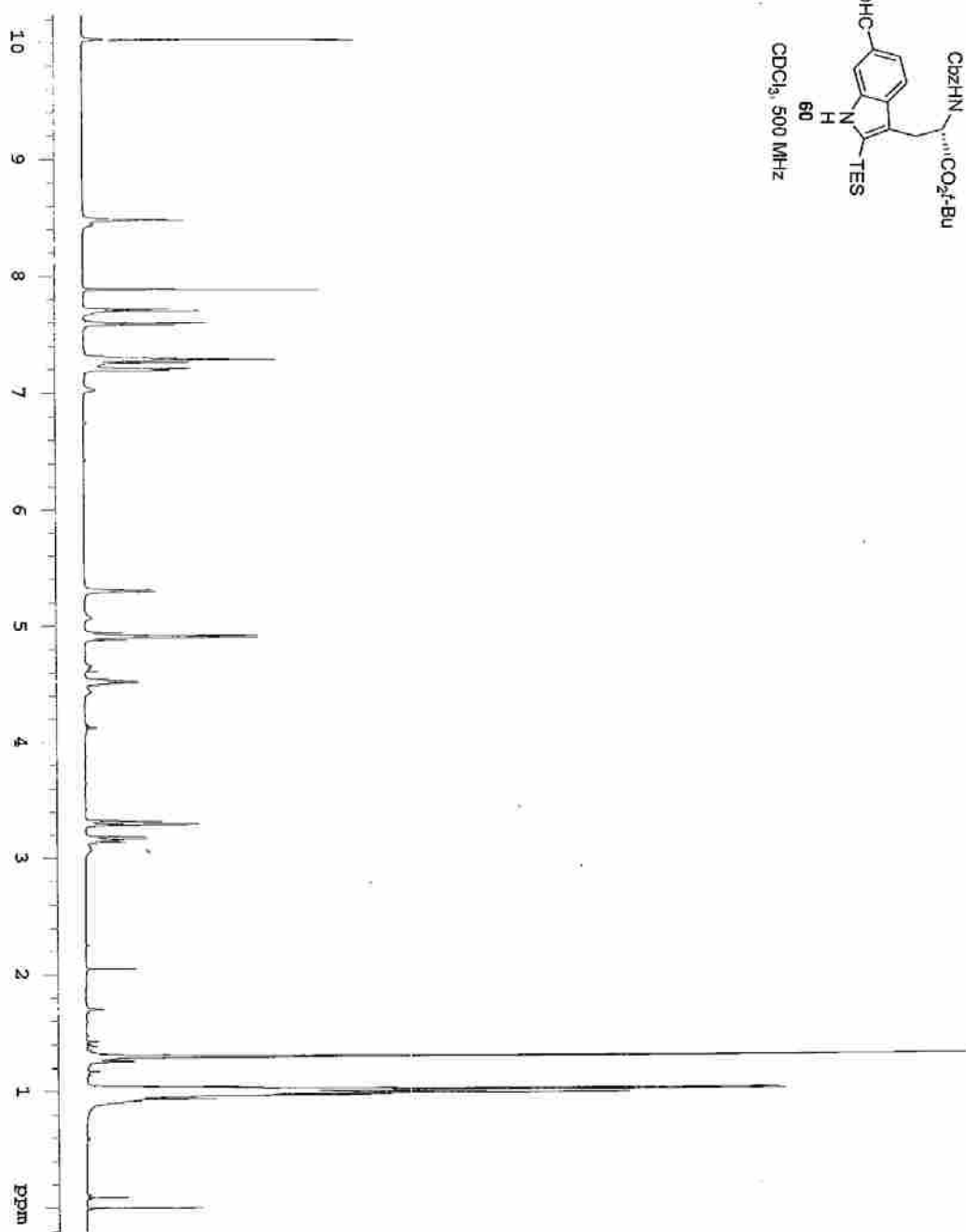
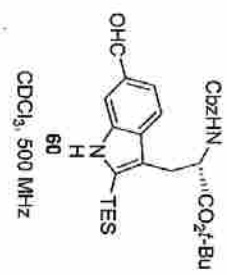


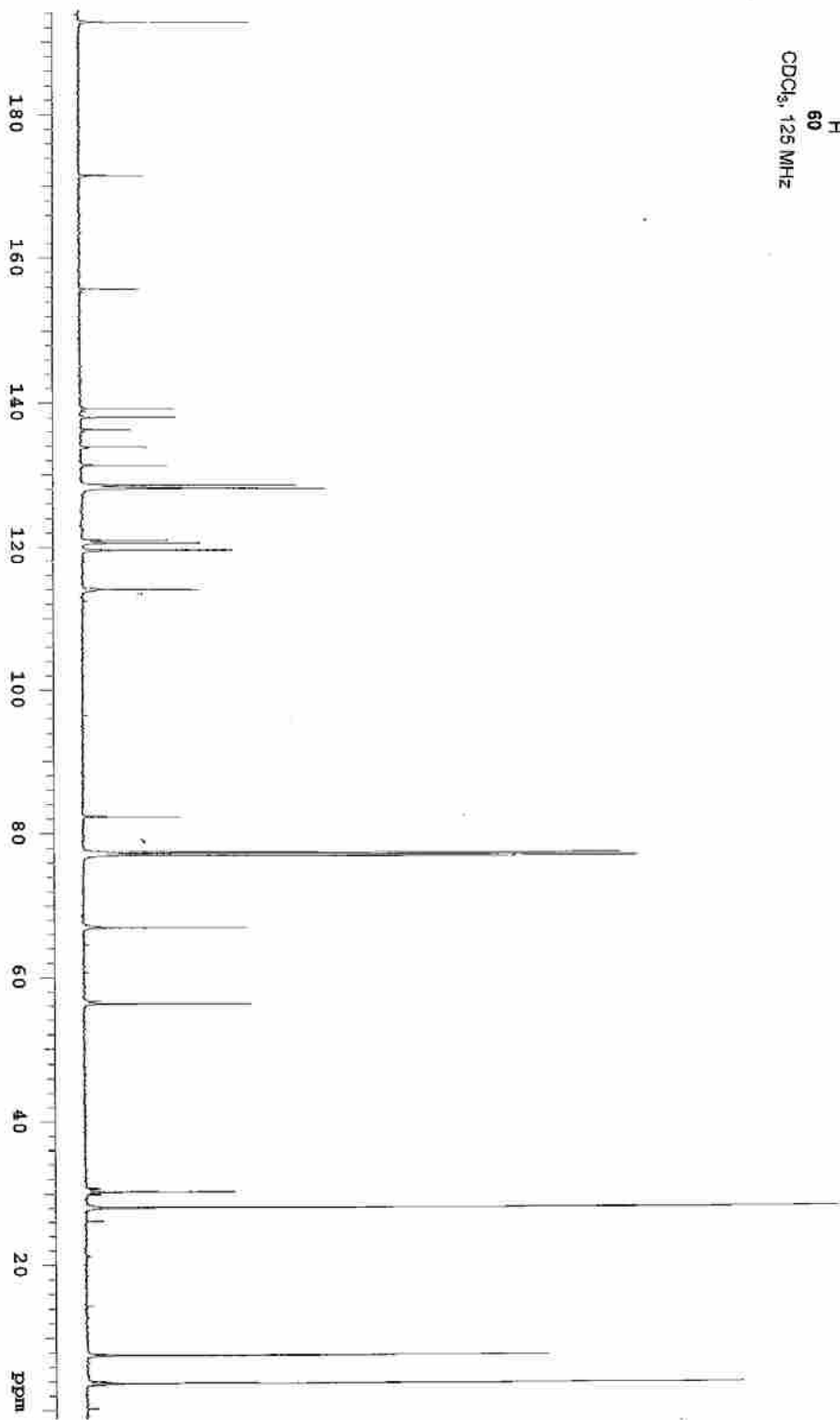
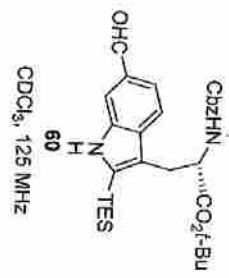


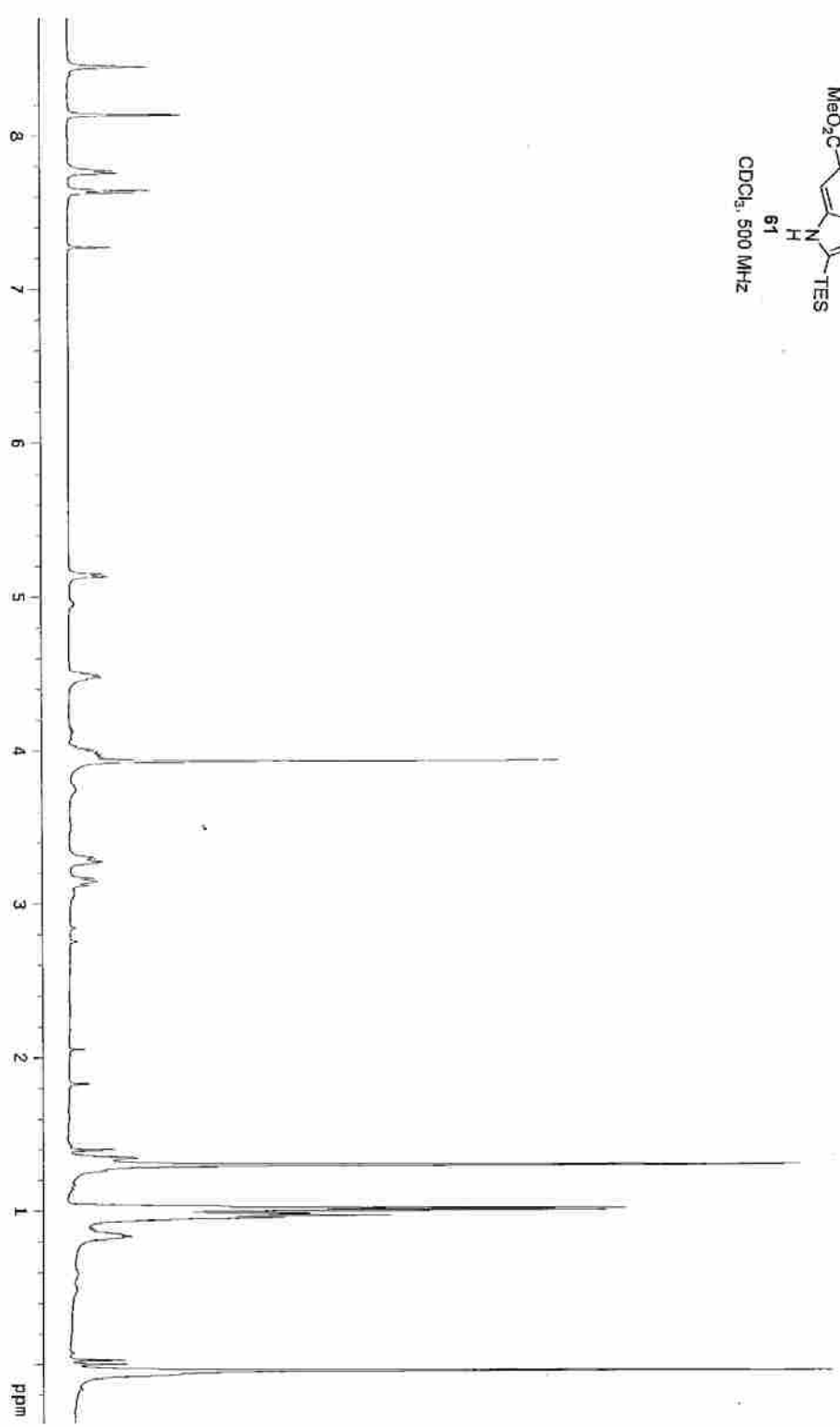
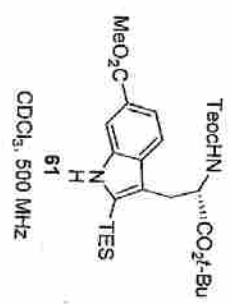


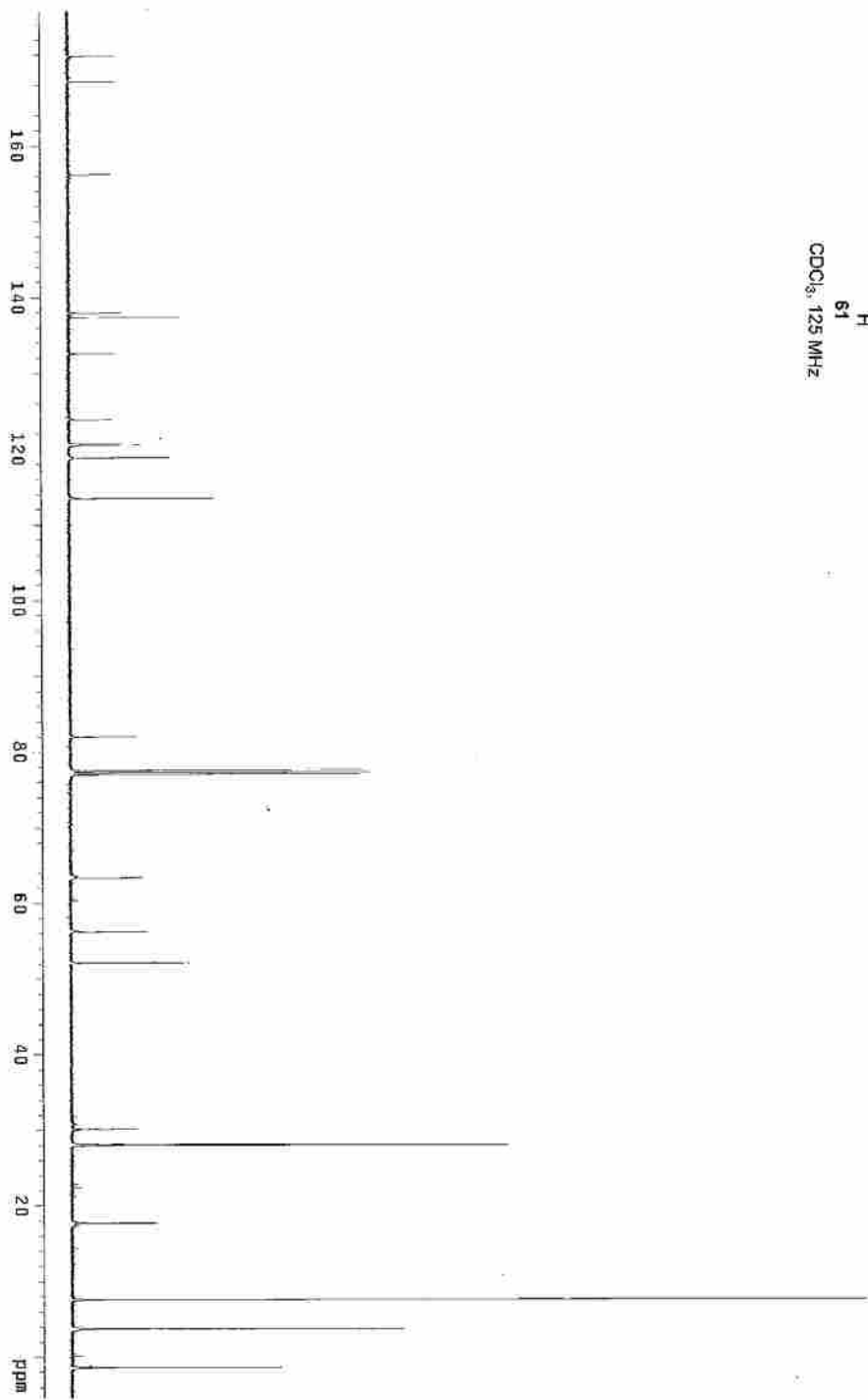
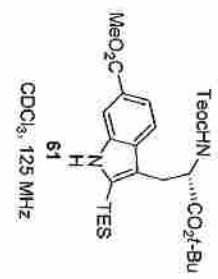
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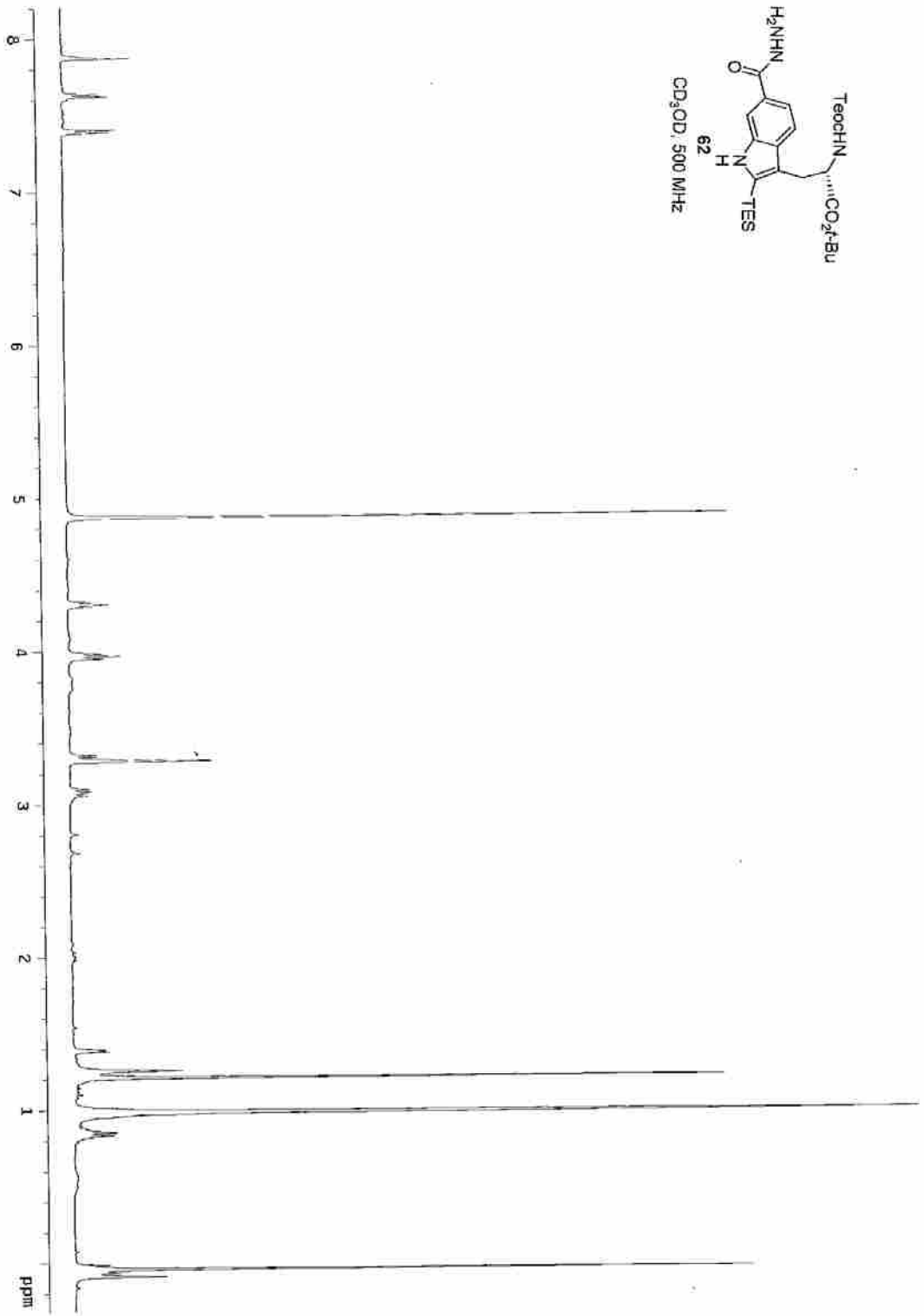
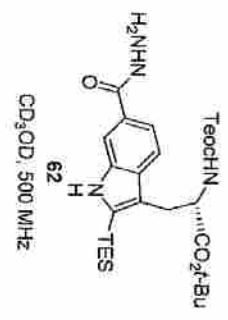




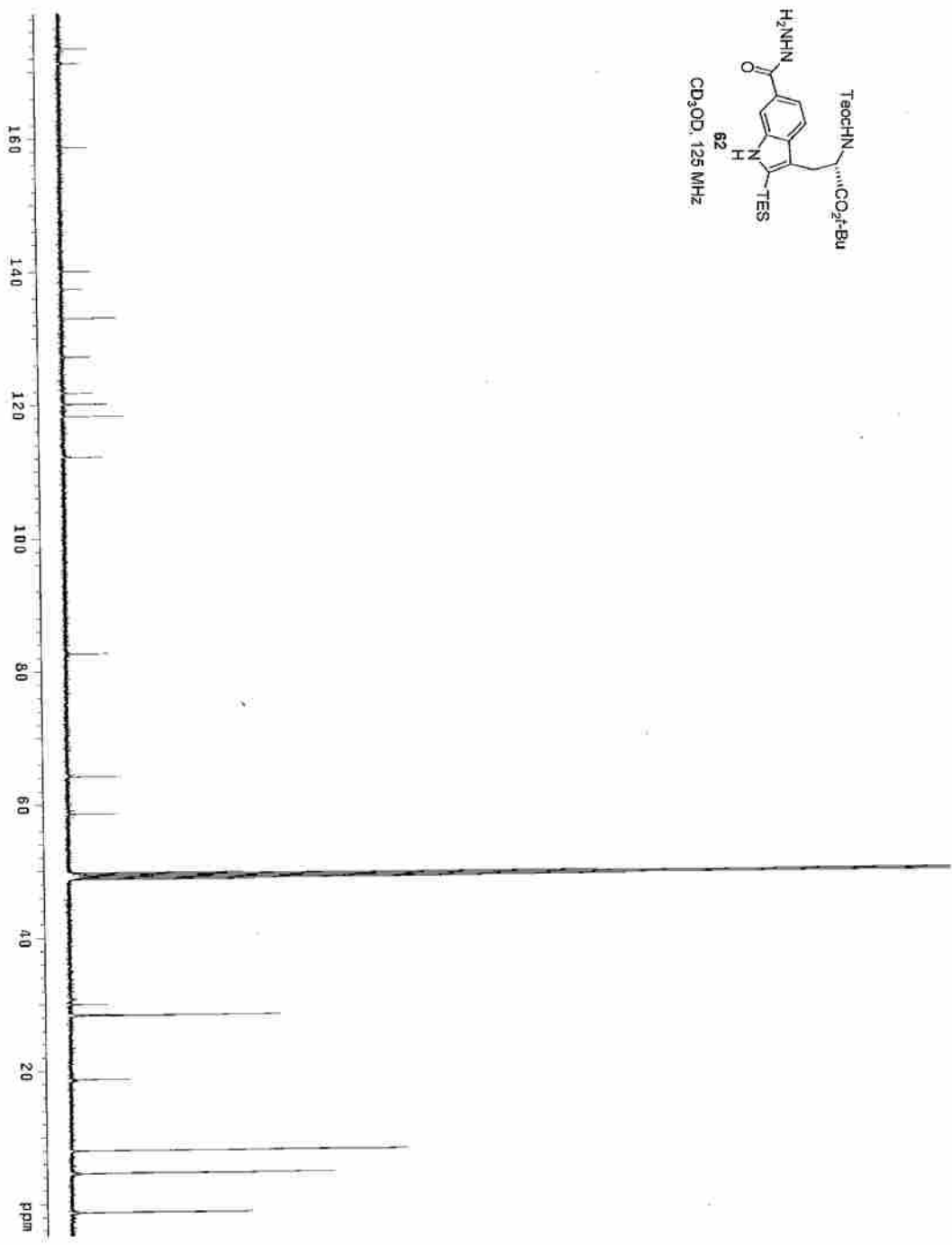
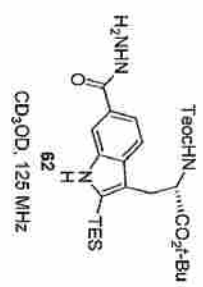


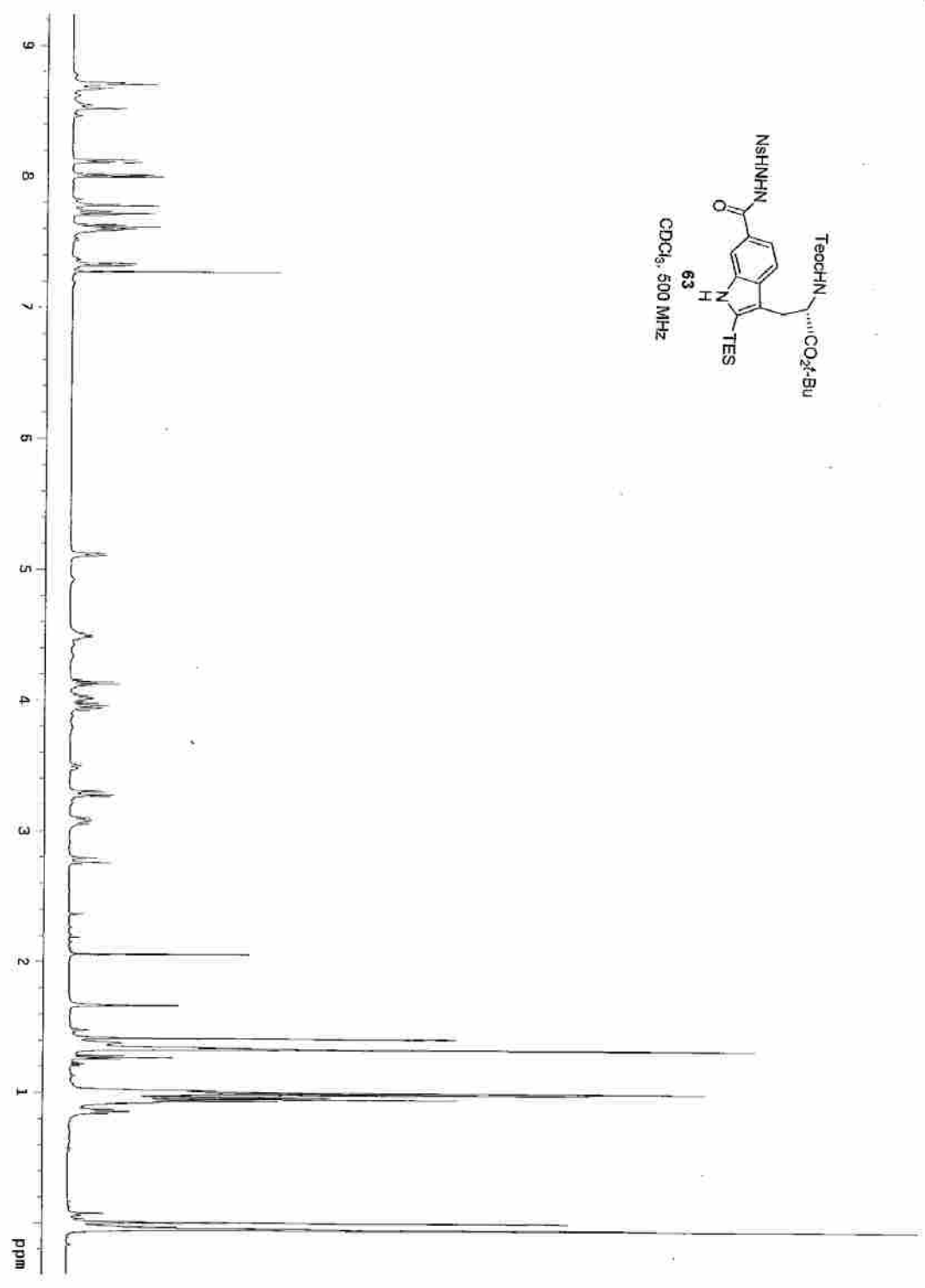
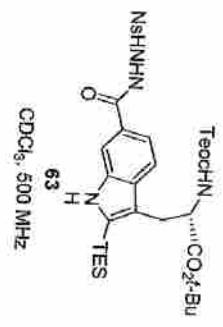


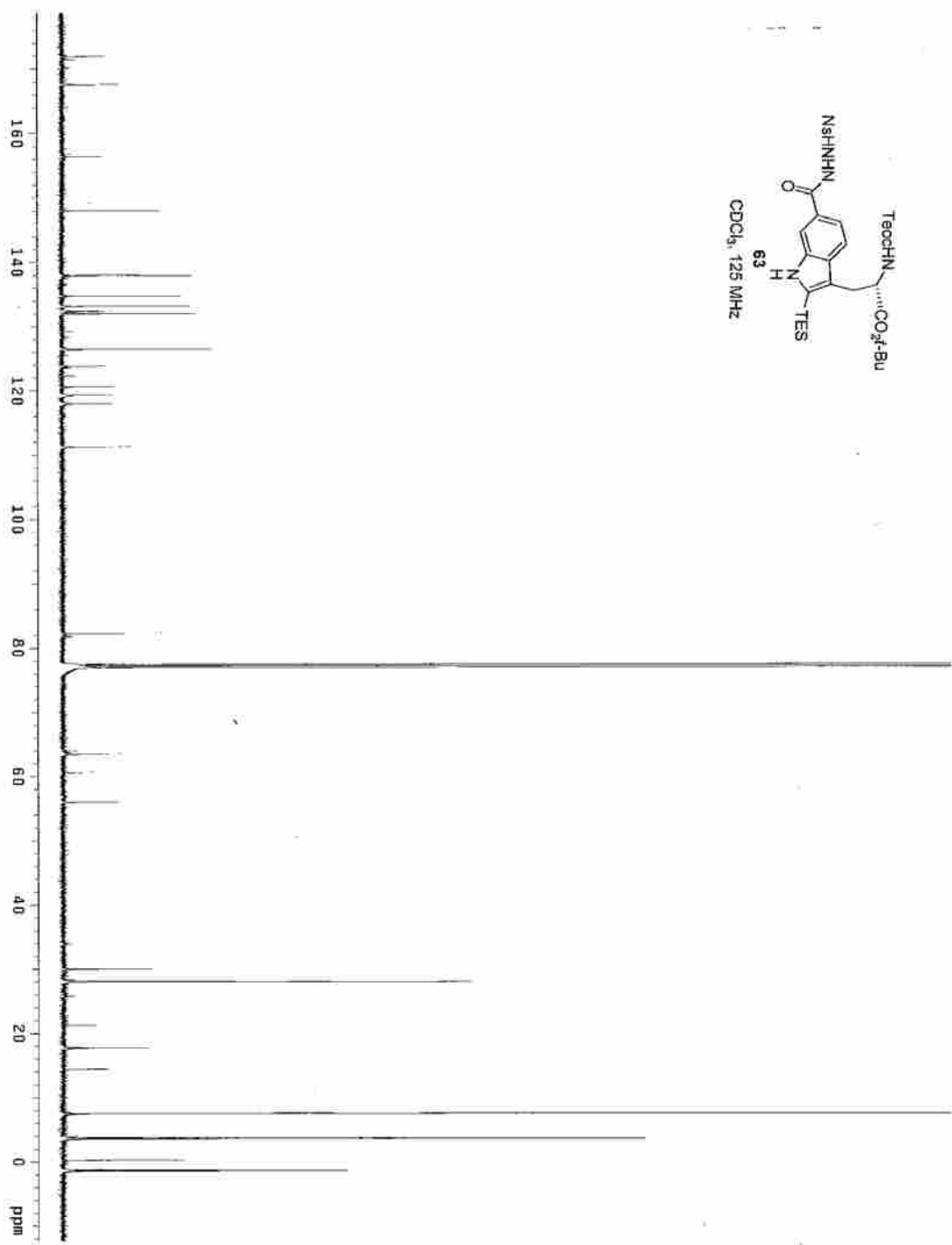


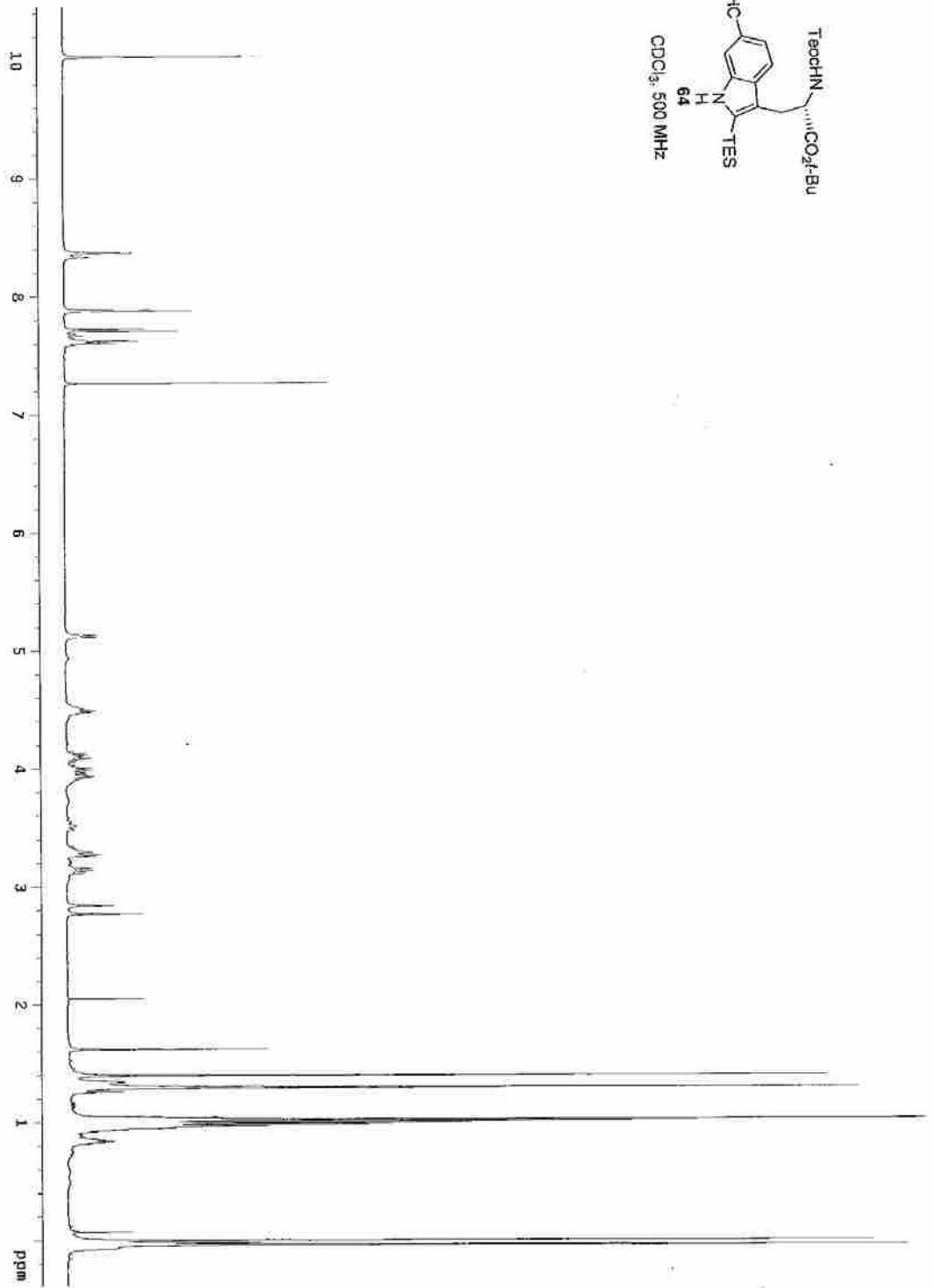
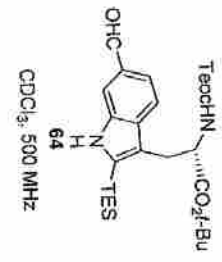


