Synthetic Studies on Haouamine A and Other Biologically Active Heterocycles

by

Chenbo Wang

BS, Peking University, 2000

MS, Washington State University, 2003

Submitted to the Graduate Faculty of

Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2010

UNIVERSITY OF PITTSBURGH

FACULTY OF ARTS AND SCIENCES

This thesis was presented

by

Chenbo Wang

It was defended on

December 16, 2009

and approved by

Craig Wilcox, Professor, Department of Chemistry

Kazunori Koide, Associate Professor, Department of Chemistry

Barry Gold, Professor, Department of Pharmaceutical Science

Thesis Director: Peter Wipf, Distinguished University Professor, Department of Chemistry

Synthetic Studies on Haouamine A and Other Biologically Active Heterocycles

Chenbo Wang, PhD

University of Pittsburgh, 2010

The first section of this dissertation describes the synthesis of a tethered macrocyclic ring system based on the natural product westiellamide. As expected, this system was shown to increase the affinity and ease of complexation to Ag(I) ions as confirmed by NMR and fluorescence Ag(I) titration studies.

The second section describes the synthesis of a new series of heterocyclic inhibitors of the BoNT serotype A metalloprotease based on the therapeutic lead NSC 240898. Preliminary structure-activity relationship studies afford detailed insights into the steric and electrostatic properties of the pharmacophore of this molecular scaffold. Four of the newly synthesized inhibitors exhibited elevated inhibition against BoNT/A LC when compared to the lead agent.

The third section describes an approach towards the total synthesis of haouamine A. A promising route to the marine alkaloid was established, including a highly efficient Suzuki cross-coupling reaction, aldol condensation and aromatization reaction. Several late-stage intermediates were analyzed by X-ray diffraction to provide valuable information about the relationships between conformation and reactivity.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

Ac.....acetyl

Bpin…….. 4,4,5,5-tetramethyl-1,3,2-dioxaborolane

Bn.....benzyl

Boc.....*tert*-butyloxycarbonyl

BuLi..…….*n*-butyllithium

cat.....catalytic

Cbz.....benzyloxycarbonyl

COSY…….correlation spectroscopy

Cp.....cyclopentadienyl

CSA……camphorsulfonic acid

Cy…….. cyclohexyl

DBU.....1,8-diazabicyclo[5.4.0]undec-7-ene

DCC……...dicyclohexylcarbodiimide

DCE……dichloroethane

DEAD…….diethyl azodicarboxylate

DIBAL……diisobutylaluminium hydride

DIPEA……N,N-diisopropylethylamine

DMAP.....4-dimethylaminopyridine

DMDO…..…dimethyldioxirane

DMF.....*N*,*N*-dimethylformamide

DMPU……1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

DMS……...dimethyl sulfide

DMSO.....dimethylsulfoxide

DMPU……1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone

DPEPhos…….Bis(2-diphenylphosphinophenyl)ether

DPPA…..... diphenylphosphoryl azide

dr.....diastereomeric ratio

EDCI……..1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

ESI…….electrospray ionization

equiv...……...equivalent(s)

HATU...…….2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

HMBC……heteronuclear multiple bond correlation

HMQC……heteronuclear multiple quantum coherence

HPLC.....high performance liquid chromatography

HRMS……high resolution mass spectroscopy

IBCF……...isobutylchloroformate

IR……...infrared spectroscopy

KHMDS..... potassium bis(trimethylsilyl)amide

LAH.....lithium aluminum hydride

LCMS……liquid chromatography mass spectroscopy

LDA…...……lithium diisopropylamide

LHMDS…….lithium bis(trimethylsilyl)amide

MCPBA…….3-chloroperbenzoic acid

NMR……..nuclear magnetic resonance

NMO……..*N*-methylmorpholine oxide

Nu……...…nucleophile

PD……...product

Py……pyridine

TPAP.....tetrapropylammonium perruthenate

RCM……..ring closing metathesis

rt.....room temperature

SM……..…..starting material

TBAF.....tetrabutylammonium fluoride

TBAB……..tetrabutylammonium bromide

TBDPS……...*tert*-butyldiphenylsilyl

TBS.....*tert*-butyldimethylsilyl

TEA……triethyl amine

Tf……trifluoromethanesulfonyl

TFA.....trifluoroacetic acid

THF.....tetrahydrofuran

TIPS.....triisopropylsilyl

TLC.....thin layer chromatography

TMS.....trimethylsilyl

Tosyl.....*p*-toluenesulfonyl

TS……...……transition state

PREFACE

I extend my sincere appreciation to Professor Peter Wipf for the opportunity to study in his laboratories and giving me a vigorous training. I also thank the members of my dissertation committee, Professor Craig Wilcox, Professor Kazunori Koide and Professor Barry Gold. Our collaborators at the National Cancer Institute are acknowledged for conducting the biological evaluations of Botulinum Neurotoxin Metalloprotease inhibitors. I'd like to thank Dr. Markus Furegati for his excellent work on a model system of haouamine A. I thank the past and present members of the Wipf group and Michelle Woodring for her help throughout the years. I also thank Dr. Fu-Tyan Lin and Dr. Damodaran Krishnanachary for NMR spectroscopy, Dr. Kasi Somayajula and Dr. John Williams for mass spectroscopy and Dr. Steven J. Geib for x-ray crystallography. Funding was provided by the National Institutes of Health. Roche is acknowledged for providing a graduate research award. I thank Prof. Timothy Jamison and Prof. Amos B Smith for helpful suggestions. On a personal note, I thank Filip Petronijevic for his friendship and inspiring spirit. I thank Professor Jiaxi Xu for introducing me to organic synthesis. Finally, I thank my family for their continued support and encouragement.

1.0 SYNTHESIS OF TETHERED BIS-OXAZOLINE LIGANDS FOR SILVER(I) BINDING STUDY

1.1 INTRODUCTION

1.1.1 Silver Recovery

Silver has long been an important metal in industry. It finds broad applications in areas such as medicine, photography, electronic industry and jewelry. The recovery of silver from waste solutions has not only commercial importance, but also an environmental advantage. Because there are legal limits on silver concentrations in municipal water supplies.[1] It has been estimated[2] that over 1000 tons of silver are recycled annually in the US, followed by Japan with about 500 tons.

The concentration of silver in photographic waste ranges from over 5 g/L to less than 1 mg/L.[3] Several traditional silver recovery methods are available (Table 1).[3-4] Generally, these methods suffer from a high silver leaching level and low cation selectivity. Owing to the low silver concentration and abundance of other cations in waste solutions, new methods are needed for recycling silver.

Table 1 Comparison of conventional silver recovery methods

Recovery Method	*Description*	*Advantages*	*Disadvantages*
Electrolysis	An electric current reduces the silver and plates silver metal onto an electrode	Obtain >90% pure silver	High capital costs, low removal efficiency (90%), requires high silver concentration in waste
Ion Exchange	Exchange the silver on an ion-exchange resin	98 – 99.99% removal efficiency from dilute solutions	High capital costs, low capacity of the resin
Metallic Replacement	Exchange silver with solid iron through an oxidation-reduction reaction	Low capital costs, low maintenance, 99% removal possible with 2 units	High smelting and refining costs, monitoring required for replacement
Precipitation	Precipitate silver by Na_2S	>99% removal possible	Moderate to high operation costs, , handling of harsh chemicals, messy sludge
Reverse Osmosis	A semi-permeable membrane separates large molecules from small ones	Up to 90% efficiency on dilute waste	High capital and operation costs

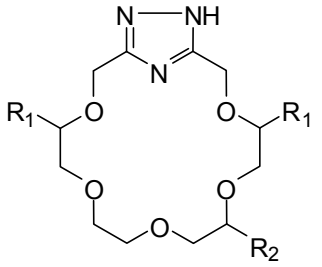
Recently, a few new methods utilizing ligands with high affinity and selectivity towards silver have emerged. Tri-isobutylphosphine sulfide (TIBPS) was found to bind to silver, forming a $Ag(TIBPS)_2NO_3$ complex.[5] It was demonstrated that TIBPS was able to selectively extract silver in the presence of Cu(II), Ni(II) and Fe(III)[6] (Table 2). However, in this experiment a nitrate counter anion was required.

Table 2 Extraction of silver in the presence of other metals by TIBPS

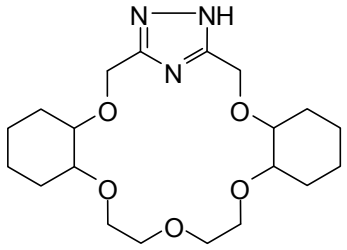
Metal	Initial concentration in donor solution (mM)	Concentration in acceptor solution after 4 h (mM)
Ag(I)	12.0	7.18
Cu(II)	107.0	0.17
Zn(II)	88.7	0.31
Ni(II)	78.3	0.09

Another extracting method is the use of macrocyclic compounds, in particular hetero crown ethers. Hetero crown ethers are known to interact with soft cations better than hard ones due to the soft nature of the nitrogen or sulfur atoms in the ring.[7] Izatt *et al.*[8] demonstrated the feasibility of selective uptake of Ag(I) over Pb(II) and Tl(I) using 18-crown-6 type macrocycles **1-1a**, **1-1b** and **1-2** (Figure 1). The uptake speed of the metals by the macrocycles is listed in Table 3. Other more commonly found transition metals were not tested for selectivity. Another shortcoming is that the concentration of metals used in the experiment is much higher than the concentration found in waste.

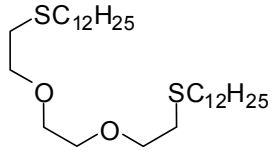
Figure 1 Macrocyclic ligands for silver recovery



1-1a, R_1=H, R_2=*n*-C_8H_{17}
1-1b, R_1=*n*-C_8H_{17}, R_2=H



1-2



1-3

Table 3 Extraction of silver (I) ion in the presence of lead(II) ion by **1-1a**, **1-1b** and **1-2**[a]

Ligand	Ag(I) flux (mol·s^{-1}·m^{-2}×10^8)	Pb(II) flux (mol·s^{-1}·m^{-2}×10^8)
1-1a	1303	73
1-1b	601	8
1-2	1549	8

[a]Initial concentration: 1 M $AgNO_3$, 1 M $Pb(NO_3)_2$

Another group[9] adopted polythioether **1-3** as a ligand and was able to recover the silver (I) in the presence of Cu(II) (Figure 1). However, this ligand class was totally inhibited by Pd(II).

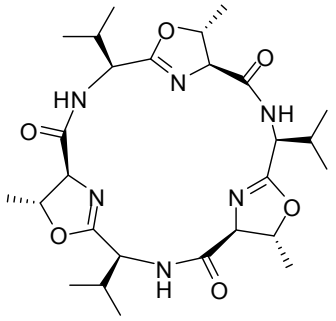
An even more appealing idea is to extract silver from sea water. The major difficulty is the low abundance of Ag(I) in sea water (average 0.24 ug/L[10]). Precipitation by a $NaOH/FeCl_2/Na_2CO_3$ mixture has been tested[11] and proved to be both cost and labor intensive. Another report[12] suggested the use of ion-exchange resins, which may suffer from selectivity, capacity and durability.

In the search for a better ligand for silver, we turned our attention to the marine metabolites, or more specifically, *Lissoclinum* cyclic peptides.

1.1.2 Lissoclinum Cyclopeptides and Their Binding to Metal Ions

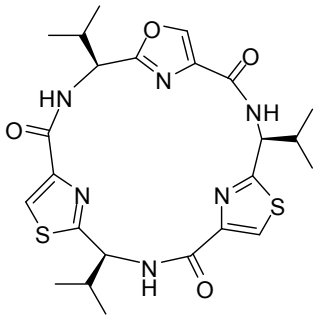
Marine metabolites have received much attention in recent years due to their unprecedented structures and attractive biological activities.[13] The genus Lissoclinum has proven itself as a rich source of cyclopeptide alkaloids featuring multiple oxazolines, thiazolines, oxazoles, or thiazoles (Figure 2). [13-14]

Figure 2 *Lissoclinum* cyclopeptides



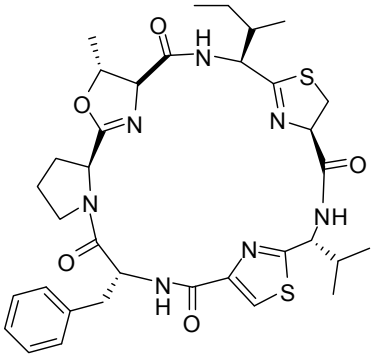
Cycloxazoline (Westiellamide)

1-4



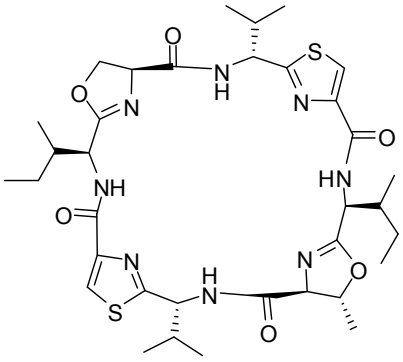
Bistratamide C

1-5



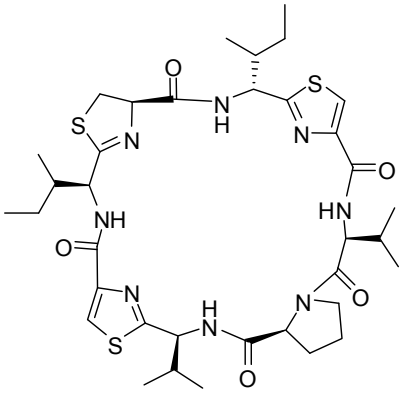
Lissoclinamide 9

1-6



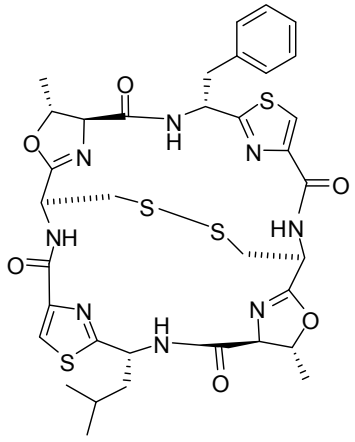
Patellamide A

1-7



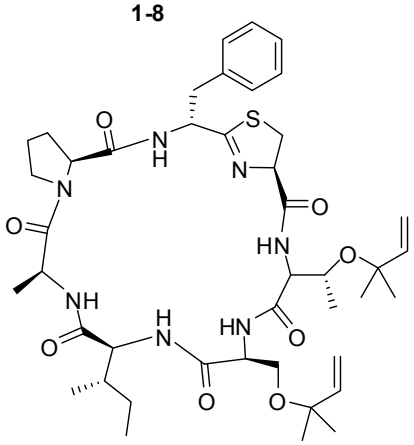
Tawicyclamide B

1-8



Ulithiacyclamide B

1-9



Trunkamide A

1-10

Since these polyheterocycles share structure features with some common macrocyclic ionophores, such as hetero crown ethers and porphyrins,[15] it has been postulated that they might complex to metals, and subsequently transport them *in vivo*. However, so far no metal-complexed *Lissoclinum* cyclopeptides have been isolated from natural sources. In contrast, quite a few studies regarding the complexation of synthetic *Lissoclinum* cyclopeptides with metals have been published. Wipf *et al.*[16] reported the first example of a *Lissoclinum* cyclopeptide complexed with a metal. In this case, westiellamide (**1-4**) was synthesized[17] and screened by NMR with a variety of metal salts for binding, including Na(I), Li(I), K(I), Mg(II), Ce(III), Fe(II), Fe(III), Ni(II), Cu(I), Cu(II), Ag(I), Au(III), Zn(II), Cd(II) and Hg(II). Most of these metal cations showed weak interactions with westiellamide. The sole exception was Ag(I), which was found to form a $[(\mathbf{1\text{-}4})_2Ag_4]^{4+}$ complex with an association constant of $>10^5 M^{-5}$. The binding of four silver ions was a highly cooperative process, and no intermediates could be seen by NMR. The structure of the complex was determined by X-ray crystallography (Figure 3). In this complex, a trigonal-planar Ag_4 cluster was sandwiched between two westiellamide molecules. The center Ag ion coordinated to the six backbone carbonyls, while the outside Ag ions bound to the nitrogen atoms of the oxazoline rings in a nearly linear arrangement. It is also worthy to mention the conformational change of westiellamide upon binding. Figure 4 compares the crystal structure of **1-4** with and without[18]Ag. The unbound **1-4** is rather flat and has its isopropyl sidechains adopting pseudoaxial positions while the oxazoline nitrogens point inwards. Upon binding, the sidechains adopt pseudoequatorial positions, while the backbone carbonyl oxygens point inwards.

Figure 3 Crystal structure of $[(\mathbf{1\text{-}4})_2Ag_4]^{4+}$ complex

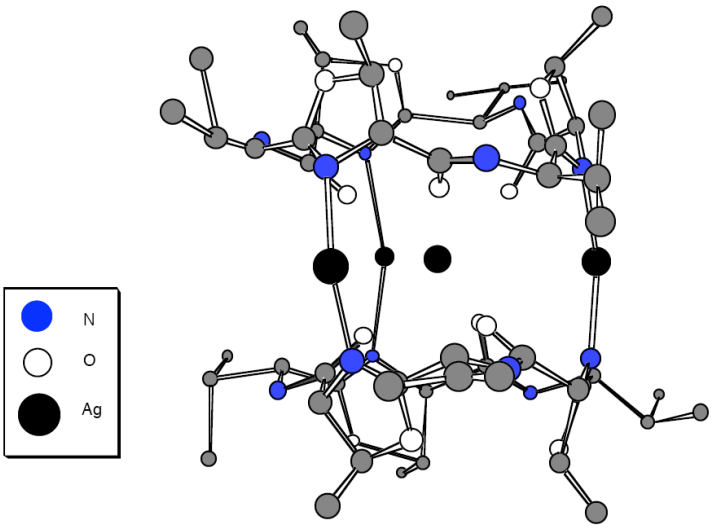
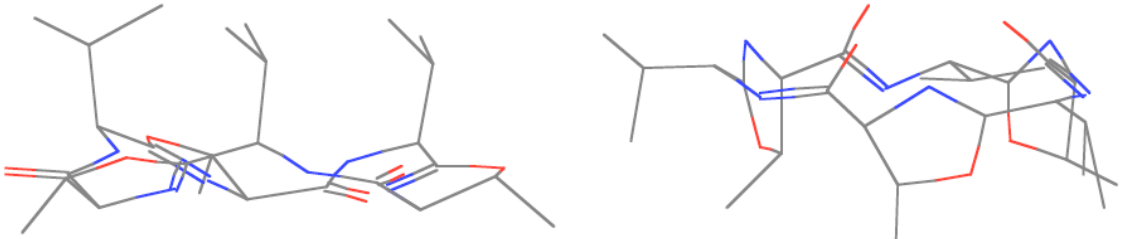
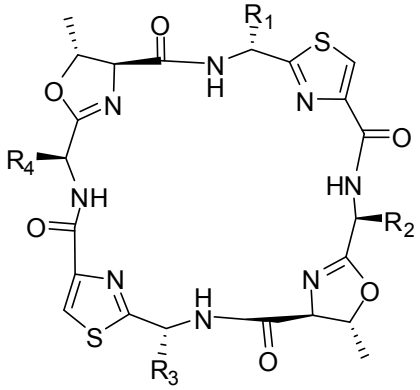


Figure 4 Comparison of crystal structures of uncomplexed and complexed westiellamide



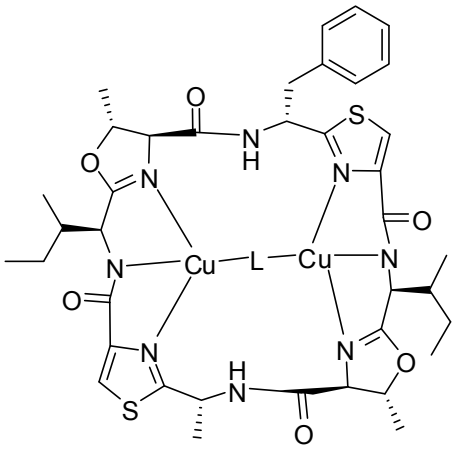
The Hanson group[19] investigated the binding of Cu(II) to patellamide D (**1-13**) ($patH_4$, Figure 5) by electron paramagnetic resonance (EPR), circular dichroism (CD) and mass spectrometry. Multiple mononuclear copper(II) complexes were identified as well as three binuclear complexes ($[Cu_2(patH_2)]^{2+}$, $[Cu_2(patH_2)(OH)]^{+}$ and $[Cu_2(patH_2)(CO_3)]$). A plausible structure for the latter based on the CD spectra is shown in Figure 6 (**1-16**).

Figure 5 Patellamide B-E and ascidiacyclamide

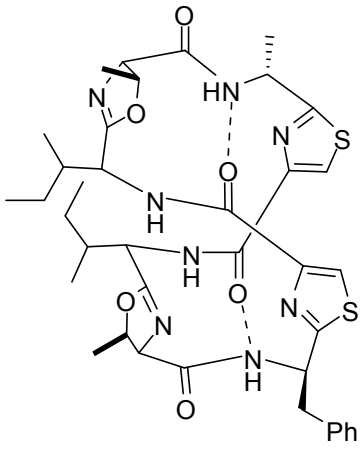


(**1-11**) Patellamide B R_1=D-Phe, R_2=L-Leu, R_3=D-Ala, R_4=L-Ile
(**1-12**) Patellamide C R_1=D-Phe, R_2=L-Val, R_3=D-Ala, R_4=L-Ile
(**1-13**) Patellamide D R_1=D-Phe, R_2=R_4=L-Ile, R_3=D-Ala
(**1-14**) Patellamide E R_1=D-Phe, R_2=R_3=L-Val, R_4=D-Ile
(**1-15**) Ascidiacyclamide R_1=R_3=D-Val, R_2=R_4=L-Ile

Figure 6 $[Cu_2(patH_2)(CO_3)]$ complex (**1-12**) (L=CO_3^{2-}) and solid state structure of patellamide D (**1-13**)



1-16



1-13

The square conformation of **1-16** is in sharp contrast[20] to the twisted "figure eight" conformation of **1-13** in the solid state[21-22] (Figure 6). In the solid state, the cyclopeptide backbone is held together by two intramolecular hydrogen bonds to form a type-II β-turn structure.[23] It was found that symmetrically substituted patellamides (e.g. **1-7**, **1-13**) adopt a square conformation both in the solid state and in solution.[22,24-26] For the asymmetrically

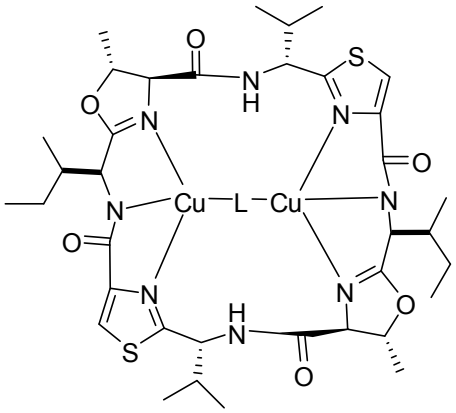
substituted patellamides (e.g. **1-11** to **1-14**), the predominant conformation in the solid state is the twisted "figure eight". In solution, the molecule adopts a relaxed "figure eight" conformation. This preference over the extended square conformation was attributed to the lack of *C*2 symmetry[25] in the molecule or the presence of the dipeptidyl oxazoline moiety in the structure.[27] The same preference was also observed for tawicyclamide (**8**) in the solid state.[25]

Later, patellamides A (**1-7**), B (**1-11**) and E (**1-14**) (Figure 5) were found to bind to Cu(II) and Zn(II) as well.[28] The CD spectra of their metal complex as suggested a square conformation as in the case of patellamide D. The association constants for both Cu(II) and Zn(II) were determined to be in the range of 2×10^4 to 2×10^5 M^{-1} for the first metal complexation. The binding of a second metal to patellamide B has a K_a=230 M^{-1} (Cu^{2+}) and K_a=16-20 M^{-1} (Zn^{2+})[28].

Morris *et al.*[29] further investigated the interaction between patellamides and metal ions and found that patellamide C exhibited excellent selectivity towards Cu(II) in the presence of Zn(II), while patellamide A was less selective. This finding was attributed to the distortion of the planarity of the square conformation of patellamide C and the metal complex by the phenyl side chain. A similar selectivity for lissoclinamide 9 (**1-6**) was found[30] with a $K_a(Cu^{2+})$ value close to that of patellamide B.

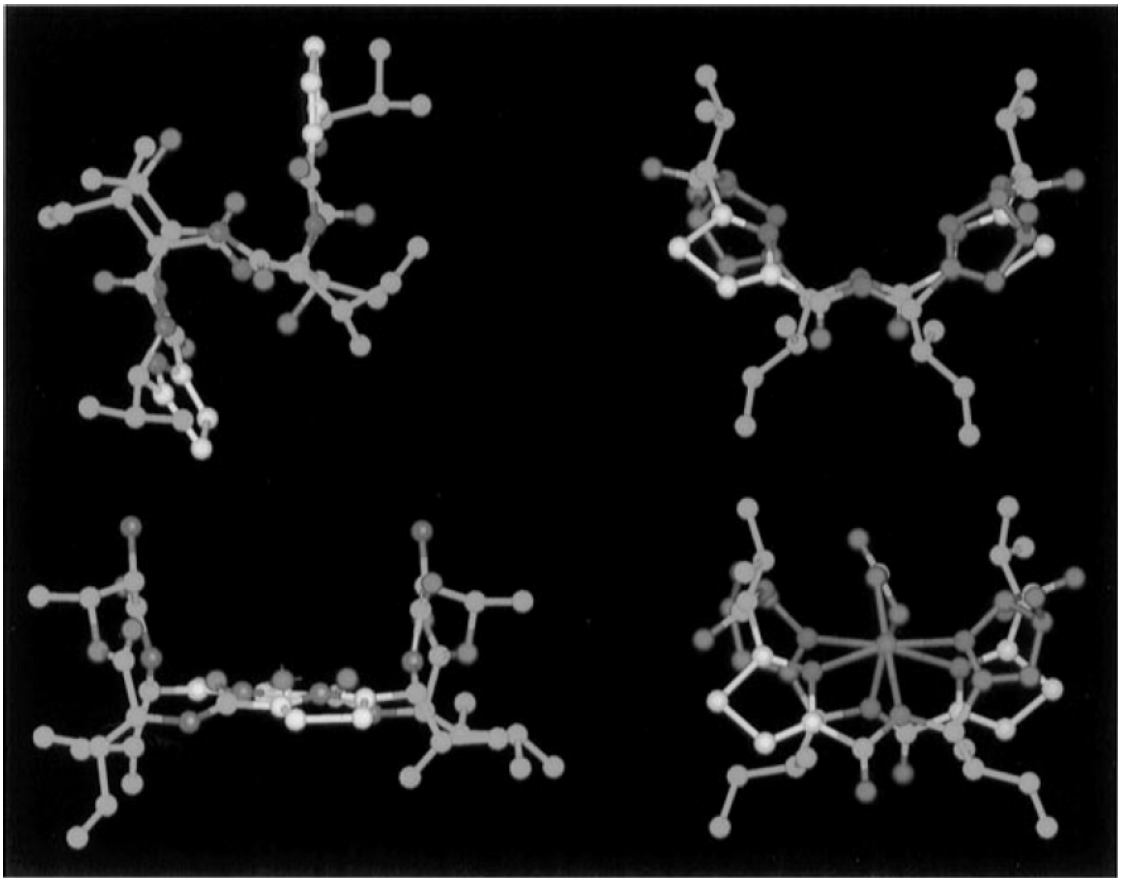
A bis(copper(II)) complex (**1-17**, Figure 7) of ascidiacyclamide (**1-15**) was characterized[31] and its crystal structure (Figure 8, bottom right) was found to be very similar to the binuclear patellamide D-Cu complex. The cyclopeptide backbone in the complex adopts a pseudo-boat rectangular conformation, which is very similar to its metal-free form[32] (Figure 8, top right).

Figure 7 Ascidiacyclamide-Cu complex ($L=CO_3^{2-}$)



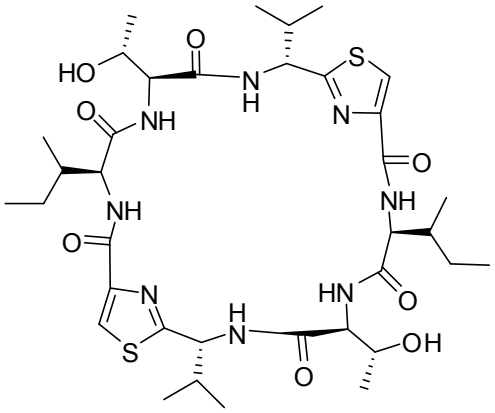
1-17

Figure 8 Conformations of **1-15** (top right)**, 1-17** (bottom right)**, 1-18** (top left)**, 1-19** (bottom left)

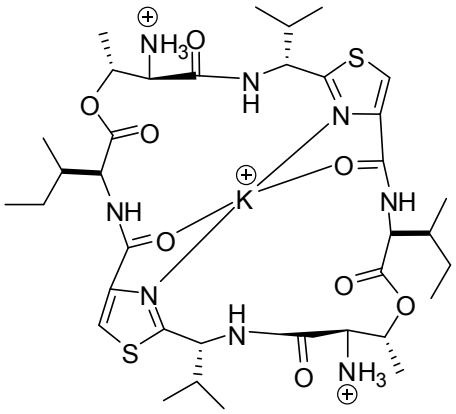


The Hanson group also conducted an in-depth study on the conformation of ascidiacyclamide analogues (Figure 9).[33]

Figure 9 Ascidiacyclamide analogues



1-18



1-19

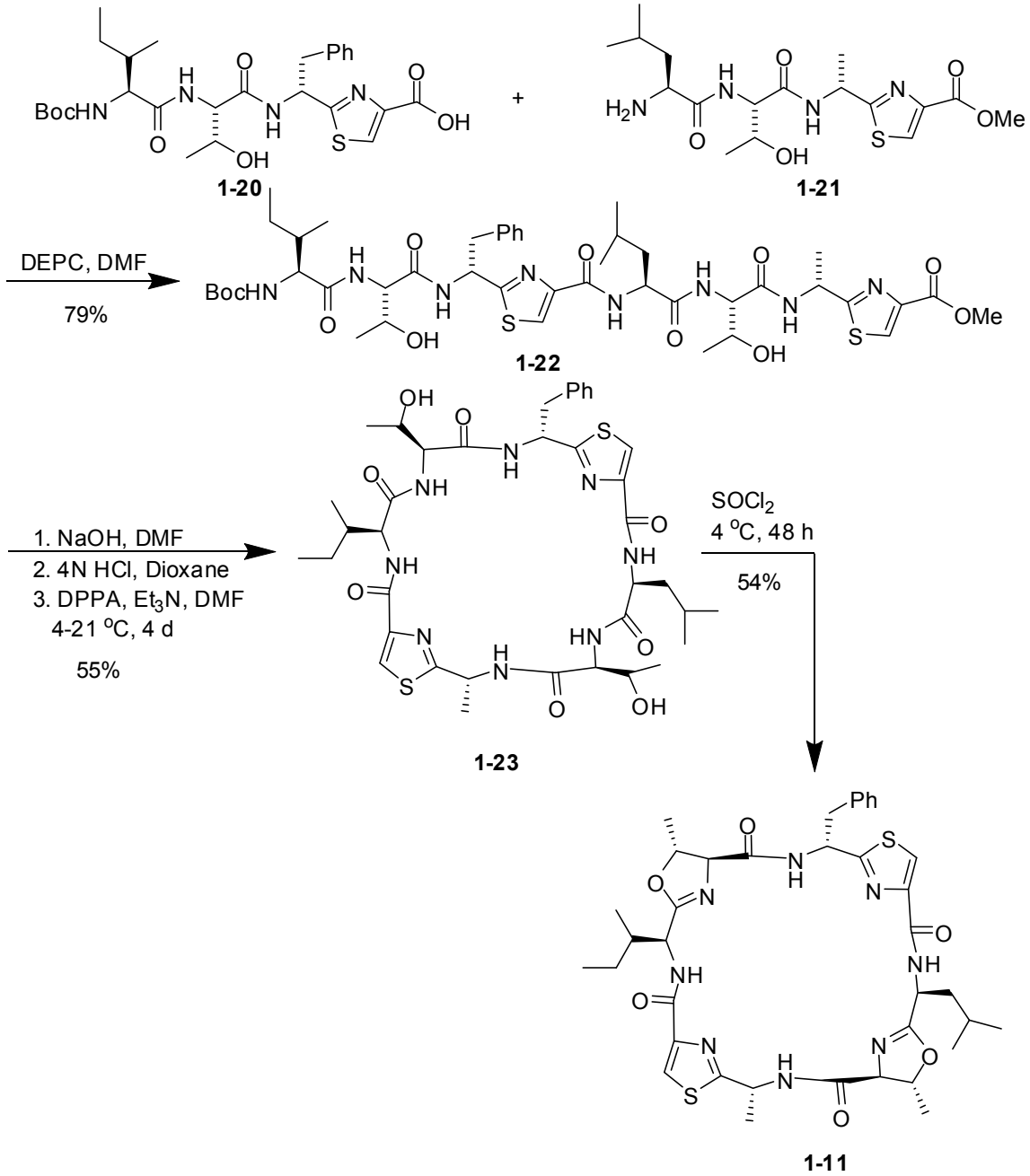
Compound **1-18** is the synthesis precursor of ascidiacyclamide, lacking the oxazoline moiety. It adopted a pseudo-chair conformation in solution as determined by NMR (Figure 8, top left). Compound **1-19** is the hydrolysis product of ascidiacyclamide and was found to bind to a potassium cation.[34] Its crystal structure revealed a pseudo-boat conformation (Figure 8, bottom left).

The Hanson group[35-37] also prepared a series of patellamide analogues and studied their binding to Zn(II) and Ca(II). These analogues differ from their natural counterparts by either shorter side chains (to increase the flexibility of the cyclic peptide) or opened oxazoline rings which reduce ring constraints. Both modifications facilitated the metal binding. Thus, their affinity towards metals increased with the increasing flexibility of the cyclopeptide.

1.1.3 Synthesis of Lissoclinum Cyclopeptides and Their Analogues

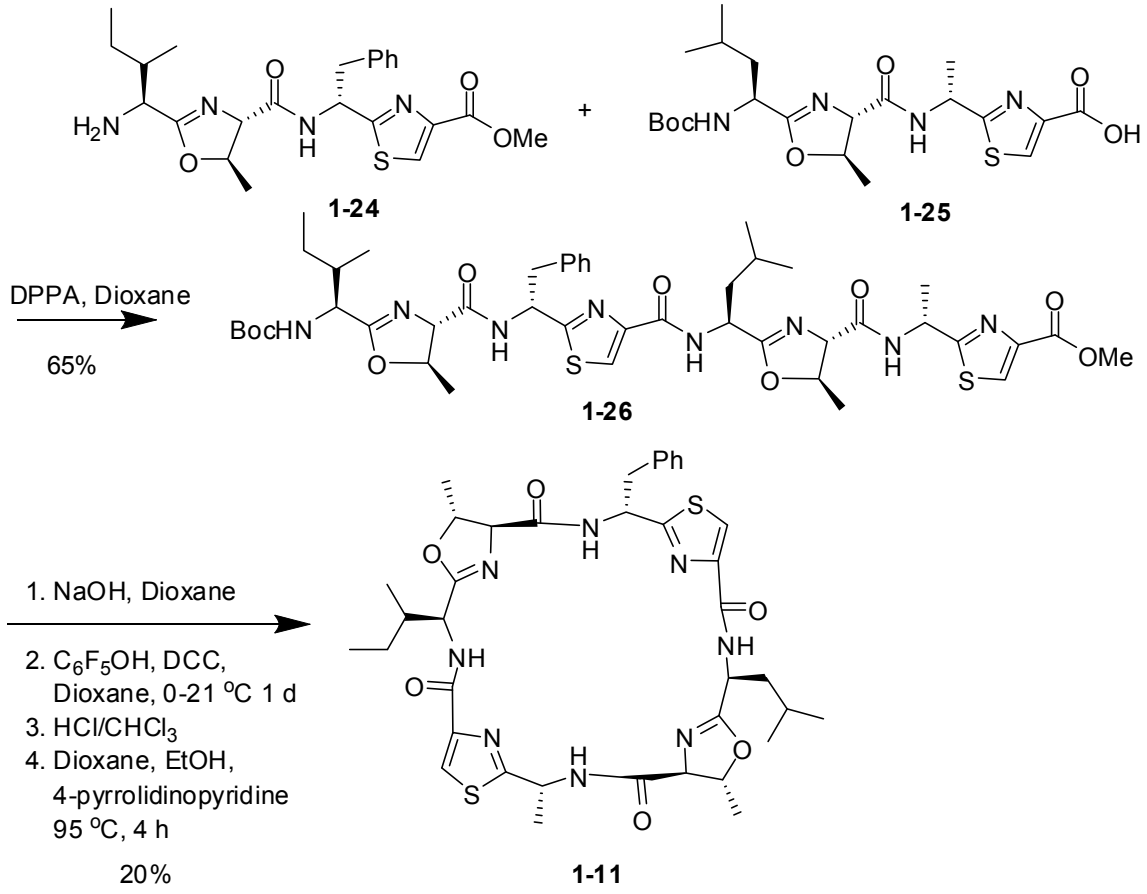
Organic synthesis plays an important role in the study of marine metabolites due to the limited biological availability of these natural products.

Scheme 1 Total synthesis of patellamide B (**1-11**)



The most widely adopted synthetic method for *Lissoclinum* peptides is the macrocyclization strategy as demonstrated in the synthesis of patellamide B[38-39] (Scheme 1). The two segments **1-20** and **1-21,** prepared by stepwise coupling of amino acid building blocks, were coupled to afford **1-22**. Deprotection followed by macrocyclization provided **1-23** in excellent yield (55%). Treatment of **1-23** with thionyl chloride afforded the natural product **1-11** in 54% yield. An alternative approach[40] used the precursor **1-26** with a preformed oxazoline moiety for macrocyclization (Scheme 2). In this case, the troublesome[41] dehydration step to the oxazoline was avoided.

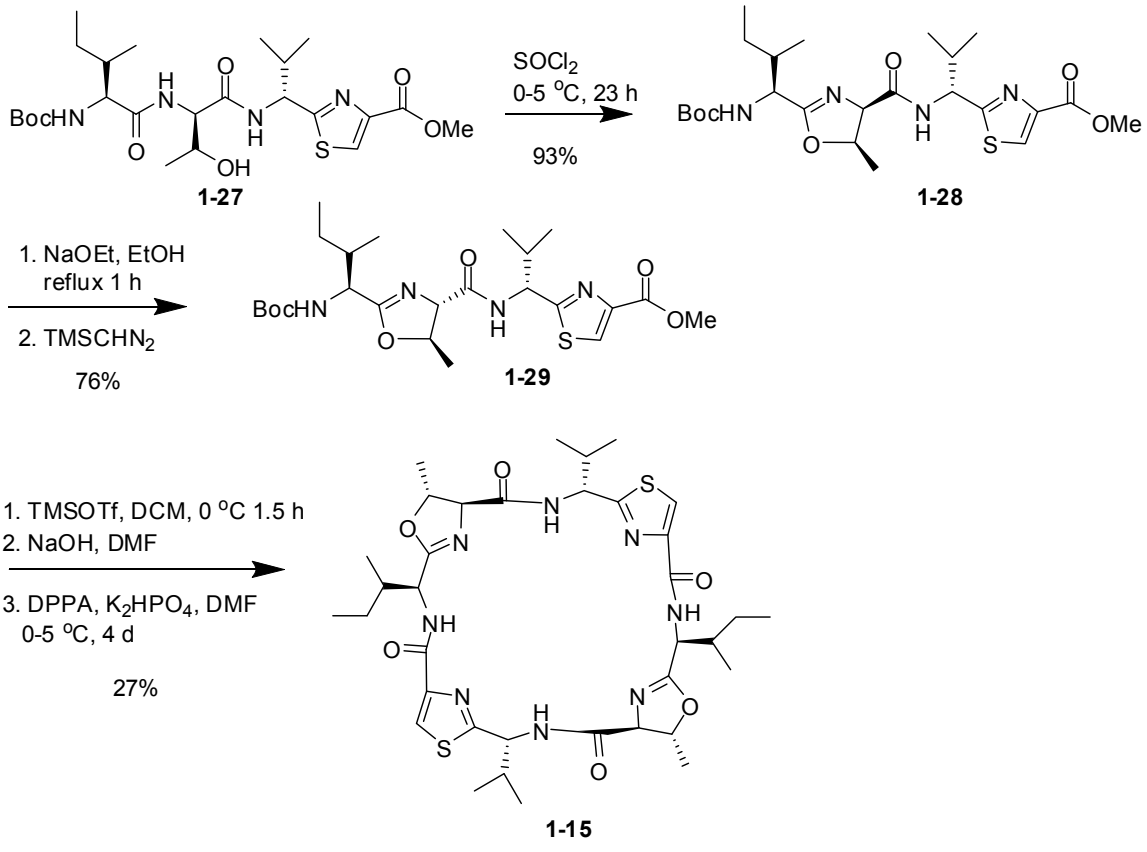
Scheme 2 Synthesis of patellamide B **1-11** with pre-formed oxazoline moiety



One interesting feature of the *Lissoclinum* cyclopeptide synthesis is the ease of macrocyclization. Macrocyclization of polypeptides with α-amino acids devoid of Gly or Pro as building blocks can be troublesome.[42] For *Lissoclinum* peptides, the oxazole/thiazole moiety limits the flexibility of the peptide backbone, while the oxazoline moiety can induce a type II or II' β-turn conformation in the molecule (e.g. patellamide D (**1-13**)), bringing both N- and C-termini together. Both factors are able to facilitate ring closure.

For cyclopeptides with molecular symmetries, a cyclooligomerization approach may be viable. Hamada *et al.*[32] reported the total synthesis of the *C*2 symmetric ascidiacyclamide (**1-15**) (Scheme 3).

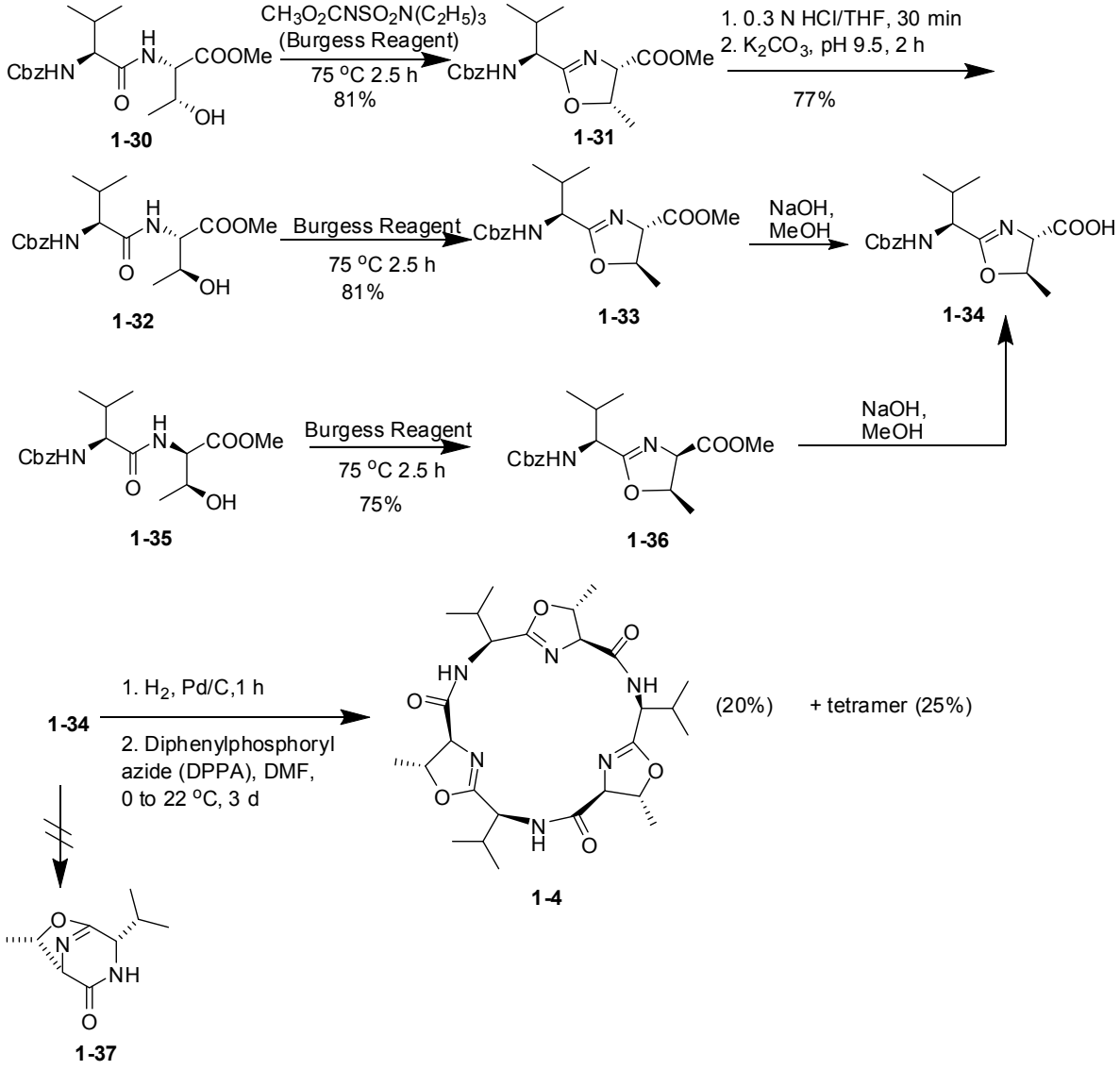
Scheme 3 Total synthesis of ascidiacyclamide **1-15**



The tetrapeptide fragment **1-27** was treated with thionyl chloride to form the oxazoline ring. Epimerization of the oxazoline by NaOMe followed by reesterification with $TMSCHN_2$ afforded building block **1-29**. Deprotection at both termini was followed by cyclodimerization with DPPA, which afforded the natural product in 27% yield.

Wipf *et al.*[17] adopted a cyclotrimerization strategy in the total synthesis of the *C*3 symmetric westiellamide (Scheme 4).

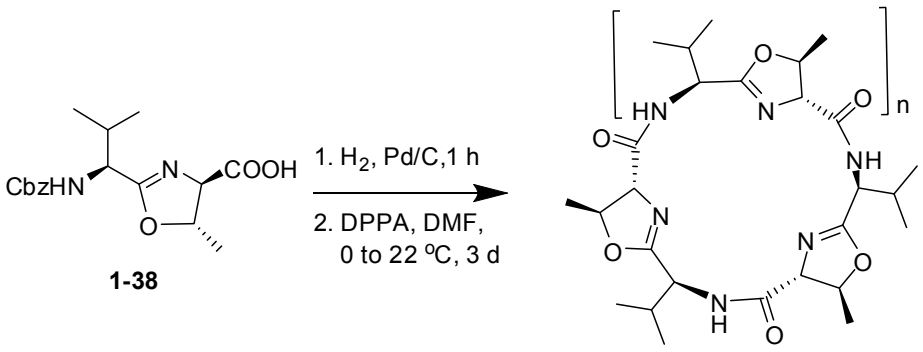
Scheme 4 Total synthesis of westiellamide



The original approach, which included the macrocyclization of the linear hexapeptide sequence followed by oxazoline formation, failed. Thus, attention turned to a cyclooligomerization strategy. Dipeptide **1-30** was treated with Burgess reagent to form the dipeptidyl oxazoline **1-31**.[43] The oxazoline was opened by acid hydrolysis to provide an *O*-acyl amine, which was then rearranged to give Cbz-Val-*allo*-Thr-OMe (**1-32**).[44] Reclosing the oxazoline with Burgess reagent followed by saponification provided **1-34**. Alternatively, **1-34** could be prepared from Cbz-Val-D-Thr-OMe (**1-35**) in two steps. Formation of oxazoline **1-36** was followed by treatment with NaOH to deprotect the methyl ester as well as epimerize the *cis*-oxazoline to the *trans*-configuration. The N-terminus in **1-34** was unmasked and DPPA effected the cyclooligomerization to afford the cyclic trimer **1-4** in 20% yield along with 25% of the cyclic tetramer. The deprotected **1-34** did not cyclize to diketopiperazine **1-37**[42] as a consequence of the rigid *trans*-amide linkage fused in the oxazoline ring.

A double epimer of **1-34** at the C(4) and C(5) position of the oxazoline was prepared[45] and subjected to the same cyclooligomerization conditions (Scheme 5).

Scheme 5 Synthesis of westiellamide analogues

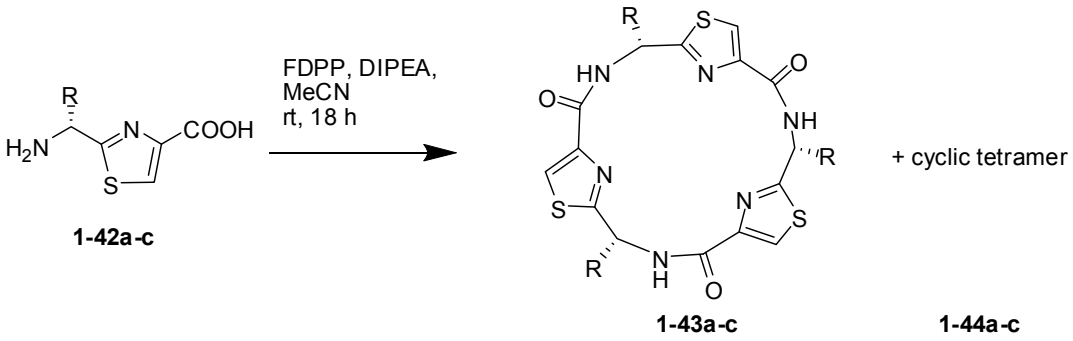


1-39, n=0, 15%
1-40, n=1, 20%
1-41, n=2, 10%

Interestingly, when compared to the westiellamide synthesis, a significant amount of dimer **1-39** was obtained along with less tetramer **1-41**. The x-ray structure of dimer **1-39** revealed that all isopropyl sidechains adopted pseudoequatorial positions, while in case of westiellamide all sidechains were in pseudoaxial positions. Thus, the cyclooligomerization process might be kinetically controlled. The lower repulsion between equatorial sidechains allowed for the formation of smaller ring structures from **1-38**.

The Pattenden group applied the cyclooligomerization strategy to thiazole-containing building blocks[46] and synthesized a series of analogues of *Lissoclinum* cyclopeptides (Scheme 6).

Scheme 6 Cyclooligomerization of dipeptidyl thiazoles



1-42a-c **1-43a-c** **1-44a-c**

R	Yield of cyclic products (%)	Trimer to tetramer ratio
i-Pr (**1-42a**)	91	5:2
Me (**1-42b**)	55	9:2
CH_2Ph (**1-42c**)	63	1:3
i-Pr (*rac*-**1-42a**)	75	1:1 (mixture of diastereomers)

Similar to westiellamide, the sidechains in **1-43a** were found to adopt pseudoaxial orientations. Due to steric reasons, building blocks with larger sidechains favored larger rings (cyclotetramer). As expected, the racemic building block *rac*-**1-42a** yielded a product that contained stereocenters of both configurations to minimize steric repulsion, along with a small amount of product in which all sidechains were in the same configuration.

The Pattenden group has also pioneered the templating effect of metal ions in the cyclooligomerization of **1-42a**[47] (Table 4). They found that small metal ions favor the formation of cyclotrimer while large ions favor cyclotetramer. A silver(I) complex of **1-44a** was identified and shown to be comprised of five silver ions sandwiched between two macrocycles.

Table 4 Cyclooligomerization of **1-42a** with various metal salts

Metal Salt	*Yield %*	*Ratio (trimer:tetramer)*	*Metal*	*Yield %*	*Ratio (trimer:tetramer)*
No metal	95	3:1	$NiCl_2$	78	7:3
$LiBF_4$	57	4:1	$CuCl_2$	-	-
$NaBF_4$	56	3:1	$Cu(BF_4)_2$	-	-
KBF_4	91	7:3	$CoCl_2$	-	-
$CsBF_4$	93	3:1	$AgBF_4$	57	2:1
$ZnCl_2$	81	4:1	NH_4PF_6	30	11:2
$CdCl_2$	41	2:1	$Zn(BF_4)_2$	42	4:1
$Hg(ClO_4)_2$	35	3:1	$Zn(OAc)_2$	-	-

The same group also investigated the templating effect of metal ions in the synthesis of nostocyclamide (**1-48**), which bears no symmetry element (Scheme 7).[48]

Cyclization of a 1:1:1 mixture of **1-45, 1-46** and **1-47** yielded 21% of the natural product **1-48** together with 23% of the positional isomer **1-49** and 21% of by-product **1-50** plus other cyclotrimers. When metal salts were added, the overall yield dropped significantly. The ratio of the three major isomers **1-48, 1-49** and **1-50** also underwent significant changes (Table 5). It is noteworthy that in the presence of $AgBF_4$ the cyclic trimer **1-50** was the only product. However, no explanation was provided for this selectivity.

Scheme 7 Metal ion templated synthesis of nostocyclamide

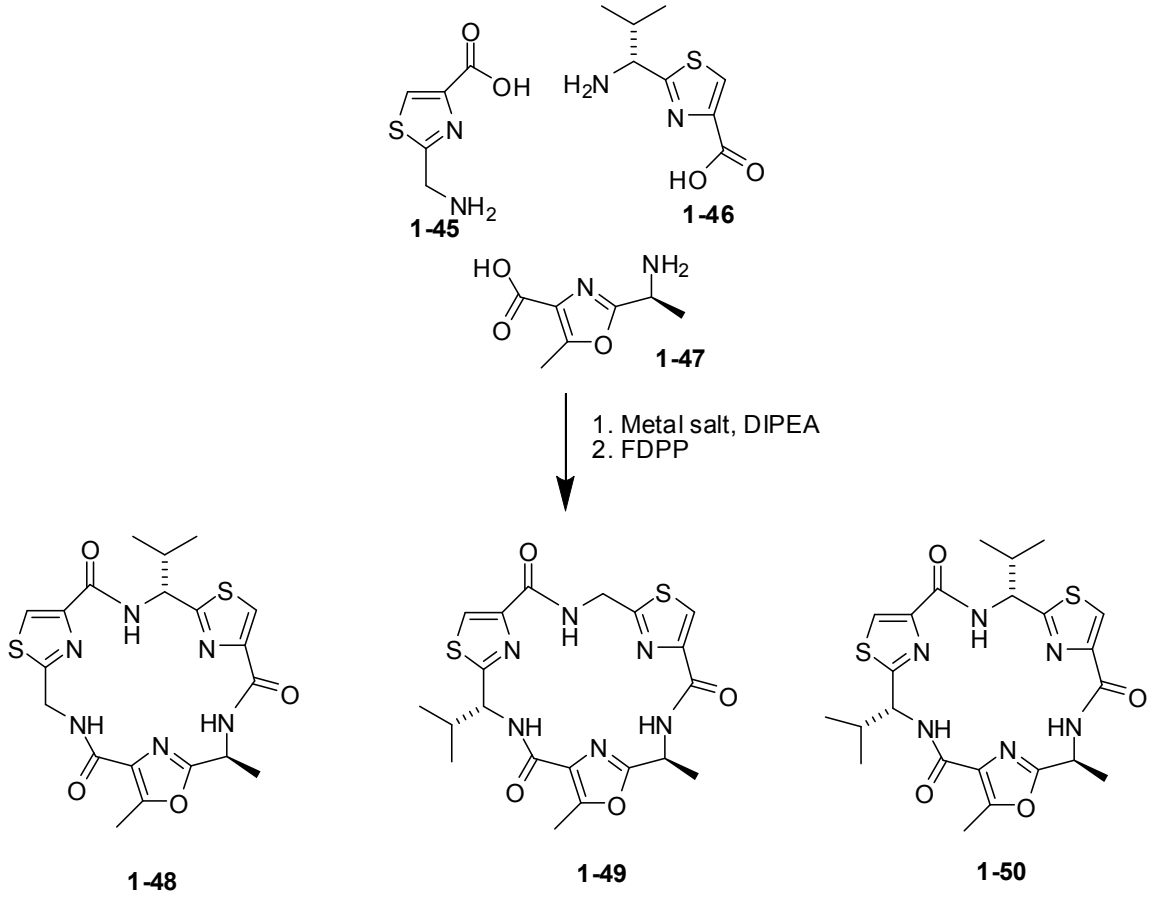
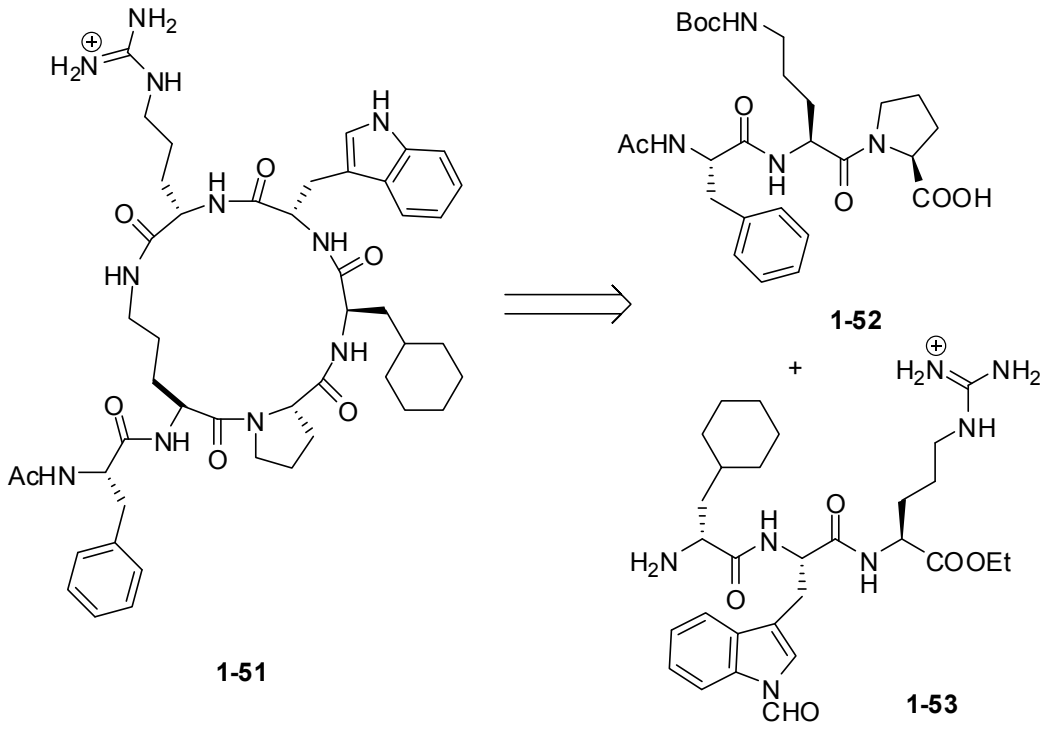


Table 5 Metal effect on the cyclization of **1-48, 1-49** and **1-50**

Metal Salt	Overal Yield %	Composition of Cyclic Products		
		1-48	**1-49**	**1-50**
No Metal	71	21	23	21
$Cu(BF_4)_2$	9	66	34	-
$LiBF_4$	26	45	13	-
$Ca(BF_4)_2$	28	48	29	-
$Zn(BF_4)_2$	23	25	38	36
$AgBF_4$	14	-	-	100
$NaBF_4$	34	28	28	44
KBF_4	40	26	26	48

The Fairlie group demonstrated the feasibility of medium to large scale synthesis of the non-*Lissoclinum* cyclopeptide 3D53 (**1-51**, Scheme 8).[49]

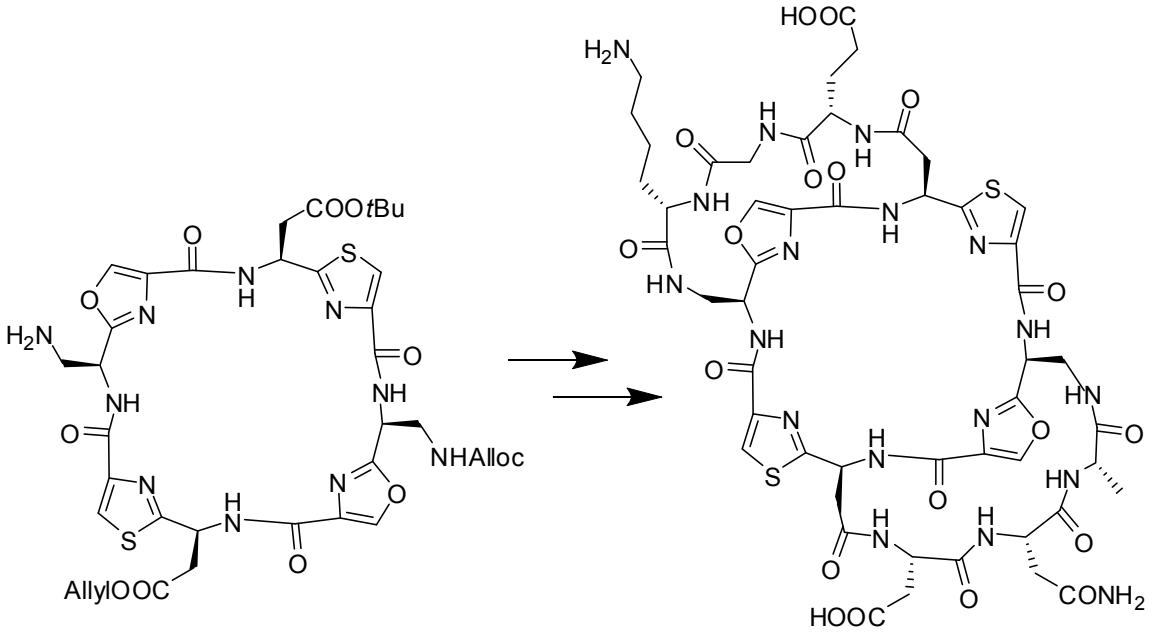
Scheme 8 Cyclopeptide 3D53 and its synthetic precursors



Sequential couplings of commercially available amino acids with mixed anhydride provided segments **1-52** and **1-53**, which were then coupled and cyclized to **1-51** (31 g) in an overall yield of 13%. The key to the success of this synthesis was a minimal use of protection groups on the sidechains and no purification of the intermediates throughout the entire synthesis.

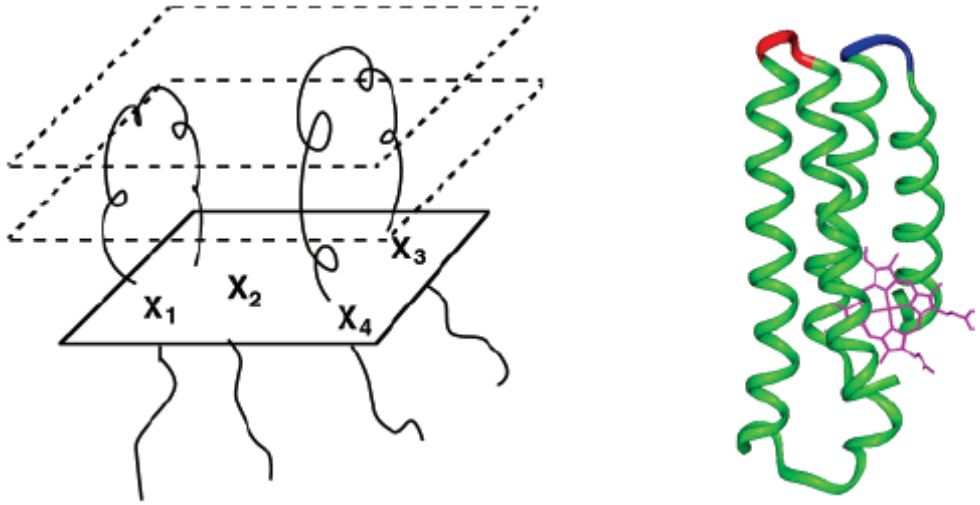
The same group also explored the synthesis of a protein mimetic with a *Lissoclinum* cyclopeptide analogue as a scaffold (Scheme 9).[50] The cyclopeptide **1-54** was prepared from dipeptidyl oxazoles and thiazoles by sequential couplings and macrocyclization. The sidechains in **1-54** were then coupled with two tripeptide segments to provide tricyclic peptide **1-55**. The rigid polythiazole and -oxazole backbone functioned as a scaffold, supporting two short peptide loops projecting orthogonally from the same face of the backbone. This mimicked the two interhelical loops of cytochrome b562 illustrated in Figure 10. Thus **1-55** could function as an artificial protein.

Scheme 9 Synthesis of a protein mimetic with a cyclopeptide scaffold



1-54 **1-55**

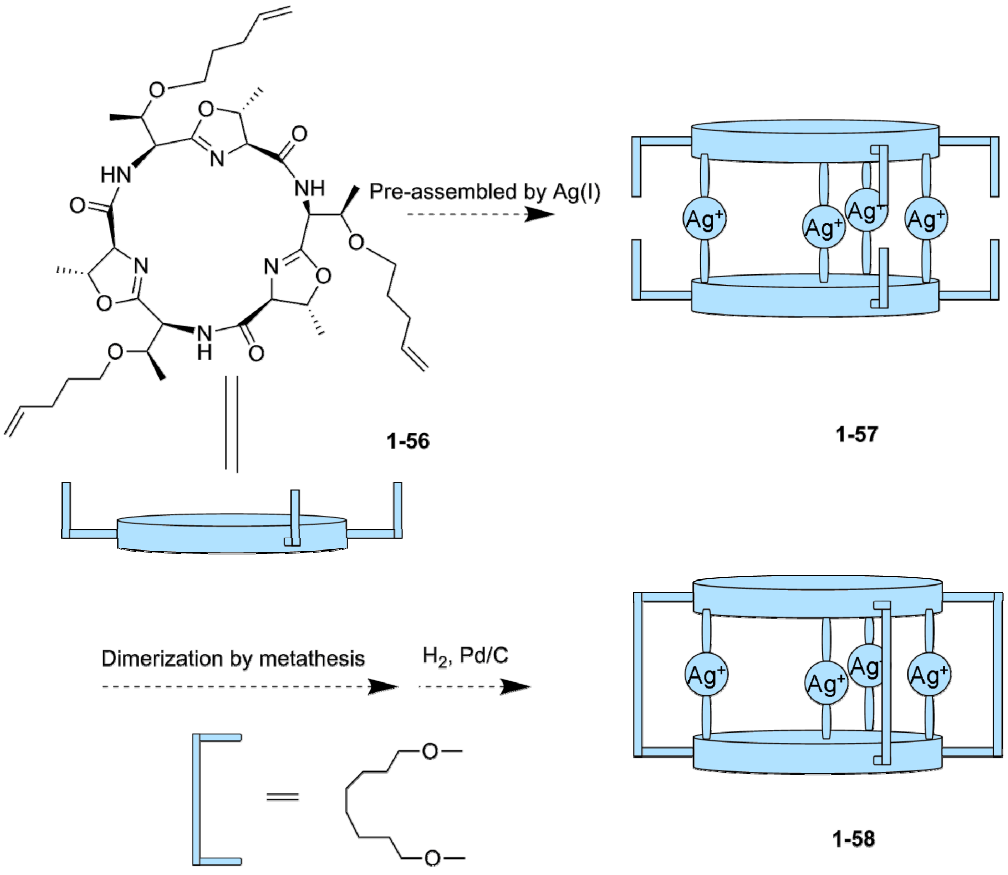
Figure 10 Discontinuous loop surfaces in cytochrome *b*562.
Reproduced from Ref. 51.



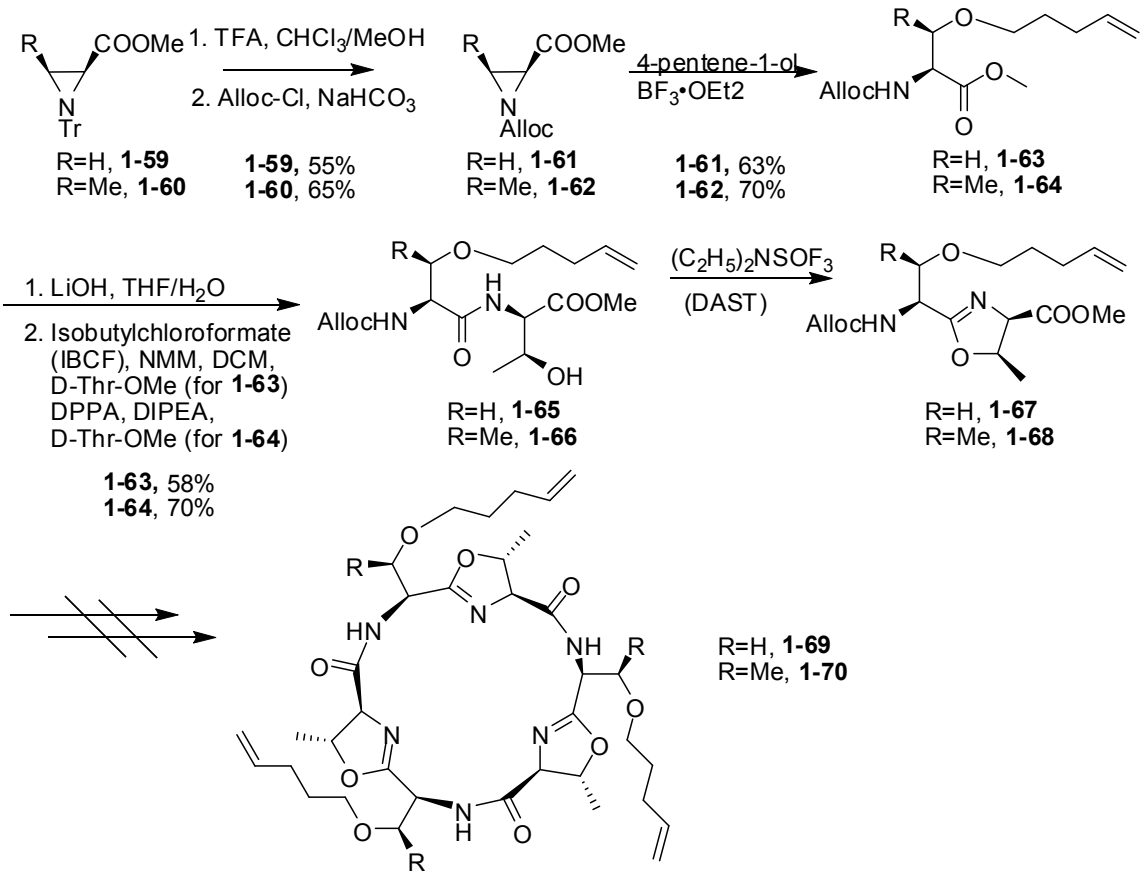
1.1.4 Design of a Tethered Bis-oxazoline Ligand for Ag(I) Binding (Generation I)

Encouraged by the discovery of a westiellamide-Ag(I) complex, we desired to improve the ligand's affinity towards silver. For the purpose of extracting silver out of sea water, a $K_a \sim 10^{33} M^{-5}$ is required for a westiellamide ($[\mathbf{1\text{-}4}_2Ag_4]^{4+}$) system (assuming 0.24 ug/L silver concentration, 10 mM ligand concentration and 90% Ag extraction per cycle). Upon inspection of westiellamide's silver binding pattern, one may recognize the huge entropy loss (ΔS=-191 J K^{-1} mol^{-1})[16] due to the requirement of bringing 6 molecules together for complexing. This can be partially compensated by tethering two westiellamides into a cage-like molecule[51-54] (Scheme 10). The linker also allows a potential attachment of the macrocycles to a solid support.

Scheme 10 Ligand design (generation I)



Scheme 11 Synthetic effort towards generation I ligand



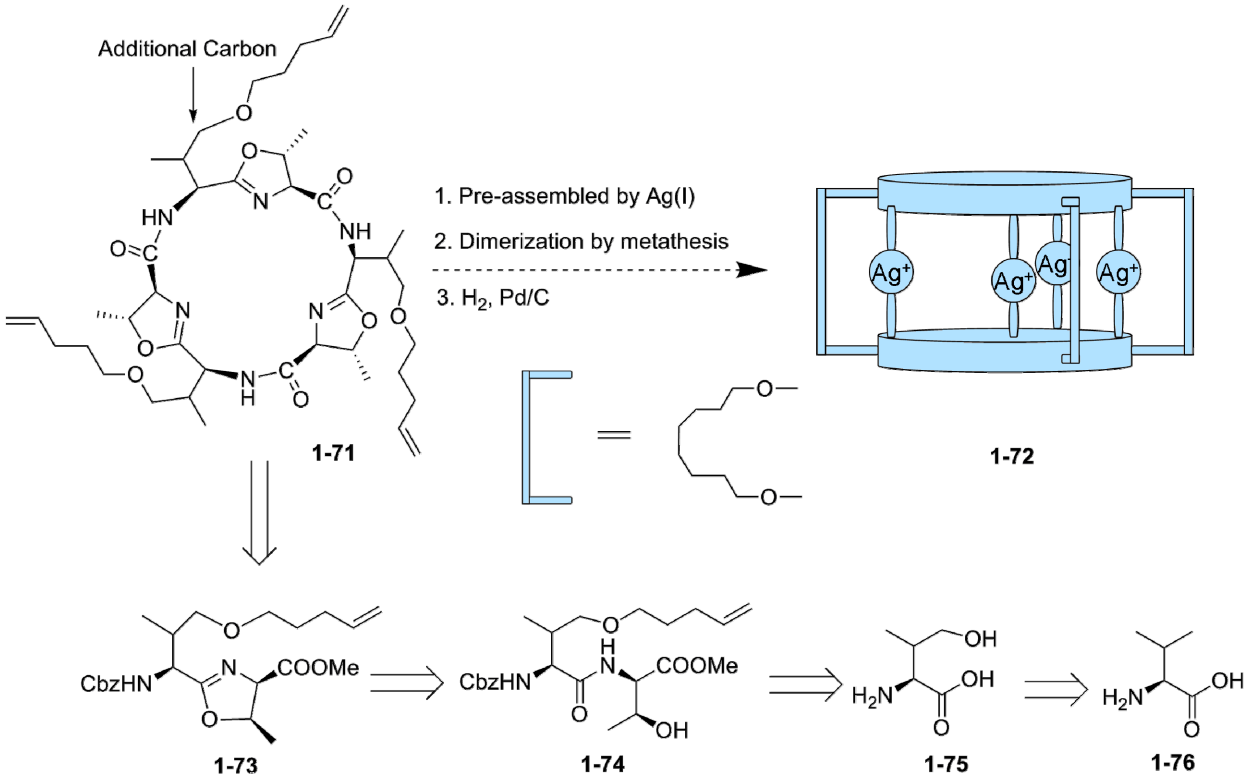
The aziridines **1-59** and **1-60** were prepared from L-serine and L-threonine,[55-56] respectively (Scheme 11)[57]. The N-trityl groups were replaced with an Alloc group to activate the aziridine ring towards nucleophilic attack. Aziridines **1-61** and **1-62** was successfully opened with the assistance of a Lewis acid.[58-59] Saponification of **1-63** and **1-64** followed by coupling to D-Thr-OMe yielded dipeptides **1-65** and **1-66**. DAST effected the formation of oxazoline[60] to provide **1-67** and **1-68**. However, these heterocycles were unstable and unable to tolerate the subsequent deprotection steps. After repeated attempts failed, it was concluded that **1-67** and **1-68** decomposed at their ether moiety by β-elimination of the α-proton on the amino acid backbone.

1.2 RESULTS AND DISCUSSION

1.2.1 Generation II Ligand

Cyclic peptide **1-71** was selected to circumvent the stability problem with the Generation I ligand (Scheme 12). We proposed that an additional carbon inserted between the ether linkage and the β-position of the amino acid backbone would prevent elimination of the sidechain.

Scheme 12 Ligand design (generation II)

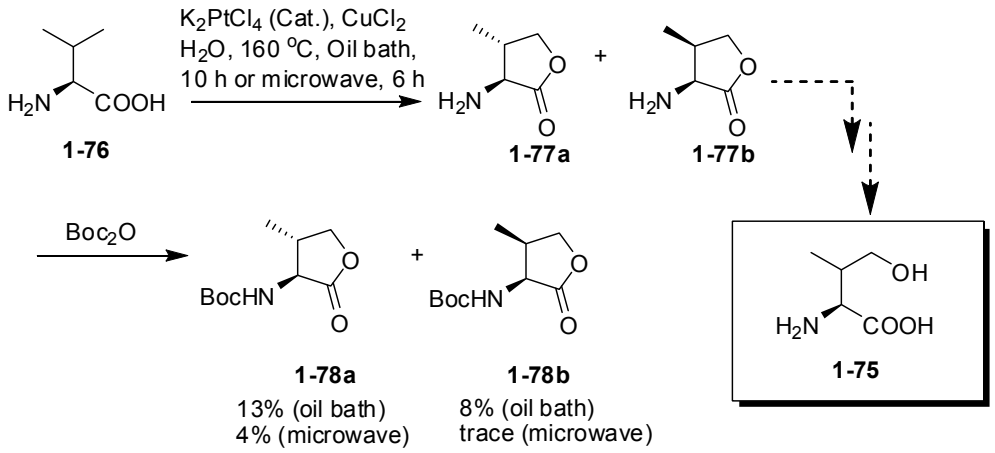


Retrosynthetically, **1-71** can be prepared from **1-73** by cyclooligomerization. Cyclodehydration of dipeptide **1-74** with Burgess reagent or DAST yields **1-73**. **1-74** can be

prepared from the coupling of **1-75** and D-Thr. The γ-hydroxy valine **1-75** might be derived from a Shilov-type oxidation of L-valine[61](Scheme 13).

In the Shilov reaction, the Pt(IV) is oxidized in situ to Pt(VI) by $CuCl_2$. The Pt(VI) species complexes with valine and subsequently oxidizes the methyl group to a primary alcohol. The resulting γ-hydroxy valine spontaneously closes to lactones **1-77a** and **1-77b**. The overall yield was determined after Boc protection. However, Shilov type reactions often suffer from low yields.[62] This reaction was no exception (21% overall yield). Another problem was the low diastereoselectivity (1.6:1). Repeated attempts (including microwave conditions) to improve the yield failed.

Scheme 13 Oxidation of valine by Pt(VI)

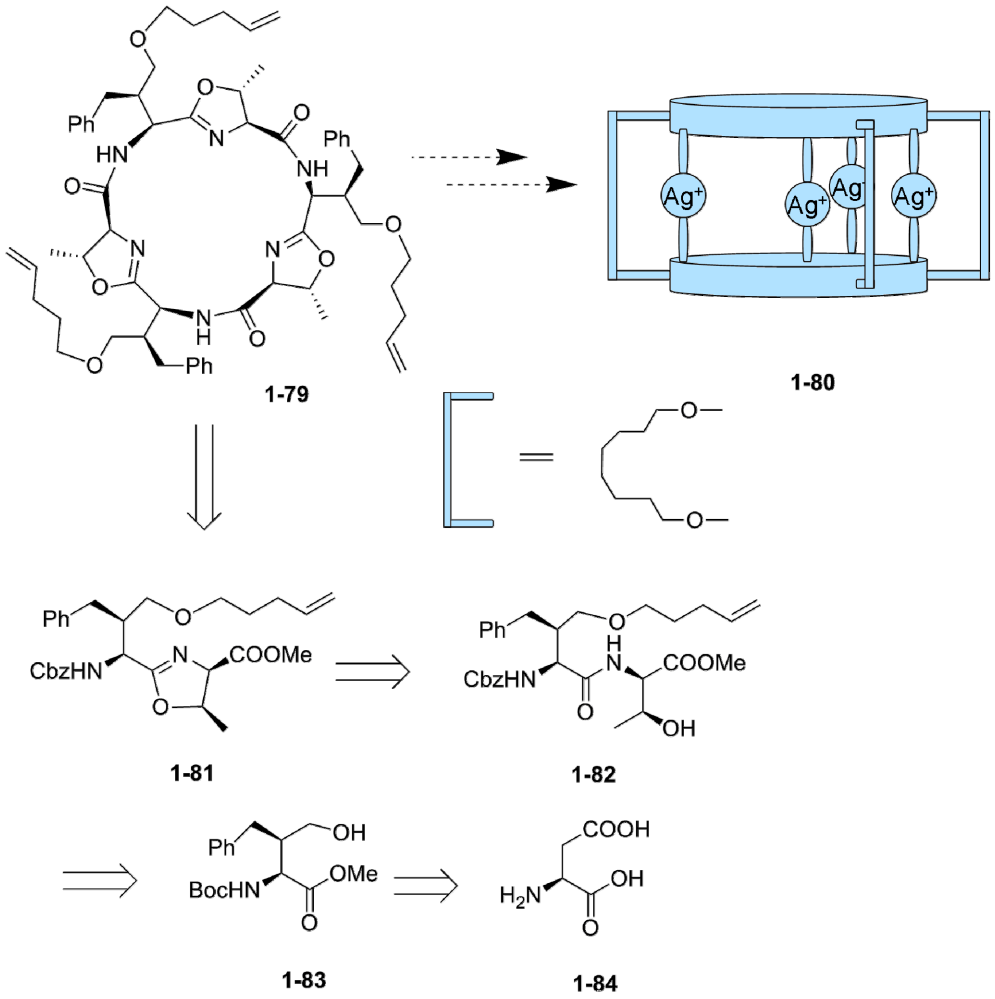


1.2.2 Generation III Ligand

Next we turned our attention to a rather conventional approach (Scheme 14). The cyclic trimer **1-79** can be prepared from monomer **1-81**, which in turn was made from modified amino acid **1-83** and D-Thr. **1-83** has been previously prepared from protected L-aspartic acid.[63] The benzyl

group on its side chain was designed to mimic the methyl group in the natural product, which may play an important role in the success of the cyclooligomerization step.

Scheme 14 Ligand design (generation III)

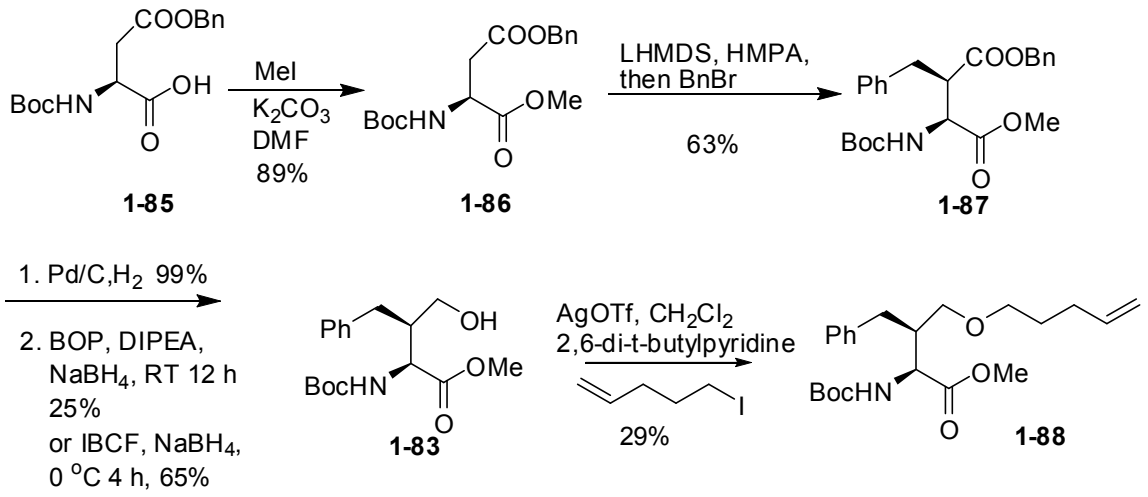


The synthesis of **1-79** started with the commercially available protected aspartic acid **1-85** (Scheme 15). Protection of the carboxyl group as a methyl ester followed by β-benzylation with LHMDS and benzyl bromide provided **1-86** as the exclusive diastereoisomer.[63] The Boc protection group was required as its bulky size suppresses enolate formation at the α-carbon.

The β-carboxyl group was unmasked and reduced to the primary alcohol **1-83**. Initially, we followed the literature procedure[63] using BOP/$NaBH_4$, which resulted in 25-35% yield depending on the reaction scale. The major by-product was the lactone resulting from

transesterification. After some experimentation, a combination of isobutylchloroformate and $NaBH_4$ was found to provide a better yield (65%).

Scheme 15 Synthetic efforts towards **1-88**

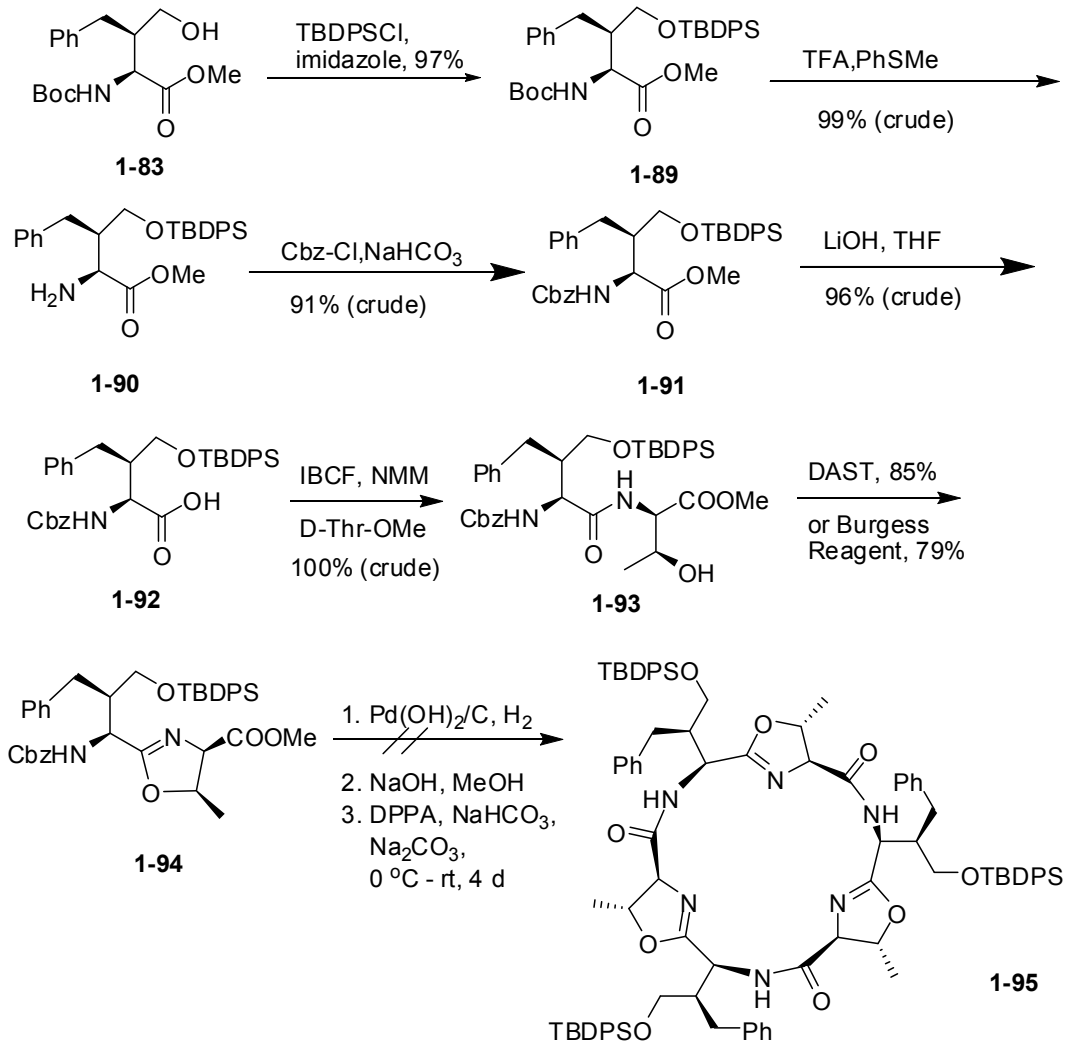


Etherification of **1-83** by AgOTf/5-iodopentene yielded only 29% of **1-88** along with the lactone and N-alkylation product. Other ether formation conditions including NaH/5-bromopentene, 2,6-di-*t*-BuPy/pent-4-enyl triflate and reductive etherification[64] were tested and found to be ineffective. Therefore we decided to protect **1-83** using a silyl group and form the ether side chain at a later stage (Scheme 16).

Protection of **1-83** by the TBDPS group went smoothly to provide **1-89** in 97% yield. The Boc group in **1-89** was switched to a Cbz group as mild deprotection conditions are essential for oxazoline-containing compounds. Saponification followed by coupling to D-Thr-OMe yielded dipeptide **1-93** in quantitative yield. DAST effected the formation of oxazoline **1-94** in 85% yield. However, **1-94** was found to be resistant to hydrogenolysis, indicating the contamination by sulfur from DAST. Thus, Burgess reagent was used instead to yield 75% of **1-94**. Deprotection of Cbz by hydrogenolysis was followed by saponification as well as epimerization of the *cis*-oxazoline to the *trans*-configuration with NaOH. This reaction was quenched with

$NaHCO_3$ and the resulting mixture was carried on to the next step without purification. This was a critical modification since all acidic workups were found to decompose the intermediate.

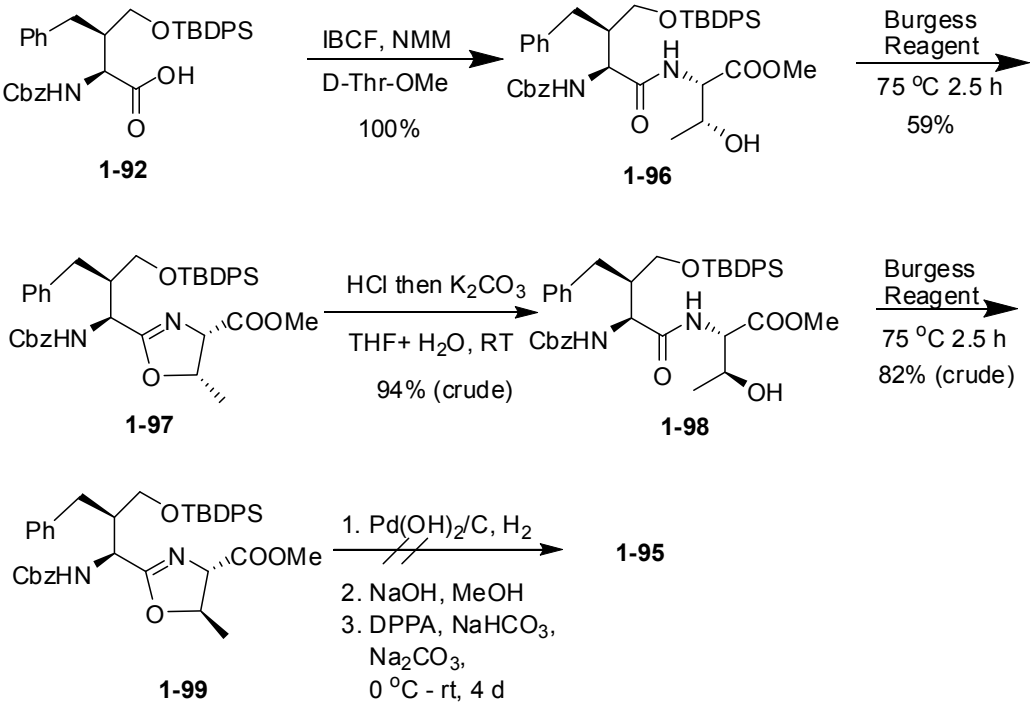
Scheme 16 Revised approach towards **1-95**



Unfortunately, DPPA was unable to effect a cyclooligomerization. Screening of other coupling reagents including FDPP and DEPBT proved to be unsuccessful. In light of these results and the difficulty characterizing the epimerized oxazoline, we decided to prepare the oxazoline **1-99** with the desired *trans*-stereochemistry in a way analogous to the westiellamide synthesis (Scheme 17).

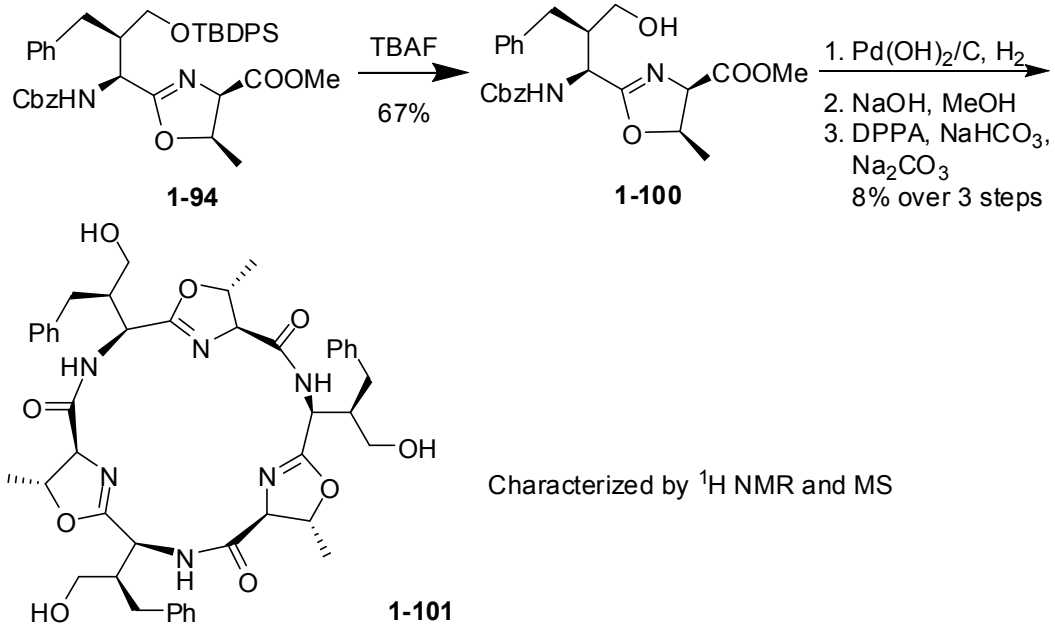
Coupling of **1-92** to L-Thr-OMe followed by treatment with Burgess reagent yielded oxazoline **1-97**. The oxazoline was opened and re-closed to provide **1-99** with suitable stereochemistry for cyclooligomerization. Exposure to the cyclization conditions failed to give the cyclic trimer **95.** This result suggested that the bulky TBDPS group in **1-99** as well as in **1-94** was the cause for the failure in the cyclooligomerization step.

Scheme 17 Cyclooligomerization with confirmed stereochemistry on the oxazoline



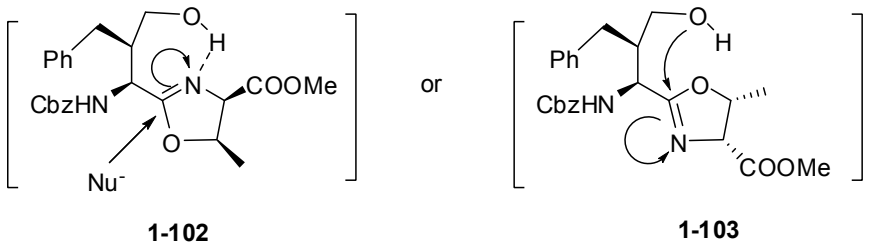
The next course of action was to remove the TBDPS group prior to cyclooligomerization (Scheme 18). The desilylation of **1-94** proved to be surprisingly difficult. TBAF was able to remove the TBDPS group, but the product was only obtained crude. Other desilylating reagents, including TBAF-AcOH, TAS-F, HF-Pyridine and Et_3N-HF, were unable to provide clean material either. Crude **1-100** was then subjected to the deprotection and cyclooligomerization conditions to yield 8% (0.6 mg) of the cyclic trimer **1-101,** which was identified by ^1H NMR and MS. However, attempts to scale up this process failed, possibly due to the instability of **1-100**.

Scheme 18 Cyclooligomerization of desilylated oxazoline



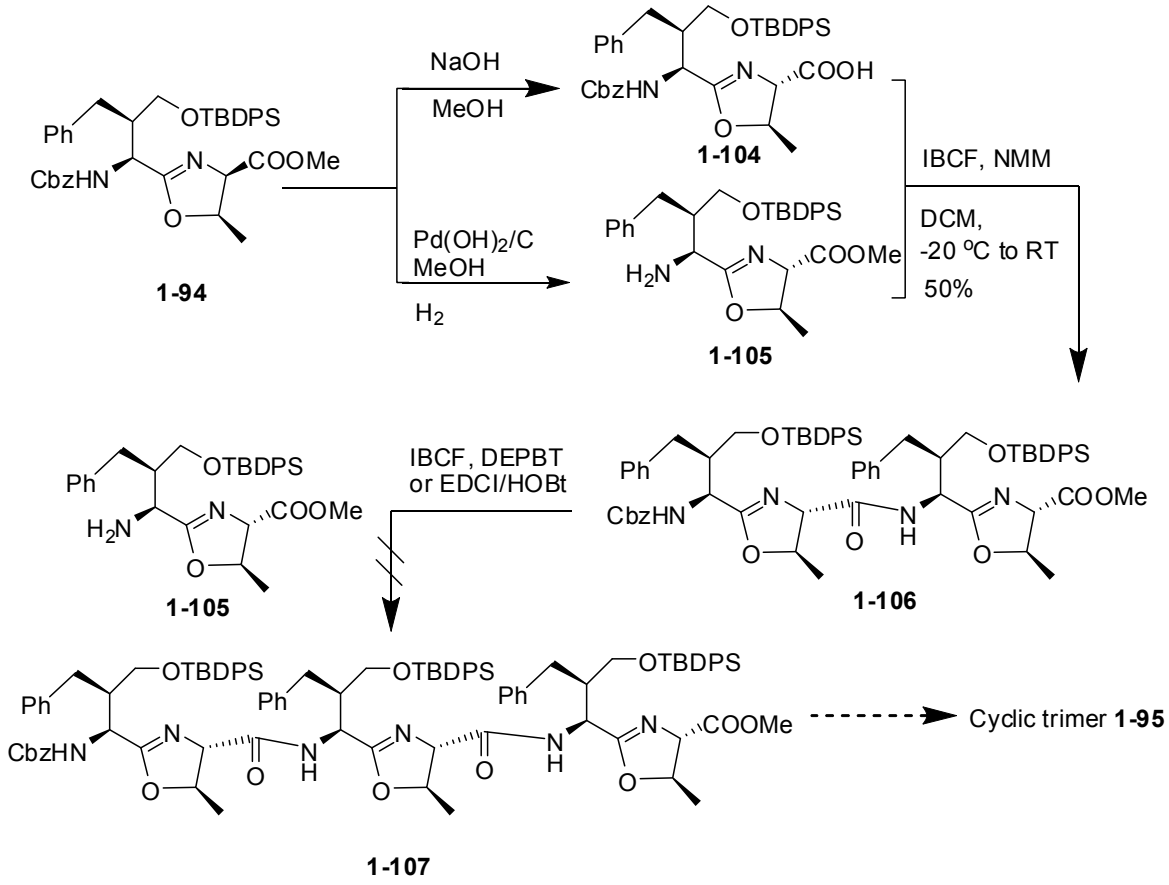
Presumably, the oxazoline in **1-100** could be destabilized by an intramolecular hydrogen bonding interaction (**1-102**, Scheme 19). Another possibility is that the free hydroxyl group might be able to ring-open the oxazoline (**1-103**, Scheme 19).

Scheme 19 Possible decomposition pathways of **1-100**



At this stage, the cyclooligomerization approach did not seem to be viable. Therefore, a macrocyclization strategy was investigated (Scheme 20). Dimerization of **1-94** was realized by deprotection and subsequent coupling using isobutylchloroformate. The yield, however, was low (51%). Unfortunately, all attempts to construct the linear trimer **1-107** failed. A possible cause could be the steric hindrance of the substrate. No further studies on this substrate were conducted.

Scheme 20 Macrocyclization approach towards **1-95**

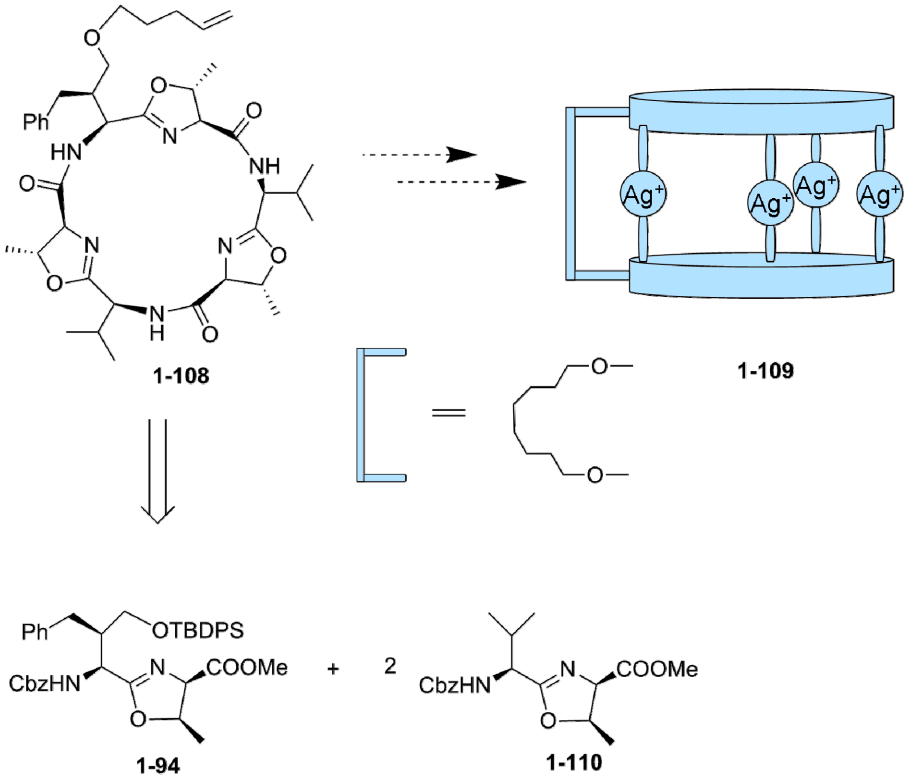


1.2.3 Generation IV Ligand

A decision was made to make a major modification to our target molecule (Scheme 21). The hetero-cyclotrimer **1-108** consists of one functionalized oxazoline **1-94** and two unfunctionalized oxazolines **110**. There are a couple of advantages of this design over the originally proposed homo-cyclotrimer **1-95**. First, compound **1-108** more closely resembles westiellamide. This should increase the chances for success in the macrocyclization step as well as the binding of the

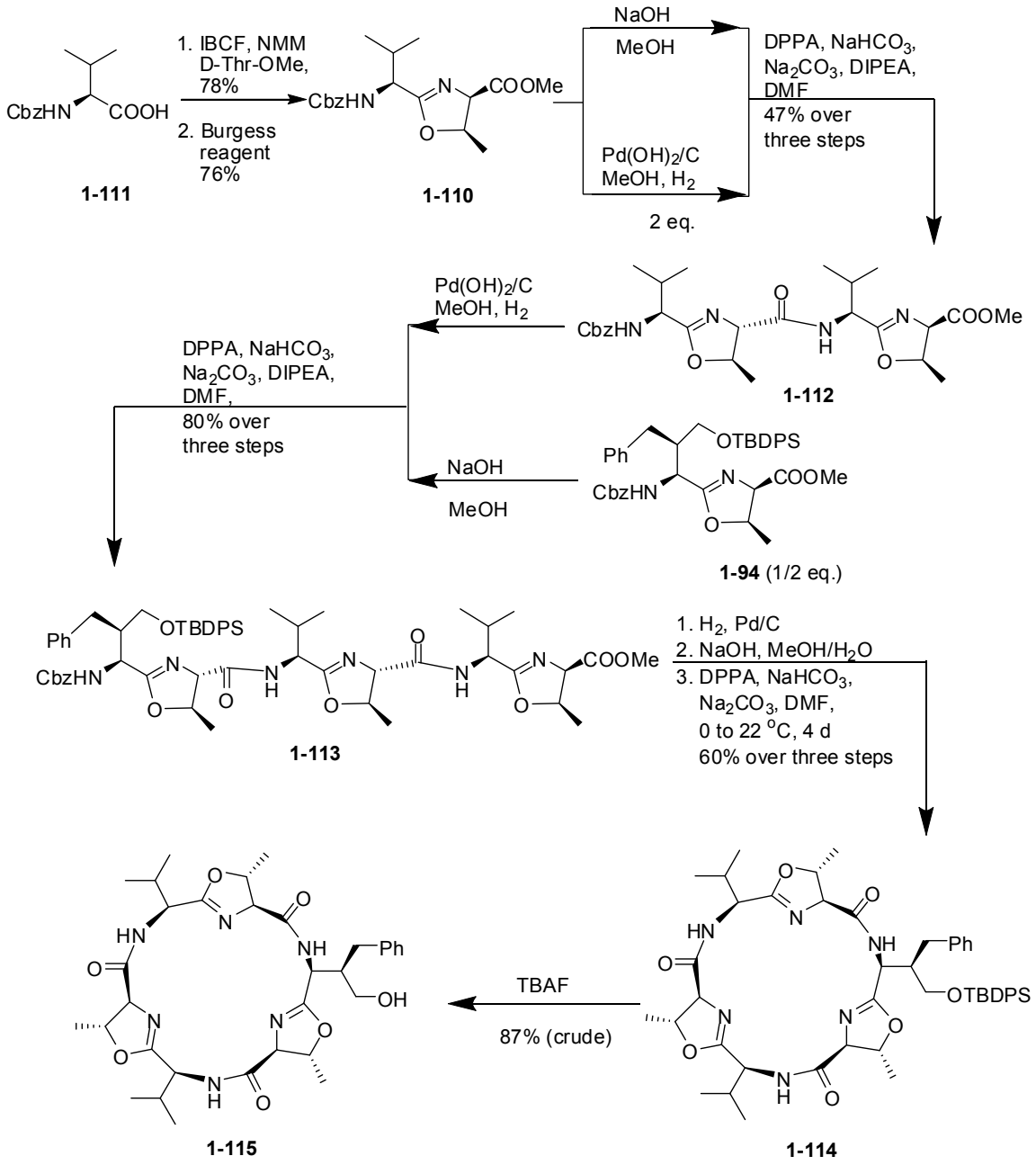
macrocycle to silver. Furthermore, compound **1-97** is readily available and decreases the required amount of the precious oxazoline **1-94**.

Scheme 21 Ligand design (generation IV)



Commercially available Cbz-L-Val-OH was converted to **1-110** in the same fashion as in the westiellamide synthesis (Scheme 22). Dimerization of **1-110** using either IBCF or EDCI was unsuccessful due to the decomposition of the oxazoline upon acidic workup of the saponification step. This problem was solved by quenching the reaction with $NaHCO_3$ followed by a DPPA-mediated peptide coupling. To compensate for the decomposition of the oxazoline during the coupling reaction, a two fold excess of the free N-terminal compound was used.

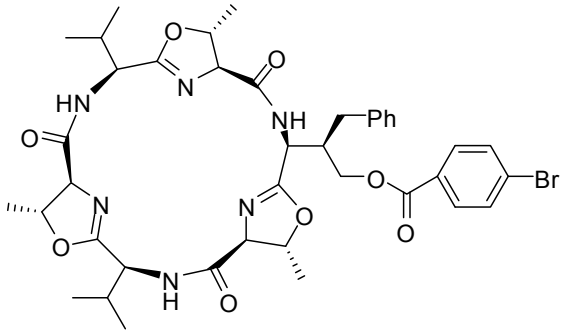
Scheme 22 Macrocyclization approach towards the heterocyclotrimer **1-115**



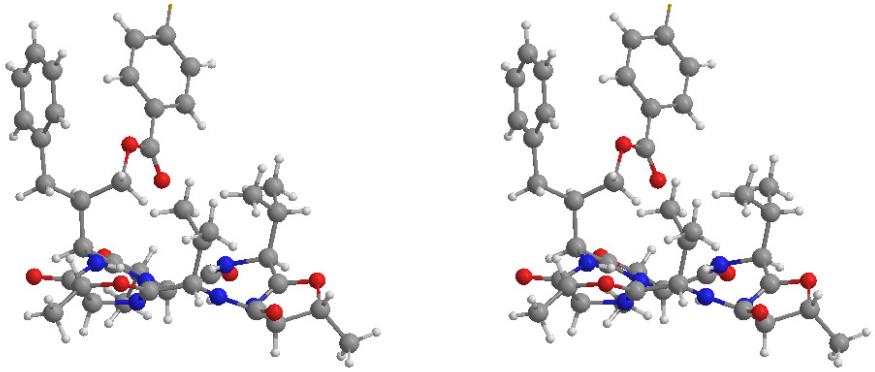
Next, the linear trimer **1-113** was prepared in 80% yield by coupling the dimer **1-112** to the functionalized oxazoline **1-94**. As expected, the cyclization of **1-113** with DPPA proceeded very well to provide the cyclic trimer **1-114** in 60% yield. The use of FDPP as coupling reagent or $AgBF_4$ as an additive significantly decreased the yield. Treatment of **1-114** with TBAF afforded 90% of the desilylated **1-115**. Possibly, the rigid structure in **1-115** accounts for its better

stability compared to dipeptidyl oxazoline **1-100**. **1-115** was converted to its *p*-bromobenzoyl ester **1-116**, whose crystal structure was solved (Figure 11). The backbone of **1-116** adopt a planar conformation with all the side chains adopt a pseudo-equatorial position. This is consistent with the crystal structure of westiellamide (Figure 4).

Figure 11 Stereoview of the crystal structure of **1-116**



1-116

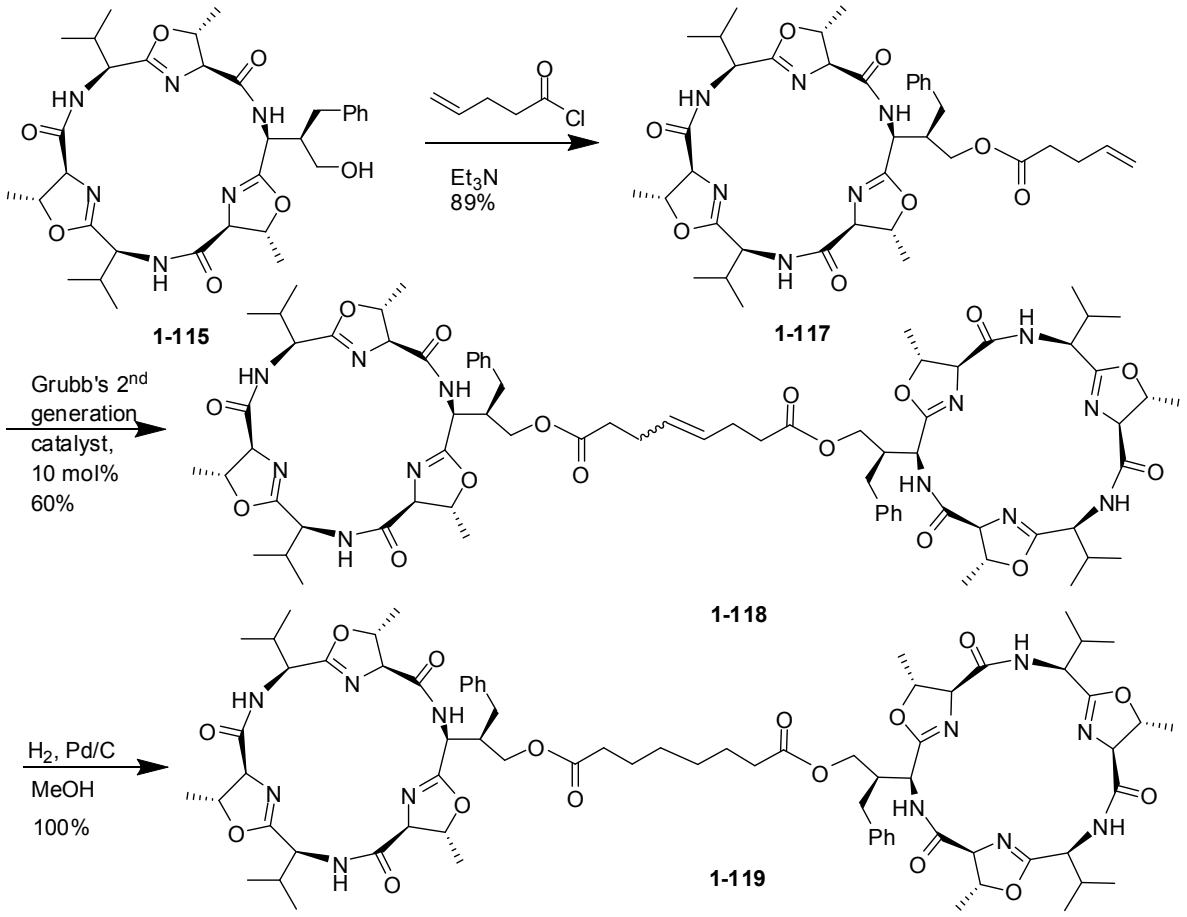


To determine the ability of **1-115** to bind silver(I), an NMR titration experiment with $AgClO_4$ in CD_3OD+D_2O (9:1, v/v)[16] was conducted. Surprisingly, **1-115** showed weak and complex association to Ag^+. This could possibly be attributed to the absence of *C*3 symmetry in the molecule. Thus, we decided to tether the two hetero-cyclotrimers together, hoping to minimize the entropic penalty to improve its affinity towards Ag(I).

Ether formation with **1-115** was found to be difficult, presumably due to its highly functionalized nature. Protocols tested included NaH/5-iodopentene, NaHMDS/5-iodopentene,

2,6-di-*t*Bupyridine/pent-4-enyl triflate, AgOAc/5-iodopentene and Mitsunobu conditions, all of which proved unsuccessful. In contrast, the esterification of **1-115** was found to be a viable alternative (Scheme 23).

