

**Development and Synthetic Application of Iodine(III)- and
Chromium(VI)-Mediated Alkene Oxamidation**

BY

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THESIS

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This thesis is dedicated to my adoring family, Liudmila, Vladimir, Catherine,
Elena and Alexander.

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MVG

The Obstacle is the Path.

Zen proverb

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LIST OF ABBREVIATIONS

app	apparent
aq	aqueous
9-BBN	9-borabicyclononane
BINOL	1,1'-bi-2,2'-naphthol
Bn	benzyl
BOC	<i>tert</i> -butoxycarbonyl
br	broad
BTMSA	<i>bis</i> (trimethylsilyl) acetylene
<i>t</i> -Bu	<i>tert</i> -butyl
Bz	benzoyl
<i>c</i>	concentration
CCE	constant current electrolysis
Cbz	carbobenzyloxy
CI	chemical ionization
COD	1,5-cyclooctadiene
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CSA	10-camphorsulfonic acid
Cy	cyclohexyl
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet
dd	doublet of doublets

LIST OF ABBREVIATIONS (continued)

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,1-dichloroethane
DDO	dimethyldioxirane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEPT	distortionless enhanced polarization transfer
DEAD	diethyl azodicarboxylate
DFT	density functional theory
DIB	(diacetoxyiodo)benzene
DIAD	diisopropyl azodicarboxylate
DIEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	dimethyl sulfoxide
E	electrophile
ee	enantiomeric excess
equiv	equivalents
EDC	<i>N</i> -ethyl- <i>N'</i> -(3-dimethylaminopropyl)carbodiimide hydrochloride
EI	electron impact

LIST OF ABBREVIATIONS (continued)

FAB	fast atom bombardment
FTIR	Fourier transform infrared spectroscopy
h	hours
$h\nu$	light
HFIP	hexafluoroisopropanol
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple-quantum correlation
HOBt	1-hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
IBX	2-iodoxybenzoic acid
Im	imidazole
<i>i</i> -Pr	isopropyl
Ipc	isopinocampheyl
IR	infrared spectroscopy
KHMDS	potassium hexamethyldisilylamide
LA	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LFP	laser flash photolysis

LIST OF ABBREVIATIONS (continued)

LUMO	lowest unoccupied molecular orbital
M	molar
m	multiplet
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
min	minutes
MM2	molecular mechanics 2
MTPA	methoxy(trifluoromethyl)phenylacetic acid
MNDO	modified neglect of diatomic overlap
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
MOM	methoxymethyl
MVK	methyl vinyl ketone
NADP	nicotinimide adenine dinucleotide phosphate
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NMM	<i>N</i> -methylmorpholine
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
NMR	nuclear magnetic resonance
NPhth	<i>N</i> -phthalimido
Nuc	nucleophile
NOESY	nuclear Overhauser enhancement spectroscopy

LIST OF ABBREVIATIONS (continued)

OTFA	trifluoroacetate
PDC	pyridinium dichromate
PCC	pyridinium chlorochromate
Phth	phthaloyl
PIFA	phenyliodine(III) bis(trifluoroacetate)
PMB	<i>para</i> -methoxybenzyl
PMSF	phenylmethanesulfonyl fluoride
PPTS	pyridinium 4-toluenesulfonate
<i>p</i> TSA	<i>para</i> -toluenesulphonic acid
py	pyridine
q	quartet
RCM	ring-closing metathesis
R _f	retention factor
rms	root mean square speed
rt	room temperature
s	singlet
sat	saturated
SIR	specific incorporation rate
SOMO	singly occupied molecular orbital
t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl

LIST OF ABBREVIATIONS (continued)

TBS	<i>tert</i> -butyldimethylsilyl
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFEA	trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	trimethylethylenediamine
TMS	trimethylsilyl
Tol	4-tolyl
TPAP	tetrapropylammonium perruthenate
Troc	2,2,2-trichloroethyl carbamate
Ts	4-toluenesulfonyl

SUMMARY

This thesis describes the development of the iodine(III)- and chromium(VI)-mediated oxidative cyclization of unsaturated *O*-alkyl hydroxamates and the use of these transformations use for the preparation of usefully functionalized lactam ring products.

Chapter 1 describes recent advances in inter- and intramolecular alkene oxamination reactions involving both metal and hypervalent iodine-mediated protocols. Methods for the generation of nitrenium ions and their application to the total synthesis of natural products are also discussed in Chapter 1. Earlier studies have shown that unsaturated *O*-alkyl hydroxamates undergo oxidative cyclization in the presence of phenyliodine(III) bis(trifluoroacetate) (PIFA) to form the lactam products. The mechanism of this transformation is thought to proceed *via* formation of an *N*-acylnitrenium ion, which undergoes alkene cycloaddition to form an *N*-acyl-*N*-alkoxy-aziridinium ion. Stereospecific and regioselective ion-pair collapse of this reactive intermediate then gives rise to the products of intramolecular amidotrifluoroacetoxylation. Chapter 1 describes the extension of this methodology to include [hydroxy(organosulfonyloxy)iodo]arenes, [hydroxy(diphenylphosphoryloxy)iodo]arenes and chromium(VI) oxidants, thereby providing access to a wide range of nitrogen-containing, saturated heterocycles, including pyrrolidines, piperidines, morpholines and piperazines. The broad functionalization scope of these simple methods allow for the efficient generation of sulfonates, phosphates, amino ketones, as well as spirolactams.

The latter part of this thesis discusses the application of alkene oxamidations towards natural product synthesis. The formal synthesis of kainic acid, an agonist of kainate ionotropic glutamate receptors, is discussed in Chapter 2. Chapter 3 is devoted to a review of methods for the preparation of azabicyclo[3.3.1]nonanes, also known as morphans, which are found in more

SUMMARY (continued)

than 300 natural products. The preparation of an advanced bicyclic intermediate for the synthesis of the madangamine alkaloids is also discussed. In addition, our oxamidation methodology was successfully applied to the preparation of advanced tetracyclic intermediates for the synthesis of the anti-inflammatory natural products *E*- and *Z*-alstoscholarine.

PART ONE:
DEVELOPMENT OF NEW METHODS FOR ALKENE OXAMIDATION

1. OXAMIDATION OF ALKENES

1.1. Introduction

The vicinal hydroxy amine functionality is a widespread structural fragment, found in a bewildering array of naturally-occurring molecules, synthetic ligands and chiral auxiliaries. The presence of this functionality and its relative and absolute stereochemical configuration are often essential in order to maintain the bioactivity of systems that contain it. In Nature, the most widely found amino alcohols are the amino acids serine and threonine. Several other important and synthetically inspirational bioactive compounds are shown in Figure 1.

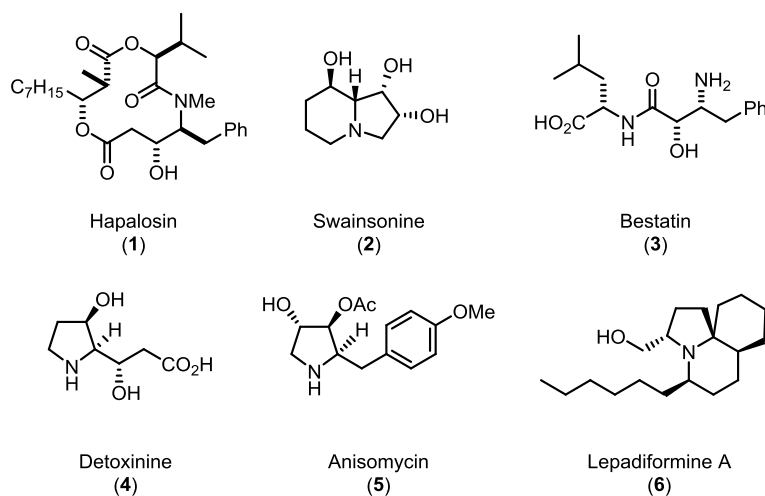


Figure 1 Examples of natural products containing the vicinal amino alcohol moiety

Hapalosin (**1**), a novel cyclic depsipeptide from the blue-green alga *Hapalosiphon welwitschii* shows inhibition of multidrug resistance activity in tumor cells,¹ while the indolizidine alkaloid swainsonine (**2**) has been shown to enhance cellular immune system responses and reduce the growth of solid tumor in rodents.² Bestatin (**3**), a naturally occurring small peptide containing a nonproteinogenic α -hydroxy- β -amino acid, is a specific

aminopeptidase inhibitor that is used in cancer chemotherapy.³ The unusual amino acid detoxinine (**4**) is present as the core structure in a number of active compounds that comprise the detoxin complex.⁴ Anisomycin (**5**) is an antibiotic produced by *Streptomyces griseolus* and used in cancer chemotherapy.⁵ Lepadiformine (**6**), a pyrroloperhydroquinoline marine alkaloid, displays *in vitro* cytotoxic activity against non-small-cell lung carcinoma (NSCLC-N6) and nasopharynx carcinoma (KB).⁶

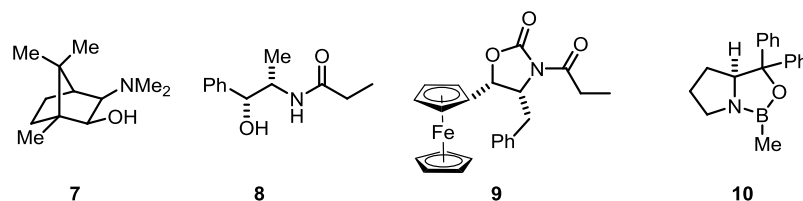


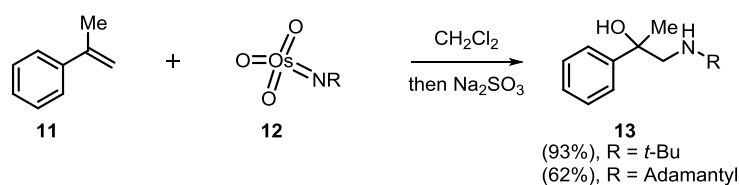
Figure 2 Synthetic ligands and chiral auxiliaries used for C-alkylation (**7**, **8**, **9**), aldol (**9**) reactions and catalytic reduction of ketones (**10**)

Chiral amino alcohols have been found to be effective ligands for a number of asymmetric transformations catalyzed by transition metal complexes with enolate alkylations and aldol reactions being the most common applications (Figure 2). For example, the complexes generated *in situ* from $\text{Ni}(\text{acac})_2$ and 3-dimethylaminoborneol (**7**) catalyze the addition of ZnEt_2 to chalcones.⁷ Although many of amino alcohol ligands consist of ring structures, acyclic ephedrine derivatives **8** has been widely used for the asymmetric alkylation of amides.⁸ Ueberbacher and co-workers established that ferrocenyl-oxazolidinones **9** are effective as chiral auxiliaries in aldol and alkylation reactions,⁹ while the Corey-Bakshi-Shibata catalysts, exemplified by **10**, have been extensively used for the enantioselective reductions of ketones.¹⁰

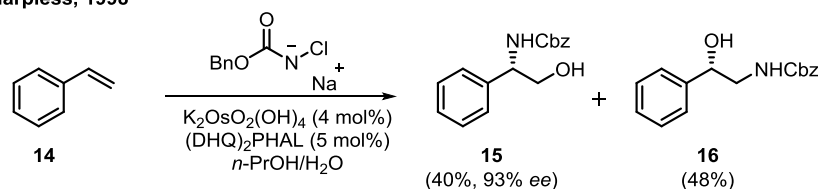
1.2. Recent Advances in Intermolecular Alkene Oxamination

The direct oxidative aminohydroxylation of alkenes is a powerful, yet challenging, chemical transformation. The intramolecular version of this process yields nitrogen heterocycle derivatives that are common among natural products and pharmaceutically useful synthetic molecules.¹¹ Despite the development of numerous protocols for the preparation of vicinal amino alcohols, new approaches are needed in order to achieve better stereoselectivity and improve efficiency. The functionalization of olefins is among the most versatile methods used for the preparation amino alcohols and for that reason has traditionally been a primary method of choice. Of these processes, the Sharpless aminohydroxylation, mediated by osmium(VIII) complexes, proved to be a starting point in the modern development of this type of reaction. A representative example, involving the oxidation of 1-methyl styrene, is shown in Scheme 1.¹² The catalytic version of the Sharpless aminohydroxylation remains one of the most useful methods for the stereospecific synthesis of vicinal amino alcohols starting from olefins.¹³

Sharpless, 1975



Sharpless, 1998

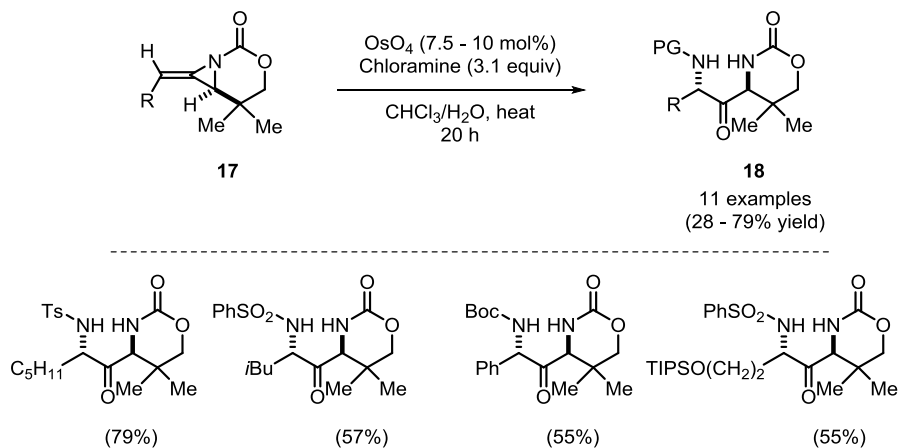


Scheme 1

Aminohydroxylation methods, including stereoselective ones, for the preparation of 1,2-amino alcohols were reviewed in 1996¹⁴ and again in 2000.¹⁵ In 2011, Donohoe and co-workers published a review summarizing recent advances in the direct conversion of alkenes to vicinal amino alcohol derivatives.¹⁶ Due to the significant scope of these articles, only the most prominent of recent methods will be discussed in the proceeding overview.

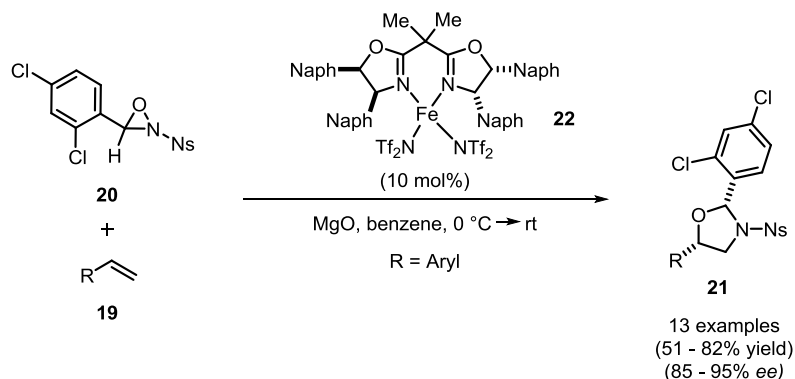
Although Donohoe and co-workers have developed a number of novel osmium-catalyzed amidohydroxylation reactions, there remains a need for strategies to control absolute stereoselectivity, either through auxiliaries or directing groups.¹⁷ Blakey and co-workers have reported an interesting copper-catalyzed intramolecular olefin aminoacetoxylation,¹⁸ which in contrast to previously published Pd and Cu-catalyzed systems, favors the formation of piperidines *via* 6-*endo-trig* cyclization as opposed to the more commonly observed 5-*exo-trig* pathways that yield pyrrolidines. Michael has also reported Pd(II)-catalyzed alkoxyamination promoted by *N*-fluorobenzenesulfonimide.¹⁹ The author noted that the regioselective outcome of this reaction can be controlled by variation of the solvent media, allowing the selective formation of either *exo* or *endo* product.

In 2013, Schomaker and co-workers published a stereoselective protocol for the preparation of 1,3-diamino ketones **18** using Os(VIII)-catalyzed oxamination of bicyclic methylene-aziridines **17** (Scheme 2).²⁰ Notably, the products were formed in good yields and with excellent regio- and diastereoselectivity.



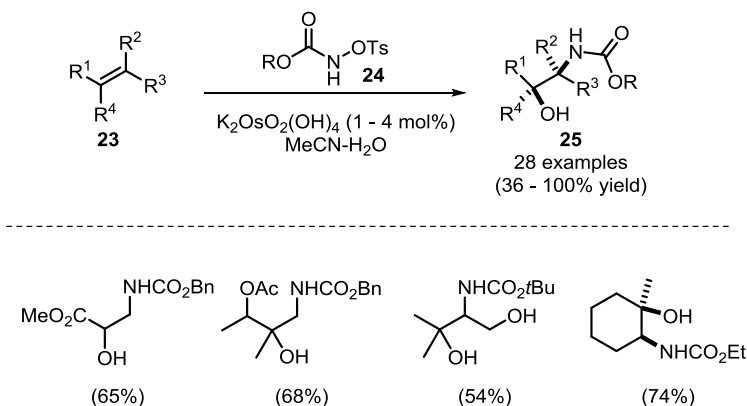
Scheme 2

Enantioselective oxamination of terminal alkenes **19** with *N*-sulfonyl oxaziridines **20** was utilized by Yoon as a means to access oxazolidines **21** (Scheme 3).²¹ This transformation was catalyzed by the novel Fe(II) bis(oxazoline) complex **22**. Interestingly, the regioselectivity of this transformation was opposite to that observed for the related Cu(II)-catalyzed reaction.²² Thus, by varying the choice of low-cost transition metal catalyst for the oxaziridine-mediated oxamination processes, it is possible to prepare both regioisomers of 1,2-amino alcohols in enantiopure form.



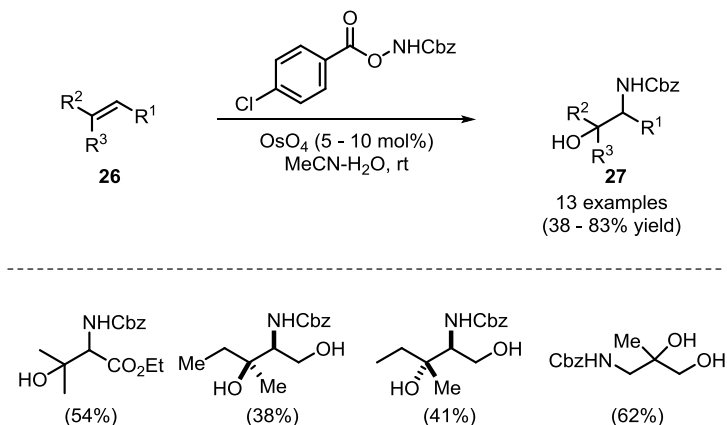
Scheme 3

In 2012, McLeod reported a direct intermolecular osmium-catalyzed aminohydroxylation of a variety of mono-, di-, and trisubstituted alkenes **23** using *N*-toluenesulfonyloxy carbamates **24** (Scheme 4).²³ The reaction required low catalyst loading and the products **25** were prepared in good yields and high regioselectivity for unsymmetrically substituted alkenes.



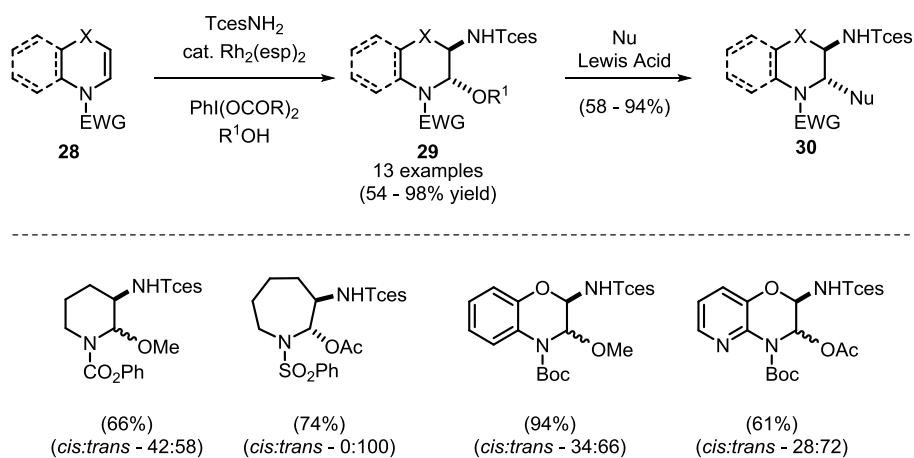
Scheme 4

Castle and co-workers recently published a base-free intermolecular aminohydroxylation of functionalized trisubstituted and 1,1-disubstituted alkenes **26** employing a benzoyloxycarbamate (Scheme 5).²⁴ Notably, in some cases, increased catalytic loading of OsO₄ was required to efficiently promote the transformation. In all cases, the more substituted alcohols **27** were favored.



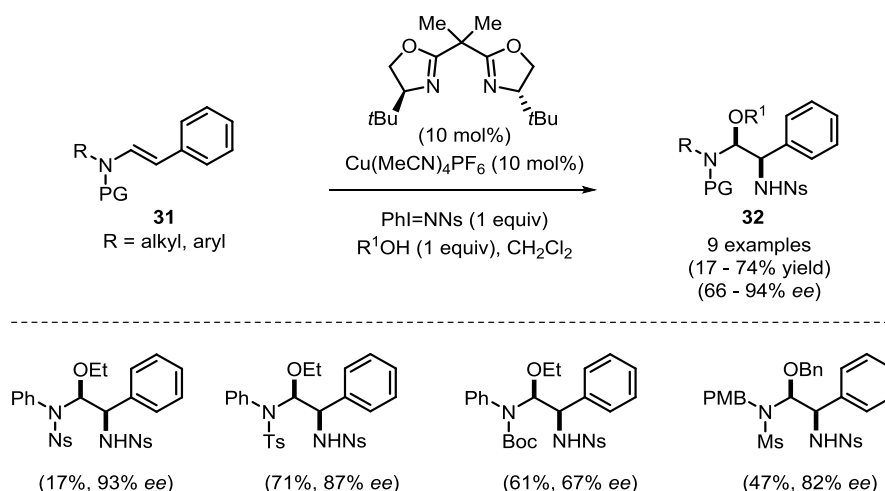
Scheme 5

Dauban and co-workers reported an intermolecular addition of nitrenes to enecarbamates and enesulfonamides **28** (Scheme 6).²⁵ In this work, the authors were able to prepare a variety of oxyamidated products **29** in excellent yields and with good stereoselectivity. The *N,O*-acetal products were formed with complete regioselectivity and shown to react further with a variety of nucleophiles under Lewis acid catalysis.



Scheme 6

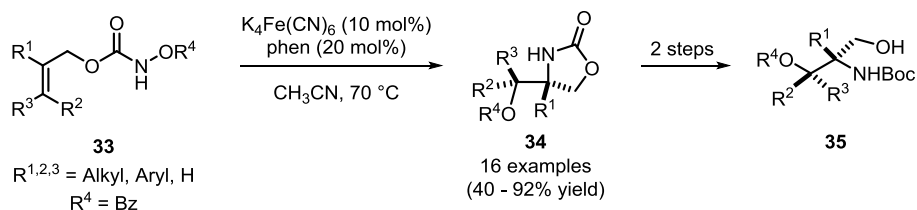
In 2011, Dodd established that copper(I) hexafluorophosphates can be used as catalysts for the intermolecular alkoxyamination of alkenes (Scheme 7).²⁶ Exposure of *N*-phenyl enamides **31** to an iminoiodane in the presence of primary alcohols delivered *cis* alkoxyamides **32** in good yields and high enantioselectivity. This transformation can be utilized for direct access to α -amino aminals in a completely regio- and diastereoselective manner. The authors established that this transformation can be performed in enantioselective fashion through the use of chiral bidentate Box ligand.



Scheme 7

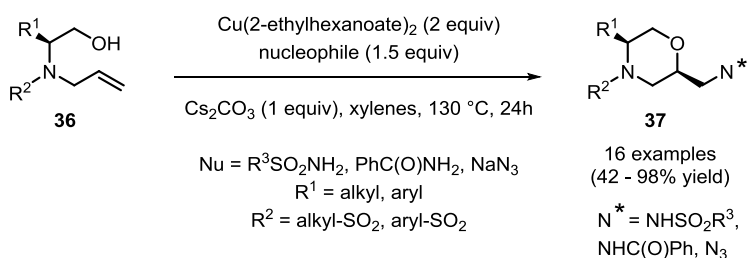
1.3. Recent Advances in Intramolecular Alkene Oxamination

Xu and co-workers recently reported an iron(II)-catalyzed intramolecular alkene oxyamination of functionalized *O*-benzoyl hydroxamates **33** (Scheme 8).²⁷ Preliminary mechanistic studies suggested the intermediacy of an iron nitrenoid, which can undergo either alkene aminohydroxylation or aziridination.



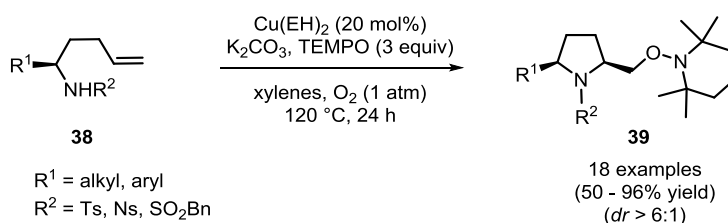
Scheme 8

As outlined in Scheme 9, Chelmer and co-workers have reported the Cu(II)-mediated addition of an amine moiety and alcohol to alkenes of general structure **36**.²⁸ Interestingly, amine trapping occurs intermolecularly, while the alcohol is added in an intramolecular sense. A variety of 2-aminomethyl morpholines **37** were generated in moderate to excellent yields and with good diastereoselectivity.



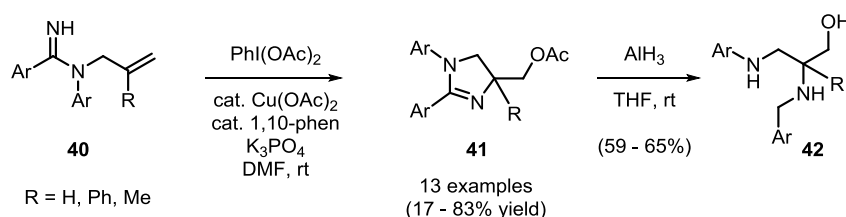
Scheme 9

The same group subsequently published an extension of this methodology involving a protocol for diastereoselective Cu-catalyzed intramolecular oxamination of γ -alkenylsulfonamides and *N*-allylureas **38** to generate disubstituted pyrrolidines **39** (Scheme 10).²⁹



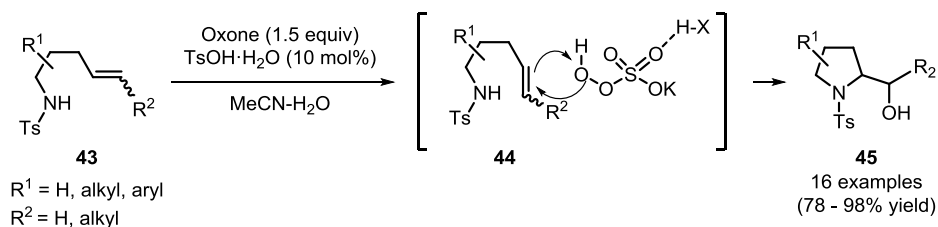
Scheme 10

The Cu-catalyzed oxyamination of *N*-alkenylamidines **40** to form 4-acetoxymethyl-4,5-dihydroimidazoles **41** was accomplished by Chiba, who employed $\text{PhI}(\text{OAc})_2$ as the oxidant (Scheme 11).³⁰ It was proposed that this transformation could be mediated by the high-valent N-Cu(III) species, resulted from the reaction of $\text{Cu}(\text{OAc})_2$ and $\text{PhI}(\text{OAc})_2$ with an amidine. The products could be reduced into useful 2,3-diaminopropanol derivatives **42** using AlH_3 .



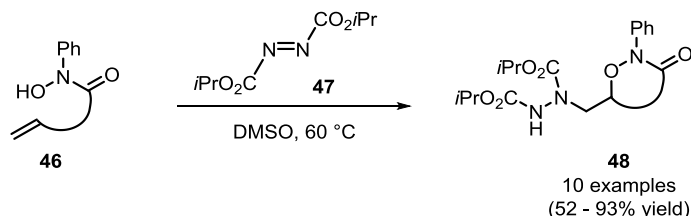
Scheme 11

In 2012, Moriyama and Togo published the transition-metal-free intramolecular aminohydroxylation reaction shown in Scheme 12.³¹ In this work, *N*-alkenylsulfonamides **43** in the presence of catalytic quantities of Brønsted acids underwent cyclization to form substituted prolinol derivatives **45** in high yields. The reaction is believed to proceed *via* oxone-mediated epoxidation of alkene function, followed by the epoxide amination with the sulfonamide tether.



Scheme 12

A radical-mediated alkene oxyamination was described by Alexanian in 2011 (Scheme 13).³² Using the reagent DIAD as a radical trap, this method serves to demonstrate the unique reactivity of amidoxyl radicals. In case of cyclic alkenes, this transformation provided *trans* oxyamination products, which are difficult to obtain using alternative methods.

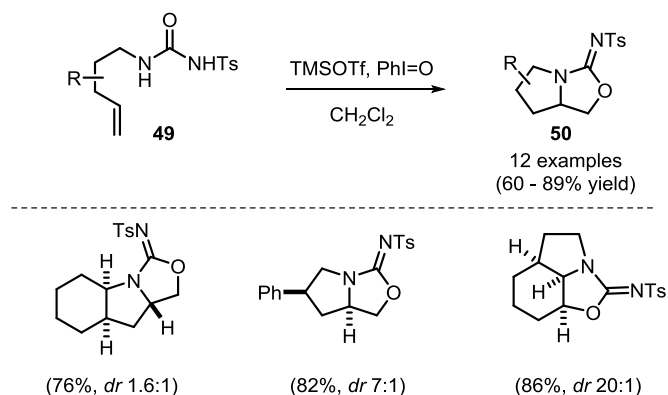


Scheme 13

1.4. Metal-Free Hypervalent Iodine-Mediated Oxamination Protocols

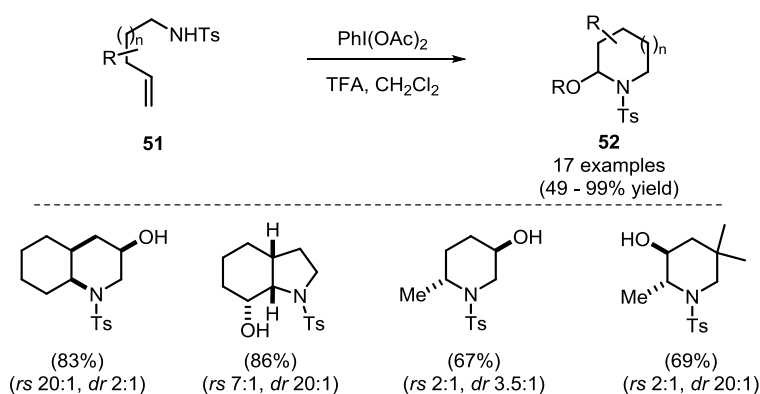
In recent years, hypervalent iodine reagents have become an important component in the synthetic chemist's tool box.³³ They continue to prove useful as synthetic tools due to their low cost, ease of handling, ready availability, and reactivity under mild conditions.³⁴

Michael and co-workers successfully employed iodosylbenzene (PhIO) in the oxidative cyclization of unsaturated ureas (Scheme 14).³⁵ The isolated products are primarily bicyclic isoureas **49** as a result from an intramolecular oxamination process. A variety of substrates **50** generate the isoureas in good yields and with high diastereoselectivity.



Scheme 14

More recently, the same research group has reported another oxidative cyclization of sulfonamide-tethered alkenes **51** using (diacetoxyiodo)benzene (DIB) together with Brønsted acids (Scheme 15).³⁶ The products **52** were furnished in good yields and good to excellent diastereoselectivities. In contrast to alternative *exo* selective oxyamination methods, this process yields *endo* ring closure products.



Scheme 15

1.5. Nitrenium Ion Chemistry

Nitrenium ions are reactive divalent intermediates that are isoelectric with carbenes, nitrenes and carbenium ions.³⁷ Nitrenium species play an important role in the genotoxic activity displayed by aromatic amines.³⁸ It has also been demonstrated that appropriately substituted aryl nitrenium ions are selectively capped by the C-8 position of guanine bases in DNA.³⁹ Despite being involved in many important chemical and biological processes, nitrenium ions have not received the attention of synthetic chemists to the same degree as their isoelectric isologs (Figure 3).

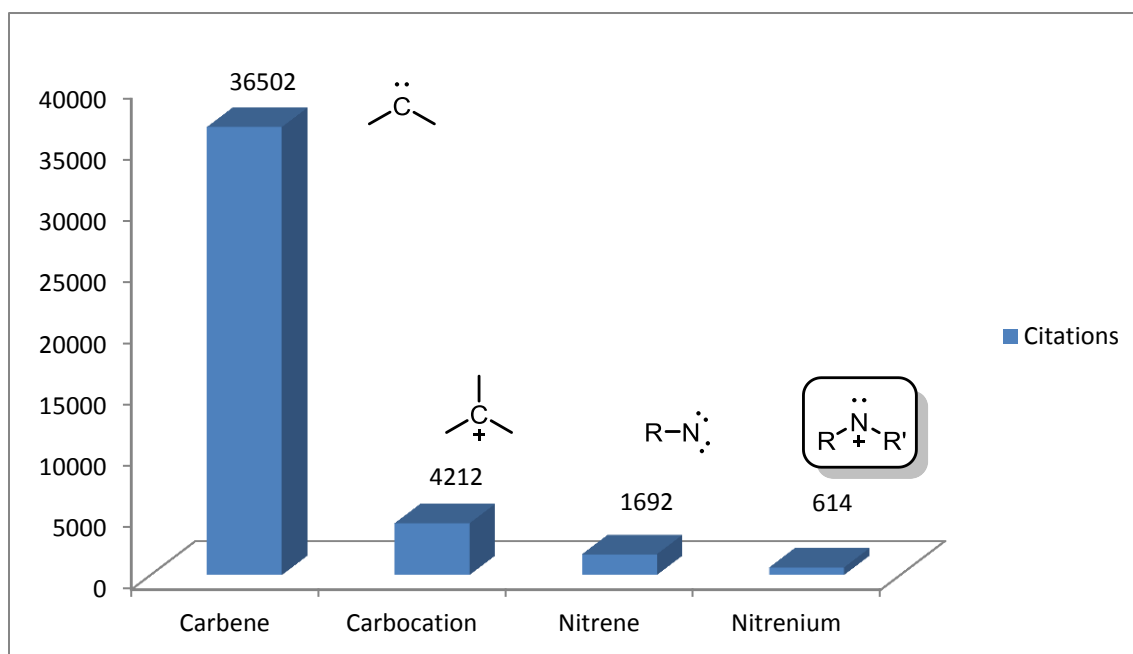
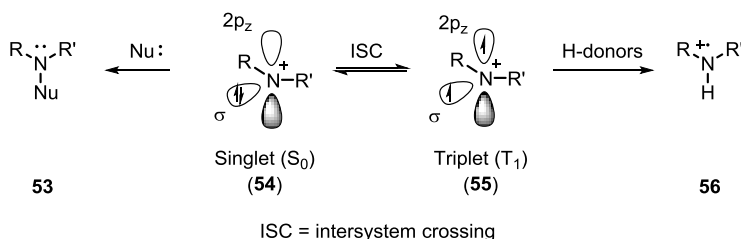


Figure 3 Number of citations in Web of Science topic search conducted on July 7, 2014

The majority of nitrenium ions characterized to date are very reactive and hence, relatively short-lived electron-deficient species.⁴⁰ However, aryl nitrenium ions are generally more stable than alkyl nitrenium ions due to the delocalizing effect of the aromatic ring.⁴¹ In

this regard, electron-rich donor substituents on the nitrogen atom are also stabilizing nitrenium ions.

In nitrenium ions, a non-bonding electron pair and two bonding orbitals potentially allow two energetically accessible electronic states: singlet (S_0) **54** or triplet (T_1) **55** (Scheme 16). Singlet nitrenium ions are characterized by the presence of a non-bonding pair of electrons with opposite spin orientations, occupying a single σ -type orbital. Essentially, these species behave as Lewis acids and react with nucleophiles. In contrast, the triplet electronic configuration of nitrenium ion exists as two unpaired electrons that separately occupy two orthogonal orbitals. These species can behave like radicals, most commonly abstracting hydrogen atoms to form radical cations. The energy difference between the singlet and triplet states is indicated by the singlet-triplet gap, or ΔE_{st} . In addition, R-N-R' bond angles influenced by geometric constraints have a substantial effect on ΔE_{st} .⁴²



Scheme 16

Semi-empirical MNDO calculations have revealed that in the presence of heteroatoms or aromatic substituents, the singlet state becomes the favored electronic configuration. Calculations performed by Falvey,⁴³ Glover⁴⁴ and Ford⁴⁵ suggest the ground state of NH_2^+ (Table 1, entry 1) to be a triplet, which is about 21.2 kcal/mol more stabilized than the corresponding singlet state. Substitution of the hydrogen atoms of the parent nitrenium ion

results in significant electron density transfer to the nitrogen atom. This is particularly evident for the *N*-aryl series, where the NH group was found to carry only about 20% of the positive charge (Table 1, entries 6, 7). In addition, electron density equally stabilizes singlet and triplet states. Even though the actual transfer of charge in the singlet state leads to a greater stability, the overall stabilization difference of the singlet in aromatic nitrenium ions is found lower than the triplet state. The singlet electronic state stabilization in the heteroatom series (Table 1, entries 8-10) can be explained by π -donation from the adjacent filled heteroatom $2p_z$ orbital to the empty $2p_z$ orbital on the nitrenium ion. These long-lived, stabilized nitrenium ions provide an excellent opportunity for the development of new synthetic methodologies.

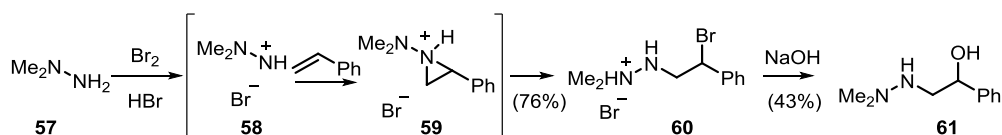
Table 1. Nitrenium Ion Stabilization Energies (ΔE_{st}) Relative to NH_2^+

entry	ion	ΔE_{st} , kcal/mol ^a	entry	ion	ΔE_{st} , kcal/mol ^a
1		21.2 ^b	6		-26.1 ^b
2		6.2 ^b	7		-28.9 ^b
3		7.0 ^b	8		-32.3 ^d
4		8.0 ^b	9		-13.6 ^d
5		-7.4 ^c	10		-22.8 ^d

^aThe negative values represent a higher stability of a singlet state compared to the triplet state. ^bMNDO data reported by Ford.⁴⁵ ^cMNDO data reported by Falvey.⁴³ ^dMNDO data reported by Glover.⁴⁴

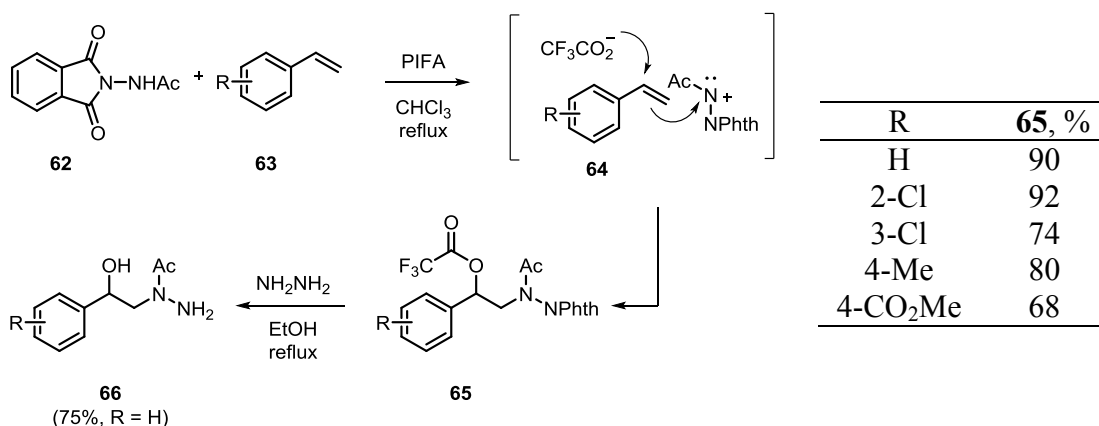
The chemistry of nitrenium ions has been reviewed several times over the last decade.⁴⁶ In analogy to carbenes and nitrenes, stabilized nitrenium ions can undergo

concerted, [2+1] cycloaddition to alkenes, which lead to formation of aziridinium ions. For example, Urry and co-workers described the formation of an aminonitrenium (diazenium) ion by treatment of 1,1-dimethylhydrazine **57** with an aqueous mixture of Br₂ and HBr (Scheme 17).⁴⁷ When styrene was added to this solution, β-bromohydrazinium salt **60** was formed in good yield. Unfortunately, minimal to no conversion was observed for 1,1- and 1,2-disubstituted alkenes. The ammonium salt products can be further transformed into the corresponding hydrazino alcohols **61** by treatment with aqueous sodium hydroxide.



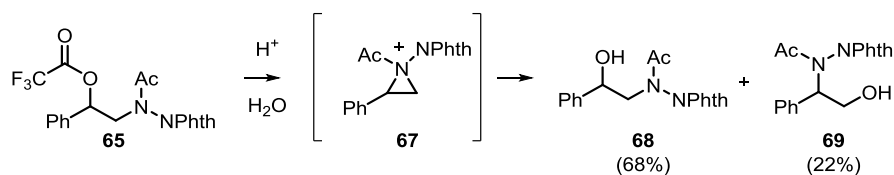
Scheme 17

A more practical example of intermolecular hydrazidohydroxylation of styrenes was developed by Kikugawa (Scheme 18).⁴⁸ Thus, exposure of *N*-acetylaminophthalimide (**62**) to PIFA in the presence of styrenes **63** provided trifluoroacetoxy hydrazide derivatives **65** in good yields with high regioselectivity. Subsequent cleavage of trifluoroacetyl and phthalimido groups was accomplished through hydrazine-mediated hydrolysis.



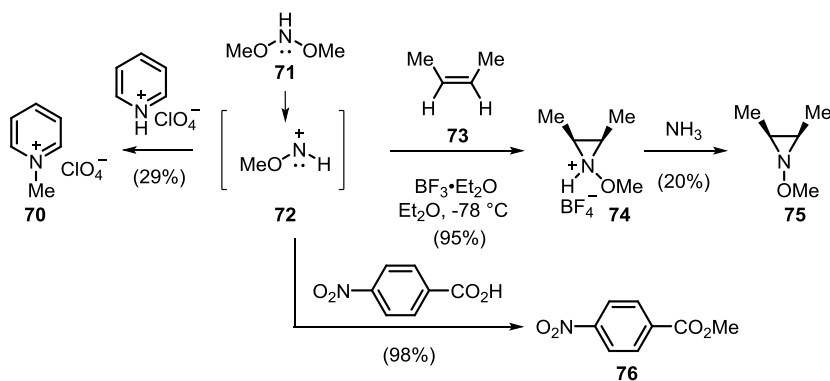
Scheme 18

Interestingly, the acidic hydrolysis of **65** under mild conditions (AcOH-H₂O, 2:1) generated two regioisomeric alcohols (Scheme 19). The authors postulated that the adjacent acetamido group assists the elimination of trifluoroacetyl group to generate the aziridinium ion **66**, which is attacked by water non-regioselectively to form a mixture of regioisomers **68** and **69**. Taking the mechanism of hydrolysis into consideration, the authors proposed that the hydrazidohydroxylation reaction proceeds *via* electrophilic attack of the nitrenium ion upon the alkene without generation of aziridinium ion, i.e., a termolecular addition process. No kinetic evidence was presented for this hypothesis.



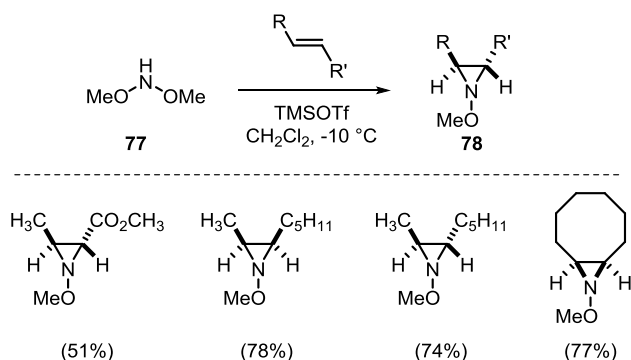
Scheme 19

The formation of putative *N*-methoxynitrenium ion **72** *via* the reaction of *N,N*-dimethoxyamine with BF₃•Et₂O was exploited by Rudchenko and co-workers (Scheme 20).⁴⁹ It was found that **72** can serve as an ambidentate cation: it methylates *n* nucleophiles and forms aziridinium ions **74** upon reaction with alkenes (e.g., *cis*-2-butene). The complete stereospecificity of this process strongly points towards the existence of a singlet nitrenium ion intermediate.



Scheme 20

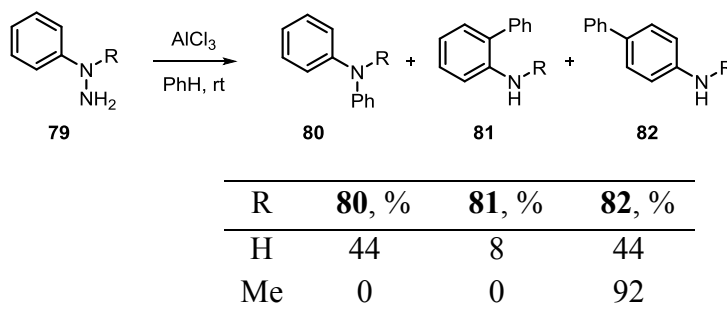
Vedejs further improved Rudchenko's method by utilizing trimethylsilyl triflate as an activating agent (Scheme 21).⁵⁰ Treatment of simple olefins with *N,N*-dimethoxyamine in the presence of 1 equivalent of TMSOTf delivered aziridines **78** in good yield. However, the method was found to have significant limitations of functional group tolerance due to the high reactivity of the nitrenium intermediate. Furthermore, no conversion was detected for electron-deficient substrates, such as dimethyl fumarate.



Scheme 21

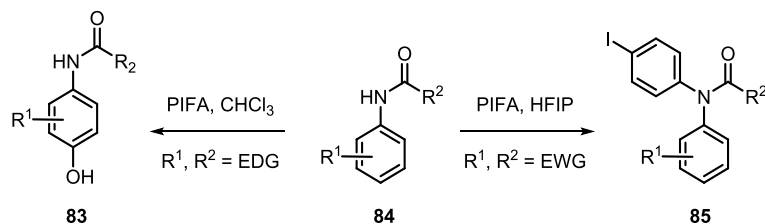
That nucleophilic attack on singlet arylnitrenium ions typically occurs at the *ortho* and *para* aromatic positions rather than at the nitrogen center reflects the fact that positive

charge in these species is largely delocalized onto the aromatic ring. Kikugawa reported that the putative arylnitrenium species generated from phenylhydrazines **79** in the presence of AlCl_3 can be trapped by aromatic solvents to form mixtures of *C*- and *N*-substitution products (**80**, **81**, **82**) (Scheme 22).⁵¹ On the other hand, the more sterically encumbered ion generated from *N*-methyl-*N*-phenylhydrazine, exclusively undergoes attack at the *para* position.



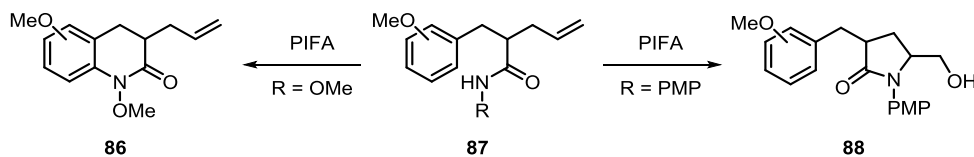
Scheme 22

More recently, it was reported that certain hypervalent iodine oxidants, such as phenyliodine bis(trifluoroacetate) (PIFA), may react with the N-H group of *N*-aryl amides **84** in acidic conditions to generate *N*-acylnitrenium ions. To this point, treatment of anilides with PIFA in TFA provided *C*- or *N*-substitution products, depending on the substituents on the aryl and acyl group (Scheme 23).⁵² In case of highly electronegative anilide acyl groups or electron-deficient *N*-aryl groups, *N*-arylation of iodobenzene was observed. In contrast, when the *N*-aryl acyl group contains electron-donating substituents, the trifluoroacetate from PIFA attacks the *para* position with respect to the anilide substituent generating aryl esters, which are converted into the corresponding phenol derivatives **83** during the work-up procedure.



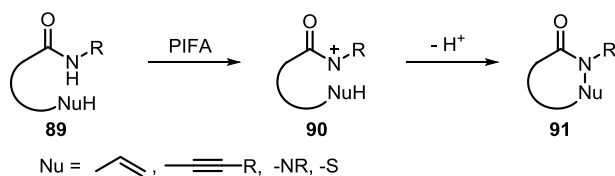
Scheme 23

SanMartin and Dominguez have utilized PIFA in the intramolecular oxamination of terminal alkenes (Scheme 24).⁵³ The authors have posited that in the first step of this transformation, a stabilized *N*-acylnitrenium intermediate is generated. Starting from *O*-methyl hydroxamates, these species are intramolecularly trapped by nucleophilic arene moieties to generate the quinolinone derivatives **86**. In contrast, when *N*-methoxyphenylamides are subjected to the same conditions, pyrrolidinones **88** are formed *via* an alkene oxamidation.



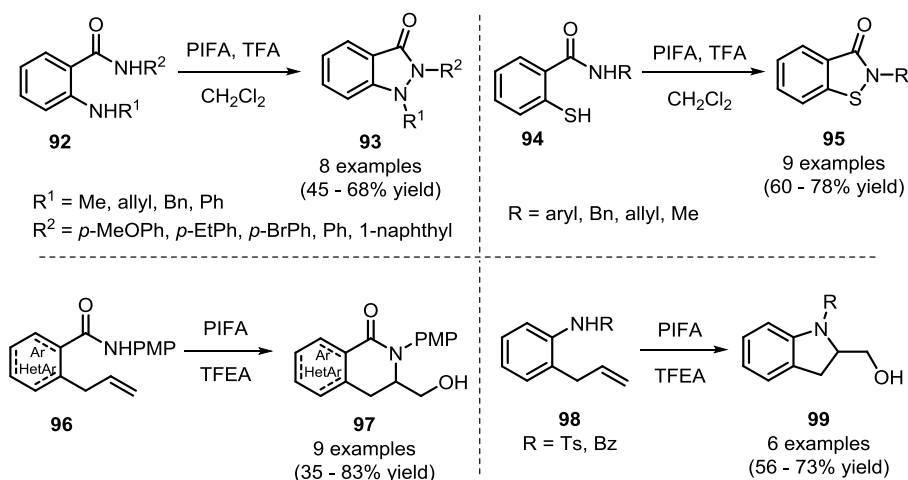
Scheme 24

In 2006, the same group effectively used this novel strategy for the preparation of a wide range of heterocycles. The key cyclization step features PIFA-mediated oxidation of *N*-substituted amides **89** into *N*-acylnitrenium ions **90** which can be intercepted by a wide variety of nucleophilic groups (Scheme 25).



Scheme 25

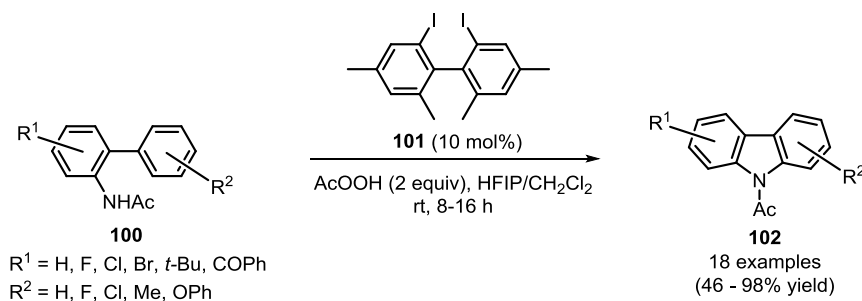
Thus, the synthesis of a series of *N,N*-disubstituted pyrazolones, ⁵⁴ indazolones (**93**)⁵⁵ and benzisothiazolones (**95**)⁵⁶ derivatives *via* nitrenium ion trapping of amino and thiol functionalities was accomplished (Scheme 26). In case of N-N bond formation, the substrate scope is limited to *N*-arylamides as *N*-alkyl or *N*-alkoxy amides failed to undergo cyclization. Difunctionalization of alkenes was achieved when suitably substituted amides **96** were exposed to PIFA in trifluoroethanol (TFEA).⁵⁷ Cyclization of **96** occurs *via* an *exo* mode to provide a wide range of α -hydroxy pyrrolidines and piperidines **97**. Indoline derivatives **99** were also prepared similarly using this approach.⁵⁸ The use of TFEA as a solvent was found to be essential and is proposed to stabilize the nitrenium species. No reaction took place in other solvents, including CH₂Cl₂ and CH₃CN.



Scheme 26

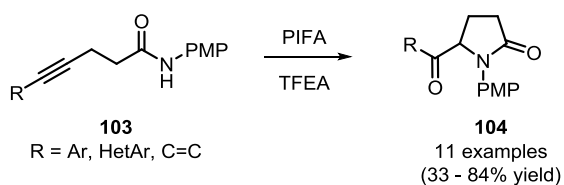
In 2011, Antonchick and co-workers published an I(III)-catalyzed intramolecular C-H amidation of anilides **100** using Kita's 2,2'-diiodo-4,4',6,6'-tetramethylbiphenyl **101**⁵⁹ catalyst to form an I(III) active species *in situ* by means of peracetic acid.⁶⁰ The amidation process proceeded efficiently, generating carbazoles **102** in moderate to excellent yields

(Scheme 27). A variety of electron-rich and electron-deficient arenes could be cyclized using these catalytic conditions.



Scheme 27

Interestingly, alkynes can undergo intramolecular oxamidation in addition to alkenes. Oxidation of amides **103** with PIFA led to the generation of pyrrolidinones **104**, which are proposed to arise from intramolecular interception of *N*-acylnitrenium ions by tethered alkynes (Scheme 28).⁶¹

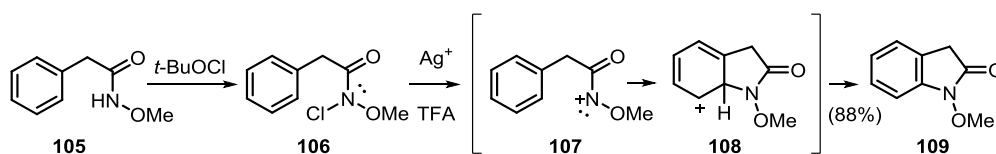


Scheme 28

1.6. *N*-Acyl-*N*-alkoxynitrenium Ions

As discussed in Section 1.5., nitrenium ions in general are short-lived and very reactive electrophilic species. In order to overcome the associated limitations of their use and increase their synthetic value, the selection of suitable *N*-substituents is of key importance.

Among the most useful and easily accessible members of this family are *N*-acyl-*N*-alkoxynitrenium ions. After being independently discovered in 1984 by Glover⁶² and Kikugawa,⁶³ these remarkable electrophiles have proved their utility in the reactions with a broad variety of aromatic systems. In initial reports, the generation of these putative species was achieved through the treatment of *N*-chloro-*N*-methoxyamides **105** with Ag(I) salts (Scheme 29).

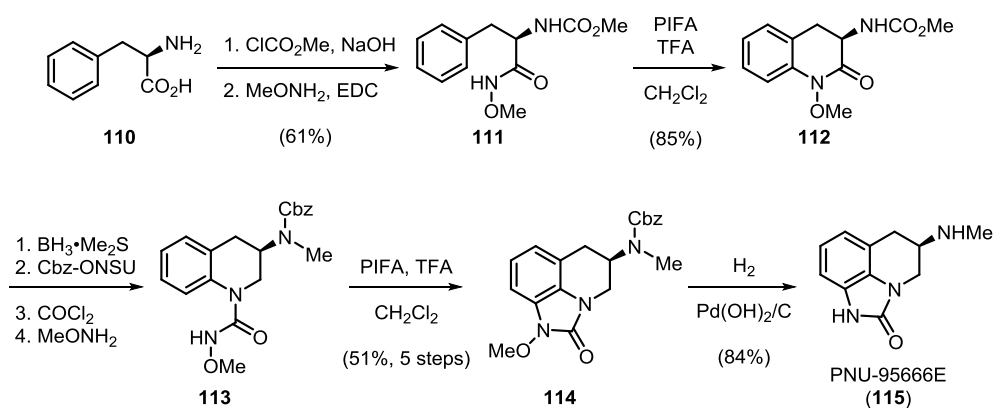


Scheme 29

It was also found that acidic media is essential for successful cyclization. In the second generation of this method, Kikugawa developed milder conditions involving anhydrous zinc acetate in nitromethane.⁶⁴ In addition to the *N*-methoxy group, *N*-allyloxy group was found to be tolerated. The resultant *N*-allyloxy heterocycles could be deprotected to form the corresponding *N*-hydroxy compounds by palladium-catalyzed deallylation. Attempts to cyclize the substrates bearing *N*-benzyl and *N*-methoxyethoxymethyl groups were unsuccessful.

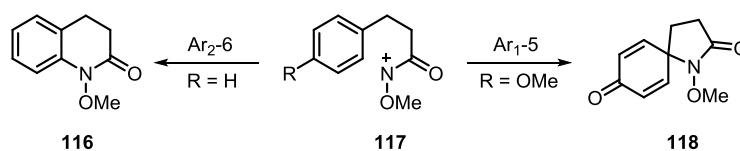
Unfortunately, both Glover's and Kikugawa's initial procedures suffered from the need to employ the stoichiometric quantities of *t*-butyl hypochlorite, which is restricted in most countries due to its toxic and explosive nature. In the search for more environmentally friendly methods, it was discovered by Kikugawa that hypervalent iodine reagents can mediate the formation of *N*-acyl-*N*-alkoxynitrenium ions directly from *N*-alkoxyamides, thus

avoiding the chlorination step.⁶⁵ PIFA was also successfully utilized by Romero in the synthesis of dopamine D₂ receptor agonist PNU-95666E (**115**) (Scheme 30).⁶⁶



Scheme 30

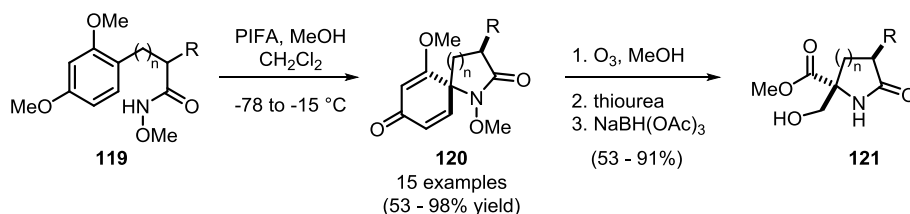
Interestingly, the general outcome of the cyclization of aryl-tethered nitrenium ions **117** is highly dependent on the substituents on the aromatic ring (Scheme 31). Thus, electron-neutral aromatic rings undergo Ar₂-6 type cyclization, generating *N*-methoxybenzolactams **116**, whereas substrates possessing electron-rich arenes undergo spirocyclization *via* the Ar₁-5 pathway to form dienones **118**, after loss of methanol.



Scheme 31

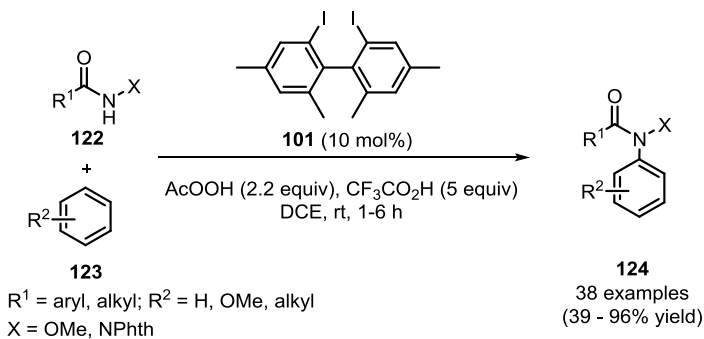
The dearomatization of benzene is an energetically unfavorable process, but provides a rapid entry into complex synthetic building blocks containing unmasked functionalities and new stereogenic centers, unavailable from other synthetic methods. Wardrop and Burge demonstrated that *N*-methoxy-*N*-acylnitrenium ions undergo *ipso* cyclization when tethered

with electron-rich arenes (Scheme 32).⁶⁷ To this point, treatment of ω -arylhdroxamates **119** with PIFA furnished azaspirocyclic 2,5-cyclohexadienones **120** in good yields and with moderate to high stereoselectivities. Subsequent ozonolytic cleavage of dienone moiety afforded pyrrolidinone, piperidinones, di- and trisubstituted azetidinone derivatives **121**.



Scheme 32

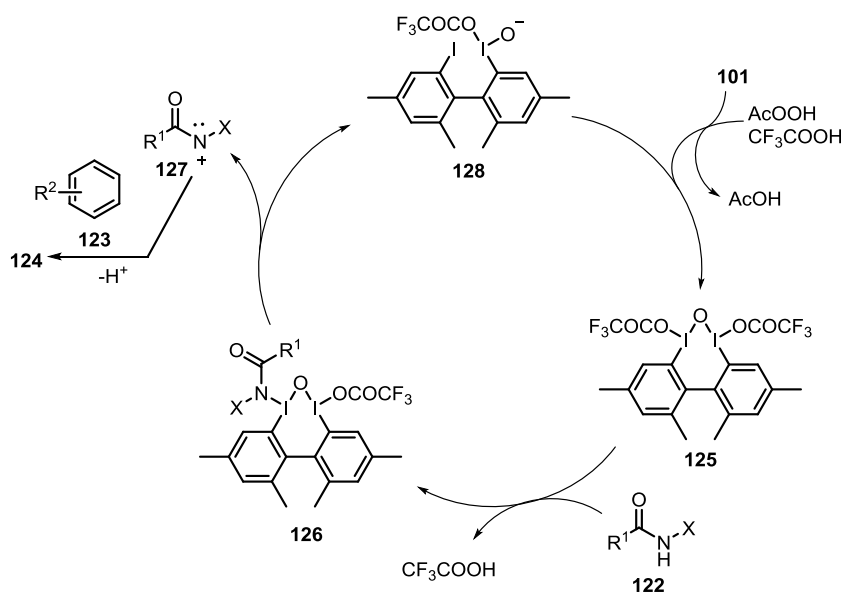
Antonchick and co-workers employed bis(iodoarene) **101**⁵⁹ with co-oxidant peracetic acid catalytic system for the formation of anilides and *N*-aryl hydrazines from unactivated arenes **123** at ambient temperature (Scheme 33).⁶⁸ The corresponding products **124** were obtained in high yields and with excellent regioselectivity.



Scheme 33

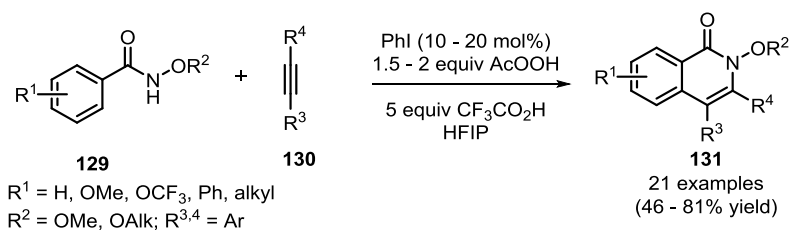
The proposed catalytic cycle for this process is shown in Scheme 34. First, aryl iodide **101** is oxidized with CH₃CO₃H to provide the hypervalent μ -oxo-bridged iodane **125**. The ligand exchange at the iodine center by **122** affords intermediate **126**, which undergoes

oxidative fragmentation to generate putative nitrenium ion **127** as well as I(III) species **128**, which then formed **125** and continues the catalytic cycle. At the same time, the arene **123** attacks the electrophilic nitrenium ion **127** to furnish anilides **124**.



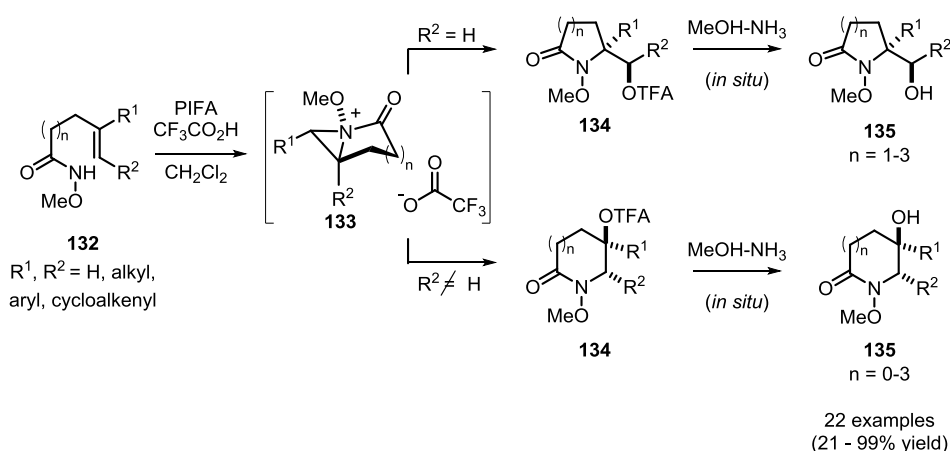
Scheme 34

The same research group later developed organocatalytic annulation by functionalization of benzamide derivatives **129** with alkynes **130** (Scheme 35).⁶⁹ The authors utilized catalytic PhI with the oxidant peracetic acid, providing a straightforward synthesis of isoquinolones **131**. Notable selectivity in the annulation of unsymmetrically disubstituted alkynes was demonstrated.



Scheme 35

In 2010, Wardrop and co-workers utilized PIFA-mediated oxamidation for the diastereoselective formation of five- to eight-membered hydroxy lactams **135** (Scheme 36). The authors proposed the ionic mechanism for this transformation, the first step of which is oxidation of *N*-methoxyamide moiety by the iodine(III) reagent. The resultant singlet nitrenium ion is then attacked by the alkene to afford bicyclic *N*-acyl-*N*-alkoxyaziridinium ion intermediate **133**. Subsequent diastereoselective, preferably *exo* opening by the TFA group delivers trifluoroacetate derivatives **134** with high *anti* selectivity. Further hydrolysis with methanolic ammonia affords hydroxy lactams **135** in high yields and with excellent diastereoselectivity.

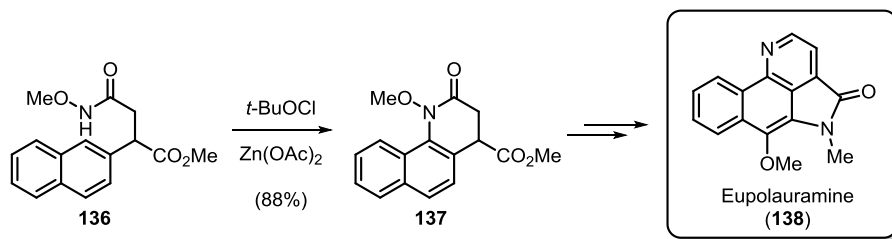


Scheme 36

1.7. Nitrenium Ion Chemistry in Natural Product Synthesis

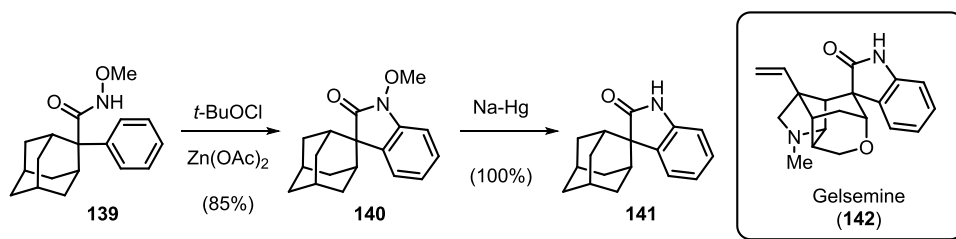
The total synthesis of biologically active natural products has become increasingly important to a range of disciplines outside of organic chemistry, including cell biology, immunology and medicine. Although there has been limited application of nitrenium ion

chemistry in natural product synthesis, it nonetheless provides chemists a unique opportunity for the efficient preparation of complex *N*-bearing molecules. Kikugawa and co-workers applied $\text{Zn}(\text{OAc})_2$ -mediated nitrenium ion cyclization of *N*-chloro-*N*-methoxyamide **136** to the synthesis of alkaloid eupolauramine (**138**),⁷⁰ which is a structurally unique azaphenanthrene alkaloid isolated from *Eupomatia laurina* (Scheme 37).⁷¹



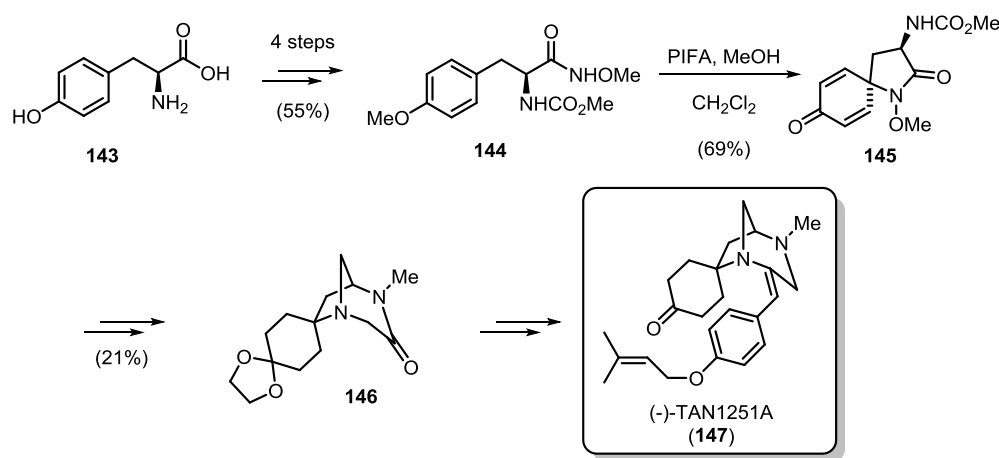
Scheme 37

Using the same methodology, the Fleming group developed a route to the core oxindole moiety of the challenging target of gelsemine (**142**) (Scheme 38).⁷² The authors note that cyclization in the case of **139** was faster than the one reported by Kikugawa.⁷¹ This was ascribed to the Thorpe-Ingold effect mediated by the cyclic adamantyl structure. Incidental formation of the *para* chlorinated *N*-methoxyoxindole was also observed under these conditions. Finally, reduction of the N-O bond with Na/Hg provided the oxindole **141** in quantitative yield.



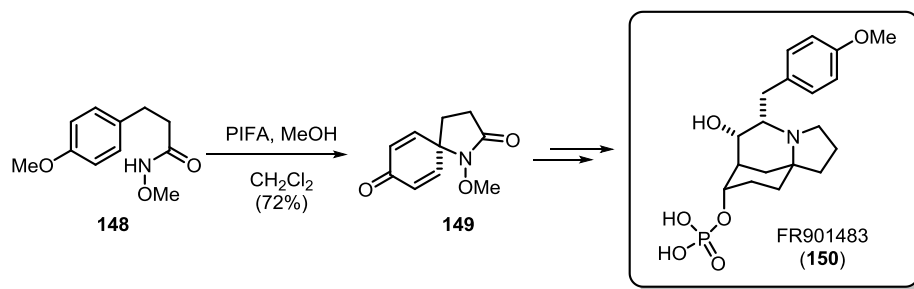
Scheme 38

Notably, the utility of the PIFA-mediated intramolecular dearomatization strategy utilizing *N*-methoxy-*N*-acyl nitrenium ions was demonstrated by the Wardrop group in the synthesis of a number of bioactive natural products. Thus, the formal synthesis of (-)-TAN1251A (**147**), an antagonist of M1 muscarinic receptor, from L-tyrosine (**143**) was accomplished by Wardrop and Basak (Scheme 39).⁷³ The key step of the synthesis was the construction of the core 1-azaspiro[4.5]decane system *via* a spirocyclization of **144**. The dienone product **145** was further elaborated to intermediate **146**, which was used by Kawahara in his synthesis of the target alkaloid.⁷⁴



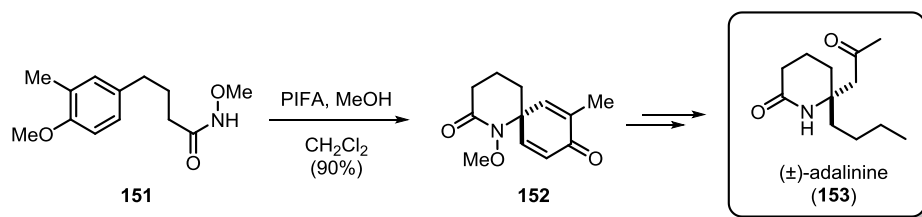
Scheme 39

Similarly, the formal synthesis of (±)-desmethyldamino FR901483 (**150**) was carried out from commercially available 3-(4-methoxyphenyl)propanoic acid. The assembly of the azatricyclic system of **150** was achieved *via* cyclization of **148** (Scheme 40). FR901483, a secondary metabolite of *Cladobotryum* sp. No. 11231 isolated at Fujisawa, has demonstrated superior immunosuppressant potency, significantly increasing the graft survival times in rat transplant models.⁷⁵



Scheme 40

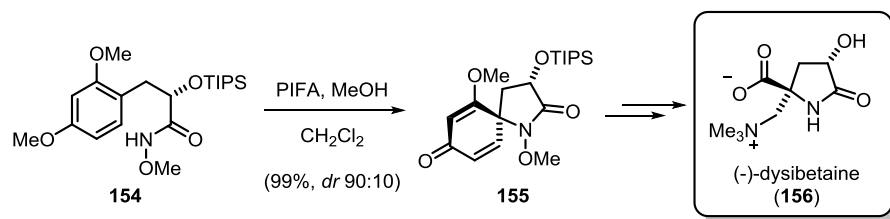
In the total synthesis of piperidine alkaloid (\pm)-adalinine (**153**), Wardrop and co-workers utilized a PIFA-mediated spirocyclization to install the lactam core of the target molecule (Scheme 41).⁷⁶ (\pm)-Adalinine, isolated from the European two-spotted ladybird *Adalia bipunctata*, is emitted when the reflex bleeding, an insect defensive mechanism, is triggered. It also exhibits deterrent and toxic properties.⁷⁷



Scheme 41

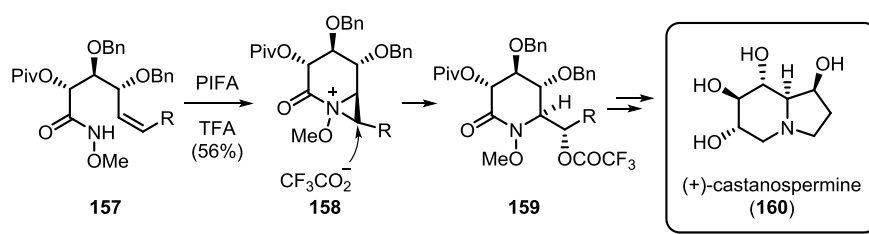
Furthermore, the total synthesis of the neuroexcitotoxin (-)-dysibetaine (**156**) was reported by Wardrop and Burge (Scheme 42).⁷⁸ (-)-Dysibetaine, an unusual amino acid isolated by Sakai from the marine sponge *Dysidea herbacea*, is known for its harmful binding and damaging activity in the central nervous system of rodents.⁷⁹ The centerpiece of this synthesis was a nitrenium ion-induced spirocyclization, which diastereoselectively

generated core dienone **155** containing two chiral centers. Oxidative cleavage of the dienone moiety furnished the core of the natural product.



Scheme 42

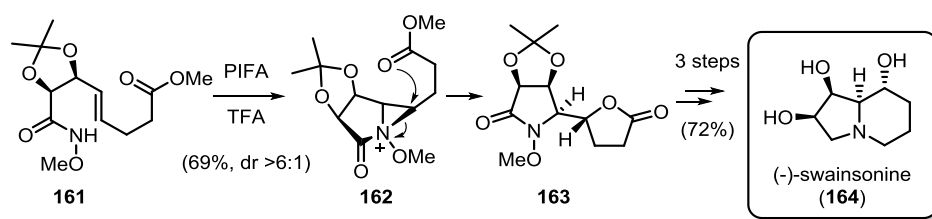
In 2010, the total synthesis of polyhydroxy indolizidine alkaloid (+)-castanospermine (**160**) was reported by Bowen and Wardrop.⁸⁰ (+)-Castanospermine, isolated from the chestnut tree *Castanospermum australe* at Moreton Bay,⁸¹ demonstrates a wide range of bioactivities.⁸² The central theme in this approach was the diastereoselective generation of piperidine **159** via the intramolecular oxidative cyclization of an unsaturated *O*-methyl hydroxamate **157** (Scheme 43).



Scheme 43

In 2011, Bowen and Wardrop utilized PIFA-mediated *bis*-cyclofunctionalization of an γ,δ -unsaturated *O*-alkyl hydroxamate **161** in the total synthesis of indolizidine alkaloid (-)-swainsonine (**164**).⁸³ (-)-Swainsonine, a Golgi alpha-mannosidase II inhibitor, is known as a potent inhibitor of tumor cells metastasis by boosting immune responses, which also

decreases the tumor progression in rodents.² The pivotal transformation to this alkaloid was the formation of the pyrrolidine **163** through the diastereoselective capture of an *N*-acyl-*N*-alkoxyaziridinium ion generated by the intramolecular addition of an *N*-acyl-*N*-alkoxynitrenium ion to the alkene (Scheme 44).



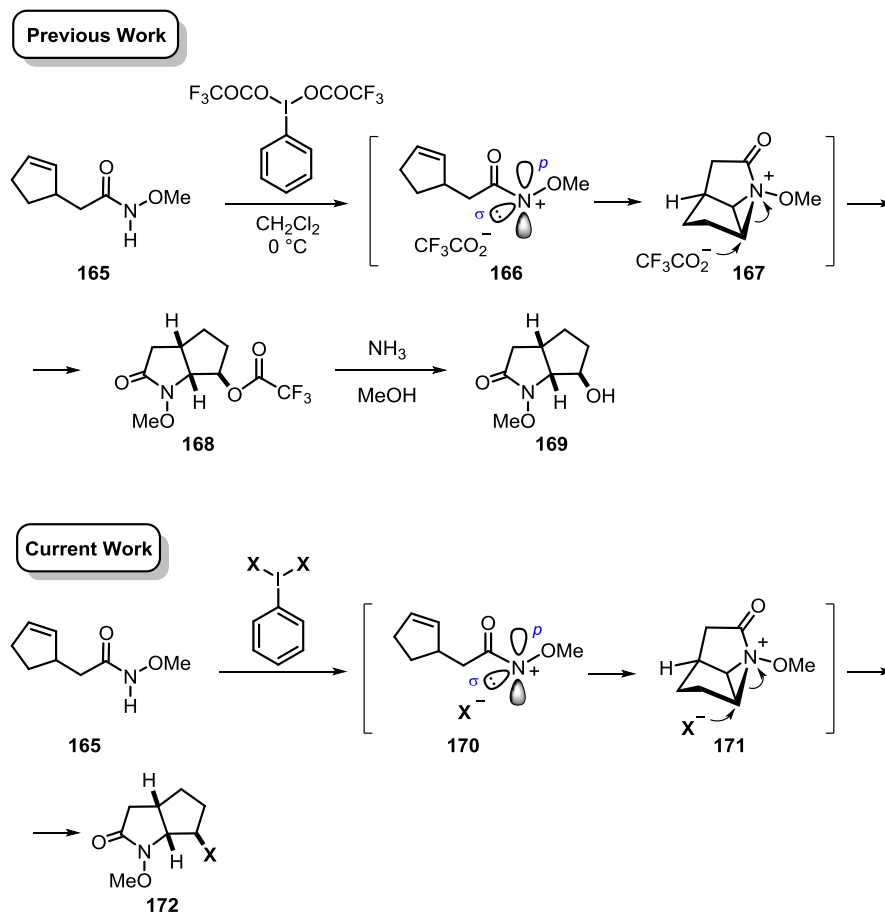
Scheme 44

1.8. I(III)-Mediated Oxamidation Methodological Study

1.8.1 Introduction

Since lactam rings are an important structural component found in a wealth of physiologically active pharmaceutical agents and naturally occurring systems, new synthetic approaches that expedite the direct preparation of these saturated *N*-heterocycles are of considerable importance. While the oxidation of hydroxamic acids has been widely studied in light of their role in the generation of acyl nitroso compounds,⁸⁴ the reactions of the corresponding *O*-alkyl hydroxamate esters have received less attention. Recently, we published a useful method for the preparation of 5 to 8-membered functionalized lactams **169**, involving the I(III)-mediated oxamidation of unsaturated *O*-alkyl hydroxamates **165**.⁸⁵ We believe that this transformation proceeds through the intermediacy of a singlet nitrenium ion **166** and bicyclic *N*-acyl-*N*-alkoxyaziridinium ion **167**. This reaction demonstrated high

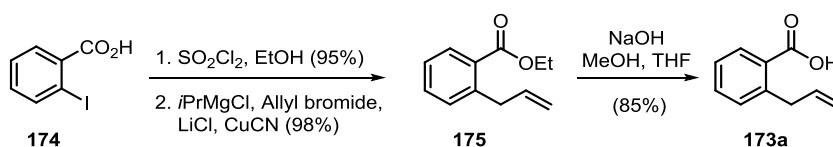
regioselectivity and stereospecificity, forming the *trans* *exo*-oxamidation products. We hypothesized that switching from PIFA to other hypervalent iodine reagents might result in the formation of a differently functionalized class of cyclization products **172**. To this end, we decided to search for new intramolecular I(III)-mediated oxamidation protocols of *O*-alkyl hydroxamates (Scheme 45).



Scheme 45

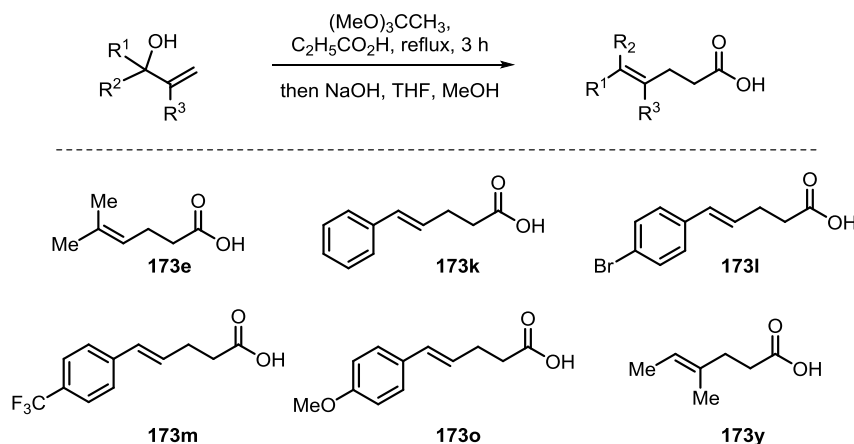
1.8.2 Preparation of Unsaturated *O*-Alkyl Hydroxamate Substrates

Our investigation commenced with the preparation of the requisite unsaturated carboxylic acids (**173a-z**). Synthesis of **173a** was completed in 3 steps starting from commercially available 2-iodobenzoic acid (**174**) (Scheme 46).⁸⁶ Thus, treatment of the latter with thionyl chloride in ethanol resulted in ester formation. Next, iodine-magnesium exchange followed by quenching of the resulting Grignard reagent with allyl bromide generated ethyl 2-allyl benzoate (**175**) in excellent yield.⁸⁷ The ester was then readily transformed into acid **173a** by saponification with sodium hydroxide in methanol and THF. This hydrolysis had to be performed at room temperature since olefin isomerization was observed at temperatures over 50 °C.



