CYCLIC ENAMINONES: METHODOLOGY DEVELOPMENT, TOTAL SYNTHESIS, AND LIBRARY CONSTRUCTION

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THIS WORK IS DEDICATED TO MY PARENTS, YOJIRO & MACHIKO.

ABSTRACT

The cyclic enaminone lies at the core of this entire doctoral work. It possesses exceptionally versatile reactivities, and can thus be utilized in the synthesis of various alkaloids. The first chiral-pool approach to synthesize enaminones was reported in 2006 from the Georg group. However, partial racemization was observed in some cases. Also, homologated amino acids were synthesized or purchased as a starting material. To address these issues a novel strategy, that retained the use of amino acids was sought.

We found that enaminones can be synthesized using a ketene cyclization. In this approach, a pendant enamine moiety underwent a nucleophilic addition to a ketene generated by the Wolff rearrangement of a diazoketone. The diazoketone can be synthesized from *α*-amino acid in a one-pot procedure. Although this approach utilizes *α*-amino acids and provides enantiopure enaminones, the solubility of amino acids as well as the use of diazomethane to prepare diazoketone became major obstacles to the scalable synthesis of various enaminones.

In this regard, alternative methods to synthesize the diazoketones were explored. We found that diazoketones could be obtained from three readily available components: a primary amine, an alkyne, and bromo diazoacetone. Although the incorporation of chirality was not achieved, a wide variety of enaminones were synthesized in two steps from commercially available compounds, providing a facile access to an enaminone library.

Enantiospecific syntheses of (–)-(5*S*,8*R*,9*S*)-5-(3-furyl)-8-methyl-octahydroindolizin and its C8-epimer were accomplished using our enaminone chemistry. The devised synthetic routes are conventional but reliable and scalable, providing access to Nuphar alkaloids in 9 steps from *N*-Boc-(L)-proline. This work led to the correction of multiple prior publications. We were able to disclose the bindings of the major isomer to the central nervous system receptors.

Although phenanthropiperidines are promising anti-cancer agents due to their potency, their neurological toxicities thwart therapeutic use. Assuming that the side-effects are caused by the blood brain barrier permeation of phenanthropiperidines due to their extremely lipophilic nature, endeavors to prepare a polar phenanthropiperidine library were made. Specifically, the synthesis of hydroxylated phenanthroquinolizidines was attempted. However, most of those compounds were found to be unstable.

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List of Abbreviations

Ac	acetyl
ACN	azobis-cyclohexanecarbonitrile
AFP	alpha-fetoprotein
Ag	silver
AIBN	azobisisobutyronitrile
Alpha	Adrenergic receptor α
Ar	aryl
BBB	blood-brain barrier
Beta	Adrenergic receptor β
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
BZP	GABA benzodiazepine receptor
CAN	ammonium cerium (IV) nitrate
Cbz	carbobenzyloxy
CNS	central nervous system
Co	cobalt
Cp	cyclopentadienyl
Cr	chromium
D	Dopamine receptor
d	doublet
d.r.	diastereomeric ratio
DA	dopamine
DAT	dopamine active transporter
DCC	N,N'-dicyclohexylcarbodiimide
DCM	dichloromethane
dCK	deoxycytidine kinase
DIAD	diisopropyl azodicarboxylate

DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DOR	delta opioid receptor
e.r.	enantiomeric ratio
EDCI	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
EI	electron ionization
EtOAc	ethyl acetate
EtOH	ethanol
FDA	food and drug administration
GABA	gamma aminobutyric acid
GCMS	gas chromatography mass spectrometry
GPCR	G-protein coupled receptor
H	Histamine receptor
h	hour
HBD	hydrogen bond donor
HIF-1	hypoxia-inducible factor I
HIR	humoral immune response
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRP	horseradish peroxidase
HT	5-hydroxytryptamine receptor
HU	hydroxyurea
HWE	Horner-Wadsworth-Emmons
IBX	2-iodobenzoic acid
i-Pr	isopropyl
i.p.	intraperitoneal
i.v.	intravenous
IR	infrared

KD	dissociation constant
KOR	kappa opioid receptor
LAH	lithium aluminum hydride
LDA	lithium diisopropyl amide
LPS	lipopolysaccharide
M	muscarinic receptor
m	multiplet
min	minutes
MCF-7	Michigan Cancer Foundation - 7
MDR	multidrug resistant
Me	methyl
MeOH	methanol
MOR	mu opioid receptor
MRP	multidrug resistance protein
Ms	mesyl
MW	molecular weight / microwave
NBS	*N*-bromosuccinamide
NCI	National Cancer Institute
NET	norepinephrine transporter
NIMH	National Institute of Mental Health
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
PDSP	psychoactive drug screening program
Ph	phenyl
PIFA	(bis(trifluoroacetoxy)iodo)benzene
PMP	p-methoxyphenyl
PNS	peripheral nervous system
PSA	polar surface area
q	quartet
rac	racemic
rt	room temperature

s	singlet
s-Bu	*sec*-butyl
SAR	structure-activity relationship
SERT	serotonin transporter
t	triplet
t-Bu	*tert*-butyl
TBAF	tetra-*N*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMS	trimethylsilyl
TsOH	toluenesulfonic acid
V	vasopressin receptor

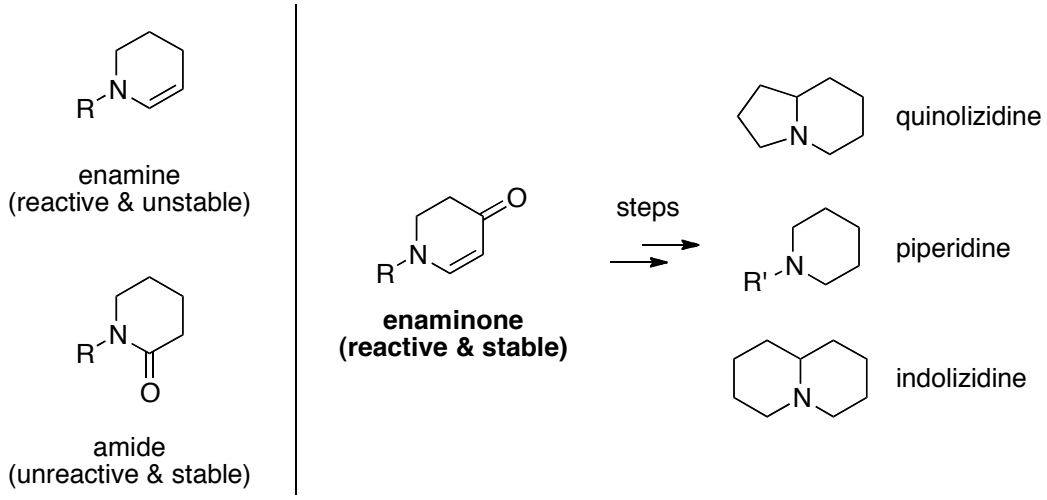
Chapter 1 THE ENAMINONE CHEMISTRY

1.1 Introduction

Piperidine, indolizidine, and quinolizidine alkaloids display important biological properties and therefore have been frequent targets for synthetic chemistry efforts.[1] It is well known that monocyclic and bicyclic enaminones (2,3-dihydropyridin-4(1*H*)-ones) can serve as superb intermediates for their synthesis (Scheme 1-1).[2]

The chemical property of these enaminones is quite different from those of enamines or amides. Enamines, known as neutral nucleophiles, have been used in a number of reactions.[3] However, they are quite unstable under hydrolytic and oxidative conditions. On the other hand, an amide is a stable functionality and easily isolated. Due to this stability, it typically requires very strong reagents to functionalize an amide.

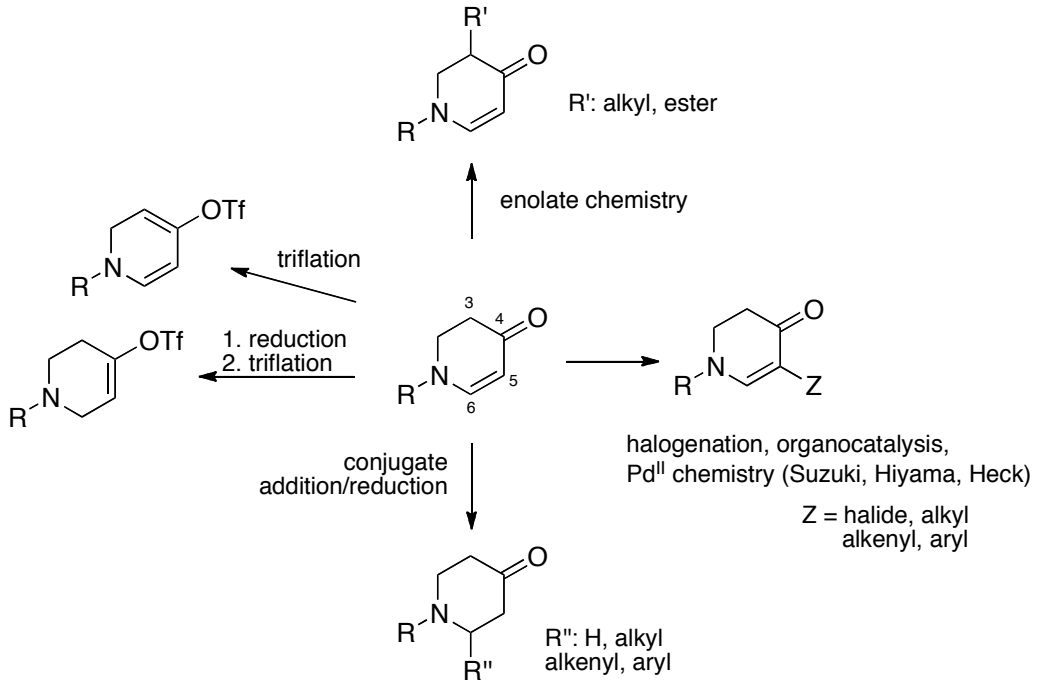
Scheme 1-1. Enaminone



The reactivity and stability of enaminones lie between enamines and amides. Unlike enamines, enaminones are stable even under hydrolytic and oxidative conditions, but still maintain nucleophilicity to a certain degree, which clearly differs from amide. This stable but reactive property is what makes enaminones such an attractive intermediate in the synthesis of alkaloids.

A number of transformations for enaminones are known (Scheme 1-2).[2] The C3 position can be functionalized by conventional enolate chemistry.[4] The nucleophilic additions of soft nucleophiles such as cuprates take place at the C6 position.[4b, 5] Triflation can be practiced in two different ways.[6] The functionalization of the C5 position has been extensively studied. Halogenation was traditionally known, which was utilized in Pd-catalyzed cross-couplings.[7] However, recent developments realized direct C−H coupling under Suzuki, Hiyama, and Heck conditions, as well as an organocatalytic reaction.[8] The details of C5 functionalization will be discussed in the section **1.3**.

Scheme 1-2. Selected transformations of the enaminone



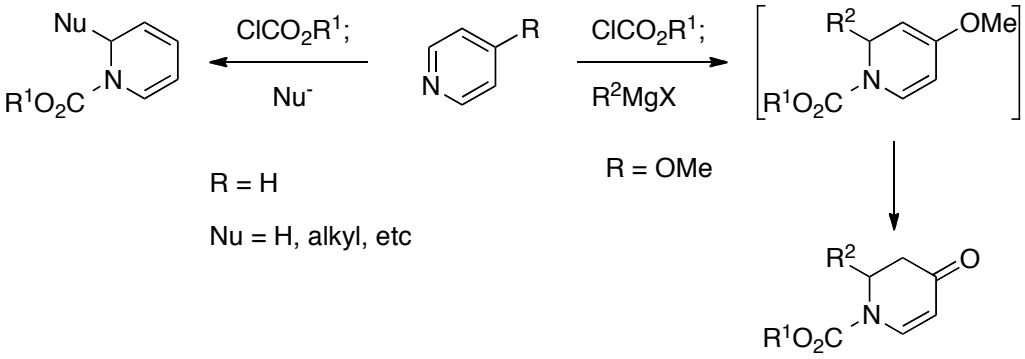
1.2 Various synthetic approaches to enaminones

1.2.1 Nucleophilic addition to pyridinium salts

Pyridines, if possible, serve as the most ideal source of functionalized piperidines since they already contain the appropriate carbon skeleton. It has been known that upon treatment with alkyl chloroformate, the resulting acylpyridinium salt can be subjected to nucleophilic addition reactions such as hydride reduction or a Grignard addition (Scheme 1-3).[9]

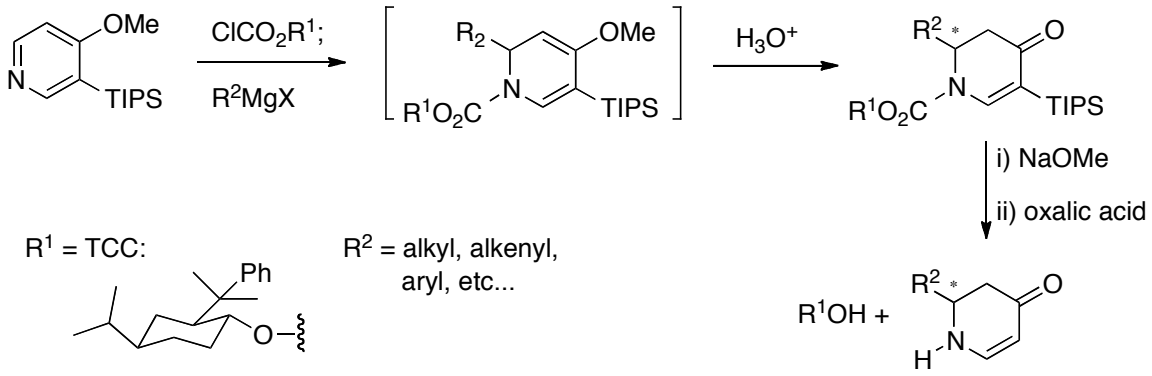
Based on this observation, Comins utilized 4-methoxypyridine as a starting material.[2a] A nucleophilic addition occurred to acylpyridinium salt, and upon hydrolysis of the enol ether, the substituted enaminone was prepared.[10]

Scheme 1-3. Derivatizations of pyridines



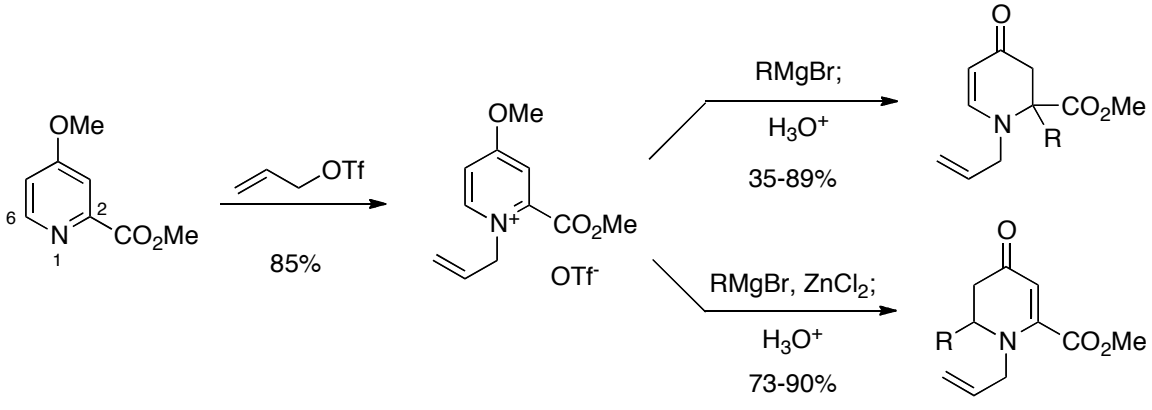
His approach was applied to the synthesis of enantioenriched enaminones (Scheme 1-4).[11] It was found that chiral pyridinium salt from TCC chloroformate regulated the trajectory of the nucleophile, affording the enaminone with excellent diastereoselectivity.[5, 12] A TIPS group was a crucial substituent to attain high stereoselectivity. Using this method, Comins demonstrated a number of alkaloid syntheses, proving that this chemistry is reliable and scalable.

Scheme 1-4. Comins' procedure to obtain enaminones in enantio-enriched form

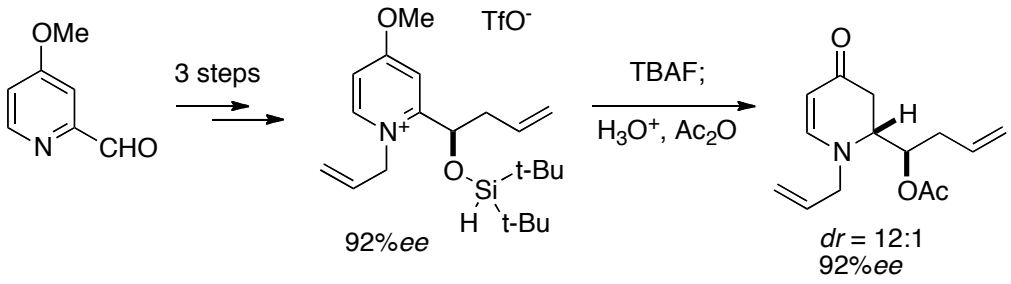


Donohoe has reported a few variants of Comins' method. Employing a 4-methoxylpyridine and an ester group at the C2 position, nucleophilic additions were achieved in a regioselective manner (Scheme 1-5).[13] Grignard reagents were found to add to the C2 position presumably because of the hard character of nucleophiles. On the other hand, soft zinc nucleophiles added to the C6 position, which is probably a more soft and less sterically hindered site.

