DISSERTATION

APPROACHES TOWARDS THE SYNTHESIS OF SAXITOXIN ALKALOIDS

Submitted by

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ABSTRACT

APPROACHES TOWARDS THE SYNTHESIS OF SAXITOXIN ANALOGS

Zetekitoxin AB is a toxin isolated from the Panamanian golden frog (*Atelopus zeteki*). The structure and activity of zetekitoxin AB was a mystery for 30 years until 2004 when it was elucidated by Yamashita and coworkers[1]. It was found to be a potent analog of Saxitoxin, a marine neurotoxin. Saxitoxin is a sodium channel blocker and has been used extensively as a research probe. Zetekitoxin AB shows an affinity profile similar to saxitoxin, but is considerably more potent. Due to the endangerment of the Panamanian golden frog there is no source of zetekitoxin AB, preventing further studies.

Presented herein is a concise synthesis of 4,5-epi-11-hydroxy-saxitoxinol, which utilizes D-ribose to direct an asymmetric Mannich reaction. This approach allows many modes of reactivity, which can be used to potentially access various analogs of saxitoxin with novel bioactivity.

ACKNOWLEDGEMENTS

The work contained herein would not have been possible without the support of my colleagues, family and friends.

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Chapter 1: Introduction

1.1 Neurotoxins

Neurotoxins represent one of the many types of toxins, which are classified by their biological target. The common classifications of toxins are: cytotoxins, which affect cells; hepatotoxins, which affect the liver; and neurotoxins, which affect the nervous system. The classes of toxins themselves are divided into different groups based on their mode of action. Neurotoxins, for example, can exhibit toxicity by ion channel disruption, altering the blood brain barrier, synaptic vesicle release inhibition and cytoskeleton disruption.

1.1.1 Ion Channels

The basis of nerve transmissions is the action potential, which is the buildup and fall of an electrical membrane potential. This potential is controlled by the flow of ions through membrane-bound proteins known as ion channels. There two main classes of ion channels: voltage-gated and ligand-gated. Voltage-gated channels rely on a membrane potential to open or close the channel, whereas a ligand-gated channel requires the binding of a small messenger molecule. The most common voltage-gated channels are the sodium, potassium, calcium and chloride channels. Sodium and potassium channels control the action potential of a nerve and calcium channels are responsible for smooth muscle and cardiac muscle contraction. Chloride channels are less understood than the rest, but have been shown to be responsible for regulating cell pH and maintaining the proper cell volume.

1.1.2 Neurotoxins Affecting Ion Channels

There are many toxins that act on ion channels. A few examples are shown in Figure 1. Saxitoxin (**1**), from marine dinoflagellates and tetrodotoxin (**2**), from species of puffer fish are

very potent sodium channel blockers, which prevent the transport of sodium ions. Aconitine (**3**), a toxin isolated from *Aconitum spp*., displays a different mode of toxicity by binding to sodium channels leaving them open to the transport of sodium ions. Besides small molecule toxins there are also peptide toxins such as the conatoxins. Conatoxins are isolated from the venom of marine cone snails and act on the potassium, sodium or calcium ion channels, depending on the individual toxin.

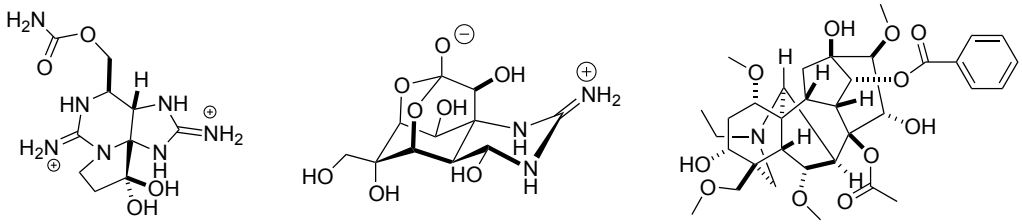
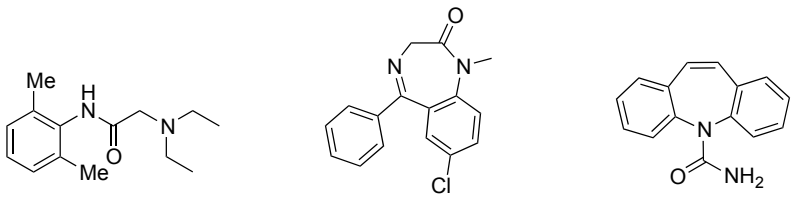


Figure 1 Ion Channel toxins

1.1.3 Therapeutics Targeting Ion Channels

Since ion channels are paramount in the transmission of nerve signals and the overall function of the nervous system, there are many disorders that result from ion channel problems. Modulation of the sodium channel, for instance, can cause increased or decreased sensitivity to pain.[1] Epilepsy and migraines can be the result of changes in various ion channels.[2] Due to the wide variety of disorders related to ion channels, many drug discovery programs targeting them have been created. Many drugs targeting ion channels have been approved (Figure 2) and there are many in clinical trials.[3] An early example, currently in use, is Lidocaine (**4**), which was developed in 1943, and has been used for many years in surgical and topical applications as an analgesic. It prevents pain signals by blocking fast voltage-gated sodium channels. Valium (Diazepam, **5**), another famous ion channel modulator, is used for the treatment of anxiety, insomnia and seizures and works by binding to the $GABA_A$ receptors, which increases the flow

of chloride ions. The anticonvulsant carbamazepine (**6**) stabilizes the closed form of the sodium channels and potentiates GABA receptors.



Lidocaine, 4 **Diazapam, 5** **Carbamazepine, 6**

Figure 2 Drugs targeting Sodium Channels

Naturally occurring toxins have not only allowed for the isolation and determination of the different ion channels, but have been useful as starting points for the development of new therapeutics. A good example of a natural product derived drug is Ziconotide, which was developed by the Elan Corporation for the treatment of severe and chronic pain. Ziconotide is a synthetic version of a ω-conotoxin peptide, which modulates pain by selectively blocking the N-type voltage-gated calcium channel. The saxitoxin family of compounds, described below, shows good potential for the development of molecular probes and therapeutics.

1.2 Saxitoxin and Analogs

1.2.1 Isolation and Structure Determination

During the summer of 1927, San Francisco was the site of mass poisoning.[4] The result was 6 dead and over 100 people ill, all from consuming poisoned mussels collected in the area. These shellfish became toxic when they consumed the marine plankton, *Gonyaulax catenella*.[5] Sommer and coworkers were able to isolate the toxin by extracting the livers from 4360 kg of mussels collected in California.[6,7] Rapoport and coworkers originally proposed the structure of saxitoxin as **7** and **8**,[8] which they later revised to saxitoxin (**1**), after obtaining an x-ray structure (Figure 3).[9,10]

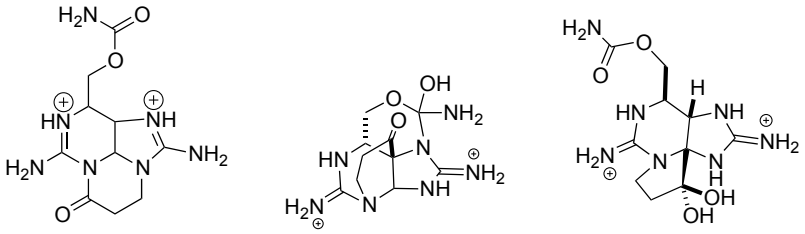


Figure 3 Saxitoxin and proposed structures.

Saxitoxin (**1**) was found to be a tricycle containing a bisguanidine, purine core, a geminal diol and a carbamoyl group. Modifications at five key positions of the core, gives the saxitoxin family (Figure 4). Since the discovery of saxitoxin, over 50 analogs have been isolated and characterized.[11]

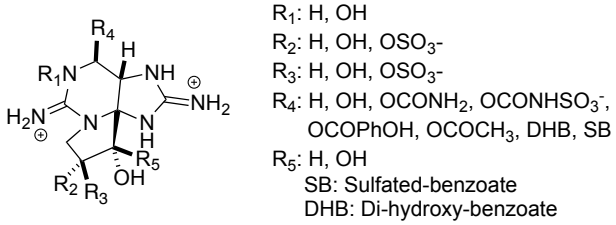


Figure 4 Analogs of saxitoxin

The most notable structures are saxitoxin (**1**), neosaxitoxin (**9**), gonyautoxin 3 (**10**) and the most complex zetekitoxin AB (**11**) (Figure 5).

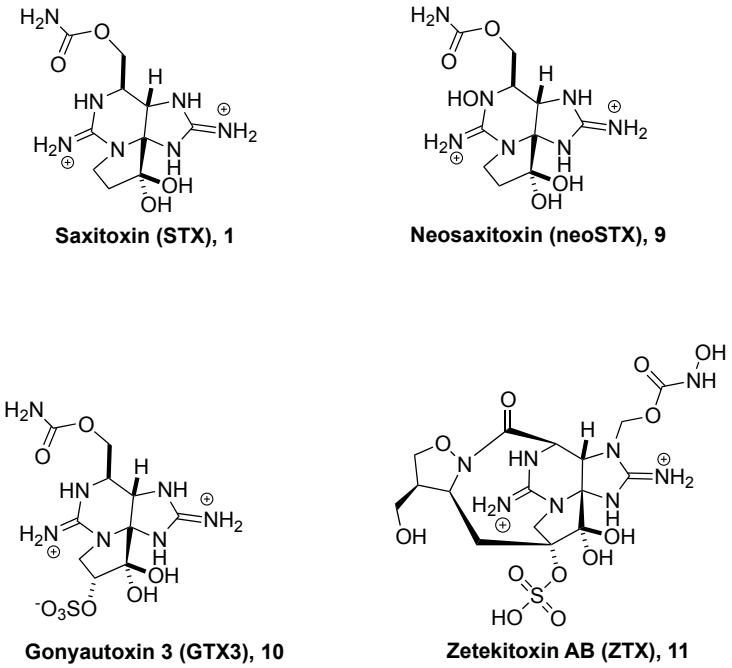


Figure 5 Common saxitoxin analogs

1.2.2 Zetekitoxin AB

Zetekitoxin AB is the most interesting member of the saxitoxin family due to its highly complex structure and extreme toxicity. As such it deserves its own section. First isolated from the skins of the Panamanian golden frog (*Atelopus zeteki*) by Mosher and coworkers in 1969, the toxicity of these brightly colored frogs has been known since the late 1800's.[12] Unlike other *Atelopus sp.*, A. zeteki is only found in a single local region (Valle de Anton) in Panama, where as the other species can be found in northern Panama and Costa Rica.[13] Originally named atelopidtoxin, it was renamed to zetekitoxin AB after isolating tetrodotoxin from *Atelopus varius* and chiriquitoxin from *Atelopus chiriquiensis,* indicating its unique occurrence in *Atelopus zeteki.* The designation AB comes from initial suggestion that it was a mixture of two different toxins. Unlike toxins found in both terrestrial and marine environments like tetrodotoxin, zetekitoxin AB has only been isolated from one species of frog. In fact zetekitoxin AB is the

only terrestrial saxitoxin analog known to date, all other analogs being isolated from marine environments.

Studies on zetekitoxin AB were halted due to the endangerment of the Panamanian golden frog. It wasn't until 2004 when Yotsu-Yamashita and coworkers were able to determine the structure, from a ~0.3 mg sample that was originally collected in the early 1980's.[14]

Amphibian toxins are not biosynthesized within the organism and instead are sequestered from their dietary sources.[15,16] Daly and coworkers were able to demonstrate this by showing frogs raised in captivity do not contain any of the toxins. They were later able to collect various species of arthropods and find many of the amphibian toxins in their extracts.[17] Also, when puffer fish are raised in captivity they contain no toxin. Since the frogs require a specific diet to sequester the toxin, studying the biosynthesis of zetekitoxin AB is not possible at the moment because the dietary source is unknown.

1.2.3 Toxicity

Saxitoxin (**1**) and analogs are potent sodium channel blockers. They work by directly binding to the pore opening of sodium channels cutting off the flow of sodium ions and thereby shutting down nerve signals. Zetekitoxin AB (**11**) is by far the most potent member of the saxitoxin family, exhibiting an IC50 of 280 pm towards human heart cells, making it ~1000 times as potent of saxitoxin (Table 1). Zetekitoxin AB's (**11**) remarkable potency makes it a great target for synthesis, as no natural material can be isolated from nature due to the endangerment of *Atelopus zeteki.*

Table 1 The IC_{50} of Saxitoxin and Zetekitoxin AB on human heart (hH1A), rat brain (μ1), and rat skeletal muscle (rBr2A) voltage-dependent sodium channels**.**

Sodium channel	Human heart	Rat brain	Rat skeletal muscle
Saxitoxin (nM)	160± 14	0.97±0.01	4.1±0.5
Zetekitoxin AB (pM)	280± 3	6.1±0.4	65±10

1.2.4 Human Impact and Control

Paralytic shellfish poisoning is the result of consuming shellfish containing various toxins, such as saxitoxin (**1**). The shellfish accumulate toxins by consuming toxin-producing dinoflagellates. These toxic shellfish result in major losses to the fishing industry due to costly toxin monitoring programs and loss of shellfish. This creates the need to develop cost-effective methods to assay the level of marine toxins found in shellfish.

1.3 Saxitoxin Biogenesis

The origin of the saxitoxin skeleton has been the subject of intense research since its discovery. There were several different proposals of the biogenesis of saxitoxin (Figure 6). Since the core contains a purine skeleton, the simplest possibility is that saxitoxin is derived from a Michael addition of a purine unit into an acrylate type derivative (Figure 6A). Saxitoxin could also be derived from C7 sugar **16** (Figure 6B). The proposal of the saxitoxin skeleton being derived from a unit of arginine (**18**) with an additional C2 building block (Figure 6C) was the best proposal. This is because several other similar guanidine-containing natural products, such as dibromophakellin (**21**) and oroidin (**20**), are hypothesized to come from arginine (Figure 7).[18]

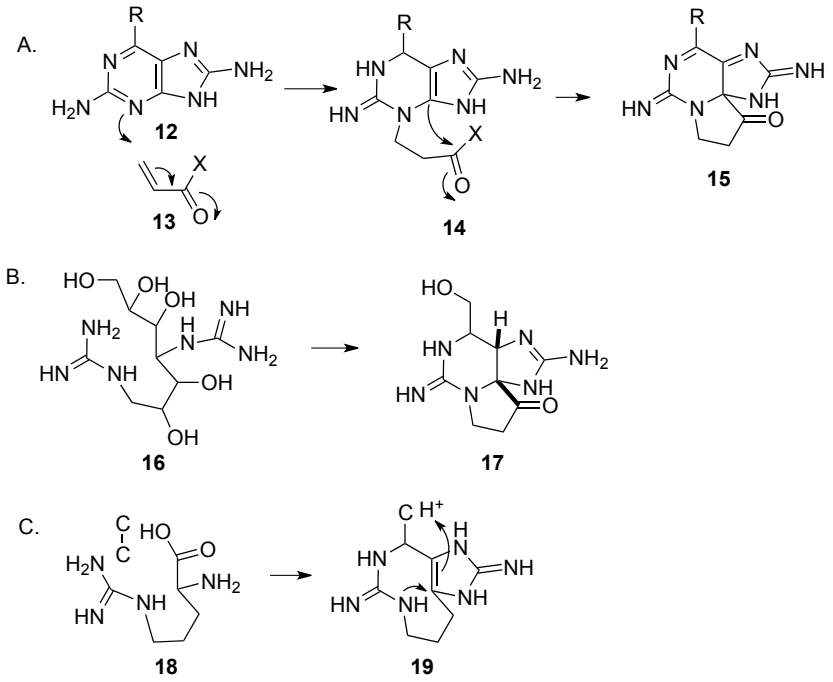


Figure 6 Possible biosynthetic origins of saxitoxin.[19]

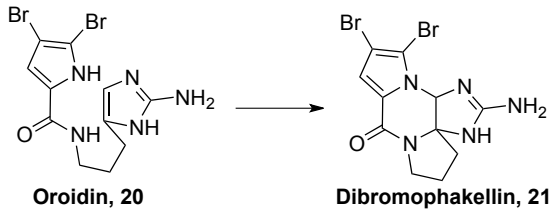
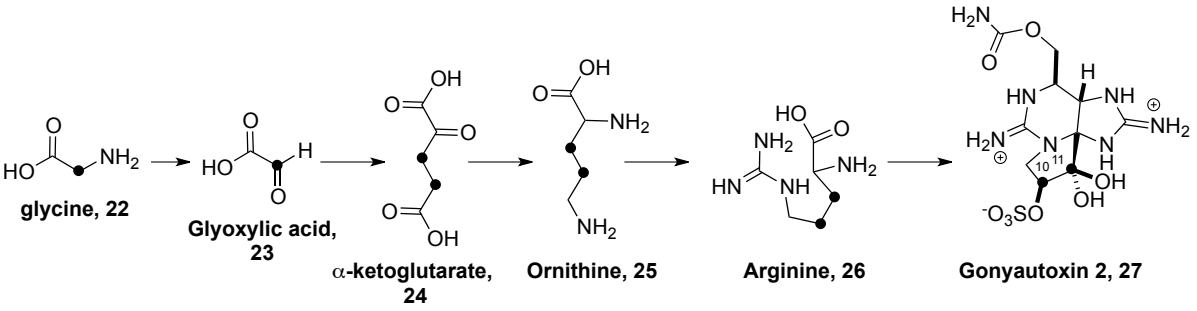


Figure 7 Possible biosynthetic origin of phakellin.

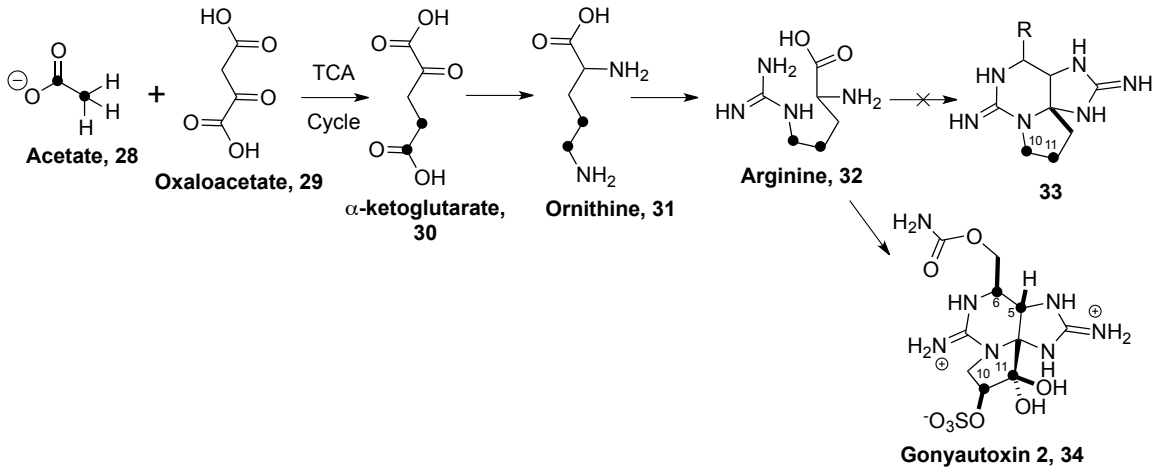
1.3.1 Feeding Experiments

Shimizu and coworkers pioneered the work on saxitoxin biogenesis, by relying heavily on feeding studies. Initial feeding studies with labeled arginine, ornithine, and histidine led to random incorporation of ^{13}C, indicating that they never reached the site of synthesis in intact form.[20] Their first success came when a [2-^{13}C] glycine feeding study showed significantly higher labeling at the C12 and C11.[20] Labeled glycine (**22**) enters the tricarboxylic acid (TCA) cycle, eventually scrambling the radiolabeling at the C3 and C4 position of arginine (**18**), which when incorporated gives [10,11-^{13}C]gonyautoxin 2 (**27**) (Scheme 1).



Scheme 1 [2-^{13}C]Glycine feeding experiment.

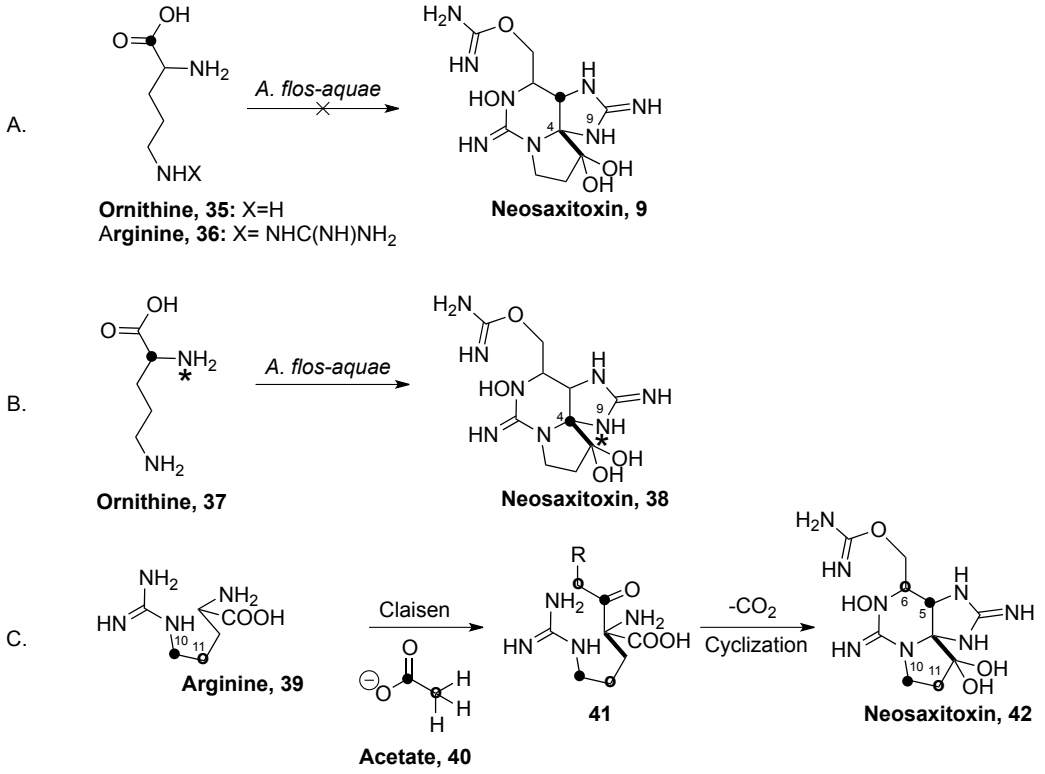
A feeding study of [1,2-^{13}C]acetate (**28**) to *Gonyaulax tamarensis* resulted in an unexpected labeling pattern.[21] Labeled acetate (**28**) should give [10,11-^{13}C]gonyautoxin (**33**), however radiolabeled carbon was also incorporated in the C5 and C6 position giving gonyautoxin **34** (Scheme 2).



Scheme 2 [1,2-^{13}C]Acetate feeding study showing radiolabel incorporation at C10 and C11 and unexpectedly at C5 and C6.

An exciting turn in the elucidation of the biosynthetic pathway came when Shimizu discovered that using *Aphanizomenon flos-aquae,* instead of *Gonyaulax tamarensis,* in feeding studies allowed larger labeled molecules to be absorbed while remaining intact, avoiding the scrambling they observed previously. Feeding studies with labeled [1-^{13}C]arginine **35** and [1-^{13}C]ornithine (**36**) showed no incorporation into neosaxitoxin (Scheme 3A). This indicated

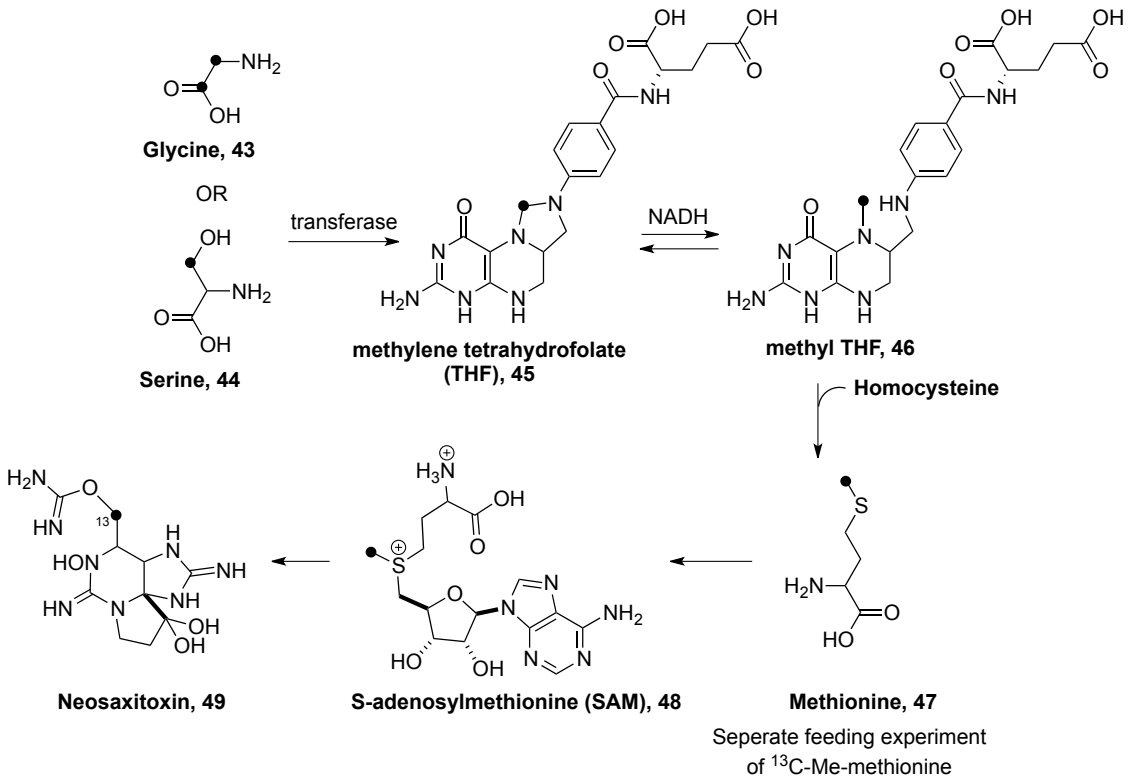
that C1 in arginine was lost during the synthesis as CO_2 and C6 is from a Claisen-type condensation of an acetate unit (Scheme 3C).[21] Further a doubly labeled [2-^{13}C,2-^{15}N]ornithine (**37**) was synthesized and fed to *Aphanizomenon flos-aquae*, which resulted in the expected incorporation into neosaxitoxin (Scheme 3B).[19] Two experiments with mono-labeled acetate showed the direction of the acetate incorporation (Scheme 3C).



Scheme 3 Origin of C5 and C6.

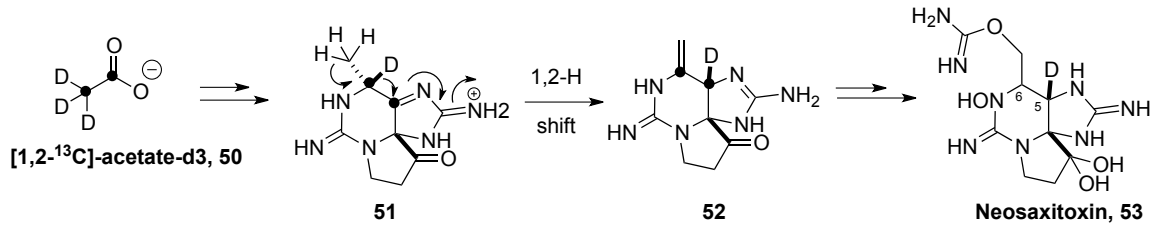
The last piece of the puzzle was the origin of C13. After failed feeding studies with labeled CO_2 and formate, Shimizu observed that feeding [1,2-^{13}C]glycine (**43**) gave [13-^{13}C]neosaxitoxin (**49**). This can be explained by glycine transferring the C2 carbon to tetrahydrofolate, forming methylene tetrahydrofolate (**45**). This was further solidified by a feeding study with [3-^{13}C]serine (**44**), which is a good methyl donor to tetrahydrofolate. Since methylene tetrahydrofolate can transfer a methyl group to methionine making the methylating reagent

S-adenosylmethionine (SAM), a feeding study with [methyl-^{13}C]methionine (**47**) was done. This feeding study resulted in the strongest incorporation of radiolabeling at C13, demonstrating that SAM is the active methylating reagent (Scheme 4).[19]



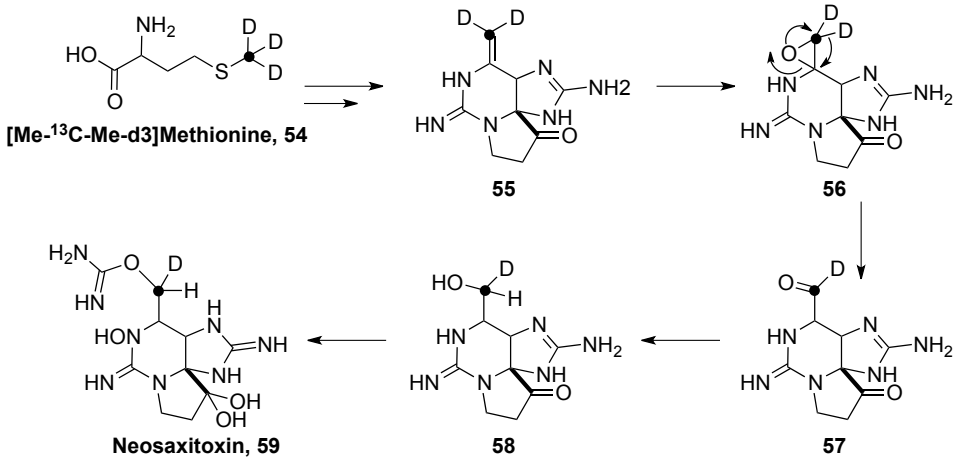
Scheme 4 Origin of C13.

To study the mechanism of the methylation several deuterium labeling experiments were conducted.[22] In the first experiment, [1,2-^{13}C]acetate-d3 (**50**) was fed to *Aphanizomenon flos-aquae* resulting in the incorporation of deuterium at C5, which is indicative of a 1,2-hydride shift (Scheme 5).



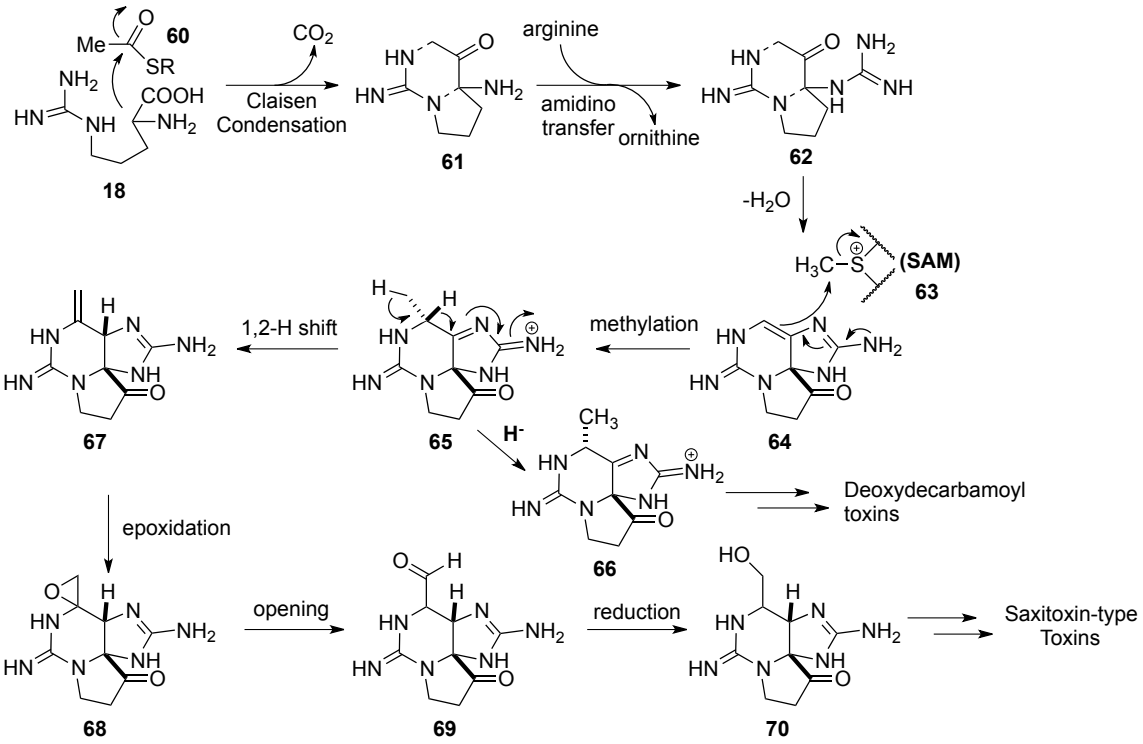
Scheme 5 [1,2-^{13}C]acetate-d3 feeding experiment.

A second feeding study with [Me-^{13}C-Me-*d3*]Methionine (**54**) was conducted showing the loss of one of the methyl deuteriums. This indicates that the methylene is epoxidized followed by ring opening to aldehyde **57**, which is then reduced to the alcohol **58** (Scheme 6).



Scheme 6 [Me-^{13}C-Me-*d3*]Methionine feeding experiment.

After piecing together all of the labeling experiments, Shimizu proposed a biosynthetic pathway (Scheme 7).[23] The biosynthesis of saxitoxin starts with a Claisen-type condensation of an acetate **60** with arginine (**18**) followed by an amidino transfer from guanidine giving **62**. After cyclization of guanidine **62**, C6 is methylated by SAM (**63**). The resulting methyl group undergoes a 1,2-hydride shift to form olefin **67**, which is then epoxidized. Epoxide **68** opens to the aldehyde **69**, which is reduced to alcohol **70**. This proposal is missing a few key details. There is neither indication of the timing of the formation of the 6-membered ring nor any details on how C12 carbon is oxidized.

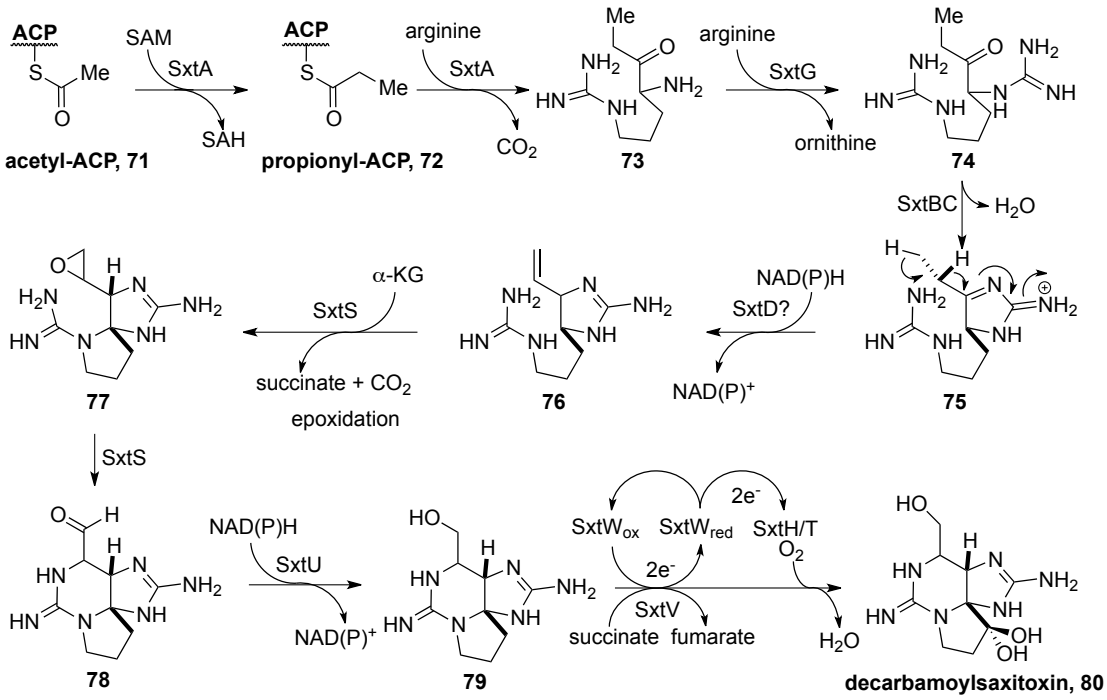


Scheme 7 Hypothetical biosynthesis proposed by Shimizu based of various feeding studies.

1.3.2 Isolation and Characterization of the Saxitoxin Gene Cluster

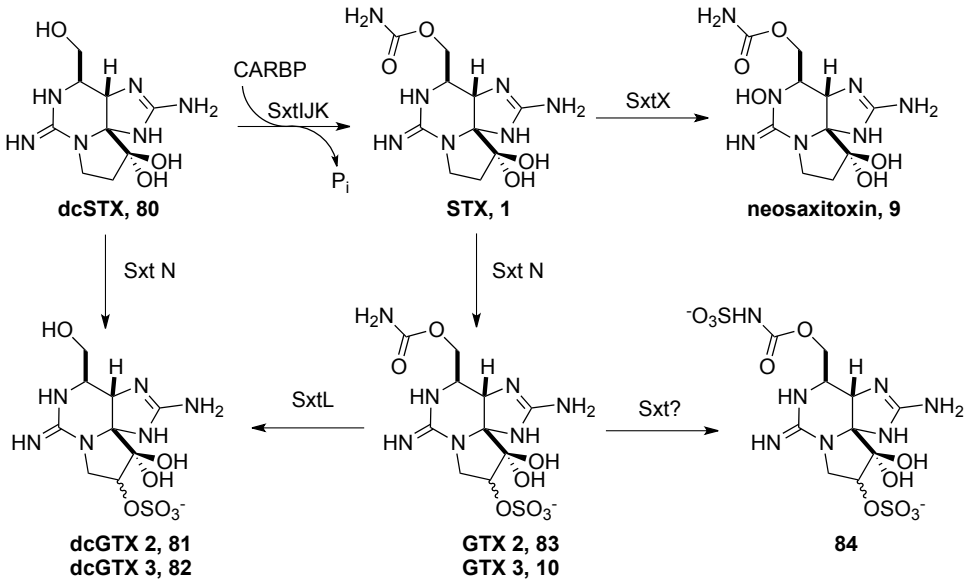
In 2008, many years after Shimizu's research Neilan and coworkers were able to isolate the saxitoxin gene cluster.[24] Neilan cleverly was able to locate the gene cluster by noticing that several other natural products contained a carbamoyl group and that saxitoxin probably had a gene similar to those natural products. He proposed that an O-carbamoyltransferase (OCTASE) was responsible for the installation of the carbamoyl group. By aligning the gene sequence of several different OCTASE gene sequences from different organisms he was able to create a primer sequence that contained degenerate residues in the positions that were not conserved amongst all the different OCTASE genes. Using this synthetic PCR primer Neilan and coworkers were able to use gene-walking techniques to isolate the entire saxitoxin gene cluster. By combining mass spectrometry techniques and a blast analysis, Neilan was able to revise saxitoxin's biosynthetic pathway (Scheme 8).[25] This revised pathway is very similar to

Shimizu's, but it indicates that the cyclization of the 6-membered ring occurs just after the formation of olefin **72**.



Scheme 8 Revised biosynthesis based on STX gene cluster analysis.

Neilan later isolated and compared the genes from several different cyanobacteria that produce different saxitoxin analogs. Using this data he was able to deduce the genes responsible for the various tailoring reactions of saxitoxin analogs (Scheme 9).[26]



Scheme 9 Revised biosynthesis tailoring reactions of dcSTX based on STX gene cluster analysis.

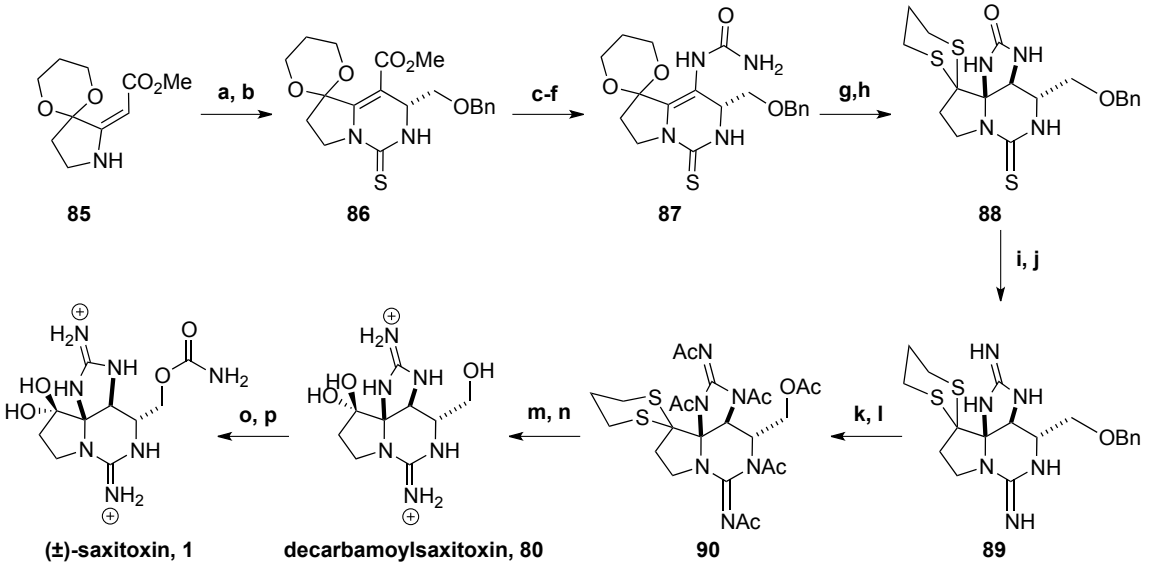
1.4 Previous Synthetic Achievements

Saxitoxin has attracted much attention from the synthetic community since its discovery due to its dense highly substituted core, which contains more heteroatoms than carbons. The highly polar nature of Saxitoxin also leads to new synthetic challenges. A detailed description of all the previous work towards the synthesis of Saxitoxin and its analogs are described in the following sections.

1.4.1 Kishi

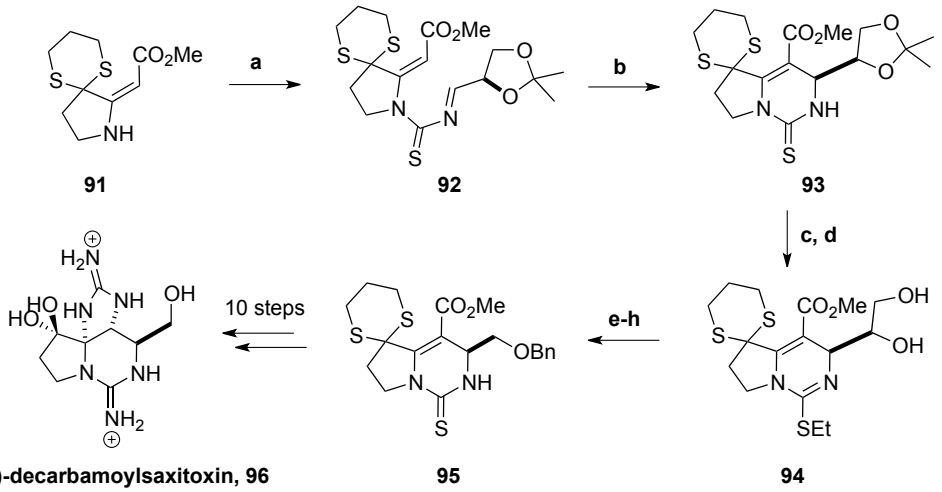
Kishi completed the first total synthesis of (±)-saxitoxin in 1977 (Scheme 10)[27]. Starting from vinylogous carbamate **85**, condensation with benzyloxyacetaldehyde and silicon tetraisothiocyanate followed by a hot toluene workup resulted in bicyclic thiourea ester **86**.[28] Treatment of the ester with hydrazine and then nitrosyl chloride followed by heating in benzene resulted in a Curtius rearrangement, which was quenched with ammonia giving urea **87**. Conversion of the ketal to thioketal was effected by treatment with 1,3-propanedithiol and boron

trifluoride etherate in acetonitrile followed by acidic ring closure of the urea in a warm acetic acid and trifluoroacetic acid mixture giving tricycle **88**. Tricyclic urea **88** was converted to diguanidine **89** by treatment by treatment with triethyloxonium tetrafluoroborate and sodium bicarbonate in dichloromethane followed by heating in ammonium propionate at 135°C. Bisguanidine **89** was debenzylated with boron trichloride in dichloromethane at 0°C and was isolated as the hexaacetate (treated with acetic anhydride and pyridine). Treatment of hexaacetate **90** with N-bromosuccinimide in wet acetonitrile followed by heating in methanol at 100°C gave decarbamoylsaxitoxin (**80**). Decarbamoylsaxitoxin (**80**) was treated with chlorosulfonyl isocyanate in formic acid at 5°C, followed by a hot water workup giving (±)-saxitoxin (**1**).



Scheme 10 Kishi's racemic synthesis of saxitoxin. (a) benzyloxyacetaldehyde, $Si(NCS)_4$, PhH, rt; (b) MePh, 110°C, 75% (2 steps); (c) NH_2NH_2, H_2O, CH_2Cl_2; (d) NOCl, CH_2Cl_2, -50°C; (e) PhH, 90ºC; (f) NH_3, PhH, rt, 75% (4 steps); (g) 1,3-propanedithiol, BF_3•OEt_2, MeCN, rt; (h) AcOH, TFA, 50°C, 18hr, 50%; (i) Et_3OBF_4, $NaHCO_3$, CH_2Cl_2, rt; (j) $EtCO_2NH_4$, 135°C, 33% (2 steps); (k) BCl_3, CH_2Cl_2, 0°C; (l) Ac_2O, py, rt, 75% (2 steps); (m) NBS, wet MeCN, 15°C; (n) MeOH, 100°C, 30% (2 steps); (o) Chlorosulfonyl isocyanate, HCO_2H, 5°C then hot H_2O, 50%

Later, in 1992, Kishi published the asymmetric synthesis of (-)-decarbamoylsaxitoxin (**96**) (Scheme 11) proving that the unnatural enantiomer of saxitoxin was not active towards the sodium channel.[29] This was accomplished using (R)-glyceraldehyde 2,3-acetonide, instead of using benzyloxyacetaldehyde, to induce enantioselectivity in the cyclization reaction. Acetonide **93** was cleaved to the diol with tosylic acid and the thiourea was protected with Meerwein's reagent to give iminothioester **94**. The diol was then cleaved with lead tetraacetate and the resulting aldehyde was reduced with sodium borohydride. The alcohol was benzylated under acidic conditions followed by treatment with hydrogen sulfide to give thiourea **95**. This thiourea was then taken through the same sequence of reactions described above to furnish (-)-decarbamoylsaxitoxin (**96**).

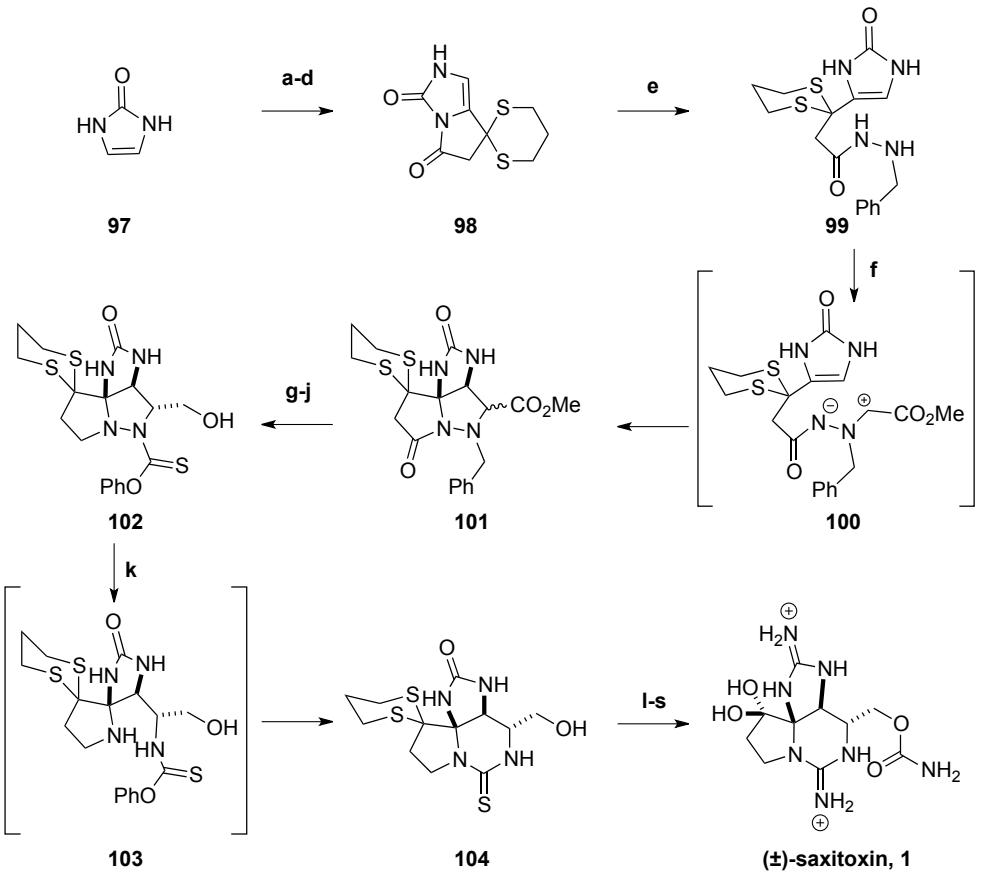


Scheme 11 Kishi's asymmetric synthesis of decarbamoylsaxitoxin. (a) (R)-glyceraldehyde 2,3 acetonide, $Si(NCS)_4$, PhH, rt; (b) MePh, 110°C, 72% (2 steps); (c) p-TsOH, MeOH, quant.; (d) Et_3OBF_4, $NaHCO_3$, CH_2Cl_2, 85%; (e) $Pb(OAc)_4$, EtOAc; (f) $NaBH_4$, MeOH, 0ºC, 82% (2 steps); (g) $Cl_3CC(=NH)OBn$, TfOH, 4Å MS, CH_2Cl_2, 63%; (h) H_2S, 91%

1.4.2 Jacobi

The second synthesis of (±)-saxitoxin was completed by Jacobi in 1984 (Scheme 12).[30] Jacobi started by acylating imidazolone **97** with ethyl 3-chloro-3-oxopropanoate in the

precedence of tin tetrachloride followed by the protection of the carbonyl as the thioketal with 1,3-propanedithiol and boron trifluoride etherate. The ester was then hydrolyzed to the acid with potassium hydroxide and then activated with trifluoroacetic acid anhydride which cyclized to bicyclic imide **98**. The imide was opened with benzylhydrazine and was converted to azomethine imine **100** with methyl glyoxylate hemiacetal and boron trifluoride etherate, which underwent a kinetically controlled 1,3-dipolar cycloaddition giving pyrazolidine derivative **101**.[31] The resulting stereochemistry was corrected by first epimerization with sodium methoxide in methanol followed by reduction of the ester with sodium borohydride. The hydrazide was reduced to the hydrazine with borane dimethyl sulfide complex, which was then debenzylated with transfer hydrogenation conditions and then acylated to give activated species **102**. The activated hydrazine was then submitted to sodium in liquid ammonia, which cleaved the nitrogen-nitrogen bond and spontaneously cyclized to tricycle **104**. Tricycle **104** intercepts Kishi's synthesis and in 5 steps was converted to (±)-saxitoxin.

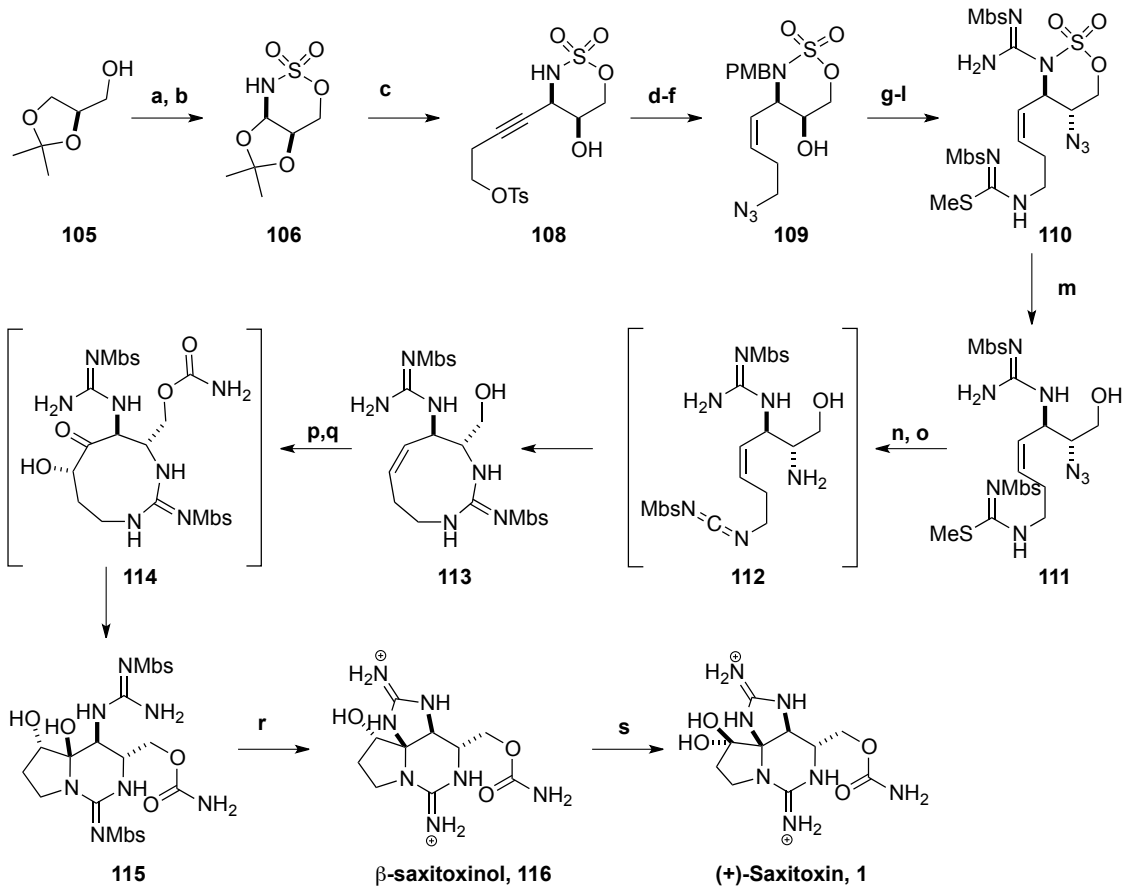


Scheme 12 Jacobi's synthesis of saxitoxin. (a) $ClCOCH_2CO_2Et$, $SnCl_4$, $MeNO_2$, 60%; (b) 1,3-propanedithiol, BF_3•Et_2O, 74%; (c) KOH, H_2O, 80%; (d) TFAA, PhH, 92%; (e) $PhCH_2NHNH_2$, THF, 74%; (f) $MeOCH(OH)CO_2Me$, BF_3•EtO_2; (g) NaOMe, MeOH then $NaBH_4$, 72%; (h) BH_3•DMS, 98%; (i) Pd, AcOH, HCO_2H; (j) PhOCSCl, 80%; (k) Na, NH_3, -78°C; (l) Ac_2O, py.; (m) Et_3OBF_4, $KHCO_3$ (2 steps); (n) $EtCO_2NH_4$, 130°C then Ac_2O, py. 40-50%; (o) NBS, wet MeCN, 15°C; (p) MeOH, 100°C, 30% (2 steps); (q) NBS, wet MeCN, 15°C; (r) MeOH, 100°C, 30% (2 steps); (s) Chlorosulfonyl isocyanate, HCO_2H, 5°C then hot H_2O, 50%

1.4.3 Du Bois

After years of no new saxitoxin synthesis papers, Du Bois published the total synthesis of (+)-saxitoxin (Scheme 13Scheme 10)[32]. Du Bois approach to saxitoxin forms the last ring similarly to Kishi's route, but his strategy proceeds through the initial formation of guanidine containing macrocycle **113**, which contains all the necessary functional groups and stereochemistry. The synthesis starts from (R)-glycerol-2,3-acetonide (**105**), which is sulfamated

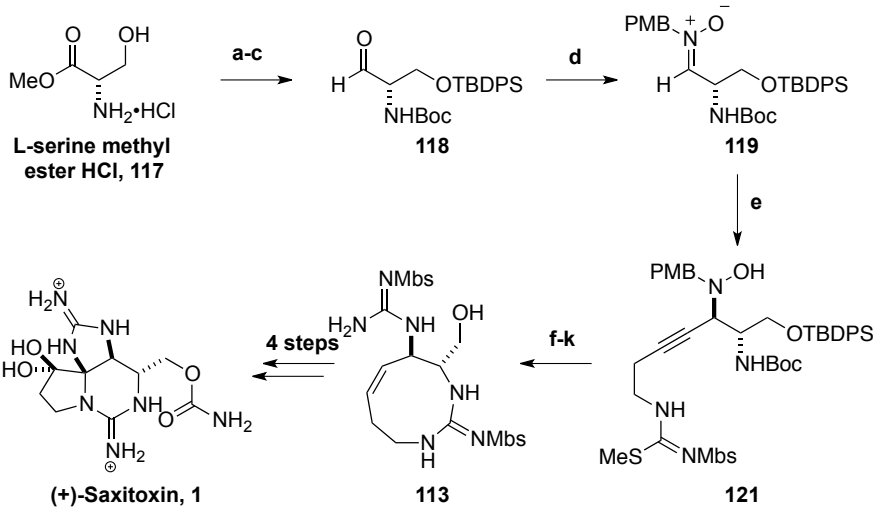
and then submitted to Du Bois' rhodium-catalyzed sulfamate C-H insertion reaction, giving hemiaminal **106**.[33] This hemiaminal undergoes an acid-promoted addition of zinc acetylide **107** giving acetylene **108**.[34] The acetylene was hydrogenated with Lindlar's catalyst to afford the desired cis-olefin followed by displacement of the tosyl group with sodium azide followed by protection of the sulfamate with p-methoxybenzyl chloride. Azide **104** was then reduced with Staudinger's conditions followed by the installation of the pseudothiourea. The alcohol was then converted to the azide by first converting to the tosyl group followed by SN2 displacement by sodium azide. The PMB group was then removed with ceric ammonium nitrate (CAN) and guanidinylated via a two-step process using a N-dichloromethylenesulfonamide followed by displacement of the remaining chloride with hexamethyldisilazane (HMDS) giving guanidine **104**. The sulfamate protecting group was then hydrolyzed in hot aqueous acetonitrile giving azido alcohol **111**. The azide was reduced with trimethylphosphine followed by immediate exposure to silver nitrate and triethylamine, generating carbodiimide **112** which spontaneously cyclized to guanidine-containing 9-membered ring **113**. The primary carbamoyl group was installed by treatment with trichloroacetyl isocyanate. The olefin then underwent stereoselective ketohydroxylation with a catalytic osmium trichloride and Oxone system. Hydroxyketone **114** undergoes spontaneous ring contraction giving [6,5]-ring **115**. Further treatment with boron trifluoroacetate in trifluoroacetic acid (TFA) gave saxitoxinol (**116**), which was oxidized to saxitoxin (**1**) using a Moffatt oxidation (dicyclohexylcarbodiimide (DCC) and dimethyl sulfoxide (DMSO)).



Scheme 13 Du Bois' first-generation synthesis of saxitoxin. (a) $ClSO_2NH_2$, DMA/MeCN (b) 2-4 mol% $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2 92% (2 steps) (c) $TsOCH_2CH_2C{\equiv}CZnCl$, $BF_3{\bullet}OEt_2$, 70% (d) H_2, $Pd/CaCO_3/Pb$, THF; (e) NaN_3, $^nBu_4NI$, DMF, 90% (2 steps); (f) PMBCl, $^nBu_4NI$, K_2CO_3, MeCN, 85%; (g) Me_3P, THF/H_2O; (h) MeS(Cl)C=NMbs, $^iPr_2NEt$, MeCN, 72% (2 steps); (i) Tf_2O, py., DMAP, CH_2Cl_2; (j) NaN_3, DMF, -15°C, 70% (2 steps); (k) CAN, $^tBuOH/CH^2Cl^2$, 74%; (l) KO^tBu, Cl_2C=NMbs; then $(Me_3Si)_2NH$, 70% (+20% of 6); (m) aq. MeCN, 70°C, 95%; (n) Me_3P, THF/H_2O; (o) $AgNO_3$, Et_3N, MeCN, 65% (2 steps); (p) $Cl_3CC(O)NCO$, THF/MeCN, -78°C; then K_2CO_3, MeOH, 82%; (q) 10 mol% of $OsCl_3$, Oxone, Na_2CO_3, EtOAc/MeCN/H_2O, 57%; (r) $B(TFA)_3$, TFA, 82%; (s) DCC, TFA•py., DMSO, 70%. Mbs = p-$MeOC_6H_4SO_2$.

Du Bois later published a second-generation synthesis which was higher yielding and more scalable (Scheme 14).[35] This synthesis changed the preparation of 9-membered ring **113**. The synthesis starts from L-serine methyl ester (**117**) which is converted in 3 steps to aldehyde **118** by first protecting the amine with Boc anhydride (Boc_2O), protection of the alcohol with tert-butyldiphenylsilyl chloride (TBDPSCl) and reduction of the ester with diisobutylaluminum

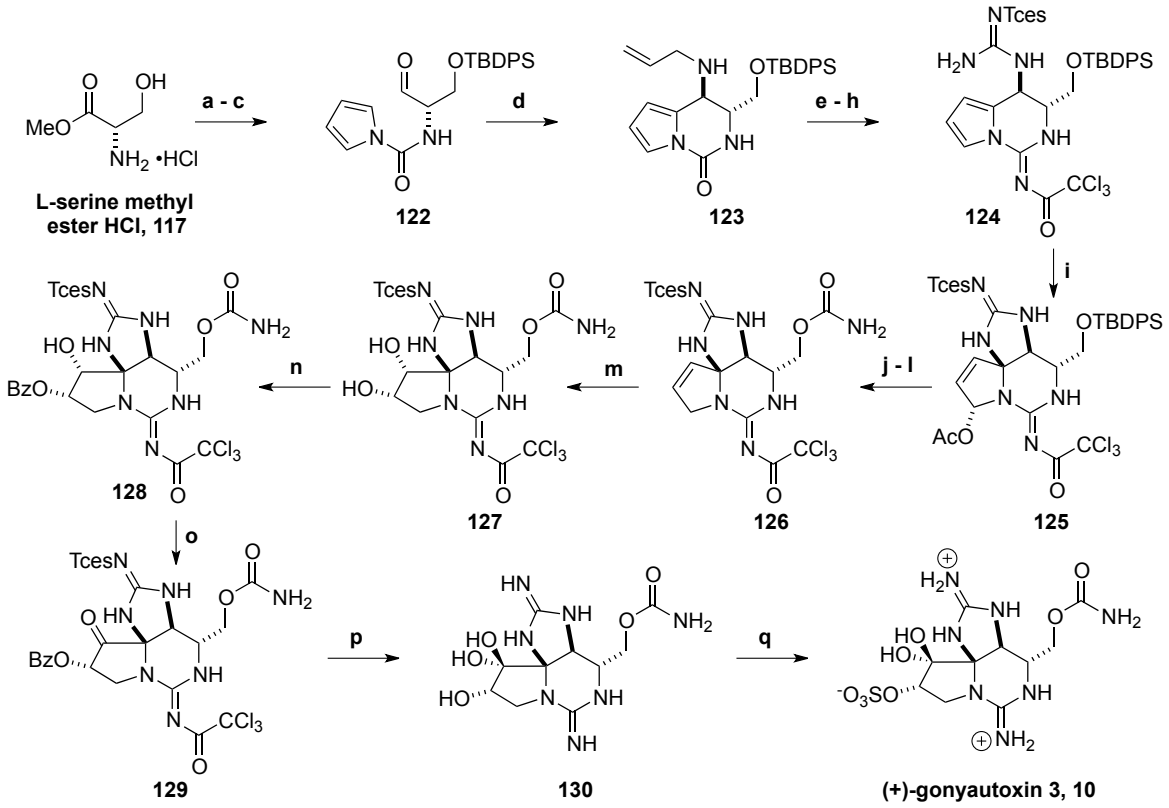
hydride (DIBAL). Aldehyde **118** was converted to nitrone **119** by condensation with N-(4-methoxybenzyl)hydroxylamine followed by nucleophilic attack by magnesium acetylide **120** giving hydroxylamine **121**. This acetylene was converted to 9-member ring **113** in 6 steps (Scheme 14).



Scheme 14 Du Bois' second generation synthesis of saxitoxin. (a) Boc_2O, Et_3N, THF, 95-99% (b) TBDPSCl, im., DMF, 95%; (c) $^{i}Bu_2AlH$, CH_2Cl_2, 71%; (d) PMBNHOH, $MgSO_4$, CH_2Cl_2, 76%; (e) MbsN=C(SMe)NH-$CH_2CH_2C{\equiv}CMgCl$ (**120**), THF, -78°C, 78%; (f) p-$TsNHNH_2$, NaOAc, THF, H_2O, 100°C, 78%; (g) Zn, $Cu(OAc)_2$, AcOH, H_2O, 70°C, 81%; (h) MbsN=C(SMe)NHBoc 65, $HgCl_2$, Et_3N, CH_2Cl_2, 74%; (i) HCl, MeOH, 52%; (j) $AgNO_3$, Et_3N, MeCN, 73%; (k) TFA, 60°C, 91%.

In Du Bois' effort to create many saxitoxin analogs, he later published the total synthesis of gonyautoxin 3 (**10**), for which he came up with new methodology (Scheme 15).[36] This synthesis deviated from Du Bois' original synthesis, as it no longer proceeded through his novel 9-membered ring intermediate. Instead Du Bois uses a rhodium-catalyzed amination reaction, which he developed. The preparation of amination precursor **122** starts by coupling L-serine methyl ester (**117**) to pyrrole-1-carboxylic acid, which is later cyclized in a Pictet-Spengler type reaction to form bicycle **123**.

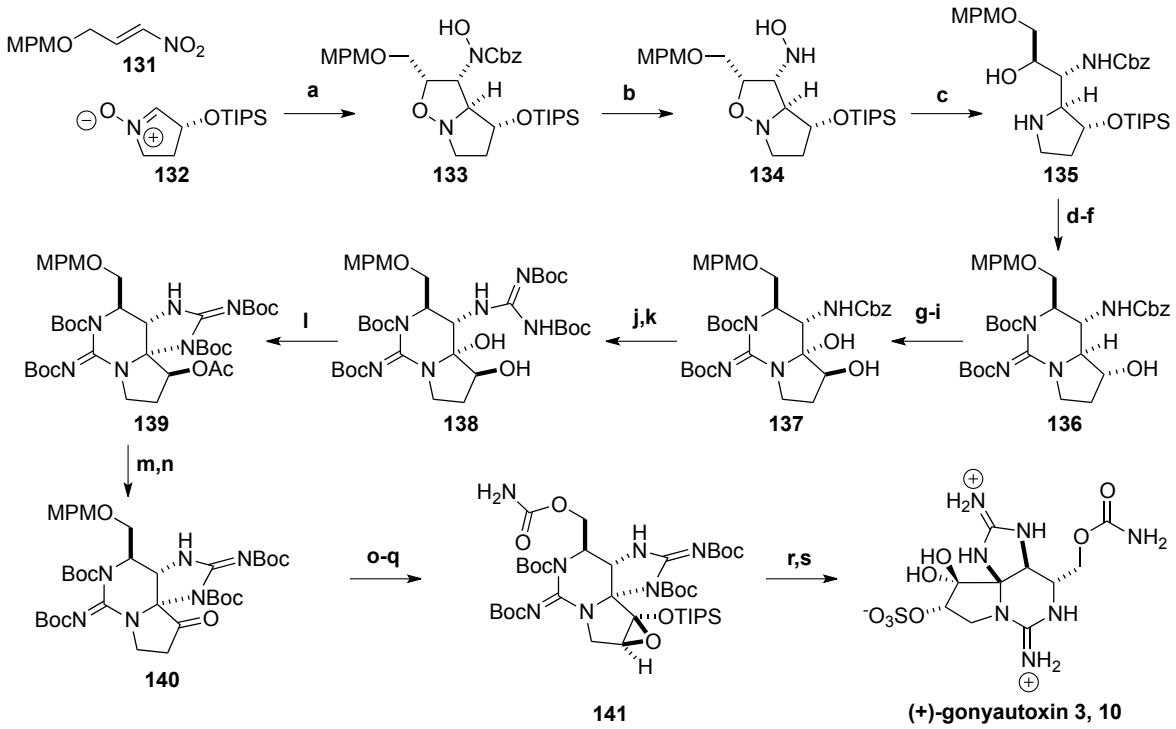
Treatment of precursor **124** with $Rh_2(esp.)_2$ and $PhI(OAc)_2$ generates tricycle **125**, which presumably goes through a nitrene intermediate.[36] Functional group manipulation of tricycle **125** leads to olefin **126**, which is then dihydroxylated to diol **127**, which is further elaborated to gonyautoxin 3 (**10**) in 4 steps.



Scheme 15 Du Bois' synthesis of gonyautoxin 3. (a) pyrrole-1-carboxylic acid, DCC, Et_3N, CH_2Cl_2, 65%; (b) TBDPSCl, im., DMF, 97%; (c) $^{i}Bu_2AlH$, CH_2Cl_2, -90°C; (d) allylamine, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 56% (2 steps, >20:1 trans/cis); (e) $Pd(PPh_3)_4$, 1,3-dimethylbarbituric acid, CH_2Cl_2; then Na_2CO_3, TcesN=C(SMe)Cl, 94%; (f) $EtOSO_2CF_3$, 2,4,6-tri-tert-butylpyrimidine, CH_2Cl_2, 47°C, 78%; (g) NH_3, NH_4OAc, MeOH, 60°C, 82%; (h) $CCl_3C(O)Cl$, $^{i}Pr_2NEt$, CH_2Cl_2, -20°C, 87%; (i) 5 mol% $Rh_2(esp.)_2$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 42°C, 61%; (j) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 81%; (k) $^{n}Bu_4NF$, THF; (l) $Cl_3CC(O)NCO$, CH_2Cl_2, -20°C; then MeOH,76% (2 steps); (m) 2 mol % OsO_4, NMO, THF/H_2O, 81%; (n) PhC(O)CN, DMAP, CH_2Cl_2/MeCN, -78°C, 67%; (o) DMP, CH_2Cl_2, 79%; (p) H_2, Pd/C, TFA, MeOH; then NH_3, MeOH, 83%; (q) $DMF{\cdot}SO_3$, 2,6-di-tert-butyl-4-methylpyridine, NMP, 71%.

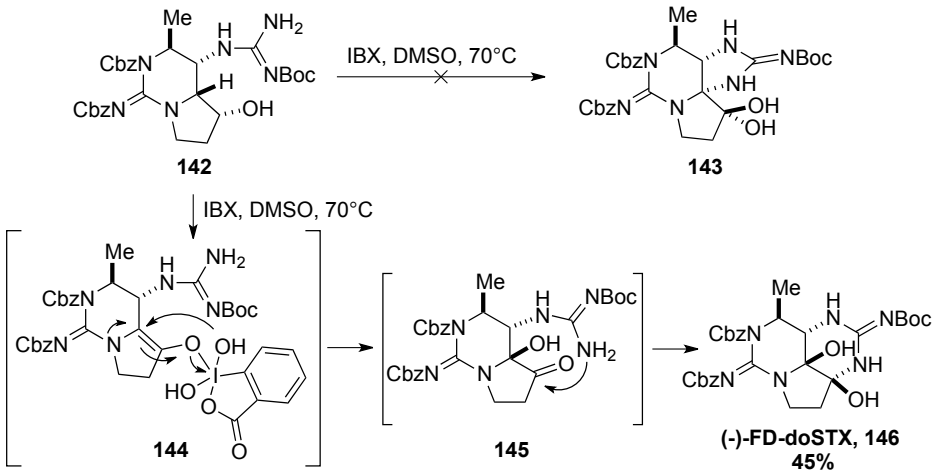
1.4.4 Nagasawa

After publishing the synthesis of decarbamoyloxysaxitoxin in 2007[37] and the synthesis of saxitoxin in 2009,[38] Nagasawa published the second synthesis of (+)-gonyautoxin 3 (**10**) (Scheme 16) using his previously developed methodology.[39] This synthesis starts by utilizing a 1,3-dipolar cycloaddition between methyl crotonate **131** and nitrone **132** to install the required stereocenters. Functional group manipulation and guanidine installation leads to bicycle **136**. Nagasawa utilizes a novel 2-iodoxybenzoic acid (IBX) oxidation to install the required hemiaminal. The last ring was closed by first activating the hemiaminal with an acetate and then zinc chloride-promoted ring closure. Protecting group manipulation followed by oxidation gave ketone **140**, which could be elaborated to decarbamoylsaxitoxin. To further elaborate this substrate to gonyautoxin 3, Nagasawa forms the triisopropylsilyl (TIPS) enol ether, which is then epoxidized to give compound **141**, which is then opened to the alcohol. The alcohol was then sulfated using Du Bois' conditions to give gonyautoxin 3 (**10**).



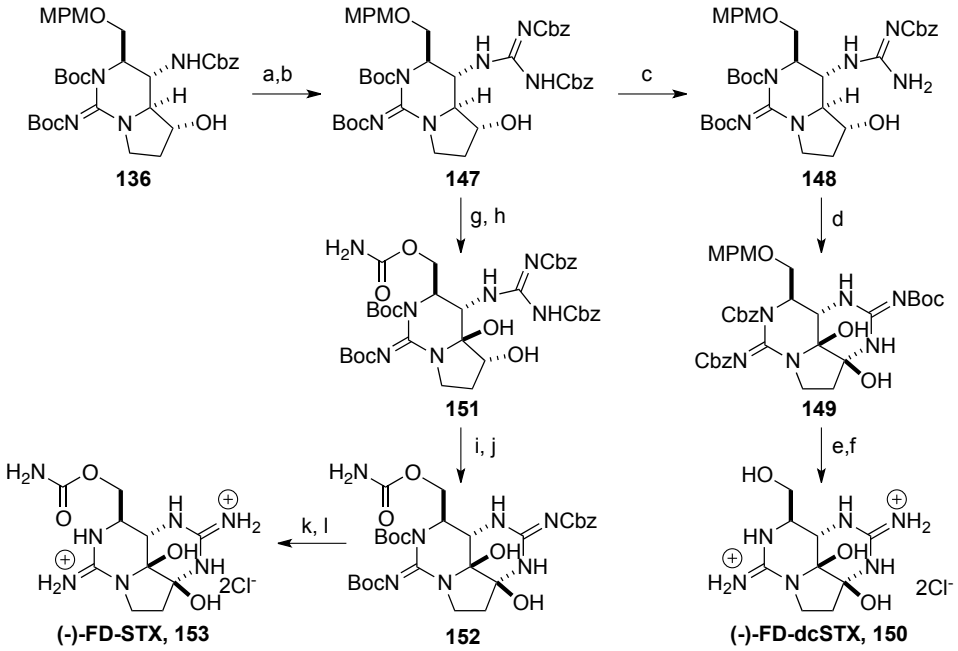
Scheme 16 Nagasawa's synthesis of gonyautoxin 3. (a) No solvent, 40°C then DBU, CH_2Cl_2, -60°C then Zn dust, AcOH, -60°C to r.t. 70%; (b) CbzCl, K_2CO_3, CH_2Cl_2, 0°C then MeOH, r.t; (c) $TiCl_3$, Zn dust NaOAc, HCl, MeOH CH_2Cl_2, 0°C; (d) BocN=(SMe)NHBoc, $HgCl_2$, Et_3N, DMF; (e) $ClCH_2SO_2Cl$, $^iPr_2NEt$, CH_2Cl_2, 98%; (f) TBAF, THF, 0°C, 83%; (g) $(COCl)_2$, DMSO, Et_3N, -78°C; (h) IBX, DMSO, Et_3N, 50°C, 94%; (i) $NaBH_4$, MeOH, 0°C, 77%; (j) $Pd(OH)_2/C$, H_2, MeOH; (k) BocN=(SMe)NHBoc, $HgCl_2$, Et_3N, DMF 60% (2 steps); (l) i. Ac_2O, cat. DMAP, py. then evaporate ii. $ZnCl_2$, CH_2Cl_2 98% one pot; (m) K_2CO_3, MeOH, 0°C, 94%; (n) DMP, CH_2Cl_2 99%; (o) NaHMDS CH_2Cl_2, -40°C then TIPSCl, 97%; (p) *m*CPBA, CH_2Cl_2, aq. $NaHCO_3$, 33%; (q) CH_2Cl_2 0°C then Et_3N, MeOH, 76%; (r) TFA then H_2O; (s) SO_3-DMF 2,6-$^tBu_2$-4-Me-Py, NMP, 51% (2 steps).

During Nagasawa's studies towards the synthesis of saxitoxin he came across an interesting byproduct. When alcohol **142** was treated with IBX and DMSO, instead of getting aminal **143**, he obtained hemiaminal **146** in a 45% yield. Looking into the mechanism gave him the idea of using oxalyl chloride instead of IBX, which would prevent the hydroxyl transfer shown in intermediate **144**.



Scheme 17 Unexpected cyclization

Even though byproduct **146** was unexpected, Nagasawa was interested in the biological properties of this type of compound and decided to synthesize some other similar analogs and test their ability to block sodium channels (Scheme 18).[40] Once saxitoxin analogs (-)-FD-STX (**153**), (-)-FD-dcSTX (**150**), and (-)-FD-doSTX (**146**) were prepared they were tested for activity. Patch clamp studies with $Na_v1.4$ (TTX sensitive) and $Na_v1.5$ (TTX resistant) channels were tested with both (-)-FD-STX (**153**) and (-)-FD-dcSTX (**150**). (-)-FD-STX (**153**) showed concentration-dependent inhibitory effect with IC_{50} values of 3.8 and 118 μm towards $Na_v1.4$ and $Na_v1.5$ respectively. (-)-FD-dcSTX (**121)** showed concentration-dependent inhibitory effect with IC_{50} values 16 and 182 μm towards $Na_v1.4$ and $Na_v1.5$ respectively. On the other hand, (-)-FD-doSTX (**146**) showed no activity. Interestingly, (-)-FD-dcSTX (**150**) showed irreversible binding to the sodium channel, which is unprecedented for all STX and TTX type molecules. This irreversible binding is currently under investigation.

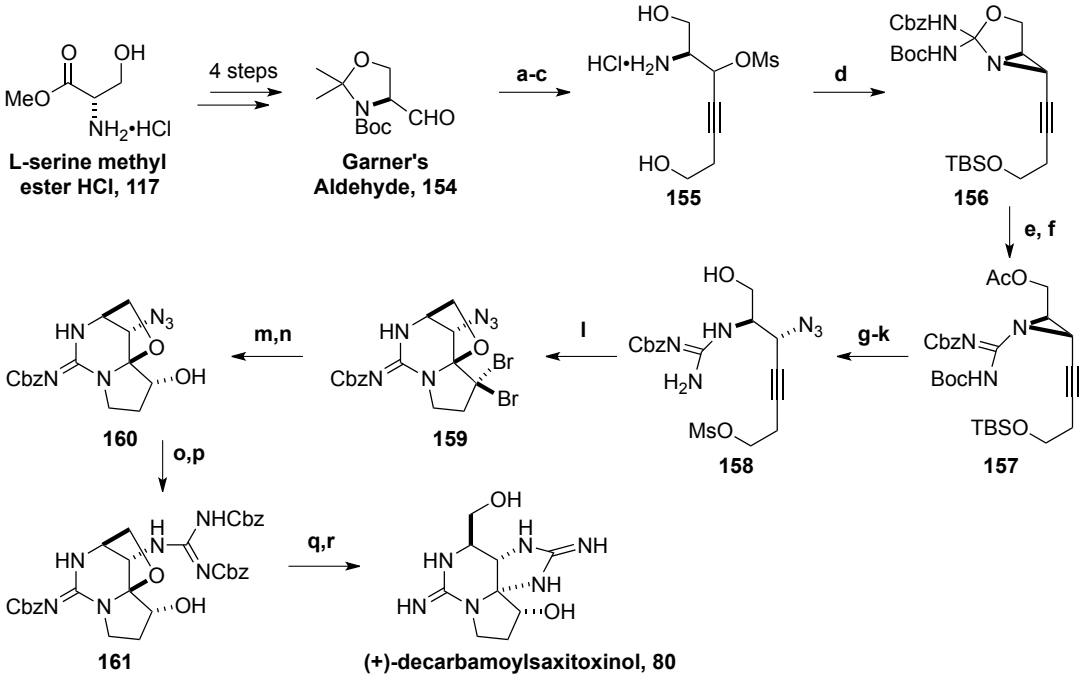


Scheme 18 Synthesis of tricyclic saxitoxin analogs. (a) H_2, $Pd(OH)_2/C$, MeOH; b) CbzN=C(SMe)NHCbz, $HgCl_2$, Et_3N, DMF, 85%(2 steps); c) NaOMe, THF/MeOH, 0°C, 65%; d) IBX, DMSO, 70°C, 24%; e) H_2, $Pd(OH)_2/C$, MeOH; f) 3N HCl, 78% (2 steps); g) Ac_2O, pyridine (py), 50°8C, 96%; h) DDQ, CH_2Cl_2, H_2O, 94%; (i) trichloroacetyl isocyanate, CH_2Cl_2, then K_2CO_3, MeOH, 34%; j) IBX, DMSO, 70°C, 20%; k) H_2, $Pd(OH)_2/C$, MeOH; l) TFA, CH_2Cl_2, 82% (2 steps).

1.4.5 Nishikawa

Nishikawa takes a completely different approach towards saxitoxin analogs (Scheme 19) by utilizing a bromocyclization of propargyl and homopropargyl guanidines.[41] Using this approach, Nishikawa published the synthesis of decarbamoylsaxitoxinol in 2011.[42] Starting from Garner's aldehyde (derived from L-serine) in 3 steps Nishikawa prepared alkyne **155**, which was guanidinylated with concomitant displacement of the mesylate and hemiaminal formation giving aziridine alkyne **156**. Sodium azide opening of the aziridine, deprotection and mesylation of the primary alcohol, acetate deprotection and Boc deprotection gave cyclization precursor **158**. When alkyne **158** was treated with pyridinium hydrobromide perbromide ($pyHBr_3$) and potassium carbonate in dichloromethane it underwent cyclization to intermediate **159**. Azide **160** was then reduced with trimethylphosphine and the final guanidine was installed. Removal

of the N-benzyloxycarbamoyl (Cbz) groups by hydrogenation over palladium on carbon, followed by treatment with boron trifluoroacetate in trifluoroacetic acid, furnished decarbamoylsaxitoxinol (**80**) in good yield.

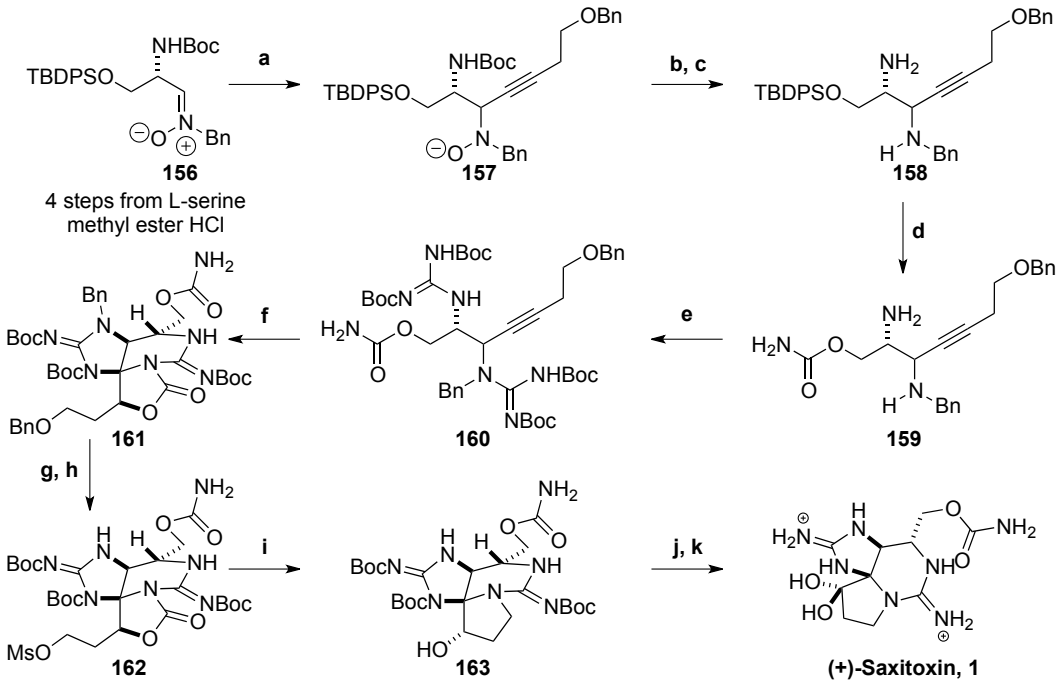


Scheme 19 Nishikawa's synthesis of decarbamoylsaxitoxinol. (a) TBSOCH2CH2C≡CH, ^{n}BuLi, HMPA toluene, -78°C, 54%; (b) MsCl, Et_3N, CH_2Cl_2 r.t quant.; (c) TFA, CH_2Cl_2, H_2O then Amberlite IRA-410, MeOH; (d) Et_3N, DMF then CbzN=C(SMe)NHBoc, $HgCl_2$ Et_3N DMF, 95% (3 steps); (e) TBSCl, Et_3N, CH_2Cl_2, DMF, r.t. (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, r.t., 90% (2 steps); (g) NaN_3 DMF, r.t; (h) TBAF, THF, r.t; (i) MsCl, Et_3N, 0°C to r.t.; (j) KCN, EtOH, r.t; (k) TFA, CH_2Cl_2, r.t; (l) $PyHBr_3$, K_2CO_3, CH_2Cl_2, H_2O, 24% (6 steps); (m) Ac_2O, Et_3N, CH_2Cl_2; (n) $NaBH_4$, MeOH 32% (2 steps); (o) Me_3P, CH_2Cl_2 then MeOH/12M HCl (5:1); (p) CbzN=C(SMe)NHCbz, $HgCl_2$, Et_3N, DMF, 60°C, 51% (2 steps); (q) 10% Pd/C, H_2, MeOH, EtOAc; (r) $B(TFA)_3$, TFA, 73% (2 steps).

1.4.6 Looper

Just after Nishikawa published the synthesis of decarbamoylsaxitoxinol, Looper and coworkers published the elegant synthesis of saxitoxin using a similar approach (Scheme 20).[43] Like Nishikawa, Looper also cyclized a propargyl guanidine, but he utilized his silver acetate-promoted cyclization methodology.[44] Starting with a similar pathway as Du Bois, Looper was

able to assemble propargyl/homopropargyl bisguanidine **160** in 9 steps from L-serine methyl ester. Propargyl guanine **160** was transformed into tricycle **161** by adding 1 equivalent of silver acetate followed by another equivalent of silver acetate and 2 equivalents iodine followed by 5 equivalents of acetic acid (AcOH). Tricycle **161** was hydrogenated over palladium hydroxide followed by mesylation of the primary alcohol. Hydrolysis of oxazolidinone **162** with cesium carbonate in ethanol gave the alcohol, which underwent spontaneous cyclization to the tricyclic core **163**. Alcohol **163** was oxidized with Dess-Martin periodinane (DMP) and deprotected with trifluoroacetic acid to give (+)-saxitoxin (**1**) in good yield.



Scheme 20 Looper's synthesis of saxitoxin. (a) $BnOCH_2CH_2C{\equiv}CH$, $^{i}PrMgCl$, THF -78°C to -55°C 9:1 dr (86% brsm); (b) $Cu(OAc)_2$, Zn, AcOH, H_2O, 92%; (c) 1M HCl in MeOH 40°C, 89%; (d) KOCN, MsCl, CH_2Cl_2, 78%; (e) BocN=C(MeS)NHBoc, HgO, Et_3N, CH_2Cl_2, 83%; (f) i. AgOAc (1eq.) ii. AgOAc (1eq.), I_2 (2eq.) iii. AcOH (5eq.) 57-67%; (g) $Pd(OH)_2$, $^{i}PrOH$ H_2 @ 80 PSI, 67%; (h) MsCl, Et_3N, DMAP, CH_2Cl_2, 77%; (i) Cs_2CO_3, EtOH, 0°C to r.t, 61%; (j) DMP, CH_2Cl_2; (k) TFA, CH_2Cl_2 81% (2 steps)

1.5 Conclusion and Goals

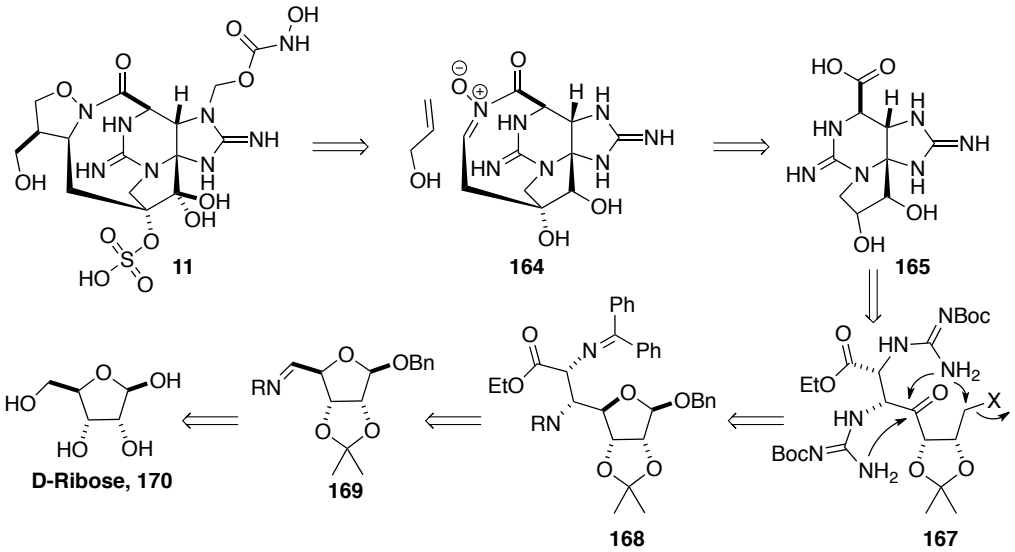
Saxitoxin and its analogs have attracted the attention of many researchers since its discovery. Recently, isolation of the biosynthetic gene cluster and many years of feeding studies have allowed the biosynthetic pathway to be elucidated. Synthetic achievements by numerous chemists have allowed the synthesis of many natural products and analogs. The combined effort of chemists and biologists has given us a better understanding of sodium and other ion channels resulting in a better understanding of neuroscience.

This research will focus on total synthesis of saxitoxin analogs, Zetekitoxin AB being the primary goal. The total synthesis of Zetekitoxin AB will prove (or disprove) the structural assignment and advance methodology in the synthesis of these dense, highly functionalized polar molecules. Synthesis will allow a variety of analogs to be produced, which can be used towards the development of molecular probes and/or pharmaceuticals.

Chapter 2: Synthesis of Saxitoxin Analogs

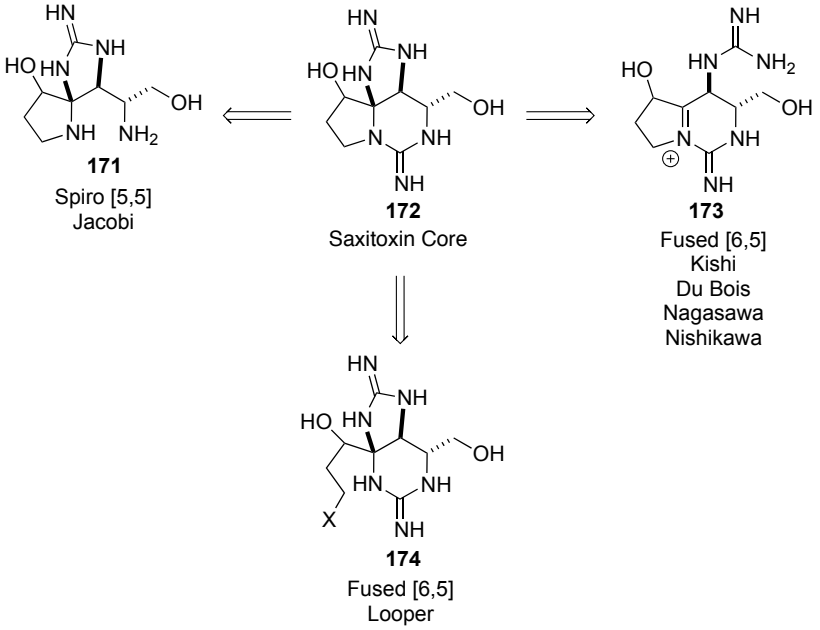
Retrosynthetic Analysis of Zetekitoxin AB

A retrosynthetic analysis of Zetekitoxin AB (**11**) reveals that it could arise from core structure **165**, followed by a late stage installation of the oxazolidine (Scheme 21). This oxazolidine could come from a 1,3-dipolar cycloaddition of allyl alcohol on nitrone **164**. The sulfate ester and N-hydroxycarbamoyl group would be installed at the very end of the synthesis. The core structure **165**, which is very similar to saxitoxin, could arise from the condensation of two guanidines on a central carbonyl and the nucleophilic attack on carbon 12, displacing a leaving group. The order of these cyclizations can be changed allowing many different approaches in this synthesis. Ketone **167** could arise from protected diamino ester **168**, which in turn could be formed from a Mannich-type reaction on ribose-derived imine **169**. Mannich precursor **169** could be formed from D-ribose (**8**) in a few steps. D-Ribose was chosen as a starting material because it contains the entire backbone of saxitoxin and all the necessary functional group handles minus a glycine equivalent.



Scheme 21 **Retrosynthesis of zetekitoxin AB.**

Initial investigation into the synthesis of zetekitoxin AB (**11**) began with the study of saxitoxin (**1**), as it is the core. Disconnecting one of the three rings of saxitoxin reveals three different approaches to the bicycle (Scheme 22). All three of these intermediates have been used in the synthesis of saxitoxin and its analogs.[27,30,32,37,41,43] The current retrosynthetic plan should allow access to all three of these intermediates. Determining which of these three routes will be useful for the D-ribose approach represents a major synthetic challenge, as there are essentially unlimited choices to explore. The first step in this synthesis is the development of a successful Mannich reaction so that each of these intermediates can be explored.



