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Macrocyclization of ω-Isocyanoaldehydes and Towards the Total Synthesis of Jamaicensamide A

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par

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Abstract

In the first chapter of this thesis, the macrocyclization of a new type of bifunctional substrates, *ω*-isocyanoaldehyde derivatives, is described. Ten different *ω*-isocyanoaldehydes in terms of different ring sizes and functional groups were prepared. They were smoothly proceeded under the simple multicomponent reactions including Passerini reaction, Ugi reaction and modified Ugi reaction. A wide range of 9- to 22-membered macrocyclic lactams were obtained in low to excellent yields with up to four bonds were formed in a single step.

In the second chapter, synthetic studies towards the total synthesis of cyclic peptide jamaicensamide A are presented. We applied our strategy to cyclize the advanced intermediate containing *ω*-isocyanoaldehyde into the cyclic peptide in one-pot procedure. The precursors for the preparation of *ω*-isocyanoaldehydes with different functional groups and protecting groups were prepared. The derived 24-membered cyclic peptides were formed in good yields. The study on the deprotection of protecting groups is still on-going to complete the total synthesis of jamaicensamide A.

Keywords

macrocyclization, *ω*-isocyanoaldehyde, multicomponent reactions (MCRs), total synthesis, cyclic peptide, jamaicensamide A

Résumé

Dans le premier chapitre de cette thèse est décrite la macrocyclisation d'un nouveau type de substrats bifonctionnels, les dérivés de ω-isocyanoaldehyde. Dix différents substrats de tailles de cycles variable et aborant différents groupements fonctionnels ont été préparés. Ces substrats ont réagit lors de réactions multicomposants de type Passerini, Ugi, ainsi qu'une version modifié de Ugi. Un large spectre de lactames macrocycliques (de 9 à 22 chaînons) a été obtenus avec des rendements allant de faibles à excellents. Jusqu'à quatre liaisons ont été formés lors de cette synthèse monotope.

Le deuxième chapitre de cette thèse est consacré à nos études visant à accomplir la synthèse totale du peptide cyclique jamaicensamide A. La stratégie de cyclisation d'un substrat avancé transformant un ω-isocyanoaldehyde en peptide cyclique a été appliqué avec succès de facon monotope. Les précurseurs nécessaires à la préparation du substrat contenant le ω-isocyanoaldehydes ont été préparés avec différents groupements fonctionnels et protecteurs. Les peptides cycliques à 24 chaînons ont été formés avec de bons rendements. Les études de la déprotection finale de l'ensemble des groupements protecteurs sont en cours dans l'objectif de terminer la synthèse totale de jamaicensamide A.

Mots-clés

Macrocyclisation, ω-isocyanoaldehyde, reactions multicomposants (MRC), synthèse totale, peptide cyclique, jamaicensamide A

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List of Abbreviations

s	=	singlet
d	=	doublet
t	=	triplet
m	=	multiplet
br	=	broad
dd	=	doublet of doublet
td	=	triplet of doublet
δ	=	chemical shift relative to TMS
J	=	coupling constant
c	=	concentration
$^{\circ}$C	=	degree Celsius
Å	=	angstrom (10^{-10} meters)
calcd.	=	calculated
equiv	=	equivalent
h	=	hour
m/z	=	a value of mass divided by charge
mg	=	milligram
mL	=	milliliter
mmol	=	millimole
M	=	molar
cm^{-1}	=	reciprocal centimeter (wavenumber)
ppm	=	part per million
ν	=	absorption frequencies
Hz	=	Hertz
MHz	=	megaHertz
TLC	=	thin-layer chromatography
FT-IR	=	Fourier Transform Infrared
HRMS	=	High Resolution Mass Spectroscopy
ESI	=	Electronspray Ionization

NMR	=	Nuclear Magnetic Resonance
$CDCl_3$	=	deuterochloroform
DMSO-d_6	=	deuterated dimethyl sulfoxide
CH_2Cl_2	=	dichloromethane
CH_3CN	=	acetronitrile
EtOH	=	ethanol
EtOAc	=	ethyl acetate
H_2O	=	water
MeOH	=	methanol
$NaHCO_3$	=	sodium hydrogen carbonate
NaOH	=	sodium hydroxide
Na_2SO_4	=	sodium sulfate
MRSA	=	Methicillin-resistant *Staphylococcus aureus*
MCRs	=	multicomponent reactions
Boc	=	*tert*-butyloxycarbonyl
Cbz	=	carboxybenzyl
DMAP	=	4-(dimethylamino)pyridine
CDI	=	carbonyldiimidazole
DEAD	=	diethyl azodicarboxylate
DBU	=	1,8-diazabicyclo(5.4.0)undec-7-ene
DAST	=	(diethylamino)sulfur trifluoride
DIBAL	=	diisobutylaluminium hydride
DMP	=	Dess–Martin periodinane
EDTA	=	ethylenediaminetetraacetic acid
IBX	=	2-iodoxybenzoic acid
HWE	=	Horner–Wadsworth–Emmons
LAH	=	lithium aluminium hydride
PCC	=	pyridinium chlorochromate
TMS	=	tetramethylsilane
TBS	=	*tert*-Butyldimethylsilyl
TBAF	=	tetra-*n*-butylammonium fluoride
TASF	=	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TFA	=	trifluoroacetic acid
TIPS	=	triisopropylsilyl

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Chapter 1
Macrocyclization of *ω*-Isocyanoaldehydes

1.1 Introduction

1.1.1 Bioactive macrolactams

A wide variety of macrolactams have been isolated from natural sources. Many of them showed interesting biological activities (Figure 1).[1] Vicenistatin, a 20-membered macrocyclic lactam isolated from the culture broth of *Streptomyces* sp. HC34, exhibited antitumor activity.[2] Leinamycin also showed potent antitumor activity against tumor cell lines that were resistant to anticancer drugs.[3] The polyene macrolactam salinilactam was first isolated from marine Actinomycete *Salinispora tropica*.[4] A *Streptomyces* strain produced BE-14106 which inhibited the growth of leukemia cell lines and displayed antimicrobial activity.[5] A 22-membered macrolactam, aureoverticilactam, from the marine Actinomycete *Streptomyces aureoverticillatus* showed cytotoxicity against various tumor cell lines.[6] An antibiotic Fluvirucin B1 exhibited potent inhibitory activity against influenza A.[7] Hitachimycin, a 19-membered macrolactam possessing a β-phenylalanine, exhibited antitumor activity.[8] Cremimycin, another example of 19-membered macrolactam, showed broad antimicrobial activities against Gram-positive bacteria as well as MRSA.[9] A potent antiproliferative silvalactam was produced by *Streptomyces* strain.[10]

1.1.2 Macrocyclizations of bifunctional substrates

Because of the biological activities of macrocyclic lactams, many methods have been developed for their synthesis. One of the most interest of our group is the macrocyclization using the chemistry of multicomponent reactions (MCRs), especially the Passerini and Ugi reactions. To construct the macrocycles in one step, bifunctional substrates have been used. Six theoretical possibilities of the bifunctional substrates for macrocyclizations through the Ugi reaction was represented in Figure 2.[11]

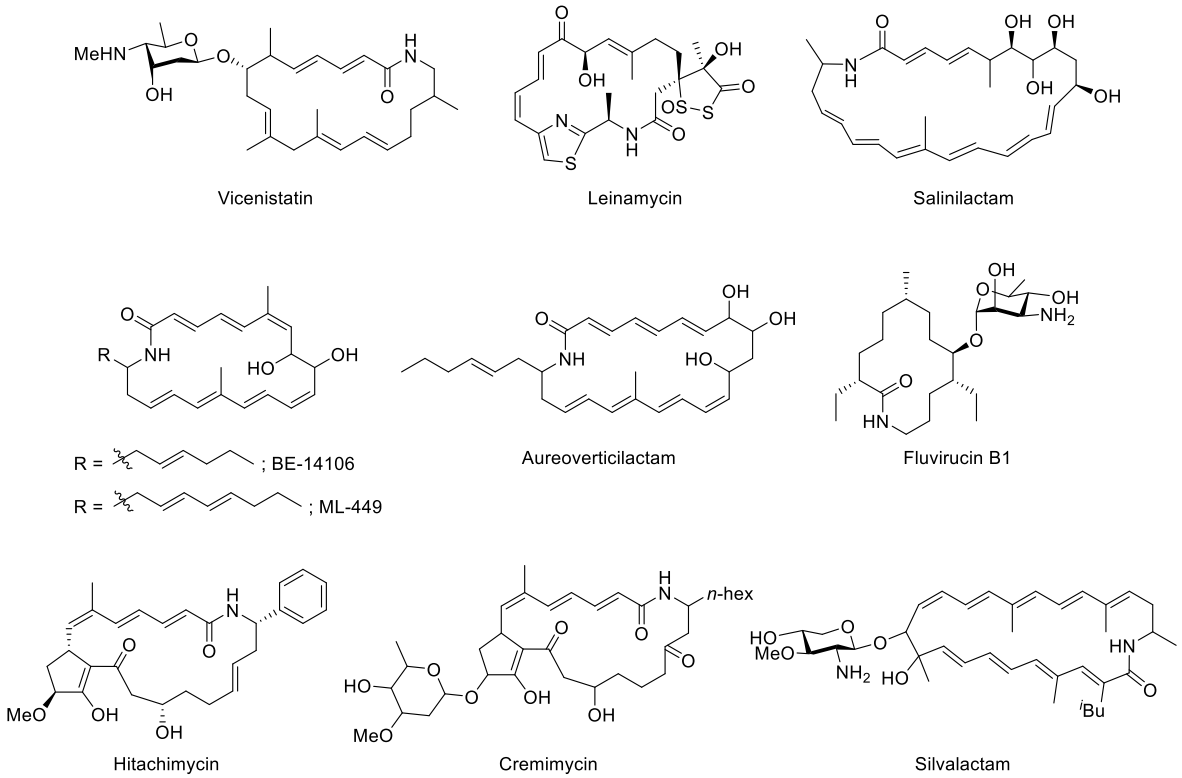


Figure 1. Structures of bioactive macrolactams.

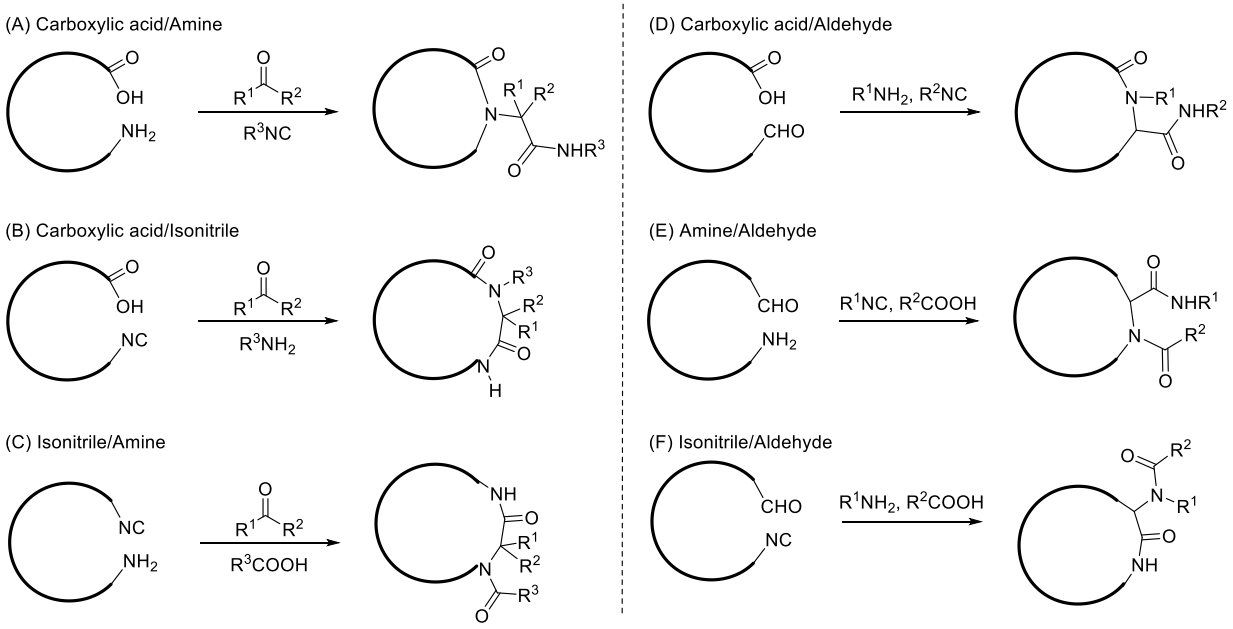
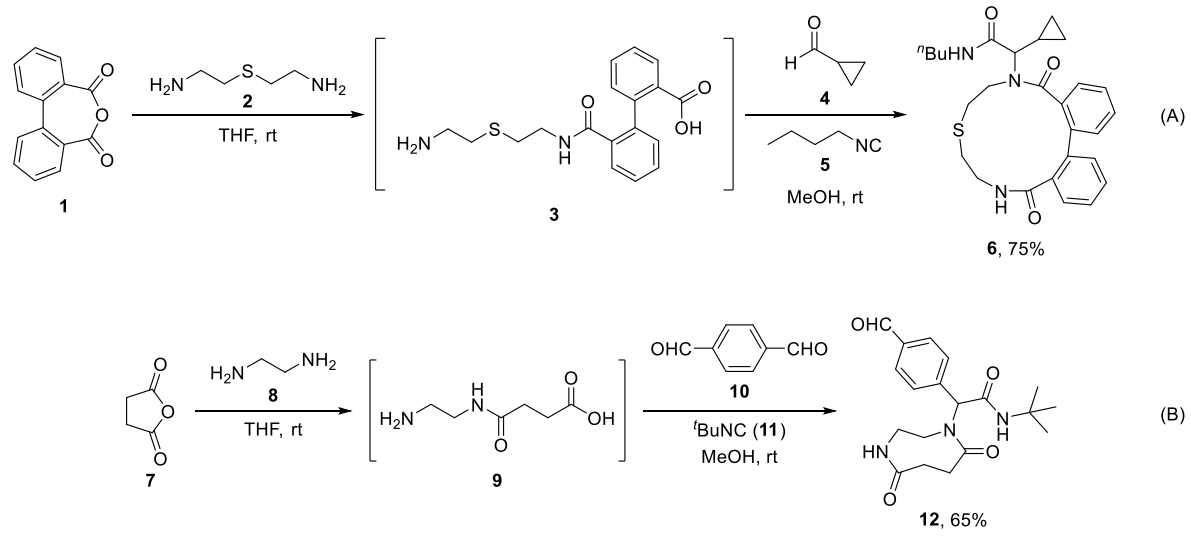


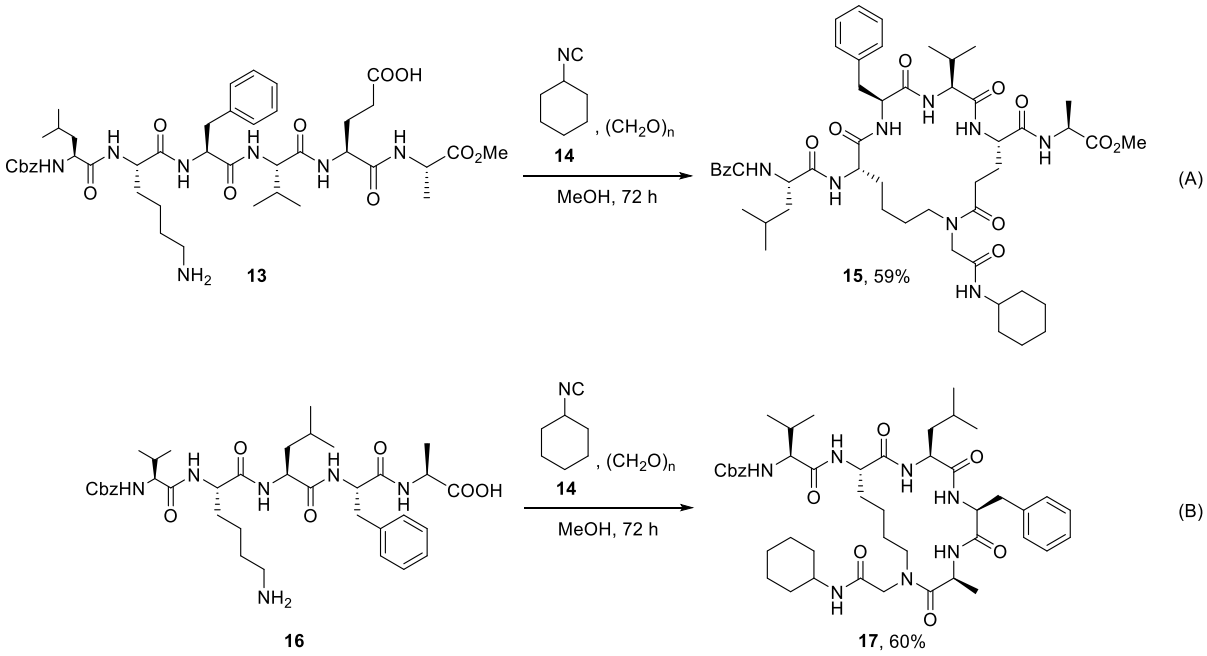
Figure 2. Six possibilities of bifunctional substrates for macrocyclizations via the Ugi reaction.

The most widely explored bifunctional substrate is the tethering of carboxylic acid and amine (ω-amino acid) (Figure 2, A). In 2017, Dömling and coworkers applied the Ugi-4-center 3-component reaction for the ω-amino acids (**3** for instance) to afford various 8- to 19-membered macrocycles in low to good yields (Scheme 1, A).[12] In the same year, they reported the synthesis of medium-sized rings by using the same strategy. 8- to 11-membered cyclic products were obtained in 22-65% yields (Scheme 1, B).[13] ω-Amino acids **3** and **9** were prepared from the condensation of cyclic anhydrides **1** and **7** with alkyl diamines **2** and **8**, respectively.



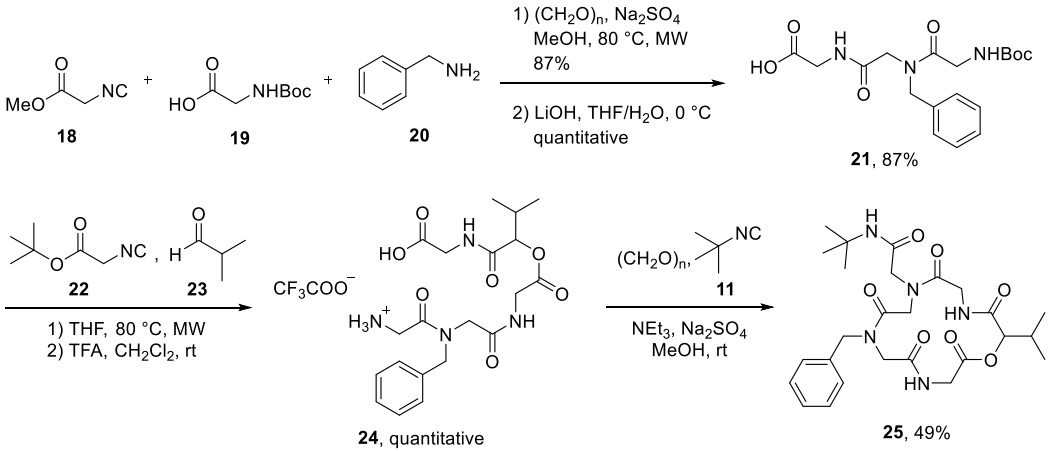
Scheme 1. The synthesis of macrocycles and medium-sized rings from ω-amino acids.

The ω-amino acids were applied for the macrocyclizations of peptides. Side chain-to-side chain peptide macrocyclization precursor **13** for the Ugi reaction was reacted with cyclohexyl isocyanide (**14**) and paraformaldehyde in MeOH for 72 hours. Macrocycle **15** was obtained in 59% yield (Scheme 2, A). In addition, the Ugi reaction of the peptide **16** for the side chain-to-termini peptide macrocyclization yielded macrocycle **17** in 60% (Scheme 2, B).[14]



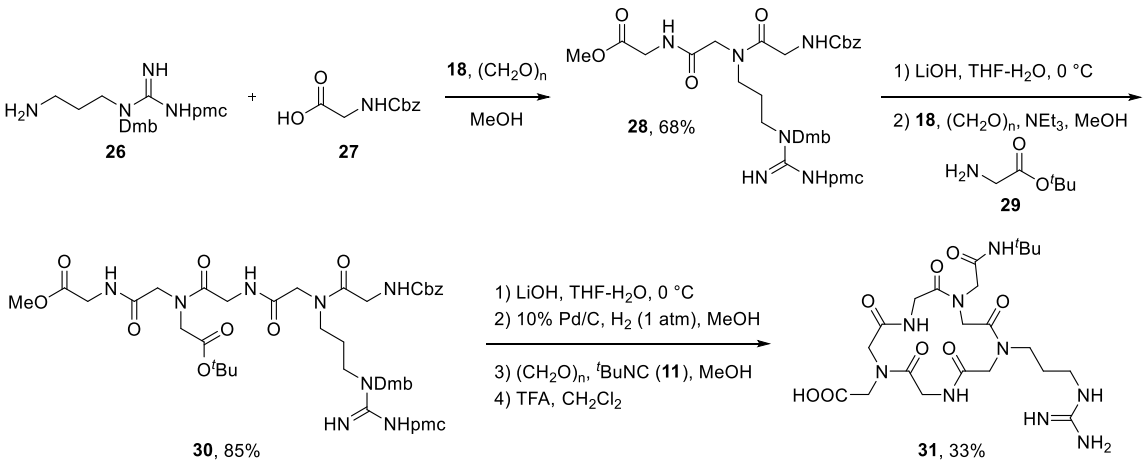
Scheme 2. Macrocyclizations of peptide side chains by the Ugi reaction.

Sequential Ugi reaction was applied for the synthesis of cyclic pentadepsipeptoids. An example was depicted in Scheme 3. The first Ugi 4-component reaction using methyl isocyanoacetate (**18**), *N*-Boc-glycine (**19**), benzylamine (**20**) and paraformaldehyde, followed by hydrolysis provided peptoid **21**. A Passerini reaction of acid **21** with *tert*-butyl isocyanoacetate (**22**) and isobutyraldehyde (**23**) gave acyclic depsipeptoid **24** in quantitative yield. The ω-amino acid **24** was subjected to the Ugi three-component four-center reaction (U-3C4CR), affording cyclic pentadepsipeptoid **25** in moderate yield.[15]



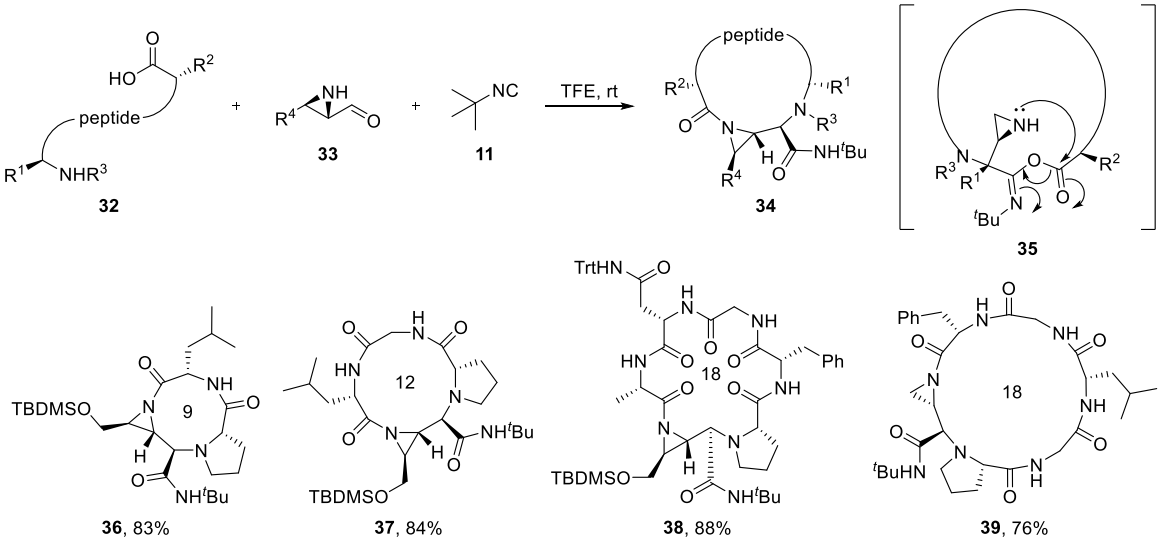
Scheme 3. Synthesis of cyclic pentadepsipeptoids by sequential Ugi reaction.

Cyclopeptoid **31** was also synthesized by the consecutive Ugi reactions. For the last Ugi reaction of ω-amino acid derived from **30**, pseudo-high-dilution conditions was applied to avoid oligomerization (Scheme 4).[16]



Scheme 4. Synthesis of cyclopeptoid 31.

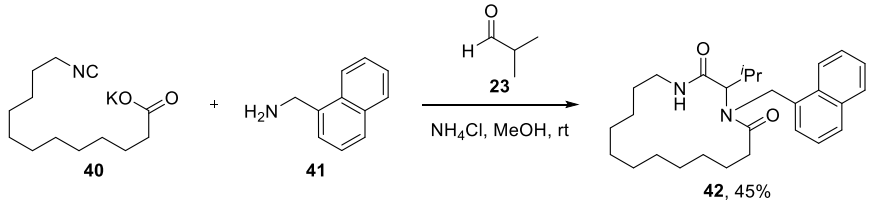
Yudin and coworkers reported the macrocyclizations of linear peptides enabled by amphoteric amino aldehydes (**33**). The nucleophilic center at the α-position of the amphoteric amino aldehyde is responsible for the Mumm rearrangement instead of the amino group of the ω-amino acid **32**. 9- to 18-membered cyclic peptides were produced in good yields (Scheme 5).[17]



Scheme 5. The Ugi reaction of linear peptides and amphoteric amino aldehydes.

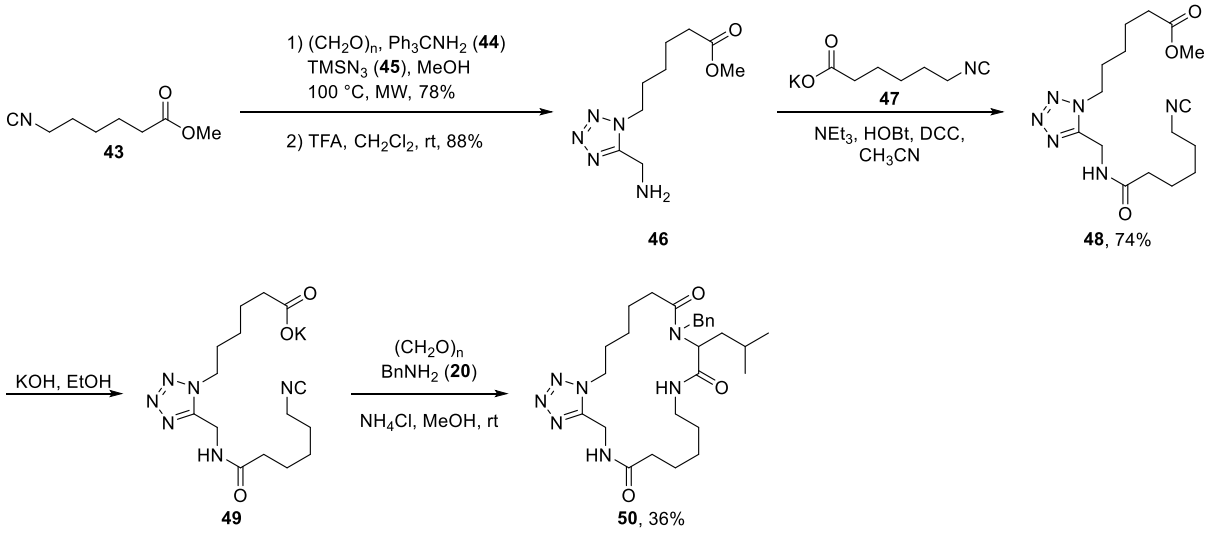
α-Isocyano-ω-carboxylic acid (Figure 2, B), a type of the bifunctional substrates, is also investigated for the macrocyclizations. A few research groups have studied on this type of substrate. In

2015, Dömling reported the macrocyclizations of *α*-isocyano-*ω*-carboxylic acid **40**. The cyclic Ugi products were obtained in 34-45% yields (Scheme 6).[18]



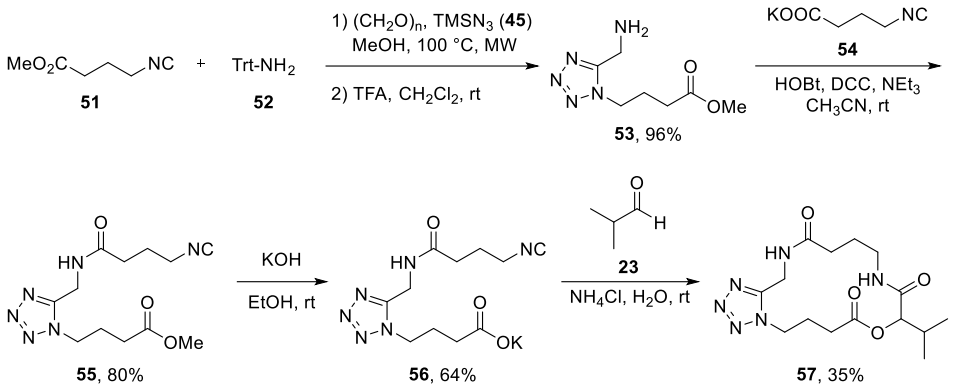
Scheme 6. An example of cyclic Ugi products derived from *α*-isocyano-*ω*-carboxylic acid 40.

In order to introduce more complexity and flexibility, the overall macrocycle was achieved by the union of two orthogonal MCRs. The first Ugi 4-component reaction was applied to provide a suitable substrate for the second multicomponent reaction. The tetrazole ring (**46**) was constructed via the first Ugi tetrazole synthesis by using $TMSN_3$ as the source of HN_3. After the intramolecular Ugi reaction of **49**, macrolactam **50** was obtained in 36% (Scheme 7).[18]



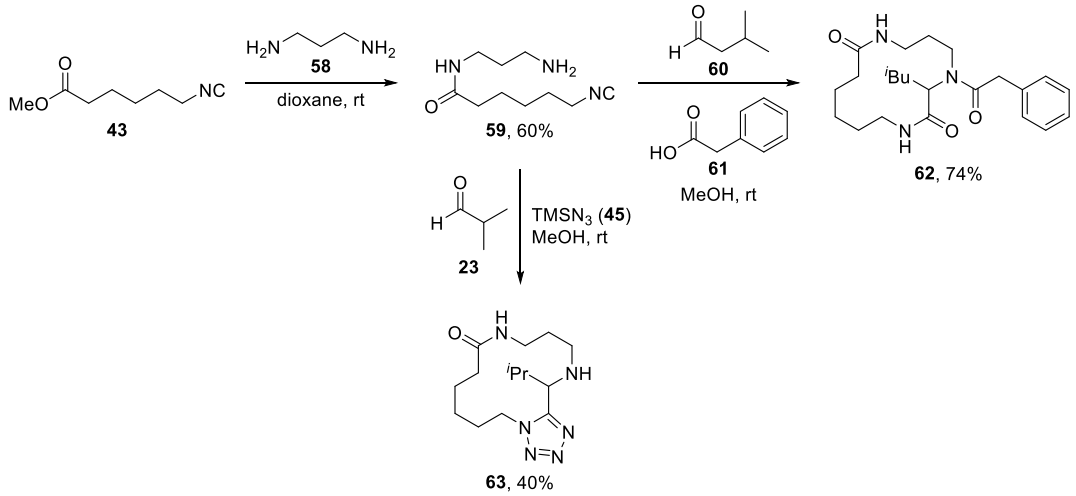
Scheme 7. An example of macrocycles synthesis using the union of two MCRs.

In 2016, Dömling and coworkers used the same strategy for the synthesis of macrocyclic depsipeptides. Yields of the first linear Ugi products (**53** for instance) were moderate to excellent. On the other hand, the macrocyclization process gave the cyclic depsipeptides (**57** for instance) in low yields (20-36%) (Scheme 8).[19]



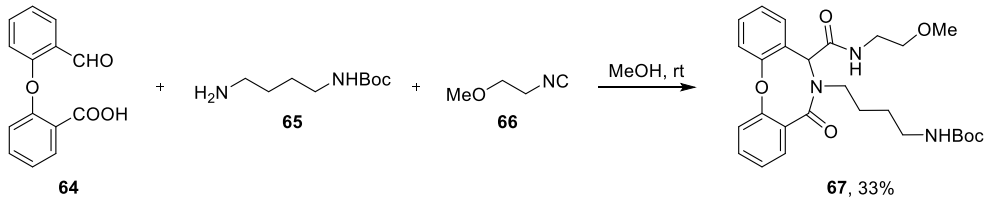
Scheme 8. The synthesis of macrocyclic depsipeptides under 4-step procedure.

Recently, Dömling group introduced *α*-isocyano-*ω*-amines (Figure 2, C), a type of bifunctional substrates, for the macrocyclization. For example, *α*-isocyano-*ω*-amine **59** was prepared from the amidation of isocynoester **43** and 1,3-diaminopropane (**58**). The Ugi reaction of **59** with isovaleraldehyde (**60**) and 2-phenylacetic acid (**61**) produced the macrolactam **62** in 74%.[11] In addition, Ugi tetrazole **63** was obtained in 40% from the reaction of **59** with isobutyraldehyde (**23**) and $TMSN_3$ (**45**) (Scheme 9).[20]



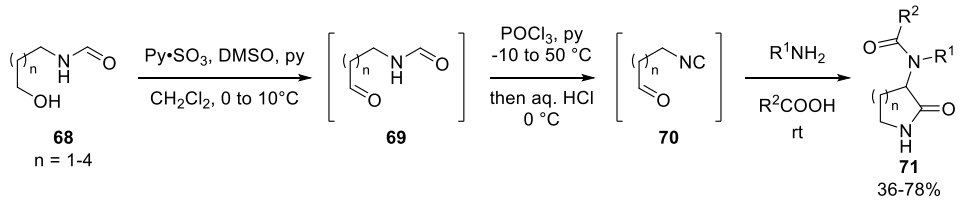
Scheme 9. Synthesis of macrocyclic lactams using *α*-isocyano-*ω*-amine.

In 1999, Zhang and coworkers introduced the bifunctional starting materials containing aldehyde and carboxylic acid (Figure 2, D) for the synthesis of medium-sized lactams. 5- to 8-membered rings were investigated and 8-membered ring lactams were produced in low yields (19-42%), presumably due to the difficulties of forming that 8-membered ring (Scheme 10).[21]



Scheme 10. 8-membered ring lactam form the Ugi reaction of aldehyde tethering acid substrate.

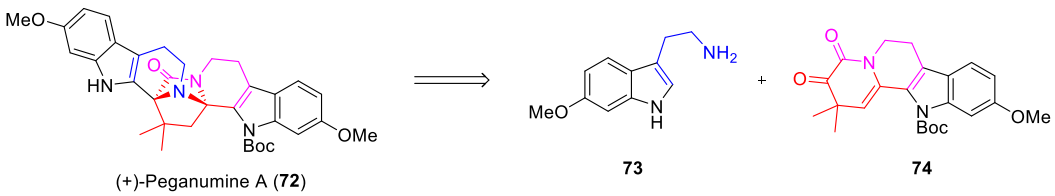
In 2012, Saxena group used the alcohol/formamide (**68**) as the substrates for the intramolecular Ugi reaction to synthesized 5- to 8-membered lactams via the sequential procedure. The sequence was the Parikh-Doering oxidation of primary alcohol, dehydration of formamide followed by Ugi reaction. The synthesized 5- to 8-membered rings were obtained in moderate to good yields (Scheme 11).[22]



Scheme 11. Sequential procedure for the synthesis of medium-sized lactams.

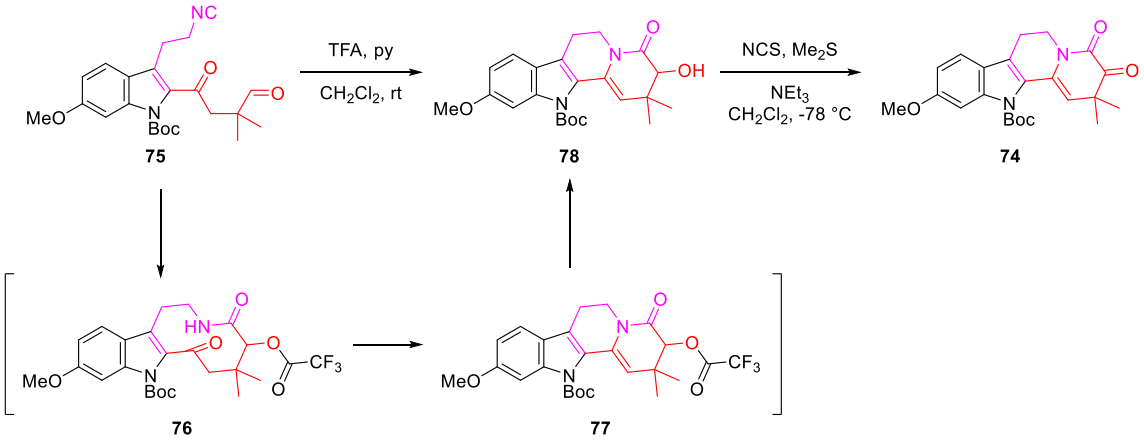
1.1.3 Synthesis of (+)-peganumine A

In 2016, our group reported the enantioselective synthesis of (+)-peganumine A (**72**). The octacyclic structure of **72** was constructed through the enantioselective Pictet-Spengler reaction of two achiral building blocks (**73** and **74**) (Scheme 12).[23]



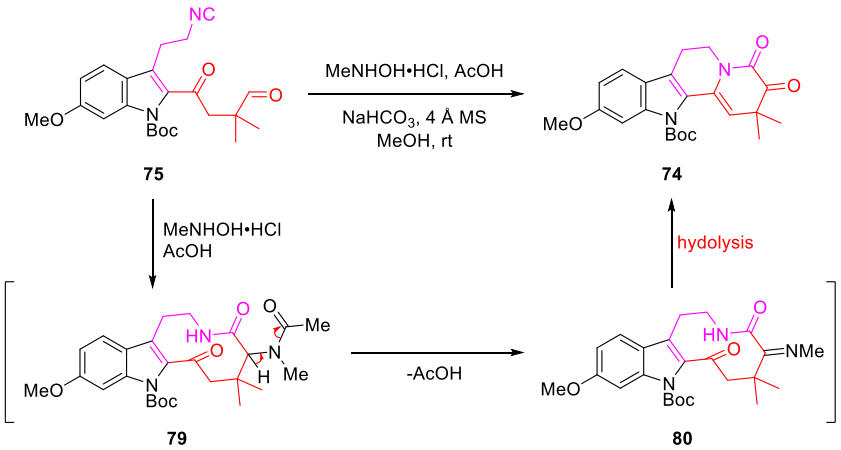
Scheme 12. Retrosynthesis of the (+)-peganumine A.

Both achiral building blocks (**73** and **74**) were prepared from 6-methoxytryptamine. Interestingly, tetracyclic **74** was prepared from the multicomponent reactions of ω-isocyano-γ-oxoaldehyde **75**. Tetracyclic **74** could be obtained in two steps from **75** by the Passerini 3-center-2-component with TFA in the present of pyridine, followed by the Corey-Kim oxidation of corresponding alcohol **78** (Scheme 13).



Scheme 13. Two-step synthesis of tetracyclic 74.

Moreover, a single-step preparation of tetracyclic *α*-ketoamide **74** was achieved by hydroxylamine-mediated intramolecular oxidative coupling of *ω*-isocyano-*γ*-oxoaldehyde **75** (Scheme 14).



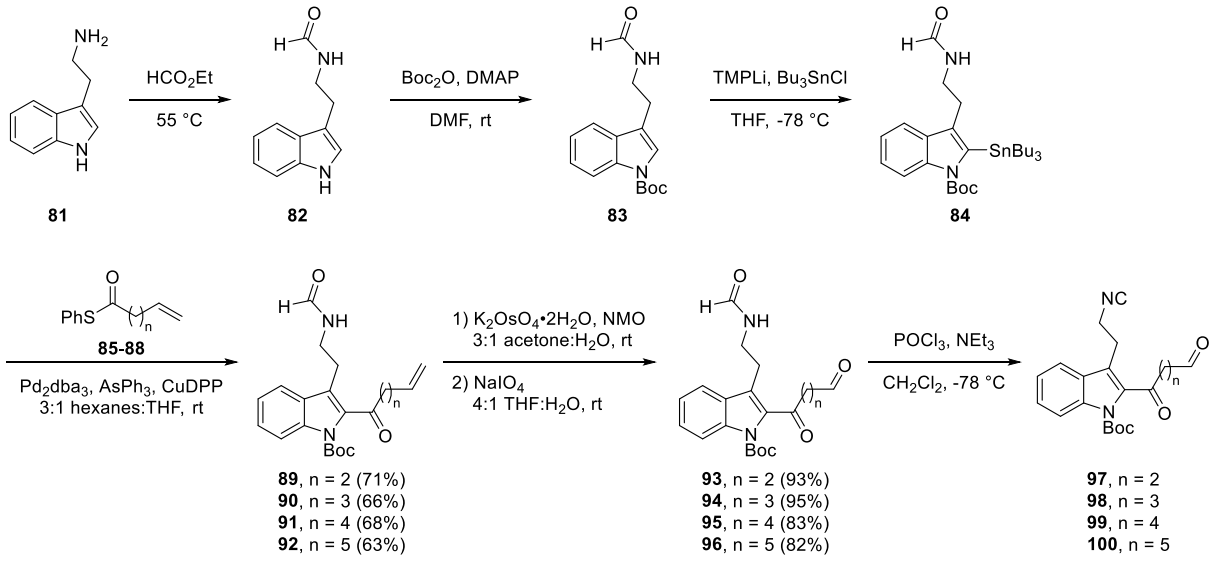
Scheme 14. Single-step synthesis of tetracyclic 74.

From this report, we realized that the macrocyclization of a new type of the bifunctional substrates, *ω*-isocyanoaldehyde (Figure 2, F), could be applied to other substrates to provide a wide range of macrocyclic lactams which displayed various biological activities (Figure 1).

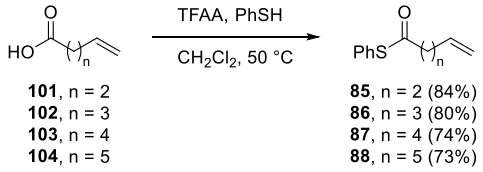
1.2 Results

1.2.1 Synthesis of starting materials

The indole-containing compounds was the first type of substrates that was tried for the macrocyclization. It was prepared from tryptamine as follow in Scheme 15. The primary aliphatic amine of tryptamine (**81**) was formylated chemoselectively with ethyl formate under reflux conditions to give **82** as brown oil. Without further purification, the indolic nitrogen of compound **82** was protected with Boc_2O in the present of DMAP in DMF to afford compound **83** in 75% yield (over 2 steps).[23,24] To prepare the material for the Liebeskind−Srogl cross-coupling reaction, stannylated indole **84** was furnished in 75% yield by C2-lithiation of **83** using TMPLi followed by quenching with tributyltin chloride.[25] The other coupling partner is thioester derivative. Four thioesters (**85-88**) were prepared in one step in 73-84% yields from alkenyl acids and thiophenol (Scheme 16).[23,26] The Liebeskind−Srogl cross-coupling reaction was performed under the optimized conditions: [Pd_2dba_3 (10 mol%), $AsPh_3$ (10 mol%), copper(I) diphenylphosphinate (CuDPP, 2.0 equiv) in 3:1 hexanes:THF (*c* 0.067 M) at room temperature for 6 h].[23] The coupling products (**89-92**) were obtained in 63-71% yields. The coupling reaction between **84** and *S*-phenyl 4-oxobutanethioate was performed and the corresponding product (**93**) was obtained in low yield (37%). As the ozonolysis of alkene **89** gave trace amount of aldehyde **93**, two-step conversion of alkene moiety to aldehyde was performed. The sequential dihydroxylation and oxidative cleavage of compounds **89-92** gave the aldehydes **93-96** in 82-95% yields.[27] To obtain the *ω*-isocyanoaldehydes, dehydration of *N*-formamides **93-96** by using $POCl_3$ and NEt_3 afforded compounds **97-100**, which were used directly for the macrocyclization reactions.

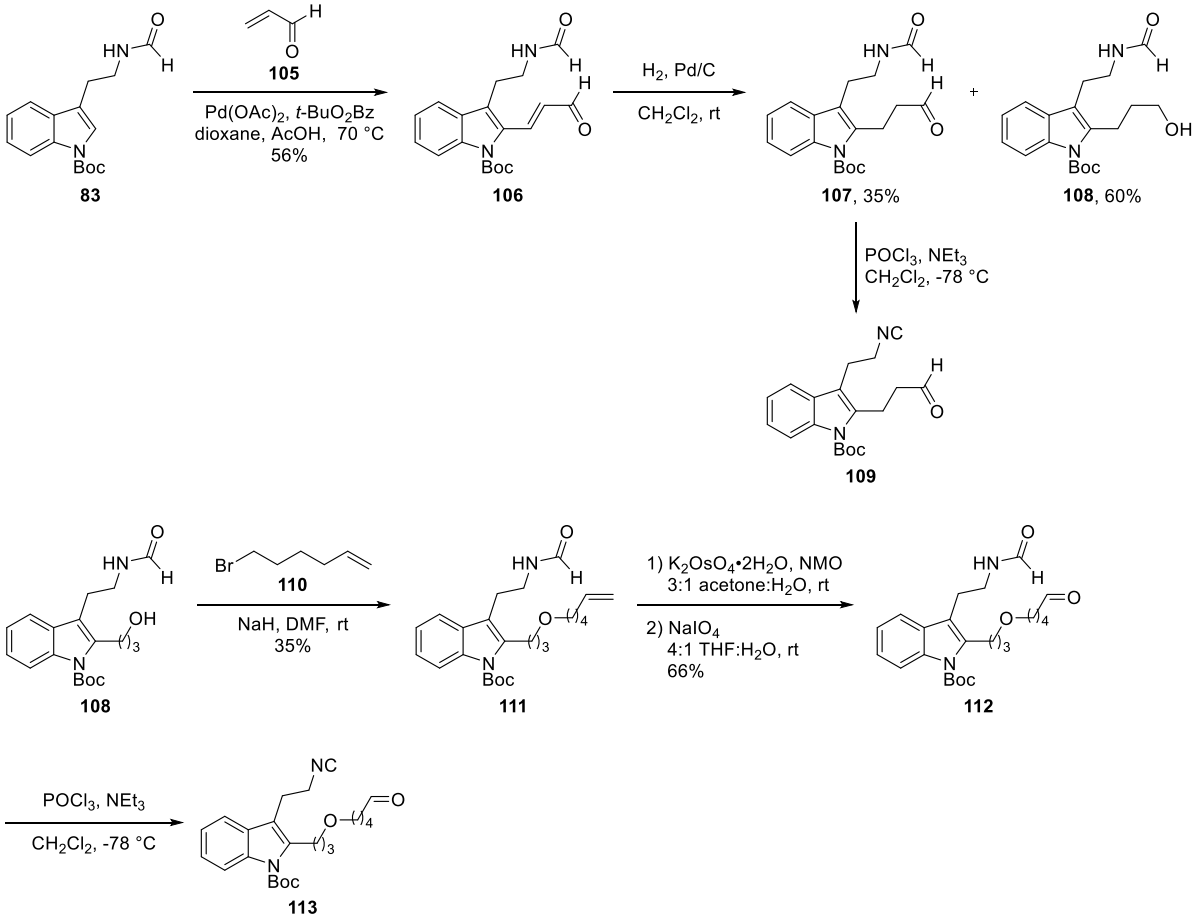


Scheme 15. The synthesis of indole-containing *ω*-isocyanoaldehydes 97-100.



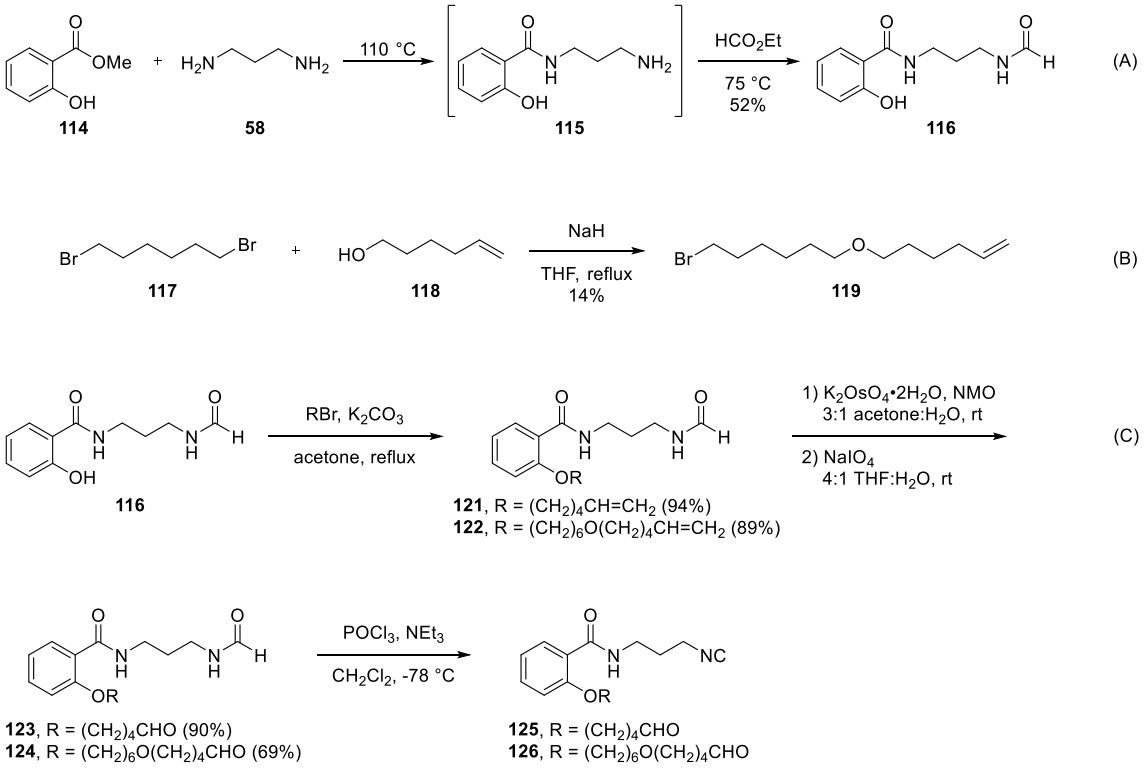
Scheme 16. The synthesis of thiophenols 85-88.