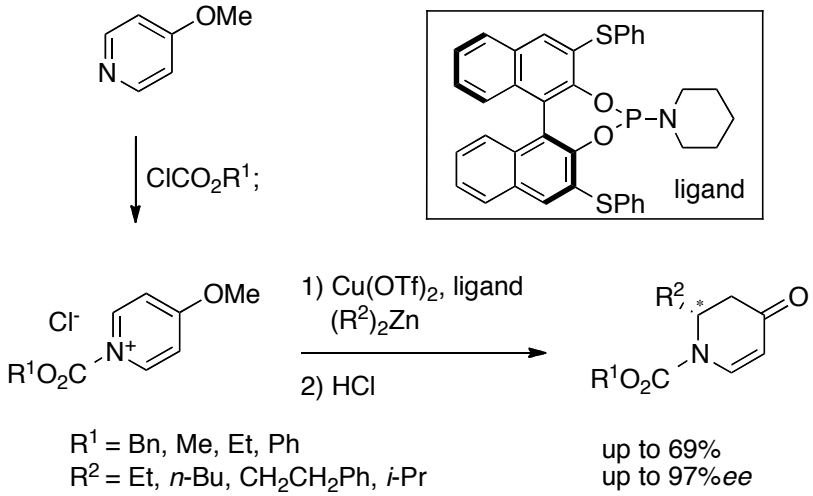
Scheme 1-5. Regioselective nucleophilic addition to pyridinium salts



Scheme 1-6. Internal hydride delivery to pyridinium salts



Scheme 1-7. Catalytic enantioselective addition to acylpyridinium salts



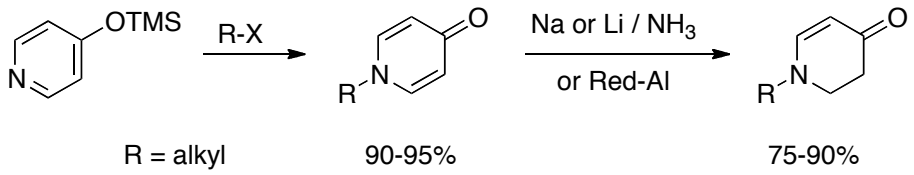
In 2011, he also reported the reduction of pyridinium salts by internal hydride delivery (Scheme 1-6).[14] The starting material, the pyridinium salts containing a dialkylhydroxysilane group, was prepared from the functionalized pyridine in three steps. Upon treatment with TBAF, hydride was delivered to the C2 position in a stereospecific fashion, followed by an acidic work up and acetate protection to afford the enaminone. In a typical enaminone synthesis from

pyridinium salts, carbon nucleophiles such as a Grignard reagent are required. In this respect, hydride reduction is rare and worthy of attention. Recently, Feringa reported the catalytic enantioselective addition of zinc reagents to acylpyridinium salts (Scheme 1-7).[15]

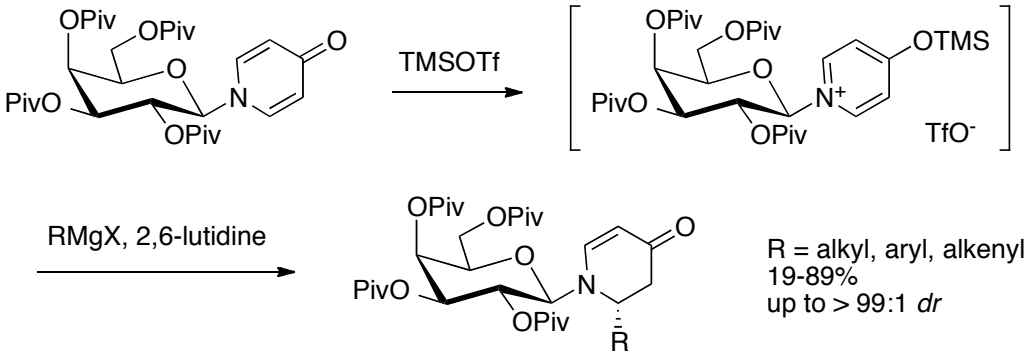
Comins' approach has a fairly wide scope and good scalability, although silyl substituted pyridines and TCC are not easily accessible. Feringa's method employs the simple starting material, but zinc nucleophiles are limited to a few alkyl zincate, affording enaminones with an excellent enantioselectivity in only modest yields.

1.2.2 Nucleophilic addition to 4-pyridones

Scheme 1-8. Reduction of 4-pyridone

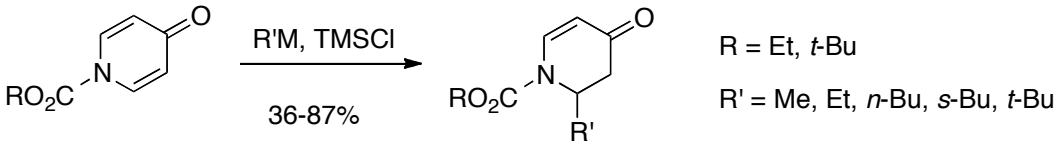


Scheme 1-9. Diastereoselective addition of Grignard reagents to 4-pyridone

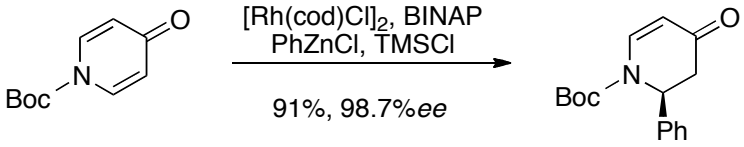


Considering the nucleophilic addition to pyridinium salts, it is quite natural to presume the possible utility of 4-pyridone due to the structural similarity between the two intermediates. Indeed, there are several successful examples of converting 4-pyridones to enaminones. Simple reduction of 4-pyridone under Birch conditions or using Red-Al has been known to provide enaminones (Scheme 1-8).[16] As an application of this method, Kunz reported a diastereoselective addition of Grignard reagents using the *O*-pivaloylated galactosyl group as a chiral auxiliary (Scheme 1-9).[17]

Scheme 1-10. Conjugate additions to *N*-acyl-4-pyridones



Scheme 1-11. Enantioselective addition of a zincate to *N*-Boc-4-pyridone



Recently, the nucleophilic addition of various organometallic reagents was systematically investigated by Dieter using *N*-acyl-4-pyridones (Scheme 1-10).[18] Zincates and cuprates were found to be viable nucleophiles. Interestingly, they have also reported an enantioselective addition of an ethyl group to a pyridone under very similar conditions to ones by Feringa. Corey showed that the addition

of zincate to *N*-Boc-4-pyridone could be achieved with superb enantioselectivity by using a Rh catalyst and BINAP (Scheme 1-11).[19]

Kunz' and Dieter's approaches equally show good scopes. However, in Kunz's method, the removal of galactosyl group requires acidic conditions, and is typically carried out after the 1,4-reduction of an enaminone due to the vulnerability of enaminones in acidic conditions. On the other hand, Diether's method uses carbamates for *N*-substitution, which can be removed under basic condition without difficulty. Although Corey's reaction excels in yield and enantioselectivity, no subsequent investigation was followed after this one specific example.

1.2.3 Hetero Diels-Alder reaction

Enaminones can be synthesized by one of the classic transformations, that is the Diels-Alder reaction (Scheme 1-12). With the aid of a catalyst, imines and dienes undergo [4 + 2] cycloaddition to form the enaminone structure. Due to its excellent reactivity, the Danishefsky's diene is commonly used.[20]

Scheme 1-12. Hetero Diels-Alder reaction to synthesize enaminones

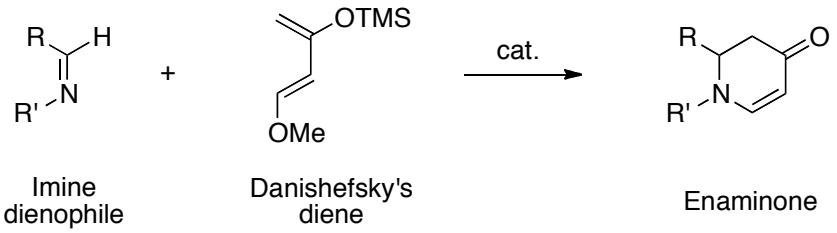
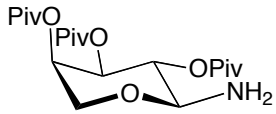
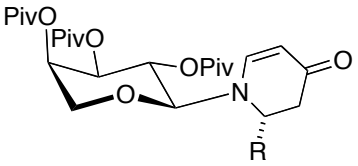
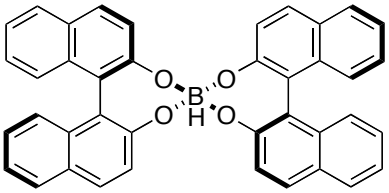
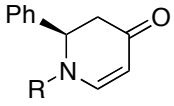
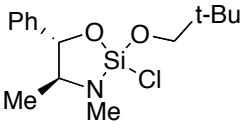


Table 1-1. Diastereoselective and non-catalytic enantioselective hetero Diels-Alder reactions

chemist	catalysts/chiral auxiliary	product
Kunz	$ZnCl_2$ 	 R = alkyl, aryl 49-96% up to 99:1 *dr*
Yamamoto		 R = Bn 78%, 86%*ee* R = (*S*)-PhMeCH, 64%, 99%*de*
Leighton		 R = aryl, alkyl R' = Ar 33-85% 45-92%*ee*

Kunz employed an arabinopyranosylamine as a chiral auxiliary to obtain the enaminone diastereoselectively (Table 1-1).[21] Upon cleavage of the pyranosyl moiety, this enaminone was converted to (*S*)-anabasin in a few steps. Yamamoto showed that his Brønsted acid-assisted chiral Lewis acid (BLA) exhibits excellent stereoselectivity in this transformation.[22] It is hypothesized that boron forms an *N*-chelation with the imine dienophile, and this transition state assembly is stabilized by hydrogen bonding between a proton and a hydroxyl group of binaphthol. Leighton utilized his silicon Lewis acid to promote the hetero Diels-Alder reaction to give the enaminone scaffold.[23] Hydrazons were used as dienophiles in this reaction.

Among three methodologies, Leighton's approach gives a relatively better scope and yields. However, all three suffer from the removal of *N*-substituents,

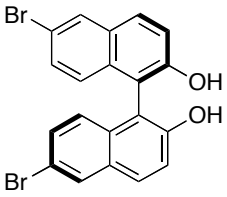
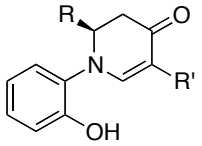
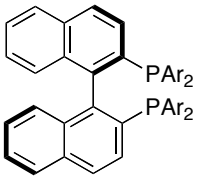
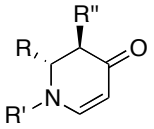
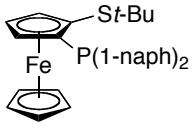
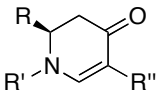
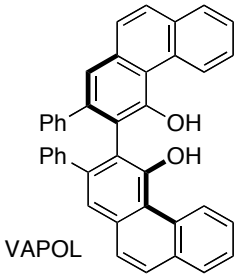
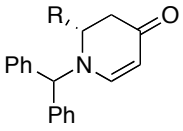
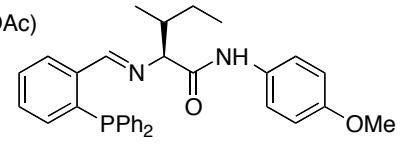
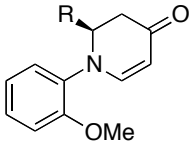
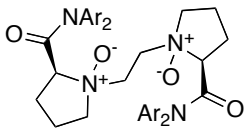
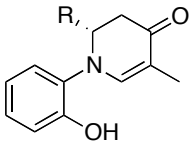
being unable to provide *N*-H enaminones without retaining the enaminone structure.

The first catalytic enantioselective hetero Diels-Alder reaction to construct the enaminone structure was reported by Kobayashi in 1998 (Table 1-2).[24] He found that the Zr-binaphtol complex facilitated the cycloadditions with good to excellent chiral inductions. In the same year, Jørgensen also reported a catalytic enantioselective synthesis of enaminones from an activated tosyl imine using the Cu-phosphine system.[25] The use of a simple tosyl imine for the reaction, however, waited for Carretero's report in 2004, where the Cu-ferrocene complex was found to give satisfactory yields and enantioselectivities.[26]

Based on Yamamoto's work, efforts to develop a catalytic enantioselective reaction with a boron catalyst were continued. In 2007, Wulff succeeded in the development of the catalytic version of Yamamoto's reaction by using $B(OPh)_3$ and VAPOL.[27] Hoveyda reported Ag-catalyzed cycloadditions between arylimines and dienes, affording enaminones.[28] The loading of Ag and amino acid-derived ligand can be as small as 1 mol%, which makes this reaction the most efficient to date. Another amino acid-derived ligand was found to provide good enantioselectivity. Feng prepared this ligand from proline, and synthesized disubstituted enaminones in enantio-enriched form.[29] In this reaction, no reaction was observed when phenoic hydroxyl group was methylated. Thus, it is suggested that both the nitrogen of imine and phenoic hydroxyl groups have coordination to the metal center, creating a good chiral environment for the reaction.

Among the enantioselective hetero Diels-Alder reactions, Hoveyda, Wolff, and Carretero's methods provide good enantioselectivities although it is only when Rs are aryl group that the reactions work with good selectivities. As for the manipulation of *N*-substituents, none of the products can be easily functionalized. However, Ts, PMP, SO_2PMP, and benzyl groups at the *N*-position of the enaminones from Jorgensen, Carretero, and Wolff's approaches can be removed reductively or by hydrogenolysis after the 1,4-reduction of enaminones.

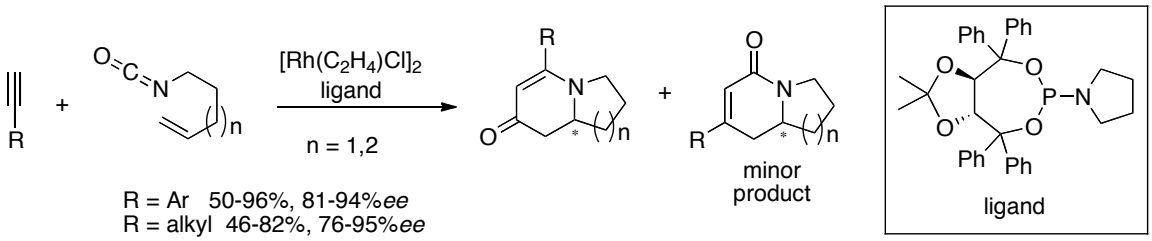
Table 1-2. Catalytic enantioselective hetero Diels-Alder reactions

chemist	catalysts		product	
Kobayashi	Zr^{IV}			R = alkyl, aryl R' = H, Me 47-98% 64-93%*ee*
Jorgensen	Cu^{I}			23-93% 58-91%*ee*
			R = CO_2Et, Ph R' = Ts, PMP	R" = H, Me
Carretero	Cu^{I}			
			R = aryl R' = Ts, SO_2PMP R" = H, Me	39-90% 76-97%*ee*
Wulff	$B(OPh)_3$			0-90% 73-93%*ee*
		VAPOL	R = aryl, alkyl	
Hoveyda	Ag(OAc)			78->98% 88-95%*ee*
			R = aryl	
Feng	$Sc(OTf)_3$			41-92% 71-90%*ee*
		Ar = 2,6-diisopropylphenyl	R = aryl	

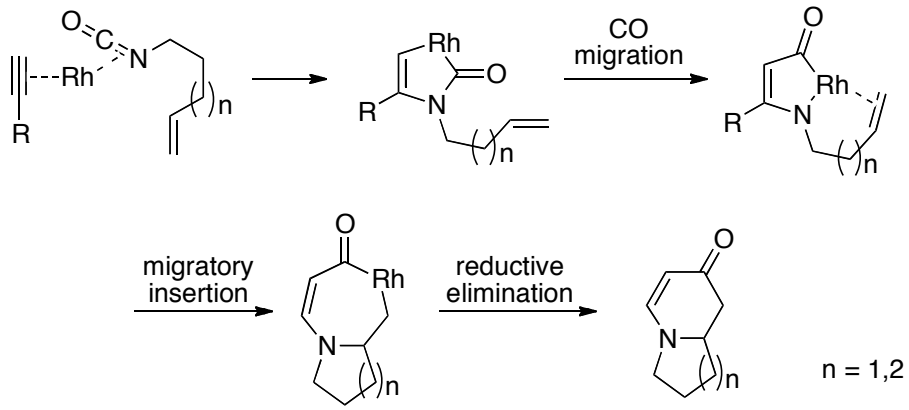
1.2.4 Rh-catalyzed [2 + 2 + 2] cycloaddition

Rovis developed a novel [2 + 2 + 2] cycloaddition catalyzed by a Rh complex to generate the enaminone scaffold (Scheme 1-13).[30] In their early work using a Rh/phosphine system, dimerization of the terminal alkyne was observed. With the condition using Rh and phosphoramidite, the dimerization was suppressed, and mono-substituted enaminone could be synthesized with satisfactory enantioselectivity. (+)-Lasubine II was synthesized efficiently by taking advantage of this methodology.