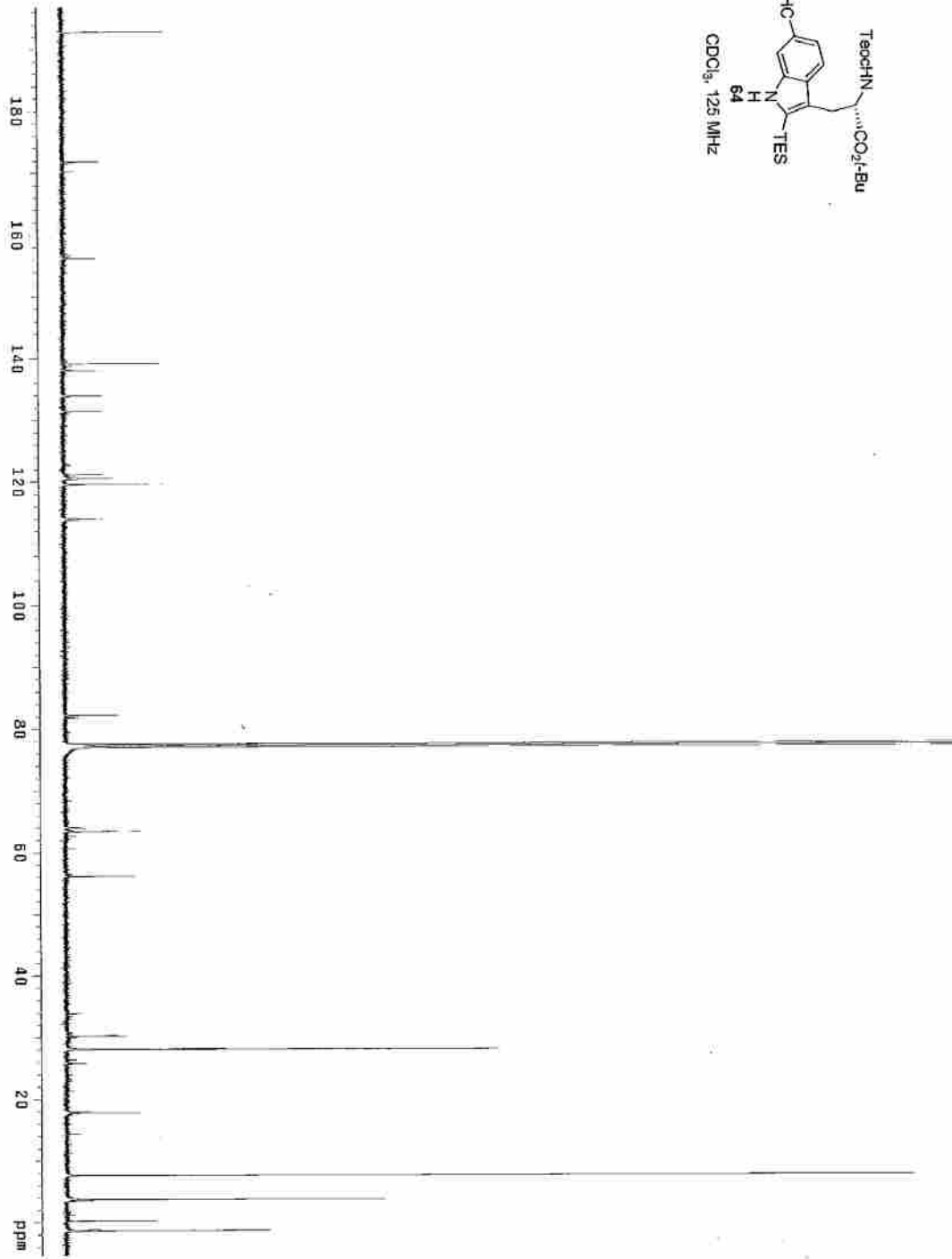
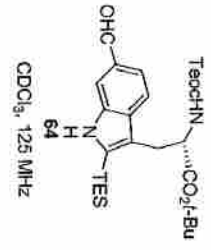


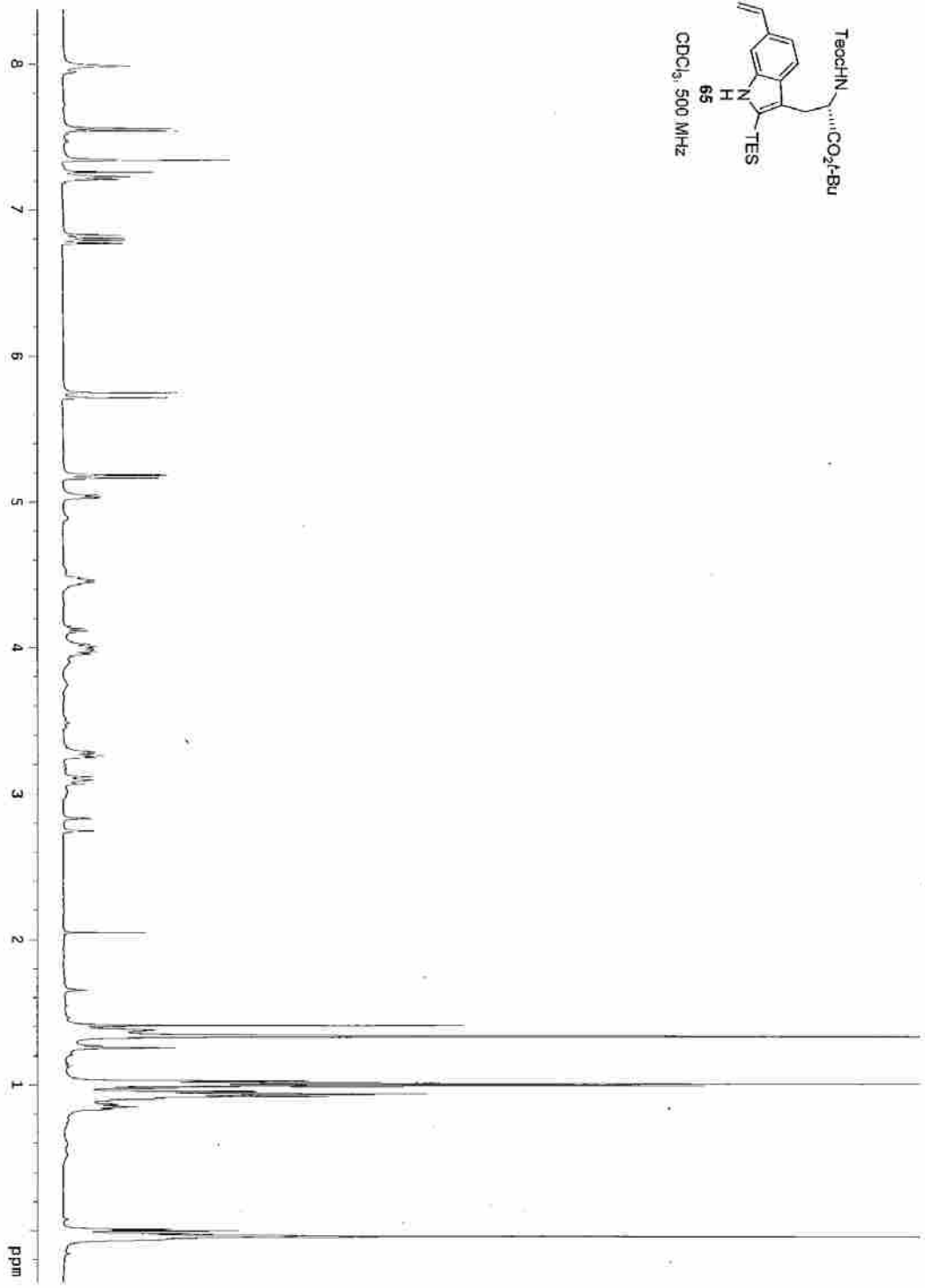
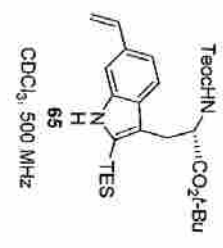


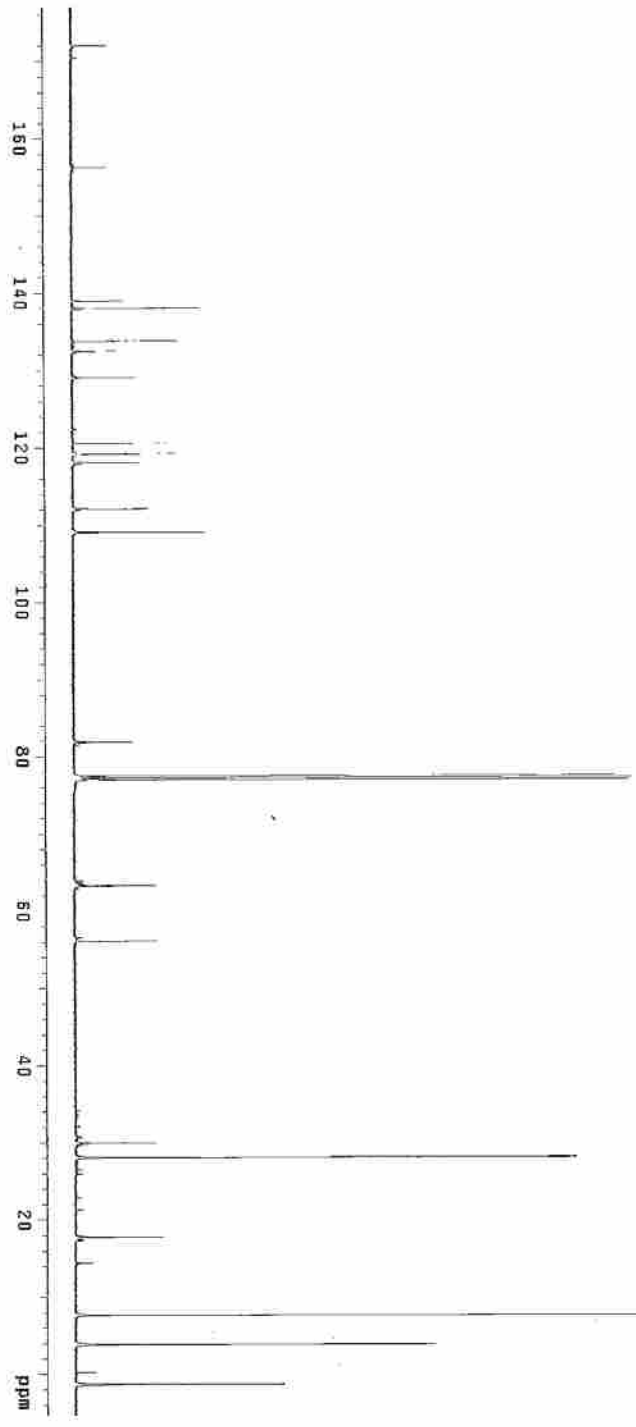
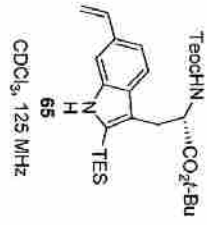


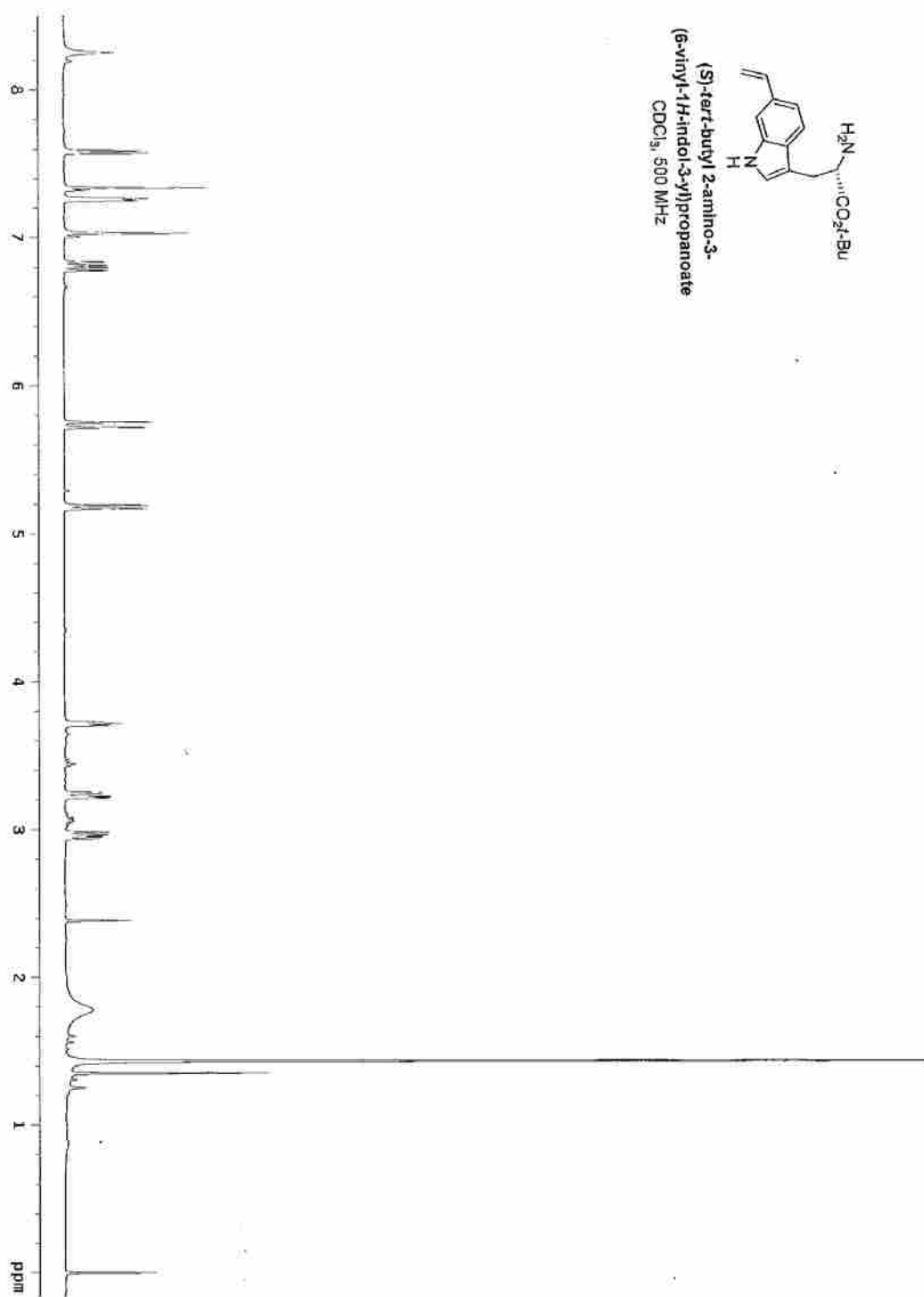
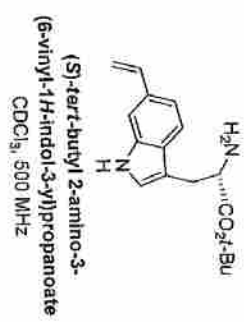