The alkyl-substituted indole derivatives were the next target. 9- and 15-membered ring precursors were prepared from **83**. The C−H functionalization via palladium-catalyzed alkenylation at C2 of indole **83** with acrolein (**105**) afforded unsaturated aldehyde **106** in 56% yield.[28] Hydrogenation of **106** in CH_2Cl_2 at room temperature for 6 h gave the corresponding aldehyde **107** and alcohol **108** in 35% and 60%, respectively.[28] The *N*-formamide **107** was converted to isonitrile **109** which was ready for the 9-membered ring cyclization. For the primary alcohol **108**, it was alkylated with 6-bromo-1-hexene (**110**) and the alkylated product was isolated in 35%.[29] The alkene **111** was converted to aldehyde **112** through dihydroxylation-oxidative cleavage process in 66% followed by the dehydration of *N*-formamide group to give isonitrile **113** for the 15-membered ring macrocyclization (Scheme 17).



Scheme 17. The synthesis of indole-containing *ω*-isocyanoaldehydes 109 and 113.

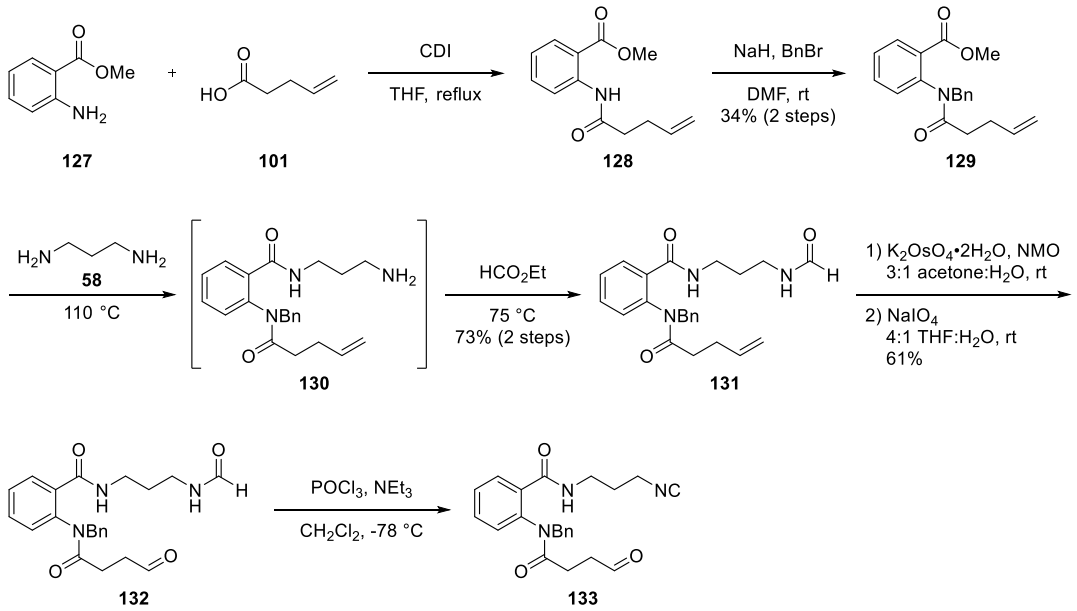
To provide the phenol-containing precursors, the synthesis began with the amide formation of methyl salicylate (**114**) with 1,3-diamino propane (**58**), yielding *N*-(3-aminopropyl)-2-hydroxybenzamide (**115**) which was used directly for the next step without purification. The formylation of crude primary amine **115** with ethyl formate at reflux temperature afforded phenol **116** in 52% (over 2 steps) and the diamide compound which was formed in the first reaction was also isolated in 31% (Scheme 18, A). Phenol **116** was alkylated with two different alkyl bromides, 6-bromo-1-hexene (**110**) and 6-((6-bromohexyl)oxy)hex-1-ene (**119**). Alkyl bromide **119** was obtained in 14% from the nucleophilic substitution reaction of 1,6-dibromohexane (**117**) and hex-5-en-1-ol (**118**) (Scheme 18, B). The alkylated products (**121** and **122**) were obtained in good yields. The conversion of terminal alkenes under the dihydroxylation-oxidative cleavage process yielded the corresponding aldehydes **123** in 90% and **124** in 69%. The phenol-containing precursors for the cyclization reaction were obtained from the dehydration of *N*-formamides **125** and **126** (Scheme 18, C).



Scheme 18. The synthesis of phenol-containing precursors.

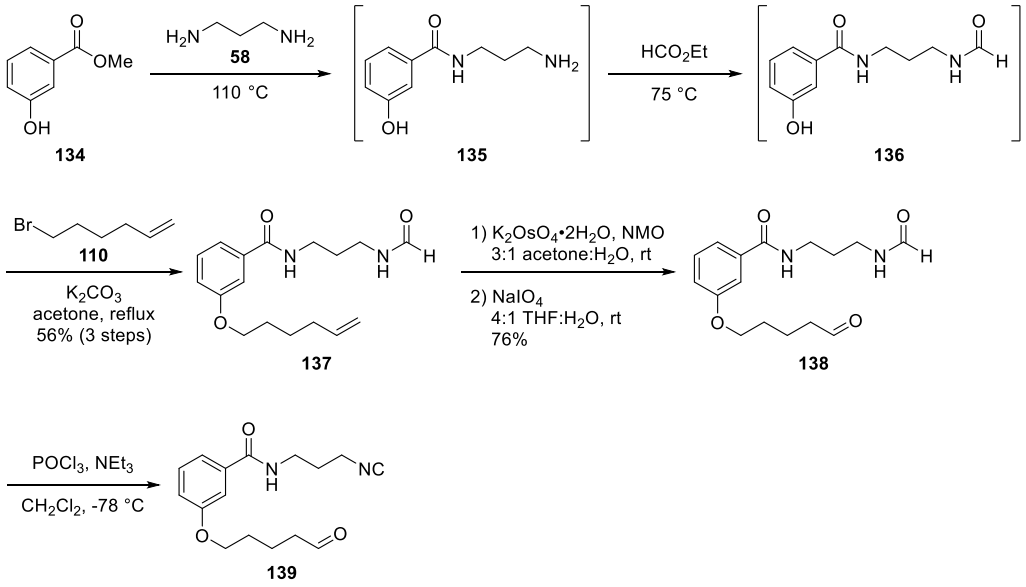
A benzamide precursor **133** for 14-membered ring cyclization was prepared from methyl anthranilate (**127**). 4-Pentenoic acid (**101**) was underwent mild decarboxylation in the present of CDI to generate a carbonyl imidazole intermediate which was reacted with methyl anthranilate (**127**) at reflux conditions to give amide **128**. The N-H of amide should be protected in order to avoid the hemiaminal formation with the terminal aldehyde functional group. Therefore, the crude of amide **128** was used directly for the *N*-benzylation step to afford the benzyl-protected amide **129** in 34% yield (over 2 steps).

The condensation of ester **129** and 1,3-diaminopropane (**58**) followed by the formylation of corresponding primary amino group yielded compound **131** in 73%. Aldehyde **132** was formed in 61% from a two-step procedure and the *ω*-isocyanoaldehyde **133** was obtained after the dehydration of *N*-formamide group (Scheme 19).



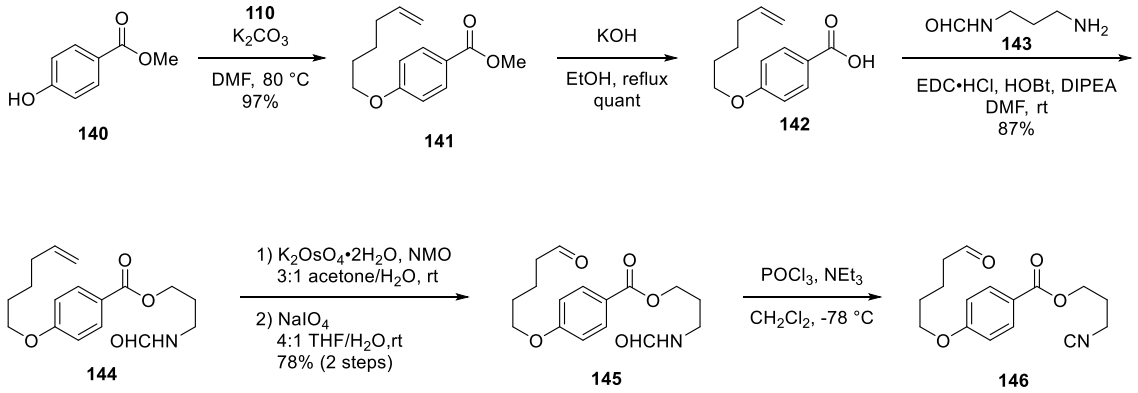
Scheme 19. The synthesis of benzamide precursor for the 14-membered ring cyclization.

A *m*-cyclophane precursor was obtained using the similar strategy of **125** (Scheme 20). Methyl 3-hydroxybenzoate (**134**) was subjected to a condensation reaction with 1,3-diaminopropane (**58**) at 110 °C, followed by the formylation of the present primary amine (**135**) with ethyl formate to give phenol **136**. The alkylation of **136** with 6-bromo-1-hexene (**110**) yielded **137** in 56% (over 3 steps). Conversion of terminal alkene **137** to aldehyde **138** was accomplished in 76% and the dehydration of *N*-formamide furnished the precursor of *m*-cyclophane **139**.



Scheme 20. The synthesis of *m*-cyclophane precursor.

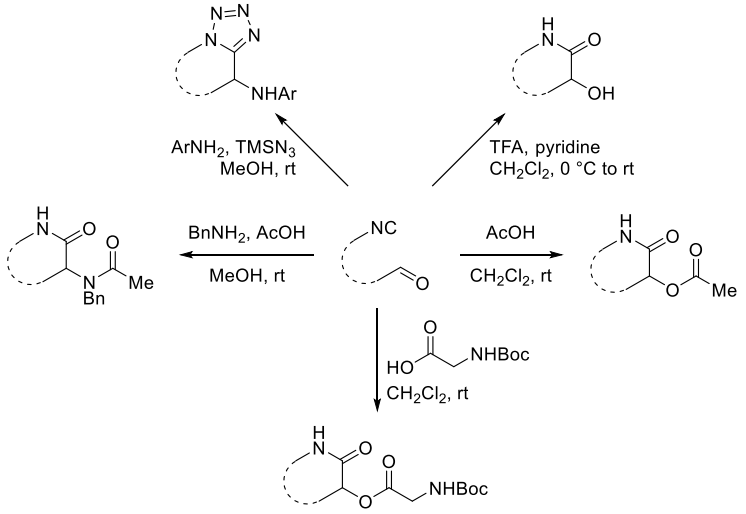
A *p*-cyclophane precursor was prepared using the methyl 4-hydroxybenzoate (**140**) as starting material (Scheme 21). The alkylation of **140** with 6-bromo-1-hexene (**110**) yielded **141** in 97%. Hydrolysis of methyl ester **141** under the basic conditions, followed by the coupling reaction between the corresponding carboxylic acid (**142**) with *N*-(3-aminopropyl)formamide (**143**) at room temperature, affording the coupling product **144** in 87%. Conversion of terminal alkene **144** to aldehyde **145** was accomplished in 78% under 2 steps and the dehydration of *N*-formamide furnished the precursor of *p*-cyclophane **146**.



Scheme 21. The synthesis of *m*-cyclophane precursor.

1.2.2 Macrocyclization

Having some starting materials in hand, the cyclization reactions were investigated (Scheme 22).



Scheme 22. Outline of multicomponent reactions for macrocyclizations of *ω*-isocyanoaldehydes.

An indole-containing *ω*-isocyano-*γ*-oxoaldehyde **97** was selected as the first substrate. Various cyclization reactions were performed with **97** in 0.05 mmol scale (Figure 3). A Passerini 3-center-2-component reaction of **97** with trifluoroacetic acid in the present of pyridine in dichloromethane (*c* 0.01 M, 5 days) at room temperature afforded tetracycle **147** in 51%.[30] The reaction underwent through a 10-membered macrolactam **153** and the tetracycle **154** was formed via the transannular cyclization. After hydrolysis under the basic conditions, *α*-hydroxy macrolactam **147** was furnished (Scheme 23).[23] The first intermediate (**153**) or its hydrolyzed adduct could not be determined due to the rapid transannular cyclization process under the acidic conditions even in silica gel (SiO_2) and $CDCl_3$. This Passerini reaction could be scalable and 59% yield of **147** was obtained with 0.58 mmol scale of starting material **97**. Other carboxylic acids were applied for the Passerini reaction of **97**. A reaction with acetic acid (1.3 equiv) gave the tetracyclic product **148** in 62% (0.05 mmol scale). The yield dropped a bit when the reaction was performed with 1.14 mmol of **97**. A Passerini reaction with benzoic acid gave the tetracycle **149** in moderate yield (55%). An example of Ugi 4-center-3-component reaction of **97** was performed with benzylamine (1.2 equiv) and acetic acid (1.5 equiv) to provide **150** in 89% yield. Finally, the oxidative Ugi reaction for the *α*-ketoamide synthesis was performed with *N*-methylhydroxylamine hydrochloride and acetic acid in MeOH (*c* 0.01 M) in the presence of 4 Å molecular sieves and $NaHCO_3$.[31] After filtration and direct purification, 3-(methylamino)pyridine-2(1*H*)-one derivative **151** was obtained in 89% yield. On the other hand, *α*-ketoamide product **152** was obtained in 79% yield after quenching the reaction with 2 M HCl. The formation of pyridinone ring started with the Ugi 4-center-

3-component reaction of **97** gave 10-membered ring intermediate **155**. The β-elimination of **155** afforded the α-iminolactam **156**, which underwent tautomerization to furnish the observed product **151**. The α-ketoamide **152** could be formed from **156** via the hydrolysis under the acidic conditions (Scheme 24).

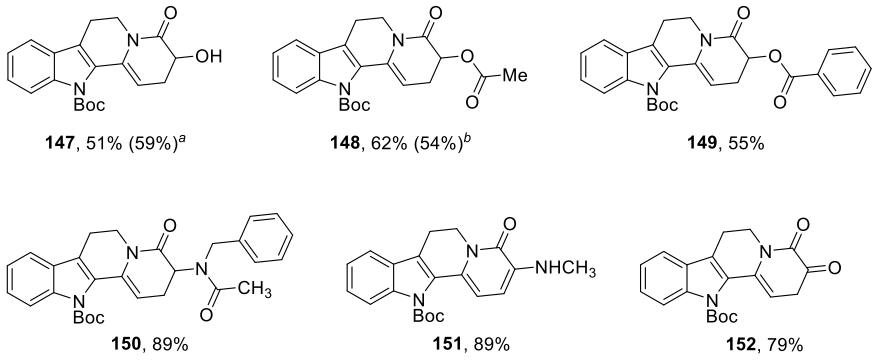
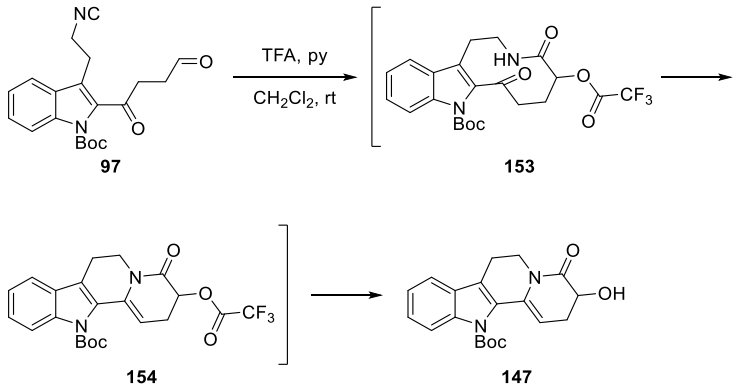
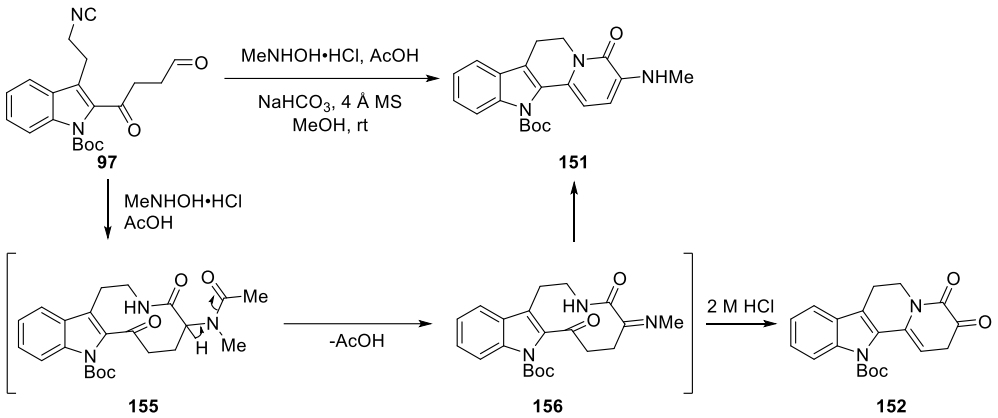


Figure 3. Tetracycle products obtained from ω-isocyano-γ-oxoaldehyde 97.

[a]The reaction was performed in 0.58 mmol. [b]The reaction was performed in 1.14 mmol.



Scheme 23. The formation of tetracyclic α-hydroxy lactam 147.



Scheme 24. The formation of 3-(methylamino)pyridine-2(1*H*)-one derivative 151 and *α*-ketoamide 152.

The cyclization reactions of indole-containing *ω*-isocyano-*γ*-oxoaldehyde **98** which extended with one more methylene group gave the 11-membered macrolactams in moderate to good yields (Figure 4). Notably, no transannular cyclized product was formed. Three Passerini reactions were performed with different carboxylic acid derivatives. The reaction with TFA in the present of pyridine gave the *α*-hydroxy macrolactam **157** in 68% yield. Compound **158** was isolated in 72% after performing the reaction of **98** with acetic acid (1.3 equiv) at room temperature for 3 days. *N*-(*tert*-Butoxycarbonyl)glycine (**19**) was also used as an example of carboxylic acids and cyclized product **159** was obtained in 78%. The Ugi 4-center-3-component reaction of **98** afforded Ugi product **160** in 61%.

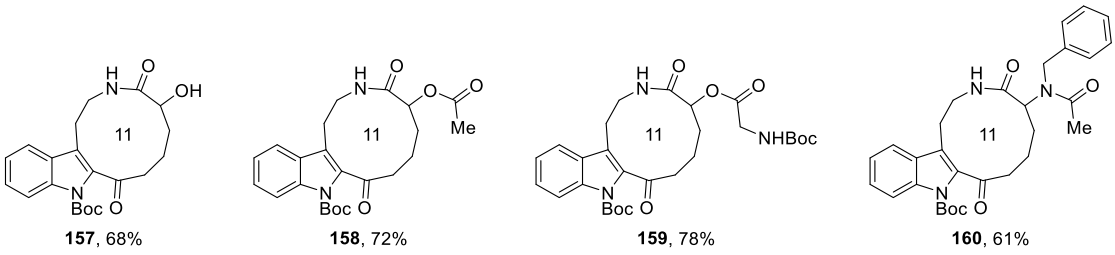


Figure 4. 11-membered macrolactams from the macrocyclization of 98.

The precursor for 12-membered ring cyclization (**99**) was subjected to four reactions. The Passerini reaction with TFA afforded the *α*-hydroxy lactam **161** in excellent yield (92%). Two Passerini reactions which **99** was performed with acetic acid and *N*-(*tert*-Butoxycarbonyl)glycine (**19**) gave the same activity. 85% of compounds **162** and **163** were obtained in high yields. While, the Ugi reaction of **99** gave the *α*-amino lactam **164** in moderate yield (57%) (Figure 5).

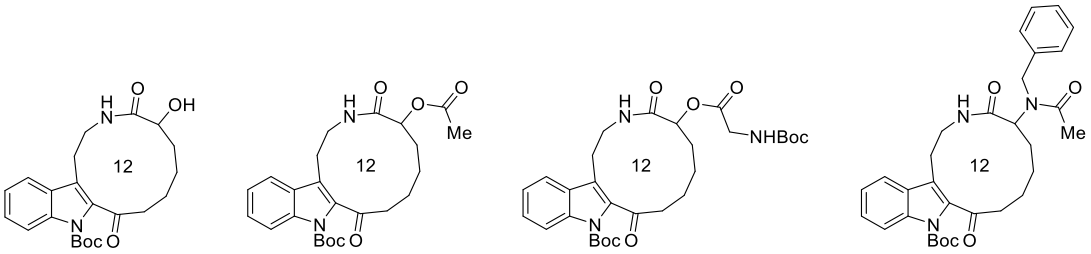


Figure 5. 12-membered macrolactams from the macrocyclization of 99.

Next, the cyclizations of 13-membered ring precursor **100** were then explored. The *α*-hydroxy lactam **165** was obtained in 83% yield. The other two Passerini reactions of **100** gave the corresponding cyclized products **166** and **167** in 62% and 73%, respectively. The Ugi product **168** was obtained in moderate yield (54%). The *α*-ketoamide **169** was obtained in 60% yield under the oxidative Ugi conditions (Figure 6). The structure of compound **159** is confirmed by X-ray crystallography (Figure 7).

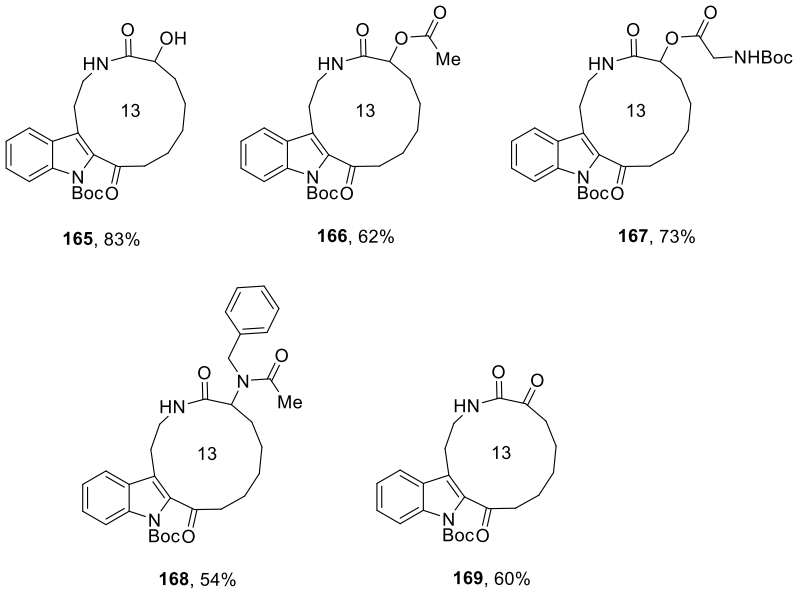


Figure 6. 13-membered macrolactams from the macrocyclization of 100.

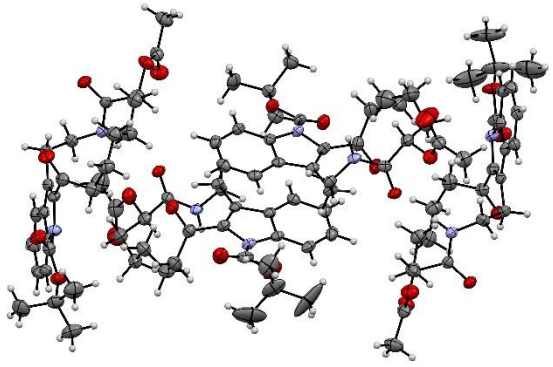


Figure 7. The X-ray structure of compound 159.

The 9-membered medium-sized ring precursor **109** was subjected to three Passerini reactions, one Ugi reaction and one Ugi tetrazole reaction (Figure 8). The Passerini reaction with TFA in the present of pyridine gave the hydroxyl-containing lactam **170** in 44%. The other two ester-containing products **171** and **172** were also obtained in moderate yields (50% and 55%, respectively). The Ugi 4-center-3-component reaction of **109** with benzylamine (**20**) and acetic acid yielded the corresponding *α*-amino 9-membered lactam (**173**) in 43%. Compound **109** was subjected to the Ugi tetrazole reaction together with 4-aminobenzonitrile (**175**) and trimethylsilyl azide (**45**) (as a convenient source for hydrazoic acid).[32] The reaction was performed in MeOH (*c* 0.1 M) at room temperature for 2 days and the tetrazole product **174** was obtained in 35% yield. The formation of tetrazole **174** was described in Scheme 25. The imine formation between aldehyde **109** and 4-aminobenzonitrile (**175**) gives imine intermediate **176**. The intramolecular nucleophilic attack of isocyano group to the imine affords cyclic nitrilium intermediate **177**. This intermediate is then trapped with hydrazoic acid which is generated *in situ* from $TMSN_3$ in the present of MeOH to give intermediate **178**. Finally, the intramolecular cyclization forms the tetrazole ring and yields the Ugi tetrazole product **174**.

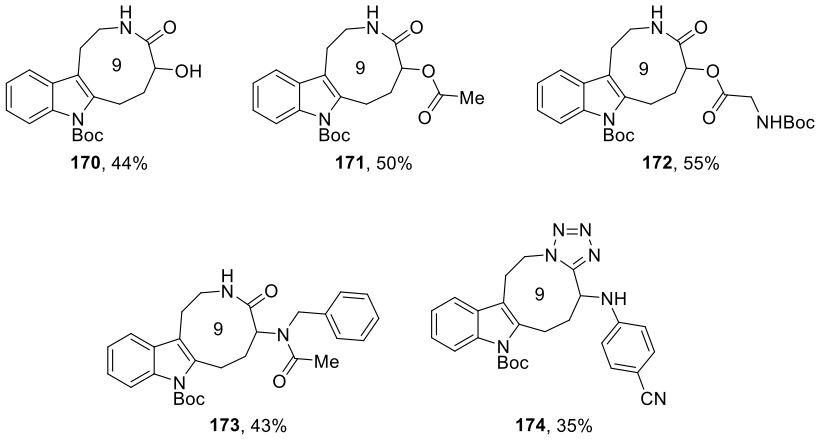
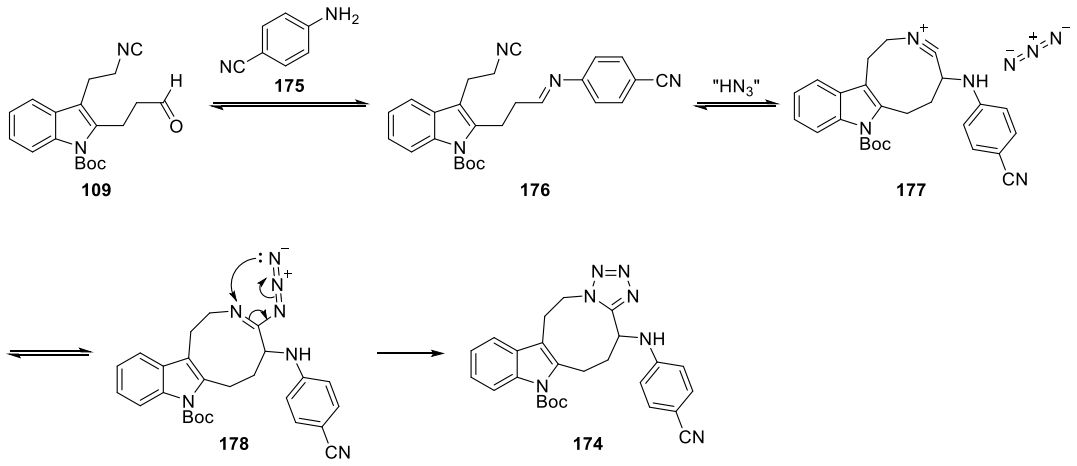


Figure 8. 9-membered cycles from the cyclization of 109.



Scheme 25. The formation of Ugi tetrazole product 166.

The precursor of 15-membered macrocyclic ring system (**113**) was investigated (Figure 9). The Passerini reactions gave the cyclized products in moderate yields. The *α*-hydroxy lactam **179** was obtained in 51% and products (**180** and **181**) derived from acetic acid and *N*-(*tert*-butoxycarbonyl)glycine (**19**) were isolated in 52% and 58%, respectively. The Ugi product **182** was obtained in 30% after **113** was reacted with benzylamine (**20**) and acetic acid in CH_2Cl_2 (*c* 0.01 M) at room temperature for 4 days. Low yield (23%) of Ugi tetrazole product **183** was afforded after reacting **113** with aniline (**184**) and $TMSN_3$ (**45**) in MeOH (*c* 0.1 M) at room temperature for 1 day.

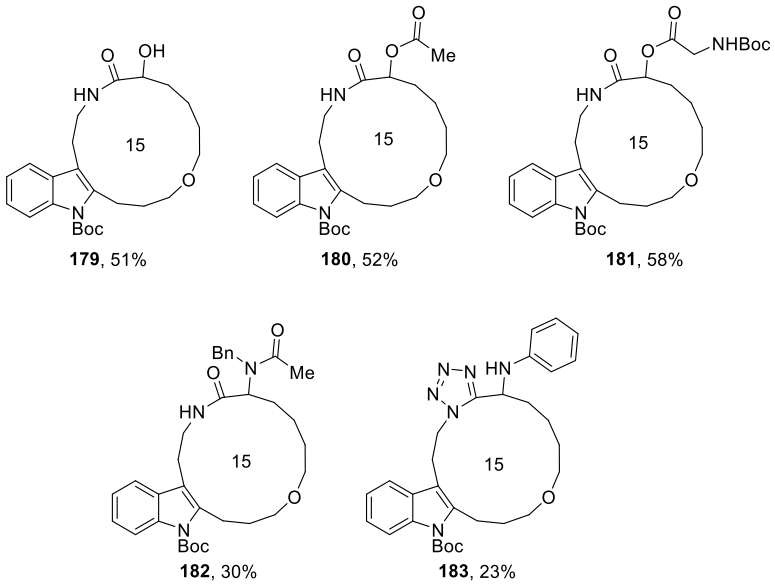


Figure 9. 15-membered cycles from the cyclization of 113.

The phenyl-based substrates were then explored, starting with a precursor containing phenol moiety. The phenyl-based *ω*-isocyanoaldehyde **125**, a precursor for 15-membered macrocycles, was subjected to various cyclization reactions (Figure 10). The Passerini reaction with TFA and pyridine gave the hydrolyzed product **185** in 84%. The 15-membered macrolactam with the acetoxy group (**186**) was obtained in 91% from the Passerini reaction of **125** and acetic acid. The other Passerini reaction with protected glycine (**19**) gave the excellent yield of product **187** (95%). The Ugi 4-center-3-component reaction of **125** occurred smoothly to afford the Ugi product **188** in 97%. However, the Ugi tetrazole product **189** was obtained in moderate yield (43%) after reacting **125** with aniline (**184**) and $TMSN_3$ (**45**) in MeOH (*c* 0.1 M) at room temperature for 4 days. The structure of compound **189** is confirmed by X-ray crystallography (Figure 11). The Ugi 4-center-3-component reaction with *N*-hydroxysuccinimide (**192**) as the acid component instead of carboxylic acid derivatives was performed.[33] The *α*-hydrazino macrolactam **190** was obtained in low yield (22%). The reaction mechanism related to normal Ugi reaction (Scheme 26). The imine **193** is first formed from the condensation of aldehyde **125** with benzylamine (**20**). The intramolecular nucleophilic addition of isocyano group to imine which is activated by $ZnCl_2$ takes place to give nitrilium intermediate **195**. Intermediate **195** is trapped with hydroxamate anion **196** followed by the Mumm-like rearrangement to form the N-N bond and give the *α*-hydrazino macrolactam **190**. The oxidative Ugi reaction of the *ω*-isocyanoaldehyde **125** gave the *α*-ketoamide **191** in 71% yield.

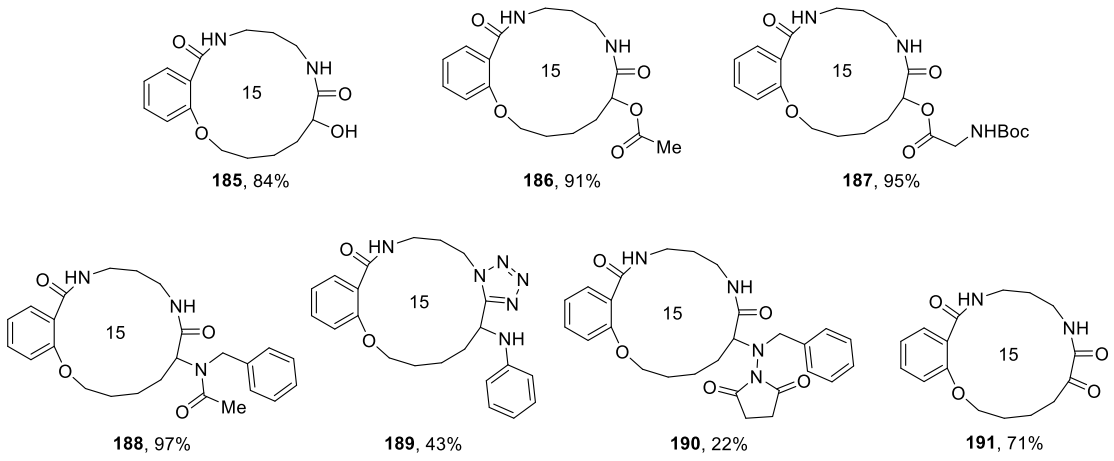


Figure 10. 15-membered cycles from the phenyl-based *ω*-isocyanoaldehyde 125.

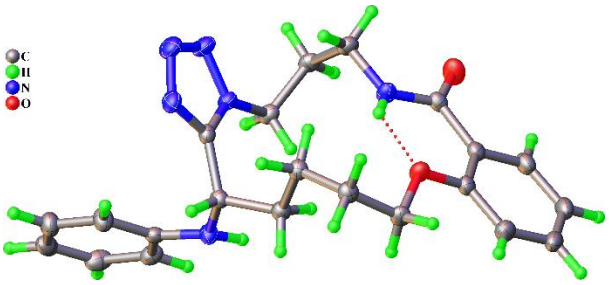
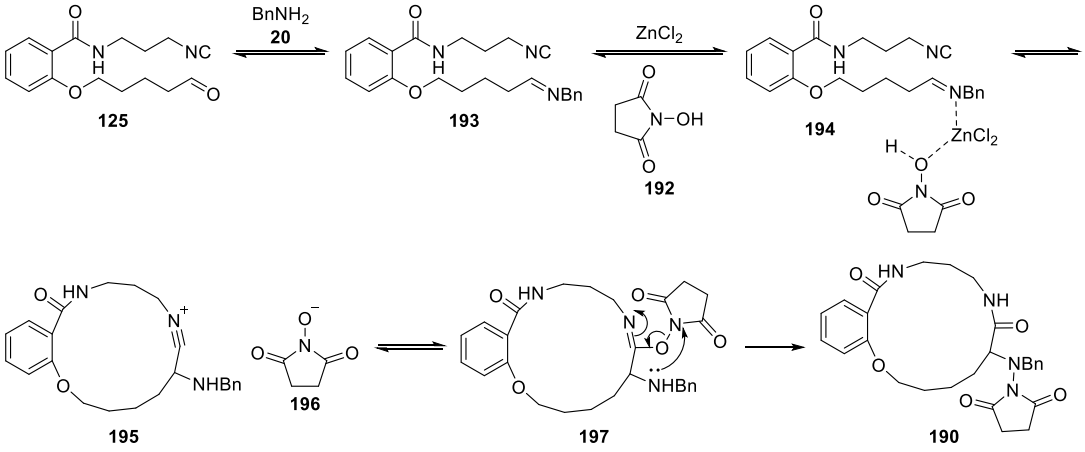
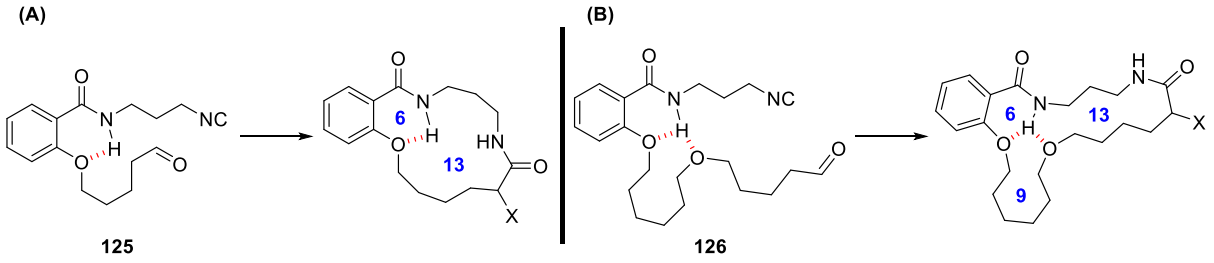


Figure 11. The X-ray structure of compound 189.



Scheme 26. The formation of *α*-hydrazino macrolactam 190.

According to the X-ray structure of compound **189** (Figure 11), there is a hydrogen-bonding between the amide NH and the phenol oxygen. The pre-organization of the *ω*-isocyanoaldehyde **125** (Scheme 27, A) could lower the conformational freedom of the side chains to give products in the better yields than the other indole-series 15-membered rings in Figure 9 which lacked of this interaction.



Scheme 27. Possible conformational pre-organization for the phenol based substrates.

The phenol-containing precursor **126** was then investigated. 22-membered macrocycles were obtained in moderate to good yields (Figure 12). The Passerini reaction of **126** with TFA and pyridine yielded the *α*-hydroxy lactam **198** in 71%. Acetate **199** and glycinate **200** products were afforded in 85% and 80% yields, respectively. The Ugi reaction of **126** with benzylamine (**20**) and acetic acid gave the macrocycle **201** in 78% yield. The tetrazole product **202** was produced in 53% yield after subjecting precursor **126** in the Ugi tetrazole conditions. The oxidative Ugi reaction of the *ω*-isocyanoaldehyde **126** gave the *α*-ketoamide **203** in 68% yield. The possible pre-organization of substrate **126** could explain the high yields observed. Additional hydrogen-bond could occur with the NH of the amide and the ether oxygen (Scheme 27, B).

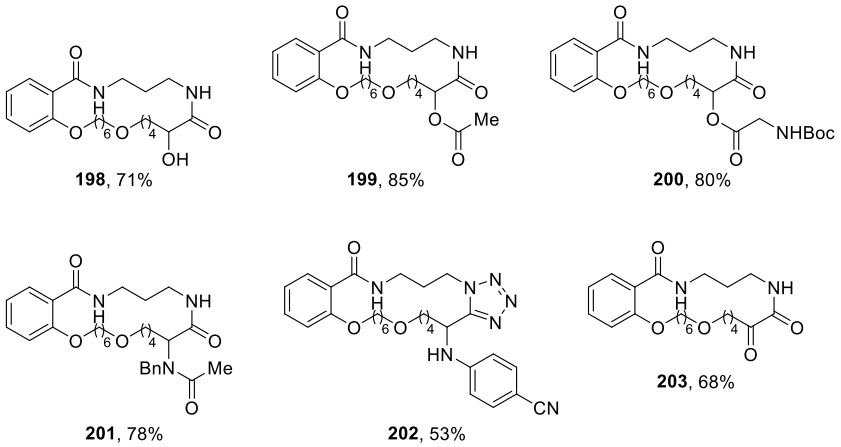


Figure 12. 22-membered rings derived from the phenyl-based *ω*-isocyanoaldehyde 126.

The cyclization reactions of benzamide precursor **133** were performed. Three Passerini products were obtained in moderate to excellent yields. The reaction with TFA in the present of pyridine gave the hydroxylated product **204** in 66%. The Passerini reaction with acetic acid was completed in 2.5 days and gave product **205** in 77% yield. The Passerini reaction with *N*-(*tert*-butoxycarbonyl)glycine (**19**) was performed with the same reaction time and the 14-membered lactam **206** was isolated in 93% yield. The Ugi 4-center-3-component reaction of **133** yielded the Ugi product **207** in moderate yield (56%). Two tetrazole Ugi reaction of **133** with aniline (**184**) and 4-aminobenzonitrile (**175**) were performed and the corresponding products were obtained in low yields (28% and 24%, respectively) (Figure 13).

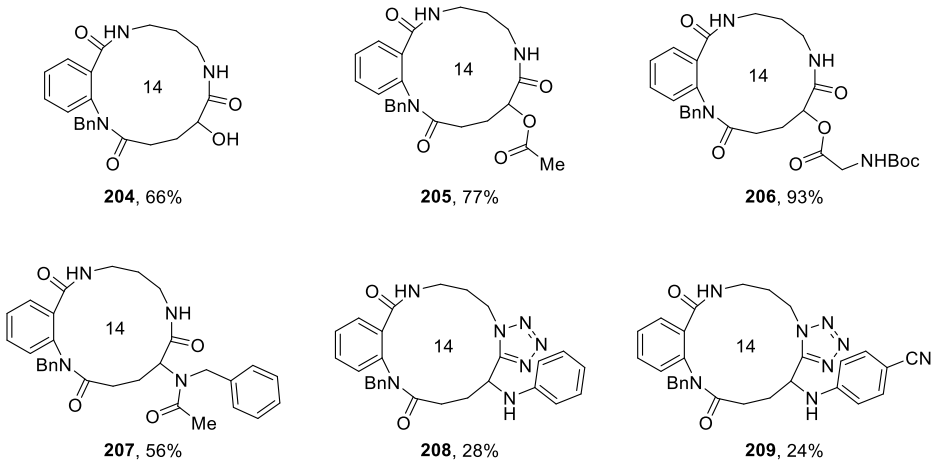
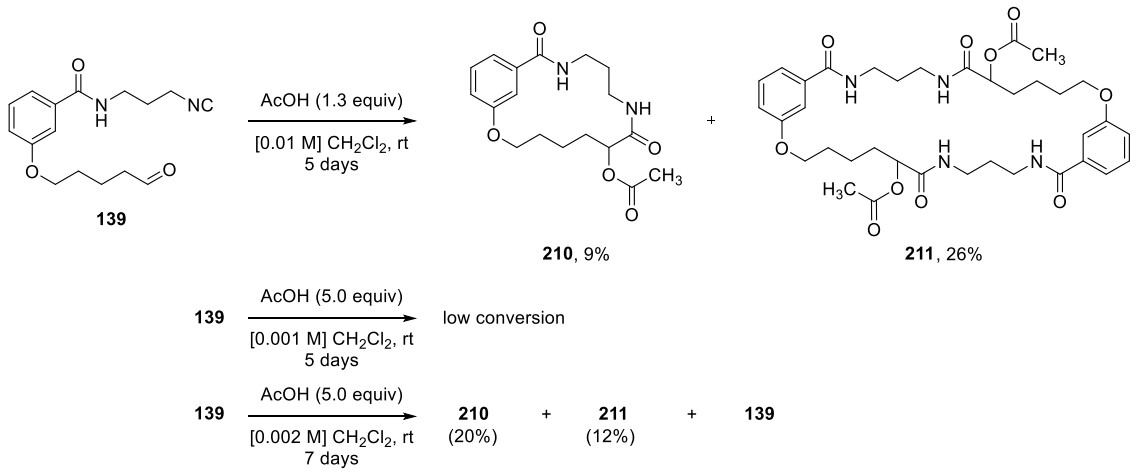


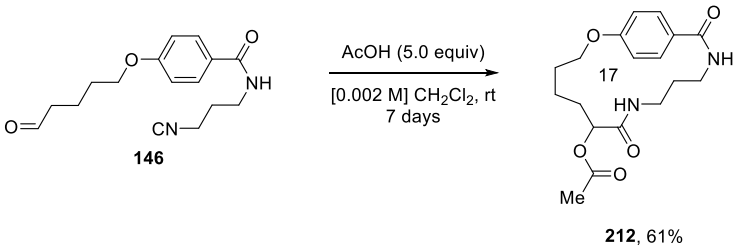
Figure 13. 14-membered macrocycles from the multicomponent reactions of precursor 133.

The *m*-cyclophane precursor **139** was subjected to a Passerini reaction with acetic acid (1.3 equiv) in CH_2Cl_2 (*c* 0.01 M). The reaction was allowed to stir at room temperature for 5 days. After the purification, the desired cyclized product **210** was isolated in 9% together with the cyclodimer **211** in 26%. To reduce the cyclodimerization, the reaction was performed in the lower concentration (0.001 M of CH_2Cl_2) with an increase amount of acetic acid (5.0 equiv) and the reaction gave low conversion after 5 days. To improve the conversion, a new batch of this Passerini reaction was performed in CH_2Cl_2 (*c* 0.002 M). After 7 days, the desired 16-membered *m*-cyclophane **210** was produced in 20% and the cyclodimer **211** was obtained in the lower yield (12%) (Scheme 28).



Scheme 28. The cyclization of *m*-cyclophane precursor 139.

Finally, under the Passerini reaction of precursor **146**, the *p*-cyclophane **212** was isolated in 61% without the formation of dimer product (Scheme 29).



Scheme 29. The cyclization of *p*-cyclophane precursor 146.

The higher yield obtained for **212** compared to the apparently less strained *m*-cyclophane **210** could be attributed to the transannular interaction between the *ortho* proton with the macrocycle ring which did not exist in the *p*-cyclophane **212** (Figure 14).

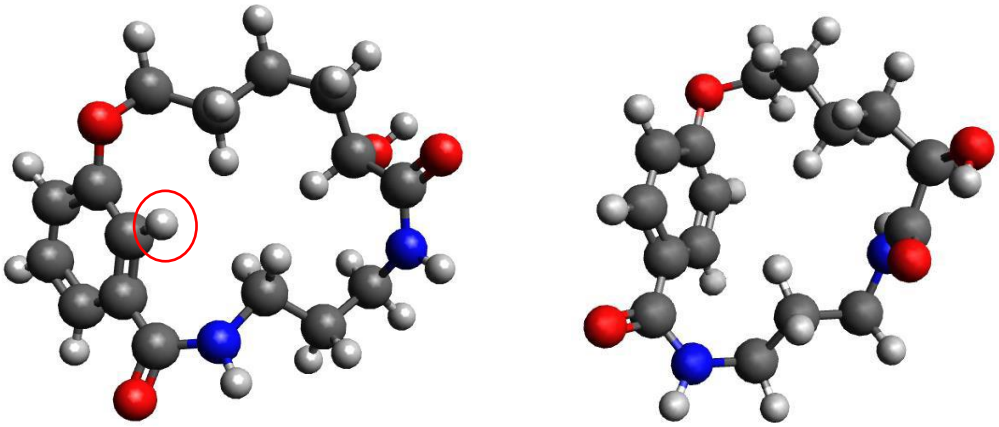


Figure 14. Optimized (DFT, 6-31G(1)d, B3LYP) geometry of the obtained *m*- and *p*-cyclophanes.

1.3 Conclusion

The macrocyclizations of a new type of bifunctional substrates, ω-isocyanoaldehyde derivatives, smoothly proceeded under the Passerini and Ugi reactions. Ten ω-isocyanoaldehydes with different ring sizes and functional groups were prepared. 9- to 22-membered macrocyclic lactams were obtained in low to excellent yields (Figure 14). In our investigation, Passerini reaction gave the higher yield than the Ugi reaction. The pre-organization of the phenol-tethered substrates by intramolecular hydrogen bonding could lower the conformational freedom of the side chains to give products in the better yields than that of indole series.

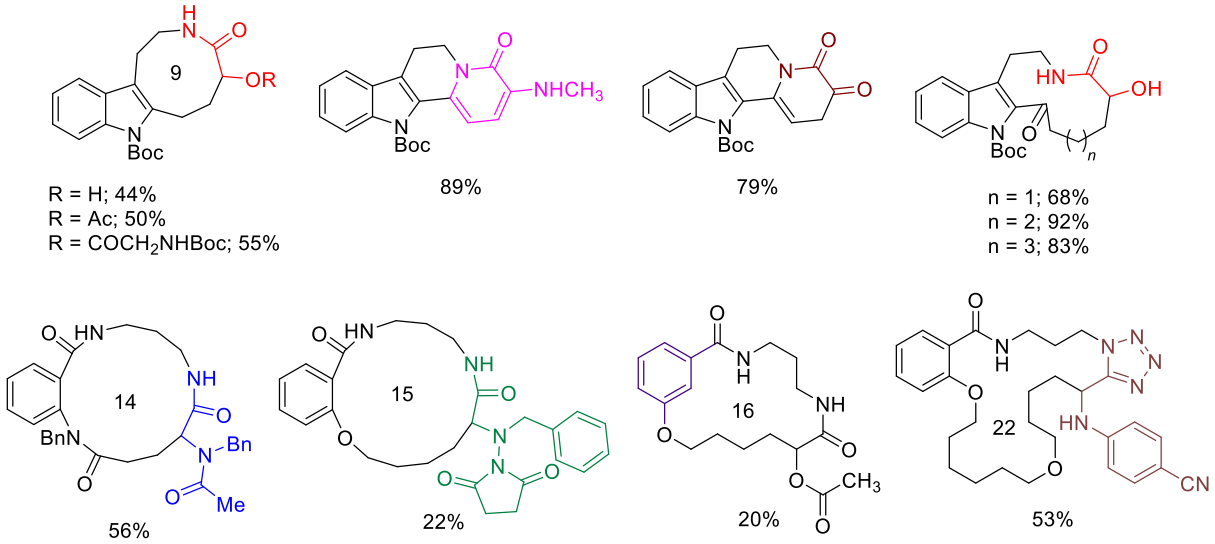


Figure 15. Examples of obtained macrocycles.

Chapter 2

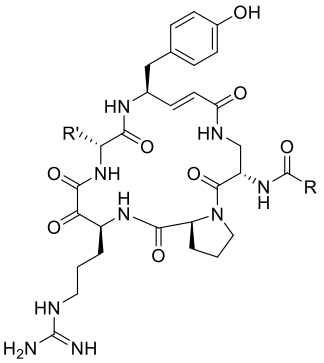
Towards the Total Synthesis of Jamaicensamide A

2.1 Introduction

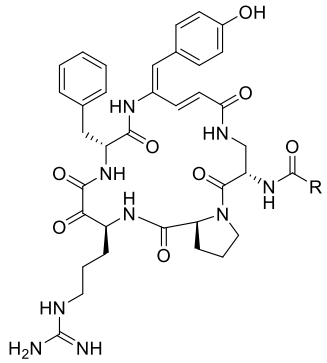
As the macrocyclizations of the ω-isocyanoaldehydes were accomplished, we would like to apply our strategy for the total synthesis of a natural product.