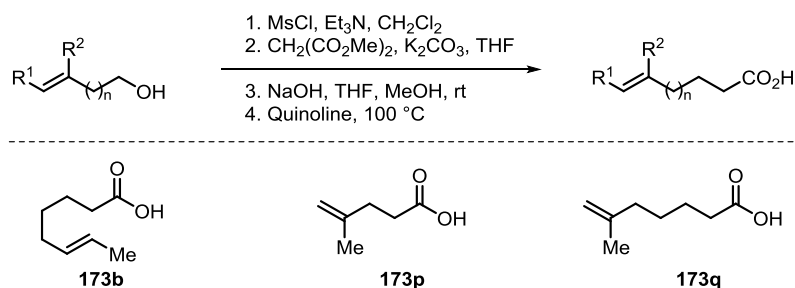
Scheme 46

Carboxylic acids **173e**, **173k**, **173l**, **173m**, **173o** and **173y** were prepared through Ireland-Claisen rearrangement of the corresponding allylic alcohols using the conditions developed by Johnson (Scheme 47).⁸⁸ Overall, the reaction was highly stereoselective, exclusively producing *E*-alkenes in good yields.



Scheme 47

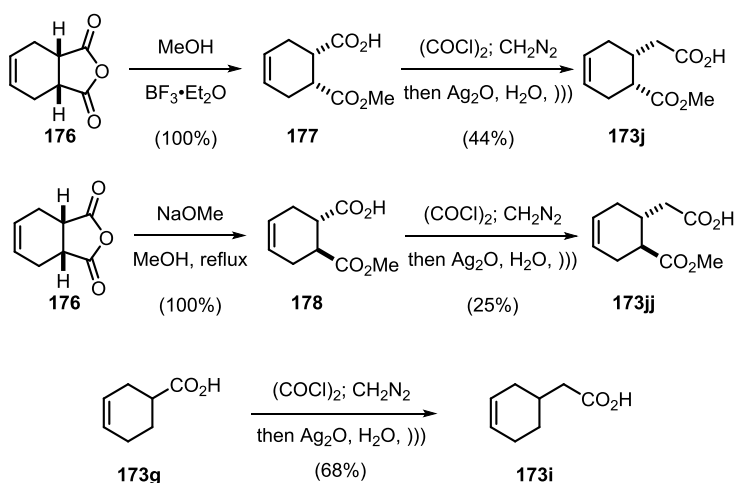
Compounds **173b**, **173p**, **173q** were accessed through the malonic ester synthesis strategy outlined in Scheme 48. Thus, appropriate alcohols were initially converted to the corresponding mesylates *via* treatment with methanesulfonyl chloride and triethylamine. These compounds were then used to alkylate the anion of dimethyl malonate. Hydrolysis of the resulting substituted diesters and decarboxylation with quinoline at 100 °C afforded corresponding acids in good yields.



Scheme 48

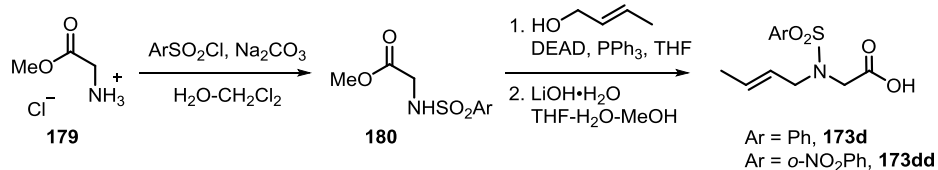
Cyclohexeneacetic acid derivatives **173i**, **173j** and **173jj** were synthesized *via* the Arndt-Eistert homologation method (Scheme 49). Ring opening of *cis*-1,2,3,6-

tetrahydrophthalic anhydride **176** using methanol and boron fluoride etherate provided half-ester **177**,⁸⁹ which was subsequently converted to diazoketone upon sequential treatment with oxalyl chloride and diazomethane. Sonication with freshly prepared silver(I) oxide triggered Wolff rearrangement to furnish desired acid **173j** in moderate yield. In order to prepare *trans* acid **173jj**, anhydride **176** was heated with NaOMe in methanol at reflux for 3 h. Elongation of the carbon chain of **178** was achieved using the procedure developed for **173j**, providing compound **173jj** in low yield. Acid **173i** was prepared following the same procedure starting from known acid **173g**.⁹⁰



Scheme 49

The synthesis of **173d** and **173dd** is outlined in Scheme 50. Thus, sulfonylation of glycine methyl ester (**179**) followed by Mitsunobu-type condensation of the *N*-sulphonyl derivatives with *E*-crotyl alcohol gave the protected esters. Sequential hydrolysis provided the required *N*-alkylated carboxylic acids **173d** and **173dd**.

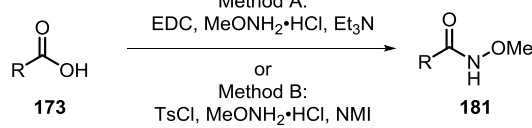
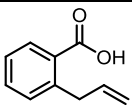
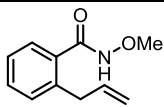
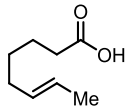
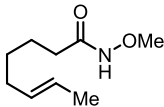
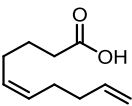
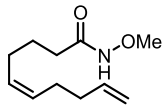
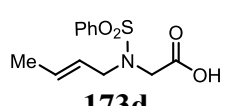
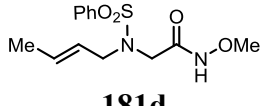
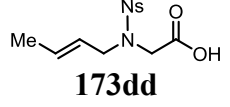
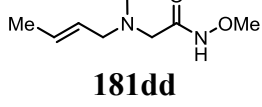
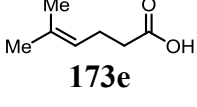
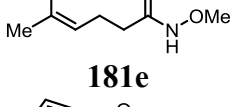
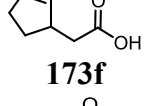
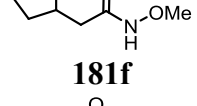
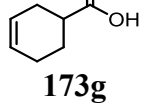
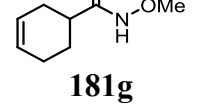
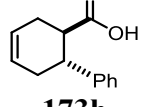
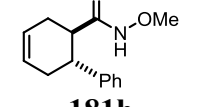


Scheme 50

Diene **173c** was obtained from (4-carboxybutyl)triphenylphosphonium bromide and pentenal *via* Wittig reaction.⁹¹ (1*R**, 6*R**)-6-Phenylcyclohex-3-enecarboxylic acid (**173h**),⁹² 2-(cinnamyloxy)acetic acid (**173n**)⁹³ and 2-(but-2-yn-1-yloxy)acetic acid (**173z**)⁹⁴ were prepared according to literature methods.

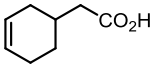
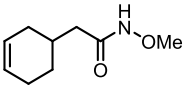
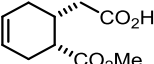
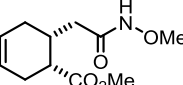
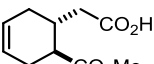
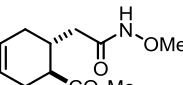
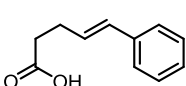
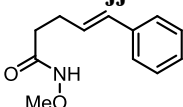
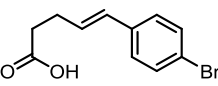
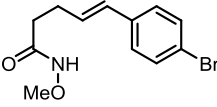
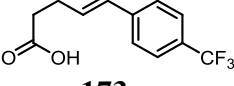
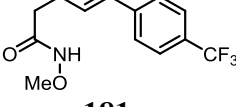
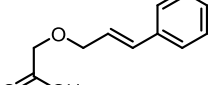
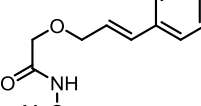
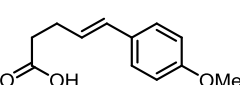
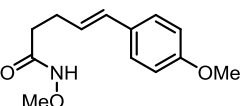
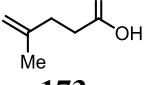
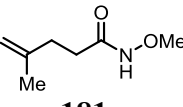
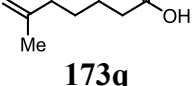
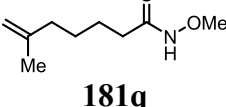
Each acid (**173a-z**) was coupled with methoxyamine hydrochloride to form the *O*-methyl hydroxamates **181a-z** listed in Table 2. This transformation was accomplished using one of two methods. Treatment of the carboxylic acids with Et₃N and subsequent addition of a mixture of EDC and MeONH₂·HCl provided the corresponding *O*-methyl hydroxamates in good to excellent yields, after overnight stirring at room temperature. Alternatively, the methoxyamide moiety can be installed *via* the procedure of Tanabe.⁹⁵ Thus, treatment of the carboxylic acids with tosyl chloride and *N*-methylimidazole in CH₃CN at 0 °C, followed by the addition of MeONH₂·HCl afforded *O*-methyl hydroxamates in high yields, after purification by flash chromatography.

Table 2. Preparation of *O*-Methyl Hydroxamates

$ \begin{array}{ccc} \text{Method A:} & & \\ \text{EDC, MeONH}_2\cdot\text{HCl, Et}_3\text{N} & \longrightarrow & \\ \text{or} & & \\ \text{Method B:} & & \\ \text{TsCl, MeONH}_2\cdot\text{HCl, NMI} & & \end{array} $				
				
entry	acid	<i>O</i> -methyl hydroxamate	method	yield, % ^a
1	 173a	 181a	B	82
2	 173b	 181b	A	76
3	 173c	 181c	B	97
4	 173d	 181d	A	80
5	 173dd	 181dd	A	68
6	 173e	 181e	A	99
7	 173f	 181f	B	99
8	 173g	 181g	A	93
9	 173h	 181h	B	73

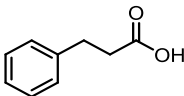
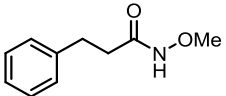
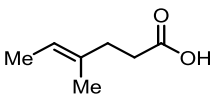
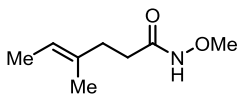
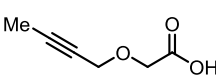
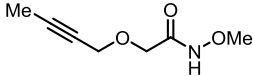
^aIsolated yields, after purification by flash chromatography.

Table 2. Preparation of *O*-Methyl Hydroxamates (continued)

entry	acid	<i>O</i> -methyl hydroxamate	method	yield, % ^a
10	 173i	 181i	B	89
11	 173j	 181j	B	97
12	 173jj	 181jj	B	78
13	 173k	 181k	A	99
14	 173l	 181l	B	82
15	 173m	 181m	A	86
16	 173n	 181n	A	85
17	 173o	 181o	B	76
18	 173p	 181p	A	94
19	 173q	 181q	A	69

^aIsolated yields, after purification by flash chromatography.

Table 2. Preparation of *O*-Methyl Hydroxamates (*continued*)

entry	acid	<i>O</i> -methyl hydroxamate	method	yield, % ^a
20	 173x	 181x	B	91
21	 173y	 181y	A	93
22	 173z	 181z	B	61

^aIsolated yields, after purification by flash chromatography.

The *O*-methyl hydroxamates **181r-w** shown below had been previously prepared by Burge for the initial azaspirocyclization study (Figure 4).⁶⁷

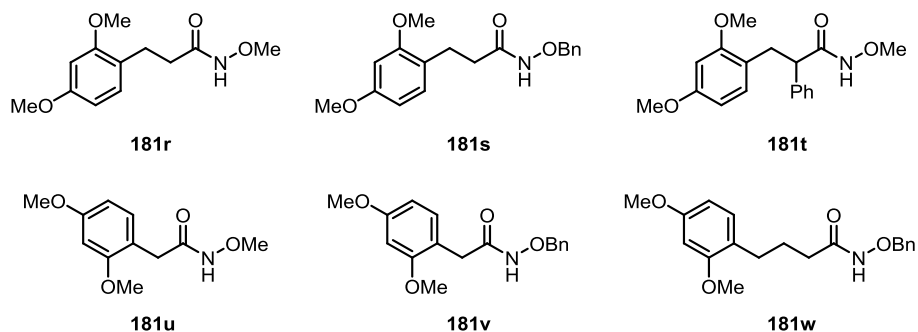


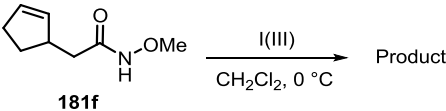
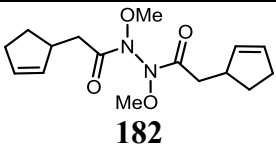
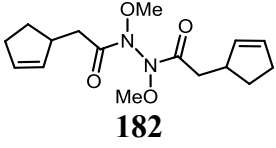
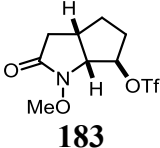
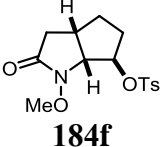
Figure 4 Previously synthesized aryl hydroxamates

1.8.3 Oxamidation of *O*-Alkyl Hydroxamates using HTIB

Our initial studies of the intramolecular oxamidation reaction focused on the reaction of **181f** with a variety of I(III) reagents (Table 3). Our original, general procedure for PIFA-promoted cyclization of *O*-alkyl hydroxamates involved treatment of a solution of the cyclization precursor in CH₂Cl₂ (0.05 M) with PIFA (1.2 equiv) at 0 °C. We chose these conditions to screen several available hypervalent iodine(III) reagents. Employment of DIB did not provide the expected cyclization product, but led to the formation of 1,2-diacetylhydrazine **182**. An attempt to mediate aminocyanation using (dicyanoiodo)benzene, obtained by premixing DIB with 2 equivalents of cyanotrimethylsilane,⁹⁶ failed to provide the expected product, but also generated **182**. A combination of DIB and 2 equiv of TMS-OTf, which is known to form PhI(OTf)₂ *in situ*,⁹⁷ provided moisture-sensitive triflate **183**, albeit in low yield. Further experiments revealed that employment of

[hydroxy(tosyloxy)iodo]benzene (PhI(OH)OTs),⁹⁸ more commonly known as Koser's reagent led to formation of lactam **184f** in a reasonable yield.

Table 3. Exploratory Oxamidation Study using I(III) Reagents

			
entry	I(III) reagent	product	yield, % ^a
1	PhI(OAc) ₂	 182	90
2	PhI(OAc) ₂ + TMS-CN (2 equiv)	 182	65
3	PhI(OAc) ₂ + TMS-OTf (2 equiv)	 183	23 ^b
4	PhI(OH)OTs (HTIB)	 184f	51 ^b

^aIsolated yields, after purification by flash chromatography. ^bSingle diastereomer by ¹H NMR analysis.

Encouraged by the success of Koser's reagent in mediating alkene oxamidation, we opted to optimize the reaction conditions for HTIB. Changing solvent from CH₂Cl₂ to CH₃CN or CH₃NO₂ did not improve the yield of product **184f**. When the oxamidation was conducted in THF, hydrolysis of the amide moiety to the corresponding carboxylic acid **173f** was observed. When the reaction was carried out at lower temperatures (-40 °C) the yield diminished, an observation that likely reflects the poor solubility of Koser's reagent in

CH_2Cl_2 under these conditions. Based on previous reports involving nitrenium ion intermediates, addition of Brønsted acids is often associated with increases in efficiency, possibly by preventing dimerization.^{62,99} Attempts to perform the oxamidation in the presence of *p*-toluenesulfonic acid (1 or 5 equivalents) were ineffective and resulted in lower yields. Notably, when 1 equiv of TFA was added to the reaction mixture prior to I(III) reagent, the rate of the process was significantly accelerated. This led to a more efficient cyclization, increasing the overall yield of tosylate **184f** from 51% to 73%. Use of greater than one molar equivalent of TFA led to lower yields.

The stereochemistry of **184f** was confirmed by collation and correlation of ^1H NMR spectra of **184f** with structurally related lactams (*anti*-**185**, *anti*-**186** and *syn*-**187**) prepared in an earlier study (Figure 5).⁸⁵ The vicinal coupling constant value (7.6 Hz) for H-4/H-5 of **184f** was comparable to those previously observed for compounds *anti*-**185** (7.6 Hz) and *anti*-**186** (7.3 Hz). The H-5/H-6 coupling constant was found to be 0 Hz for all three *anti* compounds, whereas for *syn* alcohol **187**, the same coupling constant value was found to be significantly different (4.4 Hz). NOESY experiments provided additional evidence of the stereospecific/*anti* nature of this reaction.

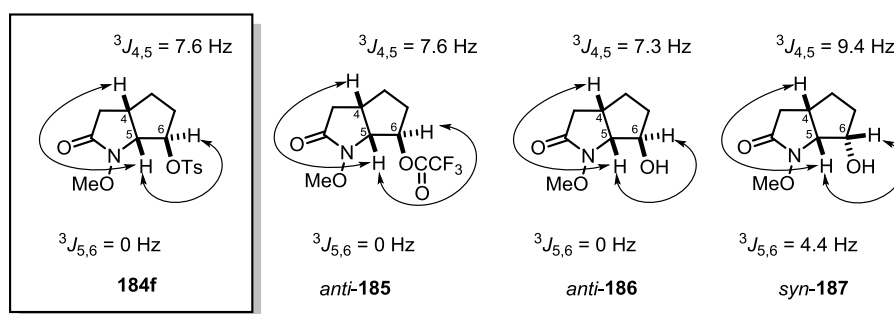
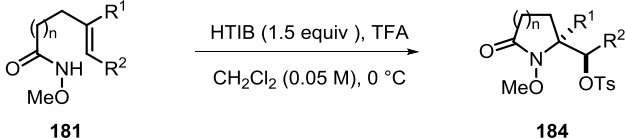
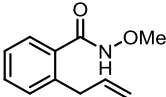
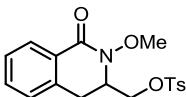
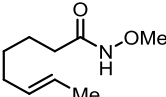
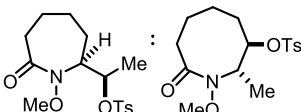
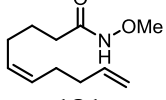
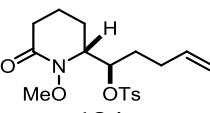
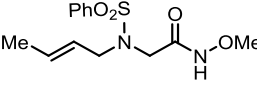
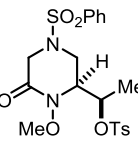
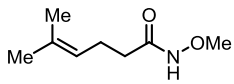
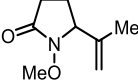
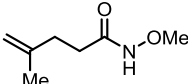
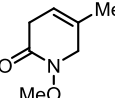
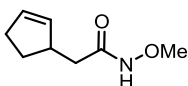
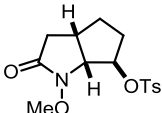


Figure 5 Comparison of the coupling constants for **184f**, *anti*-**185**, *anti*-**186** and *syn*-**187**

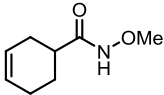
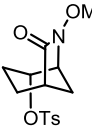
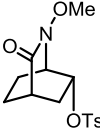
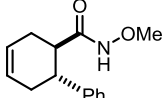
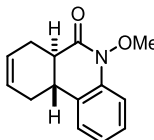
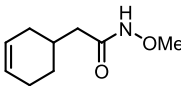
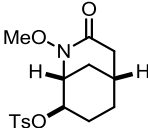
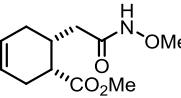
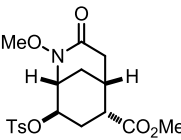
With conditions thus established we proceeded to examine the scope of this novel oxamidation protocol. Functional groups tolerance as well as the stereo- and regioselectivity of this transformation were evaluated. Encouragingly, a variety of unsaturated *O*-alkyl hydroxamates smoothly underwent cyclization to produce α -tosyloxy lactams in good to excellent yields (Table 4). Employing this method we were able to generate a number of 5- and 6- membered heterocycles including pyrrolidones (entry 7), piperidinones (entries 1, 3), morpholinones and piperazinones (entry 4). The reaction was highly regioselective, providing solely *exo* ring closure products in most cases. This method appears tolerant of a number of other functional groups, including alkenes (entry 3), heteroatoms (entries 4), and esters (entry 11).

Table 4. Scope of Hydroxamate Oxamidation with HTIB

			
entry	substrate	product(s)	yield, % ^{a,b}
<i>Monosubstituted Alkenes</i>			
1	 181a	 184a	76/65
<i>1,2-Disubstituted and Trisubstituted Alkenes</i>			
2	 181b	 184b 188b	32 (3:1)/ 34 (2.8:1)
3	 181c	 184c	63/62
4	 181d	 184d	76/58
5	 181e	 189	55/41
6	 181p	 190	72/60
<i>Cyclic Alkenes</i>			
7	 181f	 184f	73/51

^aConditions: *O*-methyl hydroxamate (1.0 equiv), HTIB (1.5 equiv), TFA (1.0/0.0 equiv), DCM (0.05 M), 0 °C, 0.5-2 h reaction time. ^bIsolated yields, after purification by flash chromatography.

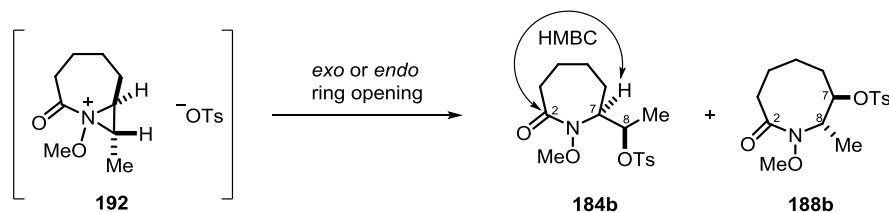
Table 4. Scope of Hydroxamate Oxamidation with HTIB (*continued*)

entry	substrate	product(s)	yield, % ^{a,b}
8	 181g	 :  184g 188g	99 (1:2.0)/ 65 (1:1.4)
9	 181h	 191	92/90
10	 181i	 184i	91/71
11	 181j	 184j	99/81

^aConditions: *O*-methyl hydroxamate (1.0 equiv), HTIB (1.5 equiv), TFA (1.0/0.0 equiv), DCM (0.05 M), 0 °C, 0.5-2 h reaction time. ^bIsolated yields, after purification by flash chromatography.

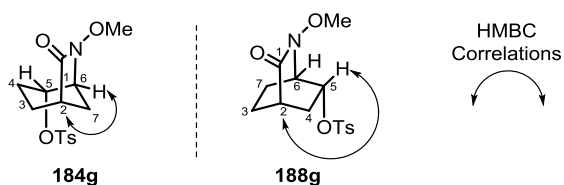
Examination of Table 4 reveals that addition of TFA significantly improves the yield of cyclization, as previously observed by our group.⁸⁵ In general, when 1 equivalent of TFA was used, a 10 to 20% increase in yield was observed for most substrates: the most notable improvement being observed for the cyclization of *N*-methoxycyclohex-3-ene-1-carboxamide **181g** (entry 8), where a 34% increase in combined yield was observed. Overall, this cyclization method proved to be most effective for oxamidation of 1,2-disubstituted and cyclic alkenes. For trisubstituted olefins **181e**, **181p** (Table 4, entries 5, 6), the unsaturated lactams **189**, **190** were obtained in moderate yield. The expected tertiary tosylates, retrieved in trace amounts from the reaction mixture, were unstable and underwent spontaneous elimination reaction to afford **189** and **190** after short-term storage.

The construction of larger rings was challenging and not regiospecific (Table 4, entry 2). Cyclization of substrate **181b** produced a mixture of 7- and 8- membered lactams in modest yield (Scheme 51). As anticipated, the observed product ratio was close to unity as previously noted during development of the PIFA oxamidation methodology.⁸⁵ HMBC and HMQC were used to confirm the identity of **184b** and **188b**. The HMBC spectrum of **184b** showed a cross peak between C-2 and H-7 and therefore was assigned as the 7-membered ring. Additionally, this assignment was confirmed by the ¹H NMR spectrum, where the multiplicity of H-8 signal was found to be quintet. This can be rationalized from H-8 signal coupling on H-7 and CH₃ groups with identical coupling constants ($J = 6.6$ Hz). The identity of 8-membered lactam **188b** was confirmed in a similar fashion: the H-7 signal in the ¹H NMR spectrum was found to be a double of triplets ($J = 2.3, 9.9$ Hz).



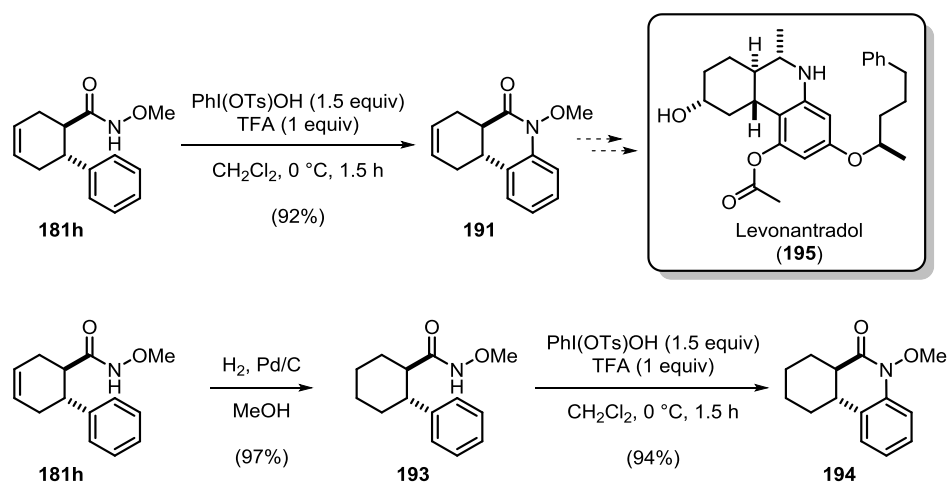
Scheme 51

Interestingly, upon treatment with HTIB, cyclohexene **181g** underwent cyclization to provide a mixture of bicyclic [3.2.1] and [2.2.2]azabicyclooctanes. In the presence of TFA, the regioselectivity towards the [2.2.2]-fused product was slightly improved from 1:1.4 to 1:2.0. The structure of these isomeric bicyclic oxamidation products was carefully established by 2D NMR experiments (Figure 6). The HMBC spectrum of **184g** showed a cross peak between C-2 and H-6, while no cross peak was observed between C-2 and H-5 and thus, this compound was assigned as being an azabicyclo[3.2.1]octane ring system. In contrast, the HMBC spectrum of more polar **188g** indicated no cross peak between C-2 and H-6, while a cross peak was observed between C-2 and H-5. This evidence suggests that **188g** is an azabicyclo[2.2.2]octane.

Figure 6 HMBC correlations observed within **184g** and **188g**

Notably, structurally related hydroxamate **181g**, bearing a C-2 phenyl substituent, cyclized to afford tetrahydrophenanthridine derivative **191** (Scheme 52). In this case, it appears that the putative nitrenium ion, generated upon treatment with Koser's reagent, was

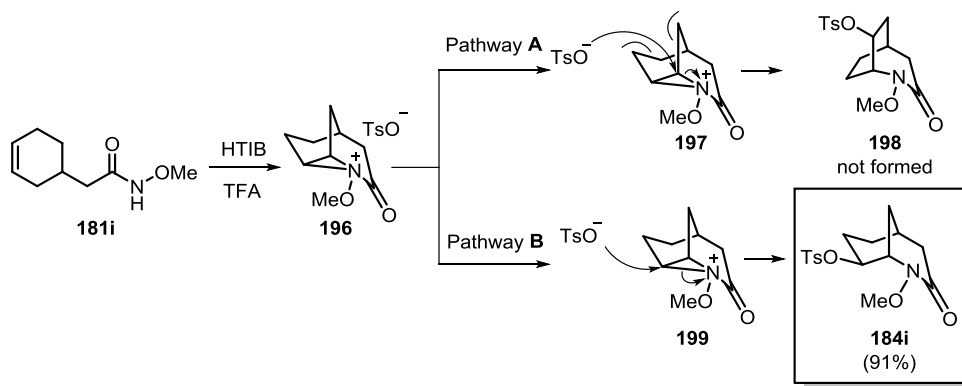
trapped by the arene in preference to the cyclic alkene. In order to corroborate the observed outcome, saturated hydroxamate **193** was prepared through the catalytic hydrogenation of **181h**. Treatment of **193** with 1.5 equivalents of Koser's reagent furnished hexahydrophenanthridinone **194** in excellent yield. We foresee that a transformation of this type could expedite the assembly of the novel synthetic cannabinoid levonantradol (**195**).¹⁰⁰ It has been demonstrated that **195** is 30 times more effective than Δ^9 -THC (the main psychoactive component in cannabis) in stimulating the CB₁ and CB₂ receptors as well as possesses promising analgesic and antiemetic properties.¹⁰¹



Scheme 52

It is interesting to note that substrates **181i** and **181j** (Table 4, entries 10, 11), which have an extra methylene group on the methoxyamide side chain, but are otherwise structurally similar to **181g**, exclusively yielded azabicyclo[3.3.1]nonanes upon cyclization (Scheme 53). This observation was rationalized in terms of steric factors. Upon formation, the steric bulk of bridged tricyclic aziridinium ion deters nucleophilic attack of the tosylate

ion on the proximal carbon (Pathway A). Thus, preferential tosylate anion attack on the less hindered, distal carbon generates product **184i** (Pathway B).



Scheme 53

In light of previous studies conducted in the Wardrop group,⁸⁵ it was expected that styrene substrates, which react to generate aryl-substituted aziridinium ions would undergo facile ring opening at the benzylic position since this would be electronically favored. This prediction was borne out experimentally: cyclization proceeded with nucleophilic attack occurring only at the benzylic position (Table 5).

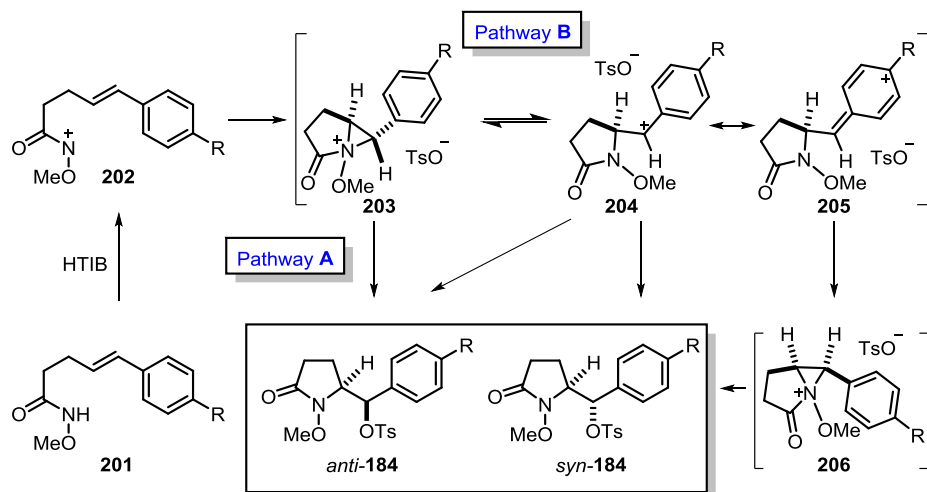
Table 5. Styrene Oxamidation using HTIB

entry	substrate	major product	<i>anti:syn</i> ratio ^{a,b}	yield, % ^{a,c}
Styrenes				
1	 181k	 184k	2.2:1/ 11:1	88/68
2	 181l	 184l	15:1/ 26:1	62/53
3	 181m	 184m	>100:1/ 13:1	66/64
4	 181n	 184n	3:1/ 7:1	48/62
5	 181o	 200	45:1/ 48:1	42/50

^aConditions: *O*-methyl hydroxamate (1.0 equiv), HTIB (1.5 equiv), TFA (1.0/0.0 equiv), DCM (0.05 M), 0 °C, 0.5-2 h reaction time. ^bRatio determined by integration of ¹H NMR peaks. ^cIsolated yields, after purification by flash chromatography.

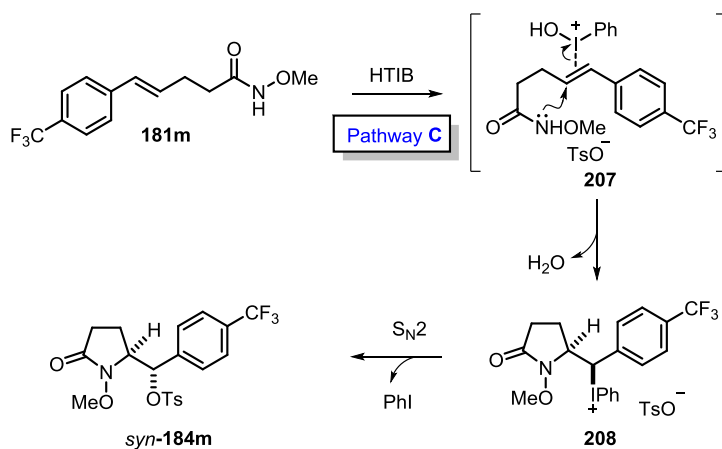
Yields of the tosylate products were dependent upon the aryl substitution pattern. With strongly electron-donating group, such as methoxy (Table 5, entry 5), alcohol **200** was formed instead of the desired tosylate. In contrast, *O*-alkyl hydroxamates **181k-n** possessing electron-neutral and electron-deficient aryl rings (Table 5, entries 1-4) cyclized smoothly, although inseparable mixtures of diastereomers were obtained. The ratio of *anti* and *syn* isomers in each case was determined by integration of the ^1H NMR spectra. The *anti* isomer, expected from *syn* addition of the nitrenium ion to the olefin followed by ring opening with inversion, was predominant in all cases. Selectivity without added TFA ranged from 26:1 in entry 2 to 7:1 in entry 4 and seems to be unaffected by the electron withdrawing or electron donating nature of the substituents on the aromatic ring. Interestingly, the presence of TFA greatly influenced the diastereomeric ratio. For most substrates it dropped dramatically when TFA was present in the reaction mixture. On the other hand, the reaction of **181m** with HTIB was significantly more diastereoselective with the addition of 1 equivalent of trifluoroacetic acid.

The stereochemical outcome of these cyclizations can be rationalized in terms of the formation of benzylic carbocation intermediate **204** (Scheme 54). The electron donating substituents on the aromatic ring would favor carbocation formation *via* pathway **B**. Thus, the nucleophilic attack of tosylate may occur from either face of the planar benzylic carbon **204**, generating both *syn* and *anti* isomers. An electron withdrawing trifluoromethyl substituent would destabilize such an intermediate, leading to the formation of the *anti* isomer (pathway **A**).



Scheme 54

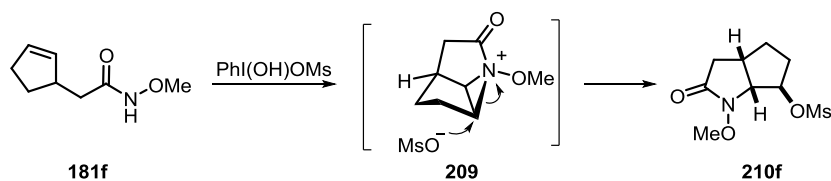
The drop (from >100:1 to 13:1) in stereoselectivity observed for cyclization of **181m** without TFA was harder to rationalize since *anti/syn* ratio was improved for other substrates in this class (Scheme 55). One could hypothesize that, in case of electron-deficient alkene **181m**, the cycloaddition of nitrenium ion with the olefin may be sluggish due to decreased nucleophilicity of the alkene. This consequence may allow the alternative mechanism to operate (Pathway C). First, HTIB activates the double bond (instead of nitrogen oxidation) to give an electrophilic intermediate **207**. The latter reacts intramolecularly with the nucleophilic amide. In this mechanism, observed formation of *syn* isomer may arise from S_N2 substitution of arylodonium species **208** with the tosylate. However, as shown in the literature, if iodonium ion is formed, one should be intercepted by more nucleophilic carbonyl oxygen atom and not nitrogen during ring-opening. As a result, such cyclizations of urea-tethered alkenes in similar conditions often generate isoureas.^{35,102} Since we had not observed the formation such byproducts, this path was ruled out.



Scheme 55

1.8.4 Oxamidation of *O*-Alkyl Hydroxamates using HMIB

Encouraged by the successful oxamidation of *O*-alkyl hydroxamates using Koser's tosylate reagent, we were interested in extending this methodology to the preparation of other useful products, such as mesylates. We anticipated that the reaction of (hydroxymesyloxy)iodobenzene (HMIB) with unsaturated hydroxamate **181f** would lead to formation of nitrenium ion intermediate, which upon intramolecular alkene cycloaddition may eventually form aziridinium ion **209**. A subsequent ion pair collapse of the latter should produce **210f** (Scheme 56).



Scheme 56

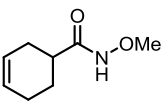
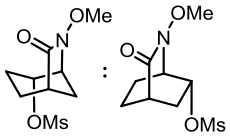
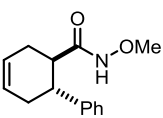
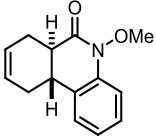
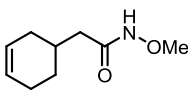
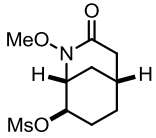
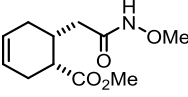
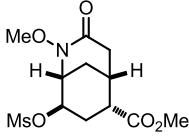
Accordingly, the scope of hydroxamate oxamidation (**181a-j**) with HMIB was examined (Table 6). We found that this reaction was efficient for a wide range of mono- and 1,2-disubstituted alkenes. Various functional groups, such as alkenes (entry 3), aminosulfonyls (entry 4) and esters (entry 11) were tolerated. It was found that oxamidation of trisubstituted alkenes **181e,p** proceeds to the formation of alkenes **189**, **190**, which results from spontaneous elimination of the first-formed 3° mesylate products. As in the case of HTIB, the yields of the mesylate esters improved dramatically in the presence of TFA. We also observed that trifluoroacetic acid greatly accelerated the oxamidation and led to cleaner reactions.

Table 6. Scope of Hydroxamate Oxamidation with HMIB

181	210		
entry	substrate	product(s)	yield, % ^{a,b}
Monosubstituted Alkenes			
1			76/60
1,2-Disubstituted Alkenes and Trisubstituted Alkenes			
2			30 (3:2)/ 20 (3:1)
3			98/43
4			81/53
5			53/35
6			35/37
Cyclic Alkenes			
7			89/59

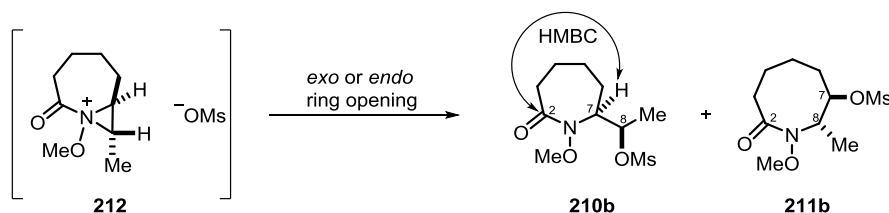
^aConditions: *O*-methyl hydroxamate (1.0 equiv), HMIB (1.5 equiv), TFA (1.0/0.0 equiv), DCM (0.05 M), 0 °C, 0.5-2 h reaction time. ^bIsolated yields, after purification by flash chromatography.

Table 6. Scope of Hydroxamate Oxamidation with HMIB (continued)

entry	substrate	product(s)	yield, % ^{a,b}
8	 181g	 210g 211g	97 (1:2.1)/ 68 (1:2.4)
9	 181h	 191	78/80
10	 181i	 210i	98/70
11	 181j	 210j	99/73

^aConditions: *O*-methyl hydroxamate (1.0 equiv), HMIB (1.5 equiv), TFA (1.0/0.0 equiv), DCM (0.05 M), 0 °C, 0.5-2 h reaction time. ^bIsolated yields, after purification by flash chromatography.

Cyclization of substrate **181b** produced a mixture of 7- and 8- membered α -mesyloxylactams in moderate yield (Scheme 57). HMBC and HMQC were used to confirm the identity of *exo* opening and *endo* opening **210b** and **211b**. The HMBC spectrum of **210b** showed a cross peak between C-2 and H-7 and therefore was assigned as the 7-membered ring. Additionally, this assignment was confirmed by ^1H NMR spectrum, where the multiplicity of H-8 signal was found to be quintet. This can be rationalized from H-8 signal coupling on H-7 and CH_3 groups with identical coupling constants ($J = 6.2$ Hz). The identity of 8-membered lactam **211b** was confirmed in a similar fashion as H-7 signal in ^1H NMR spectrum was found to be double of triplets ($J = 2.6, 10$ Hz).



Scheme 57

Styrene derivatives **181k-n** were cyclized in good yields (Table 7). Inseparable mixtures of diastereomers were isolated in most cases. Notably, addition of 1 equivalent of TFA greatly improved (by 7-37%) the yields of oxamidation products. In the presence of TFA, the stereoselectivity dropped for substrates with electron-neutral or moderate electron-donating aryl groups (Table 7, entries 1, 2, 4). However, for substrate **181m** possessing strong electron withdrawing *p*-trifluoromethyl moiety, *anti/syn* ratio increased from 16:1 to >100:1 with the employment of TFA. As expected, *para*-methoxy styrene **181o** cyclized to provide alcohol **200** instead of the desired mesylate.

Table 7. Styrene Oxamidation using HMIB

entry	substrate	major product	<i>anti:syn</i> ratio ^{a,b}	yield, % ^{a,c}
Styrenes				
1	 181k	 210k	5:1/ 6:1	93/56
2	 181l	 210l	6:1/ 73:1	67/56
3	 181m	 210m	>100:1/ 16:1	67/60
4	 181n	 210n	5:1/ 8:1	65/42
5	 181o	 200	41:1/ 45:1	45/30

^aConditions: *O*-methyl hydroxamate (1.0 equiv), HMIB (1.5 equiv), TFA (1.0/0.0 equiv), DCM (0.05 M), 0 °C, 0.5-2 h reaction time. ^bRatio determined by integration of ¹H NMR peaks. ^cIsolated yields, after purification by flash chromatography.

1.8.5 Oxamidation of *O*-Alkyl Hydroxamates using HPIB

Having successfully established two novel oxamidation processes for the synthesis of functionalized lactams, we now proceeded to examine the possibility of employing this process to install the biologically relevant phosphate moiety. Organic phosphates play a crucial role in biochemistry, agriculture and medicine (Figure 7). For instance, ATP (**213**), one of the most well-known molecules in Biology, is involved in human body metabolism and essential to the flow of energy in living cells.¹⁰³ Sphingosine-1-phosphate (S1P) (**214**) is a member of lipid mediators family that act as agonists both inside cells as well on the surface of epithelial cells.¹⁰⁴ FdUMP (**215**) functions as an effective inhibitor of thymidylate synthase enzyme (TS), which plays a central role in the generation of DNA precursor thymidylate (dTMP).¹⁰⁵ Masking functional groups as phosphates is a vital tool in drug discovery in order to facilitate transport across certain cell barriers or overcome low affinity towards certain enzymes.¹⁰⁶ This approach was undertaken for the preparation of 3/5-methyl *cyclo*Sal derivatives of acyclovir (**216**), a well-known drug used to treat herpes.¹⁰⁷ The phosphate derivatives proved to be potent antiviral agents against TK-deficient HSV-1 virus strains as well as display strong activity against EBV and HSV-1 infected cells.

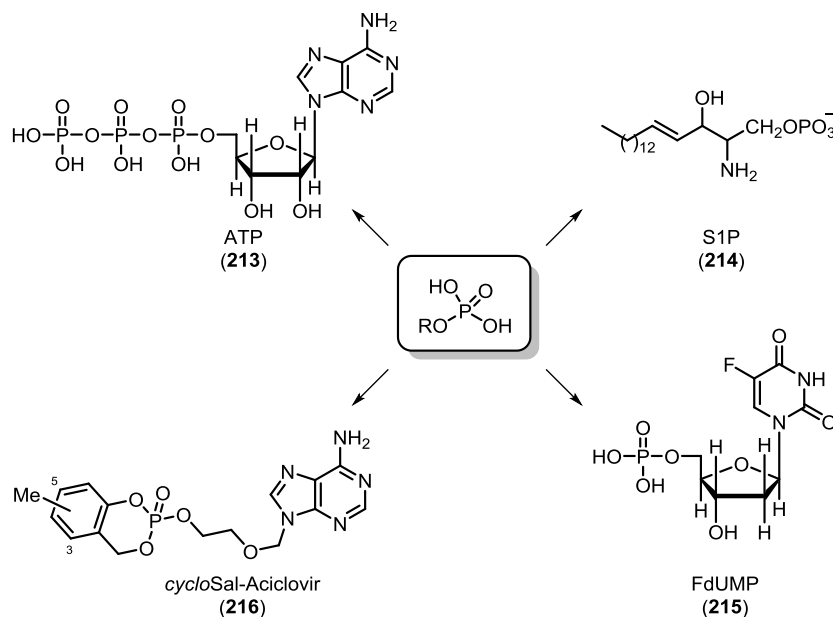
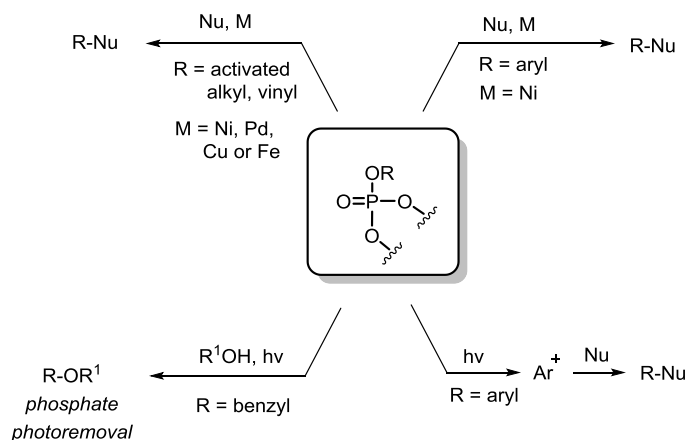


Figure 7 Examples of biologically important phosphate esters

Despite the diminished reactivity in comparison with sulfonates or halides, electrophilic phosphate esters have proven of significant utility in organic synthesis (Scheme 58). Metal-catalyzed C-C forming reactions of activated (allyl, propargyl, benzyl) sp^3 -hybridized phosphates with Grignard nucleophiles have been particularly useful.¹⁰⁸ Switching between $\text{S}_{\text{N}}2$ and $\text{S}_{\text{N}}2'$ mechanisms is possible with the employment of $\text{CuCN} \cdot 2\text{LiCl}$.¹⁰⁹ Vinyl phosphates are often used in Kumada, Sonogashira, Nozaki-Hiyama, Stille, Suzuki and Negishi cross-coupling reactions.¹¹⁰ Nicolaou has demonstrated the utility of cyclic ketene aminal phosphates as coupling partners for the construction of a range of *N*-heterocycles.¹¹¹ In contrast, aryl phosphates have received much less attention likely due to the ready availability and the low cost of aryl halide analogs. However, as shown in 1956 by Havinga,¹¹² aryl phosphates undergo photohydrolysis and generate phenyl cations under UV irradiation, which opens up great possibility for $\text{ArS}_{\text{N}}1$ reactions.¹¹³ Similarly, convenient

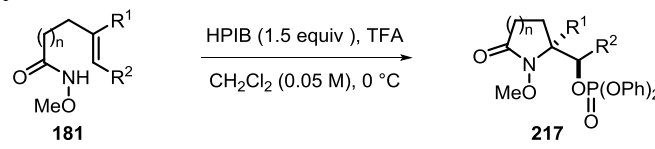
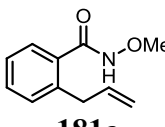
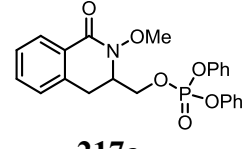
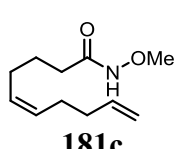
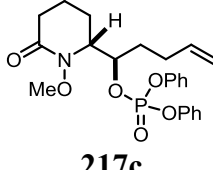
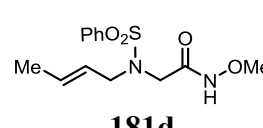
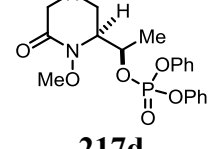
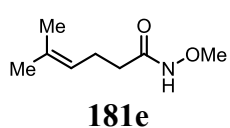
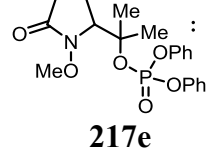
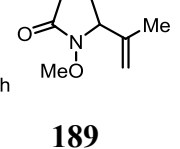
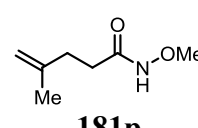
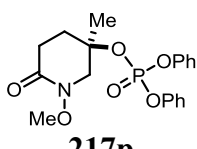
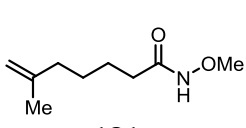
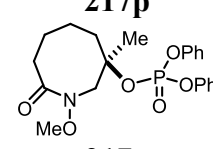
photoremovable protecting benzyl phosphates have found their niche in biological applications.¹¹⁴



Scheme 58

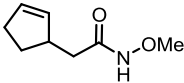
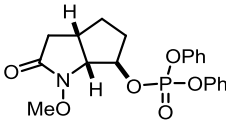
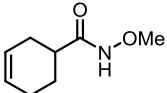
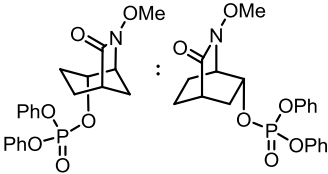
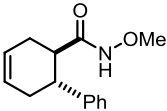
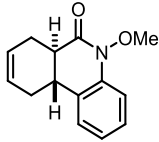
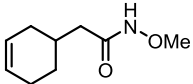
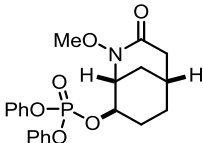
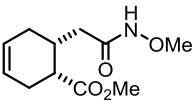
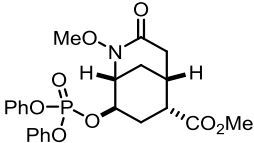
Thus, in order to introduce the phosphate ligand to hypervalent iodine reagent, hydroxy(diphenylphosphoryloxy)iodobenzene¹¹⁵ (HPIB) was prepared by grinding DIB with commercially available diphenyl phosphate. Subjecting our test substrate **181f** to the oxamidation protocol with 1.5 equiv of HPIB, we were pleased to find that the desired α -phosphoryloxylactam was obtained in good yield (Table 8, entry 7). Similarly, we found that this reaction was efficient for wide range of *O*-methyl hydroxamates (**181a-j**) providing the phosphorylated lactams (**217a-j**) in moderate to good yields (Table 8).

Table 8. Scope of Hydroxamate Oxamidation with HPIB

			
entry	substrate	product(s)	yield, % ^{a,b}
<i>Monosubstituted Alkenes</i>			
1	 181a	 217a	79/57
<i>1,2-Disubstituted Alkenes</i>			
2	 181c	 217c	53/34
3	 181d	 217d	53/46
<i>1,1-Disubstituted and Trisubstituted Alkenes</i>			
4	 181e	 217e	36 (1:0)/ 90 (1:1.3)
		 189	
5	 181p	 217p	58/31
6	 181q	 217q	64/33

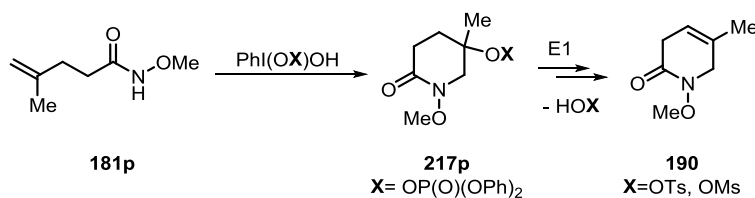
^aConditions: *O*-methyl hydroxamate (1.0 equiv), HPIB (1.5 equiv), TFA (1.0/0.0 equiv), DCM (0.05 M), 0 °C, 0.5–2 h reaction time. ^bIsolated yields, after purification by flash chromatography.

Table 8. Scope of Hydroxamate Oxamidation with HPIB (*continued*)

entry	substrate	product(s)	yield, % ^{a,b}
<i>Cyclic Alkenes</i>			
7	 181f	 217f	58/47
8	 181g	 217g	80 (1:2.3)/ 62 (1:2.1)
9	 181h	 191	85/78
10	 181i	 217i	48/45
11	 181j	 217j	76/53

^aConditions: *O*-methyl hydroxamate (1.0 equiv), HPIB (1.5 equiv), TFA (1.0/0.0 equiv), DCM (0.05 M), 0 °C, 0.5-2 h reaction time. ^bIsolated yields, after purification by flash chromatography.

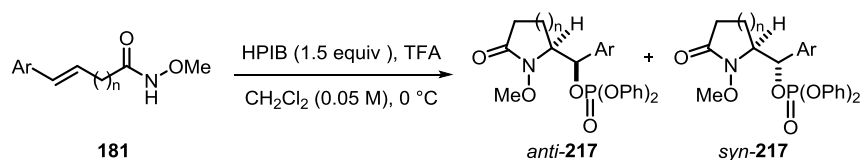
In all cases, the cyclization with HPIB proceeded less rapidly and in lower yields than that with HTIB or HMIB. It appears that the addition of 1 equiv of trifluoroacetic acid to the reaction mixture slightly increases the yield of the cyclized products. In addition to previously successful hydroxamates, we were able to isolate the oxamidation products of 1,1-disubstituted alkenes **181p,q** (Table 8, entries 5, 6). In contrast, attempted cyclization of alkene **181p** with HTIB or HMIB could not be interrupted at the stage of oxamidation and yielded only alkene **190** resulting from elimination (Scheme 59). These results reflect the significant difference between the nucleofugality of the tertiary diphenyl phosphate vs. tosylate/mesylate groups. Similarly, upon oxamidation of trisubstituted olefin **181e**, phosphate **217e** was obtained in addition to alkene **189** (Table 8, entry 4).



Scheme 59

Styrene hydroxamates **181k-n** were cyclized in good to excellent yields (Table 9). The addition of 1 equiv of trifluoroacetic acid to the reaction mixture was advantageous and led to considerable increase in yields of the lactams. The observed diastereoselectivity trends were similar to those, described in Sections 1.8.3 and 1.8.4. The highest selectivity (>100:1) in the presence of TFA were obtained for substrates **181k,m**. Cyclization of **181o**, bearing an electron-donating methoxy substituent on the aryl moiety, led to alcohol **200** instead of the desired diphenyl phosphate.

Table 9. Styrene Oxamidation using HPIB

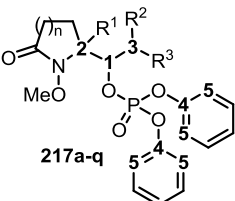
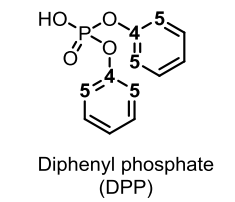


entry	substrate	major product	<i>anti:syn</i> ratio ^{a,b}	yield, % ^{a,c}
Styrenes				
1	<p style="text-align: center;">181k</p>	<p style="text-align: center;">217k</p>	>100:1/ 8:1	75/25
2	<p style="text-align: center;">181l</p>	<p style="text-align: center;">217l</p>	16:1/ 49:1	56/60
3	<p style="text-align: center;">181m</p>	<p style="text-align: center;">217m</p>	>100:1/ 57:1	97/43
4	<p style="text-align: center;">181n</p>	<p style="text-align: center;">217n</p>	6:1/ 10:1	67/21
5	<p style="text-align: center;">181o</p>	<p style="text-align: center;">200</p>	40:1/ 50:1	35/51

^aConditions: *O*-methyl hydroxamate (1.0 equiv), HPIB (1.5 equiv), TFA (1.0/0.0 equiv), DCM (0.05 M), 0 °C, 0.5-2 h reaction time. ^bRatio determined by integration of ¹H NMR peaks. ^cIsolated yields, after purification by flash chromatography.

Upon examination of the ^{13}C NMR spectra of phosphorylated products it was noted that carbon signals two or three bonds away from the phosphorus atom appear as doublets because of P-C coupling. In some cases we also observed splitting of the diphenyl phosphate signals due to diastereotopic nature of these groups. $^nJ(\text{P},\text{O},\text{C})$ values of **217a-q** are shown in Table 10.

Table 10. $^nJ(\text{P},\text{O},\text{C})$ Coupling Constants (in Hz)

	product	$^2J(\text{P}, \text{O}, \text{C}_1)$	$^3J(\text{P}, \text{O}, \text{C}_2)$	$^3J(\text{P}, \text{O}, \text{C}_3)$	$^2J(\text{P}, \text{O}, \text{C}_4)$	$^3J(\text{P}, \text{O}, \text{C}_5)$
 217a-q	217a	6.5	8.3	-	6.9	4.2
	217c	6.5	1.8	6.5	6.9	4.6
	217d	6.0	7.9	1.8	7.4	4.6
	217f	6.5	6.9	5.1	7.4	4.6
	217g	6.5	5.5	4.6	7.4	4.6
 Diphenyl phosphate (DPP)	218g	6.5	5.5	5.5	6.9	5.1
	217i	6.9	6.0	4.6	6.9	4.6
	217j	6.5	5.5	4.2	7.4	4.6
	217k	6.0	7.9	1.8	7.4	4.6
	217l	6.0	7.9	1.8	7.4	4.6
	217m	6.0	7.9	-	6.9	5.1
	217n	5.5	8.3	1.4	6.9	4.6
	217p	6.9	4.6	6.9;0	7.4	4.6
	217q	6.9	4.2	6.0;0	7.9	4.6
	DPP	-	-	-	7.2	4.8

As noted in the literature, an introduction of the bulky substituents on phosphorus atom can lead to an increase in $^nJ(\text{P},\text{C})$.¹¹⁶ This fact is frequently attribute to an increase in the X-P-X bond lengths and angles due to the increasing *s* orbital character in those bonds.¹¹⁷ As shown in Table 10, no definite differences were found between the $^2J(\text{P},\text{O},\text{C}_1)$, $^2J(\text{P},\text{O},\text{C}_4)$ and $^3J(\text{P},\text{O},\text{C}_5)$ coupling constants. In fact, the latter two were congruous to those known for

commercially available diphenyl phosphate (CAS # 838-85-7).¹¹⁸ The three bond $^3J(\text{P},\text{O},\text{C}_3)$ showed the widest range between 0 and 6.9 Hz. Notably, the lower $^3J(\text{P},\text{O},\text{C}_3)$ coupling constant values (1.4-1.8 Hz) were detected for α -aryl phosphates **217k,l,n** and piperazinone **217d**. The reduction of coupling constants is likely a consequence of decreased steric interference around sp^2 -hybridized C-3 in **217k,l,n** and the rather small methyl group in **217d**. For tertiary phosphates **217p,q**, the two C-3 atoms are non-equivalent, therefore two different $^3J(\text{P},\text{O},\text{C}_3)$ are possible (Figure 8). Interestingly, no signal splitting was observed for the methyl group, whereas higher $^3J(\text{P},\text{O},\text{C}_3)$ constants were found between P and cyclic methylene group (6.9 and 6.0 Hz, respectfully).

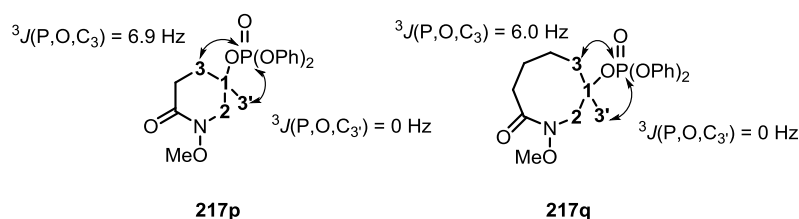


Figure 8 $^3J(\text{P},\text{O},\text{C}_3)$ coupling constants of **217p,q**

Surprisingly low $^3J(\text{P},\text{O},\text{C}_2)$ was found for piperidine **217c**. On comparing with the rest of the products the observed value is 2-4 times lower. This could be attributed to less sterically congested environment on C-2 due to relative stereochemical configuration between the lactam nitrogen and phosphate substituent, since **217c** derived from from *cis* alkene **181c**.

1.8.6 Hypervalent Iodine-Mediated Azaspirocyclization

The dearomatization of aromatic rings is a powerful strategy for the rapid stereo- and regiocontrolled preparation of saturated and unsaturated cyclic compounds.¹¹⁹ Earlier studies in the Wardrop group have demonstrated that electron rich aryl hydroxamates are readily oxidized in the presence of PIFA to generate 2,5-cyclohexadienone systems in high yields.⁶⁷ The dienone moiety can be cleaved to furnish di- and trisubstituted lactams, which are embedded in a diverse array of biologically important molecules. However, this method suffers from low temperature requirements, leading to a necessity to employ methanol as a co-solvent for better solubility of expensive PIFA. As a result, methanol adducts, arising from the conjugate addition of methanol to the dienone system, may form as by-products. We were therefore interested to establish if whether Koser's hypervalent iodine reagents would offer certain advantages for this intramolecular oxamidation process. To test our hypothesis, aryl hydroxamates **181r-x** were treated with HTIB and HMIB using the conditions (*O*-alkyl hydroxamate (1.0 equiv), I(III) reagent (1.5 equiv), DCM (0.05 M), 0 °C) previously developed for alkene oxamidation.

To our delight, we found that substrates **181r-w**, with various alkyl tethers, efficiently underwent cyclization to provide the corresponding 4- to 6-membered spirolactams **219r-w** in excellent yields (Table 11). *O*-Benzyl hydroxamates **181s,v,w** cyclized smoothly to give products **219s,v,w** in high yields. Substrate **181t** underwent spirocyclization to provide the *anti* spirolactam diastereomer with reasonable selectivity (6:1), which was determined by integration of the appropriate proton signals in the ¹H NMR spectrum. The stereoselectivity observed during formation of **219t** was lower than observed in the PIFA-mediated protocol (10:1), which was carried out at much lower temperature (-78 °C). In a control experiment

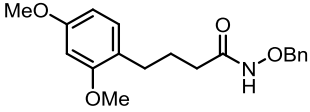
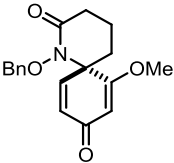
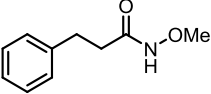
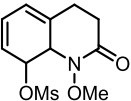
with *N*-methoxy-3-phenylpropanamide **181x** and HMIB, we found that the reaction did not proceed to the formation of spirolactam indicating that an electron-rich arene is required. The reaction did, however, yield some hexahydroquinoline derivative **220** in addition to the 1,2-diacetylhydrazine. We note that the reaction did not require the addition of 1 equivalent of TFA in order to achieve high yields. In general, our yields were normally higher for than those previously reported for the PIFA-mediated spirocyclization.⁶⁷ In similarity to HMIB and HTIB, exposure **181r** to hydroxy(diphenylphosphoryloxy)iodobenzene (HPIB) resulted in formation of **219r** in 99% yield. Overall, among three reagents, HMIB was found to be the most practical and efficient.

Table 11. Scope of Hydroxamate Azaspirocyclization using I(III) Reagents

entry	substrate	product	yield, % ^a	yield, % ^{b,c}
1	 181r	 219r	81	96/86
2	 181s	 219s	98	99/88
3	 181t	 219t	85	88/91
4	 181u	 219u	67	99/80
5	 181v	 219v	86	99/84

^aIsolated yields with the employment of PIFA reported by Burge.⁶⁷ ^bConditions: *O*-alkyl hydroxamate (1.0 equiv), I(III) reagent (1.5 equiv), DCM (0.05 M), 0 °C, 0.5-2 h reaction time. ^cIsolated yields with the employment of HMIB / HTIB reagents, after purification by flash chromatography.

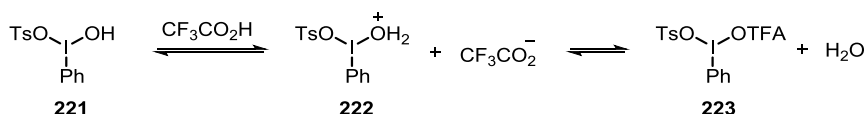
Table 11. Scope of Hydroxamate Azaspirocyclization using I(III) Reagents (*continued*)

entry	substrate	product	yield, % ^a	yield, % ^{b,c}
6	 <p>181w</p>	 <p>219w</p>	83	96/85
7	 <p>181x</p>	 <p>220</p>	NR	<10

^aIsolated yields with the employment of PIFA reported by Burge.⁶⁷ ^bConditions: *O*-alkyl hydroxamate (1.0 equiv), I(III) reagent (1.5 equiv), DCM (0.05 M), 0 °C, 0.5-2 h reaction time. ^cIsolated yields with the employment of HMIB / HTIB reagents, after purification by flash chromatography.

1.8.7 Mechanistic Considerations

Aryl- λ^3 -iodanes are electrophilic species that readily participate in ligand exchange reactions.¹²⁰ The observed rate acceleration in the presence of TFA in the three processes studied suggests the initial protonation of the hydroxyl group of HTIB and a subsequent nucleophilic substitution at trivalent iodine by trifluoroacetate would afford mixed reagent **223**, which we believe would be significantly more reactive than Koser's reagent itself (Scheme 60).



Scheme 60

In order to test this hypothesis and shed light on the oxamidation mechanism, we performed ^{19}F NMR studies (Figure 9). Indeed, new deshielded signals in respect to TFA, appeared in the ^{19}F NMR spectrum immediately after the addition of 1 equivalent TFA to HTIB solution in CDCl_3 . Although the nature of these signals has not been confirmed, they could arise from the initial displacement step thus providing a mixture of mixed iodanes. The chemical shifts of these peaks were similar to that observed for PIFA. With the addition of another equivalent of TFA, these two peaks merge into one. However, this could be a result of peak broadening due to the more acidic media.

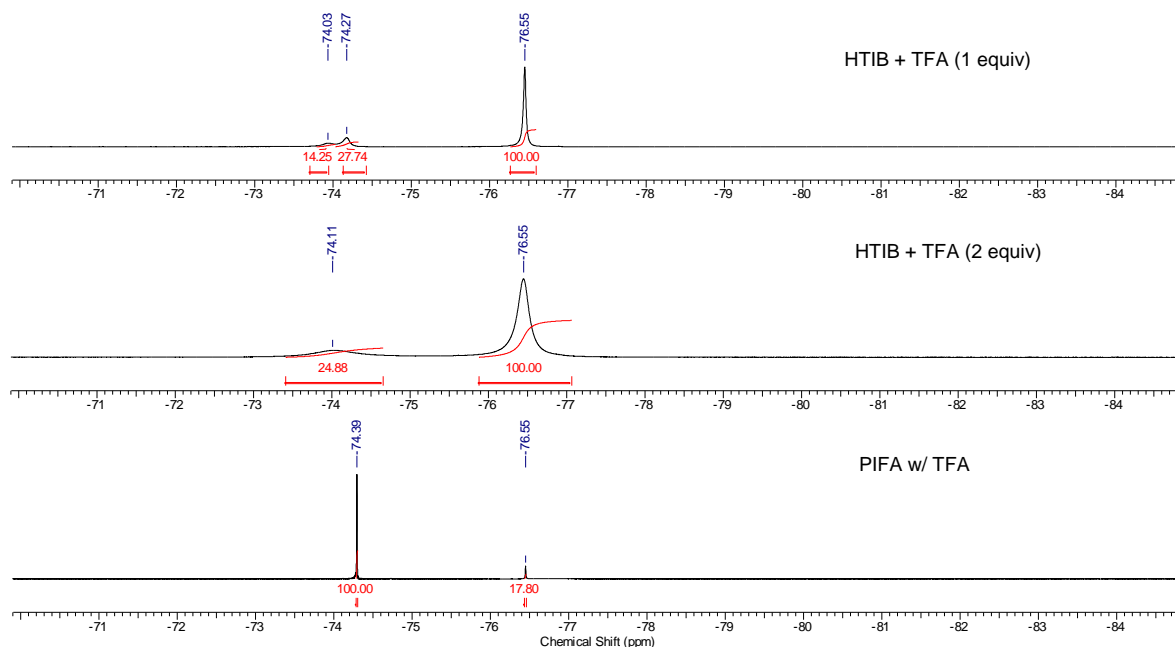
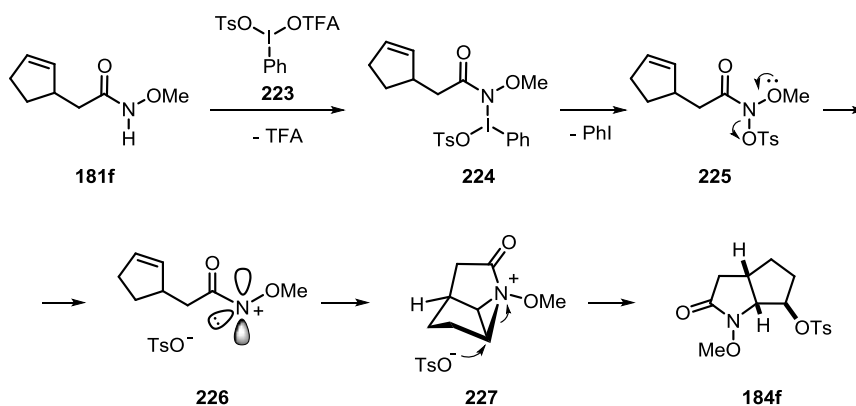


Figure 9 ^{19}F NMR spectra of HTIB+TFA and PIFA

The ligand exchange with a relatively acidic *O*-alkyl hydroxamate **181f** would now form aminoiodane **224**, which upon reductive elimination of iodobenzene, would produce *N*-tosyloxy-*N*-methoxy amide **225** (Scheme 61). The formation of TFA-analogs of **225** and **224** was confirmed by Bowen in his studies of PIFA-mediated oxamidation by *in situ* NMR analysis.¹²¹ Subsequent dissociation could now form transient nitrenium ion **226**. Due to the low dielectric constant of CH_2Cl_2 ($\epsilon = 8.93$) intermediate **226** should presumably exist as a tight ion pair with the tosylate counter ion. Intramolecular cycloaddition with the alkene moiety would generate aziridinium ion intermediate **227**, which upon rapid regioselective ion-pair collapse would furnish tosylate product **184f**. Taking into account the high *anti* stereoselectivity of this process, we conclude that the addition of the nitrenium ion across the alkene, followed by tosylate-mediated opening of the aziridinium ion occur with inversion in a concerted fashion. Remarkably, no TFA-adducts were isolated, which strongly supports the

proposed rapid ion pair collapse. Our current assumption is that the oxamidations mediated by HMIB and HPIB proceed *via* similar mechanisms.



Scheme 61

1.9. Cr(VI)-Mediated Oxoamidation of Alkenes

Transition metal oxidants and catalysts have found great utility in both the direct and intermolecular oxamination of olefins.^{16,122} Their use offers certain advantages such as the ability of metal (atom or ion) to coordinate ligands that results in formation of chiral metal-organic frameworks. Indeed, the employment of metal catalysts, provide facile synthetic routes for the synthesis of chiral compounds, including enantiopure amino alcohols. Historically, hypervalent iodine oxidants have been utilized to mediate the formation of nitrenium ions.^{46b} In contrast, studies on metal-mediated nitrenium ion formation are particularly limited. In 1993, Smith reported that photolysis or thermolysis of bis(*N,N*-dimethyldithiocarbamato)bis[*N*-alkyl-*N*-phenylhydrazido(2-)]-molybdenum(VI) complexes in 1,1,2,2-tetrachloroethane led to transfer of the hydrazido group to the solvent with formation of dichloroacetohydrazides. The products generated in this transformation can be formally

derived from nitrenium ions. However, the attempts to trap the nitrenium ions by carrying out the reaction in the presence of various olefins and aromatics failed, suggesting that these species are not involved as free entities.

In 2011, the first example of the use of nitrenium ions as ligands for transition-metal chemistry was published by Gandelman and co-workers (Figure 10).¹²³ The authors were able to isolate and characterize several Rh(I) and Ru(II)-metal complexes featuring a nitrenium ion ligand (**228**, **229**). More recently, Ni(I) and Ni(II) complexes bound *N*-heterocyclic nitrenium units (**230**, **231**) were studied using DFT and spectroscopic methods by Ray and co-workers.¹²⁴ It was shown that the electrophilic property of a Ni(II) center featuring a nitrenium ligand can be effectively employed in formate oxidation. This finding opens the door for the use of *N*-heterocyclic nitrenium ligands in the transformations catalyzed by transition metals.

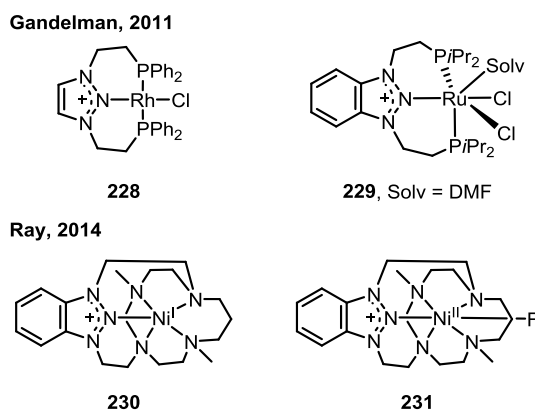
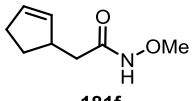
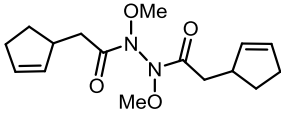
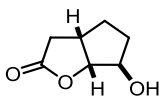
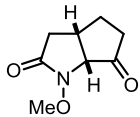


Figure 10 Recent examples of transition-metal complexes containing nitrenium ion ligands

In an effort to identify metal-based oxidants for our alkene oxamidation process, we treated the unsaturated *O*-methyl hydroxamate **181f** with various transition metal catalysts and oxidants. Herein we report the result of this investigation (Table 12).

Table 12. Exploratory Oxidation Studies

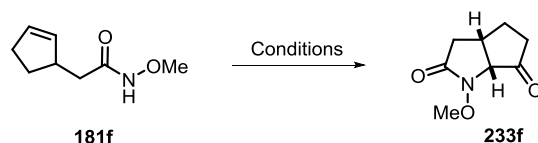
<div style="text-align: center;">  181f </div> <div style="text-align: center; margin-top: 10px;"> $\xrightarrow{\text{Oxidant}}$ </div> <div style="text-align: center;"> Product(s) </div>					
entry	oxidant	loading	solvent	<i>T</i> (°C)	product (isolated yield, %)
1	Cu(acac) ₂	1 equiv	CH ₂ Cl ₂	40	no reaction
2	CuBr ₂	1 equiv	CH ₂ Cl ₂	40	
3	Fe(acac) ₃	1 equiv	CH ₂ Cl ₂	40	
4	Mn(OAc) ₃	1 equiv	CH ₂ Cl ₂	40	
5	CeO ₂	1 equiv	CH ₂ Cl ₂	40	
6	TPAP/NMO	10 mol%	CH ₃ CN	25	no isolable products
7	Pd(OAc) ₂ /BQ	10 mol%	DMF	80	
8	FeCl ₃	1 equiv	CH ₂ Cl ₂	40	no isolable products
9	OsO ₄ /NMO	10 mol%	CH ₃ CN/H ₂ O	25	
10	Pb(OAc) ₄	1 equiv	DCE	25	<div style="text-align: center;">  182 (89%) </div>
11	RuCl ₃ /H ₂ O ₂	10 mol%	CH ₃ CN	25	<div style="text-align: center;">  232 (81 - 95%) </div>
12	CH ₃ ReO ₃ /H ₂ O ₂	10 mol%	CH ₃ CN	25	
13	K ₂ S ₂ O ₈	1 equiv	CH ₃ CN/H ₂ O	25	
14	PCC	3 equiv	CH ₂ Cl ₂	25	<div style="text-align: center;">  233f (26%) </div>

No reaction was observed with the use of the following oxidants: Cu(acac)₂, CuBr₂, Fe(acac)₃, Mn(OAc)₃,¹²⁵ CeO₂,¹²⁶ and TPAP.¹²⁷ The Pd(II)/(IV) catalytic system also failed to mediate the cyclization. Heating **181f** with ferric chloride¹²⁸ led to cleavage of N-O bond and formation of multiple chlorination products. Even more disappointing, the use of osmium(VIII) catalysts, best known for their application in intramolecular aminohydroxylation reactions,¹²² failed to generate the expected lactam, instead forming a mixture of polar vicinal diols. Employment of lead(IV) acetate provided hydrazine species **182** from dimerization of the starting material.¹²⁹ Treatment of *O*-methyl hydroxamate **181f** with RuCl₃,¹³⁰ methylrhenium trioxide¹³¹ or oxone³¹ peroxide-driven systems yielded lactone **232**. The *anti* isomer is believed to arise *via* alkene epoxidation, nucleophilic epoxide opening by the carbonyl oxygen followed by the hydrolysis of the resulting imine in the acidic media.¹³² Gratifyingly, we found that employment of 3 equivalents of pyridinium chlorochromate (PCC) as the oxidant in CH₂Cl₂ produced pyrrolidinone **233f** in 26% yield after stirring for 24 h. In this case, 1,2-amido ketone was generated instead of the expected 1,2-amido alcohol product. This finding is proposed to result from *in situ* secondary oxidation by excess of PCC.¹³³

1.9.1 Optimization of Reaction Conditions, Scope and Limitations

Encouraged by the success of PCC, we explored the feasibility of other Cr(VI) oxidants to mediate the intramolecular oxoamidation of alkenes. Substrate **181f** was chosen for this undertaking. While optimizing the conditions for the cyclization, we found that the oxoamidation reaction generally requires heating in order to reach completion in a reasonable

timeframe (Table 13). The reaction proceeds in a number of aprotic solvents suitable for Cr(VI) oxidations and, indeed, a strong solvent effect was noted. The oxoamidation was found to be faster in solvents with low dielectric constant (e.g., DCM, toluene) and slower in more polar solvents (e.g., acetone, DMF). Agarwal and co-workers have noted that the oxidation of alcohols by PCC is accelerated by Brønsted acids.¹³⁴ We also observed that the cyclization process accelerates in the presence of acids, while bases, such as pyridine, inhibit the process (Table 13, entry 2). Activated molecular sieves (4 Å) were added in all cases to facilitate the work-up process. The highest isolated yield (61%) of product **233f** was obtained when the reaction was performed in the presence of 5 equivalents of anhydrous acetic acid. Employment of other organic acids, including TFA and TfOH, decreased yields (Table 13, entries 11-13). Cyclization using pyridinium¹³⁵ and quinolinium¹³⁶ dichromates (PDC, QDC) proved to be easier to work-up as a result of the more polar chromium byproducts generated with these reagents. Despite this, cyclization in the presence of dichromate was slow and the prolonged reaction times led to a reduction in yields. Maintaining anhydrous conditions was crucial for the success of the cyclization: aqueous-based Cr(VI) oxidants such as potassium dichromate or Jones reagent were found to hydrolyze the *N*-methoxyamide moiety to the carboxylic acid (Table 13, entries 16, 17).

Table 13. Optimization of Cr(VI)-Mediated Oxoamidation

entry	oxidant	additive	solvent	<i>T</i> (°C)	time, h	yield of 233f , % ^a
1	PCC	-	DCM	25	120	26
2	PCC	py (3 equiv)	DCM	25	120	0
3	PCC	AcOH (3 equiv)	DCM	25	120	38
4	PCC	AcOH (3 equiv)	DCM	40	5	42
6	PCC	AcOH (5 equiv)	acetone	56	5	36
6	PCC	AcOH (3 equiv)	CH ₃ CN	81	8	52
7	PCC	AcOH (3 equiv)	toluene	111	0.5	50
8	PCC	AcOH (3 equiv)	DCE	84	1	56
9	PCC	AcOH (5 equiv)	DCE	84	0.25	61
10	PCC	AcOH (100 equiv)	DCE	84	0.25	54
11	PCC	TFA (1 equiv)	DCE	84	0.25	44
12	PCC	TfOH (1 equiv)	DCM	40	1	0 ^b
13	PCC	Ac ₂ O (6 equiv)	DCE	84	4	40
14	PDC	AcOH (5 equiv)	DCE	84	2	47
15	QDC	AcOH (5 equiv)	DCE	84	8	28
16	K ₂ Cr ₂ O ₇	1M H ₂ SO ₄	H ₂ O	25	2	0 ^c
17	CrO ₃	8M H ₂ SO ₄	acetone	25	2	0 ^c

^aIsolated yields, after purification by flash chromatography. ^bDecomposition of the starting material was observed. ^cHydrolysis of *O*-methyl hydroxamate to form the corresponding carboxylic acid was observed.

Having thus established optimized conditions, the scope of the Cr(VI)-mediated oxoamidation was examined. As summarized in Table 14, the scope of this oxidative cyclization is quite broad with a variety of 1,2- and trisubstituted alkenes undergoing cyclization. While hypervalent iodine-mediated oxamidations do, in some cases, generate mixtures of regioisomers arising from the opening of the intermediate aziridinium ion, the Cr(VI)-mediated methodology provides excellent regioselectivity. The *exo* products, i.e., those bearing an exocyclic keto group, are preferred. Using this methodology we were able to prepare pyrrolidinones, morpholinones and piperazinones **233b-y**. For tri- or tetrasubstituted alkenes, such as **181e**, cyclization proceeds only to form tertiary alcohols, as further oxidation is not possible without C-C bond cleavage. Cyclic substrates **181g-jj** were transformed into various bicyclic systems, including azabicyclo[2.2.2]octanes and azabicyclo[3.3.1]nonanes. For *O*-alkyl β -arylhydroxamates, azaspirocyclization was possible for electron-rich compounds bearing aromatic *ortho* and *para* methoxy groups. We note that the presence of strongly activating groups on the aromatic ring is crucial for the success of spirocyclization. Compounds with an unsubstituted phenyl ring, such as **181x**, exhibit a lack of reactivity under the standard reaction conditions.

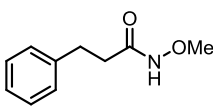
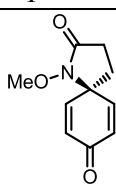
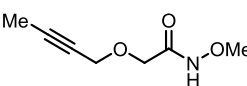
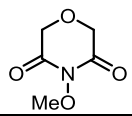
Although starting material was consumed, no product(s) were observed with 1,1-disubstituted olefin **181p**, suggesting that the primary alcohol product is prone to over-oxidation and decomposition under these conditions. Only starting material was recovered with **234**, which may be due to deactivation of the nitrenium ion by the electron-withdrawing nature of the carbamate. Also, no reaction was noted with unsaturated amides **236** and **238**, suggesting that the electron-donating *N*-OMe group is required for nitrenium ion generation.

