SYNTHETIC STUDIES TOWARDS THE SYNTHESIS OF ANATOXIN-A(S)

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Three routes toward the total synthesis of the neurotoxin anatoxin-a(s) have been explored. They focus on the assembly of the backbone utilizing both Pd(0)- and Pd(II)-mediated processes. Our current route leads to a late-stage precursor of anatoxin-a(s), hydroxy guanidine **134**, in 18 steps and in 8.0% overall yield utilizing an amidoalkylation step in the key cyclization.

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Lastly, I need to thank my family for always being there. Thanks to my nephew who calls me his friend Uncle Eric. You helped me more than you know little buddy.

ABBREVIATIONS

Ac	acetyl
AIBN	2,2'-azo *bis*isobutyronitrile
atm	atmosphere
ATR	Attenuated Total Reflectance
Boc	*tert*-butoxycarbonyl
Bn	benzyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DIC	diisopropyl carbodiimide
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DMAP	*N*,*N*-4-dimethylaminopyridine

DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*-dimethyl propylene urea
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
DSS	4,4-dimethyl-4-silapentane-1-sulfonic acid
EDA	ethylenediamine
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
FDA	Food and Drug Administration
Fmoc	9-fluorenylmethoxycarbonyl
HMPA	hexamethylphosphoramide
IBBO	(+)-2,2'-isopropylidenebis[(4*R*)-4-benzyl-2-oxazoline)]
LD_{50}	lethal dose required to kill 50% of the population
LDA	lithium diisopropylamine
m-CPBA	*meta*-chloroperbenzoic acid
MOM	methoxymethyl
Ms	methanesulfonyl
MVK	methyl vinyl ketone
ND	not determined
NMM	*N*-methylmorpholine
NMP	*N*-methylproline

NR	no reaction
Ph	phenyl
phthNH	phthalimide
phthNK	potassium phthalimide
PIDA	phenyliodonium diacetate
PIFA	phenyliodonium *bis*(trifluoroacetate)
PNS	peripheral nervous system
Pyr	pyridine
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

1.0 SYNTHETIC STUDIES TOWARDS THE SYNTHESIS OF ANATOXIN-A(S)

1.1 INTRODUCTION

1.1.1 Cyanobacteria

Cyanobacteria, or blue-green algae, are prokaryotic microorganisms predominately found in ponds, lakes, rivers and oceanic waters. Fossil records date these photosynthetic microorganisms as far back as 2.15 billion years ago, and their ability to produce oxygen was a large factor in turning earth's early atmosphere into an oxygen-rich system.[1] A rapid growth of cyanobacteria can occur when large amounts of sunlight and food rich in nitrogen and phosphorus are present. This rapid growth is referred to as an algal bacterial bloom and is often detrimental to surrounding plant, animal, and human life.[2,3] One example of a harmful algal bloom occurred in 1993 when a sudden increase in the salinity of several freshwater bodies of water in Florida, due to a tidal surge, caused a dramatic decrease in local plant life.[4] In the past 20 years, cyanobacteria have emerged as interesting sources of biologically active secondary metabolites that are commonly referred to as cyanotoxins. These cyanotoxins are classified into two groups according to their modes of toxicity: cytotoxins that are assayed using cultured mammalian cells, and highly lethal biotoxins that are assayed using small animals.[3]

While the cytotoxins are typically less deadly than the biotoxins, they are known for their antialgal, antimycotic, and antibacterial properties. Cytotoxins also exhibit modest antitumor activity.[3] The presence of blue-green algae of the genus *Lyngbya majuscula*, which produces the protein kinase C activator aplysiatoxin (**1**, Figure 1**)**, on the surface of the red alga *G. coronopifolia* was eventually determined to be the cause of food poisoning and dermatitis in Hawaii in 1994 (Figure 1).[4,5]

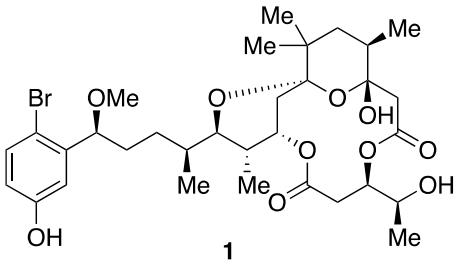

Figure 1. Structure of the cytotoxin aplysiatoxin (**1**).

Biotoxins are highly lethal metabolites that are further divided into hepatotoxins and neurotoxins. Hepatotoxins, or molecules that target the liver, include three common types: microcystins, nodularins, and cylindrospermopsins. Microcystins are identified by their macrocyclic heptapeptide backbone. The presence of five non-proteinogenic amino acids is characteristic to microcystins, while the two proteinogenic amino acids are varied throughout the microcystin family. Microcystin LR (microcystin leucine arginine) (**2**, Figure 2) is the most lethal and abundant hepatotoxin with an LD_{50} of 25-125 μg/Kg (mice). This natural product was responsible for 50 fatal human poisonings at a hemodialysis center in Brazil.[6] Its mechanism of action consists of blocking protein phosphatases, leading to hemorrhaging of the liver.[3]

Another family of hepatotoxins, the nodularins, resembles the microcystins structurally and has a characteristic pentapeptide macrocycle. These secondary metabolites are inhibitors of

serine/threonine protein phosphatase 1 and 2A, and this inhibition will lead to hemorrhaging.[6] Nodularin (**2**, Figure 3), the parent compound in this family, possesses an LD_{50} of 50 – 70 μg/Kg (mice).[7]

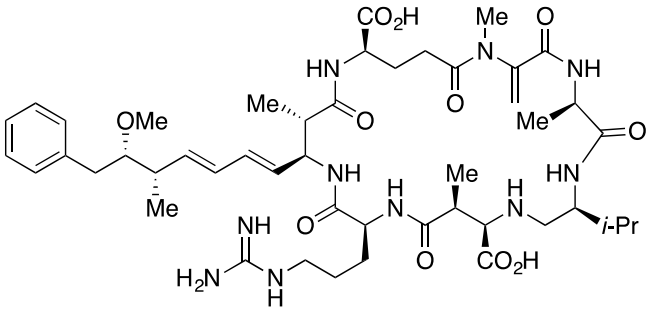

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Figure 2. The structure of microcystin LR (**2**).

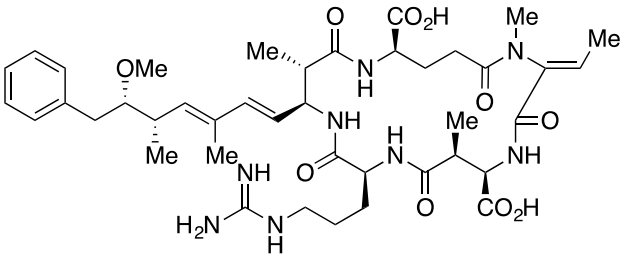

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Figure 3. The structure of nodularin (**3**).

Cylindrospermopsin (**4**, Figure 4), isolated from *C. raciborskii*, is a unique member of the hepatotoxin family due to its lack of a macrocyclic peptide backbone. In 1979, it was responsible for the hospitalization of 140 children on Palm Island, Queensland, Australia, and it can also be found in Europe and America. Cylindrospermopsin exhibits an LD_{50} of 2.1 mg/Kg (mice) and its mechanism of action is to block protein synthesis, leading to kidney and liver failure. Recently, there is new evidence suggesting that protein synthesis inhibition is not the only mechanism responsible for its toxicity.[8,9]

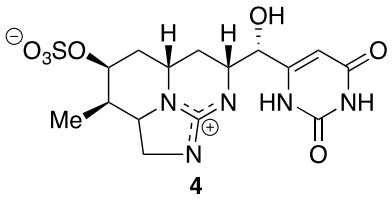

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Figure 4. Structure of cylindrospermopsin (**4**).

In addition to producing cytotoxins, cyanobacteria produce several neurotoxins, in particular anatoxin-a (**5)** and homoanatoxin-a (**6**), the saxitoxins (**7**), and the organophosphate anatoxin-a(s) (**8**, Figure 5). Anatoxin-a, produced by several strains of *Anabaena*, is a neurotoxic alkaloid with an LD_{50} of 200 – 250 μg/Kg (mice). It binds to nicotinic receptors, leading to respiratory failure within a few hours.[2,6] As a result, **5** is commonly known as "very fast death factor". To date, there are several reported total syntheses of anatoxin-a and its structural analog homoanatoxin-a, with the most recent being Stockman's approach published in 2008.[10] Homoanatoxin-a, isolated from *Oscillatoria formosa*, has a similar mechanism of action as anatoxin-a.[2]

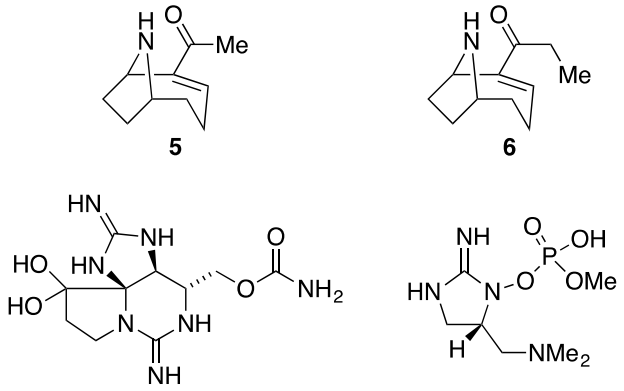
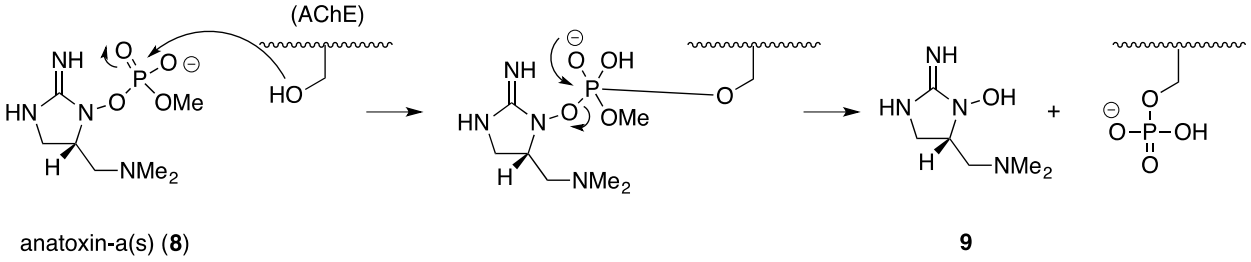


Figure 5. Selected structures of neurotoxins produced by cyanobacteria.

The saxitoxins, also known as paralytic shellfish poisons, block voltage gated sodium channels, leading to neuromuscular paralysis and death by respiratory failure. With an LD_{50} of 10 μg/Kg in mice, saxitoxin (**7**) is the most lethal of the saxitoxins and has been linked to a number of sheep deaths in Australia.[2,6]

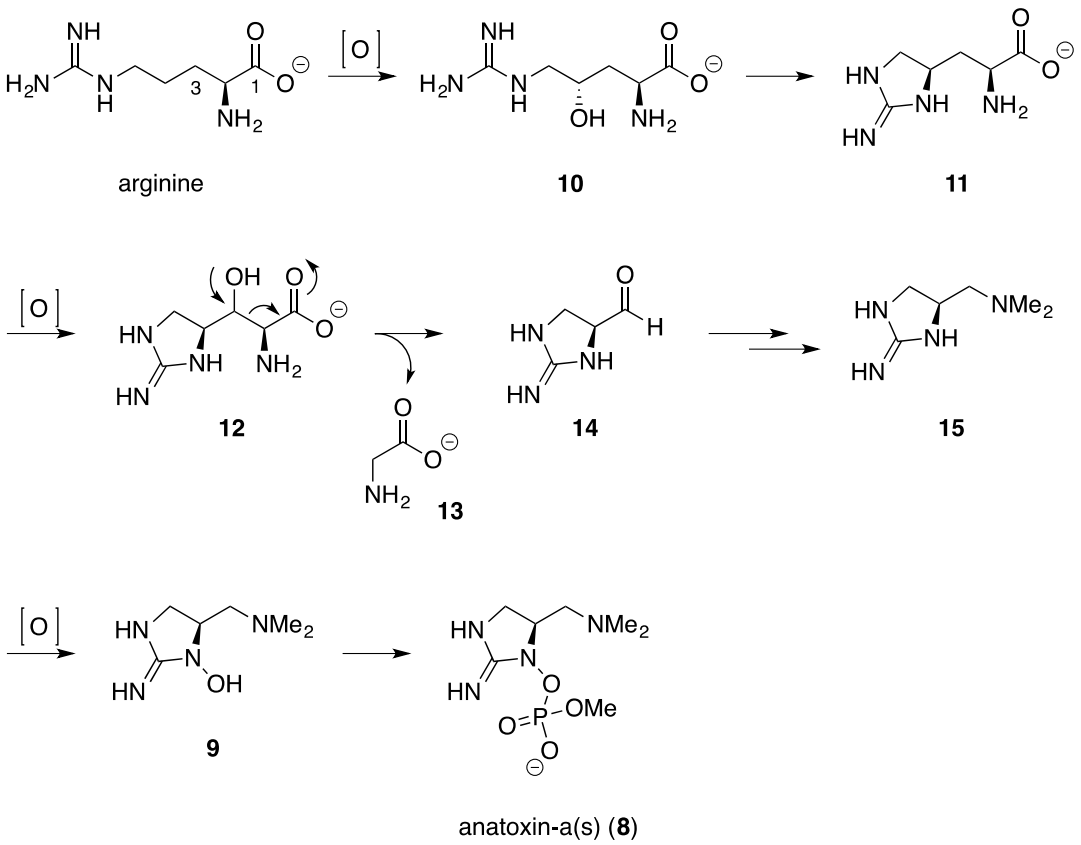
Anatoxin-a(s) (**8**) is an organophosphate isolated from *Anabeana flos-aque* in North America, *A. lemmermannii* in Denmark, and *Anabeana crassa* in South America. In North America, it has been linked to the deaths of dogs, birds, and swine; in Denmark it has been associated with the death of wild birds.[2,11,12] Anatoxin-a(s) was also detected in the Faxinal Reservior (the main reservoir for the Caxias do Dul, Brazil), which commonly experiences *Anabeana crassa* blooms. To date there are no reports of neurotoxicity caused by anatoxin-a(s) in Brazil.[13] It is a strong anticholinesterase (LD_{50} of 20 - 40 μg/Kg in mice) that acts only in the peripheral nervous system (PNS) and has a similar mechanism of action as the insecticide paraoxon and the chemical weapon sarin.[14-16] It is proposed that anatoxin-a(s) irreversibly phosphorylates a serine residue in the active site of acetylcholinesterase. As shown in Scheme 1, the hydroxyl functionality of an acetylcholinesterase serine residue adding into the phosphate moiety of anatoxin-a(s), which will then lead to the release of hydroxy guanidine **9**. One could envision activation of the guanidine functionality could occur prior to serine hydroxyl addition to help promote phosphorylation. It is this irreversible phosphorylation which leads to the build up of acetylcholine in the synaptic cleft.[17] This accumulation of acetylcholine leads to neuromuscular paralysis and eventually death by respiratory failure. Symptoms of anatoxin-a(s) poisoning include muscle weakness, respiratory distress, rhinorrhea, and eventually convulsions followed by death.[2]

Scheme 1. Proposed mechanism of action of anatoxin-a(s).



In 1992, Moore proposed a biosynthesis of anatoxin-a(s) (Scheme 2). An arginine molecule undergoes a stereoselective oxidation at the γ-position (**10**) followed by a nucleophilic displacement by the guanidine functionality to form cyclic guanidine **11**. Activation of the hydroxy group to promote displacement probably occurs prior to nucleophilic displacement; however, this exact mechanism is unknown at this time. Another methylene oxidation at the β-position (**12**) precedes a possible retro-aldol mechanism that releases a unit of glycine (**13**) and aldehyde **14**. Feeding experiments with two deuterium atoms incorporated at the C-3 position and their subsequent replacement, gives some support to the proposed oxidation and retro-aldol mechanism. However, by this proposed mechanism there should be a deuterium atom attached to the aldehyde. The mechanism by which the dimethylamine portion is added to intermediate **14** to give **15** remains unknown. The proposed mechanism by Moore, involving a reductive amination and dimethylation pathway, does not explain the loss of the remaining deuterium atom that was observed during the feeding experiments. With the backbone framework in place, tertiary amine **15** undergoes another selective oxidation (**9**) followed by phosphorylation, probably by an enzymatic-mediated pathway, of the resulting hydroxyguanidine to provide anatoxin-a(s) (**8**).[18-21] To date, there is no information provided on the specific enzymes involved in the biosynthesis of anatoxin-a(s).

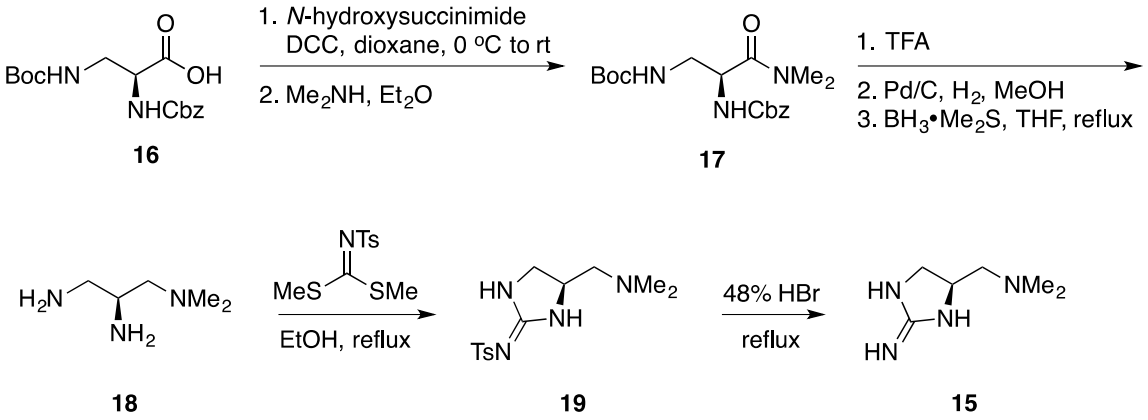
Scheme 2. Biosynthesis of anatoxin-a(s) (**8**).



To determine the absolute stereochemistry of anatoxin-a(s), Moore prepared guanidine **15** (and its enantiomer) from L-asparagine (or D-asparagine, respectively) (Scheme 3). First, carboxylic acid **16** was synthesized in two-steps from *N*-benzyloxycarbonyl-L-asparagine.[22] Treatment of **16** with *N*-hydroxysuccinimide in the presence of DCC formed the *N*-hydroxysuccinimide ester, which upon exposure to dimethyl amine gave amide **17**. Next, removal of the Boc group with TFA followed by Cbz deprotection with Pd/C and H_2 gave the corresponding diamine. Reduction of the amide with borane gave **18**. Formation of the guanidine **19** was accomplished by the treatment of **18** with *S*,*S*-dimethyl-*N*-tosyliminodithiocarbonimidate in refluxing ethanol, which after removal of the toluenesulfonyl

group with HBr, gave guanidine **15**. The circular dichroism (CD) spectrum of **15** matched the CD spectrum of **15** that was generated from a natural source of anatoxin-a(s).

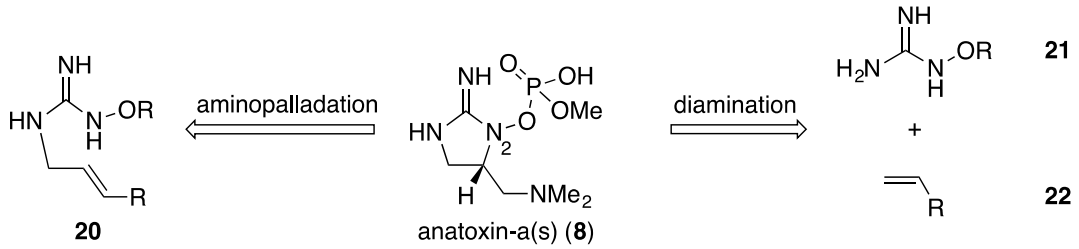
Scheme 3: Synthesis of guanidine **15**.



1.1.2 Strategies for the formation of anatoxin-a(s)'s guanidine backbone: Inspiration from related heterocycles.

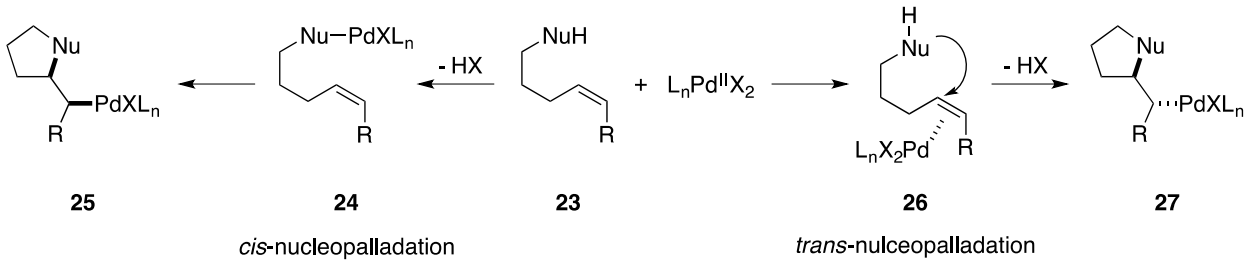
The formation of nitrogen containing five-membered rings and related heterocycles can be accomplished through metal-mediated methods, which provide an opportunity to control the regioselectivity of the carbon-nitrogen bond forming event as well as the potential for reagent controlled stereoselectivity.[23] The challenge to synthesizing anatoxin-a(s) comes from the N-O bond to be attached to the lone stereocenter present in the molecule. Two distinct strategies were envisioned: formation of the carbon-nitrogen bond through a pre-tethered olefin or through a diamination sequence (Scheme 4). For developing a synthetic strategy towards anatoxin-a(s), we turned to the use of aminopalladation methods that have been developed for the construction of guanidines, pyrrolidines, and ureas. A second strategy for the construction of 1,2-diamino containing compounds is the diamination of olefins.

Scheme 4: Possible synthetic strategies for the synthesis of anatoxin-a(s).



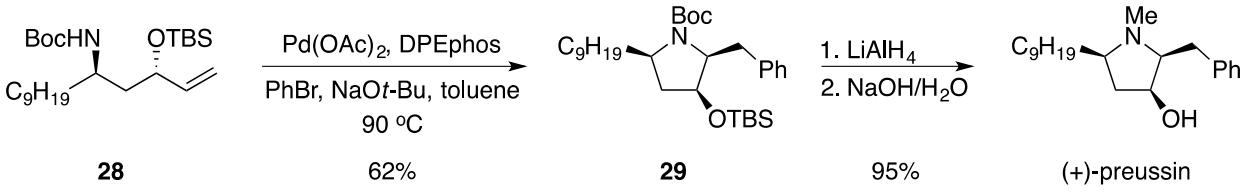
One could envision two possible pathways for the amination of unactivated olefins through palladium catalysis. The first pathway consists of *cis*-nucleopalladiation, or the formation of a palladium-nitrogen complex (**24**), prior to the cyclization event (Scheme 5). The second pathway involves the precoordination of palladium to the olefin (**26**), thereby activating it towards nucleophilic addition and is generally referred to as *trans*-nucleopalladation. This possibility of two different mechanistic pathways makes the development of an enantioselective process difficult to achieve. Also, when applied to the construction of guanidines through a similar transformation, the regioselectivity of the catalyst between the two available nitrogens will play a key role in the outcome of the cyclization.

Scheme 5: Two possible pathways for nucleopalladation.



One strategy for the construction of nitrogen-containing heterocycles is through palladium-catalyzed intramolecular ring closure of olefin containing aliphatic amines or related nitrogen functionality. The Wolfe group in 2006 used this strategy for the synthesis of the natural product (+)-preussin (Scheme 6).[24] Treatment of amino-olefin **28** with phenylbromide in the presence of the $Pd(OAc)_2$/DPEphos catalyst system generated pyrrolidine **29** in 62% yield. A likely mechanism involves oxidative insertion into the aryl bromide bond by Pd(0) followed by formation of the aminopalladium complex. This complex then proceeds through a *cis*-nucleopalladation pathway to give **29**, after reductive coupling. This cyclization added the flexibility to install various aryl groups at a late stage in order to probe the biological activity of different (+)-preussin analogs. Pyrrolidine **29** was subjected to a one-pot reduction and deprotection to afford (+)-preussin in 95% yield (96% ee).

Scheme 6. Synthesis of (+)-preussin.

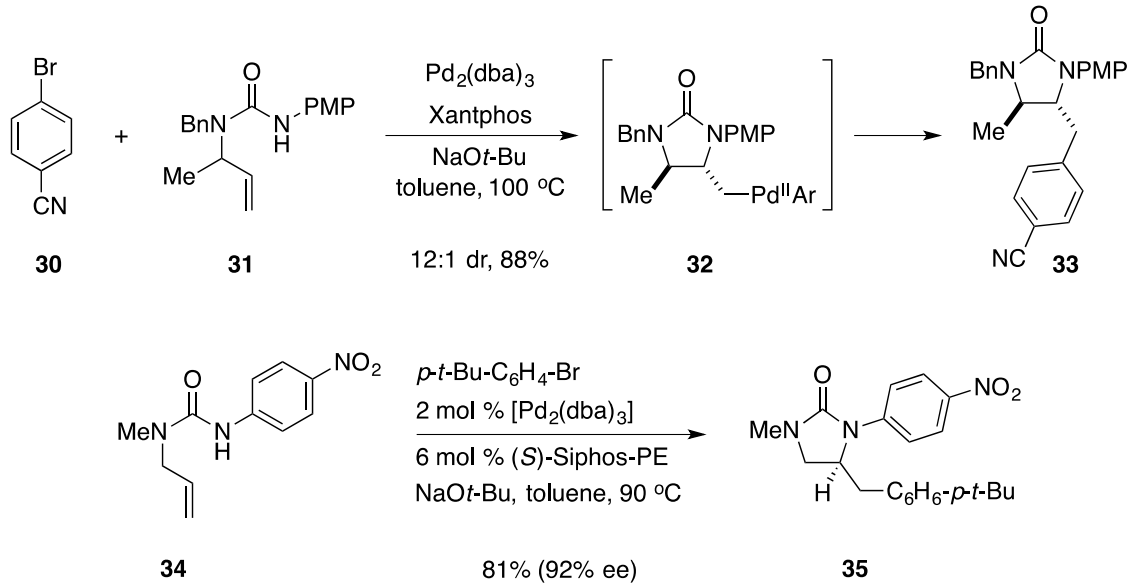


28 62% **29** 95% (+)-preussin

The Wolfe group expanded on their pyrrolidine formation by optimizing the previous reaction conditions for use in the construction of cyclic ureas.[25] They treated arylbromide **30** with $Pd_2(dba)_3$/Xantphos, which undergoes oxidative insertion of the arylbromide bond (Scheme 7). The resulting palladium complex undergoes amidopalladation of allylic urea **31**, followed by nitrogen alkylation, and the formation of alkyl-palladium complex **32**. This complex then undergoes a reductive elimination to generate cyclic urea **33** in 88% yield and a 12:1 dr. The use of base is necessary to promote amidopalladation. In 2012, they reported an enantioselective

variant of this methodology using the diastereomeric phosphoramidite ligand, (*S*)-Siphos-PE to give **35** in 81% yield (92% ee).[26] These examples by the Wolfe group all report a mechanism that proceeds through *cis*-nucleopalladation mechanism and the formation of that complex is facilitated by the presence of base.

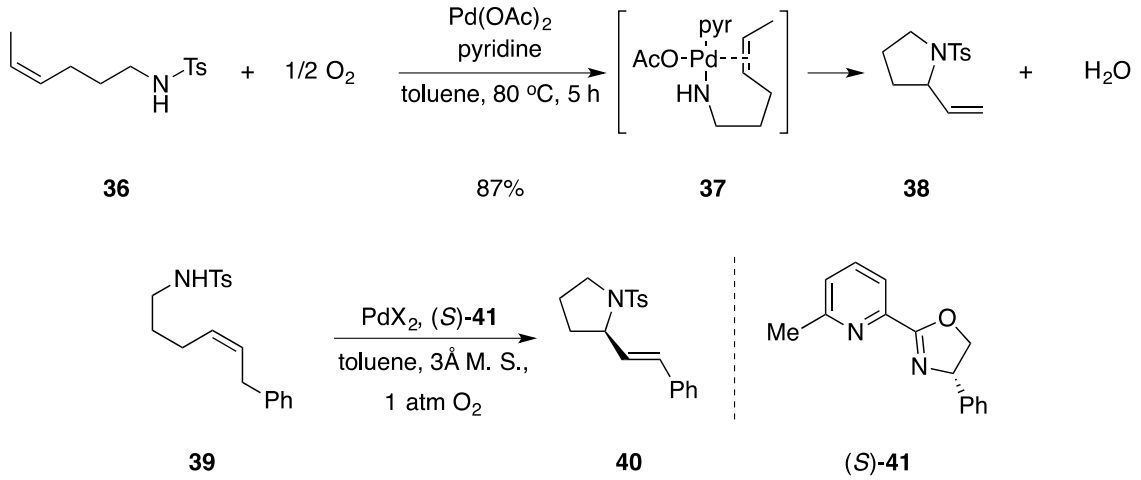
Scheme 7. The synthesis of urea derivatives using the $Pd_2(dba)_3$/Xantphos catalyst system.



In 2011, the Stahl group reported their mechanistic studies of Wacker-type intramolecular amination of alkenes (Scheme 8).[27] Treatment of tosylamide **36** with $Pd(OAc)_2$ in the presence of pyridine produce pyrrolidine **38** in 87% yield. During the course of their mechanistic studies, they observed that the rate of the reaction did not depend on the concentration of O_2 but did show a dependence on the concentrations of palladium catalyst and substrate. This observation provided evidence toward a *cis*-aminopalladation pathway by which the mechanism would proceed through likely intermediate **37**. The Stahl group followed this work with a report in 2012 on an enantioselective variation of this reaction. Using the chiral pyridine oxazoline ligand

(*S*)-**41** and $Pd(TFA)_2$ they were able to form pyrrolidine **40** in 93% yield and 98% ee.

Scheme 8: Intramolecular amination of alkenes through aminopalladation.

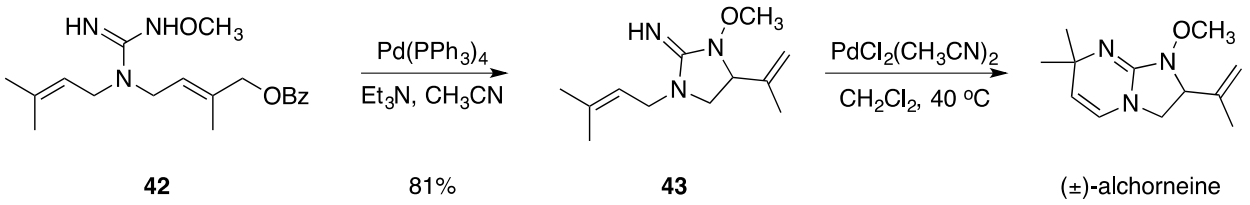


Interestingly, they reported a low yield and almost a complete loss of enantioselectivity when using $Pd(OAc)_2$. They attributed this observation to the acetate ligands promoting a change in the mechanistic pathway from a *cis*-nucleopalladation sequence to a *trans*-nucleopalladation pathway. This is one of the few examples indicating the influence of the anionic ligands on the mechanistic pathway of this type of cyclization.

A variation of the nucleopalladation of olefins is through the activation of the olefin by the presence of a leaving group (typically carbonates) in the β-position of the olefin. The Büchi group reported in 1989 the use of this strategy in the synthesis of (±)-alchorneine and (±)-isoalchorneine (Scheme 9).[28] First, methoxy guanidine **42** was subjected to a Pd(0)-mediated annulation that could proceed through either a π-allyl Pd(II) intermediate or a *cis*-amidopalladation complex to generate methoxy cyclic guanidine **43** in 81% yield. Methoxy

cyclic guanidine **43** was treated with two equivalents of $PdCl_2(CH_3CN)_2$ in CH_2Cl_2 at 40 °C to give (±)-alchorneine in 46% yield.

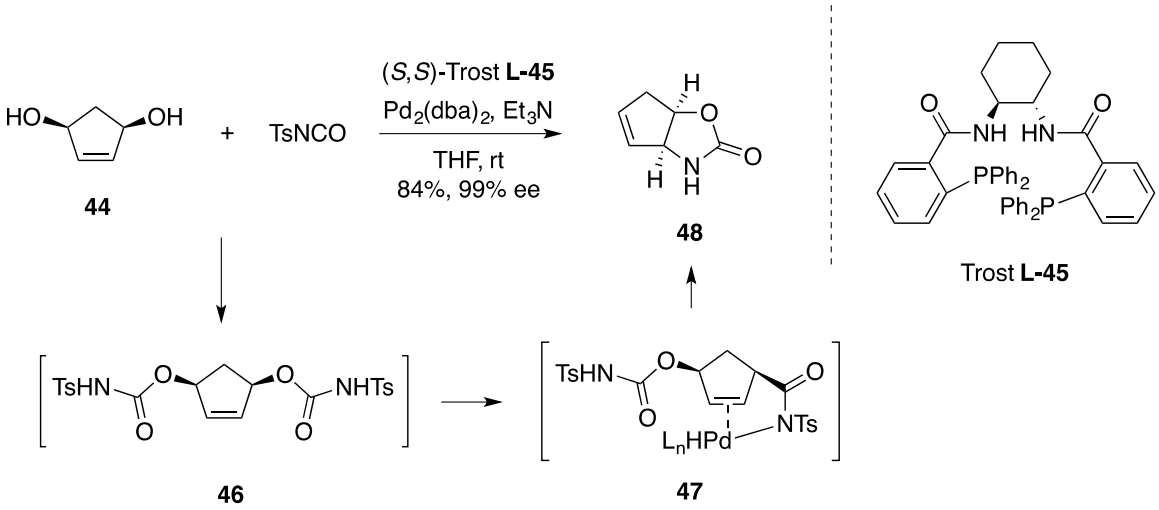
Scheme 9. Synthesis of (±)-alchorneine.



42 81% **43** (±)-alchorneine

In 1998, an enatioselective version of this strategy was applied by Trost as a method for the desymmetrization of meso-alcohols. Treatment of a solution of allylic diol **44** and TsNCO in THF with $Pd_2(dba)_3$/**L-45** led to oxazolidin-2-one **48** in 84% yield and 99% ee (Scheme 10).[29] A significant enhancement of enantiomeric enrichment was observed upon the addition of an external base, which has been shown to facilitate formation of the amidopalladium complex.

Scheme 10. Stereoselective formation of cyclic carbamates**.**



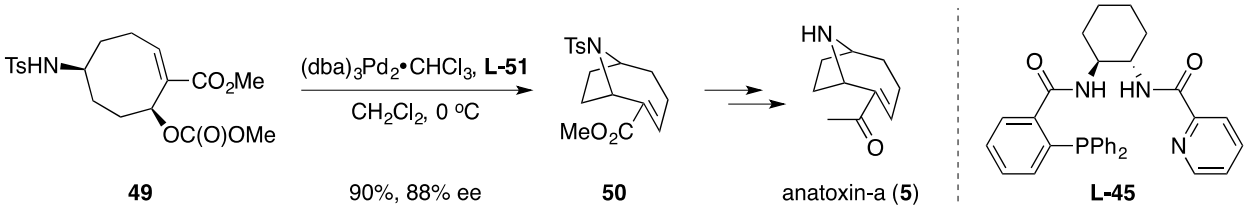
44 **48** Trost **L-45**

46 **47**

The reaction likely proceeds through dicarbamate **46**, followed by formation of a *cis*-amidopalladation complex (**47**). The regioselectivity of the *cis*-amidopalladation complex is controlled through the use of chiral ligand **L-45**. The carbamate then cyclizes and, after elimination of the carbamate, results in the stereoselective formation of oxazolidinone **48**. Another possibility would be the formation of a π-allyl intermediate as the first-step, followed by the formation a *cis*-amidopalladation complex. This complex would then undergo cyclization to give **48**.

In 1999, the Trost group applied this strategy to the asymmetric synthesis of the cyanotoxin (–)-anatoxin-a by utilizing a similar π-allyl Pd(II) complex to promote cyclization (Scheme 11).[30] Their end game strategy for the synthesis of (–)-anatoxin-a involved treatment of allylic carbonate **49** with $(dba)_3Pd_2 \bullet CHCl_3$/**L-51** to give [2.4.1] bicyclic amine **50** in 90% yield and 88% ee. Pyrrolidine derivative **50** was then transformed into (-)-anatoxin-a.

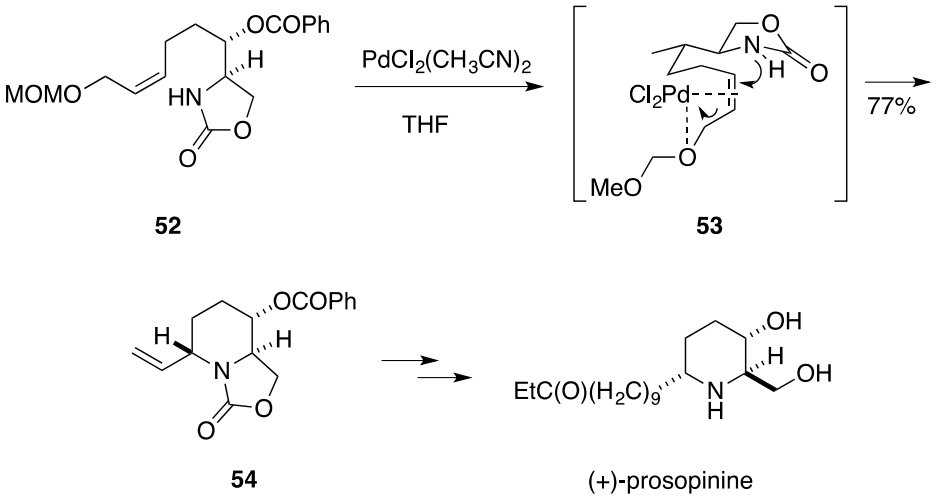
Scheme 11. Asymmetric synthesis of (-)-anatoxin-a.