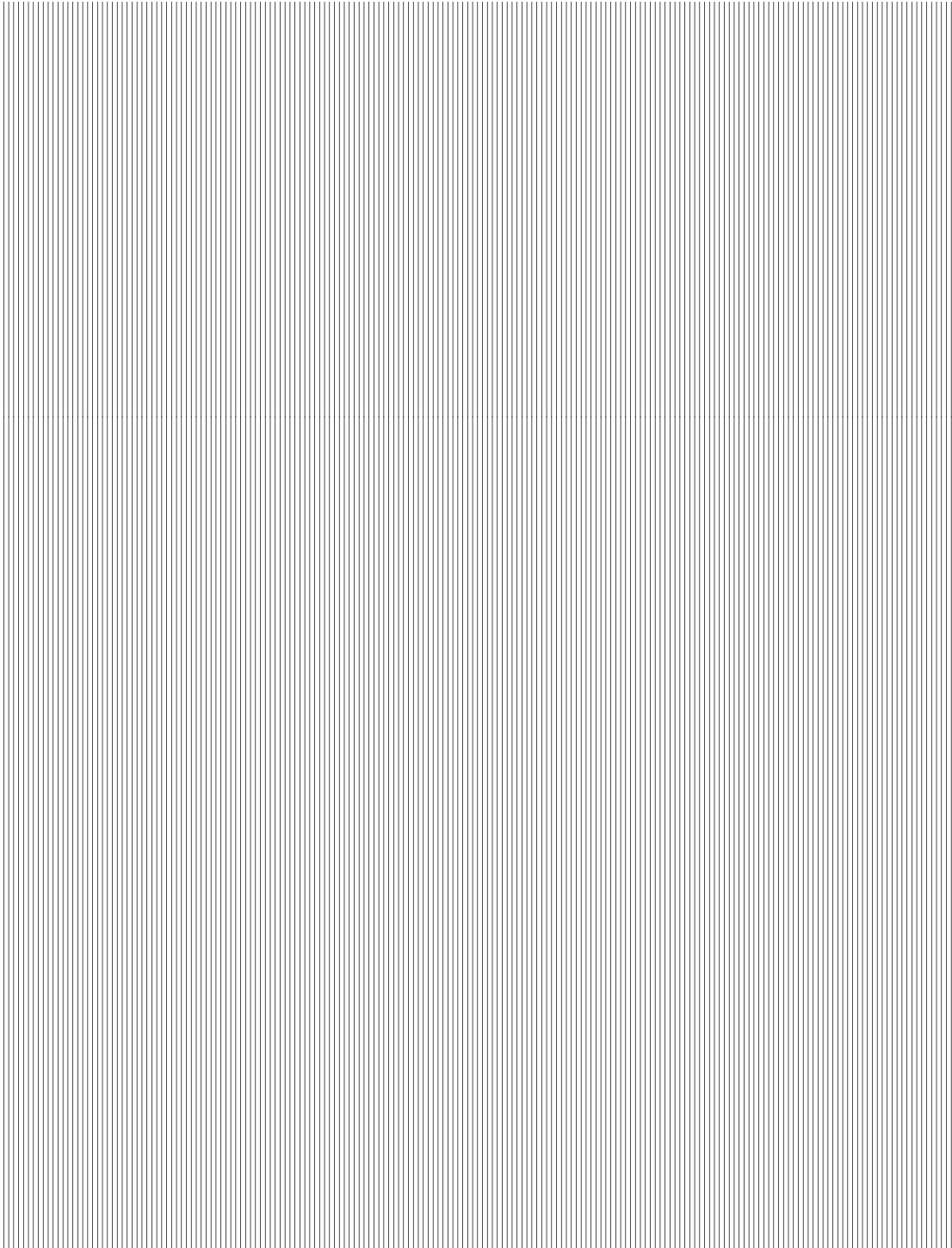


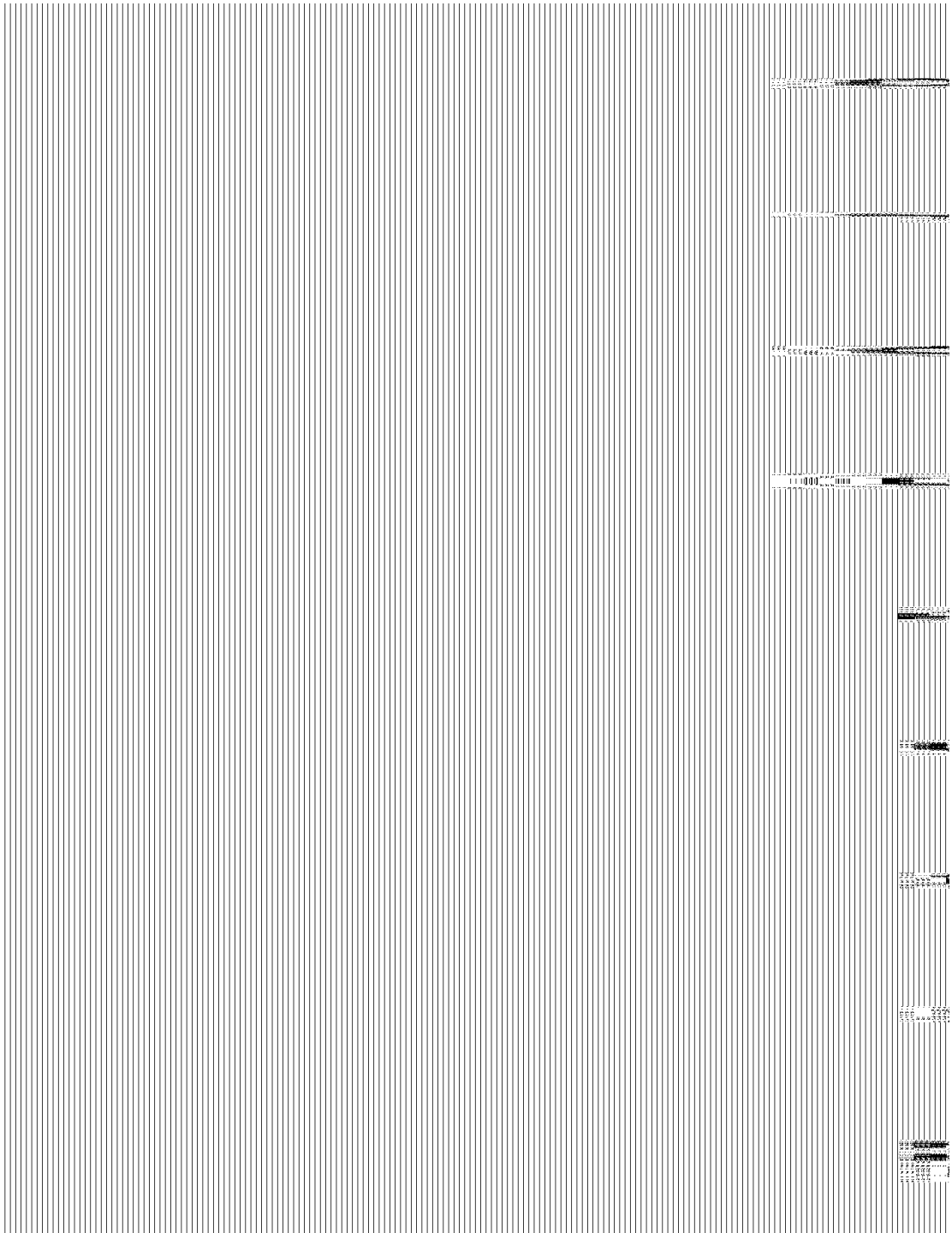


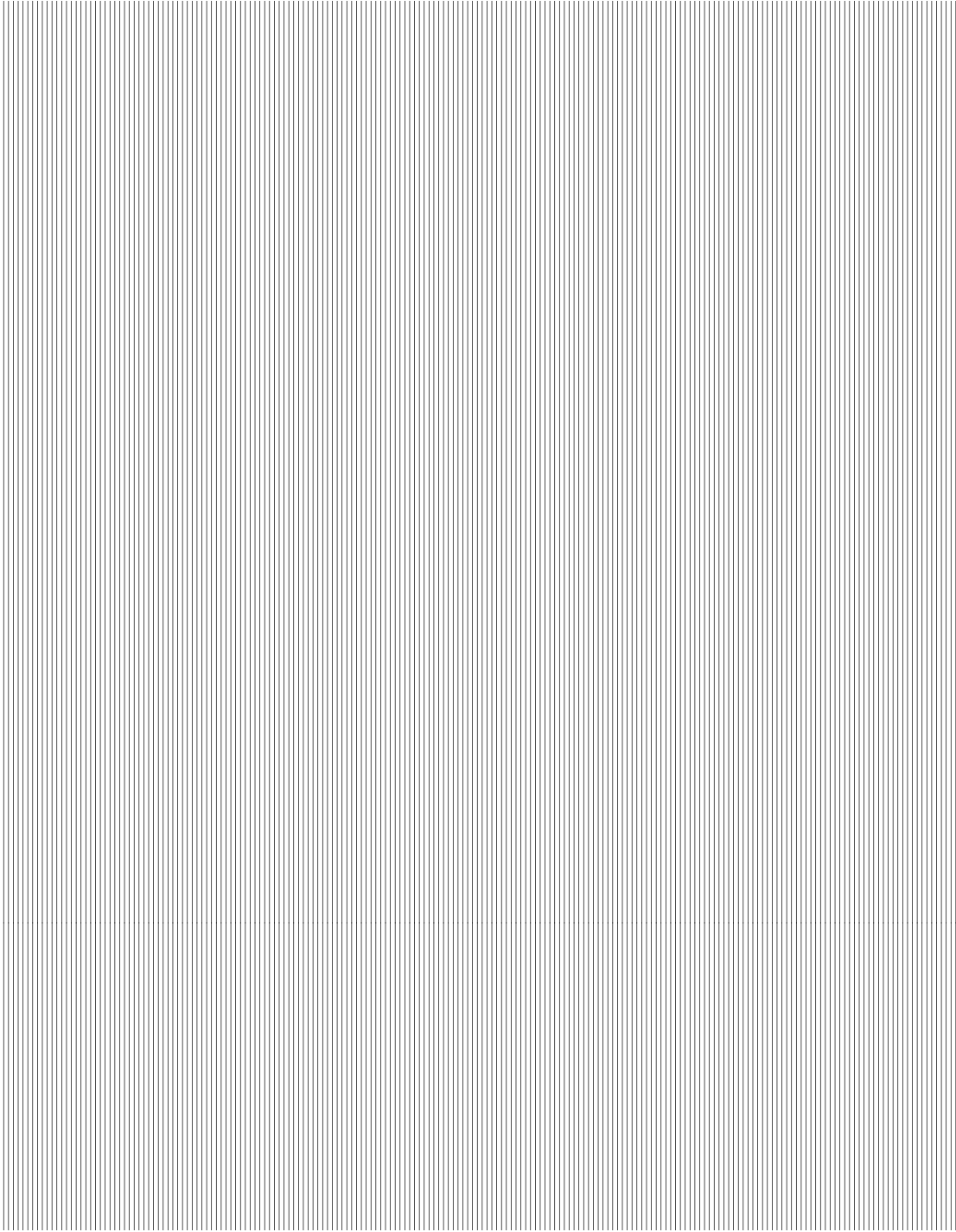


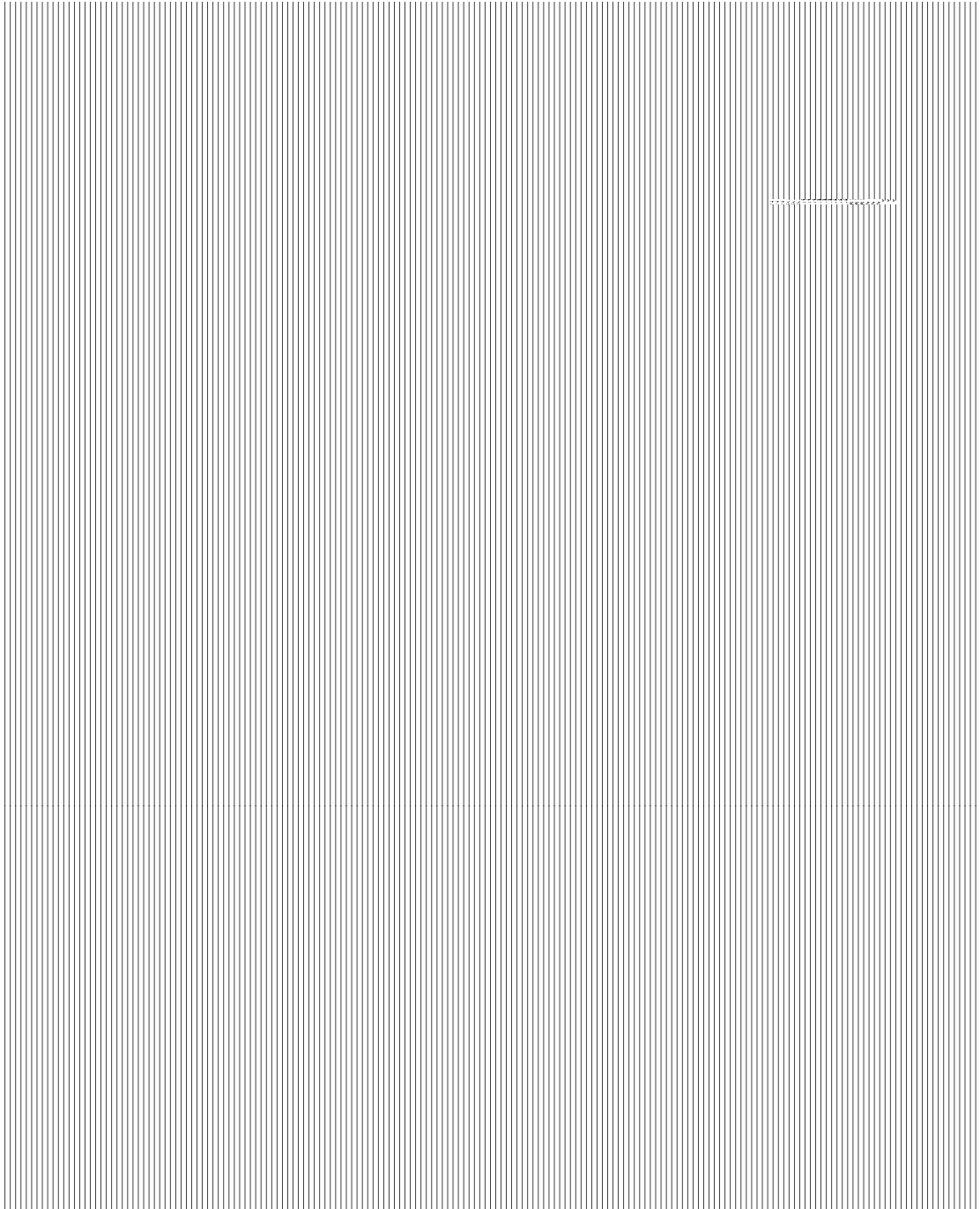


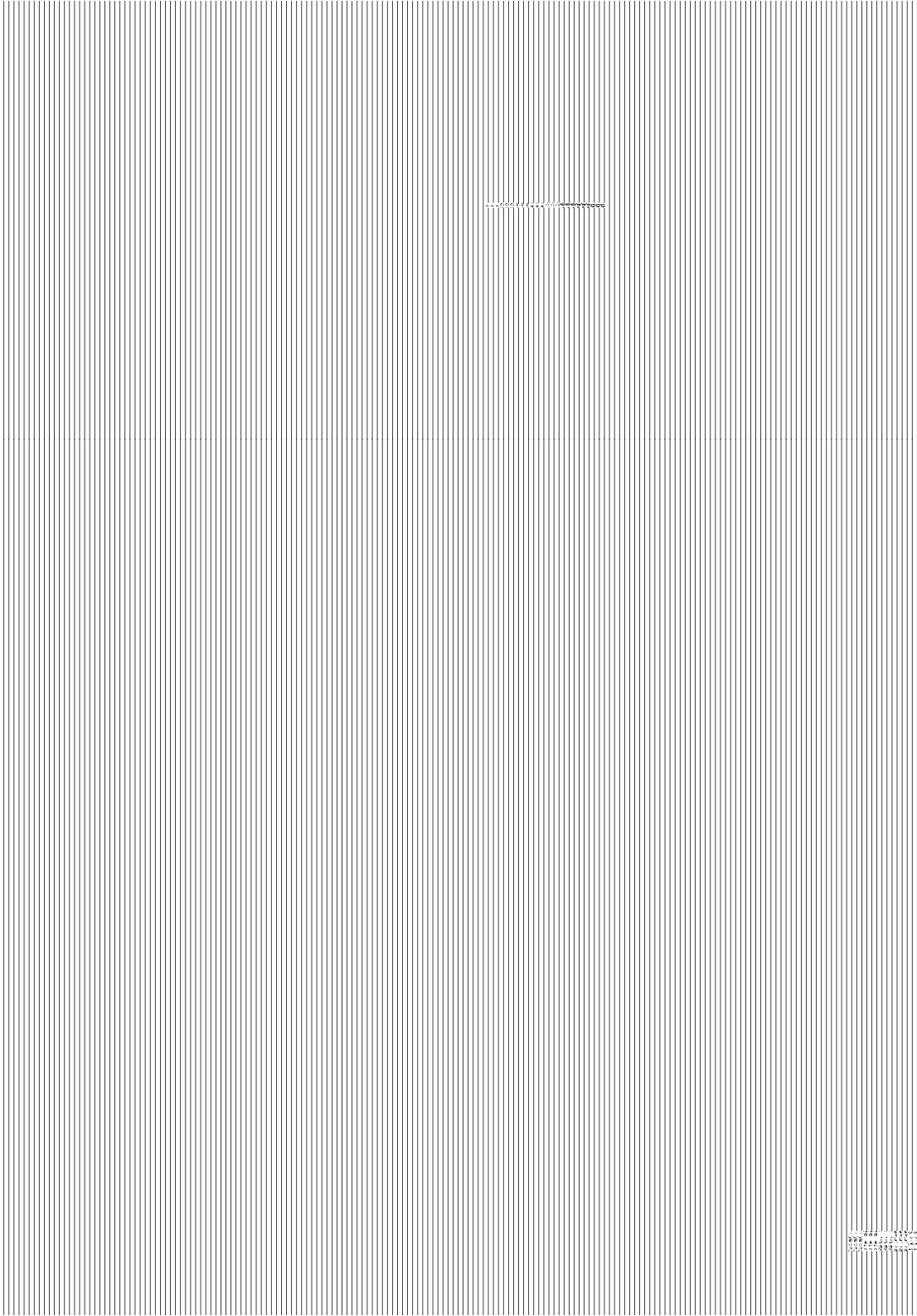


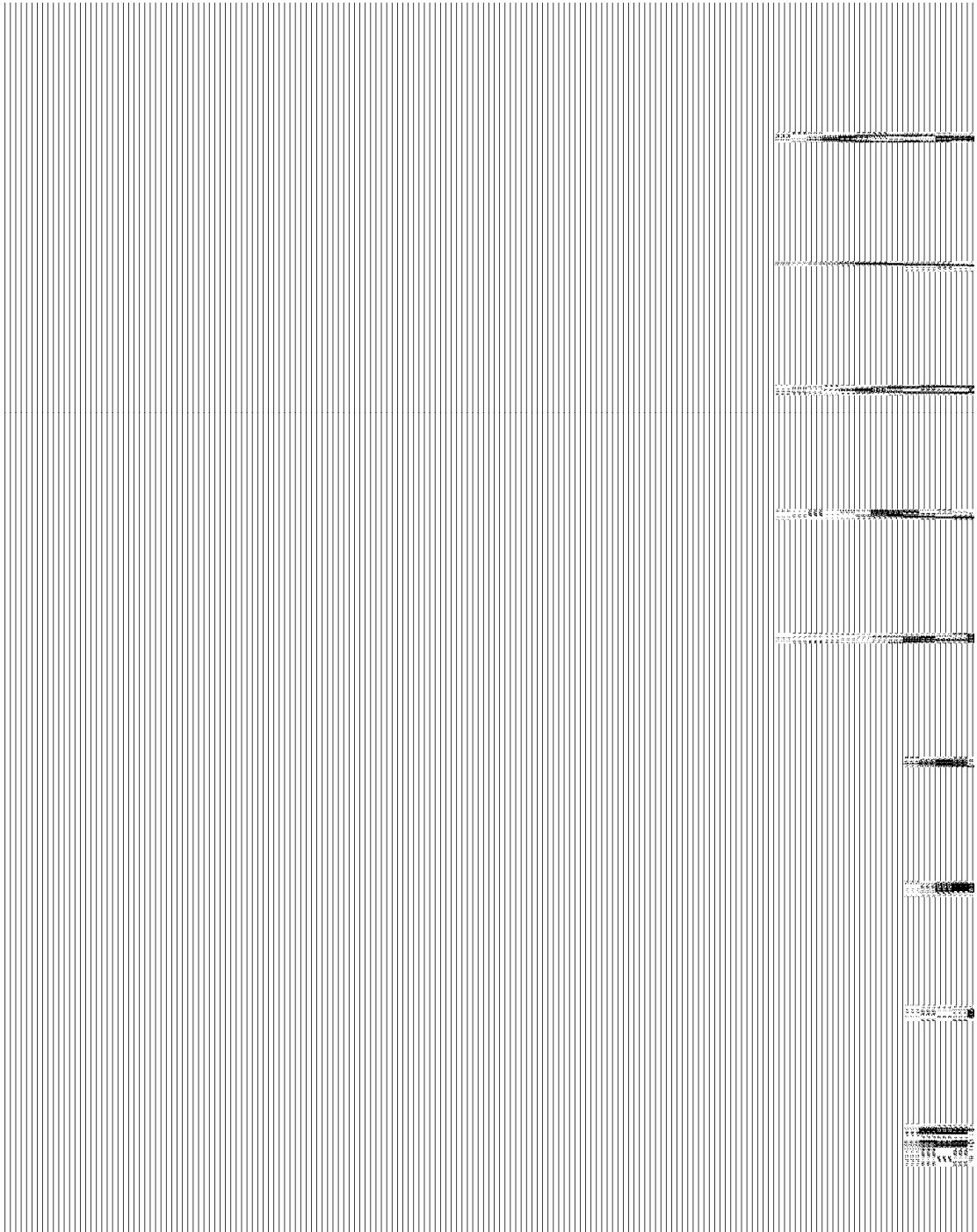




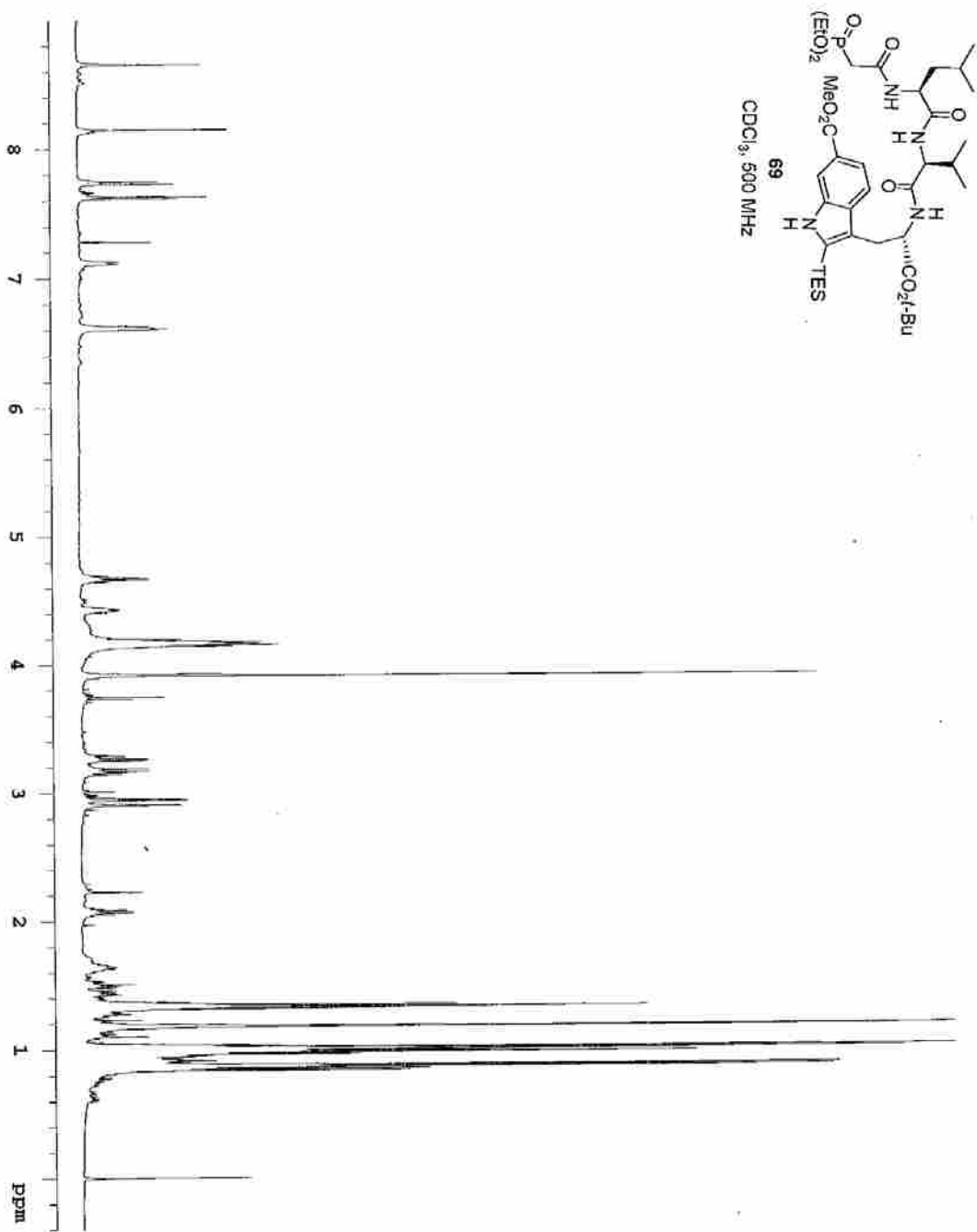








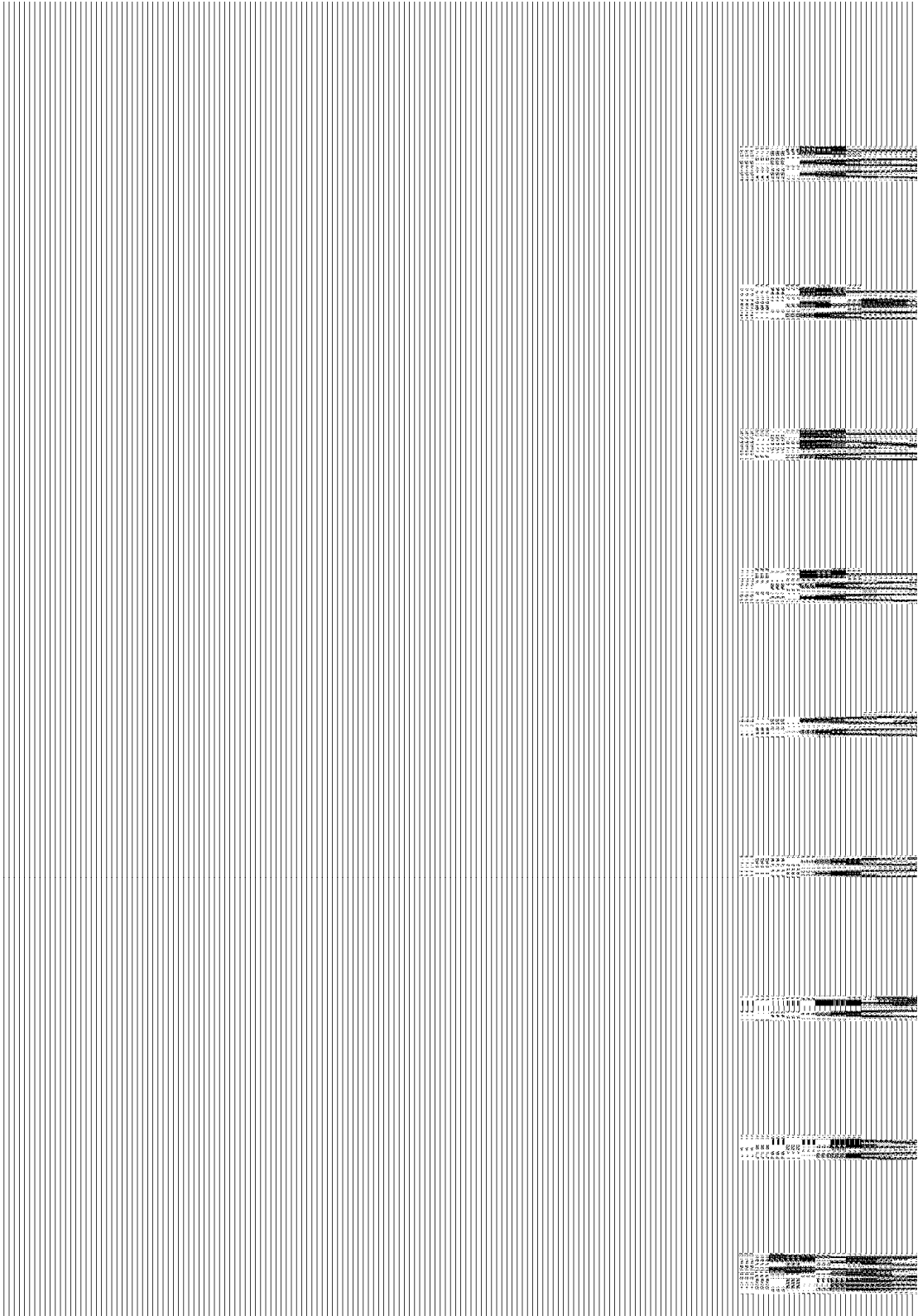




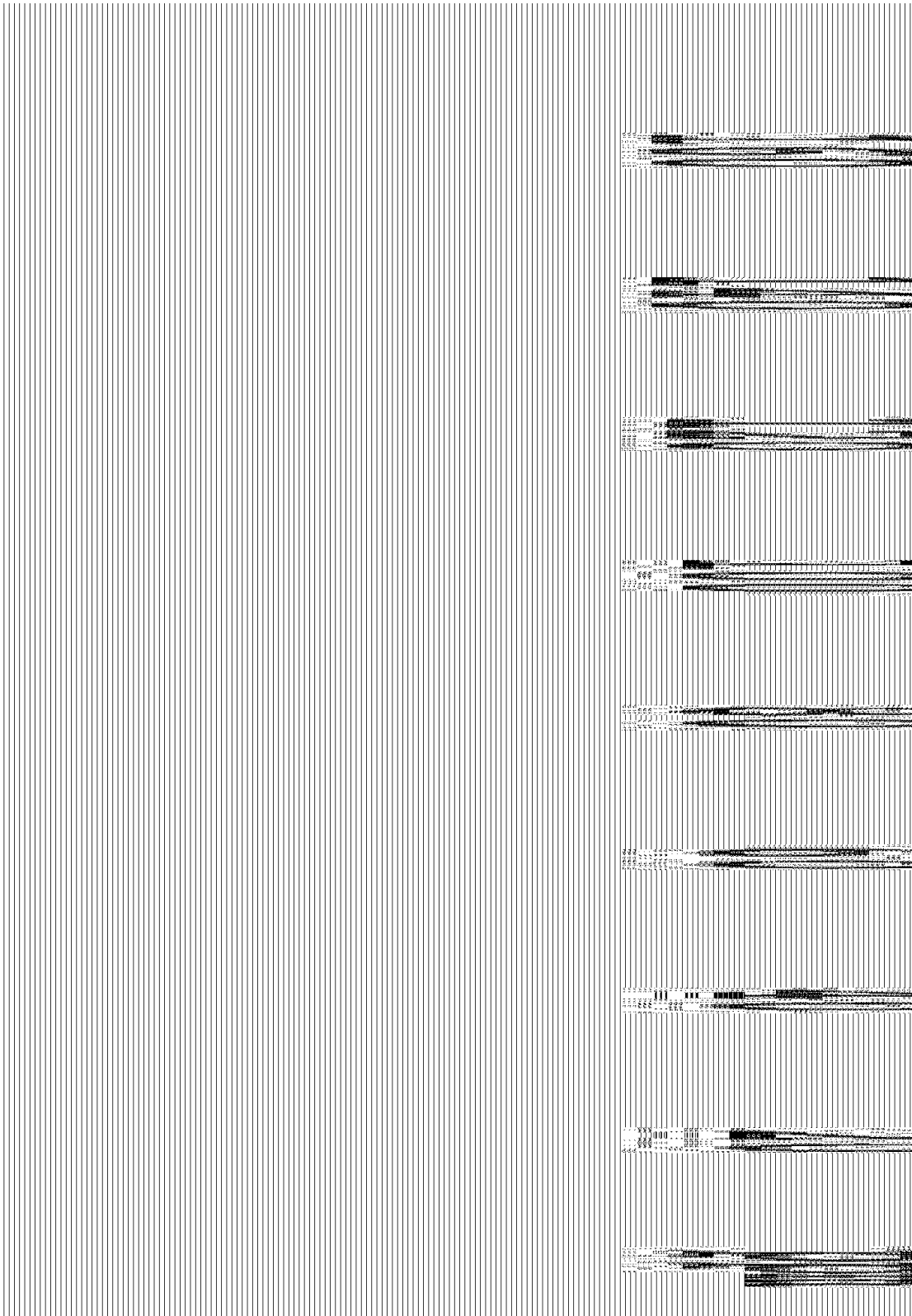


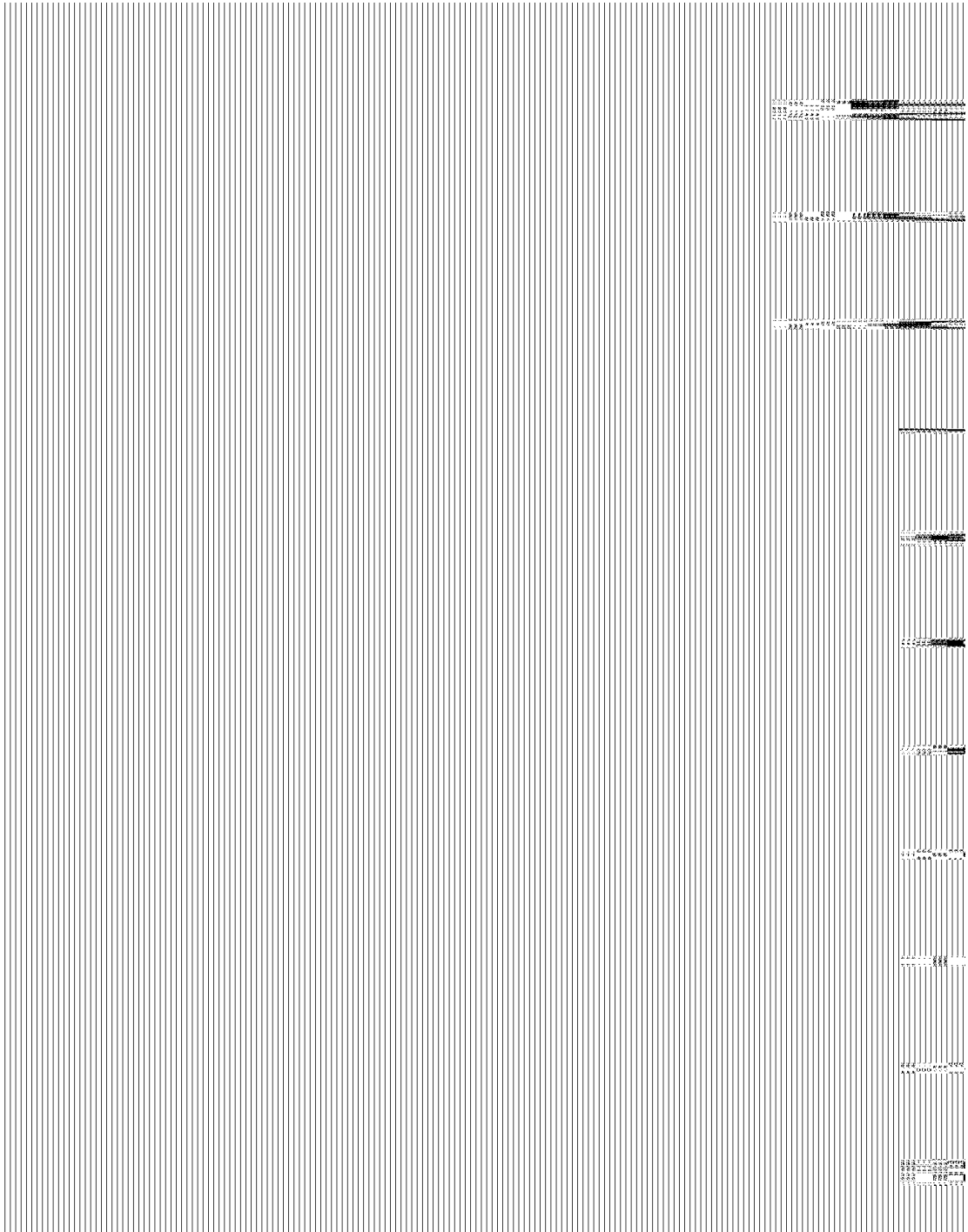


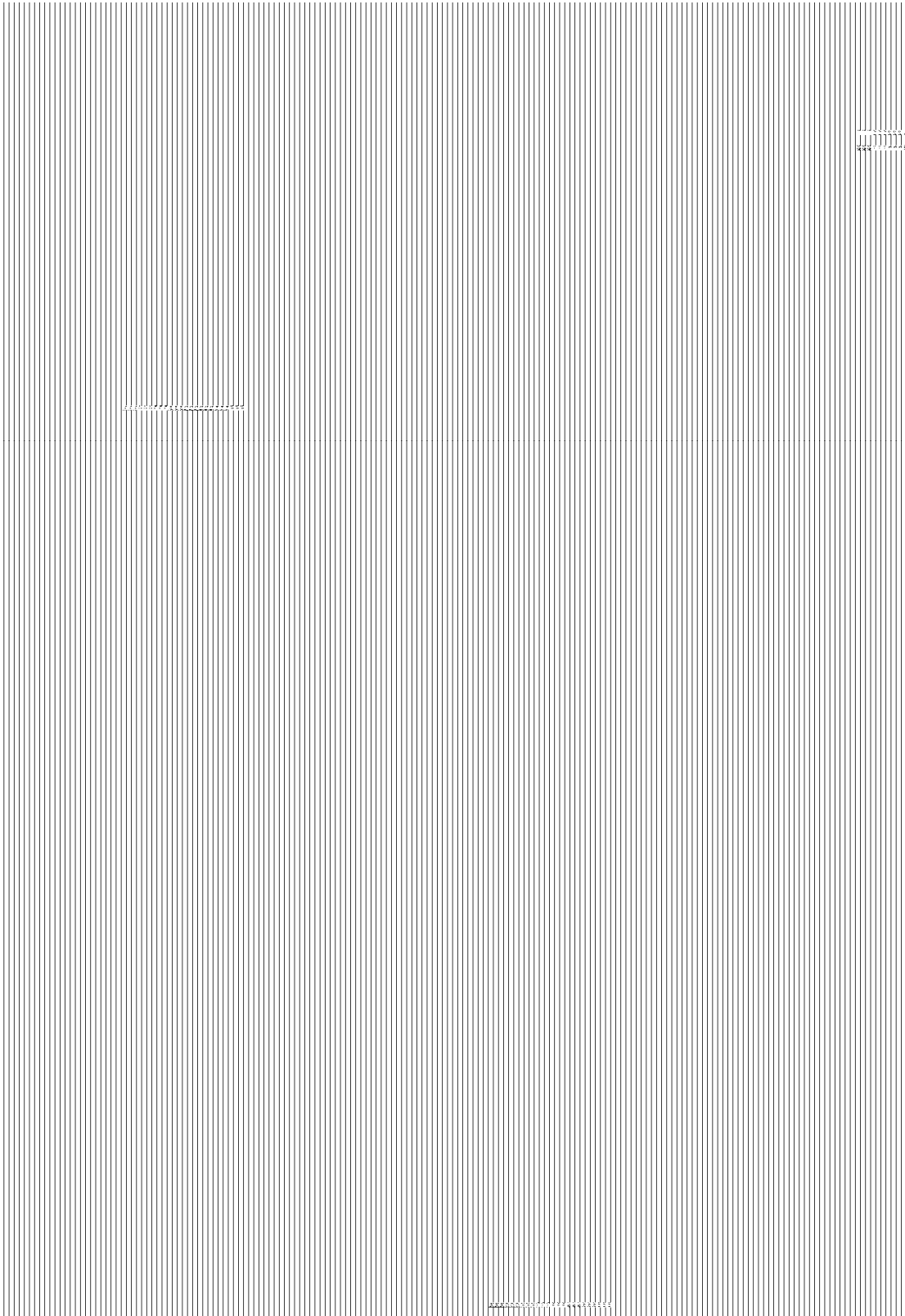


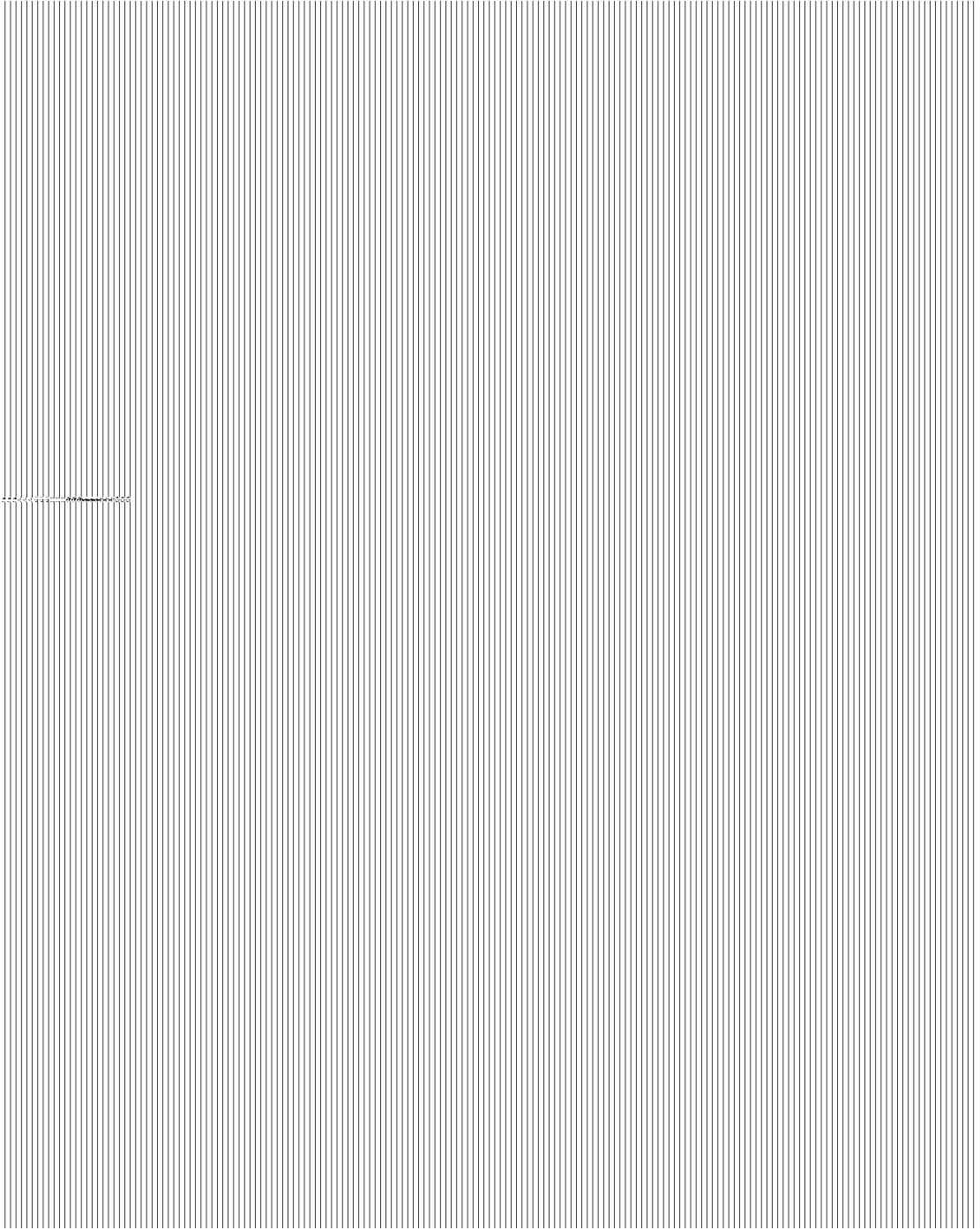




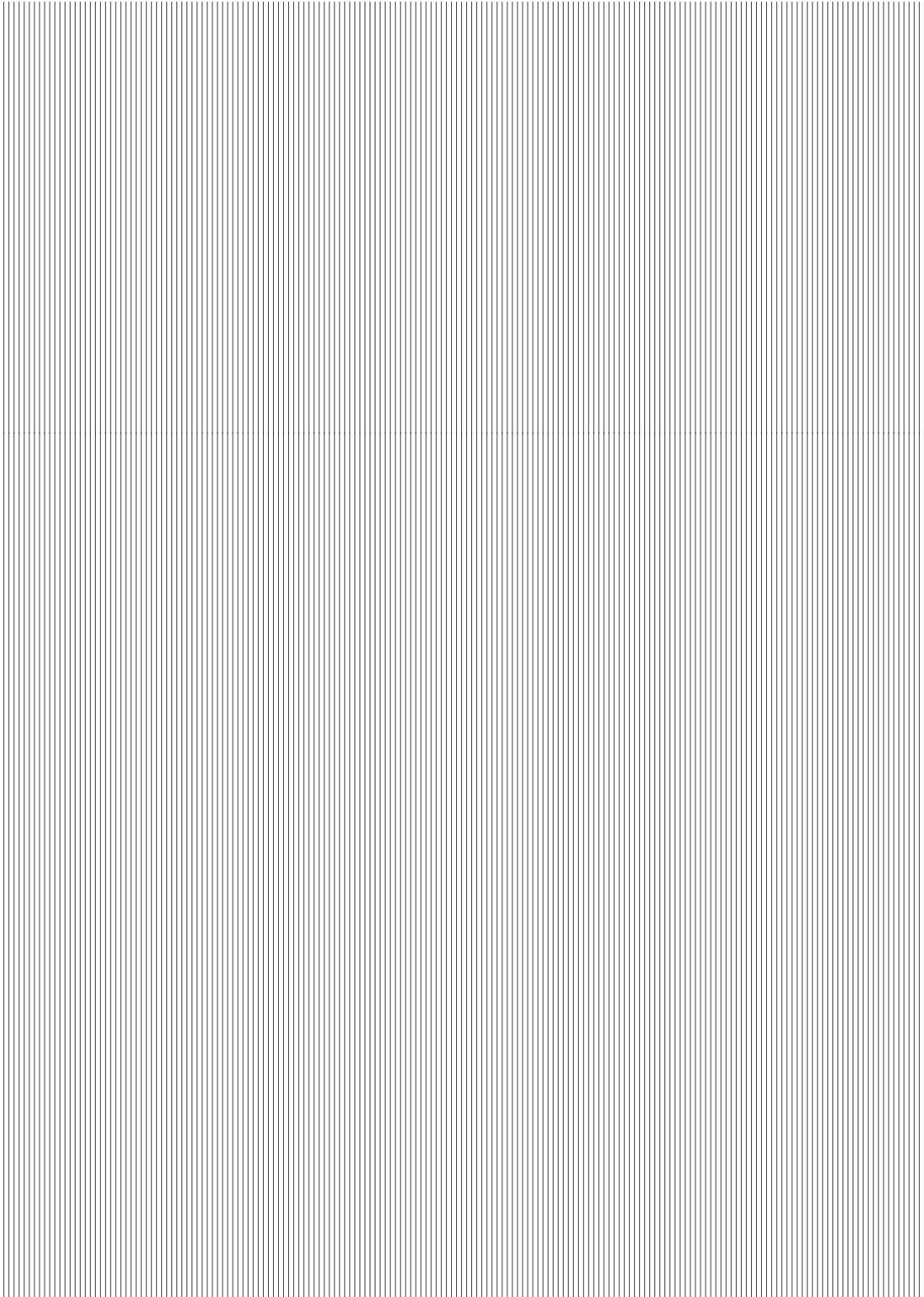




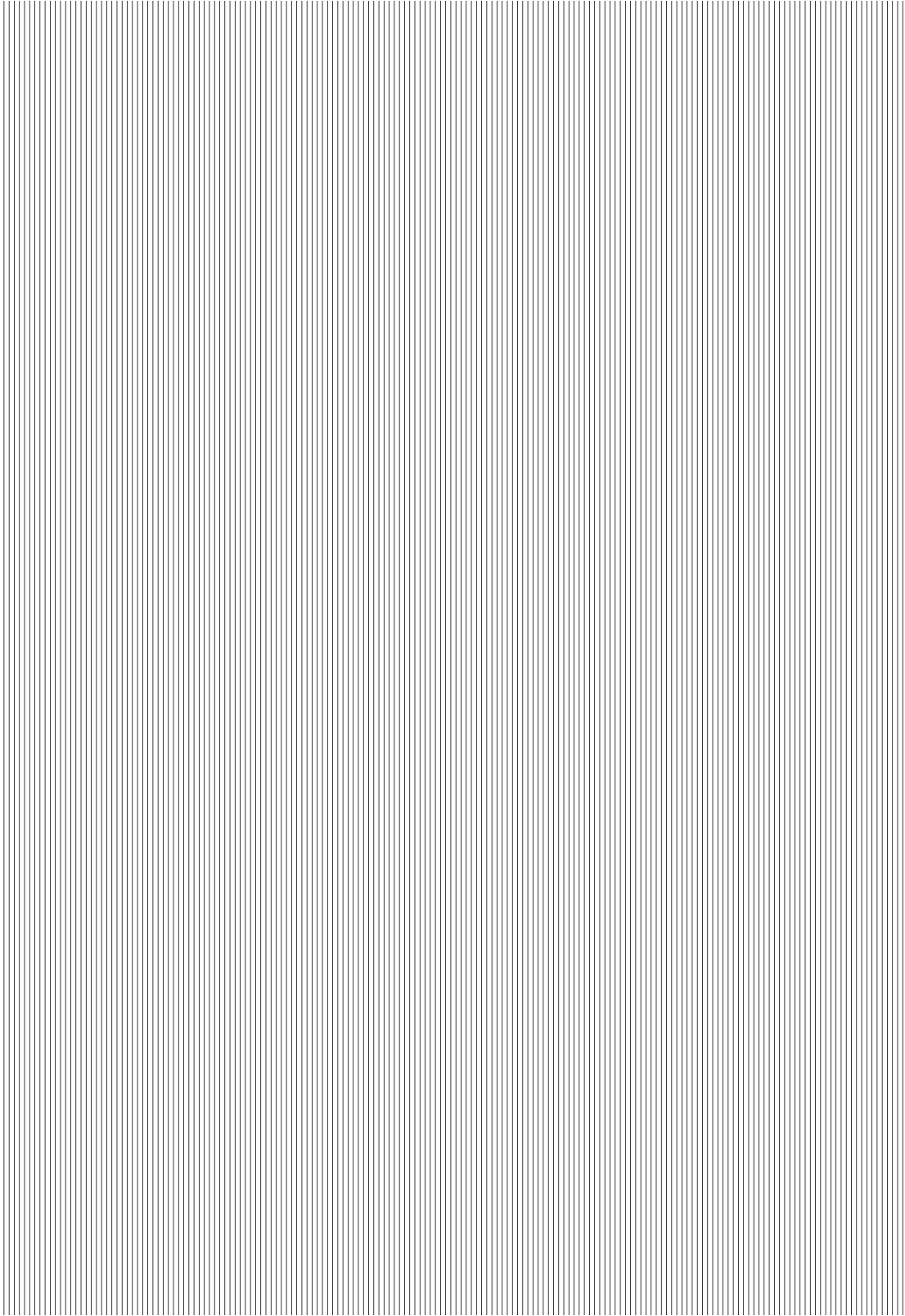


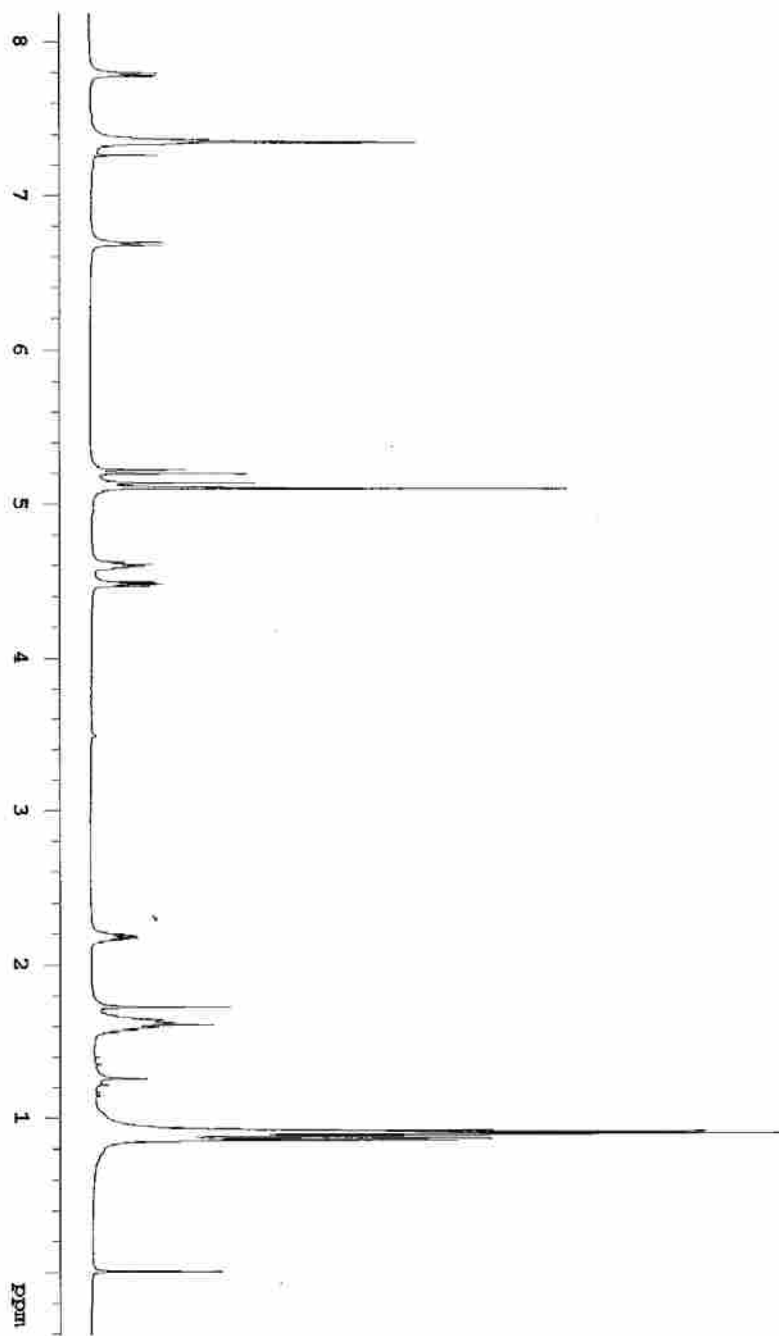
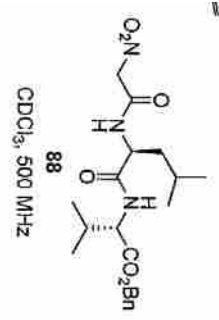