Table 14. Scope of Cr(VI)-Mediated Hydroxamate Oxoamidation (*continued*)

entry	substrate		product		yield, % ^{a,b}
11		181h		233h	63
12		181i		233i	26
13		181j		233j	36
14		181jj		233jj	56
Styrenes					
15		181k		233k	59
16		181l		233l	63
17		181m		233m	68
18		181n		233n	45
Arylhydroxamates					
19		181r		219r	50
20		181s		219s	32

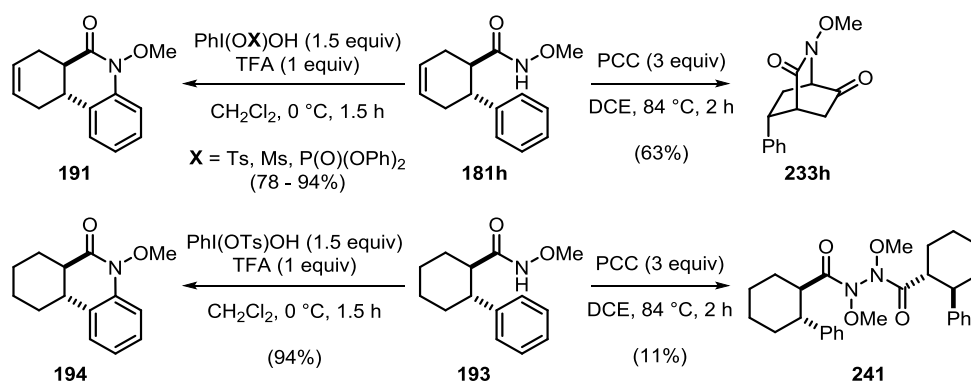
^aConditions: *O*-alkyl hydroxamate (1 equiv), PCC (3 equiv), AcOH (5 equiv), DCE (0.05 M), 84 °C, 0.25-2 h reaction time. ^bIsolated yields, after purification by flash chromatography.

Table 14. Scope of Cr(VI)-Mediated Hydroxamate Oxoamidation (*continued*)

entry	substrate		product		yield, % ^{a,b}
21		181x		233x	NR
<i>Alkynes</i>					
22		181z		240	31

^aConditions: *O*-alkyl hydroxamate (1 equiv), PCC (3 equiv), AcOH (5 equiv), DCE (0.05 M), 84 °C, 0.25-2 h reaction time. ^bIsolated yields, after purification by flash chromatography.

Notably, substrate **181h** smoothly underwent cyclization with PCC to provide ketone **233h** (Table 14, entry 11). Treatment of saturated hydroxamate **193** with 3 equivalents of PCC in the control experiment failed to generate the cyclized product with the arene moiety, providing hydrazine **241** in low yield. It seems that Cr(VI)-mediated oxoamidation, which is carried out at higher (84 °C) temperatures, can only take place with the more nucleophilic alkene system. The observed outcome reflects a distinct contrast to the transformation using hypervalent iodine-mediated reagents, which produce tetrahydrophenanthridine derivatives **191**, **194** (Scheme 62).

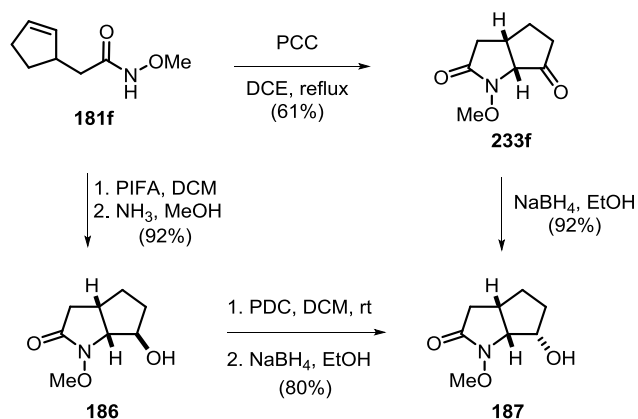


Scheme 62

Interestingly, reaction of substrate **181z** with PCC gave imide **240** as well as some hydrazine (Table 14, entry 22). In this case, cyclization required additional time for completion. We believe that upon cyclization, an addition-fragmentation process mediated by a chromate ester takes place, cleaving the carbon-carbon bond. In the next chapter we will discuss the possible mechanism of this cascade transformation.

Overall, this Cr(VI)-mediated methodology serves as a useful adjunct to our previous work featuring hypervalent iodine oxamidation (Scheme 63). Oxidative cyclization of **181f** by PIFA with subsequent hydrolysis of the trifluoroacetate group affords *trans* amido alcohol

186, which can be converted into its diastereomer **187** by an oxidation-reduction sequence. Alternatively, treatment of *O*-methyl hydroxamate **181f** with PDC yields 1,2-oxoamidation product **233f**, which can be reduced using NaBH₄ to generate *cis* α -hydroxyalkyl lactam **187** in diastereoselective fashion.

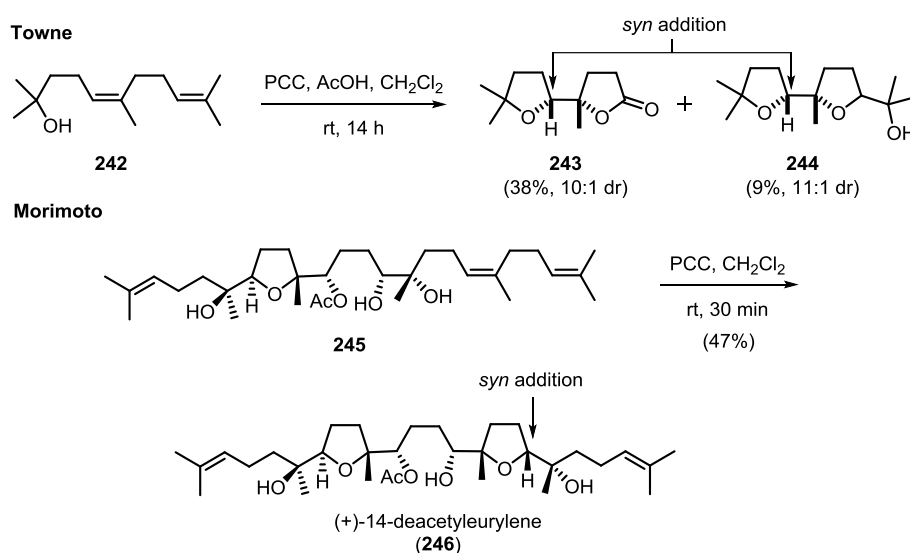


Scheme 63

1.9.2 Mechanistic Studies

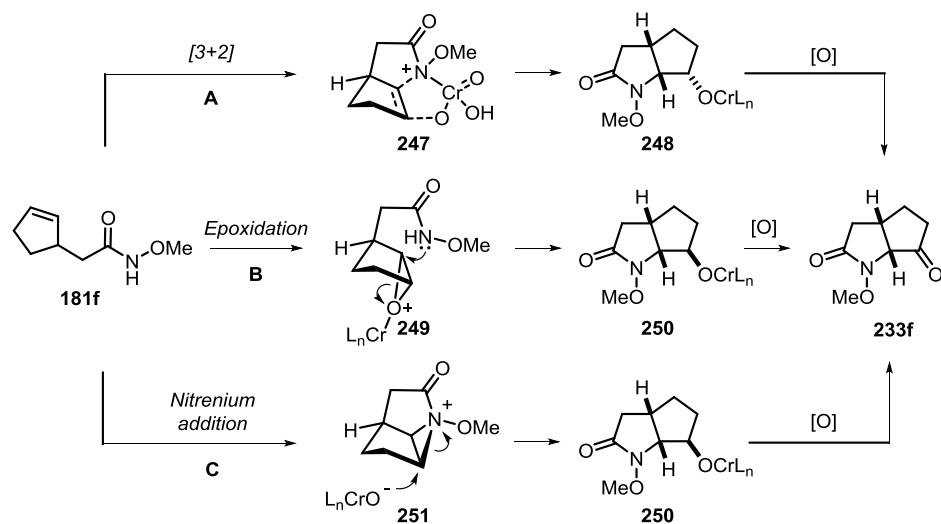
In this study, we sought to investigate the mechanism of Cr(VI)-mediated oxoamidation. Both PCC and PDC are known to mediate the oxidative cyclizations of bishomoallylic alcohols into tetrahydrofuran products¹³⁷ (Scheme 64) and, for alcohols bearing suitably positioned alkene groups, highly stereoselective generation of THF rings is feasible.¹³⁸ *Syn*-oxidative cyclization of a bishomoallylic diol induced by a chromium(VI) species was utilized by Morimoto and co-workers in their total synthesis of (+)-eurylene and (+)-14-deacetylene (246).¹³⁹ The authors hypothesized that the reaction proceeds *via* a chelated dialkoxochromium intermediate in order to account for the stereoselective formation of the THF ring. Wandell and co-workers performed a structure-reactivity study of this

process with bishomoallylic alcohols.¹⁴⁰ It was found that conformationally restricted alkenes are less reactive and attempts to generate 7-membered rings were ineffective. Perumal and co-workers employed PCC on silica gel to mediate a cyclization of *N*-phenolic and thiophenolic derivatives of aroylimines, generating a small library of 2-arylbenzothiazoles and 2-arylbenzoxazoles.¹⁴¹ In this process, the role of PCC was ascribed to aiding the aromatization step. To date, there are no reports concerning the formation of saturated *N*-heterocycles using Cr(VI) oxidants.



Scheme 64

Despite a number of experimental and theoretical studies on the addition of transition metal oxo compounds to olefins, a straightforward mechanistic rationale of this transformation is still unclear. Thus, drawing from known studies of metal-mediated oxidative cyclizations,¹⁴² we can propose three different pathways as illustrated in Scheme 65: a) [3+2] cycloaddition, b) epoxidation and ring closure, and c) a nitrenium-ion based mechanism.⁸⁵

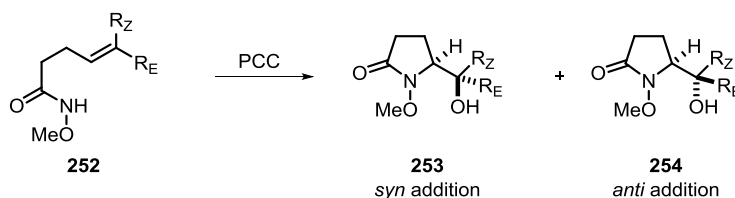


Scheme 65

It is recognized that the [3+2] cycloaddition, shown in pathway **A**, is often observed during metal-promoted aminohydroxylations¹⁶ and dihydroxylations.¹⁴³ Moreover, such oxidations are stereospecific for *syn*-addition of the two heteroatoms across the olefin giving intermediate **248**, which then oxidizes further to the corresponding ketone **233f**. In alternative pathway **B**, the transformation would proceed through Cr(VI)-mediated epoxidation of this alkene, which could react further to give the products ultimately observed. In this process, nucleophilic opening of the epoxide by the amide nitrogen would form *trans* intermediate **250**, which would then undergo oxidation to ketone **233f**. Pathway **C**, involving a singlet nitrenium ion, is also possible. Intermolecular cycloaddition would generate aziridinium ion **251**, which would then trap chromous acid to form *trans* intermediate **250**. Oxidation of the latter would afford the observed heterocycle **233f** featuring the vicinal ketoamino moiety.

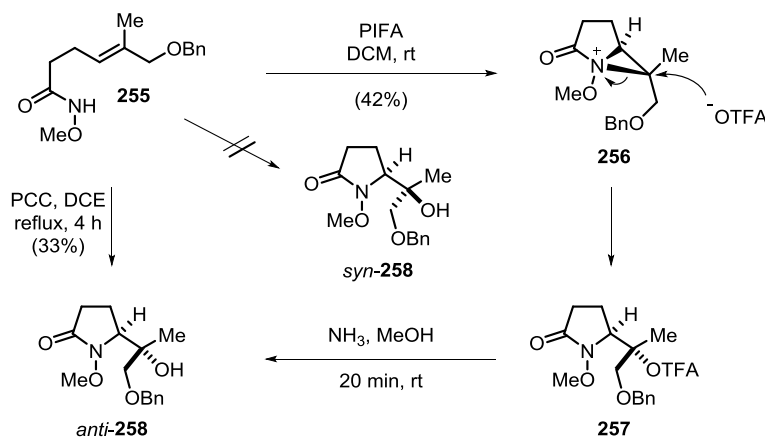
In order to elucidate the mechanism of this transformation and distinguish between pathways **A**, **B** and **C**, it was initially necessary to determine whether the formation of the C-N and C-O bonds proceeds with *syn* or *anti* selectivity. We envisioned that analysis of the

outcome of the oxoamidation of 1,1,2-trisubstituted alkenes, where $R_Z \neq R_E$, would potentially shed light on the possible reaction mechanism (Scheme 66).



Scheme 66

To pursue this approach, *O*-methyl hydroxamate **255** was prepared and submitted to the cyclization conditions (Scheme 67). Based on our earlier studies,⁸⁵ treatment of **255** with PIFA afforded 5-*exo* cyclization TFA-adduct **257**, where the regio- and stereoselective *anti* attack of trifluoroacetate occurred on the putative aziridinium ion **256**. Quenching with methanolic ammonia gave **258** as a single diastereomer. When **255** was treated with PCC in dichloroethane heated at reflux, the same diastereomer of **258** was obtained. Traces of benzyl group cleavage were also observed under these conditions.

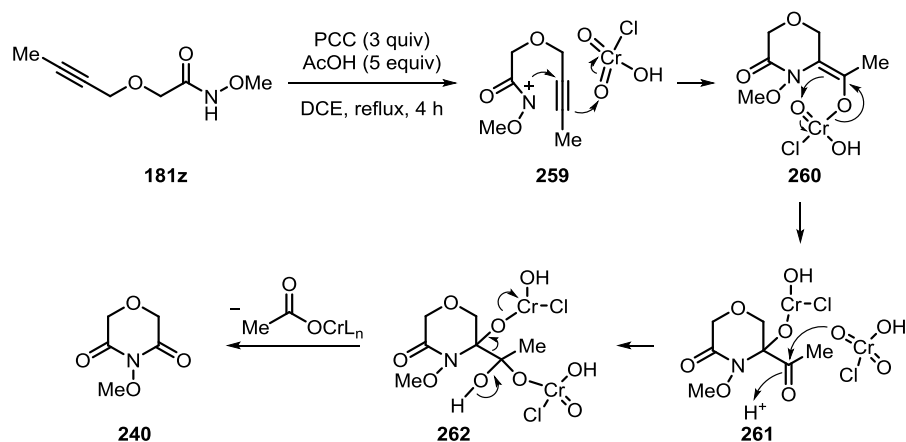


Scheme 67

These experimental results rule out pathway **A** on the basis of the formation of the *anti* diastereomer of **258** in both cases. Although some stronger Cr(VI) oxidants, such as Fieser's reagent (CrO₃ in AcOH/Ac₂O), can generate intermediate epoxides in reactions with alkenes, milder reagents, such as PCC, are generally unreactive under these conditions.¹⁴⁴ In addition, pathway **B** is unlikely due to the nucleophilic properties of *O*-alkyl hydroxamates. Entries 11-13 of Table 12 serve to illustrate that in reaction with epoxides, *O*-alkyl hydroxamates behave as *O*-nucleophiles rather than *N*-nucleophiles and so lactone formation would be the favored product of pathway **B**. As suggested by our earlier studies involving hypervalent iodine reagents, the formation of a *N*-methoxynitrenium ion is entirely feasible.⁶⁷ It is equally important to note that no conversion was observed for substrate **238** that lacks a methoxy group (Table 14, entry 8). Based on this accumulated evidence, we currently believe that Cr(VI)-mediated oxoamidation of unsaturated *O*-alkyl hydroxamates proceeds through Pathway **C**, i.e., *via* a nitrenium ion formation and addition.

The mechanism of the oxidative cyclization of hydroxamate **181z** to form imide **240** was also investigated (Scheme 68). Cr(VI) oxidants are known to oxidatively cleave tetrahydrofurfuryl alcohol derivatives to yield γ -butyrolactones when stirred under reflux in CH₂Cl₂ for 3-8 h.¹⁴⁵ More recently, Stark has reported a catalytic version of this process, utilizing 1 mol% PCC and 4 equivalents of H₅IO₆ in CH₃CN at 0 °C.¹⁴⁶ This transformation can be rationalized on the basis of the glycol cleavage or as an example of Criegee-type fragmentation of vicinal diols. In light of this literature precedent, it was rather surprising that no fragmentation product was detected during the preparation of tertiary alcohol **233e**, which was isolated in moderate yield (Table 14, entry 5). Given the findings of our current and previous study, we believe that formation of nitrenium ion **259** occurs through oxidation of

181z with PCC. A subsequent termolecular addition of nitrenium moiety and an oxochromium species across an alkyne would provide chromium enolate **260**. Then, following either intramolecular or intramolecular pathway, hemiaminal **261** is formed. Nucleophilic attack of chlorochromate on the carbonyl group in **261** would produce hemiacetal-like intermediate **262**. The latter, upon subsequent scission of C-C bond, would furnish the observed imide **240**.



Scheme 68

1.10. Conclusions

In summary, we have developed a set of methodologies for the regio- and stereoselective construction of 5 to 8-membered α -substituted lactams from unsaturated *O*-alkyl hydroxamates in the presence of iodine(III) or chromium(VI) oxidants. The intramolecular oxamidation of unsaturated *O*-alkyl hydroxamates provides easy access to various pyrrolidones, piperidinones, morpholinones, piperazinones and their bicyclic counterparts in good to excellent yields. Mechanistic studies suggest that these

transformations proceed *via* a nitrenium-ion mechanism and form the products of *anti* aminohydroxylation. The good functional group tolerance of these methods allows for their application in the synthesis of nitrogen-containing heterocycles found in a variety of natural products.

1.11. Experimental Procedures

1.11.1 General Procedures

All non-aqueous reactions were carried out in oven or flame-dried glassware under an atmosphere of dry nitrogen or argon, unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using Merck pre-coated silica gel plates with F₂₅₄ indicator. Visualization was accomplished by UV and/or potassium permanganate solution. Flash column chromatograph was performed using Silicycle Silica-P flash silica gel (40-63 μm). Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted.

1.11.2 Materials

Dichloromethane (DCM), purchased from Sigma-Aldrich, was additionally purified on PureSolv PS-400-4 by Innovative Technology, Inc. purification system. Acetonitrile (CH_3CN) and *N*-methylimidazole (NMI) were distilled from calcium hydride under an atmosphere of dry nitrogen. Acetic acid (AcOH) was distilled from phosphorus pentoxide under an atmosphere of dry nitrogen. 1,2-Dichloroethane (DCE) was distilled from and stored over activated 4Å molecular sieves. Pyridinium chlorochromate (PCC) was prepared according to the method of Corey and Suggs,¹³³ while pyridinium dichromate (PDC) was prepared according to the method of Corey and Schmidt.¹³⁵ Quinolinium dichromate (QDC) was prepared according to the method of Balasubramanian.¹³⁶ All other reagents and starting materials, unless otherwise noted, were purchased from commercial vendors and used without further purification.

1.11.3 Instrumentation

All melting points were determined in open Pyrex capillaries using a Thomas Hoover Unimelt melting point apparatus and are uncorrected. Infrared spectra were recorded as thin films on sodium chloride plates using an ATI Mattson Genesis Series IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 (400 MHz, ^1H , 100 MHz ^{13}C) or a Bruker Avance 500 (500 MHz ^1H , 125 MHz ^{13}C). Chemical shift values (δ) are reported in ppm relative to residual chloroform (δ 7.27 ppm for ^1H ; 77.00 ppm for ^{13}C), residual acetone (δ 2.05 ppm for ^1H ; 29.92 ppm for ^{13}C), residual methanol (δ 3.31 ppm for ^1H ; 49.15 ppm for ^{13}C) and residual DMSO (δ 2.50 ppm for ^1H ; 39.51 ppm for ^{13}C). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet) and br (broad). DEPT 135 and two-dimensional (COSY, HMQC, HMBC, NOESY) NMR experiments were employed, where appropriate, to aid in the assignment of signals in the ^1H NMR spectra. High-resolution electron spray ionization mass spectra (HRMS-ESI) were obtained on a Micromass Q-TOF 2 at the University of Illinois Research Resources Center or on a Micromass Q-TOF Ultima at the Mass Spectroscopy Laboratory at the University of Illinois, Urbana-Champaign.

1.11.4 Literature Preparations

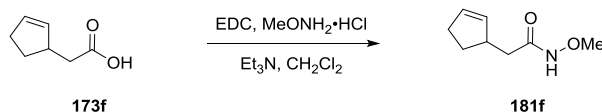
5-Methylhex-4-enoic acid (**173e**), (*E*)-5-phenylpent-4-enoic acid (**173k**), (*E*)-5-(4-bromophenyl)pent-4-enoic acid (**173l**), (*E*)-5-(4-trifluoromethylphenyl)pent-4-enoic acid (**173m**), (*E*)-5-(4-methoxyphenyl)pent-4-enoic acid (**173o**) and (*E*)-4-methylhex-4-enoic acid (**173y**) were prepared by the method of Johnson.⁸⁸ 2-Allylbenzoic acid (**173a**),⁸⁶ (1*R**,6*R**)-6-phenylcyclohex-3-enecarboxylic acid (**173h**),⁹² cyclohex-3-enecarboxylic acid (**173g**),⁹⁰ 2-

(cinnamyloxy)acetic acid (**173n**),⁹³ 2-(but-2-yn-1-yloxy)acetic acid (**173z**)⁹⁴ and pent-4-enamide (**236**)¹⁴⁷ were prepared according to literature methods.

1.11.5 Preparation of Cyclization Substrates

Representative Procedure 1. Preparation of *O*-Alkyl Hydroxamates (EDC)

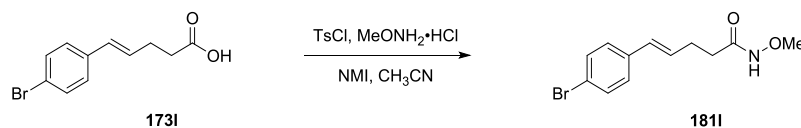
(±)-*O*-Methyl 2-(cyclopent-2-enyl)-acetohydroxamate (**181f**)



To a solution of **173f** (750 mg, 5.94 mmol, 1.0 equiv) in CH₂Cl₂ (8.0 mL) was added Et₃N (1.33 mL, 9.50 mmol, 1.6 equiv) and the mixture stirred for 5 min. EDC (2.05 g, 10.69 mmol, 1.8 equiv) and MeONH₂·HCl (793 mg, 9.50 mmol, 1.6 equiv) were then added in one portion. After 10 h, aqueous HCl (1 M, 20 mL) was added and the aqueous phase extracted with EtOAc (4 x 15 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue purified by flash chromatography on silica gel (EtOAc) to provide **181f** (921 mg, 99%) as a colorless oil; *R*_f 0.33 (EtOAc); IR (film) ν_{max} 3180, 2940, 1659, 1518, 1361, 1191, 982, 943, 697 cm⁻¹; ¹H NMR (CD₃OD, 500 MHz): δ 5.82-5.74 (m, 1 H), 5.70-5.62 (m, 1 H), 3.68 (s, 3 H), 3.09-3.02 (m, 1 H), 2.44-2.34 (m, 1 H), 2.34-2.24 (m, 1 H), 2.14 (dd, *J* = 13.8, 6.9 Hz, 1 H), 2.11-2.04 (m, 1 H), 2.02 (dd, *J* = 13.8, 8.2 Hz, 1 H), 1.48 (ddt, *J* = 12.6, 9.0, 6.2 Hz, 1 H); ¹³C NMR (CD₃OD, 125 MHz): δ 170.3, 133.2, 131.0, 62.9, 42.3, 38.4, 31.2, 28.9; HRMS-ESI calcd for C₈H₁₃NO₂Na [M+Na]⁺ 178.0844, found: 178.0840.

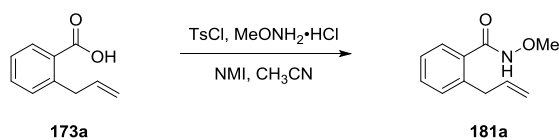
Representative Procedure 2. Preparation of *O*-Alkyl Hydroxamates (TsCl/NMI)

O-Methyl (*E*)-5-(4-bromophenyl)-pent-4-enohydroxamate (**181I**)



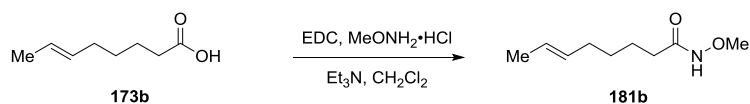
A mixture of compound **173I** (1.91 g, 10.8 mmol, 1.0 equiv) and *N*-methylimidazole (3.1 mL, 33.4 mmol, 3.0 equiv) in CH₃CN (20 mL) was cooled to 0 °C and then treated with a solution of TsCl (2.48 g, 13 mmol, 1.2 equiv) in CH₃CN (10 mL) *via* cannula. The reaction mixture was stirred for 30 min in an ice bath and then a solution of MeONH₂•HCl (1.1 g, 13.0 mmol, 1.02 equiv) in CH₃CN and *N*-methylimidazole (1.0 mL, 10.0 mmol, 1.0 equiv) was added *via* cannula. After warming to rt, the reaction was stirred for 2 h and then concentrated and the residue purified by flash chromatography on silica gel (EtOAc/hexanes, 1:1) to provide **181I** (1.81 g, 82%) as a white solid; mp 102-104 °C (EtOAc/hexanes); *R*_f 0.16 (EtOAc/hexanes, 1:1); IR (film) ν_{max} 3220, 3010, 2974, 2934, 2894, 1653, 1523, 1485, 1441, 1076, 970, 806 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.41 (d, *J* = 8.4 Hz, 2 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 6.41 (d, *J* = 15.8, 1H), 6.24 (dt, *J* = 6.9, 15.8 Hz, 1 H), 3.65 (s, 3 H), 2.49 (dd, *J* = 6.9, 7.2 Hz, 2 H), 2.23 (t, *J* = 7.2 Hz, 2 H); ¹³C NMR (CDCl₃, 125 MHz): δ 171.9, 138.1, 132.8, 131.4, 130.4, 129, 121.8, 64.5, 33.5, 29.9; HRMS-ESI calcd for C₁₂H₁₅NO₂Br [M+H]⁺ 284.0286, found: 284.0285.

O-Methyl 2-allylphenylhydroxamate (**181a**)



Following Representative Procedure 2, a mixture of compound **173a** (360 mg, 2.2 mmol, 1.0 equiv) and *N*-methylimidazole (0.53 mL, 6.7 mmol, 3.0 equiv) in CH₃CN (10 mL) was treated with a solution of TsCl (510 mg, 2.7 mmol, 1.2 equiv) in CH₃CN (5 mL) at 0 °C. After 1 h, a solution of MeONH₂•HCl (189 mg, 2.3 mmol, 1.02 equiv) in CH₃CN (5 mL) and *N*-methylimidazole (0.18 mL, 2.2 mmol, 1.0 equiv) was added and the reaction mixture warmed to rt. The reaction was concentrated after 2 h and the residue purified by flash chromatography on silica gel (EtOAc/hexanes, 1:2) to provide **181a** (424 mg, 82%) as a white solid; mp 85-87 °C (EtOAc/hexanes); *R*_f 0.50 (EtOAc); IR (film) ν_{max} 3129, 2936, 2822, 1632, 1576, 1531, 1443, 1317, 1162, 1039, 902, 747, 687 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 8.40 (br. s., 1H), 7.37-7.44 (m, 2H), 7.24-7.30 (m, 2H), 6.01 (ddt, *J* = 16.9, 10.3, 6.4 Hz, 1H), 5.10 (d, *J* = 10.3 Hz, 1H), 5.03 (d, *J* = 16.9 Hz, 1H), 3.90 (br. s., 3H), 3.58 (d, *J* = 6.4 Hz, 2H); ¹³C NMR (CDCl₃, 126 MHz): δ 169.2, 138.4, 137.3, 132.6, 130.8, 130.6, 127.7, 126.4, 116.4, 64.7, 37.3; HRMS-ESI calcd for C₁₁H₁₄NO₂ [M+H]⁺ 192.1025, found: 192.1017.

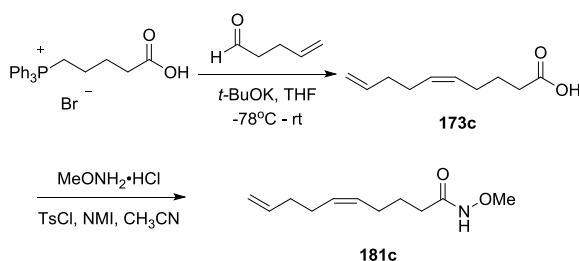
***O*-Methyl (*E*)-oct-6-enohydroxamate (181b)**



Following Representative Procedure 1, a solution of **173b** (1.00 g, 7.04 mmol, 1.0 equiv) in CH₂Cl₂ (6.0 mL) was treated sequentially with Et₃N (1.56 mL, 11.3 mmol, 1.6 equiv), EDC (2.44 g, 12.7 mmol, 1.8 equiv) and MeONH₂•HCl (940 mg, 11.3 mmol, 1.6 equiv) to provide **181b** (910 mg, 76%) as a colorless oil; *R*_f 0.55 (EtOAc); IR (film) ν_{max} 3181, 2934, 2856, 1657, 1515, 1439, 1376, 1059, 967 cm⁻¹; ¹H NMR (CD₃OD, 500 MHz): δ 5.48-5.36 (m, 2 H), 3.67 (s, 3 H), 2.06 (t, *J* = 7.5 Hz, 2 H), 2.02-1.96 (m, 2 H), 1.63 (d, *J* = 4.8 Hz, 3 H), 1.60

(p, $J = 7.5$ Hz, 2 H), 1.36 (p, $J = 7.5$ Hz, 2 H); ^{13}C NMR (CD_3OD , 125 MHz): δ 171.7, 131.0, 125.2, 63.3, 32.6, 32.2, 29.0, 25.1, 17.1; HRMS-ESI calcd for $\text{C}_9\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 172.1338, found: 172.1342.

***O*-Methyl (Z)-deca-5,9-dienenohydroxamate (181c)**

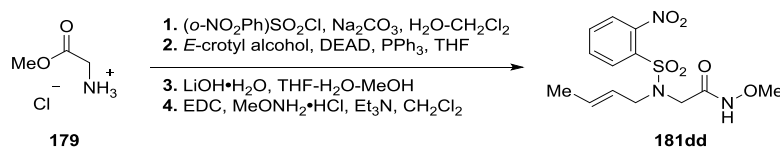


173c: To a stirred solution of 4-(carboxybutyl)triphenylphosphonium bromide (14.80 g, 33.5 mmol, 1.5 equiv) in THF (100 mL) was added a solution of *tert*-BuOK (7.90 g, 70.4 mmol, 3.1 equiv) in THF (100 mL) *via* cannula. The reaction was heated at reflux for 2 h, cooled to -78°C and a cold (-78°C) solution of 4-pentenal (2.2 mL, 22.3 mmol, 1.0 equiv) in THF (20 mL) transferred to the phosphonium ylide solution *via* dry ice-packed cannula. The reaction mixture was allowed to slowly warm to rt over 16h and then quenched with H_2O (20 mL), acidified to pH 5 using 1N HCl and concentrated to approximately 60 mL under reduced pressure. The biphasic mixture was treated with 10% aqueous Na_2CO_3 (150 mL) and extracted with toluene (100 mL). The aqueous layer was cooled in an ice bath and acidified to pH 2 with concentrated HCl, then extracted with EtOAc (3 x 200 mL). The combined organic extracts were dried over Na_2SO_4 , concentrated *in vacuo* and purified by flash chromatography (EtOAc/hexanes, 1:4) to provide **173c** (3.10 g) as a mixture of geometric isomers [*Z/E*, 41:1]: colorless oil; R_f 0.12 (EtOAc/hexanes, 1:4); IR (film) ν_{max} 3100 (br), 3076, 3006, 2933, 1710, 1641, 1437, 1415, 1243, 1204, 1163, 913 cm^{-1} ; ^1H NMR (CD_3OD , 400 MHz): δ 11.1 (br s, 1 H), 5.87-5.77 (m, 1 H), 5.46-5.33 (m, 2 H), 5.05-4.95 (m, 2 H),

2.37 (dd, $J = 7.5, 7.5$ Hz, 2 H), 2.14-2.08 (m, 6 H), 1.75-1.67 (ddd, $J = 7.5, 7.5, 15.0$ Hz, 2 H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 180.4, 138.5, 130.5, 128.9, 114.9, 34.0, 33.6, 26.9, 26.7, 24.7; HRMS-ESI calcd for $\text{C}_{10}\text{H}_{15}\text{O}_2$ $[\text{M}-\text{H}]^-$ 167.1072, found: 167.1069.

181c: Following Representative Procedure 2, a mixture of compound **173c** (870 mg, 5.2 mmol, 1.0 equiv) and *N*-methylimidazole (1.25 mL, 15.6 mmol, 3.0 equiv) in CH_3CN (10 mL) was treated with a solution of TsCl (1.18 g, 6.2 mmol, 1.2 equiv) in CH_3CN (5 mL) at 0 °C. After 1 h, a solution of $\text{MeONH}_2\cdot\text{HCl}$ (440 mg, 5.3 mmol, 1.02 equiv) in CH_3CN (5 mL) and *N*-methylimidazole (0.41 mL, 5.3 mmol, 1.0 equiv) was added and the reaction mixture warmed to rt. The reaction was concentrated after 2 h and the residue purified by flash chromatography on silica gel (EtOAc/hexanes, 1:4) to provide **181c** (990 mg, 97%) as a colorless oil; R_f 0.16 (EtOAc/hexanes, 1:4); IR (film) ν_{max} 3181 (br), 3077, 3002, 2935, 2863, 1659, 1528, 1439, 1082, 912 cm^{-1} ; ^1H NMR (CD_3CN , 500 MHz): δ 9.92 (br s, 1 H), 5.85-5.77 (m, 1 H), 5.43-5.33 (m, 2 H), 5.01 (dd, $J = 17.1, 1.9$ Hz, 1 H), 4.94 (dd, $J = 10.2, 1.14$ Hz, 1 H), 3.64 (s, 3 H), 2.12-2.02 (m, 8 H), 1.61 (ddd, $J = 7.35, 7.35, 14.7$ Hz, 2 H); ^{13}C NMR (CD_3CN , 125 MHz): δ 170.2, 138.5, 129.8, 129.1, 114.3, 63.3, 33.6, 32.0, 26.4, 26.3, 25.2; HRMS-ESI calcd for $\text{C}_{11}\text{H}_{19}\text{NO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 220.1313, found: 220.1321.

***O*-Methyl (*E*)-2-(*N*-(but-2-enyl)-2-nitrophenylsulfonamido)acetohydroxamate (181dd)**



Step 1: To a stirred biphasic mixture of Na_2CO_3 (33.8 g, 318 mmol, 2.4 equiv) in H_2O (100 mL) and CH_2Cl_2 (200 mL) at room temperature was sequentially added methyl glycine hydrochloride (**179**) (20.0 g, 159 mmol, 1.2 equiv) and *o*-nitrobenzenesulfonyl chloride (29.4 g, 133 mmol, 1.0 equiv). After 6 h, the contents were acidified with 6 N HCl (100 mL) then

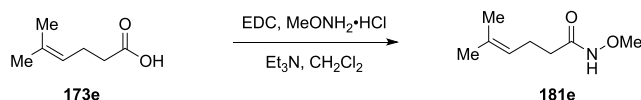
extracted with CH₂Cl₂ (4 x 100 mL). The combined organic extracts were then washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduced pressure to yield an off-white solid. This material was recrystallized from EtOH to provide ethyl 2-(2-nitrosulphonamido)acetate (39.7 g, 91%) as a white solid.

Step 2: To a cooled (0 °C) solution of methyl 2-(2-nitrosulphonamido)acetate (387 mg, 1.41 mmol, 1.0 equiv), PPh₃ (444 mg, 1.69 mmol, 1.2 equiv) and *E*-crotyl alcohol (122 mg, 1.69 mmol, 1.2 equiv) in THF (10 mL) was added over 5 min, *via* cannula, DEAD (295 mg, 1.69 mmol, 1.2 equiv) in THF (2 mL). The reaction mixture was warmed to rt and stirred for 24 h before the volatile components were removed under reduced pressure. The residual oil was purified by flash chromatography (EtOAc/hexanes, 1:2) to yield methyl (*E*)-*N*-(but-2-en-1-yl)-*N*-((2-nitrophenyl)sulfonyl)glycinate (462 mg, 99%): *R*_f = 0.57 (EtOAc/hexanes, 1:1); ¹H NMR (CDCl₃, 500 MHz): δ 8.12-8.06 (m, 1 H), 7.73-7.67 (m, 2 H), 7.67-7.61 (m, 1 H), 5.68-5.60 (m, 1 H), 5.39-5.31 (m, 1 H), 4.13 (s, 2 H), 3.96 (d, *J* = 6.9 Hz, 2 H), 3.65 (s, 3 H), 1.70-1.63 (m, 3 H); ¹³C NMR (CDCl₃, 125 MHz): δ 169.3, 147.8, 133.5, 132.3, 131.7, 130.8, 124.4, 124.2, 52.1, 50.3, 46.7, 17.6.

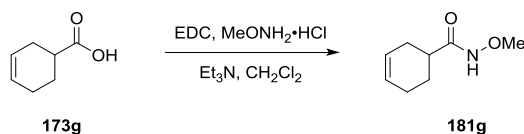
Step 3: To a stirred solution of methyl (*E*)-*N*-(but-2-en-1-yl)-*N*-((2-nitrophenyl)sulfonyl)glycinate (1.60 g, 4.87 mmol, 1.0 equiv) in THF/H₂O/MeOH (3:2:1) at rt, was added LiOH•H₂O (220 mg, 5.36 mmol, 1.1 equiv). The yellowish solution was then stirred for 40 min until the starting material had been consumed. Upon completion, the solution was poured into 30 mL of 1N HCl and extracted with CH₂Cl₂ (4 x 15 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide **173dd** (1.49 g) as an off-white solid, which was used in the next step without further purification.

Step 4: Following Representative Procedure 1, a solution of **173dd** (1.49 g, 4.74 mmol, 1.0 equiv) in CH₂Cl₂ (80.0 mL) was treated sequentially with Et₃N (700 μ L, 4.97 mmol, 1.05 equiv), EDC (1.0 g, 5.21 mmol, 1.1 equiv) and MeONH₂•HCl (455 mg, 5.45 mmol, 1.15 equiv) to provide, after work-up and purification by flash chromatography (acetone/hexanes, 1:1), **181dd** (1.12 g, 68%, 2 steps) as a white solid; mp 111-113 °C (EtOAc/hexanes); R_f 0.45 (acetone/hexanes, 1:1); IR (film) ν_{\max} 3216, 2938, 1657, 1590, 1544, 1348, 1085, 974, 765 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 8.09 (d, J = 6.1 Hz, 1 H), 7.78-7.63 (m, 3 H), 5.77-5.65 (m, 1 H), 5.41-5.32 (m, 1 H), 4.01-3.88 (m, 4 H), 3.68 (br. s., 3 H), 1.67 (d, J = 6.2 Hz, 3 H); ¹³C NMR (CDCl₃, 125 MHz): δ 165.4, 147.9, 134.1, 133.3, 132.3, 132.1, 131.1, 124.3, 123.7, 64.4, 51.4, 47.4, 17.7; HRMS-ESI calcd for C₁₃H₁₈N₃O₆S [M+H]⁺ 344.0916, found: 344.0914.

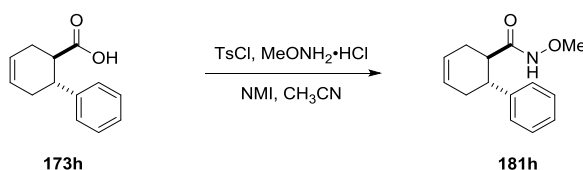
***O*-Methyl 5-methyl-hex-4-enohydroxamate (181e)**



Following Representative Procedure 1, a solution of **173e** (510 mg, 3.97 mmol, 1.0 equiv) in CH₂Cl₂ (5.0 mL) was treated sequentially with Et₃N (893 μ L, 6.36 mmol, 1.6 equiv), EDC (1.37 g, 7.16 mmol, 1.8 equiv) and MeONH₂•HCl (531 mg, 6.36 mmol, 1.6 equiv) to provide **181e** (624 mg, 99%) as a colorless oil; R_f 0.41 (EtOAc); IR (film) ν_{\max} 3147, 2975, 2927, 1649, 1520, 1444, 1384, 1057, 985, 936, 829, 668 cm⁻¹; ¹H NMR (CD₃OD, 400 MHz): δ 5.05-5.03 (m, 1H), 3.64 (s, 3H), 2.28-2.25 (m, 2H), 2.05 (t, J = 7.2, 2H), 1.66 (s, 3H), 1.61 (s, 3H); ¹³C NMR (CD₃OD, 100 MHz): δ 170.0, 131.8, 120.9, 61.6, 31.1, 23.1, 22.3, 14.9; HRMS-ESI calcd for C₈H₁₅NO₂Na [M+Na]⁺ 180.1000, found: 180.0999.

(±)-O-Methyl cyclohex-3-enecarbohydroxamate (181g)

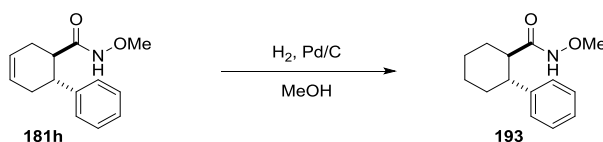
Following Representative Procedure 1, a solution of **173g** (1.00 g, 7.93 mmol, 1.0 equiv) in CH_2Cl_2 (11.0 mL) was treated sequentially with Et_3N (1.78 mL, 12.7 mmol, 1.6 equiv), EDC (2.73 g, 14.2 mmol, 1.8 equiv) and $\text{MeONH}_2\cdot\text{HCl}$ (1.06 g, 12.7 mmol, 1.6 equiv) to provide **181g** (1.15 g, 93%) as a white solid; mp 68-69 °C (EtOAc/hexanes); R_f 0.43 (EtOAc); IR (film) ν_{max} 3164, 2930, 1655, 1516, 1444, 1087, 1944, 918, 744, 650 cm^{-1} ; ^1H NMR (CD_3OD , 400 MHz): δ 5.71-5.56 (m, 2 H), 3.68 (s, 3 H), 2.33-2.12 (m, 2 H), 2.12-1.93 (m, 3 H), 1.83-1.69 (m, 1 H), 1.69-1.54 (m, 1 H); ^{13}C NMR (CD_3OD , 100 MHz): δ 175.7, 127.6, 126.3, 64.4, 39.4, 28.8, 26.8, 25.8; HRMS-ESI calcd for $\text{C}_8\text{H}_{13}\text{NO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 178.0844, found: 178.0836.

(±)-O-Methyl *trans*-6-phenylcyclohex-3-enehydroxamate (181h)

Following Representative Procedure 2, to a solution of **173h** (5.0 g, 24.72 mmol, 1.0 equiv) in CH_3CN (85 mL) was added *N*-methylimidazole (6.09 g, 74.16 mmol, 3.0 equiv) and TsCl (5.65 g, 29.66 mmol, 1.2 equiv) at 0 °C. After 1 h, $\text{MeONH}_2\cdot\text{HCl}$ (2.06 g, 24.72 mmol, 1.0 equiv) and *N*-methylimidazole (2.03 g, 24.72 mmol, 1.0 equiv) were added and allowed to warm to rt. After 1.5 h, reaction mixture was concentrated *in vacuo*, purified by flash chromatography (EtOAc/hexanes, 1:1) and recrystallized from EtOAc to provide **181h** (2.4 g, 73%) as a white solid; mp 142-144 °C (EtOAc); R_f 0.66 (EtOAc); IR (film) ν_{max} 3179,

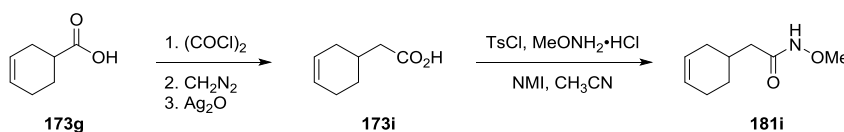
3026, 3000, 2972, 2904, 2839, 1649, 1435, 1059, 835, 758, 702, 662 cm^{-1} ; ^1H NMR (CD_3OD , 400 MHz): δ 7.26-7.00 (m, 5 H), 5.71 (s, 2 H), 4.59 (br. s., 1 H), 3.04 (s, 3 H), 2.91 (td, J = 8.4, 10.8 Hz, 1 H), 2.57-2.33 (m, 2 H), 2.26-2.19 (m, 2 H), 2.18-2.10 (m, 1 H); ^{13}C NMR (CD_3OD , 100 MHz): δ 173.5, 144.8, 129.5 (2 C), 129.2 (2 C), 127.8, 127.6, 126.2, 64.0, 45.4, 44.3, 34.8, 30.3; HRMS-ESI calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 232.1332, found: 232.1329.

(\pm)-*O*-Methyl *trans*-2-phenylcyclohexanecarboxamate (193)



A mixture of **181h** (120 mg, 0.52 mmol) and 10% Pd/C (6 mg, 0.05 mmol) in MeOH (50 mL) was stirred under 1 atm of H_2 for 4 h. Filtration of the mixture through a pad of Celite followed by concentration provided **193** (117 mg, 97%) as a white solid; mp 130-132 $^\circ\text{C}$ (EtOAc); R_f 0.67 (EtOAc); IR (film) ν_{max} 3161, 3006, 2925, 2853, 1652, 1525, 1492, 1382, 1060, 953, 704, 652 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 8.69 (br. s., 1H), 7.13-7.28 (m, 5H), 3.23 (s, 3H), 2.82 (t, J = 10.3 Hz, 1H), 2.15 (t, J = 10.3 Hz, 1H), 1.72-1.94 (m, 5H), 1.32-1.56 (m, 3H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 172.1, 144.3, 128.3, 127.4, 126.4, 63.5, 48.6, 46.4, 33.6, 29.4, 26.0, 25.2; HRMS-ESI calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 234.1494, found: 234.1492.

(\pm)-*O*-Methyl 2-(cyclohex-3-enyl)-acetohydroxamate (181i)

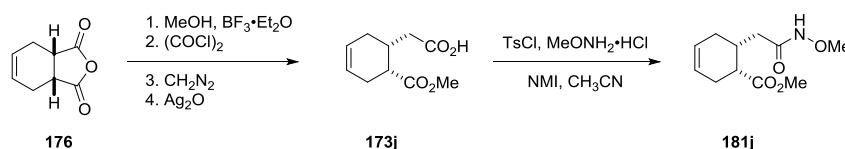


173i: Cyclohex-3-enecarboxylic acid (**173g**) (2.0 g, 15.9 mmol, 1.0 equiv) was dissolved in dry benzene (15 mL) and oxalyl chloride (2.7 mL, 31.8 mmol, 2 equiv) was slowly added at rt. DMF (200 μ L) was then added dropwise and the reaction was stirred for 2 h. The reaction was then concentrated *in vacuo* and dissolved in ether (30 mL) and slowly added to a cold solution of diazomethane in ether (0.5M, 150 mL, 75 mmol, 4.7 equiv). The reaction mixture was left overnight. After removal of ether *in vacuo*, the dark orange residue was dissolved in a mixture of dioxane and water (100 mL, 4:1) and sonicated with freshly prepared silver oxide (370 mg, 1.6 mmol, 0.1 equiv) for 1 h. The black suspension was then filtered, concentrated *in vacuo* and the product separated by flash chromatography (EtOAc/hexanes, 1:1) to provide **173i** (1.5 g, 68%) as a white solid; mp 50-52 °C (EtOAc/hexanes); ^1H NMR (CDCl_3 , 500 MHz): δ 5.70-5.61 (m, 2 H), 2.33 (d, J = 7.3 Hz, 2 H), 2.22-2.06 (m, 4 H), 1.83-1.73 (m, 2 H), 1.38-1.30 (m, 1 H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 179.7, 126.8, 125.6, 40.8, 31.2, 30.4, 28.3, 24.6.

181i: Following Representative Procedure 2, a mixture of compound **173i** (1.5 g, 10.7 mmol, 1.0 equiv) and *N*-methylimidazole (2.64 mL, 32.1 mmol, 3.0 equiv) in CH_3CN (50 mL) was treated with a solution of TsCl (2.65 g, 13.9 mmol, 1.3 equiv) in CH_3CN (20 mL) at 0 °C. After 1 h, a solution of $\text{MeONH}_2\cdot\text{HCl}$ (1.07 g, 2.0 mmol, 1.2 equiv) in CH_3CN (15 mL) and *N*-methylimidazole (0.88 mL, 10.8 mmol, 1.0 equiv) was added and the reaction mixture warmed to rt. The reaction was concentrated after 2 h and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:1) to provide **181i** (1.81 g, 89%) as a colorless oil; R_f 0.41 (EtOAc); IR (film) ν_{max} 3160, 3024, 2914, 1643, 1627, 1451, 1372, 1081, 1038, 938, 643 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 8.77 (br. s., 1 H), 5.64 (d, J = 13.4 Hz, 2 H), 3.76 (br. s., 3 H), 2.14 (br. s., 3 H), 2.05 (br. s., 3 H), 1.76 (br. s., 2 H), 1.30

(br. s., 1 H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 170.2, 126.8, 125.6, 64.4, 39.8, 31.2, 30.8, 28.3, 24.6; HRMS-ESI calcd for $\text{C}_9\text{H}_{16}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 170.1181, found: 170.1181.

(\pm)-Methyl *cis*-6-(2-(methoxyamino)-2-oxyethyl)-cyclohex-3-enecarboxylate (181j**)**



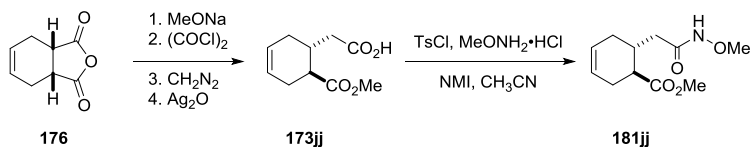
177: To a well stirred solution of *cis*-1,2,3,6-tetrahydrophthalic anhydride (**176**) (5.0 g, 33 mmol, 1.0 equiv) in methanol (20 mL, 494 mmol, 15 equiv), $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2.0 mL, 16 mmol, 0.5 equiv) was added dropwise. After 2 h, starting material was consumed and a saturated solution of Na_2CO_3 (60 mL) was added. Traces of starting material were removed by ether extraction (3 x 60 mL). The aqueous layer was neutralized with concentrated HCl at 0 °C and extracted with ether (3 x 60 mL). The organic extracts were washed with brine (3 x 60 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give **177** (6.0 g, 100%) as a white solid; ^1H NMR (CDCl_3 , 400 MHz): δ 5.69 (s, 2 H), 3.70 (s, 3 H), 3.12-3.03 (m, 2 H), 2.64-2.53 (m, 2 H), 2.43-2.32 (m, 2 H); ^{13}C NMR (CDCl_3 , 101 MHz): δ 179.3, 173.7, 125.1, 125.0, 51.9, 39.5, 39.4, 25.7, 25.5.

173j: Compound **177** (2.0 g, 10.9 mmol, 1.0 equiv) was dissolved in dry benzene (15 mL) and oxalyl chloride (1.9 mL, 21.7 mmol, 2 equiv) was slowly added at rt. DMF (200 μL) was then added dropwise and the reaction stirred for 2 h. The reaction was then concentrated *in vacuo* and dissolved in ether (30 mL) and slowly added to a cold solution of diazomethane in ether (0.5M, 100 mL, 50 mmol, 4.5 equiv). The reaction mixture was left overnight. After removal of ether *in vacuo*, the dark orange residue was dissolved in a mixture of dioxane and water (100 mL, 4:1) and sonicated with freshly prepared silver(I) oxide (252 mg, 1.1 mmol, 0.1 equiv) for 1 h. The black suspension was then filtered, concentrated *in vacuo* and the

product separated by flash chromatography (EtOAc/hexanes, 1:1) to provide **173j** (950 mg, 44%) as a colorless oil; ^1H NMR (CDCl_3 , 500 MHz): δ 5.78-5.54 (m, 2 H), 3.68 (s, 3 H), 2.78 (dt, $J = 3.1, 7.2$ Hz, 1 H), 2.68-2.61 (m, 1 H), 2.48 (dd, $J = 4.7, 16.3$ Hz, 1 H), 2.40 (dd, $J = 9.3, 16.3$ Hz, 1 H), 2.32-2.24 (m, 3 H), 2.11-2.03 (m, 1 H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 178.9, 174.5, 124.9, 124.8, 51.6, 41.5, 34.7, 30.4, 29.6, 24.9.

181j: Following Representative Procedure 2, a mixture of compound **173j** (590 mg, 3.0 mmol, 1.0 equiv) and *N*-methylimidazole (0.74 mL, 9.0 mmol, 3.0 equiv) in CH_3CN (20 mL) was treated with a solution of TsCl (740 mg, 3.9 mmol, 1.3 equiv) in CH_3CN (10 mL) at 0 °C. After 1 h, a solution of $\text{MeONH}_2\cdot\text{HCl}$ (300 mg, 3.6 mmol, 1.2 equiv) in CH_3CN (5 mL) and *N*-methylimidazole (0.25 mL, 3.0 mmol, 1.0 equiv) was added and the reaction mixture warmed to rt. The reaction was concentrated after 2 h and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:1) to provide **181j** (657 mg, 97%) as a white solid; mp 66-68 °C (EtOAc/hexanes); R_f 0.39 (EtOAc); IR (film) ν_{max} 3155, 2992, 1842, 1729, 1633, 1528, 1434, 1339, 1183, 1044, 930, 678 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 8.91 (br. s., 1 H), 5.73-5.53 (m, 2 H), 3.74 (br. s., 3 H), 3.67 (s, 3 H), 2.79-2.73 (m, 1 H), 2.64 (br. s., 1 H), 2.34-1.97 (m, 6 H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 174.8, 170.1, 125.1, 124.7, 64.3, 51.6, 41.4, 34.3, 31.3, 29.3, 25.2; HRMS-ESI calcd for $\text{C}_{11}\text{H}_{18}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 228.1236, found: 228.1231.

(±)-Methyl *trans*-6-(2-(methoxyamino)-2-oxyethyl)-cyclohex-3-enecarboxylate (181jj)



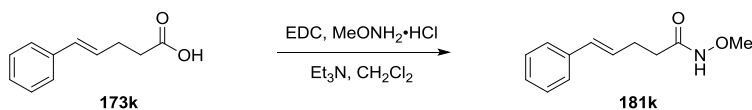
178: Sodium (1.4 g, 61 mmol, 1.5 equiv) was dissolved in dry methanol (100 mL) at rt. *Cis*-1,2,3,6-tetrahydrophthalic anhydride (**176**) (5.0 g, 41 mmol, 1.0 equiv) was then added in one portion and the reaction mixture was heated at reflux for 3 h. Upon completion, the reaction was cooled, diluted with H₂O (100 mL) and neutralized with concentrated HCl at 0 °C. The aqueous layer was extracted with ether (3 x 60 mL). The organic extracts were washed with brine (3 x 60 mL), dried over Na₂SO₄ and concentrated *in vacuo* to give **178** (6.0 g, 100%) as a white solid; ¹H NMR (CDCl₃, 500 MHz): δ 5.58 (s, 2 H), 3.59 (s, 3 H), 2.98 (d, *J* = 6.3 Hz, 2 H), 2.48 (d, *J* = 16.8 Hz, 2 H), 2.27 (d, *J* = 16.8 Hz, 2 H); ¹³C NMR (CDCl₃, 126 MHz): δ 179.4, 173.4, 124.8, 124.7, 51.6, 39.2, 39.1, 25.4, 25.2; HRMS-ESI calcd for C₉H₁₃O₄ [M+H]⁺ 185.0814, found: 185.0813.

173jj: Compound **178** (2.0 g, 10.9 mmol, 1.0 equiv) was dissolved in dry benzene (15 mL) and oxalyl chloride (1.9 mL, 21.7 mmol, 2 equiv) was slowly added at rt. DMF (200 μL) was then added dropwise and the reaction stirred for 2 h. The reaction was then concentrated *in vacuo*, the residue dissolved in ether (30 mL) and slowly added to a cold solution of diazomethane in ether (0.5M, 100 mL, 50 mmol, 4.5 equiv). The reaction mixture was left overnight. After removal of ether *in vacuo*, the dark orange residue was dissolved in a dioxane-water mixture (100 mL, 4:1) and sonicated with freshly prepared silver oxide (252 mg, 1.1 mmol, 0.1 equiv) for 1 h. The black suspension was then filtered, concentrated *in vacuo* and the residue purified by flash chromatography (EtOAc/hexanes, 1:1) to provide **173jj** (540 mg, 25%) as a colorless oil; IR (film) ν_{max} 2926, 1721, 1691, 1658, 1440, 1305, 1206, 954, 941, 654 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 5.71 (d, *J* = 10.1 Hz, 1 H), 5.63 (d, *J* = 10.2 Hz, 1 H), 3.82 (s, 3 H), 2.96-2.90 (m, 1 H), 2.82-2.71 (m, 2 H), 2.62 (d, *J* = 18.2 Hz, 1 H), 2.44 (qd, *J* = 5.8, 11.7 Hz, 1 H), 2.39-2.31 (m, 1 H), 2.26-2.17 (m, 1 H), 1.92-1.83 (m,

1 H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 169.9, 167.6, 124.6, 124.3, 63.7, 40.7, 37.5, 27.0, 26.7, 24.1.

181jj: Following Representative Procedure 2, a mixture of compound **173jj** (539 mg, 2.72 mmol, 1.0 equiv) and *N*-methylimidazole (0.67 mL, 8.2 mmol, 3.0 equiv) in CH_3CN (20 mL) was treated with a solution of TsCl (670 mg, 3.5 mmol, 1.3 equiv) in CH_3CN (10 mL) at 0 °C. After 1 h, a solution of $\text{MeONH}_2\cdot\text{HCl}$ (272 mg, 3.3 mmol, 1.2 equiv) in CH_3CN (5 mL) and *N*-methylimidazole (0.23 mL, 2.7 mmol, 1.0 equiv) was added and the reaction mixture warmed to rt. After 2 h, the reaction was concentrated and the residue purified by flash chromatography on silica gel (EtOAc/hexanes, 1:1) to provide **181jj** (482 mg, 78%) as a colorless oil; R_f 0.41 (EtOAc); ^1H NMR (CDCl_3 , 400 MHz): δ 5.69-5.59 (m, 2 H), 3.66 (s, 3 H), 3.62 (s, 3 H), 3.04-2.91 (m, 1 H), 2.86-2.67 (m, 1 H), 2.62-1.90 (m, 5 H); HRMS-ESI calcd for $\text{C}_{11}\text{H}_{17}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 250.1055, found: 250.1057.

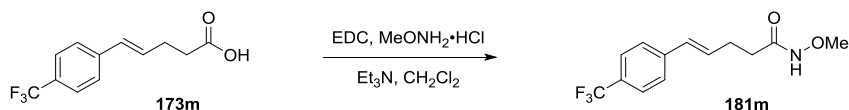
***O*-Methyl (*E*)-5-phenyl-pent-4-enohydroxamate (181k)**



Following Representative Procedure 1, a solution of **173k** (501 mg, 2.84 mmol, 1.0 equiv) in CH_2Cl_2 (4.0 mL) was treated sequentially with Et_3N (638 μL , 4.54 mmol, 1.6 equiv), EDC (980 mg, 5.11 mmol, 1.8 equiv) and $\text{MeONH}_2\cdot\text{HCl}$ (379 mg, 4.54 mmol, 1.6 equiv) to provide **181k** (579 mg, 99%) as a white solid; mp 55-56 °C (EtOAc/hexanes); R_f 0.48 (EtOAc); IR (film) ν_{max} 3181, 2996, 2936, 1656, 1516, 1494, 1440, 1071, 965, 745 cm^{-1} ; ^1H NMR (CD_3OD , 500 MHz): δ 7.34 (d, J = 7.5 Hz, 2 H), 7.26 (t, J = 7.5 Hz, 2 H), 7.17 (t, J = 7.3 Hz, 1 H), 6.44 (d, J = 15.7 Hz, 1 H), 6.21 (dt, J = 15.7, 7.0 Hz, 1 H), 3.64 (s, 3 H), 2.53-2.48 (m, 2 H), 2.23 (t, J = 7.3 Hz, 2 H); ^{13}C NMR (CD_3OD , 125 MHz): δ 170.5, 137.3,

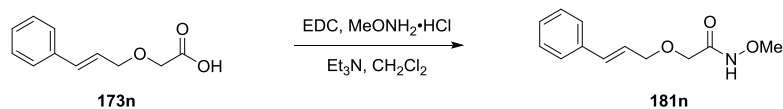
131.1, 128.1, 127.6, 126.8, 125.6, 63.0, 32.2, 28.4; HRMS-ESI calcd for $C_{12}H_{15}NO_2Na$ $[M+Na]^+$ 228.1000, found: 228.0992.

***O*-Methyl (*E*)-5-(4-trifluoromethylphenyl)-pent-4-eno hydroxamate (181m)**



Following Representative Procedure 1, a solution of **173m** (1.01 g, 4.14 mmol, 1.0 equiv) in CH_2Cl_2 (6.0 mL) was treated sequentially with Et_3N (620 μ L, 4.35 mmol, 1.05 equiv), EDC (870 mg, 4.6 mmol, 1.1 equiv) and $MeONH_2 \cdot HCl$ (360 mg, 4.35 mmol, 1.05 equiv) to provide **181m** (970 mg, 86%) as a white solid; mp 79-81 $^{\circ}C$ (CH_2Cl_2 /hexanes); R_f 0.38 (EtOAc); IR (film) ν_{max} 3217, 3004, 2819, 1652, 1591, 1330, 1110, 1068 cm^{-1} ; 1H NMR (CD_3OD , 500 MHz): δ 7.57 (d, J = 8.4 Hz, 2 H), 7.52 (d, J = 8.4 Hz, 2 H), 6.52 (d, J = 15.9 Hz, 1 H), 6.44-6.35 (m, 1 H), 3.65 (s, 3 H), 2.58-2.51 (m, 2 H), 2.26 (t, J = 7.3 Hz, 2 H); ^{13}C NMR (CD_3OD , 125 MHz): δ 171.9, 142.8, 132.6, 131.2, 130.0 (q, J_{C-F} = 32.0 Hz), 127.6, 126.6, 125.9 (q, J_{C-F} = 269 Hz), 64.5, 33.4, 30.0; HRMS-ESI calcd for $C_{13}H_{15}NO_2F_3$ $[M+H]^+$ 274.1055, found: 274.1061.

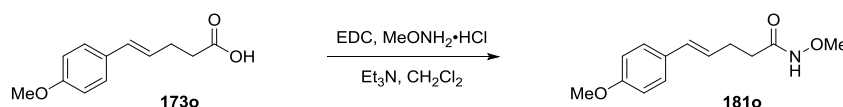
***O*-Methyl (2-cinnamyloxy)-acetohydroxamate (181n)**



Following Representative Procedure 1, a solution of **173n** (824 mg, 4.29 mmol, 1.0 equiv) in CH_2Cl_2 (15.0 mL) was treated sequentially with Et_3N (633 μ L, 4.50 mmol, 1.05 equiv), EDC (944 mg, 4.71 mmol, 1.1 equiv) and $MeONH_2 \cdot HCl$ (412 mg, 4.93 mmol, 1.15 equiv) to provide, after work-up and purification by flash chromatography (EtOAc/hexanes, 1:1), **181n** (807 mg, 85%) as a white solid; 81-83 $^{\circ}C$ (EtOAc/hexanes); R_f 0.34 (EtOAc); IR (film) ν_{max}

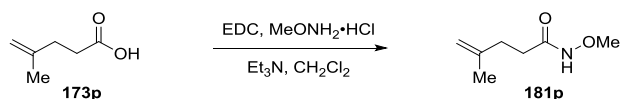
3191, 2950, 2817, 1663, 1502, 1449, 1280, 1094, 965, 692 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 9.25 (br. s., 1 H), 7.43-7.23 (m, 5 H), 6.61 (d, $J = 15.9$ Hz, 1 H), 6.23 (td, $J = 6.1$, 15.9 Hz, 1 H), 4.17 (d, $J = 6.1$ Hz, 2 H), 4.07 (s, 2 H), 3.80 (s, 3 H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 166.6, 135.9, 133.9, 128.5, 128.0, 126.4, 124.0, 72.1, 68.7, 64.5; HRMS-ESI calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 222.1130, found: 222.1125.

***O*-Methyl (*E*)-5-(4-trifluoromethylphenyl)-pent-4-enohydroxamate (181o)**



Following Representative Procedure 1, a solution of **173o** (950 mg, 4.28 mmol, 1.0 equiv) in CH_2Cl_2 (6.0 mL) was treated sequentially with Et₃N (620 μL , 4.49 mmol, 1.05 equiv), EDC (900 mg, 4.71 mmol, 1.1 equiv) and MeONH₂·HCl (370 mg, 4.49 mmol, 1.05 equiv) to provide **181o** (810 mg, 76%) as a white solid; mp 106-108 $^\circ\text{C}$ (CH_2Cl_2 /hexanes); R_f 0.41 (EtOAc); IR (film) ν_{max} 3219, 3012, 2956, 2937, 1653, 1558, 1540, 1506, 1253, 966 cm^{-1} ; ^1H NMR (CD_3OD , 500 MHz): δ 7.30-7.22 (m, 2 H), 6.85-6.79 (m, 2 H), 6.38 (d, $J = 15.8$ Hz, 1 H), 6.05 (dt, $J = 15.8$, 7.3 Hz, 1 H), 3.76 (s, 3 H), 3.64 (s, 3 H), 2.47 (m, 2 H), 2.21 (t, $J = 7.3$ Hz, 2 H); ^{13}C NMR (CD_3OD , 125 MHz): δ 171.0, 159.5, 131.0, 130.5, 127.2, 125.6, 113.9, 63.4, 54.6, 32.8, 28.9; HRMS-ESI calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 236.1287, found: 236.1288.

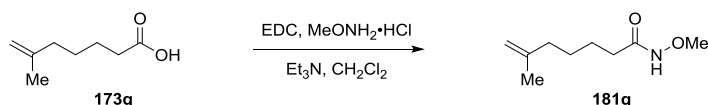
***O*-Methyl 4-methyl-pent-4-enohydroxamate (181p)**



Following Representative Procedure 1, a solution of **173p** (500 mg, 4.38 mmol, 1.0 equiv) in CH_2Cl_2 (6.0 mL) was treated sequentially with Et₃N (984 μL , 7.00 mmol, 1.6 equiv), EDC (1.47 g, 7.70 mmol, 1.8 equiv) and MeONH₂·HCl (585 mg, 7.00 mmol, 1.6 equiv) to provide

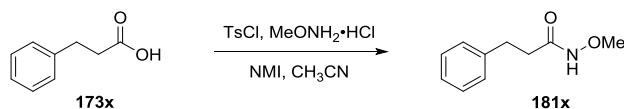
181p (589 mg, 94%) as a colorless oil; R_f 0.38 (EtOAc); IR (film) ν_{\max} 3413, 2971, 2929, 1692, 1590, 1380, 1050, 750, 704 cm^{-1} ; ^1H NMR (CD_3OD , 500 MHz): δ 4.75 (s, 1 H), 4.71 (s, 1 H), 3.67 (s, 3 H), 2.31 (t, $J = 7.7$ Hz, 2 H), 2.21 (t, $J = 7.7$ Hz, 2 H), 1.74 (s, 3 H); ^{13}C NMR (CD_3OD , 125 MHz): δ 170.7, 143.8, 109.9, 62.9, 32.8, 30.8, 21.1; HRMS-ESI calcd for $\text{C}_7\text{H}_{13}\text{NO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 166.0844, found: 166.0851.

***O*-Methyl 6-methyl-hept-6-enohydroxamate (181q)**



Following Representative Procedure 1, a solution of **173q** (1.03 g, 7.26 mmol, 1.0 equiv) in CH_2Cl_2 (15.0 mL) was treated sequentially with Et_3N (1.6 mL, 11.7 mmol, 1.6 equiv), EDC (2.49 g, 13.1 mmol, 1.8 equiv) and $\text{MeONH}_2\cdot\text{HCl}$ (970 mg, 11.6 mmol, 1.6 equiv) to provide **181q** (850 mg, 69%) as a colorless oil; R_f 0.51 (EtOAc); IR (film) ν_{\max} 3182, 2967, 2935, 1653, 1520, 1507, 1456, 1438, 1089, 1053, 886 cm^{-1} ; ^1H NMR (CD_3OD , 400 MHz): δ 4.69 (s, 1 H), 4.67 (s, 1 H), 3.68 (s, 3 H), 2.08 (t, $J = 7.4$ Hz, 2 H), 2.04 (t, $J = 7.4$ Hz, 2 H), 1.70 (s, 3 H), 1.64-1.54 (m, 2 H), 1.51-1.40 (m, 2 H); ^{13}C NMR (CD_3OD , 125 MHz): δ 171.2, 145.1, 109.4, 62.9, 37.0, 32.2, 26.6, 24.7, 21.0; HRMS-ESI calcd for $\text{C}_9\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 172.1338, found: 172.1342.

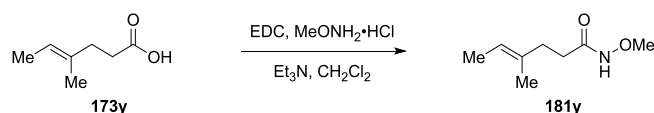
***O*-Methyl 3-phenylpropanohydroxamate (181x)**



Following Representative Procedure 2, to a stirred solution of **173x** (3.0 g, 20.55 mmol, 1.0 equiv) in CH_3CN (50 mL) at 0 $^\circ\text{C}$ was added *N*-methylimidazole (5.05 g, 61.64 mmol, 3.0 equiv) and TsCl (4.70 g, 24.66 mmol, 1.2 equiv). After 1 h, $\text{MeONH}_2\cdot\text{HCl}$ (1.72 g, 20.55

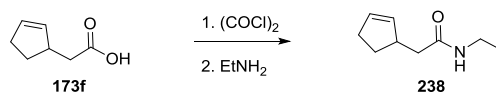
mmol, 1.0 equiv) and *N*-methylimidazole (1.68 g, 20.55 mmol, 1.0 equiv) were added and the reaction allowed to warm to rt. After 3 h, reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc/hexanes, 1:4) to provide **181x** (3.27 g, 91%) as a colorless oil; R_f 0.48 (EtOAc); IR (film) ν_{\max} 3174, 2971, 2935, 1651, 1603, 1515, 1496, 1065, 931, 748, 698 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 9.08 (br. s., 1 H), 7.31-7.23 (m, 2 H), 7.19 (t, $J = 6.3$ Hz, 3 H), 3.65 (br. s., 3 H), 2.96 (t, $J = 7.7$ Hz, 2 H), 2.38 (br. s., 2 H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 170.0, 140.3, 128.5, 128.3, 126.3, 64.2, 34.9, 31.3; HRMS-ESI calcd for $\text{C}_{10}\text{H}_{14}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 180.1025, found: 180.1023.

***O*-Methyl (*E*)-4-methyl-hex-4-enohydroxamate (181y)**



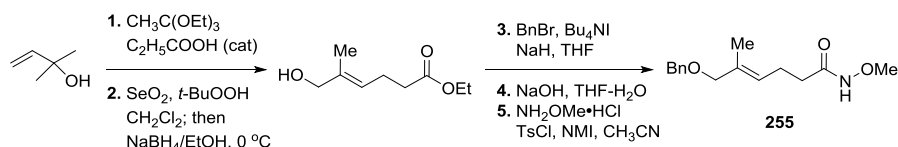
Following Representative Procedure 1, a solution of **173y** (200 mg, 1.55 mmol, 1.0 equiv) in CH_2Cl_2 (3.0 mL) was treated sequentially with Et_3N (348 μL , 2.48 mmol, 1.6 equiv), EDC (533 mg, 2.79 mmol, 1.8 equiv) and $\text{MeONH}_2\cdot\text{HCl}$ (207 mg, 2.48 mmol, 1.6 equiv) to provide **181y** (229 mg, 93%) as a colorless oil; R_f 0.48 (EtOAc); IR (film) ν_{\max} 3216, 2977, 2937, 2859, 1654, 1436, 1383, 1201, 1076, 976 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 9.23 (br s, 1 H), 5.24 (q, $J = 6.8$ Hz, 1 H), 3.67 (s, 3 H), 2.31-2.18 (m, 2 H), 2.13-2.05 (m, 2 H), 1.59 (s, 3 H), 1.54 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 171.3, 134.3, 120.2, 64.6, 35.4, 32.4, 15.9, 13.8; HRMS-ESI calcd for $\text{C}_8\text{H}_{15}\text{NO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 181.1000, found: 181.1007.

(\pm)-2-(Cyclopent-2-enyl)-*N*-ethylacetamide (238)



A solution of **173f** (275 mg, 2.18 mmol, 1.0 equiv) in THF (5.0 mL) was stirred with oxalyl chloride (281 μ l, 3.27 mmol, 1.5 equiv) for 2 h, then concentrated, dissolved in THF (2.0 mL) and quenched with ethylamine (0.5 mL, 6.3 equiv, 70% in water). The reaction was concentrated and the residue purified by flash chromatography on silica gel (EtOAc/hexanes, 1:1) to **238** (254 mg, 76%) as a colorless oil; R_f 0.50 (EtOAc); IR (film) ν_{\max} 3292, 2972, 2933, 1640, 1547, 1293, 1153, 1031, 720 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 5.77 (dd, J = 2.2, 5.5 Hz, 1 H), 5.70-5.65 (m, 1 H), 5.51 (br. s., 1 H), 3.34-3.26 (m, 2 H), 3.16-3.07 (m, 1 H), 2.41-2.26 (m, 2 H), 2.25-2.18 (m, 1 H), 2.18-2.08 (m, 2 H), 1.36-1.46 (m, 1 H), 1.14 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 172.0, 133.9, 131.4, 42.9, 42.6, 34.3, 31.8, 29.6, 14.9; HRMS-ESI calcd for $\text{C}_9\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}]^+$ 154.1232, found: 154.1237.

***O*-Methyl (*E*)-6-(benzyloxy)-5-methylhex-4-enhydroxamate (255)**



Step 1: A mixture of 2-methylbut-3-en-2-ol (1.8 g, 20.9 mmol) and triethyl orthoacetate (6.0 mL, 32.8 mmol, 1.6 equiv) and propionic acid (0.2 mL, 2.7 mmol, 0.13 equiv) was heated at 100 $^{\circ}\text{C}$ for 18 h. The reaction mixture was then cooled, concentrated *in vacuo* and purified by flash chromatography (EtOAc/hexanes, 1:10) to provide ethyl 5-methylhex-4-enoate (1.66 g, 51%) as a colorless oil.

Step 2: To a solution of ethyl 5-methylhex-4-enoate (1.5 g, 9.61 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) was added selenium dioxide (533 mg, 4.8 mmol, 0.5 equiv). A 70% aqueous solution of *t*-BuOOH (3.8 mL, 29 mmol, 3 equiv) was then added and the reaction mixture stirred for 12 h at rt. Upon completion, the reaction was poured into saturated aqueous

Na₂CO₃ (50 mL) and extracted with CH₂Cl₂ (2 x 60 mL). The combined organic extracts were dried over Na₂SO₄, concentrated *in vacuo* and purified by flash chromatography (EtOAc/hexanes, 1:9) to provide (*E*)-ethyl 5-methyl-6-oxohex-4-enoate (1.42 g, 87%) as a colorless oil; ¹H NMR (CDCl₃, 500 MHz): δ 9.46 (s, 1 H), 6.50 (dt, *J* = 1.1, 5.9 Hz, 1 H), 4.91 (d, *J* = 5.9 Hz, 2 H), 2.40 (q, *J* = 7.6 Hz, 2 H), 1.81 (s, 3 H), 1.18 (t, *J* = 7.6 Hz, 3 H); ¹³C NMR (CDCl₃, 126 MHz): δ 194.0, 174.0, 145.7, 140.5, 60.7, 27.4, 9.5, 9.0.

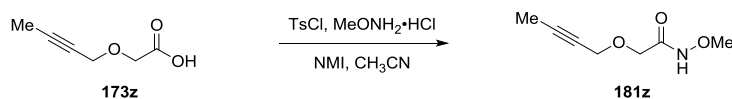
To a solution of (*E*)-ethyl 5-methyl-6-oxohex-4-enoate (1.42 g, 8.35 mmol, 1.0 equiv) in ethanol (50 mL) at 0 °C was added NaBH₄ (950 mg, 25.1 mmol, 3 equiv) portionwise over 30 min. The reaction mixture was stirred for 2 h at rt. The resulting mixture was then poured into 1N HCl (100 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over Na₂SO₄ and purified by flash chromatography to provide (*E*)-ethyl 6-hydroxy-5-methylhex-4-enoate (1.12 g, 78%) as a colorless oil; ¹H NMR (CDCl₃, 500 MHz): δ 5.40 (br. s., 1 H), 4.14 (q, *J* = 6.8 Hz, 2 H), 4.01 (s, 2 H), 2.37 (br. s., 4 H), 1.69 (s, 3 H), 1.49 (br. s., 1 H), 1.27 (t, *J* = 6.8 Hz, 3 H); ¹³C NMR (CDCl₃, 126 MHz): δ 173.2, 136.2, 123.8, 68.6, 60.3, 34.1, 23.2, 14.2, 13.6.

Step 3: To a solution of (*E*)-ethyl 6-hydroxy-5-methylhex-4-enoate (500 mg, 2.91 mmol, 1.0 equiv) in THF (20 mL) at 0 °C was added NaH (175 mg, 60% in mineral oil, 4.37 mmol, 1.5 equiv). The mixture was stirred at room temperature for 30 min and Bu₄NI (90 mg, 0.24 mmol) and benzyl bromide (0.52 mL, 4.37 mmol, 1.5 equiv) were added to the mixture. The reaction was stirred at room temperature for 12 h and then quenched by addition of saturated aqueous NH₄Cl (30 mL). The resulting mixture was extracted with diethyl ether (3 x 30 mL), the combined organic extracts dried over Na₂SO₄ and concentrated *in vacuo*. The residue was

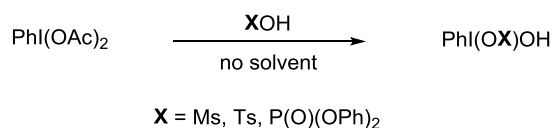
purified by flash chromatography (hexane/EtOAc, 10:1) to afford ethyl (*E*)-6-(benzyloxy)-5-methylhex-4-enoate (457 mg, 60%).

Step 4: Ethyl (*E*)-6-(benzyloxy)-5-methylhex-4-enoate (457 mg, 1.74 mmol, 1.0 equiv), obtained from the previous step, was dissolved in THF (10 mL) and a solution of sodium hydroxide (105 mg, 2.61 mmol, 1.5 equiv) in water (5 mL) was added. The reaction mixture was stirred for 30 min, then acidified with 1N HCl to pH 3. The layers were separated and the aqueous layer extracted with diethyl ether (3 x 25 mL). The combined extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/EtOAc, 1:1) to afford (*E*)-6-(benzyloxy)-5-methylhex-4-enoic acid (188 mg, 46%).

Step 5: Following Representative Procedure 2, to a solution of (*E*)-6-(benzyloxy)-5-methylhex-4-enoic acid (638 mg, 2.73 mmol, 1.0 equiv) in CH₃CN (15 mL) was added *N*-methylimidazole (0.7 mL, 8.19 mmol, 3.0 equiv) and TsCl (676 mg, 3.55 mmol, 1.3 equiv) at 0 °C. After 1 h, MeONH₂•HCl (260 mg, 3.11 mmol, 1.2 equiv) and *N*-methylimidazole (0.23 mL, 2.73 mmol, 1.0 equiv) were added and the reaction mixture allowed to warm to rt. After 3 h, reaction mixture was concentrated *in vacuo* and the residue purified by flash chromatography (EtOAc/hexanes, 1:2) to provide **255** (610 mg, 85%) as a colorless oil; *R*_f 0.39 (EtOAc); IR (film) ν_{max} 2937, 1771, 1715, 1496, 1452, 1271, 1166, 1027, 714 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 8.87 (br. s., 1 H), 7.39-7.27 (m, 5 H), 5.43 (br. s., 1 H), 4.47 (s, 2 H), 3.91 (s, 2 H), 3.74 (br. s., 3 H), 2.46-2.39 (m, 2 H), 2.14 (br. s., 1 H), 1.71 (s, 3 H); ¹³C NMR (CDCl₃, 126 MHz): δ 170.2, 138.1, 133.4, 128.0, 127.4, 127.2, 125.6, 75.6, 71.3, 63.6, 32.4, 23.4, 13.9; HRMS-ESI calcd for C₁₅H₂₂NO₃ [M+H]⁺ 264.1600, found: 264.1590.

***O*-Methyl 2-(but-2-yn-1-yloxy)acetohydroxamate (181z)**

Following Representative Procedure 2, to a solution of **173z** (781 mg, 6.1 mmol, 1.0 equiv) in CH₃CN (50 mL) was added *N*-methylimidazole (1.51 mL, 18.3 mmol, 3.0 equiv) and TsCl (1.51 mg, 7.9 mmol, 1.3 equiv) at 0 °C. After 1 h, MeONH₂·HCl (610 mg, 7.3 mmol, 1.2 equiv) and *N*-methylimidazole (0.5 mL, 6.1 mmol, 1.0 equiv) were added and the reaction allowed to warm to rt. After 6 h, reaction mixture was concentrated *in vacuo* and the residue purified by flash chromatography (EtOAc/hexanes, 1:1) to provide **181z** (580 mg, 61%) as a yellowish needles; mp 68-70 °C (EtOAc); *R_f* 0.53 (EtOAc); IR (film) ν_{max} 3196, 2921, 2214, 1661, 1505, 1452, 1357, 1134, 1087, 955, 721, 679, 584 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 9.07 (br. s., 1H), 4.12-4.16 (m, 2H), 4.08 (s, 2H), 3.77 (s, 3H), 1.83 (t, *J* = 2.2 Hz, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ 166.4, 84.3, 73.4, 68.2, 64.5, 59.3, 3.4; HRMS-ESI calcd for C₇H₁₂NO₃ [M+H]⁺ 158.0817, found: 158.0816.

1.11.6 Preparation Hypervalent Iodine Reagents**Representative Procedure 3. Preparation of Hydroxy(mesyloxy)iodobenzene (HMIB)**

A mixture of (diacetoxyiodo)benzene (10.1 g, 31 mmol, 1.0 equiv) and methanesulfonic acid (2.0 mL, 31 mmol, 1.0 equiv) was gently blended in a porcelain mortar. The resulting homogeneous mixture was then ground by hand for 2 h. During this time, the formation of acetic anhydride and wetting of the reaction mixture was observed. The solid residue was filtered, washed with Et₂O (2 x 15 mL) and dried under vacuum for 2 days to afford

hydroxy(mesyloxy)iodobenzene (9.9 g, 100%) as a white solid; mp 117-119 °C (CH₃CN) (lit. mp¹⁴⁸ 119-121 °C).