2.1.1 Cyclic α-ketoamides

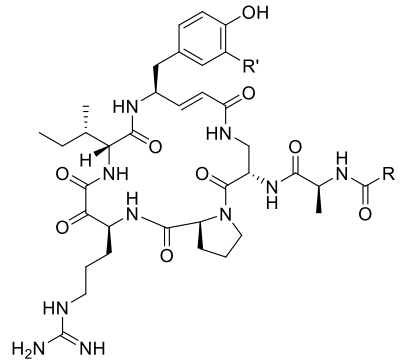
Natural cyclic α-ketoamides have shown interesting biological activities. They have been isolated from many natural sources including sponges, bacteria, fungi and ascidians. Examples of natural cyclic α-ketoamides were depicted in Figure 16. A series of cyclotheonamides A-E5 have been isolated from marine sponges. They showed significant serine protease inhibitor and thrombin inhibitor.[34-37] A series of keramamides showed cytotoxic activity towards many cell lines. They were isolated from Okinawan marine sponge *Theonella swinhoei*. [38-42] Oriamide[43] and cyclotheonellazoles A–C[44] showed similar core structure. These four compounds were also isolated from marine sponge *Theonella swinhoei* and acted as potent protease inhibitors. Calyxamides A and B, showing moderate cytotoxicity against murine leukemia P388 cell-line, were isolated from a marine sponge *Discodermia calyx* in 2012.[45] Antifungal discobahamins A and B were isolated in 1994 from a Bahamian marine sponge *Discodermia* sp.[46] They showed the similar core structure to the cytotoxic orbiculamide A which was isolated from a marine sponge *Theonella* sp in 1991.[47] Jahnellamides A and B were isolated from myxobacterium *Jahnella* sp in 2013.[48] Eurystatins A and B were isolated in 1991 from the bacteria *Streptomyces eurythermus* R353-21 which was collected from a soil sample in India.[49] Scleritodermin A was isolated from lithistid sponge *Scleritoderma nodosum*. It inhibited tubulin polymerization and showed cytotoxic activity against human tumor cell lines.[50]



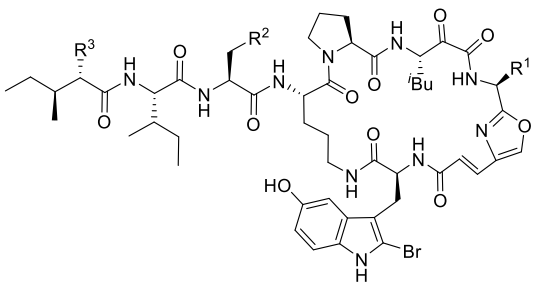
Cyclotheonamide A: R = H, R' = Bn
Cyclotheonamide B: R = Me, R' = Bn
Cyclotheonamide D: R = H, R' = ^{i}Bu



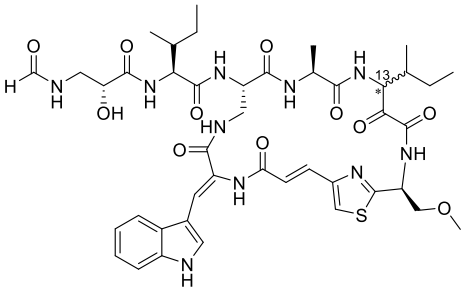
Cyclotheonamide C: R = H



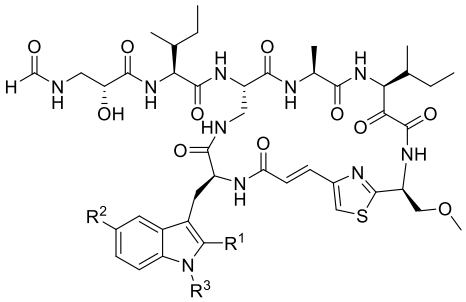
Cyclotheonamide E: R = Bn, R' = H
Cyclotheonamide E2: R = Ph, R' = H
Cyclotheonamide E3: R = ^{i}Bu, R' = H
Cyclotheonamide E4: R = 2-methylbutyl, R' = H
Cyclotheonamide E5: R = 2-methylbutyl, R' = OH



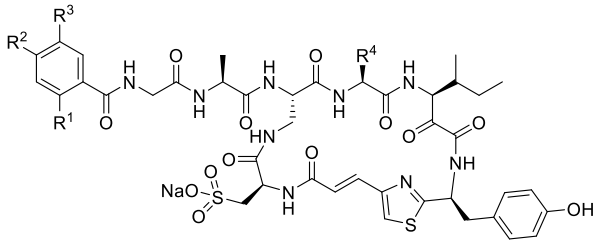
Keramamide B: R^1 = Et, R^2 = Et, R^3 = OH
Keramamide C: R^1 = Et, R^2 = Me, R^3 = OH
Keramamide D: R^1 = Me, R^2 = Me, R^3 = OH
Keramamide E: R^1 = Me, R^2 = Et, R^3 = OH
Keramamide M: R^1 = Me, R^2 = Me, R^3 = OSO_3H
Keramamide N: R^1 = Me, R^2 = Et, R^3 = OSO_3H



Keramamide F: *13*R*
Keramamide G: *13*S*



Keramamide H: R^1 = Br, R^2 = OH, R^3 = H
Keramamide J: R^1 = H, R^2 = H, R^3 = H
Keramamide K: R^1 =H, R^2 = H, R^3 = Me



Oriamide: R^1 = OH, R^2 = H, R^3 = OH, R^4 = ^{n}Pr
Cyclotheonellazole A: R^1 = H, R^2 = OH, R^3 = H, R^4 = ^{n}Pr
Cyclotheonellazole B: R^1 = H, R^2 = OH, R^3 = H, R^4 = ^{i}Bu
Cyclotheonellazole C: R^1 = H, R^2 = OH, R^3 = H, R^4 = Et

Figure 16. Examples of cyclic *α*-ketoamides.

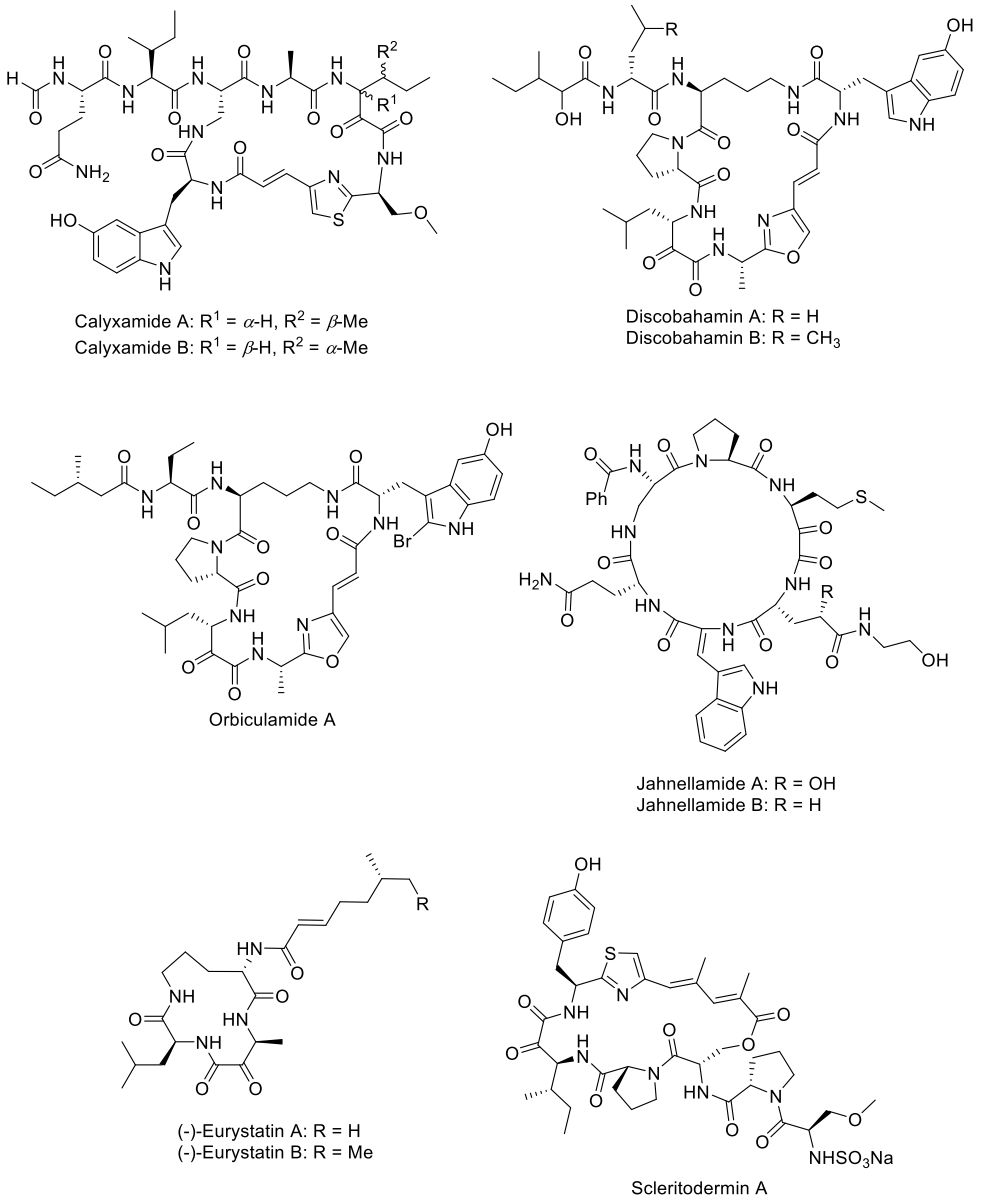


Figure 16 (cont). Examples of cyclic *α*-ketoamides.

2.1.2 Jamaicensamide A

The 24-membered cyclic peptide jamaicensamide A (**201**) (Figure 17) was selected as the target molecule for the total synthesis. This new cyclic peptide was isolated from the Bahamian sponge *Plakina jamaicensis* by the group of Professor Tadeusz F. Molinski in 2016. It composed of six amino acids, a thiazole-homologated amino acid, and an α-keto amide group which was expected to be formed under our strategy. As it was obtained in very low amount, 33 μg, and no biological activities were reported,[51] we would like to study the total synthesis of this molecule by applying our strategy to confirm the structure of this molecule and to obtain more amount that useful for the biological activities study.

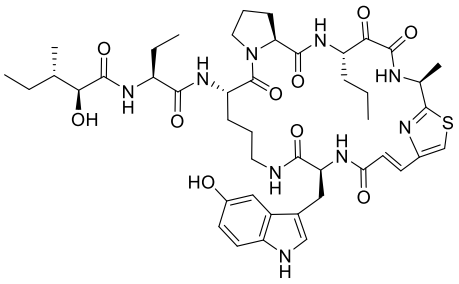
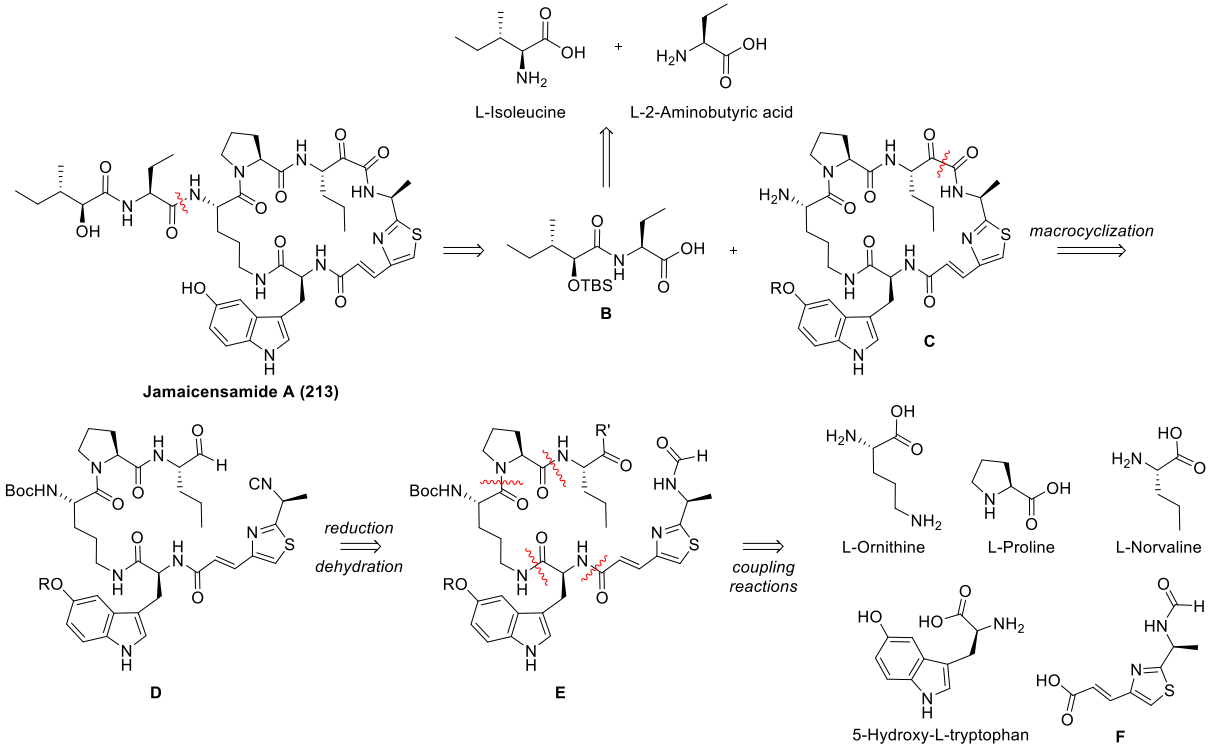


Figure 17. Structure of jamaicensamide A (213).

2.2 Results

2.2.1 Retrosynthesis

Our retrosynthesis started by the disconnection of the side chain **B** which can be prepared from L-isoleucine and L-2-aminobutyric acid. The macrocycle **C** was expected to form by using our macrocyclization method on the ω-isocyanoaldehyde precursor **D**. This sensitive precursor **D** can be formed from **E** by the reduction of Weinreb amide or ester to aldehyde and the dehydration of formyl group to isocyanide. Further disconnection of pentapeptide **E** showed that it can be prepared from the amide coupling reactions between the small amino acids including L-ornithine, L-proline, L-norvaline and 5-hydroxy-L-tryptophan together with the thiazole **F** (Scheme 30).



Scheme 30. Retrosynthesis of jamaicensamide A.

2.2.2 Synthesis

Some precursors **E1-E3** for the formation of *ω*-isocyanoaldehyde **D** were designed with different reduced groups on the L-norvaline and protecting groups on the 5-hydroxy-L-tryptophan (Figure 18). **E1** was selected to study first.

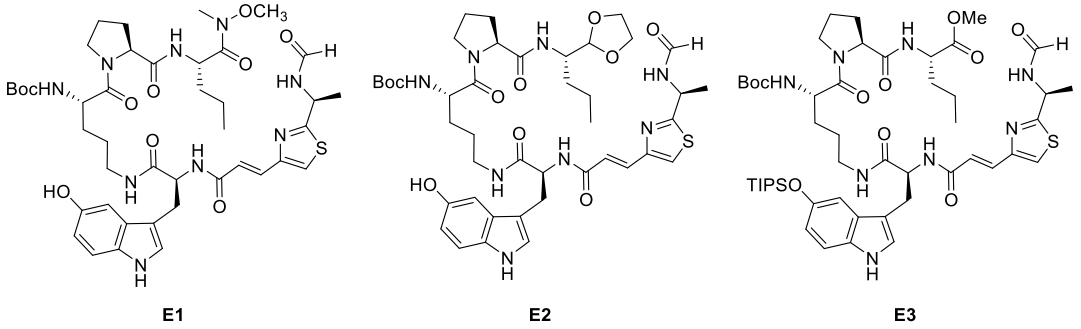
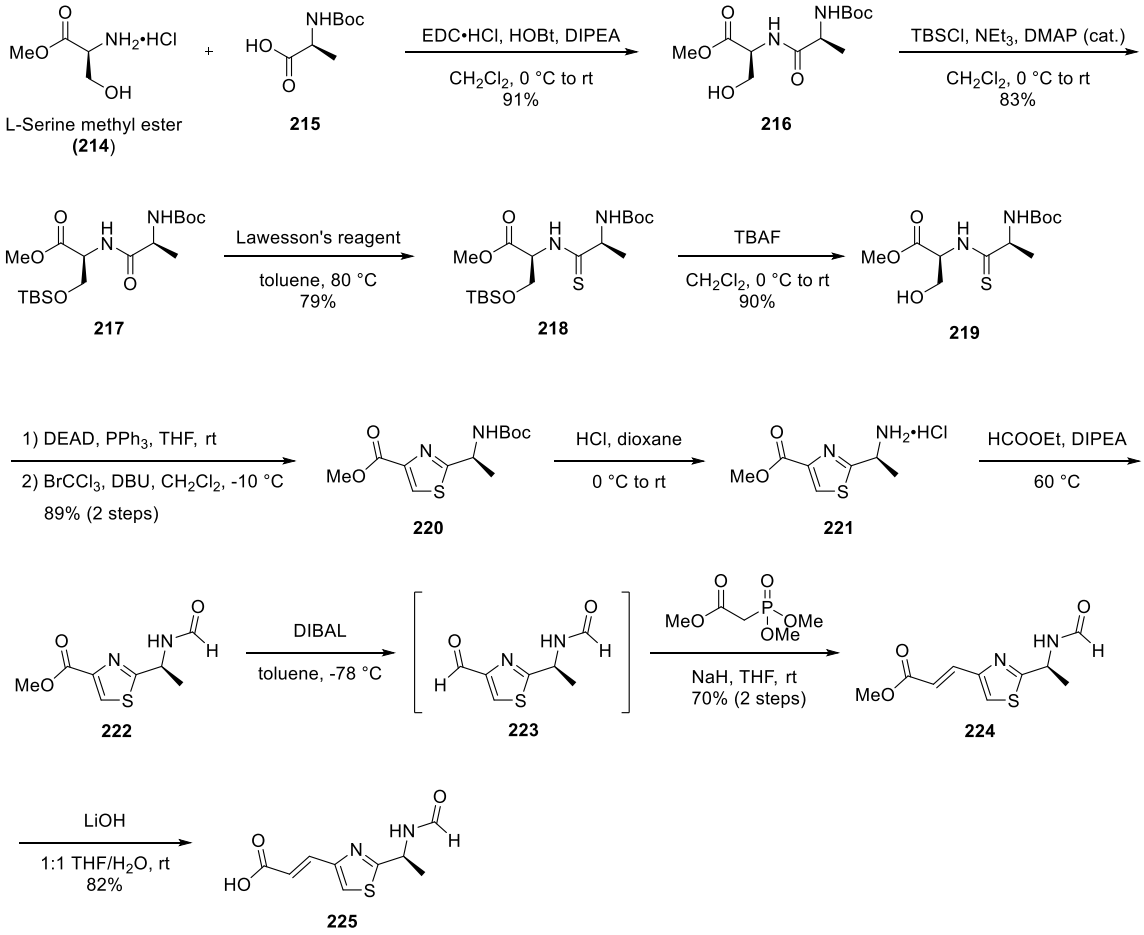


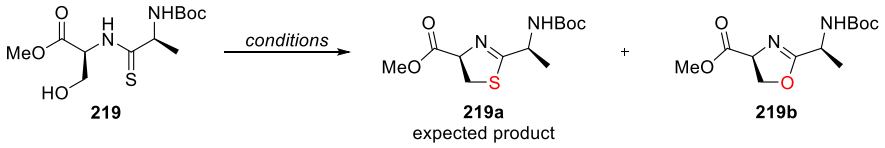
Figure 18. Precursors to prepare *ω*-isocyanoaldehydes D.

Our total synthesis started with the formation of thiazole fragment **F** (Scheme 31). The peptide coupling reaction between L-serine methyl ester (**214**) and Boc protected L-alanine (**215**) in 15.0 mmol scale gave 91% yield of product. The TBS protection of the primary alcohol **216** gave good yield. The transformation of amide **217** using Lawesson's reagent gave 79% yield of thioamide **218**. Deprotection of TBS yielded primary alcohol **219** in 90% which was ready for the thiazole formation. Ring formation by using DEAD and PPh_3 followed by the oxidation using $BrCCl_3$ and DBU gave the thiazole product **220** in 89% yield over two steps. Note that, when DAST was used as the reagent for the thiazoline formation, oxazoline was found as the major product while Burgess reagent gave the thiazoline compound in low conversion (Table 1). The Boc protecting group of thiazole **220** was converted to formyl group under two step synthesis. The DIBAL reduction converted the methyl ester group of **222** to aldehyde which was ready for the HWE reaction. The reaction of corresponding aldehyde **223** with the trimethyl phosphonoacetate gave the *α,β*-unsaturated ester in 70% over two steps. Finally, the hydrolysis of methyl ester gave the *α,β*-unsaturated carboxylic acid substituted thiazole **225** (fragment **F**) in good yield.



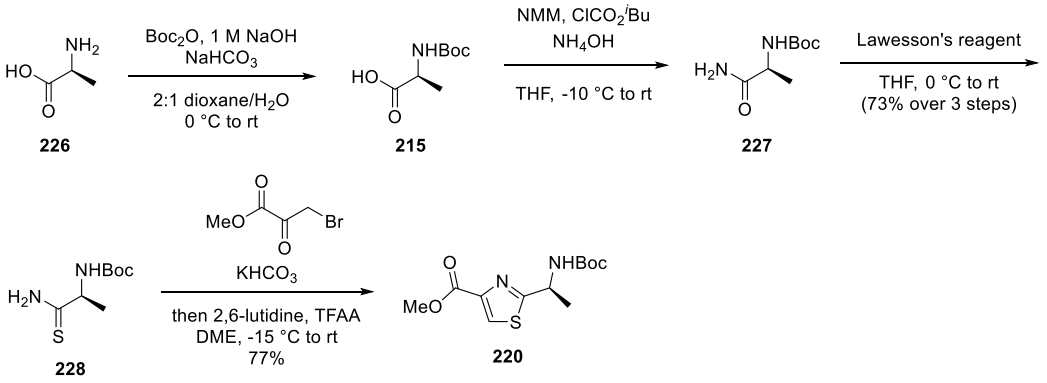
Scheme 31. Synthesis of thiazole F (route 1).

Table 1. Thiazoline formation of 219 with different reagent.



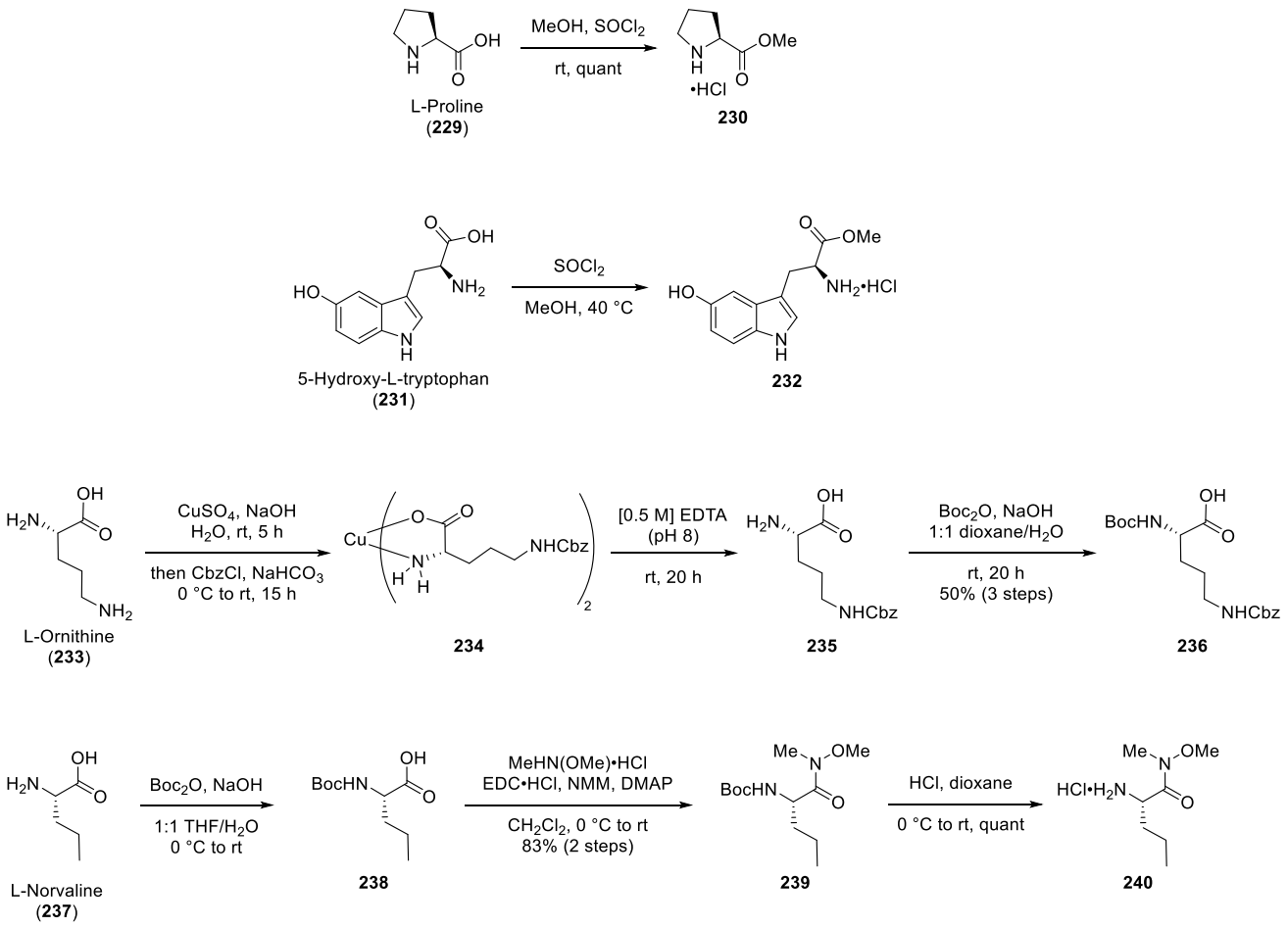
Entry	Conditions	Results
1	DAST, K_2CO_3, CH_2Cl_2, -78 °C to rt	**219a** (20%) and **219b** (77%)
2	Burgess reagent (1.1 eq), THF, 0 °C to rt	low conversion and no production of **219b**
3	Burgess reagent (2.0 eq), CH_2Cl_2, 0 °C to rt	low conversion and no production of **219b**
4	Burgess reagent (1.2 eq), THF, reflux	**219a** (37%)
5	DEAD, PPh_3, THF, rt	full conversion and no production of **219b**

As the previous route was quite long to form the thiazole ring (**220**), we therefore change to another route (Scheme 32). This route started with the Boc protection of L-alanine (**226**) followed by the amide and thioamide formations respectively to yield the thioamide **228** in 73% over three steps. Under the modified Hantzsch thiazole synthesis,[52] the thiazole **220** was obtained in 77% in one step.



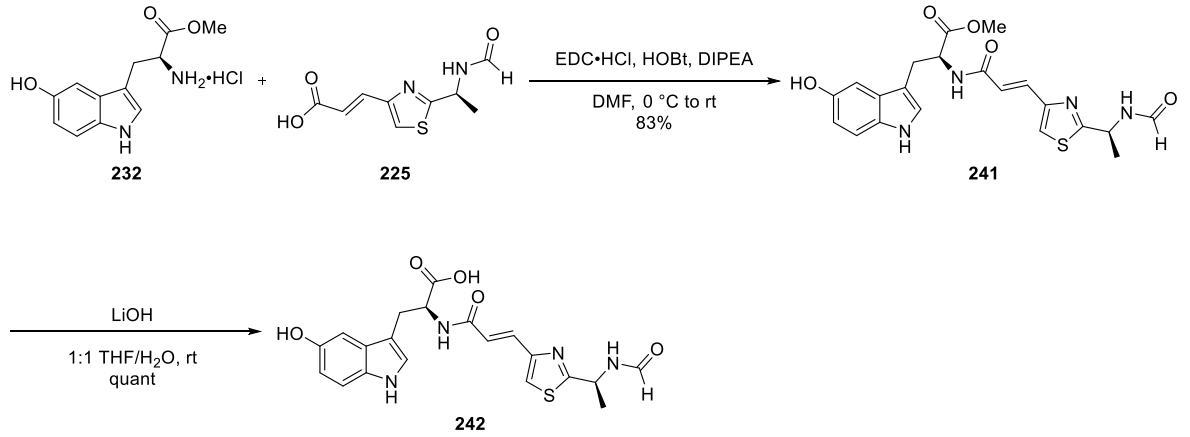
Scheme 32. New route for the synthesis of thiazole ring.

The other 4 different amino acids were prepared for the coupling reactions. The esterification with methanol and $SOCl_2$ of L-proline and 5-hydroxy-L-tryptophan gave quantitative yield. Both amino groups of L-ornithine were protected.[53] Treatment of L-ornithine with $CuSO_4$ and NaOH allowed the *α*-amino acid to form a copper dimer. Addition of CbzCl and K_2CO_3 to protect the terminal amino group afforded complex **234**. Then, decomposition of dimer using EDTA and NaOH led to free *α*-amino acid **235** which was used directly for the *N*-Boc protection to furnish the desired ornithine derivative **236** in 50% yield over three steps. Finally, the Weinreb amide of L-norvaline was prepared through a three-step procedure. Boc protection followed by the Weinreb amide formation gave **239** in 83% over two steps. The deprotection of Boc under the acidic conditions gave **240** in quantitative yield (Scheme 33).

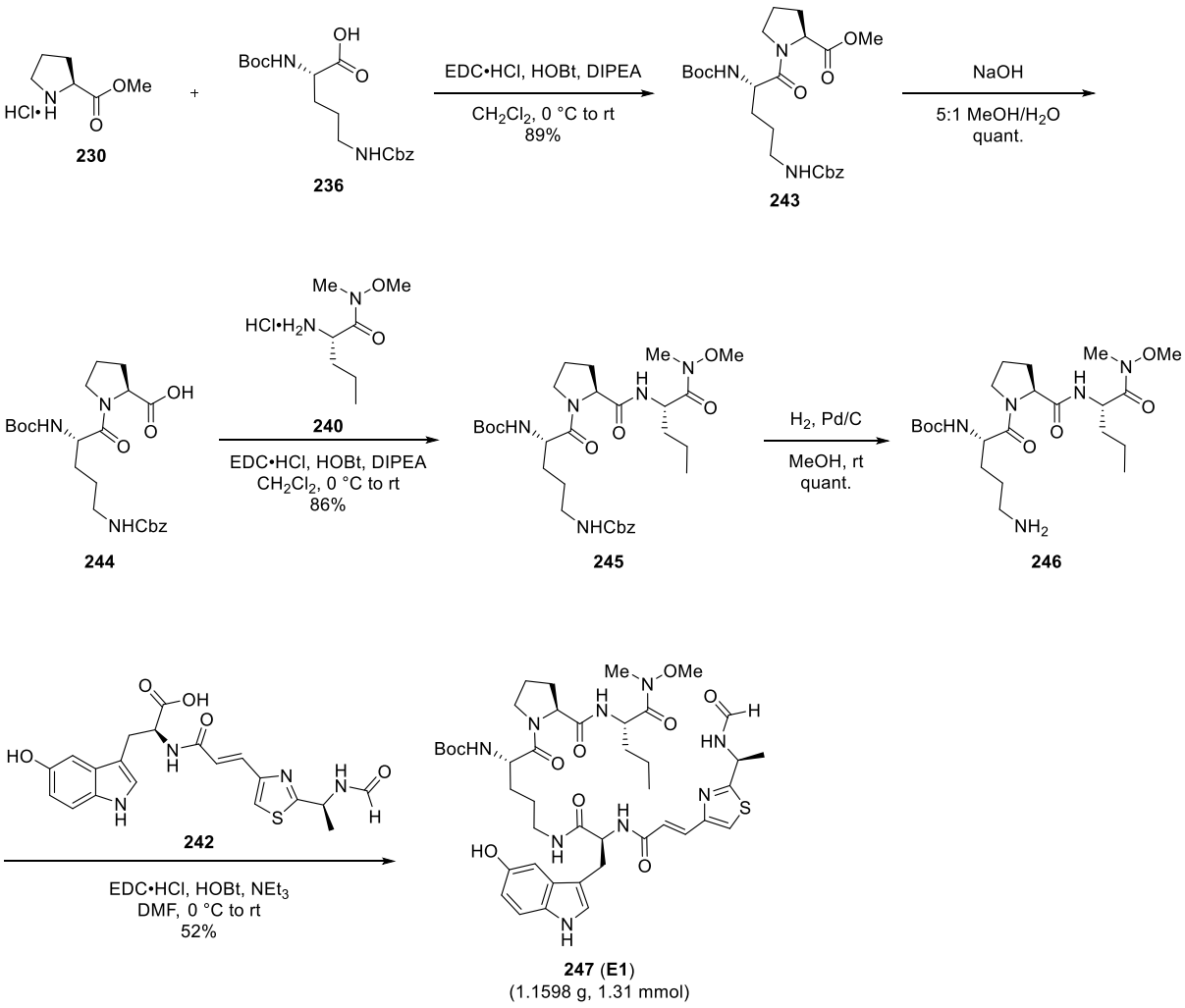


Scheme 33. Synthesis of the starting amino acid derivatives.

With all amino acid fragments and thiazole **F** in hands, the coupling reactions of these five fragments were performed starting with the amide formation of 5-hydroxy-L-tryptophan methyl ester (**232**) and thiazole fragment **F** (**225**) afforded coupling product in 83% yield. The methyl ester of **241** was hydrolysed using LiOH in THF/H_2O to give the carboxylic acid **242** in quantitative yield (Scheme 34). Meanwhile, the L-proline methyl ester (**230**) was coupled with the protected L-ornithine **236** to yield **243** in 89%. After the hydrolysis of **243**, the coupling reaction of corresponding carboxylic acid **244** and Weinreb amide **240** was performed and the tripeptide product **245** was obtained in 86% yield. Hydrogenolysis of Cbz protecting group gave free amino compound **246** which was a coupling partner of dipeptide **242** to obtain the final pentapeptide **E1** (**247**) in moderate yield (Scheme 35).



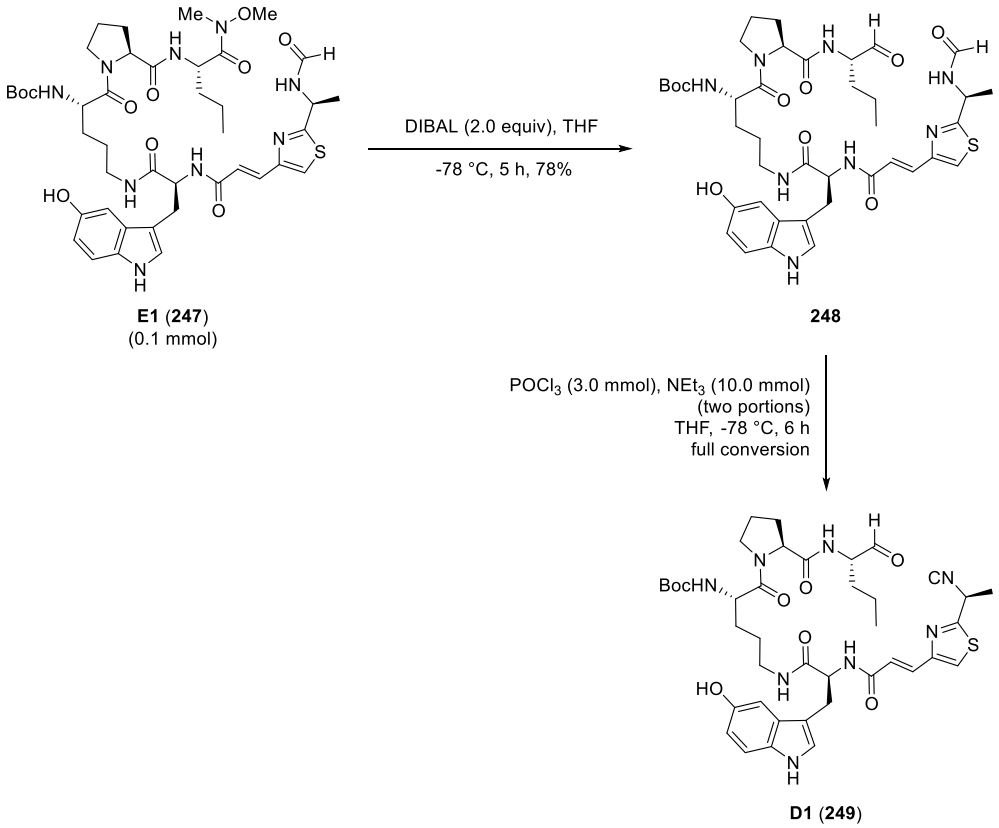
Scheme 34. Coupling reaction between compound 232 and fragment F.



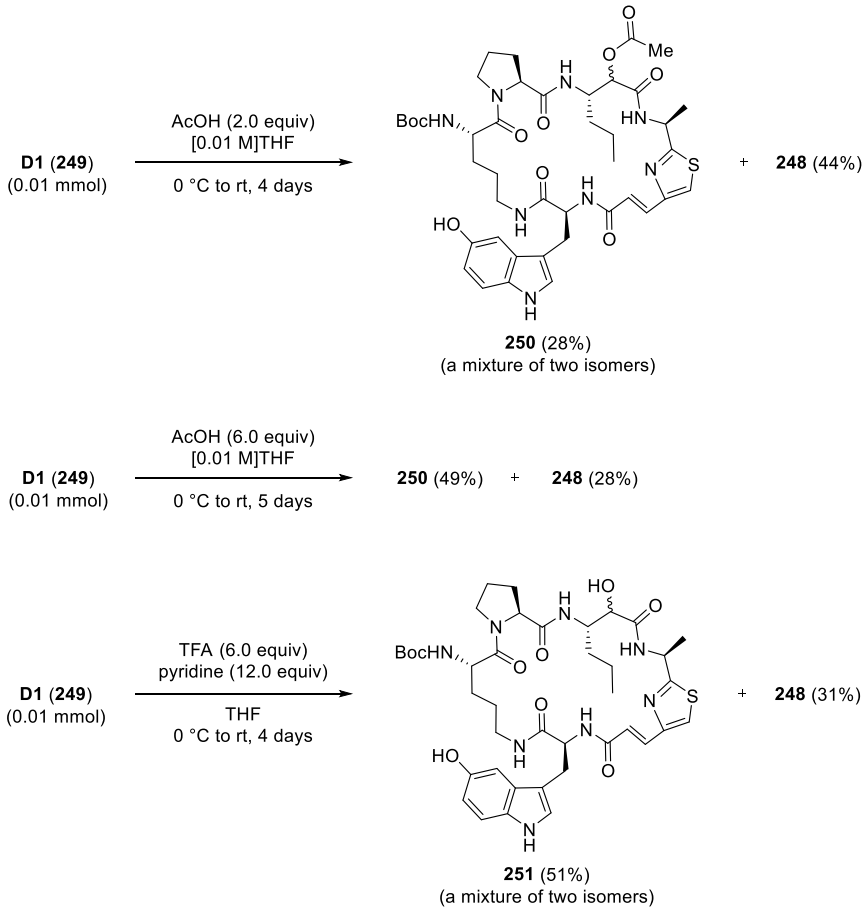
Scheme 35. Preparation of pentapeptide E1.

A small-scale reduction/dehydration of precursor **E1** (0.1 mmol) accomplished the ω-isocyanoaldehyde **D1** (**249**) in good yield. The crude **D1** was used directly without further purification to test the macrocyclization reaction (Scheme 36). Interestingly, the Passerini reaction with AcOH and TFA/pyridine gave the corresponding 24-membered rings in pleasant yields (Scheme 37). With 0.01 mmol scale, the macrocyclization of **D1** with AcOH (2.0 equiv) in THF (0.01 M) for 4 days gave the cyclized product in 28%. The hydrolyzed compound **248** which was formed from the remaining starting material during the workup process was isolated in 44%. Adding more AcOH into the reaction with prolong the reaction time improved the yield to 49%. The Passerini reaction of **D1** with TFA (6.0 equiv) and pyridine (12.0 equiv) gave the α-hydroxy lactam **251** in 51% together with the hydrolyzed product in 31%.

Unfortunately, the reduction of the Weinreb amide **E1** to get the aldehyde **248** by using LAH and DIBAL as reducing agents in the bigger scale gave unreproducible results. The over reduction at formyl group was observed. Therefore, compound **E2** (Figure 18) was chosen to be the next precursor to prepare the reactive intermediate **D1**.



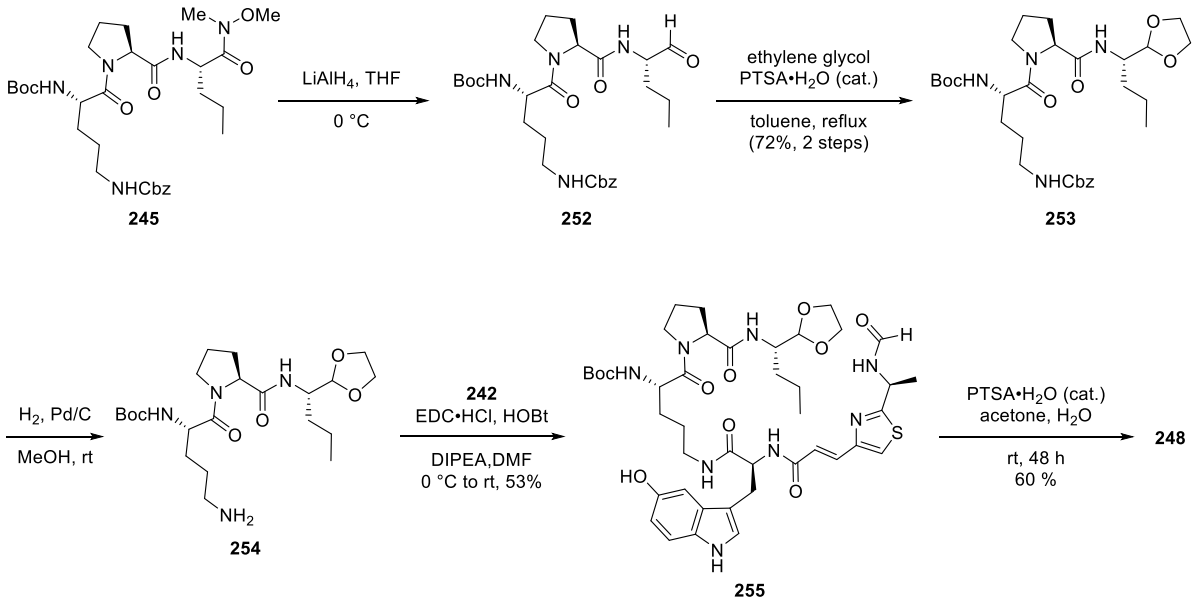
Scheme 36. Preparation of ω-isocyanoaldehyde D1.



Scheme 37. Macrocyclization of *ω*-isocyanoaldehyde D1.

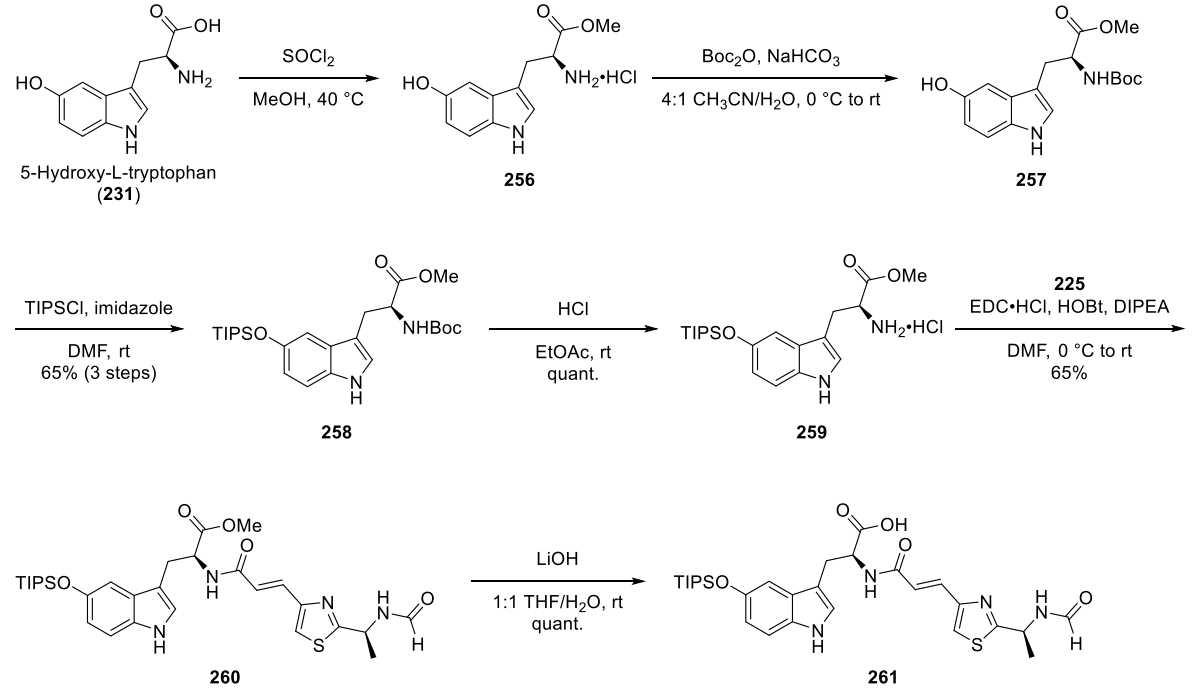
To prepare the precursor **E2**, Weinreb amide **245** was used as the starting material. It was reduced by LAH to give the corresponding aldehyde **252** which was directly protected with ethylene glycol under the acidic conditions to give compound **253** in 72% over two steps. The Cbz protecting group was cleaved by hydrogenolysis and the corresponding free amine (**254**) was coupled with carboxylic acid **242** to give pentapeptide **255** (precursor **E2**) in moderate yield. Deprotection of the 1,3-dioxolane ring under the mild acidic conditions gave compound **248** in 60% yield (Scheme 38).

The *α*-hydroxy lactam **251** was prepared in the bigger scale in order to have sufficient amount for the next step. The oxidation of *α*-hydroxyamide to the *α*-ketoamide was investigated. With different oxidation conditions including DMP, PCC, Swern oxidation, giving complex mixture. On the other hand, MnO_2 oxidation gave no reaction. The presence of unprotected 5-hydroxy indole ring might cause the complex mixture results. Thus, compound **E3** (Figure 18) with the TIPS protection on the hydroxyl group of the indole ring was prepared. The functional group on L-norvaline was converted to methyl ester instead of Weinreb amide as it is easier to prepare.



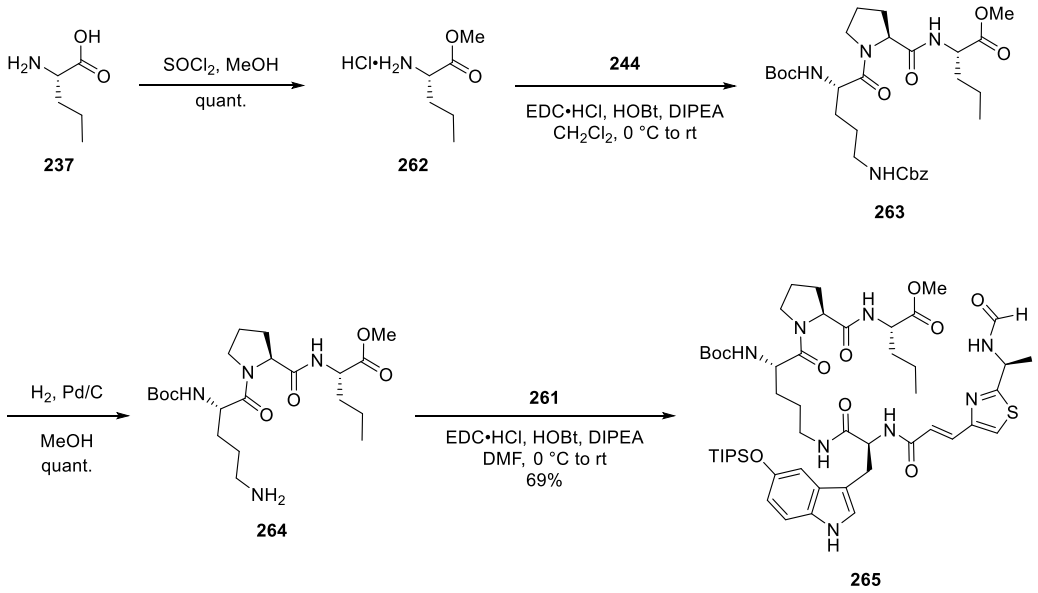
Scheme 38. Preparation of precursor E2.

The esterification of 5-hydroxy-L-tryptophan (**231**) followed by the Boc protection of amino group gave compound **257** which was used directly for the TIPS protection to give the protected tryptophan **258** in 65% yield over three steps. The Boc group was cleaved under the acidic conditions to give compound **259** which was coupled with fragment **F** (**225**) to give the coupling product (**260**) in 65% yield. Saponification of the methyl ester **260** gave the corresponding carboxylic acid **261** in quantitative yield.



Scheme 39. Preparation of precursor E3.

To complete the synthesis of precursor **E3**, L-norvaline (**237**) was converted to methyl ester and coupled with dipeptide **244** to give tripeptide **263** in good yield. Hydrogenolysis of Cbz protecting group gave pure free amine **264** which was coupled with coupling partner **261** to give precursor **E3** (**265**) in 69% yield (Scheme 40).

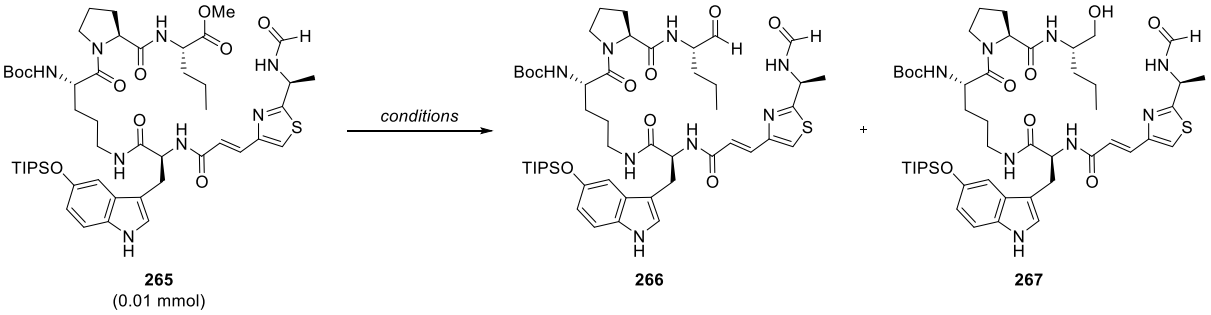


Scheme 40. Preparation of precursor E3 (cont).

The reduction of methyl ester **265** to the corresponding aldehyde **266** or primary alcohol **267** was investigated (Table 2). The DIBAL reduction was very slow and no desired products were observed (entry 1). Reduction with $NaBH_4$ upto 30 equiv to give the full conversion of substrate and yield the primary alcohol **267** in 91% (entry 2). $LiBH_4$ in 20 equiv gave the same result as $NaBH_4$ (entries 3 and 4). Surprisingly, $LiAlH_4$ in 3.0 equiv could stop at the first reduction to give the corresponding aldehyde **266** as a major product (entries 5 and 6). The reduction of compound **265** (4.2 mmol) with $LiAlH_4$ (3.0 equiv) in THF for 24 hours gave the desired aldehyde **266** in 72% together with alcohol **267** in 13%. Note that, the primary alcohol **267** could be converted to the aldehyde **266** by the DMP oxidation.