Scheme 23 Tethering the cyclic trimer

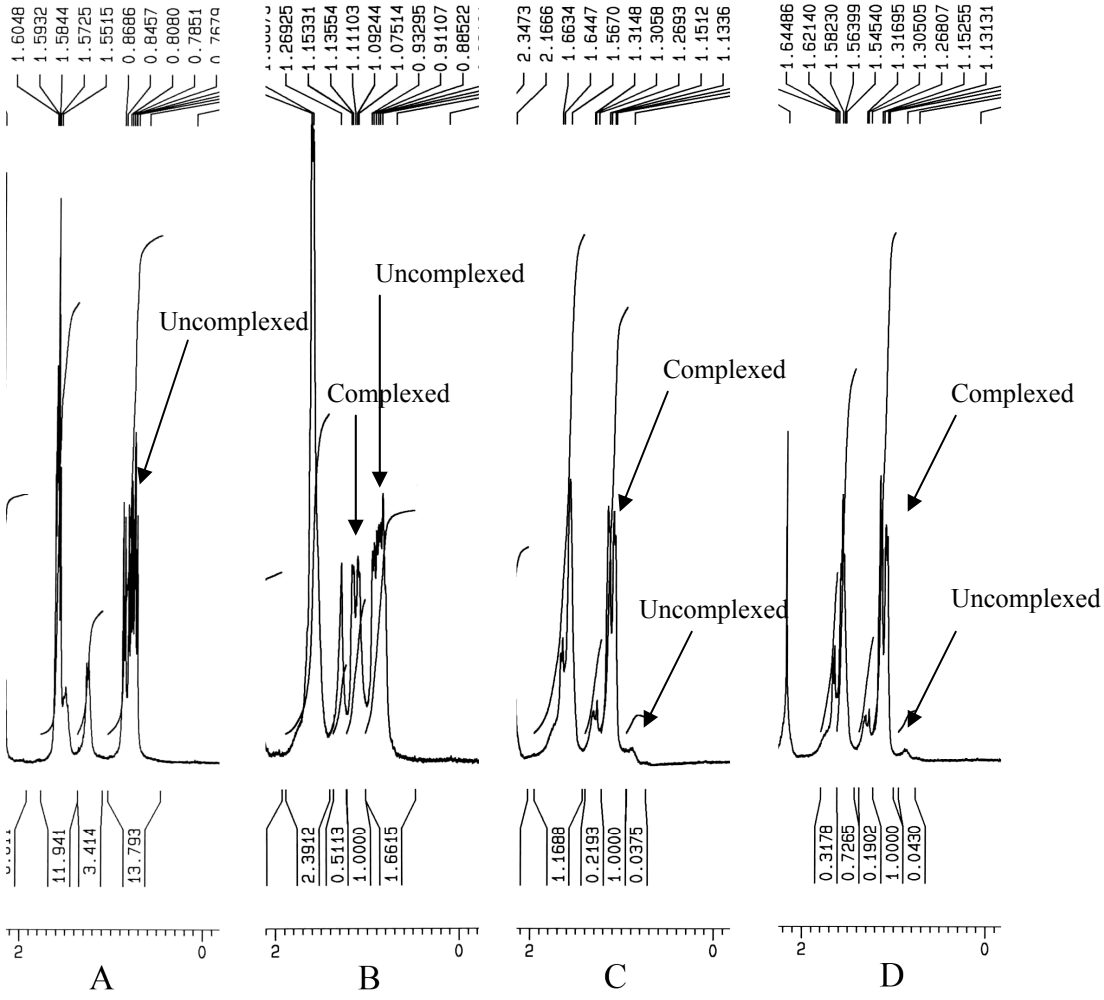


Alcohol **1-115** was transformed into ester **1-119** with acyl chloride. Dimerization of **1-119** by metathesis[51] catalyzed by Grubb's 2nd generation catalyst provided 60% of **1-118** as a mixture of *cis/trans*-isomers. Other common metathesis catalysts, including Grubbs' 1st generation and Schrock's catalyst, were unable to effect the reaction. Pre-assembly of the monomers with $AgClO_4$ followed by dimerization with Grubb's 2nd generation catalyst failed. This could be due the decomposition of the catalyst by removal of the chloride ligand by silver(I). Hydrogenation of **1-118** with Pd/C yielded the tethered ligand **1-119**. A more direct way to prepare **1-119** by

using half an equivalent of octanedioyl dichloride failed, presumably due to ketene formation and the low concentration of the acyl chloride.

With **1-119** in hand, an NMR titration with $AgClO_4$ was conducted. To our relief, upon treatment with silver, **1-119** showed a similar NMR pattern to the westiellamide-Ag complex, forming a $[(\mathbf{1\text{-}119})Ag_4]^{4+}$ complex. A series of typical NMR spectra are shown in Figure 12. The peak that corresponds to the methyl group in the Val residue (Spectrum **A**) was split into two sets of peaks upon treatment with Ag(I) (Spectrum **B**). The downfield peak corresponded to complexed **1-119**, while the upfield peak corresponded to uncomplexed **1-119**. After the addition of 4 equivalents of Ag(I), nearly all of **1-119** was in complexed form (Spectrum **C**). The spectrum underwent little change when adding more than 4 equivalents of Ag(I) (Spectrum **D**). The small uncomplexed peak in Spectrum D may be attributed to the presence of the epimer of **1-119**. Thus, a stoichiometry of 1:4 ($\mathbf{1\text{-}119}$:Ag^+) was determined. This result was in sharp contrast to most NMR titrations in the literature,[65] in which no splitting of peaks were observed due to the fast equilibrium between the two species. In those cases, the peak underwent concentration-dependent changes in its chemical shift. Thus, the splitting pattern in **1-119** and in westiellamide suggested a slow exchange between complexed and uncomplexed forms according to the NMR time scale. However, the reaction speed between **1-119** and Ag(I) was fast, as the equilibrium was achieved instantaneously upon mixing the reactants.

Figure 12 NMR titration of **1-119** with $AgClO_4$.
A: No Ag(I); **B**: 2 equivalents Ag(I); **C**: 4 equivalents Ag(I); **D**: 20 equivalents Ag(I)

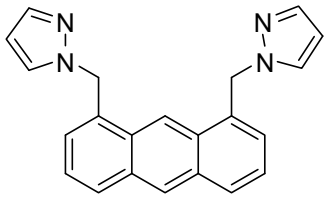


Also worth mentioning is that the binding of **1-119** to four Ag(I) was a highly cooperative process, as no intermediate states were observed during the titration. The calculation of K_a was based on the integration of the complexed peak (1.18-1.00 ppm) and uncomplexed peak (1.00-0.74 ppm). A K_a of $1.8\pm1.4\times10^{11}$ M^{-4} in CD_3OD and D_2O (9:1, v/v) was determined for **1-119**. The K_a for westiellamide ($2.8\times10^{13}M^{-5}$) was determined in a similar fashion.[16] Several factors may have attributed to the significant error range observed in the NMR titration. Generally, the NMR titration only works well for $K_a < 10^5$ M^{-1} for a 1:1 complex.[65] Also, the error may be

linked to the partial overlap of peaks in NMR as well as the presence of a trace amount of epimers. We attempted the determination of ΔS for Ag binding of **1-119** by using variable temperature NMR. Unfortunately, these results were highly variable due to the inconsistencies between measurements, which may have resulted from errors in the integration of the NMR peaks as well.

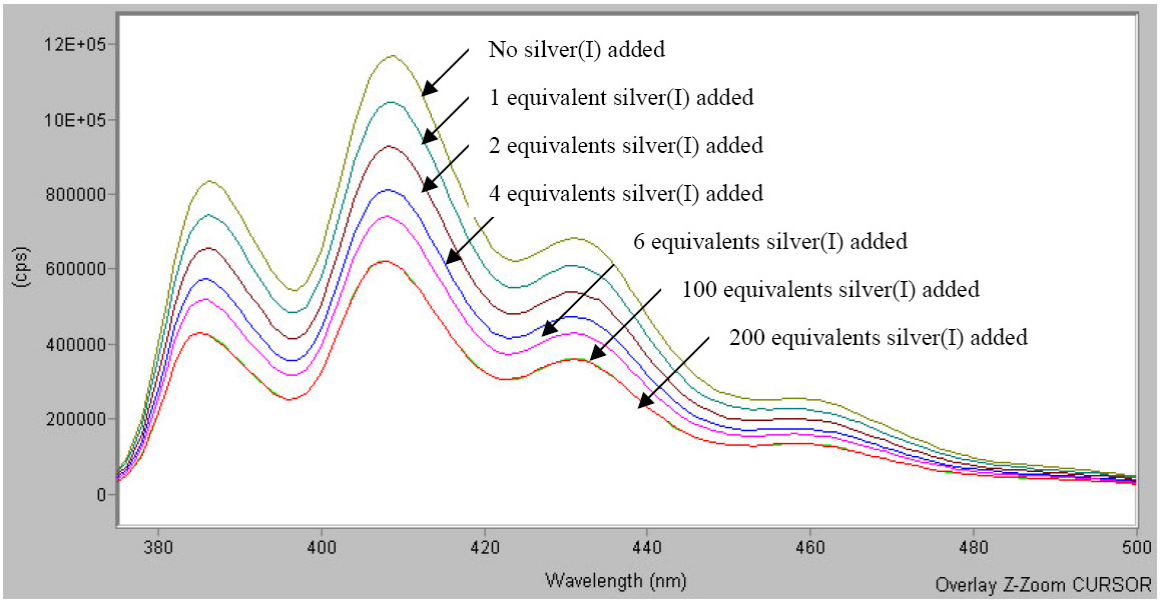
In order to address the issues associated with NMR titration, a competitive binding study of **1-119** with a fluorophore **1-120** (Figure 13) was conducted. It was demonstrated that Ag(I) binds to this fluorophore and causes fluorescence quenching (Figure 14).[66]

Figure 13 Fluorophore for competitive binding study.



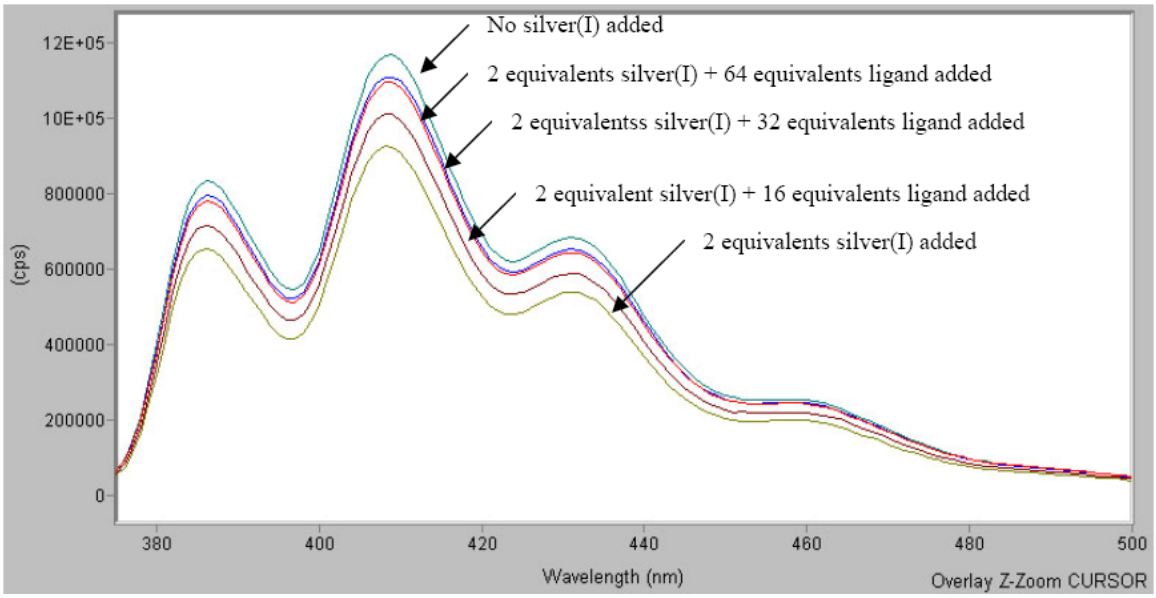
1-120

Figure 14 Changes in fluorescence emission spectra of **1-120** upon the addition of $AgClO_4$ in MeOH and H_2O (9:1, v/v).



The addition of **1-119** to the mixture of Ag(I) and **1-120** restored the intensity of fluorescence, indicating its competitive binding to Ag(I) cation (Figure 15). In this study, both westiellamide and **1-119** exhibited considerably higher Ka's of $2.8\pm1.9\times10^{22}$ M^{-5} and $3.5\pm3.9\times10^{21}$ M^{-4}, respectively.[67-68] The competitive binding experiment with a fluorophore represents a more sensitive tool for the determination of high association constants. Most importantly, both analytical methods demonstrate that the tether considerably improves potential practical applications of the cyclooxazoline scaffold for silver complexation and delivery in the low micromolar range. For example, 50% complexation of a 10 μM solution of Ag(I) would require 270 μM of westiellamide vs 2 μM of **1-119**.

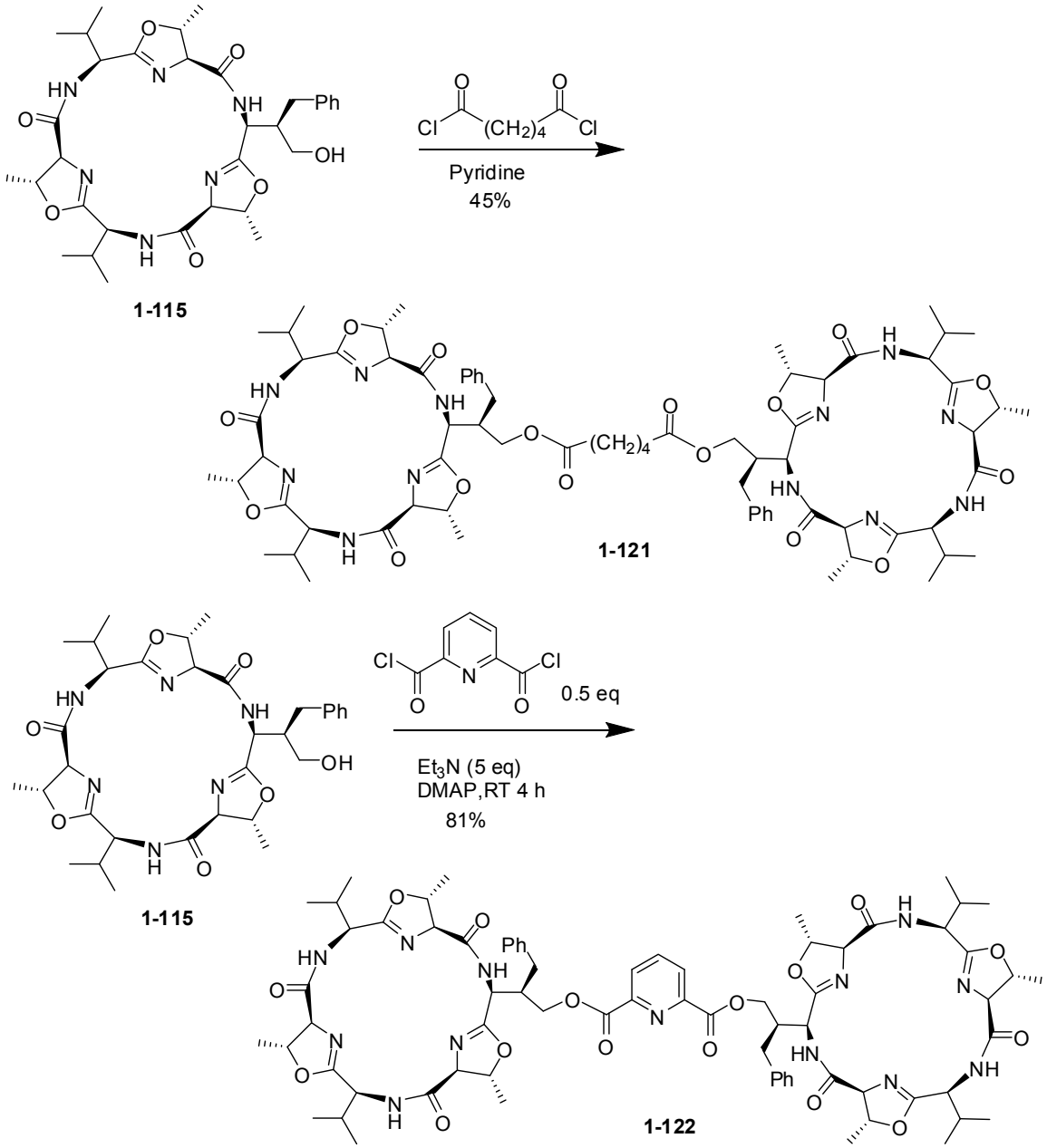
Figure 15 Competitive binding study of **1-119** with **1-120.** Ligand refers to **1-119**.



Next, we examined the effect of the linker's length on Ag-binding (Scheme 24). Acylation of **1-115** with adipoyl chloride provided ligand **1-121**, which has two fewer methylene groups in the tether chain than **1-119**. As expected on the basis of the reduction in entropy loss during complexation, the result was a slightly higher *K*a of $3.20\pm2.98\times10^{22}$ M^{-4} (determined by competitive binding with **1-120**) than **1-119**. In a similar fashion, **1-115** was cross-linked with

pyridine-2,6-dicarboxylate to give ligand **1-122**. However, NMR titration of **1-122** showed a complex binding pattern to Ag(I), presumably due to the shortness or rigidity of the tether, or additional silver-pyridine interactions.

Scheme 24 Further linker variations

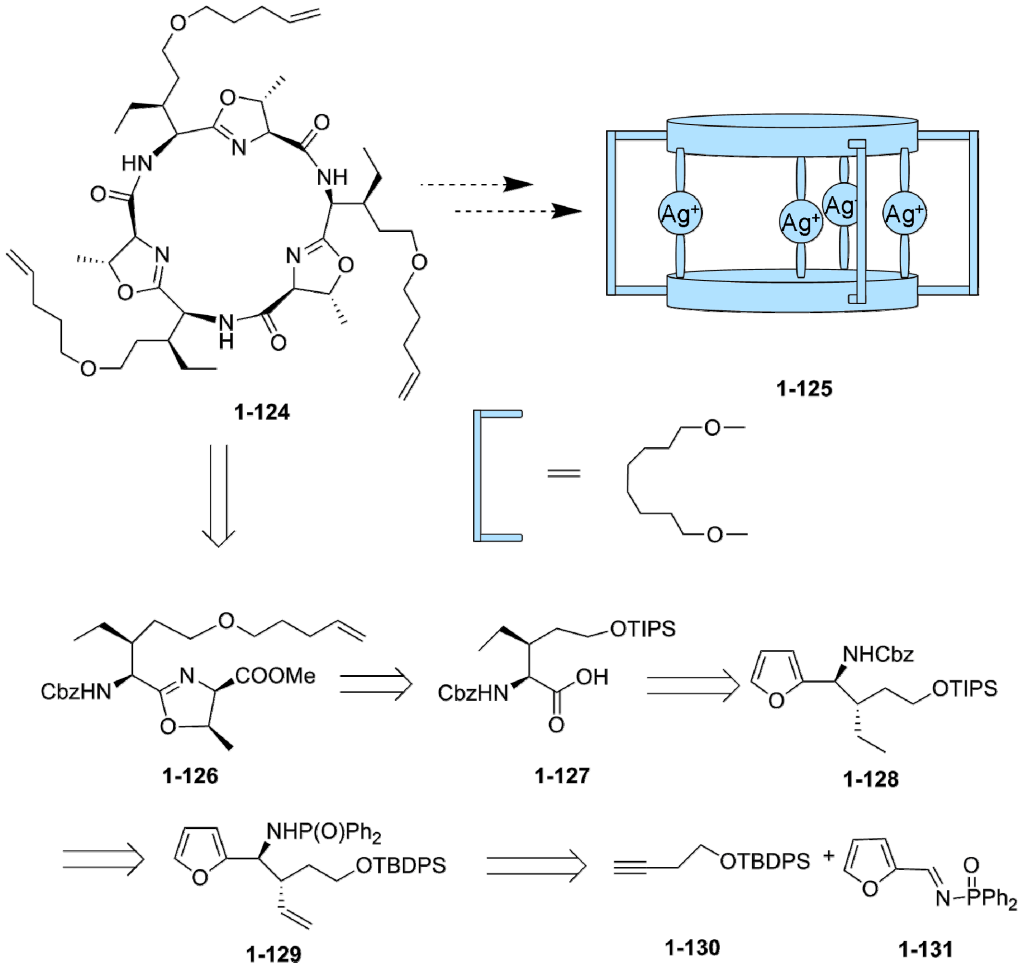


1.2.4 Generation V and VI Ligands

While working on the Generation IV ligand, we also started investigating other modifications on westiellamide (Scheme 25). In principle, a *C*3 symmetric tethered dimer would provide the highest affinity towards Ag(I). Thus cyclic trimer **1-124** was chosen instead of an unsymmetrical trimer. In **1-124**, an additional carbon atom was inserted between the sidechain ether and the backbone, in the hope to solve the stability issue with the desilylated oxazoline **1-100**. Since the decomposition of **1-100** may involve a cyclic transition state (Scheme 19), enlarging the ring may disfavor the process. **1-124** may be prepared from monomer **1-126** by cyclooligomerization, while **1-126** is derived from amino acid **1-127**. This amino acid would arise from the oxidation of **128**, which can be prepared by hydrogenation of **1-129.** Compund **1-129** is readily available by homoallylation of imine **1-131**.[69]

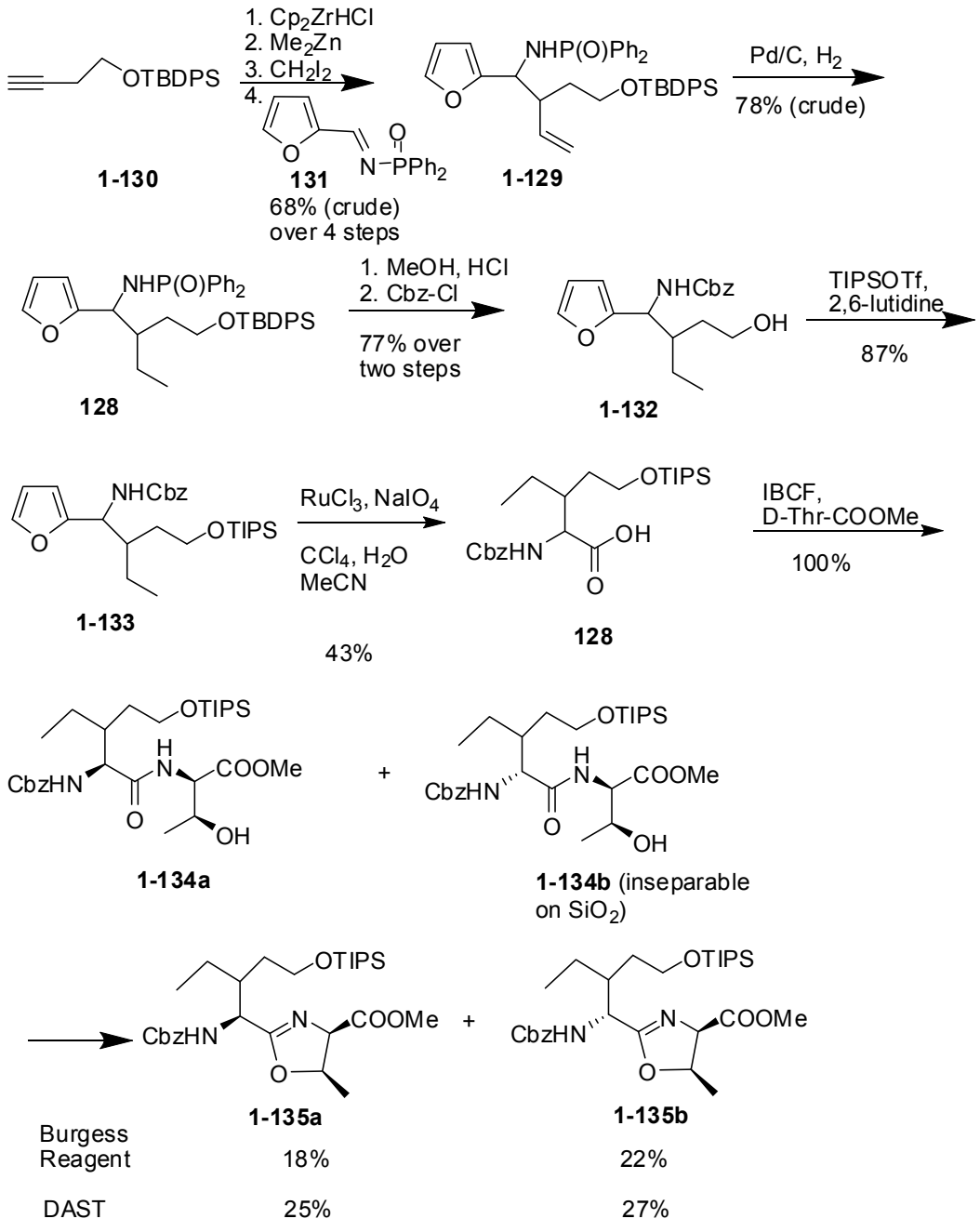
The synthesis started with the hydrozirconation of protected 3-butyne-1-ol (**1-130**) with Schwartz' reagent (Cp_2ZrHCl), transmetallation to zinc, addition to diiodomethane, subsequent rearrangement and addition to imine (prepared by the condensation of furaldehyde and diphenylphosphinic amide[70]) to yield 68% of **1-129** (Scheme 26). At this stage, **1-129** seemed to be a single diastereomer as demonstrated by LC-MS and NMR data. The relative configration of the phosphoramide and olefin groups in **1-129** was unknown.

Scheme 25 Ligand design (generation V)



Compound **1-129** was then hydrogenated to give **1-128**. The low yield (78%) was attributed to the low purity of **1-129** (unknown contaminant). Global deprotection of **1-128** by HCl in MeOH and subsequent reprotection with Cbz and TIPS yielded **1-133**. The switch of both N- and O- protection groups was necessary as the N-diphenylphosphinyl group is critical for the homoallylation step, and its selective removal vs the TBDPS group failed. Initially, we used a benzyl group for O-protection, allowing a mild deprotection step at a later stage. However, the benzyl group was found to be partially oxidized in the next step. Thus, a TIPS group was used instead.

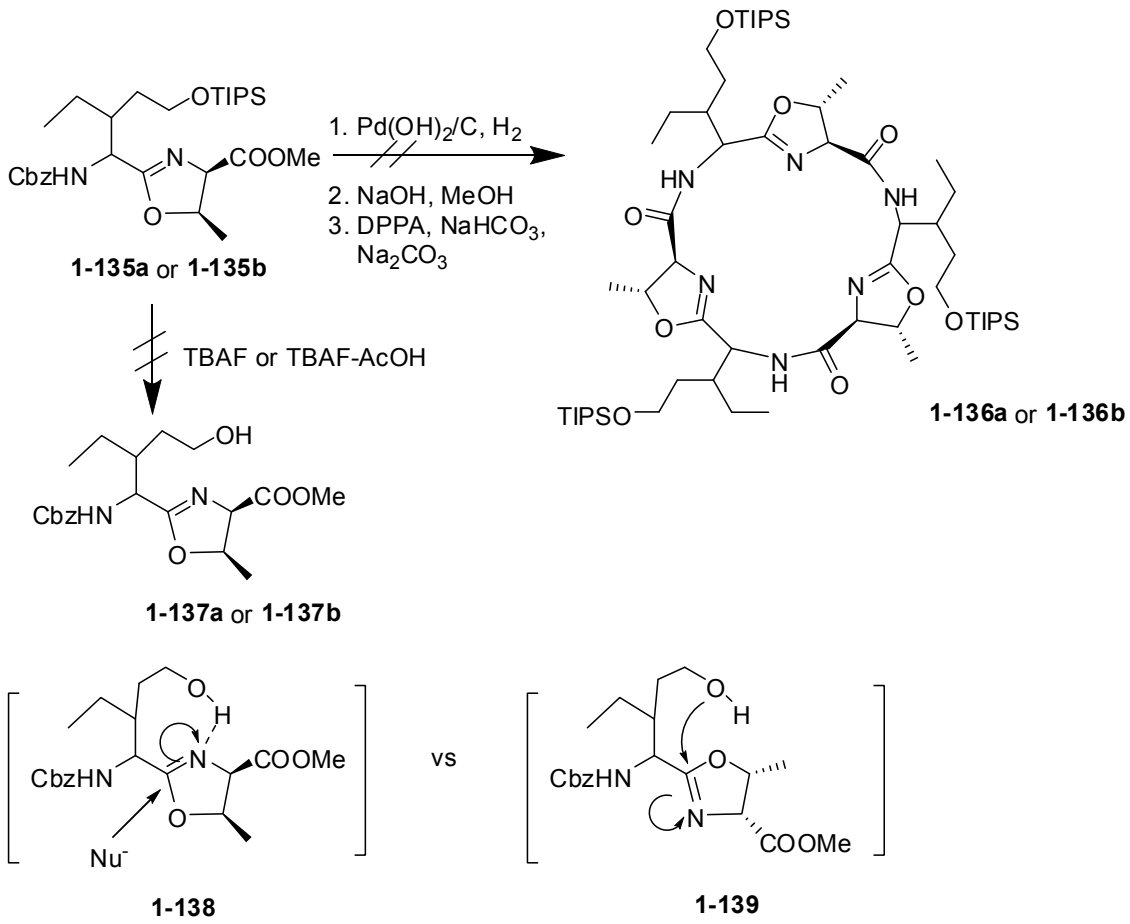
Scheme 26 Approach utilizing a homoallylation strategy



Oxidation of the furan moiety in **1-133** with in situ generated RuO_4[71] provided 43% of **1-128** while ozonolysis gave a complex mixture. We could have resolved the enantiomers of **1-128** by means of a chiral base. However, a decision was made to explore the feasibility of this route first, postponing further optimizations. Therefore, racemic **1-128** was coupled to D-Thr-OMe to

yield a 1:1 mixture of diastereomers **1-134a** and **1-134b** (inseparable on SiO_2). Their relative configration was assigned arbitrarily. Formation of the oxazoline by Burgess reagent or DAST was rather low yielding (40% and 52% overall yield, respectively). The two diastereomers **1-135a** and **1-135b** were successfully separated while their absolute stereochemistry was unknown. Therefore, both of them were subjected to the N- and C-termini deprotection and cyclooligomerization conditions (Scheme 27). Unfortunately, no cyclic oligomers were observed.

Scheme 27 Cyclooligomerization of oxazolines **1-135a** and **1-135b**

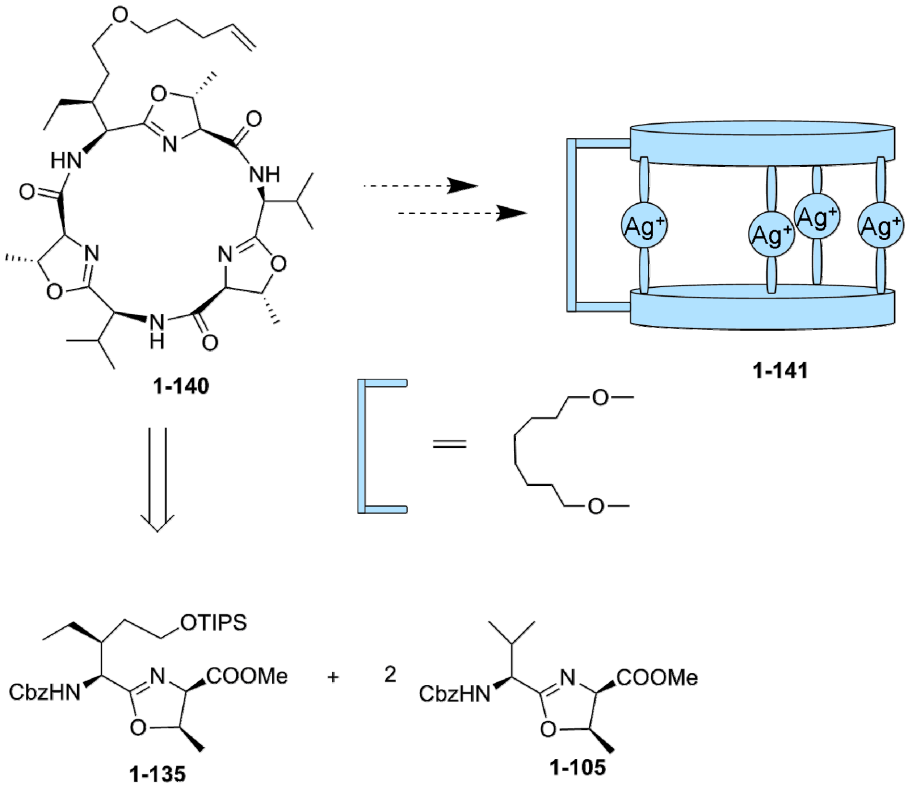


Deprotection of the TIPS group in **1-135a** or **1-135b** by TBAF provided the unstable **1-137a** and **1-137b** (Scheme 27). Their decomposition pattern was similar to oxazoline **1-100** (Scheme 19) according to ^{1}H NMR. Therefore, analogous decomposition pathways (**1-138, 1-139**) can be proposed. When comparing **1-138** and **1-139**, a seven-membered ring is formed for

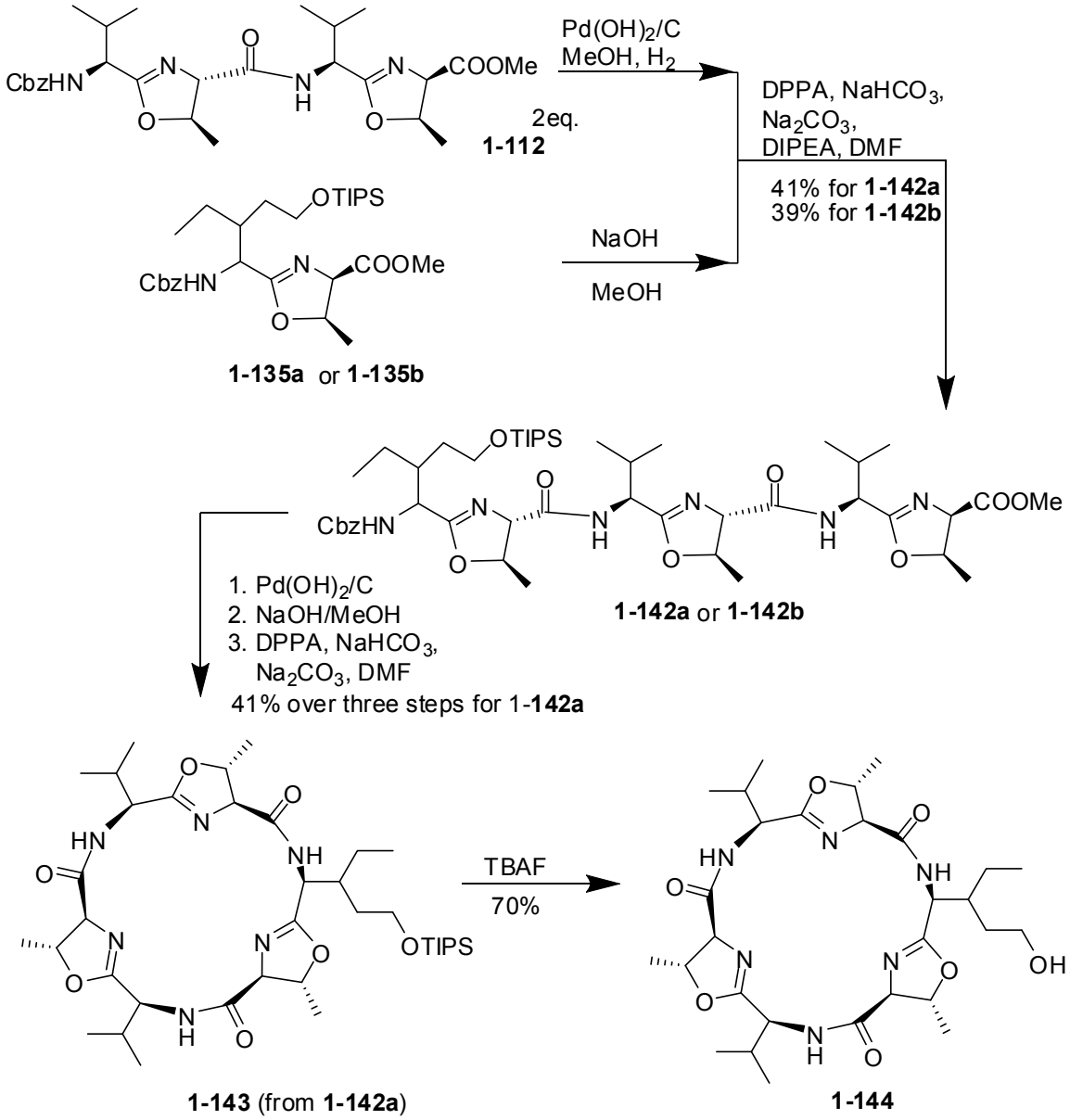
1-138, while **1-139** has a six-membered cycle. Therefore, **1-139** may resemble the actual decomposition pathway.

We also considered the synthesis of the heterocyclotrimer **1-140** (Generation VI) (Scheme 28). This compound can be prepared from oxazolines **1-135** and **1-105** in the same fashion as the Generation IV ligand (Scheme 29).

Scheme 28 Design of ligand (generation VI)



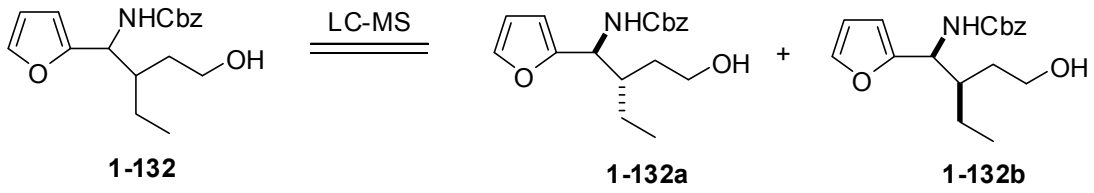
Scheme 29 Macrocyclization approach towards the heterocyclotrimer **1-144**



The coupling of **1-135a** to **1-112** yielded 41% of the linear trimer **1-142a**. Similarly, the coupling with **1-135b** afforded 39% of **1-142b** (Scheme 29). Both compounds were subjected to deprotection and macrocyclization conditions. Interestingly, among the two diastereomers, only the trimer **1-142a,** which was derived from **1-145a**, cyclized to provide 41% of cyclotrimer **1-143**. Hence our initial arbitrary stereochemistry assignment for **1-135a** and **1-135b** was correct. We made the assumption that only the diastereomer with a backbone stereochemistry resembling

westiellamide could be cyclized. Desilylation of **1-143** by TBAF provided 70% of **1-144.** An ^{1}H NMR of **1-144** in $CDCl_3$ showed 3 signals which corresponded to the three backbone NHs in the molecule. However, when **1-144** was dissolved in CD_3OD-D_2O (9:1, v/v), the peaks were split into two sets with a ratio of integration of 1:1. Possibly, **1-144** is a mixture of either diastereomers at the β-position of the functionalized residue or epimers at the C-2 positions of the backbone oxazolines or rotamers. An LC-MS study on the precursor **1-132** revealed that it was a 1:1 mixture of diastereomers (Scheme 30). Due to the difficulty separating the diastereomers and the success of the Generation IV ligand, work on this route was suspended.

Scheme 30 LC-MS study of precursor **1-132**



1-132 **1-132a** **1-132b**

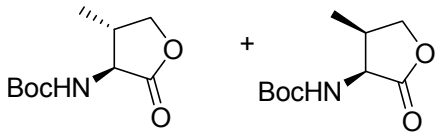
1.3 CONCLUSIONS

We have demonstrated the feasibility of improving the unique affinity of the natural product westiellamide toward silver ions by structural modifications. The tethered ligands **1-119** and **1-121** show higher affinities toward Ag(I) than westiellamide and improve the potential for practical applications of cyclic oligooxazolines in Ag(I) detection, transport, detoxification, and targeted delivery.

1.4 EXPERIMENTAL PART

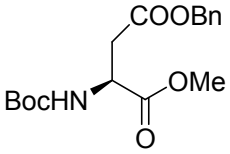
General: All moisture-sensitive reactions were performed under an atmosphere of N_2. Glassware was flame dried prior to use. THF and Et_2O were dried by distillation over Na/benzophenone. DCM was dried by distillation over CaH_2. Unless otherwise stated, solvents and reagents were used as received. Analytical thin layer chromatography was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualization was accomplished with a 254 nm UV light or by staining with an anisaldehyde solution (7.5 mL of *p*-anisaldehyde, 25 mL of concentrated H_2SO_4 and 7.5 mL of glacial acetic acid in 675 mL of 95% ethanol) or $KMnO_4$ solution (1.5 g of $KMnO_4$, 10 g of potassium carbonate and 2.5 mL of 5% aqueous NaOH in 150 mL of H_2O). Flash chromatography on SiO_2 was used to separate and purify the crude reaction mixtures. NMR spectra were recorded at 300 MHz/75 MHz (^{1}H NMR/^{13}C NMR) at 21 ^{o}C in $CDCl_3$ unless otherwise noted. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, dd=doublet of doublet, ddd= doublet of doublet of doublet, dt=doublet of triplet, dq=doublet of quartet, m=multiplet, br=broad, app=apparent). LC/MS analyses were obtained from a Hewlett Packard Series 1100 MSD. Infrared spectra were measured on a Nicolet AVATAR 360 FTIR E.S.P. spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 25 ^{o}C.

For NMR titration and competitive binding study, ^{1}H NMR spectra were recorded at 300 MHz at 21 ^{o}C. Fluorescence spectra were measured on an ISA Instruments Spex Fluorolog fluorescence spectrometer at 23 ^{o}C.

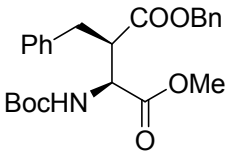


***tert*-Butyl (3*S*,4*S*)-4-methyl-2-oxotetrahydrofuran-3-ylcarbamate (1-78a) and *tert*-butyl (3*S*,4*R*)-4-methyl-2-oxotetrahydrofuran-3-ylcarbamate (1-78b).**[61] A solution of L-valine (117 mg, 1.00 mmol), $CuCl_2$•H_2O (1.19 g, 7.00 mmol) and K_2PtCl_4 (20.8 mg, 0.050 mmol, 5 mol%) in water (3.00 mL) was heated to 160°C (oil bath) for 10 h or 160 ^{o}C (microwave) for 6 h. The reaction mixture was then cooled to room temperature, treated with H_2S and filtered through a pad of Celite. The solution was concentrated to dryness under reduced pressure. The residue was dissolved in EtOH (2.00 mL) and 1 N NaOH (4.00 mL) and treated with a solution of Boc_2O (300 mg, 1.40 mmol) in THF (1.00 mL). The mixture was stirred at room temperature for 2.5 h. THF was removed under reduced pressure and the resulting solution was diluted with water (10.0 mL), cooled to 0 °C and adjusted to pH = 3 (pH paper) with 1 N HCl. The aqueous mixture was extracted with EtOAc (3x). The combined organic phases were then combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was redissolved in $CHCl_3$ (0.50 mL) followed by treatment with glacial HOAc (1 drop) and Na_2SO_4 (0.500 g). The reaction mixture was stirred at room temperature for 2 h. Solvent was removed under reduced pressure and purification by chromatography on SiO_2 (Hexanes:EtOAc=1:1) yielded 28.0 mg (13%) of **1-78a** and 17.0 mg (8%) of **1-78b** (oil bath heating) or 8.6 mg (4%) of **1-78a** (microwave heating) as a clear oil. **1-78a**: ^{1}H NMR ($CDCl_3$) δ

5.02 (br s, 1 H), 4.38 (app t, 1 H, J = 8.0 Hz), 4.13–3.92 (m, 1 H), 3.79 (app t, 1 H, J = 10.1 Hz), 2.58-2.37 (m, 1 H), 1.43 (s, 9 H), 1.19 (d, 3 H, J = 6.5 Hz). **1-78b**: ^{1}H NMR ($CDCl_3$) δ 4.99 (br s, 1 H), 4.47 (app t, 1 H, J = 6.2 Hz), 4.37 (dd, 1 H, J = 9.3, 5.1 Hz), 4.07 (d, 1 H, J = 9.3 Hz), 3.02-2.96 (m, 1 H), 1.44 (s, 9 H), 0.97 (d, 3 H, J = 6.5 Hz).

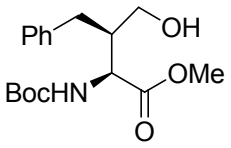


Boc-L-Asp(OBn)-OMe (1-86).[72] A suspension of Boc-Asp(OBzl)-OH (25.0 g, 77.0 mmol) and K_2CO_3 (15.5 g, 114 mmol) in anhydrous DMF (178 mL) at 0 °C was treated with iodomethane (9.66 mL, 144 mmol) and stirred for 3 h. Water (250 mL) was added and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (3x) and brine (4x), dried (Na_2SO_4), filtered through a pad of SiO_2 and concentrated to dryness under reduced pressure to yield 23.0 g (89%) of **1-86** as a clear oil: ^{1}H NMR ($CDCl_3$), δ 7.41-7.25 (m, 5 H), 5.49 (br d, 1 H, J = 8.2 Hz), 5.14 (AB, 1 H, J = 12.3 Hz), 5.12 (AB, 1 H, J = 12.3 Hz), 4.63-4.55 (m, 1 H), 3.70 (s, 3 H), 3.05 (ABX, 1 H, J = 17.0, 4.5 Hz), 2.87 (ABX, 1 H, J = 17.0, 4.7 Hz), 1.45 (s, 9 H).



Methyl 2-*tert*-butoxycarbonylamino-3-carbobenzyloxy-(2*S*,3*S*)-hex-5-enoate (1-87).[63] A solution of **1-86** (20.4 g, 60.5 mmol) in THF (40.0 mL) at -42 °C was treated with a solution of LHMDS (prepared by treatment of a solution of HMDS (31.7 mL, 150 mmol) in THF (150 mL) at -60 °C with *n*-BuLi (1.6 M in hexanes, 93.8 mL), warmed to room temperature for 30 min then re-cooled to -42 °C, followed by addition of HMPA (6.89 mL, 140 mmol). The reaction mixture

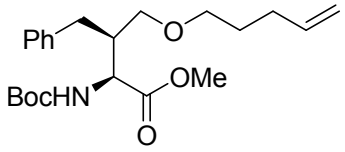
was stirred at -42 °C for 30 min before adding benzyl bromide (8.97 mL, 75.0 mmol). The mixture was stirred for an additional 4 h at -42 °C, and saturated aqueous NH_4Cl (81 mL) was added. The solution was warmed to room temperature and concentrated under reduced pressure. The crude product was redissolved in DCM and washed with aqueous NH_4Cl (2x) and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=4:1) yielded 16.3 g (63%) of **1-87** as a clear oil: ^1H NMR ($CDCl_3$), δ 7.35-7.18 (m, 10 H), 5.56 (d, 1 H, *J* = 9.8 Hz), 5.07 (app s, 2 H), 4.47 (dd, 1 H, *J* = 8.3, 2.1 Hz), 3.59 (s, 3 H), 3.41 (app dt, 1 H, *J* = 7.3, 3.8 Hz), 3.11 (dd, 1 H, *J* = 13.8, 7.2 Hz), 2.85 (dd, 1 H, *J* = 13.8, 8.2 Hz), 1.48 (s, 9 H).



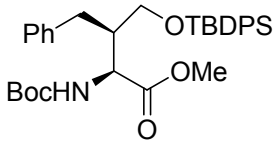
Methyl 3-benzyl-2-*tert*-butoxycarbonylamino-4-hydroxy-(2*S*,3*R*)-butanoate (1-83). [63]

A suspension of **1-87** (11.2 g, 26.3 mmol) and 10% Pd/C (0.570 g) in methanol (156 mL) was exposed to hydrogen gas (1 atm) for 3 h. The mixture was filtered through celite and the solvent was evaporated under reduced pressure. A solution of the crude product (5.53 g, 16.4 mmol) in THF (161 mL) at -40 ºC was treated with triethylamine (3.06 mL, 21.3 mmol) followed by isobutylchloroformate (2.76 mL, 21.3 mmol) and stirred for 1 h. $NaBH_4$ (1.88 g, 49.2 mmol) was added and the reaction mixture was allowed to warm up to 0 ºC over 2 h and stirred for 3.5 h. After addition of 5% HCl (125 mL), the organic solvent was removed under reduced pressure. The residue was dissolved in EtOAc, washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=2:1) afforded 3.27 g (65%) of **1-83** as a clear oil: ^1H NMR ($CDCl_3$) δ 7.33-

7.17 (m, 5 H), 5.59 (d, 1 H, J = 8.9 Hz), 4.42 (dd, 1 H, J =7.8, 6.1 Hz), 3.73 (s, 3 H), 3.65-3.49 (m, 2 H), 2.76-2.71 (m, 2 H), 2.28 (br s, 1 H), 2.04 (br s, 1 H), 1.46 (s, 9 H).

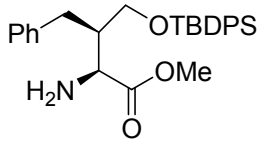


(2*S*,3*R*)-Methyl 3-benzyl-2-(*tert*-butoxycarbonylamino)-4-(pent-4-enyloxy)-butanoate (1-88). A solution of **1-83** (18.9 mg, 0.0585 mmol), 2,6-di-*tert*-butylpyridine (0.0459 mL, 0.210 mmol) and AgOTf (45.0 mg, 0.172 mmol) in DCM (0.5 mL) at 0 ^{o}C was treated with 5-iodopent-1-ene (21.0 μL, 0.187 mmol) and stirred at 0 ^{o}C for 2 h. The reaction mixture was filtered and diluted with DCM, washed with 1 M $NaHSO_4$ and saturated $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=5:1 to 2:1) afforded 6.6 mg (29%) of **1-88** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.32-7.18 (m, 5 H), 5.87-5.75 (m, 2 H), 5.06 (d, 1 H, J = 17.1 Hz), 4.99 (d, 1 H, J = 10.1 Hz), 4.38 (dd, 1 H, J =5.3, 3.4 Hz), 3.70 (s, 3 H), 3.42-3.23 (m, 4 H), 2.78 (app d, 2 H, J = 7.7 Hz), 2.51-2.39 (m, 1 H), 2.15 (app dd, 2 H, J = 14.3, 7.2 Hz), 1.66 (app qn, 2 H, J = 7.4 Hz), 1.47 (s, 9 H). HRMS (ESI) *m/z* calcd for $C_{22}H_{33}NO_5Na$ (M+Na) 414.2256, found 414.2277.



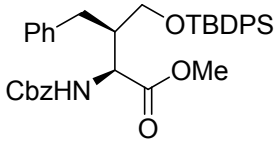
(6*R*,7*S*)-Methyl 6-benzyl-2,2,11,11-tetramethyl-9-oxo-3,3-diphenyl-4,10-dioxa-8-aza-3-siladodecane-7-carboxylate (1-89). A solution of **1-83** (5.42 g, 16.7 mmol) and imidazole (1.47 g, 21.8 mmol) in DMF (60.0 mL) was treated with *tert*-butyldiphenylchlorosilane (5.54 mL, 21.8 mmol). The resulting mixture was stirred at room temperature for 36 h. After addition of a mixture of saturated NH_4Cl (25 mL) and water (250 mL), the aqueous layer was extracted

with EtOAc (3x). The organic layers were combined, washed with brine, dried ($NaSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=5:1) afforded 9.14 g (97%) of **1-89** as a clear oil: $[\alpha]_D^{25}$ +1.0 (*c* 5.0, $CHCl_3$); IR (neat) 3418, 2931, 1748, 1716, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74-7.62 (m, 4 H), 7.48-7.34 (m, 7 H), 7.26-7.09 (m, 4 H), 6.28 (d, 1 H, *J* = 8.9 Hz), 4.40 (dd, 1 H, *J* = 3.7, 8.9 Hz), 3.71-3.61 (m, 1 H), 3.67 (s, 3 H), 3.51 (dd, 1 H, *J* = 3.6, 10.8 Hz), 2.88 (ABX, 1 H, *J* = 14.1, 7.7 Hz), 2.82 (ABX, 1 H, *J* = 13.3, 7.4 Hz), 2.42-2.34 (m, 1 H), 1.50 (s, 9 H), 1.14 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 173.1, 156.3, 139.4, 136.0, 132.5, 130.1, 129.3, 128.6, 128.0, 126.5, 79.6, 63.9, 56.6, 52.3, 43.3, 35.2, 28.6, 27.1, 19.3; HRMS (ESI) *m/z* calcd for $C_{33}H_{43}NO_5SiNa$ (M+Na) 584.2808, found 584.2804.

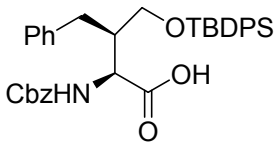


(2*S*,3*R*)-Methyl 2-amino-3-benzyl-4-(*tert*-butyldiphenylsilyloxy)butanoate (1-90). A solution of **1-89** (9.14 g, 16.3 mmol) in DCM (125 mL) at 0 °C was treated with thioanisole (2.00 mL, 19.0 mmol) and trifluoroacetic acid (30.6 mL, 0.456 mol). The mixture was stirred at 17 °C for 40 min. The reaction mixture was quenched with saturated $NaHCO_3$ (600 mL) at 0 °C and extracted with DCM (3x). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=8:1 to 1:1, all with 1% Et_3N) afforded 7.47 g (99%) of crude **1-90** as a clear oil: $[\alpha]_D^{25}$ +23.4 (*c* 0.68, $CHCl_3$); IR (neat) 3391, 2951, 2931, 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74-7.62 (m, 4 H), 7.48-7.34 (m, 7 H), 7.28-7.15 (m, 4 H), 3.69-3.59 (m, 2 H), 3.62 (s, 3 H), 3.48 (app d, 1 H, *J* = 3.6 Hz), 2.76 (ABX, 1 H, *J* = 13.7, 7.3 Hz), 2.70 (ABX, 1 H, *J* = 13.8, 7.9 Hz), 2.50-2.39 (m, 1 H), 1.67 (s, 2 H), 1.16 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 176.3, 139.9, 135.6,

133.2, 129.7, 129.0, 128.3, 127.7, 126.0, 62.9, 54.6, 51.7, 45.6, 34.6, 26.8, 19.2; HRMS (ESI) *m/z* calcd for $C_{28}H_{36}NO_3Si$ (M+H) 462.2482, found 462.2464.

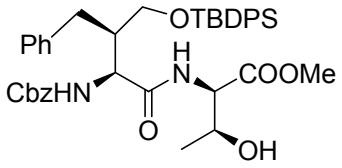


(5*S*,6*R*)-Methyl 6-benzyl-10,10-dimethyl-3-oxo-1,9,9-triphenyl-2,8-dioxa-4-aza-9-silaundecane-5-carboxylate (1-91). A solution of **1-90** (7.47 g, 16.2 mmol) and $NaHCO_3$ (6.80 g, 77.3 mmol) in EtOAc (660 mL) and water (660 mL) at 0 ^oC was treated with benzyl chloroformate (2.57 mL, 18.5 mmol) in EtOAc (260 mL). The reaction mixture was warmed to room temperature, stirred for 14 h, and diluted with EtOAc. The aqueous phase was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=6:1 to 4:1) yielded 8.77 g (91%) of crude **1-91** as a clear oil: $[\alpha]_D^{25}$ -6.7 (*c* 2.3, $CHCl_3$); IR (neat) 3411, 3069, 2952, 1731, 1499 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75-7.68 (m, 4 H), 7.49-7.30 (m, 12 H), 7.30-7.13 (m, 4 H), 6.58 (d, 1 H, *J* = 9.0 Hz), 5.29-5.20 (m, 2 H), 4.59 (dd, 1 H, *J* = 8.9, 3.5 Hz), 3.79 (dd, 1 H, *J* = 10.9, 2.7 Hz), 3.67 (s, 3 H), 3.73-3.58 (m, 1 H), 2.93 (ABX, 1 H, *J* = 13.8, 7.8 Hz), 2.86 (ABX, 1 H, *J* = 13.8, 7.6 Hz), 2.58-2.45 (m, 1 H), 1.19 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 172.5, 156.6, 138.9, 136.6, 135.7, 132.2, 130.0, 129.9, 129.0, 128.5, 128.4, 127.8, 126.3, 66.7, 63.8, 56.3, 52.1, 43.2, 34.9, 26.9, 19.1; HRMS (ESI) *m/z* calcd for $C_{36}H_{41}NO_5SiNa$ (M+Na) 618.2621, found 618.2652.



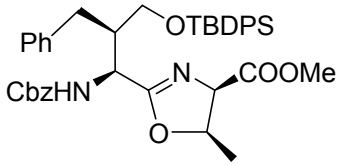
(5*S*,6*R*)-6-Benzyl-10,10-dimethyl-3-oxo-1,9,9-triphenyl-2,8-dioxa-4-aza-9-

silaundecane-5-carboxylic acid (1-92). A solution of **1-91** (8.77 g, 14.7 mmol) in THF:H_2O=3:1 (v/v, 119 mL) was treated with $LiOH \cdot H_2O$ (0.771 g, 18.4 mmol) and stirred at room temperature for 36 h. THF was evaporated and the residue was treated with 1 M aqueous $KHSO_4$ (22.3 mL). The resulting solution was extracted with EtOAc (3x), dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield 8.22 g (96%) of crude **1-92** as a clear oil: $[\alpha]_D^{25}$ –8.2 (*c* 2.2, CH_2Cl_2); IR (neat) 3404, 3069, 3030, 2930, 2858, 1720, 1509, 1471, 1427 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25 (br s, 1 H), 7.58-7.54 (m, 4 H), 7.40-6.97 (m, 16 H), 6.45 (d, 1 H, *J* = 8.8 Hz), 5.17 (AB, 1 H, *J* = 12.6 Hz), 5.14 (AB, 1 H, *J* = 12.5 Hz), 4.46 (dd, 1 H, *J* = 8.6, 2.9 Hz), 3.71 (app d, 1 H, *J* = 10.8 Hz), 3.48 (dd, 1 H, *J* = 10.8, 3.9 Hz), 2.81 (ABX, 1 H, *J* = 13.8, 7.2 Hz), 2.73 (ABX, 1 H, *J* = 13.7, 7.6 Hz), 2.49-2.38 (m, 1 H), 1.02 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 177.3, 156.9, 139.0, 136.6, 135.9, 132.2, 130.1, 129.2, 128.7, 128.6, 128.0, 126.6, 67.1, 64.0, 56.4, 43.1, 35.1, 27.0, 19.2; HRMS (ESI) *m/z* calcd for $C_{35}H_{39}NO_5SiNa$ (M+Na) 604.2495, found 604.2517.



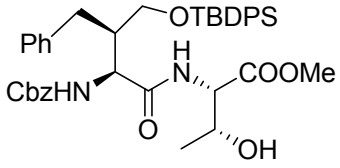
(2*R*,3*S*)-Methyl 2-((2*S*,3*R*)-3-benzyl-2-(benzyloxycarbonylamino)-4-(*tert*-butyl diphenylsilyloxy)butanamido)-3-hydroxybutanoate (1-93). A solution of **1-92** (3.20 g, 5.50 mmol) and N-methylmorpholine (0.664 mL, 6.10 mmol) in DCM (21.0 mL) at -20 °C was treated with isobutylchloroformate (0.787 mL, 6.10 mmol). After 5 min, a suspension of D-threonine methyl ester hydrochloride[73] (1.12 g, 6.60 mmol) and Et_3N (0.934 mL, 6.60 mmol) in DMF (10.0 mL) was added dropwise. The reaction mixture was warmed to room temperature, stirred for 1 h and quenched with saturated $NaHCO_3$ solution. The mixture was diluted with EtOAc and the organic layer was washed with 0.1 M HCl, saturated aqueous $NaHCO_3$ and brine,

dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=1:1) yielded 3.83 g (100%) of crude **1-93** as a clear oil: $[\alpha]_D^{25}$ -12.6 (*c* 2.0, $CHCl_3$); IR (neat) 3369, 3069, 3029, 2953, 2931, 1731, 1669, 1514, 1428 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68-7.57 (m, 4 H), 7.46-6.92 (m, 17 H), 5.48-5.08 (m, 2 H), 4.56 (app d, 1 H, *J* = 8.5 Hz), 4.41-4.26 (m, 2 H), 3.98 (app d, 1 H, *J* = 9.6 Hz), 3.67 (s, 3 H), 3.76-3.56 (m, 1 H), 2.88 (dd, 1 H, *J* = 13.5, 7.9 Hz), 2.73 (dd, 1 H, *J* = 13.7, 7.3 Hz), 2.62-2.49 (m, 1 H), 2.26 (d, 1 H, *J* = 4.6 Hz), 1.20-1.05 (m, 3 H), 1.12 (s, 9 H), 0.94 (d, 1 H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 171.9, 171.0, 156.8, 139.0, 136.6, 136.0, 135.9, 132.4, 130.2, 130.1, 129.1, 128.7, 128.3, 128.0, 126.5, 68.3, 67.3, 64.5, 58.2, 57.5, 52.7, 42.3, 35.1, 27.1, 19.3, 19.2; HRMS (ESI) *m/z* calcd for $C_{40}H_{48}N_2O_7SiNa$ (M+Na) 719.3124, found 719.3129.



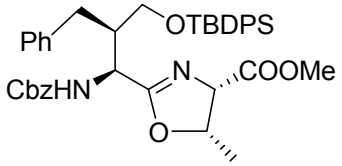
(4*R*,5*R*)-Methyl 2-((5*S*,6*R*)-6-benzyl-10,10-dimethyl-3-oxo-1,9,9-triphenyl-2,8- dioxa-4-aza-9-silaundecan-5-yl)-5-methyl-4,5-dihydrooxazole-4-carboxylate (1-94). A solution of **1-93** (0.908 g, 1.30 mmol) and Burgess reagent (0.336 g, 1.43 mmol) in THF (7.65 mL) was heated to 75 ^oC for 2.5 h in a sealed tube. The resulting mixture was evaporated onto SiO_2 and purified by chromatography on SiO_2 (Hexanes:EtOAc=2:1 to 1:1) to yield 0.701 g (79%) of **1-94** as a clear oil: $[\alpha]_D^{25}$ –35.0 (*c* 2.0, $CHCl_3$); IR (neat) 3408, 3069, 3029, 2953, 2931, 2857, 1731, 1662, 1506, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67-7.59 (m, 4 H), 7.46-7.29 (m, 12 H), 7.24-7.15 (m, 2 H), 7.10-7.05 (m, 2 H), 6.51 (d, 1 H, *J* = 8.7 Hz), 5.23 (AB, 1 H, *J* = 12.5 Hz), 5.15 (AB, 1 H, *J* = 12.5 Hz), 4.88-4.75 (m, 1 H), 4.75-4.60 (m, 2 H), 3.94 (dd, 1 H, *J* = 10.8, 2.6 Hz), 3.67 (s, 3 H), 3.72-3.58 (m, 1 H), 2.95 (ABX, 1 H, *J* = 13.8, 7.0 Hz), 2.84 (ABX, 1 H, *J* = 13.9, 7.9 Hz), 2.44-2.26 (m, 1 H), 1.28 (d, 3 H, *J* =6.3 Hz), 1.10 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 170.0, 169.9,

156.3, 139.2, 136.8, 135.80, 135.75, 132.7, 132.5, 129.9, 129.8, 129.1, 128.5, 128.4, 127.9, 127.7, 126.3, 78.5, 71.3, 66.8, 63.6, 52.4, 52.0, 44.4, 34.7, 27.1, 19.3, 16.0; HRMS (ESI) *m/z* calcd for $C_{40}H_{47}N_2O_6Si$ (M+H) 679.3203, found 679.3181.

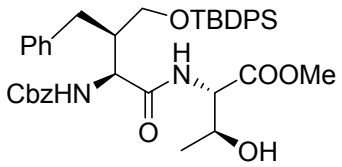


(2*S*,3*R*)-Methyl 2-((2*S*,3*R*)-3-benzyl-2-(benzyloxycarbonylamino)-4-(*tert*-butyl diphenylsilyloxy)butanamido)-3-hydroxybutanoate (1-96). A solution of **1-92** (1.12 g, 1.93 mmol) and N-methylmorpholine (0.232 mL, 2.12 mmol) in DCM (7.60 mL) at -20 ^{o}C was treated with isobutylchloroformate (0.275 mL, 2.12 mmol). After 5 min, a suspension of D-threonine methyl ester hydrochloride (0.396 g, 2.12 mmol) and Et_3N (0.327 mL, 2.12 mmol) in DMF (3.54 mL) was added dropwise. The reaction mixture was warmed to room temperature, stirred for 1 h and quenched with saturated aqueous $NaHCO_3$ solution. The mixture was diluted with EtOAc and the organic layer was washed with 0.1 M HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=1:1) yielded 1.24 g (93%) of **1-96** as a clear oil: $[\alpha]_D^{25}$ -8.48 (*c* 2.0, DCM); IR (neat) 3368, 3066, 2953, 2930, 2891, 2857, 1728, 1689, 1666, 1514, 1471, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ ^{1}H NMR ($CDCl_3$) δ 7.70-7.54 (m, 4 H), 7.45-7.28 (m, 12 H), 7.20-7.13 (m, 2 H), 7.08-6.95 (m, 2 H), 6.64 (d, 1 H, *J* = 7.3 Hz) 5.20 (AB, 1 H, *J* = 12.3 Hz), 5.16 (AB, 1 H, *J* = 12.1 Hz), 4.54 (dd, 1 H, *J* = 8.6, 2.4 Hz), 4.44 (dd, 1 H, *J* = 7.1, 4.6 Hz), 4.35-4.25 (m, 1 H), 3.89 (dd, 1 H, *J* = 10.9, 2.7 Hz), 3.73 (s, 3 H), 3.81-3.60 (m, 1 H), 2.86 (dd, 1 H, *J* = 14.0, 7.0 Hz), 2.63 (dd, 1 H, *J* = 13.7, 8.2 Hz), 2.57-2.45 (m, 1 H), 2.03 (d, 1 H, *J* = 5.4 Hz), 1.14 (dd, 3 H, *J* = 6.4 Hz), 1.10 (s, 9 H), 0.94 (d, 1 H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ172.0, 171.2, 156.7, 139.2, 136.7, 135.9, 132.8, 132.7, 130.1, 129.1, 128.7, 128.3, 128.2,

128.01, 127.98, 126.5, 76.5, 68.3, 67.3, 64.3, 57.5, 52.7, 42.9, 34.7, 27.2, 20.3, 19.4; HRMS (ESI) *m/z* calcd for $C_{40}H_{48}N_2O_7SiNa$ (M+Na) 719.3129, found 719.3107.

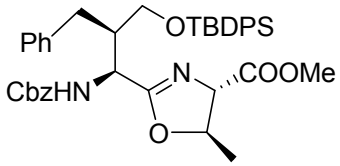


(4*S*,5*S*)-Methyl 2-((5*S*,6*R*)-6-benzyl-10,10-dimethyl-3-oxo-1,9,9-triphenyl-2,8-dioxa-4-aza-9-silaundecan-5-yl)-5-methyl-4,5-dihydrooxazole-4-carboxylate (1-97). A solution of **1-96** (56.8 mg, 0.0815 mmol) and Burgess reagent (21.0 mg, 0.0900 mmol) in THF (0.480 mL) was heated to 75 ^oC for 2.5 h in a sealed tube. The resulting mixture was evaporated onto SiO_2 and purified by chromatography on SiO_2 (Hexanes:EtOAc=2:1 to 1:1) to yield 32.4 mg (59%) of **1-97** as a clear thick oil: $[\alpha]_D^{25}$ +0.22 (*c* 0.89, DCM); IR (neat) 3407, 3230, 3030, 2952, 2931, 2857, 1727, 1663, 1603, 1588, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76-7.61 (m, 4 H), 7.50-7.28 (m, 12 H), 7.23-7.13 (m, 2 H), 7.10-7.05 (m, 2 H), 6.62 (d, 1 H, *J* = 8.6 Hz), 5.22 (AB, 1 H, *J* = 12.5 Hz), 5.11 (AB, 1 H, *J* = 12.5 Hz), 4.90-4.75 (m, 1 H), 4.77 (d, 1 H, *J* = 8.4, 3.5 Hz), 4.61 (dd, 1 H, *J* = 7.1, 2.8 Hz), 3.61 (s, 3 H), 3.66-3.57 (m, 1 H), 2.92 (ABX, 1 H, *J* = 13.8, 7.5 Hz), 2.85 (ABX, 1 H, *J* = 13.8, 7.5 Hz), 2.35-2.25 (m, 1 H), 1.21 (d, 3 H, *J* =6.2 Hz), 1.10 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ170.1, 156.4, 139.5, 136.9, 136.0, 132.7, 130.1, 129.9, 129.3, 128.7, 128.5, 128.00, 127.95, 127.88, 126.4, 78.6, 71.5, 66.9, 64.5, 53.6, 52.2, 52.1, 43.9, 34.8, 27.1, 19.4, 16.1; HRMS (ESI) *m/z* calcd for $C_{40}H_{47}N_2O_6Si$ (M+H) 679.3203, found 679.3201.



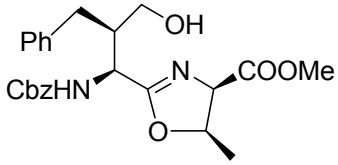
(2*S*,3*S*)-Methyl 2-((2*S*,3*R*)-3-benzyl-2-(benzyloxycarbonylamino)-4-(*tert*-butyl

diphenylsilyloxy)butanamido)-3-hydroxybutanoate (1-98). A solution of **1-97** (32.4 mg, 0.0477 mmol) THF (1.82 mL) was treated with 0.5 M HCl (1.82 mL, 0.910 mmol). After 15 min, the pH was adjusted to 9.5 by 1 M K_2CO_3. The reaction mixture was stirred for 16 h and neutralized by 1 M HCl. THF was evaporated and the residue was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=2:1 to 1:2) yielded 31.0 mg (93%) of crude **1-98** as a clear oil: $[\alpha]_D^{25}$ -1.68 (*c* 1.1, DCM); IR (neat) 3390, 3068, 2952, 2930, 2359, 2341, 1739, 1711, 1683, 1514, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75-7.53 (m, 4 H), 7.49-7.27 (m, 12 H), 7.23-7.15 (m, 2 H), 7.02-6.95 (m, 2 H), 6.82 (d, 1 H, *J* = 7.1 Hz), 5.22 (AB, 1 H, *J* = 12.3 Hz), 5.17 (AB, 1 H, *J* = 12.4 Hz), 4.58 (dd, 1 H, *J* = 6.7, 3.5 Hz), 4.34 (dd, 1 H, *J* = 6.9, 4.7 Hz), 4.18-4.07 (m, 1 H), 3.91 (dd, 1 H, *J* = 10.9, 2.1 Hz), 3.76 (s, 3 H,), 3.80-3.60 (m, 1 H), 2.85 (dd, 1 H, *J* = 13.4, 7.1 Hz), 2.68 (dd, 1 H, *J* = 13.7, 7.9 Hz), 2.56-2.44 (m, 1 H), 1.76-1.62 (m, 1 H), 1.10 (s, 9 H), 1.20-1.10 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ172.0, 171.2, 156.7, 139.1, 136.6, 135.9, 132.7, 132.6, 130.1, 129.1, 128.7, 128.3, 128.2, 128.00, 127.97, 126.5, 77.4, 68.2, 67.3, 64.2, 57.8, 57.4, 52.7, 42.8, 34.7, 27.2, 20.3, 19.3; HRMS (ESI) *m/z* calcd for $C_{40}H_{48}N_2O_7SiNa$ (M+Na) 719.3129, found 719.3146.



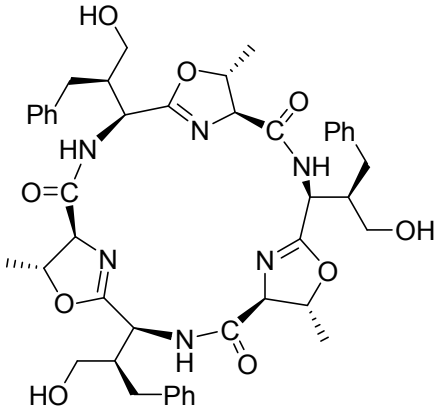
(4*S*,5*R*)-Methyl 2-((5*S*,6*R*)-6-benzyl-10,10-dimethyl-3-oxo-1,9,9-triphenyl-2,8-dioxa-4-aza-9-silaundecan-5-yl)-5-methyl-4,5-dihydrooxazole-4-carboxylate (1-99). A solution of **1-98** (31.0 mg, 0.0440 mmol) and Burgess reagent (11.5 mg, 0.0484 mmol) in THF (0.260 mL) was heated to 75 ^oC for 2.5 h in a sealed tube. The resulting mixture was evaporated onto SiO_2 and purified by chromatography on SiO_2 (Hexanes:EtOAc=2:1 to 1:1) to yield 22.0 mg (74%) of

crude **1-99** as a clear oil: $[\alpha]_D^{25}$ +19.1 (*c* 1.0, DCM); IR (neat) 3406, 3231, 3068, 3030, 2998, 2952, 2930, 2857, 1727, 1659, 1497, 1471 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68-7.60 (m, 4 H), 7.45-7.27 (m, 12 H), 7.23-7.13 (m, 2 H), 7.08-7.02 (m, 2 H), 6.56 (d, 1 H, *J* = 8.7 Hz), 5.23 (AB, 1 H, *J* = 12.5 Hz), 5.12 (AB, 1 H, *J* = 12.5 Hz), 4.82-4.71 (m, 1 H), 4.63 (dd, 1 H, *J* = 8.4, 3.5 Hz), 4.29 (d, 1 H, *J* = 7.1 Hz), 3.97 (dd, 1 H, *J* = 10.6, 2.6 Hz), 3.65 (s, 3 H), 3.59 (dd, 1 H, *J* =10.6, 3.2), 2.94-2.78 (m, 1 H), 2.35-2.28 (m, 1 H), 1.39 (d, 3 H, *J* =6.3 Hz), 1.10 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 171.5, 168.3, 156.4, 139.4, 136.9, 136.0, 132.7, 130.1, 130.0, 129.3, 128.7, 128.6, 128.0, 137.9, 126.4, 79.9, 74.8, 66.9, 63.7, 52.6, 52.2, 44.1, 34.8, 27.1, 21.1, 19.4; HRMS (ESI) *m/z* calcd for $C_{40}H_{47}N_2O_6Si$ (M+H) 679.3203, found 679.3193.



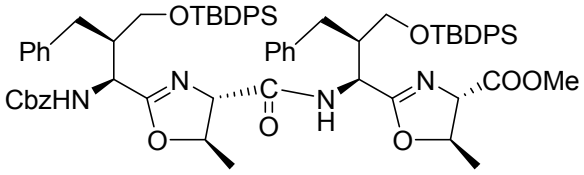
(4*R*,5*R*)-Methyl 2-((1*S*,2*R*)-2-benzyl-1-(benzyloxycarbonylamino)-3-hydroxypropyl)-5-methyl-4,5-dihydrooxazole-4-carboxylate (1-100). A solution of **1-94** (16.0 mg, 0.0236 mmol) in THF (0.250 mL) was treated with TBAF (1.0 M in THF, 47.1 μL, 0.0471 mmol) and stirred at room temperature for 4 h. Water (1 mL) was added and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=1:1 to 100% EtOAc) yielded 7.4 mg (70%) of **1-100** (impure) as a clear oil: ^1H NMR ($CDCl_3$) δ 7.45-7.11 (m, 10 H), 6.08 (d, 1 H, *J* = 8.7 Hz), 5.18 (AB, 1 H, *J* = 12.1 Hz), 5.10 (AB, 1 H, *J* = 12.4 Hz), 4.87-4.76 (m, 1 H), 4.68-4.58 (m, 1 H), 4.30 (d, 1 H, *J* = 6.6 Hz), 3.90-3.60 (m, 1 H), 3.77 (s, 3 H), 3.55 (dd, 1 H, *J* =11.5, 3.2), 2.93-2.67 (m, 4 H), 2.36-2.18 (m, 2 H), 1.51-1.20 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 171.6, 171.3, 170.0, 156.6, 139.6, 136.5,

129.3, 129.0, 128.5, 128.1, 126.3, 80.2, 73.9, 67.1, 60.8, 60.5, 52.7, 51.7, 44.4, 34.5, 21.0, 14.3; HRMS (ESI) *m/z* calcd for $C_{24}H_{28}N_2O_6Na$ (M+Na) 463.1845, found 463.1852.



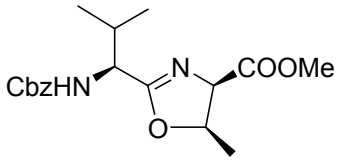
Homocyclic trimer (1-101). A solution of **1-100** (11.7 mg, 0.0266 mmol) and 10% $Pd(OH)_2/C$ (2.4 mg) in MeOH (0.23 mL) was exposed to H_2 (1 atm) for 90 min. The mixture was filtered through celite and the filtrate was treated with aqueous NaOH (1 M, 33.0 μL, 0.0330 mmol) and stirred at room temperature for 2.5 h. After addition of $NaHCO_3$ (11.9 mg, 0.135 mmol), the solvent was evaporated under reduced pressure. The residual water was removed by azeotropic distillation with benzene (2x). The residue was dissolved in DMF (2.00 mL), treated with DPPA (8.8 μL, 0.0410 mmol) at 0 ^oC and stirred for 24 h at 0 ^oC, 24 h at 4 ^oC and 24 h at room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (0.250 mL) and stirring was continued for 1 h. The solvent was evaporated under reduced pressure and the residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (DCM:MeOH=18:1) yielded 0.6 mg (8%) of **1-101** as a clear solid: ^1H NMR ($CDCl_3$) δ 7.86 (d, 1 H, *J* = 8.4 Hz), 7.32-6.92 (m, 5 H), 5.00-4.87 (m, 1 H), 4.87-4.73 (m, 1 H), 4.30 (dd, 1 H, *J* = 8.5, 1.9 Hz), 3.67-3.39 (m, 3 H), 2.93 (dd, 1 H, *J* =13.6, 4.9), 2.70-2.55 (m, 1 H), 2.39 (dd, 1 H, *J*

= 13.8, 9.6 Hz), 1.61 (d, 3 H, *J* = 6.1 Hz); HRMS (ESI) *m/z* calcd for $C_{45}H_{55}N_6O_9$ (M+H) 823.4031, found 823.4009.

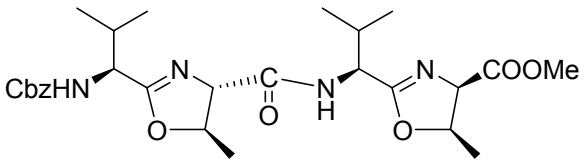


(4*S*,5*R*)-Methyl 2-((1*S*,2*R*)-2-benzyl-1-((4*S*,5*R*)-2-((5*S*,6*R*)-6-benzyl-10,10-dimethyl-3-oxo-1,9,9-triphenyl-2,8-dioxa-4-aza-9-silaundecan-5-yl)-5-methyl-4,5-dihydrooxa-zole-4-carboxamido)-3-(*tert*-butyldiphenylsilyloxy)propyl)-5-methyl-4,5-dihydro-oxazole-4-carboxylate (1-106). A solution of **1-94** (0.331 g, 0.490 mmol) in 4.30 mL MeOH was treated with 1 M aqueous NaOH (0.586 mL, 0.586 mmol). The reaction mixture was stirred at room temperature for 90 min. 5% citric acid was added and the resulting solution was extracted with EtOAc (3x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. A solution of the crude product and N-methylmorpholine (0.0432 mL, 0.541 mmol) in DCM (1.40 mL) at -20 ^oC was treated with isobutylchloroformate (0.0512 mL, 0.541 mmol). After 5 min, a solution of the oxazoline with free N-terminal (0.490 mmol, prepared by the hydrogenolysis of **1-94** (0.243 g, 0.490 mmol) with 10% $Pd(OH)_2/C$ (24.3 mg) in MeOH (4.50 mL)) in DCM (0.660 mL) was added dropwise. The reaction mixture was warmed to room temperature, stirred for 1 h and quenched with saturated aqueous $NaHCO_3$ solution. The mixture was diluted with EtOAc and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=3:1 to 1:1) yielded 0.213 g (50%) of **1-106** as a clear oil: $[\alpha]_D^{25}$ +3.0 (*c* 0.1, DCM); IR (neat) 3399, 3068, 3028, 2930, 2891, 1728, 1685, 1660, 1509 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62-7.49 (m, 8 H), 7.44-6.90 (m, 32 H), 6.50 (d, 1 H, *J* = 7.6 Hz), 5.10-5.00 (m, 2 H), 4.90-4.61 (m, 6 H), 4.15 (d, 1 H, *J* = 7.5 Hz), 3.87 (app d, 1 H, *J* = 10.3 Hz), 3.66 (s, 3 H), 3.76-3.61

(m, 1 H), 3.59-3.47 (m, 2 H), 2.90-2.64 (m, 4 H), 2.39-2.17 (m, 2 H), 1.39 (d, 1 H, *J* = 6.2 Hz), 1.28 (d, 3 H, *J* =6.2 Hz), 1.07 (s, 9 H), 1.06 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 170.9, 170.2, 168.9, 168.7, 156.1, 139.2, 136.7, 136.00, 135.9, 135.8, 133.5, 133.3, 132.5, 130.0, 129.8, 129.3, 129.2, 128.7, 128.5, 127.9, 127.8, 127.7, 126.5, 78.4, 77.4, 75.3, 71.4, 67.0, 63.5, 1.9, 52.2, 48.9, 44.6, 34.6, 34.8, 27.2, 27.1, 22.0, 19.4, 16.3, 14.4; HRMS (ESI) *m/z* calcd for $C_{71}H_{83}N_4O_9Si_2$ (M+H) 1191.5699, found 1191.5710.



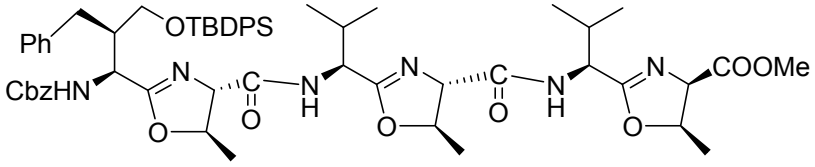
(4*R*,5*R*)-Methyl 2-((*S*)-1-(benzyloxycarbonylamino)-2-methylpropyl)-5-methyl-4,5-dihydrooxazole-4-carboxylate (1-110). Compound **1-110** was prepared from Cbz-Val-OH in 59% overall yield according to the literature[45]: $[\alpha]_D^{25}$ -38 (*c* 0.35, DCM); IR (neat) 3324, 3033, 2962, 2359, 1727, 1662, 1586, 1526, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37-7.25 (m, 5 H), 5.43 (d, 1 H, *J* = 9.0 Hz), 5.12 (AB, 1 H, *J* = 12.1 Hz), 5.08 (AB, 1 H, *J* = 12.3 Hz), 4.94-4.83 (m, 1 H), 4.76 (d, 1 H, *J* = 10.1 Hz), 4.42 (dd, 1 H, *J* = 9.0, 5.6 Hz), 3.72 (s, 3 H), 2.18-2.03 (m, 1 H), 1.28 (d, 1 H, *J* = 6.3 Hz), 0.98 (d, 3 H, *J* = 6.8 Hz), 0.94 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 169.6, 168.6, 155.8, 136.2, 128.2, 128.1, 128.0, 127.7, 77.9, 70.5, 66.4, 54.5, 51.6, 31.3, 18.4, 17.5, 15.7; MS (EI) *m/z* (rel intensity) 348 (20%), 198 (50%),91 (100%),; HRMS (EI) *m/z* calcd for $C_{18}H_{24}N_2O_5$ 348.1685, found 348.1696.



(4*R*,5*R*)-Methyl 2-((*S*)-1-((4*S*,5*R*)-2-((*S*)-1-(benzyloxycarbonylamino)-2-methyl-

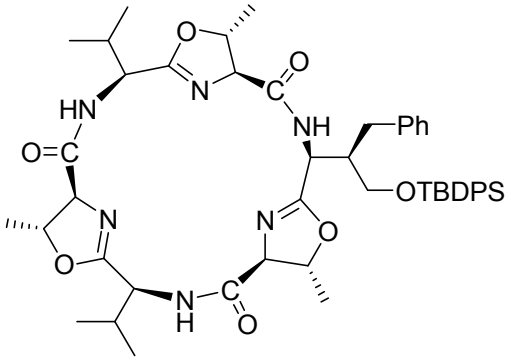
propyl)-5-methyl-4,5-dihydrooxazole-4-carboxamido)-2-methylpropyl)-5-methyl-4,5-dihydrooxazole-4-carboxylate (1-112). A solution of **1-110** (2.69 g, 7.70 mmol) in MeOH (67.2 mL) was treated with 1 M aqueous NaOH (18.5 mL, 18.5 mmol) at room temperature and the mixture was stirred for 90 min. $NaHCO_3$ (3.40 g, 38.5 mmol) was added and the solvent was evaporated under reduced pressure. The water was removed by azeotropic distillation with benzene (2x). The residue was dissolved in DMF (78.0 mL) together with the oxazoline with free N-terminal (15.4 mmol, prepared by the hydrogenolysis of **1-110** (5.37 g, 15.4 mmol) with 10% Pd/C (0.537 g) in MeOH (134 mL)). The resulting solution was cooled to 0 ^{o}C and treated with DIPEA (3.09 mL, 18.5 mmol) followed by DPPA (2.51 mL, 11.6 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 48 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (25 mL) and stirring was continued for 1 h. The solvent was evaporated under reduced pressure and the residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=1:1 to 100% EtOAc, all with 1% Et_3N) yielded 1.94 g (47%) of **1-112** as a yellow oil: $[\alpha]_D^{25}$ -10.4 (*c* 1.1, DCM); IR (neat) 3324, 3034, 2964, 2934, 2875, 2359, 2341, 1724, 1658, 1521, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.42-7.28 (m, 5 H), 6.90 (d, 1 H, *J* = 9.2 Hz), 5.40 (d, 1 H, *J* = 8.8 Hz), 5.15 (AB, 1 H, *J* = 11.9 Hz), 5.10 (AB, 1 H, *J* = 12.1 Hz), 4.89-4.82 (m, 1 H), 4.81-4.73 (m, 2 H), 4.68 (dd, 1 H, *J* = 9.4, 6.2 Hz), 4.41 (dd, 1 H, *J* = 8.4, 4.9 Hz), 4.18 (app d, 1 H, *J* = 7.7 Hz), 3.74 (s, 3 H), 2.20-2.03 (m, 2 H), 1.50 (d, 3 H, *J* = 6.2 Hz), 1.32 (d, 3 H, *J* = 6.4 Hz), 1.03-0.76 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 171.0, 170.1, 168.8, 168.6, 156.2, 136.5, 128.8, 128.4, 81.0, 78.5, 74.8, 71.2, 67.3, 54.9, 52.6,

52.2, 32.8, 18.9, 18.1, 17.8, 16.2; HRMS (ESI) *m/z* calcd for $C_{27}H_{38}N_4O_7$ (M+H) 531.2819, found 531.2819.



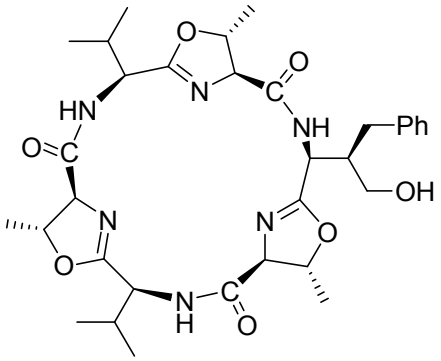
(4*R*,5*R*)-Methyl 2-((*S*)-1-((4*S*,5*R*)-2-((*S*)-1-((4*S*,5*R*)-2-((5*S*,6*R*)-6-benzyl-10,10-dimethyl-3-oxo-1,9,9-triphenyl-2,8-dioxa-4-aza-9-silaundecan-5-yl)-5-methyl-4,5-dihydrooxazole-4-carboxamido)-2-methylpropyl)-5-methyl-4,5-dihydrooxazole-4-carboxamido)-2-methylpropyl)-5-methyl-4,5-dihydrooxazole-4-carboxylate (1-113). A solution of **1-94** (1.24 g, 1.83 mmol) in MeOH (16.0 mL) was treated with 1 M aqueous NaOH (2.16 mL, 2.16 mmol) at room temperature and the mixture was stirred for 2 h. After addition of $NaHCO_3$ (0.791 g, 9.15 mmol), the solvent was evaporated under reduced pressure. The water was removed by azeotropic distillation with benzene (2x). The residue was dissolved in DMF (36.6 mL) together with the oxazoline dimer with free N-terminal (3.66 mmol, prepared by the hydrogenolysis of **1-112** (1.94 g, 3.66 mmol) with 10% $Pd(OH)_2/C$ (0.194 g) in MeOH (44 mL)). The resulting solution was cooled to 0 ^oC and treated with DIPEA (1.45 mL, 9.32 mmol) followed by DPPA (1.19 mL, 5.52 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 48 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) and stirring was continued for 1 h. The solvent was evaporated under reduced pressure and the residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=1:2 to 100% EtOAc, all with 1% Et_3N) yielded 1.54 g (80%) of **1-113** as a yellow oil: $[\alpha]_D^{25}$ +6.5 (*c* 0.40, DCM); IR (neat) 3390, 3305, 3030, 2962, 2931, 2857, 1727,

1680, 1659, 1518, 1454, 1428 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62-7.54 (m, 4 H), 7.46-7.26 (m, 12 H), 7.24-7.14 (m, 2 H), 7.06-6.90 (m, 4 H), 6.53 (d, 1 H, *J* = 7.8 Hz), 5.16 (AB, 1 H, *J* = 12.2 Hz), 5.12 (AB, 1 H, *J* = 12.5 Hz), 4.95-4.83 (m, 1 H), 4.82-4.58 (m, 5 H), 4.57-4.47 (m, 1 H), 4.18 (app d, 1 H, *J* = 7.5 Hz), 4.15-4.06 (m, 1 H), 3.93-3.82 (m, 1 H), 3.76-3.65 (m, 1 H), 3.72 (s, 3 H), 3.59 (dd, 1 H, *J* = 10.7, 4.6 Hz), 2.97-2.69 (m, 2 H), 2.37-2.25 (m, 1 H), 2.18-1.97 (m, 2 H), 1.47 (d, 3 H, *J* = 5.7 Hz), 1.41 (d, 3 H, *J* = 6.2 Hz), 1.30 (d, 3 H, *J* = 6.4 Hz), 1.07 (s, 9 H), 0.96 (d, 3 H, *J* = 6.8 Hz), 0.94 (d, 3 H, *J* = 5.2 Hz), 0.90 (d, 3 H, *J* = 7.2 Hz), 0.87 (d, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 171.1, 171.0, 170.1, 169.1, 168.4, 168.0, 156.1, 39.0, 136.6, 135.7, 135.6, 132.5, 132.4, 130.0, 129.9, 129.0, 128.6, 128.5, 128.1, 127.8, 126.4, 80.8, 80.5, 78.2, 75.0, 74.7, 71.0, 66.8, 63.4, 60.4, 52.74, 52.65, 52.57, 52.1, 44.2, 34.6, 31.4, 31.2, 27.0, 21.9, 21.8, 21.1, 19.2, 18.9, 18.3, 18.1, 16.1, 14.3; HRMS (ESI) *m/z* calcd for $C_{58}H_{75}N_6O_{10}Si$ (M+H) 1043.5314, found 1043.5310.

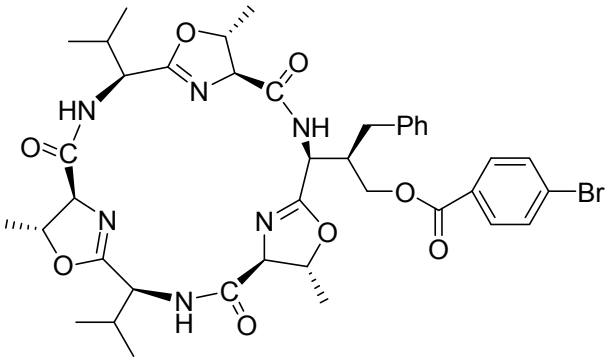


Cyclo[γ-phenyl-*allo*-homoThr(TBDPS)-D-Thr(oxaz)-Val-D-Thr(oxaz)-Val-D-Thr(oxaz)] (1-114). A solution of **1-113** (1.16 g, 1.12 mmol) and 10% $Pd(OH)_2/C$ (117 mg) was exposed to H_2 (1 atm) for 90 min. The mixture was filtered through celite and the filtrate was treated with 1 M aqueous NaOH (1.34 mL, 1.34 mmol) and stirred at room temperature for 2 h. After addition of $NaHCO_3$ (0.468 g, 5.60 mmol), the solvent was evaporated under reduced pressure. The residual water was removed by azeotropic distillation with benzene (2x). The

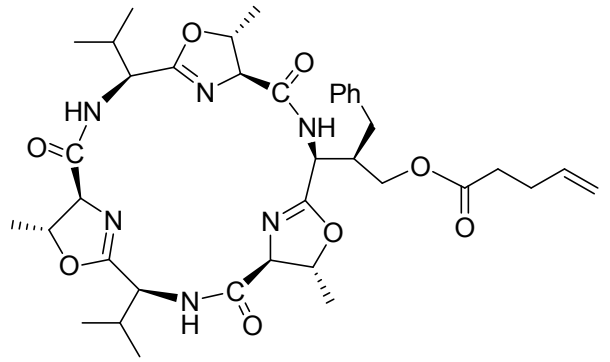
residue was dissolved in DMF (84.0 mL), treated with DPPA (0.362 mL, 1.60 mmol) at 0 ^{o}C and stirred for 24 h at 0 ^{o}C, 24 h at 4 ^{o}C and 24 h at room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15.0 mL) and stirring was continued for 1 h. The solvent was evaporated under reduced pressure and the residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=1:1 with 1% Et_3N) yielded 0.589 g (60%) of **1-114** as a white solid: mp 116.0-119.0 ^{o}C (DCM); $[\alpha]_D^{25}$ +105 (*c* 0.10, DCM); IR (KBr) 3376, 3070, 3027, 2962, 2931, 2858, 1738, 1690, 1651, 1589, 1525 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.94 (d, 1 H, *J* = 6.9 Hz), 7.72 (d, 1 H, *J* = 6.7 Hz), 7.68-7.63 (m, 1 H), 7.60-7.55 (m, 1 H), 7.47-7.27 (m, 9 H), 7.22-7.10 (m, 3 H), 7.05-7.00 (m, 2 H), 5.24-5.16 (m, 1 H), 5.05-4.90 (m, 1 H), 4.85-4.72 (m, 1 H), 4.72-4.52 (m, 3 H), 4.28 (dd, 1 H, *J* = 8.4, 2.0 Hz), 4.20 (dd, 2 H, *J* = 8.6, 1.8 Hz), 3.78-3.69 (m, 1 H), 3.48 (dd, 1 H, *J* = 10.0, 6.4 Hz), 2.77-2.59 (m, 2 H), 2.38-2.06 (m, 3 H), 1.66-1.46 (m, 9 H), 1.02 (s, 9 H), 0.79 (d, 3 H, *J* = 6.9 Hz), 0.71 (d, 3 H, *J* = 6.9 Hz) , 0.67 (d, 3 H, *J* = 6.9 Hz) , 0.61 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 170.7, 170.4, 170.3, 168.7, 168.5, 168.4, 139.1, 135.7, 133.3, 129.9, 129.8, 128.8, 128.5, 127.9, 127.8, 126.4, 82.9, 82.3, 77.4, 74.2, 73.9, 73.7, 62.7, 52.5, 48.1, 46.4, 32.8, 31.7, 31.5, 26.9, 22.2, 22.1, 21.9, 21.3, 19.4, 18.7, 18.6, 17.03, 16.95, 14.4; HRMS (ESI) *m/z* calcd for $C_{49}H_{65}N_6O_7Si$ (M+H) 877.4684, found 877.4692.



Cyclo[γ-phenyl-*allo*-homoThr-D-Thr(oxaz)-Val-D-Thr(oxaz)-Val-D-Thr(oxaz)] (1-115). A solution of **1-114** (0.372 g, 0.424 mmol) in THF (4.43 mL) was treated with TBAF (1.0 M in THF, 0.848 mL, 0.848 mmol). The mixture was stirred at room temperature for 4 h. Water (4.00 mL) was added and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (100% EtOAc with 1% Et_3N) yielded 0.236 g (87%) of crude **1-115** as a white solid: mp 117.0-122.0 ^oC (DCM); $[\alpha]_D^{25}$ +148 (*c* 0.12, DCM); IR (KBr) 3370, 2963, 2930, 2873, 1686, 1652, 1528, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (d, 1 H, *J* = 7.6 Hz), 7.80 (d, 1 H, *J* = 7.8 Hz), 7.73 (d, 1 H, *J* = 7.9 Hz), 7.34-7.07 (m, 5 H), 4.96-4.74 (m, 1 H), 4.68 (app t, 1 H, *J* = 2.9 Hz), 4.65 (app t, 1 H, *J* = 2.6 Hz), 4.34-4.18 (m, 3 H), 3.58-3.40 (m, 2 H), 2.88 (dd, 1 H, *J* = 11.2, 2.0 Hz), 2.51-2.18 (m, 3 H), 1.66-1.52 (m, 11 H), 0.89 (d, 3 H, *J* = 6.9 Hz), 0.88 (d, 3 H, *J* = 6.9 Hz), 0.82 (d, 3 H, *J* = 6.8 Hz), 0.81 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 170.9, 170.7, 170.5, 168.75, 168.71, 168.65, 139.2, 129.0, 128.6, 126.5, 82.9, 82.7, 82.6, 73.94, 73.89, 61.5, 52.43, 52.36, 49.1, 46.4, 34.4, 31.6, 31.5, 22.0, 21.9, 18.7, 16.91, 16.87; *m/z* calcd for $C_{33}H_{46}N_6O_7Na$ (M+Na) 661.3326, found 661.3306.

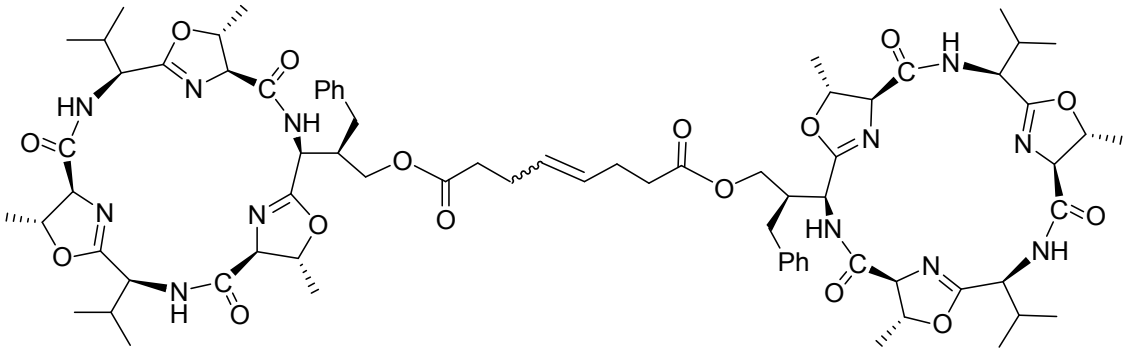


Cyclo[γ-phenyl-*allo*-homoThr-D-Thr(oxaz)-Val-D-Thr(oxaz)-Val-D-Thr(oxaz)] *p*-bromo-benzoate (1-116). A solution of **1-115** (6.8 mg, 0.011 mmol), triethylamine (15 μL, 0.11 mmol) and catalytic DMAP (0.5 mg, 0.004 mmol) in DCM (0.50 mL) at 0 ^{o}C was treated with *p*-bromobenzoyl chloride (6.9 mg, 0.033 mmol). The mixture was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure. Purification by preparative TLC (Hexanes:EtOAc=2:1) yielded 6.8 mg (78%) of **1-116** as a clear solid. A crystal was obtained from DCM-Hexanes: mp 119.0-123.0 ^{o}C (DCM); ^{1}H NMR ($CDCl_3$) δ 8.19 (d, 1 H, *J* = 6.4 Hz), 7.84 (d, 1 H, *J* = 7.7 Hz), 7.79-7.69 (m, 3 H), 7.57-7.47 (m, 2 H), 7.27-7.14 (m, 3 H), 7.09-7.02 (m, 2 H), 5.04-4.90 (m, 3 H), 4.85-4.76 (m, 1 H), 4.71-4.60 (m, 2 H), 4.45 (dd, 1 H, *J* = 11.3, 7.9 Hz), 4.32-4.20 (m, 3 H), 4.18-4.09 (m, 1 H), 2.90-2.78 (m, 2 H), 2.35-2.17 (m, 3 H), 1.68-1.56 (m, 9 H), 0.85 (d, 3 H, *J* = 6.9 Hz), 0.83 (d, 3 H, *J* = 6.9 Hz), 0.75 (app d, 6 H, *J* = 6.8 Hz).



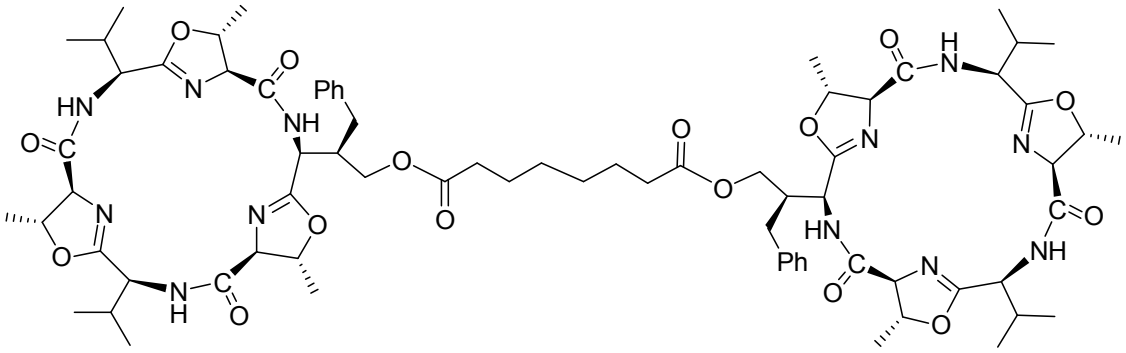
Cyclo[γ-phenyl-*allo*-homoThr-D-Thr(oxaz)-Val-D-Thr(oxaz)-Val-D-Thr(oxaz)] pent-4-enoate (1-117). A solution of **1-115** (0.121 g, 0.190 mmol), triethylamine (77.0 μL,

0.570 mmol) and catalytic DMAP (2.0 mg, 0.016 mmol) in DCM (7.06 mL) at 0 °C was treated with pent-4-enoyl chloride (29.2 μL, 0.285 mmol). The mixture was stirred at room temperature for 2 h. Brine (4.00 mL) was added and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=1:2) yielded 0.123 g (90%) of **1-117** as a sticky clear solid: $[\alpha]_D^{25}$ +401 (*c* 0.45, DCM); IR (neat) 3376, 2963, 2930, 1738, 1689, 1652, 1523, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.09 (d, 1 H, *J* = 6.6 Hz), 7.83 (d, 1 H, *J* = 7.7 Hz), 7.73 (d, 1 H, *J* = 8.0 Hz), 7.29-7.16 (m, 3 H), 7.10-7.05 (m, 2 H), 5.85-5.66 (m, 1 H), 5.10-4.82 (m, 5 H), 4.82-4.74 (m, 1 H), 4.74-4.60 (m, 2 H), 4.30-4.14 (m, 3 H), 4.10 (dd, 1 H, *J* = 7.0, 3.5 Hz), 3.98 (dd, 1 H, *J* = 11.3, 5.9 Hz), 2.84-2.61 (m, 2 H), 2.34-2.14 (m, 7 H), 1.65-1.52 (m, 9 H), 0.87 (d, 3 H, *J* = 6.9 Hz), 0.83 (d, 3 H, *J* = 6.9 Hz), 0.77 (d, 3 H, *J* = 7.1 Hz), 0.74 (d, 3 H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 172.7, 170.7, 170.2, 168.7, 168.6, 167.6, 138.2, 136.8, 128.9, 128.7, 126.8, 115.7, 83.2, 82.9, 82.2, 74.1, 73.9, 63.7, 53.6, 52.7, 52.5, 48.8, 43.2, 34.0, 33.5, 31.7, 31.6, 28.9, 22.1, 22.0, 18.7, 17.2, 17.1; HRMS (ESI) *m/z* calcd for $C_{38}H_{52}N_6O_8Na$ (M+Na) 743.3744, found 743.3727.



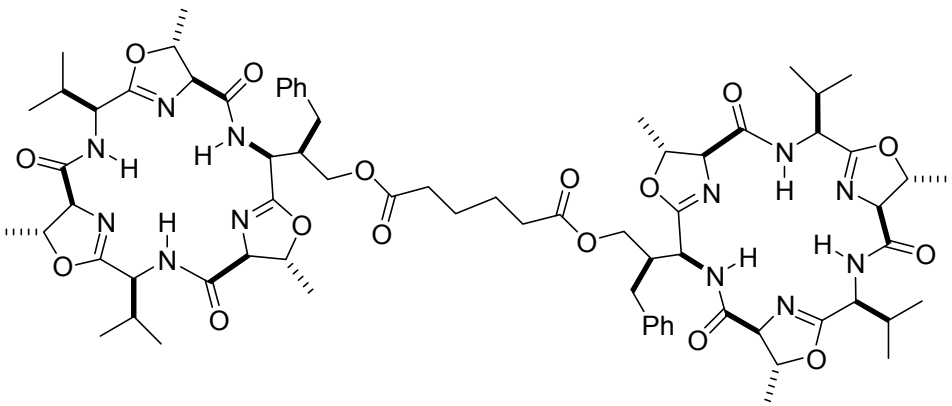
Di-cyclo[γ-phenyl-*allo*-homoThr-D-Thr(oxaz)-Val-D-Thr(oxaz)-Val-D-Thr(oxaz)] oct-4-enedioate (1-118). A solution of **1-117** (0.123 g, 0.171 mmol) in DCM (1.00 mL) at room temperature was treated with Grubb's 2nd generation catalyst (14.5 mg, 0.0171 mmol). The

mixture was stirred at room temperature for 14 h. water (2.00 mL) was added and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=1:1 to 1:3, all with 1% Et_3N) yielded 47.5 mg (39%) of **1-118** and 50.7 mg (41%) of starting material **1-117**. The recovered **1-117** was re-subjected to the above condition to provide **1-118** (72.5 mg) in a combined yield of 60%. **1-118** is a sticky brown solid: $[\alpha]_D^{25}$ +127 (*c* 2.21, DCM); IR (neat) 3376, 2963, 2928, 2872, 1739, 1689, 1652, 1524, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08 (d, 1 H, *J* = 6.5 Hz), 7.81 (d, 1 H, *J* = 7.7 Hz), 7.71 (d, 1 H, *J* = 8.0 Hz), 7.28-7.11 (m, 3 H), 7.07-7.02 (m, 2 H), 5.48-5.27 (m, 1 H), 4.99-4.84 (m, 3 H), 4.84-4.74 (m, 1 H), 4.68-4.59 (m, 2 H), 4.29-4.18 (m, 3 H), 4.14-4.04 (m, 1 H), 4.01-3.92 (m, 1 H), 2.80-2.62 (m, 2 H), 2.30-2.11 (m, 7 H), 1.65-1.55 (m, 9 H), 0.85 (d, 3 H, *J* = 6.9 Hz), 0.82 (d, 3 H, *J* = 6.9 Hz), 0.75 (d, 3 H, *J* = 8.1 Hz), 0.72 (d, 3 H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 172.8, 170.7, 170.6, 168.7, 168.6, 167.6, 138.1, 129.5, 128.8, 128.7, 126.8, 83.2, 83.0, 82.2, 74.0, 73.9, 73.8, 63.7, 52.7, 52.4, 48.7, 43.2, 34.0, 33.8, 31.7, 31.6, 27.8, 22.2, 22.1, 22.0, 18.7, 17.1, 17.0; HRMS (ESI) *m/z* calcd for $C_{74}H_{100}N_{12}O_{16}Na$ (M+Na) 1435.7278, found 1435.7157.



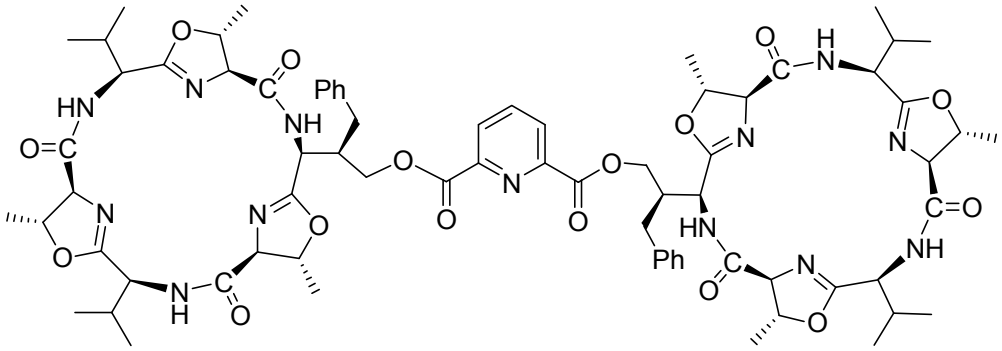
Di-cyclo[γ-phenyl-*allo*-homoThr-D-Thr(oxaz)-Val-D-Thr(oxaz)-Val-D-Thr(oxaz)] suberate (1-119). A solution of **1-118** (47.5 mg, 0.0336 mmol) and 10% Pd/C (24.0 mg) in MeOH (0.750 mL) at room temperature was exposed to H_2 (1 atm) for 4 h. The mixture was

filtered and concentrated under reduced pressure to provide 48.0 mg (100%) of **1-119** as a sticky tan solid: $[\alpha]_D^{25}$ +132 (*c* 3.6, DCM); IR (neat) 3376, 2963, 2928, 2872, 1737, 1689, 1652, 1524, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08 (d, 1 H, *J* = 6.5 Hz), 7.82 (d, 1 H, *J* = 7.7 Hz), 7.73 (d, 1 H, *J* = 8.0 Hz), 7.30-7.11 (m, 3 H), 7.08-7.04 (m, 2 H), 4.99-4.84 (m, 3 H), 4.84-4.75 (m, 1 H), 4.70-4.59 (m, 2 H), 4.30-4.16 (m, 3 H), 4.09 (dd, 1 H, *J* = 11.3, 8.5 Hz), 3.97 (dd, 1 H, *J* = 11.2, 5.8 Hz), 2.82-2.58 (m, 2 H), 2.32-2.03 (m, 5 H), 1.67-1.48 (m, 11 H), 1.27-1.22 (m, 2 H), 0.86 (d, 3 H, *J* = 7.0 Hz), 0.83 (d, 3 H, *J* = 6.9 Hz), 0.76 (d, 3 H, *J* = 7.6 Hz), 0.74 (d, 3 H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 173.4, 170.6, 170.2, 168.7, 168.5, 167.6, 138.1, 128.8, 128.7, 126.7, 83.2, 82.9, 82.2, 74.0, 73.8, 73.7, 63.5, 52.6, 52.4, 48.6, 43.1, 34.1, 33.9, 31.7, 31.6, 28.9, 24.7, 22.10, 22.06, 21.99, 18.7, 18.6, 17.1, 17.0; HRMS (ESI) *m/z* calcd for $C_{74}H_{103}N_{12}O_{16}$ (M+H) 1415.7615, found 1415.7627.



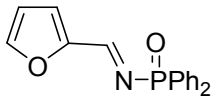
Di-cyclo[γ-phenyl-*allo*-homoThr-D-Thr(oxaz)-Val-D-Thr(oxaz)-Val-D-Thr(oxaz)] adipate (1-121). A solution of **1-119** (59.9 mg, 0.0938 mmol) and pyridine (45.5 μL, 0.563 mmol) in DCM (1.00 mL) at 0 °C was treated with adipoyl chloride (6.82 μL, 0.0469 mmol). The mixture was stirred at room temperature for 18 h. Purification by chromatography on SiO_2 ((Hexanes:EtOAc=1:2 with 1% Et_3N) followed by preparative HPLC on a Rainin® Dynamax™ 60 normal phase column (Hexanes:EtOAc=3:7 to 100% EtOAc) yielded 29.4 mg (45%) of **1-121**

as a clear sticky solid: $[\alpha]_D^{25}$ +120 (*c* 0.38, DCM); IR (neat) 3376, 2963, 2929, 2872, 1737, 1689, 1653, 1525, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.09 (d, 1 H, *J* = 6.6 Hz), 7.82 (d, 1 H, *J* = 7.7 Hz), 7.72 (d, 1 H, *J* = 7.7 Hz), 7.28-7.14 (m, 3 H), 7.07-7.03 (m, 2 H), 5.00-4.84 (m, 3 H), 4.84-4.75 (m, 1 H), 4.69-4.60 (m, 2 H), 4.30-4.18 (m, 3 H), 4.09 (dd, 1 H, *J* = 11.3, 8.5 Hz), 3.97 (dd, 1 H, *J* = 11.3, 5.9 Hz), 2.81-2.63 (m, 2 H), 2.35-2.09 (m, 5 H), 1.79-1.47 (m, 11 H), 0.86 (d, 3 H, *J* = 7.0 Hz), 0.82 (d, 3 H, *J* = 6.9 Hz), 0.75 (d, 3 H, *J* = 7.4 Hz), 0.73 (d, 3 H, *J* = 7.4 Hz); ^{13}C NMR (125MHz) ($CDCl_3$) δ 173.0, 170.7, 170.2, 168.8, 168.6, 167.6, 138.2, 128.9, 128.8, 126.8, 83.3, 83.0, 82.2, 74.0, 73.9, 73.8, 63.7, 52.7, 52.5, 48.7, 43.2, 33.9, 33.8, 31.6, 24.3, 22.1, 22.0, 18.7, 17.1; HRMS (ESI) *m/z* calcd for $C_{72}H_{99}N_{12}O_{16}$ (M+H) 1387.7302, found 1387.7324.