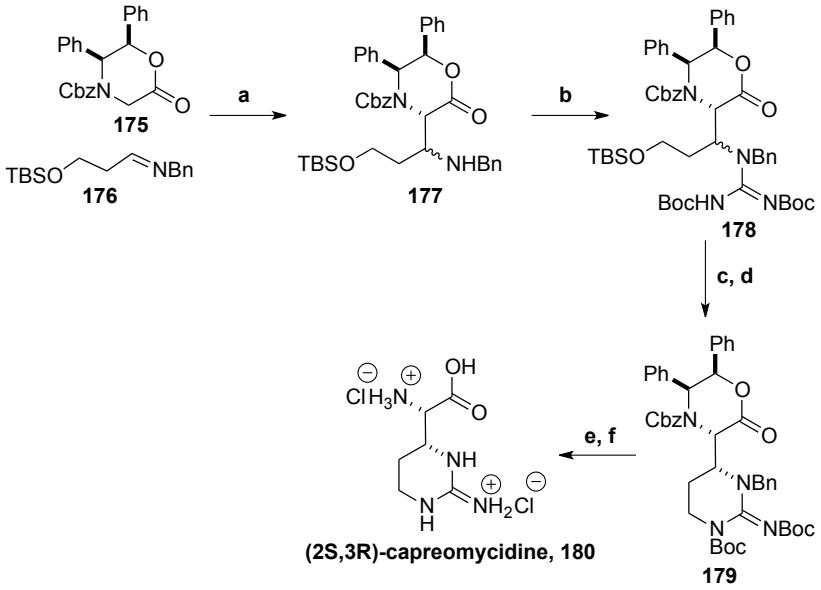
Scheme 22 **Previous breakdown of saxitoxin core.**

2.1 Development of the Mannich Reaction

2.1.1 Precedence

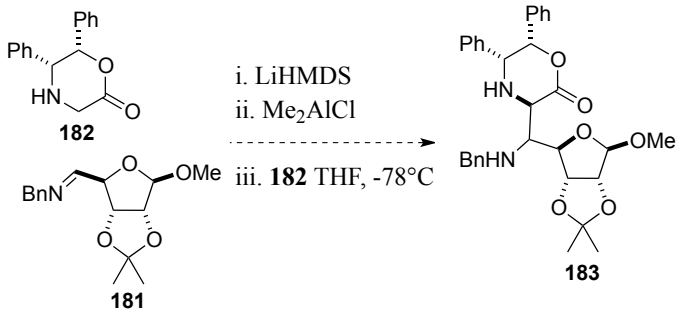
There are a variety of natural products and therapeutic compounds that contain α,β-diaminoacids.[45] Previous group research established the usefulness of the Mannich in the

total synthesis of (2S,3R)-capreomycidine (**180**) (Scheme 23).[46] The key step in this sequence is the addition of the aluminum enolate of Williams' glycine template **175** to imine **176**. This reaction proved to be very difficult as most imine substrates for this reaction failed to give any product. This demonstrated that the reaction was very substrate dependent, which would make it very difficult to apply towards the synthesis of saxitoxin.



Scheme 23 Williams' synthesis of capreomycidine. (a) i. LiHMDS ii. Me_2AlCl iii. 9 THF, -78°C, 60% (b) BocN=C(SMe)NHBoc, Et_3N, AgOTf, DMF, rt, 3hr. 74% (c) 1.7% HF, MeCN, rt, 2 hr., 70-91% (d) DIAD, PPh_3, THF, 0°C, 15 min to rt 1 hr. 87% (e) H_2, $PdCl_2$, 115 psi, 4 days (f) 0.5M HCl, Δ 1.5 hr. 95% (2 steps)

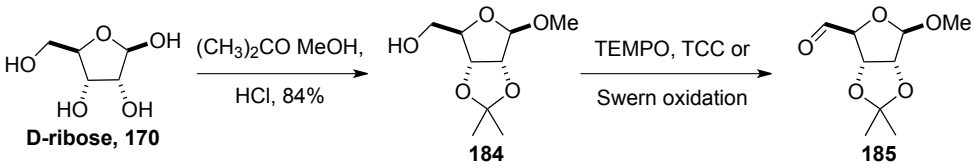
The goal was to use ribose-derived imine **181** and Williams' lactone **182** to form the saxitoxin backbone with the desired stereochemistry in a manner similar to the above precedents (Scheme 24).



Scheme 24 Proposed Mannich reaction.

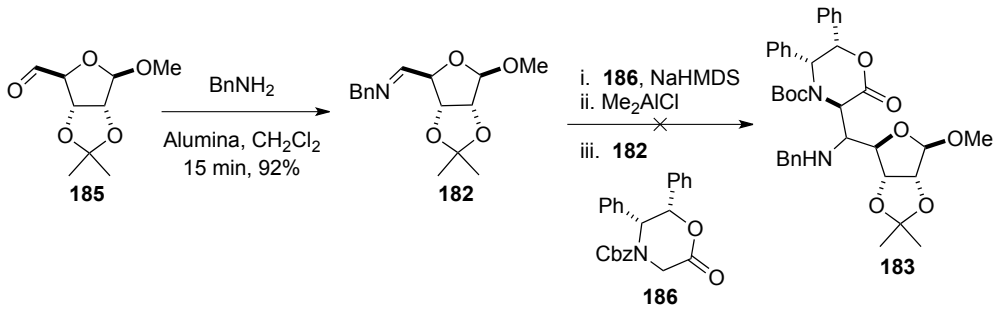
2.1.2 Initial Attempts

To test out the Mannich reaction the imine of protected ribose was synthesized in 3 steps. The diol and lactol of ribose were protected in a single step by treating ribose with acetone and methanol in the presence of hydrochloric acid (Scheme 25).[47] With protected ribose **185** in hand, it was then submitted to Swern oxidation conditions, which gave the aldehyde in a 79% yield.[48] It was later discovered that a TEMPO and TCC oxidation was superior to the Swern oxidation because it was complete in 15 min. and required no column chromatography.[49,50]



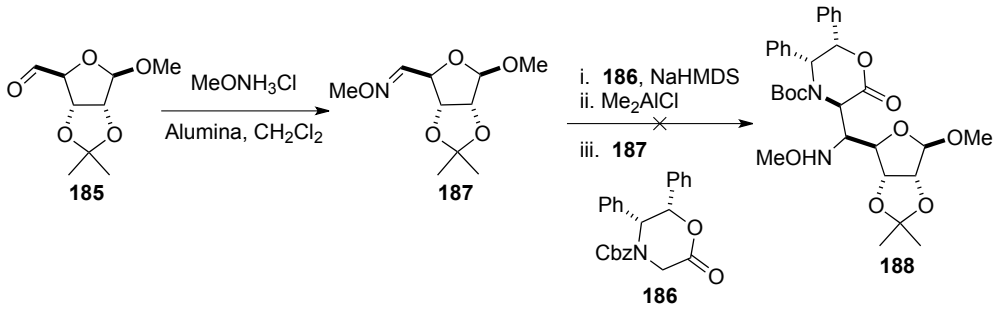
Scheme 25 Formation of ribose derived aldehyde **185**.

Ribose-derived aldehyde **185** was treated with benzylamine and alumina to give benzylimine **182**. This imine was then subjected to the conditions previously developed in the group. After treatment of the Williams' lactone with NaHMDS followed by transmetallation with dimethylaluminum chloride, benzyl imine **182** was added. Unfortunately, the reaction only led to the recovery of starting material.



Scheme 26 Initial Mannich reaction attempts.

Since there was no reaction with benzylimine **182**, O-methyloxime **187** was prepared because it is much smaller and a successful reaction would indicate that the problem is due to the sterics of the benzyl group. Oxime **187** was submitted to the same conditions, resulting only in the recovery of starting material. Since this reaction did not give any product it was assumed that the reaction was failing because the imine was not electrophilic enough for the addition of the aluminum enolate. This result was not too surprising because in the synthesis of capreomycidine (**180**), as mentioned earlier, the Mannich reaction was found to be very substrate dependent.



Scheme 27 Failed Mannich reaction

2.1.3 Masked Imines as Reactive Mannich Precursors

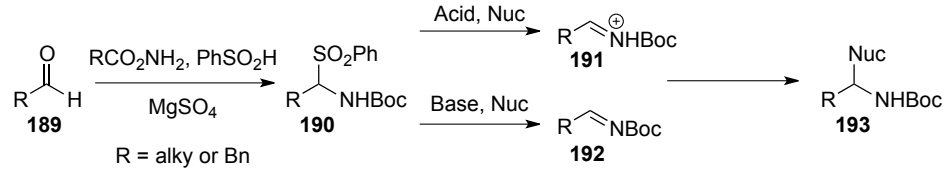
To overcome this synthetic hurdle, it was thought that installing a strong electron-withdrawing group on the nitrogen would lead to a successful reaction. In literature, most Mannich reactions use tosyl imines or imines derived from aniline to activate imines for

nucleophilic attack.[51] These imines are not very useful in this synthesis because of the harsh reaction conditions required to deprotect the resulting amine. There are two criteria that need to be met in order for the Mannich product to be useful. First the withdrawing group needs to be easy to remove and second it must be stable to the basic nucleophilic conditions required for the Mannich reaction.

After careful examination of various amine-protecting groups, the carbamate protecting groups seemed to be the best choice as they can be conveniently removed under a variety of different conditions. A literature study into acyliminium ions and acylimines indicated that they were not stable intermediates and hydrolyze rapidly. This also indicates that they should be highly reactive electrophiles in the desired Mannich reaction. The majority of acyliminium or acylimines in literature were masked and then formed in-situ. Such examples are benzotriazole and sulfone adducts of acylimines.[52,53] Petrini and coworkers have pioneered the use of α-amido sulfones, demonstrating their stability and versatility in chemical synthesis.[53] The standard conditions used to prepare amido sulfones use the appropriate aldehyde, sodium benzenesulfinate, and a carbamate in the presence of formic acid.[54] After developing these conditions, Petrini and coworkers developed methodology to prepare amido sulfones from acid-sensitive aldehydes using a carbamate, benzenesulfinic acid and magnesium sulfate as a dehydrating agent.[55]

Amido sulfones are versatile because they eliminate under acidic or basic conditions to generate acyliminium ions (**191**) or acylimines (**192**), which can undergo addition reactions by a variety of different nucleophiles (Scheme 28). This allows the simultaneous formation of electrophilic acylimines (**192**) and nucleophilic metal enolates under basic conditions and acyliminium ions (**191**) and enols under acidic conditions, allowing for the formation of a

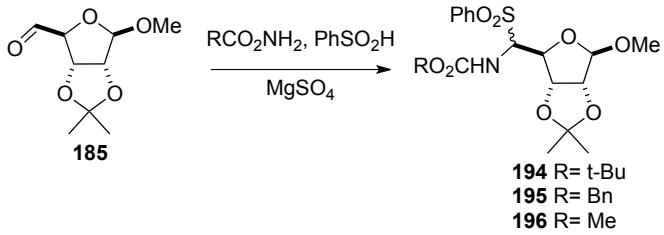
carbon-carbon bond. This methodology looked promising and was applied towards the synthesis of saxitoxin analogs.



Scheme 28 Amido sulfones.

2.1.4 Successful Mannich Reaction

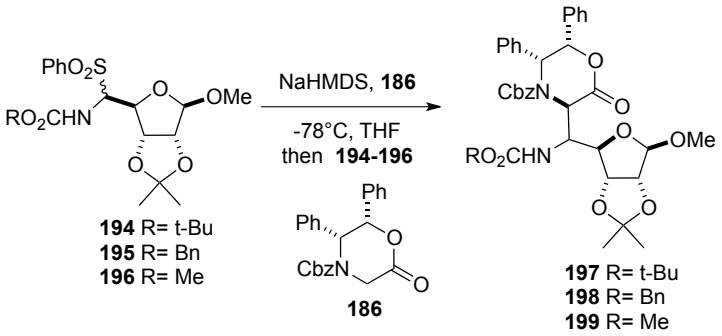
Ribose-derived aldehyde **185** was submitted to Petrini's conditions using t-butyl, benzyl or methyl carbamate resulting in the formation of amido sulfones **194**, **195** and **196** (Scheme 29). These amido sulfones were stable to chromatography and could be stored in the freezer with no apparent decomposition.



Scheme 29 Formation of amido sulfones **194-196**

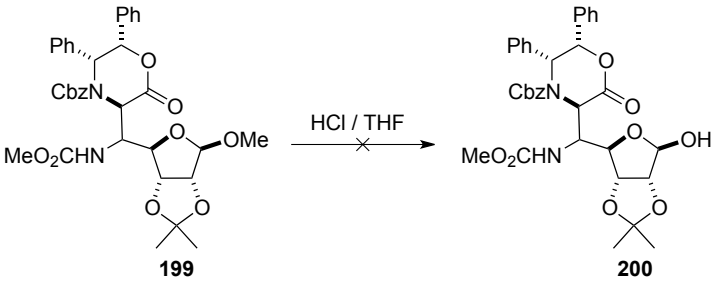
Amido sulfone **195** (1 eq.) was added dropwise to cold THF containing 2.5 eq. of the sodium enolate of glycine template **186,** which was prepared by stirring with sodium hexamethyldisilazane (NaHMDS), and allowing to stir for 1 hr. at -78°C. After quenching with sodium bicarbonate, Mannich product **198** was isolated in a 78% yield (Scheme 30). This reaction utilized an extra equivalent of lactone **186** because formation of the amido sulfone requires one equivalent of base. To minimize the use of the glycine template it was thought that simply adding more NaHMDS could fix this problem. Unfortunately, when one equivalent of

lactone **186** was used along with 2 equivalents of NaHMDS the yield was diminished to 57%. NMR analysis of the resulting product showed a single diastereomer and at this point the stereochemistry was a mystery. These results solidify the conclusion that benzylimine simply was not reactive enough to participate in the Mannich reaction. This methodology was also applied to amido sulfones **194** or **196** giving products **197** or **199**, respectively.



Scheme 30 Successful Mannich reaction.

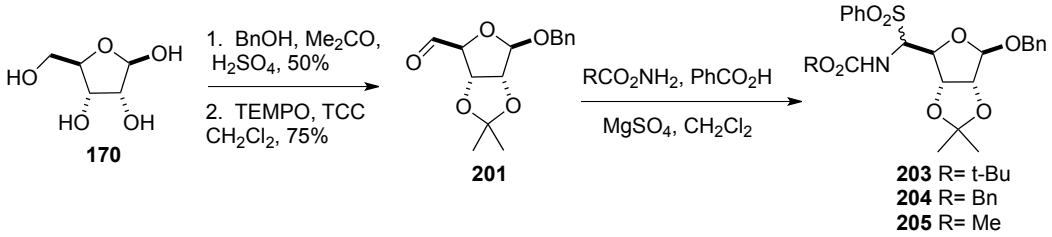
With several Mannich products in hand, the next step was to develop conditions to deprotect the lactol, which is necessary to access the secondary alcohol. Mannich product **199** was used because the methyl carbamate group is stable to acidic conditions, which will be necessary for the desired transformation. This reaction was expected to be difficult as it would be nearly impossible to deprotect the lactol without deprotection of the acetonide. This was indeed the case as, when compound **199** was treated with aqueous HCl in THF, no product was observed (Scheme 31). Since this seemed to be a problem that could not be resolved, new substrates were sought.



Scheme 31 Failed hydrolysis of lactol.

2.1.5 Useful Mannich Substrate

This problem could be remedied by replacing the lactol-protecting group with one that could be deprotected under conditions that don't require aqueous acid. A benzyl group was decided to be the best option as it could be removed by hydrogenation and could be installed in the same fashion as the methyl ether. Benzyl ether protected ribose acetonide **214** was previously prepared in literature by treating D-ribose with benzyl alcohol and acetone in the presence of sulfuric acid.[56] The alcohol was then submitted to the TEMPO/TCC oxidation, which proceeded smoothly to give desired aldehyde **201**, which was converted to the amido sulfone as previously described (Scheme 32).

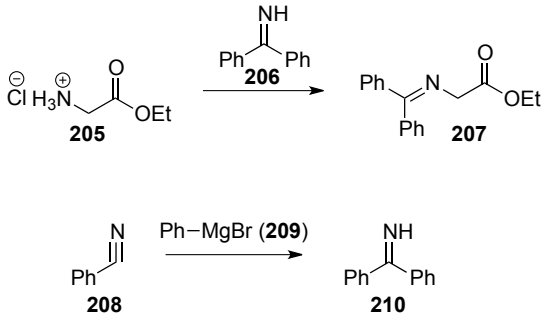


Scheme 32 Synthesis of amido sulfones **203**-**205**.

This new substrate could potentially solve the deprotection problem, it created a new problem. The glycine template used contains several groups that are sensitive to hydrogenation conditions and cleavage would lead to the formation of a very polar amino acid, which would

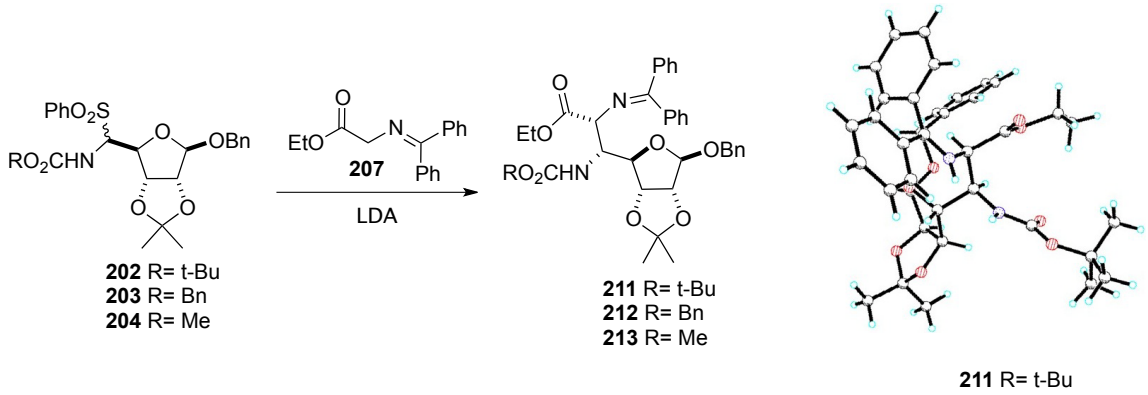
require reprotection. Also, since ribose is a chiral molecule it has the potential to direct the Mannich reaction without requiring the expensive enantiopure glycine template.

Glycine ethyl ester benzophenone imine (**207**) has been used in Mannich addition reactions and the benzophenone imine can be removed under mild aqueous conditions.[57] This template is commercially available, but it is more economically prepared via glycine ethyl ester HCl (**205**) and benzophenone imine (**206**), which can be prepared by a Grignard reaction between phenyl magnesium bromide (**209**) and benzonitrile (**208**) (Scheme 33).[58]



Scheme 33 Preparation of the benzophenone imine of glycine ethyl ester.

Amido sulfones **202**-**204** were treated with the lithium enolate of glycine **207**, which was formed by pretreatment with LDA. This reaction proceeded smoothly as expected giving a good yield of Mannich products **211**-**213**. The purification of these substrates was difficult as the glycine template co-spotted with the product. Mannich product **211** could be purified by crystallization from hexanes. Crystals of Mannich product **211** allowed for the absolute stereochemistry to be determined by x-ray crystallography. Since the absolute stereochemistry was determined, Mannich product **211** was the starting point for the all-future syntheses.



Scheme 34 Preparation of Mannich Products **211**-**213**

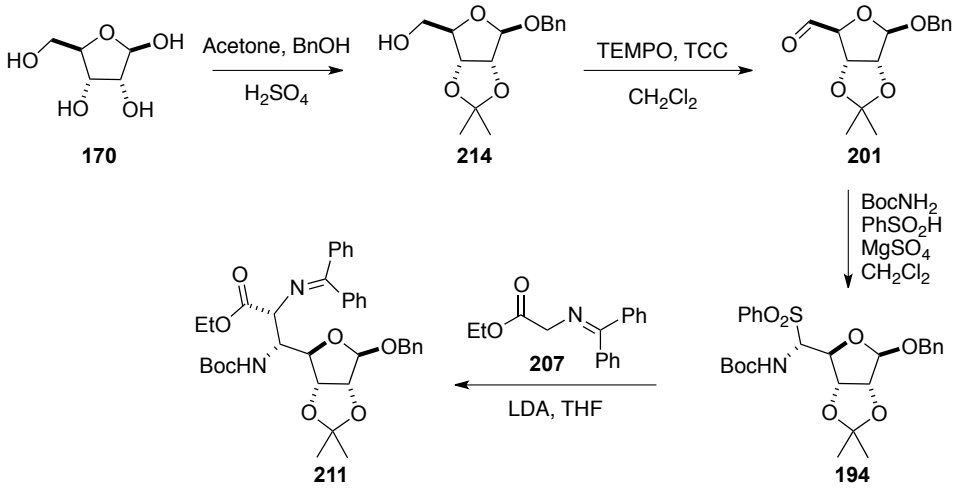
2.1.6 Scale-up of Mannich Substrate

Previous attempts to produce protected ribose **214** from D-ribose (**170**) on 100-gram scale gave low yields (9%). Decreasing the temperature from reflux to 70-75 degrees significantly increased the yield. It was also noticed that the sodium carbonate was not effective in neutralizing all the acid. If the acid was not completely neutralized, when the temperature was increased to remove the benzyl alcohol the mixture turned black, reducing the yield. Neutralizing with Et_3N was more effective due to solubility and effectively solved the problem. These two modifications increased the yield to 51% on a 150-gram scale. This reaction was then scaled up to 400g giving a 50% yield (Scheme 35).

Conversion of sodium benzenesulfinic acid to benzene sulfinic acid by treatment of a solution of the salt in water with HCl followed by an ether extraction was low yielding. This procedure was simplified by dissolving the salt in a small amount of water and then acidifying with 12M HCl and filtering off the product. The product was then dried under vacuum overnight to giving a much better yield with much less work.

Purification of amido sulfone **194** was previously done by column chromatography. Later it was discovered that it could be crashed out with 10% EtOAc/Hexanes. This method,

although better than chromatography, led to a gel-like product that was not always pure and was hard to reproduce. This procedure was optimized after noticing that the product is not soluble in ether, but the starting materials are. When the crude product was stirred in ether, amido sulfone **194** crashed out resulting in a 62% yield on ~40g scale (Scheme 35).

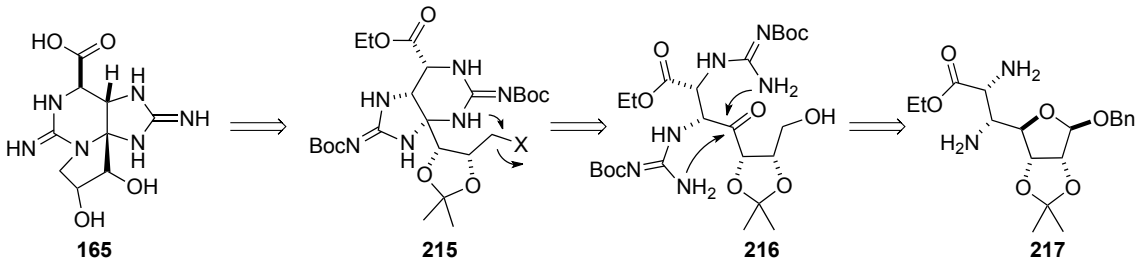


Scheme 35 Optimized synthesis of Mannich product **211.**

2.2 Bis-Guanidinylation Approach

2.2.1 Retrosynthesis

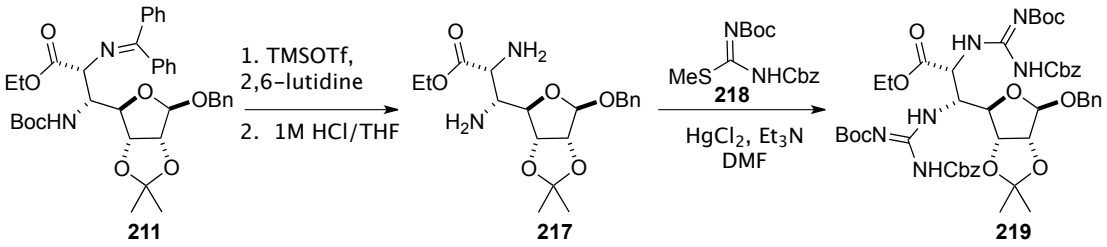
The first approach taken toward synthesis of the core of zetekitoxin AB was to deprotect both of the amines and install both guanidines simultaneously (Scheme 36). At the start of this project this approach was unprecedented, until Looper's synthesis in 2011.[43] Both guanidines would then be condensed on a centralized ketone to give a [6,5]-fused ring system **215**. The primary alcohol could then be converted to a leaving group, which could then undergo an attack by a guanidine leading to tricyclic core **165**.



Scheme 36 Retrosynthesis of the saxitoxin core via diamine **217**.

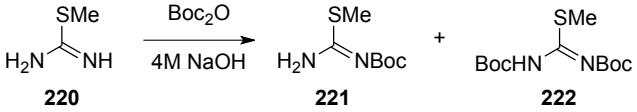
2.2.2 Formation of diamine and installation of guanidines

In order to access diamine **217** the Boc and benzophenone imine protecting groups would have to be removed (Scheme 37). The removal of the Boc group was more problematic then expected, as treatment with TFA, HCl and a variety of other acids failed to give the desired product. Thermal and microwave conditions also proved to be problematic. It was later discovered that Ohfune's conditions worked very well for this transformation.[59] Treatment of **211** with TMSOTf and 2,6-lutidine in CH_2Cl_2 cleanly removed the Boc group in ~20 minutes. The benzophenone imine was then hydrolyzed with 1M HCl in THF to give diamine **217**. The isolation of the diamine was problematic at first because it was very soluble in water. The first isolation technique was a simple biphasic extraction. Unfortunately, this resulted in a low yield (~30%). Neutralization with sodium bicarbonate followed by removal of the solvent under vacuum followed by lyophilization of the water gave a mixture of diamine **217** and mixed salts, which were then extracted with EtOAc. This gave a better yield, but was still not acceptable. A biphasic extraction with n-butanol improved the yield drastically, but it was found that evaporation of the mixture without neutralization gave the best yield of the diamine **217** as the bis-hydrochloride salt. This crude mixture of diamine **217** HCl was of sufficient purity for the next reaction. The diamine was then guanidinylated with pseudothiourea **218**, $HgCl_2$, and Et_3N in CH_2Cl_2 to give bisguanidine **219**.



Scheme 37 Synthesis of bisguanidine **219**.

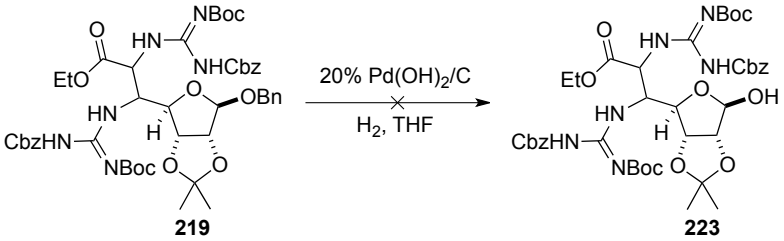
Guanidinylating agent **218** was prepared by treating S-methylisothiourea hemisulfate (**220**) with 1 eq. of Boc_2O and 4M NaOH in CH_2Cl_2. Bis-Boc-protected product **222** was observed, but compound **221** was the major product.



Scheme 38 Preparation of reagent **221**.

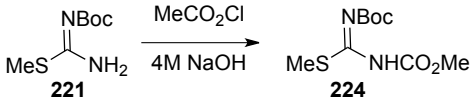
2.2.3 Debenzylation

With bisguanidine **219** in hand the next goal is the removal of the benzyl ether to access lactol **223**, which would then need to be reduced. To affect this transformation several hydrogenation conditions were screened. Hydrogenation with 10% Pd/C or 20% $Pd(OH)_2/C$ at 80 psi led to a complex mixture (Scheme 39).



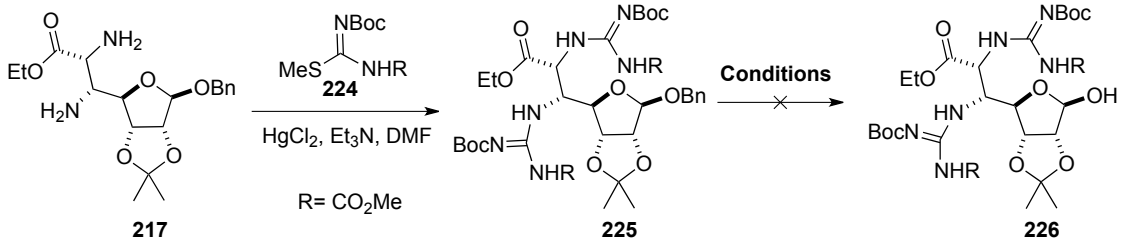
Scheme 39 Unsuccessful hydrogenolysis of substrate **219**.

To simplify the reaction the labile Cbz groups were changed to a methyl carbamate. Guanidinylation reagent **224** was synthesized by treating known Boc-protected S-methyl isothiourea **221** with methyl chloroformate and 4M NaOH.



Scheme 40 Preparation of reagent **224**.

Diamine **217** was then treated with reagent **224** along with mercuric chloride, and triethylamine in dimethylformamide to give bisguanidine **225**. Unfortunately, hydrogenation of compound **225** with palladium hydroxide at 80 psi gave back starting material after 2 days. Compound **225** was also treated with DDQ in an attempt to remove the benzyl group, but this resulted in decomposition. Several other conditions were screened, but none led to the desired product (Scheme 41).

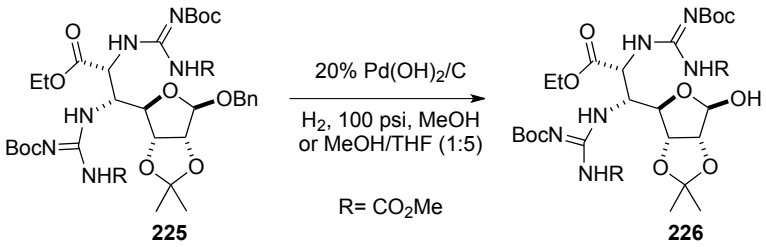


Scheme 41 Failed hydrogenation of benzyl ether **226.** Conditions: 20% $Pd(OH)_2/C$ or 10% Pd/C, H_2, 80 psi, THF; DDQ, CH_2Cl_2/H_2O, 45ºC; Na, NH_3 or hν

Since removal of the benzyl ether proved difficult in the presence of the guanidines it was thought that removing the benzyl group before installation of the guanidines could be effective (See section Late-Stage Guanidine installation for more detailed information).

After putting this route on hold for a while, screening more hydrogenation conditions led to the success of the reaction. Benzyl ether **225** was hydrogenated with a large excess of 20%

$Pd(OH)_2/C$ at 100 psi in MeOH for ~18 hours to give lactol **226** in good yield (Scheme 42). The success of this reaction was due to the combination of high catalyst loading, high pressure and methanol as the solvent. Using THF instead of methanol slowed the reaction down so much the reaction only returned starting material. Another issue was the purity of the starting material. When insufficiently purified the reaction shuts down, probably due to residual sulfide contaminates from the guanidinylation. This reaction was later optimized by switching the solvent system to a 5:1 THF/MeOH, improving the yield from ~70% to 85%, but increasing the reaction time to ~30 hours.

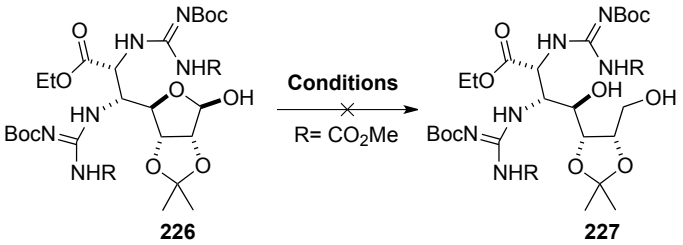


225 **226**

Scheme 42 Successful deprotection of benzyl ether **225**.

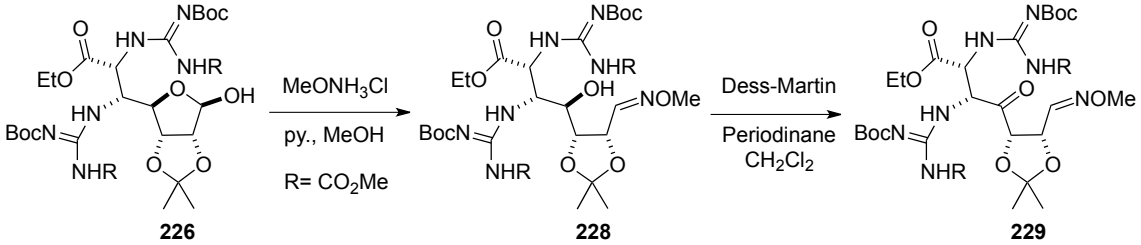
2.2.4 Reduction of Lactol and Oxidation of Alcohol

To access the secondary alcohol the lactol must first be reduced. Treatment of lactol **226** with excess sodium borohydride in methanol gave a complex mixture (Scheme 43). Reduction conditions using stoichiometric borohydride as well as the slow addition of borohydride also failed to give results. Other reducing agents such as $NaHB(OAc)_3$, $NaCNBH_3$ were screened, all of them failing to produce any results (Scheme 43).



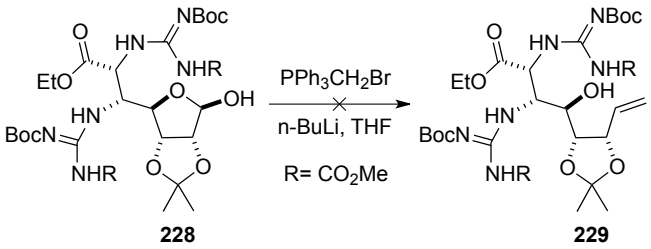
Scheme 43 Failed lactol reduction. Conditions: $NaBH_4$, THF or MeOH; $NaHB(OAc)_3$, MeOH; $NaCNBH_3$, MeOH

To avoid the problems that occur under reducing conditions, a couple of different attempts to open the lactol with nucleophiles were made. Compound **226** was treated with methoxyamine HCl and pyridine in methanol giving ring-opened oxime **228** (Scheme 44). The secondary alcohol was oxidized with Dess-Martin periodinane giving ketone **229**. This reaction was not reproducible. Most times the reaction was low yielding, except in one case the reaction went spot to spot by TLC. Fresh oxidant was tested to try to reproduce reaction, but in all cases the clean reaction was never reproduced.



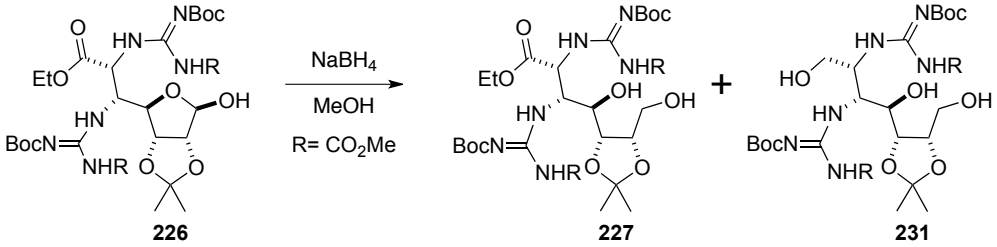
Scheme 44 Preparation of ketone **229**.

Since phosphorus ylides are nucleophilic, but not very basic a Wittig reaction was attempted on the lactol **226**. The lactol was added to the phosphorus ylide of PPh_3CH_2Br, which was preformed by treatment with n-BuLi in THF, giving no reaction (Scheme 45).



Scheme 45 Unsuccessful Wittig reaction.

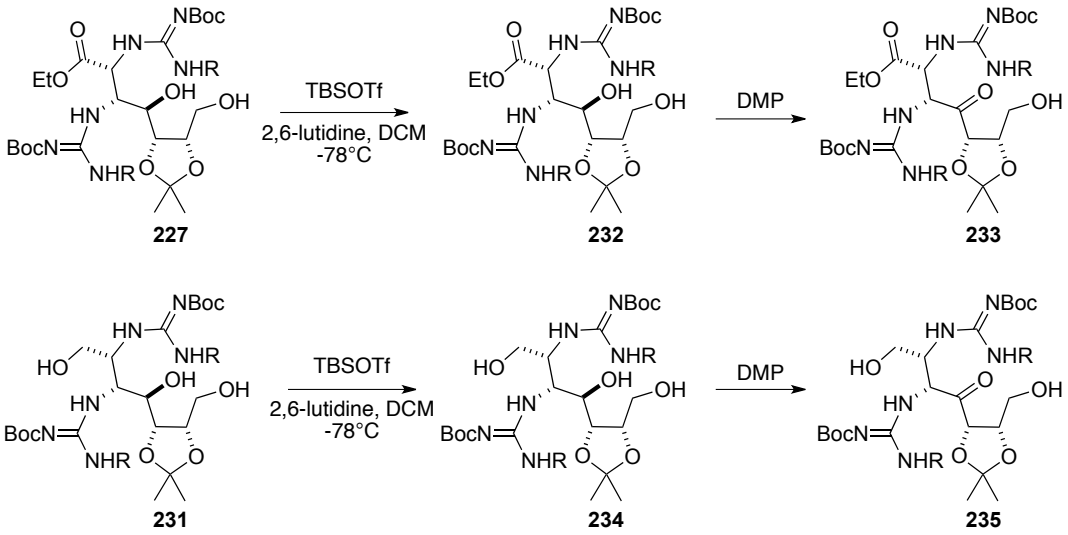
After considerable frustration it was discovered that lactol **226** could be reduced by $NaBH_4$ in MeOH at 0°C to give a mixture of the diol **227** and triol **231** (Scheme 46). This reaction went unnoticed for a very long time because the reaction time is very short (~5 min.) and it requires a large excess of hydride. If the amount of hydride is reduced the reaction time is increased and no product is isolated. If the reaction goes a minute over, which is very easy to do, the yields drop off terribly. To further complicate things, the starting material co-spots with the product on TLC and the only difference is a slight difference in color when stained in ninhydrin.



Scheme 46 Sucessful lactol reduction.

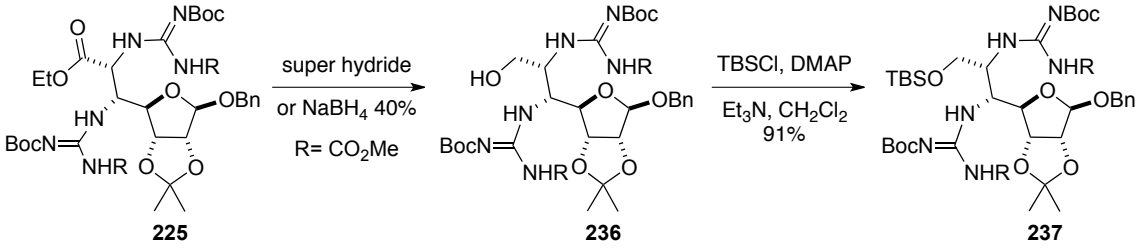
Standard TBS conditions of the diol (TBSCl, DMAP or imidazole and Et_3N in DMF or CH_2Cl_2) gave no reaction so more reactive conditions were used. Treatment of diol **227** with TBSOTf and 2,6-lutidine at -78°C in CH_2Cl_2 proceeded very quickly giving rise to TBS ether **232**. This reaction had to be carefully monitored to avoid the bis-TBS protection of the primary and secondary alcohol. The same conditions were also successful for TBS protecting both of the

primary alcohols of triol **231**. Treatment of both secondary alcohols with Dess-Martin periodinane gave ketones **233** and **235** (Scheme 47).



Scheme 47 Preparation of ketone **233** and **235**.

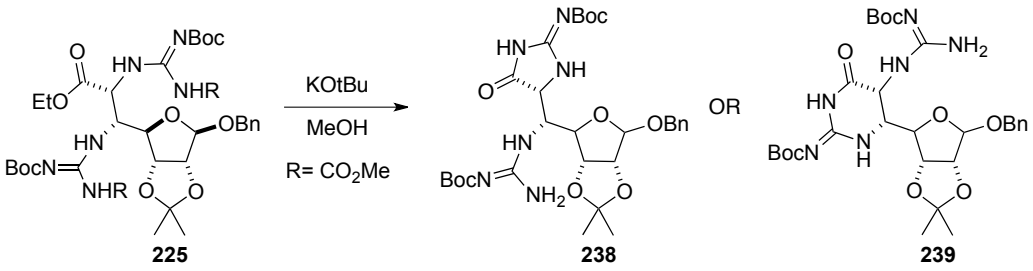
The yield of triol **231** was ~10% so a more economical synthetic route was explored (Scheme 48). Thus by treating ester **225** with super hydride or sodium borohydride a low yield of the primary alcohol was obtained. Alcohol **236** was then TBS-protected using TBSCl, DMAP, and Et_3N in CH_2Cl_2 to give silyl ether **237**. This methodology was put on hold as the small quantity of triol previously obtained was taken forward.



Scheme 48 Preparation of silyl ether **237**.

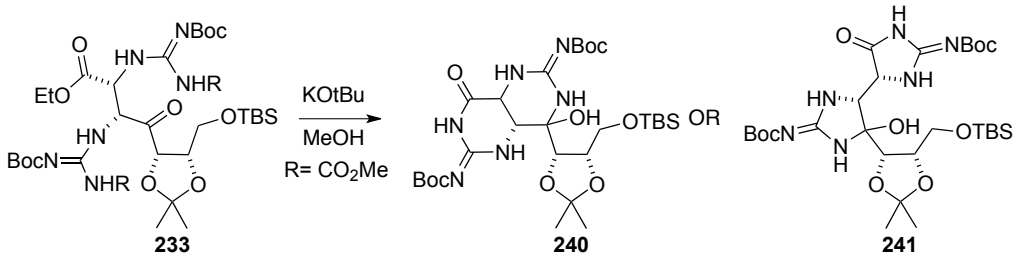
2.2.5 Deprotection of Guanidines

Before attempting the guanidine deprotection of ketone **233** or **235** a model study was completed. Bisguanidine **225** was treated with potassium tert-butoxide (KO^{t}Bu) in methanol, which gave what looks to be a mixture of compounds **238** and **239** (Scheme 49). Both the NMR and MS data agreed that both methyl carbamates were gone, but the ethyl ester also was missing. It is assumed that one of the guanidines cyclized on the ester forming either a 5 or 6 membered ring, unfortunately the mixture could not be sufficiently purified to fully characterize.



Scheme 49 Deprotection of methyl carbamates.

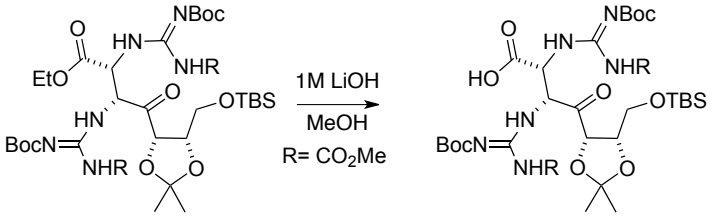
Even with the failed model study, ketone **233** was treated with KO^{t}Bu in methanol. This reaction led to the deprotection of the methyl carbamates and the loss of the ethyl ester giving compounds **240** and **241** as expected from the previously described model system.



Scheme 50 Deprotection of ketone **233**.

To prevent this side reaction it was thought that using aqueous hydroxide instead of tert-butoxide could simultaneously hydrolyze methyl carbamates and the ester, giving the free acid, which can not react with the guanidines (Scheme 51). Ester **233** was treated with 1M LiOH

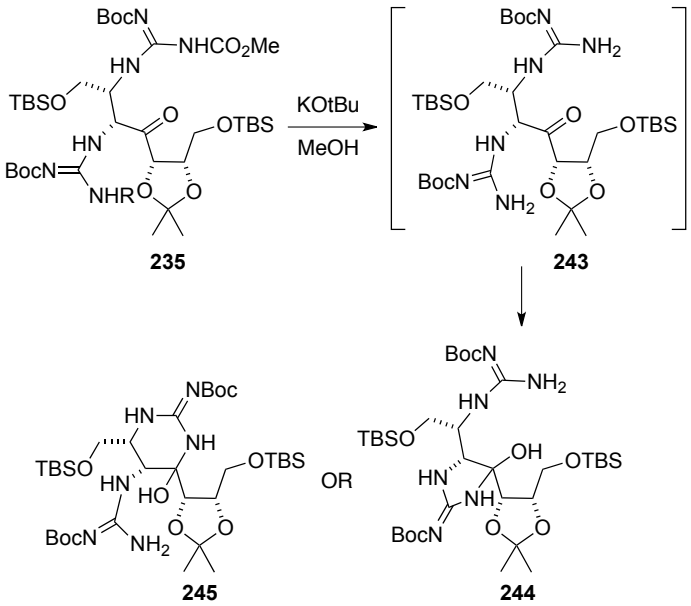
in methanol and stopped as soon as the starting material was gone by TLC. This resulted in a mixture of products containing the methyl carbamates and loss of the ester by NMR but the MS showed a single mass. This indicated that the ester was successfully hydrolyzed, but the basic reaction conditions were racemizing the center next to the ketone or the ester. If the reaction was allowed to continue longer than the time required to consume starting material the products became increasingly polar and purification became impossible.



233 **242**

Scheme 51 Hydrolysis of ester **233**.

In order to prevent the cyclization of the guanidines on the ester, ketone **235** was taken forward. Treatment of ketone **235** with KOtBu in methanol led to the deprotection of both guanidines which spontaneously cyclized on the central ketone (verified by IR) giving products like **244** and **245** (Scheme 52). Unfortunately, racemization was still a problem and no compounds could be fully characterized.



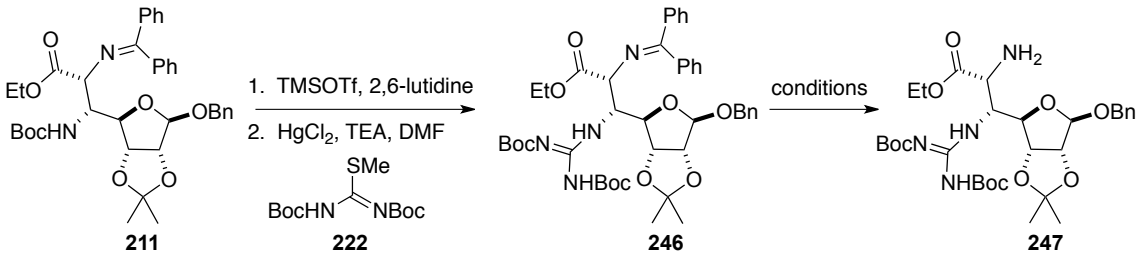
Scheme 52 Cyclization of ketone **243**.

2.2.6 Differentiated guanidines

To simplify the problems of cyclization as previously mentioned (Deprotection of Guanidines) it was thought that by differentiating the guanidines that the number of products could be reduced in half, possibly allowing some to be purified and characterized. Also, the use of the Teoc protecting group instead of the methyl carbamate would allow neutral or slightly acidic deprotection conditions, which could prevent racemization (Scheme 54). The path towards differentiating the guanidines proved to be much more difficult than expected, but led to some interesting new discoveries.

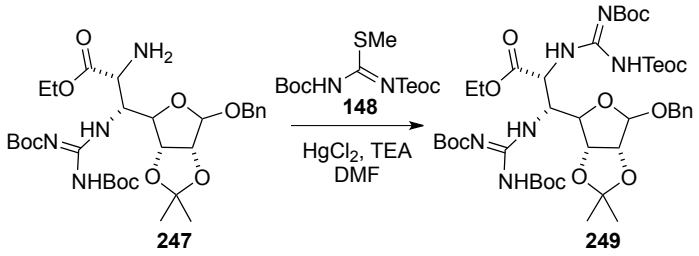
The most straightforward approach, starting from Mannich product **211**, was to remove the Boc group and then install the first guanidine, followed by acid hydrolysis of the benzophenone imine and subsequent installation of the second guanidine (Scheme 53). Thus, Mannich product **211** was treated with TMSOTf and 2,6-lutidine to remove the Boc group and the crude material was guanidinylated with reagent **222**, triethylamine and mercuric chloride to give guanidinylated compound **246**.

The hurdle and death of this route came unexpectedly from what was thought to be the simple removal of the benzophenone imine-protecting group. When imine **246** was treated with the previously developed conditions (1M HCl/THF), only trace amine **247** was obtained. Treatment with various conditions all resulted in failure (Scheme 53).



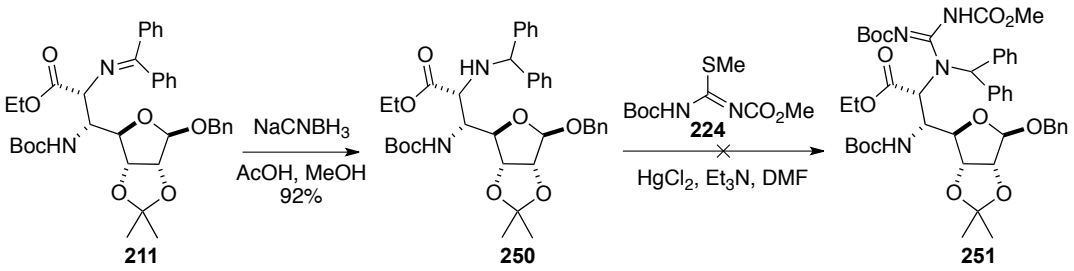
Scheme 53 Hydrolysis of benzophenone imine **246**. Conditions: 10% Pd/C or 20% $Pd(OH)_2$, H_2, MeOH EtOAc or THF; 2M citric acid, THF; hydroxylamine or hydrazine, MeOH.

Nevertheless, the miniscule amount of amine **247** obtained was guanidinylated to give differentiated guanidine product **249**. Unfortunately, due to the low yielding step this methodology had to be abandoned and other routes were investigated.



Scheme 54 Preparation of bisguanidine **249**.

It was thought that if the benzophenone imine could be reduced to amine **250** and the nitrogen was not too sterically hindered (unlikely!) that it could then be guanidinylated to compound **251** (Scheme 55). Imine **246** was treated with sodium cyanoborohydride and acetic acid in methanol giving amine **250**, which when submitted to guanidinylation conditions only starting material was recovered.

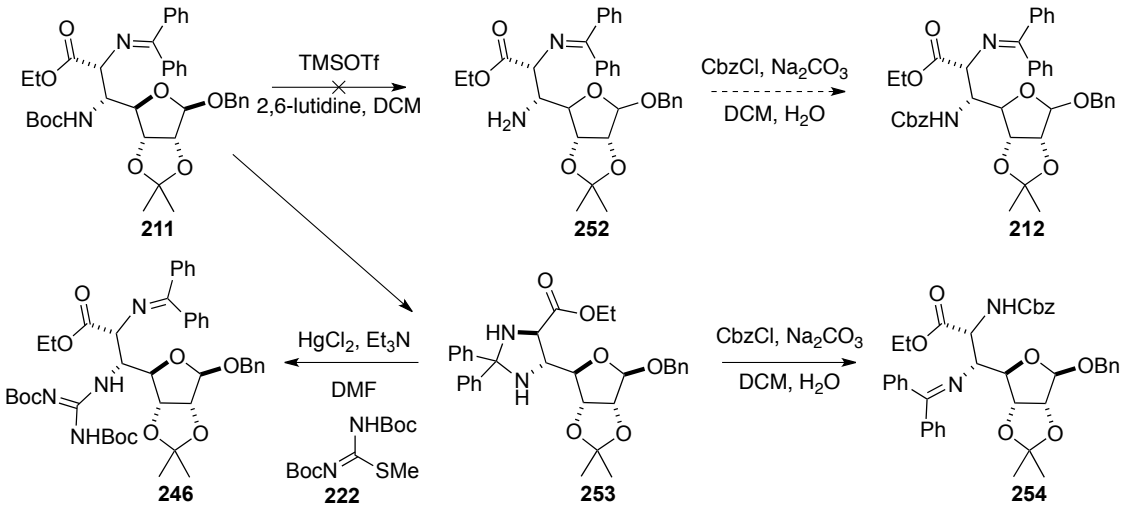


Scheme 55 Failed guanidinylation of amine **250**.

Since removing the benzophenone imine was not successful, an alternate sequence of reactions was necessary. It was thought that removal of the benzophenone imine first followed by guanylation would be best. Unfortunately, this would not be possible because the next step would require removal of the Boc group and the other Boc groups would interfere. It was hypothesized that swapping the Boc group out for a Cbz group would fix this problem. With large quantities of Mannich product **211** on hand, it was thought that the fast route to this compound was to just swap protecting groups. Thus, Mannich product **211** was submitted to the previously developed deprotection conditions and the product was taken on crude (Scheme 56). The crude material was treated with CbzCl, and sodium carbonate in a biphasic mixture of CH_2Cl_2 and water. Interestingly the results were not as expected. The Cbz group and benzophenone imine was found to be on the opposite nitrogens. The migration was due to the formation of intermediate aminal **253**. Since all previous reactions utilized diamine **217,** this compound remained mischaracterized until now.

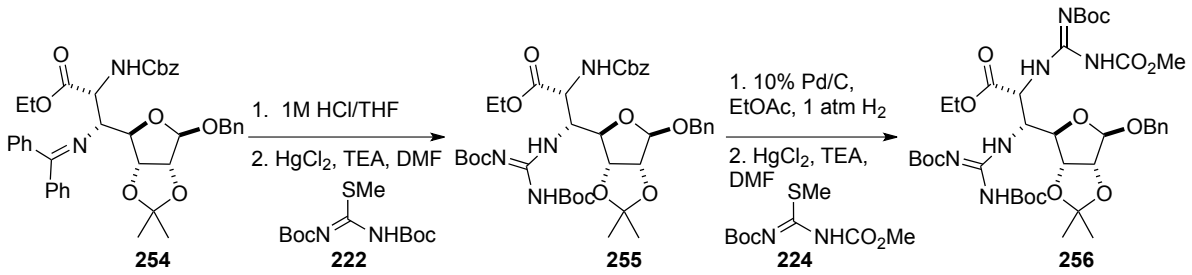
This result required going back through all previous work to make sure that no other compounds were mischaracterized. It turns out that all the previous compounds, except for hemiaminal **253**, were characterized correctly. Of particular interest is preparation of compound **246**, which does shows the opposite regioselectivity. It is unknown why there is different

regioselectivity when aminal **253** is treated with CbzCl versus when it is guanidinylated. The fact that it shows 100% regioselectivity is even more baffling.



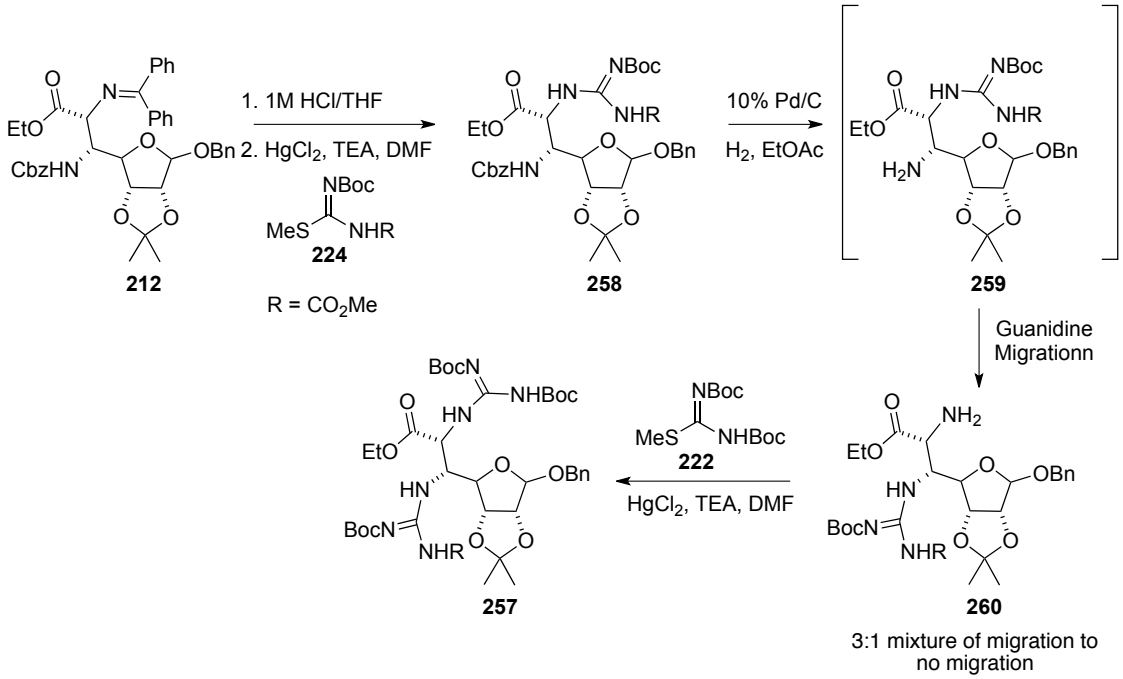
Scheme 56 Regioselectivity of aminal **253**.

Cbz migration product **254** was unexpected, but still is just as useful as compound **212** (Scheme 57). When product **254** was treated with the previous developed imine deprotection conditions (1M HCl/THF) there was no reaction. This was a bit worrisome at first, but when treated with 4M HCl the reaction was successful, giving the amine. The requirement of a lower pH could be due to the increased steric environment surrounding the imine. The amine was guanidinylated with reagent **222**, using standard conditions, giving compound **255**. The Cbz group was easily removed over the benzyl ether by hydrogenation with 10% Pd/C at 1 atm hydrogen. The resulting amine was guanidinylated to give differentiated guanidine **256**. Its worth mentioning now that when this reaction was first run there was an unknown impurity that looked strikingly similar to the product, but was discarded and wasn't looked into. The identification of this compound turned out to be an interesting discovery and will be discussed in detail in the next paragraph.



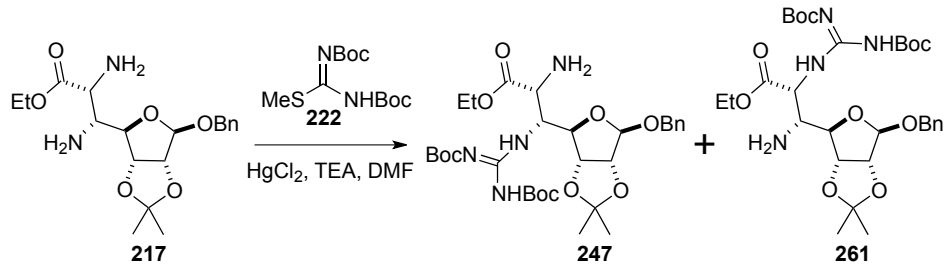
Scheme 57 Preparation of bisguanidine **256**.

To make sure this sequence produced the correct product and to reduce the step count by 1, Cbz Mannich **254** was submitted to the same sequence of reactions to get to the differentiated guanidine product. When the NMRs of the two differentiated products were compared, they did not match as expected (Scheme 48). This result meant another migration occurs somewhere else in the sequence. There are only two possibilities of migration. Either a Cbz group migrated or a guanidine migrated. An intense NMR analysis of all the free amine intermediates led to the discovery of a guanidine migration. This migration occurred after removal of the Cbz group from compound **258**. Upon further analysis of this reaction it actually was a 3:1 mixture of migration to no migration. Further analysis of the Cbz deprotection of Cbz migration product **255** also showed the same 3:1 mixture, meaning migration is not favored (Scheme 57).



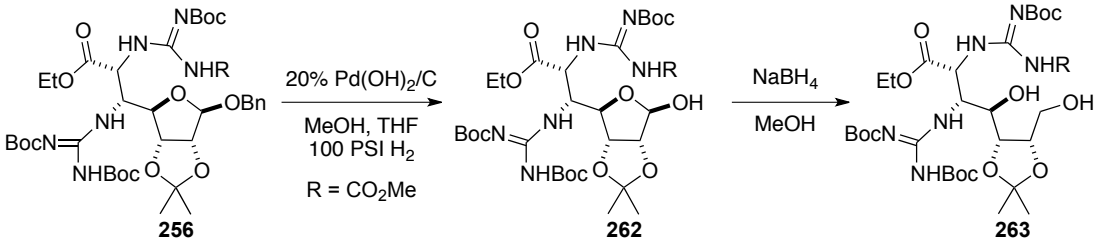
Scheme 58 Guanidine migration.

This led to the idea that it might be possible to exploit this migration and differentiate the guanidines directly from diamine **217**, that was previously prepared (Scheme 59). Treatment of diamine **217** with one equivalent of guanidinylating reagent led to a 2:1 mixture of **246** and **261**. This indicates that the migration only occurs due to the formation of a nucleophilic N-anion during the Cbz deprotection. Only a trace amount of bisguanidinylated product was observed. Unfortunately, it was not possible to migrate the guanidines under the reaction conditions, slightly acidic or basic conditions. This further supports the idea that the N-anion is required to enact the migration.



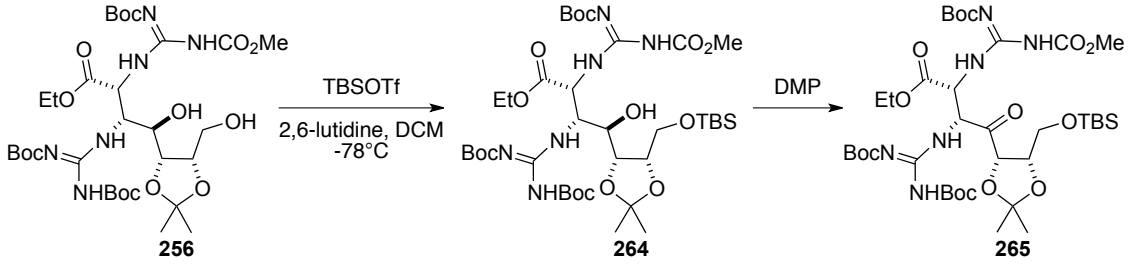
Scheme 59 Selective guanidinylation

With differentiated bisguanidine compound **256** in hand, the next known sequence of reactions were carried out as shown in Scheme 60. Compound **256** was hydrogenated with 20% $Pd(OH)_2/C$ at 100 psi in THF/MeOH (5:1) to give lactol **262**. This lactol was then reduced to diol **263** with sodium borohydride.



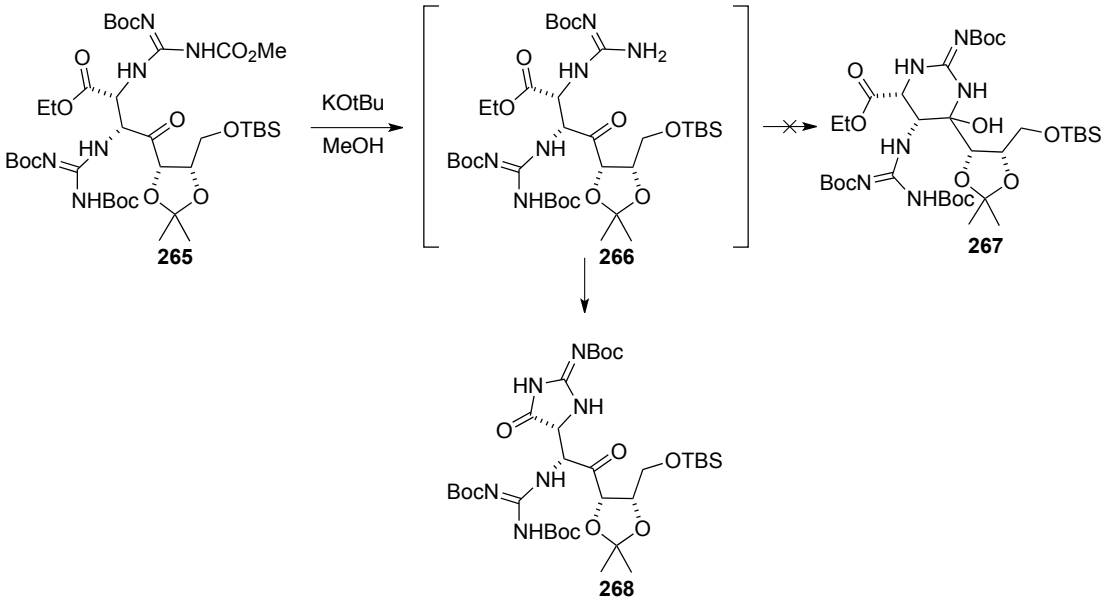
Scheme 60 Preparation of diol **263**.

The primary alcohol of diol **263** was TBS protected using TMSOTf and 2,6-lutidine in dichloromethane giving TBS ether **264**. Once protected the secondary alcohol was oxidized to ketone **265** with Dess-Martin periodinane (Scheme 61).



Scheme 61 Preparation of ketone **265**.

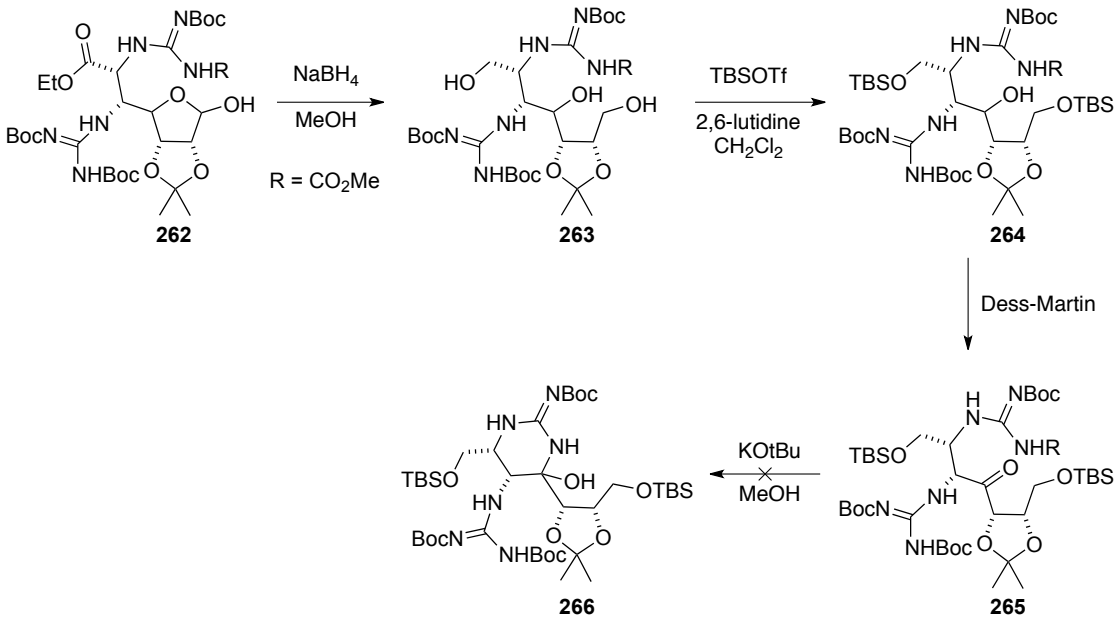
It was expected that differentiated guanidine product **265** would undergo the same side reactions as previously shown (Scheme 49). Nevertheless with the differentiated guanidine product **268** in hand the deprotection and cyclization was attempted (Scheme 62). The result, as expected, was the deprotection of the methyl carbamate with cyclization onto the ethyl ester, resulting in compound **268**, which showed signs of racemization.



Scheme 62 Undesired cyclization of guanidine.

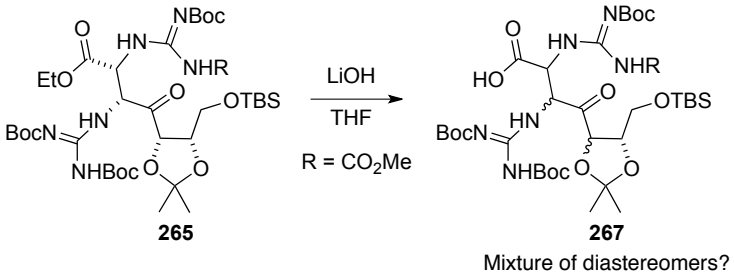
To prevent the unwanted cyclization it was thought that reducing the ester to the alcohol or forming the acid would allow the desired transformation (Scheme 63). Reduction of lactol **262** to triol **263** with sodium borohydride did not work as well as expected from previous results. However, enough material was generated to move forward. Triol **263** was bis-TBS protected using TBSOTf and 2,6-lutidine to give compound **264**. Alcohol **264** was then converted to ketone **265** in good yield using the Dess-Martin oxidation. When ketone **265** was treated with KO^{t}Bu in MeOH starting material was consumed, but the product was a complex mixture and

could not be characterized by NMR. It seems that the basic conditions led to racemization next to the ketone.



Scheme 63 Unsuccessful guanidine cyclization.

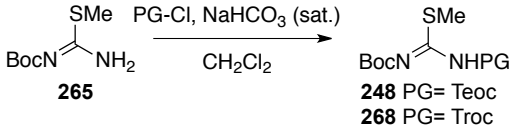
When ketone **265** was treated with LiOH in THF (Scheme 64), the ester was hydrolyzed, (as seen by NMR and mass spectrometry), but the product could not be fully characterized because it looks like the basic conditions also led to a complex mixture of diastereomers.



Scheme 64 Hydrolysis of ester **265**.

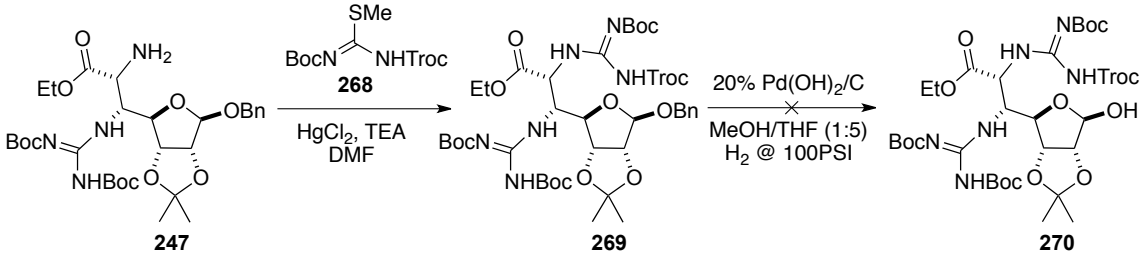
After having several problems with basic deprotection conditions, the methyl carbamate group was abandoned. The Teoc and Troc carbamates were the next logical choices because of their mild deprotection conditions. Isothiourea **248** and **268** were prepared by treating

isothiourea **221** with Teoc-Cl or Troc-Cl and triethylamine in CH_2Cl_2. The yield of this reaction was surprisingly low (~30%) and was optimized (>90%) by using saturated sodium bicarbonate instead of triethylamine as the base (Scheme 65).



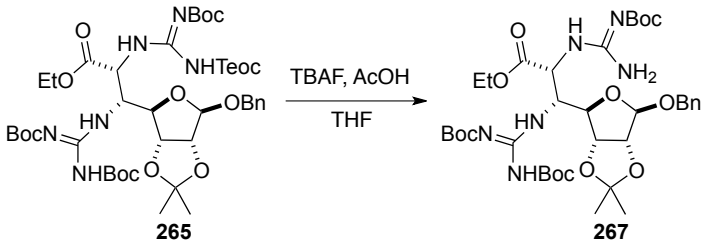
Scheme 65 Preparation of reagents **248** and **268**.

Troc-containing benzyl ether **269** was made using the same methodology that produced compound **249**. Unfortunately, the Troc group did not hold up to the hydrogenation required to remove the benzyl ether (Scheme 66).



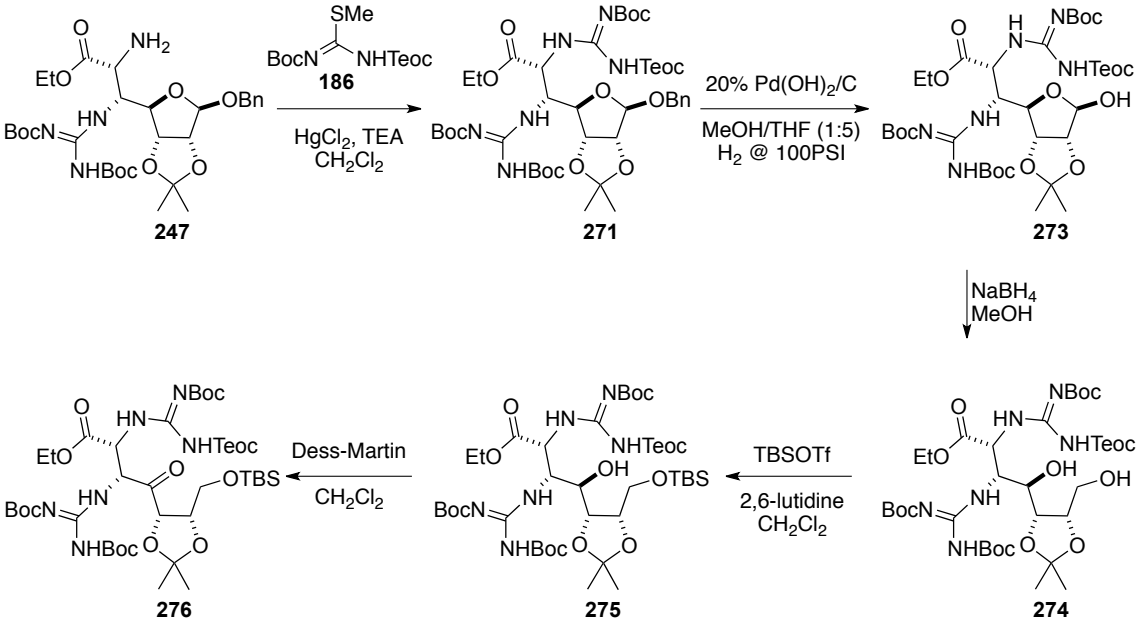
Scheme 66 Preparation of lactol **270**.

A model study was used to verify that the Teoc group could be removed in the presence of the ethyl ester (Scheme 67). When compound **249** was treated with TBAF and AcOH in THF the Teoc group was successfully removed with no signs of cyclization.



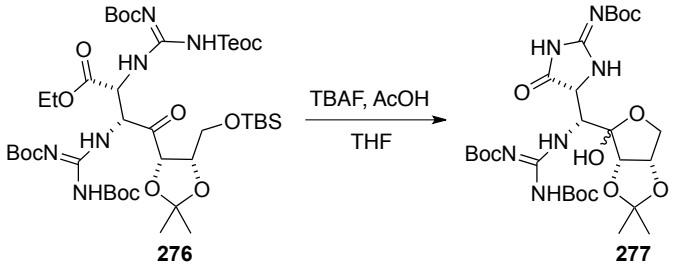
Scheme 67 Model desilylation.

After this result, benzyl ether **247** converted to ketone **276** using known methodology (Scheme 68).



Scheme 68 Preparation of ketone **276**.

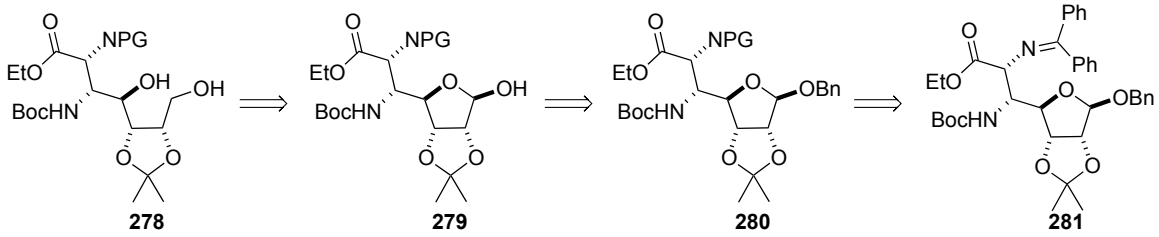
Unfortunately, the model study did not accurately portray the outcome of the deprotection of the advanced substrate. When ketone **276** was treated with the same deprotection conditions (TBAF, AcOH in THF) the deprotected guanidine cyclized on the ester and also removed the TBS group (Scheme 69). The result was probably lactol **277**, which showed up as a mixture of diastereomers.



Scheme 69 Undesired guanidine cyclization.

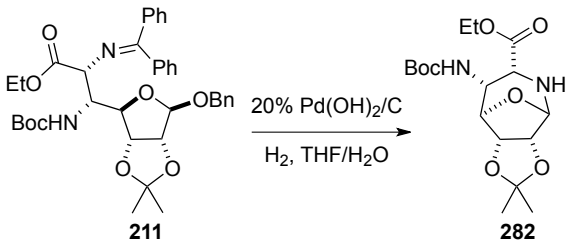
2.2.7 Late-Stage Guanidine installation

Before it was known that the benzyl group could be removed by hydrogenation (2.2.3 Debenzylation), a modified route that installed the guanidines later in the synthesis was attempted (Scheme 70). The idea was to leave both nitrogens protected, until after the debenzylation and reduction of the lactol to diol **278**. The nitrogens would then be deprotected and guanidinylated.



Scheme 70 Late stage guanidinylation retrosynthesis.

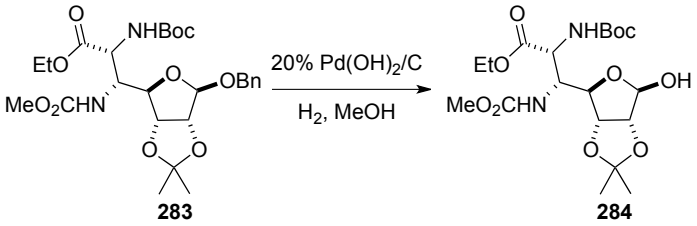
The first approach was to hydrogenate Mannich product **211** to remove the benzyl ether and the benzophenone imine at the same time (Scheme 71). Hydrogenation with 10% Pd/C was sluggish and led to a complex mixture of products at elevated pressure and temperature. When compound **211** was dissolved in THF/H_2O and treated with 20% $Pd(OH)_2$/C at 80 PSI the reaction took 5 days, eventually leading to a single product. The temperature was raised to 100ºC, which gave the same results in 21 hours. Unfortunately, the product was not the lactol and free amine as expected. The amine intermediate that formed cyclized on the lactol to give bridged bicycle **282**.



211 282

Scheme 71 Unexpected bridged bicycle formation.

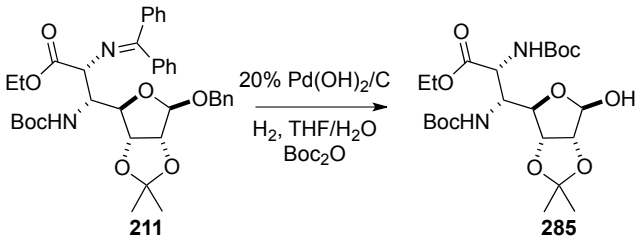
It was thought that if the amine were protected with a withdrawing group, i.e. Boc, then the amine would no longer be nucleophilic enough to cyclize (Scheme 72). This tactic worked very well, as when compound **283** was treated with the same hydrogenation conditions it led exclusively to lactol **284**.



283 284

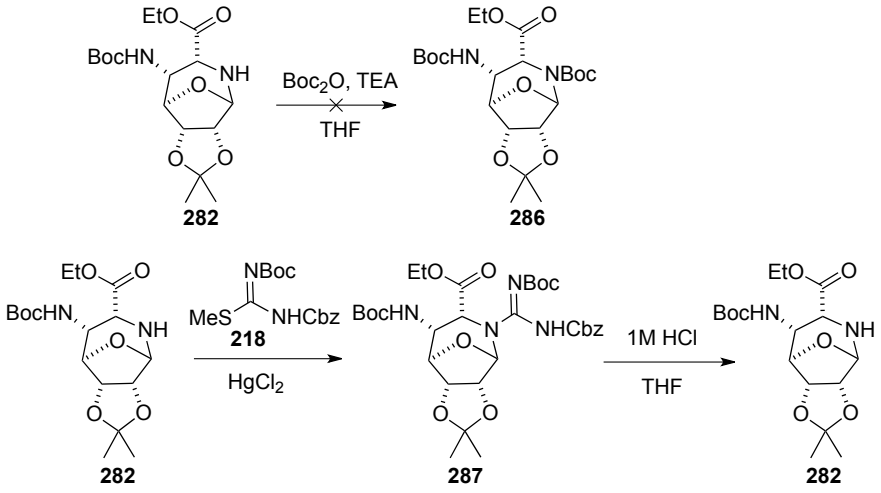
Scheme 72 Hydrogenation of benzy ether **283**.

Monitoring the reaction shown in Scheme 71 by TLC showed that the benzophenone imine fell off first in the reaction followed by benzyl group. This led to the idea of trapping the amine in situ, preventing the cyclization and saving a couple steps (Scheme 73). Since Boc anhydride is well known in literature to trap amines formed during hydrogenation it was the first reagent chosen. This ended up working very nicely, as when Boc anhydride was added to the hydrogenation, lactol **285** was isolated in high yield along with trace cyclization product **282**.



Scheme 73 Boc protection/hydrogenation of compound **211**.

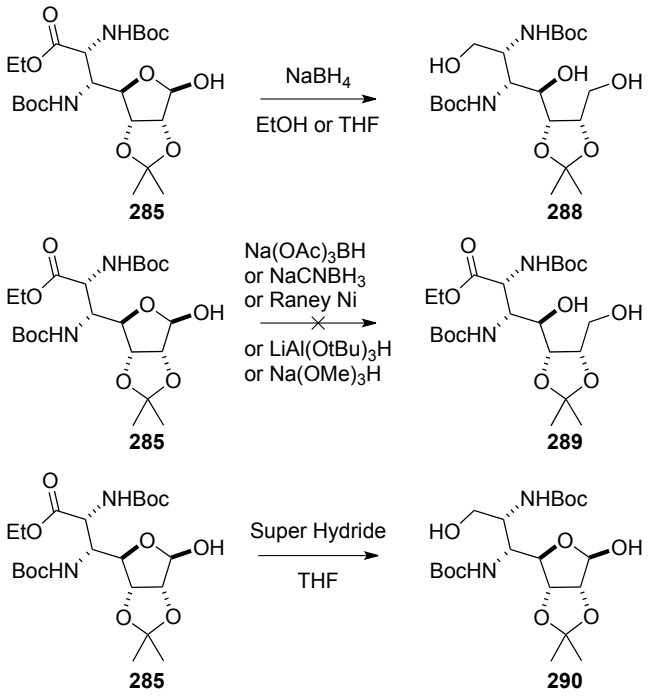
It looked like the little bit of bicycle **282** that formed the reaction was getting converted to the product. It was thought that if a withdrawing group such as a Boc or a guanidine was attached to the secondary amine, it might allow the opening of the hemiaminal ether to the lactol (Scheme 74). Unfortunately, the treatment of bicycle **282** with Boc anhydride at 100ºC led to no reaction. Looking back, this reaction might have been successful if a stronger base was used under aqueous conditions. The guanidinylation of bicycle **282** was successful, but when compound **287** was treated with 1M HCl to hydrolyze the hemiaminal ether, the guanidine was hydrolyzed instead.



Scheme 74 Unsuccessful ring opening strategy of biycycle **282**.

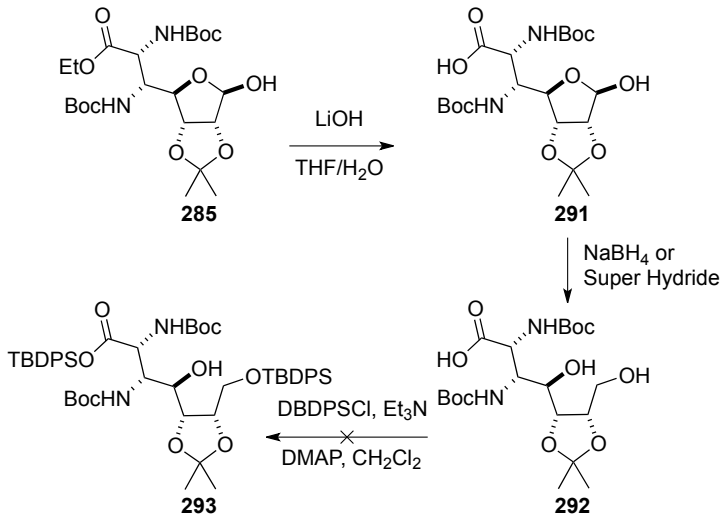
Regardless, with lactol **285** in hand the next step was to reduce the lactol to the diol (Scheme 75). This however was much more difficult than expected as treatment of lactol **285** with

sodium borohydride gave the triol exclusively. Many different hydride reagents were screened to effect this transformation, but no conditions worked. All the reactions using milder reagents resulted in the recovery of starting material. Interestingly, super hydride (lithium triethylborohydride) reduced the ester over the lactol in low yield.



Scheme 75 Reactions of lactol **285**.

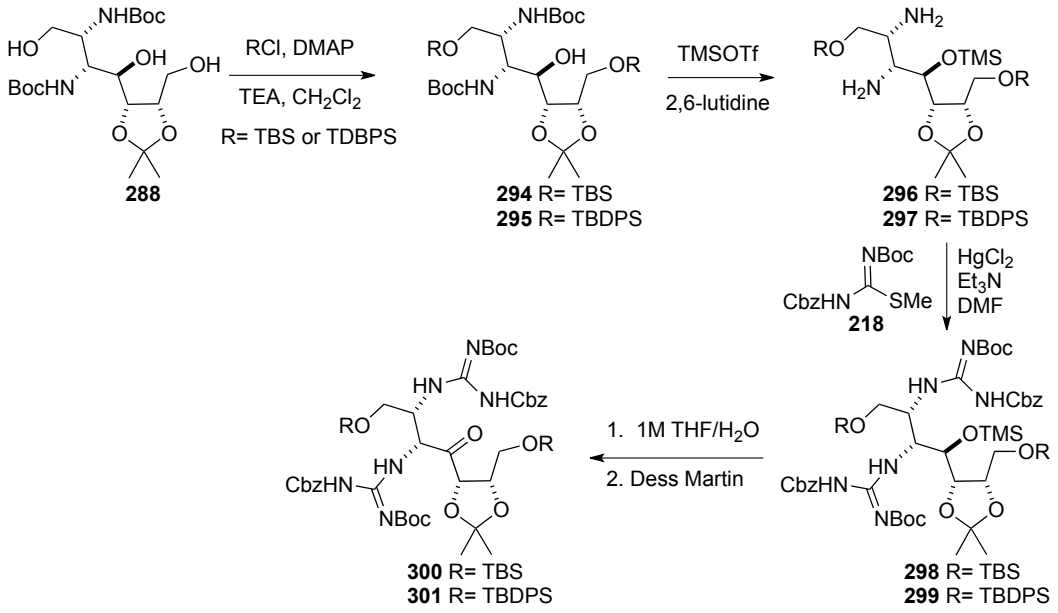
To prevent the reduction of the ester group, **285** was hydrolyzed to carboxylic acid **291** using LiOH and THF/H_2O (Scheme 76). The lactol was then reduced to the diol using either sodium borohydride or Super Hydride. Super hydride was found to work better because no over-reduction occurred. Protection of compound **291** with TBDPS groups was ineffective.



Scheme 76 Failed reduction strategy of lactol **285**.

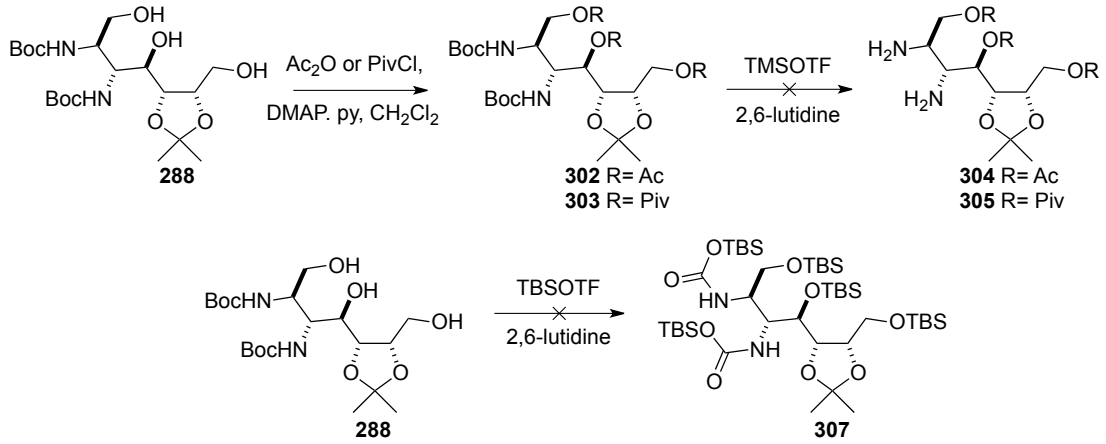
Even though the synthesis of the desired diol could not be achieved, triol **288** was taken forward in the synthesis (Scheme 77). Both of the primary alcohols were protected by treatment with TBSCl, Et_3N and DMAP in CH_2Cl_2 to give bis-TBS ether **294** in good yield. The Boc groups were then removed by treating compound **294** with TMSOTf and 2,6-lutidine to give diamine **296**. Unfortunately the yield for this reaction was very low and would not be useful for a multistep synthesis. The small amount of diamine **296** was then guanidinylated to give bisguanidine **298**. Initially, the oxidation of compound **298** was sluggish and required many equivalents of Dess-Martin periodinane to give ketone **300**. It was eventually noticed that the alcohol was protected as a TMS ether, which for some reason was stable. This was easily removed by stirring in 1M HCl in THF. After the alcohol was successfully deprotected the oxidation with Dess-Martin periodinane proceeded smoothly. This alcohol was then oxidized to ketone **300** with Dess-Martin periodinane.

The Boc deprotection seemed to be troublesome because of the labile TBS protecting groups. It was thought that replacing them with the more robust TBDPS groups might solve this problem. Unfortunately, this approach was not fruitful.



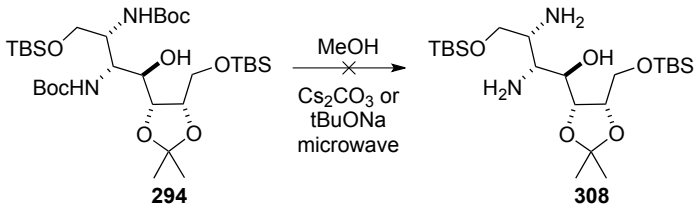
Scheme 77 Preparation of ketone **300** and **301**.

The triol was also protected as triacetate or tripivoyl ester (**302** and **303**) and submitted to Ohfune's conditions, but the reactions were very messy and no product was isolated (Scheme 78). The Boc deprotection of TBS-protected triol **288** was also attempted with the milder TBSOTf, but this reaction was not successful.



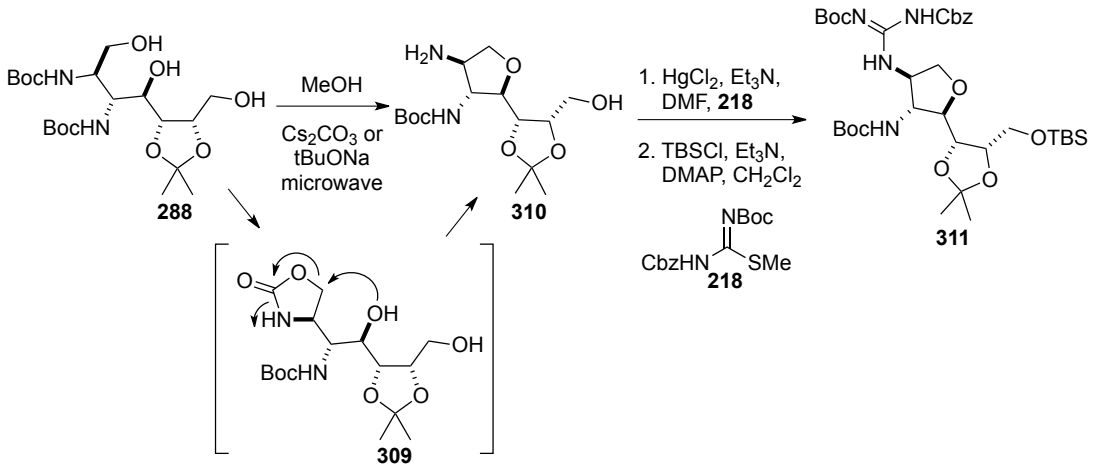
Scheme 78 Failed Boc protections.

The next series of Boc deprotections were carried out in the microwave (Scheme 79). TBS ether **294** was dissolved in DMF or MeCN and heated at various temperatures (up to 200ºC) in the microwave resulting only in complex mixtures.



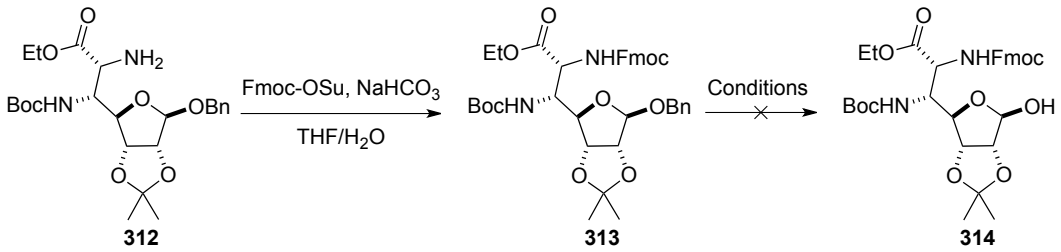
Scheme 79 Failed thermal lysis of Boc groups.

Pfizer developed some base-promoted Boc deprotections using KO^{t}Bu in THF/H_2O and another group reported a similar reaction using cesium carbonate/methanol.[60] When TBS-protected triol **294** treated with cesium carbonate or KO^{t}Bu and microwaved in methanol, it led to a complex mixture of products. However when triol **288** was microwaved under the same conditions it led to a single product (Scheme 80). Compound **310** was guanidinylated and then TBS-protected to give TBS ether **311**. The MS gave a peak that corresponded to incorporation of one guanidine and the loss of a water molecule. The NMR showed only one guanidine, but two t-butyl groups and no olefin protons. The data indicated the presence of a tetrahydrofuran, but unfortunately, the data was not conclusive. Mechanistically, to form tetrahydrofuran **310**, the secondary alcohol would have to attack oxazolidinone **309** losing CO_2. This reaction is interesting, but not useful for this synthesis. This does however show preferential deprotection of the Boc group with the primary alcohol. If the secondary alcohol were protected, it should allow the Boc group to be selectively differentiated (see 2.3.1 Oxazolidinone Formation).