With the proper amount of aldehyde **266** in hands, we turn our interest to the optimization of the macrocyclization conditions (Table 3). The reaction of the ω-isocyanoaldehyde **267** in the presence of TFA and pyridine was used as the model substrate, giving cyclic α-hydroxyamide **268** as product. With different solvents including CH_2Cl_2, $CHCl_3$, THF, dioxane, toluene and MeOH, CH_2Cl_2 gave the best yield (entries 1-6). The amount of reagents were tested and the reaction with 6.0 equiv of TFA and 12.0 equiv of pyridine gave the best result (entries 7-11). The concentration of 0.02 M gave the best yield. With higher concentration, the reaction produced other products (entries 12-17).

Table 2. The reduction of methyl ester of 265.



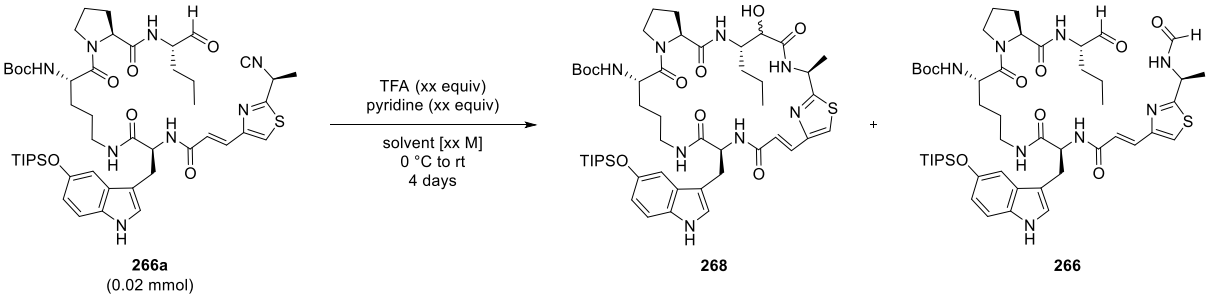
265 (0.01 mmol) **266** **267**

Entry	Conditions	Results
1	DIBAL (2 to 10 equiv), THF, -78 °C	low conversion, both **266** and **267** were not observed
2	$NaBH_4$ (30 equiv), THF, 0 °C to rt	full conversion to give **267** in 91%
3	$LiBH_4$ (10 equiv), THF, 0 °C to rt	50% conversion to **267**
4	$LiBH_4$ (20 equiv), 1:1 THF/MeOH, 0 °C to rt	full conversion to give **267**
5	$LiAlH_4$ (5 equiv), THF, 0 °C to rt	full conversion to give **267**
6	$LiAlH_4$ (3 equiv), THF, 0 °C to rt	full conversion to give **266** as major product

The cyclic *α*-hydroxyamide **268** containing the TIPS protecting group was tested for the oxidation reaction to give the corresponding *α*-hydroxy amide **269**. The results were shown in Table 4. The DMP oxidation in THF at room temperature could not complete the conversion of starting material, only 20% of product were obtained (entry 1). The PCC oxidation gave lower yield than DMP oxidation (entry 2). Swern oxidation and Parikh-Doering oxidation gave the complex mixture (entries 3 and 4). On the other hand, IBX oxidation in DMSO gave no reaction. The DMP oxidation was selected for further optimization. With high loading of DMP in the reaction, the higher yields were observed (entries 6-9). Running the reaction at higher temperature (60 °C) was help to accelerate the reaction to the completion and gave the product in good yield (entry 10).

The side chain acid **277** was prepared for the coupling reaction with the macrocycle **269**. It was prepared from L-2-aminobutyric acid (**271**) and L-isoleucine (**273**) (Scheme 41). The diazotization of L-isoleucine converted the α-amino acid to α-hydroxy acid (**274**) in 75% yield with the retention of configuration.[54a] The present hydroxyl group was protected with TBS to give carboxylic acid **275** in good yield. It was coupled with the L-2-Aminobutyric acid methyl ester hydrochloride (**272**) to give compound **276** in 83% yield. The hydrolysis of methyl ester to carboxylic acid **277** was obtained in quantitative yield.

Table 3. Optimization of macrocyclization conditions.



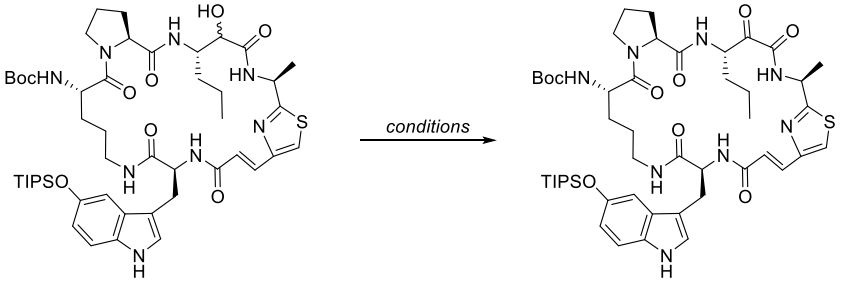
266a
(0.02 mmol)

268

266

Entry	Equiv of TFA/pyridine	Solvent	Concentration [M]	Results
1	6/12	CH_2Cl_2	0.01	**268** (59%) and **266** (28%) were isolated
2	6/12	$CHCl_3$	0.01	**268** (55%) and **266** (28%) were isolated.
3	6/12	THF	0.01	**268** (52%) and **266** (32%) were isolated.
4	6/12	dioxane	0.01	**268** (47%) and **266** (33%) were isolated.
5	6/12	toluene	0.01	slow conversion
6	6/12	MeOH	0.01	slow conversion
7	2/4	CH_2Cl_2	0.01	slow conversion
8	3/6	CH_2Cl_2	0.01	slow conversion
9	5/10	CH_2Cl_2	0.01	**268** (52%) and **266** (32%) were isolated
10	8/16	CH_2Cl_2	0.01	**268** (52%) and **266** (30%) were isolated
11	10/20	CH_2Cl_2	0.01	**268** (40%) and **266** (43%) were isolated
12	6/12	CH_2Cl_2	0.02	**268** (63%) and **266** (25%) were isolated
13	6/12	CH_2Cl_2	0.03	**268** + **266** + other product
14	6/12	CH_2Cl_2	0.05	**268** + **266** + other product
15	6/12	CH_2Cl_2	0.1	**268** + **266** + other product
16	6/12	CH_2Cl_2	0.005	slow conversion
17	6/12	CH_2Cl_2	0.001	slow conversion

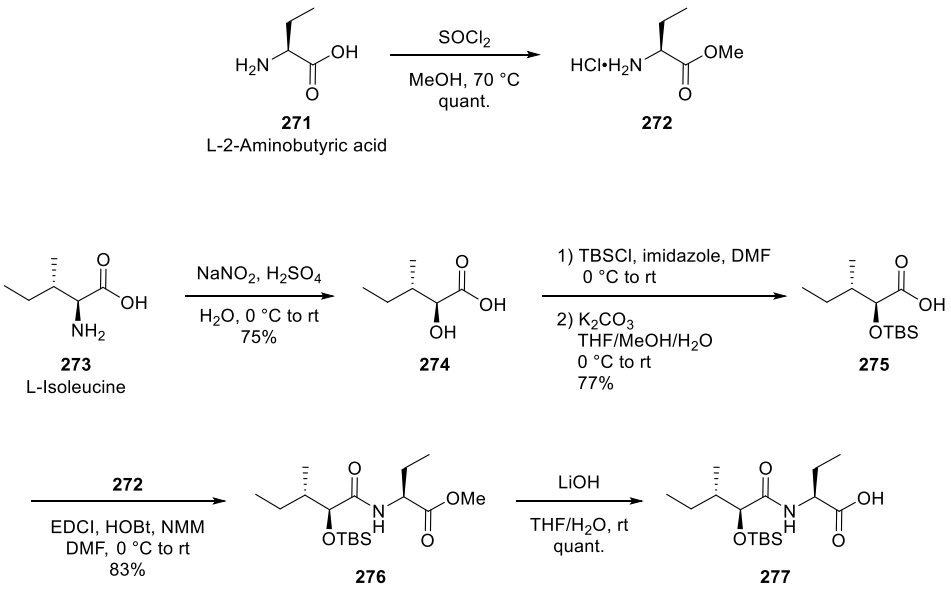
Table 4. Optimization of the oxidation conditions.



268
0.01 mmol (10 mg)

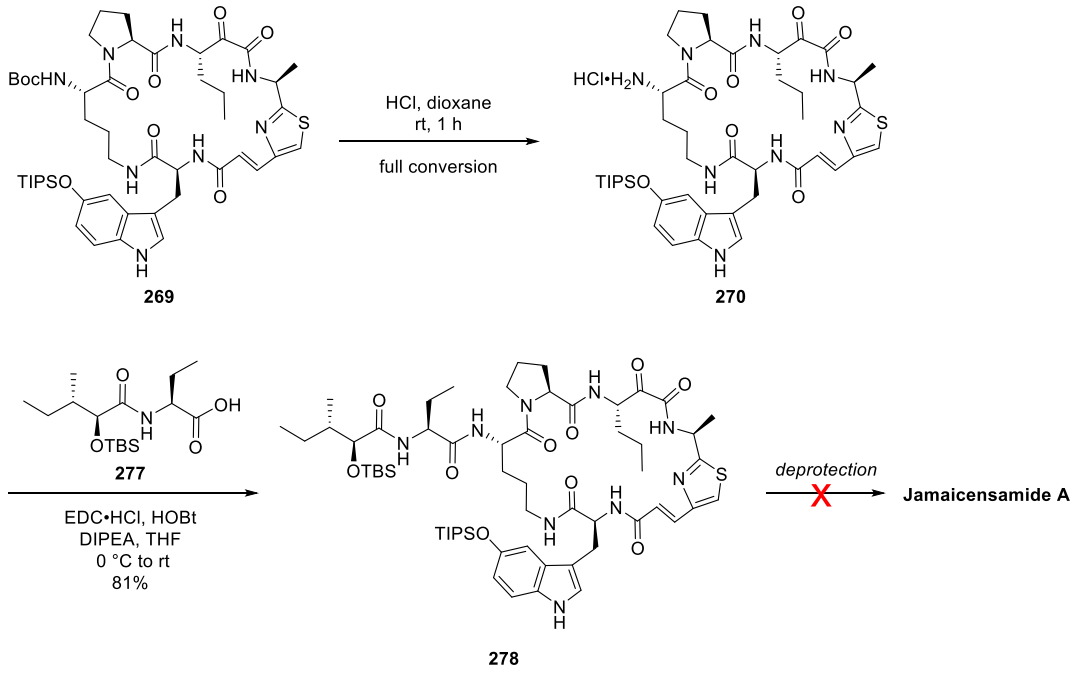
269

Entry	Conditions	Results
1	DMP (1.5 equiv), THF, 0 °C to rt, 24 h	not complete, 20% of product was obtained
2	PCC (1.5 equiv), THF, 0 °C to rt, 24 h	not complete, 12% of product was obtained
3	Swern oxidation, 24 h	not complete, complex mixture
4	Parikh-Doering oxidation, 24 h	not complete, complex mixture
5	IBX (1.5 equiv), DMSO, 0 °C to rt, 24 h	no reaction
6	DMP (2.0 equiv), THF, 0 °C to rt, 24 h	not complete, 20% of product was obtained
7	DMP (4.0 equiv), THF, 0 °C to rt, 24 h	not complete, 26% of product was obtained
8	DMP (6.0 equiv), THF, 0 °C to rt, 24 h	not complete, 41% of product was obtained
9	DMP (10.0 equiv), THF, 0 °C to rt, 24 h	full conversion, 79% of product was obtained
10	DMP (5.0 equiv), THF, 60 °C, 24 h	full conversion, 72% of product was obtained



Scheme 41. Preparation of side chain carboxylic acid 277.

To connect the side chain carboxylic acid **277** to the cyclic peptide **269**, the deprotection of Boc using HCl in dioxane smoothly gave amine salt **270** which was directly coupled with the freshly prepared carboxylic acid **277** to give the protected jamaicensamide A (**278**) in 81% yield (Scheme 42). Attempts to deprotect TIPS and TBS protecting groups with various conditions failed to give the target molecule. Deprotection using the fluorine sources including TBAF, TASF, HF-pyridine, HF-NEt_3, CsF and KF gave the complex mixture. No desired product was observed. Deprotection under the strong acidic conditions also gave the same results.



Scheme 42. Coupling reaction of side chain acid with macrocycle.

We also prepared the cyclic compound with a milder silyl protecting group, TBS, (compound **279**) to try the deprotection in the last step. The structure was shown in Figure 19. The synthetic route was similar to compound **278**. The deprotection of this compound is still on going.

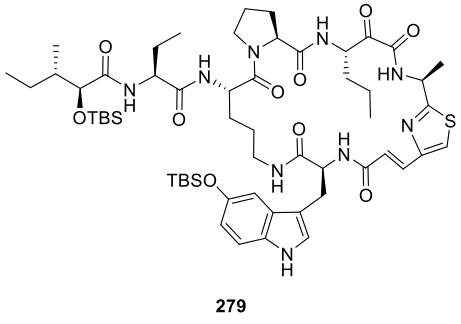
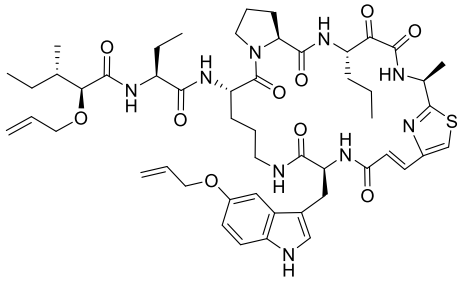


Figure 19. The TBS protected jamaicensamide A.

We also decided to change the protecting groups that having the different deprotection process to the silyl enol ethers. The allyl group is the good choice because its deprotection conditions based on the palladium chemistry. The structure of this compound (**280**) was depicted in Figure 20. The synthetic route was similar to compound **278**.

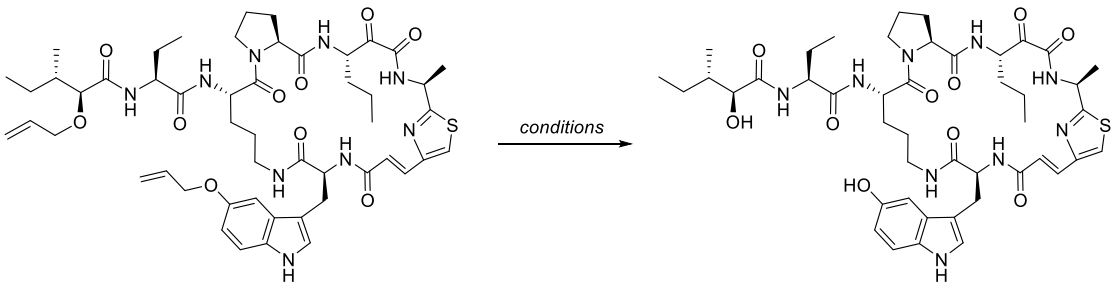


280

Figure 20. The allyl protected jamaicensamide A.

Various deprotection conditions were employed to cleave the allyl groups. Most of conditions using the palladium in catalytic amount gave no reaction. This molecule contained many amide groups together with a *α*-ketoamide which could be problematic for the palladium to selective coordinate with the allyl groups instead of the amide bonds. Higher loading of palladium did not help, the starting material started to decomposed. Some of reactions were shown in Table 5.

Table 5. Deprotection of allyl groups.



280 **jamaicensamide A**

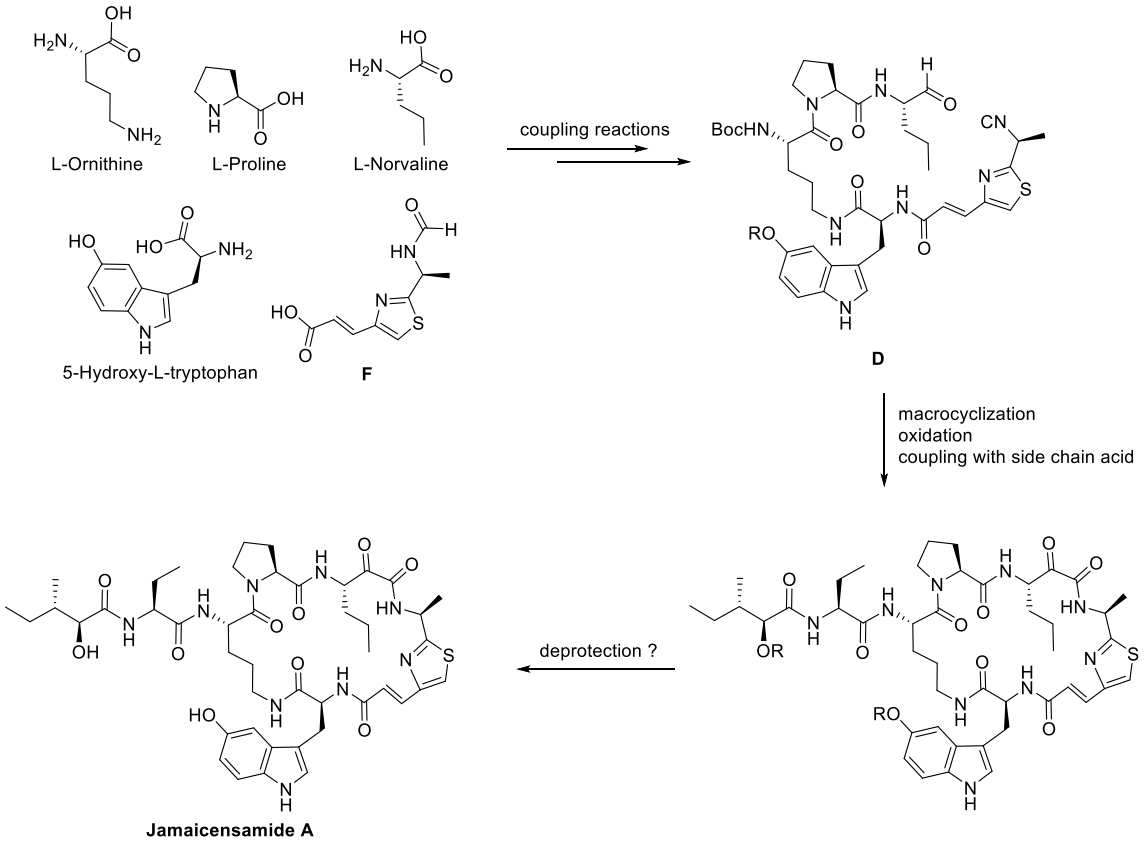
Entry	Conditions	Results
1	$Pd(PPh_3)_4$ (10-50 mol%), morpholine, CH_2Cl_2, H_2O, rt	no reaction
2	10% Pd/C, 10% KOH in MeOH, rt	no reaction
3	10% Pd/C, PTSA, MeOH, rt	no reaction
4	$Pd(OAc)_2$ (10 mol% to 1.1 equiv), PPh_3, HCOOH, rt	no reaction
5	$Pd(PPh_3)_4$ (10 mol% to 1.1 equiv), K_2CO_3, MeOH, rt	no reaction

Table 5. Deprotection of allyl groups (cont).

Entry	Conditions	Results
6	$Pd(PPh_3)_4$ (1.1 equiv), morpholine, CH_2Cl_2, H_2O, rt	no reaction
7	$Pd(PPh_3)_4$ (2.0 equiv), morpholine, CH_2Cl_2, H_2O, rt	start to decompose
8	$Pd(PPh_3)_4$ (10 mol%), morpholine, CH_2Cl_2, H_2O, reflux	no reaction
9	$Pd(PPh_3)_4$ (1.1 equiv), morpholine, CH_2Cl_2, H_2O, reflux	start to decompose
10	$Pd(PPh_3)_4$ (1.1 equiv), K_2CO_3, MeOH, reflux	start to decompose
11	$Pd(PPh_3)_4$ (2 mol%), $NaBH_4$ (2.0 equiv), THF, 0 °C to rt	complex mixture
12	$Pd(PPh_3)_2Cl_2$ (10 mol%), $NaBH_4$ (2.0 equiv), THF, 0 °C to rt	complex mixture
13	$Pd(OH)_2/C$ (10 mol%), MeOH or ^{i}PrOH or ^{t}BuOH, rt or reflux	no reaction
14	$Pd(PPh_3)_4$ (5-20mol%), 1,3-dimethylbarbituric acid (2.0 equiv), MeOH, rt	no reaction
15	$Pd(PPh_3)_4$ (1.0 equiv), 1,3-dimethylbarbituric acid (2.0 equiv), MeOH, rt	start to decompose

2.3 Conclusion

To apply our strategy on the macrocyclization of ω-isocyanoaldehyde in the total synthesis of a natural product. The 24-membered cyclic peptide jamaicensamide A was selected to be studied. The construction of a reactive precursor ω-isocyanoaldehyde **D** was prepared through the peptide coupling reactions between L-norvaline, L-proline, L-ornithine, 5-hydroxy-L-tryptophan and a thiazole fragment **F**. The ω-isocyanoaldehyde **D** smoothly underwent the Passerini reaction to afford the cyclic peptide in satisfactory yield. To complete the total synthesis of jamaicensamide A, the last step deprotection of protecting groups have to be further investigated.



Scheme 43. Outline for the total synthesis of jamaicensamide A.

Chapter 3
Supporting Information

3.1 General Information

Reagents and solvents were purchased from commercial sources. More sensitive compounds were stored in a desiccator or glove-box if required. Reagents were used without further purification unless otherwise noted.

All reactions were performed under argon (or nitrogen) and stirring unless otherwise noted. When needed, glassware was dried in an oven (T°>100 °C) or under vacuum with a heat gun (T°>200 °C).

When solvents are indicated as dry they were either purchased as such, distilled prior to use or were dried by a passage through a column of anhydrous alumina or copper using a Puresolv MD 5 from Innovative Technology Inc., based on the Grubbs' design.

Flash column chromatography was performed using Silicycle SiliaFlash® P60 230-400 mesh. Reactions were monitored using Merck Kieselgel 60F254 aluminium plates. TLCs were visualized by UV fluorescence (254 nm) then one of the following: $KMnO_4$, 2,4-dinitrophenol solution.

NMR spectra were recorded on a Brüker AvanceIII-400, Brüker Avance-400 or Brüker DPX-400 spectrometer at room temperature, ^{1}H frequency is at 400.13 MHz, ^{13}C frequency is at 100.62 MHz. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 for proton and 0.1 for carbon (ref: $CHCl_3$ [^{1}H: 7.26, ^{13}C: 77.16 ppm]). Coupling constants (*J*) were reported in Hz to the nearest 0.1 Hz. Peak multiplicity was indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Attribution of peaks was done using the multiplicities and integrals of the peaks.

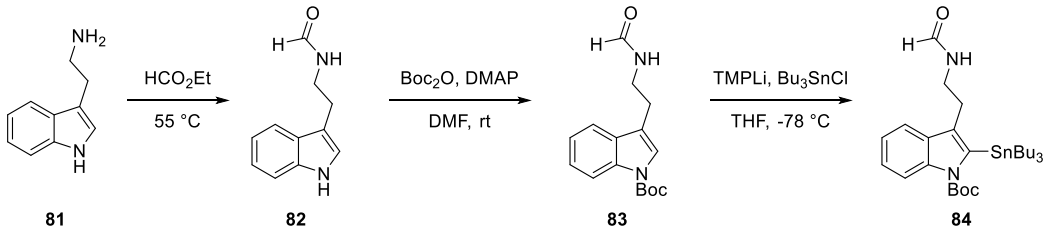
IR spectra were recorded in a Jasco FT/IR-4100 spectrometer outfitted with a PIKE technology MIRacleTM ATR accessory as neat films compressed onto a Zinc Selenide window or a Perkin Elmer Spectrum BX FT-IR. The spectra are reported in cm^{-1}. Abbreviations used are: w (weak), m (medium), s (strong) and br (broad).

Mass spectra were determined with a Waters ACQUITY H-class UPLC/MS ACQ-SQD by electron ionization (EI positive and negative) or a Finnigan TSQ7000 by electrospray ionization (ESI+). The

accurate masses were done by the mass spectrometry service of the EPFL by ESI-TOF using a QTOF Ultima from Waters.

3.2 Macrocyclization of ω-Isocyanoaldehydes

3.2.1 Synthesis of starting materials



Compound **84** was prepared in three steps from tryptamine (**81**).

***tert*-Butyl 3-(2-formamidoethyl)-1*H*-indole-1-carboxylate (83)**

A solution of tryptamine (**81**) (8.01 g, 50 mmol, 1.0 equiv) in dry ethyl formate (30 mL, 1.67 M) was heated to reflux and stirred for 21 h. The solution was cooled to room temperature and evaporated to dryness to give **82** as brown oil which was used for the next step without any purification.

To a solution of crude **82** (50 mmol, 1.0 equiv) and DMAP (152.7 mg, 1.25 mmol, 0.025 equiv) in dry DMF (150 mL) was added a solution of Boc_2O (10.9 g, 50 mmol, 1.0 equiv) in dry DMF (50 mL) dropwise. The resulting solution was stirred at room temperature for 24 h. After completion of the reaction, water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water (3 times) and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 2% to 5% $MeOH/CH_2Cl_2$) to yield **83** in 75% yield (10.75 g, 37.3 mmol) as yellow solid.

The spectral data were in accordance with those reported in the literature.[23]

***tert*-Butyl 3-(2-formamidoethyl)-2-(tributylstannyl)-1*H*-indole-1-carboxylate (84)**

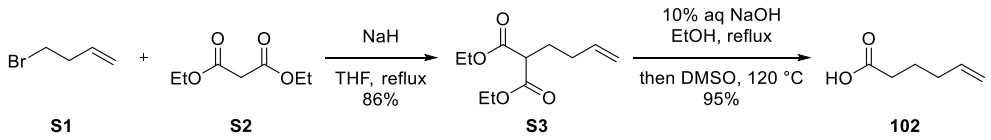
To a solution of tetramethylpiperidine (6.6 mL, 39.1 mmol, 2.3 equiv) in dry THF (70 mL) was added *n*-BuLi (2.2 M, 19.3 mL, 42.5 mmol, 2.5 equiv) dropwise at -78 °C. After stirring at -78 °C for 10 minutes, a solution of **83** (4.90 g, 17.0 mmol, 1.0 equiv) in dry THF (15 mL) was added dropwise and the solution was stirred at -78 °C for 1 h. After that time, Bu_3SnCl (13.8 mL, 51.0 mmol, 3.0 equiv) was added dropwise and the resulting solution was stirred at -78 °C for 1 h. The mixture was quenched with water at -78 °C and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 5% to 30% EtOAc/PE + 3% NEt_3) to yield **84** in 75% yield (7.41 g, 12.8 mmol) as yellowish viscous oil.

^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.60 (d, *J* = 7.0 Hz, 1H), 7.27 – 7.17 (m, 2H), 3.42 (t, *J* = 7.3 Hz, 2H), 2.96 (t, *J* = 7.6 Hz, 2H), 1.71 (s, 9H), 1.59 – 1.47 (m, 6H), 1.39 – 1.30 (m, 6H), 1.16 – 1.11 (m, 6H), 0.88 (t, *J* = 7.3 Hz, 9H).

^{13}C NMR (101 MHz, CD_3OD) δ 163.7, 153.9, 140.2, 138.8, 133.5, 130.6, 124.9, 123.4, 119.4, 116.4, 85.4, 40.4, 39.0, 30.4, 28.5, 28.4, 14.1, 14.0.

The spectral data were in accordance with those reported in the literature.[23]

Synthesis of 5-hexenoic acid (102)



Diethyl 2-(but-3-en-1-yl)malonate (S3)

According to a reported procedure,[34] to a suspension of NaH (60% dispersion in mineral oil, 440.0 mg, 11.0 mL, 1.1 equiv) in dry THF (40 mL) was added diethyl malonate (**S2**) (1.67 mL, 11.0 mmol, 1.1 equiv) dropwise at 0 °C. The mixture was stirred at 0 °C for 15 min, then at room temperature for 30 min before being cooled again to 0 °C. A solution of 4-bromo-1-butene (**S1**) (1.35 g, 10.0 mmol, 1.0 equiv) in dry THF (10 mL) was added dropwise. The resulting mixture was allowed to warm to room temperature and was heated to reflux for 20 h. After completion, the mixture was allowed to cool to room temperature and quenched with water. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with bine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 5% Et_2O/PE) to yield **S3** in 86% yield (1.85 g, 8.63 mmol) as colorless oil (R_f = 0.27 (10% Et_2O/PE)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.09 – 4.97 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 4H), 3.35 (t, *J* = 7.3 Hz, 1H), 2.13 – 2.07 (m, *J* = 6.9 Hz, 2H), 2.02 – 1.97 (m, *J* = 7.3 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 137.0, 116.1, 61.5, 51.4, 31.4, 28.0, 14.2.

5-Hexenoic acid (102)

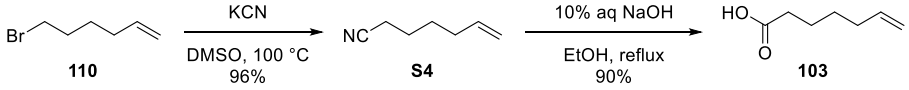
According to a reported procedure,[27] to a solution of diester **S3** (1.71 g, 8.0 mmol, 1.0 equiv) in EtOH (40 mL) was added 10% aqueous NaOH (9.6 mL). After heating the mixture to reflux for 6 h, the mixture was allowed to cool to room temperature and EtOH was removed. The aqueous layer was acidified with 2 M HCl to pH~1 and extracted with Et_2O. The combined organic layers were washed with brine, dried

over Na_2SO_4, filtered and evaporated to dryness to give the diacid intermediate. The crude diacid was dissolved in DMSO (10 mL) and the resulting solution was stirred at 120 °C for 4 h. The mixture was allowed to cool to room temperature, diluted with Et_2O, and washed with brine (3 times). The organic layers were dried over Na_2SO_4, filtered and evaporated to dryness to afford **102** in 95% yield (868.6 mg, 7.61 mmol) as colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (br s, 1H), 5.78 (ddt, *J* = 16.9, 10.3, 6.7 Hz, 1H), 5.09 – 4.96 (m, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.12 (q, *J* = 7.1 Hz, 2H), 1.75 (p, *J* = 7.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1, 137.6, 115.7, 33.4, 33.1, 23.9.

Synthesis of 6-heptenoic acid (103)



110 **S4** **103**

6-Heptenenitrile (S4)

According to a reported procedure,[35] to a solution of potassium cyanide (716.3 mg, 11.0 mmol, 2.2 equiv) in DMSO (40 mL) was added a solution of 6-bromo-1-hexene (**110**) (815.3 mg, 5.0 mmol, 1.0 equiv) in DMSO (10 mL). The resulting solution was stirred at 100 °C for 3 h. The mixture was allowed to cool to room temperature, quenched with water and extracted with Et_2O. The combined organic layers were washed with water (3 times) and brine, dried over Na_2SO_4, filtered and evaporated to dryness to give **S4** in 96% yield (522.5 mg, 4.79 mmol) as colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.07 – 4.94 (m, 2H), 2.34 (t, *J* = 7.0 Hz, 2H), 2.09 (qt, *J* = 6.9, 1.4 Hz, 2H), 1.71 – 1.63 (m, 2H), 1.59 – 1.51 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 119.8, 115.5, 32.9, 27.8, 24.8, 17.1.

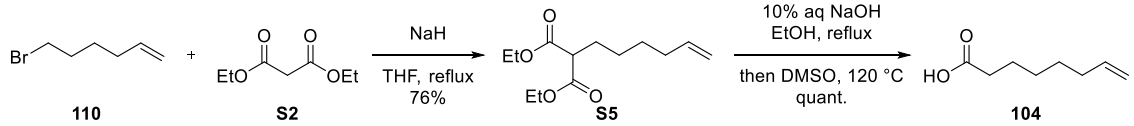
6-Heptenoic acid (103)

According to a reported procedure,[27] to a solution of nitrile **S4** (409.4 mg, 3.75 mmol, 1.0 equiv) in EtOH (19 mL) was added 10% aqueous NaOH (4.5 mL). After heating the mixture to reflux overnight, the mixture was allowed to cool to room temperature and EtOH was removed. The aqueous layer was acidified with 2 M HCl to pH~1 and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness to give **103** in 90% yield (430.7 mg, 3.36 mmol) as colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.01 (dq, *J* = 17.2, 1.8 Hz, 1H), 4.96 (dq, *J* = 10.1, 1.5 Hz, 1H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.08 (qt, *J* = 7.2, 1.5 Hz, 2H), 1.69 – 1.62 (m, 2H), 1.49 – 1.41 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.0, 138.4, 114.9, 34.0, 33.5, 28.4, 24.2.

Synthesis of 7-octenoic acid (104)



Diethyl 2-(hex-5-en-1-yl)malonate (S5)

To a suspension of NaH (60% dispersion in mineral oil, 220.0 mg, 5.5 mL, 1.1 equiv) in dry THF (10 mL) was added diethyl malonate (**S2**) (0.84 mL, 5.5 mmol, 1.1 equiv) dropwise at 0 °C. The mixture was stirred at 0 °C for 15 min, then at room temperature for 30 min before being cooled again to 0 °C. A solution of 6-bromo-1-hexene (**110**) (0.67 mL, 5.0 mmol, 1.0 equiv) in dry THF (10 mL) was added dropwise. The resulting mixture was allowed to warm to room temperature and was heated to reflux for 15 h. After completion, the mixture was allowed to cool to room temperature and quenched with water. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with bine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 5% Et_2O/PE) to yield **S5** in 76% yield (923.4 mg, 3.81 mmol) as colorless oil (R_f = 0.29 (10% Et_2O/PE)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (dq, *J* = 17.2, 1.7 Hz, 1H), 4.93 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 4.19 (qd, *J* = 7.1, 0.9 Hz, 4H), 3.31 (t, *J* = 7.5 Hz, 1H), 2.08 – 2.01 (m, 2H), 1.92 – 1.86 (m, 2H), 1.46 – 1.39 (m, 2H), 1.38 – 1.31 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 138.7, 114.7, 61.4, 52.2, 33.5, 28.7, 28.6, 26.9, 14.2.

7-Octenoic acid (104)

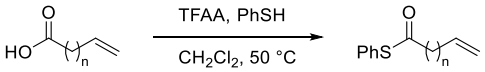
To a solution of diester **S5** (654.5 mg, 2.7 mmol, 1.0 equiv) in EtOH (13.5 mL) was added 10% aqueous NaOH (3.3 mL). After heating the mixture to reflux overnight, the mixture was allowed to cool to room temperature and EtOH was removed. The aqueous layer was acidified with 2 M HCl to pH~1 and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness to give the diacid intermediate. The crude diacid was dissolved in DMSO (6 mL) and the resulting solution was stirred at 120 °C for 4 h. The mixture was allowed to cool to room

temperature, diluted with Et_2O, and washed with brine (3 times). The organic layers were dried over Na_2SO_4, filtered and evaporated to dryness to afford **104** in quantitative yield (387.0 mg, 2.72 mmol) as colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.00 (dt, *J* = 17.1, 1.8 Hz, 1H), 4.94 (d, *J* = 10.2 Hz, 1H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.05 (q, *J* = 7.0 Hz, 2H), 1.65 (p, *J* = 7.4 Hz, 2H), 1.43 – 1.36 (m, 4H).

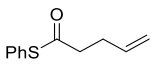
^{13}C NMR (101 MHz, $CDCl_3$) δ 179.7, 138.9, 114.6, 34.0, 33.7, 28.6, 24.7.

General procedure for the synthesis of the thioesters



101-104 **85-88**

To a solution of the carboxylic acid (1.0 equiv) in dry CH_2Cl_2 (0.3 M) was added trifluoroacetic anhydride (TFAA) (1.0 equiv). The solution was stirred at room temperature for 2 h and thiophenol was then added. The resulting solution was stirred at 50 °C for 21 h. The mixture was allowed to cool to room temperature and quenched with saturated $NaHCO_3$. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2) to afford the thioester product.



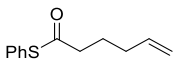
***S*-Phenyl pent-4-enethioate (85)**

Yield: 84%, R_f = 0.47 (5% Et_2O/PE)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 5H), 5.85 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.11 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.06 (dq, *J* = 10.2, 1.4 Hz, 1H), 2.77 (t, *J* = 7.2 Hz, 2H), 2.51 – 2.44 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8, 136.1, 134.6, 129.5, 129.3, 127.8, 116.1, 42.9, 29.5.

HRMS (ESI/QTOF) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{13}OS^+$ 193.0682; found 193.0684.



_S_-Phenyl hex-5-enethioate (86)

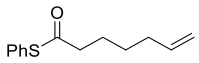
Yield: 80%, Eluent: 2% Et_2O/PE, R_f = 0.47 (5% Et_2O/PE)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 5H), 5.79 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.13 – 4.94 (m, 2H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.14 (q, *J* = 7.1 Hz, 2H), 1.82 (p, *J* = 7.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5, 137.6, 134.6, 129.5, 129.3, 128.0, 115.8, 43.0, 33.0, 24.8.

HRMS (ESI/QTOF) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{15}OS^+$ 207.0838; found 207.0841.

IR: ν (cm^{-1}) 3072, 2925, 1702, 1477, 1438, 993, 912, 742, 719, 686.



_S_-Phenyl hept-6-enethioate (87)

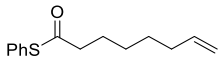
Yield: 74%, Eluent: 2% Et_2O/PE, R_f = 0.50 (5% Et_2O/PE)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 5H), 5.80 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.02 (dd, *J* = 17.2, 1.7 Hz, 1H), 4.97 (d, *J* = 10.2 Hz, 1H), 2.67 (t, *J* = 7.4 Hz, 2H), 2.09 (q, *J* = 7.1 Hz, 2H), 1.74 (p, *J* = 7.5 Hz, 2H), 1.47 (p, *J* = 7.7 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 138.4, 134.6, 129.5, 129.3, 128.0, 115.0, 43.7, 33.5, 28.3, 25.2.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{16}NaOS^+$ 243.0814; found 243.0821.

IR: ν (cm^{-1}) 3075, 2928, 2858, 1703, 1474, 1438, 990, 905, 740, 686.



_S_-Phenyl oct-7-enethioate (88)

Yield: 73%, Eluent: 2% Et_2O/PE, R_f = 0.50 (5% Et_2O/PE)

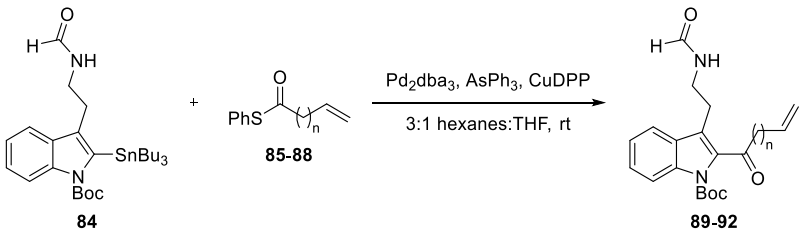
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 5H), 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (dq, *J* = 17.2, 1.7 Hz, 1H), 4.95 (ddt, *J* = 10.1, 2.3, 1.2 Hz, 1H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.06 (q, *J* = 6.7 Hz, 2H), 1.73 (p, *J* = 7.3 Hz, 2H), 1.47 – 1.35 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 138.9, 134.6, 129.4, 129.3, 128.0, 114.6, 43.8, 33.6, 28.6, 28.5, 25.6.

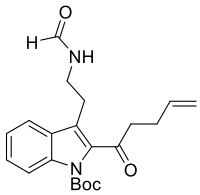
HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{18}NaOS^+$ 257.0971; found 257.0974.

IR: ν (cm^{-1}) 2925, 2856, 1706, 1475, 1442, 997, 912, 740, 686.

General procedure A: synthesis of the C2 acylated tryptamine derivatives[23]



A mixture of **84** (1.1 equiv), the thioester (1.0 equiv), Pd_2dba_3 (0.1 equiv), $AsPh_3$ (0.1 equiv) and CuDPP (2.0 equiv) in dry degassed 3:1 hexanes/THF (0.067 M) was stirred at room temperature for 6 h. After completion of reaction, the mixture was filtered through a pad of Celite (rinsed with EtOAc). The filtrate was washed with 2 M HCl, 10% NH_4OH and brine, dried over Na_2SO_4, filtered and evaporated to dryness. Purification of the crude mixture by column chromatography (SiO_2) afforded the desired compound.



***tert*-Butyl 3-(2-formamidoethyl)-2-(pent-4-enoyl)-1*H*-indole-1-carboxylate (89)**

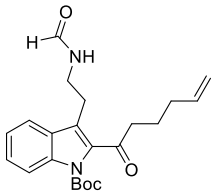
Yield: 71%, Eluent: 1:1 EtOAc/PE, R_f = 0.30 (2:1 EtOAc/PE)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.02 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.59 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.45 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.32 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H), 7.13 (br s, 1H), 5.80 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.02 (apparent dq, *J* = 17.1, 1.7 Hz, 1H), 4.97 (apparent dq, *J* = 10.2, 1.4 Hz, 1H), 3.59 – 3.55 (m, 2H), 2.89 – 2.83 (m, 4H), 2.47 – 2.41 (m, 2H), 1.68 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3, 162.0, 150.2, 136.9, 136.4, 136.3, 129.0, 127.5, 124.0, 122.6, 120.5, 116.0, 115.8, 85.9, 42.9, 38.5, 29.3, 28.3, 23.2.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{21}H_{26}N_2NaO_4^+$ 393.1785; found 393.1779.

IR: ν (cm^{-1}) 3304, 2979, 2931, 1725, 1676, 1450, 1369, 1323, 1231, 1146, 839, 749.



tert-Butyl 3-(2-formamidoethyl)-2-(hex-5-enoyl)-1*H*-indole-1-carboxylate (90)

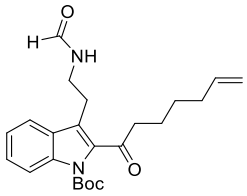
Yield: 66%, Eluent: 1:1 EtOAc/PE, R_f = 0.32 (1:1 EtOAc/PE)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.44 (ddd, *J* = 8.3, 7.4, 1.2 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.11 (br s, 1H), 5.76 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 1H), 5.03 – 4.93 (m, 2H), 3.60 – 3.54 (m, 2H), 2.88 (t, *J* = 6.5 Hz, 2H), 2.74 (t, *J* = 7.6 Hz, 2H), 2.10 (q, *J* = 7.1 Hz, 2H), 1.78 (p, *J* = 7.4 Hz, 2H), 1.68 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9, 161.9, 150.1, 137.8, 136.5, 136.2, 128.9, 127.3, 123.9, 122.2, 120.4, 115.9, 115.7, 85.8, 43.1, 38.3, 33.3, 28.3, 24.1, 23.1.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{28}N_2NaO_4^+$ 407.1941; found 407.1936.

IR: ν (cm^{-1}) 3298, 2976, 2931, 1727, 1672, 1450, 1369, 1321, 1231, 1143, 834, 767, 749.



tert-Butyl 3-(2-formamidoethyl)-2-(hept-6-enoyl)-1*H*-indole-1-carboxylate (91)

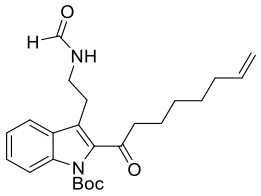
Yield: 68%, Eluent: 2:1 EtOAc/PE, R_f = 0.34 (2:1 EtOAc/PE)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.12 (br s, 1H), 5.76 (ddt, *J* = 16.6, 10.7, 5.3 Hz, 1H), 5.01 – 4.91 (m, 2H), 3.59 – 3.54 (m, 2H), 2.88 (t, *J* = 5.8 Hz, 2H), 2.74 (t, *J* = 7.6 Hz, 2H), 2.05 (q, *J* = 7.0 Hz, 2H), 1.70 – 1.65 (m, 2H), 1.67 (s, 9H), 1.42 (p, *J* = 7.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9, 161.8, 150.0, 138.4, 136.4, 136.1, 128.9, 127.3, 123.8, 122.1, 120.4, 115.8, 114.9, 85.7, 43.6, 38.3, 33.5, 28.5, 28.2, 24.5, 23.1.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{30}N_2NaO_4^+$ 421.2098; found 421.2090.

IR: ν (cm^{-1}) 1727, 1679, 1367, 1321, 1228, 1143, 746.



***tert*-Butyl 3-(2-formamidoethyl)-2-(oct-7-enoyl)-1*H*-indole-1-carboxylate (92)**

Yield: 63%, Eluent: 1:1 EtOAc/PE, R_f = 0.55 (1:1 EtOAc/PE)

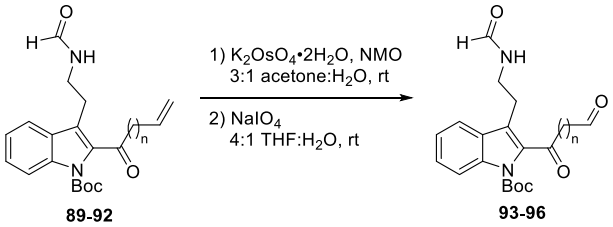
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.16 (br s, 1H), 5.76 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 4.97 (dq, *J* = 17.1, 1.9 Hz, 1H), 4.92 (dd, *J* = 10.2, 1.2 Hz, 1H), 3.59 – 3.55 (m, 2H), 2.88 (t, *J* = 6.5 Hz, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 2.03 (q, *J* = 6.9 Hz, 2H), 1.67 (s, 9H), 1.66 – 1.62 (m, 2H), 1.43 – 1.28 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.1, 161.9, 150.1, 138.8, 136.5, 136.1, 128.9, 127.3, 123.8, 122.1, 120.4, 115.8, 114.6, 85.7, 43.7, 38.3, 33.6, 28.8, 28.7, 28.2, 24.9, 23.1.

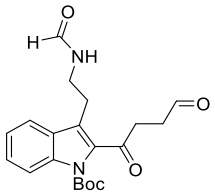
HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{24}H_{32}N_2NaO_4^+$ 435.2254; found 435.2245.

IR: ν (cm^{-1}) 3311, 2976, 2931, 2856, 1727, 1682, 1450, 1369, 1318, 1255, 1231, 1143, 749.

General procedure B: conversion of the alkenes to the aldehydes[27]



To a solution of the alkene (1.0 equiv) in 3:1 acetone/H_2O (0.13 M) was added $K_2OsO_4 \cdot 2H_2O$ (0.05 equiv) and NMO (2.0 equiv). The resulting mixture was stirred at room temperature for 5 h. Acetone was removed and the mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness to give the crude diol. The crude diol was dissolved in 4:1 THF/H_2O (0.13 M). $NaIO_4$ (2.0 equiv) was added and the resulting mixture was stirred at room temperature for 1 h. The mixture was filtered through a pad of Celite (rinsed with CH_2Cl_2) and the filtrate was washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. Purification of the crude mixture by column chromatography (SiO_2) afforded the desired compound.



tert-Butyl 3-(2-formamidoethyl)-2-(4-oxobutanoyl)-1*H*-indole-1-carboxylate (93)

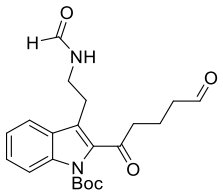
Yield: 93%, Eluent: 3% MeOH/CH_2Cl_2, R_f = 0.32 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.13 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.44 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 6.87 (br s, 1H), 3.58 (q, *J* = 5.6 Hz, 2H), 3.09 (t, *J* = 6.3 Hz, 2H), 2.95 (t, *J* = 6.3 Hz, 2H), 2.92 (t, *J* = 6.1 Hz, 2H), 1.68 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.6, 196.7, 161.8, 150.3, 136.1, 136.0, 129.1, 127.4, 123.9, 122.9, 120.6, 115.9, 85.9, 38.7, 38.2, 35.7, 28.3, 23.1.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{24}N_2NaO_5^+$ 395.1577; found 395.1576.

IR: ν (cm^{-1}) 3319, 2979, 2934, 1718, 1676, 1450, 1387, 1369, 1321, 1234, 1143, 1086, 1028, 836, 767, 752.



tert-Butyl 3-(2-formamidoethyl)-2-(5-oxopentanoyl)-1*H*-indole-1-carboxylate (94)

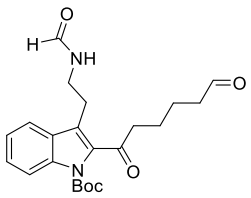
Yield: 95%, Eluent: 2% to 5% MeOH/CH_2Cl_2, R_f = 0.29 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.3 Hz, 1H), 8.14 (s, 1H), 7.98 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.59 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.43 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.31 (ddd, *J* = 8.0, 7.3, 1.0 Hz, 1H), 6.98 (br s, 1H), 3.59 – 3.54 (m, 2H), 2.92 – 2.84 (m, 2H), 2.79 (t, *J* = 7.1 Hz, 2H), 2.59 (td, *J* = 7.0, 1.3 Hz, 2H), 2.05 (p, *J* = 7.0 Hz, 2H), 1.68 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.9, 197.9, 161.8, 150.2, 136.3, 136.0, 128.9, 127.3, 123.9, 122.2, 120.4, 115.9, 85.9, 42.8, 42.4, 38.3, 28.3, 23.2, 17.0.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{21}H_{26}N_2NaO_5^+$ 409.1734; found 409.1727.

IR: ν (cm^{-1}) 1718, 1679, 1359, 1321, 1139, 755.



***tert*-Butyl 3-(2-formamidoethyl)-2-(6-oxohexanoyl)-1*H*-indole-1-carboxylate (95)**

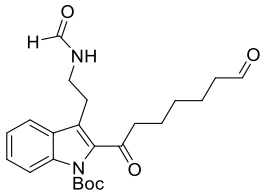
Yield: 83%, Eluent: 2% to 5% MeOH/CH_2Cl_2, R_f = 0.26 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.5 Hz, 1H), 8.14 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.07 (br s, 1H), 3.56 (q, *J* = 5.1 Hz, 2H), 2.88 (t, *J* = 6.3 Hz, 2H), 2.76 (t, *J* = 7.0 Hz, 2H), 2.47 (t, *J* = 6.3 Hz, 2H), 1.75 – 1.62 (m, 4H), 1.68 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2, 198.3, 161.9, 150.1, 136.3, 136.1, 128.9, 127.3, 123.9, 122.3, 120.4, 115.8, 85.8, 43.7, 43.3, 38.3, 28.2, 24.4, 23.1, 21.7.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{28}N_2NaO_5^+$ 423.1890; found 423.1881.

IR: ν (cm^{-1}) 1718, 1679, 1367, 1324, 1143, 755.



