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Targeting Complex Cyclic Peptides for Synthesis: The Celogentin and Theonellamide Families

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Targeting Complex Cyclic Peptides for Synthesis: The Celogentin and Theonellamide Families

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Master of Science

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ABSTRACT

TARGETING COMPLEX CYCLIC PEPTIDES FOR SYNTHESIS:

THE CELOGENTIN AND THEONELLAMIDE FAMILIES

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Celogentin C and theonellamide F are a class of natural products that have potential antimitotic behavior. They both contain interesting bicyclic structures with unusual linkages within a central moiety. Celogentin C's highly functionalized tryptophan moiety has two unusual linkages, a β-substituted Leu connection to the C6 of the indole structure that makes up the left-hand ring, and a τ-*N* connection of the imidazole to the C2 of the indole constructing the right-hand ring. This right-hand ring connection was solved via a novel oxidative coupling procedure developed in our group and the left-hand ring was initially constructed via a radical conjugated addition of an isopropyl group. Due to stereoselective concerns, our group explored hydrogen bond donors as potential catalyst candidates. Unfortunately, there were challenges in limiting the background reaction and obtaining reproducible results. We then designed an alternative route to solve this left-hand ring connection which would have utilized MacMillan asymmetric hydrogenation and α-chlorination procedures. Further work towards a second generation synthesis of the β-Leu-(C6)Trp connection was halted with the publication of two formal syntheses of celogentin C.

Theonellamide F contains a τ-L-histidino-D-alanine (τ-HAL) bridging unit that separates the left-and right-hand rings. Previous efforts in the synthesis of this natural product were hindered due to an inefficient regioselective synthesis of τ-HAL. Our proposed synthesis of τ-HAL began with commercially available L- and D-Ser methyl esters which were then chemically transformed and coupled to one another to create a bis-amino subunit. Further preparations afforded us with an important cyclic intermediate which should readily lead to the first regioselective synthesis of a τ-HAL.

Keywords: cyclic peptide, celogentin, theonellamide, τ-HAL

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List of Abbreviations

AAA	α-aminoadipic acid
Aboa	(3*S*,4*S*,5*E*,7*E*)-3-amino-8-(4-bromophenyl)-4-hydroxy-6-methyl-5,7-octadienoic acid
AcOH	acetic acid
ADME	absorption distribution metabolism excretion
Ahad	(2*S*,4*R*)-2-amino-4-hydroxyadipic acid
Ala	alanine
allo-Thr	*allo*-threonine
Apoa	(3*S*,4*S*,5*E*,7*E*)-3-amino-4-hydroxy-6-methyl-8-phenyl-5,7-octadienoic acid
Aq.	aqueous
Arg	arginine
Asn	asparagine
β-Ala	β-alanine
BAr_4F_{24}	tetrakis[bis(trifluoromethyl)]boron
β-D-Ara	β-D-arabinose
β-D-Gal	β-D-galactose
β-L-Ara	β-L-arabinose
BMPA	β-metyl-*p*-bromophenylalanine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
β-OHAsn	(2*S*,3*R*)-3-hydroxyasparagine

BPA	*p*-bromophenylalanine
Camphor	(*S*)-(+)-10-camphorsulfonate
Cbz	benzyloxycarbonyl
DBFOX	(*R*,*R*)-4,6-dibenzylfurandiyl-2,2'-bis(4-phenyloxazoline); 4,6-bis((*R*)-4-(naphthalen-2-yl)-4,5-dihydrooxazol-2-yl); or (*R*,*R*)-4,6-dibenzofurandiyl-2,2'-bis(4-phenyloxazoline) dibenzo[*b*,*d*]furan.
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
EDCI·HCl	1-ethyl-3(3'-dimethylaminopropyl)carbodiimide-HCl
g	gram
HBTU	*O*-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
His	histidine
HOBt	1-Hydroxybenzotriazole hydrate
Hz	hertz
Iser	isoserine
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
Leu	leucine
M	moles/liter
mg	milligram(s)
mL	milliliter(s)
μL	microliter(s)
mol	mole(s)

MS	mass spectrometry
NCS	*N*-chlorosuccinimide
NMM	*N*-methyl morpholine
p	para
Pbf	pentamethyldihydrobenzofuran sulfonyl
Phth	phthaloyl
ppm	part per million
Pro	proline
PTC	phase-transfer catalyst
sat.	saturated
RCA	radical conjugate addition
rt.	room temperature
Ser	serine
TBAF	tetra-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TES	triethylsilyl
TFA	trifluoroacetic acid
TLC	thin layer chromatography
Trp	tryptophan
Val	valine

1. Introduction

1.1 Cyclic Peptides

Cyclic peptides are a unique class of compounds that show promise as lead structures in drug development. They typically are more selective towards protein pockets/receptors (a common medicinal target) than are non-peptide small molecules (which can intercalate with DNA) and linear peptides.[1] The interacting forces observed in drug-receptor complexation[2] are increased for cyclic peptides due to amino acid pairing (such as Arg-Cys hydrogen bonding exchange) and rigidity (conformational restraint) of the cyclic structure, which in turn promotes potency and longevity within the receptor.[3] Other benefits of cyclic peptides include increased bioavailability and metabolic stability.[1] One notable concern of cyclization is the increase in lipophilicity which leads to a higher excretion rate.[1] Designing a synthetic route that allows for direct modifications can readily solve this ADME (absorption distribution metabolism excretion) issue.

Natural sources of cyclic peptides include animals, plants, sponges, and microorganisms.[4] In general, these amino-acid-based structures are believed to be metabolites of larger proteins.[5-7] There are an infinite number of possible cyclic peptide structures, and the abundance of each one varies from organism to organism. Therefore, isolation and structural elucidation is both challenging and time-consuming, but is important due to promising bioactivity such as antimicrobial, antiviral, antimitotic, and protein (i.e., hormone) inhibition behavior.[6]

Octreotide (**1**, Figure 1), developed by Novartis and initially marketed in 1988, is a somatostatin (**2**) analog that inhibits a variety of hormones secreted in the body.[1] Somatostatin was first isolated in 1973 from an endocrine gland by Brazeau and co-workers.[8-10] Due to the impracticality of harvesting these organs to isolate **2** in therapeutic quantities, the synthesis of

this sulfide bridged cyclic peptide was carried out.[11] Many structural modifications were made to elucidate structural activity relationships[12-15] (SAR), which in turn provided a stronger understanding of drug-receptor interaction for hormone proteins, thereby affording further insight into the mechanism of hormonal disorders.[3,10]

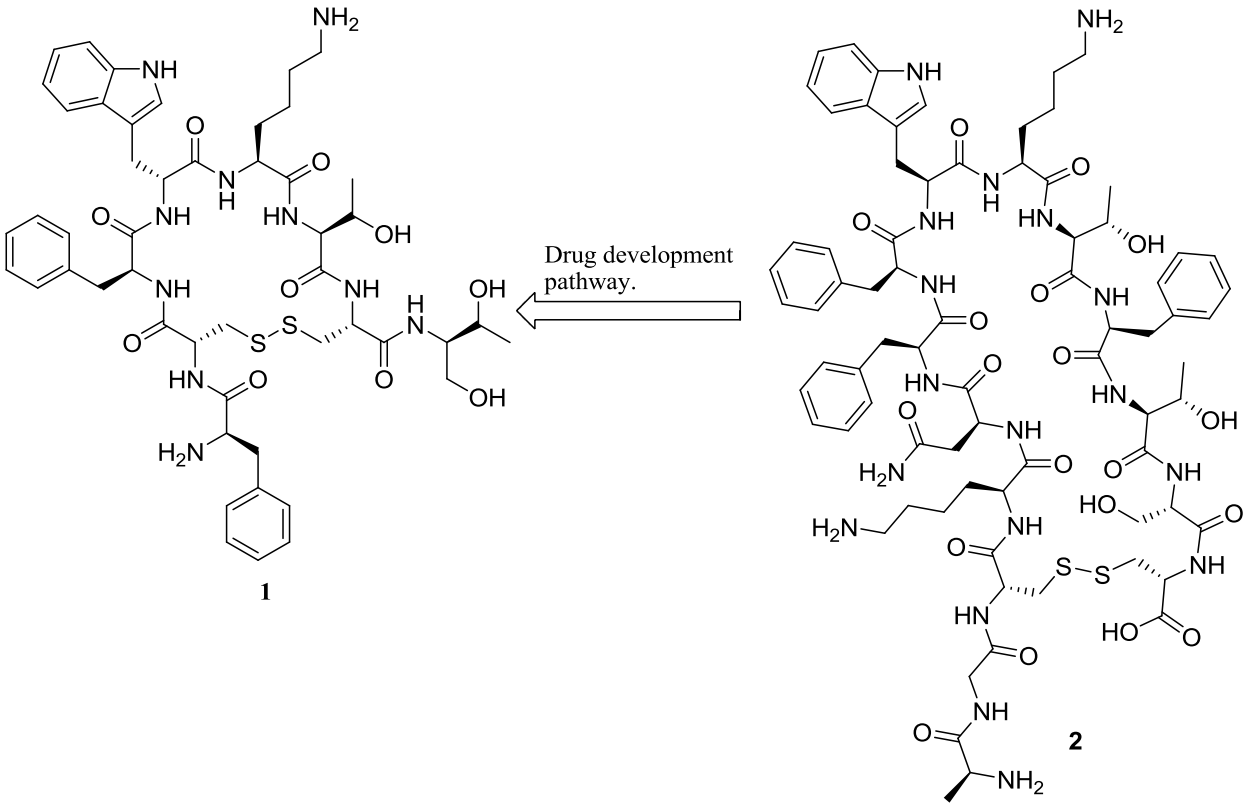
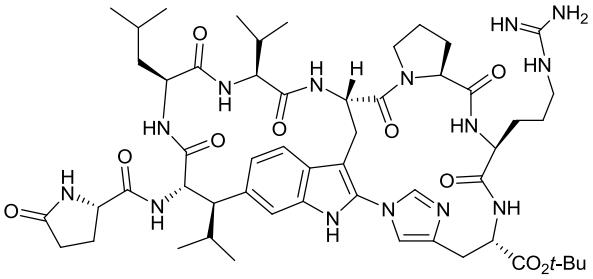


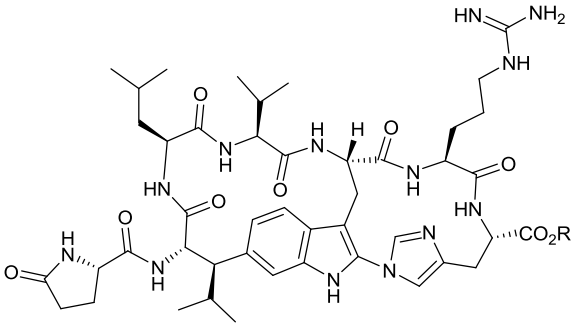
Figure 1. Octreotide (**1**) and somatostatin (**2**).

This linear pathway towards drug development (isolation, characterization, bioactivity screening, synthesis, and SAR analysis) described for **1** is one of the most common and accepted approaches towards lead structure discovery. I will attempt to illustrate the importance of this lead structure drug development approach by describing my lab's efforts in the synthesis of complex bicyclic peptides, namely celogentin C (**5**, Figure 2) and the central moiety of theonellamide F (**33**, Figure 5).

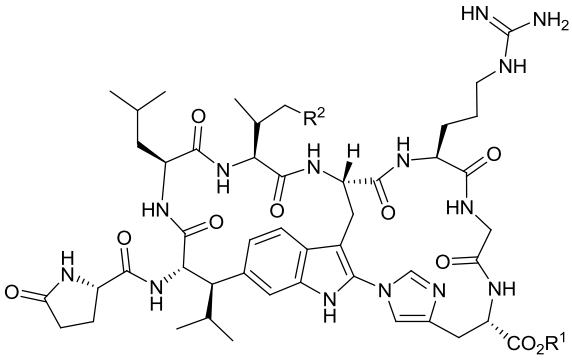
Celosia argentea



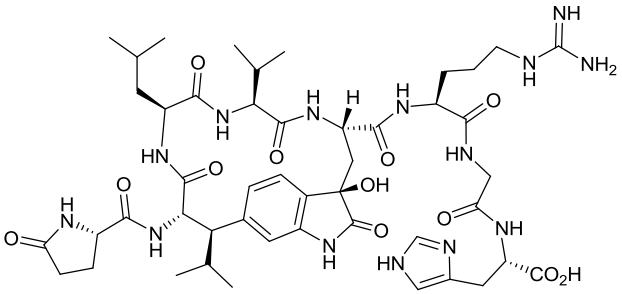
Celogentin C (**5**)



Celogentin A (**3**): R = H
Celogentin B (**4**): R = His
Celogentin D (**6**): R = His–Lys



Celogentin E (**7**): R^1 = Asp, R^2 = H
Celogentin F (**8**): R^1 = Arg, R^2 = H
Celogentin G (**9**): R^1 = H, R^2 = Me
Celogentin H (**10**): R^1 = Asp, R^2 = Me
Celogentin J (**11**): R^1 = Arg, R^2 = Me
Moroidin (**13**): R^1 = R^2 = H



Celogentin K (**12**)

Figure 2. *Celosia argentea*, celogentins A–H, J–K, and moroidin.

1.2 Celogentin C

Isolation

Moroidin (**13**) was initially extracted from the leaves and leaf stalks of the bush *Laportea moroides* (Urticaceae) by Williams and coworkers in 1986.[16,17] Kobayashi's group discovered

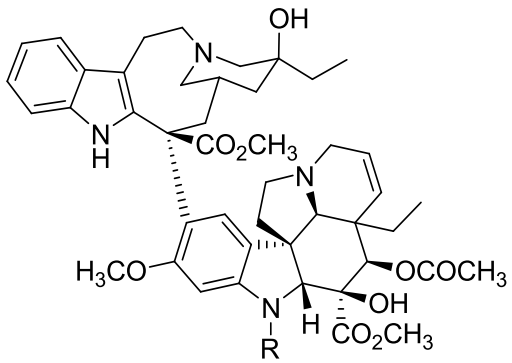
this bicyclic peptide in the seeds of *Celosia argentea* (Amaranthaceae) and published the results in 2000.[18] Further purification of the extracts of this plumed cockscomb produced similar macrocycles called celogentin A (**3**), B (**4**), C (**5**), D (**6**), E (**7**), F (**8**), G (**9**), H (**10**), J (**11**), and K (**12**).[19-21] This moroidin family of natural products, referring to the common structural features, were isolated in trace quantities (Table 1, 2×10^{-5} to 2×10^{-2}% by weight) making harvesting an impractical means of production.

Table 1. Isolation yield and cytotoxicity (microtubulin inhibition) values for the moroidin family.

Compound	Isolation Yield (% by wt.)	IC_{50} Value (μM)
Celogentin A (**3**)	2×10^{-4}	20
Celogentin B (**4**)	1×10^{-4}	30
Celogentin C (**5**)	1×10^{-3}	0.8
Celogentin D (**6**)	4×10^{-5}	20
Celogentin E (**7**)	8×10^{-4}	2.5
Celogentin F (**8**)	1×10^{-3}	3.0
Celogentin G (**9**)	7×10^{-4}	4.0
Celogentin H (**10**)	4×10^{-5}	2.0
Celogentin J (**11**)	3×10^{-5}	3.0
Celogentin K (**12**)	2×10^{-5}	>100
Moroidin (**13**)	2×10^{-2}	3.0

Bioactivity

Microtubules are made up of two globular proteins, α- and β-tubulin, that are intimately involved with mitosis (cell division), and interference with this process leads to apoptosis (cell death).[22] Anticancer agents, such as vinblastine (**14**, Figure 3) and vincristine (**15**), have been shown to inhibit tubulin polymerization.[23] Kobayashi and coworkers reported that moroidin, celogentins A–H, and celogentin J inhibit the polymerization of tubulin.[18-21] Bioassay studies showed that moroidin (Table 1, **13:** IC_{50} 3.0 μM), celogentin C (**5:** IC_{50} 0.8 μM), E (**7:** IC_{50} 2.5 μM), F (**8:** IC_{50} 3.0 μM), H (**10:** IC_{50} 2.0 μM) and J (**11:** IC_{50} 3.0 μM) have potency greater than or equal to that of vinblastine (**14:** IC_{50} 3.0 μM).[18-21,24]



Vinblastine (**14**): R = CH_3
Vincristine (**15**):R = CHO

Figure 3. Stuctures of vinblastine and vincristine.

Structural Features

The moroidin family, except for **12**, are classified as heterodicyclopeptides (traditional peptide connections leading to a two ring system separated by a central unit).[6] As illustrated in Figure 2, natural products **3–11** and **13** have a left and right hand ring separated by a central tryptophan moiety. Peptides **3–8,** and **12** have identical left-hand-rings (*Trp*-Val-Leu-[β^S]Leu[PyroGlu]-*Trp*^{C6}) with variations seen in the right-hand-ring (**5:** *Trp*-Pro-Arg-His-*Trp*^{C2}; **3–4**, and **6:** *Trp*-Arg-His[R]-*Trp*^{C2}; **13** and **7–8**: *Trp*-Arg-Gly-His[R^1]-*Trp*^{C2}; **12**^{25}**:** *Trp*-Arg-Gly-His). Likewise **9–11** have an identical left-hand-ring (*Trp*-Ile-Leu-[β^S]Leu[PyroGlu]-*Trp*^{C6}) with variations in the right-hand-ring (*Trp*-Arg-Gly-His[R^1]-*Trp*^{C2}). The commonality between these structures, except for **12**, is a highly functionalized tryptophan moiety (Figure 4). There are two unusual connections, one between the leucine β-carbon and the indole C6 of tryptophan, and the other between the indole C2 and the τ-nitrogen of the histidine residue.

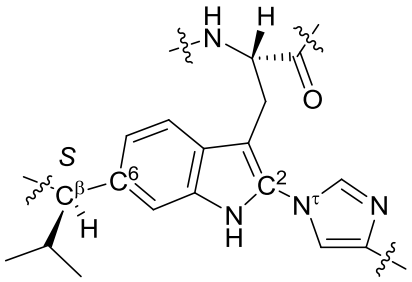


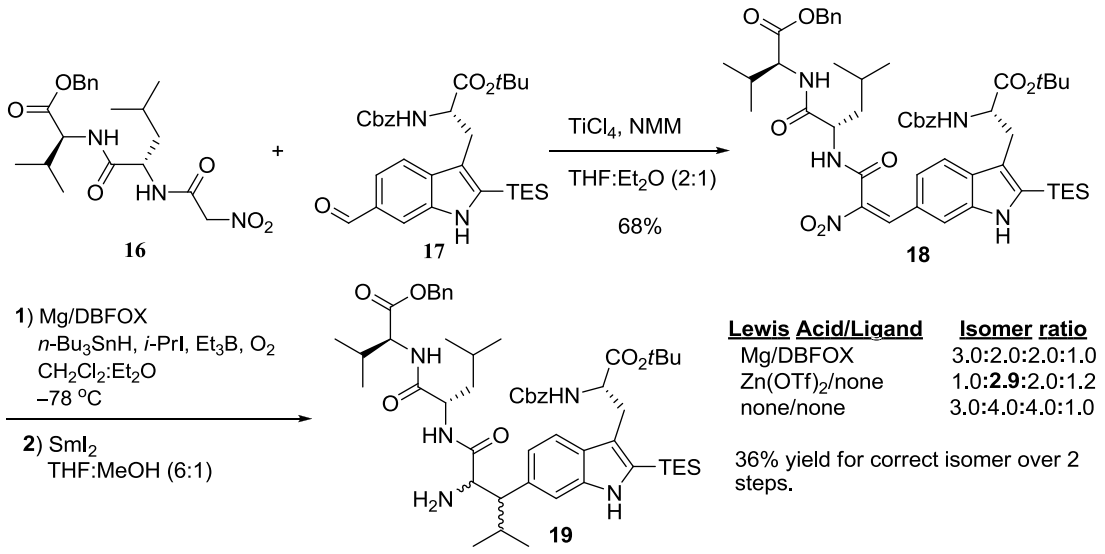
Figure 4. Highly functionalized tryptophan moiety.

Total Synthesis

Due to the low abundance, potential bioactivity, and synthetic challenges of the highly functionalized tryptophan moiety, many laboratories have targeted **5** for total synthesis.[26-31] Our group completed the first total synthesis of **5** in 2009.[32] This was accomplished by the previous construction of a functionalized tryptophan derivative[33] and later the synthesis of the right-hand ring of **5**.[34] Our laboratory had previously envisioned a right- to left-hand construction approach, but ultimately they adopted a left- to right-hand approach.[35]

Construction of the left-hand ring included a Knoevenagel condensation reaction followed by radical conjugate addition (Scheme 1) and macrolactamization. The coupling between the α-nitro dipeptide (**16**) and aldehyde (**17**) was promoted with the Lewis acid $TiCl_4$, and afforded the unsaturated *Z*-tripeptide (**18**). Exposure of the α,β unsaturated tripeptide (**18**) to radical conditions (O_2/Et_3B/*n*-Bu_3SnH) and isopropyl iodide, followed by a samarium iodide (reducing agent), afforded product **19.** Unfortunately, the stereocontrol observed in the model studies[36,37] (with Mg/DBFOX as a chiral Lewis acid) did not carry over. Interestingly, there was a small preference for the desired isomer of **19** when $Zn(OTf)_2$ was utilized. Even with these short comings in stereoselectivity, we were able to obtain the desired isomer, over two synthetic steps, at a 36% yield. Further functionalization followed by macrolactamization afforded the left-hand ring of **5** in good overall yield.

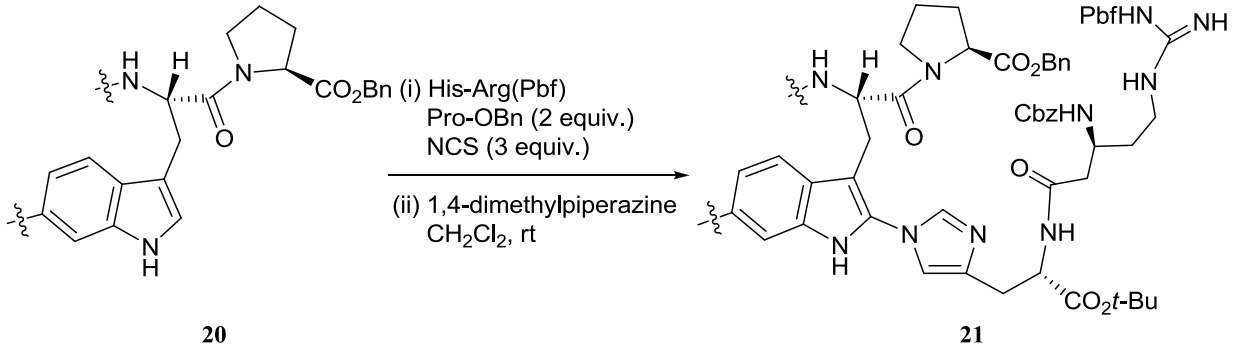
Scheme 1. Knoevenagel condensation followed by radical conjugate addition.



Construction of the right-hand ring included a novel oxidative coupling reaction[34] (Scheme 2) and a macrolactamization. The union of left-hand ring, intermediate **20** and the dipeptide His-Arg(Pbf) was facilitated with 3 equivalents of *N*-chlorosuccinimide (NCS) and 2

equivalents of Pro-OBn (which is used to modulate the concentration of NCS) to afford oxidative product **21**. Deprotection, macrolactamization, and final deprotection concluded the first total synthesis of **5**.

Scheme 2. Oxidative coupling of His-Arg(Pbf) to the left-hand ring of **5** (abbreviated, with Pro).