Scheme 1-13. Rh-catalyzed [2 + 2 + 2] cycloaddition



Scheme 1-14. Postulated mechanism of Rh-catalyzed [2 + 2 + 2] cycloaddition

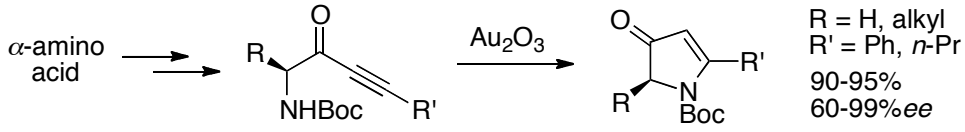


The proposed mechanism starts with an oxidative cyclization of the alkyne and the isocyanate, forming the 5-membered rhodacycle (Scheme 1-14). A CO-migration occurs to give an enaminone structure, followed by migratory insertion on the pendant olefin. Lastly, a reductive elimination to form a C−C bond gives the enaminone product.

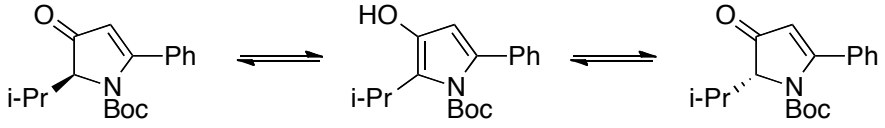
This method worked best when aryl alkynes were used. When alkyl alkynes were used, the amide products became major instead of the enaminone products. When diaryl alkynes were used, although the products were racemic, disubstituted enaminones could be obtained, which is a unique point of the methodology.

1.2.5 Gold-catalyzed ynone cyclization

Scheme 1-15. Au-catalyzed ynone cyclization to afford 5-membered enaminones



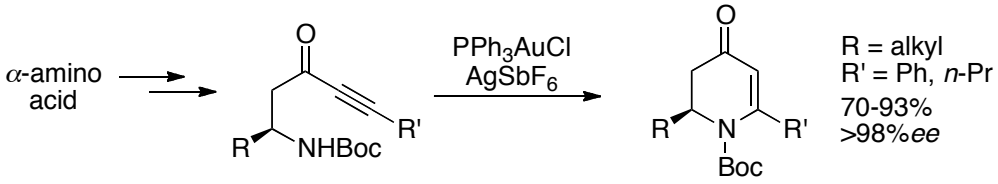
Scheme 1-16. Mechanism of racemization



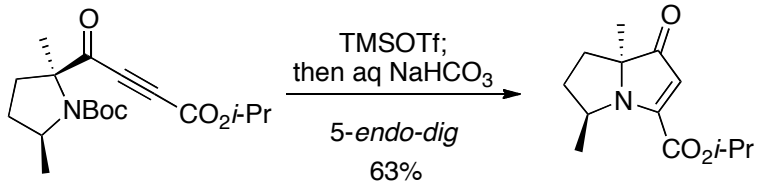
Gouault reported a concise cyclization of the *N*-Boc amino ynone to provide a 5-membered enaminone by using a Au catalyst (Scheme 1-15).[31] The

initial condition using AuCl as a catalyst completely racemized the enaminone product, presumably due to a keto-enol equilibrium (Scheme 1-16). After screening additives and catalysts, Au_2O_3 was selected for the catalyst of this transformation to give enaminones in good yields with retention of chirality from amino acids.

Scheme 1-17. Au-catalyzed ynone cyclization to give 6-membered enaminone



Scheme 1-18. 5-*endo-dig* cyclization of the activated ynone



This Au-catalyzed cyclization was also applied to construct the 6-membered enaminone scaffold (Scheme 1-17).[32] The lack of racemization was confirmed by HPLC analysis. The use of *N*-Boc group makes this reaction quite attractive since it can be easily removed. Interestingly, cyclization of the ynone to form a 5-membered enaminone was recently reported without any catalyst (Scheme 1-18).[33] Although specific details of this cyclization were not provided, one can speculate that the terminal *i*-Pr ester activates the ynone to a great

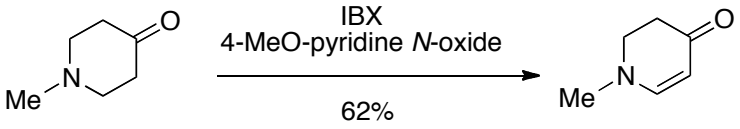
extent so that simple deprotection leads to a 5-*endo*-*dig* cyclization, and also prevents an intermolecular dimerization reaction.

1.2.6 Miscellaneous work

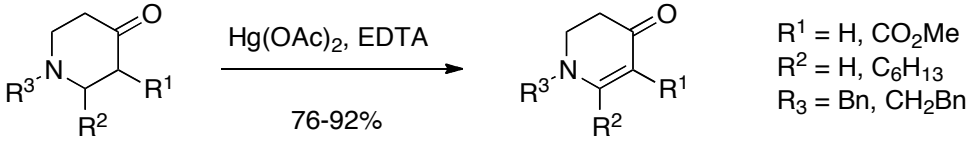
1.2.6.1 Direct oxidation of 4-piperidone

Although it has not been fully explored, one of the simplest methods to synthesize enaminones is to oxidize 4-piperidones. Nicolaou showed the oxidation of *N*-methyl-4-piperidone by IBX.[34] The use of transition metals is also effective for this transformation.[35] Padwa reported the oxidation using $Hg(OAc)_2$, which seemingly has a relatively wide scope.[36] Most recently, Pd-catalyzed aerobic dehydrogenation of cyclic ketones was reported by Stahl.[37] *N*-Boc and *N*-methyl-4-piperidones were found to be viable substrates in this dehydrogenation, affording enaminones.

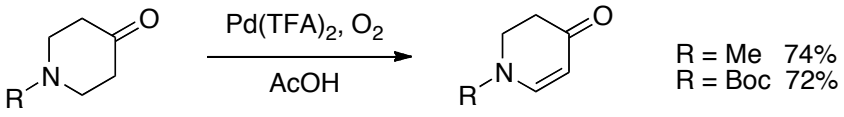
Scheme 1-19. Oxidation of 4-piperidone by IBX



Scheme 1-20. Oxidation of 4-piperidones by $Hg(OAc)_2$



Scheme 1-21. Aerobic dehydrogenation of 4-piperidones

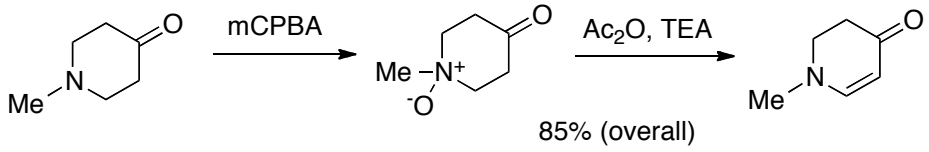


Although piperidones are quite available starting materials, the oxidation to enaminones were shown in only a few examples, which place the scope and synthetic utility of the method into question.

1.2.6.2 Oxidation of 4-piperidone via *N*-oxide formation

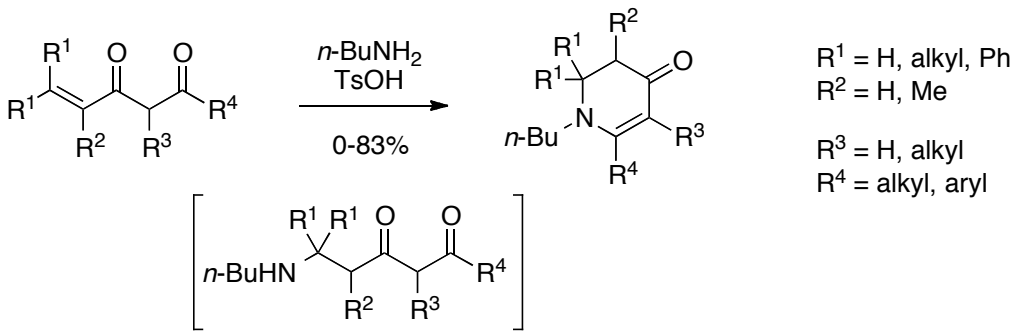
Without the aid of transition metals, *N*-methyl-4-piperidone was oxidized by the Polonovski reaction.[38] First, the piperidone was oxidized to *N*-oxide by mCPBA. This *N*-oxide was protected with an acetate, rendering it a good leaving group. Subsequent elimination of AcOH would provide an iminium species, which was then converted to the enaminones.

Scheme 1-22. Oxidation of 4-piperidone in two steps



1.2.6.3 Condensation of primary amine and diketone

Scheme 1-23. Synthesis of enaminones from a primary amine and diketones



In 2009, Burnell showed that enaminones could be synthesized from a primary amine and diketones.[39] Although this methodology does not have wide scope, it is worth noting since this new disconnection allows the formation of the enaminone scaffold from a primary amine and diketones, a reaction that has been underutilized.

1.3 Georg's enaminone chemistry

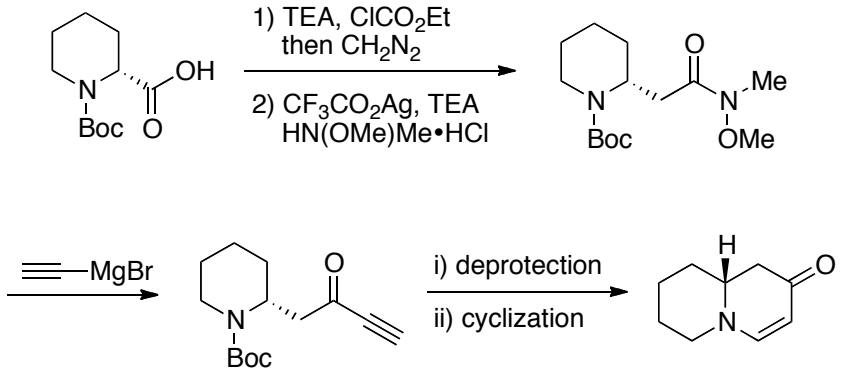
As summarized above, there are multiple methods to synthesize various enaminones in enantio-enriched form. However, each approach suffers from at least one drawback. In using Comins' approach, although scalable, the chiral auxiliary is not readily available and has to be recovered and recycled. Hetero Diels-Alder reactions, on the other hand, utilize a variety of chiral sources that are quite accessible. Only a few types of enaminones can be synthesized with good enantioselectivity, however. Rovis' Rh-catalyzed cycloaddition generally gives good enantioselectivity, but alkynes are limited to aryl alkynes and a few alkyl alkynes. Also, isocyanate was prepared from acid via the Curtius rearrangement and purified by distillation prior to the cycloaddition.

Given the advantages and disadvantages of contemporary synthetic methods, our attention turned to using a chiral pool approach to utilize amino acids as starting materials. The following section is a summary of the enaminone chemistry conducted in the Georg group.

1.3.1 Synthesis of enaminones

1.3.1.1 Ynone cyclization[40]

Scheme 1-24. Protocol to form the enaminone from the *N*-Boc amino acid



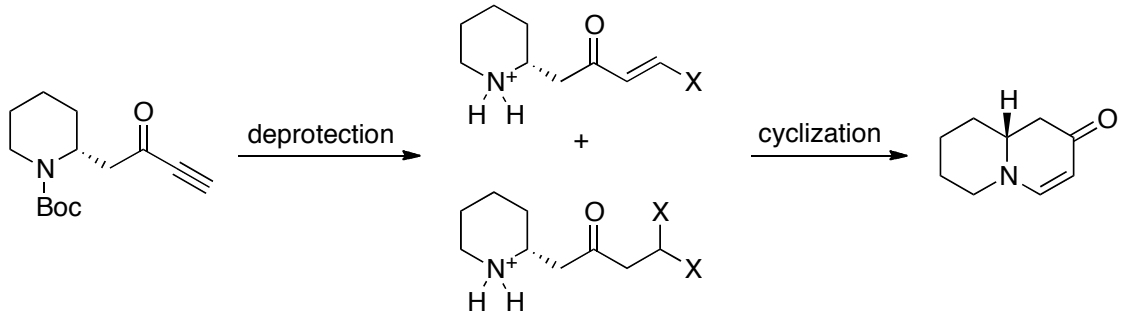
i) deprotection	ii) cyclization	yield (%)
TFA, CH_2Cl_2	CH_2Cl_2, aq.$NaHCO_3$	30
TFA, CH_2Cl_2	CH_2Cl_2, K_2CO_3	0
TFA, CH_2Cl_2	THF, K_2CO_3	0
TFA, CH_2Cl_2	CH_2Cl_2, H_2O, K_2CO_3	38
4 N HCl/dioxane	CH_2Cl_2, K_2CO_3	0
4 N HCl/dioxane	THF, K_2CO_3	0
4 N HCl/dioxane	CH_2Cl_2, H_2O, K_2CO_3	74
4 N HCl/dioxane	THF, H_2O, K_2CO_3	75
4 N HCl/dioxane	MeOH, K_2CO_3	87
TMS-I, CH_2Cl_2	MeOH, K_2CO_3	95

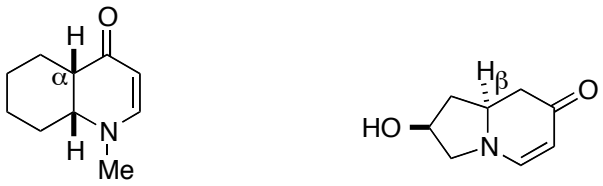
The initial attempt to synthesize enaminones was to cyclize the corresponding amino ynone via a 6-*endo*-*dig* fashion (Scheme 1-24). Although the intermolecular Michael addition to ynones is well known, the intramolecular variant had not been reported despite the fact that cyclization is a favorable transformation according to Baldwin's rules.

The investigation started by synthesizing a simple 6,6-enaminone structure. *N*-Boc pipecolic acid was converted to the homologated Weinreb amide via the Wolff rearrangement. This amide was reacted with an ethynyl Grignard reagent to furnish the *N*-Boc amino ynone. The conditions for deprotection of the Boc group and subsequent cyclization were screened. The desired quinolizidine system was obtained by treating the ynone with HCl or TMS-I, followed by K_2CO_3 in MeOH. The chiral HPLC analysis revealed that the *er* of the product was 97:3 when HCl was used for the deprotection.

Considering the results of the screening, apparently halides play an important role in this protocol since TFA only gave modest, if any, yields. Based on this observation, the mechanism via halide activation was proposed (Scheme 1-25). It was speculated that under the deprotection condition, vinylogous acid halides formed as intermediates, possibly preventing intermolecular reactions.

Scheme 1-25. Speculated mechanism of ynone cyclization





dr = 80:20
(racemization at α-position)

dr = 86:14
(racemization at β-position)

Figure 1-1. Examples of racemized enaminones (TMS-I for the deprotection).

When investigating the scope of this method, however, severe racemizations were observed in some cases (Figure 1-1). For example, the enaminone derived from hydroxyl proline was racemized during the cyclization, giving 86:14 as a *dr* ratio. Since the proline-derived enaminones are useful indolizidine scaffolds, this racemization could jeopardize the usefulness of the chiral pool approach.

1.3.1.2 Reaction optimization[41]

Given the short period of time for the cyclization, racemization is likely to take place during the Boc deprotection step. Since racemization was observed on two positions (*α* & *β*), two different pathways were proposed (Scheme 1-26).

One possible mechanism is a retro-Mannich reaction, cleaving the C−C bond and racemizing the *α*-stereocenter. The other path is a retro-Michael reaction, cleaving the C−N bond and racemizing the *β*-stereocenter. Assuming that strong acidity in the deprotection step is responsible for these racemizations, a wide variety of acids were screened (Table 1-3). Among the acids tested, formic acid was found to be the mildest. The cyclization was successful using this formic acid and NaI as an external halide source. Under these conditions, racemization was minimized, affording the enantio-enriched enaminone product.