***tert*-Butyl 3-(2-formamidoethyl)-2-(7-oxoheptanoyl)-1*H*-indole-1-carboxylate (96)**

Yield: 82%, Eluent: 2% MeOH/CH_2Cl_2, R_f = 0.34 (5% MeOH/CH_2Cl_2)

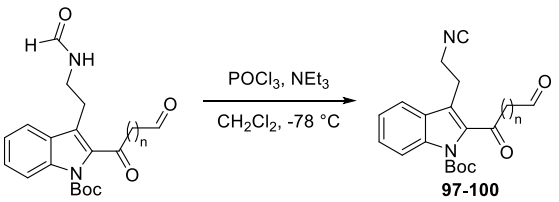
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.7 Hz, 1H), 8.14 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.04 (br s, 1H), 3.55 (q, *J* = 6.2 Hz, 2H), 2.87 (t, *J* = 6.2 Hz, 2H), 2.74 (t, *J* = 7.6 Hz, 2H), 2.43 (td, *J* = 7.2, 1.6 Hz, 2H), 1.77 – 1.68 (m, 2H), 1.67 (s, 9H), 1.66 – 1.58 (m, 2H), 1.41 – 1.33 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.5, 198.7, 161.9, 150.1, 136.4, 136.1, 128.9, 127.3, 123.8, 122.2, 120.4, 115.8, 85.8, 43.7, 43.4, 38.3, 28.7, 28.2, 24.7, 23.1, 21.8.

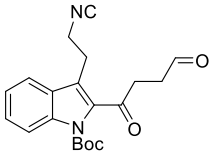
HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{30}N_2NaO_5^+$ 437.2047; found 437.2038.

IR: ν (cm^{-1}) 2946, 1722, 1681, 1386, 1367, 1324, 1147, 755.

General procedure C: dehydration of the formamides to the isocyanides[23]



To a solution of the formamide (1.0 equiv) in dry CH_2Cl_2 (0.3 M) was added NEt_3 (5.0 equiv) and $POCl_3$ (1.5 equiv) dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 3 h. After completion of reaction, the mixture was quenched with saturated Na_2CO_3 at -78 °C, allowed to warm to room temperature and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness to provide the *ω*-isocyanoaldehyde which was used for the next step without further purification.



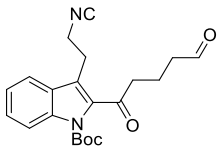
***tert*-Butyl 3-(2-isocyanoethyl)-2-(4-oxobutanoyl)-1*H*-indole-1-carboxylate (97)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (t, *J* = 0.7 Hz, 1H), 8.01 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.64 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.45 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.34 (ddd, *J* = 8.1, 7.3, 1.0 Hz, 1H), 3.72 (t, *J* = 7.2 Hz, 2H), 3.12 – 3.08 (m, 4H), 2.95 (t, *J* = 6.4 Hz, 2H), 1.67 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.6, 195.6, 157.2 (t, *J* = 5.4 Hz), 150.1, 136.2, 136.0, 129.1, 127.3, 123.9, 120.8, 120.4, 115.9, 85.9, 42.3 (t, *J* = 6.6 Hz), 38.6, 35.9, 28.2, 24.7.

HRMS (ESI/QTOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{23}N_2O_4^+$ 355.1652; found 355.1653.

IR: ν (cm^{-1}) 2976, 2922, 2142, 1727, 1682, 1454, 1366, 1323, 1258, 1237, 1143, 1079, 752.



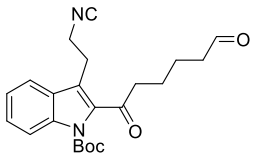
***tert*-Butyl 3-(2-isocyanoethyl)-2-(5-oxopentanoyl)-1*H*-indole-1-carboxylate (98)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.3 Hz, 1H), 8.00 (dt, *J* = 8.5, 0.9 Hz, 1H), 7.61 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.44 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.33 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H), 3.72 (t, *J* = 7.1 Hz, 2H), 3.07 (t, *J* = 7.1 Hz, 2H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.59 (td, *J* = 7.0, 1.3 Hz, 2H), 2.06 (p, *J* = 7.1 Hz, 2H), 1.67 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.0, 196.7, 157.2, 150.1, 136.6, 135.8, 128.9, 127.2, 123.9, 120.2, 120.0, 115.9, 85.9, 42.9, 42.6, 42.3 (t, *J* = 6.2 Hz), 28.2, 24.8, 16.9.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{21}H_{24}N_2NaO_4^+$ 391.1628; found 391.1629.

IR: ν (cm^{-1}) 2979, 2929, 2146, 1722, 1689, 1450, 1394, 1369, 1321, 1257, 1236, 1143, 1079, 750.



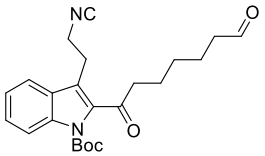
***tert*-Butyl 3-(2-isocyanoethyl)-2-(6-oxohexanoyl)-1*H*-indole-1-carboxylate (99)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 3.72 (t, *J* = 7.1 Hz, 2H), 3.07 (t, *J* = 7.2 Hz, 2H), 2.78 (t, *J* = 6.9 Hz, 2H), 2.48 (t, *J* = 6.8 Hz, 2H), 1.77 – 1.70 (m, 2H), 1.67 (s, 9H), 1.20 (t, *J* = 7.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.3, 197.1, 157.2, 150.0, 136.6, 135.9, 128.9, 127.2, 123.9, 120.2, 120.1, 115.9, 85.9, 46.2, 43.8, 43.6, 42.3 (t, *J* = 5.7 Hz), 28.2, 24.9, 24.2, 21.7.

HRMS (QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{26}N_2NaO_4^+$ 405.1790; found 405.1790.

IR: ν (cm^{-1}) 2979, 2931, 2146, 1727, 1685, 1454, 1367, 1321, 1257, 1236, 1147, 1078, 750.



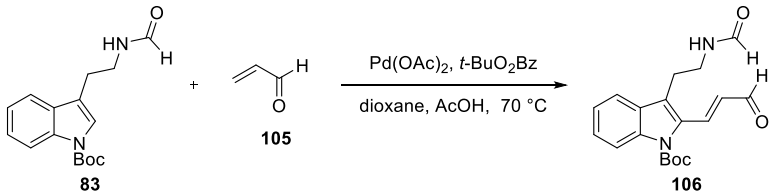
***tert*-Butyl 3-(2-isocyanoethyl)-2-(7-oxoheptanoyl)-1*H*-indole-1-carboxylate (100)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 3.72 (t, *J* = 7.1 Hz, 2H), 3.07 (t, *J* = 7.2 Hz, 2H), 2.75 (t, *J* = 7.6 Hz, 2H), 2.44 (t, *J* = 7.3 Hz, 2H), 1.73 – 1.60 (m, 4H), 1.66 (s, 9H), 1.43 – 1.35 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6, 197.4, 157.0, 150.0, 136.6, 135.9, 128.9, 127.2, 123.8, 120.2, 120.1, 115.8, 85.8, 45.9, 43.8, 43.7, 42.3 (t, *J* = 5.9 Hz), 28.8, 28.2, 24.9, 24.5, 21.9.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{28}N_2NaO_4^+$ 419.1941; found 419.1933.

IR: ν (cm^{-1}) 2979, 2937, 2275, 1727, 1681, 1517, 1455, 1367, 1321, 1261, 1147, 1008, 755, 719.



***tert*-Butyl (*E*)-3-(2-formamidoethyl)-2-(3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate (106)**

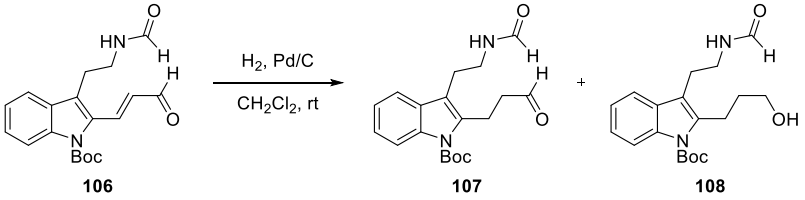
According to a reported procedure,[36] acrolein (**105**) (2.1 mL, 32.0 mmol, 4.0 equiv), *t*-BuO_2Bz (2.1 mL, 11.2 mmol, 1.4 equiv) and $Pd(OAc)_2$ (179.6 mg, 0.8 mmol, 0.1 equiv) were added to a solution of **83** in dioxane (12 mL) and AcOH (4 mL). The resulting mixture was stirred at 70 °C for 24 h. The mixture was allowed to cool to room temperature, neutralized with saturated $NaHCO_3$ and filtered through a pad of Celite (rinsed with EtOAc). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by flash column chromatography (1% to 2% MeOH/CH_2Cl_2) to afford compound **106** in 56% yield (1.53 g, 4.46 mmol) as yellow solid (R_f = 0.39 (5% MeOH/CH_2Cl_2)).

^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 9.71 (d, *J* = 7.7 Hz, 1H), 8.18 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 16.1 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 6.46 (dd, *J* = 16.2, 7.7 Hz, 1H), 6.20 (br s, 1H), 3.56 (q, *J* = 7.1 Hz, 2H), 3.08 (t, *J* = 7.5 Hz, 2H), 1.68 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) Major rotamer: δ 193.9, 161.7, 150.4, 143.8, 136.8, 131.8, 129.9, 129.6, 126.9, 123.7, 122.8, 120.1, 115.9, 85.3, 38.3, 28.3, 25.4.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{22}N_2NaO_4^+$ 365.1472; found 365.1470.

IR: ν (cm^{-1}) 1724, 1673, 1616, 1550, 1455, 1357, 1321, 1228, 1143, 1120, 746.



According to a reported procedure,[36] to a solution of the unsaturated aldehyde **106** (684.8 mg, 2.0 mmol, 1.0 equiv) in dry CH_2Cl_2 (20 mL) was added 10% Pd/C (94.0 mg). The resulting mixture was stirred under H_2 balloon (1 atm) at room temperature for 6 h. The mixture was filtered through a pad of Celite (rinsed with CH_2Cl_2) and the filtrate was evaporated to dryness. The crude mixture was purified by flash column chromatography (2% to 3% MeOH/CH_2Cl_2) to afford compound **107** in 35% yield (239.4 mg, 0.70 mmol) as yellowish oil together with compound **108** in 60% yield (412.5 mg, 1.20 mmol) as yellowish oil.

***tert*-Butyl 3-(2-formamidoethyl)-2-(3-oxopropyl)-1*H*-indole-1-carboxylate (107)**

Yield: 35%, Eluent: 2% to 3% MeOH/CH_2Cl_2, R_f = 0.37 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (t, *J* = 1.1 Hz, 1H), 8.15 (s, 1H), 8.05 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.60 – 7.48 (m, 1H), 7.32 – 7.21 (m, 2H), 5.71 (br s, 1H), 3.54 (q, *J* = 6.8 Hz, 2H), 3.33 (t, *J* = 7.3 Hz, 2H), 2.96 (t, *J* = 7.1 Hz, 2H), 2.84 (td, *J* = 7.3, 1.2 Hz, 2H), 1.68 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3, 161.3, 150.3, 136.3, 135.8, 129.4, 124.1, 122.9, 118.2, 115.9, 115.8, 84.2, 44.2, 38.1, 28.2, 24.1, 19.4.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{24}N_2NaO_4^+$ 367.1628; found 367.1629.

IR: ν (cm^{-1}) 2977, 2931, 1722, 1660, 1454, 1367, 1324, 1249, 1224, 1159, 1132, 730.

***tert*-Butyl 3-(2-formamidoethyl)-2-(3-hydroxypropyl)-1*H*-indole-1-carboxylate (108)**

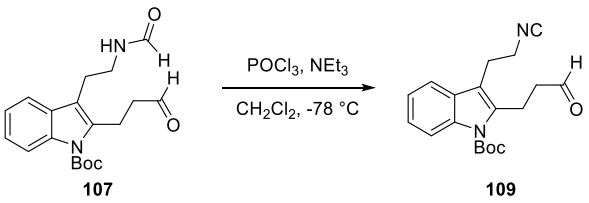
Yield: 60%, Eluent: 2% to 3% MeOH/CH_2Cl_2, R_f = 0.37 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 6.9 Hz, 1H), 7.28 – 7.21 (m, 2H), 5.86 (br s, 1H), 3.69 (t, *J* = 5.9 Hz, 2H), 3.56 (q, *J* = 7.2 Hz, 2H), 3.17 (t, *J* = 7.3 Hz, 2H), 2.96 (t, *J* = 7.4 Hz, 2H), 2.29 (br s, 1H), 1.90 (p, *J* = 6.6 Hz, 2H), 1.69 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 150.7, 138.3, 136.0, 129.7, 123.9, 122.9, 118.1, 115.9, 115.5, 84.2, 61.8, 38.4, 33.2, 28.4, 24.4, 22.9.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{26}N_2NaO_4^+$ 369.1785; found 369.1784.

IR: ν (cm^{-1}) 3853, 3729, 3704, 3367, 1727, 1668, 1454, 1363, 1321, 1160, 1132, 752.



107 **109**

***tert*-Butyl 3-(2-isocyanoethyl)-2-(3-oxopropyl)-1*H*-indole-1-carboxylate (109)**

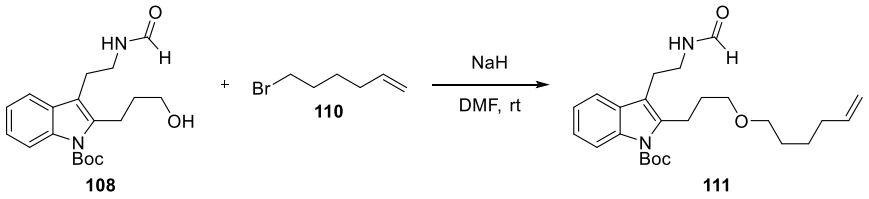
Prepared according to general procedure C from compound **107** (218.9 mg, 0.64 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.41 (dd, *J* = 6.8, 1.4 Hz, 1H), 7.29 (td, *J* = 7.3, 1.4 Hz, 1H), 7.26 – 7.24 (m, 1H), 3.63 (t, *J* = 7.1 Hz, 2H), 3.36 (t, *J* = 7.2 Hz, 2H), 3.15 (t, *J* = 7.1 Hz, 2H), 2.91 (t, *J* = 7.3 Hz, 2H), 1.69 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.1, 156.9, 150.3, 137.4, 136.0, 128.8, 124.3, 123.0, 117.7, 116.1, 114.2, 84.5, 45.8, 44.6, 28.3, 24.7, 19.4.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{22}N_2NaO_3^+$ 349.1528; found 349.1525.

IR: ν (cm^{-1}) 2979, 2146, 1724, 1454, 1367, 1324, 1276, 1257, 1132, 1079, 752.



***tert*-Butyl 3-(2-formamidoethyl)-2-(3-(hex-5-en-1-yloxy)propyl)-1*H*-indole-1-carboxylate (111)**

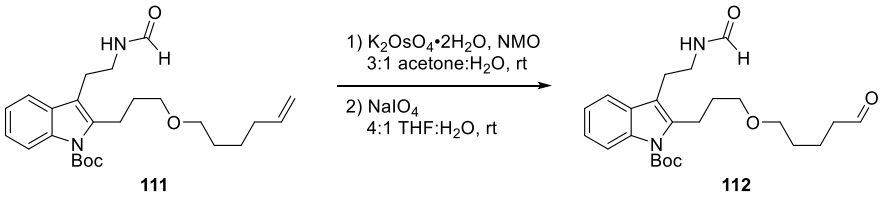
According to a reported procedure[3], NaH (60% dispersion in mineral oil, 127.6 mg, 3.19 mmol, 1.1 equiv) was added to a solution of primary alcohol **108** (1.00 g, 2.90 mmol, 1.0 equiv) in dry DMF (10 mL) at 0 °C. After stirring at the same temperature for 30 min, a solution of 6-bromo-1-hexene (**110**) (520.2 mg, 3.19 mmol, 1.1 equiv) in dry DMF (4.5 mL) was added dropwise at 0 °C. The resulting mixture was allowed to warm to room temperature and stir for 15 h. The mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with water (3 times) and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO_2, 2% MeOH/CH_2Cl_2) to afford compound **111** in 35% yield (438.2 mg, 1.02 mmol) as yellowish oil (R_f = 0.35 (5% MeOH/CH_2Cl_2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 1.6 Hz, 1H), 7.55 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.28 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.17 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.09 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 5.86 – 5.72 (m, 2H), 5.05 – 4.96 (m, 2H), 4.12 (t, *J* = 6.2 Hz, 2H), 4.07 (t, *J* = 7.6 Hz, 2H), 3.56 (q, *J* = 6.7 Hz, 2H), 2.96 (t, *J* = 7.0 Hz, 2H), 2.89 – 2.83 (m, 2H), 2.14 – 2.08 (m, 2H), 1.98 – 1.90 (m, 2H), 1.81 – 1.72 (m, 2H), 1.53 – 1.47 (m, 2H), 1.49 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 153.5, 138.1, 136.2, 136.1, 127.8, 121.1, 119.2, 118.3, 115.1, 109.4, 108.0, 82.2, 66.0, 43.3, 38.8, 33.3, 29.7, 29.5, 27.8, 26.3, 24.6, 20.8.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{25}H_{36}N_2NaO_4^+$ 451.2567; found 451.2576.

IR: ν (cm^{-1}) 3853, 1737, 1675, 1276, 1251, 755.



***tert*-Butyl 3-(2-formamidoethyl)-2-(3-((5-oxopentyl)oxy)propyl)-1*H*-indole-1-carboxylate (112)**

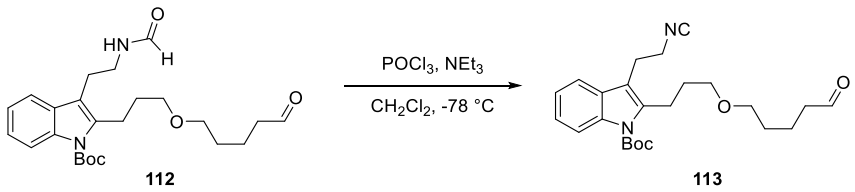
Prepared according to general procedure B from alkene **111** (362.3 mg, 0.85 mmol) to give aldehyde **112** in 66% yield (242.6 mg, 0.56 mmol) as brown oil (R_f = 0.26 (5% MeOH/CH_2Cl_2)) after purification by flash column chromatography (SiO_2, 2% MeOH/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.4 Hz, 1H), 8.13 (d, *J* = 1.2 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.18 (td, *J* = 8.2, 1.2 Hz, 1H), 7.09 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 5.68 (br s, 1H), 4.12 – 4.07 (m, 4H), 3.58 (q, *J* = 6.7 Hz, 2H), 2.96 (t, *J* = 6.9 Hz, 2H), 2.85 (t, *J* = 7.8 Hz, 2H), 2.46 (td, *J* = 7.1, 1.4 Hz, 2H), 1.97 – 1.89 (m, 2H), 1.82 – 1.74 (m, 2H), 1.69 – 1.61 (m, 2H), 1.49 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.8, 161.3, 153.6, 136.3, 136.2, 127.9, 121.4, 119.5, 118.5, 109.4, 108.5, 82.4, 66.1, 43.5, 43.2, 38.8, 29.9, 29.6, 27.9, 24.7, 21.0, 19.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{35}N_2O_5^+$ 431.2540; found 431.2531.

IR: ν (cm^{-1}) 2929, 1733, 1664, 1465, 1367, 1276, 1255, 1155, 1099, 736.



112 **113**

***tert*-Butyl 3-(2-isocyanoethyl)-2-(3-((5-oxopentyl)oxy)propyl)-1*H*-indole-1-carboxylate (113)**

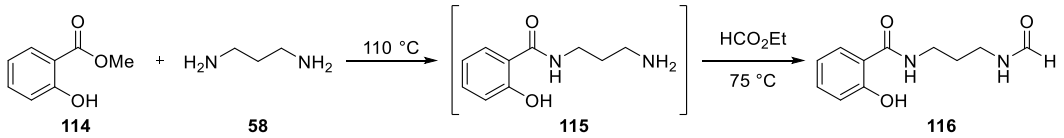
Prepared according to general procedure C from compound **112** (242.6 mg, 0.56 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.4 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 7.19 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.11 (td, *J* = 7.4, 6.9, 1.1 Hz, 1H), 4.12 – 4.08 (m, 4H), 3.60 (t, *J* = 7.4 Hz, 2H), 3.14 (t, *J* = 7.3 Hz, 2H), 2.92 – 2.88 (m, 2H), 2.47 (td, *J* = 7.0, 1.4 Hz, 2H), 1.98 – 1.91 (m, 2H), 1.82 – 1.75 (m, 2H), 1.72 – 1.64 (m, 2H), 1.50 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7, 156.2, 153.6, 136.8, 136.2, 127.3, 121.6, 119.6, 117.9, 109.6, 106.9, 82.4, 65.9, 43.5, 43.3, 42.2, 29.8, 29.6, 27.9, 25.4, 21.0, 19.6.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{24}H_{32}N_2NaO_4^+$ 435.2254; found 435.2247.

IR: ν (cm^{-1})



***N*-(3-Formamidopropyl)-2-hydroxybenzamide (116)**

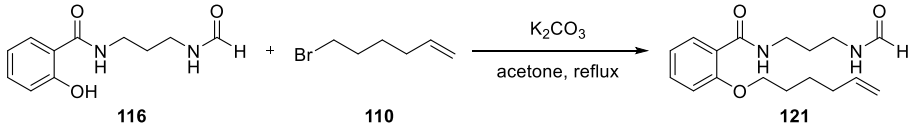
A mixture of methyl salicylate (**114**) (3.04 g, 20.0 mmol, 1.0 equiv) and 1,3-diaminopropane (**58**) (1.67 mL, 20.0 mmol, 1.0 equiv) was stirred vigorously at 110 °C for 3 h. The mixture was allowed to cool to room temperature and evaporate to dryness to give the adduct **115**,[37] which was formylated with ethyl formate (12.0 mL, 1.67 M) at 75 °C for 21 h. After cooling down to room temperature, the reaction solution was evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO_2, 2% to 5% MeOH/CH_2Cl_2) to afford compound **116** in 52% yield (over 2 steps) (2.31 g, 10.47 mmol) as yellowish viscous oil (R_f = 0.19 (5% MeOH/CH_2Cl_2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.72 (br s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 6.24 (br s, 1H), 3.49 (q, *J* = 6.0 Hz, 2H), 3.42 (q, *J* = 6.2 Hz, 2H), 1.76 (p, *J* = 6.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 162.7, 161.6, 134.3, 126.0, 119.0, 118.5, 114.4, 35.5, 35.0, 29.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{14}N_2NaO_3^+$ 245.0897; found 245.0892.

IR: ν (cm^{-1}) 3318, 1660, 1637, 1594, 1540, 1490, 1378, 1234, 755.



***N*-(3-Formamidopropyl)-2-(hex-5-en-1-yloxy)benzamide (121)**

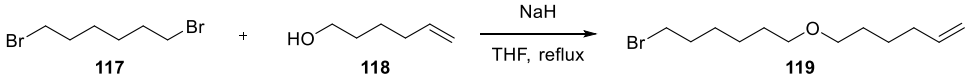
According to a reported procedure[6], to a solution of phenol **116** (881.0 mg, 4.0 mmol, 1.0 equiv) in acetone (20 mL) were added K_2CO_3 (1.11 g, 8.0 mmol, 2.0 equiv) and 6-bromo-1-hexene (**110**) (0.59 mL, 4.4 mmol, 1.1 equiv). The resulting mixture was heated to reflux and stirred for 14 h. The mixture was allowed to cool to room temperature and evaporated to dryness. Water was added to the residue and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO_2, 2% to 3% MeOH/CH_2Cl_2) to afford compound **121** in 94% yield (1.15 g, 3.78 mmol) as colorless viscous oil (R_f = 0.42 (5% MeOH/CH_2Cl_2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 8.12 (br s, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.97 (br s, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 5.79 (ddt, *J* = 16.9, 9.8, 6.6 Hz, 1H), 5.07 – 4.95 (m, 2H), 4.13 (t, *J* = 6.0 Hz, 2H), 3.52 (q, *J* = 6.3 Hz, 2H), 3.32 (q, *J* = 6.3 Hz, 2H), 2.13 (q, *J* = 7.2 Hz, 2H), 1.88 (p, *J* = 6.7 Hz, 2H), 1.73 (p, *J* = 6.2 Hz, 2H), 1.56 (p, *J* = 7.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 161.5, 157.0, 138.0, 133.0, 132.1, 121.3, 121.2, 115.3, 112.4, 68.9, 36.3, 34.5, 33.3, 30.0, 28.6, 25.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{25}N_2O_3^+$ 305.1860; found 305.1866.

IR: ν (cm^{-1}) 3853, 3731, 3031, 1641, 1523, 1294, 1234, 755.



6-((6-Bromohexyl)oxy)hex-1-ene (119)

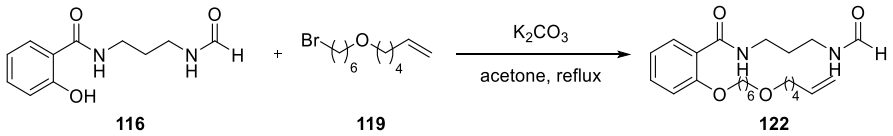
According to a reported procedure,[38] to a suspension of NaH (60% dispersion in mineral oil, 1.60 g, 40.0 mmol, 2.0 equiv) in dry THF (110 mL) was added a solution of 5-hexen-1-ol (**118**) (2.00 g, 20.0 mmol, 1.0 equiv) in dry THF (20 mL) dropwise at 0 °C. After stirring the mixture at 0 °C for 30 min, 1,6-dibromohexane (**117**) (3.03 mL, 20.0 mmol, 1.0 equiv) was added dropwise at 0 °C. The resulting mixture was heated to reflux for 22 h. The mixture was allowed to cool to room temperature and quench with water at 0 °C. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO_2, 20% CH_2Cl_2/PE) to afford compound **119** in 14% yield (727.63 mg, 2.76 mmol) as colorless liquid (R_f = 0.16 (20% CH_2Cl_2/PE)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.00 (dq, *J* = 17.1, 1.8 Hz, 1H), 4.94 (dq, *J* = 10.2, 1.4 Hz, 1H), 3.43 – 3.38 (m, 6H), 2.07 (q, *J* = 7.1 Hz, 2H), 1.87 (p, *J* = 6.9 Hz, 2H), 1.61 – 1.55 (m, 4H), 1.49 – 1.33 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.0, 114.6, 70.9, 70.8, 34.1, 33.7, 32.9, 29.7, 29.4, 28.2, 25.7, 25.6.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{24}BrO^+$ 263.1005; found 263.1000.

IR: ν (cm^{-1}) 2933.2, 2857, 1637, 1455, 1436, 1116, 993, 910, 719.



116 119 122

***N*-(3-Formamidopropyl)-2-((6-(hex-5-en-1-yloxy)hexyl)oxy)benzamide (122)**

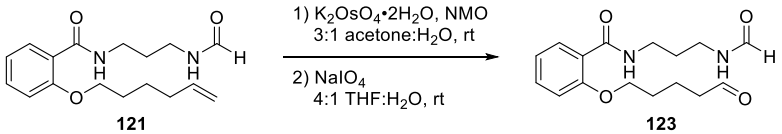
According to a reported procedure[6], to a solution of phenol **116** (506.6 mg, 2.3 mmol, 1.0 equiv) in acetone (11.5 mL) were added K_2CO_3 (635.8 mg, 4.6 mmol, 2.0 equiv) and bromide **119** (666.0 mg, 2.53 mmol, 1.1 equiv). The resulting mixture was heated to reflux and stirred for 17 h. The mixture was allowed to cool to room temperature and evaporated to dryness. Water was added to the residue and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO_2, 2% to 3% MeOH/CH_2Cl_2) to afford compound **122** in 89% yield (825.1 mg, 2.04 mmol) as colorless viscous oil (R_f = 0.23 (5% MeOH/CH_2Cl_2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.17 (br s, 1H), 8.15 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.44 (ddd, *J* = 8.3, 7.3, 1.9 Hz, 1H), 7.07 (td, *J* = 7.6, 1.0 Hz, 1H), 7.00 (br s, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.00 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.94 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 4.14 (t, *J* = 6.5 Hz, 2H), 3.55 (q, *J* = 6.3 Hz, 2H), 3.43 – 3.38 (m, 4H), 3.35 (q, *J* = 6.1 Hz, 2H), 2.10 – 2.03 (m, 2H), 1.96 – 1.85 (m, 4H), 1.75 (p, *J* = 6.2 Hz, 2H), 1.64 – 1.55 (m, 4H), 1.51 – 1.42 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 161.6, 157.1, 138.9, 133.2, 132.3, 121.4, 121.2, 114.7, 112.4, 71.0, 70.7, 69.1, 36.3, 34.5, 33.7, 30.2, 29.9, 29.33, 29.26, 26.3, 26.1, 25.6.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{36}N_2NaO_4^+$ 427.2567; found 427.2563.

IR: ν (cm^{-1}) 3855, 3602, 2931, 2859, 1643, 1525, 1230, 1106, 755.



121 123

***N*-(3-Formamidopropyl)-2-((5-oxopentyl)oxy)benzamide (123)**

Prepared according to general procedure B from alkene **121** (761.0 mg, 2.5 mmol) to give aldehyde **123** in 90% yield (687.1 mg, 2.24 mmol) as yellowish oil (R_f = 0.23 (5% MeOH/CH_2Cl_2)) after purification by flash column chromatography (SiO_2, 3% to 5% MeOH/CH_2Cl_2).

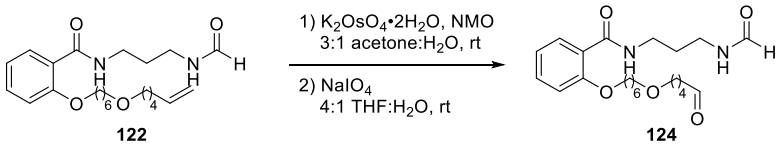
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.21 (s, 1H), 8.16 (br dd, *J* = 7.8, 1.9 Hz, 2H), 7.44 (ddd, *J* = 8.7, 7.4, 1.9 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.95 (br d, *J* = 8.3 Hz, 2H), 4.15 (t, *J* = 5.9 Hz, 2H),

3.58 (q, *J* = 6.3 Hz, 2H), 3.36 (q, *J* = 6.0 Hz, 2H), 2.61 (t, *J* = 6.5 Hz, 2H), 1.94 – 1.87 (m, 2H), 1.86 – 1.74 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.8, 166.6, 161.7, 157.0, 133.1, 132.4, 121.5, 121.4, 112.3, 68.7, 43.4, 36.5, 34.7, 30.1, 28.7, 18.8.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{23}N_2O_4^+$ 307.1652; found 307.1647.

IR: ν (cm^{-1}) 3392, 3284, 2937, 2883, 1643, 1535, 1517, 1299, 1236, 719.



122 124

***N*-(3-Formamidopropyl)-2-((6-((5-oxopentyl)oxy)hexyl)oxy)benzamide (124)**

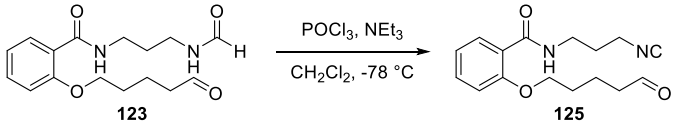
Prepared according to general procedure B from alkene **122** (768.7 mg, 1.9 mmol) to give aldehyde **124** in 69% yield (532.0 mg, 1.31 mmol) as yellowish oil (R_f = 0.28 (5% MeOH/CH_2Cl_2)) after purification by flash column chromatography (SiO_2, 3% to 5% MeOH/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.18 (s, 1H), 8.12 (dd, *J* = 8.0, 1.9 Hz, 1H), 8.12 (br s, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 2H), 4.12 (t, *J* = 6.5 Hz, 3H), 3.52 (q, *J* = 6.3 Hz, 2H), 3.43 – 3.31 (m, 6H), 2.44 (t, *J* = 7.1 Hz, 3H), 1.87 (p, *J* = 6.6 Hz, 3H), 1.78 – 1.64 (m, 4H), 1.57 (p, *J* = 6.6 Hz, 4H), 1.50 – 1.40 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6, 166.6, 161.6, 157.1, 133.0, 132.1, 121.3, 121.2, 112.4, 70.8, 70.4, 69.0, 43.7, 36.3, 34.5, 30.1, 29.8, 29.2, 29.2, 26.2, 26.0, 19.0.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{34}N_2NaO_5^+$ 429.2360; found 429.2353.

IR: ν (cm^{-1}) 2940, 2861, 1675, 1648, 1525, 1481, 1297, 1234, 1106, 755.



123 125

***N*-(3-Isocyanopropyl)-2-((5-oxopentyl)oxy)benzamide (125)**

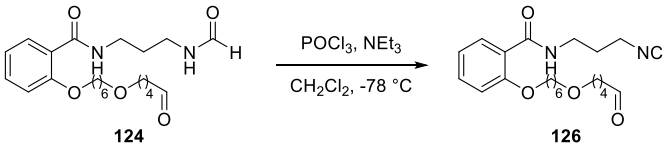
Prepared according to general procedure C from compound **123** (459.5 mg, 1.5 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 8.16 (br s, 1H), 7.44 (t, *J* = 8.1 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 4.15 (t, *J* = 5.4 Hz, 2H), 3.64 (q, *J* = 5.5 Hz, 2H), 3.50 (t, *J* = 7.0 Hz, 2H), 2.63 (t, *J* = 6.3 Hz, 2H), 2.07 – 2.02 (m, 2H), 1.97 – 1.89 (m, 2H), 1.88 – 1.80 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.6, 166.0, 157.0, 156.7 (t, *J* = 5.7 Hz), 133.1, 132.5, 121.5, 121.3, 112.2, 68.7, 43.4, 39.5 (t, *J* = 6.4 Hz), 36.7, 29.0, 28.8, 18.8.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{21}N_2O_3^+$ 289.1547; found 289.1540.

IR: ν (cm^{-1}) 3399, 2933, 2146, 1716, 1646, 1598, 1531, 1482, 1452, 1295, 1232, 755, 719.



***N*-(3-Isocyanopropyl)-2-((6-((5-oxopentyl)oxy)hexyl)oxy)benzamide (126)**

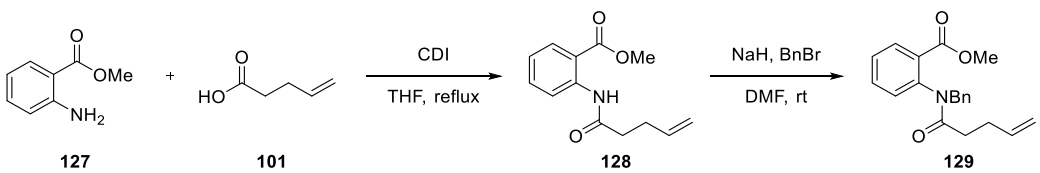
Prepared according to general procedure C from compound **124** (487.8 mg, 1.2 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.7 Hz, 1H), 8.18 (dd, *J* = 7.8, 1.9 Hz, 1H), 8.15 (br s, 1H), 7.43 (ddd, *J* = 8.4, 7.3, 1.9 Hz, 1H), 7.09 – 7.04 (m, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 4.14 (t, *J* = 6.6 Hz, 2H), 3.60 (q, *J* = 6.4 Hz, 2H), 3.51 (tt, *J* = 6.6, 1.8 Hz, 2H), 3.46 – 3.39 (m, 4H), 2.46 (td, *J* = 7.2, 1.7 Hz, 2H), 2.07 – 1.99 (m, 2H), 1.95 – 1.87 (m, 2H), 1.73 – 1.58 (m, 6H), 1.54 – 1.44 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7, 166.0, 157.1, 156.9, 133.1, 132.3, 121.4, 121.1, 112.3, 70.8, 70.4, 69.1, 43.7, 39.4, 36.6, 29.8, 29.3, 29.2, 29.1, 26.2, 26.1, 19.1.

HRMS (ESI/QTOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{33}N_2O_4^+$ 389.2435; found 389.2433.

IR: ν (cm^{-1}) 3397, 2935, 2865, 2146, 1718, 1648, 1598, 1531, 1482, 1450, 1297, 1234, 1106, 1051, 757.



To a solution of 4-pentenoic acid (**101**) (4.00 g, 40.0 mmol, 2.0 equiv) in dry THF (10 mL) was added 1,1′-carbonyldiimidazole (CDI) (6.49 g, 40.0 mmol, 2.0 equiv) portionwise. The solution was stirred at room temperature for 30 min. A solution of methyl anthranilate (**127**) (3.02 g, 20.0 mmol, 1.0 equiv) in dry THF (10 mL) was added and the resulting solution was heated to reflux for 24 h. After completion

of reaction, the mixture was allowed to cool to room temperature, quenched with water and extracted with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated to dryness to afford methyl 2-(pent-4-enamido)benzoate (**128**) which was used for the next step without further purification.

To a suspension of NaH (60% dispersion in mineral oil, 880.0 mg, 22.0 mmol, 1.1 equiv) in dry DMF (100 mL) was added a solution of crude **128** in dry DMF (100 mL) dropwise at 0 °C. After stirring at 0 °C for 30 min, benzyl bromide (4.73 mL, 40.0 mmol, 2.0 equiv) was added. The resulting mixture was allowed to warm to room temperature and stir for 17 h. The mixture was quenched with water at 0 °C and extracted with EtOAc. The combined organic layers were washed with water (3 times) and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO_2, 10% to 20% EtOAc/PE) to afford compound **129** in 34% yield (over two steps) (2.17 g, 6.71 mmol) as yellowish oil (R_f = 0.29 (20% EtOAc/PE)).

Methyl 2-(pent-4-enamido)benzoate (128)

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (br s, 1H), 8.73 (dd, *J* = 8.5, 1.2 Hz, 1H), 8.02 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.54 (ddd, *J* = 8.7, 7.3, 1.7 Hz, 1H), 7.07 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H), 5.94 – 5.83 (m, 1H), 5.11 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.02 (dq, *J* = 10.3, 1.3 Hz, 1H), 3.93 (s, 3H), 2.58 – 2.47 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 168.9, 141.7, 136.8, 134.8, 130.9, 122.5, 120.5, 115.8, 114.9, 52.5, 37.9, 29.5.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{15}NNaO_3^+$ 256.0944; found 256.0945.

IR: ν (cm^{-1}) 3307, 2983, 2956, 1685, 1589, 1519, 1444, 1255, 1159, 1085, 912, 752, 698.

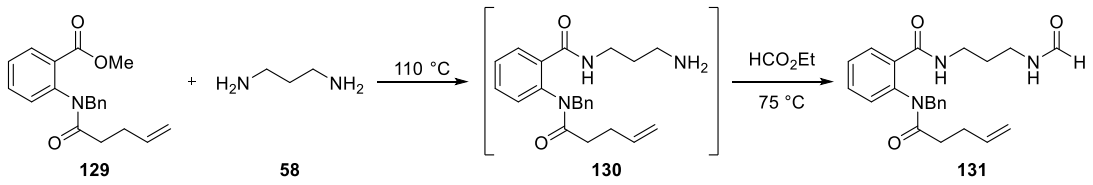
Methyl 2-(*N*-benzylpent-4-enamido)benzoate (129)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.93 (m, 1H), 7.46 – 7.38 (m, 2H), 7.26 – 7.21 (m, 3H), 7.16 – 7.14 (m, 2H), 6.89 – 6.86 (m, 1H), 5.73 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.29 (d, *J* = 14.3 Hz, 1H), 4.94 (dq, *J* = 17.3, 1.8 Hz, 1H), 4.92 – 4.87 (m, 1H), 4.31 (d, *J* = 14.2 Hz, 1H), 3.77 (s, 3H), 2.41 – 2.33 (m, 2H), 2.13 – 2.00 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 166.1, 141.8, 137.8, 137.3, 133.3, 132.0, 131.3, 129.6, 129.5, 128.5, 128.4, 127.5, 115.1, 53.1, 52.7, 34.0, 29.4.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{21}NNaO_3^+$ 346.1414; found 346.1417.

IR: ν (cm^{-1}) 3064, 2948, 1722, 1658, 1598, 1490, 1454, 1432, 1396, 1288, 1255, 1191, 1126, 1083, 914, 715, 701.



2-(*N*-Benzylpent-4-enamido)-*N*-(3-formamidopropyl)benzamide (131)

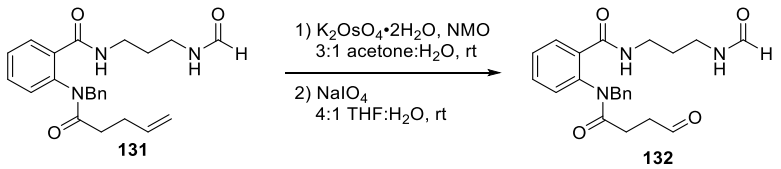
A mixture of methyl benzoate (**129**) (2.13 g, 6.6 mmol, 1.0 equiv) and 1,3-diaminopropane (**58**) (0.55 mL, 6.6 mmol, 1.0 equiv) was stirred vigorously at 110 °C for 3 h. The mixture was allowed to cool to room temperature and evaporate to dryness to give the adduct **130**, which was dissolved in ethyl formate (4.0 mL, 1.67 M). The resuling solution was stirred at 75 °C for 16 h. After cooling down to room temperature, the reaction solution was evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO_2, 2% to 3% MeOH/CH_2Cl_2) to afford compound **131** in 73% yield (over 2 steps) (1.89 g, 4.81 mmol) as yellowish viscous oil (R_f = 0.27 (5% MeOH/CH_2Cl_2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.63 (t, *J* = 3.2 Hz, 1H), 7.40 (t, *J* = 3.3 Hz, 2H), 7.26 (d, *J* = 2.1 Hz, 3H), 7.22 – 7.16 (m, 2H), 6.93 (t, *J* = 3.4 Hz, 1H), 6.36 (s, 1H), 6.16 (br t, *J* = 6.7 Hz, 1H), 5.79 – 5.66 (m, 1H), 5.15 (d, *J* = 14.1 Hz, 1H), 4.95 (d, *J* = 16.9 Hz, 1H), 4.90 (d, *J* = 10.0 Hz, 1H), 4.65 (d, *J* = 14.1 Hz, 1H), 3.41 – 3.28 (m, 2H), 3.26 – 3.12 (m, 2H), 2.35 (q, *J* = 7.4 Hz, 2H), 2.23 (dt, *J* = 14.9, 7.2 Hz, 1H), 2.09 (dt, *J* = 15.5, 7.4 Hz, 1H), 1.67 – 1.55 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 167.6, 162.0, 139.5, 137.7, 137.2, 135.0, 131.6, 130.4, 129.7, 129.5, 128.7, 127.9, 115.3, 53.4, 36.4, 34.7, 34.1, 29.7, 29.4.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{27}N_3NaO_3^+$ 416.1945; found 416.1943.

IR: ν (cm^{-1}) 3674, 3650, 2989, 2901, 1648, 1537, 1508, 1396, 1261, 1068, 761, 749.



2-(*N*-Benzyl-4-oxobutanamido)-*N*-(3-formamidopropyl)benzamide (132)

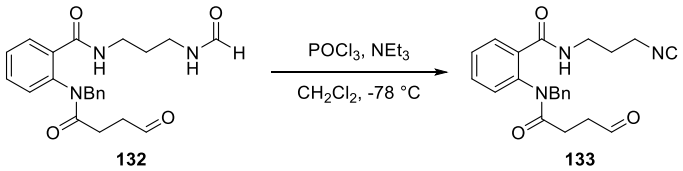
Prepared according to general procedure B from alkene **131** (1.89 g, 4.81 mmol) to give aldehyde **132** in 61% yield (1.17 g, 2.95 mmol) as pale brown oil (R_f = 0.39 (10% MeOH/CH_2Cl_2)) after purification by flash column chromatography (SiO_2, 5% MeOH/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 8.21 (d, *J* = 1.2 Hz, 1H), 7.75 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.41 (td, *J* = 7.5, 1.3 Hz, 1H), 7.34 (td, *J* = 7.7, 1.7 Hz, 1H), 7.24 – 7.20 (m, 4H), 7.15 – 7.09 (m, 2H), 6.81 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.56 (br s, 1H), 5.40 (d, *J* = 14.1 Hz, 1H), 4.21 (d, *J* = 14.1 Hz, 1H), 3.48 (q, *J* = 6.3 Hz, 2H), 3.40 – 3.32 (m, 2H), 3.15 (ddd, *J* = 19.3, 9.9, 4.1 Hz, 1H), 2.67 (ddd, *J* = 19.3, 5.9, 3.7 Hz, 1H), 2.41 (ddd, *J* = 16.8, 9.9, 3.7 Hz, 1H), 2.24 (ddd, *J* = 16.8, 5.9, 4.0 Hz, 1H), 1.78 (p, *J* = 6.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6, 171.1, 167.8, 161.7, 138.3, 136.6, 134.6, 131.4, 130.7, 130.5, 129.5, 129.0, 128.6, 127.8, 53.1, 39.3, 36.9, 34.8, 29.6, 27.8.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{25}N_3NaO_4^+$ 418.1737; found 418.1738.

IR: ν (cm^{-1}) 3289, 3067, 2934, 2861, 1640, 1444, 1387, 1302, 1264, 776, 727, 700.



2-(*N*-Benzyl-4-oxobutanamido)-*N*-(3-isocyanopropyl)benzamide (133)

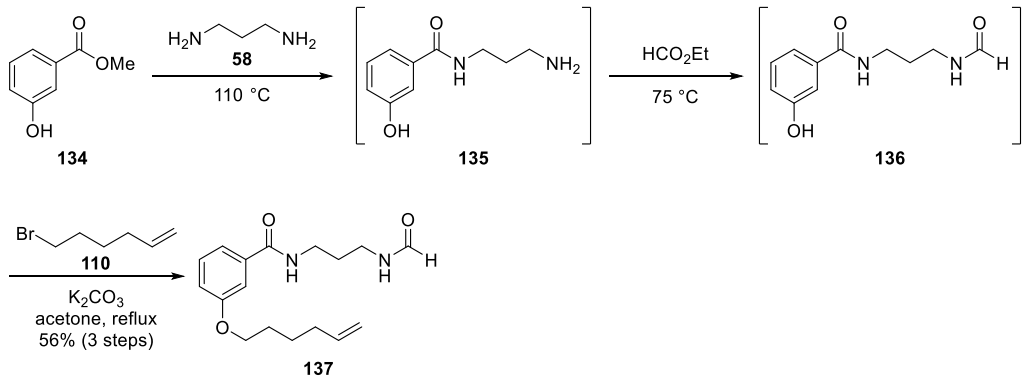
Prepared according to general procedure C from compound **132** (593.2 mg, 1.5 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.24 – 7.18 (m, 4H), 7.13 – 7.10 (m, 2H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.36 (d, *J* = 13.9 Hz, 1H), 4.22 (d, *J* = 13.9 Hz, 1H), 3.63 – 3.51 (m, 2H), 3.48 (t, *J* = 6.5 Hz, 2H), 3.24 (ddd, *J* = 19.3, 10.6, 2.8 Hz, 1H), 2.64 (ddd, *J* = 19.5, 5.8, 3.1 Hz, 1H), 2.40 (ddd, *J* = 17.0, 10.5, 2.9 Hz, 1H), 2.20 (dt, *J* = 16.9, 4.8 Hz, 1H), 2.03 (p, *J* = 7.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6, 171.0, 167.4, 156.7 (t, *J* = 5.2 Hz), 138.1, 136.4, 134.6, 131.3, 131.1, 130.3, 129.5, 129.0, 128.6, 127.9, 53.0, 39.6 (t, *J* = 6.5 Hz), 39.4, 37.5, 29.2, 27.8.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{23}N_3NaO_3^+$ 400.1632; found 400.1631.

IR: ν (cm^{-1}) 3291, 2929, 2146, 1712, 1646, 1535, 1442, 1407, 1299, 719.



***N*-(3-Formamidopropyl)-3-(hex-5-en-1-yloxy)benzamide (137)**

A mixture of methyl 3-hydroxybenzoate (**134**) (3.04 g, 20.0 mmol, 1.0 equiv) and 1,3-diaminopropane (**58**) (1.67 mL, 20.0 mmol, 1.0 equiv) was stirred vigorously at 110 °C for 3 h. The mixture was allowed to cool to room temperature and evaporate to dryness to give the adduct **135**, which was formylated with ethyl formate (12.0 mL, 1.67 M) at 75 °C for 19 h. After cooling down to room temperature, the reaction solution was evaporated to dryness. A mixture of phenol **136** and diamide compound formed in the first step was obtained. To a solution of this mixture (1.1 g, 5.0 mmol, 1.0 equiv) in acetone (25 mL) were added K_2CO_3 (1.38 g, 10.0 mmol, 2.0 equiv) and 6-bromo-1-hexene (**110**) (0.74 mL, 5.5 mmol, 1.1 equiv). The resulting mixture was heated to reflux and stirred for 19 h. The mixture was allowed to cool to room temperature and evaporated to dryness. Water was added to the residue and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO_2, 1% to 3% MeOH/CH_2Cl_2) to afford compound **137** in 56% yield (over three steps) (851.0 mg, 2.80 mmol) as white solid (R_f = 0.25 (5% MeOH/CH_2Cl_2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.40 – 7.15 (m, 4H), 6.94 (dd, *J* = 8.0, 2.5 Hz, 1H), 6.72 (br s, 1H), 5.74 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 4.95 (d, *J* = 17.1 Hz, 1H), 4.89 (d, *J* = 10.2 Hz, 1H), 3.92 (t, *J* = 6.5 Hz, 2H), 3.41 (q, *J* = 6.2 Hz, 2H), 3.29 (q, *J* = 6.3 Hz, 2H), 2.04 (q, *J* = 7.3 Hz, 2H), 1.79 – 1.58 (m, 4H), 1.48 (p, *J* = 7.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 162.2, 159.4, 138.5, 135.7, 129.7, 118.8, 118.3, 114.9, 113.0, 68.0, 36.2, 34.7, 33.5, 29.6, 28.7, 25.4.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{24}N_2NaO_3^+$ 327.1679; found 327.1680.

IR: ν (cm^{-1}) 3297, 3073, 2933, 2863, 1641, 1579, 1535, 1486, 1434, 1382, 1301, 1238, 1132, 1031, 998, 910, 750, 717, 688.

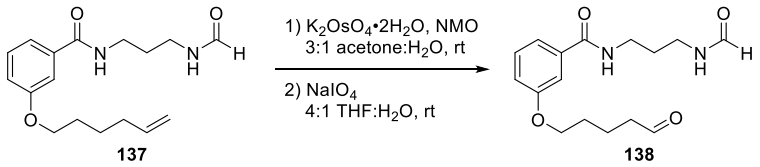
For analysis of compound **136**, the crude mixture can be purified by flash column chromatography (20% acetone/EtOAc) to yield the pure **136** as a colorless viscous oil (R_f = 0.16 (20% acetone/EtOAc)).

^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1H), 7.25 – 7.18 (m, 3H), 6.93 – 6.87 (m, 1H), 3.36 (t, *J* = 6.8 Hz, 2H), 3.26 (t, *J* = 6.8 Hz, 2H), 1.75 (p, *J* = 6.8 Hz, 2H).