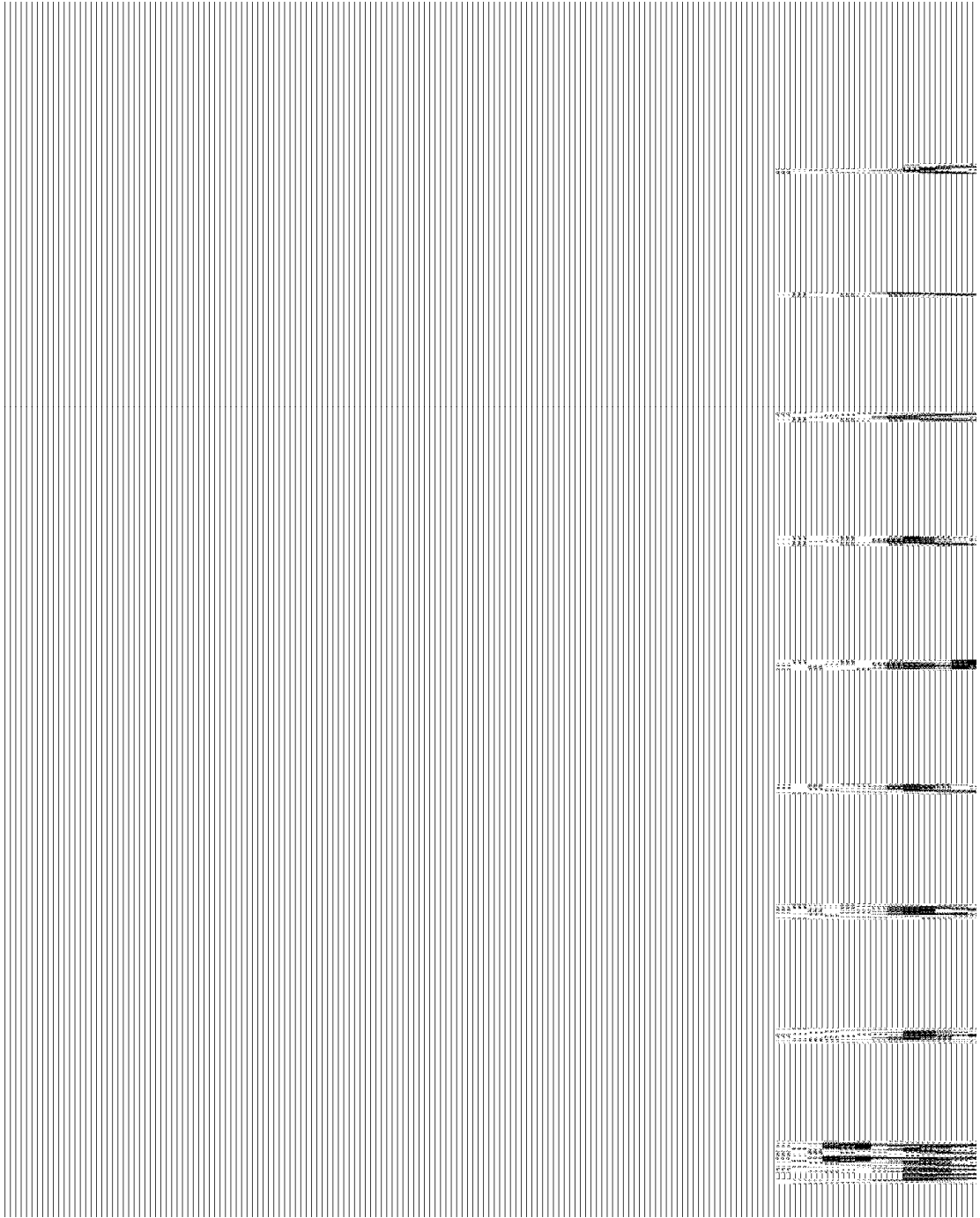


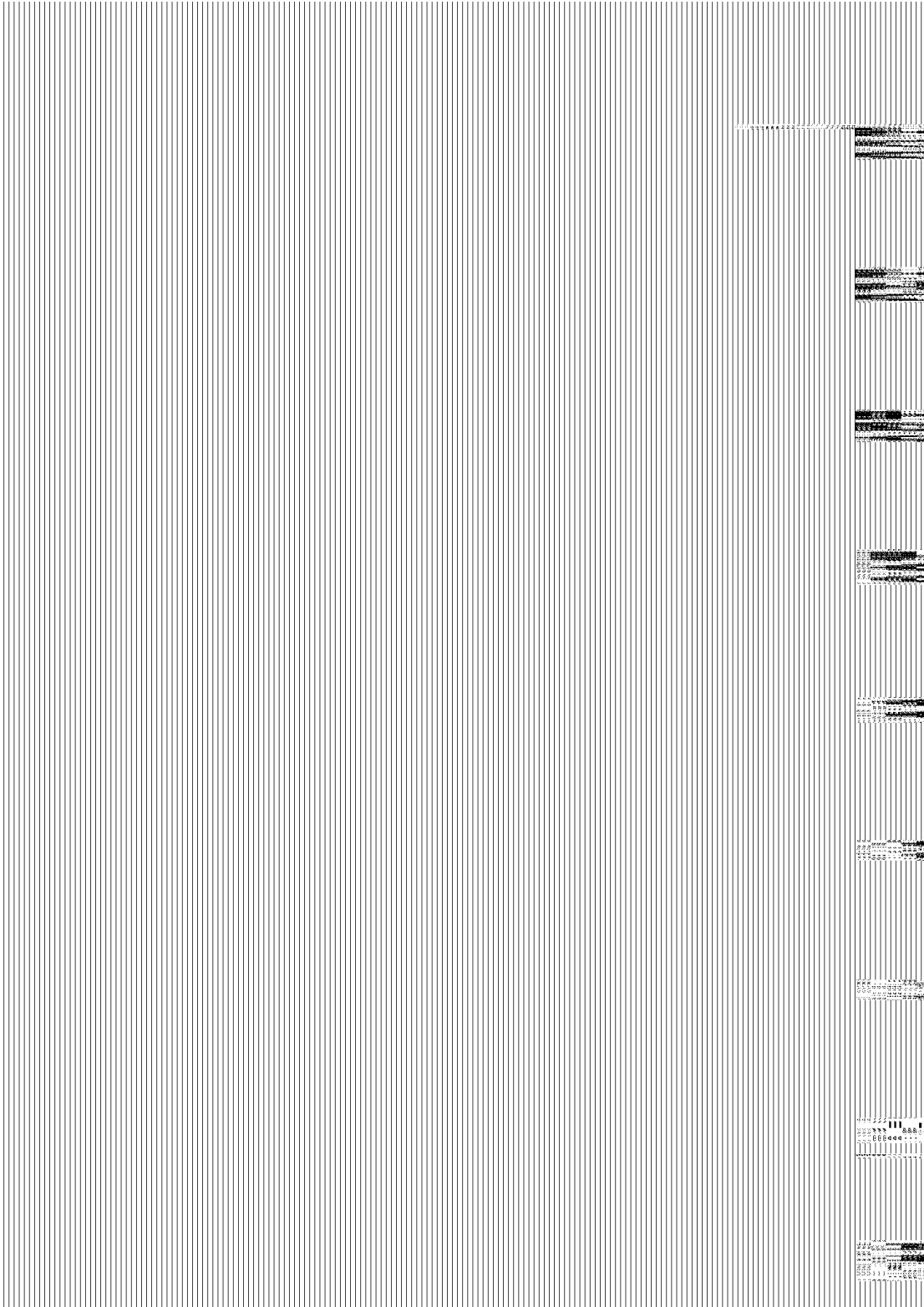


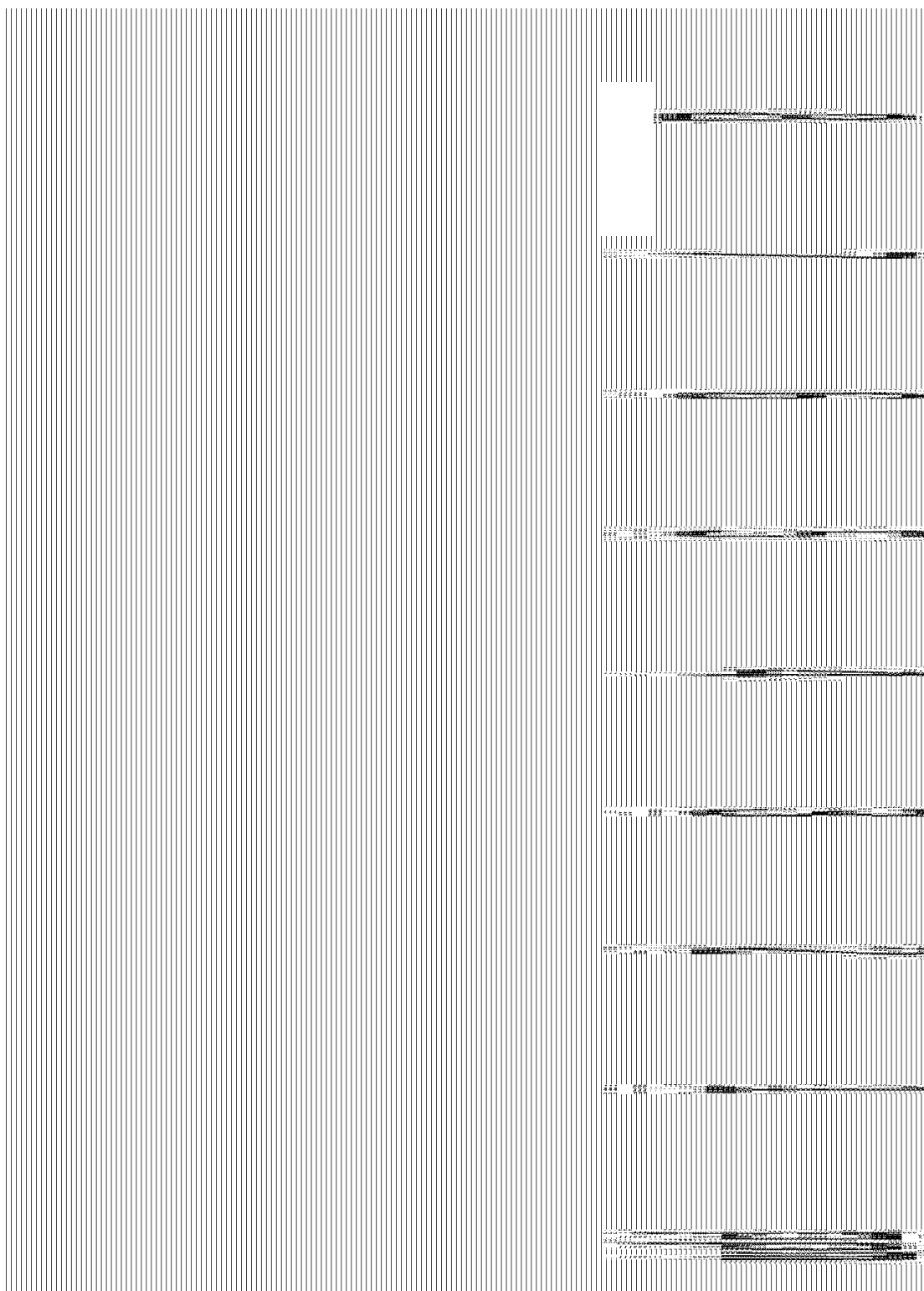








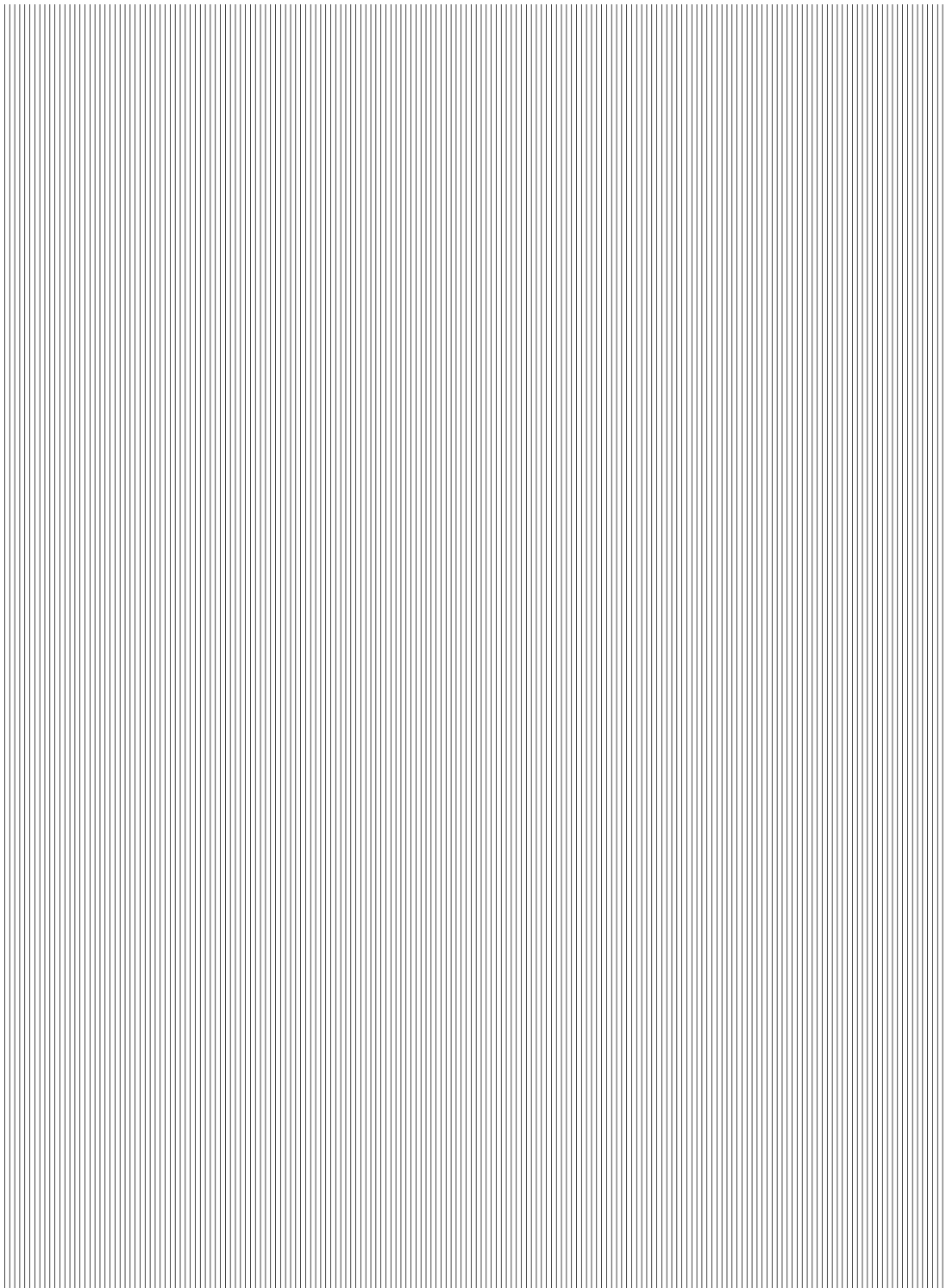




**96-A & B**

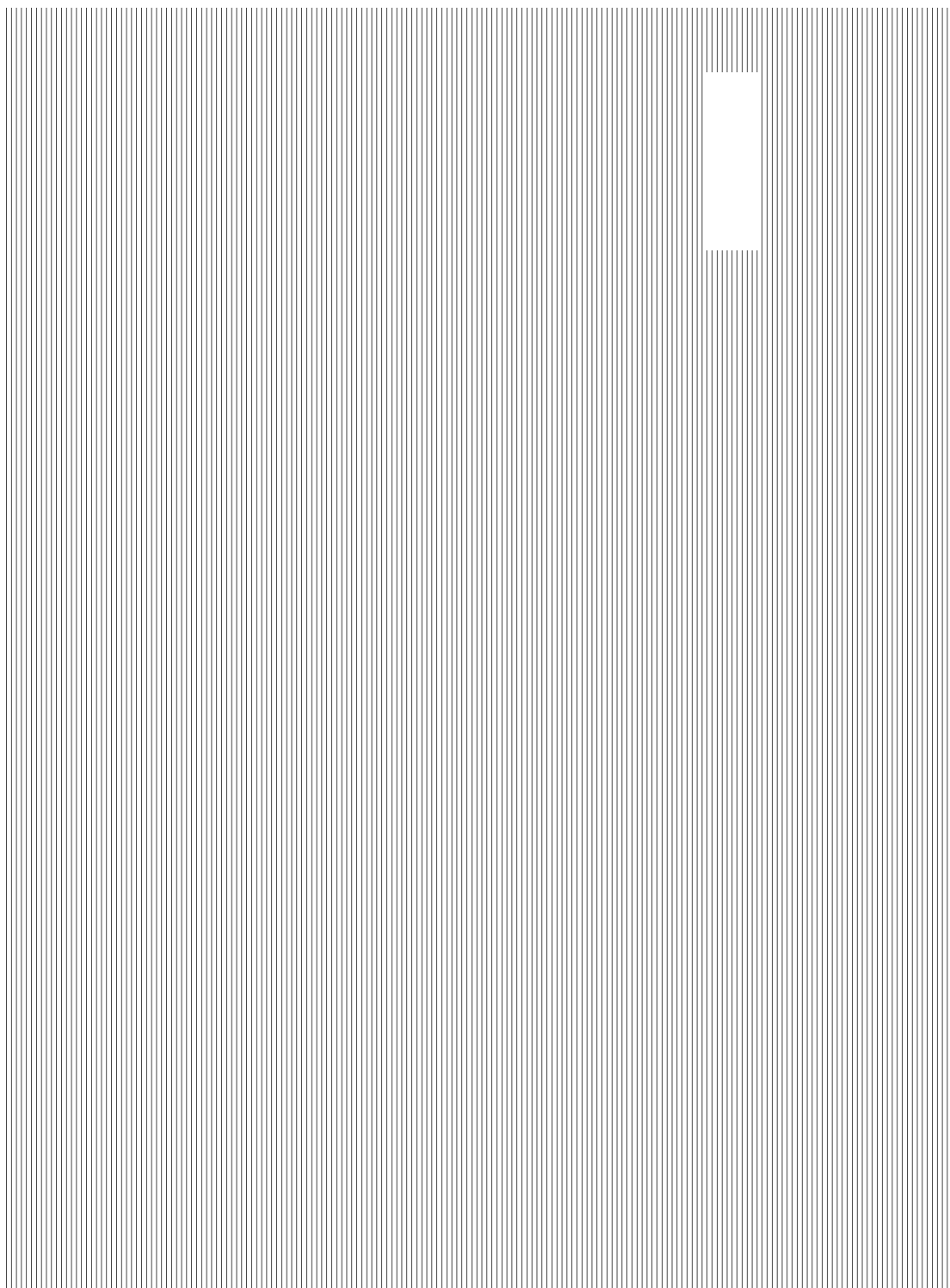
$\text{CDCl}_3$ , 500MHz





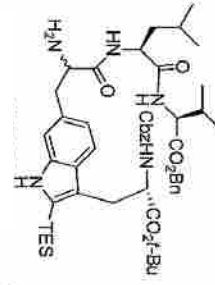
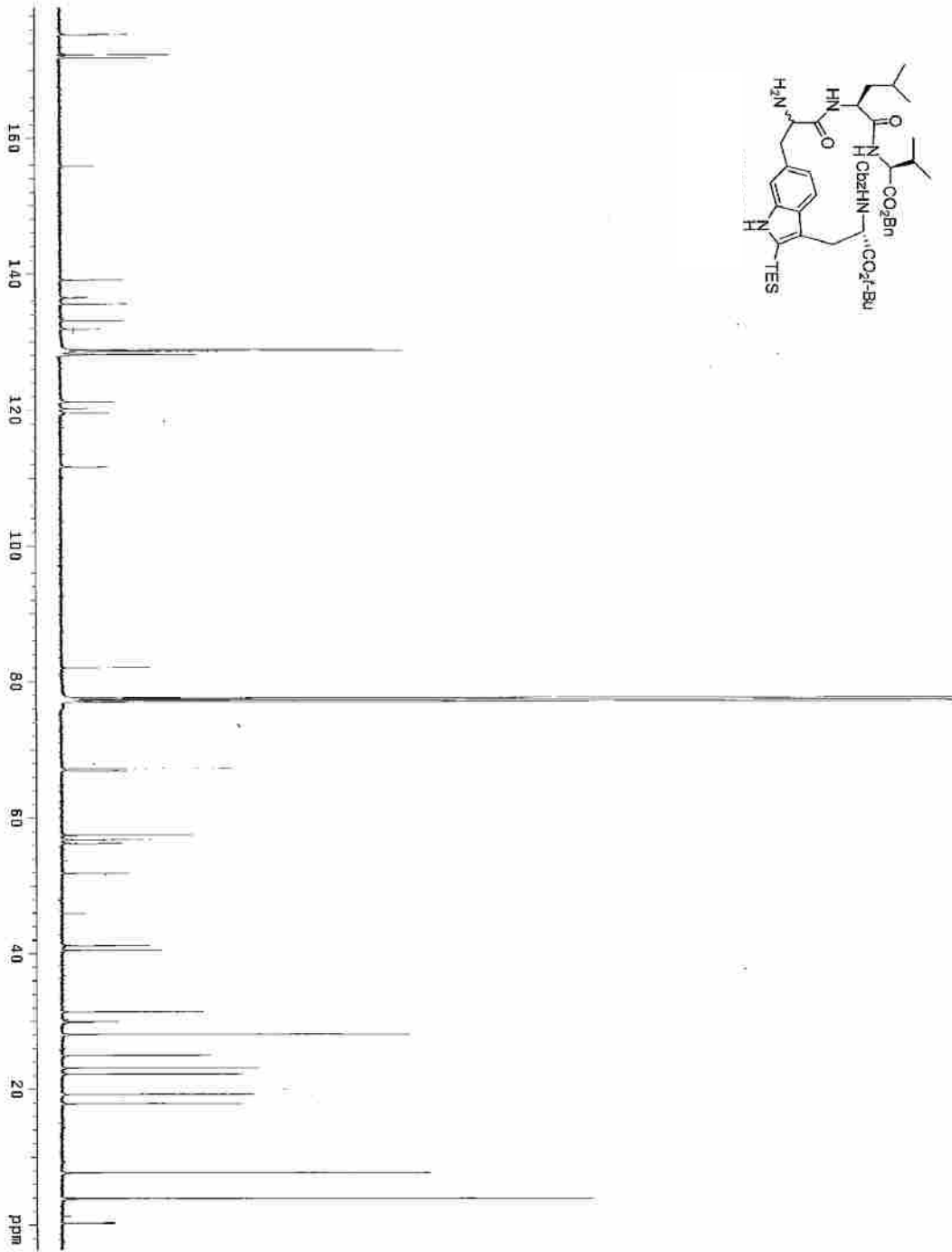
**96-A & B**

CDCl<sub>3</sub>, 125MHz



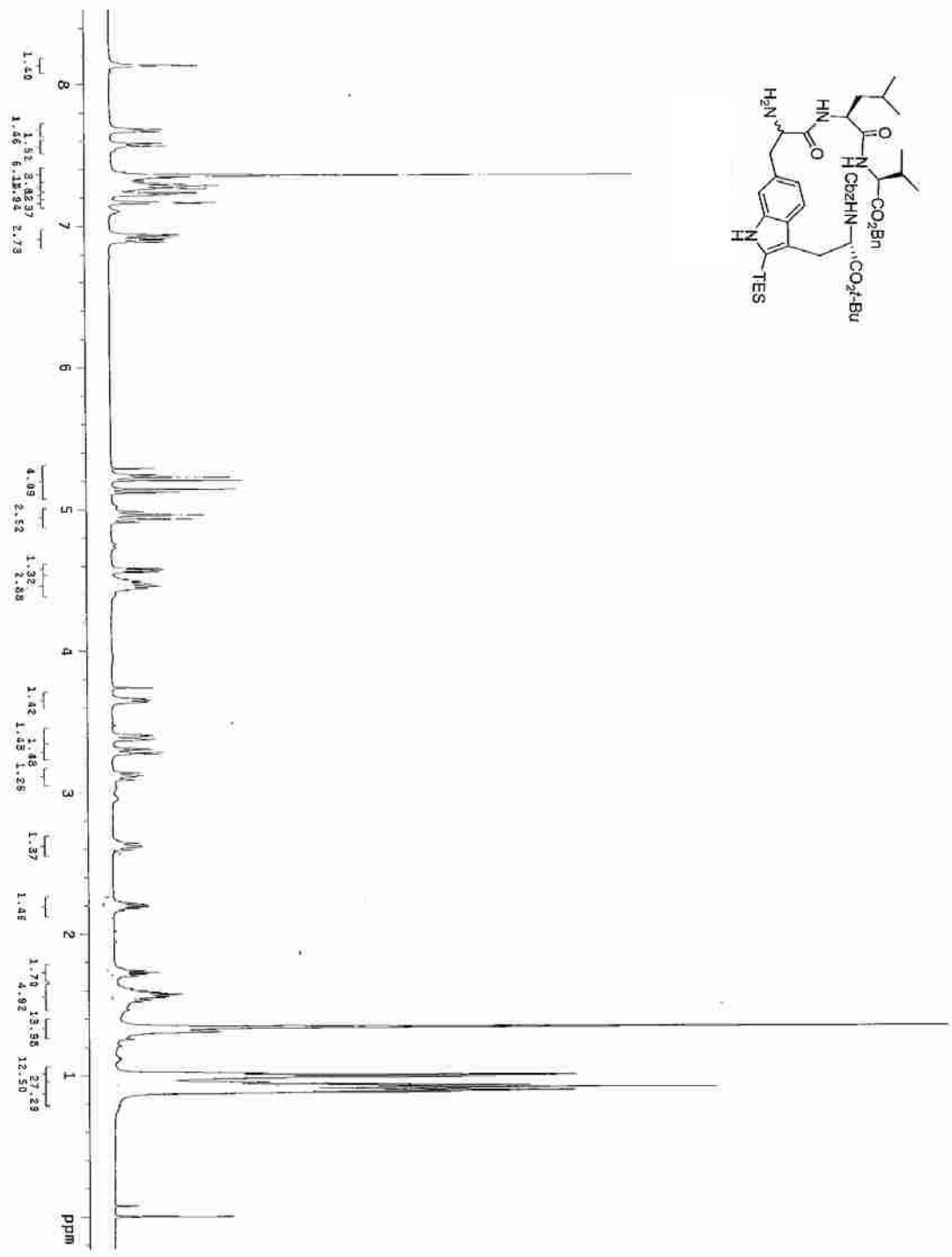
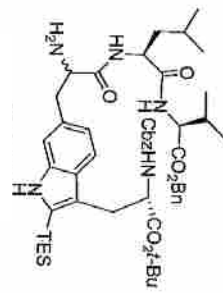
**97-A**

CDCl<sub>3</sub>, 500MHz



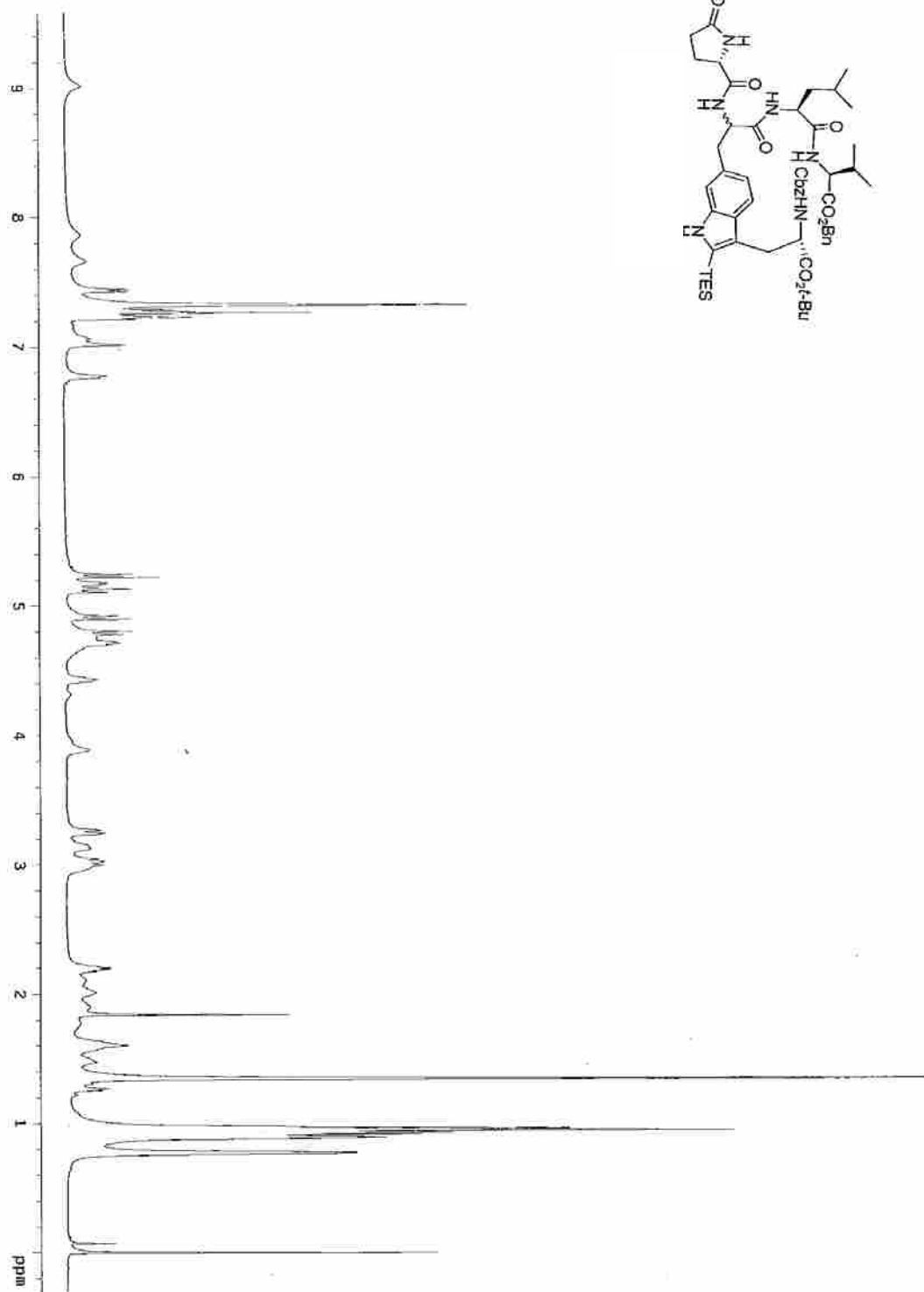
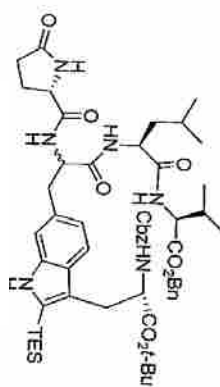
97-A