20 **21**

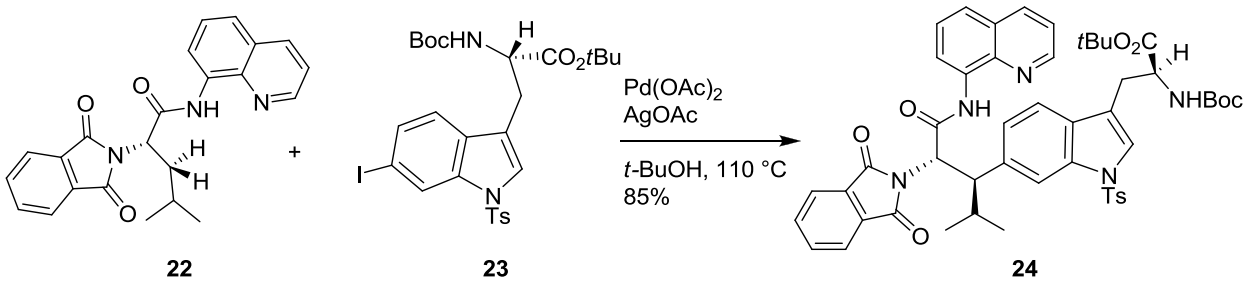
Formal Syntheses

Shortly following our group's publication of the total synthesis of **5**, two formal synthesis papers were published by Chen[38] and Jia,[39] respectively. Both of these research groups follow a left- to right-hand construction of **5**. In fact, they both utilize our published experimental proceedings to construct the right-hand ring (i.e., oxidative coupling). The differences in the complete syntheses of **5** lie in the construction of the left-hand ring. Most notable is their individual approaches in the construction of the β-Leu-(C6)Trp connection.

Chen and coworkers utilized a novel stereoselective C–H activation methodology in the construction of the β^S-Leu-(C6)Trp connection (Scheme 3). The quinoline *N*-phthaloyl leucine derivative (**22**) was the key component in this palladium (II) cross-coupling reaction to iodo-tryptophan **23**. The phthaloyl group of **22** influences the stereoselective outcome, whereas the quinoline moiety coordinates to palladium for insertion into the β C–H bond. The final cross-coupling step affords **24** as a single diastereomer in 85% yield. Chen reports some difficulty in

the removal of the quinoline auxiliary due to steric hindrance and lability of the *N*-phthaloyl group. They resolve this issue by removal of the phthaloyl group prior to hydrolysis.[38]

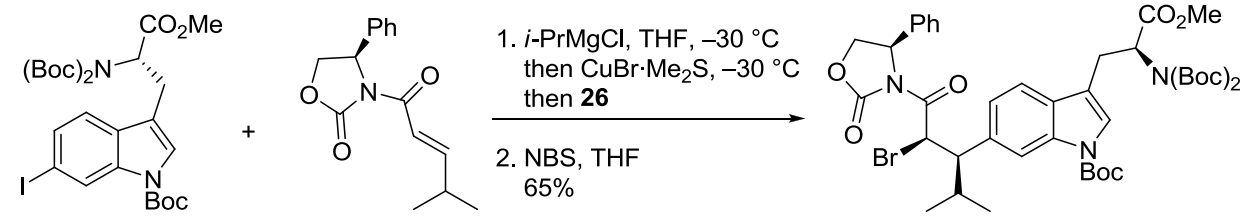
Scheme 3. Chen's stereoselective C–H activation pathway.



22 **23** **24**

Jia and coworkers report an asymmetric Michael addition as their key reaction in the synthesis of the β-Leu-(C6)Trp connection (Scheme 4).[39] They prepare iodo-tryptophan (**25**) as an aryl cuprate *in situ* via a metal-halogen exchange process. The addition of β-isopropyl α,β-unsaturated oxilidinone amide (**26**), followed by NBS, afforded functionalized **27** in reasonable yields. This challenging operational reaction allows for the most straightforward synthesis of the left-hand ring and is reported by Jia as a gram scale reaction.

Scheme 4. Jia's asymmetric Michael addition pathway.



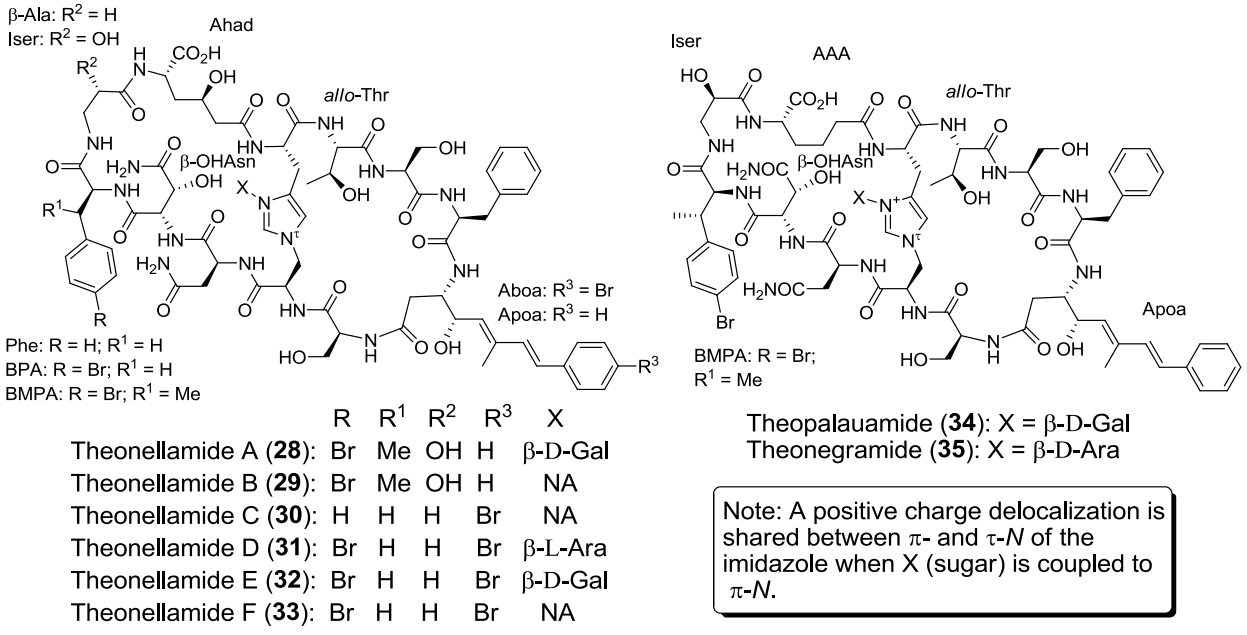
25 **26** **27**

1.3 Theonellamide F

Isolation

Picture 1. *Theonella swinhoei*.

Theonellamides A (**28**), B (**29**), C (**30**), D (**31**), E (**32**), F (**33**) were isolated from an antifungal fraction of *Theonella swinhoei* (Picture 1), a marine sponge found off the coast of the Hachijo-jima island, by Fusetani and coworkers.[40,41] Additional extractions by Faulkner and coworkers facilitated the isolation of two more members of this bicyclic family, theopalauamide (**34**)[42] and theonegramide (**35**).[43,44] It is noteworthy that several other secondary metabolites have been isolated from this marine invertebrate with linear, mono- and tri-cyclic peptide architectures.[45-47] Also, there is evidence that these marine cyclopeptides (i.e., **34** and **35**) are the byproduct of a microorganism sharing a symbiotic relationship with *T. swinhoei*.[42,48,49-50]



	R	R^1	R^2	R^3	X
Theonellamide A (**28**):	Br	Me	OH	H	β-D-Gal
Theonellamide B (**29**):	Br	Me	OH	H	NA
Theonellamide C (**30**):	H	H	H	Br	NA
Theonellamide D (**31**):	Br	H	H	Br	β-L-Ara
Theonellamide E (**32**):	Br	H	H	Br	β-D-Gal
Theonellamide F (**33**):	Br	H	H	Br	NA

Theopalauamide (**34**): X = β-D-Gal
Theonegramide (**35**): X = β-D-Ara

Note: A positive charge delocalization is shared between π- and τ-*N* of the imidazole when X (sugar) is coupled to π-*N*.

Figure 5. Theonellamides A–E, theopalauamide, and theonegramide.

Bioactivity

Marine invertebrates have produced an array of bioactive agents that are being explored for their therapeutical properties.[5,51,52] In general, the theonellamides (**28**–**33**) have shown modest growth inhibition against P388 leukemia cell lines (Table 2). Cycle peptides **34** and **35** demonstrated inhibition of growth on *Candida albicans* disks.[42,43] Theonellamide F (**33**) has demonstrated cytotoxicity in L1210 (IC_{50} of 3.2 μg/mL), antifungal activity (i.e., *Candida* spp., *Trichophyton* spp., and *Aspergillus* spp.), and promotion of large vacuole in 3Y1 rat embryonic fibroblasts.[40] Enlarged vacuole formation is indicative of microbial activity.[49]

Table 2. Isolation yield and cytotoxicity (P388 leukemia cell lines) values for the theonellamide family.

Compound	Isolation Yield (% by wt.)	IC_{50} Value (μg/mL)
Theonellamide A (**28**)	1.33×10^{-3a}	5.0
Theonellamide B (**29**)	1.26×10^{-4a}	1.7
Theonellamide C (**30**)	2.13×10^{-4a}	2.5
Theonellamide D (**31**)	9.33×10^{-5a}	1.7
Theonellamide E (**32**)	2.00×10^{-4a}	0.9
Theonellamide F (**33**)	3.33×10^{-3a}	2.7
Theopalauamide (**34**)	1.30×10^{-2b}	NA
Theonegramide (**35**)	0.20×10^{0b}	NA

Isolation values were calculated from (a) wet and (b) dry harvested sponge.

Structural Features

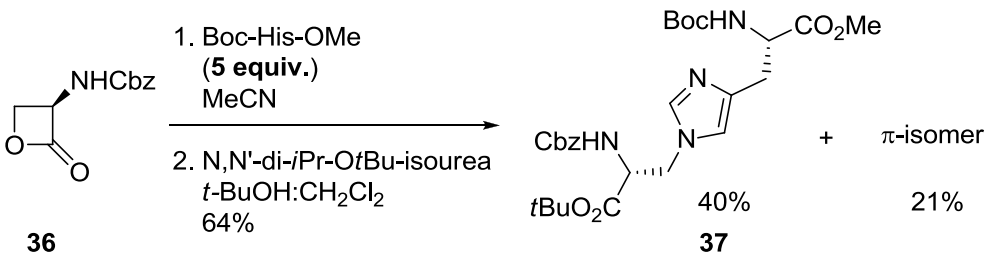
The theonellamides are a unique class of macrocycles sharing an unusual τ-L-histino-D-alanine (τ-HAL) bridge (Figure 5, highlighted in red) that separates the left- and right hand hemispheres. In general, they are a class of dodecapeptides structured around L- and D- amino acids with variations in their respective extremities. Peptides **28** and **29** have 3 amino acid residues different from **33**; **28** has an additional β-D-galactose linked to the free imidazole nitrogen; **30** is the debrominated version of **33**; and **31** and **32** are the β-L-arabinoside and β-D-galactoside saccharide analogs of **33**.

Synthetic Approaches

Shioiri and coworkers published four papers disclosing their efforts towards the total synthesis of **33**.[54-57] They initially targeted the synthesis of smaller components of **33**. This included the stereoselective synthesis of (3*S*,4*S*,5*E*,7*E*)-3-amino-8-(4-bromophenyl)-4-hydroxy-6-methyl-5,7-octadienoic acid (Aboa)[54] and (2*S*,4*R*)-2-amino-4-hydroxyadipic acid (Ahad)[55] found in the right-hand and left-hand rings, respectively. A stereo-retention synthetic route of τ-HAL (Scheme 5) lead to a synthesis of the left-hand[56] and right-hand ring[57] in 1994. Since then, no additional papers describing further progress in the total synthesis of **33** has been published. Needless to say it is highly unusual for a synthesis of such a compound (**33**) to be uncompleted when all the components to do so are in place. We speculate that the inefficient macrocyclization, coupled with the modest regioselectivity, and overall low-yielding synthetic route towards a functionalized τ-HAL moiety contributed to complications in the completion of **33**. The advancement in macrocyclization should readily resolve the 21% and 24% ring closing yields disclosed by Shioiri and coworkers.[56,57]

The regioselective synthesis of τ-HAL has proven troublesome for other research groups as well.[49,58,59] In Shioiri's case, they utilized an optically pure strained cyclic lactone (serine β-lactone, **36**) which then was subjected to ring opening via nucleophilic attack of either one of the two available imidazole nitrogens seen in the histidine ring. The subsequential transesterfication reaction affords the τ- and π-HAL residues (2:1 mixture calculated via

Scheme 5. Shiori's stereo-retention pathway towards τ-HAL.



36 **37**

HNMR/NOE studies)[56] with a combined 64% modest yield. The *tert*-butyl ester facilitates the following purification of τ-HAL.

1.4 Summary

Celogentin C (**5**) and theonellamide F (**33**) are members of a unique club of complex cyclic peptides. Their low-yielding isolation, pharmaceutical potential, and impressive bicyclic peptide structures warrant synthetic interest and pursuit. Although **5** was previously synthesized by our lab,[32,35] the lack of stereoselective addition of the isopropyl group to **18** (Scheme 1) justified further synthetic investigations (Chapter 2). Chen and Jia addressed the stereocontrol of the β-Leu connection to the C6 position of the indole by a novel C–H activation and asymmetric Michael addition, respectively.[38,39] Giving merit to our laboratory's development in a novel oxidative coupling reaction utilized to connect the C2 of the indole to the τ-N of the imidazole (Scheme 2), these two groups followed our experimental procedures in building the right hand ring of **5**. Unlike **5**, **33** has not been synthesized and appears to have generated little synthetic interest. Shioiri and coworkers previously pursued the total synthesis of **33** but was plagued with low-yielding macrocyclizations as well as a poor regioselective synthetic route for the central moiety, τ-HAL (Figure 5, highlighted in red).[49] Therefore, the design of a more efficient pathway towards HAL (Chapter 3) would contribute directly to the synthesis of **33** as well as the other members of the theonellamide family of structures.

1.5 References

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2. Results and Discussion: Celogentin C

2.1 Synthetic Efforts towards a 2nd Generation Synthesis of Celogentin C

The key reaction in the left-hand ring of celogentin C (**5**) was the radical conjugate addition (RCA) of the isopropyl group (Scheme 1).[1,2] The original methodology experiments suggested that the isopropyl group could be added to an α,β-unsaturated nitro amide moiety with excellent enantiomeric and modest diastereomeric selectivity.[3] Unfortunately, we did not observe similiar stereoselectivity in the RCA of the isopropyl group to our highly functionalized tripeptide substrate (**18**, Scheme 1) suggesting that the $Mg(NTf_2)_2$/DBFOX chiral Lewis acid was not complexing to the α-nitro amide in the desired octahedral fashion. Due to the potential foreseen in radical-promoted reactions in natural product synthesis as well as a desire to improve the stereoselectivity of the RCA in the total synthesis of **5**, we conducted further investigations utilizing organocatalysts (i.e., hydrogen bond donors and chiral imidazolidinone). We later turned to an alternative to RCA, described by MacMillan's group, which involved asymmetric reduction followed by α-chlorination.

2.2 Radical Conjugate Addition Investigations Utilizing Organocatalysts

Scope

With the understanding that Lewis acids promote reactions via removing electron density from a substrate, we hypothesized that hydrogen bond donors would function similiarly in the radical conjugate addition (RCA) reaction. Although RCA promotion via hydrogen bonding is quite rare, there has been evidence of reaction acceleration and increased diastereoselectivity with hydrogen bond donors such as alcohols, sulfoxides/sulfones, and urea catalysts in a variety of radical transformation reactions.[4-12]

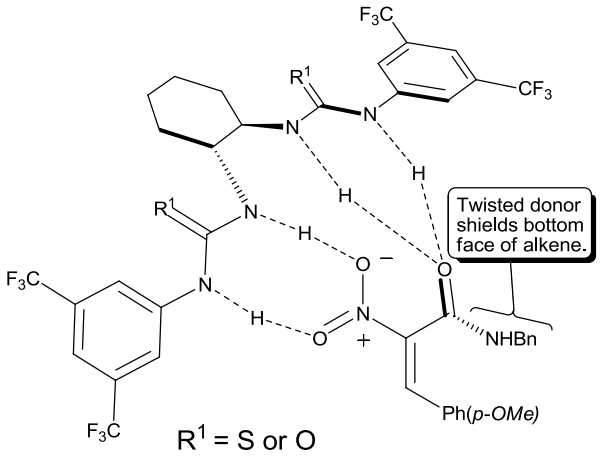


Figure 6. Proposed binding model of urea motif and α,β-unsaturated α-nitroamide substrate.

We decided to focus on urea analogs in our initial organocatalyst methodology studies. Our choice was based on the straight forward synthesis of urea analogs as well as their ability to hydrogen bond with nitro groups. We envisioned that appropriately designed chiral urea catalysts would be site-specific and fix the substrate in a single conformation, promoting a stereoselective RCA reaction (Figure 6). But, first we had to determine if hydrogen bond donors would promote the RCA.

We initiated our study with the preparation of six urea analogs (**38**–**43**, Figure 7)[13] and three 7-azaindole organic salts (**44**–**46**)[14] following published procedures. The six urea analogs were chosen for varying hydrogen bond donor potential. For example, the bis-aryl urea analog **38** is a stronger hydrogen bond donor than mono-aryl urea analog **40** due to the additional inductive electron withdrawing potential of the *meta*-triflouromethyl groups. Likewise, thiourea analogs have a greater hydrogen bond donor potential than standard urea analogs due to the poorer orbital overlap of the sulfur-carbon bond. In an effort to broaden our

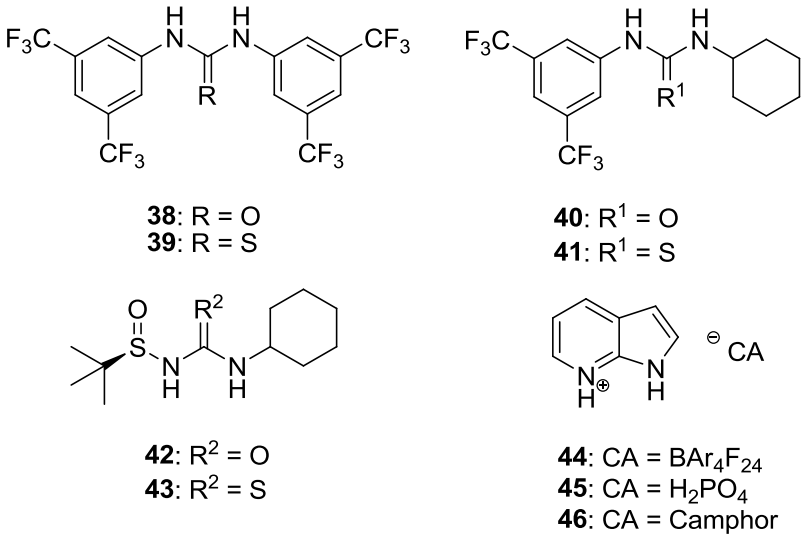
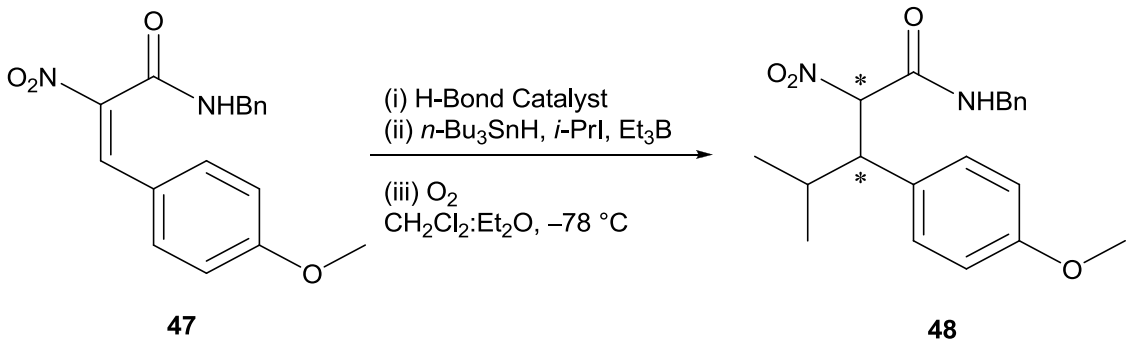


Figure 7. H-Bonding catalysts screened as RCA promoters.

study of hydrogen bond donors as potential RCA catalysts, we examined three 7-azaindole salts, with tetrakis[bis(trifluoromethyl)]boron (BAr_4F_{24}, **44**), dihydrogen phosphate ion ($H_2PO_4^-$, **45**), and (*S*)-(+)-10-camphorsulfonate (Camphor, **46**) as counter anions.

Screening

We decided to utilize substrate **47** in our initial screening of organocatalysts **38**–**46** (Scheme 6). It is important to note that at this stage of development we were only interested in the promotion of the RCA to **47** by the hydrogen-bond donors and not the stereoselective outcome. The original model studies conducted in our group, required an additional reduction of the nitro to prevent epimerization of the α-hydrogen.[15] We concluded that



Scheme 6. Radical conjugate addition of an isopropyl group to an activated conjugate system.

this additional step was unnecessary for the scope of our new study. Interestingly, the aforementioned reduction also facilitated purification of the amine, derived from **48,** from tin hydride. Further investigations into this purification issue afforded us with a new procedure that utilized hexanes and acetonitrile suspension to remove the excess tin. The remaining trace amounts of tin were removed via chromatography with 10% KF (by weight) ground into silica gel.[16]

Over the course of screening **38**–**46** as promoters in the RCA described in Scheme 6, we developed four experimental procedures A–D (described in detail in Chapter 4). These

procedures utilized stoichiometric amounts of **38**–**46**. We envisioned that if these hydrogen bond donors proved to be viable accelerators of the RCA, then we would explore catalytic loadings.

Table 3 illustrates the results of the initial screening. The 'none' describes the RCA reaction without organo-hydrogen bond promotion. Procedure A describes three separate injections of *i*-PrI (5 equiv.), *n*-Bu_3SnH (2.5 equiv.), 3.5 M Et_3B (5 equiv.), and ~2 mL of O_2 at 1.5 hour intervals.[3] The data collected in Table 3 suggests that **38** and **41** impeded the addition of the isopropyl group while **40** slightly accelerated the addition. Another derived conclusion from Table 3 is that the reaction is so efficient under the conditions described in Procedure A that it is unlikely that the hydrogen bond donors had very much influence. To test this understanding, two reactions without hydrogen bond donors were conducted utilizing experimental parameters described by former Castle group member Liwen He: one injection of *i*-PrI (5 equiv.), *n*-Bu_3SnH (2 equiv.), and 3.5 M Et_3B (5 equiv.) followed by ~2 mL of O_2 injections every 30 minutes over a 3 hour period (Procedure B).[15] The results were yields of 33% with CH_2Cl_2 as solvent and 19%, with a 1:1 CH_2Cl_2/Et_2O solvent mixture. This was a surprising result because it was thought that the addition of ether to the system would increase solubility of the reagents and therefore increase efficiency.

Table 3. Initial screening of select promoters following procedure A.