Scheme 1-26. Proposed mechanisms for the racemization

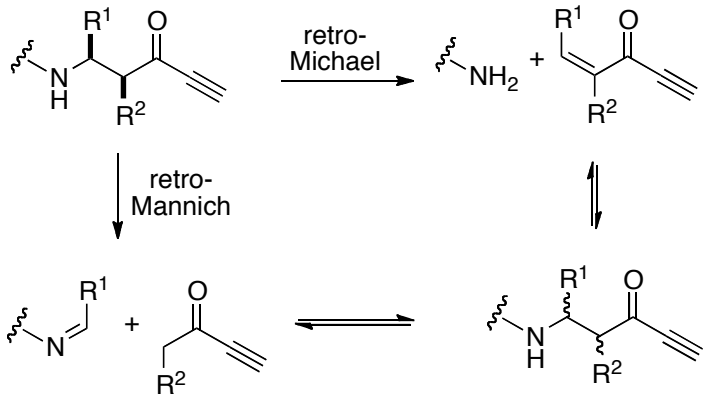
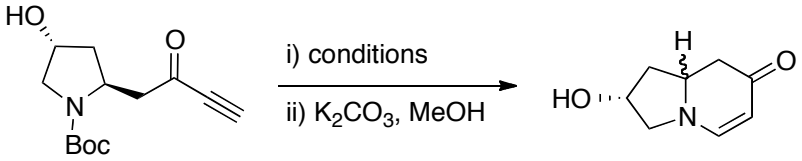


Table 1-3. Optimization of deprotection condition to suppress racemization



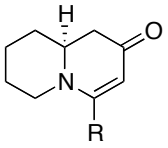
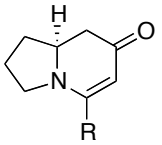
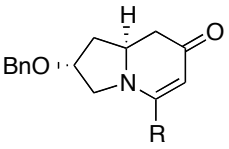
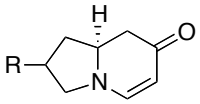
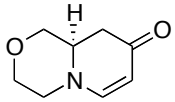
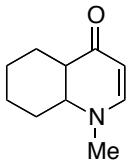
conditions	yield (%)
4 N HCl/dioxane	77 (85:15)
TFA	31 (67:33)
TFA/CH_2Cl_2 (1:1)	18 (88:12)
1 N HCl/ether	36 (67:33)
TESOTf, 2,6-lutidine, CH_2Cl_2	21 (83:17)
TMS-I (3 equiv), CH_2Cl_2, 0 °C	99 (75:25)
HCO_2H	0
NaI (3 equiv), HCO_2H	93 (> 95:5)

1.3.1.3 Scope of the reaction

A series of enaminones including bicyclic and monocyclic systems were prepared using the optimized protocol (Table 1-4, Table 1-5). The condition

using formic acid and NaI greatly suppressed the racemization in most cases. However, this condition was ineffective for the cyclization of substituted ynones, leading to *β*-racemization. The strategy allowed the synthesis of several seven-membered enaminones as well (Table 1-6). Although a decrease of yields was observed as anticipated, there has been no general method to synthesize seven-membered enaminones. In this regard, this protocol has a unique advantage.

Table 1-4. Substrate scope of bicyclic enaminones

	R	method	yield	*er* or *dr*
	H	A	87	97:3
		B	90	> 98:2
	Me	A	87	73:27
		B	80	73:27
	Ph	A	91	58:42
		B	85	69:31
	H	A	89	70:30
		B	96	98:2
	Me	A	87	
	Ph	A	89	
	H	A	94	67:33
		B	92	> 95:5
	Me	A	87	63:37
		B	94	68:32
	Ph	A	85	63:37
		B	88	60:40
	α-OH	A	77	85:15
		B	93	> 95:5
		C	94	96:4
	β-OH	A	60	60:40
		B	95	92:8
		C	70	86:14
		A	80	
		B	95	
	*cis*	A	96	80:20
		B	83	94:6
		C	80	67:33
	trans	A	99	> 95:5
		B	82	> 95:5

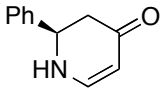
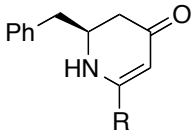
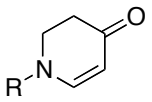
Isolated yields are specified. *er* and *dr* were determined by HPLC and ^{1}H-NMR respectively.

A: (i) 4 N HCl/dioxane, 15 min, (ii) K_2CO_3, MeOH

B: (i) NaI (3 equiv), formic acid, 6-24 h, (ii) K_2CO_3, MeOH

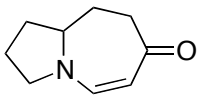
C: (i) TMS-I, CH_2Cl_2, (ii) K_2CO_3, MeOH

Table 1-5. Substrate scope of monocyclic enaminones

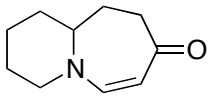
	R	method	yield	*er*
		A B	50 50	> 99:1 > 99:1
	H	A	92	> 95:5
	Me	A	96	> 95:5
	H	A B	70 92	
	CH_2Ph	A B	50 86	
	Ph	A B	50 70	

Isolated yields are specified. *er* was determined by HPLC .
A: (i) 4 N HCl/dioxane, 15 min, (ii) K_2CO_3, MeOH
B: (i) NaI (3 equiv), formic acid, 6-24 h, (ii) K_2CO_3, MeOH

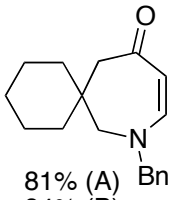
Table 1-6. Substrate scope of seven-membered enaminones



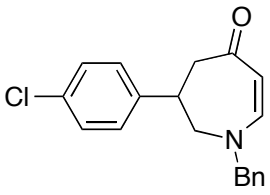
60% (A)
64% (B)



64% (A)
63% (B)



81% (A)
84% (B)



66% (A)
65% (B)

Isolated yields are specified.
A: (i) 4 N HCl/dioxane, 15 min, (ii) K_2CO_3, MeOH
B: (i) NaI (3 equiv), formic acid, 6–24 h, (ii) K_2CO_3, MeOH

1.3.1.4 Mechanistic studies

Considering the mechanism of cyclization, two pathways were proposed after the formation of vinylogous acid chloride (Figure 1-2). Initially, a simple 6-*endo*-*trig* cyclization followed by HCl liberation was proposed. However, when the reaction was carried out in bulky alcoholic (*s*-BuOH, *i*-PrOH) or non-nucleophilic solvents (CH_2Cl_2, THF), the reaction was significantly impaired. This observation was suggestive of an alternative mechanism (pathway B), in which the solvent ROH displaces chloride and leads to 6-*exo*-*trig* cyclization.

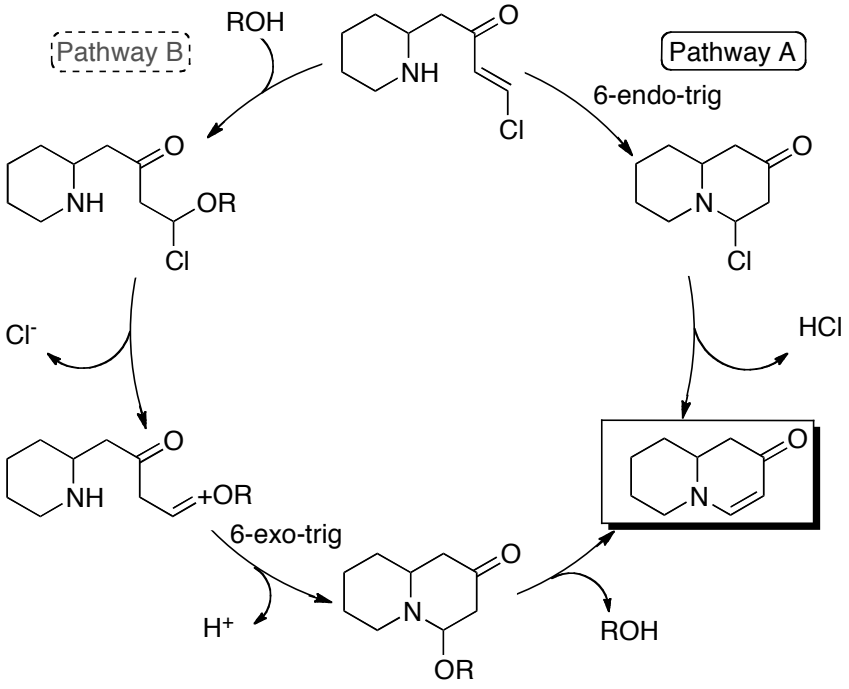
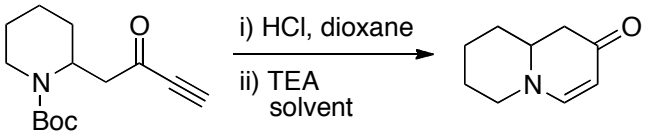


Figure 1-2. Two possible pathways for cyclization.

In an attempt to gain information of whether or not alcohol is necessary in this cyclization, the cyclization was conducted using TEA as a base in three different solvents (Scheme 1-27). These conditions successfully provided the

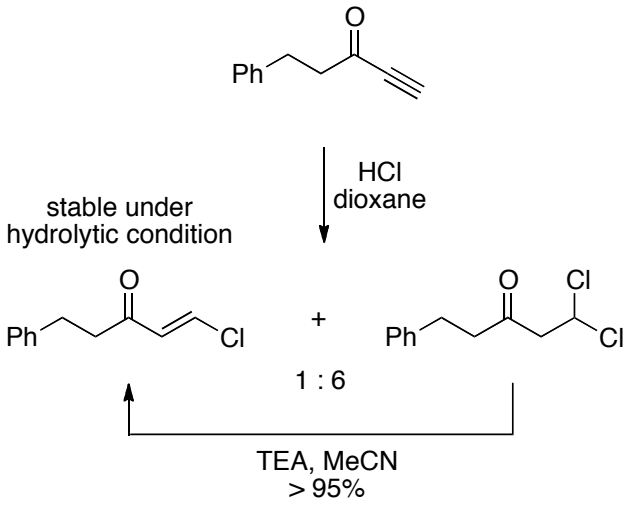
enaminone compound, suggesting that a nucleophilic solvent is not necessary. To rule out the possibility of residual water promoting the cyclization, a ynone without the amine group was prepared (Scheme 1-28). The ynone was treated with HCl, and two intermediates were confirmed with a ratio of 1:6. The two species were subjected to basic conditions, and the vinylogous acid chloride was observed as a sole product. Upon addition of excess water, this compound remained intact. These results strongly suggest that a trace amount of water does not promote the cyclization.

Scheme 1-27. Ynone cyclization using TEA as a base



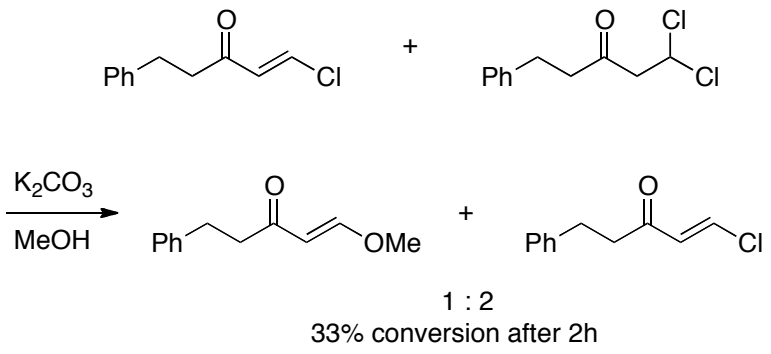
solvent: MeOH, CH_3CN, DMSO

Scheme 1-28. Treatment of ynone with HCl



Further exploring the mechanism, the two intermediates were treated with K_2CO_3 in MeOH (Scheme 1-29). After 2 h, only 33% of the conversion was detected, suggesting that the addition of MeOH to vinylogous acid chloride is much slower than the cyclization. Thus, it is reasonable to assume that the cyclization takes a 6-*endo*-*trig* mode (pathway A).

Scheme 1-29. Treatment of the two intermediates with K_2CO_3 in MeOH



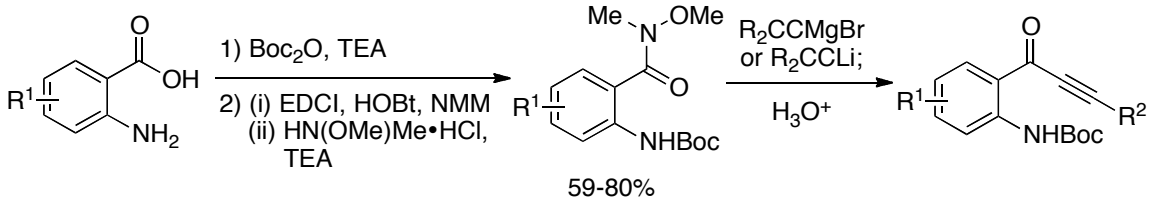
1.3.1.5 Application to the synthesis of quinolones[42]

The ynone cyclization strategy was applied to the synthesis of a quinolone library. The synthesis of the ynone started from anthranilic acids, which was protected with a Boc group and coupled with the amine to give Weinreb amides in one flask (Scheme 1-30). The amides were reacted with organo-magnesium or -lithium reagents, affording the desired ynones.

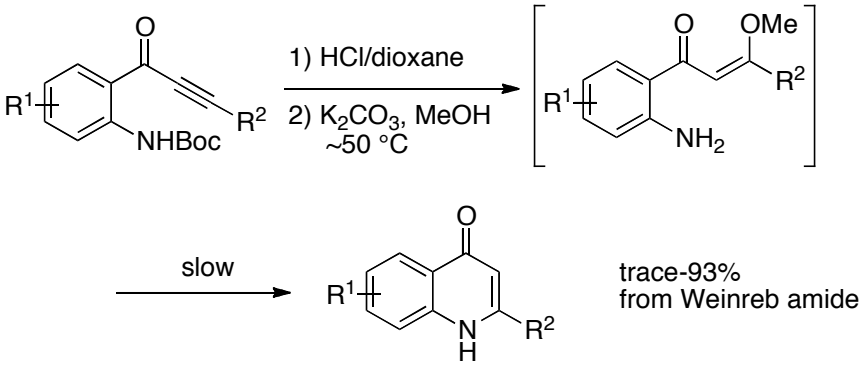
With a variety of ynones in hand, the cyclization was tried using a one-pot procedure (Scheme 1-31). First the *N*-Boc ynone was treated with HCl to remove the Boc group, and the resulting crude mixture was subjected to basic conditions using K_2CO_3 in MeOH. Interestingly, this cyclization was slow enough to observe a Michael-adduct intermediate, resulting from the addition of MeOH to

vinylogous acid chloride. Thus, in this case, the plausible mechanism is a 6-endo-dig mode, involving MeOH as the catalytic nucleophile. Due to the stability of this intermediate as well as weaker nucleophilicity of the amine group, the cyclization requires heating the reaction at 50 °C for 4 days.

Scheme 1-30. Ynone synthesis from anthranilic acids



Scheme 1-31. Synthesis of quinolones from ynones

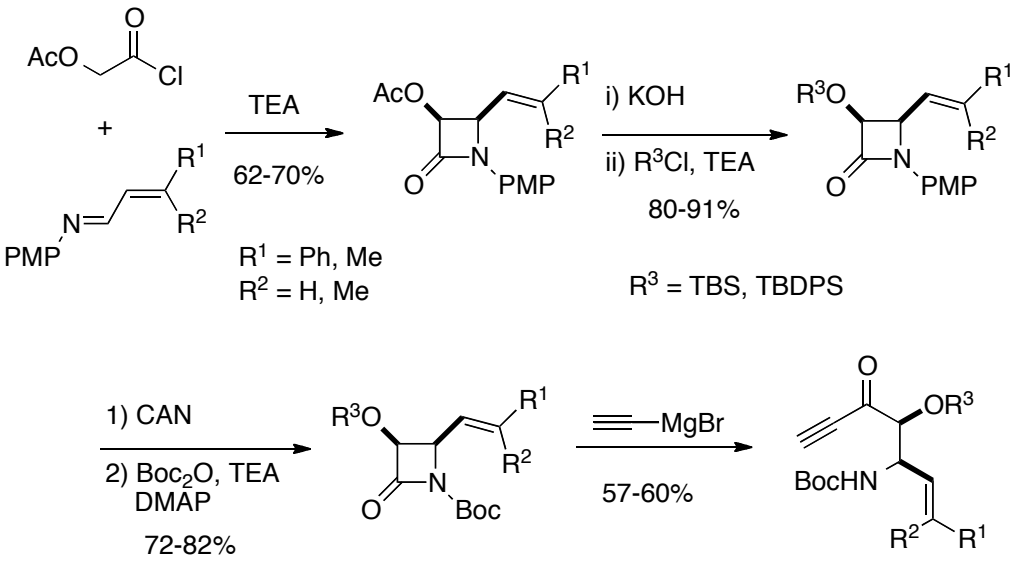


1.3.1.6 *N*-Boc *β*-lactam approach and its application[43]

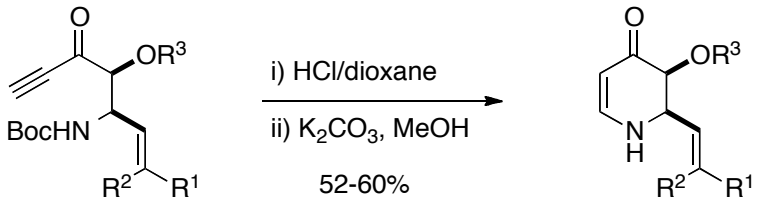
Having the established protocol to cyclize the ynone to the enaminone, the focus turned to the synthesis of functionalized ynones. Specifically, it was envisioned that the ynone could be derived from the nucleophilic ring-opening of

β-lactams (Scheme 1-32). The synthesis started with the coupling of an acid chloride and imine under the Staudinger reaction conditions, furnishing the *N*-PMP *β*-lactam with a *syn* configuration. The acetate group was cleaved, and the resulting hydroxyl group was protected with silyl groups. The *N*-protection was converted to a Boc group in two steps. This *N*-Boc *β*-lactam was reacted with an ethynyl Grignard reagent to afford the ynone. The ynone was subjected to the one-pot procedure to give the desired enaminone in modest yields (Scheme 1-33).