CDCl<sub>3</sub>, 125MHz



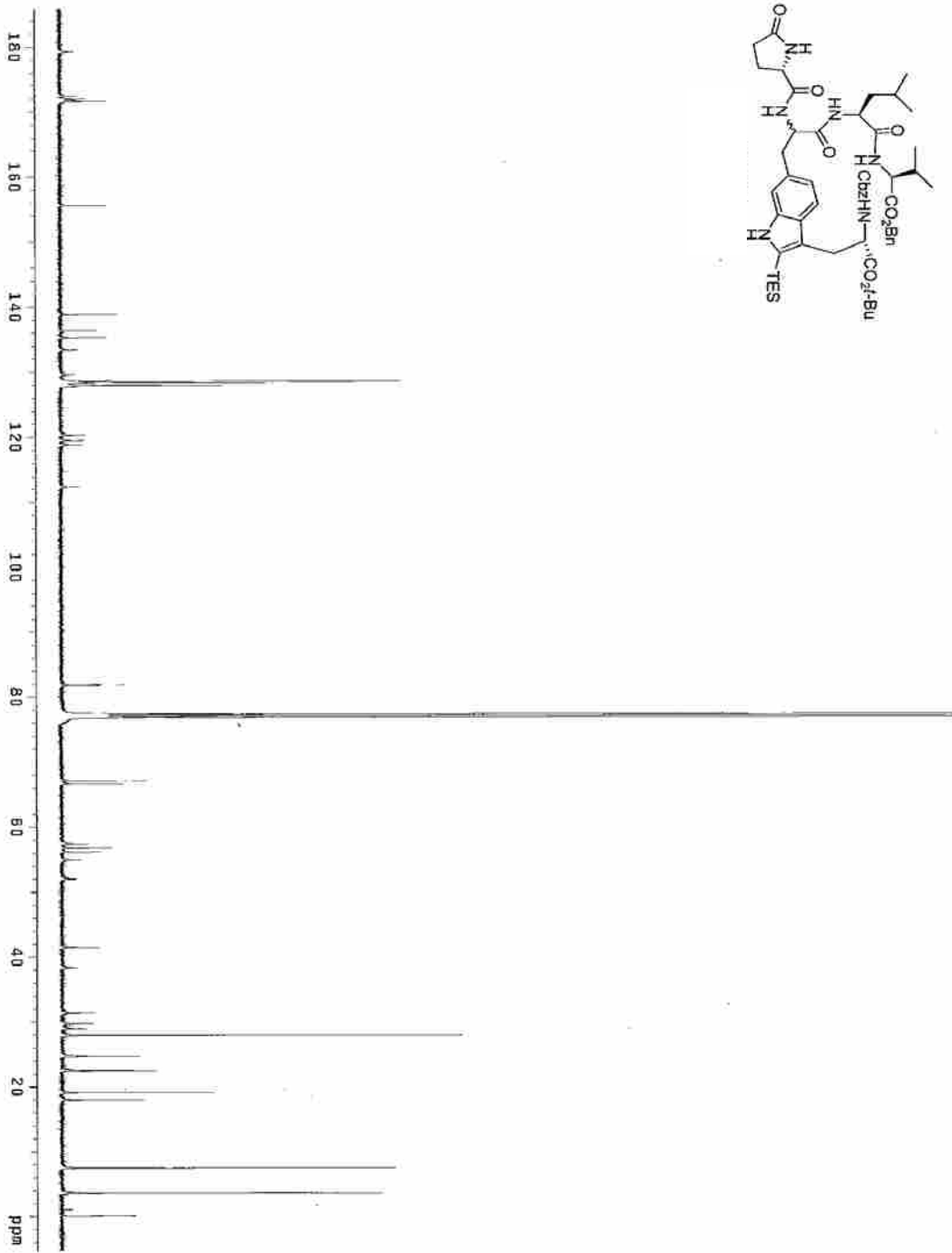
97-B  
CDCl<sub>3</sub>, 500MHz





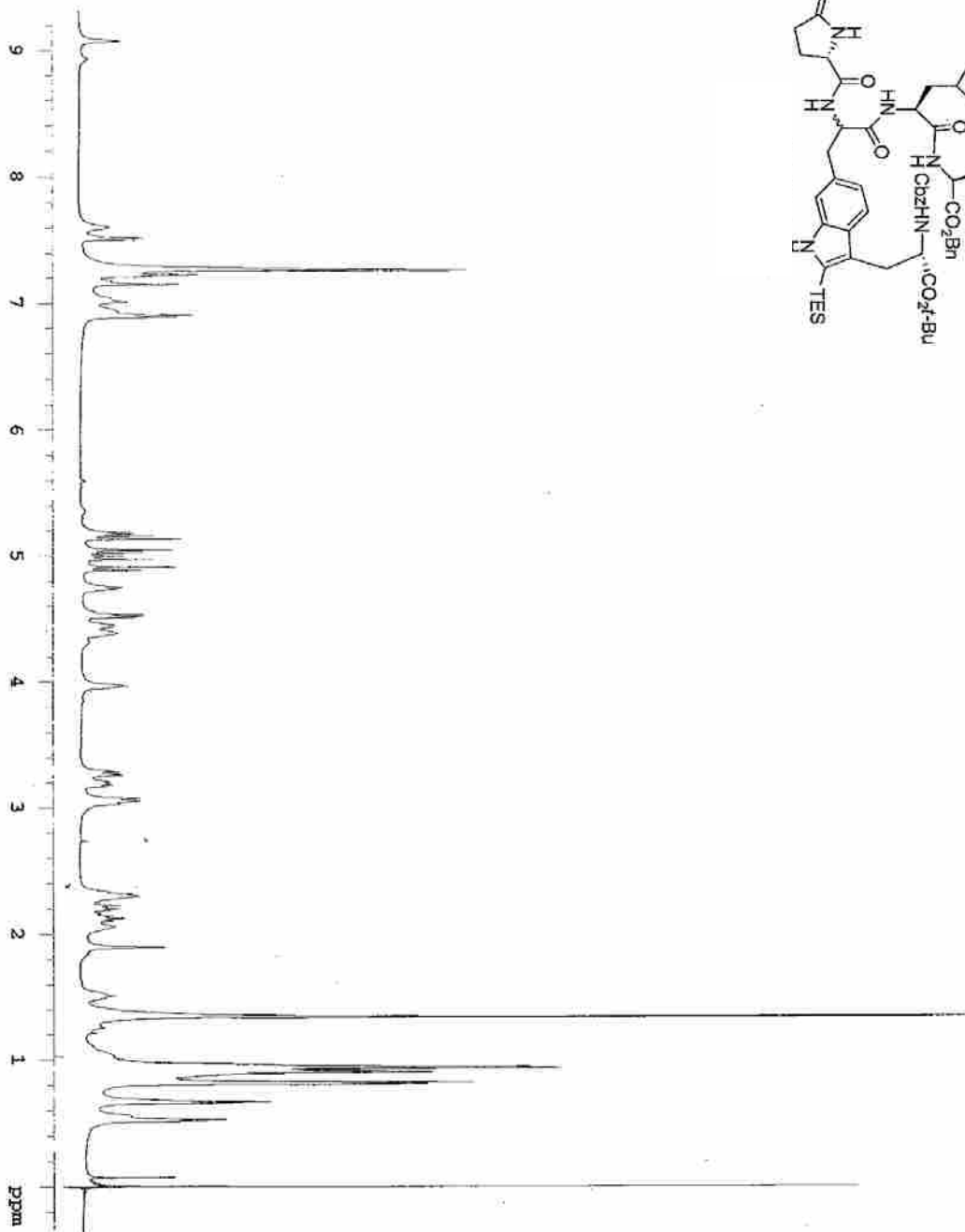
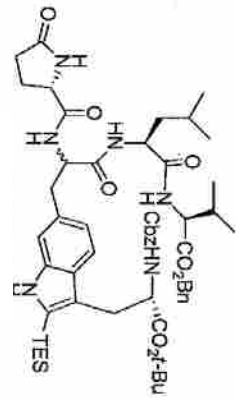
99-A

CDCl<sub>3</sub>, 500MHz



99-A

CDCl<sub>3</sub>, 125MHz

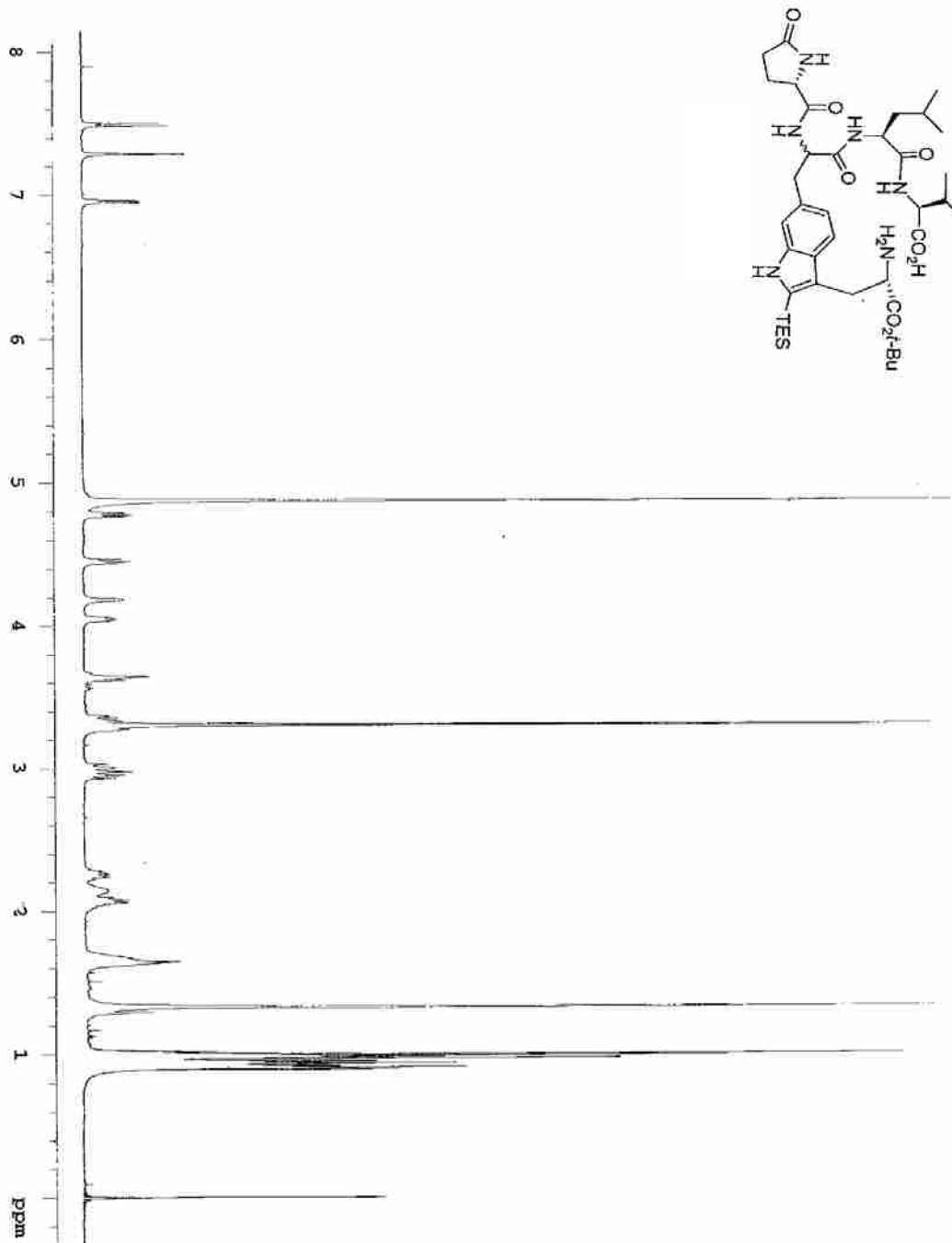


99-B

CDCl<sub>3</sub>, 500MHz







100-A

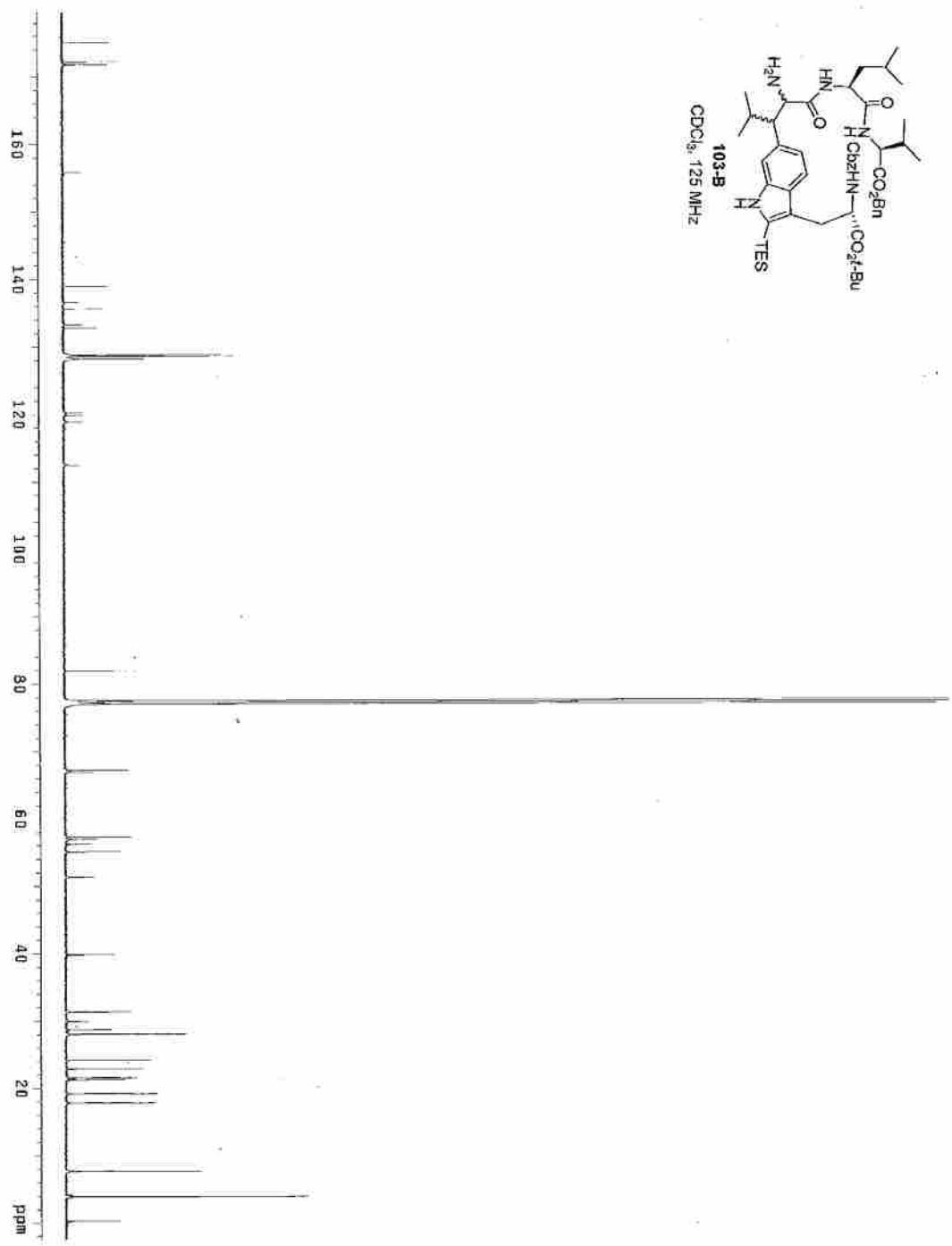
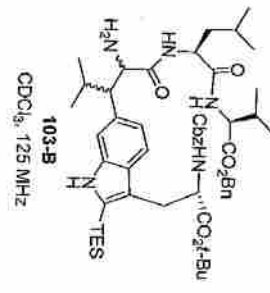
CD<sub>3</sub>OD, 500MHz







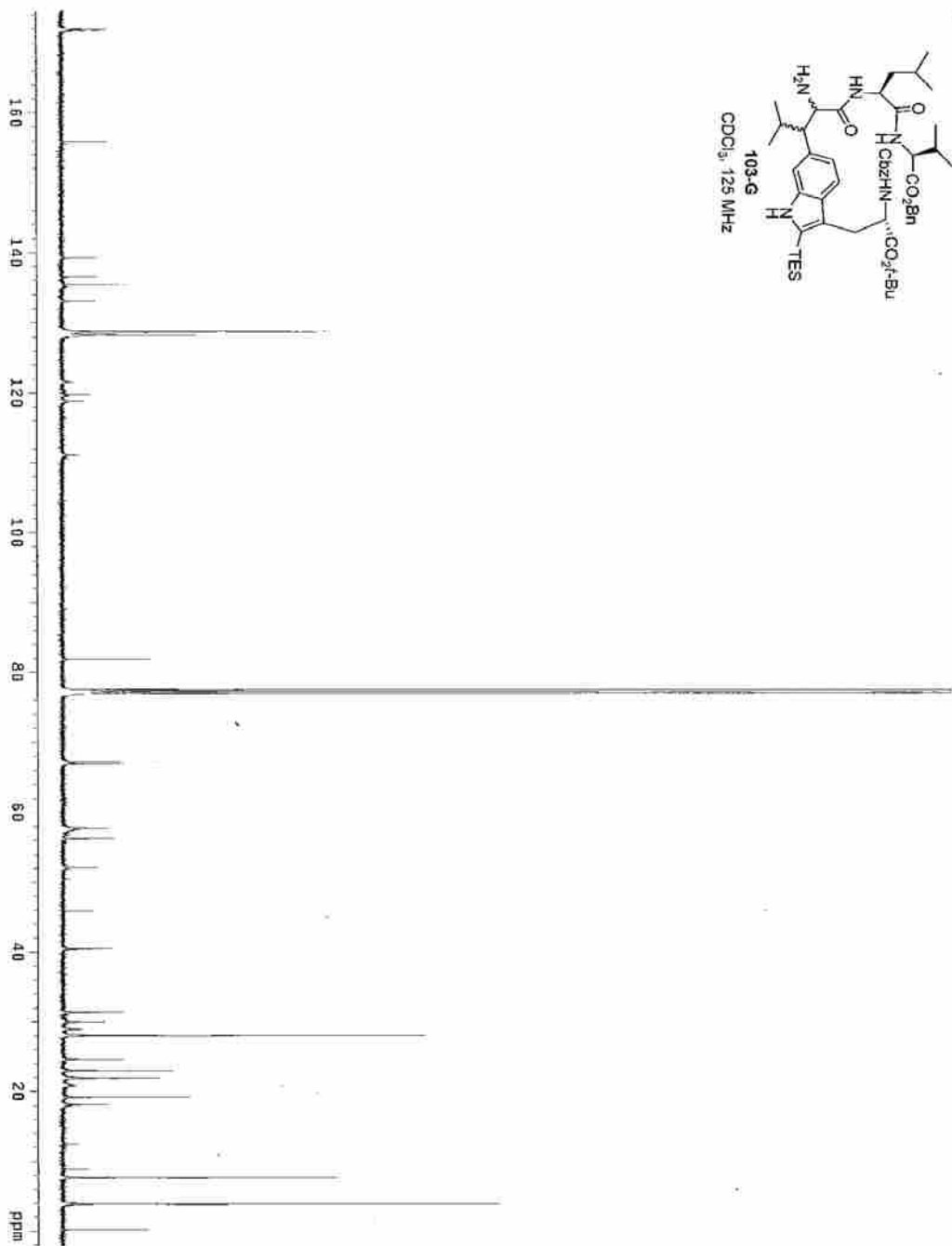
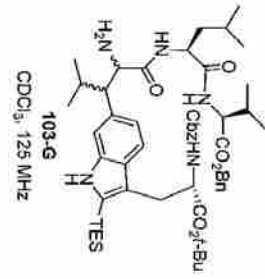


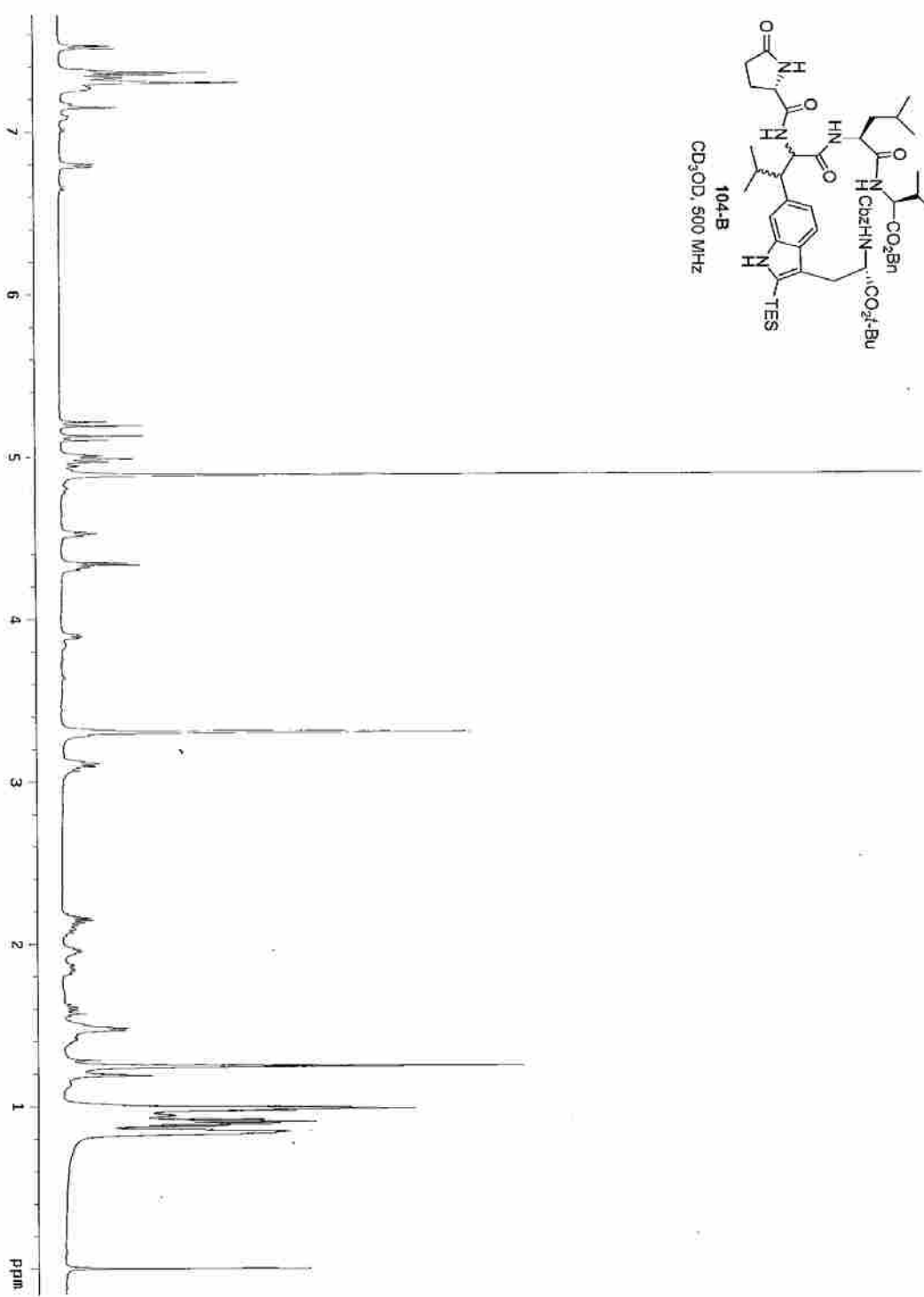
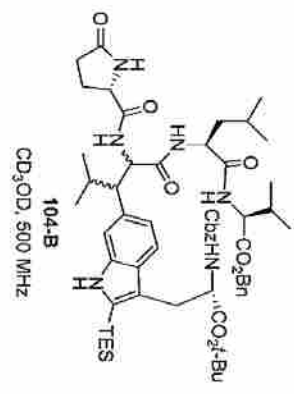






































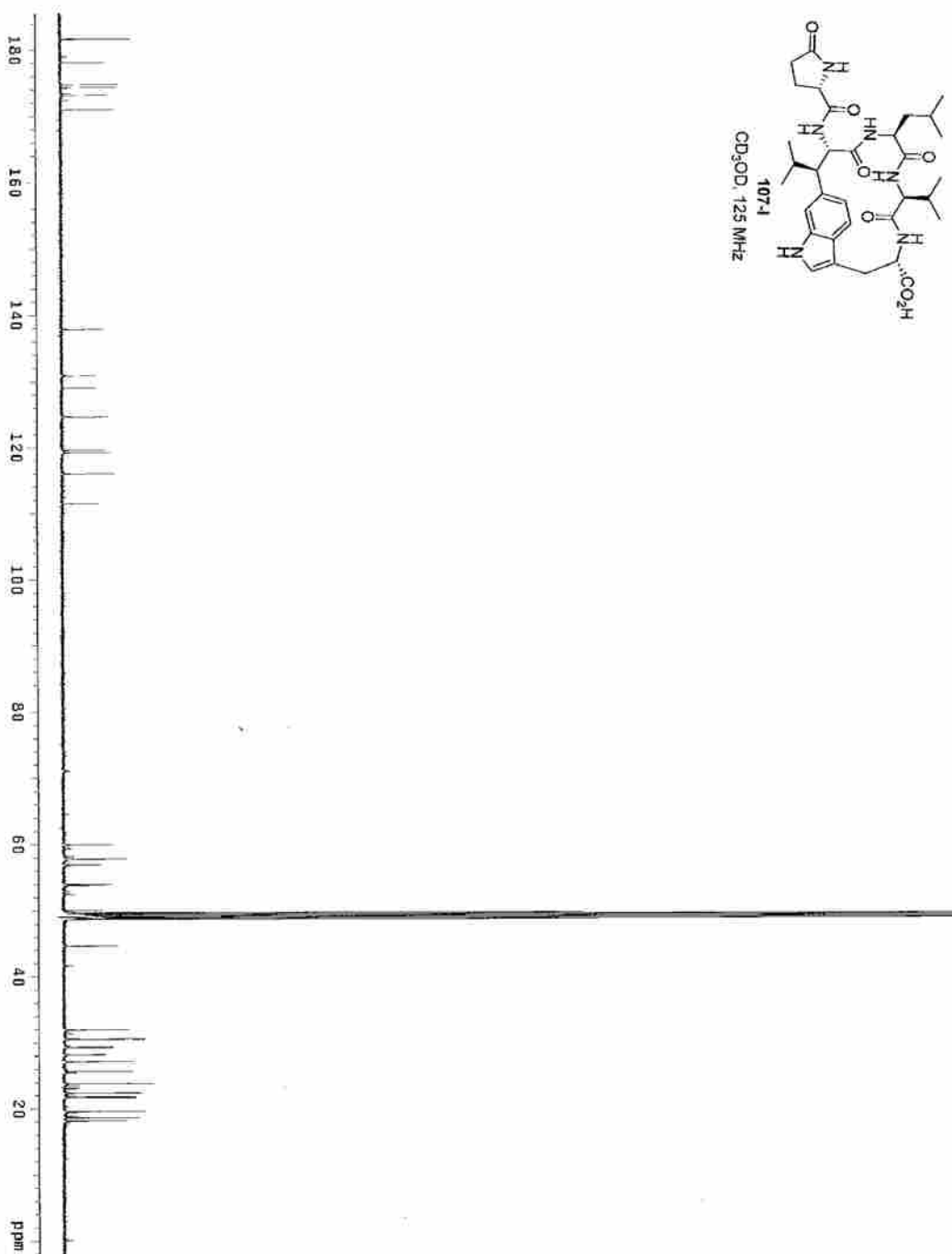
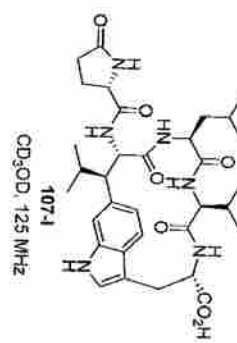




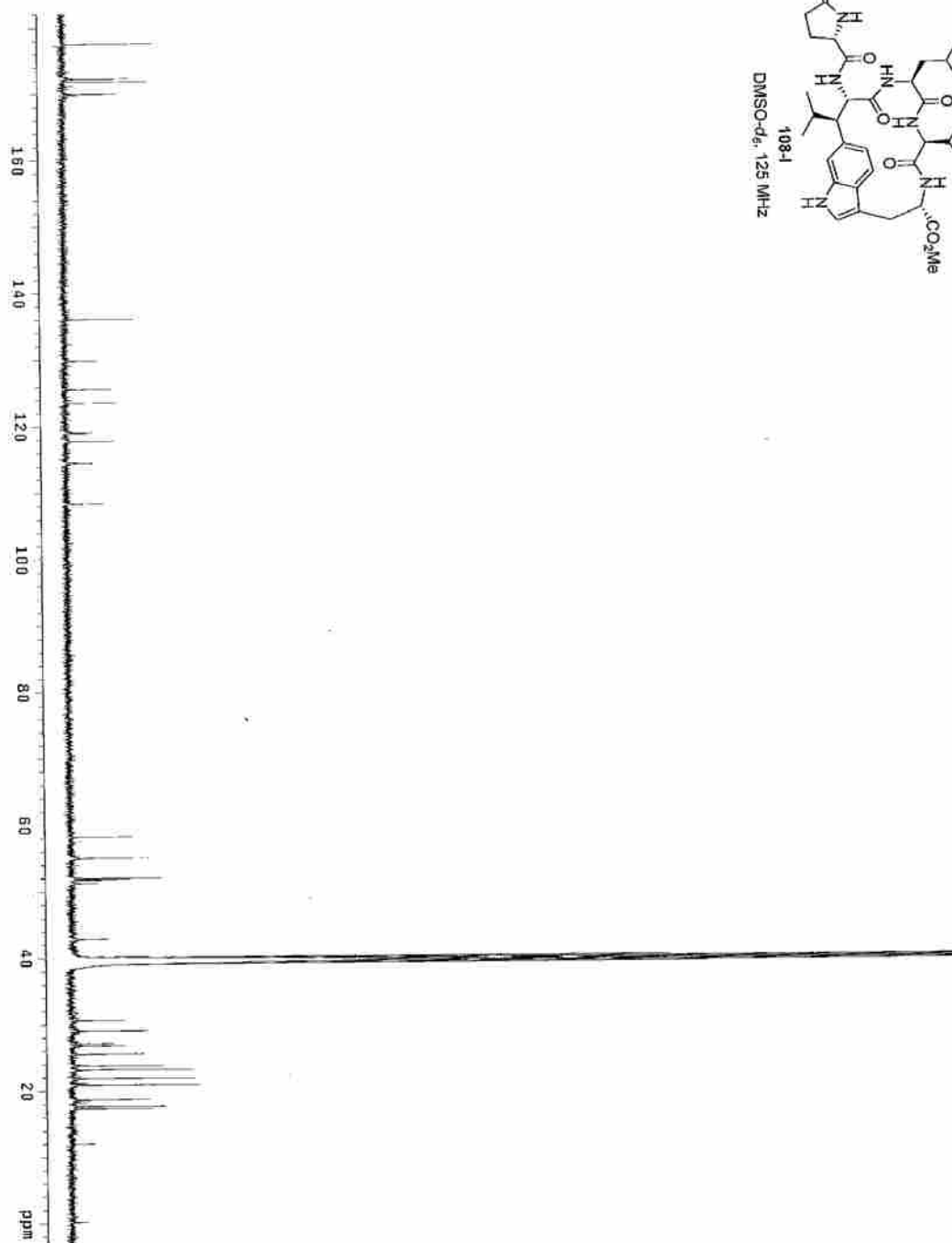
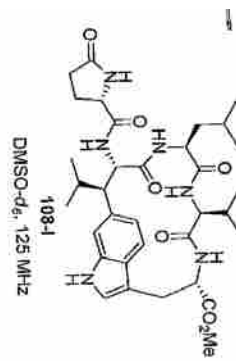