Catalyst	*n*-Bu_3SnH	*i*-PrI	3.5 M Et_3B	Duration	Yield
38	7.5 eq.	15 eq.	15 eq.	3x1.5h	38%
40	7.5 eq.	15 eq.	15 eq.	3x1.5h	76%
41	7.5 eq.	15 eq.	15 eq.	3x1.5h	49%
none	7.5 eq.	15 eq.	15 eq.	3x1.5h	54%

Table 4 shows the results of decreasing the amounts of each reagent in an attempt to minimize the background reaction. Procedure C experimental conditions included a single injection of *i*-PrI (2.5 equiv.), *n*-Bu_3SnH (2 equiv.), 3.5M Et_3B (2.5 equiv.), and ~2 mL of O_2. Every 30 minutes, an additional ~2 mL of O_2 was added over a 2 hour time period. Control 1

Table 4. Screening of select promoters following procedure C.

Catalyst	*n*-Bu_3SnH	*i*-PrI	3.5 M Et_3B	Duration[a]	Yield
Control 1[b]	2 eq.	2.5 eq.	2.5 eq.	4x30 min	15%
Control 2	2 eq.	2.5 eq.	7.2[c] eq.	3x30 min	58%
38	2 eq.	2.5 eq.	2.5 eq.	4x30 min	5%
39	2 eq.	2.5 eq.	2.5 eq.	4x30 min	14%
40	2 eq.	2.5 eq.	2.5 eq.	4x30 min	37%
41	2 eq.	2.5 eq.	2.5 eq.	4x30 min	31%
42	2 eq.	2.5 eq.	2.5 eq.	4x30 min	16%
43	2 eq.	2.5 eq.	2.5 eq.	4x30 min	5%
44	2 eq.	2.5 eq.	2.5 eq.	4x30 min	85%
44	2 eq.	2.5 eq.	2.5 eq.	4x30 min	48%
44	2 eq.	2.5 eq.	2.5 eq.	8x30 min	16%
44	2 eq.	2.5 eq.	7.3[c] eq.	5x30 min	42%
45	2 eq.	2.5 eq.	4.8[c] eq.	2x30 min	28%

(a) ~2 mL of O_2 was injected at 30 minute intervals. (b) CH_2Cl_2 was used as solvent for this reaction. (c) Additional injections, reaction taken to completion.

shows this background reaction to be about 15%. Therefore any result above this yield under these conditions should indicate promotion of the reaction by the hydrogen bond donor. We were pleased to see that **40** and **41** promoted the reaction. Surprisingly, we initially saw an acceleration of RCA (85%) with 7-azaindole **44**. This encouraged us to explore dihydrogen phosphate (**45**) as a counter anion to the protonated azaindole. As seen in Table 4 (28%), it does not appear that this alternative anion gives the same initial result as seen for **44**. On the other hand, when the reaction was repeated with **44** the initial result was not observed again. In an attempt to acquire repeatable results that could be compared to one another, further injections of 3.5 M Et_3B were added until the starting material was completely consumed. Control 2 was run under the same conditions and goal in mind. The data present in Table 4 suggests that **44** does not promote the reaction and may in fact impair the addition of the isopropyl group. It is noteworthy that BAr_4F_{24} is hygroscopic and improper storage of **44** could have influenced the overall results.

Due to the many variations in the results, we began to suspect that there may be some esternal influences in the background reaction. We then decided to run the controls simultaneously with the RCA reactions promoted by hydrogen bond donors. This would allow for a direct side-by-side comparison. Also, we wanted to explore utilizing lower loading of *n*-

Table 5. Screening of select promoters following procedure D.

Catalyst	*n*-Bu_3SnH	*i*-PrI	3.5M Et_3B[a]	Duration[b]	Yield
Control	2 eq.	2.5 eq.	15 eq.	6x30 min	76%
45	2 eq.	2.5 eq.	15 eq.	6x30 min	78%
46	2 eq.	2.5 eq.	15 eq.	6x30 min	32%

(a) Added in 2.5 eq. portions at 30 min intervals. (b) O_2 (2 mL) was injected at 30 min intervals.

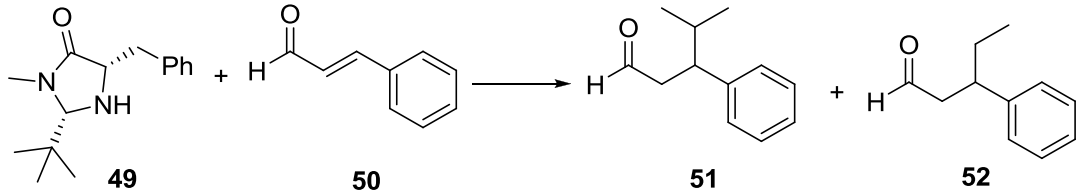
Bu_3SnH in RCA. Procedure D included an injection of *i*-PrI (2.5 equiv.), *n*-Bu_3SnH (2 equiv.), 3.5 M Et_3B (2.5 equiv.), and ~2mL of O_2. After initiation, additional 2.5 equiv. injections of Et_3B followed by ~2 mL of O_2 were added every 30 minutes for a total of 6 injections. In Table 5 we see that the control, when injected with mutlitiple aliquots of Et_3B, gave a result of 76%. It was disappointing to see that **46** actually impeded the reaction and **45** did not contribute any significant increase in yield. It was then realized that we most likely increased the background reaction.

In conclusion, our methodology studies suggest that **40**, **41**, and freshly prepared **44** may accelerate radical conjugate addition (RCA) of the isopropyl group to α,β-unsaturated α-nitroamide **47**. The ability to draw any further conclusions from this study is impeded by the variations in results as well as the efficiency of the competing background reaction. Successes include a lower loading of *n*-BuSnH (15 to 2 equivalence), efficient removal of the tin (hexanes/acetonitrile extractions followed by KF-doped SiO_2), and more insight into α,β-unsaturated α-nitroamides as excellent electron acceptors.

2.3 Radical Conjugate Addition Investigations Utilizing MacMillan Catalysts

MacMillan's group has performed extensive investigations into the utility of imidazolidinone catalysts.[17] In general, these compounds function as asymmetric organo-catalysts via iminium ion formation with carbonyl-containing substrates. At the time we were exploring our radical conjugate addition (RCA) of an isopropyl group to **47**, MacMillan's laboratory produced some preliminary results of a 1,4-addition of alkyl groups to a Michael

Table 6. Investigation of 1,4-addition of the isopropyl with imidazolidinone catalyst **49**.



49 **50** **51** **52**

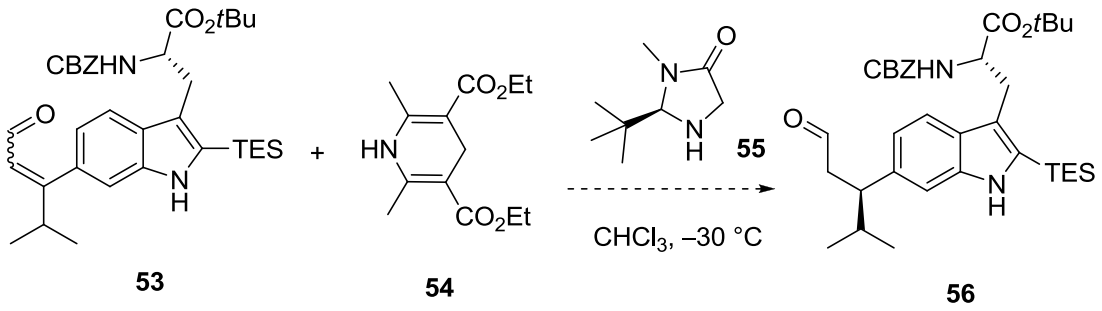
Route	Conditions	Results
1	TBAF, $Cu(NO_3)_2$, *i*-PrI, Et_3B, DCE, H_2O	**52**
2	*i*-PrI, Et_3B, CAN, TBAF, H_2O, THF, –20 °C	**51, 52**
3	*i*-PrI, $InCl_3$, In, CuI, H_2O, rt.	**51**

acceptor. Further discussions between our groups afforded a new RCA approach towards stereoselective addition of the isopropyl group (Table 6). We explored the utility of oxilidinone **49** to activate the addition of the isopropyl group to *trans*-cinnamaldehyde **50**. Unfortunately, we observed only ethyl addition with route 1 and competitive ethyl addition with route 2. The third reaction (route 3)[18] investigated utilizing indium chloride in water and produced **51** in small amounts. This latter reaction had the potential of being furthered developed with a solvent mixture (i.e., H_2O:THF) or use of a phase transfer catalyst. Further investigations of the 1,4-addition protocol were abandoned due to the lack of mechanistic insight and competitive ethyl addition.

2.4 Alternative Pathway towards β-Leu C6 Indole Connection

Scope

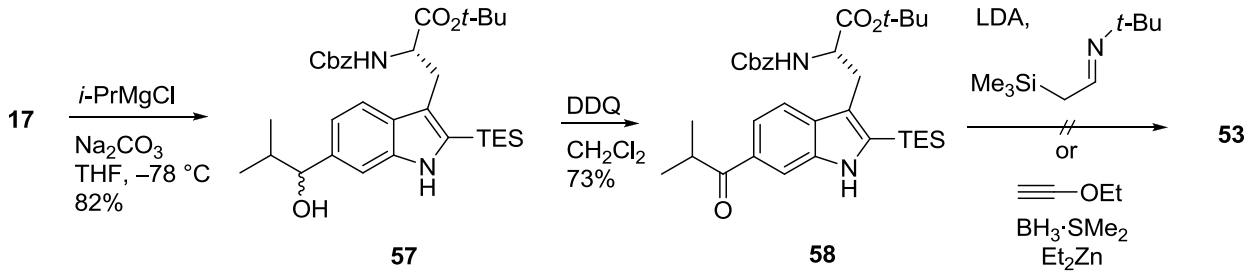
In our final efforts to stereoselectively build the isopropyl at the β-substituted Leu residue of **5** we turned our attention to better-known chemistry utilizing MacMillan catalysts for asymmetric reduction and α-chlorination.[19,20] We envisioned the asymmetric reduction of a β-isopropyl enal **53** (Scheme 7), via iminium catalyst **55** and ethyl Hantzsch reducing ester **54**, could be carried out with good stereoselectivity and efficiency. Our new approach therefore would begin with the synthesis of **53**.



Scheme 7. Asymmetric reduction utilizing MacMillan catalyst **55**.

Enal Homologation

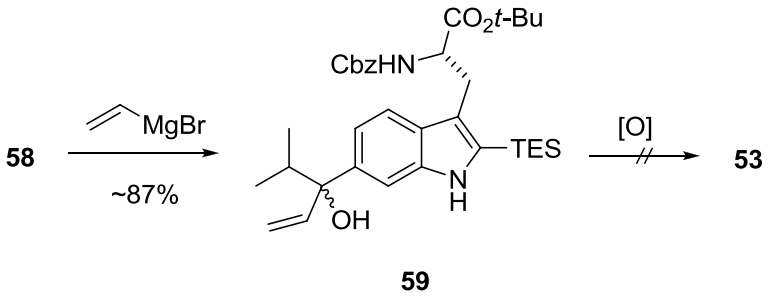
We initially focused on adding the isopropyl group to the aldehyde **17** (originally prepared for the Knoevenagel condensation reaction described in Chapter 1, Scheme 1) via a Grignard reaction (Scheme 8). This produced alcohol **57** as a mixture of diastereomers in good yield (82%). Then, DDQ was utilized to oxidize the alcohol to the ketone **58** (73%). We then



Scheme 8. Proposed synthetic route towards enal **53.**

explored two synthetic methods, one developed by Corey[21] and the other by Walsh,[22] for conversion of the ketone into enal **53**. The Corey procedure utilized lithium di-isopropyl amine (LDA) to produce an aza-enolate which ideally would have undergone nucleophilic addition to **58** followed by elimination. Unfortunately, this was not observed so we turned to the Walsh conditions utilizing diethyl zinc with ethoxy acetylene. These conditions proved to be inefficient with our substrate **58** as well.

Oxidative Rearrangement



Scheme 9. Proposed oxidative rearrangement pathway.

We then turned to an oxidative rearrangement reaction to construct enal **53**. Addition of vinyl magnesium bromide to ketone **58** formed alcohol **59** (Scheme 9). After some adjusting, this proved to be an efficient reaction (87%). We then tried to promote oxidative rearrangement under a variety of conditions (i.e., PCC,[23] IBX,[24,25] IBS,[26] and SO_3),[27] but only detected decomposition or starting material. As we began to explore additional oxidative rearrangement promoters, Chen[28] and Jia[29] published two independent papers disclosing different stereoselective pathways towards the β-substituted Leu residue of **5**. Accordingly, we halted our investigations at this point.

2.5 Summary

Investigations into a second-generation synthesis of celogentin C (**5**) were conducted due to a lack of stereoselectivity in the RCA of an isopropyl group to our highly functionalized tripeptide substrate (**18**, Scheme 1). The screening of hydrogen bond donors as radical conjugate addition (RCA) promoters suggested that mono-aryl urea **40** and thiourea **41** as well as 7-azaindole salt **44** may accelerate the RCA reaction. These studies also provided us with modified reaction conditions that utilize less tin reagent and improved the removal of tin. Additionally, these initial studies provide further evidence that α,β-unsaturated α-nitroamides are excellent electron acceptors. We then explored the utility of a chiral imidazolidinone to promote 1,4-addition to *trans*-cinnamaldehyde (**50**). Due to complications with proper addition of the

isopropyl group, we turned our attention to MacMillan's asymmetric reduction and α-chlorination procedures. Unfortunately, we were never able to explore this chemistry due to our inability to make the enal intermediate **53**. Chen's and Jia's publications describing the β-substituted Leu connection of **5** halted further investigations into the left-hand ring. Varying right-hand motifs warrant additional studies.

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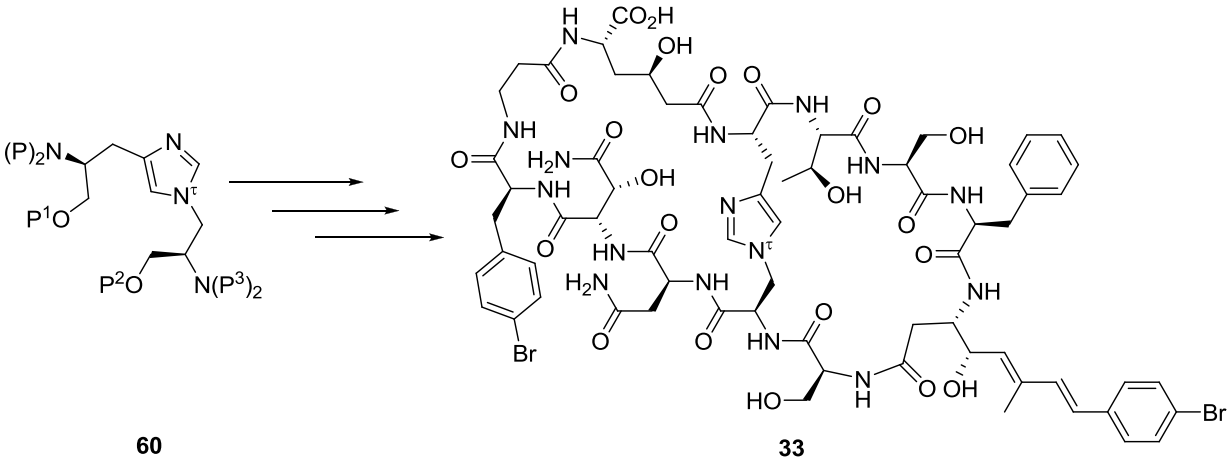
3. Results and Discussion: τ-HAL

3.1 Synthetic Efforts towards τ-HAL

As suggested in the introduction (Chapter 1.3), we believe that the efforts of Shioiri and coworkers towards the total synthesis of theonellamide F (**33**) were hindered by a lack of an efficient regioselective synthesis of the central moiety τ-L-histino-D-alanine (τ-HAL). We propose that an improved synthesis of this bridging moiety (Scheme 10) would contribute significantly towards the total synthesis of **33**. We envisioned preparing a derivative of τ-HAL (**60**), masked via four unique protecting groups (P–P^3), which would allow for selective peptide coupling of either the left- or right-hand rings. Additionally, we recognized that the earlier synthesis of τ-HAL relied solely on the nucleophilicity of the nitrogens in the imidazole to couple with an alanine precursor (Chapter 1.3, Scheme 5).[1] Therefore, we sought a completely new approach towards the regioselective synthesis of τ-HAL that starts from commercially available D- and L-Ser methyl esters that readily undergo modifications in preparation for an intramolecular cyclic annulation reaction.

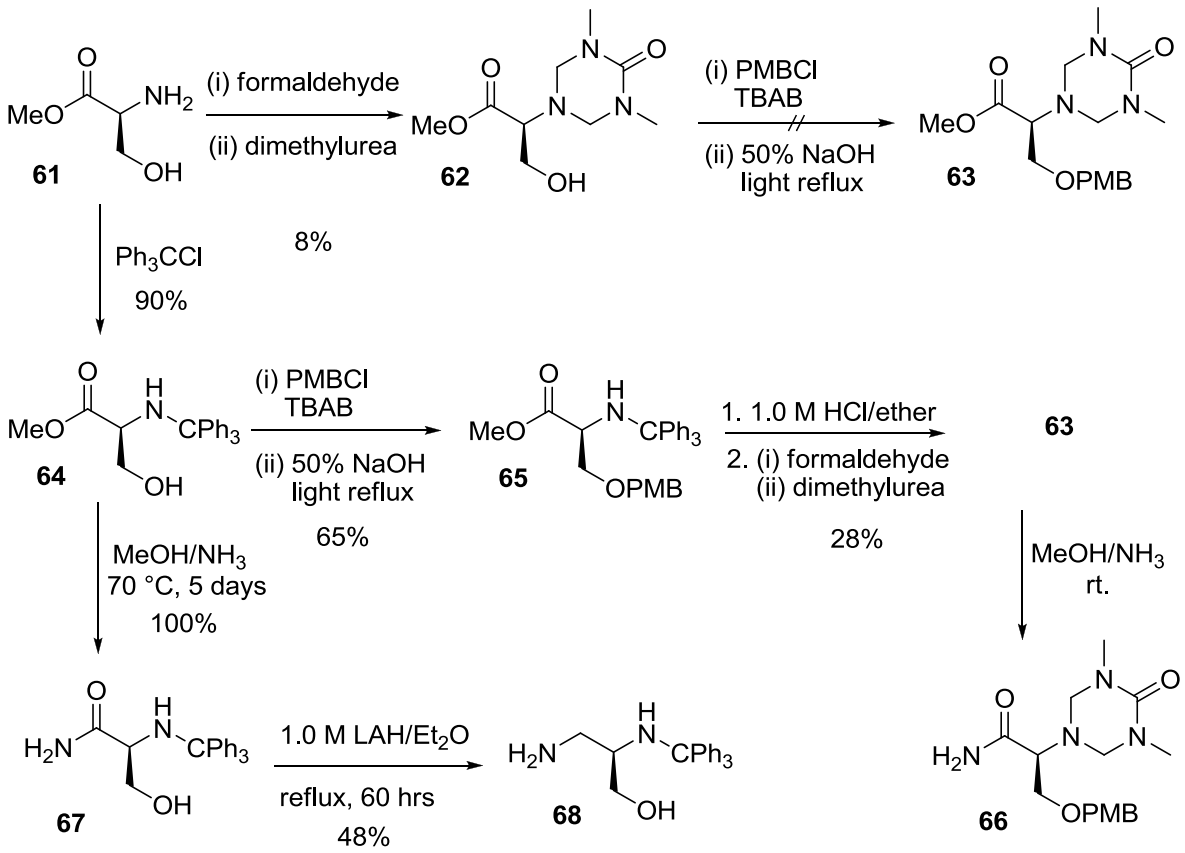
Scheme 10. Protected τ-HAL intermediate **60** readily leads towards theonellamide F (**33**).



3.2 Synthesis of D-Ala Scaffold

Synthesis of D-Ala scaffold begins with L-Ser methyl ester (**61**, Scheme 11). We initially were interested in synthesizing dimethyl triazone (DMT) intermediate **63**. We were concerned that a monoprotected α-amine could interfere with the later stage cyclic annulation reaction (described in Scheme 13). The DMT motif, which affords a bis-protected nitrogen atom, appeared to be ideal for our synthetic strategy. It was reported to be stable under the reaction conditions we planned to utilize (e.g., LAH and *t*-BuOK) and was removable under mild conditions (NH_4Cl/reflux).[2] Unfortunately, a direct synthetic path (**61→62→63**) was hindered due to low yields and difficulty in isolation of **62**.

Scheme 11. Developmental pathway towards D-Ala scaffold.



To resolve the isolation issue, we then selectively monoprotected the α-amine **61** with a strongly UV active trityl group to afford **64** in good yields (90%).[3] Our investigations of

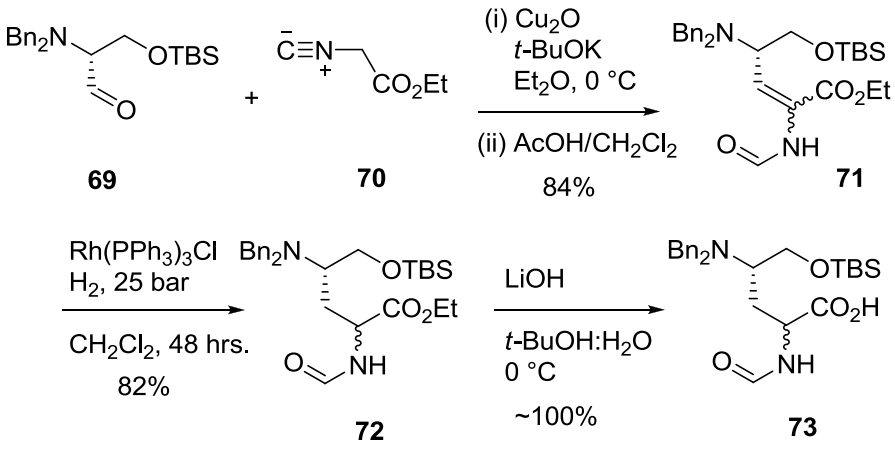
protecting the primary alcohol under different conditions led us to utilize the phase-transfer catalyst *tetra*-butylammonium bromide (TBAB) with 1 equivalent of 50% (by weight) NaOH.[4] This furnished us with **65** at a modest yield of 65%. We then de-tritylated with 1.0 M HCl/ether,[4] affording the unprotected intermediate which was bis-protected utilizing aqueous formaldehyde and dimethyl urea[2] to obtain product **63** (28%, two steps). An examination of ammonalysis reactions produced **66** (only detected by mass spectrometry), via MeOH bubbled with NH_3.[5] As we began to optimize route **61→64→65→63→66** (particularly the last two steps, **65→63→66**), a paper disclosing route **64→67→68** with good yields was discovered.

Rapoport and coworkers report a convenient and efficient synthesis of **68** via ammonalysis of **64** (92%) followed by reduction of amide **67** (84%).[6] Due to the overall efficiency, we changed course and pursued the synthesis of monoprotected **68** following Rapoport's pathway. We rationalized that the monoprotected species could be deprotected and bis-protected later in the sequence if necessary. After stirring **64** in MeOH/NH_3 solution for 5 days, we were able to obtain a quantitative yield of **67**. Refluxing in LAH in ether afforded reduced product **68** with a lower yield (48%) than reported.

3.3 Synthesis of L-His Scaffold

Aldehyde **69** (Scheme 12) was synthesized from commercially available D-Ser methyl ester following experimental procedures described by Zhu and coworkers.[7] The synthetic pathway includes 4 steps (dibenzylation; TBDMS protection; $LiBH_4$ reduction; and Swern oxidation) with an overall yield of 89%. Likewise, Minnaard and coworkers[8] describe the efficient synthesis of condensation products utilizing **70** and varying aldehyde motifs with catalytic amounts of Cu_2O. We explored these experiment procedures with aldehyde **69** and obtained a good yield (84%). The diastereomers can be separated via chromatography, but this is

Scheme 12. Synthetic pathway towards L-His scaffold.