The Hirai group reported in 1997 the synthesis of (+)-prosopinine and (+)-palustrine utilizing a key Pd(II)-mediated cyclization of urethanes.[31] Urethane **52** was treated with $PdCl_2(CH_3CN)_2$ in THF to give fused piperdine **54** in 77% yield as a single diastereomer (Scheme 12). The authors propose Pd(II) coordinates to the olefin (**53**), thereby activating it towards nucleophilic addition. The oxygen of the methoxymethylether assists in the

organization of the transition state through the chelation of Pd(II). This is an example of a *trans*-aminopalladation pathway, although it should be noted the authors do not provide any experimental evidence for this pathway. Although the Hirai group used a similar strategy to promote cyclization as the Trost group, the ability of these cyclizations to proceed through different mechanistic pathways increases the difficulty of developing enantioselective conditions for this cyclization. This difficulty will be compounded in the synthesis of guanidines due to the presence of a second nitrogen that can participate in coordination with the metal catalyst.

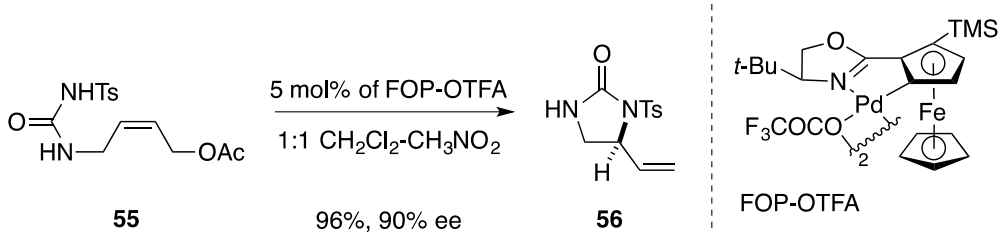
Scheme 12. Synthesis of (+)-prosopinine.



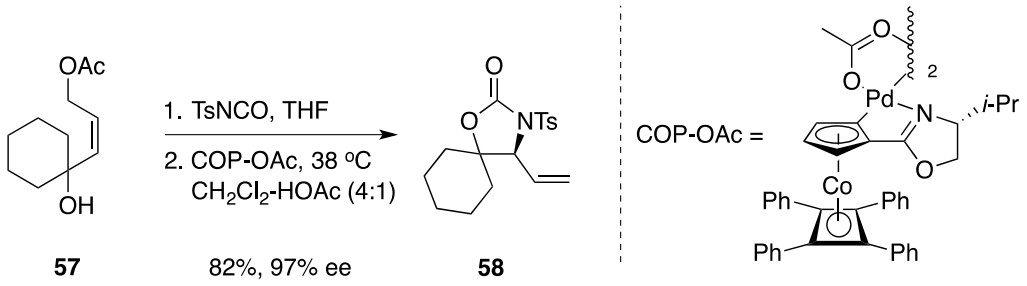
In 2002, the Overman group developed a set of chiral Pd(II) catalysts to induce asymmetric annulation of allylic ureas in the synthesis of oxazolines.[32] They treated allylic urea **55** with 5 mol% of FOP-OTFA in 1:1 CH_2Cl_2/CH_3NO_2 to give urea **56** in 96% yield and 90% ee (Scheme 13). FOP-OTFA is produced *in situ* by treating the corresponding Pd-I complex with AgOTFA. Although a variety of silver salts were investigated, the best result was achieved with silver trifluoroacetate. In 2005, a 2nd generation catalyst was developed that replaced the

ferrocene ligand with a cobalt oxazoline palladacycle (COP) (Scheme 14).[33] This catalyst offered numerous advantages over the previous ferrocene based catalyst. The COP-catalyst was not air sensitive and did not require pre-activation using silver salts. They treated allylic alcohol **57** with TsNCO in THF to generate the *N*-tosyl urea, followed by cyclization using COP-OAc in CH_2Cl_2/AcOH (4:1) to give spirocycle **58** in 82% yield and 97% ee.

Scheme 13. Asymmetric intramolecular aminopalladation.



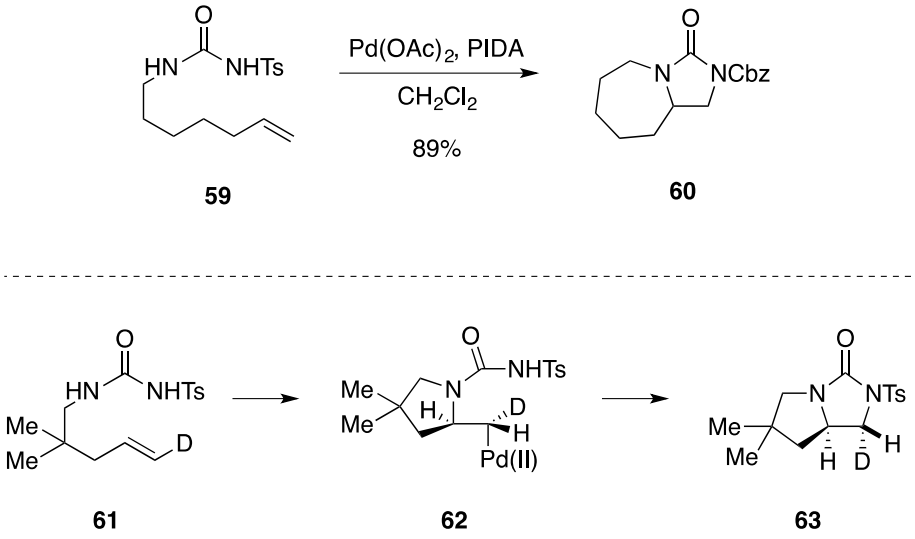
Scheme 14. Overman's 2nd generation catalysts.



A different approach to install 1,2-diamino functionality is through the diamination of olefins. In 2005, the Muñiz group developed a diamination of terminal olefins that was catalyzed by Pd(II).[34] Urea **59** was treated with $Pd(OAc)_2$ and PIDA in CH_2Cl_2 to give bicyclic urea **60** in 89% yield (Scheme 15). To probe the reaction mechanism deuterated olefin **61** was activated by Pd(II), followed by nucleophilic addition, afforded alkyl Pd(II)-species **62**. Due to the observed *trans* H-H relationship in the product, they proposed that PIDA oxidizes Pd(II) to

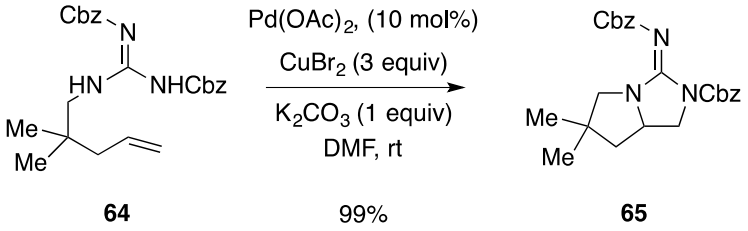
Pd(IV), and subsequent nucleophilic addition of the remaining secondary nitrogen with concomitant loss of Pd(II) gives diamination product **63** as a single diastereomer.

Scheme 15. Diamination of terminal olefins and proposed pathway.



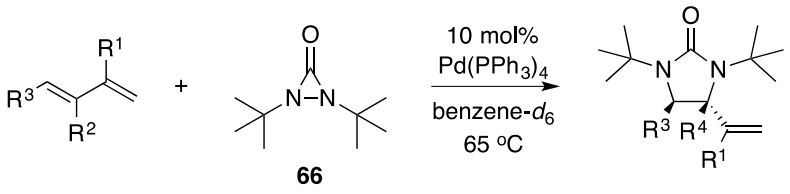
Muñiz followed their work on the cyclization of ureas by applying a similar strategy to the synthesis of bicyclic guanidines in 2008.[35] In their communication, they treated guanidine **64** with $Pd(OAc)_2$ in the presence of Copper bromide to give bicyclic guanidine **65** in 99% yield (Scheme 16). They did note that under these reaction conditions it was possible to isolate substantial quantities of the related urea compound. Switching to copper chloride eventually solved that issue. Also, the authors specifically only examined examples in which the two nitrogens that had potential to cyclization first had the same substitution to avoid issues with regioselectivity. There are few examples in the literature that address this issue of regioselectivity in guanidine synthesis.

Scheme 16: Synthesis of bicyclic guanidine.

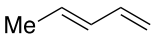
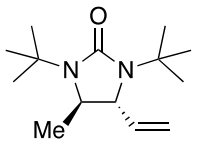
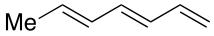
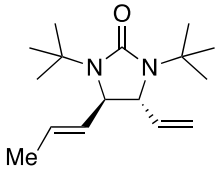
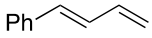
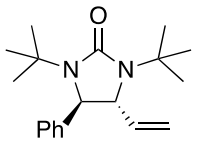
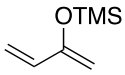
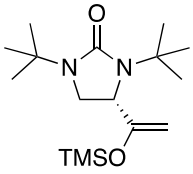
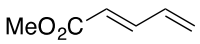
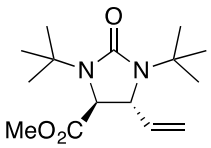


64 99% **65**

In 2007, the Shi group published a Pd(0)-catalyzed diamination of diene and trienes.[36] The various dienes combined with di-*tert*-butyldiaziridinone (**66**) were treated with 10 mol% of $Pd(PPh_3)_4$ in benzene at reflux to provide cyclic ureas in moderate to excellent yields (Table 1). Both electron-rich and conjugated dienes were well tolerated and electron-deficient dienes gave



66

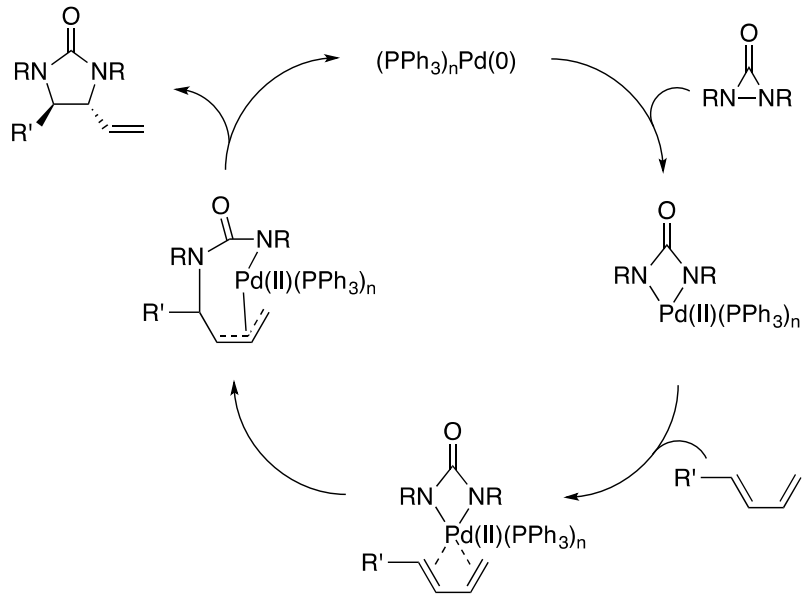
Substrate	Product	Yield[a]	Substrate	Product	Yield[a]
		94%			86%
		90%	 **67**	 **68**	90%
		60%			

[a] Isolated yield based on di-*tert*-butyldiaziridinone

Table 1. Diamination of butadiene derivatives.

the desired cyclic ureas, albeit in a modest yield compared to electron rich dienes. When conjugated trienes were used, the reaction took place at the central olefin selectively. One noteworthy example involves the use of 2-trimethysilyloxybutadiene (**67**) to give the only example of a monosubstituted cyclic urea in excellent yield (**68**, Table 1). The authors proposethat the reaction first involves Pd(0) undergoing an oxidative insertion into the *N-N* bond of di-*tert*-butyldiaziridinone followed by coordination of the diene to Pd(II) (Scheme 17). Next, stepwise carbon-nitrogen bond formation generates the π-allyl Pd(II) intermediate followed by reductive elimination to regenerate Pd(0) and provide the product. Once formed these urea compounds can be cleaved to reveal the diamino compounds that can be reclosed to form guanidines.

Scheme 17. Shi's proposed mechanism for the diamination of olefins**.**



We wanted to explore two distinct pathways for the construction of anatoxin-a(s)'s guanidine core. One pathway is through a nucleopalladation pathway that can cyclize onto activated or unactived olefins. The challenges associated with the development of an enantioselctive method for this cyclization include controlling a *cis*- or *trans*-nucleopalladation pathway. Also, for this strategy to be successful for the synthesis of anatoxin-a(s), a regioselective cyclization must be developed that can differentiate two distinct nitrogens. These same challenges are also present in proceeding through a diamination strategy.

1.2 RESULTS AND DISCUSSION

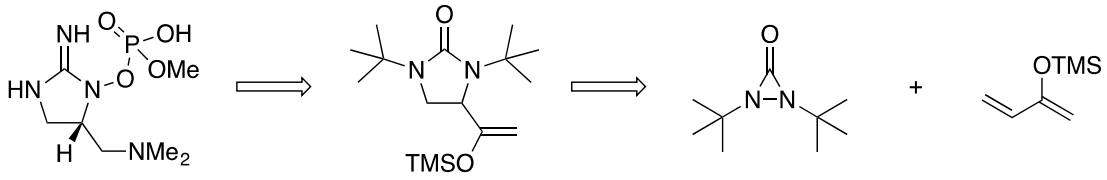
Anatoxin-a(s) (**8**) is a structurally interesting organophosphate that contains a pentacyclic guanidine moiety with a N-O bond attached to the only stereocenter. This functionality provides a unique environment to expand on current metal-catalyzed carbon-nitrogen bond forming methodology. Current methods focus on the formation of pyrrolidines and cyclic ureas through various metal-catalyzed processes. However, there is a general lack of methodology for the formation of cyclic guanidine rings with the most notable being the seminal work by Büchi[28] and the work of the Muñiz group on the Pd(II)-catalyzed formation of bicyclic guanidines,[37] on metal-catalyzed amidocarbonylations and amidoalkylations involving acyclic guanidine precursors. The methodology developed by the Muñiz group relies on identical guanidine nitrogens and does not address the regiochemistry in the cyclization. The ability to differentiate between two electronically different nitrogens still remains a synthetic challenge. Also the challenge of proceeding through a *cis*- or *trans*-nucleopalladation is a concern toward establishing an enantioselective ring cyclization. Shi's recently developed methodology for the

diamination of butadiene derivatives to give pentacyclic ureas would provide a facile route to assemble the anatoxin-a(s) backbone.[36]

1.2.1 Route 1: Palladium(0)-catalyzed diaminations

The initial synthetic efforts towards the total synthesis of the cyanotoxin anatoxin-a(s) (**8**) began by utilizing the diamination work developed by Shi (Table 1, vide supra). A retrosynthetic analysis of anatoxin-a(s) resulted in silyl enol ether **68**. Silyl enol ether **68** is synthesized from di-*tert*-butyl-diaziridinone **66** and 2-trimethylsilyloxybutadiene **67** using Pd(0) catalysis (Scheme 18).

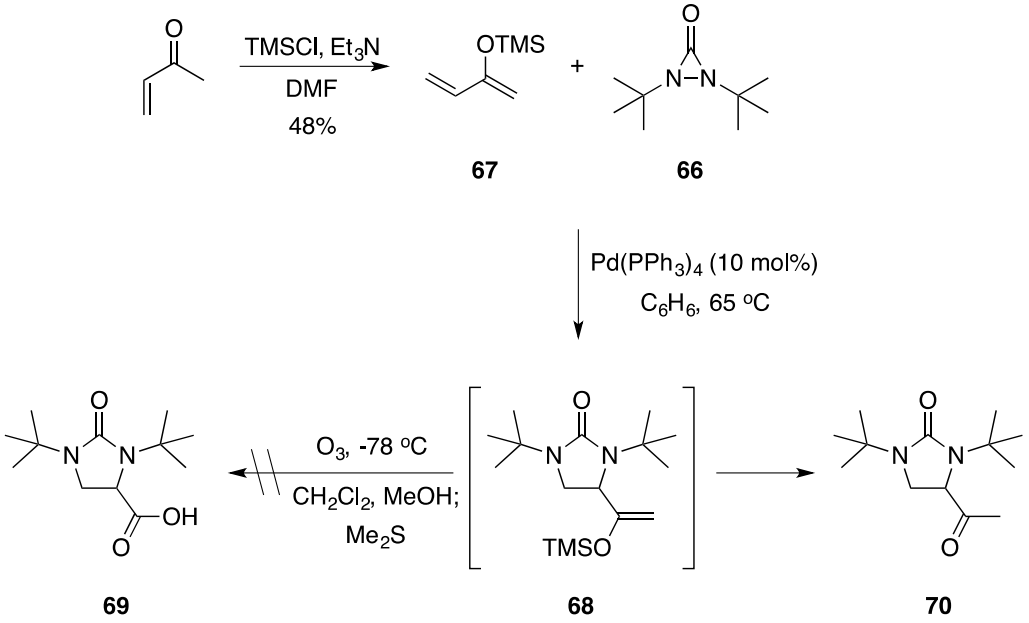
Scheme 18. 1st Generation retrosynthetic analysis of anatoxin-a(s) (**8**).



anatoxin-a(s) (**8**) **68** **66** **67**

To apply Shi's diamination protocol to a synthesis of anatoxin-a(s), methyl vinyl ketone was treated with TMSCl and triethylamine to give 2-trimethylsilyloxybutadiene **67** in 48% yield (Scheme 19). Di-*tert*-butyl-diaziridinone **66** was synthesized from di-*tert*-butylurea according to the procedure reported by Shi.[38] 2-Trimethylsilyloxybutadiene **67** and di-*tert*-butyldiaziridinone **66** were subjected to catalytic Pd(0) in benzene at 65 °C to give silyl enol ether **68**. However,

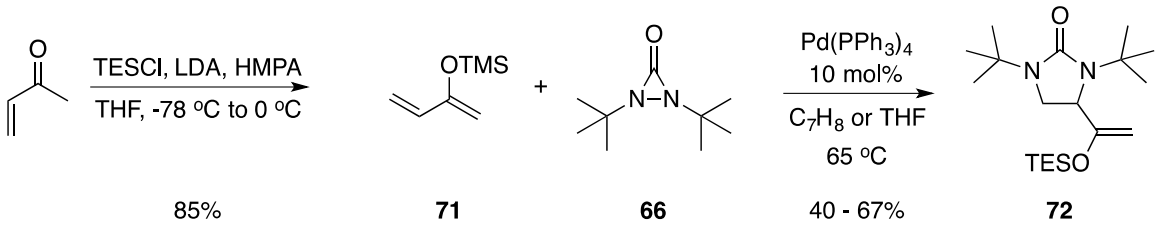
Scheme 19. Attempted synthesis of silyl enol ether **68**.



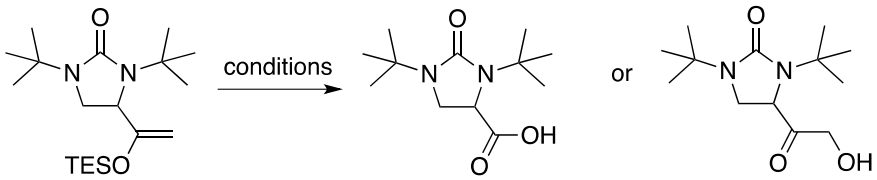
attempts at isolation of silyl enol ether **68** only resulted in desilylated ketone **70**. To counteract the instability of silyl enol ether **68,** it was carried forward without purification. When subjected to standard ozonolysis conditions, only decomposition of silyl enol ether **68** was observed.

Surmising that the difficulty with the subsequent ozonolysis was due to the inherent instability of the TMS silyl enol ether, the more stable triethyl silyl enol ether was selected. Methyl vinyl ketone in THF was subjected to a solution of LDA/ HMPA at -78 °C followed by silylation of the enolate with TESCl and warming to 0 °C to provide 2-triethylsilyloxybutadiene **71** in 85% yield (Scheme 20). Next, a solution of 2-triethylsilyloxybutadiene **71** and di-*tert*-butyldiaziridinone **66** in toluene or THF at 65 °C was treated with catalytic $Pd(PPh_3)_4$ to provide TES enol ether **72** in 40-67% yield. With TES enol ether **72** in hand, conditions towards the installation of the required nitrogen functionality were explored (Table 2). Ozone was bubbled through a solution of TES enol ether **72** in CH_2Cl_2/CH_3OH at -78 °C but after treatment with

Scheme 20. Synthesis of TES silyl enol ether **72**.



Me_2S only decomposition of the starting material was observed. Treatment of **72** with aqueous OsO_4 in the presence or absence of $NaIO_4$ in THF did not result in any dihydroxylated product or carboxylic acid **69**. Treatment of **72** with buffered *m*-CPBA in CH_2Cl_2 followed by the addition of 1 M HCl in CH_3OH gave α-hydroxy ketone **73** in 5% yield (Entry 4, Table 2).[39] In light of the difficulties pertaining to the oxidation of silyl enol ether **72** and the modest yield of the diamination reaction, an alternative route was chosen in which the backbone of anatoxin-a(s) would be assembled through a key Pd(II) catalyzed amidocarbonylation reaction.



Entry	Conditions	Result[a]
1	O_3, CH_2Cl_2, CH_3OH, -78 °C; Me_2S	decomposition
2	OsO_4, $NaIO_4$, THF, H_2O	decomposition
3	OsO_4, NMO, THF, H_2O	decomposition
4	*m*-CPBA, 5% $NaHCO_3$ (aq), CH_2Cl_2 1.5 M HCl, CH_3OH	**73**: 5%

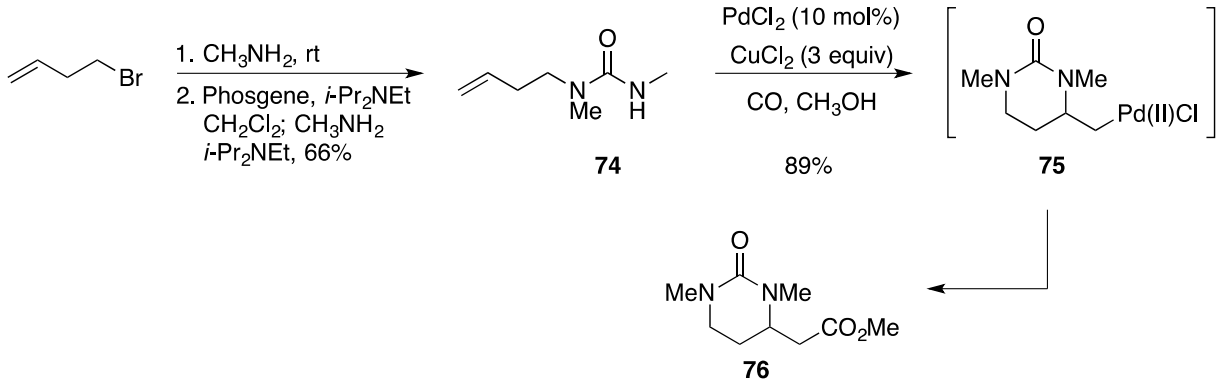
[a] Isolated yield

Table 2. Conditions for the oxidation of silyl enol ether **72**.

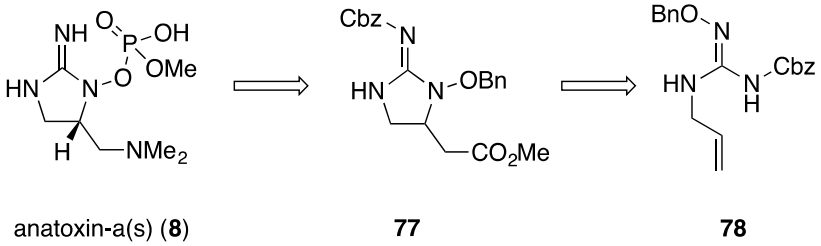
1.2.2 Route 2: Palladium(II)-catalyzed amidocarbonylations

Previous work in the Wipf group involving amidocarbonylation reactions catalyzed by Pd(II) was pursued by Gil Ma (Scheme 21).[40] Working towards the development of new cyclic urea derivatives as alternatives to DMPU, 4-bromo-1-butene was treated with neat methylamine to give *N*-methyl-3-butenylamine. The resulting homoallyic amine was treated with phosgene to give the corresponding chloroamidate, which was trapped with methylamine in the presence of diisopropylethylamine to provide urea **74** in 66% yield. Urea **74** was subjected to $PdCl_2$ (10 mol %) and $CuCl_2$ (3 equiv) in CH_3OH under 1 atm of CO to generate alkyl-Pd(II) species **75**, followed by CO insertion, and trapping of the acyl Pd(II) intermediate with CH_3OH to afford methyl ester **76** in 89% yield. By revising our previous retrosynthetic scheme to utilize a similar amidocarbonylation, one can envision that anatoxin-a(s) can be synthesized from methyl ester **77** (Scheme 22). Methyl ester **77** is the result of a Pd(II)-catalyzed amidocarbonylation of allylic guanidine **78**.

Scheme 21. Ma's work on DMPU derivatives.[40]



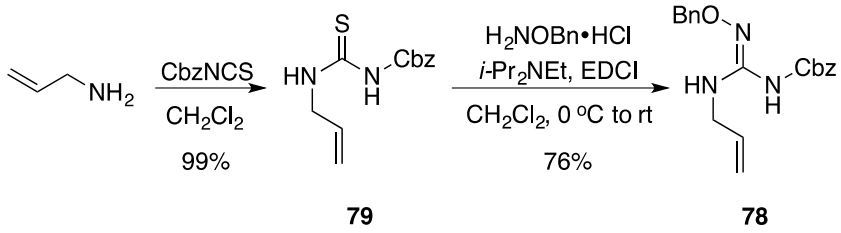
Scheme 22. 2nd Generation retrosynthetic analysis of anatoxin-a(s) (**8**).



anatoxin-a(s) (**8**) **77** **78**

The synthesis of allylic guanidine **78** commenced with the treatment of allylamine with CbzNCS[41] to give thiourea **79** in 99% yield (Scheme 23). The electron-withdrawing nature of the Cbz protecting group facilitated the formation of the guanidine functionality by increasing the electrophilic nature of the thiourea. Treatment of thiourea **79** and H_2NOBn•HCl with EDCI gave allylic guanidine **78** in 76% yield. The use of H_2NOBn•HCl serves three purposes: 1) The strong electron donating nature of the amine facilitates guanidine formation, 2) to differentiate the electronics of the two nitrogens for the key amidocarbonylation step, and 3) to install the required N-O bond that is present in the natural product.

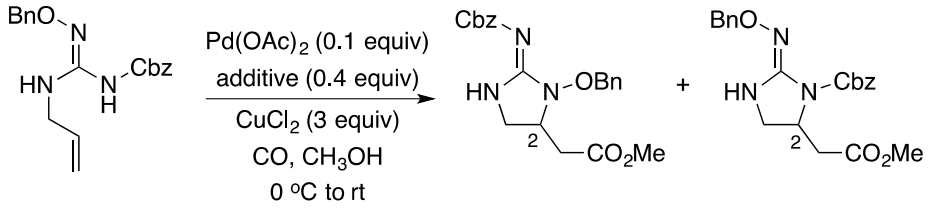
Scheme 23. Synthesis of allylic guanidine **78**.



79 **78**

With access to guanidine **78**, conditions for the key amidocarbonylation transformation catalyzed by Pd(II) were investigated. Two requirements for this reaction were considered: the regiochemistry had to be controlled and ligands for the development of an asymmetric variant

needed to be screened. Allyl guanidine **78** was treated with 10 mol% of $Pd(OAc)_2$ and $CuCl_2$ (3 equiv) in CH_3OH under 1 atm of CO to give a 2.2:1 mixture of methyl esters **77** and **80** in a combined 76% yield (Entry 1, Table 3). Other Pd(II) complexes gave complex mixtures of



78 **77** **80**

Entry	Additive	Ratio (**77**:**80**)[a]	Yield (%)
1	none	2.2:1	76[b]
2	(–)-sparteine	0:100	55[c,d]
3	NMM	0:100	64[c]
4	*N,N*-dimethylaniline	1:5	70[b]
5	hydroquinine	1:12	75[b,d]
6	IBBO	1:1.5	91[b,d]
7	*i*-Pr_2NEt	0:100	ND
8	AcOH	1:2	ND

[a] Determined by ^{1}H-NMR. [b] Isolated yield. [c] Yield of crude mixture.
[d] observed ee% was less than 5% as determined by chiral SFC

Table 3. Amidocarbonylation conditions.

products that were not isolated. The addition of chiral ligands or other additives to affect the isomeric ratio only succeeded in increasing the ratio of undesired regioisomer **77** without any significant improvement in ee. Compounds **77** and **80** were assigned based on the chemical shift of the C2-H of the Boc-derivatives **77-Boc** and **80-Boc**. By comparing the chemical shift of the C2-H of **77-Boc** (δ 3.92-3.82) and C2-H of **80-Boc** (δ 4.49) and of comparable urea compounds **81**[42] and **82**.[43] Although the guanidine and urea compounds share groups with similar electronics

attached to the nitrogen adjacent to the stereocenter, the electronics between the guanidine compounds and the ureas are different. This comparison was used as a preliminary structure assignment while the synthesis was carried forward. Ideally a crystal structure would have been obtained to unambiguously assign the structures but no crystal of these urea compounds or derivatives were obtained.

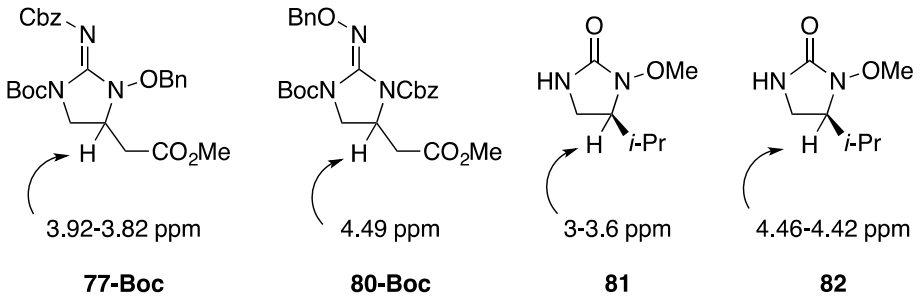
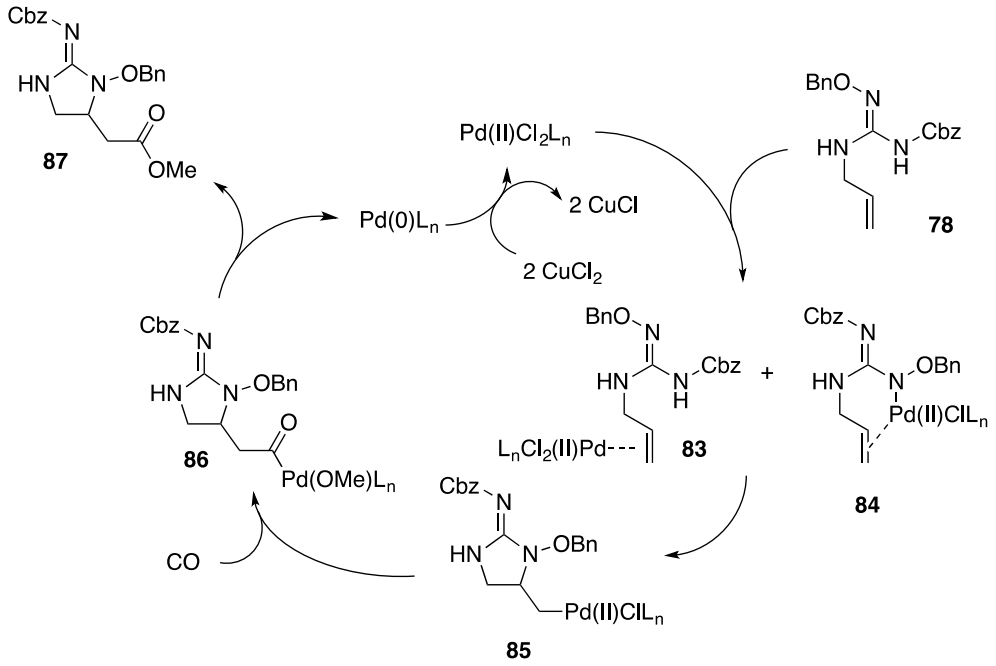


Figure 6: Structure identification of cyclization compounds and comparable urea compounds **81** and **82**.

The amidocarbonylation is thought to proceed through a Wacker-type cyclization pathway outlined below (Scheme 24).[44] First, Pd(II) may coordinate to olefin **83**, thereby activating it towards nucleophilic addition, or, alternatively, Pd(II) forms *N*-Pd(II)amido species **84** with concomitant loss of HX. Next, amidoalkylation forms alkyl-Pd(II) species **85**, followed by CO insertion to give acyl-Pd(II) species **86**. Subsequent reductive elimination forms methyl ester **77** and Pd(0), which is reoxidized by $CuCl_2$ to Pd(II). Due to the prevalence of the undesired methyl ester, by addition of the weaker nucleophile, it is thought that the reaction proceeds through amido-Pd(II) species **83** and not by simple Lewis activation of the olefin **84**.

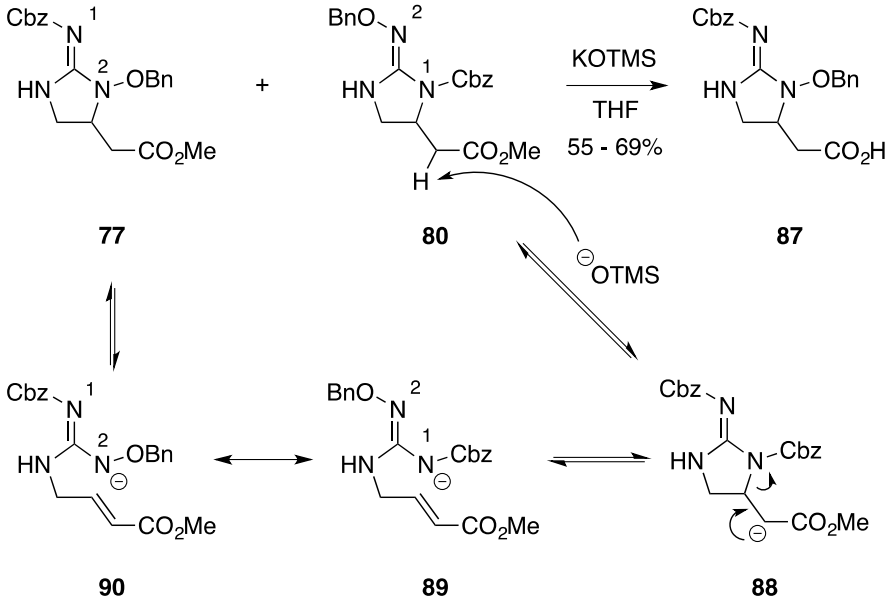
Scheme 24. Proposed mechanism of amidocarbonylation.



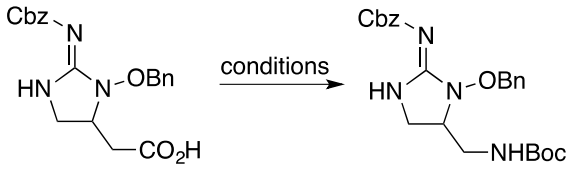
Despite the preliminary results of the amidocarbonylation giving the undesired regioisomer, it was decided to proceed with the hydrolysis of the methyl esters; however, when a solution of methyl esters **77** and **80** were subjected to KOTMS in THF, only carboxylic acid **87** was observed in 55 – 69% yield (Scheme 25). Initially, KOTMS deprotonates α to the methyl ester of regioisomer **80**, followed by ring opening to form the α,β-unsaturated ester **89**. The ring opening of ester **80** is facilitated by the electron withdrawing nature of the Cbz-protecting group. At this juncture, the negative charge is delocalized between N_1 (**89**) and N_2 (**90**). N_2 then adds back into the α-β-unsaturated ester to give the desired methyl ester **77**. Calculations show that **77** is the thermodynamically more stable compound by 5.3 Kcal/mol.* The isomerization is followed by hydrolysis.

* Calculations preformed using MMFF conformer distribution followed by PM3 equilibration of geometry using Spartan 10

Scheme 25. Synthesis of carboxylic acid **87** and proposed mechanism of ester isomerization.



With a route to carboxylic acid **87**, conditions to install the required nitrogen functionality by a Curtius rearrangement were explored. [45] Exposing of carboxylic acid **87** to DPPA and triethylamine in *tert*-BuOH at reflux resulted in decomposition of starting material (Entry 1, Table 4). In a more stepwise approach towards formation of the acyl azide, carboxylic acid **87** was treated with oxalyl chloride followed by the addition of sodium azide. To the resulting solution was added *tert*-BuOH and the reaction mixture was heated at reflux; however, only decomposition of starting material was observed (Entry 2, Table 4). In 2005, the Lebel group reported a mild one-pot procedure for the synthesis of Boc-protected amines by treating carboxylic acids with sodium azide, Boc_2O, and TBAB in the presence of $Zn(OTf)_2$ via a Curtius rearrangement.[46] Unfortunately, when carboxylic acid **87** was exposed to these conditions, no reaction of the starting material was observed (Entry 3, Table 4). Due to the unforeseen difficulty in accomplishing the Curtius rearrangement, an alternative method for the installation of the nitrogen functionality on the side chain was examined.