[Hydroxy(tosyloxy)iodo]benzene (HTIB)

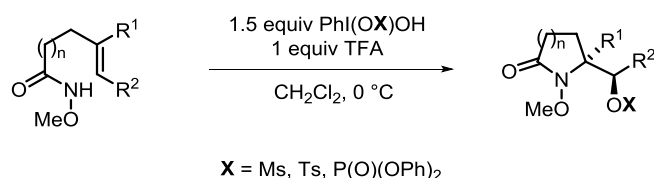
Following Representative Procedure 3, (diacetoxyiodo)benzene (5.00 g, 15.5 mmol, 1.0 equiv) and TsOH•H₂O (2.95 g, 15.5 mmol, 1.0 equiv) were ground to provide, after filtration and washing with Et₂O (2 x 10 mL), hydroxy(tosyloxy)iodobenzene (5.9 g, 97%) as a white solid; mp 129-132 °C (CH₃CN) (lit. mp¹⁴⁸ 132-134 °C).

[Hydroxy(diphenylphosphyl)iodo]benzene (HPIB)

Following Representative Procedure 3, (diacetoxyiodo)benzene (2.56 g, 8.0 mmol, 1.0 equiv) and diphenyl phosphate (1.99 g, 8.0 mmol, 1.0 equiv) were ground to provide, after filtration and washing with Et₂O (2 x 10 mL), hydroxy(diphenylphosphyl)iodobenzene (2.73 g, 73%) as a white solid; mp 101-103 °C (CH₃CN) (lit. mp¹¹⁵ 102-105 °C).

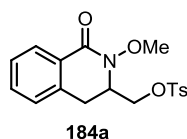
1.11.7 Cyclization of Unsaturated *O*-Alkyl Hydroxamates using I(III) Reagents

Representative Procedure 4. Hydroxamate Cyclization using I(III) Reagents

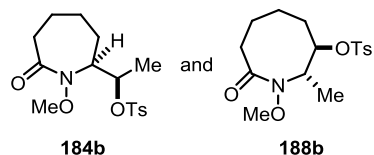


To a cooled (0° C) solution of *O*-alkyl hydroxamate (0.10 mmol) in CH₂Cl₂ (2 mL, 0.05 M) under N₂, was added TFA (0.10 mmol). After 5 min, the I(III) reagent (1.5 equivalents) was added and the reaction mixture was stirred for 1 h. Upon completion (as monitored by TLC), the reaction mixture was concentrated *in vacuo* and the residue purified by flash chromatography on silica gel (EtOAc) to provide the product.

1.11.8 HTIB-Mediated Cyclization



184a: Following Representative Procedure 4, to a solution of **181a** (14.0 mg, 0.073 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added TFA (5.6 μL, 0.073 mmol, 1.0 equiv) and HTIB (43 mg, 0.11 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **184a** (20.0 mg, 76%) as a colorless oil; R_f 0.73 (EtOAc); IR (film) ν_{max} 2936, 1670, 1598, 1459, 1360, 1174, 985, 929, 813, 664 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 8.06 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.42-7.47 (m, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 7.7 Hz, 1H), 4.17-4.25 (m, 2H), 3.98 (t, *J* = 8.5 Hz, 1H), 3.86 (s, 3H), 3.36 (dd, *J* = 16.4, 5.6 Hz, 1H), 3.22 (dd, *J* = 16.4, 3.7 Hz, 1H), 2.45 (s, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ 163.1, 145.2, 134.5, 132.8, 132.2, 130.0, 128.2, 128.0, 127.9, 127.7, 127.4, 66.3, 63.1, 57.0, 30.5, 21.6; HRMS-ESI calcd for C₁₈H₂₀NO₅S [M+H]⁺: 362.1062, found: 362.1072.

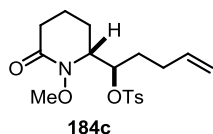


184b and 188b: Following Representative Procedure 4, to a solution of **181b** (19.7 mg, 0.12 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added TFA (9 μL, 0.12 mmol, 1.0 equiv) and HTIB (68 mg, 0.17 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **184b** (9.3 mg, 24%) and **188b** (3.1 mg, 8%).

Analytical data for 184b: colorless oil; R_f 0.33 (EtOAc); IR (film) ν_{max} 2937, 1669, 1452, 1359, 1174, 905, 792, 663 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 5.02 (quin, *J* = 6.6 Hz, 1H), 3.70 (s, 3H), 3.66-3.69 (m, 1H), 2.46

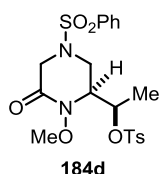
(s, 3H), 2.41-2.44 (m, 1H), 2.32 (ddd, $J = 14.9, 11.6, 3.6$ Hz, 1H), 1.99 (dd, $J = 13.1, 7.5$ Hz, 1H), 1.67-1.86 (m, 3H), 1.55-1.66 (m, 2H), 1.34 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 171.3, 145.1, 134.1, 129.9, 127.6, 77.1, 65.3, 61.5, 34.0, 26.2, 22.8, 22.3, 21.7, 18.3; HRMS-ESI calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$: 342.1375, found: 342.1365.

Analytical data for **188b**: colorless oil; R_f 0.49 (EtOAc); IR (film) ν_{max} 2737, 1661, 1448, 1356, 1174, 906, 868, 683 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.79 (d, $J = 8.3$ Hz, 2H), 7.36 (d, $J = 8.3$ Hz, 2H), 4.74 (dd, $J = 9.9, 2.3$ Hz, 1H), 4.10-4.18 (m, 1H), 3.78 (s, 3H), 2.47 (s, 3H), 2.35-2.41 (m, 2H), 1.89-2.00 (m, 7H), 1.55-1.61 (m, 2H), 1.36 (d, $J = 6.4$ Hz, 3H), 1.25-1.33 (m, 2H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 174.4, 145.0, 134.1, 129.9, 127.7, 83.8, 64.2, 55.6, 34.7, 28.8, 28.7, 21.7, 20.3, 14.7; HRMS-ESI calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$: 342.1375, found: 342.1364.

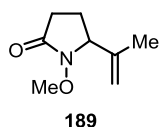


184c: Following Representative Procedure 4, to a solution of **181c** (14.5 mg, 0.073 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (5.6 μL , 0.073 mmol, 1.0 equiv) and HTIB (43 mg, 0.11 mmol, 1.5 equiv) at 0 $^\circ\text{C}$. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **184c** (16.9 mg, 63%) as a colorless oil; R_f 0.42 (EtOAc); IR (film) ν_{max} 2927, 1722, 1640, 1447, 1356, 1173, 1122, 1009, 905, 815, 682 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.83 (d, $J = 8.2$ Hz, 2H), 7.38 (d, $J = 8.2$ Hz, 2H), 5.61 (ddt, $J = 17.0, 10.4, 6.5$ Hz, 1H), 4.83-4.96 (m, 3H), 4.12-4.19 (m, 1H), 3.74 (s, 3H), 2.47 (s, 3H), 2.30-2.43 (m, 2H), 2.10 (ddd, $J = 10.9, 5.5, 2.4$ Hz, 1H), 1.93-2.04 (m, 1H), 1.80-1.90 (m, 1H), 1.71-1.80 (m, 2H), 1.60-1.68 (m, 3H); ^{13}C NMR (CDCl_3 , 101 MHz): δ 167.6, 145.2, 136.5, 133.4, 129.9, 127.9,

115.7, 80.0, 60.6, 59.4, 33.2, 29.4, 27.3, 23.0, 21.7, 19.1; HRMS-ESI calcd for $C_{18}H_{26}NO_5S$ $[M+H]^+$: 368.1532, found: 368.1533.

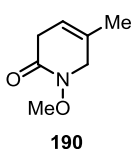


184d: Following Representative Procedure 4, to a solution of **181d** (16.4 mg, 0.058 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (4.4 μ L, 0.058 mmol, 1.0 equiv) and HTIB (34 mg, 0.087 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **184d** (19.9 mg, 76%) as a colorless oil; R_f 0.71 (EtOAc); IR (film) ν_{max} 2937, 1682, 1597, 1446, 1349, 1168, 1072, 914, 688 cm^{-1} ; 1H NMR ($CDCl_3$, 500 MHz): δ 7.75-7.81 (m, 4H), 7.68 (t, J = 7.3 Hz, 1H), 7.59 (t, J = 7.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 5.00-5.06 (m, 1H), 3.91-3.96 (m, 1H), 3.68 (s, 2H), 3.65 (s, 3H), 3.54 (dd, J = 12.8, 5.6 Hz, 1H), 3.40 (dd, J = 12.8, 4.6 Hz, 1H), 2.45 (s, 3H), 1.39 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 161.3, 145.1, 135.2, 133.8, 133.5, 129.9, 129.6, 127.8, 127.7, 76.2, 61.5, 60.7, 49.5, 44.4, 21.7, 17.4; HRMS-ESI calcd for $C_{20}H_{25}N_2O_7S_2$ $[M+H]^+$: 469.1103, found: 469.1100.

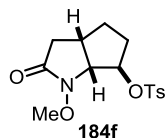


189: Following Representative Procedure 4, to a solution of **181e** (23.5 mg, 0.15 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) was added TFA (11.4 μ L, 0.15 mmol, 1.0 equiv) and HTIB (88 mg, 0.22 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **189** (12.8 mg, 55%) as a colorless oil; R_f 0.29 (EtOAc); IR (film) ν_{max} 2924, 1714, 1445, 1370, 1162, 1043, 956, 660 cm^{-1} ; 1H NMR ($CDCl_3$, 500 MHz): δ 5.03 (s, 1H), 4.98 (s, 1H), 4.28 (dd, J = 8.2, 5.2 Hz, 1H), 3.77 (s, 3H), 2.37-2.44 (m, 1H), 2.29-2.35

(m, 1H), 2.13-2.22 (m, 1H), 1.80-1.87 (m, 1H), 1.75 (s, 3H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 171.1, 142.5, 114.8, 62.4, 62.1, 26.9, 21.2, 16.9; HRMS-ESI calcd for $\text{C}_8\text{H}_{14}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 156.1025, found: 156.1021.

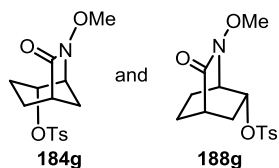


190: Following Representative Procedure 4, to a solution of **181p** (22.6 mg, 0.16 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) was added TFA (12 μL , 0.16 mmol, 1.0 equiv) and HTIB (93 mg, 0.24 mmol, 1.5 equiv) at 0 $^\circ\text{C}$. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **190** (16.0 mg, 72%) as a colorless oil; R_f 0.09 (EtOAc); IR (film) ν_{max} 2938, 1715, 1651, 1418, 1143, 1036, 777, 683 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 5.35-5.38 (m, 1H), 4.11 (t, $J = 4.4$ Hz, 2H), 3.84 (s, 3H), 3.13 (dd, $J = 3.3, 1.7$ Hz, 2H), 1.77 (s, 3H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 165.1, 127.7, 116.3, 61.1, 52.7, 32.8, 19.6; HRMS-ESI calcd for $\text{C}_7\text{H}_{12}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 142.0868, found: 142.0866.



184f: Following Representative Procedure 4, to a solution of **181f** (16.5 mg, 0.11 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (8.1 μL , 0.11 mmol, 1.0 equiv) and HTIB (63 mg, 0.16 mmol, 1.5 equiv) at 0 $^\circ\text{C}$. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **184f** (25.2 mg, 73%) as a colorless oil; R_f 0.37 (EtOAc); IR (film) ν_{max} 2939, 1699, 1597, 1356, 1173, 1096, 942, 896, 815, 783, 671 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.81 (d, $J = 8.0$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 4.86 (d, $J = 2.9$ Hz, 1H), 4.21 (d, $J = 7.7$ Hz, 1H), 3.68 (s, 3H), 2.80-2.94 (m, 1H), 2.59 (dd, $J = 17.7, 10.5$ Hz, 1H), 2.45 (s, 3H), 2.12 (s, 1H), 1.94 (dd, $J = 17.7, 3.6$ Hz, 1H), 1.72-1.88 (m, 2H), 1.45-1.60 (m, 1H); ^{13}C NMR

(CDCl₃, 101 MHz): δ 168.8, 145.1, 133.2, 129.9, 127.9, 82.7, 65.7, 61.9, 34.0, 31.4, 31.1, 29.9, 21.6; HRMS-ESI calcd for C₁₅H₂₀NO₅S [M+H]⁺: 326.1062, found: 326.1066.

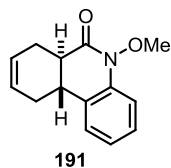


184g and **188g**: Following Representative Procedure 4, to a solution of **181g** (32.0 mg, 0.21 mmol, 1.0 equiv) in CH₂Cl₂ (4 mL) was added TFA (16 μ L, 0.21 mmol, 1.0 equiv) and HTIB (123 mg, 0.32 mmol,

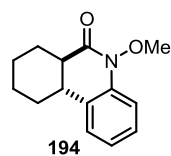
1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **184g** (23.0 mg, 34%) and **188g** (43.6 mg, 65%).

Analytical data for **184g**: white solid; mp 95-97 °C (EtOAc/hexanes); R_f 0.58 (EtOAc); IR (film) ν_{\max} 2937, 1732, 1598, 1360, 1190, 926, 884, 809, 663 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 4.80-4.83 (m, 1H), 4.00 (t, *J* = 4.4 Hz, 1H), 3.79 (s, 3H), 2.47 (s, 3H), 2.42-2.45 (m, 1H), 2.14 (d, *J* = 11.8 Hz, 1H), 1.94-2.00 (m, 1H), 1.66-1.78 (m, 4H); ¹³C NMR (CDCl₃, 126 MHz): δ 175.5, 145.2, 133.5, 130.0, 127.7, 74.1, 63.6, 57.0, 37.2, 26.3, 24.0, 22.8, 21.7; HRMS-ESI calcd for C₁₅H₂₀NO₅S [M+H]⁺: 326.1062, found: 326.1066.

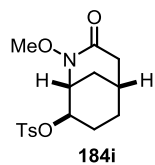
Analytical data for **188g**: white solid; mp 104-106 °C (EtOAc/hexanes); R_f 0.47 (EtOAc); IR (film) ν_{\max} 2937, 1703, 1598, 1356, 1175, 968, 667 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 4.73-4.78 (m, 1H), 4.02-4.05 (m, 1H), 3.77 (s, 3H), 2.55-2.58 (m, 1H), 2.47 (s, 3H), 2.15-2.22 (m, 2H), 1.81-1.90 (m, 2H), 1.74-1.80 (m, 1H), 1.57 (dt, *J* = 14.7, 2.9 Hz, 1H); ¹³C NMR (CDCl₃, 126 MHz): δ 172.1, 145.4, 133.1, 130.1, 127.8, 75.3, 63.7, 58.9, 38.6, 31.3, 23.2, 21.7, 20.6; HRMS-ESI calcd for C₁₅H₂₀NO₅S [M+H]⁺: 326.1062, found: 326.1063.



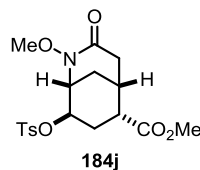
191: Following Representative Procedure 4, to a solution of **181h** (16.9 mg, 0.073 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added TFA (5.6 μL, 0.073 mmol, 1.0 equiv) and HTIB (43 mg, 0.11 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **191** (15.4 mg, 92%) as a white solid; mp 122-125 °C (EtOAc/hexanes); *R_f* 0.48 (EtOAc-hexanes, 1:3); IR (film) ν_{max} 2931, 1680, 1601, 1455, 1363, 1060, 843, 758, 678 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.31-7.36 (m, 1H), 7.24-7.30 (m, 2H), 7.11-7.16 (m, 1H), 5.77-5.92 (m, 2H), 3.95 (s, 3H), 2.91-3.00 (m, 1H), 2.80-2.88 (m, 1H), 2.70-2.79 (m, 1H), 2.54 (ddd, *J* = 14.1, 10.8, 5.5 Hz, 1H), 2.25-2.42 (m, 2H); ¹³C NMR (CDCl₃, 126 MHz): δ 167.2, 137.1, 127.8, 127.4, 125.8, 124.9, 124.6, 123.6, 112.0, 62.4, 40.2, 33.7, 29.1, 26.7; HRMS-ESI calcd for C₁₄H₁₆NO₂ [M+H]⁺ 230.1181, found: 230.1182.



194: Following Representative Procedure 4, to a solution of **193** (17.8 mg, 0.076 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added TFA (5.8 μL, 0.076 mmol, 1.0 equiv) and HTIB (45 mg, 0.11 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **194** (16.6 mg, 94%) as a white solid; mp 65-67 °C (EtOAc/hexanes); *R_f* 0.48 (EtOAc-hexanes, 1:3); IR (film) ν_{max} 2928, 2854, 1685, 1601, 1487, 1455, 1325, 1255, 1056, 757, 681 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.28-7.33 (m, 1H), 7.22-7.27 (m, 2H), 7.07-7.12 (m, 1H), 3.91 (s, 3H), 2.54-2.62 (m, 1H), 2.40-2.49 (m, 2H), 2.08-2.15 (m, 1H), 1.91-1.98 (m, 2H), 1.35-1.46 (m, 3H), 1.24-1.35 (m, 1H); ¹³C NMR (CDCl₃, 126 MHz): δ 167.9, 137.3, 128.4, 127.5, 124.0, 123.5, 112.0, 62.5, 43.9, 37.2, 28.4, 26.5, 25.1, 25.1; HRMS-ESI calcd for C₁₄H₁₈NO₂ [M+H]⁺ 232.1338, found: 232.1341.

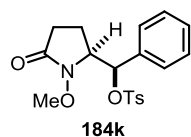


184i: Following Representative Procedure 4, to a solution of **181i** (16.0 mg, 0.095 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added TFA (7.2 μL, 0.095 mmol, 1.0 equiv) and HTIB (56 mg, 0.14 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **184i** (29.3 mg, 91%) as a white solid; mp 111-113 °C (EtOAc/hexanes); *R_f* 0.38 (EtOAc); IR (film) ν_{max} 2923, 1686, 1447, 1369, 1171, 1095, 969, 835, 672 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.80 (d, *J* = 7.1 Hz, 2H), 7.36 (d, *J* = 7.1 Hz, 2H), 4.76 (br. s., 1H), 3.86 (br. s., 1H), 3.70 (br. s., 3H), 2.66 (br. s., 1H), 2.46 (s, 3H), 2.28 (d, *J* = 10.3 Hz, 2H), 2.17 (br. s., 1H), 1.85 (br. s., 2H), 1.58 (br. s., 2H), 1.46 (d, *J* = 11.9 Hz, 1H); ¹³C NMR (CDCl₃, 126 MHz): δ 169.7, 145.0, 133.3, 129.9, 127.8, 75.0, 62.2, 56.3, 38.3, 26.9, 26.1, 25.9, 21.6, 21.6; HRMS-ESI calcd for C₁₆H₂₂NO₅S [M+H]⁺: 340.1219, found: 340.1218.

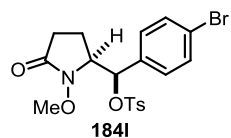


184j: Following Representative Procedure 4, to a solution of **181j** (12.8 mg, 0.056 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added TFA (4.3 μL, 0.056 mmol, 1.0 equiv) and HTIB (33 mg, 0.085 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **184j** (22.3 mg, 99%) as a white solid; mp 121-123 °C (EtOAc/hexanes); *R_f* 0.40 (EtOAc); IR (film) ν_{max} 2921, 1734, 1681, 1595, 1441, 1362, 1167, 1095, 914, 830, 668 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 4.83 (d, *J* = 2.6 Hz, 1H), 3.88 (d, *J* = 2.0 Hz, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 2.81-2.89 (m, 1H), 2.53-2.62 (m, 2H), 2.47 (s, 3H), 2.32 (d, *J* = 15.1 Hz, 2H), 1.86-2.01 (m, 2H), 1.72-1.82 (m, 1H); ¹³C NMR (CDCl₃, 101 MHz): δ 172.7, 168.1, 145.4, 133.0, 130.1, 127.8, 74.5, 62.2,

55.7, 52.1, 41.0, 34.4, 28.5, 27.3, 23.9, 21.7; HRMS-ESI calcd for $C_{18}H_{24}NO_7S$ $[M+H]^+$: 398.1273, found: 398.1278.

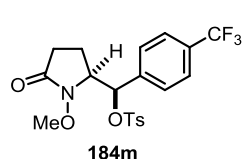


184k: Following Representative Procedure 4, to a solution of **181k** (21.4 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (8 μ L, 0.10 mmol, 1.0 equiv) and HTIB (61 mg, 0.16 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **184k** (27.4 mg, 88%) as a colorless oil; R_f 0.40 (EtOAc); IR (film) ν_{max} 2926, 1668, 1495, 1451, 1153, 1121, 1032, 1008, 815, 681 cm^{-1} ; 1H NMR ($CDCl_3$, 500 MHz): δ 7.61 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 5.4 Hz, 3H), 7.19-7.23 (m, 2H), 7.18 (d, J = 8.2 Hz, 2H), 5.81 (d, J = 2.0 Hz, 1H), 3.97 (dt, J = 8.0, 3.3 Hz, 1H), 3.82 (s, 3H), 2.37 (s, 3H), 2.10-2.16 (m, 2H), 2.05-2.09 (m, 1H), 1.84-1.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.1, 144.7, 134.4, 133.5, 129.5, 128.7, 128.5, 127.8, 126.6, 125.8, 80.6, 62.6, 61.1, 26.5, 21.6, 16.1; HRMS-ESI calcd for $C_{19}H_{22}NO_5S$ $[M+H]^+$: 376.1219, found: 376.1216.



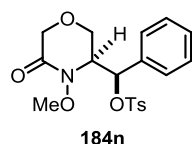
184l: Following Representative Procedure 4, to a solution of **181l** (21.1 mg, 0.074 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (6 μ L, 0.074 mmol, 1.0 equiv) and HTIB (44 mg, 0.11 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **184l** (20.9 mg, 62%) as a dark yellow oil; R_f 0.40 (EtOAc); IR (film) ν_{max} 2942, 1674, 1487, 1398, 1152, 1031, 1007, 814, 682 cm^{-1} ; 1H NMR ($CDCl_3$, 500 MHz): δ 7.61 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 5.75 (d, J = 2.2 Hz, 1H), 3.92-3.97 (m, 1H), 3.81 (s, 3H), 2.41

(s, 3H), 2.12-2.18 (m, 2H), 2.00-2.08 (m, 1H), 1.87-1.95 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 171.0, 145.1, 133.5, 133.4, 131.8, 129.7, 128.4, 127.8, 123.0, 80.0, 62.7, 60.8, 26.5, 21.6, 16.1; HRMS-ESI calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{SBr}$ $[\text{M}+\text{H}]^+$: 454.0324, found: 454.0330.



184m: Following Representative Procedure 4, to a solution of **181m** (17.2 mg, 0.063 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (5 μL , 0.063 mmol, 1.0 equiv) and HTIB (37 mg, 0.095 mmol, 1.5 equiv)

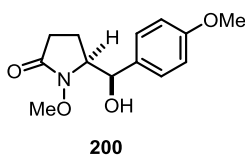
at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **184m** (18.5 mg, 66%) as a colorless oil; R_f 0.49 (EtOAc); IR (film) ν_{max} 2928, 1712, 1612, 1597, 1418, 1362, 1323, 1174, 1066, 869, 682 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.61 (d, J = 8.1 Hz, 2H), 7.52 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 5.85 (s, 1H), 3.94-3.99 (m, 1H), 3.83 (s, 3H), 2.38 (s, 3H), 2.13-2.27 (m, 2H), 2.03-2.11 (m, 1H), 1.86-1.95 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 171.1, 145.2, 138.6, 133.2, 129.7, 127.9, 127.1, 125.5, 125.5, 79.6, 62.8, 61.0, 26.5, 21.5, 15.9; HRMS-ESI calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_5\text{F}_3\text{S}$ $[\text{M}+\text{H}]^+$: 444.1093, found: 444.1081.



184n: Following Representative Procedure 4, to a solution of **181n** (15.4 mg, 0.070 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (5.3 μL , 0.070 mmol, 1.0 equiv) and HTIB (41 mg, 0.10 mmol, 1.5 equiv) at 0 °C.

After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **184n** (13.0 mg, 48%) as a colorless oil; R_f 0.44 (EtOAc); IR (film) ν_{max} 2923, 1731, 1651, 1495, 1452, 1120, 1008, 681 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.58 (d, J = 8.3 Hz, 2H), 7.12-7.27 (m, 7H), 5.91 (d, J = 4.8 Hz, 1H),

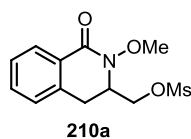
4.06-4.14 (m, 3H), 3.97 (q, $J = 4.1$ Hz, 1H), 3.75 (dd, $J = 12.2, 4.1$ Hz, 1H), 3.60 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (CDCl_3 , 101 MHz): δ 164.8, 144.7, 134.5, 133.6, 129.5, 128.9, 128.5, 127.8, 127.0, 79.9, 68.8, 64.7, 62.8, 61.9, 21.5; HRMS-ESI calcd for $\text{C}_{19}\text{H}_{22}\text{NO}_6\text{S}$ $[\text{M}+\text{H}]^+$: 392.1168, found: 392.1166.



200: Following Representative Procedure 4, to a solution of **181o** (16.1 mg, 0.069 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (5.2 μL , 0.069 mmol, 1.0 equiv) and HTIB (40.6 mg, 0.10 mmol, 1.5

equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **200** (7.2 mg, 42%) as a colorless oil; R_f 0.27 (EtOAc); IR (film) ν_{max} 3376, 2937, 2834, 1695, 1612, 1511, 1245, 1174, 1031 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.30 (d, $J = 8.5$ Hz, 2H), 6.93 (d, $J = 8.5$ Hz, 2H), 5.15 (s, 1H), 3.93 (td, $J = 4.2, 2.4$ Hz, 1H), 3.91 (s, 3H), 3.82 (s, 3H), 2.33 (ddd, $J = 17.0, 10.2, 6.4$ Hz, 1H), 2.14-2.22 (m, 1H), 2.03 (ddd, $J = 17.9, 10.2, 4.6$ Hz, 1H), 1.67-1.76 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 172.1, 159.2, 131.6, 127.0, 113.9, 70.6, 62.6, 62.0, 55.3, 27.0, 15.1; HRMS-ESI calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 274.1055, found: 274.1063.

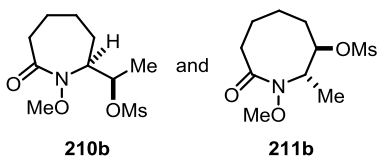
1.11.9 HMIB-Mediated Cyclization



210a: Following Representative Procedure 4, to a solution of **181a** (14.8 mg, 0.077 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (6 μL , 0.077

mmol, 1.0 equiv) and HMIB (37 mg, 0.12 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **210a** (16.8 mg, 76%) as a colorless oil; R_f 0.54 (EtOAc); IR (film) ν_{max} 2937, 1667, 1606,

1460, 1351, 1171, 996, 962, 737 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 8.12 (d, $J = 7.6$ Hz, 1H), 7.49 (t, $J = 7.6$ Hz, 1H), 7.38 (t, $J = 7.6$ Hz, 1H), 7.23 (d, $J = 7.6$ Hz, 1H), 4.42 (q, $J = 6.8$ Hz, 1H), 4.25-4.32 (m, 2H), 3.94 (s, 3H), 3.47 (dd, $J = 16.3, 5.0$ Hz, 1H), 3.26 (dd, $J = 16.3, 2.8$ Hz, 1H), 2.91 (s, 3H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 163.2, 134.6, 132.9, 128.1, 127.9, 127.8, 127.5, 66.3, 63.1, 57.2, 37.4, 30.8; HRMS-ESI calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$: 286.0749, found: 286.0740.



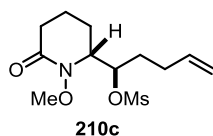
210b and **211b**: Following Representative Procedure 4, to a solution of **181b** (18.7 mg, 0.11 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (8.4 μL , 0.11 mmol, 1.0 equiv) and

HMIB (52 mg, 0.16 mmol, 1.5 equiv) at 0 $^\circ\text{C}$. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **210b** (5.1 mg, 18%) and 3.7 mg **211b** (3.7 mg, 12%).

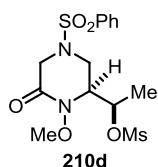
Analytical data for **210b**: colorless oil; R_f 0.23 (EtOAc); IR (film) ν_{max} 2920, 1653, 1456, 1351, 1040, 968, 835, 811, 691 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 5.10 (quin, $J = 6.2$ Hz, 1H), 3.77 (s, 3H), 3.72 (dt, $J = 8.6, 5.6$ Hz, 1H), 3.01 (s, 3H), 2.46-2.59 (m, 2H), 1.87-2.06 (m, 5H), 1.72-1.78 (m, 2H), 1.61-1.68 (m, 1H), 1.51 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 171.1, 77.1, 64.9, 61.4, 38.5, 33.4, 24.6, 22.1, 22.0, 18.4; HRMS-ESI calcd for $\text{C}_{10}\text{H}_{20}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$: 266.1062, found: 266.1068.

Analytical data for **211b**: colorless oil; R_f 0.40 (EtOAc); IR (film) ν_{max} 2941, 1700, 1418, 1337, 1143, 1039, 778 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 4.91 (dt, $J = 10.1, 2.6$ Hz, 1H), 4.17-4.24 (m, 1H), 3.83 (s, 3H), 3.04 (s, 3H), 2.41-2.46 (m, 2H), 2.26-2.33 (m, 1H), 1.97-2.05 (m, 2H), 1.78-1.87 (m, 3H), 1.61-1.67 (m, 3H), 1.59 (br. s., 6H), 1.55 (d, $J = 6.6$ Hz,

4H), 1.48-1.52 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 174.2, 83.3, 64.3, 55.5, 38.9, 34.7, 29.6, 28.8, 20.4, 15.0; HRMS-ESI calcd for $\text{C}_{10}\text{H}_{20}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$: 266.1062, found: 266.1061.

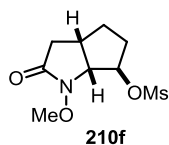


210c: Following Representative Procedure 4, to a solution of **181c** (17.5 mg, 0.089 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (7 μL , 0.089 mmol, 1.0 equiv) and HMIB (42 mg, 0.13 mmol, 1.5 equiv) at 0 $^\circ\text{C}$. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **210c** (25.8 mg, 99%) as a colorless oil; R_f 0.33 (EtOAc); IR (film) ν_{max} 2937, 1723, 1640, 1412, 1334, 1170, 1041, 905, 776 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 5.79 (ddt, J = 16.9, 10.3, 6.6 Hz, 1H), 5.02-5.13 (m, 3H), 4.25-4.31 (m, 1H), 3.77 (s, 3H), 3.08 (s, 3H), 2.47-2.54 (m, 1H), 2.35-2.44 (m, 1H), 2.25-2.34 (m, 1H), 2.12-2.19 (m, 2H), 1.86-1.93 (m, 1H), 1.63-1.85 (m, 4H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 167.4, 136.5, 116.2, 79.8, 60.6, 59.6, 38.4, 33.2, 29.8, 27.5, 23.3, 19.0; HRMS-ESI calcd for $\text{C}_{12}\text{H}_{22}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$: 292.1219, found: 292.1223.

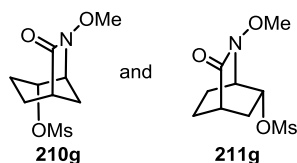


210d: Following Representative Procedure 4, to a solution of **181d** (18.8 mg, 0.066 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (5 μL , 0.066 mmol, 1.0 equiv) and HMIB (31 mg, 0.099 mmol, 1.5 equiv) at 0 $^\circ\text{C}$. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **210d** (20.3 mg, 81%) as a white solid; mp 162-165 $^\circ\text{C}$ (EtOAc/hexanes); R_f 0.44 (EtOAc); IR (film) ν_{max} 2941, 1679, 1445, 1404, 1345, 1167, 1039, 954, 910 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.82 (d, J = 7.3 Hz, 2H), 7.67-7.72 (m, 1H), 7.59-7.64 (m, 2H), 5.16

(qd, $J = 6.6, 3.1$ Hz, 1H), 3.95-4.00 (m, 1H), 3.90-3.95 (m, 1H), 3.74 (s, 3H), 3.63-3.68 (m, 2H), 3.45 (dd, $J = 12.8, 7.0$ Hz, 1H), 3.02 (s, 3H), 1.52 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 161.5, 135.4, 133.9, 129.7, 127.7, 74.9, 61.6, 60.1, 49.6, 43.3, 38.7, 17.9; HRMS-ESI calcd for $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}_7\text{S}_2$ $[\text{M}+\text{H}]^+$: 393.0790, found: 393.0787.



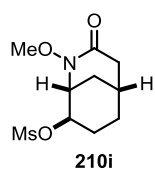
210f: Following Representative Procedure 4, to a solution of **181f** (16.7 mg, 0.11 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (8.2 μL , 0.11 mmol, 1.0 equiv) and HMIB (51 mg, 0.16 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **210f** (24.0 mg, 89%) as a colorless oil; R_f 0.23 (EtOAc); IR (film) ν_{max} 2941, 1689, 1350, 1171, 941, 898, 801 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 5.12 (br. s., 1H), 4.34 (d, $J = 7.7$ Hz, 1H), 3.84 (s, 3H), 3.06 (s, 3H), 2.89-2.96 (m, 1H), 2.66 (dd, $J = 17.7, 10.5$ Hz, 1H), 2.15-2.24 (m, 1H), 2.00-2.08 (m, 3H), 1.62 (ddt, $J = 13.0, 6.5, 3.1$ Hz, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 169.0, 82.6, 66.1, 62.2, 38.3, 34.1, 31.4, 31.1, 30.4; HRMS-ESI calcd for $\text{C}_9\text{H}_{16}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$: 250.0749, found: 250.0739.



210g and 211g: Following Representative Procedure 4, to a solution of **181g** (17.0 mg, 0.11 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (8.4 μL , 0.11 mmol, 1.0 equiv) and HMIB (52 mg, 0.16 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **210g** (8.7 mg, 32%) and **211g** (18.3 mg, 67%).

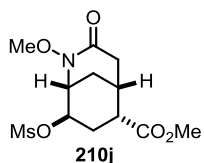
Analytical data for **210g**: colorless oil; R_f 0.37 (EtOAc); IR (film) ν_{\max} 2939, 1721, 1450, 1348, 1165, 927, 844, 656 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 5.05 (br. s., 1H), 4.13 (t, J = 4.4 Hz, 1H), 3.83 (s, 3H), 3.08 (s, 3H), 2.50 (br. s., 1H), 2.14 (d, J = 11.7 Hz, 1H), 2.01-2.07 (m, 1H), 1.94-2.01 (m, 2H), 1.84-1.90 (m, 1H), 1.75-1.82 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 175.4, 73.8, 63.7, 57.1, 38.4, 37.2, 26.3, 24.6, 22.9; HRMS-ESI calcd for $\text{C}_9\text{H}_{16}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$: 250.0749, found: 250.0739.

Analytical data for **211g**: colorless oil; R_f 0.23 (EtOAc); IR (film) ν_{\max} 2925, 1688, 1456, 1350, 1173, 1038, 967, 867 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 4.98-5.04 (m, 1H), 4.16 (br. s., 1H), 3.82 (s, 3H), 3.08 (s, 3H), 2.64-2.67 (m, 1H), 2.40-2.48 (m, 1H), 2.16-2.23 (m, 1H), 1.86-1.98 (m, 2H), 1.79-1.85 (m, 1H), 1.73 (dt, J = 14.6, 2.7 Hz, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 172.0, 74.7, 63.7, 59.1, 38.6, 38.4, 31.6, 23.2, 20.6; HRMS-ESI calcd for $\text{C}_9\text{H}_{16}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$: 250.0749, found: 250.0744.

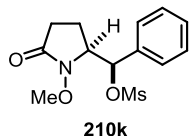


210i: Following Representative Procedure 4, to a solution of **181i** (13.2 mg, 0.078 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (6 μL , 0.078 mmol, 1.0 equiv) and HMIB (37 mg, 0.12 mmol, 1.5 equiv) at 0 $^\circ\text{C}$. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **210i** (20.5 mg, 99%) as a white solid; mp 98-100 $^\circ\text{C}$ (EtOAc/hexanes); R_f 0.26 (EtOAc); IR (film) ν_{\max} 2936, 2910, 1659, 1450, 1403, 1345, 1163, 912, 839, 750 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 5.01 (br. s., 1H), 4.04 (br. s., 1H), 3.78 (s, 3H), 3.06 (s, 3H), 2.72 (dd, J = 17.2, 5.2 Hz, 1H), 2.27-2.38 (m, 2H), 2.22 (br. s., 1H), 1.91 (d, J = 12.9 Hz, 3H), 1.77-1.87 (m, 1H), 1.58 (d, J = 12.9 Hz, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 169.2, 74.9,

62.3, 56.6, 38.4, 38.2, 26.9, 26.1, 26.0, 22.1; HRMS-ESI calcd for $C_{10}H_{18}NO_5S$ $[M+H]^+$: 264.0906, found: 264.0900.

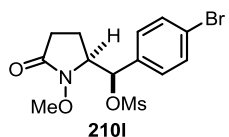


210j: Following Representative Procedure 4, to a solution of **181j** (14.2 mg, 0.063 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (5 μ L, 0.063 mmol, 1.0 equiv) and HMIB (30 mg, 0.094 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **210j** (20.0 mg, 99%) as a white solid; mp 117-119 °C (EtOAc/hexanes); R_f 0.30 (EtOAc); IR (film) ν_{max} 2940, 1721, 1655, 1444, 1164, 964, 929 cm^{-1} ; 1H NMR ($CDCl_3$, 500 MHz): δ 5.10 (d, J = 2.1 Hz, 1H), 4.05 (d, J = 2.1 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.08 (s, 3H), 2.93 (d, J = 13.4 Hz, 1H), 2.65 (br. s., 1H), 2.59-2.63 (m, 1H), 2.31-2.43 (m, 2H), 2.24 (d, J = 15.9 Hz, 1H), 1.93-2.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.6, 168.0, 74.5, 62.4, 56.0, 52.2, 41.0, 38.4, 34.5, 28.6, 27.3, 24.4; HRMS-ESI calcd for $C_{12}H_{20}NO_7S$ $[M+H]^+$: 322.0960, found: 322.0966.

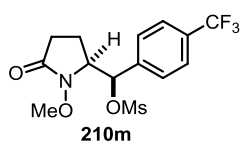


210k: Following Representative Procedure 4, to a solution of **181k** (14.7 mg, 0.072 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (5.5 μ L, 0.072 mmol, 1.0 equiv) and HMIB (34 mg, 0.11 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **210k** (20.0 mg, 93%) as a colorless oil; R_f 0.40 (EtOAc); IR (film) ν_{max} 2923, 1668, 1495, 1452, 1150, 1040, 702 cm^{-1} ; 1H NMR ($CDCl_3$, 500 MHz): δ 7.39-7.44 (m, 5H), 5.93 (s, 1H), 4.07 (s, 1H), 3.93 (s, 3H), 2.97 (s, 3H), 2.29-2.38 (m, 2H), 1.95-2.12 (m, 2H); ^{13}C

NMR (CDCl₃, 126 MHz): δ 171.6, 134.8, 129.0 (3C), 126.0 (2C), 80.6, 63.0, 60.6, 39.2, 26.6, 15.6; HRMS-ESI calcd for C₁₃H₁₈NO₅S [M+H]⁺: 300.0906, found: 300.0910.

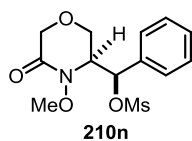


210l: Following Representative Procedure 4, to a solution of **181l** (15.5 mg, 0.055 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added TFA (4 μ L, 0.055 mmol, 1.0 equiv) and HMIB (26 mg, 0.082 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **210l** (13.7 mg, 66%) as a colorless oil; *R_f* 0.31 (EtOAc); IR (film) ν_{max} 2929, 1703, 1490, 1456, 1348, 1172, 1050, 789 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 5.86-5.89 (m, 1H), 3.99-4.04 (m, 1H), 3.91 (s, 3H), 3.00 (s, 3H), 2.38 (ddd, *J* = 17.5, 9.9, 7.8 Hz, 1H), 2.27 (ddd, *J* = 17.2, 9.9, 3.8 Hz, 1H), 1.99-2.06 (m, 1H), 1.88-1.96 (m, 1H); ¹³C NMR (CDCl₃, 126 MHz): δ 171.3, 134.1, 132.2, 127.6, 123.1, 79.8, 62.9, 60.2, 39.1, 26.5, 15.4; HRMS-ESI calcd for C₁₃H₁₇BrNO₅S [M+H]⁺: 378.0011, found: 378.0004.



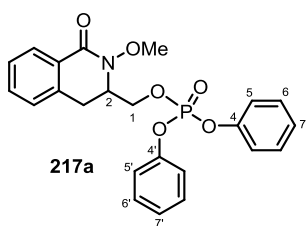
210m: Following Representative Procedure 4, to a solution of **181m** (18.9 mg, 0.069 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added TFA (5.3 μ L, 0.069 mmol, 1.0 equiv) and HMIB (33 mg, 0.10 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **210m** (17.0 mg, 67%) as a white solid; mp 157-159 °C (EtOAc/hexanes); *R_f* 0.38 (EtOAc); IR (film) ν_{max} 2924, 2853, 1705, 1387, 1351, 1173, 1105, 946, 798 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.71 (d, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 7.6 Hz, 2H), 6.01 (br. s., 1H), 4.07 (d, *J* = 7.2 Hz, 1H), 3.95 (s, 3H), 3.06 (s, 3H), 2.39-2.49

(m, 1H), 2.27-2.37 (m, 1H), 2.04 (t, $J = 11.0$ Hz, 1H), 1.87-1.97 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 171.4, 139.2, 131.1, 127.6, 126.2, 126.1, 126.0, 79.5, 63.1, 60.3, 39.2, 26.5, 15.3; HRMS-ESI calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_5\text{SF}_3$ $[\text{M}+\text{H}]^+$: 368.0780, found: 368.0776.



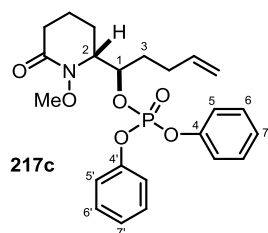
210n: Following Representative Procedure 4, to a solution of **181n** (16.4 mg, 0.074 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (6 μL , 0.074 mmol, 1.0 equiv) and HMIB (35 mg, 0.11 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **210n** (15.3 mg, 65%) as a colorless oil; R_f 0.40 (EtOAc); IR (film) ν_{max} 2924, 1667, 1454, 1418, 1325, 1121, 1039, 702 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.37-7.47 (m, 5H), 6.02 (d, $J = 4.0$ Hz, 1H), 4.22 (s, 2H), 4.04-4.11 (m, 2H), 3.76-3.81 (m, 4H), 2.94 (s, 3H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 165.2, 134.6, 129.3, 129.1, 126.4, 79.5, 69.0, 64.4, 62.1, 62.0, 39.2; HRMS-ESI calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_6\text{S}$ $[\text{M}+\text{H}]^+$: 316.0855, found: 316.0852

1.11.10 HPIB-Mediated Cyclization

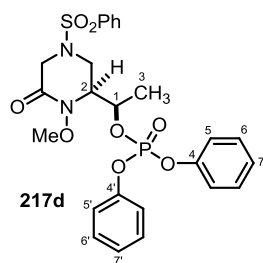


217a: Following Representative Procedure 4, to a solution of **181a** (12.7 mg, 0.066 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (5 μL , 0.066 mmol, 1.0 equiv) and HPIB (47 mg, 0.10 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **217a** (23.2 mg, 79%) as a colorless oil; R_f 0.64 (EtOAc); IR (film) ν_{max} 2935, 1668, 1589, 1487, 1459, 1284, 1162, 950, 687 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 8.10 (d, $J = 7.7$ Hz, 1H), 7.43-7.48 (m, 1H),

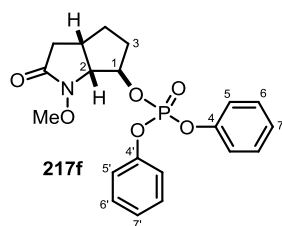
7.30-7.39 (m, 5H), 7.17-7.23 (m, 4H), 7.13 (t, $J = 8.3$ Hz, 3H), 4.45-4.51 (m, 1H), 4.18-4.28 (m, 2H), 3.91 (s, 3H), 3.34 (dd, $J = 16.5, 5.3$ Hz, 1H), 3.20 (dd, $J = 16.5, 3.8$ Hz, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 163.2, 150.30 (d, $J = 6.9$ Hz, C-4'), 150.26 (d, $J = 6.9$ Hz, C-4), 134.7, 132.7, 129.88 (C-6'), 129.85 (C-6), 128.2, 128.0, 127.8, 127.4, 125.57 (C-7'), 125.55 (C-7), 119.97 (d, $J = 4.2$ Hz, C-5'), 119.93 (d, $J = 4.2$ Hz, C-5), 65.8 (d, $J = 6.5$ Hz, C-1), 63.1, 57.8 (d, $J = 8.3$ Hz, C-2), 30.5; HRMS-ESI calcd for $\text{C}_{23}\text{H}_{23}\text{NO}_6\text{P}$ $[\text{M}+\text{H}]^+$: 440.1263, found: 440.1258.



217c: Following Representative Procedure 4, to a solution of **181c** (11.0 mg, 0.056 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (4.3 μL , 0.056 mmol, 1.0 equiv) and HPIB (40 mg, 0.084 mmol, 1.5 equiv) at 0 $^\circ\text{C}$. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **217c** (13.1 mg, 53%) as a colorless oil; R_f 0.29 (EtOAc); IR (film) ν_{max} 2937, 1668, 1641, 1589, 1487, 1283, 1186, 952, 772, 689 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.33-7.40 (m, 4H), 7.19-7.27 (m, 6H), 5.75 (ddt, $J = 17.0, 10.4, 6.7$ Hz, 1H), 4.96-5.02 (m, 3H), 4.08-4.13 (m, 1H), 3.74 (s, 3H), 2.40-2.47 (m, 1H), 2.29-2.36 (m, 1H), 2.23 (dt, $J = 14.8, 7.3$ Hz, 1H), 2.10 (dt, $J = 14.8, 7.3$ Hz, 1H), 1.88-1.95 (m, 1H), 1.70-1.82 (m, 4H), 1.49-1.56 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 167.8, 150.51 (d, $J = 6.9$ Hz, C-4'), 150.44 (d, $J = 6.9$ Hz, C-4), 136.8, 129.9 (C-6, 6'), 125.56 (C-7'), 125.50 (C-7), 120.08 (d, $J = 4.6$ Hz, C-5'), 119.98 (d, $J = 4.6$ Hz, C-5), 115.8, 78.7 (d, $J = 6.5$ Hz, C-1), 60.7, 60.0 (d, $J = 1.8$ Hz, C-2), 33.3, 29.8, 28.5 (d, $J = 6.5$ Hz, C-3), 23.2, 19.2; HRMS-ESI calcd for $\text{C}_{23}\text{H}_{29}\text{NO}_6\text{P}$ $[\text{M}+\text{H}]^+$: 446.1733, found: 446.1730.

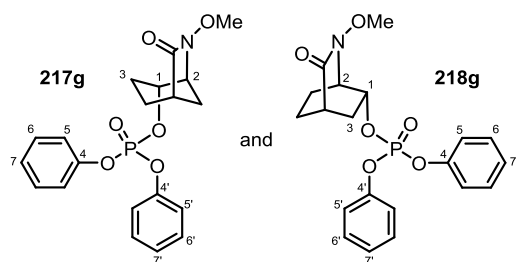


217d: Following Representative Procedure 4, to a solution of **181d** (11.2 mg, 0.039 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (3 μL , 0.039 mmol, 1.0 equiv) and HPIB (28 mg, 0.059 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **217d** (11.2 mg, 53%) as a colorless oil; R_f 0.36 (EtOAc); IR (film) ν_{max} 2923, 1683, 1590, 1488, 1327, 1282, 1164, 953, 689 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.79 (d, J = 7.7 Hz, 2H), 7.69 (t, J = 7.4 Hz, 1H), 7.60 (t, J = 7.7 Hz, 2H), 7.32-7.38 (m, 2H), 7.28-7.32 (m, 2H), 7.14-7.24 (m, 6H), 5.11-5.18 (m, 1H), 3.85 (br. s., 1H), 3.74 (d, J = 16.0 Hz, 1H), 3.67 (s, 3H), 3.53 (d, J = 16.0 Hz, 1H), 3.40-3.51 (m, 2H), 1.47 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 161.7, 150.38 (d, J = 7.4 Hz, C-4'), 150.34 (d, J = 7.4 Hz, C-4), 135.3, 133.7, 129.84 (C-6'), 129.80 (C-6), 129.6, 127.7, 125.53 (C-7'), 125.45 (C-7), 120.15 (d, J = 4.6 Hz, C-5'), 120.02 (d, J = 4.6 Hz, C-5), 74.0 (d, J = 6.0 Hz, C-1), 61.8, 61.3 (d, J = 7.9 Hz, C-2), 49.6, 43.7, 17.9 (d, J = 1.8 Hz, C-3); HRMS-ESI calcd for $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_8\text{PS}$ $[\text{M}+\text{H}]^+$: 547.1304, found: 547.1299.



217f: Following Representative Procedure 4, to a solution of **181f** (22.5 mg, 0.15 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (11 μL , 0.15 mmol, 1.0 equiv) and HPIB (102 mg, 0.22 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **217f** (34.0 mg, 58%) as a colorless oil; R_f 0.30 (EtOAc); IR (film) ν_{max} 2926, 1708, 1589, 1387, 1282, 1186, 1018, 940, 767, 689 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.33-7.39 (m, 4H), 7.19-7.26 (m, 6H), 5.11-5.15 (m, 1H), 4.25 (d, J = 7.6 Hz, 1H), 3.76 (s, 3H), 2.82-2.89 (m, 1H), 2.62 (dd, J = 17.7,

10.5 Hz, 1H), 2.10-2.19 (m, 1H), 1.98-2.06 (m, 2H), 1.88-1.97 (m, 1H), 1.53-1.59 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 169.2, 150.4 (d, $J = 7.4$ Hz, C-4, 4'), 129.8 (C-6, 6'), 125.5 (C-7, 7'), 119.99 (d, $J = 4.6$ Hz, C-5'), 119.96 (d, $J = 4.6$ Hz, C-5), 81.4 (d, $J = 6.5$ Hz, C-1), 66.5 (d, $J = 6.9$ Hz, C-2), 62.2, 34.3, 31.3, 31.0, 30.6 (d, $J = 5.1$ Hz, C-3); HRMS-ESI calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_6\text{P}$ $[\text{M}+\text{H}]^+$: 404.1263, found: 404.1265.



217g and **218g**: Following Representative

Procedure 4, to a solution of **181g** (25.0 mg, 0.16

mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added

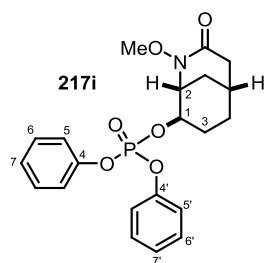
TFA (12 μL , 0.16 mmol, 1.0 equiv) and HPIB (114

mg, 0.24 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **217g** (15.6 mg, 24%) and **218g** (36.9 mg, 56%).

Analytical data for **217g**: colorless oil; R_f 0.50 (EtOAc); IR (film) ν_{max} 2940, 1728, 1589, 1487, 1285, 1186, 1009, 940, 689 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.34-7.40 (m, 4H), 7.20-7.26 (m, 6H), 4.98-5.03 (m, 1H), 4.00 (t, $J = 4.4$ Hz, 1H), 3.79 (s, 3H), 2.43 (br. s., 1H), 2.05 (d, $J = 11.7$ Hz, 1H), 1.85-1.98 (m, 3H), 1.76-1.82 (m, 1H), 1.69 (tdd, $J = 12.8, 5.9, 1.7$ Hz, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 175.5, 150.4 (d, $J = 7.4$ Hz, C-4, 4'), 129.9 (C-6, 6'), 125.6 (C-7, 7'), 120.02 (d, $J = 4.6$ Hz, C-5'), 119.99 (d, $J = 4.6$ Hz, C-5), 72.6 (d, $J = 6.5$ Hz, C-1), 63.5, 57.2 (d, $J = 5.5$ Hz, C-2), 37.4, 26.2, 24.9 (d, $J = 4.6$ Hz, C-3), 22.8; HRMS-ESI calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_6\text{P}$ $[\text{M}+\text{H}]^+$: 404.1263, found: 404.1260.

Analytical data for **218g**: colorless oil; R_f 0.38 (EtOAc); IR (film) ν_{max} 2968, 2940, 1669, 1589, 1486, 1288, 1185, 1009, 938, 755, 688 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.34-7.40

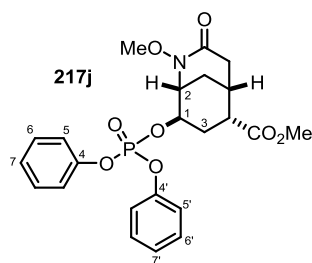
(m, 4H), 7.19-7.25 (m, 6H), 4.98 (td, $J = 9.8, 3.5$ Hz, 1H), 4.02 (br. s., 1H), 3.78 (s, 3H), 2.60 (br. s., 1H), 2.37 (t, $J = 12.0$ Hz, 1H), 2.07-2.13 (m, 1H), 1.73-1.88 (m, 3H), 1.66 (dt, $J = 14.5, 2.6$ Hz, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 172.2, 150.2 (d, $J = 6.9$ Hz, C-4, 4'), 129.9 (C-6, 6'), 125.7 (C-7, 7'), 119.9 (d, $J = 5.1$ Hz, C-5, 5'), 74.0 (d, $J = 6.5$ Hz, C-1), 63.6, 59.3 (d, $J = 5.5$ Hz, C-2), 38.7, 32.2 (d, $J = 5.5$ Hz, C-3), 23.3, 20.4; HRMS-ESI calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_6\text{P}$ $[\text{M}+\text{H}]^+$: 404.1263, found: 404.1262.



217i: Following Representative Procedure 4, to a solution of **181i**

(15.8 mg, 0.093 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (7.2 μL , 0.093 mmol, 1.0 equiv) and HPIB (66 mg, 0.14 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **217i** (18.9 mg, 48%) as a

colorless oil; R_f 0.33 (EtOAc); IR (film) ν_{max} 2937, 1694, 1589, 1487, 1455, 1285, 1186, 1009, 947, 754, 688 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.34-7.40 (m, 4H), 7.19-7.27 (m, 6H), 4.95-5.01 (m, 1H), 3.88-3.92 (m, 1H), 3.74 (s, 3H), 2.69 (dd, $J = 17.7, 6.4$ Hz, 1H), 2.29-2.35 (m, 1H), 2.22 (dd, $J = 13.5, 2.8$ Hz, 1H), 2.16 (br. s., 1H), 1.76-1.91 (m, 4H), 1.74 (br. s., 1H), 1.50 (d, $J = 11.8$ Hz, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 169.2, 150.46 (d, $J = 7.9$ Hz, C-4'), 150.43 (d, $J = 7.9$ Hz, C-4), 129.9 (C-6, 6'), 125.5 (C-7, 7'), 120.01 (d, $J = 4.6$ Hz, C-5'), 119.97 (d, $J = 4.6$ Hz, C-5), 73.5 (d, $J = 6.9$ Hz, C-1), 62.1, 56.8 (d, $J = 6.0$ Hz, C-2), 38.2, 26.8, 26.2, 26.1, 22.4 (d, $J = 4.6$ Hz, C-3); HRMS-ESI calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_6\text{P}$ $[\text{M}+\text{H}]^+$: 418.1420, found: 418.1412.



217j: Following Representative Procedure 4, to a solution of **181j**

(18.2 mg, 0.080 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added TFA

(6.2 μL, 0.080 mmol, 1.0 equiv) and HPIB (57 mg, 0.12 mmol, 1.5

equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in*

vacuo and purified by flash chromatography (EtOAc) to provide **217j** (28.9 mg, 76%) as a

colorless oil; R_f 0.29 (EtOAc); IR (film) ν_{max} 2934, 1730, 1675, 1589, 1487, 1438, 1283,

1185, 1010, 758, 689 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.33-7.41 (m, 4H), 7.24 (m, 6H),

5.06 (dd, *J* = 7.0, 3.0 Hz, 1H), 3.88-3.93 (m, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 2.79-2.86 (m,

1H), 2.55-2.62 (m, 2H), 2.34-2.41 (m, 1H), 2.16-2.26 (m, 2H), 1.85-1.96 (m, 2H); ¹³C NMR

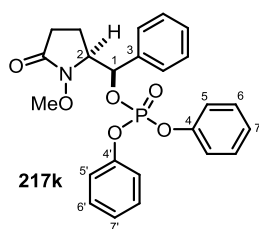
(CDCl₃, 126 MHz): δ 172.8, 168.0, 150.34 (d, *J* = 7.4 Hz, C-4'), 150.31 (d, *J* = 7.4 Hz, C-4),

129.9 (C-6, 6'), 125.6 (C-7, 7'), 119.98 (d, *J* = 4.6 Hz, C-5'), 119.94 (d, *J* = 4.6 Hz, C-5),

73.3 (d, *J* = 6.5 Hz, C-1), 62.2, 56.1 (d, *J* = 5.5 Hz, C-2), 52.1, 40.9, 34.5, 29.7, 28.7, 27.2,

24.6 (d, *J* = 4.2 Hz, C-3); HRMS-ESI calcd for C₂₃H₂₇NO₈P [M+H]⁺: 476.1474, found:

476.1478.



217k: Following Representative Procedure 4, to a solution of **181k**

(18.3 mg, 0.089 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added TFA (7

μL, 0.089 mmol, 1.0 equiv) and HPIB (63 mg, 0.13 mmol, 1.5 equiv)

at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and

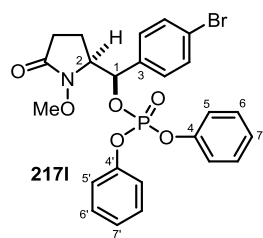
purified by flash chromatography (EtOAc) to provide **217k** (30.5 mg, 75%) as a colorless oil;

R_f 0.25 (EtOAc); IR (film) ν_{max} 2936, 1673, 1589, 1487, 1277, 1185, 1010, 941, 800 cm⁻¹; ¹H

NMR (CDCl₃, 500 MHz): δ 7.30-7.37 (m, 8H), 7.17-7.26 (m, 5H), 6.99 (d, *J* = 8.2 Hz, 2H),

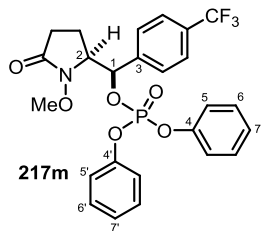
5.90 (dd, *J* = 8.2, 1.8 Hz, 1H), 3.97-4.03 (m, 1H), 3.83 (s, 3H), 2.12-2.17 (m, 3H), 1.84-1.93

(m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 171.6, 150.40 (d, $J = 7.4$ Hz, C-4'), 150.28 (d, $J = 7.4$ Hz, C-4), 135.3 (d, $J = 1.8$ Hz, C-3), 129.77 (C-6'), 129.64 (C-6), 128.9, 128.7, 126.6, 125.47 (C-7'), 125.27 (C-7), 120.13 (d, $J = 4.6$ Hz, C-5'), 119.92 (d, $J = 4.6$ Hz, C-5), 79.3 (d, $J = 6.0$ Hz, C-1), 62.7, 61.7 (d, $J = 7.9$ Hz, C-2), 26.6, 15.7; HRMS-ESI calcd for $\text{C}_{24}\text{H}_{25}\text{NO}_6\text{P}$ $[\text{M}+\text{H}]^+$: 454.1420, found: 454.1404.

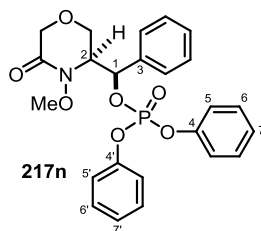


217I: Following Representative Procedure 4, to a solution of **181I** (14.6 mg, 0.051 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (4 μL , 0.051 mmol, 1.0 equiv) and HPIB (36 mg, 0.077 mmol, 1.5 equiv) at 0 $^\circ\text{C}$. After 1 h, the reaction mixture was concentrated *in vacuo* and

purified by flash chromatography (EtOAc) to provide **217I** (15.3 mg, 56%) as a colorless oil; R_f 0.42 (EtOAc); IR (film) ν_{max} 2935, 1683, 1589, 1487, 1285, 1185, 1044, 949, 800, 688 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.45 (d, $J = 8.3$ Hz, 2H), 7.30-7.36 (m, 2H), 7.12-7.28 (m, 8H), 7.01 (d, $J = 8.3$ Hz, 2H), 5.83 (d, $J = 8.2$ Hz, 1H), 3.92-3.98 (m, 1H), 3.80 (s, 3H), 2.12-2.18 (m, 2H), 2.00-2.08 (m, 1H), 1.83-1.93 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 171.5, 150.30 (d, $J = 7.4$ Hz, C-4'), 150.21 (d, $J = 7.4$ Hz, C-4), 134.4 (d, $J = 1.8$ Hz, C-3), 134.4, 131.8, 129.80 (C-6'), 129.71 (C-6), 128.2, 125.56 (C-7'), 125.39 (C-7), 123.0, 120.06 (d, $J = 4.6$ Hz, C-5'), 119.84 (d, $J = 4.6$ Hz, C-5), 78.7 (d, $J = 6.0$ Hz, C-1), 62.7, 61.4 (d, $J = 7.9$ Hz, C-2), 26.5, 15.6; HRMS-ESI calcd for $\text{C}_{24}\text{H}_{24}\text{NO}_6\text{BrP}$ $[\text{M}+\text{H}]^+$: 532.0525, found: 532.0521.

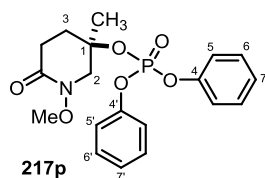


217m: Following Representative Procedure 4, to a solution of **181m** (12.5 mg, 0.046 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added TFA (3.5 μ L, 0.046 mmol, 1.0 equiv) and HPIB (32 mg, 0.069 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **217m** (23.7 mg, 99%) as a colorless oil; *R_f* 0.42 (EtOAc); IR (film) ν_{max} 2939, 1712, 1589, 1488, 1324, 1186, 1010, 947, 688 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.32-7.38 (m, 2H), 7.18-7.26 (m, 5H), 7.12-7.17 (m, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 5.96 (d, *J* = 8.0 Hz, 1H), 3.94-4.00 (m, 1H), 3.84 (s, 3H), 2.20 (dt, *J* = 9.6, 5.8 Hz, 2H), 2.04-2.14 (m, 1H), 1.83-1.92 (m, 1H); ¹³C NMR (CDCl₃, 126 MHz): δ 171.5, 150.28 (d, *J* = 6.9 Hz, C-4'), 150.16 (d, *J* = 6.9 Hz, C-4), 139.5, 131.2, 129.83 (C-6'), 129.73 (C-6), 126.9, 125.66 (C-7'), 125.63 (C-7), 125.5, 120.04 (d, *J* = 5.1 Hz, C-5'), 119.80 (d, *J* = 5.1 Hz, C-5), 78.4 (d, *J* = 6.0 Hz, C-1), 62.8, 61.6 (d, *J* = 7.9 Hz, C-2), 26.5, 15.4; HRMS-ESI calcd for C₂₅H₂₄NO₆F₃P [M+H]⁺: 522.1293, found: 522.1304.



217n: Following Representative Procedure 4, to a solution of **181n** (18.3 mg, 0.083 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added TFA (6.4 μ L, 0.083 mmol, 1.0 equiv) and HPIB (58 mg, 0.12 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **217n** (26.1 mg, 70%) as a colorless oil; *R_f* 0.41 (EtOAc); IR (film) ν_{max} 2924, 2854, 1683, 1589, 1488, 1456, 1284, 1135, 1009, 754, 689 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.30-7.38 (m, 8H), 7.22-7.27 (m, 2H), 7.15-7.22 (m, 3H), 7.01 (d, *J* = 8.1 Hz, 2H), 6.04 (dd, *J* = 8.4, 3.7 Hz, 1H), 4.07-4.12

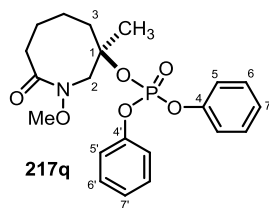
(m, 1H), 4.02 (d, $J = 16.5$ Hz, 2H), 3.90 (d, $J = 12.1$ Hz, 1H), 3.76 (dd, $J = 12.1, 4.2$ Hz, 1H), 3.71 (s, 3H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 165.3, 150.36 (d, $J = 6.9$ Hz, C-4'), 150.27 (d, $J = 6.9$ Hz, C-4), 139.3, 135.3 (d, $J = 1.4$ Hz, C-3), 129.79 (C-6'), 129.67 (C-6), 129.1, 128.7, 126.8, 125.60 (C-7'), 125.53 (C-7), 125.4, 120.04 (d, $J = 4.6$ Hz, C-5'), 119.87 (d, $J = 4.6$ Hz, C-5), 78.4 (d, $J = 5.5$ Hz, C-1), 68.9, 64.3, 63.3 (d, $J = 8.3$ Hz, C-2), 62.2; HRMS-ESI calcd for $\text{C}_{24}\text{H}_{25}\text{NO}_7\text{P}$ $[\text{M}+\text{H}]^+$: 470.1369, found: 470.1364.



217p: Following Representative Procedure 4, to a solution of **181p**

(19.6 mg, 0.14 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA (11 μL , 0.14 mmol, 1.0 equiv) and HPIB (97 mg, 0.21 mmol, 1.5

equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **217p** (31.1 mg, 58%) as a colorless oil; R_f 0.10 (EtOAc); IR (film) ν_{max} 2936, 1667, 1589, 1487, 1288, 1215, 1187, 1038, 940, 772, 689 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.36 (q, $J = 7.5$ Hz, 4H), 7.18-7.26 (m, 6H), 4.16 (dd, $J = 12.6, 2.2$ Hz, 1H), 3.59 (s, 3H), 3.54 (d, $J = 12.6$ Hz, 1H), 2.51-2.60 (m, 1H), 2.36-2.43 (m, 1H), 2.24-2.30 (m, 1H), 1.80-1.89 (m, 1H), 1.73 (s, 3H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 165.0, 150.46 (d, $J = 7.4$ Hz, C-4'), 150.35 (d, $J = 7.4$ Hz, C-4), 129.9 (C-6, 6'), 125.63 (C-7'), 125.59 (C-7), 120.13 (d, $J = 4.6$ Hz, C-5'), 120.03 (d, $J = 4.6$ Hz, C-5), 82.2 (d, $J = 6.9$ Hz, C-1), 60.7, 57.7 (d, $J = 4.6$ Hz, C-2), 33.4 (d, $J = 6.9$ Hz, C-3), 28.4, 24.9; HRMS-ESI calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_6\text{P}$ $[\text{M}+\text{H}]^+$: 392.1263, found: 392.1254.



217q: Following Representative Procedure 4, to a solution of **181q**

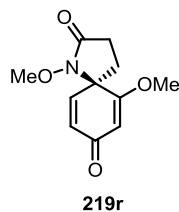
(21.4 mg, 0.13 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added TFA

(10 μ L, 0.13 mmol, 1.0 equiv) and HPIB (88 mg, 0.19 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **217q** (33.4 mg, 64%) as a colorless oil; R_f 0.23 (EtOAc); IR (film) ν_{\max} 2926, 1665, 1590, 1488, 1455, 1283, 1188, 1010, 936, 755, 688 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.32-7.38 (m, 4H), 7.18-7.25 (m, 6H), 4.03 (d, J = 15.8 Hz, 1H), 3.84 (d, J = 15.8 Hz, 1H), 3.69 (s, 3H), 2.38-2.46 (m, 1H), 2.28-2.37 (m, 1H), 1.86 (br. s., 1H), 1.73-1.80 (m, 1H), 1.70 (s, 3H), 1.54-1.65 (m, 3H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 171.1, 150.6 (d, J = 7.9 Hz, C-4, 4'), 129.74 (C-6'), 129.73 (C-6), 125.33 (C-7'), 125.27 (C-7), 120.19 (d, J = 4.6 Hz, C-5'), 120.04 (d, J = 4.6 Hz, C-5), 89.1 (d, J = 6.9 Hz, C-1), 61.1, 54.5 (d, J = 4.2 Hz, C-2), 37.3 (d, J = 6.0 Hz, C-3), 35.1, 28.0, 21.8; HRMS-ESI calcd for $\text{C}_{21}\text{H}_{27}\text{NO}_6\text{P}$ $[\text{M}+\text{H}]^+$: 420.1576, found: 420.1579.

1.11.11 I(III)-Mediated Cyclization of Aryl Hydroxamates

Representative Procedure 5. Hydroxamate Cyclization using I(III) Reagents

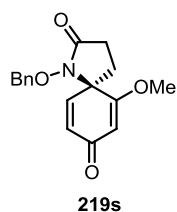
To a cooled (0° C) solution of *O*-alkyl hydroxamate (0.10 mmol) in DCM (2 mL, 0.05 M) under N_2 , was added I(III) reagent (1.5 equivalent). The reaction mixture was stirred for 1 h. Upon completion (by TLC), the reaction mixture was concentrated *in vacuo* and the residue purified by flash chromatography on silica gel (EtOAc) to provide the product.



219r: Using HMIB: Following Representative Procedure 5, to a solution of **181r** (17.4 mg, 0.073 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added HMIB (35 mg, 0.11 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to

provide **219r** (15.6 mg, 96%).

Using HTIB: Following Representative Procedure 5, to a solution of **181r** (18.9 mg, 0.079 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added HTIB (47 mg, 0.12 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **219r** (15.2 mg, 86%) as a white solid; mp 133-135 °C (EtOAc/hexanes); *R_f* 0.26 (EtOAc); IR (film) ν_{max} 2939, 1733, 1670, 1652, 1558, 1373, 1178, 1001, 856, 696 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 6.62 (d, *J* = 9.9 Hz, 1H), 6.30 (dd, *J* = 9.9, 1.5 Hz, 1H), 5.62 (d, *J* = 1.5 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.62 (ddd, *J* = 17.2, 9.9, 8.6 Hz, 1H), 2.46 (ddd, *J* = 17.1, 9.9, 3.2 Hz, 1H), 2.24 (ddd, *J* = 13.4, 9.9, 3.2 Hz, 1H), 2.08-2.18 (m, 1H); ¹³C NMR (CDCl₃, 101 MHz): δ 186.3, 173.1, 172.7, 144.2, 130.3, 103.2, 64.6, 62.8, 56.2, 27.3, 26.2; HRMS-ESI calcd for C₁₁H₁₄NO₄ [M+H]⁺: 224.0923, found: 224.0917.

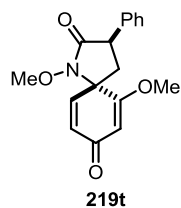


219s: Using HMIB: Following Representative Procedure 5, to a solution of **181s** (23.6 mg, 0.075 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added HMIB (36 mg, 0.11 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to

provide **219s** (22.3 mg, 100%).

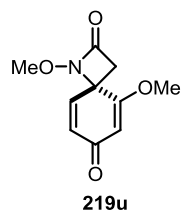
Using HTIB: Following Representative Procedure 5, to a solution of **181r** (26.5 mg, 0.084 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added HTIB (50 mg, 0.13 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **219r** (22.1 mg, 88%) as a white solid; mp 142-143 °C (EtOAc/hexanes); *R_f* 0.36 (EtOAc); IR (film) ν_{max} 2944, 1724, 1664, 1602, 1369, 1227,

1176, 1066, 999, 858, 756, 698 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.29-7.36 (m, 5H), 6.17 (d, J = 9.9 Hz, 1H), 6.10 (d, J = 9.3 Hz, 1H), 5.57 (s, 1H), 4.94 (s, 2H), 3.74 (s, 3H), 2.58-2.67 (m, 1H), 2.47 (ddd, J = 17.0, 9.9, 2.6 Hz, 1H), 2.16-2.24 (m, 1H), 2.07 (dt, J = 12.8, 9.9 Hz, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 186.4, 173.7, 172.9, 144.4, 134.7, 129.8, 129.7, 128.9, 128.4, 103.0, 78.4, 62.8, 56.2, 27.4, 26.3; HRMS-ESI calcd for $\text{C}_{17}\text{H}_{18}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 300.1236, found: 300.1227.



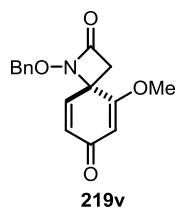
219t: Using HMIB: Following Representative Procedure 5, to a solution of **181t** (25.5 mg, 0.081 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added HMIB (38 mg, 0.12 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **219t** (21.2 mg, 88%).

Using HTIB: Following Representative Procedure 5, to a solution of **181t** (24.2 mg, 0.077 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added HTIB (45 mg, 0.12 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **219t** (21.0 mg, 91%) as a white solid; mp 129-130 °C (EtOAc/hexanes); R_f 0.58 (EtOAc); IR (film) ν_{max} 1726, 1664, 1603, 1367, 1225 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.25-7.40 (m, 5H), 6.67 (d, J = 9.9 Hz, 1H), 6.33 (dd, J = 9.9, 1.5 Hz, 1H), 5.66 (d, J = 1.4 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 2.67 (dd, J = 13.5, 9.9 Hz, 1H), 2.15-2.22 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 186.3, 173.7, 172.6, 144.3, 138.5, 130.7, 129.0 (2C), 127.6 (3C), 103.3, 64.9, 61.9, 56.3, 43.7, 37.2; HRMS-ESI calcd for $\text{C}_{17}\text{H}_{18}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 300.1236, found: 300.1242.



219u: Using HMIB: Following Representative Procedure 5, to a solution of **181u** (25.8 mg, 0.11 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added HMIB (54 mg, 0.17 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **219u** (24.0 mg, 100%).

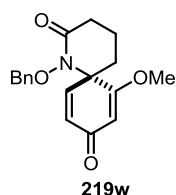
Using HTIB: Following Representative Procedure 5, to a solution of **181u** (26.4 mg, 0.12 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added HTIB (69 mg, 0.18 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **219u** (19.5 mg, 80%) as a white solid; mp 100-103 °C (EtOAc/hexanes); *R_f* 0.47 (EtOAc); IR (film) ν_{max} 1785, 1676, 1600, 1222 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 6.72 (d, *J* = 9.9 Hz, 1H), 6.35 (dd, *J* = 9.9, 1.5 Hz, 1H), 5.77 (d, *J* = 1.95 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.14 (d, *J* = 13.6 Hz, 1H), 2.82 (d, *J* = 13.6 Hz, 1H); ¹³C NMR (CDCl₃, 126 MHz): δ 186.2, 168.8, 162.9, 141.7, 131.6, 105.3, 64.9, 60.7, 56.2, 43.3; HRMS-ESI calcd for C₁₀H₁₂NO₄ [M+H]⁺: 210.0766, found: 210.0764.



219v: Using HMIB: Following Representative Procedure 5, to a solution of **181v** (21.6 mg, 0.072 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added HMIB (34 mg, 0.11 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **219v** (18.9 mg, 100%).

Using HTIB: Following Representative Procedure 5, to a solution of **181v** (26.0 mg, 0.086 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added HTIB (51 mg, 0.13 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash

chromatography (EtOAc) to provide **219v** (20.7 mg, 84%) as a white solid; mp 101-102 °C (EtOAc/hexanes); R_f 0.63 (EtOAc); IR (film) ν_{\max} 1786, 1662, 1600, 1222, 1050 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.24-7.35 (m, 5H), 6.29 (d, J = 9.9 Hz, 1H), 6.03 (dd, J = 9.9, 1.4 Hz, 1H), 5.60 (d, J = 1.4 Hz, 1H), 4.85 (s, 2H), 3.74 (s, 3H), 3.09 (d, J = 13.8 Hz, 1H), 2.75 (d, J = 13.8 Hz, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 186.3, 168.8, 164.4, 141.2, 135.0, 130.7, 129.1, 129.0, 128.6, 105.0, 79.0, 61.0, 56.1, 43.4; HRMS-ESI calcd for $\text{C}_{16}\text{H}_{16}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 286.1079, found: 286.1075.

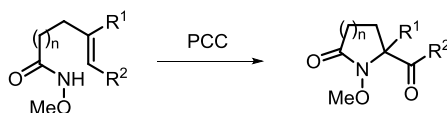


219w: Using HMIB: Following Representative Procedure 5, to a solution of **181w** (24.2 mg, 0.074 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added HMIB (35 mg, 0.11 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **219w** (22.0 mg, 96%).

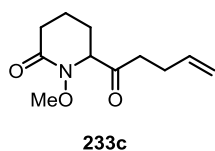
Using HTIB: Following Representative Procedure 5, to a solution of **181w** (29.6 mg, 0.090 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added HTIB (53 mg, 0.13 mmol, 1.5 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc) to provide **219w** (23.8 mg, 85%) as a white solid; mp 175-177 °C (EtOAc/hexanes); R_f 0.33 (EtOAc); IR (film) ν_{\max} 1664, 1630, 1598, 1365, 1222 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.18-7.36 (m, 5H), 6.52 (d, J = 9.9 Hz, 1H), 6.14 (dd, J = 9.9, 1.5 Hz, 1H), 5.59 (d, J = 1.5 Hz, 1H), 4.89 (s, 2H), 3.75 (s, 3H), 2.61 (t, J = 6.4 Hz, 2H), 2.14-2.20 (m, 1H), 2.00-2.10 (m, 2H), 1.82-1.89 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 186.2, 173.6, 170.0, 145.6, 134.9, 129.3, 128.6, 128.6, 128.3, 103.0, 77.6, 65.3, 56.1, 35.4, 33.3, 18.0; HRMS-ESI calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 314.1392, found: 314.1399.

1.11.12 Cyclization of Unsaturated *O*-Alkyl Hydroxamates Using PCC

Representative Procedure 6. Hydroxamate Cyclization using Pyridinium Chlorochromate (PCC)

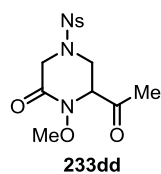


To a solution of *O*-alkyl hydroxamate (0.10 mmol) in DCE (2 mL, 0.05 M), was added PCC (0.30 mmol, 3 equiv). After purging the reaction vessel with N₂, anhydrous AcOH (5 equiv) was added *via* syringe and the reaction mixture stirred at room temperature for 30 min. A reflux condenser was then attached and the reaction mixture heated at 84 °C until TLC indicated consumption of starting material. Upon completion, the reaction mixture was cooled to room temperature, dilute with Et₂O (2 mL), filtered through Celite and poured into aqueous Na₂SO₃ (3 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 x 3 mL). The combined extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was then purified by flash chromatography on silica gel (EtOAc) to give the final product.



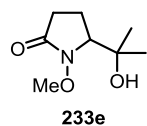
233c: Following Representative Procedure 6, to a solution of **181c** (33.7 mg, 0.17 mmol, 1.0 equiv) in DCE (4 mL) were sequentially added PCC (111 mg, 0.51 mmol, 3 equiv) and anhydrous AcOH (48 µl, 0.85 mmol, 5 equiv) to provide, after work-up and purification by flash chromatography (EtOAc), **233c** (17.0 mg, 47%) as a colorless oil; *R_f* 0.23 (EtOAc); IR (film) ν_{max} 3078, 2937, 2818, 1724, 1680, 1444, 1403, 1331, 1165, 1066, 995, 912, 864, 648 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 5.80 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 4.98-5.09 (m, 2H), 4.40 (t, *J* = 5.9 Hz, 1H), 3.76 (s,

3H), 2.70 (dt, $J = 17.8, 7.4$ Hz, 1H), 2.57 (dt, $J = 17.8, 7.4$ Hz, 1H), 2.46-2.53 (m, 2H), 2.37 (q, $J = 7.0$ Hz, 2H), 2.08-2.17 (m, 1H), 1.95-2.02 (m, 1H), 1.73 (quin, $J = 6.6$ Hz, 2H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 206.9, 167.8, 136.5, 115.7, 67.6, 61.7, 38.6, 32.9, 27.2, 26.6, 18.7; HRMS-ESI calcd for $\text{C}_{11}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 212.1287, found: 212.1291.



233dd: Following Representative Procedure 6, to a solution of **181dd** (19.9 mg, 0.056 mmol, 1.0 equiv) in DCE (2 mL) were sequentially added PCC (36 mg, 0.17 mmol, 3 equiv) and anhydrous AcOH (16 μL , 0.28 mmol, 5 equiv) to

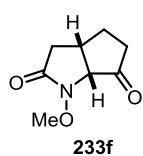
provide, after work-up and purification by flash chromatography (EtOAc), **233dd** (14.0 mg, 68%) as a colorless oil; R_f 0.23 (EtOAc); IR (film) ν_{max} 3095, 2939, 1732, 1685, 1545, 1373, 1176, 1047, 949, 852, 752, 573 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 8.02 (dd, $J = 7.6, 1.3$ Hz, 1H), 7.73-7.82 (m, 1H), 7.70 (dd, $J = 7.6, 1.3$ Hz, 1H), 4.42 (t, $J = 3.7$ Hz, 1H), 4.30 (d, $J = 17.3$ Hz, 1H), 4.20 (d, $J = 13.8$ Hz, 1H), 3.87 (d, $J = 17.3$ Hz, 1H), 3.80 (s, 3H), 3.72 (dd, $J = 13.8, 3.7$ Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 202.4, 161.5, 148.1, 134.6, 132.2, 131.5, 130.8, 124.6, 66.8, 62.4, 48.9, 46.1, 27.3; HRMS-ESI calcd for $\text{C}_{13}\text{H}_{16}\text{N}_3\text{O}_7\text{S}$ $[\text{M}+\text{H}]^+$: 358.0709, found: 358.0708.



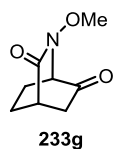
233e: Following Representative Procedure 6, to a solution of **181e** (12.0 mg, 0.076 mmol, 1.0 equiv) in DCE (2 mL) were sequentially added PCC (50 mg,

0.23 mmol, 3 equiv) and anhydrous AcOH (22 μL , 0.38 mmol, 5 equiv) to provide, after work-up and purification by flash chromatography (EtOAc), **233e** (5.5 mg, 42%) as a colorless oil; R_f 0.19 (EtOAc); IR (film) ν_{max} 3400, 2974, 2936, 1682, 1382, 1252, 1170, 959, 811, 659 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 3.77-3.88 (m, 4 H), 2.58-2.73 (m, 1 H),

2.21-2.42 (m, 2 H), 2.06-2.16 (m, 1 H), 1.72-1.83 (m, 1 H), 1.23 (d, $J = 5.8$ Hz, 6 H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 170.7, 73.3, 63.6, 61.1, 26.6, 25.9, 24.1, 18.6; HRMS-ESI calcd for $\text{C}_8\text{H}_{16}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 174.1130, found: 174.1128.