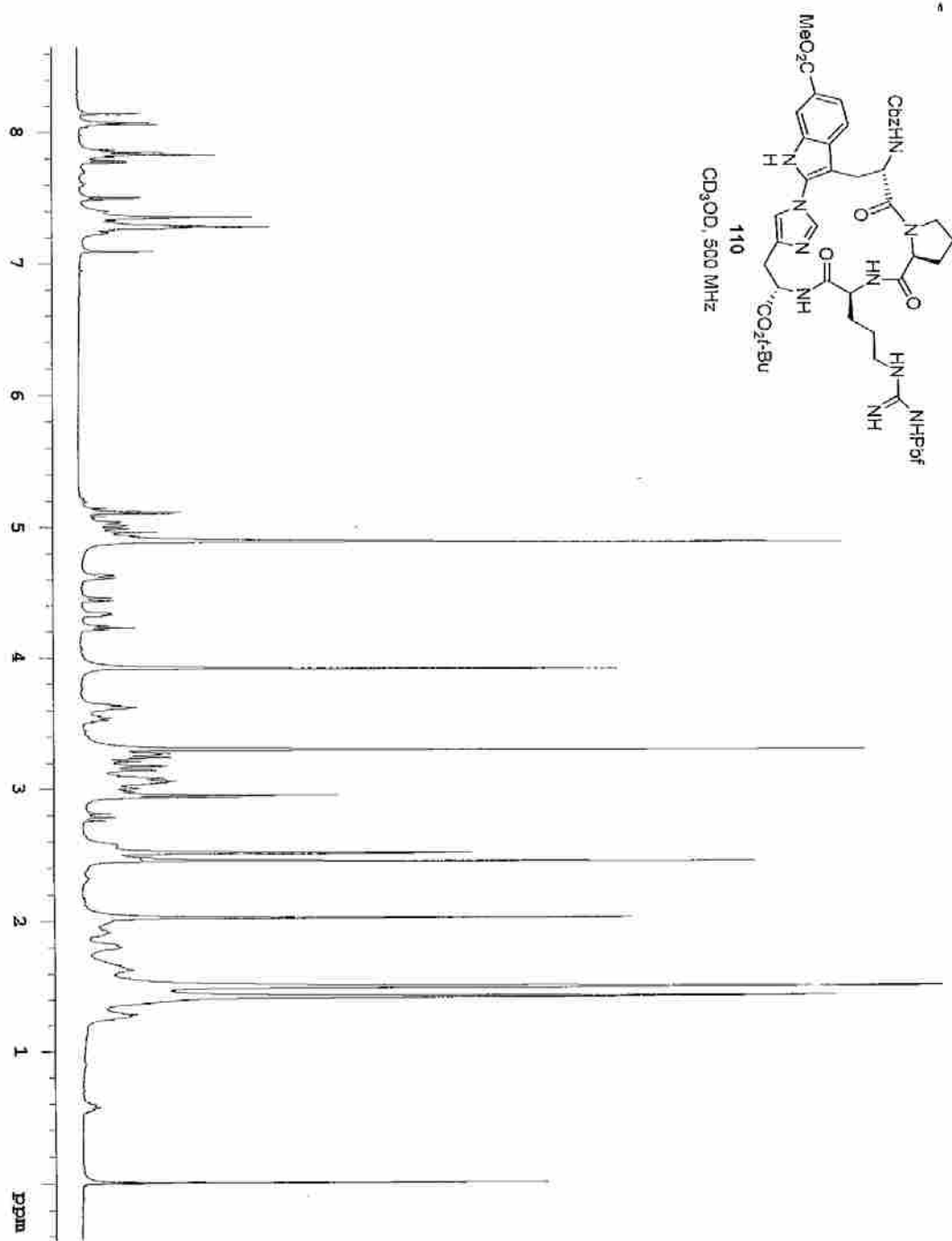


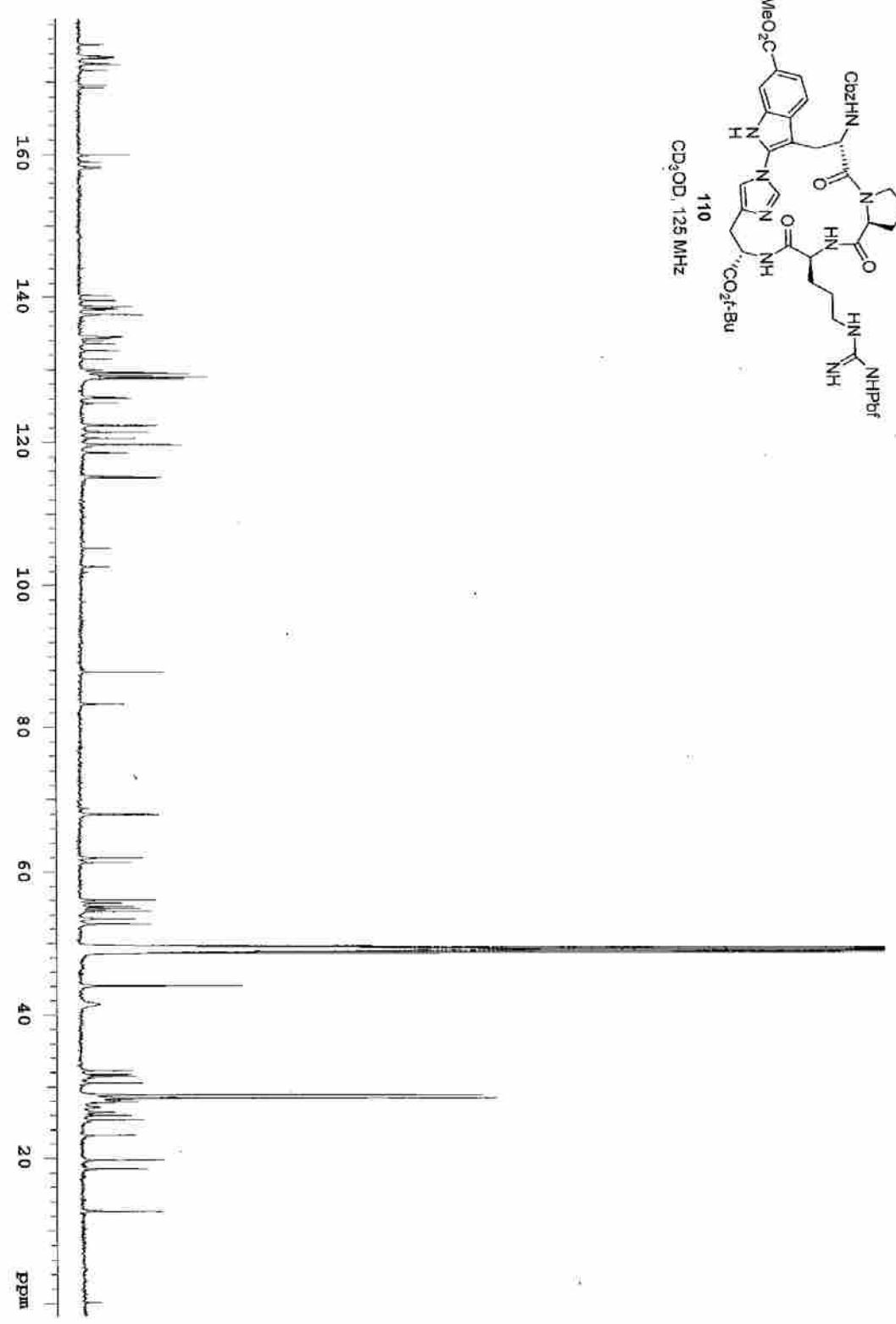
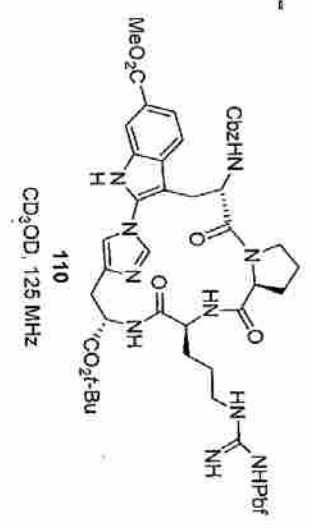