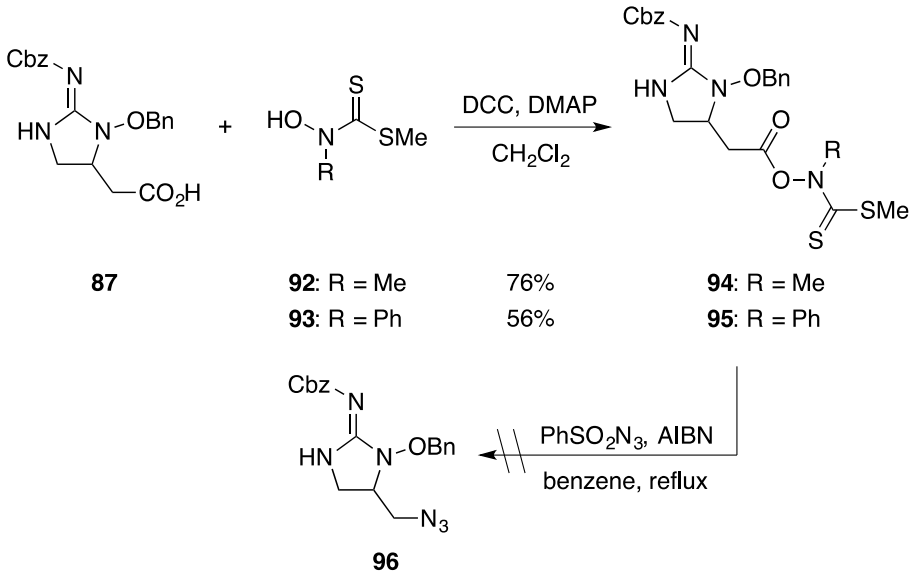
87 **91**

Entry	Conditions	Yield (%)
1	DPPA, Et_3N, *t*-BuOH, reflux	decomposition
2	$(COCl)_2$; NaN_3 *t*-BuOH, toluene, reflux	decomposition
3	NaN_3, *n*-Bu_4NBr, $Zn(OTf)_2$ Boc_2O, THF, 40 °C	SM

Table 4. Conditions for attempted Curtius rearrangement of carboxylic acid **87**.

In 2008, the Renaud group reported the synthesis of alkyl azides using the radical decarboxylation of thiohydroxamate esters.[47] These conditions were applied to the coupling of *N*-hydroxydithiocarbamates **92** and **93** with carboxylic acid **87** in the presence of DCC and DMAP. The corresponding thiohydroxamate esters **94** and **95** were produced in 76% and 56% yield, respectively (Scheme 26). Unfortunately, exposing thiohydroxamate esters **94** and **95** to AIBN in benzene at reflux in the presence of phenyl sulfonylazide slowly decomposed the thiohydroxamate esters and failed to give desired alkyl azide **96**. A possible explanation is that upon the generation of the primary radical, a 1,2-H migration occurs to produce a more stable tertiary radical or a ring-opening event occurs to produce an *N*-centered radical that subsequently decomposes.

Scheme 26. Radical decarboxylation of thiohydroxamate esters **94** and **95**.

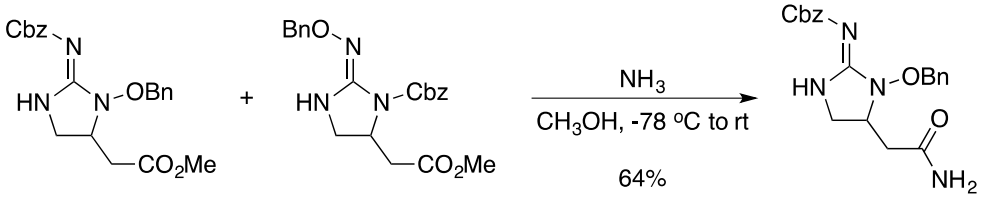


87 **92**: R = Me 76% **94**: R = Me
93: R = Ph 56% **95**: R = Ph

96

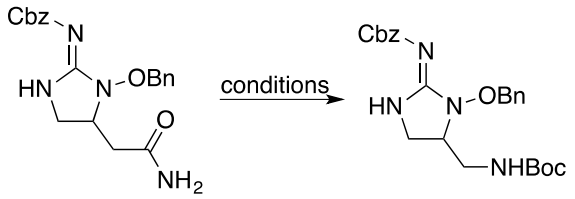
After the radical decarboxylation failed to provide alkyl azide **96**, a Hofmann rearrangement was explored for the installment of the required nitrogen functionality.[48,49] A mixture of methyl esters **77** and **80** in CH_3OH at -78 °C was treated with liquid NH_3 to give amide **97** in 64% yield (Scheme 27). In the presence of 5 equiv of $Pb(OAc)_4$ and triethylamine in *tert*-BuOH/ DMF at 100 °C none of desired rearranged Boc-protected amine **97** was observed (Table 5). Switching $Pb(OAc)_4$ to PIFA only resulted in decomposition of starting material.

Scheme 27. Formation of amide **97**.



77 **80** **97**

Examination of the less active PIDA led to similar results (Entry 3, Table 5). Due to the troubling preliminary results of the key amidocarbonylation cyclization and the difficulty of installing the required nitrogen functionality, an alternative route that utilized a Pd(II)-mediated amidoalkylation was pursued.



97 **91**

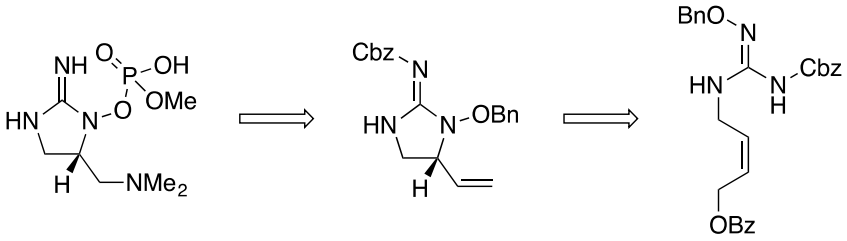
Entry	Conditions	Yield (%)
1	$Pb(OAc)_4$ (5 equiv), *t*-BuOH (0.2 M) DMF (0.2 M), Et_3N (2.5 equiv), 100 °C	NR
2	PIFA (2 equiv), pyr (3 equiv) *t*-BuOH (0.2 M), CH_3CN (0.2 M)	decomposition
3	$PhI(OAc)_2$ (2 equiv), pyr (3 equiv) *t*-BuOH (0.2 M), CH_3CN (0.2 M)	decomposition

Table 5. Conditions for attempted Hofmann rearrangement of amide **97.**

1.2.3 Route 3: Palladium(II)-catalyzed amidoalkylations

Our previous retrosynthetic analysis was revised toward an approach to anatoxin-a(s) from olefin **98**. Olefin **98** can be prepared by a Pd(II)-catalyzed amidoalkylation of allylic guanidine **99** (Scheme 28). Mono protection of commercially available 2-butenediol using TBDPSCl in the

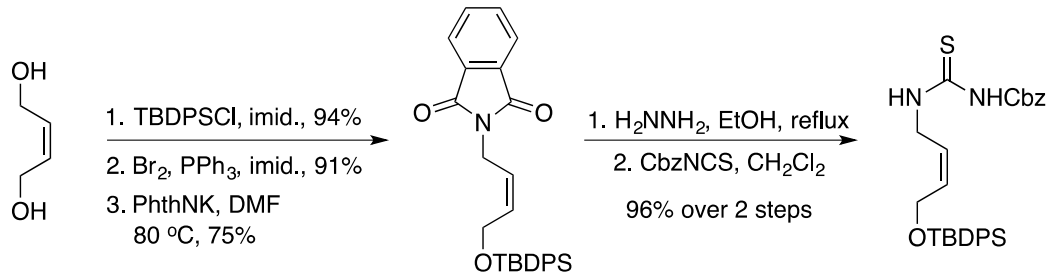
Scheme 28. 3rd Generation retrosynthetic analysis of anatoxin-a(s) (**8**).



anatoxin-a(s) (**8**) **98** **99**

presence of imidazole gave (*Z*)-4-(*tert*-butyldiphenylsilyloxy)but-2-en-1-ol in 94% yield (Scheme 29).[50] Next, bromide displacement of the free alcohol with Br_2, PPh_3 and imidazole in THF afforded the allylic bromide in 91% yield.[51] The allylic bromide was displaced with PhthNK in DMF at 80 °C to provide phthalamide **100** in 75% yield. Phthalimide **100** was carried through a two-step procedure of phthalimide removal with hydrazine in EtOH at reflux and trapping the resulting allylic amine with CbzNCS[41] in CH_2Cl_2 to yield thiourea **101** in 96% yield over the two steps. Thiourea **101** was coupled with $H_2NOBn \bullet HCl$ in the presence of diisopropylethylamine and EDCI to afforded guanidine **102** in 71% yield (Scheme 30). The guanidine was subjected to a two-step procedure to install the benzyl moiety required for the key

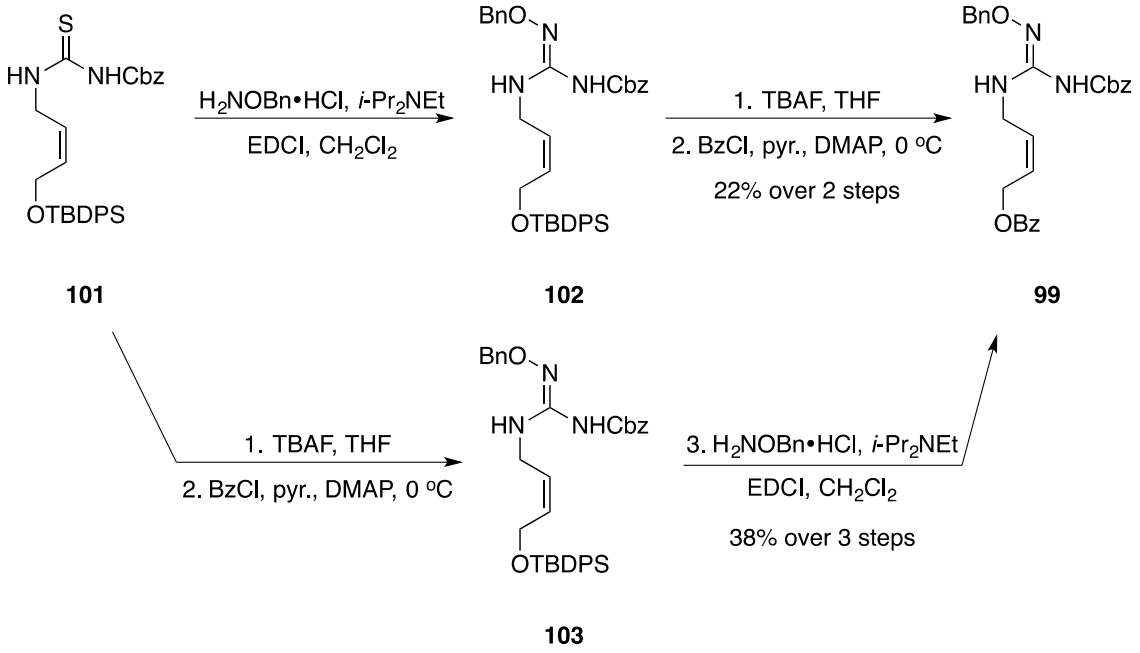
Scheme 29. Synthesis of thiourea **101**.



100 **101**

amidoalkylation step. The guanidine was treated with TBAF in THF followed by the addition of BzCl to the crude alcohol in the presence of pyridine and DMAP to provide guanidine **99** in 22% yield over the two steps. It is unclear why the isolated yield over the two steps was low, but perhaps exposing **102** to unbuffered TBAF led to cleavage of the Cbz group. Unfortunately no side-products were isolated that would provide insight on this issue. Due to the poor yield for

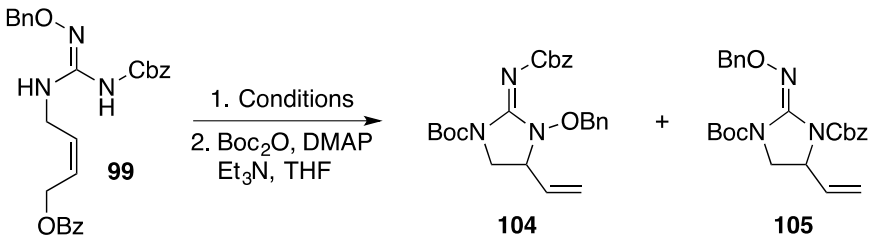
Scheme 30. Synthesis of guanidine **99**.



guanidine **99**, the synthetic sequence was changed. First, thiourea **101** was deprotected with TBAF, followed by benzoylation of the resulting allylic alcohol to give thiourea **103**, and guanidine formation with $H_2NOBn{\bullet}HCl$ in the presence of diisopropylethylamine and EDCI to afford guanidine **99** in 38% yield over three steps.

With guanidine **99** in hand, suitable conditions to effect the key amidoalkylation catalyzed by Pd(II) were explored. Initially, treatment of guanidine **99** with 20 mol% of $PdCl_2(CH_3CN)_2$ in THF (0.05 M) followed by Boc protection of the free amine gave olefin **104**

in 59% yield over the two steps (Entry 2, Table 6). The subsequent Boc protection was due to the unforeseen polarity of the unprotected compound. Although compound **98** behaves normally



Entry	Conditions	Ligand	Ratio **104**:**105**	Result[a]
1	$Pd_2(dba)_2$ (0.05 equiv), Et_3N (1.1 equiv), CH_2Cl_2 (0.05 M)	---	100:0	14%
2	$Pd(OAc)_2$ (0.2 equiv) THF (0.05 M)	---	1:1	57%
3	$PdCl_2(CH_3CN)_2$ (0.2 equiv) THF (0.2 M)	---	100:0	84%
4	$PdCl_2(CH_3CN)_2$ (0.2 equiv) Et_3N (1.1 equiv), THF (0.05 M)	---	---[b]	ND
5	(*R*)-(-)-COP-OAc (0.1 equiv) CH_2Cl_2 (0.6 M)	---	1:1	70% (**104** : 48% ee)[c]
6	$PdCl_2(CH_3CN)_2$ (0.2 equiv) DCE (0.5 M), 85 °C	**A** (0.4 equiv)	---	NR
7	$PdCl_2(CH_3CN)_2$ (0.2 equiv) THF (0.5 M)	(-)-sparteine	100:0	55% (<1% ee)[c]
8	$PdCl_2(CH_3CN)_2$ (0.2 equiv) DCE (0.5 M), 85 °C	**B** (0.4 equiv)	100:0	67% (<2% ee)[c]

[a] Isolated yields. [b] Mixture of **99**, **104**, **105**. Yield not determined. [c] % ee determined by chiral SFC (chiralpak-IA; 2.0 mL/ min; 25% MeOH.

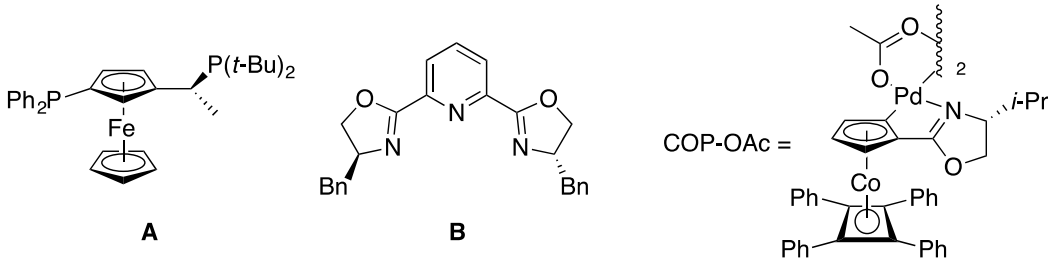


Table 6. Screening conditions for key amidoalkylation of guanidine **99**.

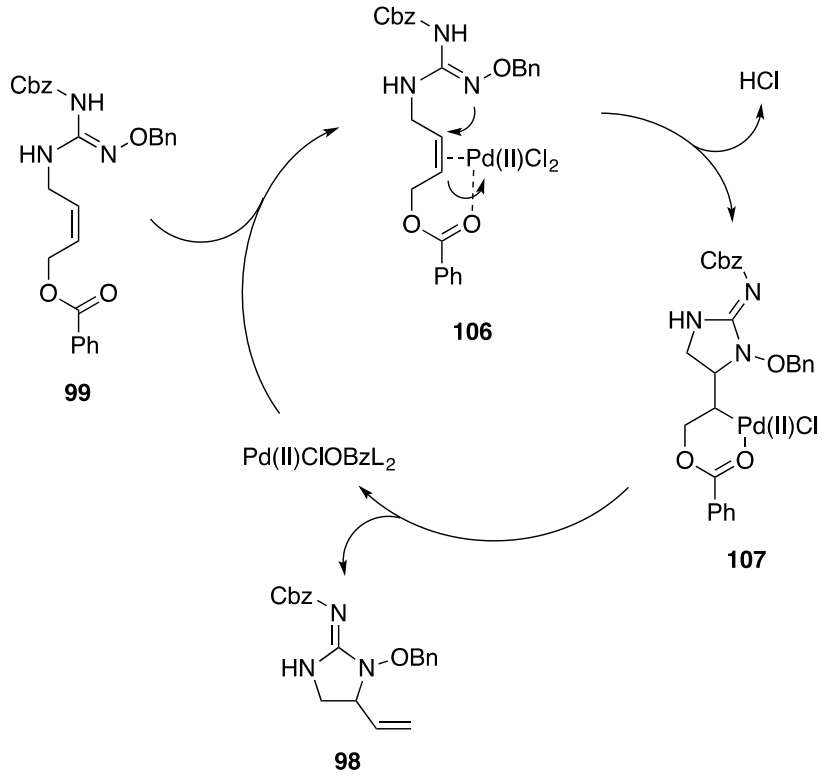
by TLC analysis, purification of **98** by chromatography on SiO_2 required a substantially more polar mobile phase than was required for TLC analysis. Increasing the concentration of the initial Pd(II)-mediated cyclization reaction resulted in an increased 79% yield of olefin **104**. The use of a Pd(0) catalyst resulted in a poor 17% yield of olefin **105** (Entry 1, Table 6). Using the palladacycle catalyst developed by Overman (Scheme 14),[33] a 1:1 ratio of **104** and **105** in a 70% combined yield with olefin **104** in 48% ee was obtained. The use of Josiphos ligand **A** completely shut down the catalytic cycle (Entry 6, Table 6).[52] Subjecting guanidine **99** to $PdCl_2(CH_3CN)_2$/pyBox **B** catalyst system in 1,2-dichloroethane at 85 °C gave the desired olefin in 67% yield and 2% ee (Entry 8, Table 6). Calculations show that isomer **104** is thermodynamically more stable than **105** by 1.91 Kcal/mol.[†]

In 2002, the Overman group proposed a mechanism for a similar transformation involving the cyclization of carbamate derivatives.[32] The Pd(II) initially coordinates to olefin **99**, directed by chelation from the benzoyl carbonyl oxygen, and activating the olefin towards intramolecular nucleophilic attack (**106**). An intramolecular nucleophilic addition of the more electron rich nitrogen of the guanidine moiety and release of HCl forms alkyl-Pd(II) intermediate **107**. Finally, elimination of olefin **98** regenerates Pd(II) that can re-enter the catalytic cycle (Scheme 31).

Facilitated by a route to racemic olefin **104**, the completion of the synthesis of anatoxin-a(s) was pursued. A solution of olefin **104** in CH_3OH/CH_2Cl_2 buffered with 10 equiv of pyridine was cooled to -78 °C (Scheme 32). Ozone was bubbled through the solution followed by treatment with $NaBH_4$ to afford alcohol **108** in 61% yield. In the absence of pyridine only

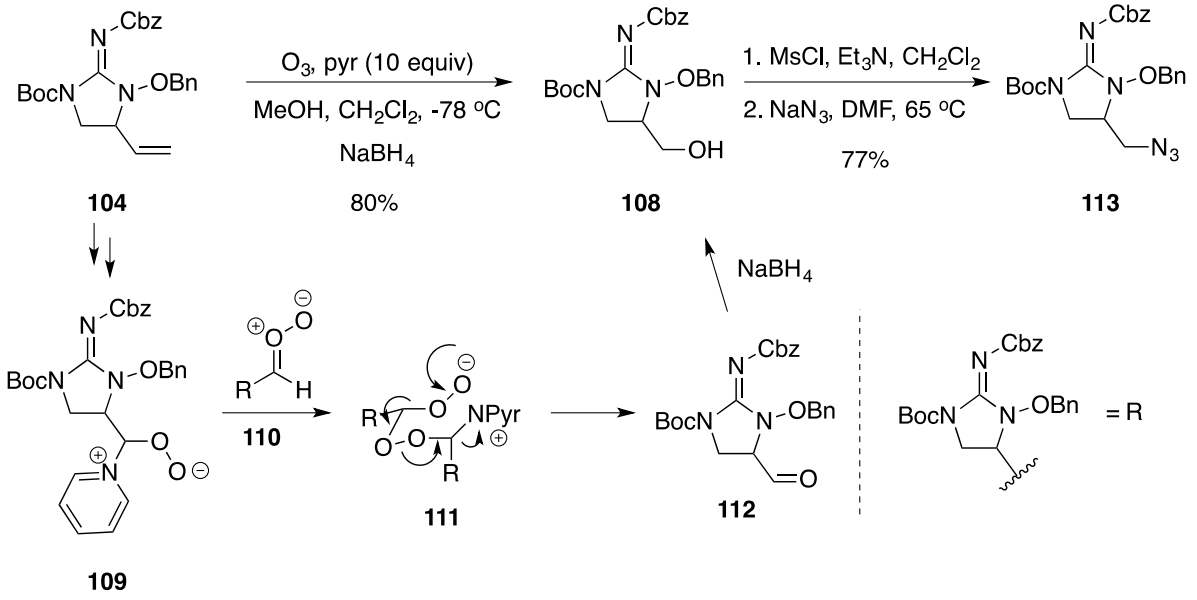
[†] Calculations preformed using MMFF conformer distribution followed by PM3 equilibration of geometry using Spartan 10

Scheme 31. Proposed catalytic cycle of amidoalkylation.



decomposition of starting material was observed. A recent report from Dussault hypothesizes that pyridine could potentially add to the carbonyl oxide that is formed after the break down of the initial ozonide to generate intermediate **109**.[53] The zwitterionic adduct **109** then adds to a second equivalent of carbonyl oxide (**110**). Then, decomposition of **111** would produce 2equivalents of the aldehyde (**112**) and release an equivalent of O_2 and pyridine. The authors observed a general trend of increased yields when pyridine was added to these reactions. Alcohol **108** was mesylated with MsCl and triethylamine in CH_2Cl_2 followed by treatment of the crude mesylate with sodium azide in DMF at 65 °C to give alkyl azide **113** in 77% yield over the two steps.

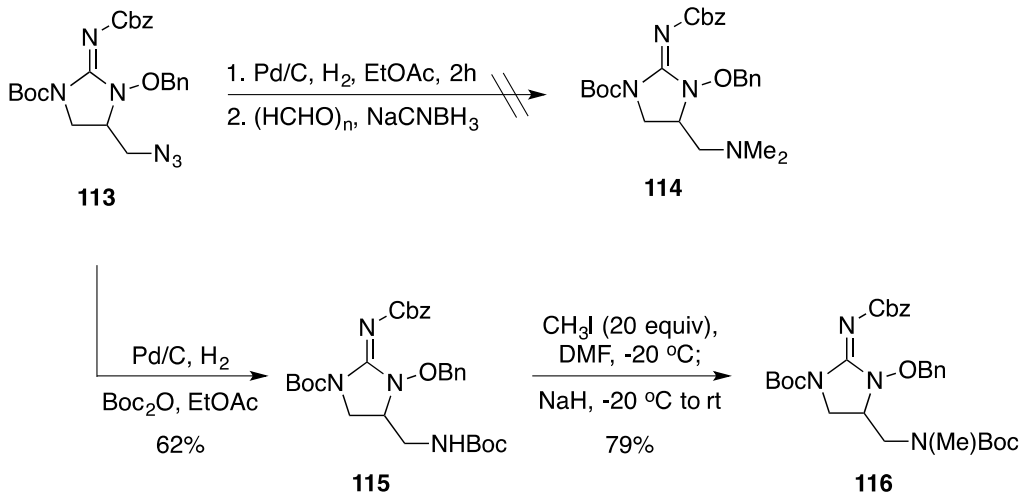
Scheme 32. Synthesis of alkyl azide **113**.



With a synthesis of azide **113** realized, conditions for reduction and subsequent dimethylation were investigated (Scheme 33). Initially, several conditions were explored to reduce the azide to the amine. Either Pd/C and H_2 or standard Staudinger conditions (not shown) gave the corresponding amine quantitatively. Surprisingly, the subsequent dimethylation of the free amine proved difficult. Several conditions were surveyed to achieve the dimethylation. Mostly variations of the Eschweiler-Clarke conditions utilizing formaldehyde and $NaCNBH_3$ were tried. However, only the primary amine was reisolated. A possible explanation for this difficulty is the ability of the guanidine nitrogens or the *O*-benzyl oxygen to form hydrogen bonds to the free amine and preventing nucleophilic addition into formaldehyde. A Merck Molecular Force Field (MMFF) lowest energy conformation calculation of the primary amine showed the presence of hydrogen bonding with the N-OBn oxygen. Accordingly, azide **113** was reduced by Pd/C and H_2 with *in situ* trapping of the resulting primary amine with di-*tert*-butyldicarbonate to give *tert*-butylcarbamate **115** in 62% yield. Methylation of *tert*-

butylcarbamate **115** was achieved in 79% yield by treating a solution of *tert*-butylcarbamate **115** and 20 equiv of iodomethane in DMF at -20 °C with NaH and warming to room temperature to give methylcarbamate **116**.

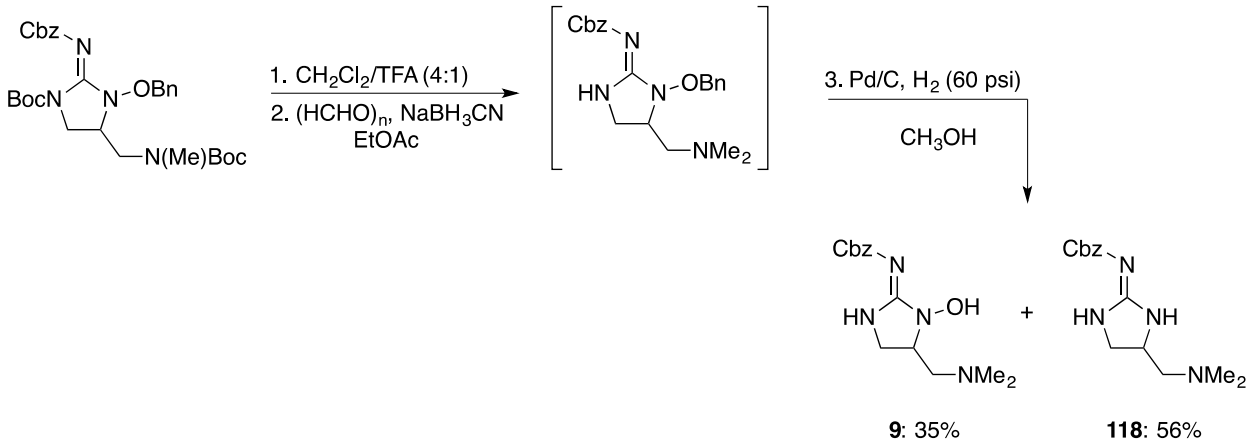
Scheme 33. Synthesis of methyl carbamate **116**.



Methyl carbamate **116** was subjected to a solution of CH_2Cl_2/TFA (4:1) to remove both Boc groups followed by a selective methylation of the secondary amine in the presence of the exposed guanidine nitrogen under Eschweiler-Clarke conditions to afford dimethylamine **117**.[54,55] Treatment of **117** with Pd/C and H_2 at 60 psi gave an inseparable mixture of *N*-hydroxyl guanidine **9** and guanidine **118** in 35% and 56% yield, respectively, over the three steps. The ^{1}H-NMR spectra of **9** and **118** matched the values for those compounds that were reported in the isolation paper (Scheme 34).[17] The original structures were assigned based on enriched 50% ^{13}C and 90% ^{15}N, which was used to confirm the guanidine core of anatoxin-a(s). The structural assignment was supported by FAB MS-MS and high-resolution data. The location of the hydroxyl group was determined based on similar chemical shifts observed in neosaxitoxin and

saxitoxin. Also, Moore and coworkers prepared synthetic **15** (the single enantiomer of **118**, Scheme 3), which matched the spectral data of **15** that had been obtained from degradation of anatoxin-s(s).

Scheme 34. Synthesis of *N*-hydroxy guanidine **9**.

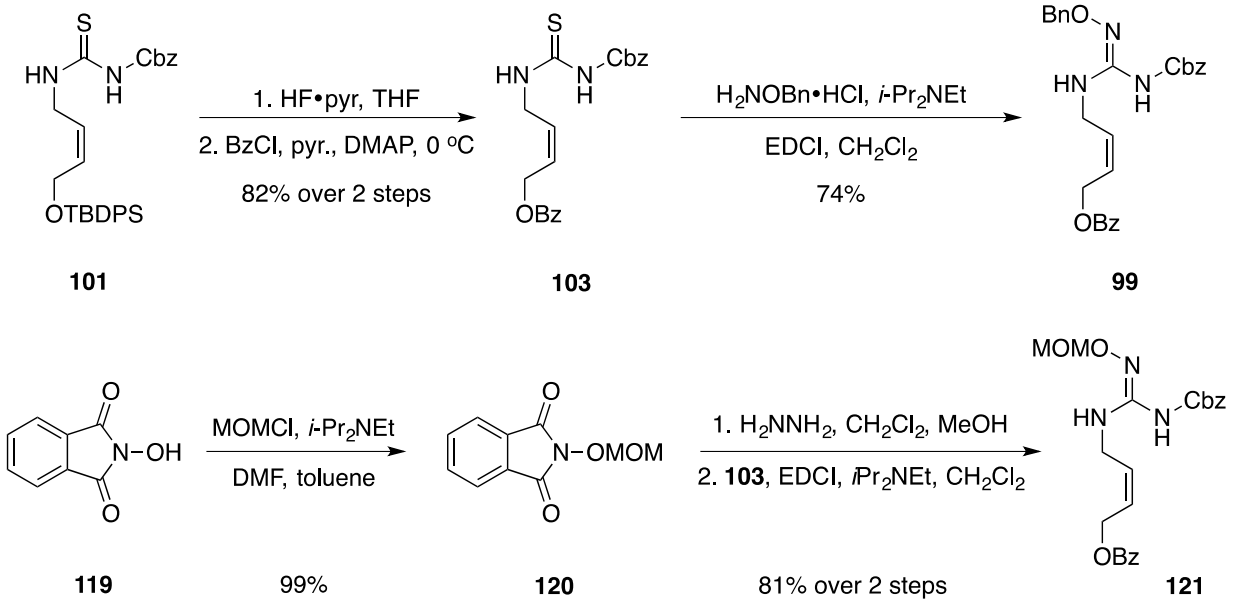


Since the major product under the only conditions that succeeded in removing the benzyl group was **118**, we decided to exchange the benzyl group with a more labile functionality. To that extent, starting with thiourea **101**, the synthetic route would be optimized and the benzyl group would be replaced with a functionality that would be more amendable to a late-stage cleavage.

Due to the low yields in the formation of the cyclization precursors using TBAF for silyl deprotection, we switched to the milder HF•pyr. Benzoylation of the alcohol produced thiourea **103** in 82% yield over the two steps (Scheme 35). Following our previously optimized conditions for guanidine formation, treatment of thiourea **103** with benzyl hydroxyl amine in the presence of diisopropylethylamine gave benzyl derivative **99** in 74% yield. Initially several silyl groups (TES, TBS, TBDPS) and THP were tried in place of the benzyl moiety but after

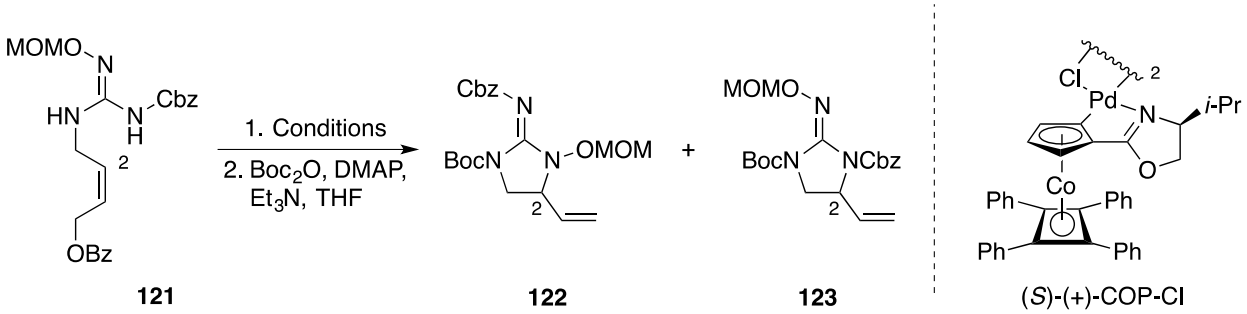
cyclization, the substrate was too labile to be viable. To install the methoxy methyl functionality, we first treated commercially available hydroxy phthalimide **119** with freshly prepared chloromethyl methyl ether to give methoxy methyl protected hydroxy phthalimide **120**. Treatment of **120** with hydrazine gave MOM-protected N-hydroxy amine, which when added to a solution of **103** in the presence of EDCI and diisopropylethylamine, gave guanidine **121** in 81% yield.

Scheme 35. Improved synthesis of **99** and synthesis of MOM derivative **121**.



Next, subjecting guanidine derivative **121** to our previously optimized cyclization conditions with $PdCl_2(CH_3CN)_2$ gave a single spot by TLC. After Boc-protection of the exposed guanidine nitrogen, olefin **122** was isolated in 95% yield as the sole regioisomer (assigned based on the chemical shift of the C2-H) (Table 7). During the cyclization studies with benzylated guanidine derivative **99**, treatment of **99** with Overman's chiral palladium(II) catalyst, COP-OAc. Unfortunately, when **99** was subjected to those conditions, a mixture of regioisomers was

observed. After SFC separation of the regioisomers, a 3:1 e.r. was observed by chiral SFC. For MOM derivative **121** we switched to the (*S*)-(+)-COP-Cl catalyst and observed only a single regioisomer of the cyclization products (**122** or **123**) was observed. Analysis by chiral SFC showed that isomer **122** was produced in a 3:1 e.r. This effect of the anionic ligand



121 **122** **123** (*S*)-(+)-COP-Cl

Entry	Conditions	Ratio (**122**:**123**)	Yield (*e.r.*)[a]
1	$PdCl_2(CH_3CN)_2$ (0.2 equiv), THF (0.2 M)	100:0	95%
2	(*S*)-(+)-COP-Cl (0.025 equiv), CH_2Cl_2 (0.6 M)	100:0	76% (3:1)[b]
3	(*R*)-(–)-COP-Cl (0.025 equiv), CH_2Cl_2 (0.6 M)	100:0	74% (1:3)[b]

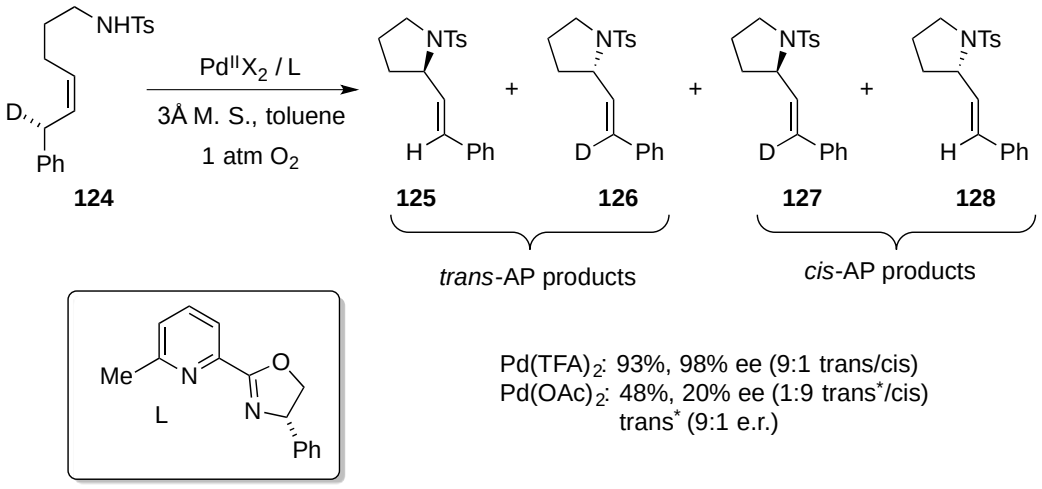
[a] Isolated yields. [b] e.r. determined by chiral SFC (chiralpak-IC; 2.0 mL/ min; 20% MeOH)

Table 7. Pd(II)-mediated cyclization of MOM-derivative **121**.

influencing the outcome of the reaction is similar to what was reported by Stahl for the cyclization of aliphatic amines to generate pyrrolidine compounds (Scheme 36).[56] This effect was attributated to a change in the mechanistic pathway from a *trans*-aminopalladation pathway to a *cis*-aminopalladation pathway (Scheme 5). In their reported cyclization with $Pd(TFA)_2$, a 90% yield (96% ee) and a 9:1 ratio of *trans*- vs. *cis*-aminopalladation (AP) products was observed; however, when $Pd(OAc)_2$ was used as a catalayst a decrease in yield, enantioselectivity (48%, 20% ee), and a reversal of the ratio of *trans*- vs. *cis*-AP products (1:9)

was observed. Interestingly, separating the *trans* products (**125** and **126**) still showed that these compounds were produced in a high enanteomeric ratio. They concluded that the poor enantioselectivity they observed was for the *cis*-aminopalladation pathway, while high enantioselectivities were observed for the *trans*-aminopalladation pathway.