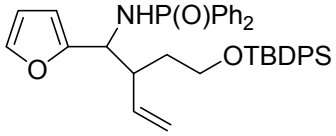


Di-cyclo[γ-phenyl-*allo*-homoThr-D-Thr(oxaz)-Val-D-Thr(oxaz)-Val-D-Thr(oxaz)] pyridine-2,6-dicarboxylate (1-122). A solution of **1-115** (10.0 mg, 0.0157 mmol), triethylamine (11.0 μL, 0.0783 mmol) and catalytic DMAP (0.5 mg, 0.006 mmol) in DCM (0.20 mL) at 0 ^oC was treated with 2,6-dicarbonylpyridine dichloride (1.6 mg, 0.0075 mmol). The mixture was stirred at room temperature for 2 h. Purification by preparative TLC (100% EtOAc with 1% Et_3N) yielded 8.5 mg (81%) of **1-123** as a sticky clear solid: $[\alpha]_D^{25}$ +12.2 (*c* 0.85, DCM); IR (neat) 3376, 2964, 2930, 2873, 1751, 1724, 1689, 1652, 1524, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.14 (d, 2 H, *J* = 6.5 Hz), 8.06 (d, 2 H, *J* = 7.7 Hz), 7.89 (app t, 1 H, *J* = 7.2 Hz), 7.85 (d, 2 H, *J* = 7.8 Hz), 7.73 (d, 2 H, *J* = 8.0 Hz), 7.27-7.08 (m, 10 H), 5.02-4.90 (m, 6 H), 4.87-4.76 (m, 2 H),

4.74-4.57 (m, 4 H), 4.50 (dd, 2 H, J = 11.5, 8.1 Hz), 4.31-4.17 (m, 8 H), 2.96-2.79 (m, 4 H), 2.44-2.17 (m, 6 H), 1.64-1.56 (m, 18 H), 0.94-0.73 (m, 24 H); ^{13}C NMR ($CDCl_3$) δ 170.8, 170.7, 170.2, 168.8, 168.7, 167.6, 163.9, 148.4, 138.3, 129.0, 128.8, 128.1, 126.8, 83.4, 83.0, 82.2, 74.1, 73.9, 65.3, 52.7, 52.5, 48.9, 43.4, 34.0, 31.8, 31.6, 22.1, 22.0, 18.7, 17.2, 17.1; HRMS (ESI) *m/z* calcd for $C_{73}H_{93}N_{13}O_{16}Na$ (M+Na) 1430.6761, found 1430.6757.

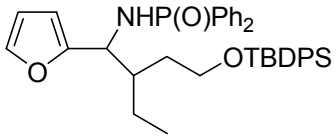


N-(Furan-2-ylmethylene)-P,P-diphenylphosphinic amide (1-131).[70,74] A solution of diphenylphosphinic amide (2 g, 9.21 mmol), furaldehyde (0.76 mL, 9.2 mmol) and triethylamine (3.8 mL, 28 mmol) in DCM (40 mL) at 0 ^{o}C was treated with a solution of $TiCl_4$ (0.56 mL, 5.1 mmol) in DCM (8 mL). The reaction mixture was stirred at room temperature for 16 h and subsequently poured into anhydrous ether (80 mL). The resulting suspension was filtered through a mixture of SiO_2 and celite (1:1 v/v) and concentrated under reduced pressure. The residue was dissolved in minimal DCM. Hexanes were added to precipitate the product (1.3 g, 48%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 9.06 (d, 1 H, J = 32.8 Hz), 8.00-7.88 (m, 2 H), 7.72 (app s, 1 H), 7.54-7.41 (m, 8 H), 7.21 (d, 1 H, J = 3.4 Hz), 6.62 (dd, 1 H, J = 3.5, 1.7 Hz).



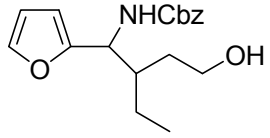
N-(2-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-1-(furan-2-yl)but-3-enyl)-P,P-diphenylphosphinic amide (1-129). A suspension of Cp_2ZrHCl (10.3 g, 11.0 mmol) in DCM (87.0 mL) at 0 ^{o}C was treated with (but-3-ynyloxy)(*tert*-butyl)diphenylsilane(11.1 g, 35.9 mmol) and stirred at room temperature for 30 min. The yellow solution was cooled to -78 ^{o}C, treated with Me_2Zn (2.0 M solution in toluene, 16.3 mL, 33.0 mmol), warmed to room temperature over

a period of 5 min, treated with CH_2I_2 (4.34 mL, 54.0 mmol), stirred for 2 min, and treated with a solution of imine **1-131** (3.19 g, 10.8 mmol) in 20.0 mL of DCM. The reaction mixture was stirred at room temperature for 3 h, quenched with saturated NH_4Cl, diluted with EtOAc and saturated $NaHCO_3$, filtered through Celite, washed with water and brine, dried (MgSO4), filtered through a pad of Florisil and concentrated in vacuo. Purification by chromatography on SiO_2 (Hexanes:EtOAc=1:1) yielded 4.52 g (68%) of crude **1-129** (yellow oil) as a 1:1 (inseparable) mixture of diastereomers: IR (neat) 3367, 3182, 3071, 2997, 2930, 2856, 1590, 1483 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90-7.73 (m, 4 H), 7.73-7.59 (m, 4 H), 7.47-7.27 (m, 12 H), 6.23 (dd, 1 H, *J* = 3.2, 1.3 Hz), 5.98 (d, 1 H, *J* = 3.2 Hz), 5.60 (app t, 0.45 H, *J* = 9.9 Hz), 5.54 (app t, 0.53 H, *J* = 9.9 Hz), 5.22-5.11 (m, 2 H), 4.31 (app t, 0.43 H, *J* = 5.1 Hz), 4.25 (app t, 0.54 H, *J* = 5.0 Hz), 3.67-3.50 (m, 4 H), 2.87-2.75 (m, 1 H), 1.43-1.23 (m, 2 H), 1.03 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 154.0, 153.9, 144.8, 141.3, 137.4, 135.3, 133.71, 133.66, 133.59, 132.9, 132.2, 132.1, 132.0, 131.6, 131.4, 131.2, 129.4, 128.3, 128.2, 128.0, 127.4, 118.7, 109.8, 107.2, 61.5, 51.8, 47.22, 47.16, 34.1, 26.7, 19.0; HRMS (ESI) *m/z* calcd for $C_{38}H_{42}NO_3SiPNa$ (M+Na) 642.2569 (product), found 642.2598, also calcd for $C_{39}H_{45}NO_3SiPNa$ 634.2906 (contaminant), found 634.2939.



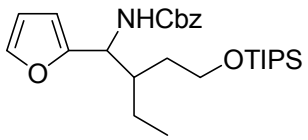
N-(4-(*tert*-Butyldiphenylsilyloxy)-2-ethyl-1-(furan-2-yl)butyl)-P,P-diphenylphosphinic amide (1-128). A solution of **1-129** (7.73 g, 12.5 mmol) and 10% Pd/C (0.773 g) in MeOH (160 mL) at room temperature was exposed to H_2 (1 atm) for 5 h. The mixture was filtered through celite and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=1:1) to provide 6.09 g (78%) of crdue **1-119** as a

yellow oil: IR (neat) 3193, 3070, 3053, 2958, 2930, 2857, 1590, 1504, 1471, 1461 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.88-7.73 (m, 4 H), 7.64-7.57 (m, 4 H), 7.48-7.27 (m, 13 H), 6.24 (dd, 1 H, *J* = 3.4, 1.9 Hz), 6.05 (d, 1 H, *J* = 3.2 Hz), 4.26 (app t, 0.49 H, *J* = 5.4 Hz), 4.21 (app t, 0.48 H, *J* = 5.5 Hz), 3.71-3.53 (m, 2 H), 3.34 (app dd, 1 H, *J* = 10.6, 8.2 Hz), 1.99-1.89 (m, 1 H), 1.88-1.75 (m, 1 H), 1.56-1.41 (m, 2 H), 1.26-1.12 (m, 2 H), 0.99 (s, 9 H), 0.73 (t, 3 H, *J* = 7.4); ^{13}C NMR ($CDCl_3$) δ 155.75, 155.69, 141.4, 135.8, 134.1, 134.0, 132.7, 132.6, 132.2, 132.1, 132.02, 131.98, 131.9, 131.8, 129.8, 128.7, 128.6, 128.4, 127.8, 110.3, 107.1, 62.5, 1.9, 42.0, 41.9, 32.7, 27.1, 23.4, 19.3, 11.6; HRMS (ESI) *m/z* calcd for $C_{38}H_{44}NO_3SiPNa$ (M+Na) 644.2726, found 644.2756.

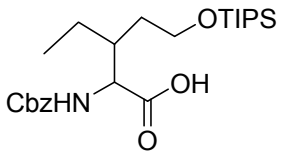


Benzyl 2-ethyl-1-(furan-2-yl)-4-hydroxybutylcarbamate (1-132). A solution of **1-128** (6.09 g, 9.79 mmol) in MeOH (52.4 mL) was treated with HCl (1 M solution in MeOH, 50.0 mL, 50.0 mmol). The reaction mixture was stirred at room temperature for 14 h and concentrated under reduced pressure. The residue was redissolved in EtOAc (70.0 mL) and water (70.0 mL), cooled to 0 ^oC and treated with $NaHCO_3$ (4.21 g, 47.8 mmol) and benzyl chloroformate (1.68 mL, 11.8 mmol). The reaction mixture was warmed to room temperature, stirred for 14 h and diluted with EtOAc. The aqueous phase was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=3:1 to 1:1) yielded 2.41 g (77%) of **1-132** as a yellow oil: IR (neat) 3411, 3322, 3065, 3033, 2960, 2936, 2877, 1701, 1587, 1535, 1504, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38-7.32 (m, 6 H), 6.31 (dd, 1 H, *J* = 3.2, 1.9 Hz), 6.18 (d, 1 H, *J* = 3.0 Hz), 5.55 (d, 1 H, *J* = 9.2 Hz), 5.12 (s, 2 H), 4.94 (dd, 1 H, *J* = 9.1, 6.2 Hz),

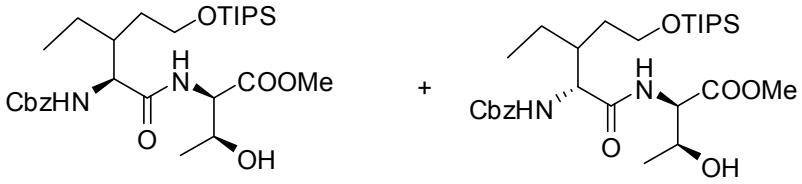
3.82-3.54 (m, 2 H), 2.05-1.94 (m, 1 H), 1.45-1.34 (m, 2 H), 1.33-1.20 (m, 2 H), 0.92 (t, 3 H, *J* = 7.4); ^{13}C NMR ($CDCl_3$) δ 156.4, 154.2, 141.5, 136.4, 128.4, 128.01, 127.97, 127.7, 110.1, 106.5, 66.8, 30.1, 51.7, 40.1, 31.9, 23.0, 11.1; HRMS (ESI) *m/z* calcd for $C_{18}H_{23}NO_4Na$ (M+Na) 340.1525, found 340.1518.



Benzyl 2-ethyl-1-(furan-2-yl)-4-(triisopropylsilyloxy)butylcarbamate (1-133). A Solution of **1-132** (0.914 g, 2.88 mmol) and 2,6-lutidine (1.00 mL, 8.70 mmol) in DCM (7.00 mL) at 0 ^{o}C was treated with triisopropylsilyl triflate (0.869 mL, 3.20 mmol). The reaction mixture was stirred at room temperature for 2 h, quenched with 2 M HCl, extracted with EtOAc (3x). The combined organic layers were washed with 2 M HCl and brine, dried (Na_2SO4), filtered and concentrated in vacuo. Purification by chromatography on SiO_2 (Hexanes:EtOAc=14:1) yielded 1.19 g (87%) of **1-133** as a yellow oil: IR (neat) 3324, 2958, 2942, 2891, 2865, 1725, 1712, 1530, 1503, 1463 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38-7.27 (m, 6 H), 6.31 (dd, 1 H, *J* = 3.1, 1.8 Hz), 6.19 (d, 1 H, *J* = 3.0 Hz), 5.81 (d, 1 H, *J* = 9.0 Hz), 5.11 (s, 2 H), 4.88 (dd, 1 H, *J* = 8.8, 6.2 Hz), 3.80-3.61 (m, 2 H), 2.10-1.95 (m, 1 H), 1.72-1.61 (m, 2 H), 1.57-1.25 (m, 5 H), 1.06 (s, 18 H), 0.95 (t, 3 H, *J* = 7.3); ^{13}C NMR ($CDCl_3$) δ 156.4, 155.0, 141.6, 136.7, 128.6, 128.2, 110.3, 106.5, 67.0, 61.5, 51.9, 40.3, 32.6, 23.8, 18.2, 12.1, 11.6; MS (EI) *m/z* (rel intensity) 473 (15), 430 (25), 338 (20), 264 (55), 221 (40), 149 (30), 91 (100); HRMS (EI) *m/z* calcd for $C_{27}H_{43}NO_4Si$ 473.2961, found 473.2959.

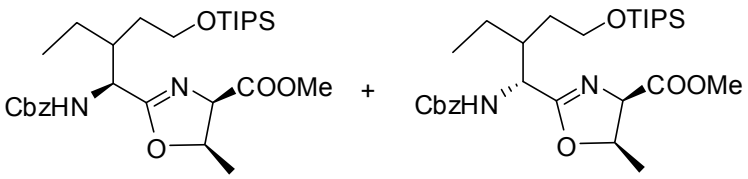


6-Ethyl-10,10-diisopropyl-11-methyl-3-oxo-1-phenyl-2,9-dioxa-4-aza-10-siladodecane-5-carboxylic acid (1-128). A mixture of $NaIO_4$ (6.64 g, 31.4 mmol), water (13.8 mL), MeCN (19.8 mL) and CCl_4 (13.8 mL) was treated with $RuCl_3 \cdot H_2O$ (3.9 mg, 0.019 mmol) and ultrasonicated for 30 min at room temperature. Compound **1-133** (0.897 g, 1.89 mmol) was added and the reaction mixture was ultrasonicated for 43 min. After the addition of 2 M HCl, the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with 20% $NaHSO_3$ (2x) and brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by chromatography on SiO_2 (Hexanes:EtOAc=2:1 with 0.5% AcOH) yielded 0.37 g (43%) of **1-128** as a yellow oil: IR (neat) 3304, 3091, 3066, 3034, 2942, 2866, 2755, 2624, 1720, 1687, 1517, 1462 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57-7.26 (m, 5 H), 5.97 (d, 1 H, J = 7.9 Hz), 5.12 (s, 2 H), 4.61 (dd, 1 H, J = 8.1, 4.2 Hz), 3.95-3.60 (m, 2 H), 2.17-1.98 (m, 2 H), 1.77-1.55 (m, 2 H), 1.55-1.40 (m, 2 H), 1.20-0.71 (s, 24 H); ^{13}C NMR ($CDCl_3$) δ 176.9, 176.2, 156.6, 136.5, 128.7, 128.5, 128.3, 67.3, 61.6, 56.0, 40.2, 32.8, 23.5, 18.1, 12.1, 11.9; HRMS (ESI) *m/z* calcd for $C_{24}H_{41}NO_5SiNa$ (M+Na) 474.2652, found 474.2642.



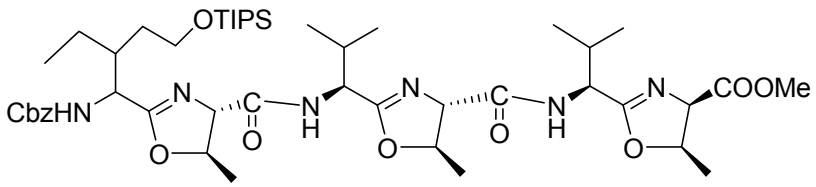
(2*R*,3*S*)-Methyl 2-((2*S*)-2-(benzyloxycarbonylamino)-3-ethyl-5-(triisopropylsilyloxy)-pentanamido)-3-hydroxybutanoate (1-134a) and (2*R*,3*S*)-methyl 2-((2*R*)-2-(benzyloxycarbonylamino)-3-ethyl-5-(triisopropylsilyloxy)pentanamido)-3-hydroxybutanoate (1-134b) A solution of **1-133** (0.454 g, 1.01 mmol) and N-methylmorpholine (0.121 mL, 1.10 mmol) in

DCM (3.87 mL) at -20 ^{o}C was treated with isobutylchloroformate (0.143 mL, 1.10 mmol). After 5 min, a suspension of D-threonine methyl ester hydrochloride (0.343 g, 2.02 mmol) and Et_3N (0.283 mL, 2.02 mmol) in DMF (1.83 mL) was added dropwise. The reaction mixture was warmed to room temperature, stirred for 1 h and quenched with saturated aqueous $NaHCO_3$ solution. The mixture was diluted with EtOAc and the organic layer was washed with 0.1 M HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=2:1) yielded 0.605 g (100%) of **1-134a** and **1-134b** (yellow oil) as an 1:1 (inseparable) mixture of diastereomers: IR (neat) 3305, 3033, 2942, 2868, 1728, 1662, 1510, 1461 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.47-7.20 (m, 5 H), 7.04 (app t, 1 H, *J* = 9.6 Hz), 6.40 (d, 0.5 H, *J* = 7.5 Hz), 6.33 (d, 0.5 H, *J* = 7.7 Hz), 5.14 (AB, 1 H, *J* = 12.0 Hz), 5.06 (AB, 1 H, *J* = 11.9 Hz), 4.57 (dq, 1 H, *J* = 8.9, 2.7 Hz), 4.32-4.24 (m, 2 H), 3.87 (d, 1 H, *J* = 6.7 Hz), 3.85-3.66 (m, 5 H), 2.33-2.10 (m, 1 H), 1.75-1.63 (m, 1 H), 1.63-1.50 (m, 1 H), 1.50-1.30 (m, 3 H), 1.25 (app d, 2 H, *J* = 6.2 Hz), 1.17 (d, 3 H, *J* = 6.3 Hz), 1.03 (s, 9 H), 1.02 (s, 9 H), 0.94 (t, 3 H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 172.54, 172.47, 171.9, 171.2, 171.1, 157.3, 156.8, 136.3, 128.4, 128.2, 128.1, 71.4, 68.0, 67.8, 67.6, 67.1, 61.8, 61.3, 59.4, 57.9, 57.6, 57.6, 52.39, 52.35, 59.3, 39.2, 32.3, 32.0, 28.0, 23.6, 23.3, 19.9, 19.0, 18.0, 11.8, 11.5, 11.2; MS (EI) *m/z* (rel intensity) 566 (10), 548 (20), 523 (35), 505 (15), 406 (15), 318 (20), 91 (100); HRMS (ESI) *m/z* calcd for $C_{29}H_{50}N_2O_7Si$ 566.3387 (M+H), found 566.3336.



(4*R*,5*R*)-Methyl 2-((5*S*)-6-ethyl-10,10-diisopropyl-11-methyl-3-oxo-1-phenyl-2,9-dioxa-4-aza-10-siladodecan-5-yl)-5-methyl-4,5-dihydrooxazole-4-carboxylate (135a) and (4*R*,5*R*)-methyl 2-((5*R*)-6-ethyl-10,10-diisopropyl-11-methyl-3-oxo-1-phenyl-2,9-dioxa-4-aza

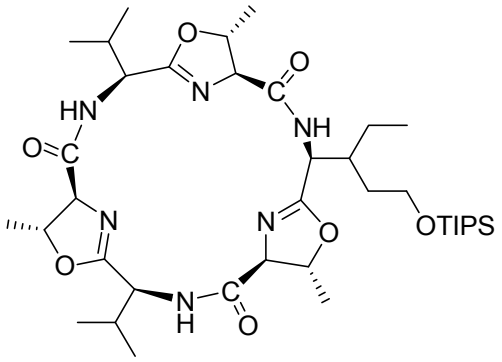
-10-siladodecan-5-yl)-5-methyl-4,5-dihydrooxazole-4-carboxylate (1-135b). A solution of **1-134a** and **1-134b** (0.103 g, 0.181 mmol) and Burgess reagent (46.6 mg, 0.198 mmol) in THF (1.06 mL) was heated to 75 ^{o}C for 2.5 h in a sealed tube. The resulting mixture was evaporated onto SiO_2 and purified by chromatography on SiO_2 (DCM:EtOAc=12:1 to 7:1, all with 1% Et_3N) to yield 18.1 mg (18%) of **1-134a** and 22.2 mg (22%) of **1-134b** as a clear oil. **1-134a**: IR (neat) 3305, 2943, 2866, 1728, 1662, 1510, 1463 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38-7.30 (m, 5 H), 5.69 (d, 1 H, *J* = 9.2 Hz), 5.13 (AB, 1 H, *J* = 5.1 Hz), 5.09 (AB, 1 H, *J* = 5.1 Hz), 5.00-4.88 (m, 1 H), 4.79 (dd, 1 H, *J* = 10.1, 1.3 Hz), 4.70-4.59 (m, 1 H), 3.79-3.73 (m, 2 H), 3.74 (s, 3 H), 2.06-1.95 (m, 1 H), 1.85-1.72 (m, 2 H), 1.51-1.35 (m, 3 H), 1.31-1.24 (m, 5 H), 1.04 (s, 18 H), 0.96 (t, 3 H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 170.3, 170.2, 156.6, 136.6, 128.6, 128.3, 128.2, 78.7, 71.2, 67.1, 61.3, 52.2, 51.3, 39.7, 32.3, 23.1, 18.2, 16.3, 12.1, 12.0; MS (ESI) *m/z* (rel intensity) 549.3 (90), 571.3 (100). **1-134b**: IR (neat) 3305, 3033, 2943, 2866, 1728, 1662, 1510, 1463 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38-7.28 (m, 5 H), 5.80 (d, 1 H, *J* = 8.9 Hz), 5.12 (app s, 2 H), 4.95-4.84 (m, 1 H), 4.78 (dd, 1 H, *J* = 10.1, 1.3 Hz), 4.64 (app dd, 1 H, *J* = 9.0, 4.9 Hz), 3.81-3.68 (m, 2 H), 3.74 (s, 3 H), 2.10-1.91 (m, 1 H), 1.81-1.58 (m, 2 H), 1.57-1.39 (m, 3 H), 1.32-1.25 (m, 5 H), 1.04 (s, 18 H), 1.00-0.93 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.2, 169.9, 156.5, 136.7, 128.6, 128.3, 128.2, 78.5, 71.3, 67.1, 61.3, 52.2, 51.8, 40.0, 32.7, 23.5, 18.2, 16.3, 12.1, 11.8; MS (ESI) *m/z* (rel intensity) 549.3 (100) (M+H), 571.3 (80) (M+Na).



(4*R*,5*R*)-Methyl 2-((*S*)-1-((4*S*,5*R*)-2-((*S*)-1-((4*S*,5*R*)-2-((5*S*)-6-ethyl-10,10-diisopropyl-11-methyl-3-oxo-1-phenyl-2,9-dioxa-4-aza-10-siladodecan-5-yl)-5-methyl-4,5-dihydro-

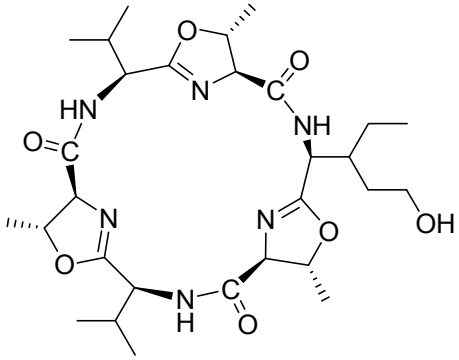
oxazole-4-carboxamido)-2-methylpropyl)-5-methyl-4,5-dihydrooxazole-4-carboxamido)-2-methylpropyl)-5-methyl-4,5-dihydrooxazole-4-carboxylate (1-142a) and (4*R*,5*R*)-Methyl 2-((*S*)-1-((4*S*,5*R*)-2-((*S*)-1-((4*S*,5*R*)-2-((5*R*)-6-ethyl-10,10-diisopropyl-11-methyl-3-oxo-1-phenyl-2,9-dioxa-4-aza-10-siladodecan-5-yl)-5-methyl-4,5-dihydro-oxazole-4-carboxamido) -2-methylpropyl)-5-methyl-4,5-dihydrooxazole-4-carboxamido)-2-methylpropyl)-5-methyl-4,5-dihydrooxazole-4-carboxylate (1-142b). A solution of **1-135a** (35.9 mg, 0.0654 mmol) in MeOH (0.560 mL) was treated with 1 M aqueous NaOH (0.158 mL, 0.158 mmol) at room temperature and the mixture was stirred for 3 h. After addition of $NaHCO_3$ (28.8 mg, 0.327 mmol), the solvent was evaporated under reduced pressure. The water was removed by azeotropic distillation with benzene (2x). The residue was dissolved in DMF (1.31 mL) together with the oxazoline dimer with free N-terminal (0.138 mmol, prepared by the hydrogenolysis of **1-112** (70.9 mg, 0.138 mmol) with 10% $Pd(OH)_2/C$ (7.1 mg) in MeOH (1.59 mL)). The resulting solution was cooled to 0 ^oC and treated with DIPEA (0.0532 mL, 0.327 mmol) followed by DPPA (0.0430 mL, 0.196 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 48 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (1 mL) and stirring was continued for 1 h. The solvent was evaporated under reduced pressure and the residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (100% EtOAc with 1% Et_3N) yielded 24.7 mg (42%) of **1-142a** as a clear oil: IR (neat) 3389, 3308, 3033, 2962, 2941, 2893, 2867, 1724, 1659, 1521, 1463 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38-7.29 (m, 5 H), 7.08-7.00 (m, 2 H), 5.93 (d, 1 H, *J* = 8.7 Hz), 5.13 (AB, 1 H, *J* = 11.9 Hz), 5.10 (AB, 1 H, *J* = 12.3 Hz), 4.93-4.72 (m, 4 H), 4.64 (app dd, 1 H, *J* = 9.7, 6.6 Hz); 4.56 (app

dd, 1 H, *J* = 8.7, 6.6 Hz); 4.48 (app dd, 1 H, *J* = 8.4, 5.6 Hz); 4.21-4.10 (m, 2 H), 3.79-3.65 (m, 2 H), 3.74 (s, 3 H), 2.19-2.07 (m, 2 H), 2.07-1.95 (m, 1 H), 1.80-1.62 (m, 2 H), 1.55-1.36 (m, 3 H), 1.44 (d, 3 H, *J* = 5.3 Hz), 1.30 (d, 6 H, *J* = 6.4 Hz), 1.34-1.22 (m, 2 H), 1.04 (s, 18 H), 1.10-1.00 (m, 3 H), 1.00-0.85 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 171.4, 171.2, 170.2, 169.3, 138.5, 138.0, 156.7, 136.5, 128.7, 128.34, 128.27, 80.9, 80.6, 78.4, 74.9, 74.8, 71.2, 67.2, 61.2, 52.9, 52.7, 52.2, 52.1, 37.1, 32.4, 32.4, 32.2, 23.5, 22.0, 21.9, 19.1, 19.0, 18.3, 18.2, 16.2, 12.1, 11.6; MS (ESI) *m/z* (rel intensity) 457.4 (100), 914.4 (90) (M+H), 935.4 (100) (M+Na).



Cyclo[3-ethyl-5-hydroxy-Nva(TIPS)-D-Thr(oxaz)-Val-D-Thr(oxaz)-Val-D-Thr(oxaz)] 1-143. A solution of **1-142a** (24.7 mg, 0.0270 mmol) and 10% $Pd(OH)_2$/C (2.5 mg) was exposed to H_2 (1 atm) for 90 min. The reaction mixture was filtered through celite and the filtrate was treated with 1 M aqueous NaOH (0.0325 mL, 0.0325 mmol) and stirred at room temperature for 2 h. After addition of $NaHCO_3$ (11.4 mg, 0.135 mmol), the solvent was evaporated under reduced pressure. The residual water was removed by azeotropic distillation with benzene (2x). The residue was dissolved in DMF (2.10 mL), treated with DPPA (8.73 μL, 0.0405 mmol) at 0 ^{o}C and stirred for 24 h at 0 ^{o}C, 24 h at 4 ^{o}C and 24 h at room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (0.500 mL) and stirring was continued for 1 h. The solvent was evaporated under reduced pressure and the residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (2x) and the

combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=2:1 with 1% Et_3N) yielded 8.2 mg (41%) of **1-114** as a sticky clear solid: IR (neat) 3379, 2962, 2866, 1688, 1651, 1524, 1463 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (d, 1 H, *J* = 7.6 Hz), 7.54 (d, 1 H, *J* = 7.7 Hz), 7.42 (d, 1 H, *J* = 6.6 Hz), 5.16-5.07 (m, 1 H), 4.87-4.75 (m, 2 H), 4.72-4.63 (m, 2 H), 4.59 (app dt, 1 H, *J* = 7.7, 2.8 Hz); 4.23 (app dd, 1 H, *J* = 7.5, 2.0 Hz); 4.17 (d, 1 H, *J* = 9.4 Hz), 4.15 (app dd, 1 H, *J* = 9.1, 2.2 Hz); 2.31-2.20 (m, 2 H), 2.13-2.04 (m, 1 H), 1.81-1.68 (m, 2 H), 1.60 (d, 3 H, *J* = 6.1 Hz), 1.55 (d, 3 H, *J* = 6.2 Hz), 1.50 (d, 3 H, *J* = 6.2 Hz), 1.46-1.36 (m, 2 H), 1.33-1.18 (m, 3 H), 1.07 (s, 18 H), 1.01 (t, 3 H, *J* = 7.2 Hz), 0.88 (d, 6 H, *J* = 6.9 Hz), 0.85 (d, 3 H, *J* = 6.9 Hz), 0.75 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 171.0, 170.5, 169.0, 168.9, 167.6, 82.8, 82.3, 79.9, 74.7, 74.5, 74.0, 62.0, 52.5, 50.7, 40.7, 33.7, 32.0, 31.7, 23.3, 22.3, 22.1, 20.9, 18.7, 18.3, 17.9, 17.1, 12.5, 12.2; HRMS (ESI) *m/z* calcd for $C_{38}H_{67}N_6O_7Si$ (M+H) 747.4841, found 747.4816.



Cyclo[3-ethyl-5-hydroxy-Nva-D-Thr(oxaz)-Val-D-Thr(oxaz)-Val-D-Thr(oxaz)] 144. A solution of **1-143** (3.8 mg, 0.0051 mmol) in THF (0.15 mL) was treated with TBAF (1.0 M in THF, 0.012 mL, 0.012 mmol). The reaction mixture was stirred at room temperature for 4 h. Water (1.0 mL) was added and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced

pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc=1:1 to 100% EtOAc, all with 1% Et_3N) yielded 2.1 mg (70%) of **1-144** as a sticky clear solid: IR (neat) 3378, 2965, 2932, 2875, 1685, 1650, 1525, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.85 (d, 1 H, *J* = 5.0 Hz), 7.72 (d, 1 H, *J* = 7.3 Hz), 7.51 (d, 1 H, *J* = 7.9 Hz), (in CD_3OD+D_2O 9:1 these three peaks splits to 8.25 (d, 0.5 H, *J* = 8.1 Hz), 8.18 (d, 0.5 H, *J* = 9.9 Hz), 7.81 (d, 0.5 H, *J* = 10.6 Hz), 7.74 (d, 0.5 H, *J* = 7.6 Hz), 7.66 (d, 0.5 H, *J* = 8.2 Hz), 7.47 (d, 0.5 H, *J* = 7.5 Hz)), 5.08-4.98 (m, 1 H), 4.88-4.81 (m, 1 H), 4.76-4.69 (m, 2 H), 4.67-4.59 (m, 2 H), 4.23 (app dd, 1 H, *J* = 7.7, 2.0 Hz), 4.21-4.15 (m, 2 H), 4.03-3.88 (m, 1 H), 3.88-3.76 (m, 1 H), 3.39-3.26 (m, 1 H), 2.36-2.18 (m, 2 H), 2.18-2.07 (m, 1 H), 1.81-1.65 (m, 4 H) 1.62 (d, 3 H, *J* = 6.2 Hz), 1.56 (d, 3 H, *J* = 6.3 Hz), 1.53 (d, 3 H, *J* = 6.3 Hz), 0.96 (t, 3 H, *J* = 7.2 Hz), 0.90 (d, 3 H, *J* = 7.0 Hz), 0.88 (d, 3 H, *J* = 6.8 Hz), 0.85 (d, 3 H, *J* = 6.9 Hz), 0.76 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 170.9, 170.3, 170.0, 168.8, 167.9, 167.8, 82.9, 82.5, 80.1, 74.3, 74.2, 73.9, 60.8, 52.8, 52.4, 50.2, 40.2, 32.8, 31.9, 31.7, 23.1, 22.3, 21.1, 18.75, 18.67, 17.9, 17.0, 12.6.

NMR Titration of 1-119: Compound **1-119** (2.8 mg, 2.0 μmol) in 0.5 mL CD_3OD and D_2O (9:1, v/v) was titrated with a solution of $AgClO_4$ (0.158 M, in CD_3OD and D_2O (9:1, v/v)). The process was monitored by ^1H NMR (see figures below). The data is summarized in Table 6.

Table 6 NMR titration data of **1-119**

Amount of $AgClO_4$ added (equivalents)	Initial conc. of $AgClO_4$ (mM)	Initial conc. of ligand **1-119** (mM)	Integration* of uncomplexed **1-119**	Integration** of complexed **1-119**	[**1-119**Ag_4]*** (mM)	[D]*** (mM)	[Ag]*** (mM)	K_a calculated (M^{-4})
0.8	3.11	3.88	5.75	1.00	0.575223	3.30713	0.80499	4.14×10^{11}
1.2	4.61	3.84	3.72	1.00	0.814029	3.030631	1.357475	7.91×10^{10}
1.6	6.09	3.81	2.30	1.00	1.153741	2.653951	1.477343	9.13×10^{10}
2.0	7.54	3.77	1.57	1.00	1.467596	2.303832	1.672473	8.14×10^{10}
2.4	8.97	3.74	1.11	1.00	1.768114	1.967735	1.89358	6.99×10^{10}
3.2	11.7	3.67	0.448	1.00	2.532928	1.133739	1.601621	3.40×10^{11}

*: Integration number of ^1H NMR peak at 1.0-0.7 ppm (sidechain methyl groups on the uncomplexed cyclic peptide)

**: Integration number of ^1H NMR peak at 1.2-1.0 ppm (sidechain methyl groups on the complexed cyclic peptide)

***: The concentrations at equilibrium were calculated by the integration number of uncomplexed and complexed **1-119**

$K_a = 1.8\pm1.4\times10^{11}\ M^{-4}$

Figure 16 ^{1}H NMR spectrum of **1-119** in CD_3OD and D_2O (9:1, v/v) and an expansion of 1.8-0 ppm region

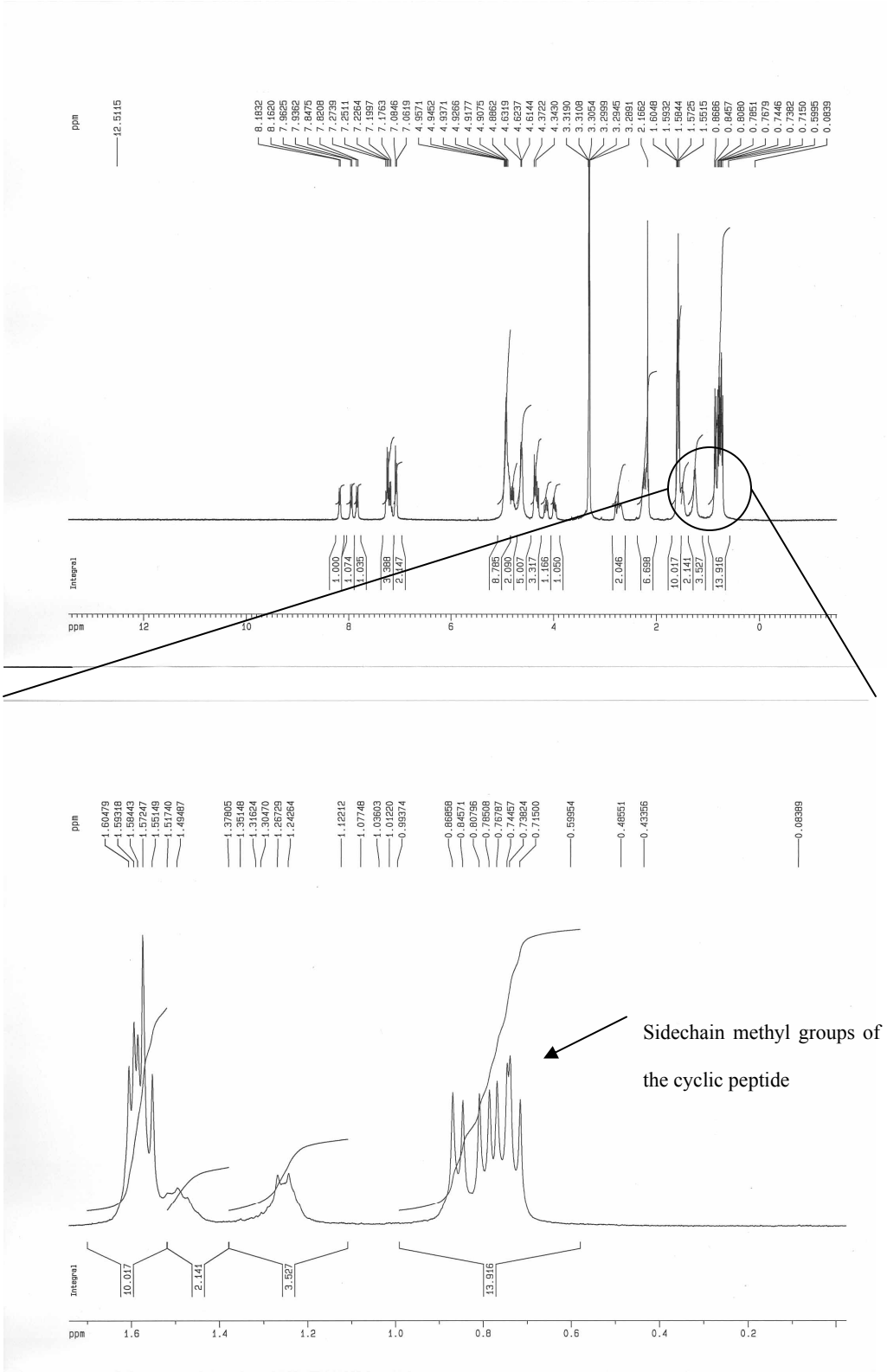


Figure 17 ^{1}H NMR spectrum (1.8-0 ppm region) of **1-119** and 0.8 equivalent of $AgClO_4$ in CD_3OD and D_2O (9:1, v/v)

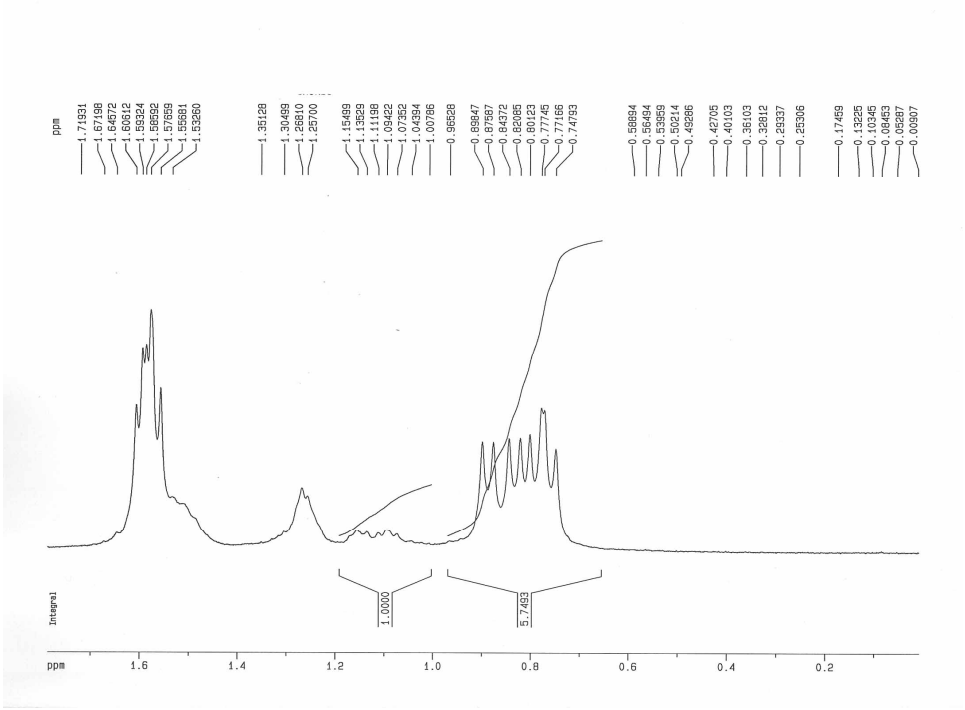


Figure 18 ^{1}H NMR spectrum (1.8-0 ppm region) of **1-119** and 1.2 equivalents of $AgClO_4$ in CD_3OD and D_2O (9:1, v/v)

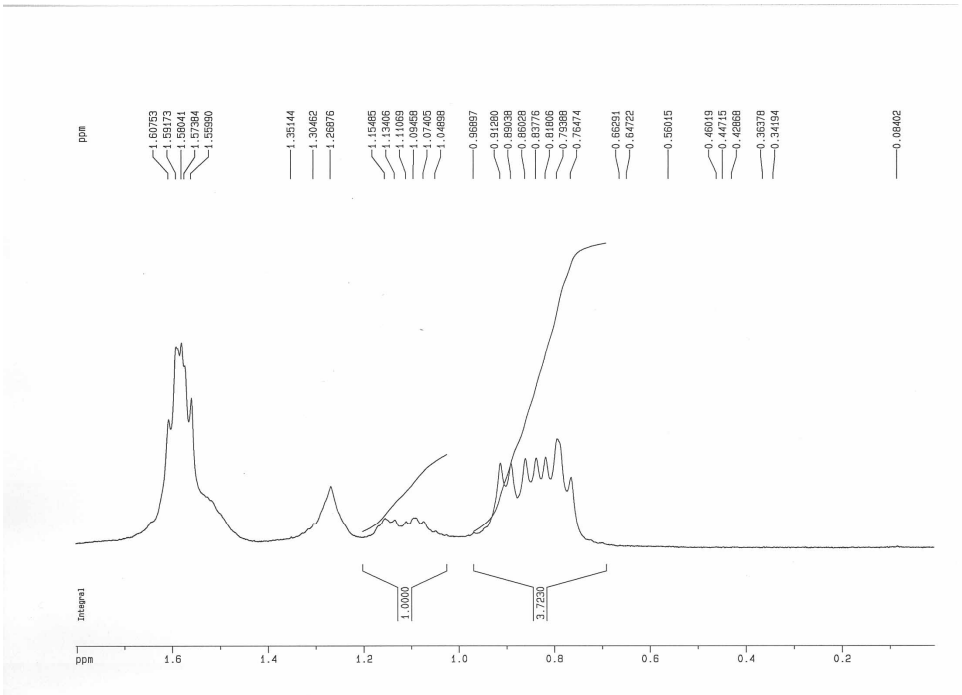


Figure 19 ^{1}H NMR spectrum (1.8-0 ppm region) of **1-119** and 1.6 equivalents of $AgClO_4$ in CD_3OD and D_2O (9:1, v/v)

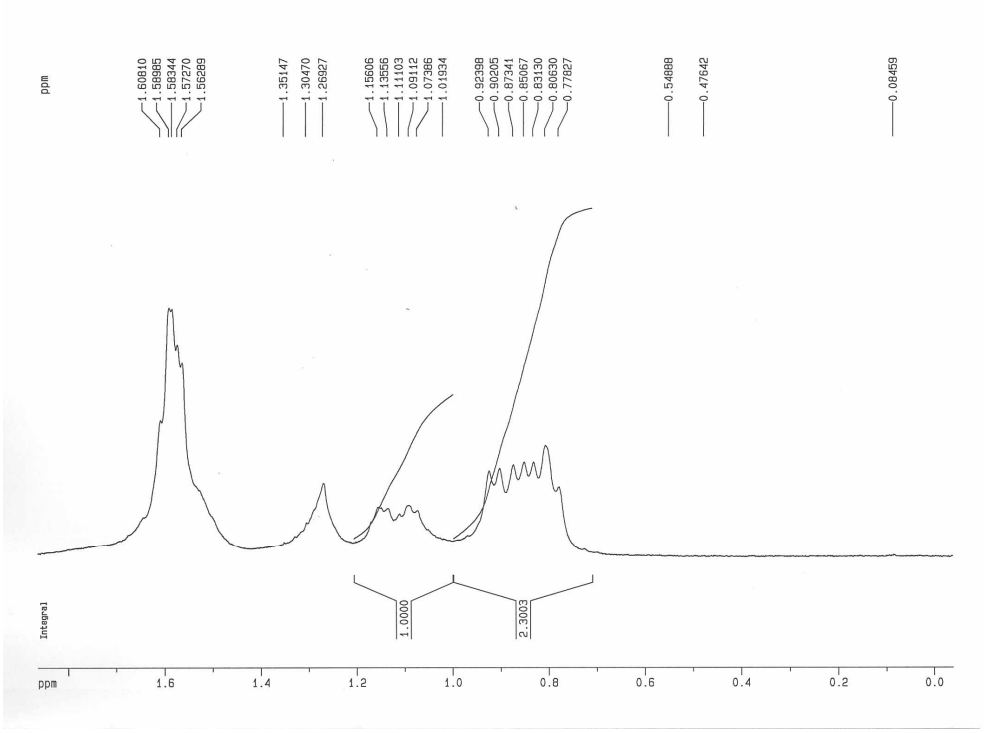


Figure 20 ^{1}H NMR spectrum (1.8-0 ppm region) of **1-119** and 2.0 equivalents of $AgClO_4$ in CD_3OD and D_2O (9:1, v/v)

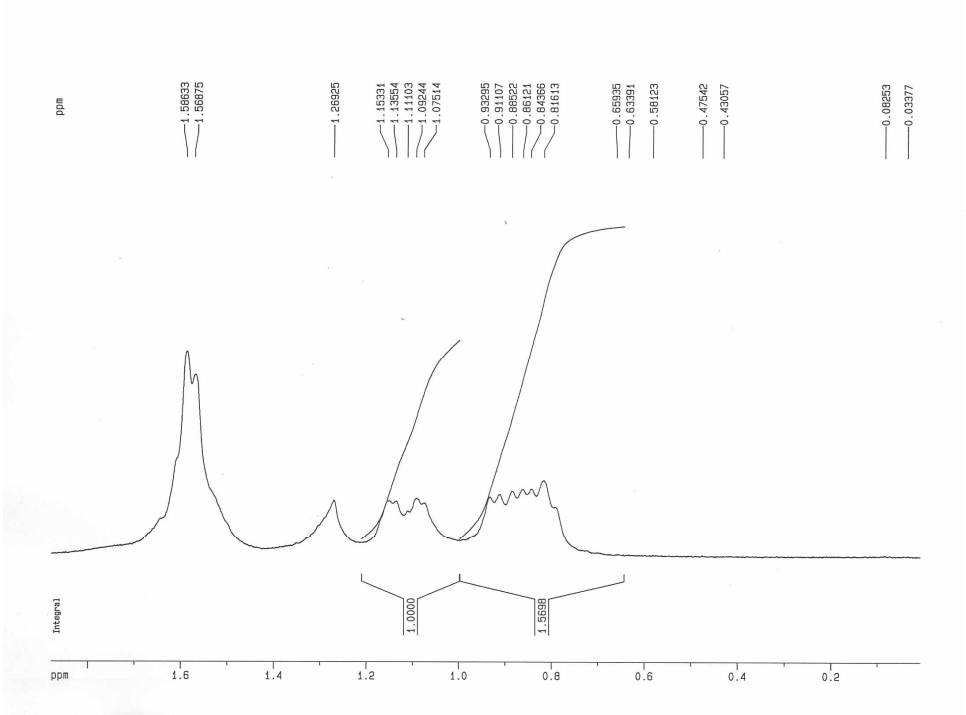


Figure 21 ^{1}H NMR spectrum (1.8-0 ppm region) of **1-119** and 2.4 equivalents of $AgClO_4$ in CD_3OD and D_2O (9:1, v/v)

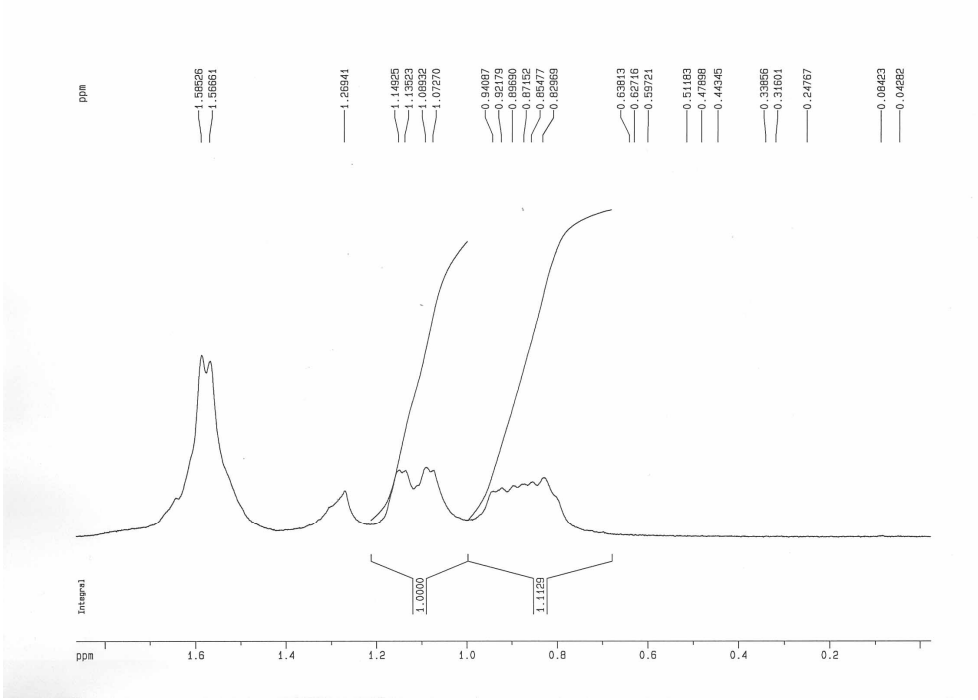


Figure 22 ^{1}H NMR spectrum (1.8-0 ppm region) of **1-119** and 3.2 equivalents of $AgClO_4$ in CD_3OD and D_2O (9:1, v/v)

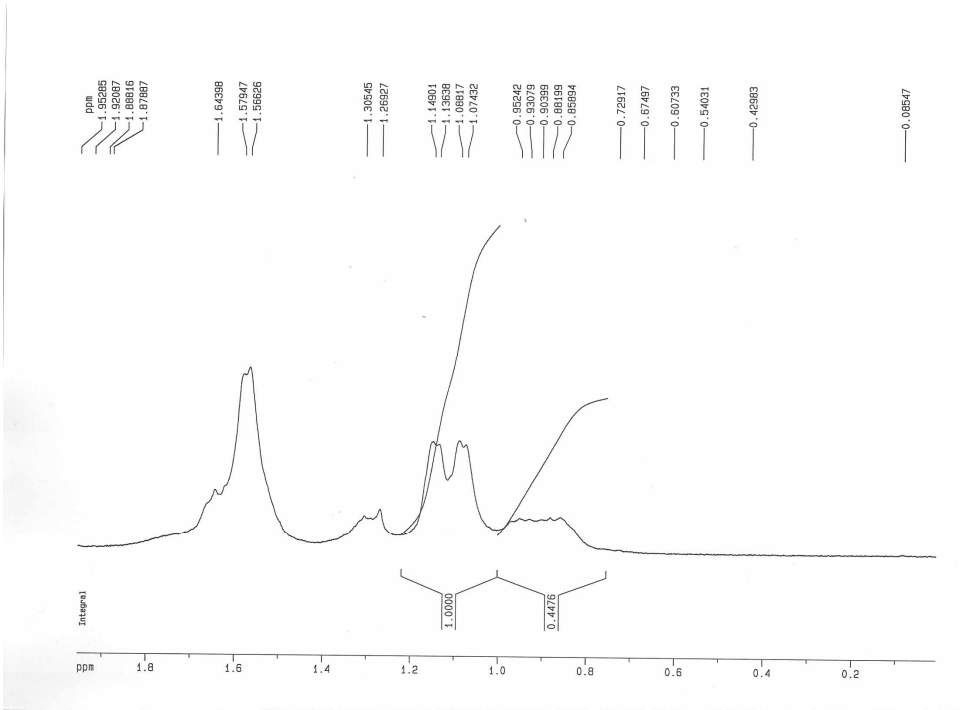


Figure 23 ^{1}H NMR spectrum (1.8-0 ppm region) of **1-119** and 4 equivalents of $AgClO_4$ in CD_3OD and D_2O (9:1, v/v)

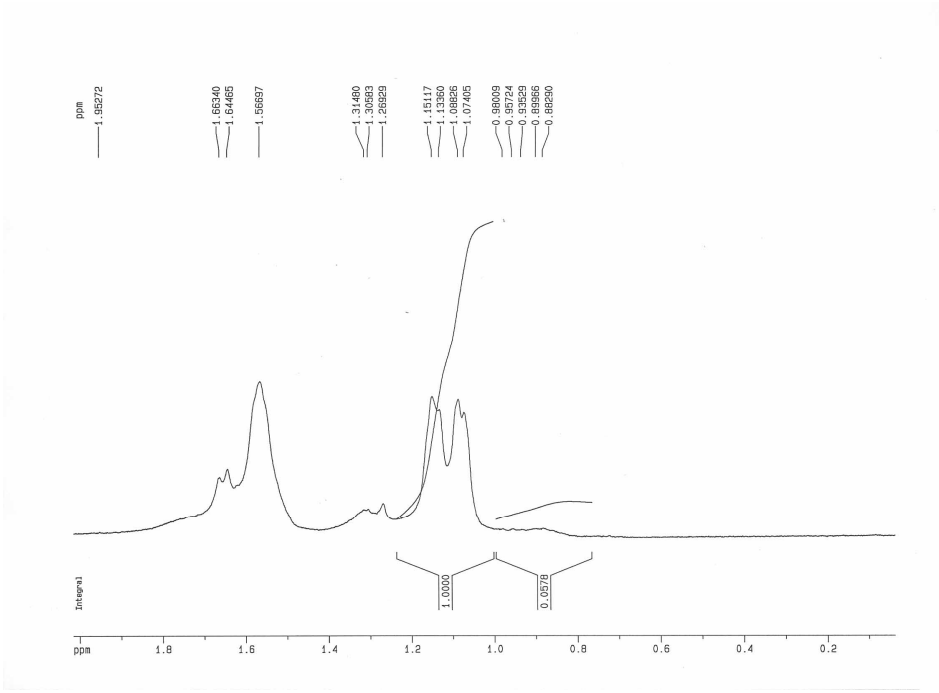
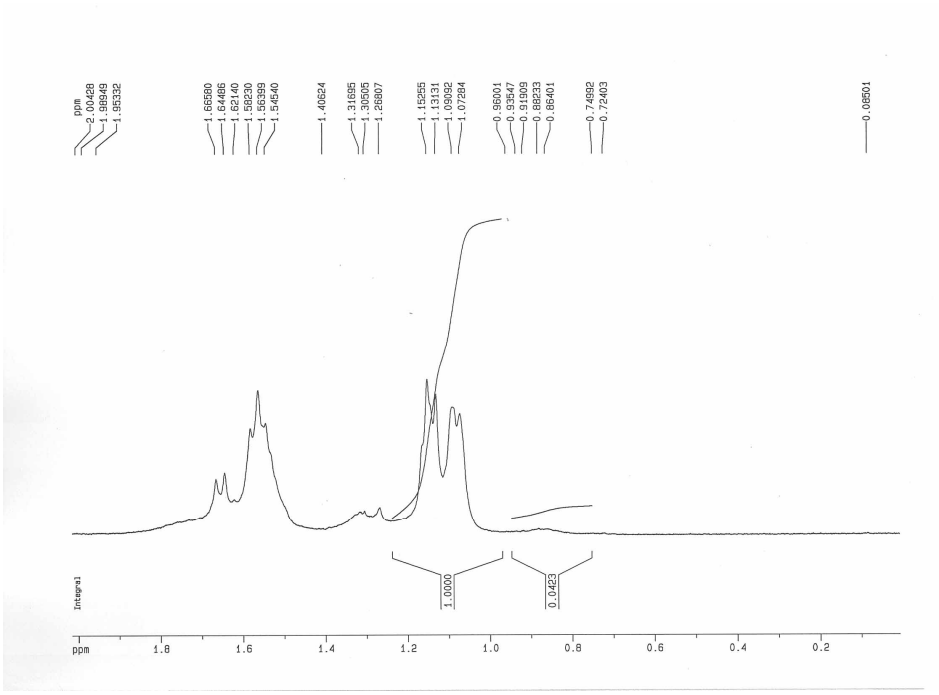


Figure 24 ^{1}H NMR spectrum (1.8-0 ppm region) of **1-119** and 8 equivalents of $AgClO_4$ in CD_3OD and D_2O (9:1, v/v).



Competitive binding study of 1-119: Stock solution of **1-120** (0.520 mM), $AgClO_4$ (1.10 mM) and **1-119** (2.72 mM) were prepared using MeOH and H_2O (9:1, v/v). Test solutions were prepared by placing 47.1 μL of the **1-120** stock solution into a volumetric flask, adding an appropriate aliquot of $AgClO_4$ stock, and diluting the solution to 5 mL with MeOH and H_2O (9:1, v/v). For all measurements, excitation was at 367 nm; emission was measured at 420 nm. The fluorescence spectra are shown in Figure 25 and the data is summarized in Table 7.

Figure 25 Changes in fluorescence emission spectra of **1-120** upon the addition of $AgClO_4$ in MeOH and H_2O (9:1, v/v).

The spectrum with 100 and 200 equivalents of $AgClO_4$ overlaps with each other, indicating the saturation of **1-120** at these $AgClO_4$ concentrations.

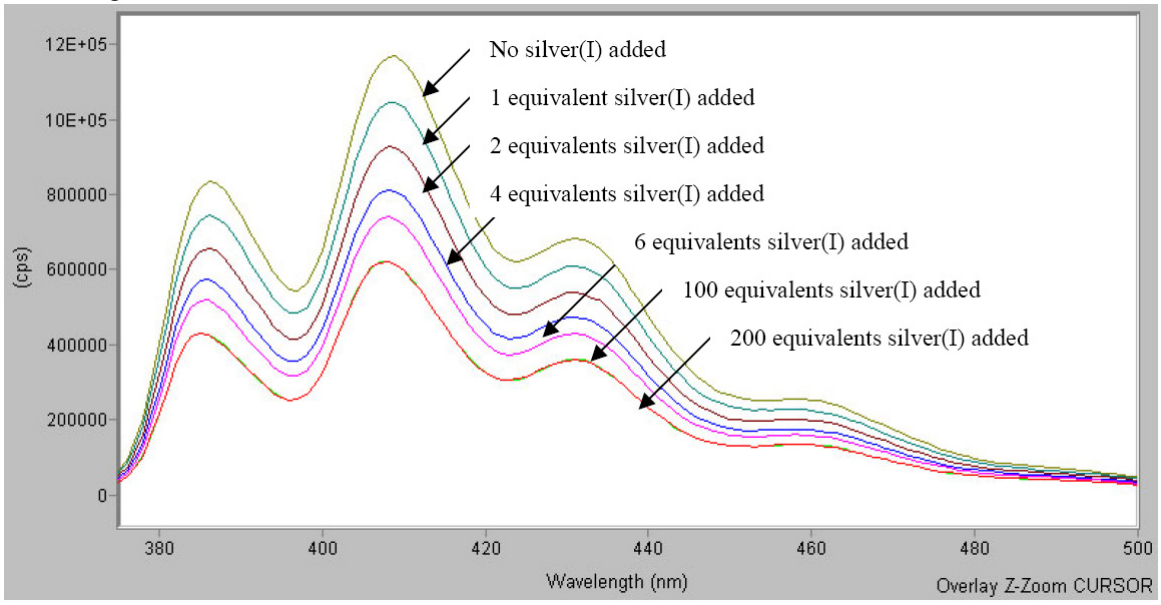


Table 7 Titration of **1-120** with $AgClO_4$ in MeOH and H_2O (9:1, v/v)

Entry	Initial Conc. of **1-120** (M)	Amount of $AgClO_4$ added (equivalents relative to **1-120**)	Observed fluorescence intensity (cps) at 420 nm	K_a calculated (M^{-1})
1	4.89×10^{-6}	0	6.91×10^{5}	
2	4.89×10^{-6}	1.0	6.06×10^{5}	8.09×10^{4}
3	4.89×10^{-6}	2.0	5.26×10^{5}	1.09×10^{5}
4	4.89×10^{-6}	4.0	4.53×10^{5}	1.15×10^{5}
5	4.89×10^{-6}	6.0	4.04×10^{5}	1.44×10^{5}
6	4.89×10^{-6}	100	3.26×10^{5}	
7	4.89×10^{-6}	200	3.25×10^{5}	

The association constant was calculated according to Equation 1:[75]

$$\frac{1}{K_a} = \frac{I - I_0}{\varepsilon_C - \varepsilon_F} - C_F - C_{Ag} + \frac{C_{Ag} C_F (\varepsilon_C - \varepsilon_F)}{I - I_0} \qquad \text{Eq. 1}$$

where K_a is the association constant, I is the observed fluorescence intensity, I_0 is the fluorescence of initial concentration of the fluorophore (without silver(I)), ε_C is the fluorescence constant of the complex (calculation based on Entry 7 in Table 7, where **1-120** was saturated with silver(I)), ε_F is the fluorescence constant of **1-120** (calculation based on Entry 1 in Table 7), C_F is the initial concentration of **1-120**, while C_{Ag} is the initial concentration of $AgClO_4$. Thus, the K_a was determined as $9.2\pm5.5\times10^4\ M^{-1}$ (Lit.[66] $1.25\times10^5 M^{-1}$ in $CHCl_3$ and Ethanol (7:3, v/v)).

Next, the competitive binding study was conducted with **1-119** (2.72 mM stock solution in MeOH and H_2O (9:1, v/v). Test solutions were prepared by mixing 47.1 μL of the **1-120** stock solution (0.520 mM), 44.6 μL (2 equivalents) of the $AgClO_4$ stock solution (1.10 mM) and an appropriate aliquot of **1-119** stock. The resulting solution was diluted to 5 mL with MeOH and H_2O (9:1, v/v). Three control experiments were conducted: a. **1-119** has no observable fluorescence emission; b. **1-119** with 8 equivalents of $AgClO_4$ showed no observable fluorescence emission; c. adding 16 equivalents of **1-119** to a solution of **1-120** had no impact on

its fluorescence intensity. The competitive binding fluorescence spectra are shown in Figure 26 and the data is summarized in Table 8.

Figure 26 Ligand **1-119** restores the fluorescence emission of Ag(I)-complexed **1-120**.

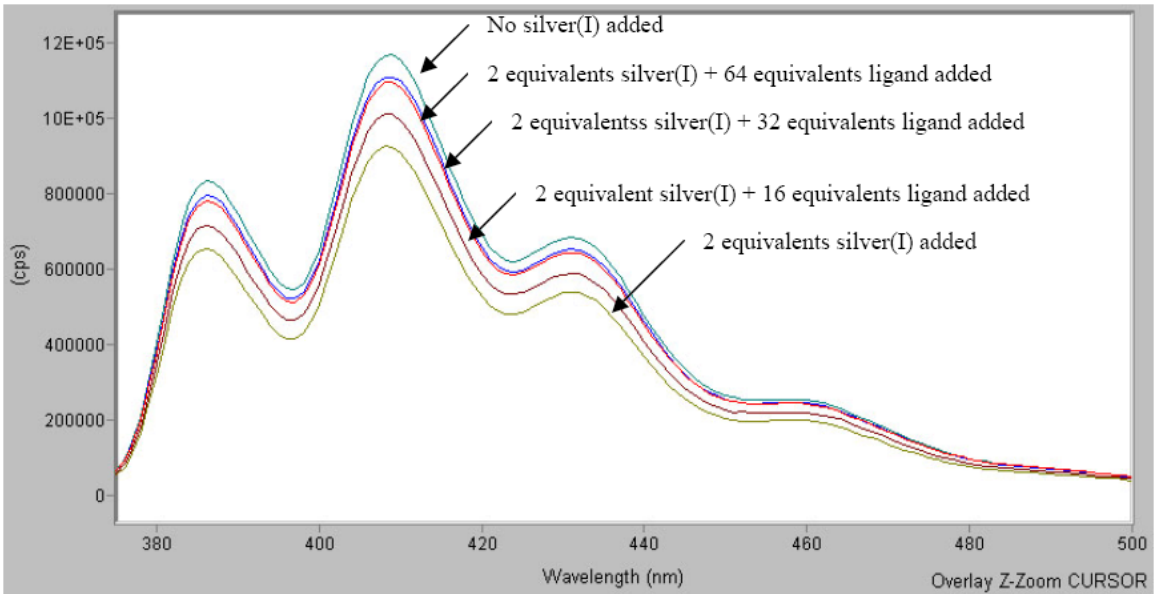


Table 8 Data for Competitive binding study of **1-119** with fluorophore **1-120**

Entry	Initial Conc. of **1-120** (M)	Initial conc. of $AgClO_4$ (M)	Amount of **1-119** added (equivalents relative to **1-120**)	Observed fluorescence intensity (cps) at 420 nm	K_a calculated (M^{-4})
1	4.89×10^{-6}	0	0	6.91×10^{5}	
2	4.89×10^{-6}	9.78×10^{-6}	0	5.26×10^{5}	
3	4.89×10^{-6}	9.78×10^{-6}	16	5.89×10^{5}	3.90×10^{19}
4	4.89×10^{-6}	9.78×10^{-6}	32	6.57×10^{5}	9.03×10^{21}
5	4.89×10^{-6}	9.78×10^{-6}	64	6.47×10^{5}	1.50×10^{21}

The association constants were calculated according to Equation 2, 3 and 4:[68]

$$K_a = \frac{PK_I{}^4Q^4}{4C_S - P} \quad \text{Eq. 2}$$

$$Q = \frac{\varepsilon - \varepsilon_I}{\varepsilon_{IAg} - \varepsilon} \quad \text{Eq. 3}$$

$$P = C_{Ag} - \frac{1}{QK_I} - \frac{C_I}{Q+1} \quad \text{Eq. 4}$$

where K_a is the association constant of **1-119**, K_I is the association constant of **1-120**, C_S is the initial concentration of **1-119**, ε is the apparent fluorescence constant of the system, ε_I is the fluorescence constant of **1-120**, ε_{IAg} is the fluorescence constant of **1-120** and silver(I) complex, C_I is the initial concentration of **1-120**, while C_{Ag} is the initial concentration of $AgClO_4$. Thus, the K_a of **1-119** was determined as $3.5 \pm 3.9 \times 10^4\ M^{-4}$.

Competitive binding study of 1-121 and westiellamide: The K_a of **1-121** was determined in a way analogous to **1-119**. For westiellamide, the following equations[68] were used for the calculation of K_a:

$$K_a = \frac{PK_I{}^4Q^4}{(P - 2C_S)^2} \quad \text{Eq. 5}$$

$$Q = \frac{\varepsilon - \varepsilon_I}{\varepsilon_{IAg} - \varepsilon} \quad \text{Eq. 3}$$

$$P = C_{Ag} - \frac{1}{QK_I} - \frac{C_I}{Q+1} \quad \text{Eq. 4}$$

where C_S is the initial concentration of westiellamide.

2.0 SYNTHESIS OF BOTULINUM A METALLOPROTEASE INHIBITORS

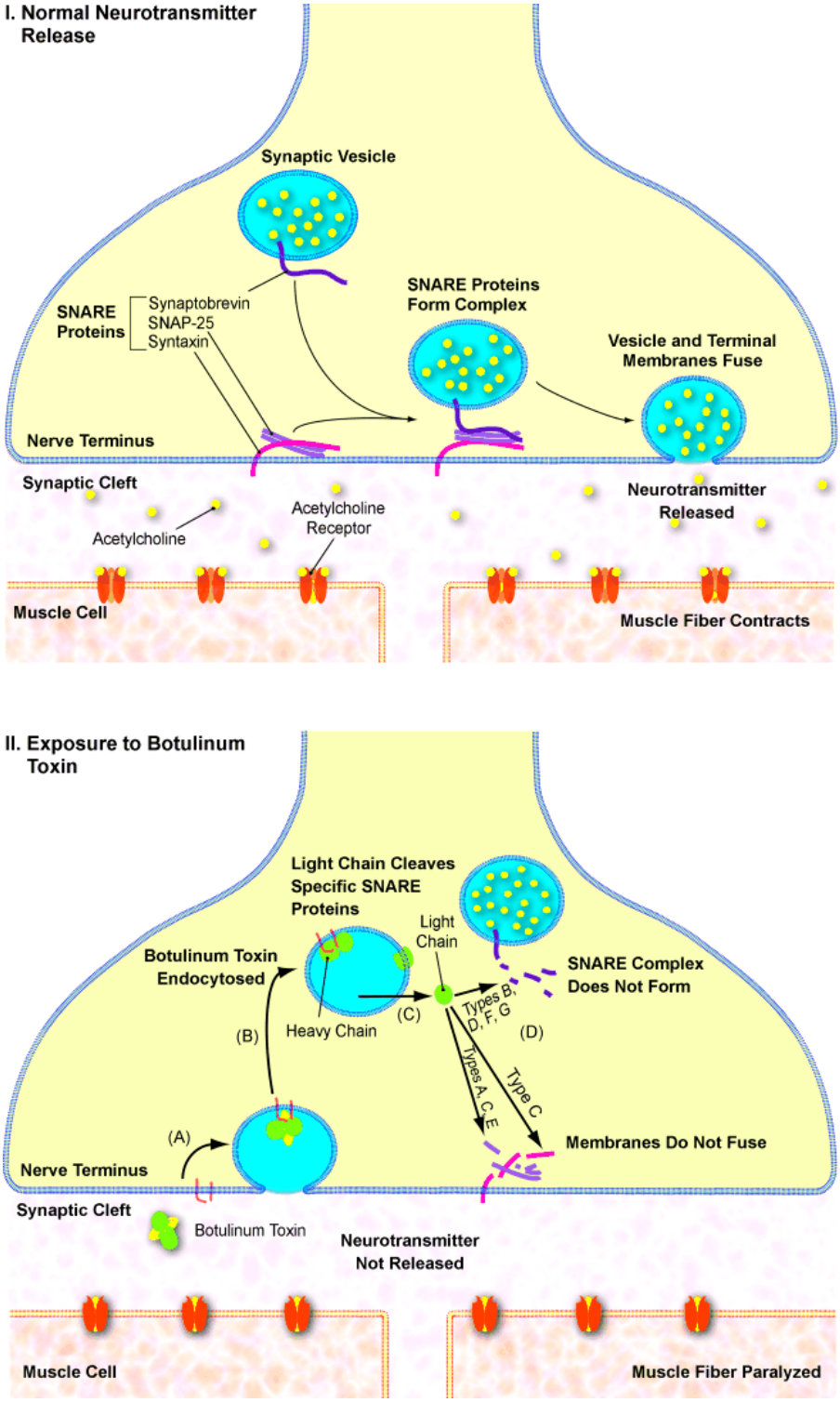
2.1 INTRODUCTION

Botulinum neurotoxins (BoNTs) are well-known for being classified as "the most toxic poisons known to humans".[76] They are produced by *Clostridium botulinum* and cause botulism, a severe neurological disease with a life-threatening flaccid paralysis affecting both humans and animals. Their potency is best recognized by the fact that they are listed as category A biowarfare agents.[77] On the other hand, BoNTs also gained popularity in the therapeutic field. Their utility includes the treatment of muscle hyperactivity and spasticity disorders, as well as cosmetic applications.[78-79]

BoNTs comprise of seven serotypes (A-G), with BoNT A being the most potent one.[80] All BoNTs are proteins consisting of a 100 kDa heavy-chain (HC) and a 50 kDa light-chain Zinc-dependent protease (LC) linked by a disulfide bridge.[81] Their mode of action is demonstrated in Figure 27.[82]

Figure 27 Mechanism of action of BoNTs.

Reproduced from Ref. [82].

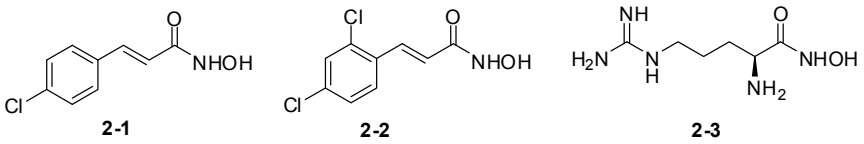


. BoNTs first bind to cholinergic nerve terminals with their HC domain and are subsequently endocytosed into an intracellular vesicle. The LC domain is then translocated into the cytosol with the cleavage of the disulfide linkage between the LC and the HC. In the cytosol, the LC performs proteolytic cleavage of SNARE proteins (SNARE: soluble N-ethylmaleimide-sensitive factor-attachment protein receptors). Each BoNT serotype cleaves one of the three SNARE proteins (BoNT /A, /E: SNAP25 (synaptosomal associated protein of 25 kD); BoNT /B, /D, /F, /G: VAMP (vesicle-associated membrane protein, VAMP); BoNT C: SNAP25 and syntaxin). SNARE are critical for the release of neurotransmitters at nerve terminals as they form a complex to mediate vesicle fusion. The cleavage of SNARE proteins by BoNT LC prevents the formation of functional SNARE complex, thus blocking the release of neurotransmitter. The result is a paralysis of muscle fibers, causing either respiratory or cardiac failure.

Due to their potency and wide therapeutic application, there is an urgent need for therapeutic strategies to counter BoNTs' toxicity. Of particular interest are small molecule inhibitors targeted at either BoNT HC or LC activity. A few HC inhibitors have been identified,[83-88] but most of the work so far has focused on LC inhibition. Early work in this field has primarily relied on peptide and peptidomimetics.[89-99] For example, Schmidt et al. developed a series of peptide mimics for the inhibition of BoNT /A LC.[97] Their design was based on cysteine's ability to complex with zinc. A 17-residue substrate containing the SNAP-25 194-200 region (the active site domain[100] with the cleavage occuring between Gln197 and Arg198) was chosen to be mutated in a Cys scan. A number of LC/A inhibitors were identified and subsequent truncation of their sequence provided several octapeptides with Ki values in the low micromolar range. Further optimization by using cysteine mimics effectively pushed the Ki value to the nanomolar range.[96] Analogous to the cysteine approach, a few zinc-complexing hydroxamic

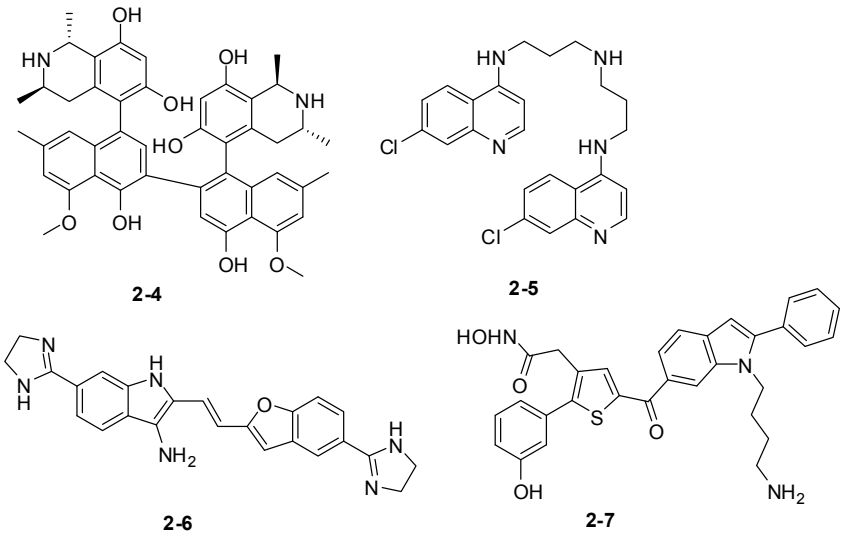
acids were also identified as LC/A inhibitors (Figure 28).[101] A crystal structure of **2-3** complexed with LC/A confirmed the interaction between the hydroxamate and the zinc cation.[102]

Figure 28 Hydroxamic acids as LC/A inhibitors



As an alternative approach to the identification of LC/A inhibitors, Gussio and coworkers conducted a high-throughput screening of the National Cancer Institute (NCI) Diversity set.[103] Several non-peptidic small molecule inhibitors were identified (Figure 29, **2-4, 2-5, 2-6**). Conformational analyses of these compounds, in conjunction with molecular docking studies, were used to model a common pharmacophore for LC/A inhibitors.[103-104] A similar approach involving in silico screening of 2.5 million compounds and molecular dynamic simulations identified hydroxamic acid **2-7** (Figure 29).[105]

Figure 29 LC/A inhibitors identified by high-throughput screening

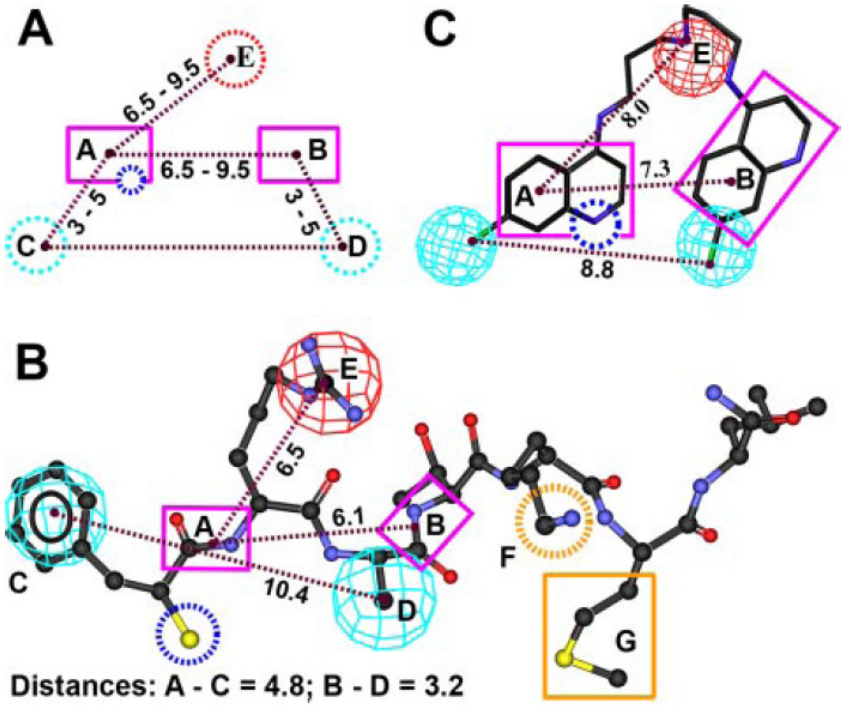


The pharmacophore proposed by Gussio et al. was further refined by the docking study of the aforementioned peptide mimic inhibitors developed by Schmidt et al. with a crystal structure of LC/A.[106] As shown in Figure 30, the newly proposed pharmacophore B contains two new

search query components (F and G) when compared to the previous pharmacophore A. Based on this hypothesis, a search in NCI's Open Repository identified several hits, which were assayed against LC/A. The four most potent inhibitors were found to occupy pharmacophore components A-C and F (Figure 31). Among the four pharmacophore components, component C was proposed to wedge between the side chain phenyls of Phe-162 and Phe-193. The heteroatom associated with pharmacophore plane A was thought to interfere with the catalytic site residues of the enzyme. Component F was believed to engage in hydrogen bonds with Glu-54 and Glu-63 of LC/A. Of the four hits, NSC 240898 (Figure 32) showed dose-dependent protection of SNAP-25 cleavage and displayed no cellular toxicity in up to 40 μM concentration. Thus, it was chosen as a lead for a structure-activity relationship (SAR) study and with the goal to find a more potent inhibitor.

Figure 30 Proposed pharmacophore for LC/A.

A: Components A and B represent two planar moieties, one of which contains a heteroatom. Components C and D are two hydrophobic substituents, while E is a positive ionizable substituent. **B**: The peptide mimic inhibitor (2-mercapto-3-phenylpropionyl-RATKML) was mapped to the common pharmacophore A. Components F (Lys side chain) and G (Met side chain) represent potential new binding sites (distance unit: Å). Reproduced from Ref. [106].



Peptide mimic inhibitor:

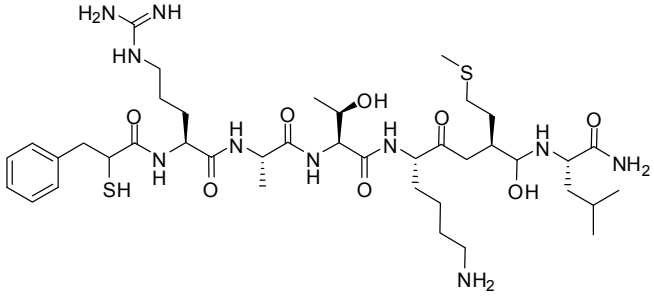
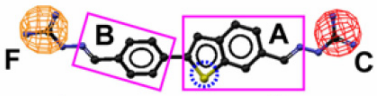
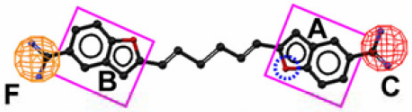
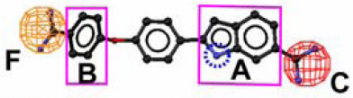


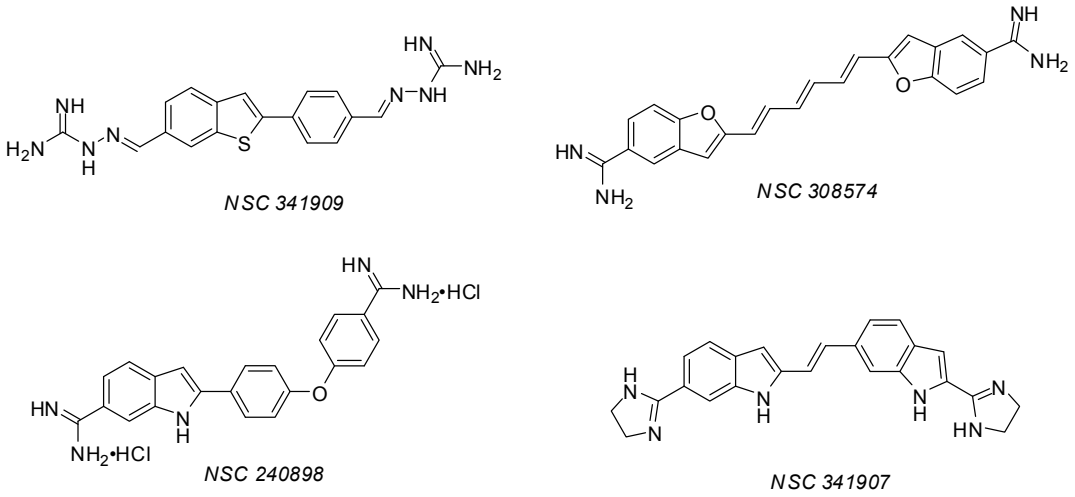
Figure 31 LC/A Inhibitors and search query mappings.

Reproduced from Ref. [106].

NSC	K_i(μM)	Query Fit	A-B[1]	A-C[1]	A-F[1]	Total[2]
341909	3.0		7.5	4.8	13.5	19.6
308574	6.0		12.8	3.9	16.6	19.9
240898	10.0		9.6	3.9	11.9	17.8
341907	10.0		8.8	4.5	12.8	19.3

1 = Distances taken from planar centroids; 2 = Total length of the compounds

Figure 32 Structures of LC/A inhibitors



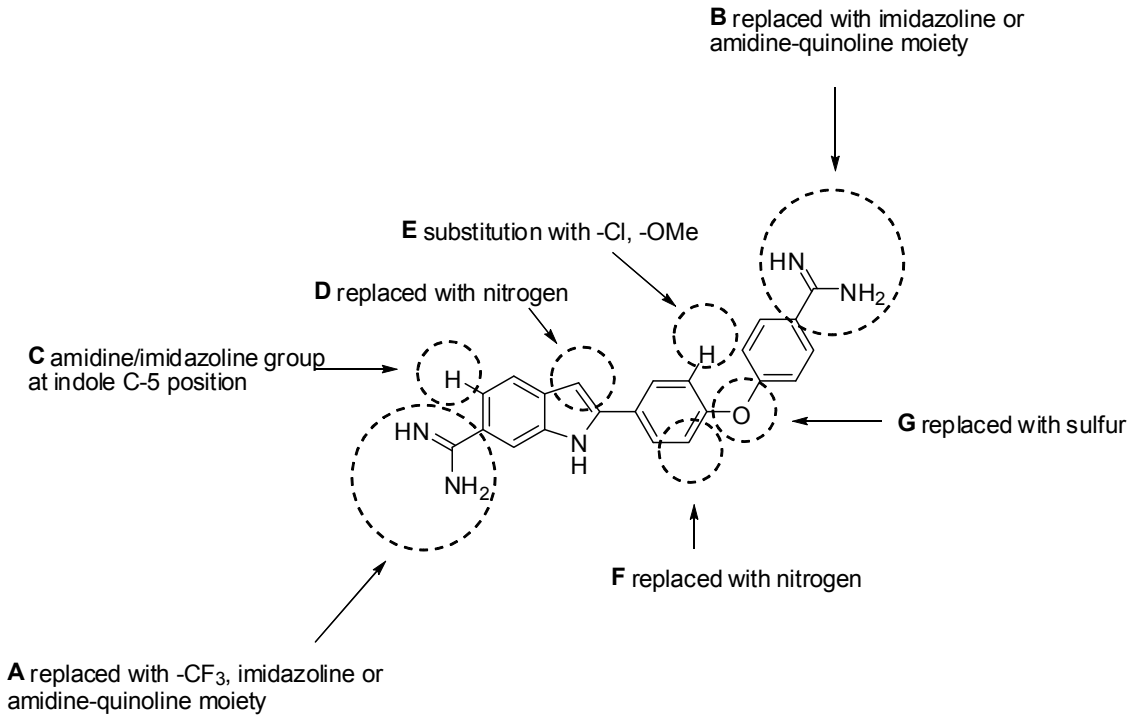
2.2 RESULTS AND DISCUSSION

2.2.1 Inhibitor Library Design

The synthetic modifications to NSC 240898 are summarized in Figure 33. Specifically, the two polar terminal amidines were replaced with more hydrophobic imidazolines, -CF_3 and an amidine-quinoline moiety to study the nature of their interaction with LC/A (**A** and **B** in Figure 33). In order to gather the information about the geometry of the binding pocket, the amidine at the indole C-6 position was shifted to the C-5 position (**C**). Similarly, the ether linkage was replaced with a thio ether (**G**). The incorporation of heteroarenes (**D** and **F**) was meant to improve solubility, decrease metabolism and/or induce additional interactions with LC/A. Finally,

substitution on the central phenyl ring (**E**) allowed us to explore further electronic and steric effects on binding.

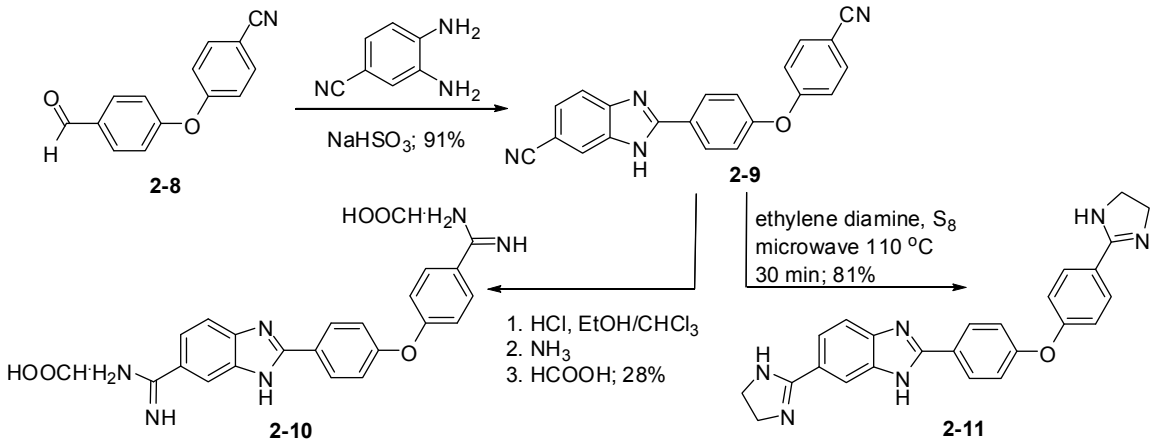
Figure 33 Summary of modifications made to NSC 240898



2.2.2 1st Generation Inhibitors

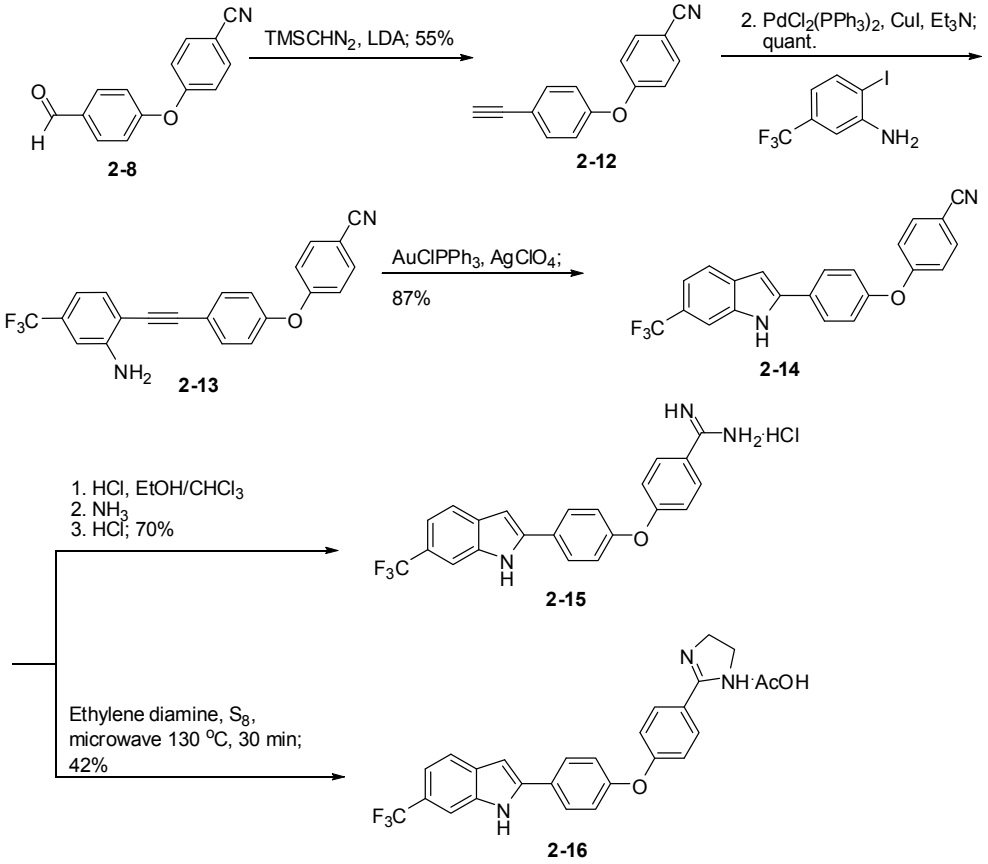
We first synthesized benzimidazoles **2-10** and **2-11** (Scheme 31). Aldehyde **2-8**[107] and diaminobenzonitrile were condensed to provide **2-9**,[108] which was further elaborated to amidine **2-11** (formic acid salt) via an imidate intermediate. The bis-nitrile functionality in **2-9** can also undergo aminolysis with neat ethylene diamine in the presence of sulfur to provide imidazoline **2-11** in good yield.[109] This microwave assisted nitrile aminolysis reaction was found to have a good substrate scope in regard to the nitrile. However, C-substitution on ethylene diamine was found to inhibit the reaction.[110]

Scheme 31 Synthesis of benzimidazole analogues



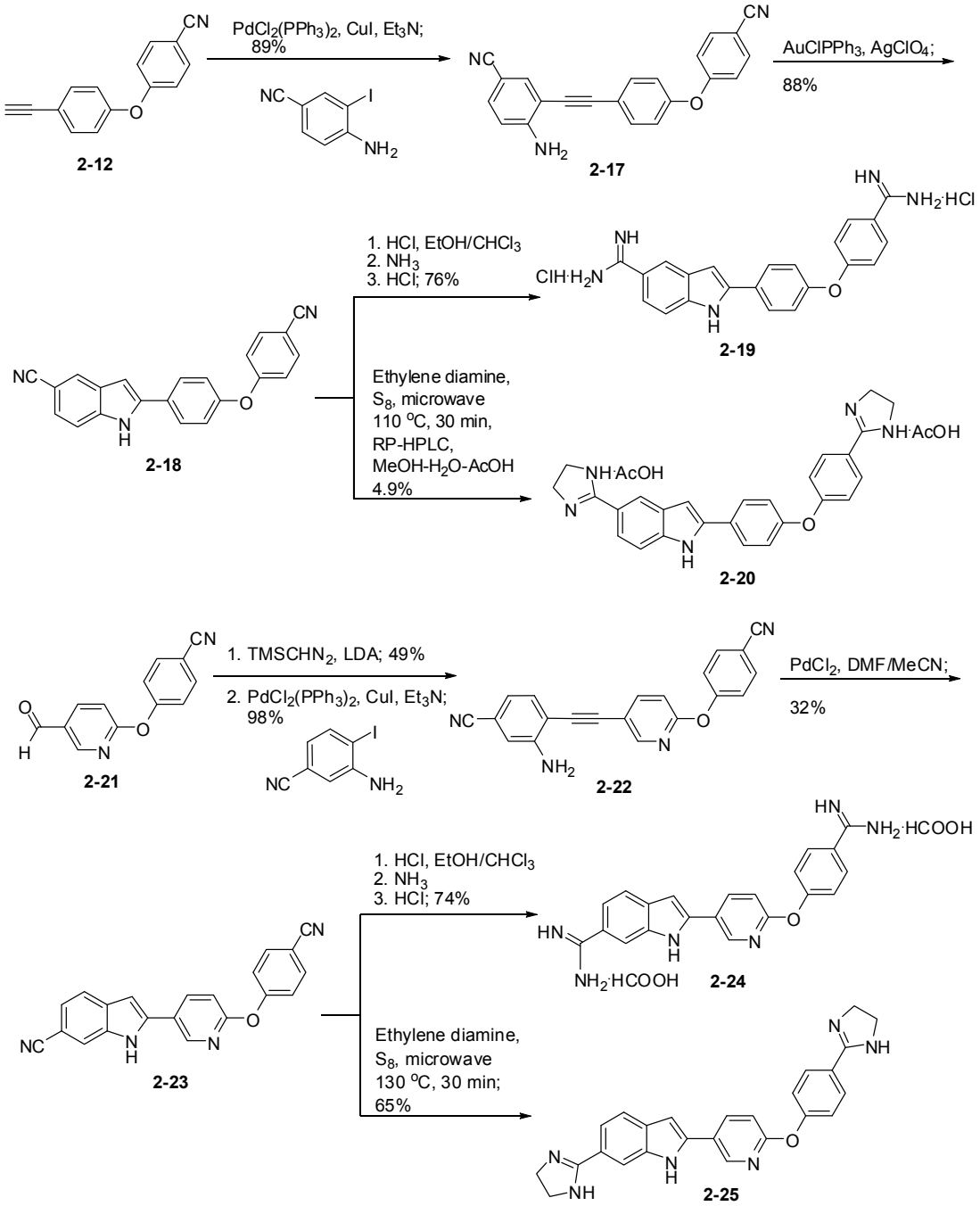
Another series of analogs possessing a CF_3 group at the C-6 position on the indole was generated as shown in Scheme 32. We expected a strong dipole induced by the CF_3 group at this position would be well tolerated in the binding pocket of the cationic substituent, without suffering the desolvation penalty. The aldehyde group in **2-8** was converted into an ethynyl group, which underwent a Sonogashira coupling to provide **2-13** in excellent yield. After extensive screening of catalysts, we found that the indole formation was best effected by 5 mol% Au(I) to provide **2-14**,[111] which was further derivatized to amidine **2-15** and imidazoline **2-16**, analogous to the preparations of **2-10** and **2-11.**

Scheme 32 Synthesis of CF_3 analogues



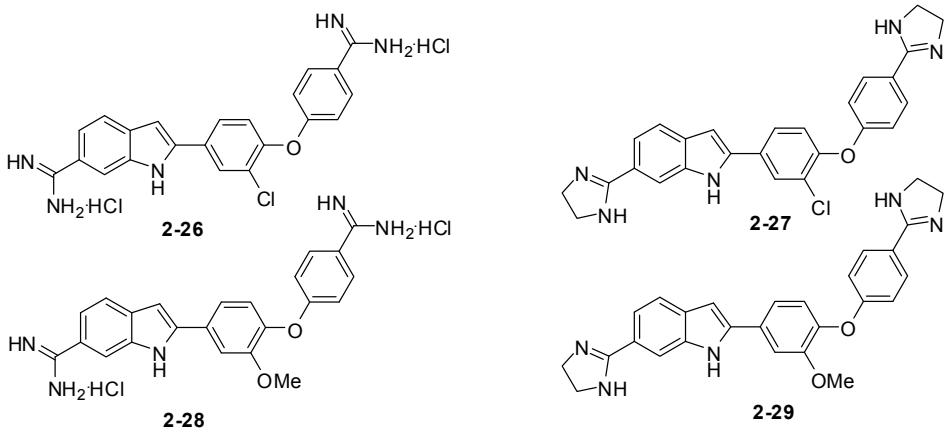
Utilizing an iterative coupling sequence, we synthesized two other groups of analogs (Scheme 33) with an amidine group at the indole C-5 position (**2-19**, **2-20**), or a pyridine group replacing the central phenyl ring (**2-24**, **2-25**). Most reactions proceeded with good to excellent yields, with the exception of the nitrile aminolysis of the indole C-5 analogue (**2-18** to **2-20**). This low yield was attributed to an incomplete reaction (mono-imidazoline was observed) and sample loss during HPLC purification. The cycloisomerization reaction of the pyridine analogue (**2-22** to **2-23**) was also found to be low yielding, presumably due to the product's low solubility in most organic solvents.

Scheme 33 Synthesis of indole C-5 and pyridine analogues



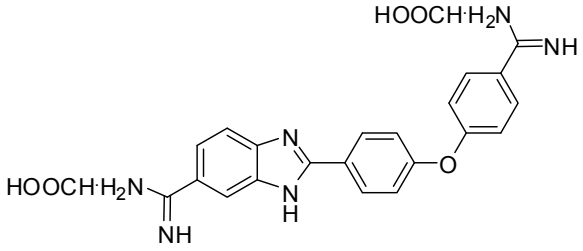
Another set of analogues bearing substituents on the central phenyl ring was prepared by Julia Widom using the same synthetic sequence (Scheme 34).[112]

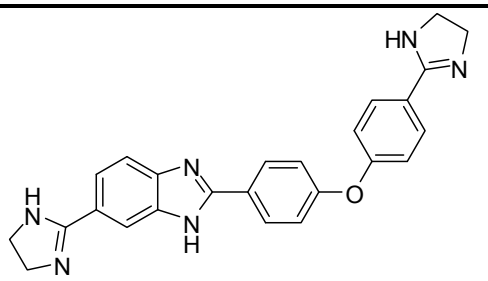
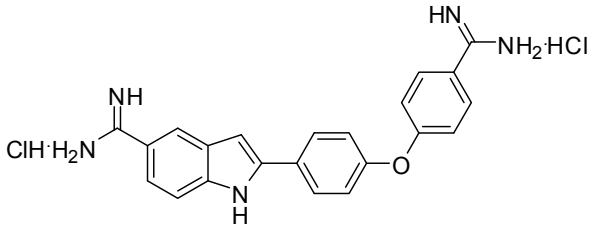
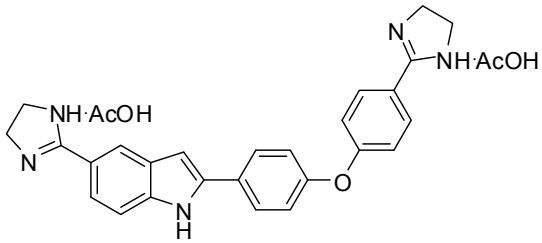
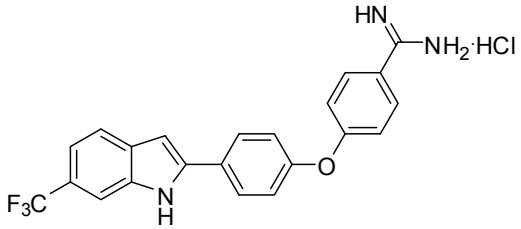
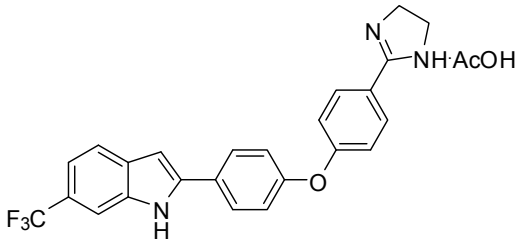
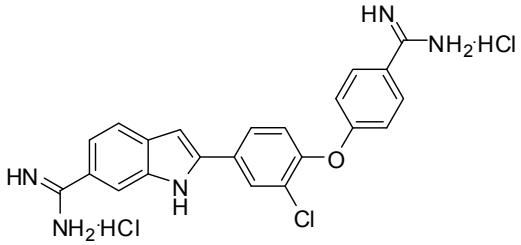
Scheme 34 Analogues bearing substitution group on the central phenyl ring

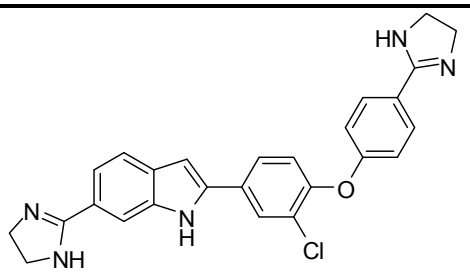
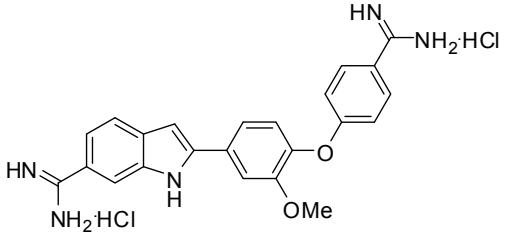
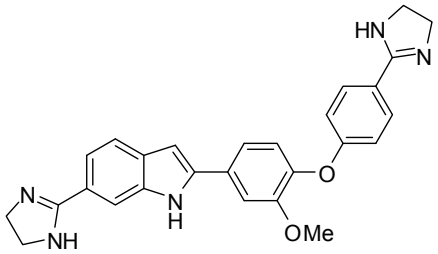
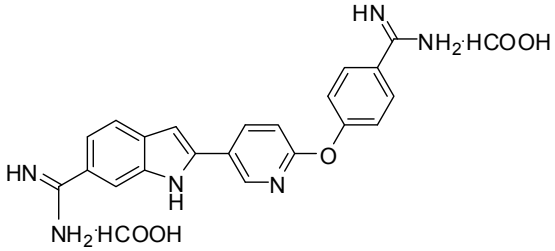
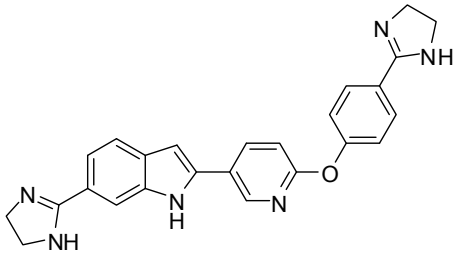
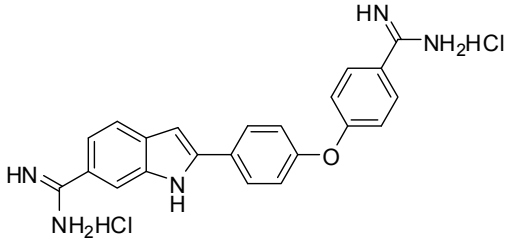


A summary of the effects of structural modifications on BoNT/A LC inhibitory potency is provided in Table 9.[112] While none of the new analogues were as potent as NSC 240898, relative degrees of inhibition ranging from one third (i.e., of NSC 240898 activity) to nearly equal potency were observed. Correlation of the biological data in Table 9 to the corresponding structures allows a better understanding of the electrostatic and steric requirements for this scaffold in its BoNT/A LC binding site and forms the foundations for future inhibitor refinements.

Table 9 List of synthetic analogues and activity against BoNT A LC

Compound	*Structure*	*% BoNT/A LC Inhibition (20 μM)**
2-10		24.7 (± 1.5)

2-11		34.8 (± 1.4)
2-19		58.8 (± 3.3)
2-20		51.4 (± 4.6)
2-15		25.2 (± 3.4)
2-16		43.3 (± 7.2)
2-26		64.4 (± 2.1)

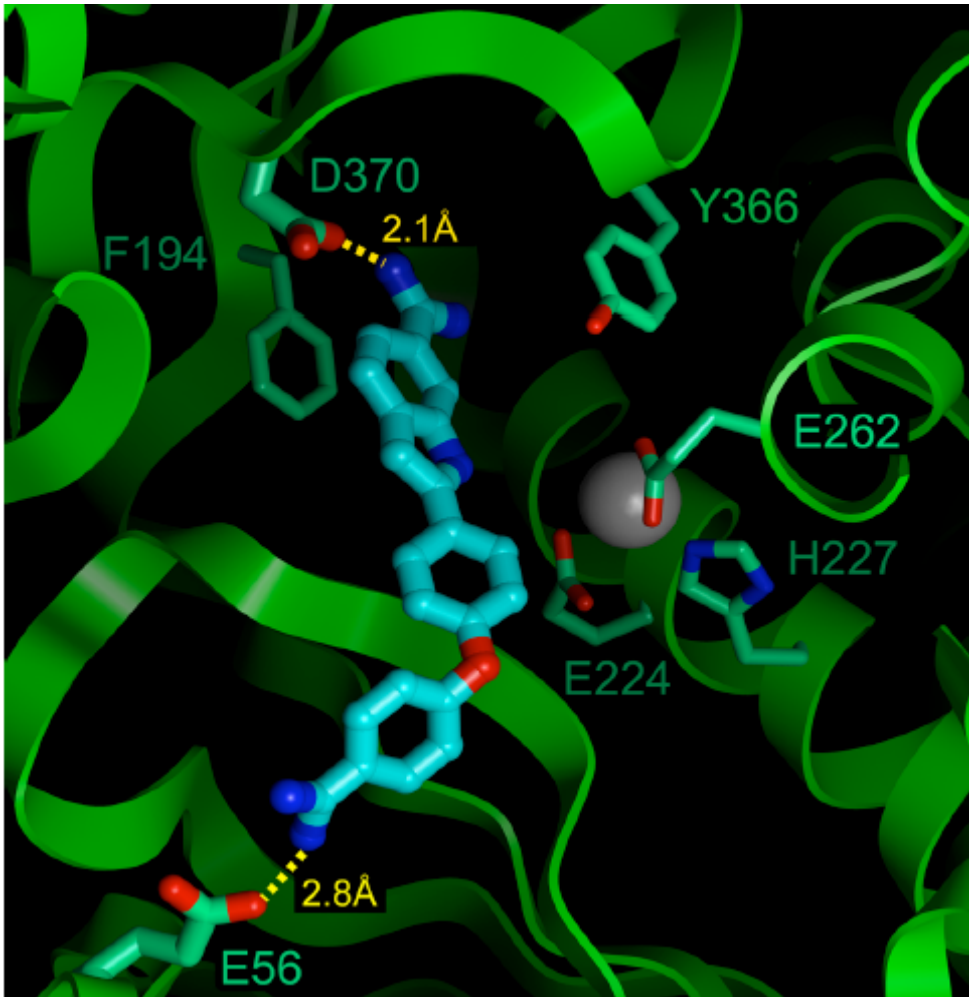
2-27		64.8 (± 4.4)
2-28		58.0 (± 6.7)
2-29		69.8 (± 1.8)
2-24		52.7 (± 5.5)
2-25		46.1 (± 1.2)
NSC 240898		73.5 (± 7.5)

* Values are the averages of two independent experiments. All bis-nitrile compounds were inactive.

Changing the substituents at sites **A, B** and **C** from bis-amidines to bis-imidazolines had no significant impact on activity (for example, **2-10** vs. **2-11** and **2-19** vs. **2-20**). However, not unexpectedly, replacing the basic amidines with neutral nitrile functions was not tolerated; in contrast, replacing the amidine group on the indole ring with trifluoromethyl (**2-15** and **2-16**) resulted in moderately active inhibitors. While our data suggests that a strongly basic amidine or imidazoline substituent is preferred at the **A** position (Figure 33), for hydrogen-bonding or ionic interactions with the binding site,[113-114] it also suggests that there is a degree of binding site plasticity. These results are consistent with recent X-ray co-crystal structures,[115] demonstrating that the BoNT/A LC 370 loop, which is adjacent to the amidine at site **A** (Figure 33) in the predicted binding mode for NSC 240898,[106] can undergo a conformational flip to present either the polar side chain of Asp370 or the hydrophobic side chain of Phe369 (Figure 34[112]). This reorientation accommodates either basic or hydrophobic inhibitor substituents at the same binding site location, but not an acidic residue as demonstrated by the inactivity of a bis-tetrazole analogue of NSC 240898 (*vide infra*). A binding site plasticity hypothesis is further supported by the fact that switching the amidine from the C-6 position of the indole to the C-5 position (**2-19** and **2-20**) results in only a moderate decrease in inhibitory potency.

Figure 34 Proposed binding mode for NSC 240898 (shown with cyan carbons).

Oxygen atoms are red and nitrogen atoms are blue. The BoNT/A LC backbone is displayed in green ribbons, and the catalytic zinc is gray (space filled). Side chain residues are rendered in stick with green carbons. Hydrogen bonds between NSC 240898 and residues Glu 56 and Asp 370 are displayed as dashed yellow lines. Reproduced from Ref. [112].

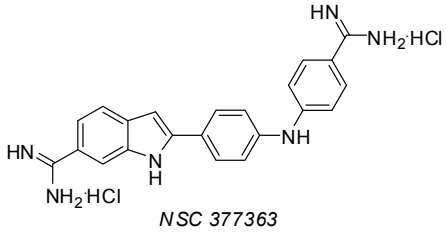


For analogues **2-10** and **2-11,** replacing the C-3 carbon of the indole ring with a nitrogen (site **D** in Figure 33), to give the benzimidazole derivative, results in a marked reduction in potency. This is indicative of the presence of a complementary hydrophobic BoNT/A LC contact for the C-3 atom. Similarly, but to a lesser degree, **2-24** and **2-25** reveal that incorporating a nitrogen in the C-3 position of the central phenyl ring is not optimal for binding. Again, this is most likely due to unfavorable contacts with a corresponding hydrophobic binding surface. In contrast, substitution on the same position in the central phenyl ring (site **F** in Figure 33) with a

chloro (**2-26** and **2-27**) or a methoxy (**2-28** and **2-29**) group results in a level of BoNT/A LC inhibition that is nearly equipotent to that of NSC 240898. This is an important finding, since it demonstrates that there is available steric volume surrounding this hydrophobic inhibitor binding site, and that this space may be accessed without incurring a dramatic loss in potency.

Finally, a 2D (molecular topology) search of the NCI Open Repository identified an analogue possessing an amine (versus an oxygen) at the biaryl hinge (marked **G** in Figure 33) of the scaffold.[112] Subsequent biological testing of this derivative, designated NSC 377363, revealed that it was equipotent to the parent (70% inhibition at 20 μ M concentration, Figure 35), and thus demonstrated that either a H-bond donor or H-bond acceptor is feasible at this position.

Figure 35 Structure of NSC 377363

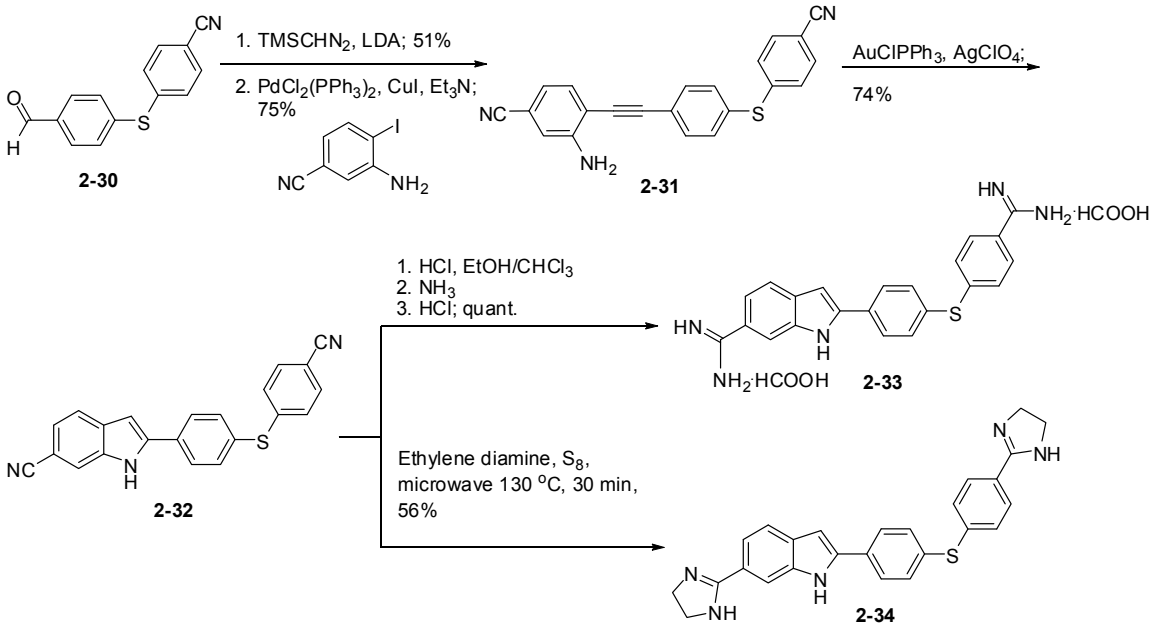


NSC 377363

In order to shed further light on the biological significance of the diarylether linkage, two thioether analogues, **2-33** and **2-34** (Scheme 35), were prepared. Biological evaluation of **2-33** and **2-34** at 20 mM concentrations revealed 67.3 (± 3.6)% and 80.3 (± 6.7)% inhibition of the BoNT/A LC, respectively. While the bis-amidine **2-33** is equipotent to the parent, i.e., NSC 240898, the bis-imidazoline **2-34** is more active. This surprising finding may indicate that the derivative with the imidazoline substituents is binding in a subtly different manner that favors desolvation. Since, for the oxygen analogue of **2-34**, the activity is always slightly less (compared to NSC 240898) for the derivative possessing imidazolines, it is hypothesized that the sharper bond angle provided by the sulfur atom of **2-34** (versus the oxygen atom at that position)

allows for better placement of the larger imidazoline head pieces in the enzyme binding site, such that hydrophobic contacts are improved.