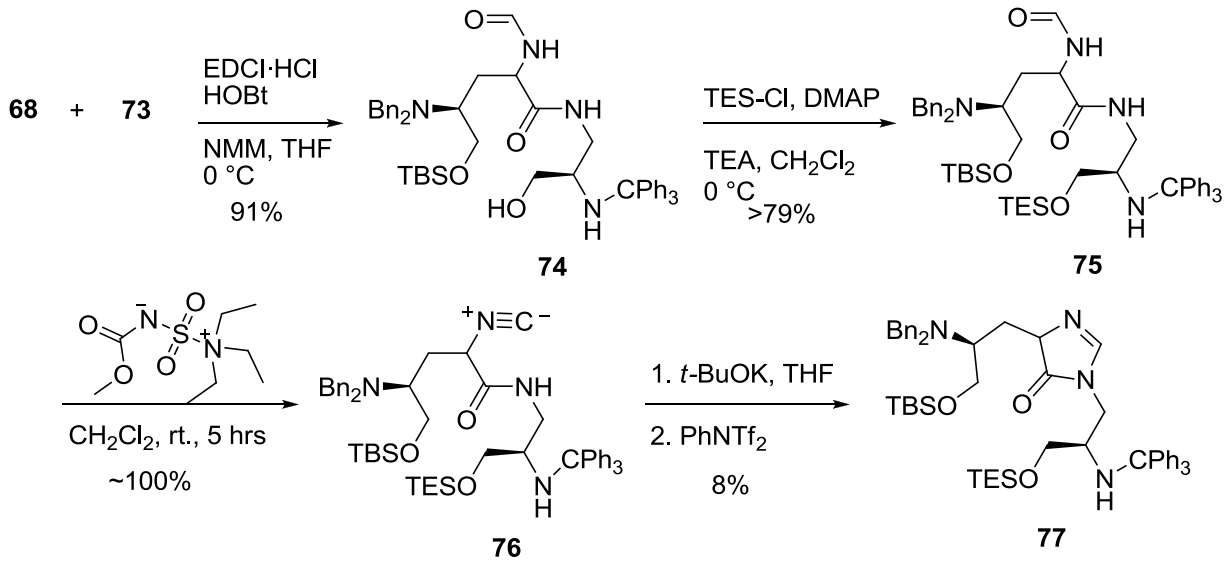
unnecessary for we plan to remove the stereocenter at a later stage. Reetz and coworkers[9,10] described stereoselective hydrogenation of the double bond (**71**→**72**) via chiral rhodium catalysts. Still unconcerned with stereochemistry, we elected to utilize the cheaper Wilkonson's catalyst which afforded **72** in good yields (82%).[11] Hydrolysis with LiOH produced L-His scaffold **73** quantitatively.

3.4 Synthetic Efforts towards τ-HAL

Utilizing standard coupling conditions (i.e., EDCI·HCl and HOBt), D-Ala (**68**) and L-His (**73**) scaffolds were joined to afford bis-amino **74** in good yields (Scheme 13, 91%). Subsequent TES protection[6] provided silyl ether **75** in greater than 79% yield. Dehydration of formamide **75** with the Burgess Reagent[12] formed isonitrile **76** quantitatively. Although **76** undergoes rapid decomposition on SiO_2, it was extracted from the aqueous workup by ether in high purity. Cyclic annulation product **77** was accomplished with 1.0 M *t*-BuOK in THF.[13] Unfortunately, this reaction has proven to be problematic. We envisioned a one-pot approach where intermediate **77**, upon formation, would undergo α-deprotonation producing an enolate that could be trapped with a triflate group (**78**, Scheme 14). Due to difficulties in monitoring this reaction (i.e., **76** and **77** have the same mass units; and **76** is suspected of decomposition on silica), future progress in the optimation of **76**→**77** will involve a time study to determine when the reaction needs to be

quenched prior to suspected decomposition. Fortunately, the amide hydrogen of **76** is readily identifiable by ^{1}H NMR (δ 6.6 ppm, triplet) and the isonitrile transformation can be monitored by FT-IR (2132.56 cm^{-1}). In fact, the loss of these two spectra signifiers with a new hydrogen signal (δ 5.98 ppm, singlet) and shift in the carbonyl (δ 165.99 to δ 170.13 and δ 170.70), via ^{13}C NMR, strongly support product **77**.

Scheme 13. Synthetic pathway towards cyclic-annulation intermediate **78**.



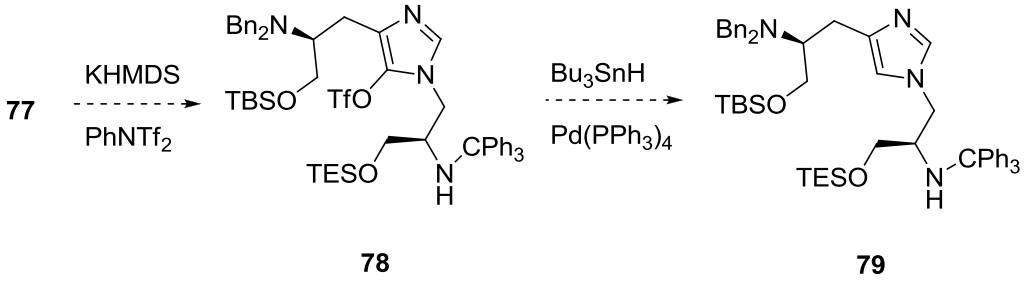
3.5 Summary

Since early March, we have managed to synthesize the D-Ala and L-His building blocks of τ-L-histino-D-alanine (τ-HAL), the bridging component of the theonellamide family of structures. The literature derived earlier steps are efficient in both yields and time. The earlier bottlenecks of the dimethyltriazone (DMT) and PMB protection reactions were resolved via Rapoport's work which readily lead to the important bis-amino intermediate **74** (Scheme 13).

Immediate future investigations will focus on the optimization of **76→77** as well as the enolate trapping, **77→78** (Scheme 14, utilizing various bases: RLi, KHMDS, NaHMDS, NaH).[14] Eventually we would like to be able to do these two reactions under a one-pot methodology. Once we have **78**, triflate reduction via palladium (II),[15] should afford protected τ-HAL **79**.

Other long term investigations will focus on the synthesis of the interesting and unusual structures found in theonellamide F (**33**) as well as their respective couplings.

Scheme 14. Proposed synthetic route towards precursor τ-HAL (**60**).



3.6 References

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4. Experimental: Celogentin C

4.1 General Experimental Details

All anhydrous solvents were dried by passage through a Glass Contour solvent drying system containing cylinders of activated alumina. All equipment was dried in an oven and cooled over desiccant prior to use. Reagents were purchased from Sigma-Aldrich, Acros, and Fluka without further purification unless otherwise stated. Flash chromatography was carried out using 60-230 mesh silica gel. ^{1}H NMR spectra were acquired on 500 MHz spectrometers with tetramethylsilane (δ 0.00 ppm) as internal reference. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), brs (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz). ^{13}C NMR specta were acquired on spectrometers operating at 125 MHz with chloroform (δ 77.23 ppm) as internal reference. Infrared spectra were obtained on an FT-IR spectrometer. Mass spectral data were obtained using ESI techniques.

4.2 Radical Conjugate Addition Investigations Utilizing Urea Catalysts

Procedure A

Substrate **47** (49.9 mg; 0.16 mmol) and catalyst (**38**, **40**, or **41**;[1] 0.16 mmol) were suspended in anhydrous CH_2Cl_2 (1.6 mL) and stirred for 30 min at rt under argon. The mixture was cooled to –78 °C where it was stirred for 30 min. The following reagents were injected into the system: *i*-PrI (80 μL; 0.800 mmol); *n*-Bu_3SnH (0.11 mL; 0.410 mmol); 3.5 M Et_3B (0.23 mL; 0.805 mmol); and ~2 mL of O_2. Three additional aliquots were injected every 90 min. Aqueous 1N HCl (5 mL) was added to quench the reaction. The organics were extracted from the aqueous layer via CH_2Cl_2 (3×5 mL). This crude mixture was dried with Na_2SO_4 and concentrated down into a residue. This crude mixture was suspended in acetonitrile (20 mL) and washed with hexanes (5×20 mL) to remove tin. The acetonitrile was rotovaporized off and the crude material

was loaded onto a column (SiO_2), doped with 10% KF (by weight of silica),[2] via CH_2Cl_2. An elution gradient of 0–4% MeOH/CH_2Cl_2 afforded product **48** (see Chapter 2, Table 3).

Procedure B [3]

Procedural guidelines were as followed in Liwen He's 2005 paper. Section titled "General Procedure for Radical Conjugate Additions to Amides 6a-c Promoted by Achiral Lewis Acids."

Procedure C

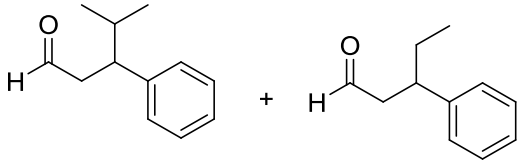
Substrate **47** (30.6 mg; 0.980 mmol) and catalyst (**38**–**45**;[1,4] 0.980 mmol) were suspended in anhydrous CH_2Cl_2/Et_2O (1:1; 2 mL) and stirred for 30 min at rt under argon. The mixture was cooled to –78 °C and stirred for 30 min. The following reagents were injected into the system: *i*-PrI (0.02 mL; 0.200 mmol); *n*-Bu_3SnH (0.05 mL; 0.186 mmol); 3.5 M Et_3B (0.07 mL; 0.245 mmol); and ~2 mL of O_2. An additional ~2 mL of O_2 was injected at 30 min. intervals over a 2 hour period. The reaction was removed from the dry ice bath, diluted with CH_2Cl_2, and quenched with 1N HCl (10 mL). The organics were extracted from the aqueous layer via CH_2Cl_2 (3×10 mL). This layer was dried with Na_2SO_4 and the volatile organics were rotovaporized off. The crude material was suspended in acetonitrile and washed by hexanes (5×10 mL) times. The acetonitrile was rotovaporized off and the remaining material was suspended in minimal amount of CH_2Cl_2 and loaded onto a doped column (10% by KF on SiO_2). An elution gradient of 0–4% MeOH/CH_2Cl_2 afforded product **48** (Table 4).

Procedure D

Substrate **47** (35.4 mg; 0.113 mmol) and catalyst (**45**–**46**;[4] 0.113 mmol) were suspended in anhydrous CH_2Cl_2/Et_2O (1:1; 2 mL) and stirred for 30 min at rt under argon. The argon balloon was removed prior to injection of the following reagents: *i*-PrI (28 μL; 0.280 mmol); *n*-

Bu_3SnH (61 μL; 0.227 mmol); 3.5 M Et_3B (81 μL; 0.284 mmol); and ~2 mL of O_2. Six additional injections of Et_3B and O_2 were added every 30 min over a three hour period. The reaction was followed by TLC. Once the starting material was consumed, the reaction was quenched with 1N HCl (10 mL). The organics were extracted from the aqueous layer via CH_2Cl_2 (3×10 mL) and dried with Na_2SO_4. The volatile organics were rotovaporized off and the crude residue was loaded onto a doped column (10% KF by SiO_2) via CH_2Cl_2. An elution gradient of 0–4% MeOH/CH_2Cl_2 afforded product **48** (Table 5).

4.3 Radical Conjugate Addition Investigations Utilizing MacMillan Catalysts



51 **52**

Product **52** was isolated via route 1. A mixture of **51** and **52** were generated under route 2 conditions. Route 3 afforded **51** in small quanitities (see Chapter 2, Table 6).

Route 1

Imidazolidinone **49** (28.7 mg; 0.117 mmol), $Cu(NO_3)_2$ (265.7 mg; 1.14 mmol), and TBAF (320.4 mg; 1.02 mmol) were added to a conical vial where it was placed under argon. Solids were suspended in DCE (1.0 mL) and cooled to −10 °C. While stirring the suspension vigorously, reagents H_2O (35 μL; 1.94 mmol), isopropyl iodide (77 μL; 0.77 mmol), *trans*-cinnamaldehyde (48 μL; 0.381 mmol), and Et_3B (120 μL; 0.828 mmol) were injected sequentially. The color of the solution began to change immediately upon addition of Et_3B (transparent green to opaque brown). After an hour of stirring, the reaction mixture was diluted with Et_2O (5 mL) and washed through a silica plug. The filtrate was rotovaporized down to a residue and loaded onto a SiO_2 column prepared in hexanes. Elution gradient of 0–10% Et_2O in hexanes afforded product **52**.

Route 2

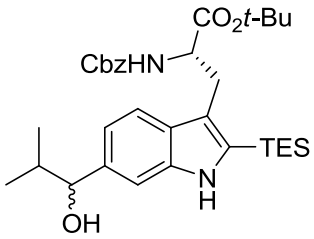
A freshly prepared imidazolidinone **49** (24.5 mg; 0.0995 mmol)/TFA salt was prepared in a 6 dram vial with CAN (0.7334 g; 1.34 mmol) and TBAF (0.4418 g; 1.40 mmol). The vial was sealed and flushed with argon. Injected H_2O (45 μL; 2.50 mmol) into this sealed system and cooled the vial to −10 °C via NaCl/ice. While stirring this mixture, freshly distilled *trans*-cinnamaldehyde (63 μL; 0.501 mmol), isopropyl iodide (99 μL; 1.01 mmol), and Et_3B (144 μL; 0.994 mmol) were injected sequentially. The reaction was then stirred for 2 hours followed by dilution with Et_2O (5 mL) and filtered through a SiO_2 plug. The filtrate was rotovaporized down to a residue which was loaded onto a SiO_2 column prepared in pentane. Elution gradient of 0−10% Et_2O in hexanes afforded products **51** and **52** as an inseparable mixture.

Route 3[5]

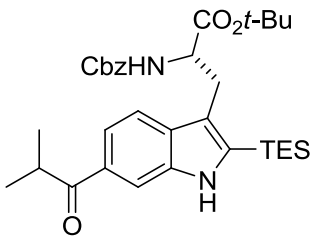
Trans-cinnamaldehyde (68 μL; 0.540 mmol), imidazolidinone **49** (26.5 mg; 0.108 mmol), and $InCl_3$ (12.4 mg; 0.0561 mmol) were suspended in H_2O/Et_2O (60:40; 10 mL). After vigorously stirring for 30 min, In (0.3737 g; 3.26 mmol), CuI (0.3091 g; 1.62 mmol), and isopropyl iodide (0.27 mL; 2.70 mmol) were added sequentially. The reaction was stirred for 24 hours at room temperature and then filtered off the particulates. The organics were extracted from the aqueous layer with Et_2O (3×10 mL) and washed with brine. A Na_2SO_4 plug was utilized for drying the organics which were rotovaporized down to a residue and loaded onto a column (SiO_2 prepared in pentane). Elution gradient 0−10% Et_2O in pentane afforded product **51** in small quantities.

4.4 MacMillan Asymmetric Reduction and α-Chlorination Route

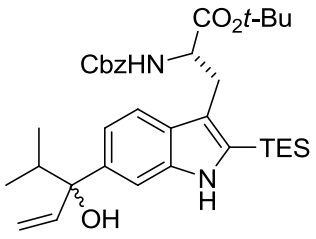
Enal Homologation Route



(2*S*)-*tert*-butyl 2-(benzyloxycarbonylamino)-3-(2-(*tert*-butyldimethylsilyl)-6-(1-hydroxy-2-methylpropyl)-1H-indol-3-yl)propanoate (57). Aldehyde **17** (365 mg; 0.68 mmol) and sodium carbonate (145 mg; 1.4 mmol) were suspended in anhydrous THF (~4 mL). Then the vial was degassed with argon and stirred at –78 °C for 15 min. Isopropylmagnesium chloride (1 mL of 2.0 M; 2 mmol) was injected slowly and the reaction was allowed to stir for 30 min. The mixture was allowed to warm to rt over a 4 hour period. The reaction was then quenched with H_2O (5 mL) and the organics were extracted in ethyl acetate (3×5 mL). The extracts were dried with Na_2SO_4 and concentrated down via rotovaporization. Constant elution of 2% MeOH/CH_2Cl_2 afforded alcohol **57** (326 mg; 0.56 mmol; 82%) as a brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.32–7.23 (m, 5H), 7.12 (s, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 5.22–5.90 (m, 1H), 4.99 (d, *J* = 12.5 Hz, 1H), 4.92 (dd, *J* = 12.0, 2.5 Hz, 1H), 4.53–4.47 (m, 1H), 4.42 (d, *J* = 7.0 Hz, 1H), 3.27 (dd, *J* = 14.3, 6.2 Hz, 1H), 3.14 (dd, *J* = 14.3, 9.2 Hz, 1H), 1.29 (s, 9H), 1.05–0.89 (m, 15H), 0.78 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.9, 155.9, 138.7, 138.5, 133.2, 128.6, 128.2, 128.1, 120.2, 119.1, 118.6, 109.0, 82.0, 81.0, 66.9, 56.2 (2C), 35.6, 30.0 (2C), 28.0, 19.4, 18.8, 7.6, 3.9, 0.2; HRMS (ESI) *m/z* 581.34292 (MH^+, $C_{33}H_{48}N_2O_5SiH^+$ requires 581.34053).



(*S*)-*tert*-butyl 2-(benzyloxycarbonylamino)-3-(2-(*tert*-butyldimethylsilyl)-6-*iso*butyryl-1H-indol-3-yl)propanoate. (58). Alcohol **57** (261 mg; 0.45 mmol) was dissolved in CH_2Cl_2 (1 mL) and stirred at 0 °C for 15 min. Added DDQ (0.1 g; 0.44 mmol) and allowed reaction to warm to rt. The mixture was concentrated onto silica and an elution gradient of 15–40% EtOAc/Hex afforded product **58** (186 mg; 0.32 mmol; 71%) as a yellowish-green oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.26 (s, 1H), 8.05 (s, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.32–7.19 (m, 5H), 5.24 (d, *J* = 8.5 Hz, 1H), 4.95 (d, *J* = 12.5 Hz, 1H), 4.90 (d, *J* = 12.0 Hz, 1H), 4.55–4.48 (m, 1H), 3.68–3.59 (m, 1H), 3.29 (dd, *J* = 14.5, 6.0 Hz, 1H), 3.16 (dd, *J* = 14.5, 9.0 Hz, 1H), 1.30 (s, 9H), 1.24 (d, *J* = 7.0 Hz, 6H), 1.05–0.91 (m, 15H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.9, 171.6, 155.8, 138.2, 137.9, 136.5, 132.5, 130.7, 128.6, 128.2 (2C), 120.6, 119.8, 119.0, 112.1, 82.2, 66.9, 56.3, 35.6, 30.2, 28.0, 19.7 (2C), 7.6, 3.8, 0.2; HRMS (ESI) *m/z* 579.32445 (MH^+, $C_{33}H_{46}N_2O_5SiH^+$ requires 579.32488).



(2*S*)-*tert*-butyl 2-(benzyloxycarbonylamino)-3-(2-(*tert*-butyldimethylsilyl)-6-(3-hydroxy-4-methylpent-1-en-3-yl)-1H-indol-3-yl)propanoate (59). Ketone **58** (10.9 mg; 0.018 mmol) was suspended in anhydrous toluene (0.5 mL), sealed and flushed with argon, and stirred at –78 °C for 15 min. Vinylmagnesium bromide (80 μL; 0.08 mmol) was added slowly and the reaction was allowed to stir for 30 min. The reaction was stirred at rt for approximately a 4 hour period of time. The reaction mixture was diluted with EtOAc (2 mL) and quenched with NH_4Cl (5 mL). The organics were extracted in EtOAc (3×2 mL), washed with brine (5 mL), and H_2O (5 mL). The organics were separated and dried via Na_2SO_4 plug and concentrated via rotovaporization. The crude material was loaded onto a column prepared in

hexanes and elution gradient 0–30% EtOAc/Hex afforded vinyl addition product **59** (10 mg; 0.016 mmol; 87%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.49 (s, 1H), 7.35–7.23 (m, 5H), 7.11 (d, *J* = 9.0 Hz, 1H), 6.33 (ddd, *J* = 17.3, 10.5, 2.2 Hz, 1H), 5.32 (d, *J* = 17.0 Hz, 1H), 5.21–5.17 (m, 1H), 5.15 (dd, *J* = 11.5, 3.5 Hz, 1H), 5.00 (d, *J* = 12.5 Hz, 1H), 4.92 (d, *J* = 12.5 Hz, 1H), 4.52–4.44 (m, 1H), 3.26 (dd, *J* = 14.0, 6.5 Hz, 1H), 3.14 (dd, *J* = 14.5, 9.0 Hz, 1H), 2.31–2.21 (m, 1H), 1.77 (s, 1H), 1.28 (d, *J* = 3.0 Hz, 9 H), 1.04–0.86 (m, 15H), 0.79 (dd, *J* = 6.75, 1.8 Hz, 6H); HRMS (ESI) *m/z* 607.35596 (MH^+, $C_{35}H_{50}N_2O_5SiH^+$ requires 607.35618).

4.5 References

(1) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

(2) Harrowven, D. C.; Guy, I. L. *Chem. Commun.* **2004**, 1968.

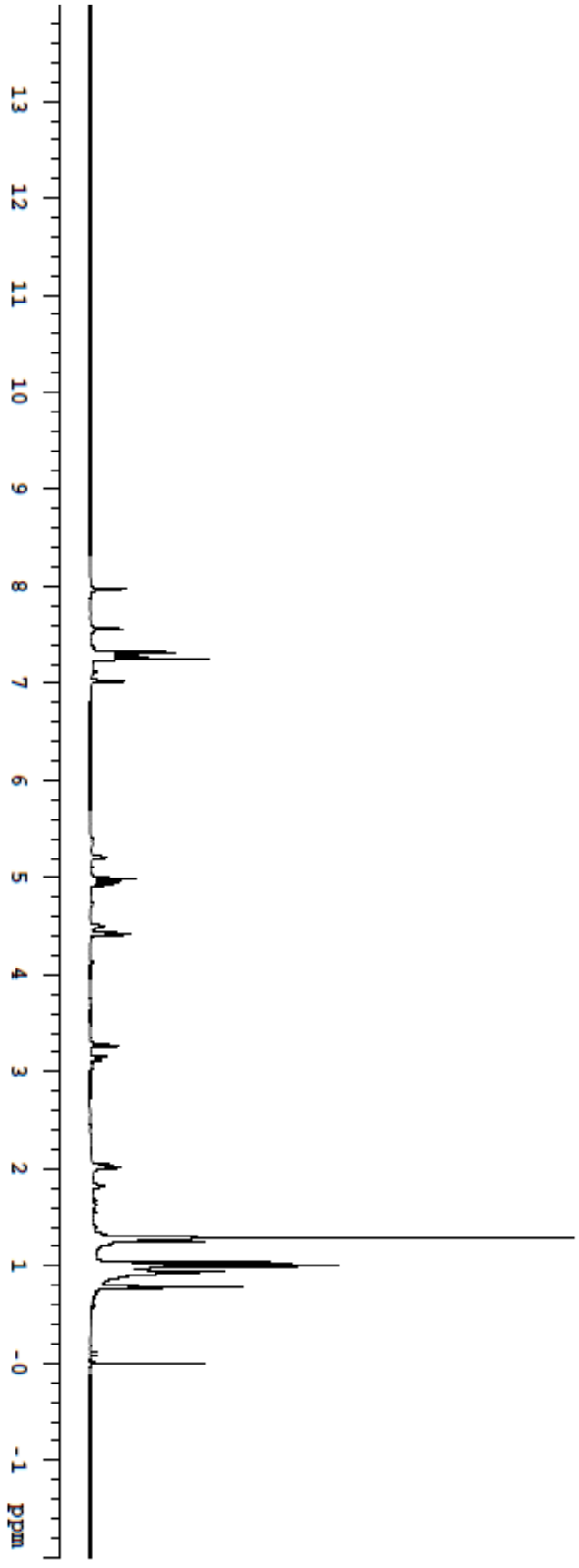
(3) He, L.; Srikanth, G. S. C.; Castle, S. L. *J Org. Chem.* **2005**, *70*, 8140.