Scheme 80 Unexpected rearrangement.

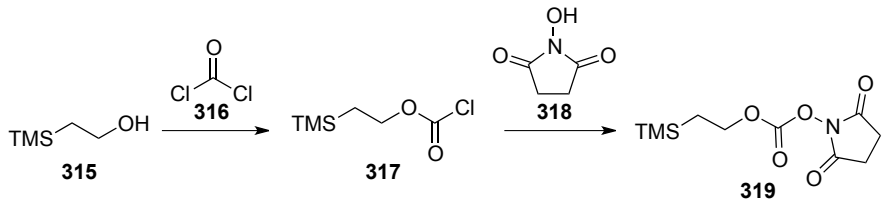
Due to the stubbornness of the BOC deprotection, the most obvious solution is to avoid using the BOC groups all together. This would require a new protecting group, which has to meet two requirements. First it must be stable to hydrogenation conditions and second it must be stable to sodium borohydride. The first group tested was the Fmoc group (Scheme 81). Amine **312** was treated with Fmoc-OSu and sodium bicarbonate in THF/H_2O giving carbamate **313**. Unfortunately, the Fmoc group was not stable to any hydrogenation conditions.



Scheme 81 Fmoc protecting group strategy. Conditions: 20% $Pd(OH)_2/C$, H_2, MeOH;10% Pd/C, H_2, MeOH; 10% Pd/C, H_2, AcOH, THF

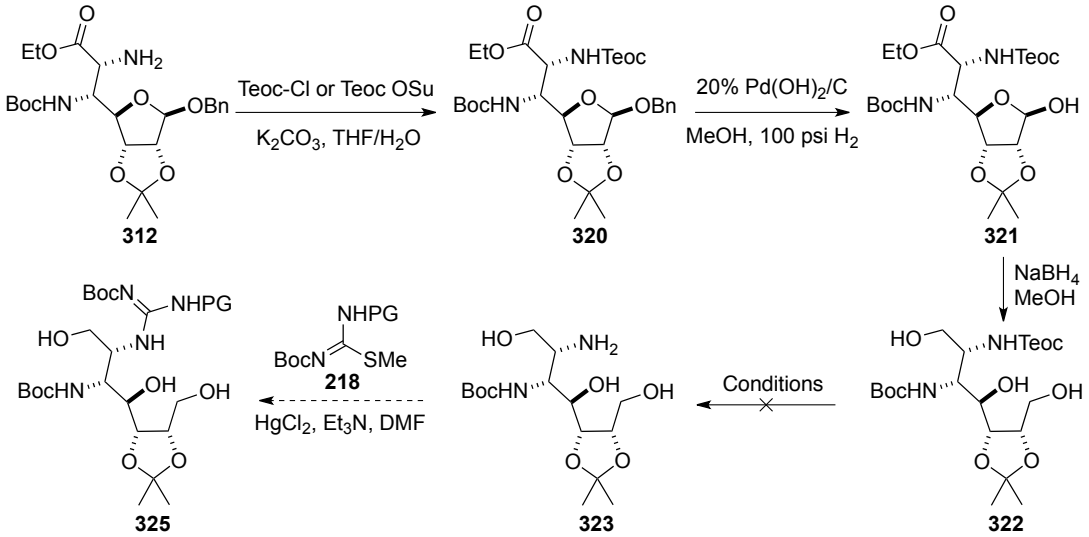
Some more research into protecting groups led to the Teoc group, which should be stable to hydrogenation conditions as well as to sodium borohydride. Teoc-Cl (**317**) was prepared from phosgene (**316**) and 2-(trimethylsilyl)ethanol (**315**) (Scheme 82). The Teoc-Cl was used immediately, as it decomposes fairly quickly in the freezer. The remaining Teoc-Cl was

converted to the more stable Teoc-OSu (**319**), by treatment with N-hydroxysuccinimide (**318**), which worked well albeit with slightly longer reaction times.



Scheme 82 Preparation of Teoc-Cl and Teoc-OSu.

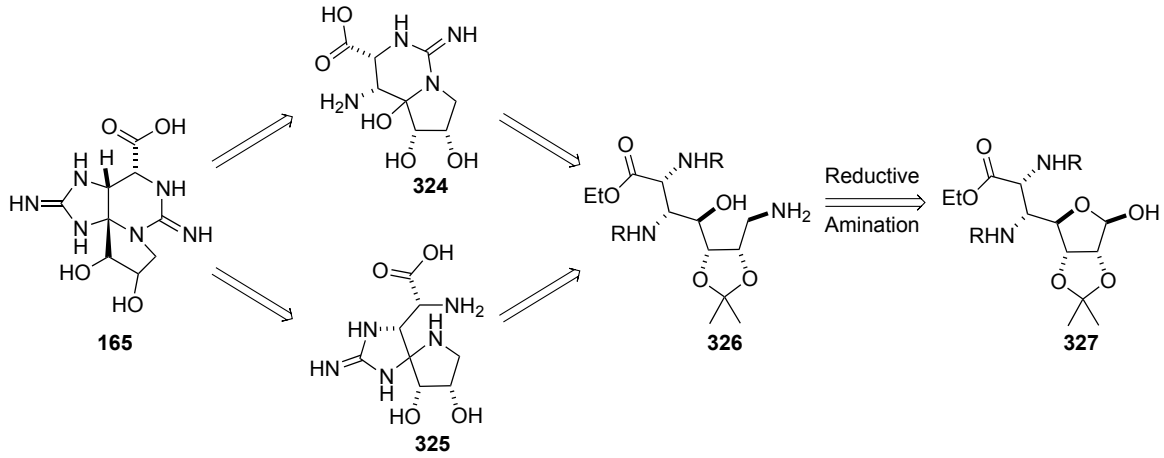
Amine **312** was treated with Teoc-Cl or Teoc-OSu to give carbamate **320**, followed by hydrogenation over palladium hydroxide on charcoal to give lactol **321**, which was subsequently reduced with sodium borohydride to give triol **322** (Scheme 83). The next step in the synthesis is the removal of the Teoc group followed by guanidinylation of the amine. The Teoc group on triol **322** was treated with various deprotection conditions, but unfortunately amine **323** was not isolated.



Scheme 83 Unsuccessfull teoc protection strategy. Conditions: TBAF, MeOH or THF; HF, MeOH; TAS-F, CH_2Cl_2

2.3 Reductive Amination Approach

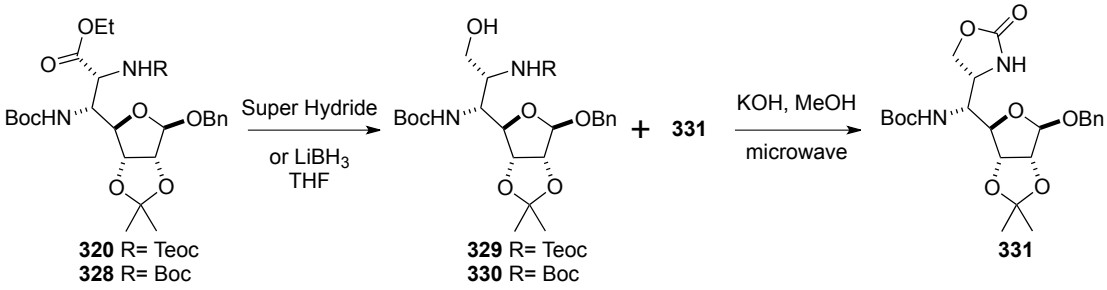
Using reductive amination to install an amine at the lactol of ribose was a goal that was attempted at many different times during the course of this project. The idea was that the core of saxitoxin (**165**) could come from hemiaminal intermediate **324** or spirohemiaminal **325**, which could be derived from amine **326** (Scheme 84). This amine could be formed directly from a reductive amination on lactol **327**.



Scheme 84 Reductive amination approach.

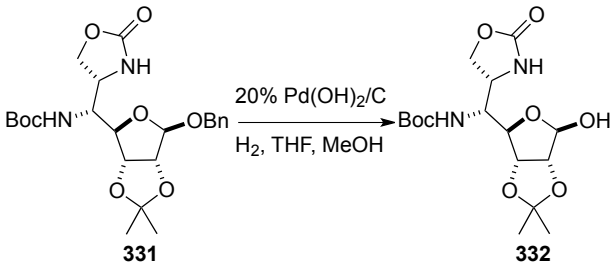
2.3.1 Oxazolidinone Formation

Investigating the reduction of ester **320** and **328** put the reductive amination route in motion by the discovery of a useful product, which was completely overlooked at first (Scheme 85). When ester **328** was treated with super hydride (lithium triethylborohydride) alcohol **329** was formed along with a significantly more polar product (**331**). Microwave irradiation of alcohol **329** resulted in a single product, which matched the unidentified compound. NMR and MS analysis revealed that the mystery compound is oxazolidinone **331**, which forms by nucleophilic of the alcohol on the carbamate. It was thought that by using a milder reducing agent that oxazolidinone byproduct **331** could be avoided, but this turned out not to be the case.



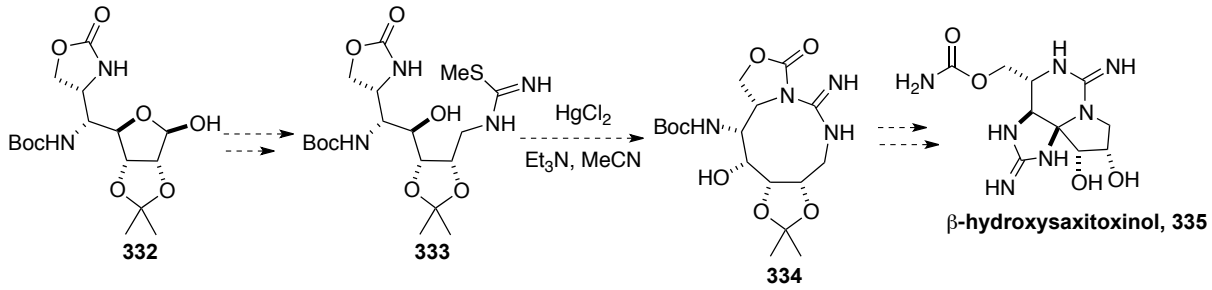
Scheme 85 Formation of oxazolidinone **331**.

Deprotection of benzyl ether was effected with palladium hydroxide on carbon in THF/MeOH giving an 88% yield of lactol **332** (Scheme 86).



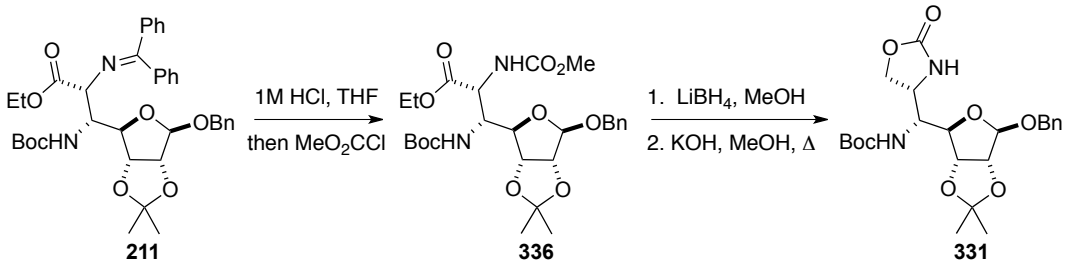
Scheme 86 Preparation of lactol **332**.

The isolation of oxazolidinone **331** led to the idea of using it in a route that utilizes reductive amination in the synthesis of saxitoxin analogs (Scheme 87). Reductive amination of lactol **332** followed by installation of an S-methylpseudothiourea could give compound **333**. This pseudothiourea could then undergo an intramolecular guanidinylation to give 9-membered ring **334**, which is similar to an intermediate in Du Bois synthesis (see 1.4.3 Du Bois). This 9-membered ring could then elaborated to β-hydroxysaxitoxinol (**335**) in a few steps.



Scheme 87 Potential 9-member ring approach to saxitoxin.

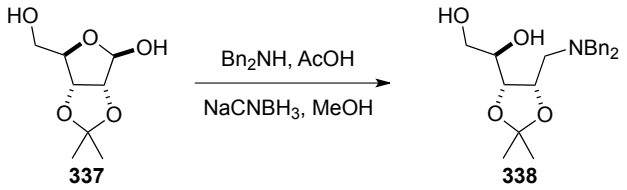
The synthesis of oxazolidinone **331** was optimized by taking Mannich product **211** and swapping out the benzophenone imine for a methyl carbamate to give compound **336** (Scheme 88). Compound **336** was reduced to the alcohol with lithium borohydride and crude mixture was refluxed in methanol with KOH to give oxazolidinone **331** in good yield.



Scheme 88 Optimized preparation of oxazolidinone **331**.

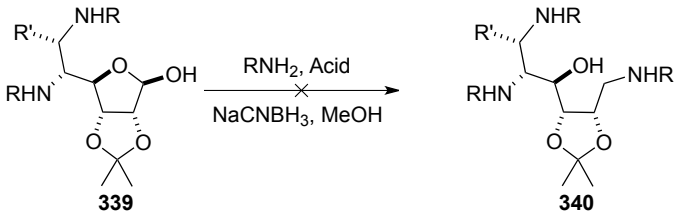
2.3.2 Initial Reductive Amination Attempts

Very early on in this project reductive amination reactions were tested on various substrates. The first success was the reductive amination of ribose-2,3-acetonide (**337**) with dibenzylamine (Scheme 89). This reaction initially failed over and over again until it was discovered that adding 3 eq. of acetic acid promoted the reaction, giving dibenzylamine **338**. This compound was taken forward in another synthetic route, which was not fruitful.



Scheme 89 First successful reductive amination.

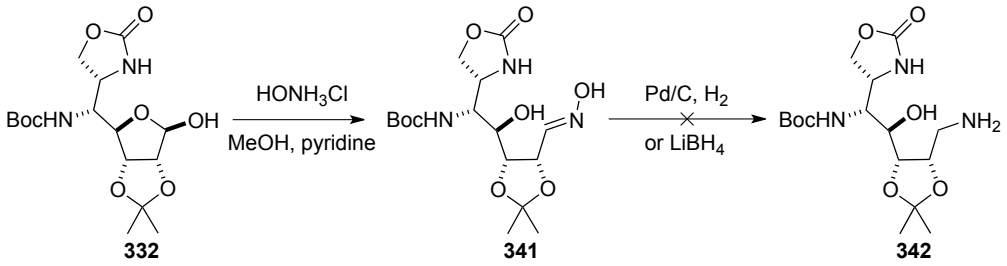
Later in the course of this project, numerous lactols were prepared and submitted to reductive amination conditions (Scheme 90). Many different acids and amines were screened, but every time the outcome was recovered starting material. Since forming oximes from the lactol was previously demonstrated on other substrates, a stepwise reductive amination was tested.



Scheme 90 Failed reductive amination.

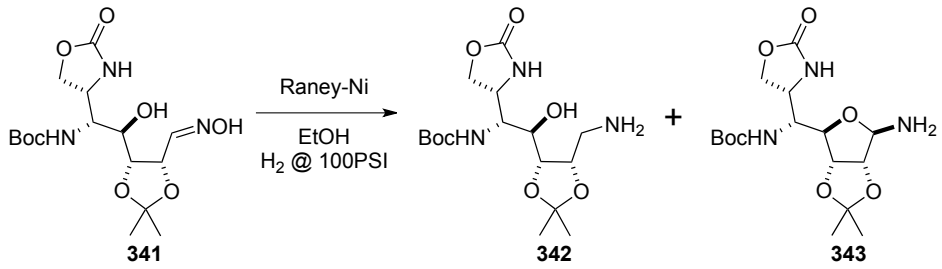
2.3.3 Reductive Amination: A Stepwise Approach

Lactol **332** was treated with hydroxylamine HCl and pyridine in methanol to give oxime **341** (Scheme 91). Treatment of the oxime with lithium borohydride failed to give amine **342**. Catalytic hydrogenation of the oxime over 10% Pd/C also failed to give amine **342**. Several other hydride conditions as well as hydrogenation condition were tested, but none led to the formation of the amine.



Scheme 91 Oxime reduction attempts.

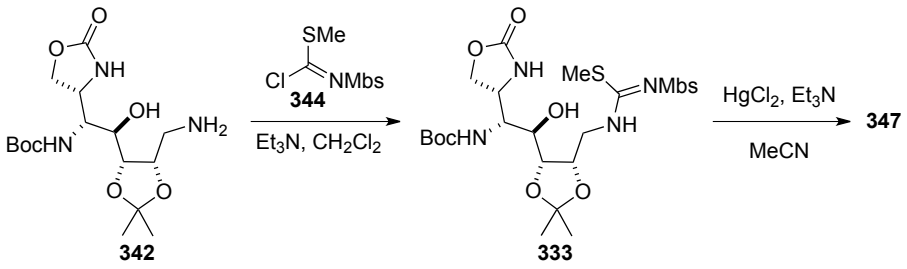
It was not until about a year later that a literature study revealed that Raney-Ni is commonly used to reduce oximes to amines. Shocked that such obvious conditions were overlooked, oxime **341** was hydrogenated over Raney-Ni, giving a low yield (~10-50%) of amine **342** (Scheme 92). The byproduct of the reaction was determined to be hemiaminal **343**. This reaction was extremely irreproducible and scale-up made the yields worthless. Many different hydrogenation conditions were screened, but all of them were low yielding.



Scheme 92 Reduction of oxime **341**.

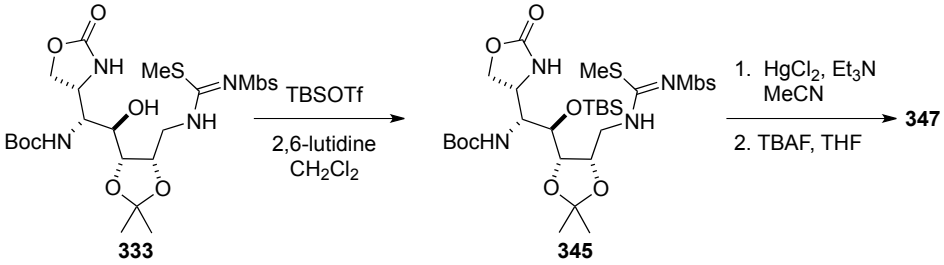
2.3.4 Formation of the 9-Member Ring

Amine **342** was treated with reagent **344** to give product **333**, in excellent yield. Isothiourea **333** was then treated with standard guanidinylation conditions to give a clean product (**347**) in very high yield with a mass matching the desired compound. Treatment of **347** with Dess-Martin periodinane gave no reaction, which was completely unexpected.



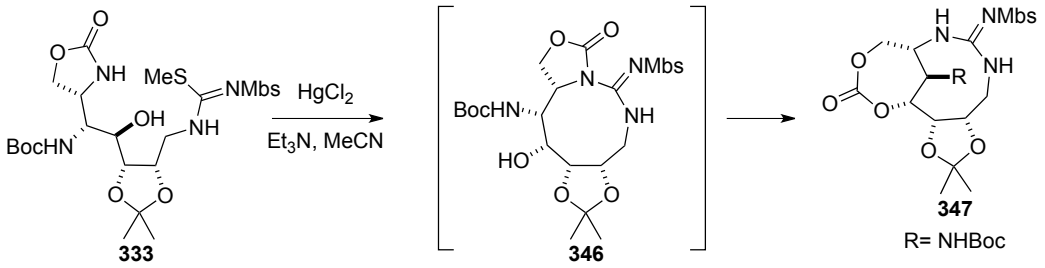
Scheme 93 Unknown cyclization of compound **333**.

The failed Dess-Martin oxidation indicated that the carbodiimide intermediate might have cyclized on the secondary alcohol. This was proven not to be the case by protecting alcohol **333** with a TBS group before the cyclization (Scheme 94). Isothiourea **345** was then cyclized and treated with TBAF, which resulted in the same mystery compound (**347**).



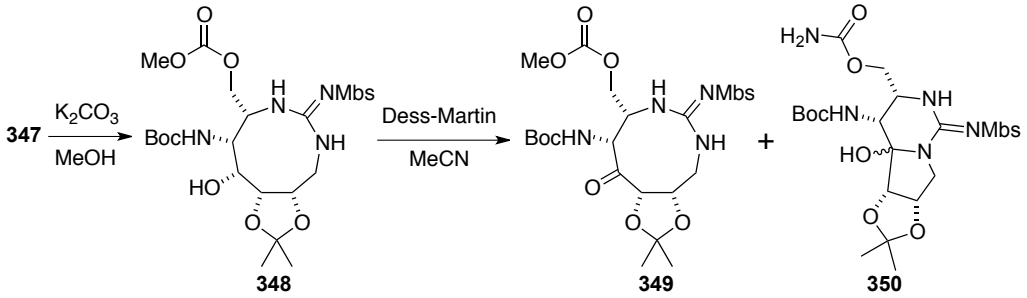
Scheme 94 Formation of compound **347**.

Since the mass of the mystery compound matched desired compound **346** and the alcohol was not free it was hypothesized that the guanidinylation of the oxazolidinone activated it enough that it was electrophilic enough to get attacked by the alcohol, forming carbonate **347** (Scheme 95).



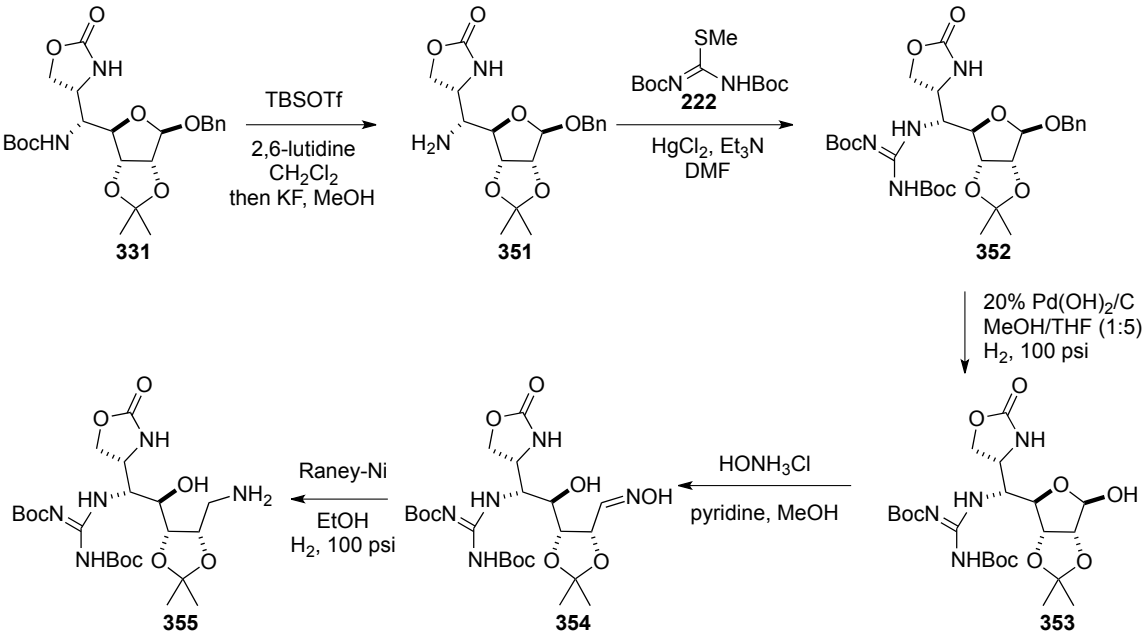
Scheme 95 Identity and formation of compound **347**.

To test this theory, the **347** was treated with potassium carbonate in methanol, which gave a single compound (Scheme 96). This compound was treated with Dess-Martin in dichloromethane to give a mixture, which was determined, by NMR and mass spectrometry to be ketone **349** and hemiaminal **350**.



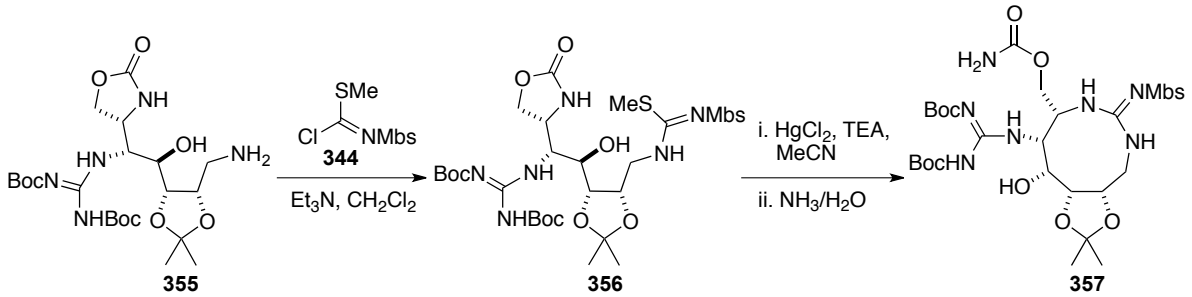
Scheme 96 Preparation of ketone **349** and hemiaminal **350**.

With this great result in hand, all that was left to get to the real system is swap out the Boc group for a guanidine and install the carbamoyl group (Scheme 97). The Boc group was removed by treating oxazolidinone **331** with TMSOTf and 2,6-lutidine in CH_2Cl_2 to give amine **351**, which was guanidinylated with isothiourea **222**. This Boc deprotection was used for a long time until it was discovered that using TBSOTf instead, followed by fluoride workup, was much more scalable and higher yielding. Guanidine-containing oxazolidinone **352** was converted to amine **355** using the previously developed steps.



Scheme 97 Synthesis of amine **355**.

With amine **355** in hand, it was converted to the isothiourea **356** with reagent **344** and triethylamine in CH_2Cl_2 (Scheme 98). It was thought that the carbonate formed after the cyclization could be opened with ammonia instead of methanol to install the carbamoyl group found in saxitoxin. This turned out to work wonderfully, as when the cyclization reaction was complete it was quenched with concentrated ammonium hydroxide giving 9-member ring **357** in great yield, containing the required carbamoyl group.

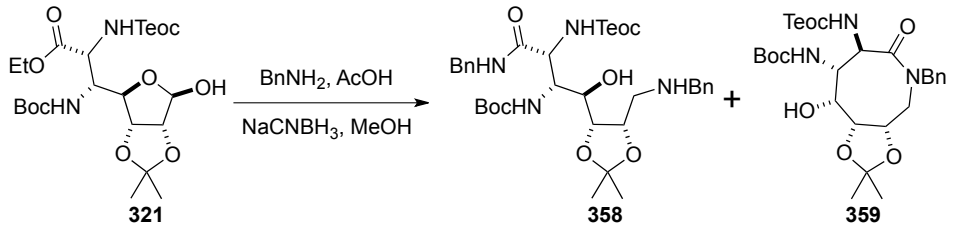


Scheme 98 Formation of 9-member ring **357**.

2.3.5 Reductive Amination

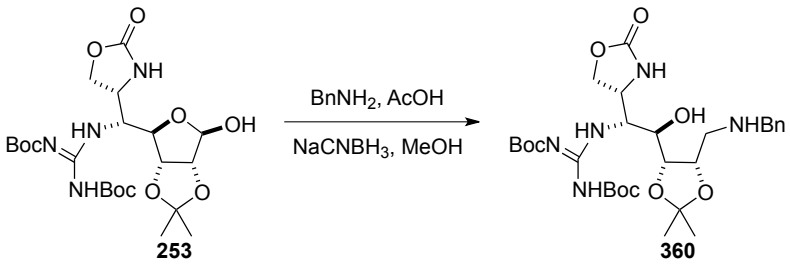
The stepwise reductive amination gave terrible yields and was difficult to reproduce, but proved that the route was viable. Determined to improve the overall yield of 9-member ring **357**, an intense study into using a "one pot" reductive amination ensued. Since the oximes are so easily formed from the lactol, it was assumed that the problem with the reaction was not a steric problem, but a problem with the nucleophilicity of benzyl amines. The only working example of reductive amination on a ribose-derived lactol required acetic acid to assist in opening the lactol to the aldehyde (Scheme 89). Since acetic acid was the key ingredient, maximizing the acetic acid without destroying the hydride reagent became the immediate goal.

Digging into the literature revealed that sodium cyanoborohydride is stable to pH 3. To get a handle on how much AcOH is required to get a pH of around 3 it was decided to add bromocresol green to the reaction mixture. Bromocresol green changes from blue to yellow at a pH of 3.8, which would indicate the maximum amount of acid possible to avoid destruction of the sodium cyanoborohydride. Lactol **321** was the first substrate tested because there were several hundred milligrams already in hand. To a mixture of lactol **321**, benzyl amine (20 eq.) and sodium cyanoborohydride (10 eq.) and trace bromocresol green was added acetic acid until the solution turned bright yellow. It turned out that it required 100 equivalents of AcOH to reach the desired pH! At this pH it took 4 days for the starting material to be consumed, resulting in an inseparable mixture of two compounds (Scheme 99). NMR data showed the loss of the ester peak and incorporation of the benzyl group. Mass spectrometry indicated the formation of amide **358** and 8-member ring amide **359**.



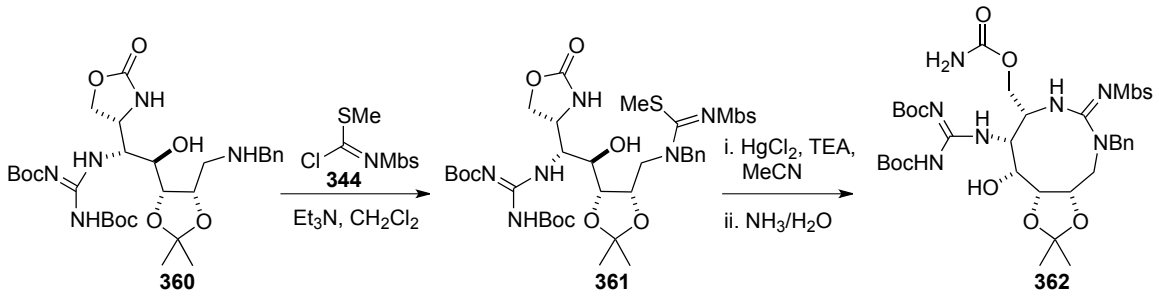
Scheme 99 Unexpected products from reductive amination.

Even though this result was not expected, it demonstrated that reductive amination is possible, just not in the presence of the ethyl ester. Fortunately, lactol **353** contains no ethyl ester and should be a great substrate for this reaction. When this reaction was tested on lactol **353** it was found that ~160 equivalents of AcOH were required to reach the desired pH. Now that the proper pH was obtained the reaction went to completion after stirring overnight to give desired benzylamine **360** in >70% yield (Scheme 100). It was later discovered that the reaction could be run at high very concentrations using AcOH as the solvent and only 3 equivalents of amine giving the desired benzyl amine in a couple of hours. At this low pH the sodium cyanoborohydride decomposes slowly, but since the reaction is fast it lasts long enough to allow the reaction to go to completion.



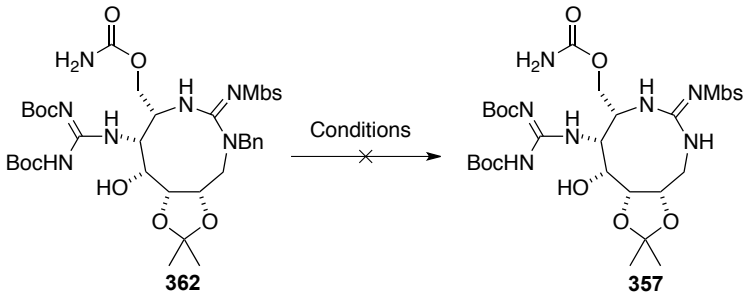
Scheme 100 Desired reductive amination product.

With benzylamine **360** in hand, the previously described sequence was used to make 9-member ring **362** (Scheme 101). This proceeds smoothly but requires more time and has a slightly lower yield than the same reactions with amine **342**.



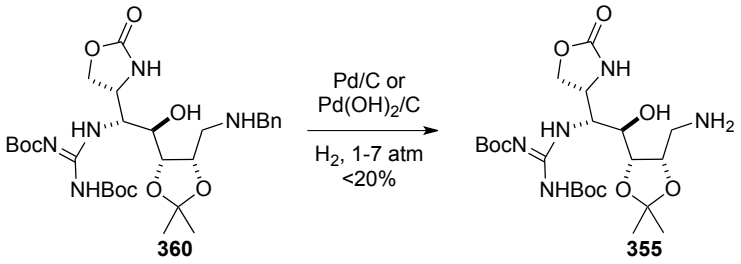
Scheme 101 Preparation of 9-member ring **362**.

The next step in the sequence was to remove the benzyl group and intercept the previously developed pathway (Scheme 102). Unfortunately, all attempts to hydrogenate off the benzyl group failed. In all cases, only starting material was recovered, even when hydrogenated with high pressure, high catalyst loading and long reaction times (>1 week).



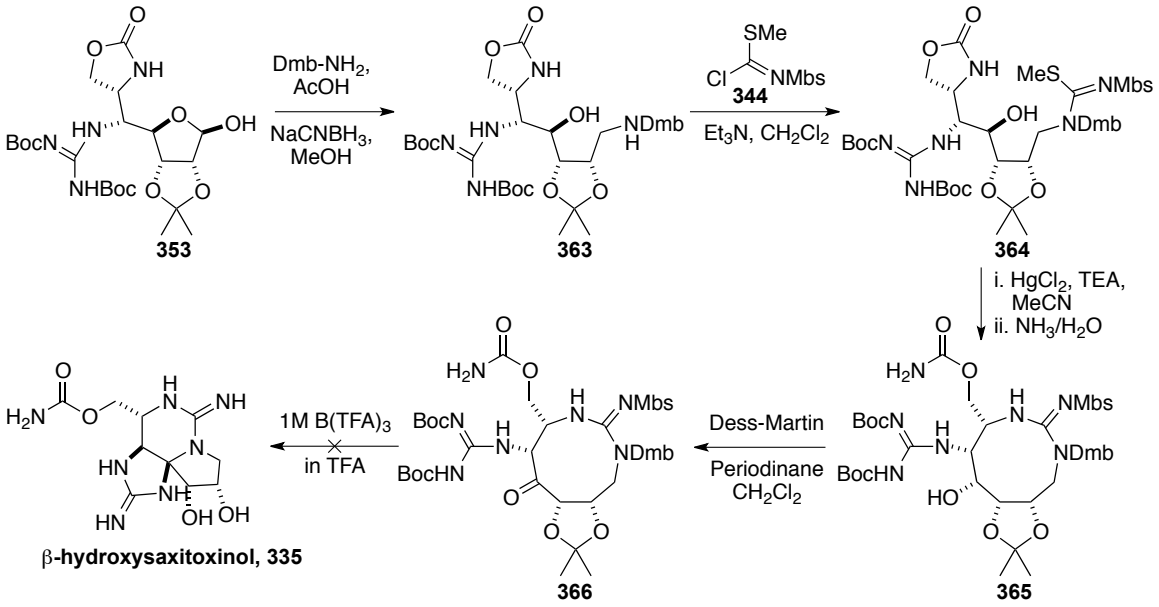
Scheme 102 Failed debenzylation of compound **162**. Conditions: Pd/C, $Pd(OH)_2C$, or $PdCl_2$; MeOH, EtOAc, THF or AcOH; H_2 100 psi; 25-100°C; with or without HCl.

Since the benzyl group could not be removed from the 9-member ring, benzylamine **360** was hydrogenated to hopefully improve the yield of amine **355** (Scheme 103). Unfortunately, the hydrogenation gave low yields, similar to the reduction of oxime **354** with Raney-Ni. The problem with forming the free amine could be similar to the problem described previously where the amine can attack the other guanidine, giving migration products or, in this case, maybe it can attack the oxazolidinone, resulting in complex mixtures.



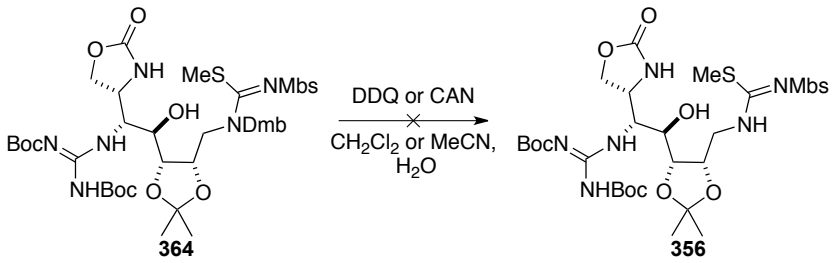
Scheme 103 Hydrogenation of benzylamine **360**.

Since hydrogenation would not work at removing the benzyl group from the 9-member ring, it was thought that a 2,4-dimethoxybenzyl (Dmb) group might be easier to remove. It could potentially be removed at the ketone stage by an oxidative cleavage (ceric ammonium nitrate (CAN) or 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)) or maybe at the end of the synthesis with an acidic global deprotection. This substrate was prepared in the same way as the benzyl ether-containing ring was. Unfortunately, when ketone **366** was treated with boron trifluoroacetate in trifluoroacetic acid and worked up the same way as previously described, nothing was isolated.



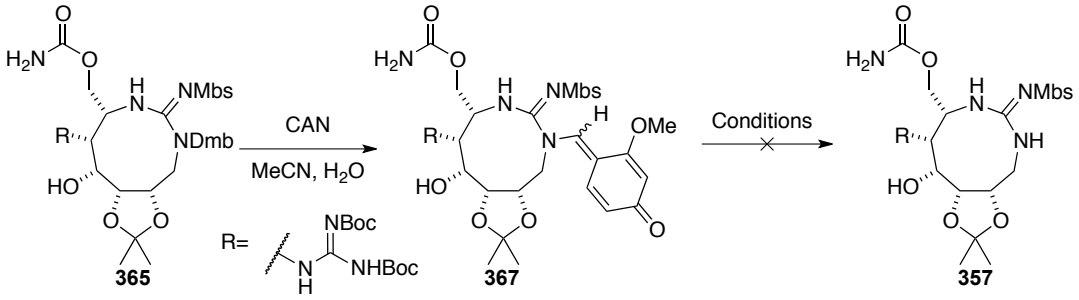
Scheme 104 Syntetic route to ketone **366.**

Since the last step did not work the same as on the deprotected substrate, the removal of the Dmb group was attempted on multiple substrates along the way to see if the other pathway could be intersected. Treatment of Dmb protected isothiourea **364** with DDQ gave no reaction and treatment with CAN was very messy (Scheme 105). This is not surprising due to the ability of CAN to oxidize sulfur atoms.



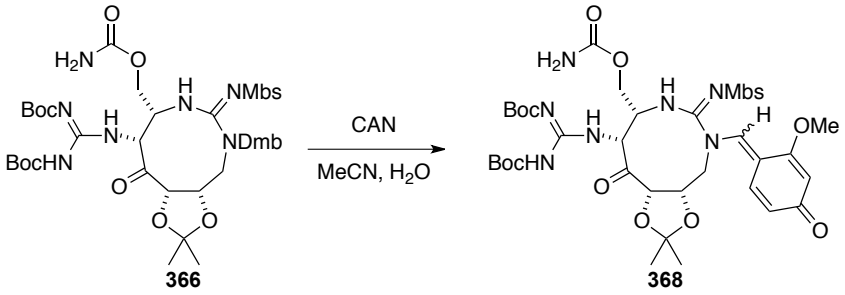
Scheme 105 Failed oxidative cleavage of Dmb.

Since the Dmb group couldn't be removed from the isothiourea, 9-member ring **365** was treated under the same conditions. DDQ gave no reaction, but CAN reacted rapidly to give an inseparable mixture of two compounds that gave a single mass, which is suspected to be a mixture of E and Z isomers of compound **367** (Scheme 106). Treatment of the mixture with various acidic conditions only returned starting material.



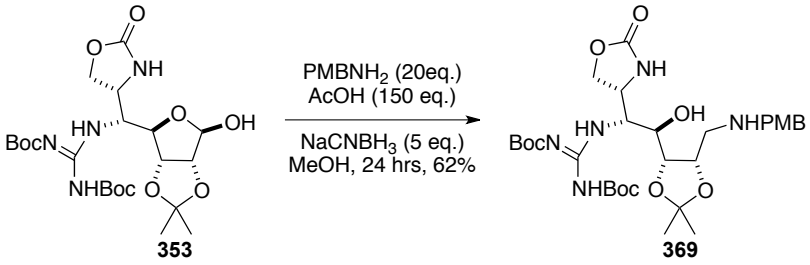
Scheme 106 Unexpected oxidation product. Conditions: HCl, or TFA; MeOH or H_2O

To make sure the free alcohol wasn't causing some sort of problem with the deprotection step, the deprotection was also attempted on ketone **366**, giving suspected compound **368**, which is similar to compound **367** (Scheme 107).



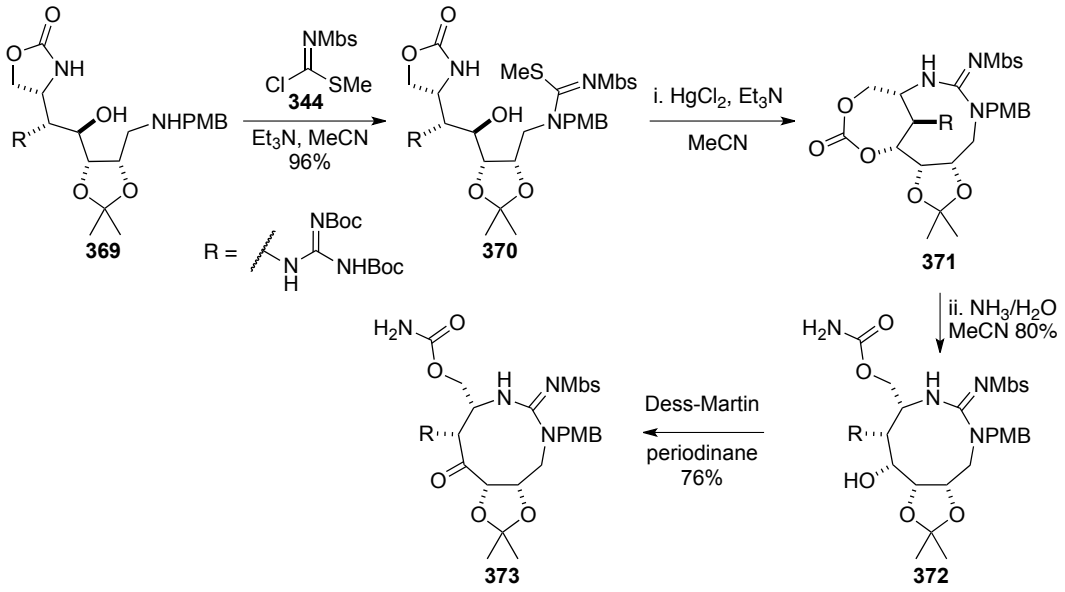
Scheme 107 Oxidation of Dmb with CAN.

The sequence of reactions previously described using Bn or Dmb amine was extended to PMB amine. Reductive amination of lactol **353** with PMB amine, acetic acid and sodium cyanoborohydride in methanol gave benzyl amine **369** in a 62% yield (Scheme 108).



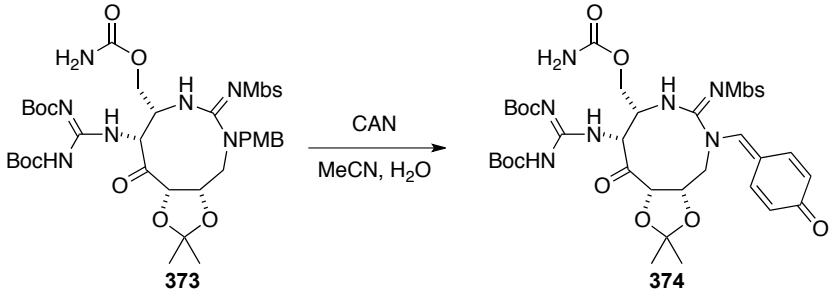
Scheme 108 Reductive amination with PMB amine.

With benzyl amine **369** in hand, it was treated with reagent **344** and triethylamine in dichloromethane to give compound **370** (Scheme 109). With this compound in hand, treatment with mercuric chloride and triethylamine followed by addition of ammonia in water gave alcohol **372**, which could be oxidized with Dess-Martin periodinane to give ketone **373** in good yield.



Scheme 109 Synthetic route to ketone **373**.

Just like in the case with the Dmb group, PMB amine **373** was treated with CAN resulting in the oxidation, but not cleavage of the PMB group (Scheme 110).

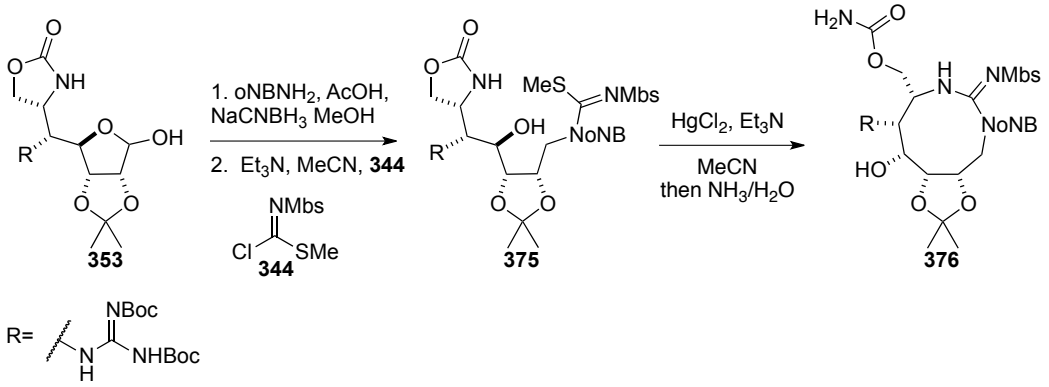


Scheme 110 CAN oxidation of PMB-protected guanidine.

Since the removal of the Bn, PMB and Dmb group did not occur under acid or oxidative conditions, access to compound **357** was not possible. Unfortunately, the only way to access this compound was by installing the amine through formation of an oxime and reduction with Raney nickel, which resulted in very low yields.

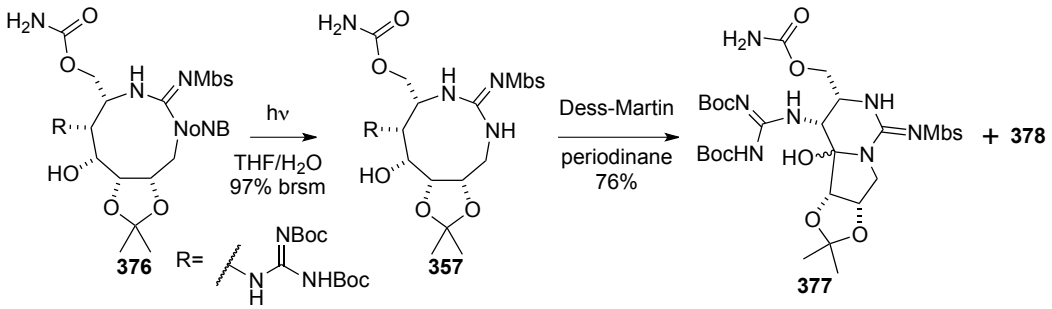
It was thought that the o-nitrobenzyl (oNB) protecting group would be easier to remove than the PMB group (Scheme 111). The oxidative cleavage of the PMB group requires the

formation and subsequent hydrolysis of an iminium ion from the enamine. Forming the iminium ion requires donation of electrons from the guanidine, which has been shown to be fairly difficult by Du Bois and other groups. It is hypothesized that this step is what is preventing the cleavage. The photolysis mechanism of an o-nitrobenzyl (oNB) shows that iminium formation is bypassed, which could allow the cleavage to occur more readily. Photolysis precursor **376** was prepared in 3 steps from lactol **353**.



Scheme 111 Preparation of oNB protected 9-member ring.

O-Nitrobenzylamine **376** was dissolved in wet THF, degassed with argon and submitted to UV radiation (Scheme 112). After ~20 minutes of irradiation the oNB group was successfully cleaved giving compound **357**, which matched all previously obtained data, thus bypassing the Raney-Ni reaction and allowing access to large quantities of hemiaminal **377**.



Scheme 112 Alternate synthesis of hemiaminal **377** and ketone **378**.

The oxidation of alcohol **357** led to a mixture of ketone **378** and hemiaminal **377**. This is unlike in Du Bois' saxitoxin synthesis, where the hemiaminal is the only product isolated. This is more than likely due to the wrong stereochemistry. The use of Spartan 10 software allowed the calculation of the energy differences between hemiaminal **377** and the **epi-377**, which has the correct stereochemistry. The energy difference between the two epimers was calculated to be 10 kcal/mol. This energy difference is significant and indicates that if the **epi-377** were synthesized then the hemiaminal should be the dominant form.

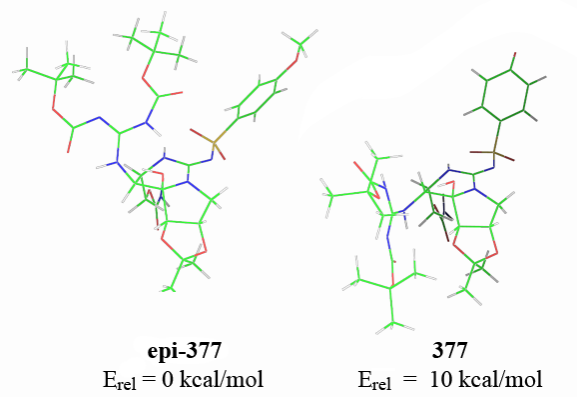
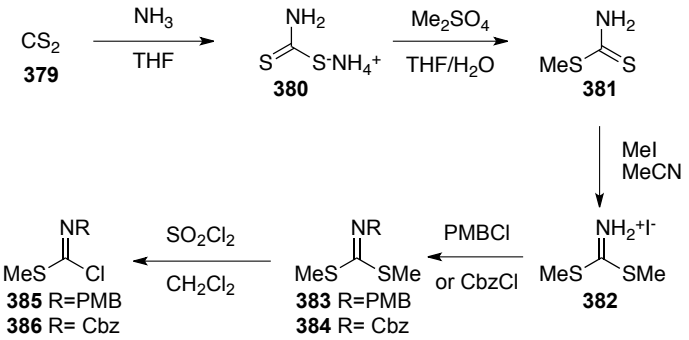


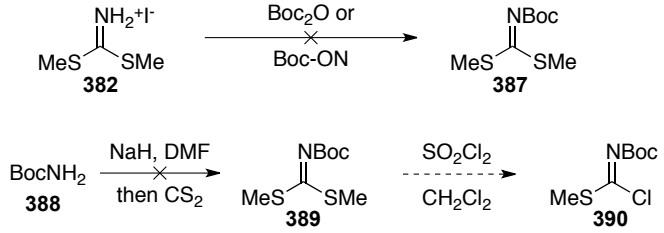
Figure 8 Energy difference (E_{rel}) between epimers **377** and **377B**

Since the Mbs group is fairly difficult to remove, alternative reagents to replace compound **344** were sought. Reagents **383** and **384** were prepared from dimethyl carbonimidodithioate **382** by treatment with their respective chloroformate (Scheme 113). Treatment of compound **382** and **384** with sulfuryl chloride gave **385** and **386**, respectively.



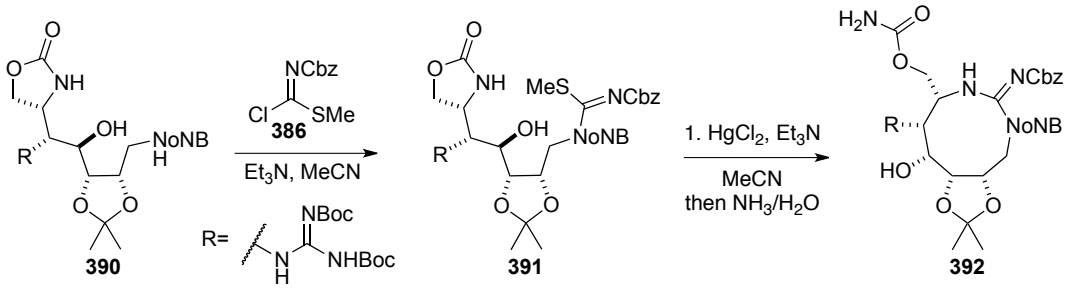
Scheme 113 Preparation of reagent **385** and **386**.

Boc-containing reagent **389** was thought to be the ideal substrate as Boc groups are very easy to remove from guanidines and it would not require an additional deprotection step. Unfortunately, all attempts to form the Boc adduct of compound **389** failed miserably (Scheme 114). Even with compound **382** in hand, no Boc protecting conditions gave any product. Using phosgene to prepare t-butyl chloroformate, which is only stable at low temperatures, has not been tested.



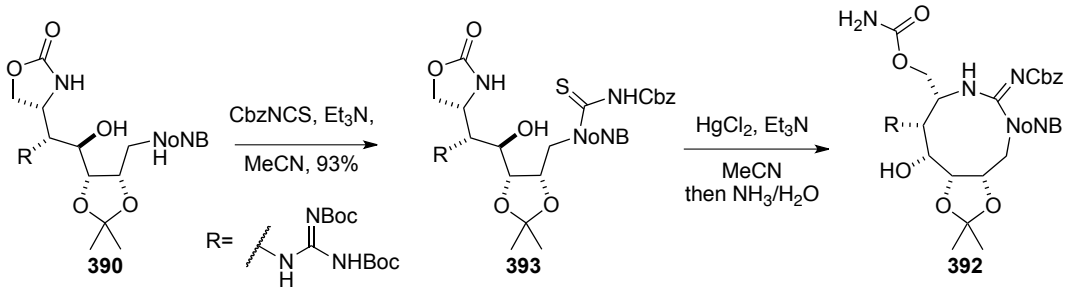
Scheme 114 Failed preparation of reagent **390**.

With reagent **386** in hand, the same the sequence was performed as previously described (Scheme 115). The sequence worked about the same except the first acylation step was much slower and required excess reagent and stirring overnight.



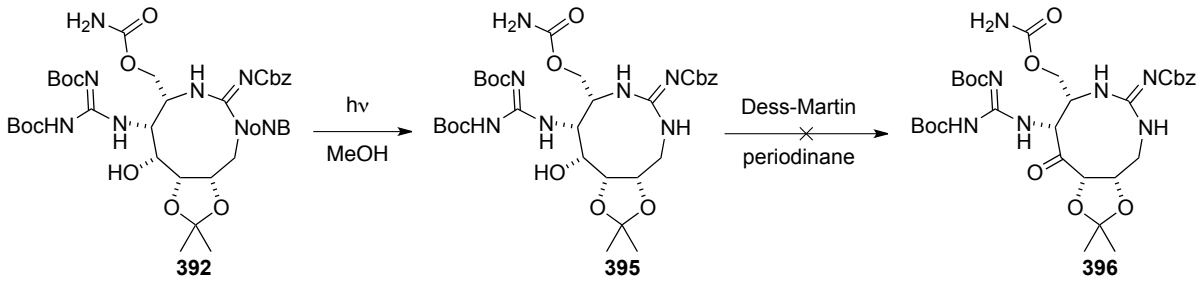
Scheme 115 Preparation of 9-member ring **392**.

Another reagent screened was CbzNCS, which was prepared in one step by treating KSCN with CbzCl in a mixture of toluene and acetonitrile.[61] Unfortunately, the yield of this reaction was very low. Treatment of amine **390** with CbzNCS gave thiourea **393**, which was then treated with mercury to form 9-membered ring **392** (Scheme 116), in low yield. The acylation step was very fast and clean, but the cyclization proved to be more problematic. The reaction when stirred with excess mercuric chloride and triethylamine would not go to completion even if left overnight. Some product was isolated, but the main product seemed to be a mercury adduct of the starting material. The NMR looked the same as the starting material, but upon standing overnight, a dark mercury precipitate formed in the NMR tube.



Scheme 116 Alternate preparation of 9-member ring **392**.

O-Nitrobenzylamine **392** was deprotected by irradiation with UV to give compound **395**, which was submitted to Dess-Martin periodinane (Scheme 117). Unfortunately, this reaction was messy and the ketone was not isolated.



Scheme 117 Failed oxidation of ketone **395**.

2.3.6 Isolation and Characterization of Polar Compounds

It was at this time when the compounds became so polar that monitoring reactions and isolating compounds became a major hurdle, so this section is devoted to the methods used to overcome these problems. The only solution to this problem was to learn how to run reverse phase column chromatography and HPLC. At the time the only materials at hand were some C18 reverse-phase TLC plates and some C18 silica gel. The outcomes of the reactions were inconclusive because of difficulties monitoring reactions by reverse-phase TLC and purifying by reverse-phase flash chromatography. The lab had two HPLC systems, a HP 1050 (analytical) and a Waters 600E (semi-preparative). Unfortunately, both machines were broken and had been sitting, covered with dust, in some cabinets for almost a decade. Out of pure frustration, chemistry was put on hold and the machines were dusted off and set up on a previously cluttered lab bench.

The HP 1050 had a broken multichannel gradient valve (MCGV), a leaky injector and system-wide clogs. The lines were all individually purged one by one until the flow was consistent. The leaky injector was found to contain a scratched rotor plate (from improper needles being used), which was easily replaced with a new part. It was at this time that several dozen old, dried-out columns were individually flushed (forwards and backwards) and tested for separation. Luckily a few columns were found to be of sufficient quality for some separations.

Since the MCGV was broken the HPLC required isocratic runs from premixed solvents. After some time for getting the hang of HPLC separations, the MCGV was replaced and the machine was in tip-top working order.

The Waters HPLC was a bit more troublesome. Setting up the machine was not easy. Since the machine lacked the data acquisition card, a computer could not be hooked up. This meant that an IEEE cable could not be used to connect the different modules (controller, detector, pump and fraction collector). All the connections had to be made via individual wire connections. After resorting to the user manuals many times the 20 or so the connections were finally made. Since the machine couldn't be hooked up to a computer, the only way to view the chromatogram was on a tiny LCD display that was smaller and had less resolution than my Ti-89 graphing calculator. Learning to operate the machine manually required the intense study of the user manuals.

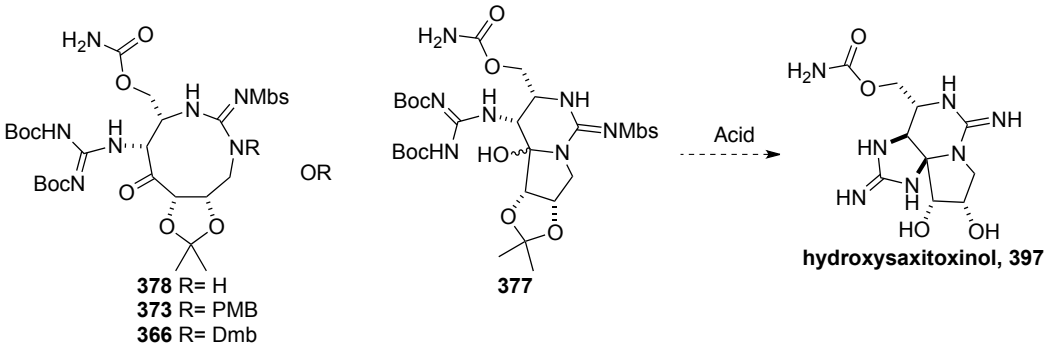
The machine functioned fairly well at first until the check valves started to get stuck. To test the valves individually required graphing the pressure. The broken pressure sensor and lack of a computer made this impossible. After replacing the pressure sensor, a method to connect to a computer was required. After obtaining a data acquisition (DAQ) card and building an OP AMP circuit to amplify the 0-10mV signal to the 0-1V range required for the DAQ card, it was finally possible to graph the pressure on a laptop (after learning how to do some basic programming in LabVIEW and DASYLab). The problems with the check valves were sorted out and eventually fixed. After the successful purification of a couple of compounds, the fraction collector broke down and the detector bulb burned out. The detector bulb was replaced and the electronics specialist fixed the fraction collector.

Using the HPLC resulted not only in the purification of some compounds, but the ability to monitor reactions by reverse-phase TLC because of the development of working solvent systems. This newly learnt technique was extended to reverse-phase flash chromatography, which allowed crude reaction mixtures to be cleaned up in preparation for further purification by HPLC. Unfortunately, in most cases what looked like one compound by TLC turned out to be several compounds by HPLC, so unless the reaction was very clean, HPLC had to be used for all reverse-phase separations.

Now that the HPLCs were fixed it was possible to monitor reactions and to isolate compounds from the reactions in the following sections. It is worth noting that many of the early attempts at these reactions probably failed simply due to the lack of reverse-phase purification techniques. Even with these newly learnt techniques, the purification and characterization of these compounds is extremely difficult. Proton NMR didn't provide too much data, as there are relatively few protons to look at. Carbon NMR spectra are also difficult to get because of very weak signals from the guanidine carbons. To overcome these limitations, 2D NMR techniques were used. Experiments such as gCOSY, HSQC, HMBS, and TOCSY were paramount in the structural determination of the polar compounds.

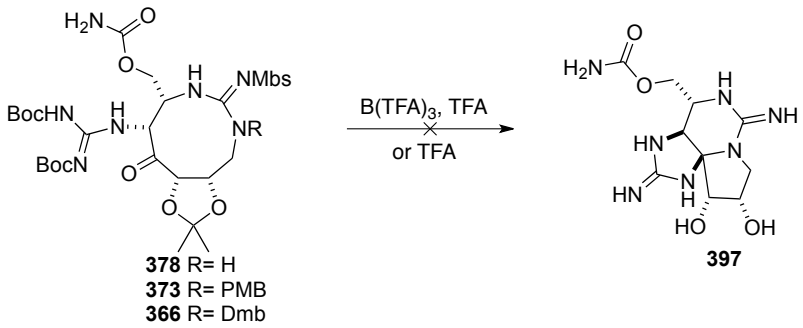
2.3.7 Progress towards β-Hydroxysaxitoxinol

Reductive amination has been the most fruitful route thus far towards the synthesis of saxitoxin analogs as it allowed the installation of the last nitrogen required on the backbone. In order to synthesize hydroxysaxitoxinol, ketone **378** or hemiaminal **377** must be deprotected and cyclized under acidic conditions (Scheme 118). The following sections will focus on these intermediates and their analogs.



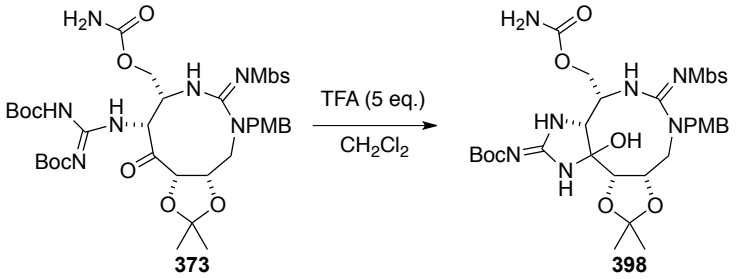
Scheme 118 Potential conversion of compound **378**, **373**, or **366** to hydroxysaxitoxinol.

Ketone **366** also has the potential to be deprotected and cyclized to hydroxysaxitoxinol (**397**) in a single step. Submitting compounds **378**, **373**, **366** to Du Bois' conditions was a messy reaction and no compounds were isolated (Scheme 119).



Scheme 119 Failed deprotection/cyclization of compound **378**, **373**, and **366**.

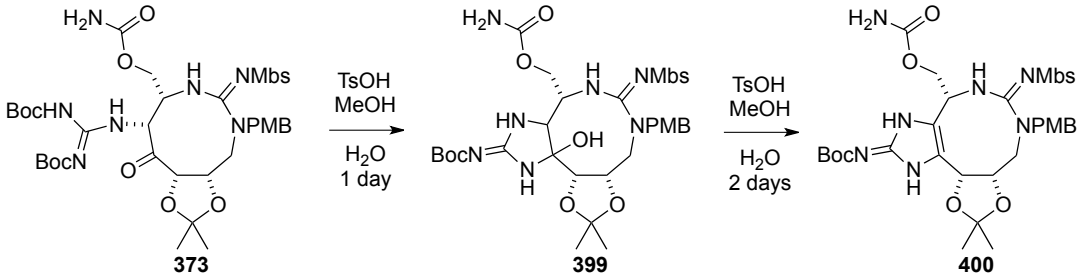
A stepwise approach was taken for this reaction. Thus treating ketone **373** with 5 eq. of TFA in dichloromethane resulted mono in Boc deprotection, and cyclization to give hemiaminal **398**.



373 398

Scheme 120 Mono-Boc deprotection.

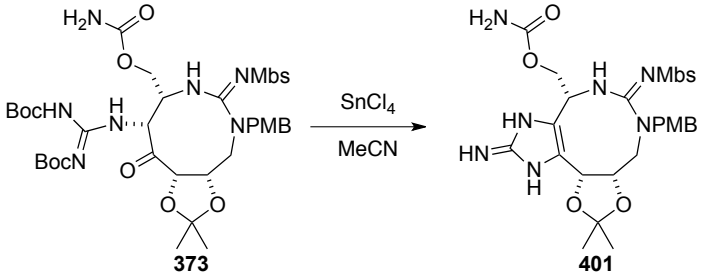
Compound **373** was treated with TsOH in MeOH and water to give hemiaminal **399** after a day (Scheme 121). Upon stirring an additional two days, elimination product **400** was isolated.



373 399 400

Scheme 121 Formation of [9,5]bicycle **400**.

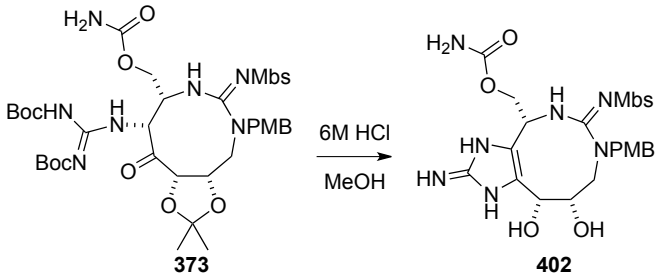
Lewis acids were also tested on ketone **373**. Ketone **373** was treated with tin tetrachloride in MeCN, effectively cleaving the Boc groups, cyclizing to the hemiaminal and eliminating to enamine **401** (Scheme 122). This compound is interesting as it is the only example where the acetonide has remained intact after a successful Boc deprotection, and elimination reaction.



373 401

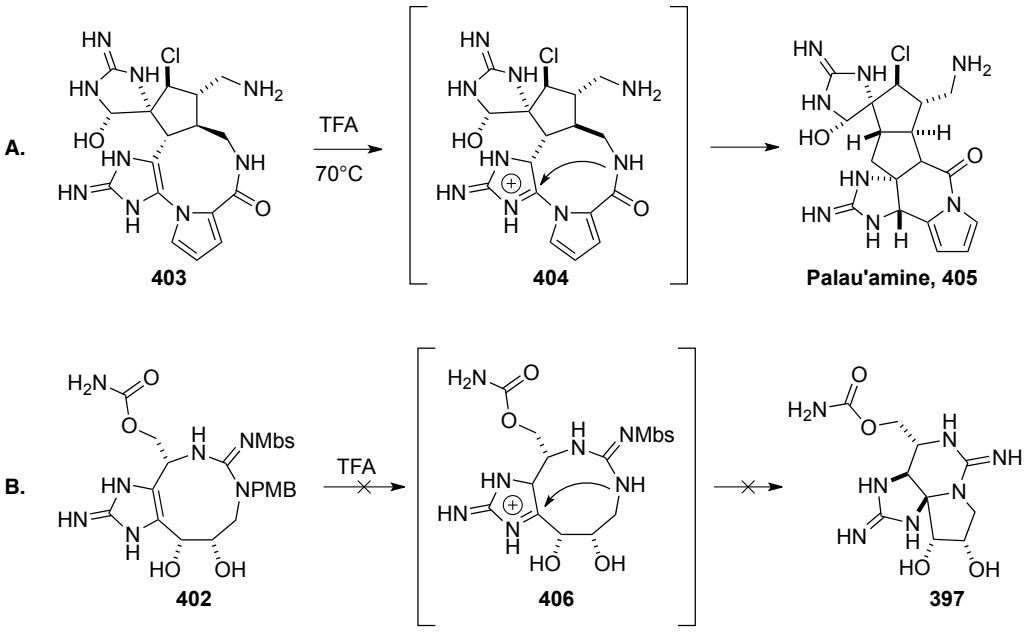
Scheme 122 Formation of bicycle **401**.

Treatment of compound **373** with 6M HCl/MeOH and stirring for 3 days gave diol **402** as the major product (Scheme 123). This reaction was fairly clean and the product was easy to purify.



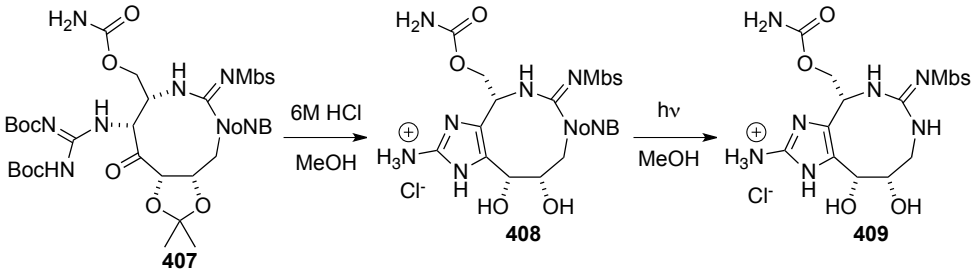
Scheme 123 Formation of bicycle **402**.

With enamine **402** in hand, treatment with acidic conditions should allow the transannular cyclization to hydroxysaxitoxinol (**397**) in a single step, as long as the PMB group is labile (Scheme 124). This type of ring closure is very similar to Baran's synthesis of palau'amine (**405**) except the amide is replaced with a guanidine.[62] Unfortunately, this reaction was messy and inconclusive.



Scheme 124 A. Barans' Palau'amine ring contraction mechanism. B. Ring contraction proposal for the synthesis of saxitoxin derivatives.

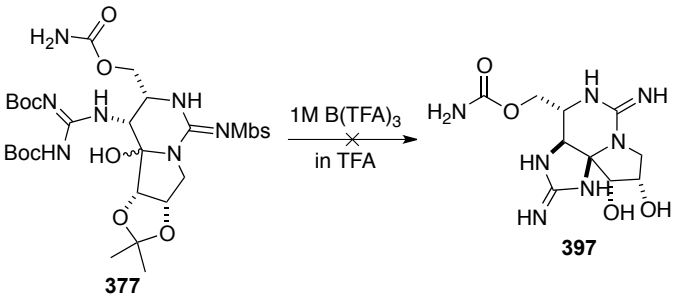
To simplify this reaction, a method to make the same substrate minus the guanidine-protecting group was explored. Enamine **408** was synthesized in the same manner as before by treating ketone **407** with 6M HCl/MeOH for 3 days (Scheme 125). The o-nitrobenzyl protecting group was easily removed by exposure to UV radiation, giving deprotected enamine **409**.



Scheme 125 Formation of compound **409**.

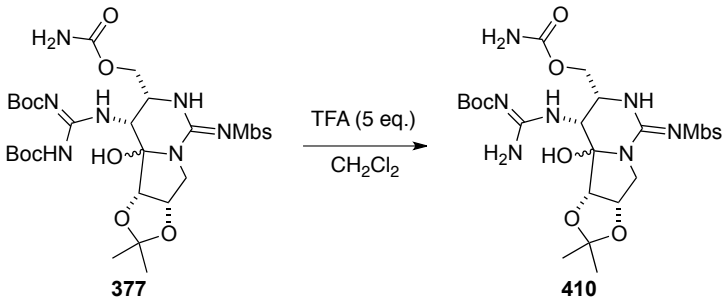
As the reactivity of ketone **407** was being explored, the analogous reactions were tested on hemiaminal **377**. Hemiaminal **377** is essentially a protected, open version of

β-hydroxysaxitoxinol (**397**). All that is required to make β-hydroxysaxitoxinol (**397**) from hemiaminal **377** is a global deprotection, epimerization and dehydrative cyclization. This could possibly be done in a single step, as all the protecting groups are acid labile and the cyclization is acid promoted. A similar reaction was accomplished at Stanford in the Du Bois research group using a boron trifluoroacetate in trifluoroacetic acid (Scheme 126).[32] Hemiaminal **377** submitted several times to Du Bois' procedure, unfortunately the desired transformation was not successful.



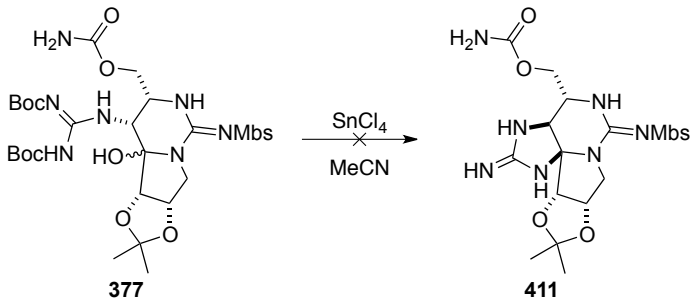
Scheme 126 Failed dehydrative cyclization.

The complexity of this reaction is very apparent. To successfully make this a one-pot reaction requires the deprotection of two Boc groups, an acetonide and an Mbs group followed by iminium ion formation, epimerization and cyclization. To figure out this reaction, all the intermediates would have to be characterized in order to see the reaction progression. In order to do this, a stepwise approach was taken. Treating hemiaminal **377** with 5 eq. of TFA in CH_2Cl_2 slowed the reaction down enough that one Boc group was removed (Scheme 127).



Scheme 127 Mono-Boc deprotection of hemiaminal **377**.

Since tin tetrachloride is known to promote mild Boc deprotections of guanidines and as an oxophilic Lewis acid, it was tested on hemiaminal **377** (Scheme 128).[63] It was thought that it would not only cleave the Boc groups but also promote iminium ion formation and cyclization. Unfortunately, when hemiaminal **377** was treated with tin tetrachloride only a messy reaction ensued and no products were isolated, although MS indicated some product was formed.

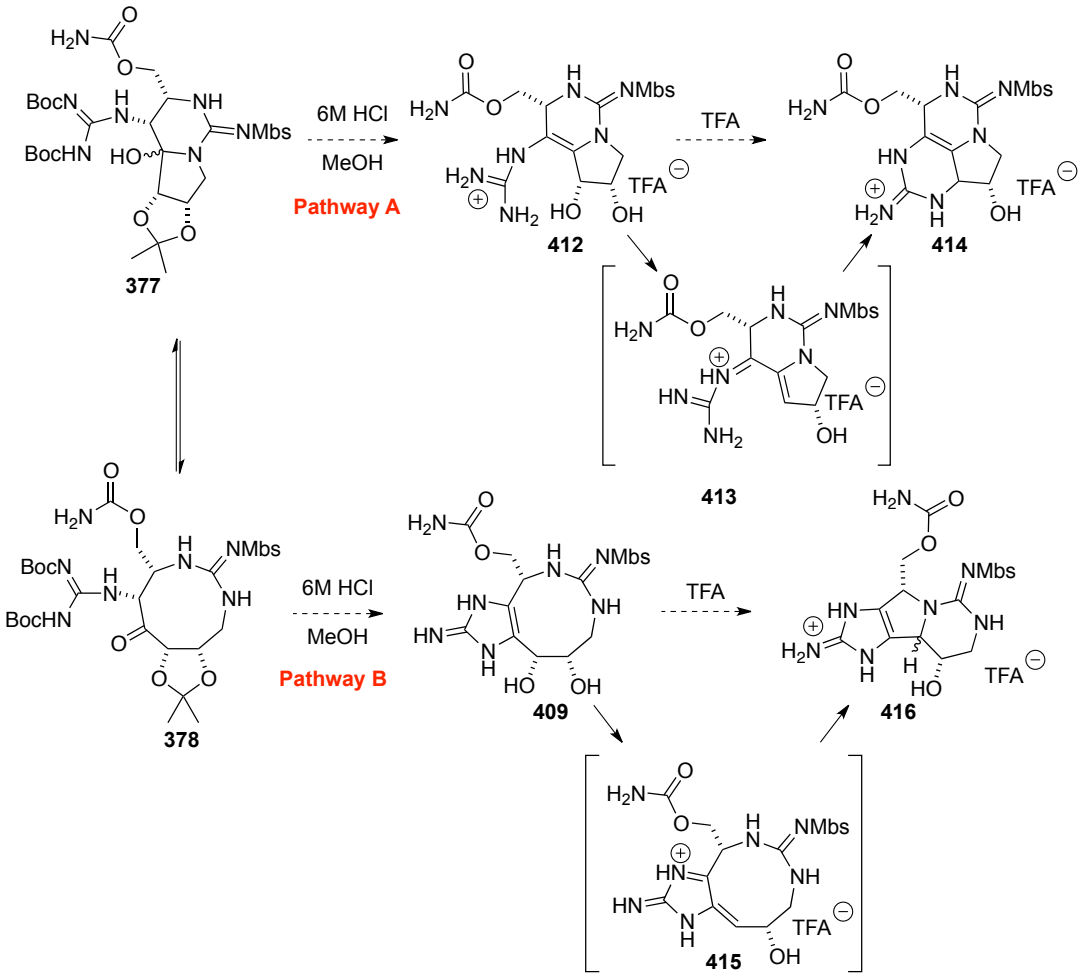


Scheme 128 Failed tin tetrachloride promoted dehydrtive cyclization.

Treatment of hemiaminal **377** with 6M HCl in MeOH gave a single product, which was shown by NMR and mass spectroscopy to be an enamine. Unfortunately, when the enamine was treated with TFA, the desired aminal formation did not occur. Instead the resulting product showed loss of water and still contained the enamine. When the ketone **377** was treated with TFA instead of HCl it was not possible to isolate the enamine intermediate and only the dehydrated product was isolated.

Characterization of these compounds was not easy as two pathways can be envisioned, both pathways giving compounds that would be indistinguishable by NMR and mass spectroscopy (Scheme 129). In pathway A, the hemiaminal could undergo elimination to give enamine **412**, which could eliminate water giving reactive intermediate **413**. This intermediate could undergo transannular attack by the guanidine to give tricycle **414**. In Pathway B, the external guanidine could cyclize on the ketone with elimination of water to form enamine **409**, which could then

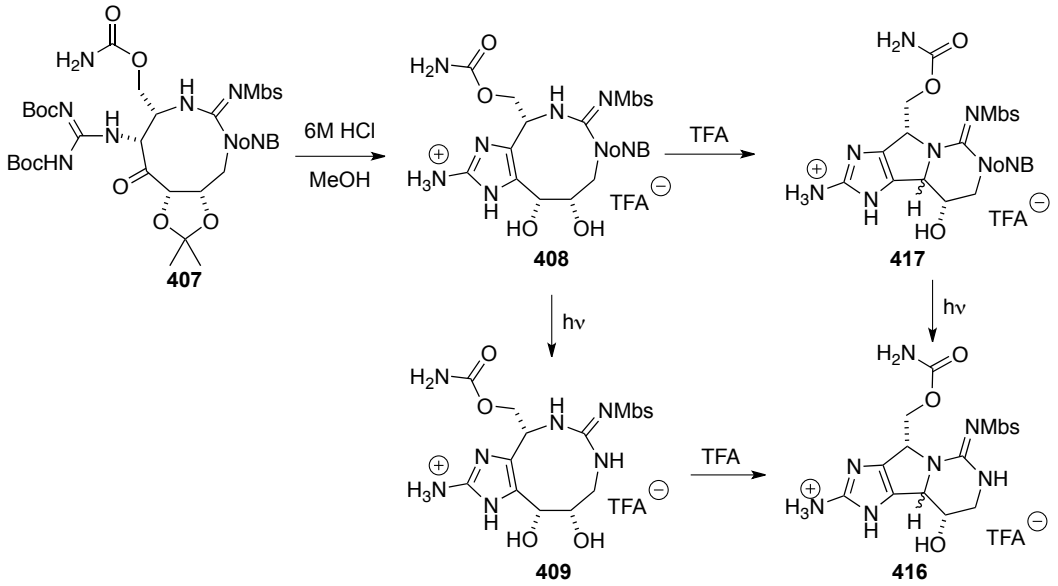
undergo similar reactions to pathway A, giving intermediate **415**, which could cyclize to tricycle **416**.



Scheme 129 Proposed Pathways

To determine which (**414** or **416)** was the product, it was necessary to go back and look at the same reactions on ketone **407** containing the o-nitrobenzyl protecting group on the guanidine (Scheme 130). This protecting group would prevent the hemiaminal formation allowing only the formation of enamine **408**. Enamine **408** was deprotected and when compared to the previously made compound, it was a perfect match. Compound **408** was then treated with TFA to give **417**, which was then deprotected. This compound also matched the previously made compound

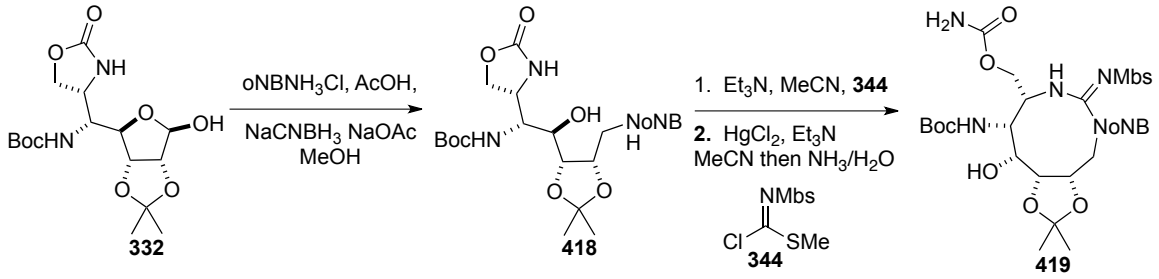
showing that it was indeed linear tricycle **416** and not fused tricycle **414**. This sequence of reactions prove that when the hemiaminal/ketone mixture is submitted to acidic conditions that the ketone state (or hemiaminal containing 5,9 ring system) is favored, as the only products formed are enamine **409** and linear tricycle **416**.



Scheme 130 Preparparation of linear tricycle **416** and **417**.

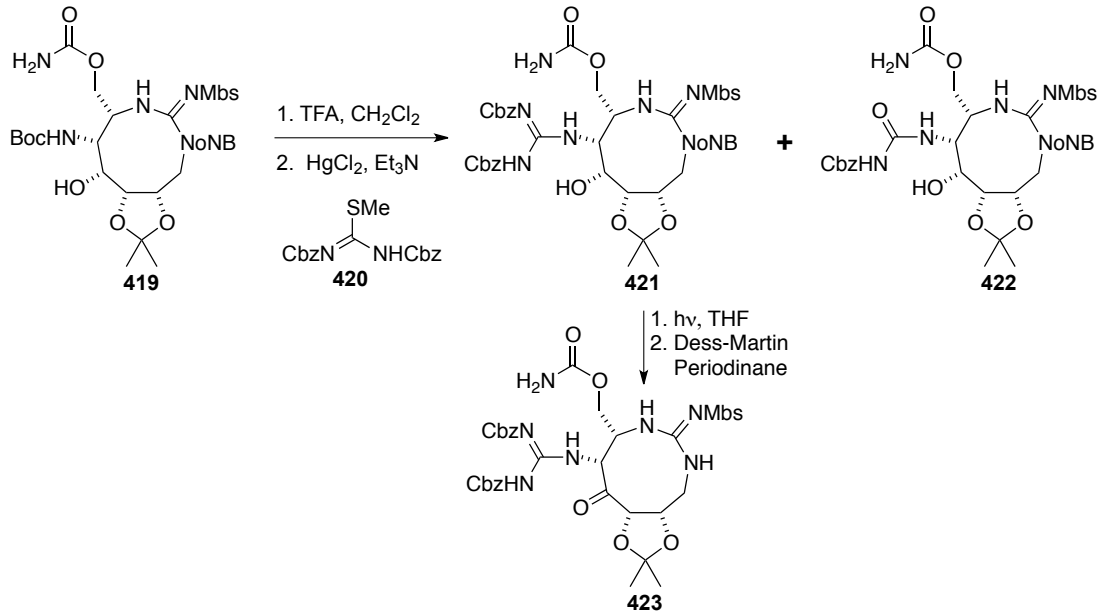
These results narrowed the focus down to hemiaminal/ketone mixture **377/378**, as leaving the o-nitrobenzyl protecting group on after the 9-membered ring is formed serves no purpose. Since linear tricycle **416** is completely useless for this synthesis, methods to avoid this side reaction became the main focus. To prevent the external guanidine from cyclizing on the ketone, the Boc protecting groups were changed to Cbz groups. Starting with lactol **332**, reductive amination with o-nitrobenzyl amine HCl, sodium cyanoborohydride, sodium acetate and acetic acid in methanol gave o-nitrobenzyl amine **418** (Scheme 131). The o-nitrobenzylamine was then converted to the S-methylpseudothiourea with reagent **344** and triethylamine. Surprisingly, this gave a mixture of the S-methylpseudothiourea and the cyclized product. This was of no

consequence because after treatment of the mixture with mercuric chloride and triethylamine, followed by ammonia, conversion to cyclic product **419** occurred in good yield.



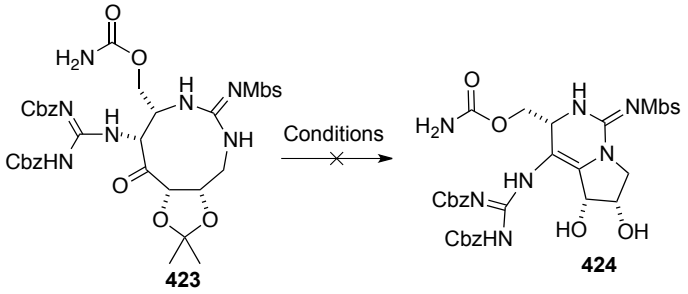
Scheme 131 Preparation of compound **419.**

The Boc group was removed from compound **419** to give the amine, which was submitted to standard guanidinylation conditions to give compound **421** (Scheme 132). The guanidinylation step gave urea **422** as the major product. This urea has not been observed in any other guanidinylation reactions thus far and it is not understood why this reaction is a special case. With compound **421** in hand, the o-nitrobenzyl group was removed by photolysis followed by oxidation of the alcohol with Dess-Martin periodinane to give desired ketone **423**.



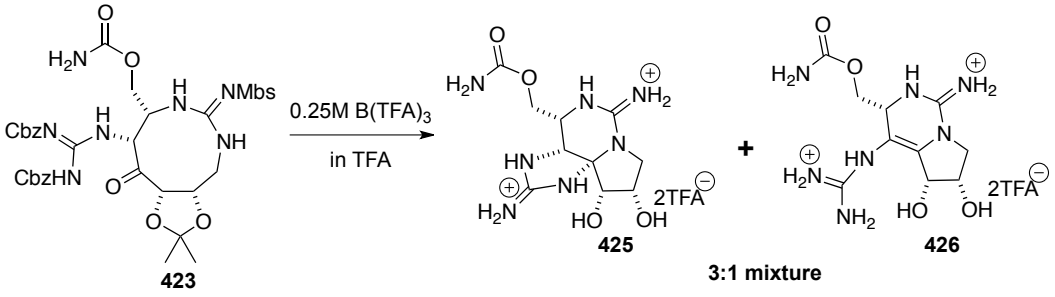
Scheme 132 Installation of bis-Cbz-protected guanidine.

Submitting ketone **423** to TFA gave no reaction (Scheme 133) and when treated with aq. HCl in methanol, the acetonide was removed after stirring overnight.



Scheme 133 Failed ring contraction. Conditions: TFA, no reaction; 6M HCl/MeOH, loss of acetonide

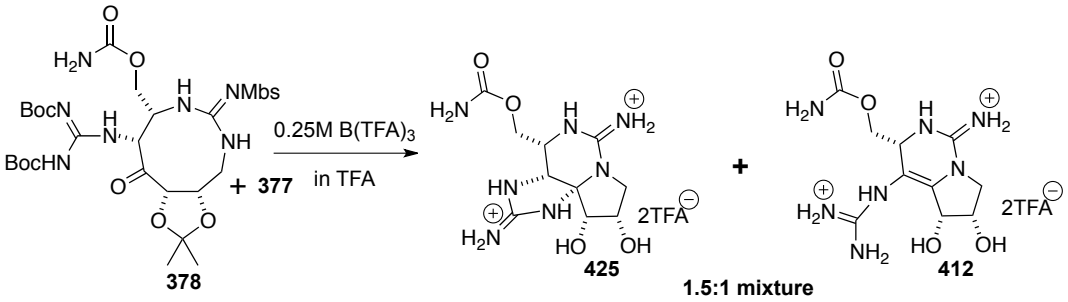
Since TFA and aq. HCl conditions failed to give results, stronger acidic conditions were sought. This led me back to the exploration of Du Bois' conditions. Treatment of ketone **423** with a solution of $B(TFA)_3$ in TFA for 20 hours gave a tremendous result. These conditions resulted in the cleavage of the remaining Cbz and Mbs protecting groups in addition to cyclization to aminal **425**. Enamine **426** was also formed along with the aminal in a 3:1 mixture favoring the aminal.



Scheme 134 Successful preparation of saxitoxin analog **425**.

This fantastic result led to the reinvestigation of Du Bois' conditions on the bis-Boc protected substrate. If the Cbz groups fall off under the reaction conditions, why does this reaction fail with Boc groups instead? The only rationale for these observations is that the boron

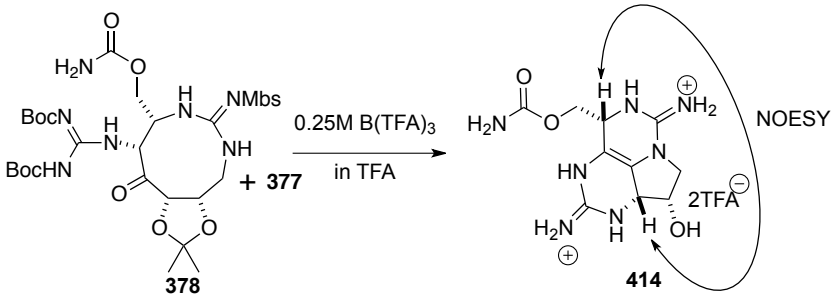
promotes the formation of the hemiaminal and traps it, leaving only the [5,6]bicycle and none of the ketone. This hypothesis indicated that the procedure used on ketone **378** has a major problem. The ketone was first dissolved in TFA followed by the addition of $B(TFA)_3$ in TFA. Since the Boc groups are so labile in TFA, they already are cleaved by the time the boron reagent is added. The free guanidine is then able to form the undesirable hemiaminal, which was then trapped by the boron! To remedy this problem a cold solution of $B(TFA)_3$ in TFA was added directly to a chilled flask containing ketone **378**. This procedural change fixed the problem, as the reaction now showed no signs of tricycle **416** and resulted in a mixture of aminal **425** and enamine **426** in a 1.5:1 ratio, favoring the aminal (Scheme 135).



Scheme 135 Preparation of **425** and **412**.

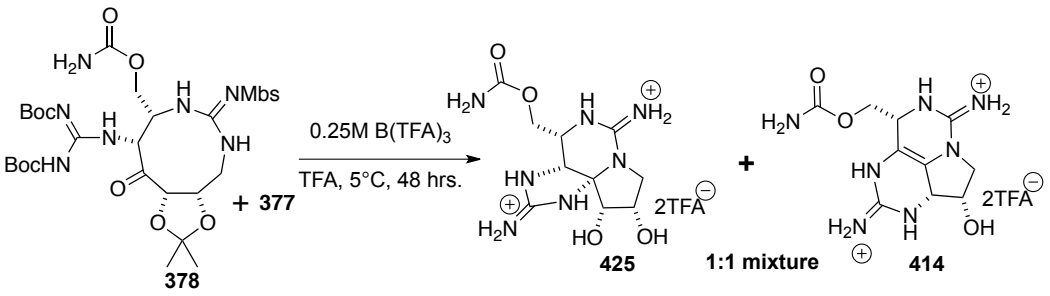
This reaction presumably proceeds by boron activation of the hemiaminal causing elimination of water giving the iminium ion. The iminium ion then undergoes elimination giving the enamine or guanidine cyclization giving the aminal. The question now is: What is the stereochemistry of the aminal? Does the aminal arise from the guanidine cyclizing on the initially formed iminium ion or from an iminium ion formed from the tautomerization of the enamine? If the enamine does tautomerize, this would effectively cause the desired epimerization of the stereocenter adjacent to the guanidine. Fortunately, this can be tested by simply letting the reaction run longer can be tested because if the enamine is tautomerizing the

reaction should go to completion leaving only the aminal. Unfortunately, after running the reaction for 48 hours the only product isolated was tricycle **426** (Scheme 136). This indicates that the absolute stereochemistry is as shown in Scheme 135. This stereochemistry was also demonstrated through NOESY correlations. Interestingly, this product arises from pathway A previously described in Scheme 129, but unlike linear tricycle **416**, fused tricycle **414** is a single diastereomer. The conformation of the formed stereocenter was confirmed by NOESY correlations as shown in Scheme 136.



Scheme 136 Formation of unique fused tricycle **352**.