Scheme 1-32. Synthesis of functionalized ynone via *β*-lactam

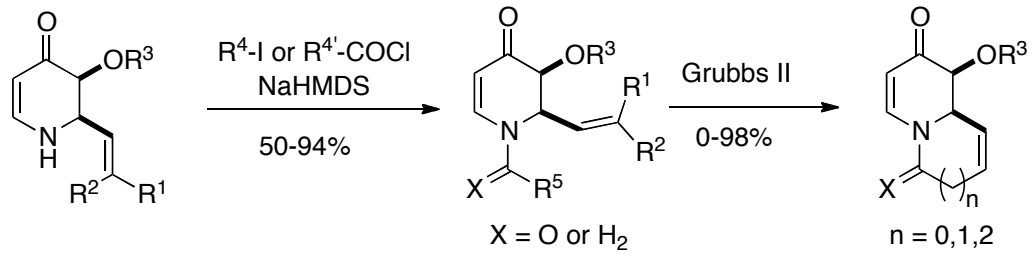


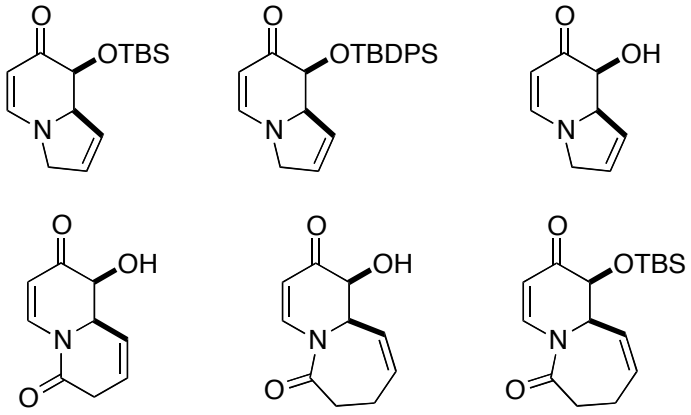
Scheme 1-33. Cyclization of functionalized ynone to the enaminone



Next, with vinyl enaminones in hand, the nitrogen was functionalized with different terminal alkenes (Scheme 1-34). These enaminones were then subjected to RCM conditions using the Grubbs II catalyst, affording a variety of 5, 6, and 7-membered bicyclic enaminones.

Scheme 1-34. Derivatization of enaminones to bicyclic nitrogenous compounds





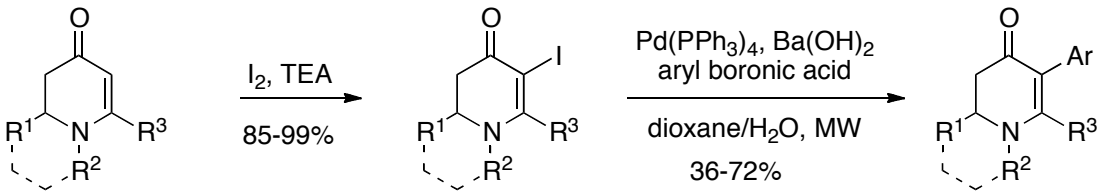
1.3.2 C-5 functionalization

1.3.2.1 Suzuki coupling of iodoenaminones[7]

Considering the embedded enamine functionality in enaminones, it is not surprising that the C5 position possesses nucleophilicity. In fact, iodination of the

C5 position is a facile process unless the substituent on the nitrogen is an electron-withdrawing group (Scheme 1-35). Comins and Kunz have shown that this iodoenaminone undergoes a variety of Pd-catalyzed reactions such as Stille and Negishi cross-couplings, although reaction conditions were not optimized.[44] The Georg group found that the iodoenaminones underwent Suzuki coupling with boronic acids under microwave conditions in good to excellent yields.

Scheme 1-35. Suzuki coupling of iodoenaminones

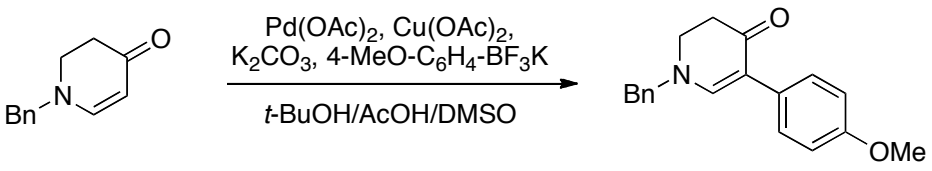


1.3.2.2 Suzuki-type direct cross-coupling[8a]

Given the two-step protocol to functionalize the C5 position, a more direct method was envisaged, which could avoid preactivation of the enaminone. By taking advantage of the innate nucleophilic character of the enaminone, it was hoped to generate a Pd-enaminone species from the non-activated enaminone, followed by a C−C bond formation with a suitable coupling partner. This would allow our two-step process to be a catalytic, one-step method. The direct arylation was successful using a trifluoroborate as a coupling partner in a mixture of the three solvents (Scheme 1-36). Acetic acid was used to promote palladation by increasing the electrophilicity of the Pd(II) center. Consequently, trifluoroborates, known as robust equivalents of oranoboronic acids were chosen since other coupling partners including boronic acids and organozinc reagents,

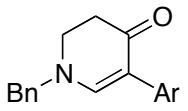
are vulnerable under acidic conditions. Slow addition of trifluoroborates was necessary to avoid their dimerization.

Scheme 1-36. Direct arylation of enaminone



slow addition of trifluoroborate 93%

With optimized conditions in hand, the scope of trifluoroborates was investigated (Figure 1-3). As anticipated, electron-rich trifluoroborates underwent coupling efficiently. Contrary, electron-deficient and sterically-hindered trifluoroborates gave moderate yields over extended period of time. Notably, halides on aryl groups remained intact, presenting positions for further derivatizations.



Ar = Ph (72%)	= 4-Br-C_6H_4 (73%)
= 4-Me-C_6H_4 (86%)	= 4-Cl-C_6H_4 (71%)
= 2-Me-C_6H_4 (40%)	= 2-Naphtyl (96%)
= 2-MeO-C_6H_4 (27%)	= 3,4,5-$(MeO)_3$-C_6H_2 (83%)
= 4-CF_3-C_6H_4 (44%)	= 3-HO-C_6H_4 (97%)
= 4-Ac-C_6H_4 (42%)	= 4-CbzNH-C_6H_4 (80%)

Figure 1-3. Scope of trifluoroborates.

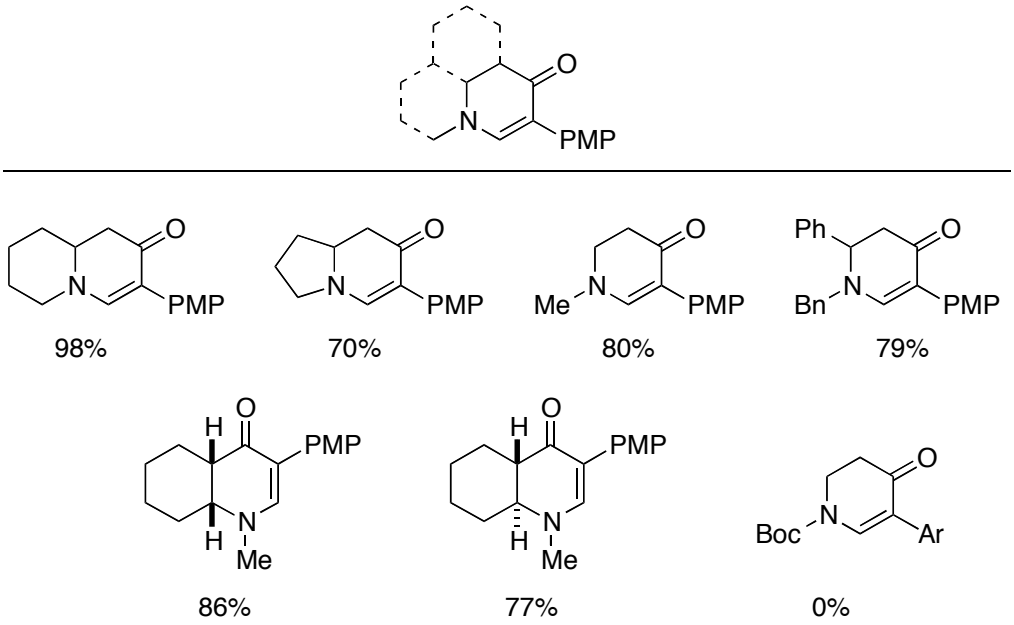


Figure 1-4. Scope of enaminones.

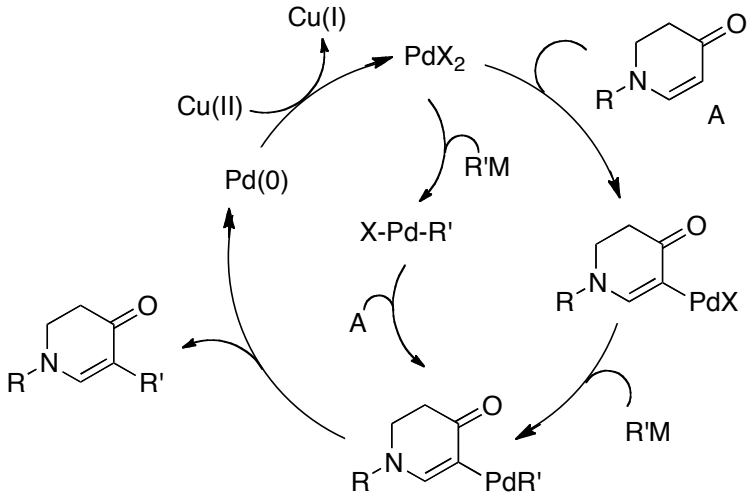


Figure 1-5. Proposed catalytic cycle for direct arylation of enaminones.

Next, the scope of enaminone formation was explored (Figure 1-4). It was found that monocyclic and bicyclic enaminones were viable substrates in the reaction. *N*-Boc protected enaminones, however were inactive to the cross-coupling.

The mechanism of this coupling could be initiated by a nucleophilic attack of the enaminone to palladium, affording a Pd-enaminone intermediate (Figure 1-5). This Pd species would then undergos transmetallation with trifluoroborates, followed by a reductive elimination to give arylated enaminones. Alternatively, the catalytic cycle could start with a transmetallation between the Pd and trifluoroborate species. The Pd-aryl intermediate would then be an electrophile to the enaminones. The formation of biaryl as a byproduct was observed, which supports the formation of the Pd-aryl intermediate.

1.3.2.3 Hiyama-type direct cross-coupling[8b]

Although the direct Suzuki-type cross-coupling of the enaminone was successful, due to the limited number of commercially available trifluoroborates, other coupling partners were explored as well. In this regard, the Hiyama coupling using organosilicon reagents was investigated.

On the basis of our results using the Suzuki coupling, a wide variety of Pd catalysts, oxidants, and silicon activators were screened. The coupling was successful using $Pd(OAc)_2$ and CuF_2 in a co-solvent system (Figure 1-6). In this reaction, CuF_2 acts as not only an oxidant for Pd but also an activator of aryl triethoxylsilane. Next, the substrate scope of the reaction was explored. Various enaminones and aryl triethoxylsilanes were found to be viable substrates for this coupling. It is worth noting that the TBS group stays intact under this reaction condition since in Hiyama coupling TBAF is commonly used, which would deprotect the TBS group. As observed in the Suzuki coupling, halides on aryl groups and enaminones remained intact.

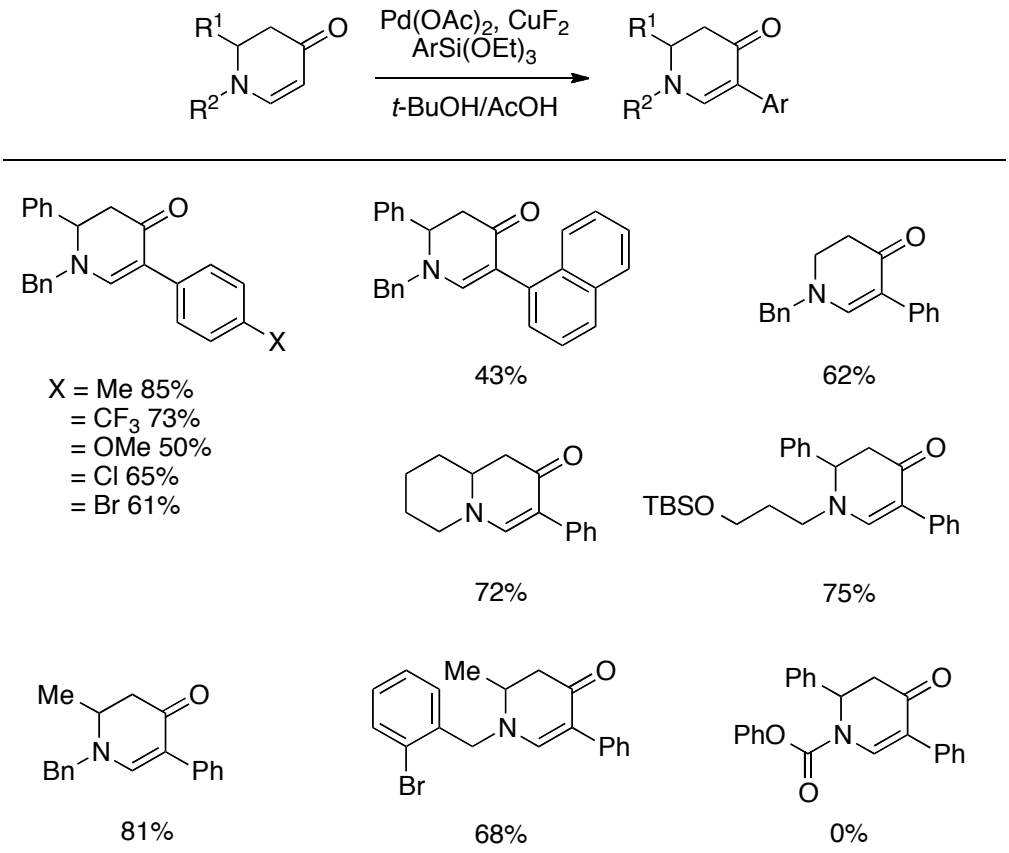


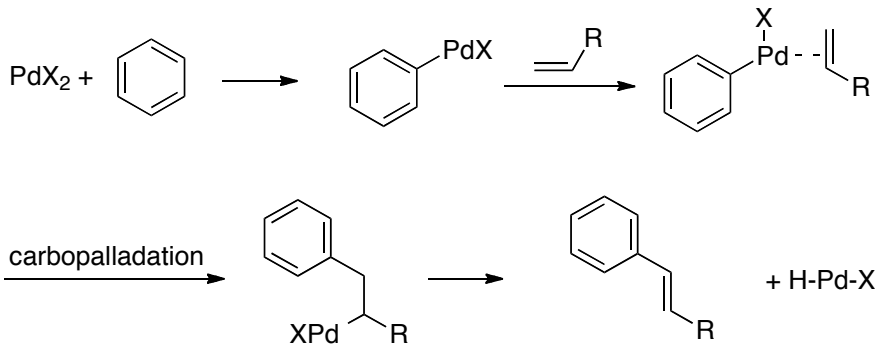
Figure 1-6. Scope of Hiyama coupling.

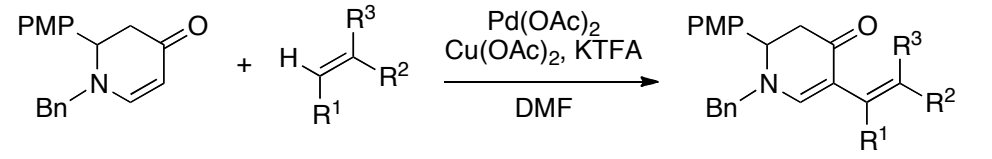
1.3.2.4 Alkenylation via the Fujiwara-Moritani reaction[8c]

Encouraged by the success of direct arylation of the enaminone, the direct alkenylation was investigated, which was unsuccessful in the Suzuki coupling due to fast homo-coupling of the alkenyl trifluoroborates. To address this issue, we considered the possible utility of the Fujiwara-Moritani reaction (Scheme 1-37).[45] The Fujiwara-Moritani reaction starts with the formation of an aryl-Pd complex, which underwent a carbopalladation with an olefin, followed by the reductive elimination to give alkenyl arenes. Assuming that a Pd-enaminone intermediate exists in our catalytic cycle and has an aryl-Pd-like property, it was

envisioned that alkenylation is possible by using terminal alkenes as coupling partners.