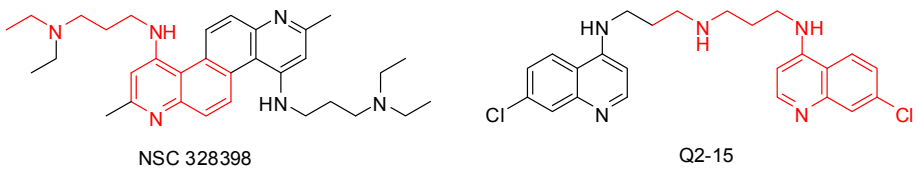
Scheme 35 Synthesis of thioether analogues



2.2.3 2nd Generation Inhibitors

At this stage, our collaborator at the National Cancer Institute conducted a search in the NCI Open Repository based on the structure elements of NSC 240898.[116] Ten small molecule hits were identified, and upon testing, three demonstrated inhibitory activity. Of these, one possessed a rigid diazachrysene scaffold (NSC 328398, Figure 36), whose structure resembles a previously identified LC/A inhibitor[103,117] (Q2-15, Figure 36).

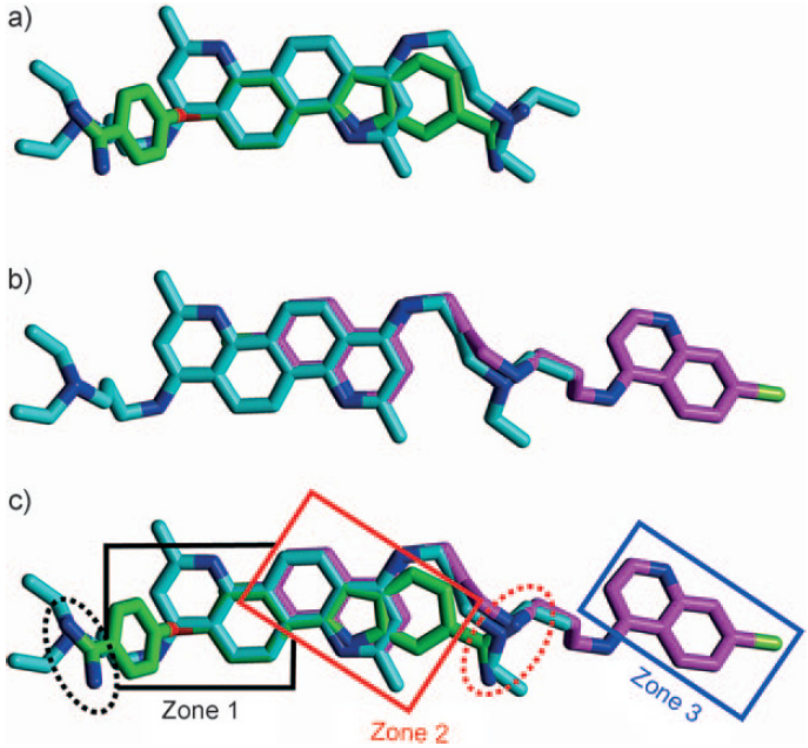
Figure 36 Structures of Q2-15 and NSC 328398, with structural similarities colored red.



Superimposing the 3D alignments of NSC 240898 and NSC 328398 demonstrated comparable steric and functional group occupancy in 3D space (Figure 37a[116]). Meanwhile, the diazachrysene moiety in NSC 328398 is comparable to the 4-aminoquinoline substructure in Q2-15 (Figure 37b[116]) and they both share the same aminoalkyl linker. This led to the superimposition of Q2-15 and NSC 328398 (Figure 37c[116]). Based on the alignment, a refined pharmacophore possessing three zones was proposed (Figure 37c[116]).

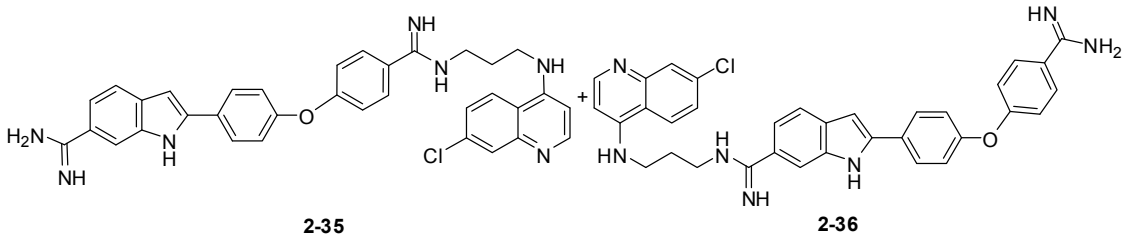
Figure 37 3D alignments of NSC 240898, Q2-15 and NSC 328398.

Reproduced from Ref. [116]. Chlorines are light green, nitrogen atoms are blue, and oxygen is red: a) NSC 240898 and NSC 328398 superimposed. NSC 240898 carbon atoms are green and NSC 328398 carbon atoms are cyan; b) NSC 328398 and Q2-15 superimposed. NSC 328398 carbons are cyan and Q2-15 carbons are magenta; c) NSC 240898, NSC 328398, and Q2-15 superimposed.



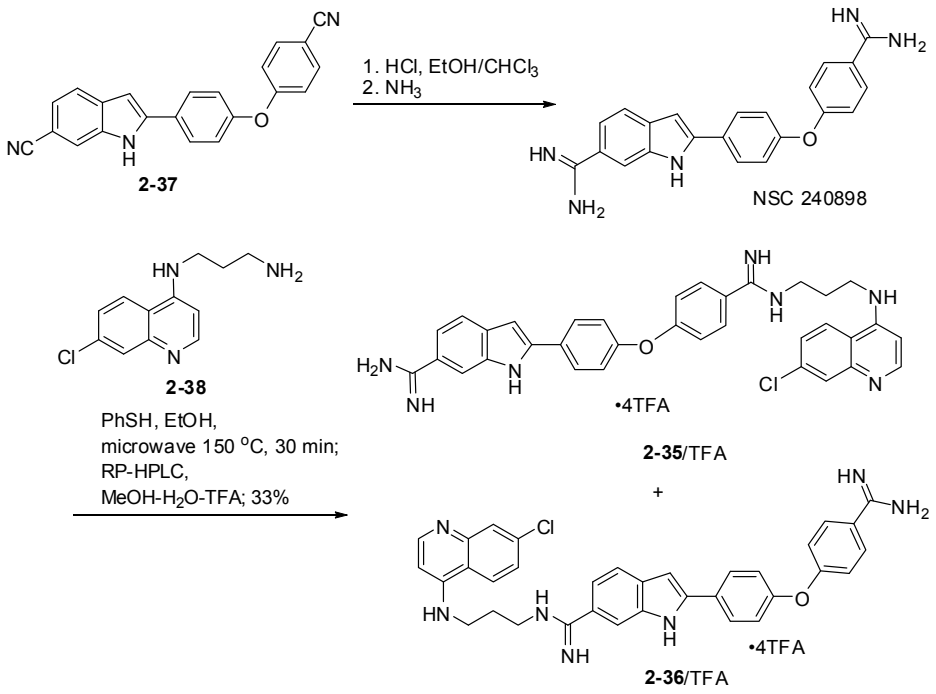
Based on this result, we proposed a new inhibitor design occupying all three zones by tethering the quinoline moiety to one of the amidine groups of NSC 240898 via a propyl linker (**2-35** and **2-36**, Figure 38).[118] At this stage, the orientation of NSC 240898 in the binding site was not clear. Therefore, a decision was made to synthesize both regioisomers (**2-35** and **2-36**).

Figure 38 Proposed three-zone inhibitors



A straightforward method to simultaneously prepare both regioisomers was the exchange reaction of NSC 240898 with one equivalent of quinoline **2-38** (Scheme 36). The reaction was carried out with thiophenol for 30 min in a microwave reactor at 150 °C, and RP-HPLC purification afforded a 4:1 mixture of TFA salts (inseparable).

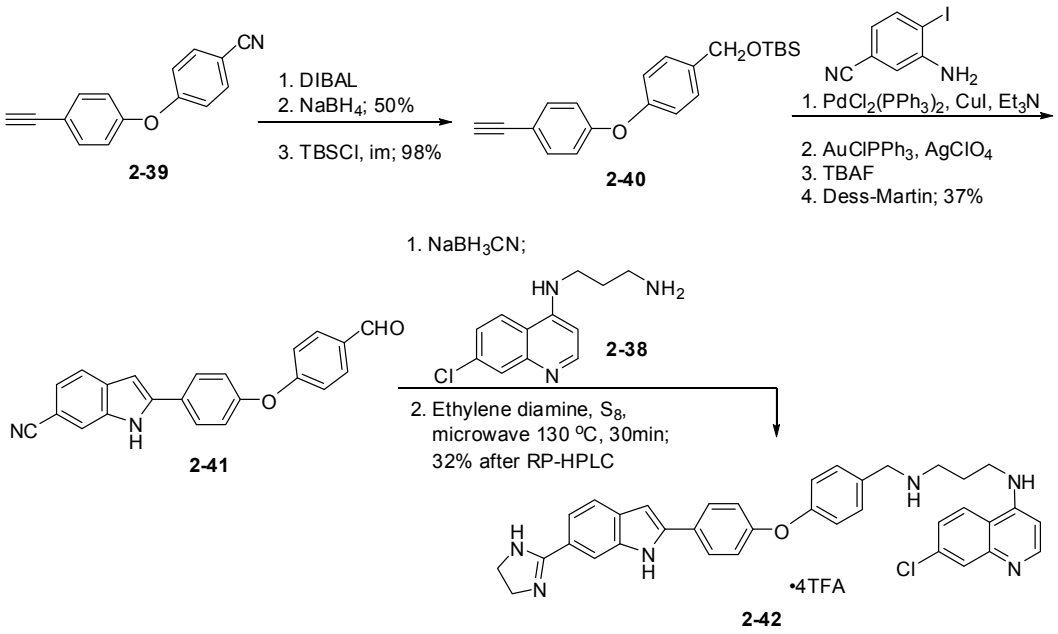
Scheme 36 Synthesis of the three-zone inhibitors **2-35** and **2-36**



In vitro testing of this mixture of **2-35** and **2-36** resulted in 95% BoNT/A LC inhibition (at 20 μM inhibitor conc.). A more detailed analysis of the inhibition kinetics revealed that the regioisomers possess a Ki = 600 nM (±100 nM) (NSC 240898: Ki = 10 μM[106]), a 15.7-fold increase in potency.

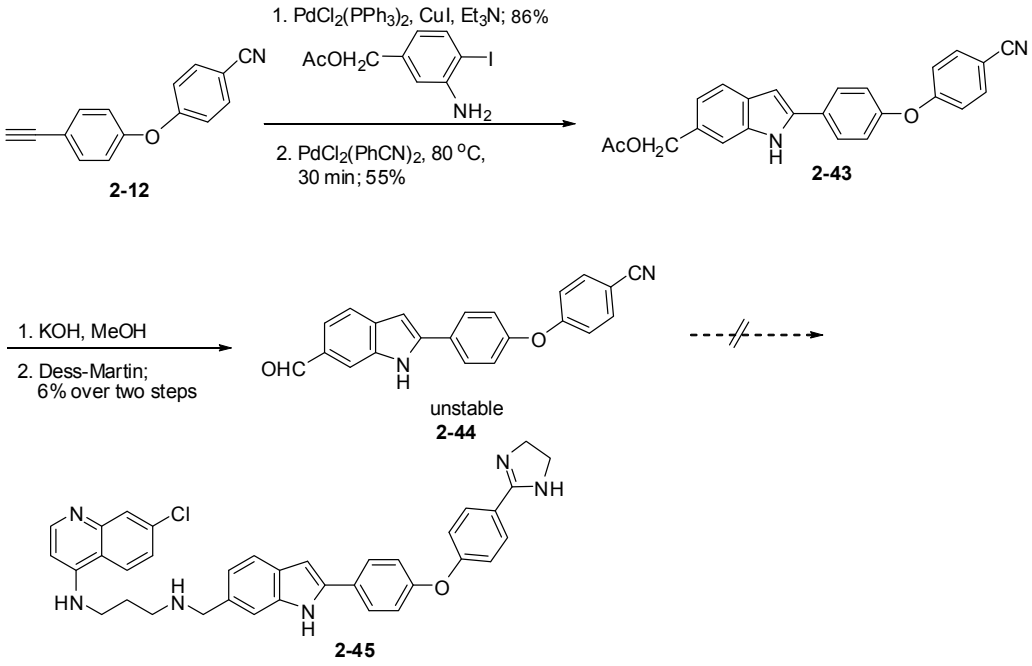
Next, we decided to investigate the relationship between activity and position of the quinoline side chain. A new series of inhibitors was prepared (**2-41** and **2-44**, Scheme 37, Scheme 38). Reduction of biaryl ether **2-12** to the benzyl alcohol followed by TBS protection provided intermediate **2-39**. A subsequent four-step sequence, including Sonogashira coupling, Au(I) catalyzed indole formation, desilylation and Dess-Martin oxidation, proceeded smoothly to provide indole **2-40**. Intermediate **2-40** underwent reductive amination with the quinoline amine **2-38** and subsequent imidazoline formation under microwave heating to provide **2-42**. Unfortunately, formation of the amidine analogue failed, presumably due to the harsh reaction conditions.

Scheme 37 Synthesis of **2-42**



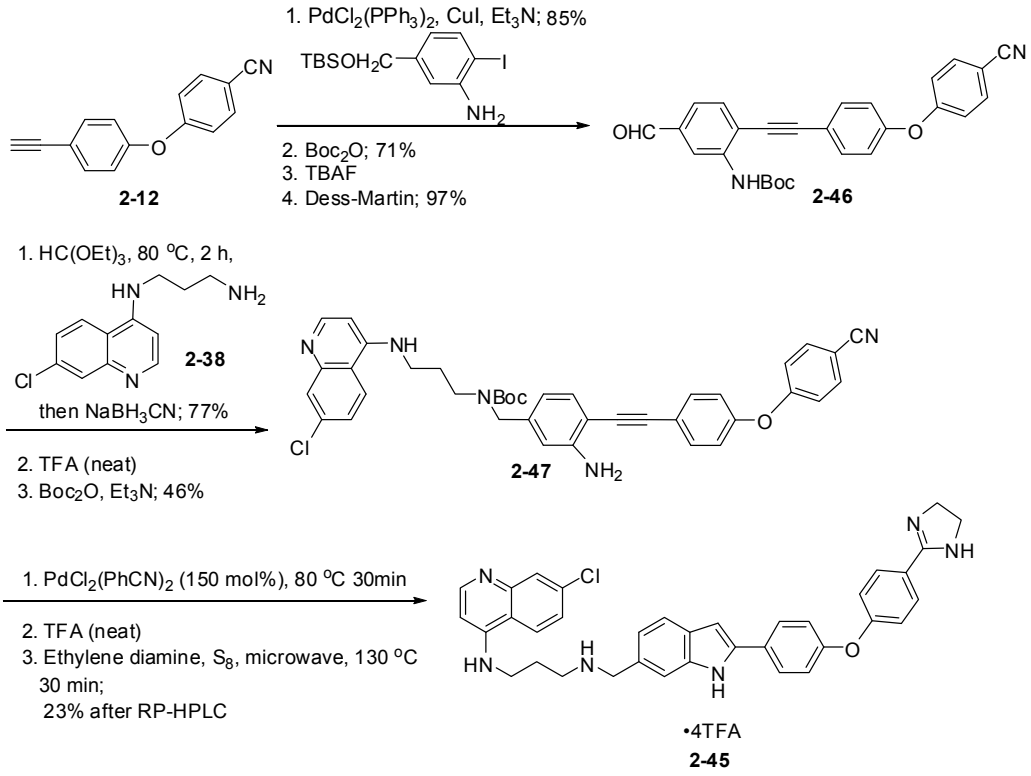
Initially, we attempted to prepare the other regioisomer via a similar route (Scheme 38). Alkyne **2-12** underwent Sonogashira coupling followed by a palladium-catalyzed cycloisomerization to provide indole **2-43**. Upon deprotection at **2-43**'s benzylic position, both the benzyl alcohol and its oxidation product **2-44** were found to be unstable (**2-44** decomposes in minutes at room temperature). Hence, an alternative route was developed (Scheme 39).

Scheme 38 Attempted synthesis of **2-45**



Intermediate **2-46** was prepared from biaryl ether **2-12** via a sequence including Sonogashira coupling, Boc protection of the aniline group, desilylation and oxidation. Reductive amination with the quinoline amine **2-38** was followed by transposition of the Boc group from the aniline position to the benzyl position. Indole formation required excess catalyst due to the strong chelation of substrate **2-47** to palladium. The Boc group was subsequently cleaved by TFA and the product was further elaborated to imidazoline **2-45**.

Scheme 39 Synthesis of **2-45**



Upon testing with BoNT/A LC, compounds **2-42** and **2-45** exhibited similar activities (65±2.2% and 69±2.2% inhibition at 10 μM), which suggests that the binding pocket in BoNT A LC may not be highly directional.

2.3 CONCLUSIONS

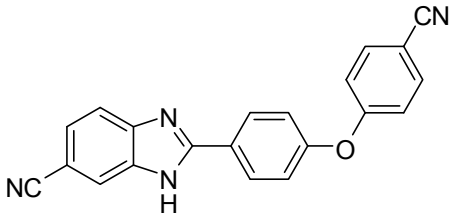
Based on the NSC 240898 scaffold, we have successfully prepared a variety of analogues by the concise use of transition metal catalyzed cross-couplings and heterocycle annulations. Examination of these derivatives for BoNT/A LC inhibition provides a rich SAR. In addition, two sets of analogues (**2-34**, **2-35** and **2-36**) displayed significantly increased potency against

BoNT LC/A when compared to NSC 240898. These findings are significant for the further optimization of the NSC 240898 lead structure during all phases of development.

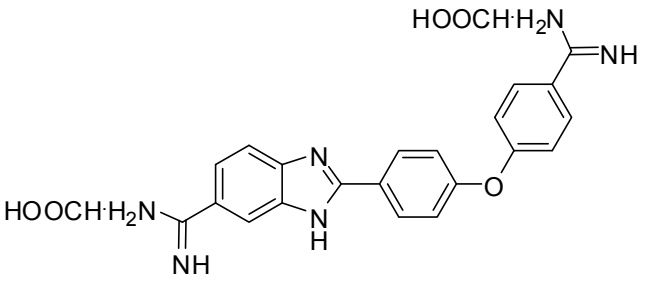
2.4 EXPERIMENTAL PART

General: All moisture-sensitive reactions were performed under an atmosphere of N_2. Glassware was flame dried prior to use. THF and Et_2O were dried by distillation over Na/benzophenone. DCM was dried by distillation over CaH_2. The solution of lithium diisopropylamide (2.0 M in a mixture of heptane, diethylbenzene and THF) was purchased from Aldrich. Unless otherwise stated, solvents and reagents were used as received. Analytical thin layer chromatography was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualization was accomplished with a 254 nm UV light or by staining with an anisaldehyde solution (7.5 mL of *p*-anisaldehyde, 25 mL of concentrated H_2SO_4 and 7.5 mL of glacial acetic acid in 675 mL of 95% ethanol) or $KMnO_4$ solution (1.5 g of $KMnO_4$, 10 g of potassium carbonate and 2.5 mL of 5% aqueous NaOH in 150 mL of H_2O). Flash chromatography on SiO_2 was used to separate and purify the crude reaction mixtures. NMR spectra were recorded at 300 MHz/75 MHz (^{1}H NMR/^{13}C NMR) at 21 ^{o}C in $CDCl_3$ unless otherwise noted. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, dd=doublet of doublet, ddd= doublet of doublet of doublet, dt=doublet of triplet, dq=doublet of quartet, m=multiplet, br=broad, app=apparent). LC/MS analyses were obtained from either a Hewlett Packard Series 1100 MSD

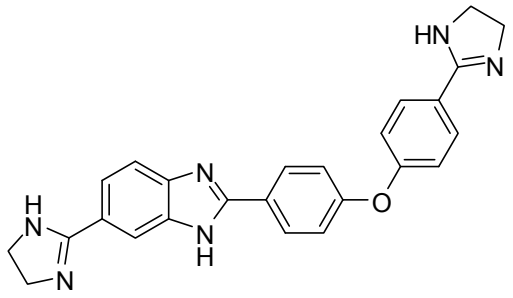
or Applied Biosystem 2100 MSD. Infrared spectra were measured on either a Nicolet AVATAR 360 FTIR E.S.P. spectrometer or Smith IdentifyIR.



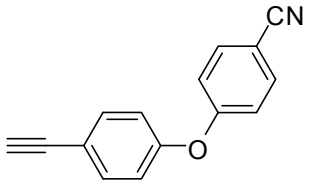
2-(4-(4-Cyanophenoxy)phenyl)-3H-benzo[d]imidazole-5-carbonitrile (2-9). A suspension of **2-8**[107] (0.224 g, 1.00 mmol) in 40% $NaHSO_3$ (2.0 mL) was stirred at room temperature for 2 h followed by the treatment with a suspension of 3,4-diaminobenzonitrile (0.173 g, 1.30 mmol) in EtOH (5.0 mL). The reaction mixture was heated at reflux for 14 h, poured into water and filtered. The precipitate was redissolved in EtOAc, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (hexanes:THF = 3:1) afforded 0.305 g (91%) of **2-9** as a yellow solid: mp 226.0 °C (decomp.) (THF); IR (KBr) 3426, 3269, 3068, 2230, 1623, 1596, 1500, 1483 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.45 (s, 1 H), 8.30-8.23 (m, 2 H), 8.12 (app br s, 1 H), 7.88 (d, 2 H, *J* = 8.7 Hz), 7.73 (app d, 1 H, *J* = 8.1 Hz), 7.58 (dd, 1 H, *J* = 8.3, 1.2 Hz), 7.35-7.29 (m, 2 H), 7.22 (d, 2 H, *J* = 8.7 Hz); ^{13}C NMR (DMSO-d_6) δ 160.1, 156.8, 153.7, 134.8, 129.1, 125.7, 120.2, 120.0, 119.0, 118.6, 106.0, 104.0, 159.2, 155.5, 134.4, 133.8, 132.0, 129.9, 127.1, 121.2, 118.6, 118.2, 107.5; MS (EI) *m/z* (rel intensity) 336 (100), 206 (12), HRMS (EI) *m/z* calcd for $C_{21}H_{12}N_4O$ 336.1011, found 336.1001.



2-(4-(4-Carbamimidoylphenoxy)phenyl)-3H-benzo[d]imidazole-5-carboximidamide diformate (2-10). A solution of **2-9** (30.4 mg, 0.0903 mmol) in EtOH:$CHCl_3$ = 1:1 (v/v, 10 mL) at 0 °C was bubbled with HCl gas for 30 min and then stirred at room temperature for 24 h. The solvent was evaporated and EtOH (6.0 mL) was added. The solution was bubbled with NH_3 gas at room temperature for 10 min. After 24 h stirring at room temperature, the reaction mixture was bubbled with NH_3 gas again and stirred for another 24 h. The solvent was evaporated and the residue was co-evaporated with EtOH (x2). The residue was redissolved in EtOH (2 mL) and filtered. The filtrate was poured into Et_2O (10 mL) and treated with formic acid (final concentration of HCOOH ~ 50% v/v) and stirred for 30 min at room temperature. The precipitate was collected by filtration to yield 11.0 mg (28%) of **2-10** as a yellow solid: mp 232.6 °C (decomp.) (DMSO); IR (KBr) 3368, 3136, 1674, 1627, 1599, 1481, 1451, 1401 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.47 (s, 2 H), 9.30 (s, 1 H), 9.26 (s, 1 H), 8.45 (d, 2 H, J = 8.3 Hz), 7.97 (d, 1 H, J = 8.4 Hz), 7.83-7.70 (m, 1 H), 7.57 (app s, 2 H), 7.40 (app s, 2 H); 7.34-7.24 (m, 2 H), 7.23 (app s, 2 H); ^{13}C NMR (DMSO-d_6) δ 166.1, 164.8, 163.0, 160.7, 167.5, 164.4, 143.2, 130.8, 129.9, 129.6, 122.9, 122.4, 121.6, 119.9, 119.2, 118.6, 118.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{19}N_6O$ (M+H) 371.1620, found 371.1594.

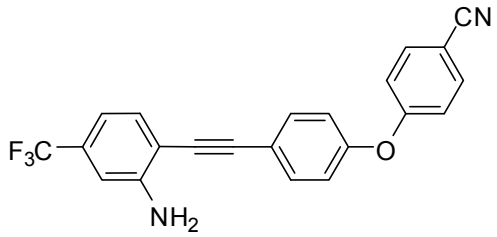


6-(4,5-Dihydro-1H-imidazol-2-yl)-2-(4-(4-(4,5-dihydro-1H-imidazol-2-yl)phenoxy)-phenyl)-1H-benzo[d]imidazole (2-11). A mixture of sulfur (1.42 mg, 0.0433 mmol) and **2-9** (30.0 mg, 0.0892 mmol) was treated with ethylene diamine (0.5 mL), then heated in the microwave at 110° C for 30 min. The reaction mixture was suspended in water and filtered, and the solid was rinsed with water (3x). The residue was then dried under vacuum, affording **2-11** (30.7 mg, 81%) as a yellow solid: mp 252.9 °C (decomp.) (DMSO); IR (KBr) 3340, 1603, 1507, 1486, 1451 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.26-8.07 (m, 2 H), 8.06-7.98 (m, 1 H), 7.91-7.81 (m, 2 H), 7.79-7.65 (m, 1 H), 7.64-7.49 (m, 1 H), 7.22-7.00 (m, 4 H), 3.64 (s, 4 H), 3.60 (s, 4 H); ^{13}C NMR (DMSO-d_6) δ 164.4, 163.0, 157.8, 157.6, 152.5, 142.9, 139.2, 129.2, 129.0, 128.6, 126.3, 125.6, 124.0, 121.6, 120.3, 119.0, 118.5, 49.6, 49.3; HRMS (ESI) *m/z* calcd for $C_{25}H_{23}N_6O$ (M+H) 423.1933, found 423.1928.



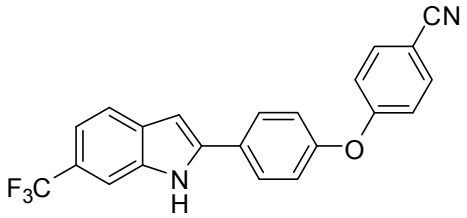
4-(4-Ethynylphenoxy)benzonitrile (2-12). A solution of lithium diisopropylamide (2.0 M in a mixture of heptane, diethylbenzene and THF, 1.40 mL, 2.80 mmol) in THF (18.6 mL) at -78 °C was treated with $TMSCHN_2$ (2.0 M in ether, 1.40 mL, 2.80 mmol). The reaction mixture was stirred at -78 °C for 30 min and a solution of **2-8**[107] (0.519 g, 2.32 mmol) in THF (4.7 mL) was added. The reaction mixture was stirred at -78 ºC for 1 h and heated at reflux for 3 h. The

reaction mixture was quenched with cold water and extracted with Et_2O (3x). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:Et_2O = 10:1) afforded 0.279 g (55%) of **2-12** as a white solid: mp 87.2-87.9 ºC (acetone); IR (KBr) 3097, 3063, 2224, 1608, 1592, 1492 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64 (d, 2 H, *J* = 9.0 Hz), 7.54 (d, 2 H, *J* = 8.8 Hz), 7.07-6.99 (m, 4 H), 3.10 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 160.8, 155.4, 134.3, 134.2, 120.0, 118.8, 118.7, 118.5, 106.6, 82.7; MS (EI) *m/z* (rel intensity) 219 (100), 190 (25); HRMS (EI) *m/z* calcd for $C_{15}H_9NO$ 219.0684, found 219.0678.

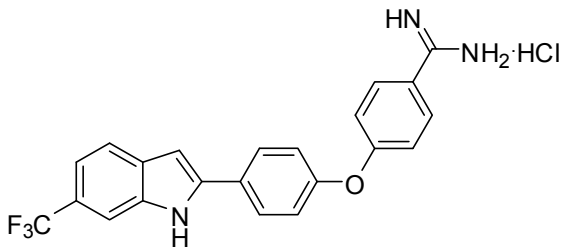


4-(4-((2-Amino-4-(trifluoromethyl)phenyl)ethynyl)-2-chlorophenoxy)benzonitrile (2-13). A solution of **2-12** (0.570 g, 2.60 mmol) and 2-iodo-5-trifluoromethylphenylamine[119] (0.672 g, 2.34 mmol) in MeCN (18 mL) was degassed and treated with $PdCl_2(PPh_3)_2$ (91.2 mg, 0.130 mmol) and CuI (54.5 mg, 0.286 mmol). The reaction mixture was degassed again and treated with Et_3N (1.81 mL, 13.0 mmol). The reaction mixture was heated at reflux for 1.5 h, diluted with Et_2O and filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with Et_2O (3x) and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:THF = 6:1 to 4:1) yielded 0.993 g (100%) of **2-13** as a yellow solid: mp 121.9-123.8 ºC (THF); IR (KBr) 3482, 3379, 2232, 1621, 1513 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (d, 2 H, *J* = 8.9 Hz), 7.58 (d, 2 H, *J* = 8.8 Hz), 7.45 (d, 1 H, *J* = 8.1 Hz), 7.10-7.04 (m, 4 H), 7.00-6.93 (m, 2 H), 4.46 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 160.8, 155.4, 148.1, 134.3, 133.6, 132.5, 131.3 (q, *J* = 31.5 Hz), 120.1, 119.3, 118.8, 118.5, 114.0 (q, *J* = 3.7 Hz), 110.8,

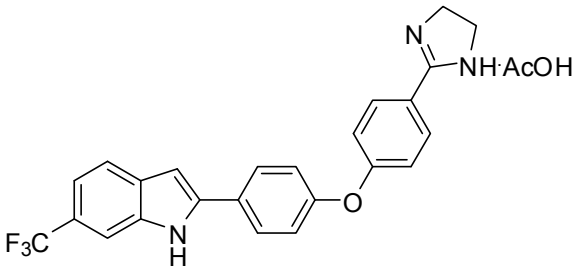
110.7 (q, J = 3.8 Hz), 106.5, 95.6, 85.0; MS (EI) *m/z* (rel intensity) 378 (100), 276 (15), 248 (10), 84 (45); HRMS (EI) *m/z* calcd for $C_{22}H_{13}N_2OF_3$ 378.0980, found 378.0993.



4-(4-(6-(Trifluoromethyl)-1H-indol-2-yl)phenoxy)benzonitrile (2-14). A solution of **2-13** (0.103 g, 0.271 mmol) in DCM (6.0 mL) was treated with $AuClPPh_3$ (6.08 mg, 0.0134 mmol) followed by $AgClO_4$ (6.080 mg, 0.0298 mmol) at room temperature. The reaction mixture was stirred in the dark at room temperature for 14 h and filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with Et_2O (3x). The organic phases were combined and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:THF = 4:1) yielded 90.2 mg (87%) of **2-14** as a yellow solid: mp 198.5-201.6 ºC (THF); IR (KBr) 3357, 2228, 1598, 1491, 1460 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.05 (s, 1 H), 7.98 (d, 2 H, J = 9.0 Hz), 7.84 (d, 2 H, J = 9.0 Hz), 7.73-7.67 (m, 2 H), 7.31-7.20 (m, 2 H), 7.15 (d, 2 H, J = 9.0 Hz), 7.00 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 160.8, 154.5, 140.2, 135.9, 134.6, 131.3, 128.4, 127.5, 121.8 (q, J = 30.8 Hz), 120.73, 120.66, 118.7, 118.3, 115.8-115.6 (m), 108.4 (q, J = 4.5 Hz), 105.4, 99.0; MS (EI) *m/z* (rel intensity) 378 (16), 276 (20), 248 (20), 102 (100), 75 (32); HRMS (EI) *m/z* calcd for $C_{22}H_{13}F_3N_2O$ 378.0980, found 378.0973.

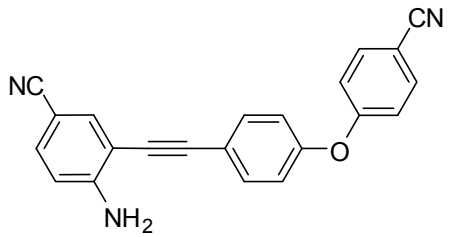


4-(4-(6-(Trifluoromethyl)-1H-indol-2-yl)phenoxy)benzimidamide hydrochloride (2-15). A solution of **2-14** (30.0 mg, 0.0793 mmol) in EtOH:$CHCl_3$ = 1:1 (v/v, 10 mL) at 0 ^oC was bubbled with HCl gas for 30 min. The reaction mixture was stirred at room temperature for 24 h and the solvent was removed. The residue was redissolved in EtOH (6.0 mL) and bubbled with NH_3 gas for 20 min at room temperature. The reaction mixture was stirred for 24 h, re-bubbled with NH_3 gas and stirred for another 24 h. The solvent was evaporated and the residue was co-evaporated with EtOH (x2). The residue was redissolved in EtOH (2.0 mL) and filtered through a pad of SiO_2. The filtrate was poured into Et_2O (10 mL) and bubbled with HCl for 1 min. After 30 min stirring, the precipitate was decanted, washed with Et_2O (2x) and dried under vacuum to afford 23.8 mg (70%) of **2-15** as a white solid: mp 206.8 ºC (decomp.; EtOH-Et_2O); IR (KBr) 3126, 1673, 1600, 1513, 1478, 1401 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.38 (s, 1 H), 9.39 (s, 1 H), 9.21 (s, 1 H), 8.18 (d, 1 H, *J* = 8.8 Hz), 8.05 (app dd, 2 H, *J* = 8.7, 2.3 Hz), 7.92 (d, 2 H, *J* = 8.7 Hz), 7.75-7.68 (m, 2 H), 7.51 (app s, 1 H), 7.35-7.15 (m, 4 H), 7.05-7.01 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 164.8, 161.4, 154.8, 140.2, 135.9, 131.2, 130.7, 128.2, 127.6, 122.3, 121.6 (q, *J* = 30.7 Hz), 120.7, 120.5, 117.8, 117.7, 115.8-115.5 (m), 108.5 (q, *J* = 3.7 Hz), 98.8, MS (EI) *m/z* (rel intensity) 396 (55), 285 (60), 273 (75), 199 (90), 125 (100); HRMS (EI) *m/z* calcd for $C_{22}H_{16}F_3N_3O$ 395.1245, found 395.1239.



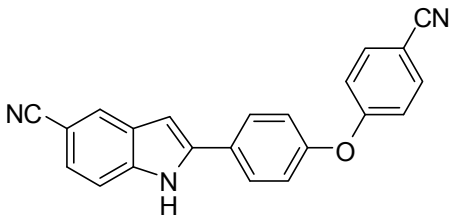
2-(4-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenoxy)phenyl)-6-(trifluoromethyl)-1H-indole (2-16). A mixture of sulfur (0.846 mg, 0.0215 mmol) and **2-14** (20.0 mg, 0.0529 mmol)

was treated with ethylene diamine (0.5 mL), then heated in the microwave at 130 °C for 30 min. The reaction mixture was suspended in water and filtered, and the solid was rinsed with water (3x) and dried under vacuum, affording **2-16** (14.2 mg, 42%) as a sticky yellow solid: IR (Neat) 3222, 1603, 1563, 1506, 1492, 1461 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.03 (s, 1 H), 7.94 (d, 2 H, *J* = 9.0 Hz), 7.86 (d, 2 H, *J* = 9.0 Hz), 7.72, 7.67 (s, 1 H), 7.28 (d, 1 H, *J* = 9.0 Hz), 7.19(d, 2 H, *J* = 9.0 Hz), 7.10 (d, 2 H, *J* = 9.0 Hz), 7.00 (s, 1 H), 3.66 (s, 4 H); ^{13}C NMR (DMSO-d_6) δ 163.0, 158.1, 156.1, 140.4, 135.8, 131.3, 129.1, 127.3, 127.2, 126.0, 123.6, 121.6 (q, *J* = 30.7 Hz), 120.6, 119.6, 118.0, 115.8-115.5 (m), 108.3 (q, *J* = 4.5 Hz); MS (EI) *m/z* (rel intensity) 421 (100), 392 (45), 378 (15), 196 (22), 177 (20); HRMS (EI) *m/z* calcd for $C_{24}H_{18}N_3OF_3$ 421.1402, found 421.1391.

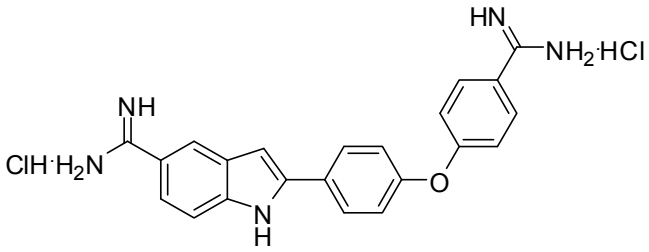


4-Amino-3-((4-(4-cyanophenoxy)phenyl)ethynyl)benzonitrile (2-17). A solution of **2-12** (16.1 mg, 0.0734 mmol) and 4-amino-3-iodobenzonitrile (28.7 mg, 0.117 mmol) in MeCN (0.5 mL) was degassed and treated with $PdCl_2(PPh_3)_2$ (2.58 mg, 0.00367 mmol) and CuI (1.54 mg, 0.00807 mmol). The reaction mixture was degassed again and treated with Et_3N (51.1 μL, 0.367 mmol). The reaction mixture was heated at reflux for 4 h, diluted with Et_2O and filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with Et_2O (3x) and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:1 to 2:1 to 1:1) yielded 21.7 mg (89%) of **2-17** as a white solid: mp 168.5-171.2 ºC (acetone); IR (KBr) 3457, 3360, 3216, 2224, 2211, 1628, 1594, 1554, 1495 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.79 (d, 2 H, *J* = 9.0 Hz), 7.69 (d, 2 H, *J* = 8.9 Hz), 7.63 (d, 1 H, *J* = 2.0

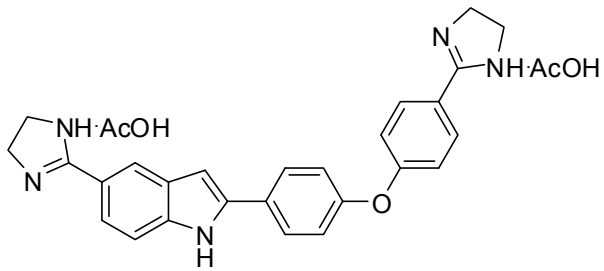
Hz), 7.41 (dd, 1 H, *J* = 8.6, 2.0 Hz), 7.19-7.13 (m, 4 H), 6.90 (d, 1 H, *J* = 8.6 Hz), 6.07 (br s, 2 H); ^{13}C NMR (acetone-d_6) δ 161.6, 156.3, 153.5, 136.9, 135.2, 134.4, 133.9, 120.9, 120.1, 119.9, 119.5, 119.0, 114.9, 107.7, 107.4, 99.2, 95.3; MS (EI) *m/z* (rel intensity) 335 (95), 239 (35), 322 (25), 278 (30), 216 (100), 199 (75); HRMS (EI) *m/z* calcd for $C_{22}H_{13}N_3O$ 335.1059, found 335.1043.



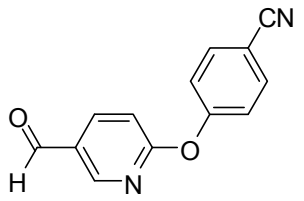
2-(4-(4-Cyanophenoxy)phenyl)-1H-indole-5-carbonitrile (2-18). A solution of **2-17** (15.0 mg, 0.0446 mmol) in DCM (1.0 mL) was treated with $AuClPPh_3$ (1.0 mg, 0.00223 mmol) followed by $AgClO_4$ (1.0 mg, 0.00491 mmol) at room temperature. The reaction mixture was stirred in the dark at room temperature for 4 h and filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with Et_2O (3x). The organic phases were combined and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Toluene:Et_2O = 4:1) yielded 13.2 mg (88%) of **2-18** as a yellow solid: mp 260 ºC (decomp.) (acetone); IR (KBr) 3385, 3123, 2961, 2924, 2220, 1597, 1493 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 11.28 (br s, 1 H), 8.04-7.96 (m, 2 H), 7.80 (d, 2 H, *J* = 8.9 Hz), 7.63-7.55 (m, 2 H), 7.42 (dd, 1 H, *J* = 8.2, 1.6 Hz), 7.26 (d, 2 H, *J* = 8.8 Hz), 7.20 (d, 2 H, *J* = 8.9 Hz), 7.06 (dd, 1 H, *J* = 2.2, 0.7 Hz); ^{13}C NMR (acetone-d_6) δ 161.9, 156.0, 140.6, 139.9, 135.2, 129.8, 126.2, 125.2, 121.5, 120.9, 119.2, 119.0, 113.1, 107.1, 103.6, 100.4; MS (EI) *m/z* (rel intensity) 335 (100), 222 (20); HRMS (EI) *m/z* calcd for $C_{22}H_{13}N_3O$ 335.1059, found 335.1062.



2-(4-(4-Carbamimidoylphenoxy)phenyl)-1H-indole-5-carboximidamide dihydrochloride (2-19). A solution of **2-18** (13.2 mg, 0.0394 mmol) in EtOH:$CHCl_3$ = 1:1 (v/v, 4.4 mL) at 0 ^oC was bubbled with HCl gas for 30 min. The reaction mixture was stirred at room temperature for 20 h and the solvent was removed. The residue was redissolved in EtOH (2.7 mL) and bubbled with NH_3 gas for 20 min at room temperature. The reaction mixture was stirred for 24 h, re-bubbled with NH_3 gas and stirred for another 24 h. The solvent was evaporated and the residue was co-evaporated with EtOH (x2), dissolved in EtOH (1.0 mL) and filtered. The filtrate was poured into Et_2O (5.0 mL) and bubbled with HCl for 1 min. After 30 min stirring, the precipitate was decanted, washed with Et_2O (2x) and dried under vacuum to afford 13.3 mg (76%) of **2-19** as a yellow solid: mp 254 ºC (decomp.) (EtOH-Et_2O); IR (KBr) 3144, 1669, 1600, 1517, 1479 cm^{-1}; ^1H NMR (CD_3OD) δ 9.21 (br s, 1 H), 9.06 (br s, 2 H), 8.74 (br s, 1 H), 8.53 (br s, 2 H), 8.12 (d, 1 H, *J* = 1.2 Hz), 7.94 (d, 2 H, *J* = 8.8 Hz), 7.85 (d, 2 H, *J* = 8.9 Hz), 7.61 (d, 1 H, *J* = 8.6 Hz), 7.56 (dd, 1 H, *J* = 8.6, 1.8 Hz), 7.24-7.15 (m, 4 H), 7.01 (s, 1 H); ^{13}C NMR (CD_3OD) δ 169.2, 167.5, 164.0, 156.5, 142.0, 141.4, 131.4, 130.4, 130.1, 128.6, 123.5, 122.3, 121.9, 121.8, 120.0, 119.2, 113.0, HRMS (ESI) *m/z* calcd for $C_{22}H_{20}N_5O$ (M+H) 370.1668, found 370.1642.

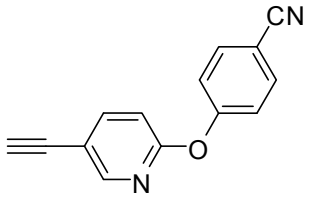


5-(4,5-Dihydro-1H-imidazol-2-yl)-2-(4-(4-(4,5-dihydro-1H-imidazol-2-yl)phenoxy)-phenyl)-1H-indole diacetate (2-20). A solution of **2-18** (17.2 mg, 0.0513 mmol) and sulfur (0.81 mg, 0.0253 mmol) in ethylenediamine 0.5 mL was heated in the microwave at 110 °C for 30 min. The product was precipitated out with water (5.0 mL). The precipitate was collected by filtration, washed with water (x3) and dried under vacuum to afford 16.2 mg of crude product. A sample of this crude product was purified by reverse-phase HPLC (MeOH-1% aq. AcOH) to yield **2-20** as a sticky yellow solid: ^{1}H NMR (DMSO-d_6) δ 11.74 (s, 1 H), 8.01-7.95 (m, 1 H), 7.94-7.88 (m, 2 H), 7.64 (dd, 2 H, *J* = 8.6, 1.4 Hz), 7.38 (d, 1 H, *J* = 8.8 Hz), 7.18-7.11 (m, 2 H), 7.10-7.05 (m. 2 H), 6.94-6.90 (m, 1 H), 3.61 (s, 4 H), 3.58 (s, 4 H), 1.81 (s, 6 H); LC-MS (ESI) (M+H) *m/z* 422.2; MS (EI) *m/z* (rel intensity) 421 (40), 392 (20), 207 (40); HRMS (EI) *m/z* calcd for $C_{26}H_{23}N_5O$ 421.1903, found 421.1922.

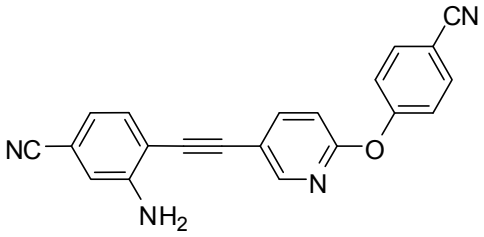


4-(5-Formylpyridin-2-yloxy)benzonitrile (2-21). A solution of 6-bromo-3-pyridinecarboxaldehyde (1.07 g, 5.75 mmol) and 4-cyanophenol (0.690 g, 5.75 mmol) in DMF (34.5 mL) was treated with potassium carbonate (3.16 g, 22.9 mmol) and heated to 150 °C for 3 h. The reaction mixture was poured into water and extracted with EtOAc (3x). The combined organic layers were washed with water (3x) and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (hexanes: EtOAc = 4:1 to 2:1) afforded 0.990 g (77%) of **2-21** as a yellow solid: mp 132.0-134.1 °C (DCM); IR (KBr) 3424, 3099, 2925, 2867, 2230, 1697, 1609, 1593, 1571, 1505 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.99 (s, 1 H), 8.60 (d, 1 H, *J* = 2.0 Hz), 8.24 (dd, 1 H, *J* = 8.5, 2.3 Hz), 7.72 (d, 2 H, *J* = 8.8 Hz), 7.29 (d, 2 H, *J*

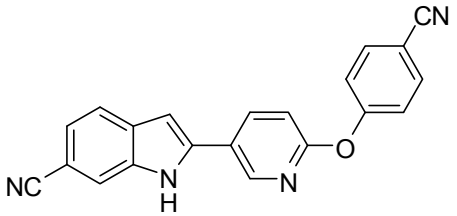
= 8.8 Hz), 7.13 (d, 1 H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 189.2, 165.9, 156.5, 152.2, 139.4, 134.0, 128.5, 122.6, 118.5, 112.9, 109.2; MS (EI) *m/z* (rel intensity) 224 (100), 195 (45), 168 (50), 142 (35); HRMS *m/z* calcd for $C_{13}H_8N_2O_2$ 224.0586, found 224.0579.



4-(5-Ethynylpyridin-2-yloxy)benzonitrile. A solution of lithium diisopropylamide (2.0 M in heptane, diethylbenzene and THF, 2.65 mL, 5.30 mmol) in THF (35.3 mL) at -78 °C was treated with $TMSCHN_2$ (2.0 M in ether, 2.65 mL, 5.30 mmol). The reaction mixture was stirred at -78 °C for 30 min and a solution of **2-21** (0.990 g, 4.41 mmol) in THF (9.00 mL) was added. The reaction mixture was stirred at -78 ºC for 1 h and heated at reflux for 3 h. The reaction mixture was quenched with cold water and extracted with Et_2O (3x). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:Et_2O = 7:1) afforded 0.475 g (49%) of the title compound as a white solid: mp 121.9-123.9 ºC (THF); IR (KBr) 3426, 3250, 3098, 3061, 2231, 2224, 1606, 1589, 1562, 1503, 1476 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.30 (d, 1 H, *J* = 1.9 Hz), 7.84 (dd, 1 H, *J* = 8.3, 2.3 Hz), 7.71 (d, 2 H, *J* = 8.8 Hz), 7.25 (d, 2 H, *J* = 8.9 Hz), 6.98 (dd, 1 H, *J* = 8.5, 0.5 Hz), 3.20 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 161.6, 157.2, 150.9, 143.0, 13.8, 121.8, 118.5, 115.1, 111.9, 108.2, 80.4, 79.7; MS (EI) *m/z* (rel intensity) 220 (100), 192 (50), 102 (40); HRMS (EI) *m/z* calcd for $C_{14}H_8N_2O$ 220.0637, found 220.0630.

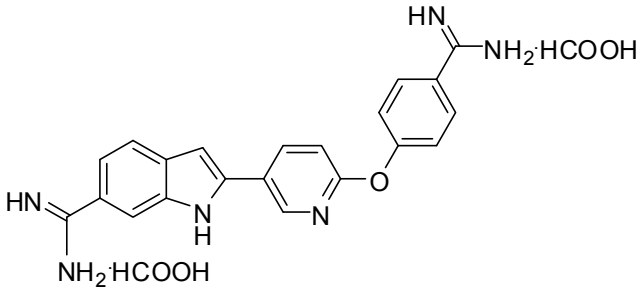


3-Amino-4-((6-(4-cyanophenoxy)pyridin-3-yl)ethynyl)benzonitrile (2-22). A solution of 4-(5-ethynylpyridin-2-yloxy)benzonitrile (0.332 g, 1.51 mmol) and 4-amino-3-iodobenzonitrile (0.334 g, 1.372 mmol) in MeCN (10 mL) was degassed and treated with $PdCl_2(PPh_3)_2$ (48.2 mg, 0.0686 mmol) and CuI (28.8 mg, 0.151 mmol). The reaction mixture was degassed again and treated with Et_3N (0.954 mL, 6.86 mmol). The reaction mixture was heated at reflux for 2 h, diluted with THF and filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with THF (3x) and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (Tolene:THF = 3:1, then repeated with DCM:THF = 10:1) yielded 0.453 g (98%) of **2-22** as a yellow solid: mp 209.2-212.8 ºC (THF); IR (KBr) 3474, 3372, 3061, 2224, 1623, 1604, 1583, 1550, 1500, 1467 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.42 (dd, 1 H, *J* = 2.4, 0.6 Hz), 8.11 (dd, 1 H, *J* = 8.7, 2.4 Hz), 7.86 (d, 2 H, *J* = 9.0 Hz), 7.46 (d, 1 H, *J* = 7.8 Hz), 7.40 (d, 2 H, *J* = 9.0 Hz), 7.19 (dd, 1 H, *J* = 8.4 , 0.6 Hz), 7.12 (d, 1 H, *J* = 1.2 Hz), 6.94 (dd, 1 H, *J* = 8.1, 1.5 Hz); ^{13}C NMR (DMSO-d_6) δ 161.3, 157.2, 150.2, 150.0, 143.1, 134.3, 132.8, 122.0, 118.9, 118.5, 116.4, 115.4, 112.2, 111.8, 109.5, 107.3, 93.2, 87.8; MS (EI) *m/z* (rel intensity) 336 (80), 262 (100), 234 (30), 219 (90), 205 (40); HRMS (EI) *m/z* calcd for $C_{21}H_{12}N_4O$ 336.1011, found 336.1008.



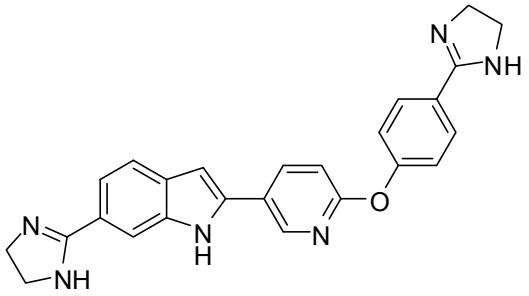
2-(6-(4-Cyanophenoxy)pyridin-3-yl)-1H-indole-6-carbonitrile (2-23). A solution of **2-22** (185 mg, 0.550 mmol) in MeCN (21.5 mL) and DMF (0.715 mL) was treated with $PdCl_2$ (103 mg, 0.578 mmol). The reaction mixture was stirred at room temperature for 24 h and filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with THF (3x). The organic

phases were combined and concentrated under reduced pressure. Purification by chromatography on SiO_2 (toluene:THF = 10:1) yielded 58.3 mg (32%) of **2-23** as a yellow solid: mp 256.0 ºC (decomp., THF); IR (KBr) 3140, 3051, 1671, 1599, 1539, 1454, 1406 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.80 (s, 1 H), 9.51 (s, 2 H), 9.37 (s, 2 H), 9.32 (s, 2 H), 9.14 (s, 2 H), 8.88 (d, 1 H, *J* = 1.8 Hz), 7.98 (s, 1 H), 7.95 (d, 2 H, *J* = 8.7 Hz), 7.71 (d, 1 H, *J* = 8.4 Hz), 7.58 (s, 1 H), 7.45 (d, 1 H, *J* = 9.9 Hz), 7.41 (d, 2 H, *J* = 8.4 Hz), 7.30 (d, 1 H, *J* = 8.7 Hz), 7.24 (s, 2 H), 7.11 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 167.0, 165.5, 163.4, 162.2, 158.6, 145.3, 139.0, 138.1, 136.6, 132.9, 130.6, 124.3, 121.7, 120.7, 120.6, 119.3, 112.8, 112.6, 100.0; HRMS (ESI) *m/z* calcd for $C_{21}H_{13}N_4O$ (M+H) 337.1089, found 337.1058.

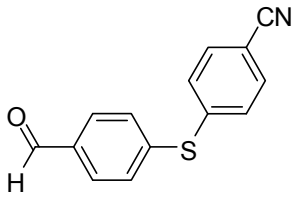


2-(6-(4-Carbamimidoylphenoxy)pyridin-3-yl)-1H-indole-6-carboximidamide diformate (2-24). A solution of **2-23** (30.0 mg, 0.0892 mmol) in EtOH:$CHCl_3$ = 1:1 (v/v, 10 mL) at 0 °C was bubbled with HCl gas for 30 min and then stirred at room temperature for 24 h. The reaction mixture was bubbled with HCl gas again and stirred for another 24 h at room temperature. The solvent was evaporated and EtOH (6.0 mL) was added. The solution was bubbled with NH_3 gas at room temperature for 10 min. After 24 h stirring at room temperature, the reaction mixture was bubbled with NH_3 gas again and stirred for another 24 h. The solvent was evaporated and the residue was co-evaporated with EtOH (x2). The residue was redissolved in EtOH (1 mL) and filtered. The filtrate was treated with formic acid (final concentration of HCOOH ~ 50% v/v) and stirred for 30 min at room temperature. Ether (10 mL) was added and

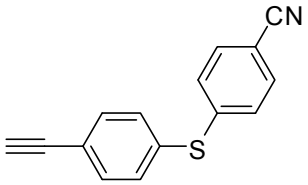
the precipitate was collected by filtration to yield 30.5 mg (74%) of **2-24** as a yellow solid: mp 232.6 °C (DMSO, dec.); IR (KBr) 3368, 3136, 1674, 1627, 1599, 1481, 1451, 1401 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.47 (s, 2 H), 9.30 (s, 1 H), 9.26 (s, 1 H), 8.45 (d, 2 H, *J* = 8.3 Hz), 7.97 (d, 1 H, *J* = 8.4 Hz), 7.83-7.70 (m, 1 H), 7.57 (app s, 2 H), 7.40 (app s, 2 H); 7.34-7.24 (m, 2 H), 7.23 (app s, 2 H); ^{13}C NMR (DMSO-d_6) δ 166.1, 164.8, 163.0, 160.7, 167.5, 164.4, 143.2, 130.8, 129.9, 129.6, 122.9, 122.4, 121.6, 119.9, 119.2, 118.6, 118.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{19}N_6O$ (M+H) 371.1621, found 371.1614.



6-(4,5-Dihydro-1H-imidazol-2-yl)-2-(6-(4-(4,5-dihydro-1H-imidazol-2-yl)phenoxy)-pyridin-3-yl)-1H-indole (2-25). A mixture of sulfur (0.723 mg, 0.0226 mmol) and **2-23** (15.2 mg, 0.0452 mmol) was treated with ethylene diamine (0.5 mL), then heated in the microwave at 110° C for 30 min. The reaction mixture was suspended in water and filtered, and the solid was rinsed with water (3x), and dried under vacuum, affording **2-25** (12.4 mg, 65%) as a yellow solid: mp 188.2 °C (ethylene diamine/H_2O, dec.); IR (KBr) 3420, 2928, 2868, 1603, 1570, 1513, 1457 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.86 (s, 1 H), 8.71 (d, 1 H, *J* = 2.0 Hz), 8.35 (dd, 1 H, *J* = 8.5, 2.2 Hz), 7.90-7.83 (m, 3 H), 7.54 (app s, 2 H), 7.24-7.17 (m, 3 H), 3.64 (s, 4 H), 3.61 (s, 4 H); ^{13}C NMR (DMSO-d_6) δ 164.7, 163.0, 162.0, 155.5, 144.3, 137.0, 136.6, 136.5, 130.2, 128.6, 126.9, 123.9, 123.4, 120.5, 119.5, 119.1, 112.0, 110.5, 99.3; MS (EI) *m/z* (rel intensity) 422 (100), 393 (30), 182 (30); HRMS (EI) *m/z* calcd for $C_{25}H_{22}N_6O$ 422.1855, found 422.1842.

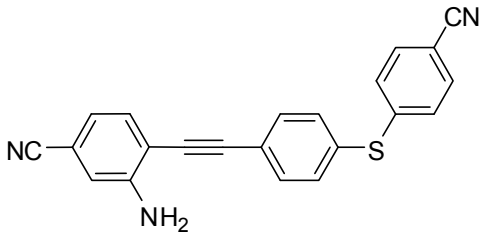


4-(4-Formylphenylthio)benzonitrile (2-30). A solution of 4-fluorobezaldehyde (1.61 mL, 15.0 mmol) and 4-mercaptobenzonitrile[120] (2.03 g, 15.0 mmol) in DMF (90 mL) was treated with potassium carbonate (2.28 g, 16.5 mmol) and heated to 120 °C for 14 h. The reaction mixture was poured into water and extracted with EtOAc (3x). The combined organic layers were washed with 5% aqueous K_2CO_3 (2x), water (3x) and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (hexanes: EtOAc = 8:1) afforded 2.93 g (77%) of **2-30** as a white solid: mp 111.7-112.5 °C (Hexanes-EtOAc); IR (neat) 3427, 3078, 2835, 2744, 2231, 2225, 1701, 1690, 1671, 1586, 1561, 1483 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.0 (s, 1 H), 7.86 (d, 2 H, *J* = 8.4 Hz), 7.61 (d, 2 H, *J* = 8.4 Hz), 7.50 (d, 2 H, *J* = 8.1 Hz), 7.42 (d, 2 H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 191.1, 141.7, 141.5, 135.6, 133.0, 131.4, 130.9, 130.7, 118.4, 111.1; MS (EI) *m/z* (rel intensity) 239 (50), 209 (15), 127 (10), 84 (100); HRMS *m/z* calcd for $C_{14}H_9NOS$ 239.0405, found 239.0393.



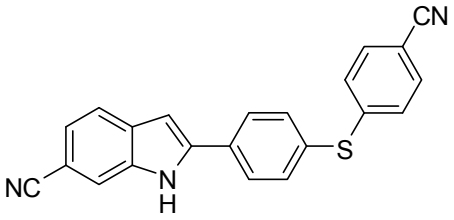
4-(4-Ethynylphenylthio)benzonitrile. A solution of lithium diisopropylamide (2.0 M in heptane, diethylbenzene and THF, 0.187 mL, 0.374 mmol) in THF (2.50 mL) at -78 °C was treated with $TMSCHN_2$ (2.0 M in ether, 0.187 mL, 0.374 mmol). The reaction mixture was stirred at -78 °C for 30 min and a solution of **2-30** (0.0747 g, 0.312 mmol) in THF 0.63 mL was added. The reaction mixture was stirred at -78 ºC for 1 h and heated at reflux for 2 h, quenched

with cold water and extracted with Et_2O (3x). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:Et_2O = 10:1) afforded 0.0397 g (54%) of the title compound as a white solid: mp 76.4-78.2 ºC (DCM); IR (neat) 3286, 2226, 1590, 1482 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52 (d, 4 H, *J* = 8.4 Hz), 7.42 (d, 2 H, *J* = 8.4 Hz), 7.23 (d, 2 H, *J* = 8.7 Hz), 3.19 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 144.4, 133.6, 133.5, 132.8, 132.7, 128.5, 123.1, 118.7, 109.7, 82.8, 79.4; MS (EI) *m/z* (rel intensity) 235 (100), 190 (10); HRMS (EI) *m/z* calcd for $C_{15}H_9NS$ 235.0456, found 235.0455.

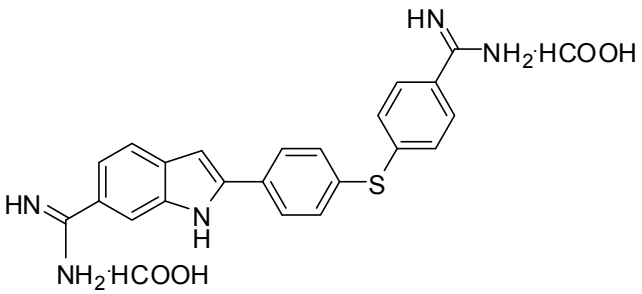


3-Amino-4-((4-(4-cyanophenylthio)phenyl)ethynyl)benzonitrile (2-31). A solution of 4-(4-ethynylphenylthio)benzonitrile (39.7 mg, 0.169 mmol) and 3-amino-4-iodobenzonitrile (41.1 mg, 0.169 mmol) in MeCN (1.23 mL) was degassed and treated with $PdCl_2(PPh_3)_2$ (5.94 mg, 0.00845 mmol) and CuI (3.55 mg, 0.0186 mmol). The reaction mixture was degassed again and treated with Et_3N (118 μL, 0.845 mmol). The reaction mixture was stirred at room temperature for 48 h, diluted with THF and filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with THF (3x) and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (first with Hexanes:THF = 4:1 to 1:1, then repurified with tolene:Et_2O = 20:1) yielded 65.5 mg (73%) of **2-31** as a yellow solid: mp 198.0-200.2 ºC (THF); IR (neat) 3468, 3369, 2221, 1621, 1586, 1506, 1481 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.76 (d, 2 H, *J* = 8.1 Hz), 7.74 (d, 2 H, *J* = 6.9 Hz), 7.53 (d, 2 H, *J* = 8.4 Hz), 7.39 (d, 1 H, *J* = 7.8 Hz), 7.32 (d, 2 H, *J* = 8.4 Hz), 7.06 (s, 1 H), 6.89 (d, 1 H, *J* = 7.8 Hz), 6.09 (br s, 2 H); ^{13}C NMR (DMSO-d_6) δ 150.0, 143.4, 133.2, 133.0, 132.9, 131.8, 128.3, 122.9, 118.9, 118.5, 118.3, 116.4,

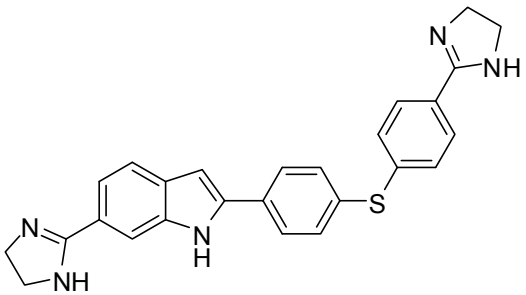
111.8, 109.6, 108.7, 96.1, 87.1; MS (EI) *m/z* (rel intensity) 351 (100), 235 (35), 117 (70); HRMS (EI) *m/z* calcd for $C_{22}H_{13}N_3S$ 351.0830, found 351.0840.



2-(4-(4-Cyanophenylthio)phenyl)-1H-indole-6-carbonitrile (2-32). A solution of **2-31** (43.3 mg, 0.123 mmol) in DCM (2.75 mL) was treated with $AuClPPh_3$ (3.04 mg, 0.00670 mmol) followed by $AgClO_4$ (3.04 mg, 0.0149 mmol) at room temperature. The reaction mixture was stirred in the dark at room temperature for 14 h and filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with THF (3x). The organic phases were combined and concentrated under reduced pressure. Purification by chromatography on SiO_2 (toluene:Et_2O = 10:1) yielded 32.0 mg (74%) of **2-32** as a yellow solid: mp 270 ºC (decomp.) (DMSO); IR (neat) 3315, 3052, 2238, 1619, 1598, 1589, 1498, 1482 cm^{-1}; ^1H NMR (acetone-d_6) δ 12.25 (s, 1 H), 7.85 (s, 1 H), 7.75 (d, 2 H, *J* = 8.4 Hz), 7.71 (d, 1 H, *J* = 8.4 Hz), 7.64 (d, 2 H, *J* = 8.4 Hz), 7.40-7.28 (m, 3 H), 7.15 (d, 1 H, *J* = 0.9 Hz); ^{13}C NMR (acetone-d_6) δ 144.6, 141.0, 136.5, 134.8, 133.4, 132.4, 130.9, 128.2, 127.4, 122.7, 121.7, 120.9, 119.0, 116.5, 108.7, 103.5, 101.0; MS (EI) *m/z* (rel intensity) 91 (100), 172 (40), 351 (30); HRMS (EI) *m/z* calcd for $C_{22}H_{13}N_3S$ 351.0830, found 351.0839.

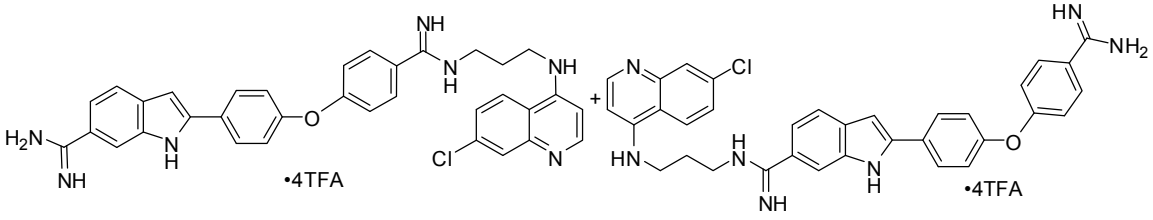


2-(4-(4-Carbamimidoylphenylthio)phenyl)-1H-indole-6-carboximidamide dihydrochloride (2-33). A solution of **2-32** (45.0 mg, 0.128 mmol) in EtOH:$CHCl_3$ = 1:1 (v/v, 10 mL) at 0 ^oC was bubbled with HCl gas for 30 min. The reaction mixture was stirred at room temperature for 24 h and the solvent was removed. The residue was redissolved in EtOH (6.0 mL) and bubbled with NH_3 gas for 20 min at room temperature. The reaction mixture was stirred for 24 h, re-bubbled with NH_3 gas and stirred for another 24 h. The solvent was evaporated and the residue was co-evaporated with EtOH (x2). The residue was redissolved in EtOH (2.0 mL) and filtered through a pad of SiO_2. The filtrate was poured into Et_2O (10 mL) and bubbled with HCl for 1 min. After 30 min stirring, the precipitate was decanted, washed with Et_2O (2x) and dried under vacuum to afford 42.0 mg (72%) of **2-33** as a brown solid: mp 246 ºC (decomp.) (EtOH-Et_2O); IR (neat) 3367, 3150, 1669, 1622, 1595, 1539, 1473, 1457 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.69 (s, 1 H), 9.49 (s, 2 H), 9.37 (s, 2 H), 9.30 (s, 2 H), 9.15 (s, 2 H), 8.12 (d, 1 H, *J* = 8.4 Hz), 7.99 (s, 1 H), 7.83 (d, 2 H, *J* = 8.4 Hz), 7.73 (d, 1 H, *J* = 8.1 Hz), 7.60 (d, 2 H, *J* = 8.4 Hz), 7.46 (d, 1 H, *J* = 8.4), 7.39 (d, 2 H, *J* = 8.7 Hz), 7.15 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 167.1, 165.4, 144.6, 141.3, 136.8, 134.3, 133.0, 132.4, 131.6, 129.6, 128.3, 127.6, 125.9, 121.0, 120.0, 120.9, 112.7, 100.6, HRMS (ESI) *m/z* calcd for $C_{22}H_{20}N_5S$ (M+H) 386.1439, found 386.1432.



6-(4,5-Dihydro-1H-imidazol-2-yl)-2-(4-(4-(4,5-dihydro-1H-imidazol-2-yl)phenylthio) phenyl)-1H-indole (2-34). A mixture of sulfur (1.46 mg, 0.0456 mmol) and **2-32** (32.0 mg,

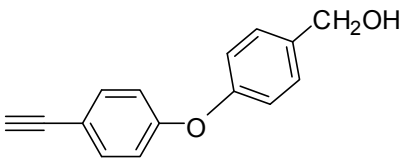
0.0911 mmol) was treated with ethylene diamine (1.0 mL), then heated in the microwave at 110 °C twice for 30 min. The reaction mixture was suspended in water and filtered, and the solid was rinsed with water (3x), and dried under vacuum, affording (22.3 mg, 56%) of **2-34** as a yellow solid: mp 154 ºC (decomp.) (Etylene diamine-H_2O); IR (neat) 3407, 2934, 2866, 1606, 1502, 1480 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.86 (s, 1 H), 7.92 (d, 2 H, *J* = 8.4 Hz), 7.88 (s, 1 H), 7.79 (d, 2 H, *J* = 8.4 Hz), 7.53 (s, 2 H), 7.48 (d, 2 H, *J* = 8.4 Hz), 7.33 (d, 2 H, *J* = 8.4 Hz), 6.98 (s, 1 H), 3.62 (s, 4 H), 3.58 (s, 4 H); ^{13}C NMR (DMSO-d_6) δ 164.7, 163.0, 138.7, 137.9, 136.7, 132.7, 132.2, 131.5, 130.1, 129.24, 129.15, 128.1, 126.3, 123.9, 119.6, 119.0, 110.5, 99.6, 49.4; HRMS (ESI) *m/z* calcd for $C_{26}H_{24}N_5S$ (M+H) 438.1752, found 438.1737.



Quinoline indoles 2-35 and 2-36 (inseparable mixture, trifluoroacetate salts). A suspension of 2-(4-(4-cyanophenoxy)phenyl)-1H-indole-6-carbonitrile[121] (100 mg, 0.298 mmol) in EtOH/$CHCl_3$ (1:1, 20 mL) at 0 °C was bubbled with HCl gas for 30 min. The reaction mixture was stirred at room temperature for 12 h and the solvent was evaporated. The residue was co-evaporated with EtOH twice to remove the remaining HCl and provide the crude iminoester intermediate.

A solution of the crude residue (0.0298 mmol) and N1-(7-chloroquinolin-4-yl)propane-1,3-diamine[122] (7.04 mg, 0.0298 mmol) in EtOH (1.0 mL) was treated with PhSH (0.306 µL, 0.00298 mmol) and heated in the microwave at 150 °C for 30 min. The solvent was evaporated under reduced pressure and the residue was purified by reverse-phase HPLC (MeOH-0.1% aq. TFA) to yield 5.8 mg (33%) of **2-35** and **2-36** as an inseparable, sticky yellow solid (ca. 4:1

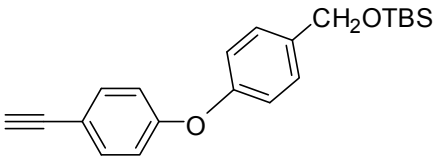
mixture of regioisomers): IR (neat) 3392, 1662, 1596, 1445, 1241, 1195, 1129 cm^{-1}; ^1H NMR of both isomers (CD_3OD) δ 8.43 (d, 1 H, *J* = 7.2 Hz), 8.41 (d, 1 H, *J* = 9.0 Hz), 7.95 (d, 2 H, *J* = 8.7 Hz), 7.93 (s, 1 H), 7.90-7.81 (m, 2 H), 7.79-7.72 (m, 2.3 H), 7.72-7.62 (m, 1 H), 7.45 (dd, 0.91 H, *J* = 8.4, 1.8 Hz), 7.36 (dd, 0.24 H, *J* = 8.4, 1.8 Hz), 7.25-7.16 (m, 4 H), 6.98-6.92 (m, 2 H), 3.82-3.73 (m, 2 H), 3.70-3.57 (m, 2 H), 2.32-2.21 (m, 2 H); ^{13}C NMR of major isomer (125 MHz, DMSO-d_6) δ 169.4, 165.6, 163.6, 163.2, 163.0, 157.9, 157.1, 144.2, 143.5, 141.3, 140.2, 138.2, 135.4, 131.6, 131.5, 130.1, 129.0, 126.2, 124.8, 122.1, 121.9, 121.7, 120.5, 119.8, 119.4, 117.2, 112.9, 100.7, 100.0, 42.5, 42.0, 27.3; HRMS (ESI) *m/z* calcd for $C_{34}H_{31}N_7OCl$ (M+H) 588.2279, found 588.2299; the content of TFA in the product was determined by adding a known amount of trifluoroethanol as an internal standard and comparing the integration of the trifluoroacetate and trifluoroethanol in the ^{19}F NMR.



(4-(4-Ethynylphenoxy)phenyl)methanol.[*] A solution of **2-39** (0.219 g, 1.00 mmol) in DCM (2.3 mL) and toluene (1.6 mL) at -78 °C was treated with DIBAL (1.0 M in hexanes, 1.00 mL, 1.00 mmol). The reaction mixture was stirred at -78 °C for 3 h, quenched with a saturated aqueous solution of NH_4Cl, warmed to room temperature and extracted with EtOAc (1x). The organic layer was washed with 0.3 M HCl (1x), water (2x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the crude aldehyde. A solution this crude aldehyde in MeOH (9.6 mL) was treated with $NaBH_4$ (23.6 mg, 0.62 mmol) at room temperature. The reaction mixture was stirred at room temperature for 30 min and quenched with

[*] (CWD095: procedure, melting point, IR, HRMS and carbon NMR; CWD079: proton NMR)

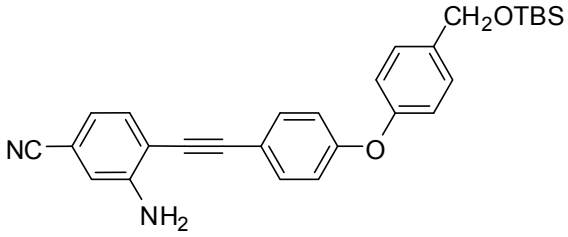
0.3 M HCl. The mixture was extracted with EtOAc (3x), washed with water (1x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:1) afforded 0.111 g (50%) of the title compound as a white solid: mp 93.0-94.3 ºC (DCM); IR (neat) 3395, 3304, 3284, 2949, 2886, 1904, 1609, 1599, 1502, 1420, 1412 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46 (d, 2 H, *J* = 8.4 Hz), 7.37 (d, 2 H, *J* = 8.4 Hz), 7.03 (d, 2 H, *J* = 8.4 Hz), 6.93 (d, 2 H, *J* = 8.7 Hz), 4.68 (s, 2 H), 2.98 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 158.1, 155.8, 136.6, 133.9, 128.9, 119.7, 118.3, 116.7, 83.4, 76.8, 64.7; MS (EI) *m/z* (rel intensity) 224 (100), 207 (10), 165 (10), 118 (20), 89 (20); HRMS (EI) *m/z* calcd for $C_{15}H_{12}O_2$ 224.0837, found 224.0838.



***tert*-Butyl(4-(4-ethynylphenoxy)benzyloxy)dimethylsilane (2-40).**[*] A solution of (4-(4-ethynylphenoxy)phenyl)methanol (0.111 g, 0.496 mmol), imidazole (0.169 g, 2.48 mmol) and TBSCl (0.180 g, 1.19 mmol) in DMF (0.67 mL) at room temperature was stirred for 16 h and quenched with water. The mixture was extracted with EtOAc (3x). The combined organic layers were washed with water (2x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:Et_2O = 20:1) afforded 0.165 g (98%) of **2-40** as a clear oil: IR (neat) 3292, 3039, 2929, 2953, 2885, 2856, 2108, 1598, 1497, 1468, 1412 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (d, 2 H, *J* = 9.0 Hz), 7.36 (d, 2 H, *J* = 8.1 Hz), 7.04 (d, 2 H, *J* = 8.4 Hz), 6.95 (d, 2 H, *J* = 8.7 Hz), 4.77 (s, 2 H), 3.06 (s, 1 H), 1.00 (s, 9 H), 0.16 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 158.5, 155.2, 137.4, 133.9, 127.9, 119.7, 118.2, 116.6, 83.5, 76.7, 64.7,

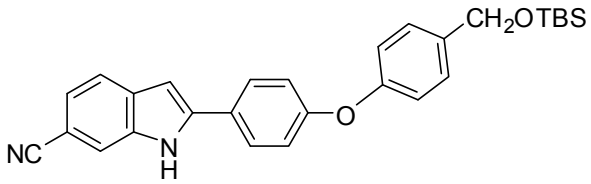
[*] (CWD096: procedure, IR, HRMS, proton and carbon NMR)

26.2, 19.0, -5.0; MS (EI) *m/z* (rel intensity) 338 (80), 221 (10), 323 (20), 295 (20), 281 (90), 207 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{26}O_2Si$ 338.1702, found 338.1703.



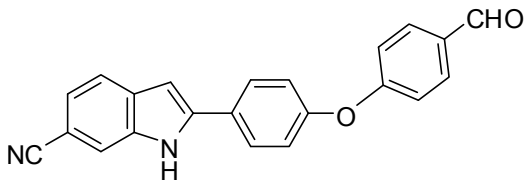
3-Amino-4-((4-(4-((*tert*-butyldimethylsilyloxy)methyl)phenoxy)phenyl)ethynyl)-benzonitrile.[*] A solution of **2-40** (0.165 g, 0.487 mmol) and 3-amino-4-iodobenzonitrile (0.119 g, 0.487 mmol) in MeCN (3.5 mL) was degassed and treated with $PdCl_2(PPh_3)_2$ (17.1 mg, 0.0244 mmol) and CuI (10.2 mg, 0.0536 mmol). The reaction mixture was degassed again and treated with Et_3N (0.339 mL, 2.44 mmol). The reaction mixture was stirred at room temperature for 14 h and at 80 °C for 3 h, diluted with THF and filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with THF (3x) and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (first with Hexanes:THF = 8:1 to 4:1, then re-chromatographed with Hexanes:THF = 4:1) yielded 0.218 g (99%) of the title compound (contaminated with BHT from THF) as a yellow solid: mp 162.1-166.7 ºC (THF); IR (neat) 3383, 2952, 2928, 2885, 2855, 2230, 1596, 1557, 1497 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50 (d, 2 H, *J* = 8.4 Hz), 7.44-7.33 (m, 3 H), 7.07-6.96 (m, 6 H), 4.76 (s, 2 H), 4.50 (s, 2 H), 0.98 (s, 9 H), 0.14 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 158.8, 155.0, 147.9, 137.6, 133.4, 132.7, 127.9, 121.2, 119.8, 119.1, 118.3, 117.0, 116.6, 112.8, 112.4, 98.1, 83.8, 64.7, 30.5, 26.1, 18.2, -5.0; MS (EI) *m/z* (rel intensity) 454 (80), 411 (30), 337 (20), 323 (100), 117 (55); HRMS (EI) *m/z* calcd for $C_{28}H_{30}N_2O_2Si$ 454.2077, found 454.2074.

[*] (CWD098: procedure, melting point, HRMS, IR; CWD084: proton and carbon NMR)



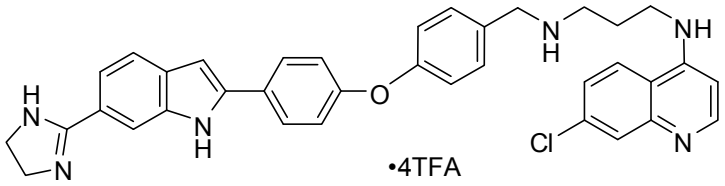
2-(4-(4-((*tert*-Butyldimethylsilyloxy)methyl)phenoxy)phenyl)-1H-indole-6-carbonitrile.[*] A solution of 3-amino-4-((4-(4-((*tert*-butyldimethylsilyloxy)methyl)-phenoxy)-phenyl)-ethynyl)-benzonitrile (0.218 g, 0.480 mmol) in DCM (11 mL) was treated with $AuClPPh_3$ (11.8 mg, 0.0240 mmol) followed by $AgClO_4$ (11.0 mg, 0.0528 mmol) at room temperature. The reaction mixture was stirred in the dark at room temperature for 16 h and filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with THF (3x). The organic phases were combined and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:THF = 8:1) yielded 0.137 g (63%) of the title compound (contaminated with BHT from THF) as a yellow solid: mp 153.4-155.8 ºC (THF); IR (neat) 3366, 2951, 2926, 2881, 2853, 2212, 1604, 1492 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.94 (s, 1 H), 7.74 (s, 1 H), 7.70-7.62 (m, 3 H), 7.36 (app d, 3 H, *J* = 8.7 Hz), 7.13-7.04 (m, 4 H), 6.82 (d, 1 H, *J* = 1.2 Hz), 4.77 (s, 2 H), 0.98 (s, 9 H), 0.15 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 158.6, 155.4, 141.8, 137.4, 135.7, 132.9, 128.0, 127.3, 126.1, 123.5, 121.2, 121.1, 119.6, 119.0, 115.7, 104.0, 100.0, 64.8, 30.5, 26.2, -5.0; MS (EI) *m/z* (rel intensity) 454 (20), 323 (100), 75 (80); HRMS (EI) *m/z* calcd for $C_{28}H_{30}N_2O_2Si$ 454.2077, found 404.2065.

[*] (CWD099: procedure, melting point, HRMS and IR; CWD086: proton and carbon NMR)



2-(4-(4-Formylphenoxy)phenyl)-1H-indole-6-carbonitrile (2-41).[*] A solution of 2-(4-(4-((*tert*-butyldimethylsilyloxy)methyl)phenoxy)phenyl)-1H-indole-6-carbonitrile (0.137 g, 0.301 mmol) in THF (3.2 mL) was treated with TBAF (1 M in THF, 0.602 mL, 0.602 mmol) at room temperature. The reaction mixture was stirred for 2 h and filtered through a pad of SiO_2. The pad was washed with THF (3x). The organic phases were combined and concentrated under reduced pressure. Purification by chromatography on SiO_2 (toluene:THF = 3:1) yielded 0.119 g of the alcohol. A solution of this alcohol in DCM (7.3 mL) and DMSO (2.5 mL) was treated with Dess-Martin periodinane (0.148 g, 0.350 mmol) at room temperature. The reaction mixture was stirred for 1 h and quenched with a mixture of 5% aqueous $Na_2S_2O_3$ and saturated $NaHCO_3$. The mixture was extracted with DCM (1x). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by chromatography on SiO_2 (toluene:Et_2O = 4:1) afforded 60.9 mg (37% over four steps) of **2-41** as a yellow solid: mp 202.6-203.6 ºC (THF); IR (neat) 3324, 2218, 1688, 1592, 1579, 1540, 1490 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.17 (s, 1 H), 9.93 (s, 1 H), 8.00 (d, 2 H, *J* = 8.7 Hz), 7.94 (d, 2 H, *J* = 8.7 Hz), 7.83 (s, 1 H), 7.69 (d, 1 H, *J* = 8.4 Hz), 7.33 (d, 1 H, *J* = 8.1, 1.2 Hz), 7.28 (d, 2 H, *J* = 8.7 Hz), 7.20 (d, 2 H, *J* = 8.4 Hz), 7.05 (d, 2 H, *J* = 0.9 Hz), 4.77 (s, 2 H), 0.98 (s, 9 H), 0.15 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ 191.6, 162.0, 155.0, 141.2, 135.9, 132.1, 131.9, 131.6, 127.8, 127.7, 122.3, 121.0, 120.68, 120.66, 118.0, 115.9, 102.6, 99.5; MS (EI) *m/z* (rel intensity) 338 (10), 257 (20), 236 (20), 165 (20), 111 (40), 97 (75), 83 (100); HRMS (EI) *m/z* calcd for $C_{22}H_{14}N_2O_2$ 338.1055, found 338.1065.

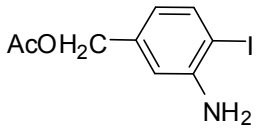
[*] (CWD101: procedure, melting point, HRMS, IR, proton and carbon NMR)



N1-(7-chloroquinolin-4-yl)-N3-(4-(4-(6-(4,5-dihydro-1H-imidazol-2-yl)-1H-indol-2-yl)phenoxy)benzyl)propane-1,3-diamine (2-42, trifluoroacetate salt).[*] A solution of **2-41** (19.0 mg, 0.0562 mmol) and N1-(7-chloroquinolin-4-yl)propane-1,3-diamine[122] (26.5 mg, 0.112 mmol) in MeOH (2.0 mL) was treated with $NaBH_3CN$ (7.1 mg, 0.112 mmol) at room temperature. The reaction mixture was stirred for 14 h and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with DCM (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by chromatography on SiO_2 (toluene:Et_2O = 1:1 with 0.2% Et_3N) afforded the crude amine (43.3 mg). A mixture of sulfur (0.9 mg, 0.028 mmol) and the crude amine (21.6 mg) was treated with ethylene diamine (0.5 mL), then heated in the microwave at 130 °C for 30 min. Additional sulfur (0.9 mg, 0.028 mmol) was added. The reaction mixture was heated in the microwave at 130 °C for 30 min, suspended in water and filtered, and the solid was rinsed with water (3x), and purified by reverse-phase HPLC (MeOH-0.1% aq. TFA) to yield 5.4 mg (32%) of **2-42** as a sticky yellow solid: IR (neat) 3416, 1668, 1485, 1456 cm^{-1}; ^1H NMR (CD_3OD) δ 8.47-8.35 (m, 2 H), 7.99-7.84 (m, 4 H), 7.76-7.67 (m, 2 H), 7.54-7.45 (m, 3 H), 7.16-7.06 (m, 4 H), 6.95 (s, 1 H), 6.92 (d, 1 H, J = 7.2 Hz), 4.23 (s, 2 H), 4.09 (s, 4 H), 3.72 (t, 2 H, J = 6.9 Hz), 3.34-3.19 (m, 2 H), 2.99 (s, 1 H), 2.85 (s, 1 H), 2.29-2.12 (m, 3 H); ^{13}C NMR (150 MHz, CD_3OD) δ 168.9, 164.9, 163.1, 162.9, 162.7, 162.4, 159.5, 158.5, 157.8, 144.3, 144.1, 141.2, 140.1, 138.0, 135.7, 135.6, 133.0, 128.9, 128.7, 127.5, 126.0, 122.0, 121.9, 120.6, 120.41, 120.37, 119.9, 117.1, 115.3, 113.1, 100.5, 99.8, 51.9, 45.9,

[*] (CWF070 and CWF065: procedure, proton and carbon NMR, HRMS, IR)

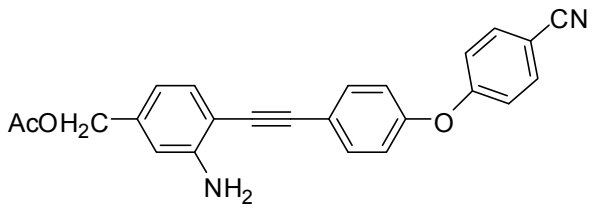
45.7, 41.8, 36.9, 31.6, 25.9; HRMS (ESI) *m/z* calcd for $C_{36}H_{34}N_6OCl$ (M+H) 601.2483, found 601.2457; the content of TFA in the product was determined by adding a known amount of trifluoroethanol as an internal standard and comparing the integration of the trifluoroacetate and trifluoroethanol in the ^{19}F NMR.



3-Amino-4-iodobenzyl acetate.[*] A solution of (4-iodo-3-nitrophenyl)methanol[123] (0.623 g, 2.50 mmol) in pyridine (20 mL) was treated with Ac_2O (1.18 mL, 12.5 mmol) at room temperature. The reaction mixture was stirred for 12 h and concentrated under reduced pressure. The residue was partitioned between EtOAc and saturated aqueous $CuSO_4$. The organic layer was washed with saturated aqueous $CuSO_4$ (2x), water (2x), brine (1x), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 6:1) yielded 0.730 g of the acetate as a yellow solid. A solution of this acetate (0.555 g, 1.73 mmol) in AcOH (3.5 mL), EtOH (3.5 mL) and conc. aqueous HCl (0.052 mL) was treated with iron powder (0.380 g, 6.79 mmol) at room temperature. The reaction mixture was heated at reflux for 4 h, quenched with a mixture of water and Na_2CO_3 and extracted with EtOAc (4x). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 6:1) afforded 0.382 g (69% over two steps) of the title compound as a white solid: mp 526.-54.4 ºC (DCM); IR (neat) 3455, 3363, 1731, 1613, 1481, 1425 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (d, 1 H, *J* = 8.1 Hz), 6.72 (app s, 1 H), 6.46 (dd, 1 H, *J* = 8.1, 1.5 Hz), 4.97 (s, 2 H), 4.17 (br s, 2 H),

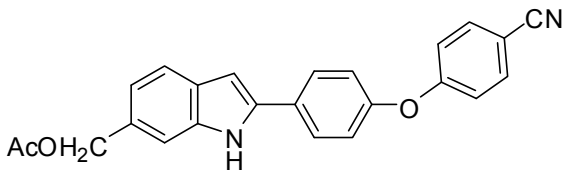
[*] . (CWD171: procedure, melting point, HRMS, IR, proton NMR, CWD162: carbon NMR)

2.10 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.0, 147.1, 139.3, 137.6, 119.7, 114.3, 83.7, 65.8, 21.2; MS (EI) *m/z* (rel intensity) 291 (80), 249 (100), 232 (30), 104 (50); HRMS (EI) *m/z* calcd for $C_9H_{10}NO_2I$ 290.9756, found 290.9767.

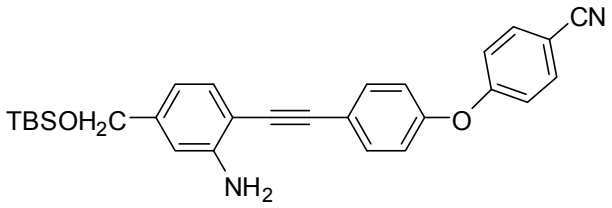


3-Amino-4-((4-(4-cyanophenoxy)phenyl)ethynyl)benzyl acetate. * A solution of 3-amino-4-iodobenzyl acetate (0.382 g, 1.31 mmol) and **2-12** (0.288 g, 1.31 mmol) in MeCN (9.5 mL) was degassed and treated with $PdCl_2(PPh_3)_2$ (46.0 mg, 0.0655 mmol) and CuI (27.5 mg, 0.144 mmol). The reaction mixture was degassed again, treated with Et_3N (0.911 mL, 6.55 mmol), heated at reflux for 1.5 h, diluted with THF and filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with THF (3x) and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 4:1 to 2:1) yielded 0.429 g (86%) of the title compound as a sticky yellow solid: IR (neat) 3460, 3363, 2225, 1731, 1619, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.64 (d, 2 H, *J* = 9.0 Hz), 7.57 (d, 2 H, *J* = 8.7 Hz), 7.36 (d, 1 H, *J* = 7.8 Hz), 7.05 (app d, 4 H, *J* = 8.1 Hz), 6.76-6.68 (m, 2 H), 5.04 (s, 2 H), 4.32 (s, 2 H), 2.13 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.9, 161.1, 155.1, 148.1, 138.0, 134.4, 133.6, 132.5, 120.3, 120.1, 118.8, 118.6, 117.7, 113.9, 107.6, 106.6, 94.1, 86.1, 66.1, 21.1; MS (EI) *m/z* (rel intensity) 382 (100), 323 (90), 193 (25).

* (CWD172: procedure, melting point, MS, proton NMR; CWD162: carbon NMR)



(2-(4-(4-cyanophenoxy)phenyl)-1H-indol-6-yl)methyl acetate (2-43). [*]A solution of 3-amino-4-((4-(4-cyanophenoxy)phenyl)ethynyl)benzyl acetate (0.429 g, 1.12 mmol) in DMF (13 mL) was treated with $PdCl_2(PhCN)_2$ (87.6 mg, 0.224 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 0.5 h, quenched with water, extracted with EtOAc (3x). The organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:1 to 2:1) yielded 0.235 g (55%) of **2-43** as a yellow solid: mp 153.9-159.0 ºC (DCM); IR (neat) 3384, 2970, 2223, 1720, 1690, 1587, 1567, 1496, 1449 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.14 (s, 1 H), 7.72 (d, 2 H, *J* = 8.4 Hz), 7.67-7.57 (m, 3 H), 7.43 (app s, 1 H), 7.20-7.00 (m, 1 H), 7.12 (d, 2 H, *J* = 9.0 Hz), 7.05 (d, 2 H, *J* = 8.7 Hz), 6.81 (d, 1 H, *J* = 0.9 Hz), 5.25 (s, 2 H), 2.11 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.5, 161.4, 154.4, 137.9, 137.0, 134.3, 129.8, 129.4, 129.3, 127.0, 121.1, 120.8, 120.7, 118.9, 118.1, 111.7, 106.0, 99.7, 67.4, 21.2; MS (EI) *m/z* (rel intensity) 382 (50%), 323 (100), 193 (25), 102 (20); HRMS (EI) *m/z* calcd for $C_{24}H_{18}N_2O_3$ 382.1317, found 382.1329.

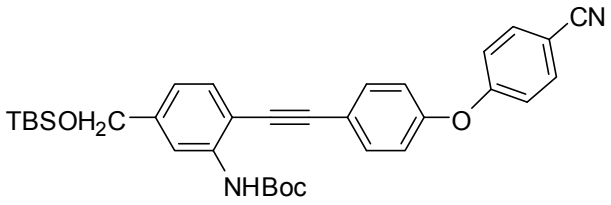


4-(4-((2-Amino-4-((*tert*-butyldimethylsilyloxy)methyl)phenyl)ethynyl)phenoxy)-benzonitrile. [†] A solution of **2-12** (3.38 g, 15.4 mmol) and 5-((*tert*-butyldimethylsilyloxy)-

[*] (CWD172 and CWD174: procedure, melting point, HRMS, proton and carbon NMR)

[†] (CWD263: procedure, proton NMR; CWD209: melting point, HRMS, IR; CWD124 carbon NMR)

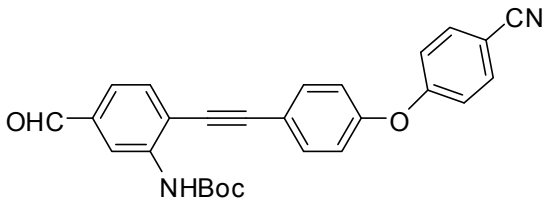
methyl)-2-iodoaniline[123] (5.60 g, 16.5 mmol) in MeCN (112 mL) was degassed and treated with $PdCl_2(PPh_3)_2$ (0.541 g, 0.770 mmol) and CuI (0.323 g, 1.69 mmol). The reaction mixture was degassed again, treated with Et_3N (10.7 mL, 77.0 mmol), heated at reflux for 3 h, diluted with THF and filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with THF (3x) and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:THF = 10:1 to 8:1) yielded 5.96 g (85%) of the title compound as a yellow solid: mp 86.3-89.3 ºC (DCM); IR (neat) 3376, 2952, 2925, 2881, 2225, 1606, 1591 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64 (d, 2 H, *J* = 8.7 Hz), 7.56 (d, 2 H, *J* = 8.7 Hz), 7.32 (d, 2 H, *J* = 7.8 Hz), 7.09-7.00 (m, 4 H), 6.75 (s, 1 H), 6.67 (d, 1 H, *J* = 7.8 Hz), 4.68 (s, 2 H), 4.29 (s, 2 H), 0.96 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 161.2, 154.9, 148.0, 143.9, 134.4, 133.5, 132.2, 125.7, 120.4, 120.3, 118.5, 115.9, 112.0, 106.6, 106.3, 93.4, 86.6, 64.9, 30.5, 26.2, 18.6, -5.1; HRMS (ESI) *m/z* calcd for $C_{28}H_{31}N_2O_2Si$ (M+H) 455.2155, found 455.2146.



***tert*-Butyl 5-((*tert*-butyldimethylsilyloxy)methyl)-2-((4-(4-cyanophenoxy)phenyl) ethy nyl)-phenylcarbamate.** * A solution of 4-(4-((2-amino-4-((*tert*-butyldimethylsilyloxy)-methyl)phenyl)-ethynyl)phenoxy)benzonitrile (5.96 g, 13.1 mmol) and Boc_2O (4.62 g, 21.0 mmol) in THF (81 mL) was heated at reflux for 24 h. The reaction mixture was treated with additional Boc_2O (4.62 g, 21.0 mmol) and heated at reflux for another 24 h. The reaction mixture was partitioned between EtOAc and water. The aqueous phase was washed with EtOAc (2x).

* (CWD264: procedure, proton NMR; CWD210: HRMS; CWD202: IR, carbon NMR)

The combined organic layers were washed with brine (1x), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography on SiO_2 (first with Hexanes:THF = 10:1, then re-chromatographed with Hexanes:Et_2O = 20:1 to 10:1) yielded 6.34 g (71%) of the title compound as a clear oil (contaminated with BHT from ether): IR (neat) 3407, 2954, 2930, 2885, 2856, 2227, 1809, 1733, 1593, 1572, 1525, 1496 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08 (s, 1 H), 7.65 (d, 2 H, *J* = 8.7 Hz), 7.59 (d, 2 H, *J* = 8.7 Hz), 7.45 (d, 1 H, *J* = 8.1 Hz), 7.29 (s, 1 H), 7.11-7.05 (m, 5 H), 1.55 (s, 12 H), 0.96 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 161.0, 155.5, 152.5, 144.0, 139.5, 134.5, 133.7, 132.0, 125.7, 120.4, 120.0, 119.7, 118.8, 118.7, 115.2, 109.6, 106.8, 94.8, 85.2, 81.1, 65.1, 27.6, 26.2, 18.6, -5.1; HRMS (ESI) *m/z* calcd for $C_{33}H_{38}N_2O_4NaSi$ (M+Na) 577.2499, found 577.2520.

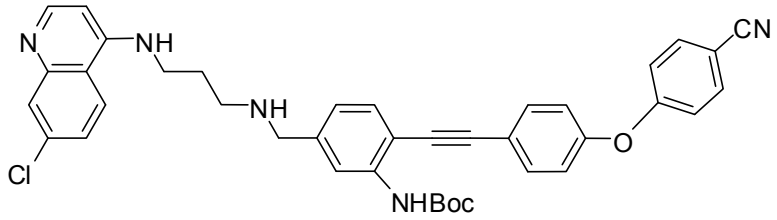


***tert*-Butyl 2-((4-(4-cyanophenoxy)phenyl)ethynyl)-5-formylphenylcarbamate (2-46).**[*]

A solution of *tert*-butyl 5-((*tert*-butyldimethylsilyloxy)methyl)-2-((4-(4-cyanophenoxy)phenyl)-ethynyl)phenylcarbamate (6.34 g, 9.34 mmol) in THF (76 mL) was treated with a solution of TBAF (1 M in THF, 18.7 mL, 18.7 mmol) at room temperature. The reaction mixture was stirred for 2 h, quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with water (2x), brine (1x), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:1 to 2:1) yielded 4.89 g (71%) of the alcohol. A solution of this alcohol and $NaHCO_3$ (2.96 g, 33.6 mmol) in DCM (100 mL) was

[*] (CWD267 and CWD268: procedure, melting point, proton NMR; CWD206: IR; CWD216: HRMS and carbon NMR)

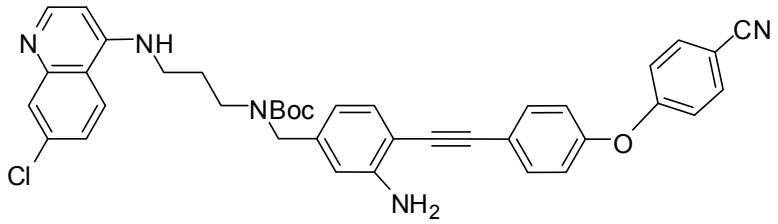
treated with Dess-Martin periodinane (6.70 g, 15.8 mmol) at room temperature. The reaction mixture was stirred for 4 h and partitioned between saturated aqueous $Na_2S_2O_3$ and EtOAc. The organic layer was washed with brine (1x), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography on SiO_2 (first with Hexanes:Et_2O = 5:1 to 2:1 to Hexanes:THF = 1:1, then re-chromatographed with Hexanes:Et_2O = 15:1 to 3:1 to 2:1 to Hexanes:THF = 5:1) yielded 4.72 g (97%) of **2-46** as a white solid: mp 163.2-164.8 (DCM); IR (neat) 3405, 2978, 2226, 1731, 1696, 1592, 1570, 1523, 1496 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.02 (s, 1 H), 8.72 (s, 1 H), 7.70-7.54 (m, 6 H), 7.38 (s, 1 H), 7.13-7.07 (m, 4 H), 1.58 (s, 12 H); ^{13}C NMR ($CDCl_3$) δ 191.6, 160.5, 156.1, 152.2, 140.2, 136.8, 134.4, 133.8, 132.3, 121.9, 120.2, 119.8, 118.9, 118.6, 118.4, 116.6, 107.0, 98.6, 84.2, 81.6, 28.3; MS (EI) *m/z* (rel intensity) 438 (5), 382 (80), 364 (90), 338 (100), 191 (30); HRMS (EI) *m/z* calcd for $C_{27}H_{22}N_2O_4$ 438.1580, found 438.1598.



***tert*-Butyl 5-((3-(7-chloroquinolin-4-ylamino)propylamino)methyl)-2-((4-(4-cyano-phenoxy)-phenyl)ethynyl)phenylcarbamate**.* A solution of **2-46** (2.69 g, 6.13 mmol) and N^1-(7-chloroquinolin-4-yl)propane-1,3-diamine[122] (2.89 g, 12.3 mmol) in $HC(OEt)_3$ (135 mL) was heated to 80 °C for 1.5 h. The reaction mixture was cooled to room temperature, diluted with MeOH (135 mL) and treated with $NaBH_3CN$ (3.86 g, 61.3 mmol). The reaction mixture was stirred for 14 h at room temperature. Most of the solvent was evaporated under reduced pressure.

* (CWD270: procedure; CWD208: proton NMR and HRMS; CWD228: carbon NMR and IR)

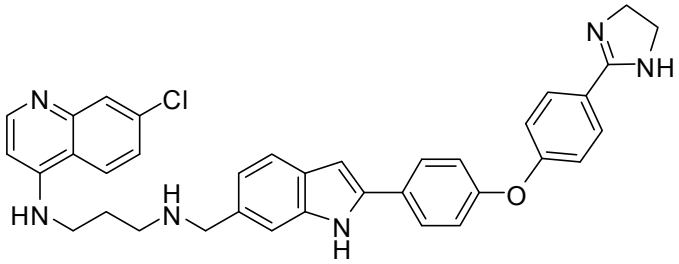
Purification of the residue by chromatography on SiO_2 (toluene:THF = 4:1 to 2:1 to 1:1 with 1% Et_3N) afforded 3.12 g (77%) of the title compound as a clear oil (contaminated with BHT from THF): IR (neat) 3636, 3404, 3247, 2956, 2227, 1730, 1609, 1581, 1495 cm-1; ^{1}H NMR ($CDCl_3$) δ 8.48 (d, 1 H, *J* = 5.4 Hz), 8.25 (s, 1 H), 7.91 (s, 1 H), 7.70-7.60 (m, 4 H), 7.59-7.43 (m, 3 H), 7.42-7.33 (m, 3 H), 7.20-6.95 (m, 6 H), 6.32 (d, 1 H, *J* = 5.4 Hz), 3.86 (s, 2 H), 3.49-3.39 (m, 2 H), 3.02-2.95 (m, 2 H), 2.00-1.92 (m, 2 H), 1.53 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 160.8, 155.6, 152.0, 150.6, 149.1, 142.0, 139.9, 137.9, 134.4, 133.7, 132.1, 129.1, 128.3, 125.4, 124.9, 122.4, 122.3, 120.3, 119.3, 118.7, 117.6, 117.4, 110.1, 106.8, 98.4, 95.5, 84.7, 81.2, 54.4, 49.2, 43.8, 28.4; HRMS (ESI) *m/z* calcd for $C_{39}H_{37}N_5O_3Cl$ (M+H) 658.2585, found 658.2548.



***tert*-Butyl 3-amino-4-((4-(4-cyanophenoxy)phenyl)ethynyl)benzyl(3-(7-chloro-quinolin-4-ylamino)propyl)carbamate (2-47)**.[*] A solution of *tert*-butyl 5-((3-(7-chloroquinolin-4-ylamino)propylamino)methyl)-2-((4-(4-cyanophenoxy)-phenyl)ethynyl)-phenylcarbamate (3.12 g, 4.74 mmol) in TFA (5.0 mL) was stirred at room temperature for 5 min. The reaction mixture was basified with 5% aqueous K_2CO_3 and extracted with EtOAc (3x). The combined organic layers were washed with water (2x), brine (1x), dried (Na_2SO_4) and concentrated under reduced pressure. A solution of this crude product in DCM (58 mL) was treated with Et_3N (1.06 mL, 7.62 mmol) and Boc_2O 1.68 g, 7.62 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 h and partitioned between EtOAc and water. The organic layer was

[*] (CWD275 and CWD276: procedure and proton NMR; CWD238: IR; CWD250: carbon NMR)

washed with water (1x), brine (1x), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography on SiO_2 (toluene:THF = 15:1 to 4:1 to 1:1) afforded 1.44 g (46%) of **2-47** as a clear oil (contaminated with BHT from THF): IR (neat) 3367, 2965, 2225, 1669, 1606, 1578, 1490 cm-1; ^{1}H NMR ($CDCl_3$) δ 8.48 (d, 1 H, *J* = 4.5 Hz), 7.94 (s, 1 H), 7.61-7.51 (m, 4 H), 7.37-7.13 (m, 4 H), 7.03-6.97 (m, 4 H), 6.62-6.57 (m, 2 H), 6.31 (d, 1 H, *J* = 5.1 Hz), 4.52 (s, 2 H), 4.36 (s, 2 H), 3.40-3.23 (m, 4 H)1.87-1.76 (m, 2 H), 1.52 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 161.1, 155.2, 151.9, 149.1, 148.2, 140.4, 135.2, 134.5, 133.6, 132.7, 129.24, 129.20, 128.7, 128.6, 128.5, 125.7, 120.4, 120.2, 118.8, 118.6, 107.1, 106.7, 94.1, 86.0, 80.9, 79.3, 51.0, 30.5, 28.7, 21.4; HRMS (ESI) *m/z* calcd for $C_{39}H_{37}N_5O_3Cl$ (M+H) 658.2585, found 658.2552.



•4TFA

N1-(7-Chloroquinolin-4-yl)-N3-((2-(4-(4-(4,5-dihydro-1H-imidazol-2-yl)phenoxy)-phenyl)-1H-indol-6-yl)methyl)propane-1,3-diamine (TFA salt, 2-45).[*] A solution of **2-47** (0.713 g, 1.08 mmol) in DMF (9.6 mL) was degassed and treated with $PdCl_2(PhCN)_2$ (0.622 g, 1.62 mmol) at room temperature. The reaction mixture was degassed again and stirred at 80 °C for 0.5 h. The solvent was evaporated under reduced pressure. The crude mixture was redissolved in TFA (20 mL) and stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure. One third of the crude mixture and sulfur (57.6 mg, 1.8 mmol) was treated with ethylene diamine (1.0 mL), then heated in the microwave at 130 °C for

[*] (CWD279 and CWD282: procedure, proton NMR, IR, HRMS and carbon NMR)

30 min. The reaction mixture was suspended in water and filtered, and the solid was rinsed with water (3x), and purified by reverse-phase HPLC (MeOH-0.1% aq. TFA) to yield 77.2 mg (23%) of **2-45** as a sticky brown solid: IR (neat) 3216, 3098, 2957, 1672, 1611, 1503, 1485 cm-1; ^{1}H NMR (CD_3OD) δ 8.35 (d, 1 H, *J* = 7.2 Hz), 8.29 (d, 1 H, *J* = 9.0 Hz), 7.91-7.83 (m, 4 H), 7.80 (d, 1 H, *J* = 1.8 Hz), 7.61 (dd, 1 H, *J* = 9.0, 2.1 Hz), 7.56-7.48 (m, 2 H), 7.19 (app d, 4 H, *J* = 8.7 Hz), 7.09 (dd, 1 H, *J* = 8.1, 1.2 Hz), 6.81 (d, 1 H, *J* = 7.2 Hz), 6.77 (s, 1 H), 4.31 (s, 2 H), 4.07 (s, 4 H), 3.65 (t, 2 H, *J* = 6.9 Hz), 3.21 (t, 2 H, *J* = 7.5 Hz), 2.23-2.12 (m, 2 H); ^{13}C NMR (CD_3OD) δ 167.1, 164.6, 157.6, 155.8, 143.9, 141.0, 140.1, 139.9, 138.7, 131.8, 131.4, 131.3, 130.9, 128.3, 125.9, 125.1, 122.1, 122.0, 120.3, 119.1, 117.6, 116.9, 114.1, 100.0, 99.7, 53.1, 45.9, 45.2, 41.7, 25.8; HRMS (ESI) *m/z* calcd for $C_{36}H_{34}N_6OCl$ (M+H) 601.2483, found 601.2489; the content of TFA in the product was determined by adding a known amount of trifluoroethanol as an internal standard and comparing the integration of the trifluoroacetate and trifluoroethanol in the ^{19}F NMR.

Assay of BoNT/A light chain proteolytic activity in the presence of different small molecule Inhibitors (performed by our collaborators at NCI). The HPLC based assay for BoNT/A SNAP-25 cleavage was conducted as described previously without modification.[124-125] The BoNT/A inhibition activities of different compounds were compared by measuring reaction velocities in the presence of 20 μM inhibitor and then calculating percent inhibition values using uninhibited control reactions. Assays were conducted at 100 μM substrate concentration and reported percent inhibition values are the averages of two independent experiments.

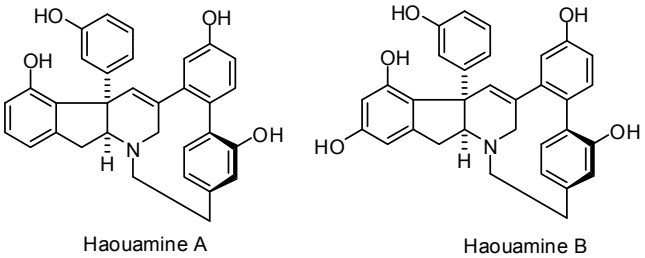
3.0 TOTAL SYNTHESIS OF HAOUAMINE A

3.1 INTRODUCTION

3.1.1 Haouamines: Structure and Biological Activity

Haouamines A and B (Figure 39) were isolated in 2003 from the tunicate *Aplidium haouarianum* collected off Tarifa Island in Spain.[126] The more stable haouamine A was obtained in significant quantity (150 mg), whereas the less stable haouamine B was isolated in minor quantity (5.8 mg). The structure of haouamine A was established by interpretation of its spectroscopic data and those of the N-methyl derivative, and confirmed by X-ray crystallographic analysis. The structure of haouamine B was deduced via spectroscopic studies of its peracetyl derivative.

Figure 39 Structures of haouamine A and B



Haouamine A Haouamine B

The most striking structure feature of the haouamines is their bent biphenol residing in the strained aza-paracyclophane system (Figure 40). Despite its boat-like conformation, the B-ring

exhibits standard aromatic chemical shifts in the ^{1}H and ^{13}C NMR spectra (Figure 41), which indicate the presence of ring current. In addition, all six carbon-carbon bonds in the ring have similar bond lengths (1.40 Å), resembling the behavior of planar aromatic systems. The presence of aromaticity in haouamines proved to be critical for their synthesis, for it served as a driving force for the formation of the strained paracyclophane.[127-129]

Figure 40 X-ray structure of haouamine A and its boat-like phenyl ring.