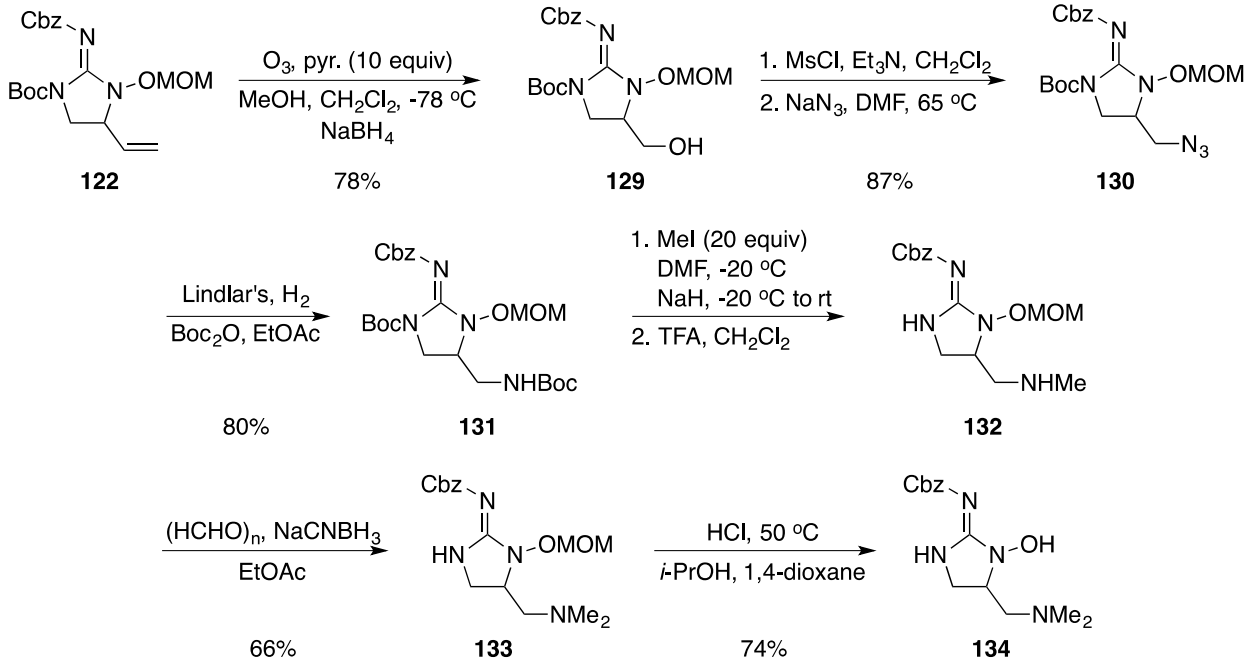
Scheme 36: *Trans*-aminopalladation (AP) vs. *cis*-aminopalladation.



With a route established for the production of **122** and conditions for a moderately enantioselective cyclization developed, completion of a synthesis of anatoxin-a(s) was pursued. To achieve that we bubbled ozone through a solution of **122** that had been buffered with 10 equiv of pyridine, as we had determined to be required in the previous route (Scheme 37). After treatment of the ozonide intermediate with $NaBH_4$ alcohol **129** was isolated in 78% yield. Next, mesylation of the alcohol with methane sulfonyl chloride, followed by nucleophilic displacement of the mesylate with NaN_3 gave alkyl azide **130** in 87% yield over the two steps. When azide **130** was reduced under the previous conditions for azide reduction (Pd/C, H_2) lower and irreproducible yields were observed. However, by switching to Lindlar's catalyst wesaw an improved and reproducible 80% yield of carbamate **131**. Presumably, the lower yield was due to

competitive cleavage of the Cbz group, which was not observed when utilizing the less reactive Lindlar's catalyst. With an efficient route to carbamate **131** established, a two-step procedure to install the dimethyl amine functionality was applied. Methylation of the carbamate with CH_3I and NaH gave, after exposure to TFA, methyl amine **132** in 73% yield over the two steps.

Scheme 37. Synthesis of hydroxy guanidine **134**.

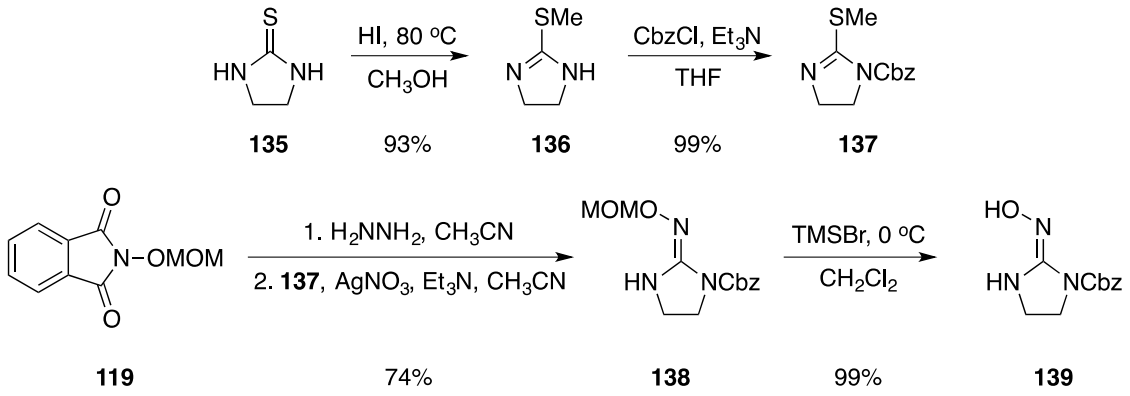


Exposing methyl amine **132** to reductive amination conditions produced dimethyl amine **133** in 66% yield. Cleavage of the methoxy methyl functionality proceeded smoothly to give hydroxy guanidine **134** in 74% yield. With the successful cleavage of the methoxy methyl group we next explored conditions for the successful phosphorylation of **134**.

Before exploring phosphorylation conditions, a model system of **134** was developed as phosphorylation of **134** would not be trivial. Towards that end commercially available ethylene thiourea (**135**) was treated with HI in CH_3OH to give alkylated thioimidate **136** in 93% yield (Scheme 38). Installation of the Cbz group proceeded smoothly by treating **136** with CbzCl and

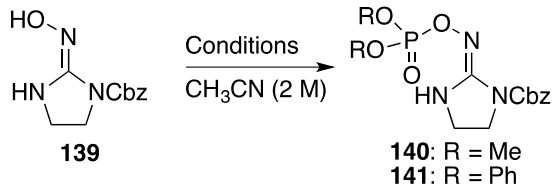
triethylamine to give **137** in 99% yield. As was worked out during the synthesis of **134**, the Cbz group is installed first to facilitate the addition of the electron rich nitrogen functionality. To finish the synthesis of the guanidine core, **119** was exposed to hydrazine and the resulting amine was added to a solution of **137**, which after treatment with $AgNO_3$ gave guanidine **138** in 74% yield. Finally, removal of the MOM group was achieved using TMSBr to give our desired model system **139** in 99% yield.

Scheme 38. A model system synthesis of **134** to explore phosphorylation conditions.



With a facile synthesis of the model system achieved, hydroxyl guanidine **139** was subjected to conditions to install the biologically important phosphate moiety. The most common conditions for the installation of phosphate groups typically involve the use of chlorophosphates as the phosphorylating agent. Initially, **139** was treated with dimethyl chlorophosphate in CH_3CN with triethylamine and **140** was isolated in a 31% yield (Entry 1, Table 8). Efforts to improve this yield were initially focused on utilizing different bases. First, deprotonation of **139** with NaH at 0 ^oC, followed the addition of dimethyl chlorophosphate and warming to rt did not yield **140**. Switching to NaHMDS we were able to isolate **140** in a similar 33% yield (Entry 3, Table 8) but no product was detected when KHMDS was used. A decrease

in the isolated yield of **140** was observed when DBU was used as the base (Entry 5, Table 8) and the use of diisopropylethylamine did not produce phosphorylated guanidine **142**. Interestingly, the use of diphenyl chlorophosphate was observed to give a slightly higher yield under the initial conditions, which may be evidence that the low yield was due to the stability of dimethyl chlorophosphate (Entry 7, Table 8).



139

140: R = Me
141: R = Ph

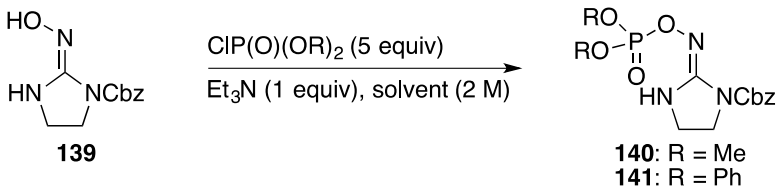
Entry	Conditions	Result
1	$ClP(O)(OMe)_2$ (2 equiv), Et_3N (1 equiv)	**140**: 31%[a]
2	$ClP(O)(OMe)_2$ (3 equiv), NaH (1.2 equiv), 0 °C to rt	**140: ---**
3	$ClP(O)(OMe)_2$ (3 equiv), NaHMDS (1.2 equiv), 0 °C to rt	**140:** 33%[a]
4	$ClP(O)(OMe)_2$ (3 equiv), KHMDS (1.2 equiv), 0 °C to rt	**140: ---**
5	$ClP(O)(OMe)_2$ (3 equiv), DBU (1.2 equiv)	**140:** 25%[a]
6	$ClP(O)(OPh)_2$ (3 equiv), *i*-Pr_2NEt (5 equiv)	**141: ---**
7	$ClP(O)(OPh)_2$ (1 equiv), Et_3N (1 equiv)	**141:** 40%[a]

[a] Yield determined after isolation.

Table 8: Exploration of different bases to optimize phosphorylation.

With no observable improvement to the phosphorylation when utilizing different bases, solvent effects on the phosphorylation of **139** were explored. It was known at this time that hydroxyguanidine compound **134** was not soluble in CH_3CN, which added another potential hurdle to the success of this reaction. Using our initial phosphorylation conditions, while increasing the equiv of dimethyl chlorophosphate from two to five equivalents, we observed a

37% yield of **140** (Entry 1, Table 9). Unfortunately, using these same conditions with different solvents (DMF, NMP, PhCN) resulted in no observable product formation.

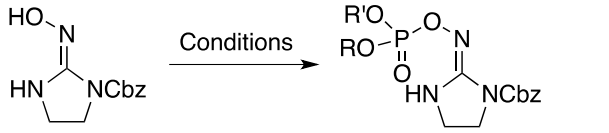


Entry	Solvent	Result
1	CH_3CN (2 M)	**140**: 37%[a]
2	CH_3CN (2 M)	**141:** 40%[a]
3	DMF (2 M)	**140: ---**
4	NMP (2 M)	**140: ---**
5	PhCN (2 M)	**140: ---**

[a] Yield determined after isolation.

Table 9: Solvent screen under the phosphorylation conditions.

With a small variation of yield observed dependent on the equivalents of the phosphorylation agent used and no improvement of the reaction utilizing different solvents, different phosphorylating reagents were explored. First, a coupling strategy was explored by treating **139** with dimethyl phosphate in the presence of diisopropyl carbodiimide (DIC) (Entry 1, Table 10). Under these conditions no observable product was detected and the starting material had disappeared by LC-MS analysis of the reaction mixture (Entry 1, Table 10). Next, a more reactive phosphorylating agent than a chlorophosphate was used. To this end, a solution of



139

140: R = R' = Me
142: R = Me, R' = Ph
143: R = R' = Bn

Entry	Conditions	Result
1	$(HO)P(O)(OMe)_2$, DIC, CH_3CN, 0 °C	**140**: ---
2	$(HO)P(O)(OMe)_2$, TFAA, Et_3N, 0 °C, CH_3CN; methyl imidazole	**140**: 49%[a]
3	$Cl_2P(O)(OPh)$ (3 equiv), CH_3CN (2 M), Et_3N (1 equiv); MeOH (10 equiv), Et_3N (1 equiv)	**142**: ---
4	$(BnO)_2PNEt_2$, DMF, tetrazole; *m*-CPBA	**143**: ---

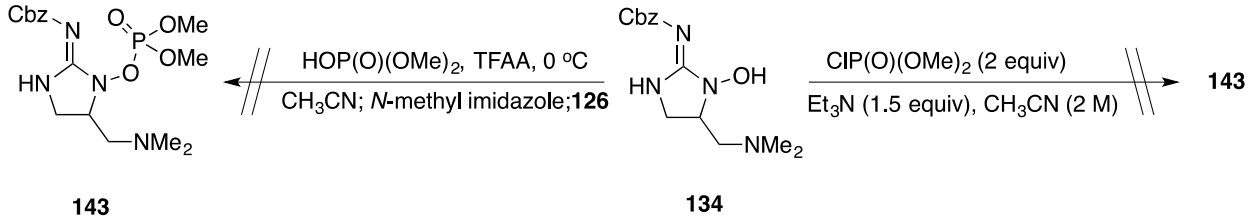
[a] Yield determined after isolation.

Table 10: Exploring different phosphorylation conditions.

dimethyl phosphate and triethylamine was treated with TFAA, followed by the addition of methyl imidazole, which generated the highly active dimethyl methyl-imidazole phosphate. The addition of this phosphorylating agent to **139** produced the desired dimethyl phosphate **140** in an improved 49% yield (Entry 2, Table 10). Attempts at using phenyl dichlorophosphate followed by the addition of methanol (Entry 3, Table 10) and the addition dibenzyl diethylphosphoramidite to **139** followed *m*-CPBA did not yield did not yield any observable product formation (Entry 4, Table 10).

Hydroxy guanidine **134** was subjected to the two phosphorylation conditions that had been successful on the model system (**139**) (Scheme 39). Unfortunately, subjecting **134** to dimethyl chlorophosphate in the presence of triethylamine did not lead to successful phosphorylation. Exposure of **134** to the more active dimethyl methylimidazole phosphate did not result in any detectable (by TLC, ^{1}H-NMR, or LC-MS) amount of **135**.

Scheme 39: Attempted phosphorylation of **134**.



Unable to achieve phosphorylation of **134** under our previously worked out conditions, we proceeded to try other methods of phosphorylation. Subjecting **134** to dimethyl chlorophosphonate in a variety of solvents and different bases did not produce any observable trace of **134**. Exposure of **134** to either dibenzyl *N*,*N*-diethyl phosphoramidite or dimethyl *N*,*N*-diethyl phosphoramidite in the presence of triethylamine resulted in the intermediate mass potentially being detected by direct inject mass spectroscopic analysis of the reaction solution ($[M + H]^+$). No ^{1}H-NMR data of this intermediate could be obtained. The addition of *m*-CPBA to the solution resulted in what appeared to be oxidation of the intermediate to the mass expected for **140**/**141** as detected by LC-MS analysis of the reaction solution. Unfortunately, this mass was never detected after work-up of the reaction mixture. Without spectroscopic proof of the intermediate or the resulting product, it is uncertain what occured under these conditions. Also, attempts at using a coupling strategy involving DCC and dimethyl phosphate resulted in loss of the starting material with no detectable product formation. In 2004, the Jones group published a procedure for the phosphorylation of alcohols utilizing *N*-phosphoryl oxazolidinones as transfer reagents.[57,58] Under their conditions, they are able to achieve phosphorylation of primary, secondary, tertiary, and aromatic alcohols. Unfortunately, under their reported conditions we saw no detectable phosphorylation of **134**. The use of a harder base to promote anion formation also did not yield **140**.

1.3 CONCLUSION

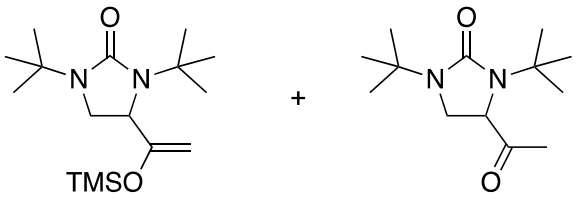
Anatoxin-a(s) (**8**) is a unique organophosphate and one of the strongest PNS-anticholinesterase agents. The backbone framework was assebled using an array of Pd(0) and Pd(II) metal-mediated reactions. The Initial effort towards the total synthesis of anatoxin-a(s) centered around assembling the heterocyclic scaffold using Shi's diamination procedure of 2-trimethylsilyloxy-butadiene (**67**) to give silyl enol ether **68** (Scheme 19, vide supra); however, difficulties in functionalizing silyl enol ether **68** led to different methods to construct the framework of anatoxin-a(s) being explored. A key amidocarbonylation reaction catalyzed by Pd(II) was pursued but preliminary results showed that the undesired regioisomer was the preferred product. Also, as in the 1st generation route, installation of the dimethylamine side-chain present in the natural product proved difficult. A 3rd generation route involved a key amidoalkylation of guanidine **121**, which led to advanced intermediate **134** in 18 steps and 8.0% overall yield. In this route, a new methodology for the regioselective cyclization of unsymmetrical guanidines was developed. Using the catalyst system developed by Overman, (*R*)-(–)-COP-Cl, we were able to achieve a 3:1 enantiomeric ratio for the key palladium-mediated cyclization sequence. Although a variety of conditions were attempted to phosphorylate **134**, none of the conditions tried were successful in generating phosphate **140**.

2.0 EXPERIMENTAL

General. All glassware was dried in an oven at 140 °C for 2 h or flame dried prior to use and all moisture-sensitive reactions were performed under a dry N_2 atmosphere unless otherwise stated. THF and Et_2O were distilled from sodium/benzophenone ketyl; triethylamine, pyridine, and diisopropylethylamine were distilled from CaH_2 and stored over KOH; DMF was through activated neutral alumina and dried for 4 days over 3 Å molecular sieves; CH_2Cl_2 and toluene were purified by passage through an activated alumina filtration system; 1,2-dichloroethane was distilled over CaH_2; CbzNCS,[41] di-*tert*-butylurea,[38] **66**,[38] **67**,[47] **71**,[47] (*Z*)-4-(*tert*-Butyldiphenylsilyloxy)but-2-en-1-ol,[50] (*Z*)-(4-Bromobut-2-enyloxy)(*tert*-butyl)diphenylsilane,[51] were prepared according to literature procedures.

Reactions were monitored by thin-layer chromatography using pre-coated silica gel 60 F254 plates (EMD, 250 μm thickness) and visualization was accomplished with a 254 nm UV light and by staining with a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution) or Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}$•4 H_2O and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution). Flash chromatography was performed using SiO_2 (Silicycle, Silia-P Flash Silica Gel, 40-63 μm) or Florisil® (purchased from Fischer chemical and used as received, 100 - 200 mesh).

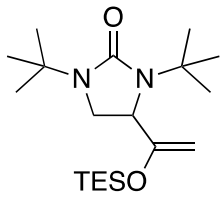
^{1}H and ^{13}C NMR spectra were obtained on a Bruker advance 300 MHz in $CDCl_3$ unless otherwise noted. Chemical shifts (δ) were reported in parts per million with the residual solvent peak used as an internal standard δ ^{1}H / ^{13}C (Solvent); 7.26 /77.23 ($CDCl_3$) and are tabulated as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, bt = broad triplet, tt = triplet of triplets, at = apparent triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). Infrared spectra were determined as neat solids or oils on a Smiths Detection IdentifyIR FT-IR spectrometer. Mass spectra were obtained on a Micromass Autospec double focusing instrument. Melting points were determined using a Laboratory Devices Mel Temp II in open capillary tubes and are uncorrected. Enantiomeric ratios were determined using a Mettler Toledo AG – Berger SFC™ Analytix.



68 **70**

1,3-Di-*tert*-butyl-4-(1-(trimethylsilyloxy)vinyl)imidazolidin-2-one (68)[36] **and 4-acetyl-1,3-di-*tert*-butylimidazolidin-2-one (70).** A solution of **66** (0.500 g, 2.94 mmol) in toluene (8.80 mL) was treated with $Pd(PPh_3)_4$ (0.339 g, 0.294 mmol). To the mixture was added **67** (1.67 g, 5.87 mmol) and the resulting solution was heated to 65 ˚C for 1 h. The reaction solution was cooled

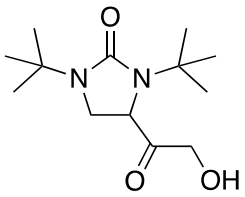
to rt and filtered through SiO_2 (9:1 hexanes/EtOAc) to give **68** (174 mg, 19 %): ^{1}H NMR (300 MHz, benzene-d_6) δ 4.33 (d, 1 H, *J* = 1.5 Hz), 4.07 (d, 1 H, *J* = 1.5 Hz) 3.71 (dd, 1 H, *J* = 3.0, 9.0 Hz), 3.10 (at, 1 H, *J* = 8.4, 9.0 Hz), 3.00 (dd, 1 H, *J* = 3.0, 8.4 Hz), 1.51 (s, 9 H), 1.34 (s, 9 H), 0.15 (s, 9 H); and **70**: IR (ATR) 1718, 1679 cm^{-1}; ^{1}H NMR (300 MHz, benzene-d_6) δ 3.72 (dd, 1 H, *J* = 4.8, 10.2 Hz), 2.85 (dd, 1 H, *J* = 9.0, 9.9 Hz) 2.54 (dd, 1 H, *J* = 4.5, 9.0 Hz), 1.83 (s, 3 H), 1.28 (s, 9 H), 1.20 (s, 9 H); ^{13}C NMR (75 MHz, benzene-d_6) δ 208.3, 160.6, 61.6, 54.5, 53.4, 43.7, 28.5, 27.5, 24.5; HRMS (ES$^+$) *m/z* calcd for $C_{13}H_{25}N_2O_2$ ([M + H]$^+$) 241.1916, found 241.1915.



72

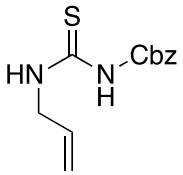
1,3-Di-*tert*-butyl-4-(1-(triethylsilyloxy)vinyl)imidazolidin-2-one (72). A solution of **66** (50.0 mg, 0.294 mmol) and $Pd(PPh_3)_4$ (33.9 mg, 0.0294 mmol) in THF (0.100 mL) was treated with **71** (108 mg, 0.587 mmol) and heated to 65 ˚C for 1 h. The reaction solution was cooled to room rt and filtered through Florisil® (9:1 hexanes/EtOAc) to give **72** (48.1 mg, 46%): IR (ATR) 1690 cm^{-1}; ^{1}H NMR (300 MHz, benzene-d_6) δ 4.26 (d, 1 H, *J* = 1.8 Hz), 4.06 (d, 1 H, *J* = 1.5 Hz), 3.74 (dd, 1 H, *J* = 3.3, 9.3 Hz), 3.11 (dd, 1 H, *J* = 8.4, 9.3 Hz), 3.02 (dd, 1 H, *J* = 3.0, 8.1 Hz), 1.51 (s, 9 H), 1.35 (s, 9 H), 0.98 (s, 9 H), 0.65 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9,

160.3, 88.3, 55.7, 54.0, 52.9, 47.2, 28.7, 27.6, 6.9, 5.0; HRMS (ES^+) *m/z* calcd for $C_{19}H_{38}N_2O_3SiNa$ ($[M + Na]^+$) 377.2600, found 377.2590.



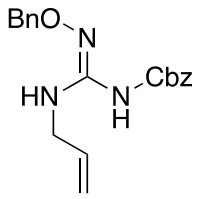
73

1,3-Di-*tert*-butyl-4-(2-hydroxyacetyl)imidazolidin-2-one (73). A solution of **72** (109 mg, 0.307 mmol) in CH_2Cl_2 (1.5 mL) and 5% aq. $NaHCO_3$ (1.5 mL) was cooled to 0 ˚C, treated with *m*-CPBA (151 mg, 0.613 mmol), stirred at rt overnight. The reaction was diluted with sat. $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with sat. Na_2SO_3, sat. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. The crude residue was dissolved in CH_3OH (1.0 mL) and treated with 1.5 M HCl (1.0 mL). The reaction mixture was stirred overnight and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with water, dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (1:1 hexanes/EtOAc) to give **73** (3.9 mg, 5%): IR (ATR) 3396, 1702 cm^{-1}; ^1H NMR (300 MHz, benzene-d_6) δ 4.35 (dd, 1 H, *J* = 5.1, 19.8 Hz), 4.13 (dd, 1 H, *J* = 4.8, 19.8 Hz) 3.72 (dd, 1 H, *J* = 4.2, 9.9 Hz), 2.86 (t, 1 H, *J* = 5.1 Hz), 2.74 (t, 1 H, *J* = 9.6 Hz), 2.44 (dd, 1 H, *J* = 4.2 9.3 Hz), 1.18 (s, 9 H), 1.13 (s, 9 H); HRMS (EI^+) *m/z* calcd for $C_{13}H_{24}N_2O_3$ ($[M]^{+\cdot}$) 256.1787, found 256.1779.



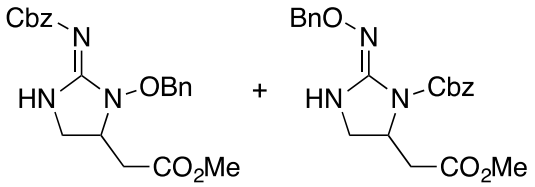
79

1-Benzyloxycarbonyl-3-allylthiourea (79). To a solution of CbzNCS[41] (0.831 g, 4.30 mmol) in CH_2Cl_2 (164 mL) at 0 °C was added allylamine (0.330 mL, 4.30 mmol). The solution was warmed to rt, stirred for 1.5 h, and quenched with 1 M HCl (10.0 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (4:1, hexanes/EtOAc) to give **79** (1.07 g, 99%) as a white solid: Mp 61.3-63.5 °C; IR (ATR) 3252, 3164, 1715, 1534 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (s, 1 H), 8.11 (s, 1 H), 7.43–7.33 (m, 5 H), 5.92 (dddd, 1 H, *J* = 5.7, 5.7, 10.5, 17.1 Hz), 5.32–5.21 (m, 2 H), 5.18 (s, 2 H), 4.30 (tt, 2 H, *J* = 1.2, 5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 152.7, 134.7, 132.1, 128.9, 128.8, 128.3, 117.7, 68.2, 48.0; HRMS (EI^+) *m/z* calcd for $C_{12}H_{14}N_2O_2S$ ($[M]^{+\cdot}$) 250.0776, found 250.0786.



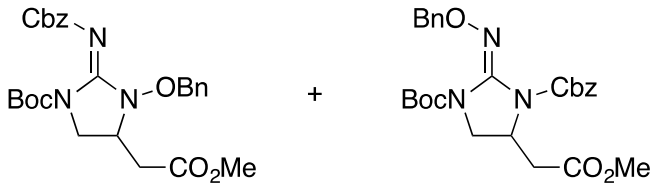
78

1- Benzyloxycarbonyl-2-benzyloxy-3-allylguanidine (78). To a solution of **79** (1.50 g, 6.87 mmol), *O*-benzylhydroxylamine (1.25 mL, 10.3 mmol), and diisopropylethylamine (1.26 mL, 7.56 mmol) in CH_2Cl_2 (68.7 mL) at 0 °C was added EDCI (2.63 g, 13.7 mmol, 2 equiv). The reaction mixture was stirred for 1 h, warmed to rt, stirred for 14 h, and quenched with 1 M HCl (5 mL). The organic solution was washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (2:1, hexanes/EtOAc to 1:1 hexanes/EtOAc) to give **78** (1.78 g, 76%) as a clear oil: IR (ATR) 3386, 1726, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1 H), 7.48–7.29 (m, 10 H), 6.41 (bs, 1 H), 5.99 (dddd, 1 H, *J* = 1.2, 5.7, 11.4, 15.9 Hz), 5.20 (m, 2 H), 5.15 (s, 2 H) 4.90 (s, 2 H), 3.79-3.75 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 148.1, 137.7, 135.2, 134.4, 128.9, 128.8, 128.5, 128.4, 128.1, 116.1, 76.0, 67.8, 43.4; HRMS (EI^+) *m/z* calcd for $C_{19}H_{21}N_3O_3$ ($[M]^{+\cdot}$) 339.1583, found 339.1581.



77 **80**

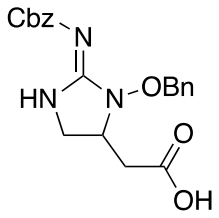
Methyl 3,4-(1-benzyloxy-2-benzyloxycarbonyl)guanidinobutanoate (77) and methyl 3,4-(1-benzyloxycarbonyl-2-benzyloxy)guanidinobutanoate (80). A 50-mL, 3-necked, round-bottomed flask fitted with rubber septum and a three-way hose adapter (with stopcock, equipped with a vacuum inlet, and a balloon filled with CO) was charged with $Pd(OAc)_2$ (56.1 mg, 0.250 mmol), $CuCl_2$ (1.02 g, 7.49 mmol), and degassed CH_3OH (4.0 mL). The flask was evacuated and back-filled with CO (3x), cooled to 0 °C, and stirred for 0.5 h. To this mixture was added a solution of **78** (848 mg, 2.50 mmol) in degassed CH_3OH (4.32 mL). The reaction mixture was stirred at 0 °C for 18 h, warmed to rt, stirred for 4 h, and concentrated. The residue was dissolved in EtOAc, and filtered through celite. The brownish filtrate was washed with sat. $NaHCO_3$ (1 x 5 mL), ethylenediamine (1 x 1 mL), and sat. $NaHCO_3$ (1 x 5 mL). The washing procedure was repeated until the organic layer remained yellow. The organic solution was dried (Na_2SO_4), concentrated, and purified by chromatography on florisil® (1:1, hexanes/EtOAc to 100% EtOAc) to give **77** and **80** (750 mg, 76%) in a isomeric ratio of 2.2:1 as a yellow oil that was not further separated: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.26 (m, 20 H), 5.26 (ad, 2 H, *J* = 1.5 Hz, minor isomer **77**), 5.16 (s, 2 H, major isomer **77**), 5.07 (d, 1 H, *J* = 11.4 Hz, major isomer **77**), 5.00 (d, 2 H, *J* = 11.4 Hz, major isomer **77**), 4.98 (s, 2 H, minor isomer **80**).



77-Boc **80-Boc**

Methyl 3,4-(1-benzyloxy-2-benzyloxycarbonyl-3-*tert*-butoxycarbonyl)guanidinobutanoate (77-Boc) and methyl 3,4-(1-benzyloxycarbonyl-2-benzyloxy-3-*tert*-butoxycarbonyl) guanidinobutanoate (80-Boc). A 50-mL, 3-necked, round-bottomed flask fitted with rubber septum and a three-way hose adapter (with stopcock, equipped with a vacuum inlet, and a balloon filled with CO) was charged with $Pd(OAc)_2$ (166 mg, 0.737 mmol), $CuCl_2$ (3.00 g, 22.1 mmol), and degassed CH_3OH (12.0 mL). The flask was evacuated and back-filled with CO (3x), cooled to 0 °C, and stirred for 0.5 h. To this mixture was added a solution of **78** (2.50 g, 7.37 mmol) in degassed CH_3OH (12.6 mL) and the resulting solution was stirred at 0 °C for 18 h, warmed to rt, stirred for 4 h, and concentrated. The residue was dissolved in EtOAc, filtered through celite, and the brownish filtrate was washed with sat. $NaHCO_3$ (10 mL), ethylenediamine (1 mL), and sat. $NaHCO_3$ (10 mL). The washing procedure was repeated until the organic layer remained yellow. The organic solution was dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture of **77** and **80** was dissolved in THF (73.7 mL) and treated with Boc_2O (1.93 g, 8.84 mmol, 1.2 equiv). To this solution was added triethylamine (2.30 mL, 1.66 mmol) followed by DMAP (182 mg, 1.47 mmol, 0.2 equiv) and the resulting mixture was stirred for 24 h, treated with sat. NH_4Cl (20 mL), and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (2:1, hexanes/EtOAc) to give **77-Boc** (1.40 g, 38%) as a white solid:

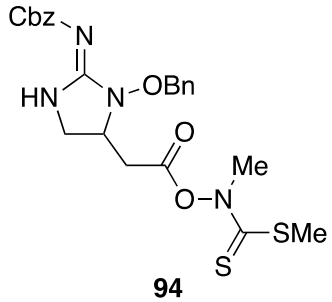
Mp 123.3–124.5 °C; IR (ATR) 1752, 1724, 1687, 1631 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.25 (m, 10 H), 5.02 (s, 2 H), 4.95 (d, 1 H, *J* = 10.5 Hz), 4.81 (d, 1 H, *J* = 10.5 Hz), 3.92–3.82 (m, 2 H), 3.62 (s, 3 H), 3.47–3.42 (m, 1 H), 2.77 (dd, 1 H, *J* = 3.9, 16.5 Hz), 2.32 (dd, 1 H, *J* = 8.4, 16.5 Hz), 1.48 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 160.0, 149.7, 136.4, 135.4, 129.5, 129.0, 128.7, 128.6, 128.4, 128.0, 83.9, 67.9, 52.2, 28.2; HRMS (EI^+) *m/z* calcd for $C_{26}H_{31}N_3O_7$ ($[M]^+$) 497.2162, found 497.2160: and **80-Boc** (0.834 g, 23%) as a yellow oil: IR (ATR) 1733, 1724, 1709, 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.25 (m, 10 H), 5.30 (d, 1 H, *J* = 12.6 Hz), 5.23 (d, 1 H, *J* = 12.3 Hz), 5.05 (s, 2 H), 4.49 (ddd, 1 H, *J* = 3.3, 6.9, 12.9 Hz), 3.78–3.76 (m, 1 H), 3.68 (s, 3), 3.67 (dd, 1 H, *J* = 3.9, 6.9 Hz), 2.87 (dd, 1 H, *J* = 3.3, 16.2 Hz), 2.46 (dd, 1 H, J = 9.9, 16.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 151.6, 151.0, 141.9, 137.4, 135.6, 129.9, 128.9, 128.7, 128.5, 128.3, 128.2, 128.0, 82.9, 68.3, 52.7, 52.2, 50.0, 37.2, 28.0; HRMS (ES^+) *m/z* calcd for $C_{26}H_{31}N_3O_7Na$ ($[M + Na]^+$) 520.2060, found 520.2038.



87

3,4-(1-Benzyloxy-2-benzyloxycarbonyl)guanidinobutanoic acid (87). To a solution of **77** and **70** (0.350 g, 0.881 mmol) in Et_2O/THF (35.2 mL, 10:1 v/v) was added KOTMS (0.314 g, 2.20 mmol) and the resulting mixture was stirred for 3 h. After the addition of water (10 mL) the biphasic solution was vigorously stirred for 5 min, the aqueous phase was separated, acidified (pH = 2) with 1 M HCl, and extracted with EtOAc (5 x 10 mL). The combined organic extracts

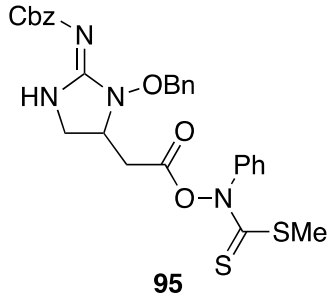
were dried (Na_2SO_4) and concentrated to give of **87** (233 mg, 69%) as a powder: Mp 150.1–151.9 °C; IR (ATR) 3340, 1702, 1638, 1610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.26 (m, 10 H), 5.16 (s, 2 H), 5.05 (d, 1 H, *J* = 11.4 Hz), 4.98 (d, 1 H, *J* = 11.1 Hz), 3.86–3.77 (m, 1 H), 3.67 (dd, 1 H, *J* = 7.8, 9.6 Hz), 3.17 (dd, 1 H, *J* = 7.2, 9.6 Hz), 2.63 (dd, 1 H, *J* = 3.9, 16.8 Hz), 2.19 (dd, 1 H, *J* = 9.3, 16.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 166.7, 164.3, 137.0, 136.0, 130.0, 129.0, 128.7, 128.6, 128.3, 128.1, 78.8, 67.5, 57.3, 45.3, 34.5; HRMS (EI^+) *m/z* calcd for $C_{20}H_{21}N_3O_5$ ($[M]^{+\cdot}$) 383.1481, found 383.1479.



94

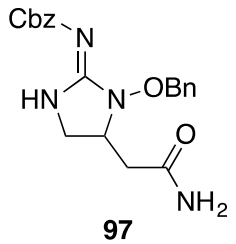
Methyl-3,4-(1-benzyloxy-2-benzyloxycarbonyl)guanidinebutanoyloxy(methyl) carbamodithioate (94). A solution of **87** (0.250 g, 0.652 mmol) in CH_2Cl_2 (10.0 mL) at 0 °C was treated with DCC (161 mg, 0.717 mmol) and DMAP (8.05 mg, 0.0652 mmol). After 0.5 h the flask was protected from light and a solution of **92**[47] (89.5 mg, 0.652 mmol) in CH_2Cl_2 (3.0 mL) was added slowly. The mixture was warmed to rt, stirred for 24 h, filtered through celite, concentrated, and purified by chromatography on SiO_2 (1:1, hexanes/EtOAc) to give of **94** (248 mg, 76%) as a foam: IR (ATR) 3319, 1621, 1569, 1536 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (bs, 1 H), 7.46–7.29 (m, 10 H), 5.17 (s, 2 H), 5.02 (s, 2 H), 3.95–3.86 (m, 1 H), 3.72 (dd, 1 H, *J* = 8.0, 9.9 Hz), 3.65 (s, 3 H), 3.27 (dd, 1 H, *J* = 6.3, 9.9 Hz), 2.76 (dd, 1 H, *J* = 4.5, 16.8 Hz),

2.53 (s, 3 H), 2.33 (dd, 1 H, *J* = 9.0, 16.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 167.4, 166.5, 164.5, 137.0, 136.0, 130.2, 129.2, 128.8, 128.6, 128.4, 128.1, 78.8, 67.5, 56.9, 45.0, 42.8, 32.4, 19.0; MS (ES^+) *m/z* 525 ($[M + Na]^+$, 70), 503 (100), 247 (80), 212 (85).