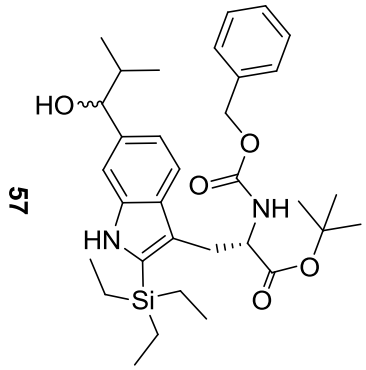
(4) Yakelis, N. A.; Bergman, R. G. *Organometallics* **2005**, *24*, 3579.

(5) Shen, Z.-L.; Cheong, H.-L.; Loh, T.-P. *Tetrahedron Lett.* **2009**, *50*, 1051.

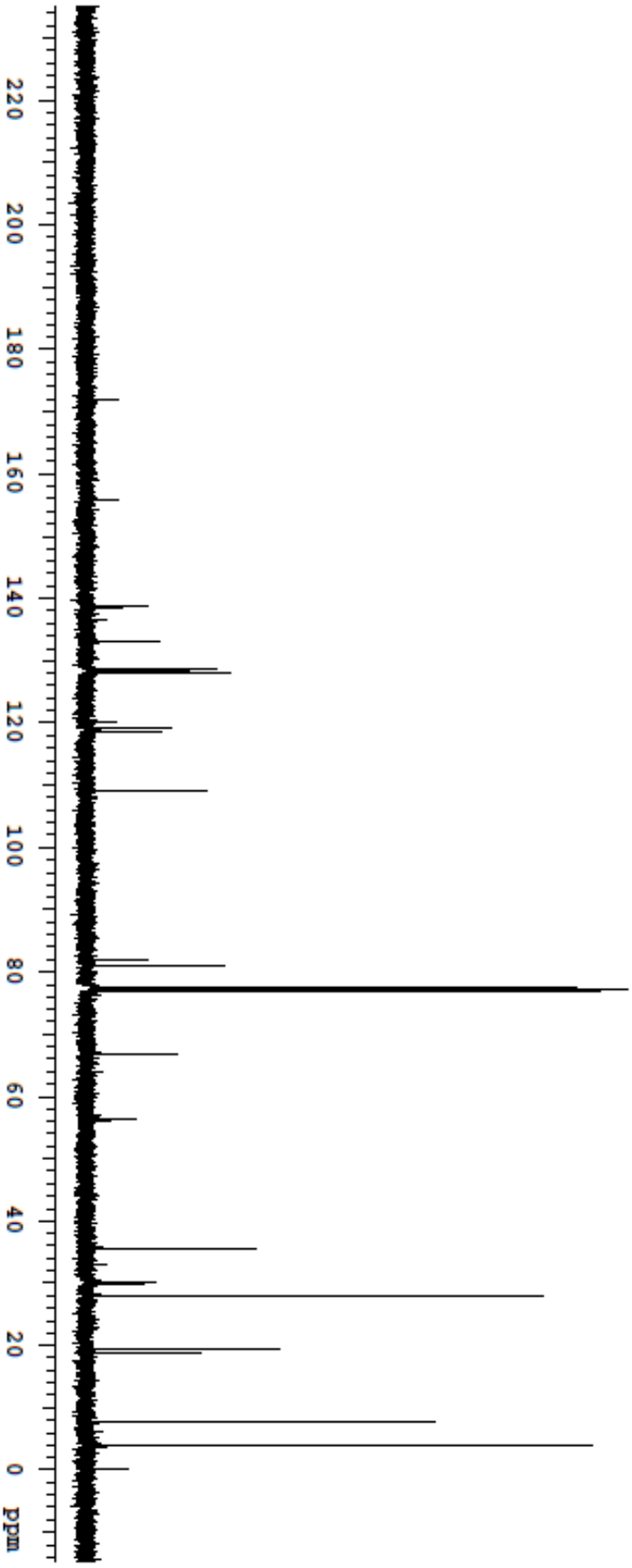
4.6 Supporting NMR Spectra

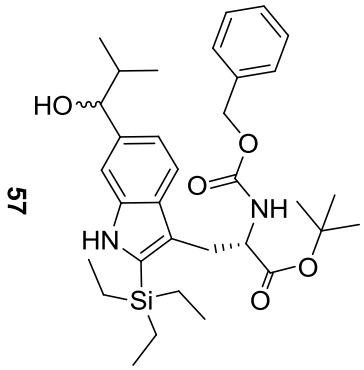
The following pages are ^{1}H and ^{13}C NMR spectra taken on a 500 MHz instrument. They include compounds **57**, **58**, and **59**.



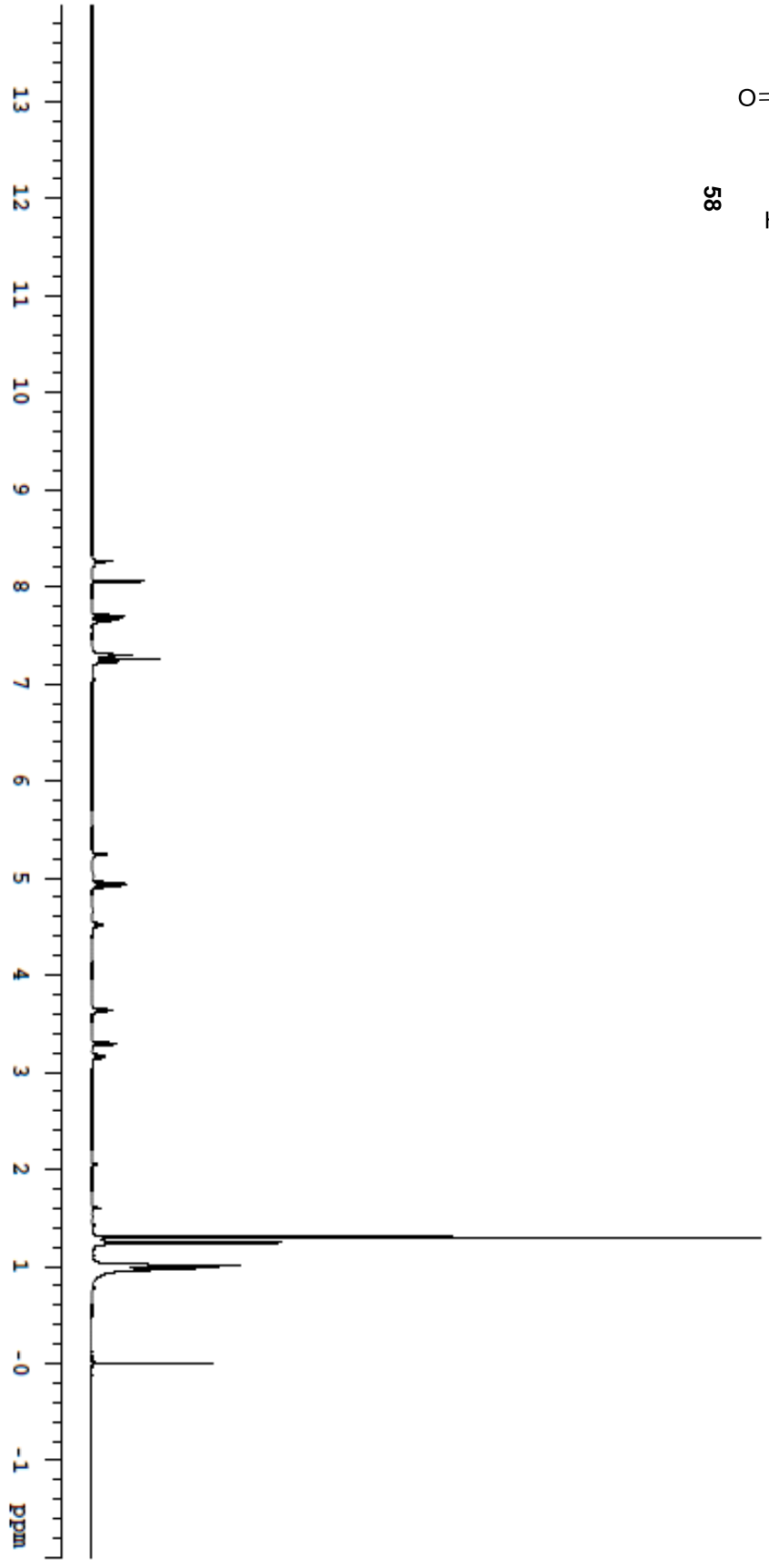


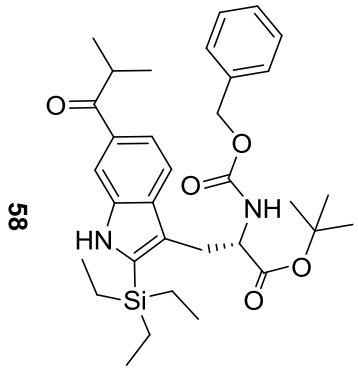
57



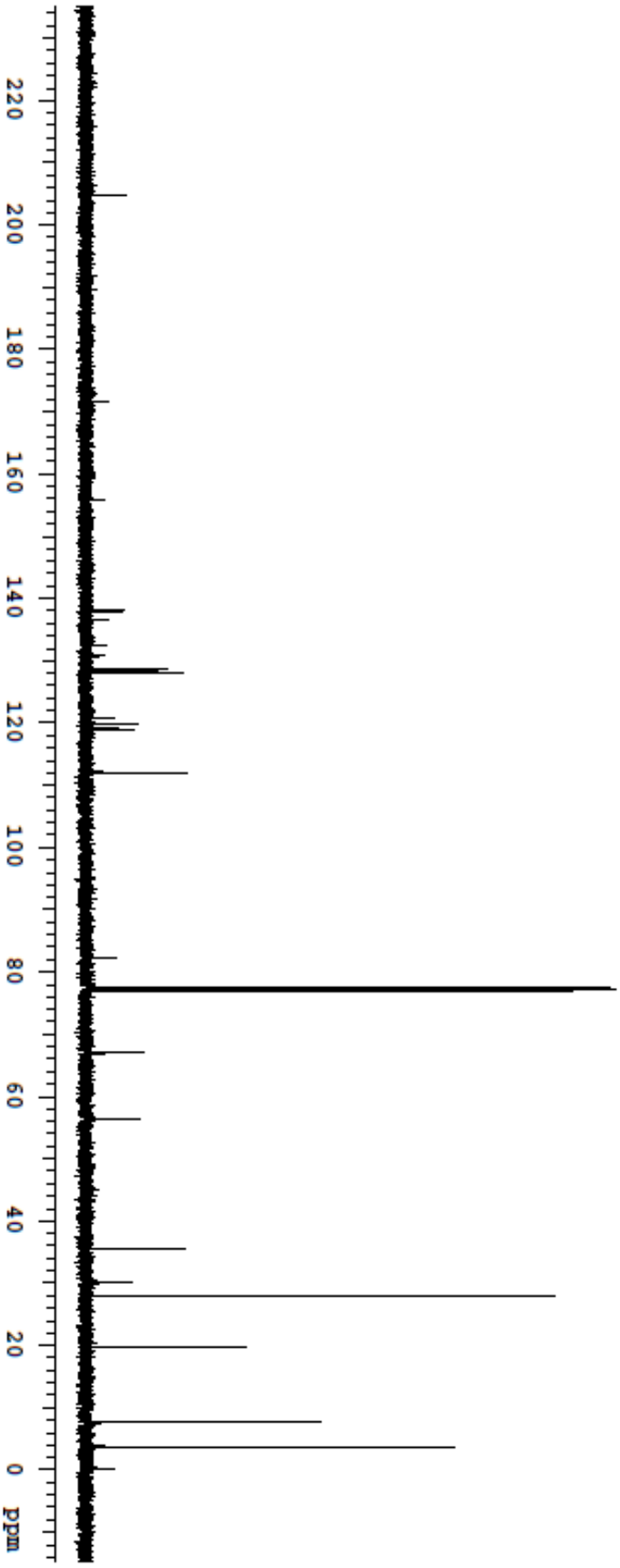


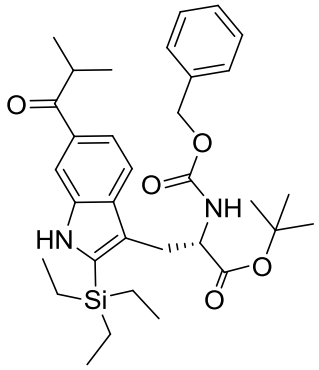
57



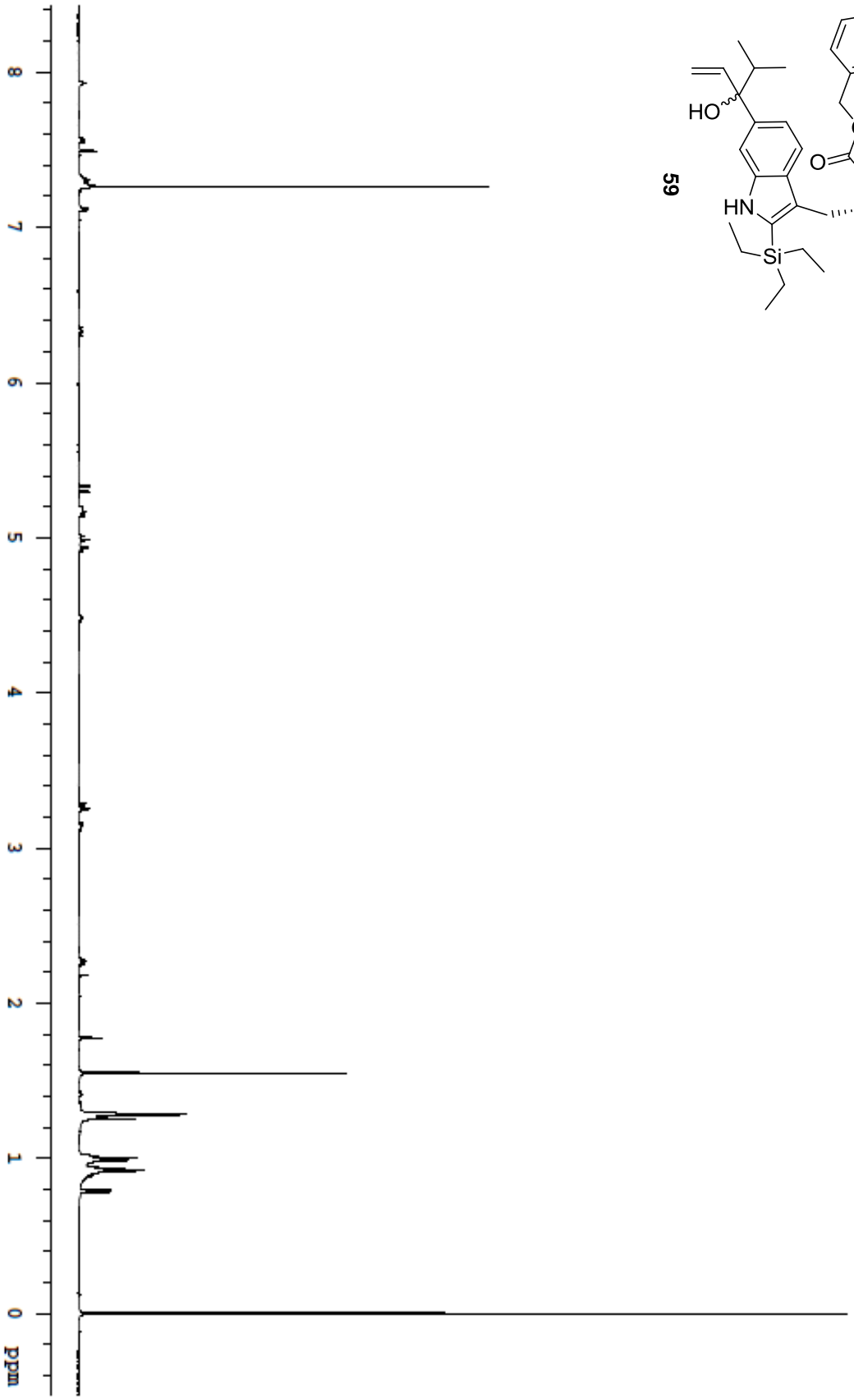


58





58



59

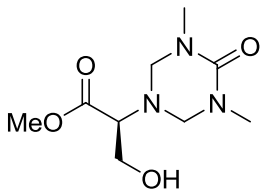
5. Experimental: τ-Hal

5.1 General Experimental Details

All anhydrous solvents were dried by passage through a Glass Contour solvent drying system containing cylinders of activated alumina. All equipment was dried in an oven and cooled over desiccant prior to use. Reagents were purchased from Sigma-Aldrich, Acros, and Fluka without further purification unless otherwise stated. Flash chromatography was carried out using 60-230 mesh silica gel. ^{1}H NMR spectra were acquired on 500 MHz spectrometers with tetramethylsilane (δ 0.00 ppm) as internal reference. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), brs (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz). ^{13}C NMR specta were acquired on spectrometers operating at 125 MHz with chloroform (δ 77.23 ppm) as internal reference. Infrared spectra were obtained on an FT-IR spectrometer. Mass spectral data were obtained using ESI techniques.

5.2 Synthesis of D-Ala Scaffold

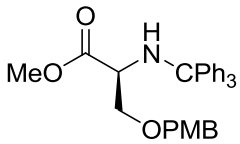
*Route **61→62→63***



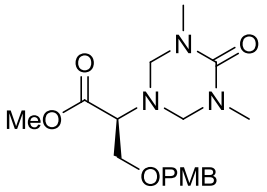
(*S*)-methyl 2-(3,5-dimethyl-4-oxo-1,3,5-triazinan-1-yl)-3-hydroxypropanoate (62).[1] L-Ser methyl ester **61** (0.2024 g; 1.30 mmol) was suspended with DIPEA (0.45 mL; 2.59 mmol) in 36% aqueous formaldehyde (1.4 mL) and stirred for an hour at rt. Anhydrous toluene (4×5 mL) was utilized to rotovaporized off the aziotrope (Tol·H_2O). The residue was then placed on high vacuum until the weight was constant. The remaining white precipitate was suspended with dimethyl urea in toluene (5 mL). The mixture was refluxed (oil bath set to 100 °C) for 24 hours. The volatile organics were rotovaporized and the remaining crude material was impregnated onto SiO_2 which was loaded onto a column prepared with Et_2O. The elution gradient of 4:1, 2:1, and 1:1

(Et_2O:Acetone) provided an impure sample of DMT **61** (24 mg; 8%). Note: Ninhydrin stain was utilized to identify **61**. The ^1H NMR verification was hindered due to impurities. Mass spectrometry was utilized to confirm presence of product. HRMS (ESI) *m/z* 232.12792 (MH^+, $C_9H_{17}N_3O_4H^+$ requires 232.12918); 254.11147 (MNa+, $C_9H_{17}N_3O_4Na^+$ requires 254.11113).

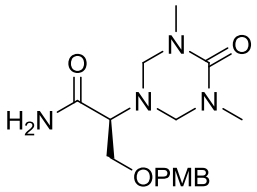
*Route **61→64→65→63→66***



(*S*)-methyl 3-(4-methoxybenzyloxy)-2-(tritylamino)propanoate (65).[2] Trityl-L-Ser methyl ester **64**[3] (0.1190 g; 0.329 mmol) was suspended in CH_2Cl_2 (3 mL) with PMB-Cl (49 μL; 0.361 mmol). TBAB was added to the vessel and the mixture was stirred at rt for 15 min. Then NaOH (14 μL; 50% by wt.) was added to the mixture and brought to gentle reflux under argon. TLC indicated reaction was complete after 12 hours. The vessel was removed from heat and allowed to cool to rt. The mixture was diluted CH_2Cl_2 (~10 mL). The reaction was quenched with H_2O (~10 mL) and the organics were extracted in CH_2Cl_2 (3×5 mL). The extracts were washed with brine (~10 mL) and re-extracted through a Na_2SO_4 plug. Volatile organics were rotovaporized off and the crude was impregnated onto SiO_2. This was loaded onto a column prepared in hexanes. The constant elution of 5% EtOAc in hexanes afforded product **65** (0.1031 g; 65%). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.48 (d, *J* = 8.0 Hz, 6H), 7.26–7.19 (m, 8H), 7.16 (t, *J* = 7.2 Hz, 3H), 6.86 (d, *J* = 9.0 Hz, 2H), 4.46 (d, *J* = 12.0 Hz, 1 H), 4.42 (d, *J* = 11.5 Hz, 1H), 3.80 (s, 3H), 3.74 (dd, *J* = 9.5, 5.0 Hz, 1H), 3.58–3.52 (m, 1H), 3.50 (dd, *J* = 9.2, 7.0 Hz, 1H), 3.20 (s, 3H), 2.75 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.4, 159.4, 146.0, 130.2, 129.3, 129.0, 128.0, 126.6, 113.9, 72.8, 72.4, 71.0, 56.6, 55.4, 51.9; IR (film) ν_{max} 3057, 2948, 2858, 2359, 1735, 1512, 1248, 1033, 707 cm^{-1}.



(*S*)-methyl 2-(3,5-dimethyl-4-oxo-1,3,5-triazinan-1-yl)-3-(4-methoxybenzyloxy)propanoate (63).[1,2] Trityl-L-Ser-OPMB methyl ester **65** (55.4 mg; 0.115 mmol) was suspended in 0.3 mL of Et_2O:MeOH (1:1) and cooled to 0 °C. While stirring this mixture, 1.0 M HCl/Et_2O (0.38 mL; 0.38 mmol) was added dropwise. The reaction went to completion in 3 hours, according to TLC. The volatile organics were rotovaporized off and the resulting residue was washed with Et_2O (4×1 mL) to remove the trityl byproduct. This residue was then suspended in 36% aqueous formaldehyde (58 μL). DIPEA (26 μL; 0.149 mmol) was added to the mixture until pH~7-8. The reaction mixture was stirred at rt for one hour. The water was removed with toluene (4×0.6 mL) via rotovaporization. This crude material was left on the high vacuum until the weight was constant. The remaining residue was re-suspended in toluene (5 mL) and refluxed for 36 hours. The reaction vessel was removed from the heating source and cooled to rt. The mixture was concentrated down and the remaining crude was suspended in EtOAc (10 mL) and washed with H_2O (10 mL). The organics were extracted in EtOAc (3×10 mL) and dried with Na_2SO_4. This crude material was then impregnated onto SiO_2 and loaded onto a column prepared in CH_2Cl_2. The elution gradient of 30–50% EtOAc in CH_2Cl_2 afforded product **63** (11.3 mg; 28%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.22 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.26 (d, *J* = 11.5 Hz, 2H), 4.19 (d, *J* = 11.5 Hz, 2H), 3.82–3.78 (m, 1H), 3.80 (s, 3H), 3.73 (dd, *J* = 10, 5.0 Hz, 1H), 3.73 (s, 3H), 3.68 (dd, *J* = 10.2, 5.2 Hz, 1H), 2.76 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.0, 159.6, 129.8, 129.6, 114.0, 73.2, 68.4, 66.8, 55.5, 52.6, 32.4, 29.9, 29.3; HRMS (ESI) *m/z* 352.1233 (MH^+, $C_{17}H_{25}N_3O_5H^+$ requires 352.1867).