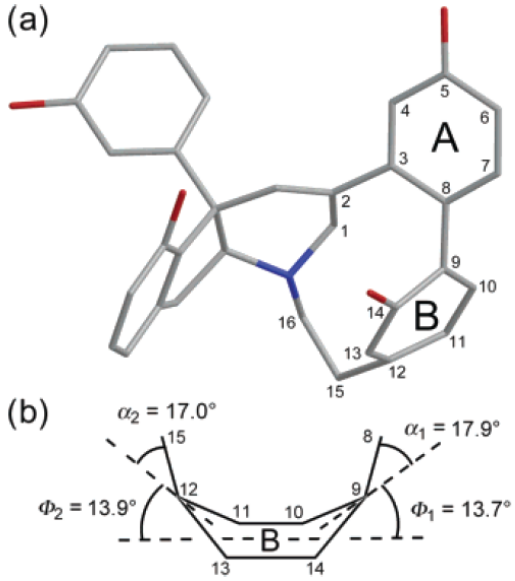
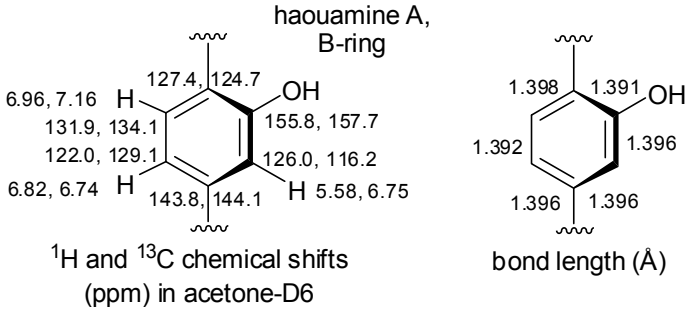


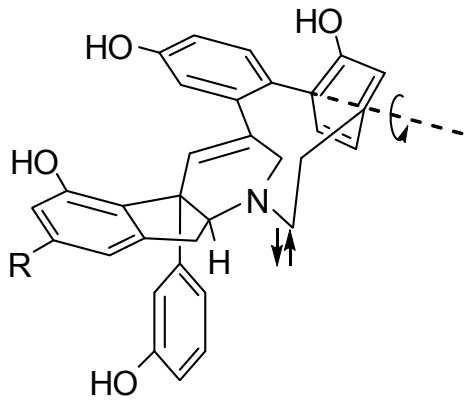
Figure 41 Chemical shift values (ppm) and C-C bond lengths (Å) of the central phenyl ring in haouamine A



At ambient temperature both haouamine A and B exist as two NMR-detectable interconverting forms in solution.[126,130] All attempts to separate the isomers by means of chromatography failed; high temperature NMR experiments also did not simplify the spectra.[126]

Additionally, the ratio of isomers was found to be dependent upon the NMR solvent used (e.g. 2:1 in acetone-d_6, 1:3 in DMSO-d_6). In contrast to the NMR study, a crystal structure of haouamine A demonstrated a pattern with a single molecular geometry (Figure 40). Redissolving the crystal resulted in the same mixture of the two equilibrating isomers as detected by NMR. Zubia and co-workers proposed that the origin of the two interconverting isomers was from either atropisomerism of the central phenyl ring or from inversion at the nitrogen center (Figure 42). Synthetic studies by Baran et al.[128] provided a pair of stable and separable haouamine A atropisomers, which indicated that the N-inversion may account for the interconverting isomers. This was further supported by a computational study.[130]

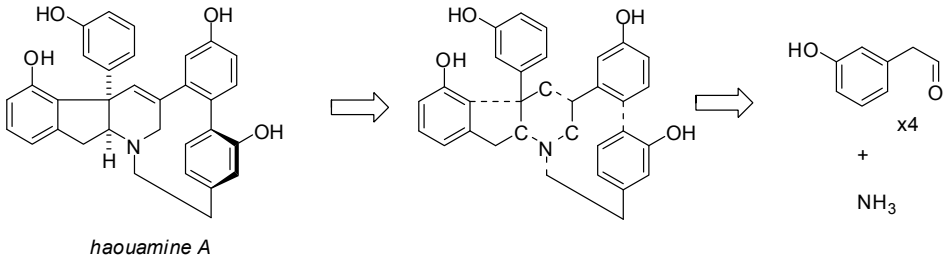
Figure 42 Proposed atropisomerism and N-inversion in haouamines



Zubia et al. tested haouamine A and B against human lung carcinoma A-549, human colon carcinoma HT-29 and HCT-116, mice endothelial cells MS-1, and human prostate carcinoma PC-3. Haouamine A showed high and selective activity against the HT-29 cell line with an IC_{50} of 0.1 μg/mL, while haouamine B (**2**) was only slightly cytotoxic against the MS-1 cell line with an IC_{50} of 5 μg/mL.[126] A subsequent study by Baran et al. using synthetic material (single enantiomer) revealed that haouamine A exhibits moderate activity against PC3 human prostate cancer cells with IC_{50} = 29±2 μM. The atropisomer of haouamine A also shows comparable activity (IC_{50} = 32±3 μM).[128]

The biosynthetic origins of the haouamines remain ambiguous. Baran et al. proposed the condensation of four meta-hydroxylated phenylacetaldehydes with ammonia followed by two oxidative couplings (Scheme 40). However, they were unable to demonstrate this process *in vitro*.[127,131]

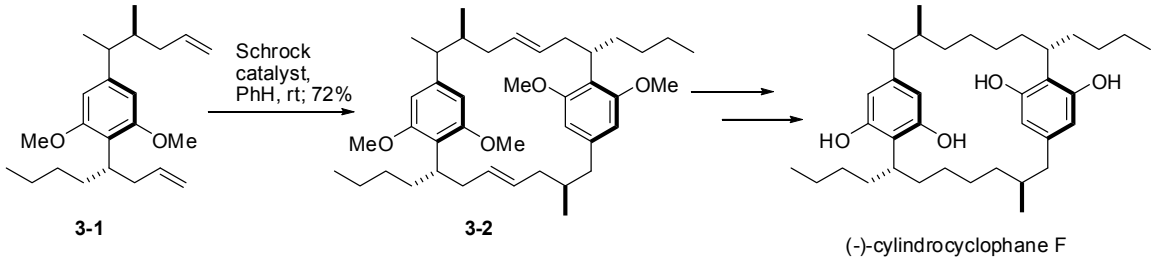
Scheme 40 Biosynthesis of haouamine A proposed by Baran et al.



3.1.2 Cyclophanes in Natural Product Synthesis

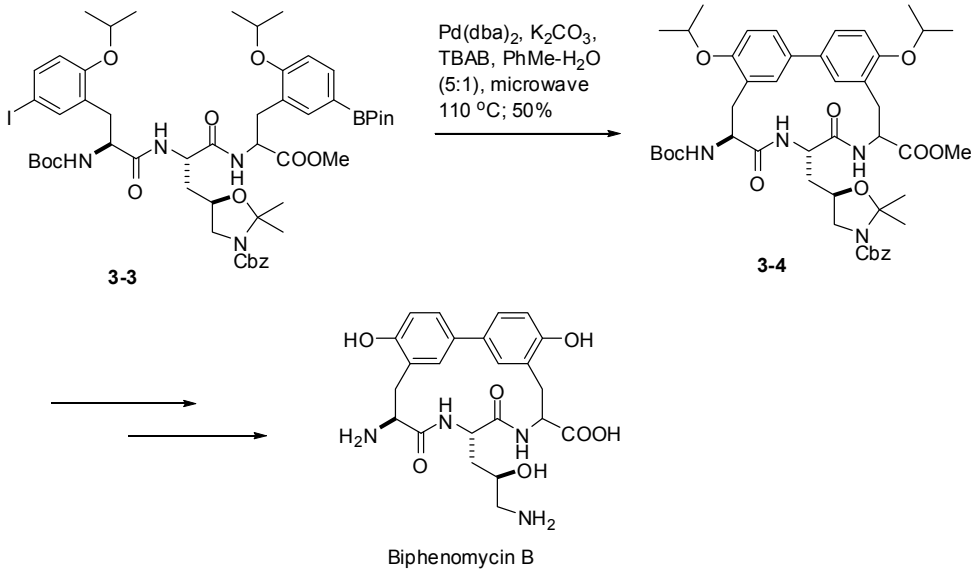
The construction of the aza-paracyclophane moiety in haouamines is arguably the most challenging part of their total synthesis. A variety of cyclophane-containing natural products are known, among which many have been synthesized. For example, Smith et al. reported the total synthesis of (-)-cylindrocyclophanes A and F with a cross-metathesis reaction as the key cyclophane formation step (Scheme 41).[132]

Scheme 41 Cross-metathesis in the total synthesis of (-)-cylindrocyclophanes F



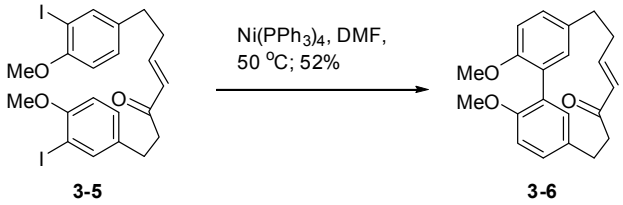
The total synthesis of biphenomycin B has been accomplished featuring a microwave-assisted intramolecular Suzuki-Miyaura reaction for the formation of a biaryl cyclophane system (Scheme 42). [133]

Scheme 42 Suzuki cross-coupling in the total synthesis of biphenomycin B



In a synthesis of alnusone dimethyl ether, Semmelhack et al. successfully constructed a *meta,meta*-biaryl cyclophane utilizing a Ni-promoted aryl iodide homocoupling procedure (Scheme 43).[134]

Scheme 43 Ni-promoted aryl iodide homocoupling in the total synthesis of alnusone dimethyl ether



A common feature of the previous work on the synthesis of naturally-occurring cyclophanes is the lack of significant strain energy in the macrocycle. The strained aza-cyclophane in haouamine poses a major challenge to synthetic chemists. Model cyclophanes with bent phenyl rings have been prepared for theoretical studies.[135] For example, Tobe et al.

prepared a [6]paracyclophane (paracyclophane with a six-carbon linker) utilizing a [2+2] cycloaddition, ring-contraction (Wolff rearrangement) and Dewar benzene isomerization sequence (Scheme 44).[136] The x-ray analysis of **3-11** revealed the distortion of the benzene ring from planarity (Figure 43).

Scheme 44 Synthesis of 8-carboxy[6]paracyclophane

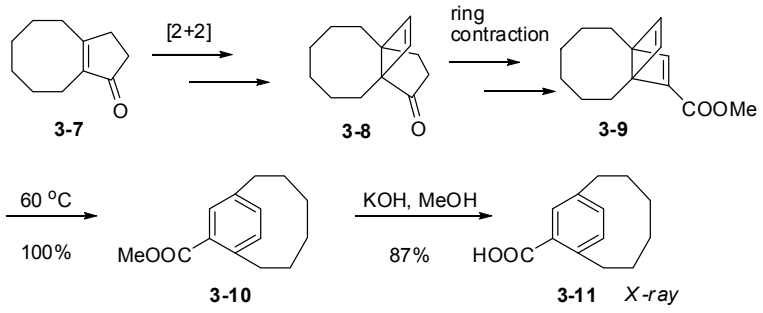
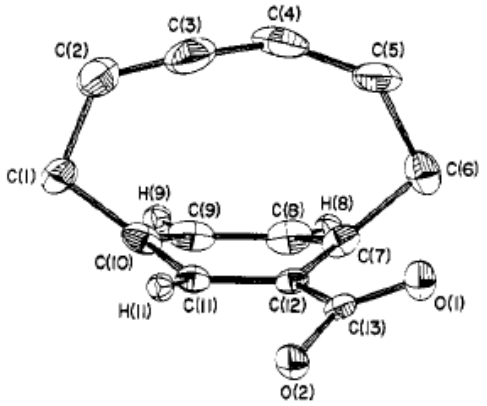
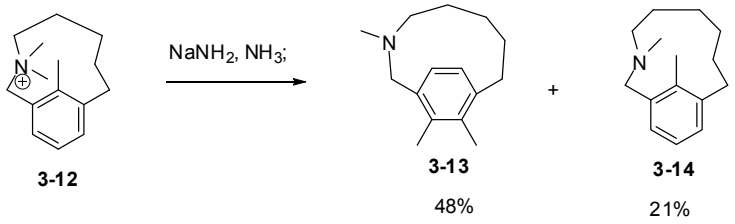


Figure 43 X-ray structure of **3-11**



Besides the haouamines, only one synthesis of a strained aza-paracyclophane system has been reported. Hasiak et al. described the preparation of 2-aza-(7)-paracyclophane **3-13** (haouamines have 3-aza-[7]-paracyclophane systems) from the methiodide of 2-aza-(7)-metacyclophane **3-12**.[137] The key step was a Sommelet-Hauser rearrangement to provide **3-13** along with a Stevens 1,2 shift to afford **3-14**.

Scheme 45 Synthesis of 2-aza-(7)-paracyclophane

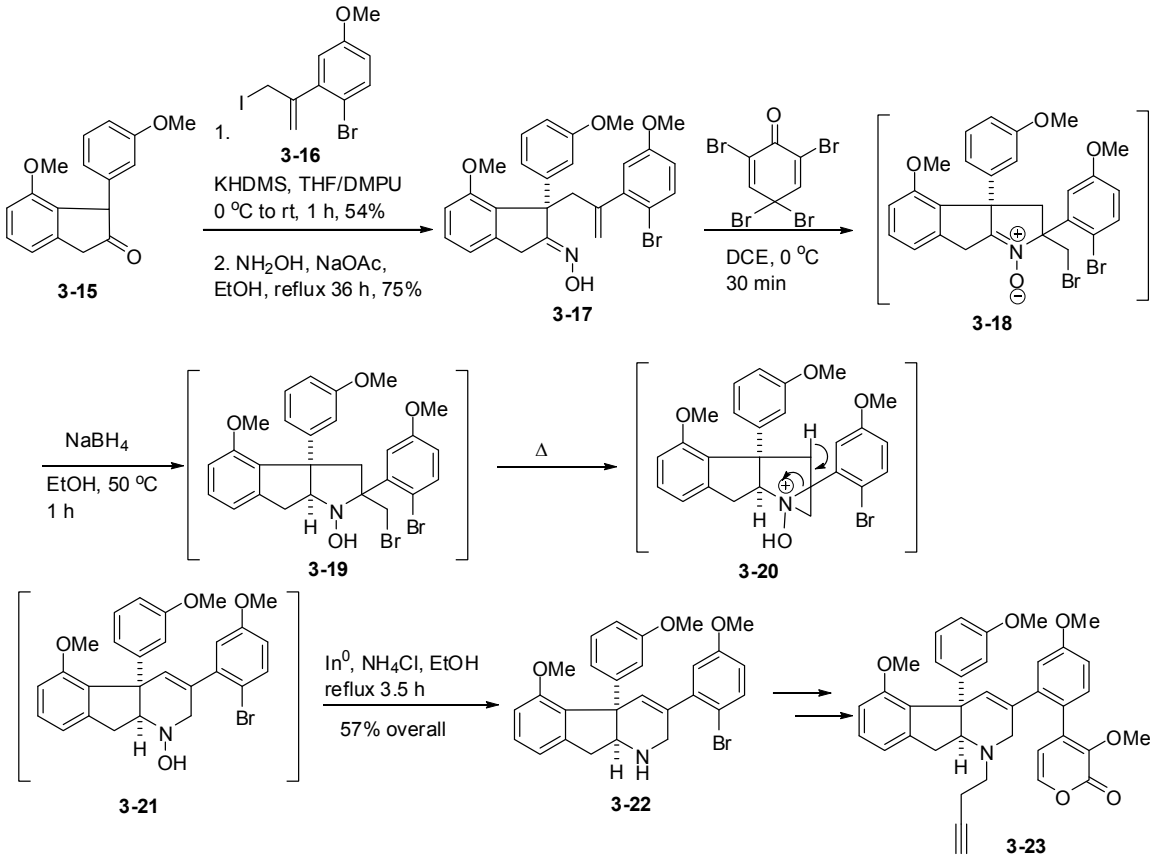


3.1.3 Previous Work on the Total Synthesis of Haouamines

The synthetic community was intrigued by haouamines' unprecedented structure features. In 2005, Rawal and co-workers reported a Friedel-Crafts approach towards a model system representing the tetrahydropyridine core of haouamine A.[138] This result coincided with Trauner and co-workers' preparation of a model system towards at haouamine B.[139]

In 2006, Baran and co-workers reported the first racemic total synthesis of haouamine A (Scheme 46).[127]

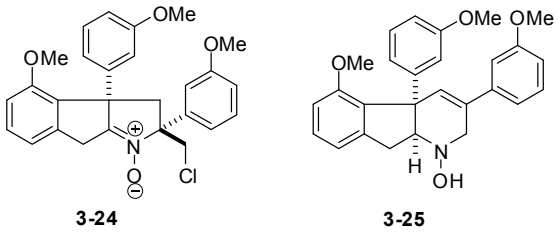
Scheme 46 Baran's 1st generation total synthesis of haouamine A: preparation of substrate for the Diels-Alder reaction



Indanone **3-15** was prepared from 7-methoxyindanone in 4 steps. Subsequent allylation with **3-16** followed by condensation with hydroxylamine provided oxime **3-17**. Bromination of **3-17** yielded the transient bromonium ion, which was trapped intramolecularly with the oxime moiety to form nitrone **3-18**. In situ reduction of **3-18** with $NaBH_4$ provided the ring-expansion product **3-21** via the intermediate hydroxylamine **3-19** and aziridinium ion **3-20**. N-O bond cleavage in **3-21** was affected with elemental indium to provide tetrahydropyridine **3-22**. The proposed mechanism of this sequence was supported by the X-ray analysis of two related intermediates (Figure 44). At this stage, the authors stated that attempted construction of the paracyclophane with several standard approaches such as transition metal based biaryl synthesis, Witkop photocyclization, and intramolecular alkylation all failed. Thus, they decided to utilize a

pyrone-alkyne Diels-Alder reaction to overcome the strain energy in the aza-paracyclophane system. Consequently, intermediate **3-22** was elaborated into **3-23** for the key intramolecular Diels-Alder reaction.

Figure 44 Related intermediate structures confirmed by X-ray analysis

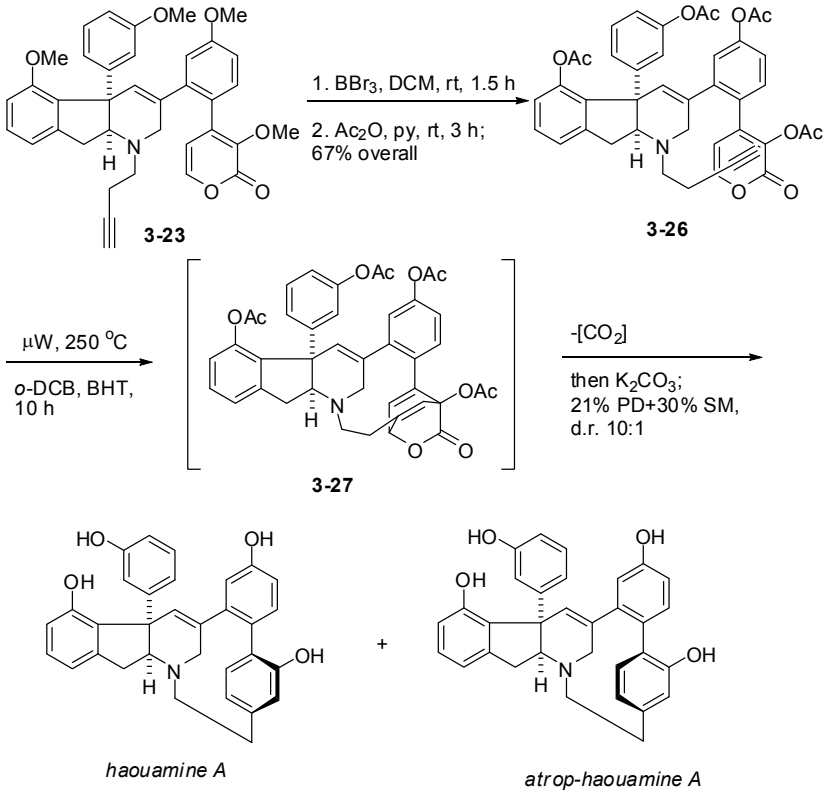


3-24 **3-25**

Before the key cycloaddition reaction, the phenol protecting groups in **3-23** were switched from methyls to acetates to suppress decomposition. After being heated in the microwave at 250 °C, acetate **3-26** underwent the pyrone Diels-Alder reaction followed by decarboxylation and acetate removal to provide a mixture of haouamine A and the atropisomer of haouamine A (10:1) in 21% overall yield.

The same group later prepared intermediate **3-17** in an enantioselective fashion (the absolute stereochemistry was established by X-ray analysis) and carried it through the synthesis. Through a comparison of the CD spectra of their synthetic material and the natural product, they established the absolute stereochemistry of haouamine A (Figure 39).

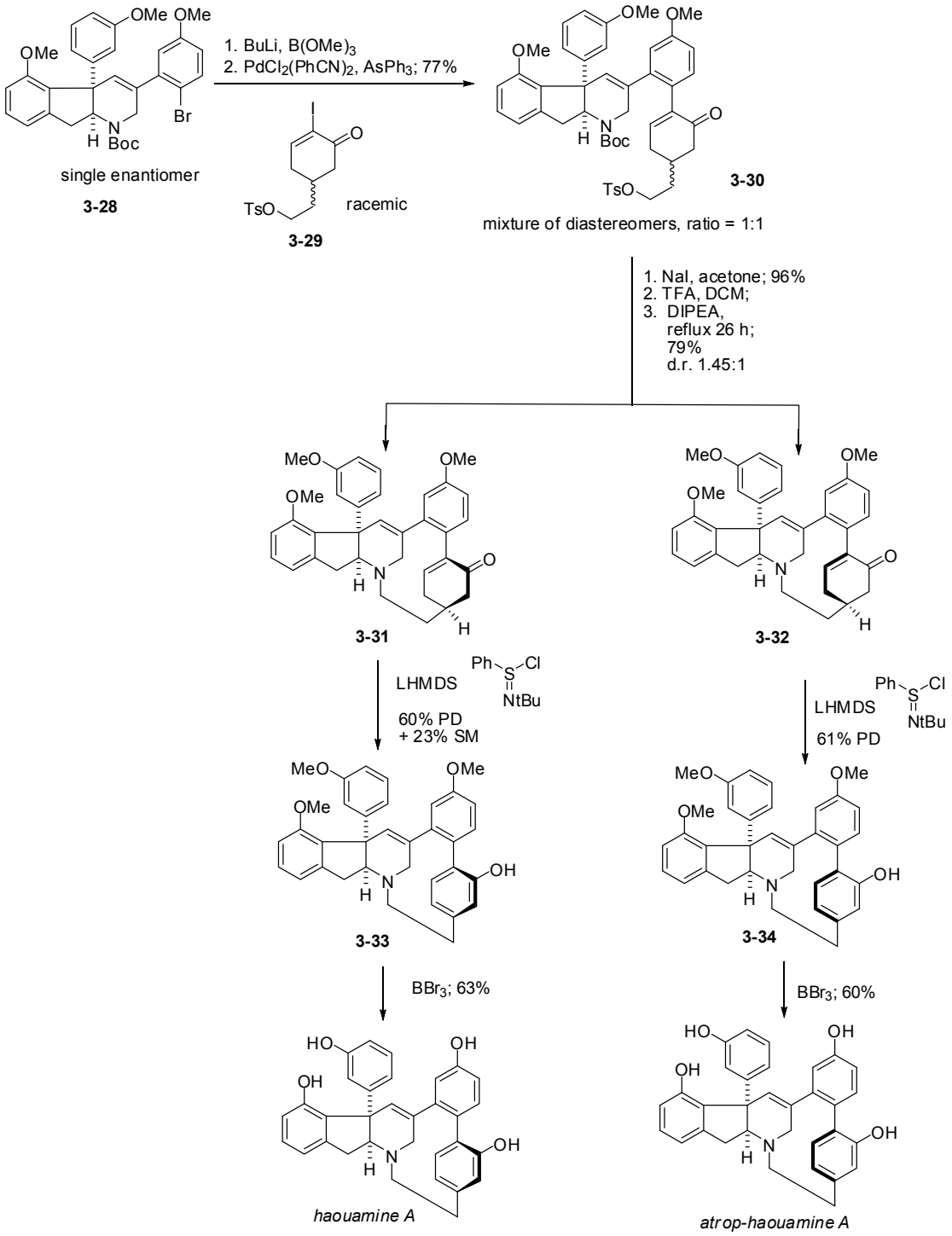
Scheme 47 Completion of the synthesis: pyrone Diels-Alder reaction



After the completion of the first total synthesis of haouamine A, it was noted that the Diels-Alder step was difficult to reproduce.[128,140] In 2009, the Baran group published their second generation total synthesis (Scheme 48).[128] Starting from **3-28** (an intermediate in their first generation total synthesis), they converted the aryl bromide to a boronic ester and coupled it to vinyl iodide **3-29**. The vinyl iodide **3-29** was a racemic mixture; thus the coupling product **3-30** was a mixture of 1:1 diastereomers. In principle, this mixture would lead to a 1:1 mixture of haouamine A and its atropisomer. Subsequent macrocyclization of **3-30** produced a 1.45:1 mixture of **3-31** and **3-32** (structures confirmed by X-ray) in 79% overall yield, indicating one diastereomer reacted with higher efficiency than the other. The two diastereomers were separated and carried on individually. Treatment of **3-31** and **3-32** with LHMDS and Mukaiyama's reagent

yielded double-enones, which tautomerized to phenol **3-33** and **3-34**. Global deprotection with BBr_3 produced haouamine A and its atropisomer in > 100 mg quantities.

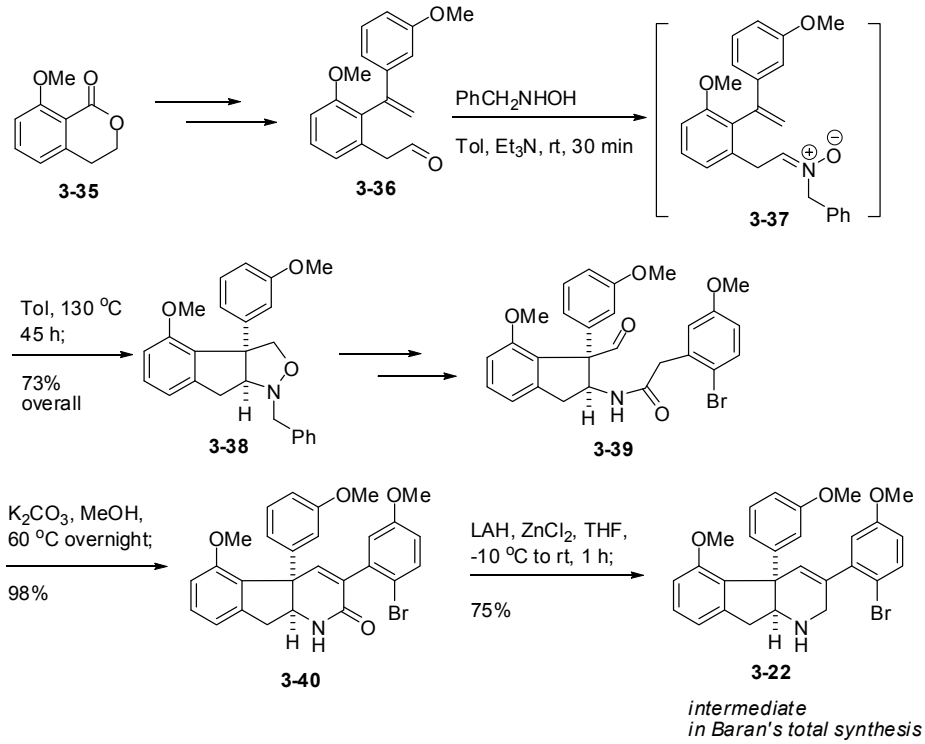
Scheme 48 Baran's 2nd generation synthesis of haouamine A and its atropisomer



Soon after the publication of Baran's first generation total synthesis, several formal syntheses were reported in the literature. Coincidentally, all of them relied on Baran's pyrone Diels-Alder strategy for access to the paracyclophane system, and the differences lie in the construction the tetrahydropyridine core.

In 2006, Weinreb et al. reported the preparation of intermediate **3-22** (racemic) in Baran's synthesis (Scheme 49).[141] Starting from isochromanone **3-35**, aldehyde **3-36** was constructed and subsequently condensed with benzyl hydroxylamine to afford nitrone **3-37.** Intramolecular dipolar cycloaddition provided isoxazolidine **3-38**, which was further elaborated into aldehyde **3-39**. A one-pot intramolecular aldol-elimination reaction furnished dihydropyridone **3-40**. The lactam moiety in **3-40** was reduced to a secondary amine to give the Baran pentacycle **3-22**.

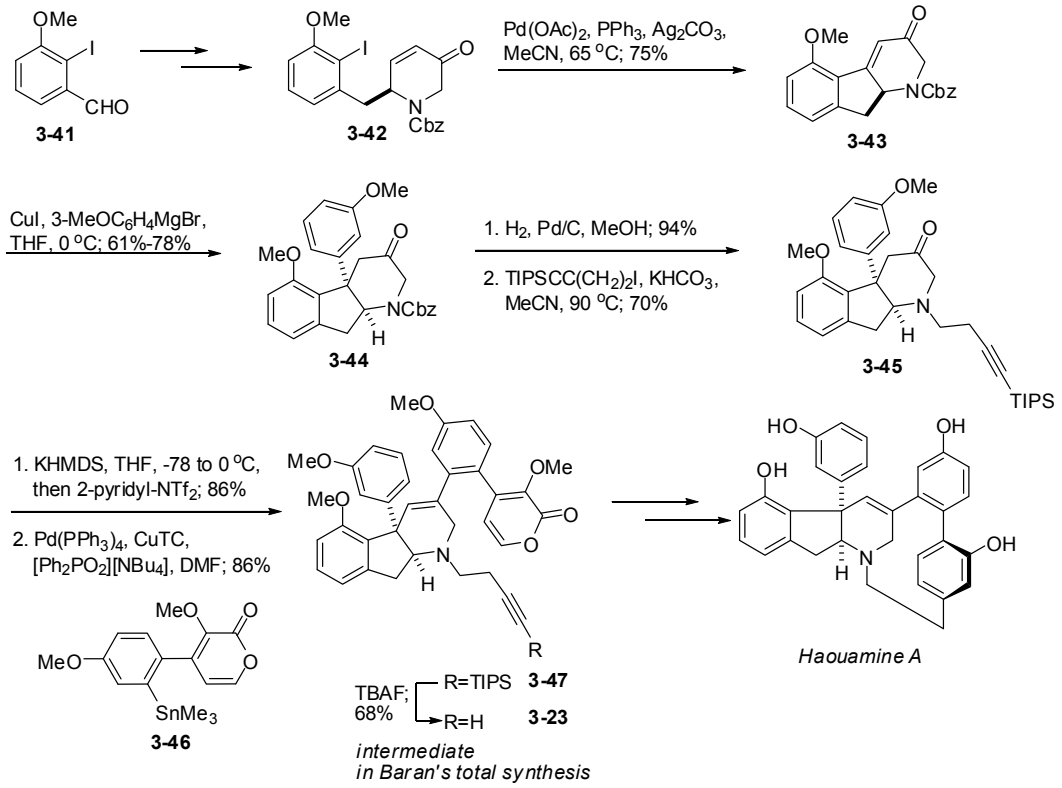
Scheme 49 Weinreb's formal synthesis of haouamine A



Two years later, Fürstner et al. reported an asymmetric formal synthesis of haouamine A (Scheme 50).[140] Starting from enone **3-42,** Heck cyclization followed by conjugate addition

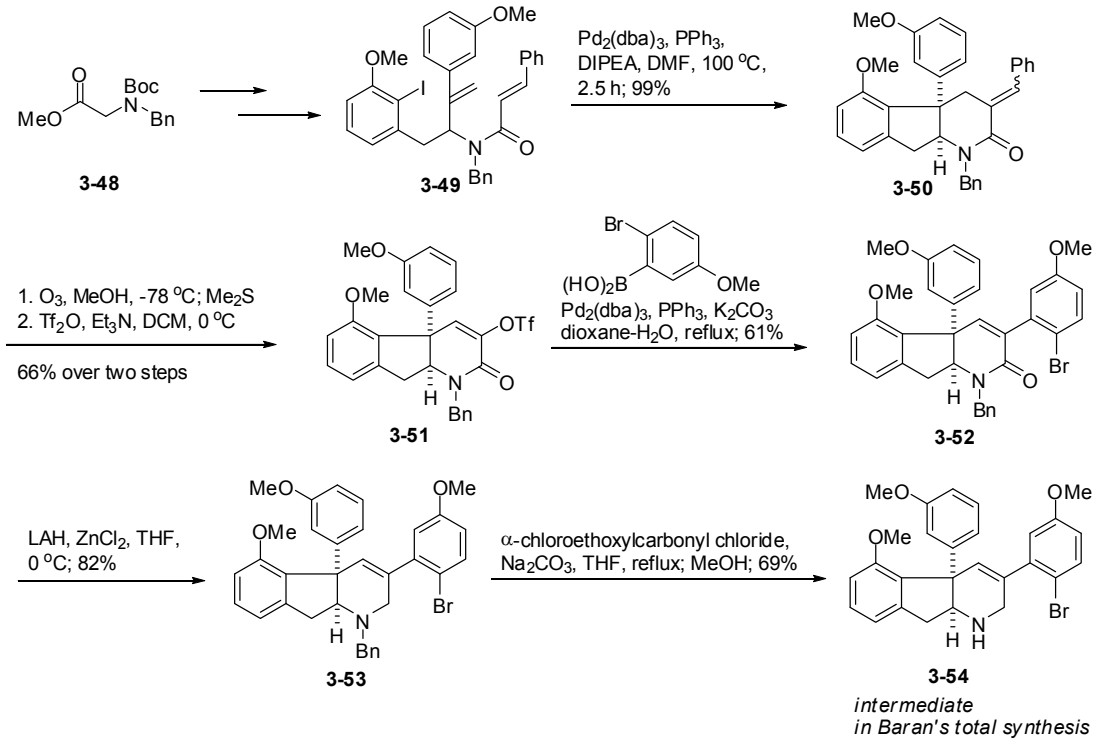
provided tetracycle **3-44**. The nitrogen in **3-44** was unmasked and alkylated with a homopropagyl iodide to give **3-45**. Regioselective enolization of the ketone moiety in **3-45,** subsequent trapping as the triflate, and Stille cross-coupling afforded **3-47**. Removal of the alkynyl silyl group yielded Baran's substrate for the Diels-Alder reaction. Compound **3-23** was carried through Baran's end-game procedures to provide haouamine A.

Scheme 50 Fürstner's formal synthesis of haouamine A



In 2009, Ishibashi et al. reported their contribution to haouamine A by synthesizing Baran's intermediate **3-22** (racemic) (Scheme 51).[142] Highlights of their synthesis include a cascade Heck reaction to access the tetracycle **3-50** in high efficiency and a Suzuki cross-coupling to install the aryl bromide moiety in **3-52**.

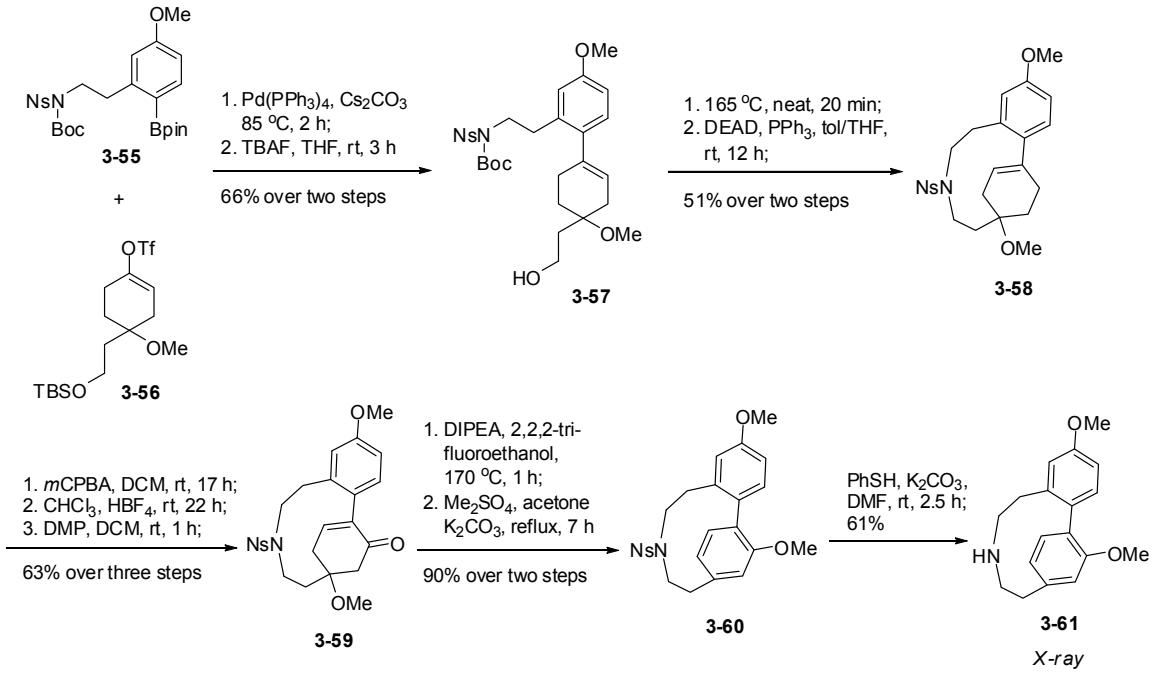
Scheme 51 Ishibashi's formal synthesis of haouamine A



Our group joined this arena soon after the isolation of the haouamines. Dr. Furegati, a former Wipf group member, evaluated strategies for the formation of the aza-paracyclophane moiety. Most of the conventional cyclization methods failed, including epoxide opening with an amine, macrolactamization, Staudinger ligation for ring-contraction and Ireland-Claisen rearrangement.[143] Therefore, attention was turned to an aromatization approach (Scheme 52).[129] Suzuki cross-coupling of boronic ester **3-55** and vinyl triflate **3-56** followed by desilylation gave bicycle **3-57**. The amine and alcohol functionalities in **3-58** were unmasked and cyclized under Mitsunobu conditions to provide macrocycle **3-58**. A formal allylic oxidation of **3-58** was performed with a three-step protocol (epoxidation of the olefin, acid-catalyzed rearrangement to an allylic alcohol and oxidation to an enone) to afford enone **3-60**. Upon heating with a weak base, enone **3-59** first lost one molecule of MeOH and tautomerized to a phenol. Protection of

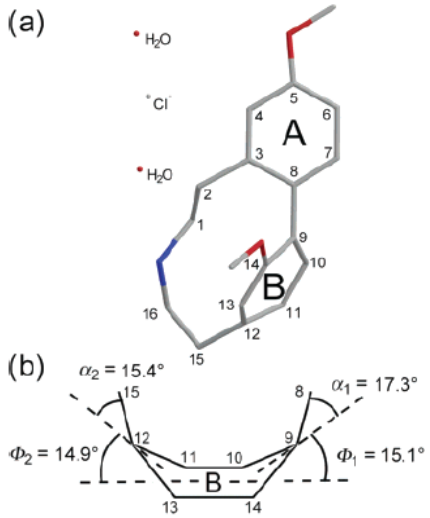
the phenol yielded biaryl system **3-60** in good yield. Deprotection of the nosyl group followed by formation of the HCl salt provided crystals suitable for x-ray analysis.

Scheme 52 Wipf's aza-paracyclophane model system synthesis



X-ray analysis of **3-61**·HCl provided convincing evidence that ring distortion and folding of this subunit are a close match of the natural product (Figure 45). This work serves as proof-of-concept for our total synthesis of haouamine A.

Figure 45 X-ray structure of **3-61**·HCl

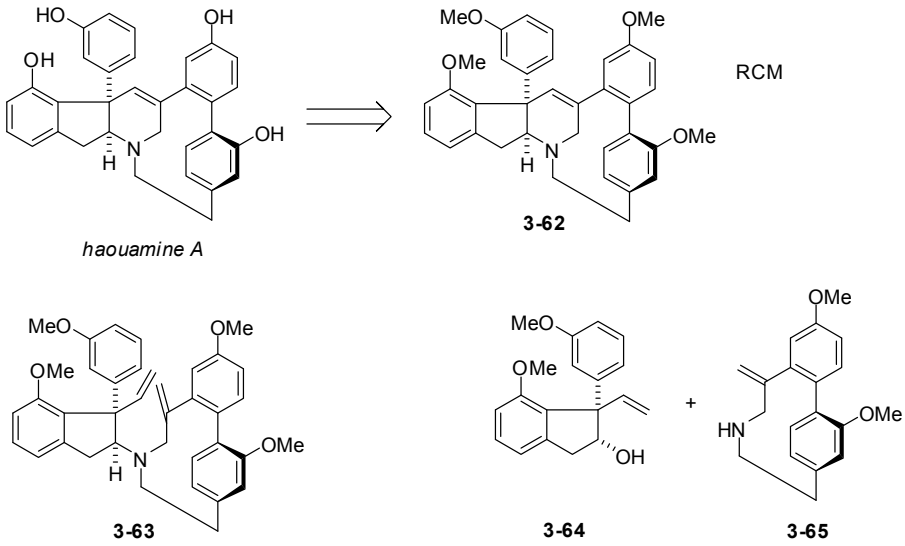


3.2 SYNTHESIS OF HAOUAMINE A

3.2.1 1st Generation Approach: Ring-Closing Metathesis

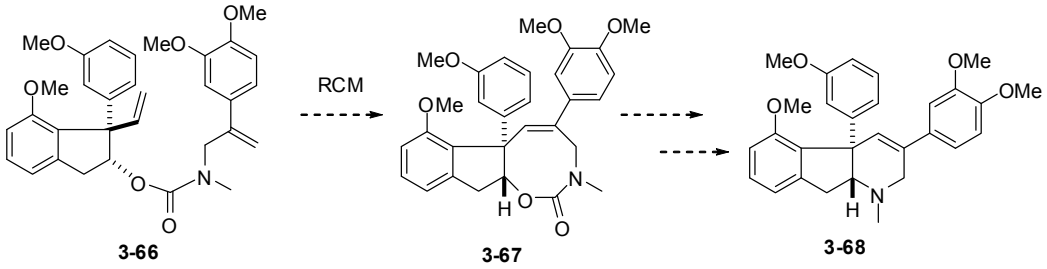
Initially, we envisioned that the olefinic subunit in the tetrahydropyridine core of haouamine A could be formed via a ring-closing metathesis reaction (**3-62** to **3-63,** Scheme 53). Subsequent N-alkylation would simplify **3-63** to alcohol **3-64**[143] and aza-paracyclophane **3-65**.

Scheme 53 1st Generation retrosynthetic analysis



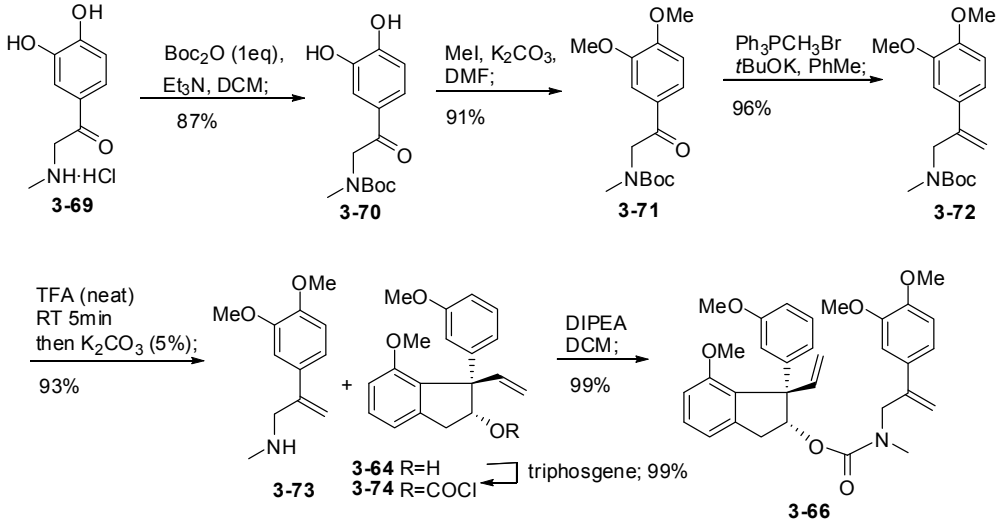
Ring-closing metathesis on a neopentyl olefin is a challenging task due to steric congestion.[144] Consequently, we prepared a model system to validate our synthetic strategy (**3-66**,Scheme 54). It was envisioned that **3-66** would undergo a ring-closing metathesis reaction to give cyclic system **3-67**. The carbonate tether in **3-67** would then be removed to expose the amino alcohol functionality. Activation of the alcohol moiety and subsequent intramolecular displacement by nitrogen (or an elimination/hydroamination sequence) would provide tetrahydropyridine **3-68**.

Scheme 54 Model system for the RCM reaction



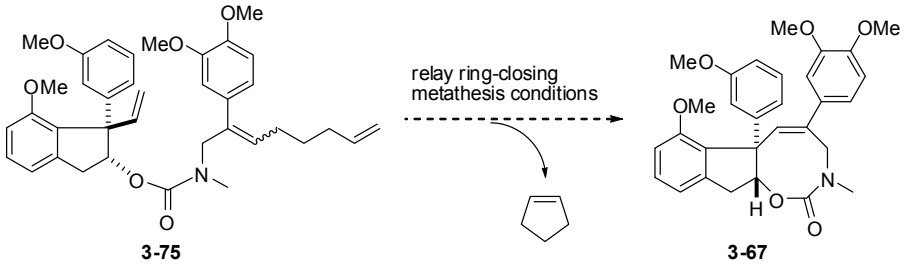
The substrate **3-66** was prepared in five steps from commercial materials (Scheme 55). The key step, segment coupling between amine **3-73** and chloroformate **3-74**, proceeded smoothly to give carbonate **3-66** in excellent yield.

Scheme 55 Preparation of model system **3-72** for the RCM reaction



The RCM reaction of **3-66** to give **3-67**, however, proved to be challenging. All attempts resulted in nearly quantitative recovery of the starting material **3-66**. The catalysts screened include Grubbs' first and second generation catalysts, Hoveyda-Grubbs' catalyst and Schrock's catalyst. This result was not unexpected due to the considerable steric hindrance around the olefin. We quickly turned to a revised strategy, namely a relay ring-closing metathesis approach (Scheme 56).[145]

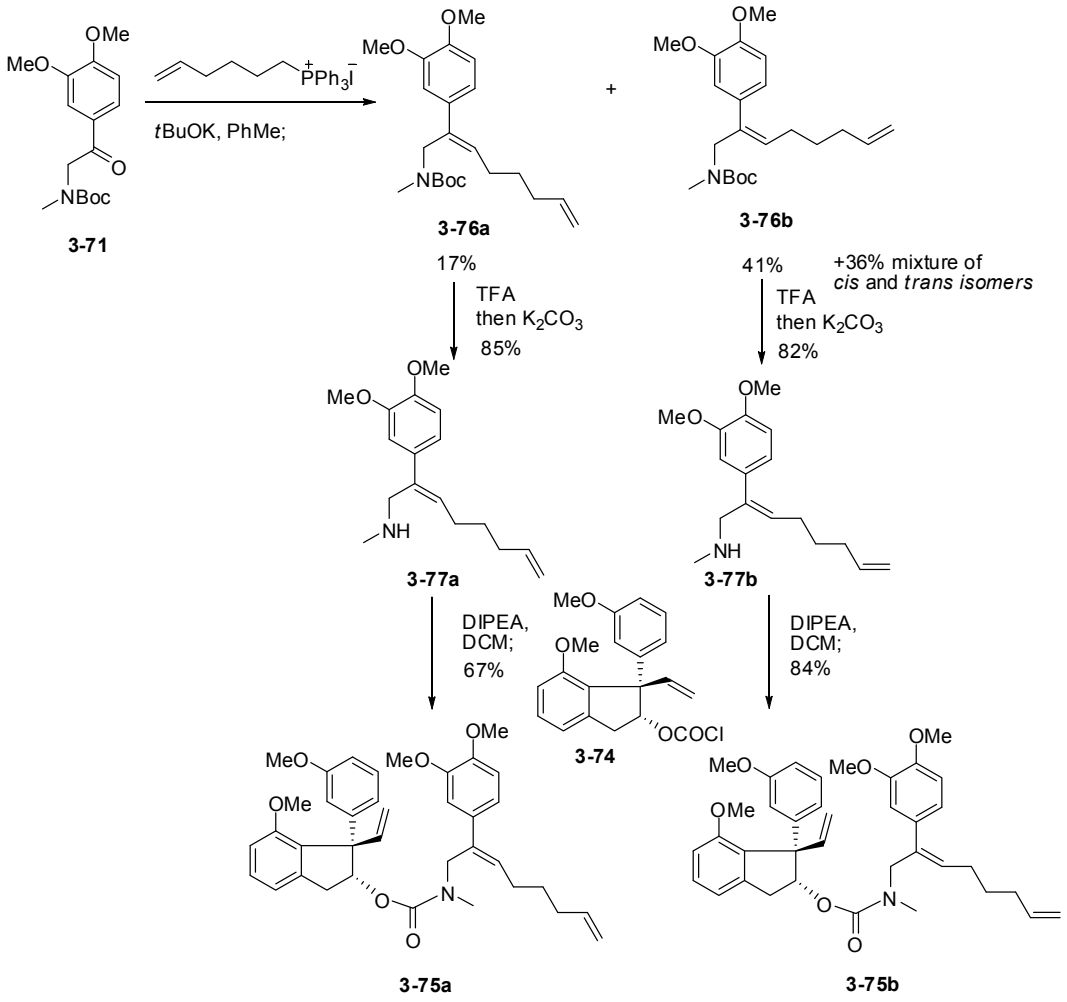
Scheme 56 Model system for the relay RCM reaction



3-75 **3-67**

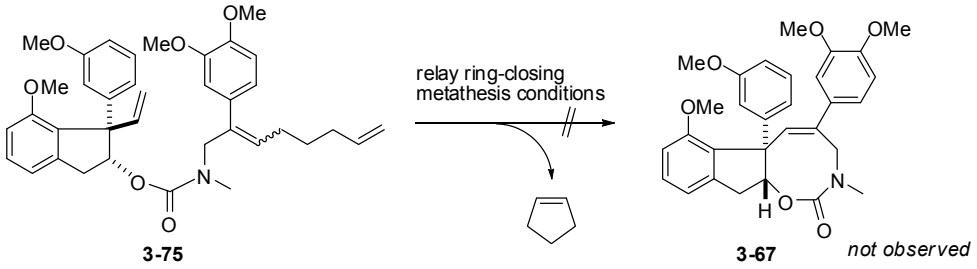
We planned to subject triene **3-75** to metathesis conditions. Compound **3-75** was expected to react with the catalyst to give a metal-carbene complex at the terminus of the heptadiene moiety. An RCM reaction would produce a cyclopentene and leave the metal-carbene complex at the benzylic position, which was expected to undergo another RCM to afford **3-67**. This strategy would generate the benzylic metal-carbene complex in an intramolecular fashion as opposed to the intermolecular case outlined in Scheme 54. To examine this approach, **3-75** was easily prepared from intermediate **3-71** (Scheme 57). The *cis/trans* isomers **3-76a** and **3-76b** were isolated and carried on separately.

Scheme 57 Preparation of model system **3-75** for the relay RCM reaction

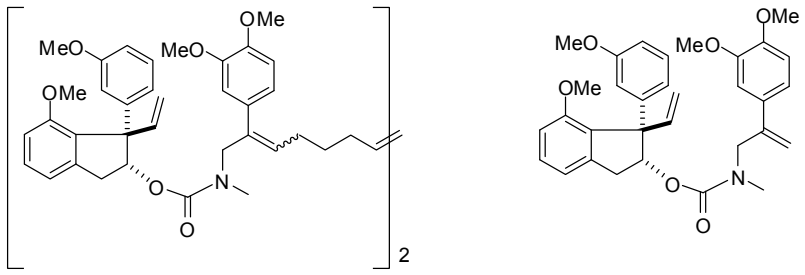


Both **3-75a** and **3-75b** were subjected to a variety of relay RCM conditions (Scheme 58), including those using Ti(*i*PrO)$_4$ as an additive to disrupt the chelation between the metal and the carbonate moiety. As expected, they exhibited a similar reactivity pattern. However, instead of the desired product **3-67**, we obtained a mixture of dimer **3-78** (even at a substrate concentration as low as 0.2 mM) and truncated product **3-68**. Based on this finding, we believe that the transient benzylic metal-carbene complex was formed in the reaction. However, it did not react with the neopentyl olefin. Instead, it abstracted a methylene group from another substrate to afford **3-66**.

Scheme 58 Byproducts observed in the relay RCM reaction

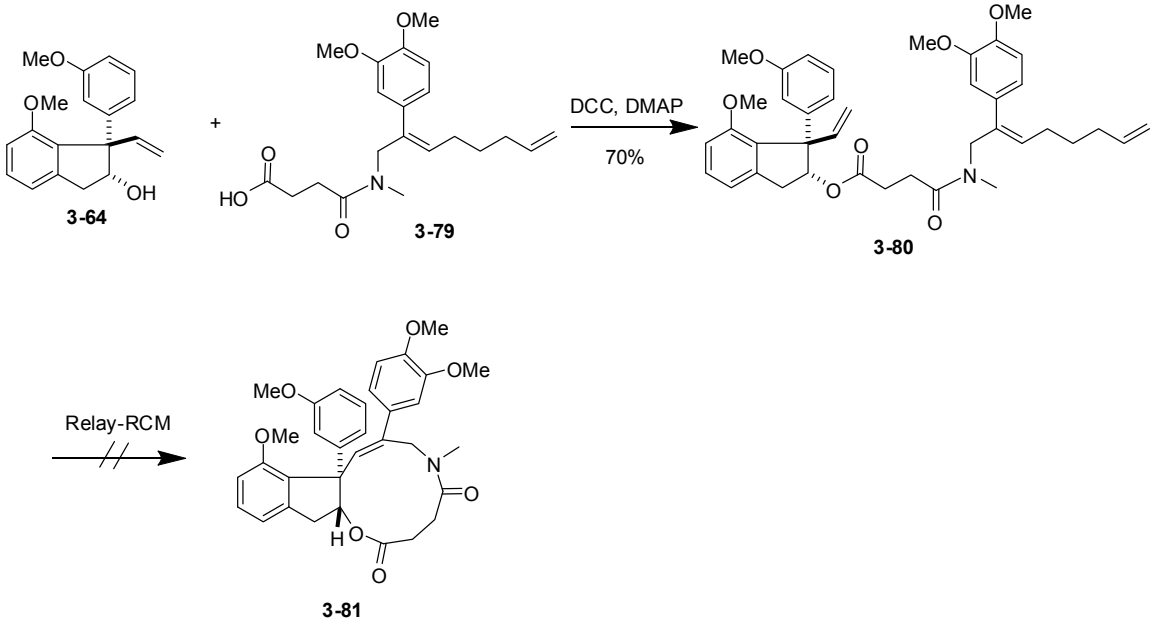


Observed:



Next, we briefly explored variations in tether length (Scheme 59). A substrate with longer tether (**3-80**) afforded no observable desired products.

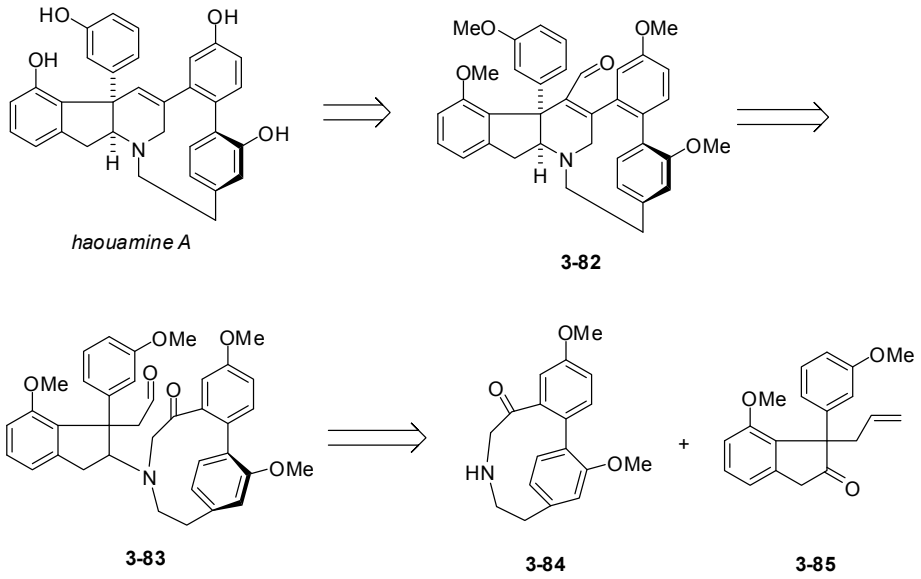
Scheme 59 Variations in tether length in the RCM reaction



3.2.2 2nd Generation Approach: Intramolecular Aldol and Reductive Amination

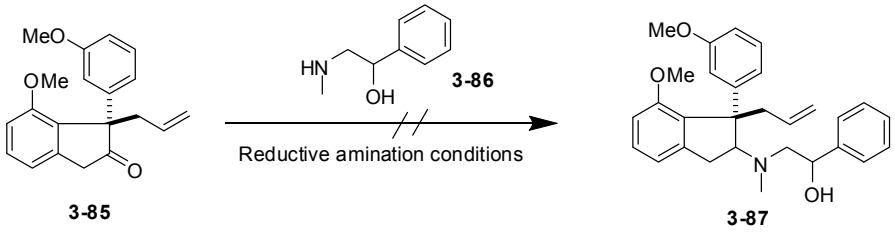
At this stage, it was clear that a more steric-tolerant strategy was needed to construct the congested tetrahydropyridine core. Inspired by Weinreb and co-worker's formal synthesis of haouamine A,[141] we decided to utilize an intramolecular aldol reaction for the central ring formation (**3-83** to **3-82**, Scheme 60). The keto-aldehyde **3-83** could be prepared from a reductive amination reaction between amine **3-84** and ketone **3-85**.

Scheme 60 2nd Generation retrosynthetic analysis



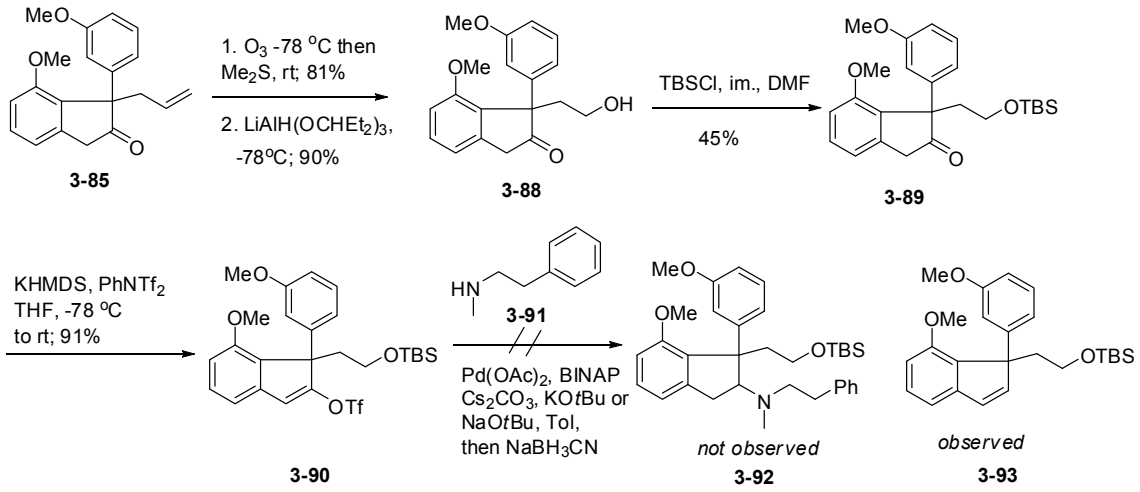
The feasibility of the key reductive amination step was tested on a model system (**3-85**[143] and **3-86**, Scheme 61). However, no desired product was observed even under forcing conditions (e.g., heating with Ti(*i*PrO)$_4$). In most cases, starting material **3-85** was recovered, presumably due to the steric hindrance around the ketone moiety.

Scheme 61 Reductive amination on model ketone **3-85**



An alternative method for reductive amination is transition metal catalyzed C-N cross-coupling.[146] Towards this end, we prepared the enol triflate of **3-85** but found that the allyl group had a detrimental effect on the palladium-catalyzed C-N cross coupling reaction, possibly due to an intramolecular Heck reaction. Therefore, the allyl group was replaced with a protected alcohol (Scheme 62), and secondary amine **3-91** was chosen as the coupling partner. Unfortunately, no desired product **3-92** was observed. In fact, reduction product **3-93** was isolated, suggesting the system was too congested to accept the nitrogen nucleophile.

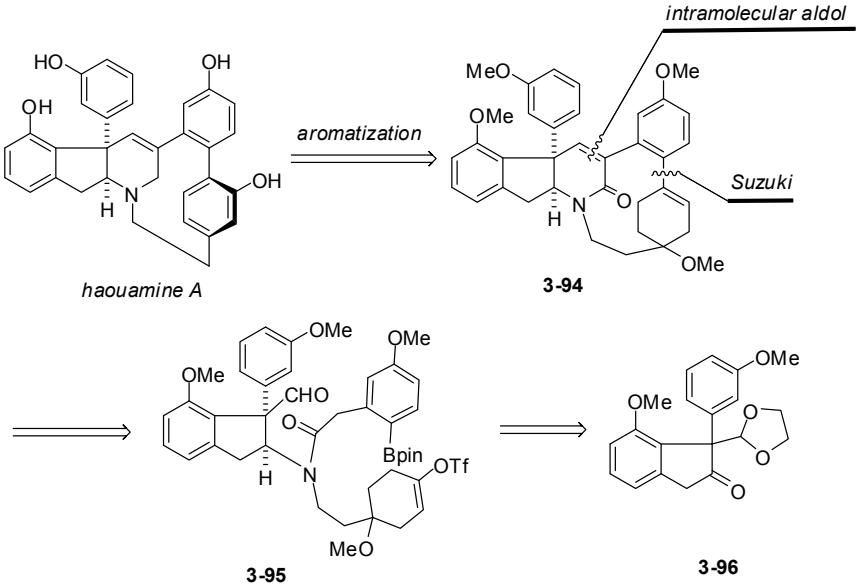
Scheme 62 Palladium-catalyzed C-N cross-coupling on model system **3-90**



3.2.3 3rd Generation Approach: Intramolecular Aldol and Suzuki Cyclization

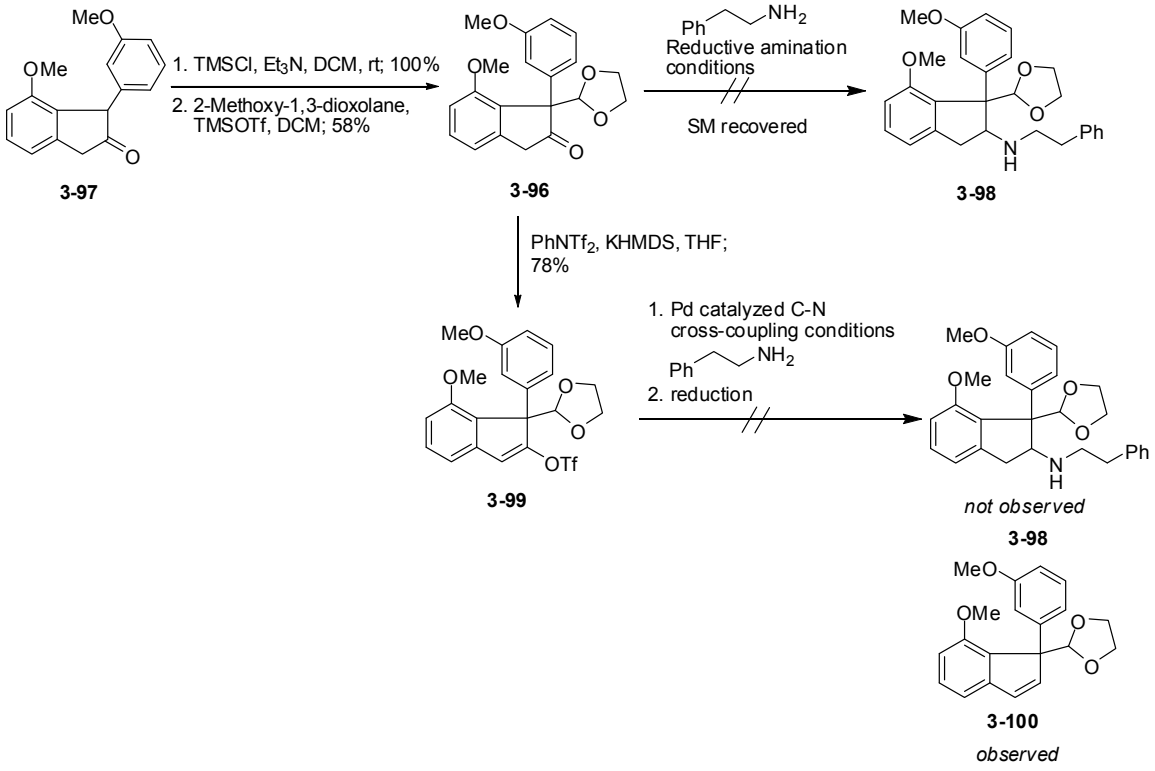
In order to address the problem associated with the reductive amination strategy, we decided to reduce the size of the nitrogen nucleophile by using a primary amine. As shown in Scheme 63, haouamine A could be simplified via our aromatization strategy to give **3-94**, which in turn could be made by means of an intramolecular aldol reaction and a Suzuki cyclization from **3-95**. Amide **3-95** would be prepared from ketone **3-96**.

Scheme 63 3rd Generation retrosynthetic analysis



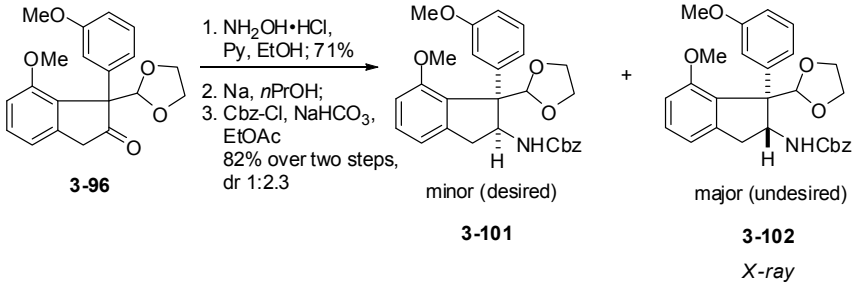
Ketone **3-96** was prepared by a Mukaiyama aldol reaction between **3-97**[143] and 2-methyoxy-1,3-dioxolane (Scheme 64). Subsequent reductive amination or C-N cross-coupling with phenethylamine proved to be difficult. In the case of C-N cross-coupling, the reduced product **3-100** was isolated.

Scheme 64 Attempted functionalization of **3-96** with phenethylamine



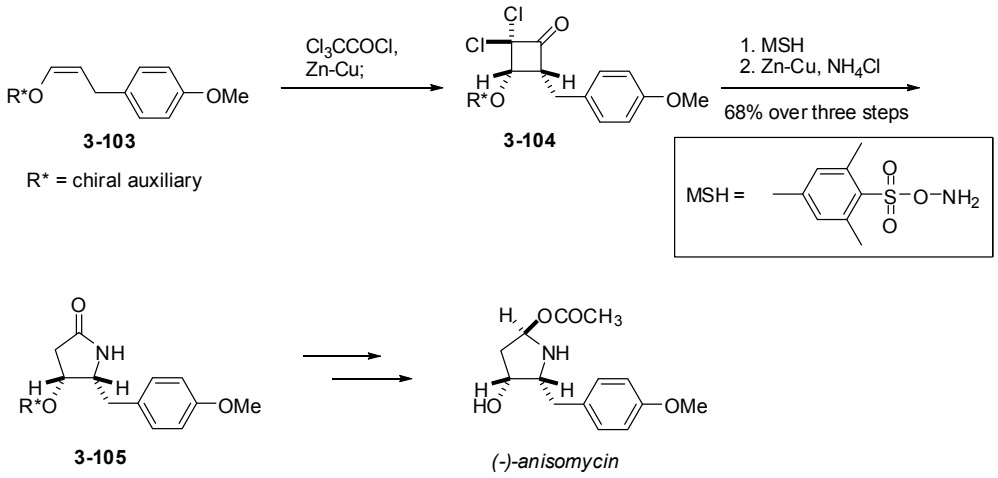
Logically, one could address the steric hindrance issue with a smaller nitrogen source, i.e. an ammonia equivalent. We chose to use an oxime intermediate (Scheme 65). Condensation of ketone **3-96** with hydroxylamine was followed by dissolving metal-reduction and Cbz protection to provide **3-101** and **3-102** in a diastereomeric ratio of 1:2.3). An X-ray analysis of major diastereomer **3-102** demonstrated the undesired *trans*-relationship between the acetal and the nitrogen moieties.

Scheme 65 Functionalization of ketone **3-96** with oxime formation/reduction



Next we needed to address the diastereoselectivity issue. The Greenè group developed a novel methodology to prepare five-membered lactam rings.[147-149] For example, in a total synthesis of (-)-anisomycin, Greenè et al. performed a [2+2] cycloaddition between the *in situ* generated dichloroketene and enol ether **3-103** to generate cyclobutanone **3-104** (Scheme 66).[147] Treatment of **3-104** with MSH effected a smooth Beckmann rearrangement to insert a nitrogen atom into the α-position of the ketone moiety with exclusive regioselectivity and retention of configuration at the adjacent stereocenter. The geminal dichloro moiety was reduced with zinc-copper couple to provide lactam **3-105**, which was further transformed into (-)-anisomycin.

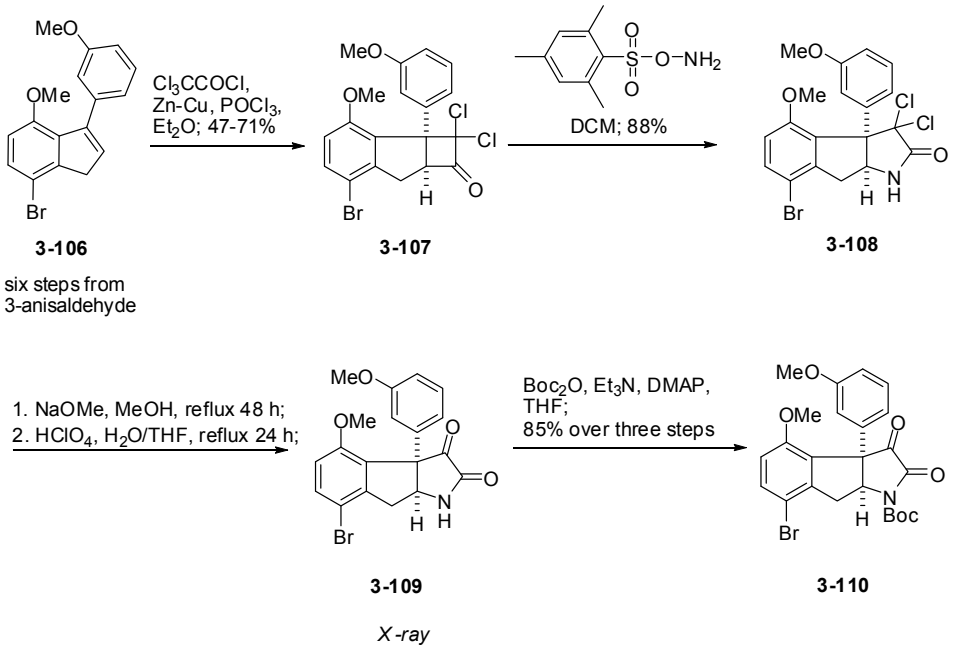
Scheme 66 Greenè's synthesis of (-)-anisomicin



We envisioned that the [2+2] cycloaddition and Beckmann rearrangement sequence was a perfect method to double-functionalize an olefin to provide β-amino aldehyde **3-95** in Scheme 63. The dichloroketene is both compact and highly energized to react with sterically congested systems. The subsequent Beckmann rearrangement has sufficient driving force through strain relieved from the cyclobutanone. In addition, it operates on the carbonyl group that is distant to the quaternary center, minimizing the steric interactions. Thus, we constructed olefin **3-106**[143,150] and subjected it to the cycloaddition reaction conditions. Gratifyingly, cyclobutanone **3-107** was obtained in good to moderate yield.[151] The Beckmann rearrangement proceeded in excellent

yield, providing **3-108** as a single regioisomer. The hydrolysis of the geminal dichloro moiety proved to be difficult due to the adjacent congested quaternary carbon. Eventually, it was found that an indirect hydrolysis via a dimethyl acetal intermediate followed by heating with perchloric acid was feasible. Despite the harsh conditions, product **3-109** was sufficiently clean without purification. In fact, **3-109** crystallized spontaneously from the crude product mixture to provide an X-ray quality crystal. Subsequent X-ray analysis confirmed the desired relative stereochemistry. Protection of the nitrogen in **3-109** with a Boc group provided α-keto lactam **3-110** in excellent overall yield.

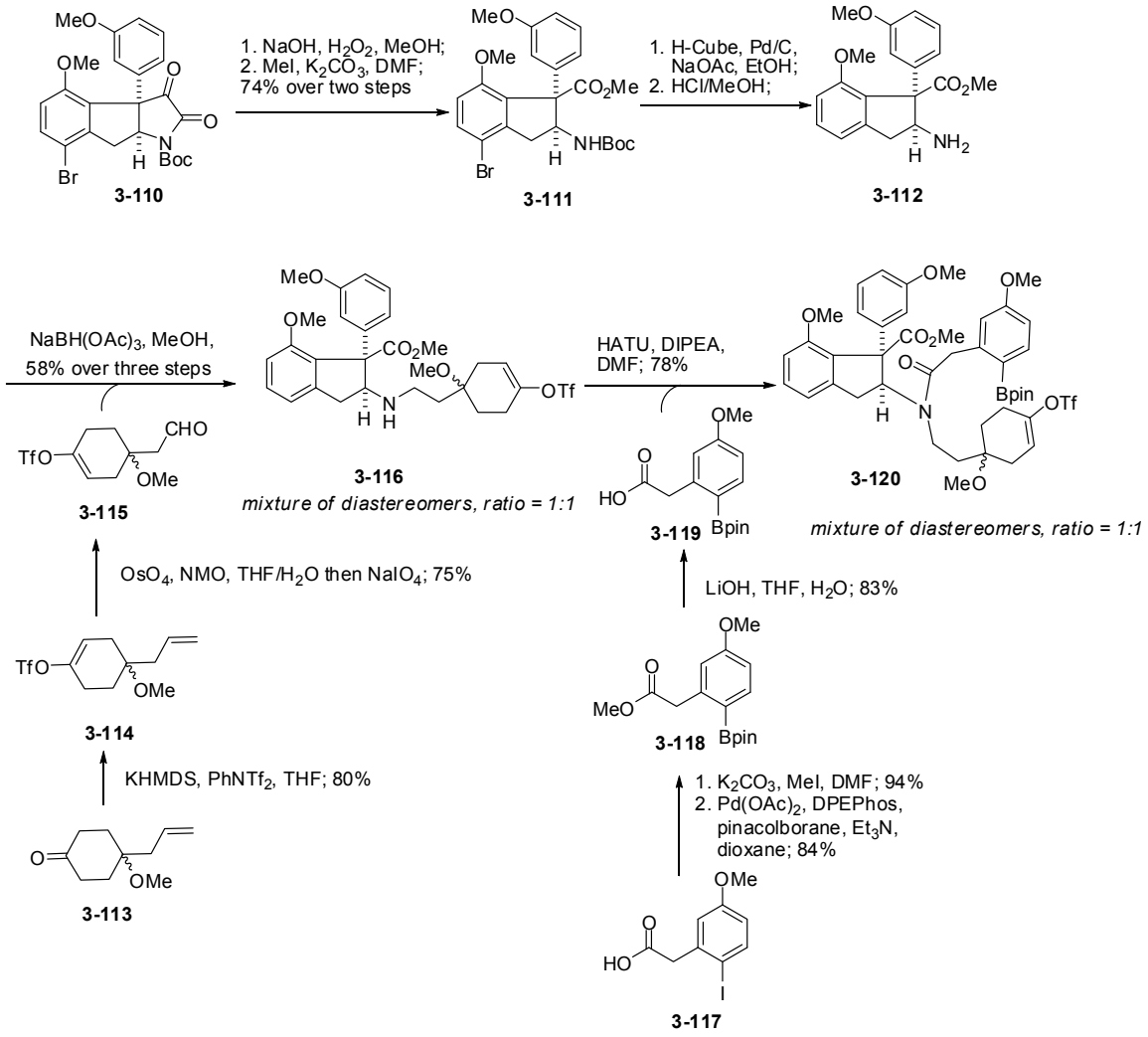
Scheme 67 Dichloroketene cycloaddition, Beckmann rearrangement and hydrolysis to intermediate **3-110**



Compared to β-amino aldehyde **3-95,** lactam **3-110** has one additional carbon. Thus, the next step was a hydrolytic decarboxylation reaction,[152-156] yielding a Boc-protected β-amino acid, which was masked as a methyl ester (**3-111**, Scheme 68). β-Amino acid **3-111** was then transformed into primary amine **3-112** via N-deprotection with HCl and debromination under hydrogenation conditions. Reductive amination of **3-112** with racemic aldehyde **3-115** (prepared

in two steps from **3-113**[129]) provided **3-116** as a 1:1 mixture of diastereomers. The two diastereomers were not separable by chromatography on SiO_2, and consequently we carried the mixture through the synthesis. Ultimately, one of them would lead to haouamine A whereas the other one would lead to atrop-haouamine A.

Scheme 68 Synthesis of substrate **3-120** for the Suzuki cyclization

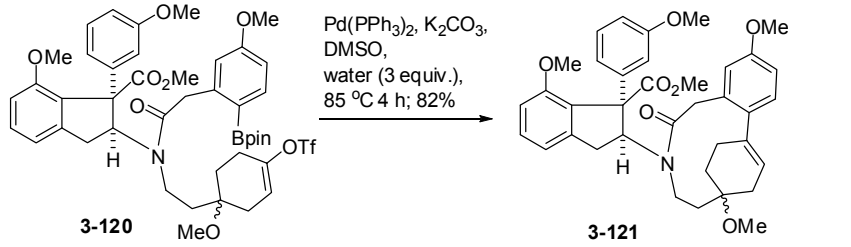


The next step was the acylation on the secondary amine. The acyl coupling partner **3-119** was prepared from iodo-3-methoxylphenylacetic acid **3-117**[129] in three steps. It is of particular interest that the pinacolboronic ester survived the saponification reaction to give crude **3-119** in high yield and purity. Despite the hindered nature of the secondary amine in **3-116**, its acylation

with **3-119** under peptide coupling conditions proceeded smoothly to provide **3-120** in excellent yield.

We were now at the stage of our first key cyclization (Scheme 69). The intramolecular Suzuki cyclization was found to work with remarkable efficiency (82% yield) as well as excellent scalability and reproducibility.[157] The key to the success of this reaction lies in the addition of water.[158-159] The initial experiment was performed without water. The reaction took 8 h and the yield was ~40%. We then experimented with adding 1, 2, 3 and 4 equivalents of water and saw a steady increase in reaction rate and yield until we added 4 equivalents of water, where the yield dropped to ~60%. Possible explanations for the water acceleration effect include acceleration of the transmetallation step with hydroxyl anions produced by water reacting with the base, or hydrolysis of the boronic ester to the acid before the transmetallation occurs. In the case of excess water, protodeboronation might become prevalent. This would be detrimental to the yield, since in our system the ratio of the two coupling components was kept strictly at 1:1, whereas most intermolecular Suzuki reactions are performed with an excess of the boronic acid.

Scheme 69 Suzuki cyclization



3-120 *mixture of diastereomers, ratio = 1:1*

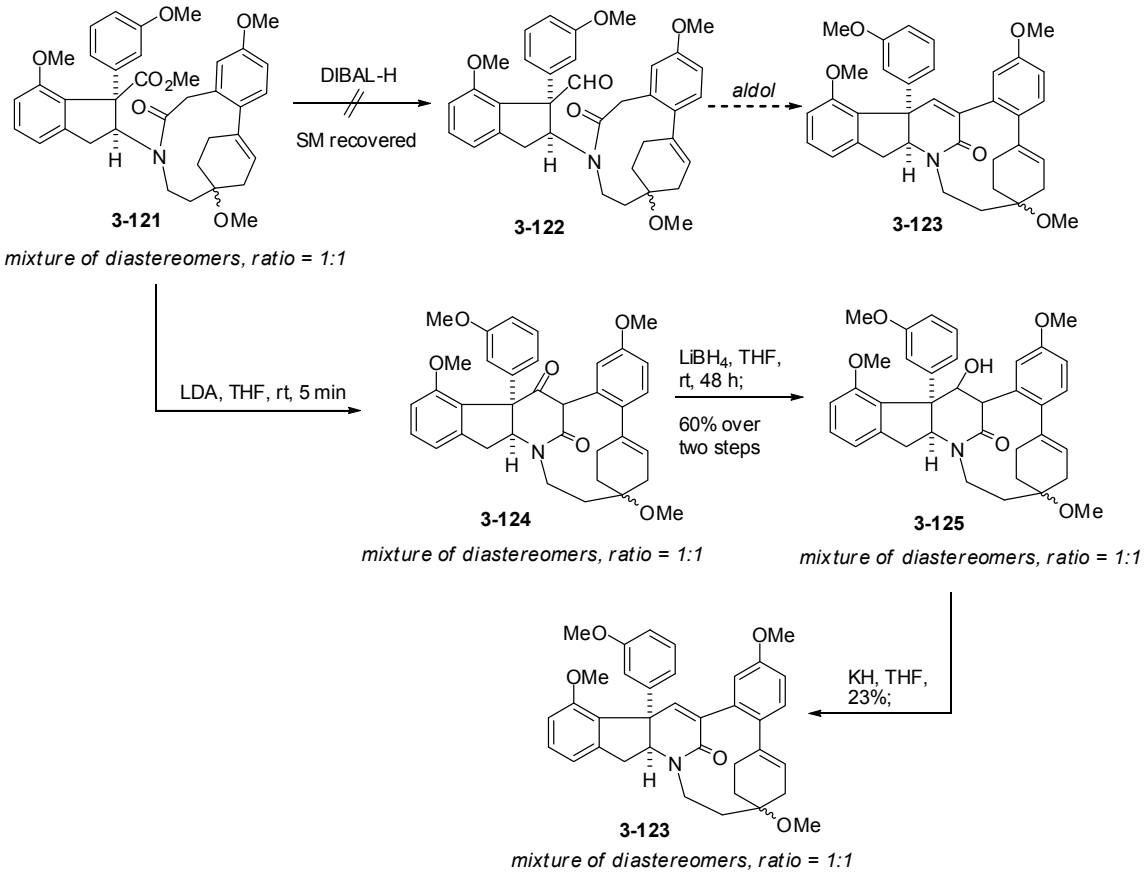
3-121 *mixture of diastereomers, ratio = 1:1*

With the desired macrocycle in hand, we set out to perform our next key cyclization reaction: the intramolecular aldol condensation (Scheme 70). Our initial attempt to directly reduce the ester functionality in **3-121** to aldehyde **3-122** was met with failure (starting material was recovered). We reasoned that steric hindrance at the neopentyl position was the cause.

Similarly, attempts to saponify the ester failed even at high temperatures (LiOH, 100 °C in sealed tube).

Alternatively, the intramolecular reaction (Dieckmann condensation) of **3-121** proceeded smoothly to provide ketoamide **3-124**. Reduction of the keto moiety with lithium borohydride was sluggish but provided alcohol **3-125** in good overall yield.

Scheme 70 Intramolecular aldol and Dieckmann condensation approaches to the tetrahydropyridine core

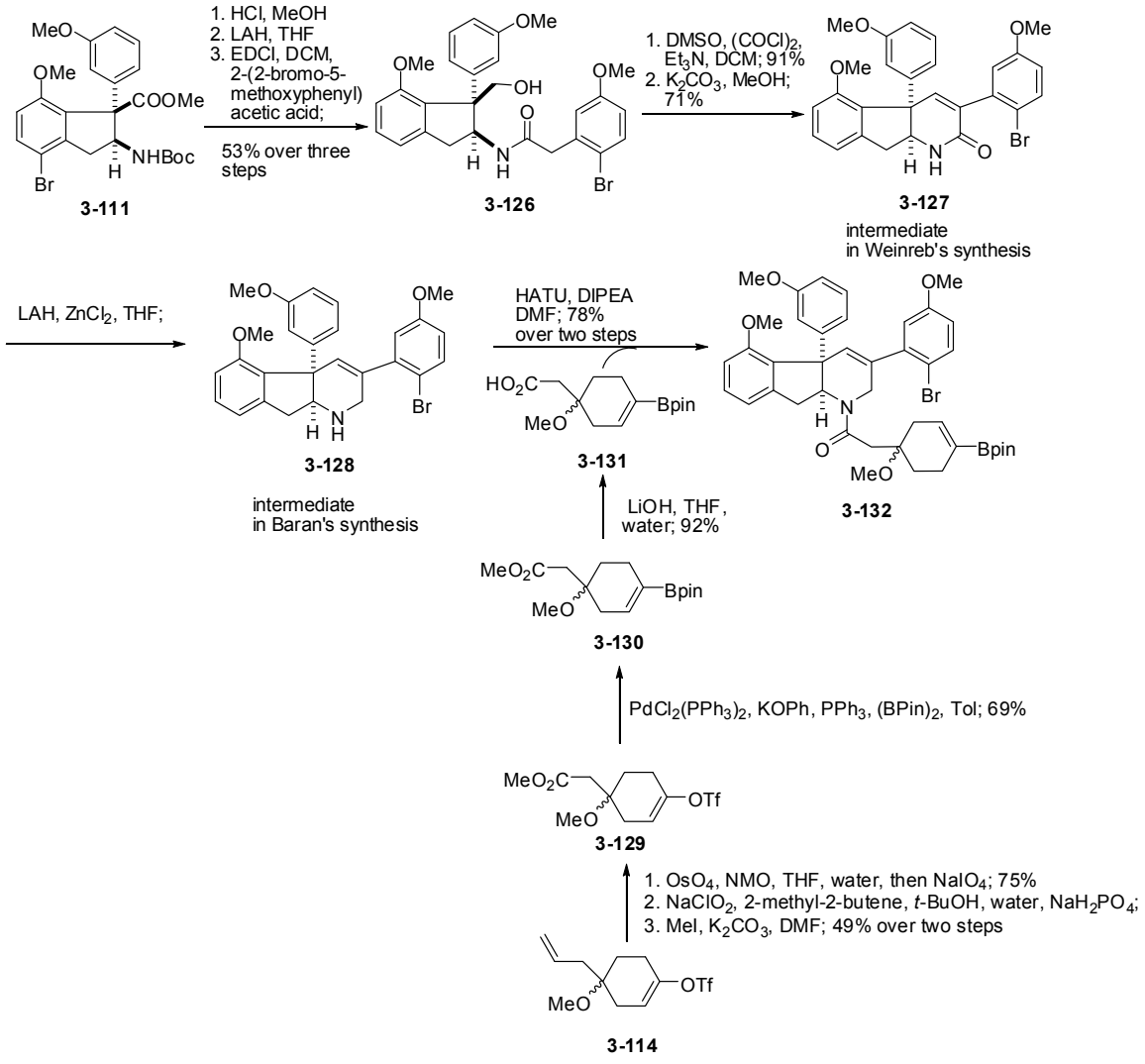


The elimination of the secondary hydroxyl group to generate dihydropyridone **3-123** proved to be challenging. Conditions screened include heating with an acid or weak base, $SOCl_2/POCl_3$, Martin Sulfurane and Burgess Reagent. We also attempted to activate the hydroxyl group with a mesylate, brosylate, acetate, triflate, phosphoramide and methyl group. All hydroxy functionalization met with failure. When heated with magic methyl or methyl

triflate, elimination of the methoxyl group on the cyclohexene ring was observed. Once again, the steric congestion might have played a role here. Finally, we found the reaction could be effected with KH, albeit with diminished yield (23%). Moreover, among all intermediates shown in Scheme 70, none of the diastereomers could be isolated by chromatography on SiO_2 without significant loss of material.

Consequently, we decided to make a major modification to our synthetic strategy. Because operations on the dihydropyridone core were difficult when the macrocyclic system was present, we decided to install the core ring prior to the Suzuki cyclization reaction (Scheme 71).

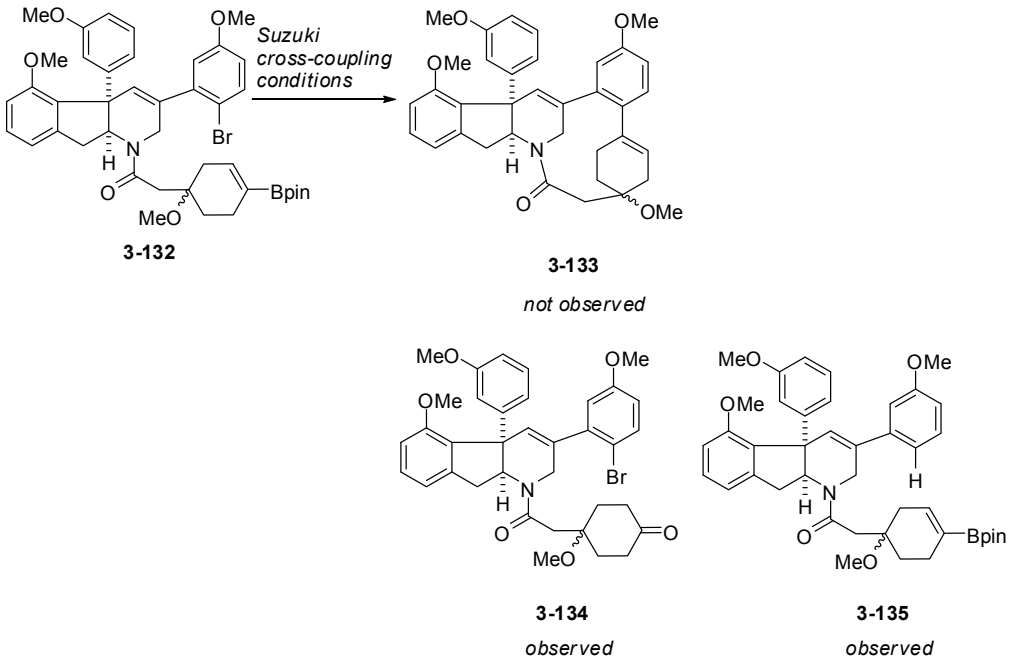
Scheme 71 Preparation of the substrate for Suzuki cyclization with preinstalled tetrahydropyridine core



Common intermediate **3-111** was reduced to a primary alcohol. Subsequent acylation on the nitrogen provided amide **3-126**. Transformation of **3-126** to tetrahydropyridine **3-128** is known,[141] although we replaced the Dess-Martin oxidation with a Swern reaction due to better reproducibility. The spectroscopic data of **3-127** matches that in the literature.[141] Acylation of **3-128** with acid **3-131** provided the substrate for the Suzuki cyclization.

When **3-132** was subjected to Suzuki cross-coupling conditions, the desired product was not obtained (Scheme 72). Instead, ketone **3-134** was isolated in low yield. When oxygen was vigorously excluded and the temperature was increased to 160 °C in order to make the amide bond freely-rotating, trace amounts of debromination product **3-135** were observed. This indicates that the oxidative addition of the aryl bromide to palladium was successful, but subsequent transmetallation did not occur.

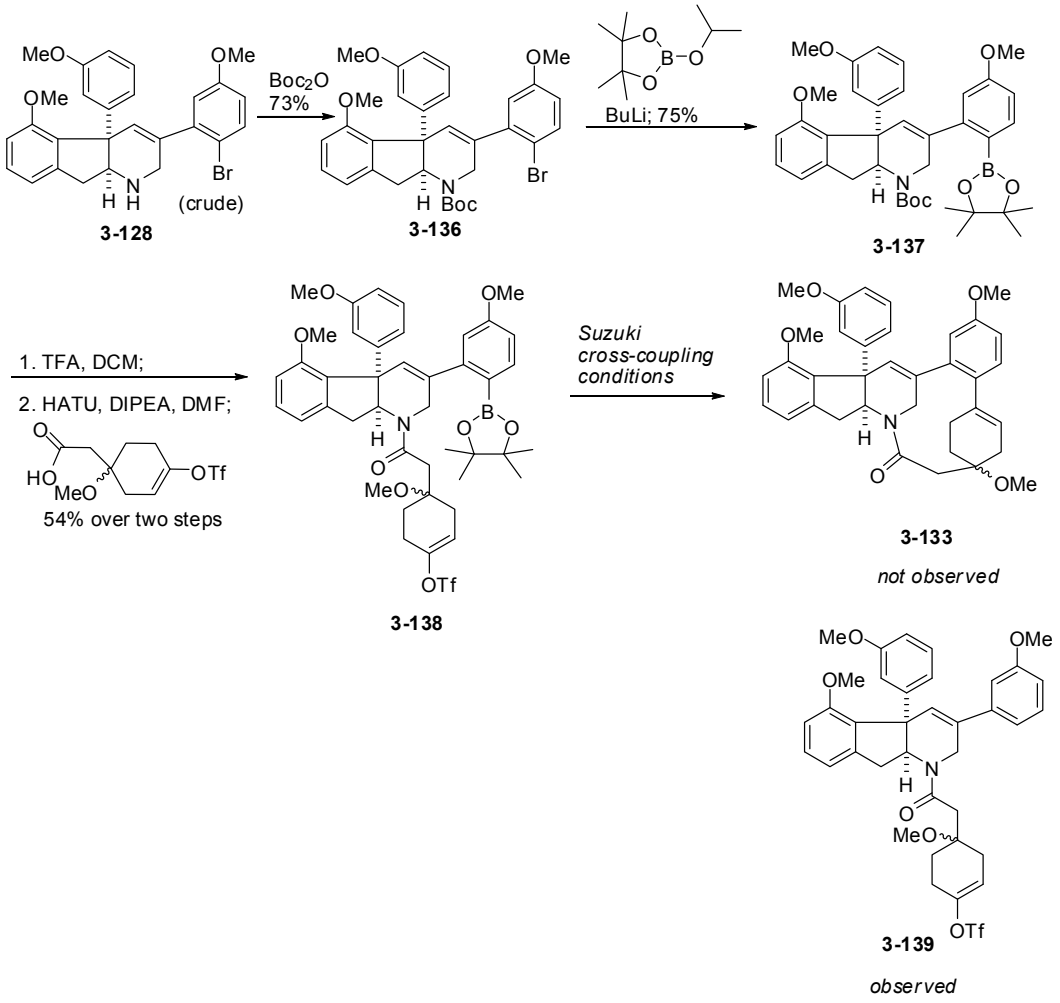
Scheme 72 Attempted Suzuki cyclization of **3-132**



Similarly, a system (**3-138,** Scheme 73) which more closely resembled our successful Suzuki cyclization system **3-120** did not yield any desired product. Protodeboronation product **3-**

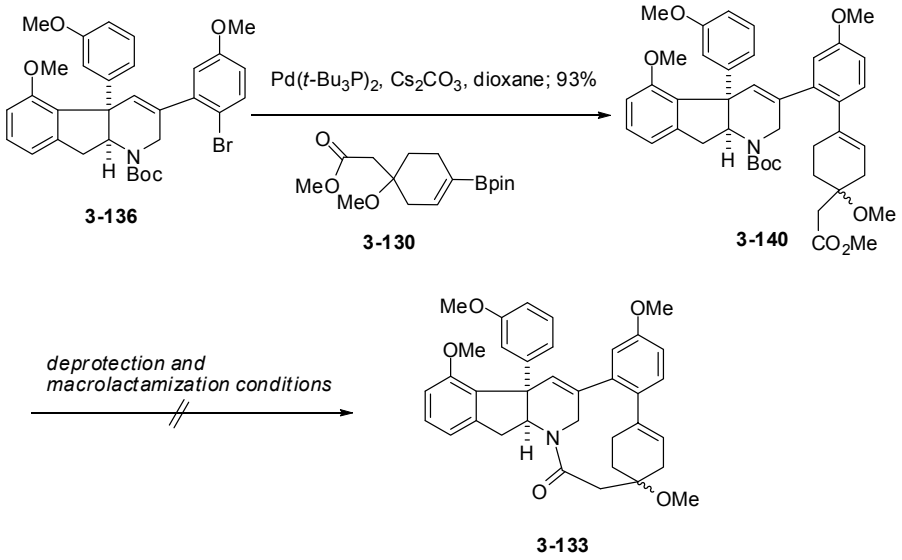
139 was isolated in good yield. One possible explanation is that the steric interaction between the pinacolboronic ester and the tetrahydropyridine core forces the boron out of conjugation with the aromatic ring, weakening the B-C bond.

Scheme 73 Attempted Suzuki cyclization of **3-138**



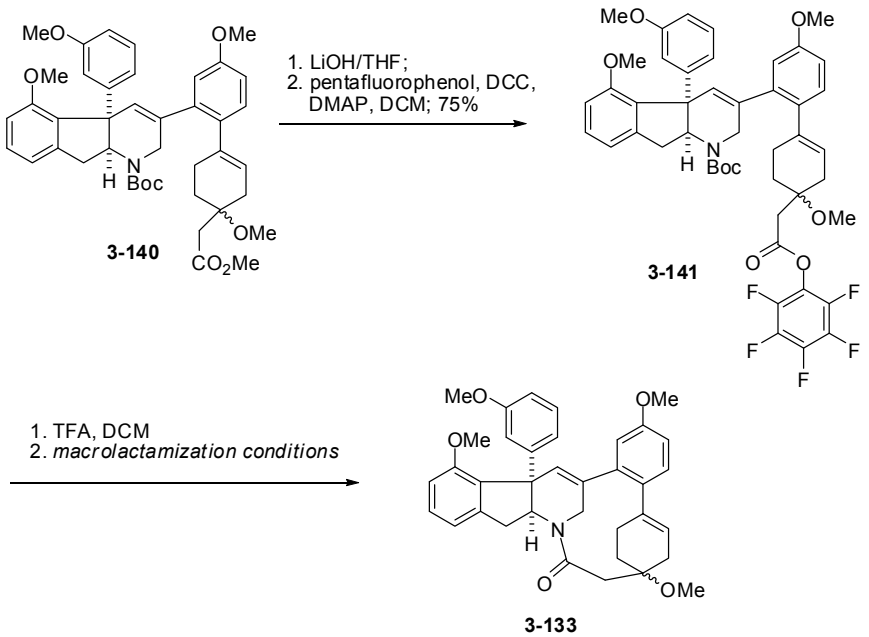
We also explored a macrolactamization approach (Scheme 74). Suzuki cross-coupling between **3-136** and **3-130** afforded protected amino acid **3-140**. Subsequent deprotection and macrolactamization failed to provide any desired macrocycle. In all cases decomposition was observed.

Scheme 74 Preparation of **3-133** via a macrolactamization approach



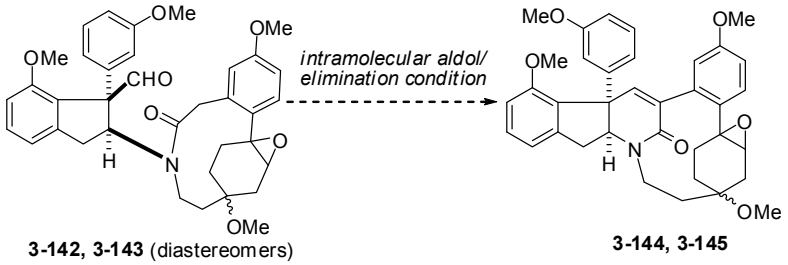
We decided to explore the macrolactamization approach more exhaustively by using a pentafluorophenyl ester **3-141**. Boc removal of **3-141** was followed by heating with 4-pyrrolidinopyridine at up to 150 °C under microwave irradiation. We observed no desired product. Instead, dimerization occurred.

Scheme 75 Macrolactamization with pentafluorophenyl ester **3-141**



At this stage, another major overhaul of our synthetic strategy was clearly needed. We believed the failure of our previous approaches could be partly attributed to the rigid nature of our intermediates (e.g., fused rings with conjugated sp^2 centers), which might prevent the molecule from accommodating incoming reagents. In addition, the products are potentially strained, disfavoring the process. In order to "relax" the molecule, we decided to convert some of the sp^2-hydridized centers in our intermediates to sp^3-hydridized centers (Scheme 76). In this design, the cyclohexene moiety would be epoxidized prior to the formation of the core ring, eliminating two sp^2-hybridized centers.

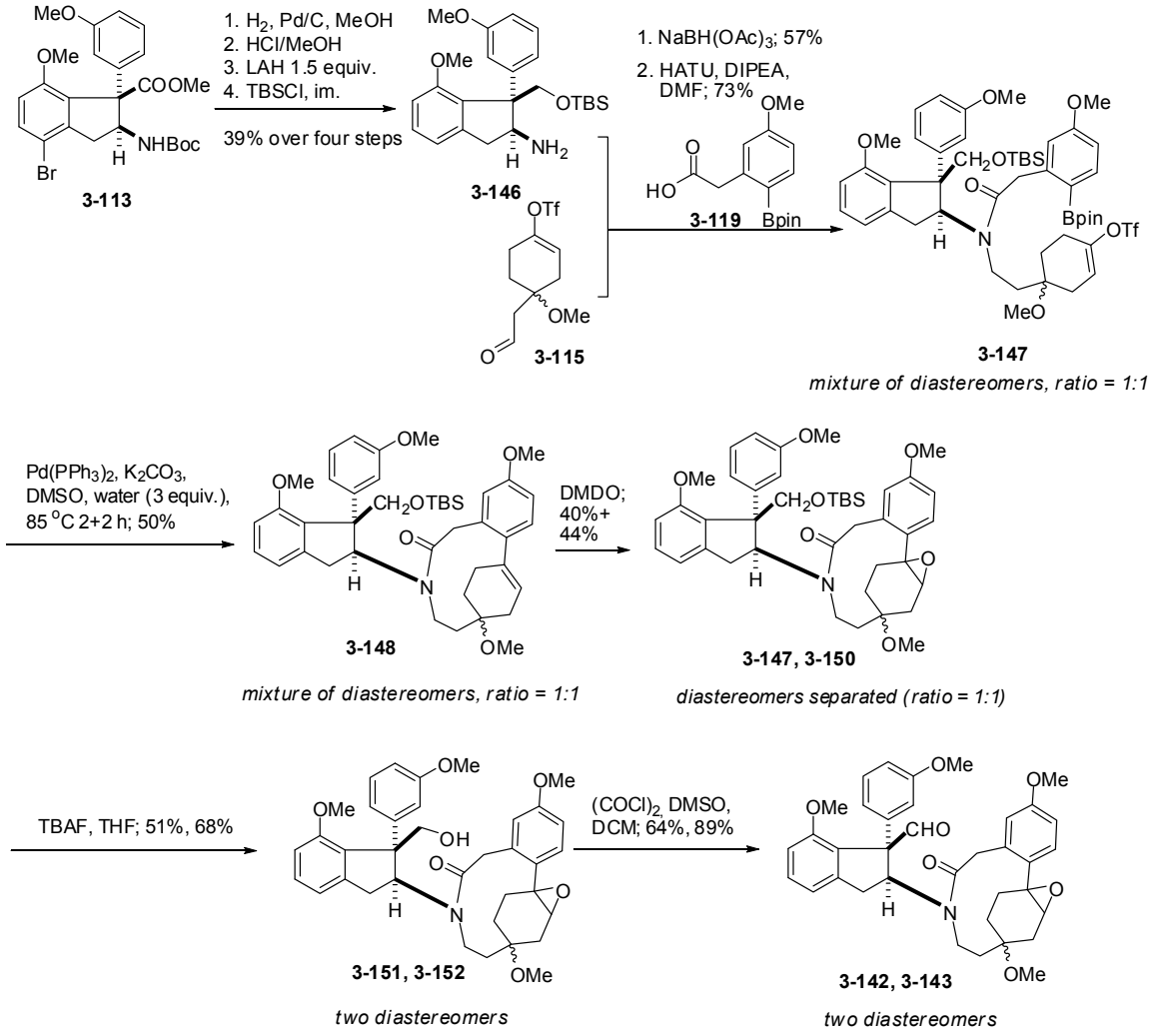
Scheme 76 Intramolecular cyclization with an epoxide substrate



3-142, 3-143 (diastereomers) **3-144, 3-145**

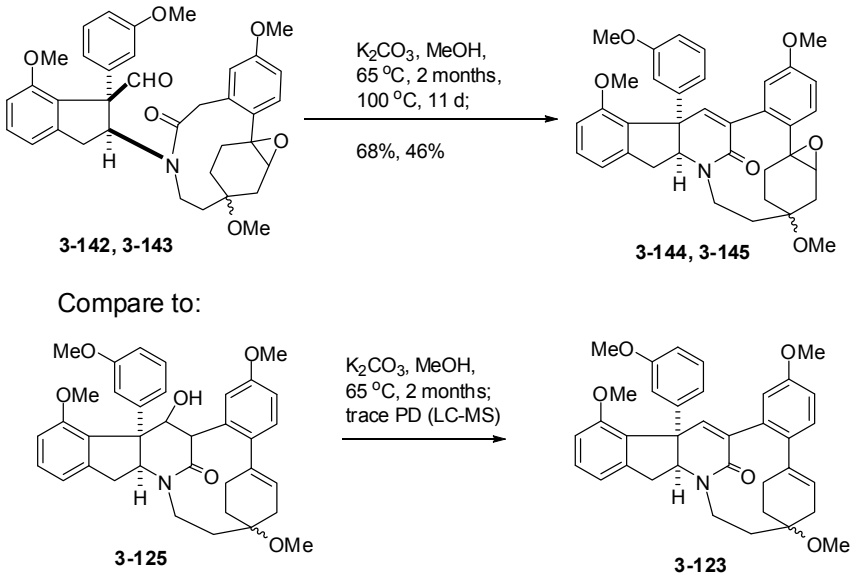
Accordingly, we synthesized substrate **3-142** and **3-143** using our established Suzuki cyclization process (Scheme 77). After the epoxidation of the macrocycle **3-148**, the two diastereomers **3-149** and **3-150** were separated by chromatography on SiO_2. They were carried through the synthesis individually as denoted by the two yields for each subsequent step. Desilylation of **3-149** and **3-150** was followed by a Swern oxidation to provide aldehydes **3-142** and **3-143**. Interestingly, in the Swern oxidation, one diastereomer reacted cleanly, while the other afforded a minor chlorination byproduct, resulting in a lower yield.

Scheme 77 Preparation of epoxide substrates for intramolecular aldol condensation



With the two aldehydes in hand, we set out to cyclize them under the aldol conditions (Scheme 78). One diastereomer was heated to 65 °C for two months to afford the desired product in 68% yield. The other diastereomer was then heated to 100 °C for 11 d to give the desired product in 46% yield. As a comparison, under the same conditions, the more rigid cyclohexene analogue **3-125** yielded only trace amounts of product **3-123**.

Scheme 78 Intramolecular aldol reaction on epoxidized substrates

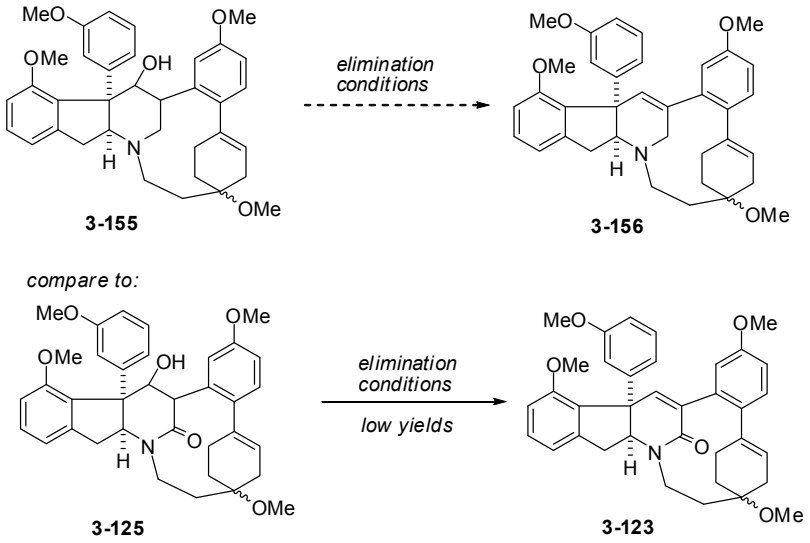


We were pleased by the success of our alternative strategy, but there was a need for further improvement as the key intranolecular aldol step was sluggish. This led to the 4th generation approach.

3.2.4 4th Generation Approach: Intramolecular Aldol/Dieckmann Condensation on a Less Strained System

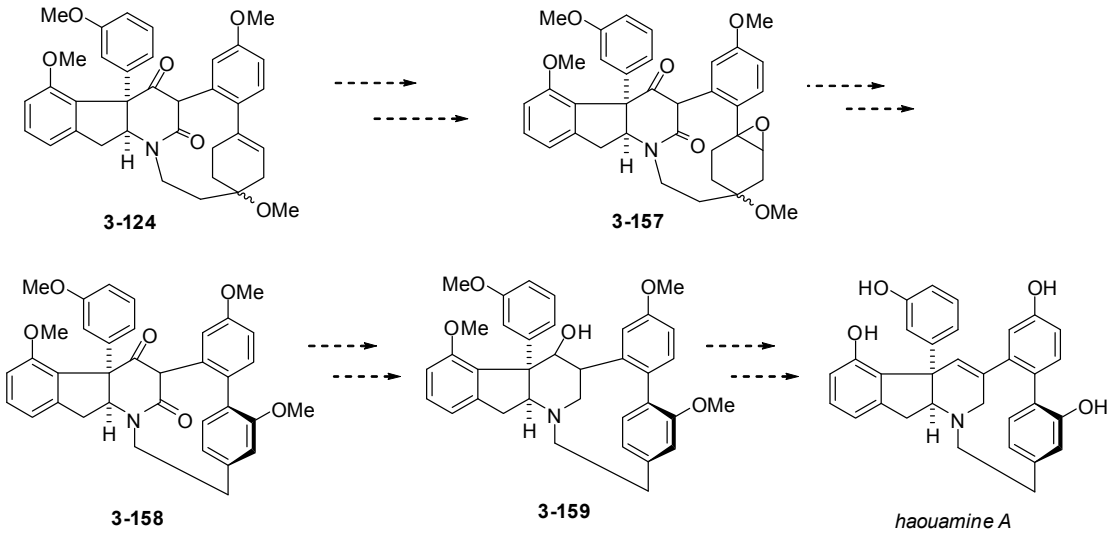
In order to have a more pronounced strain-release effect, we considered reducing the amide moiety in **3-125** to an amine (**3-155**) prior to the elimination step (Scheme 79). By removing the amide sp^2-hydridized center and its conjugation to the nitrogen, we expected to see a more flexible core ring; thus easing the elimination step to form two new sp^2-hybridized centers.

Scheme 79 Releasing strain in the molecule by reducing the amide moiety to an amine



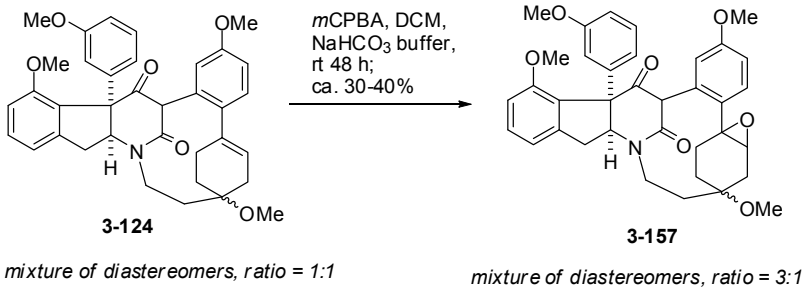
However, there was a technical challenge associated with this route. The subsequent aromatization step would require two oxidation steps that are incompatible with the tertiary amine moiety. Consequently, we decided to postpone the reduction of the amide moiety until after the aromatization step (Scheme 80). Cyclohexene **3-124** would be epoxidized and aromatized to the aza-paracyclophane **3-158**. Reduction of the amide moiety would afford the hydroxylpiperidine **3-159**. Elimination and deprotection would provide haouamine A.

Scheme 80 4th Generation synthetic plan



We started with the epoxidation of our previously synthesized ketoamide **3-124** (Scheme 81). Surprisingly, only one diastereomer exhibited normal reactivity (i.e., 100% conversion after ~ 5 h at room temperature). The other diastereomer reacted at a much slower rate (~ 48 h). This led to the decomposition of the products during the reaction, diminishing the yield. In addition, we could not separate the product from the starting material by chromatography on SiO_2, nor could we separate the diastereomers of **3-124** without significant loss of material.

Scheme 81 Epoxidation of **3-124**



3-124

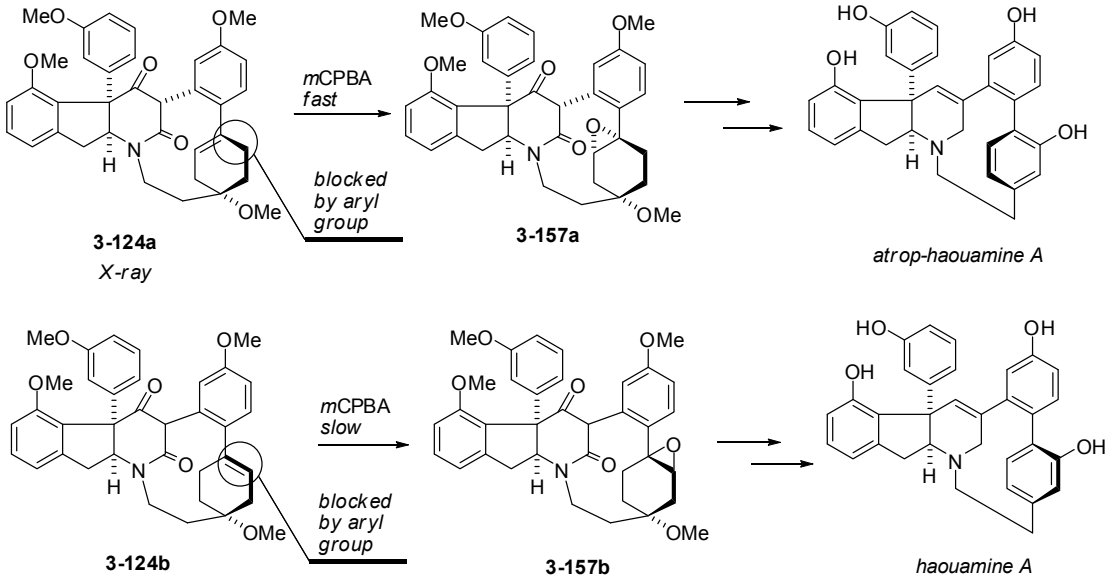
mixture of diastereomers, ratio = 1:1

3-157

mixture of diastereomers, ratio = 3:1

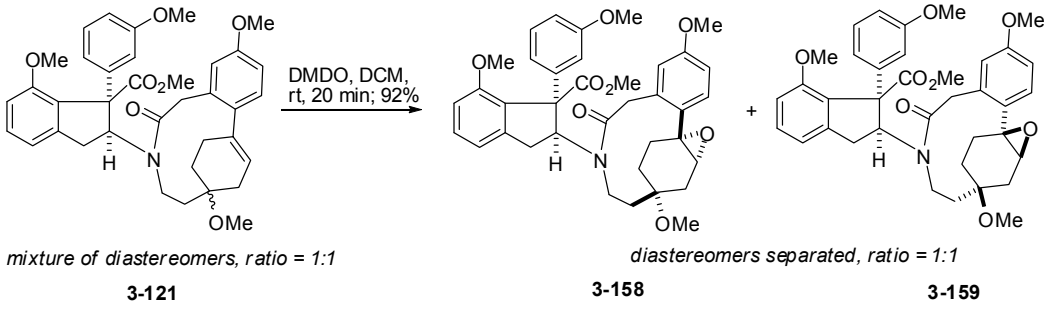
The observed differential reactivity of the two diastereomers was intriguing and coincided with the results shown in Scheme 77. We decided to investigate this problem further. After repeated chromatography, the diastereomers of **3-124** were resolved. An X-ray analysis of the diastereomer that reacted rapidly in the epoxidation reaction demonstrated a dihedral angle of 53° at the aryl-cyclohexene junction. This observation indicates that the aryl system is not perpendicular to the cyclohexene. Assuming the other diastereomer adopts a similar conformation, the aryl group will selectively block one of the two groups on the cyclohexene unit, either the methylene or the vinyl group (Scheme 82). This results in the discrimination between the two diastereomers. In addition, the fast-reacting diastereomer **3-124a** will lead to the atropisomer of haouamine A, while the slow-reacting diastereomer **3-124b** will produce haouamine A.