Scheme 1-37. Fujiwara-Moritani reaction





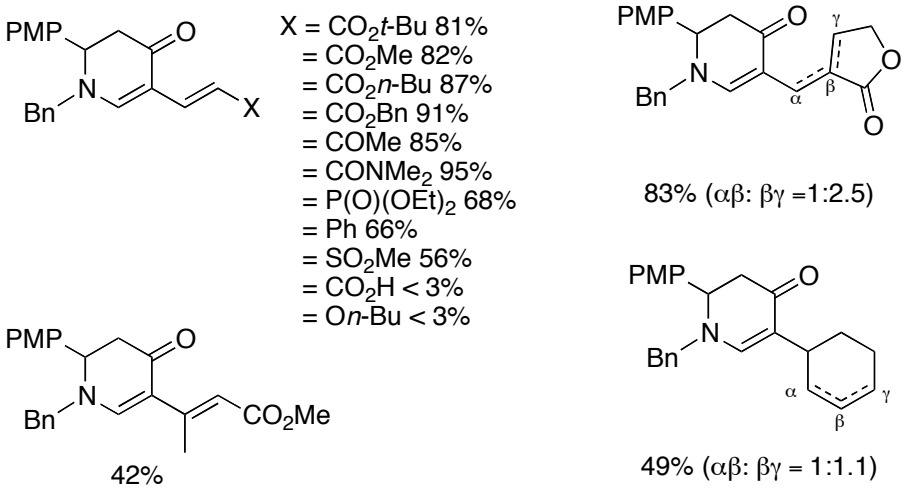


Figure 1-7. Scope of olefins in the alkenylation of enaminones.

The reaction conditions were optimized by screening Pd catalysts, oxidants and additives. Fortunately, an alkenylated enaminone product was observed using activated olefins as coupling partners and KTFA as an additive (Figure 1-7). In fact, a wide variety of olefins with electron-withdrawing groups were found to be viable substrates in this reaction. On the other hand, acrylic acid and vinyl ethers failed to afford the desired products.

Next, this alkenylation was carried out on various enaminones (Figure 1-8). It was found that the protocol is applicable to mono- and bicyclic enaminones. Importantly, alkenylation of the diastereomeric substrates took place without epimerization of the stereocenters. As observed in the previous Suzuki and Hiyama couplings, *N*-H and *N*-Cbz enaminones showed poor reactivity. Pyridone was also a poor substrate for this coupling.

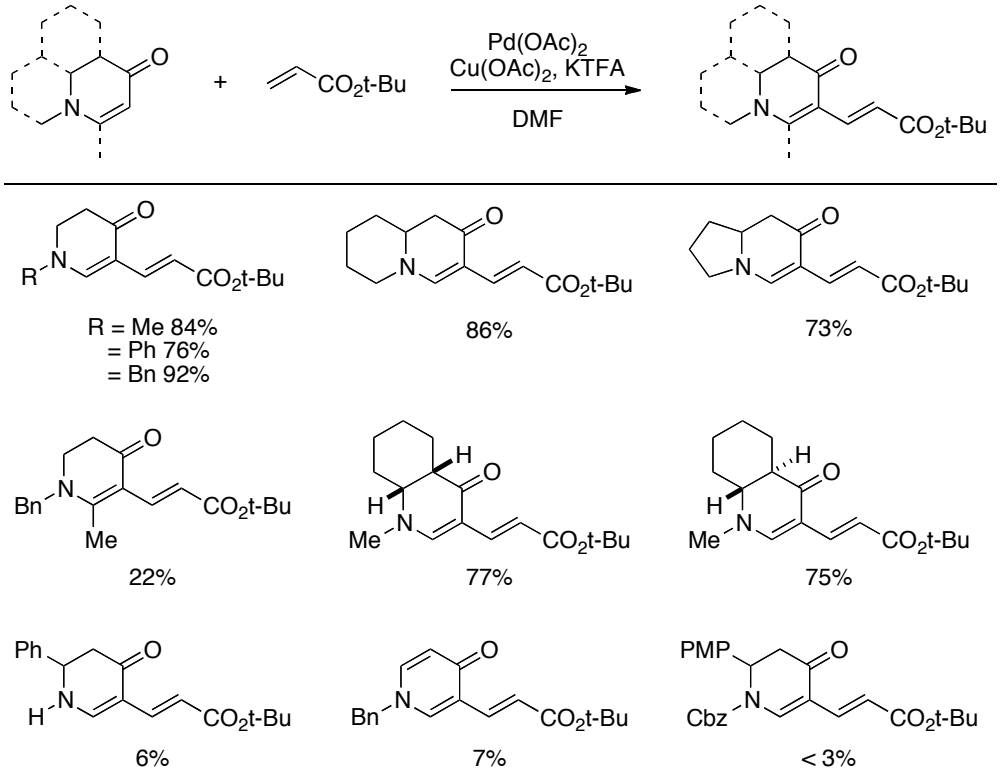


Figure 1-8. Scope of enaminones on alkenylation.

During the course of this study, NMR experiments were conducted to capture the Pd-enaminone intermediate, which has been the presumed key species for the coupling reactions (Figure 1-9). The enaminone was treated with 0.5 and 1.0 equivalents of $Pd(OAc)_2$ in DMSO for 20 min. The disappearance of two doublet peaks (7.62, 4.79 ppm) as well as the appearance of a singlet peak (7.72 ppm) were observed, indicating that the initial enaminone was converted to a Pd-enaminone intermediate. This intermediate was then subjected to alkenylation in DMSO (Scheme 1-38). Upon heating the reaction to 140 °C, the alkenylated product was observed.

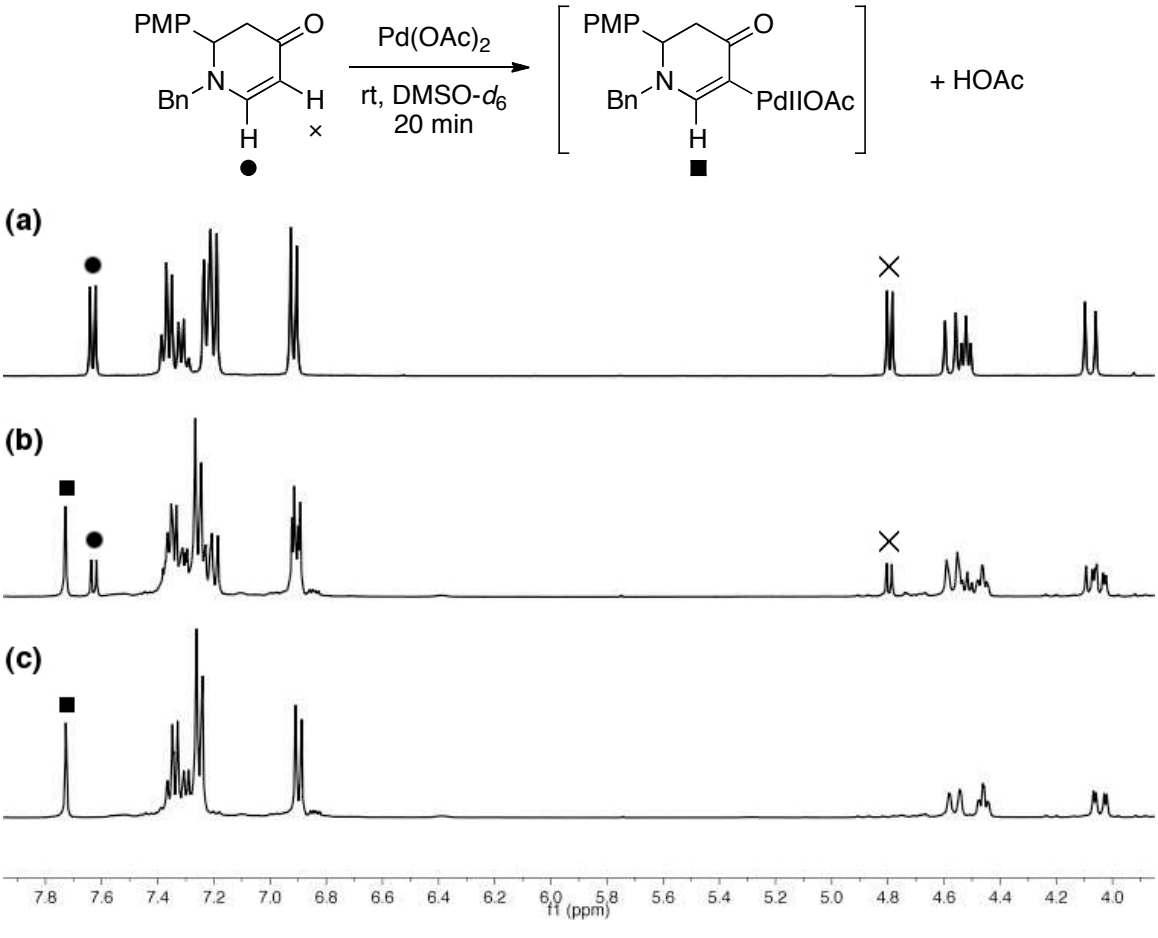
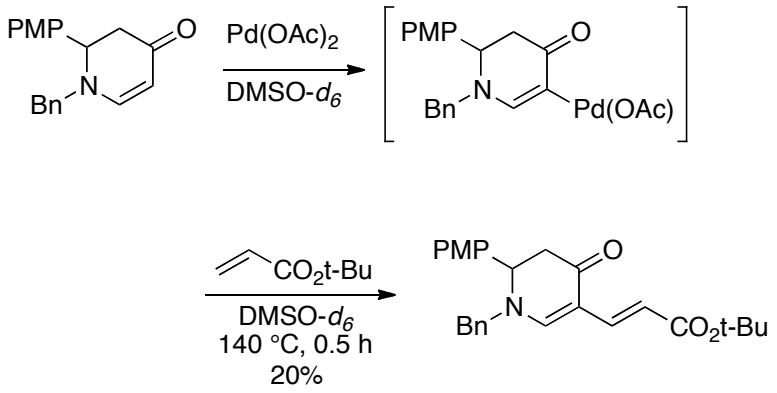


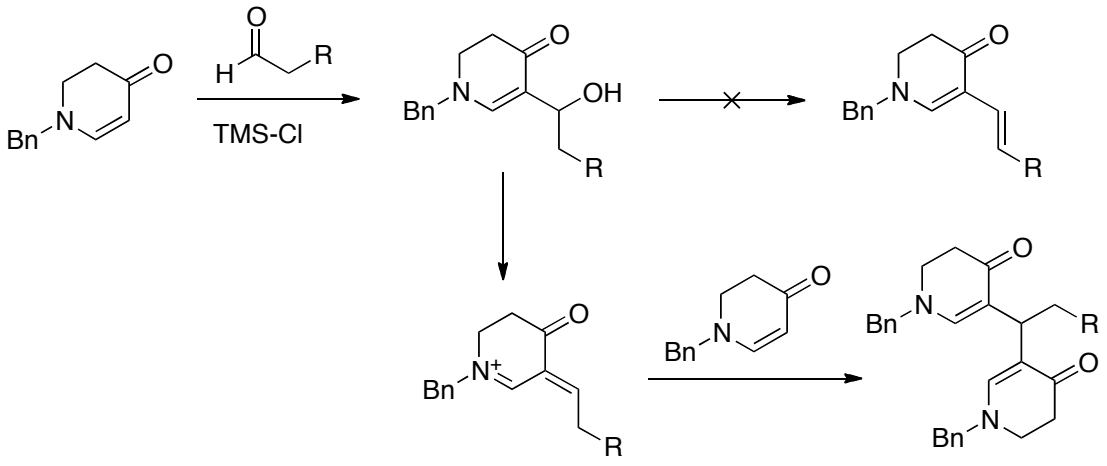
Figure 1-9. NMR studies to detect Pd-enaminone intermediate.[46]

Scheme 1-38. Stoichiometric alkenylation for mechanistic investigation



1.3.2.5 Alkylations using aldehydes[47]

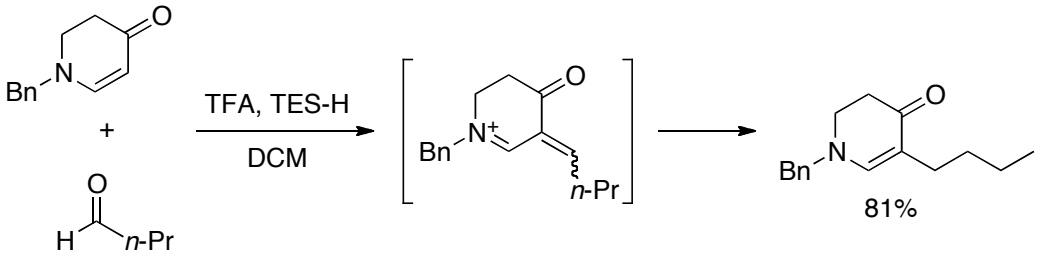
Scheme 1-39. Undesired dimer formation

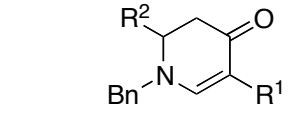


Although arylation and alkenylation of enaminones at the C5 position were achieved, installation of a simple alkyl group has not been successful using a Pd catalyst. It was assumed that this is partially because the oxidative addition step

of Pd to alkyl halides is slow. Even if this process could occur, *β*-hydride elimination prior to the transmetallation step is very facile, leading to the formation of an undesired alkene. Thus, an alternative approach was sought to alkylate the enaminone at the C5 position by taking advantage of its nucleophilicity. Specifically, it was hypothesized that the enaminone might undergo an aldol reaction with an aldehyde. Under acidic conditions, however, the formation of undesired dimmers was observed, instead of aldol or its dehydrated products (Scheme 1-39).

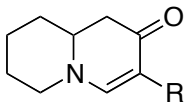
Scheme 1-40. Interception of iminium intermediate with hydride



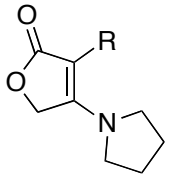


R^1 = *n*-Bu R^2 = H 81%
= Bn = H 85%

R^1 = *n*-Bu R^2 = Ph 92%
= Bn = Ph 86%
= *n*-Nonyl = Ph 77%
= *i*-Bu = Ph 93%



R = *n*-Bu 88%
Bn 93%



R = *n*-Bu 89%
= Bn 98%
= *i*-Pr 88%
= 2-$MeC_6H_4CH_2$ 97%
= 4-$ClC_6H_4CH_2$ 96%

Figure 1-10. Scope of the alkylation.

Given that an aldol reaction actually took place, it was explored to intercept the intermediate with a hydride prior to the formation of the dimer. This was successful using TES-H and TFA, affording an alkylated enaminone (Scheme 1-40). The alkylation was applied to various enaminones, providing alkylated enaminones in good yields (Figure 1-10).

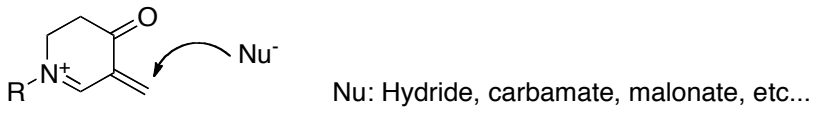


Figure 1-11. General idea to trap the iminium intermediate with nucleophiles.

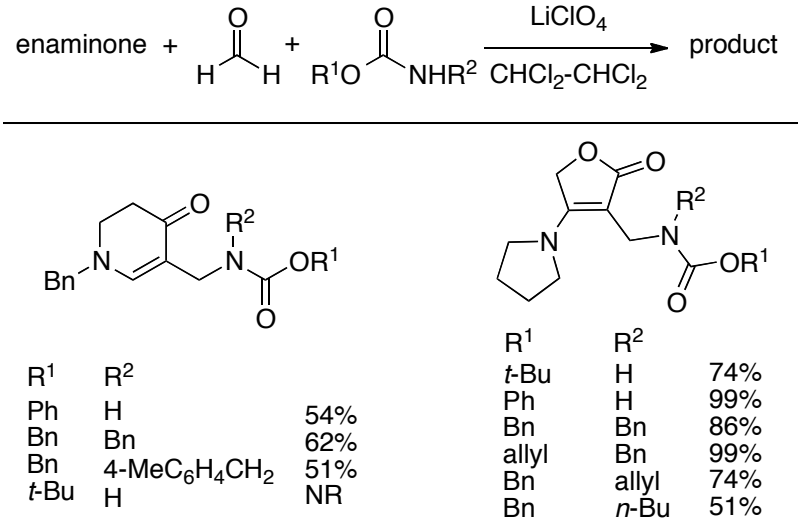
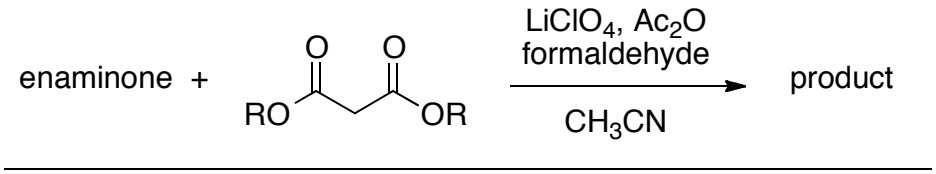


Figure 1-12. Scope of aminomethylation reaction.