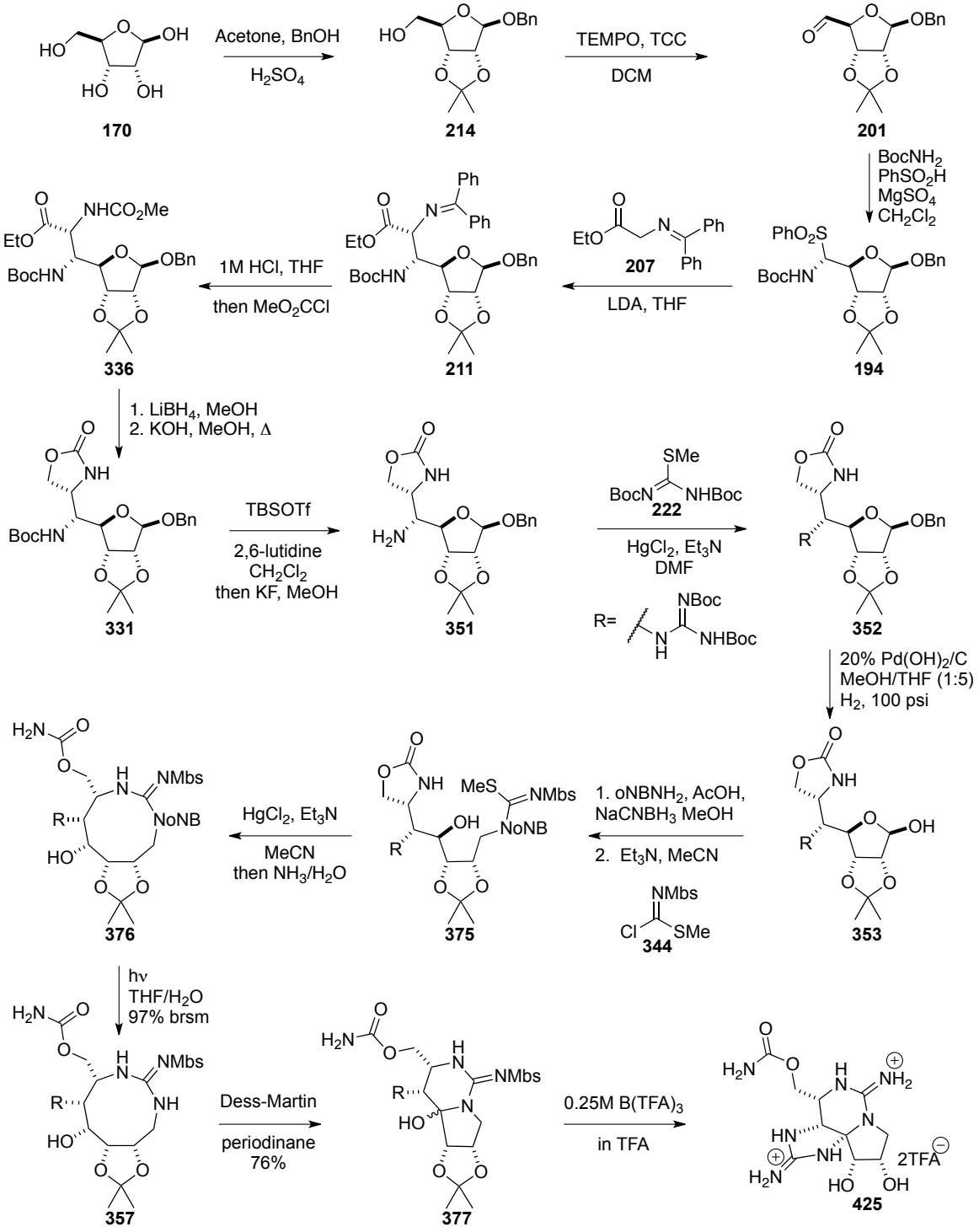
Since this reaction shows that the aminal can eliminate, forming the enamine, which continues to react forming fused tricycle **414**, does the enamine initially arise from the elimination of the aminal or the iminium ion and can the ratio of products be improved in favor of the aminal? This idea was tested by letting the reaction stir at 5°C for 20 hours, not allowing the reaction to warm up. This resulted in the same 1.5:1 mixture favoring the aminal, containing a small amount of products that were not fully deprotected. This indicates that the rate of cyclization slightly favors the aminal. When the reaction was allowed to stir for 48 hours at 5°C, a 1:1 mixture of aminal **425** and tricycle **414** was isolated (Scheme 137). This indicates that at cold reaction temperatures, the aminal is fairly stable to elimination while the enamine is rapidly converted to the tricycle.



Scheme 137 Alternative deprotection conditions.

2.4 Synthetic Summary and Conclusion

Presented below is the culmination of synthetic achievements described in this dissertation (Scheme 138). The most advanced compound produced is 4,5-episaxitoxinol, which was prepared in 17 steps overall from D-ribose. The synthesis highlights a Mannich type reaction to form the key carbon-carbon bond between a glycine building block and a D-ribose derivative. The orthogonal protecting group strategy allows complete control of the molecule, which could allow for the preparation of many different analogs. Future work on this project would focus on fixing the stereochemistry formed by the Mannich reaction early on, which should allow for the preparation of the gonyautoxin family of natural products.



Scheme 138 Overall synthetic progress.

Chapter 3: Experimental Section

3.1 General Considerations

Unless otherwise noted, materials were obtained from commercial sources and used without purification. All reactions requiring anhydrous conditions were performed under positive pressure of argon using flame dried glassware. Dichloromethane, diisopropylamine, triethylamine, tetrahydrofuran, dimethylformamide, diethyl ether, and toluene were degassed with argon and passed through a solvent purification system (J.C. Meyer of Glass Contour) containing either alumina or molecular sieves. Flash chromatography was performed on Merck silica gel Kieselgel 60 (230-400 mesh) from EM science with the indicated solvent.

^{1}H-NMR spectra were recorded on Varian, 300, 400, or 500 MHz spectrometers as indicated. The chemical shifts (δ) of proton resonances are reported relative to CDCl3, DMSO-d5, D_2O, CD_3OD, and acetone-d6 using the following format: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) (J in Hz), integral]. ^{13}C-NMR spectra were recorded at 100 or 125 MHz. The chemical shifts of carbon resonances are reported relative to the deuterated solvent peak, except D_2O, which was internally referenced.

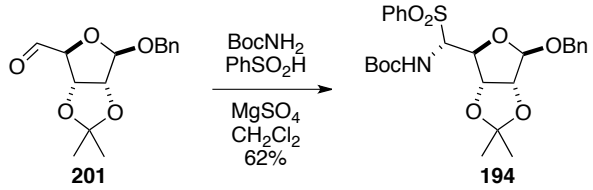
Infrared spectra were recorded on a Bruker Tensor 27 FTIR spectrometer. All absorptions are reported in cm^{-1}. Spectra were recorded as films deposited from deuterated NMR solvent solutions on NaCl plates followed by solvent evaporation. Peaks reported in the IR are described using the following conventions: w = weak, m = medium, s = strong, vs = very strong, sh = shoulder, and br = broad.

Mass spectra were obtained at the Colorado State University CIF on a Fisons VG Autospec. Optical rotations were obtained with a 1mL, 1 dm cell on a Rudolf Research Autopol

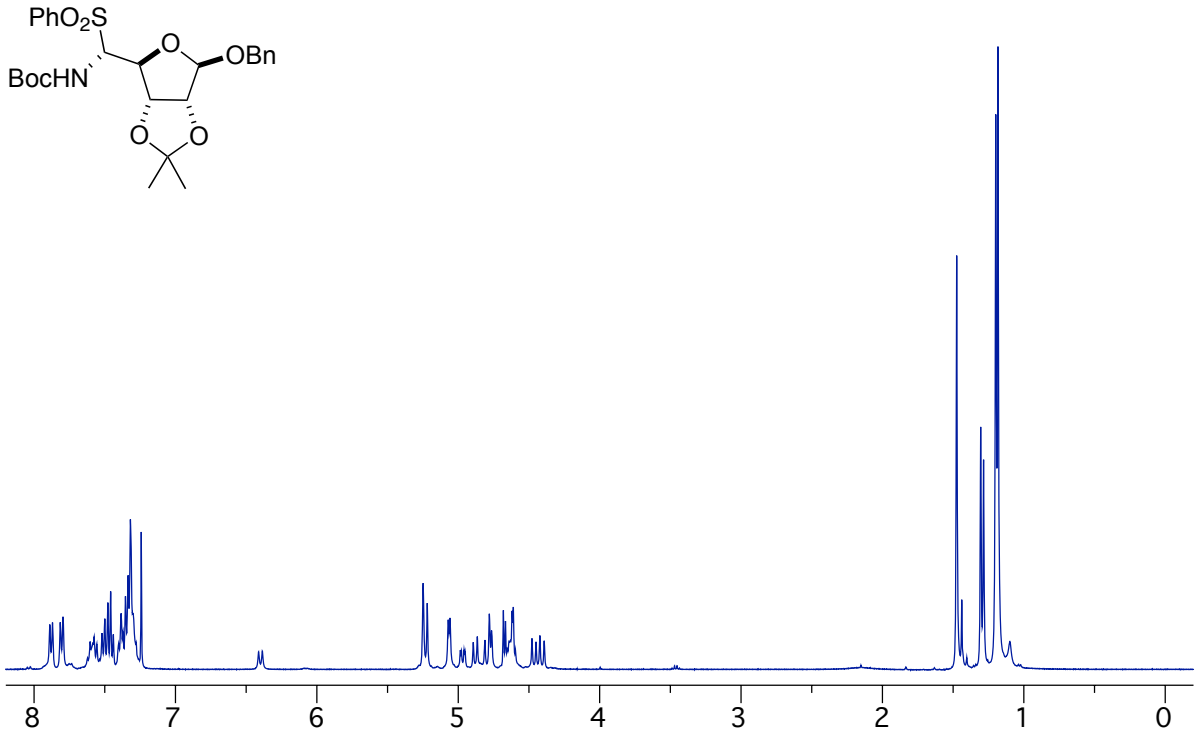
III polarimeter operating at 589 nm in $CHCl_3$. HPLC separations were obtained on a Waters 600E HPLC system using the indicated column and eluent conditions.

3.2 Experimental Procedures

Compound 194: tert-butyl ((R)-((3aS,4S,6R,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)(phenylsulfonyl)methyl)carbamate.



To a solution of aldehyde **201** (36.9 g, 1 eq.) in CH_2Cl_2 (1.3 L) was added t-butyl carbamate (18.3 g, 1.2 eq.), phenylsulfinic acid (28.3 g, 1.5 eq.), and magnesium sulfate (19 g). This mixture was allowed to stir overnight and was filtered through glass wool. The solution was then evaporated in vacuo and the product was crashed out with ether to give 42.4 g (62%) of **194** as a white powder. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.81 (s, *J* = 8.2, 1.4 Hz, 1H), 7.74 (d, *J* = 7.4 Hz, 1H), 7.47 (d, *J* = 5.1 Hz, 2H), 7.40-7.23 (m, 6H), 7.03 (dd, *J* = 7.5, 1.9 Hz, 1H), 4.99 (s, 1H), 4.88 (d, *J* = 5.9 Hz, 1H), 4.75 (d, *J* = 5.9 Hz, 1H), 4.53 (s, 1H), 4.44 (ddd, *J* = 11.6, 9.7, 1.9 Hz, 1H), 4.11 (dq, *J* = 10.6, 10.0, 7.0 Hz, 1H), 4.06 (d, *J* = 13.3 Hz, 1H), 3.90 (dq, *J* = 10.7, 7.1 Hz, 1H), 1.45 (s, 9H), 1.44 (s, 3H), 1.29 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H). 13-C NMR (101 MHz; cdcl3): δ 170.2, 155.7, 137.0, 132.4, 130.0, 128.32, 128.23, 128.10, 127.9, 127.56, 127.49, 112.0, 108.0, 86.3, 85.4, 81.9, 79.5, 69.5, 64.8, 61.1, 54.3, 28.2, 26.2, 24.6, 13.9. IR (Dep. $CDCl_3$): 3428 (s), 2980(s), 2938(s), 1739(s), 1714(s), 1491(s).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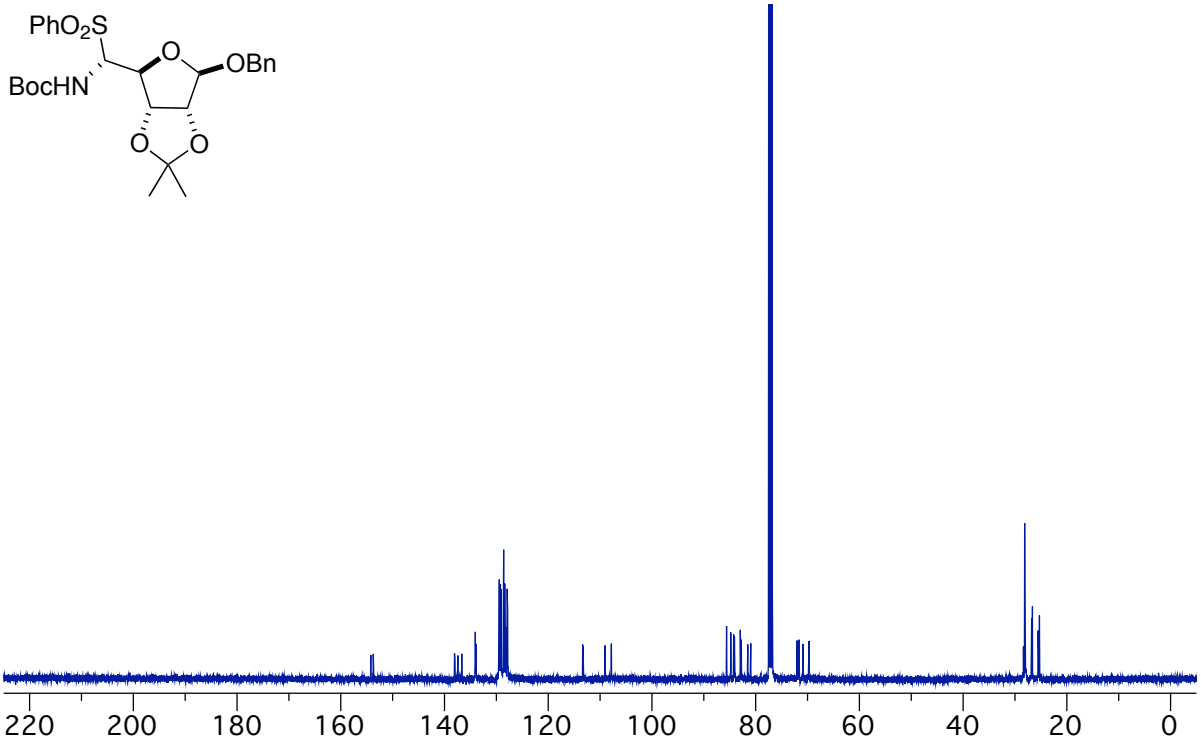
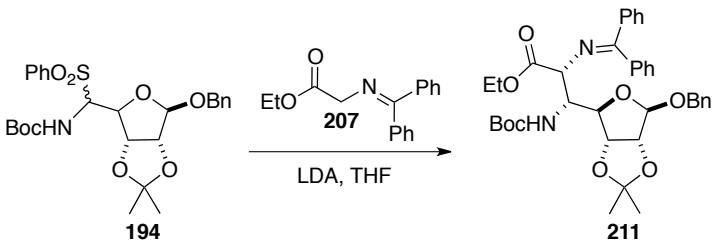
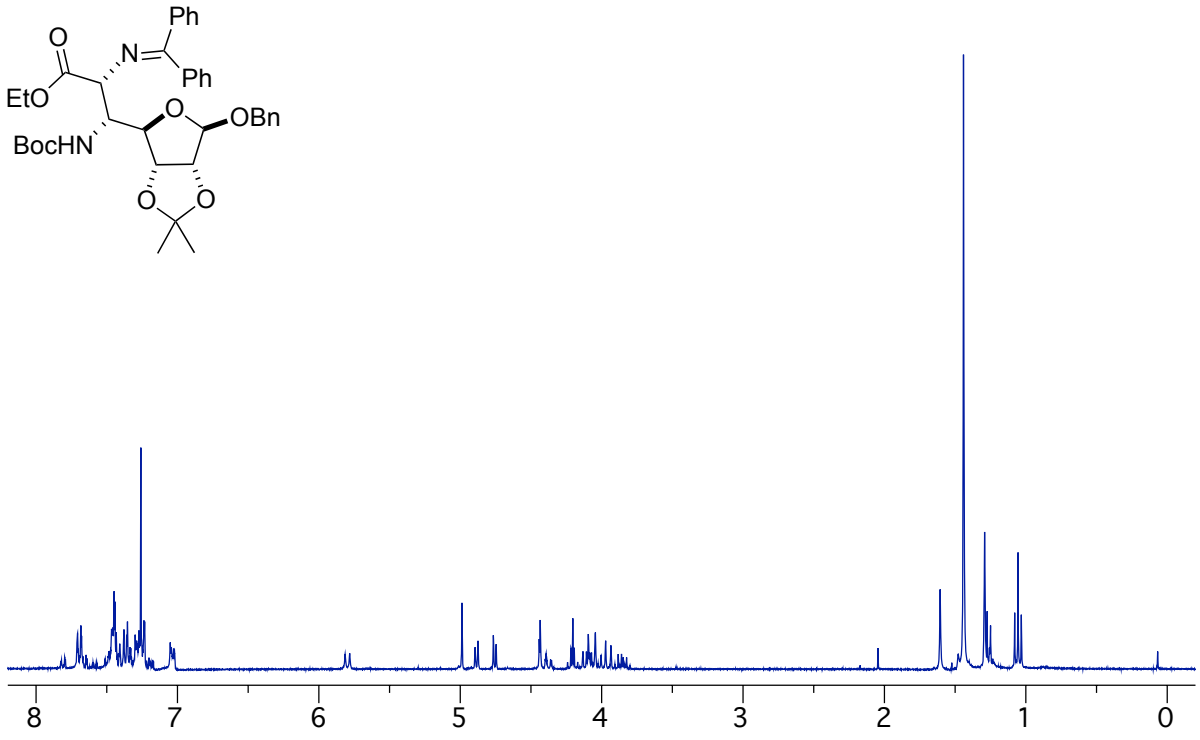
BocHN
O
OBn
O
O
8
7
6
5
4
3
2
1
0


PhO2S
BocHN
O
OBn
O
O
220
200
180
160
140
120
100
80
60
40
20
0

Compound 211: (2R,3R)-ethyl 3-((3aR,4R,6R,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro [3,4-d][1,3]dioxol-4-yl)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)propanoa te.



To a solution of LDA in dry THF at -78°C was added a glycine **207** in THF (-78°C) dropwise. The resulting yellow solution was stirred for 1 hour and amido sulfone **194** in THF (-78°C) was added dropwise. The reaction was stirred 20 min. and then quenched with sat. NH4Cl and allowed to warm to rt. The organic phase was seperated and washed with brine. The aqueous phase was extracted 3x with EtOAc followed by brine. The combined organic extracts were dried over sodium sulfate and evaporated. The resulting oil was dissolved in hexanes and was evaporated. This process was repeated until solids formed which were removed by filtration to give **211** as a white powder, which could be recrystallized from hexanes. $[\alpha]_D^{25}$= -31 (c 0.38, $CHCl_3$). ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.74 (d, *J* = 7.4 Hz, 1H), 7.49-7.26 (m, 11H), 7.03 (dd, *J* = 7.5, 1.9 Hz, 2H), 6.15 (s, 1H), 5.80 (d, *J* = 9.7 Hz, 1H), 4.99 (s, 1H), 4.88 (d, *J* = 6.0 Hz, 1H), 4.75 (d, *J* = 5.9 Hz, 1H), 4.53 (s, 1H), 4.44 (ddd, *J* = 11.6, 9.7, 1.9 Hz, 1H), 4.10 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.09 (d, *J* = 12.0 Hz, 1H), 4.05 (d, *J* = 11.2 Hz, 1H), 4.03 (d, *J* = 11.6 Hz, 1H), 3.90 (dq, *J* = 10.7, 7.1 Hz, 1H), 1.45 (s, 9H), 1.44 (s, 3H), 1.29 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H). 13-C NMR (101 MHz; cdcl3): δ 170.4, 155.9, 137.2, 132.5, 130.2, 128.60, 128.51, 128.42, 128.28, 128.07, 128.01, 127.81, 127.75, 127.67, 112.2, 108.2, 86.5, 85.5, 82.1, 79.7, 69.7, 65.0, 61.3, 54.5, 28.4, 26.4, 24.8, 14.1. IR (Dep. $CDCl_3$): 3428 (br), 2980 (vs), 2938 (vs), 1739 (vs), 1714 (vs), 1491 (s).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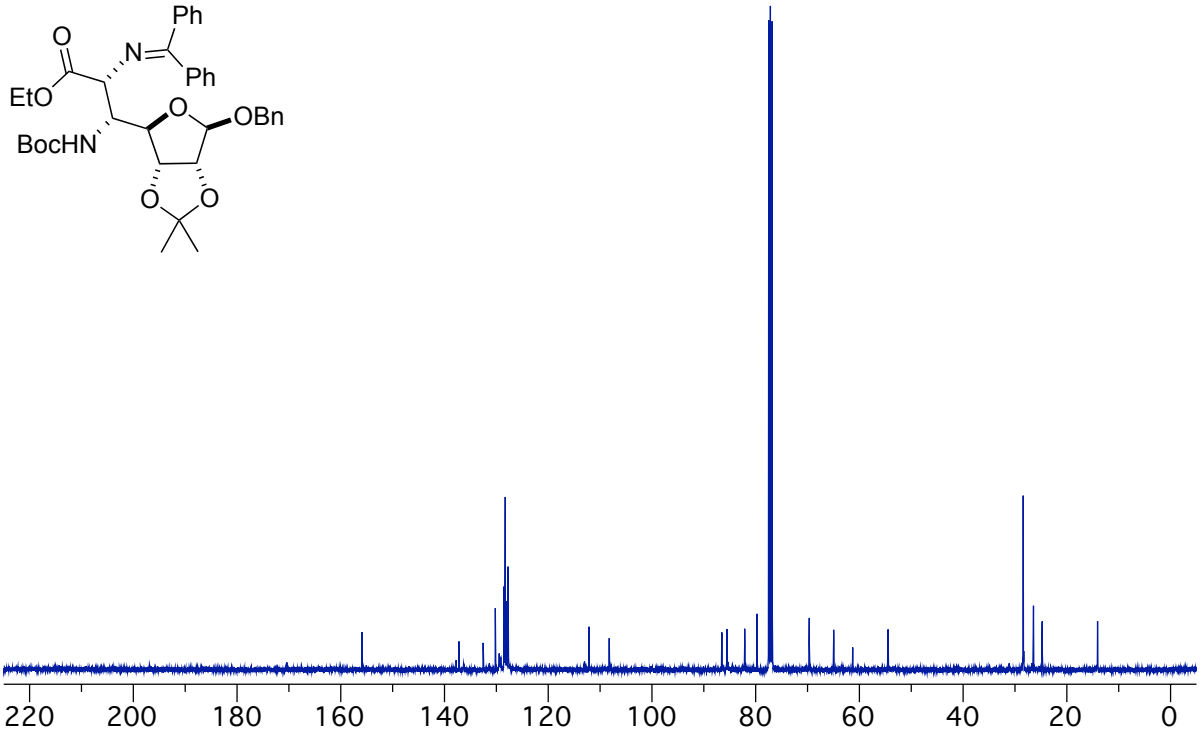
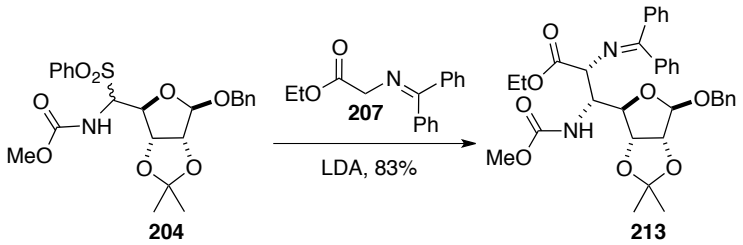
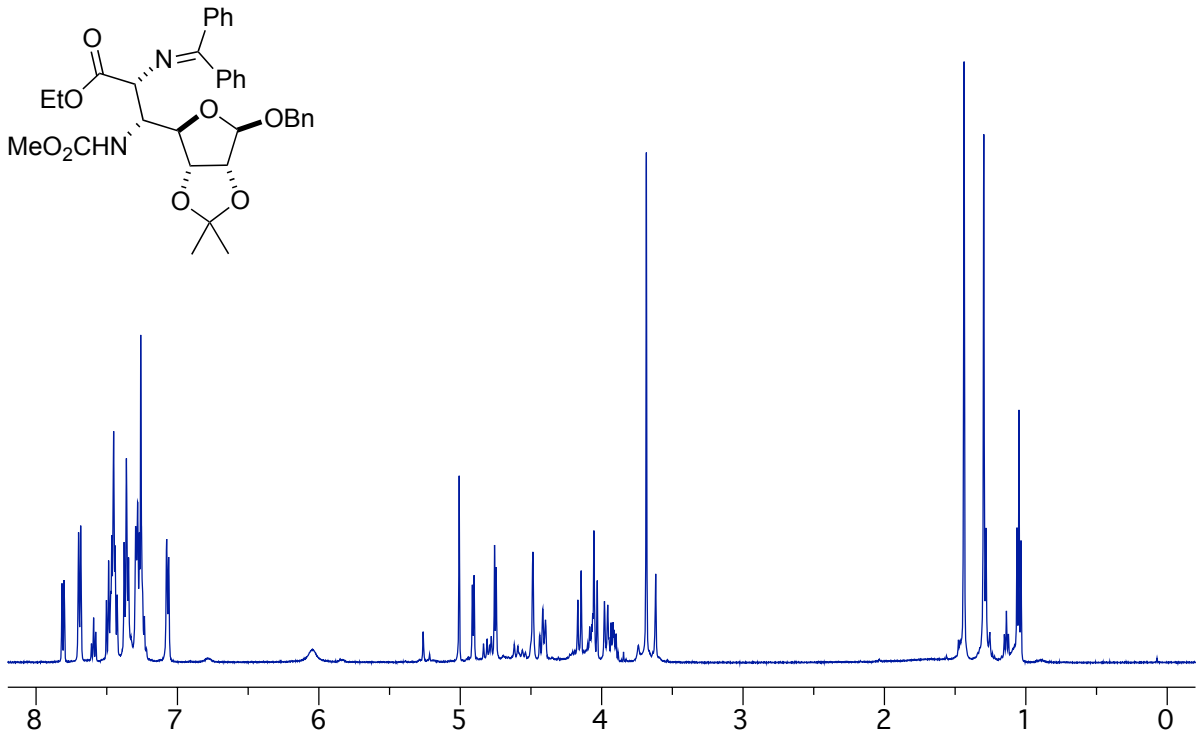
N
Ph
EtO
O
OBn
BocHN
O
O
8
7
6
5
4
3
2
1
0


Ph
O
N
Ph
EtO
O
OBn
BocHN
O
O
220
200
180
160
140
120
100
80
60
40
20
0

Compound 213: (2R,3R)-ethyl 3-((3aR,4R,6R,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydro-furo [3,4-d][1,3]dioxol-4-yl)-2-((diphenylmethylene)amino)-3-((methoxycarbonyl)amino)propanoate.



Glycine **207** (420 mg, 2.5eq.) in THF (7.5 ml) was cooled to -78C and LDA (1.58mmol, 2.5eq.) was added. The resulting bright yellow solution was stirred for 30 mins and a solution of amido sulfone **204** (300mg, 1eq. in 2ml THF) at -78C was added dropwise. The reaction was allowed to stir at -78C until complete by TLC (~5min) and quenched with $NaHCO_3$ (sat.). The mixture was allowed to warm to room temp and was extracted 3x with ethyl acetate. The organic layers were combined washed with NaCl (sat.) and dried over Na_2SO_4. The solvents were removed in vacuo and the crude material was purified via flash chromatography (20% EtOAc/hexane) to give **213** as a white solid (314mg, 83%). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.69 (d, *J* = 7.5 Hz, 2H), 7.49-7.26 (m, 11H), 7.07 (d, *J* = 7.0 Hz, 2H), 6.05 (s, 1H), 5.01 (s, 1H), 4.91 (d, *J* = 5.9 Hz, 1H), 4.75 (d, *J* = 5.9 Hz, 1H), 4.49 (s, 1H), 4.42 (t, *J* = 10.2 Hz, 1H), 4.16 (d, *J* = 12.0 Hz, 1H), 4.07 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.97 (d, *J* = 11.4 Hz, 1H), 3.92 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.68 (s, 3H), 1.44 (s, 3H), 1.30 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz; cdcl$_3$): δ 170.03, 169.93, 157.0, 137.6, 137.0, 132.4, 130.0, 128.36, 128.24, 128.20, 128.14, 127.9, 127.6, 112.1, 108.0, 86.4, 85.4, 82.0, 69.5, 64.6, 61.2, 54.9, 52.2, 26.3, 24.7, 13.9. Calcd for $C_{34}H_{39}N_2O_8$ [M+H]: 603.2706; Found 603.2697.


Ph
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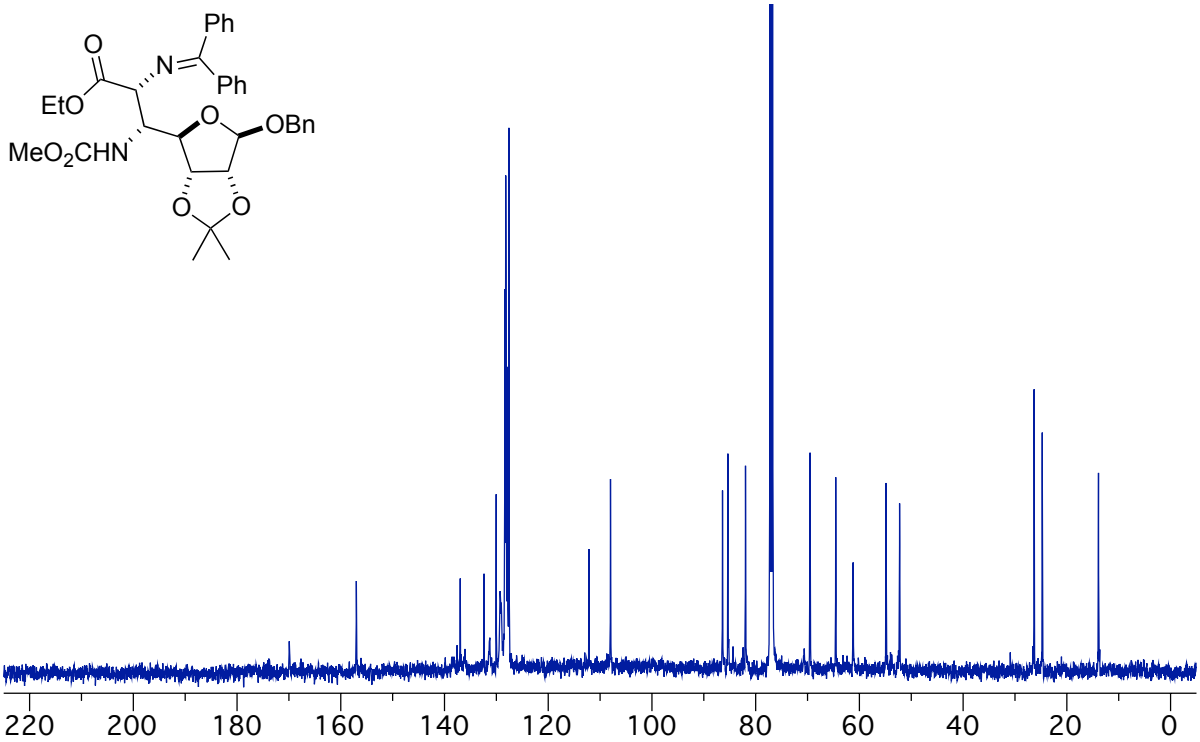
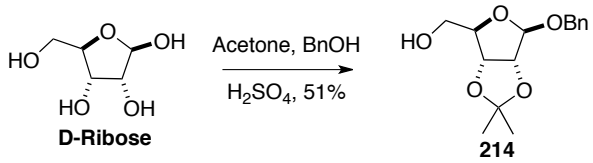
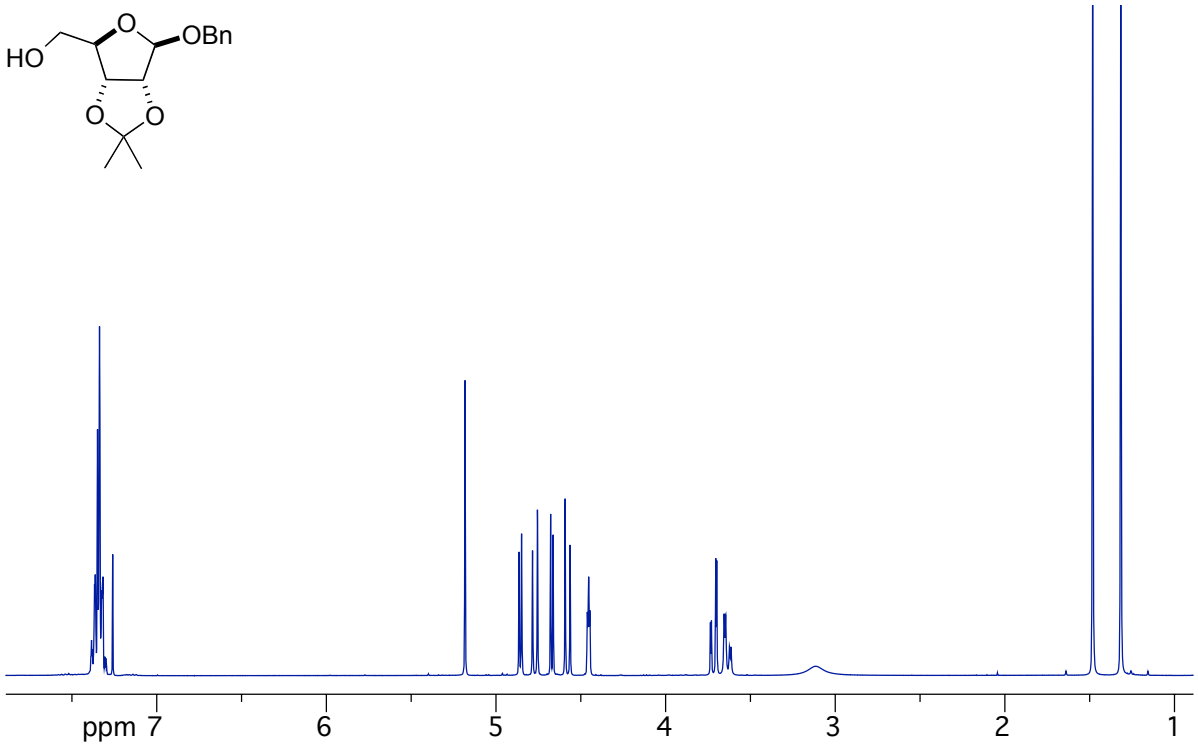
N
Ph
EtO
O
OBn
MeO2CHN
O
O
8
7
6
5
4
3
2
1
0

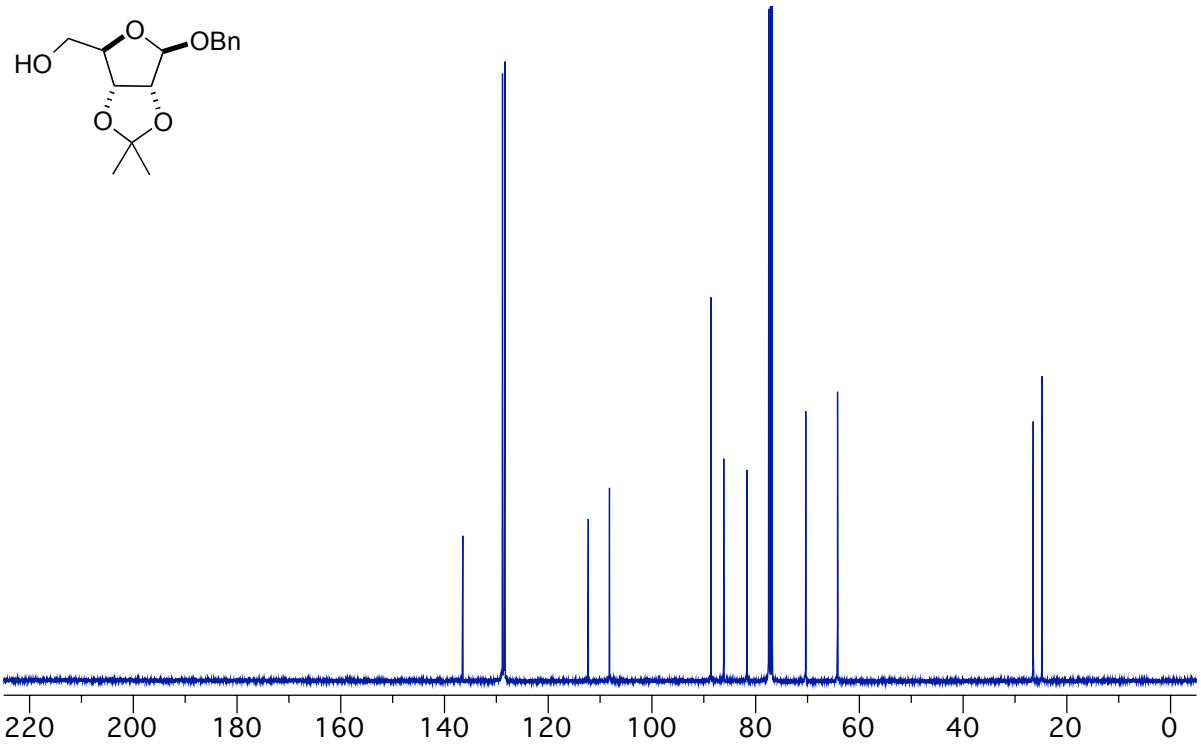

Ph
O
N
Ph
EtO
O
OBn
MeO2CHN
O
O
220
200
180
160
140
120
100
80
60
40
20
0

Compound 214: ((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methanol.

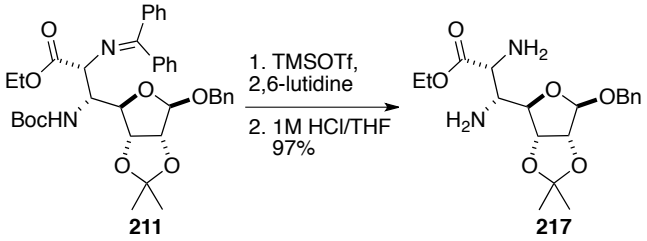


To a suspension of D-ribose (150 g) in benzyl alcohol (990 mL) and acetone (600 mL) was added sulfuric acid (12 mL) drop wise. The mixture was heated to 70-75°C and was allowed to stir for 4-5 hours. The reaction was allowed to cool to room temperature and was neutralized with Et_3N. The acetone was removed under vacuum and the solution was washed with H_2O (3x). The benzyl alcohol was removed under high vacuum. The product was crashed out with Et_2O and the solids were washed with 20% EtOAc/hexanes to give 141.7 grams (50.6%) of an off white solid. $[\alpha]_D^{25}$= -96 (c 0.44, $CHCl_3$) ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.38-7.30 (m, 5H), 5.18 (s, 1H), 4.86 (d, *J* = 5.9 Hz, 1H), 4.77 (d, *J* = 11.6 Hz, 1H), 4.67 (d, *J* = 5.9 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.45 (t, *J* = 2.9 Hz, 1H), 3.72 (dd, *J* = 12.5, 2.4 Hz, 1H), 3.63 (dd, *J* = 12.5, 3.6 Hz, 1H), 3.11 (s, 1H), 1.48 (s, 3H), 1.32 (s, 3H). 13-C NMR (101 MHz; cdcl3): δ 136.5, 128.8, 128.41, 128.35, 112.3, 108.2, 88.6, 86.1, 81.7, 70.3, 64.2, 26.5, 24.8 IR (Dep. $CDCl_3$): 3487 (br), 2930.17 (s), 2888 (s), 1454 (s), 1403 (s), 1375 (s).


HO
O
OBn
O
O
ppm 7
6
5
4
3
2
1


HO
O
OBn
O
O
220
200
180
160
140
120
100
80
60
40
20
0

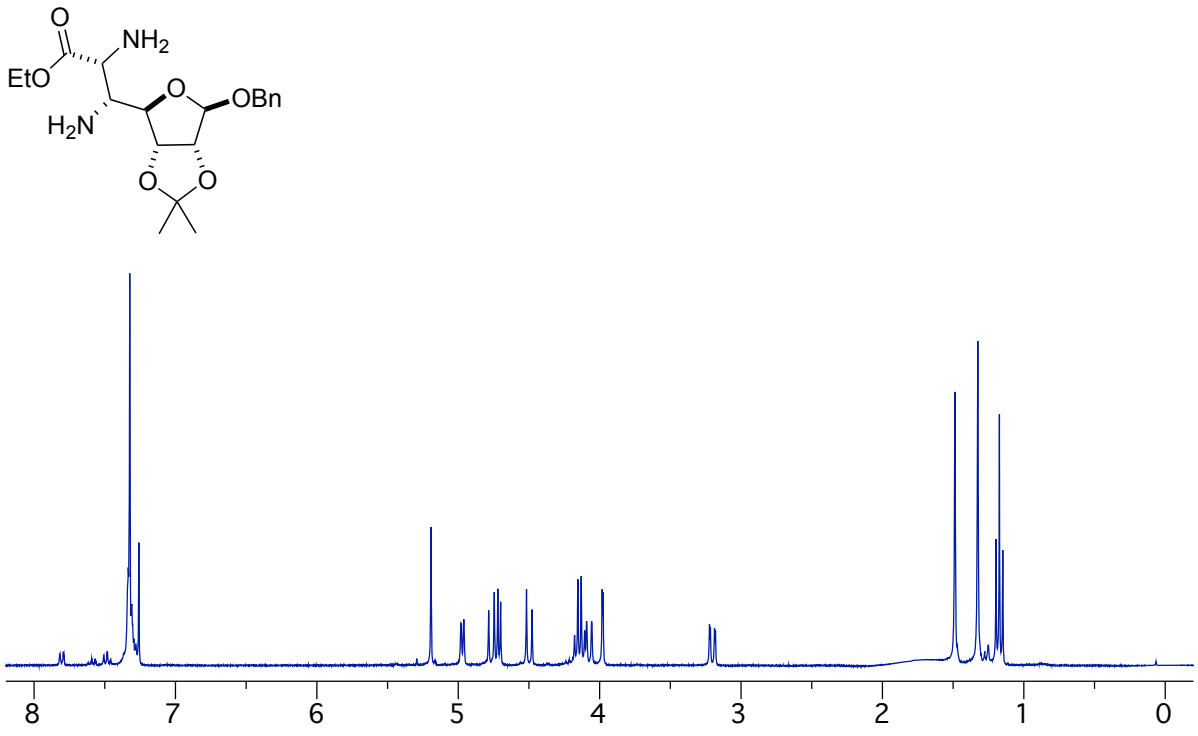
Compound 217: (2*R*,3*R*)-ethyl 2,3-diamino-3-((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propanoate.



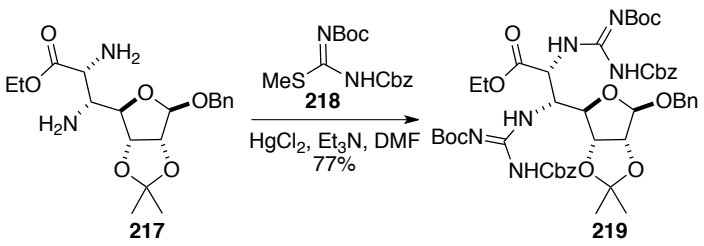
211 217

Compound **211** (1000mg, 1eq.) was dissolved in CH_2Cl_2 (15.5mL) and 2,6-lutidine (723ul, 4eq.) was added followed by TMSOTf (982uL, 3.5eq.). The mixture was stirred until complete by TLC and quenched with $NaHCO_3$ (sat.). The mixture was extracted with EtOAc (3x) dried over Na_2SO_4, evaporated in vacuo and taken on crude.

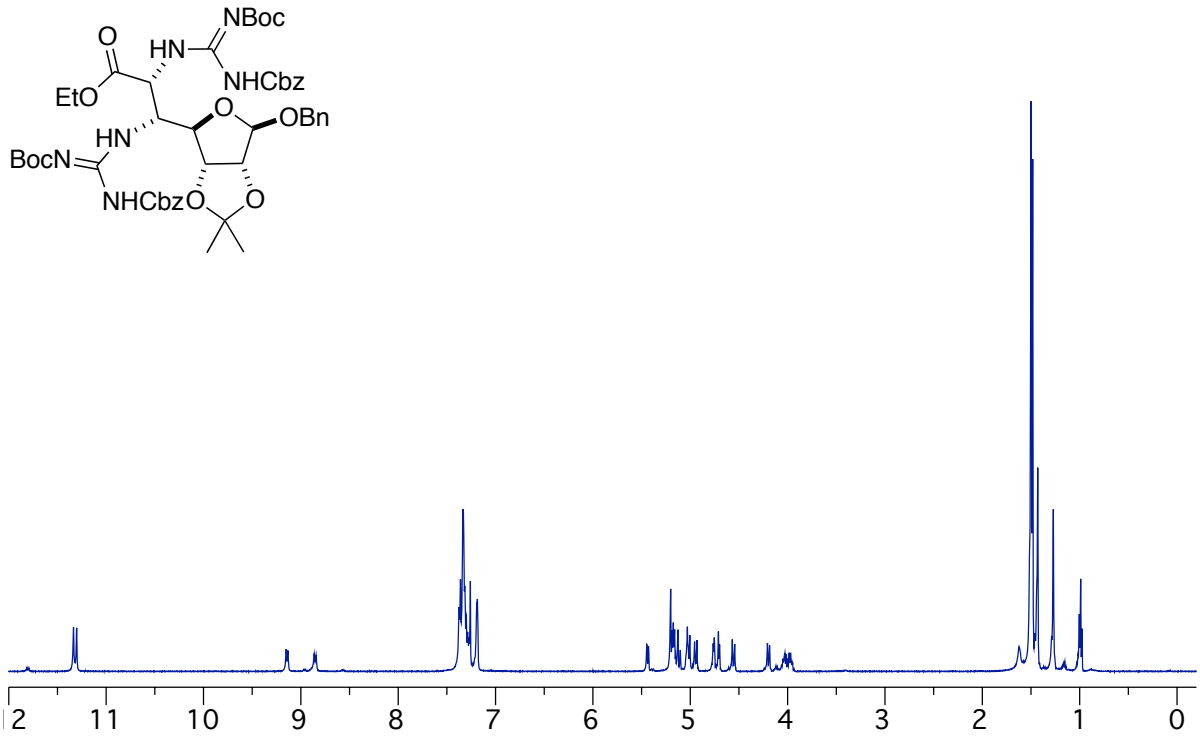
The product was dissolved in THF (5mL) and 1M HCl (5mL) was added. The mixture was stirred for ~20 minutes until complete by TLC. The mixture was washed with diethyl ether (3x) to remove the benzophenone and then the aqueous layer was basified with $NaHCO_3$. The mixture was extracted with n-butanol (5x) and the organic extracts were combined, dried over Na_2SO_4 and evaporated in vacuo to give diamine **217** (570mg, 96.6%), which was clean by NMR. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.34-7.29 (m, 5H), 5.19 (s, 1H), 4.97 (dd, *J* = 6.0, 1.1 Hz, 1H), 4.76 (d, *J* = 11.9 Hz, 1H), 4.71 (d, *J* = 6.0 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.07 (dd, *J* = 10.7, 1.2 Hz, 1H), 3.98 (d, *J* = 2.0 Hz, 1H), 3.20 (dd, *J* = 10.7, 2.0 Hz, 1H), 1.49 (s, 3H), 1.33 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H). Calcd for $C_{19}H_{29}N_2O_6$ [M+H]: 381.2026; Found 381.2022.


O
NH2
EtO
O
OBn
H2N
O
O
8
7
6
5
4
3
2
1
0

Compound 219: (2R,3R)-ethyl 3-((3aR,4R,6R,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro [3,4-d][1,3]dioxol-4-yl)-2,3-bis(3-((benzyloxy)carbonyl)-2-(tert-butoxycarbonyl)guanidino)prop anoate



To a solution of diamine **217** (31mg, 1eq.) in DMF (3 ml) was added reagent **218** (58.1mg. 1.1eq.), Hg_2Cl_2 (48.7mg,1.1eq.) and triethylamine (75ul, 3.3 eq.). The mixture was stirred until complete by TLC and the mercury salts were crashed out with ethyl acetate. The mixture was filtered and the filtrate was washed with H_2O. The organic layer was washed with NaCl (sat.), dried over Na_2SO_4 and solvents were removed in vacuo. The crude material was purified via flash chromatography to give product **219** (58.7mg, 77%). $[\alpha]_D^{25}$= -55 (c 0.50, $CHCl_3$). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 11.33 (s, 1H), 11.30 (s, 1H), 9.14 (d, *J* = 8.9 Hz, 1H), 8.85 (d, *J* = 9.3 Hz, 1H), 7.37-7.27 (m, 12H), 7.19 (m, *J* = 3.0 Hz, 3H), 5.44 (d, *J* = 8.8 Hz, 1H), 5.20 (s, 1H), 5.19-5.16 (m, 2H), 5.12 (d, *J* = 12.6 Hz, 1H), 5.02 (d, *J* = 12.5 Hz, 2H), 4.94 (d, *J* = 12.2 Hz, 1H), 4.76 (d, *J* = 5.9 Hz, 1H), 4.71 (d, *J* = 5.9 Hz, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 4.20 (d, *J* = 10.9 Hz, 1H), 4.05-4.01 (m, 1H), 4.97-4.00 (m, 1H), 1.50 (s, 9H), 1.48 (s, 9H), 1.43 (s, 3H), 1.27 (s, 3H), 0.99 (t, *J* = 7.1 Hz, 3H). 13-C NMR (126 MHz; cdcl3): δ 170.3, 163.60, 163.54, 157.11, 157.04, 152.80, 152.69, 137.4, 137.03, 136.85, 128.55, 128.53, 128.45, 128.12, 128.06, 127.90, 127.86, 127.66, 112.9, 108.1, 85.9, 85.5, 83.9, 83.6, 82.0, 70.2, 67.39, 67.36, 62.3, 54.0, 53.5, 28.1, 26.6, 25.2, 13.8. IR (Dep. $CDCl_3$): 2978.92 (w), 2934.84 (w), 1722.38 (s), 1642.19 (vs), 1619.88 (s). HRMS (FAB^+): Calcd for $C_{47}H_{61}N_6O_{14}$ [M+H]: 933.4246; Found 933.4248.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1
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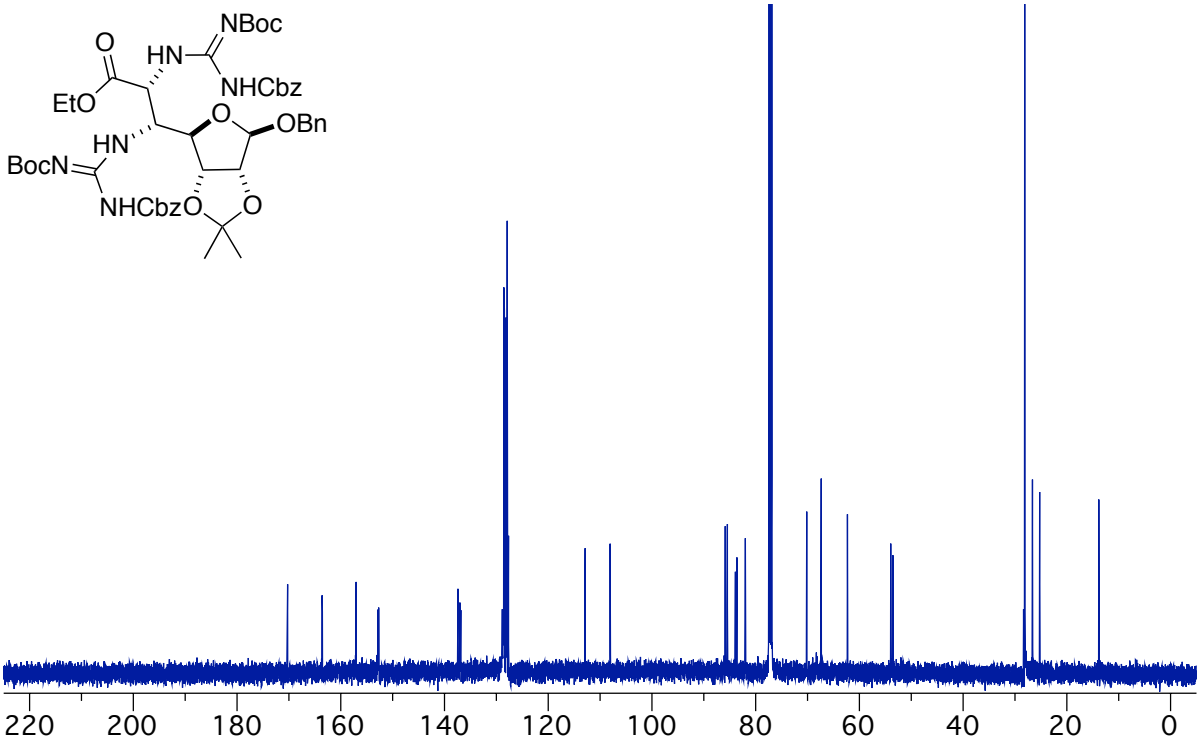
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EtO
NHCbz
O
OBn
HN
BocN
NHCbzO
O
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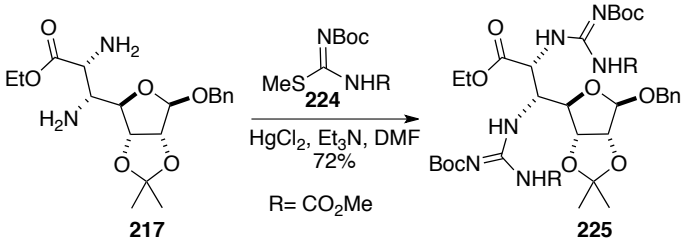
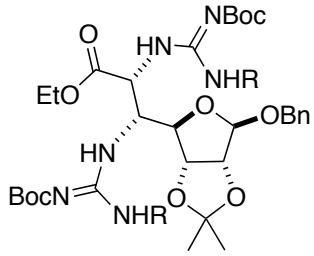
200
180
160
140
120
100
80
60
40
20
0

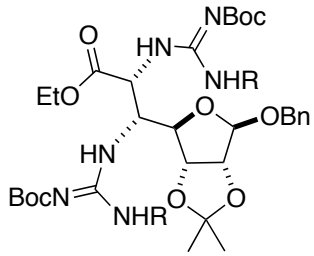
Compound 225: (2*R*,3*R*)-ethyl 3-((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-2,3-bis(2-(*tert*-butoxycarbonyl)-3-(methoxycarbonyl)guanidino)propanoate.



To a solution of diamine **217** (570mg, 1eq.) in DMF (15 ml) was added reagent **224** (1.12g, 1.1eq.), Hg_2Cl_2 (1.22g,1.1eq.) and triethylamine (1.88mL, 3.3 eq.). The mixture was stirred until complete by TLC and the mercury salts were crashed out with ethyl acetate. The mixture was filtered and the filtrate was washed with H_2O. The organic layer was washed with NaCl (sat.), dried over Na_2SO_4 and solvents were removed in vacuo. The crude material was purified via flash chromatography to give product **225** (844mg, 72%). $[\alpha]_D^{25}$= -58 (c 0.53, $CHCl_3$). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 11.34 (s, 1H), 11.30 (s, 1H), 9.14 (d, *J* = 8.9 Hz, 1H), 8.85 (d, *J* = 9.7 Hz, 1H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 5.40 (dd, *J* = 8.9, 2.1 Hz, 1H), 5.24 (s, 1H), 5.04 (td, *J* = 10.3, 1.6 Hz, 1H), 4.96 (d, *J* = 12.2 Hz, 1H), 4.77 (dd, *J* = 6.0, 1.0 Hz, 1H), 4.73 (d, *J* = 6.0 Hz, 1H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.21 (dd, *J* = 10.7, 1.1 Hz, 1H), 4.14-4.04 (m, 2H), 3.76 (d, *J* = 5.7 Hz, 1H), 3.70 (s, 3H), 3.65 (s, 3H), 1.50 (s, 9H), 1.48 (s, 9H), 1.46 (s, 3H), 1.29 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H). 13-C NMR (126 MHz; cdcl3): δ 170.1, 164.29, 164.21, 156.94, 156.88, 152.77, 152.67, 137.5, 128.5, 127.89, 127.73, 112.9, 108.1, 86.0, 85.4, 83.8, 83.6, 81.9, 70.1, 62.3, 53.86, 53.81, 52.9, 28.1, 26.6, 25.3, 13.9. IR (Dep. $CDCl_3$): 2987 (w), 2946 (w), 1722 (vs), 1644 (vs), 1620 (s), 1572 (s).

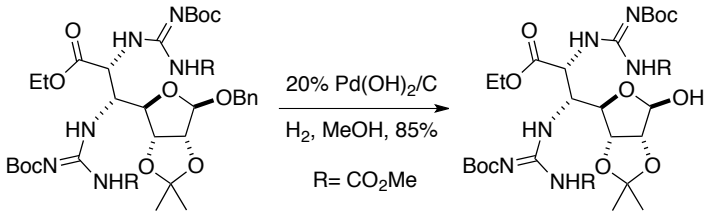


R= CO_2Me



R= CO_2Me

Compound 226: (2*R*,3*R*)-ethyl 2,3-bis(2-(*tert*-butoxycarbonyl)-3-(methoxycarbonyl)guanidino)-3-((3a*R*,4*R*,6*R*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propanoate.



Benzyl ether **225** (540mg) was dissolved in 5:1 THF/MeOH (6mL) and 20% $Pd(OH)_2/C$ (270mg) was added. Argon was bubbled through the suspension for 5 minutes and the mixture was hydrogenated at 100 psi hydrogen for 24 hours. The mixture was then filtered, evaporated, and purified via flash chromatography (30% EtOAc/Hexane) to give 404 mg (84.6%) of lactol **226**. $[\alpha]_D^{25}$= -1 (c 0.54, $CHCl_3$) ^{1}H-NMR (500 MHz; $CDCl_3$): δ 11.51 (s, 1H), 11.37 (s, 1H), 9.31 (d, *J* = 9.7 Hz, 1H), 8.97 (d, *J* = 9.0 Hz, 1H), 5.63 (s, 1H), 5.13 (dd, *J* = 8.9, 2.0 Hz, 1H), 4.93 (ddd, *J* = 11.6, 9.6, 2.3 Hz, 1H), 4.89 (d, *J* = 6.0 Hz, 1H), 4.68 (d, *J* = 5.9 Hz, 1H), 4.41 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.12 (d, *J* = 11.4 Hz, 1H), 3.69 (s, 3H), 3.67 (s, 3H), 1.50 (s, 8H), 1.49 (s, 8H), 1.45 (s, 4H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.31 (s, 3H). 13-C NMR (126 MHz; cdcl3): δ 169.3, 164.27, 164.11, 156.4, 155.5, 153.6, 152.5, 112.8, 104.0, 88.1, 85.6, 84.6, 83.7, 82.3, 62.6, 55.7, 52.91, 52.77, 52.3, 28.2, 26.8, 25.5, 14.1 IR (Dep. $CDCl_3$): 1724 (s), 1619 (m), 1440 (s), 1413 (s), 1370 (s). HRMS (FAB^+): Calcd for $C_{28}H_{47}N_6O_{14}$ [M+H]: 691.3150; Found 691.3147.

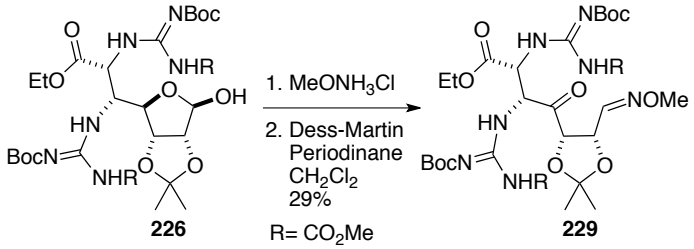

NBoc
HN
O
EtO
NHR
O
OH
HN
BocN
NHR
O
O
R= CO2Me

12
11
10
9
8
7
6
5
4
3
2
1
0


NBoc
HN
O
EtO
NHR
O
OH
HN
BocN
NHR
O
O
R= CO2Me

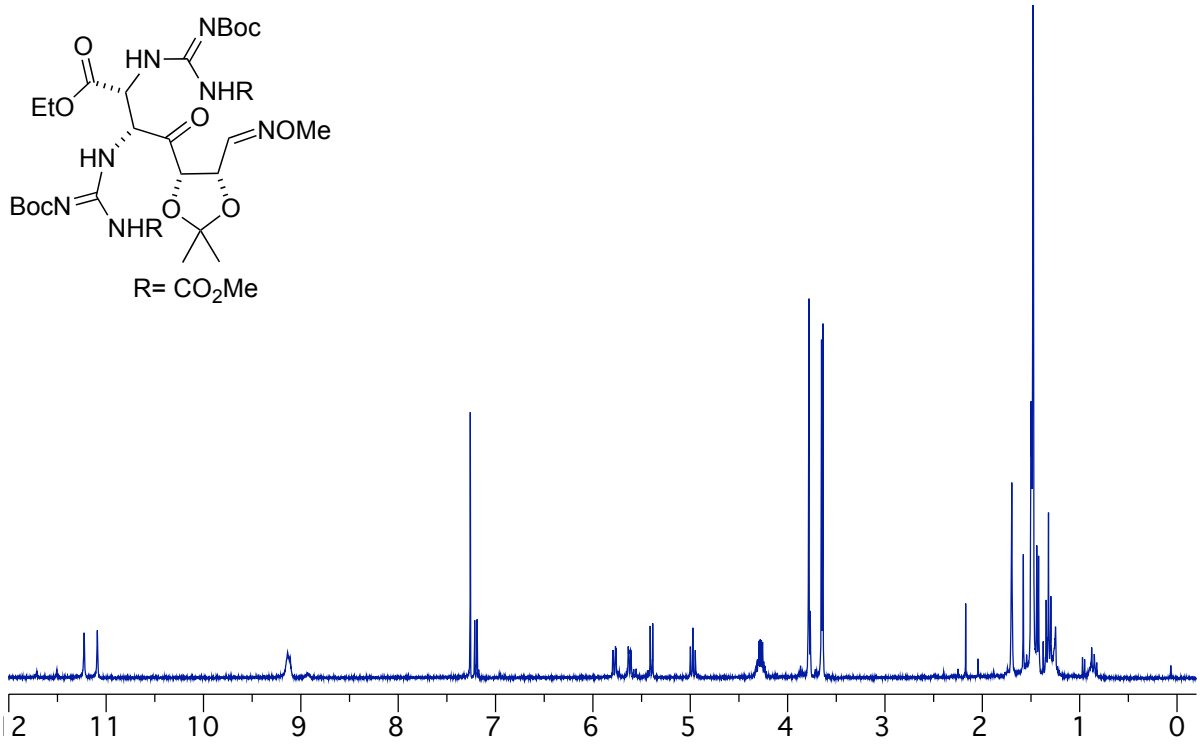
220
200
180
160
140
120
100
80
60
40
20
0

Compound 229: (2*R*,3*R*)-ethyl 2,3-bis(2-(*tert*-butoxycarbonyl)-3-(methoxycarbonyl)guanidino)-4-((4*S*,5*S*)-5-((methoxyimino)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-oxobutanoate.



To a solution of lactol **226** in MeOH (5mL) was added Methoxyamine HCl (15.6mg, 2 eq.). The reaction was stirred overnight, diluted with EtOAc and washed with H2O (3x) followed by brine. The organic layer was dried over Na_2SO_4 and evaporated in vacuo to give the oxime (45.5mg), which was taken on crude.

To a solution of the crude oxime (45.5mg, 1 eq.) in CH_2Cl_2 (5 mL) was added Dess-Martin periodinane (40.2 mg, 1.5 eq.). The solution turned cloudy over time and was allowed to stir for 2 hours. The reaction was quenched with 10% $Na_2S_2O_3$ and was allowed to stir until the biphasic system turned clear. The mixture was extracted with EtOAc (3x), dried over sodium sulfate and evaporated in vacuo to give crude ketone. The crude material was purified via flash chromatography (20% EtOAc/Hexanes) to give ketone **229** (19.5mg, 29%). ^{1}H-NMR (300 MHz; $CDCl_3$): δ 11.23 (s, 1H), 11.09 (s, 1H), 9.14-9.11 (m, 2H), 7.20 (d, *J* = 7.3 Hz, 1H), 5.78 (dd, *J* = 8.2, 1.6 Hz, 1H), 5.62 (dd, *J* = 7.3, 1.6 Hz, 1H), 5.40 (d, *J* = 7.8 Hz, 1H), 4.97 (t, *J* = 7.6 Hz, 1H), 4.28 (dtt, *J* = 10.7, 7.1, 3.5 Hz, 2H), 3.78 (s, 3H), 3.78 (d, *J* = 5.9 Hz, 1H), 3.65 (s, 3H), 3.64 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 1.48 (s, 18H), 1.32 (t, *J* = 7.1 Hz, 3H).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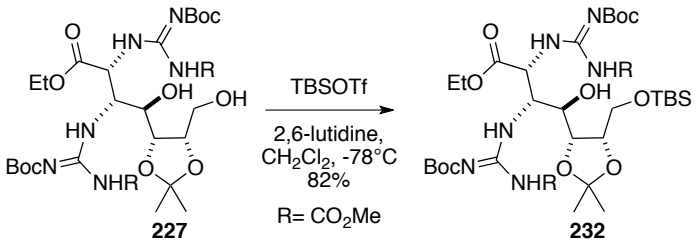
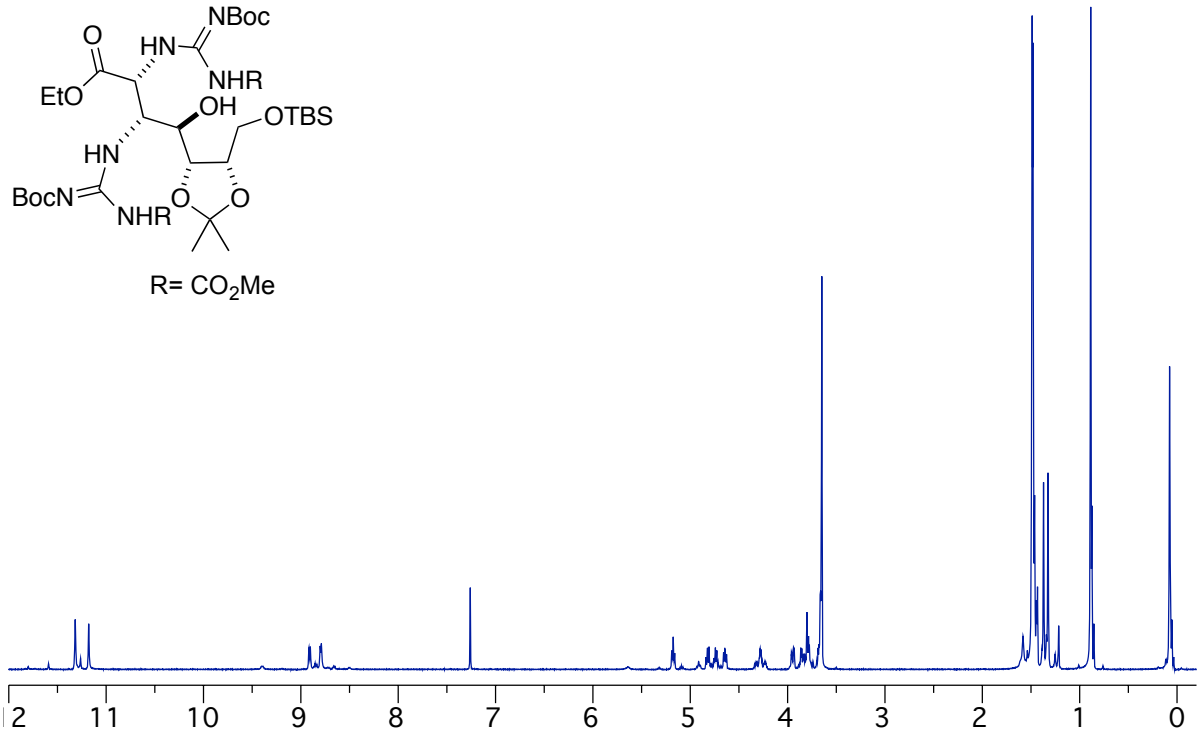
HN
NHR
O
EtO
O
NOMe
HN
BocN
NHR
O
O
R= CO2Me
12
11
10
9
8
7
6
5
4
3
2
1
0

Compound 232: (2*R*,3*R*)-ethyl 2,3-bis(2-(*tert*-butoxycarbonyl)-3-(methoxycarbonyl)guanidino)-4-((4*R*,5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-hydrox ybutanoate.



To a solution of diol **227** (240mg, 1 eq.) in CH_2Cl_2 (20 mL) was added 2,6-lutidine (242.2 µL, 6 eq.). The solution was cooled to -78°C and TBSOTf (387.8 µL, 5 eq.) was added. The reaction was stirred until complete by TLC and was quenched with sat. NH4Cl. The mixture was extracted with ethyl acetate (3x), dried over sodium sulfate and evaporated in vacuo. The crude compound was purified via column chromatography to give TBS ether **232** (230 mg, 82.3%). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 11.32 (s, 1H), 11.18 (s, 1H), 8.91 (d, *J* = 7.3 Hz, 1H), 8.80 (d, *J* = 6.1 Hz, 1H), 5.17 (t, *J* = 7.5 Hz, 1H), 4.82 (dd, *J* = 8.5, 7.0 Hz, 1H), 4.73 (q, *J* = 7.0 Hz, 1H), 4.64 (dd, *J* = 8.8, 6.3 Hz, 1H), 4.33-4.22 (m, 2H), 3.95 (dd, *J* = 10.7, 2.6 Hz, 1H), 3.85 (dd, *J* = 11.7, 5.0 Hz, 1H), 3.80-3.78 (m, 1H), 3.65 (s, 6H), 1.49 (s, 6H), 1.48 (s, 5H), 1.46 (t, *J* = 9.3 Hz, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). 13-C NMR (126 MHz; cdcl3): δ 171.6, 163.7, 163.5, 155.9, 155.6, 152.9, 152.7, 108.9, 83.98, 83.94, 78.1, 76.7, 61.5, 56.7, 54.6, 52.75, 52.66, 28.12, 28.06, 27.3, 26.00, 25.94, 25.2, 18.4, -5.2. HRMS (FAB^+): Calcd for $C_{34}H_{63}N_6O_{14}Si$ [M+H]: 807.4172; Found 807.4168.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NHR
OH
OTBS
HN
BocN
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R= CO2Me
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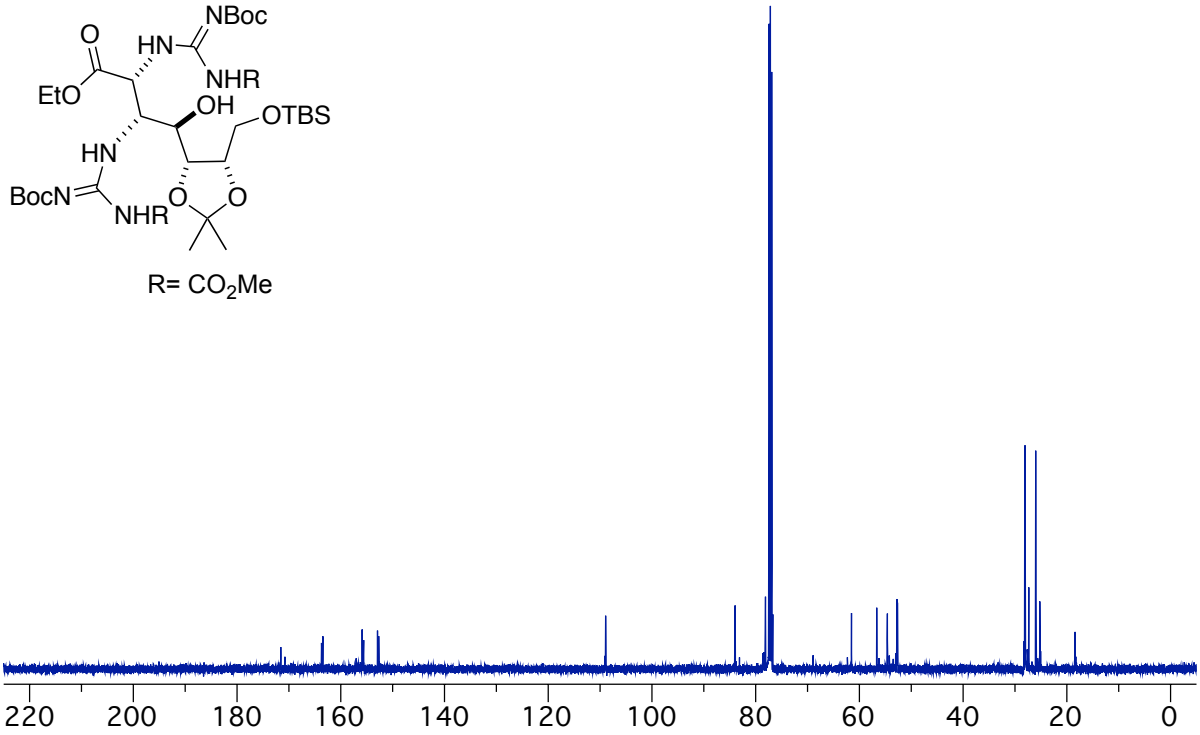
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OH
OTBS
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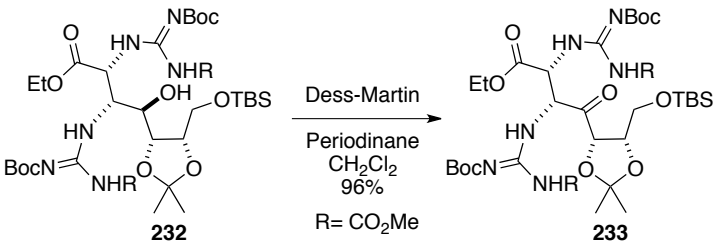
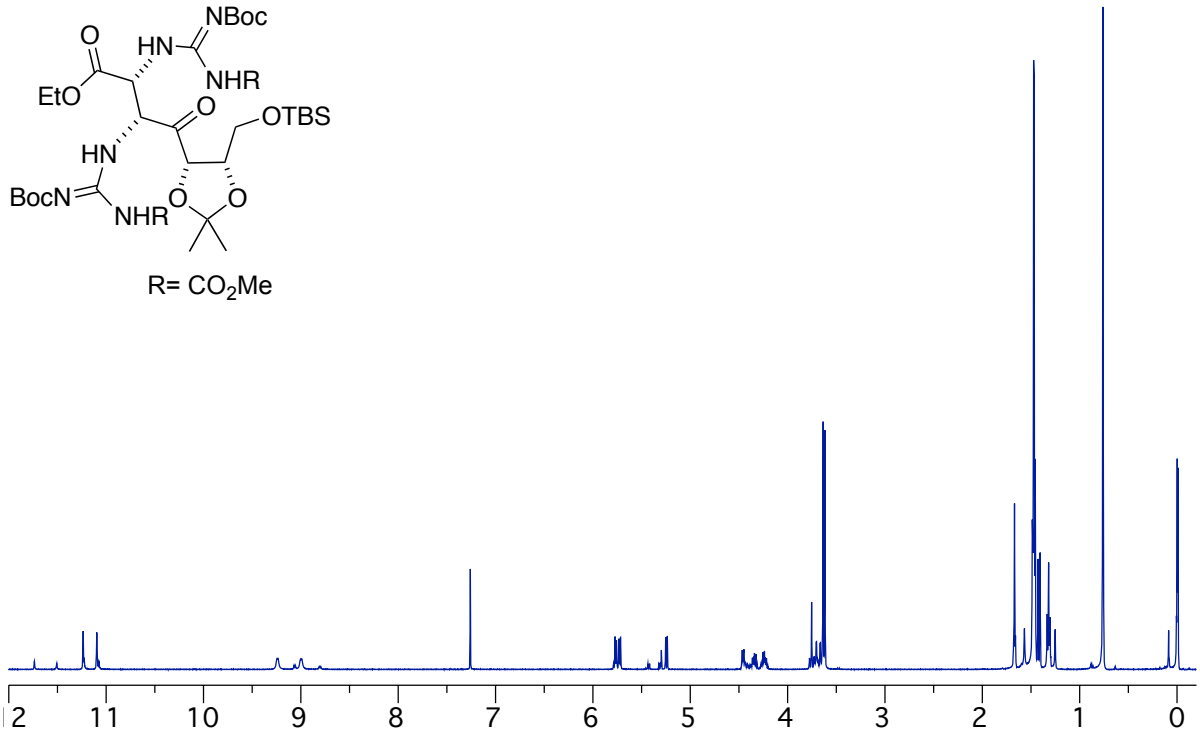
BocN
NHR
O
O
R= CO2Me
220
200
180
160
140
120
100
80
60
40
20
0

Compound 233: (2*R*,3*R*)-ethyl 2,3-bis(2-(*tert*-butoxycarbonyl)-3-(methoxycarbonyl)guanidino)-4-((4*S*,5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-oxobutanoate.



To a solution of compound **232** (49 mg, 1 eq.) in CH_2Cl_2 (5 mL) was added Dess-Martin periodinane (51.5 mg, 2 eq.). The solution turned cloudy over time and was allowed to stir for 2 hours. The reaction was quenched with $Na_2S_2O_3$ and was allowed to stir until the biphasic system turned clear. The mixture was extracted with EtOAc (3x), dried over sodium sulfate and evaporated in vacuo to give ketone **233** (47 mg, 96.2%). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 11.24 (s, 1H), 11.10 (s, 1H), 9.24 (d, *J* = 5.0 Hz, 1H), 9.00 (d, *J* = 6.5 Hz, 1H), 5.77 (d, *J* = 7.2 Hz, 1H), 5.72 (d, *J* = 8.0 Hz, 1H), 5.24 (d, *J* = 8.6 Hz, 1H), 4.46 (d, *J* = 8.6 Hz, 1H), 4.38-4.31 (m, 1H), 4.27-4.20 (m, 1H), 3.72 (dd, *J* = 11.7, 2.1 Hz, 1H), 3.67 (dd, *J* = 11.7, 2.1 Hz, 1H), 3.63 (s, 3H), 3.62 (s, 3H), 1.47 (s, 9H), 1.47 (s, 9H), 1.43 (s, 3H), 1.41 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.76 (s, 9H), -0.00 (s, 3H), -0.01 (s, 3H). 13-C NMR (126 MHz; cdcl3): δ 203.7, 169.5, 164.2, 163.7, 156.0, 155.7, 152.39, 152.36, 110.0, 83.6, 83.2, 79.78, 79.71, 62.4, 61.5, 59.7, 53.2, 52.6, 52.3, 28.34, 28.31, 28.1, 26.5, 25.82, 25.78, 24.6, 18.8, 13.9, -5.1, -5.8 HRMS (FAB^+): Calcd for $C_{34}H_{61}N_6O_{14}Si$ [M+H]: 805.4015; Found 805.4014.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EtO
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OTBS
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BocN
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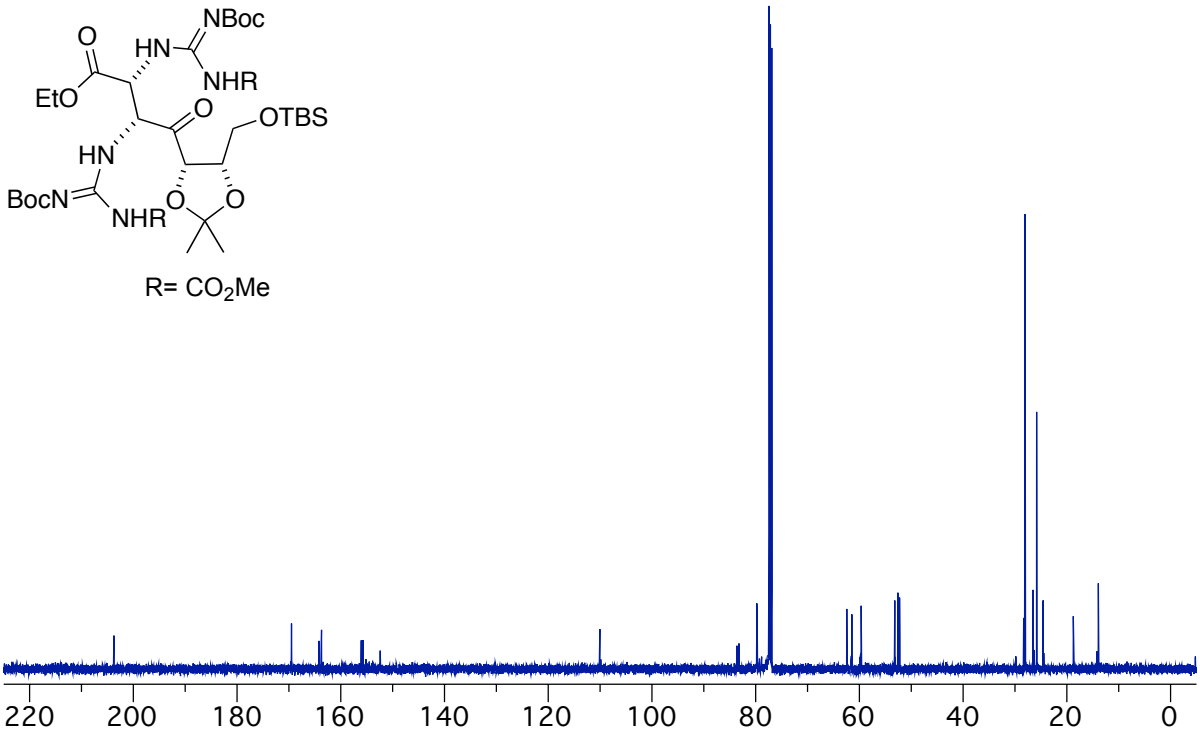
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EtO
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OTBS
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BocN
NHR
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R= CO2Me
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200
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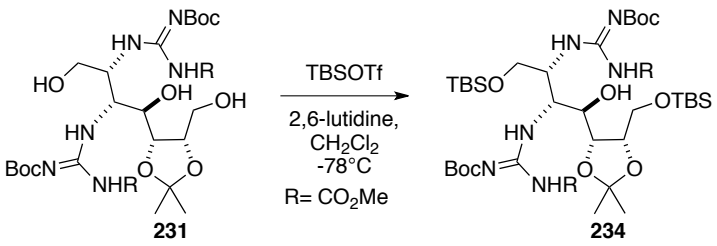
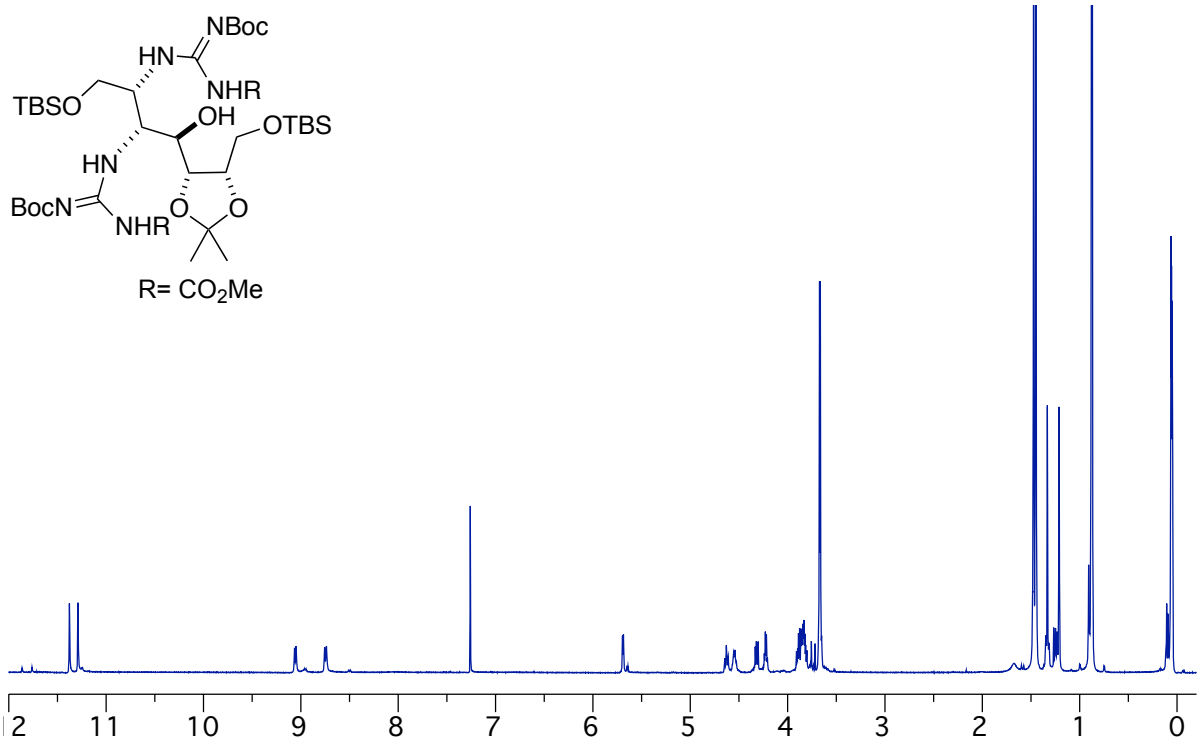
120
100
80
60
40
20
0

Compound 234: (2*R*,3*R*)-2,3-bis(2-(*tert*-butoxycarbonyl)-3-(methoxycarbonyl)guanidino)-4-((*tert*-butyldimethylsilyl)oxy)-1-((4*R*,5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)butan-1-ol.



To a solution of triol **231** (79 mg, 1 eq.) in CH_2Cl_2 (10 mL) was added 2,6-lutidine (169.7 µL, 12 eq.). The solution was cooled to -78°C and TBSOTf (278.8 µL, 10 eq.) was added. The reaction was stirred until complete by TLC, quenched with sat. NH_4Cl, and the product was extracted with EtOAc (3x). The mixture was dried over sodium sulfate, evaporated in vacuo and purified via flash chromatography (10-20% EtoAc/hexanes) to give TBS ether **234**. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 11.38 (s, 1H), 11.29 (s, 1H), 9.06 (d, *J* = 8.1 Hz, 1H), 8.75 (d, *J* = 9.4 Hz, 1H), 5.69 (d, *J* = 5.1 Hz, 1H), 4.63 (ddd, *J* = 9.6, 7.5, 2.3 Hz, 1H), 4.55 (dtd, *J* = 8.2, 5.5, 2.5 Hz, 1H), 4.32 (dd, *J* = 9.3, 5.8 Hz, 1H), 4.22 (q, *J* = 5.4 Hz, 1H), 3.89 (dd, *J* = 10.4, 5.5 Hz, 1H), 3.85 (dd, *J* = 10.7, 5.5 Hz, 1H), 3.82 (dd, *J* = 10.1, 6.0 Hz, 1H), 3.67 (s, 3H), 3.67 (dd, 1H), 3.66 (s, 3H), 1.47 (s, 9H), 1.45 (s, 9H), 1.33 (s, 3H), 1.21 (s, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H). 13-C NMR (126 MHz; cdcl3): δ 164.5, 163.9, 157.2, 157.0, 152.52, 152.44, 108.8, 83.4, 82.9, 78.9, 78.2, 69.3, 63.8, 62.5, 55.9, 52.65, 52.56, 52.0, 28.08, 28.06, 27.8, 26.02, 25.99, 25.94, 25.1, 18.44, 18.34, -5.32, -5.45, -5.58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OH
OTBS
HN
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3
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1
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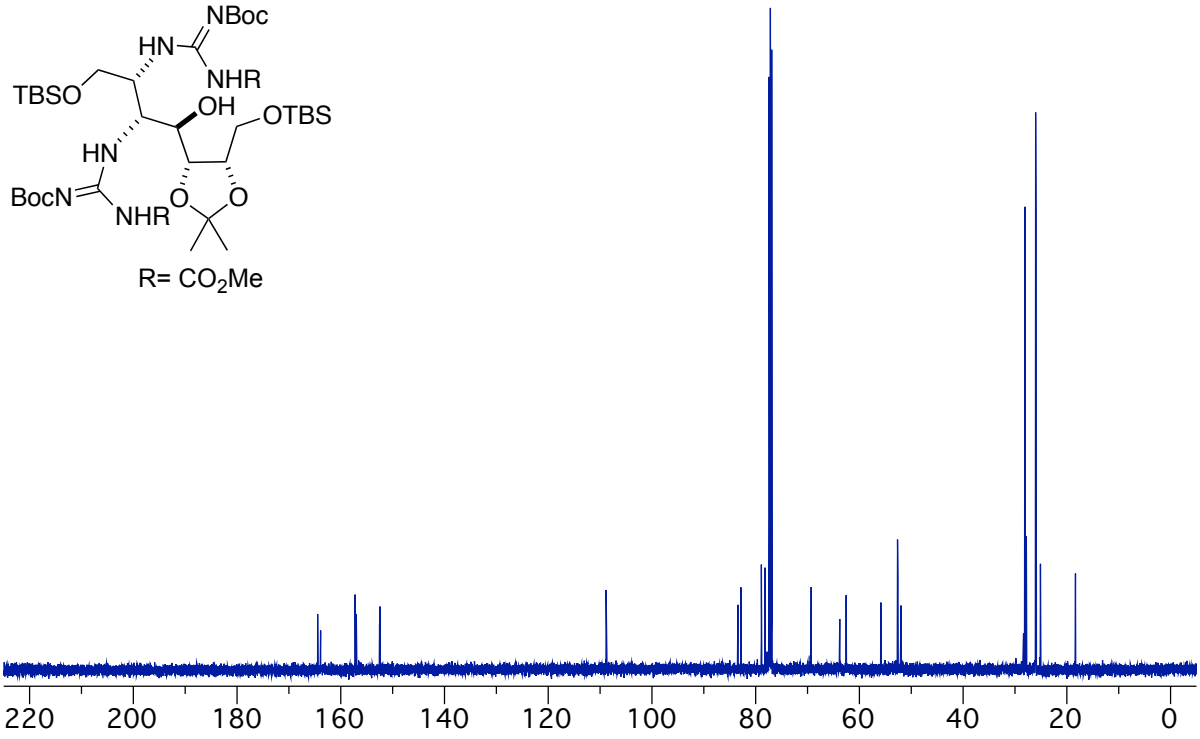
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OH
OTBS
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BocN
NHR
O
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R= CO2Me
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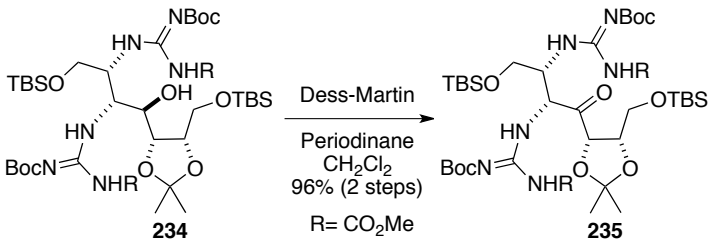
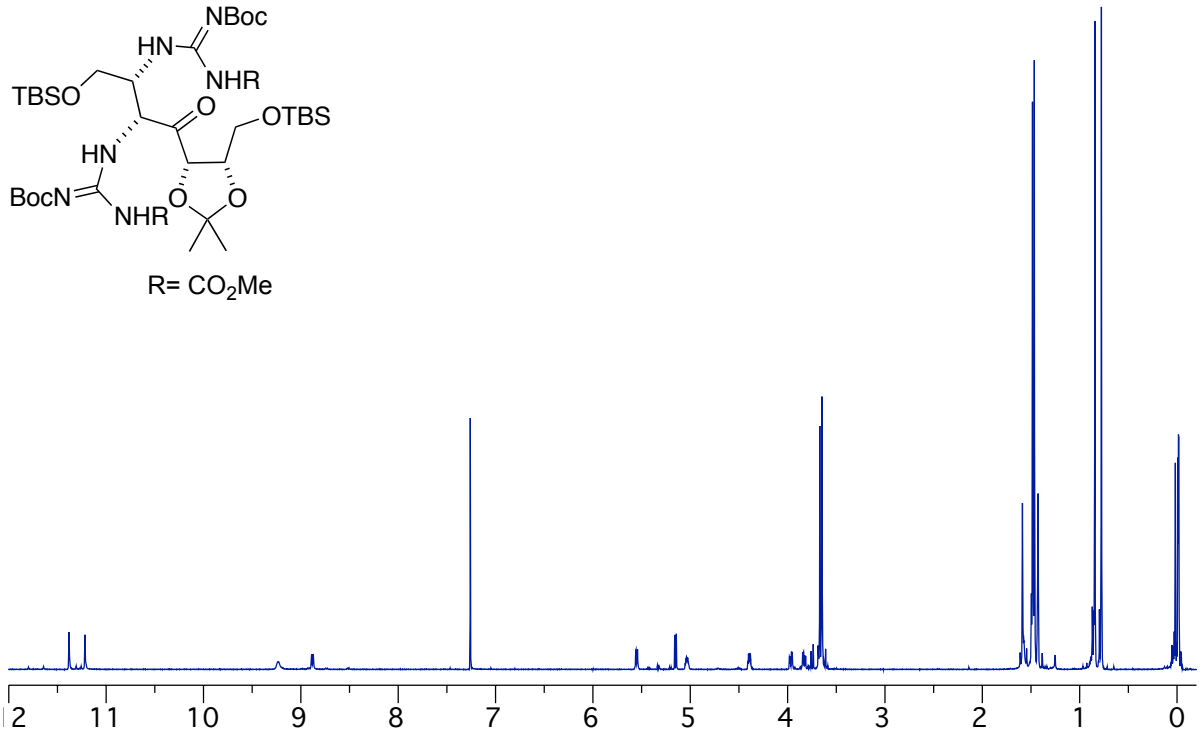
160
140
120
100
80
60
40
20
0

Compound 235: (2*R*,3*R*)-2,3-bis(2-(*tert*-butoxycarbonyl)-3-(methoxycarbonyl)guanidino)-4-((*tert*-butyldimethylsilyl)oxy)-1-((4*R*,5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)butan-1-one.