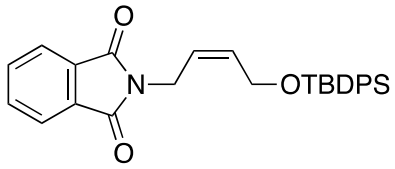
95

Methyl-3,4-(1-benzyloxy-2-benzyloxycarbonyl)guanidinobutanoyloxy(phenyl) carbamodithioate (95). A solution of **87** (0.250 g, 0.652 mmol) in CH_2Cl_2 (10.0 mL) at 0 °C was treated with DCC (161 mg, 0.717 mmol) and DMAP (8.05 mg, 0.0652 mmol). After 0.5 h the flask was protected from light and a solution of **93**[47] (0.130 g, 0.652 mmol) in CH_2Cl_2 (3.0 mL) was added slowly. The mixture was warmed to rt, stirred for 24 h, filtered through celite, concentrated, and purified by chromatography on SiO_2 (1:1, hexanes/EtOAc) to give **95** (207 mg, 56%) as a yellow oil: IR (ATR) 3360, 1653, 1603, 1577 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (bs, 1 H), 7.48–7.26 (m, 15 H), 5.17 (s, 2 H), 5.03 (d, 1 H, *J* = 11.4 Hz), 4.98 (d, 1 H, *J* = 11.4 Hz), 3.89–3.80 (m, 1 H), 3.69 (dd, 1 H, *J* = 7.8, 9.9 Hz), 3.28 (dd, 1 H, *J* = 6.6, 9.9 Hz), 2.78 (dd, 1 H, *J* = 3.9, 16.8 Hz), 2.58 (s, 3 H), 2.32 (dd, 1 H, J = 9.9 Hz, 16.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 167.3, 166.6, 164.5, 137.0, 136.0, 130.0, 129.8, 129.0, 128.7, 128.6, 128.5, 128.4, 128.0, 78.7, 77.4, 67.5, 57.1, 45.0, 32.3, 19.8; HRMS (ES^+) *m/z* calcd for $C_{28}H_{29}N_4O_5S_2$ ($[M + H]^+$) 565.1579, found 565.1559.



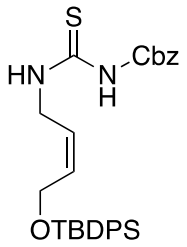
97

3,4-(1-Benzyloxy-2-benzyloxycarbonyl)guanidinobutanamide (97). A sealed tube was charged with a solution of **77** and **80** (0.250 g, 0.629 mmol, 1:1) in CH_3OH (2.1 mL), cooled to -78 °C, and treated with liquid ammonia (2.1 mL). The tube was sealed, slowly warmed to rt over 1 h, stirred 13 h, and concentrated to give **97 (**153 mg, 64%) as a white solid: Mp 141.8–143.5 °C; IR (ATR) 3362, 3178, 1668, 1649, 1579 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (bs, 1 H), 7.44–7.26 (m, 10 H), 5.65 (bs, 1 H), 5.23 (bs, 1 H), 5.18 (dd, 1 H, *J* = 12.6 Hz), 5.14 (dd, 1 H, *J* = 12.6 Hz), 5.02 (s, 2 H), 3.90–3.81 (m, 1 H), 3.65 (dd, 1 H, *J* = 7.8, 9.9 Hz), 3.23 (dd, 1 H, *J* = 6.0, 9.9 Hz), 2.41 (dd, 1 H, *J* = 4.2, 15.6 Hz), 2.10 (dd, 1 H, *J* = 9.0, 15.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 166.3, 164.3, 137.1, 135.9, 130.0, 129.0, 128.7, 128.6, 128.4, 128.1, 78.5, 67.4, 57.3, 45.0, 35.1; HRMS (ES^+) *m/z* calcd for $C_{20}H_{22}N_4O_4Na$ ($[M + Na]^+$) 405.1539, found 405.1525.



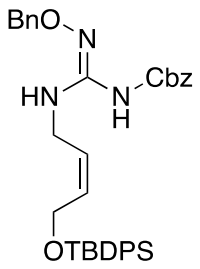
100

(*Z*)-2-(4-(*tert*-Butyldiphenylsilyloxy)but-2-enyl)phthalimide (100). To a solution of (*Z*)-(4-bromobut-2-enyloxy)(*tert*-butyl)diphenylsilane (13.4 g, 34.5 mmol) in DMF (98.5 mL) was added potassium phthalimide (9.78 g, 51.7 mmol). The resulting mixture was heated to 80 °C for 25.5 h, cooled to rt, concentrated, and diluted with CH_2Cl_2 (100 mL). The crude solution was filtered through SiO_2, concentrated, and purified by chromatography on SiO_2 (5:1, hexanes/EtOAc) to give **100** (11.8 g, 75%) as a pale yellow oil: IR (ATR) 3068, 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84–7.69 (m, 8 H), 7.48–7.37 (m, 6 H), 5.85-5.76 (m, 1 H), 5.54–5.45 (m, 1 H), 4.49 (td, 2 H, *J* = 0.6, 6.0 Hz), 4.20 (td, 2 H, *J* = 0.6, 6.9 Hz), 1.09 (2, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 135.8, 134.1, 133.7, 132.3, 129.9, 127.9, 124.2, 123.4, 60.4, 35.2, 27.0, 19.3; HRMS (EI^+) *m/z* calcd for $C_{27}H_{26}NO_3Si$ ($[M - 15]^+$) 440.1682, found 440.1694.



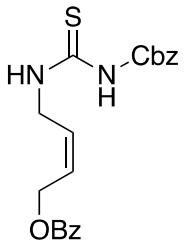
101

(*Z*)-4-(3-(Benzyloxycarbonyl)thiourea)but-2-enyl-*tert*-butyldiphenylsilyloxane (101). To a solution of **100** (11.3 g, 24.9 mmol) in EtOH (258 mL) was added hydrazine monohydrate (2.54 g, 49.8 mmol). The mixture was heated at reflux for 4 h, cooled to 0 °C, filtered, and concentrated. The crude residue was added at 0 °C to a solution of CbzNCS[41] (7.21 g, 37.3 mmol) in CH_2Cl_2 (258 mL). The solution was stirred for 15 h while slowly warming to rt, washed with 1 M HCl (25 mL), water (25 mL), and brine (25 mL). The organic phase was dried (Na_2SO_4) and concentrated. The crude material was purified by chromatography on SiO_2 (9:1, hexanes/EtOAc) to give **101** (12.3 g, 96%) as a yellow oil: IR (ATR) 3248, 3287, 1715, 1526 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.54 (bs, 1 H), 8.25 (s, 1 H), 7.72–7.67 (m, 4 H), 7.45–7.37 (m, 11 H), 5.86–5.78 (m, 1 H), 5.56-5.48 (m, 1 H), 5.18 (s, 2 H), 4.32 (dd, 2 H, *J* = 0.9, 6 Hz), 4.14 (t, 2 H, *J* = 5.4 Hz), 1.08 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 152.6, 135.7, 134.7, 133.6, 133.4, 129.9, 129.2, 128.9, 128.5, 127.9, 124.4, 77.2, 68.3, 60.4, 43.1, 27.0, 19.3; HRMS (ES^+) *m/z* calcd for $C_{29}H_{34}N_2O_3SiSNa$ ($[M + Na]^+$) 541.1957, found 541.1957.



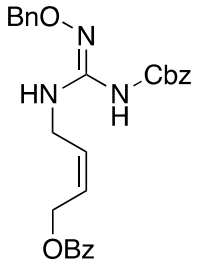
102

(*Z*)-4-(2-(Benzyloxy)-3-(benzyloxycarbonyl)guanidino)but-2-enyl-*tert*-butyldiphenylsilylane (102). To a solution of **101** (1.00 g, 1.99 mmol) and *O*-benzylhydroxylamine hydrochloride (0.397 g, 2.39 mmol) in CH_2Cl_2 (13.3 mL) was added diisopropylethylamine (0.697 mL, 4.18 mmol). The resulting mixture was cooled to 0 °C, treated with EDCI (6.41 g, 33.4 mmol, 1.5 equiv), stirred for 1 h, warmed to rt, and stirred for 41 h. The solution was washed with 1 M HCl (5 mL), water (5 mL), and brine (5 mL). The organic phase was dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (2:1, hexanes/EtOAc) to give **102** (0.84 g, 71%) as a yellow oil: IR (ATR) 3390, 1728, 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1 H), 7.76–7.74 (m, 4 H), 7.47–7.32 (m, 16 H), 6.23 (bt, 1 H, *J* = 5.4 Hz), 5.81–5.75 (m, 1 H), 5.56–5.50 (m, 1 H), 5.15 (s, 2 H), 4.85 (s, 2 H), 4.37–4.34 (m, 2 H), 3.62 (t, 2 H, *J* = 5.7 Hz), 1.12 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 147.9, 137.7, 135.8, 135.3, 133.8, 132.0, 129.9, 129.4, 128.9 (2), 128.6, 128.5, 128.1, 127.9, 127.8, 126.8, 76.1, 67.8, 60.5, 38.4, 27.0, 19.3; HRMS (EI^+) *m/z* calcd for $C_{37}H_{41}N_3O_4$ ($[M]^{+\cdot}$) 591.3097, found 591.3080.



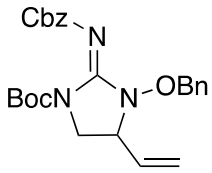
103

(*Z*)-4-(3-(Benzyloxycarbonyl)thioureido)but-2-enyl benzoate (103). A solution of **102** (8.19 g, 16.3 mmol) in THF (54.3 mL) was treated with TBAF (32.6 mL, 32.6 mmol, 1 M in THF) and stirred for 24 h. The solution was diluted with water (40 mL), extracted with EtOAc (3 x 40 mL), dried (Na_2SO_4), and concentrated. The crude oil was dissolved in pyridine (163 mL) and cooled to 0 °C. The resulting solution was treated with DMAP (1.01 g, 8.16 mmol) and BzCl (0.508 mL, 4.38 mmol) was added over 5 min via syringe. The solution was warmed to rt, stirred for 12.5 h, treated with sat. NH_4Cl (50 mL), and stirred for 1 h. The mixture was diluted with H_2O (25 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 1 M HCl (3 x 25 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (4:1, hexanes/EtOAc) to give **103** as a white solid: Mp 75.2–76.8 °C; IR (ATR) 3287, 1713, 1521 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (bs, 1 H), 8.15 (s, 1 H), 8.07–8.04 (m, 2 H), 7.57 (mt, 1 H, *J* = 7.5 Hz), 7.47–7.36 (m, 7 H), 5.93–7.75 (m, 2 H), 5.17 (s, 2 H), 4.95 (d, 2 H, *J* = 6.6 Hz), 4.47 (t, 2 H, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 166.6, 152.6, 134.7, 133.3, 129.9, 129.1, 129.0, 128.7, 128.6, 128.5, 127.9, 68.4, 60.6, 42.9; HRMS (ES^+) *m/z* calcd for $C_{20}H_{20}N_2O_4SNa$ ($[M + Na]^+$) 407.1041, found 407.1021.



99

(*Z*)-4-(2-(Benzyloxy)-3-(benzyloxycarbonyl)guanidino)but-2-enyl benzoate (99). To a solution of **103** and O-benzylhydroxylamine hydrochloride (3.15 g, 19.6 mmol, 1.2 equiv) in CH_2Cl_2 (81.5 mL) was added diisopropylamine (5.98 mL, 35.8 mmol). The resulting mixture was cooled to 0 °C, treated with EDCI (6.25 g, 32.6 mmol), stirred for 1 h, warmed to rt, and stirred for 12 h. The solution was washed with 1 M HCl (80 mL), water (80 mL), and brine (80 mL). The organic phase was dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (2:1 hexanes/EtOAc) to give **99** (4.93 g, 50%) over two steps as a yellow oil: IR (ATR) 3388, 1726, 1646, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08–8.03 (m, 2 H), 7.90 (bs, 1 H), 7.56 (tt, 1 H, *J* = 1.2, 6.6 Hz), 7.46–7.24 (m, 12 H), 6.37 (bt, 1 H, *J* = 5.4 Hz), 5.84–5.72 (m, 2 H), 5.12 (s, 2 H), 4.93 (d, 2 H, *J* = 5.4 Hz), 4.87 (s, 2 H), 3.87 (t, 2 H, *J* = 5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 147.8, 137.7, 135.2, 131.0, 129.9, 128.9 (2), 128.6, 128.5 (2), 128.1, 126.4, 76.11, 67.9, 60.9, 38.3; HRMS (EI^+) *m/z* calcd for $C_{27}H_{27}N_3O_5$ ($[M]^{+\cdot}$) 473.1951, found 473.1951.

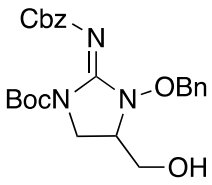


104

3,4-(1-Benzyloxy-2-benzyloxycarbonyl-3-*tert*-butoxycarbonyl)guanidinobut-1-ene (104). A solution of **99** (25.0 mg, 0.0528 mmol) in THF (0.264 mL) was treated with $PdCl_2(CH_3CN)_2$ (2.77 mg, 0.0106 mmol, 0.2 equiv) and stirred overnight. To the solution was added Boc_2O (14.3 mg, 0.0634 mmol), DMAP (2.61 mg, 0.0211 mmol), and triethylamine (8.24 µL, 0.0581 mmol). The reaction mixture was stirred for 6 h, quenched with sat. NH_4Cl (2 mL), extracted with EtOAc (3 x 2 mL), the combined organic extracts were dried (Na_2SO_4), and concentrated. The crude mixture was purified by chromatography on SiO_2 (1:1, hexanes/EtOAc) to give **104** (20.0 mg, 84%) as a yellow oil: IR (ATR) 1761, 1692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.18 (m, 10 H), 5.79 (ddd, 1 H, *J* = 8.7, 9.9, 17.1 Hz), 5.39 (d, 1 H, *J* = 17.1 Hz), 5.33 (d, 1 H, *J* = 10.5 Hz), 5.01 (d, 1 H, *J* = 9.9 Hz), 5.00 (d, 1 H, *J* = 12.3 Hz), 4.85 (d, 1 H, *J* = 11.7 Hz), 4.85 (d, 1 H, *J* = 10.5 Hz), 4.02 (aq, 1 H, *J* = 8.4 Hz), 3.83 (dd, 1 H, *J* = 8.1, 10.2 Hz), 3.39 (dd, 1 H, *J* = 8.7, 10.5 Hz), 1.49 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 149.7, 149.4, 136.3, 135.4, 133.7, 129.4, 128.8, 128.6, 128.5, 128.5, 128.0, 122.2, 83.7, 77.9, 67.9, 63.7, 46.9, 28.2; HRMS (EI^+) *m/z* calcd for $C_{25}H_{29}N_3O_5$ ($[M]^{+\cdot}$) 451.2107, found 451.2106.

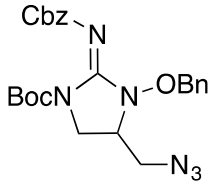
General procedure for chiral ligand screen in the amidoalkylation of compound 104. A solution of $PdCl_2(CH_3CN)_2$ (0.2 equiv) and ligand (0.4 equiv) in THF was stirred for 40 min. To this mixture was added a solution of **99** in THF and the resulting solution was stirred overnight. After the addition of THF (to a final concentration of 0.2 M), Boc_2O (1.2 equiv), DMAP (0.4

equiv), and triethylamine (1.1 equiv), the mixture was stirred for 6–24 h, quenched with sat. NH_4Cl, and extracted with EtOAc (3x). The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (1:1, hexanes/EtOAc).



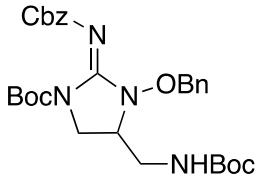
108

2,3-(1-Benzyloxy-2-benzyloxycarbonyl-3-*tert*-butoxycarbonyl)guanidinopropanol (108). Ozone was bubbled through a solution of **104** (2.62 g, 5.80 mmol) and pyridine (4.69 mL, 58.0 mmol) in CH_3OH/CH_2Cl_2 (69.6 mL/ 46.4 mL, 0.05 M) at -78 °C for 15 min. Argon was bubbled through the solution for 5 min, $NaBH_4$ (329 mg, 8.70 mmol) was added, the mixture was stirred for 1 h, and slowly warmed to rt overnight. The solution was quenched with water (25 mL), extracted with EtOAc (4 x 25 mL), the combined organic extracts were dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (1:1 hexanes/EtOAc to 100% EtOAc) to give **108** (1.51 g, 57%) as a white foam: IR (ATR) 3440, 1752, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.27 (m, 10 H), 5.09 (s, 2 H), 4.95 (s, 2 H), 3.73–3.59 (m, 2 H), 3.57 (dd, 1 H, *J* = 3.3, 12.3 Hz), 3.51–3.44 (m, 1 H), 3.40 (dd, 1 H, *J* = 2.4, 12.3 Hz), 1.98 (bs, 1 H), 1.47 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 151.2, 149.7, 136.3, 135.7, 129.7, 129.0, 128.7, 128.5, 128.3, 127.9, 83.6, 77.5, 67.9, 59.7, 59.4, 44.2, 28.0; HRMS (EI^+) *m/z* calcd for $C_{24}H_{29}N_3O_6$ ($[M]^{+\cdot}$) 455.2056, found 455.2074.



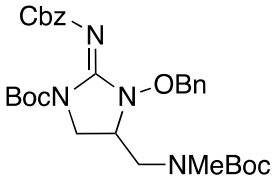
113

2,3-(1-Benzyloxy-2-benzyloxycarbonyl-3-*tert*-butoxycarbonyl)guanidin-1-azido-propane (113). To a solution of **108** (0.500 g, 1.08 mmol), triethylamine (0.467 mL, 3.29 mmol), and DMAP (27.1 mg, 0.220 mmol) in CH_2Cl_2 (5.40 mL) at 0 °C was added MsCl (0.174 mL, 2.20 mmol). The reaction mixture was stirred for 4.5 h at 0 °C, warmed to rt, and stirred for 1.5 h. The solution was diluted with CH_2Cl_2 (10 mL), and washed with sat. Na_2CO_3 (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated. The crude residue was dissolved in DMF (5.50 mL), treated with NaN_3 (79.3 mg, 1.23 mmol), and placed in a preheated 65 °C oil bath for 6 h. The solution was cooled to rt, diluted with EtOAc, washed with water, dried (Na_2SO_4), and concentrated. The crude material was purified by chromatography on SiO_2 (1:1 hexanes/EtOAc) to give **113** (405 mg, 77%) as a clear oil: IR (ATR) 2102, 1756, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.26 (m, 10 H), 5.11 (d, 1 H, *J* = 12.3 Hz), 5.06 (d, 1 H, *J* = 12.3 Hz), 4.96 (d, 1 H, *J* = 11.1 Hz), 4.76 (d, 1 H, *J* = 11.1 Hz), 3.70 (dd, 1 H, *J* = 8.1, 10.2 Hz), 3.51 (dd, 1 H, *J* = 5.4, 10.2 Hz), 3.47–3.40 (m, 1 H), 3.32 (d, 2 H, *J* = 4.5 Hz), 1.49 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 149.7, 149.6, 136.5, 135.7, 129.6, 129.1, 128.8, 128.6, 128.4, 128.0, 84.0, 78.2, 67.9, 57.3, 50.2, 45.0, 28.1; HRMS (EI^+) *m/z* calcd for $C_{24}H_{28}N_6O_5$ ($[M]^+$) 480.2121, found 480.2132.



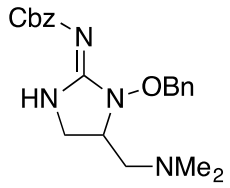
115

2,3-(1-Benzyloxy-2-benzyloxycarbonyl-3-*tert*-butoxycarbonyl)guanidino-1-(*N*-*tert*-butoxycarbonyl)propylamine (115). To a solution of **113** (0.183 mg, 0.381 mmol), Boc_2O (103 mg, 0.457 mmol), and Pd/C (40.5 mg, 0.0381 mmol) in EtOAc (3.81 mL) was added triethylamine (0.0703 mL, 0.495 mmol). The reaction vessel was evacuated and back-filled with H_2 (3x), stirred for 2 h, and the hydrogen balloon was removed. The reaction mixture was stirred for an additional 3 h and filtered through celite. The organic solution was washed with water (3 x 5 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (1:1, hexanes/EtOAc) to give **113** (0.110 g, 52%): IR (ATR) 3364, 1757, 1703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.21 (m, 10 H), 5.12 (d, 1 H, *J* = 12.3 Hz), 5.07 (d, 1 H, *J* = 12.3 Hz), 4.97 (d, 1 H, *J* = 11.4 Hz), 4.93 (d, 1 H, *J* = 11.1 Hz), 4.10 (bs, 1 H), 3.68 (dd, 1 H, *J* = 8.1, 9.9 Hz), 3.54–3.49 (m, 1 H), 3.46–3.41 (m, 1 H), 3.37 (m, 1 H), 3.00–2.94 (m, 1 H), 1.46 (s, 9 H), 1.41 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 156.2, 149.8, 136.5, 135.8, 130.1, 129.2, 128.8, 128.6, 128.4, 128.0, 83.8, 79.9, 68.0, 58.3, 44.7, 39.2, 28.4, 28.1; HRMS (ES^+) *m/z* calcd for $C_{24}H_{38}N_4O_7Na$ ($[M + Na]^+$) 577.2638, found 577.2604.

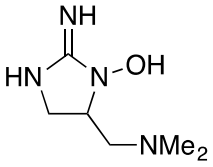


116

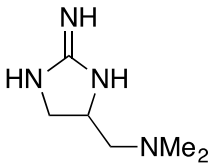
2,3-(1-Benzyloxy-2-benzyloxycarbonyl-3-*tert*-butoxycarbonyl)guanidino-1-(*N*-*tert*-butoxycarbonyl, *N*-methyl)propylamine (116). A solution of **115** (50.0 mg, 0.090 mmol) and CH_3I (0.112 mL, 1.80 mmol) in DMF (1.80 mL) at -20 ºC was treated with NaH (3.42 mg, 0.135 mmol). After 30 min, the solution was warmed to 0 ºC, stirred for 30 min, then warmed to rt. After 30 min, the reaction was quenched with water, extracted with EtOAc, and the combined organic extracts were dried (Na_2SO_4) and concentrated. The crude residue was purified by chromatography on SiO_2 (1:1 hexanes/EtOAc) to give **116** (40.4 mg, 79%): IR (ATR) 1759, 1688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 50 ºC) δ 7.41–7.26 (m, 10 H), 5.11 (d, 1 H, *J* = 12.3 Hz), 5.06 (d, 1 H, *J* = 12.3 Hz), 5.00 (d, 1 H, *J* = 11.1 Hz), 4.81 (d, 1 H, *J* = 10.8 Hz), 3.66 (d, 2 H, *J* = 6.6 Hz), 3.59–3.55 (m, 1 H), 3.35 (d, 2 H, *J* = 6.3 Hz), 2.75 (s, 3 H), 1.47 (s, 9 H), 1.44 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 149.9, 149.6, 136.9, 136.0, 129.7, 129.0, 128.8, 128.6, 128.5, 128.0, 83.8, 78.1, 67.9, 57.7, 48.7, 45.9, 28.6, 28.3; HRMS (ES^+) *m/z* calcd for $C_{30}H_{40}N_4O_7Na$ ($[M + Na]^+$) 591.2795, found 591.2757.



117



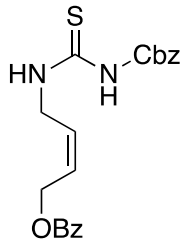
9



118

2,3-(1-Benzyloxy-2-benzyloxycarbonyl)guanidinodimethylpropylamine (117), 5-((Dimethylamino)methyl)-2-iminioimidazolidin-1-olate (9), and 1-(2-iminoimidazolidin-4-yl)-*N*,*N*-dimethylmethanamine (118).[17] A solution of **116** (0.100 g, 0.176 mmol) in THF (1.41 mL) was treated with TFA (0.352 mL) and stirred for 1 h. The reaction mixture was quenched with $NaHCO_3$ (3 mL), extracted with EtOAc (5 x 3 mL), dried (Na_2SO_4), and concentrated. The crude residue was dissolved in distilled EtOAc (1.06 mL), treated with paraformaldehyde (6.67 mg, 0.211 mmol) and $NaBH_3CN$ (24.4 mg, 0.369 mmol). The resulting mixture was stirred overnight, quenched with $NaHCO_3$ (3 mL), extracted with EtOAc (5 x 3 mL), dried (Na_2SO_4), and concentrated to give **117** as a white solid: IR (ATR) 3371, 1655, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (bs, 1 H), 7.43 (s, 5 H), 7.37–7.27 (m, 5 H), 5.18 (s, 2 H), 5.10 (d, 1 H, *J* = 12.0 Hz), 5.05 (d, 1 H, *J* = 12.0 Hz), 3.92 (t, 1 H, *J* = 9.0 Hz), 3.61 (q, 1 H, *J* = 9.4 Hz), 3.37 (t, 1 H, *J* = 9.6 Hz), 2.61 (dd, 1 H, *J* = 9.0, 13.8 Hz), 2.43 (s, 3 H), 2.40 (s, 3 H), 2.17 (ad, 1 H, *J* = 14.4 Hz); HRMS (ES^+) *m/z* calcd for $C_{21}H_{26}N_4O_3Na$ ($[M + Na]^+$) 405.1903, found 405.1867. A solution of **117** in MeOH (20 mL) was passed through an H-cube, fitted with a Pd/C cartridge at 60 psi, and at a flow rate of 1 mL/min. The solution was concentrated and the residue was purified by HPLC chromatography (flow rate: 0.7 mL/min, column 3 micron C18 100 x 4.6 mm, mobile phase 95:5 water (0.1% TFA): MeOH, wavelength 254 nm) to give an inseparable mixture of **9** (9.71 mg, 35%): ^1H NMR (600 MHz, D_2O (DSS)) δ 4.51–4.46 (m, 1

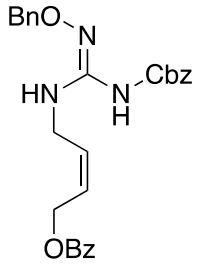
H), 3.94 (dd, 1 H, *J* = 13.8, 15.0 Hz), 3.75 (dd, 1 H, *J* = 7.2, 14.4 Hz), 3.52–3.46 (m, 2 H), 3.00 (s, 6 H); and **118** (13.9 mg, 56%): ^{1}H NMR (600 MHz, D_2O (DSS)) δ 4.58–4.53 (m, 1 H), 3.98 (dd, 1 H, *J* = 9.6, 9.6 Hz), 3.52–3.46 (m, 2 H), 3.38 (dd, 1 H, *J* = 4.8, 13.8 Hz), 2.97 (s, 6 H).



103

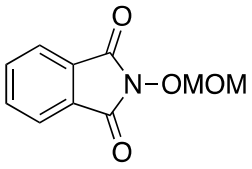
(*Z*)-4-(3-((Benzyloxy)carbonyl)thioureido)but-2-en-1-yl benzoate (103). Seven 50 mL plastic tubes were each charged with **101** (6 x 1.00 g, 1.93 mmol and 1 x 0.88 g, 1.67 mmol) in THF (6 x 19.3 mL and 1 x 17.2 mL). Each of these solutions were treated with HF•pyr (6 x 1.45 mL, 9.64 mmol and 1 x 1.25 mL, 8.43 mmol) and stirred for 5 h. The reactions were combined into a 2-L Erlenmeyer flask, quenched with sat $NaHCO_3$ (0.500 L), and extracted with EtOAc (3 x 0.100 L). The organic layer was dried (Na_2SO_4), concentrated, and the crude yellow solid was dissolved in freshly distilled pyridine (133 mL), treated with DMAP (654 mg, 5.30 mmol), and cooled to 0 ºC. To the resulting solution was added BzCl (1.85 mL, 15.9 mmol) over 5 min via syringe. The solution was warmed to rt and stirred overnight. To the solution was added sat. NH_4Cl (100 mL), the reaction was stirred for 1 h, and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with water (3 x 100 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (4:1 hexanes/EtOAc) to give 4.19 g (82%) of **103** as a white solid: IR (ATR) 3289, 1709, 1515 cm^{-1}; ^{1}H NMR (300 MHz, Acetone – d_6) δ 9.96 (s, 1

H), 9.85 (s, 1 H), 8.06-8.03 (m, 2 H), 7.64 (tt, 1 H, *J* = 1.5, 6.6 Hz), 7.54-7.49 (m, 2 H), 7.45-7.35 (m, 5 H), 5.93-5.82 (m, 2 H), 5.21 (s, 2 H), 5.02 (d, 2 H, *J* = 5.4 Hz), 4.53 (t, 2 H, *J* = 5.4 Hz); ^{13}C NMR (75 MHz, Acetone – d_6) δ 180.8, 166.6, 154.1, 136.5, 133.9, 131.2, 130.2, 129.4 (2), 129.2, 128.9, 127.8, 68.2, 61.3, 43.0; HRMS (ES^+) *m/z* calcd for $C_{20}H_{20}N_2O_4SNa$ ([M + Na]$^+$) 407.1041, found 407.1021.



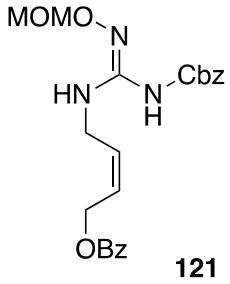
99

(*Z*)-4-(2-(Benzyloxy)-3-(benzyloxycarbonyl)guanidino)but-2-enyl benzoate (99). A solution of **103** (1.00 g, 2.60 mmol) and O-benzylhydroxylamine hydrochloride (648 mg, 3.38 mmol, 1.3 equiv) in CH_2Cl_2 (13.0 mL) was treated with diisopropylethylamine (1.43 mL) and EDCI (648 mg, 3.38 mmol). The reaction was stirred overnight, quenched with water (15.0 mL), extracted with CH_2Cl_2 (3 x 15.0 mL), dried (Na_2SO_4), and concentrated. The crude material was purified by chromatography on SiO_2 (2:1 hexanes/EtOAc) to give 1.23 g (74%) of **99** as a yellow oil. ^{1}H spectra for **99** matched with previously recorded data; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06–8.04 (m, 2 H), 7.90 (bs, 1 H), 7.54 (tt, 1 H, *J* = 1.2, 7.2 Hz), 7.43–7.28 (m, 12 H), 6.37 (bt, 1 H, *J* = 5.2 Hz), 5.82–5.72 (m, 2 H), 5.09 (s, 2 H), 4.92 (d, 2 H, *J* = 5.6 Hz), 4.86 (s, 2 H), 3.85 (t, 2 H, *J* = 5.6 Hz);



120

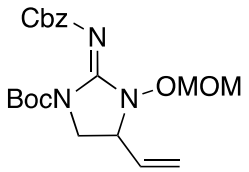
***N*-(Methoxymethoxy)phthalimide (120).**[59] A solution of *N*-hydroxyphthalimide (75.0 g, 446 mmol) and diisoproylethylamine (81.9 mL, 491 mmol) in DMF (686 mL) was treated with a freshly prepared solution of MOMCl[60] in toluene (195 mL, 535 mmol, 2.75 M). The solution was stirred for 5 h, diluted with CH_2Cl_2 (500 mL), and washed with sat. $NaHCO_3$ (5 x 100 mL). The organic phase was dried (Na_2SO_4) and concentrated to give **120** (91.4 g, 99.0 %) as a white solid. The spectra matched those previously reported: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 4 H), 5.09 (s, 2 H), 3.58 (s, 3 H): ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 134.7, 129.3, 123.7, 101.6, 58.0; HRMS (ES^+) *m/z* calcd for $C_{10}H_{10}NO_4$ ($[M + H]^+$) 208.0604, found 208.0603.



121

(*Z*)-4-(2-(Methoxymethoxy)-3-(benzyloxycarbonyl)guanidino)but-2-enyl benzoate (121). A solution of **120** (943 mg, 4.55 mmol) in CH_2Cl_2 (4.55 mL) and CH_3OH (0.592 mL) was treated with hydrazine monohydrate (223 μL, 4.55 mmol). After 5.5 h the resulting precipitate was filtered and the filtrate was washed with 5 N aq. ammonia (3 x 5 mL). The aqueous layer was

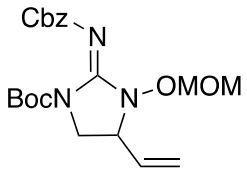
extracted with CH_2Cl_2 (3 x 5 mL), dried (Na_2SO_4), and concentrated. The resulting crude oil was dissolved in CH_2Cl_2 (3.50 mL), treated with a solution of **103** (0.500 g, 1.30 mmol), diisopropylethylamine (0.543 mL, 3.25 mmol), and EDCI (534 mg, 2.73 mmol) in CH_2Cl_2 (3.00 mL). The solution was stirred overnight, quenched with water (10 mL), extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4), and purified by chromatography on SiO_2 (2:1 hexanes/EtOAc) to give **121** (337 mg, 61%) as a pale yellow oil: IR (ATR) 3385, 1715, 1646 cm^{-1}; ^1H NMR (300 MHz, Acetone – d_6) δ 8.49 (s, 1 H), 8.04 (dd, 2 H, *J* = 1.2, 8.4 Hz), 7.65–7.60 (m, 1 H), 7.52–7.49 (m, 2 H), 7.43–7.33 (m, 5 H), 6.59 (bt, 1 H, *J* = 5.2 Hz), 5.86–5.76 (m, 2 H), 5.17 (s, 2 H), 5.00 (d, 2 H, *J* = 5.6 Hz), 4.87 (s, 2 H), 3.92 (t, 2 H, *J* = 6.0 Hz), 3.36 (s, 3 H); ^{13}C NMR (100 MHz, Acetone – d_6) δ 166.5, 153.8, 148.6, 136.7, 133.8, 132.1, 131.2, 130.1, 129.3 (2), 129.1, 129.0, 126.6, 98.7, 68.0, 56.6, 38.6; HRMS (ES^+) *m/z* calcd for $C_{22}H_{25}N_3O_5Na$ ($[M + Na]^+$) 450.1641, found 450.1656.



122

3,4-(1-Methoxymethoxy-2-benzyloxycarbonyl-3-*tert*-butoxycarbonyl)-guanidinobut-1-ene (122). A solution of **121** (325 mg, 0.760 mmol) in THF (3.80 mL) was treated with $PdCl_2(CH_3CN)_2$ (19.7 mg, 0.0760 mmol) and stirred overnight. To the solution was added Boc_2O (205 mg, 0.912 mmol), DMAP (37.5 mg, 0.304 mmol), and triethylamine (0.162 mL, 1.14 mmol). The reaction was stirred for 4 h, quenched with sat. $NaHCO_3$ (5 mL), extracted with EtOAc (3 x 5 mL), dried (Na_2SO_4), and purified by chromatography on SiO_2 (2:1

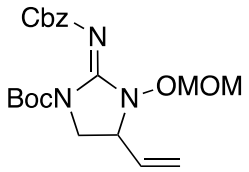
hexanes/EtOAc) to give **122** (308 mg, 95.0%) as a yellow oil: IR (ATR) 1761, 1696 cm^{-1}; ^{1}H NMR (300 MHz, Acetone – d_6) δ 7.44–7.30 (m, 5 H), 5.93 (ddd, 1 H, *J* = 8.4, 10.2, 17.1 Hz), 5.44 (d, 4 H, *J* = 17.1 Hz), 5.32 (d, 1 H, *J* = 10.5 Hz), 5.13 (d, 1 H, *J* = 12.3 Hz), 5.07 (d, 1 H, *J* = 12.6 Hz), 4.73 (d, 1 H, *J* = 7.5 Hz), 4.61 (d, 1 H, *J* = 7.5 Hz), 4.19 (q, 1 H, *J* = 8.1 Hz), 3.94 (dd, 1 H, *J* = 8.4, 10.2 Hz), 3.49 (dd, 1 H, *J* = 8.1, 10.2 Hz), 3.30 (s, 3 H), 1.48 (s, 9 H); ^{13}C NMR (100 MHz, Acetone – d_6) δ 159.8, 150.3, 150.2, 137.9, 135.4, 129.0, 128.9, 128.5, 120.5, 101.7, 83.3, 67.5, 63.7, 56.7, 47.9, 28.0; HRMS (ES^+) *m/z* calcd for $C_{20}H_{27}N_3O_6Na$ ($[M + Na]^+$) 428.1798, found 428.1802. Retention time of enantiomers was determined by chiral SFC analysis (chiralpak-IC: 250 × 4.5 mm; 2.0 mL/min; 20% methanol; 220 nm detection; Rt_1 6.52 min, Rt_2 8.39 min).