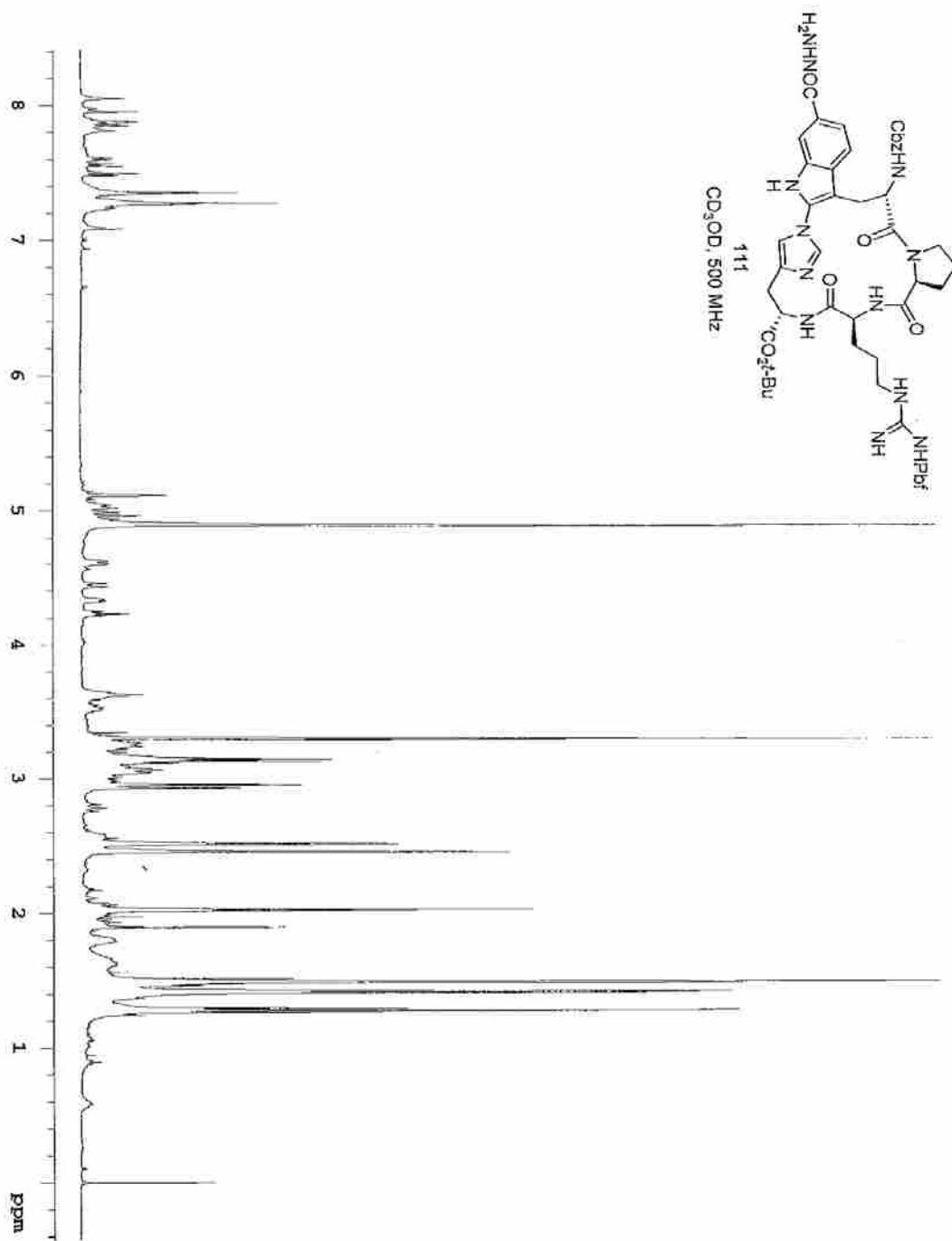






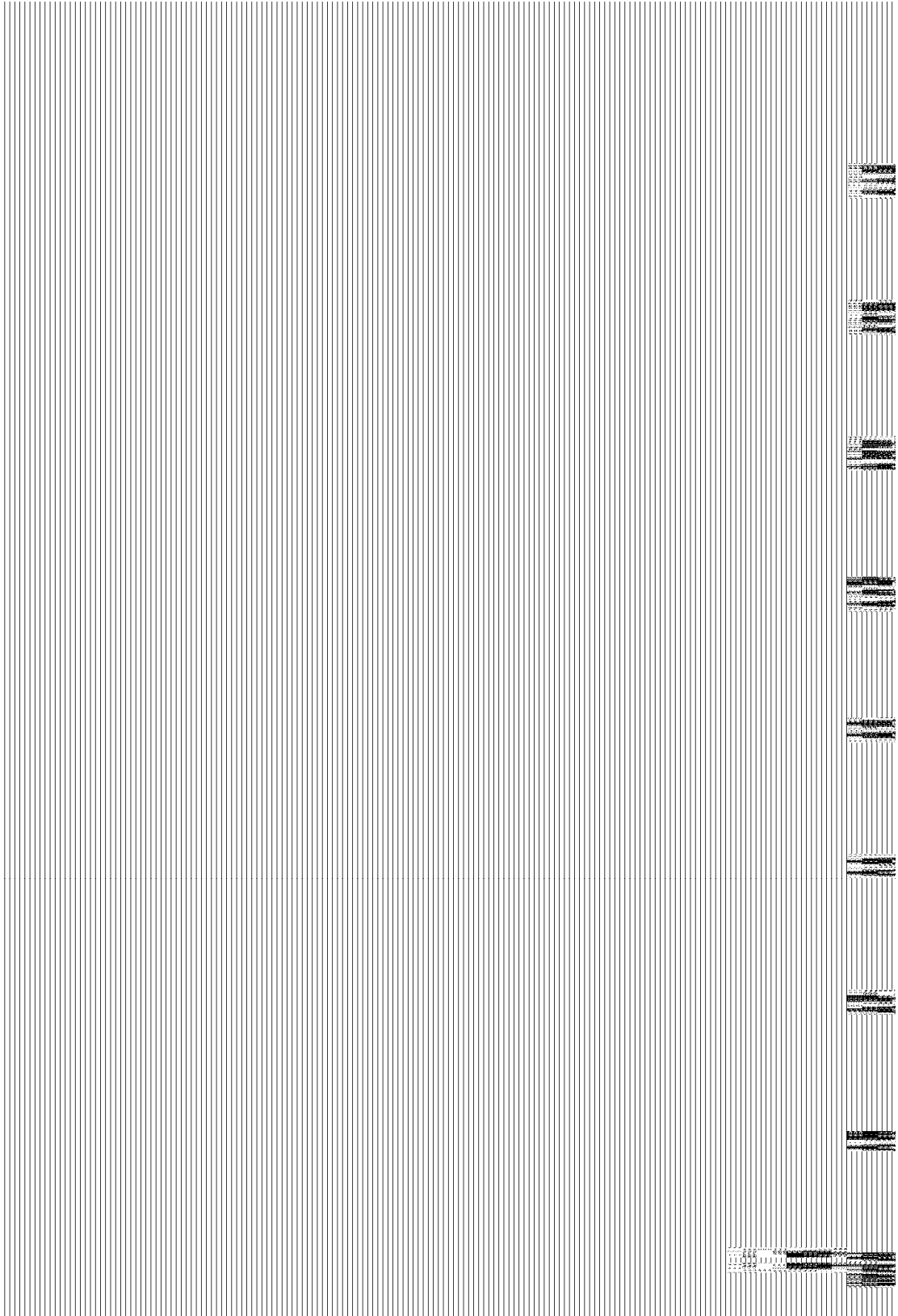




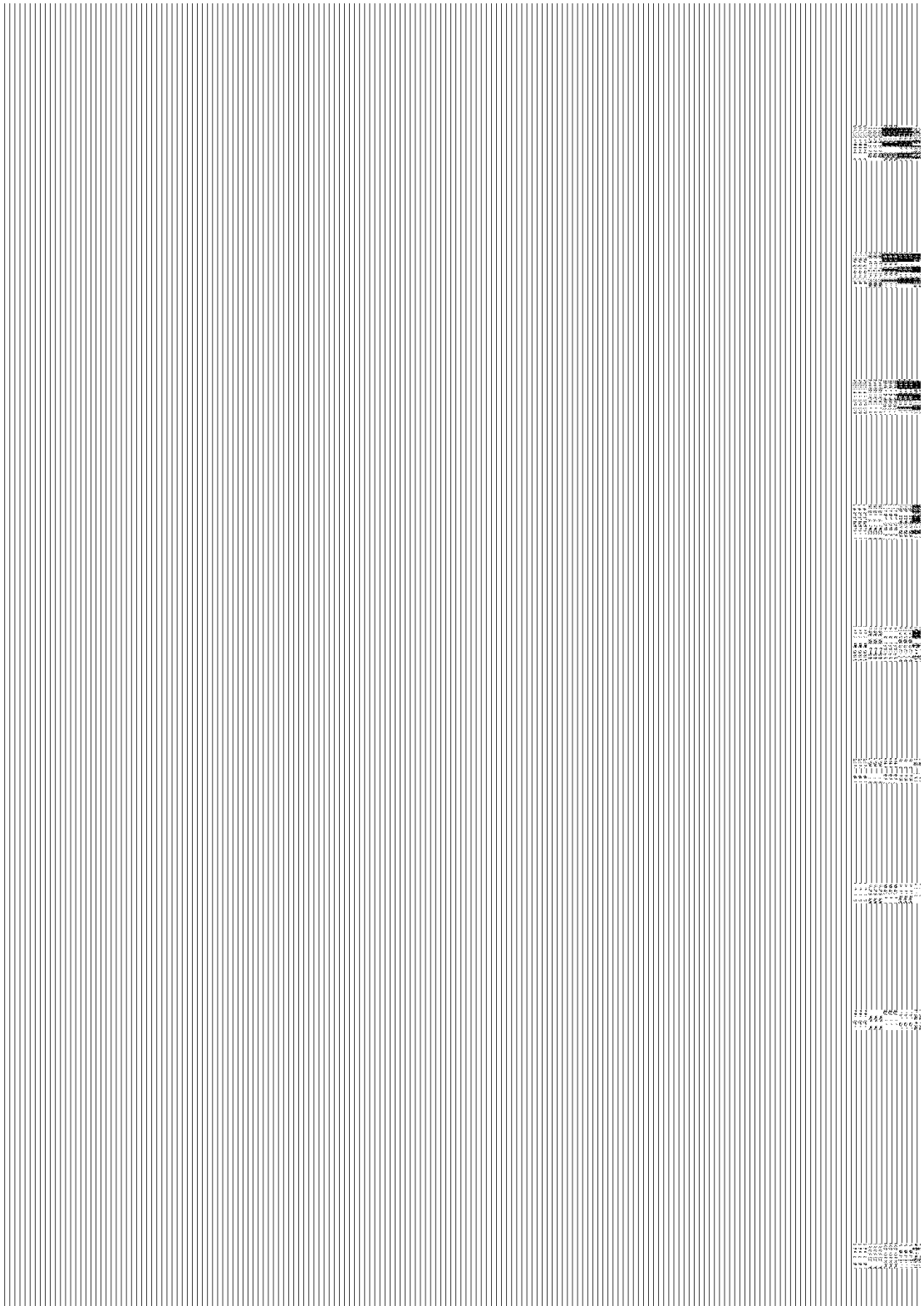


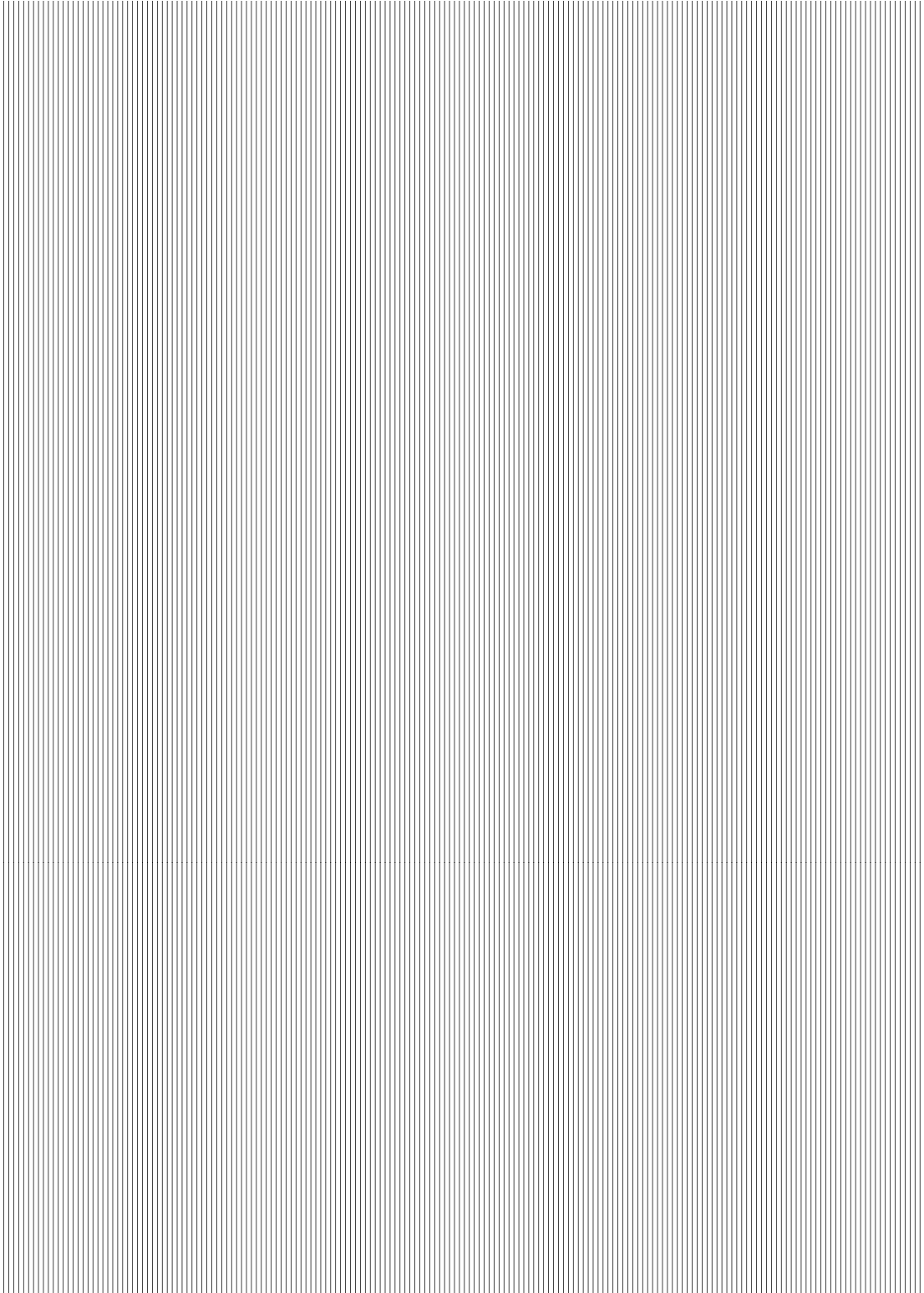


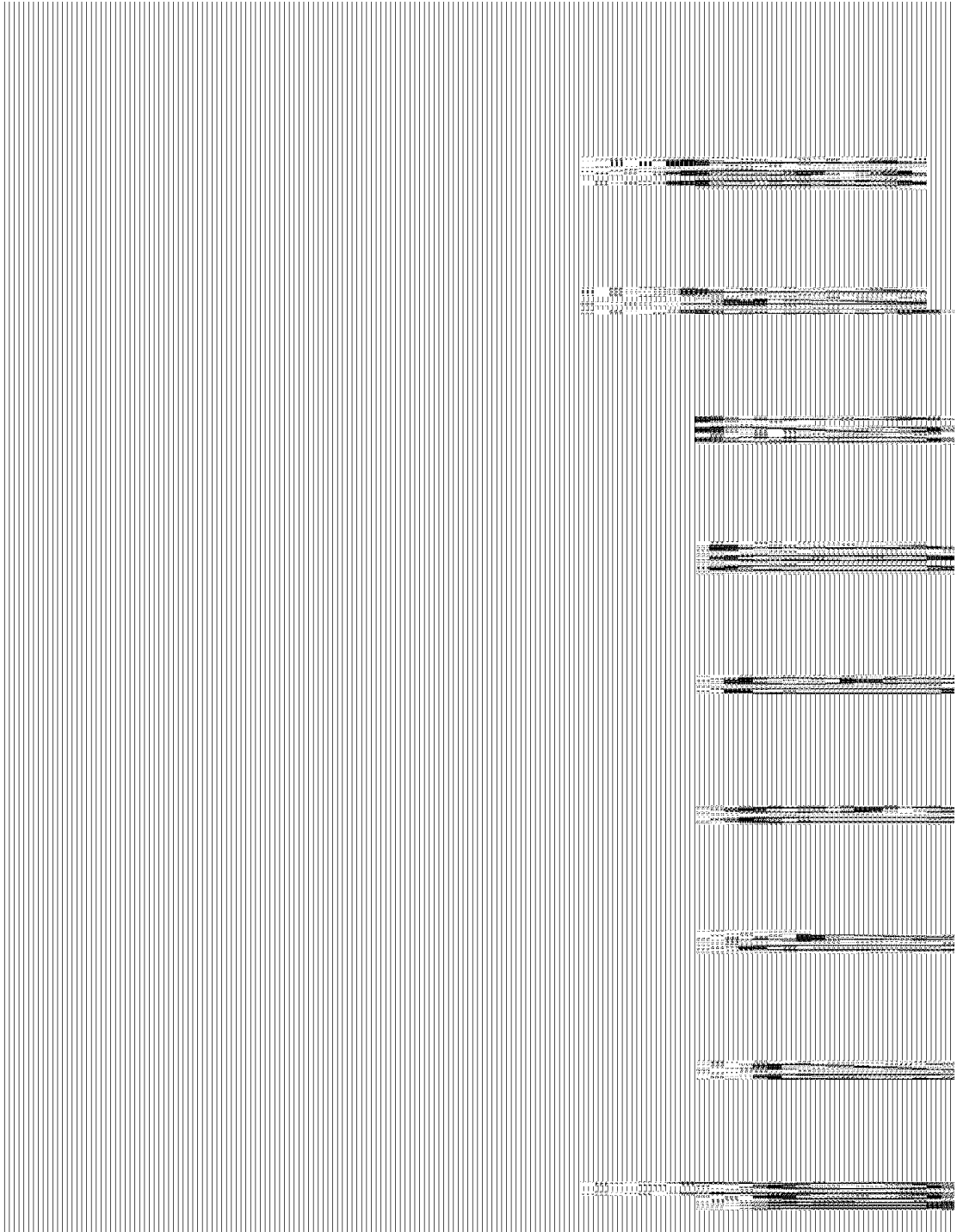




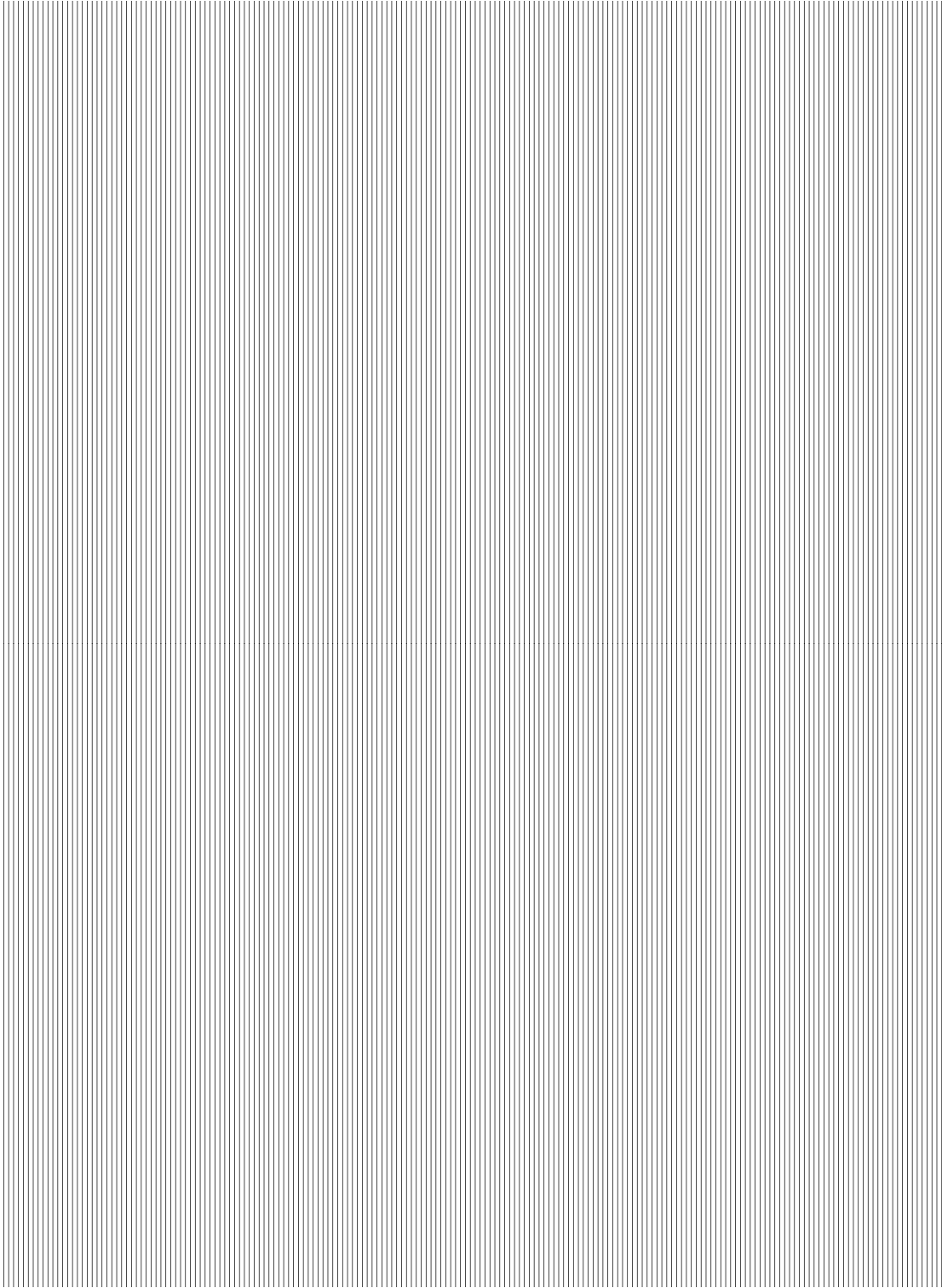


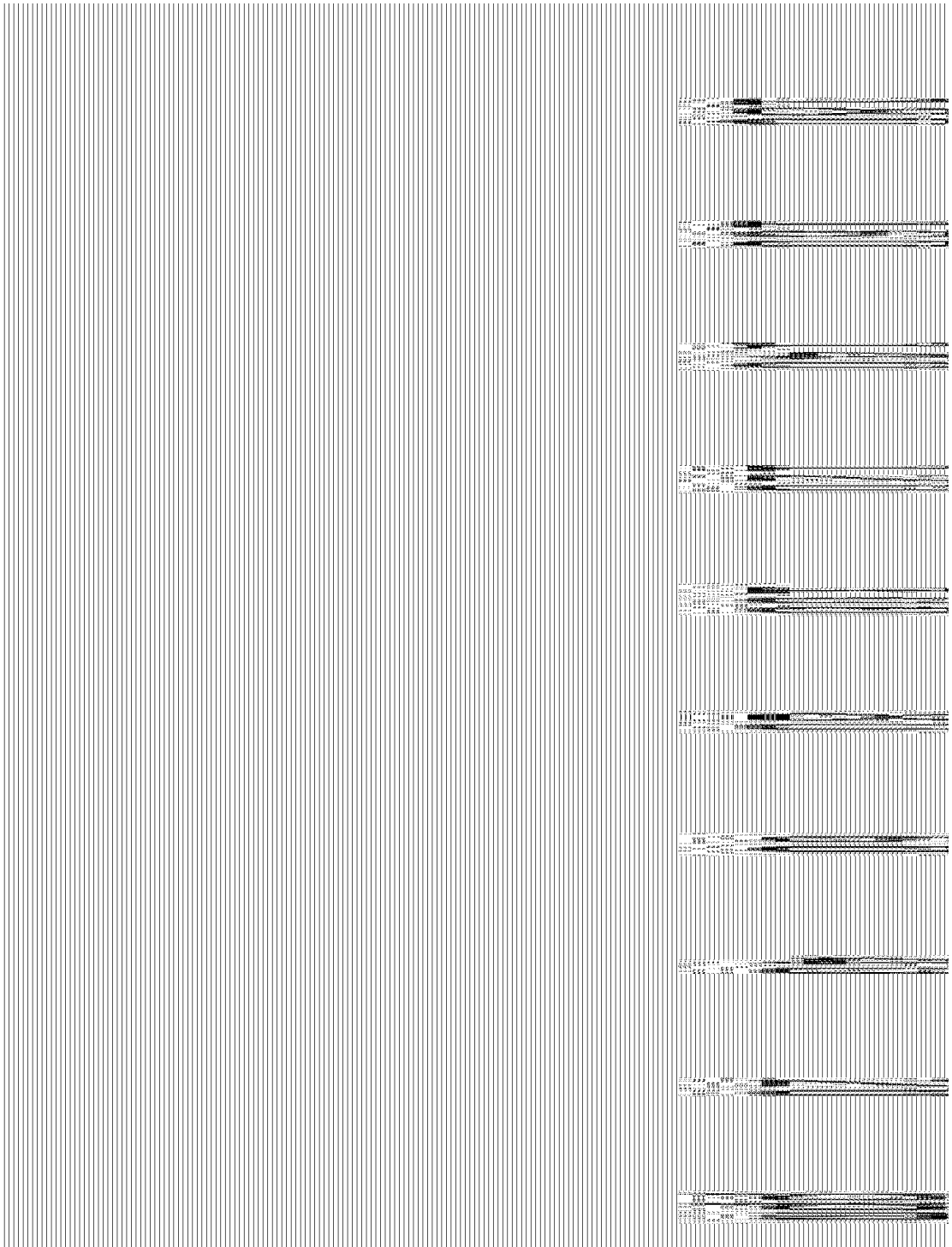


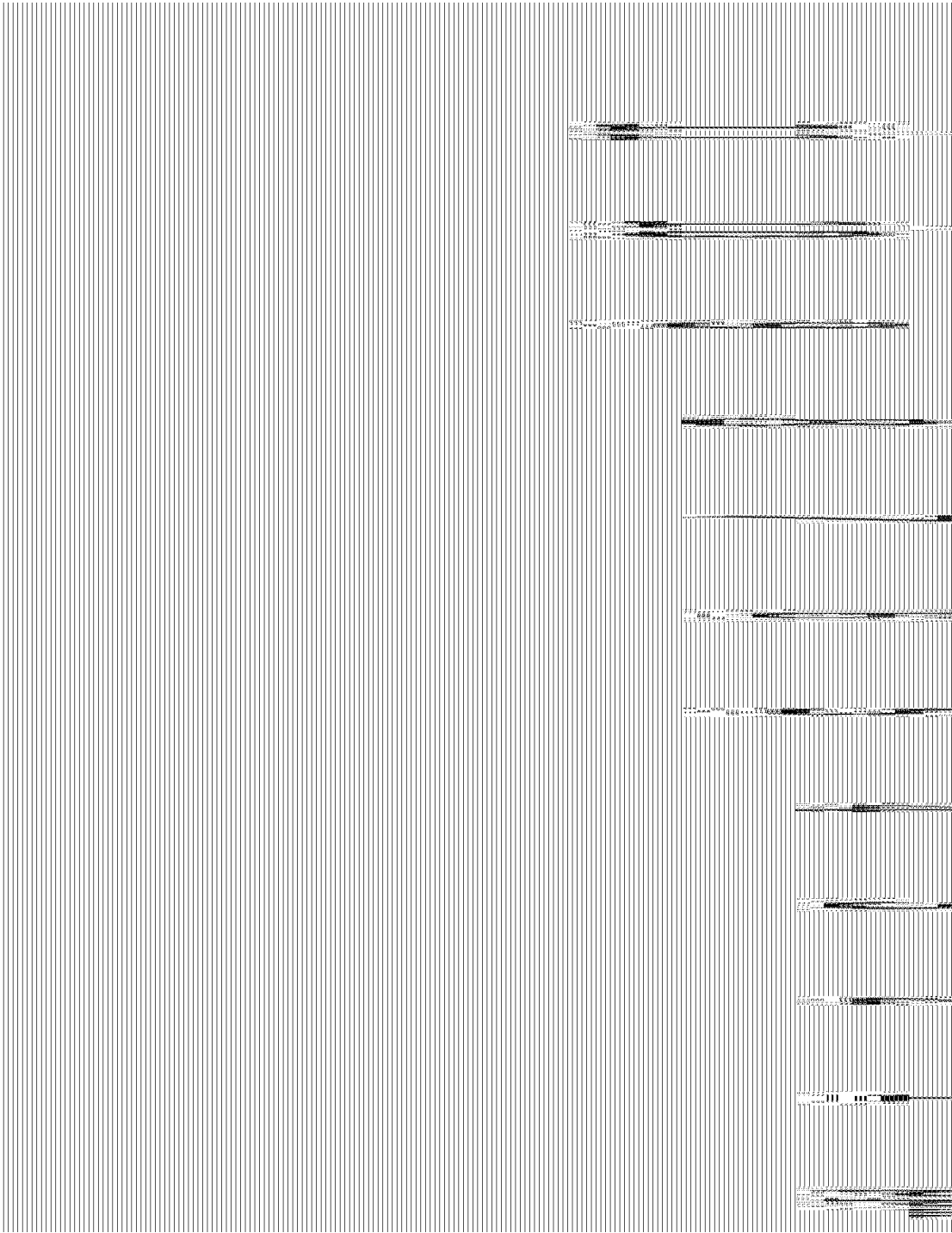


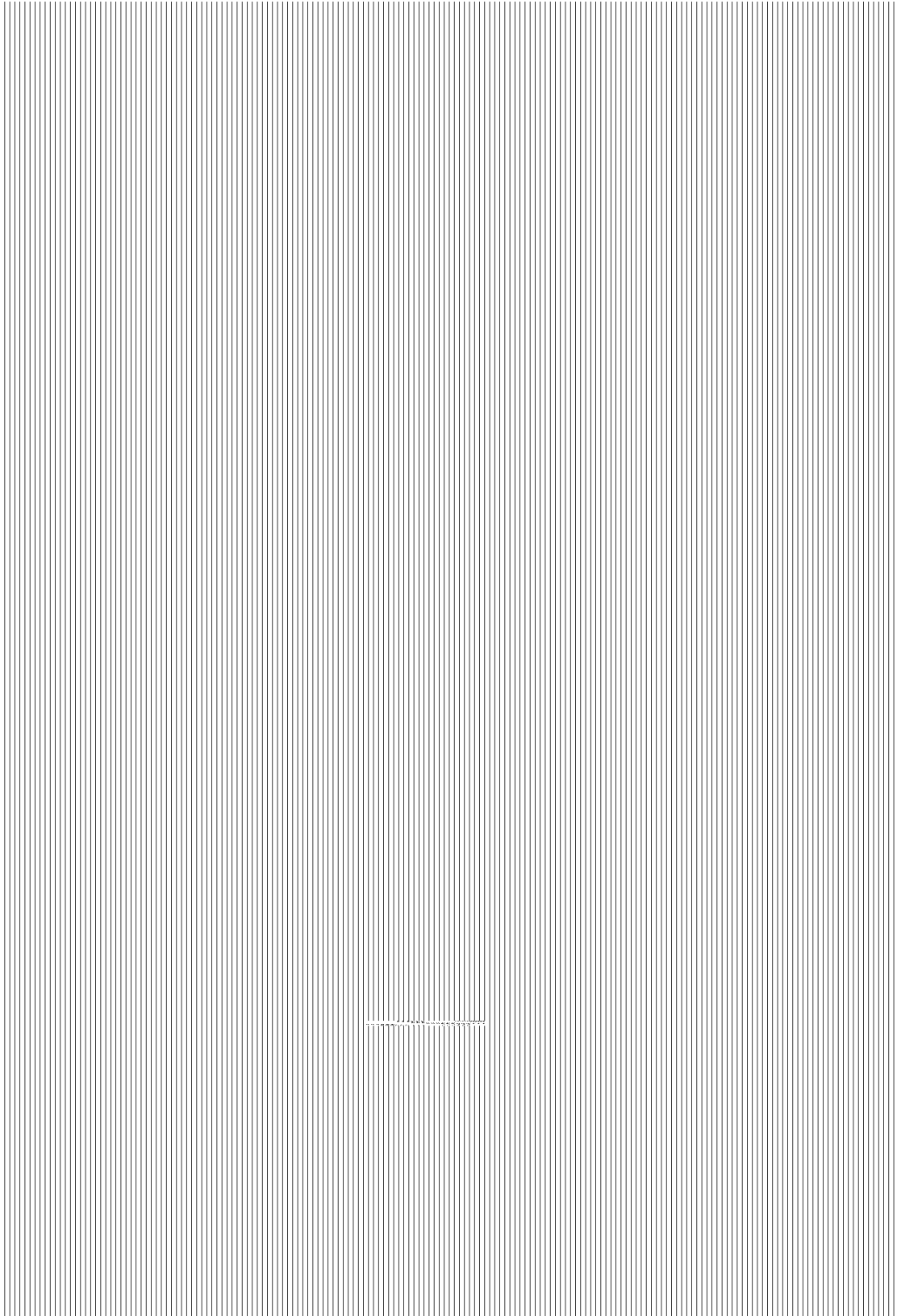




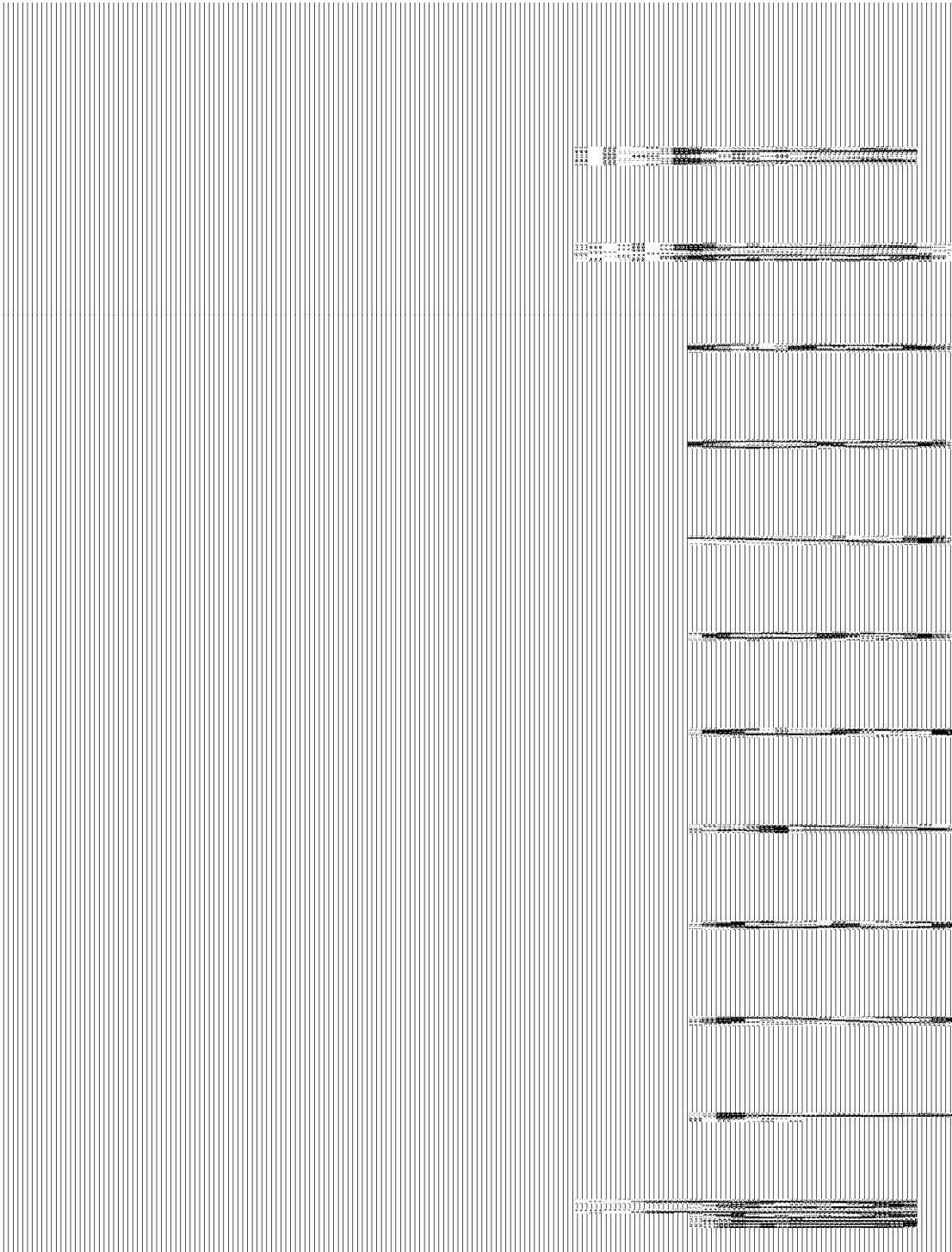


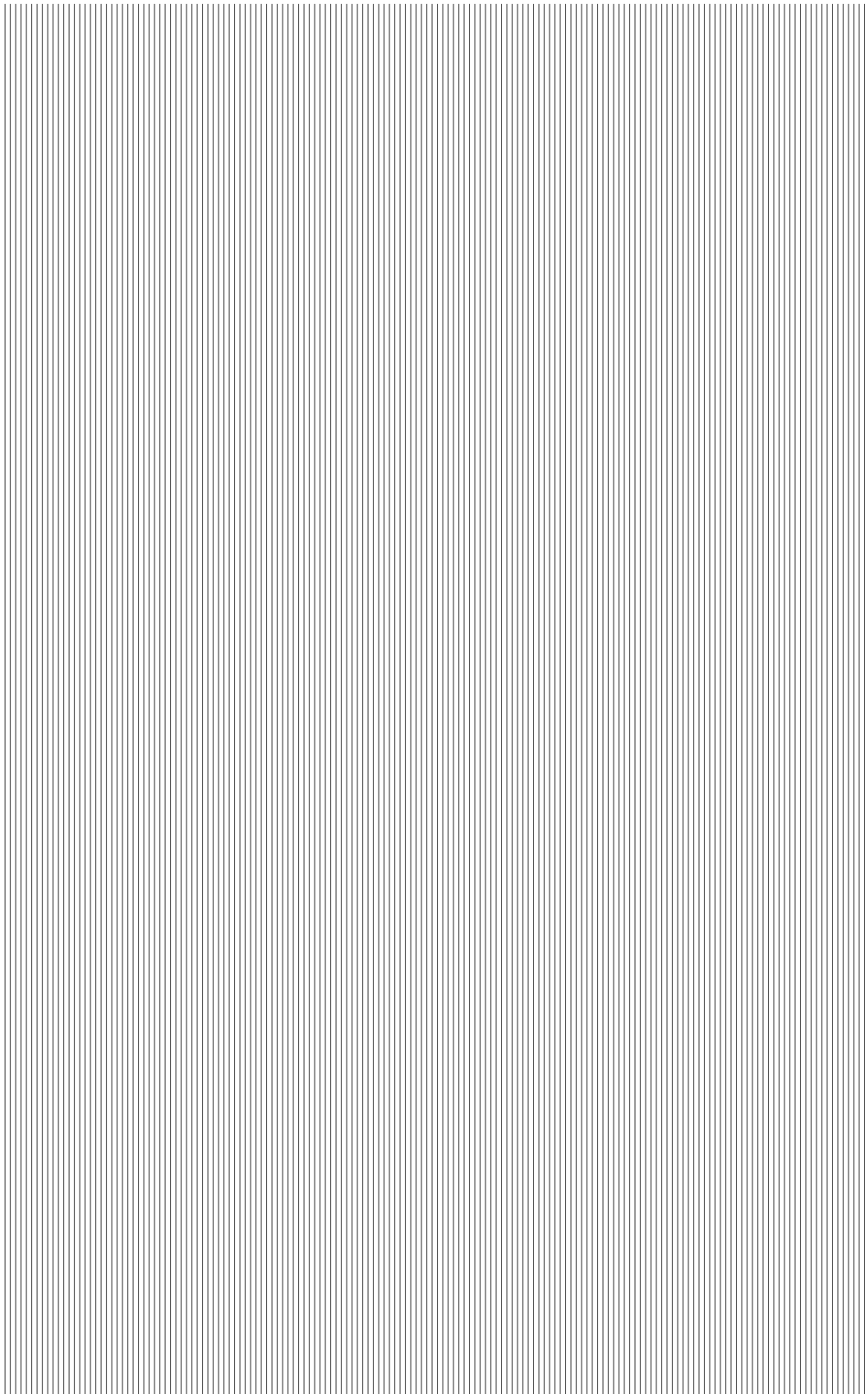


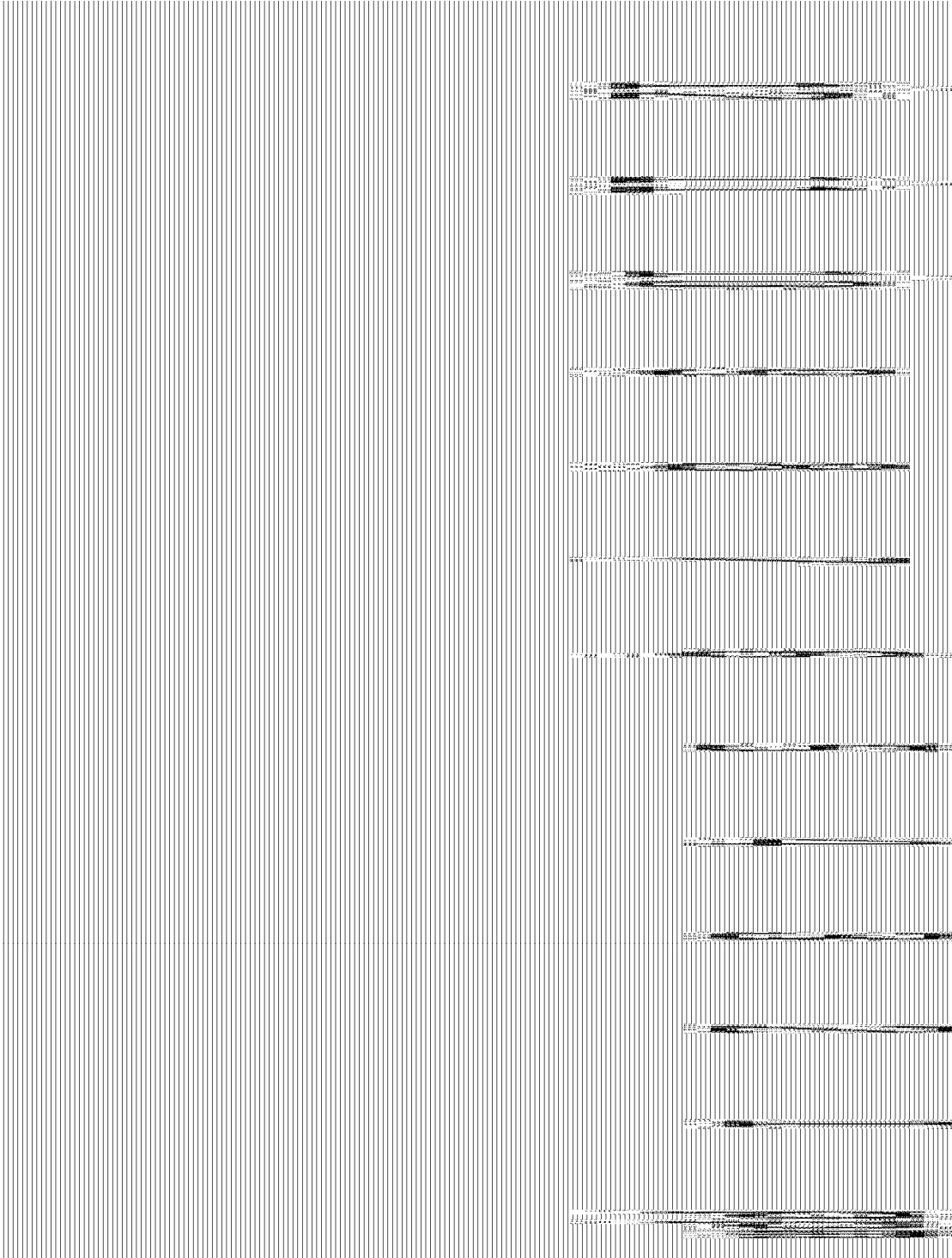


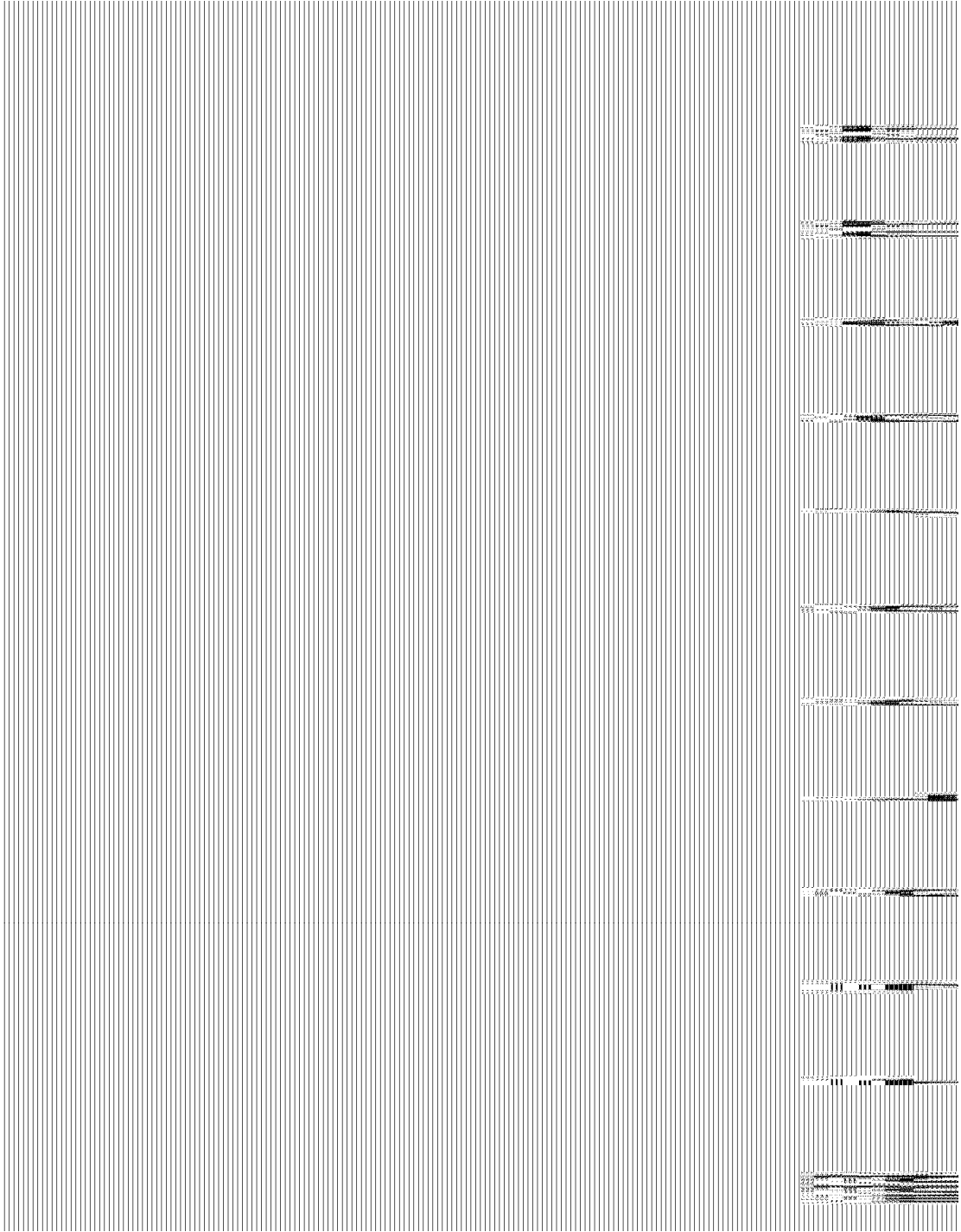


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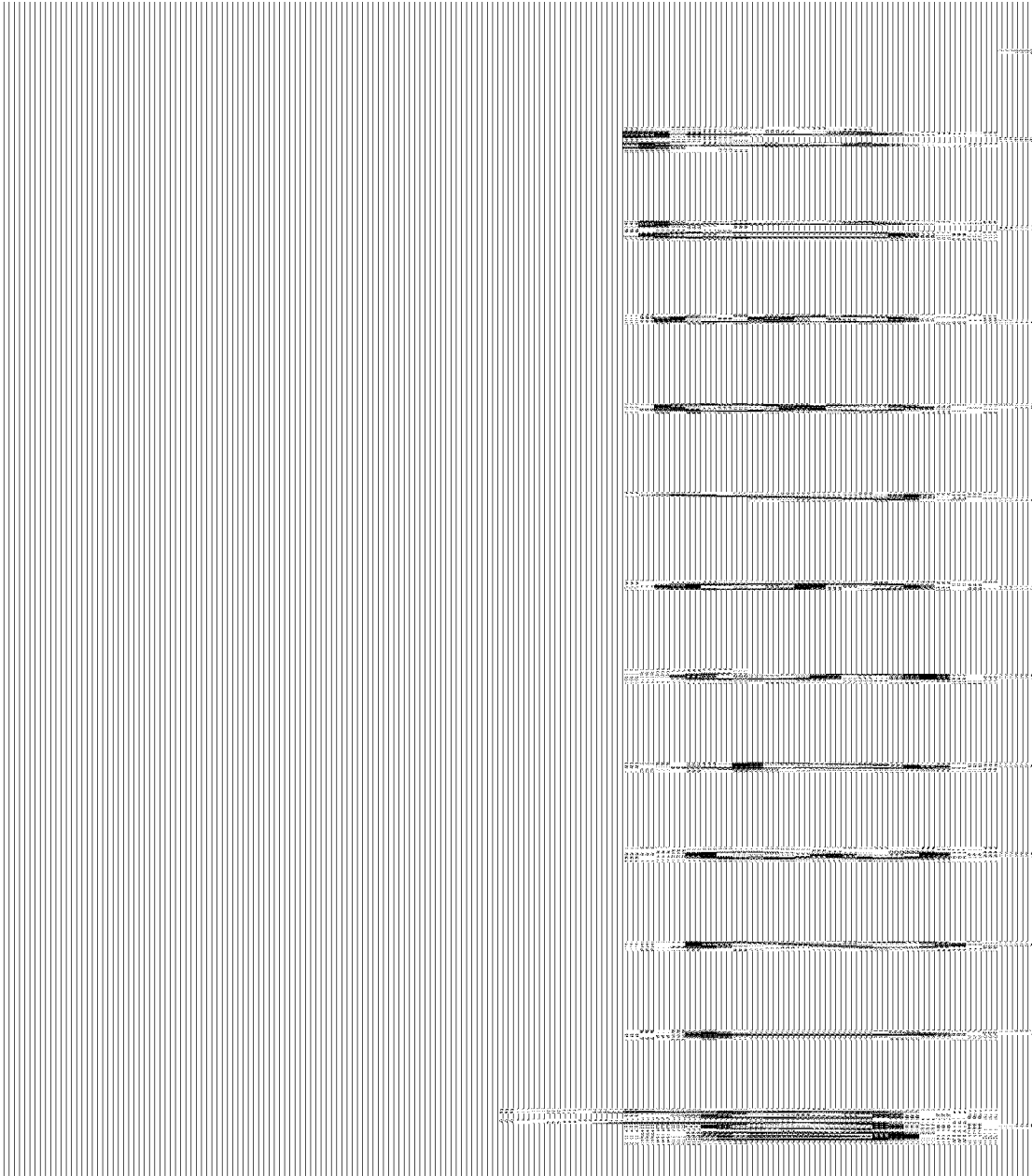