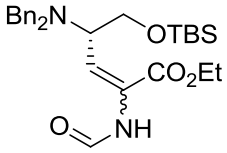
(*S*)-2-(3,5-dimethyl-4-oxo-1,3,5-triazinan-1-yl)-3-(4-methoxybenzyloxy)propanamide (66).[4] DMT-L-Ser-OPMB methyl ester **63** (10.9 mg; 0.0310 mmol) was suspended in MeOH (1.5 mL) and transferred to a sealed tube apparatus where it was stirred at 0 °C for 15 min. Ammonia gas was bubbled in the solution for 30 min. The system was sealed and allowed to warm to rt at which point it was heated to 70 °C for 2 days. The reaction vessel was removed from heat and cooled to 0 °C. The NH_3 gas was allowed to slowly evaporate off as mixture warmed to rt over 2 hours. The solution was concentrated down to a residue. ^{1}H NMR analysis showed mostly starting material with some decomposition. Mass spectrometry supports product **66**. HRMS (ESI) *m/z* 337.1860 (MH^+, $C_{16}H_{24}N_4O_4H^+$ requires 337.1870).

*Route **64→67→68***

For experimental procedures refer to Rapoport and coworkers publication.[5]

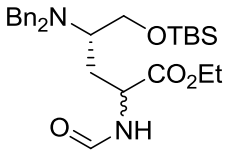
5.3 Synthesis of L-His Scaffold

*Route **69+70→71→72→73***



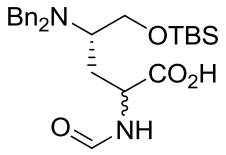
(*S*)-ethyl 5-(*tert*-butyldimethylsilyloxy)-4-(dibenzylamino)-2-formamidopent-2-enoate (71).[6,7] Aldehyde **69**[8] (1.1685 g; 3.05 mmol) and isonitrile **70** (0.2975 g; 2.63 mmol) were suspended in Et_2O (2.4 mL) and cooled to 0 °C. In one portion, Cu_2O (39.8 mg; 0.278 mmol) was added and the system was sealed and place under argon. The mixture was stirred at rt for four hours and cooled again to 0 °C. A solution of 1.0 M *t*-BuOK (2.8 mL; 2.8 mmol) was injected slowly into the reaction vessel. Two hours later, glacial acetic acid (0.15 mL; 2.61 mmol) was prepared in CH_2Cl_2 (6.7 mL) and injected slowly into the stirring mixture at 0 °C. The reaction mixture was warmed to rt, then quenched with H_2O (10 mL). The organics were extracted in CH_2Cl_2 (3×10 mL) through a

Na_2SO_4 plug. Impregnated crude material onto SiO_2 and loaded onto a column prepared with hexanes. An elution gradient of 10–20% EtOAc/Hexanes afforded product **71** (1.033 g; 2.08 mmol; 84%; mixture of diastereomers) as an orange/brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.38 (d, *J* = 2.0 Hz, 2H), 7.78 (brs, 2H), 7.72 (s, 1H), 7.44 (s, 1H), 7.44–7.14 (m, 20H), 6.42 (dd, *J* = 11.5, 7.5 Hz, 1H), 5.26 (s, 2H), 4.52–4.48 (m, 2H), 4.31–4.22 (m, 2H), 4.04–4.00 (m, 1H), 4.00–3.87 (m, 5H), 3.80–3.72 (m, 3H), 3.72–3.68 (m, 2H), 3.54 (d, *J* = 14.5 Hz, 2H), 1.32–1.28 (m, 3H), 0.93–0.87 (m, 18H), 0.85 (t, *J* = 7 Hz, 3H), 0.09 (brs, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.5, 158.9, 139.6, 138.8, 129.4, 129.1, 128.8, 128.7, 127.6, 126.4, 63.4, 62.7, 62.0, 61.6, 57.3, 56.8, 55.4, 55.2, 26.1, 18.4, 14.3, –5.2, –5.3; IR (film) ν_{max} 3296, 3062, 2954, 2856, 1722, 1470, 1252, 1096, 836, 747 cm^{-1}; HRMS (ESI) *m/z* 497.30950 (MH^+, $C_{28}H_{40}N_2O_4SiH^+$ requires 497.28301).



(*S*)-ethyl 5-(*tert*-butyldimethylsilyloxy)-4-(dibenzylamino)-2-formamidopentanoate (72).[9,10] Condensation product **71** (0.8011 g; 1.61 mmol) and Wilkinson's catalyst (0.2175 g; 0.235 mmol) were suspended in anhydrous CH_2Cl_2 (10 mL). The round bottom flask was placed into a bomb apparatus where it was flushed with argon (~15 min) and then charged with H_2 (25 bar). The reaction stirred for 48 hours at rt. The bomb apparatus was depressurized and the reaction mixture was concentrated down onto SiO_2. The crude mixture was loaded onto a column prepared in hexanes and the elution gradient of 10–20% EtOAc/Hexanes afforded product **72** (0.6565 g; 1.32 mmol; 82%; mixture of diastereomers). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.22 (s, 1H), 7.8 (s, 1H), 7.38–7.23 (m, 20H), 6.35 (brs, 1H), 6.14 (d, *J* = 7.0 Hz, 1H), 4.70–4.65 (m, 1H), 4.64–4.58 (m, 1H), 4.22 (dq, *J* = 14.1, 7.1, 1.6 Hz, 2H), 4.19–4.14 (m, 1H), 4.08 (q, *J* = 14.2, 7.2 Hz, 2H), 3.88 (d, *J* = 14.0 Hz, 2H), 3.88–3.83 (m, 1H), 3.83–3.78 (m, 1H), 3.80 (dd, *J* = 10.2, 5.8 Hz, 1H), 3.70 (dd, *J*

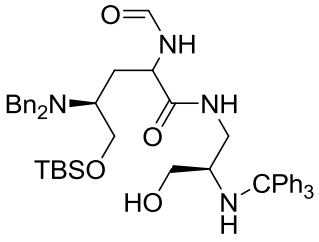
= 10.2, 5.2 Hz, 1H), 3.65–3.56 (m, 2H), 3.60 (d, *J* = 13.0 Hz, 2H), 2.90–2.82 (m, 1H), 2.12–2.05 (m, 1H), 2.00–1.92 (m, 1H), 1.85–1.76 (m, 2H), 1.60 (brs, 1H), 1.59–1.52 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.26–1.24 (m, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.93 (s, 9H), 0.89 (s, 9H), 0.10 (dd, *J* = 10.5, 4.5 Hz, 6H), 0.05 (d, *J* = 2.5 Hz, 6H); HRMS (ESI) *m/z* 499.29990 (MH^+, $C_{28}H_{42}N_2O_4SiH^+$ requires 499.29866).



(*S*)-5-(*tert*-butyldimethylsilyloxy)-4-(dibenzylamino)-2-formamidopentanoic acid (73). Reduced product **72** (0.303 g; 0.608 mmol) was suspended in 34 mL of *t*-BuOH:H_2O (2:1) and stirred at 0 °C. A 1.01 M LiOH (0.6 mL; 0.606 mmol) solution was added dropwise to the stirring mixture. The reaction went to completion in a four hour period. Citric acid (10%) was added until the pH~5-6. The crude mixture was diluted with H_2O (10 mL) and the organics were extracted in CH_2Cl_2 (7×10 mL) through a Na_2SO_4 plug. Volatile organics were rotovaporized off. The crude ^{1}H NMR analysis supported product **73** (0.2716; ~100%). Without further purification, **73** was coupled to **68**.

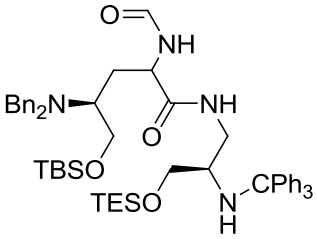
5.4 Synthetic Efforts towards τ-HAL

*Route **68**+**73**→**74**→**75**→**76**→**77***



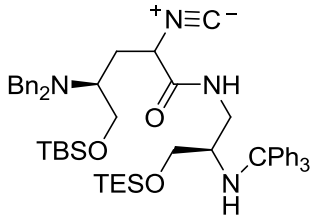
(4*S*)-5-(*tert*-butyldimethylsilyloxy)-4-(dibenzylamino)-2-formamido-*N*-((*R*)-3-hydroxy-2-(tritylamino)propyl)pentanamide (74). D-Ala scaffold **68** (0.1738 g; 0.523 mmol) and L-His scaffold **73** (0.247 g; 0.526 mmol) were suspended in anhydrous THF (2.8 mL). The system was flushed with argon and cooled to 0 °C. NMM (0.29 mL; 2.64 mmol) was added followed by HOBt (85 mg; 0.629 mmol) and EDCI·HCl (0.1210 g; 0.631 mmol). Twelve hours later, the reaction was quenched with sat. $NaHCO_3$ (5 mL). The organics were extracted in

CH_2Cl_2 (3×5 mL) through a Na_2SO_4 plug and concentrated down via rotovaporization. The crude material was loaded onto a column prepared in CH_2Cl_2. The elution gradient 0–2% EtOAc/DCM afforded product **74** (0.3744 g; 91%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.91 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 6H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.33–7.18 (m, 16H), 7.13 (t, *J* = 7.2 Hz, 3H), 6.52 (brs, 1H), 4.99 (t, *J* = 6.2 Hz, 1H), 4.46–4.40 (m, 1H), 3.82 (d, *J* = 13.5 Hz, 2H), 3.80–3.76 (m, 1H), 3.62–3.59 (m, 1H), 3.57 (d, *J* = 13.5 Hz, 2H), 3.46 (s, 2H), 3.06–2.98 (m, 1H), 1.92–1.86 (m, 1H), 2.58–2.53 (m, 1H), 2.36 (brs, 1H), 1.94 (dd, *J* = 12.0, 4.0 Hz, 1H), 1.80–1.67 (m, 2H), 0.92 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.2, 160.8, 146.9, 140.4, 129.4, 129.6, 129.1, 128.8, 128.8, 128.6, 128.6, 128.3, 128.2, 128.1, 127.4, 127.0, 126.7, 71.0, 63.0, 60.1, 56.1, 54.0, 53.0, 50.5, 41.2, 32.0, 26.2, 18.4, –5.2, –5.3; HRMS (ESI) *m/z* 785.44646 (MH^+, $C_{48}H_{60}N_4O_4SiH^+$ requires 785.44566).



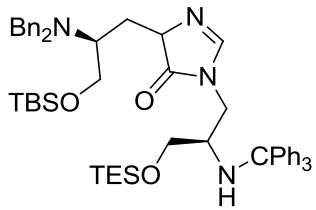
(4*S*)-5-(*tert*-butyldimethylsilyloxy)-4-(dibenzylamino)-2-formamido-*N*-((*R*)-3-(triethylsilyloxy)-2-(tritylamino)propyl)pentanamide (75).[5] Dipeptide **74** (0.2793 g: 0.356 mmol) was suspended in CH_2Cl_2 (5.8 mL) with Et_3N (94 μL; 0.674 mmol), DMAP (9.5 mg; 0.0778 mmol), and TES-Cl (0.11 mL; 0.655 mmol) which was cooled to 0 °C, under argon. The reaction was allowed to warm to rt over a two hour period of time. The reaction stirred for 24 hours at rt and was quenched with sat. $NaHCO_3$ (5 mL). The organics were extracted in CH_2Cl_2 (3×5 mL). These extracts were washed with brine (10 mL) and re-extracted through a Na_2SO_4 plug. The crude mixture was concentrated down and loaded onto a column prepared in CH_2Cl_2. The elution gradient of 0–3% EtOAc/CH_2Cl_2 afforded product **75** (0.2527 g; ~80%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 (s, 1H), 7.52 (d, *J* = 7.5 Hz, 6H), 7.32–7.22 (m, 16H), 7.18 (t, *J* = 7.2 Hz, 3H), 6.44 (d, *J* = 7.5 Hz, 1H), 5.56 (t, *J* = 5.8 Hz),

4.35 (q, *J* = 14.0, 7.5 Hz, 1H), 3.82 (d, *J* = 13.5 Hz, 2H), 3.85–3.79 (m, 1H), 3.75 (dd, *J* = 10.8, 5.2 Hz, 1H), 3.62 (d, *J* = 13.5 Hz, 2H), 3.19–3.13 (m, 1H), 2.98 (dd, *J* = 9.5, 4.0 Hz, 1H), 2.87–2.80 (m, 1H), 2.78–2.73 (m, 1H), 2.66 (dd, *J* = 10.0, 5.5 Hz, 1H), 2.60–2.55 (m, 1H), 2.40 (brs, 1H), 2.97–2.89 (m, 1H), 2.85–2.78 (m, 1H), 0.92 (s, 9H), 0.85 (t, *J* = 7.8 Hz, 9H), 0.44 (q, *J* = 16.2, 8.2 Hz, 6H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.4, 161.0, 147.0, 140.3, 129.5, 129.3, 129.0, 128.6, 128.2, 128.1, 128.0, 127.4, 127.3, 126.5, 71.0, 63.2, 56.2, 54.4, 53.5, 51.3, 42.0, 31.3, 26.1, 18.4, 7.0 (2C), 4.4, −5.2 (2C); HRMS (ESI) *m/z* 899.53347 (MH^+, $C_{54}H_{74}N_4O_4Si_2H^+$ requires 899.53214).



(4*S*)-5-(*tert*-butyldimethylsilyloxy)-4-(dibenzylamino)-2-isocyano-*N*-((*R*)-3-(triethylsilyloxy)-2-(tritylamino)propyl)pentanamide (76).[11] Formamide **75** is prepared as a 0.04 M solution in anhydrous CH_2Cl_2. The Burgess reagent was loaded into a dry flask where it was flushed with argon. The 0.04 M **75**/THF solution (1.4 mL; 0.056 mmol) was injected into this flask and stirred at rt for 5 hours. Mass spectrometry indicated reaction was complete. The mixture down was concentrated down and washed with H_2O (3 mL). The organics were extracted in Et_2O (3×3 mL) through a Na_2SO_4 plug. The volatile organics were removed via rotovaporization and no further purification was required. ^{1}H NMR spectroscopy supported product **76** (49.2 mg; ~100%) with small impurities. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55 (d, *J* = 7.5 Hz, 6H), 7.35–7.18 (m, 19H), 6.60 (t, *J* = 5.5 Hz, 1H), 4.32 (dd, *J* = 9.0, 4.5 Hz, 1H), 3.80 (d, *J* = 5.5 Hz, 2H), 3.67 (s, 4H), 3.22–3.16 (m, 1H), 3.12 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.06–2.94 (m, 3H), 2.86–2.81 (m, 1H), 2.80–2.74 (m, 1H), 2.44 (d, *J* = 6.0 Hz, 1H), 2.32–2.24 (m, 1H), 2.04–1.96 (m, 1H), 1.26 (brs, 1H), 1.20 (t, *J* = 7.0 Hz, 1H), 0.94–0.82 (m, 18H), 0.51 (q, *J* = 16.0, 8.0 Hz, 6H), 0.04 (d, *J* = 4.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ

166.0, 146.7, 140.1, 129.0, 128.9, 128.4, 128.2, 128.1, 127.4, 127.2, 126.8, 71.2, 64.4, 64.3, 55.9, 54.8, 52.6, 43.0, 33.3, 26.1, 18.4, 7.0, 4.4, –5.4; IR (film) ν_{max} 3396, 3060, 3028, 2953, 2876, 2132, 1686, 1520, 1448, 1254, 1094, 1004, 836, 775, 744 cm^{-1}; HRMS (ESI) *m/z* 881.54146 (MH^+, $C_{54}H_{72}N_4O_3Si_2H^+$ requires 881.52157), 898.51822 (MNH_4^+, $C_{54}H_{72}N_4O_3Si_2NH_4^+$ requires 898.54812).



4-((*S*)-3-(*tert*-butyldimethylsilyloxy)-2-(dibenzylamino)propyl)-1-((*R*)-3-(triethylsilyloxy)-2-(tritylamino)propyl)-1H-imidazol-5(4H)-one (77).[12] Isonitrile **76** (20.5 mg; 0.0233 mmol) was suspended in anhydrous THF (58 μL) and injected into a sealed system flushed with argon where it was cooled to –60 °C. While stirring the mixture vigorously, 1.0 M *t*-BuOK (35 mL; 0.035 mmol) was injected dropwise. After stirring for 30 min, $PhNTf_2$ (17.7 mg; 0.0495 mmol) was suspended in THF (50 μL) and half of the volume was injected into the stirring solution. The reaction was allowed to warm to 0 °C over an hour at which point the other half of the suspension of $PhNTf_2$ was injected. Three hours later, the reaction was quenched with H_2O (1 mL). The organics were extracted in CH_2Cl_2 (3×1mL) through a Na_2SO_4 plug. The crude mixture was concentrated onto SiO_2 and loaded onto a column prepared in hexanes. The elution gradient of 0–10% Et_2O in hexanes afforded product **77** (1.7 mg; 8%). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.78 (d, *J* = 8.0 Hz, 6H), 7.36–7.08 (m, 19H), 5.98 (s, 1H), 3.88–3.80 (m, 3H), 3.78 (d, *J* = 13.5 Hz, 2H), 3.64 (d, *J* = 13.5 Hz, 2H), 3.50–3.34 (m, 5H), 2.87 (dd, J = 13.8, 8.2 Hz, 1H), 2.80 (s, 1H), 2.72–2.64 (m, 2H), 0.89 (s, 9H), 0.83 (t, *J* = 8.0 Hz, 9H), 0.44 (q, *J* = 16.0, 8.0 Hz, 6H), 0.03 (d, *J* = 5.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 170.1, 147.0, 140.5, 129.8, 129.1, 128.2 (2C), 127.4, 127.1, 126.8, 99.8, 65.4, 63.6, 63.4, 56.7,

54.4, 47.4, 29.9, 28.1, 26.1, 18.4, 14.4, 6.8, 4.4, –5.2, –5.3; IR (film) ν_{max} 2920, 1731, 1489, 1094, 744 cm^{-1}; HRMS (ESI) *m/z* 881.5151 (MH^+, $C_{54}H_{72}N_4O_3Si_2H^+$ requires 881.5216).

5.5 References

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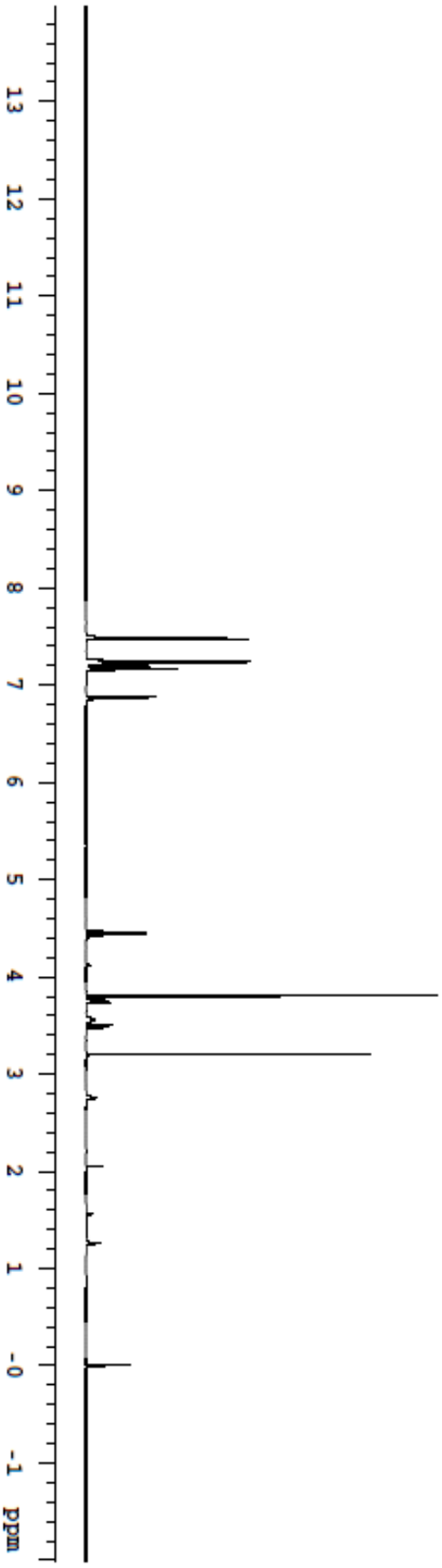
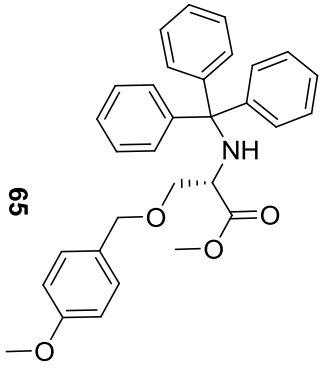
5.6 Supporting NMR Spectra





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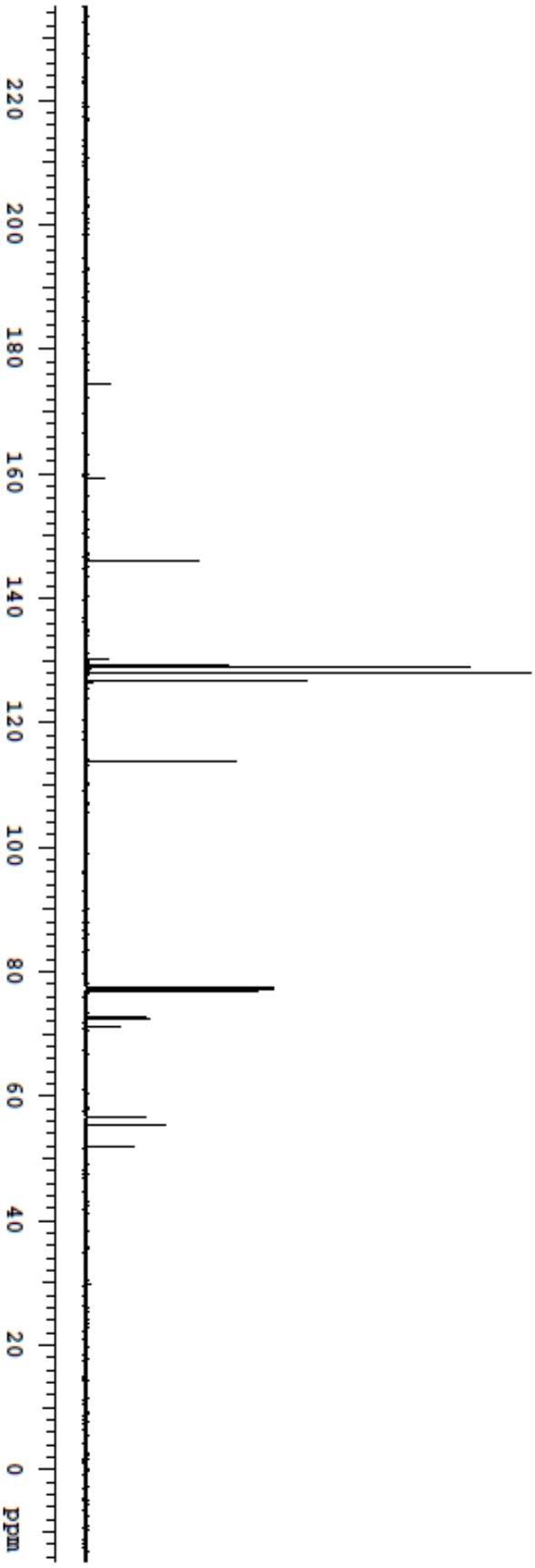