S-122

3,4-(1-Methoxymethoxy-2-benzyloxycarbonyl-3-*tert*-butoxycarbonyl)-guanidinobut-1-ene (S-122). A solution of **121** (0.500 g, 0.702 mmol) in CH_2Cl_2 (1.94 mL) was treated with (*S*)-(+)-COP-Cl (42.8 mg, 0.0292 mmol) and stirred 3 h. To the solution was added THF (3.91 mL), Boc_2O (0.309 mg, 1.40 mmol), DMAP (57.8 mg, 0.468 mmol), and triethylamine (0.249 mL, 1.75 mmol). The reaction was stirred overnight, quenched with sat. $NaHCO_3$ (6 mL), extracted with EtOAc (3 x 6 mL), dried (Na_2SO_4), and concentrated. The crude material was purified by chromatography on SiO_2 (2:1 hexanes/EtOAc) to give 359 mg (76%) of **S-122** as a yellow oil: 72.5:27.5 er was determined by chiral SFC analysis (chiralpak-IC: 250 × 4.5 mm; 2.0 mL/min;

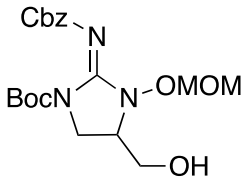
20% methanol; 220 nm detection; Rt_1 6.49 min, Rt_2 8.45 min); $[\alpha]^{20}_D$ +14.7 (*c* 1.00, $CHCl_3$); IR (ATR) 1761, 1694 cm^{-1}; ^1H NMR (400 MHz, Acetone – d_6) δ 7.43–7.29 (m, 5 H), 5.94 (ddd, 1 H, *J* = 8.4, 10.4, 16.8 Hz), 5.45 (d, 1 H, *J* = 17.2 Hz), 5.33 (d, 1 H, *J* = 10.8 Hz), 5.11 (d, 1 H, *J* = 12.4 Hz), 5.06 (d, 1 H, *J* = 12.8 Hz), 4.73 (d, 1 H, *J* = 7.2 Hz), 4.61 (d, 1 H, *J* = 7.6 Hz), 4.22 (q, 1 H, *J* = 8.0 Hz), 3.96 (dd, 1 H, *J* = 8.0, 10.0 Hz), 3.51 (dd, 1 H, *J* = 8.0, 10.4 Hz), 3.31 (s, 3 H), 1.49 (s, 9 H); ^{13}C NMR (100 MHz, Acetone – d_6) δ 159.9, 150.5, 150.4, 138.1, 135.7, 129.1, 129.0, 128.6, 120.5, 101.9, 83.5, 67.7, 63.9, 56.8, 48.0, 28.1; HRMS (ES^+) *m/z* calcd for $C_{20}H_{27}N_3O_6Na$ ($[M + Na]^+$) 428.1798, found 428.1762.



R-122

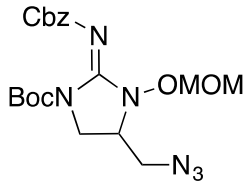
3,4-(1-Methoxymethoxy-2-benzyloxycarbonyl-3-*tert*-butoxycarbonyl)-guanidinobut-1-ene (R-122). A solution of **121** (0.500 g, 1.17 mmol) in CH_2Cl_2 (1.94 mL) was treated with (*R*)-(-)-COP-Cl (42.8 mg, 0.0292 mmol) and stirred 3 h. To the solution was added THF (3.91 mL), Boc_2O (0.309 mg, 1.40 mmol), DMAP (57.7 mg, 0.468 mmol), and triethylamine (0.166 mL, 1.17 mmol). The reaction was stirred overnight, quenched with sat. $NaHCO_3$ (6 mL), extracted with EtOAc (3 x 6 mL), dried (Na_2SO_4), and concentrated. The crude material was purified by chromatography on SiO_2 (2:1 hexanes/EtOAc) to give 351 mg (74%) of **R-122** as a yellow oil: 27.0:73.0 er was determined by chiral SFC analysis (chiralpak-IC: 250 × 4.5 mm; 2.0 mL/min; 20% methanol; 220 nm detection; Rt_1 6.49 min, Rt_2 8.38 min); $[\alpha]^{20}_D$ -15.1 (*c* 1.00, $CHCl_3$) (46% ee); IR (ATR) 1761, 1694 cm^{-1}; ^1H NMR (400 MHz, Acetone – d_6) δ 7.43–7.23 (m, 5 H),

5.94 (ddd, 1 H, *J* = 8.0, 10.0, 16.8 Hz), 5.45 (d, 1 H, *J* = 17.0 Hz), 5.33 (d, 1 H, *J* = 9.8 Hz), 5.11 (d, 1 H, *J* = 12.4 Hz), 5.06 (d, 1 H, *J* = 12.8 Hz), 4.73 (d, 1 H, *J* = 7.6 Hz), 4.61 (d, 1 H, *J* = 7.6 Hz), 4.23 (q, 1 H, *J* = 8.0 Hz), 3.96 (dd, 1 H, *J* = 8.4, 10.4 Hz), 3.51 (dd, 1 H, *J* = 8.0, 10.4 Hz), 3.31 (s, 3 H), 1.49 (s, 9 H); ^{13}C NMR (100 MHz, Acetone – d_6) δ 159.9, 150.5, 150.4, 138.1, 135.7, 129.1, 129.0, 128.6, 120.5, 101.9, 83.5, 67.7, 63.9, 56.8, 48.0, 28.1; HRMS (ES^+) *m/z* calcd for $C_{20}H_{27}N_3O_6Na$ ($[M + Na]^+$) 428.1798, found 428.1768.



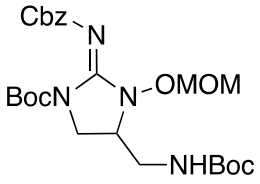
129

2,3-(1-Methoxymethoxy-2-benzyloxycarbonyl-3-*tert*-butoxycarbonyl)guanidinopropanol (129). Ozone was bubbled for 5 min through a solution of **122** (1.00 g, 2.47 mmol) in CH_2Cl_2/CH_3OH 9.87 mL/ 14.8 mL) and pyridine (1.99 mL, 24.7 mmol) at -78 ^oC. Argon was bubbled through the solution for 5 min, $NaBH_4$ (0.111 g, 2.96 mmol) was added, the solution was warmed to 0 ^oC, and stirred for 4 h. The reaction was quenched with water (25 mL), extracted with CH_2Cl_2 (3 x 30 mL), dried (Na_2SO_4), and purified by chromatography on SiO_2 (1:1 hexanes/EtOAc to 100% EtOAc) to give **129** (0.570 g, 1.39 mmol) as a yellow oil: IR (ATR) 1758, 1696 cm^{-1}; ^{1}H NMR (300 MHz, Acetone – d_6) δ 7.44–7.30 (m, 5 H), 5.11 (d, 1 H, *J* = 12.6 Hz), 5.06 (d, 1 H, *J* = 12.6 Hz), 4.78 (d, 1 H, *J* = 7.5 Hz), 4.70 (d, 1 H, *J* = 7.8 Hz), 3.94–3.73 (m, 4 H), 3.42 (s, 3 H), 1.49 (s, 9 H); ^{13}C NMR (100 MHz, Acetone – d_6) δ 160.0, 151.3, 150.4, 137.9, 129.0, 128.8, 128.5, 102.1, 83.3, 67.6, 61.0, 60.1, 57.1, 45.5, 28.1; HRMS (ES^+) *m/z* calcd for $C_{19}H_{27}N_3O_7Na$ ($[M + Na]^+$) 432.1747, found 432.1740.



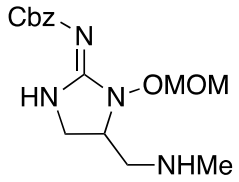
130

2,3-(1-Methoxymethoxy-2-benzyloxycarbonyl-3-*tert*-butoxycarbonyl)guanidin-1-azido-propane (130). A solution of **129** (0.250 g, 0.611 mmol) and triethylamine (0.260 mL, 1.83 mmol) in CH_2Cl_2 (3.05 mL) at 0 ^oC was treated with MsCl (0.0351 mL, 0.444 mmol) followed by DMAP (9.13 mg, 0.0740 mmol). After 1 h the reaction was quenched with $NaHCO_3$ (3 mL), extracted with CH_2Cl_2 (3 x 3 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in DMF (3.05 mL), treated with 3 Å molecular sieves, triethylamine (0.260 mL, 1.83 mmol), and NaN_3 (60.1 mg, 0.916 mmol). The reaction was placed in a preheated 50 ^oC oil bath, stirred overnight, diluted with EtOAc (3 mL), washed with water (3 x 3 mL), dried (Na_2SO_4), and purified by chromatography on SiO_2 (1:1 hexanes/EtOAc) to give **130** (0.230 g, 86.7%) as a clear oil: IR (ATR) 2104, 1756, 1689 cm^{-1}; ^1H NMR (400 MHz, Acetone – d_6) δ 7.44–7.42 (m, 2 H), 7.39–7.29 (m, 3 H), 5.12 (d, 1 H, *J* = 12.8 Hz), 5.08 (d, 1 H, *J* = 12.8 Hz), 4.77 (d, 1 H, *J* = 7.6 Hz), 4.66 (d, 1 H, *J* = 7.6 Hz), 3.97–3.90 (m, 3 H), 3.69 (q, 1 H, *J* = 10.4 Hz), 3.65–3.62 (m, 1 H), 3.43 (s, 3 H), 1.49 (s, 9 H); ^{13}C NMR (100 MHz, Acetone – d_6) δ 159.9, 150.7, 150.3, 138.2, 129.1, 129.0, 128.6, 102.5, 83.5, 67.6, 59.3, 57.0, 50.6, 45.7, 28.1; HRMS (ES^+) *m/z* calcd for $C_{19}H_{26}N_6O_6Na$ ($[M + Na]^+$) 457.1812, found 457.1803.



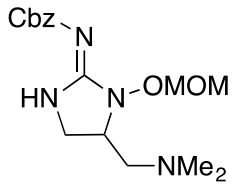
131

2,3-(1-Methoxymethoxy-2-benzyloxycarbonyl-3-*tert*-butoxycarbonyl)guanidin-1-(*N*-*tert*-butoxycarbonyl)propylamine (131). A round-bottomed flask charged with **130** (0.500 g, 1.15 mmol), Lindlar's catalyst (245 mg, 0.115 mmol), Boc_2O (381 mg, 1.73 mmol), and EtOAc (11.5 mL) was evacuated and backfilled with H_2 (3x). After 24 h the H_2 atmosphere was removed, the vessel was placed under nitrogen atmosphere, and stirred overnight. The reaction solution was filtered through celite and purified by chromatography on SiO_2 (2:1 hexanes/EtOAc) to give 468 mg (80.0%) of **131** as an oil: IR (ATR) 3377, 1760, 1700 cm^{-1}; ^1H NMR (600 MHz, Acetone – d_6) δ 7.43 (d, 2 H, *J* = 7.2 Hz), 7.37 (t, 3 H, *J* = 7.2 Hz), 7.31 (m, 1 H), 5.11 (d, 1 H, *J* = 12.0 Hz), 5.07 (d, 1 H, *J* = 12.6 Hz), 4.82 (d, 1 H, *J* = 7.8 Hz), 4.65 (d, 1 H, *J* = 7.8 Hz), 3.89 (dd, 1 H, *J* = 9.0, 9.6 Hz), 3.83–3.79 (m, 1 H), 3.69 (ddd, 1 H, *J* = 2.4, 7.8, 14.4 Hz), 3.65 (dd, 1 H, *J* = 7.2, 9.6 Hz), 3.45 (s, 3 H), 3.25 (tt, 1 H, *J* = 5.4, 5.4, 14.4 Hz), 1.48 (s, 9 H), 1.41 (s, 9 H); ^{13}C NMR (100 MHz, Acetone – d_6) δ 159.9, 157.1, 150.9, 150.5, 138.1, 129.1, 129.0, 128.6, 102.3, 83.4, 79.3, 67.6, 60.1, 57.2, 46.0, 40.0, 28.5, 28.1; HRMS (ES^+) *m/z* calcd for $C_{24}H_{36}N_4O_8Na$ ($[M + Na]^+$) 531.2431, found 531.2418.



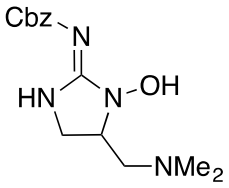
132

2,3-(1-Methoxymethoxy-2-benzyloxycarbonyl)guanidin-1-(*N*-methyl)propylamine (132). A solution of **131** (0.500 g, 0.983 mmol) and CH_3I (1.24 mL, 19.7 mmol) in DMF (98.3 mL) at 0 ^oC was treated with NaH (24.8 mg, 0.983 mmol) and stirred for 1 h. The reaction was warmed to rt, stirred for 3 h, quenched with sat. $NaHCO_3$ (10 mL), extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4), and concentrated. The crude material was purified by chromatography on SiO_2 (1:1 hexanes/EtOAc), dissolved in CH_2Cl_2 (7.86 mL), treated with TFA (1.97 mL) and stirred for 1 h. The solution was quenched with $NaHCO_3$ (25 mL), extracted with EtOAc (3 x 25 mL), dried (Na_2SO_4), and purified by chromatography on SiO_2 (95:5 CH_2Cl_2/MeOH with 1% Et_3N) to give 0.230 g (73%) of **132** as a white solid: IR (ATR) 3485, 3372, 1650, 1599 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 7.37–7.27 (m, 5 H), 5.05 (s, 2 H), 4.98 (d, 1 H, *J* = 7.6 Hz), 4.80 (d, 1 H, *J* = 7.6 Hz), 3.79–3.72 (m, 1 H), 3.57 (dd, 1 H, *J* = 8.8, 9.6 Hz), 3.48 (s, 3 H), 3.44 (dd, 1 H, *J* = 9.2, 9.6 Hz), 2.84 (dd, 1 H, *J* = 5.6, 12.4 Hz), 2.79 (dd, 1 H, *J* = 3.6, 12.8 Hz), 2.38 (s, 3 H); ^{13}C NMR (100 MHz, CD_3CN) δ 168.1, 164.7, 138.7, 129.4, 128.8, 128.7, 102.0, 67.3, 62.0, 57.6, 51.2, 44.2, 36.8; HRMS (ES^+) *m/z* calcd for $C_{15}H_{23}N_4O_4$ ($[M + H]^+$) 323.1719, found 323.1714.



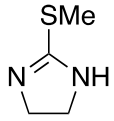
133

2,3-(1-Methoxymethoxy-2-benzyloxycarbonyl)guanidin-1-(*N*-dimethyl)propylamine (133). A solution of **132** in freshly distilled EtOAc (14.0 mL) was treated with paraformaldehyde (44.1 mg, 1.40 mmol). After 30 min $NaCNBH_3$ (0.111 mg, 1.68 mmol) was added and the reaction was stirred overnight. The reaction was quenched with water (15 mL), extracted with EtOAc (3 x 15 mL), dried (Na_2SO_4) and purified by chromatography on SiO_2 (97:3 CH_2Cl_2/MeOH with 1% Et_3N) to give 310 mg (66.1%) of **133** as an oil: IR (ATR) 3371, 1650, 1601 cm^{-1}; ^1H NMR (300 MHz, Acetone – d_6) δ 8.23 (s, 1 H), 7.40–7.28 (m, 5 H), 5.08 (s, 2 H), 4.98 (d, 1 H, *J* = 7.5 Hz), 4.88 (d, 1 H, *J* = 7.5 Hz), 3.86–3.71 (m, 2 H), 3.52 (s, 3 H), 3.37 (dd, 1 H, *J* = 8.4, 8.7 Hz), 2.73 (dd, 1 H, *J* = 3.9, 12.3 Hz), 2.52 (dd, 1 H, *J* = 8.7, 12.3 Hz), 2.24 (s, 6 H); ^{13}C NMR (100 MHz, Acetone – d_6) δ 168.1, 164.6, 138.7, 129.1, 128.6, 128.4, 101.7, 66.9, 60.9, 60.6, 57.1, 46.4, 45.8; HRMS (ES^+) *m/z* calcd for $C_{16}H_{24}N_4O_4$ ($[M + Na]^+$) 359.1695, found 359.1717.



134

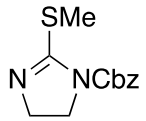
2,3-(1-Hydroxy-2-benzyloxycarbonyl)guanidin-1-(*N*-dimethyl)propylamine (134). A solution of **133** in CH_3OH (0.297 mL, 0.1 M) was treated with a solution of HCl in 1,4-dioxane (0.0743 mL, 0.149 mmol, 4M solution in 1,4-dioxane), placed in a preheated 50 ^oC oil bath, and stirred for 48 h. The solution was concentrated and purified by chromatography on C18 (100% water) to give 6.4 mg (74%) of **134** as a white solid. Diagnostic peaks for **134**: IR (ATR) 3431-2891, 1745, 1646 cm^{-1}; ^1H NMR (600 MHz, D_2O) δ 7.35–7.31 (m, 5 H), 5.21 (s, 2 H), 4.54 (m, 1 H), 4.03 (dd, 1 H, *J* = 6.4, 7.2 Hz), 3.69 (dd, 1 H, *J* = 4.8, 9.6 Hz), 3.60–3.57 (m, 1 H), 3.40 (dd, 1 H, *J* = 3.2, 9.2 Hz), 2.24 (s, 6 H); ^{13}C NMR (125 MHz, MeOD) δ 160.1, 153.1, 135.9, 129.9, 129.8, 129.7, 70.5, 59.8, 58.7; HRMS (ES^+) *m/z* calcd for $C_{14}H_{21}N_4O_3$ ($[M + H]^+$) 293.1614, found 293.1620.



136

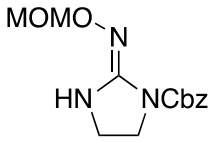
2-(Methylthio)-4,5-dihydro-1*H*-imidazole (136).[61] A solution of ethylenethiourea (1.00 g, 9.79 mmol), CH_3OH (1.19 mL), and HI (2.66 mL, 14.7 mmol, 47% wt solution) was placed in a preheated 75 ^oC oil bath and stirred overnight. The solution was cooled to rt, treated with 40%

NaOH solution until a pH of 11 was reached, and extracted with Et_2O (3 x 5 mL). The organic solution was dried ($MgSO_4$), and concentrated to give 874 mg (77%) of **136** as a solid. The spectra matched those previously reported: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (s, 1 H), 3.42 (s, 4 H), 2.23 (s, 3 H).



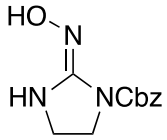
137

2-(Methylthio)-3-benzyloxycarbonyl-4,5-dihydroimidazole (137). A solution of **136** (0.200 g, 1.72 mmol) and triethylamine (0.367 mL, 2.58 mmol) in THF (4.30 mL) was treated with CbzCl (0.294 mL, 2.07 mmol) and stirred overnight. The reaction mixture was quenched with sat. NH_4Cl (5 mL), extracted with EtOAc, dried ($MgSO_4$), and purified by chromatography on SiO_2 (100% CH_2Cl_2 to 90:10 CH_2Cl_2/MeOH) to give 427 mg (99%) of **137** as a white solid: Mp 64.7-66.2 ^oC; IR (ATR) 1709, 1579 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.32 (m, 5 H), 5.18 (s, 2 H), 3.86 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 151.2, 135.1, 128.2, 128.0, 127.8, 67.3, 53.4, 47.0, 14.6; HRMS (ES^+) *m/z* calcd for $C_{12}H_{15}N_2O_2S$ ($[M + H]^+$) 251.0854, found 251.0846.



138

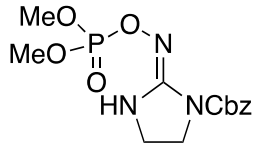
2-(Methylthio)-3-benzyloxycarbonyl-4,5-dihydroimidazole (138). A solution of **120** (1.14 g, 5.49 mmol) in CH_3CN (11.0 mL) was treated with hydrazine monohydrate (0.523 mL, 5.49 mmol). After 2 h the precipitate was filtered, the filtrate was treated with **137** (275 mg, 5.49 mmol), and Et_3N (0.199 mL, 0.137 mmol). The solution was cooled 0 ^oC, treated with $AgNO_3$ (236 mg, 1.37 mmol), and stirred overnight. The solution was filtered through celite, concentrated, and purified by chromatography on SiO_2 (95% CH_2Cl_2 5% MeOH) to give 225 mg (74%) of **138** as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.40 (m, 2 H), 7.35–7.28 (m, 3 H), 5.21 (s, 2 H), 4.99 (s, 2 H), 3.87 (t, 2 H, J = 7.2 Hz), 3.43–3.38 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 150.7, 135.5, 128.1, 127.8, 127.7, 98.4, 67.4, 56.7, 45.1, 39.8.



139

2-(*N*-Hydroxy)-3-benzyloxycarbonyl-4,5-dihydroguanidine (139). A solution of **138** (10.0 mg, 0.0358 mmol) in CH_2Cl_2 (0.179 mL) at 0 ^oC was treated with TMSBr (0.0241 mL, 0.179 mmol). After 4 h the solution was quenched with water (1 mL), extracted with CH_2Cl_2 (3 x 1 mL), and the aqueous layer was concentrated to give 3.42 mg (99%) of **139** as a white solid: ^1H

NMR (300 MHz, CD_3OD) δ 7.43–7.36 (m, 5 H), 5.31 (s, 2 H), 4.17 (dd, 2 H, *J* = 8.1, 10.5 Hz), 3.77 (dd, 2 H, *J* = 6.9, 9.3 Hz).

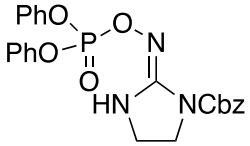


140

2-(*N*-Dimethylphosphate)-3-benzyloxycarbonyl-4,5-dihydroguanidine (140). A solution of **139** (50.0 mg, 0.213 mmol) in CH_3CN (1.07 mL) was treated with dimethyl chlorophosphate (0.0477 mL, 0.425 mmol) and Et_3N (0.0302 mL, 2.12 mmol). After 3 days, the reaction was purified by column chromatography on SiO_2 (9:1 ethyl acetate/acetone to 1:1 ethyl acetate/acetone) to give 22.5 mg (31%) of **140** as a clear oil: IR (ATR) 3336, 1743, 1702 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 7.46–7.33 (m, 5 H), 5.93 (s, 1 H), 5.18 (s, 2 H), 3.90 (dd, 2 H, *J* = 7.6, 88 Hz), 3.74 (s, 3 H), 3.71 (s, 3 H), 3.44–3.40 (m, 2 H); ^{31}P NMR (162 MHz, CD_3CN) δ 1.37; HRMS (ES^+) *m/z* calcd for $C_{13}H_{19}N_3O_6P$ ($[M + H]^+$) 344.1011, found 344.0994.

A solution of dimethyl phosphate (0.0756 mL, 0.777 mmol) and triethylamine (0.166 mL, 1.17 mmol) in CH_3CN (3.12 mL) at 0 ^oC was treated with TFAA (0.119 mL, 0.855 mmol). The solution was warmed to rt, stirred for 10 min, at rt, cooled to 0 ^oC, treated with a solution of 1-methylimidazole (70.9 mg, 0.855 mmol) in CH_3CN (0.775 mL), and stirred overnight. A portion of the above solution (3.32 mL, 0.662 mmol, 0.2 M) was added to a solution of **139** (130 mg, 0.553 mmol) in CH_3CN (0.360 mL) at 0 ^oC. The resulting solution was treated with triethylamine (0.0932 mL, 0.663 mmol), stirred overnight, and purified by column

chromatography on SiO_2 (9:1 ethyl acetate/acetone to 1:1 ethyl acetate/acetone) to give 93.6 mg (49.3 %) of **140** as an oil: ^{1}H NMR (400 MHz, CD_3CN) δ 7.48–7.36 (m, 5 H), 6.12 (s, 1 H), 5.21 (s, 2 H), 3.94 (t, 2 H, *J* = 7.6 Hz), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.46 (t, 2 H, *J* = 7.6 Hz); ^{31}P NMR (162 MHz, CD_3CN) δ 1.71.



141

2-(*N*-Diphenylphosphate)-3-benzyloxycarbonyl-4,5-dihydroguanidine (141). A solution of **139** (50.0 mg, 0.213 mmol) in CH_3CN (1.06 mL) was treated with diphenyl chlorophosphate (0.223 mL, 1.06 mmol) and triethylamine (0.0302 mL, 0.213 mmol). After 3 h the resulting solution was purified by column chromatography on SiO_2 (7:3 EtOAc / hexanes) to give 39.6 mg (40%) of **141** as a yellow oil: ^{1}H NMR (400 MHz, CD_3CN) δ 7.47–7.18 (m, 15 H), 6.02 (s, 1 H), 5.22 (s, 2 H), 3.91 (dd, 2 H, *J* = 7.6, 8.8 Hz), 3.40 (dd, 2 H, *J* = 7.6, 8.8 Hz); ^{31}P NMR (162 MHz, CD_3CN) δ -10.4.

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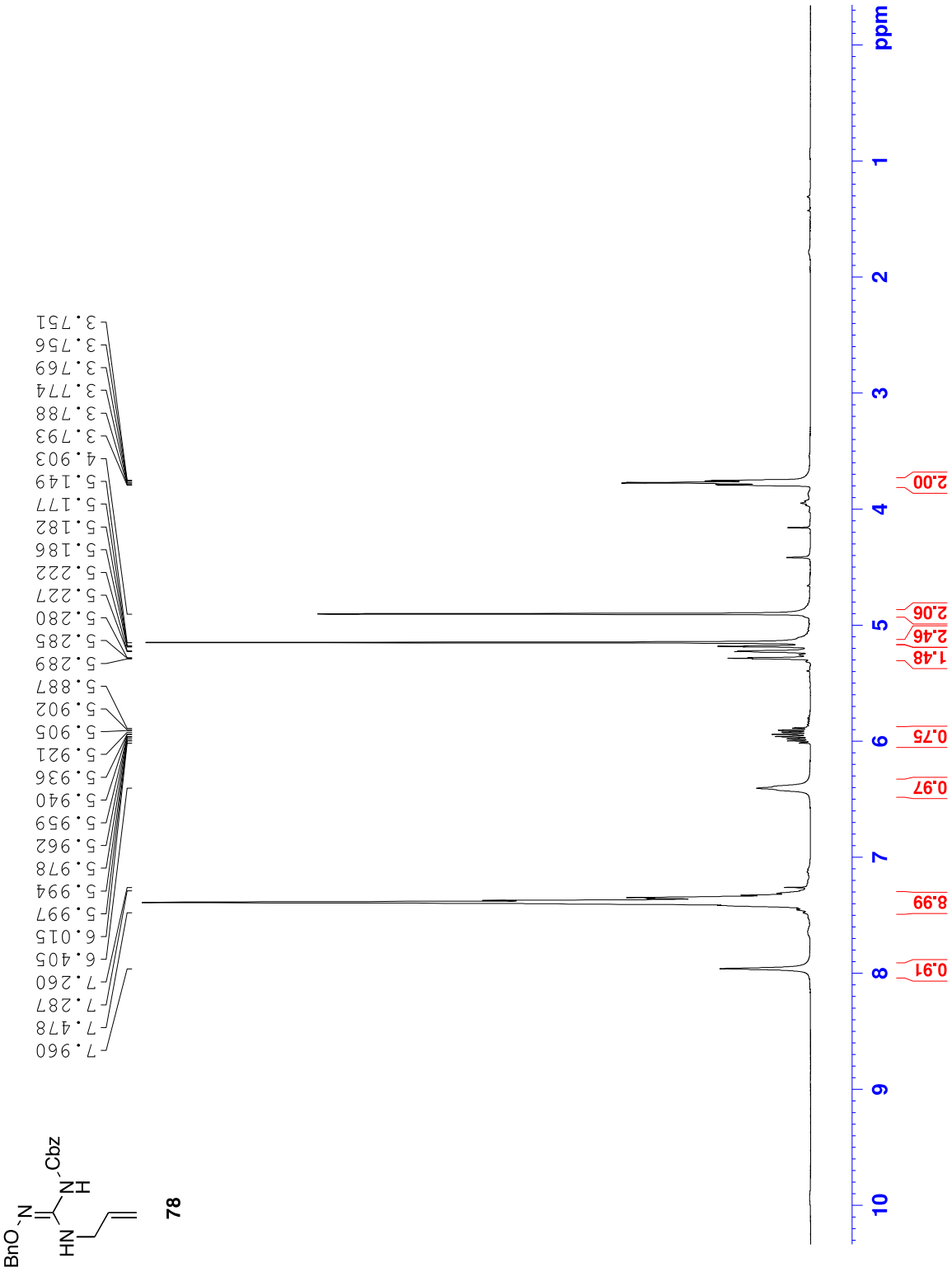
APPENDIX A

SELECTED ^{1}H AND ^{13}C SPECTRA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5.962
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5.940
5.936
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5.285
5.280
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5.182
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3.769
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3.751
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2.06
2.46
1.48
0.75
0.97
8.99
0.91
ppm

BnO
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HN
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Cbz
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128.81
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128.44
128.06
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77.23
76.02
67.76
43.44
ppm
0
20
40
60
80
100
120
140
160
180
200