Scheme 82 Comparison of reactivities of diastereomers **3-124a** and **3-124b**



A simple solution to this reactivity issue was to move back one step and use a less rigid precursor (Scheme 83). Indeed, the epoxidation of **3-121** proceeded smoothly to provide the two diastereomers in excellent yield. In addition, separation of the diastereomers was easily achieved by chromatography on SiO_2.[160]

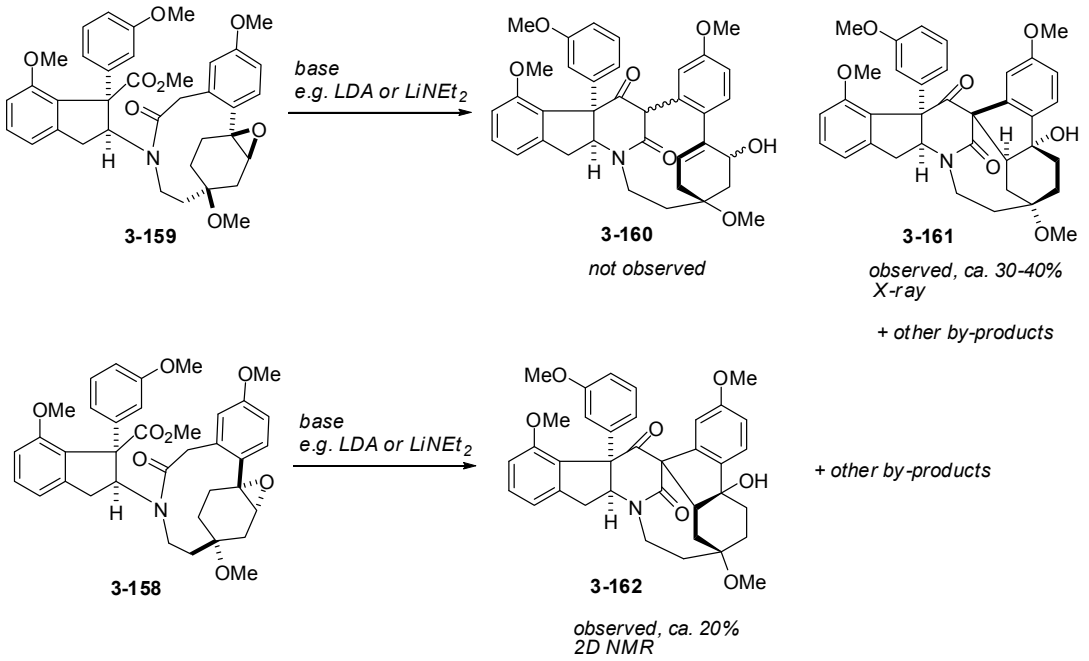
Scheme 83 Epoxidation of **3-121**



At this stage, we were uncertain about the configuration of the diastereomers. Consequently, we subjected both of them to the next set of conditions. The initial plan was to conduct a cascade Dieckmann condensation and base-promoted epoxide rearrangement to an allylic alcohol (**3-159** to **3-160**, Scheme 84). To our surprise, we obtained a mixture of products, the major one being **3-161**. The structure was elucidated with X-ray analysis and 2D NMR. We

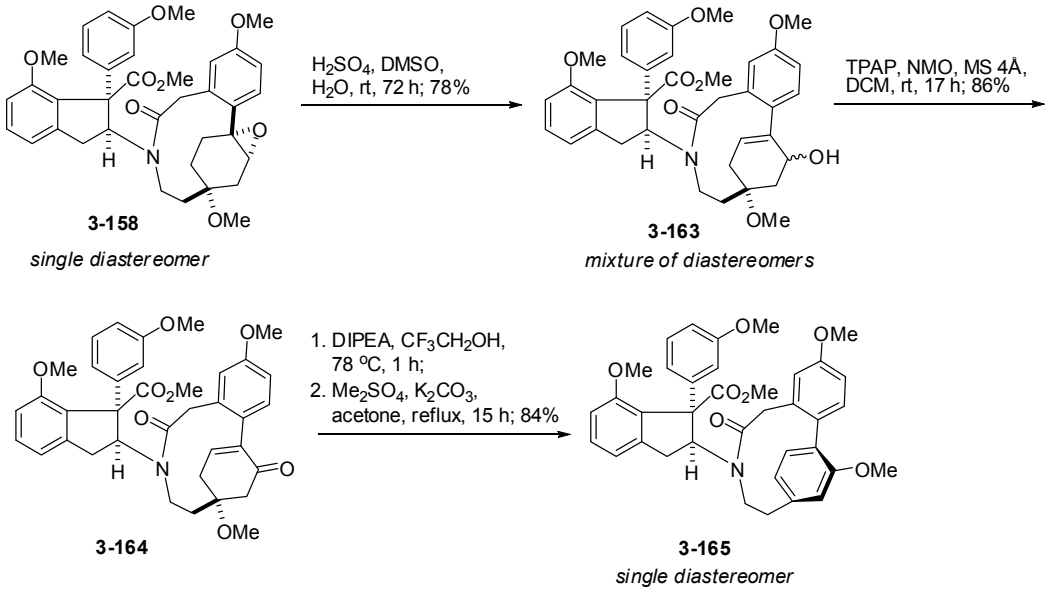
proposed a mechanism of initial Dieckmann condensation followed by an intramolecular epoxide opening with the enolate. The other diastereomer **3-158** gave a similar result.

Scheme 84 Attempted cascade of Dieckmann condensation-epoxide rearrangement



We then decided to convert the highly reactive epoxide functionality in **3-158** and **3-159** to a more inert moiety before the Dieckmann condensation, namely a methylated phenol (Scheme 85).

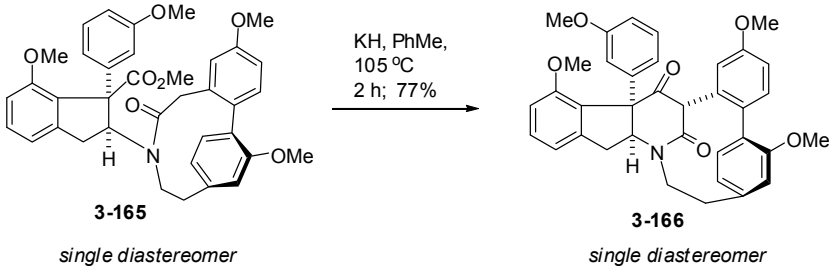
Scheme 85 Preparation of aza-paracyclophane **3-165** by aromatization reaction



Epoxide **3-158** was subjected to acidic hydrolysis conditions to provide allylic alcohol **3-163**. Oxidation of **3-163** to an enone was followed by our established aromatization process to give aza-paracyclophane **3-165** in excellent yield. Remarkably, the aromatization step required much milder conditions than in our previous model system (78 °C vs. 150 °C).

As expected, the Dieckmann condensation of aza-paracyclophane **3-165** was more difficult than the less strained **3-121**. Treatment of **3-165** with LDA at room temperature or in refluxing THF resulted in no reaction. However, when heated with KH in refluxing toluene, **3-165** was smoothly converted to the ketoamide **3-166** in good yield (Scheme 86).

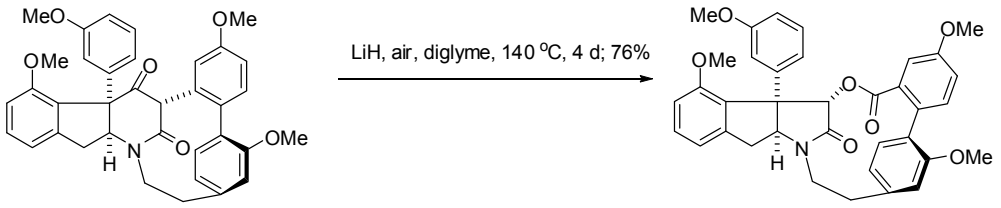
Scheme 86 Dieckmann condensation of **3-165**



The structure of **3-166** was elucidated by X-ray analysis. It clearly demonstrated a bent phenyl ring along with the correct atropisomerism. In addition, both the keto and the amide moiety sit in a deep cavity where the carbonyl carbons are completely shielded from nucleophilic attack. This prediction is in line with the experimental observations, as all attempts to reduce **3-166** failed. Conditions screened include common metal hydrides, borane/alane, thioamide formation, single electron transfer processes (e.g., dissolving metal reductions, SmI_2 etc.) and enolate trapping (vinyl triflate). In all cases the starting material was either recovered or decomposed.

As an interesting side reaction, when treated with LiH for an extended period of time, **3-166** was converted into **3-167** (Scheme 87). The structure of **3-167** was confirmed by X-ray analysis, which showed the central phenyl ring with a virtually flat conformation. Therefore, relief of the ring strain may be a driving force for this reaction. The mechanism of this transformation may resemble that of a very similar reaction found in literature,[161] with molecular oxygen being the oxidant (see appendix).

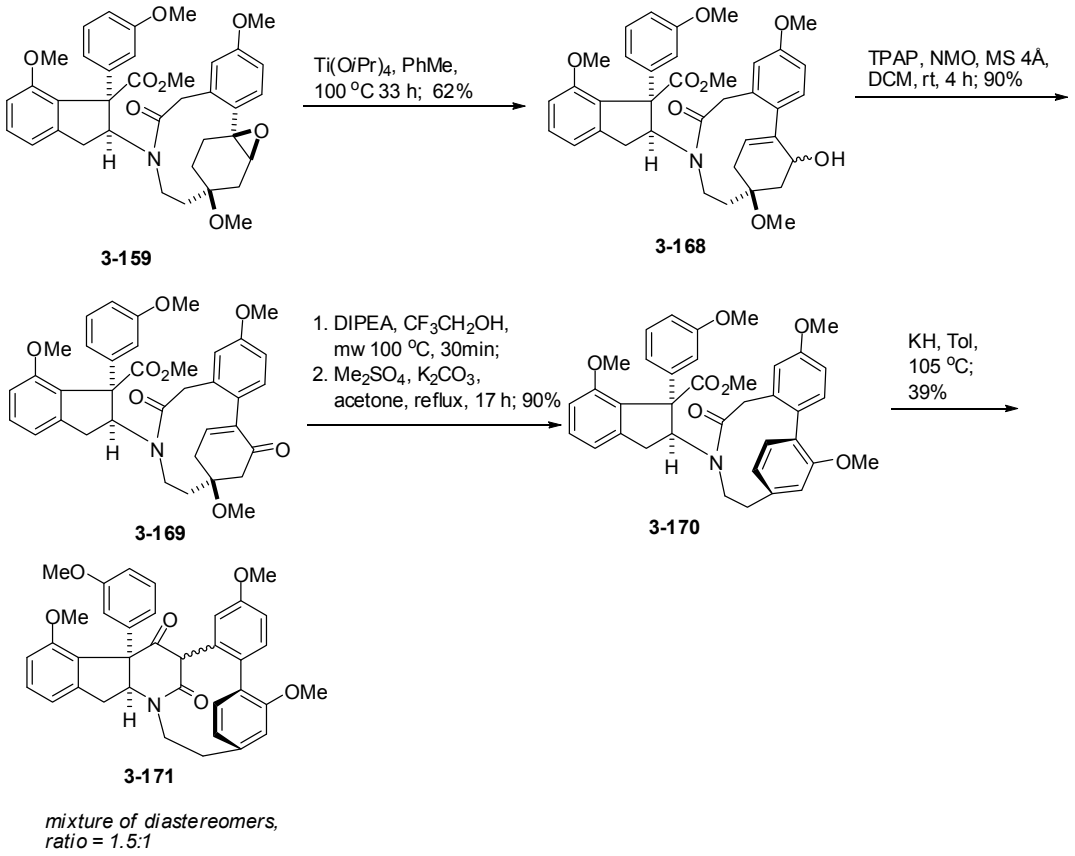
Scheme 87 "LiH oxidation" of **3-166**



3-166 **3-167**

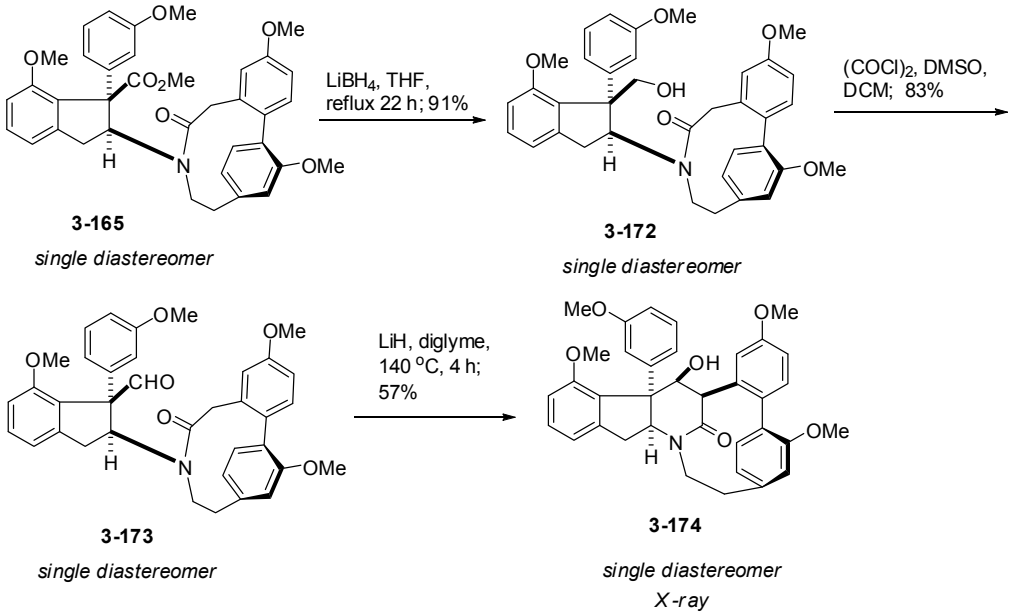
While working on haouamine A, we also briefly explored the synthetic route towards the atropisomer of haouamine A (Scheme 88). Most of the steps proceeded with comparable yields to those of haouamine A, with the exception of the Dieckmann condensation step (**3-170** to **3-171**), which was found to be low-yielding and difficult to scale-up.

Scheme 88 Aromatization and Dieckmann condensation towards atrop-haouamine A



As we encountered difficulties in the reduction of **3-166**, we considered changing the oxidation state of the neopentyl position before the cyclization step. This would allow us to bypass the reduction of a sterically encumbered center. Gratifyingly, this route turned out to be productive (Scheme 89). A two-step reduction-oxidation sequence converted ester **3-165** to aldehyde **3-173**. The key intramolecular aldol reaction provided **3-174** in 57% yield.

Scheme 89 Intramolecular aldol reaction to **3-174**



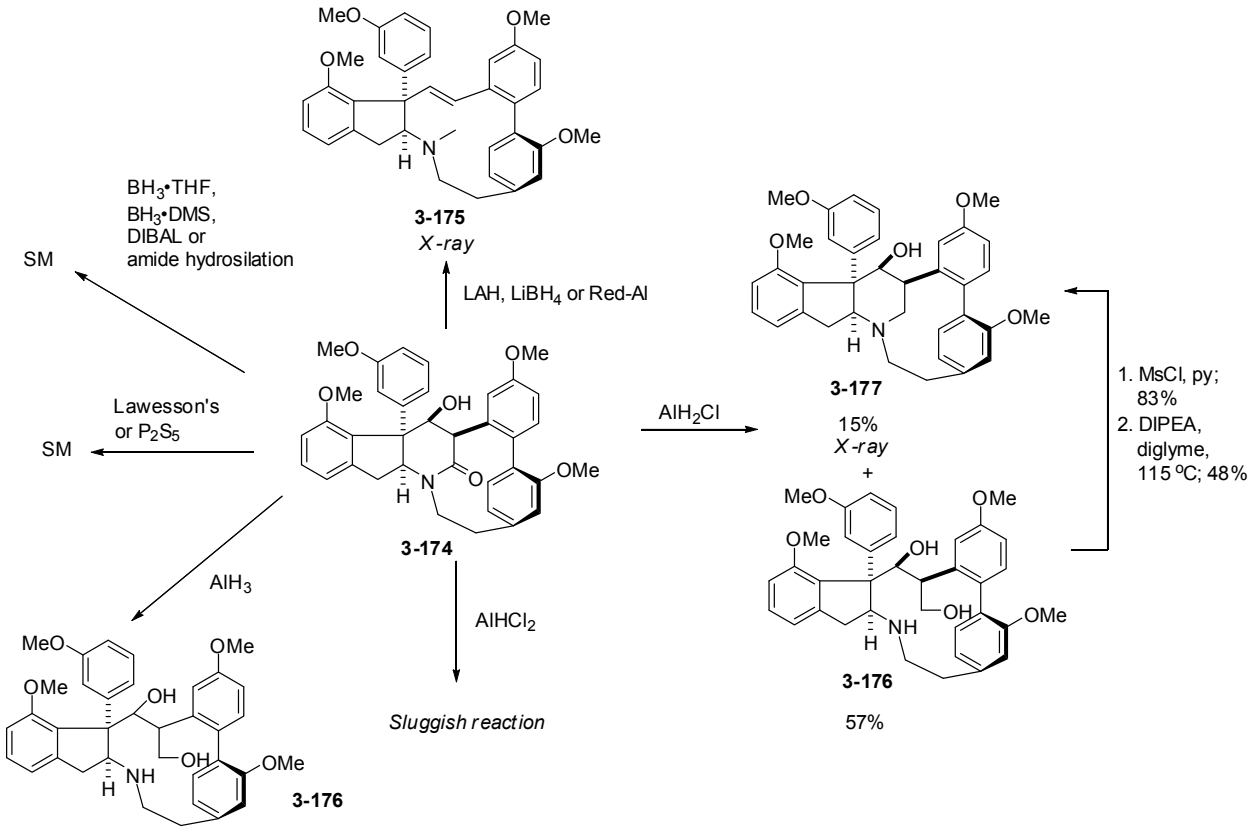
The structure of **3-174** was confirmed by X-ray analysis. Both the hydroxyl and amide groups are exposed in a more open cavity than in **3-166**, which might make subsequent transformations more feasible.

Despite the promising conformation observed in the X-ray analysis, the reduction of **3-174** proved to be challenging (Scheme 90). Surprisingly, reduction with LAH afforded ring-opened product **3-175**, presumably due to the strain in the azaparacyclophane moiety. The structure of **3-175** was confirmed by an X-ray analysis of its HCl salt, in which the central phenyl ring adopts a virtually flat conformation.

Treatment of **3-174** with common amide reduction conditions, including borane, DIBAL, hydrosilylation[162] and thioamide formations, resulted in no reaction,. Moving to the more reactive alanes, we started observing more favorable reactions. For example, treatment of **3-174** with alane afforded ring-opening product **3-176** exclusively, most likely due to the ring stain. Ojima and co-workers reported a similar problem for the reduction of β-lactams, and the authors used monochloroalane and dichloroalane to surpress the undesired ring-opening process.[163] In

our case, with monochloroalane, we observed a small amount of desired product **3-177** along with amino alcohol **3-176** as the major product. The reduction with dichloroalane was extremely sluggish and less successful. We propose that the alanes formed an ate complex with the hydroxyl group in **3-174** first, followed by an intramolecular hydride delivery to the amide bond. This helps to explain the low reactivity exhibited by dichloroalane.[164] Fortunately, we found amino alcohol **3-176** can be converted to **3-177** via a sequence of selective mesylation at the primary hydroxyl group followed by an intramolecular displacement with the secondary amine moiety. The structure of **3-177** was confirmed by X-ray analysis.

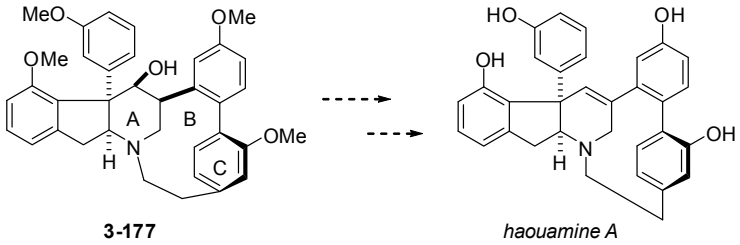
Scheme 90 Reduction of **3-174**



3.3 CONCLUSIONS

We have evaluated four generations of approaches towards the total synthesis of haouamine A. A promising route featuring a Suzuki cyclization, aromatization and intramolecular aldol reaction as the key transformations (Scheme 91) was established. A late-stage intermediate **3-177** was prepared, and its structure was secured by X-ray analysis. Currently, only two steps (elimination and global deprotection[128]) remain to finish haouamine A.

Scheme 91 Summary of the remaining synthetic transformations towards haouamine A



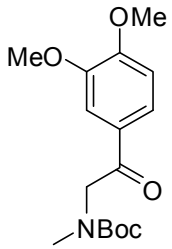
3-177 *haouamine A*

A ring: intramolecular aldol reaction
B ring: Suzuki cross-coupling reaction
C ring: aromatization

3.4 EXPERIMENTAL PART

General: All reactions were performed under an N_2 atmosphere and all glassware was dried in an oven at 140 °C for 2 h prior to use. Reactions carried out at -78 °C employed a CO_2/acetone bath. THF and Et_2O were distilled over sodium/benzophenone ketyl, Et_3N was distilled from CaH_2, and CH_2Cl_2 and toluene were purified using an alumina column filtration system.

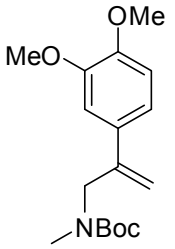
Reactions were monitored by TLC analysis (pre-coated silica gel 60 F254 plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), *p*-anisaldehyde solution (2.5 mL of p-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}$•4 H_2O and 0.2 g of $Ce(SO4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution) or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution). Flash chromatography on SiO_2 was used to purify the crude reaction mixtures. ^1H spectra were obtained at 300 MHz in $CDCl_3$ unless otherwise noted. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard. ^1H NMR spectra were obtained and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). 13C NMR spectra were run at 75 MHz using a proton-decoupled pulse sequence with a d1 of 5 sec, and are tabulated by observed peak.



***tert*-Butyl 2-(3,4-dimethoxyphenyl)-2-oxoethyl(methyl)carbamate (3-71).**[*] A solution of **3-69** (2.18 g, 10 mmol) in DMF (53 mL) and Et_3N (1.40 mL, 10 mmol) was treated with Boc_2O (2.62 g, 12 mmol) in DMF (20 mL) at room temperature. The reaction mixture was stirred overnight, diluted with DCM and treated with aqueous $NaHSO_4$ (1 M). The aqueous layer was extracted with DCM (2x). The combined organic layers were washed with water (2x), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:2 to 1:1) afforded 2.45 g (87%) of the phenol as a clear oil. This phenol was dissolved in DMF (33 mL) and treated with K_2CO_3 (2.93 g, 21.4 mmol) followed by MeI (1.32 mL, 21.4 mmol) at room temperature. The reaction mixture was stirred for 16 h and diluted with Et_2O and water. The aqueous layer was extracted with Et_2O (2x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 2:1 to 1:1) afforded 2.47 g (91%) of **3-71** as a clear sticky foam: IR (neat) 2970, 2931, 1679, 1593, 1585, 1513, 1449 cm^{-1}; ^1H NMR (mixture of rotamers) ($CDCl_3$) δ 7.36-7.30 (m, 1 H), 7.29-7.25 (m, 1 H), 6.72-6.64 (m, 1 H), 4.41 (s, 1 H), 4.36 (s, 1 H), 3.70 (s, 1 H), 3.69 (s, 3 H), 3.66 (s, 2 H), 2.73 (s, 1.5 H), 2.71 (s, 1.5 H), 1.26 (s, 5 H), 1.15 (s, 4 H); ^{13}C NMR (mixture of rotamers) ($CDCl_3$) δ 193.2, 192.9, 155.8, 155.5, 153.2, 153.1, 148.8, 148.6, 128.0, 122.0, 121.9, 109.8, 109.7, 109.5, 79.4, 79.3, 55.6, 55.5,

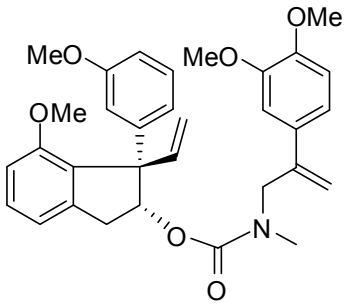
[*] (CWC225B, CWC226: procedure, IR, proton, carbon NMR and HRMS)

55.4, 54.8, 54.3, 35.3, 35.2, 28.0, 27.8; MS (EI) *m/z* (rel intensity) 309 (40%), 253 (20%), 236 (30%), 180 (50%), 165 (100%); HRMS (EI) *m/z* calcd for $C_{16}H_{23}NO_5$ 309.1576, found 309.1582.



***tert*-Butyl 2-(3,4-dimethoxyphenyl)allyl(methyl)carbamate (3-72).**[*] A suspension of Ph_3PCH_3Br (11.1 g, 31.9 mmol) in toluene (64 mL) was treated with KO*t*Bu (3.49 g, 31.9 mmol) at room temperature. The reaction mixture was stirred for 2 h at 50 °C, re-cooled to room temperature and treated with a solution of **3-71** (2.47 g, 7.97 mmol) in toluene (6.5 mL). The reaction mixture was stirred for 18 h, diluted with water and Et_2O. The aqueous layer was extracted with Et_2O (1x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 6:1) afforded 2.35 g (96%) of **3-72** as a white solid: mp 51.4-53.0 °C (DCM); IR (neat) 2970, 2931, 2834, 1684, 1600, 1578, 1515, 1449 cm^{-1}; ^1H NMR (mixture of rotamers) ($CDCl_3$) δ 7.00-6.82 (m, 2 H), 6.74 (s, 1 H), 6.71 (s, 1 H), 5.35-5.20 (m, 1 H), 5.00-4.92 (m, 1 H), 4.27-4.10 (m, 2 H), 3.81 (s, 3 H), 3.77 (s, 3 H), 2.76-2.59 (m, 3 H), 1.35 (s, 9 H); ^{13}C NMR (mixture of rotamers) ($CDCl_3$) δ 155.6, 148.6, 143.7, 132.0, 131.1, 118.5, 112.7, 111.8, 110.7, 109.5, 79.2, 55.7, 53.3, 52.6, 51.5, 33.4, 32.7, 28.2; HRMS (ESI) *m/z* calcd for $C_{17}H_{25}NO_4K$ (M+K) 346.1421, found 346.1436.

[*] (CWC228: procedure, melting point, IR, proton, carbon NMR and HRMS)



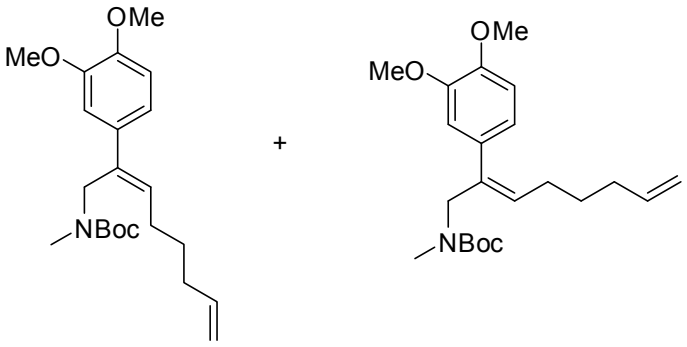
(1S*,2R*)-7-Methoxy-1-(3-methoxyphenyl)-1-vinyl-2,3-dihydro-1H-inden-2-yl 2-(3,4-dimethoxyphenyl)allyl(methyl)carbamate (3-66).[*] A solution of triphosgene (16.7 mg, 0.169 mmol) in DCM (0.5 mL) at 0 °C was treated with **3-64**[143] (25.0 mg, 0.0845 mmol) in DCM (0.5+0.5 mL) followed by the treatment with pyridine (13.7 μL, 0.169 mmol) (dropwise). The reaction mixture was stirred for 2 h at room temperature and diluted with cold water and DCM. The organic layer was washed with cold water (1x), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 30.1 mg (99%) of crude chloroformate **3-74** (used without purification).

A solution of **3-72** (0.113 g, 0.367 mmol) in TFA (neat, 2.8 mL) was stirred for 5 min at room temperature. The reaction mixture was cooled to 0 °C, quenched with 5% aqueous K_2CO_3 and diluted with DCM. The organic layer was washed with 5% aqueous K_2CO_3 (3x), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 70.5 mg (93%) of crude amine **3-73** (used without purification).

A solution of **3-73** (20.9 mg, 0.101 mmol) and DIPEA (73.4 μL, 0.420 mmol) in DCM (1.5 mL) was treated with **3-74** (30.1 mg, 0.0839 mmol) in DCM (0.5+0.5 mL) at room temperature. The reaction mixture was stirred for 14 h and diluted with DCM and water. The aqueous layer was extracted with DCM (1x). The combine organic layer was dried ($MgSO_4$),

[*] (CWC237: procedure, IR, proton, carbon NMR and HRMS)

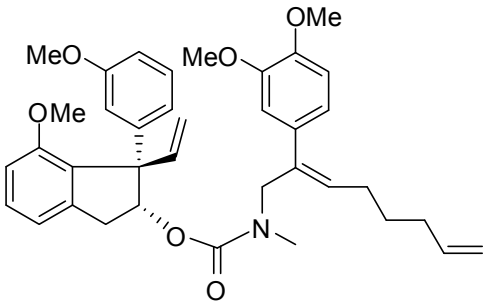
filtered and concentrated under reduced pressure. Purification by PTLC (Hexanes:EtOAc = 2:1) afforded 43.8 mg (99%) of **3-66** as a clear oil: IR (neat) 3458, 2998, 2935, 1694, 1599, 1589, 1515, 1479 cm^{-1}; ^1H NMR 348K (DMSO-d_6) δ 7.29 (t, 1 H, *J* = 7.8 Hz), 7.06 (t, 1 H, *J* = 8.1 Hz), 6.94-6.81 (m, 4 H), 6.71 (dd, 1 H, *J* = 8.1, 2.4 Hz), 6.67-6.50 (m, 3 H), 5.60 (t, 1 H, *J* = 6.6 Hz), 5.29 (app s, 1 H), 5.22-5.09 (m, 2 H), 4.82 (app s, 1 H), 4.08-3.97 (m, 1 H), 3.83-3.72 (m, 1 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 3.60 (s, 6 H), 3.29 (dd, 1 H, *J* = 16.2, 6.9 Hz), 2.75 (dd, 1 H, *J* = 16.2, 5.7 Hz), 2.41 (br s, 3 H); ^{13}C NMR 348K (DMSO-d_6) δ 158.4, 155.8, 154.4, 148.8, 148.5, 142.4, 141.1, 140.9, 140.2, 131.1, 131.0, 129.0, 127.6, 120.3, 118.2, 116.9, 114.3, 112.6, 111.9, 111.5, 110.9, 110.4, 110.2, 78.4, 61.3, 55.51, 55.48, 54.7, 54.5, 51.0, 40.4, 37.0; MS (EI) *m/z* (rel intensity) 529 (20%), 278 (35%), 251 (15%), 234 (100%); HRMS (EI) *m/z* calcd for $C_{32}H_{35}NO_6$ 529.2464, found 529.2483.



(Z)-*tert*-Butyl 2-(3,4-dimethoxyphenyl)octa-2,7-dienyl(methyl)carbamate and (E)-*tert*-butyl 2-(3,4-dimethoxyphenyl)octa-2,7-dienyl(methyl)carbamate (3-76a and **3-76b).**[*] A suspension of hex-5-enyltriphenylphosphonium iodide (3.78 g, 8.00 mmol) in toluene (16 mL) was treated with KO*t*Bu (0.896 g, 8.00 mmol) at room temperature. The reaction mixture was stirred for 2 h at 50 °C, re-cooled to room temperature and treated with a solution of **3-71** (0.618

[*] (CWD013: procedure, IR, carbon NMR and HRMS, CWC265: proton NMR and IR)

g, 2.00 mmol) in toluene (8.0+8.0 mL). The reaction mixture was stirred 50 °C for 2 h, diluted with water and Et_2O. The aqueous layer was extracted with Et_2O (1x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 6:1) afforded 0.130 g (17%) of **3-76a** as a clear oil, 0.305 g (41%) of **3-76b** as a clear oil and 0.268 g (36%) of **3-76a** + **3-76b. 3-76a**: IR (neat) 3075, 2927, 2835, 1694, 1640, 1602, 1582, 1515 cm^{-1}; ^1H NMR (mixture of rotamers) ($CDCl_3$) δ 7.02-6.75 (m, 3 H), 5.88-5.67 (m, 2 H), 5.04-4.87 (m, 2 H), 4.43-4.26 (m, 2 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 2.63-2.46 (m, 3 H), 2.27 (app dd, 2 H, *J* = 15.0, 7.5 Hz), 2.13 (app dd, 2 H, *J* = 1.7, 7.2 Hz), 1.61-1.47 (m, 2 H), 1.40 (s, 9 H); ^{13}C NMR (mixture of rotamers) ($CDCl_3$) δ 156.0, 148.5, 148.2, 138.4, 136.3, 134.4, 133.5, 131.9, 131.3, 119.3, 118.6, 114.9, 111.0, 110.6, 109.9, 79.3, 79.1, 55.9, 46.3, 44.6, 36.7, 33.4, 32.1, 29.1, 28.4, 27.7; HRMS (ESI) *m/z* calcd for $C_{22}H_{33}NO_4Na$ (M+Na) 398.2307, found 398.2324. **3-76b**: IR (neat) 2972, 2927, 2853, 1692, 1513, 1453 cm^{-1}; ^1H NMR (mixture of rotamers) ($CDCl_3$) δ 6.85-6.57 (m, 3 H), 5.81-5.62 (m, 1 H), 5.46 (t, 1 H, *J* = 7.2 Hz), 5.03-4.82 (m, 2 H), 4.17-3.95 (m, 2 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 2.83-2.62 (m, 3 H), 2.20-1.95 (m, 4 H), 1.51-1.24 (m, 11 H); ^{13}C NMR (mixture of rotamers) ($CDCl_3$) δ 155.4, 148.5, 147.9, 138.3, 136.6, 131.5, 130.9, 128.7, 128.4, 120.8, 114.4, 111.8, 110.8, 110.7, 78.9, 55.9, 55.7, 54.4, 33.4, 33.2, 33.1, 29.1, 28.2, 28.1; HRMS (ESI) *m/z* calcd for $C_{22}H_{33}NO_4Na$ (M+Na) 398.2307, found 398.2271.



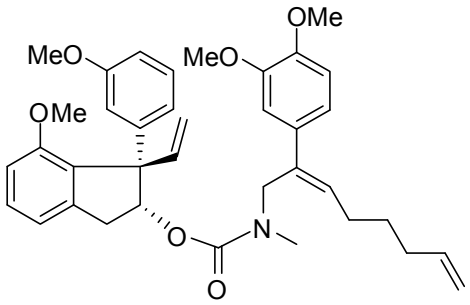
(1S*,2R*)-7-Methoxy-1-(3-methoxyphenyl)-1-vinyl-2,3-dihydro-1H-inden-2-yl (E)-2-(3,4-dimethoxyphenyl)octa-2,7-dienyl(methyl)carbamate (3-75b).[*] A solution of triphosgene (7.7 mg, 0.0260 mmol) in DCM (0.22 mL) at 0 °C was treated with **3-64**[143] (11.6 mg, 0.0391 mmol) in DCM (0.5+0.5 mL) followed by the treatment with pyridine (6.33 μL, 0.0779 mmol) (dropwise). The reaction mixture was stirred for 2 h at room temperature and diluted with cold water and DCM. The organic layer was washed with cold water (1x), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 13.3 mg (95%) of crude chloroformate **3-74** (used without purification).

A solution of **3-76b** (21.3 mg, 0.0567 mmol) in TFA (neat, 0.5 mL) was stirred for 5 min at room temperature. The reaction mixture was cooled to 0 °C, quenched with 5% aqueous K_2CO_3 and diluted with DCM. The organic layer was washed with 5% aqueous K_2CO_3 (3x), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 12.8 mg (82%) of crude amine **3-77b** (used without purification).

A solution of **3-77b** (12.8 mg, 0.0465 mmol) and DIPEA (32.4 μL, 0.185 mmol) in DCM (0.67 mL) was treated with **3-74** (13.3 mg, 0.0371 mmol) in DCM (0.2+0.2 mL) at room temperature. The reaction mixture was stirred for 16 h and diluted with DCM and water. The aqueous layer was extracted with DCM (1x). The combine organic layer was dried ($MgSO_4$),

[*] (CWC269: procedure, high temperature proton and carbon NMR; CWC256: HRMS)

filtered and concentrated under reduced pressure. Purification by PTLC (Hexanes:EtOAc = 2:1) afforded 18.6 mg (84%) of **3-75b** as a clear oil: ^{1}H NMR 348K (DMSO-d_6) δ 7.28 (dd, 1 H, *J* = 8.2, 7.5 Hz), 7.11 (t, 1 H, *J* = 8.0 Hz), 6.92-6.82 (m, 3 H), 6.74 (ddd, 1 H, *J* = 8.1, 2.6, 0.7 Hz), 6.64-6.50 (m, 5 H), 5.79-5.66 (m, 1 H), 5.51 (t, 1 H, *J* = 6.2 Hz), 5.29-5.20 (m, 1 H), 5.15 (dd, 1 H, *J* = 10.9, 0.7 Hz), 5.09 (d, 1 H, *J* = 17.8 Hz), 4.96-4.86 (m, 2 H), 3.89-3.80 (m, 1 H), 3.76 (s, 3 H), 3.70 (s, 3 H), 3.63 (s, 3 H), 3.60 (s, 3 H), 3.17 (dd, 1 H, *J* = 16.0, 6.8 Hz), 3.06 (s, 2 H), 2.63-2.54 (m, 1 H), 2.42 (br s, 3 H), 1.99-1.87 (m, 2 H), 1.42-1.31 (m, 2 H); ^{13}C NMR 348K (DMSO-d_6) δ 158.4, 155.8, 154.3, 148.3, 147.8, 141.1, 140.9, 140.2, 138.0, 135.6, 131.1, 130.6, 129.0, 127.7, 127.6, 120.4, 120.3, 116.8, 114.4, 114.2, 112.64, 112.55, 112.0, 110.9, 110.2, 78.0, 61.1, 55.5, 54.8, 54.3, 36.7, 32.2, 28.1, 27.2; MS (EI) *m/z* (rel intensity) 597 (45%), 366 (15%), 302 (100%), 279 (70%), 244 (55%); HRMS (EI) *m/z* calcd for $C_{37}H_{43}NO_6$ 597.3090, found 597.3119.



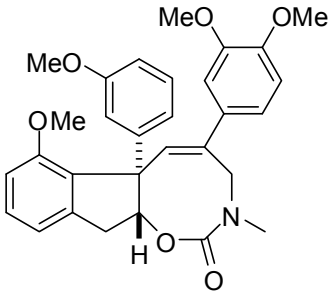
(1S*,2R*)-7-Methoxy-1-(3-methoxyphenyl)-1-vinyl-2,3-dihydro-1H-inden-2-yl (Z)-2-(3,4-dimethoxyphenyl)octa-2,7-dienyl(methyl)carbamate (3-75a).[*] in DCM (0.1 mL) at 0 °C was treated with **3-64**[143] (5.2 mg, 0.0177 mmol) in DCM (0.1+0.1 mL) followed by the treatment with pyridine (2.9 μL, 0.0354 mmol) (dropwise). The reaction mixture was stirred for 2 h at room temperature and diluted with cold water and DCM. The organic layer was washed with

[*] (CWC256B: procedure, proton, HRMS)**.** A solution of triphosgene (3.51 mg, 0.0118 mmol)

cold water (1x), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 5.9 mg (92%) of **3-74** (used without purification).

A solution of **3-76a** (8.0 mg, 0.0213 mmol) in TFA (neat, 0.25 mL) was stirred for 5 min at room temperature. The reaction mixture was cooled to 0 °C, quenched with 5% aqueous K_2CO_3 and diluted with DCM. The organic layer was washed with 5% aqueous K_2CO_3 (3x), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 5.0 mg (85%) of **3-77a** (used without purification).

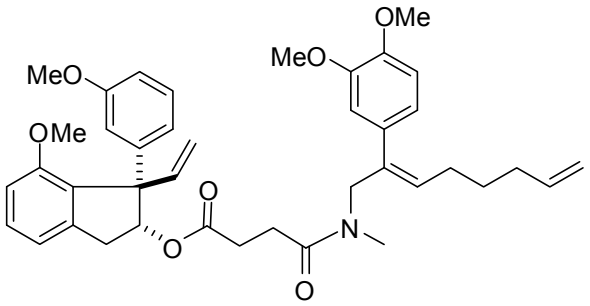
A solution of **3-77a** (5.0 mg, 0.0182 mmol) and DIPEA (15.9 μL, 0.0912 mmol) in DCM (0.33 mL) was treated with **3-74** (5.9 mg, 0.0164 mmol) in DCM (0.1+0.1 mL) at room temperature. The reaction mixture was stirred for 16 h and diluted with DCM and water. The aqueous layer was extracted with DCM (1x). The combine organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by PTLC (Hexanes:EtOAc = 2:1) afforded 7.8 mg (80%) of **3-75a** as a clear oil: ^{1}H NMR representative signals of one rotamer ($CDCl_3$) δ 6.31 (d, 1 H, J = 7.7 Hz), 3.90 (s, 3 H), 3.85 (s, 3 H), 3.66 (s, 3 H), 2.52 (s, 3 H), 2.26-2.18 (m, 2 H), 1.60-1.45 (m, 2 H); MS (EI) *m/z* (rel intensity) 597 (45%), 366 (15%), 279 (90%), 244 (80%), 163 (35%), 121 (100%); HRMS (EI) *m/z* calcd for $C_{37}H_{43}NO_6$ 597.3090, found 597.3105.



Attempted Preparation of **3-67.**[*] A solution of **3-75a** (5.0 mg, 8.35 μmol) in degassed DCM (1.0 mL) was added to a solution of Hoveyda-Grubbs' catalyst (0.523 mg, 0.835 μmol) in degassed DCM (0.5 mL) over 30 min (syringe pump) at 50 °C. The reaction mixture was stirred for 5 min and purified directly by PTLC (Hexanes:EtOAc = 3:2) to afford 1.8 mg (36%) of starting material and 2.5 mg (51%) of **3-78** as a sticky clear solid: (note the NMR data are not provided here due to the inherent low quality of spectra); HRMS (ESI) *m/z* calcd for $C_{72}H_{82}N_2O_{12}Na$ (M+Na) 1189.5765, found 1189.6106.

Alternatively, a solution of **3-75b** (3.9 mg, 6.50 μmol) in degassed toluene (32.5 mL) was treated with Grubb's 2nd generation catalyst (0.55 mg, 0.650 μmol) at 110 °C with argon sparging. The reaction mixture was stirred for 5 min and purified directly by chromatography on SiO_2 (Hexanes:EtOAc = 4:1 to 1:1) to afford 0.1 mg (3%) of starting material, 1.2 mg (35%) of **3-66** and 0.8 mg (21%) of **3-78**.

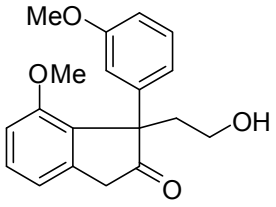
[*] (CWC258 and CWC263: procedure, proton NMR and HRMS)



(1S*,2R*)-7-Methoxy-1-(3-methoxyphenyl)-1-vinyl-2,3-dihydro-1H-inden-2-yl 4-(((E)-2-(3,4-dimethoxyphenyl)octa-2,7-dienyl)(methyl)amino)-4-oxobutanoate (3-80). [*] A solution of **3-77b** (36.7 mg, 0.133 mmol) in DCM (0.50 mL) was treated with succinic anhydride (16.0 mg, 0.160 mmol) at room temperature. The reaction mixture was heated at reflux for 20 h, cooled to room temperature and diluted with water and DCM. The aqueous layer was extracted with DCM (1x). The combine organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 ($CHCl_3$:EtOH = 95:5 to 10:1) afforded 23.1 mg (50%) of the acid. A solution of the acid and MF2060F1 (11.1 mg, 0.0375 mmol) in DCM (0.50 mL) was treated with DCC (8.5 mg, 0.0413 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 20 h. The reaction mixture was filtered through a plug of cotton and concentrated under reduced pressure. Purification by PTLC (Hexanes:EtOAc = 1:1) afforded 18.9 mg (70%) of **3-80** as a clear oil: IR (neat) 3076, 2955, 2927, 2855, 1729, 1647, 1599, 1479 cm^{-1}; ^1H NMR 348K (DMSO-d_6) δ 7.29 (t, 1 H, *J* = 8.1 Hz), 7.10 (t, 1 H, *J* = 8.1 Hz), 6.94-6.87 (m, 2 H), 6.74 (ddd, 1 H, *J* = 8.1, 2.4, 0.9 Hz), 6.70-6.48 (m, 4 H), 5.80-5.64 (m, 2 H), 5.41 (t, 1 H, *J* = 7.2 Hz), 5.16 (dd, 1 H, *J* = 11.1, 0.9 Hz), 5.11 (dd, 1 H, *J* = 17.7, 0.6 Hz), 4.97-4.85 (m, 2 H), 4.04 (br s, 2 H), 3.76 (s, 3 H), 3.73 (s, 3 H), 3.65 (s, 3 H), 3.58 (s, 3 H), 3.29 (dd, 1 H, *J* = 16.2, 6.6 Hz), 3.01 (s, 2 H), 2.79 (dd, 1 H, *J* = 16.5, 4.5 Hz), 2.72 (s, 2 H),

[*] (CWD026: procedure, IR, proton, carbon NMR and HRMS)

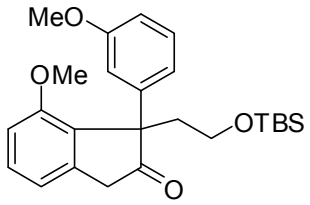
2.20-1.89 (m, 5 H), 1.47-1.35 (m, 1 H); ^{13}C NMR 348K (DMSO-d_6) δ 170.6, 158.2, 155.8, 141.2, 140.9, 139.8, 137.9, 135.5, 131.1, 130.8, 129.0, 127.6, 127.3, 120.44, 120.41, 116.8, 114.5, 114.1, 112.8, 112.6, 112.2, 111.0, 110.2, 77.3, 61.7, 55.53, 55.46, 54.7, 54.5, 36.6, 32.8, 32.1, 28.8, 28.1, 27.1; MS (EI) *m/z* (rel intensity) 653 (20%), 279 (30%), 244 (100%); HRMS (EI) *m/z* calcd for $C_{40}H_{47}NO_7$ 653.3353, found 653.3325.



1-(2-Hydroxyethyl)-7-methoxy-1-(3-methoxyphenyl)-1H-inden-2(3H)-one (3-88).[*] A solution of **3-85**[143] (50.0 mg, 0.162 mmol) in DCM (2.6 mL) and MeOH (0.65 mL) at -78 °C was bubbled with ozone until the color changed to blue. The solution was then bubbled with Ar for 20 min at -78 °C followed by the treatment with Me_2S (0.0910 mL, 1.24 mmol). The reaction mixture was stirred for 14 h at room temperature and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 4:1) afforded 40.7 mg (81%) of the aldehyde. A solution of the aldehyde in THF (1.7 mL) was treated with $LiAlH(OCHEt_2)_3$ (0.41 M in THF, 0.347 mL, 0.142 mmol, prepared by the addition of 3-ethyl-3-pentanol (1.22 mL, 8.61 mmol) to a solution of LAH (105 mg, 2.76 mmol) in THF (5.5 mL) at room temperature, then refluxing for 2 h) at -78 °C. The reaction mixture was stirred for 7 h and treated with additional $LiAlH(OCHEt_2)_3$ (0.10 mL), stirred for another 2 h and treated with additional $LiAlH(OCHEt_2)_3$ (0.10 mL). The reaction mixture was stirred for 1 h and quenched with HCl (2 M). The mixture was extracted with EtOAc (3x). The combined organic layers were washed with

[*] (CWD110: procedure, proton and carbon NMR; CWD105: IR and HRMS)

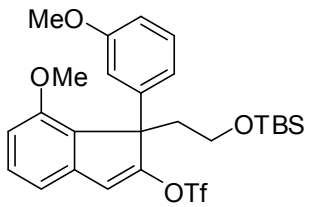
$NaHCO_3$ (2x), brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 2:1) afforded 36.8 mg (90%) of **3-88** as a clear oil (product existed as a mixture of keto alcohol and hemiacetal): IR (neat) 3400, 2953, 2933, 2883, 1748, 1602, 1584, 1481 cm^{-1}; ^1H NMR (CD_3OD) δ 7.37 (t, 0.5 H, *J* = 8.1 Hz), 7.24 (t, 0.5 H, *J* = 8.1 Hz), 7.11 (t, 1 H, *J* = 8.1 Hz), 7.03 (d, 0.5 H, *J* = 7.5 Hz), 6.94 (d, 0.5 H, *J* = 8.4 Hz), 6.85 (d, 0.5 H, *J* = 7.5 Hz), 6.79 (d, 0.5 H, *J* = 8.1 Hz), 6.75-6.64 (m, 3 H), 4.13 (dt, 0.5 H, *J* = 7.8, 2.7 Hz), 3.71-3.67 (m, 4.5 H), 3.64 (s, 1.5 H), 3.54 (s, 1 H), 3.49-3.39 (m, 1 H), 3.19-3.16 (m, 1 H), 3.14-3.06 (m, 0.5 H), 2.91-2.76 (m, 1.5 H), 2.63 (s, 0.5 H), 2.59-2.51 (m, 0.5 H); ^{13}C NMR (CD_3OD) δ 217.8, 161.1, 160.7, 158.4, 157.9, 144.4, 143.8, 143.0, 140.2, 130.6, 130.3, 130.1, 129.5, 121.3, 119.9, 118.4, 118.2, 115.3, 115.2, 113.8, 112.7, 112.2, 110.6, 110.5, 68.3, 65.3, 62.3, 60.4, 55.6, 55.53, 55.48, 44.8, 43.1, 39.3, 34.4; MS (EI) *m/z* (rel intensity) 312 (95%), 268 (100%), 239 (100%); HRMS (EI) *m/z* calcd for $C_{19}H_{20}O_4$ 312.1362, found 312.1355.



1-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-7-methoxy-1-(3-methoxyphenyl)-1H-inden-2(3H)-one (3-89).[*] A solution of **3-88** (36.8 mg, 0.118 mmol), imidazole (40.2 mg, 0.591 mmol) and TBSCl (42.8 mg, 0.283 mmol) in DMF (2.5 mL) at room temperature was stirred for 14 h, quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with water (2x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 10:1) afforded 22.8 mg (45%) of **3-**

[*] (CWD113: procedure, IR, HRMS, proton and carbon NMR)

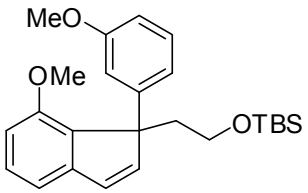
89 as a clear oil: IR (neat) 2953, 2927, 2854, 1753, 1598, 1585, 1482, 1470, 1433 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (t, 1 H, *J* = 7.8 Hz), 7.19-7.12 (m, 1 H), 6.99 (dd, 1 H, *J* = 5.7, 0.6 Hz), 6.86 (d, 2 H, *J* = 8.1 Hz), 6.77-6.71 (m, 3 H), 3.75 (s, 3 H), 3.72 (s, 3 H), 3.59-3.50 (m, 1 H), 3.53 (s, 2 H), 3.21 (dt, 1 H, *J* = 10.5, 4.8 Hz), 3.01-2.90 (m, 1 H), 0.77 (s, 9 H), -0.12 (s, 3 H), -0.16 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 214.7, 159.7, 157.2, 143.3, 139.3, 130.1, 129.4, 129.3, 119.1, 117.5, 113.0, 111.9, 109.5, 61.3, 60.9, 55.4, 55.3, 42.5, 38.8, 26.1, 18.6, -5.59, -5.62; MS (EI) *m/z* (rel intensity) 369 (100), 353 (90); HRMS (EI) *m/z* calcd for $C_{21}H_{25}O_4Si$ 369.1522, found 369.1525.



1-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-7-methoxy-1-(3-methoxyphenyl)-1H-inden-2-yl trifluoromethanesulfonate (3-90).* A solution of **3-89** (22.8 mg, 0.0534 mmol) and N-phenylbis(trifluoromethane)sulfonimide (22.9 mg, 0.0641 mmol) in THF (0.35 mL) at -78 °C was slowly treated with a solution of KHMDS (0.302 M in THF, 0.194 mL, 0.0641 mmol). The reaction mixture was then stirred for 2 h at room temperature, quenched with saturated aqueous NH_4Cl and extracted with EtOAc (1x). The organic layer was washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:Et_2O = 15:1) afforded 27.2 mg (91%) of **3-90** as a clear sticky solid: IR (neat) 2953, 2926, 2855, 1600, 1582, 1425 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (dd, 1 H, *J* = 8.1, 7.8 Hz), 7.17 (t, 1 H, *J* = 8.1 Hz), 6.99 (d, 1 H, *J* = 7.5 Hz), 6.82-6.72 (m, 4 H), 6.51 (s, 1 H), 3.74 (s, 3 H), 3.67 (s, 3 H), 3.39-3.28 (m, 1 H), 3.28-3.18 (m, 1 H), 3.00-2.89 (m, 1 H), 2.67-2.56 (m, 1 H),

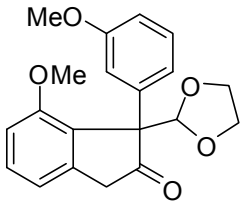
* (CWD114: procedure, proton and carbon NMR, IR and HRMS)

0.83 (s, 9 H), -0.07 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 159.8, 158.9, 155.0, 141.0, 139.5, 130.8, 129.7, 129.4, 120.6, 118.9, 116.4, 115.5, 113.9, 112.8, 112.6, 109.9, 59.6, 57.9, 55.5, 55.4, 33.4, 26.1, 18.5, -5.3; MS (EI) *m/z* (rel intensity) 501 (35), 368 (70), 293 (30), 265 (100); HRMS (EI) *m/z* calcd for $C_{22}H_{24}O_6F_3SiS$ (M-*t*Bu) 501.1015, found 501.1006.



***tert*-Butyl(2-(7-methoxy-1-(3-methoxyphenyl)-1H-inden-1-yl)ethoxy)dimethylsilane (3-93)**.* A solution of $Pd(OAc)_2$ (0.109 mg, 0.487 μmol) and rac-BINAP (0.449 mg, 0.721 μmol) in 0.10 mL PhMe was treated with **3-90** (5.44 mg, 9.74 μmol) in PhMe (0.10 mL), $PhCH_2CH_2NHCH_3$ (2.83 μL, 19.5 μmol) and KO*t*Bu (1.53 mg, 13.6 μmol, freshly sublimed) sequentially at room temperature. The reaction mixture was stirred for 3 h at 80 °C, cooled to room temperature, treated with $NaBH(OAc)_3$ (3.1 mg, 14.6 μmol) and stirred for 48 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by PTLC (Hexanes:Et_2O = 4:1) afforded 1.6 mg (39%) of **3-93** as a clear sticky solid along with 1.0 mg (18%) of **3-89**: ^{1}H NMR ($CDCl_3$) δ 7.29-7.21 (m, 1 H), 7.14 (t, 1 H, *J* = 8.1 Hz), 6.95 (d, 1 H, *J* = 7.2 Hz), 6.87-6.82 (m, 2 H), 6.74-6.66 (m, 2 H), 6.63 (d, 1 H, *J* = 5.7 Hz), 6.41 (d, 1 H, *J* = 5.4 Hz), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.35 (dt, 1 H, *J* = 9.9, 5.1 Hz), 3.20 (dt, 1 H, *J* = 9.9, 5.7 Hz), 2.87-2.76 (m, 1 H), 2.67-2.56 (m, 1 H), 0.83 (s, 9 H), -0.06 (s, 6 H).

* (CWD117: procedure, proton and COSY)

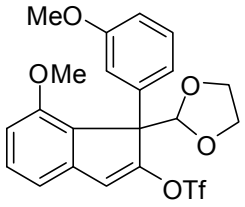


1-(1,3-Dioxolan-2-yl)-7-methoxy-1-(3-methoxyphenyl)-1H-inden-2(3H)-one (3-96). [*]

A solution of **3-97**[143] (2.47 g, 9.22 mmol) in DCM (50 mL) was treated with Et_3N (3.89 mL, 27.6 mmol) followed by TMSCl (3.53 mL, 27.6 mmol) at room temperature. The reaction mixture was stirred for 2 h, diluted with DCM, washed with cold water (1x), cold $CuSO_4$ (saturated) (2x), cold water (2x), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 9.19 g (100%) of the crude enol ether (mixture of 2.3:1 regioisomers favoring the desired one). A solution of the enol ether (0.825 g, 2.42 mmol) and 2-Methoxy-1,3-dioxolane (0.693 mL, 7.27 mmol) in DCM (75 mL) at -20 °C was treated with a solution of TMSOTf (1.0 M in DCM, 0.242 mL, 0.242 mmol). The reaction mixture was stirred for 2.5 h, quenched with saturated aqueous $NaHCO_3$ and extracted with DCM (3x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 10:1 to 3:1 to 2:1) afforded 0.383 g (46%, 58% BORSM) of **3-96** as a clear oil along with 0.131 g (20%) of **3-97**: IR (neat) 3069, 2939, 2895, 2836, 1754, 1586, 1484 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (t, 1 H, *J* = 7.8 Hz), 7.19 (t, 1 H, *J* = 8.1 Hz), 7.04-6.94 (m, 3 H), 6.85 (d, 1 H, *J* = 8.4 Hz), 6.78 (dd, 1 H, *J* = 8.1, 2.4 Hz), 5.97 (s, 1 H), 4.05-3.92 (m, 2 H), 3.87-3.75 (m, 2 H), 3.76 (s, 3 H), 3.67 (s, 3 H), 3.70-3.50 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 213.2, 159.4, 156.8, 139.3, 139.1, 130.3, 130.0, 129.0, 120.9, 117.4, 115.0, 112.2, 110.4, 105.6, 66.3, 66.1,

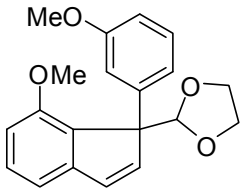
[*] (CWF055: procedure and proton NMR; CWD203: HRMS; CWD146: carbon NMR; CWD156: IR)

65.4, 55.6, 55.4, 44.4; HRMS (ESI) *m/z* calcd for $C_{20}H_{20}O_5Na$ (M+Na) 363.1208, found 363.1180.



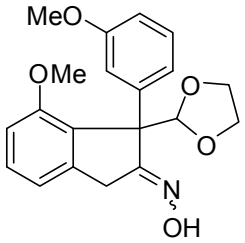
1-(1,3-Dioxolan-2-yl)-7-methoxy-1-(3-methoxyphenyl)-1H-inden-2-yl trifluoromethanesulfonate (3-99).[*] A solution of **3-96** (0.1279 g, 0.376 mmol) and N-phenylbis(trifluoromethane)sulfonimide (0.161 g, 0.451 mmol) in THF (2.4 mL) at -78 °C was slowly treated with a solution of KHMDS (0.302 M in THF, 1.50 mL, 0.451 mmol). The reaction mixture was then stirred for 1 h at room temperature, quenched with saturated aqueous NH_4Cl and extracted with EtOAc (1x). The organic layer was washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 6:1) afforded 0.139 g (78%) of **3-99** as a white solid: mp 94.0-95.4 °C (DCM); IR (neat) 3583, 2895, 1605, 1583, 1480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (t, 1 H, *J* = 8.1 Hz), 7.22 (t, 1 H, *J* = 8.1 Hz), 7.11-7.07 (m, 1 H), 7.05-6.99 (m, 2 H), 6.87-6.78 (m, 2 H), 6.68 (s, 1 H), 6.12 (s, 1 H), 4.14 (dd, 1 H, *J* = 13.5, 6.9 Hz), 4.01 (dd, 1 H, *J* = 13.8, 7.2 Hz), 3.95-3.81 (m, 2 H), 3.78 (s, 3 H), 3.69 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.6 156.1, 154.5, 140.7, 136.0, 134.2, 130.0, 129.7, 129.3, 127.4, 124.8, 123.5, 120.6, 120.2, 119.3, 116.3, 115.7, 114.3, 112.9, 112.1, 110.6, 103.9, 65.8, 65.2, 63.7, 55.6, 55.3; MS (EI) *m/z* (rel intensity) 472 (8), 340 (20), 266 (50), 238 (60), 293 (30), 165 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{19}O_7F_3S$ 472.0804, found 472.0804.

[*] (CWD218: procedure, mp, proton and carbon NMR, IR and HRMS)



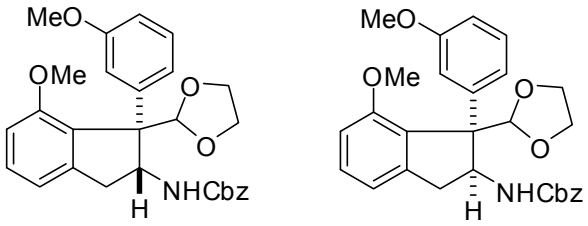
2-(7-Methoxy-1-(3-methoxyphenyl)-1H-inden-1-yl)-1,3-dioxolane (3-100).* A solution of $Pd(OAc)_2$ (0.476 mg, 2.12 μmol) in DMF (0.20 mL) was degassed and treated with $P(OMe)_3$ (0.68 μL, 5.77 μmol) **3-99** (10.0 mg, 21.2 μmol) in PhMe (0.10+0.10 mL), Et_3N (5.82 μL, 41.9 μmol), $PhCH_2CH_2NH_2$ (5.3 μL, 42.4 μmol) and KO*t*Bu (4.8 mg, 42.4 μmol) sequentially at room temperature. The reaction mixture was stirred for 1.5 h at 110 °C, diluted with Et_2O, filtered through a pad of Celite and concentrated to dryness. The residue was dissolved in DCE (0.50 mL) and treated with $NaBH(OAc)_3$ (22.5 mg, 0.106 mmol) at troom temperature. The reaction mixture was stirred for 24 h, quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by PTLC (Hexanes:Et_2O = 1:1) afforded 0.7 mg (7%) of **3-100** as a clear oil along with 2.3 mg (32%) of **3-96**: IR (neat) 3064, 2952, 2887, 2835, 1600, 1562, 1473 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (t, 1 H, *J* = 8.1 Hz), 7.23 (t, 1 H, *J* = 8.1 Hz), 7.18-7.15 (m, 1 H), 7.13-7.08 (m, 1 H), 7.05 (d, 1 H, *J* = 7.2 Hz), 6.87 (d, 1 H, *J* = 5.7 Hz), 6.84-6.78 (m, 2 H), 6.67 (d, 1 H, *J* = 5.7 Hz), 6.29 (s, 1 H), 4.12-3.98 (m, 2 H), 3.85 (app t, 2 H, *J* = 6.3 Hz), 3.80 (s, 3 H), 3.78 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.3, 155.1, 145.9, 140.7, 139.7, 134.6, 132.0, 129.5, 128.9, 120.2, 114.8, 114.3, 111.6, 109.4, 104.9, 66.5, 65.73, 65.71, 55.4, 55.1; MS (EI) *m/z* (rel intensity) 324 (0.5), 251 (2.5), 205 (4), 165 (4); HRMS (EI) *m/z* calcd for $C_{20}H_{20}O_4$ 324.1366, found 324.1347.

* (CWD219: procedure; CWD221 and CWD177: proton and carbon NMR, HRMS, IR)



2(E)-1-(1,3-Dioxolan-2-yl)-7-methoxy-1-(3-methoxyphenyl)-1H-inden-2(3H)-one oxime.[*] A solution of **3-96** (1.22 g, 3.58 mmol), pyridine (0.870 mL, 16.7 mmol) and hydroxylamine hydrochloride salt (1.25 g, 17.9 mmol) in EtOH (61 mL) was heated at reflux for 6 h, quenched with saturated aqueous $NaHCO_3$ and filtered. The filtrate was extracted with EtOAc (1x) and the organic layer was washed with water (1x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 2:1 to 1:1, all with 1% Et_3N) afforded 1.04 g (81%) of the title compound as a yellow solid: mp 201.3 °C (decomp.) (DCM); IR (neat) 3267, 2943, 2893, 2837, 1607, 1587, 1482 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 8.00 (s, 1 H), 7.25 (t, 1 H, J = 7.8 Hz), 7.09 (t, 1 H, J = 7.8 Hz), 6.96-6.88 (m, 2 H), 6.81 (d, 1 H, J = 7.8 Hz), 6.73-6.65 (m, 2 H), 5.99 (s, 1 H), 6.29 (s, 1 H), 3.96-3.70 (m, 4 H), 3.67 (s, 3 H), 3.54 (s, 3 H); ^{13}C NMR (CD_2Cl_2) δ 264.6, 159.8, 156.6, 144.1, 141.5, 132.6, 130.2, 129.1, 120.8, 117.9, 114.9, 111.7, 110.4, 105.4, 66.6, 65.6, 63.8, 55.8, 55.6, 35.1; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}NO_5Na$ (M+Na) 378.1317, found 378.1293.

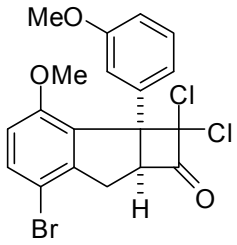
[*] (CWF058: procedure, mp, IR and proton NMR; CWD249: carbon NMR; CWE009: HRMS)



Benzyl (1R,2R)-1-(1,3-dioxolan-2-yl)-7-methoxy-1-(3-methoxyphenyl)-2,3-dihydro-1H-inden-2-ylcarbamate (3-102) and benzyl (1R,2S)-1-(1,3-dioxolan-2-yl)-7-methoxy-1-(3-methoxyphenyl)-2,3-dihydro-1H-inden-2-ylcarbamate (3-101).[*]. A solution of the oxime (0.292 g, 0.822 mmol) in boiling *n*PrOH (59 mL) was treated with Na (3.82 g, 166 mmol) in small protions over 7 h. The reaction mixture was cooled to room temperature, poured into brine and extracted with EtOAc (2x). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford crude amine **3-101** and **3-102**. A solution of 90% of the crude mixture and $NaHCO_3$ (0.297 g, 3.53 mmol) was treated with benzyl chloroformate (0.120 mL, 0.842 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h, diluted with EtOAc and washed with brine (1x). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:1) three times afforded 0.214 g (59%) of **3-102** as a clear oil and 0.0828 g (24%) of **3-101** as a clear oil. **3-102**: IR (neat) 3332, 2958, 2879, 1692, 1587, 1476 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39-7.23 (m, 6 H), 7.19 (t, 1 H, *J* = 8.1 Hz), 6.92-6.85 (m, 2 H), 6.81-6.70 (m, 3 H), 5.94 (s, 1 H), 5.10 (AB, 1 H, *J* = 12.3 Hz), 5.05 (AB, 1 H, *J* = 12.3 Hz), 5.01-4.92 (m, 1 H), 4.41 (d, 1 H, *J* = 9.6 Hz), 4.19-4.03 (m, 2 H), 4.00-3.80 (m, 2 H), 3.70 (s, 3 H), 3.64 (s, 3 H), 3.33 (dd, 1 H, *J* = 15.6, 8.1 Hz), 2.61 (dd, 1 H, *J* = 15.6, 10.2 Hz); ^{13}C NMR ($CDCl_3$) δ 159.9, 156.0, 155.8, 142.4, 139.9, 137.2, 132.4, 129.6, 129.5, 128.5, 128.0, 127.9, 121.0, 117.2, 115.1,

[*] (CWF063, CWF069: procedure, proton and carbon NMR, HRMS, IR, mp)

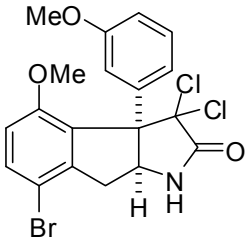
112.4, 110.0, 105.9, 66.4, 66.1, 65.1, 62.1, 55.6, 55.2, 53.4, 38.4; HRMS (ESI) *m/z* calcd for $C_{28}H_{29}NO_6$ (M+H) 498.1893, found 498.1863. Approx. 10 mg of **3-102** was dissolved in EtOAc (0.50 mL) and placed in a freezer at -20 °C for 3 days to provide X-ray quality white crystal: mp 147.9-150.0 °C (EtOAc). **3-101**: IR (neat) 3412, 2957, 2892, 1716, 1589, 1507, 1496 cm^{-1}; ^1H NMR 600 MHz ($CDCl_3$) δ 7.30-7.18 (m, 6 H), 7.10 (t, 1 H, *J* = 8.1 Hz), 6.87-6.80 (m, 3 H), 6.76 (d, 1 H, *J* = 7.8 Hz), 6.71-6.67 (m, 1 H), 6.24 (d, 1 H, *J* = 7.8 Hz), 5.61 (s, 1 H), 5.05 (AB, 1 H, *J* = 12.0 Hz), 4.99 (AB, 1 H, *J* = 12.6 Hz), 4.80-4.76 (m, 1 H), 3.83-3.77 (m, 4 H), 3.67 (s, 3 H), 3.65 (s, 3 H), 2.97 (dd, 1 H, *J* = 15.6, 6.0 Hz), 2.80 (dd, 1 H, *J* = 15.6, 3.6 Hz); ^{13}C NMR 150 MHz ($CDCl_3$) δ 159.5, 157.4, 156.0, 144.4, 143.1, 137.1, 130.5, 129.8, 129.0, 128.6, 128.14, 128.09, 120.5, 118.1, 114.6, 112.0, 110.2, 107.0, 66.5, 65.3, 64.4, 63.1, 61.6, 55.7, 55.3, 39.6; HRMS (ESI) *m/z* calcd for $C_{28}H_{29}NO_6$ (M+H) 498.1893, found 498.1881.



(2aR*,7aS*)-6-Bromo-2,2-dichloro-3-methoxy-2a-(3-methoxyphenyl)-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]inden-1-one (3-107).* A solution of **3-106**[165] (2.52 g, 7.61 mmol) and zinc-copper couple[166] (5.47 g, 83.7 mmol) in Et_2O (25 mL) at room temperature was treated with a solution of $POCl_3$ (7.24 mL, 79.1 mmol, distilled from K_2CO_3) and Cl_3CCOCl (8.83 g, 79.1 mmol) over 5 h (syringe pump). The reaction mixture was stirred for 14 h at room temperature and filtered through a pad of Celite. The filtrate was washed with ice-water (2x), cold aqueous $NaHCO_3$ (2x) and brine (1x), dried ($MgSO_4$), filtered and concentrated under

* (CWG029: procedure, proton NMR; CWG023: carbon NMR, IR, MS)

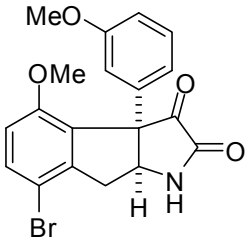
reduced pressure. Purification by recrystallization from DCM afforded 2.37 g (71%) of **3-107** as a yellow solid: mp 167.4-169.3 °C (DCM); IR (neat) 3582, 3000, 2936, 2836, 1808, 1762, 1603, 1580, 1473, 1436 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (d, 1 H, *J* = 4.5 Hz), 7.28 (t, 1 H, *J* = 7.8 Hz), 7.07 (t, 1 H, *J* = 2.1 Hz), 7.02 (d, 1 H, *J* = 7.8 Hz), 6.85 (dd, 1 H, *J* = 8.1, 2.1 Hz), 6.60 (d, 1 H, *J* = 8.7 Hz), 4.52 (d, 1 H, *J* = 2.7 Hz), 3.85 (s, 3 H), 3.74 (s, 3 H), 3.57 (d, 1 H, *J* = 17.4 Hz) , 3.35 (dd, 1 H, *J* = 17.1, 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 195.9, 158.8, 157.2, 144.0, 139.3, 134.0, 130.9, 128.6, 120.6, 115.2, 112.6, 112.4, 110.6, 71.0, 64.1, 55.33, 55.28, 36.0; MS (EI) *m/z* (rel intensity) 442 (65%), 408 (45%), 298 (30%), 264 (65%), 251 (100%); HRMS (EI) *m/z* calcd for $C_{19}H_{15}O_3Cl_2Br$ 439.9582, found 439.9601.



(3aR*,8aS*)-7-Bromo-3,3-dichloro-4-methoxy-3a-(3-methoxyphenyl)-3,3a,8,8a-tetrahydroindeno[2,1-b]pyrrol-2(1H)-one (3-108).[*] A solution of **3-107** (2.25 g, 5.11 mmol) and anhydrous Na_2SO_4 (2.61 g, 18.4 mmol) in DCM (20 mL) at room temperature was treated with Tamura's reagent[167] (3.96 g, 18.4 mmol). The reaction mixture was stirred for 72 h, treated with additional Tamura's reagent (4.00 g, 18.6 mmol, stirred for 48 h, diluted with toluene and filtered through a column of basic alumina, eluting with MeOH. The solvents were evaporated under reduced pressure. The residue was dissolved in DCM, filtered and concentrated under reduced pressure to afford 2.06 g (88%) of crude **3-108** as a white powder: mp 238.0-240.0 °C (DCM); IR (neat) 3315, 2937, 2834, 1694, 1599, 1587, 1470, 1438 cm^{-1}; ^1H NMR ($CDCl_3$) δ

[*] (CWG033: procedure, proton NMR; CWG031: carbon NMR; CW090-043: IR and mp; CWG027: MS)

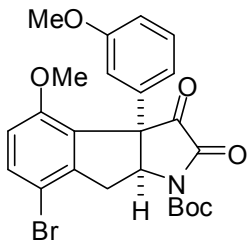
7.52 (d, 1 H, J = 8.7 Hz), 7.23 (t, 1 H, J = 8.1 Hz), 6.86-6.78 (m, 4 H), 6.57 (s, 1 H), 4.31 (ddd, 1 H, J = 8.4, 6.0, 2.1 Hz), 3.82 (s, 3 H), 3.76 (s, 3 H), 3.45 (dd, 1 H, J = 16.8, 8.4 Hz), 3.00 (dd, 1 H, J = 17.1, 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 170.8, 159.3, 157.3, 145.0, 143.0, 133.9, 129.5, 129.3, 119.1, 113.9, 112.3, 110.8, 73.0, 64.6, 55.9, 55.4, 40.8; HRMS (ESI) *m/z* calcd for $C_{19}H_{16}NO_3NaCl_2Br$ (M+Na) 477.9588, found 477.9553.



(3aR*,8aS*)-7-Bromo-4-methoxy-3a-(3-methoxyphenyl)-8,8a-dihydroindeno[2,1-b]pyrrole-2,3(1H,3aH)-dione (3-109).[*] A suspension of **3-108** (1.01 g, 2.20 mmol) in NaOMe (0.6 M in MeOH 66.1 mL) was heated at reflux for 48 h. The reaction mixture was acidified with 10% aqueous $NaHSO_4$ and extracted with EtOAc (3x). The combined organic layers were washed with water (1x), saturated $NaHCO_3$ (1x) and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the crude product. Half of the crude product was dissolved in THF (13 mL) and treated with 70% aqueous $HClO_4$ (3.29 mL, 38.5 mmol). The reaction mixture was heated at reflux for 16 h, diluted with water and extracted with EtOAc (3x). The combined organic layers were washed with water (1x), saturated $NaHCO_3$ (1x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 0.437 g (99%) of crude **3-109** as a white powder: IR (neat) 3639, 2952, 2909, 2868, 1766, 1725, 1599, 1580, 1472 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1 H), 7.51 (d, 1 H, J = 8.7 Hz), 6.84 (dd, 1 H, J = 8.4, 2.7

[*] (CWG078, CW090-008: procedure; CWG076: proton NMR; CWG076: X-ray and mp; CWG053: HRMS, carbon NMR; CWG082 : IR)

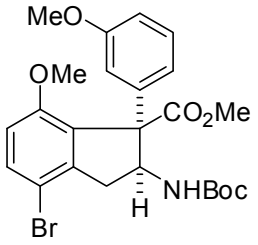
Hz), 6.73 (d, 1 H, J = 8.7 Hz), 6.58-6.49 (m, 2 H), 4.47 (d, 1 H, J = 6.0 Hz), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.37 (dd, 1 H, J = 17.7, 5.7 Hz), 3.10 (d, 1 H, J = 17.7 Hz); ^{13}C NMR ($CDCl_3$) δ 194.8, 160.8, 160.1, 158.0, 144.1, 137.8, 134.8, 130.2, 126.1, 119.8, 114.1, 113.1, 112.7, 111.2, 68.4, 62.6, 56.0, 55.5, 40.2; HRMS (ESI) *m/z* calcd for $C_{19}H_{16}NO_4NaBr$ (M+Na) 424.0160, found 424.0160. X-ray quality crystal was obtained by dissolving the crude product in EtOAc and slowly evaporating the solvent in air at room temperature: colorless needle, mp 264.0-266.7 °C (EtOAc).



(3aR*,8aS*)-*tert*-Butyl 7-bromo-4-methoxy-3a-(3-methoxyphenyl)-2,3-dioxo-3,3a,8,8a-tetrahydroindeno[2,1-b]pyrrole-1(2H)-carboxylate (3-110).[*] A solution of **3-109** (0.443 g, 1.10 mmol) and DMAP (6.72 mg, 5.50 mmol) in THF (9.0 mL) at room temperature was treated with Et_3N (0.309 mL, 2.20 mmol) and Boc_2O (0.481 g, 2.20 mmol). The reaction mixture was stirred for 18 h, diluted with water and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 6:1 to 4:1) afforded 0.469 g (85%) of **3-110** as a yellow solid: mp 86.7 °C (decomp.) (DCM); IR (neat) 2974, 2933, 2834, 1787, 1770, 1755, 1725, 1599, 1582, 1474 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.24 (d, 1 H, J = 8.1 Hz), 7.26 (t, 1 H, J = 8.1 Hz), 6.85 (dd, 1 H, J = 8.1, 2.4 Hz), 6.71 (d, 1 H, J = 8.7 Hz), 6.58-6.54 (m, 1 H), 6.51 (t, 1 H, J = 2.1 Hz), 4.76 (dd, 1 H, J = 6.3, 0.9 Hz), 3.76 (s, 3 H), 3.68 (s, 3 H), 3.51

[*] (CW090-011: procedure, MS, mp; CWG081: IR, proton and carbon NMR)

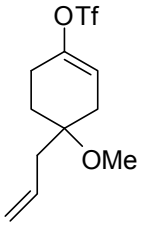
(dd, 1 H, J = 18.6, 6.6 Hz), 3.28 (d, 1 H, J = 18.3 Hz), 1.61 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 192.5, 160.1, 157.6, 157.0, 149.7, 144.3, 138.4, 135.0, 130.3, 125.2, 119.6, 113.9, 113.1, 112.7, 110.9, 85.7, 66.1, 65.6, 56.1, 55.5, 40.4, 28.1; HRMS (ESI) *m/z* calcd for $C_{24}H_{24}NO_6NaBr$ (M+Na) 524.0685, found 524.0697.



(1R*,2R*)-Methyl 4-bromo-2-(*tert*-butoxycarbonylamino)-7-methoxy-1-(3-methoxyphenyl)-2,3-dihydro-1H-indene-1-carboxylate (3-111).[*] A solution of **3-110** (4.83 g, 9.61 mmol) in MeOH (136 mL) and aqueous NaOH (3 M, 71 mL) at room temperature was treated with aqueous H_2O_2 (30%, 47.0 mL, 423 mmol). The reaction mixture was stirred for 20 h and treated with additional aqueous H_2O_2 (30%, 47.0 mL, 423 mmol), stirred at room temperature for another 20 h, acidified with 10% aqueous $NaHSO_4$ and extracted with EtOAc (3x). The combined organic layers were washed with brine (2x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was dissolved in DMF (60 mL) and treated with K_2CO_3 (1.97 g, 14.2 mmol) followed by MeI (1.13 mL, 18.1 mmol) at 0 °C. The reaction mixture was stirred for 3 h at the same temperature, quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with saturated $NaHCO_3$ (1x), water (2x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 6:1) afforded 3.58 g (74%) of **3-111** as a white foam: mp 68.4-72.7 °C (DCM); IR (neat) 3440, 2968, 1703, 1599, 1580, 1489, 1472,

[*] (CW090-059 and CW090-061: procedure, IR, MS, mp, proton NMR; CW090-004: carbon NMR)

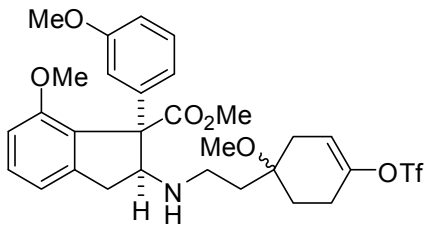
1429 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (d, 1 H, *J* = 8.7 Hz), 7.22 (t, 1 H, *J* = 8.1 Hz), 6.88-6.67 (m, 4 H), 6.59 (d, 1 H, *J* = 10.2 Hz), 4.77-4.67 (m, 1 H), 3.75 (s, 3 H), 3.72 (s, 3 H), 3.69 (s, 3 H), 3.20 (dd, 1 H, *J* = 16.5, 7.2 Hz), 2.90 (dd, 1 H, *J* = 16.5, 5.4 Hz), 1.41 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 172.4, 159.3, 156.6, 155.5, 144.0, 140.4, 133.0, 131.0, 128.9, 120.8, 114.5, 112.3, 112.1, 111.0, 79.6, 67.9, 63.1, 56.0, 55.3, 52.7, 40.0, 28.5; HRMS (ESI) *m/z* calcd for $C_{24}H_{28}NO_6NaBr$ (M+Na) 528.0998, found 528.1045.



4-Allyl-4-methoxycyclohex-1-enyl trifluoromethanesulfonate (3-114).* A solution of **3-113**[168] (13.0 g, 77.3 mmol, dried by co-evaporating with benzene (2x) and THF (1x)) and N-phenylbis(trifluoromethane)sulfonimide (29.3 g, 81.1 mmol) in THF (564 mL) at -78 °C was slowly treated with a solution of KHMDS (0.302 M in THF, 243 mL, 73.4 mmol). The reaction mixture was then stirred for 2 h at room temperature, quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:Et_2O = 40:1) afforded 18.66 g (80%) of **3-114** as a clear oil: IR (neat) 2933, 1410, 1244, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.89-5.70 (m, 1 H), 5.68-5.60 (m, 1 H), 5.19-5.07 (m, 2 H), 3.23 (s, 3 H), 2.56-2.42 (m, 1 H), 2.41-2.14 (m, 5 H), 2.03-1.93 (m, 1 H), 1.77-1.66 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 148.9, 133.0, 125.1, 120.9, 118.5, 116.6, 115.3, 112.4, 73.1, 49.1, 39.9, 39.6, 36.0, 33.0, 32.7, 32.5, 30.4, 30.2, 25.0; MS (EI) *m/z* (rel intensity) 259 (75%), 227 (10%), 167

* (CW135-070: procedure, proton NMR, IR, HRMS; CWF064: carbon NMR)

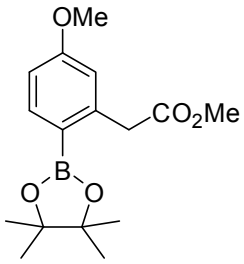
(90%), 163 (40%), 109 (50%), 97 (100%), 77 (100%); HRMS (EI) (-C_3H5, de-allylation) *m/z* calcd for $C_8H_{10}O_4F_3S$ 259.0252, found 259.0251.



(1R*,2S*)-Methyl 7-methoxy-2-(2-(1-methoxy-4-(trifluoromethylsulfonyloxy) cyclohex-3-enyl)ethylamino)-1-(3-methoxyphenyl)-2,3-dihydro-1H-indene-1-carboxylate (3-116).* A solution of **3-111** (3.57 g, 7.05 mmol) and NaOAc·$3H_2O$ (1.06 g, 7.76 mmol) in EtOH (91 mL) was subjected to H-Cube (20 bar, room temperature, 1 ml/min, Pd/C cartridge). The reaction mixture was concentrated under reduced pressure, treated with 5% aqueous K_2CO_3 and extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was dissolved in HCl/MeOH (1 M, 141 mL, 1.90 mol) and stirred at room temperature for 3 h. The reaction mixture was cooled to 0 °C, quenched with 5% aqueous K_2CO_3 and extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 1.97 g (85%) of crude product. A fraction of the crude product (1.48 g, 4.53 mmol) and aldehyde **3-115** (1.64 g, 5.44 mmol) (for preparation see **3-130**, **3-115** must be used immediately to avoid decomposition) was dissolved in MeOH (55 mL) and treated with $NaBH(OAc)_3$ (2.02 g, 9.07 mmol) at room temperature. The reaction mixture was stirred for 16 h, quenched with 5% aqueous K_2CO_3 and extracted with EtOAc (3x).

* (CW090-064, CW090-065 and CW106-068: procedure; CW090-032: proton NMR and carbon NMR; CW090-029: IR and MS)

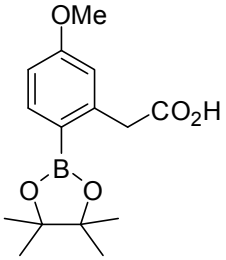
The combined organic layers were washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:1 to 1:1, with 1% Et_3N) afforded 1.88 g (58% over three steps) of **3-116** (mixture of diastereomers, ratio = 1:1) as a yellow oil: IR (neat) 2953, 2830, 1733, 1599, 1585, 1477, 1412 cm^{-1}; ^1H NMR 600 MHz (CD_2Cl_2) δ 7.30 (t, 1 H, *J* = 7.8 Hz), 7.16 (t, 1 H, *J* = 8.4 Hz), 6.90 (d, 1 H, *J* = 7.2 Hz), 6.85-6.82 (m, 2 H), 6.81 (d, 1 H, *J* = 8.4 Hz), 6.76 (dd, 1 H, *J* = 7.8, 1.8 Hz), 5.62-5.59 (m, 1 H), 3.73 (s, 3 H), 3.69 (s, 3 H), 3.65 (s, 3 H), 3.65-3.60 (m, 1 H), 3.19 (dd, 1 H, *J* = 15.6, 7.2 Hz), 3.132 (s, 1.5 H), 3.127 (s, 1.5 H), 2.90 (dd, 1 H, *J* = 15.6, 5.4 Hz), 2.80-2.74 (m, 1 H), 2.56-2.51 (m, 1 H), 2.48-2.39 (m, 1 H), 2.33-2.26 (m, 1 H), 2.26-2.11 (m, 2 H), 2.01-1.94 (m, 1 H), 1.73-1.54 (m, 4 H); ^{13}C NMR 150 MHz (CD_2Cl_2) δ 172.9, 159.3, 157.3, 149.2, 149.1, 144.9, 143.8, 130.6, 130.1, 128.5, 120.8, 120.0, 117.9, 117.8, 115.64, 115.59, 114.93, 114.90, 111.6, 109.8, 73.6, 72.9, 72.8, 67.3, 55.7, 55.4, 52.2, 49.1, 43.27, 43.25, 39.2, 35.8, 35.7, 33.7, 33.6, 30.6, 25.1, 25.0; MS (EI) *m/z* (rel intensity) 613 (50%), 582 (30%), 480 (40%), 381 (25%), 325 (100%), 280 (60%), 252 (50%), 191 (40%), 167 (30%); HRMS (EI) *m/z* calcd for $C_{29}H_{34}NO_8F_3S$ 613.1953, found 613.1957.



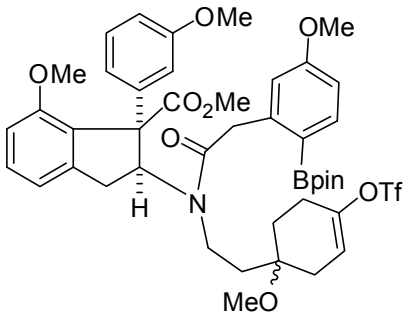
(1R*,2S*)-1-((*tert*-Butyldimethylsilyloxy)methyl)-7-methoxy-1-(3-methoxyphenyl)-2,3-dihydro-1H-inden-2-amine (3-118).[*] A solution of **3-117**[129] (12.9 g, 44.2 mmol) and

[*] (CW135-064, CW182-061: procedures; CWF076: proton and carbon NMR, HRMS; CW090-028: IR)

K_2CO_3 (9.05 g, 65.5 mmol) in DMF (103 mL) was treated with MeI (5.18 mL, 83.2 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 2 h, quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with saturated $NaHCO_3$ (3x), water (3x), brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:Et_2O = 8:1) afforded 12.7 g (94%) of the ester as a white solid. A solution of the ester (2.14 g, 6.99 mmol), $Pd(OAc)_2$ (31.4 mg, 0.140 mmol) and DPEPhos (0.113 g, 0.210 mmol) in dioxane (28 mL) was degassed by two freeze-pump-thaw cycles and treated with Et_3N (3.44 mL, 24.5 mmol) and pinacolborane (1.52 mL, 10.5 mmol) at room temperature. The reaction mixture was stirred at 85 °C for 4 h, cooled to room temperature, quenched with saturated NH_4Cl and extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:Et_2O = 10:1) afforded 1.79 g (84%) of **3-118** as a yellow oil: IR (neat) 2976, 2948, 1736, 1600, 1565, 1379 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79 (d, 1 H, *J* = 8.4 Hz), 6.81 (d, 1 H, *J* = 8.4, 2.7 Hz), 6.75 (d, 1 H, *J* = 2.4 Hz), 3.97 (s, 2 H), 3.82 (s , 3 H), 3.67 (s, 3 H), 1.31 (s, 12 H); ^{13}C NMR ($CDCl_3$) δ 172.9, 162.0, 142.7, 138.2, 116.4, 111.8, 83.6, 55.3, 51.9, 41.3, 25.0; HRMS (ESI) *m/z* calcd for $C_{16}H_{23}BO_5Na$ (M+Na) 329.1536, found 329.1542.



2-(5-Methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid (3-119).[*] A solution of **3-118** (1.77 g, 5.77 mmol) in THF (95 mL) was treated with LiOH (1 M aqueous solution, 17.3 mL, 17.3 mmol) at room temperature. The reaction mixture was stirred for 2 h, quenched with 10% $NaHSO_4$ and extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 1.40 g (83%) of **3-119** as a white solid: mp 115.7-117.7 °C (DCM); IR (neat) 2970, 2931, 1705, 1600, 1420, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79 (d, 1 H, J = 8.4 Hz), 6.90-6.80 (m, 2 H), 3.91 (s, 2 H), 3.83 (s , 3 H), 3.67 (s, 3 H), 1.37 (s, 12 H); ^{13}C NMR ($CDCl_3$) δ 162.2, 142.0, 138.3, 116.5, 112.2, 84.0, 55.3, 41.7, 24.9; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}BO_5Na$ (M+Na) 315.1404, found 315.1398.

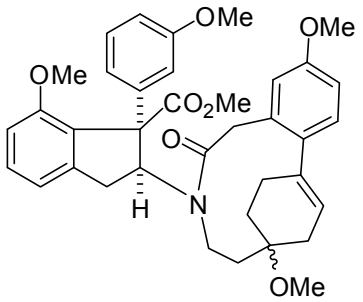


(1R*,2S*)-Methyl 7-methoxy-2-(2-(5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-

[*] (CW210-012: procedure, proton NMR, melting point; CW135-084: carbon NMR; CW182-070: HRMS; CW090-032: IR)

dioxaborolan-2-yl)phenyl)-N-(2-(1-methoxy-4-(trifluoromethylsulfonyloxy)cyclohex-3-enyl)ethyl)acetamido)-1-(3-methoxyphenyl)-2,3-dihydro-1H-indene-1-carboxylate (3-120).[*] A solution of **3-116** (1.88 g, 3.06 mmol) and **3-119** (1.07 g, 3.07 mmol) in DMF (36 mL) was treated with DIPEA (1.07 mL, 6.13 mmol) followed by HATU (1.63 g, 4.29 mmol) at room temperature. The reaction mixture was stirred for 14 h, quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with water (3x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification on SiO_2 (Hexanes:EtOAc = 3:1 to 2:1) afforded 2.11 g (78%) of **3-120** (mixture of diastereomers, ratio = 1:1) as a yellow foam: IR (neat) 2972, 2940, 2832, 1723, 1645, 1600, 1479, 1412 cm^{-1}; Representative ^1H NMR of one diastereomer 600 MHz ($CDCl_3$) δ 5.64-5.58 (m, 1 H), 3.77 (s, 3 H), 3.71 (s, 3 H), 3.14 (s, 3 H); ^{13}C NMR of a mixture of both diastereomers and rotamers 150 MHz ($CDCl_3$) δ 173.73, 173.68, 172.5, 171.8, 162.04, 161.97, 159.4, 158.9, 157.04, 156.96, 148.8, 148.70, 148.65, 148.6, 145.0, 144.9, 144.3, 144.23, 144.16, 144.1, 143.7, 143.5, 141.7, 141.6, 138.4, 138.2, 132.4, 131.3, 130.5, 130.34, 130.30, 129.2, 128.6, 123.1, 120.9, 120.8, 117.0, 116.6, 116.53, 116.49, 116.46, 116.3, 115.5, 115.4, 115.3, 115.1, 114.99, 114.96, 114.9, 112.3, 111.7, 111.62, 111.59, 111.20, 111.16, 110.3, 109.9, 83.41, 83.35, 72.7, 72.6, 70.6, 70.4, 68.0, 67.9, 67.6, 55.8, 55.7, 55.29, 55.28, 52.72, 52.66, 49.63, 49.58, 49.55, 41.5, 41.04, 41.00, 39.9, 39.8, 37.0, 36.9, 36.4, 36.2, 34.11, 34.08, 34.0, 33.9, 33.42, 33.35, 32.9, 32.5, 30.37, 30.36, 30.3, 30.0, 25.3, 25.23, 25.20, 25.1, 25.01, 25.00, 24.94, 24.92; HRMS (ESI) *m/z* calcd for $C_{44}H_{53}B_1N_1O_{12}F_3NaS$ (M+Na) 910.3231, found 910.3190.

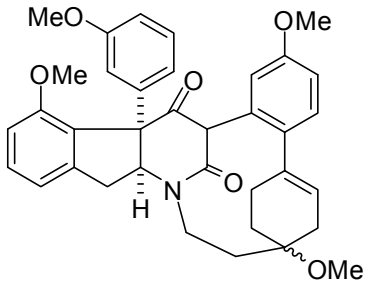
[*] (CW106-072: procedure; CW090-033: IR and NMRs; CW090-004: MS)



Preparation of **3-121.**[*] A mixture of **3-120** (1.42 g, 1.60 mmol) and K_2CO_3 (0.442 g, 3.22 mmol) in DMSO (318 mL) and water (0.0864 mL, 4.80 mmol) was degassed by two freeze and thaw cycles and treated with a solution of $Pd(PPh_3)_4$ (92.4 mg, 0.0800 mmol) in degassed DMSO (17 mL). The reaction mixture was heated to 85 °C for 1.5 h, cooled to room temperature, quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with water (2x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:THF = 3:1) afforded 0.798 g (82%) of **3-121** (mixture of diastereomers, ratio = 1:1) as a white foam: IR (neat) 2931, 2832, 1716, 1636, 1602, 1591, 1477 cm^{-1}; ^1H NMR not provided due to the complex chemical shift pattern; ^{13}C NMR of a mixture of both diastereomers 150 MHz ($CDCl_3$) 174.8, 174.5, 174.2, 173.1, 172.3, 172.1, 172.0, 171.8, 159.5, 159.3, 159.1, 158.8, 158.7, 158.3, 156.8, 156.7, 156.6, 147.1, 146.3, 144.6, 144.4, 143.7, 143.6, 141.3, 141.1, 139.4, 138.6, 137.6, 136.2, 135.9, 135.6, 135.5, 135.4, 134.8, 133.5, 132.3, 132.0, 131.8, 130.6, 130.5, 130.3, 130.0, 129.6, 129.5, 129.4, 129.2, 128.93, 128.86, 128.7, 128.3, 128.2, 127.4, 124.4, 124.3, 123.7, 122.4, 121.1, 120.0, 119.8, 118.2, 117.7, 117.3, 117.0, 116.8, 116.6, 115.5, 115.1, 114.0, 113.8, 113.4, 112.7, 112.4, 111.9, 111.8, 111.4, 111.2, 110.1, 109.9, 109.7, 109.4, 83.7, 75.9, 75.8, 74.2, 73.6, 73.3, 71.9, 70.4, 67.7, 67.0, 65.0, 64.3, 55.9, 55.7, 55.5, 55.43, 55.35, 55.33, 55.30, 52.8, 52.7, 52.6, 49.7, 49.5, 49.2, 48.7, 48.6, 48.4,

[*] (CW106-082: procedure and proton NMR; CW090-079: carbon NMR; CW090-024: MS)

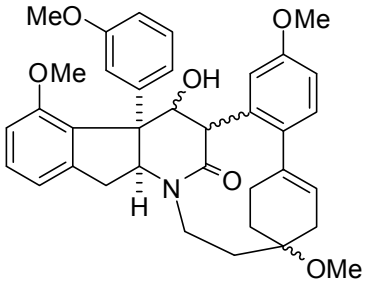
48.0, 45.2, 42.2, 40.9, 40.2, 39.4, 38.4, 37.8, 37.1, 36.8, 35.7, 34.9, 34.7, 34.6, 34.3, 33.8, 33.2, 33.1, 32.8, 31.5, 31.4, 30.3, 30.03, 29.98, 29.9, 29.7, 25.5, 25.2, 25.02, 24.97, 24.9, 24.4, 23.6, 19.0; HRMS (ESI) *m/z* calcd for $C_{37}H_{41}NO_7Na$ (M+Na) 634.2781, found 634.2772.



Preparation of **3-124.**[*] A solution of **3-121** (0.2176 g, 0.356 mmol) in THF (10.8 mL) at - 78 °C was treated with a solution of LDA (0.78 M in THF, 1.00 mL, 0.780 mmol, prepared freshly from diisopropylamine and *n*BuLi). The reaction mixture was stirred at room temperature for 10 min, quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:THF = 2:1 to 1:1, all with 0.1% Et_3N) afforded 0.2222 g of crude **3-124** as a mixture of diastereomers (ration = 1:1). The diastereomers were partially separated by chromatography (1st column with Hexanes:THF = 3:2 with 0.1% Et_3N, 2nd column with DCM:Et_2O = 10:1 to 2:1, 3rd column with DCM:Et_2O = 10:1) to afford pure **3-124a**: IR (neat) 2927, 2834, 1733, 1647, 1604, 1591 cm^{-1}; ^1H NMR 500 MHz ($CDCl_3$) δ 7.39 (d, 1 H, *J* = 8.0 Hz), 7.22 (d, 1 H, *J* = 8.0 Hz), 7.14 (d, 1 H, *J* = 8.0 Hz), 6.96 (d, 1 H, *J* = 7.0 Hz), 6.91 (d, 1 H, *J* = 8.5 Hz), 6.84-6.77 (m, 2 H), 6.53 (d, 1 H, *J* = 2.5 Hz), 6.49 (d, 1 H, *J* = 8.0 Hz), 6.36 (app s, 1 H), 5.48 (d, 1 H, *J* = 5.0 Hz), 4.46 (s, 1 H), 4.39 (d, 1 H, *J* = 4.5 Hz), 4.04-3.97 (m, 1 H), 3.88 (s, 3 H), 3.76 (d, 1 H, *J* = 6.0 Hz), 3.71 (s, 3 H), 3.31 (s, 3 H), 3.17-3.08 (m,

[*] (CW106-091: procedure; CW106-095: resolving diastereomers, X-ray, mp, IR, NMRs and HRMS)

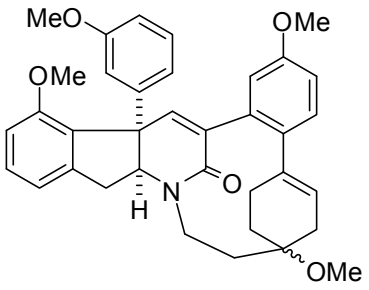
2 H), 3.08-2.99 (m, 1 H), 2.93 (dd, 1 H, 16.0, 4.0 Hz), 2.59-2.51 (m, 1 H), 2.46-2.35 (m, 2 H), 2.34-2.27 (m, 1 H), 1.90-1.76 (m, 1 H); ^{13}C NMR 150 MHz ($CDCl_3$) δ 201.9, 168.6, 159.5, 158.2, 156.6, 143.5, 138.1, 136.0, 133.6, 131.7, 129.6, 129.5, 129.2, 124.1, 121.6, 120.1, 118.9, 115.7, 112.6, 112.5, 110.0, 75.2, 72.5, 67.6, 62.3, 55.7, 55.34, 55.28, 49.4, 46.0, 37.0, 33.9, 33.2, 30.3, 30.2; HRMS (ESI) *m/z* calcd for $C_{36}H_{37}NO_6Na$ (M+Na) 602.2519, found 602.2540. **3-124a** was recrystallized from DCM to yield x-ray quality yellow crystal: mp 219.4 °C (decomp.) (DCM). The crystal was collected and redissolved in $CDCl_3$ to give a proton NMR spectrum that is identical to the sample before crystallization.



Preparation of **3-125**.* Crude **3-124** (0.2222 g) in THF (8.7 mL) was treated with $LiBH_4$ (2 M in THF, 0.356 mL, 0.711 mmol) at room temperature. The reaction mixture was stirred for 48 h, treated with additional $LiBH_4$ (2 M in THF, 0.356 mL, 0.711 mmol) and stirred for 24 h. The reaction mixture was quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:THF = 1:1, all with 0.1% Et_3N) followed by 2nd chromatography on SiO_2 (DCM:Et_2O = 10:1, with 0.1% Et_3N) afforded 97.2 mg (47% over two steps) of **3-125** (mixture of diastereomers, ratio = 1:1) as a white solid, 9.4 mg (4.5% over two steps) of **3-125a** (single diastereomer) as a clear sticky solid and 16.2 mg

* (CW106-092: procedure, proton, carbon, COSY, HMQC, HMBC, HRMS and IR)

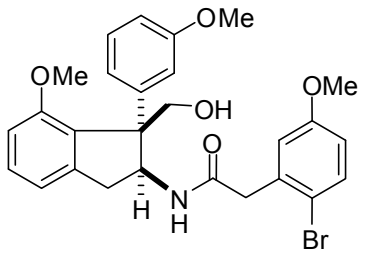
(7.8% over two steps) of **3-125b** (single diastereomer) as a clear sticky solid. **3-125a**: IR (neat) 3419, 2924, 2849, 2832, 1638, 1602, 1436 cm^{-1}; ^1H NMR 500 MHz ($CDCl_3$) δ 7.21 (d, 1 H, *J* = 8.0 Hz), 7.19 (d, 1 H, *J* = 7.5 Hz), 7.08-7.03 (m, 2 H), 7.86 (d, 1 H, *J* = 8.0 Hz), 6.80-6.71 (m, 4 H), 6.69 (d, 1 H, *J* = 8.0 Hz), 5.28 (dd, 1 H, *J* = 6.0, 3.0 Hz), 5.83 (d, 1 H, *J* = 3.5 Hz), 4.06 (s, 3 H), 3.91 (d, 1 H, *J* = 6.0 Hz), 3.79 (s, 3 H), 3.75 (s, 3 H), 3.64 (app d, 1 H, 13.0 Hz), 3.52 (app t, 1 H, *J* = 14.5 Hz), 3.33 (s, 3 H), 3.16 (d, 1 H, *J* = 16.5 Hz), 3.04 (t, 1 H, *J* = 13.0 Hz), 2.80 (dd, 1 H, *J* = 16.0, 3.0 Hz), 2.53-2.37 (m, 3 H), 2.29 (app d, 1 H, *J* = 16.5 Hz), 1.85-1.69 (m, 3 H), 1.56 (d, 1 H, *J* = 3.0 Hz); ^{13}C NMR ($CDCl_3$) δ 171.0, 159.6, 158.1, 156.7, 142.6, 142.3, 138.6, 135.9, 133.5, 130.6, 130.2, 129.2, 127.2, 120.4, 118.9, 117.6, 115.2, 111.7, 111.5, 110.2, 75.2, 72.0, 67.2, 62.2, 55.6, 55.4, 55.3, 52.8, 49.3, 47.1, 35.2, 34.6, 33.2, 30.7, 30.3; HRMS (ESI) *m/z* calcd for $C_{36}H_{39}NO_6Na$ (M+Na) 604.2675, found 604.2673. **3-125b**: IR (neat) 3436, 2931, 2836, 1641, 1602, 1477, 1436 cm^{-1}; ^1H NMR 500 MHz ($CDCl_3$) δ 7.21-7.17 (m, 2 H), 7.10-7.06 (m, 2 H), 6.95 (d, 1 H, *J* = 8.5 Hz), 6.86 (d, 1 H, *J* = 8.5 Hz), 6.79-6.72 (m, 3 H), 6.68 (d, 1 H, *J* = 2.5 Hz), 5.37 (d, 1 H, *J* = 5.0 Hz), 5.11 (d, 1 H, *J* = 4.0 Hz), 4.99 (dd, 1 H, *J* = 6.0, 2.5 Hz), 4.43 (dd, 1 H, *J* = 15.0, 12.0 Hz), 4.04 (s, 3 H), 3.88 (d, 1 H, *J* = 6.0 Hz), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.29 (s, 3 H), 3.16 (d, 1 H, 16.0 Hz), 3.05 (dd, 1 H, *J* = 15.5, 6.5 Hz), 2.80 (dd, 1 H, *J* = 16.0, 4.0 Hz), 2.44 (dd, 1 H, *J* = 17.0, 7.0 Hz), 2.28-2.12 (m, 4 H), 2.07-1.99 (m, 1 H), 1.95-1.87 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 172.8, 159.5, 158.2, 156.7, 143.0, 142.8, 138.0, 137.4, 136.7, 132.1, 130.6, 130.2, 129.1, 126.1, 120.4, 119.0, 117.6, 115.2, 111.7, 111.5, 110.2, 77.7, 71.4, 63.1, 61.5, 55.5, 55.4, 55.3, 53.6, 48.8, 38.1, 35.4, 34.9, 34.4, 33.4, 30.3; HRMS (ESI) *m/z* calcd for $C_{36}H_{39}NO_6Na$ (M+Na) 604.2675, found 604.2720.



Preparation of **3-123**.[*] A solution of **3-125** (3.2 mg, 0.00550 mmol, mixture of diastereomers, ratio = 5:1) in THF 0.1+0.1+0.1 mL was added to a suspension of KH 12.6 mg (35% in mineral oil, pre-washed with toluene three times to remove mineral oil) in THF 0.18 mL. The reaction mixture was stirred for 1 h at 63 °C, cooled to 0 °C, quenched with saturated NH_4Cl and extracted with EtOAc (1x). The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of combined crude from three reactions by chromatography on SiO_2 (Hexanes:EtOAc = 1:1) followed by supercritical fluid chromatography on cyano column with 20% MeOH in CO_2 as eluent afforded 2.5 mg (23%) of **3-123** (mixture of diastereomers, ratio = 5:1) as a clear sticky solid: IR (neat) 2931, 2834, 1669, 1630, 1600, 1477, 1464, 1433 cm^{-1}; ^1H NMR of major diastereomer 600 MHz ($CDCl_3$) δ 7.25 (d, 1 H, *J* = 7.8 Hz), 7.20 (t, 1 H, *J* = 7.8 Hz), 7.06 (d, 1 H, *J* = 7.8 Hz), 6.89-6.76 (m, 5 H), 6.68 (s, 1 H), 6.53 (app d, 1 H, *J* = 8.4 Hz), 6.47 (t, 1 H, *J* = 2.4 Hz), 5.58 (d, 1 H, *J* = 6.6 Hz), 4.34 (d, 1 H, *J* = 4.8 Hz), 4.40-4.30 (m, 1 H), 3.811 (s, 3 H), 3.806 (s, 3 H), 3.71 (s, 3 H), 3.27 (s, 3 H), 3.16-3.09 (m, 1 H), 3.12 (d, 1 H, *J* = 15.6 Hz), 2.99-2.91 (m, 2 H), 2.43 (dd, 1 H, *J* = 16.8, 6.6 Hz), 2.38-2.26 (m, 3 H), 2.12-2.06 (m, 1 H), 2.02-1.96 (m, 2 H), 1.87-1.76 (m, 1 H); ^{13}C NMR of major diastereomer 150 MHz ($CDCl_3$) δ 165.9, 160.0, 159.9, 158.8, 158.7, 156.62, 156.55, 146.3, 146.2, 142.6, 142.2, 138.7, 138.1, 137.6, 136.8, 136.12, 136.06, 135.9,

[*] (CW182-010: procedure, proton, carbon, COSY, HMQC, HMBC, HRMS and IR)

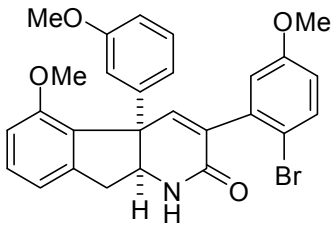
133.6, 132.0, 130.2, 130.1, 129.8, 129.4, 128.2, 127.7, 127.5, 120.0, 119.8, 117.6, 117.5, 114.9, 114.4, 114.2, 114.0, 112.8, 112.4, 112.1, 111.7, 110.4, 110.3, 75.6, 73.8, 57.0, 56.6, 55.6, 55.44, 55.39, 55.33, 55.28, 49.5, 48.9, 46.0, 36.2, 35.7, 35.3, 33.9, 33.4, 29.4, 29.1, 27.4; ; HRMS (ESI) *m/z* calcd for $C_{36}H_{38}NO_5$ (M+H) 564.2750, found 564.2700.



(1R*,2S*)-Methyl 2-amino-7-methoxy-1-(3-methoxyphenyl)-2,3-dihydro-1H-indene-1-carboxylate (3-126[141]).[*] **3-111** (1.33 g, 2.63 mmol) in a solution of HCl (1 M, prepared from mixing MeOH and acetyl chloride) in MeOH (39 mL) was stirred at room temperature for 2.5 h, quenched with 5% aqueous K_2CO_3 and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was dissolved in THF (21.6 mL) and treated with LAH (2.00 g, 52.7 mmol) at room temperature. The reaction mixture was heated at reflux for 48 h, cooled to 0 °C and quenched with a saturated solution of Rochelle's salt and filtered. The filtrate was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material and 2-(2-bromo-5-methoxyphenyl)acetic acid[169] (0.796 g, 3.25 mmol) in DCM (17.3 mL) was treated with EDCI (0.622 g, 3.25 mmol) at room temperature. The reaction mixture was stirred for 16 h, quenched with water and extracted with EtOAc (2x). The combined organic layers were washed with water (2x) and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure.

[*] (CW135-058, CW135-059, CW135-066: procedure and proton NMR; CW120-074: carbon NMR)

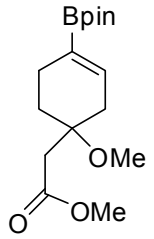
Purification by chromatography on SiO_2 (Hexanes:EtOAc = 2:1) afforded 0.7522 g (53%) of **3-126**[141] as a sticky clear solid: ^{1}H NMR ($CDCl_3$) δ 7.42 (d, 1 H, *J* = 9.0 Hz), 7.32 (t, 1 H, *J* = 7.8 Hz), 7.27-7.22 (m, 1 H), 7.15 (t, 1 H, *J* = 8.1 Hz), 6.94 (d, 1 H, *J* = 7.5 Hz), 6.89 (d, 1 H, *J* = 3.0 Hz), 6.85 (d, 1 H, *J* = 8.1 Hz), 6.72 (dd, 1 H, *J* = 8.4, 1.8 Hz), 6.69 (dd, 1 H, *J* = 9.0, 2.7 Hz), 6.60 (app d, 1 H, *J* = 7.8 Hz), 6.48 (t, 1 H, *J* = 1.8 Hz), 4.92-4.84 (m, 1 H), 4.28-4.16 (m, 2 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.71 (s, 3 H), 3.65 (s, 2 H), 3.07 (dd, 1 H, *J* = 16.2, 6.0 Hz), 2.77 (app d, 1 H, *J* = 16.5 Hz), 2.42-2.32 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 170.0, 159.7, 159.3, 156.9, 145.5, 144.3, 136.0, 133.6, 130.1, 129.53, 129.46, 119.2, 118.9, 117.2, 115.6, 115.2, 113.2, 111.8, 109.4, 66.3, 62.6, 62.3, 55.7, 55.6, 55.3, 44.6, 39.0.



(4aS*,9aS*)-3-(2-bromo-5-methoxyphenyl)-5-methoxy-4a-(3-methoxyphenyl)-9,9a-dihydro-1H-indeno[2,1-b]pyridin-2(4aH)-one (3-127[141]**).**[*] A solution of oxalyl chloride (0.405 mL, 4.72 mmol) in DCM (3.6 mL) at -60 °C was treated with DMSO (0.722 mL, 10.2 mmol) in DCM (1.5 mL). The reaction mixture was stirred at -60 °C for 10 min and treated with **3-126** (0.7522 g, 1.43 mmol) in DCM (1.5 mL). The resulting mixture was stirred for 0.5 h and treated with Et_3N (2.98 mL, 21.2 mmol). The reaction mixture was stirred at -60 °C for 5 min then room temperature for 1 h, quenched with aqueous $NaHCO_3$ and extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 2:1)

[*] (CW135-067, CW135-069: procedure and proton NMR; CW136-002: carbon NMR)

afforded 0.680 g (91%) of the aldehyde as a sticky clear solid, which was immediately dissolved in MeOH (79 mL) and treated with K_2CO_3 (1.79 g, 13.0 mmol) at room temperature. The reaction mixture was heated to 60 °C for 8 h. Concentration of the reaction mixture in vacuo gave a residue that was partitioned between brine and EtOAc. The aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 1:1 with 0.1% TEA) afforded 0.4674 g (71%) of **3-127**[141] as a sticky clear solid: ^{1}H NMR 500 MHz ($CDCl_3$) δ 7.46 (d, 1 H, *J* = 7.7 Hz), 7.30 (t, 1 H, *J* = 8.0 Hz), 7.24 (t, 1 H, *J* = 8.0 Hz), 6.95 (d, 1 H, *J* = 7.5 Hz), 6.92 (app s, 1 H), 6.82 (d, 1 H, *J* = 2.0 Hz), 6.83 - 6.78 (m, 3 H), 6.76 (dd, 1 H, *J* = 9.0, 3.0 Hz), 6.72 (br s , 1 H), 5.75 (app s, 1 H), 4.23 (app d, 1 H, *J* = 3.5 Hz), 3.80 (s, 3 H), 3.77 (s, 3 H), 3.63 (s, 3 H), 3.37 (dd, 1 H, *J* = 15.5, 7.0 Hz), 3.18-3.09 (m, 1 H); ^{13}C NMR 125MHz ($CDCl_3$) δ 163.9, 159.8, 158.9, 156.6, 145.0, 143.6, 140.9, 139.1, 133.1, 130.0, 129.8, 129.4, 119.2, 117.5, 117.2, 115.1, 114.5, 113.1, 112.0, 110.0, 64.4, 55.6, 55.34, 55.31, 55.2, 40.8.