^{13}C NMR (101 MHz, CD_3OD) δ 170.4, 164.0, 158.8, 137.1, 130.6, 119.5, 119.0, 115.2, 38.1, 36.5, 30.2.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{14}N_2NaO_3^+$ 245.0897; found 245.0896.

IR: ν (cm^{-1}) 3276, 3058, 2931, 2869, 1652, 1536, 1382, 1238, 719.



137 **138**

***N*-(3-Formamidopropyl)-3-((5-oxopentyl)oxy)benzamide (138)**

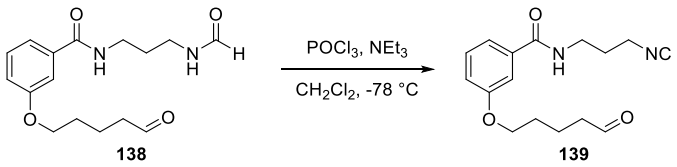
Prepared according to general procedure B from alkene **137** (791.4 mg, 2.6 mmol) to give aldehyde **138** in 76% yield (608.2 mg, 1.99 mmol) as colorless oil (R_f = 0.44 (10% MeOH/CH_2Cl_2)) after purification by flash column chromatography (SiO_2, 5% to 10% MeOH/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.23 (s, 1H), 7.39 – 7.28 (m, 3H), 7.18 (br t, *J* = 6.4 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.59 (br s, 1H), 4.05 – 3.99 (m, 2H), 3.50 (q, *J* = 6.4 Hz, 2H), 3.38 (q, *J* = 6.4 Hz, 2H), 2.52 (br t, *J* = 6.2 Hz, 2H), 1.85 – 1.80 (m, 4H), 1.75 (p, *J* = 6.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.4, 168.0, 162.2, 159.3, 135.7, 129.8, 119.0, 118.4, 112.9, 67.7, 43.6, 36.2, 34.7, 29.7, 28.7, 18.9.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{22}N_2NaO_4^+$ 329.1472; found 329.1469.

IR: ν (cm^{-1}) 3299, 3066, 2938, 2869, 1720, 1643, 1577, 1536, 1482, 1434, 1386, 1295, 1238, 1132, 1027, 719, 688.



***N*-(3-Isocyanopropyl)-3-((5-oxopentyl)oxy)benzamide (139)**

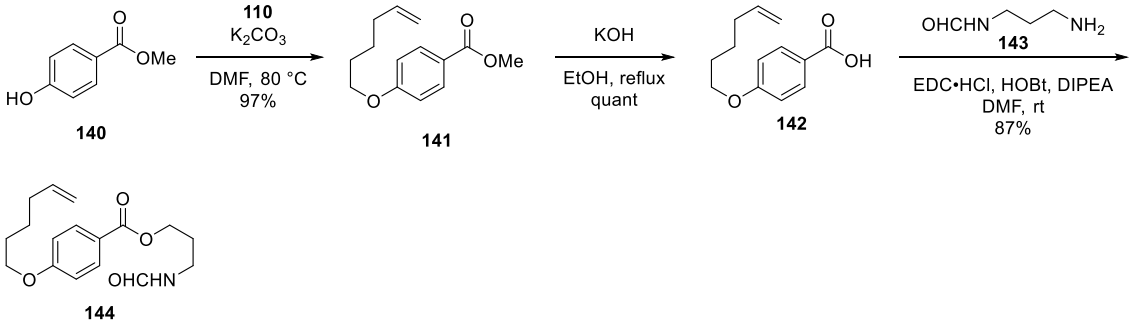
Prepared according to general procedure C from compound **138** (459.5 mg, 1.5 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (t, *J* = 1.7 Hz, 1H), 7.28 – 7.19 (m, 3H), 6.96 (dd, *J* = 7.7, 2.6 Hz, 1H), 6.39 (br t, *J* = 5.9 Hz, 1H), 3.96 (q, *J* = 5.0, 3.5 Hz, 2H), 3.54 (q, *J* = 6.4 Hz, 2H), 3.45 (t, *J* = 6.4 Hz, 2H), 2.52 – 2.40 (m, 2H), 2.01 – 1.94 (m, 2H), 1.79 – 1.72 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.4, 167.9, 159.3, 156.9, 135.6, 129.8, 118.9, 118.5, 113.0, 67.7, 43.6, 39.6, 37.3, 29.2, 28.6, 18.9.

HRMS (ESI/QTOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{21}N_2O_3^+$ 289.1547; found 289.1542.

IR: ν (cm^{-1}) 3299, 2931, 2867, 2146, 1716, 1641, 1579, 1535, 1486, 1436, 1297, 1240, 1132, 1043, 750, 717.



***N*-(3-Formamidopropyl)-4-(hex-5-en-1-yloxy)benzamide (144)**

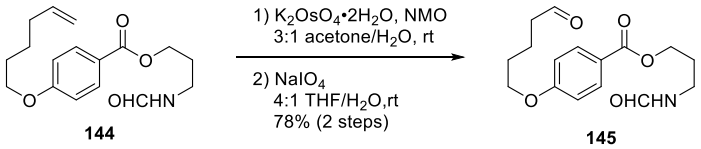
Compound **142** and **143** were prepared according to a literature procedures.[67,68] To a solution of acid **142** (1.08 g, 4.88 mmol, 1.0 equiv) in dry DMF (23 mL, 0.215 M) at room temperature were added amine **143** (850 mg, 4.88 mmol, 1.0 equiv), DIPEA (4.03 mL, 24.39 mmol, 5.0 equiv), EDC·HCl (1.08 g, 5.61 mmol, 1.15 equiv) and HOBt (725 mg, 5.37 mmol, 1.1 equiv). After being stirred at room temperature for 12 hours, the reaction mixture was quenched with HCl 1 M and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography (SiO2, PE/EtOAc 3:1) to yield the desired product **144** (87%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.78 (d, *J* = 8.7 Hz, 2H), 7.11 (s, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.73 (s, 1H), 5.82 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.10 – 4.92 (m, 2H), 3.99 (t, *J* = 6.5 Hz, 2H),

3.50 (q, *J* = 6.0 Hz, 2H), 3.38 (q, *J* = 6.2 Hz, 2H), 2.12 (q, *J* = 7.0 Hz, 2H), 1.89 – 1.68 (m, 4H), 1.57 (q, *J* = 7.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.7, 162.8, 162.2, 138.2, 132.6, 126.4, 115.1, 114.8, 68.1, 38.5, 37.6, 33.2, 28.7, 25.5.

HRMS (ESI): *m/z* calcd for $C_{17}H_{25}N_2O_3$ ($[M + H]^+$): 305.1860; found: 305.1854.



144 145

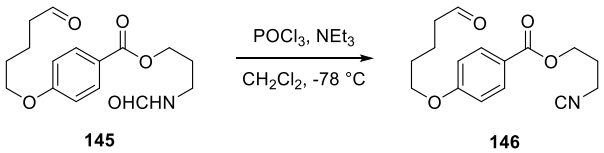
***N*-(3-Formamidopropyl)-4-((5-oxopentyl)oxy)benzamide (145)**

Prepared according to general procedure B from alkene **144** to give aldehyde **145** in 78% yield as yellowish oil after purification by flash column chromatography (SiO_2, 5% to 10% $MeOH/CH_2Cl_2$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (t, *J* = 1.5 Hz, 1H), 8.23 (d, *J* = 1.6 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.12 (s, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.69 (s, 1H), 4.05 – 3.91 (m, 2H), 3.56 – 3.43 (m, 2H), 3.37 (q, *J* = 6.2 Hz, 2H), 2.53 (ddt, *J* = 6.9, 4.9, 1.7 Hz, 2H), 1.91 – 1.79 (m, 4H), 1.73 (t, *J* = 6.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.3, 167.8, 162.2, 161.7, 128.9, 126.4, 114.4, 67.7, 43.6, 36.1, 34.7, 29.8, 28.6, 18.9.

HRMS (ESI): *m/z* calcd for $C_{16}H_{23}N_2O_4$ ($[M + H]^+$): 307.1652; found: 307.1648.



145 146

***N*-(3-Isocyanopropyl)-4-((5-oxopentyl)oxy)benzamide (146)**

Prepared according to general procedure C from compound **145**.

^{1}H NMR (400 MHz, CDCl3): δ 9.81 (t, *J* = 1.5 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 4.01 (q, *J* = 2.6 Hz, 2H), 3.60 (q, *J* = 6.5 Hz, 2H), 3.51 (tt, *J* = 6.6, 1.8 Hz, 2H), 2.55 (td, *J* = 5.2, 2.5 Hz, 2H), 2.04 (qd, *J* = 4.7, 2.2 Hz, 2H), 1.88 – 1.81 (m, 4H).

^{13}C NMR (101 MHz, CDCl3): δ 202.2, 167.5, 161.9, 157.0, 128.8, 126.4, 114.4, 67.7, 43.6, 39.7, 37.3, 29.3, 28.7, 18.9.

HRMS (ESI): *m/z* calcd for $C_{16}H_{21}N_2O_3$ ($[M + H]^+$): 289.1547; found: 289.1551.

3.2.2 Procedures for macrocyclization reactions

General Procedure D: synthesis of the α–hydroxy lactams

Pyridine (6.0 equiv) and TFA (3.0 equiv) were added dropwise to a solution of the ω-isocyanoaldehyde (1.0 equiv) in dry CH_2Cl_2 (0.01 M) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred until the completion of reaction (1-5 days). The mixture was evaporated to dryness and the residue was dissolved in EtOAc. Saturated $NaHCO_3$ was added and the mixture was stirred at room temperature for 1 h. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with 2 M HCl, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by flash column chromatography (SiO_2) to afford the α–hydroxy lactam product.

General Procedure E: Passerini reaction of the ω-isocyanoaldehydes

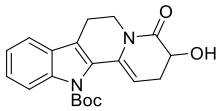
To a solution of the ω-isocyanoaldehyde (1.0 equiv) in dry CH_2Cl_2 (0.01 M) was added the carboxylic acid (acetic acid or *N*-(*tert*-butoxycarbonyl)glycine or benzoic acid) (1.3 equiv). The resulting solution was stirred at room temperature until the completion of reaction (1-5 days). Saturated $NaHCO_3$ was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by flash column chromatography (SiO_2) to yield the macrocycle product.

General Procedure F: Ugi reaction of the ω-isocyanoaldehydes

To a solution of the ω-isocyanoaldehyde (1.0 equiv) in MeOH (0.01 M) was added benzylamine (1.2 equiv). After stirring at room temperature for 1 h, glacial acetic acid (1.5 equiv) was added dropwise. The resulting solution was stirred at room temperature until the completion of reaction (1-5 days). The mixture was evaporated to dryness and the residue was purified by flash column chromatography (SiO_2) to yield the macrocycle product.

General Procedure G: Ugi tetrazole reaction of the ω-isocyanoaldehydes

To a solution of the ω-isocyanoaldehyde (1.0 equiv) in MeOH (0.1 M) was added the aniline derivative (aniline or 4-aminobenzonitrile) (1.1 equiv). After stirring at room temperature for 1 h, trimethylsilyl azide ($TMSN_3$) (1.1 equiv) was added dropwise. The resulting solution was stirred at room temperature until the completion of reaction (1-5 days). The mixture was evaporated to dryness and the residue was purified by flash column chromatography (SiO_2) to yield the macrocycle tetrazole product.



***tert*-Butyl 3-hydroxy-4-oxo-3,4,6,7-tetrahydroindolo[2,3-*a*]quinolizine-12(2*H*)-carboxylate (147)**

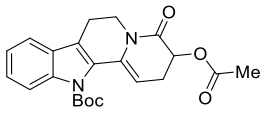
Yield: 51% (0.05 mmol sacle) and 59% (0.58 mmol scale), Eluent: 1:2 EtOAc/PE, R_f = 0.40 (1:1 EtOAc/PE)

^{1}H NMR (400 MHz, CDCl3) δ 7.99 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.35 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H), 7.26 (td, *J* = 7.4, 1.0 Hz, 1H), 5.58 (dd, *J* = 7.5, 3.0 Hz, 1H), 4.41 (dt, *J* = 12.8, 5.2 Hz, 1H), 4.23 (dd, *J* = 14.5, 7.7 Hz, 1H), 3.88 (br s, 1H), 3.81 (ddd, *J* = 12.9, 7.3, 5.6 Hz, 1H), 2.93 – 2.85 (m, 2H), 2.78 (dt, *J* = 16.5, 7.6 Hz, 1H), 2.57 – 2.45 (m, 1H), 1.66 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 150.6, 139.3, 129.5, 129.4, 127.6, 126.2, 123.4, 121.8, 119.2, 115.3, 103.1, 84.6, 66.4, 39.4, 28.3, 27.7, 21.3.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{22}N_2NaO_4^+$ 377.1472; found 377.1470.

IR: ν (cm^{-1}) 2958, 2915, 1729, 1691, 1448, 1369, 1311, 1251, 1149, 1051, 757.



***tert*-Butyl 3-acetoxy-4-oxo-3,4,6,7-tetrahydroindolo[2,3-*a*]quinolizine-12(2*H*)-carboxylate (148)**

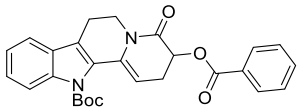
Yield: 62% (0.05 mmol sacle) and 54% (1.14 mmol sacle), Eluent: 1:2 EtOAc/PE, R_f = 0.63 (1:1 EtOAc/PE)

^{1}H NMR (400 MHz, CDCl3) δ 7.98 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.35 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H), 7.27 (t, *J* = 7.3 Hz, 1H), 5.54 (dd, *J* = 6.9, 3.5 Hz, 1H), 5.45 (dd, *J* = 13.3, 7.7 Hz, 1H), 4.40 (dt, *J* = 12.8, 5.2 Hz, 1H), 3.79 (ddd, *J* = 12.9, 7.7, 5.2 Hz, 1H), 2.98 – 2.82 (m, 2H), 2.80 – 2.60 (m, 2H), 2.21 (s, 3H), 1.67 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 166.6, 150.6, 139.3, 129.8, 129.4, 127.7, 126.2, 123.4, 122.4, 119.3, 115.3, 101.4, 84.6, 67.9, 39.0, 28.3, 25.6, 21.4, 21.1.

HRMS (APCI/QTOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{25}N_2O_5^+$ 397.1758; found 397.1748.

IR: ν (cm^{-1}) 2979, 2934, 1730, 1688, 1369, 1309, 1218, 1137, 1095, 1047, 839, 734.



tert-Butyl 3-(benzoyloxy)-4-oxo-3,4,6,7-tetrahydroindolo[2,3-*a*]quinolizine-12(2*H*)-carboxylate (149)

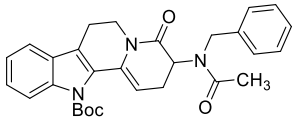
Yield: 55% (0.05 mmol sacle), Eluent: 1:3 EtOAc/PE, R_f = 0.45 (1:3 EtOAc/PE)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.5, 1.5 Hz, 2H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.57 (tt, *J* = 7.4, 1.4 Hz, 1H), 7.47 (dt, *J* = 8.5, 6.9 Hz, 3H), 7.36 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.27 (td, *J* = 7.5, 1.0 Hz, 1H), 5.70 (dd, *J* = 13.5, 7.6 Hz, 1H), 5.60 (dd, *J* = 7.1, 3.3 Hz, 1H), 4.44 (dt, *J* = 12.8, 5.2 Hz, 1H), 3.83 (ddd, *J* = 12.8, 7.9, 5.0 Hz, 1H), 3.01 – 2.74 (m, 4H), 1.68 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 166.0, 150.7, 139.4, 133.4, 130.2, 129.9, 129.9, 129.5, 128.5, 127.7, 126.3, 123.4, 122.4, 119.3, 115.3, 101.3, 84.6, 68.3, 39.1, 28.3, 25.8, 21.4.

HRMS (ESI/QTOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{27}N_2O_5^+$ 459.1914; found 459.1916.

IR: ν (cm^{-1}) 2979, 2925, 1725, 1688, 1454, 1369, 1312, 1264, 1240, 1156, 1143, 1116, 754, 706.



tert-Butyl 3-(*N*-benzylacetamido)-4-oxo-3,4,6,7-tetrahydroindolo[2,3-*a*]quinolizine-12(2*H*)-carboxylate (150)

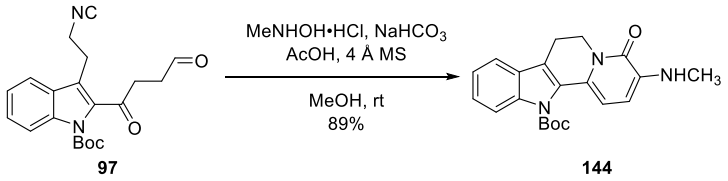
Yield: 89% (0.05 mmol sacle), Eluent: 2% MeOH/CH_2Cl_2, R_f = 0.37 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.40 – 7.32 (m, 3H), 7.31 – 7.22 (m, 4H), 5.44 (dd, *J* = 7.4, 2.9 Hz, 1H), 5.18 (dd, *J* = 14.8, 7.2 Hz, 1H), 4.80 (d, *J* = 17.9 Hz, 1H), 4.50 (d, *J* = 18.0 Hz, 1H), 4.40 (dt, *J* = 12.8, 5.4 Hz, 1H), 3.79 (ddd, *J* = 12.7, 7.6, 5.2 Hz, 1H), 2.86 (dd, *J* = 5.8, 5.2 Hz, 2H), 2.82 – 2.71 (m, 1H), 2.35 (dt, *J* = 16.4, 7.4 Hz, 1H), 2.18 (s, 3H), 1.62 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 167.8, 150.6, 139.3, 138.0, 129.8, 129.3, 129.0, 127.7, 127.6, 126.2, 126.0, 123.4, 122.1, 119.2, 115.2, 103.1, 84.4, 55.2, 51.6, 39.2, 28.3, 24.9, 22.2, 21.4.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{32}N_3O_4^+$ 486.2387; found 486.2390.

IR: ν (cm^{-1}) 2956, 2919, 1733, 1660, 1450, 1369, 1309, 1251, 1153, 1078, 1051, 755.



97 144

***tert*-Butyl 3-(methylamino)-4-oxo-6,7-dihydroindolo[2,3-*a*]quinolizine-12(4*H*)-carboxylate (151)**

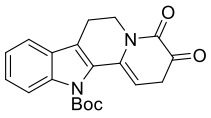
According to a reported procedure,[23] a mixture of *ω*-isocyano-*γ*-oxoaldehyde **97** (35.4 mg, 0.1 mmol, 1.0 equiv), *N*-methylhydroxylamine hydrochloride (25.1 mg, 0.3 mmol, 3.0 equiv), $NaHCO_3$ (50.4 mg, 0.6 mmol, 6.0 equiv) and 4 Å molecular sieves (75 mg) in MeOH (10 mL) was stirred at room temperature for 30 min. Acetic acid (0.15 mL, 2.7 mmol, 27.0 equiv) was added and the resulting mixture was stirred at room temperature for 5 days. The mixture was filtered (rinsed with MeOH) and the filtrate was evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO_2, 2% MeOH/CH_2Cl_2 + 3% NEt_3) to afford compound **144** in 89% (32.5 mg, 0.89 mmol) as white solid (R_f = 0.65 (5% MeOH/CH_2Cl_2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.48 – 7.44 (m, 1H), 7.32 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H), 7.26 (td, *J* = 7.4, 1.1 Hz, 1H), 6.44 (d, *J* = 7.9 Hz, 1H), 6.24 (d, *J* = 7.9 Hz, 1H), 5.21 (s, 1H), 4.52 (t, *J* = 6.3 Hz, 2H), 2.92 (t, *J* = 6.3 Hz, 2H), 2.89 (s, 3H), 1.64 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 150.6, 139.3, 138.9, 131.2, 127.9, 125.5, 123.5, 123.4, 120.1, 118.7, 115.5, 107.4, 104.9, 84.5, 40.2, 30.0, 28.3, 20.6.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{24}N_3O_3^+$ 366.1812; found 366.1813.

IR: ν (cm^{-1}) 2956, 2921, 1729, 1670, 1454, 1367, 1309, 1257, 1228, 1149, 740.

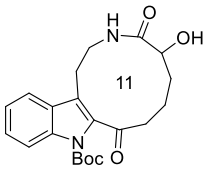


***tert*-Butyl 3,4-dioxo-3,4,6,7-tetrahydroindolo[2,3-*a*]quinolizine-12(2*H*)-carboxylate (152)**

It was prepared from the same procedure as compound **144** followed by washing with 2 M HCl.

Yield: 79%, Eluent: 5% to 10% MeOH/CH_2Cl_2

HRMS (ESI): *m/z* calcd for $C_{20}H_{20}N_2NaO_4$ ($[M + Na]^+$): 375.1315; found: 375.1311.



***tert*-Butyl 5-hydroxy-4,9-dioxo-2,3,4,5,6,7,8,9-octahydro-[1]azacycloundecino[5,4-*b*]indole-10(1*H*)-carboxylate (157)**

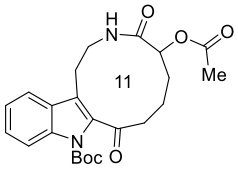
Yield: 68%, Eluent: 2% MeOH/CH_2Cl_2, R_f = 0.35 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dt, *J* = 8.3, 0.8 Hz, 1H), 7.55 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.29 (ddd, *J* = 8.0, 7.3, 1.0 Hz, 1H), 6.45 (br *t*, J = 6.2 Hz, 1H), 4.20 (dd, *J* = 5.6, 2.1 Hz, 1H), 3.68 (dtd, *J* = 13.2, 6.0, 2.7 Hz, 1H), 3.46 – 3.32 (m, 1H), 3.18 (ddd, *J* = 14.9, 10.1, 2.8 Hz, 1H), 3.04 (ddd, *J* = 14.9, 6.0, 2.3 Hz, 1H), 2.96 (ddd, *J* = 17.1, 8.9, 3.1 Hz, 1H), 2.87 – 2.80 (m, 1H), 2.12 – 1.96 (m, 3H), 1.85 – 1.75 (m, 1H), 1.59 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.4, 174.2, 149.7, 136.9, 135.5, 128.6, 127.2, 123.5, 122.1, 119.9, 115.5, 85.2, 70.2, 41.7, 39.7, 30.8, 28.1, 23.0, 16.0.

HRMS (LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{21}H_{26}N_2NaO_5^+$ 409.1734; found 409.1736.

IR: ν (cm^{-1}) 2956, 2919, 2854, 1737, 1668, 1486, 1455, 1359, 1315, 1234, 1187, 1147, 1083, 970.



***tert*-Butyl 5-acetoxy-4,9-dioxo-2,3,4,5,6,7,8,9-octahydro-[1]azacycloundecino[5,4-*b*]indole-10(1*H*)-carboxylate (158)**

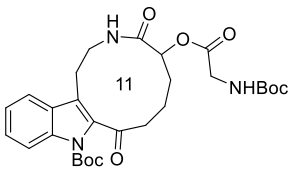
Yield: 72%, Eluent: 2% MeOH/CH_2Cl_2, R_f = 0.35 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.56 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.43 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.30 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H), 6.19 (t, *J* = 6.4 Hz, 1H), 5.13 (t, *J* = 4.5 Hz, 1H), 3.80 (dtd, *J* = 13.5, 6.7, 3.0 Hz, 1H), 3.43 – 3.34 (m, 1H), 3.18 (ddd, *J* = 14.9, 9.6, 3.0 Hz, 1H), 3.04 (ddd, *J* = 14.8, 6.4, 2.6 Hz, 1H), 2.95 – 2.82 (m, 2H), 2.10 (s, 3H), 2.08 – 2.02 (m, 2H), 2.01 – 1.91 (m, 1H), 1.88 – 1.79 (m, 1H), 1.61 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3, 169.6, 169.4, 149.8, 136.9, 135.8, 128.6, 127.0, 123.4, 121.5, 120.0, 115.5, 85.2, 72.9, 42.9, 39.3, 29.3, 28.1, 23.3, 21.1, 17.6.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{28}N_2NaO_6^+$ 451.1840; found 451.1841.

IR: ν (cm^{-1}) 3241, 2956, 2925, 2854, 1739, 1673, 1454, 1359, 1321, 1234, 1149, 746.



tert-Butyl 5-(((_tert_-butoxycarbonyl)glycyl)oxy)-4,9-dioxo-2,3,4,5,6,7,8,9-octahydro-[1]azacycloundecino[5,4-_b_]indole-10(1_H_)-carboxylate (159)

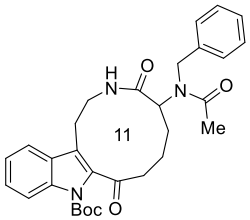
Yield: 78%, Eluent: 2% to 5% MeOH/CH_2Cl_2, R_f = 0.19 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.40 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.28 (d, *J* = 7.3 Hz, 1H), 6.63 (br t, *J* = 6.2 Hz, 1H), 5.16 (br dd, *J* = 5.9, 3.0 Hz, 2H), 3.94 – 3.72 (m, 3H), 3.36 – 3.27 (m, 1H), 3.24 – 3.18 (m, 1H), 2.99 (dd, *J* = 14.2, 4.8 Hz, 1H), 2.87 (t, *J* = 6.5 Hz, 2H), 2.11 – 1.79 (m, 4H), 1.60 (s, 9H), 1.28 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2, 169.4, 169.2, 156.2, 149.8, 136.9, 135.6, 128.7, 127.0, 123.4, 121.7, 119.9, 115.4, 85.1, 80.4, 73.7, 42.9, 42.9, 39.5, 29.0, 28.3, 28.1, 23.1, 17.7.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{28}H_{37}N_3NaO_8^+$ 566.2473; found 566.2472.

IR: ν (cm^{-1}) 2952, 2921, 2856, 1729, 1685, 1523, 1454, 1363, 1321, 1234, 1159, 742.



tert-Butyl 5-(_N_-benzylacetamido)-4,9-dioxo-2,3,4,5,6,7,8,9-octahydro-[1]azacycloundecino[5,4-_b_]-indole-10(1_H_)-carboxylate (160)

Yield: 61%, Eluent: 2% MeOH/CH_2Cl_2, R_f = 0.39 (5% MeOH/CH_2Cl_2)

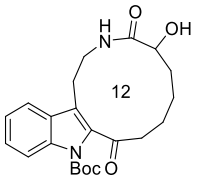
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.40 – 7.31 (m, 3H), 7.28 – 7.22 (m, 2H), 7.14 (d, *J* = 7.5 Hz, 2H), 6.92 (br s, 1H), 4.91 (d, *J* = 18.1 Hz, 1H), 4.70 (d, *J* =

11.2 Hz, 1H), 4.58 (d, *J* = 18.2 Hz, 1H), 3.88 – 3.78 (m, 1H), 3.20 – 3.08 (m, 2H), 3.03 – 2.95 (m, 1H), 2.85 (t, *J* = 6.6 Hz, 2H), 2.11 – 2.00 (m, 1H), 1.84 – 1.80 (m, 4H), 1.69 – 1.62 (m, 2H), 1.58 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 172.7, 171.3, 149.8, 138.2, 136.5, 135.6, 128.9, 128.8, 127.3, 126.9, 125.7, 123.4, 121.7, 119.8, 115.6, 85.1, 58.5, 50.0, 42.0, 39.0, 28.08, 28.05, 23.3, 22.1, 20.4.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{30}H_{35}N_3NaO_5^+$ 540.2469; found 540.2472.

IR: ν (cm^{-1}) 2956, 2921, 2867, 1729, 1675, 1627, 1450, 1359, 1324, 1234, 1143, 755.



***tert*-Butyl 5-hydroxy-4,10-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-11*H*-[1]azacyclododecino[5,4-*b*]-indole-11-carboxylate (161)**

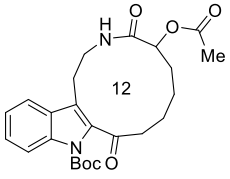
Yield: 92%, Eluent: 2% MeOH/CH_2Cl_2, R_f = 0.39 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.5 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 5.92 (t, *J* = 6.4 Hz, 1H), 4.15 (q, *J* = 4.3 Hz, 1H), 3.79 (ddt, *J* = 41.3, 12.9, 6.7 Hz, 2H), 3.09 (t, *J* = 5.8 Hz, 2H), 3.01 – 2.90 (m, 1H), 2.84 – 2.70 (m, 2H), 2.05 – 1.91 (m, 1H), 1.71 – 1.59 (m, 2H), 1.63 (s, 9H), 1.56 – 1.44 (m, 2H), 1.24 – 1.13 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.7, 173.1, 149.9, 137.1, 136.7, 128.7, 127.1, 123.7, 121.9, 120.7, 116.0, 85.7, 71.3, 42.2, 37.4, 32.4, 28.1, 24.9, 24.1, 21.8.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{28}N_2NaO_5^+$ 423.1890; found 423.1893.

IR: ν (cm^{-1}) 2956, 2919, 1729, 1675, 1454, 1369, 1321, 1234, 1143, 1078, 1051, 755.



***tert*-Butyl 5-acetoxy-4,10-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-11*H*-[1]azacyclododecino[5,4-*b*]-indole-11-carboxylate (162)**

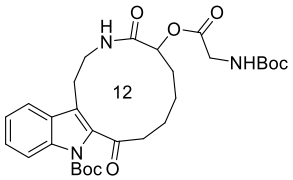
Yield: 85%, Eluent: 2% MeOH/CH_2Cl_2, R_f = 0.36 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.3 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 6.04 (t, *J* = 6.4 Hz, 1H), 5.01 (t, *J* = 5.3 Hz, 1H), 3.92 – 3.81 (m, 1H), 3.70 – 3.60 (m, 1H), 3.17 – 3.01 (m, 2H), 2.88 – 2.71 (m, 2H), 2.00 (s, 3H), 1.95 – 1.86 (m, 1H), 1.78 – 1.58 (m, 3H), 1.61 (s, 9H), 1.51 – 1.26 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.7, 169.6, 168.9, 149.9, 136.7, 136.3, 128.8, 127.2, 123.7, 122.6, 120.7, 115.9, 85.7, 73.9, 43.4, 37.4, 29.6, 28.1, 24.7, 24.6, 23.0, 21.1.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{24}H_{30}N_2NaO_6^+$ 465.1996; found 465.2000.

IR: ν (cm^{-1}) 3853, 1733, 1679, 1540, 1359, 1319, 1230, 1139, 755.



tert-Butyl 5-(((_tert_-butoxycarbonyl)glycyl)oxy)-4,10-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-11*H*-[1]-azacyclododecino[5,4-*b*]indole-11-carboxylate (163)

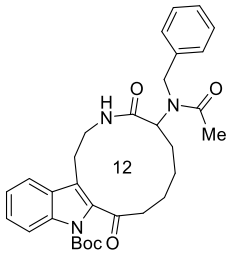
Yield: 85%, Eluent: 2% MeOH/CH_2Cl_2, R_f = 0.42 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.49 (br s, 1H), 5.19 – 5.08 (m, 1H), 5.06 (t, *J* = 5.1 Hz, 1H), 3.95 – 3.81 (m, 1H), 3.84 – 3.65 (m, 2H), 3.67 – 3.45 (m, 1H), 3.18 – 2.96 (m, 2H), 2.87 – 2.69 (m, 2H), 2.02 – 1.82 (m, 2H), 1.78 – 1.56 (m, 2H), 1.61 (s, 9H), 1.49 – 1.32 (m, 2H), 1.32 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 169.3, 168.8, 156.1, 149.9, 136.6, 136.2, 128.8, 127.0, 123.7, 122.5, 120.7, 115.9, 85.6, 80.3, 74.6, 43.1, 42.8, 37.7, 29.4, 28.3, 28.1, 24.7, 24.4, 22.8.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{29}H_{39}N_3NaO_8^+$ 580.2629; found 580.2632.

IR: ν (cm^{-1}) 3322, 2958, 2925, 1724, 1679, 1525, 1450, 1363, 1319, 1234, 1149, 1078, 1051, 757.



***tert*-Butyl 5-(*N*-benzylacetamido)-4,10-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-11*H*-[1]azacyclododecino[5,4-*b*]indole-11-carboxylate (164)**

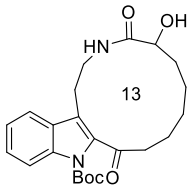
Yield: 57%, Eluent: 2:1 EtOAc/PE, R_f = 0.48 (5% 3:1 EtOAc/PE)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.34 – 7.28 (m, 3H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 2H), 6.59 (br s, 1H), 4.96 (d, *J* = 18.3 Hz, 1H), 4.83 (dd, *J* = 12.6, 3.7 Hz, 1H), 4.59 (d, *J* = 18.2 Hz, 1H), 4.11 – 3.99 (m, 1H), 3.40 – 3.29 (m, 1H), 3.11 (ddd, *J* = 13.8, 10.1, 3.4 Hz, 1H), 3.05 – 2.96 (m, 2H), 2.59 (td, *J* = 12.3, 3.4 Hz, 1H), 1.98 – 1.89 (m, 1H), 1.86 (s, 3H), 1.77 – 1.68 (m, 1H), 1.60 (s, 9H), 1.54 – 1.47 (m, 1H), 1.42 – 1.34 (m, 1H), 1.28 – 1.23 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 172.8, 170.3, 149.9, 138.3, 136.8, 136.2, 128.8, 127.2, 127.1, 125.6, 123.7, 123.0, 120.6, 116.0, 85.6, 56.3, 49.2, 43.6, 37.3, 28.11, 28.07, 24.6, 24.0, 23.9, 22.2.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{31}H_{37}N_3NaO_5^+$ 554.2625; found 554.2616.

IR: ν (cm^{-1}) 3318, 2956, 2925, 1729, 1679, 1625, 1450, 1367, 1319, 1236, 1139, 1079, 755.



***tert*-Butyl 5-hydroxy-4,11-dioxo-2,3,4,5,6,7,8,9,10,11-decahydro-[1]azacyclotridecino[5,4-*b*]indole-12(1*H*)-carboxylate (165)**

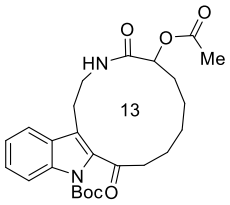
Yield: 83%, Eluent: 2% to 3% $MeOH/CH_2Cl_2$, R_f = 0.20 (5% $MeOH/CH_2Cl_2$)

^{1}H NMR (400 MHz, CDCl3) δ 8.08 (d, *J* = 8.6 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.36 – 7.27 (m, 1H), 6.23 (br t, *J* = 6.9 Hz, 1H), 4.13 (br s, 1H), 3.94 (dtd, *J* = 13.9, 6.9, 3.2 Hz, 1H), 3.81 – 3.67 (m, 1H), 3.21 (ddd, *J* = 15.7, 9.4, 3.2 Hz, 1H), 3.06 (ddd, *J* = 15.6, 6.9, 2.9 Hz, 1H), 2.96 – 2.79 (m, 2H), 2.47 (br d, *J* = 4.7 Hz, 1H), 1.95 – 1.84 (m, 2H), 1.74 – 1.67 (m, 2H), 1.63 (s, 9H), 1.34 – 1.24 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3, 173.6, 149.9, 136.9, 136.8, 128.8, 127.1, 123.6, 122.2, 120.7, 115.8, 85.4, 71.1, 42.1, 37.9, 32.3, 28.2, 27.5, 25.2, 23.4, 21.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{30}N_2NaO_5^+$ 437.2047; found 437.2040.

IR: ν (cm^{-1}) 3361, 2921, 2859, 1729, 1673, 1535, 1454, 1367, 1321, 1255, 1236, 1143, 1099, 836, 736.



***tert*-Butyl 5-acetoxy-4,11-dioxo-2,3,4,5,6,7,8,9,10,11-decahydro-[1]azacyclotridecino[5,4-*b*]indole-12(1*H*)-carboxylate (166)**

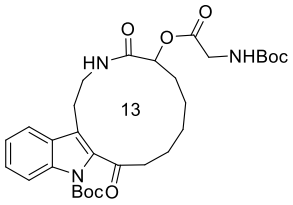
Yield: 62%, Eluent: 1:1 to 2:1 EtOAc/PE, R_f = 0.55 (2:1 EtOAc/PE)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 6.11 (t, *J* = 6.0 Hz, 1H), 5.05 (dd, *J* = 6.5, 3.4 Hz, 1H), 4.13 – 3.96 (m, 1H), 3.61 – 3.49 (m, 1H), 3.24 – 3.15 (m, 1H), 3.10 (ddd, *J* = 15.9, 6.3, 3.0 Hz, 1H), 2.88 (t, *J* = 6.0 Hz, 2H), 1.95 (s, 3H), 1.91 – 1.76 (m, 3H), 1.72 – 1.65 (m, 1H), 1.62 (s, 9H), 1.41 – 1.23 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.8, 169.7, 169.3, 149.9, 137.0, 136.8, 128.8, 127.2, 123.6, 122.4, 120.7, 115.7, 85.4, 73.7, 41.6, 37.6, 29.6, 28.1, 27.2, 25.1, 23.9, 22.7, 21.0.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{25}H_{32}N_2NaO_6^+$ 479.2153; found 479.2147.

IR: ν (cm^{-1}) 2958, 2915, 1739, 1675, 1375, 1319, 1234, 1147, 1078, 1051, 755.



***tert*-Butyl 5-(((*tert*-butoxycarbonyl)glycyl)oxy)-4,11-dioxo-2,3,4,5,6,7,8,9,10,11-decahydro-[1]aza-cyclotridecino[5,4-*b*]indole-12(1*H*)-carboxylate (167)**

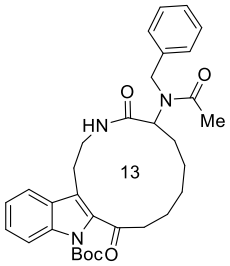
Yield: 73%, Eluent: 5% MeOH/CH_2Cl_2, R_f = 0.27 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 6.56 (t, *J* = 6.3 Hz, 1H), 5.19 – 5.04 (m, 2H), 4.08 – 3.98 (m, 1H), 3.83 – 3.67 (m, 2H), 3.58 – 3.46 (m, 1H), 3.26 – 3.01 (m, 2H), 2.94 – 2.66 (m, 3H), 1.99 – 1.87 (m, 2H), 1.83 – 1.74 (m, 2H), 1.67 – 1.64 (m, 3H), 1.61 (s, 9H), 1.30 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.8, 169.7, 169.1, 156.2, 149.9, 136.8, 136.6, 128.9, 127.0, 123.6, 122.7, 120.8, 115.6, 85.3, 80.3, 74.5, 42.8, 41.8, 38.1, 29.5, 28.3, 28.1, 27.3, 25.1, 23.8, 22.6.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{30}H_{41}N_3NaO_8^+$ 594.2786; found 594.2776.

IR: ν (cm^{-1}) 3322, 2952, 2925, 1727, 1679, 1529, 1450, 1363, 1324, 1234, 1149, 757.



***tert*-Butyl 5-(*N*-benzylacetamido)-4,11-dioxo-2,3,4,5,6,7,8,9,10,11-decahydro-[1]azacyclotrideci-no[5,4-*b*]indole-12(1*H*)-carboxylate (168)**

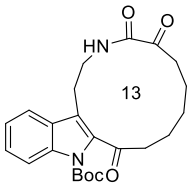
Yield: 54%, Eluent: 2:1 to 3:1 EtOAc/PE, R_f = 0.52 (3:1 EtOAc/PE)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.35 – 7.27 (m, 3H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 2H), 6.38 (dd, *J* = 8.6, 4.5 Hz, 1H), 4.92 – 4.72 (m, 2H), 4.56 (d, *J* = 18.2 Hz, 1H), 4.20 – 4.04 (m, 1H), 3.28 (ddt, *J* = 13.1, 8.5, 4.1 Hz, 1H), 3.18 – 3.04 (m, 2H), 2.98 (ddd, *J* = 17.1, 8.5, 4.5 Hz, 1H), 2.78 (ddd, *J* = 17.1, 7.1, 4.2 Hz, 1H), 1.94 (s, 3H), 1.80 – 1.73 (m, 2H), 1.62 (s, 9H), 1.41 – 1.18 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 172.7, 170.8, 150.0, 138.3, 136.9, 136.8, 128.84, 128.80, 127.2, 127.1, 125.7, 123.6, 122.7, 120.6, 115.7, 85.2, 57.0, 48.9, 41.7, 38.0, 28.1, 28.0, 26.5, 25.2, 24.8, 23.4, 22.3.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{32}H_{39}N_3NaO_5^+$ 568.2782; found 568.2773.

IR: ν (cm^{-1}) 2956, 2921, 2865, 1733, 1679, 1625, 1454, 1363, 1321, 1255, 1234, 1139, 966, 761, 734.



***tert*-Butyl 4,5,11-trioxo-2,3,4,5,6,7,8,9,10,11-decahydro-[1]azacyclotridecino[5,4-*b*]indole-12(1*H*)-carboxylate (169)**

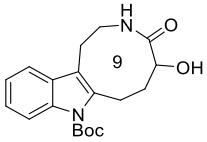
It was prepared from the same procedure as compound **144** followed by washing with 2 M HCl.

Yield: 60%, Eluent: 2:1 PE/EtOAc

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (dt, *J* = 8.8, 0.9 Hz, 1H), 7.59 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.44 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.31 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H), 6.67 (t, *J* = 6.7 Hz, 1H), 3.82 – 3.72 (m, 2H), 3.15 – 3.05 (m, 2H), 2.79 – 2.72 (m, 2H), 2.72 – 2.63 (m, 2H), 1.84 (p, *J* = 6.6 Hz, 2H), 1.62 (s, 9H), 1.57 – 1.48 (m, 2H), 1.48 – 1.40 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.4, 197.9, 161.4, 149.8, 136.5, 136.4, 128.7, 127.0, 123.6, 120.7, 120.3, 115.9, 85.5, 42.5, 38.0, 36.9, 28.2, 27.3, 24.6, 24.2, 23.6.

HRMS (ESI): *m/z* calcd for $C_{23}H_{28}N_2NaO_5$ ($[M + Na]^+$): 435.1890; found: 435.1887.

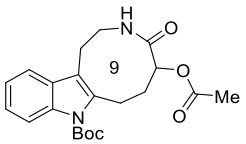


***tert*-Butyl 5-hydroxy-4-oxo-2,3,4,5,6,7-hexahydroazonino[5,4-*b*]indole-8(1*H*)-carboxylate (170)**

Yield: 44%, Eluent: 2% $MeOH/CH_2Cl_2$, R_f = 0.26 (5% $MeOH/CH_2Cl_2$)

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{24}N_2NaO_4^+$ 367.1634; found 367.1631.

IR: ν (cm^{-1}) 2946, 1727, 1664, 1454, 1363, 1321, 1132, 755.



***tert*-Butyl 5-acetoxy-4-oxo-2,3,4,5,6,7-hexahydroazonino[5,4-*b*]indole-8(1*H*)-carboxylate (171)**

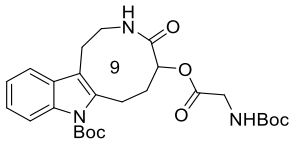
Yield: 50%, Eluent: 2% $MeOH/CH_2Cl_2$, R_f = 0.42 (5% $MeOH/CH_2Cl_2$)

^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.0 Hz, 1H), 7.27 – 7.16 (m, 2H), 4.94 – 4.87 (m, 1H), 3.68 (q, *J* = 12.0 Hz, 1H), 3.63 – 3.40 (m, 1H), 3.19 – 2.89 (m, 3H), 2.81 – 2.46 (m, 2H), 2.37 (br s, 1H), 2.18 – 1.95 (m, 3H), 1.70 (s, 9H).

^{13}C NMR (101 MHz, CD_3OD) δ 174.9, 172.0, 151.8, 138.3, 137.8, 130.8, 130.5, 125.1, 123.6, 118.8, 116.7, 85.0, 74.0, 41.1, 35.6, 28.5, 22.3, 20.9, 20.5.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{21}H_{26}N_2NaO_5^+$ 409.1734; found 409.1731.

IR: ν (cm^{-1}) 3853, 3729, 3704, 3600, 2362, 2339, 2318, 2167, 1729, 1536, 1517, 1455, 1359, 1319, 1228, 1132, 755.

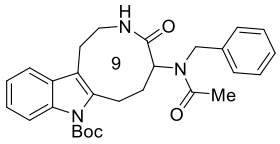


***tert*-Butyl 5-(((*tert*-butoxycarbonyl)glycyl)oxy)-4-oxo-2,3,4,5,6,7-hexahydroazonino[5,4-*b*]indole-8(1*H*)-carboxylate (172)**

Yield: 55%, Eluent: 2% $MeOH/CH_2Cl_2$, R_f = 0.35 (5% $MeOH/CH_2Cl_2$)

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{26}H_{35}N_3NaO_7^+$ 524.2367; found 524.2369.

IR: ν (cm^{-1}) 3322, 2921, 1691, 1660, 1454, 1369, 1159, 1020, 755.

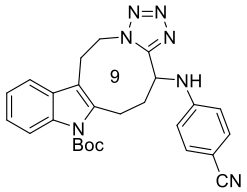


***tert*-Butyl 5-(*N*-benzylacetamido)-4-oxo-2,3,4,5,6,7-hexahydroazonino[5,4-*b*]indole-8(1*H*)-carboxylate (173)**

Yield: 43%, Eluent: 1% to 2% $MeOH/CH_2Cl_2$, R_f = 0.16 (5% $MeOH/CH_2Cl_2$)

HRMS (ESI/QTOF) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{34}N_3O_4^+$ 476.2544; found 476.2543.

IR: ν (cm^{-1}) 2969, 2908, 1727, 1643, 1450, 1367, 1324, 1251, 1224, 1164, 1132, 1116, 1074, 1052, 757, 723.



***tert*-Butyl 14-((4-cyanophenyl)amino)-6,12,13,14-tetrahydrotetrazolo[1',5':1,9]azonino[5,4-*b*]indole-11(5*H*)-carboxylate (174)**

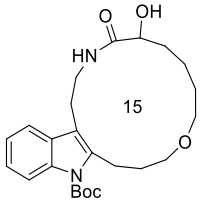
Yield: 35%, Eluent: 1% MeOH/CH_2Cl_2, R_f = 0.48 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.23 (br s, 2H), 5.37 (br s, 1H), 5.08 (br s, 1H), 4.35 (br s, 1H), 4.15 (br s, 1H), 3.55 (br s, 2H), 2.89 (br s, 1H), 2.80 (tt, *J* = 13.3, 3.6 Hz, 1H), 2.32 (br s, 1H), 1.69 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 150.2, 148.8, 136.3, 135.7, 133.9, 128.4, 125.3, 123.5, 119.7, 117.7, 116.4, 112.9, 101.0, 85.1, 49.4, 46.0, 37.0, 28.4, 25.1, 23.4.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{26}H_{27}N_7NaO_2^+$ 492.2118; found 492.2118.

IR: ν (cm^{-1}) 2952, 2925, 2217, 1729, 1604, 1519, 1454, 1363, 1321, 1159, 1133, 825, 761, 746.



***tert*-Butyl 5-hydroxy-4-oxo-1,2,3,4,5,6,7,8,9,11,12,13-dodecahydro-14*H*-[1]oxa[8]azacyclopentadecino[12,11-*b*]indole-14-carboxylate (179)**

Yield: 51%, Eluent: 2% to 3% MeOH/CH_2Cl_2, R_f = 0.42 (5% MeOH/CH_2Cl_2)

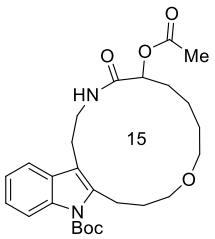
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 9.4 Hz, 1H), 7.18 – 7.06 (m, 2H), 5.48 (br t, *J* = 6.5 Hz, 0.6H), 4.88 (br s, 0.4H), 4.36 – 4.24 (m, 1H), 4.06 – 3.81 (m, 4H), 3.79 (br s, 0.6H), 3.66 (br t, *J* = 6.0 Hz, 0.4H), 3.54 (dt, *J* = 13.5, 6.6 Hz, 0.6H), 3.42 (dq, *J* = 12.2, 6.0 Hz, 0.4H), 3.09 (t, *J* = 6.9 Hz, 1H), 3.04 – 2.91 (m, 2H), 2.85 (dq, *J* = 13.9, 6.6 Hz, 1H), 2.03 – 1.87 (m, 2H), 1.86 – 1.71 (m, 2H), 1.66 – 1.57 (m, 2H), 1.49 (s, 9H), 1.15 – 1.00 (m, 1.2H), 0.38 – 0.22 (m, 0.8H).

^{13}C NMR (101 MHz, $CDCl_3$) δ Major rotamer: 173.5, 153.6, 138.7, 137.8, 129.2, 121.4, 119.7, 118.0, 110.8, 109.0, 82.2, 71.8, 65.9, 42.2, 36.9, 35.0, 29.6, 27.9, 26.2, 23.1, 22.3, 18.1. Minor rotamer: 174.0,

153.6, 139.0, 137.5, 129.1, 121.4, 119.8, 117.8, 110.8, 108.4, 82.2, 70.1, 65.8, 42.8, 37.2, 34.2, 29.5, 27.9, 26.1, 22.4, 21.9, 17.9.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{24}H_{34}N_2NaO_5^+$ 453.2360; found 453.2354.

IR: ν (cm^{-1}) 3368, 2955, 2919, 2850, 1733, 1679, 1462, 1369, 1275, 1255, 1161, 797, 764, 740.



***tert*-Butyl 5-acetoxy-4-oxo-1,2,3,4,5,6,7,8,9,11,12,13-dodecahydro-14*H*-[1]oxa[8]azacyclopentadecino[12,11-*b*]indole-14-carboxylate (180)**

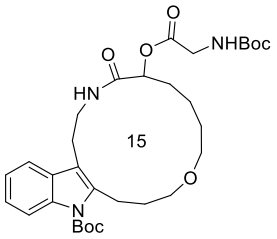
Yield: 52%, Eluent: 2% $MeOH/CH_2Cl_2$, R_f = 0.35 (5% $MeOH/CH_2Cl_2$)

^1H NMR (400 MHz, CD_3OD) δ 7.49 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.11 – 6.97 (m, 2H), 4.59 (d, *J* = 4.5 Hz, 0.5H), 4.51 (d, *J* = 7.2 Hz, 0.5H), 4.37 – 4.26 (m, 1H), 4.15 – 3.85 (m, 5H), 3.82 – 3.74 (m, 0.5H), 3.67 – 3.54 (m, 1H), 3.50 – 3.34 (m, 1.5H), 3.16 – 2.98 (m, 2.5H), 2.95 – 2.82 (m, 2.5H), 2.06 (s, 1.5H), 1.90 (s, 1.5H), 1.78 – 1.69 (m, 2H), 1.64 – 1.53 (m, 2H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, CD_3OD) δ Major rotamer: 172.0, 171.8, 155.1, 140.4, 139.5, 130.1, 122.0, 120.3, 119.4, 111.7, 110.5, 82.8, 74.9, 66.8, 42.3, 38.1, 32.2, 30.8, 28.0, 26.8, 24.4, 22.8, 20.5, 19.3. Minor rotamer: 172.1, 171.7, 155.1, 140.2, 139.5, 130.3, 121.8, 119.8, 119.4, 111.6, 110.5, 82.8, 74.8, 66.9, 43.0, 37.9, 31.8, 30.6, 28.1, 27.5, 24.0, 22.9, 20.7, 19.7.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{26}H_{36}N_2NaO_6^+$ 495.2466; found 495.2458.