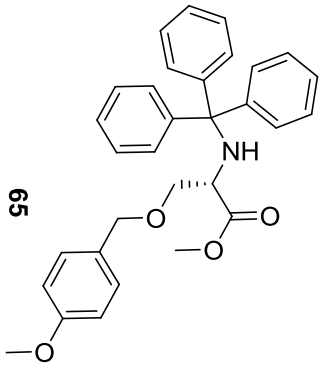

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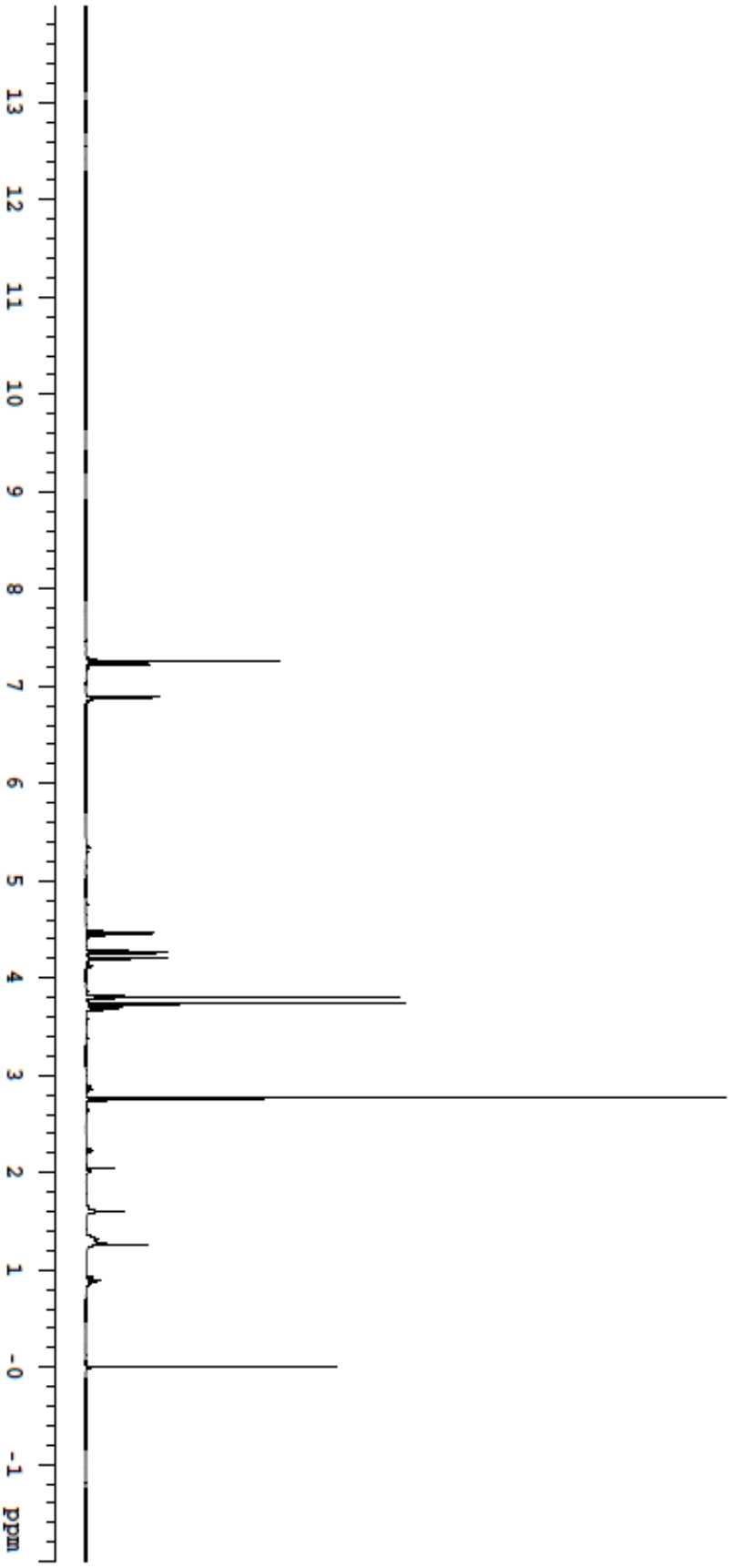

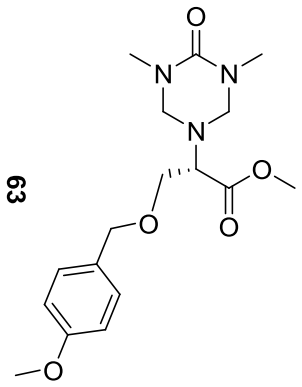

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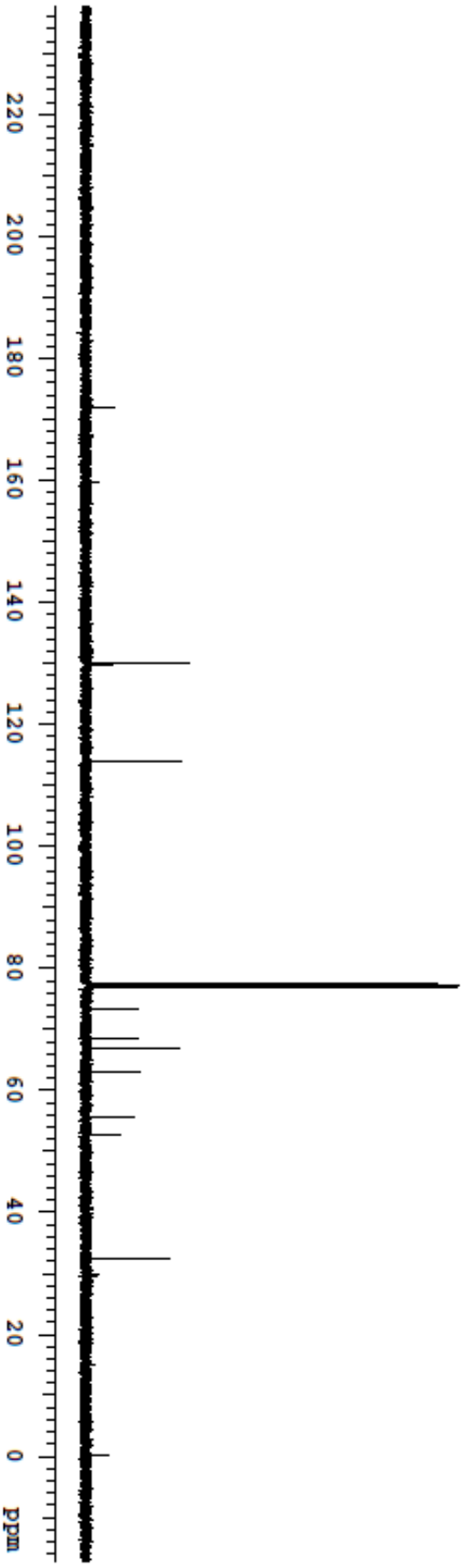

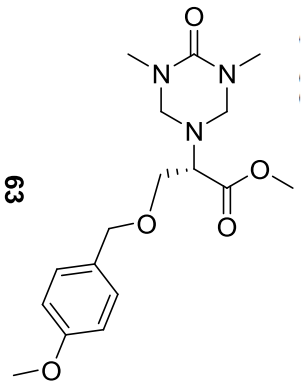

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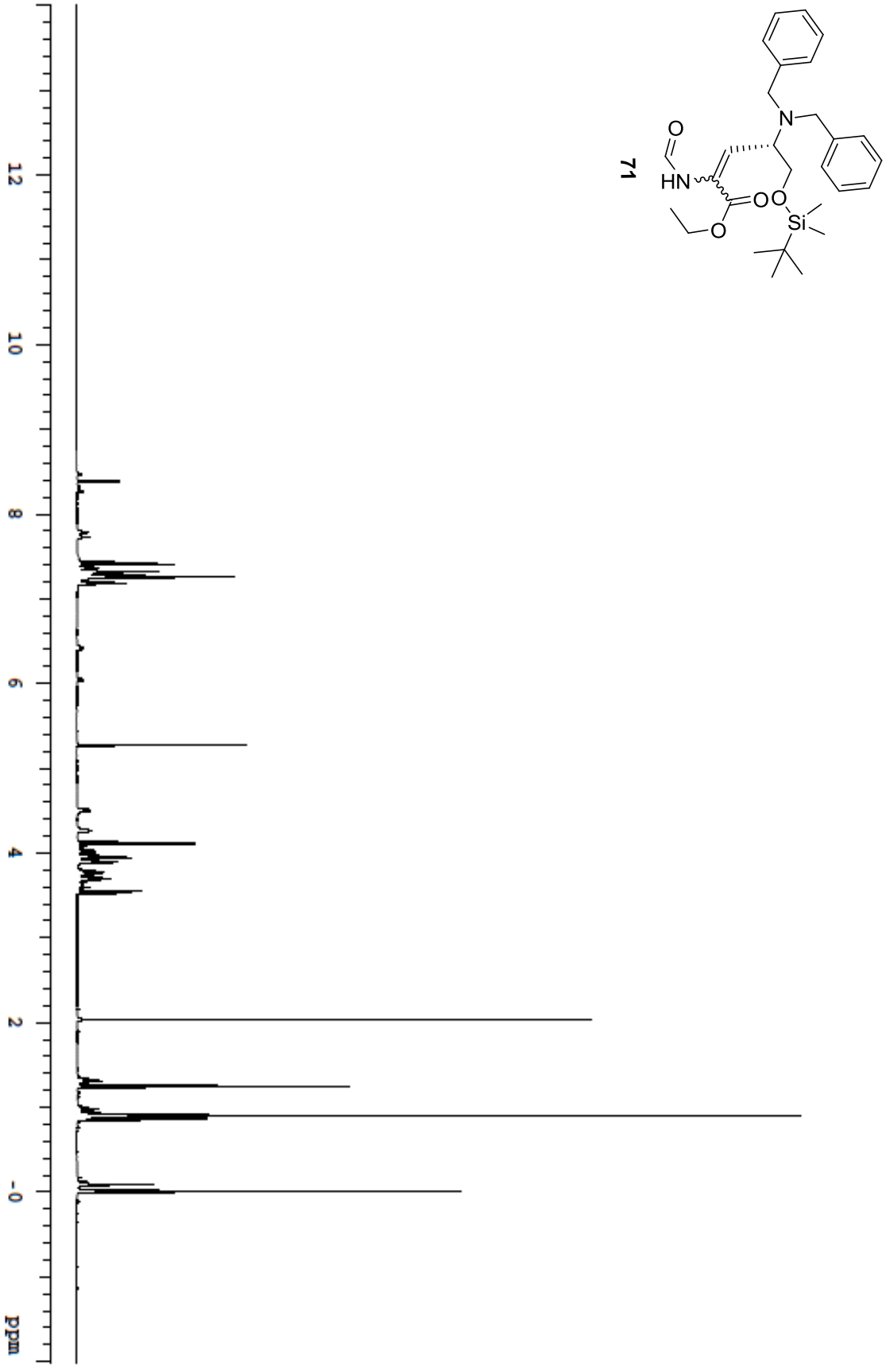

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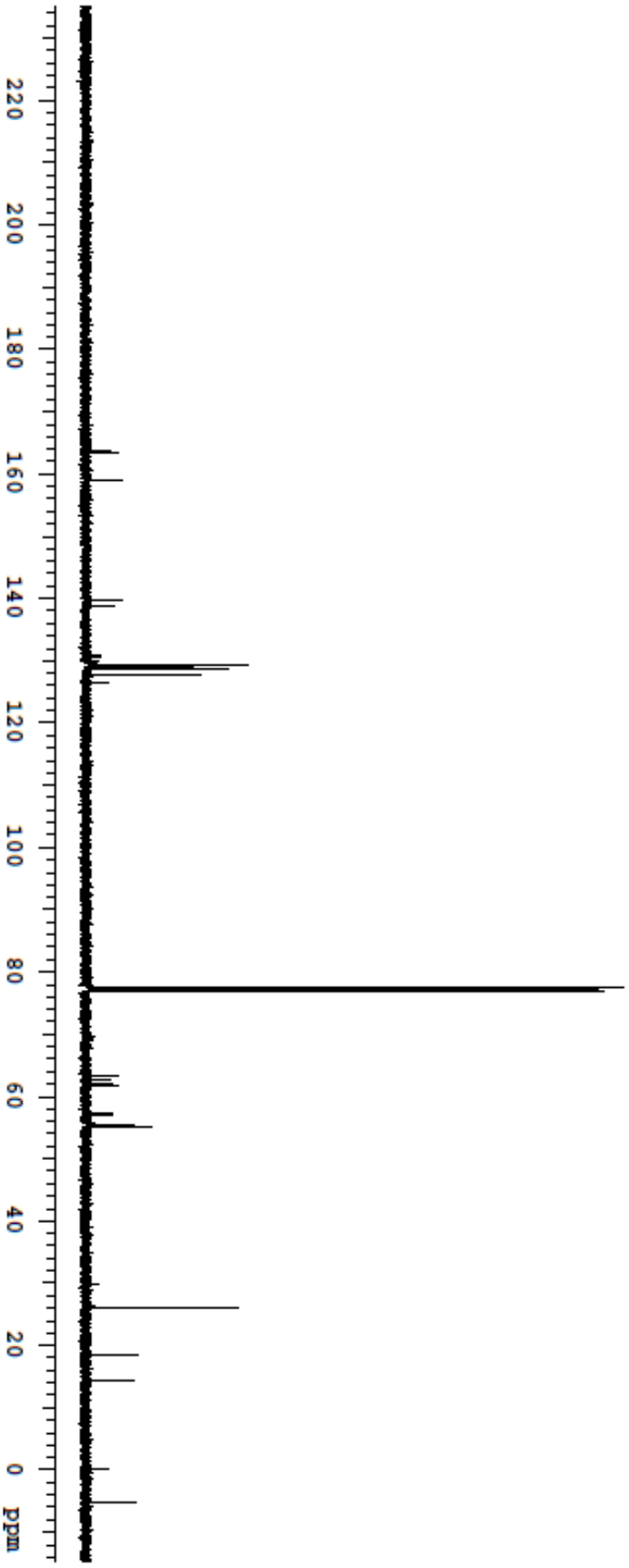

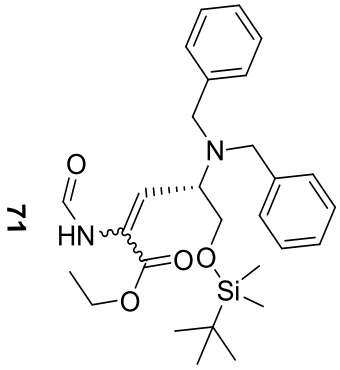

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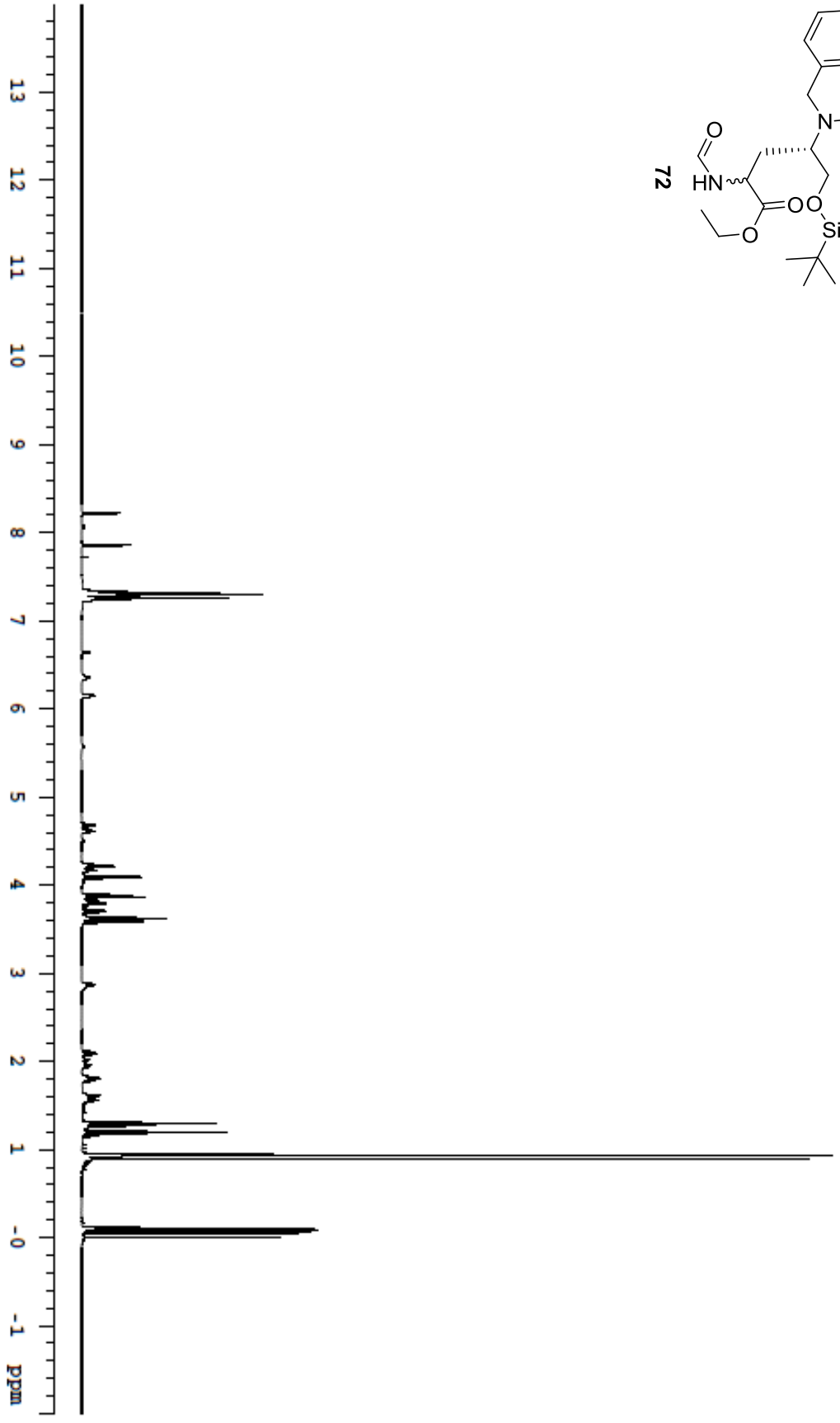

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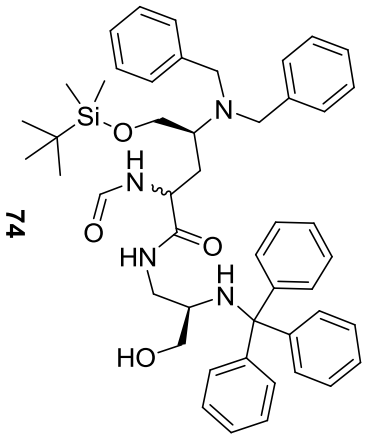

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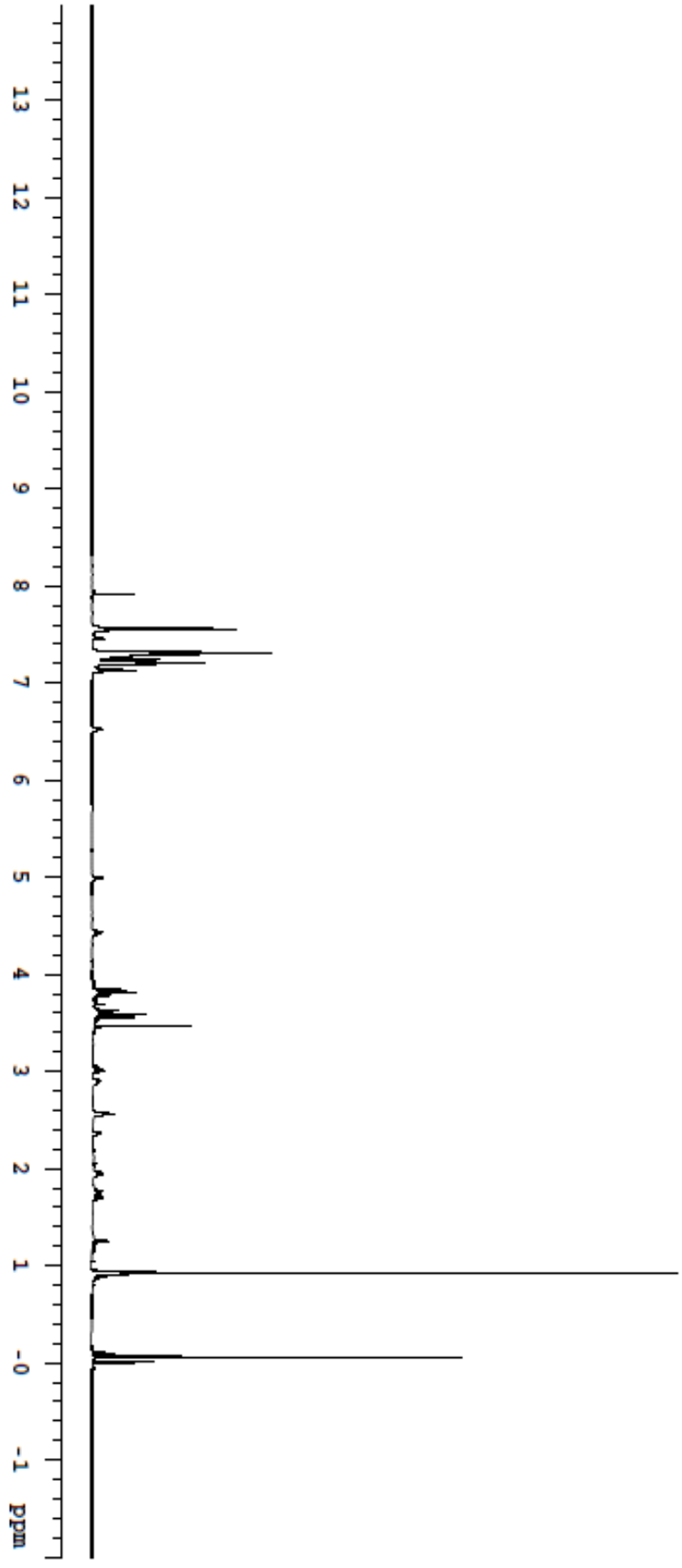