To a solution of compound **234** (0.138 mmol crude) in CH_2Cl_2 (10 mL) was added Dess-Martin periodinane (117.3 mg, 2 eq.). The solution turned cloudy over time and was allowed to stir for 2 hours. The reaction was quenched with $Na_2S_2O_3$ and was allowed to stir until the biphasic system turned clear. The mixture was extracted with EtOAc (3x), dried over sodium sulfate and evaporated in vacuo to give ketone **235** (75mg, 61.8% (2 steps)). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 11.38 (s, 1H), 11.22 (s, 1H), 9.23 (d, *J* = 3.2 Hz, 1H), 8.88 (d, *J* = 8.7 Hz, 1H), 5.55 (dd, *J* = 8.2, 1.9 Hz, 1H), 5.15 (d, *J* = 8.2 Hz, 1H), 5.03 (dtd, *J* = 8.7, 4.3, 1.7 Hz, 1H), 4.39 (ddd, *J* = 8.1, 3.7, 2.9 Hz, 1H), 3.97 (dd, *J* = 10.4, 4.1 Hz, 1H), 3.83 (dd, *J* = 10.4, 4.9 Hz, 1H), 3.75 (d, *J* = 11.4 Hz, 1H), 3.67 (s, 3H), 3.65 (s, 1H), 3.65 (s, 3H), 1.59 (s, 3H), 1.48 (s, 9H), 1.47 (s, 9H), 1.43 (s, 3H), 0.84 (s, 9H), 0.78 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H), -0.01 (s, 3H), -0.02 (s, 3H). 13-C NMR (126 MHz; cdcl3): δ 204.6, 164.2, 163.9, 156.4, 155.9, 152.3, 109.8, 83.0, 79.6, 79.3, 77.2, 63.3, 61.7, 58.6, 52.49, 52.39, 52.26, 28.2, 27.91, 27.89, 26.8, 25.73, 25.71, 24.5, 18.5, 18.2, -5.3, -5.8. Calcd. for $C_{38}H_{73}N_6O_{13}Si_2$ [M+H]: 877.4774 Found 877.4791.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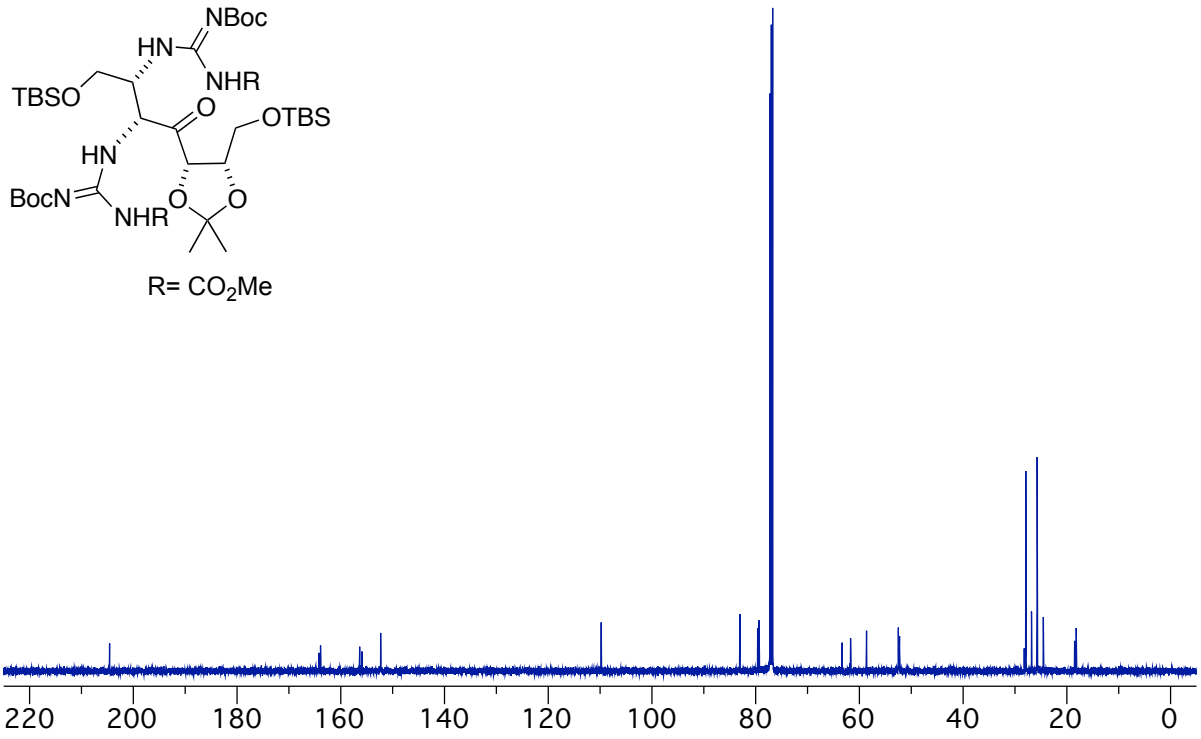
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NHR
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R= CO2Me
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200
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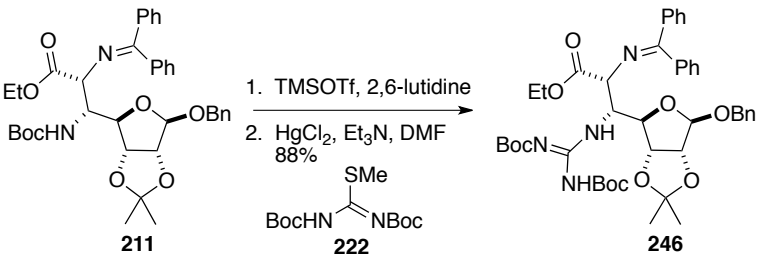
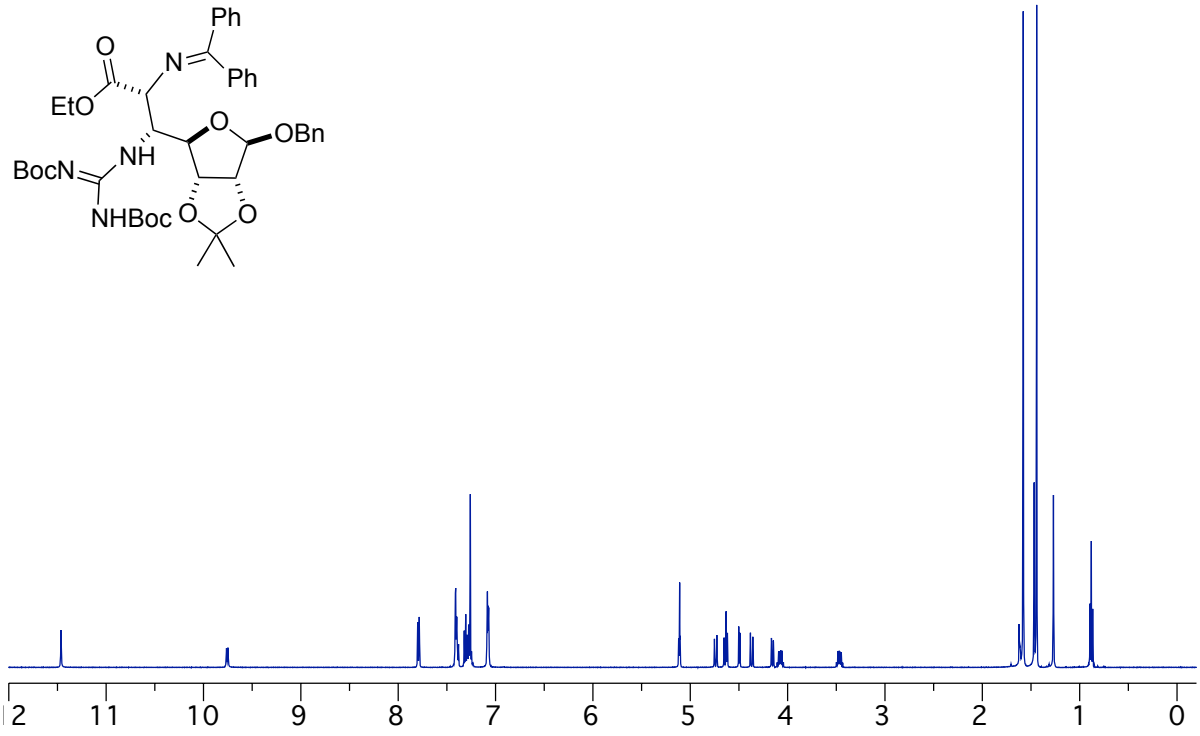
160
140
120
100
80
60
40
20
0

Compound 246: (2*R*,3*R*)-ethyl 3-((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-3-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-2-((diphenylmethylene)amino)propanoate.



To a solution of Mannich product **211** (275 mg, 1eq.) in CH_2Cl_2 (5 mL) was added 2,6-lutidine (199 µL, 4 eq.) and TMSOTf (270 µL, 3.5eq.). The solution was stirred until complete by TLC and was quenched with sat. sodium bicarbonate. The mixture was extracted with ethyl acetate (3x), dried over sodium sulfate and evaporated. Crude aminal **253** (0.427 mmol crude) was dissolved in DMF and guanylating reagent **222** (185.8 mg, 1.5 eq.), and Et_3N (267.5 µL, 4.5 eq.) was added. After cooling the solution to 0°C, mercuric chloride (173.7 mg, 1.5 eq.) was added and the mixture was stirred until complete by TLC. The reaction was quenched by adding sat. sodium bicarbonate, sat. sodium chloride and ethyl acetate. After stirring the mixture for 20 minutes the reaction was filtered through celite to remove all the mercury salts. The biphasic solution was separated and the organic layer was washed with H_2O (3x), brine and then dried over sodium sulfate and evaporated in vacuo. The crude material was purified via column chromatography (10-20% EtOAc/hexanes) to give compound **246** (295 mg, 87.9% over 2 steps). $[\alpha]_D^{25}$= -5 (c 0.42, $CHCl_3$) ^{1}H-NMR (500 MHz; $CDCl_3$): δ 11.46 (s, 1H), 9.76 (d, *J* = 7.5 Hz, 1H), 7.79 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.44-7.38 (m, 4H), 7.32-7.23 (m, 7H), 7.09-7.07 (m, 2H), 5.11 (dd, *J* = 7.4, 0.9 Hz, 1H), 5.11 (s, 1H), 4.74 (d, *J* = 12.2 Hz, 1H), 4.64 (d, *J* = 10.7 Hz, 1H), 4.63 (d, *J* = 6.5 Hz, 1H), 4.50 (d, *J* = 5.9 Hz, 1H), 4.37 (d, *J* = 12.2 Hz, 1H), 4.16 (dd, *J* = 9.9, 1.0 Hz, 1H), 4.07 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.47 (dq, *J* = 10.7, 7.1 Hz, 1H), 1.58 (s, 9H), 1.47 (s, 3H), 1.44 (s, 9H), 1.27 (s, 3H), 0.88 (t, *J* = 7.1 Hz, 3H). 13-C NMR (126

MHz; cdcl3): δ 171.2, 170.7, 163.4, 156.9, 152.9, 139.2, 137.7, 135.9, 130.8, 129.7, 128.8, 128.5, 128.3, 128.05, 128.03, 127.52, 127.45, 112.4, 108.4, 86.4, 85.6, 82.9, 81.7, 78.9, 69.7, 63.2, 61.0, 55.7, 28.48, 28.33, 26.6, 25.2, 13.9. IR (Dep. $CDCl_3$): 3307 (br), 2978 (s), 2939 (s), 1747 (s), 1727 (s), 1637 (s), 1616 (s), 1549 (s).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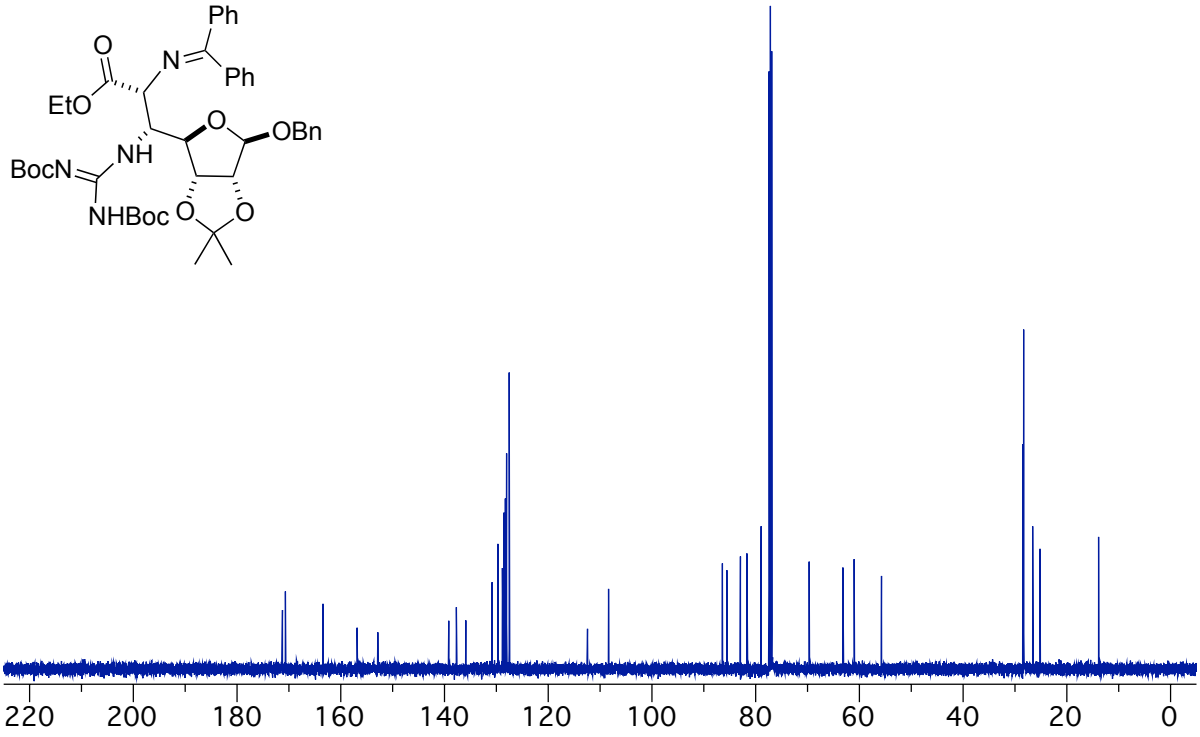
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200
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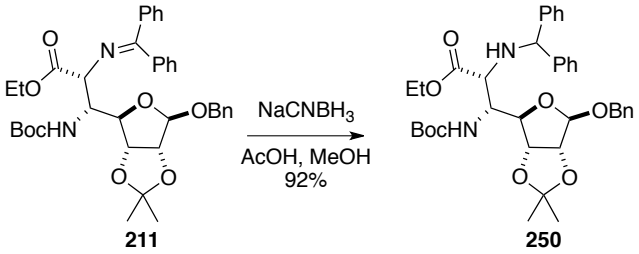
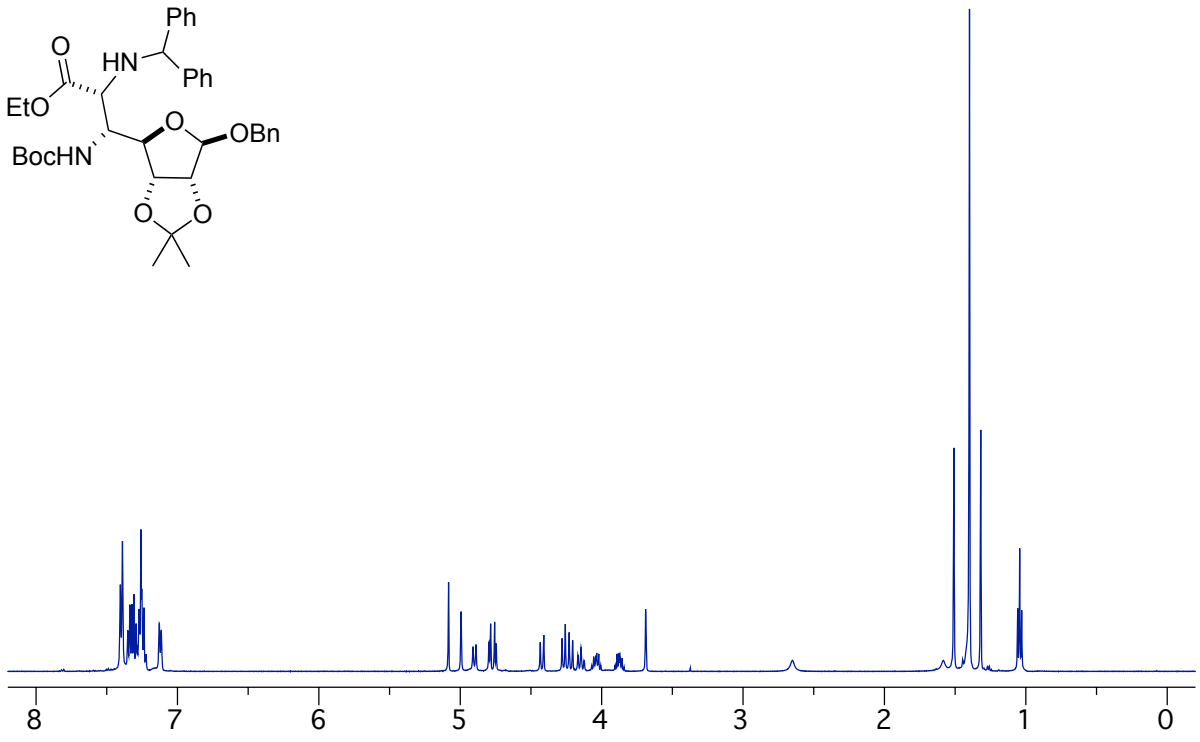
120
100
80
60
40
20
0

Compound 250: (2*R*,3*R*)-ethyl 2-(benzhydrylamino)-3-((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate.



211 250

To a solution of imine **211** (100mg, 1 eq.) in methanol (5 mL) was added acetic acid (44.4 μL, 5 eq.) and sodium cyanoborohydride (97.5 mg, 10 eq.). The mixture was stirred until complete by TLC and was diluted with ethyl acetate. The mixture was washed with H_2O (3x), brine, dried over sodium sulfate and evaporated in vacuo to give amine **250** (91.8 mg, 91.5%). $[\alpha]_D^{25}$= -79 (c 0.52, $CHCl_3$) ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.40 (d, *J* = 7.2 Hz, 3H), 7.33 (dd, *J* = 14.3, 7.3 Hz, 4H), 7.26 (dd, *J* = 19.1, 8.8 Hz, 6H), 7.12 (d, *J* = 7.3 Hz, 2H), 5.08 (s, 1H), 4.99 (s, 1H), 4.90 (d, *J* = 10.4 Hz, 1H), 4.79 (d, *J* = 6.0 Hz, 1H), 4.75 (d, *J* = 5.9 Hz, 1H), 4.42 (d, *J* = 12.2 Hz, 1H), 4.27 (d, *J* = 11.4 Hz, 1H), 4.22 (d, *J* = 12.2 Hz, 1H), 4.15 (t, *J* = 10.9 Hz, 1H), 4.15 (t, *J* = 7.1 Hz, 3H), 4.04 (dq, *J* = 10.6, 7.2 Hz, 1H), 3.87 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.69 (d, *J* = 1.8 Hz, 1H), 2.65 (s, 1H), 1.51 (s, 3H), 1.40 (s, 9H), 1.32 (s, 3H). 13-C NMR (126 MHz; cdcl3): δ 173.6, 155.4, 143.7, 142.8, 137.3, 128.7, 128.41, 128.34, 127.97, 127.93, 127.7, 127.5, 127.2, 112.4, 107.8, 86.2, 85.7, 82.5, 79.9, 69.7, 65.9, 61.5, 57.9, 55.1, 28.3, 26.6, 25.1, 14.0. IR (Dep. $CDCl_3$): 3350 (br), 2980(s), 2942(s), 1715(s), 1494(s), 1455(s), 1368(s).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BocHN
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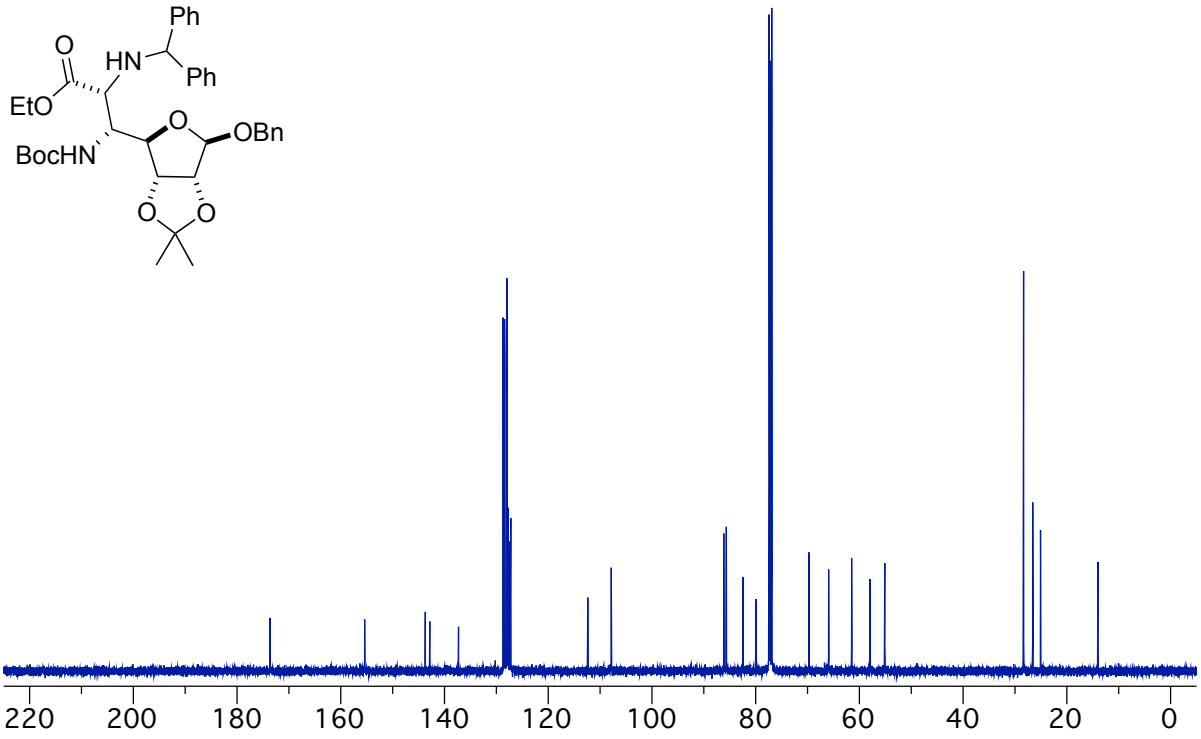
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EtO
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BocHN
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120
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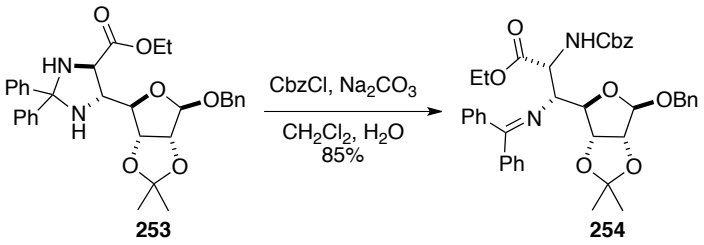
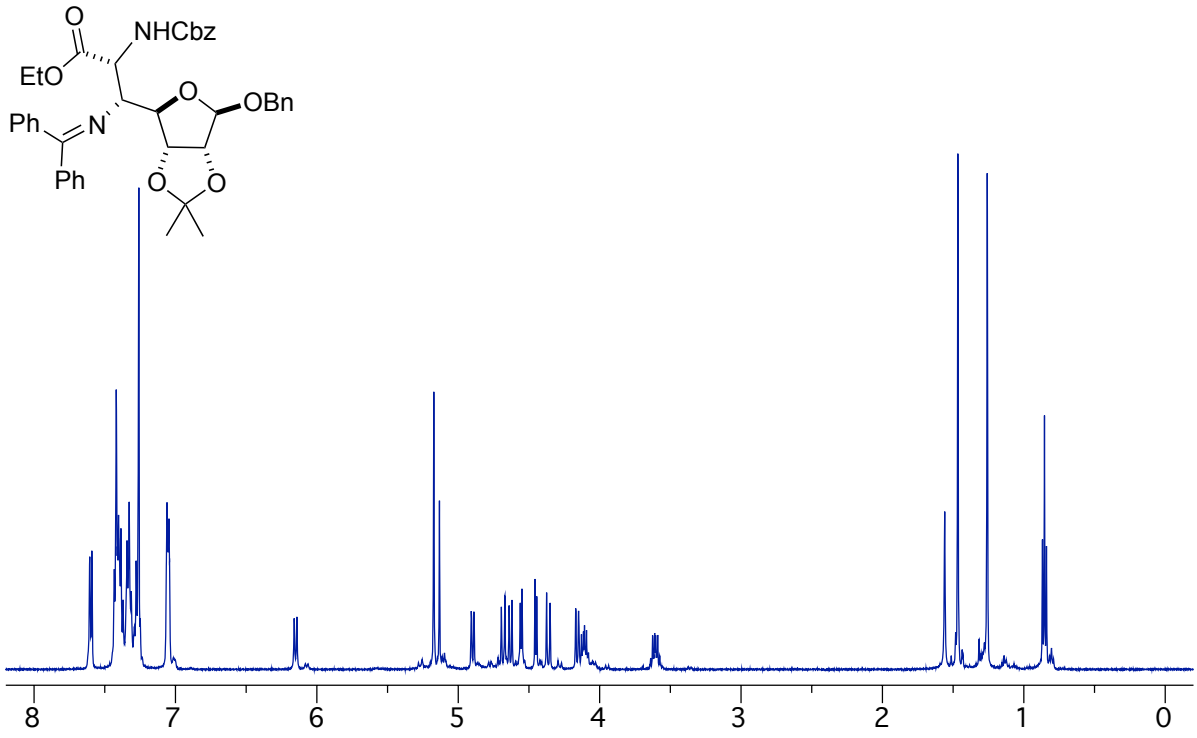
60
40
20
0

Compound 254: (2*R*,3*R*)-ethyl 3-((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-2-(((benzyloxy)carbonyl)amino)-3-((diphenylmethylene)amino)propanoate.



To a solution of aminal **253** (7.75 mmol, 1 eq.) and sodium carbonate (1.64 g, 2 eq.) in CH_2Cl_2 (50 mL) and H_2O (50 mL) at 0°C was added CbzCl (4.85 g, 30-35% in toluene, 1.1 eq.). The mixture was stirred until complete by TLC and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3x) and the combined extracts were dried over sodium sulfate and evaporated in vacuo. The crude material was purified via column chromatography (10-30% EtOAc/hexanes) to give product **254** (4.45 g, 84.6% over 2 steps). $[\alpha]_D^{25}$= -82 (c 0.22, $CHCl_3$). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.60 (d, *J* = 7.4 Hz, 2H), 7.45-7.23 (m, 10H), 7.05 (dd, *J* = 7.3, 1.6 Hz, 3H), 6.15 (d, *J* = 9.3 Hz, 1H), 5.17 (s, 2H), 5.13 (s, 1H), 4.90 (dd, *J* = 9.4, 1.4 Hz, 1H), 4.68 (d, *J* = 12.3 Hz, 1H), 4.63 (d, *J* = 10.2 Hz, 1H), 4.56 (d, *J* = 6.0 Hz, 1H), 4.45 (d, *J* = 5.9 Hz, 1H), 4.36 (d, *J* = 12.3 Hz, 1H), 4.16 (dd, *J* = 10.2, 1.4 Hz, 1H), 4.11 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.61 (dq, *J* = 10.7, 7.2 Hz, 1H), 1.47 (s, 3H), 1.26 (s, 3H), 0.85 (t, *J* = 7.1 Hz, 3H). 13-C NMR (126 MHz; cdcl3): δ 171.6, 171.3, 156.6, 139.0, 137.4, 136.3, 135.8, 130.8, 129.1, 128.8, 128.51, 128.47, 128.31, 128.12, 128.05, 127.7, 127.33, 127.20, 112.3, 108.0, 86.0, 85.4, 81.3, 77.2, 69.3, 67.1, 63.5, 61.1, 55.6, 26.4, 25.0, 13.7 IR (Dep. $CDCl_3$): 3266 (br), 1727 (s), 1496 (s), 1455 (s), 1372 (s), 1320 (s).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OBn
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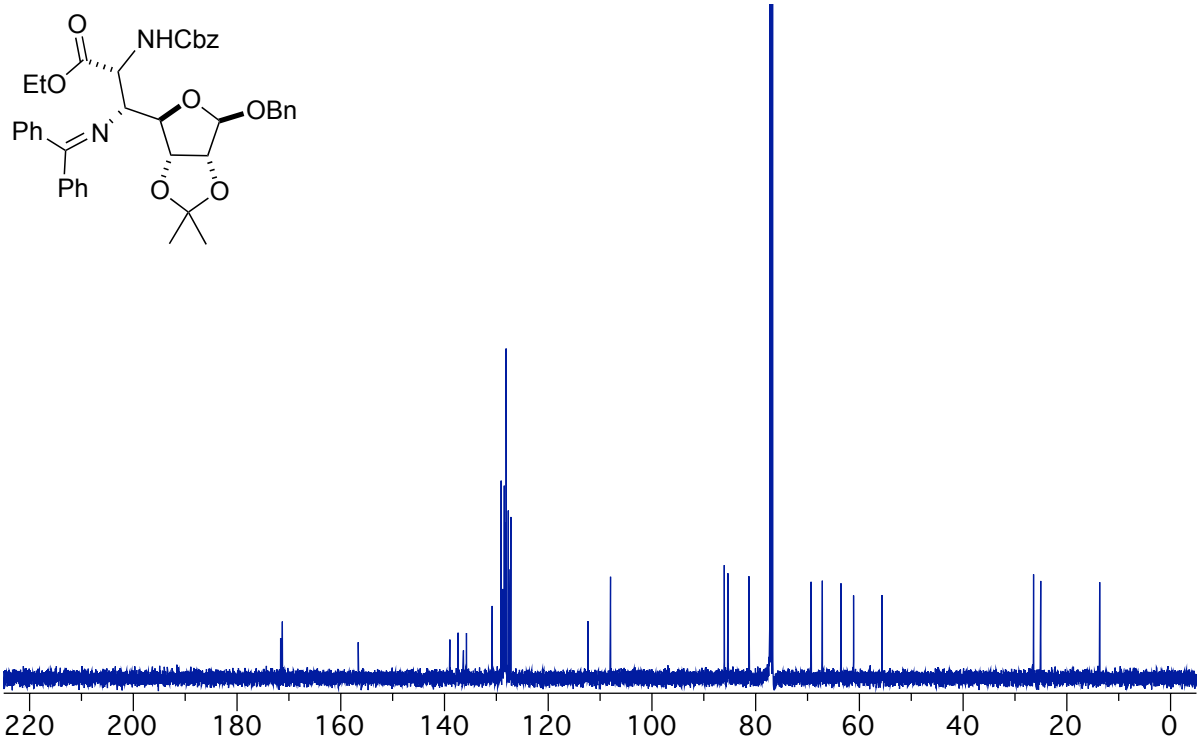
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EtO
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OBn
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Ph
O
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220
200
180
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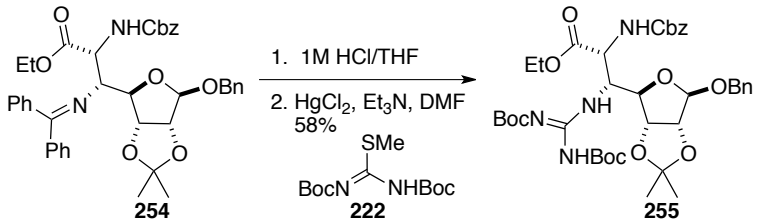
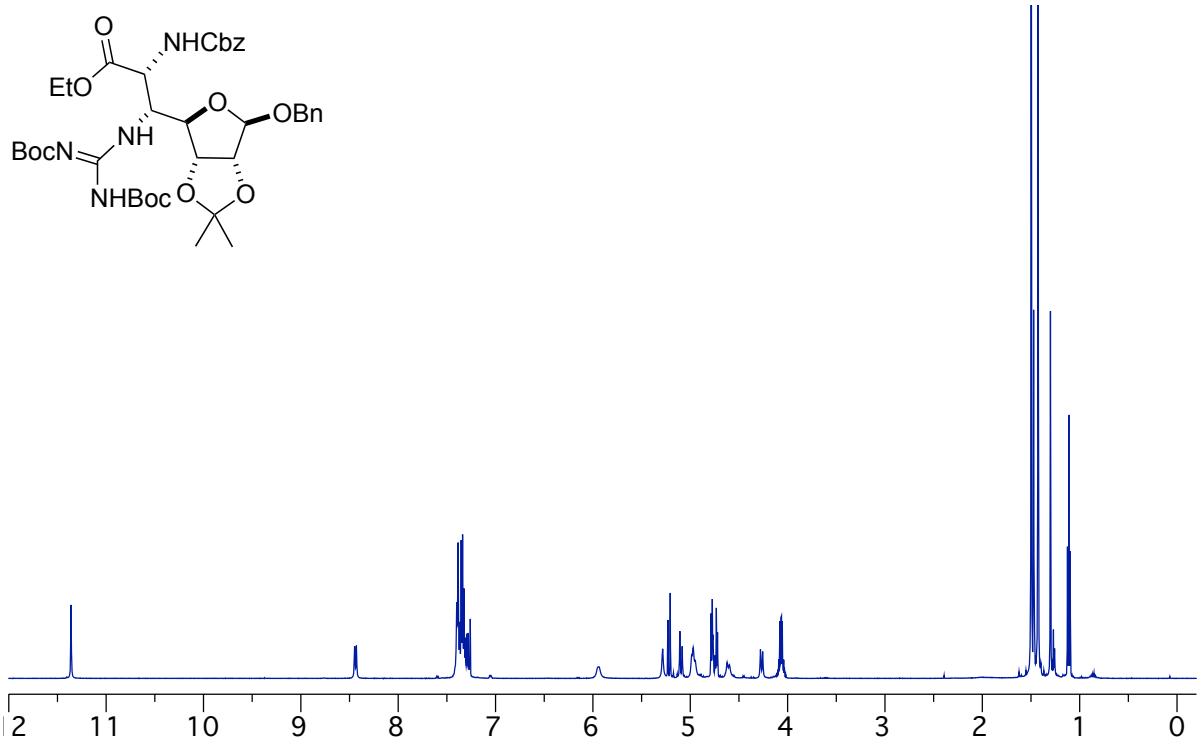
140
120
100
80
60
40
20
0

Compound 255: (2*R*,3*R*)-ethyl 3-((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-2-(((benzyloxy)carbonyl)amino)-3-(2,3-bis(*tert*-butoxycarbonyl)guanidino)propanoate.



To a solution of compound **254** (100 mg) in THF (5mL) was added 5M HCl (2 mL). The mixture was stirred until complete by TLC and was quenched with $NaHCO_3$. The mixture was extracted with EtOAc (3x), dried over sodium sulfate and evaporated in vacuo. The crude amine (0.147 mmol) was dissolved in DMF and reagent **222** (51.3 mg, 1.2 eq.), and Et_3N (92.4 μL, 4.5 eq.) was added. After cooling the solution to 0°C, $HgCl_2$ (48 mg, 1.2 eq.) was added and the mixture was stirred at r.t. until complete by TLC. The reaction was quenched by adding sat. $NaHCO_3$, sat. sodium chloride and EtOAc. After stirring the mixture for 20 minutes the reaction was filtered through celite to remove all the mercury salts. The biphasic solution was separated and the organic layer was washed with H_2O (3x), brine and then dried over sodium sulfate and evaporated in vacuo. The crude material was purified via column chromatography (10-20% EtOAc/hexanes) to give compound **255** (65 mg, 58.2% over 2 steps). $[\alpha]_D^{25}$= -96 (c 0.54, $CHCl_3$). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 11.36 (s, 1H), 8.44 (d, *J* = 9.3 Hz, 1H), 7.40-7.26 (m, 10H), 5.94 (d, *J* = 6.7 Hz, 1H), 5.28 (s, 1H), 5.22 (d, *J* = 12.2 Hz, 1H), 5.10 (d, *J* = 12.2 Hz, 1H), 4.97 (t, *J* = 9.3 Hz, 2H), 4.78 (d, *J* = 6.0 Hz, 1H), 4.75 (dd, *J* = 9.4, 2.0 Hz, 1H), 4.73 (d, *J* = 6.0 Hz, 1H), 4.61 (d, *J* = 11.9 Hz, 1H), 4.27 (d, *J* = 11.4 Hz, 1H), 4.11-4.02 (m, 2H), 4.11-4.02 (m, 2H), 1.50 (s, 9H), 1.47 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H). 13-C NMR (126 MHz; cdcl3): δ 171.1, 163.1, 156.7, 156.2, 153.1, 137.4, 136.4, 128.62, 128.52, 128.36, 128.27, 127.87, 127.81, 112.8, 108.5, 85.6, 85.2, 83.9, 82.2, 79.4, 70.2, 67.5, 62.1, 54.5, 54.1, 28.34, 28.23, 26.6, 25.2, 14.1. IR (Dep. $CDCl_3$): 3308 (br), 2980 (s), 2938 (s), 1728 (s), 1640 (s), 1616 (s).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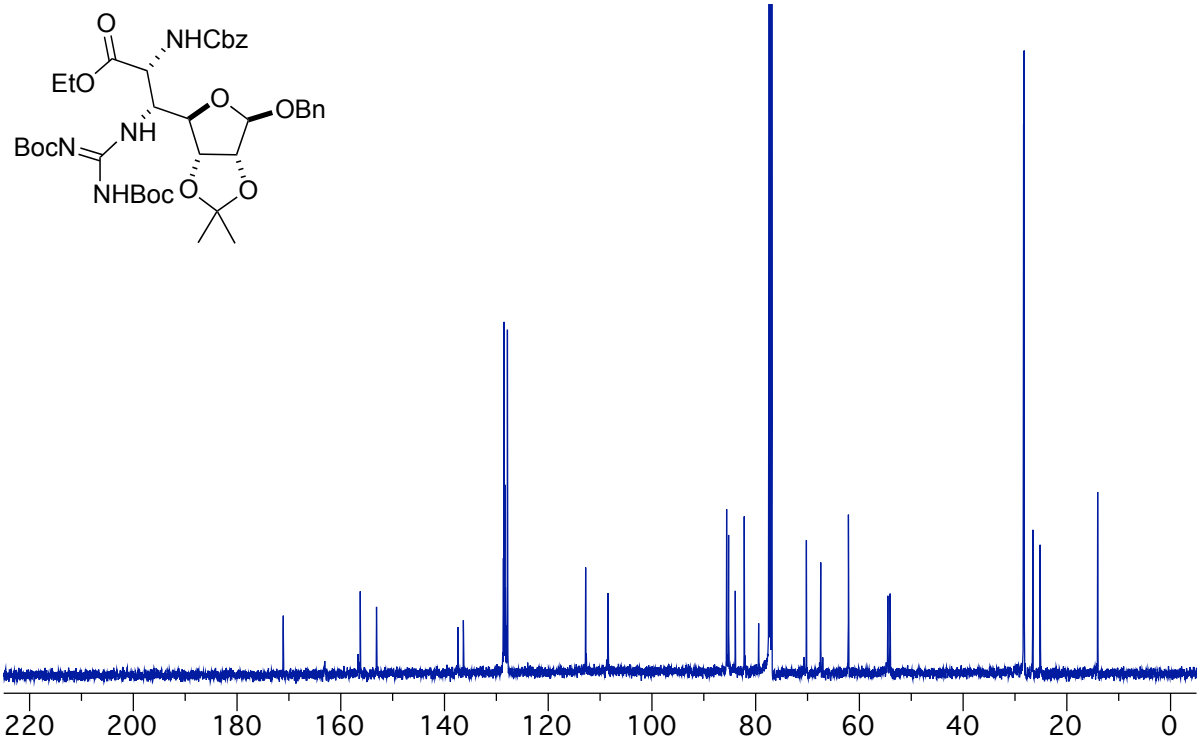
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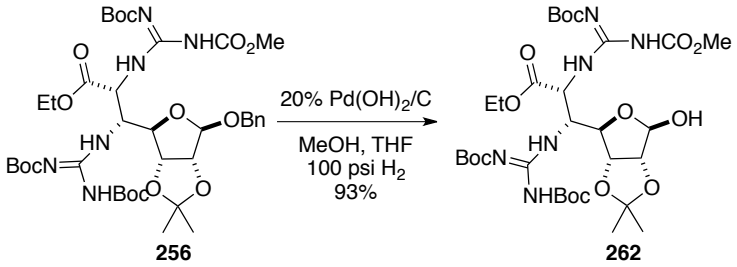
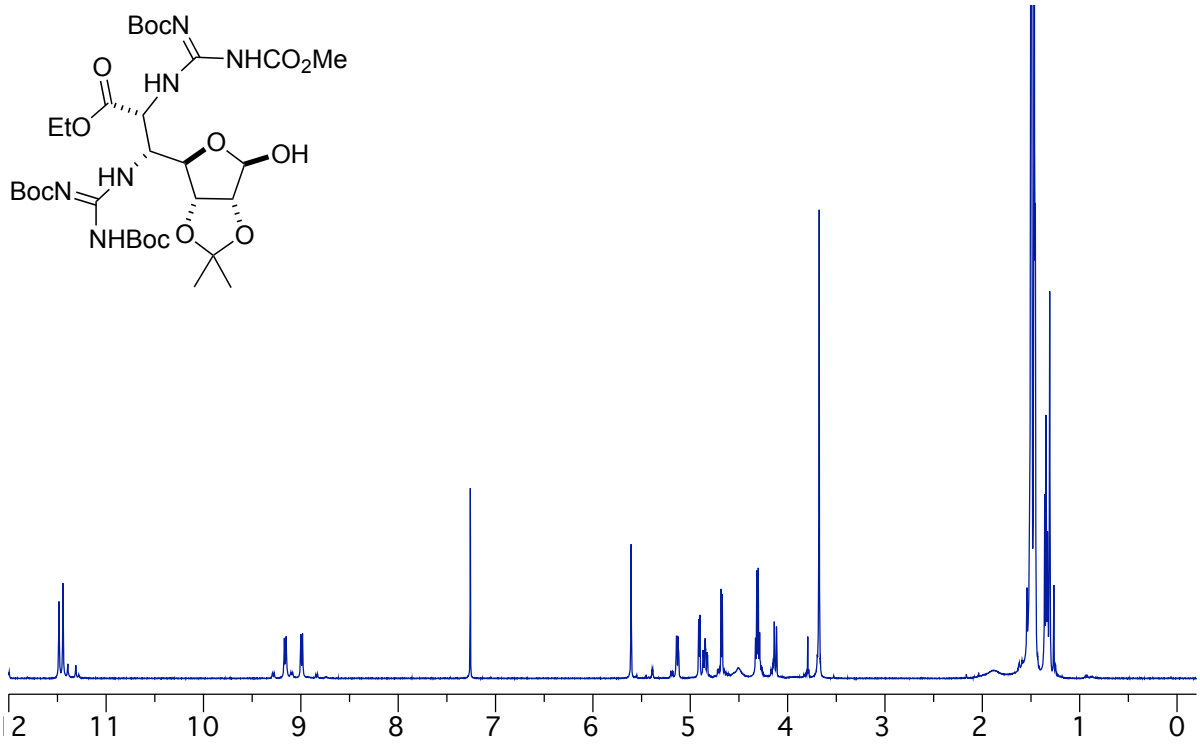
OBn
NH
BocN
NHBoc
O
O
220
200
180
160
140
120
100
80
60
40
20
0

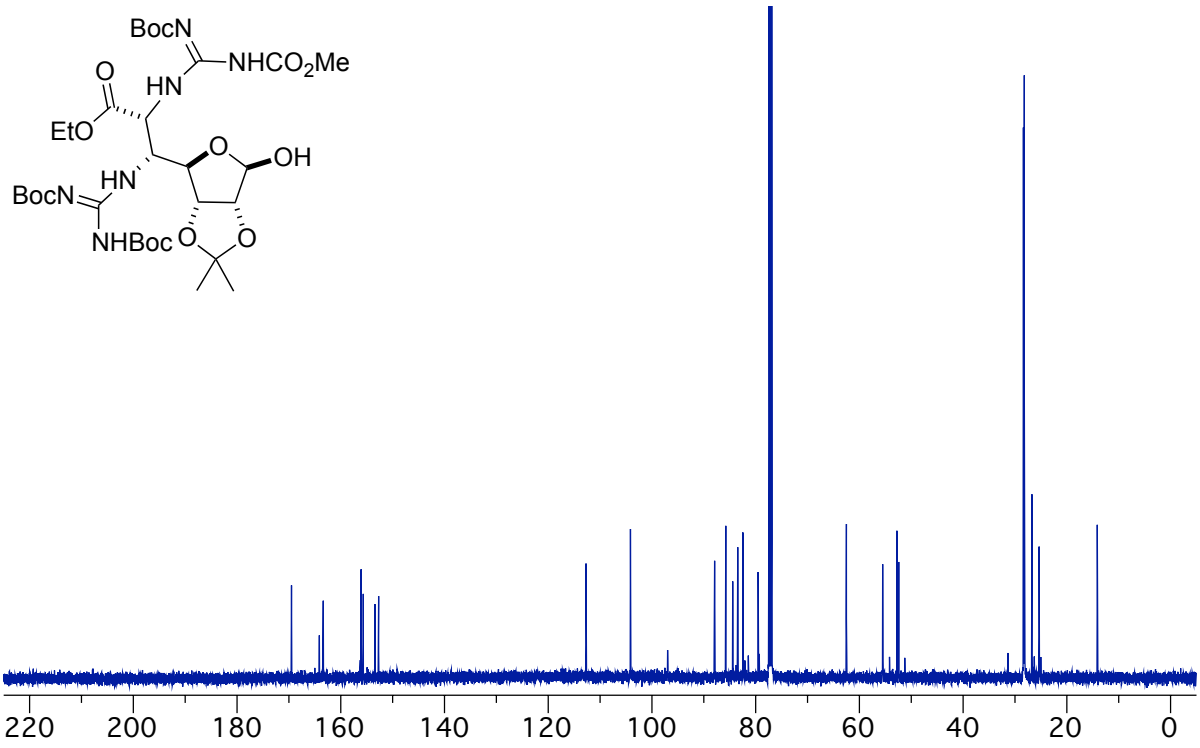
Compound 262: (2*R*,3*R*)-ethyl 3-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-2-(2-(*tert*-butoxycarbonyl)-3-(methoxycarbonyl)guanidino)-3-((3a*R*,4*R*,6*R*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propanoate.



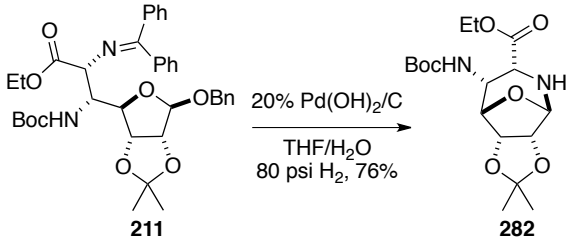
256 **262**

To a solution of benzyl ether **256** (525 mg) in 5:1 THF/methanol (6mL) was added 20% $Pd(OH)_2/C$ (262.50 mg). Argon was bubbled through the resulting suspension and then it was hydrogenated at 100 psi for 22 hours. The mixture was filtered evaporated and purified via flash chromatography to give 436 mg (93.3%) of lactol **262**. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 11.48 (s, 1H), 11.44 (s, 1H), 9.16 (d, *J* = 9.4 Hz, 1H), 8.99 (d, *J* = 8.9 Hz, 1H), 5.61 (s, 1H), 5.13 (dd, *J* = 8.9, 2.6 Hz, 1H), 4.91 (dd, *J* = 5.9, 1.0 Hz, 1H), 4.85 (ddd, *J* = 11.4, 9.3, 2.3 Hz, 1H), 4.68 (d, *J* = 5.9 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.12 (dd, *J* = 11.2, 1.0 Hz, 1H), 3.68 (t, *J* = 8.2 Hz, 1H), 3.68 (s, 3H), 1.50 (s, 9H), 1.49 (s, 9H), 1.47 (s, 9H), 1.45 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.31 (s, 3H). 13-C NMR (126 MHz; cdcl3): δ 169.5, 164.1, 163.4, 156.1, 155.7, 153.4, 152.7, 112.7, 104.1, 87.9, 85.8, 84.4, 83.5, 82.5, 79.5, 62.5, 55.5, 52.8, 52.4, 28.37, 28.22, 28.20, 26.7, 25.3, 14.1.


BocN
NHCO2Me
HN
O
EtO
O
OH
HN
BocN
NHBoc
O
O
12
11
10
9
8
7
6
5
4
3
2
1
0


BocN
NHCO2Me
HN
O
EtO
O
OH
HN
BocN
NHBoc
O
O
220
200
180
160
140
120
100
80
60
40
20
0

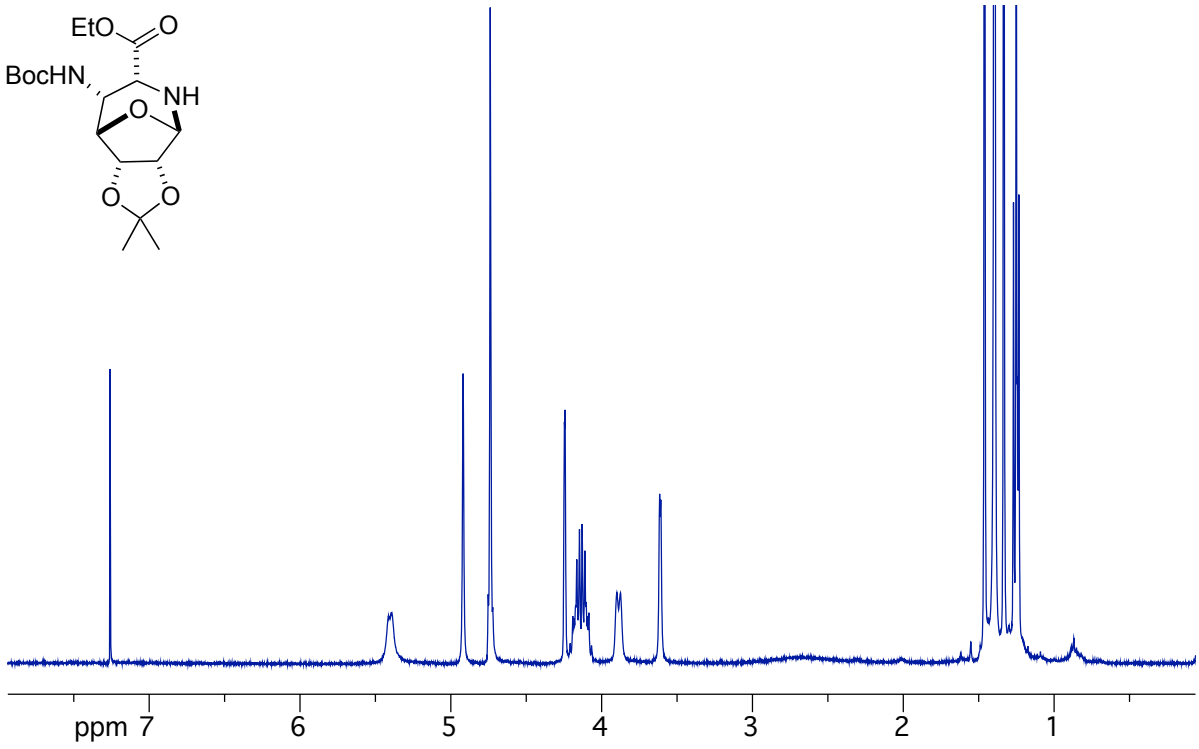
Compound 282: (3a*R*,4*R*,6*R*,7*R*,8*S*,8a*R*)-ethyl 7-((*tert*-butoxycarbonyl)amino)-2,2-dimethylhexahydro-3a*H*-4,8-epoxy[1,3]dioxolo[4,5-*c*]azepine-6-carboxylate.

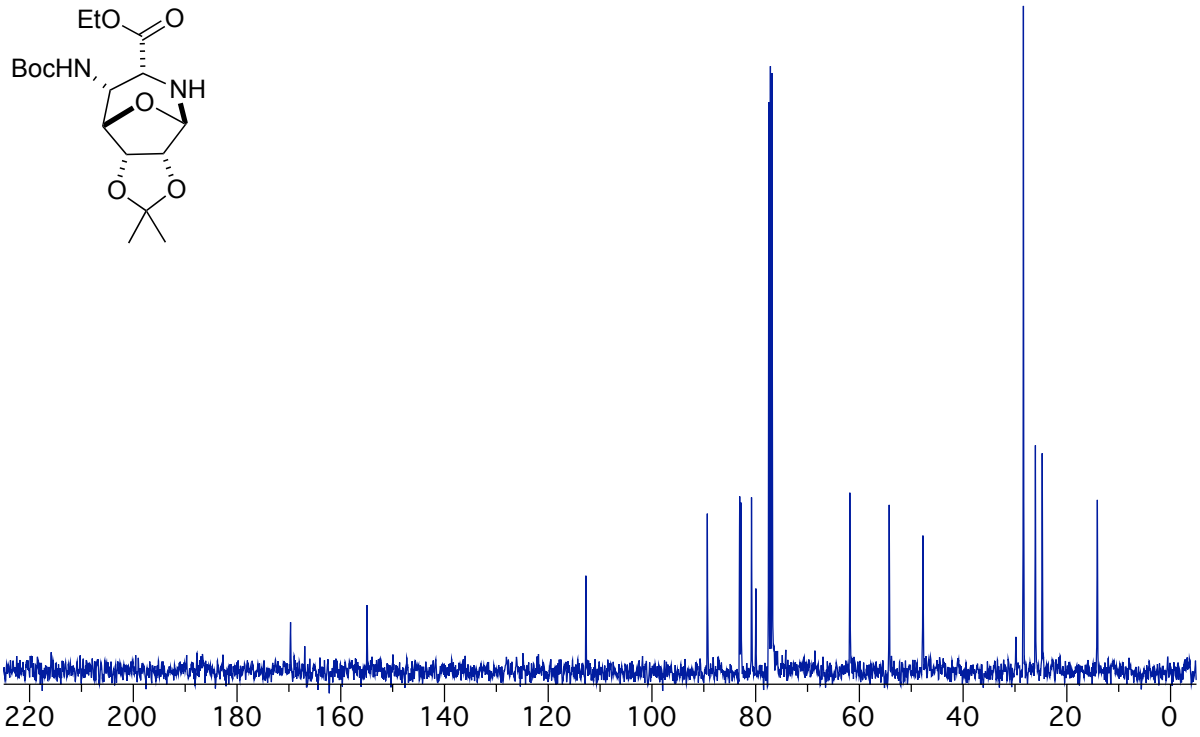


211 282

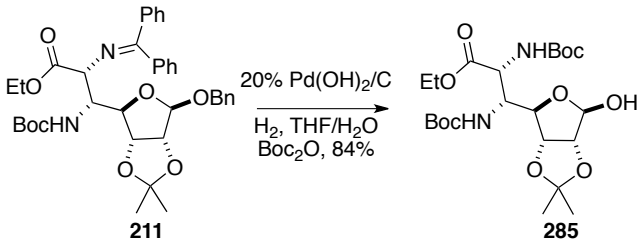
To a solution of benzyl ether **211** (50 mg) in 10:1 THF/water (2mL) was added 20% $Pd(OH)_2/C$ (25 mg). Argon was bubbled through the resulting suspension and then it was hydrogenated at 80 psi for 45 min. The mixture was filtered evaporated and purified via flash chromatography (30-35% EtOAc/hexanes) to give 22 mg (76.2%) of hemiaminal **282**.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 5.40 (d, *J* = 7.5 Hz, 1H), 4.92 (s, 1H), 4.74 (d, *J* = 5.7 Hz, 1H), 4.73 (d, *J* = 5.7 Hz, 1H), 4.24 (d, *J* = 2.0 Hz, 1H), 4.18 (dt, *J* = 10.4, 7.2 Hz, 1H), 4.10 (dt, *J* = 10.6, 7.2 Hz, 1H), 3.89 (d, *J* = 9.5 Hz, 1H), 3.61 (d, *J* = 2.9 Hz, 1H), 1.46 (s, 3H), 1.40 (s, 9H), 1.33 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). 13-C NMR (101 MHz; CDCl3): δ 169.7, 155.0, 112.7, 89.3, 83.1, 82.9, 80.8, 80.0, 61.8, 54.3, 47.8, 28.4, 26.1, 24.8, 14.1.


EtO
O
BocHN
NH
O
O
O
ppm 7
6
5
4
3
2
1

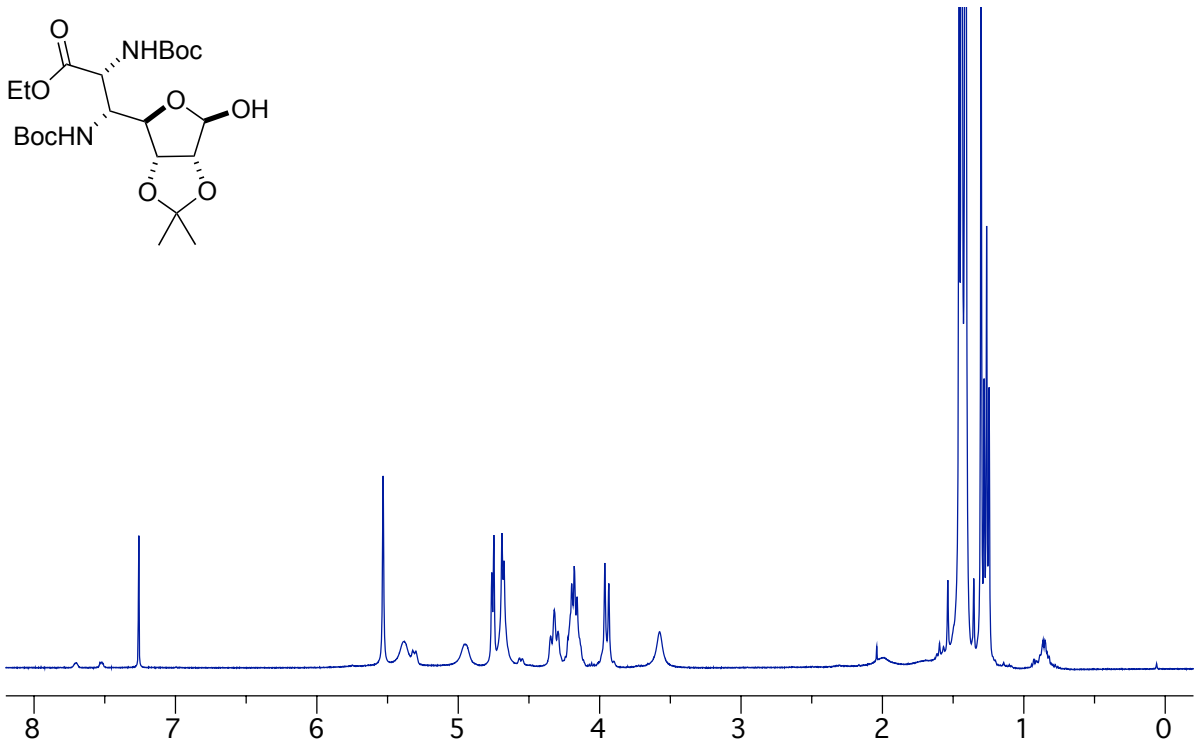

EtO
O
BocHN
NH
O
O
O
220
200
180
160
140
120
100
80
60
40
20
0

Compound 285: (2*R*,3*R*)-ethyl 2,3-bis((*tert*-butoxycarbonyl)amino)-3-((3a*R*,4*R*,6*R*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propanoate.

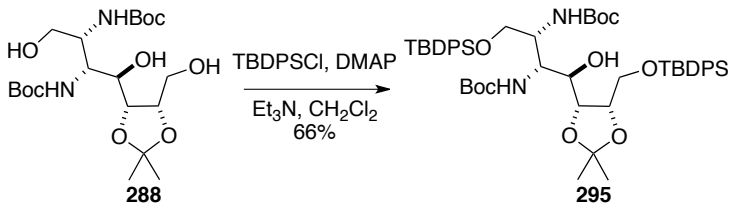


211 **285**

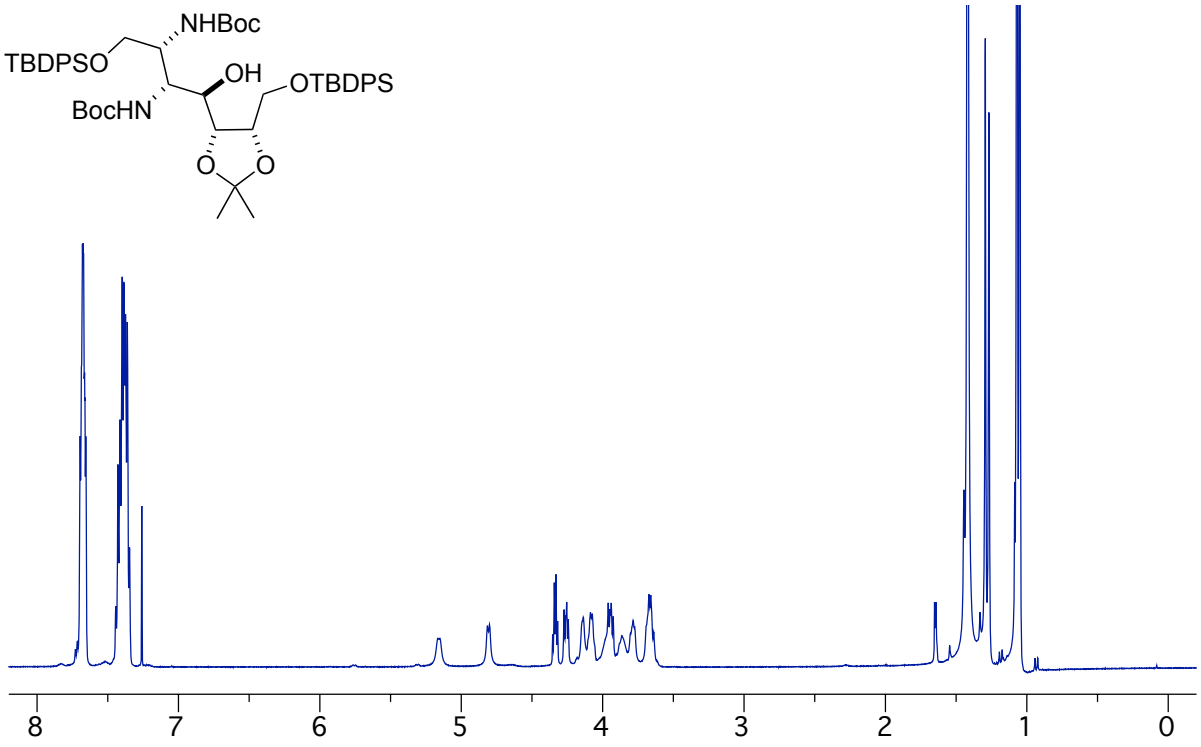
To a solution of benzyl ether **211** (100 mg, 1 eq.) and Boc_2O (169.3mg, 5 eq) in 10:1 THF/water (5mL) was added 20% $Pd(OH)_2/C$ (50 mg). Argon was bubbled through the resulting suspension and then it was hydrogenated at 80 psi at 100°C for 19 hours. The mixture was filtered evaporated and purified via flash chromatography (20-30% EtOAc/hexanes) to give 64mg (84.2%) of lactol **285**. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 5.53 (s, 1H), 5.38 (s, 1H), 4.95 (s, 1H), 4.76 (d, *J* = 5.9 Hz, 1H), 4.68 (d, *J* = 5.9 Hz, 1H), 4.32 (t, *J* = 10.7 Hz, 1H), 4.22-4.13 (m, 2H), 3.95 (d, *J* = 11.3 Hz, 1H), 3.58 (s, 1H), 1.46 (s, 3H), 1.44 (s, 9H), 1.41 (s, 9H), 1.30 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). HRMS (FAB^+): Calcd for $C_{22}H_{38}N_2NaO_{10}$ [M+Na]: 513.2442; Found 513.2418.

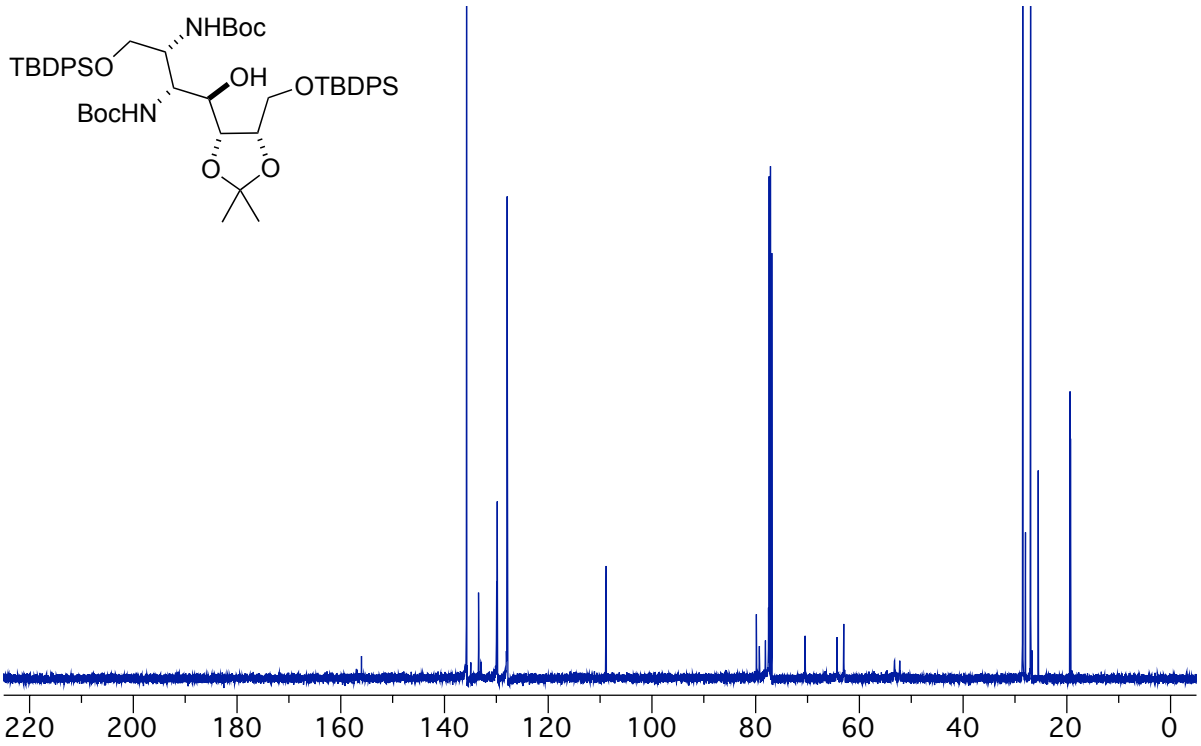

O
NHBoc
EtO
O
OH
BocHN
O
O
8
7
6
5
4
3
2
1
0

Compound 295: (di-*tert*-butyl ((1*R*,2*R*,3*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-1-((4*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-hydroxybutane-2,3-diyl)dicarbamate.

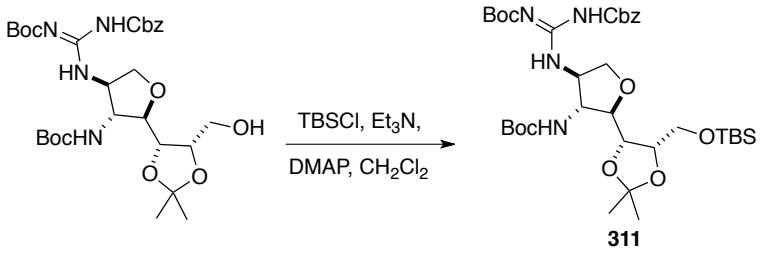


To a solution if alcohol **288** in CH_2Cl_2 (2 mL) was added Et_3N (24.7 μL, 8 eq.) and TBDPSCl (34 μL, 6 eq.). The reaction was stirred overnight and evaporated in vacuo. The crude mixture was purified via PTLC (20% EtOAc/Hexane) to give 13.6 mg (66.1%) of TBS ether **295**. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.70-7.65 (m, 8H), 7.43-7.35 (m, 12H), 5.16 (d, *J* = 7.9 Hz, 1H), 4.81 (d, *J* = 8.2 Hz, 1H), 4.34 (q, *J* = 5.9 Hz, 1H), 4.26 (dd, *J* = 9.4, 5.8 Hz, 1H), 4.14 (d, *J* = 5.3 Hz, 1H), 4.10-4.06 (m, 1H), 3.98 (s, 1H), 3.94 (dd, *J* = 11.0, 6.6 Hz, 1H), 3.87 (s, 1H), 3.79 (dd, *J* = 9.9, 5.6 Hz, 1H), 3.70-3.66 (m, 1H), 3.66 (dd, *J* = 10.4, 6.7 Hz, 1H), 1.42 (s, 18H), 1.29 (s, 3H), 1.27 (s, 3H), 1.07 (s, 9H), 1.05 (s, 9H). 13-C NMR (126 MHz; cdcl3): δ 156.9, 156.0, 135.74, 135.72, 133.44, 133.38, 129.95, 129.83, 127.91, 127.83, 108.8, 79.9, 78.1, 77.5, 70.5, 64.3, 63.0, 53.2, 52.2, 28.53, 28.50, 28.0, 27.0, 25.5, 19.38, 19.29.

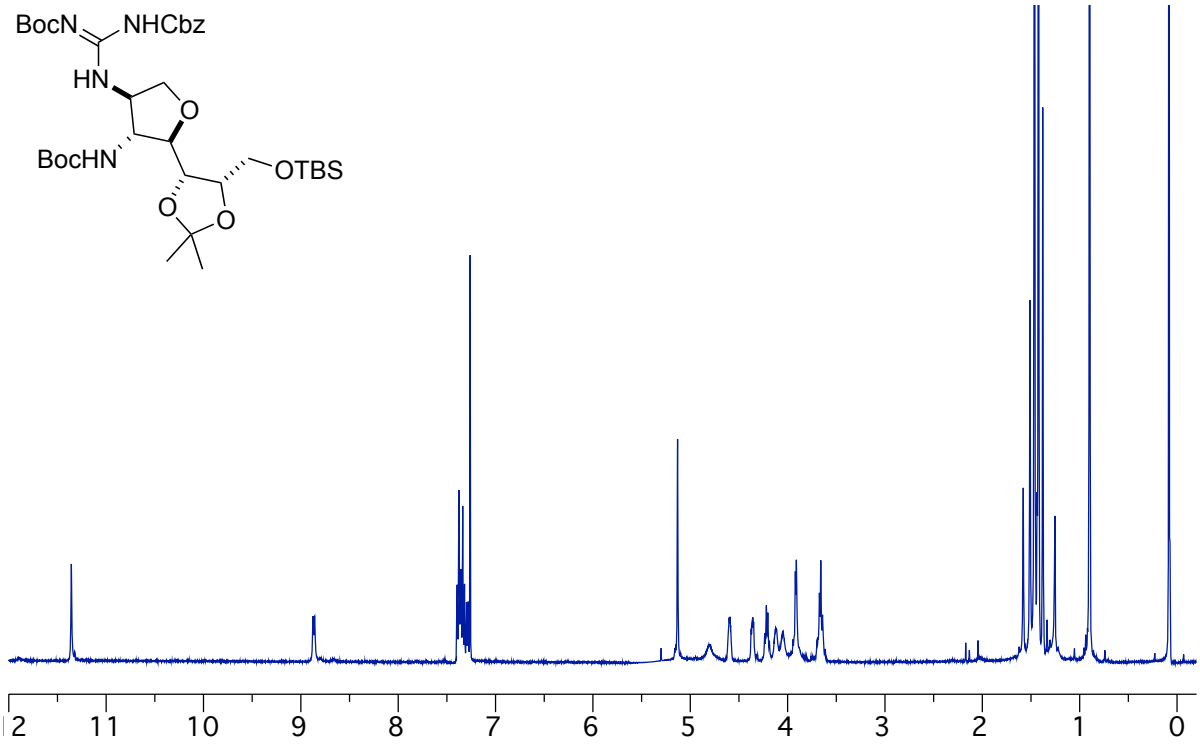

NHBoc
TBDPSO
OH
OTBDPS
BocHN
O
O
8
7
6
5
4
3
2
1
0

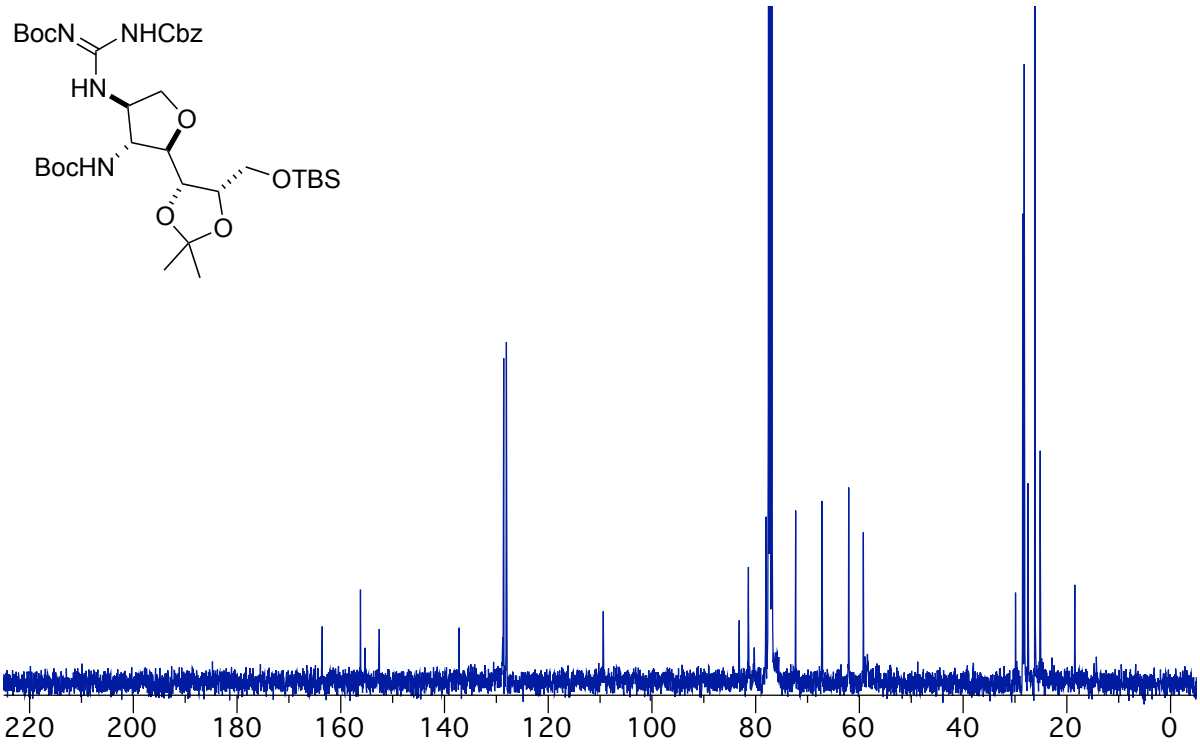

NHBoc
TBDPSO
OH
OTBDPS
BocHN
O
O
220
200
180
160
140
120
100
80
60
40
20
0

Compound 311: *tert*-butyl ((2*R*,3*R*,4*R*)-4-(2-(*tert*-butoxycarbonyl)-3-(methoxycarbonyl)guanidino)-2-((4*R*,5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)tetrahydrofuran-3-yl)carbamate.

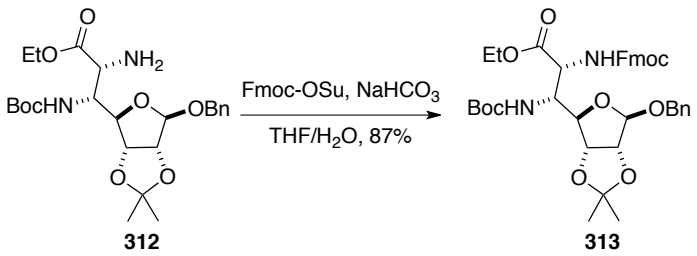


To a solution of the alcohol in CH_2Cl_2 (2 mL) was added Et_3N (12 μL, 6 eq.), DMAP (cat.), and TBSCl (9.8 mg, 6 eq.). The reaction was stirred overnight and evaporated in vacuo. The crude mixture was purified via PTLC (20% EtOAc/Hexane) to give TBS ether **311**. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 11.36 (s, 1H), 8.87 (d, *J* = 6.7 Hz, 1H), 7.39-7.28 (m, 5H), 5.13 (s, 2H), 4.80 (s, 1H), 4.60 (td, *J* = 6.4, 3.4 Hz, 1H), 4.36 (dd, *J* = 6.7, 3.7 Hz, 1H), 4.21 (q, *J* = 6.3 Hz, 1H), 4.12 (s, 1H), 4.05 (s, 1H), 3.94-3.88 (m, 2H), 3.70-3.62 (m, 2H), 1.51 (s, 3H), 1.46 (s, 9H), 1.42 (s, 9H), 1.38 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H). 13-C NMR (101 MHz; CDCl3): δ 163.6, 156.2, 155.3, 152.6, 137.2, 128.6, 128.06, 127.99, 109.4, 83.2, 81.4, 78.0, 77.40, 77.34, 72.3, 67.2, 62.1, 59.2, 58.5, 28.5, 28.2, 27.5, 26.2, 25.1, 18.5, -5.1.


BocN
NHCbz
HN
O
BocHN
OTBS
O
O
12
11
10
9
8
7
6
5
4
3
2
1
0

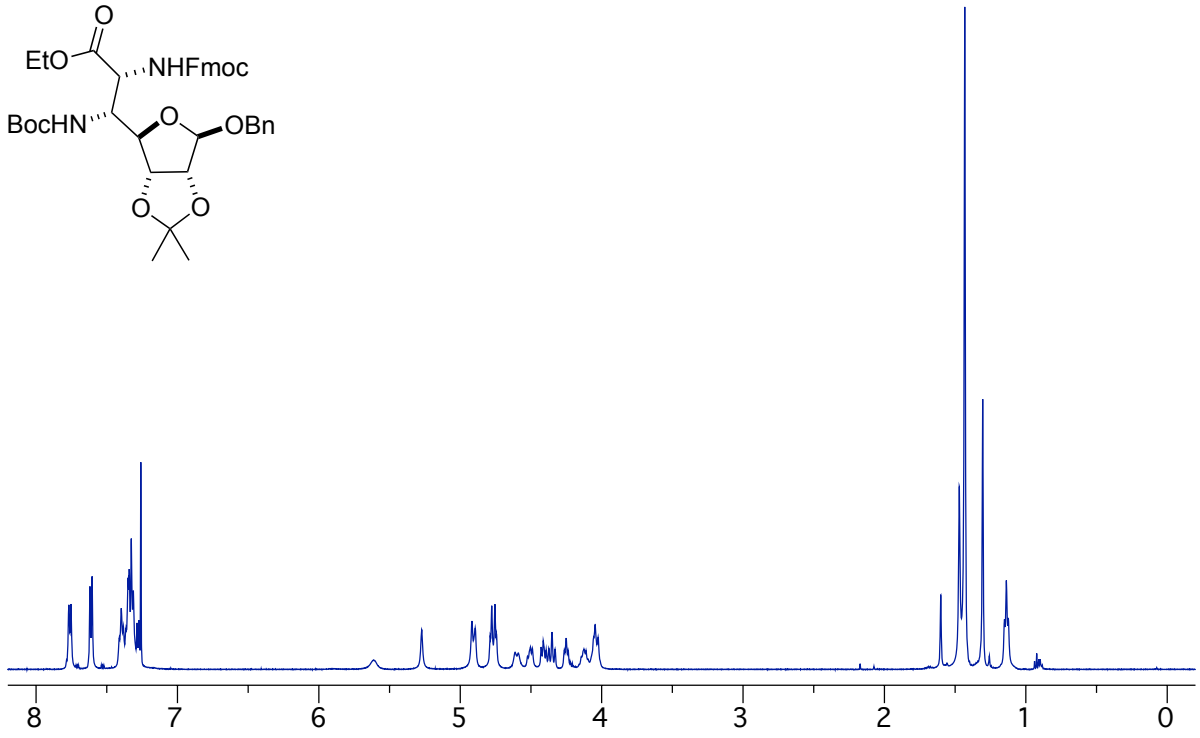

BocN
NHCbz
HN
O
BocHN
OTBS
O
O
220
200
180
160
140
120
100
80
60
40
20
0

Compound 313: (2*R*,3*R*)-ethyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-3-((*tert*-butoxycarbonyl)amino)propanoate.



312 **313**

To a stirring solution of amine **312** (0.233 mmol crude, 1eq.) in 50% THF/H_2O (6mL) was added $NaHCO_3$ (58.6mg, 3 eq.) and Fmoc-OSu (94.2mg, 1.2 eq.). The mixture was stirred overnight then extracted with EtOAc (3x), washed with NaCl (sat.), dried over sodium sulfate and evaporated. The resulting oil was purified via flash chromatography (20% EtOAc/Hexane) to give 142.5 mg (87%) of carbamate **313**. $[\alpha]_D^{25}$= -70 (c 0.49, $CHCl_3$). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.61 (d, *J* = 7.4 Hz, 2H), 7.40-7.27 (m, 9H), 5.61 (s, 1H), 5.27 (s, 1H), 4.91 (d, *J* = 11.7 Hz, 2H), 4.78 (d, *J* = 5.6 Hz, 1H), 4.75 (d, *J* = 5.6 Hz, 1H), 4.60 (d, *J* = 11.3 Hz, 1H), 4.51 (dd, *J* = 10.1, 7.0 Hz, 1H), 4.41 (dd, *J* = 10.2, 7.6 Hz, 1H), 4.35 (t, *J* = 11.0 Hz, 1H), 4.25 (t, *J* = 6.9 Hz, 1H), 4.14-4.10 (m, 1H), 4.06-4.03 (m, 1H), 4.04 (d, *J* = 10.4 Hz, 1H), 1.47 (s, 3H), 1.43 (s, 9H), 1.31 (s, 3H), 1.14 (t, *J* = 6.8 Hz, 3H). 13-C NMR (126 MHz; cdcl3): δ 171.2, 156.7, 155.2, 144.0, 143.8, 141.46, 141.42, 128.5, 127.88, 127.86, 127.80, 127.78, 127.28, 127.26, 125.25, 125.21, 120.13, 120.11, 112.7, 108.3, 85.8, 85.6, 82.1, 80.5, 70.1, 67.5, 62.2, 54.68, 54.54, 47.3, 28.3, 26.5, 25.0, 14.0 IR (Dep. $CDCl_3$): 3369 (bs), 2979 (s), 2944 (s), 1712 (vs), 1511 (s),1451 (s)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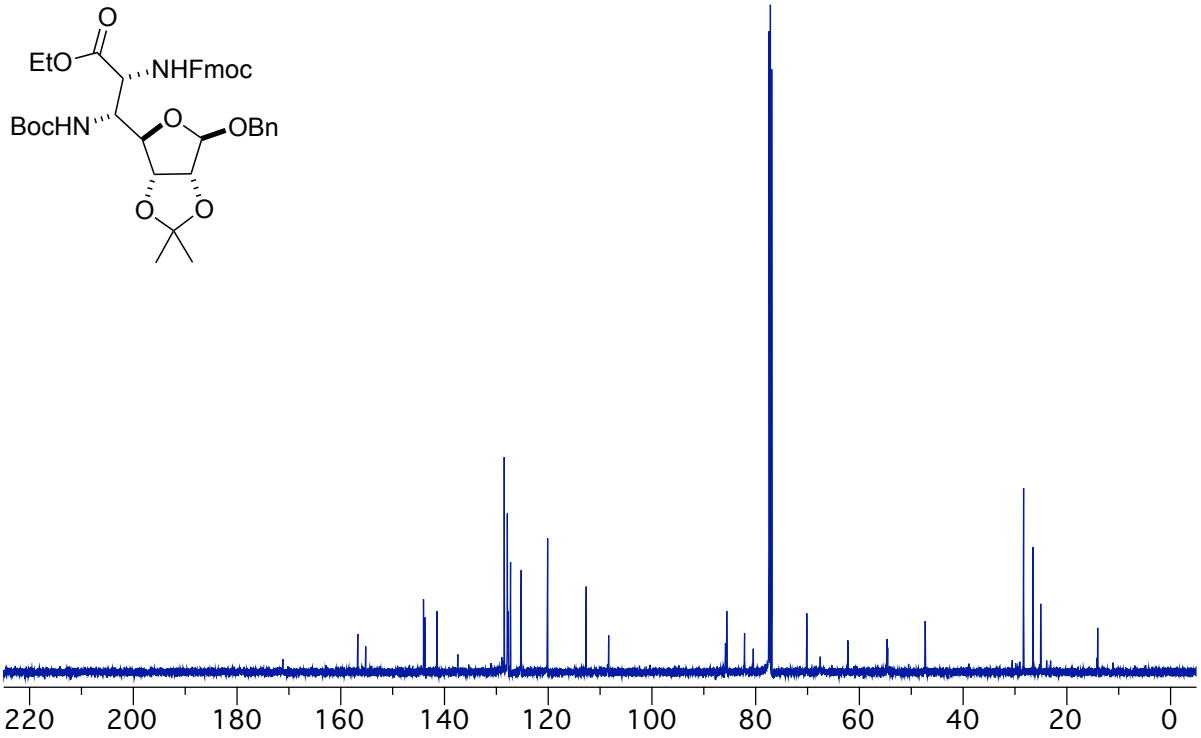
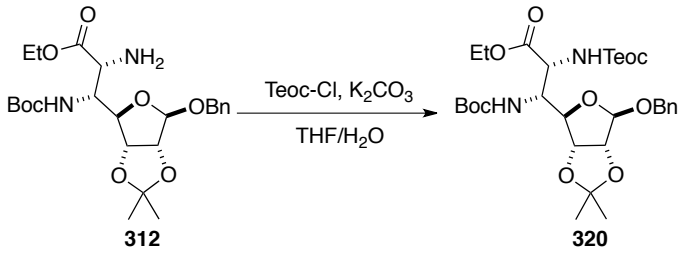
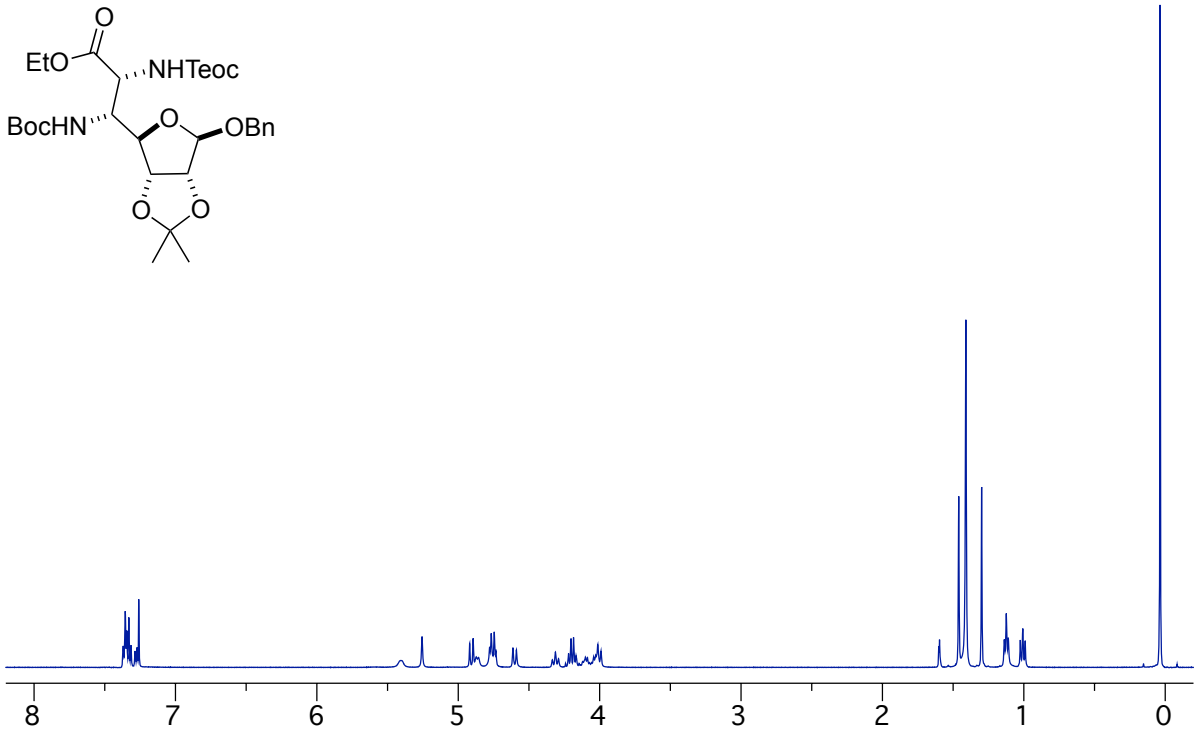
EtO
NHFmoc
BocHN
O
OBn
O
O
8
7
6
5
4
3
2
1
0


O
EtO
NHFmoc
BocHN
O
OBn
O
O
220
200
180
160
140
120
100
80
60
40
20
0

Compound 320: (2*R*,3*R*)-ethyl 3-((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-3-((*tert*-butoxycarbonyl)amino)-2-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)propanoate.



To a stirring solution of amine **312** (0.233 mmol crude, 1eq.) in 50% THF/H_2O (10mL) was added K_2CO_3 (322mg, 10 eq.) and Teoc-Cl (50.42mg, 1.2 eq.). The mixture was stirred overnight and the organic layer was separated. The aqueous layer was then extracted with EtOAc (3x), washed with NaCl (sat.), dried over sodium sulfate and evaporated. The resulting oil was purified via flash chromatography (20% EtOAc/Hexane) to give **320**. $[\alpha]_D^{25}$= -84 (c 0.49, $CHCl_3$) ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.40 (s, 1H), 5.26 (s, 1H), 4.91 (d, *J* = 12.4 Hz, 1H), 4.86 (d, *J* = 8.0 Hz, 1H), 4.77 (d, *J* = 5.9 Hz, 1H), 4.74 (d, *J* = 5.9 Hz, 1H), 4.60 (d, *J* = 12.3 Hz, 1H), 4.31 (t, *J* = 10.8 Hz, 1H), 4.21 (d, *J* = 8.7 Hz, 1H), 4.18 (d, *J* = 8.8 Hz, 1H), 4.11 (dd, *J* = 12.1, 5.4 Hz, 1H), 4.02 (dd, *J* = 12.1, 5.4 Hz, 1H), 4.00 (d, *J* = 11.3 Hz, 1H), 1.46 (s, 3H), 1.41 (s, 9H), 1.30 (s, 3H), 1.12 (t, *J* = 7.1 Hz, 3H), 1.01 (t, *J* = 8.7 Hz, 2H), 0.04 (s, 9H). 13-C NMR (126 MHz; cdcl3): δ 171.3, 157.0, 155.2, 137.5, 128.5, 127.8, 112.6, 108.29, 108.28, 108.26, 85.8, 85.6, 82.1, 80.4, 70.1, 64.1, 62.1, 54.7, 54.3, 28.3, 26.5, 25.1, 17.9, 14.0, -1.4 IR (Dep. $CDCl_3$): 3368 (br), 2979 (s), 2953 (s), 1717 (vs), 1513 (s), 1369 (s).


EtO
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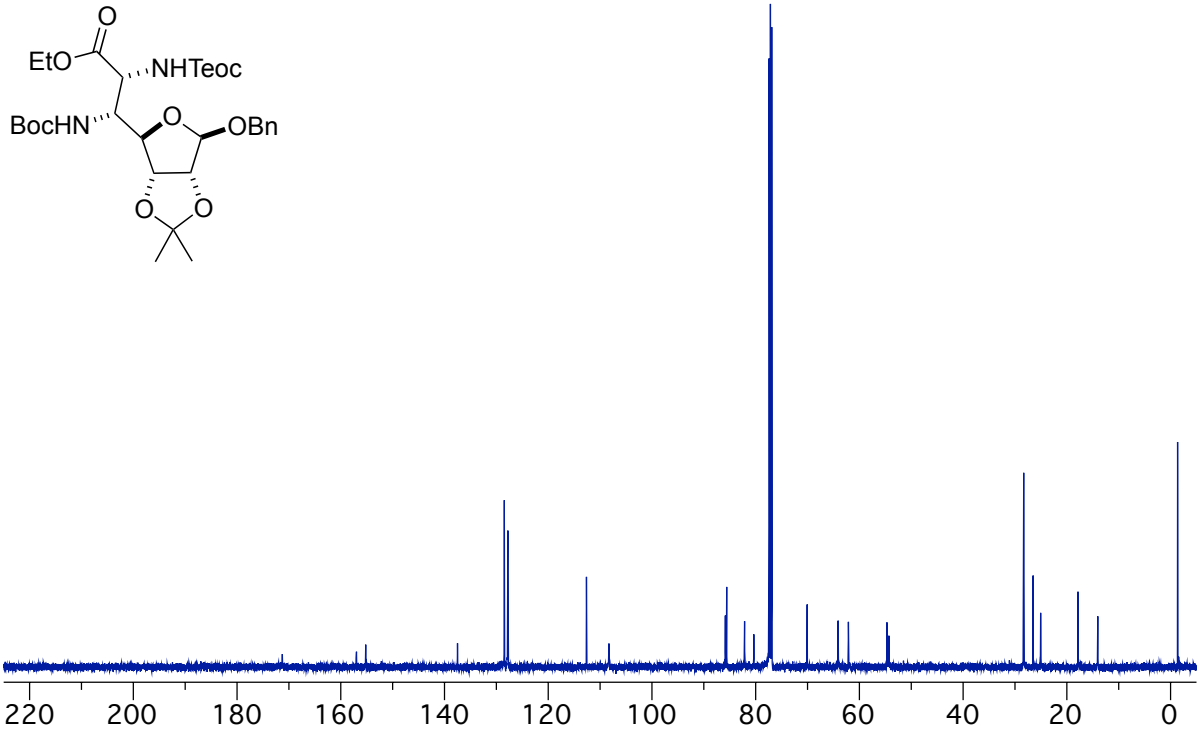
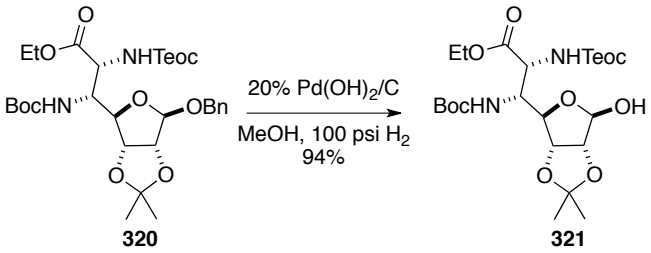
BocHN
O
OBn
O
O
8
7
6
5
4
3
2
1
0

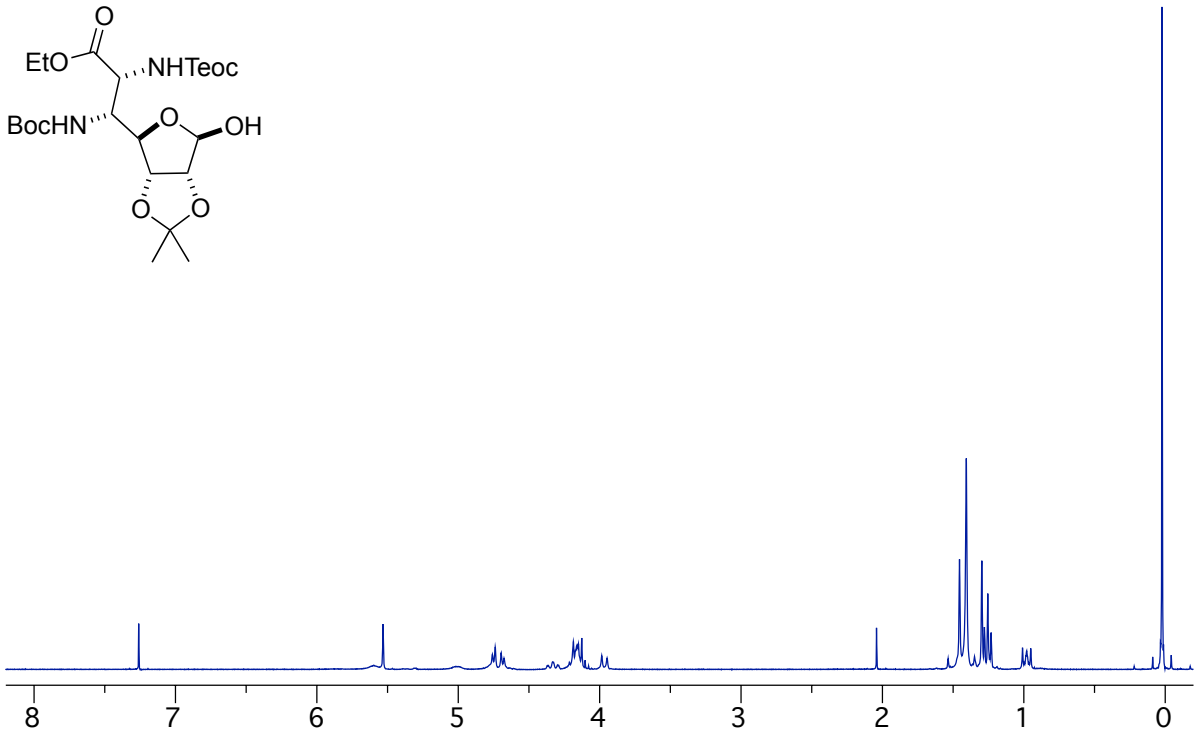

EtO
O
NHTeoc
BocHN
O
OBn
O
O
220
200
180
160
140
120
100
80
60
40
20
0

Compound 321: (2*R*,3*R*)-ethyl 3-((*tert*-butoxycarbonyl)amino)-3-((3a*R*,4*R*,6*R*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-2-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)propanoate.