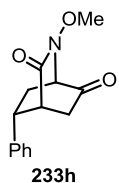


233f: Following Representative Procedure 6, to a solution of **181f** (25.3 mg, 0.16 mmol, 1.0 equiv) in DCE (3 mL) were sequentially added PCC (106 mg, 0.49 mmol, 3 equiv) and anhydrous AcOH (46 μL , 0.80 mmol, 5 equiv) to provide, after work-up and purification by flash chromatography (EtOAc), **233f** (16.8 mg, 61%) as a colorless oil; R_f 0.22 (EtOAc); IR (film) ν_{max} 2984, 2935, 1703, 1441, 1372, 1304, 1265, 1179, 1077, 1011, 890, 849, 770, 657 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 3.87 (d, $J = 7.8$ Hz, 1 H), 3.80 (s, 3 H), 3.04-2.93 (m, 1 H), 2.71-2.53 (m, 2 H), 2.45-2.29 (m, 2 H), 2.25 (dd, $J = 2.9, 17.6$ Hz, 1 H), 1.88-1.80 (m, 1 H); ^{13}C NMR (CDCl_3 , 101 MHz): δ 211.1, 170.6, 63.3, 62.8, 36.6, 33.9, 30.5, 27.4; HRMS-ESI calcd for $\text{C}_8\text{H}_{12}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 170.0817, found: 170.0815.

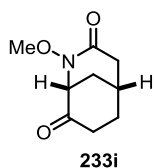


233g: Following Representative Procedure 6, to a solution of **181g** (32.0 mg, 0.21 mmol, 1.0 equiv) in DCE (4 mL) were sequentially added PCC (134 mg, 0.62 mmol, 3 equiv) and anhydrous AcOH (60 μL , 1.05 mmol, 5 equiv) to provide, after work-up and purification by flash chromatography (EtOAc), **233g** (17.6 mg, 50%) as a colorless oil; R_f 0.43 (EtOAc); IR (film) ν_{max} 2943, 1738, 1448, 1352, 1273, 1038, 951, 798, 744, 642, 544 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 4.05 (d, $J = 5.3$ Hz, 1 H), 3.79 (s, 3 H), 2.68 (br. s., 1 H), 2.64-2.42 (m, 3 H), 2.40-2.28 (m, 1 H), 1.96-1.84 (m, 2 H); ^{13}C NMR

(CDCl₃, 101 MHz): δ 205.9, 175.6, 65.4, 63.4, 37.5, 34.8, 31.0, 27.8; HRMS-ESI calcd for C₈H₁₂NO₃ [M+H]⁺: 170.0817, found: 170.0820.

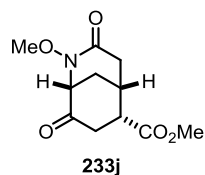


233h: Following Representative Procedure 6, to a solution of **181h** (24.0 mg, 0.10 mmol, 1.0 equiv) in DCE (2 mL) were sequentially added PCC (67 mg, 0.31 mmol, 3 equiv) and anhydrous AcOH (29 μ L, 0.50 mmol, 5 equiv) to provide, after work-up and purification by flash chromatography (EtOAc), **233h** (16.1 mg, 63%) as a colorless oil; R_f 0.71 (EtOAc); IR (film) ν_{\max} 2973, 2939, 1724, 1634, 1602, 1451, 1279, 1229, 1081, 1034, 975, 763, 701, 665 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.31-7.39 (m, 2H), 7.24-7.30 (m, 2H), 7.19 (d, J = 7.5 Hz, 2H), 4.12 (d, J = 5.4 Hz, 1H), 3.95 (d, J = 8.4 Hz, 1H), 3.85 (s, 3H), 2.97 (dd, J = 16.7, 8.4 Hz, 1H), 2.72-2.83 (m, 2H), 2.14-2.23 (m, 1H), 2.00 (d, J = 12.8 Hz, 1H); ¹³C NMR (CDCl₃, 101 MHz): δ 206.3, 175.7, 141.1, 128.9 (2 C), 127.4 (2 C), 127.2, 66.0, 63.5, 44.4, 42.3, 39.0, 25.8; HRMS-ESI calcd for C₁₄H₁₆NO₃ [M+H]⁺: 246.1130, found: 246.1129.

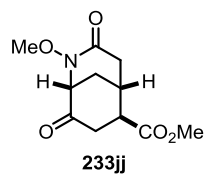


233i: Following Representative Procedure 6, to a solution of **181i** (200 mg, 1.2 mmol, 1.0 equiv) in DCE (20 mL) were sequentially added PCC (767 mg, 3.6 mmol, 3 equiv) and anhydrous AcOH (0.34 mL, 6.0 mmol, 5 equiv) to provide, after work-up and purification by flash chromatography (EtOAc), **233i** (56.0 mg, 26%) as a colorless oil; R_f 0.26 (EtOAc); IR (film) ν_{\max} 2935, 1728, 1678, 1443, 1390, 1306, 1223, 1142, 1092, 1045, 997, 806, 675, 507 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 4.03 (br. s., 1H), 3.74 (s, 3H), 2.86 (dd, J = 17.7, 6.2 Hz, 1H), 2.70 (td, J = 14.5, 7.5 Hz, 1H), 2.49-2.56 (m, 1H), 2.44 (dq, J = 14.5, 3.4 Hz, 1H), 2.29-2.37 (m, 2H), 2.13-2.21 (m, 1H), 2.04-2.13 (m,

1H), 1.93-2.03 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 207.2, 168.9, 66.3, 62.0, 38.4, 34.3, 33.5, 32.7, 26.8; HRMS-ESI calcd for $\text{C}_9\text{H}_{14}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 184.0974, found: 184.0965.

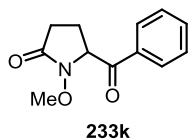


233j: Following Representative Procedure 6, to a solution of **181j** (392.0 mg, 1.7 mmol, 1.0 equiv) in DCE (50 mL) were sequentially added PCC (1.11 g, 5.2 mmol, 3 equiv) and anhydrous AcOH (0.48 mL, 8.5 mmol, 5 equiv) to provide, after work-up and purification by flash chromatography (EtOAc), **233j** (148.0 mg, 36%) as a colorless oil; R_f 0.30 (EtOAc); IR (film) ν_{max} 2923, 1732, 1683, 1592, 1147, 1027, 955, 731, 692 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 4.05 (br. s., 1 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.01-2.89 (m, 2 H), 2.81-2.74 (m, 2 H), 2.64-2.54 (m, 2 H), 2.50 (td, J = 3.1, 14.0 Hz, 1 H), 2.21-2.15 (m, 1 H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 205.2, 171.3, 167.6, 65.1, 62.2, 52.5, 47.1, 35.2, 34.5, 33.2, 29.3; HRMS-ESI calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 242.1028, found: 242.1019.

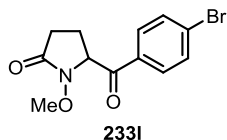


233jj: Following Representative Procedure 6, to a solution of **181jj** (43.8 mg, 0.19 mmol, 1.0 equiv) in DCE (4 mL) were sequentially added PCC (125 mg, 0.58 mmol, 3 equiv) and anhydrous AcOH (54 μL , 0.95 mmol, 5 equiv) to provide, after work-up and purification by flash chromatography (EtOAc), **233jj** (26.0 mg, 56%) as a colorless oil; R_f 0.30 (EtOAc); IR (film) ν_{max} 2939, 1726, 1653, 1497, 1340, 1279, 1064, 1020, 975, 871, 763, 701, 667 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 4.03-3.98 (m, 1 H), 3.71 (s, 3 H), 3.70 (s, 3 H), 2.96 (ddd, J = 4.0, 4.2, 13.5 Hz, 1 H), 2.91-2.82 (m, 1 H), 2.78-2.69 (m, 2 H), 2.59-2.52 (m, 2 H), 2.51-2.43 (m, 2 H), 2.15 (dd, J = 2.8, 13.5

Hz, 1 H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 205.1, 171.3, 167.5, 64.9, 62.1, 52.4, 46.9, 35.1, 34.4, 33.0, 29.2; HRMS-ESI calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 242.1028, found: 242.1021.

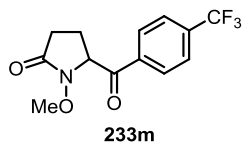


233k: Following Representative Procedure 6, to a solution of **181k** (16.0 mg, 0.078 mmol, 1.0 equiv) in DCE (2 mL) were sequentially added PCC (51 mg, 0.23 mmol, 3 equiv) and anhydrous AcOH (22 μL , 0.39 mmol, 5 equiv) to provide, after work-up and purification by flash chromatography (EtOAc), **233k** (10.0 mg, 59%) as a colorless oil; R_f 0.40 (EtOAc); IR (film) ν_{max} 2939, 1695, 1596, 1571, 1449, 1227, 1180, 1058, 1000, 964, 702 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.98 (d, J = 7.3 Hz, 2H), 7.66 (t, J = 7.3 Hz, 1H), 7.54 (t, J = 7.3 Hz, 2H), 5.30 (dd, J = 8.8, 5.0 Hz, 1H), 3.93 (s, 3H), 2.38-2.54 (m, 3H), 1.99-2.05 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 195.7, 172.2, 134.3, 134.2, 129.1, 128.4, 63.5, 61.6, 26.7, 21.1; HRMS-ESI calcd for $\text{C}_{12}\text{H}_{14}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 220.0974, found: 220.0981.

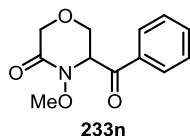


233l: Following Representative Procedure 6, to a solution of **181l** (23.0 mg, 0.081 mmol, 1.0 equiv) in DCE (2 mL) were sequentially added PCC (52 mg, 0.24 mmol, 3 equiv) and anhydrous AcOH (23 μL , 0.41 mmol, 5 equiv) to provide, after work-up and purification by flash chromatography (EtOAc), **233l** (15.2 mg, 63%) as a colorless oil; R_f 0.31 (EtOAc); IR (film) ν_{max} 2926, 2850, 1693, 1581, 1459, 1236, 1215, 1149, 964, 940, 827, 643 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.84 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.5 Hz, 2H), 5.24 (dd, J = 8.0, 5.2 Hz, 1H), 3.91 (s, 3H), 2.37-2.53 (m, 3H), 1.96-2.04 (m, 1H); ^{13}C NMR (CDCl_3 , 101 MHz): δ 194.9, 172.2, 132.9,

132.4, 129.8, 129.6, 63.5, 61.4, 26.6, 20.9; HRMS-ESI calcd for $C_{12}H_{13}BrNO_3$ $[M+H]^+$: 298.0079, found: 298.0073.

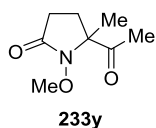


233m: Following Representative Procedure 6, to a solution of **181m** (26.9 mg, 0.099 mmol, 1.0 equiv) in DCE (2 mL) were sequentially added PCC (64 mg, 0.30 mmol, 3 equiv) and anhydrous AcOH (29 μ L, 0.50 mmol, 5 equiv) to provide, after work-up and purification by flash chromatography (EtOAc), **233m** (19.3 mg, 68%) as a colorless oil; R_f 0.34 (EtOAc); IR (film) ν_{max} 2940, 1705, 1581, 1512, 1411, 1324, 1225, 1168, 1014, 982, 833, 704 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz): δ 8.10 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H), 5.27-5.32 (m, 1H), 3.92 (s, 3H), 2.37-2.54 (m, 3H), 1.95-2.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 195.0, 172.2, 136.9, 128.8, 126.2, 126.1, 126.1, 63.5, 61.7, 26.6, 20.8; HRMS-ESI calcd for $C_{13}H_{13}NO_3F_3$ $[M+H]^+$: 288.0848, found: 288.0836.

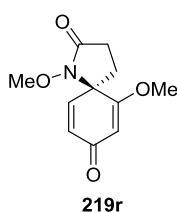


233n: Following Representative Procedure 6, to a solution of **181n** (15.5 mg, 0.070 mmol, 1.0 equiv) in DCE (2 mL) were sequentially added PCC (45 mg, 0.21 mmol, 3 equiv) and anhydrous AcOH (20 μ L, 0.35 mmol, 5 equiv) to provide, after work-up and purification by flash chromatography (EtOAc), **233n** (7.3 mg, 45%) as a colorless oil; R_f 0.40 (EtOAc); IR (film) ν_{max} 3064, 2935, 1699, 1597, 1450, 1238, 1128, 957, 854, 777, 692 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz): δ 7.97 (d, J = 7.5 Hz, 2 H), 7.71-7.62 (m, 1 H), 7.54 (t, J = 7.5 Hz, 2 H), 5.41 (br. s., 1 H), 4.35 (d, J = 16.1 Hz, 1 H), 4.25 (d, J = 16.1 Hz, 1 H), 4.20 (br. s., 2 H), 3.89 (s, 3 H); ^{13}C NMR ($CDCl_3$, 101

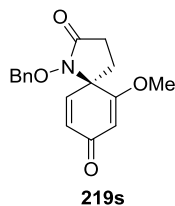
MHz): δ 192.7, 166.0, 134.3, 134.0, 129.2, 128.4, 68.9, 67.1, 64.2, 63.1; HRMS-ESI calcd for $C_{12}H_{14}NO_4$ $[M+H]^+$: 236.0923, found: 236.0918.



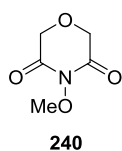
233y: Following Representative Procedure 6, to a solution of **181y** (12.5 mg, 0.080 mmol, 1.0 equiv) in DCE (2 mL) were sequentially added PCC (52 mg, 0.24 mmol, 3 equiv) and anhydrous AcOH (23 μ l, 0.40 mmol, 5 equiv) to provide, after work-up and purification by flash chromatography (EtOAc), **233y** (7.0 mg, 51%) as a colorless oil; R_f 0.42 (EtOAc); IR (film) ν_{max} 2981, 2930, 1715, 1617, 1424, 1360, 1159, 1072, 1046, 964, 838, 668 cm^{-1} ; 1H NMR ($CDCl_3$, 500 MHz): δ 3.88 (s, 3H), 2.28-2.43 (m, 2H), 2.19 (s, 3H), 2.08-2.16 (m, 1H), 1.87 (dt, J = 12.8, 9.0 Hz, 1H), 1.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 207.5, 171.2, 70.3, 64.3, 27.6, 26.2, 25.7, 20.7; HRMS-ESI calcd for $C_8H_{14}NO_3$ $[M+H]^+$: 172.0974, found: 172.0978.



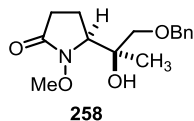
219r: Following Representative Procedure 6, to a solution of **181r** (25.0 mg, 0.10 mmol, 1.0 equiv) in DCE (2 mL) were sequentially added PCC (68 mg, 0.31 mmol, 3 equiv) and anhydrous AcOH (29 μ l, 0.50 mmol, 5 equiv) to provide, after work-up and purification by flash chromatography (EtOAc), **219r** (11.7 mg, 50%) as a white solid; mp 133-135 $^{\circ}C$ (EtOAc/hexanes); R_f 0.26 (EtOAc); IR (film) ν_{max} 2939, 1733, 1670, 1652, 1558, 1373, 1178, 1001, 856, 696 cm^{-1} ; 1H NMR ($CDCl_3$, 500 MHz): δ 6.62 (d, J = 9.9 Hz, 1H), 6.30 (d, J = 9.9 Hz, 1H), 5.63 (s, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.58-2.67 (m, 1H), 2.42-2.51 (m, 1H), 2.21-2.28 (m, 1H), 2.09-2.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 186.3, 173.0, 172.7, 144.2, 130.3, 103.2, 64.6, 62.9, 56.2, 27.3, 26.3; HRMS-ESI calcd for $C_{11}H_{14}NO_4$ $[M+H]^+$: 224.0923, found: 224.0917.



219s: Following Representative Procedure 6, to a solution of **181s** (27.0 mg, 0.082 mmol, 1.0 equiv) in DCE (2 mL) were sequentially added PCC (53 mg, 0.25 mmol, 3 equiv) and anhydrous AcOH (23 μ L, 0.41 mmol, 5 equiv) to provide, after work-up and purification by flash chromatography (EtOAc), **219s** (8.3 mg, 32%) as a white solid; mp 142-143 $^{\circ}$ C (EtOAc/hexanes); R_f 0.36 (EtOAc); IR (film) ν_{\max} 2944, 1724, 1664, 1602, 1369, 1227, 1176, 1066, 999, 858, 756, 698 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.30-7.36 (m, 5H), 6.17 (d, J = 9.9 Hz, 1H), 6.11 (d, J = 9.8 Hz, 1H), 5.58 (s, 1H), 4.95 (s, 2H), 3.75 (s, 3H), 2.59-2.68 (m, 1H), 2.44-2.52 (m, 1H), 2.17-2.24 (m, 1H), 2.04-2.12 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 186.3, 173.6, 172.8, 144.4, 134.8, 129.9, 129.7, 128.9, 128.4, 103.1, 78.4, 62.9, 56.2, 27.5, 26.3; HRMS-ESI calcd for $\text{C}_{17}\text{H}_{18}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 300.1236, found: 300.1227.



240: Following Representative Procedure 6, to a solution of **181z** (25.0 mg, 0.16 mmol, 1.0 equiv) in DCE (2 mL) were sequentially added PCC (103 mg, 0.48 mmol, 3 equiv) and anhydrous AcOH (48 μ L, 0.8 mmol, 5 equiv) to provide, after work-up and purification by flash chromatography (EtOAc), **240** (7.1 mg, 31%) as a colorless oil; R_f 0.47 (EtOAc-hexanes, 1:1); IR (film) ν_{\max} 2924, 2853, 1716, 1438, 1336, 1270, 1214, 1141, 1098, 964, 942, 877, 727, 666, 607 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 4.46 (s, 4H), 3.95 (s, 3H); ^{13}C NMR (CDCl_3 , 101 MHz): δ 165.5, 68.7, 64.7.



258: Following Representative Procedure 6, to a solution of **255** (38.6 mg, 0.14 mmol, 1.0 equiv) in DCE (5 mL) were sequentially added PCC (90 mg, 0.42 mmol, 3 equiv) and anhydrous AcOH (42 μ L, 0.7 mmol, 5 equiv) to provide, after work-

up and purification by flash chromatography (EtOAc), **258** (13.5 mg, 33%) as a colorless oil; R_f 0.23 (EtOAc); IR (film) ν_{\max} 3391, 2978, 2939, 1683, 1601, 1451, 1384, 1271, 1110, 1057, 958, 714, 660 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.29-7.39 (m, 5H), 4.51-4.60 (m, 2H), 4.02 (dd, $J = 8.8, 4.0$ Hz, 1H), 3.71 (s, 3H), 3.64 (d, $J = 9.2$ Hz, 1H), 3.42 (d, $J = 9.2$ Hz, 1H), 2.76 (s, 1H), 2.29-2.39 (m, 1H), 2.19-2.27 (m, 1H), 2.04-2.16 (m, 2H), 1.16 (s, 3H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 170.6, 137.6, 128.5, 127.9, 127.8, 75.5, 73.7, 73.7, 61.1, 59.0, 26.7, 19.4, 17.4; HRMS-ESI calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 280.1549, found: 280.1537.

PART TWO:

HYPERVALENT IODINE-MEDIATED
INTRAMOLECULAR OXAMIDATION OF ALKENES:
SYNTHESIS OF KAINIC ACID AND SYNTHETIC STUDIES
TOWARDS THE MADANGAMINE AND ALSTOSCHOLARINE FAMILIES

2. FORMAL SYNTHESIS OF KAINIC ACID

2.1. Introduction

(-)- α -Kainic acid (KA) (**263**) and its epimer allokainic acid (**264**) are the parent members of a family of natural products also known as the kainoids (Figure 11). The name “kainic acid” is derived from the word *kaininso*, which translates as “mother alga” from Japanese.¹⁴⁹ It was originally isolated from the Japanese marine alga *Digenea simplex* by Murakami and co-workers in 1953.¹⁵⁰ Subsequently, KA was found in the related alga *Centroceras clavulatum*¹⁵¹ and in the Corsican moss, *Alsidium helminthocorton*.¹⁵² Since 1953, a large number of natural products bearing the characteristic KA-framework, i.e., a proline fragment with two carboxylic groups along with a pendant isopropene substituent on the C-4 position, have been isolated. Domoic acid (**267**), a seafood environmental toxin produced by the diatom *Nitzschia pungens*, is responsible for Amnesic Shellfish Poisoning.¹⁵³ Other members of the kainoid family include several isodomoic acids (**268-274**) and the poison mushroom components acromelic acids A and B (**265, 266**). The structure and relative stereochemistry of KA was determined by X-ray analysis of the zinc dicarboxylate and its crystallohydrate.¹⁴⁹

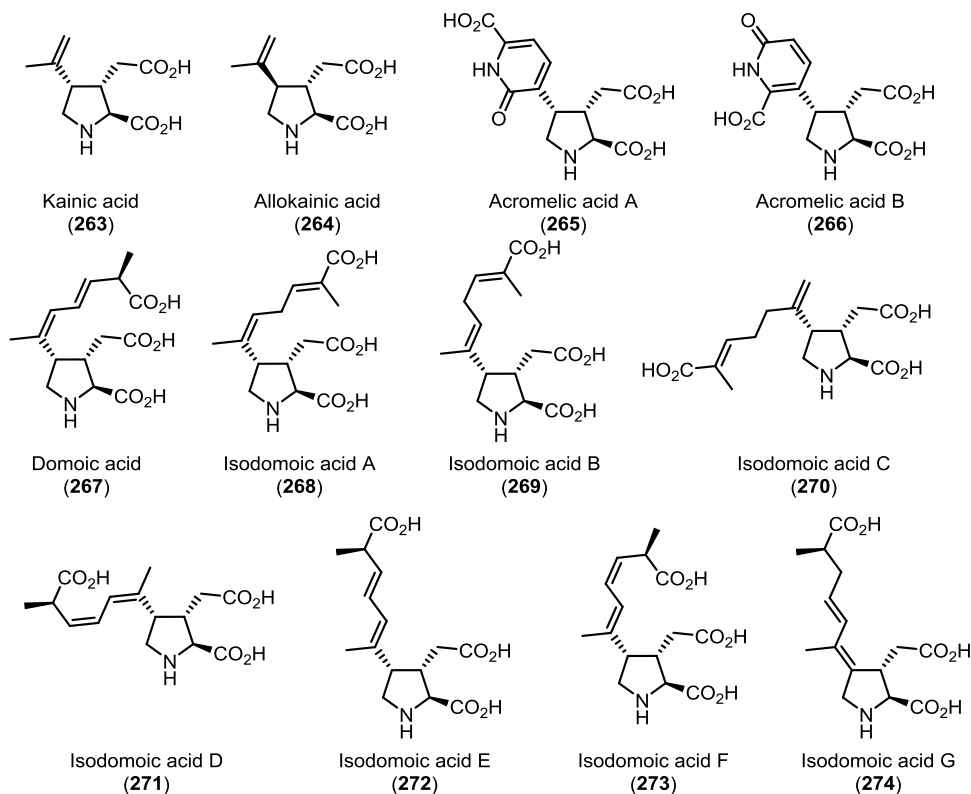


Figure 11 Members of the kainoid family of natural products are characterized by the presence of 4-substituted 3-carboxymethyl-pyrrolidine-2-carboxylic acid and found in a variety of marine and terrestrial plants and fungi

2.2. Biological Activity

Since its discovery, (-)- α -kainic acid (**263**) has received a great deal of attention as a result of its important neuroexcitatory properties. During the 1970s, KA was first employed in neuroscience as a tool for neuropathological model studies.¹⁵⁴ It was discovered by Olney that KA mimics the effects of the most abundant excitatory neurotransmitter, glutamic acid by operating on a class of kainate receptors.¹⁵⁵ KA represents the first key to unlock the neurophysiological role of glutamic acid. L-Glutamic acid (**275**), a nonessential amino acid, is the most abundant neurotransmitter that inhibits neural excitation in the central nervous

system. Structurally related to glutamate, KA is a nondegradable analog and a potent neurotoxin. Investigations by Andersson have shown that KA can elicit selective neuronal death in the brain of rodents.¹⁵⁶ Upon binding to kainate receptors (KARs), KA exerts its neuroexcitotoxic and epileptogenic properties as well as inducing a number of cellular events such as influx of cellular Ca^{2+} ,¹⁵⁷ production of reactive oxygen species,¹⁵⁸ and mitochondrial dysfunction.¹⁵⁹ Indeed, the administration of KA causes the specific neuropathological damage pattern in rat brains which is symptomatic in a number of human pathological disorders. Thus, kainic acid enables the creation of models of human diseases like Huntington's chorea,^{154a} Alzheimer disease,¹⁶⁰ and epilepsy,¹⁶¹ thereby facilitating the development of conventional medical treatments and cognitive therapies.

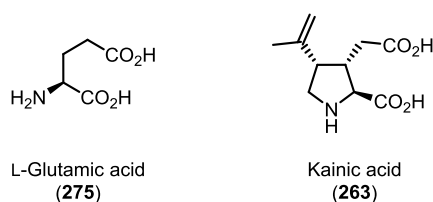
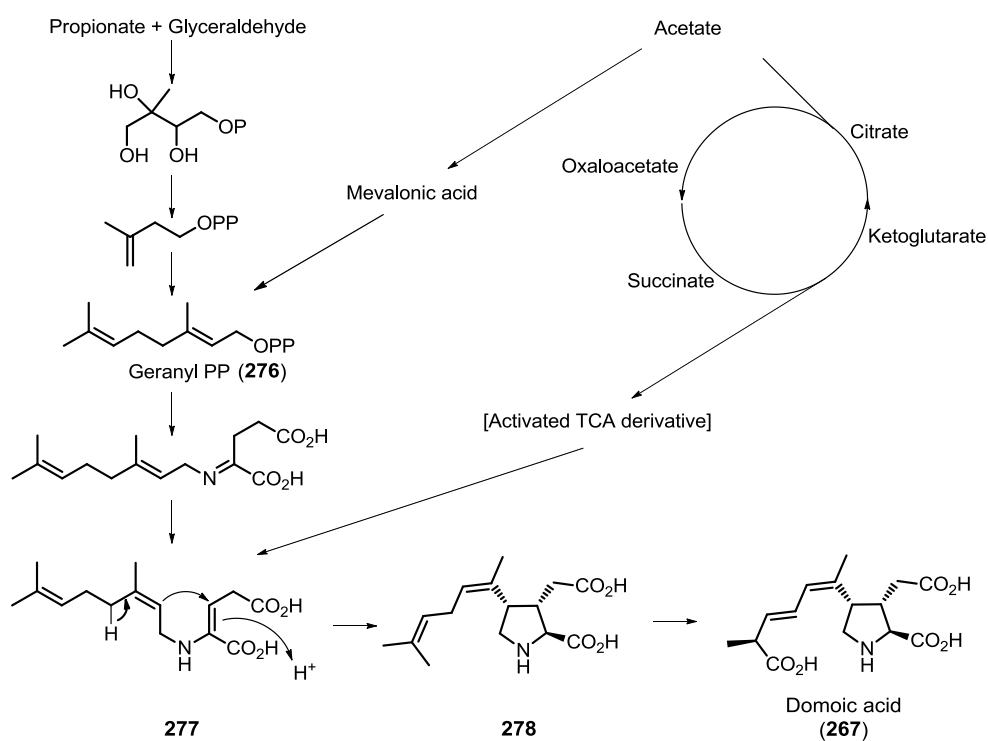


Figure 12 Neurotransmitter L-glutamic acid and its analogue, kainic acid

2.3. Biosynthesis

While studies of KA biosynthesis have yet to be reported, a number of studies on other kainoids, including the domoic acids and the acromelates have been performed. Domoic acid (DA) (**267**), originally isolated in 1958 from the red alga *Chondria armata*, is also a neurologically active amino acid which possesses structural resemblance to KA. The biosynthesis of DA in the diatom *Pseudo-nitzschia multiseries* has been investigated using ^{13}C - and ^{14}C -labelled precursors by Write and co-workers.¹⁶² In this work, acetate and [1, 2-

$^{13}\text{C}_2$]-acetate were fed to cultures under pulse-feeding conditions.¹⁶³ After biosynthesis was complete, DA was extracted from the samples and analyzed by NMR spectroscopy. The results indicated that DA was mostly isotopically enriched at C-7 and to a smaller degree at C-8, while isoprene portion of the molecule was enriched only at a low level. This isotopic incorporation to the C-6/C-7 unit versus C-2/C-8 suggests that either each unit is biosynthesized in a different part of the diatom cell, or, that the isoprene chain is not assembled by the usual acetate-mevalonate pathway.



Scheme 69

In the proposed mechanism, DA is biosynthesised by condensation of geranyl pyrophosphate (276) with glutamate intermediate derived from the tricarboxylic acid (TCA) cycle. Enamine 277, resulting from this condensation, subsequently undergoes intramolecular cyclization to form the characteristic pyrrolidine ring. Given the structural homology present

in this class, it seems likely that this pathway may be common to other kainoid natural products.

2.4. Kainic Acid as a Synthetic Target

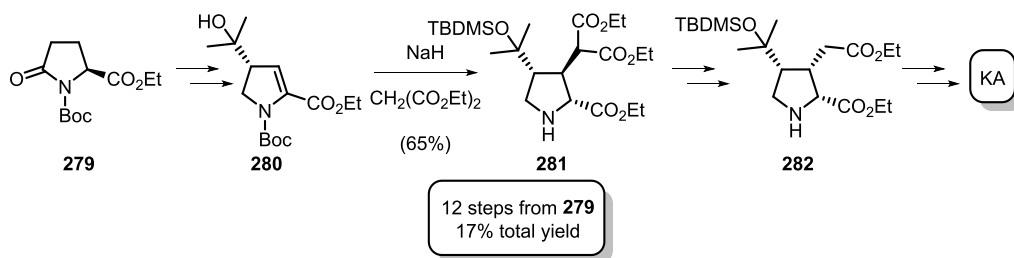
Until the mid-1990s, the commercial extraction of KA on a large scale was primarily performed for use in agriculture, where it was used as an anthelmintic agent. However, with the advent of improved remedies, KA production was discontinued creating a deficit.¹⁶⁴ Even though this pause in supply was found to be temporary,¹⁶⁵ the price of KA remains very high, currently surpassing \$10,000 per gram. The supply concern did however spark considerable interest in this deceptively simple natural product from organic chemists. To date, there have been more than 100 publications devoted to the synthesis of KA. Indeed, KA is an intriguing molecule comprising of a fully functionalized pyrrolidine core featuring 3 adjoining stereo centers. The *cis* relationship between C-3/C-4 side arms (allokainic acid excluded) requires careful consideration. An idealized kainic acid synthetic plan would allow the convergent installation of different substituents at the C-4 position in order to generate all the members and analogues of the kainoid family.

The manifold syntheses of kainoids have been reviewed several times: in 1998 by Parsons¹⁶⁶ and in 2012 by Gallos.¹⁶⁷ Due to the numerous synthetic approaches, we have chosen to classify KA total syntheses in the following manner: based on the formation of the final bond during the process of pyrrolidine ring assembly. This classification includes five sections: the syntheses employed existent pyrrolidine ring, cycloaddition reactions and the formation of C-2–C-3, C-3–C-4 and C-N bonds. Since the early syntheses¹⁶⁸ of KA were

relatively inefficient and nonstereoselective, we will focus our attention on relatively recent approaches.

2.4.1 Pyrrolidine Building Blocks

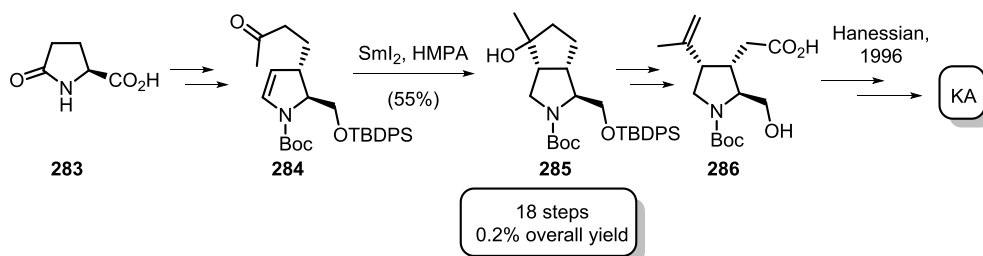
An obvious approach to KA is to employ readily available pyrrolidine building blocks. An enantioselective route to KA using pyroglutamate **279** as a starting material was reported by Rubio and co-workers in 1998 (Scheme 70).¹⁶⁹ The C-4 isopropenyl unit was accessed *via* the elimination of a 3° alcohol, accessed from the aldol condensation of **279** and acetone. The C-3 ester substituent was added through the Michael addition of malonate to 2,3-didehydroprolinate **280**. Epimerization of the C-3 stereo center was accomplished *via* alkene formation, *exo*-face hydrogenation and decarboxylation to generate **282**. Then, epimerization of the C-2 stereogenic center in **282** yielded the natural product (12 steps from **279**, 17% total yield).



Scheme 70

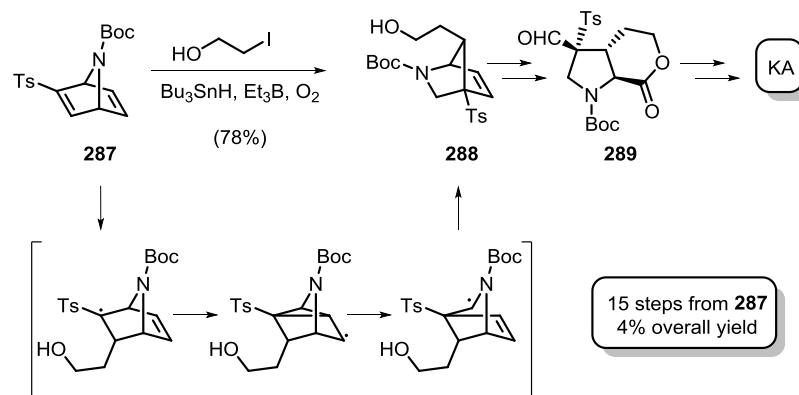
In 1999, Cossy reported an enantioselective formal synthesis of KA from L-pyroglutamic acid (**283**).¹⁷⁰ As shown in Scheme 71, the C-4 side chain of the pyrrolidine core was accessed *via* the ketyl radical cyclization of ene carbamate **284**. The resulting

carbinol **285** was converted in 5 steps into advanced intermediate **286**, which previously appeared in Hanessian's¹⁷¹ total synthesis of KA. Synthesis of **286** was completed in 18 steps with a rather modest 0.2% overall yield.



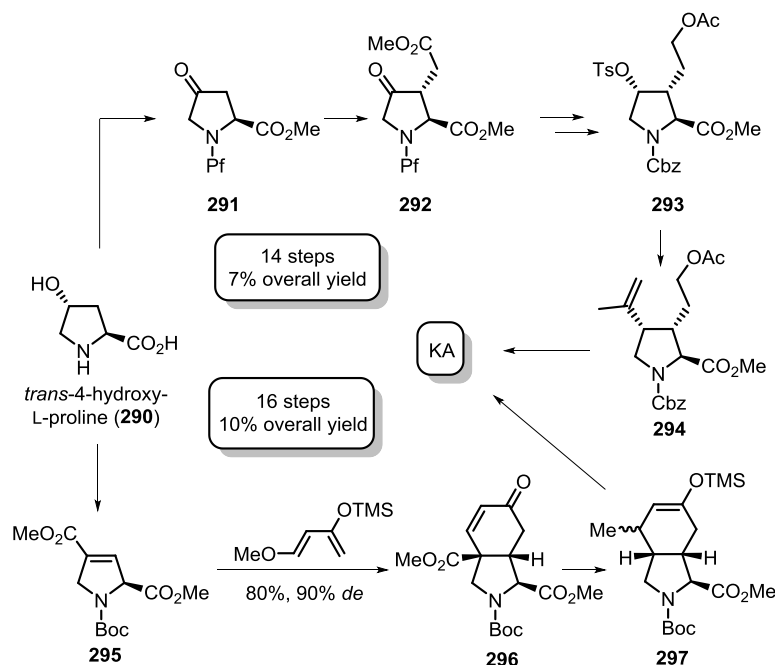
Scheme 71

In 2005, Hodgson and co-workers reported a new stereocontrolled route to trisubstituted pyrrolidines and successfully utilized their methodology in the synthesis of KA (Scheme 72).¹⁷² The authors discovered that treatment of 7-azanorbornadiene-type substrates, such as **287**, with 2-iodoethanol in the presence of radical initiators promoted a sequence of alkene addition and subsequent homoallylic radical rearrangement to generate 2-azabicyclo-[2.2.1]hept-5-enes **288**. These products provided convenient access to 2,3,4-trisubstituted pyrrolidines, specifically kainoids, *via* oxidative cleavage of alkene bridge. In this approach, 2-iodoethanol was added to enantiopure 7-azanorbornadiene **287** to form rearrangement product **288** in high yield and with excellent *syn* stereoselectivity. Ozonolysis followed by the Swern oxidation furnished lactone **289**, which was elaborated onto KA in 15 steps with an overall yield of 4%.



Scheme 72

Poisson and co-workers have employed *trans*-4-hydroxy-L-proline (**290**), an inexpensive amino acid that possesses both the core kainoid structure and the absolute configuration of the target molecule in their synthetic studies towards kainic acid (Scheme 73). Their first synthesis crucially relied on the regio- and stereoselective alkylation of 4-oxoproline **291**, as well as the stereoretentive substitution of the tosylate **293** by a high order cyanocuprate.¹⁷³ The origin of the unusual substitution was ascribed to the neighboring participation of the *N*-carboxybenzyl protecting group.¹⁷⁴ Natural KA was obtained with excellent stereocontrol and in an overall yield of 7% (14 steps).

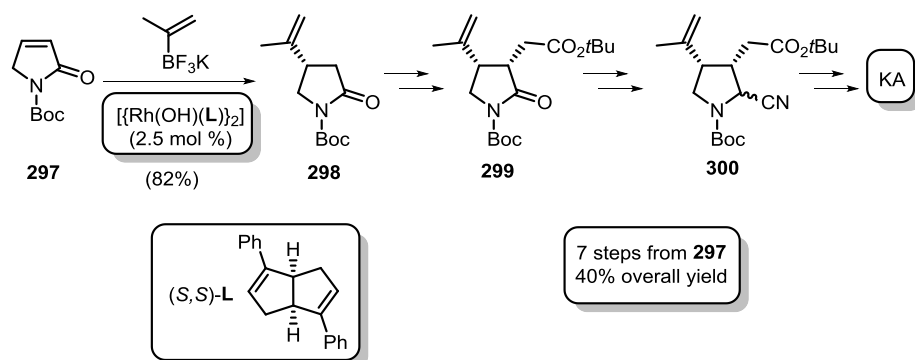


Scheme 73

In his second synthesis, Poisson employed a Diels-Alder reaction to establish the C-2/C-3/C-4 stereochemical relationship in an efficient and elegant fashion.¹⁷⁵ Starting from the same amino acid **290**, the authors prepared dienophile **295**, which underwent intermolecular Diels-Alder reaction with Danishefsky's diene. Unfortunately, high pressure (15 atm) and prolonged (72 h) reaction time were required to promote the cycloaddition of the trisubstituted olefin. Cycloadduct **296** was generated in high yield and with excellent enantiomeric excess. Introduction of the methyl group, oxidation cleavage and standard functional group manipulations concluded the total synthesis, which provided the target in an overall yield of 10% (19 steps).

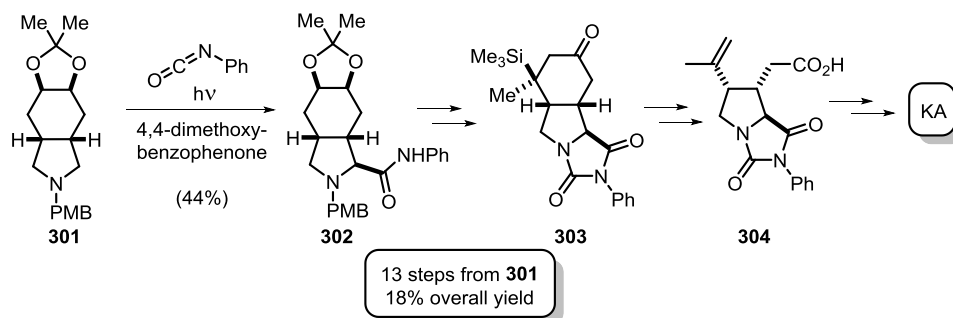
In 2012, Lin and associates reported an enantioselective synthesis of kainic acid featuring the asymmetric Michael addition of alkenyltrifluoroborates to α,β -unsaturated lactam **297**, catalyzed by a C₂ symmetric rhodium–diene complex (Scheme 74).¹⁷⁶ The syn

relationship at C-3/C-4 was then established by alkylation of **298** followed by dynamic protonation process at low temperature. Reduction of **299** with subsequent substitution at C-2 generated nitrile **300** which, upon basic hydrolysis, provided the desired product in 7 steps and excellent overall yield.



Scheme 74

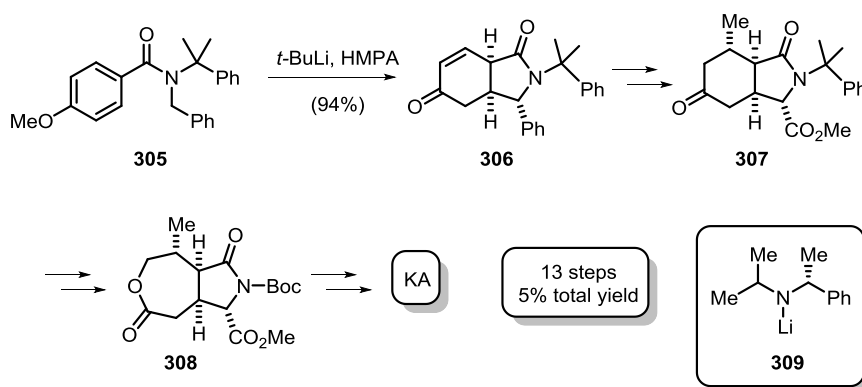
A racemic synthesis of KA, which employs photochemical C–H carbamoylation of octahydroisoidole derivative **301** with PhNCO, has recently been published by Yoshimitsu.¹⁷⁷ As shown in Scheme 75, photolytically derived monocarbamylated product **302**, was deprotected and converted into the cyclohexanone **303** in 8 steps. The product underwent Baeyer-Villiger oxidation and subsequent desilylative olefination to furnish alkene **304**. Hydrolysis of **304** afforded (±)-KA in 13 steps with an overall yield of 18%.



Scheme 75

2.4.2 Formation of C-2–C-3 Bond

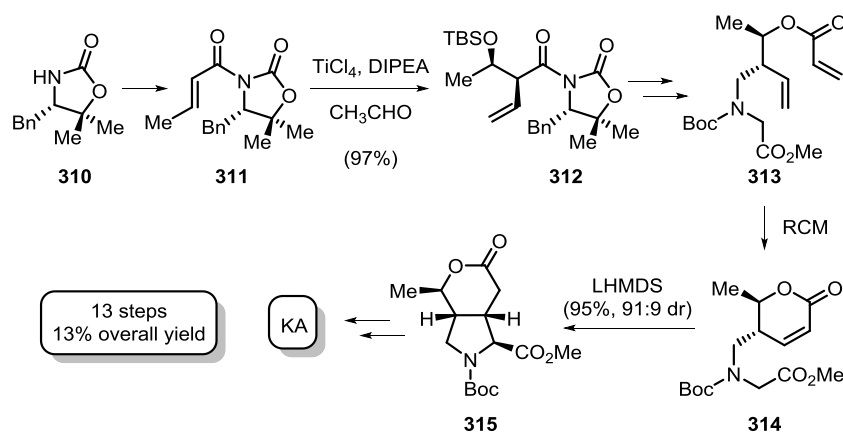
The first route to kainic acid (**263**) employing this strategy was reported by Clayden, who made use of the stereoselective dearomatizing cyclization of a lithiated *N*-benzyl-*p*-anisamide (Scheme 76).¹⁷⁸ When **305** was treated with *t*-BuLi at low temperature, the resulting benzyl lithium intermediate rapidly cyclized to provide isoindole, which yielded enone **306** after exposure to acid. Conjugate addition of dimethylcuprate occurred solely from the *exo* face and was followed by RuO₄-mediated oxidative fragmentation of the arene moiety to afford **307**. Subsequent transformations, including Baeyer-Villiger oxidative cleavage, Grieco elimination as well as lactam reduction furnished the natural product with an overall yield of 5% (13 steps).



Scheme 76

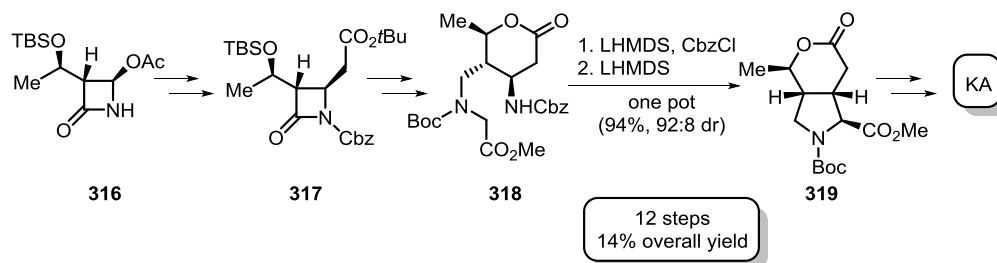
Several years later the same research group reported an enantioselective variant of their original synthesis.¹⁷⁹ In this case, enantioselective deprotonation of **305** was achieved with chiral lithium amide **309**, which provided enone **306** in good yield and excellent enantioselectivity, after a single recrystallization. In 2011 Clayden reported the application of this approach to the preparation of isodomoic acids B, E and F (**269**, **272**, **273**).¹⁸⁰

Fukuyama and co-workers have utilized a diastereoselective intramolecular Michael addition to access the kainoid family (Scheme 77).¹⁸¹ Lactone **315** was generated from Evans-type auxiliary **310** through a sequence of transformations featuring a stereoselective TiCl_4 -mediated aldol reaction and ring-closing metathesis.



Scheme 77

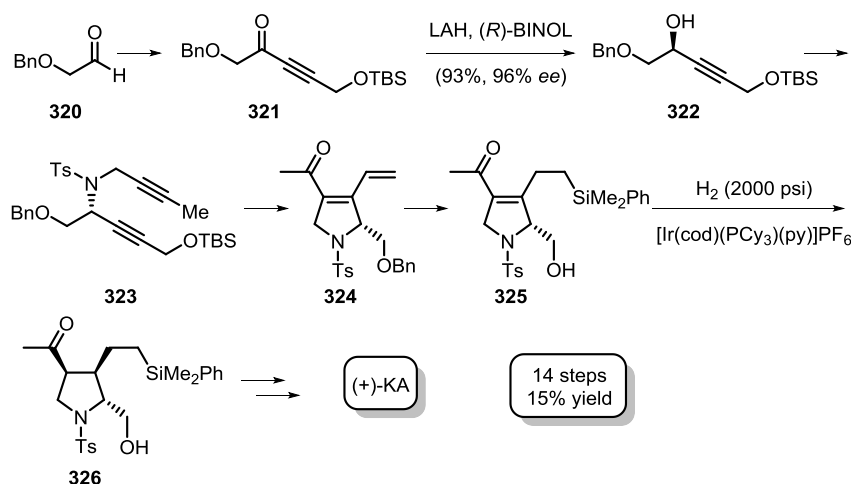
Fukuyama subsequently reported a second generation synthesis, which features a straightforward preparation of key lactone **318** from the readily available azetidinone derivative **316**. Diastereoselective construction of the highly functionalized pyrrolidine **319** was efficiently achieved *via* one-pot reaction cascade involving acylation, elimination, and intramolecular Michael addition (Scheme 78).¹⁸²



Scheme 78

2.4.3 Formation of C-3–C-4 Bond

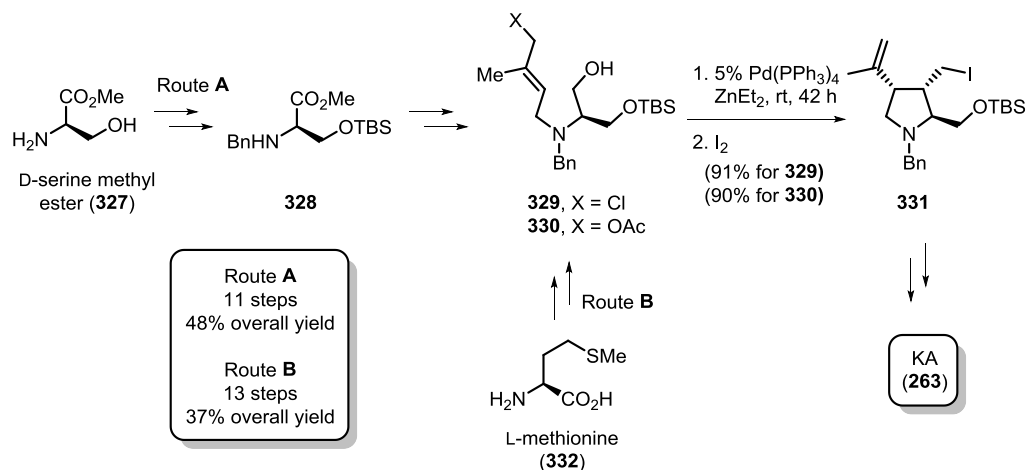
In 2003, Trost and co-workers reported the preparation of (+)-kainic acid, which is the enantiomer of the naturally-occurring form (Scheme 79).¹⁸³ In this approach, the authors utilized a Ru-catalyzed intramolecular cycloisomerization of a tethered propargyl alcohol and alkyne to generate cyclic dienone **324**. Thus, a single stereocenter, introduced by asymmetric reduction of ketone **321** using the conditions described by Noyori, set the stage for all other stereocenters.



Scheme 79

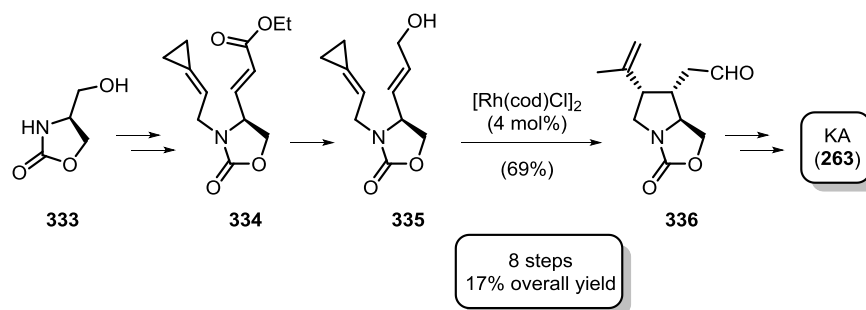
In 2007, Cohen and co-workers efficiently synthesized kainic acid (**263**) (route **A**) using a Zn-mediated palladium-catalyzed ene cyclization (Scheme 80).¹⁸⁴ It was shown that this transformation can be accomplished on a multigram scale. The cyclization precursor **329** was prepared in four steps from amino ester **328**, which was obtained from D-serine methyl ester (**327**). Treatment of **329** with excess ZnEt₂ and tetrakis(triphenylphosphine)palladium(0) furnished the cyclized product **331** as a single diastereomer (enantiomeric ratio 1.6:1). The elaboration of **331** to KA was achieved in a further five steps. The same group has also published an improved synthesis (route **B**), in

which cyclization of allylic acetate **330**, readily obtained from L-methionine (**332**), furnished pyrrolidine **331** in enantiopure form.¹⁸⁵



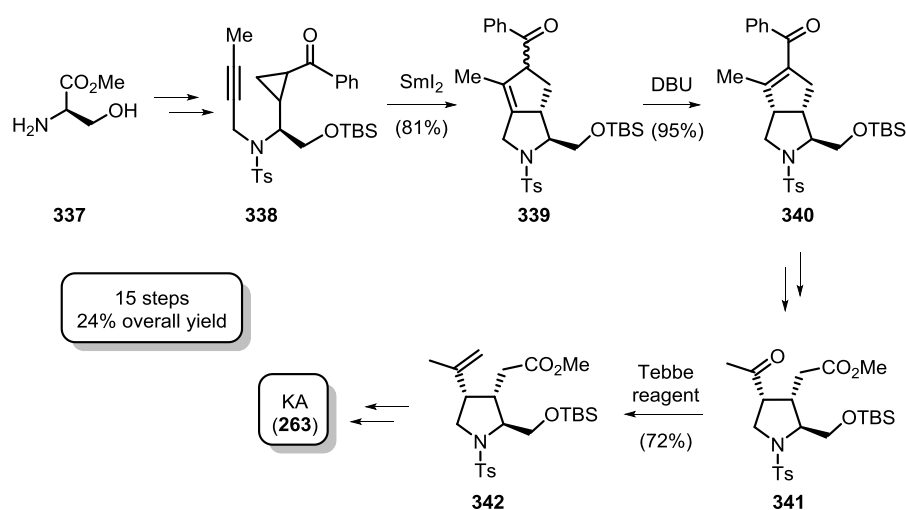
Scheme 80

Recently, Evans has utilized a rhodium-catalyzed ene-cycloisomerization of an alkenylidencyclopropane to construct **263** from commercially available amino alcohol **333** (Scheme 81).¹⁸⁶ Dess-Martin oxidation of **333** followed by Wittig homologation and palladium-catalyzed allylic amination furnished conjugate ester **334**. After ester reduction, cyclization to pyrrolidine **336** took place, upon heating with [Rh(cod)Cl]₂.



Scheme 81

Li and co-workers have reported an efficient total synthesis of **263** in which the key step involves a diastereoselective, reductive [3+2] cycloaddition (Scheme 82).¹⁸⁷ Precursor **338** was prepared in six steps from inexpensive D-serine methyl ester (**337**). Upon treatment with SmI_2 , cyclopropane **338** underwent intramolecular cycloaddition to produce pyrrolidine **339** with the desired C-2/C-3 *trans* relationship. Isomerization of the double bond, oxidative cleavage of the aryl ketone, followed by Tebbe olefination furnished **263** in excellent overall yield.

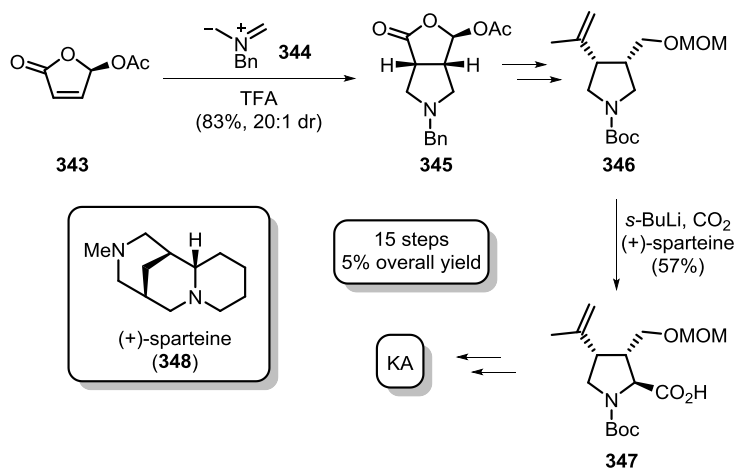


Scheme 82

2.4.4 Cycloaddition Routes

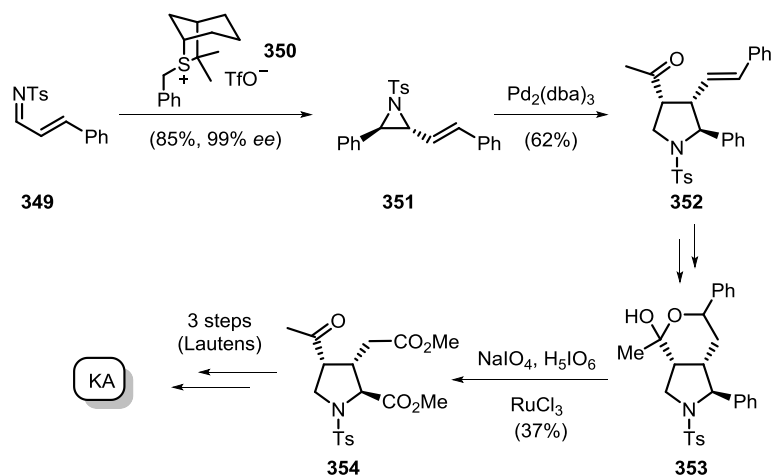
In 2005, Fukuyama and co-workers reported the use of an acid-catalyzed 1,3-dipolar cycloaddition to kainoid synthesis (Scheme 83).¹⁸⁸ Treatment of chiral butenolide **343** with reactive azomethine ylide¹⁸⁹ **344** provided the heterocyclic pyrrolidine core **345** with the required *cis* C-3-C-4 configuration. The remaining C-2 carboxyl substituent was introduced

via electrophilic substitution *via* deprotonation of compound **346** with *s*-BuLi in the presence of (+)-sparteine (**348**).



Scheme 83

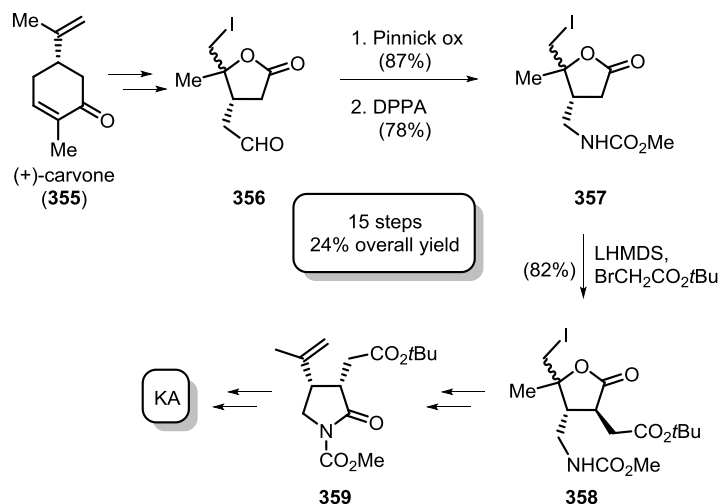
Aggarwal and co-workers have reported a formal synthesis of KA using their palladium-mediated annulation methodology involving the reaction of vinyl aziridines with Michael acceptors (Scheme 84).¹⁹⁰ Enantioselective aziridination of imine **349** with sulfonium salt **350** gave **351** in good yield and excellent enantiomeric excess. Palladium-catalyzed annulation with MVK furnished pyrrolidine **352** as a single diastereomer, after recrystallization. Simultaneous conversion of styryl and phenyl groups into carboxylic acids was performed *via* oxidation with $\text{RuCl}_3/\text{NaIO}_4$. **354** is an intermediate in Lautens total synthesis and can be converted into natural product in 3 steps.¹⁹¹



Scheme 84

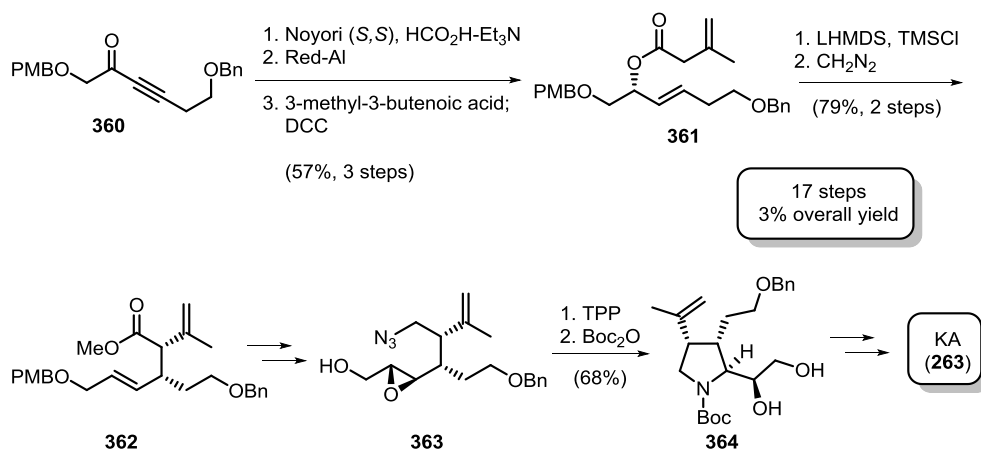
2.4.5 Formation of C-N Bond

Recently, Fukuyama published a large-scale stereoselective synthesis of KA (Scheme 85).¹⁹² Starting from (+)-carvone (**355**), aldehyde **356** was formed in 4 steps after an oxidative cleavage and an iodolactonization reaction. The amino group on the pyrrolidine ring was installed *via* Pinnick oxidation **356** followed by the Curtius rearrangement of the corresponding carboxylic acid using diphenylphosphoryl azide. Stereoselective alkylation of lactone **357** allowed installation of the C-3 carboxylic unit.



Scheme 85

In 2013, Chandrasekhar reported a linear synthesis of **263**, which utilizes chirality transfer *via* a key Ireland-Claisen rearrangement (Scheme 86).¹⁹³ Asymmetric reduction of the *bis*-protected ynone **360** using Noyori conditions gave rise to allylic alcohol, which was alkylated to generate ester **361**. Treatment of **361** with LHMDS/TMSCl accomplished formation of the C-3-C-4 side arms with the required stereochemistry. Construction of the pyrrolidine ring was accomplished by reduction of alcohol **363** with triphenylphosphine (TPP), wherein the azide was transformed to the amine, which readily underwent 5-*exo-tet* cyclization with the epoxide ring.



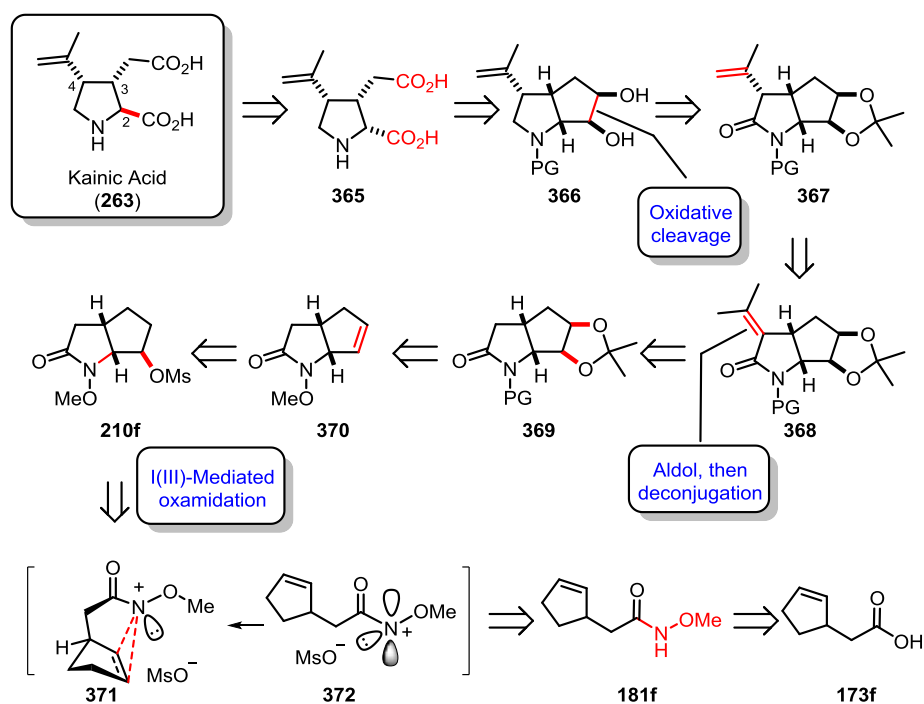
Scheme 86

2.5. Retrosynthetic Analysis of Kainic Acid

As discussed in the preceding review, kainic acid has become a popular target for showcasing the utility of novel synthetic methodologies. Wardrop and co-workers have previously shown that the oxidative intramolecular oxamidation of unsaturated *O*-methyl hydroxamates offers a convenient method to access pyrrolidine and piperidine systems.⁸⁵ In this regard, α -kainic acid with its biological relevance and highly functionalized trisubstituted pyrrolidine ring presents itself as an ideal target to evaluate this methodology.

Our synthetic strategy is outlined in Scheme 87. We planned to access **263** from the all-*cis* stereoisomer **365** using an α -epimerization at the C-2 stereogenic center.^{169,194} The diacid fragment of **365** could be accessed through the oxidative cleavage of vicinal diol **366**, which we envisioned as arising through the exhaustive amide reduction and deprotection of acetonide **367**. We posited that the C-4 isopropene substituent might be installed by base-mediated deconjugation of α,β -unsaturated amide **368**. We anticipated that the enolate

resulting from the γ -deprotonation of **368** would be quenched at the α -position from the *exo*-face to form all-*cis* pyrrolidinone **367**.¹⁹⁵ Notably, there is considerable precedence for the generation of all *cis*-isomers by *exo*-face protonation.¹⁹⁶ We anticipated that unsaturated compound **368** could be obtained through the aldol condensation of pyrrolidinone **369** with acetone. Retrosynthetic disconnection of the *O,O*-acetal through dihydroxylation leads to the olefin synthon present in alkene **370**, which itself could be prepared *via* E-2 elimination of mesylate **210f**.



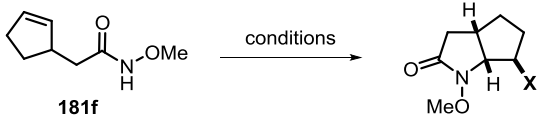
Scheme 87

Compound **210f** would be a product of the cyclization of *N*-methoxy-*N*-acylnitrenium ion **372**. Based on our oxamidation studies (*vide supra*), we expected that this cyclization would establish the desired *cis* stereochemistry at the C-3/C-4 stereocenters. Finally,

compound **181f**, the unsaturated *O*-methyl hydroxamate, could be accessed through coupling of the corresponding acid **173f** with methoxyamine hydrochloride.

2.6. Synthetic Studies Toward Kainic Acid

Our synthesis began with the preparation of *O*-methyl hydroxamate **181f**, which was obtained from 2-(cyclopent-2-en-1-yl)acetic acid (**173f**) using Tanabe's procedure.⁹⁵ Thus, treatment of **173f** with methoxyamine hydrochloride in the presence tosyl chloride and NMI resulted in the formation of **181f** in nearly quantitative yield. With regard to the cyclization of **181f**, we ideally wished to generate a product that could undergo elimination directly following the ring closure. The cyclization of this substrate was therefore conducted with a variety of hypervalent iodine reagents. The results of this investigation are summarized in Table 15. In all cases, the cyclization product was obtained as a single diastereomer with *trans* relationship between C-**X** and C-N bonds, which was established by the comparison with the structurally related pyrrolidinones discussed in Chapter 1.8. We also noted that addition of TFA resulted in yield augmentation. Overall, the cyclization of **181f** with 1.5 equivalent of [(hydroxy)mesyloxyiodo]benzene (HMIB) in the presence of 1 equivalent of TFA generated mesylate **210f** in excellent 89% yield. We were also gratified to discover that the cyclization can be successfully carried out on a multigram scale, without loss of yield.

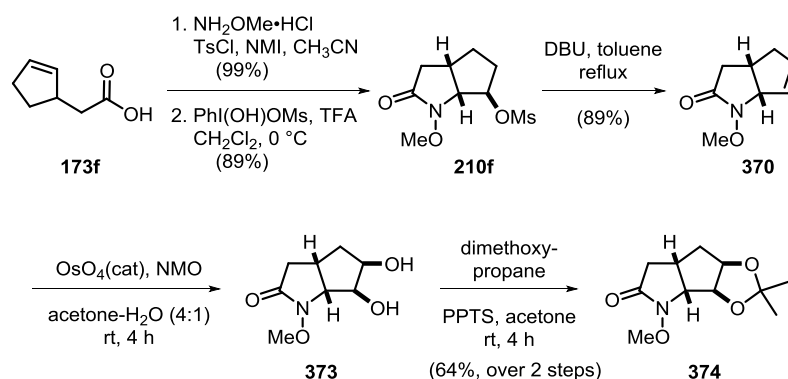
Table 15. Oxidative Cyclization of *O*-Methyl Hydroxamate 181f


entry	I(III) reagent	X	yield, % ^{a,b}
1	PhI(OTFA) ₂	OH	71/61
2	PhI(OH)OTs	OTs	73/51
3	PhI(OH)OMs	OMs	89(85 ^c)/59
4	PhI(OAc) ₂ + TMSOTf (3 equiv)	OTf	23/-

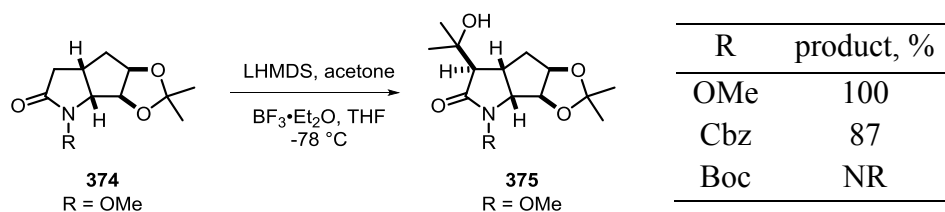
^aConditions: **181f** (1.0 equiv), I(III) reagent (1.5 equiv), TFA (1.0/0.0 equiv), DCM (0.05 M), 0 °C, 1-3 h reaction time. ^bIsolated yields, after purification by flash chromatography.

^cThe reaction was performed on a 28 mmol scale.

Alkene **370** was now formed in a high yield through treatment of mesylate **210f** with DBU in toluene for 6 h at reflux. In this case we noted only the formation of the disubstituted alkene. Dihydroxylation of **370** was achieved using OsO₄-NMO¹⁹⁷ in acetone-H₂O (4:1). The stereochemistry of this process is controlled by the cup-shaped nature of the *cis*-fused 2-azabicyclo[3.3.0]octane ring system; the pyrrolidinone ring blocks the attack by OsO₄ from the concave face of the cyclopentene, and thus favors formation of *exo-cis*-diol **373**. This compound was then protected as an acetonide with 2,2-dimethoxypropane and PPTS in acetone, furnishing **374** in good yield.¹⁹⁸

**Scheme 88**

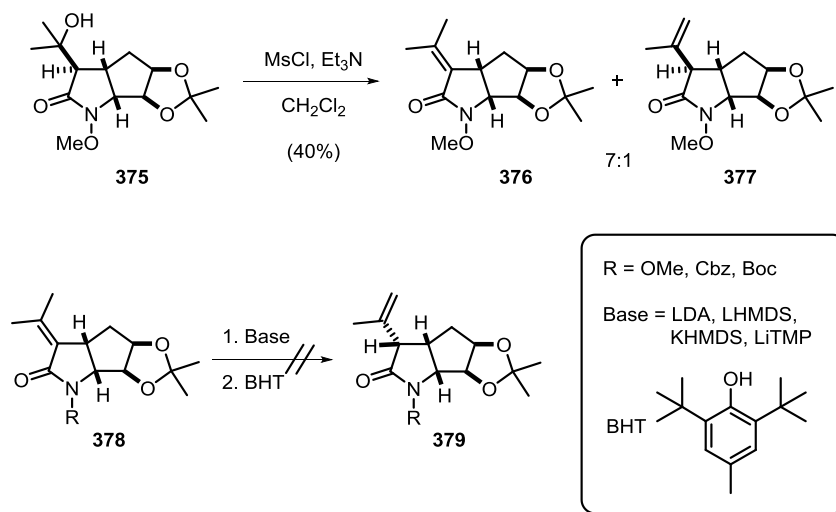
Treatment of lactam **374** with LHMDS in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ facilitated α -deprotonation of the amide to provide the enolate, which was subsequently quenched with acetone (freshly distilled over B_2O_3) to furnish alcohol **375** in quantitative yield (Scheme 89).¹⁹⁹ When stronger bases, e.g., LDA, were employed, the yield of the aldol product decreased as a result of cleavage of the *N*-methoxy group.²⁰⁰ Notably, the Boc-protected amide failed to undergo aldol condensation with acetone using LHMDS, a result which is possibly attributable to the steric effect of the carbamate group. In contrast, the less sterically encumbered *N*-Cbz group was well tolerated.



Scheme 89

We now began our evaluation of methods for the elimination of the tertiary alcohol of **375** (Scheme 90). Unexpectedly, compound **375** was found to be reluctant towards elimination under acidic conditions; i.e., **375** was fully recovered after 24 h reflux with PTSA in toluene. More encouragingly it was found that treatment of **375** with methanesulfonyl chloride and triethylamine in excess afforded a readily separable mixture (7:1) of isomeric alkenes **376** and **377** in moderate yield. The stage was thus set for examination of our key alkene deconjugation strategy. Unfortunately, all attempts to mediate alkene isomerization failed. γ -Deprotonation using a range of bases and subsequent quenching with butylated hydroxytoluene (BHT) as a hindered proton source returned the starting material intact.¹⁹⁵ Varying the amide protecting group also failed. Control experiments using base/ D_2O

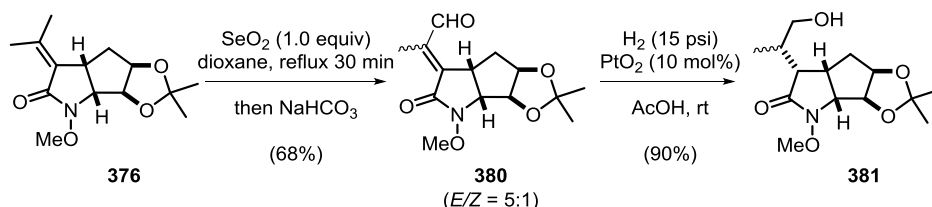
revealed no deuterium incorporation suggesting that no deprotonation of the methyl group(s) had occurred.



Scheme 90

In light of these findings, our deconjugation approach was revised to include allylic oxidation of **376** (Scheme 91). Our rationale in this case was to functionalize one of the methyl groups, then set the stereochemistry at C-4 *via* catalytic hydrogenation and finally convert the latent alcohol functionality into a terminal alkene. We examined the allylic oxidation of **376** and found that the use of SeO_2 in 1,4-dioxane gave the best results, delivering a readily separable 5:1 mixture of unsaturated aldehydes **380**.²⁰¹ We hoped that catalytic hydrogenation would allow us to selectively reduce the tetrasubstituted alkene from the α -face in order to establish *cis* C-3-C4 stereochemistry. Unfortunately, numerous attempts to perform the reduction of **380** using a range of homo- and heterogeneous metal catalysts, including Pd/C ,²⁰² $\text{Pd(0)-HCO}_2\text{NH}_4$,²⁰³ Pd(OH)_2 ,²⁰⁴ Rh/C ,²⁰⁵ $\text{Rh/Al}_2\text{O}_3$,²⁰⁶ $\text{Ir(cod)(PCy}_3\text{)(Py)PF}_6$ (Crabtree cat),²⁰⁷ Ra-Ni ²⁰⁸ met with limited success due to the lack of catalytic competence. Pleasingly, hydrogenation of **380** using 10 mol% PtO_2 provided the

desired product **381** in excellent yield.²⁰⁹ Optimization of the reaction conditions revealed that glacial acetic acid appeared to be the best solvent in terms of the observed diastereoselectivity ($\geq 10:1$). Reduction of the aldehyde moiety to the corresponding alcohol was also observed under these conditions.



Scheme 91

The relative stereochemistry of **381** was established through comparison of 2D NOESY experiments with compound **377** (Figure 13). Analysis of the spectra revealed a moderate nOe cross peak between H-3 and H-5 for **381**, which was not observed in the 2D NOESY of **377**.

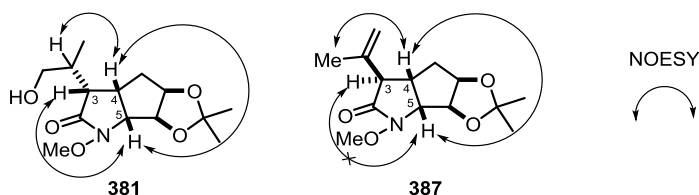
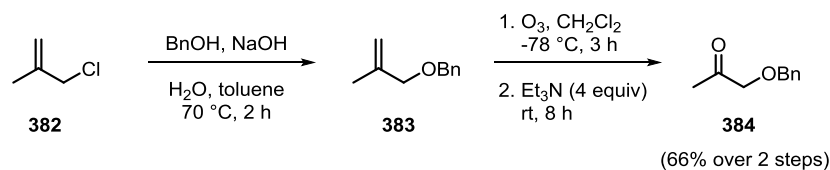


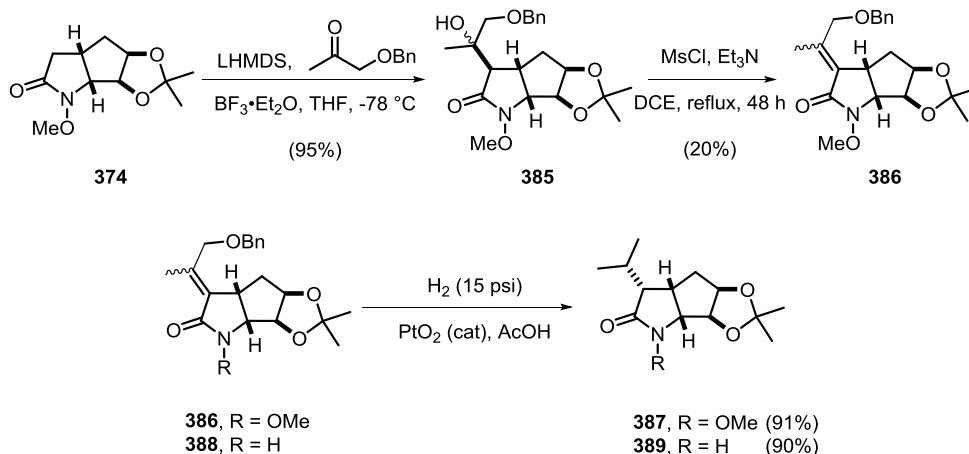
Figure 13 Comparison of nOe correlations in the spectra of **381** and **377**

Being satisfied with the initial steps of our synthesis, but looking for more concise ways to establish the *cis* isopropene substituent, we decided to employ a different α -prefunctionalized ketone for the aldol reaction. To this end, benzyloxyacetone (**384**) was prepared in two steps from 2-methallyl chloride, as shown in Scheme 92.²¹⁰



Scheme 92

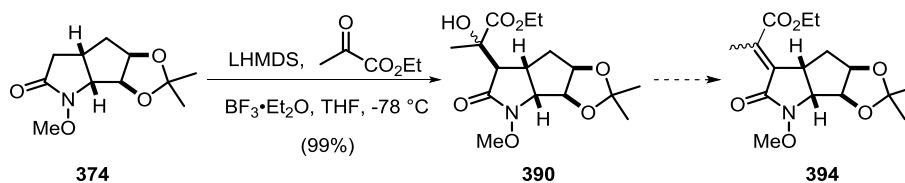
Reaction of the lithium enolate of **374** with benzyloxyacetone proceeded smoothly to provide alcohol **385** in excellent yield (Scheme 93). Although dehydration of **385** did not go to completion, was low-yielding and provided an inseparable mixture of isomeric alkenes **386**, we obtained enough material to proceed further. Unexpectedly, hydrogenation over catalytic PtO_2 in AcOH generated compound **387**, wherein both benzyl and hydroxyl groups were reduced. Attempts to hydrogenate the N-H lactam **388**, under the same conditions also led to hydrogenolysis of the benzyloxy group generating amide **389**.



Scheme 93

To address this issue, we replaced benzyloxyacetone with ethyl pyruvate for the aldol reaction. Using our established reaction conditions, we were able to generate **390** as a mixture of *syn* and *anti* β -hydroxyamides in near quantitative yield (Scheme 94). As

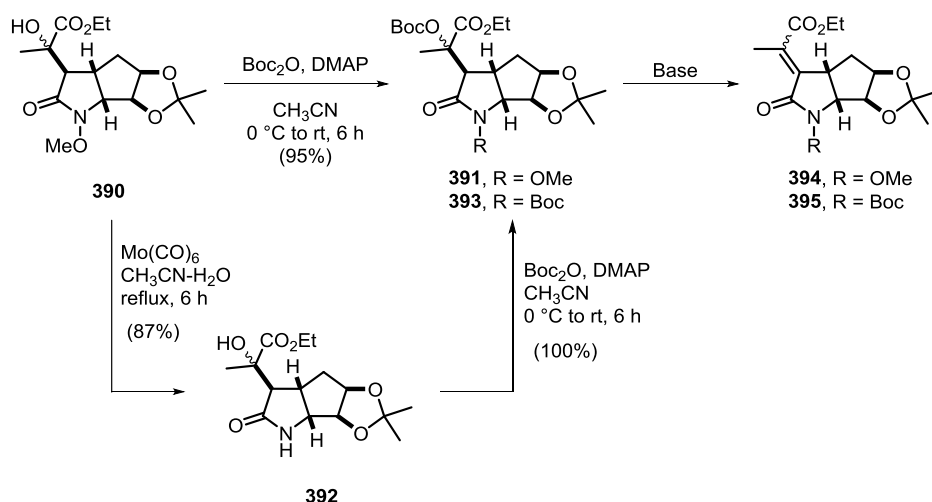
discussed before, this tertiary alcohol demonstrated considerable resistance towards dehydration. Indeed, alcohol **390** resisted dehydration using conventional MsCl and Et_3N ;²¹¹ the reaction underwent sluggishly returning conjugated amides in low yields. Use of DCC/CuCl ²¹² and $\text{Tf}_2\text{O/Et}_3\text{N}$ ²¹³ also failed and only led to recovered starting material. Compound **390** also remained unchanged after stirring with one equivalent of PTSA hydrate for 24 h in toluene held at reflux or exposed to aqueous sulfuric acid (1 M) for 12 h at room temperature. In the latter case, rapid decomposition of the starting material was observed when the reaction was heated at 70 °C. Since POCl_3 ²¹⁴ and SOCl_2 ²¹⁵ in pyridine have been effectively utilized in the dehydration of tertiary alcohols, we opted to examine these reagents. Unfortunately, treatment of **390** with POCl_3 or SOCl_2 in pyridine at room temperature failed to provide the alkene product in all but trace amounts.



Scheme 94

Ultimately, we discovered that *t*-butyl carbonate **391** and **393** underwent elimination when exposed to base. Although dehydrocarbonation of tertiary ethyl carbonates is known²¹⁶ and useful for activation of allylic alcohols towards the Tsuji-Trost reaction,²¹⁷ the elimination of *tert*-butyl carbonates has yet to be reported. Thus, reaction of alcohol **390** with Boc-anhydride and DMAP in CH_3CN afforded carbonate **391** in excellent yield (Scheme 95). Cleavage of the *N*-methoxy group was completed by treatment of **390** with molybdenum

hexacarbonyl in aqueous acetonitrile to afford N-H amide **392** in good yield.²¹⁸ Both amide and hydroxyl functionalities were then protected with Boc-anhydride to afford carbonate **393**.