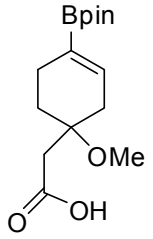


Methyl 2-(1-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enyl)acetate (3-130).[*] A solution of **3-114** (5.00 g, 16.65 mmol) in THF (139 mL) and water (5.3 mL) at 0 °C was treated with OsO_4 (0.088 M in *t*-BuOH, 7.64 mL, 0.673 mmol) followed by NMO (60%wt in water, 4.54 mL, 20.2 mmol). The reaction mixture was stirred at room

[*] (CW135-077, CW135-080, CW135-086, CW157-001: procedure, IR, proton NMR and carbon NMR; note: the intermediates are either unstable or difficult to purify).

temperature for 14 h and treated with a suspension of $NaIO_4$ (10.7 g, 50.0 mmol) in water (33.0 mL). The resulting mixture was stirred at room temperature for 4 h. The reaction mixture was partitioned between ether and water, and the aqueous layer was extracted with ether (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 5:1) afforded 3.76 g (75%) of the aldehyde as a black oil, which was immediately taken to the next step. A fraction of the aldehyde (1.63 g, 5.39 mmol) was dissolved in a mixture of *t*-BuOH (139 mL) and water (58.3 mL). The mixture was then treated with 2-methyl-2-butene (40.0 mL, 378 mmol), NaH_2PO_4 (5.95 g, 49.6 mmol) and $NaClO_2$ (3.37 g, 37.2 mmol) at room temperature. The reaction mixture was stirred overnight and extracted with EtOAc (3x). The combined organic layers were washed with 5% aqueous KH_2PO_4 (2x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 2:1 to DCM:MeOH 10:1) afforded 1.78 g of the acid as a black oil. A fraction of the acid (0.626 g, 1.97 mmol) and K_2CO_3 (0.402 g, 2.91 mmol) in DMF (12.3 mL) at 0 °C was treated with MeI (0.230 mL, 3.70 mmol). The reaction mixture was stirred at the same temperature for 3 h, diluted with water and extracted with EtOAc (3x). The combined organic layers were washed with saturated $NaHCO_3$ (1x), water (2x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:Et_2O = 4:1) afforded 0.3177 g (49% over two steps) of the ester as a clear oil. A fraction of the ester (0.2948 g, 0.926 mmol) together with $PdCl_2(PPh_3)_2$ (8.54 mg, 0.0278 mmol), Ph_3P (3.61 mg, 0.0556 mmol), bis(pinacolato)diboron (0.261 g, 1.02 mmol) and KOPh (0.121 g, 1.39 mmol) were dissolved in toluene and heated to 50 °C for 3.5 h. The reaction mixture was partitioned between water and ether and the aqueous layer was extracted with ether (2x). The combined organic layers was

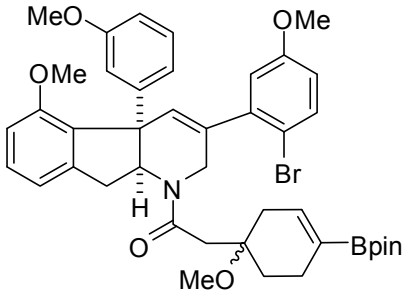
washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:Et_2O = 8:1 to 6:1) afforded 0.1969 g (69%) of **3-130** as a clear oil: IR (neat) 2974, 2929, 2845, 2827, 1735, 1634, 1433 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.39-6.33 (m, 1 H), 3.60 (s, 3 H), 3.17 (s, 3 H), 2.50 (AB, 1 H, *J* = 13.5 Hz), 2.43 (AB, 1 H, *J* = 13.8 Hz), 2.30-2.23 (m, 1 H), 2.23-2.05 (m, 2 H), 1.80-1.40 (m, 1 H), 1.80-1.60 (m, 1 H), 1.18 (s, 12 H); ^{13}C NMR ($CDCl_3$) δ 171.2, 139.3, 83.2, 73.8, 53.5, 51.5, 49.1, 40.5, 36.7, 36.4, 30.1, 24.9, 24.8, 24.1; MS (EI) *m/z* (rel intensity) 295 (8%), 278 (65%), 236 (25%), 205 (90%), 130 (65%), 101 (100%); HRMS (EI) *m/z* calcd for $C_{15}H_{24}BO_5$ (M-CH_3) 295.1717, found 295.1717.



2-(1-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enyl)acetic acid (3-131). [*] A solution of **3-130** (0.1969 g, 0.635 mmol) in THF (10.4 mL) at room temperature was treated with LiOH (1 M in water, 1.90 mL, 1.90 mmol). The reaction mixture was stirred at room temperature for 1.5 h, acidified with 10% aqueous $NaHSO_4$ and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 0.1732 g (92%) of **3-131** as a clear oil: IR (neat) 2974, 2931, 2830, 1729, 1705, 1636, 1386 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.39 (br s, 1 H), 6.41-6.34 (m, 1 H), 3.24 (s, 3 H), 2.53 (AB, 1 H, *J* = 13.8 Hz), 2.47 (AB, 1 H, *J* = 14.1 Hz), 2.34-2.26 (m, 1 H), 2.26-2.05 (m, 2 H), 1.86-1.65 (m, 2 H), 1.20 (s, 12 H); ^{13}C NMR ($CDCl_3$) δ 175.3, 139.0, 83.2, 74.1, 49.1, 40.3, 36.4, 35.9, 30.2, 29.9, 24.8, 24.7, 24.1; MS (EI) *m/z* (rel

[*] (CW157-002: procedure, IR, proton NMR and carbon NMR)

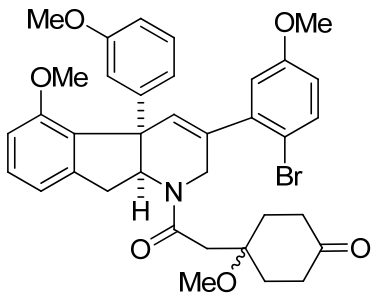
intensity) 281 (13%), 264 (80%), 236 (65%), 205 (90%), 165 (60%), 137 (60%), 116 (90%), 101 (100%); HRMS (EI) *m/z* calcd for $C_{14}H_{22}BO_5$ (M-CH_3) 281.1560, found 281.1559.



1-((4aS*,9aS*)-3-(2-Bromo-5-methoxyphenyl)-5-methoxy-4a-(3-methoxyphenyl)-2,4a,9,9a-tetrahydro-1H-indeno[2,1-b]pyridin-1-yl)-2-(1-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enyl)ethanone (3-132).[*] A solution of **3-127** (0.4527 g, 0.894 mmol) in THF (44 mL) at 0 °C was treated with LAH (0.407 g, 10.7 mmol) followed by $ZnCl_2$ (0.5 M in THF, 10.7 mL, 5.35 mmol). The reaction mixture was stirred at room temperature for 1.5 h, cooled to 0 °C, quenched with a solution of saturated Rochelle's salt and extracted with EtOAc (3x). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford crude amine **3-128**[127] (0.4402 g) which was used without purification. An analytical sample was obtained after purification by chromatography on SiO_2 (Hexanes:EtOAc = 1:1 with 0.2% Et_3N): ^{1}H NMR ($CDCl_3$) δ 7.44 (d, 1 H, *J* = 8.7 Hz), 7.27 (t, 1 H, *J* = 7.8 Hz), 7.19 (t, 1 H, *J* = 7.8 Hz), 6.96 (d, 1 H, *J* = 7.2 Hz), 6.84 (t, 1 H, *J* = 2.1 Hz), 6.81-6.72 (m, 4 H), 6.69 (dd, 1 H, *J* = 8.7, 3.0 Hz), 6.37 (s, 1 H), 3.82 (dd, 1 H, *J* = 17.4, 1.8 Hz), 3.769 (s, 3 H), 3.765 (s, 3 H), 3.68 (dd, 1 H, *J* = 6.9, 4.8 Hz), 3.63 (s, 3 H), 3.53 (d, 1 H, *J* = 17.4 Hz), 3.18 (dd, 1 H, *J* = 16.2, 6.9 Hz), 2.94 (dd, 1 H, *J* = 16.2, 4.5 Hz); ^{13}C NMR ($CDCl_3$) δ 159.7, 159.0, 157.6, 147.6, 143.9, 143.8, 139.6, 133.4, 132.6, 130.1, 129.2, 119.6, 118.0, 116.1,

[*] (CW135-073, CW157-003: procedure, NMRs, IR and MS; CW135-003: purification of **3-128**)

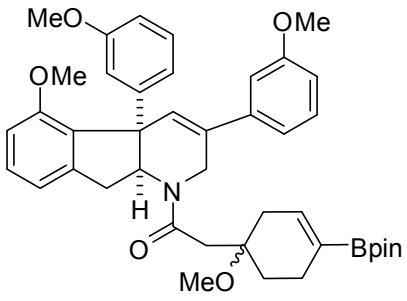
114.3, 113.3, 113.0, 111.4, 109.7, 66.7, 55.7, 55.4, 55.3, 45.4, 36.3. A fraction of the crude amine (0.2057 g) and **3-131** (0.1732 g, 0.585 mmol) was dissolved in DMF (4.9 mL) and treated with DIPEA (0.145 mL, 0.835 mmol) followed by HATU (0.2223 g, 0.585 mmol) at room temperature. The reaction mixture was stirred at room temperature for 14 h, quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with water (3x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:1 to 2:1) afforded 0.2522 g (78% over two steps) of **3-132** (mixture of diastereomers, ratio = 1:1) as a sticky yellow solid: IR (neat) 2972, 2931, 2832, 1815, 1733, 1632, 1589, 1477, 1462 cm^{-1}; Representative ^1H NMR of one diastereomer ($CDCl_3$) δ 8.66 (dd, 1 H, *J* = 4.5, 1.2 Hz), 6.50-6.44 (m, 1 H), 5.82 (s, 1 H), 5.18 (dd, 1 H, *J* = 9.3, 1.8 Hz), 4.72 (AB, 1 H, *J* = 8.4 Hz), 4.67 (AB, 1 H, *J* = 8.7 Hz), 3.73 (s, 3 H), 3.72 (s, 3 H), 3.35 (s, 3 H), 3.01 (s, 3 H), 1.24 (s, 12 H); ^{13}C NMR of a mixture of both diastereomers and rotamers ($CDCl_3$) δ 170.3, 166.2, 159.53, 159.49, 158.8, 156.0, 151.8, 146.44, 146.37, 142.1, 141.9, 140.5, 140.1, 139.5, 138.7, 135.9, 135.8, 134.9, 133.4, 131.6, 130.74, 130.66, 129.4, 129.1, 126.5, 120.9, 119.0, 117.4, 116.3, 114.7, 113.1, 112.9, 112.7, 111.7, 111.6, 109.8, 83.3, 83.1, 74.4, 74.3, 74.1, 66.1, 66.0, 55.7, 55.63, 55.55, 55.3, 55.0, 49.5, 49.2, 48.9, 48.8, 41.0, 38.8, 38.1, 37.5, 36.7, 36.1, 35.3, 34.7, 33.9, 30.1, 29.6, 29.0, 24.8, 24.3, 23.8; MS (ESI) *m/z* 770.2 (M+1), 1563 (2M+23); HRMS (ESI) *m/z* calcd for $C_{42}H_{49}BNO_7NaBr$ (M+Na) 792.2683, found 792.2680.



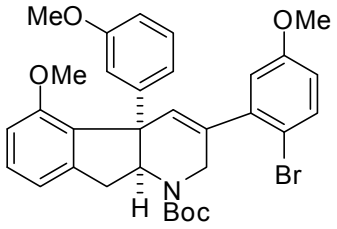
Attempted preparation of **3-134.**[*] A mixture of **3-132** (15.2 mg, 0.0197 mmol) and K_2CO_3 (5.5 mg, 0.039 mmol) in DMSO (3.9 mL) was degassed by two freeze-pump-thaw cycles and treated with a solution of $Pd(PPh_3)_4$ (1.1 mg, 0. 99 μmol) in degassed DMSO (0.21 mL). The reaction mixture was heated to 85 °C for 24 h, treated with additional $Pd(PPh_3)_4$ (1.1 mg, 0.99 μmol) in degassed DMSO (0.21 mL) and heated to 85 °C for another 24 h. After cooling to room temperature, the mixture was partitioned between saturated aqueous NH_4Cl and EtOAc. The aqueous phase was extracted with EtOAc (2x). The combined organic layers were washed with water (2x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes : EtOAc = 1:1) afforded 3.3 mg (30%) of **3-134** (mixture of diastereomers) as a clear sticky solid: IR (neat) 2931, 2832, 1708, 1634, 1589, 1462 cm^{-1}; Representative ^1H NMR of one diastereomer 600 MHz ($CDCl_3$) δ 7.43 (d, 1 H, J = 9.07 Hz), 7.22 (t, 1 H, J = 7.8 Hz), 5.85 (s, 1 H), 4.64 (t, 1 H, J = 8.4 Hz), 3.80 (s, 3 H), 3.77 (s, 3 H), 3.55 (s, 3 H), 3.39 (dd, 1 H, J = 15.0, 10.2 Hz), 3.08 (s, 3 H), 2.49 (dt, 1 H, J = 13.8, 6.6 Hz), 2.38 (dt, 1 H, J = 13.8, 6.6 Hz); ^{13}C NMR of a mixture of both diastereomers and rotamers 150 MHz ($CDCl_3$) 211.6, 169.8, 169.7, 159.8, 159.5, 159.2, 159.1, 156.2, 146.9, 146.7, 142.4, 141.9, 141.8, 141.7, 135.8, 133.9, 133.7, 131.7, 131.0, 130.8, 129.7, 129.5, 129.4, 129.0, 126.5, 126.4, 119.3, 117.6, 117.5, 117.2, 116.7, 116.6, 115.1, 115.0, 114.8, 113.4, 113.3, 113.24, 113.18,

[*] (CW135-094: procedure and NMRs; CW157-004: HRMS)

111.8, 111.2, 110.2, 110.1, 74.5, 73.9, 66.4, 56.2, 56.0, 55.9, 55.8, 55.52, 55.48, 55.34, 55.25, 55.2, 55.1, 55.0, 49.28, 49.26, 41.4, 41.3, 38.2, 38.1, 38.0, 36.8, 34.2, 33.1, 32.4, 29.9; MS (ESI) *m/z* 660.2 (M+H), 1342.8 (2M+Na); HRMS (ESI) *m/z* calcd for $C_{36}H_{38}NO_6NaBr$ (M+Na) 682.1780, found 682.1804.



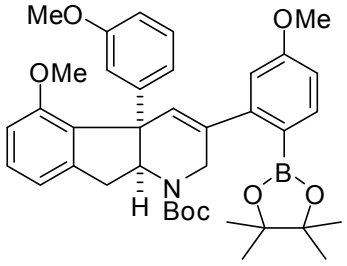
Attempted preparation of **3-133.**[*] A mixture of **3-132** (5.0 mg, 0.0065 mmol), Pd(*t*-$Bu_3P)_2$ (0.17 mg, 0.00032 mmol), K_2CO_3 (2.7 mg, 0.020 mmol) and DMSO (1.29 mL) in a glass tube was frozen in LN_2 under vacuum. The tube was flame-sealed and heated to 150 °C for 3 h. The reaction mixture was partitioned between water and EtOAc and the aqueous phase was extracted with EtOAc (2x). The combined organic layers were washed with water (2x) and brine (1x), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by PTLC (Hexanes:EtOAc = 1:1) afforded 1.2 mg (24%) of SM and 0.2 mg of by-PD **3-135**: MS (ESI) *m/z* (M+H) 692.3.



(4aS*,9aS*)-*tert*-Butyl 3-(2-bromo-5-methoxyphenyl)-5-methoxy-4a-(3-

[*] (CW161-022: procedure and MS)

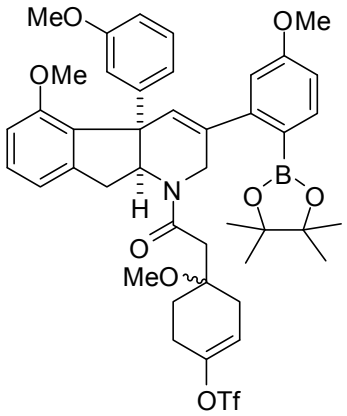
methoxyphenyl)-2,4a,9,9a-tetrahydro-1H-indeno[2,1-b]pyridine-1-carboxylate (3-136).[*] A solution of **3-128** (0.100 g, 0.203 mmol) in DCM (2.0 mL) at room temperature was treated with Boc_2O (0.0532 g, 0.244 mmol). The reaction mixture was stirred at room temperature for 0.5 h and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:Et_2O = 4:1) afforded 0.0879 g (73%) of **3-136** as a sticky clear solid: IR (neat) 2998, 2966, 2954, 2832, 1688, 1589, 1567, 1477 cm^{-1}; ^1H NMR of a mixture of both rotamers 600 MHz ($CDCl_3$) δ 7.48-7.40 (m, 1 H), 7.25 (t, 1 H, 7.8 Hz), 7.20 (t, 1 H, 7.8 Hz), 6.95-6.87 (m, 3 H), 6.85-6.75 (m, 2 H), 6.75-6.68 (m, 2 H), 5.93-5.84 (m, 1 H), 5.09-5.02 (m, 0.3 H), 4.96 (t, 0.7 H, *J* = 9.0 Hz), 4.87 (d, 0.7 H, *J* = 18.6 Hz), 4.67 (d, 0.3 H, *J* = 18.0 Hz), 3.91 (d, 1 H, *J* = 18.5 Hz), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.53 (s, 3 H), 3.29 (t, 0.7 H, *J* = 13.8 Hz), 3.17 (br s, 0.7 H), 3.07 (dd, 0.7 H, *J* = 15.0, 8.4 Hz), 1.15 (s, 9 H); ^{13}C NMR of a mixture of both rotamers 150 MHz ($CDCl_3$) δ 159.5, 159.0, 156.3, 154.9, 147.3, 142.7, 142.3, 136.1, 135.2, 133.6, 131.8, 131.5, 129.3, 128.9, 127.5, 127.2, 119.4, 118.0, 117.5, 117.0, 116.5, 114.9, 114.6, 113.4, 112.7, 112.6, 111.8, 111.6, 110.0, 109.9, 80.1, 79.8, 63.5, 61.9, 55.8, 55.6, 55.5, 55.4, 55.3, 55.2, 43.0, 41.9, 33.2, 33.0, 28.6, 28.5, 28.1; HRMS (ESI) *m/z* calcd for $C_{32}H_{34}NO_5NaBr$ (M+Na) 614.1518, found 614.1526.



(4aS*,9aS*)-*tert*-Butyl 5-methoxy-3-(5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-

[*] (CW157-035: procedure, IR, HRMS and NMRs)

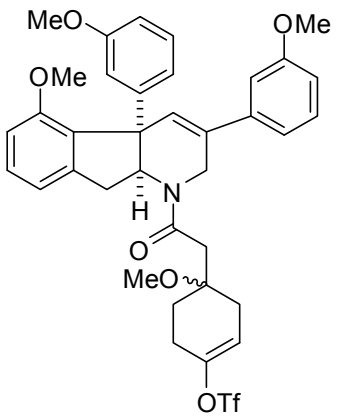
dioxaborolan-2-yl)phenyl)-4a-(3-methoxyphenyl)-2,4a,9,9a-tetrahydro-1H-indeno[2,1-b]pyridine-1-carboxylate (3-137) (CW157-066: procedure, IR and NMRs). A solution of **3-136** (0.0100 g, 0.0169 mmol) in ether (0.35 mL) at -78 °C was treated with butyllithium (1.38 M in hexane, 0.0245 mL, 0.0338 mmol) dropwise. The reaction mixture was stirred for 20 min and treated with 2-isopropoxy-4,4,5,5-tetramethyldioxaborolane. The reaction mixture was then warmed to -40 °C over 20 min and quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (2x). The organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by PTLC (Hexanes:EtOAc = 2:1) afforded 0.0081 g (75%) of **3-137** as a sticky clear solid: ^{1}H NMR of a mixture of both rotamers 600 MHz ($CDCl_3$) δ 7.81-7.76 (m, 1 H), 7.44-7.41 (m, 0.3 H), 7.27-7.16 (m, 3.7 H), 7.06 (d, 0.3 H, 6.6 Hz), 6.98 (d, 1.3 H, *J* = 7.2 Hz), 6.92-6.71 (m, 9 H), 6.69 (d, 1.4 H, *J* = 8.4 Hz), 6.31 (s, 0.3 H), 5.85-5.76 (m, 1 H), 5.10-5.01 (m, 0.3 H), 5.00-4.88 (m, 1.4 H), 4.76 (d, 0.7 H, *J* = 18.0 Hz), 4.44 (d, 0.3 H, *J* = 18.0 Hz), 4.08-3.97 (m, 1.3 H), 3.84 (s, 3 H), 3.83 (s, 1 H), 3.79 (m, 0.6 H), 3.77 (s, 0.7 H), 3.75 (s, 3 H), 3.73 (s, 1 H), 3.59 (s, 1 H), 3.53 (s, 0.8 H), 3.52 (s, 3 H), 3.32-3.27 (m, 0.5 H), 3.18-3.02 (m, 1 H), 2.98 (dd, 1 H, *J* = 14.4, 7.8 Hz), 1.27 (s, 8 H), 1.20 (s, 7 H), 1.13 (s, 9 H); ^{13}C NMR of a mixture of both rotamers 150MHz ($CDCl_3$) δ 161.9, 160.0, 159.5, 156.3, 154.9, 149.6, 148.2, 143.2, 142.8, 142.7, 138.6, 138.1, 133.6, 132.2, 129.6, 129.3, 129.0, 128.9, 128.7, 124.5, 119.8, 119.4, 118.0, 117.5, 115.9, 113.2, 112.9, 111.8, 111.4, 111.2, 110.0, 109.7, 83.7, 79.9, 79.4, 63.7, 55.8, 55.6, 55.4, 55.32, 55.30, 55.2, 55.1, 43.5, 36.8, 33.4, 29.9, 28.7, 28.2, 24.9, 24.7, 23.5.



4-Methoxy-4-(2-((4aS*,9aS*)-5-methoxy-3-(5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4a-(3-methoxyphenyl)-2,4a,9,9a-tetrahydro-1H-indeno[2,1-b]pyridin-1-yl)-2-oxoethyl)cyclohex-1-enyl trifluoromethanesulfonate (3-138).[*] Compound **3-137** (0.0081 g, 0.0127 mmol) was dissolved in DCM/TFA (10:1 v/v, 0.35 mL). The reaction mixture was stirred at room temperature for 0.5 h, cooled to 0 °C, quenched with 5% aqueous K_2CO_3 and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the crude amine, which was dissolved together with 2-(1-methoxy-4-(trifluoromethylsulfonyloxy)-cyclohex-3-enyl)-acetic acid in DMF (0.15 mL) and treated with DIPEA (0.0044 mL, 0.025 mmol) followed by HATU (0.0067 g, 0.018 mmol) at room temperature. The reaction mixture was stirred for 14 h, quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with water (3x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by PTLC (Hexanes:EtOAc = 1:1) afforded 0.0106 g (54%) of **3-138** (mixture of diastereomers, ratio = 1:1) as a sticky clear solid: IR (neat) 2970, 2933, 2834, 1634, 1593, 1479, 1412 cm^{-1}; Representative ^1H NMR of one diastereomer 600 MHz ($CDCl_3$) δ 7.79

[*] (CW157-070, CW157-073: procedure and NMRs; CW157-057: IR, HRMS; CW135-011: MS)

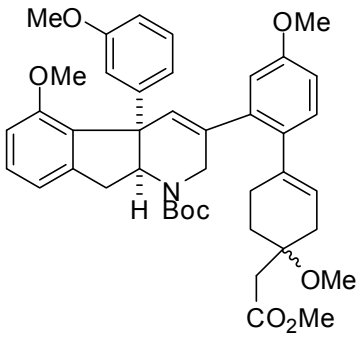
(d, 1 H, *J* = 8.4 Hz), 5.79 (s, 1 H), 5.06 (dd, 1 H, *J* = 18.6, 6.6 Hz), 4.64 (d, 1 H, *J* = 8.4 Hz), 3.97-3.91 (m, 1 H), 3.84 (s, 3 H), 3.76 (s, 3 H), 3.58 (dd, 1 H, *J* = 15.0, 10.8 Hz), 3.54 (s, 3 H), 3.16 (d, 1 H, *J* = 16.2 Hz), 2.98 (s, 3 H), 1.26 (s, 12 H); ^{13}C NMR of a mixture of both diastereomers 150 MHz ($CDCl_3$) δ 169.8, 169.55, 169.53, 162.1, 161.9, 159.8, 156.2, 149.2, 148.8, 148.7, 148.5, 148.4, 147.59, 147.56, 142.1, 138.6, 138.34, 138.31, 138.28, 138.26, 136.32, 136.28, 131.6, 131.5, 129.4, 129.2, 128.7, 125.5, 123.74, 123.73, 119.8, 119.7, 119.5, 117.7, 117.6, 117.5, 116.31, 116.26, 116.0, 115.5, 115.3, 115.2, 114.9, 113.6, 111.8, 111.7, 111.1, 110.9, 110.7, 110.0, 109.8, 83.83, 83.79, 73.9, 73.8, 73.1, 73.0, 66.5, 66.4, 66.1, 60.3, 55.81, 55.79, 55.47, 55.45, 55.3, 55.2, 49.83, 49.81, 49.39, 49.36, 46.9, 46.8, 43.03, 42.98, 40.2, 39.9, 38.3, 38.2, 34.3, 33.1, 31.9, 31.8, 31.2, 30.54, 30.48, 30.2, 30.0, 29.9, 29.5, 25.2, 24.90, 24.86, 24.7, 18.7, 15.5; MS (EI) *m/z* (rel intensity) 839 (25%), 706 (15%), 674 (10%), 621 (10%), 580 (10%), 538 (10%), 451 (10%), 252 (100%); HRMS (EI) *m/z* calcd for $C_{43}H_{49}B_1N_1O_{10}F_3S$ 839.3122, found 839.3100.



Attempted cyclization of **3-133.**[*] A mixture of Pd(P*t*-Bu_3)$_2$ (0.6 mg, 0.00011 mmol), **3-138** (1.9 mg, 0.0023 mmol) and Cs_2CO_3 (2.2 mg, 0.0068 mmol) in dioxane (0.44 ml) was heated

[*] (CW157-058: procedure, NMR and MS)

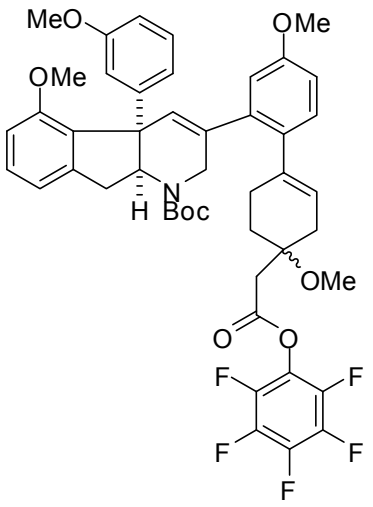
to 85 °C for 4 h. The reaction mixture was quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes : EtOAc = 2:1) afforded 1.3 mg (80%) of by-product **3-139** (mixture of diastereomers) as a clear sticky solid: Representative ^{1}H NMR of one diastereomer 300MHz ($CDCl_3$) δ 6.28 (s, 1 H), 4.67 (t, 1 H, *J* = 9.0 Hz), 3.82 (s, 3 H), 3.74 (s, 3 H), 3.61 (s, 3 H), 2.98 (s, 3 H); MS (ESI) *m/z* 713.9 (M+H), 735.8 (M+Na).



(4aS*,9aS*)-*tert*-Butyl 5-methoxy-3-(5-methoxy-2-(4-methoxy-4-(2-methoxy-2-oxoethyl)cyclohex-1-enyl)phenyl)-4a-(3-methoxyphenyl)-2,4a,9,9a-tetrahydro-1H-indeno[2,1-b]pyridine-1-carboxylate (3-140).[*] A mixture of Pd(P*t*-Bu_3)$_2$ (4.5 mg, 0.0088 mmol), **3-136** (52.3 mg, 0.0883 mmol), **10** (68.5 mg, 0.221 mmol) and Cs_2CO_3 (86.3 mg, 0.265 mmol) in dioxane (0.75 ml) was heated to 95 °C for 15 h. The reaction mixture was cooled to room temperature, passed through a pad of SiO_2 and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes : EtOAc = 6:1 to 4:1) afforded 57.2 mg (93%) of **3-140** (mixture of diastereomers, ratio = 1:1) as a sticky clear solid: IR (neat) 2944, 2935, 2832, 1735, 1688, 1599, 1585, 1477 cm^{-1}; Representative ^{1}H NMR of one diastereomer ($CDCl_3$) δ 5.95 (s, 1 H), 5.39 (app s, 1 H), 5.02-4.78 (m, 2 H), 3.81 (s, 3 H), 3.74 (s, 3 H), 3.70 (s, 3 H),

[*] (CW157-063: procedure, NMRs, IR and HRMS)

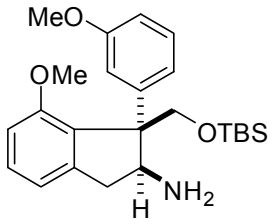
3.52 (s, 3 H), 3.26 (s, 3 H), 3.15-2.96 (m, 2 H), 1.12 (s, 9 H); ^{13}C NMR of a mixture of both diastereomers and rotamers 150 MHz ($CDCl_3$) δ 171.4, 170.8, 159.5, 158.5, 158.4, 156.41, 156.38, 155.0, 154.9, 148.0, 147.8, 142.6, 142.5, 139.9, 139.6, 138.0, 137.3, 136.2, 135.7, 135.40, 135.36, 135.1, 135.0, 132.4, 132.2, 130.2, 129.8, 129.3, 128.8, 127.1, 126.8, 126.4, 122.9, 122.8, 119.4, 118.8, 117.7, 117.6, 115.13, 115.06, 113.1, 112.9, 112.7, 112.6, 112.3, 111.2, 111.0, 110.0, 92.2, 81.7, 80.1, 79.7, 79.6, 75.2, 74.1, 73.7, 73.6, 73.4, 63.42, 63.38, 61.9, 55.6, 55.5, 55.3, 55.21, 55.20, 52.0, 51.7, 49.7, 49.5, 43.4, 42.0, 41.9, 41.6, 40.8, 40.7, 40.4, 36.8, 36.7, 35.6, 35.5, 35.3, 34.9, 33.9, 33.8, 33.7, 33.23, 33.20, 30.5, 30.3, 30.1, 29.9, 29.2, 28.62, 28.58, 28.5, 28.4, 28.1, 27.8, 25.0, 24.9, 23.6; MS (ESI) *m/z* 695.9 (M+H), 717.8 (M+Na); HRMS (ESI) *m/z* calcd for $C_{42}H_{49}NO_8$ (M+H) 718.3356, found 718.3383.



(4aS*,9aS*)-*tert*-Butyl 5-methoxy-3-(5-methoxy-2-(4-methoxy-4-(2-methoxy-2-oxoethyl)cyclohex-1-enyl)phenyl)-4a-(3-methoxyphenyl)-2,4a,9,9a-tetrahydro-1H-indeno[2,1-b]pyridine-1-carboxylate (3-141).[*] A solution of **3-140** (35.7 mg, 0.0513 mmol) in THF (0.70 mL) was treated with aqueous LiOH (1.0 M, 1.03 mL, 1.03 mmol) at room

[*] (CW161-010, CW161-019: procedure, NMRs, HRMS and IR; CW161-013: MS)

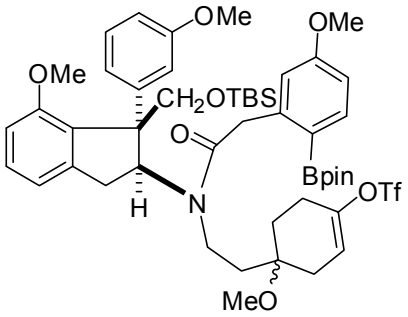
temperature. The reaction mixture was stirred for 4 days, acidified with 10% aqueous $NaHSO_4$ and extracted with EtOAc (2x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford 36.9 mg of the crude acid. A fraction of the crude acid (12.0 mg, 0.0176 mmol) was dissolved in DCM (0.23 mL) together with pentafluorophenol (6.5 mg, 0.0352 mmol). To this solution was added DCC (7.9 mg, 0.0352 mmol) at room temperature. The reaction mixture was stirred for 20 h, filtered through Celite and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes : EtOAc = 10:1) afforded 11.2 mg (75%) of **3-141** (mixture of diastereomers, ratio = 1:1) as a clear oil: IR (neat) 2935, 2832, 1785, 1688, 1654, 1599, 1585, 1518, 1464 cm^{-1}; Representative ^1H NMR of one diastereomer 600 MHz ($CDCl_3$) δ 5.97 (s, 1 H), 5.45 (app s, 1 H), 3.82 (s, 3 H), 3.74 (s, 3 H), 3.53 (s, 3 H), 3.34 (s, 3 H), 2.92 (d, 1 H, *J* = 13.8 Hz), 2.75 (d, 1 H, *J* = 13.8 Hz), 1.13 (s, 9 H); ^{13}C NMR of a mixture of both diastereomers and rotamers 150 MHz ($CDCl_3$) δ 166.5, 159.6, 158.6, 158.5, 156.5, 156.4, 155.0, 147.9, 142.7, 142.6, 142.2, 140.5, 140.0, 139.6, 138.9, 138.2, 137.3, 136.3, 135.7, 134.9, 134.7, 132.2, 130.3, 129.8, 129.3, 128.9, 126.9, 126.5, 122.7, 122.6, 119.40, 119.37, 117.7, 117.6, 115.4, 115.2, 113.00, 112.95, 112.7, 112.6, 111.1, 110.03, 109.99, 79.8, 79.7, 74.0, 63.5, 63.4, 55.6, 55.5, 55.3, 55.2, 49.7, 42.1, 41.9, 40.1, 40.0, 36.8, 35.2, 34.6, 33.25, 33.18, 30.2, 30.1, 28.6, 28.4, 28.3, 28.1, 24.9, 23.5; MS (ESI) *m/z* 848.4 (M+H); HRMS (ESI) *m/z* calcd for $C_{47}H_{46}NO_8F_5Na$ (M+Na) 870.3041, found 870.3055.



(1R*,2S*)-1-((*tert*-Butyldimethylsilyloxy)methyl)-7-methoxy-1-(3-methoxyphenyl)-2,3-dihydro-1H-inden-2-amine (3-144[141]**).**[*] A solution of **3-113** (0.216 g, 0.427 mmol) and Pd (10% on carbon, 22.7 mg) in MeOH (3.1 mL) was exposed to H_2 at 1 atm for 7 h at room temperature. The balloon was removed and the reaction mixture was treated with HCl (1 M in MeOH, 3.11 mL, 76.8 mmol) at room temperature. The reaction mixture was stirred for 2 h and filtered through a pad of Celite. The pad was washed with EtOAc. The combined filtrates were treated with 5% aqueous K_2CO_3 and extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. A solution of the crude product in THF (1.0 mL) at room temperature was treated with LAH in Et_2O (1 M, 0.853 mL, 0.853 mmol). The reaction mixture was stirred for 17 h, cooled to 0 °C and quenched with 10% aqueous H_2SO_4. The mixture was stirred for approximately 30 min until all of the solids had dissolved. The solution was basified with saturated aqueous $NaHCO_3$ and Rochelle's salt. The mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. A solution of the crude product in DMF/THF (2:3 v/v, 4.0 mL) was treated with imidazole (30.4 mg, 0.446 mmol) and TBSCl (66.2 mg, 0.435 mmol) at room temperature. The reaction mixture was stirred for 15 h, quenched with water and extracted with Et_2O (3x). The combined organic layers were washed with water (2x), brine (2x), dried (Na_2SO_4), filtered and concentrated under

[*] (CW182-050, CW182-052, CW182-054: procedure and proton NMR; CW182-016: carbon NMR)

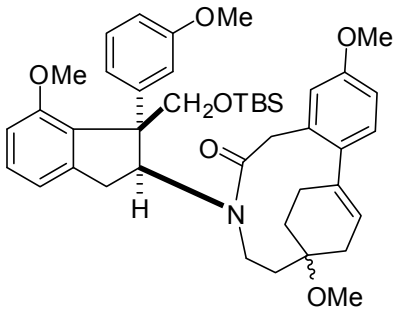
reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:1 with 0.1% Et_3N) afforded 0.0687 g (39%) of **3-144**[141] as a sticky clear solid: ^{1}H NMR ($CDCl_3$) δ 7.27-7.12 (m, 2 H), 6.85 (d, 1 H, *J* = 7.5 Hz), 6.79-6.67 (m, 4 H), 4.58 (d, 1 H, *J* = 9.9 Hz), 4.22 (d, 1 H, *J* = 9.9 Hz), 3.75 (s, 3 H), 3.69 (t, 1 H, *J* = 7.8 Hz), 3.60 (s , 3 H), 3.18 (dd, 1 H, *J* = 15.3, 7.8 Hz), 2.78 (dd, 1 H, *J* = 15.3, 7.8 Hz), 1.92 (br s, 2 H), 0.77 (s, 9 H), -0.08 (s, 3 H), -0.28 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.4, 157.0, 147.6, 145.4, 132.0, 128.9, 128.8, 118.9, 117.3, 112.9, 110.5, 109.0, 65.2, 65.0, 60.5, 60.3, 55.2, 55.0, 42.1, 25.8, 18.1, -5.8, -6.0.



4-(2-(N-((1R*,2S*)-1-((*tert*-Butyldimethylsilyloxy)methyl)-7-methoxy-1-(3-methoxyphenyl)-2,3-dihydro-1H-inden-2-yl)-2-(5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamido)ethyl)-4-methoxycyclohex-1-enyl trifluoromethanesulfonate (3-147).[*] A solution of **3-146** (66.9 mg, 0.162 mmol) and aldehyde **3-115** (53.8 mg, 0.178 mmol) in MeOH (1.97 mL) was treated with $NaBH(OAc)_3$ (0.108 g, 0.485 mmol) at room temperature. The reaction mixture was stirred for 16 h, quenched with 5% aqueous K_2CO_3 and extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:1 to 1:1, with 1% Et_3N) afforded 64.1 mg (57%) of product (mixture of diastereomers, ratio = 1:1) as a yellow oil. A fraction of the product (52.7

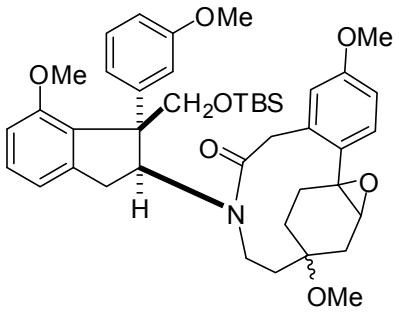
[*] (CW161-081, CW161-084: procedure; CW161-086: NMRs, HRMS; CW182-021: IR)

mg, 0.0753 mmol) and **3-119** (26.4 g, 0.0904 mmol) in DMF (0.88 mL) was treated with DIPEA (0.0262 mL, 0.151 mmol) followed by HATU (40.1 mg, 0.105 mmol) at room temperature. The reaction mixture was stirred for 17 h, quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with water (3x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification on SiO_2 (Hexanes:EtOAc = 6:1 to 3:1) afforded 53.9 mg (73%) of **3-147** (mixture of diastereomers, ratio = 1:1) as a yellow oil: IR (neat) 2927, 2851, 1645, 1600, 1462, 1412 cm^{-1}; Representative ^1H NMR of one diastereomer 500 MHz ($CDCl_3$) δ 7.70 (d, 1 H, *J* = 8.5 Hz), 7.25 (t, 1 H, *J* = 8.0 Hz), 5.61-5.57 (m, 1 H), 4.74 (t, 1 H, *J* = 8.5 Hz), 4.48 (d, 1 H, *J* = 10.5 Hz), 4.26 (d, 1 H, *J* = 10.5 Hz), 4.10 (dt, 1 H, *J* = 12.5, 3.0 Hz), 3.80 (s, 3 H), 3.76 (s, 3 H), 3.60 (s, 3 H), 3.27 (s, 3 H), 1.27 (s, 12 H), 0.72 (s, 9 H), -0.13 (s, 3 H), -0.25 (m, 3 H); ^{13}C NMR of a mixture of both diastereomers and rotamers 125 MHz ($CDCl_3$) δ 173.5, 173.4, 161.7, 160.0, 156.3, 148.9, 148.8, 146.80, 146.76, 144.88, 144.86, 143.9, 143.8, 137.9, 130.3, 128.5, 128.3, 119.1, 116.8, 116.32, 116.30, 115.2, 114.1, 111.70, 111.66, 111.48, 111.46, 83.19, 83.17, 72.63, 72.56, 69.5, 64.0, 60.5, 55.4, 55.2, 54.8, 49.7, 39.5, 38.6, 36.43, 36.36, 33.7, 33.6, 33.3, 30.7, 30.2, 26.0, 25.40, 25.38, 25.1, 24.9, 18.42, 18.38, -5.48, -5.52, -5.76, -5.85; MS (EI) *m/z* (rel intensity) 973 (15%), 916 (90%), 841 (20%), 828 (15%), 816 (10%), 784 (15%), 566 (15%), 397 (20%), 340 (95%), 265 (100%); HRMS (ESI) *m/z* calcd for $C_{49}H_{67}NO_{11}F_3NaS$ (M+Na) 996.4439, found 996.4423.



Preparation of **3-148.**[*] A mixture of **3-147** (10.0 mg, 0.0103 mmol) and K_2CO_3 (2.84 mg, 0.0205 mmol) in DMSO (2.0 mL) and water (0.555 μL, 0.0308 mmol) was degassed by two freeze-pump-thaw cycles and treated with a solution of $Pd(PPh_3)_4$ (0.593 mg, 0.513 μmol) in degassed DMSO (0.11 mL). The reaction mixture was heated to 85 °C for 2 h, cooled to room temperature, quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with water (2x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:1) afforded 3.6 mg (50%) of **3-148** (mixture of diastereomers, ratio = 1:1) as a clear oil: ^{1}H NMR not provided due to the complex chemical shift pattern; ^{13}C NMR of a mixture of both diastereomers 75 MHz ($CDCl_3$) 176.4, 175.1, 160.1, 160.0, 158.3, 158.1, 156.1, 156.0, 147.1, 146.2, 143.9, 143.6, 137.9, 136.2, 135.5, 135.3, 134.3, 133.7, 130.6, 130.2, 129.8, 129.6, 129.5, 129.3, 129.2, 129.1, 128.8, 126.4, 124.4, 119.5, 118.6, 117.0, 116.8, 116.6, 116.4, 113.1, 112.9, 112.3, 112.0, 111.8, 111.1, 110.9, 109.5, 109.4, 109.2, 75.7, 72.0, 70.6, 65.2, 64.2, 63.3, 62.3, 61.6, 60.6, 55.7, 55.6, 55.3, 55.2, 54.94, 54.90, 50.0, 49.7, 49.2, 42.7, 42.1, 40.9, 39.4, 38.9, 37.1, 36.9, 35.5, 35.1, 32.9, 32.4, 30.2, 30.0, 29.9, 29.2, 26.1, 25.7, 24.9, 23.6, 21.3, 18.0, 17.9, 14.4, -5.3, -5.7, -6.1, -6.2.

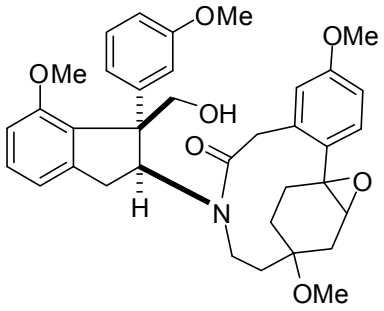
[*] (CW161-085: procedure and proton NMR; CW161-089: carbon NMR)



Preparation of **3-149** and **3-150**.[*] **3-148** (13.9 mg, 0.0199 mmol) was dissolved in a solution of DMDO[170] (0.0301 M in DCM, 1.32 mL, 0.0398 mmol) at room temperature. The reaction mixture was stirred for 20 min, quenched with 5% aqueous $Na_2S_2O_3$ and extracted with DCM (2x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes : EtOAc = 4:1) afforded 6.3 mg (44%) of **3-149** (single diastereomer) as a clear oil and 5.8 mg (41%) of **3-150** (single diastereomer) as a clear oil. **3-149:** IR (neat) 2925, 2851, 1690, 1653, 1606, 1587, 1477, 1462 cm^{-1}; Representative ^1H NMR of one rotamer ($CDCl_3$) δ 7.36 (d, 1 H, *J* = 8.7 Hz), 7.23 (t, 1 H, *J* = 8.4 Hz), 6.02 (d, 1 H, *J* = 2.4 Hz), 5.19-5.05 (m, 1 H), 4.69 (dd, 1 H, *J* = 11.7, 7.8 Hz), 4.41 (d, 1 H, *J* = 10.2 Hz), 4.22 (d, 1 H, *J* = 9.9 Hz), 3.75 (s, 3 H), 3.72 (s, 3 H), 3.19 (s, 3 H), 3.92 (d, 1 H, *J* = 3.9 Hz), 2.49 (dd, 1 H, *J* = 16.2, 3.9 Hz), 2.14 (d, 1 H, *J* = 15.9 Hz), 0.67 (s, 9 H), -0.07 (s, 3 H), -0.40 (s, 3 H); HRMS (ESI) *m/z* calcd for $C_{42}H_{55}NO_7NaSi$ (M+Na) 736.3646, found 736.3606; **3-150:** IR (neat) 2924, 2851, 1645, 1606, 1587, 1462, 1433 cm^{-1}; Representative ^1H NMR of one rotamer ($CDCl_3$) δ 6.10 (d, 1 H, *J* = 2.7 Hz), 4.72 (dd, 1 H, *J* = 11.1, 8.7 Hz), 4.52 (d, 1 H, *J* = 10.2 Hz), 4.22 (d, 1 H, *J* = 10.2 Hz), 3.76 (s, 3 H), 3.73 (s, 3 H), 3.57 (s, 3 H), 3.29 (d, 1 H, *J* = 3.9 Hz), 2.69-2.58 (m, 1 H), 0.68 (s, 9 H), -0.10 (s, 3 H), -0.37 (s, 3 H); HRMS (ESI) *m/z* calcd for $C_{42}H_{55}NO_7NaSi$ (M+Na) 736.3646, found 736.3717; ^{13}C NMR of a mixture of both

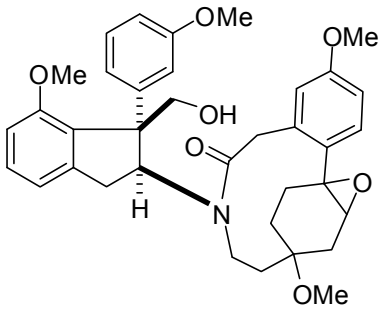
[*] (CW182-026: procedure, proton NMR, CW182-093: IR and HRMS)

diastereomers (**3-149**+**3-150**) ($CDCl_3$) δ 174.8, 173.7, 172.6, 160.3, 160.2, 159.4, 159.3, 158.8, 158.6, 156.1, 156.0, 146.8, 146.0, 143.8, 143.2, 135.8, 134.9, 132.1, 131.14, 131.07, 130.2, 130.0, 129.8, 129.7, 129.5, 129.4, 128.1, 119.59, 119.56, 118.1, 117.8, 117.1, 116.9, 116.7, 113.4, 113.2, 112.1, 111.9, 111.8, 111.0, 109.7, 109.6, 109.2, 74.5, 73.7, 72.1, 70.8, 64.2, 63.4, 62.6, 62.5, 61.2, 60.2, 59.8, 57.7, 55.73, 55.67, 55.6, 55.33, 55.26, 55.0, 54.9, 49.3, 48.7, 46.0, 43.2, 39.7, 39.4, 37.4, 37.3, 35.3, 32.3, 31.9, 31.2, 30.3, 29.6, 29.4, 26.1, 25.7, 24.8, 18.0, 17.9, -5.3, -5.7, -6.1, -6.2.



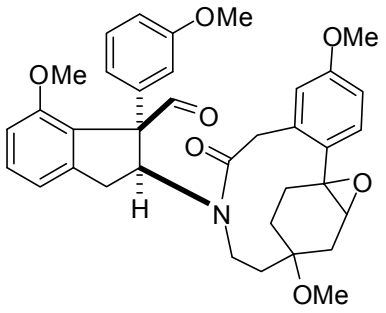
Preparation of **3-151**.[*] A solution of **3-149** (12.3 mg, 0.0172 mmol) in THF 0.50 mL was treated with a solution of TBAF (1.0 M in THF, 0.172 mL, 0.172 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 7.5 h, quenched with water and extracted with EtOAc (2x). The combined organic layers were washed with water (1x), brine (1x), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes : EtOAc = 3:2) afforded 5.3 mg (51%) of **3-151** as a clear sticky solid: IR (neat) 3432, 2929, 2837, 1606, 1587, 1477, 1461 cm^{-1}; (note the NMR data is not provided here due to the inherent low quality of spectras); HRMS (ESI) *m/z* calcd for $C_{36}H_{41}NO_7Na$ (M+Na) 622.2781, found 622.2775.

[*] (CW192-003: procedure, proton NMR, IR and HRMS)



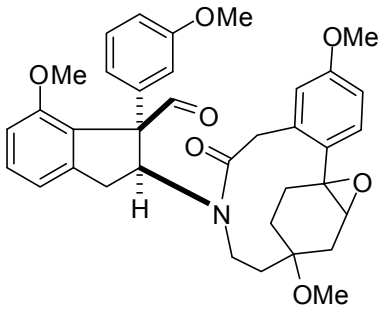
Preparation of **3-152**.* A solution of **3-150** (15.9 mg, 0.0223 mmol) in THF (0.64 mL) was treated with a solution of TBAF (1.0 M in THF, 0.223 mL, 0.223 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 8.5 h, room temperature for 13 h then 50 °C for 5 h. The reaction mixture was quenched with water and extracted with EtOAc (2x). The combined organic layers were washed with water (1x), brine (1x), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes : EtOAc = 3:2) afforded 9.1 mg (68%) of **3-152** as a clear sticky solid: IR (neat) 3417, 2931, 2832, 1619, 1606, 1589, 1505, 1477, 1457 cm^{-1}; (note the NMR data is not provided here due to the inherent low quality of spectras); HRMS (ESI) *m/z* calcd for $C_{36}H_{41}NO_7Na$ (M+Na) 622.2781, found 622.2802.

* (CW192-004: procedure, proton NMR, IR and HRMS)



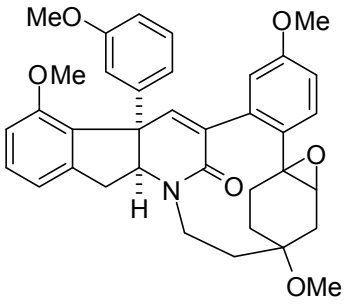
Preparation of **3-142**.* A solution of oxalyl chloride (4.7 μL, 0.0550 mmol) in DCM (0.20 mL) at -60 °C was treated with DMSO (8.4 μL, 0.119 mmol). The reaction mixture was stirred at -60 °C for 10 min and treated with **3-151** (2.5 mg, 4.17 μmol) in DCM (0.30 mL). The resulting mixture was stirred for 15 min and treated with Et_3N (0.0348 mL, 0.248 mmol). The reaction mixture was stirred at -60 °C for 5 min then room temperature for 3 h, quenched with aqueous $NaHCO_3$ and extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:2) afforded 1.6 mg (64%) of **3-142** as a sticky clear solid along with 0.5 mg (19%) chlorination product. **3-142**: IR (neat) 2931, 2832, 1707, 1628, 1602, 1578, 1505, 1477 cm^{-1}; (note the NMR data is not provided here due to the inherent low quality of spectras); HRMS (ESI) *m/z* calcd for $C_{36}H_{39}NO_7Na$ (M+Na) 620.2624, found 620.2584.

* (CW182-035: procedure and proton NMR; CW192-007: IR and HRMS)



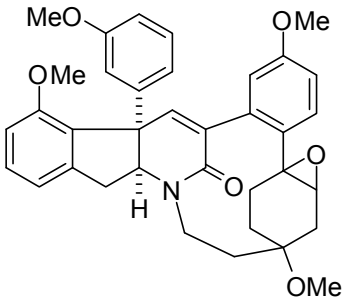
Preparation of **3-143**.* A solution of oxalyl chloride (23.3 μL, 0.271 mmol) in DCM (0.60 mL) at -60 °C was treated with DMSO (41.4 μL, 0.583 mmol). The reaction mixture was stirred at -60 °C for 10 min and treated with **3-152** (12.3 mg, 20.5 μmol) in DCM (0.3 mL). The resulting mixture was stirred for 15 min and treated with Et_3N (0.171 mL, 1.22 mmol). The reaction mixture was stirred at -60 °C for 5 min then room temperature for 20 min, quenched with aqueous $NaHCO_3$ and extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:2) afforded 10.9 mg (89%) of **3-143** as a sticky clear solid: IR (neat) 2933, 2832, 1707, 1628, 1604, 1578, 1505, 1477 cm^{-1}; (note the NMR data is not provided here due to the inherent low quality of spectras); HRMS (ESI) *m/z* calcd for $C_{36}H_{39}NO_7Na$ (M+Na) 620.2624, found 620.2599.

* (CW192-008: procedure, proton NMR, IR and HRMS)



Preparation of **3-144**.[*] A solution of **3-142** (1.7 mg, 2.84 μmol) in MeOH (0.35 mL) was treated with K_2CO_3 (3.93 mg, 0.0284 mmol) at room temperature. The reaction mixture was heated to 65 °C for 2 months in a sealed tube. Concentration of the reaction mixture in vacuo gave a residue that was partitioned between brine and EtOAc. The aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by PTLC on SiO_2 (Hexanes:EtOAc = 1:2) afforded 1.3 mg (68%) of **3-144** as a sticky clear solid: IR (neat) 2927, 2832, 1667, 1623, 1602, 1479, 1462 cm^{-1}; ^1H NMR 500 MHz ($CDCl_3$) δ 7.45 (d, 1 H, *J* = 8.5 Hz), 7.30 (t, 1 H, *J* = 8.0 Hz), 7.22 (t, 1 H, *J* = 8.0 Hz), 6.91 (d, 1 H, *J* = 7.5 Hz), 6.87 (s, 1 H), 6.86-6.78 (m, 4 H), 6.55 (dd, 1 H, *J* = 7.5, 0.5 Hz), 6.47 (t, 1 H, *J* = 2.0 Hz), 4.98 (app t , 1 H, *J* = 14.0 Hz), 4.43 (d, 1 H, *J* = 4.5 Hz), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.71 (s, 3 H), 3.23-3.13 (m, 2 H), 3.18 (s, 3 H), 3.06 (d, 1 H, *J* = 4.0 Hz), 3.00 (dd, 1 H, *J* = 16.5, 5.0 Hz), 2.71-2.63 (m, 1 H), 2.49 (ddd, 1 H, *J* = 16.0, 4.5, 1.0 Hz), 2.18-2.03 (m, 4 H), 1.86 (dd, 1 H, *J* = 16.0, 5.0 Hz), 1.54-1.47 (m, 1 H); ^{13}C NMR 150MHz ($CDCl_3$) δ 164.5, 160.0, 159.2, 156.5, 146.1, 142.6, 139.5, 137.2, 136.1, 131.9, 131.6, 130.3, 130.0, 126.8, 119.8, 117.5, 114.7, 114.1, 112.5, 112.0, 110.4, 74.7, 67.7, 62.9, 59.9, 56.4, 55.6, 55.4, 55.3, 48.6, 39.1, 38.5, 35.9, 31.7, 30.7, 24.7; MS (EI) *m/z* (rel intensity) 579 (30%), 264 (35%), 252 (40%), 121 (90%); HRMS (EI) *m/z* calcd for $C_{36}H_{37}NO_6$ 579.2621, found 579.2620.

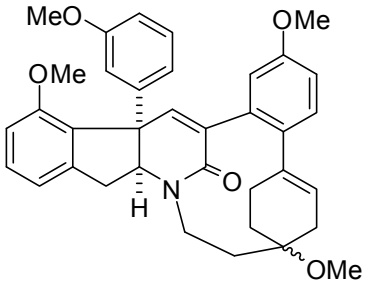
[*] (CW192-013: procedure and IR, HRMS, proton NMR, carbon NMR)



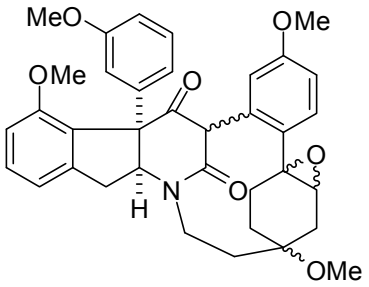
Preparation of **3-145**.* A solution of **3-143** (3.4 mg, 5.69 μmol) in MeOH (3.1 mL) was treated with K_2CO_3 (7.86 mg, 0.0569 mmol) at room temperature. The reaction mixture was heated to 100 °C for 11 days in a sealed tube. Concentration of the reaction mixture in vacuo gave a residue that was partitioned between brine and EtOAc. The aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by PTLC on SiO_2 (Hexanes:EtOAc = 1:2) afforded 1.5 mg (45%) of **3-145** as a sticky clear solid: IR (neat) 2994, 2957, 2942, 2832, 1666, 1625, 1602, 1580, 1457 cm^{-1}; ^1H NMR 600 MHz ($CDCl_3$) δ 7.45 (d, 1 H, *J* = 9.0 Hz), 7.29 (t, 1 H, *J* = 7.8 Hz), 7.23 (t, 1 H, *J* = 7.8 Hz), 6.91-6.88 (m, 2 H), 6.83 (d, 1 H, *J* = 8.4 Hz), 6.79 (dd, 1 H, *J* = 7.8, 2.4 Hz), 6.74 (d, 1 H, *J* = 2.4 Hz), 6.72 (s, 1 H), 6.57 (dd, 1 H, *J* = 8.4, 0.6 Hz), 6.39 (t , 1 H, *J* = 2.4 Hz), 4.30 (d, 1 H, *J* = 2.8 Hz), 3.83 (s, 3 H), 3.86-3.77 (m, 1 H), 3.79 (s, 3 H), 3.76 (d, 1 H, *J* = 6.0 Hz), 3.71 (s, 3 H), 3.61-3.54 (m, 1 H), 3.21 (s, 3 H), 3.18 (d, 1 H, *J* = 16.2 Hz), 3.06 (dd, 1 H, *J* = 16.2, 4.8 Hz), 2.96 (dt, 1 H, *J* = 13.2, 1.8 Hz), 2.45-2.38 (m, 1 H), 2.34 (dd, 1 H, *J* = 16.2, 5.4 Hz), 2.27 (ddd, 1 H, *J* = 15.0, 5.4, 2.4 Hz), 2.05 (d, 1 H, *J* = 15.0 Hz), 1.72-1.67 (m, 1 H), 1.46-1.41 (m, 1 H); ^{13}C NMR 150MHz ($CDCl_3$) δ 165.3, 160.0, 159.4, 156.4, 145.5, 141.9, 138.2, 138.0, 137.3, 132.2, 130.7, 130.4, 130.1, 130.0, 120.0, 117.5, 114.5, 114.1, 113.8, 111.8, 110.3, 73.7, 73.5, 60.8, 59.1, 57.1, 55.5, 55.38, 55.37, 49.2, 46.4, 36.4, 31.4, 30.6, 30.5, 28.0; MS

* (CW192-009: procedure and IR, HRMS, proton NMR, carbon NMR, COSY, HMBC, HMQC)

(EI) *m/z* (rel intensity) 252 (55%), 328 (10%), 368 (10%), 520 (10%), 548 (35%), 579 (90%), HRMS (EI) *m/z* calcd for $C_{36}H_{37}NO_6$ 579.2621, found 579.2615.



Attempted Preparation of **3-123** by means of hydroxyl group elimination with K_2CO_3/MeOH.* A solution of **3-125** (5.5 mg, 9.46 μmol) in MeOH (0.38 mL) was treated with K_2CO_3 (13.1 mg, 0.0946 mmol) at room temperature. The reaction mixture was heated to 65 °C for 2 months in a sealed tube. Concentration of the reaction mixture in vacuo gave a residue that was partitioned between brine and EtOAc. The aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by PTLC on SiO_2 (EtOAc 100%) afforded 2.6 mg (49%) of starting material. LC-MS analysis of the crude material revealed trace amount of product (*m/z* = 564).



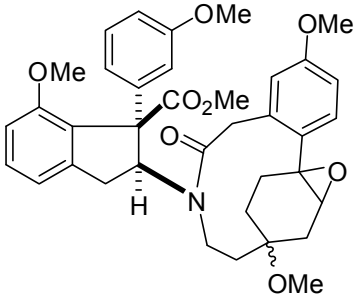
Preparation of **3-157.**† A solution of **3-124** (5.0 mg, 0.00863 mmol) in DCM (0.28 mL) and $NaHCO_3$ buffer (0.5M, pH = 8.3, 0.10 mL) was treated with *m*CPBA (7.44 mg, 0.0431

---

* (CW182-076: procedure and proton NMR, LC-MS)

† (CW135-008: procedure, NMRs and MS)

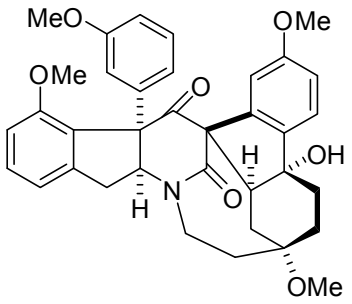
mmol) in small portions at room temperature. The reaction mixture was stirred at room temperature for 48 h, diluted with water and extracted with DCM (3x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (DCM:Et_2O = 10:1) afforded 1.6 mg (31%) of **3-157** (mixture of two diastereomers, ratio = 1.6:1) as a sticky clear solid: IR (neat) 2927, 2832, 1731, 1645, 1604, 1479 cm^{-1}; Representative ^1H NMR of one diastereomer 600 MHz ($CDCl_3$) δ 4.50 (d, 1 H, *J* = 4.8 Hz), 3.96 (app d, 1 H, *J* = 13.8 Hz), 3.87 (s, 3 H), 3.76 (s, 3 H), 3.71 (s, 3 H), 3.31 (d, I H, *J* = 5.4 Hz), 3.20 (s, 3 H); ^{13}C NMR of a mixture of both diastereomers 150 MHz ($CDCl_3$) δ 201.2, 200.7, 169.0, 167.7, 159.58, 159.55, 158.9, 158.7, 156.5, 156.4, 143.9, 143.2, 138.2, 137.4, 133.5, 133.4, 132.0, 131.91, 131.88, 131.4, 131.1, 129.7, 129.3, 129.0, 121.6, 121.4, 120.1, 120.0, 119.6, 118.9, 115.8, 115.5, 113.4, 112.6, 112.4, 112.3, 110.2, 110.1, 74.0, 73.5, 73.3, 68.1, 67.8, 67.4, 62.4, 61.9, 61.6, 60.3, 59.7, 57.2, 55.72, 55.66, 55.35, 55.33, 55.30, 55.26, 49.1, 48.8, 47.0, 39.3, 39.0, 36.8, 36.6, 31.8, 31.2, 31.0, 30.9, 30.3, 29.9, 29.6, 26.8; HRMS (ESI) *m/z* calcd for $C_{36}H_{37}NO_7Na$ (M+Na) 618.2468, found 618.2450.



Preparation of **3-158** and **3-159**.[*] **3-121** (0.136 g, 0.222 mmol) was dissolved in a solution of DMDO[170] (0.0298 M in DCM, 14.9 mL, 0.445 mmol) at room temperature. The reaction mixture was stirred for 20 min, quenched with 5% aqueous $Na_2S_2O_3$ and extracted with

[*] (CW161-017: procedure, NMRs, IR and LC-MS, CW135-043: HRMS)

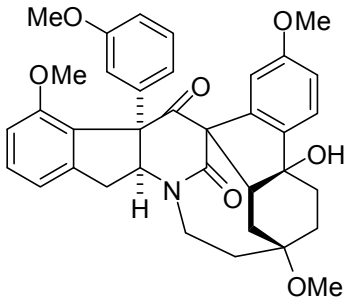
DCM (2x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes : Et_2O = 1:3) afforded 63.9 mg (46%) of **3-158** (single diastereomer) as a sticky clear solid and 64.9 mg (47%) of **3-159** (single diastereomer) as a sticky clear solid (note the NMR data is not provided here due to the low quality of spectra). **3-158:** IR (neat) 2925, 2834, 1714, 1643, 1604, 1479, 1464 cm^{-1}; LC-MS (ESI) *m/z* 628.1 (M+H) and 650.3 (M+Na); MS (EI) *m/z* (rel intensity) 117 (35%), 251 (20%), 280 (25%), 310 (100%), 595 (5%), 627 (15%); HRMS (EI) *m/z* calcd for $C_{37}H_{41}NO_8$ 627.283218, found 627.284410; **3-159:** IR (neat) 2938, 2933, 2832, 1720, 1640, 1604, 1479 cm^{-1}; LC-MS (ESI) *m/z* 628.3 (M+H) and 650.2 (M+Na); MS (EI) *m/z* (rel intensity) 117 (40%), 252 (20%), 280 (20%), 310 (100%), 627 (10%); HRMS (EI) *m/z* calcd for $C_{37}H_{41}NO_8$ 627.2832, found 627.2809.



Preparation of **3-161.**[*] Stock solution of $LiNEt_2$ was prepared as follows: a solution of diethylamine (0.200 mL, 1.93 mmol) in THF (1.0 mL) at -78 °C was treated with BuLi (1.6 M in hexane, 1.2 mL, 1.92 mmol). The mixture was warmed to 0 °C and titrated with Menthol/Fluorene in THF. A fraction of the stock solution (0.841 M, 0.0961 mL, 0.0808 mmol) was diluted with THF (0.98 mL) and treated at 0 °C with a solution of **3-159** (0.0203 g, 0.0323 mmol) in THF (0.40 mL). The flask containing **3-159** was washed twice with THF (2 x 0.4 mL)

[*] (CW161-065: procedure, X-ray, NMR (1D and 2D) and IR; CW161-015: MS)

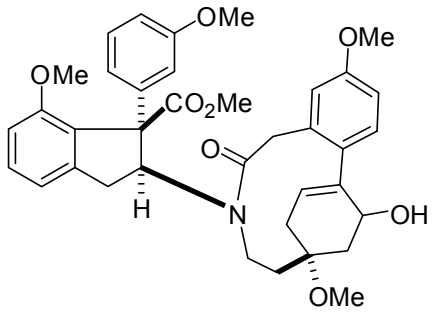
and the eluent was added to the reaction mixture. The reaction mixture was stirred at room temperature for 23 h, quenched with brine and extracted with EtOAc (1x). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:2 to 1:2, all with 0.1% TEA) afforded 0.9 mg (4%) of starting material, 6.3 mg (33%) of **3-161** as a sticky clear solid: IR (neat) 3428, 2929, 2834, 1723, 1664, 1602, 1587, 1479, 1464 cm^{-1}; ^1H NMR 600 MHz ($CDCl_3$) δ 7.39 (t, 1 H, *J* = 8.4 Hz), 7.28 (d, 1 H, *J* = 8.4 Hz), 7.21 (t, 1 H, *J* = 7.8 Hz), 6.97 (d, 1 H, 7.2 Hz), 6.92 (d, 1 H, *J* = 7.8 Hz), 6.87 (dd, 1 H, *J* = 8.4, 2.4 Hz), 6.79 (dd, 1 H, *J* = 7.8, 2.4 Hz), 6.48-6.43 (m, 2 H), 6.26 (s, 1 H), 4.46 (d, 1 H, *J* = 3.6 Hz), 3.83 (s, 3 H), 3.80-3.76 (m, 1 H), 3.74 (s, 3 H), 3.70 (s, 3 H), 3.29 (s, 3 H), 3.25-3.23 (m, 1 H), 3.09 (dt, 1 H, *J* = 13.8, 3.6 Hz), 3.01 (d, 1 H, *J* = 15.6 Hz), 2.86 (dd, 1 H, *J* = 16.2, 4.2 Hz), 2.72-2.65 (m, 1 H), 2.36-2.32 (m, 2 H), 1.98-1.93 (m, 1 H), 1.90 (s, 1 H), 1.88-1.84 (m, 1 H), 1.84-1.80 (m, 1 H), 1.80-1.73 (m, 2 H), 1.62-1.60 (m, 1 H); ^{13}C NMR 150 MHz ($CDCl_3$) δ 207.5, 172.6, 160.3, 159.6, 157.8, 144.5, 142.1, 140.1, 140.0, 131.9, 129.5, 129.0, 125.7, 123.3, 121.4, 119.3, 115.9, 114.1, 112.2, 112.0, 110.4, 78.3, 75.7, 72.6, 72.4, 71.0, 68.4, 67.7, 60.6, 56.1, 55.7, 55.6, 55.4, 55.3, 53.7, 49.0, 45.7, 37.8, 34.1, 33.1, 32.9, 31.7, 29.5, 28.7; MS (EI) *m/z* (rel intensity) 198 (85%), 252 (100%), 567 (10%), 577 (15%), 595 (20%); HRMS (EI) *m/z* calcd for $C_{36}H_{37}NO_7$ 595.2570, found 595.2556. The product was recrystallized from DCM-toluene to give X-ray quality colorless crystals: m.p. 198.5-204.6 °C (lost solvent). The crystal was collected and redissolved in $CDCl_3$ to give a proton NMR spectrum that is identical to the sample before crystallization.



Preparation of **3-162**.* Stock solution of $LiNEt_2$ was prepared as follows: a solution of diethylamine (0.200 mL, 1.93 mmol) in glyme (1.0 mL) at 0 °C was treated with BuLi (1.6 M in hexane, 1.2 mL, 1.92 mmol). The mixture was titrated with Menthol/Fluorene in THF. A solution of **3-158** (5.0 mg, 0.0080 mmol) in glyme (0.24 mL) was treated with the stock solution (0.817M, 0.0244 mL, 0.0199 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 18 h, quenched with brine and extracted with EtOAc (1x). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 1:1 to 1:2, all with 0.1% TEA) afforded 0.8 mg (16%) of starting material, 1.1 mg (23%) of **3-162** as a sticky clear solid: IR (neat) 3417, 2933, 2832, 1636, 1571, 1479, 1435 cm^{-1}; ^1H NMR 600 MHz ($CDCl_3$) δ 7.61 (d, 1 H, *J* = 9.0 Hz), 7.28-7.26 (m, 1 H), 7.25 (d, 1 H, *J* = 7.8 Hz), 7.12 (t, 1 H, 7.8 Hz), 6.90 (d, 1 H, *J* = 7.8 Hz), 6.82-6.78 (m, 2 H), 6.76 (dd, 1 H, *J* = 8.4, 2.4 Hz), 6.70 (d, 1 H, *J* = 7.2 Hz), 6.61 (s, 1 H), 4.60 (app s, 1 H), 4.40 (t, 1 H, *J* = 5.4 Hz), 4.19 (dd, 1 H, *J* = 15.6, 10.2 Hz), 3.80 (s, 3 H), 3.71 (s, 3 H), 3.65 (s, 3 H), 3.15 (s, 3 H), 3.17-3.13 (m, 1 H), 3.09 (dd, 2 H, *J* = 15.0, 5.4 Hz), 2.90-2.82 (m, 1 H), 2.54 (d, 1 H, *J* = 14.4 Hz), 2.19 (dd, 1 H, *J* = 15.0, 3.6 Hz), 2.06-1.96 (m, 2 H), 1.60-1.50 (m, 1 H), 1.48-1.43 (m, 1 H); ^{13}C NMR 150 MHz ($CDCl_3$) δ 188.8, 163.5, 159.6, 158.8, 158.0, 143.0, 142.0, 134.2, 132.3, 131.5, 129.8, 129.1, 124.8, 117.1, 116.7, 115.5, 113.0, 111.5,

* (CW161-067: procedure, NMR (1D and 2D), IR and HRMS)

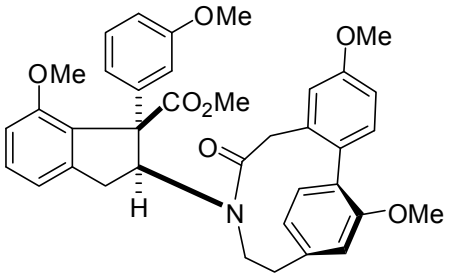
111.2, 105.9, 91.0, 74.7, 72.4, 71.3, 64.9, 56.0, 55.6, 55.5, 48.7, 46.4, 38.7, 36.8, 35.1, 34.5, 30.4; MS (ESI) *m/z* 596.3 (M+H); MS (EI) *m/z* (rel intensity) 252 (100%), 577 (10%), 595 (30%); HRMS (EI) *m/z* calcd for $C_{36}H_{37}NO_7$ 595.2570, found 595.2567.



Preparation of **3-163**.* **3-158** (1.05 g, 1.68 mmol) was dissolved in a mixture of H_2SO_4 (10% aqueous solution, 6.16 mL, 6.71 mmol) and DMSO (29.8 mL) at room temperature. The reaction mixture was stirred for 3 days at the same temperature, poured into cold saturated aqueous $NaHCO_3$ and extracted with EtOAc (3x). The combined organic layers were washed with water (2x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 1:1) afforded 0.828 g (78%) of **3-163** as a white foam (mixture of diastereomers): IR (neat) 3488, 2927, 2849, 1714, 1636, 1604, 1479, 1464, 1431 cm^{-1}; ^1H NMR of major diastereomer 500 MHz ($CDCl_3$) δ 7.23 (t, 1 H, *J* = 8.0 Hz), 7.15 (t, 1 H, *J* = 8.0 Hz), 7.13-7.10 (m, 2 H), 6.97 (app d, 1 H, *J* = 7.5 Hz), 6.90-6.84 (m, 1 H), 6.82-6.72 (m, 3 H), 6.67 (d, 1 H, *J* = 8.5 Hz), 5.67 (d, 1 H, *J* = 5.0 Hz), 4.40 (t, 1 H, *J* = 8.5 Hz), 4.32 (d, 1 H, *J* = 13.5 Hz), 4.25-4.18 (m, 1 H), 4.14-4.04 (m, 2 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.62 (s, 3 H), 3.49 (s, 3 H), 3.32-3.26 (m, 1 H), 3.24 (s, 3 H), 3.09 (dd, 1 H, *J* = 15.0, 9.0 Hz), 2.88 (d, 1 H, *J* = 13.5 Hz), 2.62 (d, 1 H, *J* = 17.0 Hz), 2.24-2.15 (m, 2 H), 2.04-1.93 (m, 2 H),

* (CW210-024: procedure; CW192-040: IR, HRMS; CW182-048: proton and COSY, HMQC, HMBC; CW182-034; carbon NMR)

1.69 (dd, 1 H, J = 15.5, 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 173.5, 171.8, 159.4, 159.3, 156.8, 146.8, 143.5, 140.8, 137.1, 131.9, 131.7, 130.2, 129.7, 129.0, 127.1, 119.8, 118.2, 116.9, 113.9, 112.3, 111.3, 109.8, 73.4, 68.2, 64.2, 55.6, 55.5, 55.4, 52.8, 49.0, 48.5, 40.7, 39.8, 39.1, 35.5, 33.9; HRMS (ESI) *m/z* calcd for $C_{37}H_{41}NO_8Na$ (M+Na) 650.2730, found 650.2680.

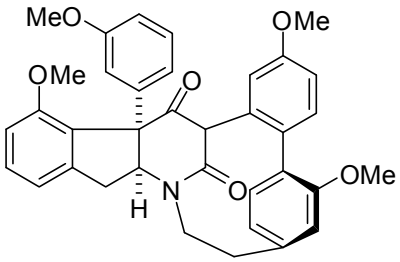


Preparation of **3-165**.* A mixture of **3-163** (0.828 g, 1.32 mmol), molecular sieves 4 Å (1.26 g) and NMO (0.637 g, 5.27 mmol) in DCM (34 mL) was treated with TPAP (92.7 mg, 0.264 mmol) at room temperature. The reaction mixture was stirred for 17 h and directly purified by chromatography on SiO_2 (Hexanes:EtOAc = 2:3) to afford 0.711 g (86%) of the enone as a clear oil. A fraction of the enone (0.131 g, 0.209 mmol) was dissolved in a mixture of DIPEA and trifluoroethanol (1.0 + 1.0 mL) and heated in the microwave at 100 °C for 30 min. The reaction mixture was concentrated under reduced pressure and co-evaporated with acetone (2x). The residue was redissolved in acetone (2.0 mL) and treated with K_2CO_3 (0.289 g, 2.09 mmol) and Me_2SO_4 (0.120 mL, 1.26 mmol) at room temperature. The reaction mixture was heated at reflux for 15 h, cooled to room temperature, diluted with water and extracted with EtOAc (2x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:2)

* (CW210-027, CW210-029, CW224-015: procedure; CW224-015: HRMS; CW192-060: IR; CW192-048: proton and carbon NMR)

afforded 0.1079 g (85%) of **3-165** as a sticky white foam: IR (neat) 2998, 2946, 1725, 1662, 1591, 1567, 1479 cm^{-1}; ^1H NMR 500 MHz ($CDCl_3$) δ 7.48 (d, 1 H, *J* = 8.0 Hz), 7.37 (t, 1 H, *J* = 8.0 Hz), 7.18 (t, 1 H, *J* = 8.0 Hz), 7.01 (d, 1 H, *J* = 7.5 Hz), 6.96 (d, 1 H, *J* = 11.0 Hz), 6.89-6.76 (m, 6 H), 6.56 (d, 1 H, *J* = 2.5 Hz), 4.76 (dd, 1 H, *J* = 7.0, 5.0 Hz), 4.22-4.14 (m, 1 H), 3.82 (s, 3 H), 3.76 (d, 1 H, *J* = 4.5 Hz), 3.73 (s, 3 H), 3.70 (s, 3 H), 3.69 (s, 3 H), 3.52 (s, 3 H), 3.49 (d, 1 H, *J* = 4.5 Hz), 3.33 (dd, 1 H, *J* = 16.0, 7.0 Hz), 2.84-2.67 (m, 3 H), 2.33 (d, 1 H, *J* = 16.0 Hz); ^{13}C NMR 150 MHz ($CDCl_3$) δ 171.6, 171.5, 161.1, 159.5, 158.6, 156.8, 143.5, 143.0, 141.7, 137.6, 131.3, 130.6, 130.44, 130.42, 129.7, 129.1, 126.1, 124.5, 120.9, 119.0, 116.7, 115.5, 115.0, 112.2, 111.7, 110.2, 71.6, 68.0, 55.6, 55.5, 55.39, 55.37, 52.6, 44.1, 41.5, 38.3, 35.3; HRMS (ESI) *m/z* calcd for $C_{37}H_{37}NO_7Na$ (M+Na) 630.2468, found 630.2457.

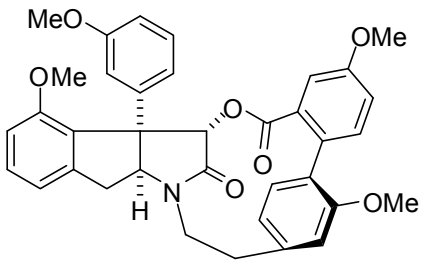
Alternatively, the microwave heating can be substituted by oil bath heating (CW224-015): Enone **3-163** (336 mg, 0.537 mmol) was dissolved in a mixture of DIPEA and trifluoroethanol (3.4 + 3.4 mL) and heated at 78 °C for 50 min. The reaction mixture was concentrated under reduced pressure. The residue was redissolved in acetone (3.4 mL) and treated with K_2CO_3 (0.742 g, 5.37 mmol) and Me_2SO_4 (0.308 mL, 3.22 mmol) at room temperature. The reaction mixture was heated at reflux for 13 h, cooled to room temperature, diluted with water and extracted with EtOAc (2x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:2) afforded 0.273 g (84%) of **3-165** as a sticky white foam with spectroscopy data identical to that of the microwave condition.



Preparation of **3-166**.* A solution of **3-165** (0.103 g, 0.169 mmol) in boiling toluene 1.0x5 mL was added to a suspension of KH (96.7 mg, 0.844 mmol, 35% in mineral oil, pre-washed with toluene three times to remove mineral oil) in toluene 1.0 mL at room temperature. The reaction mixture was stirred for 1.5 h at 108 °C, cooled to 0 °C, quenched with saturated NH_4Cl and extracted with DCM (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 1:1) afforded 75.2 mg (77%) of **3-166** as a white solid: IR (neat) 2929, 2849, 2834, 1733, 1647, 1593, 1464 cm^{-1}; ^1H NMR 600 MHz ($CDCl_3$) δ 7.55 (d, 1 H, *J* = 8.4 Hz), 7.32 (t, 1 H, *J* = 7.8 Hz), 7.25 (t, 1 H, *J* = 7.8 Hz), 7.03 (app s, 1 H), 6.94 (dd, 1 H, *J* = 8.4, 3.0 Hz), 6.88 (d, 1 H, *J* = 7.2 Hz), 6.86 (app s, 1 H), 6.85-6.80 (m, 2 H), 6.62 (d, 1 H, *J* = 7.8 Hz), 6.52 (app s, 1 H), 6.46 (d, 1 H, *J* = 2.4 Hz), 4.39 (app dt, 1 H, *J* = 13.2, 5.4 Hz), 4.28 (s, 1 H), 4.11 (d, 1 H, *J* = 4.8 Hz), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.763 (s, 3 H), 3.758 (s, 3 H), 3.02 (d, 1 H, *J* = 16.2 Hz), 2.97-2.91 (m, 2 H), 2.86-2.77 (m, 2 H); ^{13}C NMR 150 MHz ($CDCl_3$) δ 200.7, 166.5, 161.2, 159.5, 158.7. 156.3, 144.1, 143.4, 138.8, 136.1, 131.4, 131.1, 130.6, 130.4, 130.2, 129.2, 125.8, 121.7, 121.5, 120.5, 118.6, 115.6, 114.4, 112.5, 112.2, 109.7, 67.63, 67.55, 62.9, 55.6, 55.4, 55.30, 55.28, 45.8, 36.3, 33.3; HRMS (ESI) *m/z* calcd for $C_{36}H_{33}NO_6Na$ (M+Na) 598.2206, found 598.2181. A fraction of **3-166** was recrystallized from

* (CW210-040: procedure; CW192-063: mp, IR, HRMS, X-ray; CW192-028: proton NMR, CW192-050 carbon NMR and COSY, HMQC, HMBC)

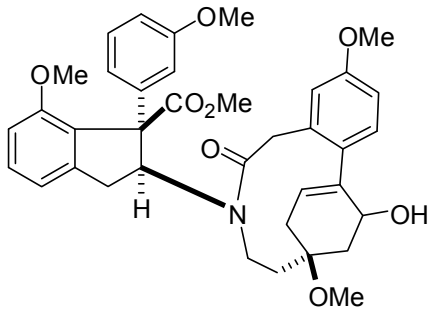
hot toluene to yield X-ray quality colorless crystal: mp 307.2-309.3 °C (toluene). The crystal was collected and redissolved in $CDCl_3$ to give a proton NMR spectrum that is identical to the sample before crystallization.



Preparation of **3-167**.* A solution of **3-166** (2.3 mg, 4.00 μmol) and LiH (1.6 mg, 0.200 mmol) in diglyme 0.5 mL was stirred for 4 days at 140 °C. The reaction mixture was cooled to room temperature, quenched with saturated NH_4Cl and extracted with DCM (2x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by PTLC (Hexanes:EtOAc = 1:2) afforded 1.7 mg (72%) of **3-167** as a clear sticky solid: IR (neat) 2916, 2847, 1708, 1701, 1602, 1477 cm^{-1}; ^1H NMR 500 MHz ($CDCl_3$) δ 7.45 (d, 1 H, *J* = 2.5 Hz), 7.34 (d, 1 H, *J* = 8.5 Hz), 7.20 (t, 1 H, *J* = 8.0 Hz), 7.10 (dd, 1 H, *J* = 8.04, 2.5 Hz), 6.98 (t, 1 H, *J* = 8.0 Hz), 6.95-6.92 (m, 1 H), 6.92-6.89 (m, 2 H), 6.80 (t, 1 H, *J* = 2.0 Hz), 6.78 (d, 1 H, *J* = 7.5 Hz), 6.75-6.71 (m, 2 H), 6.59 (ddd, 1 H, *J* = 5.5, 2.5, 0.5 Hz), 6.40 (s, 1 H), 4.43-4.34 (m, 2 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 3.76 (s, 3 H), 3.61 (s, 3 H), 3.24 (dd, 1 H, *J* = 14.0, 7.0 Hz), 3.13 (dd, 1 H, *J* = 14.0, 6.0 Hz), 3.10-3.02 (m, 2 H), 2.82 (app dt, 1 H, *J* = 12.5, 6.5 Hz); ^{13}C NMR 75 MHz ($CDCl_3$) δ 169.2, 166.3, 159.1, 158.6, 158.2, 157.5, 141.7, 138.9, 138.6, 132.3, 131.8, 130.7, 130.0, 129.7, 129.4, 129.0, 128.7, 121.7, 120.4, 118.8, 118.4, 116.0, 114.7, 112.6, 112.0, 110.0, 72.9, 66.8, 62.0, 55.7, 55.5, 55.3, 38.9, 33.7, 32.8; HRMS (ESI) *m/z*

* (CW210-063: procedure; CW210-050: IR, HRMS, X-ray, proton NMR, carbon NMR and COSY, HMQC, HMBC)

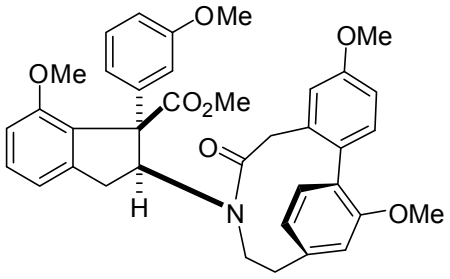
calcd for $C_{36}H_{33}NO_7Na$ (M+Na) 614.2155, found 614.2149. A fraction of **3-167** was recrystallized from hot toluene to yield X-ray quality colorless crystal: mp 274.0-276.0 °C (toluene).



Preparation of **3-168**.* **3-159** (28.2 mg, 0.0449 mmol) was dissolved in a mixture of $Ti(OiPr)_4$ (0.0165 mL, 0.0539 mmol) and toluene (0.50 mL) at room temperature. The reaction mixture was stirred for 33 h at 100 ºC, poured into cold saturated aqueous $NaHCO_3$ and extracted with EtOAc (3x). The combined organic layers were washed with water (1x) and brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 2:3) afforded 17.7 mg (63%) of **3-168** as a clear sticky solid (mixture of diastereomers): IR (neat) 3445, 3337, 2972, 2924, 1714, 1615, 1587, 1550, 1541, 1531, 1425 cm^{-1}; ^1H NMR of major diastereomer 700 MHz ($CDCl_3$) δ 7.23 (t, 1 H, *J* = 7.7 Hz), 7.16 (t, 1 H, *J* = 8.4 Hz), 7.06 (t, 1 H, *J* = 2.1 Hz), 7.02 (d, 1 H, *J* = 8.4 Hz), 6.94-6.92 (m, 1 H), 6.82-6.79 (m, 2 H), 6.77-6.73 (m, 2 H), 6.67 (d, 1 H, *J* = 7.7 Hz), 5.55 (dd, 1 H, *J* = 6.3, 1.4 Hz), 4.75 (t, 1 H, *J* = 8.4 Hz), 4.47 (dd, 1 H, *J* = 9.1, 7.7 Hz), 4.06 (d, 1 H, *J* = 14.0 Hz), 3.99 (t, 1 H, *J* = 14.7 Hz), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.63 (s, 3 H), 3.51 (s, 3 H), 3.31-3.27 (m, 1 H), 3.26 (s, 3 H), 3.15 (dd, 1 H, *J* = 17.5, 9.1 Hz), 2.95 (d, 1 H, *J* = 14.7 Hz), 2.55 (d, 1 H, *J* = 16.8 Hz), 2.41 (ddd, 1 H, *J* = 12.6, 7.0, 2.1 Hz), 2.17-2.12 (m, 1 H), 2.09-1.96 (m, 2 H), 1.82 (d,

* (CW192-088: procedure, IR, HRMS; CW192-081: proton and carbon NMR)

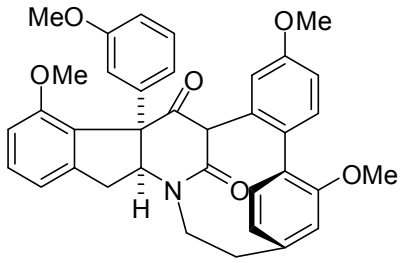
1 H, J = 3.5 Hz), 1.73-1.68 (m, 1 H); ^{13}C NMR 175 MHz ($CDCl_3$) δ 174.2, 172.0, 159.5, 159.4, 156.6, 146.4, 144.2, 137.4, 136.1, 131.9, 131.4, 130.8, 129.7, 129.0, 120.0, 118.0, 116.8, 114.1, 112.3, 111.4, 109.5, 72.0, 67.9, 65.0, 55.8, 55.6, 55.5, 55.4, 52.8, 48.8, 47.9, 40.5, 39.4, 38.0, 35.7, 34.7; HRMS (ESI) *m/z* calcd for $C_{37}H_{41}NO_8Na$ (M+Na) 650.2730, found 650.2731.



Preparation of **3-170**.* A mixture of **3-168** (17.7 mg, 0.0282 mmol), molecular sieves 4 Å (26.9 g) and NMO (13.6 mg, 0.113 mmol) in DCM (0.54 mL) was treated with TPAP (1.98 mg, 0.00564 mmol) at room temperature. The reaction mixture was stirred for 4 h at the same temperature and directly purified by chromatography on SiO_2 (Hexanes:EtOAc = 3:2) to afford 17.0 mg (96%) of enone as a clear oil. A fraction of the enone (13.9 mg, 0.0222 mmol) was dissolved in a mixture of DIPEA and trifluoroethanol (0.6 + 0.6 mL) and heated in the microwave at 100 °C for 30 min. The reaction mixture was concentrated under reduced pressure and co-evaporated with acetone (2x). The residue was redissolved in acetone (0.50 mL) and treated with K_2CO_3 (30.7 mg, 0.222 mmol) and Me_2SO_4 (0.0128 mL, 0.133 mmol) at room temperature. The reaction mixture was heated at reflux for 15 h, cooled to room temperature, diluted with water and extracted with EtOAc (2x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:1) afforded 11.5 mg (85%) of **3-170** as a clear

* (CW192-094, CW210-006: procedure; CW192-091: IR, MS; CW192-096: proton and carbon NMR)

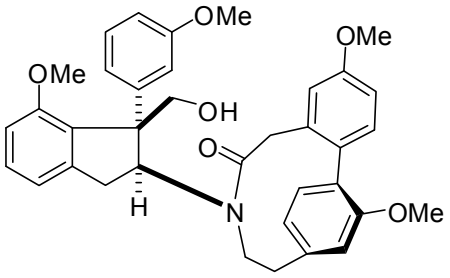
sticky solid: IR (neat) 2994, 2944, 2832, 1725, 1664, 1591, 1569, 1479, 1429 cm^{-1}; ^1H NMR 700 MHz ($CDCl_3$) δ 7.44 (d, 1 H, *J* = 8.4 Hz), 7.38 (t, 1 H, *J* = 7.7 Hz), 7.20 (t, 1 H, *J* = 8.4 Hz), 7.07 (dd, 1 H, *J* = 7.7, 1.4 Hz), 7.01 (d, 1 H, *J* = 7.7 Hz), 6.90-6.81 (m, 6 H), 6.66 (d, 1 H, *J* = 1.4 Hz), 6.59 (d, 1 H, *J* = 2.8 Hz), 4.72 (dd, 1 H, *J* = 7.0, 4.2 Hz), 4.19-4.13 (m, 1 H), 3.82 (s, 3 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 3.71 (s, 3 H), 3.59 (d, 1 H, *J* = 16.8 Hz), 3.51 (s, 3 H), 3.52-3.48 (m, 1 H), 3.33 (dd, 1 H, *J* = 16.1, 7.7 Hz), 2.79 (dd, 1 H, *J* = 11.9, 5.6 Hz), 2.75 (dd, 1 H, *J* = 14.7, 6.3 Hz), 2.69 (dt, 1 H, *J* = 11.9, 5.6 Hz), 2.50 (d, 1 H, *J* = 16.1 Hz); ^{13}C NMR 175 MHz ($CDCl_3$) δ 171.6, 170.9, 159.5, 158.7, 157.5, 156.9, 143.5, 142.6, 141.4, 137.2, 137.1, 132.9, 130.5, 130.3, 129.2, 127.7, 127.4, 125.4, 120.9, 119.2, 118.8, 116.6, 115.0, 112.6, 112.5, 110.2, 71.4, 68.2, 57.8, 55.6, 55.5, 55.4, 52.6, 44.3, 41.8, 38.3, 35.2; HRMS (ESI) *m/z* calcd for $C_{37}H_{37}NO_7Na$ (M+Na) 630.2431, found 630.2468.



Preparation of **3-171**.* A solution of **3-170** (3.8 mg, 6.25 μmol) in toluene 0.1+0.1+0.1 mL was added to a suspension of KH (15.6 mg, 0.136 mmol, 35% in mineral oil, pre-washed with toluene three times to remove mineral oil) in toluene 0.2 mL at room temperature. The reaction mixture was stirred for 4 h at 106 °C, cooled to 0 °C, quenched with saturated NH_4Cl and extracted with EtOAc (1x). The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by PTLC (Hexanes:EtOAc = 1:2)

* (CW210-005: procedure, proton NMR; CW210-065: IR, HRMS)

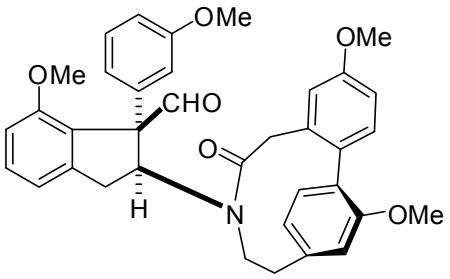
afforded 1.4 mg (39%) of **3-171** (mixture of diastereomers, ratio = 1.5:1) as a clear sticky solid: IR (neat) 3507, 2931, 2832, 1736, 1645, 1599, 1565, 1477 cm^{-1}; Representative ^{1}H NMR of one diastereomer 700 MHz ($CDCl_3$) δ 4.48 (app dt, 1 H, *J* = 13.3, 4.9 Hz), 4.02 (d, 1 H, *J* = 4.2 Hz), 3.85 (s, 3 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.72 (s, 3 H); ^{13}C NMR 150 MHz ($CDCl_3$) δ 196.3, 166.4, 161.1, 159.6, 158.71, 158.66, 157.8, 156.7, 156.5, 144.2, 143.5, 142.9, 142.1, 140.5, 139.0, 138.9, 138.0, 137.2, 136.6, 133.6, 132.3, 131.3, 130.3, 130.08, 130.05, 129.6, 129.5, 129.0, 127.6, 127.4, 124.8, 123.9, 123.2, 121.0, 120.9, 120.6, 118.5, 118.3, 117.9, 117.7, 115.1, 114.2, 113.6, 113.0, 110.1, 109.9, 72.2, 70.8, 67.99, 67.95, 67.4, 62.6, 61.0, 60.4, 59.9, 59.3, 55.63, 55.60, 55.5, 55.4, 55.3, 45.32, 45.25, 36.1, 34.9, 33.4, 33.3, 29.9; HRMS (ESI) *m/z* calcd for $C_{36}H_{34}NO_6$ (M+H) 576.2386, found 576.2399.



Preparation of **3-172.**[*] A solution of **3-165** (23.9 mg, 0.0393 mmol) in THF (0.50 mL) at room temperature was treated with $LiBH_4$ (2 M in THF, 0.0983 mL, 0.197 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 22 h, cooled to room temperature, quenched with water and extracted with EtOAc (2x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:2 to 1:2) afforded 20.8 mg (91%) of **3-172** as a clear sticky solid: IR (neat) 3488, 2996, 2931, 2832, 1653, 1645, 1587, 1569, 1476, 1462 cm^{-1};

[*] (CW210-052: procedure, proton and carbon NMR; CW210-042: IR; CW224-008: HRMS)

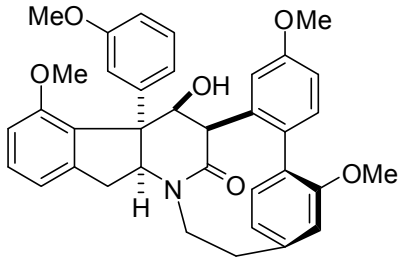
^{1}H NMR 500 MHz ($CDCl_3$) δ 7.42 (d, 1 H, *J* = 8.5 Hz), 7.35 (t, 1 H, *J* = 8.0 Hz), 7.18 (t, 1 H, *J* = 8.0 Hz), 7.06 (d, 1 H, *J* = 7.5 Hz), 6.89 (dd, 1 H, *J* = 8.0, 2.0 Hz), 6.86-6.78 (m, 4 H), 6.74 (dd, 1 H, *J* = 8.0, 1.5 Hz), 6.65-6.63 (m, 1 H), 6.58 (t, 1 H, *J* = 2.0 Hz), 4.56 (ddd, 1 H, *J* = 14.0, 12.0, 5.5 Hz), 4.33 (t, 1 H, *J* = 9.5 Hz), 4.18 (dd, 1 H, *J* = 11.0, 5.0 Hz), 4.06 (dd, 1 H, *J* = 10.5, 7.0 Hz), 3.77 (s, 3 H), 3.70 (s, 3 H), 3.69 (s, 3 H), 3.57 (s, 3 H), 3.43 (d, 2 H, *J* = 9.5 Hz), 3.30 (dd, 1 H, *J* = 14.0, 5.0 Hz), 3.20 (d, 1 H, *J* = 16.5 Hz), 2.95 (dd, 1 H, *J* = 12.5, 5.0 Hz), 2.71 (dt, 1 H, *J* = 12.5, 5.5 Hz), 1.88 (dd, 1 H, *J* = 7.0, 5.0 Hz), 0.68 (d, 1 H, *J* = 16.5 Hz); ^{13}C NMR 125 MHz ($CDCl_3$) δ 172.7, 161.1, 160.3, 158.4, 156.2, 145.8, 143.3, 143.1, 137.9, 131.5, 130.2, 130.0, 129.9, 129.7, 126.0, 124.8, 119.8, 119.0, 117.7, 115.2, 113.4, 111.9, 111.1, 110.5, 70.2, 63.7, 62.7, 55.6, 55.43, 55.36, 55.2, 44.6, 39.9, 38.0, 36.0; HRMS (ESI) *m/z* calcd for $C_{36}H_{37}NO_6Na$ (M+Na) 602.2519, found 602.2548.



Preparation of **3-173**.* A solution of oxalyl chloride (20.3 μL, 0.237 mmol) in DCM (0.30 mL) at -60 °C was treated with DMSO (36.2 μL, 0.510 mmol). The reaction mixture was stirred at -60 °C for 10 min and treated with **3-172** (20.8 mg, 35.9 μmol) in DCM (0.6 mL). The resulting mixture was stirred for 15 min, treated with Et_3N (0.150 mL, 1.07 mmol), stirred at -60 °C for 5 min then room temperature for 10 min. The reaction was quenched with aqueous $NaHCO_3$ and the mixture was extracted with EtOAc (3x). The combined organic layers were

* (CW210-054: procedure, proton NMR; CW210-048: carbon NMR, IR and HRMS)

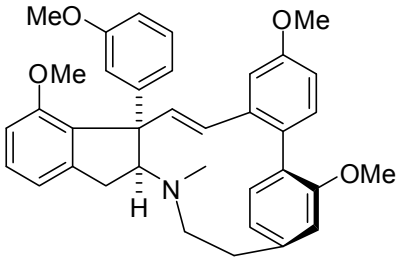
washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 2:1 to 1:1) afforded 17.2 mg (83%) of **3-173** as a sticky clear solid: IR (neat) 2924, 2849, 2834, 1718, 1662, 1589, 1567, 1479, 1464 cm^{-1}; ^1H NMR 500 MHz ($CDCl_3$) δ 9.92 (d, 1 H, *J* = 0.5 Hz), 7.47 (d, 1 H, *J* = 3.0 Hz), 7.40 (t, 1 H, *J* = 7.5 Hz), 7.25 (t, 1 H, *J* = 8.0 Hz), 7.08 (d, 1 H, *J* = 7.5 Hz), 6.94 (app dd, 1 H, *J* = 7.5, 2.0 Hz), 6.86-6.81 (m, 3 H), 6.79-6.77 (m, 1 H), 6.75 (dd, 1 H, *J* = 8.0, 1.0 Hz), 6.70-6.67 (m, 1 H), 6.62 (t, 1 H, *J* = 2.5 Hz), 6.19 (d, 1 H, *J* = 3.0 Hz), 4.48-4.37 (m, 2 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 3.70 (s, 3 H), 3.60 (s, 3 H), 3.57-3.44 (m, 2 H), 3.40-3.30 (m, 2 H), 2.93 (dd, 1 H, *J* = 13.0, 5.5 Hz), 2.73 (dt, 1 H, *J* = 12.0, 5.5 Hz), 1.04 (d, 1 H, *J* = 16.5 Hz); ^{13}C NMR 125 MHz ($CDCl_3$) δ 198.7, 172.5, 161.2, 160.3, 158.5, 156.6, 143.7, 143.0, 141.1, 137.6, 131.4, 131.0, 130.4, 130.0, 129.9, 126.4, 125.9, 124.5, 120.5, 119.1, 117.6, 115.2, 113.9, 112.9, 111.1, 110.3, 71.7, 71.2, 55.6, 55.4, 55.3, 45.5, 40.4, 37.9, 35.7; HRMS (ESI) *m/z* calcd for $C_{36}H_{35}NO_6Na$ (M+Na) 600.2362, found 600.2368.



Preparation of **3-174**.* A mixture of **3-173** (0.0203 g, 0.0351 mmol) and LiH (1.1 mg, 0.141 mmol) in diglyme (1.0 mL) was heated to 140 °C for 4 h. The reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl and extracted with DCM (3x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by

* (CW224-090: procedure; CW224-014: HRMS, IR; CW224-005: X-ray, melting point; CW210-089: proton, carbon and COSY, HMQC, HMBC)

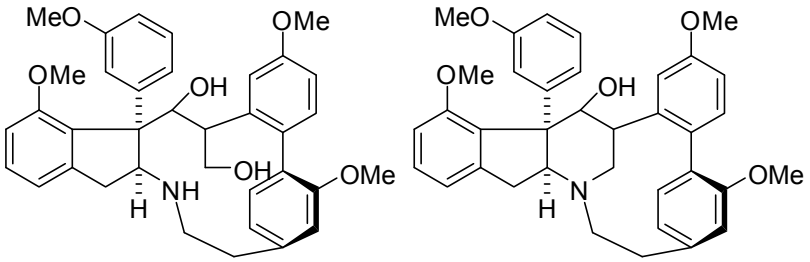
chromatography on SiO_2 (Hexanes:EtOAc = 1:1 to 1:2) afforded 11.5 mg (57%) of **3-174** as a clear sticky solid: IR (neat) 3499, 2933, 1686, 1602, 1582, 1464 cm^{-1}; ^1H NMR 600 MHz ($CDCl_3$) δ 7.62 (d, 1 H, *J* = 8.4 Hz), 7.29-7.25 (m, 1 H), 7.25 (d, 1 H, *J* = 1.8 Hz), 7.19 (t, 1 H, *J* = 8.4 Hz), 7.14 (d, 1 H, *J* = 7.8 Hz), 7.00 (d, 1 H, *J* = 7.8 Hz), 6.94-6.90 (m, 2 H), 6.85-6.80 (m, 2 H), 6.76 (app d, 1 H, *J* = 8.4 Hz), 6.57 (d, 1 H, *J* = 7.8 Hz), 6.36 (app s, 1 H), 4.95 (app s, 1 H), 4.36 (app dt, 1 H, *J* = 13.2, 4.2 Hz), 4.29 (app s, 1 H), 4.16-4.11 (m, 2 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.777 (s, 3 H), 3.68 (s, 3 H), 3.14 (d, 1 H, *J* = 16.8 Hz), 3.09 (dd, 1 H, *J* = 15.0, 4.2 Hz), 2.93 (dd, 1 H, *J* = 13.2, 4.8 Hz), 2.84 (dd, 1 H, *J* = 16.8, 5.4 Hz), 2.57 (dt, 1 H, *J* = 12.6, 4.2 Hz); ^{13}C NMR 150 MHz ($CDCl_3$) δ 172.3, 163.0, 160.0, 159.2, 156.0, 145.4, 144.9, 142.9, 138.0, 132.8, 131.6, 131.1, 130.2, 130.1, 125.2, 121.6, 118.6, 118.2, 116.7, 116.1, 113.3, 111.6, 110.6, 110.2, 75.2, 68.7, 66.7, 55.8, 55.53, 55.52, 55.2, 51.0, 44.8, 34.7, 32.9; HRMS (ESI) *m/z* calcd for $C_{36}H_{35}NO_6Na$ (M+Na) 600.2362, found 600.2351. A fraction of **3-174** was recrystallized from hot toluene to yield X-ray quality colorless crystal: mp 116.3-118.0 °C (toluene). The crystal was collected and redissolved in $CDCl_3$ to give a proton NMR spectrum that is identical to the sample before crystallization.



Preparation of **3-175.**[*] A solution of **3-174** (9.1 mg, 0.0158 mmol) in THF (0.65 mL) was treated with a solution of LAH (2.4 M in THF, 32.8 μL, 0.0788 mmol) at room temperature. The

[*] CW224-045: procedure, HRMS, IR, X-ray, mp; CW224-018 and CW224-001(combined): proton, carbon and COSY, HMQC, HMBC

reaction mixture was heated to 63 °C for 9 h, cooled to 0 °C, quenched with EtOAc followed by saturated aqueous Rochelle's salt. The mixture was extracted with EtOAc (1x). The organic layer was washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by PTLC (Hexanes:EtOAc = 2:1 with 0.5% Et_3N) afforded 4.3 mg (50%) of **3-175** (mixture of N-inversion isomers) as a clear sticky solid: IR (neat) 2926, 1847, 1599, 1559, 1477 cm^{-1}; ^1H NMR of both isomers 500 MHz ($CDCl_3$) δ 7.35 (d, 1 H, *J* = 8.5 Hz), 7.21 (t, 1 H, *J* = 7.5 Hz), 7.14 (t, 1 H, *J* = 7.5 Hz), 7.05 (t, 1 H, *J* = 8.0 Hz), 6.83 (dd, 1 H, *J* = 8.0, 2.5 Hz), 6.79 (d, 2 H, *J* = 7.0 Hz), 6.77-6.73 (m, 1 H), 6.72 (s, 1 H), 6.67-6.53 (m, 4 H), 5.90-5.81 (m, 1 H), 5.03-4.93 (m, 1 H), 3.82 (s, 3 H), 3.78-3.65 (m, 3 H), 3.59 (s, 3 H), 3.49-3.43 (m, 1 H), 3.80 (s, 3 H), 2.93-2.80 (m, 3 H), 2.71-2.64 (m, 1 H), 2.53-2.46 (m, 2 H), 1.59 (s, 3 H); ^{13}C NMR not provided due to its low quality; HRMS (ESI) *m/z* calcd for $C_{36}H_{38}NO_4$ (M+H) 548.2801, found 548.2769. X-ray quality crystal was obtained by dissolving the product in MeOH (~0.5 mL) and aqueous HCl (37%, 1 equivalent) and slowly evaprorate the solvent over 1 month: colorless crystal, mp 209.1 °C (decomp.) (MeOH-HCl). The crystal was dissolved in EtOAc and washed with 5% K_2CO_3 (2x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ^1H NMR of the residue is identical to that of the sample before crystallization.



Preparation of **3-176** and **3-177**.* A solution of $AlCl_3$ (10.5 mg, 0.0788 mmol) in THF (0.50 mL) was prepared by adding THF to $AlCl_3$ at -78 °C then warming up to room temperature. This solution was treated with $NaAlH_4$ (0.5 M in THF, 0.158 mL, 0.0788 mmol) at room temperature and stirred for 0.5 h. This reaction mixture was then treated with a solution of **3-174** (9.1 mg, 0.0158 mmol) in THF (0.10x3 mL) at room temperature. The reaction mixture was stirred for 17 h, cooled to 0 °C, quenched with MeOH followed by saturated aqueous Rochelle's salt. The mixture was extracted with EtOAc (2x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by PTLC (Hexanes:EtOAc = 1:1 with 0.5% Et_3N) afforded 1.3 mg (15%) of **3-177** and 5.1 mg (57%) of **3-176** as clear sticky solids. **3-176**: IR (neat) 3311, 2931, 2834, 1600, 1479 cm^{-1}; ^1H NMR 500 MHz (CD_2Cl_2) δ 7.38 (d, 1 H, *J* = 8.0 Hz), 7.34 (t, 1 H, *J* = 7.5 Hz), 7.12-7.06 (m, 2 H), 7.01 (d, 1 H, *J* = 2.5 Hz), 6.96 (d, 1 H, *J* = 7.0 Hz), 6.93-6.83 (m, 4 H), 6.71-6.62 (m, 2 H), 6.57 (s, 1 H), 3.92 (app d, 1 H, *J* = 5.0 Hz), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.67 (s, 3 H), 3.62 (s, 3 H), 3.51 (d, 1 H, *J* = 6.0 Hz), 3.29-3.21 (m, 2 H), 3.11 (dd, 1 H, *J* = 11.5, 4.0 Hz), 3.05 (dd, 1 H, *J* = 14.5, 6.5 Hz), 2.76-2.70 (m, 1 H), 2.66-2.58 (m, 1 H), 2.58-2.48 (m, 2 H), 2.32 (t, 1 H, *J* = 13.0 Hz), 0.94-0.87 (m, 1 H), -0.56--0.64 (m, 1 H); ^{13}C NMR 150 MHz (CD_2Cl_2) δ 159.7,

* (CW241-015: procedure and proton, carbon, COSY, HMQC and HMBC; CW241-014 and CW224-096: carbon and COSY, HMQC, HMBC; CW224-060: HRMS, IR; CW224-093: HRMS; CW241-023: X-ray; CW241-033 and CW241-042: conversion of **3-176** to **3-177**)

158.8, 158.2, 156.3, 148.2, 145.4, 144.4, 141.2, 133.6, 133.0, 131.8, 130.3, 129.0, 128.7, 127.8, 125.4, 119.20, 119.15, 117.6, 113.5, 111.2, 111.1, 110.9, 73.8, 72.8, 64.6, 60.6, 58.6, 56.1, 56.0, 55.5, 55.4, 49.1, 47.5, 37.5, 35.6; HRMS (ESI) *m/z* calcd for $C_{36}H_{40}NO_6$ (M+H) 582.2856, found 582.2873. **3-177**: IR (neat) 3565, 2927, 2830, 1599, 1582, 1476, 1462 cm^{-1}; ^1H NMR 500 MHz (CD_2Cl_2) δ 7.53 (d, 1 H, *J* = 8.5 Hz), 7.25 (d, 1 H, *J* = 2.0 Hz), 7.22-7.14 (m, 2 H), 7.04 (d, 1 H, *J* = 7.5 Hz), 6.87 (d, 1 H, *J* = 7.5 Hz), 6.82 (dd, 1 H, *J* = 8.5, 2.5 Hz), 6.79-6.71 (m, 3 H), 6.69 (s, 1 H), 6.65 (d, 1 H, *J* = 8.0 Hz), 6.30 (d, 1 H, *J* = 7.5 Hz), 4.99 (s, 1 H), 3.85-3.80 (m, 1 H), 3.77 (s, 3 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 3.45 (d, 1 H, *J* = 9.5 Hz), 3.37 (s, 3 H), 2.98 (dd, 1 H, *J* = 9.0, 6.3 Hz), 2.78-2.62 (m, 3 H), 2.40-2.28 (m, 2 H), 2.21-2.13 (m, 1 H), 0.97 (s, 1 H), -0.07 (d, 1 H, *J* = 12.0 Hz); ^{13}C NMR 150 MHz (CD_2Cl_2) δ 161.8, 159.5, 159.4, 156.6, 150.2, 146.7, 145.9, 144.4, 133.3, 132.9, 132.5, 130.4, 129.5, 128.4, 127.7, 126.0, 120.6, 118.3, 115.8, 115.3, 112.9, 110.3, 109.8, 109.7, 75.7, 70.1, 60.1, 57.1, 55.8, 55.7, 55.6, 45.3, 42.0, 39.0, 30.5; HRMS (ESI) *m/z* calcd for $C_{36}H_{38}NO_5$ (M+H) 564.2750, found 564.2795.

Conversion of **3-176** to **3-177**: A solution of **3-176** (11.3 mg, 0.0194 mmol) in pyridine (0.66 mL) was treated with MsCl (15.4 μL, 0.194 mmol) at room temperature. The reaction mixture was stirred for 2 h, quenched with saturated $NaHCO_3$ and extracted with EtOAc (2x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by PTLC (Hexanes:EtOAc = 1:2 with 0.5% Et_3N) afforded 10.7 mg (83%) of the mesylate as a clear wticky solid. A fraction of this mesylate (7.5 mg, 0.0111 mmol) in a mixture of diglyme (1.3 mL) and DIPEA (0.68 mL) was heated to 115 °C for 24 h, treated with additional DIPEA (0.20 mL) and heated to 115 °C for 6 h. The solvent was evaporated at room temperature. Purification by PTLC (Hexanes:EtOAc = 2:1 with

0.5% Et_3N) afforded 3.0 mg (48%) of **3-177** as a clear sticky solid with ^1H NMR identical to that of the sample from the reduction of **3-174** with AlH_2Cl.