Cbz
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O
OMe
77-Boc
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7.260
7.250
5.022
4.965
4.930
4.827
4.792
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3.906
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3.865
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3.823
3.616
3.490
3.473
3.461
3.443
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2.749
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2.362
2.334
2.307
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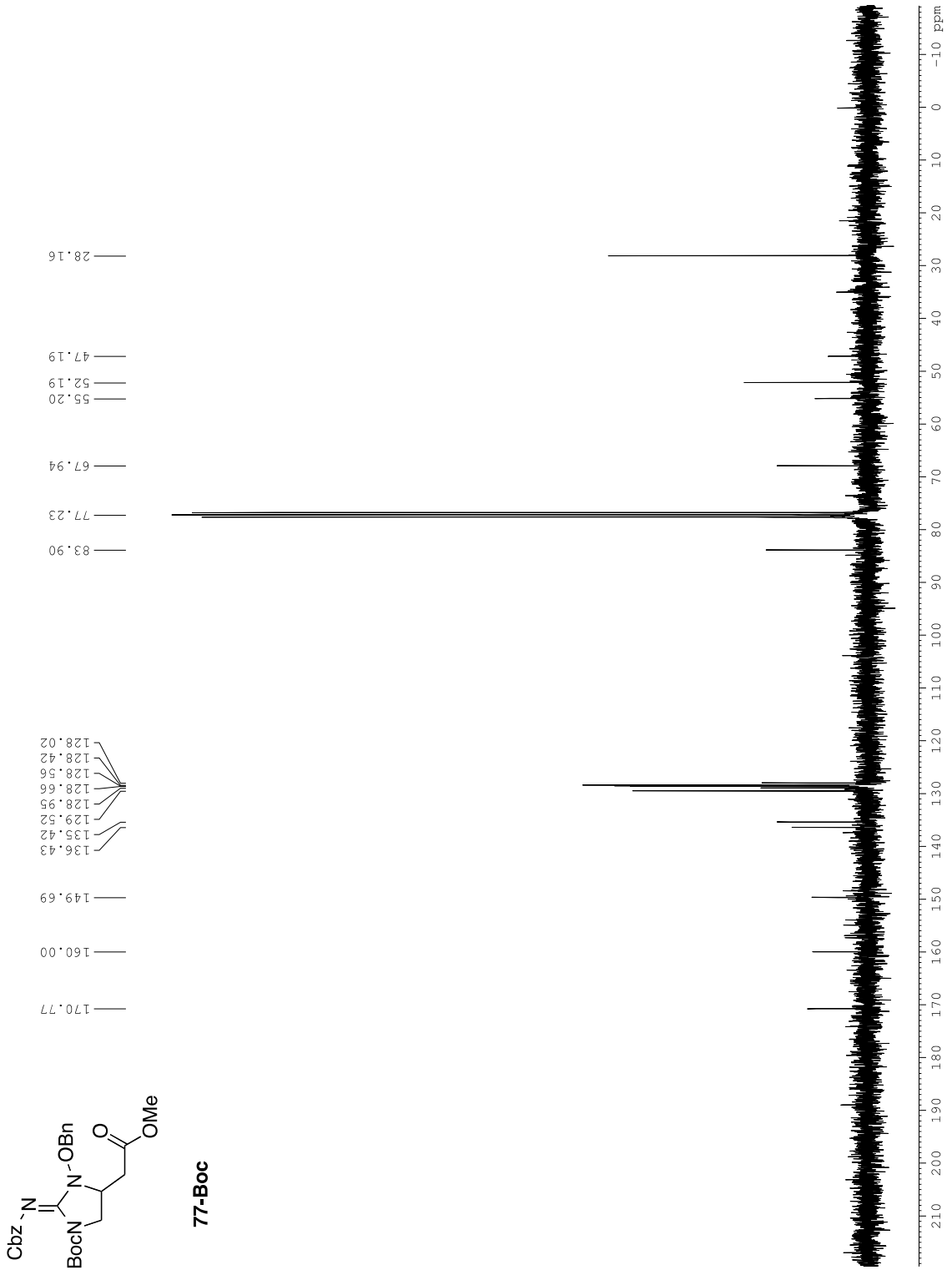
1.11
1.92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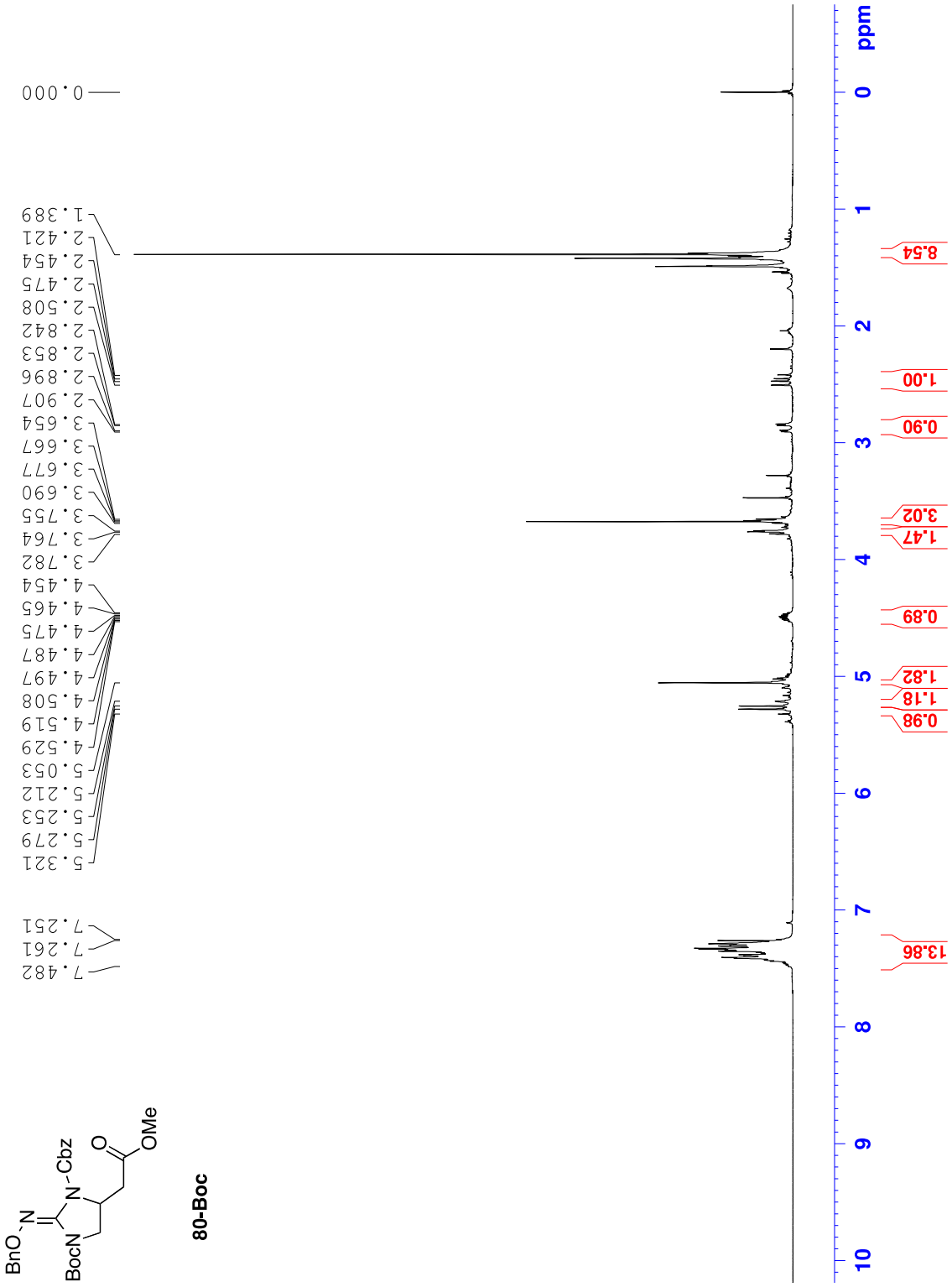
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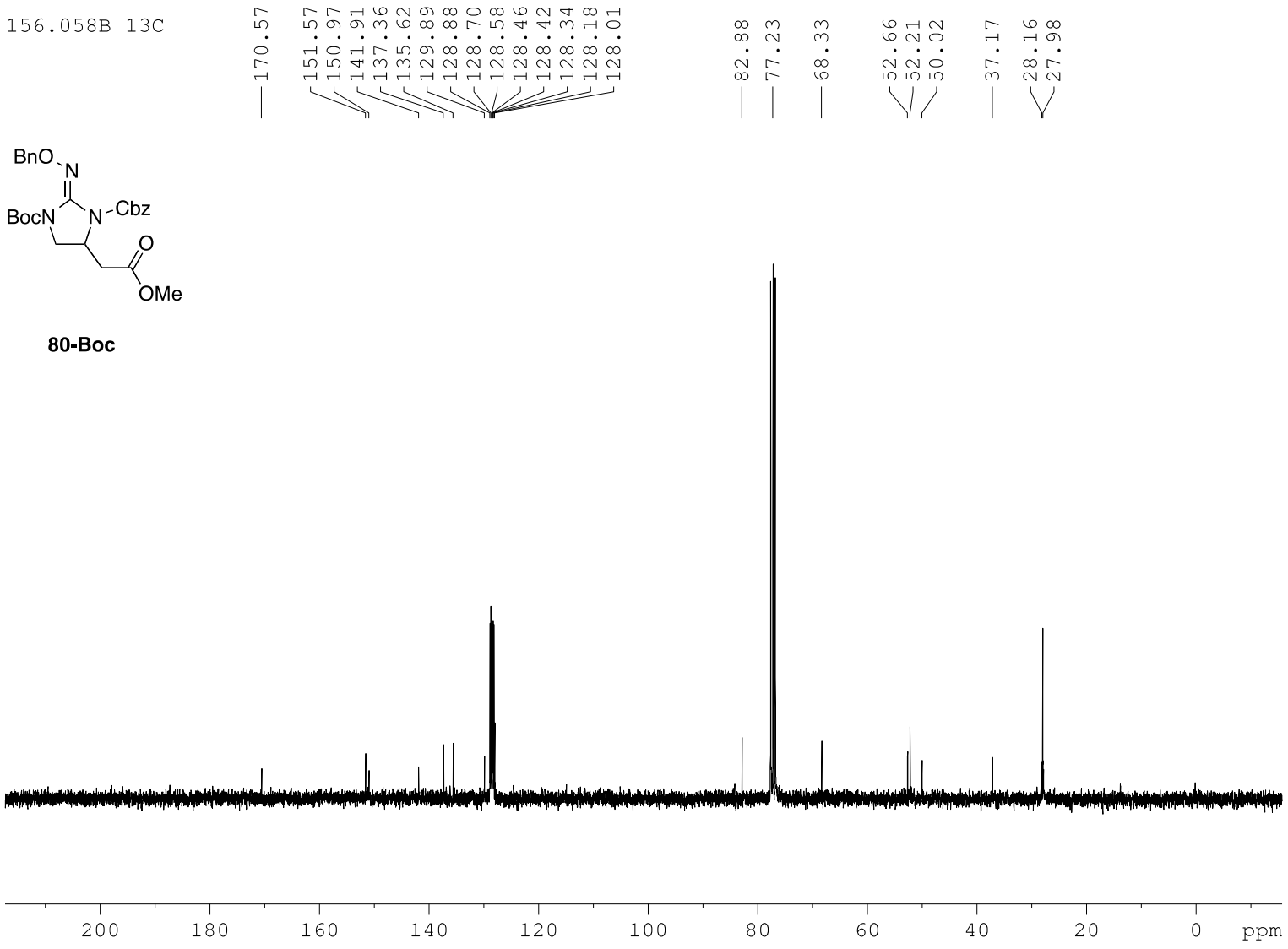
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37.17
28.16
27.98
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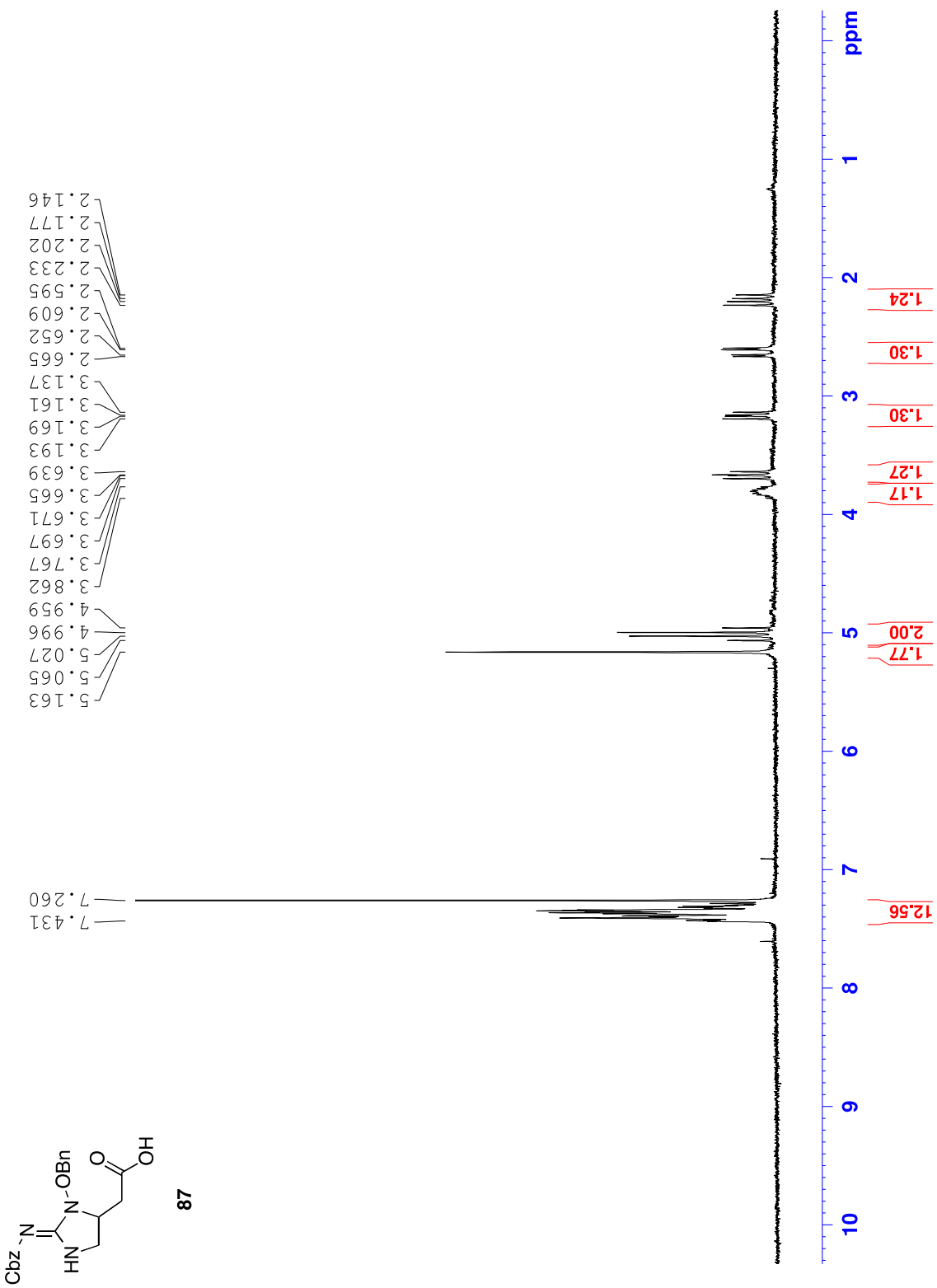
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1.27
1.30
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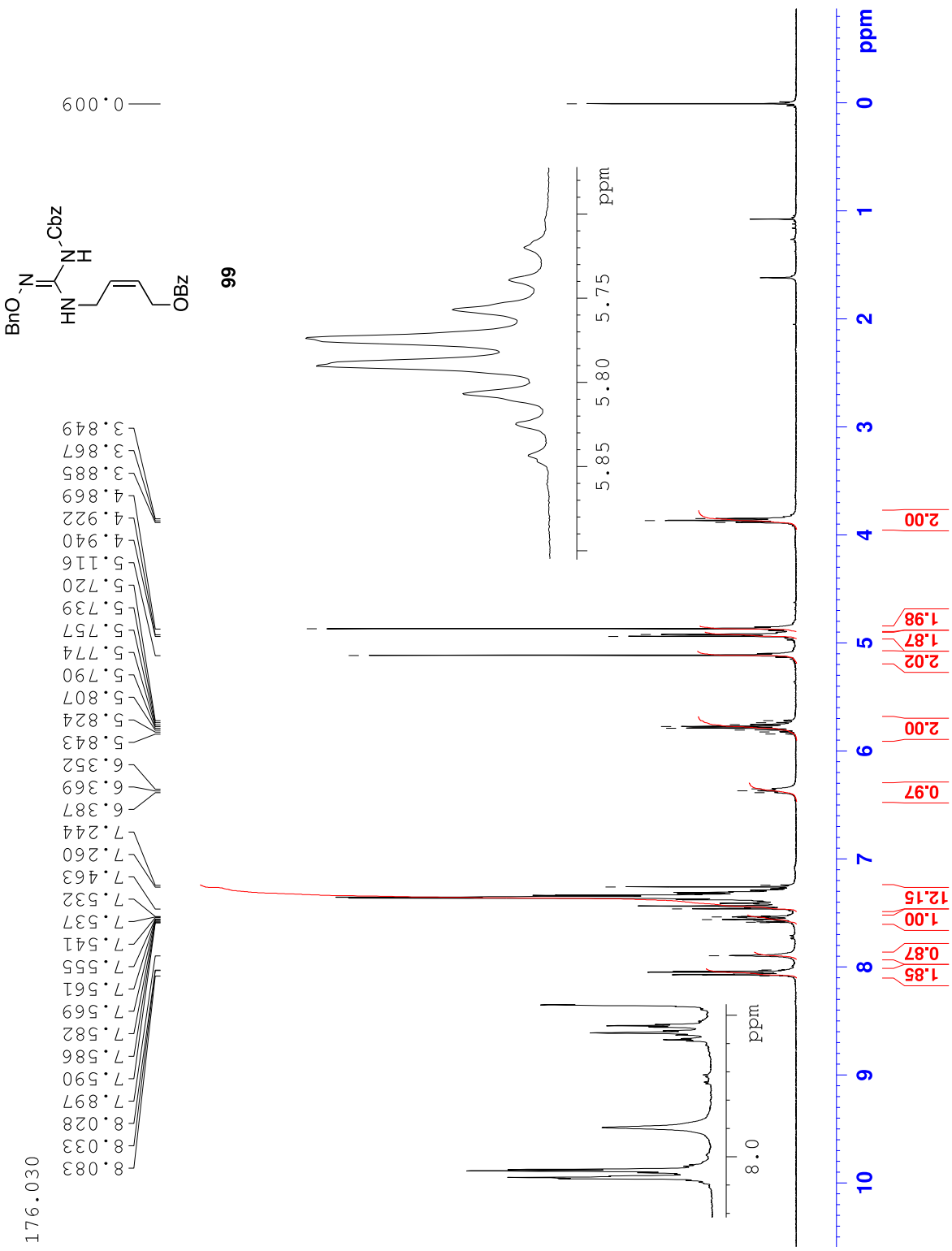
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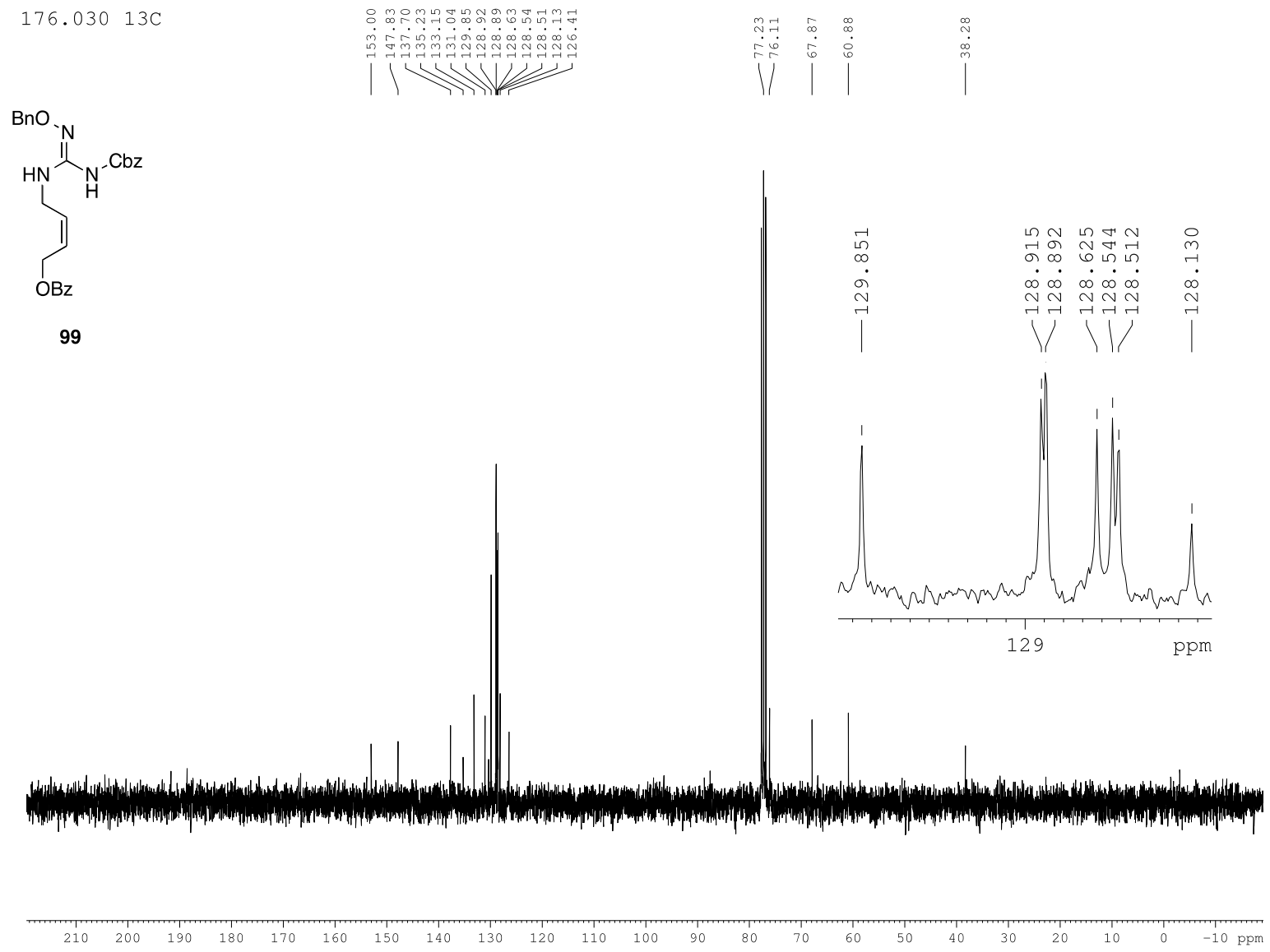
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H
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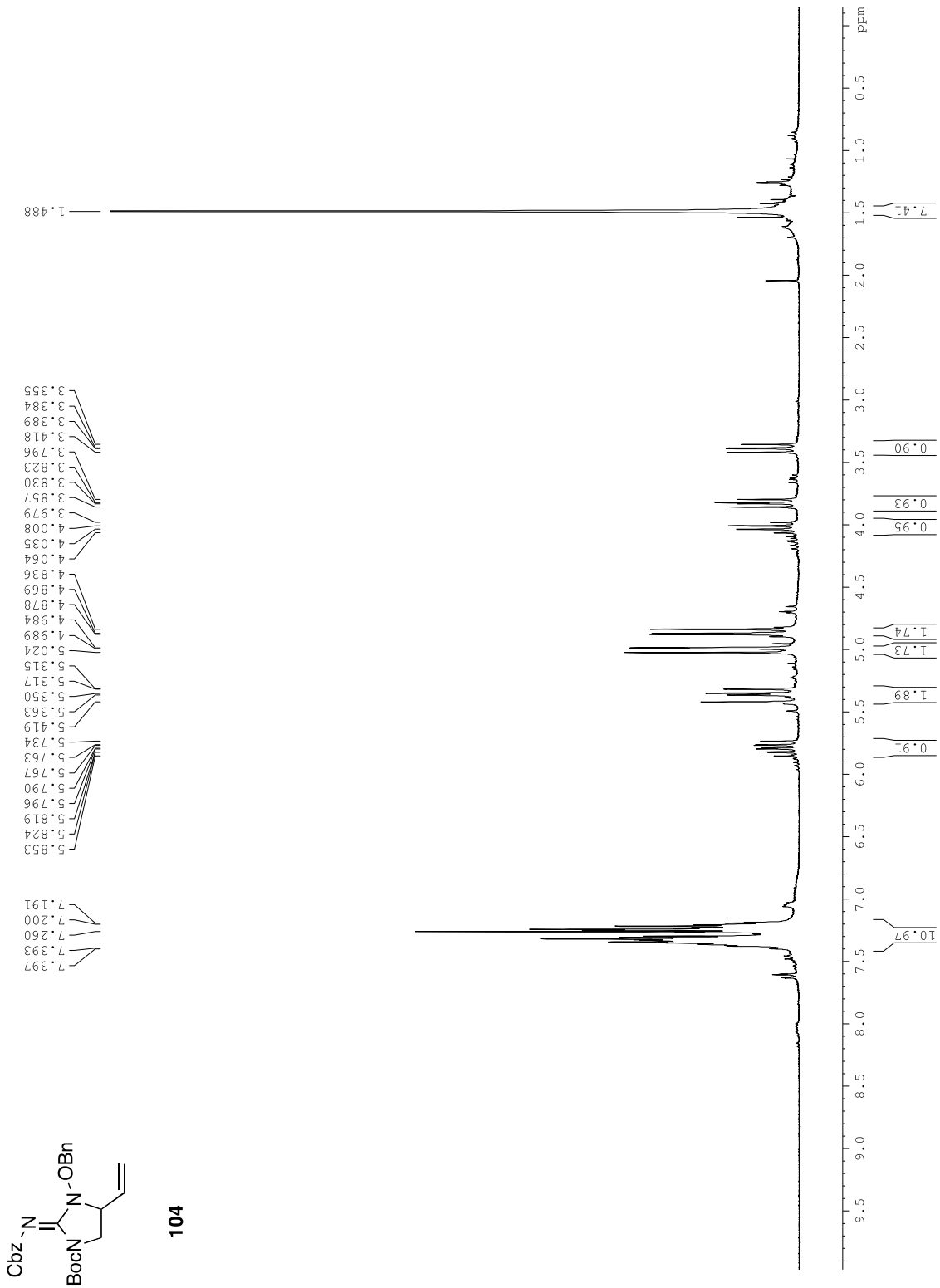
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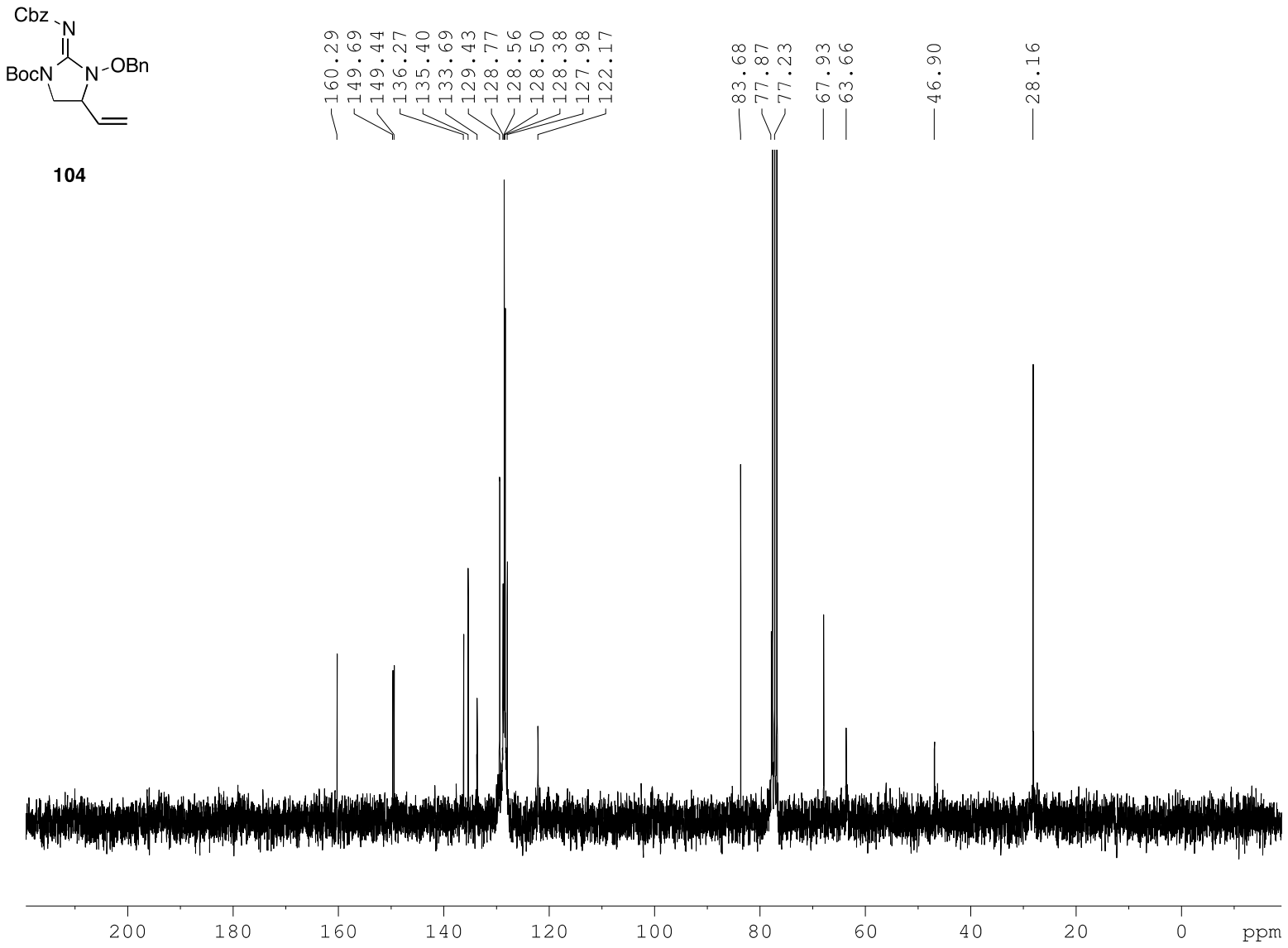
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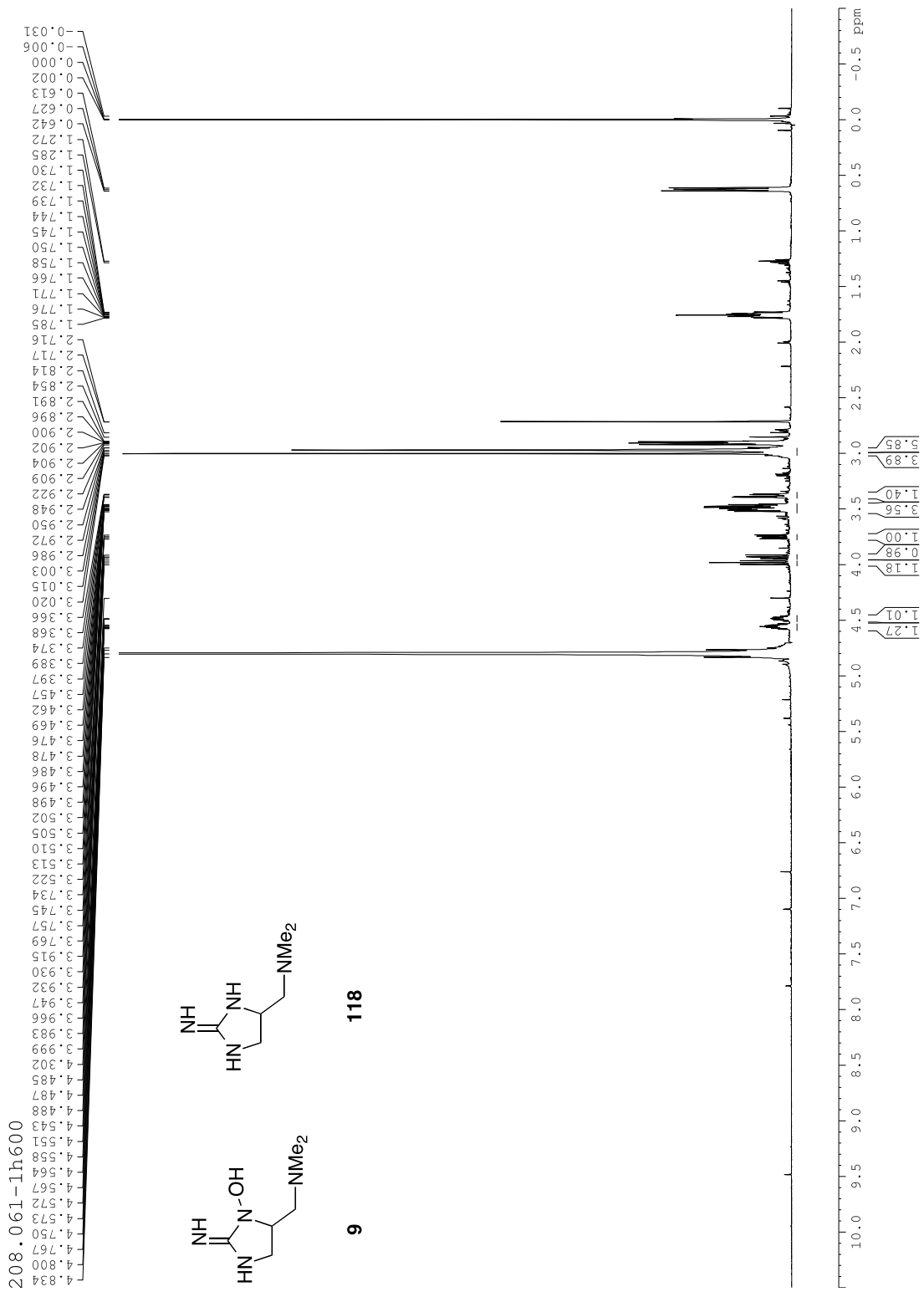
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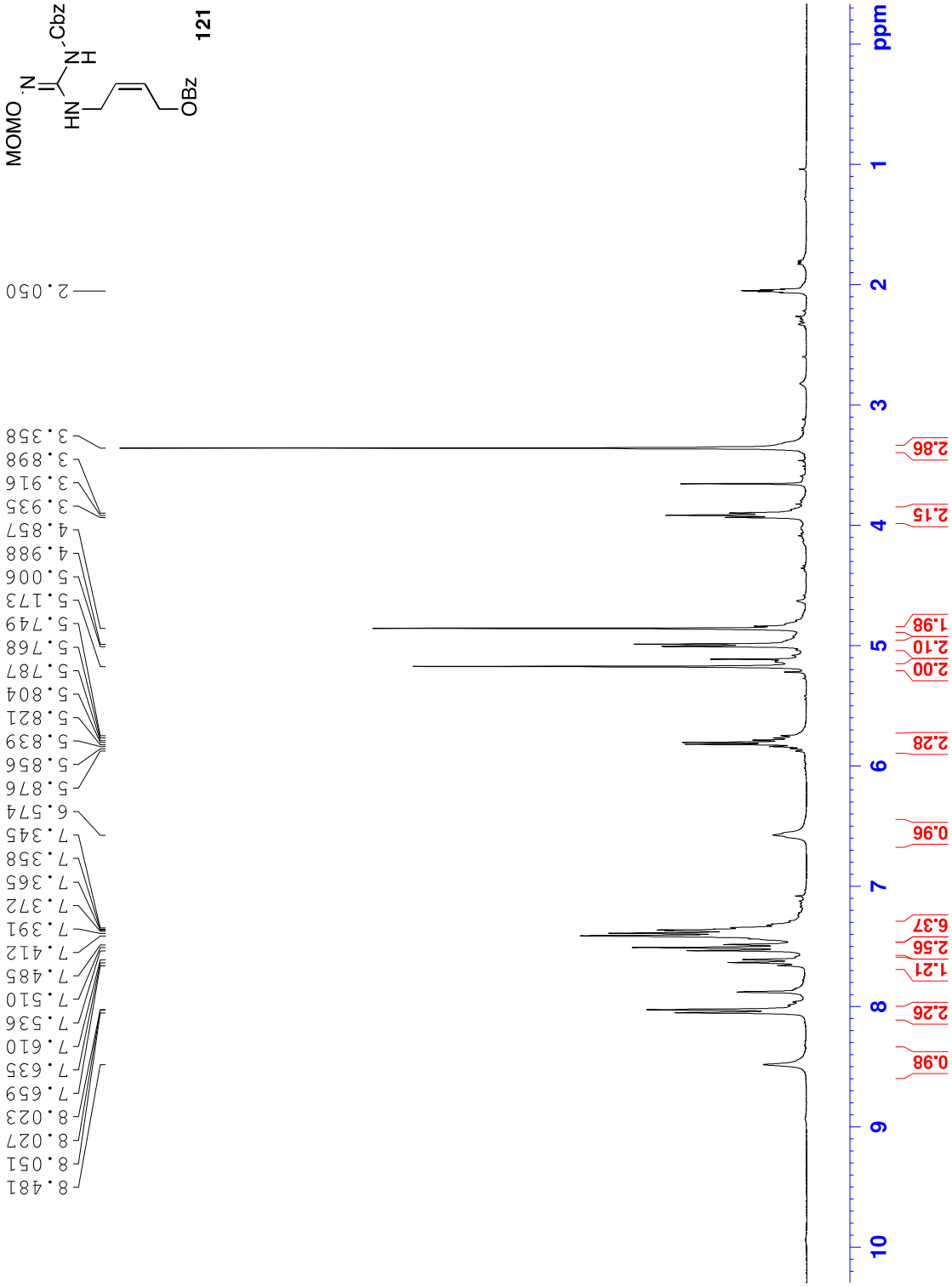
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N
Cbz
N
H
HN
OBz
121
ppm
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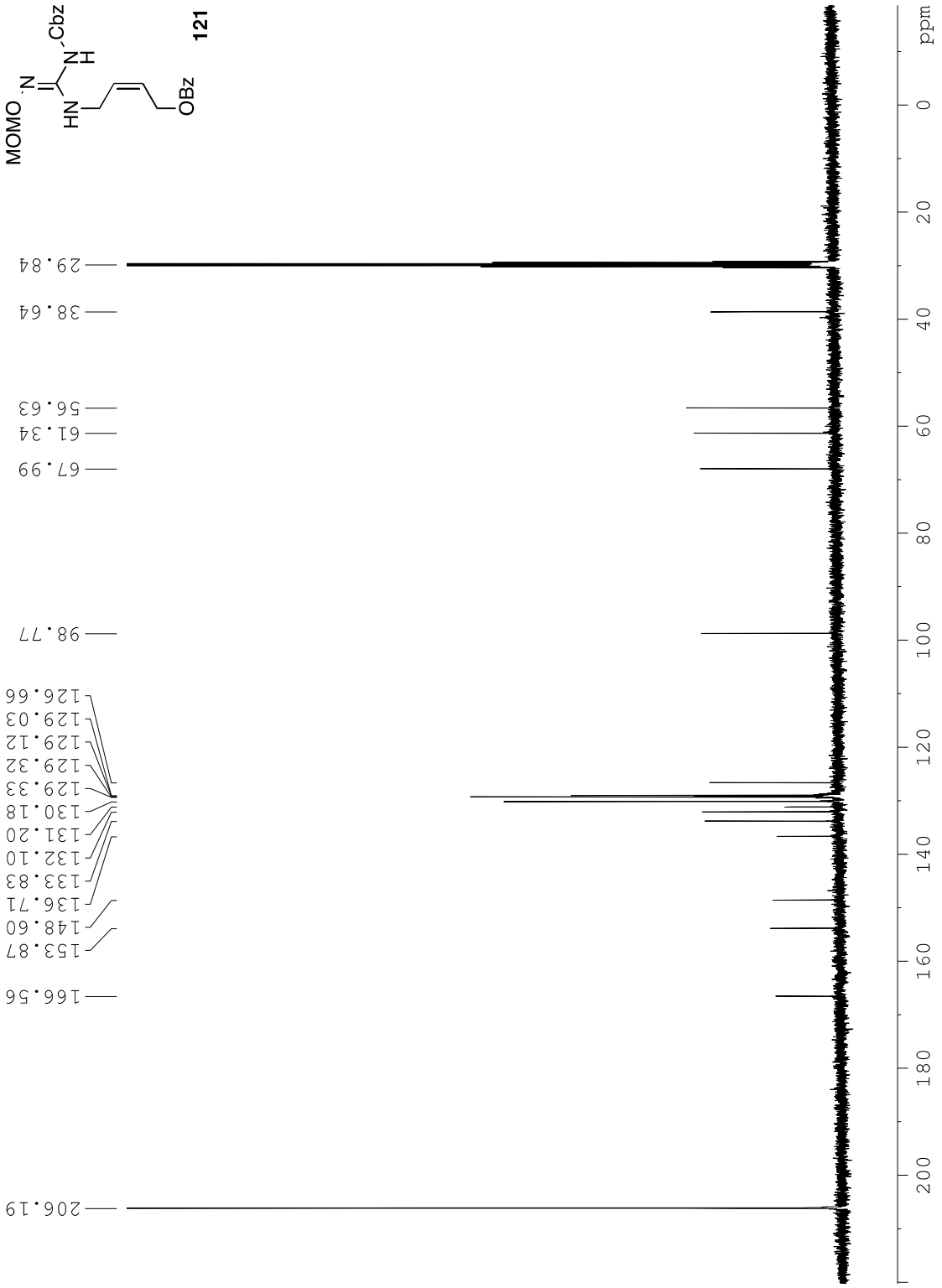
2
3
4
5
6
7
8
9
10
2.86
2.15
1.98
2.10
2.00
2.28
0.96
6.37
2.56
1.21
2.26
0.98
2.050
3.358
3.898
3.916
3.935
4.857
4.988
5.006
5.173
5.749
5.768
5.787
5.804
5.821
5.839
5.856
5.876
6.574
7.345
7.358
7.365
7.372
7.391
7.412
7.485
7.510
7.536
7.610
7.635
7.659
8.023
8.027
8.051
8.481


MOMO
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N
H
HN
OBz
121
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38.64
56.63
61.34
67.99
98.77
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129.03
129.12
129.32
129.33
130.18
131.20
132.10
133.83
136.71
148.60
153.87
166.56
206.19
ppm
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20
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60
80
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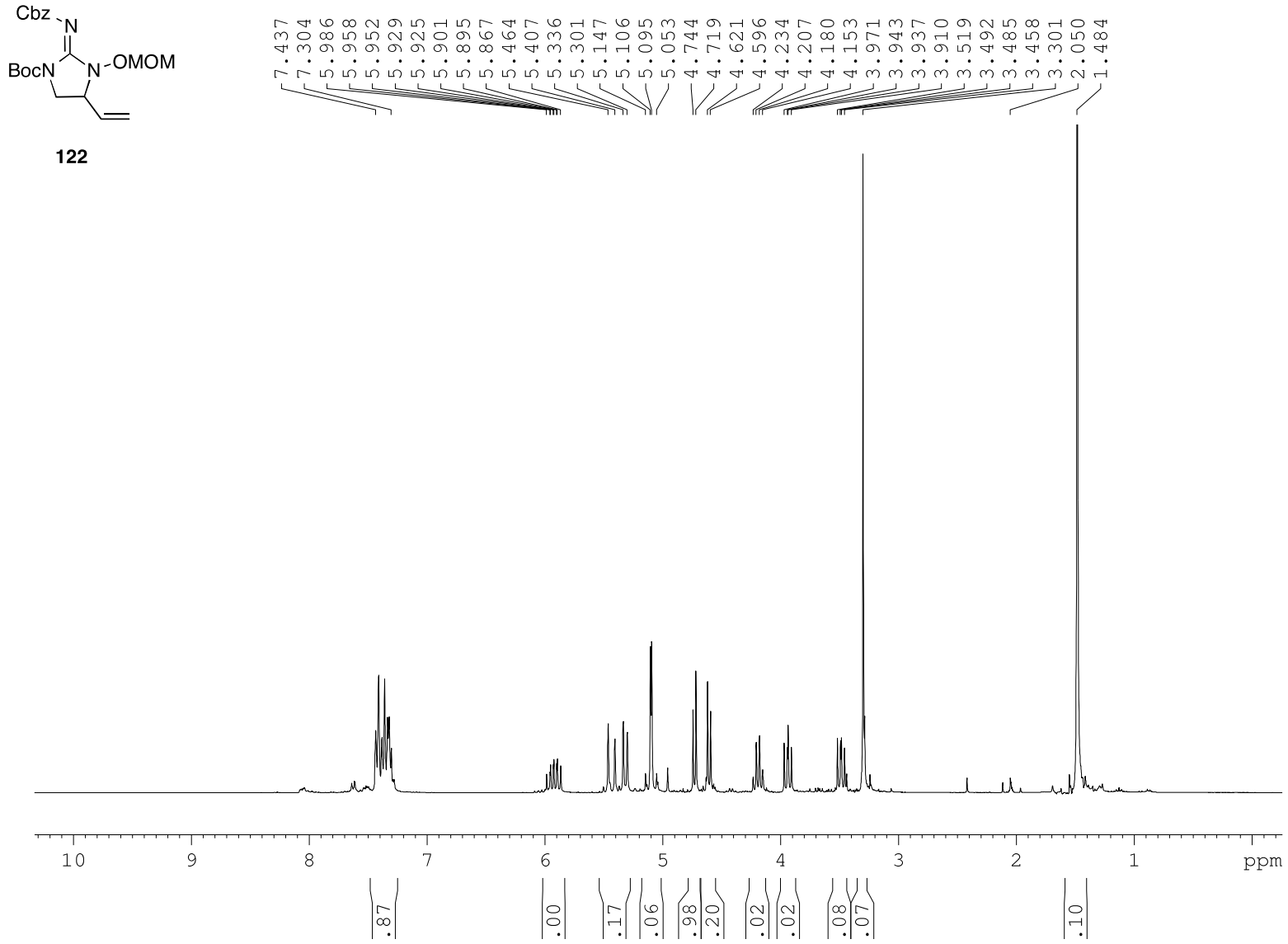
120
140
160
180
200