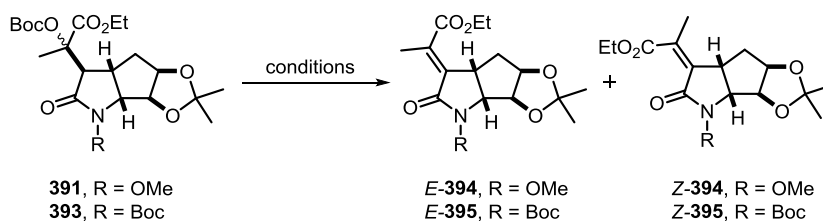


Scheme 95

Carbonates **391**, **393** were now submitted to dehydrocarbonation with a range of bases. The results of this elimination study are outlined in Table 16. Treatment of **391** with potassium *tert*-butoxide in THF at ambient temperature provided a mixture of *E*- and *Z*-**394**, albeit in moderate yield. Minor quantities of the corresponding N-H products resulting from *N*-methoxy group cleavage were also observed.²⁰⁰ In all cases, the *E*-alkene was the major product of this transformation. Attempts to accomplish this reaction by heating a solution of **391** in pyridine at 100°C proved fruitless and led only to recovering of starting material. The best results were obtained using 5 equivalents of DBU in toluene at 100°C . The elimination reaction of *N*-Boc derivative **393** was more successful, generating mixtures of separable alkenes *E* and *Z*-**395** in higher yields. These ratios were similar to those observed for the elimination of carbonate **391** and the *E*-alkene predominated in all instances. We also noted that dehydrocarbonation of carbonate **393** with DBU in toluene proceeds at a significantly lower (50°C) temperature. We believe that this may be a consequence of the electron-

withdrawing ability of the *N*-Boc group, which would serve to increase the acidity of the β -hydrogen and thus promote elimination.

Table 16. Carbonate Elimination Studies



entry	substrate	base	equiv	solvent	<i>T</i> (°C)	time, h	yield, % ^a (<i>E:Z</i>)
1	391	<i>t</i> -BuOK	3	THF	25	48	38 (4.1:1)
2	391	KOH	3	toluene	100	6	42 (3.5:1)
3	391	DBU	5	toluene	100	6	63 (4.3:1)
4	391	py	-	py	100	6	NR
5	393	<i>t</i> -BuOK	3	THF	25	24	81 (3.2:1)
6	393	<i>t</i> -BuOK	3	toluene	50	4	85 (3.5:1)
7	393	<i>t</i> -BuOK	3	<i>t</i> -BuOH	25	4	decomp
8	393	DBU	10	DCM	40	12	77 (3.7:1)
9	393	DBU	5	toluene	50	5	86 (3.3:1)
10	393	KOH	3	THF	50	5	52 (3.9:1)
11	393	KHMDS	3	THF	25	5	NR

^aIsolated yields, after flash chromatography.

The structures of *E,Z*-**394** and *E,Z*-**395** were elucidated using ¹H NMR experiments (Figure 14). It was found the allyl methyl group protons for major *E*-isomers of **394** and **395** are deshielded (δ 2.36 and 2.38 ppm, respectively) relative to *Z*-**394**, **395** (δ 2.00 and 2.03 ppm, respectively) as a result of their close proximity to the amide carbonyl group. In addition, protons H-4 for *E*-**394**, **395** are more downfield (δ ~ 4.00 ppm) relative to *Z*-**394**, **395** (δ ~ 3.55 ppm) due to their close proximity to the ester carbonyl group.

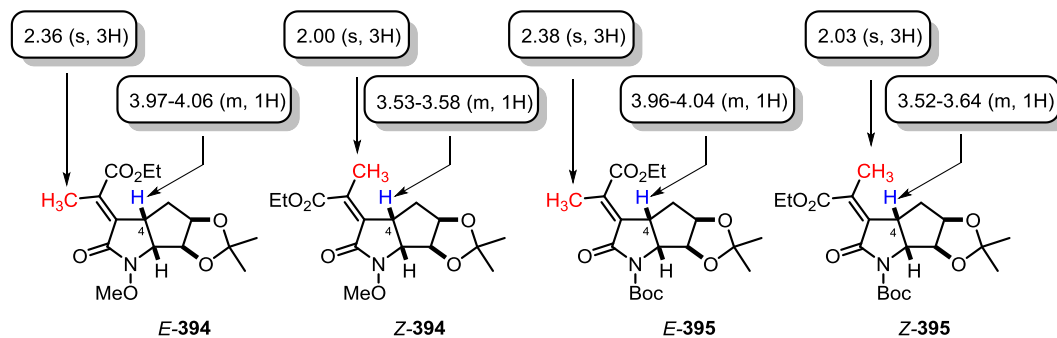
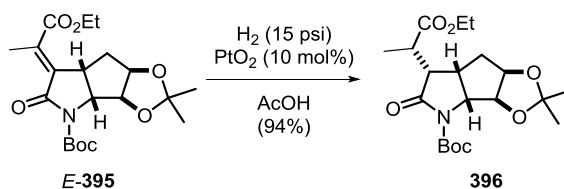


Figure 14 Comparison of peaks in ^1H NMR spectra of *E,Z*-**394** and *E,Z*-**395**

Catalytic hydrogenation of tetrasubstituted alkene *E*-**395** over PtO_2 in glacial acetic acid provided *cis-cis*-2,3,4-trisubstituted pyrrolidinone **396** with excellent stereoselectivity (10:1) and high yield (Scheme 96). Attempts to perform this reaction in other solvents, including EtOAc, THF, MeOH and EtOH, resulted in a decrease in diastereoselectivity. No reaction or alkene isomerization was observed when the reduction was carried out over other transition metal catalysts (*vide supra*).



Scheme 96

The relative configuration of **396** was confirmed by a 2D NOESY experiment (Figure 15). Analysis of the spectra revealed strong nOe correlations between H-3/H-4, H-3/H-5 and H-4/H-5 for compound **396**, which was proven to contain the required all-*cis* stereochemistry at C-3/C-4/C-5.

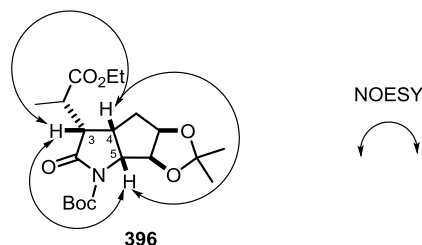
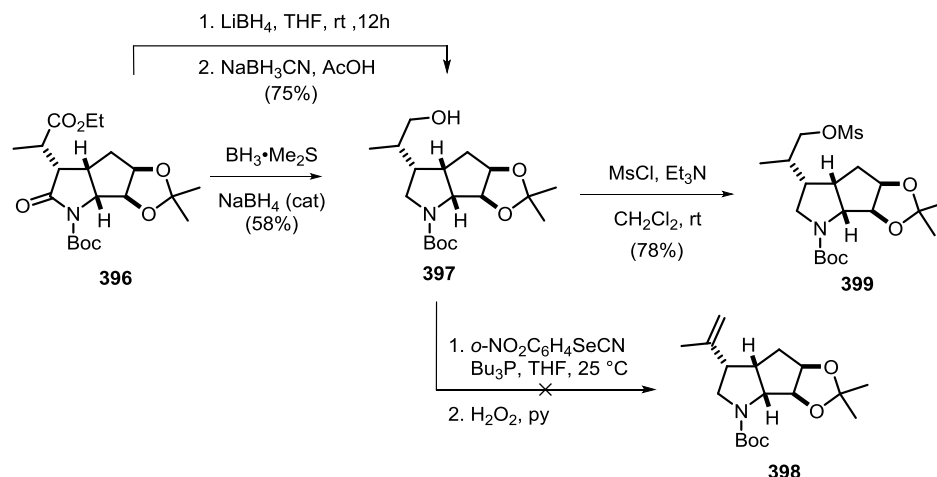


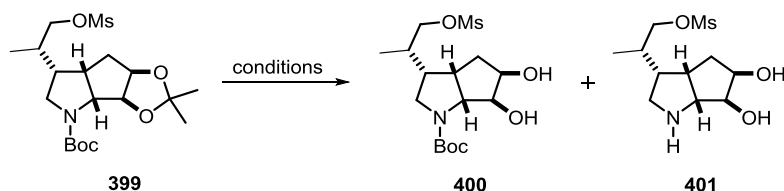
Figure 15 nOe correlations in the spectra of **396**

Simultaneous ester and amide reduction of **396** was accomplished by treatment with a 15-fold excess of $\text{BH}_3\text{-Me}_2\text{S}$ complex in the presence of catalytic NaBH_4 (Scheme 97).²¹⁹ Alternatively, this transformation could be performed using a 2-step procedure. Thus, ester and amide moieties were initially reduced with LiBH_4 in THF to the corresponding primary alcohol and hemiaminal functionalities. Dissolution of the crude product in AcOH and treatment with an excess of NaBH_3CN then afforded pyrrolidine **397** in good yield. Unfortunately, application of Grieco's²²⁰ dehydration protocol (*via* selenide and selenoxide) failed to provide **398**. This result was rather surprising since this method has been widely employed for the construction of the isoprene unit in kainoid syntheses.^{178,179b,221} We therefore elected to convert the primary alcohol to the corresponding mesylate in order to have more flexibility with the elimination step. Treatment of alcohol **397** with methanesulfonyl chloride in the presence of triethylamine generated stable mesylate derivative **399** in good yield.



Scheme 97

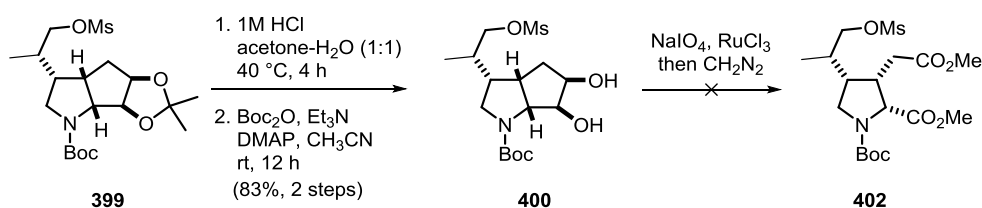
In order to remove the acetonide group from **399**, a range of conditions known to mediate this transformation was qualitatively screened (Table 13). However, selective acetonide deprotection in the presence of the Boc carbamate was found to be more challenging than anticipated. Aqueous TFA and HCl, PTSA in methanol, 50X8 DOWEX acidic ion-exchange resin in refluxing methanol all generated the free amine in addition to the desired 1,2-diol. No acetonide cleavage was detected when **399** was treated with aqueous AcOH or 50X8 DOWEX in methanol at ambient temperature. The use of a solution of iodine in MeOH as milder cleaving agent led to the formation of **400** and **401** (1:7).

Table 17. Acetonide Deprotection Studies

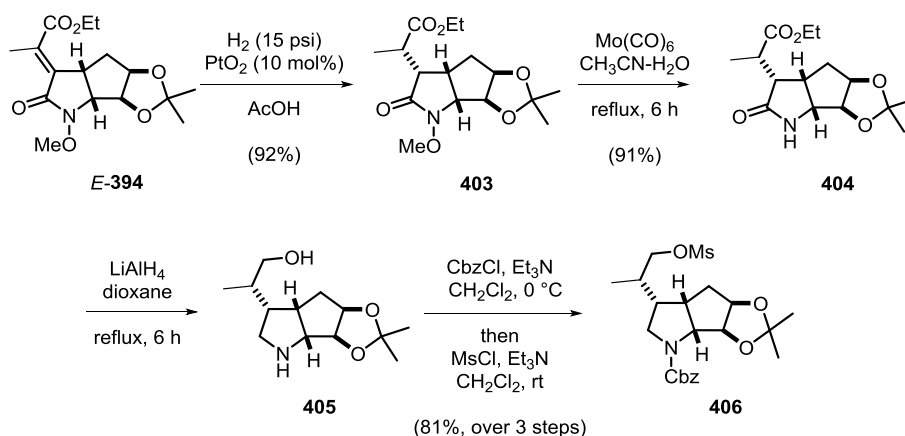
entry	reagent	solvent	T (°C)	time, h	product(s) ^a
1	80% TFA	H ₂ O	25	0.5	only 401
2	3M HCl	THF-H ₂ O (1:1)	25	12	only 401
3	0.1M HCl	THF-H ₂ O (1:1)	25	24	only 401
4	1M HCl	acetone-H ₂ O (1:1)	40	4	only 401
5	50% AcOH	H ₂ O	25	12	no reaction
6	PTSA	MeOH	25	12	only 401
7	I ₂	MeOH	65	24	400 + 401 (1:7)
8	DOWEX 50X8-100	MeOH	25	12	no reaction
9	DOWEX 50X8-100	MeOH	65	12	only 401

^aMonitored by TLC.

Since we were unable to retain the Boc protecting group, we simply opt to reprotect the free amine of **401** using Boc anhydride with Et₃N and DMAP in CH₂Cl₂ (Scheme 98). Following this method, we were pleased to discover that *N*-Boc protected diol **400** can be synthesized from pyrrolidine **401** in high yield. Initial attempts to mediate oxidative cleavage of the diol moiety in **400** by treatment with NaIO₄/RuCl₃ in CH₃CN-CCl₄-H₂O (2:2:3) solvent mixture were unsuccessful and led to the decomposition of starting material. We believe this reflects the inherent instability of Boc groups to sodium iodide²²² and strongly Lewis acidic conditions.²²³

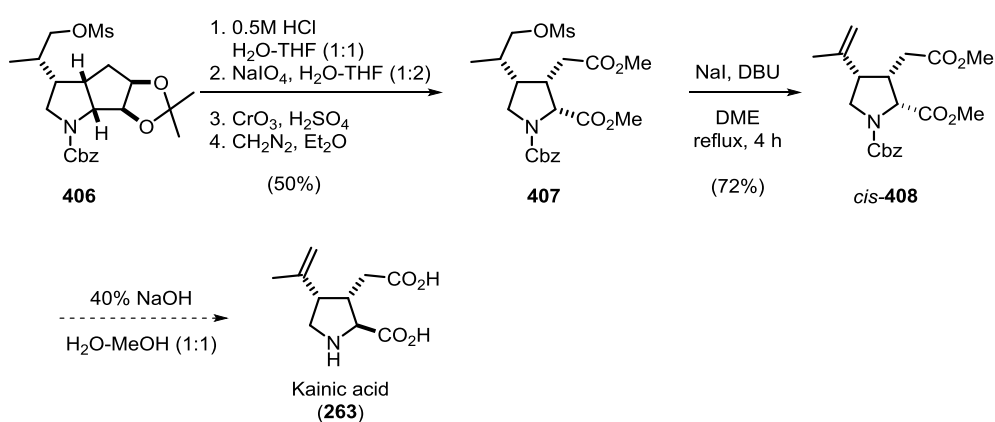
**Scheme 98**

Our protecting group strategy was revised to involve *N*-Cbz derivative **406**, which was readily prepared from alkene *E*-**394** (Scheme 99). Using our established hydrogenation procedure, *cis* ester **403** was prepared in excellent yield and with high stereoselectivity (10:1). We envisioned the removal of the *N*-OMe group prior to reduction, since the direct reduction of *N*-methoxyamides is not generally a high-yielding process. Thus, reaction of **403** with Mo(CO)_6 in a mixture of CH_3CN and H_2O at reflux temperature generated **404** in high yield. Treatment with LiAlH_4 in dioxane at reflux afforded amino alcohol **405**, which was used directly in the next step. Thus, sequential, one-pot treatment of **405** with CbzCl and MsCl delivered carbamate **406** in 81% over 3 steps.



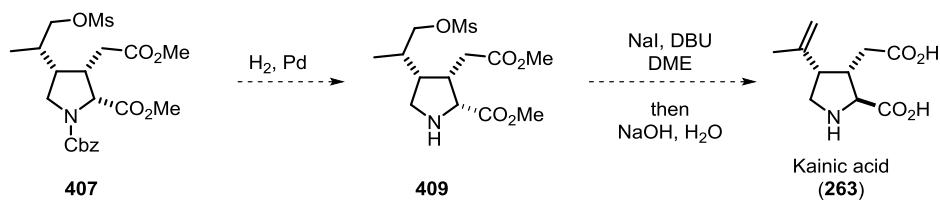
Removal of the acetonide protecting group of **406** was efficiently accomplished by acidic hydrolysis, generating vicinal diol, which was oxidatively cleaved using sodium periodate in H_2O -THF at ambient temperature (Scheme 100). The crude diol was immediately treated with 8M Jones reagent, followed by an ethereal solution of diazomethane to furnish diester **407** in a reasonable overall yield. Compound **407** then underwent $\text{S}_{\text{N}}2$ substitution and elimination to form **408** upon heating to reflux with NaI and

DBU in dimethoxyethane. In this step, we hoped that such base treatment would also epimerize C-2 center to provide the natural *trans* C-2/C-3 diastereomer. According to Ogasawara,²²⁴ *cis*- and *trans*-**408** can distinguished by ¹H NMR spectroscopy. Thus, the signal for the characteristic C-2 methine proton is observed at δ 4.46 (dd, J = 6.4, 2.7 Hz) for *cis*-**408**, while the same signal is shifted to δ 4.24 (dd, J = 4.2, 2.9 Hz) for the natural *trans*-**408** isomer. Given the fact that we observed the signal at δ 4.47 (dd, J = 16.7, 6.2 Hz), we conclude that the desired epimerization did not occur under these conditions. In order to complete the synthesis of the target itself, basic hydrolysis as well as Cbz deprotection step was required. It is known that benzyl carbamates are cleaved to the corresponding amines upon heating with aqueous NaOH.^{169,194a,225} Unfortunately, attempts to cleave the Cbz group under these conditions failed to provide the desired natural product.



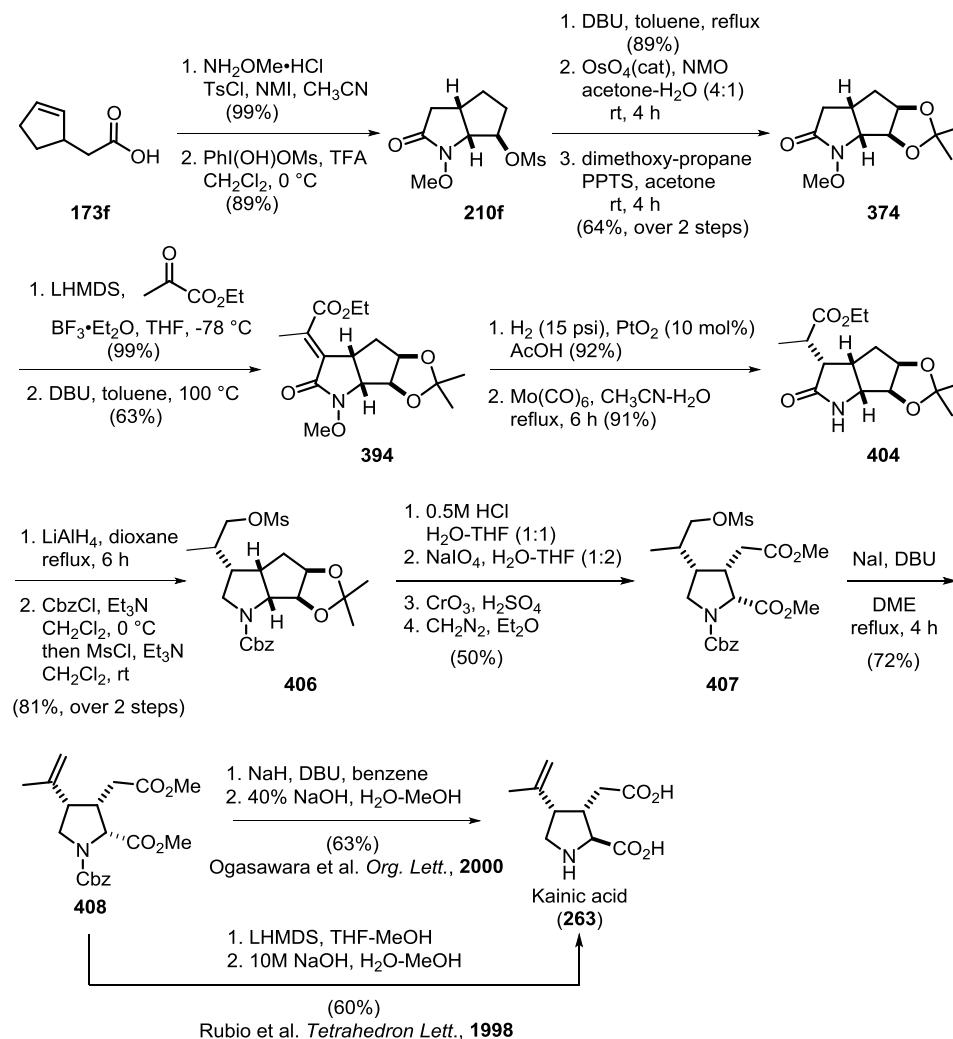
Scheme 100

Our plan to complete the synthesis is outlined below (Scheme 101). It was now decided to reverse the last two steps: first removing Cbz group under catalytic hydrogenolysis and then forming the isopropene appendage by mesylate elimination, followed by diester hydrolysis.



Scheme 101

Here is a consolidated diagram, summarizing our progress towards neurotransmitter α -kainic acid (Scheme 102). An advanced intermediate **408** was synthesized with 7.6% overall yield over a total of 17 steps starting from commercially available 2-(cyclopent-2-en-1-yl)acetic acid (**173f**). Compound **408** can be converted to α -kainic acid by following the previously reported studies by Ogasawara^{190a} and Rubio,¹⁶⁵ respectively.



Scheme 102

2.7. Conclusions

Employing the HMIB-mediated intramolecular oxamidation of unsaturated *O*-alkyl hydroxamates, a strategy for the preparation of neurotransmitter α -kainic acid has been developed. Construction of an advanced intermediate **408** has demonstrated the synthetic utility of *N*-methoxy-*N*-acylnitrenium ions for the preparation of complex natural products.

2.8. Experimental Procedures

2.8.1 General Procedures

All non-aqueous reactions were carried out in oven or flame-dried glassware under an atmosphere of dry nitrogen or argon, unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using Merck pre-coated silica gel plates with F₂₅₄ indicator. Visualization was accomplished by UV and/or potassium permanganate solution. Flash column chromatograph was performed using Silicycle Silica-P flash silica gel (40-63 μ m). Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted.

2.8.2 Materials

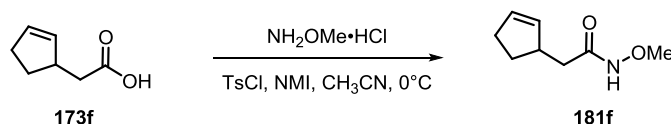
Dichloromethane (DCM), diethyl ether (Et₂O), toluene, tetrahydrofuran (THF) and methanol (CH₃OH) after purchase from Aldrich were additionally purified on PureSolv PS-400-4 by Innovative Technology, Inc. purification system. Acetonitrile (CH₃CN) and *N*-methylimidazole (NMI) were distilled from calcium hydride under an atmosphere of dry nitrogen. Acetic acid (AcOH) was distilled from phosphorus pentoxide under an atmosphere of dry nitrogen. Hydroxy(tosyloxy)iodobenzene (HTIB) and hydroxy(mesyloxy)iodobenzene (HMIB) were prepared according to the method of Yusubov and Wirth.²²⁶ PIFA was prepared following the procedure reported by Varvoglis.²²⁷ All other reagents and starting materials, unless otherwise noted, were purchased from commercial vendors and used without further purification.

2.8.3 Instrumentation

All melting points were determined in open Pyrex capillaries using a Thomas Hoover Unimelt melting point apparatus and are uncorrected. Infrared spectra were recorded as thin films on sodium chloride plates using an ATI Mattson Genesis Series FTIR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 (400 MHz, ^1H , 101 MHz ^{13}C) or a Bruker Avance 500 (500 MHz ^1H , 126 MHz ^{13}C). Chemical shift values (δ) are reported in ppm relative to residual chloroform (δ 7.27 ppm for ^1H ; 77.00 ppm for ^{13}C), residual acetone (δ 2.05 ppm for ^1H ; 29.92 ppm for ^{13}C), residual methanol (δ 3.31 ppm for ^1H ; 49.15 ppm for ^{13}C) and residual DMSO (δ 2.50 ppm for ^1H ; 39.51 ppm for ^{13}C). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet) and br (broad). DEPT 135 and two-dimensional (COSY, HMQC, HMBC, NOESY) NMR experiments were employed, where appropriate, to aid in the assignment of signals in the ^1H NMR spectra. High-resolution electron spray ionization mass spectra (HRMS-ESI) were obtained on a Micromass Q-TOF 2 at the University of Illinois Research Resources Center or on a Micromass Q-TOF Ultima at the Mass Spectroscopy Laboratory at the University of Illinois, Urbana-Champaign.

2.8.4 Experimental Procedures

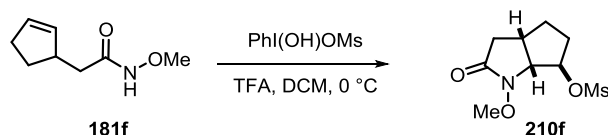
(\pm)-*O*-Methyl cyclopent-2-enyl-acetohydroxamate (**181f**)



A mixture of compound **173f** (2.0 g, 15.9 mmol, 1.0 equiv) and *N*-methylimidazole (3.8 mL, 44.7 mmol, 3.0 equiv) in CH_3CN (50 mL) was cooled to 0 °C and then treated with a solution of TsCl (3.93 g, 20.6 mmol, 1.3 equiv) in CH_3CN (25 mL) *via* cannula. The reaction mixture

was stirred for 1 h in an ice bath and then a solution of $\text{NH}_2\text{OMe}\cdot\text{HCl}$ (1.72 g, 20.6 mmol, 1.3 equiv) in CH_3CN (20 mL) and *N*-methylimidazole (1.27 mL, 15.9 mmol, 1.0 equiv) was added *via* cannula. After warming to rt, the reaction was stirred overnight and then concentrated and the residue purified by flash chromatography on silica gel (EtOAc/hexanes, 1:1 to EtOAc) to provide **181f** (2.46 g, quant) as a colorless oil; R_f 0.33 (EtOAc); IR (film) ν_{max} 3180, 2940, 1659, 1518, 1361, 1191, 982, 943, 697 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 8.71 (br. s., 1H), 5.78 (dd, $J = 5.5, 2.3$ Hz, 1H), 5.68 (br. s., 1H), 3.76 (br. s., 3H), 3.08-3.20 (m, 1H), 2.25-2.41 (m, 2H), 2.02-2.21 (m, 3H), 1.47 (dq, $J = 14.7, 6.4$ Hz, 1H); ^{13}C NMR (CDCl_3 , 101 MHz): δ 170.1, 133.4, 131.8, 64.4, 42.2, 39.3, 31.8, 29.4; HRMS-ESI calcd for $\text{C}_8\text{H}_{13}\text{NO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 178.0844, found: 178.0840.

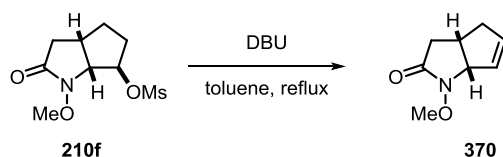
(3a*S,6a*R**)-1-Methoxy-2-oxooctahydrocyclopenta[*b*]pyrrol-6-yl methanesulfonate (210f)**



A solution of compound **181f** (4.3 g, 27.7 mmol, 1.0 equiv) in DCM (400 mL) was cooled to 0 °C (ice bath) and sequentially treated with TFA (2.1 mL, 27.7 mmol, 1.0 equiv) and a solution of HMIB (13.1 g, 41.6 mmol, 1.2 equiv) in DCM (100 mL) rapidly *via* syringe. After 1 h, the reaction was allowed to warm to rt and stirred for 5 h. The reaction mixture was then concentrated under reduced pressure to yield a brown oil, which was immediately purified by flash chromatography on silica gel (EtOAc) to provide **210f** (5.9 g, 85%) as a colorless oil; R_f 0.23 (EtOAc); IR (film) ν_{max} 2941, 1689, 1350, 1171, 941, 898, 801 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 5.12 (br. s., 1H), 4.34 (d, $J = 7.7$ Hz, 1H), 3.84 (s, 3H), 3.06 (s, 3H), 2.89-2.96 (m, 1H), 2.66 (dd, $J = 17.7, 10.5$ Hz, 1H), 2.15-2.24 (m, 1H), 2.00-2.08 (m,

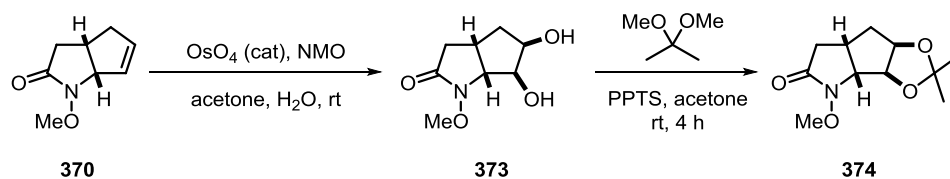
3H), 1.62 (ddt, $J = 13.0, 6.5, 3.1$ Hz, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 169.0, 82.6, 66.1, 62.2, 38.3, 34.1, 31.4, 31.1, 30.4; HRMS-ESI calcd for $\text{C}_9\text{H}_{16}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$: 250.0749, found: 250.0739.

(3aS*,6aR*)-1-Methoxy-1,3a,4,6a-tetrahydrocyclopenta[*b*]pyrrol-2(3*H*)-one (370)



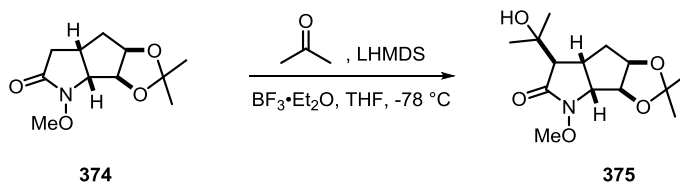
To a solution of compound **210f** (2.73 g, 11.0 mmol, 1.0 equiv) in toluene (70 mL) was added DBU (4.0 mL, 26.8 mmol, 2.4 equiv) *via* syringe. The mixture was stirred for 10 min then heated to reflux. The reaction was stirred at reflux for 6 h, at which point TLC indicated complete consumption of substrate. The reaction mixture was then concentrated under reduced pressure to yield a dark oil, which was immediately purified by flash chromatography on silica gel (EtOAc) to provide **370** (1.49 g, 89%) as a colorless oil; R_f 0.23 (EtOAc); IR (film) ν_{max} 2938, 1705, 1647 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 6.00 (d, $J = 5.6$ Hz, 1H), 5.94 (dd, $J = 5.6, 1.8$ Hz, 1H), 4.70 (d, $J = 7.9$ Hz, 1H), 3.84 (s, 3H), 2.90-2.99 (m, 1H), 2.78 (dd, $J = 17.1, 7.9$ Hz, 1H), 2.68 (dd, $J = 17.4, 10.4$ Hz, 1H), 2.24 (d, $J = 17.1$ Hz, 1H), 2.14 (dd, $J = 17.1, 5.0$ Hz, 1H); ^{13}C NMR (CDCl_3 , 101 MHz): δ 169.0, 135.2, 128.2, 67.0, 62.9, 40.1, 35.6, 30.5; HRMS-ESI calcd for $\text{C}_8\text{H}_{11}\text{NO}_2$ $[\text{M}]^+$ 153.0790, found: 153.0789.

(3aS*,3bR*,6aS*,7aR*)-4-Methoxy-2,2-dimethylhexahydro-[1,3]dioxolo[4',5':4,5]-cyclopenta[1,2-*b*]pyrrol-5(3a*H*)-one (374)



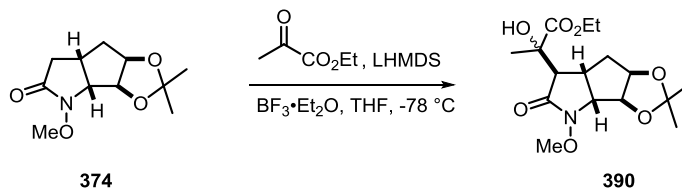
To a solution of compound **370** (783 mg, 5.1 mmol, 1.0 equiv) in acetone (20 mL) and H₂O (5 mL) was added a solution of OsO₄ (4 wt% in H₂O, 0.16 mL, 0.005 equiv) *via* syringe. The mixture was stirred for 10 min, and then *N*-methylmorpholine *N*-oxide hydrate (830 mg, 6.1 mmol, 1.2 equiv) was added in one portion. The reaction was stirred for 4 h before a saturated solution of Na₂SO₃ (2 mL) was added. The mixture was stirred for 20 min and then diluted with DCM (75 mL). The organic layer was separated and washed with brine (20 mL). The organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was dissolved in acetone (20 mL) and PPTS (128 mg, 0.51 mmol, 0.1 equiv) and 2,2-dimethoxypropane (1.9 mL, 15.3 mmol, 3.0 equiv) were added *via* syringe. After stirring at room temperature for 4 h, the reaction mixture was concentrated under reduced pressure. The residual material was purified by flash chromatography on silica gel (EtOAc) to provide **374** (743 mg, 65%, over 2 steps) as a colorless oil; *R*_f 0.25 (EtOAc); IR (film) ν_{max} 2983, 2936, 1718, 1437, 1374, 1212, 1052 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 4.73-4.79 (m, 1H), 4.68-4.73 (m, 1H), 4.03 (d, *J* = 6.6 Hz, 1H), 3.83 (s, 3H), 2.98 (dd, *J* = 10.1, 7.7 Hz, 1H), 2.51 (dd, *J* = 17.1, 8.3 Hz, 1H), 2.36 (dd, *J* = 14.5, 7.7 Hz, 1H), 2.12 (d, *J* = 17.1 Hz, 1H), 1.64 (ddd, *J* = 14.5, 10.5, 4.5 Hz, 1H), 1.46 (s, 3H), 1.33 (s, 3H); ¹³C NMR (CDCl₃, 101 MHz): δ 169.5, 110.6, 81.6, 81.4, 68.0, 62.0, 37.8, 33.3, 32.2, 26.7, 24.3; HRMS-ESI calcd for C₁₁H₁₇NO₄ [M]⁺ 227.1158, found: 227.1156.

(3a*S,3b*R**,6*R**,6a*S**,7a*R**)-6-(2-Hydroxypropan-2-yl)-4-methoxy-2,2-dimethylhexahydro-[1,3]-dioxolo[4',5':4,5]cyclopenta[1,2-*b*]pyrrol-5(3a*H*)-one (375)**



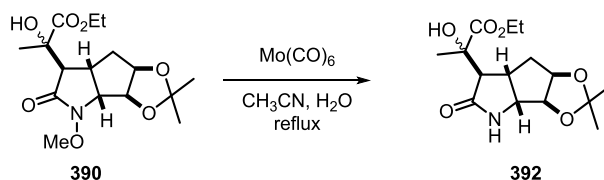
To a solution of compound **374** (212 mg, 0.93 mmol, 1.0 equiv) in THF (20 mL) cooled to -78 °C was added LHMDS (1M solution in THF, 2.24 mL, 2.24 mmol, 2.4 equiv) *via* syringe. After stirring for 1 h, acetone (103 μ L, 1.4 mmol, 1.5 equiv) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (172 μ L, 1.4 mmol, 1.5 equiv) were sequentially added *via* syringe. The reaction mixture was stirred for 4 h at -78 °C then allowed to warm to rt and quenched with aqueous saturated NH_4Cl (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were then dried with Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc-hexanes, 1:1) to provide **375** (265 mg, 100%) as a colorless oil; R_f 0.49 (EtOAc); IR (film) ν_{max} 3445, 2983, 2935, 1698, 1457, 1437, 1211, 1056 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 4.75 (t, J = 4.7 Hz, 1H), 4.67 (d, J = 5.1 Hz, 1H), 4.00 (d, J = 7.3 Hz, 1H), 3.85 (s, 3H), 3.64 (s, 1H), 2.78 (q, J = 8.2 Hz, 1H), 2.44 (dd, J = 14.5, 8.2 Hz, 1H), 1.63-1.72 (m, 2H), 1.48 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (CDCl_3 , 101 MHz): δ 170.9, 110.9, 81.5, 81.1, 72.1, 67.6, 61.8, 55.2, 38.4, 36.0, 27.5, 26.8, 26.0, 24.4; HRMS-ESI calcd for $\text{C}_{14}\text{H}_{23}\text{NO}_5$ $[\text{M}]^+$ 285.1576, found: 285.1577.

Ethyl (S)-2-hydroxy-2-((3aS*,3bR*,6R*,6aS*,7aR*)-4-methoxy-2,2-dimethyl-5-oxooctahydro-[1,3]-dioxolo[4',5':4,5]cyclopenta[1,2-b]pyrrol-6-yl)propanoate and ethyl (R)-2-hydroxy-2-((3aS*,3bR*,6R*,6aS*,7aR*)-4-methoxy-2,2-dimethyl-5-oxooctahydro-[1,3]-dioxolo-[4',5':4,5]cyclopenta[1,2-b]pyrrol-6-yl)propanoate (**390**)



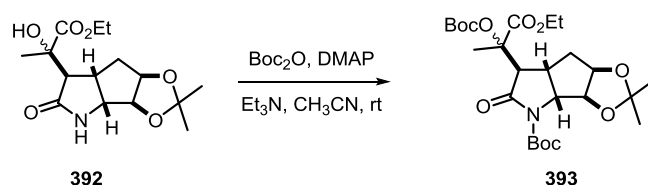
To a solution of compound **374** (2.46 g, 10.8 mmol, 1.0 equiv) in THF (200 mL) cooled to -78 °C was added LHMDS (1M solution in THF, 30 mL, 30 mmol, 2.4 equiv) was added *via* syringe. After stirring for 1 h, ethyl pyruvate (1.9 mL, 16.2 mmol, 1.5 equiv) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2.0 mL, 16.2 mmol, 1.5 equiv) were sequentially added *via* syringe. The reaction mixture was stirred for 4 h at -78 °C then allowed to warm to rt and quenched with aqueous saturated NH_4Cl (100 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were then dried with Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc-hexanes, 1:1) to provide **390** (3.68 g, 99%) as a mixture of diastereomers: white solid; mp 109-111 °C (EtOAc/hexanes); R_f 0.57 (EtOAc); IR (film) ν_{max} 3511, 2983, 2936, 1713, 1472, 1379, 1204, 1011, 888, 698 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 4.73 (t, J = 4.7 Hz, 1H), 4.62 (d, J = 5.1 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 4.06 (d, J = 6.9 Hz, 1H), 3.76 (s, 3H), 3.57 (s, 1H), 3.00-3.09 (m, 1H), 2.51 (s, 1H), 2.39 (dd, J = 14.4, 7.8 Hz, 1H), 1.58-1.71 (m, 1H), 1.46 (br. s., 3H), 1.45 (br. s., 3H), 1.28-1.35 (m, 6H); ^{13}C NMR (CDCl_3 , 101 MHz): δ 175.6, 168.5, 110.6, 81.3, 81.0, 74.7, 67.3, 62.6, 61.3, 52.7, 37.9, 34.4, 26.6, 24.4, 24.3, 14.0; HRMS-ESI calcd for $\text{C}_{16}\text{H}_{26}\text{NO}_7$ $[\text{M}+\text{H}]^+$: 344.1709, found: 344.1705.

Ethyl (S)-2-((3aS*,3bR*,6R*,6aS*,7aR*)-2,2-dimethyl-5-oxooctahydro-[1,3]dioxolo[4',5':4,5]-cyclopenta[1,2-b]pyrrol-6-yl)-2-hydroxypropanoate and ethyl (R)-2-((3aS*,3bR*,6R*,6aS*,7aR*)-2,2-dimethyl-5-oxooctahydro-[1,3]dioxolo[4',5':4,5]-cyclopenta-[1,2-b]pyrrol-6-yl)-2-hydroxypropanoate (392)



To a solution of **390** (250 mg, 0.72 mmol, 1.0 equiv) in MeCN-H₂O (15:1, 10 mL) was added Mo(CO)₆ (280 mg, 1.07 mmol, 1.5 equiv) in one portion. The reaction was heated at reflux for 6 h and then allowed to cool to rt. The reaction was opened to air and stirred for 12 hours. The reaction mixture was then concentrated under reduced pressure and purified by flash chromatography on silica gel to provide **392** (200 mg, 87%) as a white solid; mp 156-160 °C (EtOAc/hexanes); R_f 0.28 (EtOAc); IR (film) ν_{max} 3311, 2983, 2937, 1731, 1699, 1444, 1373, 1269, 1055, 866, 737 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 6.46 (s, 1H), 4.67-4.74 (m, 1H), 4.37-4.41 (m, 1H), 4.24-4.34 (m, 2H), 3.95 (d, *J* = 6.7 Hz, 1H), 3.81-3.89 (m, 1H), 3.16 (q, *J* = 7.9 Hz, 1H), 2.56 (s, 1H), 2.36 (dd, *J* = 14.5, 7.9 Hz, 1H), 1.72 (ddd, *J* = 14.5, 10.2, 4.5 Hz, 1H), 1.47 (s, 3H), 1.45 (s, 3H), 1.27-1.35 (m, 6H); ¹³C NMR (CDCl₃, 101 MHz): δ 176.2, 175.9, 110.5, 84.7, 81.2, 74.7, 65.3, 62.4, 56.3, 38.9, 38.0, 26.7, 24.6, 24.4, 14.0; HRMS-ESI calcd for C₁₅H₂₄NO₆ [M+H]⁺: 314.1604, found: 314.1595.

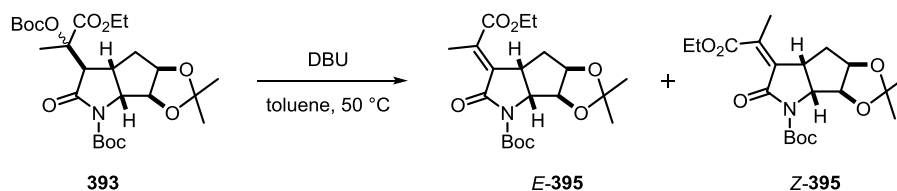
tert-Butyl (3a*S,3b*R**,6*R**,6a*S**,7a*R**)-6-((*R*)-2-((*tert*-butoxycarbonyl)oxy)-1-ethoxy-1-oxopropan-2-yl)-2,2-dimethyl-5-oxohexahydro-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-*b*]pyrrole-4(3a*H*)-carboxylate and tert-butyl (3a*S**,3b*R**,6*R**,6a*S**,7a*R**)-6-((*S*)-2-((*tert*-butoxycarbonyl)oxy)-1-ethoxy-1-oxopropan-2-yl)-2,2-dimethyl-5-oxohexahydro-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-*b*]pyrrole-4(3a*H*)-carboxylate (**393**)**



To a stirred solution of compound **392** (1.15 g, 3.69 mmol, 1.0 equiv) in CH₃CN (30 mL) cooled to 0 °C were sequentially added triethylamine (4.10 mL, 29.52 mmol, 8.0 equiv) and DMAP (450 mg, 3.69 mmol, 1.0 equiv). A solution of Boc₂O (3.22 g, 14.8 mmol, 4.0 equiv)

in CH₃CN (10 mL) was then added *via* cannula. The reaction mixture was stirred for 20 min at 0 °C and then allowed to warm to rt. After 6 h, the reaction was concentrated under reduced pressure and the residual oil purified by flash chromatography (EtOAc-hexanes, 1:4) to yield **393** (1.89 g, 100%) as a mixture of diastereomers: colorless oil; *R_f* 0.17 (EtOAc-hexanes, 1:4); IR (film) ν_{max} 2981, 2937, 1789, 1747, 1722, 1458, 1362, 1290, 1157, 1117, 1061, 852, 737 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 4.63 (t, *J* = 4.6 Hz, 2H), 4.54 (d, *J* = 5.1 Hz, 1H), 4.51 (d, *J* = 5.1 Hz, 1H), 4.17-4.31 (m, 4H), 4.08 (d, *J* = 7.6 Hz, 1H), 3.10-3.18 (m, 1H), 3.07 (q, *J* = 8.3 Hz, 1H), 2.88-2.90 (m, 1H), 2.72-2.74 (m, 1H), 2.46 (dd, *J* = 14.6, 7.6 Hz, 1H), 2.37 (dd, *J* = 14.5, 7.6 Hz, 1H), 1.76 (s, 5H), 1.58-1.65 (m, 3H), 1.52-1.58 (m, 15H), 1.48 (s, 14H), 1.46 (s, 7H), 1.31 (s, 5H), 1.25-1.30 (m, 5H); ¹³C NMR (CDCl₃, 126 MHz): δ 170.5, 170.3, 169.9, 169.7, 151.6, 151.4, 150.0, 149.9, 110.9, 85.8, 85.6, 83.8, 83.7, 83.0, 82.9, 82.0, 81.2, 80.2, 80.1, 68.9, 68.8, 62.0, 61.9, 56.5, 56.0, 37.7, 37.6, 34.9, 34.9, 28.0, 28.0, 27.7, 27.6, 27.0, 26.9, 24.7, 24.6, 20.8, 19.0, 14.0, 13.9; HRMS-ESI calcd for C₂₅H₄₀NO₁₀ [M+H]⁺: 514.2652, found: 514.2647.

(3aS*,3bR*,6aS*,7aR*,E)-*tert*-Butyl 6-(1-ethoxy-1-oxopropan-2-ylidene)-2,2-dimethyl-5-oxohexahydro-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-*b*]pyrrole-4(3aH)-carboxylate (*E*-395) and *tert*-butyl (3aS*,3bR*,6aS*,7aR*,Z)-6-(1-ethoxy-1-oxopropan-2-ylidene)-2,2-dimethyl-5-oxohexahydro-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-*b*]pyrrole-4(3aH)-carboxylate (*Z*-395)



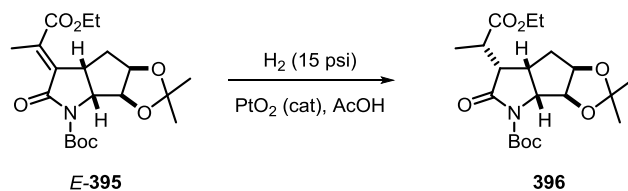
To a stirred solution of compound **393** (405 mg, 0.79 mmol, 1.0 equiv) in toluene (20 mL) was added DBU (0.60 mL, 3.95 mmol, 5.0 equiv) *via* syringe. The reaction was heated to 50

°C, stirred for 4 h, cooled to rt and quenched with aqueous NH₄Cl (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc-hexanes, 1:5) to yield *E*-**395** (205.7 mg, 66%) and *Z*-**395** (62.3 mg, 20%).

Analytical data for *E*-**395**: colorless oil; *R_f* 0.30 (EtOAc-hexanes, 1:4); IR (film) ν_{\max} 2981, 2939, 1772, 1734, 1716, 1701, 1456, 1371, 1238, 1157, 1059, 852 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 4.62-4.65 (m, 1H), 4.57 (d, *J* = 5.0 Hz, 1H), 4.21-4.33 (m, 2H), 4.07 (d, *J* = 7.5 Hz, 1H), 3.96-4.04 (m, 1H), 2.65 (dd, *J* = 14.7, 7.5 Hz, 1H), 2.38 (s, 3H), 1.59-1.65 (m, 1H), 1.57 (s, 9H), 1.45 (s, 3H), 1.34 (t, *J* = 7.5 Hz, 3H), 1.30 (s, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ 167.6, 166.4, 150.6, 138.3, 137.2, 110.9, 85.8, 83.8, 81.1, 67.0, 61.3, 39.5, 37.3, 28.0, 27.0, 24.7, 14.3, 14.1; HRMS-ESI calcd for C₂₀H₃₀NO₇ [M+H]⁺: 396.2022, found: 396.2015.

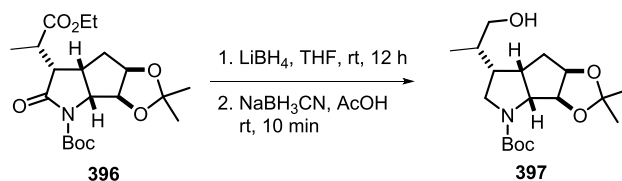
Analytical data for *Z*-**395**: colorless oil; *R_f* 0.13 (EtOAc-hexanes, 1:4); IR (film) ν_{\max} 2982, 2935, 1777, 1716, 1653, 1457, 1368, 1239, 1151, 1052, 974, 853, 770 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 4.68 (t, *J* = 4.4 Hz, 1H), 4.56 (d, *J* = 4.4 Hz, 1H), 4.31 (qd, *J* = 7.1, 2.6 Hz, 2H), 4.18 (d, *J* = 8.0 Hz, 1H), 3.52-3.61 (m, 1H), 2.52 (dd, *J* = 14.6, 8.0 Hz, 1H), 2.03 (s, 3H), 1.68 (ddd, *J* = 14.6, 10.6, 4.4 Hz, 1H), 1.54 (s, 9H), 1.48 (s, 3H), 1.28-1.35 (m, 6H); ¹³C NMR (CDCl₃, 101 MHz): δ 169.6, 163.9, 150.4, 138.0, 131.9, 111.1, 86.0, 83.7, 81.4, 67.9, 61.5, 36.3, 36.3, 28.0, 27.1, 24.8, 17.8, 13.9; HRMS-ESI calcd for C₂₀H₃₀NO₇ [M+H]⁺: 396.2022, found: 396.2030.

(3a*S,3b*R**,6*S**,6a*S**,7a*R**)-tert-Butyl 6-(1-ethoxy-1-oxopropan-2-yl)-2,2-dimethyl-5-oxohexahydro-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-*b*]pyrrole-4(3a*H*)-carboxylate (**396**)**



A mixture of compound *E*-**395** (29.6 mg, 0.075 mmol, 1.0 equiv) and PtO₂ (1.7 mg, 7.5x10⁻³ mmol, 0.1 equiv) in AcOH (5 mL) was placed in a Parr hydrogenation apparatus. The reaction mixture was shaken for 24 h under an atmosphere of hydrogen (15 psi). The Parr apparatus was flushed with nitrogen and the reaction mixture filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc-hexanes, 1:5) to provide **396** (28.0 mg, 94%) as a white solid; mp 95-97 °C (EtOAc/hexanes); R_f 0.61 (EtOAc-hexanes, 1:1); IR (film) ν_{max} 2981, 2937, 1721, 1718, 1456, 1375, 1211, 1178, 1053, 881 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 4.64-4.68 (m, 1H), 4.61-4.64 (m, 1H), 4.16-4.29 (m, 2H), 4.12 (d, *J* = 6.1 Hz, 1H), 3.15 (dd, *J* = 11.0, 7.5 Hz, 1H), 3.01-3.10 (m, 1H), 2.50 (dq, *J* = 11.0, 7.0 Hz, 1H), 2.11-2.15 (m, 1H), 1.52-1.59 (m, 9H), 1.48 (s, 3H), 1.27-1.34 (m, 6H), 1.24 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ 175.4, 173.0, 150.1, 110.6, 84.2, 83.7, 80.5, 67.7, 60.8, 49.1, 37.7, 35.2, 31.7, 28.0, 26.6, 24.3, 16.4, 14.1; HRMS-ESI calcd for C₂₀H₃₂NO₇ [M+H]⁺: 398.2179, found: 398.2170.

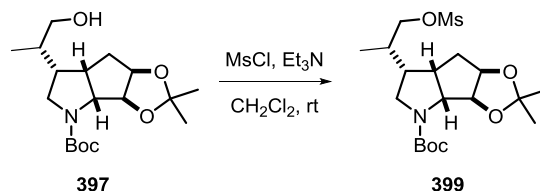
***tert*-Butyl (3a*S**,3b*R**,6*S**,6a*S**,7a*R**)-6-((*S*)-1-hydroxypropan-2-yl)-2,2-dimethylhexahydro-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-*b*]pyrrole-4(3a*H*)-carboxylate (397)**



To a stirred solution of **396** (120 mg, 0.30 mmol, 1.0 equiv) in THF (25 mL) at room temperature, was added LiBH₄ (26.4 mg, 1.2 mmol, 4 equiv). After stirring for 12 h, saturated aqueous sodium tartrate (15 mL) was added and stirring continued for 30 min. EtOAc (20 mL) was then added, the layers separated and the aqueous layer extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over Na₂SO₄, concentrated and dissolved in glacial AcOH (10 mL). NaBH₃CN (4 equiv) was added to the solution portionwise. After 10 min, the reaction mixture was slowly poured to cold 2M aqueous KOH (100 mL) and extracted with EtOAc (3 x 30 mL). Combined organic extracts were dried over Na₂SO₄, concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (EtOAc-hexanes, 1:1) to provide **397** (78 mg, 75%) as a colorless oil; *R_f* 0.34 (EtOAc-hexanes, 1:1); IR (film) ν_{max} 3510, 2977, 1675, 1507, 1394, 1367, 1257, 1205, 1170, 1118, 1051, 886, 778 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ (mixture of rotamers) 4.70 (br. s., 1H), 4.53-4.67 (m, 1H), 3.80-3.93 (m, 1H), 3.60-3.79 (m, 1H), 3.57 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.35-3.47 (m, 1H), 2.91-3.03 (m, 1H), 1.90-2.09 (m, 2H), 1.61-1.74 (m, 2H), 1.52-1.60 (m, 1H), 1.42-1.51 (m, 12H), 1.29 (s, 3H), 1.05 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ (mixture of rotamers) 154.8, 154.5, 110.1, 109.8, 85.6, 84.7, 81.4, 81.3, 79.9, 79.7, 69.8, 67.1, 66.9, 49.1, 49.0, 43.8, 43.0, 42.4, 41.8, 36.1, 30.4, 30.2,

29.7, 28.5, 26.6, 24.4, 24.3, 15.7, 14.3; HRMS-ESI calcd for C₁₈H₃₂NO₅ [M+H]⁺: 342.2280, found: 342.2278.

***tert*-Butyl (3a*S**,3b*R**,6*S**,6a*S**,7a*R**)-2,2-dimethyl-6-((*S*)-1-((methylsulfonyl)oxy)-propan-2-yl)-hexahydro-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-*b*]pyrrole-4(3a*H*)-carboxylate (399)**



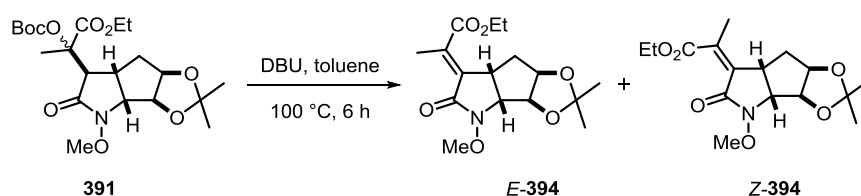
A stirred solution of crude compound **397** (100 mg, 0.33 mmol, 1.0 equiv) in CH₂Cl₂ (20 mL) was cooled to 0 °C then triethylamine (684 μL, 5 mmol, 15 equiv) and MsCl (129 μL, 1.6 mmol, 5.0 equiv) were sequentially added *via* syringe. The reaction mixture was stirred for 20 min at 0 °C and then allowed to warm to rt. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (EtOAc-hexanes, 1:1) to provide **399** (96 mg, 78%) as a colorless oil; R_f 0.27 (EtOAc/hexanes, 1:1); IR (film) ν_{max} 2923, 2853, 1696, 1558, 1393, 1169, 1129, 1046, 968, 842, 668 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ (mixture of rotamers) 4.68 (br. s., 1H), 4.50-4.65 (m, 1H), 4.06-4.11 (m, 1H), 3.97 (dd, *J* = 9.5, 6.0 Hz, 1H), 3.79-3.92 (m, 1H), 3.58-3.78 (m, 1H), 3.00 (d, *J* = 8.3 Hz, 5H), 2.04 (d, *J* = 16.1 Hz, 1H), 1.91-1.99 (m, 1H), 1.74-1.81 (m, 1H), 1.45 (s, 4H), 1.47 (s, 5H), 1.42 (s, 3H), 1.27 (s, 3H), 1.09 (d, *J* = 6.3 Hz, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ (mixture of rotamers) 154.5, 154.3, 110.1, 109.8, 85.4, 84.5, 81.2, 81.1, 80.0, 79.8, 73.0, 72.9, 69.7, 69.6, 48.7, 48.6, 43.7, 42.8, 42.2, 41.5, 37.3, 33.9, 30.2, 30.1, 28.4, 26.6, 26.5, 24.3, 24.2, 15.7; HRMS-ESI calcd for C₁₉H₃₃NO₇SNa [M+Na]⁺: 442.1875, found: 442.1876.

Ethyl (S)-2-((tert-butoxycarbonyl)oxy)-2-((3aS*,3bR*,6R*,6aS*,7aR*)-4-methoxy-2,2-dimethyl-5-oxooctahydro-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-b]pyrrol-6-yl)propanoate and ethyl (R)-2-((tert-butoxycarbonyl)oxy)-2-((3aS*,3bR*,6R*,6aS*,7aR*)-4-methoxy-2,2-dimethyl-5-oxooctahydro-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-b]pyrrol-6-yl)propanoate (391)



A stirred solution of compound **390** (1.22 g, 3.80 mmol, 1.0 equiv) in CH₃CN (30 mL) was cooled to 0 °C then triethylamine (2.0 mL, 14.4 mmol, 8.0 equiv) and DMAP (470 mg, 3.80 mmol, 1.0 equiv) were sequentially added. A solution of Boc₂O (2.5 g, 11.4 mmol, 3.0 equiv) in CH₃CN (10 mL) was then added *via* cannula. The reaction mixture was stirred for 20 min at 0 °C and then allowed to warm to rt. After 12 h, the reaction was concentrated under reduced pressure and the residual oil purified by flash chromatography (EtOAc-hexanes, 1:4) to yield **391** (1.60 g, 95%) as a mixture of diastereomers: white solid; mp 81-83 °C (EtOAc/hexanes); R_f 0.70 (EtOAc); IR (film) ν_{max} 2935, 1739, 1716, 1706, 1457, 1374, 1259, 1208, 1168, 1110, 1057, 950, 860, 759, 659 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 4.67-4.71 (m, 1H), 4.62-4.67 (m, 1H), 4.18-4.27 (m, 2H), 3.96 (d, *J* = 6.7 Hz, 1H), 3.77 (s, 3H), 3.13 (dt, *J* = 10.3, 7.3 Hz, 1H), 2.57 (s, 1H), 2.44 (dd, *J* = 14.8, 7.8 Hz, 1H), 1.79 (s, 3H), 1.59 (ddd, *J* = 14.8, 10.3, 4.5 Hz, 1H), 1.46 (s, 9H), 1.44 (s, 3H), 1.31 (s, 3H), 1.25-1.29 (m, 3H); ¹³C NMR (CDCl₃, 101 MHz): δ 169.9, 165.4, 151.5, 110.6, 81.0, 80.8, 66.4, 61.9, 61.2, 52.1, 37.7, 35.3, 27.6, 26.7, 24.3, 20.8, 19.1, 13.9; HRMS-ESI calcd for C₂₁H₃₄NO₉ [M+H]⁺: 444.2234, found: 444.2236.

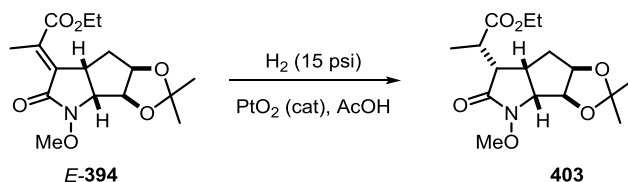
Ethyl (E)-2-((3aS*,3bR*,6aS*,7aR*)-4-methoxy-2,2-dimethyl-5-oxohexahydro-[1,3]dioxolo-[4',5':4,5]cyclopenta[1,2-*b*]pyrrol-6(3a*H*)-ylidene)propanoate (E-394) and ethyl (Z)-2-((3aS*,3bR*,6aS*,7aR*)-4-methoxy-2,2-dimethyl-5-oxohexahydro-[1,3]-dioxolo-[4',5':4,5]-cyclopenta[1,2-*b*]pyrrol-6(3a*H*)-ylidene)propanoate (Z-394)



To a stirred solution of compound **391** (211 mg, 0.48 mmol, 1.0 equiv) in toluene (20 mL) was added DBU (0.36 mL, 2.38 mmol, 5.0 equiv) *via* syringe. The reaction was heated to 100 °C and stirred for 4 h, then cooled to rt and quenched with aqueous NH₄Cl (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). Combined organic extracts were dried over Na₂SO₄ and then concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc-hexanes, 1:5) to yield *E*-**394** (77.9 mg, 51%) and *Z*-**394** (20.1 mg, 12%).

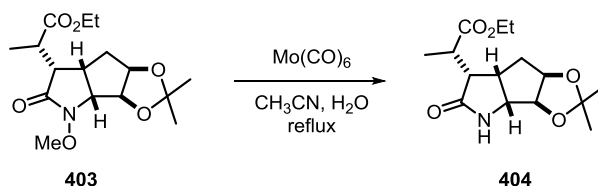
Analytical data for *E*-**394**: colorless oil; *R*_f 0.45 (EtOAc-hexanes, 1:1); IR (film) ν_{max} 2984, 2935, 1716, 1682, 1436, 1373, 1276, 1185, 1101, 1051, 1006, 885, 769, 668 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 4.70-4.75 (m, 1H), 4.65-4.69 (m, 1H), 4.18-4.28 (m, 2H), 3.97-4.06 (m, 1H), 3.90 (d, *J* = 6.6 Hz, 1H), 3.84 (s, 3H), 2.63 (dd, *J* = 14.6, 7.9 Hz, 1H), 2.36 (s, 3H), 1.64 (ddd, *J* = 14.6, 10.3, 4.3 Hz, 1H), 1.42 (s, 3H), 1.27-1.34 (m, 6H); ¹³C NMR (CDCl₃, 101 MHz): δ 167.3, 164.5, 136.5, 134.9, 110.7, 81.9, 81.3, 66.5, 62.2, 61.1, 40.5, 37.3, 26.7, 24.4, 14.1, 13.7; HRMS-ESI calcd for C₁₆H₂₄NO₆ [M+H]⁺: 326.1604, found: 326.1603.

Ethyl (S)-2-((3a*S,3b*R**,6*S**,6a*S**,7a*R**)-4-methoxy-2,2-dimethyl-5-oxooctahydro-[1,3]dioxolo-[4',5':4,5]cyclopenta[1,2-*b*]pyrrol-6-yl)propanoate (403)**



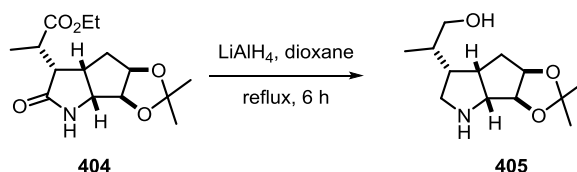
A mixture of compound *E*-**394** (151 mg, 0.47 mmol, 1.0 equiv) and PtO₂ (10.7 mg, 0.047 mmol, 0.1 equiv) in AcOH (20 mL) was placed in a Parr hydrogenation apparatus. The reaction mixture was shaken for 24 h under an atmosphere of hydrogen (15 psi). The Parr apparatus was flushed with nitrogen and the reaction mixture filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc-hexanes, 1:5) to provide **403** (140.0 mg, 92%) as a white solid; mp 87-89 °C (EtOAc/hexanes); *R_f* 0.65 (EtOAc); IR (film) ν_{max} 2981, 2937, 1732, 1718, 1456, 1375, 1211, 1178, 1053, 881 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 4.73-4.78 (m, 1H), 4.69-4.73 (m, 1H), 4.17-4.27 (m, 2H), 3.99 (d, *J* = 5.7 Hz, 1H), 3.78 (s, 3H), 3.03-3.13 (m, 1H), 2.93 (dd, *J* = 11.1, 7.3 Hz, 1H), 2.44-2.54 (m, 1H), 2.11 (dd, *J* = 14.2, 6.7 Hz, 1H), 1.63-1.72 (m, 1H), 1.62 (s, 3H), 1.47 (s, 3H), 1.33 (s, 3H), 1.30 (t, *J* = 7.3 Hz, 3H), 1.22 (d, *J* = 7.3 Hz, 3H); ¹³C NMR (CDCl₃, 101 MHz): δ 175.2, 168.8, 110.5, 81.3, 80.2, 66.6, 62.0, 60.8, 45.0, 37.6, 36.1, 31.7, 26.4, 24.2, 16.2, 14.1; HRMS-ESI calcd for C₁₆H₂₆NO₆ [M+H]⁺: 328.1760, found: 328.1772.

Ethyl (S)-2-((3aS*,3bR*,6S*,6aS*,7aR*)-2,2-dimethyl-5-oxooctahydro-[1,3]dioxolo[4',5':4,5]-cyclopenta[1,2-b]pyrrol-6-yl)propanoate (404)



To a solution of **403** (270 mg, 0.83 mmol, 1.0 equiv) in MeCN-H₂O (15:1, 20 mL) was added Mo(CO)₆ (330 mg, 1.24 mmol, 1.5 equiv) in one portion. The reaction was heated at reflux for 6 h, and then allowed to cool to rt. The reaction was opened to air and stirred for 12 hours. The reaction mixture was then concentrated under reduced pressure and purified by flash chromatography on silica gel (EtOAc) to provide **404** (220 mg, 91%) as a white solid; mp 181-183 °C (EtOAc/hexanes); R_f 0.53 (EtOAc); IR (film) ν_{max} 3169, 3085, 2979, 2908, 1721, 1696, 1383, 1270, 1067, 1026, 859, 839, 762, 668 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.01 (s, 1H), 4.69 (t, *J* = 4.8 Hz, 1H), 4.37 (d, *J* = 5.2 Hz, 1H), 4.17 (dddd, *J* = 17.8, 10.7, 7.1, 3.6 Hz, 2H), 3.80 (d, *J* = 5.2 Hz, 1H), 3.03-3.10 (m, 1H), 2.99 (dd, *J* = 11.2, 6.8 Hz, 1H), 2.38-2.45 (m, 1H), 2.01 (dd, *J* = 14.2, 6.6 Hz, 1H), 1.57-1.64 (m, 1H), 1.41 (s, 3H), 1.22-1.27 (m, 6H), 1.17 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ 176.7, 175.6, 110.1, 83.4, 81.5, 63.9, 60.4, 48.1, 40.0, 37.5, 31.6, 26.2, 23.9, 16.6, 14.0; HRMS-ESI calcd for C₁₅H₂₄NO₅ [M+H]⁺: 298.1654, found: 298.1648.

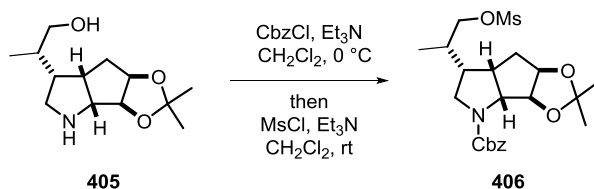
(S)-2-((3aS*,3bR*,6S*,6aS*,7aR*)-2,2-Dimethyloctahydro-[1,3]dioxolo[4',5':4,5]-cyclopenta-[1,2-b]pyrrol-6-yl)propan-1-ol (405)



To a solution of **404** (110 mg, 0.43 mmol, 1.0 equiv) in dioxane (20 mL) under nitrogen was added LiAlH₄ (163 mg, 4.3 mmol, 10 equiv) in single portion. The reaction was heated at reflux for 6 h, after which it was cooled to rt. The reaction mixture was then concentrated under reduced pressure and the residue (90 mg) used directly in the next step.

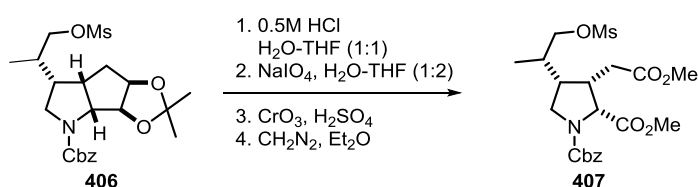
Analytical data for **405**: colorless oil; ¹H NMR (CDCl₃, 500 MHz): δ 4.79 (t, *J* = 5.1 Hz, 1H), 4.64 (d, *J* = 5.1 Hz, 1H), 4.50 (br. s., 1H), 3.42-3.51 (m, 2H), 3.35-3.39 (m, 1H), 3.13-3.20 (m, 1H), 2.96 (td, *J* = 12.0, 6.0 Hz, 1H), 2.32-2.41 (m, 1H), 1.98-2.05 (m, 1H), 1.52 (dd, *J* = 12.0, 5.1 Hz, 2H), 1.44 (s, 3H), 1.30 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ 110.5, 83.2, 81.4, 77.7, 67.2, 56.9, 44.8, 42.9, 37.1, 30.6, 26.2, 23.9, 16.2; HRMS-ESI calcd for C₁₃H₂₄NO₃ [M+H]⁺: 242.1756, found: 242.1756.

Benzyl (3a*S,3b*R**,6*S**,6a*S**,7a*R**)-2,2-dimethyl-6-((*S*)-1-((methylsulfonyl)oxy)propan-2-yl)hexahydro-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-*b*]pyrrole-4(3a*H*)-carboxylate (**406**)**



(film) ν_{\max} 2977, 2937, 1698, 1410, 1353, 1206, 1109, 955, 839, 699 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ (mixture of rotamers) 7.28-7.46 (m, 5H), 5.10-5.30 (m, 2H), 4.58-4.74 (m, 2H), 4.06-4.13 (m, 1H), 3.95-4.01 (m, 2H), 3.71-3.85 (m, 1H), 3.02-3.09 (m, 2H), 3.00 (d, J = 14.5 Hz, 3H), 2.05-2.14 (m, 1H), 1.98 (dd, J = 14.5, 7.0 Hz, 1H), 1.76-1.84 (m, 1H), 1.52-1.60 (m, 1H), 1.46 (d, J = 4.2 Hz, 3H), 1.29 (s, 3H), 1.11 (d, J = 7.0 Hz, 3H); ^{13}C NMR (CDCl_3 , 126 MHz): δ (mixture of rotamers) 155.0, 154.8, 136.8, 136.6, 128.5, 128.4, 128.3, 128.1, 127.8, 127.7, 110.1, 85.3, 84.0, 81.2, 81.1, 72.9, 72.8, 70.0, 69.7, 66.9, 66.9, 49.3, 48.8, 43.9, 43.0, 42.2, 41.7, 37.4, 33.9, 33.9, 30.3, 26.5, 24.2, 15.7; HRMS-ESI calcd for $\text{C}_{22}\text{H}_{32}\text{NO}_7\text{S}$ $[\text{M}+\text{H}]^+$ 454.1899, found: 454.1892.

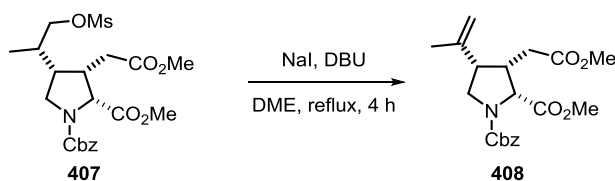
1-Benzyl 2-methyl (3*S,4*S**)-3-(2-methoxy-2-oxoethyl)-4-((*S*)-1-((methylsulfonyl)oxy)-propan-2-yl)pyrrolidine-1,2-dicarboxylate (407)**



Compound **406** (46 mg, 0.1 mmol, 1 equiv) was dissolved in THF (5 mL) and aqueous HCl (1M, 5 mL). The mixture was then heated to 40 °C for 4 h. The volatiles were then removed under reduced pressure, and the remaining residue dissolved in H_2O (5 mL) and THF (10 mL). To this solution was added NaIO_4 (217 mg, 1.0 mmol, 10 equiv). After stirring for 8 h, the solution was filtered through Celite, and the filter cake washed with EtOAc. The organic filtrate was separated and brine was added to the aqueous phase before the extraction with EtOAc (3 x 15 mL). The combined organic extracts were dried over Na_2SO_4 , concentrated and the residue dissolved in acetone (10 mL). This solution was cooled to 0 °C and treated with 8M Jones reagent (125 μL , 1.0 mmol, 10 equiv) for 10 min. The reaction mixture was

allowed to warm to rt, stirred for 30 min and quenched with 2-propanol (1 mL). The resulting green mixture was diluted with EtOAc (20 mL) and H₂O (20 mL). The organic layer was separated and the aqueous fraction extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure to provide the crude diacid as a yellow oil. This material was dissolved in methanol (5 mL) and treated with excess ethereal diazomethane. The reaction mixture was then concentrated under reduced pressure to leave an oily residue, which was chromatographed on silica gel (EtOAc-hexanes, 1:1) to provide **407** (24 mg, 50%) as a colorless oil; *R_f* 0.21 (EtOAc-hexanes, 1:1); IR (film) ν_{max} 2952, 1745, 1703, 1414, 1350, 1120, 956, 748, 689 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ (mixture of rotamers) 7.28-7.41 (m, 5H), 4.98 (d, *J* = 12.2 Hz, 3H), 4.36 (dd, *J* = 11.3, 5.8 Hz, 1H), 4.09-4.19 (m, 2H), 4.01-4.08 (m, 1H), 3.77 (br. s., 1H), 3.69-3.74 (m, 2H), 3.66 (d, *J* = 10.8 Hz, 3H), 3.41 (s, 1H), 3.15-3.23 (m, 1H), 3.08-3.15 (m, 1H), 3.04 (s, 2H), 2.99 (s, 1H), 2.54-2.62 (m, 1H), 2.29 (br. s., 1H), 2.11-2.18 (m, 1H), 1.88 (dt, *J* = 10.8, 5.3 Hz, 1H), 1.07 (d, *J* = 5.3 Hz, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ (mixture of rotamers) 172.3, 155.0, 154.6, 136.3, 128.5, 128.4, 128.2, 128.0, 72.5, 72.3, 67.6, 67.4, 62.8, 62.6, 60.4, 52.1, 51.8, 49.1, 48.5, 44.7, 44.0, 39.3, 38.2, 37.5, 32.4, 29.7, 28.5, 28.4, 21.0, 17.4, 15.2, 14.2; HRMS-ESI calcd for C₂₁H₃₀NO₉S [M+H]⁺ 472.1641, found: 472.1636.

1-Benzyl 2-methyl (2*R,3*S**,4*S**)-3-(2-methoxy-2-oxoethyl)-4-(prop-1-en-2-yl)-pyrrolidine-1,2-dicarboxylate (**408**)**



To a solution of **407** (17.5 mg, 0.037 mmol, 1 equiv) in DME (15 mL) was added NaI (15 mg, 0.1 mmol, 2.7 equiv) and the mixture was heated to reflux. After 4 h, the reaction mixture was allowed to cool to rt and saturated aqueous NaCl (10 mL) was added. The resulting mixture was extracted with EtOAc (3 x 7 mL) and the organic extracts combined and dried over Na₂SO₄. After concentration, the remaining residue was purified by flash chromatography (EtOAc-hexanes, 1:1) to provide **408** (10.0 mg, 72%) as a colorless oil; *R_f* 0.66 (EtOAc-hexanes, 1:1); IR (film) ν_{max} 2952, 1734, 1705, 1653, 1559, 1414, 1353, 1258, 1201, 1174, 1114, 1011, 769, 698 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ (mixture of rotamers) 7.28-7.40 (m, 5H), 5.19 (dd, *J* = 12.2, 7.6 Hz, 1H), 4.94-5.11 (m, 2H), 4.47 (dd, *J* = 16.7, 6.2 Hz, 1H), 3.82 (dd, *J* = 10.7, 7.6 Hz, 1H), 3.68-3.73 (m, 2H), 3.63 (d, *J* = 8.8 Hz, 2H), 3.49 (d, *J* = 14.0 Hz, 1H), 3.44 (s, 1H), 3.22 (d, *J* = 5.7 Hz, 1H), 2.79-2.87 (m, 1H), 2.45 (ddd, *J* = 17.6, 10.2, 2.3 Hz, 1H), 2.22 (dt, *J* = 17.6, 3.3 Hz, 1H), 1.74 (s, 3H), 1.68-1.72 (m, 1H); ¹³C NMR (CDCl₃, 126 MHz): δ (mixture of rotamers) 172.6, 170.9, 170.5, 155.0, 154.6, 140.6, 140.5, 136.4, 136.2, 128.5, 128.4, 128.1, 128.0, 128.0, 113.7, 113.5, 67.4, 67.3, 63.0, 62.8, 52.1, 51.7, 51.7, 48.0, 47.4, 47.3, 39.4, 38.3, 29.6, 29.5, 22.7, 22.6; HRMS-ESI calcd for C₂₀H₂₅NO₆Na [M+Na]⁺: 398.1580, found: 398.1574.

3. TOWARDS THE SYNTHESIS OF THE MADANGAMINE AND ALSTOSCHOLARINE FAMILIES

3.1. An Introduction to the Morphan Ring System

The 2-azabicyclo[3.3.1]nonane framework, also known as the morphan ring system (Figure 16), encompasses more than 300 natural products, including the familiar alkaloids morphine (**410**)²²⁸ and strychnine (**411**).²²⁹ The morphan moiety also constitutes the monoterpene alkaloid kopsone (**412**),²³⁰ isolated from a Malayan shrub. Other alkaloids featuring this promiscuous system include the cytotoxic diterpenoid aspernomine (**413**),²³¹ the securinega alkaloid secu'amamine A (**414**),²³² himgaline (**415**),²³³ the magangamines (**416**),²³⁴ the unique polycyclic alkaloid sarain A (**417**)²³⁵ and the immunosuppressant FR901483 (**418**).^{75,236} Other examples include the *Daphniphyllum* alkaloids (**419**)²³⁷ and monoterpene indole alkaloids alstoscholarines (**420**),²³⁸ isolated from a genus of evergreen trees and shrubs, are widely used in traditional medicine. They have demonstrated important pharmacological activities, including antioxidant, anticancer and antibacterial properties.

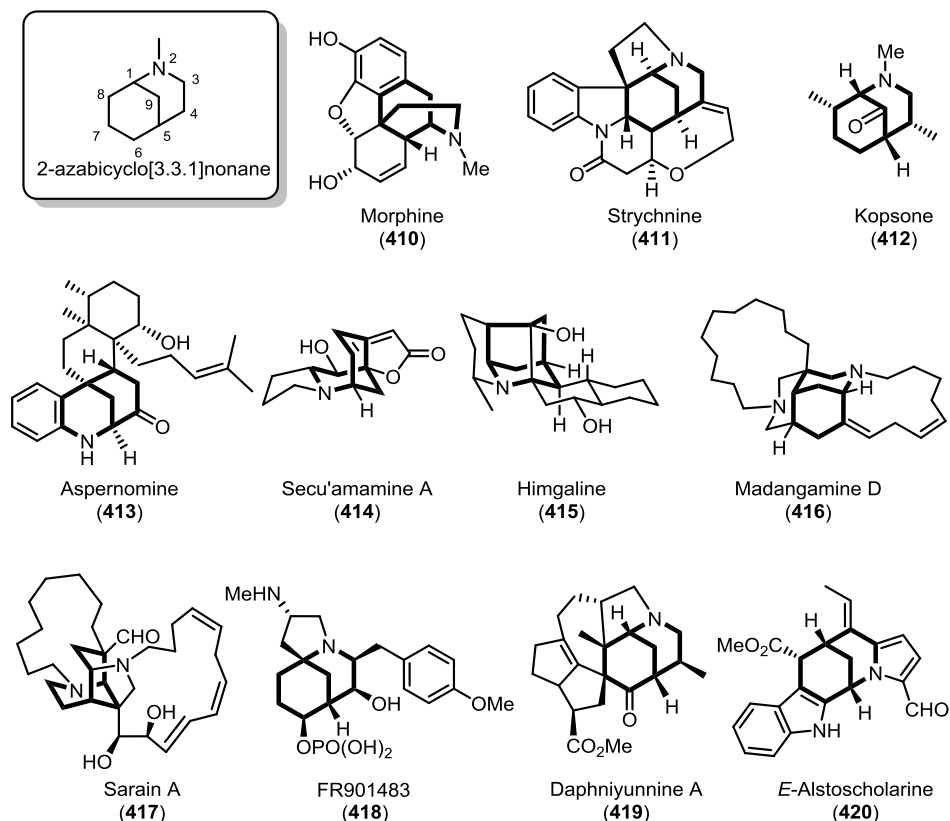


Figure 16 The morphan ring system and examples of natural products that encompass it

In 2011, Bonjoch and co-workers published an excellent review on the construction of the 2-azabicyclo[3.3.1]nonane motif for the purpose of assembling either morphan derivatives or polycyclic systems with more complex structures *en route* to the synthesis of natural products.²³⁹ We envisioned that we might be able to construct the bridged heterocyclic core of the madangamine and alstoscholarine natural product families by implementing our oxamidation methodology. Now follows a brief overview of the synthetic methods developed towards the madangamines and alstoscholarines.

3.2. Studies Towards the Synthesis of the Madangamine Alkaloids

The madangamines (Figure 17) are a small family of marine alkaloids, which are encompassed by a common diazatricyclic core (ABC ring system) and two linear bridges (rings D and E). Madangamines A-E (**421**, **422**, **423**, **416**, **424**) were isolated from the sponge *Xestospongia ingens* found at Madang in Papua New Guinea by Andersen and co-workers.^{234,240} This group of alkaloids differs only in the macrocyclic ring E. The structure of this chain varies in terms of carbon content (13-15 atoms) as well as the degree, type and position of unsaturation. In 2007, Madangamine F was isolated from the Brazilian marine sponge *Pachychalina alcaloidifera* along with the other bis-piperidine alkaloids by Berlinck and co-workers.²⁴¹ In contrast to the other members of this family, madangamine F contains a 13-membered D ring, while the others possess an 11-membered ring. Also, madangamine F (**425**) incorporates an extra hydroxyl group on the B ring at C-4.

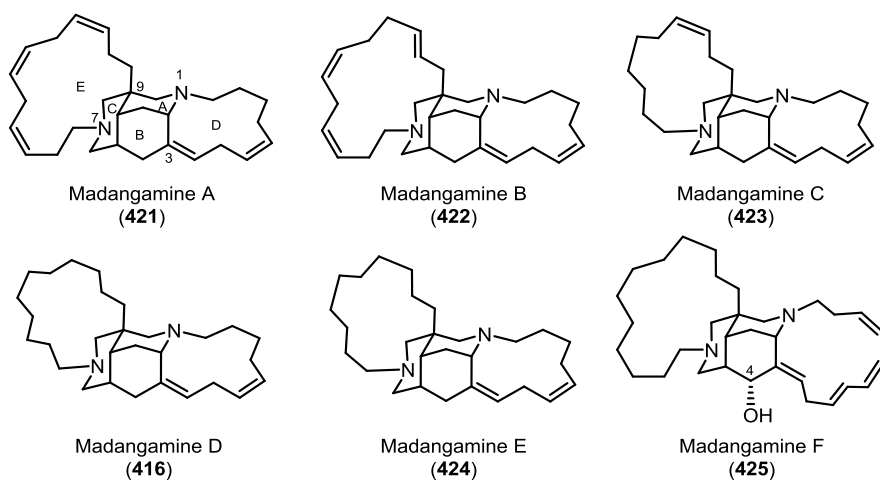


Figure 17 The madangamine alkaloid family

The madangamines are surprisingly nonpolar compounds as compared to the closely associated ingenamine natural products. For instance they can be efficiently extracted using

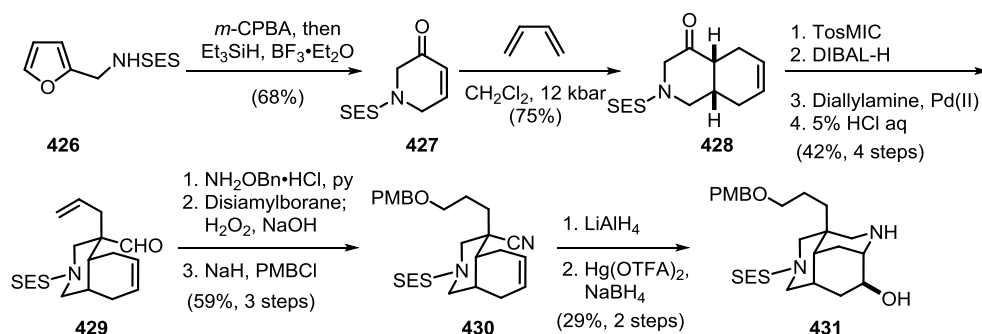
hexanes from aqueous media.²⁴² This can be attributed to the rigidity of their structure. As a result, the lone pair on the N-7 nitrogen is directed to the center of the tricyclic system and thereby shielded from protonation and hydrogen bonding. In biological assays, the madangamines showed significant *in vitro* cytotoxicity against human lung A549, brain U373 and breast MFC-7 cancer cell lines. In 2014, the absolute configuration of the madangamines was confirmed by Amat and Bosch.²⁴³

3.2.1 Synthetic Approaches to the Madangamines

Due to their synthetically challenging structures, the madangamines remain a relatively little-studied group of alkaloids. Until recently, there have been only a handful of synthetic approaches to the assembly of the diazatricyclic ABC core and a few reports describing the assembly of the macrocyclic rings D and E. In 2014, the first total synthesis of (+)-madangamine D was reported by Amat and Bosch.²⁴³ Herein we will review the synthetic methods developed for assembling of the polycyclic core of the madangamines.