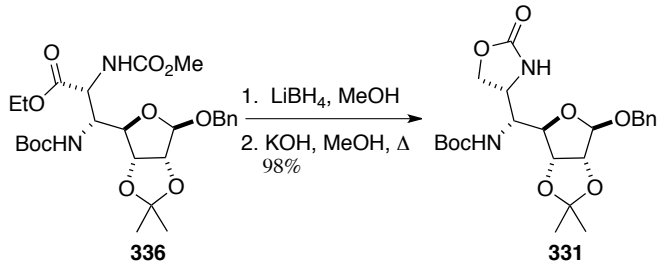


320 **321**

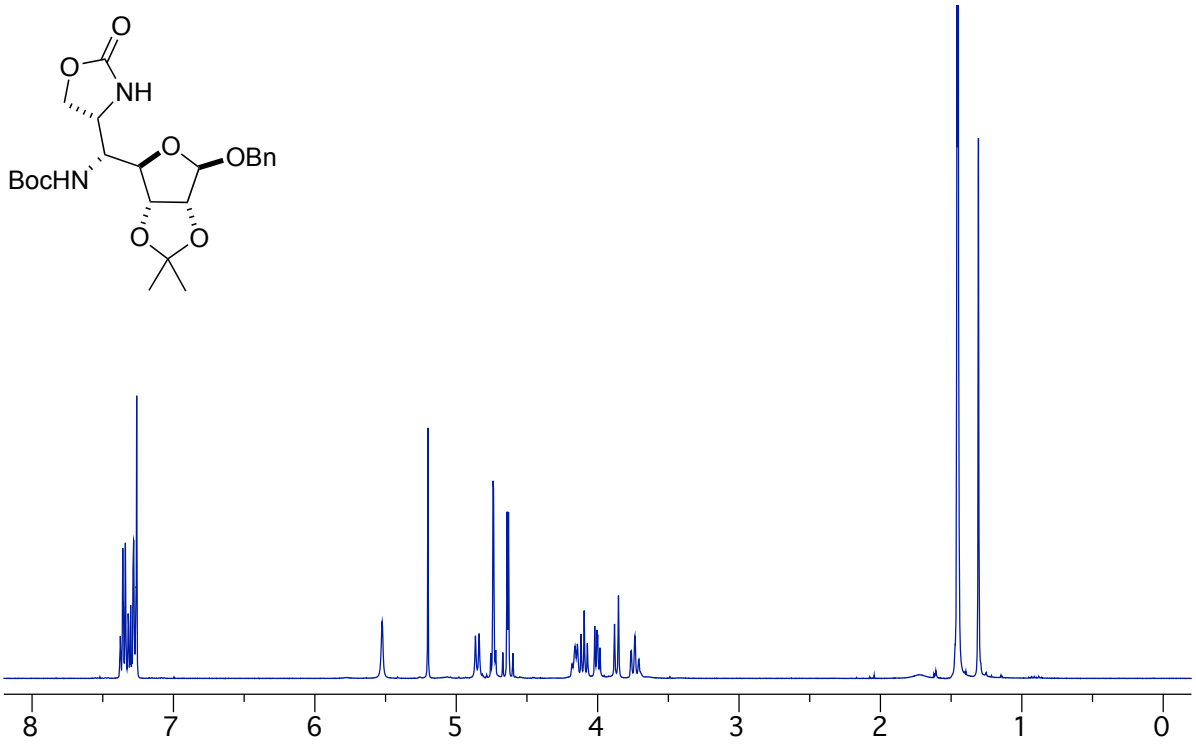
To a solution of carbamate **320** (100mg) in methanol (5mL) was added 20% $Pd(OH)_2/C$ (100mg). Argon was bubbled through the resulting suspension and then it was hydrogenated at 100 psi for 6 hours. The mixture was filtered evaporated and purified via flash chromatography to give 80.5 mg (94%) of lactol **321**. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 5.60 (s, 1H), 5.53 (s, 1H), 5.01 (d, J = 5.9 Hz, 1H), 4.75 (d, J = 6.0 Hz, 1H), 4.69 (d, J = 6.0 Hz, 1H), 4.33 (td, J = 10.8, 2.3 Hz, 1H), 4.19-4.13 (m, 4H), 3.97 (d, J = 11.3 Hz, 1H), 1.45 (s, 3H), 1.41 (s, 9H), 1.30 (s, 3H), 1.25 (t, J = 7.0 Hz, 3H), 1.01-0.95 (m, 2H), 0.02 (s, 9H).


O
EtO
NHTeoc
BocHN
O
OH
O
O
8
7
6
5
4
3
2
1
0

Compound 331: *tert*-butyl ((*R*)-((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)((*R*)-2-oxooxazolidin-4-yl)methyl)carbamate.



To a solution of methyl carbamate **336** (1.08 g, 1 eq.) in THF (20 mL) was added lithium borohydride (436 mg, 10 eq.). The mixture was allowed to stir 10 hours or until complete by TLC. The mixture was poured over cracked ice and sat. ammonium chloride (100 mL) was added and allowed to stir for 30 minutes. The mixture was extracted with EtOAc (3x) and the combined extracts were washed with brine dried over sodium sulfate and evaporated. The crude alcohol was dissolved in MeOH (20 mL) and finely powdered KOH (1.02 g, 10 eq.) was added. The mixture was refluxed until complete by TLC, allowed to cool and evaporated. The crude oxazolidinone was purified via a plug of silica gel (10% MeOH/DCM) to give oxazolidinone **331** (906 mg, 97.6%) as a white solid. $[\alpha]_D^{25}$= -72 (c 0.45, $CHCl_3$) ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.38-7.26 (m, 5H), 5.52 (s, 1H), 5.20 (s, 1H), 4.85 (d, *J* = 10.4 Hz, 1H), 4.74 (d, *J* = 6.0 Hz, 1H), 4.73 (d, *J* = 6.0 Hz, 1H), 4.65 (d, *J* = 12.2 Hz, 1H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.16 (t, *J* = 7.6 Hz, 1H), 4.09 (t, *J* = 8.8 Hz, 1H), 4.00 (dd, *J* = 8.5, 6.2 Hz, 1H), 3.87 (d, *J* = 11.2 Hz, 1H), 3.74 (td, *J* = 10.8, 1.7 Hz, 1H), 1.46 (s, 3H), 1.45 (s, 9H), 1.31 (s, 3H). 13-C NMR (101 MHz; cdcl3): δ 160.0, 156.2, 137.0, 128.8, 128.2, 127.4, 112.8, 109.0, 86.5, 85.2, 82.4, 80.9, 70.7, 67.0, 53.1, 52.0, 28.4, 26.6, 25.0. IR (Dep. $CDCl_3$): 3305 (br), 2980 (s), 2938 (s), 1756 (s), 1708 (s), 1499 (s), 1455 (s).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NH
O
OBn
BocHN
O
O
8
7
6
5
4
3
2
1
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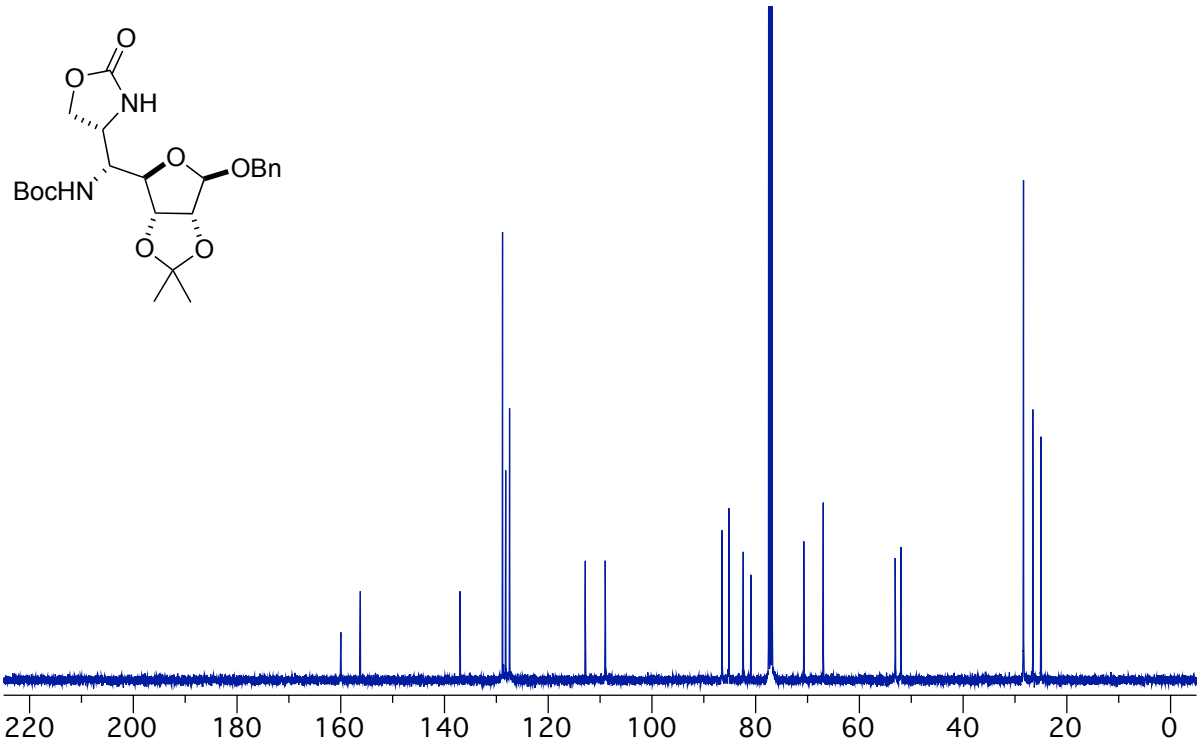
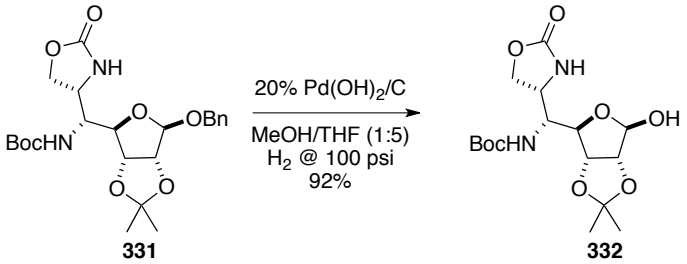
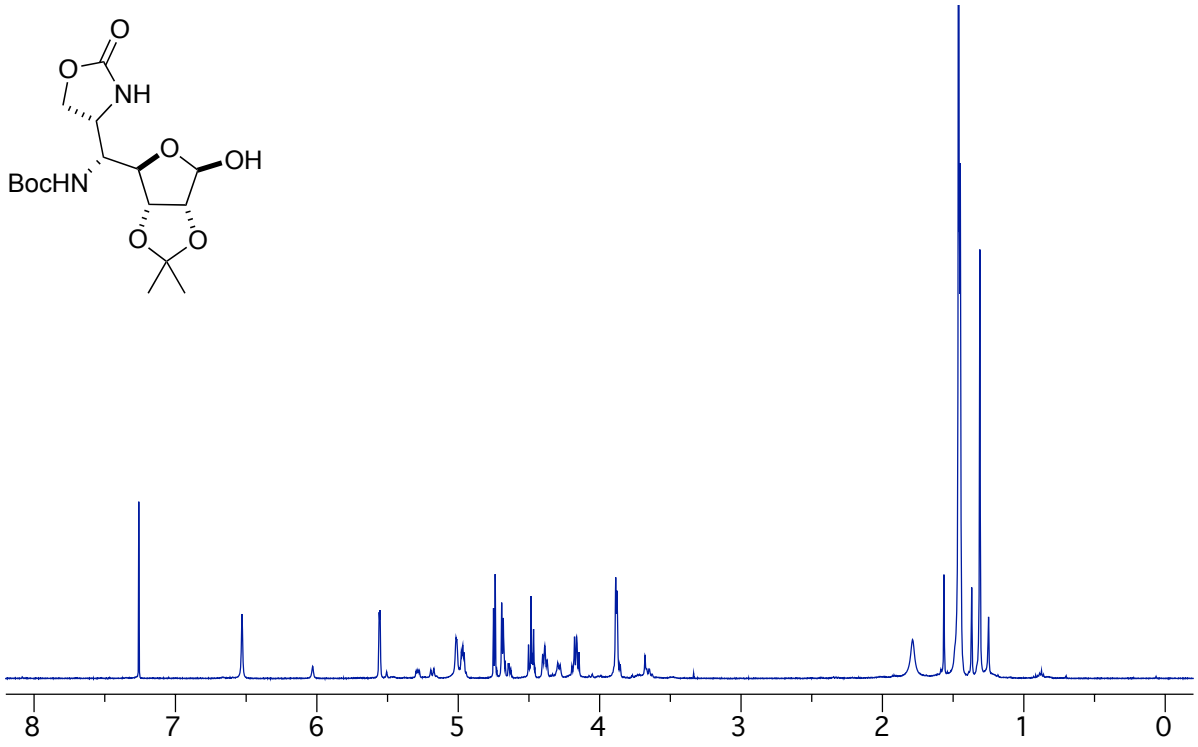

O
O
NH
O
OBn
BocHN
O
O
220
200
180
160
140
120
100
80
60
40
20
0

Compound 332: *tert*-butyl ((*R*)-((3a*R*,4*R*,6*R*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)((*R*)-2-oxooxazolidin-4-yl)methyl)carbamate.



331 **332**

To a solution of benzyl ether **331** (249 mg) in 4:1 THF/methanol (5 mL) was added 20% $Pd(OH)_2/C$ (125 mg). Argon was bubbled through the resulting suspension and then it was hydrogenated at 100 psi until complete by TLC. The mixture was filtered evaporated and purified via flash chromatography (10-20% EtOAc/Hexanes) to give 184.2 mg (91.8%) of lactol **332**. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 6.53 (s, 1H), 5.56 (d, *J* = 3.0 Hz, 1H), 5.01 (d, *J* = 2.5 Hz, 1H), 4.97 (t, *J* = 5.0 Hz, 1H), 4.74 (d, *J* = 5.9 Hz, 1H), 4.69 (d, *J* = 5.8 Hz, 1H), 4.49 (t, *J* = 8.9 Hz, 1H), 4.39 (t, *J* = 7.9 Hz, 1H), 4.16 (dd, *J* = 8.1, 7.5 Hz, 1H), 3.88 (d, *J* = 4.1 Hz, 2H), 1.46 (s, 10H), 1.45 (s, 2H), 1.31 (s, 3H). 13-C NMR (126 MHz; cdcl3): δ 161.0, 156.2, 112.8, 103.8, 86.7, 85.6, 83.0, 81.0, 67.1, 52.9, 52.6, 28.4, 26.6, 25.0. Calcd. for $C_{16}H_{26}N_2NaO_8$ [M+Na]: 397.1587 Found 397.1582.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O
OH
BocHN
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O
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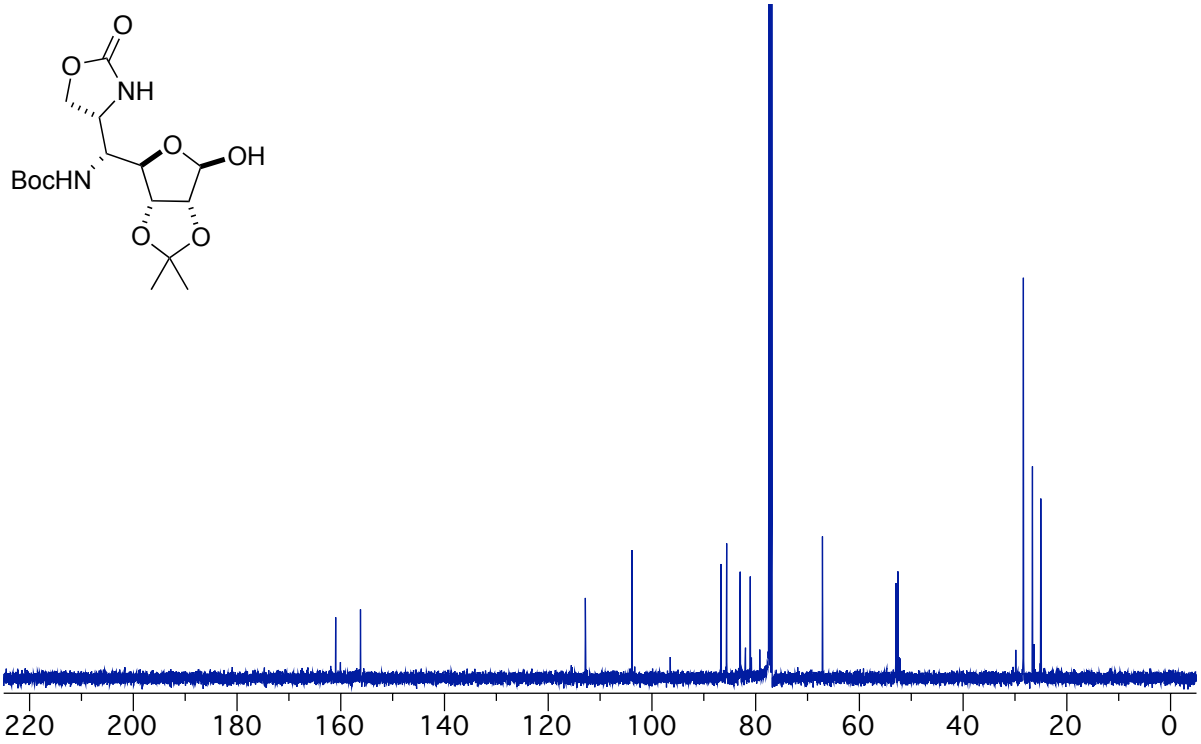
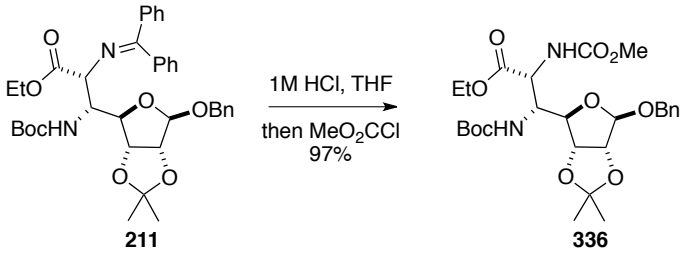
7
6
5
4
3
2
1
0

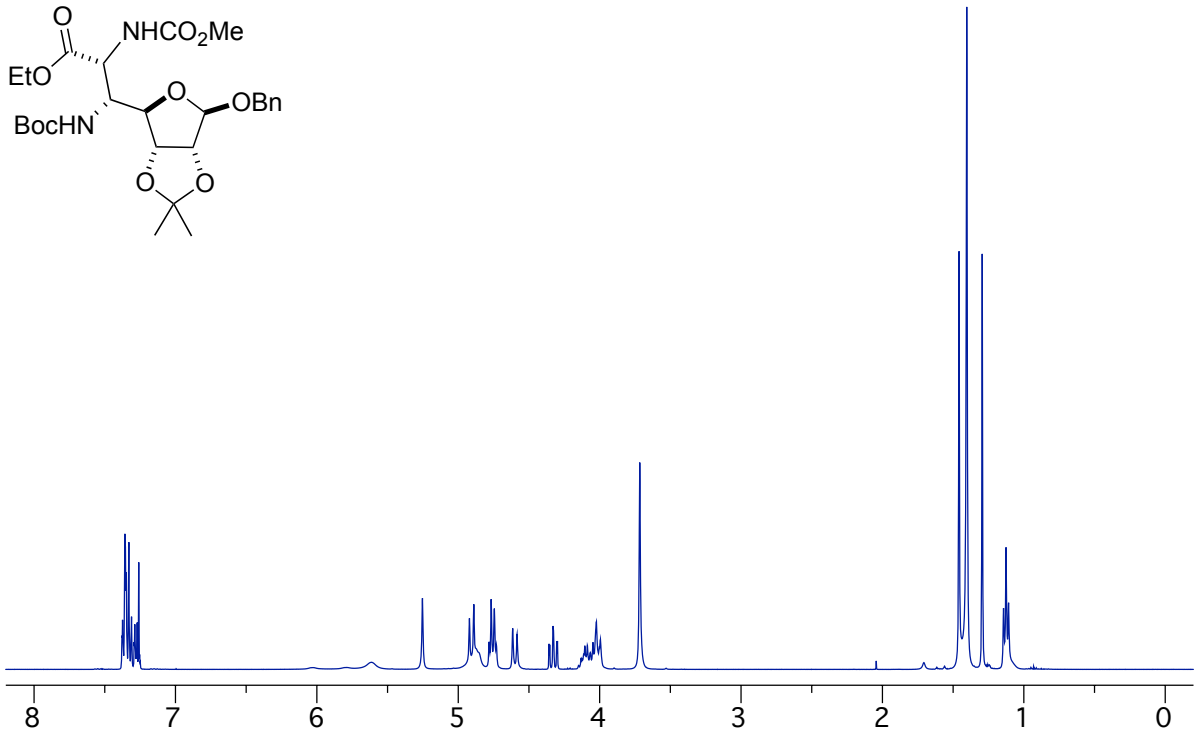

O
O
NH
O
OH
BocHN
O
O
220
200
180
160
140
120
100
80
60
40
20
0

Compound 336: (2*R*,3*R*)-ethyl 3-((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-3-((*tert*-butoxycarbonyl)amino)-2-((methoxycarbonyl)amino)propanoate.



211 336

To a solution of Mannich product **211** (5 grams, 1 eq.) in THF (150 mL) was added 1M HCl (150 mL). The mixture was stirred ~30 minutes and quenched with $NaHCO_3$ (15 g). Methyl chloroformate (599.2 μL, 1 eq.) was added to the mixture and stirred until complete by TLC. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x) the combined extracts were washed with brine, dried over sodium sulfate and evaporated. The crude material was purified via flash chromatography (20-50% EtOAc/Hexanes) to give methyl carbamate **336** (4.07 g, 97.4%) as a white powder. $[\alpha]_D^{25}$= -96 (c 1.04, $CHCl_3$) ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.38-7.27 (m, 4H), 5.61 (s, 1H), 5.25 (s, 1H), 4.90 (d, *J* = 12.3 Hz, 2H), 4.86 (d, *J* = 7.7 Hz, 1H), 4.77 (d, *J* = 5.9 Hz, 1H), 4.74 (d, *J* = 5.8 Hz, 1H), 4.60 (d, *J* = 12.3 Hz, 1H), 4.33 (td, *J* = 10.9, 2.1 Hz, 1H), 4.15-4.06 (m, 1H), 4.06-3.99 (m, 1H), 4.01 (d, *J* = 7.7 Hz, 1H), 3.72 (s, 3H), 1.46 (s, 3H), 1.40 (s, 9H), 1.29 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H). 13-C NMR (101 MHz; cdcl3): δ 171.3, 157.3, 155.2, 137.4, 128.5, 127.78, 127.64, 112.6, 108.3, 85.73, 85.55, 82.1, 80.3, 77.4, 70.1, 62.1, 54.67, 54.56, 54.52, 52.83, 52.76, 28.3, 26.5, 25.0, 14.0. IR (Dep. $CDCl_3$): 3584 (br), 3362 (s), 2980(s), 2940(s), 1715(s), 1514(s).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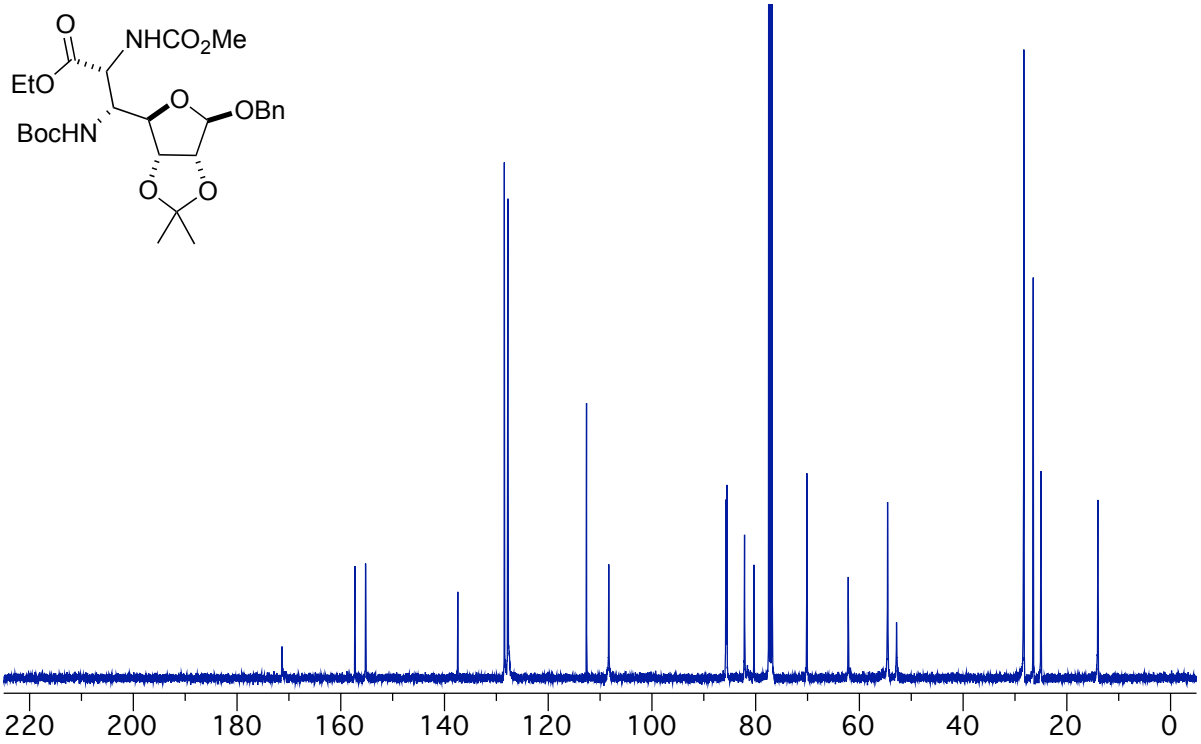
EtO
O
OBn
BocHN
O
O
8
7
6
5
4
3
2
1
0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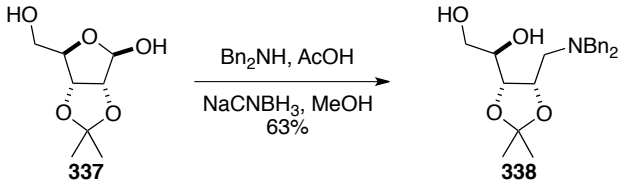
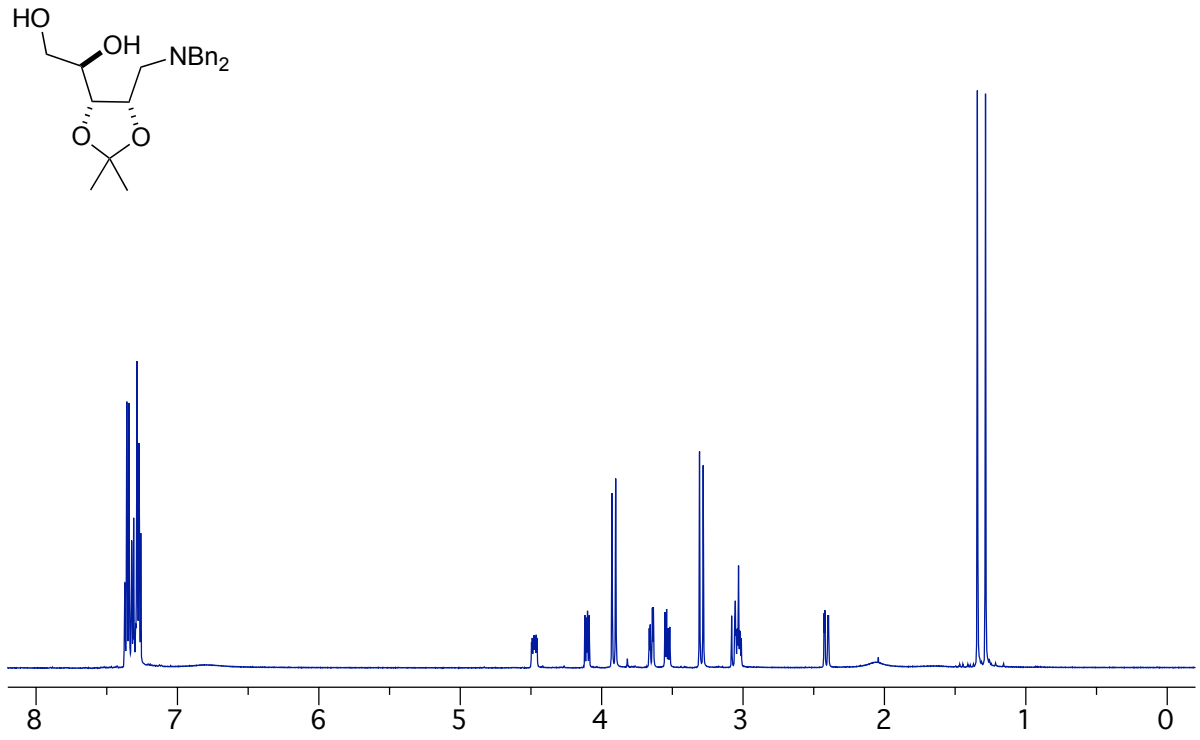
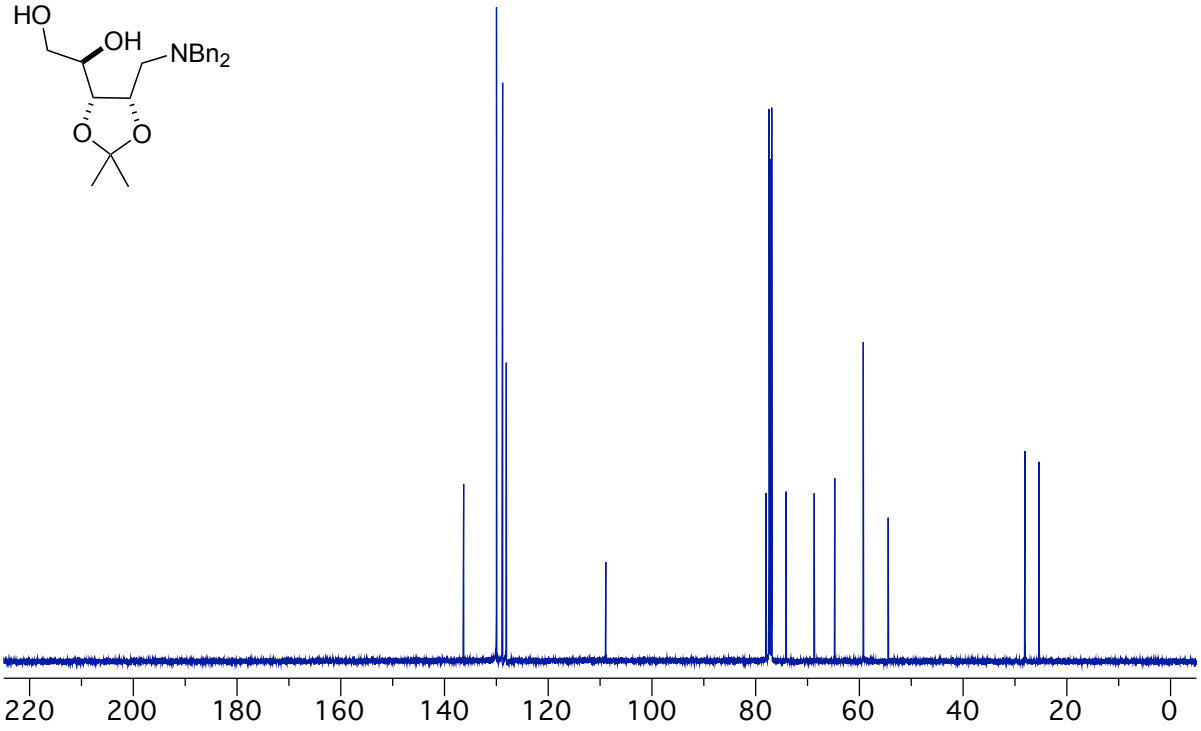
NHCO2Me
EtO
O
OBn
BocHN
O
O
220
200
180
160
140
120
100
80
60
40
20
0

Compound 338: (*R*)-1-((4*R*,5*S*)-5-((dibenzylamino)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol.

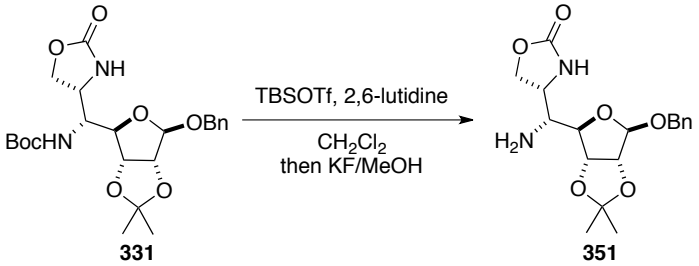


A solution of lactol **337** (1.0g , 1 eq.), dibenzylamine (1.2mL µL, 1.2 eq.), AcOH (913 uL mL, 3 eq.) and sodium cyanoborohydride (1.0g, 3 eq.) in MeOH (10 mL) was allowed to stir 4 days. The reaction was carefully quenched with sat. sodium bicarbonate, extracted with EtOAc (3x) and the combined extracts were dried over sodium sulfate and evaporated to give amine **338** (1.24g, 63%), which was clean by NMR. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.37-7.24 (m, 10H), 4.48 (ddd, *J* = 11.1, 5.8, 2.7 Hz, 1H), 4.10 (dd, *J* = 9.6, 5.8 Hz, 1H), 3.91 (d, *J* = 13.0 Hz, 2H), 3.65 (dd, *J* = 11.2, 3.5 Hz, 1H), 3.54 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.30 (d, *J* = 13.0 Hz, 2H), 3.06 (dd, *J* = 13.0, 11.4 Hz, 1H), 3.03 (ddd, *J* = 9.5, 5.7, 3.7 Hz, 1H), 2.41 (dd, *J* = 13.0, 2.6 Hz, 1H), 2.07 (s, 1H), 1.34 (s, 3H), 1.29 (s, 3H). 13-C NMR (126 MHz; cdcl3): δ 136.3, 130.0, 128.8, 128.1, 108.9, 78.0, 74.1, 68.7, 64.8, 59.2, 54.4, 28.1, 25.4.

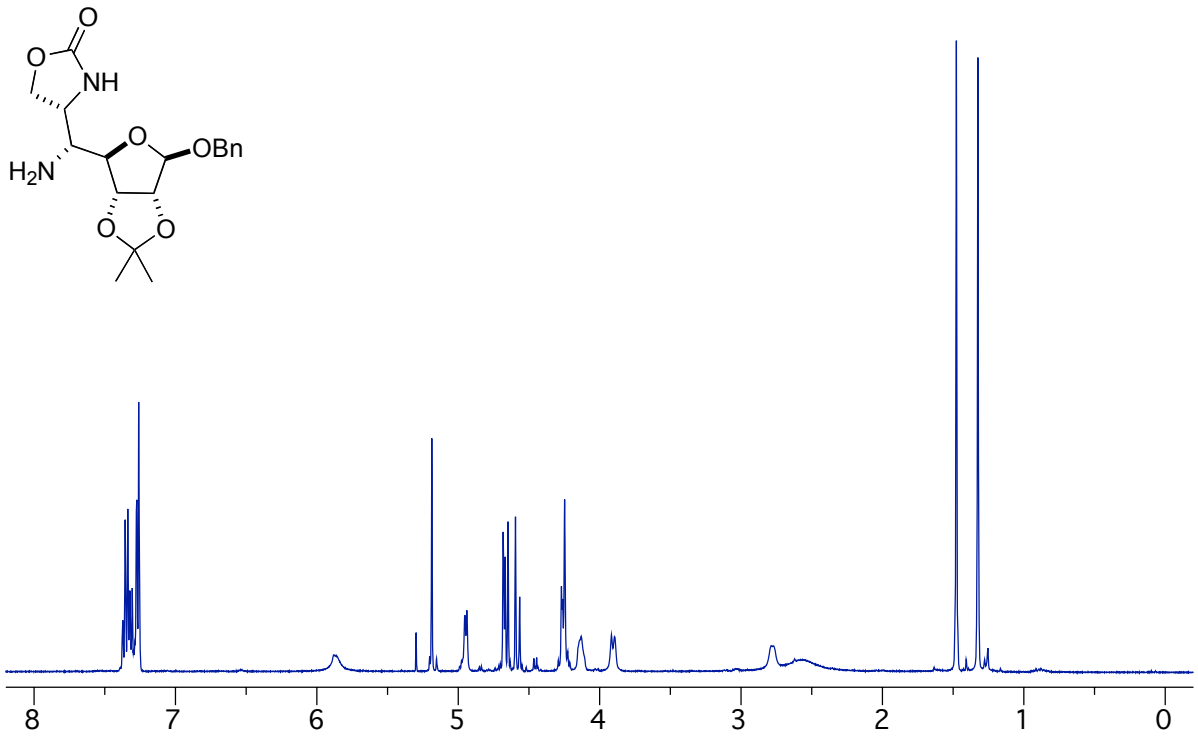

HO
OH
NBn2
O
O
8
7
6
5
4
3
2
1
0


HO
OH
NBn2
O
O
220
200
180
160
140
120
100
80
60
40
20
0

Compound 351: (*R*)-4-((*R*)-amino((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro [3,4-*d*][1,3]dioxol-4-yl)methyl)oxazolidin-2-one



To a solution of carbamate **331** and 2,6-lutidine in CH_2Cl_2 was added TBSOTf dropwise. The solution was allowed to stir ~30 min and was quenched with KF/MeOH. The mixture was stirred an additional 30 min. until all the spots by TLC coalesced. The reaction mixture was diluted with CH_2Cl_2 and washed with water followed by brine. The organic extracts were dried over sodium sulfate and evaporated and the resulting oil was purified by flash chromatography to give **351** as a white solid. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.88-5.85 (m, 1H), 5.19 (s, 1H), 4.95 (d, *J* = 5.7 Hz, 1H), 4.68 (d, *J* = 5.6 Hz, 1H), 4.66 (d, *J* = 11.9 Hz, 1H), 4.58 (d, *J* = 11.9 Hz, 1H), 4.27-4.24 (m, 1H), 4.26 (d, *J* = 8.8 Hz, 1H), 4.16-4.09 (m, 1H), 3.91 (d, *J* = 8.4 Hz, 1H), 2.78 (d, *J* = 5.1 Hz, 1H), 2.57 (s, 2H), 1.48 (s, 3H), 1.32 (s, 3H). 13-C NMR (101 MHz; cdcl3): δ 160.0, 136.9, 128.8, 128.3, 127.7, 113.1, 108.2, 88.2, 85.2, 82.1, 67.5, 55.4, 53.3, 26.7, 25.1. Calcd. for $C_{18}H_{25}N_2O_6$ [M+H]: 365.1713 Found 365.1693.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OBn
H2N
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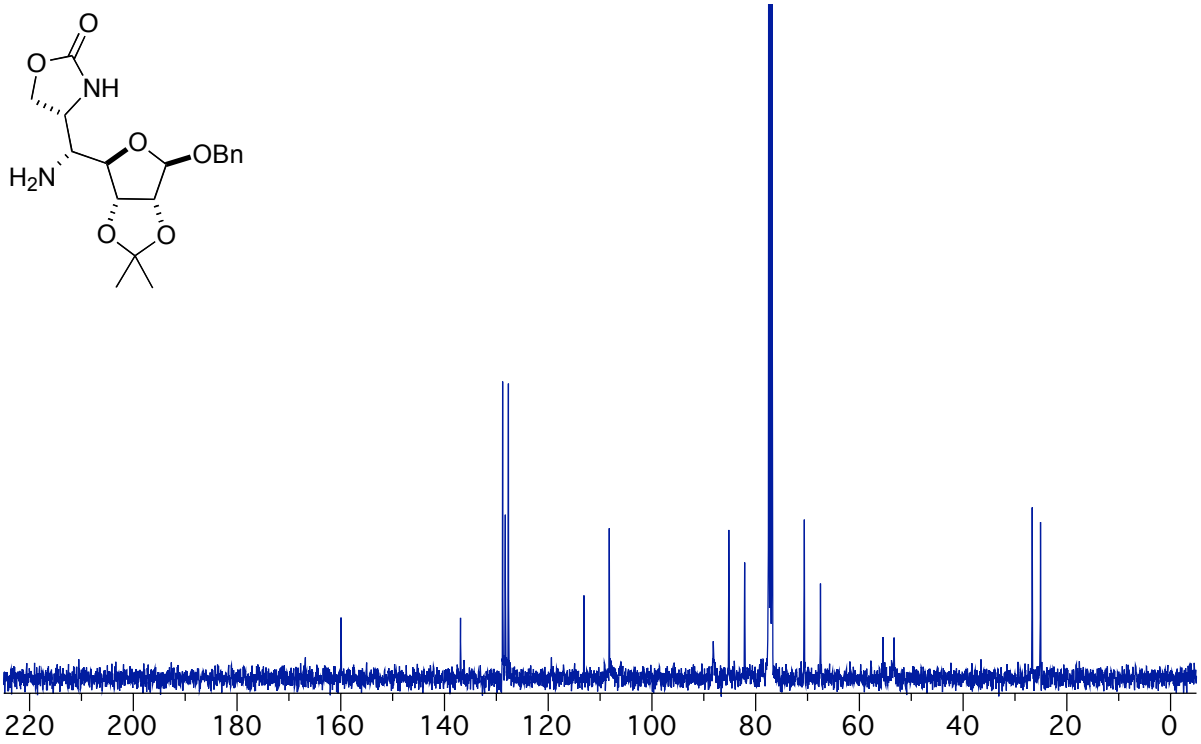
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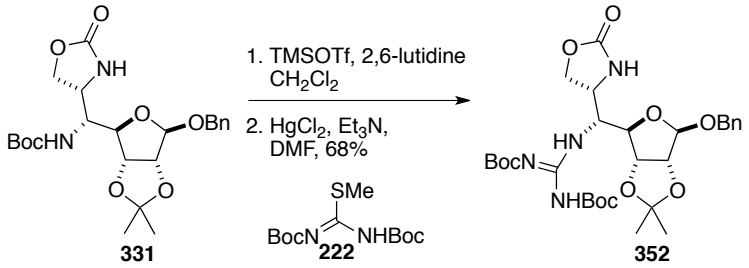
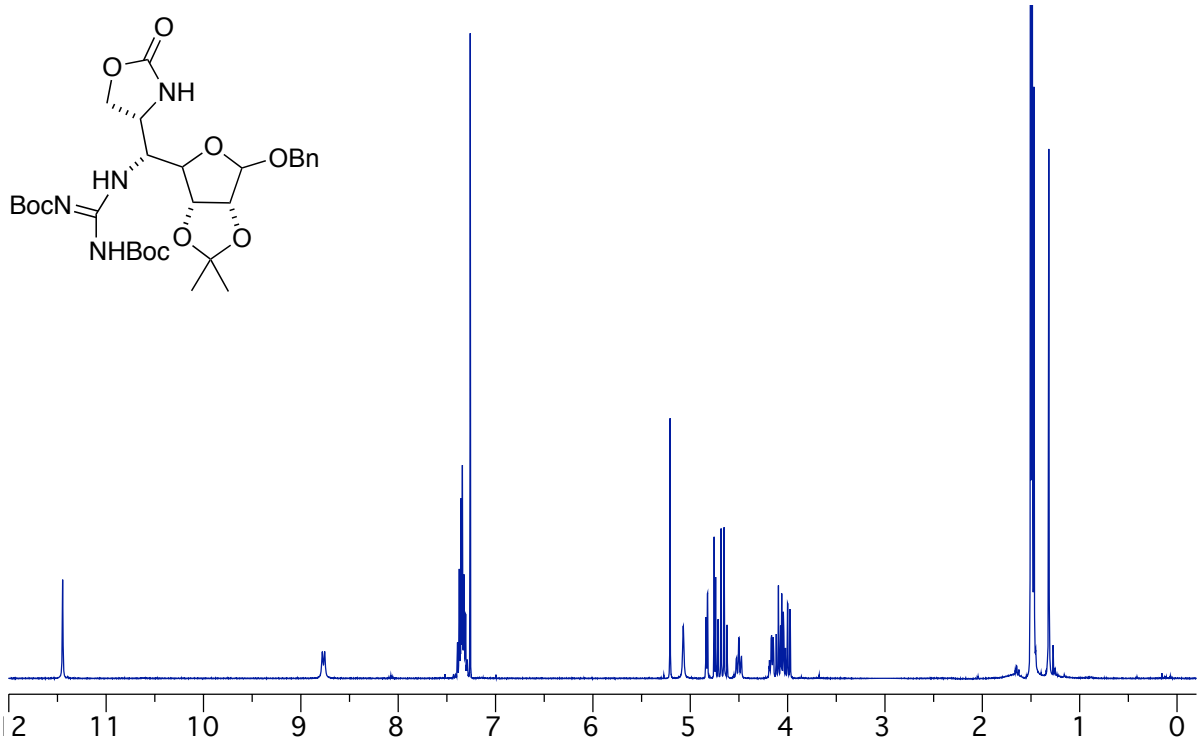
O
NH
O
OBn
H2N
O
O
220
200
180
160
140
120
100
80
60
40
20
0

Compound 352: (*R*)-4-((*R*)-(2,3-bis(*tert*-butoxycarbonyl)guanidino)((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)oxazolidin-2-one.



To a solution of oxazolidinone **331** (245 mg, 1eq.) and 2,6-lutidine (245.7 μL, 3eq.) in CH_2Cl_2 (5 mL) was added TMSOTf (286.4 μL, 3 eq.). The mixture was allowed to stir until complete by TLC and quenched with sat. sodium bicarbonate, extracted with EtOAc (3x). The combined extracts were dried over sodium sulfate and evaporate. The crude amine was dissolved in DMF (5mL) and triethylamine (330.8 μL, 4.5 eq.) and guanylating reagent **222** (153.3 mg, 1eq.) was added. The mixture was cooled to 0°C and mercuric chloride (157.5mg, 1.1 eq.) was added. The cloudy suspension was allowed to room temperature and stirred until complete by TLC. The reaction was quenched by adding sat. sodium chloride and ethyl acetate. After stirring the mixture for 20 minutes the reaction was filtered through celite to remove all the mercury salts. The biphasic solution was separated and the organic layer was washed with H_2O (3x), brine and then dried over sodium sulfate and evaporated in vacuo. The crude material was purified via column chromatography (20-50% EtOAc/Hexanes) to give compound **352** (216 mg, 67.5%). $[\alpha]_D^{25}$= -91 (c 0.23, $CHCl_3$) ^{1}H-NMR (400 MHz; $CDCl_3$): δ 11.45 (s, 1H), 8.77 (d, *J* = 9.4 Hz, 1H), 7.39-7.29 (m, 5H), 5.21 (s, 1H), 5.07 (s, 1H), 4.83 (dd, *J* = 6.0, 1.1 Hz, 1H), 4.75 (d, *J* = 6.0 Hz, 1H), 4.70 (d, *J* = 12.4 Hz, 1H), 4.64 (d, *J* = 12.3 Hz, 1H), 4.50 (td, *J* = 10.0, 1.5 Hz, 1H), 4.17 (ddt, *J* = 8.7, 6.7, 2.0 Hz, 1H), 4.09 (t, *J* = 8.8 Hz, 1H), 4.04 (dd, *J* = 8.8, 6.7 Hz, 1H), 3.99 (dd, *J* = 10.2, 1.1 Hz, 1H), 1.49 (s, 9H), 1.49 (s, 9H), 1.47 (s, 3H), 1.32 (s, 3H). 13-C NMR (101 MHz; cdcl3): δ 163.3, 159.2, 157.2, 153.0, 136.9, 128.8, 128.2, 127.6, 113.1, 108.9, 98.7,

86.6, 85.2, 84.2, 82.0, 70.6, 66.8, 52.33, 52.17, 28.4, 28.20, 28.14, 26.7, 25.2. IR (Dep. $CDCl_3$): 3263 (br), 2981 (s), 2936(s), 1763(s), 1725(s), 1641(s), 1613(s).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BocN
NHBoc
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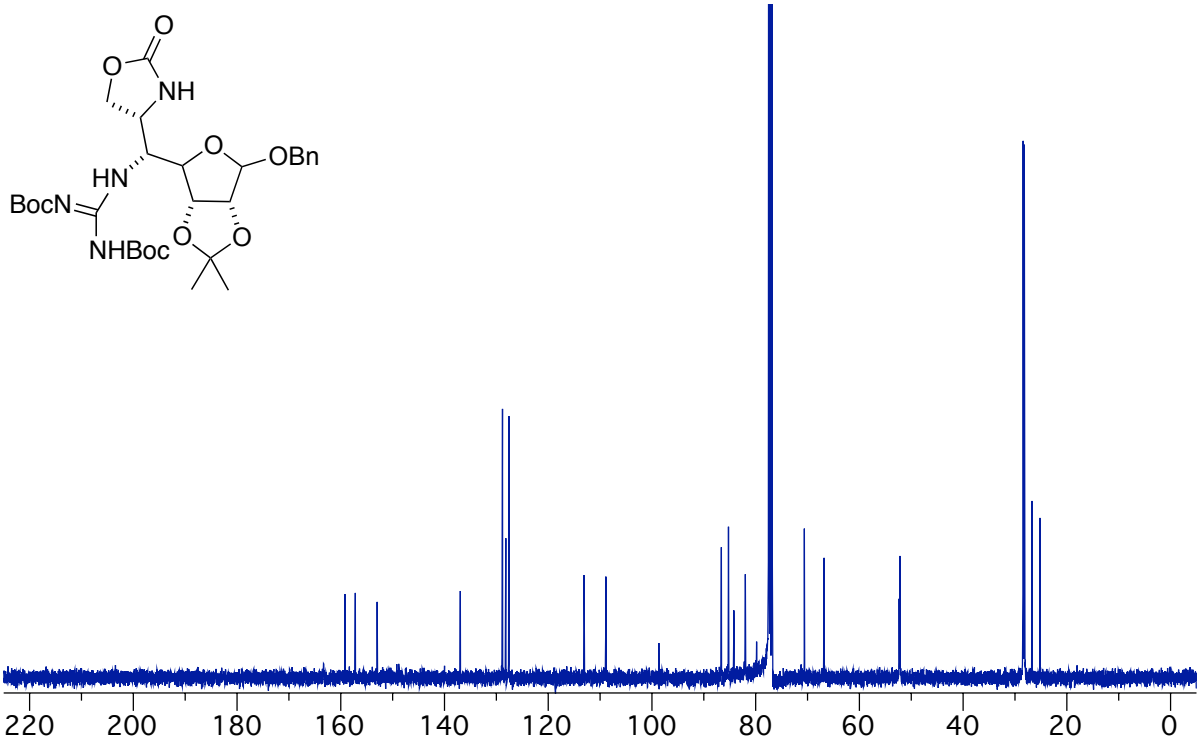
0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NH
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OBn
HN
BocN
NHBoc
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O
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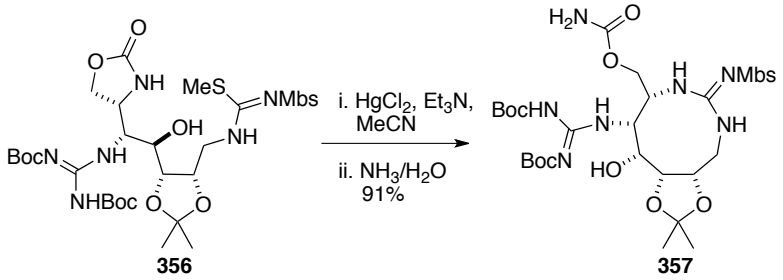
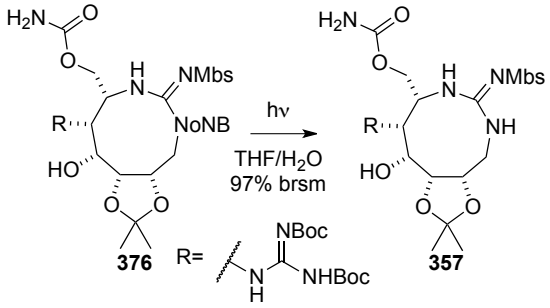
120
100
80
60
40
20
0

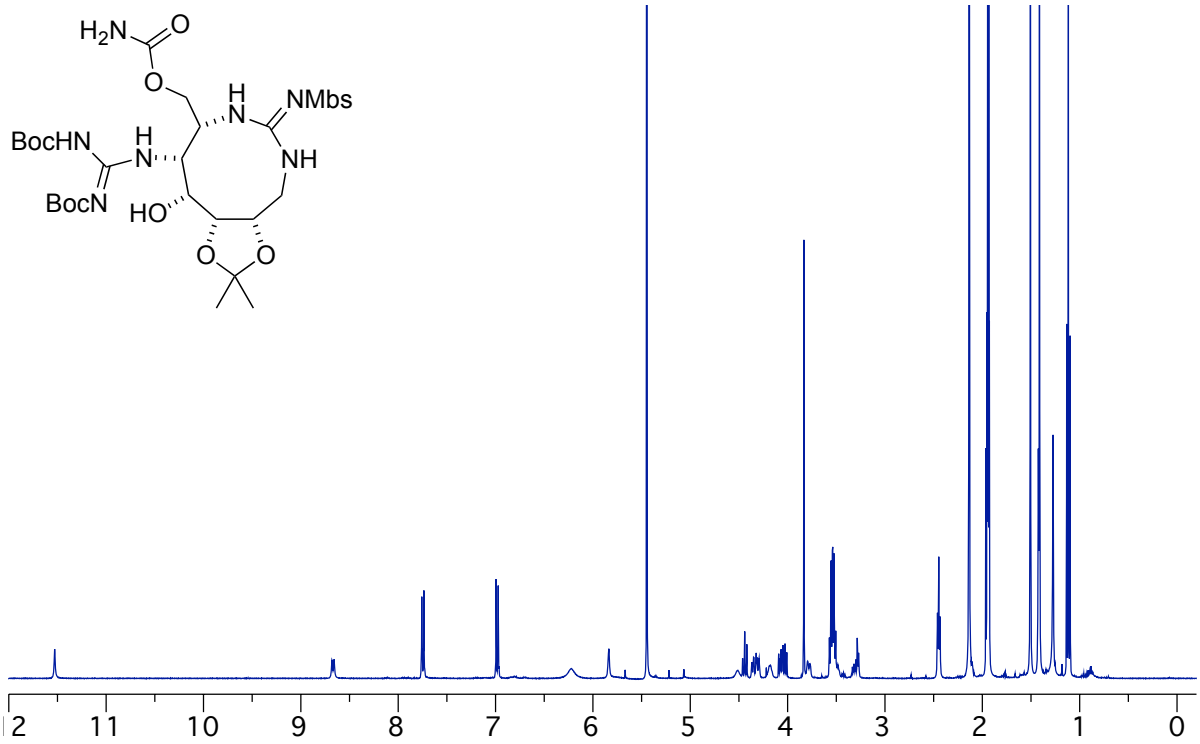
Compound 357: ((3a*S*,8*R*,9*R*,10*R*,10a*R*)-9-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-10-hydroxy-6-(((4-methoxyphenyl)sulfonyl)imino)-2,2-dimethyloctahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3]diazonin-8-yl)methyl carbamate.



Method A: To a solution of compound **356** (15 mg, 1eq.) and triethylamine (12.4 μL, 4.5 eq.) in acetonitrile (2 mL) was added mercuric chloride (5.9 mg, 1.1 eq.). The reaction was stirred ~20 min. until the disappearance of stating material by TLC. The reaction was quenched with conc. ammonium hydroxide (1 mL) and stirred an additional 20 min. until the disappearance of stating material by TLC. The reaction mixture was filtered through celite to remove mercury and the mixture was extracted 3x with EtOAc. The combined organic layers were dried over sodium sulfate and evaporated. The crude material was purified by flash chromatography (1-5% MeOH/DCM) to give **357** as a white solid (13.1 mg, 91.1%).



Method B: Argon was bubbled through a vial containing **376** (53 mg) in THF (6 mL, wet) for 5 min. The vial was sealed and irradiated by a Hg vapor lamp for 30 min. The mixture was evaporated and purified via flash chromatography (1-5% MeOH/DCM) to give **357** (40 mg, 89.4%, 96.7% brsm) and recovered starting material (4 mg). ^{1}H-NMR (400 MHz; cd3cn): δ 11.53 (s, 1H), 8.67 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.22 (s, 2H), 5.84 (s, 1H), 4.51 (s, 1H), 4.45 (d, *J* = 8.6 Hz, 1H), 4.43 (d, *J* = 8.6 Hz, 1H), 4.37-4.35 (m, 1H), 4.30 (dt, *J* = 8.9, 2.7 Hz, 1H), 4.18 (dd, *J* = 12.5, 5.5 Hz, 1H), 4.07 (dd, *J* = 9.8, 5.7 Hz, 1H), 4.03 (dd, *J* = 8.3, 7.1 Hz, 1H), 3.83 (s, 3H), 3.78 (d, *J* = 10.3 Hz, 1H), 3.32 (dd, *J* = 7.7, 5.9 Hz, 1H), 3.28 (d, *J* = 5.7 Hz, 1H), 1.51 (s, 9H), 1.42 (s, 3H), 1.41 (s, 9H), 1.27 (s, 3H).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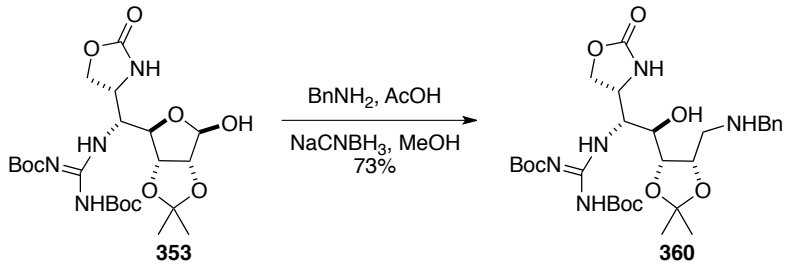
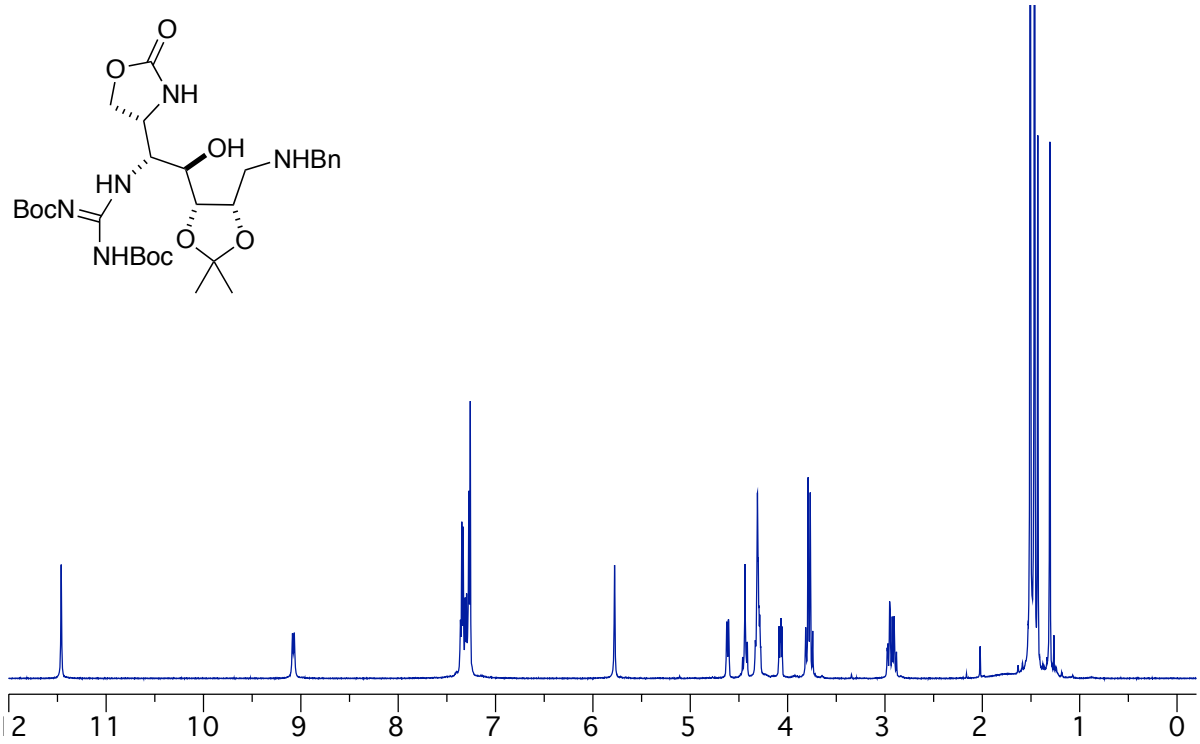
Compound 360: (*R*)-4-((1*R*,2*R*)-1-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-2-((4*R*,5*S*)-5-((benzylamino)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyethyl)oxazolidin-2-one.



353 360

A solution of lactol **353** (10 mg, 1 eq.), benzylamine (43 µL, 20 eq.), AcOH (150 µL, 135 eq.) and sodium cyanoborohydride (12.2mg 10 eq.) in MeOH (0.5 mL) was allowed to stir 6 hours. The reaction was carefully quenched with sat. sodium bicarbonate, extracted with EtOAc (3x) and the combined extracts were dried over sodium sulfate and evaporated. The crude product wad purified via PTLC (10% MeOH/DCM) to give benzylamine **360** (8.5mg, 72.3%). $[\alpha]_D^{25}$= -1 (c 0.77, $CHCl_3$). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 11.46 (s, 1H), 9.08 (d, *J* = 9.4 Hz, 1H), 7.36-7.26 (m, 5H), 5.78 (s, 1H), 4.62 (dd, *J* = 9.4, 2.4 Hz, 1H), 4.44 (t, *J* = 12.0 Hz, 1H), 4.33-4.28 (m, 3H), 4.07 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.80 (d, *J* = 12.6 Hz, 1H), 3.76 (d, *J* = 12.7 Hz, 1H), 2.96 (dd, *J* = 12.3, 3.4 Hz, 1H), 2.90 (dd, *J* = 12.3, 9.6 Hz, 1H), 1.51 (s, 9H), 1.46 (s, 9H), 1.43 (s, 3H), 1.31 (s, 3H). 13-C NMR (126 MHz; cdcl3): δ 163.6, 159.3, 156.8, 152.9, 137.8, 129.0, 128.7, 128.0, 109.2, 83.5, 79.3, 77.6, 75.8, 71.2, 67.4, 54.0, 51.9, 50.7, 48.1, 28.42, 28.23, 27.9, 25.4. IR (Dep. $CDCl_3$): 3306 (br), 3273 (br), 3119 (s), 2982 (s),2933 (s),1758 (s),1726 (s),1639 (s),1613 (s),1563 (s).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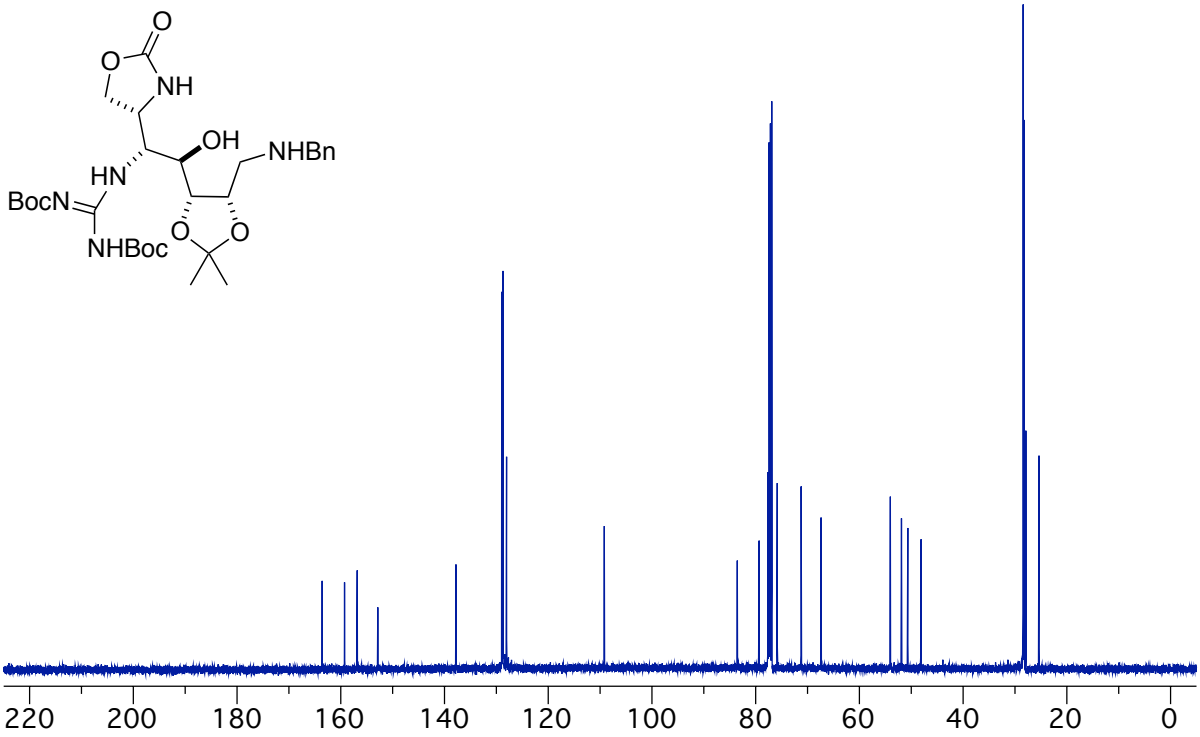
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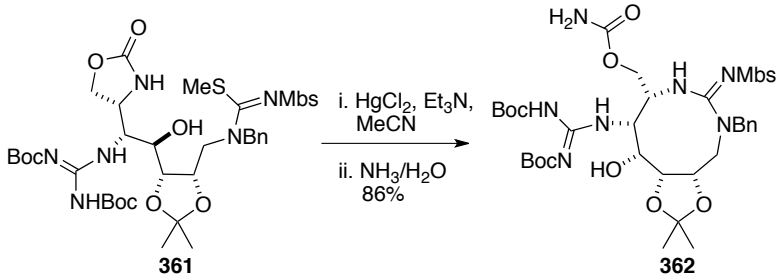
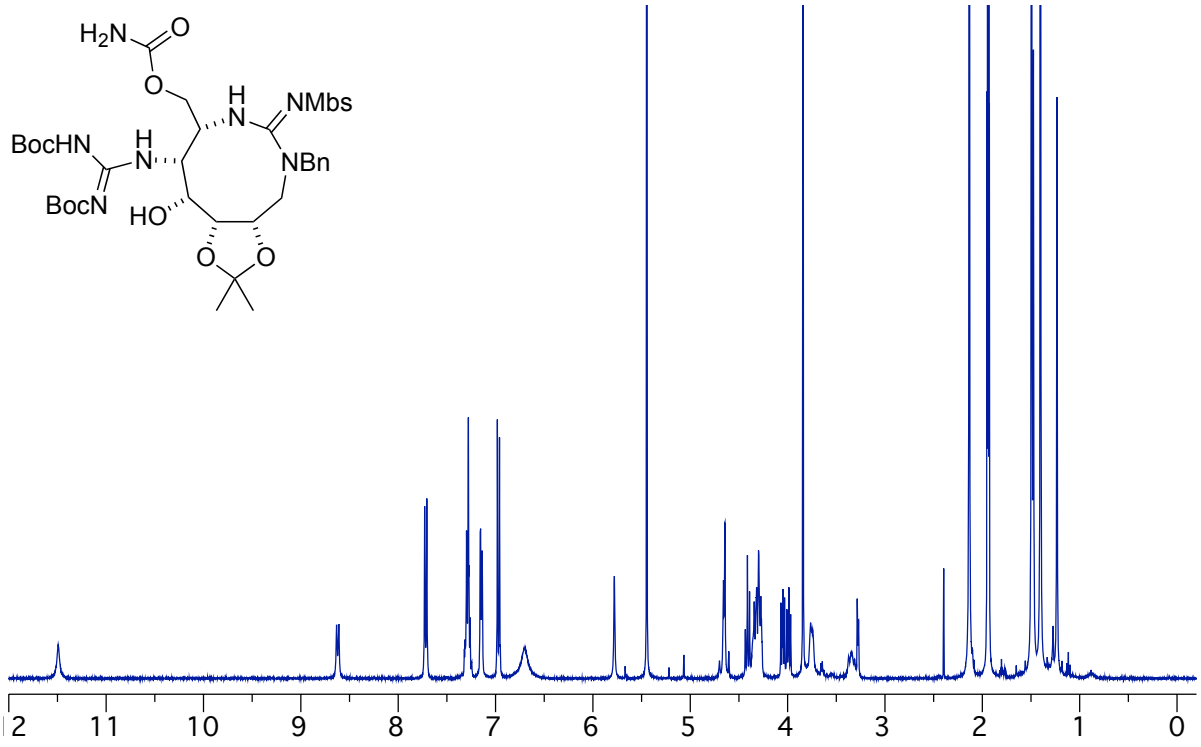
Compound 362: ((3a*S*,8*R*,9*R*,10*R*,10a*R*)-9-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-5-benzyl-10-hydroxy-6-(((4-methoxyphenyl)sulfonyl)imino)-2,2-dimethyloctahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3]diazonin-8-yl)methyl carbamate.



To a solution of compound **361** (23.5 mg, 1eq.) and triethylamine (19.3 μL, 5 eq.) in acetonitrile (1 mL) was added mercury (II) chloride (9 mg, 1.2 eq.). The reaction was stirred ~20 min. until the disappearance of stating material by TLC. The reaction was quenched with conc. ammonium hydroxide (1 mL) and stirred an additional 20 min. until the disappearance of stating material by TLC. The reaction mixture was filtered through celite to remove mercury and the mixture was extracted 3x with EtOAc. The combined organic layers were dried over sodium sulfate and evaporated. The crude material was purified by flash chromatography (1-5% MeOH/DCM) to give **362** as a white solid (19.5 mg, 86.0%). ^{1}H-NMR (400 MHz; cd3cn): δ 11.49 (s, 1H), 8.62 (d, *J* = 9.1 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 7.7 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.70 (s, 2H), 5.78 (s, 1H), 4.67 (d, *J* = 16.5 Hz, 1H), 4.63 (d, *J* = 16.1 Hz, 1H), 4.41 (t, *J* = 8.7 Hz, 1H), 4.34-4.27 (m, 3H), 4.05 (dd, *J* = 9.4, 6.0 Hz, 1H), 3.99 (dd, *J* = 8.4, 7.1 Hz, 1H), 3.84 (s, 2H), 3.76-3.74 (m, 1H), 3.37-3.31 (m, 1H), 3.28-3.27 (m, 1H), 1.49 (s, 9H), 1.48 (s, 3H), 1.40 (s, 9H), 1.23 (s, 3H).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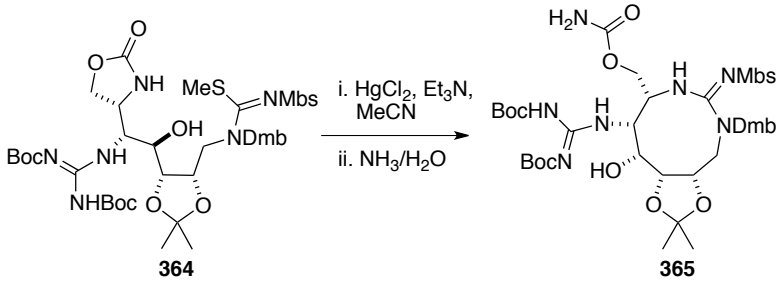
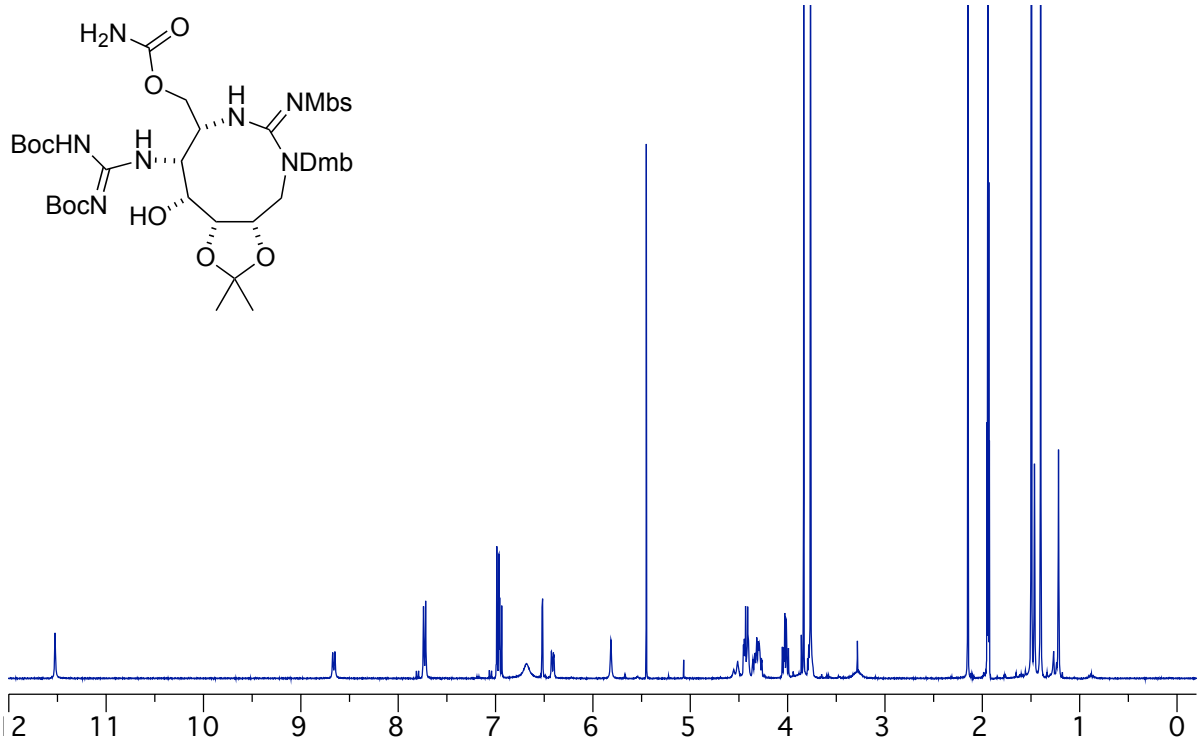
Compound 365: ((3a*S*,8*R*,9*R*,10*R*,10a*R*)-9-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-5-(2,4-dimethoxybenzyl)-10-hydroxy-6-(((4-methoxyphenyl)sulfonyl)imino)-2,2-dimethyloctahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3]diazonin-8-yl)methyl carbamate.



To a solution of compound **364** (95 mg, 1eq.) and triethylamine (73 µL, 5 eq.) in acetonitrile (5 mL) was added mercury (II) chloride (49.9 mg, 2 eq.). The reaction was stirred ~20 min. until the disappearance of stating material by TLC. The reaction was quenched with conc. ammonium hydroxide (5 mL) and stirred an additional 20 min. until the disappearance of stating material by TLC. The reaction mixture was filtered through celite to remove mercury and the mixture was extracted 3x with EtOAc. The combined organic layers were dried over sodium sulfate and evaporated. The crude material was purified by flash chromatography (1-5% MeOH/DCM) to give **365** as a white solid (65 mg, 70.1%). $[\alpha]_D^{25}$= -23 (c 0.32, $CHCl_3$). ^{1}H-NMR (400 MHz; cd3cn): δ 11.53 (s, 1H), 8.66 (d, *J* = 9.0 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.68 (s, 2H), 6.52 (d, *J* = 2.3 Hz, 1H), 6.41 (dd, *J* = 8.3, 2.1 Hz, 1H), 5.82 (s, 1H), 4.53 (d, *J* = 16.0 Hz, 1H), 4.45-4.40 (m, 3H), 4.36-4.26 (m, 3H), 4.05-4.03 (dd, 1H), 4.01 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.83 (s, 3H), 3.76 (s, 1H), 3.76 (s, 3H), 3.28 (s, 2H), 1.50 (s, 9H), 1.46 (s, 3H), 1.40 (s, 9H), 1.22 (s, 3H). 13-C NMR (101 MHz; cdcl3): δ 162.8, 162.1, 160.9, 159.2, 158.0, 157.5, 156.9, 152.8, 135.8, 130.7, 128.1, 113.8, 109.7, 104.7, 98.75, 98.69, 84.0, 79.8, 77.9, 76.4, 71.4, 67.6, 55.63, 55.52, 55.51, 54.1, 52.0, 49.1, 47.3, 28.32, 28.14, 27.9, 25.4.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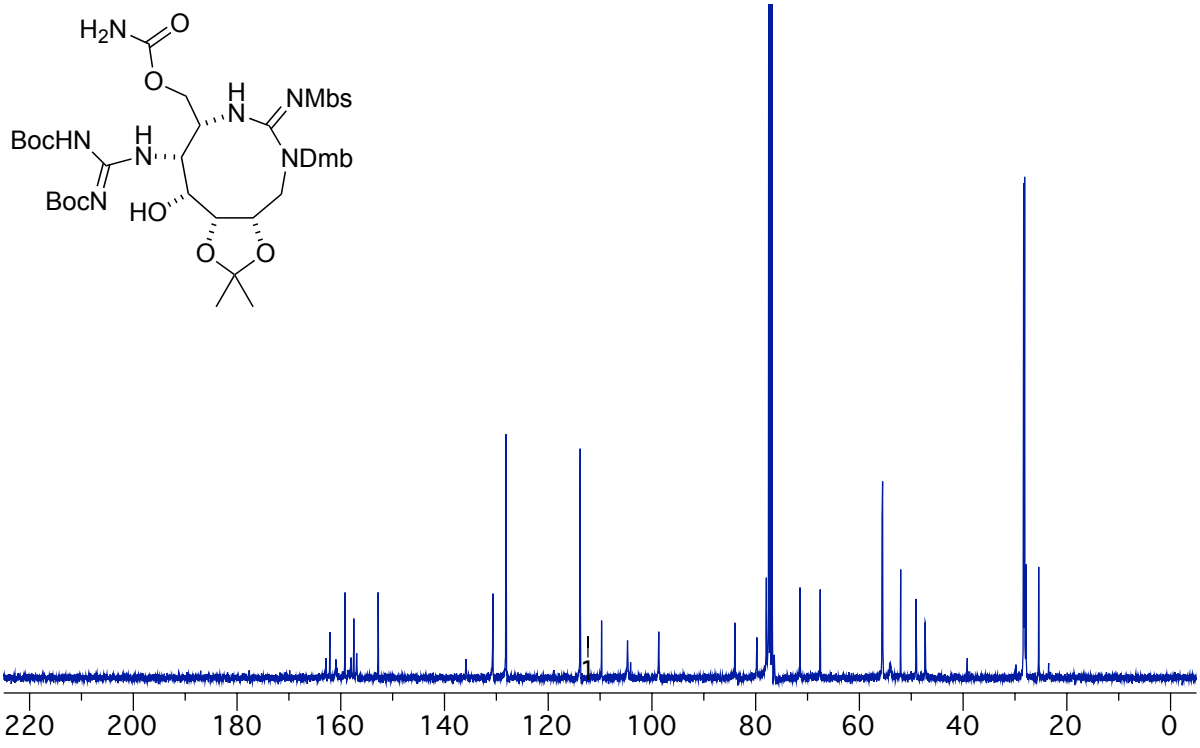
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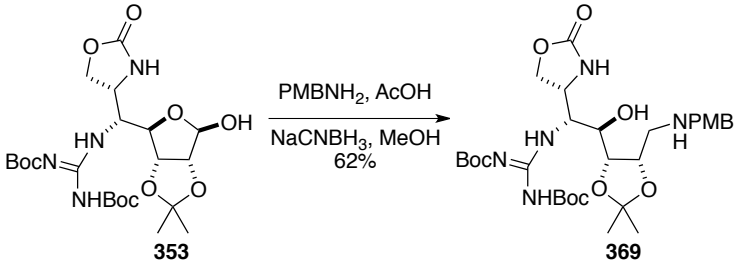
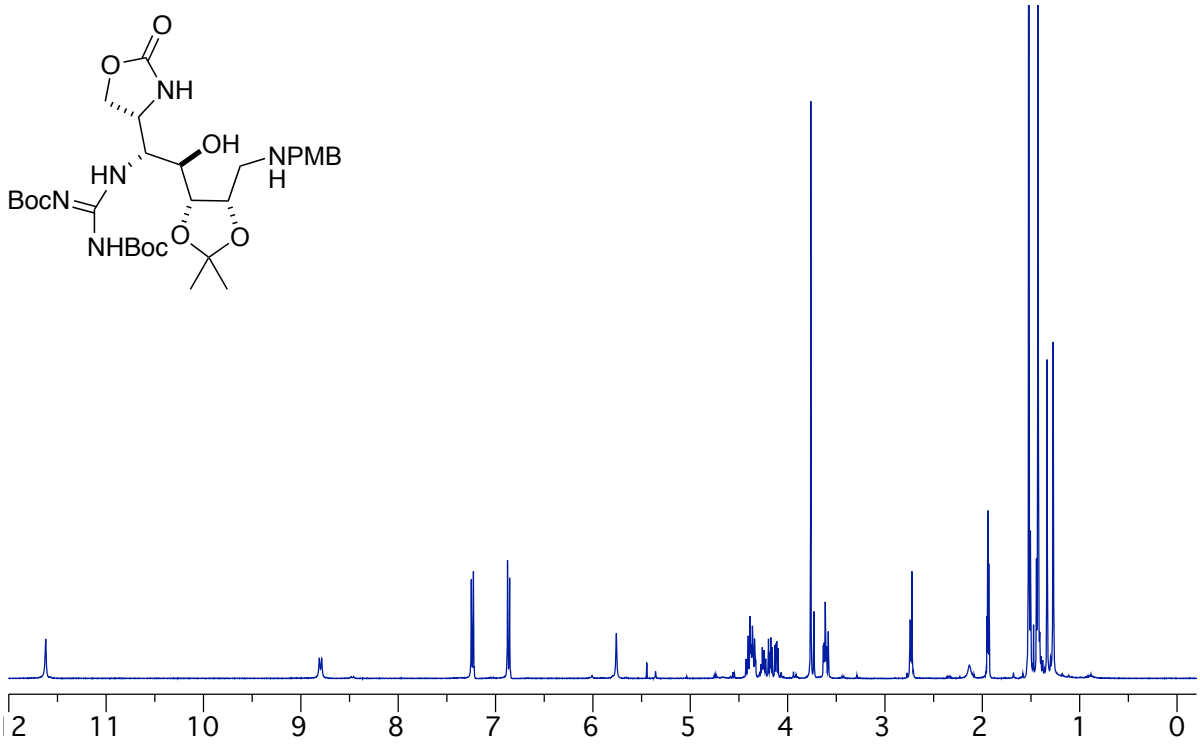
Compound 369: (*R*)-4-((1*R*,2*R*)-1-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-2-hydroxy-2-((4*R*,5*S*)-5-(((4-methoxybenzyl)amino)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)oxazolidin-2-one.



A solution of lactol **353** (50 mg, 1 eq.), p-methoxybenzylamine (253 µL, 20 eq.), AcOH (887 µL, 160 eq.) and sodium cyanoborohydride (30.4 mg, 5 eq.) in MeOH (3 mL) was allowed to stir 6 hours. The reaction was carefully quenched with sat. sodium bicarbonate, extracted with EtOAc (3x) and the combined extracts were dried over sodium sulfate and evaporated. The crude product wad purified via PTLC (10% MeOH/DCM) to give benzylamine **369** (36 mg, 61.7%). $[\alpha]_D^{25}$= -7 (c 0.37, $CHCl_3$) ^{1}H-NMR (400 MHz; cd3cn): δ 11.62 (s, 1H), 8.80 (d, *J* = 9.6 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.76 (s, 1H), 4.40-4.33 (m, 3H), 4.24 (dd, *J* = 8.0, 5.8 Hz, 1H), 4.18 (dd, *J* = 9.6, 5.8 Hz, 1H), 4.11 (dd, *J* = 7.4, 5.1 Hz, 1H), 3.76 (s, 3H), 3.75 (d, *J* = 12.4 Hz, 1H), 3.62 (dd, *J* = 9.6, 3.4 Hz, 1H), 3.60 (d, *J* = 12.4 Hz, 1H), 2.74-2.72 (m, 2H), 1.52 (s, 9H), 1.43 (s, 9H), 1.33 (s, 3H), 1.27 (s, 3H). 13-C NMR (101 MHz; cd3cn): δ 164.6, 160.1, 159.8, 157.8, 153.8, 131.8, 131.1, 114.7, 109.6, 84.4, 79.7, 78.4, 76.7, 71.6, 67.9, 55.8, 53.2, 52.7, 52.2, 48.9, 28.4, 28.21, 28.15, 25.4 HRMS (FAB^+): Calcd for $C_{30}H_{48}N_5O_{10}$ [M+H]: 638.3401; Found 638.3392.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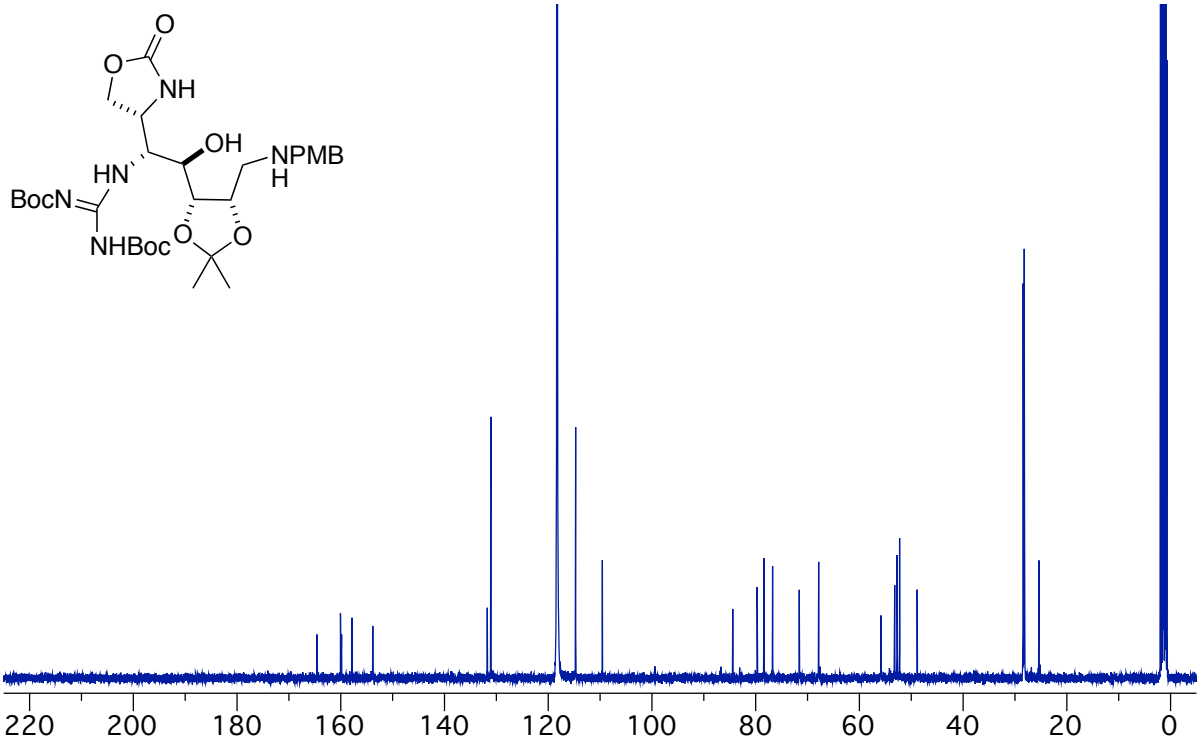
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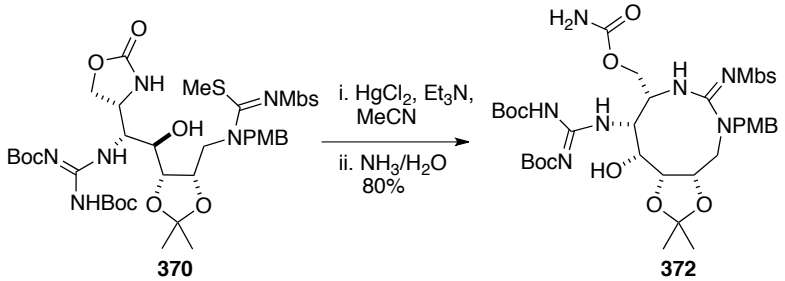
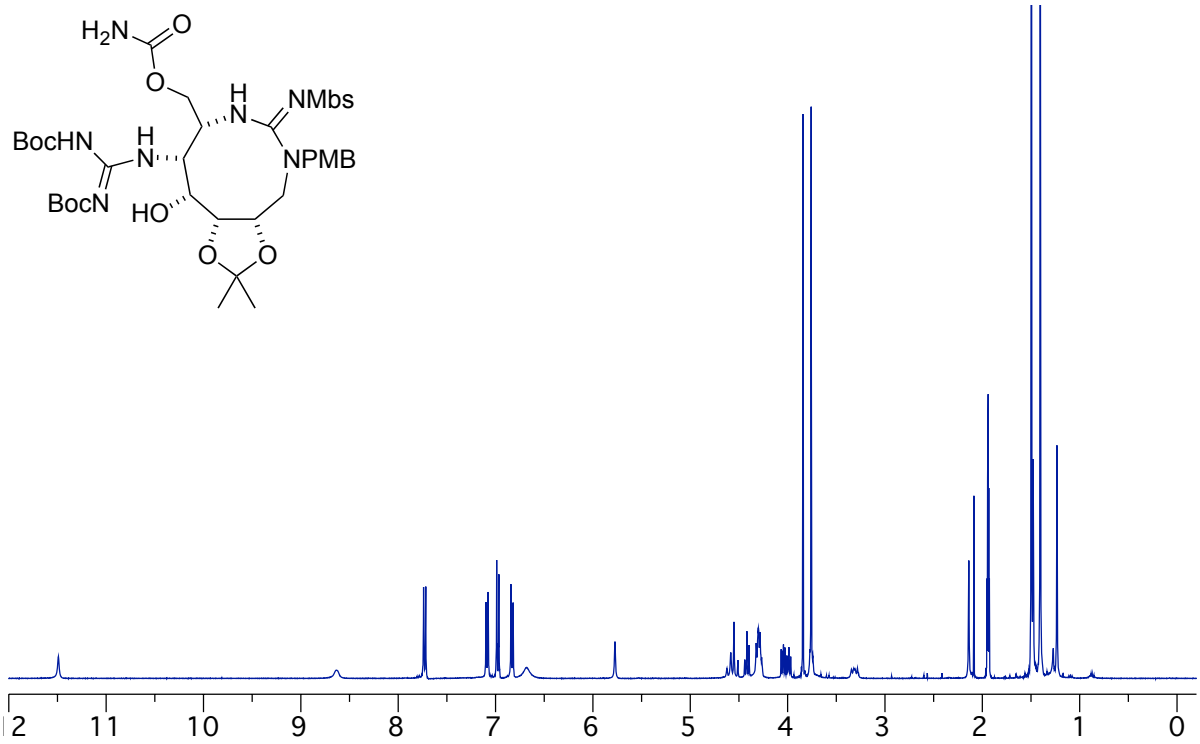
Compound 372: ((3a*S*,8*R*,9*R*,10*R*,10a*R*)-9-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-10-hydrox y-5-(4-methoxybenzyl)-6-(((4-methoxyphenyl)sulfonyl)imino)-2,2-dimethyloctahydro-3a*H*-[1,3] dioxolo[4,5-*e*][1,3]diazonin-8-yl)methyl carbamate.