IR: ν (cm^{-1}) 2958, 2921, 1737, 1668, 1459, 1369, 1276, 1251, 1159, 1079, 1037, 755, 736.

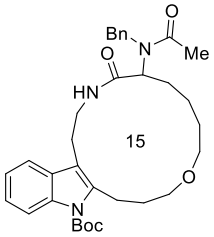


***tert*-Butyl 5-(((*tert*-butoxycarbonyl)glycyl)oxy)-4-oxo-1,2,3,4,5,6,7,8,9,11,12,13-dodecahydro-14*H*-[1]oxa[8]azacyclopentadecino[12,11-*b*]indole-14-carboxylate (181)**

Yield: 58%, Eluent: 2% MeOH/CH_2Cl_2, R_f = 0.42 (5% MeOH/CH_2Cl_2)

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{31}H_{45}N_3NaO_8^+$ 610.3099; found 610.3089.

IR: ν (cm^{-1}) 2967, 2925, 1739, 1673, 1373, 1276, 1255, 1164, 1074, 757.

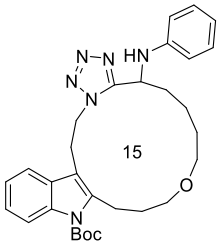


***tert*-Butyl 5-(*N*-benzylacetamido)-4-oxo-1,2,3,4,5,6,7,8,9,11,12,13-dodecahydro-14*H*-[1]oxa[8]azacyclopentadecino[12,11-*b*]indole-14-carboxylate (182)**

Yield: 30%, Eluent: 2% to 5% MeOH/CH_2Cl_2, R_f = 0.41 (5% MeOH/CH_2Cl_2)

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{33}H_{43}N_3NaO_5^+$ 584.3095; found 584.3091.

IR: ν (cm^{-1}) 2956, 2921, 2865, 1733, 1679, 1625, 1454, 1363, 1321, 1255, 1234, 1139, 966, 761, 734.

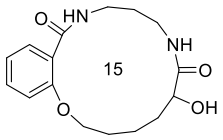


***tert*-Butyl 4-(phenylamino)-5,6,7,8,11,12,18,19-octahydro-4*H*-tetrazolo[5',1':7,8][1]oxa[8]azacyclopentadecino[12,11-*b*]indole-13(10*H*)-carboxylate (183)**

Yield: 23%, Eluent: 1% to 3% MeOH/CH_2Cl_2, R_f = 0.42 (5% MeOH/CH_2Cl_2)

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{30}H_{38}N_6NaO_3^+$ 553.2898; found 553.2892.

IR: ν (cm^{-1}) 3311, 1648, 1598, 1498, 1444, 1405, 1299, 1261, 730, 692.



6-Hydroxy-3,4,5,6,9,10,11,12-octahydrobenzo[*b*][1]oxa[5,9]diazacyclopentadecine-7,13(2*H*,8*H*)-dione (185)

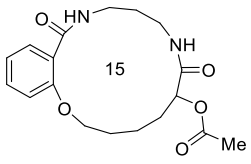
Yield: 84%, Eluent: 3% to 5% MeOH/CH_2Cl_2, R_f = 0.32 (10% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (br s, 1H), 8.14 br (s, 1H), 7.82 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.45 (ddd, *J* = 8.9, 7.3, 1.8 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 7.03 (t, *J* = 7.3 Hz, 1H), 4.26 – 4.09 (m, 3H), 3.65 – 3.55 (m, 2H), 3.51 – 3.44 (m, 1H), 3.18 – 3.07 (m, 1H), 2.00 – 1.84 (m, 4H), 1.83 – 1.71 (m, 2H), 1.69 – 1.58 (m, 1H), 1.52 – 1.43 (m, 1H).

^{13}C NMR (101 MHz, CD_3OD) δ 176.9, 168.7, 158.2, 133.8, 131.6, 123.7, 121.8, 113.7, 72.5, 68.6, 37.8, 37.7, 33.6, 29.5, 29.4, 21.0.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{22}N_2NaO_4^+$ 329.1472; found 329.1469.

IR: ν (cm^{-1}) 2958, 2915, 1799, 1459, 1375, 1078, 1052, 755.



7,13-Dioxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydrobenzo[*b*][1]oxa[5,9]diazacyclopentadecin-6-yl acetate (186)

Yield: 91%, Eluent: 2% MeOH/CH_2Cl_2, R_f = 0.39 (5% MeOH/CH_2Cl_2)

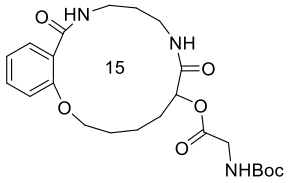
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.87 (br t, *J* = 6.3 Hz, 1H), 7.38 (ddd, *J* = 8.3, 7.3, 1.9 Hz, 1H), 7.02 (td, *J* = 7.6, 1.0 Hz, 1H), 6.94 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.73 (br t, *J* = 6.2 Hz, 1H), 5.19 (dd, *J* = 5.8, 3.2 Hz, 1H), 4.16 (t, *J* = 5.3 Hz, 2H), 3.73 – 3.61 (m, 2H), 3.56 – 3.49 (m, 1H),

3.22 – 3.14 (m, 1H), 2.06 (dtd, *J* = 14.8, 7.5, 3.3 Hz, 1H), 1.99 (s, 3H), 1.97 – 1.87 (m, 1H), 1.86 – 1.68 (m, 4H), 1.55 (p, *J* = 7.7 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 169.5, 166.3, 156.3, 132.6, 131.7, 122.6, 121.3, 112.6, 73.9, 67.7, 38.0, 37.8, 29.8, 29.2, 28.2, 20.9, 20.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{24}N_2NaO_5^+$ 371.1577; found 371.1574.

IR: ν (cm^{-1}) 2952, 2929, 1739, 1646, 1535, 1454, 1373, 1299, 1230, 755.



7,13-Dioxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydrobenzo[*b*][1]oxa[5,9]diazacyclopentadecin-6-yl (*tert*-butoxycarbonyl)glycinate (187)

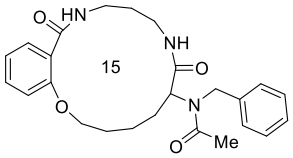
Yield: 95%, Eluent: 2% to 3% MeOH/CH_2Cl_2, R_f = 0.39 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.86 (br t, *J* = 6.3 Hz, 1H), 7.36 (ddd, *J* = 8.8, 7.4, 1.9 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 5.53 (br t, *J* = 6.0 Hz, 1H), 5.28 (dd, *J* = 5.4, 2.9 Hz, 1H), 4.14 (ddd, *J* = 10.4, 7.4, 3.2 Hz, 1H), 4.06 (m, 1H), 3.80 (d, *J* = 5.6 Hz, 2H), 3.74 – 3.62 (m, 1H), 3.57 (m, 2H), 3.06 (m, 1H), 2.16 – 2.06 (m, 1H), 2.00 – 1.69 (m, 5H), 1.64 – 1.50 (m, 2H), 1.35 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 169.3, 166.3, 156.6, 156.4, 132.6, 131.5, 122.5, 121.2, 112.2, 80.4, 74.6, 67.4, 43.0, 37.8, 37.2, 29.6, 29.1, 28.33, 28.28, 20.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{33}N_3NaO_7^+$ 486.2211; found 486.2205.

IR: ν (cm^{-1}) 3407, 3313, 2948, 2925, 1751, 1712, 1648, 1535, 1454, 1369, 1297, 1234, 1160, 755.



***N*-Benzyl-*N*-(7,13-dioxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydrobenzo[*b*][1]oxa[5,9]diazacyclopentadecin-6-yl)acetamide (188)**

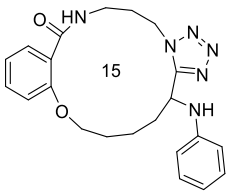
Yield: 97%, Eluent: 2% to 3% MeOH/CH_2Cl_2, R_f = 0.23 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.81 (br t, *J* = 6.2 Hz, 1H), 7.38 – 7.28 (m, 3H), 7.25 (t, *J* = 7.0 Hz, 1H), 7.18 – 7.11 (m, 3H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 4.92 (dd, *J* = 12.4, 2.8 Hz, 1H), 4.80 (d, *J* = 18.1 Hz, 1H), 4.61 (d, *J* = 18.1 Hz, 1H), 4.10 – 4.00 (m, 2H), 3.80 – 3.64 (m, 2H), 3.40 (ddt, *J* = 14.0, 9.1, 4.3 Hz, 1H), 2.98 (dq, *J* = 13.8, 4.5 Hz, 1H), 2.23 – 2.11 (m, 1H), 2.02 (s, 3H), 1.99 – 1.88 (m, 2H), 1.82 – 1.71 (m, 1H), 1.63 – 1.35 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 171.1, 166.1, 156.4, 137.8, 132.3, 131.7, 128.9, 127.3, 125.6, 122.6, 121.0, 111.8, 66.5, 57.6, 49.3, 37.3, 36.7, 28.6, 28.1, 27.3, 22.4, 22.3.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{25}H_{31}N_3NaO_4^+$ 460.2207; found 460.2203.

IR: ν (cm^{-1}) 3397, 3299, 2952, 2925, 1643, 1535, 1450, 1299, 1240, 1078, 1047, 755.



19-(Phenylamino)-5,6,7,8,16,17,18,19-octahydro-9*H*,15*H*-benzo[*b*]tetrazolo[1,5-*i*][1]oxa[5,9]diazacyclopentadecin-9-one (189)

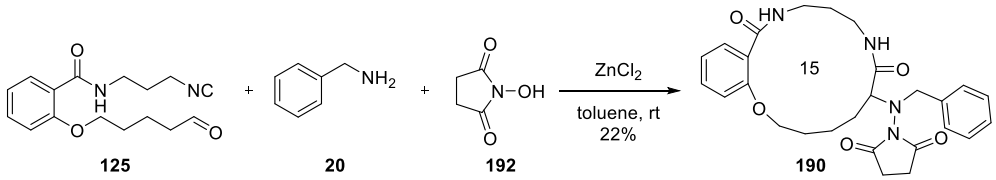
Yield: 43%, Eluent: 2% MeOH/CH_2Cl_2, R_f = 0.32 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.78 (t, *J* = 5.9 Hz, 1H), 7.52 – 7.39 (m, 1H), 7.12 – 7.09 (m, 3H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.74 (t, *J* = 7.4 Hz, 1H), 6.55 (d, *J* = 7.9 Hz, 2H), 4.93 (t, *J* = 6.7 Hz, 1H), 4.49 (dt, *J* = 13.4, 6.5 Hz, 1H), 4.32 – 4.16 (m, 3H), 3.59 – 3.51 (m, 1H), 3.50 – 3.41 (m, 1H), 2.61 – 2.49 (m, 2H), 2.27 – 2.09 (m, 2H), 2.05 – 1.96 (m, 1H), 1.92 – 1.83 (m, 1H), 1.68 – 1.48 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 156.5, 145.7, 133.2, 132.3, 129.6, 121.8, 121.6, 119.6, 113.9, 112.4, 68.5, 49.9, 44.6, 35.9, 34.5, 27.62, 27.57, 23.7.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{26}N_6NaO_2^+$ 429.2009; found 429.2008.

IR: ν (cm^{-1}) 3401, 3328, 2952, 2925, 2873, 1646, 1598., 1529, 1498, 1448, 1299, 1236, 1051, 755.



125 20 192 190

6-(Benzyl(2,5-dioxopyrrolidin-1-yl)amino)-3,4,5,6,9,10,11,12-octahydrobenzo[*b*][1]oxa[5,9]diaza-cyclopentadecine-7,13(2*H*,8*H*)-dione (190)

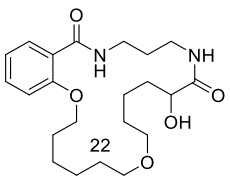
According to a reported procedure,[33] a mixture of *ω*-isocyanoaldehyde **125** (28.8 mg, 0.1 mmol, 1.0 equiv), benzylamine (**20**) (12.0 μL, 0.11 mmol, 1.1 equiv), *N*-hydroxysuccinimide (**182**) (17.3 mg, 0.15 mmol, 1.5 equiv) and $ZnCl_2$ (4.1 mg, 0.03 mmol, 0.3 equiv) in toluene (1 mL) was stirred at room temperature for 3 days. The mixture was filtered (rinsed with EtOAc) and the filtrate was evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO_2, 2% to 5% MeOH/CH_2Cl_2) to afford compound **190** in 22% (10.9 mg, 0.022 mmol) as white solid (R_f = 0.31 (5% MeOH/CH_2Cl_2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.73 (dd, *J* = 8.1, 4.4 Hz, 1H), 7.50 – 7.39 (m, 3H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.31 – 7.24 (m, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 4.17 (h, *J* = 5.6, 5.2 Hz, 2H), 4.08 (d, *J* = 12.4 Hz, 1H), 4.02 – 3.94 (m, 1H), 3.82 (dd, *J* = 11.5, 3.6 Hz, 1H), 3.77 (d, *J* = 12.4 Hz, 1H), 3.36 – 3.21 (m, 2H), 3.03 – 2.95 (m, 1H), 2.92 – 2.77 (m, 4H), 2.21 – 2.12 (m, 1H), 2.03 – 1.85 (m, 3H), 1.80 – 1.65 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 165.7, 156.9, 156.4, 139.1, 132.7, 132.3, 128.7, 128.6, 127.5, 121.8, 121.3, 111.8, 69.0, 54.6, 51.6, 42.8, 35.5, 32.8, 29.9, 29.5, 25.8, 23.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{33}N_4O_5^+$ 493.2445; found 493.2439.

IR: ν (cm^{-1}) 2956, 2925, 1712, 1643, 1450, 1378, 1240, 1078, 1051, 755.



13-Hydroxy-2,3,4,5,6,7,10,11,12,13,16,17,18,19-tetradecahydrobenzo[*b*][1,16]dioxa[5,9]diaza-cyclododecosine-14,20(9*H*,15*H*)-dione (198)

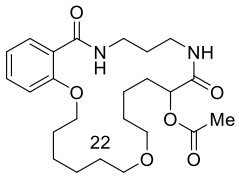
Yield: 71%, Eluent: 3% to 5% MeOH/CH_2Cl_2, R_f = 0.28 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.16 (m, 2H), 7.41 (td, *J* = 7.8, 1.9 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.88 (t, *J* = 6.2 Hz, 1H), 4.18 – 4.09 (m, 3H), 3.86 (d, *J* = 5.1 Hz, 1H), 3.56 – 3.29 (m, 8H), 2.04 – 1.49 (m, 16H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 165.8, 157.2, 132.8, 132.3, 121.7, 121.3, 112.3, 72.8, 71.1, 70.8, 69.3, 37.1, 36.5, 33.6, 30.1, 29.9, 29.6, 28.4, 26.8, 26.6, 23.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{34}N_2NaO_5^+$ 429.2360; found 429.2356.

IR: ν (cm^{-1}) 3606, 3392, 2952, 2915, 2867, 1641, 1525, 1454, 1378, 1240, 1078, 1051, 755.



14,20-Dioxo-2,3,4,5,6,7,9,10,11,12,13,14,15,16,17,18,19,20-octadecahydrobenzo[*b*][1,16]dioxa-[5,9]diazacyclodocosin-13-yl acetate (199)

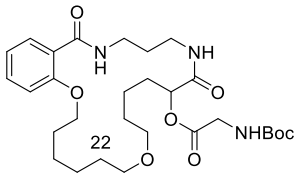
Yield: 85%, Eluent: 2% MeOH/CH_2Cl_2, R_f = 0.35 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ Major rotamer: 8.17 (br t, *J* = 5.7 Hz, 1H), 8.08 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.33 (ddd, *J* = 8.8, 7.3, 1.9 Hz, 1H), 6.96 (td, *J* = 7.6, 1.1 Hz, 1H), 6.88 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.41 (br t, *J* = 6.3 Hz, 1H), 5.11 (t, *J* = 5.6 Hz, 1H), 4.14 – 4.02 (m, 2H), 3.51 – 3.29 (m, 7H), 3.28 – 3.17 (m, 1H), 2.07 (s, 3H), 1.92 – 1.79 (m, 4H), 1.73 (p, *J* = 6.8 Hz, 2H), 1.61 – 1.36 (m, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ Major rotamer: 170.1, 169.8, 165.8, 157.1, 132.6, 132.1, 121.8, 121.0, 112.3, 74.2, 70.2, 70.0, 69.2, 37.0, 36.8, 31.4, 30.1, 29.6, 29.5, 29.2, 28.9, 26.4, 26.1, 21.8, 21.1.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{24}H_{36}N_2NaO_6^+$ 471.2466; found 471.2460.

IR: ν (cm^{-1}) 3388, 2952, 2921, 2861, 1739, 1643, 1531, 1230, 1051, 755.



14,20-Dioxo-2,3,4,5,6,7,9,10,11,12,13,14,15,16,17,18,19,20-octadecahydrobenzo[*b*][1,16]dioxa-[5,9]diazacyclodocosin-13-yl (*tert*-butoxycarbonyl)glycinate (200)

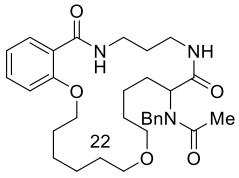
Yield: 80%, Eluent: 2% to 5% MeOH/CH_2Cl_2, R_f = 0.31 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (br t, *J* = 5.8 Hz, 1H), 8.12 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.37 (ddd, *J* = 8.2, 7.3, 1.9 Hz, 1H), 7.05 – 6.98 (m, 2H), 6.92 (dd, *J* = 8.4, 1.0 Hz, 1H), 5.45 (br t, *J* = 5.8 Hz, 1H), 5.22 (t, *J* = 5.4 Hz, 1H), 4.17 (dt, *J* = 9.5, 6.4 Hz, 1H), 4.08 (dt, *J* = 9.2, 6.8 Hz, 1H), 3.97 – 3.83 (m, 2H), 3.54 – 3.19 (m, 8H), 2.06 – 1.84 (m, 4H), 1.83 – 1.71 (m, 2H), 1.58 – 1.45 (m, 10H), 1.41 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.4, 165.8, 157.1, 156.7, 132.6, 132.1, 121.8, 120.9, 112.3, 80.5, 74.9, 70.2, 70.0, 69.2, 43.1, 37.0, 36.6, 31.3, 29.8, 29.5, 29.2, 28.9, 28.4, 26.4, 26.0, 21.9.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{29}H_{45}N_3NaO_8^+$ 586.3099; found 586.3091.

IR: ν (cm^{-1}) 3338, 2929, 2856, 1745, 1641, 1529, 1450, 1369, 1294, 1234, 1159, 1120, 966, 757.



***N*-Benzyl-*N*-(14,20-dioxo-2,3,4,5,6,7,9,10,11,12,13,14,15,16,17,18,19,20-octadecahydrobenzo[*b*]-[1,16]dioxa[5,9]diazacyclodocosin-13-yl)acetamide (201)**

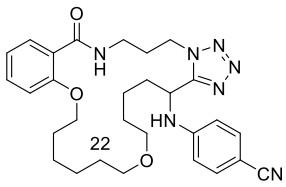
Yield: 78%, Eluent: 2% to 3% MeOH/CH_2Cl_2, R_f = 0.34 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.15 (m, 2H), 7.40 – 7.35 (m, 1H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.70 (br t, *J* = 6.2 Hz, 1H), 4.91 (dd, *J* = 10.3, 4.2 Hz, 1H), 4.70 (d, *J* = 17.6 Hz, 1H), 4.59 (d, *J* = 18.0 Hz, 1H), 4.15 – 4.06 (m, 2H), 3.50 – 3.31 (m, 7H), 3.22 – 3.09 (m, 1H), 2.14 – 2.08 (m, 1H), 2.04 (s, 3H), 1.94 – 1.88 (m, 2H), 1.81 – 1.73 (m, 2H), 1.61 – 1.37 (m, 10H), 1.32 – 1.23 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 170.9, 165.6, 157.1, 137.8, 132.6, 132.2, 128.8, 127.3, 125.9, 121.6, 121.0, 112.2, 70.1, 70.0, 69.1, 57.9, 49.2, 37.2, 37.0, 29.9, 29.6, 29.4, 29.1, 28.4, 26.5, 26.1, 23.8, 22.4.

HRMS (nanochip-ESI/LTQ-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{31}H_{43}N_3NaO_5^+$ 560.3095; found 560.3084.

IR: ν (cm^{-1}) 3397, 3311, 2929, 2859, 1641, 1529, 1450, 1294, 1230, 1105, 755.



4-((21-Oxo-5,6,7,8,10,11,12,13,14,15,22,23,24,25-tetradecahydro-4*H*,21*H*-benzo[*b*]tetrazolo[1,5-*i*][1,16]dioxa[5,9]diazacyclododocosin-4-yl)amino)benzonitrile (202)

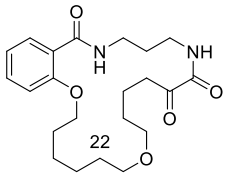
Yield: 53%, Eluent: 1% to 3% MeOH/CH_2Cl_2, R_f = 0.39 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (t, *J* = 6.0 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 2H), 4.95 (t, *J* = 7.0 Hz, 1H), 4.52 (t, *J* = 7.1 Hz, 2H), 4.16 (t, *J* = 5.9 Hz, 2H), 3.57 – 3.32 (m, 6H), 2.36 – 2.03 (m, 4H), 1.92 – 1.82 (m, 2H), 1.71 – 1.31 (m, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 157.0, 155.4, 149.5, 134.0, 133.1, 132.1, 121.42, 121.38, 119.9, 113.0, 112.4, 100.8, 70.5, 70.2, 69.1, 49.1, 45.5, 36.7, 33.7, 30.1, 29.9, 29.3, 28.4, 26.6, 26.3, 23.5.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{29}H_{37}N_7NaO_3^+$ 554.2850; found 554.2853.

IR: ν (cm^{-1}) 3600, 2952, 1770, 1604, 1041, 755, 719.



2,3,4,5,6,7,9,10,11,12,16,17,18,19-Tetradecahydrobenzo[*b*][1,16]dioxa[5,9]diazacyclododocosine-13,14,20(15*H*)-trione (203)

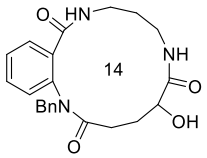
It was prepared from the same procedure as compound **144** followed by washing with 2 M HCl.

Yield: 68%, Eluent: 2% MeOH/CH_2Cl_2

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (t, *J* = 6.0 Hz, 1H), 8.21 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.41 (ddd, *J* = 8.2, 7.3, 1.9 Hz, 1H), 7.10 (t, *J* = 6.3 Hz, 1H), 7.04 (ddd, *J* = 8.1, 7.3, 1.0 Hz, 1H), 6.95 (dd, *J* = 8.4, 1.1

Hz, 1H), 4.16 (t, *J* = 6.8 Hz, 2H), 3.55 – 3.28 (m, 8H), 3.10 (t, *J* = 7.0 Hz, 2H), 2.03 – 1.91 (m, 2H), 1.89 – 1.73 (m, 5H), 1.72 – 1.59 (m, 2H), 1.58 – 1.38 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.2, 165.8, 161.0, 157.3, 132.8, 132.4, 121.4, 121.1, 112.2, 71.3, 70.8, 69.2, 37.0, 36.7, 36.5, 29.8, 29.7, 29.3, 27.9, 26.8, 26.3, 21.6.



1-Benzyl-5-hydroxy-4,5,8,9,10,11-hexahydrobenzo[*b*][1,5,9]triazacyclotetradecine-2,6,12-(1*H*,3*H*,7*H*)-trione (204)

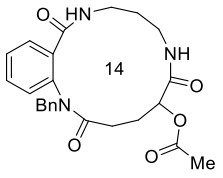
Yield: 66%, Eluent: 2% to 3% MeOH/CH_2Cl_2, R_f = 0.29 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 1H), 7.45 (br s, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.29 – 7.23 (m, 4H), 7.23 – 7.17 (m, 2H), 6.75 (br s, 1H), 6.57 (d, *J* = 7.9 Hz, 1H), 5.67 (d, *J* = 14.4 Hz, 1H), 4.18 (d, *J* = 14.4 Hz, 2H), 3.99 – 3.88 (m, 1H), 3.68 (dt, *J* = 15.5, 8.1 Hz, 1H), 3.18 (t, *J* = 12.1 Hz, 1H), 3.12 – 3.02 (m, 1H), 2.21 – 2.07 (m, 3H), 2.01 – 1.82 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 174.4, 167.8, 138.2, 136.9, 136.1, 131.0, 130.3, 129.5, 129.3, 129.1, 128.6, 127.8, 71.6, 53.6, 40.7, 38.9, 32.5, 29.0, 26.9.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{25}N_3NaO_4^+$ 418.1737; found 418.1744.

IR: ν (cm^{-1}) 3064, 3037, 1641, 1535, 1442, 1303, 1261, 1197, 790, 723.

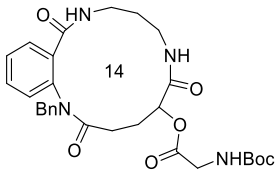


1-Benzyl-2,6,12-trioxo-1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrobenzo[*b*][1,5,9]triazacyclotetradecin-5-yl acetate (205)

Yield: 77%, Eluent: 2% to 3% MeOH/CH_2Cl_2, R_f = 0.22 (5% MeOH/CH_2Cl_2)

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{24}H_{27}N_3NaO_5^+$ 460.1843; found 460.1840.

IR: ν (cm^{-1}) 2956, 2925, 1739, 1652, 1525, 1230, 755.



1-Benzyl-2,6,12-trioxo-1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrobenzo[*b*][1,5,9]triazacyclotetradecin-5-yl (*tert*-butoxycarbonyl)glycinate (206)

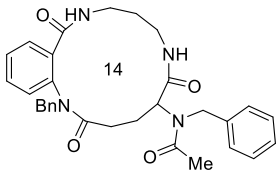
Yield: 93%, Eluent: 2% to 3% MeOH/CH_2Cl_2, R_f = 0.22 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, MeOD) δ 7.68 (dd, *J* = 7.7, 1.5 Hz, 0.3H), 7.63 (dd, *J* = 7.7, 1.6 Hz, 0.7H), 7.47 – 7.43 (m, 1H), 7.34 – 7.20 (m, 6H), 6.68 – 6.64 (m, 1H), 5.71 – 5.67 (m, 1H), 5.23 (dd, *J* = 7.2, 3.4 Hz, 0.7H), 4.79 (dd, *J* = 9.5, 3.3 Hz, 0.3H), 4.15 – 4.09 (m, 1H), 3.95 – 3.73 (m, 3H), 3.51 – 3.33 (m, 2H), 3.24 – 3.14 (m, 1H), 2.38 – 2.29 (m, 1H), 2.22 – 2.07 (m, 2H), 1.99 – 1.86 (m, 3H), 1.45 (s, 3H), 1.42 (s, 6H).

^{13}C NMR (101 MHz, MeOD) δ Major rotamer: 172.8, 171.6, 171.1, 169.7, 158.4, 140.2, 138.9, 136.5, 132.2, 131.6, 130.2, 130.1, 130.0, 129.4, 128.6, 80.6, 74.6, 54.6, 42.9, 40.6, 39.5, 29.5, 28.7, 28.5, 27.0. Minor rotamer: 172.6, 171.8, 171.0, 169.3, 158.6, 140.5, 138.9, 135.7, 132.3, 131.8, 130.2, 130.0, 130.0, 129.4, 128.5, 80.7, 75.2, 54.7, 43.2, 39.2, 37.7, 30.2, 28.7, 27.5, 26.6.

HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ calcd for $C_{29}H_{36}N_4NaO_7^+$ 575.2476; found 575.2485.

IR: ν (cm^{-1}) 3318, 2956, 2921, 2856, 1718, 1654, 1525, 1450, 1369, 1257, 1164, 707.



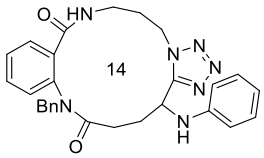
***N*-Benzyl-*N*-(1-benzyl-2,6,12-trioxo-1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrobenzo[*b*][1,5,9]triazacyclotetradecin-5-yl)acetamide (207)**

Yield: 56%, Eluent: 2% to 3% MeOH/CH_2Cl_2, R_f = 0.23 (5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, DMSO- d_6) δ 8.34 (dd, *J* = 7.4, 3.1 Hz, 0.6H), 8.21 (dd, *J* = 8.0, 3.5 Hz, 0.4H), 8.11 (dd, *J* = 7.2, 2.5 Hz, 0.6H), 8.01 (dd, *J* = 8.0, 3.8 Hz, 0.4H), 7.56 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.46 – 7.39 (m, 1H), 7.36 – 7.12 (m, 10H), 7.08 – 7.06 (m, 1H), 6.65 (ddd, *J* = 20.0, 7.9, 1.2 Hz, 1H), 5.64 (d, J = 15.0 Hz, 1H), 5.40 (d, J = 15.0 Hz, 1H), 4.94 (d, J = 18.7 Hz, 1H), 4.75 (d, J = 18.7 Hz, 1H), 4.62 – 4.40 (m, 2H), 4.09 (d, J = 14.9 Hz, 1H), 4.04 (d, J = 15.0 Hz, 1H), 3.78 – 3.54 (m, 2H), 3.05 – 2.90 (m, 1H), 2.79 – 2.72 (m, 1H), 2.40 (s, 2H), 2.34 – 2.25 (m, 1H), 2.02 – 1.94 (m, 1H), 1.81 (s, 1H), 1.77 – 1.53 (m, 4H), 1.39 – 1.32 (m, 1H).

HRMS (ESI/QTOF) *m/z*: $[M + H]^+$ calcd for $C_{31}H_{35}N_4O_4^+$ 527.2653; found 527.2644.

IR: ν (cm^{-1}) 3596, 3538, 3307, 1652, 1529, 1434, 1413, 1303, 1261, 777, 707, 686.

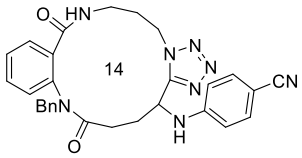


14-Benzyl-18-(phenylamino)-5,6,7,8,17,18-hexahydrobenzo[*b*]tetrazolo[1,5-*i*][1,5,9]triazacyclotetradecine-9,15(14*H*,16*H*)-dione (208)

Yield: 28%, Eluent: 1% to 3% MeOH/CH_2Cl_2, R_f = 0.45 (5% MeOH/CH_2Cl_2)

HRMS (ESI/QTOF) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{30}N_7O_2^+$ 496.2455; found 496.2462.

IR: ν (cm^{-1}) 3311, 1648, 1598, 1498, 1444, 1405, 1299, 1261, 730, 692.

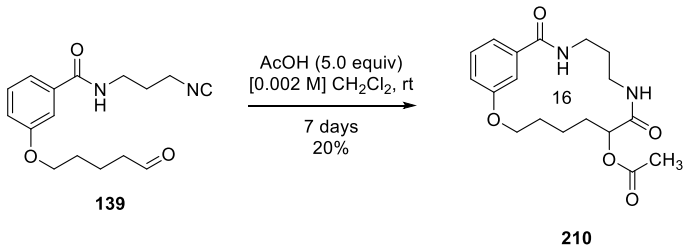


4-((14-Benzyl-9,15-dioxo-5,6,7,8,9,14,15,16,17,18-decahydrobenzo[*b*]tetrazolo[1,5-*i*][1,5,9]triazacyclotetradecin-18-yl)amino)benzonitrile (209)

Yield: 24%, Eluent: 1% to 5% MeOH/CH_2Cl_2, R_f = 0.40 (5% MeOH/CH_2Cl_2)

HRMS (ESI/QTOF) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{29}N_8O_2^+$ 521.2408; found 521.2422.

IR: ν (cm^{-1}) 3326, 2952, 2921, 2850, 2215, 1648, 1604, 1523, 1450, 1332, 1303, 1267, 1176, 827, 730, 698.



To a solution of ω-isocyanoaldehyde **139** (28.8 mg, 1.0 equiv) in dry CH_2Cl_2 (50 mL, 0.002 M) was added acetic acid (28.6 µL, 0.5 mmol, 5.0 equiv). The resulting solution was stirred at room temperature

for 7 days. Saturated $NaHCO_3$ was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO_2) (eluent: 2% to 5% MeOH/CH_2Cl_2) to yield compound **210** in 20% (6.8 mg, 0.02 mmol) (R_f = 0.45 (5% MeOH/CH_2Cl_2)).

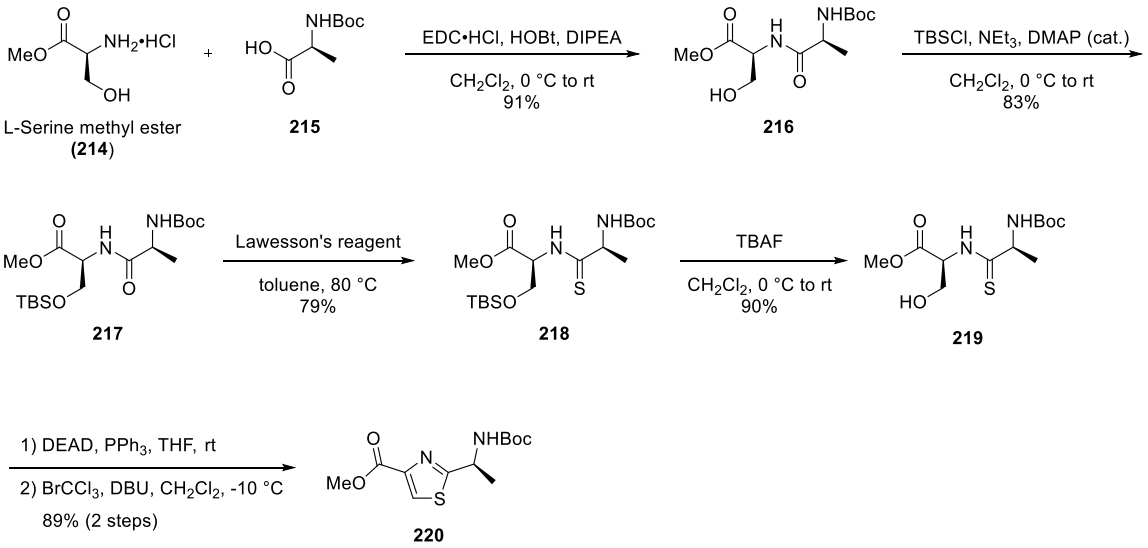
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.28 – 7.21 (m, 1H), 7.12 (br s, 1H), 7.06 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.54 (s, 1H), 5.09 (t, *J* = 6.1 Hz, 1H), 4.28 – 4.18 (m, 2H), 3.76 – 3.68 (m, 1H), 3.61 – 3.47 (m, 2H), 3.43 – 3.35 (m, 1H), 1.98 (s, 3H), 2.04 – 1.53 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 169.8, 167.6, 158.5, 135.8, 130.3, 121.5, 121.4, 112.3, 73.4, 68.4, 40.2, 40.0, 30.8, 29.5, 28.0, 21.8, 21.0.

HRMS *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{24}N_2NaO_5^+$ 371.1577; found 371.1579.

IR: ν (cm^{-1}) 3288, 2927, 2852, 1737, 1648, 1583, 1536, 1434, 1238, 1025, 717.

3.3 Towards the Total Synthesis of Jamaicensamide A



Methyl (*tert*-butoxycarbonyl)-*L*-alanyl-*L*-serinate (216)

According to a reported procedure,[59] to a solution of L-serine methyl ester hydrochloride (**214**) (3.03 g, 19.5 mmol, 1.3 equiv) and *N*-(*tert*-butoxycarbonyl)glycine (**215**) (2.84 g, 15.0 mmol, 1.0 equiv) in dry CH_2Cl_2 (100 mL) was added DIPEA (4.0 mL, 24.0 mmol, 1.6 equiv) dropwise at 0 °C. After stirring at 0 °C for 20 min, EDC·HCl (3.45 g, 18.0 mmol, 1.2 equiv) was added and the mixture was stirred at 0 °C for 20 min followed by the addition of HOBt (2.43 g, 18.0 mmol, 1.2 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 18 h. The mixture was quenched with 0.5 M HCl and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with H_2O and sat. aq. NH_4Cl, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 2% to 3% MeOH/CH_2Cl_2) to yield **216** in 48% yield (2.11 g, 7.26 mmol) as colorless oil (R_f = 0.42 (5% MeOH/CH_2Cl_2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 7.6 Hz, 1H), 5.07 (d, *J* = 7.1 Hz, 1H), 4.64 (dt, *J* = 7.3, 3.5 Hz, 1H), 4.14 (p, *J* = 7.0 Hz, 1H), 3.96 (dd, *J* = 6.6, 3.6 Hz, 2H), 3.79 (s, 3H), 1.44 (s, 9H), 1.39 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 170.8, 155.7, 80.3, 62.4, 54.6, 52.4, 50.5, 28.2, 18.1.

Methyl *N*-((*tert*-butoxycarbonyl)-*L*-alanyl)-*O*-(*tert*-butyldimethylsilyl)-*L*-serinate (217)

To a solution of **216** (2.11 g, 7.26 mmol, 1.0 equiv) and DMAP (115.3 mg, 0.94 mmol, 0.13 equiv) in CH_2Cl_2 (15 mL) were added TBSCl (1.42 g, 9.44 mmol, 1.3 equiv) and NEt_3 (2.0 mL, 14.52 mmol, 2.0 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 19 h.

After completion, the mixture was quenched with sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with sat. aq. NH_4Cl and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 15% to 20% EtOAc/PE) to yield **217** in 83% yield (2.43 g, 6.02 mmol) as white solid (R_f = 0.26 (5% 20% EtOAc/PE)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, *J* = 8.3 Hz, 1H), 5.01 (br s, 1H), 4.62 (dt, *J* = 8.3, 3.0 Hz, 1H), 4.22 (br s, 1H), 4.07 (dd, *J* = 10.1, 2.7 Hz, 1H), 3.81 (dd, *J* = 10.1, 3.2 Hz, 1H), 3.74 (s, 3H), 1.45 (s, 9H), 1.39 (d, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 170.6, 63.4, 54.2, 52.4, 28.3, 25.7, 18.8, 18.2, -5.5, -5.7.

Methyl *N*-((*S*)-2-((*tert*-butoxycarbonyl)amino)propanethioyl)-*O*-(*tert*-butyldimethylsilyl)-*L*-serinate (218)

According to a reported procedure,[60] to a solution of **217** (2.43 g, 6.02 mmol, 1.0 equiv) in toluene (60 mL) was added Lawesson's reagent (1.70 g, 4.21 mmol, 0.7 equiv) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred at 80 °C for 14 h. The mixture was allowed to cool to room temperature and quenched with sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 5% to 10% EtOAc/PE) to yield **218** in 79% yield (1.99 g, 4.73 mmol) as white solid (R_f = 0.26 (5% 20% EtOAc/PE)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (br d, *J* = 5.6 Hz, 1H), 5.20 (dt, *J* = 7.7, 2.7 Hz, 2H), 4.50 (p, *J* = 7.0 Hz, 1H), 4.11 (dd, *J* = 10.3, 2.5 Hz, 1H), 4.03 (dd, *J* = 10.3, 2.9 Hz, 1H), 3.77 (s, 3H), 1.48 (d, *J* = 7.0 Hz, 3H), 1.44 (s, 9H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 205.5, 169.7, 154.9, 62.3, 59.4, 52.6, 28.3, 25.7, 22.1, 18.2, -5.50, -5.7.

Methyl ((*S*)-2-((*tert*-butoxycarbonyl)amino)propanethioyl)-*L*-serinate (219)

According to a reported procedure,[60] to a solution of **218** (1.98 g, 4.70 mmol, 1.0 equiv) in CH_2Cl_2 (24 mL) was added TBAF (1 M in THF) (7.1 mL, 7.05 mmol, 1.5 equiv) dropwise at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 4 h. After completion, the mixture was quenched with H_2O at 0 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2,

40% EtOAc/PE) to yield **219** in 90% yield (1.30 g, 4.25 mmol) as yellowish viscous oil (R_f = 0.35 (50% EtOAc/PE)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 5.40 – 5.15 (m, 2H), 4.45 (p, *J* = 6.6 Hz, 1H), 4.20 (d, *J* = 11.9 Hz, 1H), 4.02 (d, *J* = 11.4 Hz, 1H), 3.83 (s, 3H), 1.74 (s, 1H), 1.48 (d, *J* = 6.9 Hz, 3H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.5, 170.2, 156.3, 80.8, 61.4, 60.0, 59.8, 53.0, 44.2, 28.4, 24.9, 22.9, 22.3.

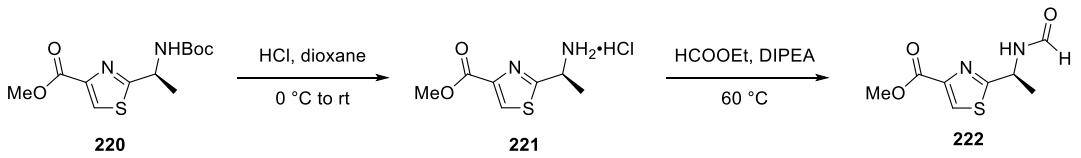
Methyl (*S*)-2-(1-((*tert*-butoxycarbonyl)amino)ethyl)thiazole-4-carboxylate (220)

To a solution of **219** (1.03 g, 3.35 mmol, 1.0 equiv) and PPh_3 (878.7 mg, 3.35 mmol, 1.0 equiv) in THF (34 mL) was added DEAD (2.2 M in toluene) (1.5 mL, 3.35 mmol, 1.0 equiv) dropwise at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 17 h. After completion, the mixture was quenched with sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated to dryness.

The crude mixture was dissolved in CH_2Cl_2 (34 mL) and cooled to -10 °C. DBU (1.5 mL, 10.05 mmol, 3.0 equiv) was added dropwise and the solution was stirred at -10 °C for 10 min followed by the slow addition of bromotrichloromethane (1.0 mL, 10.05 mmol, 3.0 equiv) at the same temperature. The resulting solution was stirred at -10 °C for 2 h. The mixture was quenched with sat. aq. $NaHSO_4$ and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was washed dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 20% EtOAc/PE) to yield **220** in 89% yield over two steps (850.4 mg, 2.97 mmol) as white solid (R_f = 0.44 (40% EtOAc/PE)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 5.23 (br s, 1H), 5.10 – 5.07 (m, 1H), 3.92 (s, 3H), 1.60 (d, *J* = 6.9 Hz, 3H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 161.9, 155.0, 146.9, 127.5, 80.4, 52.5, 49.0, 28.4, 21.8.

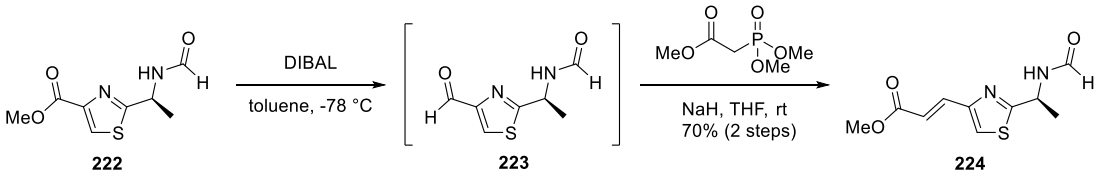


Methyl (*S*)-2-(1-formamidoethyl)thiazole-4-carboxylate (222)

A solution of **220** (621.9 mg, 2.17 mmol, 1.0 equiv) in 4 M HCl in dioxane (22 mL) was stirred at room temperature for 2 h. After the completion of reaction, the mixture was evaporated to dryness. To the crude mixture in dry ethyl formate (5.2 mL, 65.1 mmol, 30.0 equiv) was added DIPEA (1.4 mL, 8.68 mmol, 4.0 equiv). The resulting mixture was heated to reflux and stirred for 16 h. The mixture was allowed to cool to room temperature and evaporated to dryness. The crude mixture was purified by flash column chromatography (SiO_2, 2% MeOH/CH_2Cl_2) to afford compound **222** in 79% yield (368.9 mg, 1.72 mmol) as pale yellow solid (R_f = 0.35 (5% MeOH/CH_2Cl_2)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.13 (s, 1H), 6.49 (br s, 1H), 5.51 (p, *J* = 7.4 Hz, 1H), 3.95 (s, 3H), 1.68 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 161.7, 160.5, 146.8, 127.9, 52.7, 46.2, 22.1.



Methyl (*S*,*E*)-3-(2-(1-formamidoethyl)thiazol-4-yl)acrylate (224)

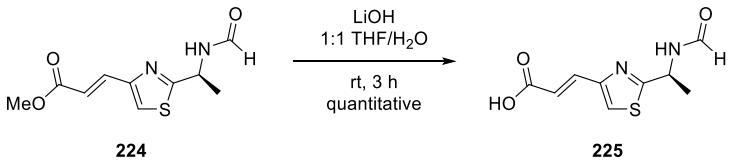
To a solution of **222** (278.3 mg, 1.3 mmol, 1.0 equiv) in THF (13 mL) was added DIBAL (1.2 M in toluene) (3.3 mL, 3.9 mmol, 3.0 equiv) dropwise at -78 °C. The resulting solution was stirred at -78 °C for 4 h. MeOH was then added and the resulting solution was evaporated to dryness. The residue was dissolved in EtOAc. Sat. aq. NH_4Cl was then added and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness to give crude aldehyde **223**.

To a suspension of NaH (60 % dispersion in mineral oil) (126.0 mg, 3.15 mmol, 1.5 equiv) in THF (10 mL) was added trimethyl phosphonoacetate (0.37 mL, 2.31 mmol, 1.1 equiv) dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred for 30 min before the addition of the solution of crude **223** in THF (11 mL) dropwise at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 16 h. After completion of reaction, sat. aq. $NaHCO_3$ was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography

(SiO_2, 30% acetone/PE) to yield **224** in 70% yield over two steps (217.3 mg, 0.90 mmol) as white solid (R_f = 0.42 (40% acetone/PE)).

^{1}H NMR (400 MHz, CDCl3) δ 8.24 (s, 1H), 8.13 (s, 1H), 6.49 (br s, 1H), 5.51 (p, *J* = 7.4 Hz, 1H), 3.95 (s, 3H), 1.68 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 13C NMR (101 MHz, CDCl3) δ 172.32, 161.74, 160.47, 146.75, 127.92, 52.68, 46.16, 22.09.



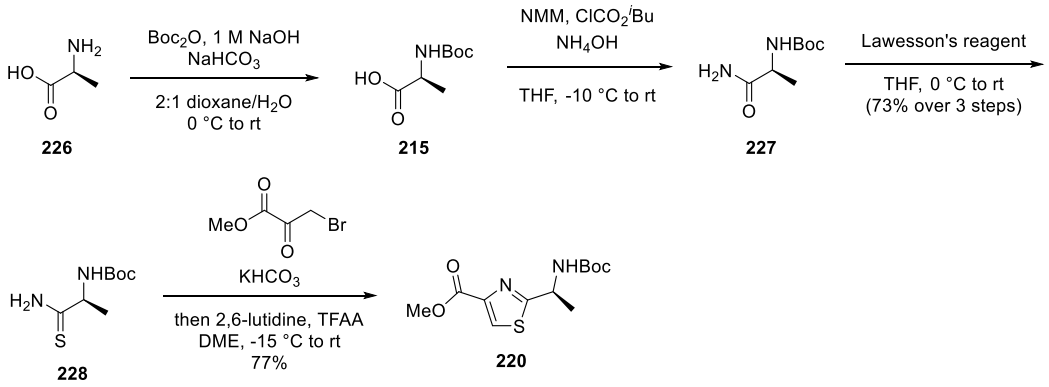
224 225

(*S*,*E*)-3-(2-(1-formamidoethyl)thiazol-4-yl)acrylic acid (225)

To a solution of **224** (58.5 mg, 0.24 mmol, 1.0 equiv) in THF (2.4 mL) and H_2O (2.4 mL) was added LiOH (17.2 mL, 0.72 mmol, 3.0 equiv). The resulting solution was stirred at room temperature for 3 h. The mixture was extracted with sat. aq. $NaHCO_3$, the aqueous layer was acidified with 1 M HCl until pH = 4 and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness to give **225** in quantitative yield (54.1 mg, 0.239 mmol) as white solid which was used directly for the next step without purification.

^{1}H NMR (400 MHz, MeOD) δ 8.16 (s, 1H), 7.71 (s, 1H), 7.59 (d, *J* = 17.3 Hz, 1H), 6.66 (d, *J* = 15.6 Hz, 1H), 5.39 (q, *J* = 7.0 Hz, 1H), 1.63 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, MeOD) δ 175.5, 170.4, 163.3, 152.8, 138.0, 123.3, 121.6, 47.3, 21.1.



226 215 227 228 220

tert-Butyl (_S_)-(1-amino-1-thioxopropan-2-yl)carbamate (228)

According to a reported procedure,[61] to a solution of *L*-alanine (**226**) (2.67 g, 30.0 mmol, 1.0 equiv) in 1,4-dioxane (67 mL) and H_2O (33 mL) were added 1 M NaOH (30 mL), Boc_2O (9.82 g, 45.0 mmol, 1.5 equiv) and $NaHCO_3$ (2.52 g, 30.0 mmol, 1.0 equiv) respectively at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 20 h. After completion of reaction, solvent was removed to a half of the original volume and the residue was diluted with EtOAc. The mixture was acidified with 1 M $KHSO_4$ until pH = 2 at 0 °C. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washws with H_2O and brine, dried over Na_2SO_4, filtered and evaporated to dryness to give crude (*tert*-butoxycarbonyl)-*L*-alanine (**215**).

According to a reported procedure,[62] to a solution of the crude **215** in THF (150) mL were added 4-methylmorpholine (3.6 mL, 33.0 mmol, 1.1 equiv) and isobutyl chloroformate (4.3 mL, 33.0 mmol, 1.1 equiv) respectively at -10 °C. After stirring the solution at -10 °C for 20 min, 25% ammonia (10.2 mL) was added at the same temperature. The resulting solution was allowed to warm to room temperature and stirred for 14 h. THF was removed and the residue was dissolved in EtOAc and H_2O. The pH of solution was adjusted to 3 with 1 M $KHSO_4$ and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with sat. aq. $NaHCO_3$, H_2O and brine, dried over Na_2SO_4, filtered and evaporated to dryness to give crude *tert*-butyl (*S*)-(1-amino-1-oxopropan-2-yl)carbamate (**227**).