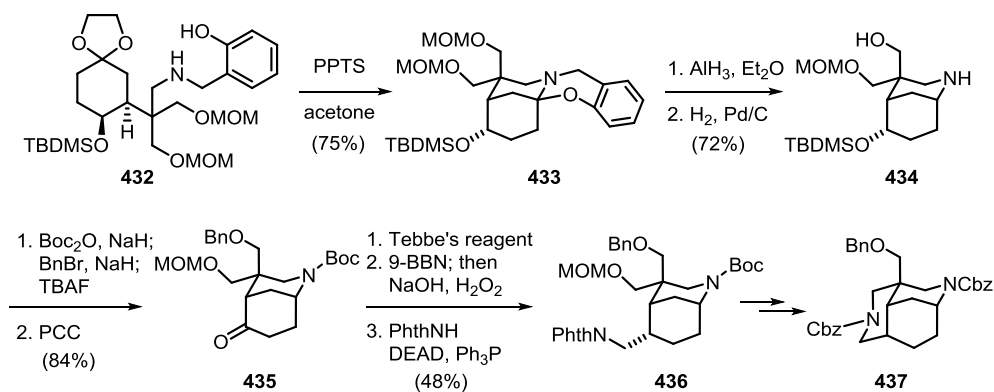
In 1997, Weinreb and co-workers reported the first work towards the synthesis of the madangamines, involving a concise synthesis of the ABC ring system (Scheme 103).²⁴⁴ SES-protected furfurylamine **426** was oxidized by *m*-CPBA to generate an *N*-sulfonyliminium species, which was reduced with triethylsilane to provide **427**. A high pressure Diels-Alder reaction then furnished enone **428**. Homologation of the ketone functionality using TosMIC followed by palladium-promoted [3,3]-sigmatropic rearrangement afforded aldehyde **429**, after acidic hydrolysis. The azabicyclononane framework was assembled in the final step by

an aminomercuration process. Starting from furfurylamine, tricyclic compound **431** was prepared in 12 steps.



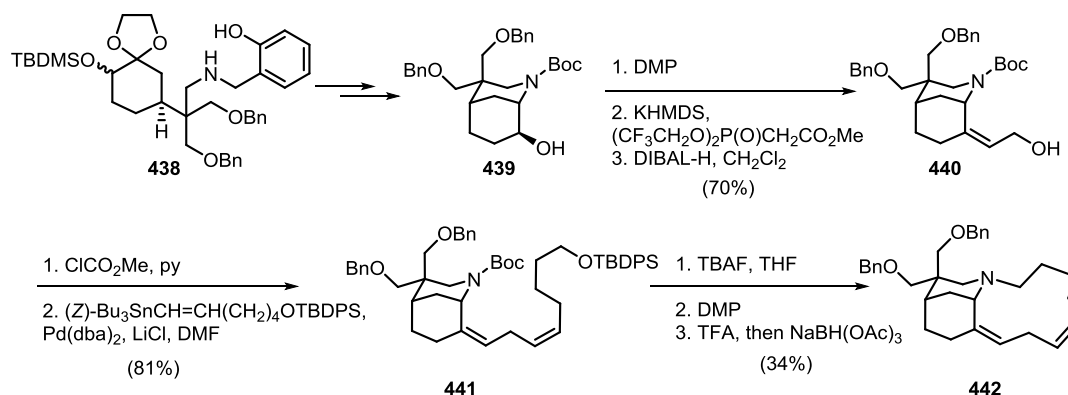
Scheme 103

Kibayashi and Yamazaki demonstrated that the intramolecular cyclization of keto-aminophenol **432** generated cyclic *N,O*-acetal **433** (Scheme 104).²⁴⁵ Chemoselective MOM monodeprotection and subsequent removal of the (2-hydroxyphenyl)methyl group by catalytic hydrogenation afforded amino alcohol **434**, which was further elaborated into the ABC-core system **437**.



Scheme 104

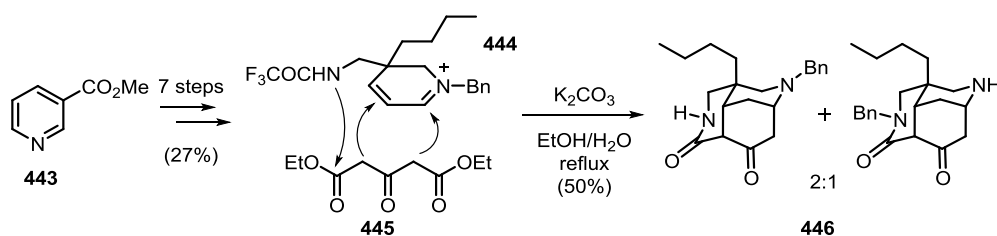
The same research group later reported a modified version of their initial approach (Scheme 105).²⁴⁶ Starting from C-3 functionalized keto-aminophenol **438**, the authors were able to fabricate the morphan skeleton by initial *N,O*-acetalization. Alcohol **439** was then treated with DMP to generate the corresponding ketone, which underwent Wittig-Horner olefination with Still's reagent to generate the *Z*-unsaturated ester. Allylic derivative **440** was accessed *via* reduction of this compound with DIBAL-H. Acylation of **440** and palladium-catalyzed coupling of the resulting carbonate with a (*Z*)-vinylstannane in the presence of lithium chloride yielded skipped diene **441**, as a single stereoisomer. Finally, deprotection of the TBDPS group, oxidation with Dess-Martin periodinane, Boc deprotection with TFA and intramolecular reductive amination delivered tricyclic product **442**, albeit in rather modest yield.



Scheme 105

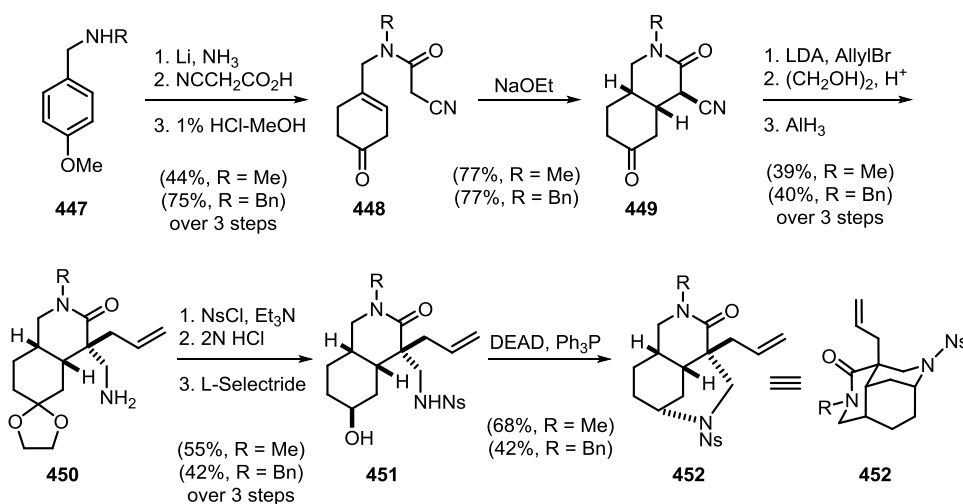
In 2005, a short synthesis of the tricyclic ABC ring system **446** was described by Marazano and co-workers (Scheme 106).²⁴⁷ The key reaction of this remarkable process entails condensation of the sodium salt of diethylacetone dicarboxylate (**445**) with dihydropyridinium salt **444**, which was obtained in 7 steps from methyl nicotinate (**443**) with

27% yield. This approach is modeled on a proposed biogenetic pathway, which may link the madangamines to the ircinals (related alkaloids found in sponges of the same order).²⁴⁸



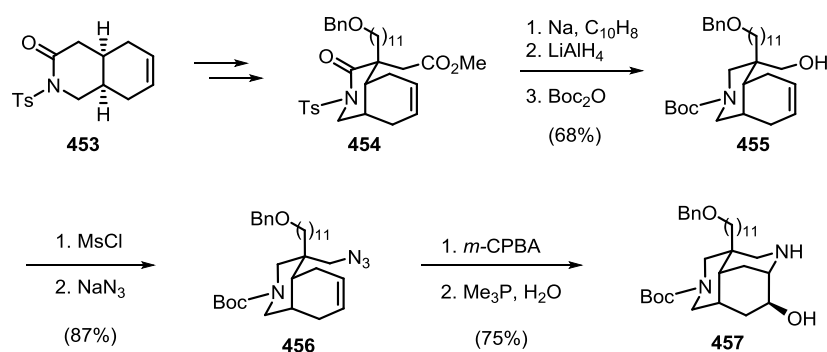
Scheme 106

In 2008, Bonjoch and co-workers reported the synthesis of diazatricycle **452** from *cis*-perhydroisoquinolines **449** that are available in four steps from 4-methoxybenzylamine (**447**) (Scheme 107).²⁴⁹ Sterically-controlled kinetic alkylation, followed by carbonyl protection and amide reduction afforded amine **450** in moderate yield. In order to accomplish the final cyclization, *N*-nosylation, acetal cleavage and stereoselective ketone reduction using L-selectride were undertaken to furnish the corresponding axial alcohol **451** in good yield. Finally, the construction of the bridged subunit was achieved in good yield by an intramolecular Mitsunobu reaction.



Scheme 107

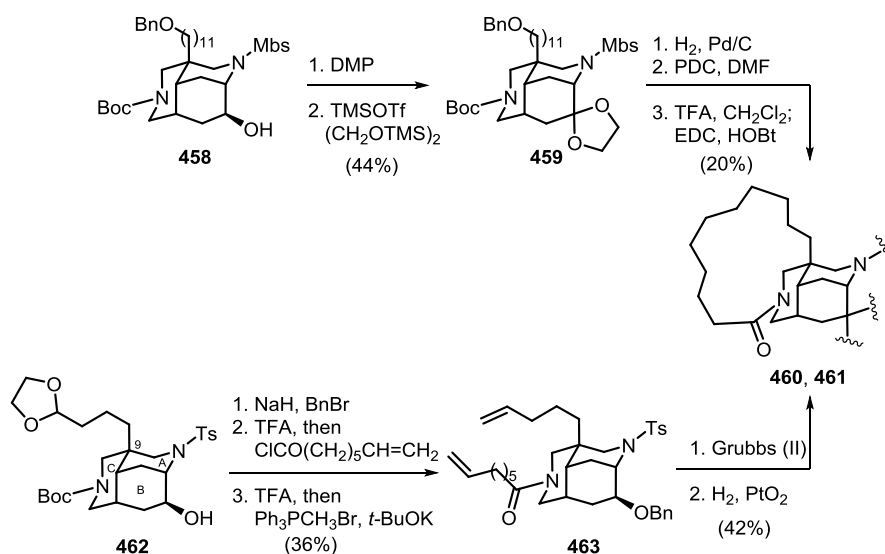
In 2010, Bosch and Amat reported the first enantioselective synthesis of the tricyclic core of the madangamines, utilizing an intramolecular hydroxyamination step to build the morphan system (Scheme 108).²⁵⁰ Isoquinolone **453**, produced from enantiopure oxazolopiperidone, was alkylated sequentially to afford ester **454** as a single diastereomer. Cleavage of the tosylate group followed by global reduction with LiAlH_4 and Boc protection of the secondary amine yielded alcohol **455**. Mesylation of alcohol **455** with subsequent nucleophilic substitution using NaN_3 yielded azide **456**. *m*-CPBA-mediated oxidation of the cyclohexene system followed by an *in situ* Staudinger reduction formed a reactive amino epoxide. The latter underwent the key cyclization to produce diazatricyclic amino alcohol **457**, a potential precursor of madangamine D.



Scheme 108

In 2013, the enantioselective synthesis of advanced tetracyclic precursors of madangamine D, containing rings A, B, C, E, was reported by the same group.²⁵¹ The 14-membered ring E was constructed from previously discussed diazatricyclic compounds *via* either Ru-catalyzed ring-closing metathesis or macrolactamization approaches (Scheme 109). Using conventional group manipulations, prefunctionalized diazatricyclic alcohol **458** was elaborated to acetal **459** in moderate yield. Then, a sequential debenzoylation-oxidation

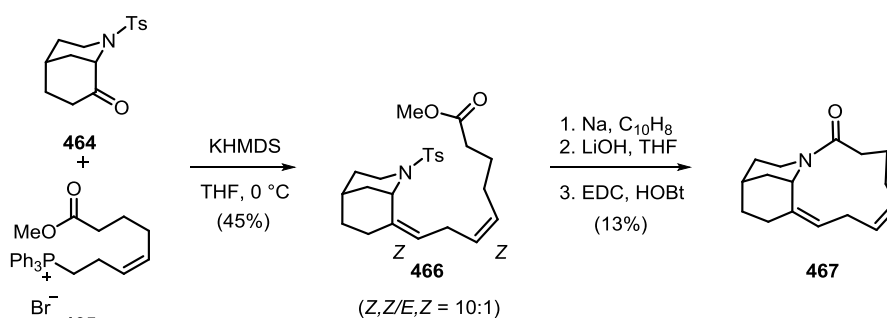
procedure, followed by Boc removal and macrolactamization using high-dilution conditions afforded tetracyclic amide **460**. Alternatively, structurally-related tetracyclic compound **461** could be synthesized from alcohol **462**, featuring a five-carbon substituent at C-9. Protection of the hydroxy group by benzylation, then selective deprotection of the piperidine C ring by TFA, followed by acylation with 7-octenoyl chloride afforded the tricyclic amide. The latter was then converted to the diene **463** by acetal deprotection followed by Wittig methylenation. Next, diene **463** underwent a Ru-catalyzed ring-closing metathesis under high-dilution conditions. Treatment of the resulting *Z-E* mixture of alkenes with H₂ over PtO₂ accomplished both the alkene hydrogenation and hydrogenolysis of the benzyloxy group to furnish tetracyclic alcohol **461**.



Scheme 109

The construction of the macrocyclic rings of the madangamine family using a simplified model system has also been studied by Amat and Bosch.²⁵² The authors envisaged a direct approach to solve this problem using the eight-carbon phosphonium salt **465**, already

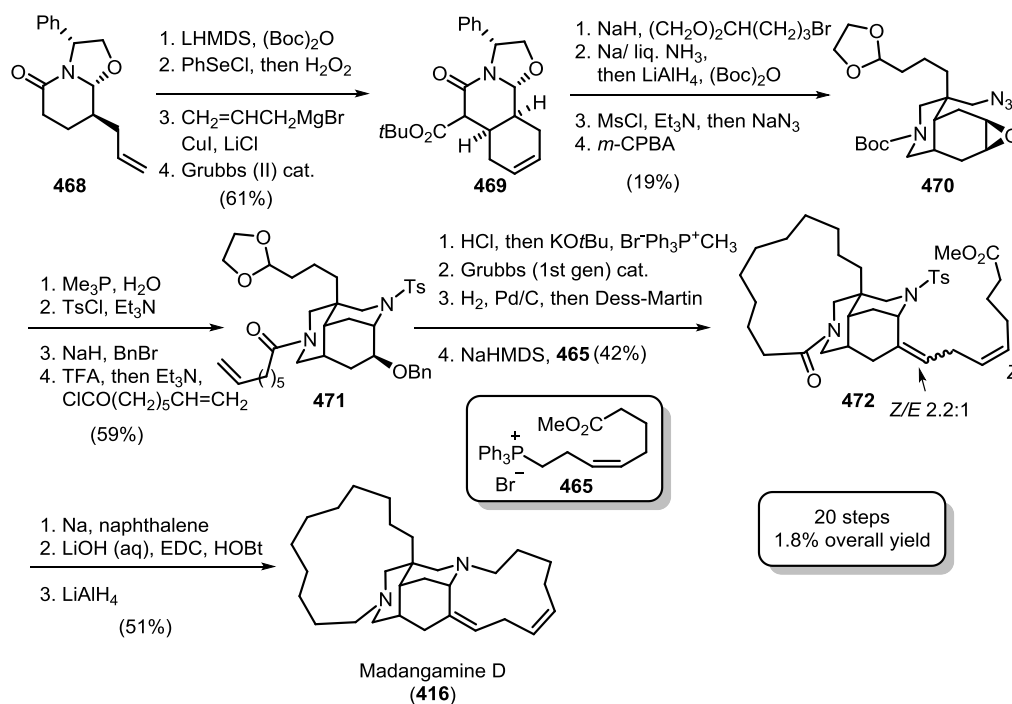
containing both the central Z C₁₇-C₁₈ double bond present in the D ring of madangamines A-E and the ester group necessary for the final macrolactamization step (Scheme 110). Thus, treatment of bicyclic ketone **464** with a nonstabilized ylide prepared from phosphonium bromide **465** and KHMDS yielded an enriched mixture (Z/E, 10:1) of alkenes **466**. Deprotection of the *N*-tosyl group followed by alkaline hydrolysis and macrolactamization using HOBt/EDC at low concentrations (0.02 M) provided a single tricyclic lactam **467** in low yield.



Scheme 110

In 2014, Amat and Bosch completed their synthetic studies and published the first total synthesis of madangamine D (**416**) (Scheme 111).²⁴³ It involved the stereoselective assembly of the ABC ring system starting from an enantiomerically pure phenylglycinol-derived lactam and the subsequent construction of the macrocyclic rings D, E. The authors were able to obtain a pure sample of synthetic madangamine D and confirm the absolute configuration of this alkaloid family for the first time. The synthesis commenced with enantiopure lactam **468**, which was readily accessible in one step from (*R*)-phenylglycinol. α -Acylation, followed by the conversion to the unsaturated lactam *via* an intermediate seleno derivative provided an unsaturated lactam, which underwent a stereoselective conjugate

addition with an allyl cuprate to generate the *cis*-diallyl-substituted lactam. The assembly of B ring was now achieved by a RCM reaction, generating the *cis*-octahydroisoquinolone derivative **469**. Next, a stereoselective alkylation from the most accessible face of the β -ketoester moiety and the removal of the phenylethanol chiral auxiliary by successive treatment of with Na/NH₃ and LiAlH₄ resulted in an unstable *N*-unsubstituted piperidine derivative, which was immediately protected with Boc. The alcohol functionality was then transformed into the azide through a mesylate and the cyclohexene double bond was epoxidized with *m*-CPBA to give **470**.



Scheme 111

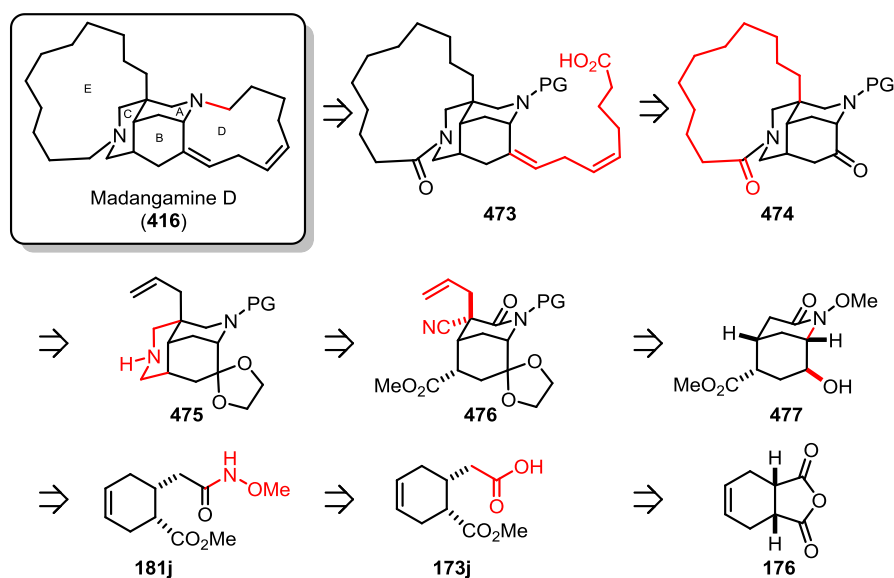
Staudinger reduction of **470** furnished an amino epoxide, which spontaneously cyclized *in situ*. Protection of the resulting amine and alcohol moieties through *N*-tosylation and *O*-benzylation provided an unsymmetrically protected diamino derivative. Selective

deprotection of N-7, followed by acylation with 7-octenoyl chloride, gave rise to amide **471**. Hydrolysis of the acetal protecting group and Wittig methylenation of the corresponding aldehyde furnished a diene, which readily participated in a ring-closing metathesis using the Grubbs (I) catalyst under dilute conditions. A subsequent catalytic hydrogenation of the alkene isomers (2:1, *Z/E*) simultaneously removed the benzyl ether, furnishing 2° alcohol. DMP oxidation of this alcohol generated the ketone. The (*Z,Z*)-unsaturated 8-carbon fragment essential for the completion of the total synthesis was attached *via* a Wittig reaction using the ylide prepared from phosphonium salt **465**. The resulting mixture of alkenes **472** (2.2:1, *Z/E*) was treated with sodium naphthalenide, which removed of *N*-tosyl group. Hydrolysis of the ester group and macrolactamization provided the pentacyclic dilactam. Ultimately, amide reduction with LiAlH₄ provided madangamine D (**416**), thus completing the synthesis with 1.8% overall yield over a total of 20 steps.

3.2.2 Retrosynthetic Analysis of the Madangamines

Our strategy for the synthesis of madangamine D is outlined in Scheme 112. It was envisioned that the natural product **416** could be accessed through a two-step macrolactamization and reduction sequence from amino acid **473**. This compound could be accessed *via* the Wittig reaction of ketone **474** with the appropriate phosphonium ylide. We anticipated that the peripheral 13-membered E-ring could be formed from unsaturated amine **475** *via* *N*-acylation followed by ring-closing metathesis. We envisioned that formation of Ring C could be achieved *via* a dual reduction of both the nitrile and ester functionalities of compound **476**, followed by *N*-sulfonylation and ring closure *via* a Mitsunobu reaction.

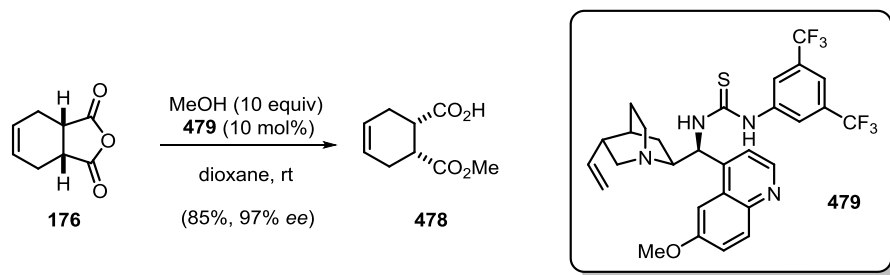
Nitrile **476** could be synthesized from amide **477** by cyanation, followed by allylation. In this case, a stereoselective enolate attack on the allyl bromide could establish a *syn* relationship between the nitrile substituent and the ester group at C-5. We proposed that bicyclic alcohol **477** could be obtained through nitrenium ion-mediated cyclization of *O*-methyl hydroxamate **181j**, which could be accessed by coupling of the corresponding carboxylic acid, **173j**, with methoxyamine hydrochloride. Finally, the known acid **173j** could be prepared from inexpensive *cis*-1,2,3,6-tetrahydrophthalic anhydride **176** using the Arndt-Eistert homologation reaction.²⁵³



Scheme 112

While our initial studies were conducted in the racemic series, our plan was conceived in such a manner that it could be switched to an enantioselective mode through the use of a chiral catalyst for the methanolic desymmetrization of the original tetrahydrophthalic anhydride **176**. In 1999, Bolm reported that the necessary (1*S*,6*R*) monoester **478** could be produced in 99% yield and 93% *ee* by the treatment of **176** with 3 equivalents of methanol in

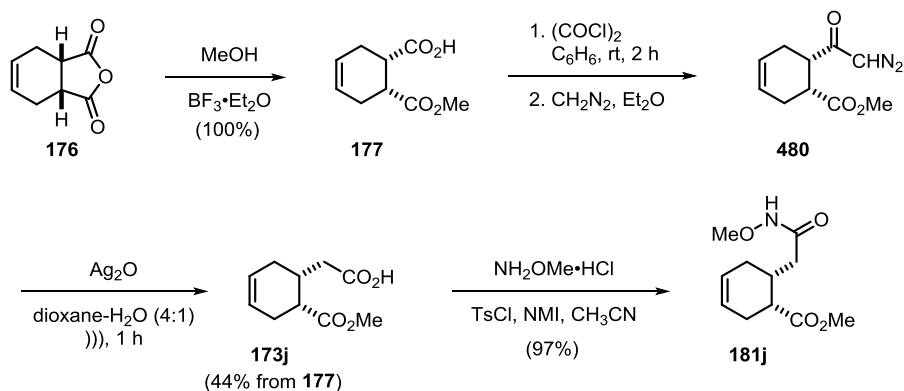
the presence of stoichiometric amounts of quinine.²⁵⁴ Later reports showed that 5-10 mol% of quinine-thiourea bifunctional organocatalysts (e.g., **479**) can be used in place of quinine (Scheme 113).²⁵⁵ Computational studies suggest that the quinuclidine group of the catalyst functions as a general base and activates the alcohol, while the thiourea group simultaneously



Scheme 113

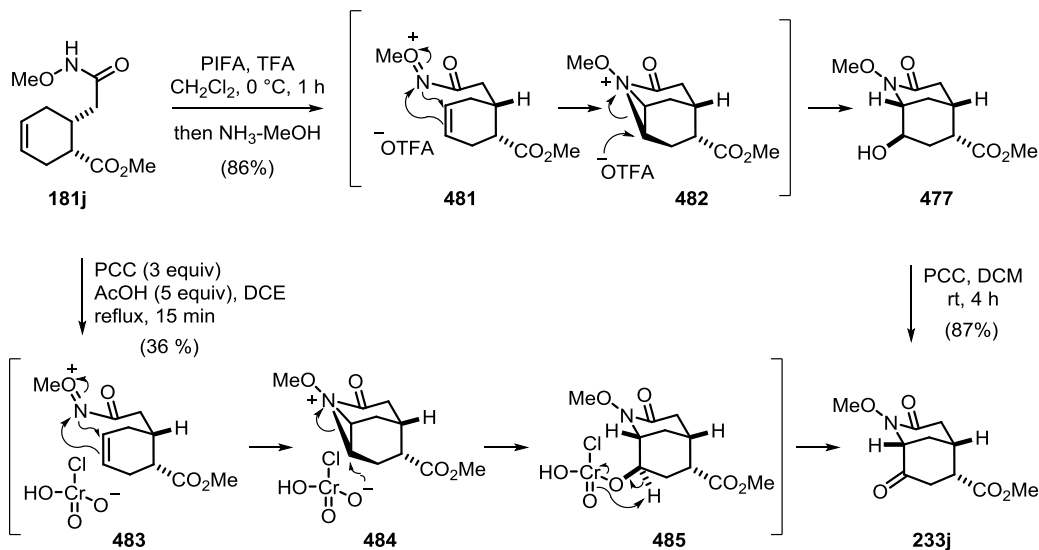
3.2.3 Towards the Synthesis of the Madangamines

Our route to madangamine D began from commercially available *cis*-1,2,3,6-tetrahydrophthalic anhydride **176**, which was converted to half-ester **177** in quantitative yield through BF_3 -catalyzed methanolysis (Scheme 114). 1-Carbon homologation was now accomplished utilizing the Arndt-Eistert reaction. Thus, treatment of **177** with oxalyl chloride followed by reaction with diazomethane afforded diazoketone **480**, which was used directly in a Wolf rearrangement. Sonication **480** of with silver oxide under aqueous conditions gave **173j** in low yield. Acid **173j** was then converted into *O*-methyl hydroxamate **181j** using Tanabe's coupling procedure.⁹⁵



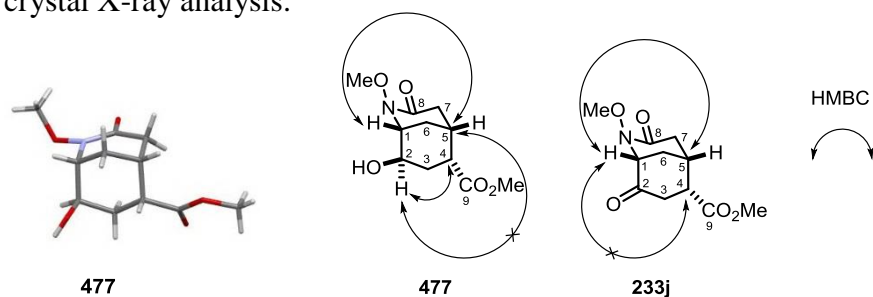
Scheme 114

Submission of **181j** to standard PIFA-mediated oxamidation conditions provided azabicyclic **477** in 86% yield (Scheme 115). In this case, stereospecific opening of **472** by trifluoroacetate at the *exo* position affords *anti* alcohol **477** as a single diastereomer, after hydrolysis of the labile trifluoroacetate ester with methanolic ammonia. The secondary alcohol was then oxidized with pyridinium chlorochromate in dichloromethane to afford ketone **233j** in good overall yield. Alternatively, intramolecular oxoamidation of the substrate **181j** could be accomplished in one step utilizing our Cr(VI)-mediated methodology. Thus, treatment of **181j** with 3 equivalents of PCC in the presence of 5 equivalents of acetic acid at 84 °C provided **233j** in modest yield. We believe that this reaction proceeds *via* formation of chromate ester **485**, which further oxidizes in the presence of an excess of PCC to form ketone **233j**. Interestingly, we have not observed any of the acetoxyamidation products resulting from the aziridinium ion trapping by acetate, despite the increased nucleophilicity of the acetate compared to trifluoroacetate and, possibly, chlorochromate. As previously discussed, we believe that the putative nitrenium and aziridinium ions are short-lived reactive species that exist as tight ion-pairs.

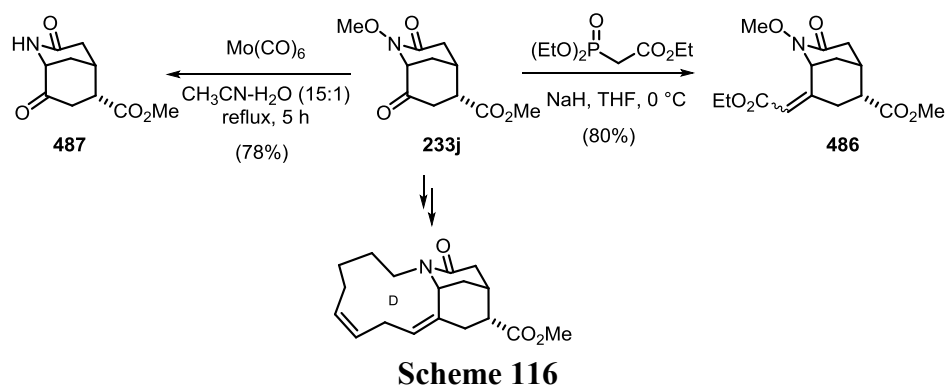


Scheme 115

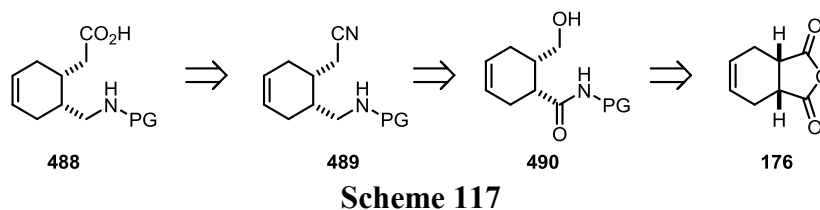
The structures of 2-azabicyclo[3.3.1]nonane derivatives **477** and **233j** were elucidated by 2D NMR experiments (Figure 18). The HMBC spectrum of **477** showed cross peaks between C-4/H-2 and C-5/H-1, while no cross peaks were observed between C-4/H-1 and C-5/H-2, thus suggesting a 2-azabicyclo[3.3.1]nonane ring system. Similarly, the HMBC spectrum of **233j** demonstrated cross peak between C-5 and H-1, whereas no cross peak was observed between C-4 and H-1. In addition, the relative configuration of **477** was confirmed by single crystal X-ray analysis.

Figure 18 Crystal structure of alcohol **477** and HMBC correlations of **477** and **233j**

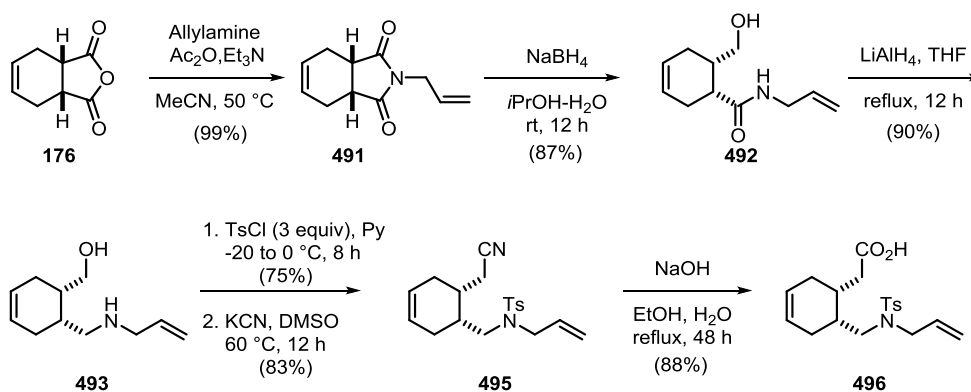
Ketone **233j** was viewed as an appropriate model to probe the Wittig or Horner-Wadsworth-Emmons reaction required to append the D ring to the 2-azabicyclo[3.3.1]nonane skeleton (Scheme 116). Thus, treatment of **233j** with 1.5 equivalents of ethyl 2-(diethoxyphosphoryl)acetate²⁵⁶ at 0 °C in the presence of NaH provided an inseparable mixture (2:1) of alkenes **486** in 80% unoptimized yield. At this point, cleavage of the *N*-methoxy group of **233j** was accomplished with molybdenum hexacarbonyl in acetonitrile to produce amide **487** in high yield.



While we were able to construct the morphan core relatively efficiently, the Arndt-Eistert homologation proved to be a significant bottleneck in the synthesis. In particular, this reaction was not scalable and necessitated the use of toxic and potentially explosive diazomethane. Moreover, we sought to introduce the N-7 amino functionality, necessary for the construction of Ring C. As a result, a revised synthetic plan was adopted in which one carbon homologation would be achieved *via* displacement of a primary sulfonate ester by cyanide (Scheme 117).



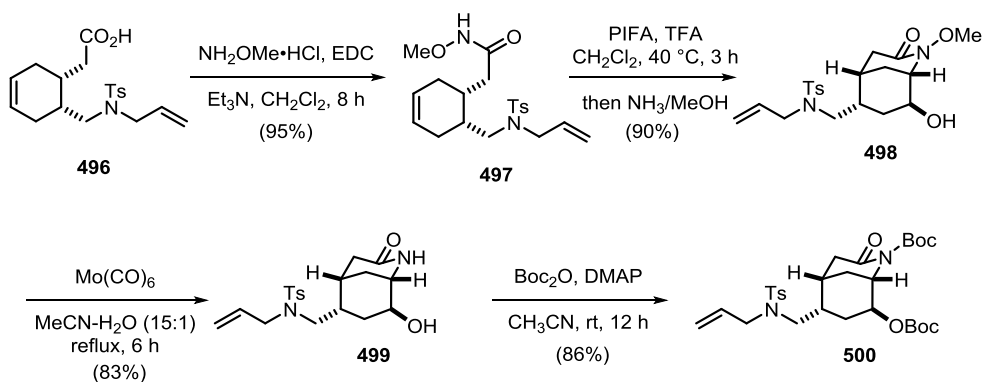
Commencing from **176**, heating with allylamine, followed by the addition of acetic anhydride afforded *N*-allyl imide **491**, which was partially reduced by sodium borohydride in an isopropanol-water solvent mixture²⁵⁷ to provide alcohol **492** in 87% yield (Scheme 118). The amide carbonyl group was then reduced with LiAlH_4 to furnish amino alcohol **493** in excellent yield. Simultaneous protection of the amino group and the conversion of the primary alcohol to the corresponding tosylate **494** were performed by treatment of **493** with an excess of tosyl chloride and pyridine. Substitution of the primary tosylate with KCN in DMSO provided nitrile **495** in 83% yield. The formation of carboxylic acid **496** was finally accomplished by hydrolysis of the nitrile with sodium hydroxide in aqueous ethanol.



Scheme 118

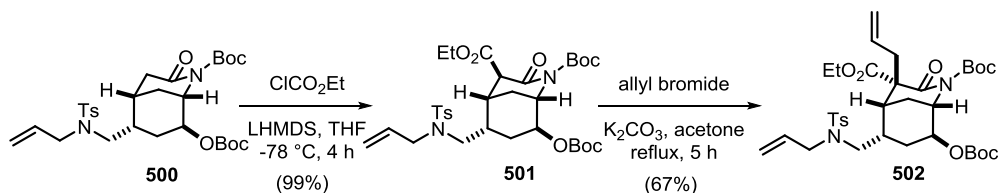
Carboxylic acid **496** was coupled with methoxyamine hydrochloride using EDC in CH_2Cl_2 to afford *O*-methyl hydroxamate **497** in high yield (Scheme 119). As expected, treatment of **497** with PIFA in CH_2Cl_2 , followed by hydrolysis with methanolic ammonia, generated alcohol **498** as a single diastereomer. At this point, we decided to cleave the N-O bond and reprotect both the alcohol and the amide with Boc groups. Treatment of **498** with molybdenum hexacarbonyl in the mixture of acetonitrile and water furnished N-H amide

499, which upon reaction with Boc anhydride in the presence of DMAP, delivered *bis*-Boc adduct **500** in good yield.



Scheme 119

We now anticipated that acylation of the enolate of 1,3-dicarbonyl compound **500** from the less hindered *exo* face with a formate derivative and then subsequently with allyl bromide would establish the *cis* relationship between the ester substituent and the amine appendage. The enolate of **501** is convex in shape with the adjacent ring shielding the *endo* face, so the second alkylation was anticipated to occur from the *exo* face. Initial attempts to perform enolate acylation with CbzCl or ethyl cyanoformate led only to recovery of starting material. More successfully, deprotonation of **500** with 2.4 equivalents of LHMDS and treatment of the resulting enolate with 1.2 equivalents of freshly opened ethyl chloroformate resulted in the formation of compound **501** in nearly quantitative yield. Treatment of **501** with excess allyl bromide and potassium carbonate in refluxing acetone now afforded alkylated product **502** as a single diastereomer in a reasonable yield.



Scheme 120

The structure and the relative configuration of compound **502** were confirmed by single crystal X-ray analysis (Figure 19). Gratifyingly, the *cis* relationship between C-5 methyleneamino side chain and the ethyl carboxylate at C-7, required for the construction of C ring of madangamine D (**416**), was clearly visible.

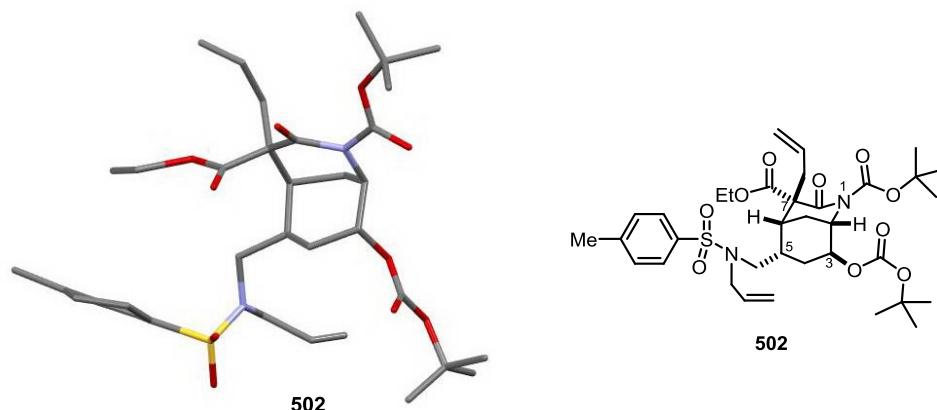
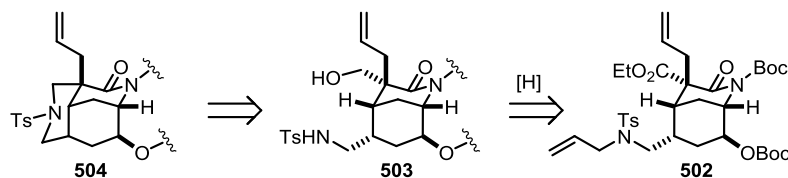


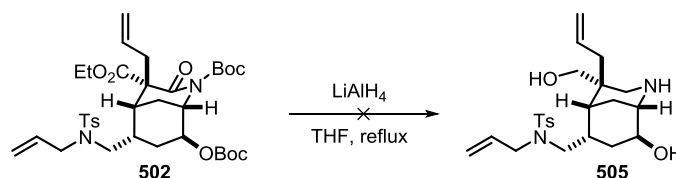
Figure 19 Crystal structure of compound **502**

Having established the relative configuration of the C-5 and C-7 stereogenic centers, we now proceeded to the construction of the C ring. In this regard, we envisioned that cyclization could be achieved *via* an Appel reaction involving the secondary amine with the primary alcohol of **503** accessible *via* reduction of ester **502** (Scheme 121). An alkylative cyclizations such as this has been previously used by Bowen and Wardrop in their preparation of the pyrrolidine ring in (+)-castanospermine⁸⁰ and the piperidine ring in (-)-swainsonine.⁸³



Scheme 121

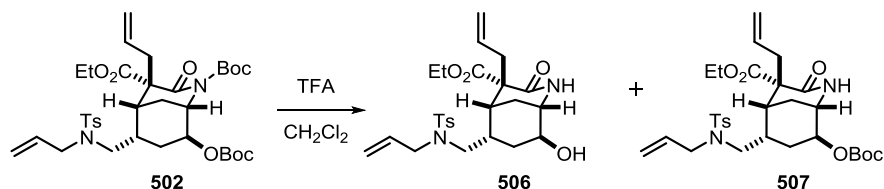
Unfortunately, treatment of **502** with LiAlH_4 failed to accomplish exhaustive reduction of the substrate to amino diol **505**, but instead yielded a complex mixture of products (Scheme 122). In light of this result, we decided to first cleave the Boc protection.



Scheme 122

The Boc carbonate showed significant stability towards acidic conditions (Table 18, entry 1). Treatment of **502** with 10 equivalents of TFA in CH_2Cl_2 produced a mixture of *bis*- and *mono*-deprotected alcohols **506** and **507** even after prolonged heating. We thus elected to keep the Boc carbonate group and proceed with selective deprotection of the amide by quenching the reaction with sodium bicarbonate after 1 h of stirring at room temperature (Table 18, entry 2).

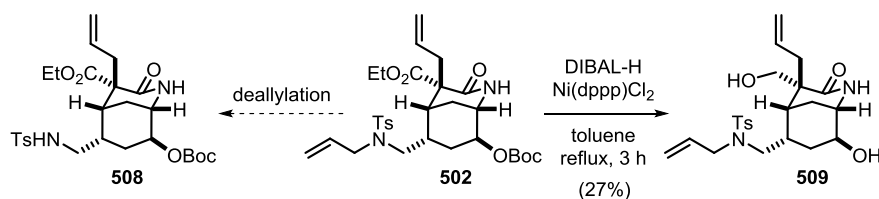
Table 18. Boc Deprotection of 502



entry	conditions	yield of 506 , % ^a	yield of 507 , % ^a
1	TFA (10 equiv), CH_2Cl_2 , reflux, 8 h	39	30
2	TFA (5 equiv), CH_2Cl_2 , rt, 1 h	0	92

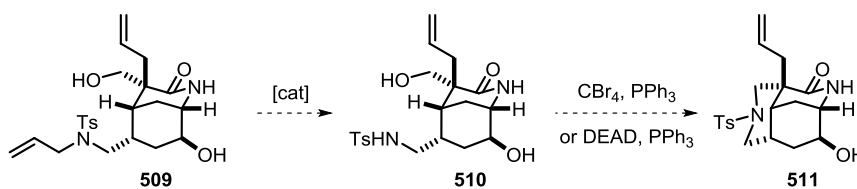
^aIsolated yields, after purification by flash chromatography.

Although there is significant literature precedent for the successful deallylation of amides and sulfonamides,²⁵⁸ our attempts to cleave the *N*-allyl group of **507** proved troublesome. Indeed, all methods investigated, including Pd(PPh₃)₄ and vinylmagnesium bromide,²⁵⁹ Pd/C and ethanolamine²⁶⁰ and Pd(dba)₂ with dppb and 2-mercaptobenzoic acid²⁶¹ failed to provide **508**. Exposure of **507** to RhCl₃ in refluxing *n*-propanol,²⁶² followed by analysis of the crude NMR, indicated cleavage of the allyl group, however product recovery was difficult. Our attempt to cleave the *N*-allyl group by adopting Ogasawara's nickel-catalyzed deallylation procedure²⁶³ using DIBAL-H and Ni(dppp)Cl₂ in refluxing toluene led to diol **509** in low yield (Scheme 123). Disappointingly, the allyl group withstood these conditions while collateral ester reduction and Boc removal were observed. We noted that the cleavage of *t*-butyl carbonate occurs immediately after DIBAL-H addition, while the ester reduction requires reflux temperatures. Neither the use of Me₃Al instead of DIBAL-H, nor increasing the loading of Ni(dppp)Cl₂ was found to be fruitful.



Scheme 123

Our plan to finish ABC core of the madangamine is outlined in Scheme 124. Catalytic deallylation of **509** followed by the Appel (or Mitsunobu) reaction is anticipated to provide ABC core intermediate **511**.



Scheme 124

3.3. Studies Towards the Synthesis of the Alstoscholarines

3.3.1 Introduction

Alstonia is a widespread genus of evergreen trees and shrubs found in the tropical regions of Africa and Southeast Asia and comprises of more than 50 species. *Alstonia* trees are widely used in traditional medicine. For example, its bark decoction and leaf extract from it are used throughout Southeast Asia region as remedy for urinary tract infections,²⁶⁴ skin diseases and the alleviation of malaria.²⁶⁵ The phytochemical components of the *Alstonia* species have been studied extensively. To date, more than 400 secondary metabolites have been isolated. Many of these compounds are monoterpene indole alkaloids containing 18 or 19 carbon atoms at the core. Potent anticancer, antibacterial, anti-inflammatory, and antitussive activities for several of these natural compounds have been documented.²⁶⁶ In 2007, two monoterpenoid indole alkaloids, named *E*- and *Z*-alstoscholarine (**420**, **512**), were isolated from *Alstonia scholaris* leaves by Luo and co-workers (Figure 20).²³⁸

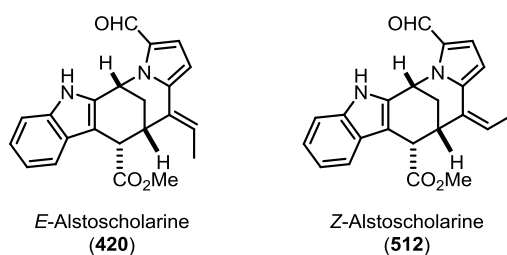
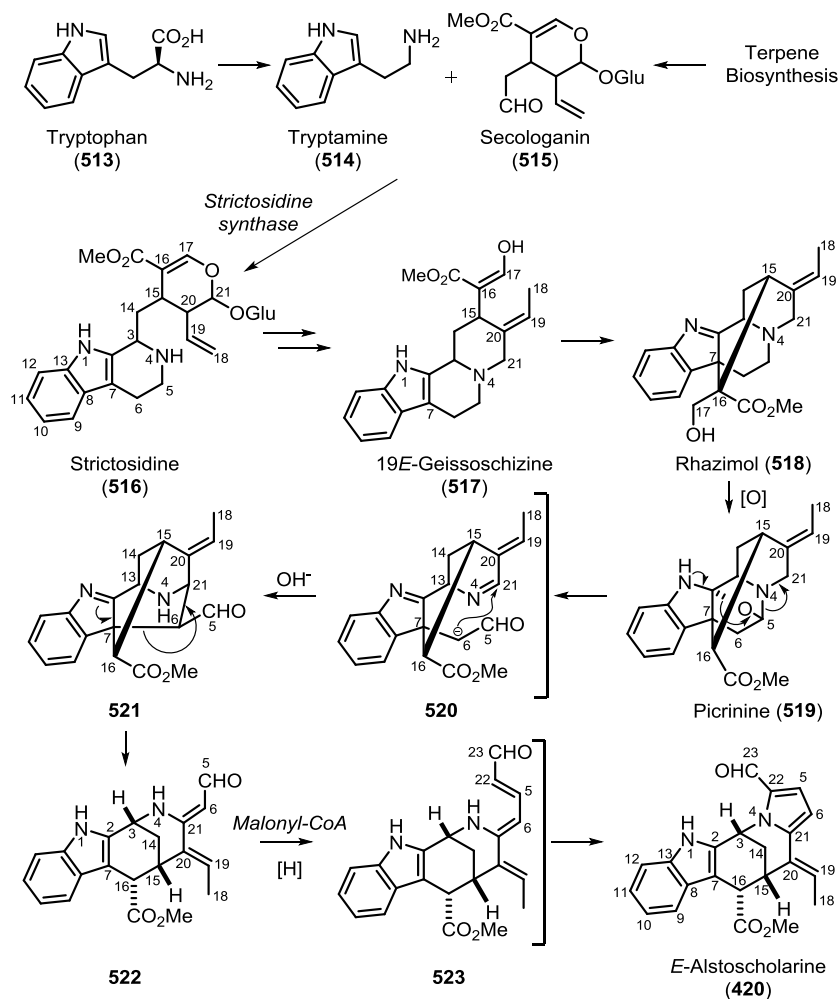


Figure 20 Structure of the anti-inflammatory natural products *E*- and *Z*-alstoscholarine (**420**, **512**)

Although initial screening did not reveal antibacterial activity, it was later discovered that both indole alkaloids exhibit significant anti-inflammatory and anti-asthmatic properties at low concentrations during *in vitro* biological evaluations.²⁶⁷ *Z*-Alstoscholarine in particular was noted as a worthy lead candidate for the development of a therapy for chronic airway inflammatory disease.²⁶⁸

3.3.2 Biosynthesis of Alstoscholarines

The biogenetic origin of the alstoscholarines was first proposed by Luo and co-workers and is outlined in Scheme 125.²³⁸ The authors believe that alstoscholarines belong to a special class of monoterpenoid indole alkaloids, containing 2 extra carbons in its structure. It is known that all of members of terpene indole alkaloid family are tryptophan and secologanin derivatives. Initially, tryptophan decarboxylase generates tryptamine from tryptophan.²⁶⁹ Then, following the common biosynthetic pathway for terpene indole alkaloids, tryptamine and secologanin undergo stereoselective Pictet–Spengler condensation, which is catalyzed by the enzyme strictosidine synthase to generate strictosidine (**516**).²⁷⁰ Next, nucleophilic attack of electron-rich indolic C-7 on C-16 of 19-*E*-geissoschizine (**517**) provides rhazimol (**518**). Oxidation and dehydroxymethylation at C-17 of rhazimol furnishes picrinine. Subsequent cleavage of both C-2-O and C-5-N-4 bonds produces C-5 aldehyde and N-4-C-21 alkene functions. Then, the C-6 intramolecular attack on C-21 cleaves C-6-C-7 bond, thus generating C-6-C-21 alkene functionality. Ultimately, the construction of pyrrole ring could be accomplished by means of malonyl-coenzyme A.²⁷¹

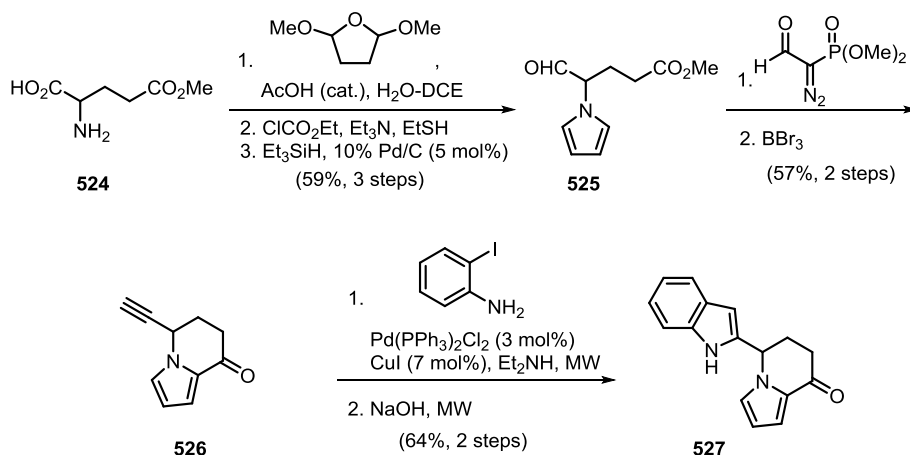


Scheme 125

As noted before, the alstoscholarines **420** and **512** contain a different double bond configuration at C-19/20. Apparently, the juncture of those geometrical isomers could arise during the biosynthesis of geissoschizine, where a double bond is formed, providing 19-*E* as well as 19-*Z* products. Thus, *Z*-alstoscholarine is likely to be formed *via* the similar biosynthetic pathway starting from *Z*-geissoschizine.

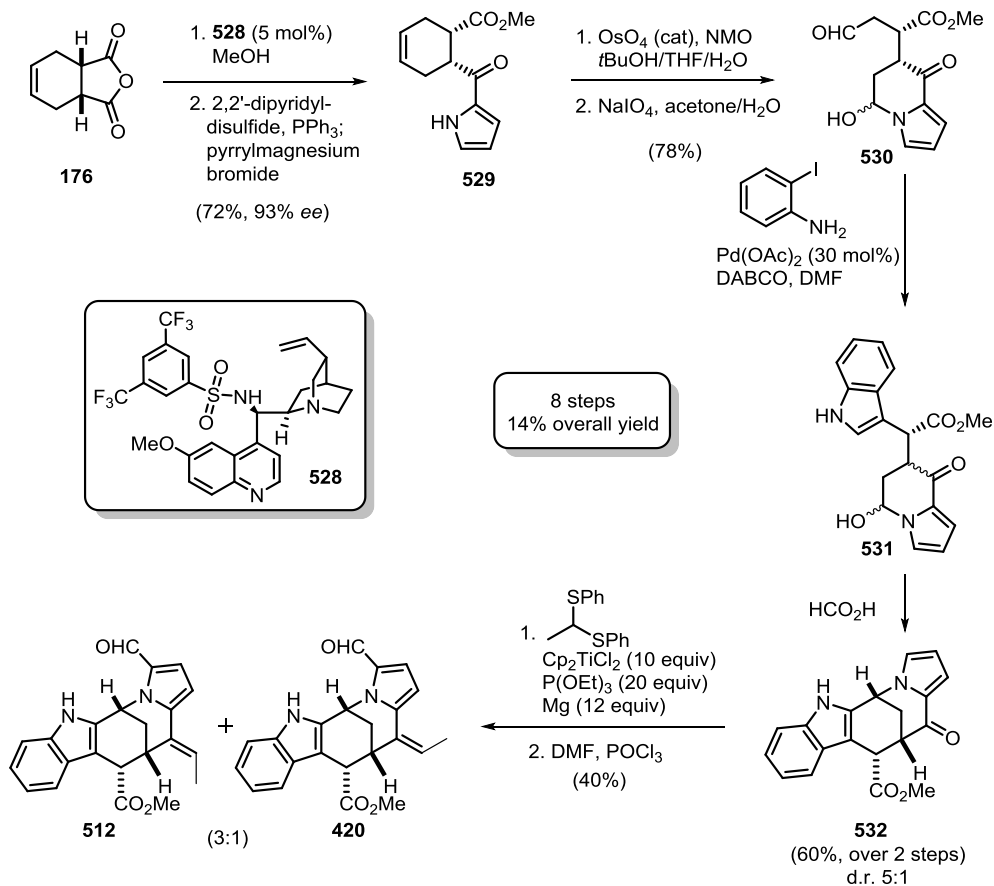
3.3.3 Recent Alstoscholarines Syntheses

Since the discovery of the alstoscholarines, only one total synthesis and one partial synthesis have been reported. In 2012, Miranda and co-workers published a synthesis for the preparation of the tetracyclic core of alstoscholarine alkaloids (Scheme 126).²⁷² Their approach began with readily available methyl ester of glutamic acid (**524**), which was converted to pyrrole after treatment with 2,5-dimethoxytetrahydrofuran. Consequently, subjection of the carboxylic acid to ethyl chloroformate in the presence of ethanethiol afforded a thioester, which was reduced using triethylsilane and 10% Pd/C. Carboxylic acid functionality was reduced to the corresponding aldehyde **525** without affecting the distal ester group.²⁷³ The alkynyl group was then installed using the Bestmann-Ohira reagent. Alkynylindolizinone **526** was efficiently obtained *via* boron tribromide-mediated cyclization. Finally, employing Sonogashira cross-coupling conditions with *o*-iodoaniline, followed by microwave-mediated intramolecular cyclization, tetracyclic system **527** was obtained in good yield.



Scheme 126

In 2011, Zhu and co-workers reported a protecting-group-free total synthesis of both alstoscholarines.²⁷⁴ As shown in Scheme 127, the synthesis began with tetrahydrophthalic anhydride **176**, which underwent asymmetric desymmetrization with methanol in the presence of catalyst **528**. The carboxylic acid moiety was converted to a 2-pyridylthioester, followed by addition of pyrrolmagnesium bromide, using the method developed by Nicolaou,²⁷⁵ furnished 2-ketopyrrole **529** as a single diastereomer. Dihydroxylation of **529** and then oxidative cleavage provided 1,6-dial, which cyclized spontaneously *in situ* to generate hemiaminal **530** as a mixture of two diastereomers. Palladium-catalyzed heteroannulation between *o*-iodoaniline and aldehyde **530**, then a Pictet-Spengler reaction afforded pentacycle **532** as a 5:1 mixture of diastereomers. It was concluded that the basic heteroannulation conditions may be a cause of the observed epimerization. Finally, ethylidenation of **532** using Takeda's reagent and subsequent Vilsmeier-Haack formylation provided a 3:1 mixture of *E/Z*-alstoscholarines in moderate yield. It was noted that the two geometric isomers can be separated by preparative TLC on silica gel.

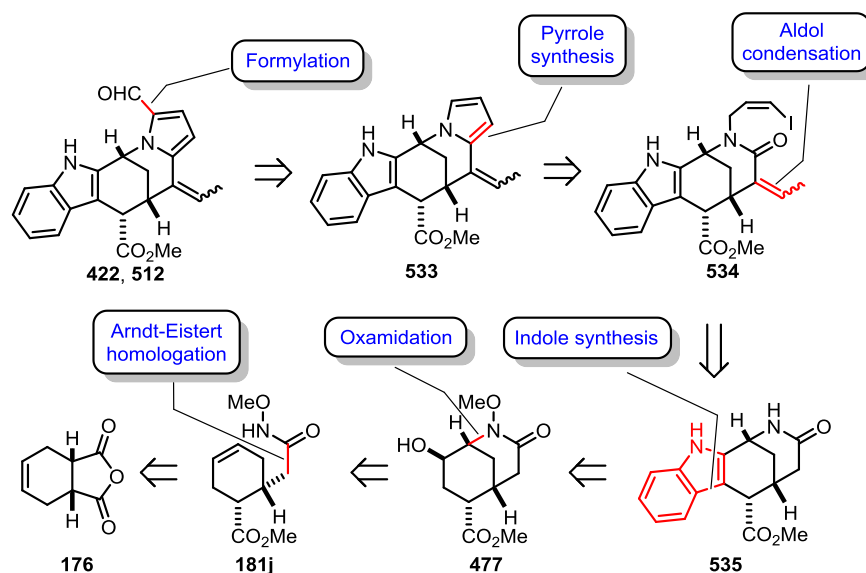


Scheme 127

3.3.4 Alstoscholarines Retrosynthesis

Our retrosynthetic analysis of *Z*- and *E*-alstoscholarine (**420**, **512**) is outlined in Scheme 128. In common with Zhu,²⁷⁴ we envisioned accessing the natural product from pentacycle **533** via a Vilsmeier-Haack formylation. In turn, the pyrrole ring synthesis could be accessed from vinyl iodide **534** through a TMS-SnBu₃-mediated anionic cyclization.²⁷⁶ The ethylidene appendage could be easily installed by the aldol condensation of amide **535** with acetaldehyde. Oxidation of alcohol **477** by PCC followed by Fischer indole synthesis could construct the indole synthon. Based on our study of the madangamines, we posited that

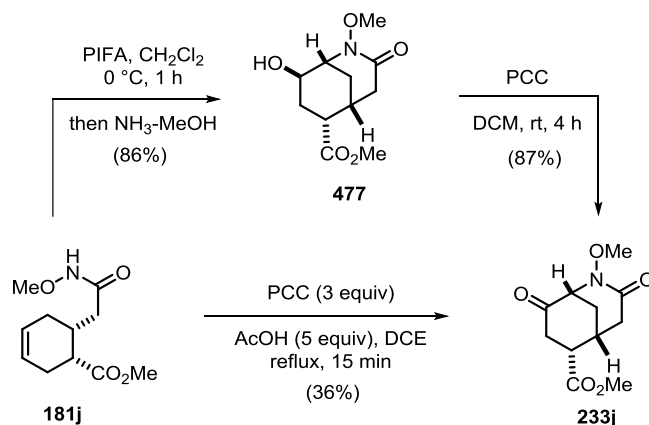
the bicyclic system **477** could be prepared from **181j** via intramolecular oxamidation. We anticipated that **181j**, the precursor for the cyclization, could be derived from *cis*-1,2,3,6-tetrahydrophthalic anhydride **176** via an Arndt-Eistert homologation procedure.



Scheme 128

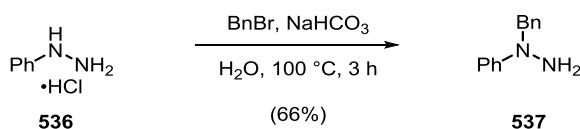
3.3.5 Model Studies Towards the Alstoscholarines

As described in this chapter, our proposed madangamine and alstoscholarine syntheses share **181j** as the same intermediate. Treatment of **181j** with PIFA in CH₂Cl₂ at 0 °C with subsequent hydrolysis by methanolic ammonia gave 2-azabicyclo[3.3.1]nonane **477** in 86% yield (Scheme 129). This compound was then transformed to ketone **233j** via oxidation with PCC, as previously described. Alternatively, intramolecular oxamidation of **181j** could be accomplished in one step by employing our Cr(VI) methodology. Thus, treatment of **181j** with 3 equivalents of PCC in the presence of 5 equivalents of acetic acid at 84 °C delivered **233j** albeit in low yield.



Scheme 129

With the bicyclic skeleton structure established, it was now necessary to install the indole system through a Fischer synthesis. We envisaged that employment of *N*-benzyl phenylhydrazine as a coupling partner would provide a flexible entry to the alstoscholarine series. To accomplish this, phenylbenzyl hydrazine (**537**) was prepared from commercially available phenyl hydrazine hydrochloride *via* alkylation with benzyl bromide (Scheme 130).²⁷⁷

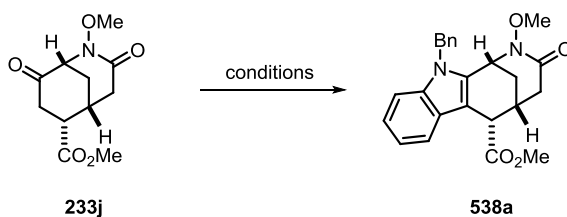


Scheme 130

Traditionally, rather harsh reaction conditions, such as higher temperatures and the use of stoichiometric quantities of acid, are necessary in order to expedite this classic multistep transformation efficiently. The stoichiometric formation of ammonia as the byproduct, may account for the necessity of using excess of Brønsted acids. We initially conducted the Fischer indolization using five equivalents of trifluoroacetic acid in

dichloroethane at 55 °C. After 15 h, we found that the reaction was completed, providing indole derivative **538a** in reasonable yield (Table 19, entry 1). Smith, in his synthesis of the monoterpene indole alkaloid scholarisine A, employed pyridine hydrochloride (**539**) in pyridine to carry out indolization on a structurally related substrate.²⁷⁸ Applying Smith's conditions, **233j** was heated with 1.3 equivalents of **537** and 10 equivalents of py•HCl in pyridine at 110 °C for 15 h. Encouragingly, product **538a** was cleanly generated in 72% yield (Table 19, entry 2).

Table 19. Fischer Indole Synthesis



entry	conditions	yield of 538a , % ^a
1	Ph(Bn)NNH ₂ (1.3 equiv), TFA (5 equiv), DCE, 55 °C, 12 h	59
2	Ph(Bn)NNH ₂ (1.3 equiv), py•HCl (10 equiv), py, 110 °C, 15 h	72

^aIsolated yields, after flash chromatography.

3.3.6 Entry to Indole Natural Product-Like Compounds

The diversity-oriented synthesis of natural product-like molecules is of great interest as a means to develop leads in drug discovery. The indole moiety is present in a number of clinically-approved drugs on the market, many of which belong to the triptan family of which frovatriptan (**540**),²⁷⁹ used for the treatment of migraines, is a well-known example (Figure 21). Recent studies have highlighted the numerous biological and pharmacological properties

of the psychoactive compound mitragynine (**541**),²⁸⁰ including analgesic, antitussive, antidiarrheal, adrenergic and antimalarial activities. Yohimbine (**542**),²⁸¹ structurally related to mitragynine, is a common male intimacy supplement. Tadalafil (**543**), a PDE5 inhibitor, is available under the name Cialis as an erectile dysfunction remedy and under the name Adcirca for pulmonary arterial hypertension (PAH) treatment.²⁸² The spiroindolone drug candidate NITD609 (**544**) is known for its inhibition of gametocytogenesis and transmission blockade of *Plasmodium falciparum* to *Anopheles* mosquito vectors.²⁸³ Indoles are also commonly found in alkaloids. The indolizidino[8,7-*b*]indole alkaloid (+)-harmicine (**545**),²⁸⁴ one of nineteen indole alkaloids extracted from the Malaysian plant *Kopsia griffithii*, has been evaluated as a potent anti-leishmania agent.

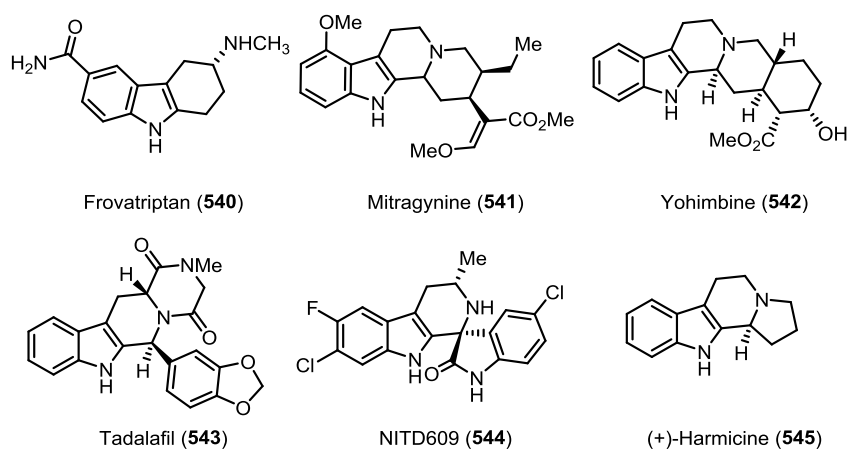


Figure 21 Examples of biologically important indole-containing molecules

In the Wardrop group we have used *O*-methyl hydroxamates to stereoselectively construct cyclic and bicyclic α -oxy lactams. We felt that given the wide substrate scope of this process, it offered an excellent means to access a focused series of complex polycyclic compounds with different ring sizes using the Fischer annulation.

A series of ketones was prepared from the corresponding *O*-methyl hydroxamates utilizing our Cr(VI)-mediated oxamidation methodology (Part 1). Then, following the indolization procedure published by Smith,²⁷⁸ ketones **233f,i,j** and **546** were converted into the corresponding indoles **538a-d**. The results of the indolization study are shown in Table 20.

Table 20. Indolization Study

entry	ketone	indole	time, h	yield, % ^a
1	233j	538a	15	72
2	233i	538b	12	78
3	546	538c	15	70
4	233f	538d	5	44

^aIsolated yields, after purification by flash chromatography.

It was found that the Fischer annulation protocol appeared to be general and effective, producing indole derivatives in good yields. We observed that reaction times are strongly dependent upon ketone structure. Most probably as a result of the steric interactions caused

by the ester substituent of substrates **233j**, **546** the reaction time in these cases was slower than for substrate **233i**. In addition, the reaction was substantially faster for substrate **233f** (Table 20, entry 4) which lacks the bicyclic bridge. Neither the formation of other by-products, nor epimerization among the stereocenters of the substrates was noted during the course of the indolization.

3.4. Conclusions

In summary, utilizing the I(III)- or Cr(VI)-mediated oxamidation of alkenes, we developed a wide-ranging strategy for the stereoselective construction of the morphan ring system, which is found in over 300 natural products. In work directed toward a total synthesis of the marine alkaloid madangamine D, an advanced, functionalized bicyclic intermediate was synthesized. In model studies towards the synthesis of monoterpene indole alkaloids of the alstoscholarine family, an advanced tetracyclic intermediate was constructed. Finally, the utility of our *N*-methoxy-*N*-acylnitrenium ion cyclization methodology was demonstrated in the preparation of polycyclic natural product-like molecules using the Fischer indolization protocol.

3.5. Experimental Procedures

3.5.1 General Procedures

All non-aqueous reactions were carried out in oven or flame-dried glassware under an atmosphere of dry nitrogen, unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using Merck pre-coated silica gel plates with F₂₅₄ indicator. Visualization was accomplished by UV and/or potassium permanganate solution. Flash column chromatograph was performed using Silicycle Silica-P flash silica gel (40-63 μ m). Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted.

3.5.2 Materials

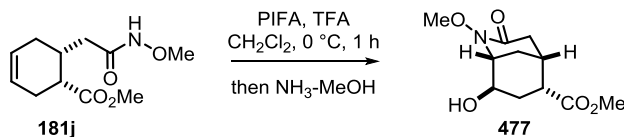
Dichloromethane (DCM), diethyl ether (Et₂O), tetrahydrofuran (THF), methanol (MeOH) and toluene, purchased from Sigma-Aldrich, were additionally purified on PureSolv PS-400-4 (Innovative Technology, Inc.) purification system. Acetonitrile (CH₃CN) and *N*-methylimidazole (NMI) was distilled from calcium hydride under an atmosphere of dry nitrogen. Triethylamine (Et₃N) was distilled from NaOH under an atmosphere of dry nitrogen. Acetic acid (AcOH) was distilled from P₂O₅ under an atmosphere of dry nitrogen. 1,2-Dichloroethane (DCE) was distilled from and stored over activated 4 Å molecular sieves. PIFA was prepared following the procedure reported by Varvoglis.²²⁷ Pyridinium chlorochromate (PCC) was prepared according to the method of Corey and Suggs.¹³³ All other reagents and starting materials, unless otherwise noted, were purchased from commercial vendors and used without further purification.

3.5.3 Instrumentation

All melting points were determined in open Pyrex capillaries using a Thomas Hoover Unimelt melting point apparatus and are uncorrected. Infrared spectra were recorded as thin films on sodium chloride plates using an ATI Mattson Genesis Series FTIR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 (400 MHz, ^1H , 100 MHz ^{13}C) or a Bruker Avance 500 (500 MHz ^1H , 125 MHz ^{13}C). Chemical shift values (δ) are reported in ppm relative to residual chloroform (δ 7.27 ppm for ^1H ; 77.00 ppm for ^{13}C), residual acetone (δ 2.05 ppm for ^1H ; 29.92 ppm for ^{13}C), residual methanol (δ 3.31 ppm for ^1H ; 49.15 ppm for ^{13}C) and residual DMSO (δ 2.50 ppm for ^1H ; 39.51 ppm for ^{13}C). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet) and br (broad). DEPT 135 and two-dimensional (COSY, HMQC, HMBC, NOESY) NMR experiments were employed, where appropriate, to aid in the assignment of signals in the ^1H NMR spectra. High-resolution electron spray ionization mass spectra (HRMS-ESI) were obtained on a Micromass Q-TOF 2 at the University of Illinois Research Resources Center or on a Micromass Q-TOF Ultima at the Mass Spectroscopy Laboratory at the University of Illinois, Urbana-Champaign.

3.5.4 Madangamine Project Experimental Procedures

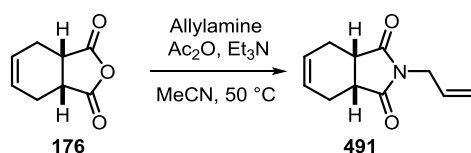
Methyl (1*R,5*R**,6*R**,8*R**)-8-hydroxy-2-methoxy-3-oxo-2-azabicyclo[3.3.1]nonane-6-carboxylate (477)**



A solution of **181j** (28.9 mg, 0.13 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at rt was first treated with trifluoroacetic acid (10 μL , 0.13 mmol, 1.0 equiv), and then with a solution of PIFA (60

mg, 0.14 mmol, 1.1 equiv) in CH_2Cl_2 (5 mL). After stirring for 1 h, ammonia in methanol (0.5 mL) was added and the reaction stirred for additional 20 min. The reaction was then concentrated and the residue purified by flash chromatography on silica gel (EtOAc-acetone, 1:1) to provide **477** (26.6 mg, 86%) as a colorless oil, which crystallized upon standing; mp 92-94 °C (EtOAc/hexanes); R_f 0.19 (EtOAc); IR (film) ν_{max} 3331, 2962, 2931, 1725, 1637, 1441, 1378, 1089, 930, 790, 640 cm^{-1} ; ^1H NMR (CD_3OD , 500 MHz): δ 4.15 (br. s., 1H), 3.80 (br. s., 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.97-3.03 (m, 1H), 2.60-2.67 (m, 1H), 2.50 (br. s., 1H), 2.40 (dd, $J = 13.4, 2.4$ Hz, 1H), 2.30 (d, $J = 18.2$ Hz, 1H), 1.85-1.97 (m, 2H), 1.63-1.71 (m, 1H); ^{13}C NMR (CD_3OD , 126 MHz): δ 175.9, 170.6, 66.0, 62.4, 59.2, 52.5, 42.1, 35.1, 30.5, 27.9, 27.5; HRMS-ESI calcd for $\text{C}_{11}\text{H}_{18}\text{NO}_5$ $[\text{M}+\text{H}]^+$ 244.1185, found: 244.1180.

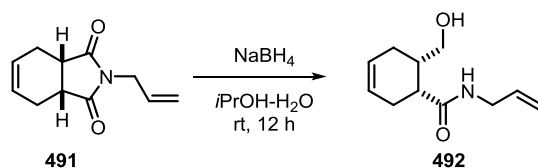
(3a*R,7a*S**)-2-Allyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (**491**)**



Et_3N (2.74 mL, 19.7 mmol, 3.3 equiv) was added to CH_3CN (10 mL) in a round-bottomed flask equipped with a stir bar, under nitrogen. Allylamine (0.44 mL, 5.97 mmol, 1.0 equiv) was then added to the flask, followed by *cis*-1,2,3,6-tetrahydrophthalic anhydride (**176**) (1.00 g, 6.57 mmol, 1.1 equiv) dissolved in CH_3CN (5 mL). The solution was then heated to 50 °C and stirred for 2 h. The reaction was then allowed to cool to room temperature, followed by the addition of Ac_2O (0.67 mL, 7.16 mmol, 1.2 equiv). Once addition was complete, the reaction was heated to 50 °C again and monitored by TLC. Once the reaction was complete, it was cooled to room temperature, and the pH adjusted to 1-2 with 1M HCl. The product was extracted with dichloromethane (3 x 25 mL) and the combined extracts dried over Na_2SO_4 . Removal of the solvent provided **491** (1.13 g, 99%) as a yellowish oil that was used

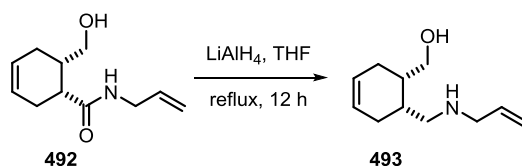
directly in the next step; R_f 0.57 (EtOAc-hexanes, 3:7); IR (film) ν_{\max} 3042, 2948, 2850, 1776, 1695, 1646, 1425, 1389, 1331, 1192, 1169, 987, 926 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 5.87-5.95 (m, 2H), 5.74 (ddt, $J = 16.7, 10.9, 5.4$ Hz, 1H), 5.08-5.16 (m, 2H), 4.08 (d, $J = 5.5$ Hz, 2H), 3.08-3.15 (m, 2H), 2.58-2.68 (m, 2H), 2.19-2.29 (m, 2H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 179.6, 130.6, 127.8, 117.5, 40.9, 39.1, 23.5; HRMS-ESI calcd for $\text{C}_{11}\text{H}_{14}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 192.1025, found: 192.1017.

(1*R,6*S**)-*N*-Allyl-6-(hydroxymethyl)cyclohex-3-ene-1-carboxamide (**492**)**



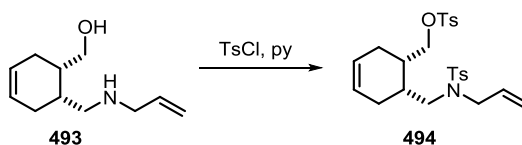
To a solution of **491** (250 mg, 1.31 mmol, 1.0 equiv) in 2-propanol/water (6:1, 10 mL), sodium borohydride (250 mg, 6.55 mmol, 5.0 equiv) was added. The reaction was placed under nitrogen and stirred at room temperature overnight. The reaction was then poured into saturated sodium bicarbonate, extracted with CH_2Cl_2 (3 x 15 mL), dried over Na_2SO_4 , and concentrated to give **492** (220 mg, 87%) as a colorless oil that was used directly in the next step; R_f 0.68 (EtOAc); IR (film) ν_{\max} 3296, 3080, 2909, 1636, 1532, 1418, 1247, 1036, 919, 656 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 6.15 (br. s., 1H), 5.71-5.88 (m, 3H), 5.10-5.20 (m, 2H), 3.82-3.97 (m, 2H), 3.63 (d, $J = 7.0$ Hz, 2H), 3.48 (br. s., 1H), 2.84-2.90 (m, 1H), 2.36-2.45 (m, 1H), 2.19-2.35 (m, 2H), 2.11-2.19 (m, 1H), 1.83-1.93 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 175.2, 134.0, 127.3, 124.8, 116.4, 64.2, 41.9, 41.7, 37.1, 26.8, 26.3; HRMS-ESI calcd for $\text{C}_{11}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 196.1338, found: 196.1333.

((1*S,6*R**)-6-((Allylamino)methyl)cyclohex-3-en-1-yl)methanol (**493**)**



To a suspension of LiAlH_4 (1.22 g, 32.0 mmol, 2.0 equiv) in THF (75 mL), was added a solution of **492** (3.13 g, 16.0 mmol, 1.0 equiv) in THF (20 mL) at a rate which maintained a gentle reflux. The reaction was then heated at reflux overnight, and then quenched by careful, dropwise addition of water. The fine white precipitate that formed was filtered off, washed with THF and then discarded. The filtrate was concentrated to give **493** (2.60 g, 90%) as a colorless oil, which was directly used in the next step; R_f 0.12 (acetone); IR (film) ν_{max} 3267, 3020, 2891, 2838, 1644, 1437, 1103, 993, 734, 660 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 5.89 (ddt, $J = 16.9, 10.5, 6.2$ Hz, 1H), 5.63-5.70 (m, 1H), 5.53-5.61 (m, 1H), 5.09-5.23 (m, 2H), 3.55-3.65 (m, 2H), 3.19-3.32 (m, 2H), 2.75 (dd, $J = 12.0, 9.5$ Hz, 1H), 2.50 (dd, $J = 12.0, 2.0$ Hz, 1H), 2.20-2.31 (m, 2H), 2.05 (d, $J = 4.3$ Hz, 1H), 1.89-2.02 (m, 4H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 135.5, 126.7, 124.6, 116.9, 64.7, 52.1, 50.0, 39.1, 37.2, 30.8, 25.6; HRMS-ESI calcd for $\text{C}_{11}\text{H}_{20}\text{NO}$ $[\text{M}+\text{H}]^+$: 182.1545, found: 182.1546.

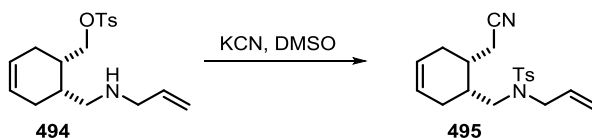
((1*S,6*R**)-6-(((*N*-Allyl-4-methylphenyl)sulfonamido)methyl)cyclohex-3-en-1-yl)methyl 4-methylbenzenesulfonate (**494**)**



A solution of **493** (640 mg, 3.53 mmol, 1.0 equiv) in 15 mL of dry pyridine was stirred at -20°C for 10 minutes under nitrogen. TsCl (2.02 g, 10.6 mmol, 3.0 equiv) was added in small portions over an hour. The reaction was allowed to warm to 0°C over the next hour, and then

moved to the refrigerator overnight. The reaction was then added to 130 mL of cold water, and the product was extracted with EtOAc (3 x 30 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (EtOAc-hexanes, 1:3) to provide **494** (740 mg, 43%) as a colorless oil; *R_f* 0.67 (EtOAc/Hexane 1:3); IR (film) ν_{max} 2922, 1736, 1597, 1439, 1338, 1174, 1095, 954, 815, 660 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 5.48-5.61 (m, 3H), 5.08-5.17 (m, 2H), 4.05 (dd, *J* = 9.5, 6.5 Hz, 1H), 3.95 (t, *J* = 8.7 Hz, 1H), 3.69-3.80 (m, 2H), 3.12 (dd, *J* = 13.7, 9.0 Hz, 1H), 2.95 (dd, *J* = 13.7, 5.4 Hz, 1H), 2.45 (d, *J* = 5.0 Hz, 6H), 2.22 (br. s., 2H), 2.07 (d, *J* = 18.0 Hz, 2H), 1.86 (t, *J* = 18.0 Hz, 2H); ¹³C NMR (CDCl₃, 126 MHz): δ 144.8, 143.3, 136.5, 132.9, 129.9, 129.7, 127.9, 127.3, 125.6, 124.4, 119.3, 70.4, 51.4, 48.2, 34.2, 32.7, 26.7, 26.2, 21.6, 21.5; HRMS-ESI calcd for C₂₅H₃₂NO₅S₂ [M+H]⁺: 490.1722, found: 490.1717.