Cbz
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BocN
N
OMOM
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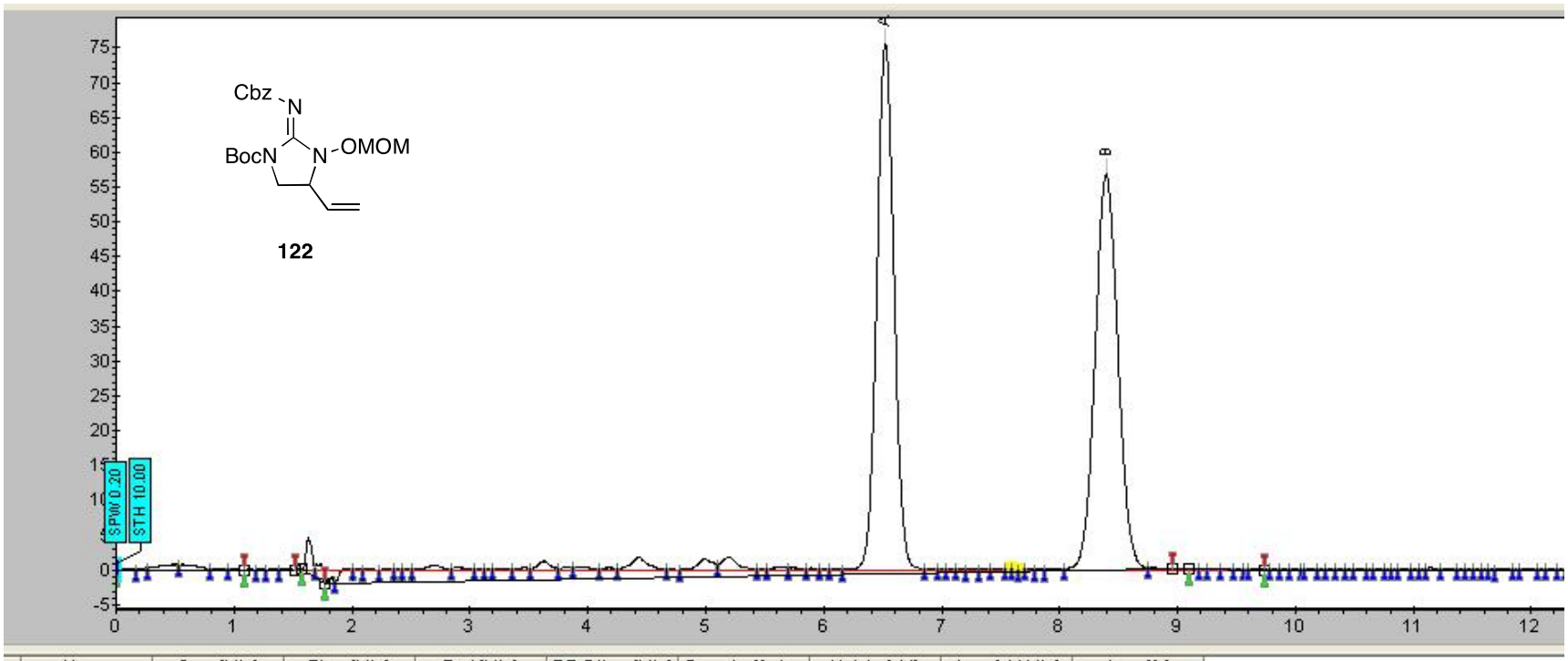
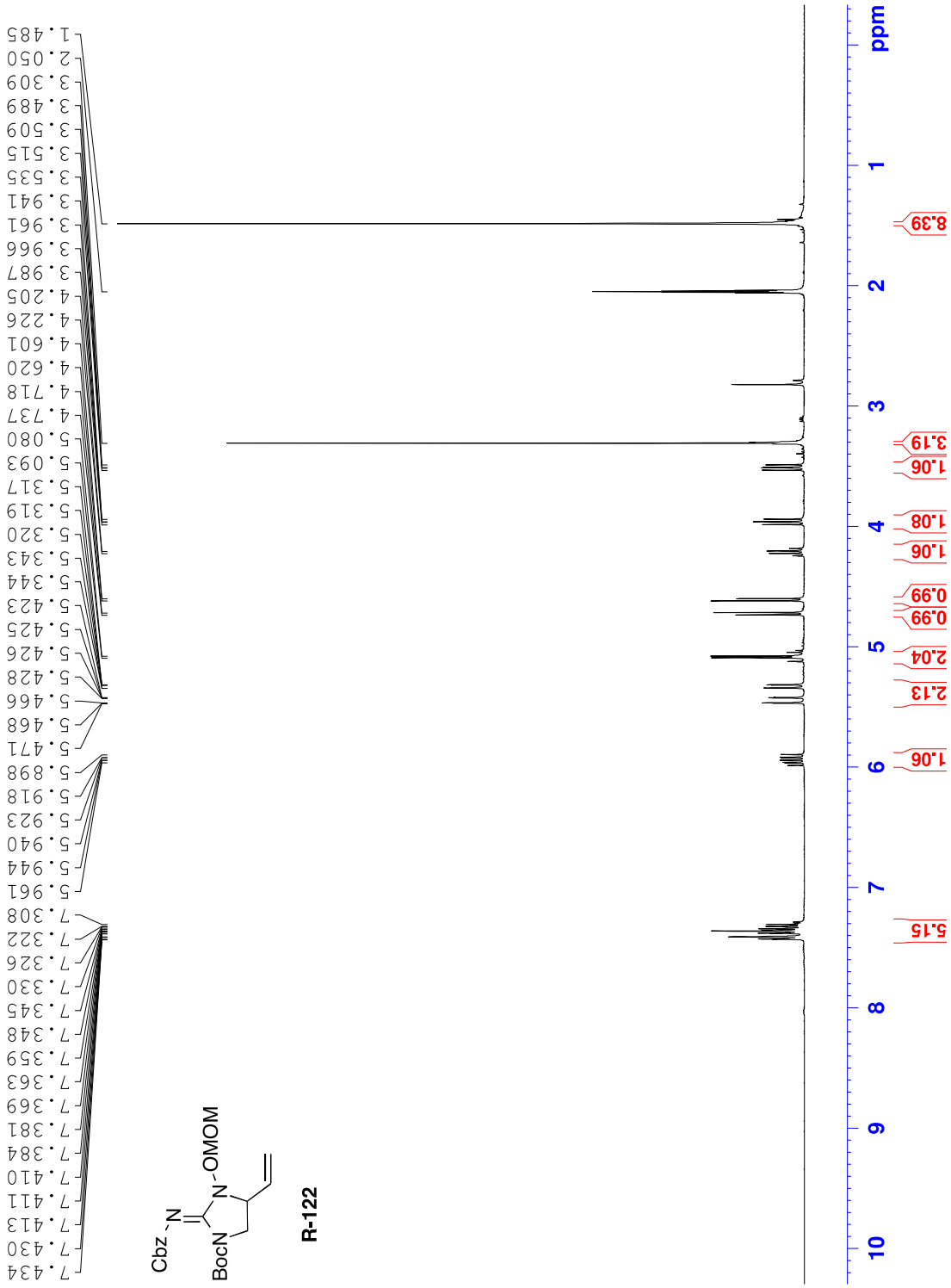
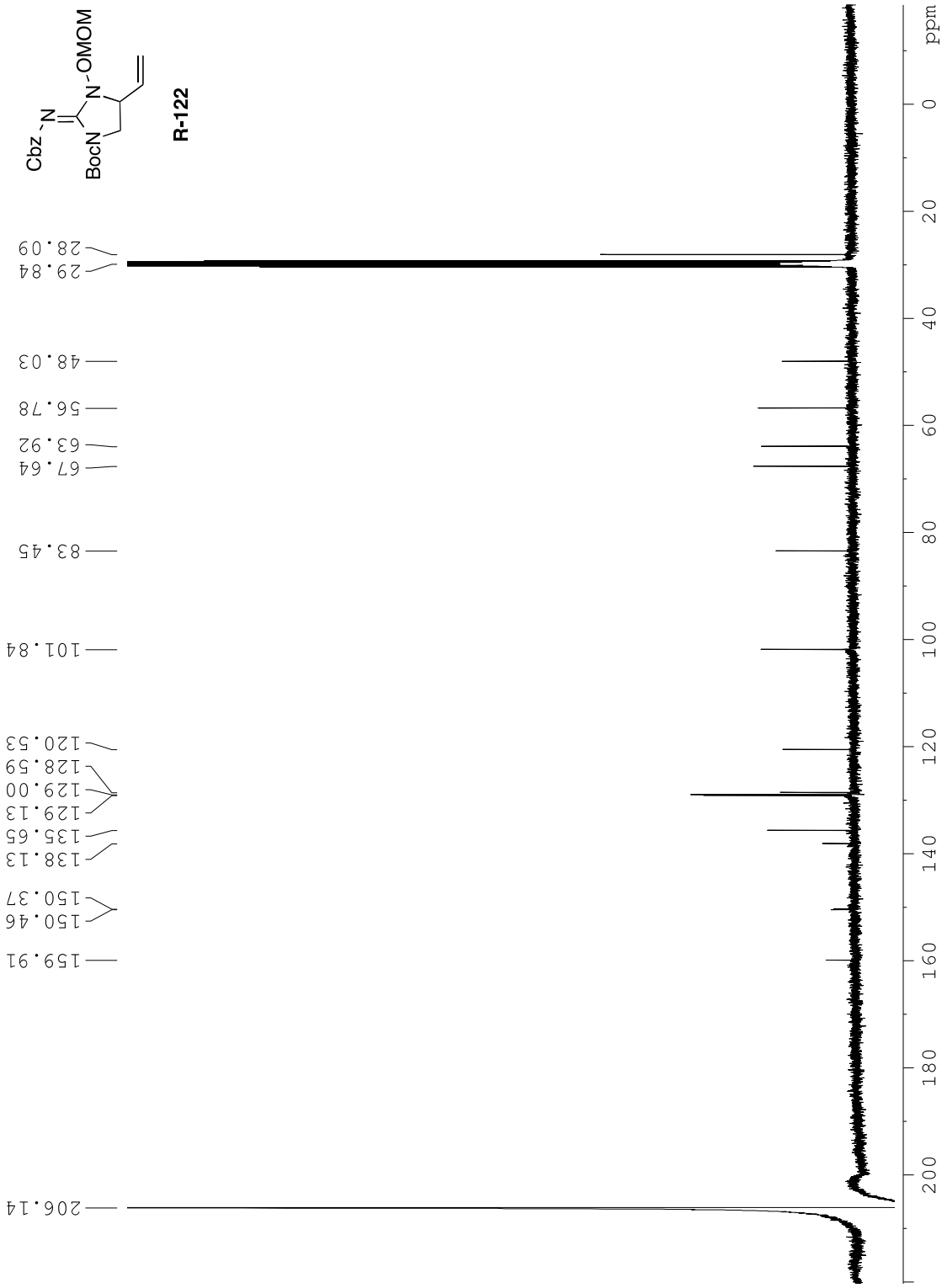
5.958
5.952
5.929
5.925
5.901
5.895
5.867
5.464
5.407
5.336
5.301
5.147
5.106
5.095
5.053
4.744
4.719
4.621
4.596
4.234
4.207
4.180
4.153
3.971
3.943
3.937
3.910
3.519
3.492
3.485
3.458
3.301
2.050
1.484
10
9
8
7
6
5
4
3
2
1
ppm
.87
.00
.17
.06
.98
.20
.02
.02
.08
.07
.10

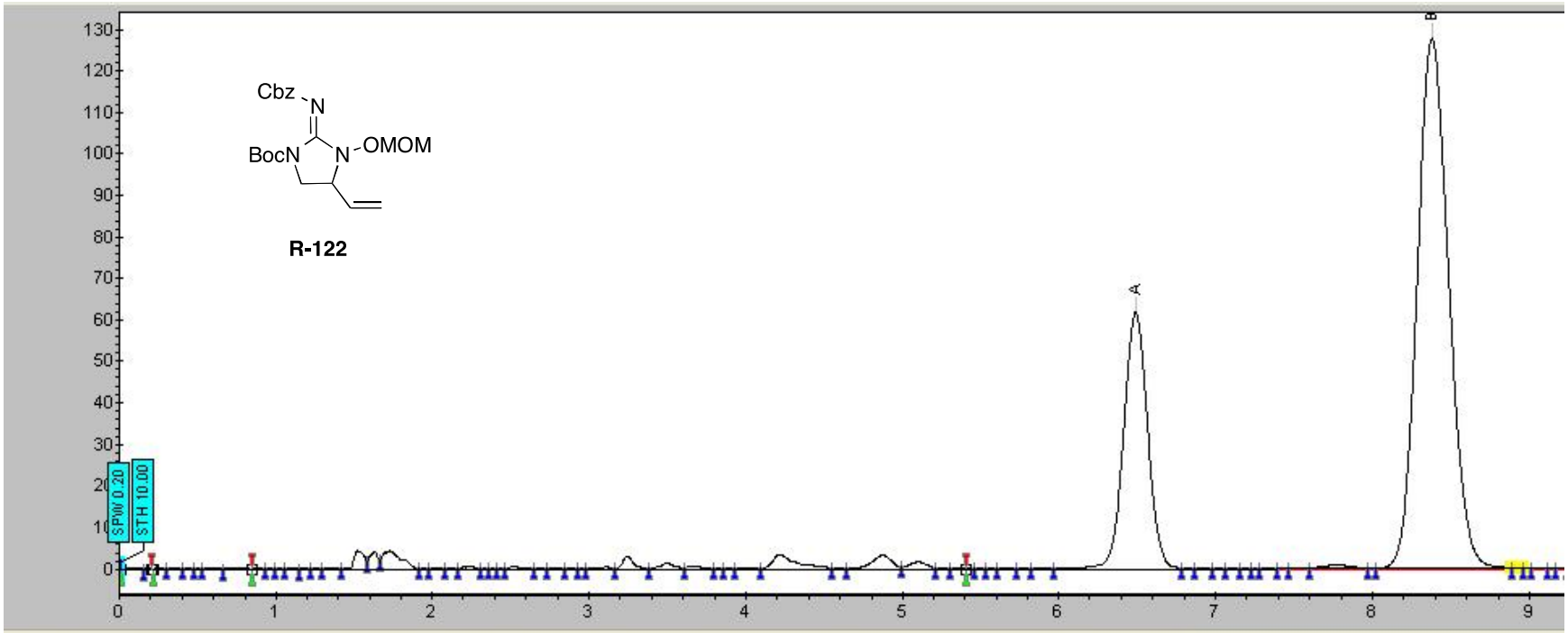
Cbz
N
BocN
N
OMOM
122
28.03
29.84
47.86
56.69
63.71
67.53
83.33
101.66
120.51
128.46
128.85
128.99
135.40
137.90
150.18
150.26
159.77
206.12
ppm
0
20
40
60
80
100
120
140
160
180
200



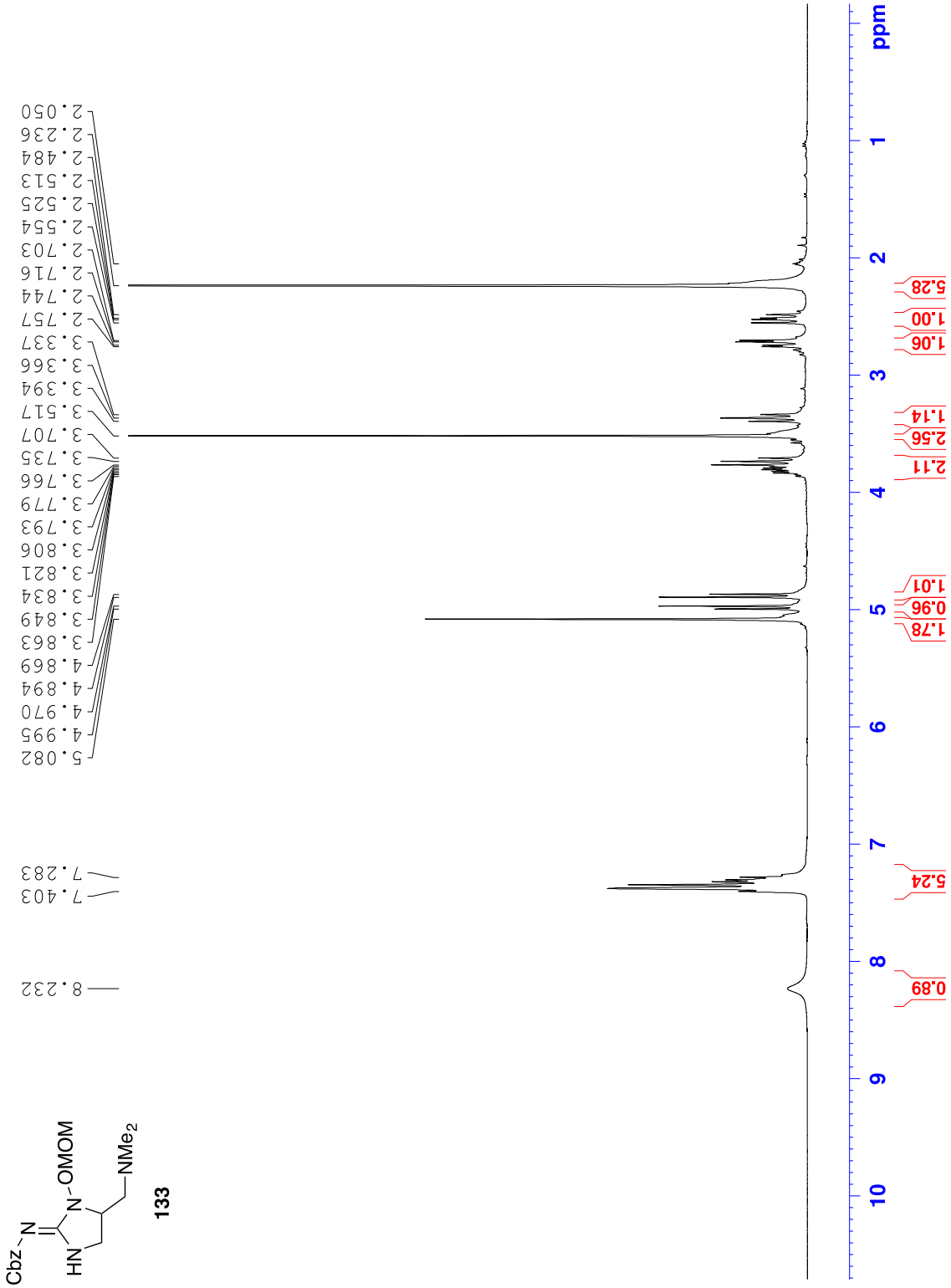
	Name	Start [Min]	Time [Min]	End [Min]	RT Offset [Min]	Quantity [% Area]	Height [µV]	Area [µV.Min]	Area [%]
	A	6.15	6.52	6.86	0.00	38.06	76.0	13.1	38.064
	B	8.04	8.39	8.75	0.00	36.90	56.8	12.7	36.898
						100.00	202.0	34.5	100.000

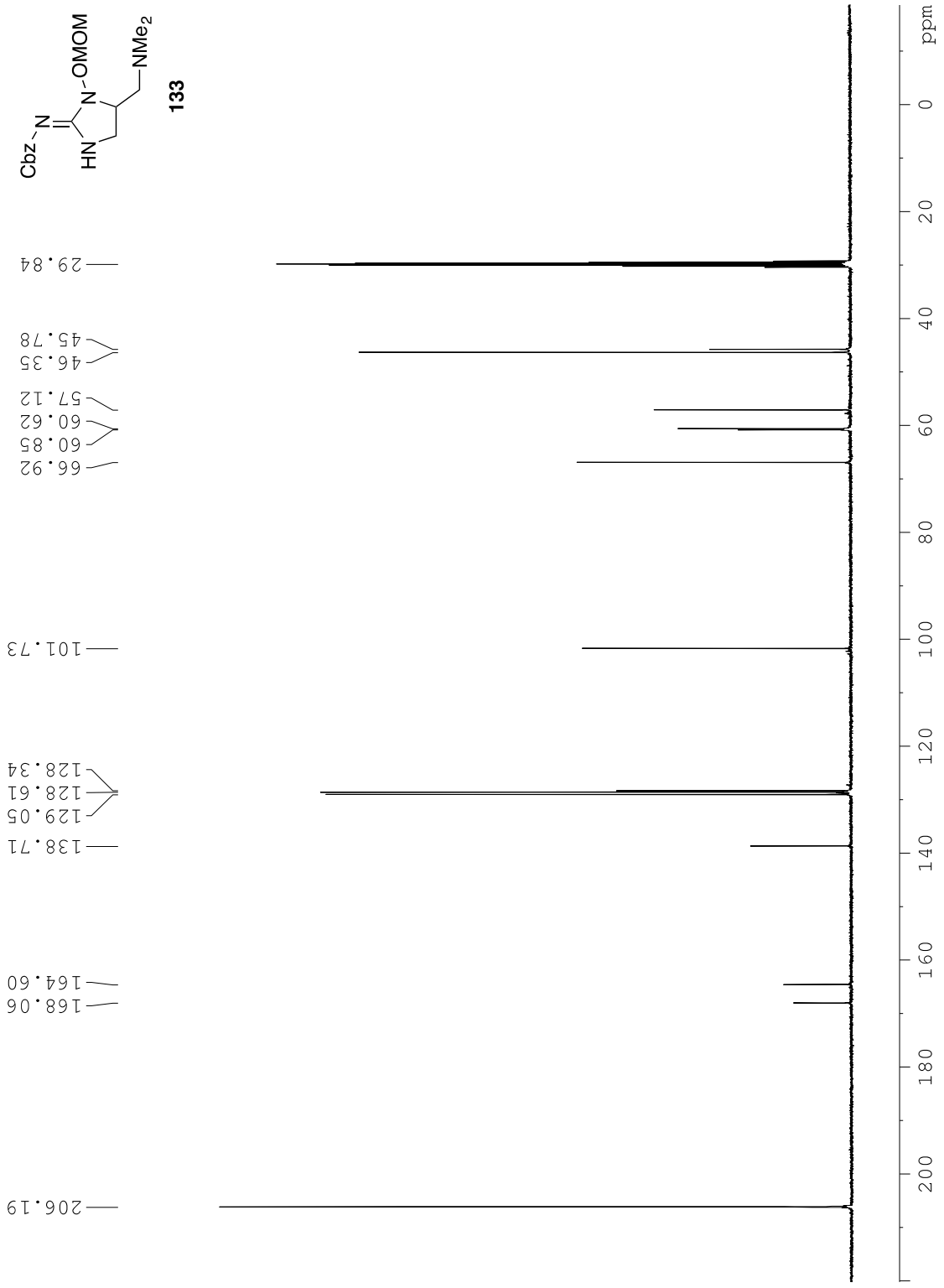

7.434
7.430
7.413
7.411
7.410
7.384
7.381
7.369
7.363
7.359
7.348
7.345
7.330
7.326
7.322
7.308
5.961
5.944
5.940
5.923
5.918
5.898
5.471
5.468
5.466
5.428
5.426
5.425
5.423
5.344
5.343
5.320
5.319
5.317
5.093
5.080
4.737
4.718
4.620
4.601
4.226
4.205
3.987
3.966
3.961
3.941
3.535
3.515
3.509
3.489
3.309
2.050
1.485
Cbz
N
BocN
N
OMOM
R-122
ppm
1
2
3
4
5
6
7
8
9
10
8.39
3.19
1.06
1.08
1.06
0.99
0.99
2.04
2.13
1.06
5.15

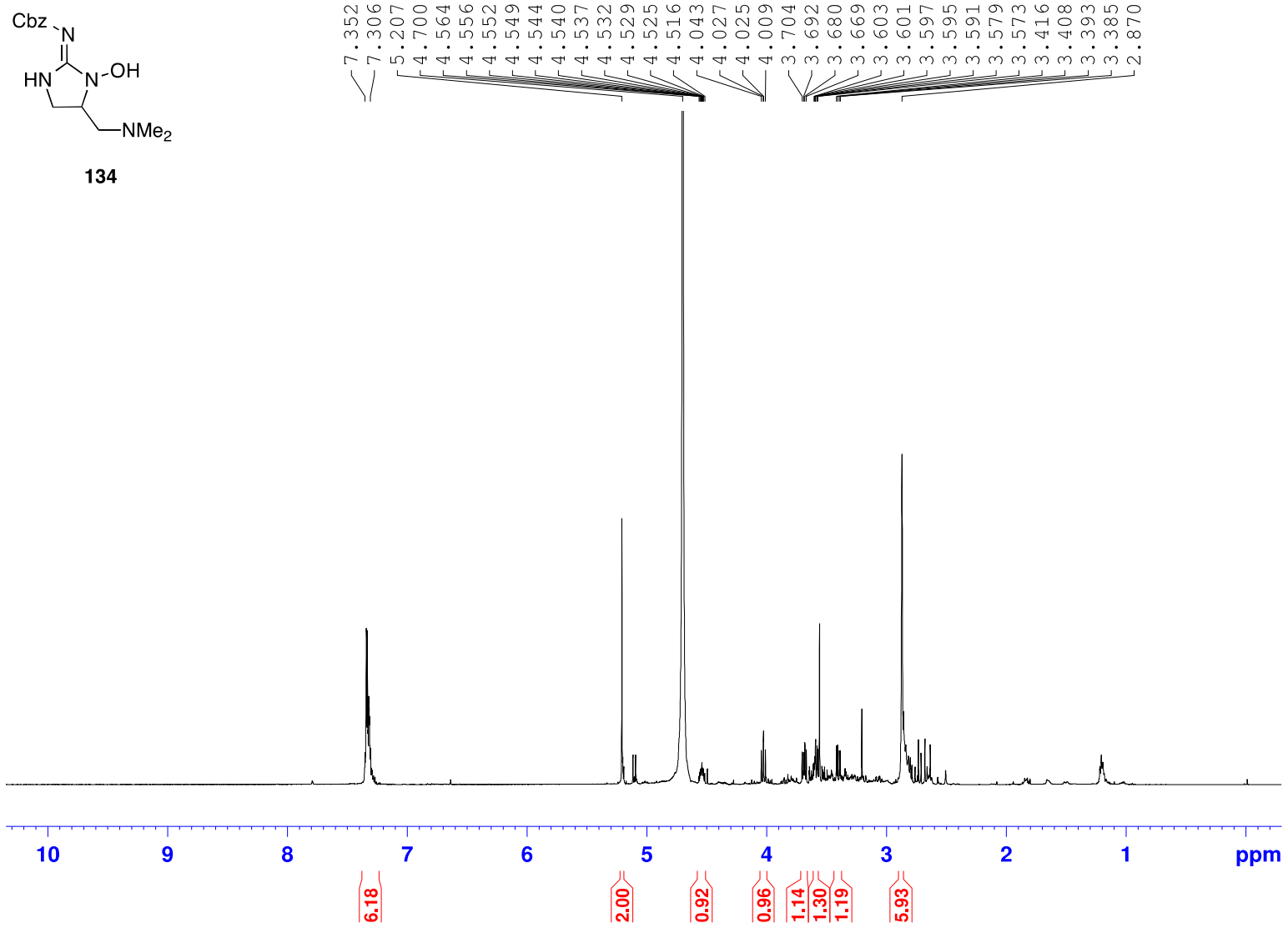

Cbz
N
BocN
N
OMOM
R-122
28.09
29.84
48.03
56.78
63.92
67.64
83.45
101.84
120.53
128.59
129.00
129.13
135.65
138.13
150.37
150.46
159.91
206.14
ppm



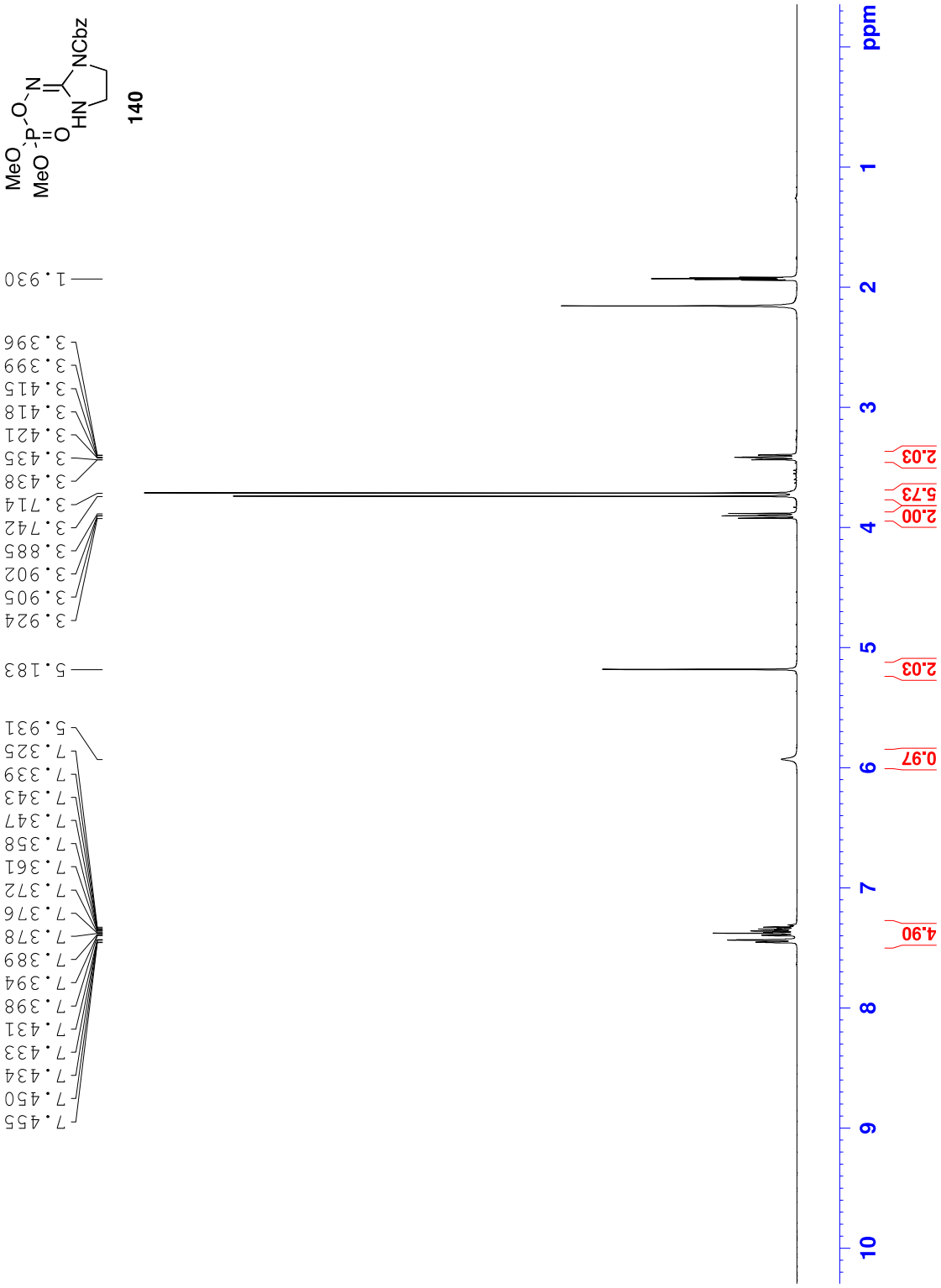
Name	Start [Min]	Time [Min]	End [Min]	RT Offset [Min]	Quantity [% Area]	Height [µV]	Area [µV.Min]	Area [%]
A	5.97	6.49	6.78	0.00	24.44	61.9	10.9	24.445
B	8.03	8.38	8.89	0.00	66.47	127.7	29.7	66.468
					100.00	229.7	44.7	100.000


Cbz
N
HN
N
OMOM
NMe2
133
8.232
7.403
7.283
5.082
4.995
4.970
4.894
4.869
3.863
3.849
3.834
3.821
3.806
3.793
3.779
3.766
3.735
3.707
3.517
3.394
3.366
3.337
2.757
2.744
2.716
2.703
2.554
2.525
2.513
2.484
2.236
2.050
ppm
1
2
3
4
5
6
7
8
9
10
5.28
1.00
1.06
1.14
2.56
2.11
1.01
0.96
1.78
5.24
0.89


Cbz
N
HN
N
OMOM
NMe2
133
29.84
45.78
46.35
57.12
60.62
60.85
66.92
101.73
128.34
128.61
129.05
138.71
164.60
168.06
206.19
ppm
0
20
40
60
80
100
120
140
160
180
200


Cbz
N
HN
N
OH
NMe2
134
7.352
7.306
5.207
4.700
4.564
4.556
4.552
4.549
4.544
4.540
4.537
4.532
4.529
4.525
4.516
4.043
4.027
4.025
4.009
3.704
3.692
3.680
3.669
3.603
3.601
3.597
3.595
3.591
3.579
3.573
3.416
3.408
3.393
3.385
2.870
10
9
8
7
6
5
4
3
2
1
ppm
6.18
2.00
0.92
0.96
1.14
1.30
1.19
5.93

Cbz
N
HN
N
OH
NMe2
134
160.09
153.13
135.91
129.91
129.78
129.67
70.54
59.84
58.67
49.00
ppm


MeO
MeO
P
O
N
O
HN
NCbz
140
1.930
3.396
3.399
3.415
3.418
3.421
3.435
3.438
3.714
3.742
3.885
3.902
3.905
3.924
5.183
5.931
7.325
7.339
7.343
7.347
7.358
7.361
7.372
7.376
7.378
7.389
7.394
7.398
7.431
7.433
7.434
7.450
7.455
ppm
1
2
3
4
5
6
7
8
9
10
2.03
5.73
2.00
2.03
0.97
4.90

MeO
MeO
P
O
N
O
HN
NCbz
140
158.69
151.70
137.11
129.45
129.08
128.82
118.30
68.51
55.55
55.49
46.79
40.74
1.30
ppm
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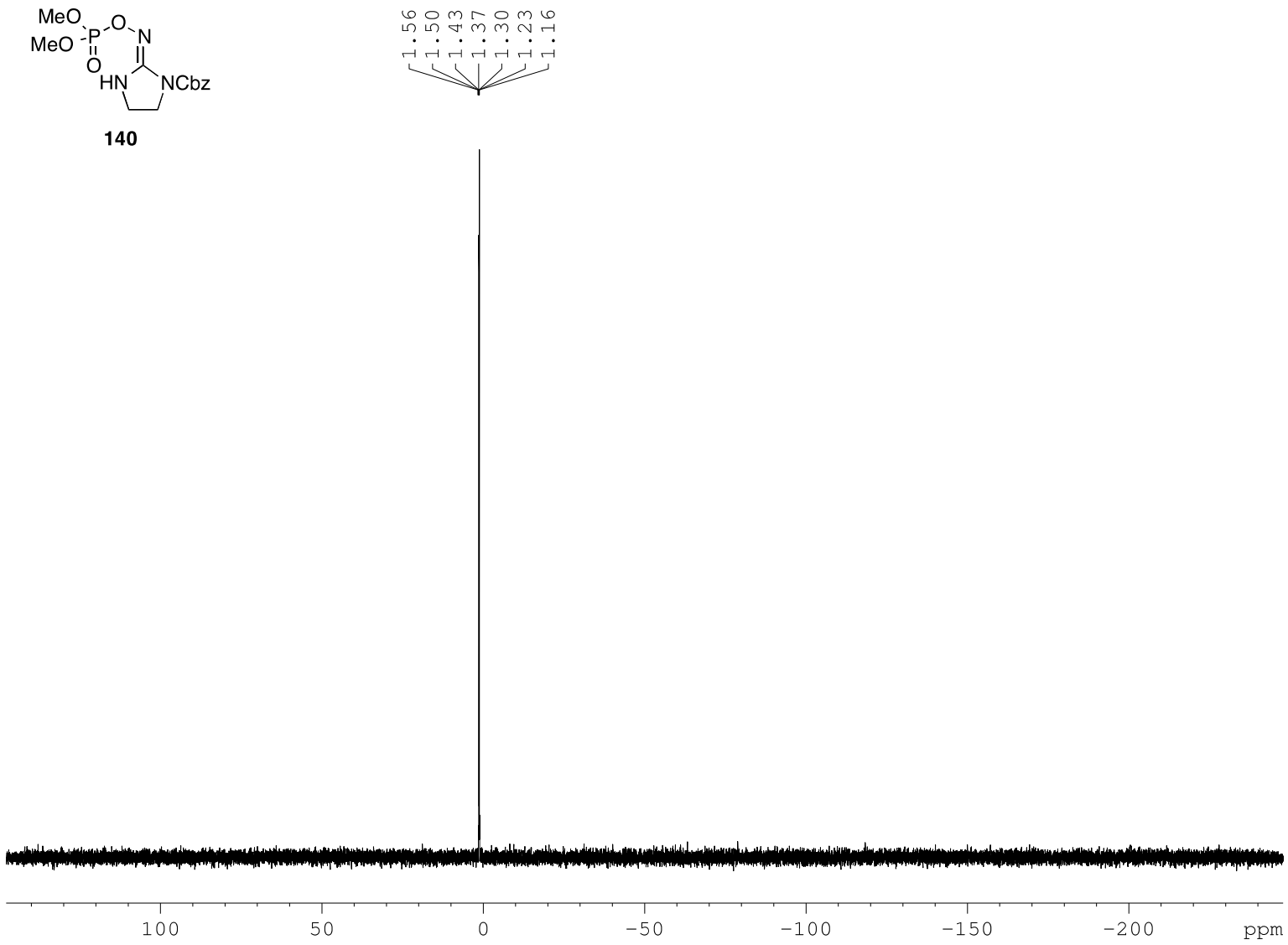
20
40
60
80
100
120
140
160
180
200


MeO
MeO
P
O
O
N
HN
NCbz
140
1.56
1.50
1.43
1.37
1.30
1.23
1.16
100
50
0
-50
-100
-150
-200
ppm