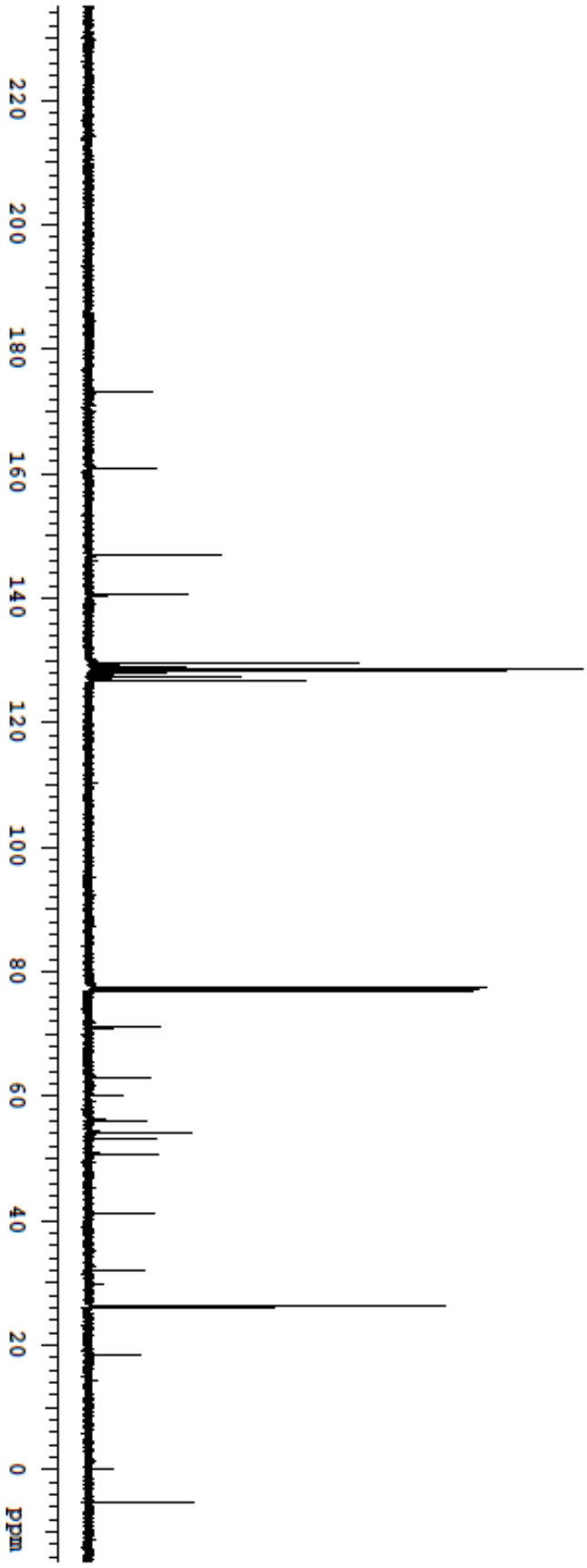

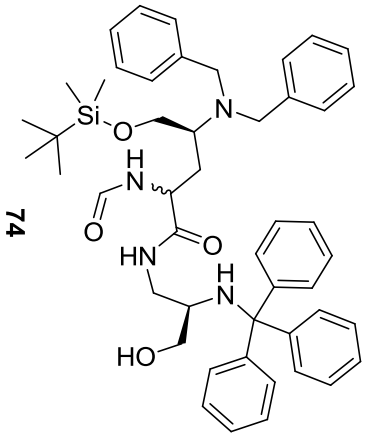

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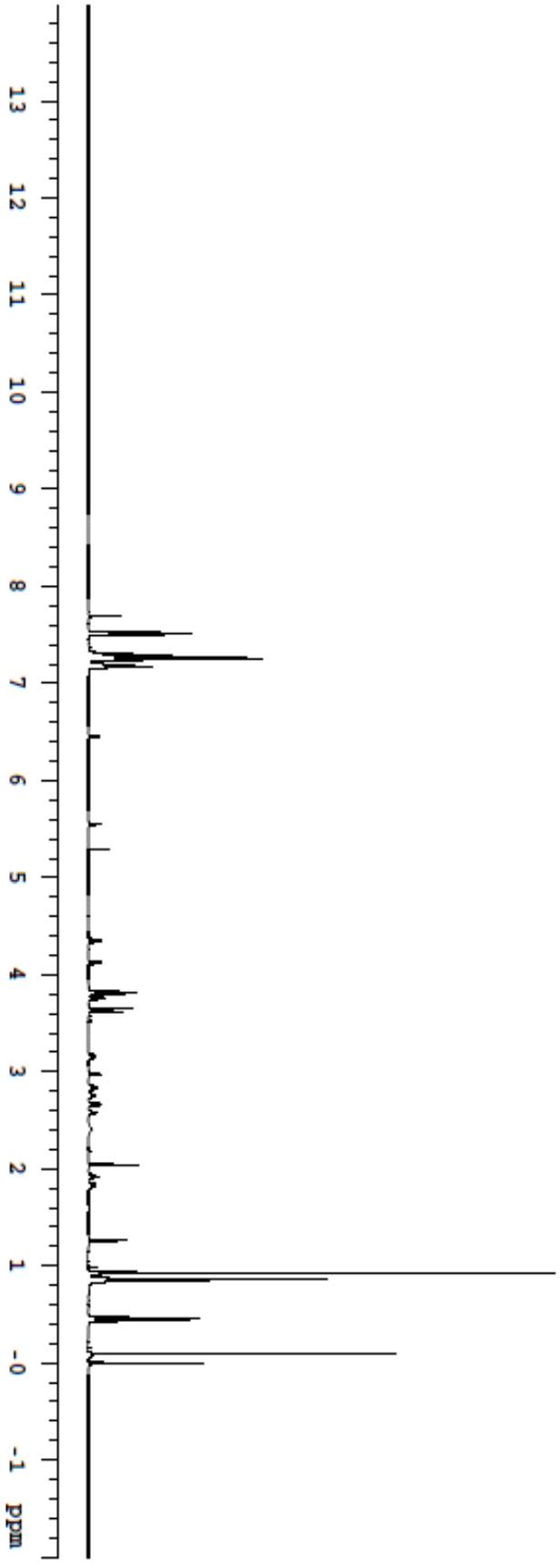

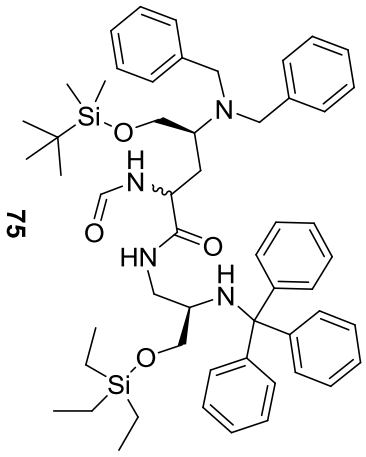

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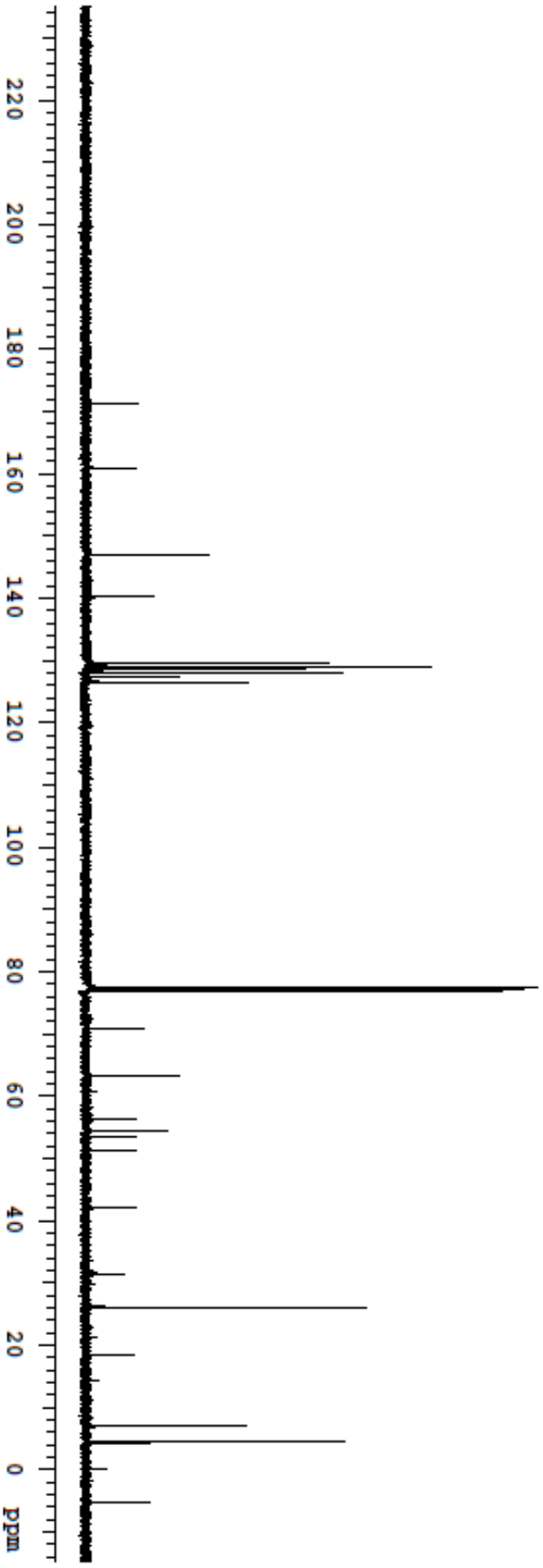

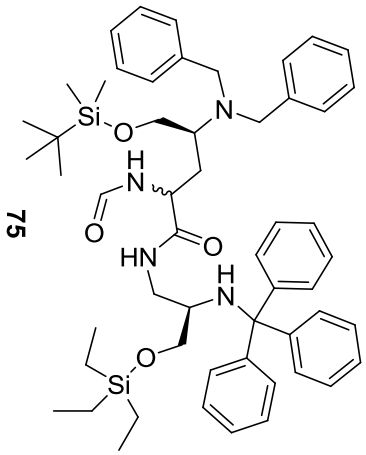

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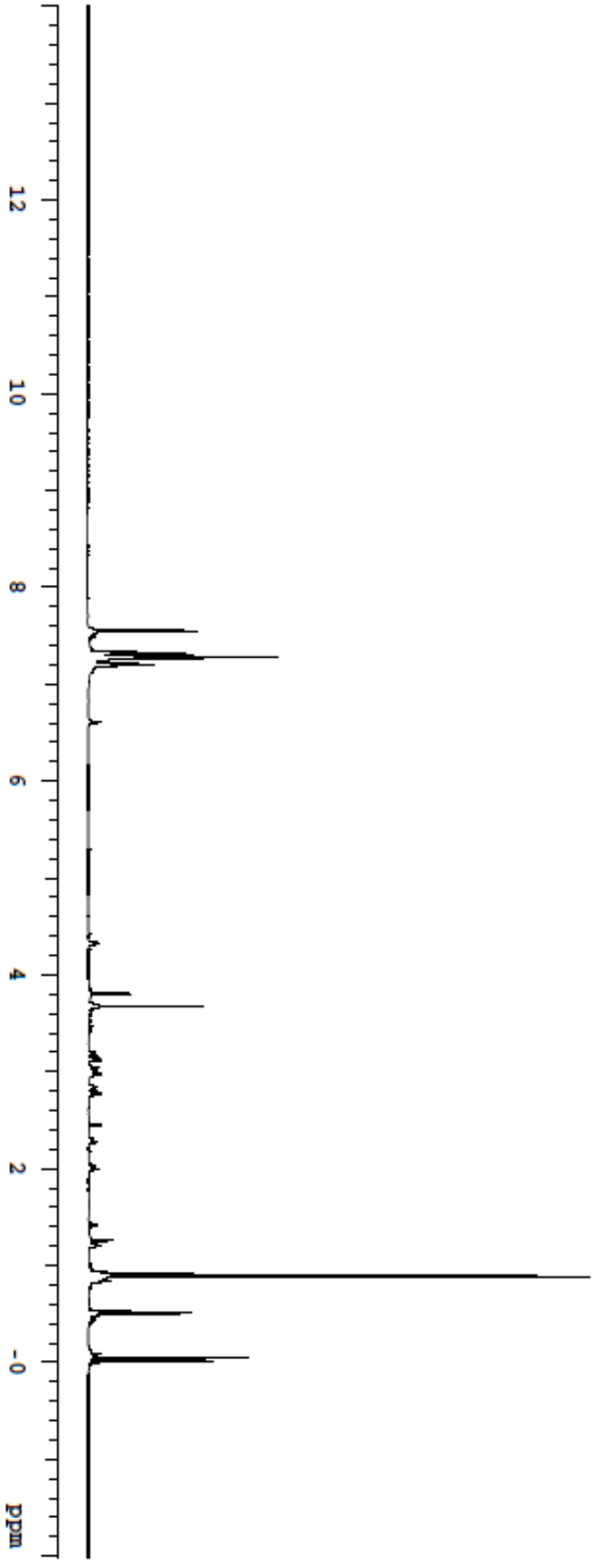

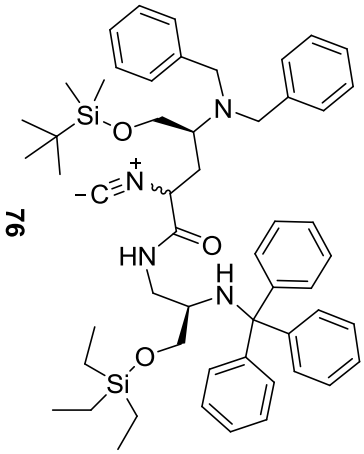

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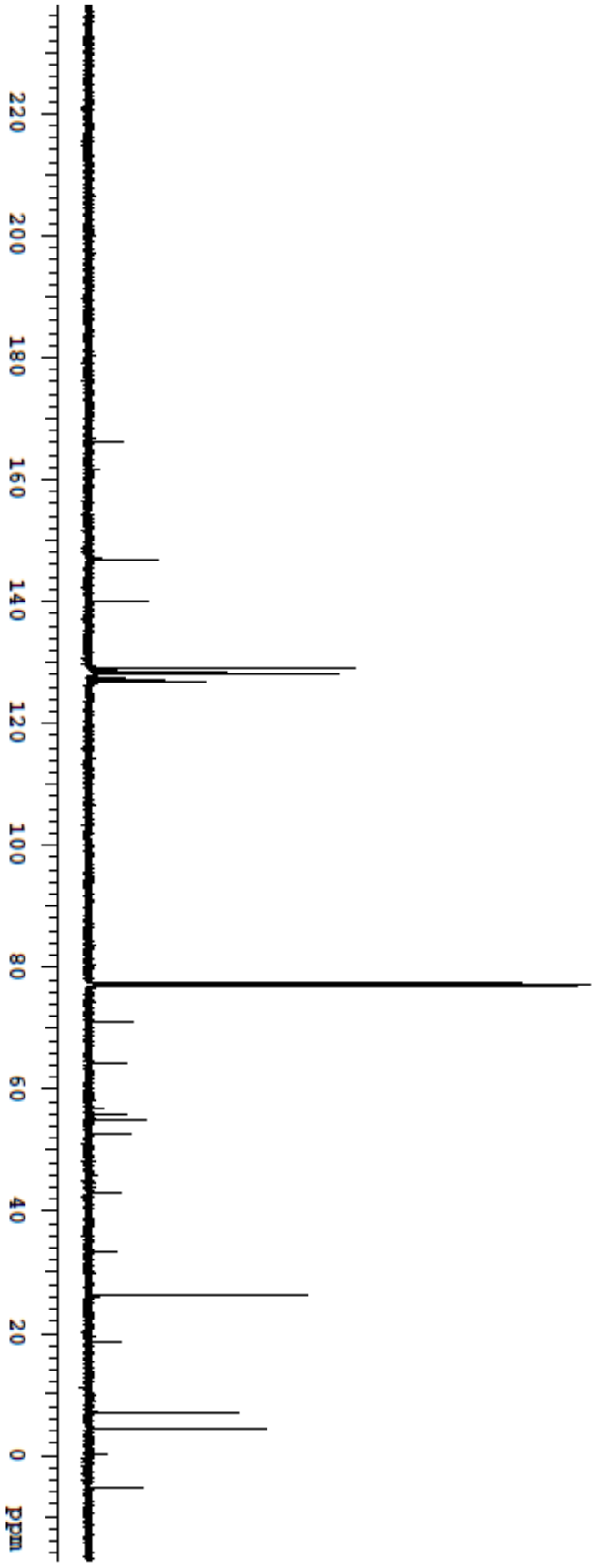

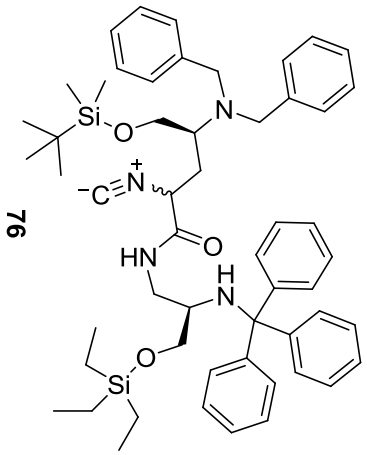

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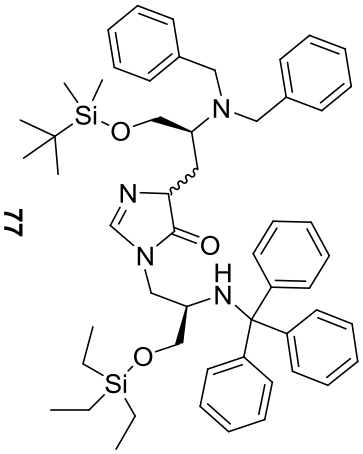

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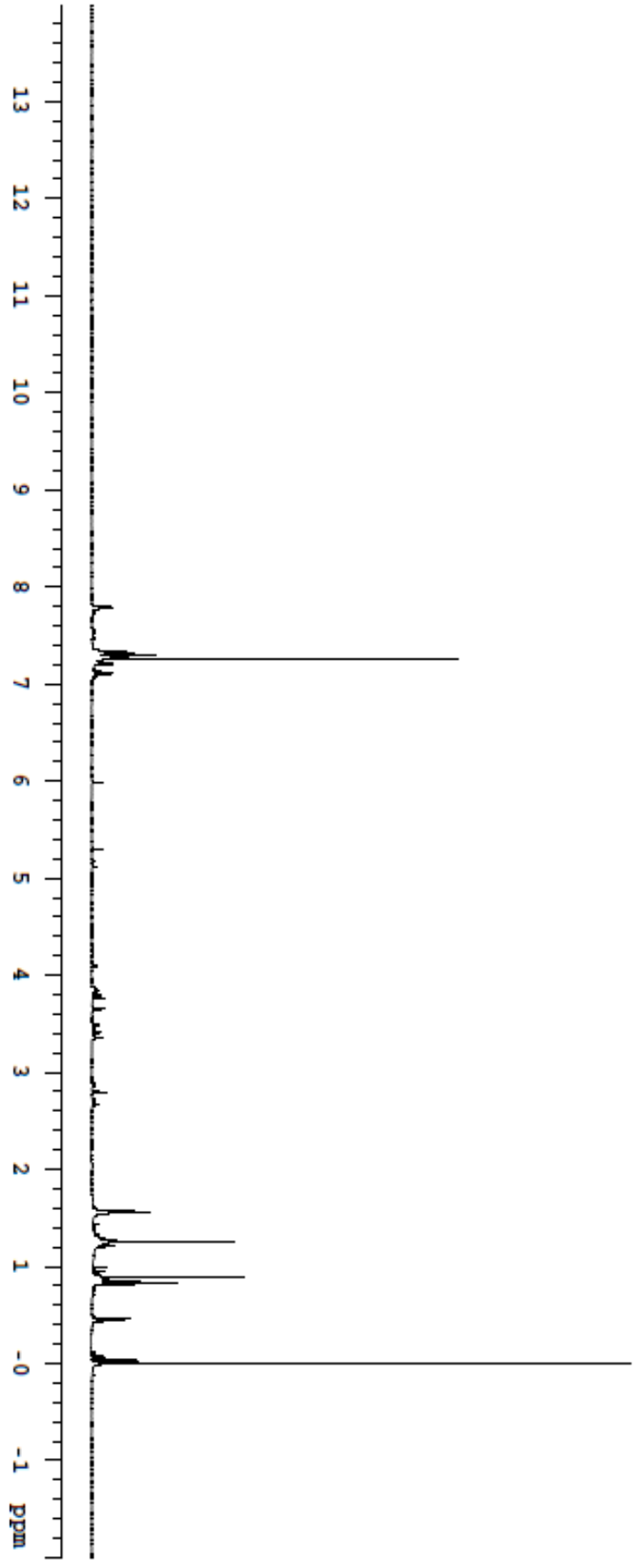

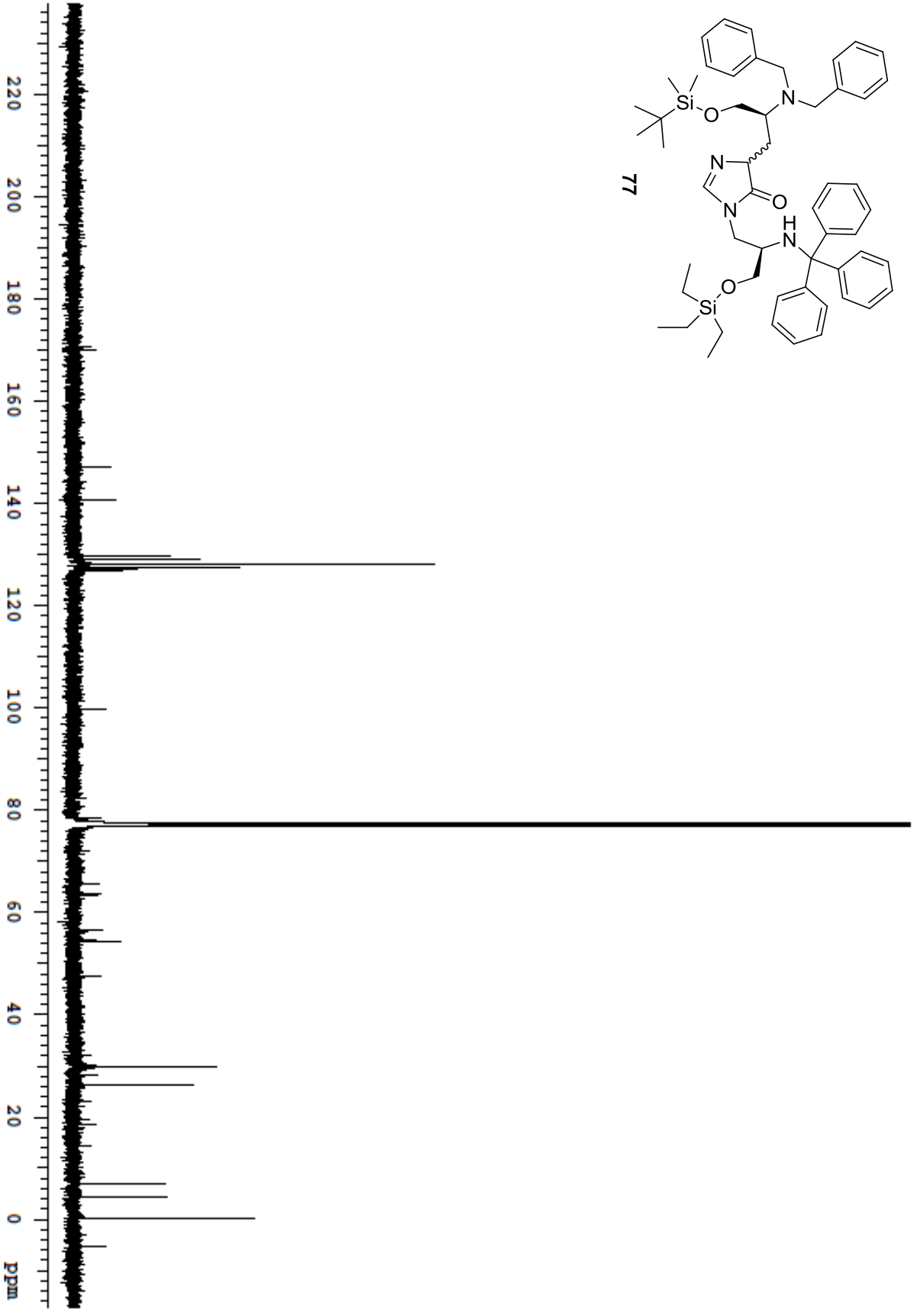

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