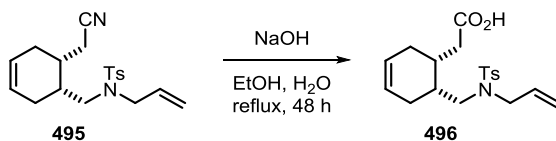
***N*-Allyl-*N*-(((1*R**,6*R**)-6-(cyanomethyl)cyclohex-3-en-1-yl)methyl)-4-methylbenzenesulfonamide (**495**)**



A solution of **494** (1.62 g, 3.30 mmol, 1.0 equiv) in DMSO (7 mL) was added dropwise over 10 minutes to a stirred mixture of KCN (1.37 g, 21.1 mmol, 6.4 equiv) in DMSO (17 mL) at 60 °C under nitrogen. The reaction was allowed to stir overnight, and then poured into water (100 mL). The product was extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (EtOAc-hexanes, 1:1) giving **495** (940 mg, 83%) as a colorless oil; *R_f* 0.56 (EtOAc-hexanes, 1:3); IR (film) ν_{max} 2913, 2243, 1598, 1449, 1327, 1154, 1003, 900, 760,

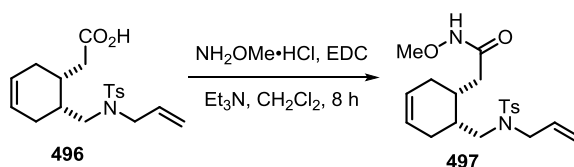
683 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.69 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 5.64 (s, 2H), 5.52-5.60 (m, 1H), 5.13-5.21 (m, 2H), 3.74-3.85 (m, 2H), 3.10 (dd, J = 13.9, 7.9 Hz, 1H), 2.94 (dd, J = 13.9, 7.1 Hz, 1H), 2.44 (s, 4H), 2.23-2.34 (m, 3H), 2.13-2.23 (m, 2H), 2.03-2.11 (m, 1H), 1.75 (dd, J = 18.6, 8.5 Hz, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 143.6, 136.3, 132.8, 129.8, 129.7, 127.2, 127.1, 125.3, 124.5, 119.5, 51.3, 48.5, 33.8, 31.1, 29.1, 26.2, 21.5, 16.9; HRMS-ESI calcd for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 345.1637, found: 345.1638.

2-((1*R,6*R**)-6-(((*N*-Allyl-4-methylphenyl)sulfonamido)methyl)cyclohex-3-en-1-yl)acetic acid (**496**)**



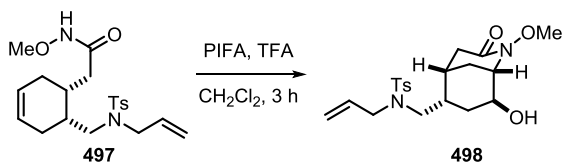
A mixture of a 1M solution of NaOH in ethanol ($\text{EtOH-H}_2\text{O}$, 9:1) (15 mL) and **495** (940 mg, 2.73 mmol, 1.0 equiv) was heated at reflux for 48 h. The reaction was then concentrated, and acidified with 1M HCl. The product was extracted with EtOAc (3x25 mL), washed with brine, dried over Na_2SO_4 and concentrated to give **496** (870 mg, 88%) as a yellow oil that was used directly in the next step; R_f 0.34 (EtOAc/Hexane 1:3); IR (film) ν_{max} 3022, 1704, 1597, 1436, 1155, 1089, 922, 818, 657 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.65 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2, 2H), 5.49-5.60 (m, 3H), 5.04-5.15 (m, 2H), 3.68-3.82 (m, 2H), 2.92-3.06 (m, 2H), 2.37 (s, 3H), 2.29-2.35 (m, 2H), 2.19-2.27 (m, 1H), 2.07-2.17 (m, 2H), 1.97-2.04 (m, 1H), 1.89 (d, J = 17.1 Hz, 1H), 1.73-1.83 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 179.2, 143.1, 136.3, 132.8, 129.5, 127.0, 125.2, 124.8, 118.9, 51.0, 47.9, 33.9, 33.5, 30.2, 29.1, 26.3, 21.2; HRMS-ESI calcd for $\text{C}_{19}\text{H}_{26}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 364.1583, found: 364.1585.

2-((1*R,6*R**)-6-(((*N*-Allyl-4-methylphenyl)sulfonamido)methyl)cyclohex-3-en-1-yl)-*N*-methoxyacetamide (**497**)**

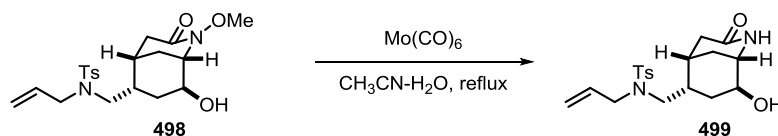


To a stirred solution of **496** (2.25 g, 6.19 mmol, 1.0 equiv) and methoxyamine hydrochloride (570 mg, 6.81 mmol, 1.1 equiv) in CH₂Cl₂ (50 mL) at room temperature, were sequentially added EDC (1.31 g, 6.81 mmol, 1.1 equiv) and Et₃N (0.94 mL, 6.81 mmol, 1.1 equiv). After stirring for 12 h, the reaction was acidified with 1M aqueous HCl (1 mL), quenched with water (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (EtOAc-hexanes, 1:1) to afford **497** (2.31 g, 95%) as a white solid: mp 73-74 °C (EtOAc/hexanes); *R_f* 0.34 (EtOAc/hexanes 1:1); IR (film) ν_{max} 3020, 2913, 1654, 1439, 1331, 1149, 1086, 910, 659 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 9.72 (s, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 5.49 (s, 2H), 5.39-5.47 (m, 1H), 5.05 (d, *J* = 17.1 Hz, 1H), 5.00 (d, *J* = 10.2 Hz, 1H), 3.70-3.77 (m, 1H), 3.67 (d, *J* = 6.8 Hz, 1H), 3.63 (s, 3H), 3.10 (dd, *J* = 13.8, 7.9 Hz, 1H), 2.81 (dd, *J* = 13.8, 6.8 Hz, 1H), 2.32 (s, 3H), 2.24 (br. s., 1H), 2.05-2.10 (m, 1H), 1.96-2.03 (m, 3H), 1.83-1.92 (m, 2H), 1.58-1.68 (m, 1H); ¹³C NMR (CDCl₃, 126 MHz): δ 170.3, 143.2, 136.1, 132.5, 129.5, 126.7, 125.1, 124.9, 118.9, 63.7, 50.8, 48.4, 34.2, 31.5, 30.9, 28.8, 26.0, 21.1; HRMS-ESI calcd for C₂₀H₂₉N₂O₄S [M+H]⁺: 393.1848, found: 393.1847.

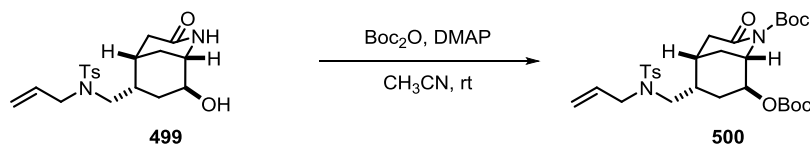
***N*-Allyl-*N*-(((1*S**,5*S**,6*S**,8*S**)-8-hydroxy-2-methoxy-3-oxo-2-azabicyclo[3.3.1]nonan-6-yl)methyl)-4-methylbenzenesulfonamide (**498**)**



A solution of **497** (1.17 g, 2.98 mmol, 1.0 equiv) in CH₂Cl₂ (20 mL) at 40 °C was sequentially treated with trifluoroacetic acid (0.23 mL, 2.98 mmol, 1.0 equiv) and a solution of PIFA (1.54 g, 3.58 mmol, 1.2 equiv) in CH₂Cl₂ (15 mL). After stirring for 3 h under nitrogen, the reaction was cooled to room temperature, ammonia in methanol (35 mL) added and the reaction stirred for 20 min. After 20 min, the reaction was concentrated and the residue purified by flash chromatography on silica gel (EtOAc) to provide **498** (1.10 g, 90%) as a light yellow oil, which crystallized upon standing; mp 158-160 °C (EtOAc/hexanes); *R*_f 0.30 (EtOAc); IR (film) ν_{max} 3336, 2924, 1658, 1629, 1597, 1450, 1339, 1216, 903, 646 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.69 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 5.50-5.61 (m, 1H), 5.09-5.20 (m, 2H), 4.27 (br. s., 1H), 3.78-3.85 (m, 3H), 3.71-3.78 (m, 4H), 3.16 (dd, *J* = 14.0, 9.1 Hz, 1H), 2.73 (dd, *J* = 14.0, 5.8 Hz, 1H), 2.48-2.53 (m, 2H), 2.44 (s, 3H), 2.29-2.40 (m, 3H), 2.22 (br. s., 1H), 1.92 (d, *J* = 13.2 Hz, 1H), 1.58 (d, *J* = 14.6 Hz, 1H), 1.29-1.37 (m, 1H); ¹³C NMR (CDCl₃, 126 MHz): δ 168.6, 143.4, 136.4, 132.9, 129.7, 127.2, 119.3, 65.6, 61.9, 58.5, 51.7, 50.4, 33.6, 32.5, 28.9, 28.2, 28.0, 21.5; HRMS-ESI calcd for C₂₀H₂₉N₂O₅S [M+H]⁺: 409.1797, found: 409.1793.

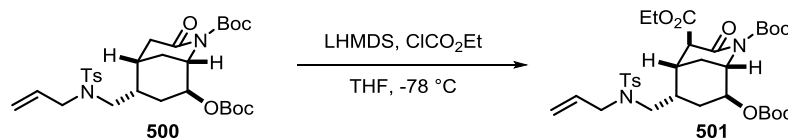


***tert*-Butyl (1*S**,5*S**,6*S**,8*S**)-6-(((*N*-allyl-4-methylphenyl)sulfonamido)methyl)-8-((*tert*-butoxycarbonyl)oxy)-3-oxo-2-azabicyclo[3.3.1]nonane-2-carboxylate (500)**



To a solution of **499** (480 mg, 1.26 mmol, 1.0 equiv) in 50 mL acetonitrile at room temperature was added Boc₂O (1.37 g, 6.3 mmol, 5.0 equiv) followed by DMAP (154 mg, 1.26 mmol, 1 equiv). The solution was stirred at room temperature for 12 h. The reaction mixture was then concentrated under reduced pressure, and the residue purified by flash chromatography (SiO₂, EtOAc-hexanes, 1:2) to afford **500** (627 mg, 86%) as a colorless oil; *R*_f 0.77 (EtOAc-hexanes, 1:1); IR (film) ν_{max} 2980, 1768, 1739, 1718, 1598, 1451, 1394, 1333, 1271, 1152, 1089, 925, 734, 661 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.55 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.11-5.18 (m, 2H), 4.88-4.92 (m, 1H), 4.32 (br. s., 1H), 3.78 (d, *J* = 6.7 Hz, 2H), 3.12 (dd, *J* = 14.0, 9.0 Hz, 1H), 2.73 (dd, *J* = 14.1, 5.5 Hz, 1H), 2.55-2.59 (m, 2H), 2.44 (s, 3H), 2.28 (br. s., 2H), 2.18 (d, *J* = 14.0 Hz, 1H), 1.91 (d, *J* = 14.0 Hz, 1H), 1.76 (d, *J* = 15.4 Hz, 1H), 1.63 (br. s., 1H), 1.53 (s, 11H), 1.49 (s, 10H), 1.32-1.39 (m, 1H), 0.82-0.88 (m, 1H); ¹³C NMR (CDCl₃, 126 MHz): δ 170.9, 152.3, 151.6, 143.5, 136.4, 132.9, 129.8, 127.2, 119.3, 83.6, 82.4, 71.8, 52.6, 51.6, 50.1, 34.4, 33.7, 27.9, 27.8, 27.5, 27.2, 25.8, 21.5; HRMS-ESI calcd for C₂₉H₄₃N₂O₈S [M+H]⁺: 579.2740, found: 579.2736.

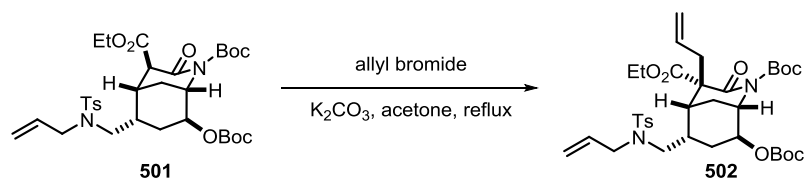
2-(*tert*-Butyl) 4-ethyl (1*S,4*R**,5*R**,6*S**,8*S**)-6-(((*N*-allyl-4-methylphenyl)sulfonamido)-methyl)-8-((*tert*-butoxycarbonyl)oxy)-3-oxo-2-azabicyclo[3.3.1]nonane-2,4-dicarboxylate (501)**



To a solution of compound **500** (116 mg, 0.20 mmol, 1.0 equiv) in THF (30 mL) cooled to -78 °C was added *via* syringe LHMDS (1M solution in THF, 0.48 mL, 0.48 mmol, 2.4 equiv). After stirring for 1 h, ethyl chloroformate (23 µL, 0.24 mmol, 1.2 equiv) was added *via*

syringe. The reaction mixture was stirred for 4 h at -78 °C then allowed to warm to rt and quenched with saturated aqueous NH₄Cl (30 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organic extracts were dried with Na₂SO₄ and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc-hexanes, 1:2) to provide **501** (129.2 mg, 99%) as a colorless oil; R_f 0.84 (EtOAc-hexanes, 1:1); IR (film) ν_{max} 2941, 2931, 1774, 1732, 1454, 1335, 1257, 1146 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.65 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.53 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.09-5.16 (m, 2H), 4.86-4.89 (m, 1H), 4.27-4.32 (m, 1H), 4.10 (q, *J* = 7.2 Hz, 3H), 3.75 (d, *J* = 6.6 Hz, 2H), 3.11 (dd, *J* = 14.0, 8.9 Hz, 1H), 2.71 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.53-2.57 (m, 2H), 2.41 (s, 4H), 2.21-2.28 (m, 2H), 2.02 (s, 4H), 1.86-1.92 (m, 1H), 1.74 (d, *J* = 14.9 Hz, 1H), 1.51 (s, 12H), 1.47 (s, 12H), 1.32-1.38 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 6H), 0.79-0.88 (m, 1H); ¹³C NMR (CDCl₃, 126 MHz): δ 171.0, 170.9, 152.2, 151.5, 143.4, 136.3, 132.8, 129.7, 127.2, 119.2, 83.6, 82.3, 71.7, 60.3, 52.5, 51.5, 50.0, 34.3, 33.6, 27.8, 27.7, 27.5, 27.1, 25.7, 21.4, 20.9, 14.1; HRMS-ESI calcd for C₃₂H₄₇N₂O₁₀S [M+H]⁺: 651.2951, found: 651.2953.

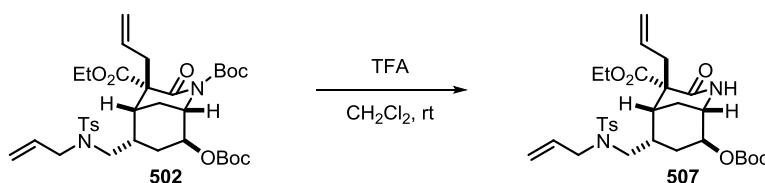
2-(*tert*-Butyl) 4-ethyl (1*S,4*S**,5*R**,6*S**,8*S**)-4-allyl-6-(((*N*-allyl-4-methylphenyl)-sulfonamido)-methyl)-8-((*tert*-butoxycarbonyl)oxy)-3-oxo-2-azabicyclo[3.3.1]-nonane-2,4-dicarboxylate (502)**



To a solution of **501** (142 mg, 0.22 mmol) in acetone (5 mL) was added potassium carbonate (200 mg, 1.45 mmol). The mixture was stirred for 10 min and then allyl bromide (57 μ L, 0.66

mmol, 3.0 equiv) added. After heating at 56 °C for 5 h, the slurry was filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc-hexanes, 1:3) to provide **502** (101 mg, 67%) and recovered starting material **501** (10 mg, 7%); R_f 0.73 (EtOAc-hexanes, 2:3); IR (film) ν_{\max} 2982, 1772, 1724, 1450, 1395, 1275, 1252, 1138, 1090, 924, 657 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.65 (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 5.88-6.00 (m, 1H), 5.57 (ddt, $J = 16.9, 10.3, 6.4$ Hz, 1H), 5.05-5.19 (m, 4H), 4.91-4.97 (m, 1H), 4.24-4.29 (m, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 3.64-3.78 (m, 2H), 3.09 (dd, $J = 13.8, 9.6$ Hz, 1H), 2.79 (dd, $J = 13.8, 3.3$ Hz, 2H), 2.66-2.74 (m, 1H), 2.43 (s, 3H), 2.24 (br. s., 2H), 2.17 (s, 3H), 2.03-2.09 (m, 2H), 1.53 (s, 9H), 1.50 (s, 9H), 1.24-1.32 (m, 5H); ^{13}C NMR (CDCl_3 , 101 MHz): δ 172.0, 169.7, 152.2, 152.0, 143.4, 136.5, 133.6, 133.2, 129.7, 127.2, 119.1, 118.8, 83.8, 82.3, 71.6, 61.7, 57.6, 52.9, 51.6, 50.7, 43.7, 39.5, 36.6, 30.9, 29.2, 27.9, 27.8, 26.6, 25.5, 21.5, 13.6; HRMS-ESI calcd for $\text{C}_{35}\text{H}_{50}\text{N}_2\text{O}_{10}\text{SNa}$ $[\text{M}+\text{Na}]^+$: 713.3084, found: 713.3081.

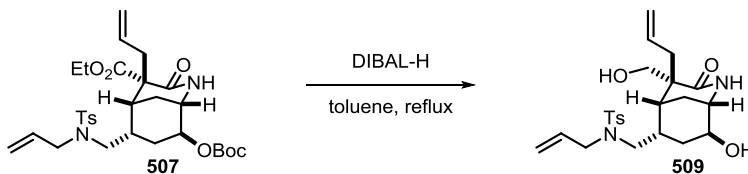
Ethyl (1*S,4*S**,5*R**,6*S**,8*S**)-4-allyl-6-(((*N*-allyl-4-methylphenyl)sulfonamido)methyl)-8-((*tert*-butoxycarbonyl)oxy)-3-oxo-2-azabicyclo[3.3.1]nonane-4-carboxylate (**507**)**



To a solution of **502** (77.4 mg, 0.112 mmol) in CH_2Cl_2 (15 mL) cooled to 0 °C, was added TFA (45 μL , 0.59 mmol, 5 equiv) and the solution then allowed to warm to room temperature. After stirring for 1 h, saturated aqueous NaHCO_3 (10 mL) was added and the mixture extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 , filtered, evaporated *in vacuo* and purified by flash chromatography (EtOAc-

hexanes, 2:1) to yield **507** (61.0 mg, 92%) as a colorless oil; R_f 0.26 (EtOAc-hexanes, 2:3); IR (film) ν_{\max} 2923, 2853, 1733, 1653, 1559, 1457, 1368, 1275, 1254, 1089, 864, 659 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.65 (d, $J = 8.1$ Hz, 2H), 7.30 (d, $J = 8.1$ Hz, 2H), 6.38-6.49 (m, 1H), 5.94-6.04 (m, 1H), 5.57 (ddt, $J = 16.9, 10.2, 6.4$ Hz, 1H), 5.11-5.19 (m, 2H), 5.04-5.11 (m, 2H), 4.70 (br. s., 1H), 4.11-4.18 (m, 2H), 3.64-3.78 (m, 2H), 3.58 (br. s., 1H), 3.07 (dd, $J = 13.8, 9.2$ Hz, 1H), 2.74-2.83 (m, 2H), 2.60-2.69 (m, 1H), 2.42 (s, 3H), 2.19-2.30 (m, 3H), 2.09 (d, $J = 13.8$ Hz, 1H), 1.96 (d, $J = 12.7$ Hz, 2H), 1.44-1.52 (m, 10H), 1.22-1.32 (m, 5H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 172.4, 171.3, 152.6, 143.3, 136.6, 134.2, 133.1, 129.7, 127.2, 119.1, 118.1, 82.4, 73.2, 61.6, 55.3, 51.5, 50.6, 48.8, 43.5, 39.5, 37.2, 27.7, 26.5, 24.9, 21.4, 13.6; HRMS-ESI calcd for $\text{C}_{30}\text{H}_{42}\text{N}_2\text{O}_8\text{SNa}$ $[\text{M}+\text{Na}]^+$: 613.2560, found: 613.2560.

***N*-Allyl-*N*-(((1*S**,4*R**,5*R**,6*S**,8*S**)-4-allyl-8-hydroxy-4-(hydroxymethyl)-3-oxo-2-azabicyclo-[3.3.1]nonan-6-yl)methyl)-4-methylbenzenesulfonamide (509)**

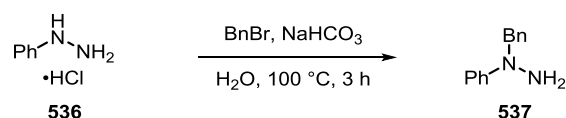


To a solution of **507** (125.7 mg, 0.213 mmol, 1.0 equiv) in toluene (25 mL) at 0 °C was slowly added DIBAL-H (2.13 mL, 1M in toluene, 2.13 mmol, 10 equiv) and reaction mixture allowed to stir for 1 h before warming to rt. The mixture was then heated at 110 °C for 3 h, cooled to room temperature and quenched with saturated aqueous NH₄Cl. The biphasic layers were separated and aqueous phase extracted with EtOAc (4 x 25 mL). The combined organic extracts were dried with Na₂SO₄, filtered and concentrated. The crude residue was purified by flash chromatography (EtOAc) to provide **509** (26 mg, 27%) as a colorless oil; *R*_f 0.63 (acetone); IR (film) ν_{max} 3327, 2925, 1717, 1635, 1558, 1507, 1456, 1337, 1205, 1154,

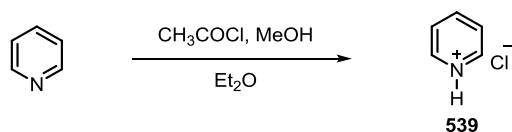
1089, 1032, 916, 814, 660 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.67 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 6.39-6.44 (m, 1H), 5.74-5.84 (m, 1H), 5.53-5.63 (m, 1H), 5.10-5.19 (m, 4H), 4.23-4.30 (m, 1H), 3.95 (br. s., 1H), 3.72-3.84 (m, 3H), 3.69 (t, J = 5.7 Hz, 1H), 3.41-3.48 (m, 2H), 3.37 (dd, J = 13.6, 10.5 Hz, 1H), 2.81-2.88 (m, 2H), 2.43 (s, 4H), 2.35-2.40 (m, 1H), 2.32 (dd, J = 13.6, 8.9 Hz, 1H), 2.04-2.17 (m, 2H), 1.88-1.96 (m, 2H), 1.77-1.86 (m, 1H), 1.69 (t, J = 5.7 Hz, 1H), 1.26 (d, J = 4.0 Hz, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 179.6, 143.5, 136.3, 133.1, 133.1, 129.8, 127.2, 119.3, 119.3, 68.8, 64.6, 62.7, 52.2, 51.8, 51.4, 48.8, 39.7, 36.5, 35.6, 29.8, 28.9, 25.3, 21.5; HRMS-ESI calcd for $\text{C}_{23}\text{H}_{33}\text{N}_2\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 449.2110, found: 449.2099.

3.5.5 Alstoscholarine Project Experimental Procedures

1-Benzyl-1-phenylhydrazine (**537**)



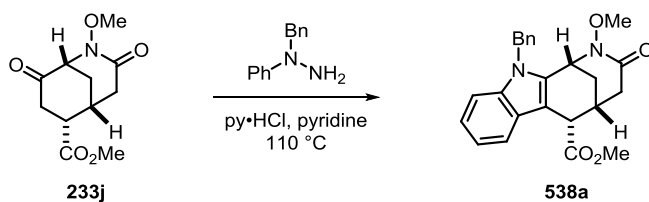
Phenylhydrazine hydrochloride salt (**536**) (1.32 g, 9.1 mmol, 1.0 equiv), benzyl bromide (1.08 mL, 9.1 mmol, 1.0 equiv) and NaHCO_3 (1.53 g, 18.2 mmol, 2.0 equiv) were mixed in H_2O (8 mL) and heated to 100 $^\circ\text{C}$ under vigorous stirring. After 3 h, the mixture was cooled to room temperature and diluted with Et_2O (30 mL). The layers were separated and the aqueous phase extracted with Et_2O (3 x 25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes- Et_2O , 4:1) to afford **537** (1.19 g, 66%) as a yellow oil; ^1H NMR (CDCl_3 , 500 MHz): δ 7.27-7.41 (m, 7H), 7.14 (d, J = 8.0 Hz, 2H), 6.87 (t, J = 7.2 Hz, 1H), 4.63 (s, 2H), 3.73 (br. s., 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 151.5, 137.4, 129.1, 128.7, 127.9, 127.4, 118.9, 113.9, 60.4.

Pyridine hydrochloride (539)

A mixture of methanol (1.28 g, 40 mmol, 1.0 equiv) and pyridine (3.16 g, 40 mmol, 1.0 equiv) in diethyl ether (25 mL) was cooled to 0 °C. A solution of acetyl chloride (3.14 g, 40 mmol, 1.0 equiv) in diethyl ether was added slowly over 5 min. The reaction mixture was stirred for 30 min, then filtered to provide a white solid which was dried *in vacuo* to afford **539** (4.09 g, 90%) as a white solid.

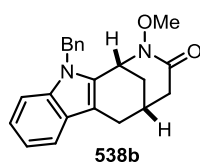
Representative Procedure 7. Preparation of Indoles

Methyl (1*R,5*R**,6*S**)-11-benzyl-2-methoxy-3-oxo-2,3,4,5,6,11-hexahydro-1*H*-1,5-methano-azocino[3,4-*b*]indole-6-carboxylate (538a)**



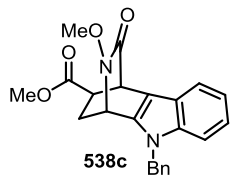
A mixture of ketone **233j** (31.3 mg, 0.13 mmol, 1.0 equiv), benzyl phenylhydrazine (**537**) (33.0 mg, 0.17 mmol, 1.3 equiv), pyridine hydrochloride (**539**) (149 mg, 1.3 mmol, 10 equiv), and pyridine (1 mL) was stirred at 110 °C for 15 h and then cooled to room temperature. The solvent was removed *in vacuo*, and the resulting residue was diluted with ethyl acetate and washed with hydrochloric acid (1N aqueous, 2x). The aqueous layers were back-extracted with ethyl acetate (3 x 15 mL) and the combined organic extracts washed with hydrochloric acid (1N aqueous, 2x), saturated aqueous sodium bicarbonate, brine, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to afford a yellow oil, which was purified by flash chromatography (EtOAc-acetone, 100:1) to furnish indole **538a**.

(37.9 mg, 72%) as a clear oil; R_f 0.35 (EtOAc); IR (film) ν_{\max} 2949, 1730, 1673, 1610, 1489, 1464, 1436, 1251, 1189, 912, 727 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.36 (d, $J = 7.9$ Hz, 1H), 7.22-7.34 (m, 4H), 7.19 (t, $J = 7.3$ Hz, 1H), 7.08-7.14 (m, 1H), 7.00 (d, $J = 6.9$ Hz, 2H), 5.60 (d, $J = 17.1$ Hz, 1H), 5.48 (d, $J = 17.1$ Hz, 1H), 4.69 (t, $J = 2.8$ Hz, 1H), 4.30 (d, $J = 6.0$ Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.09 (br. s., 1H), 2.73-2.84 (m, 1H), 2.54-2.62 (m, 1H), 2.38-2.47 (m, 1H), 2.26 (dd, $J = 13.1, 2.8$ Hz, 1H); ^{13}C NMR (CDCl_3 , 101 MHz): δ 173.2, 169.8, 138.0, 137.2, 136.2, 128.9, 127.4, 126.0, 125.8, 122.6, 119.9, 119.7, 110.1, 105.1, 62.3, 52.1, 50.7, 46.7, 45.7, 35.8, 33.3, 30.2; HRMS-ESI calcd for $\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 405.1814, found: 405.1802.



538b: Following Representative Procedure 7, a mixture of **233i** (12.4 mg, 0.07 mmol, 1.0 equiv), benzyl phenylhydrazine (17.4 mg, 0.09 mmol, 1.3 equiv), pyridine hydrochloride (78 mg, 0.7 mmol, 10 equiv), and pyridine

(1 mL) was stirred at 110 °C for 12 h to provide, after work-up and purification by flash chromatography (EtOAc-acetone, 100:1), **538b** (18.4 mg, 78%) as a colorless oil; R_f 0.44 (EtOAc); IR (film) ν_{\max} 2929, 1667, 1611, 1492, 1452, 1379, 1079, 729 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.50 (d, $J = 7.7$ Hz, 1H), 7.13-7.32 (m, 5H), 7.06-7.12 (m, 1H), 6.99 (d, $J = 7.0$ Hz, 2H), 5.56 (d, $J = 17.1$ Hz, 1H), 5.43 (d, $J = 17.1$ Hz, 1H), 4.64 (t, $J = 2.9$ Hz, 1H), 3.81 (s, 3H), 3.17 (dd, $J = 16.5, 6.0$ Hz, 1H), 2.94 (dd, $J = 17.7, 7.5$ Hz, 1H), 2.85 (d, $J = 17.1$ Hz, 1H), 2.78 (br. s., 1H), 2.40-2.53 (m, 2H), 2.24 (dd, $J = 12.9, 2.9$ Hz, 1H); ^{13}C NMR (CDCl_3 , 101 MHz): δ 171.7, 138.4, 137.1, 135.6, 128.8, 127.3, 126.6, 125.9, 122.4, 119.4, 118.7, 109.9, 107.2, 62.1, 51.2, 46.7, 40.8, 32.5, 29.3, 26.5; HRMS-ESI calcd for $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 347.1760, found: 347.1751.



538c: Following Representative Procedure 7, a mixture of **546** (19.9 mg,

0.09 mmol, 1.0 equiv), benzyl phenylhydrazine (22.6 mg, 0.11 mmol,

1.3 equiv), pyridine hydrochloride (101 mg, 0.9 mmol, 10 equiv), and

pyridine (1 mL) was stirred at 110 °C for 15 h to provide, after work-up and purification by

flash chromatography (EtOAc-acetone, 100:1), **538c** (24.0 mg, 70%) as a pale yellow oil; R_f

0.60 (EtOAc); IR (film) ν_{\max} 2934, 1723, 1678, 1612, 1496, 1452, 1255, 1174, 1067, 728 cm^{-1} ;

^1H NMR (CDCl_3 , 500 MHz): δ 7.43 (d, $J = 7.8$ Hz, 1H), 7.24-7.36 (m, 4H), 7.09-7.21 (m,

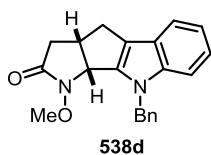
4H), 5.46 (d, $J = 17.1$ Hz, 1H), 5.36 (d, $J = 17.1$ Hz, 1H), 4.63 (d, $J = 4.3$ Hz, 1H), 4.26 (d, J

$= 4.7$ Hz, 1H), 3.81 (s, 3H), 3.65 (s, 3H), 3.44 (t, $J = 4.9$ Hz, 1H), 2.61-2.67 (m, 1H), 2.16 (d,

$J = 11.1$ Hz, 1H); ^{13}C NMR (CDCl_3 , 126 MHz): δ 174.4, 171.4, 137.4, 137.0, 136.7, 128.9,

127.6, 126.6, 126.0, 122.2, 120.3, 119.9, 109.9, 104.3, 62.9, 52.3, 51.6, 46.8, 43.7, 41.7,

32.4; HRMS-ESI calcd for $\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 391.1658, found: 391.1647.



538d: Following Representative Procedure 7, a mixture of **233f** (14.3

mg, 0.08 mmol, 1.0 equiv), benzyl phenylhydrazine (21.8 mg, 0.11

mmol, 1.3 equiv), pyridine hydrochloride (97 mg, 0.8 mmol, 10 equiv),

and pyridine (1 mL) was stirred at 110 °C for 5 h to provide, after work-up and purification

by flash chromatography (EtOAc-acetone, 100:1), **538d** (12.3 mg, 44%) as a pale yellow oil;

R_f 0.42 (EtOAc); IR (film) ν_{\max} 2930, 1699, 1612, 1452, 1380, 1299, 1057, 735 cm^{-1} ; ^1H

NMR (CDCl_3 , 400 MHz): δ 7.53 (d, $J = 7.7$ Hz, 1H), 7.25-7.34 (m, 4H), 7.21 (t, $J = 7.7$ Hz,

1H), 7.12-7.18 (m, 1H), 7.07 (d, $J = 6.9$ Hz, 2H), 5.49 (s, 2H), 5.03 (d, $J = 7.7$ Hz, 1H), 3.77

(s, 3H), 3.56-3.65 (m, 1H), 3.31 (dd, $J = 14.8, 8.5$ Hz, 1H), 2.76-2.86 (m, 2H), 2.45 (dd, $J =$

17.4, 4.5 Hz, 1H); ^{13}C NMR (CDCl_3 , 101 MHz): δ 169.1, 141.9, 141.6, 137.8, 128.7, 127.4,

126.4, 123.7, 122.3, 120.4, 119.8, 119.7, 110.7, 62.7, 59.0, 48.3, 38.5, 35.5, 32.1; HRMS-ESI
calcd for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 333.1603, found: 333.1602.

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APPENDICES

X-ray data collected from **477**

Table 21. Crystal Data and Structure Refinement for 477

Empirical Formula	C ₁₁ H ₁₇ NO ₅
Formula weight	243.26
Z	8
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	C2/c
Unit cell dimensions	$\alpha = 27.646(5) \text{ Å}$ $\beta = 6.3613(11) \text{ Å}$ $\chi = 13.531(2) \text{ Å}$
Volume	2351.7 Å ³
Density (calc)	1.374 Mg/m ³
Absorption coefficient	0.109 mm ⁻¹
F(000)	1040
Crystal size	Not recorded
θ range for data collection	1.49 to 28.29°
Limiting indices	-34 < h < 36, -8 < k < 8, -17 < l < 17
Reflections collected	10456
Independent reflections	2766 (R _{int} = 0.0476)
Completeness to $\theta = 28.29$	0.949
Refinement method	Full-matrix least squares on F ²
Data / restraints / parameters	2766 / 0 / 157
Goodness-of-fit on F ²	0.682
Final R indices [I > 2s(I)]	R1 = 0.0476, wR2 = 0.1565
R indices (all data)	R1 = 0.0673, wR2 = 0.1892
Largest diff. Peak and hole	0.25 and -0.15 e Å ⁻³

APPENDICES (continued)

X-ray Data Collected from **477****Table 22. Atomic Coordinates and Equivalent Isotopic Displacement Parameters for 477**

atom	x	y	z	Uiso*/Ueq
O11''	0.03223 (4)	0.2553 (2)	0.15281 (10)	0.0545 (4)
C7	0.08589 (6)	0.5353 (2)	0.20092 (11)	0.0415 (4)
H7	0.092	0.4767	0.2687	0.050*
O9	0.15466 (6)	0.79539 (19)	0.35623 (9)	0.0604 (4)
H9	0.1483	0.8952	0.3904	0.091*
O1	0.13666 (5)	0.8146 (2)	−0.06494 (9)	0.0642 (4)
O10'	0.00159 (5)	0.5780 (2)	0.12310 (11)	0.0619 (4)
N2	0.17425 (5)	0.8097 (2)	0.09509 (10)	0.0470 (4)
O2	0.19213 (5)	1.01433 (17)	0.08461 (10)	0.0577 (4)
C3	0.17973 (6)	0.7400 (3)	0.19903 (11)	0.0449 (4)
H3	0.2124	0.779	0.2326	0.054*
C10	0.03516 (6)	0.4657 (3)	0.15446 (12)	0.0451 (4)
C4	0.17512 (6)	0.5028 (3)	0.19940 (13)	0.0466 (4)
H4A	0.1785	0.4515	0.2676	0.056*
H4B	0.2007	0.4398	0.1673	0.056*
C8	0.09000 (6)	0.7743 (3)	0.21097 (13)	0.0479 (4)
H8A	0.0805	0.8378	0.1457	0.057*
H8B	0.0675	0.8233	0.2543	0.057*
C5	0.12509 (6)	0.4436 (2)	0.14315 (11)	0.0401 (4)
H5	0.1222	0.2901	0.1428	0.048*
C6	0.12113 (6)	0.5196 (3)	0.03459 (12)	0.0442 (4)
H6A	0.1361	0.4144	−0.0029	0.053*
H6B	0.0867	0.5259	0.0066	0.053*
C9	0.14146 (7)	0.8456 (2)	0.25331 (12)	0.0457 (4)
H9A	0.1436	0.9982	0.2451	0.055*

APPENDICES (continued)

X-ray Data Collected from **477****Table 22. Atomic Coordinates and Equivalent Isotopic Displacement Parameters for 477**
(*continued*)

atom	x	y	z	Uiso*/Ueq
C1	0.14376 (6)	0.7292 (3)	0.01744 (12)	0.0442 (4)
C11	−0.01374 (7)	0.1648 (3)	0.10874 (15)	0.0567 (5)
H11A	−0.0396	0.2234	0.1399	0.085*
H11B	−0.0127	0.0153	0.1185	0.085*
H11C	−0.0195	0.1953	0.0384	0.085*
C12	0.23969 (8)	1.0023 (4)	0.05565 (17)	0.0695 (6)
H12A	0.2584	0.8944	0.0937	0.104*
H12B	0.2561	1.1349	0.0681	0.104*
H12C	0.2365	0.9695	−0.0143	0.104*

APPENDICES (continued)

X-ray Data Collected from **477****Table 23. Atomic Displacement Parameters (\AA^2) for 477**

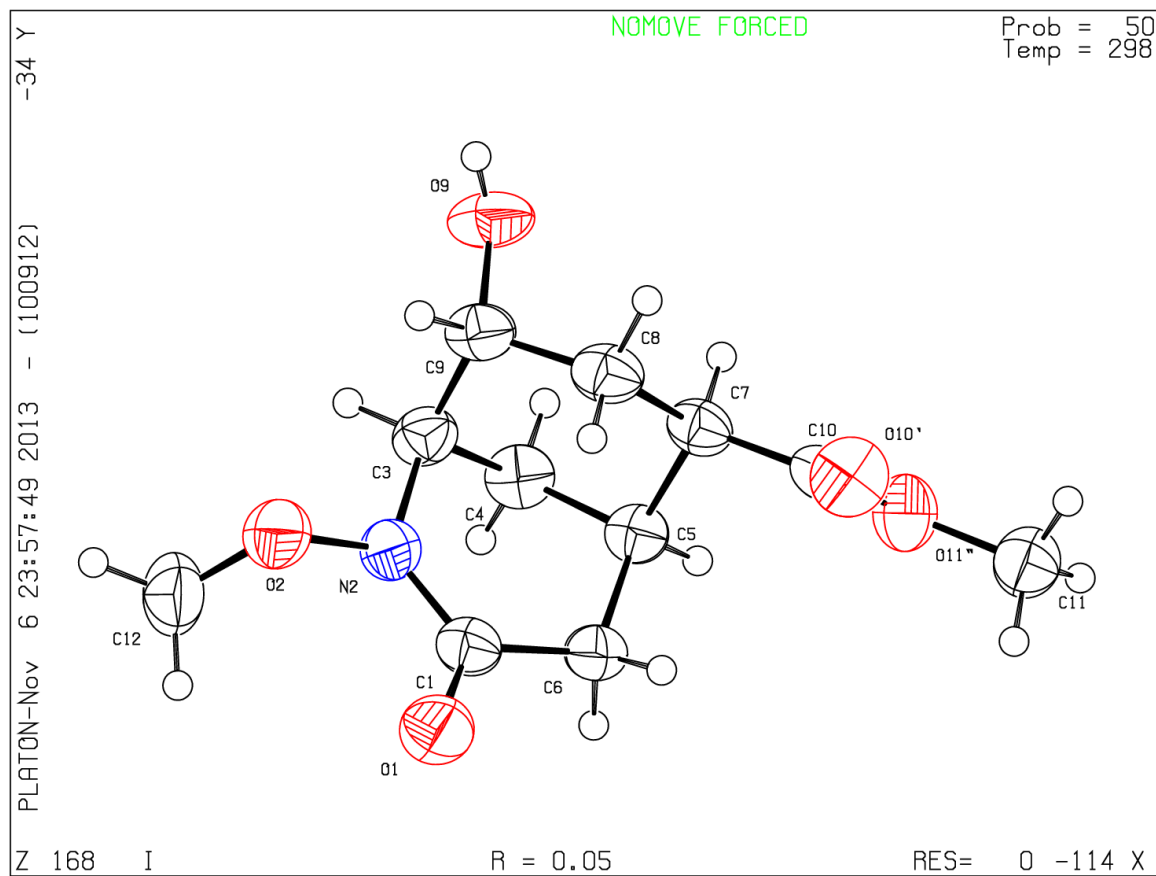
atom	U11	U22	U33	U12	U13	U23
O11''	0.0498 (7)	0.0474 (7)	0.0656 (9)	−0.0007 (5)	0.0066 (6)	0.0063 (6)
C7	0.0508 (9)	0.0389 (8)	0.0361 (8)	0.0048 (6)	0.0107 (6)	0.0055 (6)
O9	0.0976 (11)	0.0488 (7)	0.0339 (7)	0.0064 (6)	0.0068 (6)	−0.0003 (5)
O1	0.0827 (10)	0.0664 (9)	0.0410 (7)	−0.0133 (6)	0.0012 (6)	0.0132 (6)
O10'	0.0572 (8)	0.0562 (8)	0.0700 (9)	0.0132 (6)	0.0023 (6)	0.0052 (6)
N2	0.0581 (9)	0.0422 (7)	0.0414 (8)	−0.0097 (6)	0.0092 (6)	0.0014 (6)
O2	0.0776 (9)	0.0398 (7)	0.0568 (8)	−0.0104 (6)	0.0138 (6)	−0.0001 (5)
C3	0.0517 (9)	0.0445 (9)	0.0367 (8)	−0.0016 (7)	0.0007 (7)	0.0010 (6)
C10	0.0522 (9)	0.0479 (9)	0.0378 (8)	0.0055 (7)	0.0154 (7)	0.0045 (6)
C4	0.0505 (9)	0.0434 (9)	0.0446 (9)	0.0079 (7)	0.0034 (7)	0.0036 (6)
C8	0.0604 (11)	0.0404 (9)	0.0452 (9)	0.0096 (7)	0.0150 (7)	−0.0013 (6)
C5	0.0482 (8)	0.0312 (7)	0.0414 (8)	0.0056 (6)	0.0084 (6)	0.0014 (6)
C6	0.0497 (9)	0.0456 (9)	0.0385 (9)	−0.0019 (7)	0.0107 (6)	−0.0046 (6)
C9	0.0664 (10)	0.0345 (8)	0.0361 (8)	0.0029 (7)	0.0077 (7)	0.0024 (6)
C1	0.0495 (9)	0.0461 (9)	0.0377 (8)	0.0018 (7)	0.0083 (6)	0.0026 (6)
C11	0.0551 (10)	0.0576 (11)	0.0568 (11)	−0.0051 (8)	0.0063 (8)	−0.0006 (8)
C12	0.0668 (13)	0.0683 (13)	0.0728 (14)	−0.0251 (10)	0.0087 (10)	0.0073 (10)

APPENDICES (continued)

X-ray Data Collected from **477****Table 24. Geometric Parameters (Å, °) for 477**

O11"—C10	1.341 (2)	N2—O2	1.4072 (18)
O11"—C11	1.439 (2)	N2—C3	1.460 (2)
C7—C10	1.513 (2)	O2—C12	1.430 (3)
C7—C5	1.544 (2)	C3—C4	1.515 (2)
C7—C8	1.529 (2)	C3—C9	1.532 (2)
O9—C9	1.4209 (19)	C4—C5	1.521 (2)
O1—C1	1.228 (2)	C8—C9	1.519 (2)
O10'—C10	1.196 (2)	C5—C6	1.534 (2)
N2—C1	1.344 (2)	C6—C1	1.506 (2)
C10—O11"—C11	116.98 (13)	O11"—C10—C7	110.42 (13)
C10—C7—C5	110.91 (13)	C3—C4—C5	108.39 (12)
C10—C7—C8	112.30 (13)	C9—C8—C7	112.50 (13)
C5—C7—C8	111.84 (13)	C4—C5—C7	107.95 (13)
C1—N2—O2	117.49 (13)	C4—C5—C6	109.13 (13)
C1—N2—C3	126.71 (14)	C7—C5—C6	114.38 (12)
O2—N2—C3	113.05 (12)	C1—C6—C5	117.12 (13)
N2—O2—C12	109.26 (14)	O9—C9—C8	112.83 (14)
N2—C3—C4	108.02 (13)	O9—C9—C3	106.18 (13)
N2—C3—C9	110.56 (13)	C8—C9—C3	111.34 (13)
C4—C3—C9	111.74 (13)	O1—C1—N2	122.37 (15)
O10'—C10—O11"	123.25 (16)	O1—C1—C6	121.24 (15)
O10'—C10—C7	126.33 (16)	N2—C1—C6	116.27 (14)

APPENDICES (continued)

**Figure 22** X-ray crystal structure of **477**

APPENDICES (continued)

X-ray data collected from **502****Table 25. Crystal Data and Structure Refinement for 502**

Empirical Formula	C ₃₅ H ₅₀ N ₂ O ₁₀ S
Formula weight	690.84
Z	8
Temperature	296 (2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	C1c1
Unit cell dimensions	$\alpha = 43.753(12)$ Å $\beta = 14.664(4)$ Å $\chi = 11.972(3)$ Å
Volume	7651(4) Å ³
Density (calc)	1.172 Mg/m ³
Absorption coefficient	0.136 mm ⁻¹
F(000)	2896
Crystal size	Not recorded
θ range for data collection	0.9 to 28.39°
Limiting indices	$-56 < h < 58$, $-18 < k < 18$, $-15 < l < 15$
Reflections collected	33964 ($R_{\text{int}} = 0.08$)
Independent reflections	16281
Completeness to $\theta = 28.38$	0.85
Refinement method	Full-matrix least squares on F ²
Data / restraints / parameters	16281 / 2 / 865
Goodness-of-fit on F ²	0.756
Final R indices [$I > 2s(I)$]	R1 = 0.0791, wR2 = 0.1833
R indices (all data)	R1 = 0.3301, wR2 = 0.2845
Largest diff. Peak and hole	0.27 and -0.21 e Å ⁻³

APPENDICES (continued)

X-ray data collected from **502****Table 26. Atomic Coordinates and Equivalent Isotopic Displacement Parameters for 502**

atom	x	y	z	Uiso*/Ueq
S51	0.32757 (12)	0.2960 (4)	0.3137 (4)	0.1024 (16)
S2	0.23954 (13)	0.7949 (4)	0.3672 (4)	0.1081 (16)
O56	0.4579 (2)	0.3108 (8)	0.3265 (8)	0.081 (3)
O7	0.0736 (3)	1.1665 (7)	0.2170 (9)	0.087 (3)
O52	0.4950 (2)	0.6645 (8)	0.4602 (8)	0.091 (3)
O11	0.1019 (3)	0.6662 (7)	0.3594 (9)	0.096 (4)
O58	0.4651 (3)	0.1625 (8)	0.3196 (9)	0.098 (4)
O54	0.4344 (3)	0.6554 (9)	0.4570 (11)	0.109 (4)
N1	0.2135 (3)	0.8236 (8)	0.4408 (10)	0.081 (4)
N2	0.1036 (3)	1.0546 (9)	0.3000 (10)	0.074 (3)
O9	0.1352 (3)	1.1593 (9)	0.2183 (9)	0.103 (4)
N52	0.4645 (3)	0.5541 (9)	0.3808 (11)	0.080 (4)
C102	0.4133 (4)	0.5961 (11)	0.2832 (12)	0.091 (5)
C103	0.1536 (3)	1.1006 (10)	0.3989 (12)	0.063 (4)
N51	0.3572 (3)	0.3244 (12)	0.2393 (12)	0.105 (5)
O59	0.3376 (3)	0.3108 (9)	0.4220 (10)	0.115 (4)
O10	0.1117 (3)	0.7320 (8)	0.1945 (10)	0.118 (5)
C104	0.4700 (5)	0.0686 (11)	0.370 (2)	0.122 (7)
O57	0.4565 (3)	0.2324 (7)	0.4818 (10)	0.098 (4)
C105	0.0147 (4)	1.1852 (12)	0.1730 (13)	0.106 (6)
C106	0.4395 (4)	0.6003 (11)	0.3792 (11)	0.075 (5)
O6	0.2058 (3)	1.1357 (7)	0.4430 (11)	0.108 (4)
C108	0.1310 (3)	1.1109 (13)	0.2896 (16)	0.092 (6)
C109	0.1181 (3)	0.9790 (9)	0.4854 (10)	0.069 (4)
O8	0.0595 (3)	1.0212 (9)	0.1972 (12)	0.129 (5)

APPENDICES (continued)

X-ray data collected from **502****Table 26. Atomic Coordinates and Equivalent Isotopic Displacement Parameters for 502** (*continued*)

atom	x	y	z	Uiso*/Ueq
O2	0.2299 (3)	0.8158 (12)	0.2465 (10)	0.154 (6)
C110	0.2025 (4)	0.9206 (11)	0.4251 (16)	0.107 (6)
O53	0.5094 (3)	0.5172 (9)	0.4890 (11)	0.118 (5)
C112	0.1537 (4)	1.0101 (10)	0.4758 (13)	0.095 (5)
O5	0.1924 (2)	1.0909 (9)	0.2652 (9)	0.104 (4)
C113	0.5227 (4)	0.7067 (11)	0.5342 (14)	0.094 (6)
C114	0.4599 (4)	0.2246 (14)	0.3812 (16)	0.098 (6)
C93	0.4239 (4)	0.6793 (10)	0.2048 (12)	0.093 (5)
O3	0.2506 (3)	0.7071 (9)	0.3973 (13)	0.137 (5)
O60	0.3192 (3)	0.2020 (8)	0.2759 (10)	0.124 (5)
C115	0.0490 (3)	1.2073 (12)	0.1405 (13)	0.075 (4)
C40	0.1488 (4)	1.1817 (11)	0.4854 (14)	0.090 (5)
C116	0.5112 (5)	0.8081 (11)	0.5102 (17)	0.123 (7)
C117	0.4927 (4)	0.5699 (13)	0.4511 (13)	0.076 (5)
C118	0.3794 (6)	0.1901 (16)	0.1577 (19)	0.135 (8)
C119	0.1076 (4)	0.7392 (11)	0.2943 (16)	0.078 (5)
C120	0.0776 (4)	1.0818 (12)	0.2282 (14)	0.083 (5)
C121	0.4167 (4)	0.5080 (10)	0.2126 (9)	0.073 (4)
C122	0.3580 (5)	0.2733 (17)	0.1272 (15)	0.111 (7)
C123	0.4512 (4)	0.4933 (11)	0.2008 (13)	0.096 (6)
C124	0.1666 (4)	0.9248 (9)	0.4223 (11)	0.069 (4)
C125	0.2405 (4)	1.165 (2)	0.3970 (18)	0.185 (12)
C126	0.4032 (3)	0.4124 (11)	0.2545 (14)	0.095 (5)
C127	0.2621 (5)	0.4941 (12)	0.324 (2)	0.133 (7)
C128	0.2726 (4)	0.8750 (11)	0.4051 (18)	0.095 (5)

APPENDICES (continued)

X-ray data collected from **502****Table 26. Atomic Coordinates and Equivalent Isotropic Displacement Parameters for 502** (*continued*)

atom	x	y	z	Uiso*/Ueq
C129	0.2992 (4)	0.3668 (13)	0.2755 (14)	0.099 (6)
C130	0.1004 (5)	0.5702 (10)	0.3116 (14)	0.103 (6)
C131	0.2840 (4)	0.8811 (14)	0.5103 (16)	0.098 (6)
C132	0.0481 (4)	1.1724 (14)	0.0155 (14)	0.118 (7)
C133	0.3191 (3)	0.9875 (10)	0.4671 (15)	0.088 (5)
C135	0.3666 (4)	0.4216 (11)	0.2457 (12)	0.081 (5)
C136	0.1489 (5)	1.2767 (13)	0.4276 (14)	0.101 (6)
C137	0.4164 (5)	0.7680 (15)	0.262 (2)	0.143 (8)
C138	0.2845 (6)	0.3561 (15)	0.1625 (19)	0.149 (9)
C139	0.2598 (6)	0.4245 (18)	0.1509 (17)	0.148 (9)
C140	0.2790 (6)	0.9320 (15)	0.3151 (18)	0.144 (8)
C141	0.4940 (5)	0.0672 (16)	0.4700 (17)	0.136 (7)
C142	0.4345 (5)	0.0454 (13)	0.3914 (15)	0.135 (7)
C143	0.2174 (8)	0.547 (2)	0.167 (3)	0.239 (18)
C144	0.5140 (4)	0.6803 (11)	0.6557 (11)	0.090 (5)
C145	0.0706 (5)	0.5671 (13)	0.2295 (17)	0.126 (7)
C146	0.5503 (3)	0.6780 (14)	0.4910 (14)	0.117 (7)
C147	0.0904 (5)	0.5218 (12)	0.4234 (15)	0.132 (8)
C148	0.3084 (4)	0.9356 (13)	0.5518 (16)	0.117 (7)
C149	0.1699 (5)	1.3409 (15)	0.4597 (16)	0.145 (8)
C150	0.0528 (5)	1.3116 (12)	0.1524 (17)	0.119 (6)
C151	0.4727 (4)	0.0102 (13)	0.2713 (16)	0.121 (6)
C152	0.2858 (6)	0.4284 (19)	0.3521 (14)	0.146 (8)
C153	0.2095 (5)	0.7783 (14)	0.5520 (16)	0.124 (7)
C154	0.1650 (10)	0.673 (2)	0.564 (3)	0.200 (14)

APPENDICES (continued)

X-ray data collected from **502****Table 26. Atomic Coordinates and Equivalent Isotropic Displacement Parameters for 502** (*continued*)

atom	x	y	z	Uiso*/Ueq
C155	0.4040 (8)	0.8278 (15)	0.195 (3)	0.220 (14)
C156	0.2368 (10)	0.515 (2)	0.220 (2)	0.34 (2)
C157	0.1844 (6)	0.695 (2)	0.523 (3)	0.192 (15)
C158	0.3104 (8)	0.981 (2)	0.359 (2)	0.213 (14)
C159	0.1293 (4)	0.5462 (14)	0.2530 (14)	0.118 (6)
C163	0.3463 (6)	1.061 (2)	0.500 (2)	0.188 (11)
C167	0.4673 (4)	0.4706 (11)	0.3147 (12)	0.089 (5)
C168	0.1026 (3)	0.9692 (10)	0.3625 (12)	0.063 (4)
O62	0.3612 (3)	0.6380 (9)	0.2442 (11)	0.124 (5)
O61	0.3743 (3)	0.5878 (8)	0.4120 (11)	0.108 (4)
C169	0.2593 (5)	1.1692 (19)	0.4909 (17)	0.177 (10)
C170	0.1508 (4)	0.9012 (13)	0.2939 (12)	0.089 (5)
C171	0.3813 (3)	0.6112 (10)	0.3143 (13)	0.073 (4)
C172	0.1168 (4)	0.8949 (10)	0.3024 (11)	0.071 (4)
C173	0.4140 (3)	0.3976 (10)	0.3743 (11)	0.062 (4)
C174	0.4509 (4)	0.3933 (10)	0.3911 (13)	0.080 (5)
C175	0.3306 (4)	0.6393 (14)	0.262 (2)	0.159 (10)
O20	0.1084 (2)	0.8088 (7)	0.3581 (8)	0.079 (3)
C176	0.1854 (5)	1.1065 (11)	0.3522 (16)	0.122 (9)
C94	0.3169 (6)	0.717 (2)	0.205 (3)	0.259 (16)
C92	0.3979 (6)	0.168 (2)	0.071 (3)	0.215 (12)

APPENDICES (continued)

X-ray Data Collected from **502****Table 27. Atomic Displacement Parameters (\AA^2) for 502**

atom	U11	U22	U33	U12	U13	U23
S51	0.111 (4)	0.107 (4)	0.093 (4)	−0.015 (3)	0.034 (3)	0.007 (3)
S2	0.127 (4)	0.098 (4)	0.101 (4)	−0.006 (3)	0.013 (3)	−0.014 (3)
O56	0.102 (8)	0.086 (8)	0.055 (6)	−0.009 (6)	0.004 (5)	0.005 (6)
O7	0.107 (9)	0.049 (7)	0.101 (8)	−0.002 (6)	−0.015 (7)	−0.008 (6)
O52	0.077 (7)	0.097 (9)	0.098 (8)	0.001 (6)	0.009 (6)	−0.021 (7)
O11	0.131 (11)	0.069 (8)	0.088 (7)	−0.015 (7)	0.007 (7)	−0.003 (6)
O58	0.129 (10)	0.094 (10)	0.079 (7)	−0.026 (7)	0.043 (7)	−0.048 (7)
O54	0.081 (8)	0.113 (10)	0.130 (10)	0.012 (7)	0.001 (7)	0.020 (8)
N1	0.105 (9)	0.066 (8)	0.079 (8)	0.022 (7)	0.050 (7)	0.027 (7)
N2	0.084 (9)	0.079 (9)	0.059 (7)	−0.003 (8)	0.004 (7)	−0.006 (7)
O9	0.111 (9)	0.125 (10)	0.069 (7)	−0.031 (7)	−0.009 (6)	0.062 (7)
N52	0.066 (8)	0.072 (9)	0.100 (10)	0.010 (7)	−0.009 (8)	−0.019 (8)
C102	0.130 (14)	0.075 (12)	0.067 (10)	0.030 (10)	−0.003 (10)	0.006 (9)
C103	0.028 (7)	0.080 (11)	0.080 (10)	0.005 (7)	0.010 (7)	0.016 (9)
N51	0.055 (9)	0.162 (15)	0.100 (10)	−0.006 (9)	0.014 (8)	0.040 (10)
O59	0.149 (12)	0.124 (10)	0.074 (8)	−0.009 (8)	0.020 (8)	−0.012 (7)
O10	0.194 (14)	0.087 (9)	0.077 (9)	−0.007 (8)	0.037 (9)	−0.002 (6)
C104	0.147 (16)	0.043 (10)	0.19 (2)	0.007 (10)	0.081 (15)	0.008 (12)
O57	0.137 (10)	0.074 (8)	0.082 (9)	−0.003 (7)	−0.001 (8)	0.012 (6)
C105	0.102 (12)	0.139 (14)	0.084 (11)	−0.029 (10)	0.047 (9)	−0.021 (9)
C106	0.119 (13)	0.065 (10)	0.041 (8)	−0.006 (9)	0.017 (8)	−0.037 (7)
O6	0.098 (9)	0.072 (8)	0.148 (10)	0.002 (6)	−0.028 (8)	−0.004 (7)
C108	0.057 (9)	0.088 (14)	0.126 (15)	−0.007 (10)	−0.020 (11)	−0.048 (11)
C109	0.071 (9)	0.078 (8)	0.057 (8)	0.024 (7)	0.006 (7)	−0.028 (6)
O8	0.100 (9)	0.076 (9)	0.196 (13)	−0.024 (7)	−0.062 (9)	0.022 (8)

APPENDICES (continued)

X-ray Data Collected from **502****Table 27. Atomic Displacement Parameters (\AA^2) for **502** (*continued*)**

atom	U11	U22	U33	U12	U13	U23
O2	0.137 (11)	0.250 (17)	0.079 (9)	−0.039 (10)	0.030 (8)	−0.048 (9)
C110	0.070 (11)	0.061 (12)	0.185 (18)	0.025 (8)	−0.019 (11)	−0.011 (11)
O53	0.156 (12)	0.082 (9)	0.106 (9)	0.029 (8)	−0.048 (8)	−0.001 (7)
C112	0.101 (13)	0.052 (10)	0.139 (13)	0.020 (8)	0.049 (10)	0.026 (9)
O5	0.076 (7)	0.164 (11)	0.071 (7)	−0.016 (7)	−0.006 (6)	−0.010 (7)
C113	0.124 (15)	0.078 (11)	0.073 (12)	−0.020 (10)	−0.033 (11)	−0.014 (9)
C114	0.084 (13)	0.140 (18)	0.067 (11)	−0.040 (11)	−0.014 (10)	0.047 (11)
C93	0.159 (15)	0.046 (9)	0.068 (9)	−0.010 (9)	−0.021 (9)	0.008 (7)
O3	0.122 (11)	0.066 (8)	0.228 (15)	0.016 (7)	0.043 (10)	−0.008 (9)
O60	0.183 (12)	0.088 (9)	0.111 (9)	−0.034 (8)	0.061 (9)	−0.026 (7)
C115	0.048 (8)	0.097 (12)	0.081 (10)	0.011 (8)	0.008 (7)	0.025 (9)
C40	0.100 (12)	0.052 (9)	0.121 (12)	−0.007 (8)	0.035 (10)	−0.024 (9)
C116	0.157 (17)	0.042 (10)	0.157 (16)	−0.029 (10)	−0.061 (13)	−0.024 (9)
C117	0.104 (14)	0.066 (13)	0.061 (9)	−0.012 (10)	0.024 (9)	−0.017 (8)
C118	0.136 (18)	0.121 (18)	0.151 (18)	−0.014 (14)	0.022 (14)	−0.048 (14)
C119	0.103 (12)	0.050 (11)	0.083 (13)	−0.012 (8)	0.028 (10)	0.013 (10)
C120	0.079 (11)	0.061 (11)	0.104 (12)	−0.014 (9)	−0.017 (9)	0.001 (9)
C121	0.121 (12)	0.074 (11)	0.022 (6)	0.006 (9)	−0.009 (7)	0.004 (6)
C122	0.102 (15)	0.16 (2)	0.076 (13)	−0.012 (14)	0.030 (11)	−0.042 (13)
C123	0.096 (12)	0.100 (12)	0.093 (11)	0.035 (9)	0.009 (9)	−0.061 (9)
C124	0.103 (12)	0.049 (8)	0.055 (8)	−0.010 (8)	0.010 (8)	0.011 (6)
C125	0.068 (12)	0.36 (4)	0.130 (17)	0.014 (16)	0.011 (12)	0.035 (18)
C126	0.059 (9)	0.100 (12)	0.124 (13)	−0.044 (8)	−0.006 (9)	0.037 (10)
C127	0.131 (14)	0.078 (12)	0.19 (2)	0.033 (10)	−0.016 (14)	−0.008 (12)
C128	0.085 (12)	0.070 (11)	0.130 (14)	0.013 (9)	0.011 (11)	−0.011 (11)

APPENDICES (continued)

X-ray Data Collected from **502****Table 27. Atomic Displacement Parameters (\AA^2) for 502** (*continued*)

atom	U11	U22	U33	U12	U13	U23
C129	0.102 (13)	0.131 (15)	0.063 (10)	0.037 (11)	0.007 (10)	0.006 (10)
C130	0.181 (19)	0.038 (10)	0.083 (11)	0.007 (11)	−0.019 (12)	0.006 (9)
C131	0.095 (13)	0.114 (13)	0.087 (12)	0.020 (10)	0.018 (10)	0.061 (10)
C132	0.101 (12)	0.189 (19)	0.068 (11)	−0.020 (11)	0.034 (9)	0.005 (11)
C133	0.080 (9)	0.077 (9)	0.106 (13)	−0.027 (7)	−0.002 (9)	0.042 (9)
C135	0.093 (12)	0.072 (11)	0.081 (10)	−0.032 (9)	0.032 (9)	−0.009 (8)
C136	0.146 (16)	0.074 (12)	0.081 (10)	0.005 (11)	0.000 (10)	−0.021 (9)
C137	0.132 (17)	0.068 (13)	0.23 (2)	−0.011 (11)	0.041 (15)	0.022 (14)
C138	0.150 (18)	0.110 (16)	0.17 (2)	0.013 (13)	−0.065 (14)	0.022 (13)
C139	0.157 (19)	0.17 (2)	0.109 (14)	−0.086 (16)	−0.039 (14)	−0.002 (14)
C140	0.195 (19)	0.098 (15)	0.150 (18)	−0.043 (13)	0.069 (15)	0.043 (13)
C141	0.102 (13)	0.161 (19)	0.137 (14)	0.025 (12)	−0.035 (12)	0.031 (12)
C142	0.172 (18)	0.102 (13)	0.141 (15)	−0.045 (11)	0.073 (13)	−0.038 (10)
C143	0.29 (3)	0.17 (3)	0.24 (4)	0.15 (3)	−0.06 (2)	−0.05 (2)
C144	0.130 (14)	0.087 (11)	0.050 (8)	−0.025 (9)	−0.015 (8)	0.007 (7)
C145	0.147 (16)	0.088 (13)	0.131 (15)	−0.032 (11)	−0.041 (13)	0.038 (11)
C146	0.033 (8)	0.199 (17)	0.120 (12)	−0.035 (9)	0.013 (8)	−0.085 (12)
C147	0.25 (2)	0.049 (10)	0.102 (11)	−0.027 (11)	0.045 (13)	0.015 (9)
C148	0.106 (14)	0.112 (14)	0.131 (14)	−0.050 (11)	−0.006 (11)	−0.029 (11)
C149	0.175 (19)	0.124 (16)	0.126 (14)	−0.029 (14)	−0.046 (13)	−0.015 (11)
C150	0.141 (16)	0.078 (13)	0.136 (15)	−0.001 (11)	−0.001 (12)	−0.036 (11)
C151	0.123 (13)	0.109 (14)	0.135 (14)	−0.033 (10)	0.039 (11)	−0.048 (11)
C152	0.20 (2)	0.19 (2)	0.057 (10)	−0.016 (17)	0.001 (12)	−0.023 (12)
C153	0.18 (2)	0.083 (13)	0.103 (14)	0.011 (13)	−0.003 (14)	0.008 (11)
C154	0.29 (4)	0.15 (2)	0.17 (2)	0.02 (2)	0.04 (2)	−0.001 (17)
C155	0.32 (4)	0.050 (12)	0.29 (3)	−0.052 (16)	0.07 (3)	−0.028 (14)

APPENDICES (continued)

X-ray Data Collected from **502****Table 27. Atomic Displacement Parameters (\AA^2) for **502** (*continued*)**

atom	U11	U22	U33	U12	U13	U23
C156	0.55 (6)	0.30 (4)	0.15 (2)	−0.31 (4)	−0.08 (3)	−0.03 (3)
C157	0.140 (18)	0.17 (3)	0.28 (3)	0.044 (16)	0.12 (2)	0.15 (2)
C158	0.29 (4)	0.20 (3)	0.15 (2)	−0.07 (3)	0.06 (3)	0.05 (2)
C159	0.109 (13)	0.149 (15)	0.098 (11)	0.053 (11)	0.018 (9)	−0.028 (10)
C163	0.16 (2)	0.21 (3)	0.19 (2)	−0.042 (18)	−0.03 (2)	−0.018 (18)
C167	0.151 (14)	0.064 (10)	0.049 (9)	0.005 (9)	−0.010 (9)	−0.026 (8)
C168	0.074 (11)	0.050 (9)	0.065 (9)	0.004 (8)	0.002 (8)	0.006 (8)
O62	0.112 (11)	0.149 (12)	0.107 (9)	0.029 (8)	−0.015 (8)	0.039 (8)
O61	0.128 (10)	0.078 (8)	0.121 (10)	0.003 (6)	0.027 (8)	−0.023 (7)
C169	0.140 (17)	0.30 (3)	0.093 (12)	−0.008 (17)	−0.007 (13)	−0.029 (14)
C170	0.090 (11)	0.116 (14)	0.060 (10)	−0.002 (10)	0.001 (9)	−0.008 (9)
C171	0.066 (10)	0.092 (11)	0.064 (10)	0.001 (8)	0.024 (9)	0.016 (8)
C172	0.093 (11)	0.059 (10)	0.059 (8)	−0.012 (9)	−0.001 (8)	0.017 (7)
C173	0.064 (9)	0.073 (9)	0.048 (8)	0.009 (7)	0.005 (7)	−0.004 (7)
C174	0.092 (12)	0.041 (9)	0.112 (12)	0.012 (8)	0.032 (10)	−0.012 (8)
C175	0.044 (10)	0.124 (14)	0.30 (3)	0.055 (9)	−0.020 (14)	0.043 (16)
O20	0.096 (8)	0.063 (7)	0.081 (7)	−0.012 (6)	0.029 (6)	−0.001 (6)
C176	0.19 (2)	0.068 (11)	0.089 (12)	−0.061 (12)	−0.086 (14)	0.018 (10)
C94	0.18 (2)	0.33 (3)	0.28 (3)	0.11 (2)	0.12 (2)	0.14 (3)
C92	0.158 (19)	0.25 (3)	0.25 (3)	0.038 (17)	0.09 (2)	−0.01 (2)

APPENDICES (continued)

X-ray Data Collected from **502****Table 28. Geometric Parameters (Å, °) for 502**

S51—O59	1.348 (12)	O53—C117	1.130 (18)
S51—O60	1.488 (12)	C112—C124	1.536 (19)
S51—C129	1.651 (17)	O5—C176	1.13 (2)
S51—N51	1.691 (14)	C113—C146	1.42 (2)
S2—O3	1.412 (13)	C113—C144	1.58 (2)
S2—O2	1.500 (14)	C113—C116	1.59 (2)
S2—N1	1.561 (12)	C93—C137	1.52 (3)
S2—C128	1.888 (18)	C115—C150	1.54 (2)
O56—C114	1.423 (19)	C115—C132	1.58 (2)
O56—C174	1.483 (16)	C40—C136	1.56 (2)
O7—C120	1.260 (17)	C118—C92	1.41 (3)
O7—C115	1.476 (17)	C118—C122	1.56 (3)
O52—C117	1.394 (18)	C119—O20	1.274 (19)
O52—C113	1.566 (18)	C121—C123	1.543 (19)
O11—C119	1.360 (17)	C121—C126	1.619 (19)
O11—C130	1.518 (18)	C123—C167	1.51 (2)
O58—C114	1.21 (2)	C124—C170	1.67 (2)
O58—C104	1.509 (19)	C125—C169	1.33 (2)
O54—C106	1.268 (15)	C126—C173	1.48 (2)
N1—C153	1.51 (2)	C126—C135	1.60 (2)
N1—C110	1.508 (18)	C127—C152	1.43 (3)
N2—C120	1.423 (19)	C127—C156	1.62 (4)
N2—C108	1.47 (2)	C128—C131	1.32 (2)
N2—C168	1.462 (18)	C128—C140	1.41 (2)
O9—C108	1.14 (2)	C129—C152	1.45 (3)
N52—C106	1.286 (18)	C129—C138	1.45 (2)

APPENDICES (continued)

X-ray Data Collected from **502****Table 28. Geometric Parameters (Å, °) for 502** (*continued*)

N52—C117	1.45 (2)	C130—C159	1.54 (2)
N52—C167	1.468 (18)	C130—C145	1.56 (2)
C102—C171	1.50 (2)	C130—C147	1.61 (2)
C102—C106	1.55 (2)	C131—C148	1.39 (2)
C102—C121	1.56 (2)	C133—C158	1.31 (3)
C102—C93	1.63 (2)	C133—C148	1.38 (2)
C103—C176	1.55 (3)	C133—C163	1.63 (3)
C103—C108	1.58 (2)	C136—C149	1.35 (2)
C103—C112	1.615 (19)	C137—C155	1.28 (3)
C103—C40	1.60 (2)	C138—C139	1.47 (3)
N51—C135	1.48 (2)	C139—C156	1.90 (5)
N51—C122	1.54 (2)	C140—C158	1.60 (4)
O10—C119	1.228 (19)	C143—C156	1.12 (4)
C104—C151	1.47 (2)	C153—C157	1.66 (4)
C104—C141	1.52 (3)	C154—C157	1.07 (4)
C104—C142	1.63 (2)	C167—C174	1.66 (2)
O57—C114	1.232 (19)	C168—C172	1.47 (2)
C105—C115	1.61 (2)	O62—C171	1.224 (17)
O6—C176	1.409 (17)	O62—C175	1.38 (2)
O6—C125	1.71 (2)	O61—C171	1.281 (16)
C109—C168	1.570 (18)	C170—C172	1.50 (2)
C109—C112	1.635 (19)	C172—O20	1.490 (16)
O8—C120	1.224 (17)	C173—C174	1.61 (2)
C110—C124	1.57 (2)	C175—C94	1.43 (3)
O59—S51—O60	119.5 (8)	O53—C117—N52	127.6 (17)
O59—S51—C129	109.8 (9)	O53—C117—O52	127.6 (18)

APPENDICES (continued)

X-ray Data Collected from **502****Table 28. Geometric Parameters (Å, °) for 502** (*continued*)

O60—S51—C129	109.9 (10)	N52—C117—O52	104.8 (15)
O59—S51—N51	105.5 (8)	C92—C118—C122	112 (2)
O60—S51—N51	104.3 (8)	O10—C119—O20	130.8 (15)
C129—S51—N51	107.0 (9)	O10—C119—O11	122.7 (16)
O3—S2—O2	119.5 (10)	O20—C119—O11	106.5 (16)
O3—S2—N1	110.6 (8)	O8—C120—O7	127.2 (17)
O2—S2—N1	109.5 (8)	O8—C120—N2	116.1 (15)
O3—S2—C128	105.6 (9)	O7—C120—N2	115.8 (14)
O2—S2—C128	104.4 (10)	C123—C121—C102	107.9 (12)
N1—S2—C128	106.3 (8)	C123—C121—C126	107.1 (12)
C114—O56—C174	119.5 (13)	C102—C121—C126	119.7 (12)
C120—O7—C115	123.4 (13)	N51—C122—C118	103.6 (16)
C117—O52—C113	118.9 (13)	C167—C123—C121	109.2 (12)
C119—O11—C130	121.1 (14)	C112—C124—C110	115.3 (12)
C114—O58—C104	118.3 (14)	C112—C124—C170	114.6 (12)
C153—N1—C110	117.7 (13)	C110—C124—C170	110.2 (12)
C153—N1—S2	121.7 (11)	C169—C125—O6	103.8 (16)
C110—N1—S2	115.1 (10)	C173—C126—C135	107.8 (12)
C120—N2—C108	114.0 (14)	C173—C126—C121	109.4 (11)
C120—N2—C168	119.4 (13)	C135—C126—C121	107.2 (12)
C108—N2—C168	125.9 (14)	C152—C127—C156	137 (2)
C106—N52—C117	127.1 (14)	C131—C128—C140	127.4 (19)
C106—N52—C167	122.9 (13)	C131—C128—S2	119.3 (16)
C117—N52—C167	109.9 (13)	C140—C128—S2	112.6 (16)
C171—C102—C106	117.1 (13)	C152—C129—C138	119.2 (18)
C171—C102—C121	113.2 (14)	C152—C129—S51	123.6 (15)
C106—C102—C121	109.6 (12)	C138—C129—S51	116.6 (16)

APPENDICES (continued)

X-ray Data Collected from **502****Table 28. Geometric Parameters (Å, °) for 502** (*continued*)

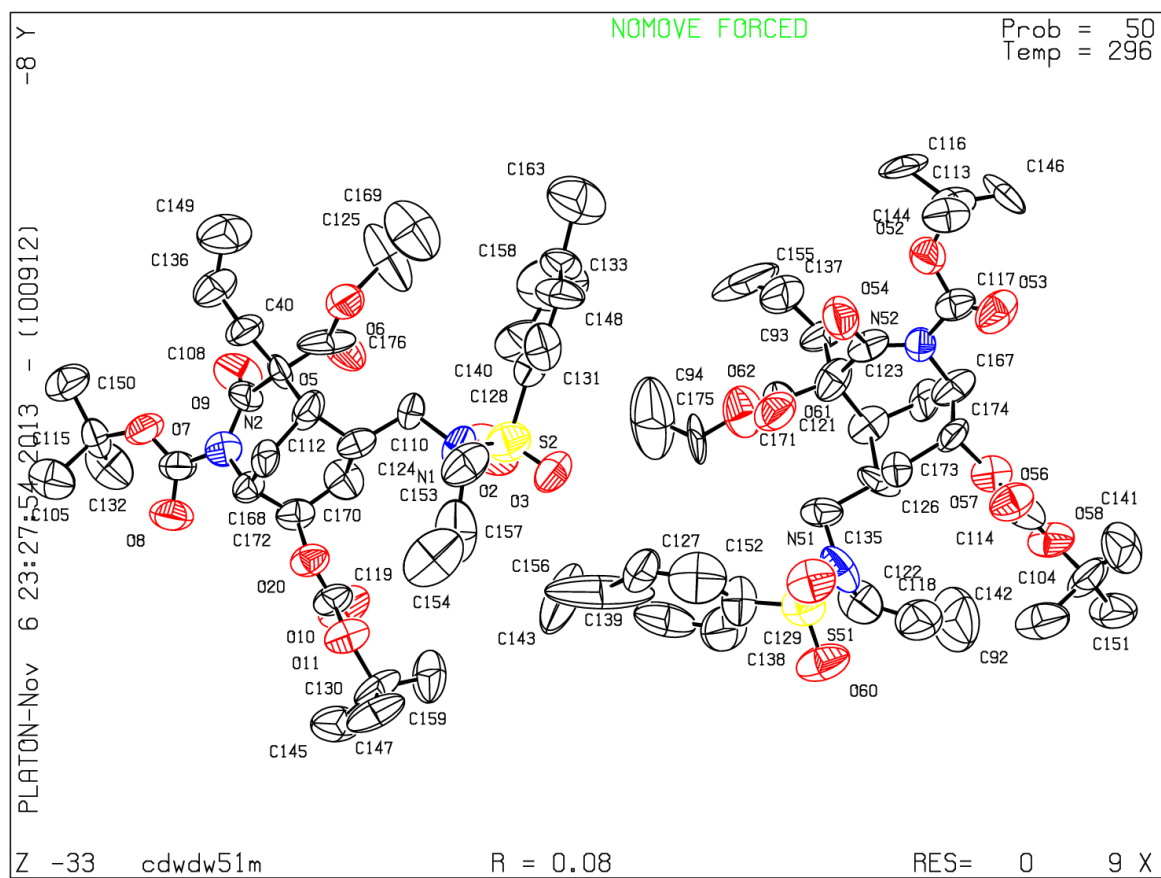
C171—C102—C93	110.7 (13)	O11—C130—C159	112.0 (16)
C106—C102—C93	99.7 (13)	O11—C130—C145	105.7 (14)
C121—C102—C93	105.2 (12)	C159—C130—C145	112.3 (15)
C176—C103—C108	102.3 (12)	O11—C130—C147	95.8 (12)
C176—C103—C112	107.2 (11)	C159—C130—C147	125.0 (15)
C108—C103—C112	121.5 (13)	C145—C130—C147	103.6 (16)
C176—C103—C40	111.5 (13)	C128—C131—C148	126.5 (16)
C108—C103—C40	110.8 (11)	C158—C133—C148	126.4 (18)
C112—C103—C40	103.6 (11)	C158—C133—C163	115 (2)
C135—N51—C122	119.1 (14)	C148—C133—C163	118.5 (17)
C135—N51—S51	115.5 (12)	N51—C135—C126	101.1 (12)
C122—N51—S51	114.6 (12)	C149—C136—C40	122.0 (17)
C151—C104—O58	103.4 (16)	C155—C137—C93	114 (2)
C151—C104—C141	121.7 (17)	C139—C138—C129	106 (2)
O58—C104—C141	112.9 (16)	C138—C139—C156	148.0 (19)
C151—C104—C142	98.7 (16)	C128—C140—C158	103.7 (19)
O58—C104—C142	98.6 (14)	C133—C148—C131	110.7 (15)
C141—C104—C142	118.0 (17)	C127—C152—C129	126.8 (18)
O54—C106—N52	122.1 (15)	N1—C153—C157	105.4 (17)
O54—C106—C102	113.8 (15)	C143—C156—C127	161 (4)
N52—C106—C102	124.1 (12)	C143—C156—C139	117 (3)
C176—O6—C125	110.2 (15)	C127—C156—C139	82 (2)
O9—C108—N2	126.9 (15)	C154—C157—C153	132 (4)
O9—C108—C103	123.5 (15)	C133—C158—C140	121 (2)
N2—C108—C103	109.4 (16)	N52—C167—C123	104.3 (12)
C168—C109—C112	107.1 (11)	N52—C167—C174	102.2 (11)
N1—C110—C124	110.3 (12)	C123—C167—C174	117.2 (13)

APPENDICES (continued)

X-ray Data Collected from **502****Table 28. Geometric Parameters (Å, °) for 502** (*continued*)

C124—C112—C103	114.4 (12)	N2—C168—C172	110.5 (12)
C124—C112—C109	101.0 (11)	N2—C168—C109	111.8 (12)
C103—C112—C109	108.3 (11)	C172—C168—C109	111.1 (11)
C146—C113—C144	123.0 (16)	C171—O62—C175	123.1 (15)
C146—C113—C116	118.6 (17)	C172—C170—C124	106.4 (12)
C144—C113—C116	107.3 (15)	O61—C171—O62	119.9 (14)
C146—C113—O52	108.5 (13)	O61—C171—C102	119.4 (14)
C144—C113—O52	100.7 (13)	O62—C171—C102	120.4 (14)
C116—C113—O52	92.9 (12)	C168—C172—O20	106.0 (12)
O57—C114—O58	135.5 (18)	C168—C172—C170	116.8 (13)
O57—C114—O56	111.0 (19)	O20—C172—C170	111.6 (12)
O58—C114—O56	113.4 (15)	C126—C173—C174	110.8 (11)
C137—C93—C102	107.2 (15)	O56—C174—C173	102.6 (11)
O7—C115—C150	106.0 (13)	O56—C174—C167	98.7 (11)
O7—C115—C132	114.4 (13)	C173—C174—C167	112.4 (12)
C150—C115—C132	113.7 (14)	O62—C175—C94	107.9 (19)
O7—C115—C105	114.2 (12)	C119—O20—C172	113.9 (12)
C150—C115—C105	105.8 (13)	O5—C176—O6	124 (2)
C132—C115—C105	102.6 (12)	O5—C176—C103	130.1 (15)
C136—C40—C103	111.8 (13)	O6—C176—C103	105.4 (17)

APPENDICES (continued)

**Figure 23** X-ray crystal structure of **502**

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