Next, other nucleophiles were tested to trap the iminium intermediate (Figure 1-11). After screening a wide variety of nucleophiles, some of them, such as carbamates were found to give desired products when formaldehyde was

used as an aldehyde (Figure 1-12). The presence of $LiClO_4$ was necessary to facilitate this three-component reaction and to prevent the dimerization of enaminones. Malonates were found to be viable nucleophiles as well (Figure 1-13). In this case, Ac_2O was added to boost the yields of the reactions.

It was proposed that the reaction mechanism involves the Knoevenagel condensation of the enaminone. In fact, the desired alkylated product was obtained when the enaminone was treated with dimethyl 2-methylenemalonate regardless of the presence of $LiClO_4$ (Scheme 1-41). It is believed that $LiClO_4$ acts as a Lewis acid to promote the formation of methylenemalonate and to prevent the enaminone from adverse dimerization.



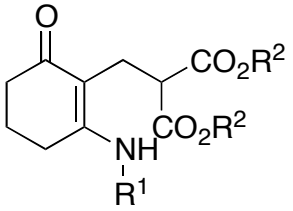
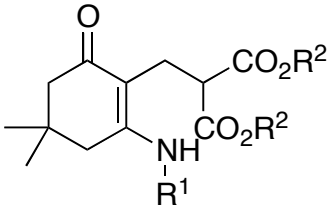
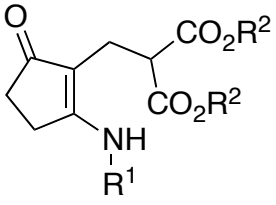
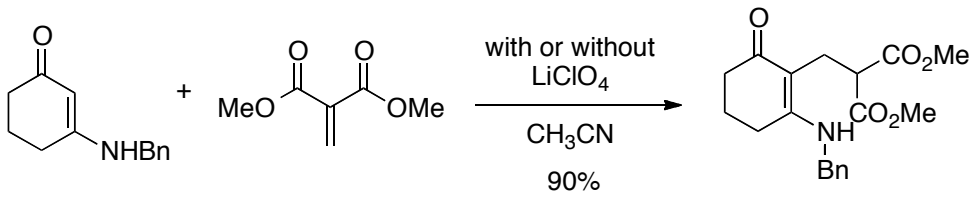
	R^1	R^2	
	Ph	Me	90%
	Ph	Bn	97%
	Bn	Me, Bn	73%
	Bn	Bn	90%
	n-Bu	Me	66%
	n-Bu	Bn	83%
	N-morpholino	Me	72%
	N-morpholino	Bn	86%
	Ph	Me	83%
	Ph	Bn	87%
	Bn	Me	95%
	Bn	Bn	88%
	n-Bu	Me	88%
	Ph	Me	96%
	Bn	Me	94%

Figure 1-13. Scope of alkylation using malonates.

Scheme 1-41. Knoevenagel condensation of the enaminone



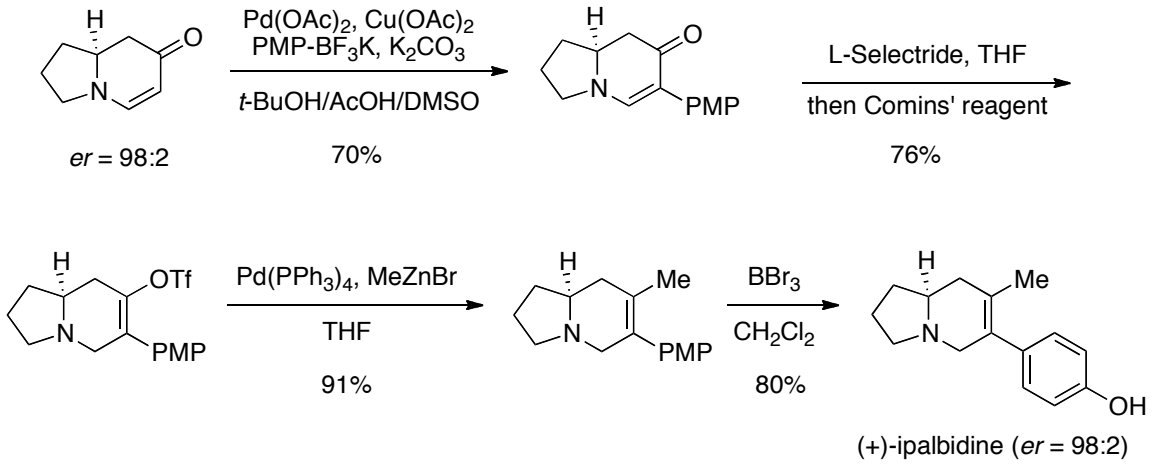
1.3.3 Application to the total synthesis

The development of the enaminone chemistry provided an opportunity to synthesize indolizidine and quinolizidine alkaloids in a concise manner. The syntheses of multiple natural products and their closely-related analogs as well as their biological investigations have been reported by the Georg group.

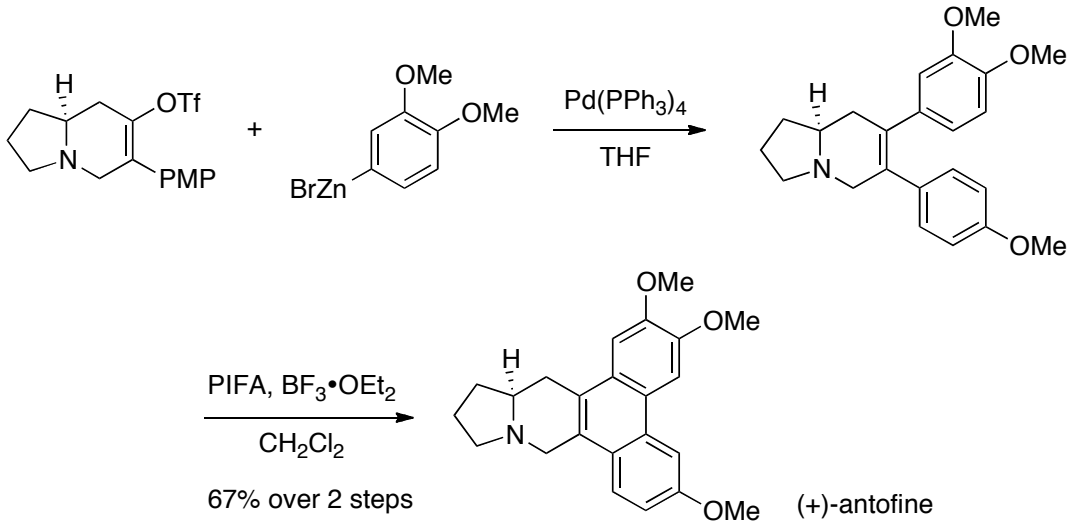
1.3.3.1 Total synthesis of (+)-ipalbidine and (+)-antofine[48]

The enaminone chemistry was first applied to the synthesis of (+)-ipalbidine, which is a non-addictive analgesic, an oxygen-free radical scavenger, and has demonstrated inhibitory effects on the respiratory burst of leukocytes (Scheme 1-42).[49] Utilizing the ynone cyclization, the 5,6-enaminone was obtained with an enantiomeric ratio of 98:2. This enaminone was subjected to the direct arylation protocol, giving the arylated product. The arylated enaminone was reduced by L-Selectride and a resulting boron enolate was trapped with Comins' reagent. The methyl group was then installed by Negishi coupling. Lastly, the methyl group of the PMP substituent was removed by BBr_3 to furnish (+)-ipalbidine with an enantiomeric ratio of 98:2, indicating that stereochemical integrity was retained throughout the synthetic process.

Scheme 1-42. Enantiospecific synthesis of (+)-ipalbidine



Scheme 1-43. Enantiospecific synthesis of (+)-antofine



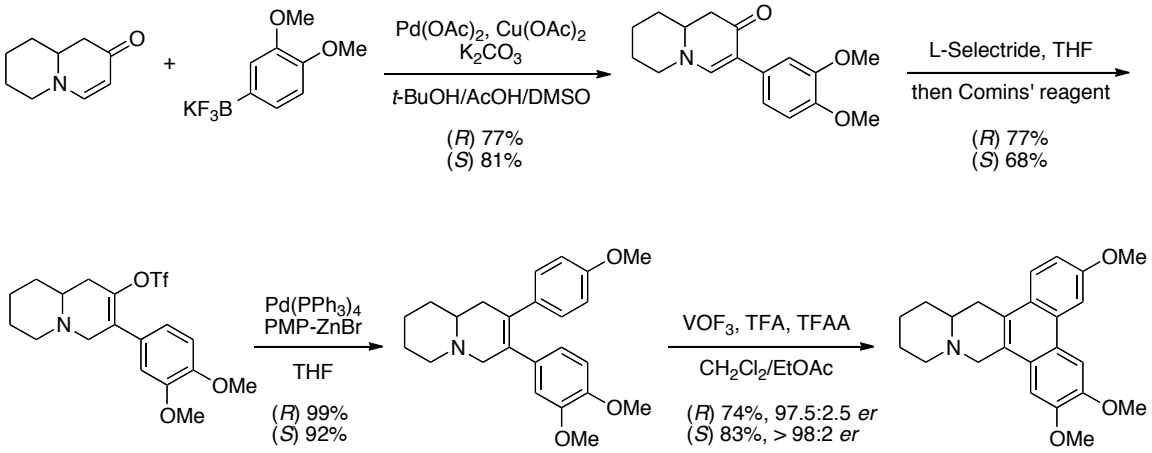
Having established the synthetic route for (+)-ipalbidine, (+)-antofine was selected as the next target, which exhibits low nanomolar antiproliferative activity in drug-sensitive and multidrug resistant cancer cell lines as well as antiviral activity (Scheme 1-43).[50] It was found that (+)-antofine can be synthesized

using the triflate in Scheme 1-42. The triflate was subjected to Negishi coupling with aryl-ZnBr to give the biaryl product (Scheme 1-43). This biaryl was oxidized by PIFA to furnish (+)-antofine.

1.3.3.2 Total synthesis of (*R*)- and (*S*)-boehmeriasin A[51]

The Georg group also succeeded in the synthesis of boehmeriasin A, which was recently isolated without assignment of the absolute stereochemistry.[52] This compound was found to be more potent than paclitaxel in most cancer cell lines, with GI_{50} values ranging from 0.8 to 265 nM.[53] Due to the unknown stereocenter, both enantiomers of Boehmeriasin A were synthesized.

Scheme 1-44. Enantiospecific syntheses of (*R*)- and (*S*)-boehmeriasin A



The strategy used in the synthesis of ipalbidine was exploited, and the triflate was obtained in two steps from the 6,6-enaminone (Scheme 1-44). The triflate was subjected to Negishi coupling to give the biarylamine, which was

oxidized using VOF_3 to afford Boehmeriasin A. (*R*)- and (*S*)- enantiomers were obtained with an enantiomeric ratio of 97.5: 2.5 and 98:2, respectively. In comparison with the literature, the (*R*)-product was found to be the natural product.

Lastly, our synthetic compounds were tested in three cancer cell lines with paclitaxel as a control (Table 1-7). It was found that the (*R*)-enantiomer was more potent than the (*S*)-enantiomer, and most importantly it showed activity in the drug resistant cancer cell line, where paclitaxel is inactive.

Table 1-7. Cytotoxicity of (*R*)- and (*S*)-boehmeriasin A

	IC_{50} (nM)		
Compound	COLO-205	MCF-7	NCI-ADR-RES
paclitaxel	3.31	1.62	> 6400
(*R*)-Boehmeriasin A • HCl	4.18	43.4	36.7
(*S*)-Boehmeriasin A • HCl	103	92.7	434

1.3.3.3 Total synthesis of tylocrebrine and related phenanthroindolizidines

Among the more than 60 phenanthropiperidines known to date, tylocrebrine is the only compound that has been tested in a clinical trial, which was immediately terminated due to side effects such as ataxia and disorientation, clear signs of CNS toxicity. Due to its potency, however, interest to develop a phenanthropiperidine for chemotherapeutic use still persists. In pursuit of developing a safe phenanthropiperidine for an anti-cancer agent, the Georg group embarked on the synthesis of tylocrebrine and its closely-related analogs.

As shown in Figure 1-14, an indolizidine triflate was connected with a variety of biaryl groups using a Negishi coupling, followed by VOF_3-mediated

oxidative C−C bond formation to give various phenanthroindolizidines (Figure 1-14). Synthesized alkaloids were then tested in three cancer cell lines for the evaluation of their antiproliferative activity (Table 1-8). As seen in Table 1-8, they showed very potent cytotoxicity with a broad spectrum. Based on these results, the removal or relocation of each of the methoxy groups has an effect on their activity against NCI/ADR-RES, although most of the compounds are still potent against COLO-205 and MCF-7 with the exception of compound **B**.

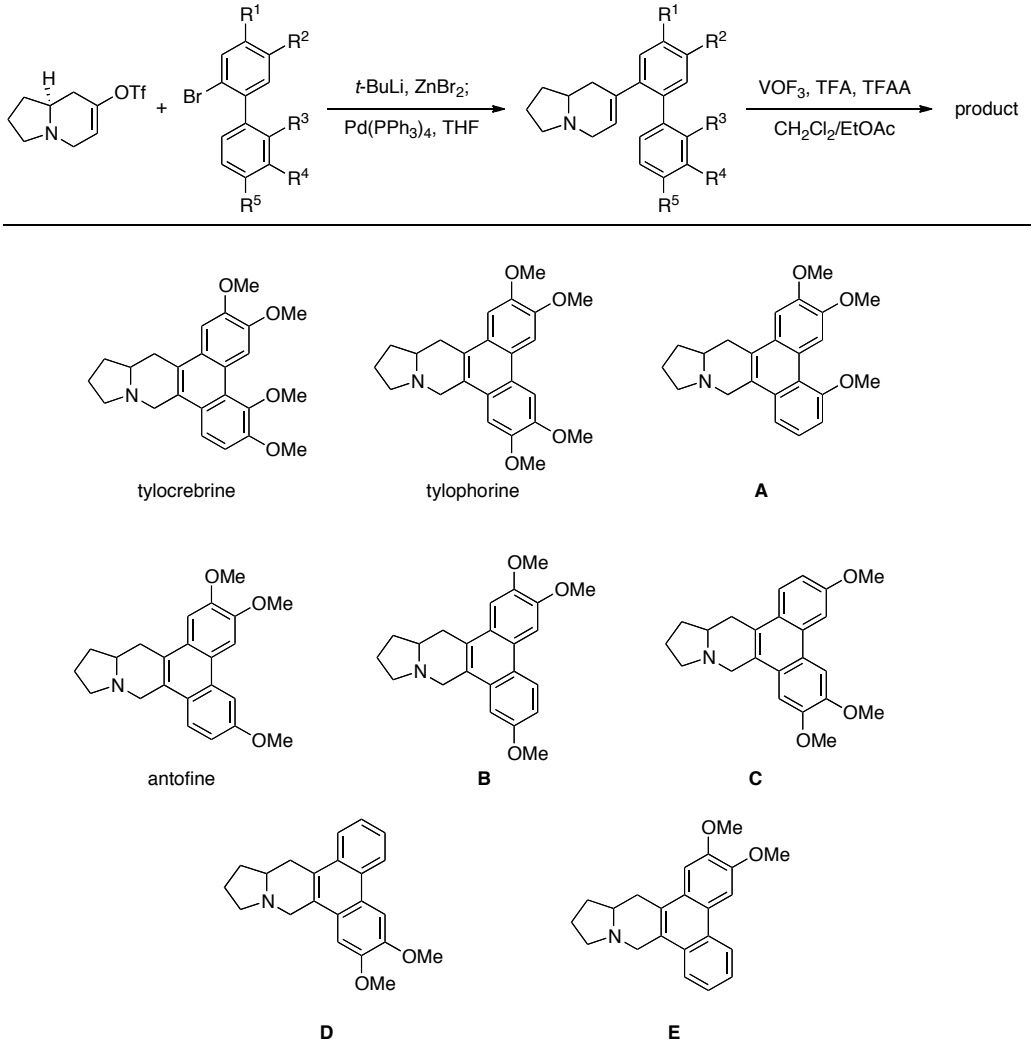


Figure 1-14. Synthesis of tylocrebrine and its analogs.

Table 1-8. Antiproliferative activity of phenanthroindolizidines

Antiproliferative Activity			
Compound	IC_{50} (nM)		
	COLO-205	MCF-7	NCI/ADR-RES
paclitaxel	5.3	2.3	>6400
(*R*)-tylocrebrine	1.3	15	26
tylocrebrine	12	39	46
(*R*)-tylophorine	17	32	160
tylophorine	10	42	50
A	9.5	22	16
antofine	2.8	21	23
B	270	530	1300
C	8.5	5.8	200
D	48	25	180
E	29	21	180

CHAPTER 2. SYNTHESIS OF ENAMINONE VIA KETENE CYCLIZATION

2.1 Introduction

As we discussed in Chapter 1, our approach to synthesize enaminones has an unique advantage, that is, the use of amino acids. However, partial racemization of the product was observed during the cyclization in some instances. Also, *β*-amino acids are not readily accessible. To address these issues, a different approach was sought. In this chapter, we would like to discuss a novel strategy to synthesize enaminones via ketene cyclization. To begin with, the following two sections are reviews of ketene chemistry and the Wolff rearrangement.