370 372

To a solution of isothiourea **370** (53mg, 1eq.) and triethylamine (75 µL, 9 eq.) in MeCN (2 mL) was added mercuric chloride (32.7 mg, 2 eq.) and the mixture was stirred until complete by TLC. The reaction was quenched by adding conc. Ammonium hydroxide (2 mL) and allowed to stir until complete by TLC. The reaction was diluted with EtOAc, filtered and evaporated. The crude alcohol was purified via flash chromatography to give alcohol **372** (41 mg, 79.6%). $[\alpha]_D^{25}$= -23 (c 0.31, $CHCl_3$) ^{1}H-NMR (400 MHz; cd3cn): δ 11.49 (s, 1H), 8.64 (s, 1H), 7.73 (d, *J* = 8.9 Hz, 2H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.68 (s, 2H), 5.77 (s, 1H), 4.60 (d, *J* = 15.5 Hz, 1H), 4.54 (d, *J* = 15.9 Hz, 1H), 4.42 (t, *J* = 8.7 Hz, 1H), 4.32-4.26 (m, 3H), 4.05 (dd, *J* = 9.3, 6.0 Hz, 1H), 3.99 (dd, *J* = 8.5, 7.2 Hz, 1H), 3.84 (s, 3H), 3.76 (d, 1H), 3.76 (s, 3H), 3.31 (dd, *J* = 15.0, 9.7 Hz, 1H), 1.50 (s, 9H), 1.48 (s, 3H), 1.40 (s, 9H), 1.23 (s, 3H). 13-C NMR (101 MHz; cd3cn): δ 162.9, 160.1, 159.8, 158.2, 158.0, 153.7, 137.4, 129.6, 128.7, 114.87, 114.75, 110.4, 84.5, 79.9, 77.9, 76.9, 70.9, 68.0, 56.3, 55.9, 54.4, 52.0, 51.8, 49.2, 28.4, 28.15, 28.05, 25.5. (Dep. CH_3CN): 3416 (br), 3321 (br), 2982 (s), 2936(s), 1752(s), 1727(s), 1638(s), 1613(s), 1542(s).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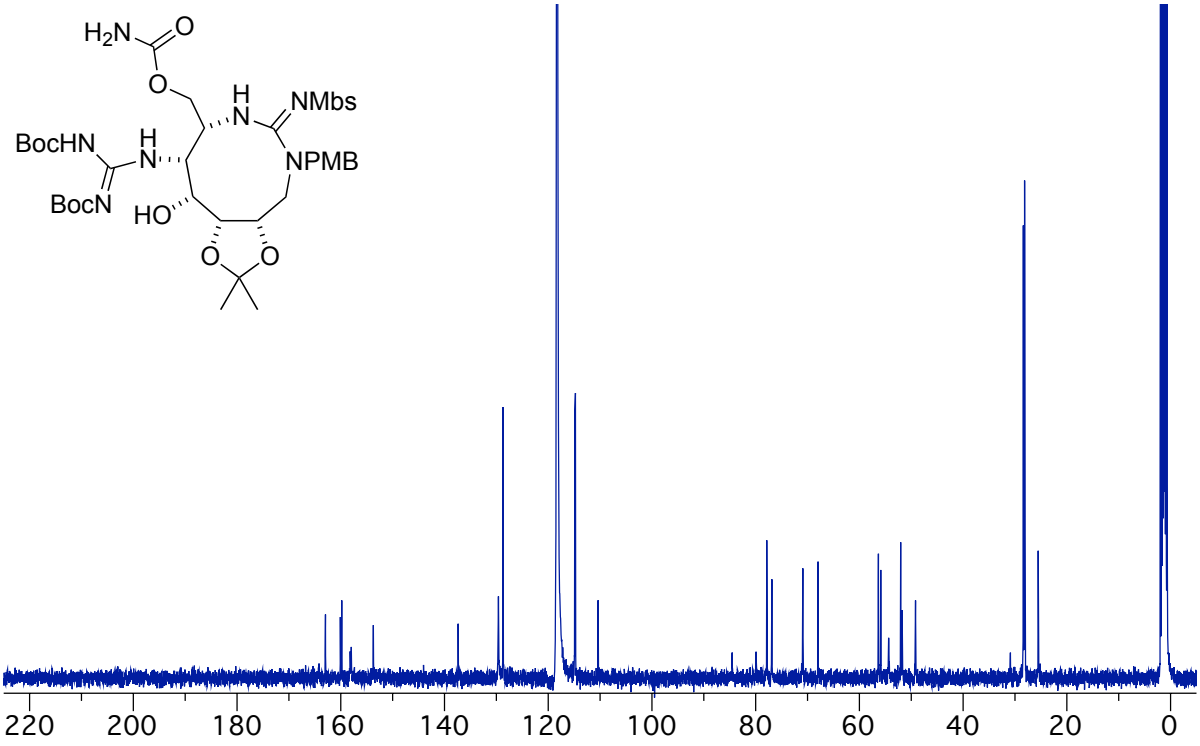
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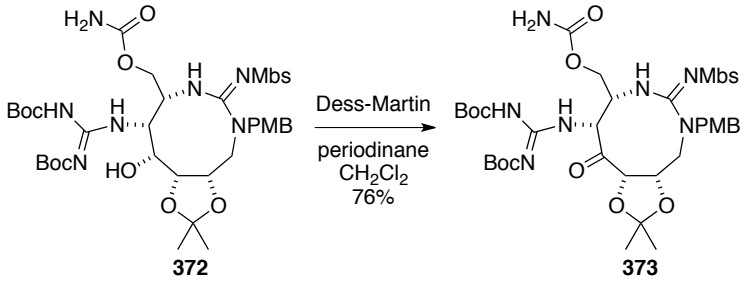
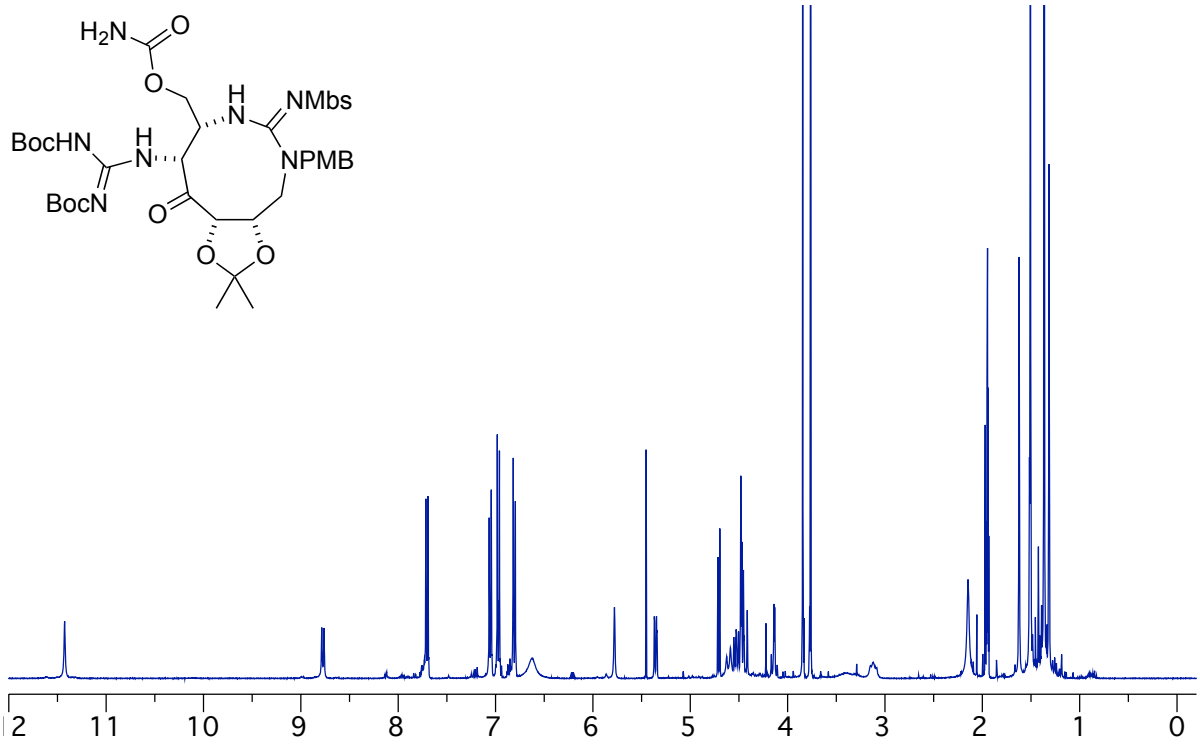
Compound 373: ((3a*S*,8*R*,9*R*,10a*S*)-9-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-5-(4-methoxybenzyl)-6-(((4-methoxyphenyl)sulfonyl)imino)-2,2-dimethyl-10-oxooctahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3]diazonin-8-yl)methyl carbamate.



To a solution of alcohol **372** (37 mg, 1 eq.) in CH_2Cl_2 (2 mL) was added Dess-Martin periodinane (36.9 mg, 2 eq.). The solution turned cloudy over time and was allowed to stir for ~1 hour. The reaction was quenched with $Na_2S_2O_3$ and was allowed to stir until the biphasic system turned clear. The mixture was extracted with EtOAc (3x), dried over sodium sulfate and evaporated in vacuo to give crude ketone 6. The crude material was purified via column chromatography (20% EtOAc/Hexanes) to give ketone **373** (28 mg, 75.9%). ^{1}H-NMR (400 MHz; cd3cn): δ 11.43 (s, 1H), 8.77 (d, *J* = 9.1 Hz, 1H), 7.71 (d, *J* = 8.9 Hz, 2H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.62 (s, 2H), 5.78 (s, 1H), 5.36 (dd, *J* = 9.1, 2.0 Hz, 1H), 4.71 (d, *J* = 7.9 Hz, 1H), 4.61 (d, *J* = 15.4 Hz, 1H), 4.53 (ddd, *J* = 9.8, 8.0, 1.8 Hz, 1H), 4.48 (s, 1H), 4.44 (d, *J* = 15.7 Hz, 1H), 4.14 (d, *J* = 3.4 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.15-3.08 (m, 1H), 1.62 (s, 3H), 1.51 (s, 9H), 1.37 (s, 9H), 1.31 (s, 3H). 13-C NMR (101 MHz; cd3cn): δ 207.0, 164.1, 162.9, 160.1, 159.6, 158.0, 157.6, 153.7, 137.4, 129.7, 128.81, 128.67, 114.86, 114.75, 112.3, 84.8, 80.9, 80.2, 77.8, 67.6, 59.0, 56.3, 55.9, 52.3, 51.9, 49.5, 28.38, 28.36, 28.34, 28.14, 28.11, 26.9, 24.9.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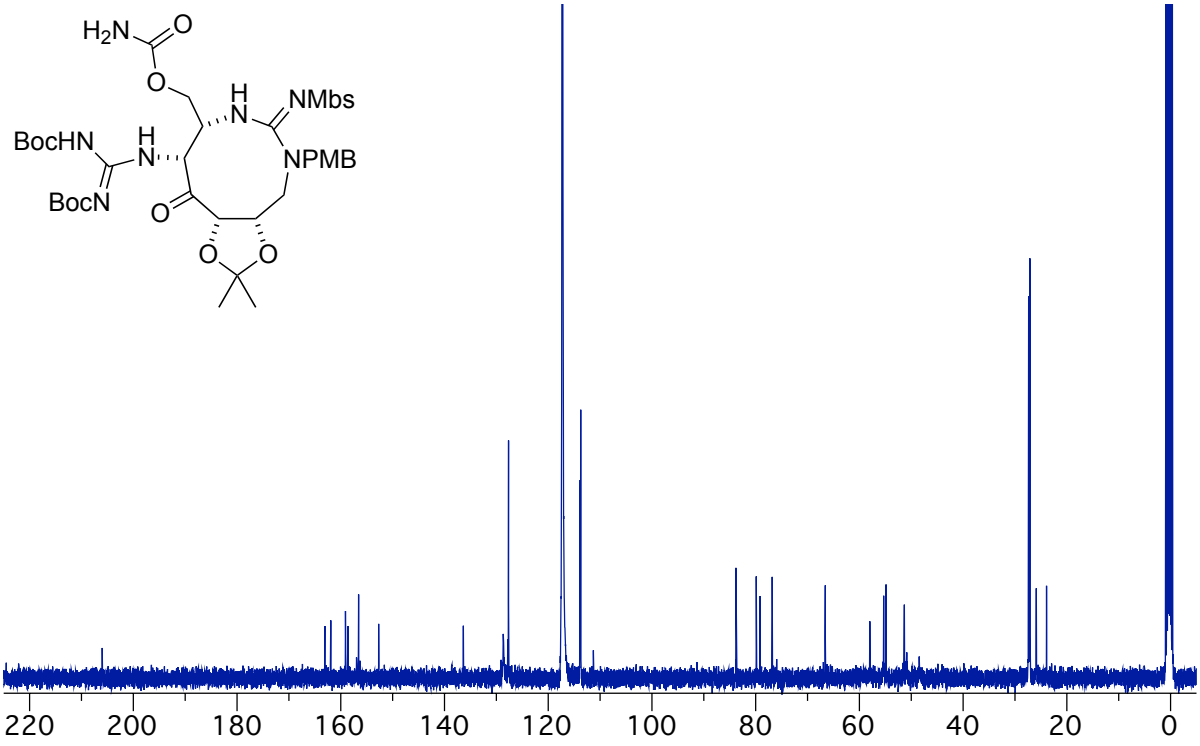
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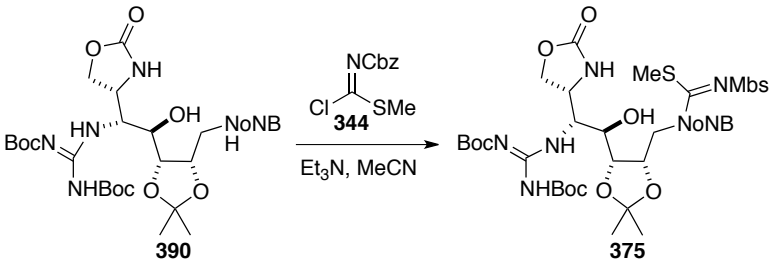
120
100
80
60
40
20
0

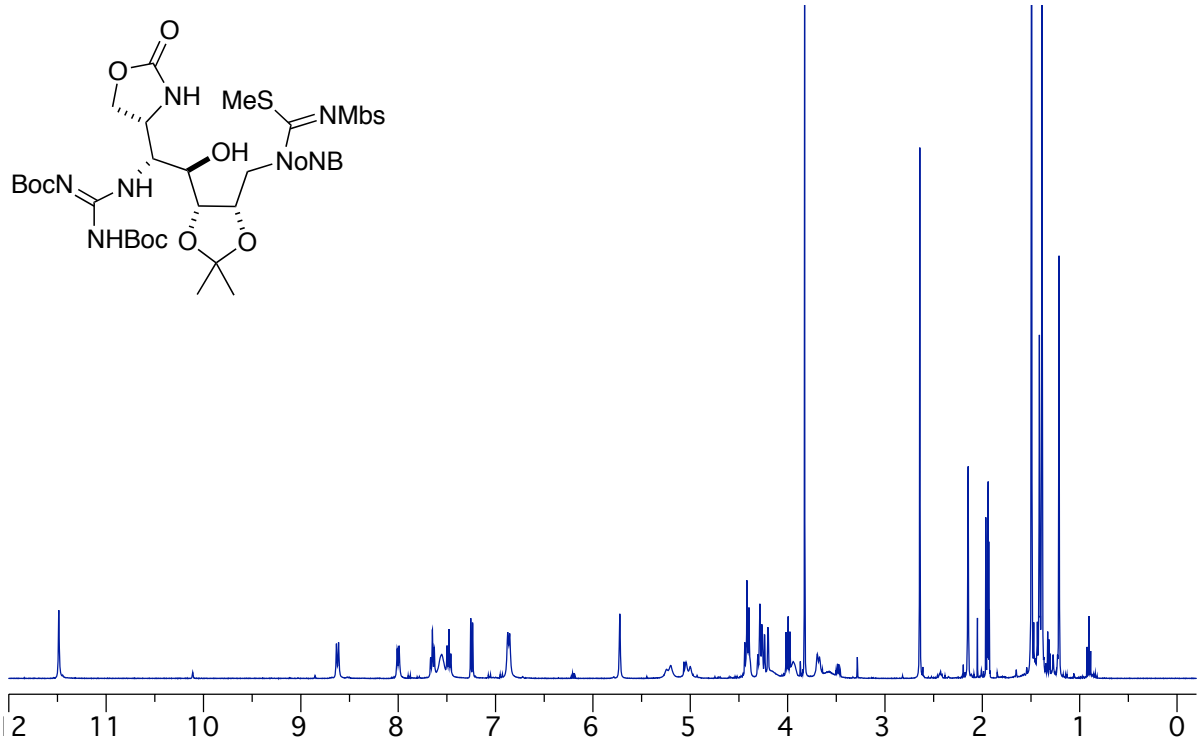
Compound 375: methyl *N*-(((4*S*,5*R*)-5-((1*R*,2*R*)-2-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-1-hydroxy-2-((*R*)-2-oxooxazolidin-4-yl)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-*N*'-((4-methoxyphenyl)sulfonyl)-*N*-(2-nitrobenzyl)carbamimidothioate.



To a solution of amine **390** (209 mg, 1 eq.) and triethylamine (171 µL, 3 eq.) in CH_2Cl_2 (4 mL, 0.1M) was added **344** (229.1 mg, 2 eq.). The mixture was allowed to stir until complete by TLC. The crude compound was cleaned up via flash chromatography (1-5% MeOH/DCM) to give the isothiourea. The isothiourea was dissolved in MeCN (10 mL) and triethylamine (171 µL, 3 eq.) was added followed by mercuric chloride (166.7 mg, 1.5 eq.) and the mixture was stirred until complete by TLC. The reaction was quenched by adding conc. Ammonium hydroxide (2 mL) and allowed to stir ~20 min. The reaction was diluted with EtOAc, filtered and evaporated. The crude alcohol was purified via flash chromatography to give alcohol **419** (235 mg, 79.4%). ^{1}H-NMR (400 MHz; cd3cn): δ 11.49 (s, 1H), 8.62 (d, *J* = 8.7 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.55 (s, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 5.72 (s, 1H), 5.22 (d, *J* = 16.3 Hz, 1H), 5.02 (d, *J* = 17.6 Hz, 1H), 4.42 (t, *J* = 8.6 Hz, 1H), 4.41 (s, 1H), 4.31-4.27 (m, 1H), 4.22 (dd, *J* = 14.4, 1.8 Hz, 1H), 4.00 (dd, *J* = 8.5, 7.2 Hz, 1H), 3.94 (s, 1H), 3.83 (s, 3H), 3.68 (d, *J* = 8.8 Hz, 1H), 2.64 (s, 3H), 1.49 (s, 9H), 1.41 (s, 3H), 1.39 (s, 9H), 1.21 (s, 3H).

13-C NMR (101 MHz; cd3cn): δ 168.6, 164.3, 162.9, 159.8, 157.9, 153.7, 148.7, 137.2, 134.9, 133.0, 129.4, 129.0, 128.6, 126.2, 114.7, 110.5, 84.5, 79.8, 76.88, 76.74, 70.6, 68.0, 56.4, 54.3, 54.0, 53.0, 51.9, 28.4, 28.15, 28.05, 25.6, 19.0. (Dep. MeCN): 3317 (br), 2980 (s), 2935 (s),

1762 (s), 1727 (s), 1639 (s), 1613 (s), 1579 (s), 1529 (s). HRMS (FAB^+): Calcd for $C_{38}H_{54}N_7O_{14}S_2$ [M+H]: 896.3170; Found 896.3177.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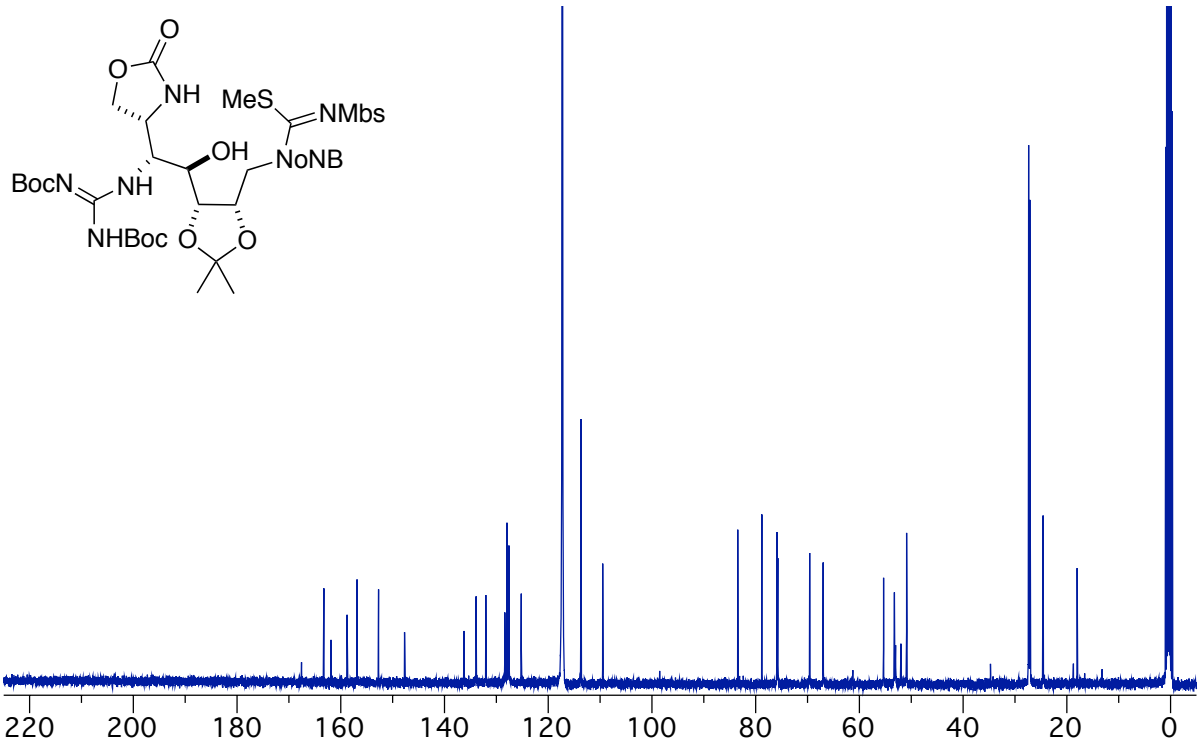
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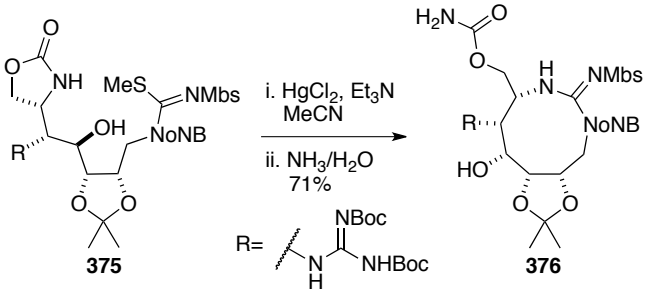
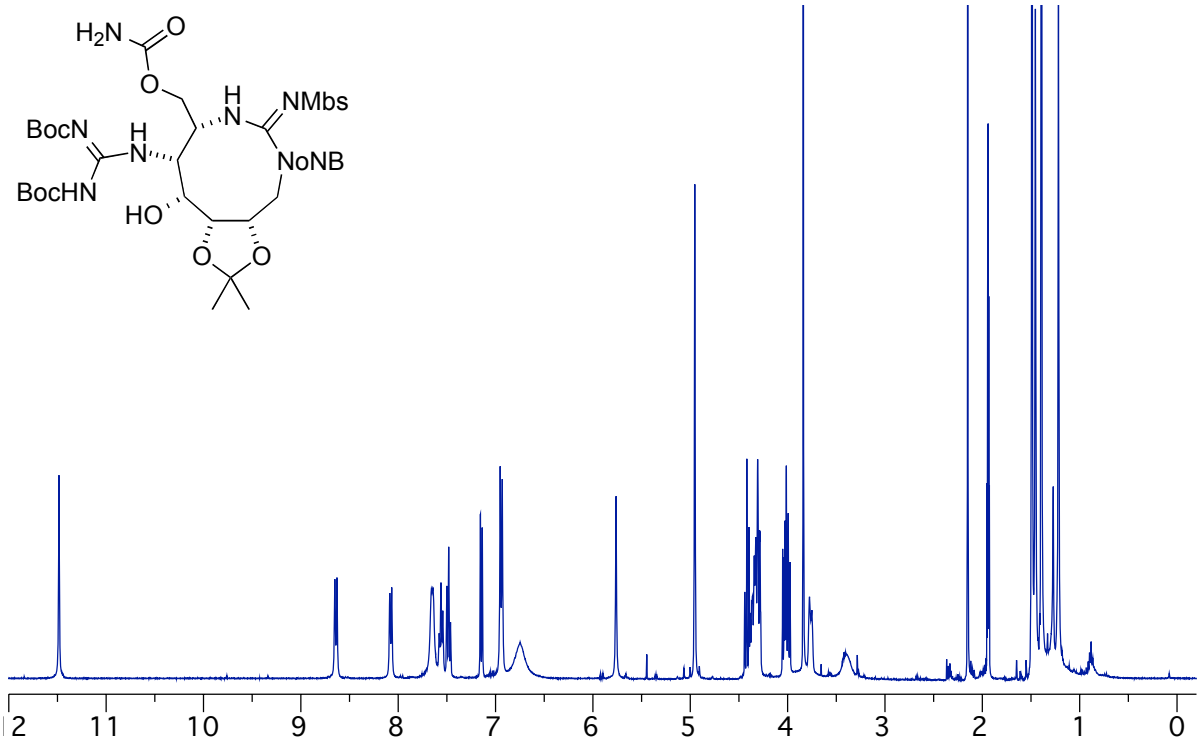
Compound 376: ((3a*S*,8*R*,9*R*,10*R*,10a*R*)-9-(2,3-(tert-butoxycarbonyl)guanidino)-10-hydroxy-6-(((4-methoxyphenyl)sulfonyl)imino)-2,2-dimethyl-5-(2-nitrobenzyl)octahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3]diazonin-8-yl)methyl carbamate.



To a solution of compound **375** (22 mg, 1eq.) and triethylamine (31 µL, 5 eq.) in acetonitrile (2 mL) was added mercury (II) chloride (13.3 mg, 2 eq.). The reaction was stirred ~20 min. until the disappearance of stating material by TLC. The reaction was quenched with conc. ammonium hydroxide (2 mL) and stirred an additional 20 min. until the disappearance of stating material by TLC. The reaction mixture was filtered through celite to remove mercury and the mixture was extracted 3x with EtOAc. The combined organic layers were dried over sodium sulfate and evaporated. The crude material was purified by flash chromatography (1-5% MeOH/DCM) to give **376** as a white solid (15.1 mg, 71.1%). ^{1}H-NMR (400 MHz; cd3cn): δ 11.48 (s, 1H), 8.64 (d, *J* = 8.8 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 7.3 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.75 (s, 2H), 5.76 (s, 1H), 4.95 (s, 1H), 4.42 (t, *J* = 8.6 Hz, 1H), 4.36 (ddd, *J* = 9.7, 6.1, 1.7 Hz, 1H), 4.34-4.28 (m, 2H), 4.03 (dd, *J* = 9.6, 5.7 Hz, 1H), 3.99 (dd, *J* = 8.2, 6.7 Hz, 1H), 3.84 (s, 3H), 3.76 (d, *J* = 10.0 Hz, 1H), 3.40 (s, 2H), 1.49 (s, 9H), 1.45 (s, 3H), 1.39 (s, 1H), 1.22 (s, 3H). 13-C NMR (101 MHz; cd3cn): δ 164.2, 163.0, 159.8, 158.3, 157.9, 153.7, 149.0, 137.1, 134.9, 133.8, 129.3, 128.67, 128.62, 126.2, 114.7, 110.5, 84.5, 79.9, 77.7, 76.8, 70.9, 68.0, 56.3, 54.3, 52.0, 51.1, 50.2, 28.4, 28.14, 28.04, 25.5. Calcd. for $C_{37}H_{53}N_8O_{14}S$ [M+H]: 865.3402 Found 865.3413.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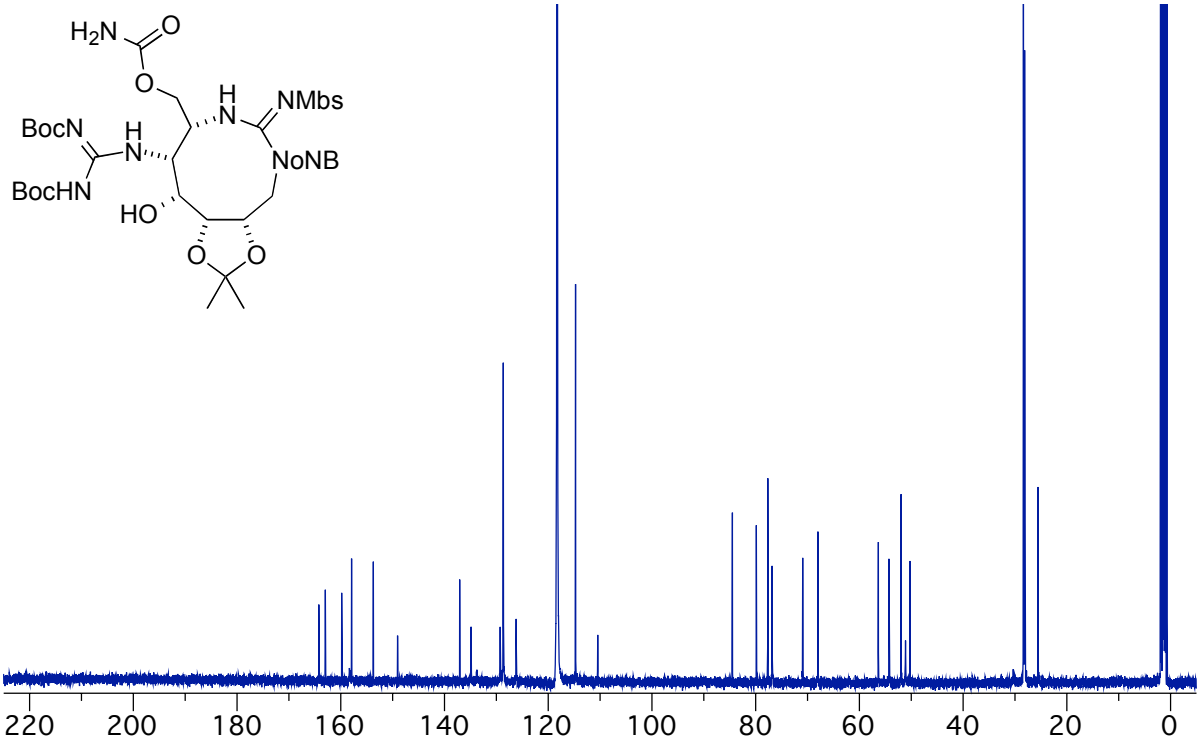
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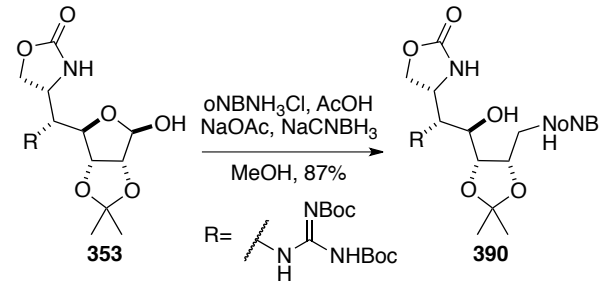
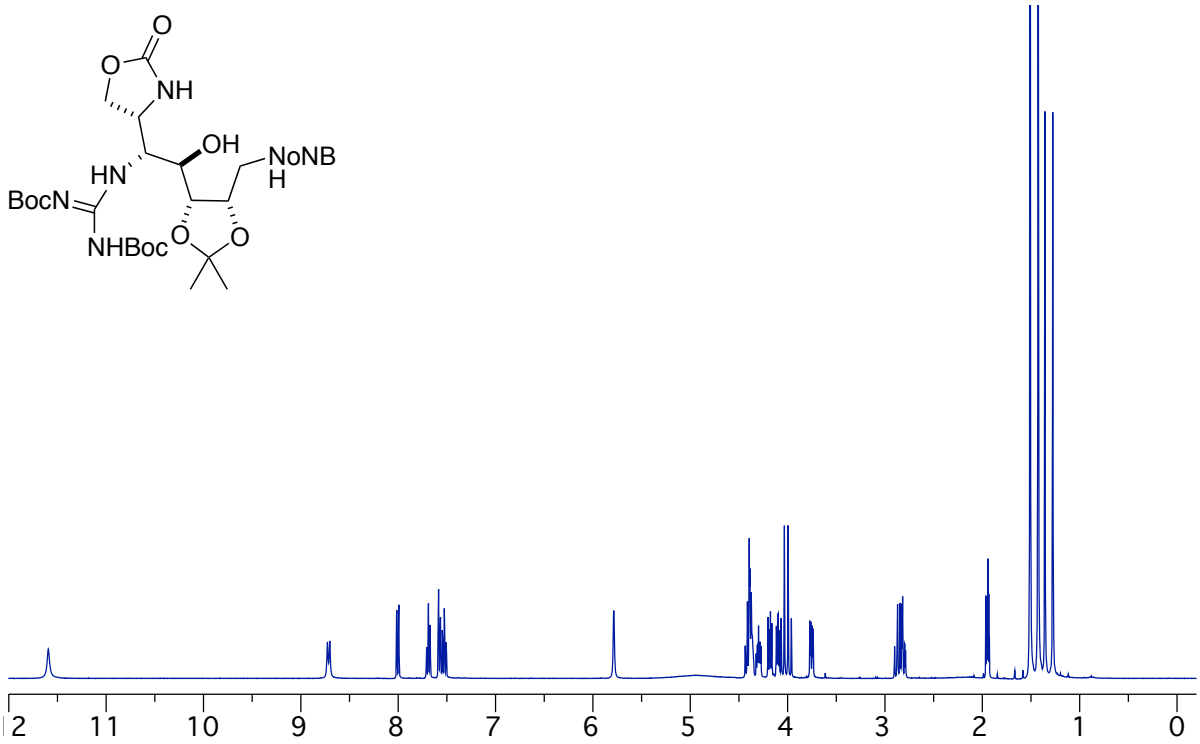
120
100
80
60
40
20
0

Compound 390: (*R*)-4-((1*R*,2*R*)-1-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-2-((4*R*,5*S*)-2,2-dimethyl-5-(((2-nitrobenzyl)amino)methyl)-1,3-dioxolan-4-yl)-2-hydroxyethyl)oxazolidin-2-one.



A solution of lactol **353** (250 mg, 1 eq.), o-nitrobenzylamine HCl (456.4 mg, 5 eq.), AcOH (693 µL, 25 eq.), sodium acetate (397 mg, 10 eq.) and sodium cyanoborohydride (152 mg, 5 eq.) in MeOH (2.4 mL) was allowed to stir 1.5 hours. The reaction was carefully quenched with sat. sodium bicarbonate, extracted with EtOAc (3x) and the combined extracts were dried over sodium sulfate and evaporated. The crude product wad purified via PTLC (10% MeOH/DCM) to give benzylamine **390** (276 mg, 87.4%). $[\alpha]_D^{25}$= -23 (c 0.54, $CHCl_3$). ^{1}H-NMR (400 MHz; cd3cn): δ 11.59 (s, 1H), 8.72 (d, *J* = 9.6 Hz, 1H), 8.00 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.69 (td, *J* = 7.5, 1.1 Hz, 1H), 7.58 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.55-7.50 (m, 1H), 5.79 (s, 1H), 4.44-4.36 (m, 3H), 4.30 (ddd, *J* = 9.9, 5.9, 3.9 Hz, 1H), 4.18 (dd, *J* = 9.7, 5.7 Hz, 1H), 4.10 (dd, *J* = 7.2, 4.9 Hz, 1H), 4.05 (d, *J* = 13.5 Hz, 1H), 3.98 (d, *J* = 13.5 Hz, 1H), 3.75 (dd, *J* = 9.7, 3.7 Hz, 1H), 2.87 (dd, *J* = 12.1, 10.1 Hz, 1H), 2.81 (dd, *J* = 12.2, 3.7 Hz, 1H), 1.51 (s, 9H), 1.43 (s, 9H), 1.36 (s, 3H), 1.28 (s, 3H). 13-C NMR (101 MHz; cd3cn): δ 164.6, 159.9, 157.9, 153.8, 150.0, 134.7, 134.5, 133.2, 129.9, 125.9, 109.6, 84.3, 79.7, 78.5, 76.7, 71.6, 67.9, 53.0, 52.2, 50.7, 49.3, 28.4, 28.20, 28.18, 25.4 HRMS (FAB$^+$): Calcd for $C_{29}H_{45}N_6O_{11}$ [M+H]: 653.3146; Found 653.3138.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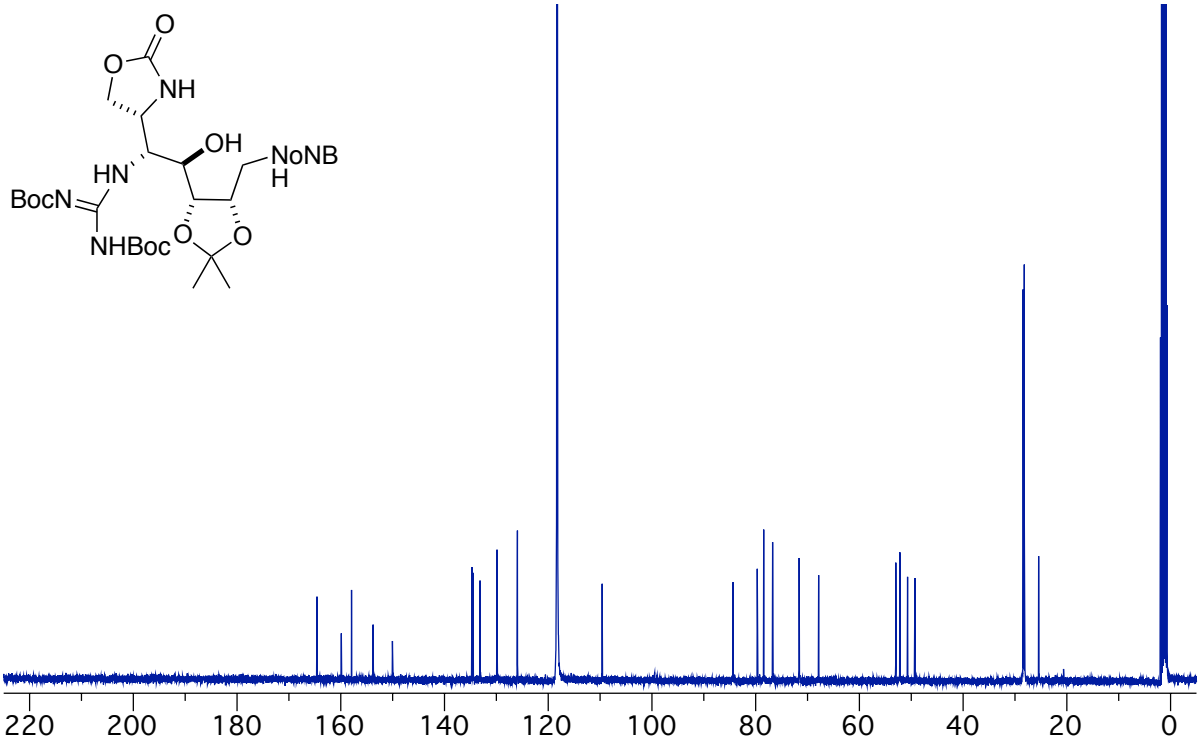
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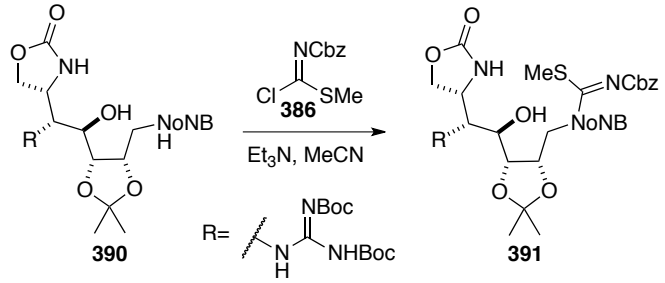
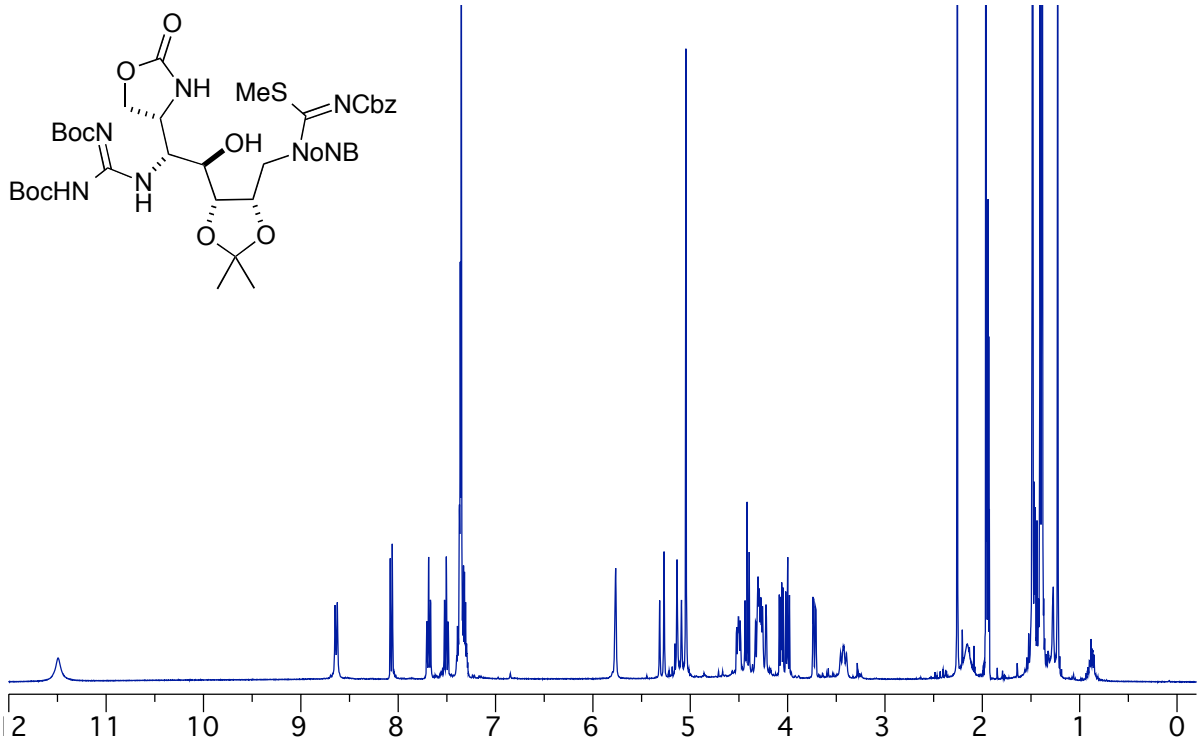
Compound 391: benzyl (((((4*S*,5*R*)-5-((1*R*,2*R*)-2-(2,3-(tert-butoxycarbonyl)guanidino)-1-hydroxy-2-((*R*)-2-oxooxazolidin-4-yl)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)(2-nitrobenzyl)amino)(methylthio)methylene)carbamate.



To a solution of amine **390** (62.4 mg, 1 eq.) and triethylamine (53 μL, 4 eq.) in MeCN (3 mL) was added **386** (57.4 mg, 2 eq.). The mixture was allowed to stir until complete by TLC. The crude compound was cleaned up via flash chromatography (10% ^{i}PrOH/Hexanes) to give the isothiourea **391** (37 mg, 45%). ^{1}H-NMR (400 MHz; cd3cn): δ 11.49 (s, 1H), 8.64 (d, *J* = 8.9 Hz, 1H), 8.07 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.69 (td, *J* = 7.6, 1.2 Hz, 1H), 7.51 (ddd, *J* = 8.1, 7.4, 1.4 Hz, 1H), 7.36 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.37-7.31 (m, 5H), 5.77 (s, 1H), 5.29 (d, *J* = 18.1 Hz, 1H), 5.12 (d, *J* = 18.1 Hz, 1H), 5.04 (s, 2H), 4.50 (ddd, *J* = 9.8, 5.9, 2.1 Hz, 1H), 4.42 (t, *J* = 8.6 Hz, 1H), 4.33-4.27 (m, 2H), 4.24 (d, *J* = 14.3 Hz, 1H), 4.07 (dd, *J* = 9.9, 5.9 Hz, 1H), 4.00 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.72 (dd, *J* = 9.9, 3.0 Hz, 1H), 3.43 (dd, *J* = 13.9, 11.0 Hz, 1H), 2.26 (s, 3H), 1.48 (s, 9H), 1.41 (s, 3H), 1.39 (s, 9H), 1.23 (s, 3H). 13-C NMR (101 MHz; cd3cn): δ 168.5, 164.3, 159.8, 158.8, 157.9, 153.7, 149.1, 138.1, 134.9, 133.3, 129.38, 129.33, 129.13, 129.09, 128.9, 126.2, 110.4, 84.4, 79.8, 77.0, 70.7, 68.15, 67.99, 54.4, 53.2, 51.95, 51.92, 28.4, 28.14, 28.09, 25.6, 16.0.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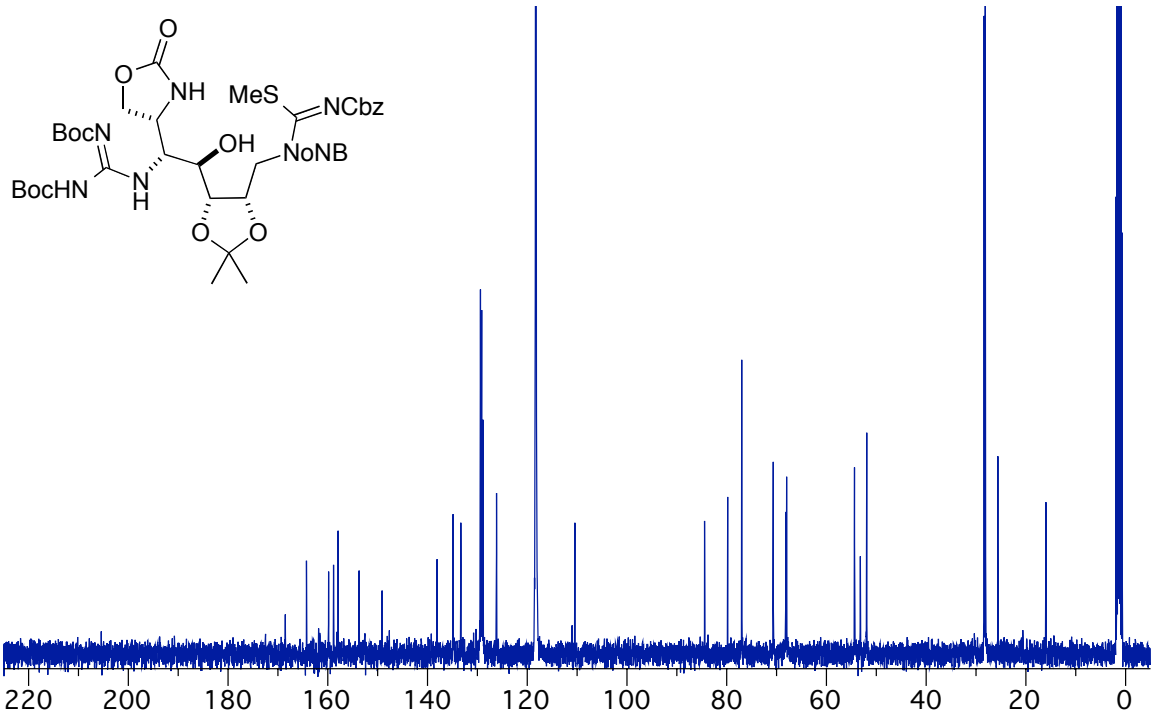
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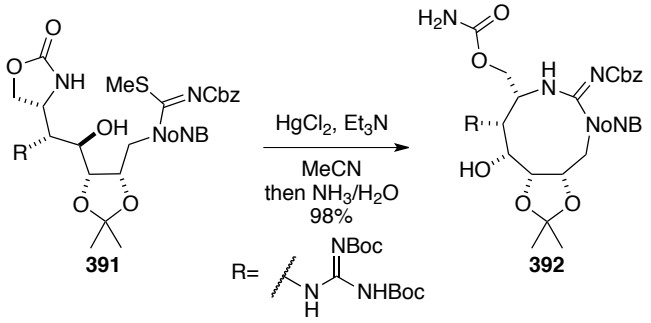
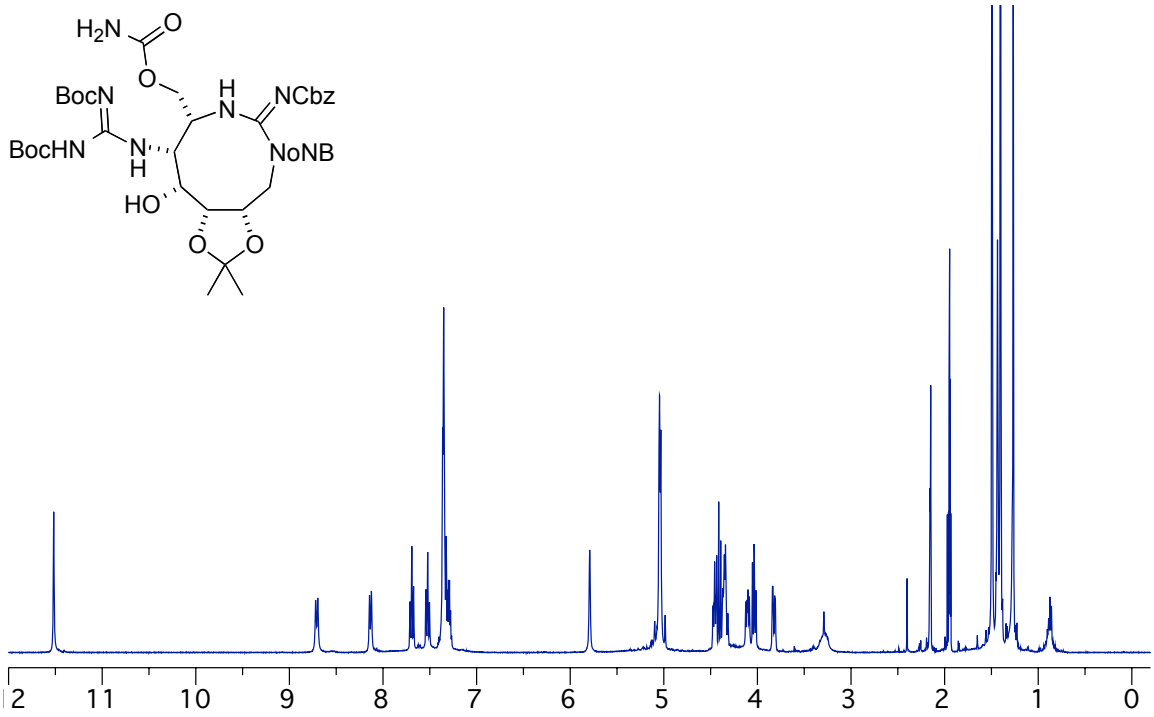
Compound 392: ((3a*S*,8*R*,9*R*,10*R*,10a*R*)-9-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-10-hydroxy-6-(((4-methoxyphenyl)sulfonyl)imino)-2,2-dimethyl-5-(2-nitrobenzyl)octahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3]diazonin-8-yl)methyl carbamate.



To a solution of isothiourea **391** (15 mg, 1eq.) and triethylamine (22 μL, 9 eq.) in MeCN (2 mL) was added mercuric chloride (9.5 mg, 2 eq.). The mixture was stirred 20 min, then was quenched with adding conc. ammonium hydroxide (3 mL) and allowed to stir another 20 min. The reaction was diluted with EtOAc, filtered and evaporated. The crude alcohol was purified via flash chromatography to give alcohol **392** (14.2 mg, 98.2%). ^{1}H-NMR (400 MHz; cd3cn): δ 11.52 (s, 1H), 8.71 (d, *J* = 8.9 Hz, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.36-7.27 (m, 6H), 5.79 (s, 1H), 5.07 (d, *J* = 18.8 Hz, 1H), 5.05 (s, 2H), 5.01 (d, *J* = 18.7 Hz, 1H), 4.46 (ddd, *J* = 8.0, 6.1, 2.2 Hz, 1H), 4.41 (t, *J* = 8.7 Hz, 1H), 4.37-4.32 (m, 2H), 4.11 (dd, *J* = 9.7, 5.8 Hz, 1H), 4.03 (dd, *J* = 8.1, 7.0 Hz, 1H), 3.82 (dd, *J* = 9.8, 2.7 Hz, 1H), 3.29 (s, 2H), 1.49 (s, 9H), 1.43 (s, 3H), 1.40 (s, 9H), 1.27 (s, 3H). 13-C NMR (101 MHz; cd3cn): δ 164.3, 163.0, 159.8, 157.9, 153.7, 149.1, 138.9, 135.1, 133.7, 129.38, 129.35, 128.77, 128.61, 128.59, 126.3, 110.3, 84.4, 79.8, 78.5, 77.3, 71.5, 68.0, 67.0, 53.9, 52.1, 51.0, 49.9, 28.4, 28.16, 28.08, 25.7. Calcd. for $C_{38}H_{53}N_8O_{13}$ [M+H]: 829.3732 Found 829.3726.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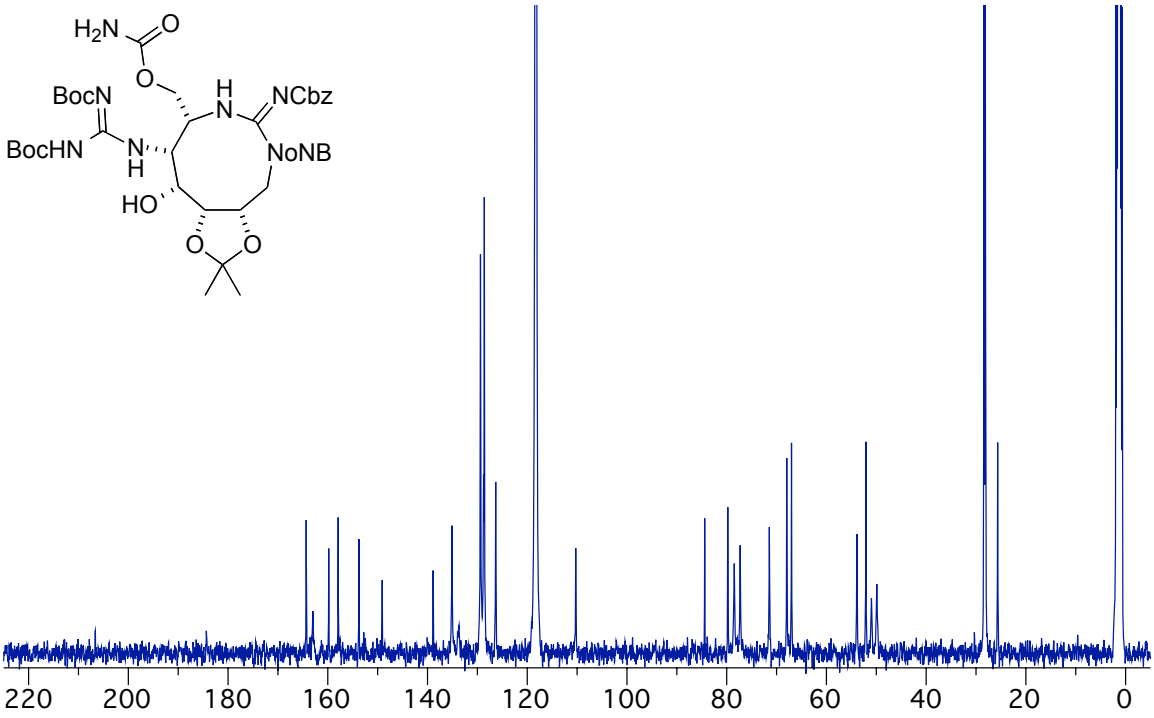
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100
80
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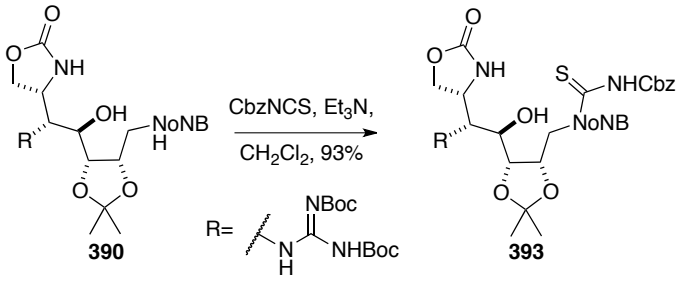
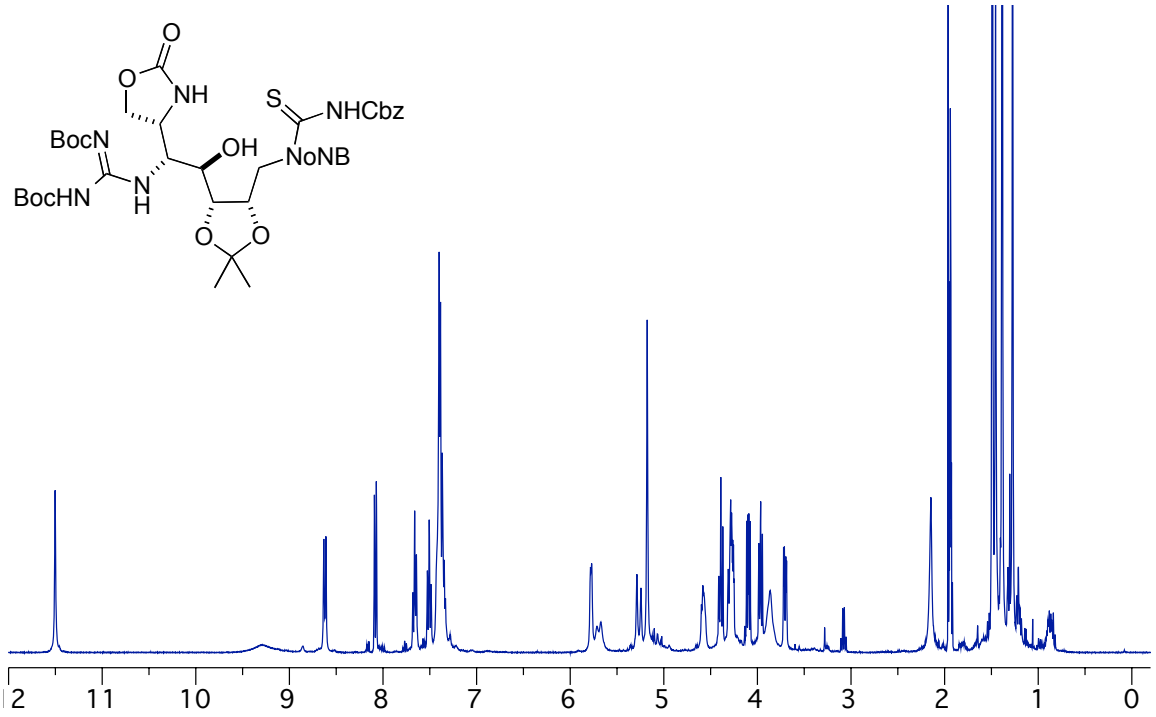
20
0

Compound 393: 1-(((4*S*,5*R*)-5-((1*R*,2*R*)-2-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-1-hydroxy-2-((*R*)-2-oxooxazolidin-4-yl)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3-(benzoxycarbonyl)-1-(2-nitrobenzyl)thiourea.



To a solution of **390** (10 mg, 1 eq.) in CH_2Cl_2 (1 mL) was added CbzNCS (3.8 mg, 1.2 eq.). The reaction was stirred for 5 min. and then evaporated. The crude material was purified via flash chromatography (1-5% MeOH/DCM) to give **393** (12.2 mg, 92.6%). ^{1}H-NMR (400 MHz; cd3cn): δ 11.50 (s, 1H), 9.29 (s, 1H), 8.62 (d, *J* = 8.9 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.45-7.32 (m, 5H), 5.78 (d, *J* = 5.0 Hz, 1H), 5.69 (d, *J* = 16.8 Hz, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.18 (s, 2H), 4.58 (dd, *J* = 10.7, 5.9 Hz, 1H), 4.39 (t, *J* = 8.7 Hz, 1H), 4.32-4.26 (m, 3H), 4.10 (dd, *J* = 9.5, 6.2 Hz, 1H), 3.97 (dd, *J* = 8.4, 7.1 Hz, 1H), 3.86 (s, 1H), 3.70 (dd, *J* = 9.5, 3.5 Hz, 1H), 1.49 (s, 9H), 1.46 (s, 3H), 1.39 (s, 9H), 1.27 (s, 3H). Calcd. for $C_{38}H_{52}N_7O_{13}S$ [M+H]: 846.3344 Found 846.3344.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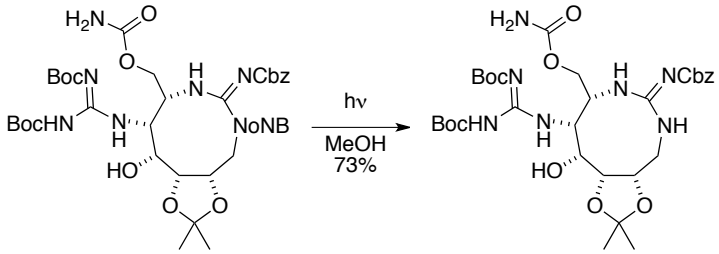
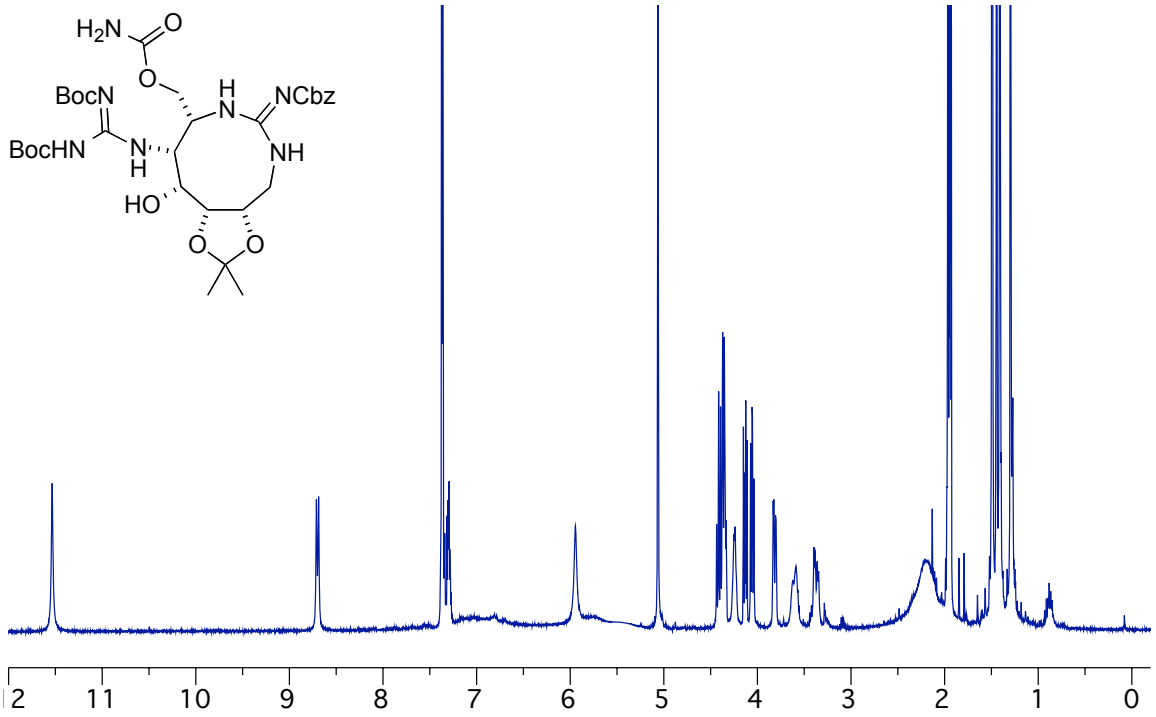
1
0

Compound 395: benzyl ((3a*S*,8*R*,9*R*,10*R*,10a*R*)-9-(2,3-(tert-butoxycarbonyl)guanidino)-8-((carbamoyloxy)methyl)-10-hydroxy-2,2-dimethylhexahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3]diazonin-6(7*H*)-ylidene)carbamate.



394 **395**

Argon was bubbled through a vial containing **394** (14 mg) in THF (1 mL, wet) for 5 min. The vial was sealed and irradiated by a Hg vapor lamp for 30 min. The mixture was evaporated and purified via flash chromatography (2-5% MeOH/DCM) to give **395** (8.5 mg, 72.5%). ^{1}H-NMR (400 MHz; cd3cn): δ 11.53 (s, 1H), 8.70 (d, *J* = 9.1 Hz, 1H), 7.38-7.27 (m, 5H), 5.94 (s, 1H), 5.06 (s, 2H), 4.40 (dd, *J* = 16.9, 8.8 Hz, 1H), 4.37-4.33 (m, 2H), 4.13 (dd, *J* = 9.9, 5.7 Hz, 1H), 4.06 (dd, *J* = 7.8, 6.6 Hz, 1H), 3.82 (dd, *J* = 9.8, 2.7 Hz, 1H), 3.60 (d, *J* = 13.9 Hz, 1H), 3.37 (dd, *J* = 14.4, 5.6 Hz, 1H). 13-C NMR (101 MHz; cd3cn): δ 164.4, 162.5, 159.9, 158.0, 153.8, 138.9, 129.4, 128.67, 128.62, 109.6, 84.4, 79.7, 78.0, 77.4, 71.1, 68.0, 66.9, 53.9, 52.2, 41.2, 28.4, 28.2, 25.7. Calcd. for $C_{31}H_{48}N_7O_{11}$ [M+H]: 694.3412 Found 694.3427.


H2N
O
O
BocN
H
N
NCbz
BocHN
N
H
NH
HO
O
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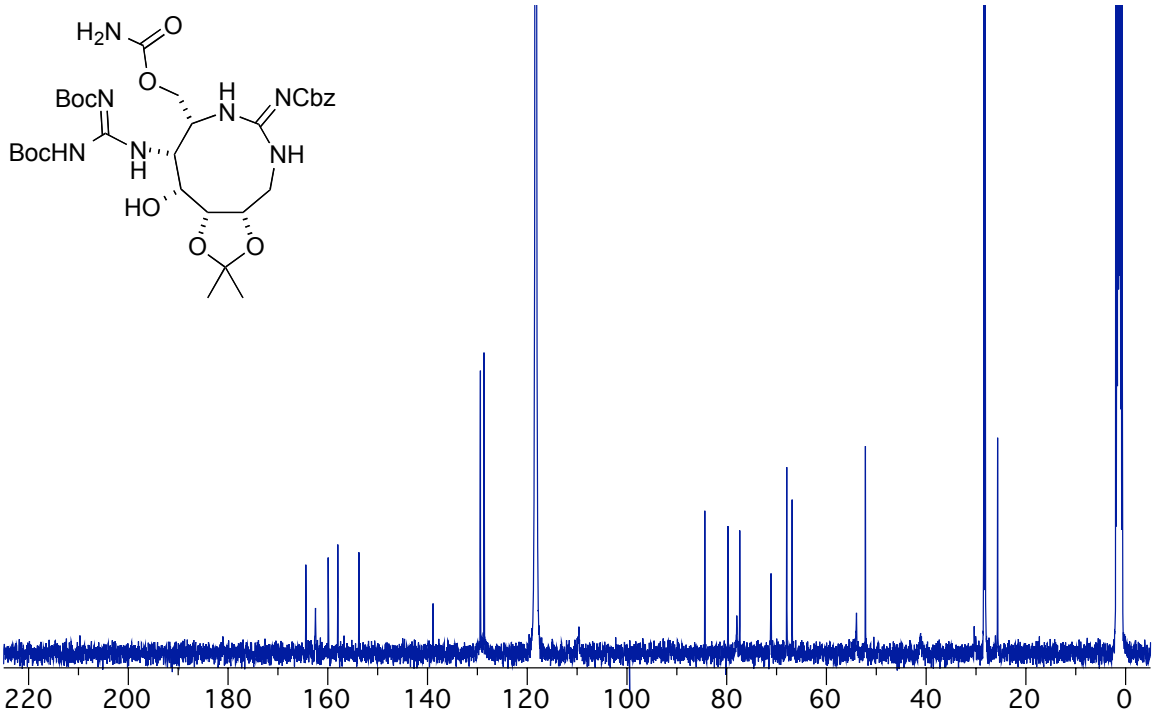
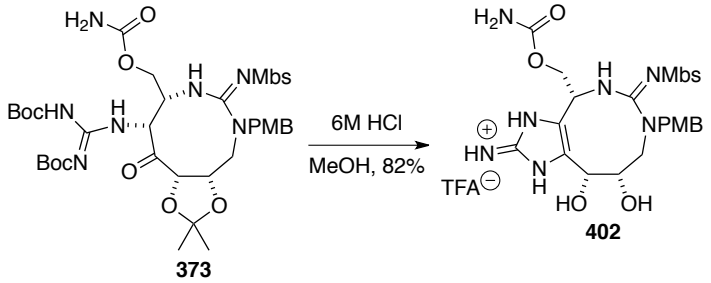
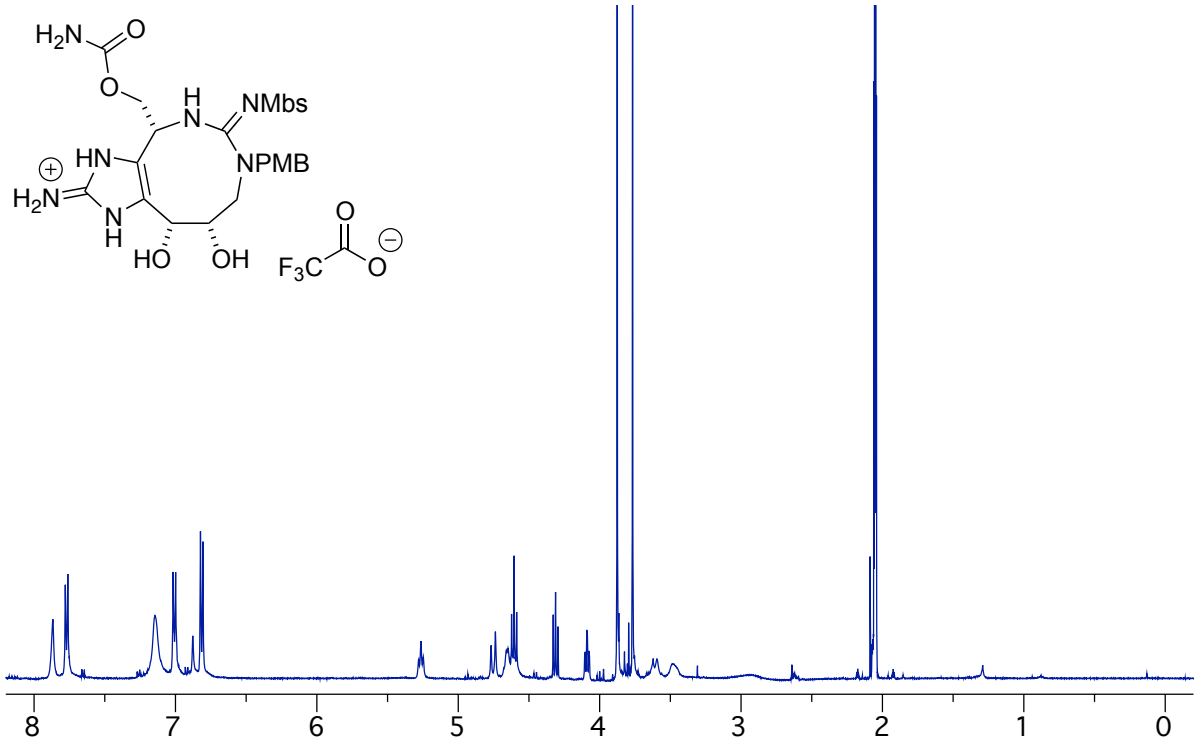
12
11
10
9
8
7
6
5
4
3
2
1
0


H2N
O
O
BocN
H
N
NCbz
BocHN
N
H
NH
HO
O
O
220
200
180
160
140
120
100
80
60
40
20
0

Compound 402: (4*R*,9*S*,10*R*)-4-((carbamoyloxy)methyl)-9,10-dihydroxy-7-(4-methoxybenzyl)-6-(((4-methoxyphenyl)sulfonyl)imino)-3,4,5,6,7,8,9,10-octahydroimidazo[4,5-*e*][1,3]diazonin-2(1*H*)-iminium 2,2,2-trifluoroacetate.



To a solution of **373** (10 mg) in MeOH (1.5 mL) was added 6M HCl (0.5 mL). The mixture was allowed to stir for 3 days and then evaporated. The mixture was purified via RP-18 flash chromatography (100-80% 0.1% TFA in H_2O/MeCN) to give **402** (5.7 mg, 82.0%) as the TFA salt. ^{1}H-NMR (500 MHz; aceton-d_6): δ 7.87 (s, 1H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.14 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.26 (t, *J* = 8.3 Hz, 1H), 4.75 (d, *J* = 15.4 Hz, 1H), 4.65 (d, *J* = 5.9 Hz, 1H), 4.63 (s, 1H), 4.60 (t, *J* = 8.9 Hz, 1H), 4.31 (t, *J* = 8.4 Hz, 1H), 4.09 (td, *J* = 7.5, 2.2 Hz, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.61 (d, *J* = 14.5 Hz, 1H), 3.47 (dd, *J* = 14.1, 7.5 Hz, 1H). 13-C NMR (126 MHz; acetone): δ 161.8, 161.3, 159.1, 158.0, 157.8, 148.4, 129.1, 127.8, 125.0, 121.7, 113.73, 113.56, 72.2, 68.3, 66.1, 55.0, 54.6, 50.6, 50.1, 46.8. Calcd. for $C_{25}H_{32}N_7O_8S$ [M+H]: 590.2028 Found 590.2029.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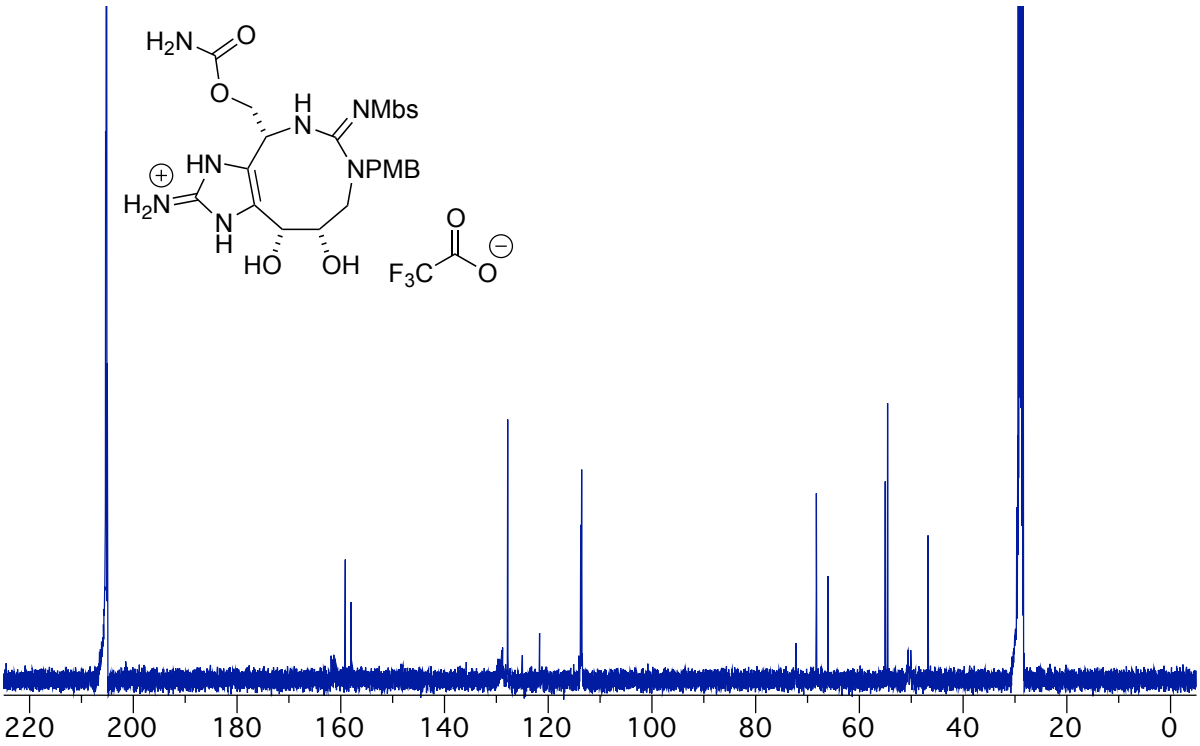
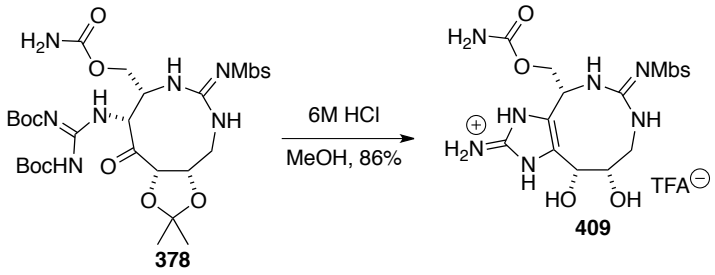
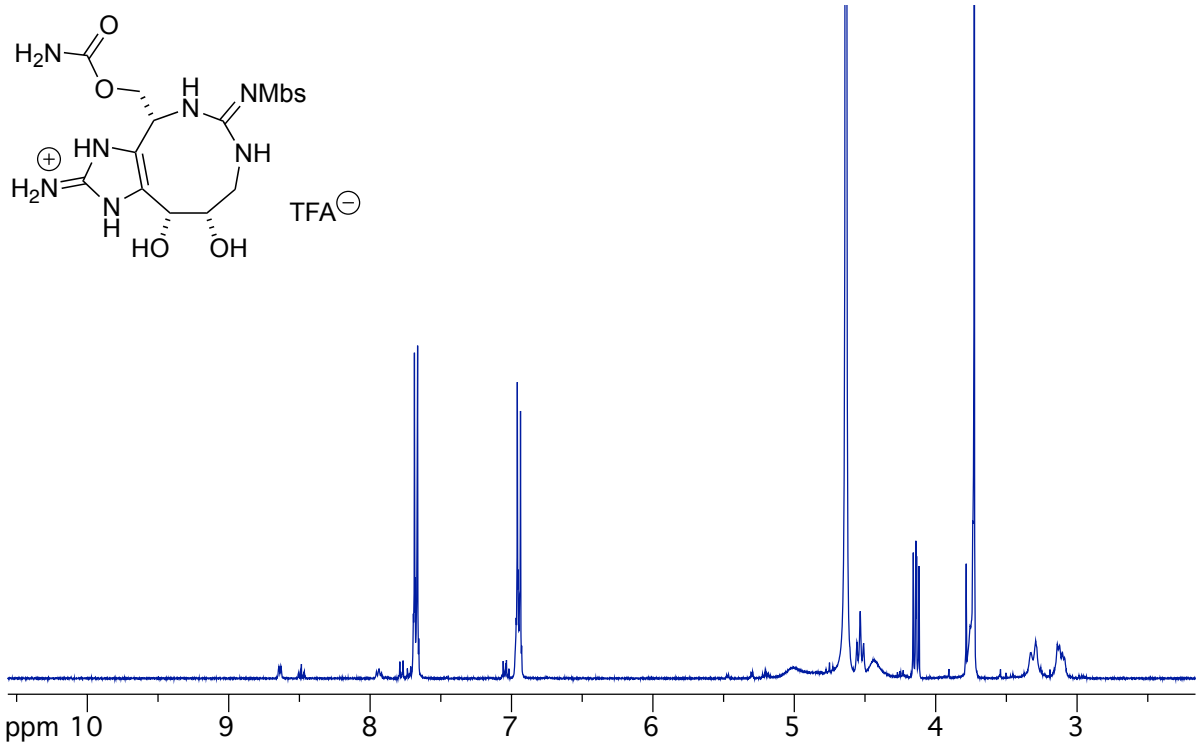
O
O
H
N
NMbs
HN
NPMB
H2N
N
H
HO
OH
O
F3C
O
8
7
6
5
4
3
2
1
0


H2N
O
O
H
N
NMbs
HN
NPMB
H2N
N
H
HO
OH
O
F3C
O
220
200
180
160
140
120
100
80
60
40
20
0

Compound 409: (4*R*,9*S*,10*R*)-4-((carbamoyloxy)methyl)-9,10-dihydroxy-6-(((4-methoxypheny l)sulfonyl)imino)-3,4,5,6,7,8,9,10-octahydroimidazo[4,5-*e*][1,3]diazonin-2(1*H*)-iminium 2,2,2-trifluoroacetate.



To a solution of **378** (29 mg) in THF (3 mL) was added 6M HCl (3 mL). The mixture was allowed to stir for 24 hr. and then evaporated. The mixture was purified via RP-18 flash chromatography (100-80% 0.1% TFA in H_2O/MeCN) to give **409** (16 mg, 85.5%) as the TFA salt. ^{1}H-NMR (400 MHz; D_2O): δ 7.67 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 5.01 (s, 1H), 4.53 (t, *J* = 9.5 Hz, 1H), 4.44 (s, 1H), 4.14 (dd, *J* = 9.2, 7.2 Hz, 1H), 3.78-3.74 (m, 1H), 3.73 (s, 3H), 3.31 (d, *J* = 12.8 Hz, 1H), 3.11 (dd, *J* = 13.9, 5.8 Hz, 1H). 13-C NMR (101 MHz; D_2O): δ 162.3, 161.0, 157.3, 147.4, 133.0, 127.9, 123.5, 121.8, 114.3, 71.4, 69.5, 64.7, 55.6, 46.6, 43.7. Calcd. for $C_{17}H_{24}N_7O_7S$ [M+H]: 470.1458 Found 470.1445.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HO
OH
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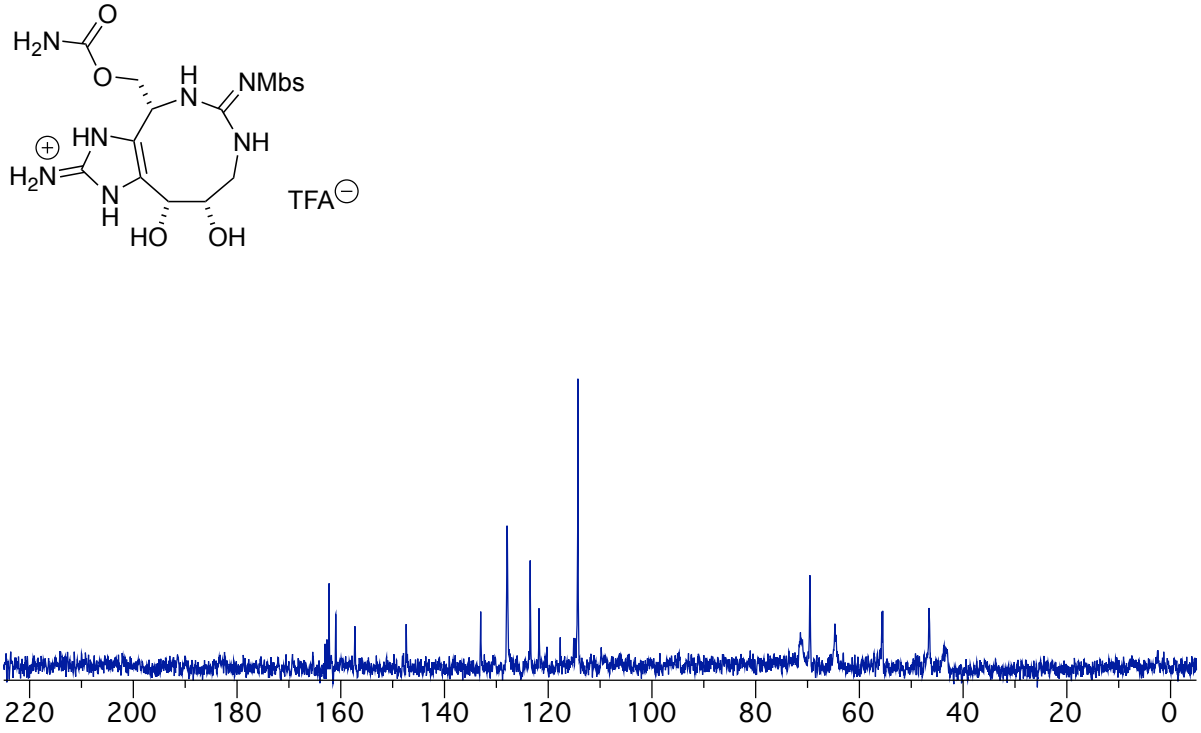
5
4
3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N
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HN
NH
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HO
OH
TFA
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200
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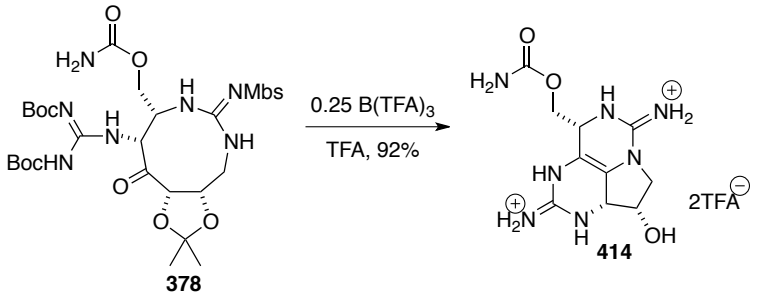
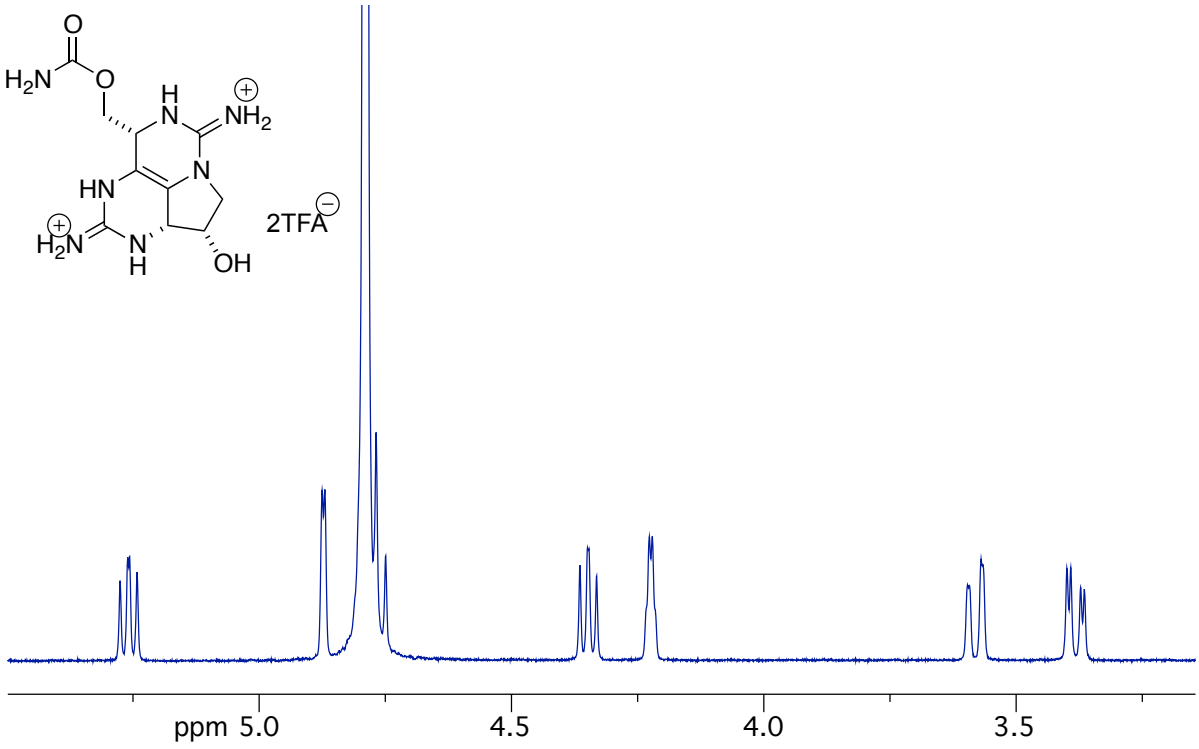
160
140
120
100
80
60
40
20
0

Compound 414: (1*S*,5*R*,8a*R*)-5-((carbamoyloxy)methyl)-1-hydroxy-4,5,8,8a-tetrahydro-1*H*-2a, 4,6,8-tetraazaacenaphthylene-3,7(2*H*,6*H*)-diiminium 2,2,2-trifluoroacetate.



Ketone **378** (10 mg) was cooled to 0°C and 0.25 $B(TFA)_3$ in TFA (1 mL) was added. The mixture was allowed to warm to rt slowly (leave in the ice bath) and stirred a total of 48 hours. The mixture was cooled to 0°C and quenched with methanol. The reaction was evaporated and diluted with methanol 3x. The crude solid was purified via RP-18 flash chromatography (100-80% 0.1% TFA in H_2O/MeCN) to give **414** (5 mg, 92%). ^{1}H-NMR (500 MHz; D_2O): δ 5.26 (dd, *J* = 9.5, 7.3 Hz, 1H), 4.87 (d, *J* = 2.9 Hz, 1H), 4.77 (t, *J* = 9.5 Hz, 1H), 4.35 (dd, *J* = 9.5, 7.4 Hz, 1H), 4.22 (q, *J* = 3.1 Hz, 1H), 3.58 (dd, *J* = 13.6, 2.1 Hz, 1H), 3.38 (dd, *J* = 13.5, 3.8 Hz, 1H). 13-C NMR (126 MHz; d2o): δ 161.84, 161.75, 158.01, 158.01, 157.54, 157.54, 91.80, 91.80, 72.57, 72.57, 69.84, 69.84, 68.09, 68.09, 63.05, 63.05, 51.62, 51.62, 44.85, 44.85**.** Calcd. for $C_{10}H_{16}N_7O_3$ [M+H]: 282.1304 Found 282.1311.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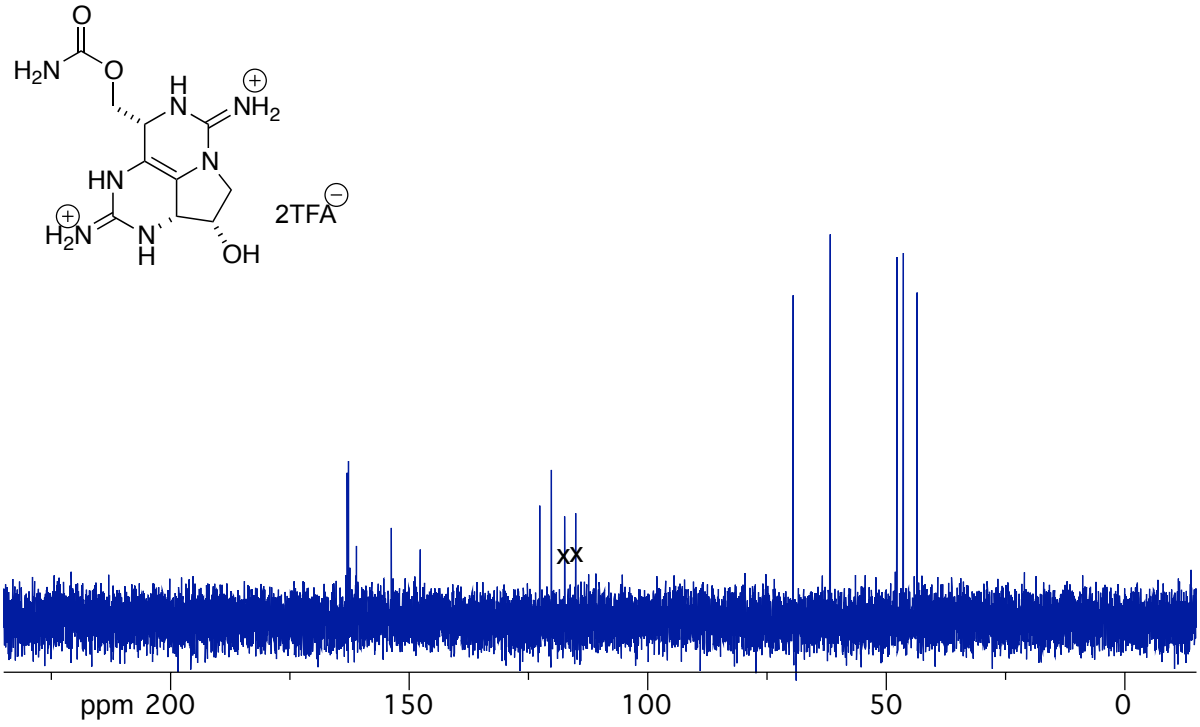
3.5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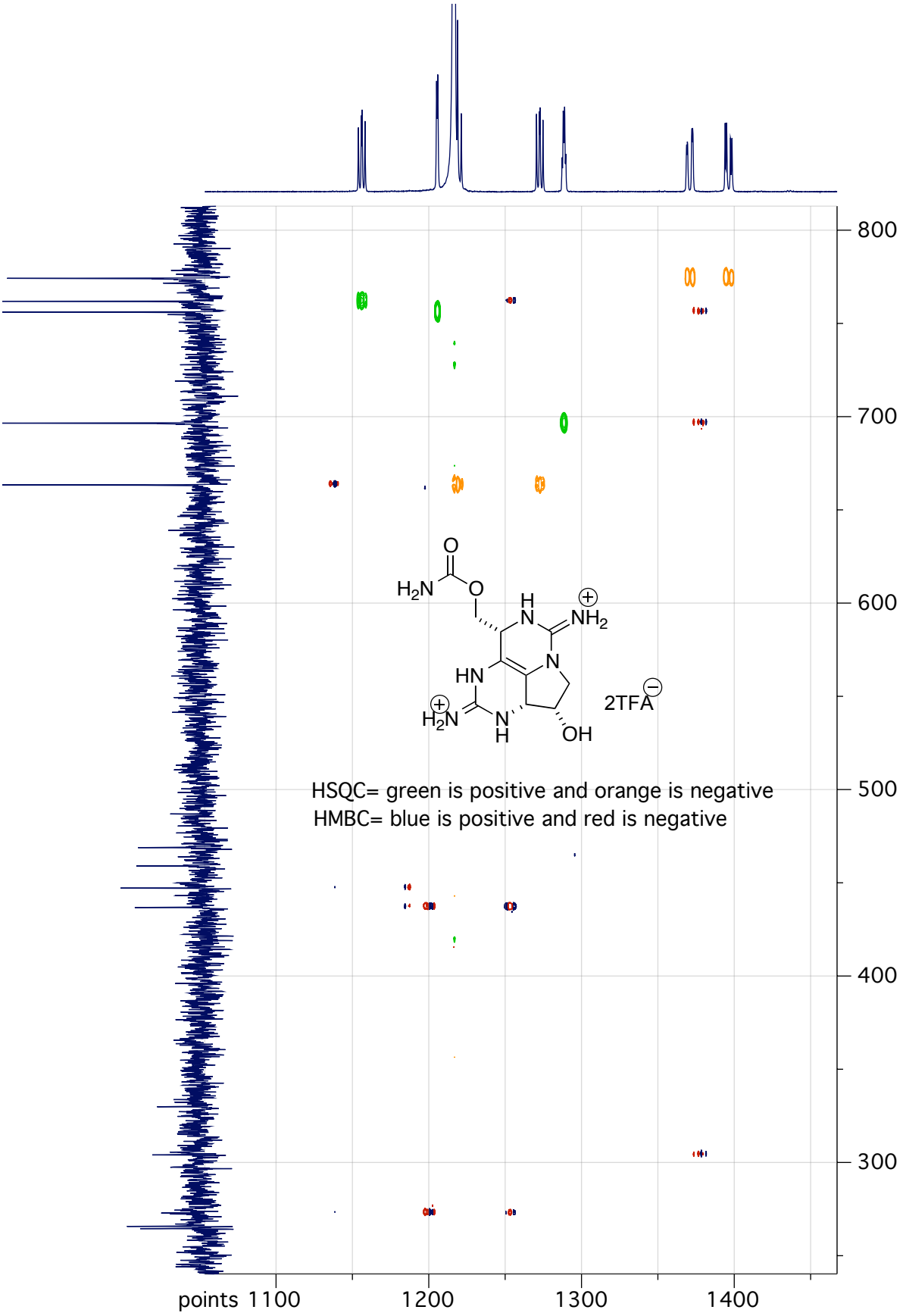
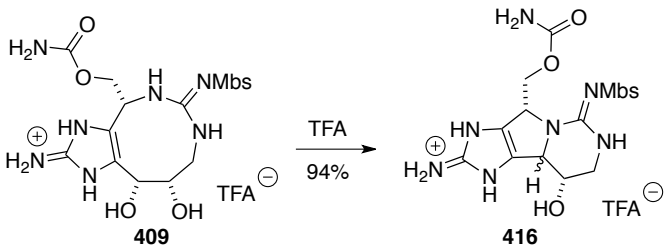
xx
ppm 200
150
100
50
0


800
700
600
500
400
300
points 1100
1200
1300
1400
HSQC= green is positive and orange is negative
HMBC= blue is positive and red is negative
2TFA

Compound 416: (4*R*,9*S*)-4-((carbamoyloxy)methyl)-9-hydroxy-6-(((4-methoxyphenyl)sulfonyl)imino)-4,6,7,8,9,9a-hexahydro-1*H*-imidazo[4',5':3,4]pyrrolo[1,2-*c*]pyrimidin-2(3*H*)-iminium 2,2,2-trifluoroacetate.