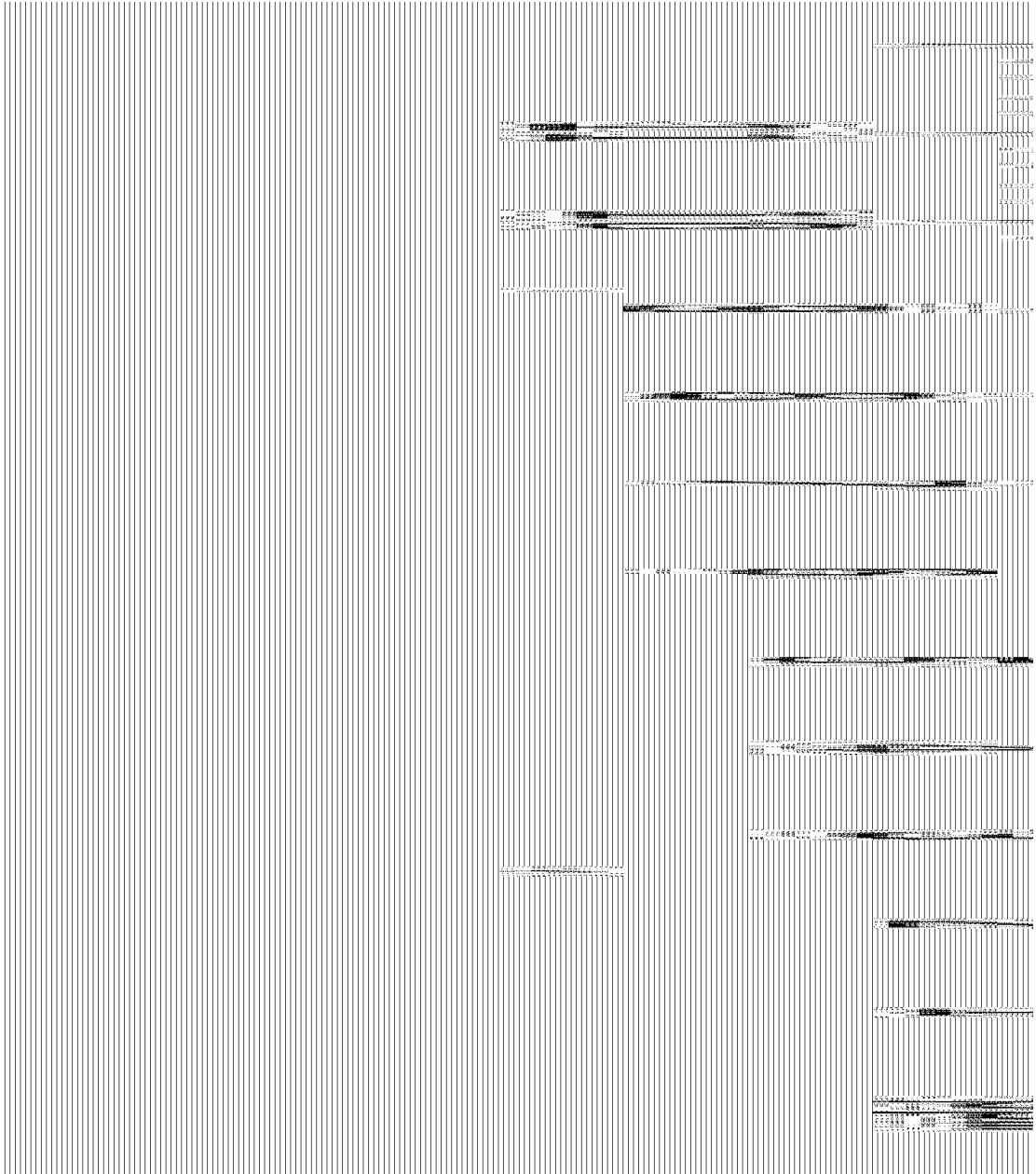


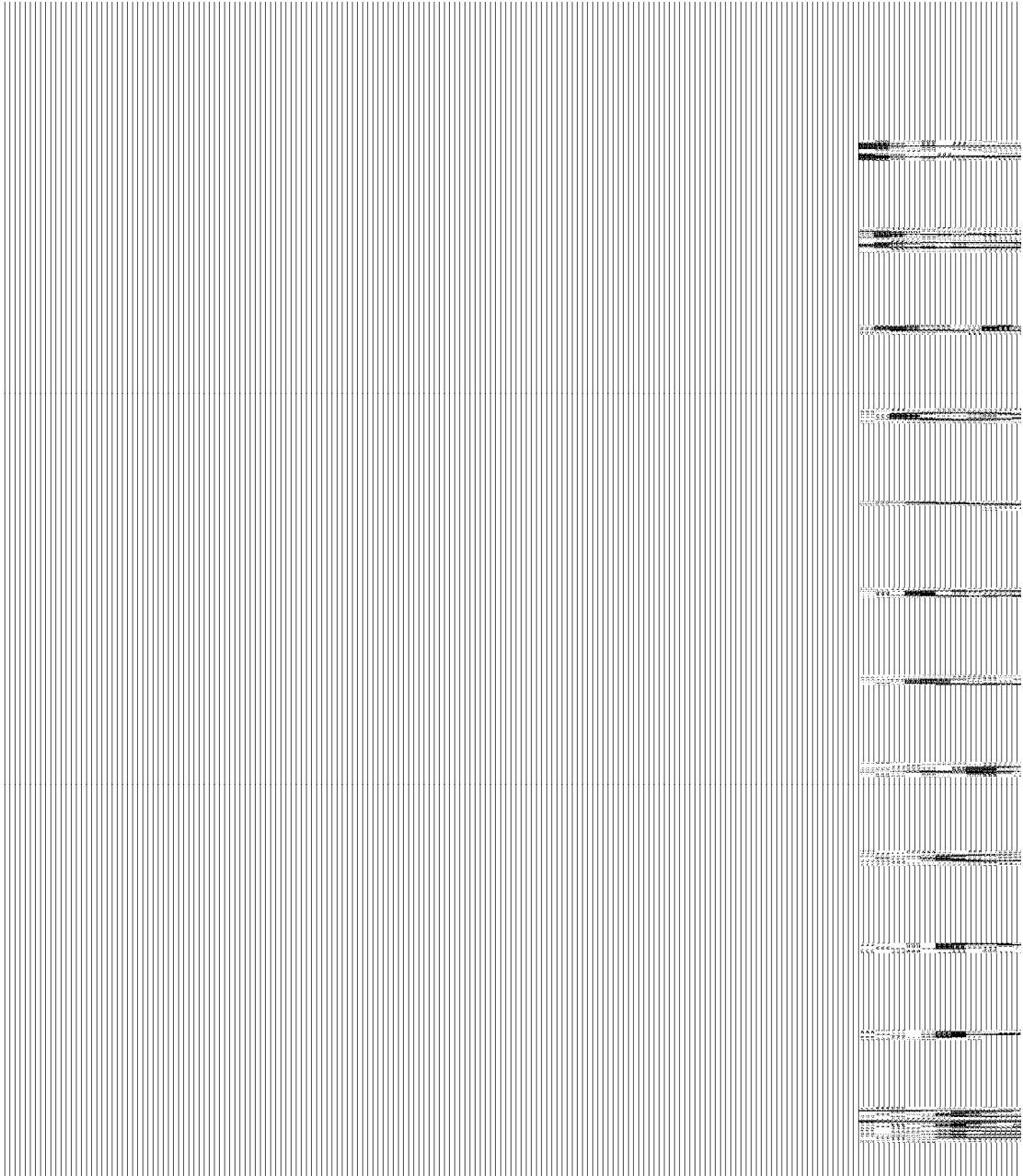


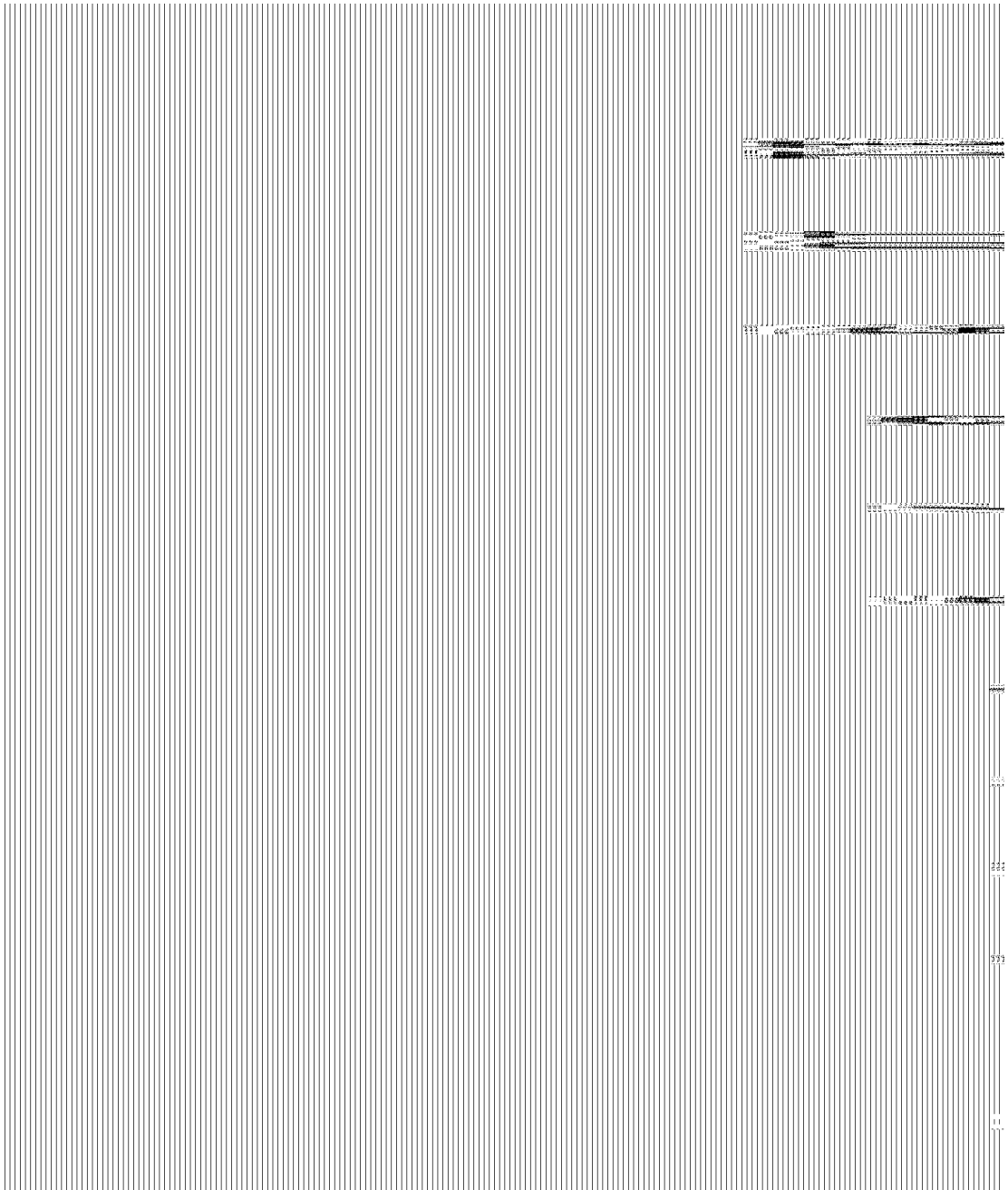






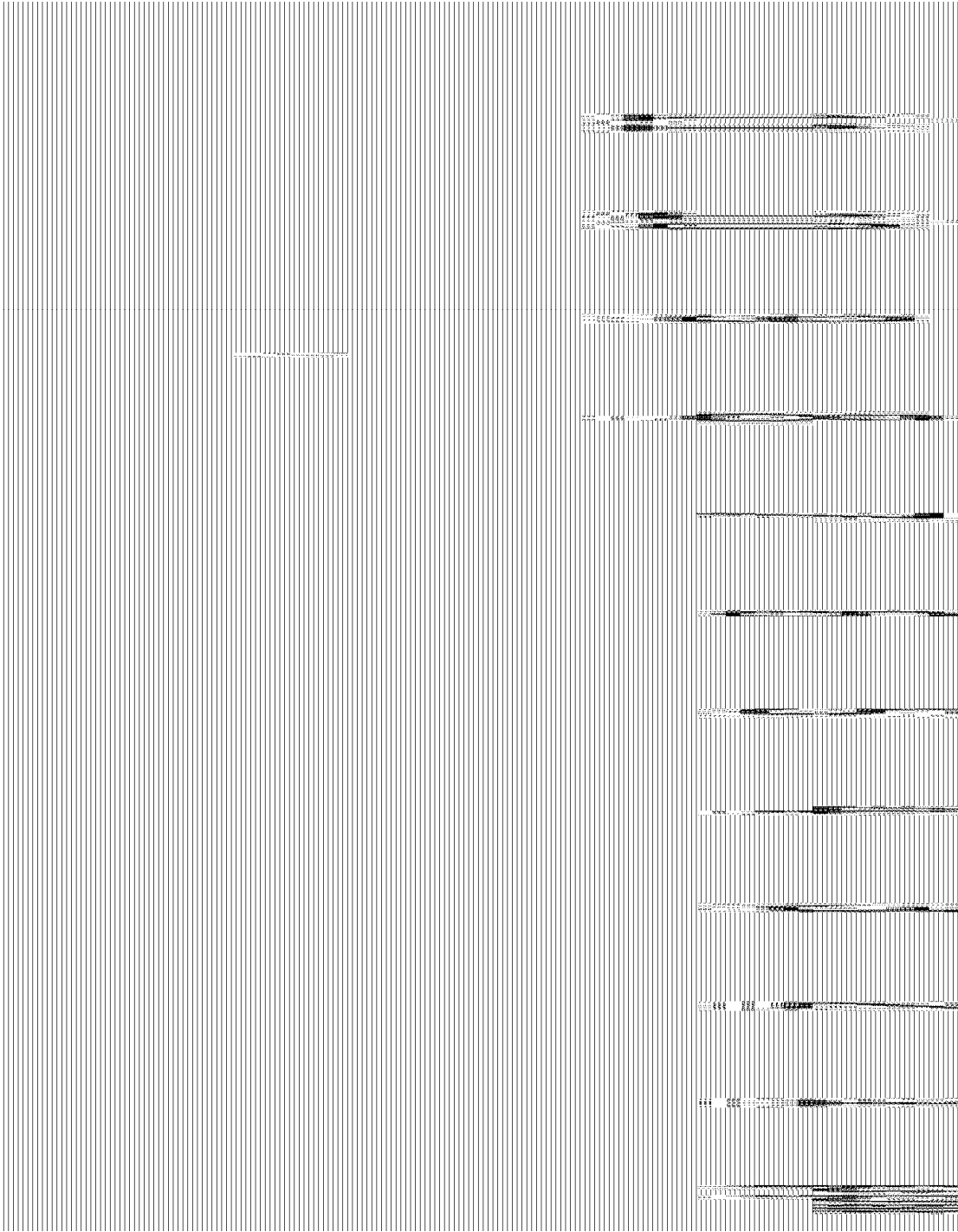


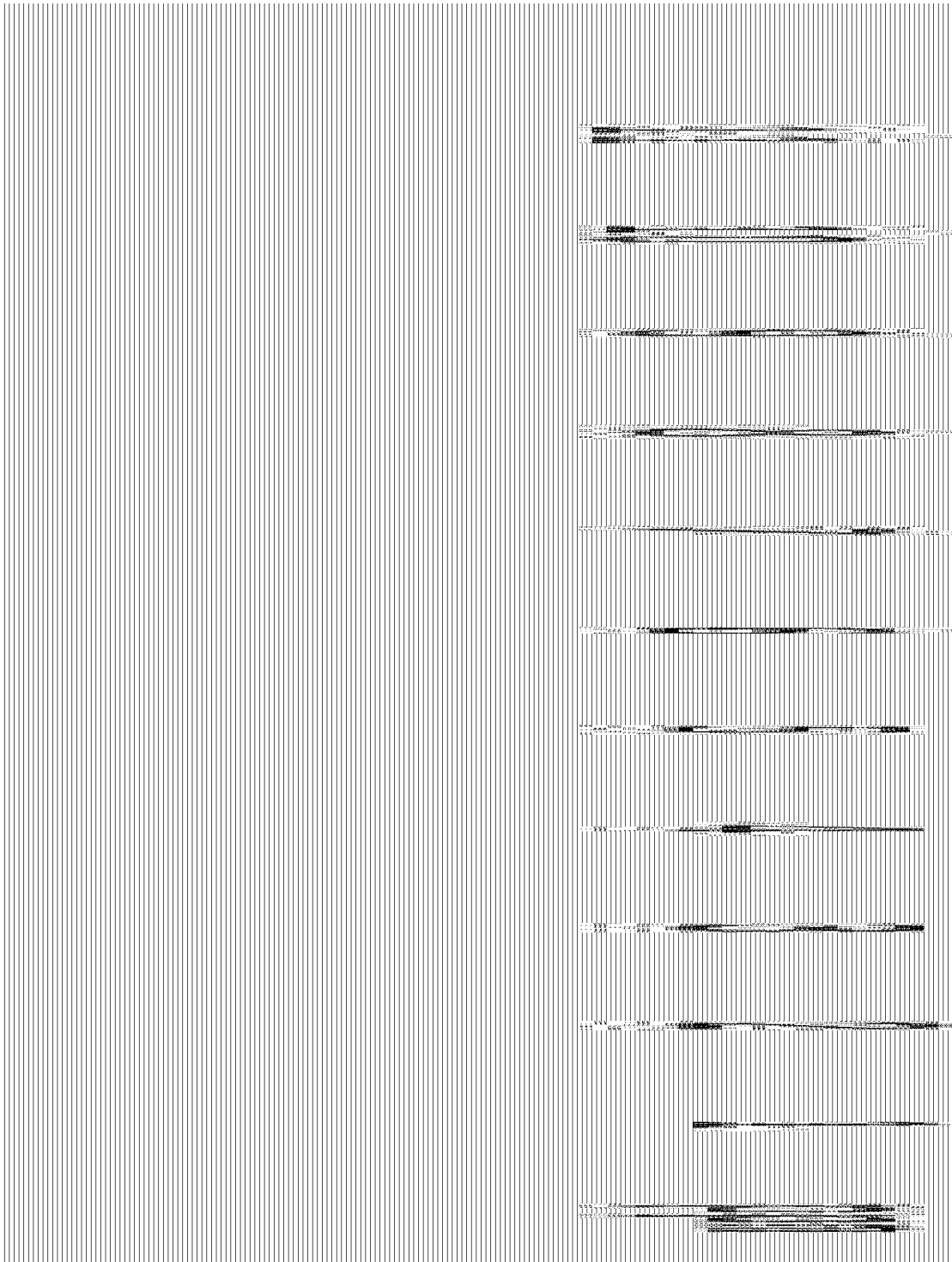




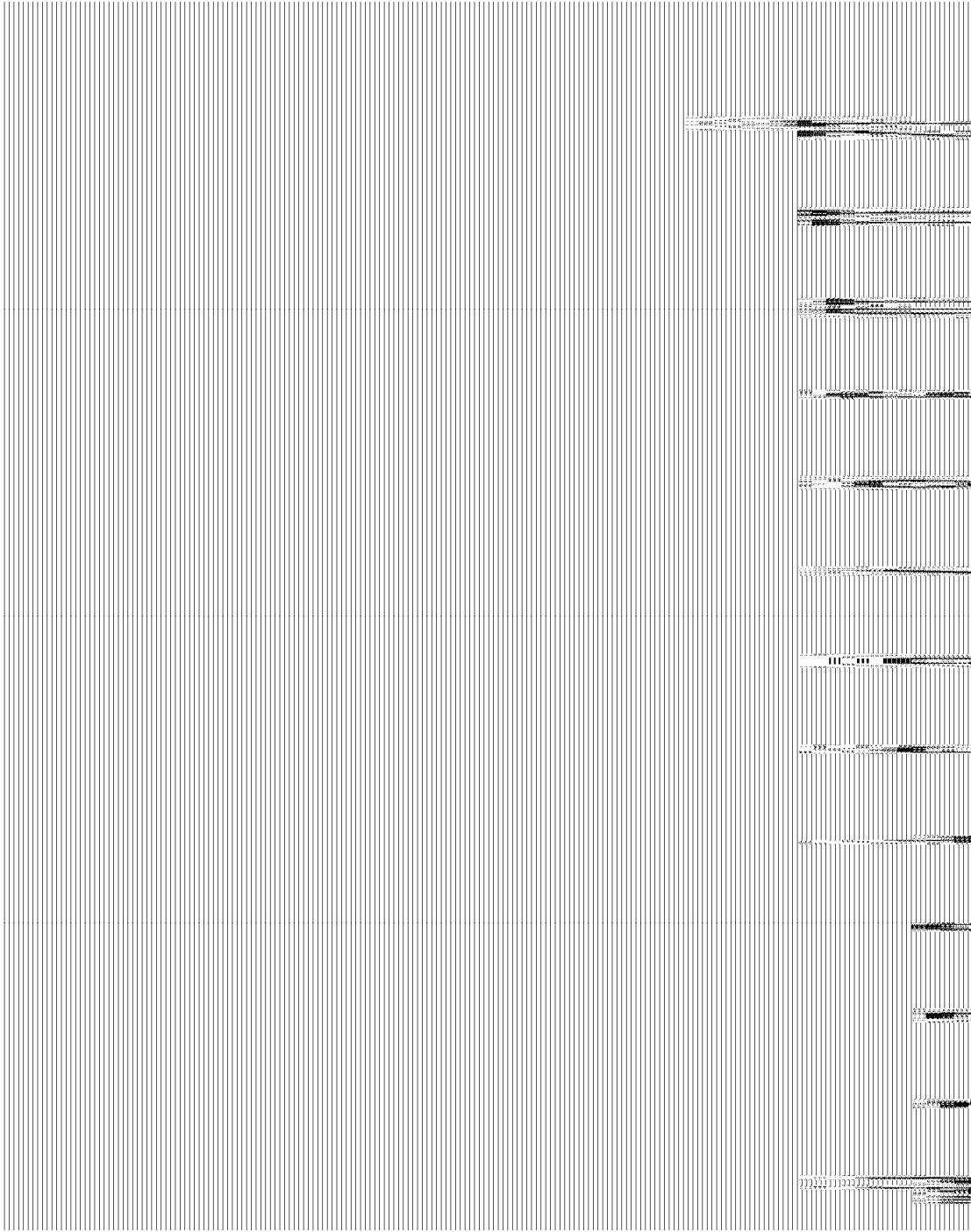


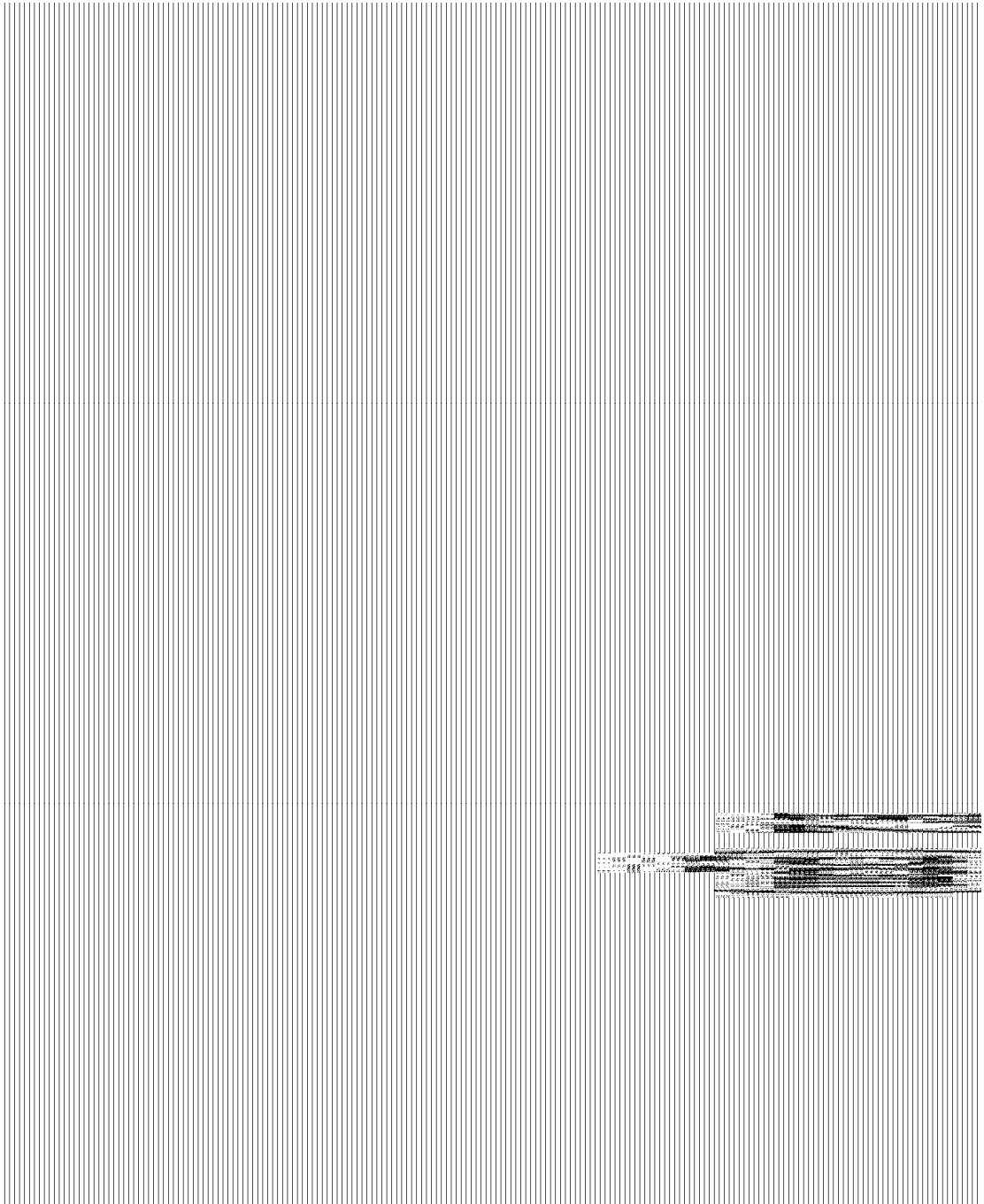


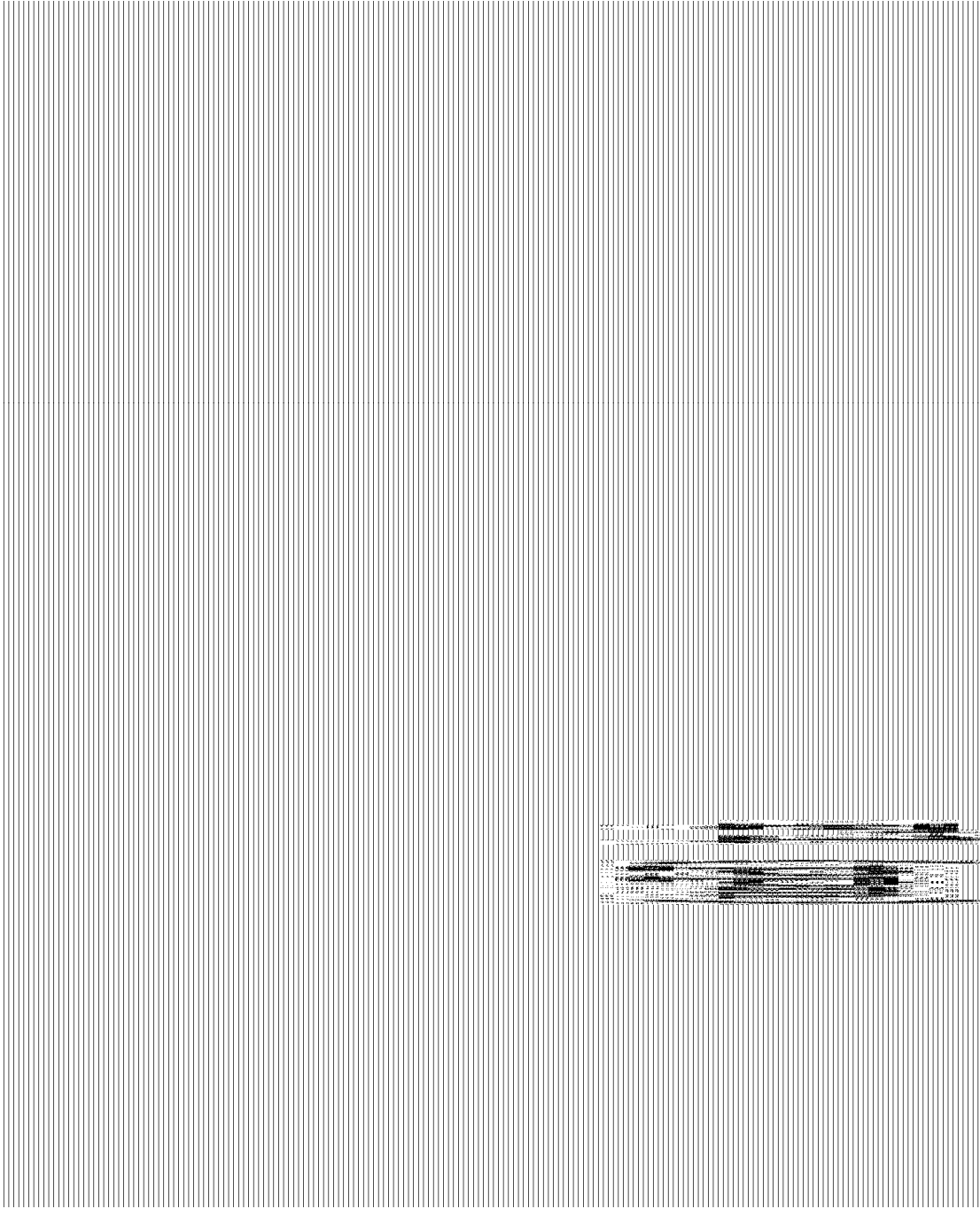


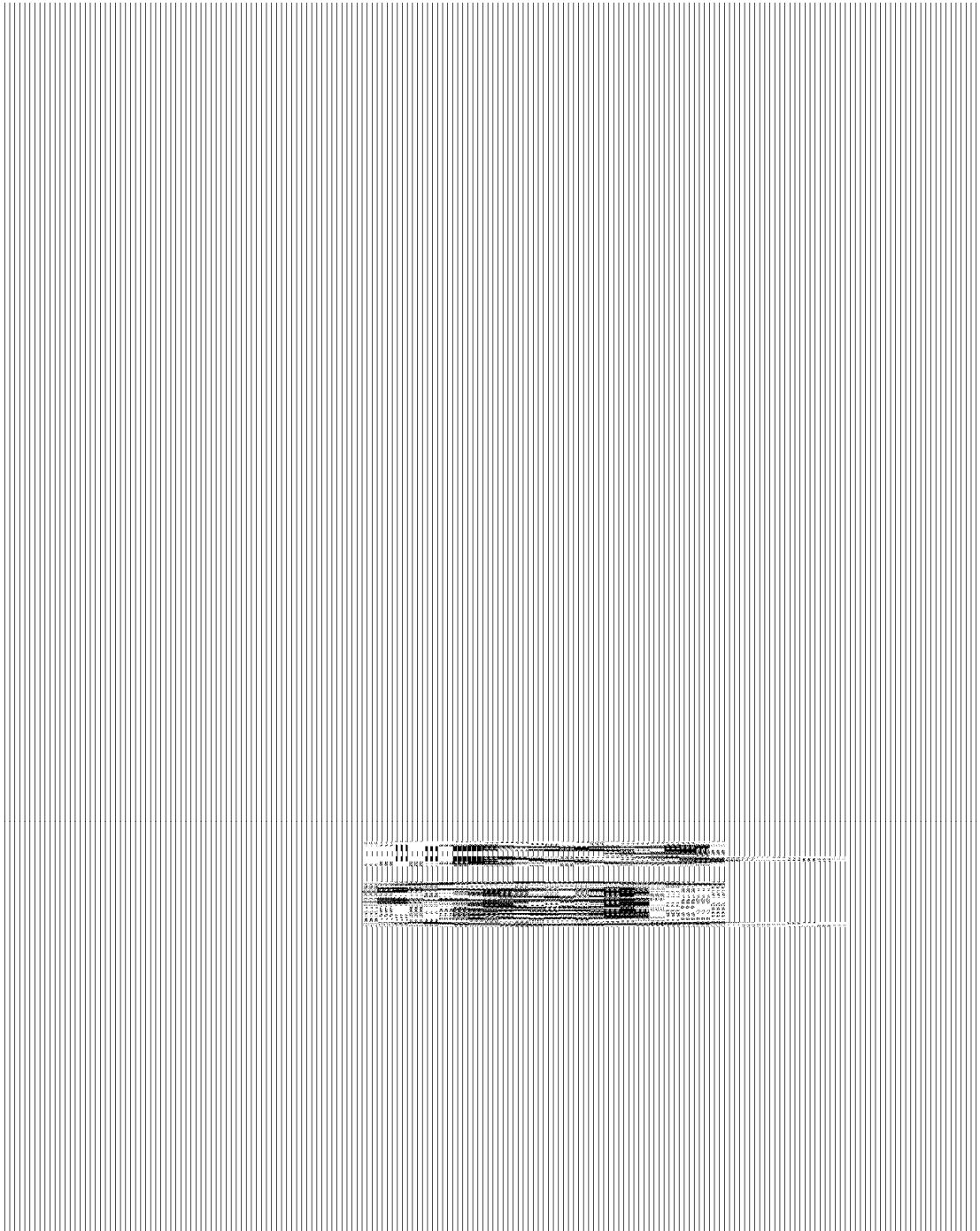


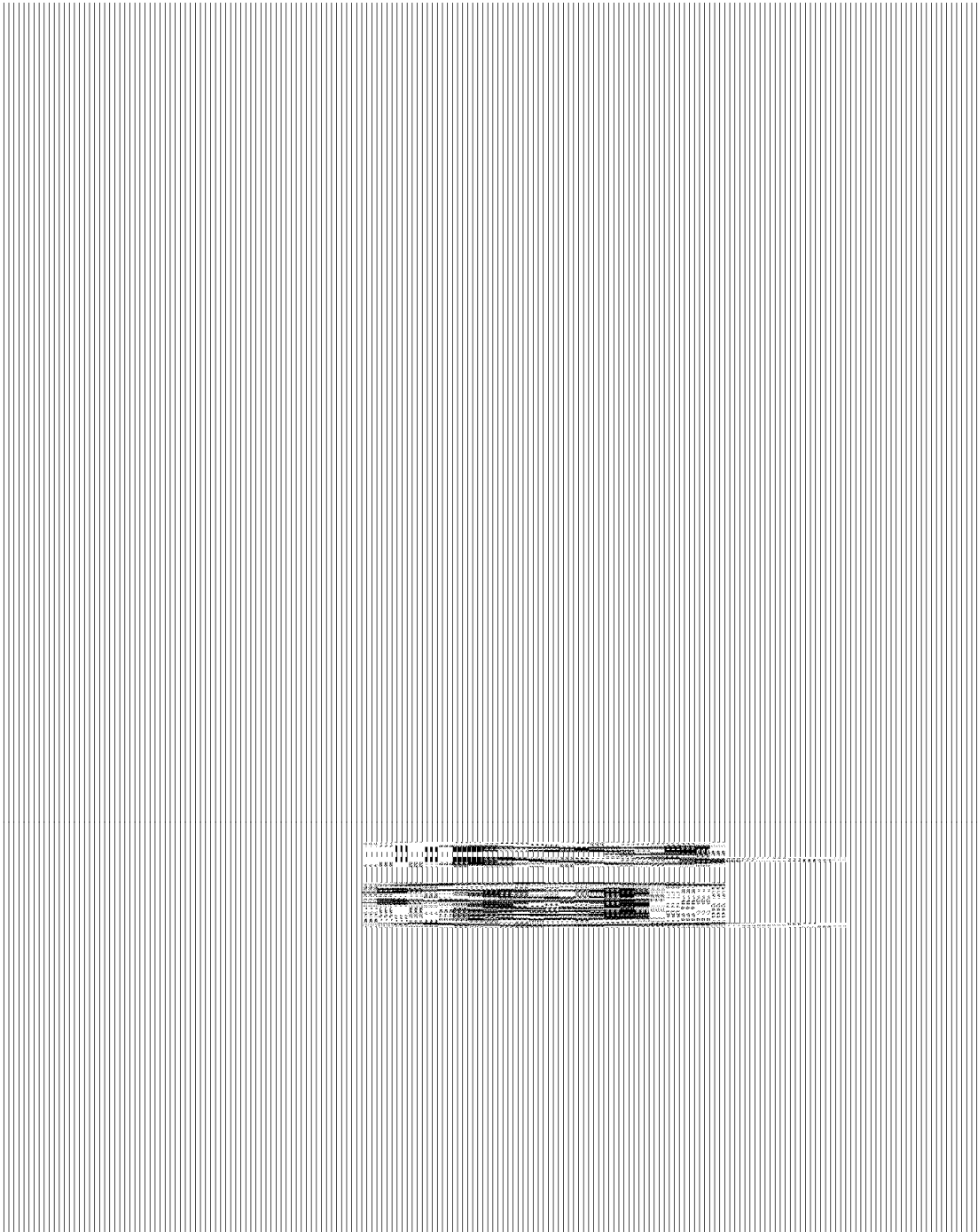


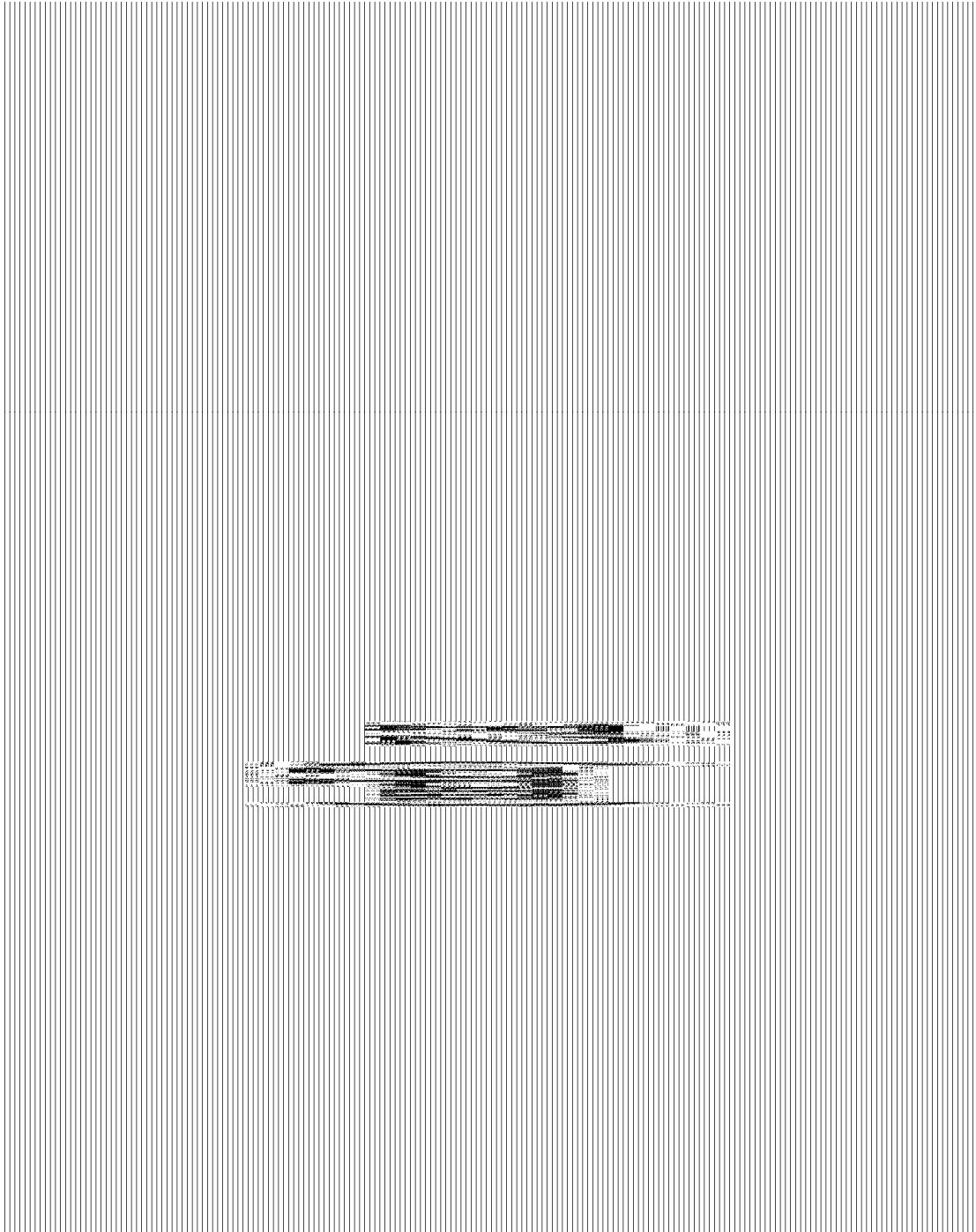










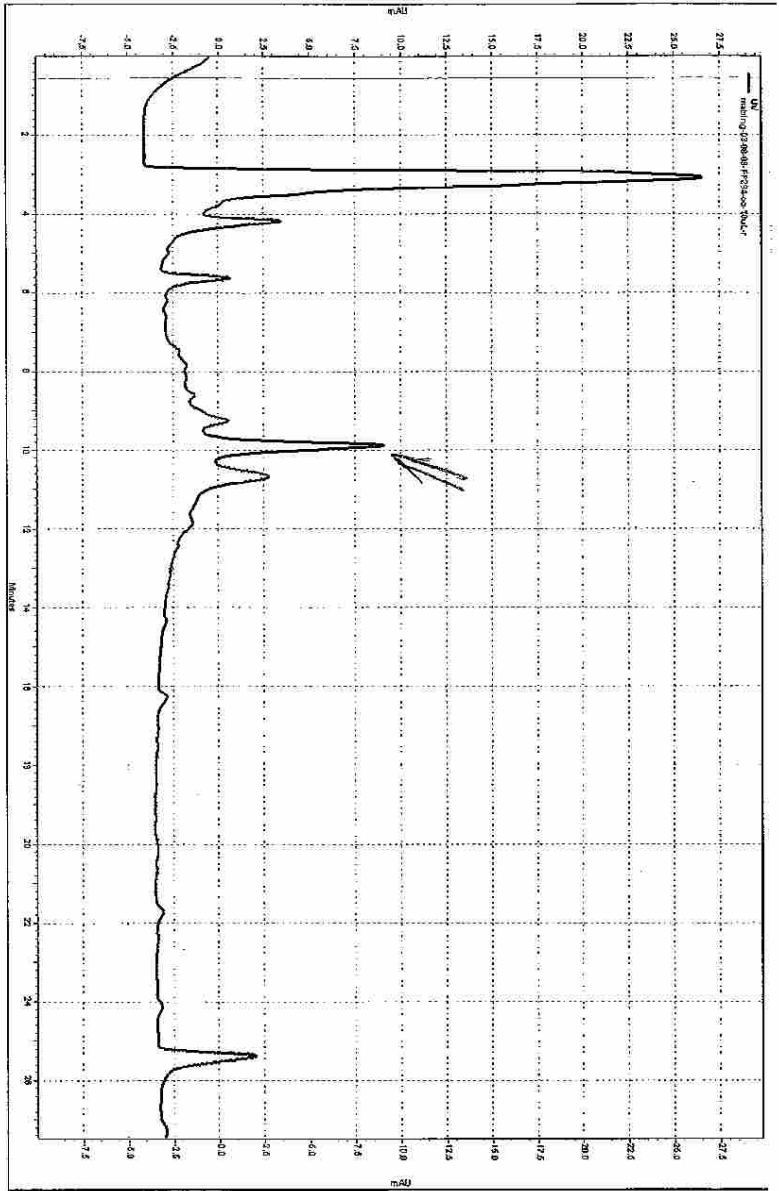




HPLC conditions:

C<sub>18</sub> monomeric reverse phase column

gradient elution 15% → 50% CH<sub>3</sub>CN/0.1% TFA in H<sub>2</sub>O, 1 mL/min



Coinjection of natural Celogentin C and synthesized Celogentin C