BIBLIOGRAPHY

[1] Culp, R. L. *Water Engineering & Management* **1981**, *128*, 72, 74-6.

[2] "World silver survey," Silver Institute, 1998.

[3] "Health and Natural Resources (http://www.p2pays.org/ref/01/00048.htm)," NC Department of Envirmental.

[4] "http://www.epa.gov/epaoswer/hazwaste/id/infocus/photofin.pdf," U.S. Environmental Protection Agency.

[5] Baba, Y.; Umezaki, Y.; Inoue, K. *J. Chem. Eng. Japan* **1986**, *19*, 27-30.

[6] Dimitrov, K.; Boyadzhiev, L.; Saboni, A.; Alexandrova, S. *Chem. Eng. Technol.* **2002**, *25*, 663-666.

[7] Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; John Wiley and Sons, Ltd.

[8] Izatt, R. M.; LindH, G. C.; Bruening, R. L.; Huszthy, P.; McDaniel, C. W.; Bradshaw, J. S.; Christensen, J. J. *Anal. Chem.* **1988**, *60*, 16941699.

[9] Sirlin, C.; Bungard, M.; Leroy, M. J. F.; Prevost, M. *J. Membrane Sci.* **1990**, *54*, 299-305.

[10] "http://www.speclab.com/elements/silver.htm," Spectrum Laboratories.

[11] Gnizdovitsch, Y.; Gnizdovitch, U. Eur. Patent IL19670027275, 1970.

[12] Novikov, P. D.; Kandybina, G. M.; Balakin, V. M.; Chetverikov, A. F. *Okeanologiya* **1975**, *15*, 636-8.

[13] Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771-1791.

[14] Wipf, P.; Uto, Y. *J. Org. Chem.* **2000**, *65*, 1037-1049.

[15] Michael, J. P.; Pattenden, G. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1-23.

[16] Wipf, P.; Venkatraman, S.; Miller, C.; Geib, S. J. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1516-1518.

[17] Wipf, P.; Miller, C. P. *J. Am. Chem. Soc.* **1992**, *114*, 10975-10977.

[18] Hambley, T. W.; Hawkins, C. J.; Lavin, M. F.; van den Brenk, A.; Watters, D. J. *Tetrahedron* **1992**, *48*, 341-348.

[19] van den Brenk, A. L.; Fairlie, D. P.; Hanson, G. R.; Gahan, L. R.; Hawkins, C. J.; Jones, A. *Inorg. Chem.* **1994**, *33*, 2280-2289.

[20] Morris, L. A.; Milne, B. F.; Thompson, G. S.; Jaspars, M. *J. Chem. Soc. Perkin Trans. 2* **2002**, 1072-1075.

[21] Ishida, T.; Inoue, M.; Hamada, Y.; Kato, S.; Shioiri, T. *J. Chem. Soc. Chem. Commmun.* **1987**, 370-371.

[22] Schmitz, F. J.; Ksebati, M. B.; Chang, J. S.; Wang, J. L.; Hossain, M. B.; van der Helm, D.; Engel, M. H.; Serban, A.; Silfer, J. A. *J. Org. Chem.* **1989**, *54*, 3463-3472.

[23] Chou, P. Y.; Fasman, G. D. *J. Mol. Biol.* **1977**, *115*, 135-175.

[24] Hamamoto, Y.; Endo, M.; Nakagawa, M.; Nakanishi, T.; Mizukawa, K. *J. Chem. Soc. Chem. Commun.* **1983**, 323-324.

[25] Ishida, T.; In, Y.; Shinozaki, F.; Doi, M.; Yamamoto, D.; Hamada, Y.; Shioiri, T.; Kamigauchi, M.; Sugiura, M. *J. Org. Chem.* **1995**, *60*, 3944-3952.

[26] Doi, M.; Shinozaki, F.; In, Y.; Ishida, T.; Yamamoto, D.; Kamigauchi, M.; Sugiura, M.; Hamada, Y.; Khoda, K.; Shioiri, T. *Biopolymers* **1999**, *49*, 459-469.

[27] Wipf, P.; Fritch, P. C.; Geib, S. J.; Sefler, A. M. *J. Am. Soc. Chem.* **1998**, *120*, 4105-4112.

[28] Freeman, D. J.; Pattenden, G.; Drake, A. F.; Siligardi, G. *J. Chem. Soc. Perkin Trans. 2* **1998**, 129-136.

[29] Morries, L. A.; Jaspers, M.; van den Bosch, J. J. K.; Versluis, K.; Heck, A. J. R.; Kelly, S. M.; Price, N. C. *Tetrahedron* **2001**, *57*, 3185-3197.

[30] Morries, L. A.; Jaspers, M.; van den Bosch, J. J. K.; Versluis, K.; Heck, A. J. R.; Kelly, S. M.; Price, N. C. *Tetrahedron* **2001**, *57*, 3199-3207.

[31] van den Brenk, A. L.; Byriel, K. A.; Fairlie, D. P.; Hanson, G. R.; Gahan, L. R.; Hawkins, C. J.; Jones, A.; Kennard, C. H. L.; Moubaraki, B.; Murray, K. S. *Inorg. Chem.* **1994**, *33*, 3549-3557.

[32] Hamada, Y.; Kato, S.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 3223-3226.

[33] Abbenante, G.; Fairlie, D. P.; Gahan, L. R.; Hanson, G. R.; Pierens, G. K.; van den Brenk, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 10384-10388.

[34] van den Brenk, A. L.; Fairlie, D. P.; Hanson, G. R.; Gahan, L. R.; Hambley, T. W. *Inorg. Chem.* **1996**, *35*, 1095-1100.

[35] Grondahl, L.; Sokolenko, N.; Abbenante, G.; Fairlie, D. P.; Hanson, G. R.; Gahan, L. R. *J. Chem. Soc. Dalton Trans.* **1999**, 1227-1234.

[36] Cusack, R. M.; Grondahl, L.; Fairlie, D. P.; Gahan, L. R.; Hanson, G. R. *J. Chem. Soc. Perkin Trans. 2* **2000**, 323-331.

[37] Cusack, R. M.; Grondahl, L.; Fairlie, D. P.; Gahan, L. R.; Hanson, G. R. *J. Chem. Soc. Perkin Trans. 2* **2002**, 556-563.

[38] Hamada, Y.; Kato, S.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 5155-5158.

[39] Hamada, Y.; Kato, S.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 5159-5162.

[40] Schmidt, U.; Griesser, H. *Tetrahedron Lett.* **1986**, *27*, 163-166.

[41] Hamada, Y.; Kato, S.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 6501-6504.

[42] Davis, J. S. *J. Peptide Sci.* **2003**, *9*, 471-501.

[43] Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907-910.

[44] Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 1575-1578.

[45] Wipf, P.; Miller, C. P.; Grant, C. M. *Tetrahedron* **2000**, *56*, 9143-9150.

[46] Bertram, A.; Blake, A. J.; Gonzalez-Lopez de Turiso, F.; Hannam, J. S.; Jolliffe, K. A.; Pattenden G.; Skae, M. *Tetrahedron* **2003**, *59*, 6979-6990.

[47] Blake, A.; Hannam, J. S.; Jolliffe, K. A.; Pattenden, G. *Synlett* **2000**, *10*, 1515-1518.

[48] Bertam, A.; Patterden, G. *Heterocycles* **2002**, *58*, 521.

[49] Bertram, A.; Pattenden, G. *Heterocycles* **2002**, *58*, 521-561.

[50] Singh, Y.; Stoermer, M. J.; Lucke, A. J.; Guthrie, T.; Fairlie, D. P. *J. Am. Chem. Soc.* **2005**, *127*, 6563-6572.

[51] Clark, T. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1995**, *117*, 12364-12365.

[52] van Maarseveen, J. H.; Horne, W. S.; Ghadiri, M. R. *Org. Lett.* **2005**, *7*, 4503-4506.

[53] Pattenden, G.; Thompson, T. *Tetrahedron Lett.* **2002**, *43*, 2459-2461.

[54] Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 3910-3915.

[55] Tanaka, T.; Nakajima, K.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1352-1355.

[56] Larsson, U.; Carlson, R. *Acta Chem. Scand.* **1994**, *48*, 511-516.

[57] Majumdar, D., Master's thesis, University of Pittsburgh, 2000.

[58] Lee, T.; Jones, J. B. *Tetrahedron* **1995**, *51*, 7331-7346.

[59] Wipf, P.; Uto, Y. *Tetrahedron Lett.* **1999**, *40*, 5165-5169.

[60] Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165-1168.

[61] Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149-8150.

[62] Shilov, A. E.; Shui'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879-2932.

[63] Ndungu, J. M.; Gu, X.; Gross, D. E.; Cain, J. P.; Carducci, M. D.; Hruby, V. J. *Tetrahedron Lett.* **2004**, *45*, 4139-4142.

[64] Yang, W. C.; Lu, X. A.; Kulkarni, S. S.; Hung, S. C. *Tetrahedron Lett.* **2003**, *44*, 7837-7840.

[65] Fielding, L. *Tetrahedron* **2000**, *56*, 6151-6170.

[66] Kang, J.; Choi, M.; Kwon, J. Y.; Lee, E. Y.; Yoon, J. *J. Org. Chem.* **2002**, *67*, 4384-4386.

[67] The error range is relatively large due to the limited dynamic range of the fluorescence titration method (see Experimental Part).

[68] Connors, K. A. *Binding Constants, The Measurement of Molecular Complex Stabiliy*; John Wiley & Sons, New York, 1987.

[69] Wipf, P.; Kendall, C. *Org. Lett.* **2001**, *3*, 2773-2776.

[70] Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561-5568.

[71] Demir, A. S.; Sesenoglu, O. *Helv. Chim. Acta* **2003**, *86*, 91-105.

[72] Englund, E. A.; Gopi, H. N.; Appella, D. H. *Org. Lett.* **2004**, *6*, 213-215.

[73] Lall, M. S.; Ramtohul, Y. K.; James, M. N. G.; Vederas, J. C. *J. Org. Chem.* **2002**, *67*, 1536-1547.

[74] Soai, K.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc. Chem. Commun.* **1992**, 1097-1098.

[75] Rose, N. J.; Drago, R. S. *J. Am. Chem. Soc.* **2002**, *81*, 6138-6141.

[76] Schantz, E. J.; Johnson, E. A. *Microbiol. Rev.* **1992**, *56*, 80-99.

[77] Arnon, S. S.; Schechter, R.; Inglesby, T. V.; Henderson, D. A.; Bartlett, J. G.; Ascher, M. S.; Eitzen, E.; Fine, A. D.; Hauer, J.; Layton, M.; Lillibridge, S.; Osterholm, M. T.; O'Toole, T.; Parker, G.; Perl, T. M.; Russell, P. K.; Swerdlow, D. L.; Tonat, K. *JAMA, J. Am. Med. Assoc.* **2001**, *285*, 1059-1070.

[78] Johnson, E. A. *Annu. Rev. Microbiol.* **1999**, *53*, 551-575.

[79] Baumann Leslie, S.; Halem Monica, L. *Clin. Dermatol.* **2004**, *22*, 60-65.

[80] Singh, B. R. *Nat. Struct. Biol.* **2000**, *7*, 617-619.

[81] Lacy, D. B.; Stevens, R. C. *J. Mol. Biol.* **1999**, *291*, 1091-1104.

[82] Willis, B.; Eubanks, Lisa M.; Dickerson, Tobin J.; Janda, Kim D. *Angew. Chem. Int. Ed.* **2008**, *47*, 8360-8379.

[83] Adler, M.; Dinterman, R. E.; Wannemacher, R. W. *Toxicon* **1997**, *35*, 1089-1100.

[84] Deshpande, S. S.; Sheridan, R. E.; Adler, M. *Toxicon* **1997**, *35*, 433-445.

[85] Keller, J. E.; Cai, F.; Neale, E. A. *Biochemistry* **2004**, *43*, 526-532.

[86] Sheridan, R. E. *Toxicon* **1996**, *34*, 849-855.

[87] Simpson, L. L. *J. Pharmacol. Exp. Ther.* **1983**, *225*, 546-552.

[88] Simpson, L. L.; Coffield, J. A.; Bakry, N. *J. Pharmacol. Exp. Ther.* **1994**, *269*, 256-262.

[89] Anne, C.; Turcaud, S.; Quancard, J.; Teffo, F.; Meudal, H.; Fournie-Zaluski, M.-C.; Roques, B. P. *J. Med. Chem.* **2003**, *46*, 4648-4656.

[90] Brewer, M.; James, C. A.; Rich, D. H. *Org. Lett.* **2004**, *6*, 4779-4782.

[91] Hayden, J.; Pires, J.; Hamilton, M.; Moore, G. *Proc. West. Pharmacol. Soc.* **2000**, *43*, 71-74.

[92] Hayden, J.; Pires, J.; Roy, S.; Hamilton, M.; Moore, G. J. *J. Appl. Toxicol.* **2003**, *23*, 1-7.

[93] Moore, G. J.; Moore, D. M.; Roy, S. S.; Hayden, L. J.; Hamilton, M. G.; Chan, N. W. C.; Lee, W. E. *Mol. Diversity* **2006**, *10*, 9-16.

[94] Oost, T.; Sukonpan, C.; Brewer, M.; Goodnough, M.; Tepp, W.; Johnson, E. A.; Rich, D. H. *Biopolymers* **2003**, *71*, 602-619.

[95] Rossetto, O.; Schiavo, G.; Montecucco, C.; Poulain, B.; Deloye, F.; Lozzi, L.; Shone, C. C. *Nature* **1994**, *372*, 415-416.

[96] Schmidt, J. J.; Stafford, R. G. *FEBS Lett.* **2002**, *532*, 423-426.

[97] Schmidt, J. J.; Stafford, R. G.; Bostian, K. A. *FEBS Lett.* **1998**, *435*, 61-64.

[98] Sollner, T.; Whiteheart, S. W.; Brunner, M.; Erdjument-Bromage, H.; Geromanos, S.; Tempst, P.; Rothman, J. E. *Nature* **1993**, *362*, 318-324.

[99] Sukonpan, C.; Oost, T.; Goodnough, M.; Tepp, W.; Johnson, E. A.; Rich, D. H. *J. Pept. Res.* **2004**, *63*, 181-193.

[100] Chen, S.; Barbieri, J. T. *J. Biol. Chem.* **2006**, *281*, 10906-10911.

[101] Boldt, G. E.; Kennedy, J. P.; Hixon, M. S.; McAllister, L. A.; Barbieri, J. T.; Tzipori, S.; Janda, K. D. *J. Comb. Chem.* **2006**, *8*, 513-521.

[102] Fu, Z.; Chen, S.; Baldwin, M. R.; Boldt, G. E.; Crawford, A.; Janda, K. D.; Barbieri, J. T.; Kim, J.-J. P. *Biochemistry* **2006**, *45*, 8903-8911.

[103] Burnett, J. C.; Schmidt, J. J.; Stafford, R. G.; Panchal, R. G.; Nguyen, T. L.; Hermone, A. R.; Vennerstrom, J. L.; McGrath, C. F.; Lane, D. J.; Sausville, E. A.; Zaharevitz, D. W.; Gussio, R.; Bavari, S. *Biochem. Biophys. Res. Commun.* **2003**, *310*, 84-93.

[104] Burnett, J. C.; Schmidt, J. J.; McGrath, C. F.; Nguyen, T. L.; Hermone, A. R.; Panchal, R. G.; Vennerstrom, J. L.; Kodukula, K.; Zaharevitz, D. W.; Gussio, R.; Bavari, S. *Bioorg. Med. Chem.* **2005**, *13*, 333-341.

[105] Park, J. G.; Sill, P. C.; Makiyi, E. F.; Garcia-Sosa, A. T.; Millard, C. B.; Schmidt, J. J.; Pang, Y.-P. *Bioorg. Med. Chem.* **2006**, *14*, 395-408.

[106] Burnett, J. C.; Ruthel, G.; Stegmann, C. M.; Panchal, R. G.; Nguyen, T. L.; Hermone, A. R.; Stafford, R. G.; Lane, D. J.; Kenny, T. A.; McGrath, C. F.; Wipf, P.; Stahl, A. M.; Schmidt, J. J.; Gussio, R.; Brunger, A. T.; Bavari, S. *J. Biol. Chem.* **2007**, *282*, 5004-5014.

[107] Picard, F.; Hartmann, R. W. *J. Enzyme Inhib. Med. Chem.* **2002**, *17*, 187-196.

[108] Ohemeng, K. A.; Nguyen, V. N. Preparation of 2-substituted phenyl-benzimidazole antibacterial agents. 98-US18586 9911627, 19980904, 1999.

[109] de la Hoz, A.; Diaz-Ortiz, A.; Mateo, M. d. C.; Moral, M.; Moreno, A.; Elguero, J.; Foces-Foces, C.; Rodriguez, M. L.; Sanchez-Migallon, A. *Tetrahedron* **2006**, *62*, 5868-5874.

[110] Wipf, P.; Widom, J.; Wang, C., unpublished results.

[111] Wipf, P.; Graham, T., unpublished results.

[112] Wang, C.; Widom, J.; Petronijevic, F.; Burnett, J. C.; Nuss, J. E.; Bavari, S.; Gussio, R.; Wipf, P. *Heterocycles* **2009**, *79*, 487-520.

[113] Burnett, J. C.; Schmidt, J. J.; McGrath, C. F.; Nguyen, T. L.; Hermone, A. R.; Panchal, R. G.; Vennerstrom, J. L.; Kodukula, K.; Zaharevitz, D. W.; Gussio, R.; Bavari, S. *Bioorg. Med. Chem.* **2005**, *13*, 333-341.

[114] Burnett, J. C.; Schmidt, J. J.; Stafford, R. G.; Panchal, R. G.; Nguyen, T. L.; Hermone, A. R.; Vennerstrom, J. L.; McGrath, C. F.; Lane, D. J.; Sausville, E. A.; Zaharevitz, D. W.; Gussio, R.; Bavari, S. *Biochem. Biophys. Res. Commun.* **2003**, *310*, 84-93.

[115] Silvaggi, N. R.; Boldt, G. E.; Hixon, M. S.; Kennedy, J. P.; Tzipori, S.; Janda, K. D.; Allen, K. N. *Chem. Biol.* **2007**, *14*, 533-542.

[116] Hermone, A. R.; Burnett, J. C.; Nuss, J. E.; Tressler, L. E.; Nguyen, T. L.; Solaja, B. A.; Vennerstrom, J. L.; Schmidt, J. J.; Wipf, P.; Bavari, S.; Gussio, R. *ChemMedChem* **2008**, *3*, 1905-1912.

[117] Burnett, J. C.; Opsenica, D.; Sriraghavan, K.; Panchal, R. G.; Ruthel, G.; Hermone, A. R.; Nguyen, T. L.; Kenny, T. A.; Lane, D. J.; McGrath, C. F.; Schmidt, J. J.; Vennerstrom, J. L.; Gussio, R.; Solaja, B. A.; Bavari, S. *J. Med. Chem.* **2007**, *50*, 2127-2136.

[118] Burnett, J. C.; Wang, C.; Nuss, J. E.; Nguyen, T. L.; Hermone, A. R.; Schmidt, J. J.; Gussio, R.; Wipf, P.; Bavari, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5811-5813.

[119] Tullberg, E.; Schacher, F.; Peters, D.; Frejd, T. *Synthesis* **2006**, 1183-1189.

[120] Krishnamurthy, S.; Aimino, D. *J. Org. Chem.* **1989**, *54*, 4458-62.

[121] Lazo, J. S.; Nunes, R.; Skoko, J. J.; Queiroz de Oliveira, P. E.; Vogt, A.; Wipf, P. *Bioorg. Med. Chem.* **2006**, *14*, 5643-5650.

[122] Madrid, P. B.; Wilson, N. T.; DeRisi, J. L.; Guy, R. K. *J. Com. Chem.* **2004**, *6*, 437-442.

[123] Castle, S. L.; Srikanth, G. S. C. *Org. Lett.* **2003**, *5*, 3611-3614.

[124] Schmidt, J. J.; Bostian, K. A. *J. Protein Chem.* **1995**, *14*, 703-708.

[125] Schmidt, J. J.; Bostian, K. A. *J. Protein Chem.* **1997**, *16*, 19-26.

[126] Garrido, L.; Zubia, E.; Ortega, M. J.; Salva, J. *J. Org. Chem.* **2003**, *68*, 293-299.

[127] Baran, P. S.; Burns, N. Z. *J. Am. Chem. Soc.* **2006**, *128*, 3908-3909.

[128] Burns, N. Z.; Krylova, I. N.; Hannoush, R. N.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 9172-9173.

[129] Wipf, P.; Furegati, M. *Org. Lett.* **2006**, *8*, 1901-1904.

[130] Belostotskii, A. M. *J. Org. Chem.* **2008**, *73*, 5723-5731.

[131] Burns, N. Z.; Baran, P. S. *Angew Chem Int Ed Engl* **2008**, *47*, 205-208.

[132] Smith, A. B.; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925-5937.

[133] Lepine, R.; Zhu, J. *Org. Lett.* **2005**, *7*, 2981-2984.

[134] Semmelhack, M. F.; Ryono, L. S. *J. Am. Chem. Soc.* **2002**, *97*, 3873-3875.

[135] Gleiter, R.; Hopf, H. *Modern cyclophane chemistry*; Wiley-VCH ; John Wiley: Weinheim, Chichester, 2004.

[136] Tobe, Y.; Kakiuchi, K.; Odaira, Y.; Hosaki, T.; Kai, Y.; Kasai, N. *J. Am. Chem. Soc.* **2002**, *105*, 1376-1377.

[137] Hasiak, B.; Barbry, D.; Couturier, D. *Tetrahedron Lett.* **1990**, *31*, 5769-5770.

[138] Smith, N. D.; Hayashida, J.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 4309-4312.

[139] Grundl, M. A.; Trauner, D. *Org. Lett.* **2005**, *8*, 23-25.

[140] Furstner, A.; Ackerstaff, J. *Chem Commun (Camb)* **2008**, 2870-2872.

[141] Jeong, J. H.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 2309-2312.

[142] Taniguchi, T.; Zaimoku, H.; Ishibashi, H. *J. Org. Chem.* **2009**, *74*, 2624-2626.

[143] Furegati, M.; Wipf, P., unpublished results.

[144] For a recent example, see: Wakefield, B.; Halter, R. J.; Wipf, P. *Org. Lett.* **2007**, *9*, 3121-3124.

[145] Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210-10211.

[146] Willis, M. C.; Brace, G. N. *Tetrahedron Lett.* **2002**, *43*, 9085-9088.

[147] Delair, P.; Brot, E.; Kanazawa, A.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1383-1386.

[148] Greene, A. E.; Charbonnier, F.; Luche, M. J.; Moyano, A. *J. Am. Chem. Soc.* **2002**, *109*, 4752-4753.

[149] Nebois, P.; Greene, A. E. *J. Org. Chem.* **1996**, *61*, 5210-5211.

[150] The aryl bromide moiety was installed in one of the earlier steps as a blocking group. .

[151] The yield was found to be dependent on the reaction scale. At 2.5 g scale, yield was 71%. At 30 g scale, yield dropped to 47%.

[152] Baker, B. R.; Schaub, R. E.; Joseph, J. P.; McEvoy, F. J.; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 141-148.

[153] MacPhillamy, H. B.; Dziemian, R. L.; Lucas, R. A.; Kuehne, M. E. *J. Am. Chem. Soc.* **1958**, *80*, 2172-2178.

[154] Newman, M. S.; Lilje, K. C. *J. Org. Chem.* **1979**, *44*, 4944-4946.

[155] Sheibley, F. E.; McNulty, J. S. *J. Org. Chem.* **1956**, *21*, 171-173.

[156] Sumpter, W. C.; Jones, W. F. *J. Am. Chem. Soc.* **1943**, *65*, 1802-1803.

[157] The reaction was repeated three times on gram scale with different batches of starting material. The yields were consistent (~80%).

[158] Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696.

[159] Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **2002**, *115*, 11014-11015.

[160] The NMR spetra of **3-154** and **3-155** are of extremely low quality regardless of the instrument used. This was also observed with several other advanced intermediates. We are uncertain about the origin of this phenomenon.

[161] Klásek, A.; Koristek, K.; Polis, J.; Kosmrlj, J. *Tetrahedron* **2000**, *56*, 1551-1560.

[162] Kuwano, R.; Takahashi, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 1017-1020.

[163] Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. *J. Org. Chem.* **2002**, *56*, 5263-5277.

[164] Reduction of an O-methylated derivative of **3-174** with alanes resulted in sluggish reactions as well.

[165] Furegati, M.; Wipf, P. 2006, Unpublished results.

[166] Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879-82.

[167] Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, *1977*, 1-17.

[168] Wipf, P.; Furegati, M. *Org. Lett.* **2006**, *8*, 1901-1904.

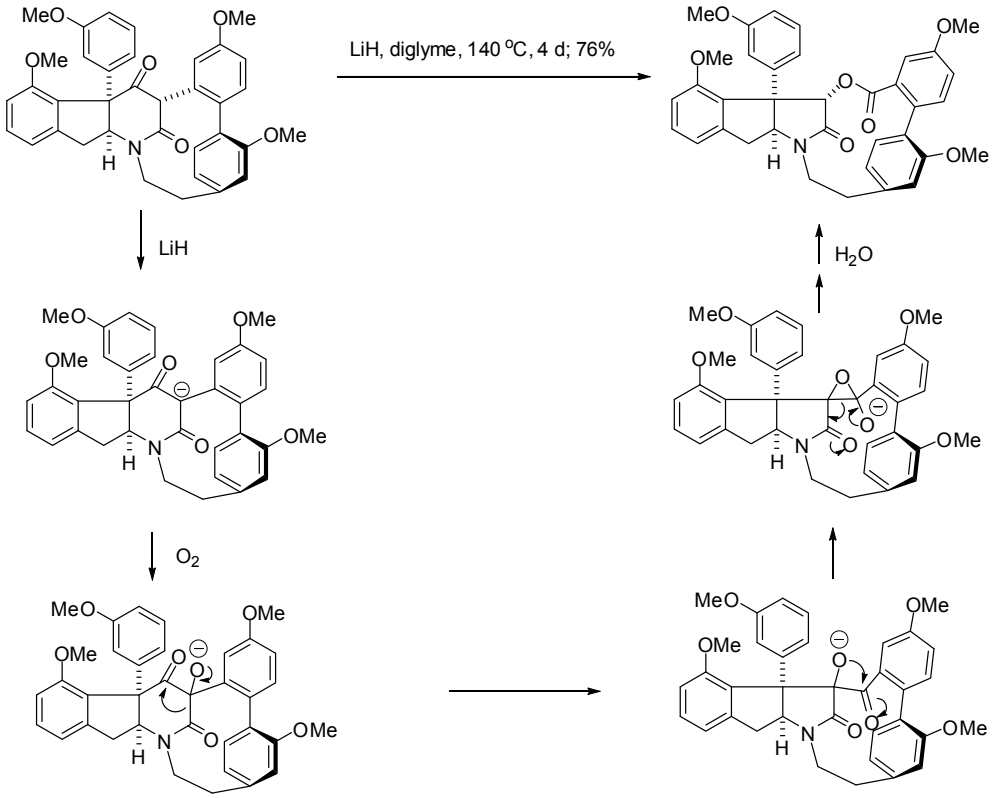
[169] Lebegue, N.; Bethegnies, G.; Berthelot, P. *Synth. Commun.* **2004**, *34*, 1041-1048.

[170] Cerre, C.; Hofmann, A. F.; Schteingart, C. D.; Jia, W.; Maltby, D. *Tetrahedron* **1997**, *53*, 435-446.

APPENDIX A

PROPOSED MECHANISM FOR THE FORMATION OF 3-167

Scheme 92 Proposed mechanism for the formation of **3-167**



APPENDIX B

X-RAY DATA

Figure 46 X-ray structure of **3-102**

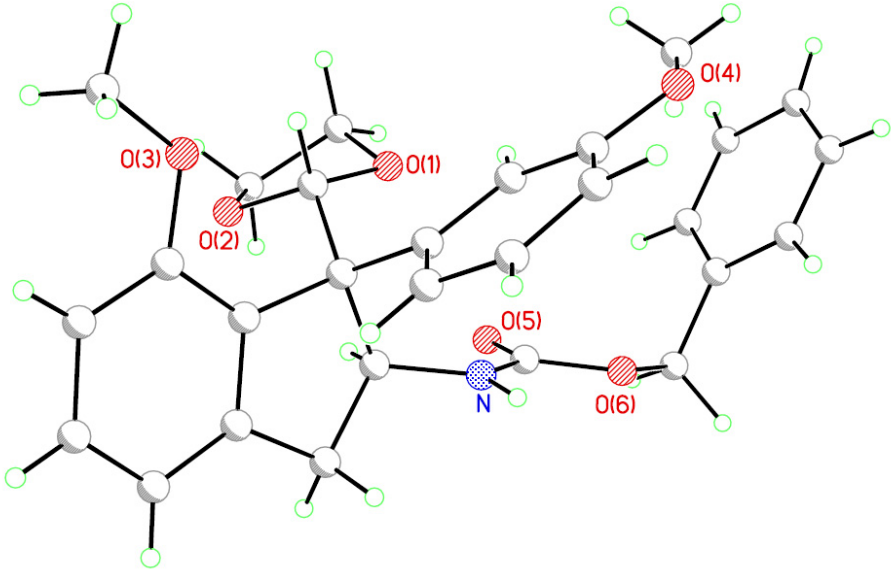


Figure 47 X-ray structure of **3-109**

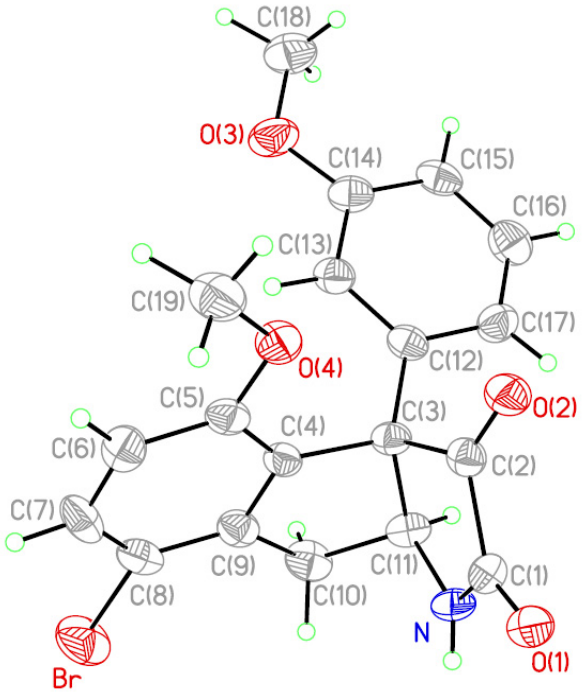


Figure 48 X-ray structure of **3-124a**

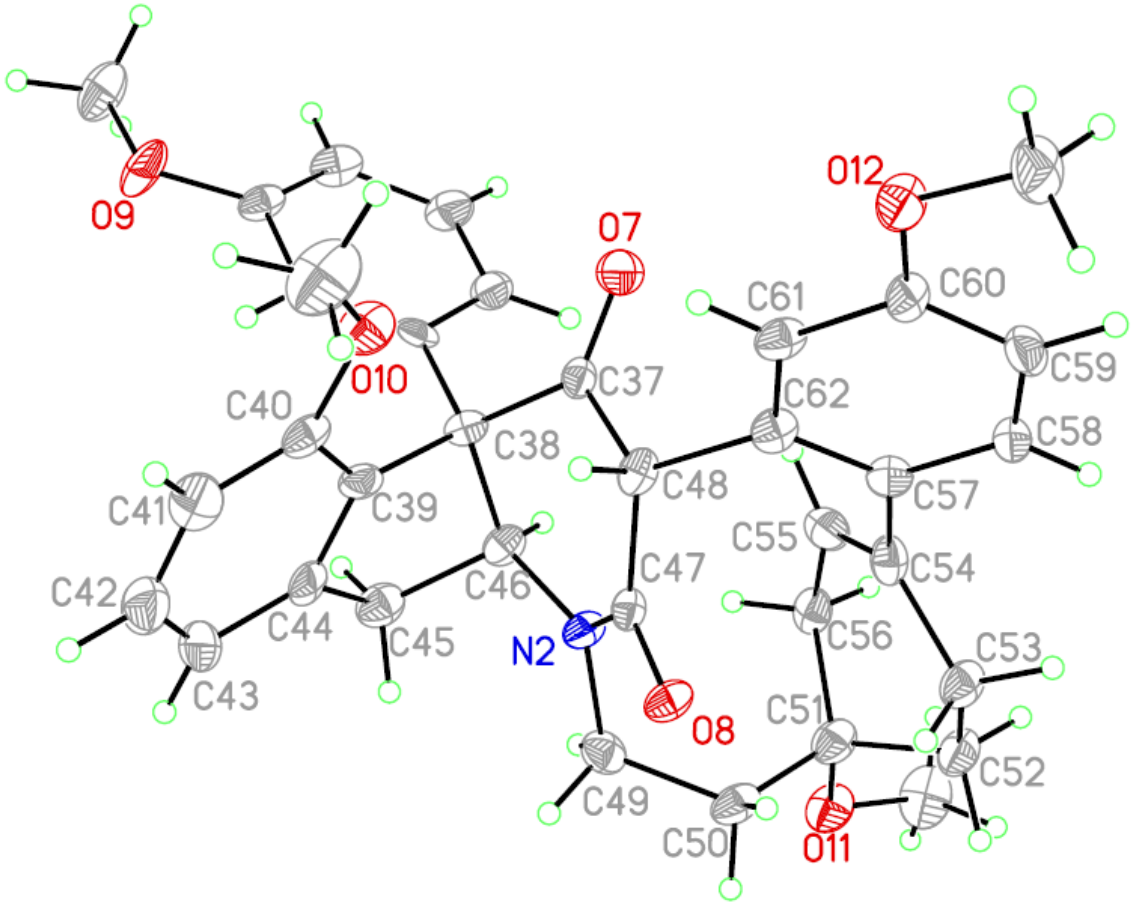


Figure 49 X-ray structure of **3-161**

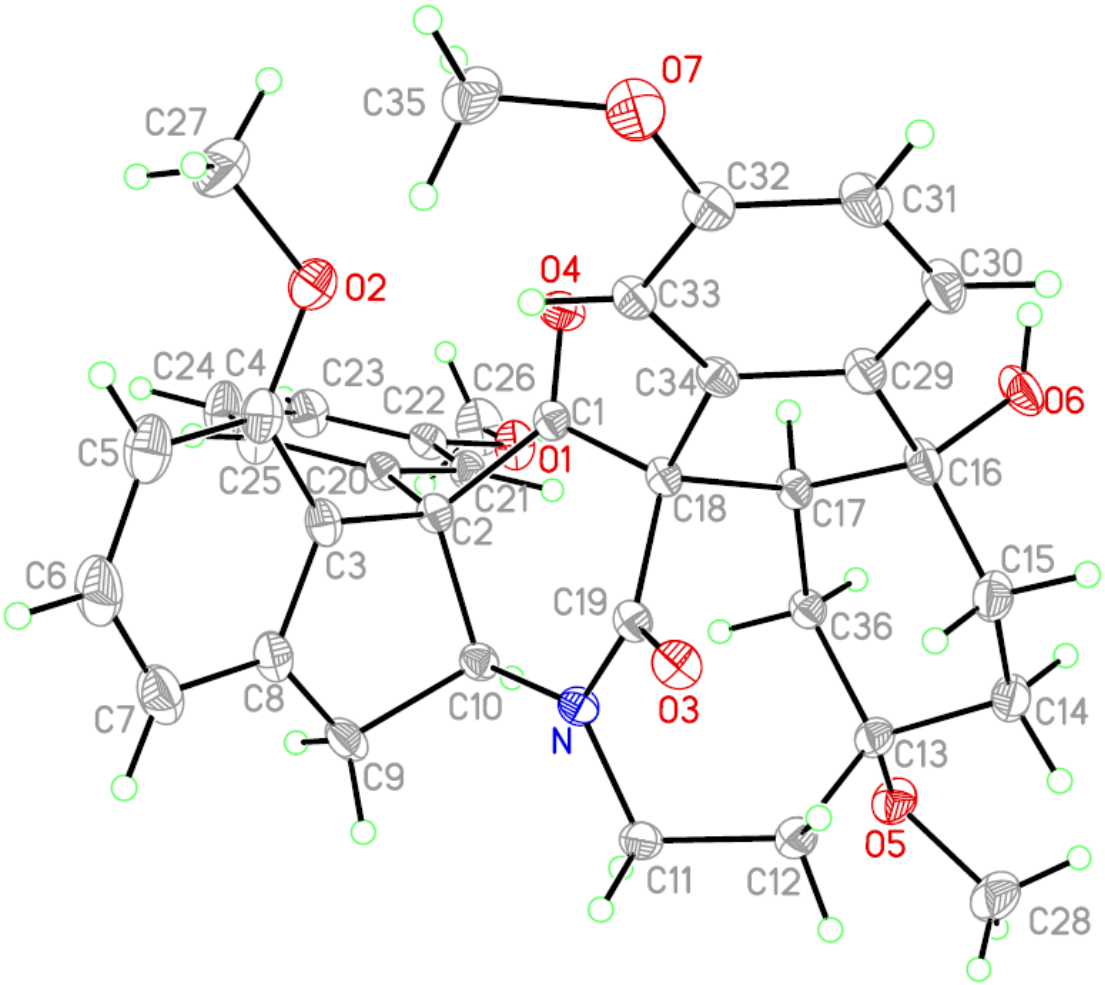


Figure 50 X-ray structure of **3-166**

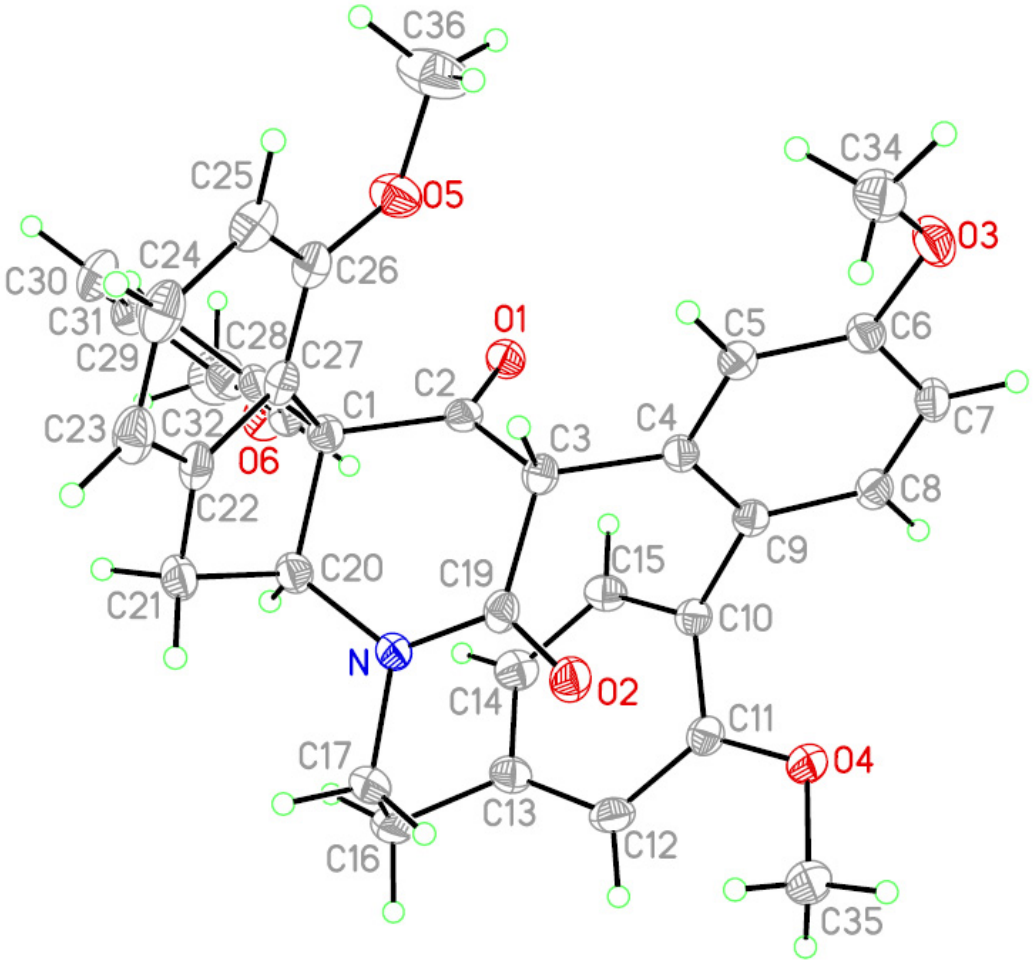


Figure 51 X-ray structure of **3-167**

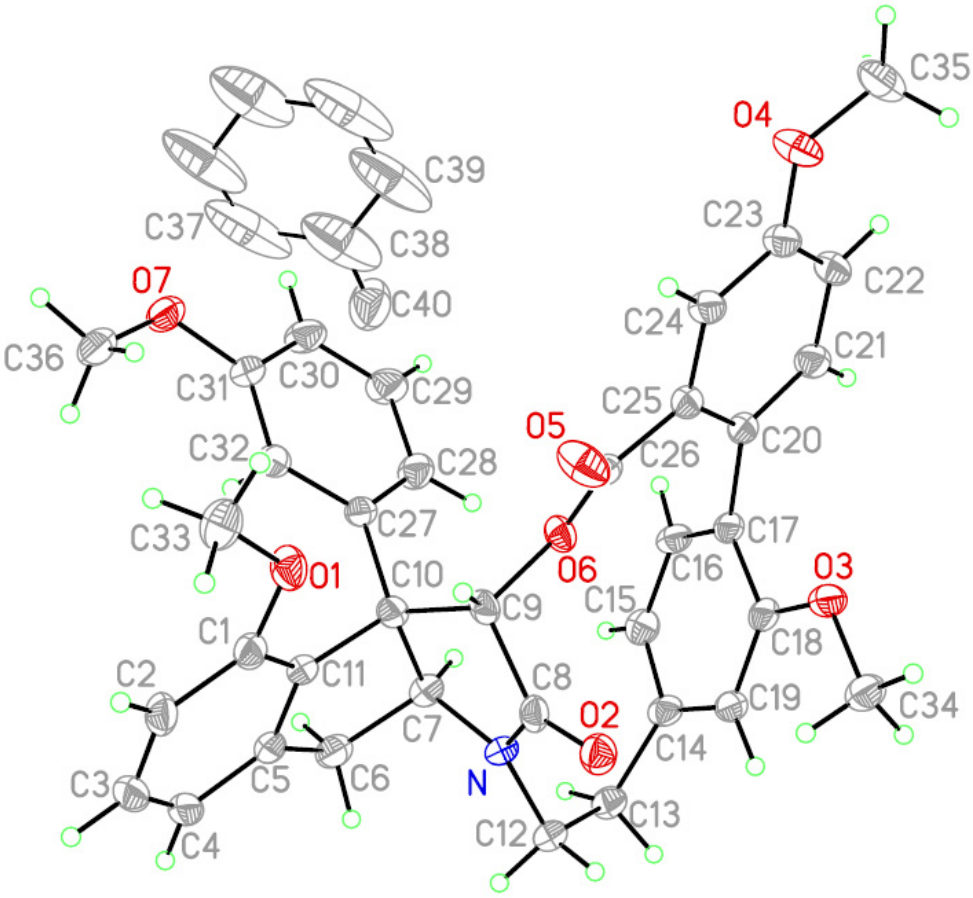


Figure 52 X-ray structure of **3-174**

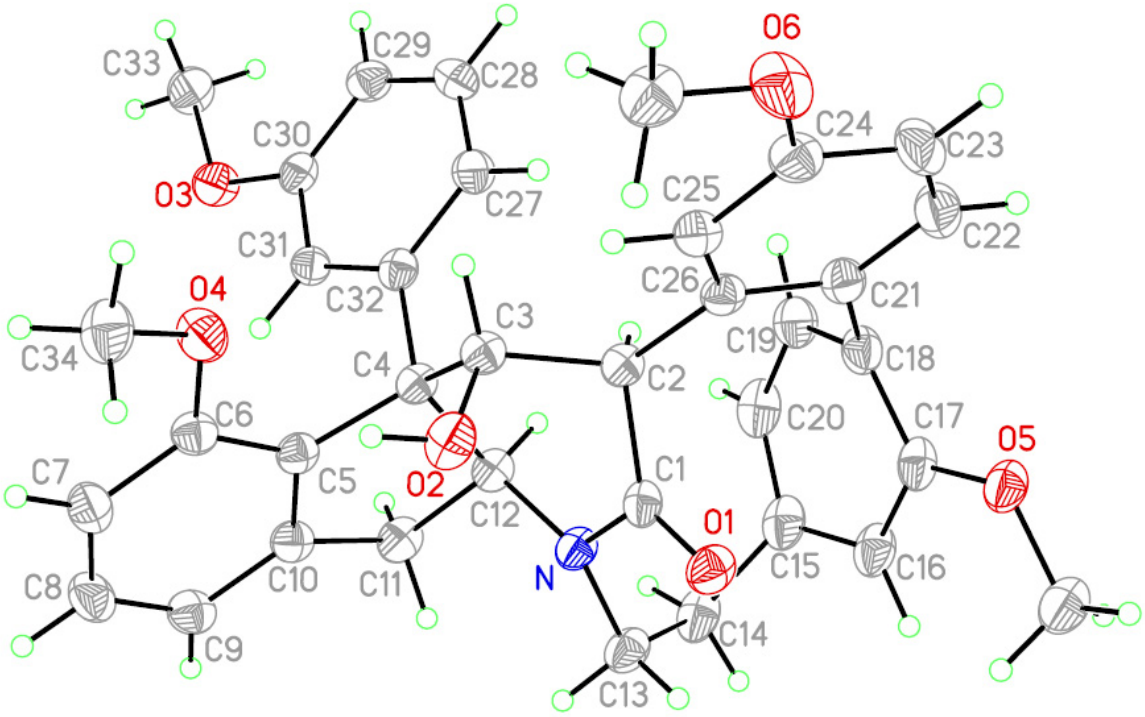


Figure 53 X-ray structure of **3-175**

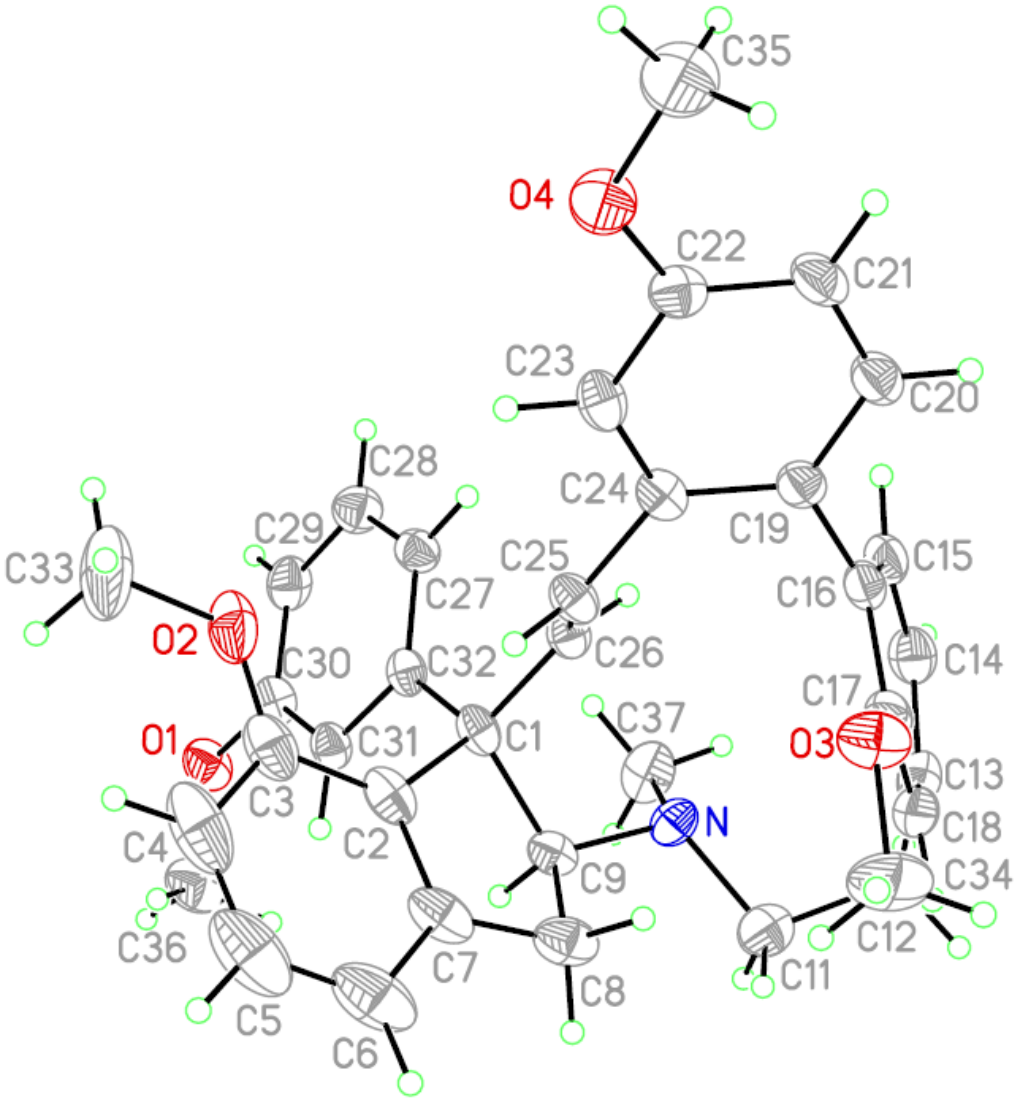
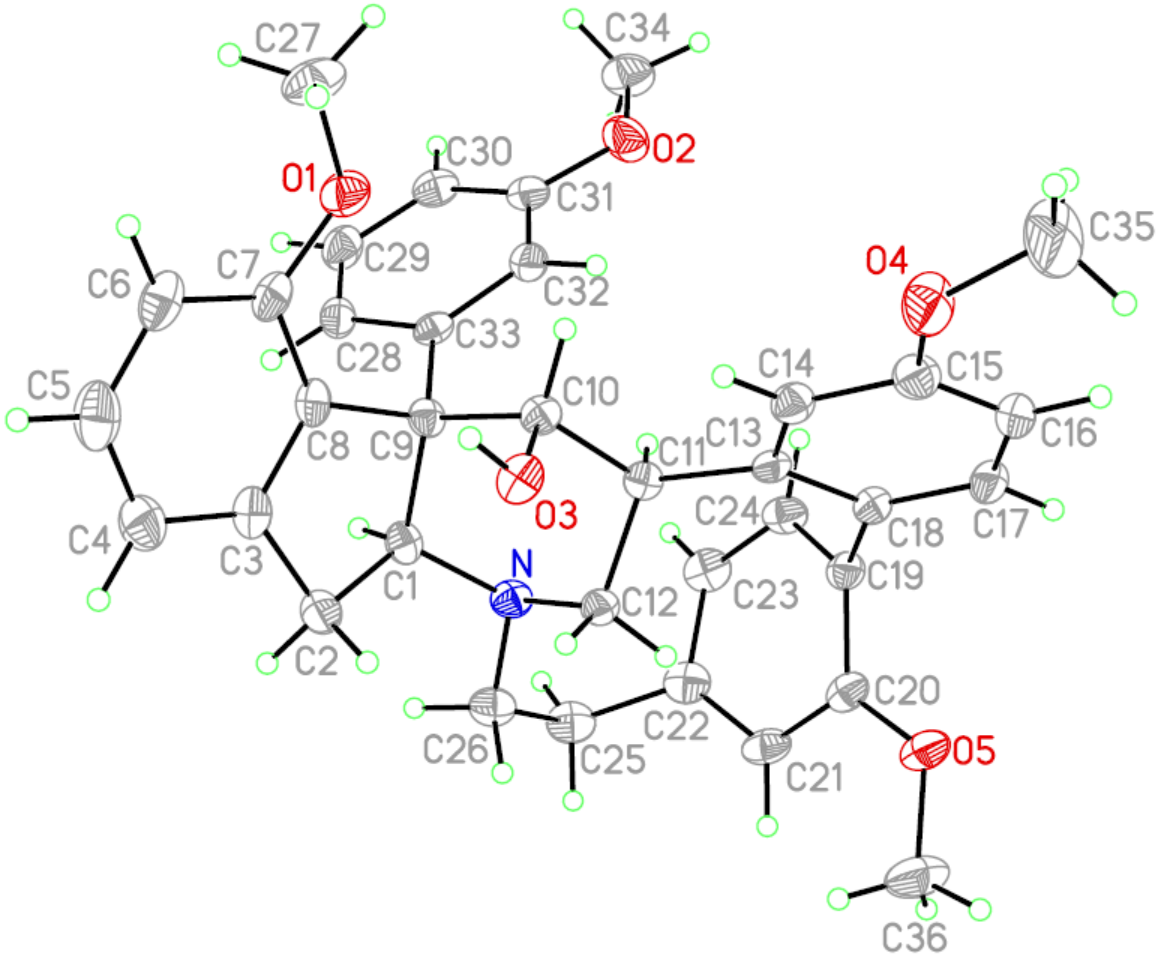
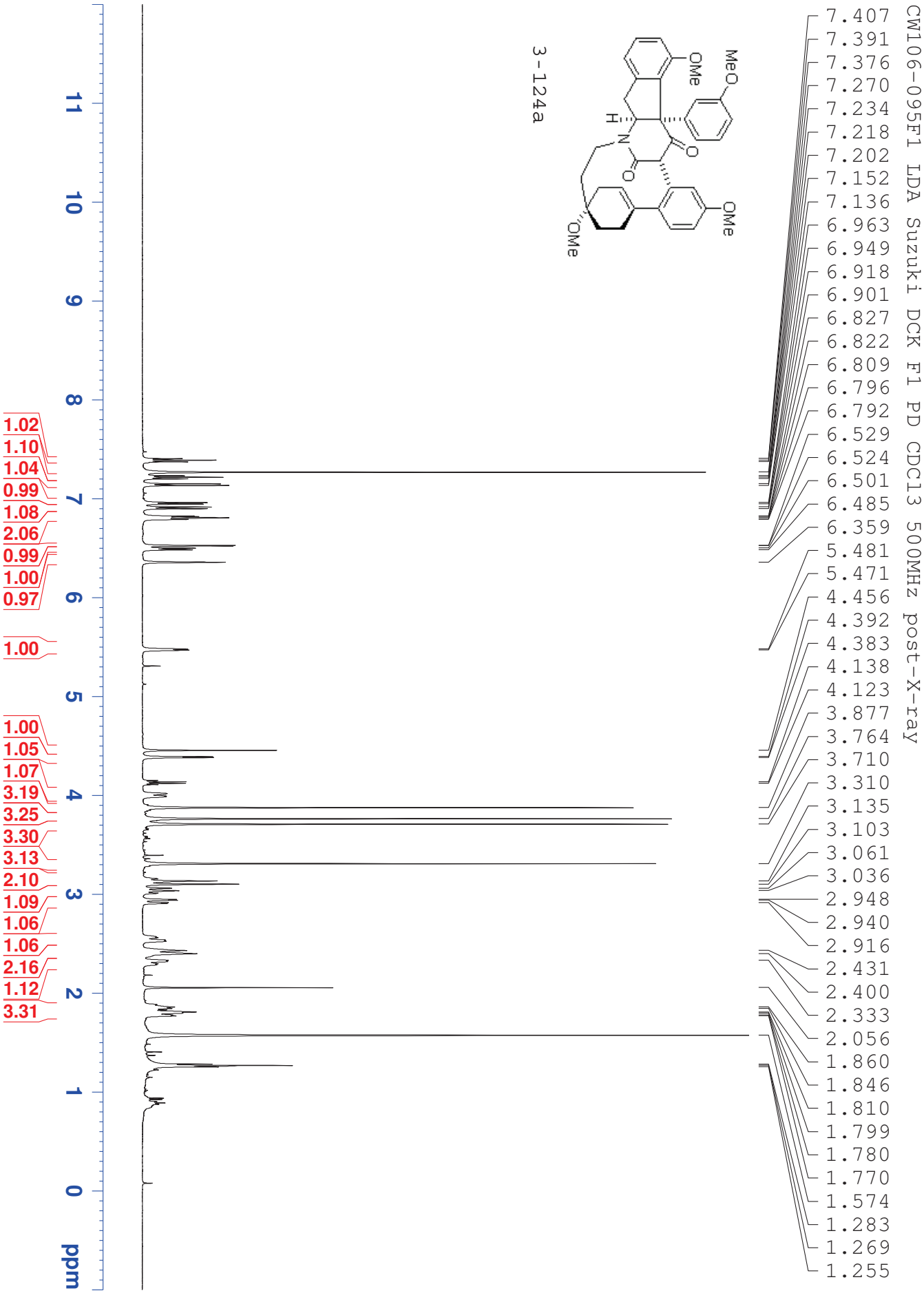


Figure 54 X-ray structure of **3-177**



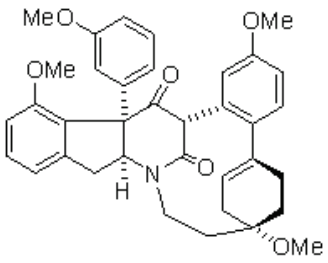
APPENDIX C

SELECTED NMR DATA


CW106-095F1 LDA Suzuki DCK F1 PD CDC13 500MHz post-X-ray
7.407
7.391
7.376
7.270
7.234
7.218
7.202
7.152
7.136
6.963
6.949
6.918
6.901
6.827
6.822
6.809
6.796
6.792
6.529
6.524
6.501
6.485
6.359
5.481
5.471
4.456
4.392
4.383
4.138
4.123
3.877
3.764
3.710
3.310
3.135
3.103
3.061
3.036
2.948
2.940
2.916
2.431
2.400
2.333
2.056
1.860
1.846
1.810
1.799
1.780
1.770
1.574
1.283
1.269
1.255
3-124a
MeO
OMe
OMe
OMe
H
N
O
O
1.02
1.10
1.04
0.99
1.08
2.06
0.99
1.00
0.97
1.00
1.00
1.05
1.07
3.19
3.25
3.30
3.13
2.10
1.09
1.06
1.06
2.16
1.12
3.31
11
10
9
8
7
6
5
4
3
2
1
0
ppm

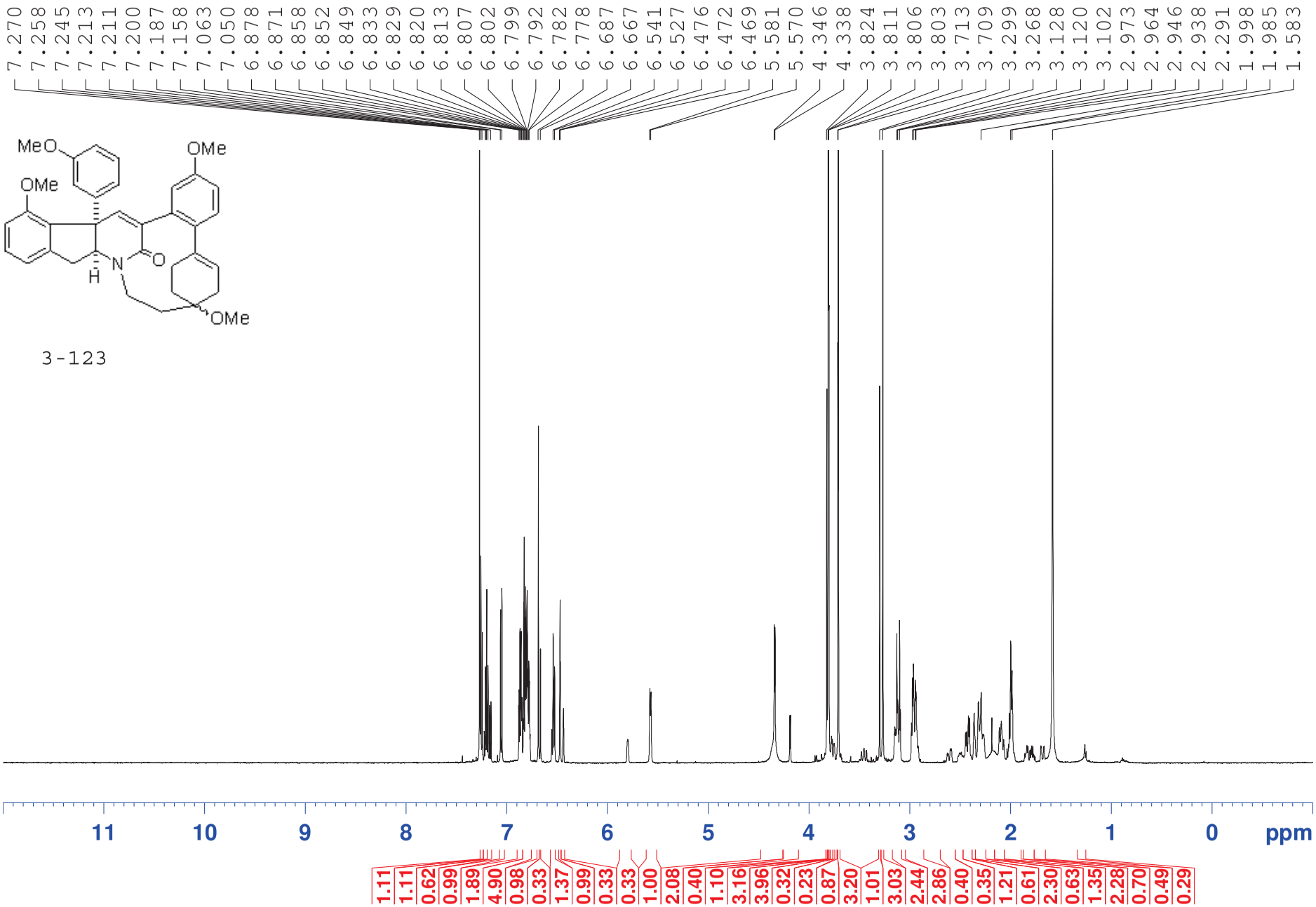
CW106-095F1 LDA Suzuki DCK F1 150MHz

201.90
168.63
159.50
158.20
156.56
143.54
138.13
136.01
133.58
131.73
129.57
129.52
129.21
124.11
121.57
120.12
118.89
115.68
112.57
112.46
110.00
77.44
77.23
77.02
75.19
72.49
67.55
62.25
60.64
55.65
55.34
55.28
49.40
45.99
36.99
33.88
33.23
30.30
30.23
14.42



3-124a

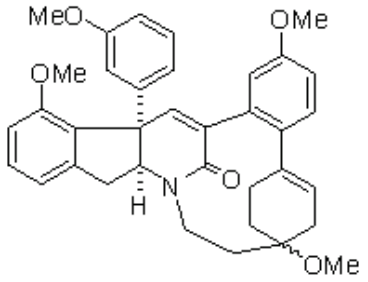
Chenbo 0041809a CW182-010 KH LiBH4 DCK SFC RP 600MHz



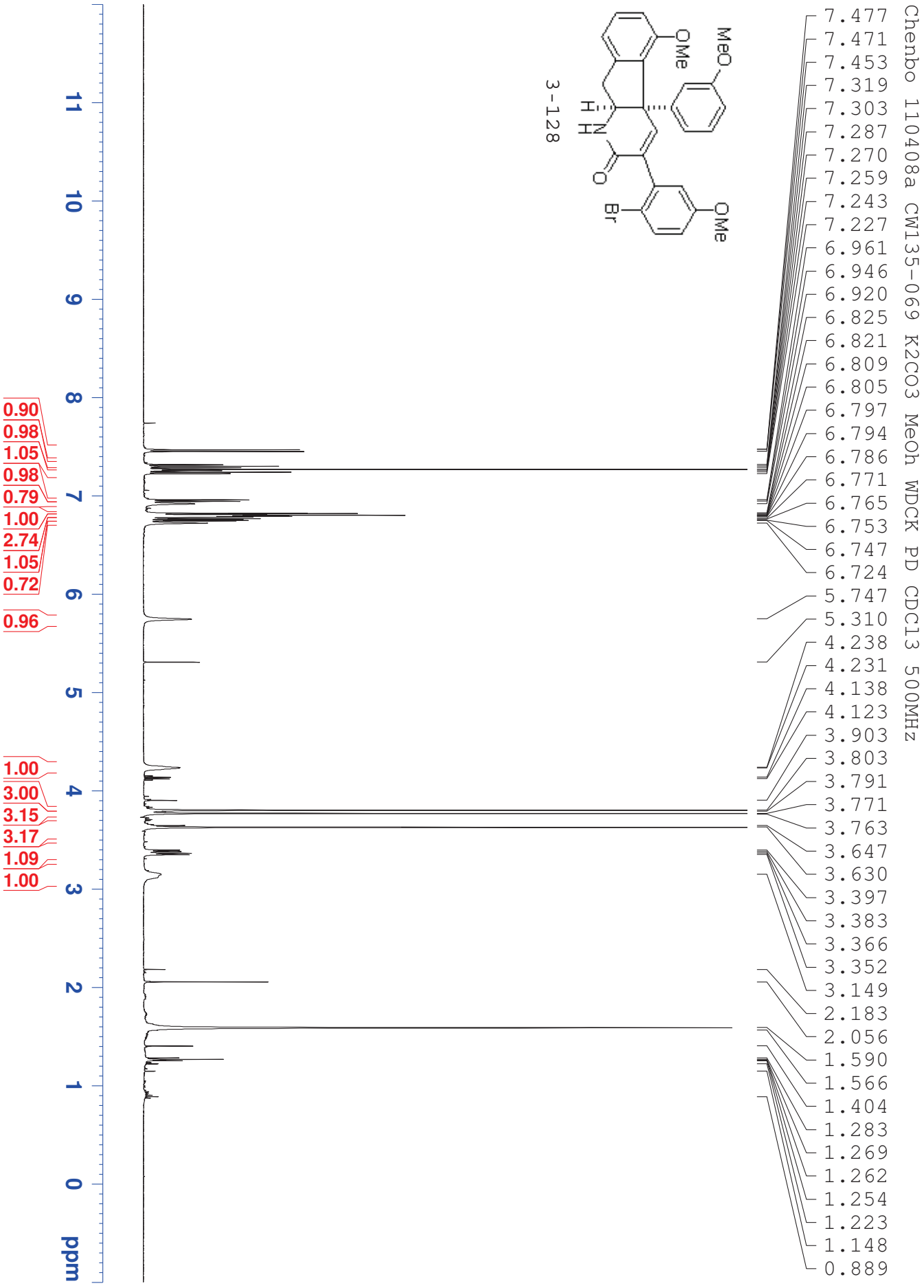
3-123

Chenbo 0041809a CW182-010 KH LiBH4 DCK SFC RP 600MHz

165.90
159.94
159.90
158.75
158.69
156.62
156.55
146.28
146.21
142.60
142.22
138.69
138.14
137.57
136.82
136.12
136.06
135.88
133.57
132.02
130.16
130.08
129.80
129.43
128.18
127.73
127.54
120.01
119.84
117.58
117.53
114.91
114.37
114.18
113.99
112.80
112.43
112.08
111.74
110.35
110.28
77.44
77.23
77.02
75.62
73.78
56.96
56.55
55.63
55.44
55.39
55.33
55.28
49.51
48.88
45.98
36.20
35.73
35.30
33.89
33.37
29.44
29.13
27.40

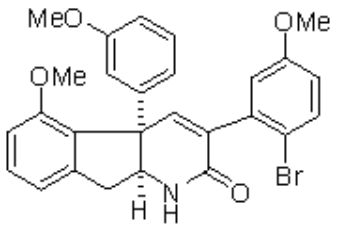


3-123

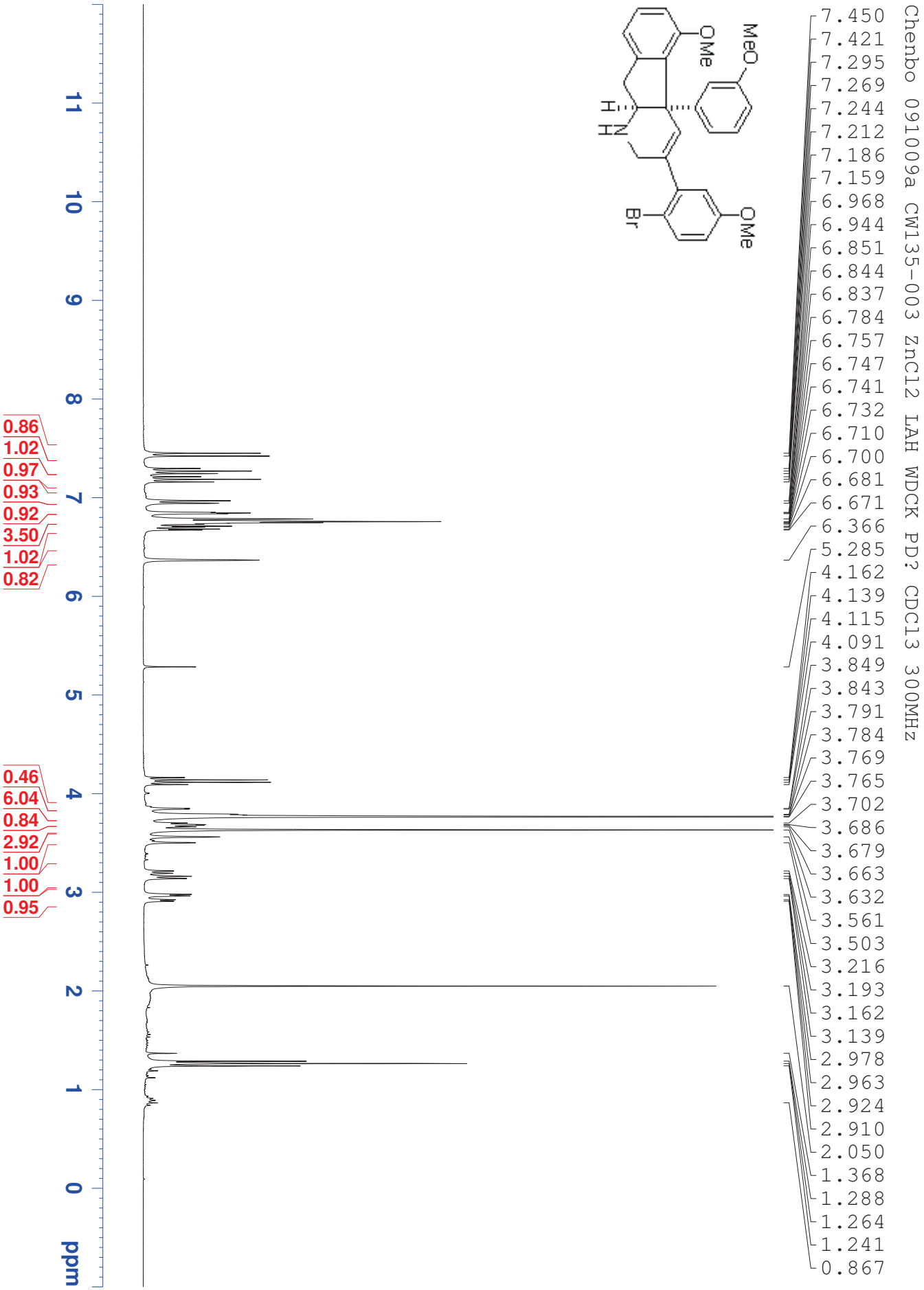

Chenbo 110408a CW135-069 K2CO3 MeOh WDCK PD CDCl3 500MHz
7.477
7.471
7.453
7.319
7.303
7.287
7.270
7.259
7.243
7.227
6.961
6.946
6.920
6.825
6.821
6.809
6.805
6.797
6.794
6.786
6.771
6.765
6.753
6.747
6.724
5.747
5.310
4.238
4.231
4.138
4.123
3.903
3.803
3.791
3.771
3.763
3.647
3.630
3.397
3.383
3.366
3.352
3.149
2.183
2.056
1.590
1.566
1.404
1.283
1.269
1.262
1.254
1.223
1.148
0.889
3-128
MeO
OMe
H
N
H
O
Br
OMe
0.90
0.98
1.05
0.98
0.79
1.00
2.74
1.05
0.72
0.96
1.00
3.00
3.15
3.17
1.09
1.00
11
10
9
8
7
6
5
4
3
2
1
0
ppm

Chenbo 090908a CW136-002 K2CO3 MeOH WDCK PD CDCl3 125MHz

163.87
159.78
158.85
156.56
144.99
143.59
140.91
139.07
133.11
130.00
129.84
129.44
119.20
117.53
117.18
115.05
114.47
113.06
112.01
110.03
77.49
77.23
76.98
64.36
60.51
55.61
55.34
55.31
55.23
40.78
21.16
14.31

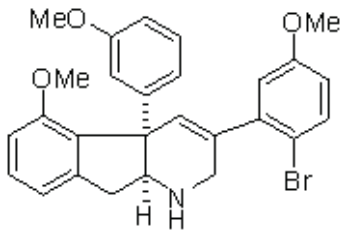


3-128

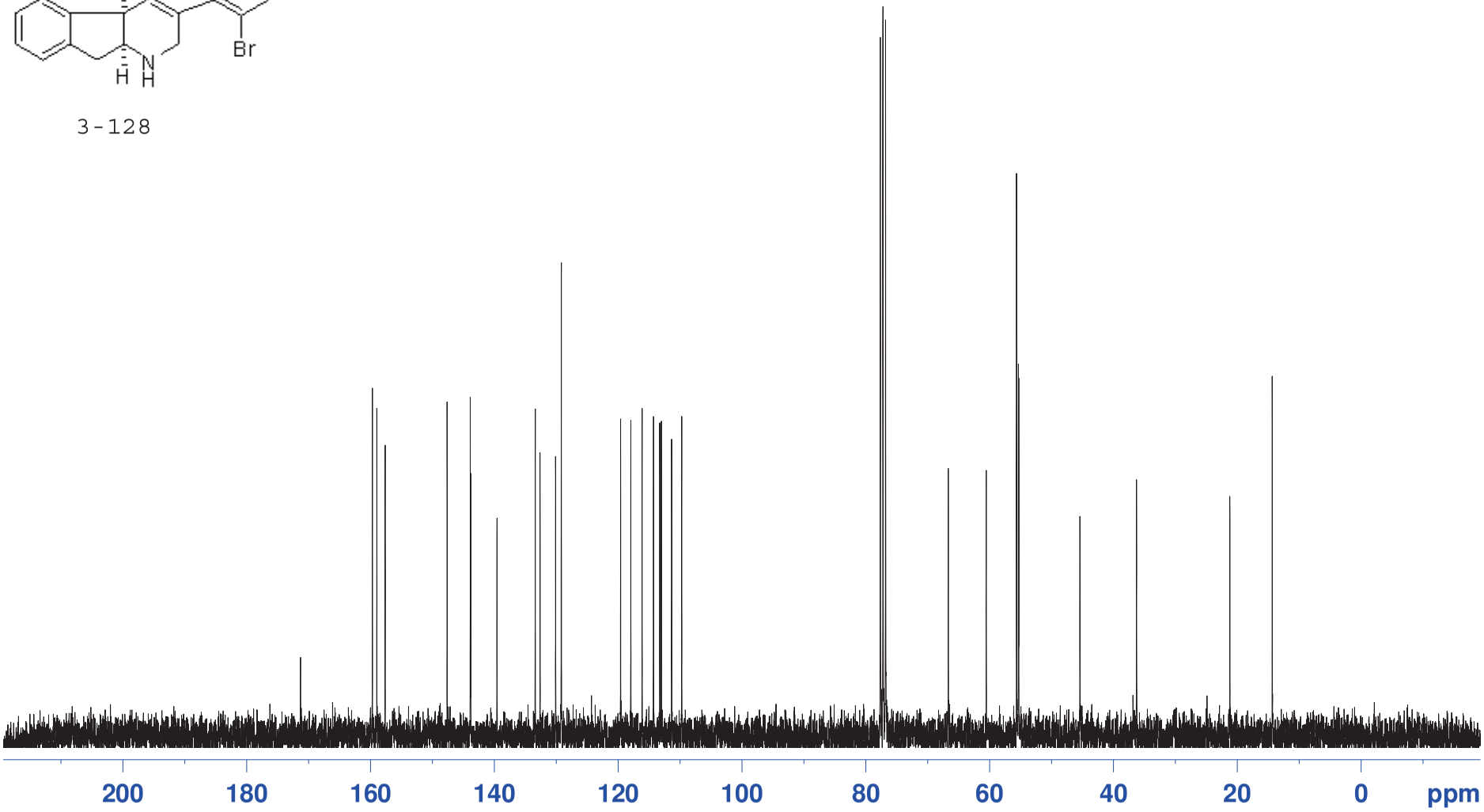

Chenbo 091009a CW135-003 ZnCl2 LAH WDCK PD? CDCl3 300MHz
7.450
7.421
7.295
7.269
7.244
7.212
7.186
7.159
6.968
6.944
6.851
6.844
6.837
6.784
6.757
6.747
6.741
6.732
6.710
6.700
6.681
6.671
6.366
5.285
4.162
4.139
4.115
4.091
3.849
3.843
3.791
3.784
3.769
3.765
3.702
3.686
3.679
3.663
3.632
3.561
3.503
3.216
3.193
3.162
3.139
2.978
2.963
2.924
2.910
2.050
1.368
1.288
1.264
1.241
0.867
MeO
OMe
H
N
H
Br
OMe
0.86
1.02
0.97
0.93
0.92
3.50
1.02
0.82
0.46
6.04
0.84
2.92
1.00
1.00
0.95
ppm
11
10
9
8
7
6
5
4
3
2
1
0

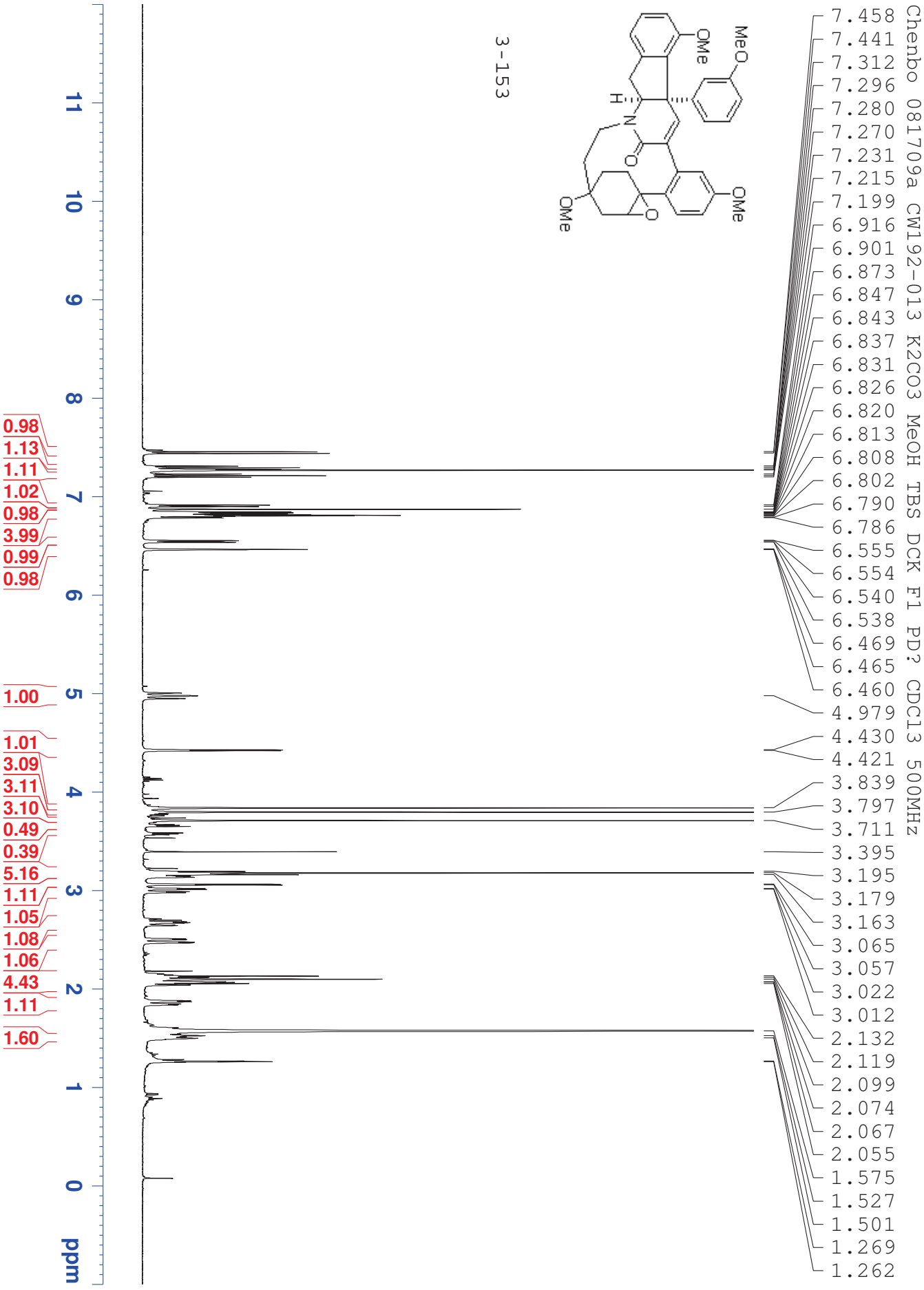
Chenbo 091009a CW135-003 ZnCl2 LAH WDCK PD? CDCl3 300MHz

171.30
159.69
158.97
157.63
147.62
143.88
143.80
139.56
133.39
132.61
130.10
129.18
119.60
117.95
116.13
114.29
113.27
113.02
111.36
109.73
77.65
77.23
76.80
66.67
60.54
55.65
55.35
55.29
45.41
36.27
21.20
14.35



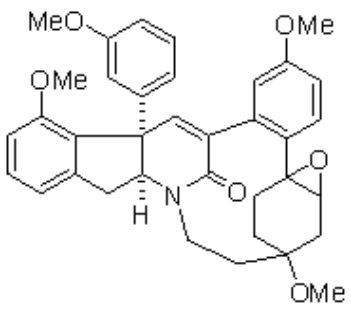
3-128



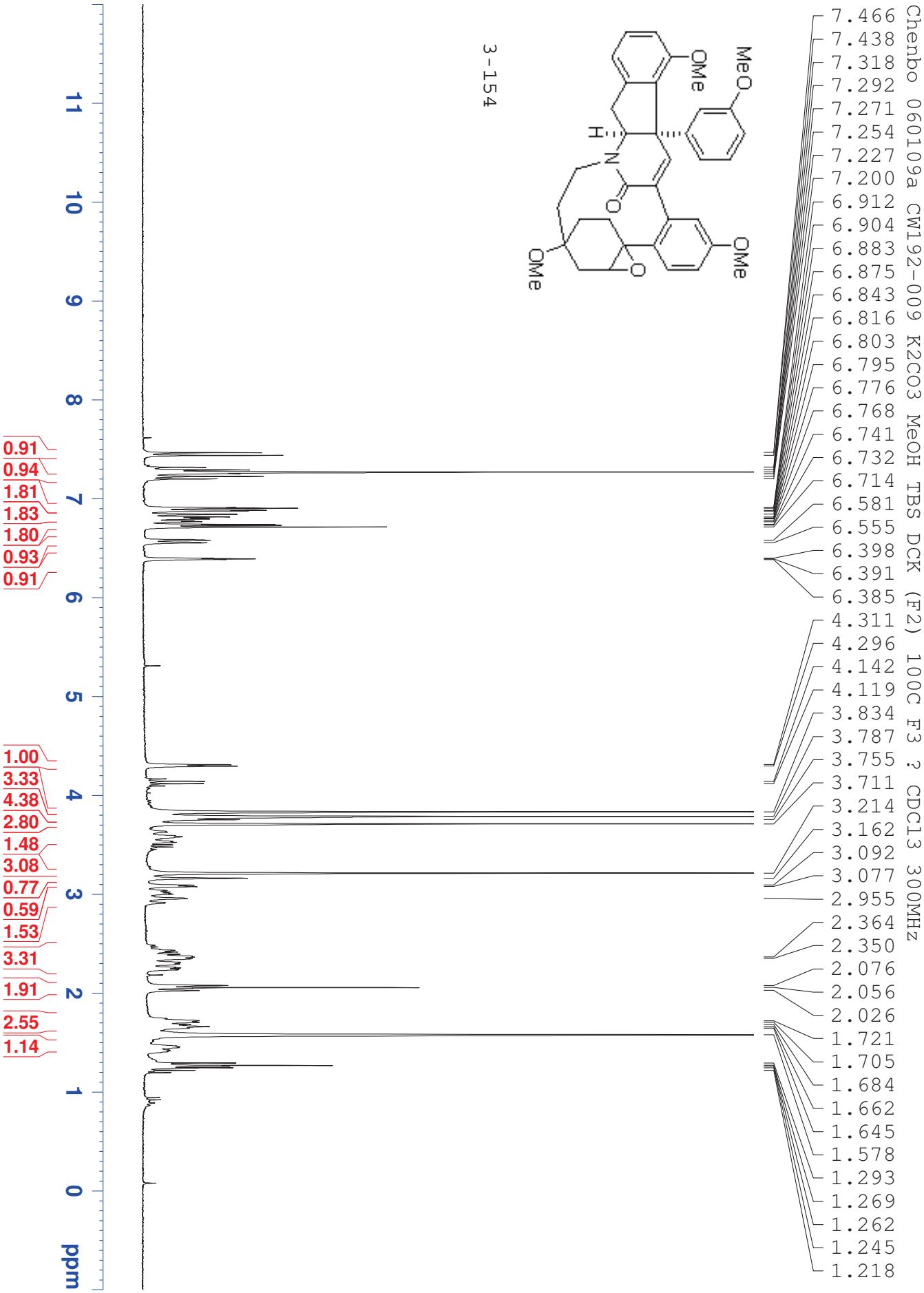

Chenbo 081709a CW192-013 K2CO3 MeOH TBS DCK F1 PD? CDC13 500MHz
7.458
7.441
7.312
7.296
7.280
7.270
7.231
7.215
7.199
6.916
6.901
6.873
6.847
6.843
6.837
6.831
6.826
6.820
6.813
6.808
6.802
6.790
6.786
6.555
6.554
6.540
6.538
6.469
6.465
6.460
4.979
4.430
4.421
3.839
3.797
3.711
3.395
3.195
3.179
3.163
3.065
3.057
3.022
3.012
2.132
2.119
2.099
2.074
2.067
2.055
1.575
1.527
1.501
1.269
1.262
3-153
MeO
OMe
OMe
OMe
H
N
O
O
0.98
1.13
1.11
1.02
0.98
3.99
0.99
0.98
1.00
1.01
3.09
3.11
3.10
0.49
0.39
5.16
1.11
1.05
1.08
1.06
4.43
1.11
1.60
11
10
9
8
7
6
5
4
3
2
1
0
ppm

Chenbo 081809b CW192-013 K2CO3 MeOH DMDO TBS DCK (F1) PD? CDCl3 150MHz

164.48
160.00
159.19
156.54
146.07
142.63
139.45
137.23
136.14
131.93
131.62
130.30
129.95
126.82
119.81
117.54
114.67
114.10
112.46
112.04
110.35
77.44
77.23
77.02
74.70
70.78
67.71
62.92
59.90
56.36
55.64
55.39
55.31
48.62
39.12
38.54
35.94
31.72
30.73
24.66

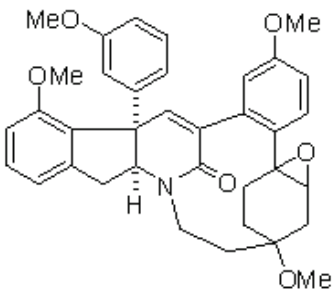


3-153


Chenbo 060109a CW192-009 K2CO3 MeOH TBS DCK (F2) 100C F3 ? CDCl3 300MHz
3-154
MeO
OMe
OMe
OMe
H
N
O
O
7.466
7.438
7.318
7.292
7.271
7.254
7.227
7.200
6.912
6.904
6.883
6.875
6.843
6.816
6.803
6.795
6.776
6.768
6.741
6.732
6.714
6.581
6.555
6.398
6.391
6.385
4.311
4.296
4.142
4.119
3.834
3.787
3.755
3.711
3.214
3.162
3.092
3.077
2.955
2.364
2.350
2.076
2.056
2.026
1.721
1.705
1.684
1.662
1.645
1.578
1.293
1.269
1.262
1.245
1.218
0.91
0.94
1.81
1.83
1.80
0.93
0.91
1.00
3.33
4.38
2.80
1.48
3.08
0.77
0.59
1.53
3.31
1.91
2.55
1.14
ppm

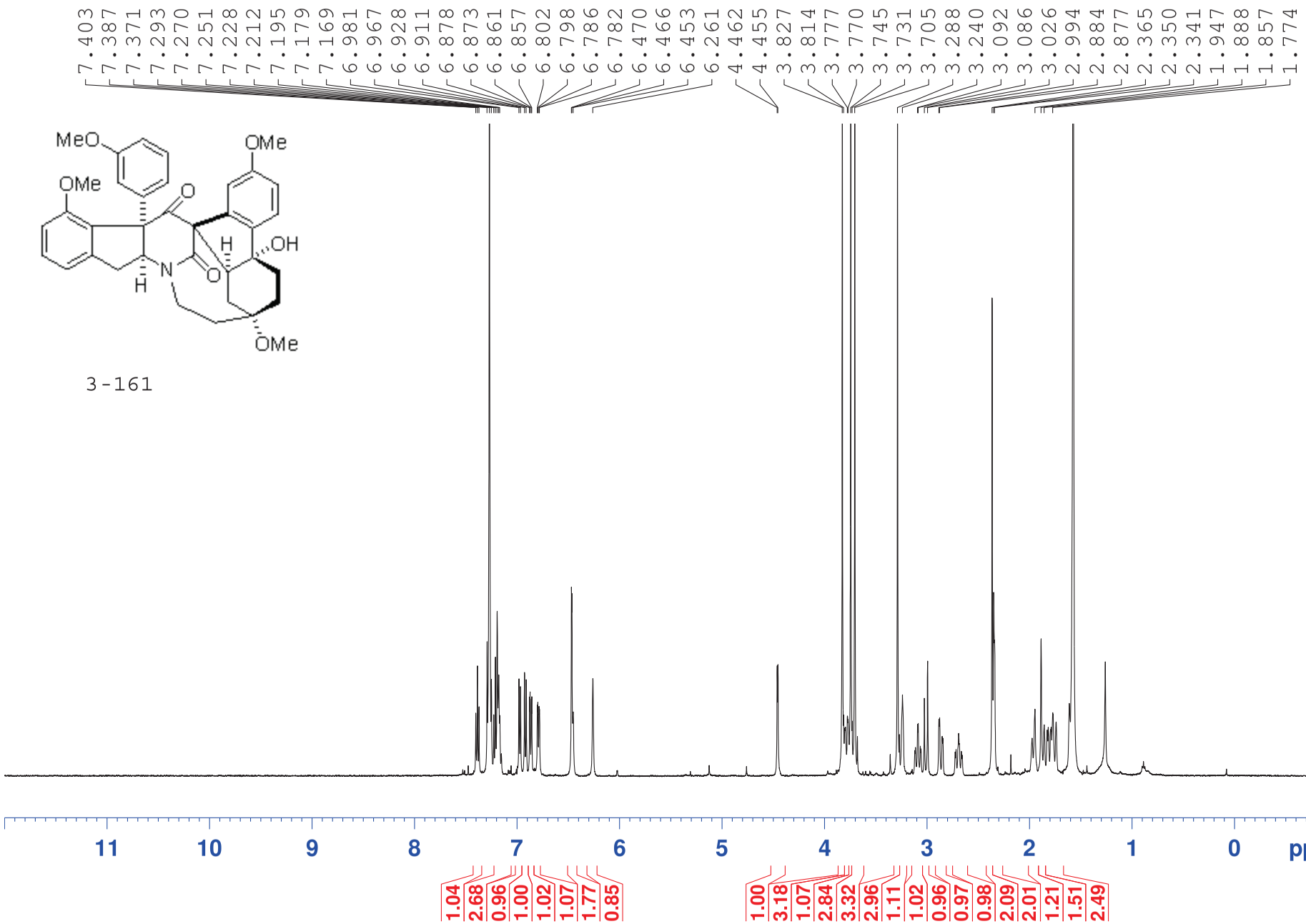
Chenbo 060109b CW192-009 K2CO3 MeOH TBS DCK (F2) F3 PD? CDCl3 150MHz

165.30
160.00
159.41
156.38
145.50
141.90
138.16
138.04
137.33
132.19
130.74
130.36
130.12
130.02
119.99
117.48
114.47
114.14
113.81
111.80
110.30
77.44
77.23
77.02
73.74
73.50
60.76
59.05
57.09
55.51
55.38
55.37
49.18
46.39
36.36
31.39
30.57
30.54
27.99
21.30
14.42

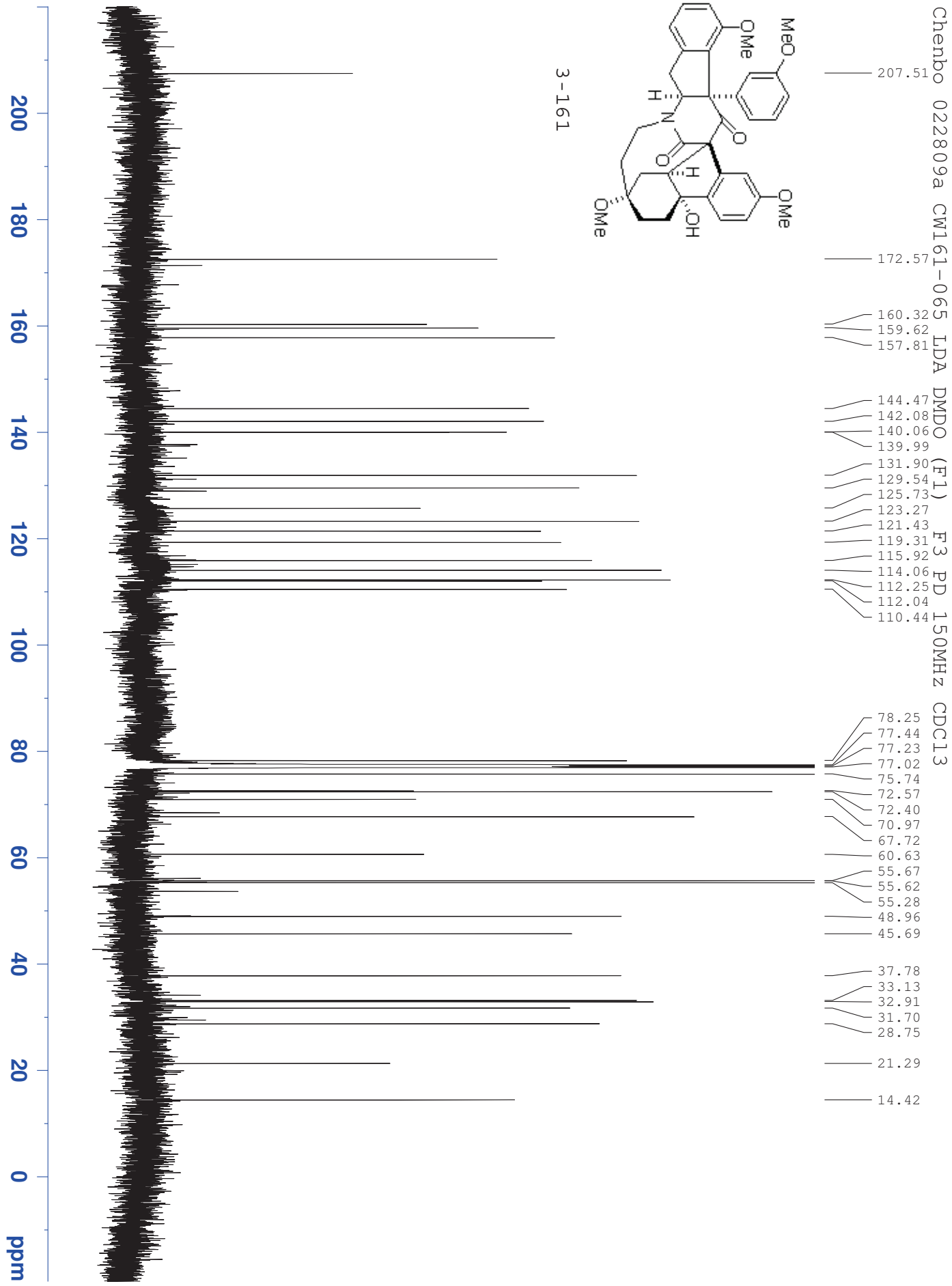


3-153

Cw161-065F3 LDA DMDO DCK post-xray CDCl3 500MHz

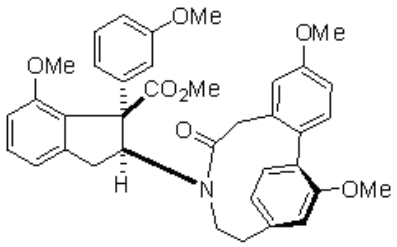


3-161


Chenbo 022809a CW161-065 LDA DMDO (F1) F3 PD 150MHz CDC13
3-161
MeO
OMe
OMe
OMe
OH
H
N
H
O
O
207.51
172.57
160.32
159.62
157.81
144.47
142.08
140.06
139.99
131.90
129.54
125.73
123.27
121.43
119.31
115.92
114.06
112.25
112.04
110.44
78.25
77.44
77.23
77.02
75.74
72.57
72.40
70.97
67.72
60.63
55.67
55.62
55.28
48.96
45.69
37.78
33.13
32.91
31.70
28.75
21.29
14.42
200
180
160
140
120
100
80
60
40
20
0
ppm

Chenbo 061309d CW192-048II Aroma DCK (F2) Me2SO4x2 PD? CDCl3 500MHz

7.489 7.473 7.384 7.368 7.353 7.270 7.198 7.182 7.166 7.019 7.004 6.949 6.934 6.883 6.878 6.861 6.857 6.835 6.829 6.812 6.808 6.797 6.781 6.766 6.567 6.562 4.758 4.754 4.139 4.125 3.820 3.766 3.754 3.751 3.726 3.703 3.693 3.522 3.498 3.489 3.355 3.341 2.810 2.798 2.783 2.772 2.744 2.718 2.347 2.315 2.055 1.572 1.284 1.270 1.255



3-165

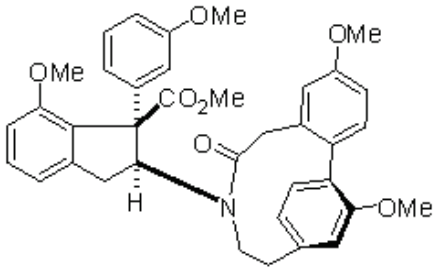
11 10 9 8 7 6 5 4 3 2 1 0 ppm

0.94 1.03 1.05 1.04 1.05 6.91 1.00

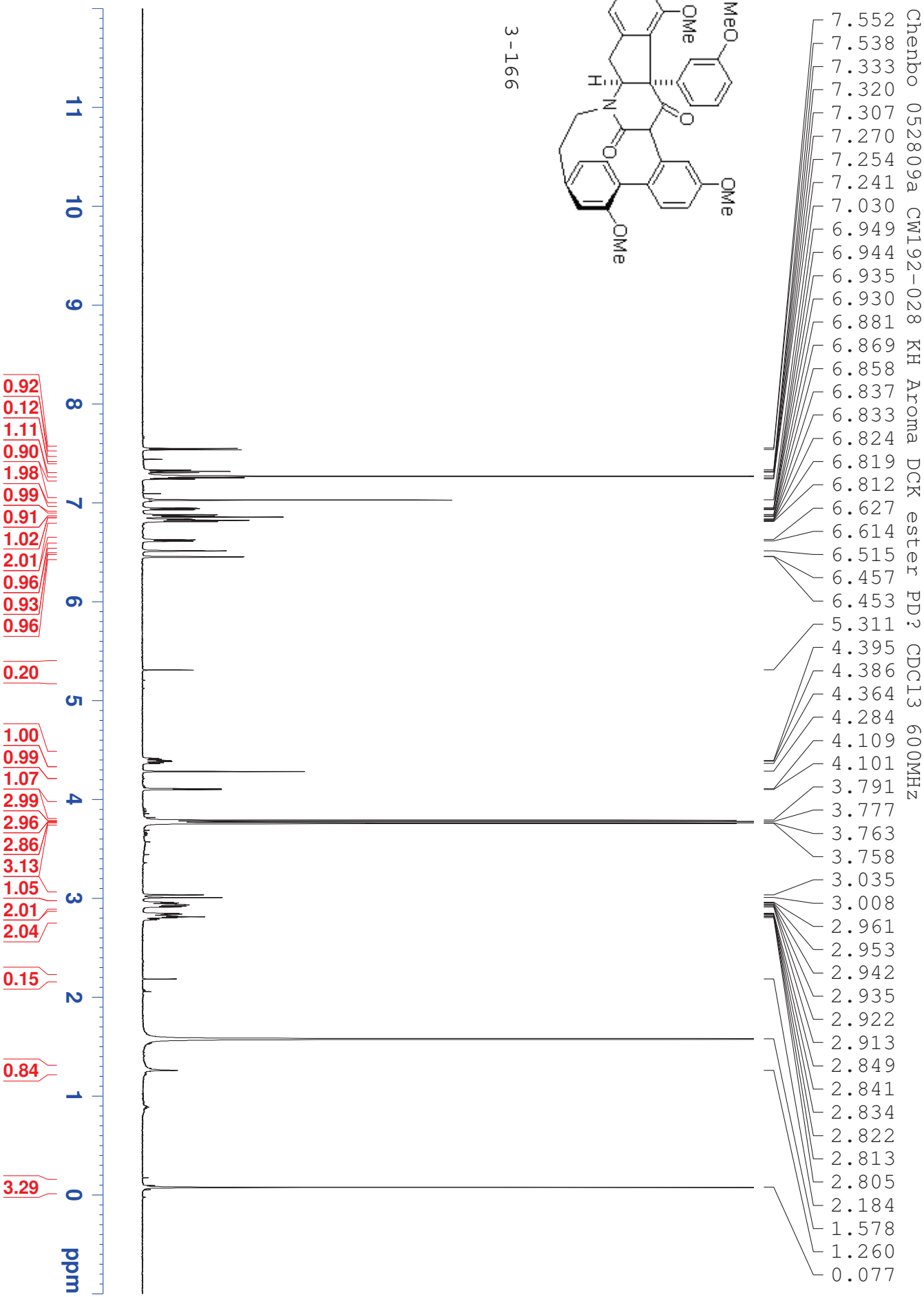
1.00 1.57 3.24 0.86 3.53 2.63 3.40 3.16 0.69 1.02 3.11 1.00

Chenbo 061409a CW192-048 Aroma DCK PD (F2) CDCl3 150MHz

171.63
171.53
161.13
159.46
158.64
156.77
143.50
142.98
141.66
137.58
131.30
130.60
130.44
130.42
129.74
129.12
126.09
124.45
120.94
118.97
116.65
115.48
114.95
112.20
111.67
110.23
77.44
77.23
77.02
71.56
68.04
55.63
55.46
55.39
55.37
52.61
44.10
41.50
38.33
35.33

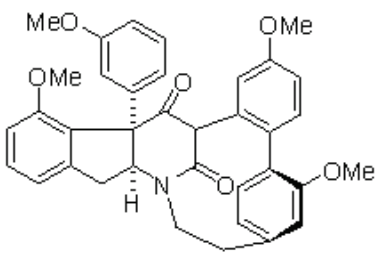


3-165


Chenbo 052809a CW192-028 KH Aroma DCK ester PD? CDC13 600MHz
7.552
7.538
7.333
7.320
7.307
7.270
7.254
7.241
7.030
6.949
6.944
6.935
6.930
6.881
6.869
6.858
6.837
6.833
6.824
6.819
6.812
6.627
6.614
6.515
6.457
6.453
5.311
4.395
4.386
4.364
4.284
4.109
4.101
3.791
3.777
3.763
3.758
3.035
3.008
2.961
2.953
2.942
2.935
2.922
2.913
2.849
2.841
2.834
2.822
2.813
2.805
2.184
1.578
1.260
0.077
3-166
MeO
OMe
OMe
OMe
H
N
O
O
0.92
0.12
1.11
0.90
1.98
0.99
0.91
1.02
2.01
0.96
0.93
0.96
0.20
1.00
0.99
1.07
2.99
2.96
2.86
3.13
1.05
2.01
2.04
0.15
0.84
3.29
11
10
9
8
7
6
5
4
3
2
1
0
ppm

Chenbo 061409b CW192-050 KH Aroma DCK PD (F2) CDCl3 150MHz

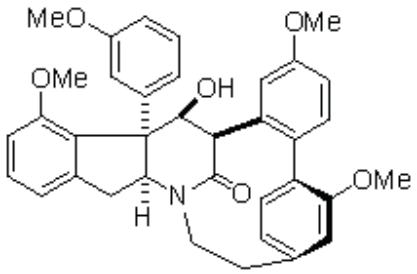
200.72
166.50
161.19
159.46
158.67
156.25
144.06
143.43
138.82
136.09
131.42
131.07
130.59
130.35
130.18
129.18
125.80
121.68
121.45
120.49
118.61
115.57
114.37
112.54
112.22
109.71
67.63
67.55
62.92
55.58
55.43
55.30
55.28
45.76
36.34
33.30
14.42



3-166

CW224-090 LiH CHO Aroma CDCl3 500MHz

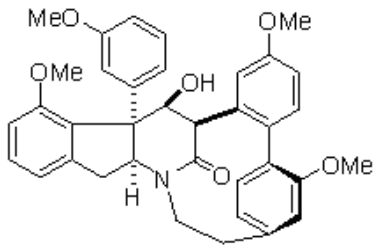
7.630 7.613 7.286 7.270 7.255 7.249 7.244 7.208 7.192 7.176 7.153 7.137 7.006 6.990 6.945 6.939 6.928 6.922 6.906 6.836 6.819 6.775 6.771 6.759 6.755 6.577 6.562 6.358 4.947 4.287 4.155 4.139 4.128 3.852 3.821 3.771 3.757 3.744 3.681 3.395 3.158 3.125 3.113 3.105 2.921 2.577 2.568 1.876 1.870 1.863 1.857 1.850 1.593 1.263 0.078



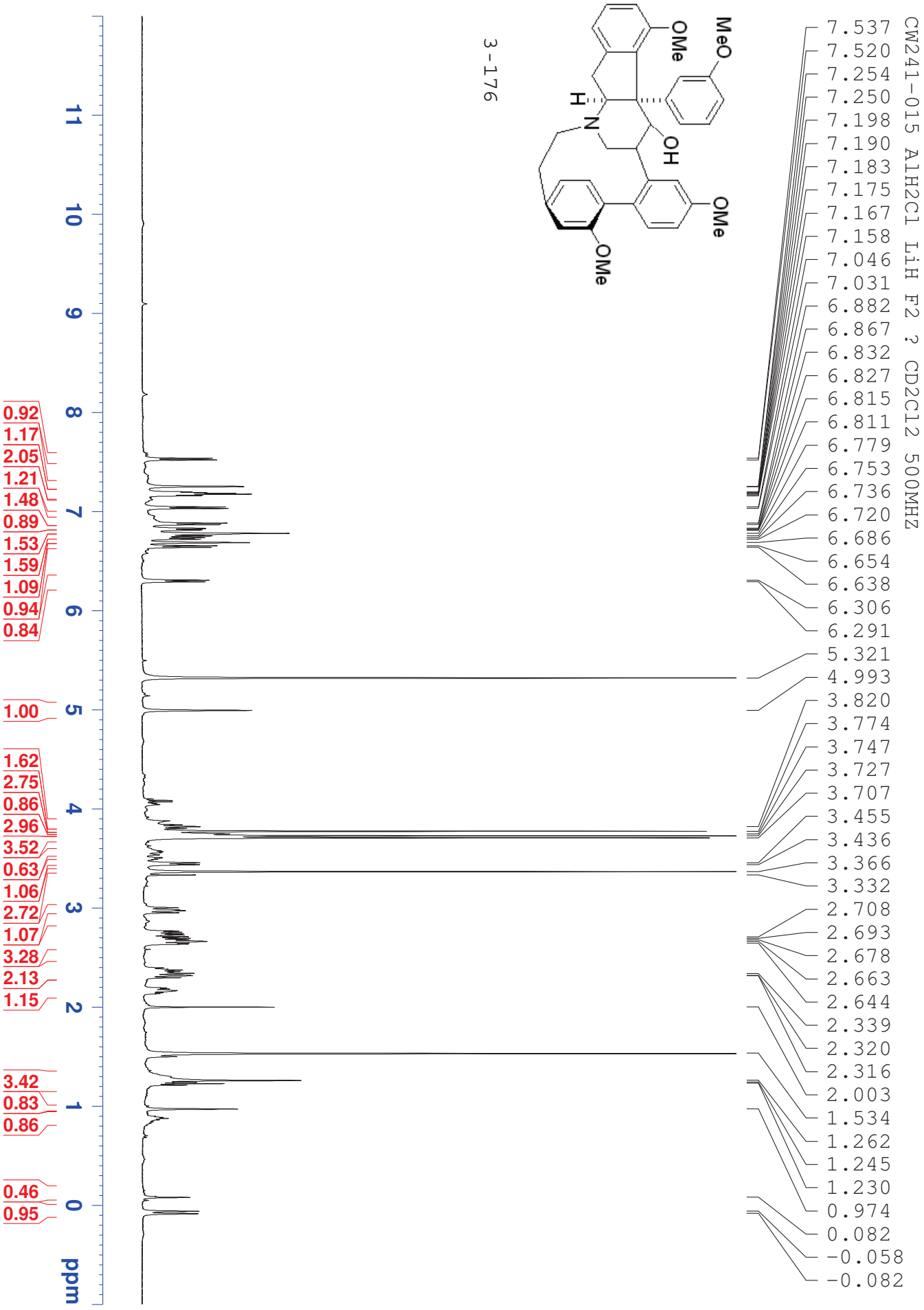
3-174

Chenbo 090409a CW210-089 LHMDS CHO Aroma DCK (F2) F1 PD ? CDCl3 150MHz

172.26
163.04
159.96
159.21
155.98
145.41
144.91
142.92
138.04
132.76
131.64
131.05
130.15
130.07
125.19
121.64
118.64
118.20
116.71
116.09
113.33
111.61
110.56
110.16
77.44
77.23
77.02
75.24
72.16
68.74
66.73
59.27
55.81
55.53
55.52
55.22
51.04
44.83
34.68
32.93



3-174

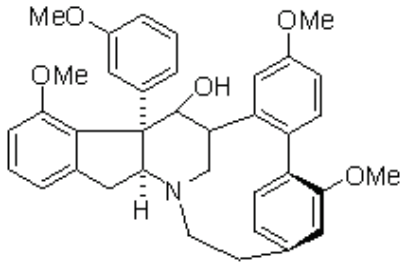

CW241-015 A1H2C1 LiH F2 ? CD2C12 500MHZ
7.537
7.520
7.254
7.250
7.198
7.190
7.183
7.175
7.167
7.158
7.046
7.031
6.882
6.867
6.832
6.827
6.815
6.811
6.779
6.753
6.736
6.720
6.686
6.654
6.638
6.306
6.291
5.321
4.993
3.820
3.774
3.747
3.727
3.707
3.455
3.436
3.366
3.332
2.708
2.693
2.678
2.663
2.644
2.339
2.320
2.316
2.003
1.534
1.262
1.245
1.230
0.974
0.082
-0.058
-0.082
3-176
MeO
OMe
OH
OMe
OMe
H
N
0.92
1.17
2.05
1.21
1.48
0.89
1.53
1.59
1.09
0.94
0.84
1.00
1.62
2.75
0.86
2.96
3.52
0.63
1.06
2.72
1.07
3.28
2.13
1.15
3.42
0.83
0.86
0.46
0.95
11
10
9
8
7
6
5
4
3
2
1
0
ppm

CW241-015 F2 AlH2Cl PD CDCl3 150MHz

161.80
159.54
159.44
156.61
150.24
146.72
145.87
144.35
133.28
132.86
132.54
130.35
129.53
128.43
127.65
125.99
120.61
118.28
115.82
115.30
112.94
110.33
109.83
109.67

75.65
70.12
60.14
57.06
55.83
55.67
55.64
54.37
54.18
54.01
53.82
53.64
45.32
41.99
39.00
30.51
30.24

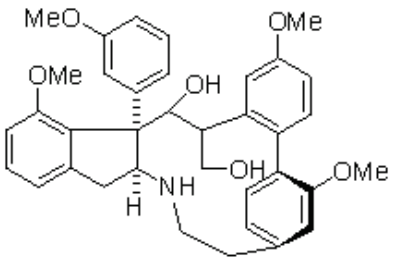
14.54



3-176

CW241-015 AlH2Cl LiH F3 amino alcohol ? CD2Cl2 500MHZ

7.392 7.376 7.357 7.342 7.326 7.113 7.097 7.082 7.008 7.004 6.969 6.955 6.917 6.905 6.894 6.882 6.877 6.860 6.843 6.691 6.688 6.671 6.566 5.320 4.086 4.072 3.928 3.918 3.781 3.736 3.669 3.622 3.511 3.498 3.258 3.235 3.103 3.094 3.069 3.055 3.039 3.025 2.743 2.616 2.566 2.553 2.522 2.321 2.004 1.542 1.246 1.232 1.217 0.913 0.903



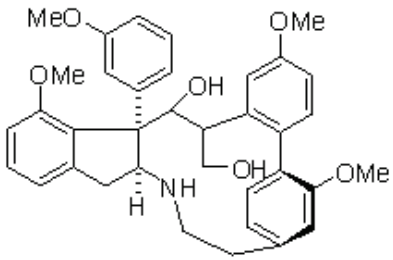
3-177

CW224-096F2 amino alcohol CD2Cl2 150MHz

159.90
158.96
158.37
156.45
148.39
145.60
144.63
141.40
133.76
133.21
132.00
130.52
129.19
128.92
127.96
125.56
119.40
119.35
117.80
113.68
111.43
111.31
111.11

74.01
72.97
64.81
60.79
58.79
56.29
56.23
55.68
55.55
54.36
54.18
54.00
53.82
53.64
49.29
47.72
37.74
35.78

14.55



3-176