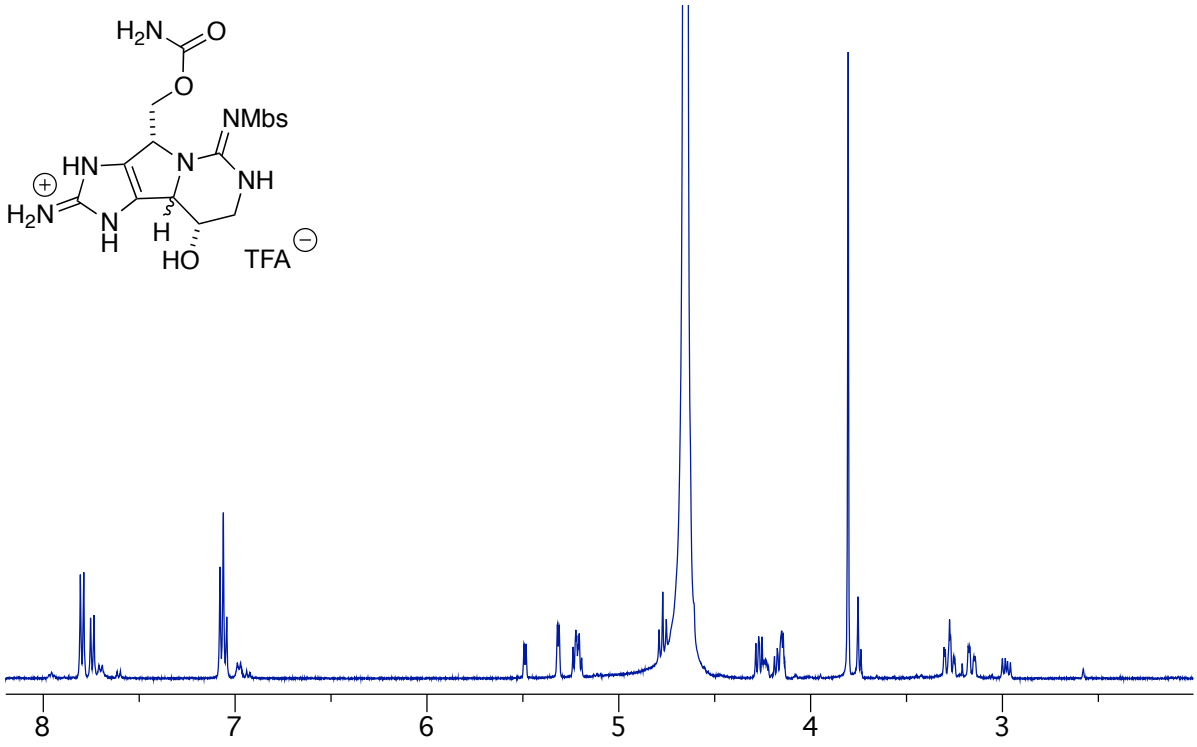


409 **416**

To a flask containing compound **409** (10 mg) was added TFA (2 mL). The reaction was stirred 48 hr. and evaporated. The compound was purified via HPLC (YMC-Pack ODS-AM-322, 150x10mm, 5Å; 95-0% 0.1% TFA H_2O/MeCN over 45 min; t_r= 14.409 min.) to give **416** (9 mg, 94%) as a 1:1 mixture of diastereomers.

anti-**416**: ^{1}H-NMR (500 MHz; D_2O): δ 7.80 (d, *J* = 9.0 Hz, 2H), 7.07 (d, *J* = 8.9 Hz, 2H), 5.32 (d, *J* = 4.1 Hz, 1H), 5.22 (dd, *J* = 9.2, 6.9 Hz, 1H), 4.77 (t, *J* = 9.4 Hz, 1H), 4.27 (dd, *J* = 9.2, 7.2 Hz, 1H), 4.15 (dd, *J* = 7.3, 3.1 Hz, 1H), 3.80 (s, 3H), 3.29 (dd, *J* = 14.2, 3.2 Hz, 1H), 3.16 (dd, *J* = 14.2, 4.1 Hz, 2H). 13-C NMR (126 MHz; d2o): δ 165.5, 162.7, 161.0, 152.0, 130.6, 125.6, 123.1, 119.1, 115.1, 69.4, 63.7, 56.0, 54.1, 46.5, 42.0

syn-**416**: ^{1}H-NMR (500 MHz; D_2O): δ 7.74 (d, *J* = 9.0 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 5.49 (d, *J* = 5.1 Hz, 1H), 5.21 (dd, *J* = 9.2, 6.0 Hz, 1H), 4.63 (t, *J* = 9.5 Hz, 1H), 4.24 (dt, *J* = 7.9, 4.1 Hz, 1H), 4.17 (dd, *J* = 7.9, 6.8 Hz, 1H), 3.80 (s, 3H), 3.26 (dd, *J* = 13.0, 3.5 Hz, 1H), 2.98 (dd, *J* = 13.4, 7.6 Hz, 1H). 13-C NMR (126 MHz; d2o): δ 165.5, 162.7, 161.0, 152.0, 148.2, 130.6, 125.6, 123.1, 119.1, 115.1, 69.4, 63.7, 56.0, 54.1, 46.5, 42.0. Calcd. for $C_{17}H_{22}N_7O_6S$ [M+H]: 452.1347 Found 452.1353.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HO
TFA
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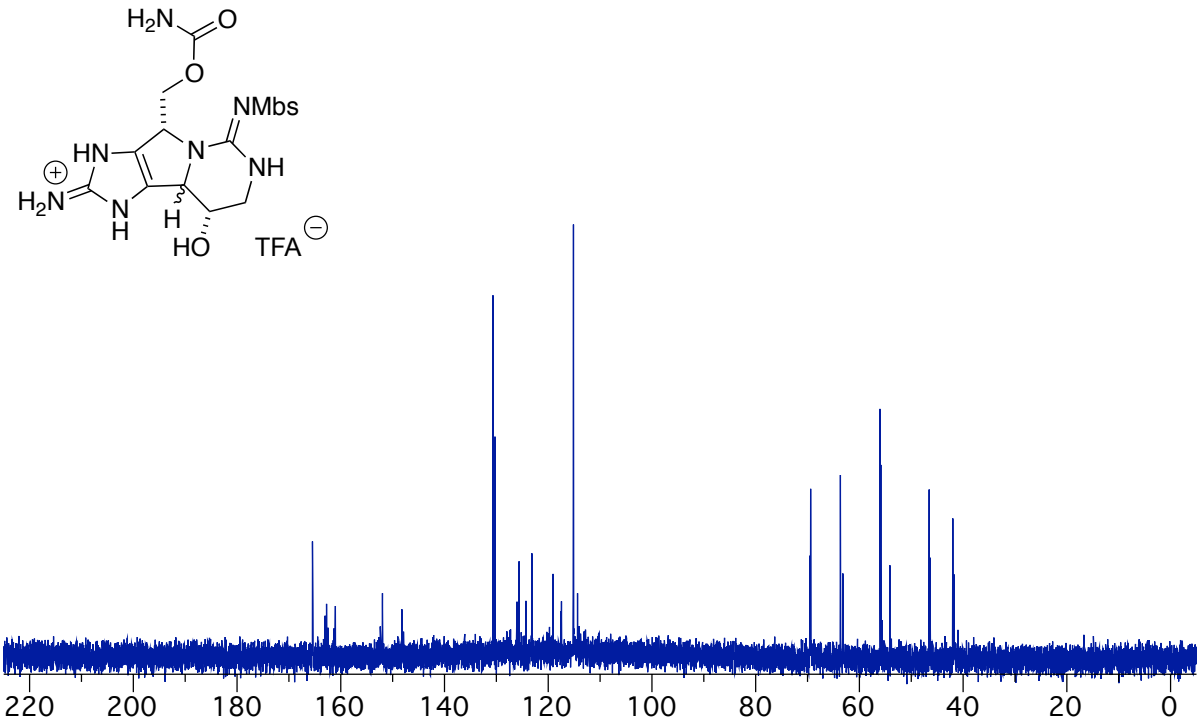
4
3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NH
H2N
N
H
H
HO
TFA
220
200
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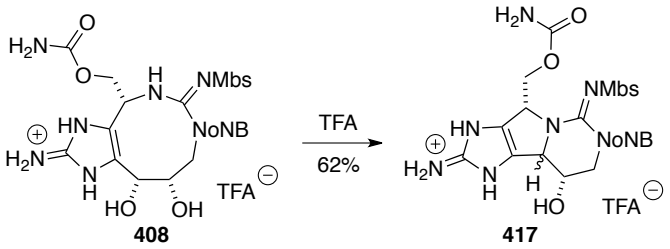
140
120
100
80
60
40
20
0

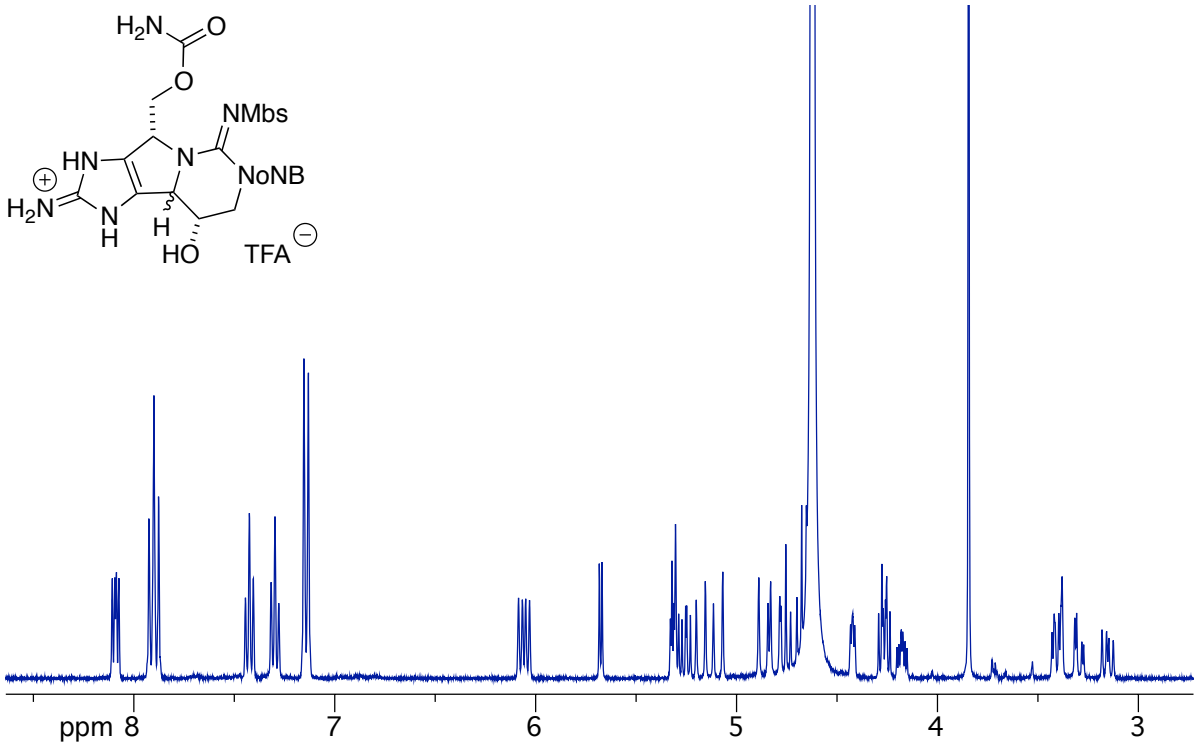
Compound 417: (4*R*,9*S*)-4-((carbamoyloxy)methyl)-9-hydroxy-6-(((4-methoxyphenyl)sulfonyl)imino)-7-(2-nitrobenzyl)-4,6,7,8,9,9a-hexahydro-1*H*-imidazo[4',5':3,4]pyrrolo[1,2-*c*]pyrimidin-2(3*H*)-iminium 2,2,2-trifluoroacetate.



To a flask containing compound **408** (10mg) was added TFA (2 mL). The reaction was stirred 24 hr. and evaporated. The compound was purified via HPLC (YMC-Pack ODS-AM-322, 150x10mm, 5Å; 95-0% 0.1% TFA H_2O/MeCN over 45 min; t_r= 14.409 min.) to give **417** (6 mg, 62%) as a 1:1 mixture of diastereomers.

anti-**417**: ^{1}H-NMR (400 MHz; D_2O): δ 8.10 (d, *J* = 4.9 Hz, 1H), 7.91 (d, *J* = 9.1 Hz, 2H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 9.0 Hz, 2H), 6.08 (d, *J* = 7.9 Hz, 1H), 5.31 (d, *J* = 7.2 Hz, 1H), 5.31 (dd, *J* = 9.5, 6.7 Hz, 1H), 5.09 (d, *J* = 18.5 Hz, 1H), 4.87 (d, *J* = 18.4 Hz, 1H), 4.76 (t, *J* = 9.5 Hz, 1H), 4.28 (t, *J* = 6.7 Hz, 1H), 4.18 (ddd, *J* = 8.7, 7.5, 3.9 Hz, 1H), 3.85 (s, 3H), 3.41 (dd, *J* = 13.7, 6.5 Hz, 1H), 3.15 (dd, *J* = 13.4, 9.0 Hz, 1H).

syn-**417**: ^{1}H-NMR (400 MHz; D_2O): δ 8.08 (d, *J* = 4.9 Hz, 1H), 7.89 (d, *J* = 9.4 Hz, 2H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 9.0 Hz, 2H), 6.04 (d, *J* = 7.7 Hz, 1H), 5.68 (d, *J* = 5.4 Hz, 1H), 5.25 (dd, *J* = 9.5, 7.3 Hz, 1H), 5.18 (d, *J* = 18.1 Hz, 1H), 4.81 (d, *J* = 18.2 Hz, 1H), 4.68 (t, *J* = 9.4 Hz, 1H), 4.42 (dd, *J* = 4.9, 3.6 Hz, 1H), 4.25 (t, *J* = 6.6 Hz, 1H), 3.85 (s, 3H), 3.40 (d, *J* = 14.0 Hz, 1H), 3.30 (dd, *J* = 14.1, 3.7 Hz, 1H).


H2N
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NMbs
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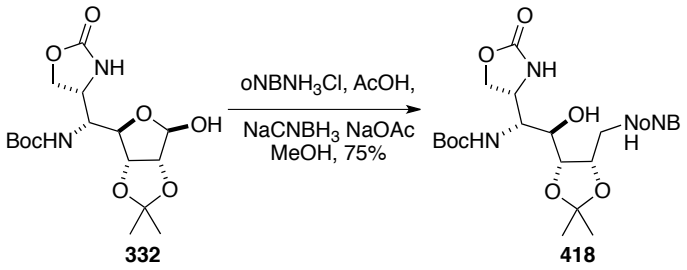
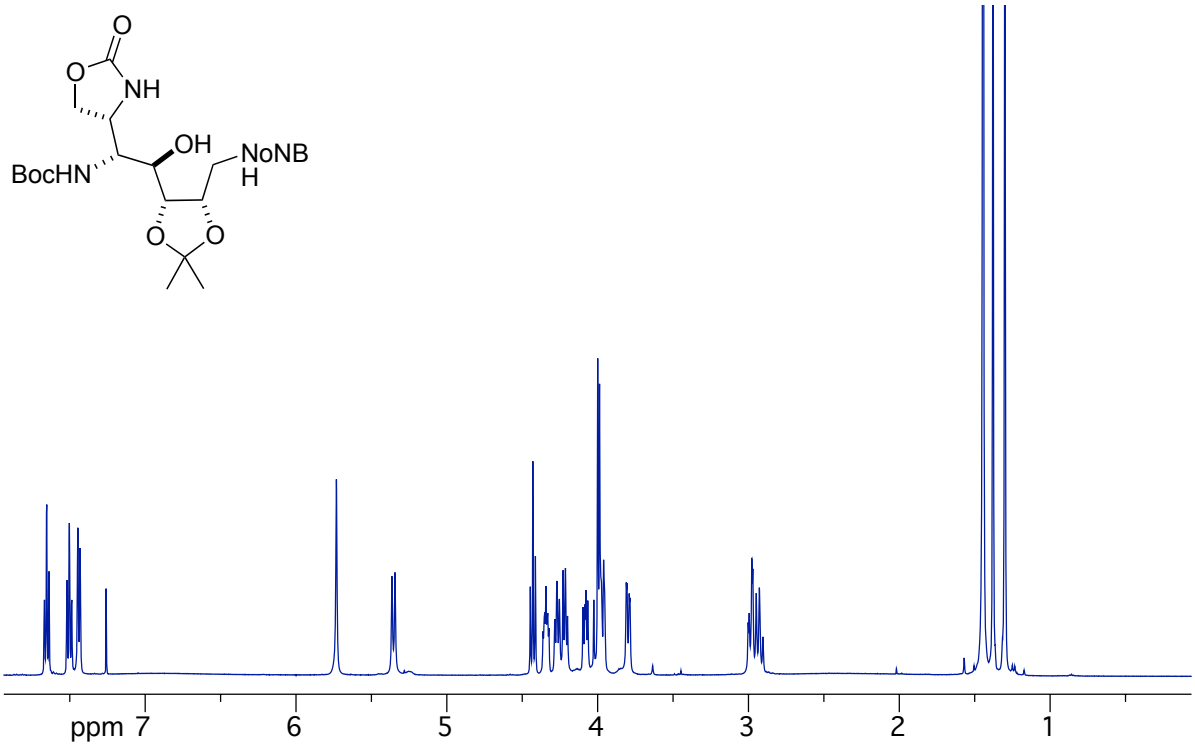
N
NoNB
H2N
N
H
H
HO
TFA
ppm 8
7
6
5
4
3

Compound 418: *tert*-butyl ((1*R*,2*R*)-2-((4*R*,5*S*)-2,2-dimethyl-5-(((2-nitrobenzyl)amino)methyl)-1,3-dioxolan-4-yl)-2-hydroxy-1-((*R*)-2-oxooxazolidin-4-yl)ethyl)carbamate.



332 418

A solution of lactol **332** (204 mg, 1 eq.), o-nitrobenzylamine HCl (414 mg, 5 eq.), AcOH (693 µL, 25 eq.), sodium acetate (447 mg, 10 eq.) and sodium cyanoborohydride (171 mg, 5 eq.) in MeOH (3 mL) was allowed to stir 1.5 hours. The reaction was carefully quenched with sat. sodium bicarbonate, extracted with EtOAc (3x) and the combined extracts were dried over sodium sulfate and evaporated. The crude product wad purified via flash chromatography (0-2% MeOH/DCM) to give benzylamine **418** (209 mg, 75.1%). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 8.03 (d, *J* = 8.2 Hz, 1H), 7.65 (td, *J* = 7.5, 1.1 Hz, 1H), 7.50 (td, *J* = 7.8, 1.1 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 5.73 (s, 1H), 5.35 (d, *J* = 10.2 Hz, 1H), 4.43 (t, *J* = 8.4 Hz, 1H), 4.34 (ddd, *J* = 9.9, 6.0, 3.8 Hz, 1H), 4.27 (t, *J* = 7.6 Hz, 1H), 4.21 (t, *J* = 7.4 Hz, 1H), 4.08 (dd, *J* = 9.8, 5.9 Hz, 1H), 4.01 (d, *J* = 13.0 Hz, 1H), 3.97 (d, *J* = 13.1 Hz, 1H), 3.97 (dd, *J* = 9.2, 2.4 Hz, 1H), 3.80 (dd, *J* = 9.8, 2.7 Hz, 1H), 2.99 (dd, *J* = 12.1, 3.5 Hz, 1H), 2.93 (dd, *J* = 12.1, 10.2 Hz, 1H), 1.45 (s, 9H), 1.38 (s, 3H), 1.30 (s, 3H). 13-C NMR (126 MHz; cdcl3): δ 159.7, 156.1, 149.1, 134.1, 132.8, 132.6, 129.4, 125.5, 109.1, 80.1, 77.7, 75.6, 72.0, 67.5, 51.9, 51.11, 50.96, 48.3, 28.4, 27.8, 25.1. Calcd. for $C_{23}H_{35}N_4O_9$ [M+H]: 511.2404 Found 511.2396.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6
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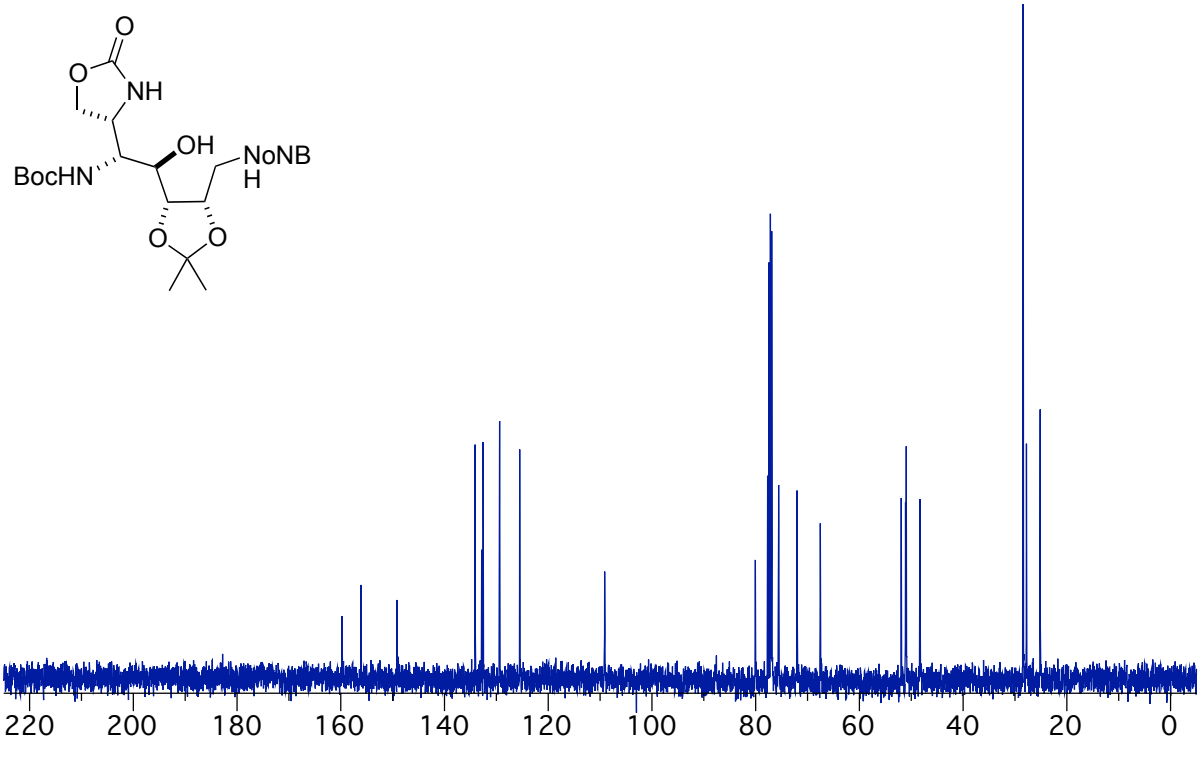
1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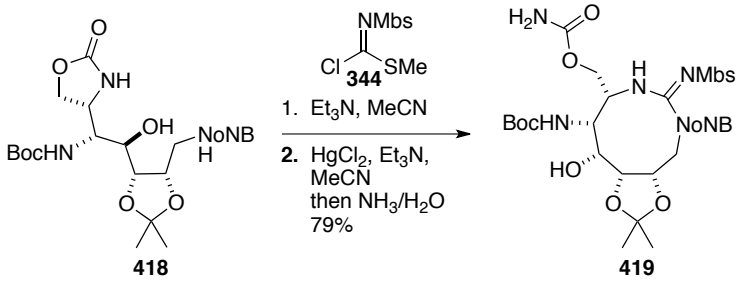
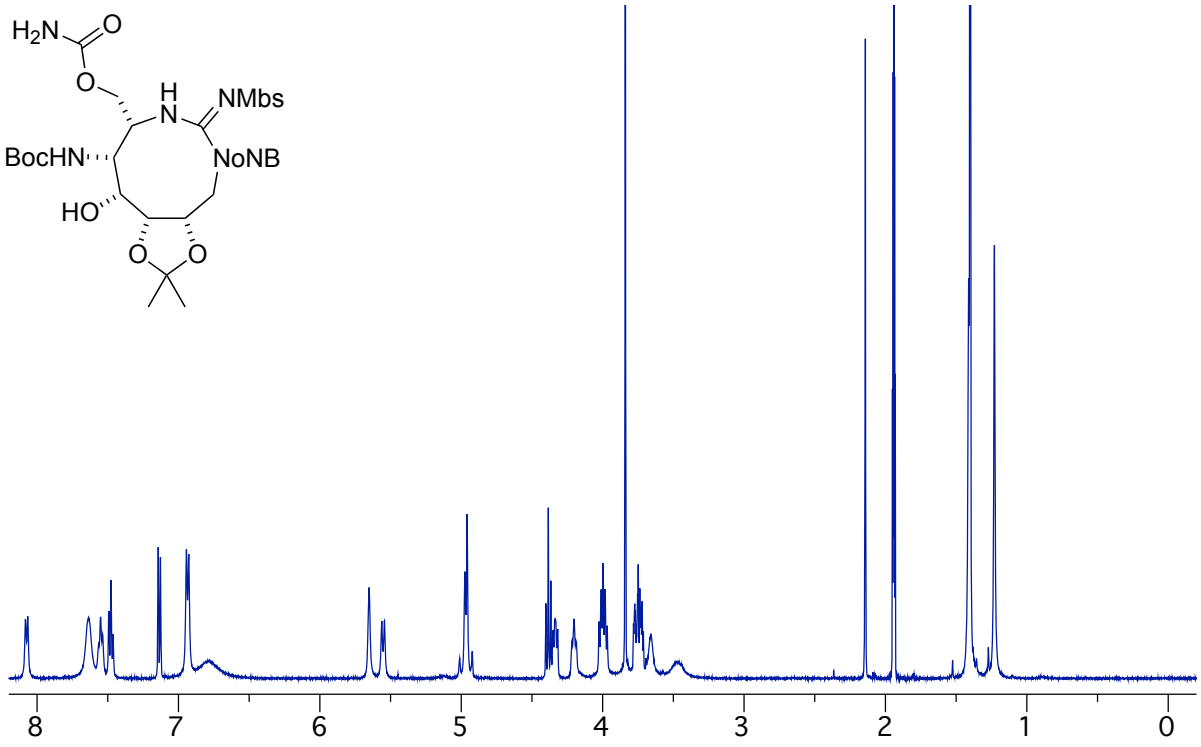
Compound 419: *tert*-butyl ((3a*S*,8*R*,9*R*,10*R*,10a*R*)-8-((carbamoyloxy)methyl)-10-hydroxy-6-(((4-methoxyphenyl)sulfonyl)imino)-2,2-dimethyl-5-(2-nitrobenzyl)octahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3]diazonin-9-yl)carbamate.



To a solution of amine **418** (209 mg, 1 eq.) and triethylamine (171 µL, 3 eq.) in DCM (4 mL, 0.1M) was added **344** (229.1 mg, 2 eq.). The mixture was allowed to stir until complete by TLC. The crude compound was cleaned up via flash chromatography (1-5% MeOH/DCM) to give the isothiourea. The isothiourea was dissolved in MeCN (10 mL) and triethylamine (171 µL, 3 eq.) was added followed by mercuric chloride (166.7 mg, 1.5 eq.) and the mixture was stirred until complete by TLC. The reaction was quenched by adding conc. Ammonium hydroxide (2 mL) and allowed to stir ~20 min. The reaction was diluted with EtOAc, filtered and evaporated. The crude alcohol was purified via flash chromatography to give alcohol **419** (235 mg, 79.4%). ^{1}H-NMR (500 MHz; cd3cn): δ 8.07 (d, *J* = 7.9 Hz, 1H), 7.64 (s, 2H), 7.55 (t, *J* = 6.9 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 2H), 6.78 (s, 2H), 5.65 (s, 1H), 5.55 (d, *J* = 9.7 Hz, 1H), 4.99 (d, *J* = 18.6 Hz, 1H), 4.95 (d, *J* = 18.1 Hz, 1H), 4.38 (t, *J* = 8.8 Hz, 1H), 4.34 (dd, *J* = 10.6, 6.6 Hz, 1H), 4.20 (t, *J* = 7.5 Hz, 1H), 4.03-3.97 (m, 2H), 3.84 (s, 3H), 3.78-3.71 (m, 2H), 3.66 (s, 1H), 3.47 (s, 1H), 1.41 (s, 3H), 1.40 (s, 9H), 1.23 (s, 3H). 13-C NMR (126 MHz; cd3cn): δ 163.0, 160.0, 157.3, 149.0, 137.1, 134.8, 129.2, 128.7, 126.1, 114.7, 109.9, 80.3, 77.5, 77.1, 71.6, 68.2, 56.3, 54.1, 52.3, 51.1, 50.4, 28.5, 27.8, 25.3. Calcd. for $C_{31}H_{43}N_6O_{12}S$ [M+H]: 723.2660 Found 723.2658.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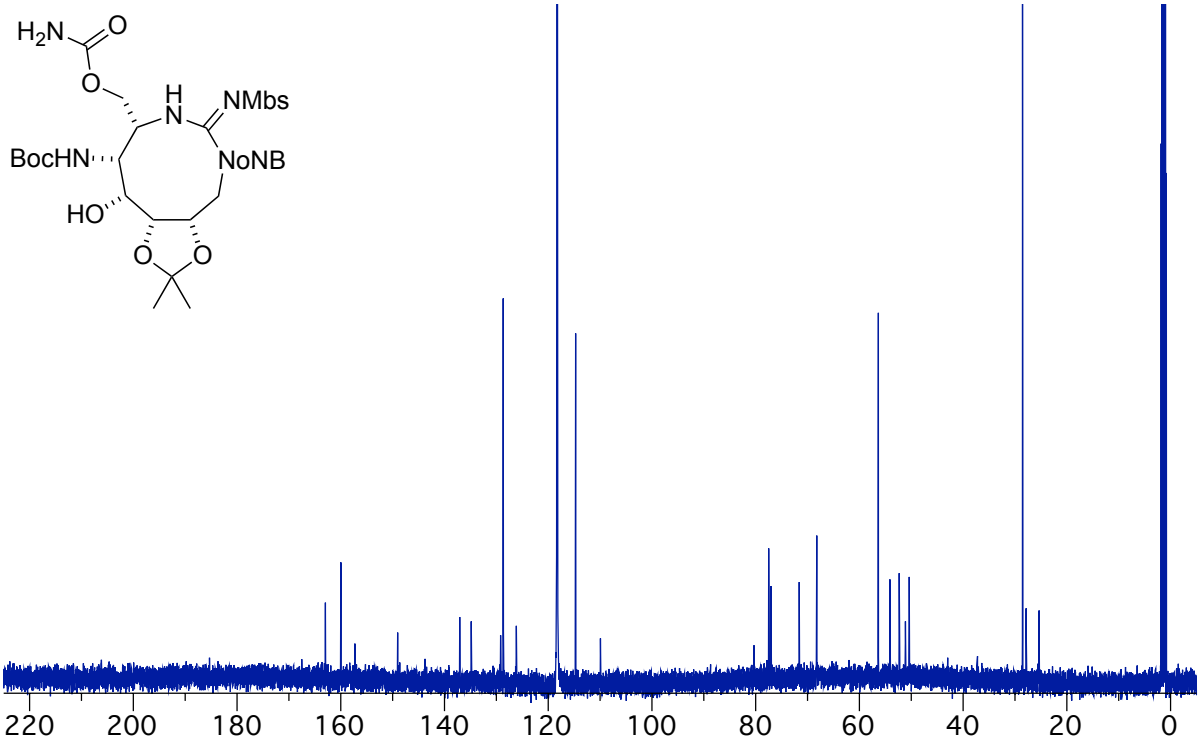
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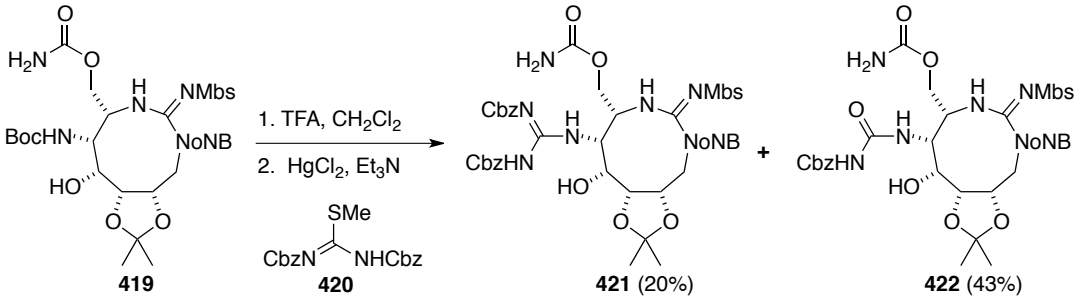
Compound 421: ((3a*S*,8*R*,9*R*,10*R*,10a*R*)-9-(2,3-bis(benzoxy*c*arbonyl)guanidino)--10-hydroxy-6-(((4-methoxyphenyl)sulfonyl)imino)-2,2-dimethyl-5-(2-nitrobenzyl)octahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3]diazonin-8-yl)methyl carbamate.

Compound 422: ((3a*S*,8*R*,9*R*,10*R*,10a*R*)-9-(3-(benzoxycarbonyl)ureido)-10-hydroxy-6-(((4-methoxyphenyl)sulfonyl)imino)-2,2-dimethyl-5-(2-nitrobenzyl)octahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3]diazonin-8-yl)methyl carbamate.

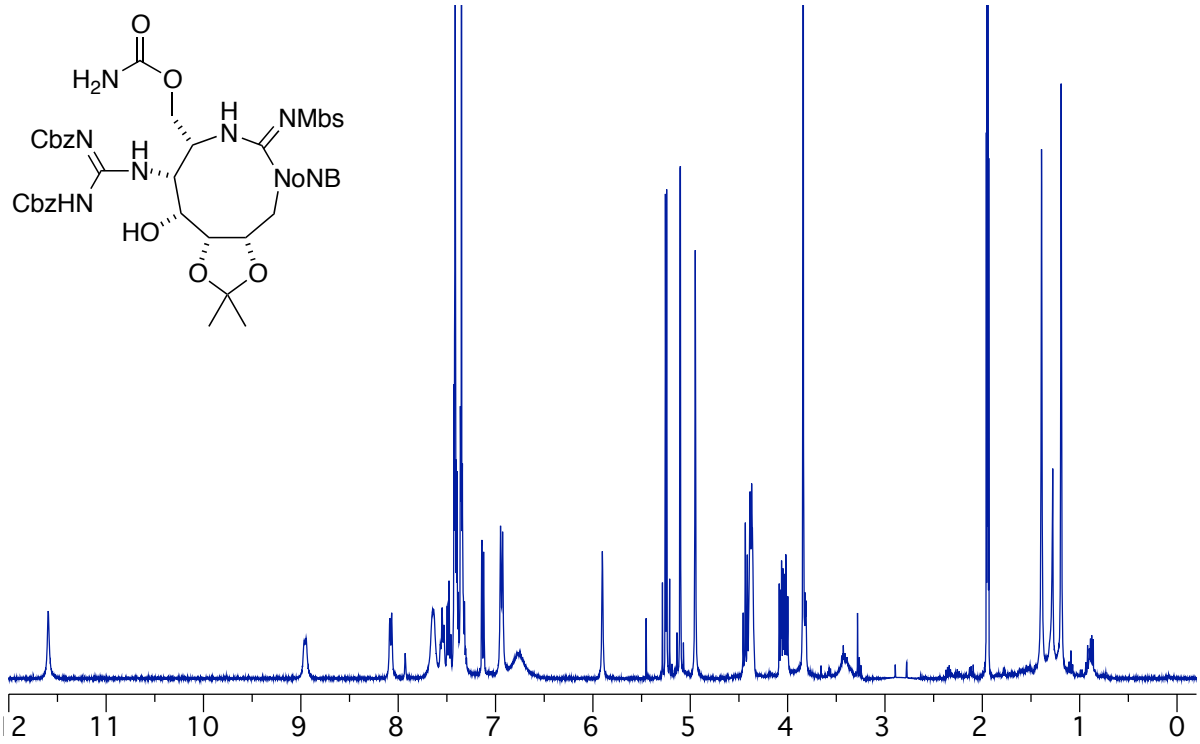


To a solution of **419** (69 mg, 1 eq.) in CH_2Cl_2 (1 mL) was added TFA (1 mL). The solution was stirred ~30 min. until complete by TLC. The mixture was evaporated and diluted with CH_2Cl_2 and reevaporated (3x) to remove trace TFA. The crude amine was dissolved in DMF (3mL) and triethylamine (66 μL, 5 eq.) and guanylating reagent **420** (40.1 mg, 1.5eq.) was added. The mixture was cooled to 0°C and mercuric chloride (38.9 mg, 1.5 eq.) was added. The cloudy suspension was allowed to room temperature and stirred until complete by TLC. The reaction was quenched by adding sat. sodium chloride and ethyl acetate. After stirring the mixture for 20 minutes the reaction was filtered through celite to remove all the mercury salts. The biphasic solution was separated and the organic layer was washed with H_2O (3x), brine and then dried over sodium sulfate and evaporated in vacuo. The crude material was purified via column chromatography (20-50% EtOAc/Hexanes) to give compound **421** (18 mg, 20.2%) and **422** (33 mg, 43.2%).

Compound 421: ^{1}H-NMR (400 MHz; cd3cn): δ 11.59 (s, 1H), 8.95 (d, *J* = 8.6 Hz, 1H), 8.08 (d, *J* = 7.7 Hz, 1H), 7.64 (s, 2H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.43-7.41

(m, 5H), 7.37-7.31 (m, 5H), 7.13 (d, *J* = 6.8 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 3H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.76 (s, 2H), 5.90 (s, 1H), 5.27 (d, *J* = 12.2 Hz, 1H), 5.23 (d, *J* = 12.2 Hz, 1H), 5.11 (d, *J* = 12.5 Hz, 1H), 5.09 (d, *J* = 12.5 Hz, 1H), 4.95 (s, 2H), 4.43 (t, *J* = 8.6 Hz, 1H), 4.40-4.35 (m, 3H), 4.07 (dd, *J* = 9.6, 6.0 Hz, 1H), 4.02 (dd, *J* = 8.3, 6.5 Hz, 1H), 3.84 (s, 3H), 3.82 (q, *J* = 2.9 Hz, 1H), 3.43 (s, 2H), 1.39 (s, 3H), 1.19 (s, 3H). 13-C NMR (101 MHz; d2o): δ 164.5, 163.0, 159.9, 157.8, 154.4, 149.0, 138.0, 137.0, 136.2, 134.9, 129.65, 129.63, 129.40, 129.29, 128.9, 128.7, 126.2, 114.7, 110.3, 77.6, 76.9, 70.7, 69.1, 68.0, 67.8, 56.3, 54.3, 51.8, 51.15, 51.13, 50.2, 28.0, 25.5. Calcd. for $C_{43}H_{49}N_8O_{14}S$ [M+H]: 933.3089 Found 933.3095.

Compound 422: ^{1}H-NMR (400 MHz; cd3cn): δ 8.25 (s, 1H), 8.21 (d, *J* = 9.4 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.64 (s, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.41-7.35 (m, 5H), 7.13 (d, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 2H), 6.79 (s, 2H), 5.85 (s, 1H), 5.18 (d, *J* = 12.5 Hz, 1H), 5.15 (d, *J* = 12.4 Hz, 1H), 4.95 (s, 2H), 4.40 (t, *J* = 8.8 Hz, 1H), 4.39-4.33 (m, 1H), 4.30 (ddt, *J* = 8.8, 7.0, 1.7 Hz, 1H), 4.05 (ddd, *J* = 9.2, 3.6, 2.2 Hz, 1H), 4.03 (dd, *J* = 9.0, 5.9 Hz, 1H), 4.00 (dd, *J* = 8.5, 6.8 Hz, 1H), 3.90 (d, *J* = 5.7 Hz, 1H), 3.84 (s, 3H), 3.79 (ddd, *J* = 9.2, 5.8, 3.5 Hz, 1H), 3.45 (s, 2H), 1.40 (s, 2H), 1.21 (s, 2H). 13-C NMR (101 MHz; cd3cn): δ 162.9, 160.0, 158.3, 155.4, 154.2, 149.0, 137.0, 136.7, 134.9, 129.6, 129.4, 129.17, 129.01, 128.95, 128.7, 126.2, 114.7, 110.1, 77.5, 77.0, 71.0, 68.34, 68.16, 56.3, 53.2, 51.9, 51.1, 50.2, 27.9, 25.5. Calcd. for $C_{35}H_{42}N_7O_{13}S$ [M+H]: 800.2561 Found 800.2568.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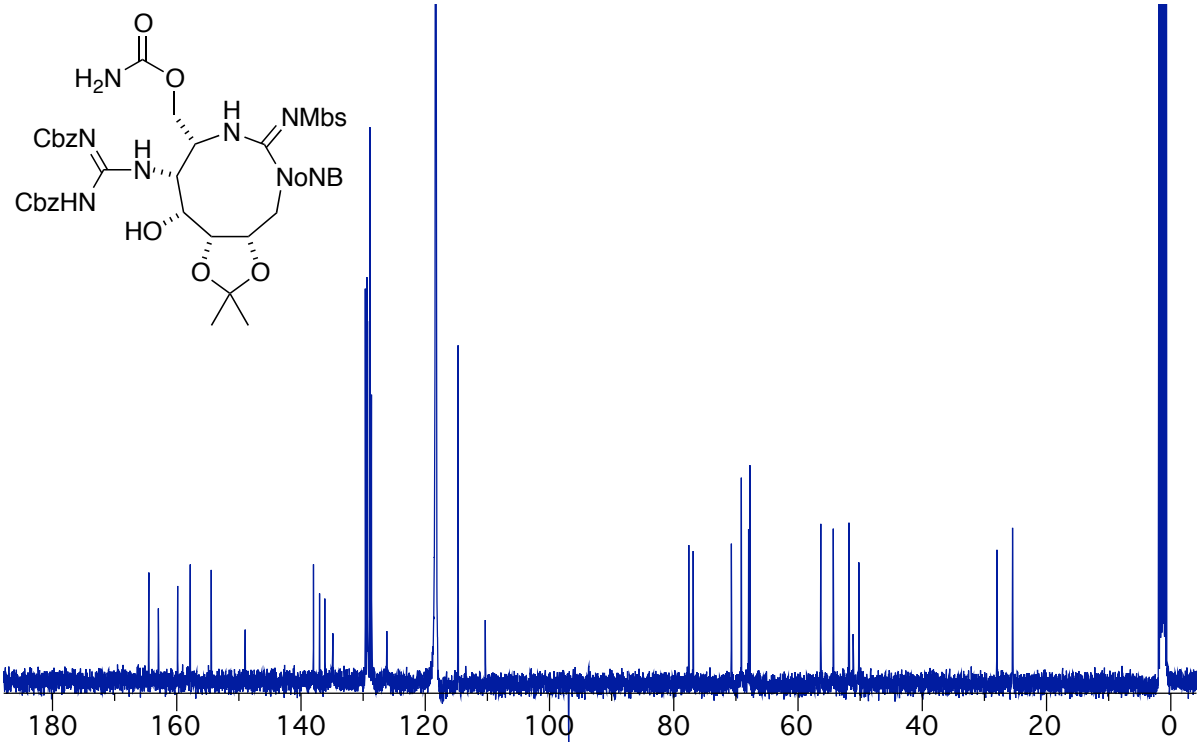
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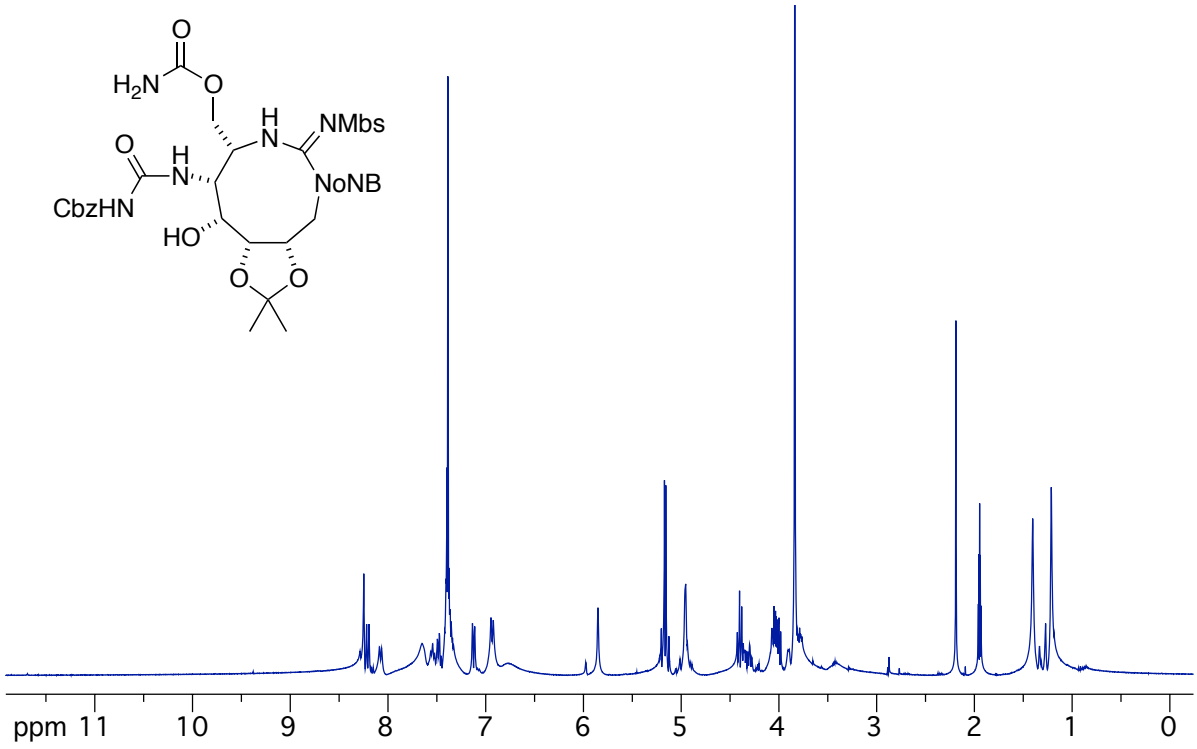
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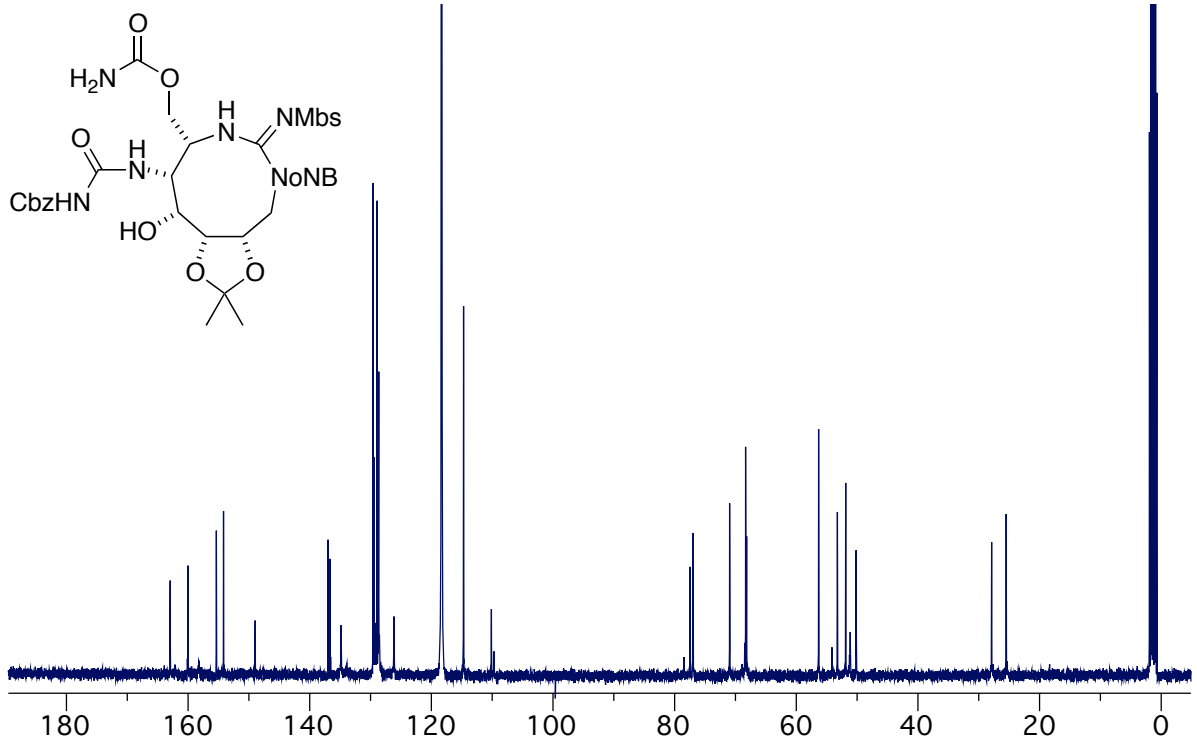
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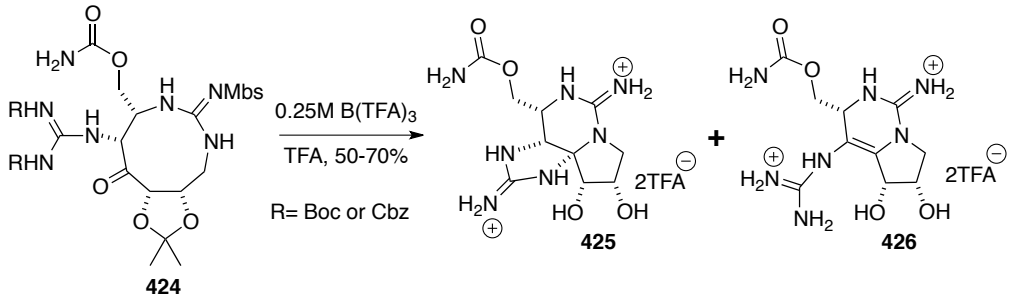
Compound 425: (3a*R*,4*R*,9*S*,10*R*,10a*R*)-4-((carbamoyloxy)methyl)-9,10-dihydroxyhexahydropyrrolo[1,2-*c*]purine-2,6(1*H*,8*H*)-diiminium 2,2,2-trifluoroacetate.

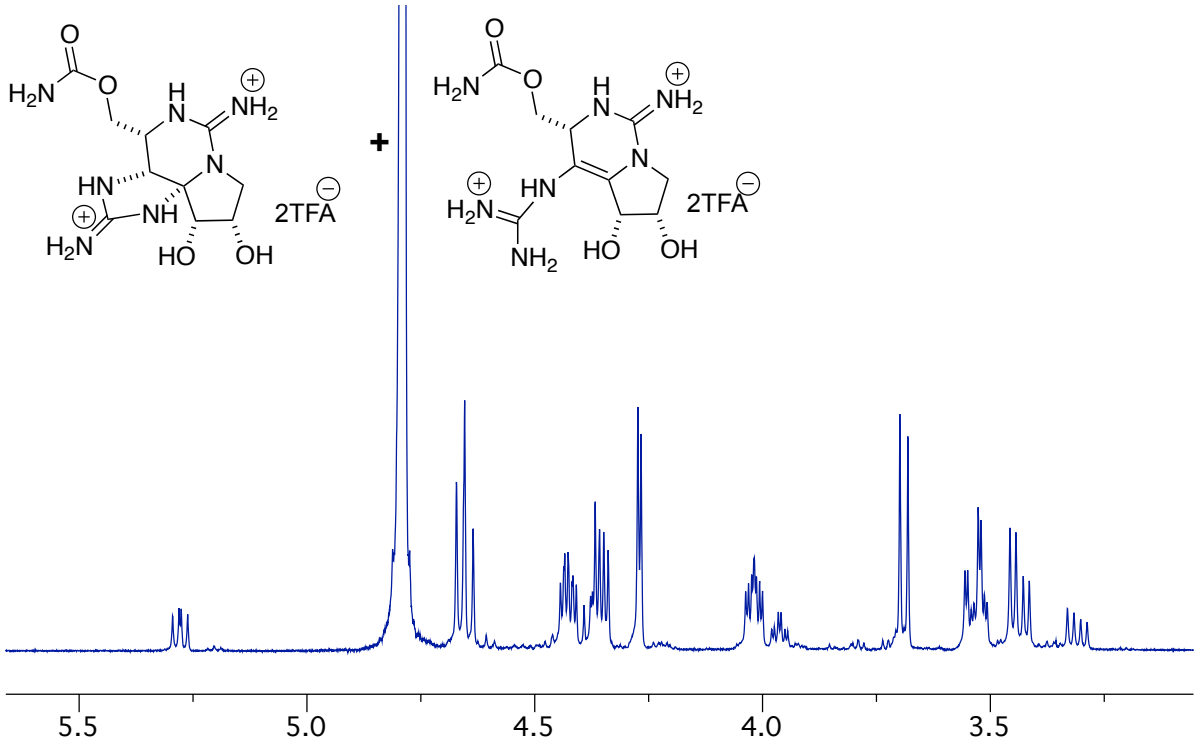
Compound 426: (3*R*,5*R*,6*S*)-4-((amino(iminio)methyl)amino)-3-((carbamoyloxy)methyl)-5,6-dihydroxy-2,3,6,7-tetrahydropyrrolo[1,2-*c*]pyrimidin-1(5*H*)-iminium 2,2,2-trifluoroacetate.



Ketone **424** (10 mg) was cooled to 0°C and 0.25 $B(TFA)_3$ in TFA (1 mL) was added. The mixture was allowed to warm to rt slowly (leave in the ice bath) and stirred a total of 20 hours. The mixture was cooled to 0°C and quenched with methanol. The reaction was evaporated and diluted with methanol 3x. The crude solid was purified via RP-18 flash chromatography (100-80% 0.1% TFA in H_2O/MeCN) to give a mixture of 3:1 **425**/**426** (5mg, 69%).

Compound 425: ^{1}H-NMR (500 MHz; D_2O): δ 4.65 (dd, *J* = 9.7, 8.6 Hz, 1H), 4.43 (ddd, *J* = 8.9, 5.0, 3.8 Hz, 1H), 4.35 (dd, *J* = 9.5, 4.8 Hz, 1H), 4.27 (d, *J* = 3.5 Hz, 1H), 4.02 (ddd, *J* = 8.8, 6.5, 3.0 Hz, 1H), 3.69 (d, *J* = 8.8 Hz, 1H), 3.54 (dd, *J* = 14.6, 3.1 Hz, 1H), 3.44 (dd, *J* = 14.6, 6.6 Hz, 1H). 13-C NMR (126 MHz; d2o): δ 161.84, 161.75, 158.01, 158.01, 157.54, 157.54, 91.80, 91.80, 72.57, 72.57, 69.84, 69.84, 68.09, 68.09, 63.05, 63.05, 51.62, 51.62, 44.85, 44.85. Calcd. for $C_{10}H_{18}N_7O_4$ [M+H]: 300.1409 Found 300.1414.

Compound 426: ^{1}H-NMR (500 MHz; D_2O): δ 5.28 (dd, *J* = 9.5, 7.0 Hz, 1H), 4.79 (t, *J* = 9.5 Hz, 1H), 4.66 (d, *J* = 7.4 Hz, 1H), 4.38 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.96 (td, *J* = 7.2, 3.0 Hz, 1H), 3.52 (dd, *J* = 14.4, 3.0 Hz, 1H), 3.31 (dd, *J* = 14.5, 7.2 Hz, 1H). Calcd. for $C_{10}H_{18}N_7O_4$ [M+H]: 300.1409 Found 300.1414.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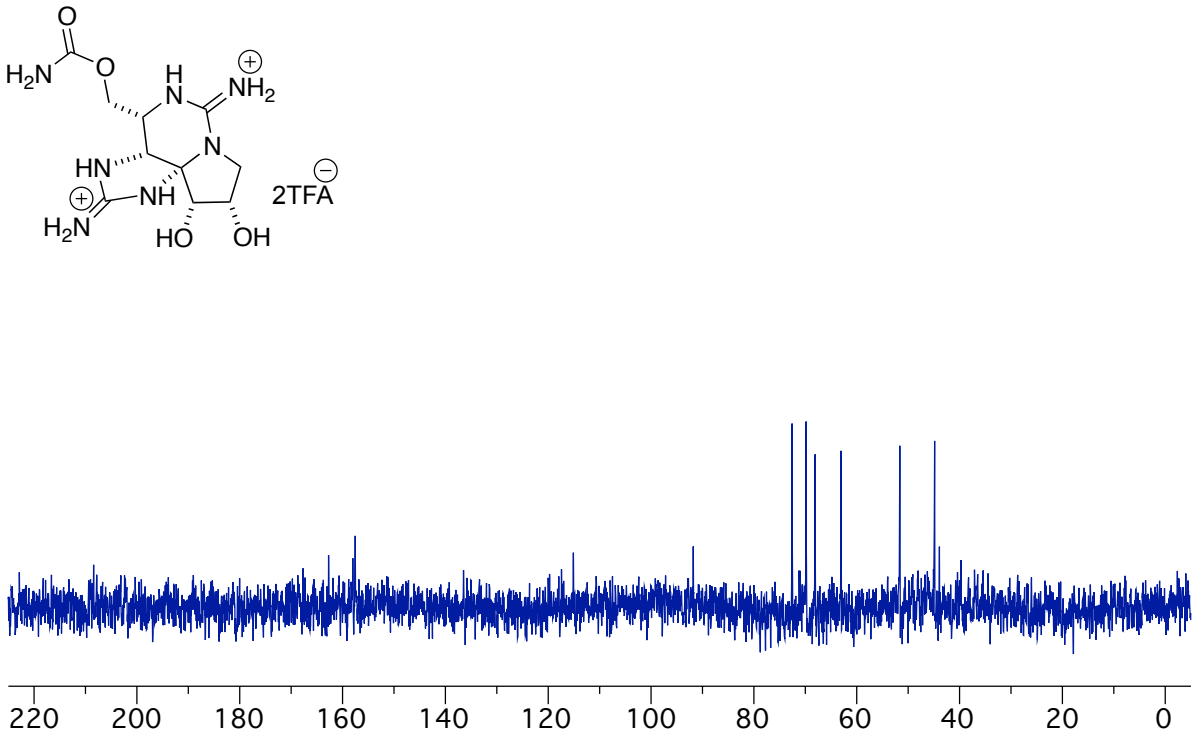
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References

(1) *From genes to pain: Nav1.7 and human pain disorders*. Dib-Hajj, S. D., Cummins, T. R., Black, J. A.; Waxman, S. G. *Trends in Neurosciences* **2007**, 30, 555-563.

(2) *Inherited neuronal ion channelopathies: new windows on complex neurological diseases*. Catterall, W. A., Dib-Hajj, S., Meisler, M. H.; Pietrobon, D. *J Neurosci* **2008**, 28, 11768-11777.

(3) *Ion Channels as Therapeutic Targets: A Drug Discovery Perspective*. Bagal, S. K., Brown, A. D., Cox, P. J., Omoto, K., Owen, R. M., et al. *J. Med. Chem.* **2012**,

(4) *Mussel poisoning*. Meyer, K. F., Sommer, H.; Schoenholz, P. *Am. J. Prev. Med.* **1928**, 2, 365-394.

(5) *Relation of Paralytic Shell-Fish Poison to Certain Plankton Organisms of the Genus Gonyaulax*. Sommer, H., Whedon, W. F., Kofoid, C. A.; Stohler, R. *Arch. Path.* **1937**, 24, 537.

(6) *Mussel Poisoning*. Sommer, H.; Meyer, K. F. *Cal West Med* **1935**, 42, 423-426.

(7) *Paralytic Shellfish Poison. I. Occurrence and Concentration by Ion Exchange1,2,3*. Sommer, H., Monnier, R. P., Riegel, B., Stanger, D. W., Mold, J. D., et al. *J. Am. Chem. Soc.* **1948**, 70, 1015-1018.

(8) *Structure of saxitoxin*. Wong, J. L., Oesterlin, R.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, 93, 7344-7345.

(9) *The Structure of Saxitoxin*. Schantz, E. J., Ghazarossian, V. E., Schnoes, H. K., Strong, F. M., Springer, J. P., et al. *J. Am. Chem. Soc.* **1975**, 97, 1238-1239.

(10) *Structure of a crystalline derivative of saxitoxin. Structure of saxitoxin*. Bordner, J., Thiessen, W. E., Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1975**, 97, 6008-6012.

(11) *Neurotoxic alkaloids: saxitoxin and its analogs*. Wiese, M., D'Agostino, P. M., Mihali, T. K., Moffitt, M. C.; Neilan, B. A. *Mar Drugs* **2010**, 8, 2185-2211.

(12) *Atelopidtoxin from the Panamanian Frog, Atelopus Zeteki*. Mosher, H. S., Fuhrman, F. A.; Shindelman, J. *Toxicon* **1969**, 7, 315-319.

(13) *Potent Neurotoxins: Tetrodotoxin, Chiriquitoxin, and Zetekitoxin fromAtelopusFrogs in Central America*. Kim, Y. H., Kim, Y. B.; Yotsu-Yamashita, M. *Toxin Reviews* **2003**, 22, 521-532.

(14) *The structure of zetekitoxin AB, a saxitoxin analog from the Panamanian golden frog Atelopus zeteki: a potent sodium-channel blocker*. Yotsu-Yamashita, M., Kim, Y. H., Dudley, S. C., Jr., Choudhary, G., Pfahnl, A., et al. *Proc Natl Acad Sci U S A* **2004**, 101, 4346-4351.

(15) *Oribatid mites as a major dietary source for alkaloids in poison frogs*. Saporito, R. A., Donnelly, M. A., Norton, R. A., Garraffo, H. M., Spande, T. F., et al. *Proceedings of the National Academy of Sciences* **2007**, 104, 8885-8890.

(16) *The chemistry of poisons in amphibian skin*. Daly, J. W. *Proceedings of the National Academy of Sciences* **1995**, 92, 9-13.

(17) *Arthropod-Frog Connection: Decahydroquinoline and Pyrrolizidine Alkaloids Common to Microsympatric Myrmicine Ants and Dendrobatid Frogs*. Daly, J., Garraffo, H. M., Jain, P., Spande, T., Snelling, R., et al. *J. Chem. Ecol.* **2000**, 26, 73-85.

(18) *Biomimetic synthesis of dibromophakellin*. Foley, L. H.; Buechi, G. *J. Am. Chem. Soc.* **1982**, 104, 1776-1777.

(19) *Toxigenesis and biosynthesis of saxitoxin analogues*. Shimizu, Y. *Pure & App. Chem.* **1986**, 58, 257-262.

(20) *Recent Progress In Marine Toxin Research*. Shimizu, Y. *Pure Appl.Chem.* **1982**, 54, 1973-1980.

(21) *Biosynthesis of Saxitoxin Analogues: The Unexpected Pathway*. Shimizu, Y., Norte, M., Hori, A., Genenah, A.; Kobayashi, M. *J. Am. Chem. Soc.* **1984**, 106, 6433-6434.

(22) *Dinoflagellate and other microalgal toxins: chemistry and biochemistry*. Shimizu, Y., Gupta, S., Masuda, K., Maranda, L., Walker, C. K., et al. *Pure and App. Chern* **1989**, 61, 513-516.

(23) *Microalgal Metabolites: A New Perspective*. Shimizu, Y. *Annu. Rev. Microbiol.* **1996**, 50, 431-465.

(24) *Identification of a saxitoxin biosynthesis gene with a history of frequent horizontal gene transfers*. Kellmann, R., Mihali, T. K.; Neilan, B. A. *J Mol Evol* **2008**, 67, 526-538.

(25) *Biosynthetic intermediate analysis and functional homology reveal a saxitoxin gene cluster in cyanobacteria*. Kellmann, R., Mihali, T. K., Jeon, Y. J., Pickford, R., Pomati, F., et al. *Appl Environ Microbiol* **2008**, 74, 4044-4053.

(26) *Characterisation of the paralytic shellfish toxin biosynthesis gene clusters in Anabaena circinalis AWQC131C and Aphanizomenon sp. NH-5*. Mihali, T. K., Kellmann, R.; Neilan, B. A. *BMC Biochem* **2009**, 10, 8.

(27) *A stereospecific total synthesis of dl-saxitoxin*. Tanino, H., Nakata, T., Kaneko, T.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, 99, 2818-2819.

(28) *An improved procedure for the Blaise reaction: a short, practical route to the key intermediates of the saxitoxin synthesis*. Hannick, S. M.; Kishi, Y. *The Journal of Organic Chemistry* **1983**, 48, 3833-3835.

(29) *Enantioselective total synthesis of (-)-decarbamoylsaxitoxin*. Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1992**, 114, 7001-7006.

(30) *Total synthesis of (±)-saxitoxin*. Jacobi, P. A., Martinelli, M. J.; Polanc, S. *J. Am. Chem. Soc.* **1984**, 106, 5594-5598.

(31) *A mild procedure for the generation of azomethine imines. Stereochemical factors in the intramolecular 1,3-dipolar addition of azomethine imines and a synthetic approach to saxitoxin*. Jacobi, P. A., Brownstein, A., Martinelli, M.; Grozinger, K. *J. Am. Chem. Soc.* **1981**, 103, 239-241.

(32) *A Synthesis of (+)-Saxitoxin*. Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, 128, 3926-3927.

(33) *Expanding the Scope of C-H Amination through Catalyst Design*. Espino, C. G., Fiori, K. W., Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, 126, 15378-15379.

(34) *Novel Iminium Ion Equivalents Prepared through C-H Oxidation for the Stereocontrolled Synthesis of Functionalized Propargylic Amine Derivatives*. Fleming, J. J., Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, 125, 2028-2029.

(35) *(+)-Saxitoxin: A First and Second Generation Stereoselective Synthesis*. Fleming, J. J., McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, 129, 9964-9975.

(36) *A Stereoselective Synthesis of (+)-Gonyautoxin 3*. Mulcahy, J. V.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, 130, 12630-12631.

(37) *Total Synthesis of (−)-Decarbamoyloxysaxitoxin*. Iwamoto, O., Koshino, H., Hashizume, D.; Nagasawa, K. *Angew. Chem. Int. Ed.* **2007**, 46, 8625-8628.

(38) *Total Synthesis of (−)- and (+)-Decarbamoyloxysaxitoxin and (+)-Saxitoxin*. Iwamoto, O., Shinohara, R.; Nagasawa, K. *Chemistry - An Asian Journal* **2009**, 4, 277-285.

(39) *Total Synthesis of (+)-Decarbamoylsaxitoxin and (+)-Gonyautoxin 3*. Iwamoto, O.; Nagasawa, K. *Organic Letters* **2010**, 12, 2150-2153.

(40) *Synthesis of Skeletal Analogues of Saxitoxin Derivatives and Evaluation of Their Inhibitory Activity on Sodium Ion Channels NaV1.4 and NaV1.5*. Shinohara, R., Akimoto, T., Iwamoto, O., Hirokawa, T., Yotsu-Yamashita, M., et al. *Chemistry – A European Journal* **2011**, 17, 12144-12152.

(41) *Bromocyclization of Alkynyl Guanidine: A New Approach to the Synthesis of Cyclic Guanidines of Saxitoxin*. Nishikawa, T.; Sawayama, Y. *Synlett* **2011**, 2011, 651-654.

(42) *A Synthetic Route to the Saxitoxin Skeleton: Synthesis of Decarbamoyl α-Saxitoxinol, an Analogue of Saxitoxin Produced by the Cyanobacterium Lyngbya wollei*. Sawayama, Y.; Nishikawa, T. *Angew. Chem. Int. Ed.* **2011**, 50, 7176-7178.

(43) *A Stereocontrolled Synthesis of (+)-Saxitoxin*. Bhonde, V. R.; Looper, R. E. *J. Am. Chem. Soc.* **2011**, 133, 20172-20174.

(44) *Addition-Hydroamination Reactions of Propargyl Cyanamides: Rapid Access to Highly Substituted 2-Aminoimidazoles*. Giles, R. L., Sullivan, J. D., Steiner, A. M.; Looper, R. E. *Angew. Chem. Int. Ed.* **2009**, 48, 3116-3120.

(45) *α,β-Diamino Acids: Biological Significance and Synthetic Approaches*. Viso, A., Fernández de la Pradilla, R., García, A.; Flores, A. *Chemical Reviews* **2005**, 105, 3167-3196.

(46) *Asymmetric Synthesis of (2S,3R)-Capreomycidine and the Total Synthesis of Capreomycin IB*. DeMong, D. E.; Williams, R. M. *J. Am. Chem. Soc.* **2003**, 125, 8561-8565.

(47) *Synthesis of [18F]Xeloda as a novel potential PET radiotracer for imaging enzymes in cancers*. Fei, X., Wang, J.-Q., Miller, K. D., Sledge, G. W., Hutchins, G. D., et al. *Nuclear Medicine and Biology* **2004**, 31, 1033-1041.

(48) *The reaction of acetyliron [(Œ∑5-C5H5)Fe(CO)(PPh3)(COCH3)] with sugar aldehydes. New synthesis of deoxysugars*. Pakulski, Z.; Zamojski, A. *Tetrahedron* **1995**, 51, 871-908.

(49) *A Very Mild and Chemoselective Oxidation of Alcohols to Carbonyl Compounds*. De Luca, L., Giacomelli, G.; Porcheddu, A. *Organic Letters* **2001**, 3, 3041-3043.

(50) *Direct, Mild, and Selective Synthesis of Unprotected Dialdo-Glycosides*. Angelin, M., Hermansson, M., Dong, H.; Ramström, O. *European Journal of Organic Chemistry* **2006**, 2006, 4323-4326.

(51) *Modern Variants of the Mannich Reaction*. Arend, M., Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, 37, 1044-1070.

(52) *Benzotriazole mediated amino-, amido-, alkoxy- and alkylthio-alkylation*. Katritzky, A. R., Manju, K., Singh, S. K.; Meher, N. K. *Tetrahedron* **2005**, 61, 2555-2581.

(53) *alpha-Amido Sulfones as Stable Precursors of Reactive N-Acylimino Derivatives*. Petrini, M. *Chemical Reviews* **2005**, 105, 3949-3977.

(54) *Synthesis of Allylic and Propargylic Primary Amines by Reaction of Organometallic Reagents with (±)-Amidoalkyl Sulfones*. Mecozzi, T.; Petrini, M. *The Journal of Organic Chemistry* **1999**, 64, 8970-8972.

(55) *Highly diastereoselective addition of nitromethane anion to chiral amidoalkylphenyl sulfones: Synthesis of optically active amino acid derivatives*. Foresti, E., Palmieri, G., Petrini, M.; Profeta, R. *Org. Biomol. Chem.* **2003**, 1, 4275-4281.

(56) *Benzyl 2,3-O-isopropylidene-Œ≤-D-ribo-1,4-pentodialdofuranoside as a D-ribose chiron for the synthesis of terpenyl tetraols and aminotriols*. Duvold, T., Francis, G. W.; Papaioannou, D. *Tetrahedron Letters* **1995**, 36, 3153-3156.

(57) *Catalytic Asymmetric Mannich Reactions of Glycine Derivatives with Imines. A New Approach to Optically Active Œ±,Œ≤-Diamino Acid Derivatives*. Bernardi, L., Gothelf, A. S., Hazell, R. G.; J√∏rgensen, K. A. *The Journal of Organic Chemistry* **2003**, 68, 2583-2591.

(58) *A mild and efficient route to Schiff base derivatives of amino acids*. O'Donnell, M. J.; Polt, R. L. *The Journal of Organic Chemistry* **1982**, 47, 2663-2666.

(59) *Syntheses and reactions of silyl carbamates. 1. Chemoselective transformation of amino protecting groups via tert-butyldimethylsilyl carbamates*. Sakaitani, M.; Ohfune, Y. *The Journal of Organic Chemistry* **1990**, 55, 870-876.

(60) *Deprotection of a primary Boc group under basic conditions*. Tom, N. J., Simon, W. M., Frost, H. N.; Ewing, M. *Tetrahedron Letters* **2004**, 45, 905-906.

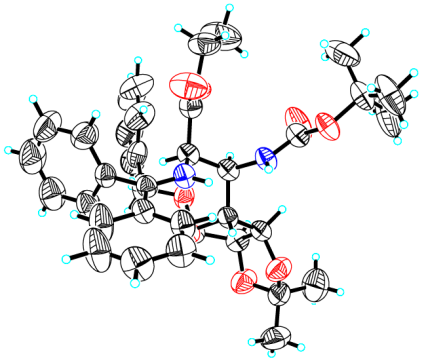
(61) *A Versatile One-Pot Synthesis of 1,3-Substituted Guanidines from Carbamoyl Isothiocyanates*. Linton, B. R., Carr, A. J., Orner, B. P.; Hamilton, A. D. *The Journal of Organic Chemistry* **2000**, 65, 1566-1568.

(62) *Total Synthesis of Palau'amine*. Seiple, I. B., Su, S., Young, I. S., Lewis, C. A., Yamaguchi, J., et al. *Angew. Chem. Int. Ed.* **2009**, 49, 1095-1098.

(63) *Total deprotection of N,N,Ä≤-bis(tert-butoxycarbonyl)guanidines using SnCl4*. Miel, H.; Rault, S. *Tetrahedron Letters* **1997**, 38, 7865-7866.

Appendix 1: X-ray Data

Compound 211



Empirical formula	$C_{37}H_{45}N_2O_8$
Formula weight	645.75
Temperature	298 (2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 10.2637(4) Å
	b = 15.9663(7) Å

	c = 22.8323(10) Å
Volume	3741.6(3) $Å^3$
Z	4
Density (calculated)	1.146 Mg/m^3
Absorption coefficient	0.080 mm^{-1}
F(000)	1380
Crystal size	0.68 x 0.42 x 0.23 mm^3
Theta range for data collection	2.18 to 23.26°.
Index ranges	-11<=h<=8, -17<=k<=17, -19<=l<=25
Reflections collected 14581	
Independent reflections	5321 [R(int) = 0.0278]
Completeness to theta = 23.26°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9816 and 0.9473
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5321 / 0 / 430
Goodness-of-fit on F^2	1.048
Final R indices [I>2sigma(I)]	R1 = 0.0433, wR2 = 0.0982
R indices (all data)	R1 = 0.0647, wR2 = 0.1094
Largest diff. peak and hole	0.116 and -0.264 $e.Å^{-3}$

Comment: Large thermal ellipsoids are due to the room temperature data.

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	3639(3)	5001(2)	3674(1)	47(1)
C(2)	4550(3)	4752(2)	4078(1)	86(1)
C(3)	4198(4)	4592(3)	4656(1)	100(1)
C(4)	2949(4)	4689(2)	4831(1)	77(1)
C(5)	2024(3)	4941(2)	4436(1)	74(1)
C(6)	2364(3)	5089(2)	3865(1)	60(1)
C(7)	5374(3)	5011(2)	2874(1)	49(1)
C(8)	6262(3)	5657(2)	2880(2)	80(1)
C(9)	7548(4)	5517(3)	2700(2)	102(1)
C(10)	7916(4)	4737(3)	2524(2)	102(1)
C(11)	7058(4)	4104(3)	2515(2)	90(1)
C(12)	5786(3)	4233(2)	2693(1)	67(1)
C(13)	5085(3)	3923(2)	918(1)	75(1)
C(14)	5758(3)	4354(2)	421(1)	63(1)
C(15)	5974(4)	5204(3)	428(2)	93(1)
C(16)	6535(4)	5598(3)	-46(2)	112(2)
C(17)	6866(4)	5148(3)	-534(2)	102(1)
C(18)	6666(4)	4308(3)	-541(2)	96(1)
C(19)	6093(3)	3919(2)	-70(2)	77(1)
C(20)	1820(2)	4369(2)	1818(1)	47(1)
C(21)	820(3)	4067(2)	1376(1)	54(1)
C(22)	1579(3)	3478(2)	971(1)	60(1)
C(23)	2962(3)	3483(2)	1198(1)	55(1)
C(24)	-267(3)	2812(2)	1297(2)	66(1)
C(25)	-618(4)	2089(2)	1684(2)	96(1)
C(26)	-1238(4)	2962(3)	812(2)	116(2)
C(27)	2218(2)	5285(2)	1723(1)	45(1)
C(28)	3413(3)	5526(2)	2085(1)	46(1)
C(29)	477(3)	6308(2)	1505(1)	51(1)
C(30)	-1088(3)	7458(2)	1496(1)	70(1)
C(31)	-120(5)	8072(3)	1275(3)	186(3)
C(32)	-1943(4)	7810(2)	1977(2)	110(2)

C(33)	-1937(5)	7120(3)	1023(2)	144(2)
C(34)	3915(6)	7451(3)	592(2)	133(2)
C(35)	3996(3)	5149(2)	3055(1)	44(1)
C(36)	3745(3)	6445(2)	1978(1)	55(1)
C(37)	4114(4)	7429(2)	1216(2)	86(1)
N(1)	3122(2)	5394(1)	2702(1)	49(1)
N(2)	1124(2)	5813(1)	1886(1)	48(1)
O(1)	-390(2)	6781(1)	1791(1)	59(1)
O(2)	666(2)	6302(2)	985(1)	84(1)
O(3)	-111(2)	3538(1)	1651(1)	71(1)
O(4)	999(2)	2688(1)	1059(1)	76(1)
O(5)	2904(2)	3807(1)	1772(1)	52(1)
O(6)	3811(3)	6974(1)	2342(1)	89(1)
O(7)	3952(2)	6561(1)	1411(1)	68(1)
O(8)	3706(2)	3975(1)	821(1)	62(1)

Table 2. Bond lengths [Å] and angles [°]

C(1)-C(2)	1.373(4)	C(24)-C(26)	1.509(5)
C(1)-C(6)	1.387(4)	C(27)-N(2)	1.453(3)
C(1)-C(35)	1.479(4)	C(27)-C(28)	1.529(4)
C(2)-C(3)	1.392(5)	C(28)-N(1)	1.455(3)
C(3)-C(4)	1.351(5)	C(28)-C(36)	1.525(4)
C(4)-C(5)	1.370(5)	C(29)-O(2)	1.202(3)
C(5)-C(6)	1.369(4)	C(29)-O(1)	1.338(3)
C(7)-C(12)	1.375(4)	C(29)-N(2)	1.351(3)
C(7)-C(8)	1.377(4)	C(30)-O(1)	1.463(3)
C(7)-C(35)	1.490(4)	C(30)-C(31)	1.484(5)
C(8)-C(9)	1.400(5)	C(30)-C(33)	1.489(5)
C(9)-C(10)	1.362(6)	C(30)-C(32)	1.514(5)
C(10)-C(11)	1.340(6)	C(34)-C(37)	1.440(5)
C(11)-C(12)	1.383(4)	C(35)-N(1)	1.267(3)
C(13)-O(8)	1.435(3)	C(36)-O(6)	1.187(3)
C(13)-C(14)	1.496(4)	C(36)-O(7)	1.327(3)
C(14)-C(19)	1.362(4)	C(37)-O(7)	1.464(4)
C(14)-C(15)	1.374(5)	C(2)-C(1)-C(6)	117.4(3)
C(15)-C(16)	1.376(5)	C(2)-C(1)-C(35)	121.4(3)
C(16)-C(17)	1.370(6)	C(6)-C(1)-C(35)	121.2(2)
C(17)-C(18)	1.358(6)	C(1)-C(2)-C(3)	121.0(3)
C(18)-C(19)	1.375(5)	C(4)-C(3)-C(2)	120.3(3)
C(20)-O(5)	1.434(3)	C(3)-C(4)-C(5)	119.8(3)
C(20)-C(21)	1.518(4)	C(6)-C(5)-C(4)	120.1(3)
C(20)-C(27)	1.534(4)	C(5)-C(6)-C(1)	121.5(3)
C(21)-O(3)	1.421(3)	C(12)-C(7)-C(8)	118.4(3)
C(21)-C(22)	1.532(4)	C(12)-C(7)-C(35)	120.6(3)
C(22)-O(4)	1.408(3)	C(8)-C(7)-C(35)	121.0(3)
C(22)-C(23)	1.512(4)	C(7)-C(8)-C(9)	120.1(4)
C(23)-O(8)	1.393(3)	C(10)-C(9)-C(8)	119.6(4)
C(23)-O(5)	1.410(3)	C(11)-C(10)-C(9)	120.7(4)
C(24)-O(4)	1.422(4)	C(10)-C(11)-C(12)	120.2(4)
C(24)-O(3)	1.422(4)	C(7)-C(12)-C(11)	120.9(3)
C(24)-C(25)	1.498(4)	O(8)-C(13)-C(14)	108.2(2)

C(19)-C(14)-C(15)	118.2(3)	C(28)-C(27)-C(20)	112.1(2)
C(19)-C(14)-C(13)	120.4(3)	N(1)-C(28)-C(36)	109.9(2)
C(15)-C(14)-C(13)	121.3(3)	N(1)-C(28)-C(27)	108.8(2)
C(14)-C(15)-C(16)	120.6(4)	C(36)-C(28)-C(27)	109.6(2)
C(17)-C(16)-C(15)	120.3(4)	O(2)-C(29)-O(1)	126.4(3)
C(18)-C(17)-C(16)	119.3(4)	O(2)-C(29)-N(2)	123.6(3)
C(17)-C(18)-C(19)	120.1(4)	O(1)-C(29)-N(2)	110.0(2)
C(14)-C(19)-C(18)	121.4(4)	O(1)-C(30)-C(31)	108.5(3)
O(5)-C(20)-C(21)	106.0(2)	O(1)-C(30)-C(33)	110.7(3)
O(5)-C(20)-C(27)	112.3(2)	C(31)-C(30)-C(33)	112.7(4)
C(21)-C(20)-C(27)	112.9(2)	O(1)-C(30)-C(32)	103.0(2)
O(3)-C(21)-C(20)	110.5(2)	C(31)-C(30)-C(32)	112.9(4)
O(3)-C(21)-C(22)	104.1(2)	C(33)-C(30)-C(32)	108.8(3)
C(20)-C(21)-C(22)	104.7(2)	N(1)-C(35)-C(1)	118.8(2)
O(4)-C(22)-C(23)	110.7(2)	N(1)-C(35)-C(7)	122.8(2)
O(4)-C(22)-C(21)	104.4(2)	C(1)-C(35)-C(7)	118.4(2)
C(23)-C(22)-C(21)	105.4(2)	O(6)-C(36)-O(7)	125.0(3)
O(8)-C(23)-O(5)	113.0(2)	O(6)-C(36)-C(28)	125.9(3)
O(8)-C(23)-C(22)	107.8(2)	O(7)-C(36)-C(28)	109.1(2)
O(5)-C(23)-C(22)	106.4(2)	C(34)-C(37)-O(7)	107.9(3)
O(4)-C(24)-O(3)	103.2(2)	C(35)-N(1)-C(28)	120.9(2)
O(4)-C(24)-C(25)	109.8(3)	C(29)-N(2)-C(27)	123.6(2)
O(3)-C(24)-C(25)	108.7(3)	C(29)-O(1)-C(30)	121.2(2)
O(4)-C(24)-C(26)	110.2(3)	C(21)-O(3)-C(24)	108.0(2)
O(3)-C(24)-C(26)	111.2(3)	C(22)-O(4)-C(24)	108.4(2)
C(25)-C(24)-C(26)	113.3(3)	C(23)-O(5)-C(20)	109.3(2)
N(2)-C(27)-C(28)	109.5(2)	C(36)-O(7)-C(37)	116.6(2)
N(2)-C(27)-C(20)	108.1(2)	C(23)-O(8)-C(13)	114.5(2)

Symmetry transformations used to generate equivalent atoms:

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

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	50(2)	52(2)	37(2)	-2(1)	-1(1)	6(1)
C(2)	63(2)	149(4)	44(2)	10(2)	0(2)	29(2)
C(3)	91(3)	169(4)	41(2)	15(2)	-9(2)	42(3)
C(4)	95(3)	102(3)	35(2)	3(2)	12(2)	14(2)
C(5)	73(2)	101(3)	47(2)	2(2)	15(2)	9(2)
C(6)	59(2)	79(2)	42(2)	2(2)	0(2)	13(2)
C(7)	47(2)	63(2)	38(2)	7(1)	0(1)	5(2)
C(8)	66(2)	78(2)	96(3)	0(2)	9(2)	-4(2)
C(9)	58(3)	122(4)	125(4)	15(3)	6(2)	-22(2)
C(10)	61(3)	140(4)	106(3)	10(3)	21(2)	16(3)
C(11)	72(3)	109(3)	88(3)	-4(2)	13(2)	25(2)
C(12)	59(2)	75(2)	68(2)	6(2)	7(2)	14(2)
C(13)	54(2)	102(3)	69(2)	2(2)	-4(2)	17(2)
C(14)	44(2)	87(3)	59(2)	-12(2)	4(2)	3(2)
C(15)	94(3)	101(3)	84(3)	-27(2)	14(2)	-17(2)
C(16)	116(4)	102(3)	117(4)	-6(3)	17(3)	-47(3)
C(17)	77(3)	139(4)	89(3)	-1(3)	31(2)	-22(3)
C(18)	84(3)	119(4)	85(3)	-18(3)	23(2)	3(2)
C(19)	73(2)	85(2)	74(2)	-12(2)	6(2)	6(2)
C(20)	46(2)	54(2)	41(2)	8(1)	5(1)	7(1)
C(21)	54(2)	43(2)	64(2)	4(1)	-3(2)	6(1)
C(22)	61(2)	62(2)	56(2)	-2(2)	1(2)	-3(2)
C(23)	60(2)	54(2)	52(2)	-3(2)	5(2)	7(2)
C(24)	56(2)	65(2)	78(2)	-3(2)	-8(2)	-5(2)
C(25)	95(3)	74(2)	117(3)	9(2)	-8(2)	-30(2)
C(26)	92(3)	133(4)	124(4)	0(3)	-40(3)	-8(3)
C(27)	55(2)	48(2)	31(1)	1(1)	5(1)	7(1)
C(28)	54(2)	51(2)	33(2)	1(1)	3(1)	5(1)
C(29)	61(2)	53(2)	40(2)	-3(1)	-4(2)	7(2)
C(30)	77(2)	66(2)	68(2)	3(2)	-12(2)	29(2)
C(31)	134(4)	81(3)	342(9)	94(5)	42(5)	27(3)

C(32)	133(4)	106(3)	91(3)	-23(2)	-15(3)	74(3)
C(33)	128(4)	208(6)	95(3)	-56(4)	-58(3)	82(4)
C(34)	212(6)	103(3)	84(3)	36(3)	-23(3)	-20(4)
C(35)	44(2)	49(2)	39(2)	4(1)	-2(1)	3(1)
C(36)	56(2)	64(2)	45(2)	4(2)	1(1)	3(2)
C(37)	114(3)	70(2)	74(3)	21(2)	-2(2)	-21(2)
N(1)	48(1)	61(2)	39(1)	2(1)	7(1)	8(1)
N(2)	56(1)	56(1)	34(1)	5(1)	4(1)	16(1)
O(1)	75(1)	57(1)	45(1)	-4(1)	-3(1)	28(1)
O(2)	105(2)	109(2)	38(1)	4(1)	1(1)	52(2)
O(3)	59(1)	65(1)	88(2)	-9(1)	19(1)	-8(1)
O(4)	70(2)	59(1)	98(2)	-21(1)	7(1)	-9(1)
O(5)	56(1)	51(1)	50(1)	4(1)	-3(1)	12(1)
O(6)	146(2)	63(1)	59(1)	-14(1)	-3(2)	-11(1)
O(7)	96(2)	59(1)	50(1)	9(1)	7(1)	-12(1)
O(8)	46(1)	81(1)	58(1)	7(1)	5(1)	4(1)

Table 4. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$)

	x	y	z	U(eq)
H(2)	5433	4687	3962	103
H(3)	4839	4414	4929	120
H(4)	2713	4583	5226	93
H(5)	1146	5013	4558	88
H(6)	1711	5255	3594	72
H(8)	6002	6198	3006	96
H(9)	8160	5963	2701	122
H(10)	8792	4640	2407	123
H(11)	7325	3565	2386	108
H(12)	5189	3778	2690	81
H(13A)	5361	3330	938	90
H(13B)	5315	4197	1293	90
H(15)	5735	5522	762	111
H(16)	6692	6184	-33	134
H(17)	7232	5422	-865	122
H(18)	6922	3988	-873	115
H(19)	5928	3334	-86	92
H(20)	1438	4315	2219	57
H(21)	403	4539	1158	64
H(22)	1529	3659	552	71
H(23)	3313	2899	1206	66
H(25A)	-593	1569	1456	143
H(25B)	-1497	2172	1841	143
H(25C)	6	2053	2008	143
H(26A)	-952	3438	573	175
H(26B)	-2094	3085	982	175
H(26C)	-1300	2461	566	175
H(27)	2417	5373	1298	54
H(28)	4169	5168	1969	55
H(31A)	422	8268	1601	279
H(31B)	-576	8550	1100	279
H(31C)	432	7805	979	279

H(32A)	-2580	7387	2097	165
H(32B)	-2401	8307	1831	165
H(32C)	-1401	7965	2313	165
H(33A)	-1394	6910	702	216
H(33B)	-2508	7565	877	216
H(33C)	-2469	6661	1179	216
H(34A)	4613	7139	397	200
H(34B)	3924	8034	457	200
H(34C)	3072	7196	497	200
H(37A)	3472	7795	1415	103
H(37B)	5000	7631	1314	103
H(1)	2327	5485	2832	59
H(2A)	869	5810	2254	58

List of Abbreviations

Ac	Acetyl
AcOH	Acetic acid
2,6-lutidine	2,6-dimethylpyridine
Boc	tert-Buty carbamoyl
BOC_2O	di-tert-butyldicarbonate
brsm	Based on recovered starting material
BuLi	Butyl Lithium
CAN	Ceric ammonium nitrate
cat.	Catalytic
Cbz	benzylcarbamoyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
Dmb	Dimethylbenzyl
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
eq.	Equivalent
Et_2O	Diethyl ether
EtOAc	Ethyl acetate

EtOH	Ethanol
Fmoc	9-Fluorenylmethoxycarbonyl
HMDS	Hexamethyldisilazane
IBX	2-Iodoxybenzoic acid
im.	Imidazole
IR	Infrared spectroscopy
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
Mbs	Methoxybenzyl sulfonamide
Ms	Methanesulfonyl
NaHMDS	Sodium bis(trimethylsilyl)amide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
oNB	ortho-Nitrobenzyl
Ph	Phenyl
Piv	Pivaloyl
PMB	Para-methoxybenzyl
psi	Pound per square inch
PTLC	Preparative thin layer chromatography
py.	Pyridine
t-BuOK	Potassium tert-butoxide
TBAF	Tetrabutylammonium fluoride

TBDPS	tert-Butyldiphenylsilyl
TBS	tert-Butyldimethylsilyl
TCC	Trichloroisocyanuric Acid
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
Teoc	2-(Trimethylsilyl)ethylcarbamoyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride
TMSOTf	Trimethylsilyl triflate