According to a reported procedure,[59] to a solution of the crude **227** in THF (300 mL) was added Lawesson's reagent (9.10 g, 22.5 mmol, 0.75 equiv) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 16 h. After completion of reaction, the mixture was quenched with sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 30% acetone/PE) to yield **228** in 73% yield over three steps (4.49 g, 22.0 mmol) as white solid (R_f = 0.42 (40% acetone/PE)).

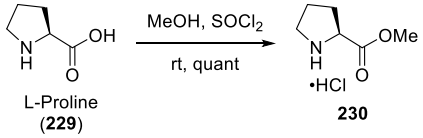
^{1}H NMR (400 MHz, CDCl3) δ 8.34 (br s, 1H), 7.94 (br s, 1H), 5.47 (br s, 1H), 4.59 (p, *J* = 7.0 Hz, 1H), 1.45 (d, *J* = 6.9 Hz, 3H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.7, 155.6, 80.6, 55.2, 28.5, 22.0.

Methyl (_S_)-2-(1-((_tert_-butoxycarbonyl)amino)ethyl)thiazole-4-carboxylate (220)

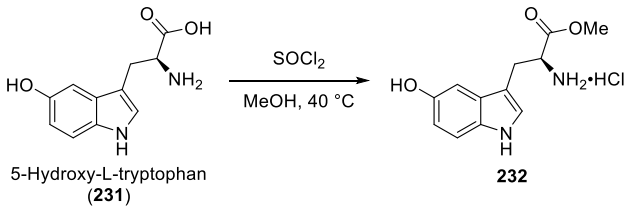
According to a reported procedure,[52] to a solution of **228** in DME (190 mL) was added $KHCO_3$ (18.73 g, 187.0 mmol, 8.7 equiv) at -15 °C. After stirring at the -15 °C for 15 min, methyl bromopyruvate (7.6 mL, 71.0 mmol, 3.3 equiv) was added dropwise at -15 °C. The mixture was stirred at -15 °C for 30 min

and then at room temperature for 30 min. A solution of TFAA (13.4 mL, 95.5 mmol, 4.44 equiv) and 2,6-lutidine (23.2 mL, 199.3 mmol, 9.27 equiv) was added dropwise at -15 °C. The resulting mixture was allowed to warm to rrom temperature and stirred for 18 h. After completion of reaction, DME was removed. The residue was dissolved in H_2O and extracted with CH_2Cl_2. The combined organic layers was dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 10% to 20% EtOAc/PE) to yield **220** in 77% yield (4.71 g, 16.4 mmol) as white solid (R_f = 0.44 (40% EtOAc /PE)).



Methyl *L*-prolinate hydrochloride (230)

According to a reported procedure,[63] to a solution of *L*-proline (**229**) (2.30 g, 20.0 mmol, 1.0 equiv) in MeOH (20 mL) was added $SOCl_2$ (1.9 mL, 26.0 mmol, 1.3 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 16 h. After completion of reaction, the reaction mixture was evaporated to dryness to give **230** as colorless viscous oil in quantitative yield which was used directly for the next step without purification.

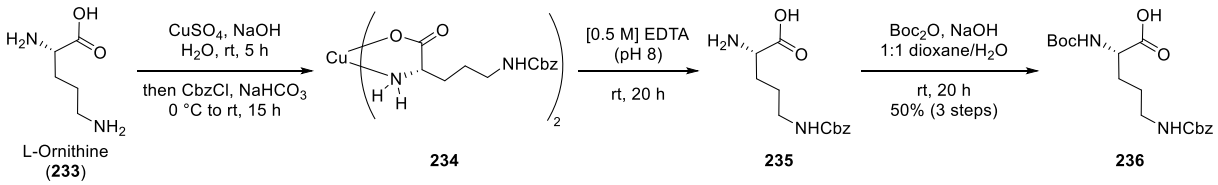


Methyl (*S*)-2-amino-3-(5-hydroxy-1*H*-indol-3-yl)propanoate hydrochloride (232)

According to a reported procedure,[64] to a solution of 5-Hydroxy-*L*-tryptophan (**231**) (4.40 g, 20.0 mmol, 1.0 equiv) in MeOH (67 mL) was added $SOCl_2$ (2.9 mL, 40.0 mmol, 2.0 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred at 40 °C for 16 h. After completion of reaction, the reaction mixture was cooled down to room temperature and evaporated to dryness to give **232** as black solid in quantitative yield which was used directly for the next step without purification.

^{1}H NMR (400 MHz, MeOD) δ 7.20 – 7.17 (m, 1H), 7.12 (d, *J* = 2.5 Hz, 1H), 6.68 (dd, *J* = 8.9, 2.5 Hz, 1H), 4.26 (t, *J* = 6.6 Hz, 1H), 3.76 (s, 3H), 3.31 – 3.24 (m, 2H).

^{13}C NMR (101 MHz, MeOD) δ 170.8, 151.7, 133.1, 128.8, 126.4, 113.1, 113.0, 106.5, 54.5, 53.7, 27.6.

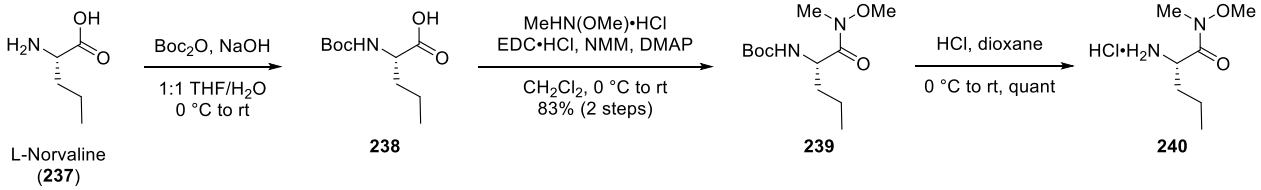


(*S*)-5-(((benzyloxy)carbonyl)amino)-2-((*tert*-butoxycarbonyl)amino)pentanoic acid (236)

According to a reported procedure,[53] to a solution of *L*-ornithine hydrochloride (**233**) (3.37 g, 20.0 mmol, 1.0 equiv) in 0.5 M NaOH (43 mL) was added a solution of $CuSO_4$ (1.88 g, 11.8 mmol, 0.59 equiv) in H_2O (200 mL). After stirring the resulting blue solution at room temperature for 5 h, $NaHCO_3$ (3.36 g, 40.0 mmol, 2.0 equiv) and CbzCl (3.84 g, 27.0 mmol, 1.35 equiv) were added at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 15 h. The blue precipitate was collected by filtration and washed with a small amount of H_2O. It was dissolved in 100 mL of 0.5 M EDTA (pH = 8) and the resulting mixture was stirred at room temperature for 14 h. After filtration, the white solid was collected and washed with a small amount of H_2O. It was suspended in 1,4-dioxane (100 mL) and H_2O (100 mL) followed by the addition of Boc_2O (7.42g, 34.0 mmol, 1.7 equiv). The resulting mixture was basified to pH = 10 with 4 M NaOH and stirred for 15 h. After completion of reaction, MeOH (44 mL) was added and the resulting solution was stirred at room temperature for another 14 h. Organic solvents were removed, the aqueous layer was acidified until pH = 3 with 2 M HCl at 0 °C and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 2% to 10% MeOH/CH_2Cl_2) to yield **236** in 50% yield (3.67 g, 10.0 mmol) as colorless solid (R_f = 0.26 (5% MeOH/CH_2Cl_2)).

^{1}H NMR (400 MHz, MeOD) δ 7.34 – 7.28 (m, 5H), 5.06 (s, 2H), 4.07 (dd, *J* = 8.6, 4.9 Hz, 1H), 3.13 (t, *J* = 6.6 Hz, 2H), 1.88 – 1.80 (m, 1H), 1.69 – 1.53 (m, 3H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, MeOD) δ 176.1, 158.9, 158.1, 138.4, 129.4, 128.9, 128.7, 80.5, 67.3, 54.7, 41.3, 30.1, 28.7, 27.4.



***tert*-Butyl (*S*)-(1-(methoxy(methyl)amino)-1-oxopentan-2-yl)carbamate (239)**

According to a reported procedure,[65] to a solution of *L*-norvaline (**237**) (2.34 g, 20.0 mmol, 1.0 equiv) in THF (20 mL) and H_2O (15 mL) was added a solution of NaOH (800 mg, 20.0 mmol, 1.0 equiv) in H_2O (5 mL) at 0 °C. After stirring at 0 °C for 10 min, Boc_2O (5.24 g, 24.0 mmol, 1.2 equiv) was added at the same temperature. The resulting solution was allowed to warm to room temperature and stirred for 14 h. The mixture was acidified with 2 M HCl until pH = 2 at 0 °C and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, filtered and evaporated to dryness.

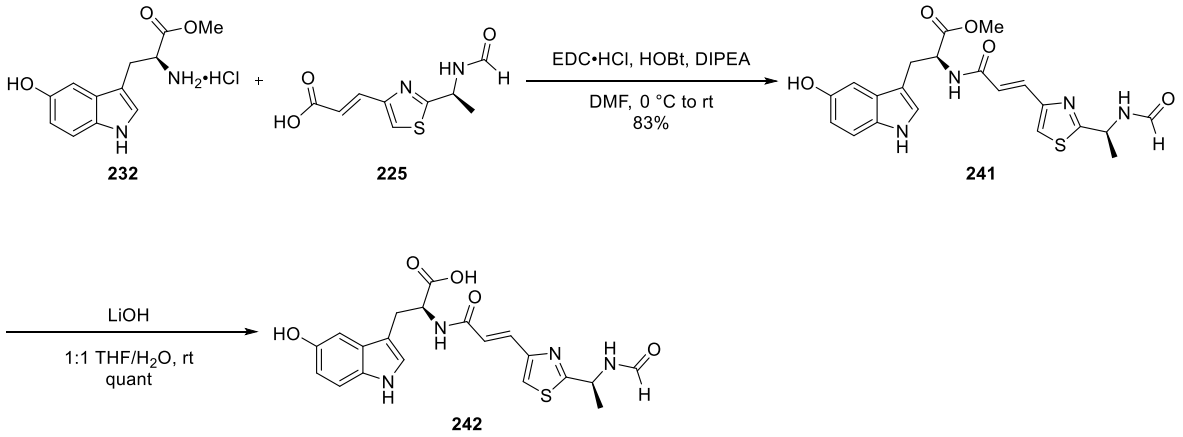
According to a reported procedure,[66] the residue was dissolved in CH_2Cl_2 (80 mL) and placed at 0 °C. DMAP (2.44 g, 20.0 mmol, 1.0 equiv), *N*,*O*-dimethylhydroxylamine (1.95 g, 20.0 mmol, 1.0 equiv), EDC·HCl (3.83 g, 20.0 mmol, 1.0 equiv) and 4-methylmorpholine (2.2 mL, 20.0 mmol, 1.0 equiv) were added respectively. The resulting mixture was allowed to warm to room temperature and stirred for 16 h. After completion of reaction, 2 M HCl was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 20% to 30% EtOAc/PE) to yield **239** in 83% yield (4.34 g, 16.7 mmol) as colorless oil (R_f = 0.29 (30% EtOAc/PE)).

^{1}H NMR (400 MHz, CDCl3) δ 5.13 (br d, *J* = 9.4 Hz, 1H), 4.68 (br s, 1H), 3.77 (s, 3H), 3.20 (s, 3H), 1.71 – 1.62 (m, 1H), 1.54 – 1.32 (m, 3H), 1.43 (s, 9H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 79.6, 61.7, 50.3, 35.3, 32.2, 28.5, 18.8, 13.9.

(*S*)-2-Amino-*N*-methoxy-*N*-methylpentanamide hydrochloride (240)

A solution of **239** (1.30 g, 5.0 mmol, 1.0 equiv) in 4 M HCl in dioxane (37.5 mL) was stirred at room temperature for 2 h. The mixture was then evaporated to dryness to give **240** as yellowish oil in quantitative yield which was used directly for the next step without purification.



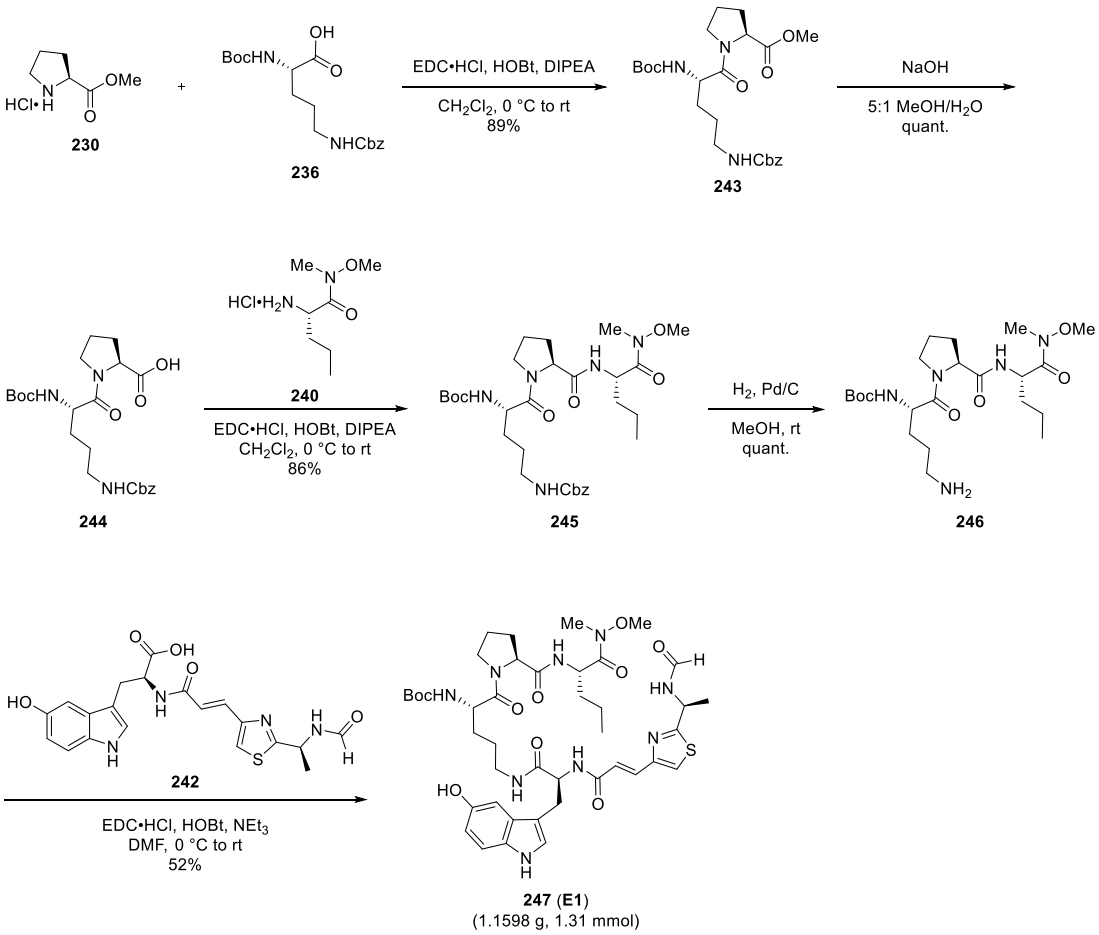
232 225 241 242

Methyl (*S*)-2-((*E*)-3-(2-((*S*)-1-formamidoethyl)thiazol-4-yl)acrylamido)-3-(5-hydroxy-1*H*-indol-3-yl)propanoate (241)

To a solution of **232** (828.4 mg, 3.06 mmol, 1.0 equiv) and **225** (693.0 mg, 3.06 mmol, 1.0 equiv) in CH_2Cl_2 (26 mL) and DMF (4 mL) were added NEt_3 (1.3 mL, 9.18 mmol, 3.0 equiv), EDC·HCl (654.3 mg, 3.37 mmol, 1.1 equiv) and HOBt (454.8 mg, 3.37 mmol, 1.1 equiv) respectively at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 16 h. Sat. aq. NH_4Cl was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with H_2O (6 times) and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 2% to 5% MeOH/CH_2Cl_2) to yield **241** in 83% yield (1.12 g, 2.5 mmol) as colorless oil (R_f = 0.29 (5% MeOH/CH_2Cl_2)).

(*S*)-2-((*E*)-3-(2-((*S*)-1-Formamidoethyl)thiazol-4-yl)acrylamido)-3-(5-hydroxy-1*H*-indol-3-yl)propanoic acid (242)

To a solution of **241** (1.12 g, 2.54 mmol, 1.0 equiv) in MeOH (8.5 mL), THF (8.5 mL) and H_2O (8.5 mL) was added LiOH (182.5 mg, 7.6 mmol, 3.0 equiv). The resulting solution was stirred at room temperature for 4 h. The mixture was then evaporated to dryness, the residue was dissolved in H_2O and then acidified with 1 M HCl until pH = 4. The mixture was extracted with EtOAc and the combined organic layer was dried over Na_2SO_4, filtered and evaporated to dryness to give **242** in quantitative yield which was used directly for the next step without purification.



Methyl ((*S*)-5-(((benzyloxy)carbonyl)amino)-2-((*tert*-butoxycarbonyl)amino)pentanoyl)-*L*-prolinate (243)

To a solution of **230** (2.91 g, 17.6 mmol, 1.0 equiv) and **236** (6.45 g, 17.6 mmol, 1.0 equiv) in CH_2Cl_2 (60 mL) was added DIPEA (14.5 mL, 88.0 mmol, 5.0 equiv) dropwise at 0 °C. After stirring at 0 °C for 20 min, HOBt (4.76 g, 35.2 mmol, 2.0 equiv) was added and the mixture was stirred at the same temperature for 20 min before the addition of EDC·HCl (6.74 g, 35.2 mmol, 2.0 equiv). The resulting mixture was allowed to warm to room temperature and stirred for 20 h. After completion of reaction, 10% aq. citric acid (100 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with sat. aq. $NaHCO_3$, H_2O and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 1% to 2% MeOH/CH_2Cl_2) to yield **243** in 89% yield (7.44 g, 15.58 mmol) as colorless viscous oil (R_f = 0.45 (5% MeOH/CH_2Cl_2)).

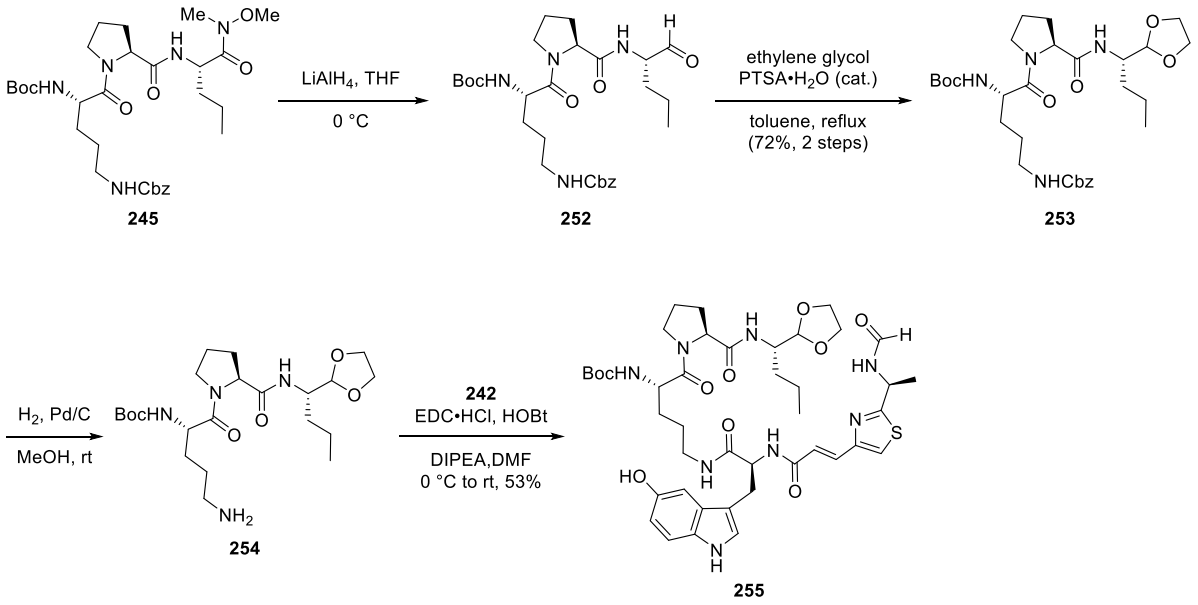
Benzyl *tert*-butyl ((*S*)-5-((*S*)-2-(((*S*)-1-(methoxy(methyl)amino)-1-oxopentan-2-yl)carbamoyl)pyrrolidin-1-yl)-5-oxopentane-1,4-diyl)dicarbamate (245)

To a solution of **243** (7.81 g, 16.34 mmol, 1.0 equiv) in MeOH (68 mL) at 0 °C was added the solution of NaOH in H_2O (14 mL) dropwise. The resulting solution was allowed to warm to room temperature and stirred for 4 h. MeOH was evaporated and the pH of the residue was adjusted to 3 with 10% aq. citric acid. The mixture was extracted with EtOAc and the combined organic layers were washed with brine dried over Na_2SO_4, filtered and evaporated to dryness to give crude **244** which was used directly for the next step without purification.

To a solution of the crude **244** and **240** (3.21 g, 16.34 mmol, 1.0 equiv) in CH_2Cl_2 (163 mL) was added DIPEA (8.1 mL, 49.04 mmol, 3.0 equiv) at 0 °C. After stirring at 0 °C for 20 min, HOBt (2.65 g, 19.61 mmol, 1.2 equiv) and EDC·HCl (3.76 g, 19.61 mmol, 1.2 equiv) were added at the same temperature. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. H_2O was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 2% MeOH/CH_2Cl_2) to yield **245** in 53% yield (5.26 g, 8.69 mmol) as colorless solid (R_f = 0.45 (5% MeOH/CH_2Cl_2)).

***tert*-Butyl ((*S*)-5-((*S*)-2-((*E*)-3-(2-((*S*)-1-formamidoethyl)thiazol-4-yl)acrylamido)-3-(5-hydroxy-1*H*-indol-3-yl)propanamido)-1-((*S*)-2-(((*S*)-1-(methoxy(methyl)amino)-1-oxopentan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxopentan-2-yl)carbamate (247)**

To a solution of **245** (1.88 g, 3.11 mmol, 1.2 equiv) in MeOH (31 mL) was added 10% Pd/C (155.5 mg). The resulting mixture was stirred at room temperature under H_2 balloon for 4 h. The mixture was filtered through a pad of Celite (rinsed with MeOH) and the filtrate was evaporated to dryness. The residue together with the crude **242** (2.54 mmol) was dissolved in DMF (25 mL). DIPEA (1.7 mL, 10.16 mmol, 4.0 equiv) was added dropwise at 0 °C. After stirring at 0 °C for 20 min, HOBt (686.4 mg, 5.08 mmol, 2.0 equiv) and EDC·HCl (973.8 mg, 5.08 mmol, 2.0 equiv) were added at the same temperature. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. Sat. aq. NH_4Cl was added and the mixture was extracted with EtOAc. The combined organic layers were washed with H_2O (6 times) and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 2% MeOH/CH_2Cl_2) to yield **247** in 52% yield (1.16 g, 1.31 mmol) as colorless solid (R_f = 0.45 (5% MeOH/CH_2Cl_2)).



Benzyl *tert*-butyl ((*S*)-5-((*S*)-2-(((S)-1-(1,3-dioxolan-2-yl)butyl)carbamoyl)pyrrolidin-1-yl)-5-oxopentane-1,4-diyl)dicarbamate (253)

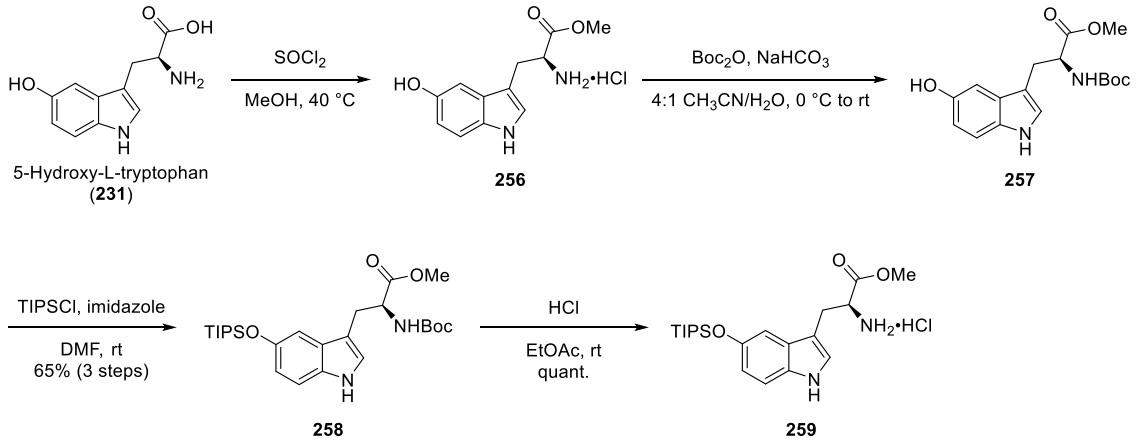
To a solution of 245 (1.82 g, 3.0 mmol, 1.0 equiv) in THF (30 mL) was added $LiAlH_4$ (91.0 mg, 2.4 mmol, 0.8 equiv) portionwise at 0 °C. The resulting suspension was allowed to stir at 0 °C for 1 h. The mixture was quenched with 1 M HCl at 0 °C and extracted with EtOAc. The combined organic layers were washed with sat. $NaHCO_3$, H_2O and brine, dried over Na_2SO_4, filtered and evaporated to dryness to give crude **252** which was used directly for the next step without purification.

To a solution of crude **252** in toluene (30 mL) were added ethylene glycol (4 mL) and *p*-toluenesulfonic acid monohydrate (57.0 mg, 0.3 mmol, 0.1 equiv). The resulting solution was heated to reflux and stirred for 14 h. After completion, the mixture was allowed to cool to room temperature, sat. $NaHCO_3$ was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 2% MeOH/CH_2Cl_2) to yield **253** in 72% yield over two steps (1.27 g, 2.15 mmol).

***tert*-Butyl ((*S*)-1-((S)-2-(((*S*)-1-(1,3-dioxolan-2-yl)butyl)carbamoyl)pyrrolidin-1-yl)-5-((*S*)-2-((*E*)-3-(2-((*S*)-1-formamidoethyl)thiazol-4-yl)acrylamido)-3-(5-hydroxy-1*H*-indol-3-yl)propanamido)-1-oxopentan-2-yl)carbamate (255)**

To a solution of **253** (1.25 g, 2.1 mmol, 1.0 equiv) in MeOH (21 mL) was added 10% Pd/C (106.0 mg). The resulting mixture was stirred at room temperature under H_2 balloon for 4 h. The mixture was filtered through a pad of Celite (rinsed with MeOH) and the filtrate was evaporated to dryness. The residue together with the crude **242** (2.0 mmol) was dissolved in DMF (20 mL). DIPEA (1.4 mL, 8.0 mmol, 4.0

equiv) was added dropwise at 0 °C. After stirring at 0 °C for 20 min, HOBt (540.5 mg, 4.0 mmol, 2.0 equiv) and EDC·HCl (767.0 mg, 4.0 mmol, 2.0 equiv) were added at the same temperature. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. Sat. aq. NH_4Cl was added and the mixture was extracted with EtOAc. The combined organic layers were washed with H_2O (6 times) and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 2% to 10% MeOH/CH_2Cl_2) to yield **255** in 53% yield (919.0 mg, 1.06 mmol).



Methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(5-((triisopropylsilyl)oxy)-1*H*-indol-3-yl)propanoate (258)

According to a reported procedure,[69] to a solution of 5-hydroxy-L-tryptophan (4.4 g, 20.0 mmol, 1.0 equiv) in MeOH (20 mL) was added $SOCl_2$ (1.9 mL, 26.0 mmol, 1.3 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred at 40 °C for 16 h. After completion of reaction, the reaction mixture was evaporated to dryness to give **256** as black solid in quantitative yield which was used directly for the next step without purification.

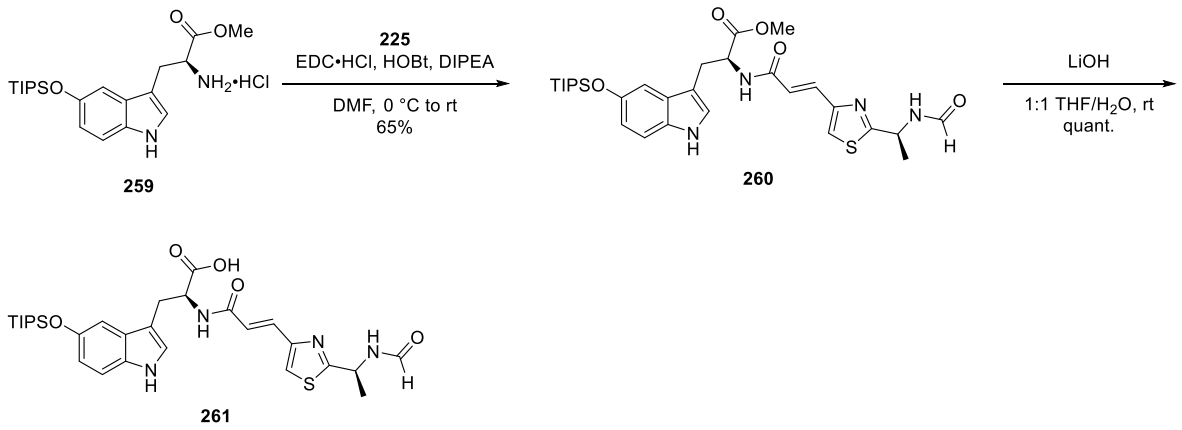
To a solution of crude **256** in CH_3CH (80 mL) and H_2O (20 mL) was added $NaHCO_3$ at 0°C to adjust the pH of the solution to 8. Boc_2O (5.24 g, 24.0 mmol, 1.2 equiv). The resulting mixture was allowed to warm to room temperature and stirred for 16 h. Sat. aq. $NaHCO_3$ was added and the mixture was extracted with EtOAc. The combined organic layers were washed brine, dried over Na_2SO_4, filtered and evaporated to dryness to give **257** as yellowish solid which was used directly for the next step without purification.

According to a reported procedure,[70] to a solution of crude **257** and imidazole (10.9 g, 160.0 mmol, 8.0 equiv) in DMF (40 mL) was added TIPSCl (5.1 mL, 24.0 mmol, 1.2 equiv). The resulting solution was stirred at room temperature for 16 h. Sat. aq. $NaHCO_3$ was added and the mixture was extracted with EtOAc. The combined organic layers were washed H_2O (6 times) and brine, dried over Na_2SO_4, filtered

and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 2% to 3% MeOH/CH_2Cl_2) to yield **258** in 65% yield (6.38 g, 13.0 mmol).

Methyl (*S*)-2-amino-3-(5-((triisopropylsilyl)oxy)-1*H*-indol-3-yl)propanoate (259)

To a solution of **258** (5.89 g, 12.0 mmol, 1.0 equiv) in EtOAc (60 mL) was added concentrated HCl (20 mL). The resulting solution was stirred at room temperature for 2 h. The mixture was then evaporated to dryness to give **259** in quantitative yield which was used directly for the next step without purification.



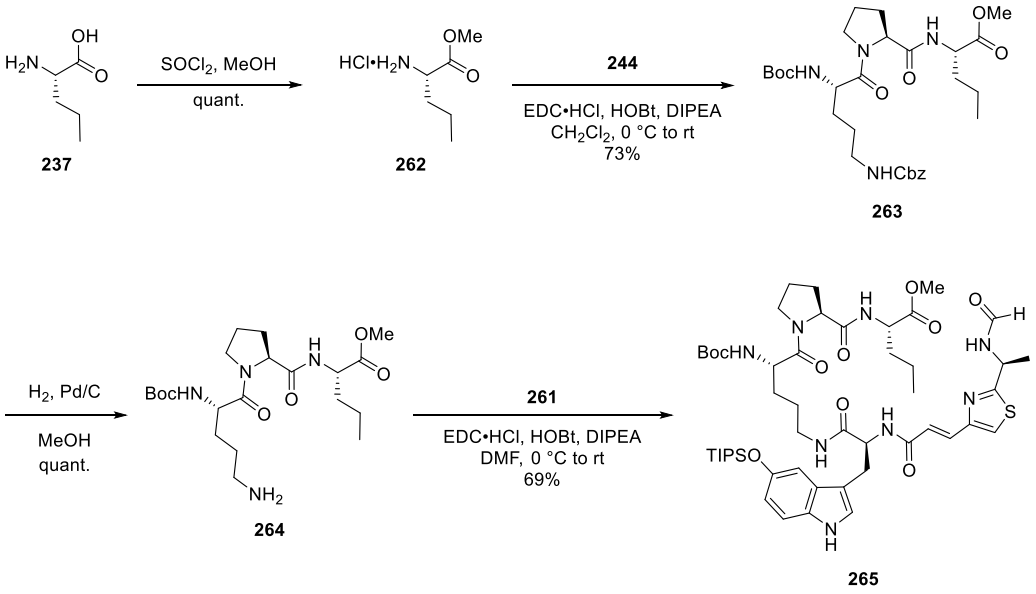
Methyl (*S*)-2-((*E*)-3-(2-((S)-1-formamidoethyl)thiazol-4-yl)acrylamido)-3-(5-((triisopropylsilyl)oxy)-1*H*-indol-3-yl)propanoate (260)

To a solution of crude **259** (12.0 mmol) and crude **225** (12.0 mmol) in DMF (120 mL) was added DIPEA (8.4 mL, 48.0 mmol, 4.0 equiv) dropwise at 0 °C. After stirring at 0 °C for 20 min, HOBt (3.24 g, 24.0 mmol, 2.0 equiv) and EDC·HCl (4.60 g, 24.0 mmol, 2.0 equiv) were added at the same temperature. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. Sat. aq. NH_4Cl was added and the mixture was extracted with EtOAc. The combined organic layers were washed with H_2O (6 times) and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 2% to 5% MeOH/CH_2Cl_2) to yield **260** in 65% yield (4.67 g, 7.80 mmol).

(*S*)-2-((*E*)-3-(2-((*S*)-1-Formamidoethyl)thiazol-4-yl)acrylamido)-3-(5-((triisopropylsilyl)oxy)-1*H*-indol-3-yl)propanoic acid (261)

To a solution of **260** (4.67 g, 7.80 mmol, 1.0 equiv) in THF (39 mL) and H_2O (39 mL) was added LiOH (560.4 mg, 23.4 mmol, 3.0 equiv). The resulting solution was stirred at room temperature for 4 h. The mixture was then evaporated to dryness, the residue was dissolved in H_2O and then acidified with 1 M

HCl until pH = 4. The mixture was extracted with EtOAc and the combined organic layer was dried over Na_2SO_4, filtered and evaporated to dryness to give **261** in quantitative yield which was used directly for the next step without purification.



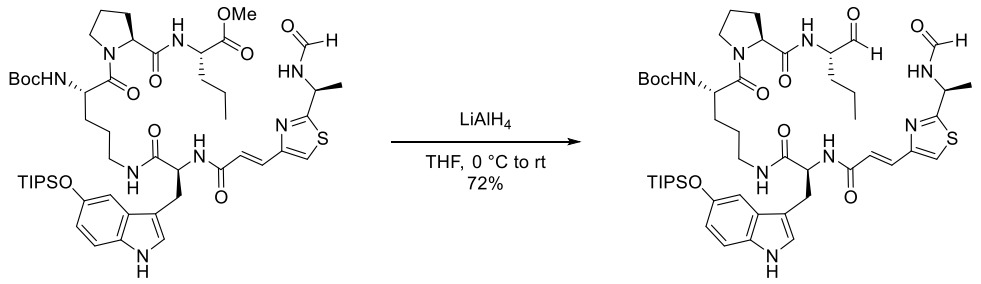
Methyl (*S*)-2-((*S*)-1-((*S*)-5-(((benzyloxy)carbonyl)amino)-2-((*tert*-butoxycarbonyl)amino)-pentanoyl)pyrrolidine-2-carboxamido)pentanoate (263)

To a solution of L-norvaline (2.34 g, 20.0 mmol, 1.0 equiv) in MeOH (20 mL) was added $SOCl_2$ (1.9 mL, 26.0 mmol, 1.3 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred at 40 °C for 16 h. After completion of reaction, the reaction mixture was evaporated to dryness to give **262** as colorless solid in quantitative yield which was used directly for the next step without purification.

To a solution of crude **262** (20.0 mmol) and crude **244** (20.0 mmol) in CH_2Cl_2 (200 mL) was added DIPEA (14.0 mL, 80.0 mmol, 4.0 equiv) dropwise at 0 °C. After stirring at 0 °C for 20 min, HOBt (5.40 g, 40.0 mmol, 2.0 equiv) and EDC·HCl (7.67 g, 40.0 mmol, 2.0 equiv) were added at the same temperature. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. Sat. aq. NH_4Cl was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 2% to 5% MeOH/CH_2Cl_2) to yield **263** in 73% yield (8.36 g, 14.5 mmol).

Methyl (*S*)-2-((*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-5-((*S*)-2-((*E*)-3-(2-((*S*)-1-formamidoethyl)thiazol-4-yl)acrylamido)-3-(5-((triisopropylsilyl)oxy)-1*H*-indol-3-yl)propanamido)pentanoyl)pyrrolidine-2-carboxamido)pentanoate (265)

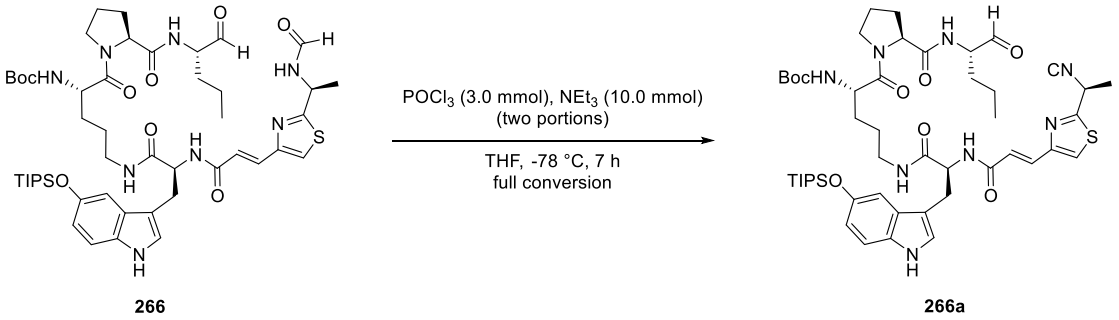
To a solution of **263** (4.50 g, 7.8 mmol, 1.0 equiv) in MeOH (78 mL) was added 10% Pd/C (393.7 mg). The resulting mixture was stirred at room temperature under H_2 balloon for 4 h. The mixture was filtered through a pad of Celite (rinsed with MeOH) and the filtrate was evaporated to dryness. The residue together with the crude **261** (7.8 mmol) was dissolved in DMF (78 mL). DIPEA (5.4 mL, 31.2 mmol, 4.0 equiv) was added dropwise at 0 °C. After stirring at 0 °C for 20 min, HOBt (2.11 g, 15.6 mmol, 2.0 equiv) and EDC·HCl (2.99 g, 15.6 mmol, 2.0 equiv) were added at the same temperature. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. Sat. aq. NH_4Cl was added and the mixture was extracted with EtOAc. The combined organic layers were washed with H_2O (6 times) and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 2% to 10% MeOH/CH_2Cl_2) to yield **265** in 69% yield (5.43 g, 5.38 mmol).



265 266

***tert*-Butyl ((*S*)-5-((*S*)-2-((*E*)-3-(2-((*S*)-1-formamidoethyl)thiazol-4-yl)acrylamido)-3-(5-((triisopropylsilyl)oxy)-1*H*-indol-3-yl)propanamido)-1-oxo-1-((*S*)-2-(((*S*)-1-oxopentan-2-yl)carbamoyl)pyrrolidin-1-yl)pentan-2-yl)carbamate (266)**

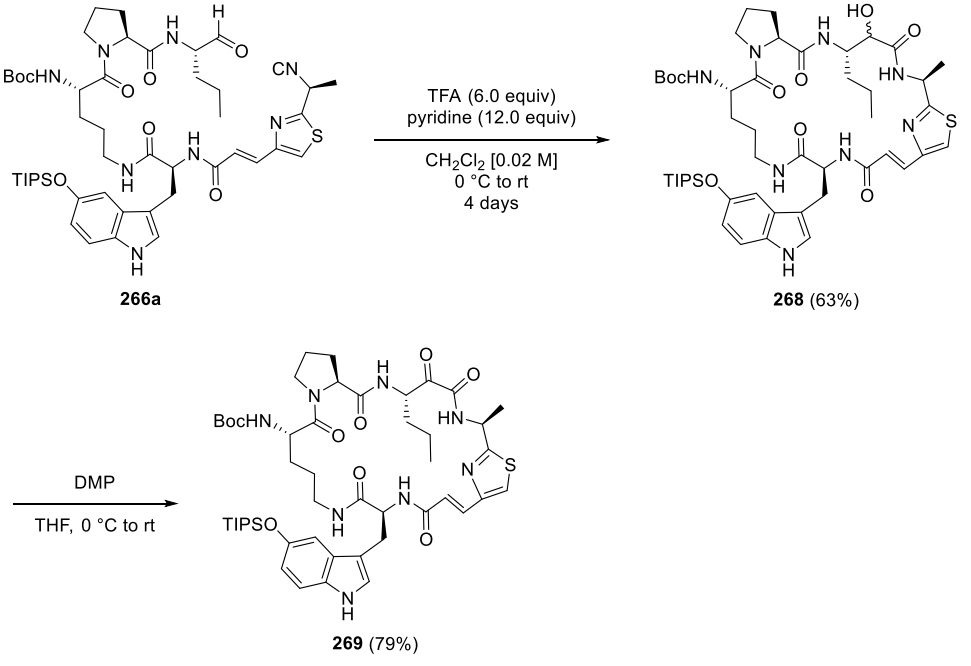
To a solution of **265** (4.24 g, 4.2 mmol, 1.0 equiv) in THF (42 mL) was added $LiAlH_4$ (478.2 mg, 12.6 mmol, 3.0 equiv) portionwise at 0 °C. The resulting suspension was allowed to warm to room temperature and stirred for 15 h. After completion, MeOH (5 mL) was added followed by the addition of sat. aq. Rochelle's salt. After stirring for 2 h, the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 2% to 10% MeOH/CH_2Cl_2) to yield **266** in 72% yield (2.94 g, 3.0 mmol).



266 **266a**

***tert*-Butyl ((*S*)-5-((*S*)-2-((*E*)-3-(2-((*S*)-1-isocyanoethyl)thiazol-4-yl)acrylamido)-3-(5-((triisopropylsilyl)oxy)-1*H*-indol-3-yl)propanamido)-1-oxo-1-((S)-2-(((S)-1-oxopentan-2-yl)carbamoyl)pyrrolidin-1-yl)pentan-2-yl)carbamate (266a)**

To a solution of **266** (1.0 equiv) in dry CH_2Cl_2 (0.3 M) was added NEt_3 (5.0 equiv) and $POCl_3$ (1.5 equiv) dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 3 h. After completion of reaction, the mixture was quenched with saturated Na_2CO_3 at -78 °C, allowed to warm to room temperature and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness to provide the ω-isocyanoaldehyde which was used for the next step without further purification.

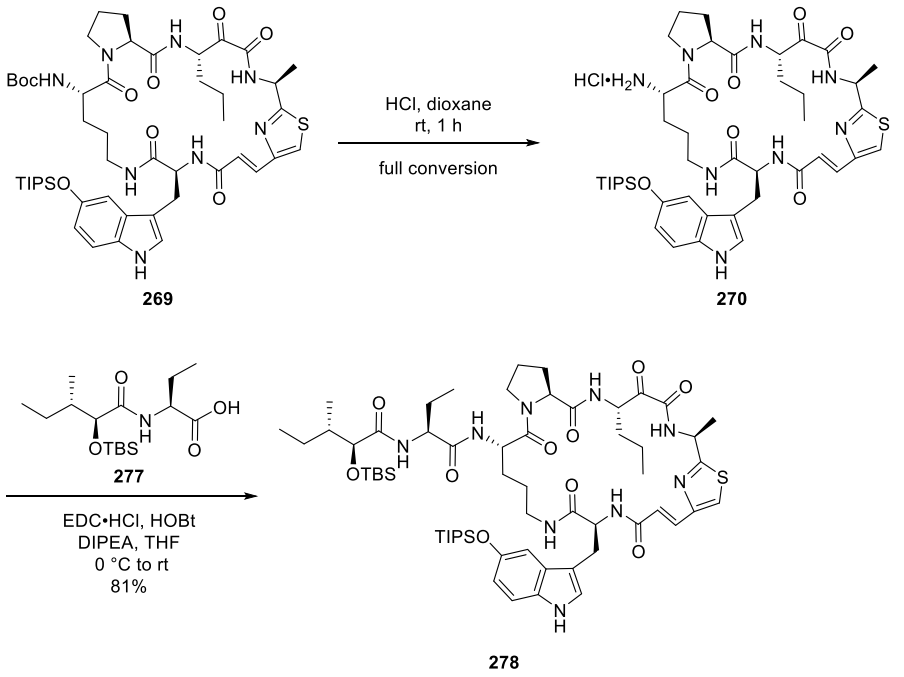


266a **268** (63%) **269** (79%)

***tert*-Butyl ((1^2*Z*,9^2*S*,2*S*,6*S*,11*S*,17*S*,20*E*)-2-methyl-4,5,8,10,16,19-hexaoxo-6-propyl-17-((5-((triisopropylsilyl)oxy)-1*H*-indol-3-yl)methyl)-3,7,15,18-tetraaza-1(2,4)-thiazola-9(2,1)-pyrrolidinacyclohenicosaphan-20-en-11-yl)carbamate (269)**

To a solution of crude **266a** (19.2 mg, 0.02 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) were added pyridine (20 μL, 0.24 mmol, 12.0 equiv) and TFA (10 μL, 0.12 mmol, 6.0 equiv) respectively at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 4 days. The mixture was evaporated to dryness and the residue was dissolved in EtOAc. Saturated $NaHCO_3$ was added and the mixture was stirred at room temperature for 1 h. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 3% to 10% MeOH/CH_2Cl_2) to yield **268** in 63% yield (12.3 mg, 0.013 mmol).

To a solution of **268** (303.6 mg, 0.31 mmol, 1.0 equiv) in THF (31 mL) was added DMP (657.4 mg, 1.55 mmol, 5.0 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 24 h. Saturated $NaHCO_3$ was added and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 3% to 10% MeOH/CH_2Cl_2) to yield **269** in 75% yield (227.2 mg, 0.23 mmol).



(2*S*,3*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methyl-*N*-((*S*)-1-(((1^2*Z*,9^2*S*,2*S*,6*S*,11*S*,17*S*,20*E*)-2-methyl-4,5,8,10,16,19-hexaoxo-6-propyl-17-((5-((triisopropylsilyl)oxy)-1*H*-indol-3-yl)methyl)-3,7,15,18-tetraaza-1(2,4)-thiazola-9(2,1)-pyrrolidinacyclohenicosaphan-20-en-11-yl)amino)-1-oxobutan-2-yl)pentanamide (278)

A solution of **269** (97.7 mg, 0.1 mmol, 1.0 equiv) in 4 M HCl in dioxane (1.0 mL) was stirred at room temperature for 1 h. The mixture was then evaporated to dryness. The residue and **277** (132.6 mg, 0.4

mmol, 4.0 equiv) were dissolved in THF (10 mL). DIPEA (0.3 mL, 1.6 mmol, 16.0 equiv) was added dropwise at 0 °C. After stirring at 0 °C for 20 min, HOBt (108.1 mg, 0.8 mmol, 8.0 equiv) and EDC·HCl (153.4 mg, 0.8 mmol, 8.0 equiv) were added at the same temperature. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. Sat. aq. NH_4Cl was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, 3% to 10% MeOH/CH_2Cl_2) to yield **278** in 81% yield (95.2 mg, 0.08 mmol).

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EDUCATION

2008-2012	Prince of Songkla University, Hat Yai, Thailand Bachelor of Science in Chemistry; GPA: 3.75 (first class honors)
2012-2015	Prince of Songkla University, Hat Yai, Thailand Master of Science in Organic Chemistry; GPA: 4.00
2015-2016	Mahidol University, Bangkok, Thailand Doctor of Philosophy Program in Chemistry (International Program); GPA: 4.00
2017-2021	Ecole Polytechnique Fédérale de Lausanne (EPFL), Switzerland Doctor of Philosophy Program in Chemistry

SCHOLARSHIP

2008-present	A scholarship from the Development and Promotion of Science and Technology Talents Project (DPST Project)

RESEARCH EXPERIENCE

2017-2021	Ecole Polytechnique Fédérale de Lausanne (EPFL), Switzerland
	Doctoral assistant
	Advisor: Professor Jieping Zhu
	Topic: Macrocyclization of ω-Isocyanoaldehydes and Towards the Total Synthesis of Jamaicensamide A
2015-2016	Mahidol University, Bangkok, Thailand
	Graduate Research Assistant
	Advisor: Associate Professor Dr. Chutima Kuhakarn
	Topic: Iodine catalysis
June, 2014-	Swiss Federal Institute of Technology Zürich (ETH Zürich), Switzerland
March, 2015	Visiting Student
	Advisor: Professor Dr. Jeffrey W. Bode
	Topic: SnAP Hydrazine Reagent for the Synthesis of Oxadiazepine Derivatives
April, 2012-	Prince of Songkla University, Hat Yai, Thailand
2015	Graduate Research Assistant
	Advisor: Assistant Professor Dr. Juthanat Kaeobamrung
	Topic: Cu(I)-Catalyzed Domino Synthesis of Quinazolinone Derivatives
November, 2011-	Prince of Songkla University, Hat Yai, Thailand
March, 2012	Undergraduate Research Assistant
	Advisor: Dr. Juthanat Kaeobamrung
	Topic: Convenient One-pot Reaction for Fast Access to Dihydroisoxazole Derivatives via 1,3-Dipolar Cycloaddition Reactions
June-October, 2011	Prince of Songkla University, Hat Yai, Thailand
	Undergraduate Research Assistant
	Advisor: Professor Dr. Vatcharin Rukachaisirikul
	Topic: Metabolites from the Endophytic Ascomycete Fungus PSU-PE0124

March-May, 2010 Prince of Songkla University, Hat Yai, Thailand

Undergraduate Research Assistant

Advisor: Professor Dr. Vatcharin Rukachaisirikul

Topic: Chemical Constituents from the Leaves of *Garcinia bancana*

PERSONAL SKILL

Skills in Organic Chemistry

- Natural products (structural elucidation, separation)
- Methodology

Technical Skills

- UV-Vis spectroscopy
- NMR spectroscopy
- IR spectroscopy
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Computer Skills

- Microsoft Offices (Word, Excel, Powerpoint)
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