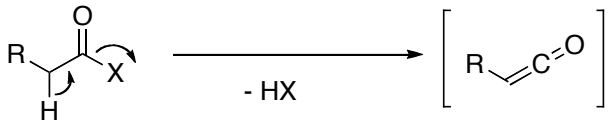
2.2 Ketene chemistry

Since its discovery by Hermann Staudinger in 1905, ketene has been extensively studied due to its extraordinary reactivity, which is exemplified by multiple name reactions such as Staudinger reaction, Arndt-Eistert homologation, Wolff rearrangement, and Döz benzannulation.[54]

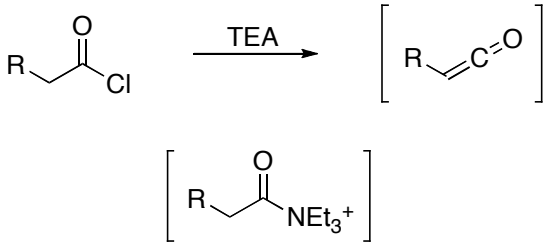
2.2.1 Preparation of ketene

There are a number of ways to generate a ketene.[55] The Wolff rearrangement will be separately discussed in the following section (**2.3**) due to its importance in our methodology.

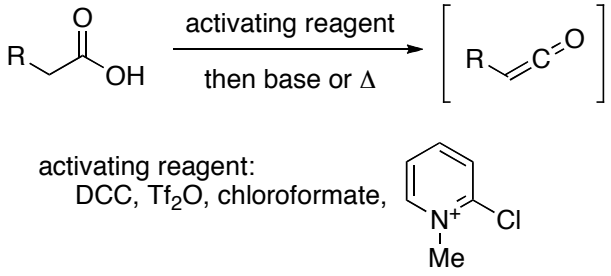
Scheme 2-1. Common principle to generate ketene



Scheme 2-2. Preparation of ketene from an acid chloride



Scheme 2-3. Preparation of ketene from acid

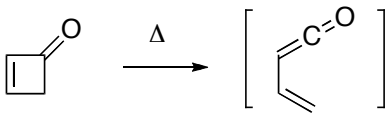


In most cases, ketenes are generated from the carbonyl functionality. A general strategy is to deprotonate the α-proton along with the elimination of X^- (Scheme 2-1). Acid chloride is commonly used as the precursor (Scheme 2-2).[56] Upon treatment with base such as TEA, the ketene is readily prepared. Based on this principle, acids can also be converted to a ketene via the activation

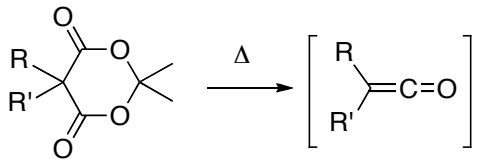
of the acid (Scheme 2-3). [57] Due to its stability, the generation of a ketene from ester requires harsh conditions.[58]

Ketene can be generated by pyrolysis of certain precursors. For example, upon heating, cyclobutenone forms vinyl ketene (Scheme 2-4).[59] Meldrum's acid derivatives are also known to afford ketene intermediates via rearrangement, (Scheme 2-5).[60] A few methods utilize transition metals such as Cr and Co. It is known that irradiation of the $Cr(CO)_5$ complex could generate a ketene-Cr complex (Scheme 2-6).[61]

Scheme 2-4. Preparation of ketene from cyclobutenone

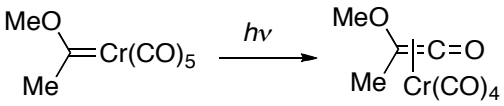


Scheme 2-5. Preparation of ketene from Meldrum's acid derivative



Meldrum's acid derivative

Scheme 2-6. Generation of ketene-Cr complex

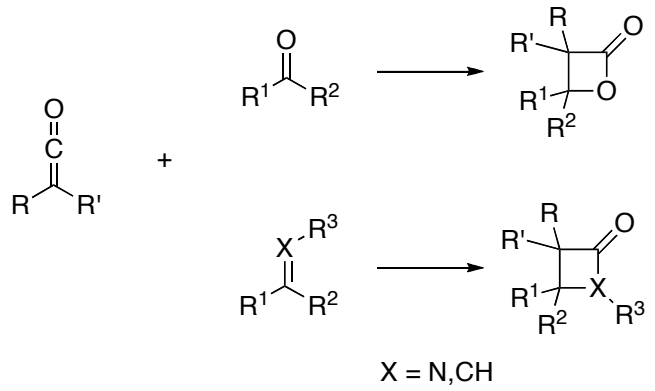


2.2.2 Reactions of ketene

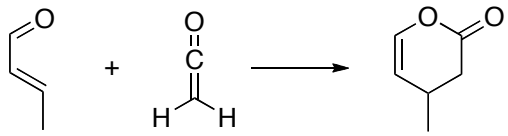
Reactions involving ketenes are mainly classified as either cycloaddition or nucleophilic addition reactions, along with many miscellaneous reactions.[54, 62]

2.2.2.1 Cycloaddition reaction

Scheme 2-7. Staudinger ketene cycloaddition



Scheme 2-8. Lactone formation via [4 + 2] cycloaddition

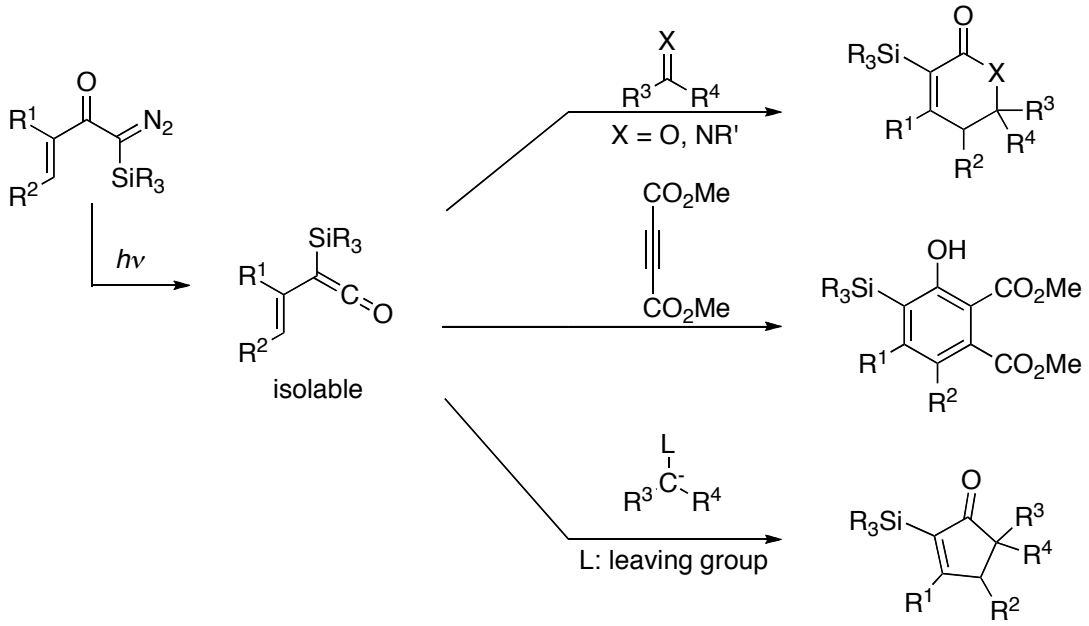


One of the most well known reactions involving ketene is the Staudinger cycloaddition reaction (Scheme 2-7).[63] Ketene undergoes [2 + 2] cycloaddition with other π-systems such as ketones, imines, and olefins, affording *β*-lactone, *β*-lactam, and cyclobutanone derivatives, respectively. Although examples of [4 +

2] cycloadditions are rather limited, compared to [2 + 2] cycloadditions, the formation of lactone from ketene and aldehyde has long been known (Scheme 2-8).[64]

Due to ketene's high reactivity, however, the reaction sometimes suffers from a dimerization of the ketene species. Addressing this issue, Danheiser introduced a sily substitutent to the ketene (Scheme 2-9).[65] It was found that the silyl substituents stabilize ketenes and suppress their tendency to dimerize, allowing the isolation of the silylketene intermediates. Using this elegant approach, highly functionalized silyl ketenes are able to participate in a variety of reactions, such as [4 + 2] and [4 + 1] annulations.[66]

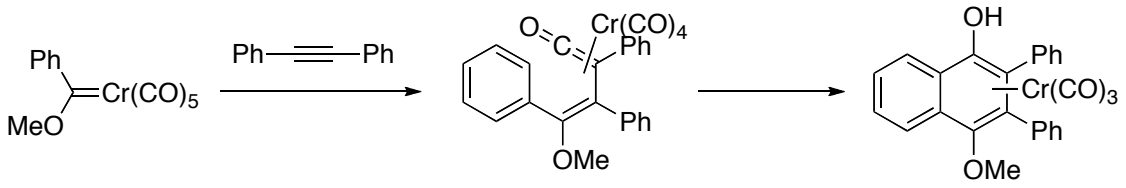
Scheme 2-9. Danheiser's silylketene chemistry



Döz benzannulation is another reaction involving a stabilized ketene (Scheme 2-10).[67] In this case, stabilization was attributed to the coordination

from chromium complex. Formal [4 + 2] cycloaddition affords a densely functionalized arene.

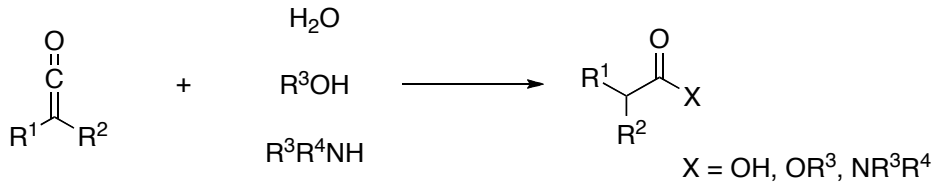
Scheme 2-10. Döz benzannulation



2.2.2.2 Nucleophilic addition

Ketenes serve as not only π donors of cycloaddition, but also excellent electrophiles in nucleophilic addition reactions, as seen in the Arndt-Eistert homologation.[68] In most cases, nucleophiles are water, alcohols, or amines (Scheme 2-11).

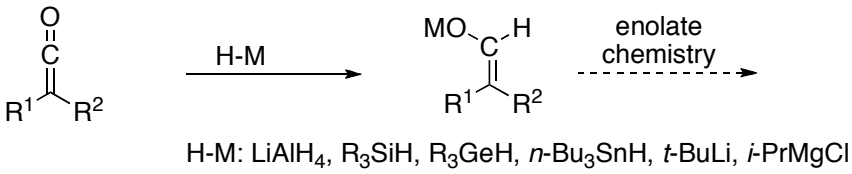
Scheme 2-11. Intermolecular nucleophilic addition reactions to ketene



Other types of nucleophiles were also explored in ketene chemistry.[69] Ketenes can be reduced by various hydride donors such as LAH (Scheme

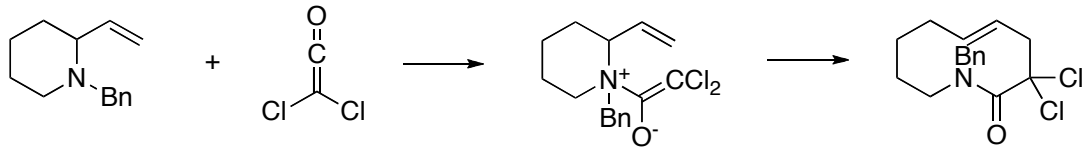
2-12).[70] The resulting enolates could be further employed in electrophilic reactions. Reactive ketenes are even able to react with tertiary amines (Scheme 2-13).[71] Although this process is reversible, the equilibrium can be altered by the formation of thermodynamically stable product via the sequence of reactions that is, in this case, [3,3] rearrangement.

Scheme 2-12. Reaction of ketene with hydride



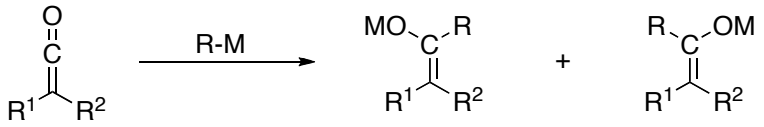
H-M: $LiAlH_4$, R_3SiH, R_3GeH, *n*-Bu_3SnH, *t*-BuLi, *i*-PrMgCl

Scheme 2-13. Synthesis of azacyclodecane via the formation of a zwitterionic intermediate and subsequent [3,3] rearrangement



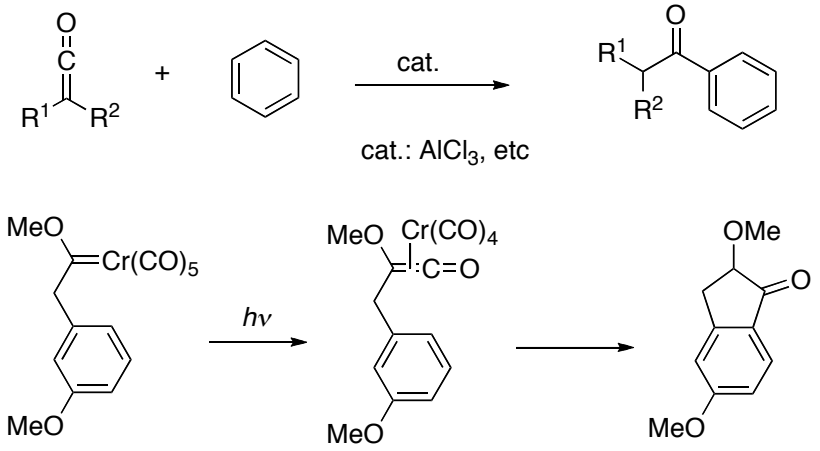
Presumably due to ketene's hard character, carbon nucleophiles are rarely used in nucleophilic addition reactions. This is one of the reasons that esters or amides are first prepared by the Arndt-Eistert homologations, which are then further functionalized by carbon nucleophiles. Thus, most of the examples where carbon nucleophiles were reacted with ketenes were to investigate the chemical property of the ketene itself, and only a few reactions seem to have synthetic utility.

Scheme 2-14. Addition of organometallic reagents to ketenes



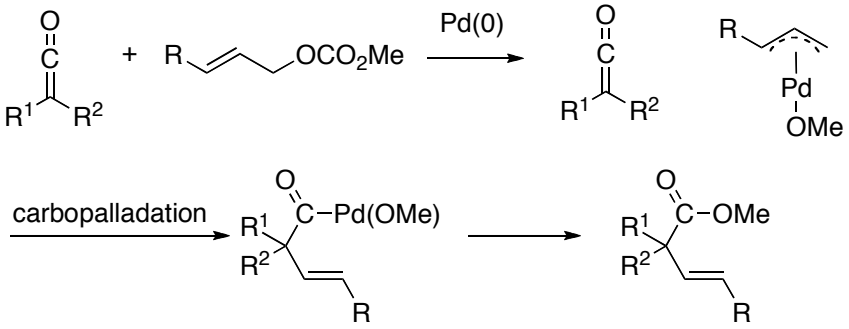
R-M: RLi, RMgX, $RCeCl_2$

Scheme 2-15. Examples of a Friedel-Crafts-type nucleophilic addition to a ketene

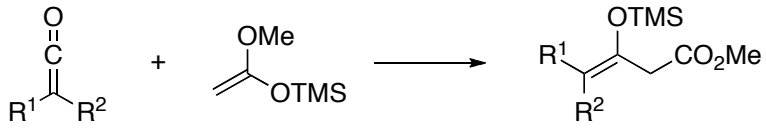


The addition of a variety of organometallic reagents to ketene sets a precedent (Scheme 2-14).[69f, 72] The steric bulkiness of R_1, R_2 and R is a predominant factor that affects the ratio of two regioisomers. Again, the resulting enolate could be utilized in subsequent electrophilic reactions. Other conventional nucleophiles have been known to react with ketenes. For example, arenes undergo nucleophilic addition to ketenes with the aid of catalysts, as a variant of Friedel-Crafts reactions (Scheme 2-15).[73]

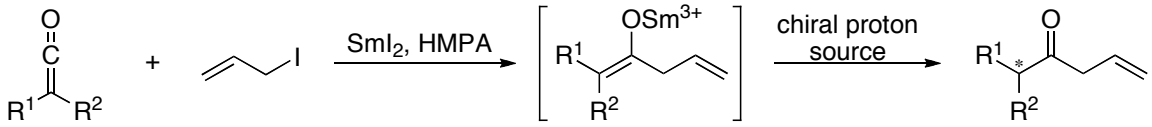
Scheme 2-16. Pd π-allyl complex as a nucleophile adding to a ketene



Scheme 2-17. Silyl enolether as a nucleophile adding to a ketene



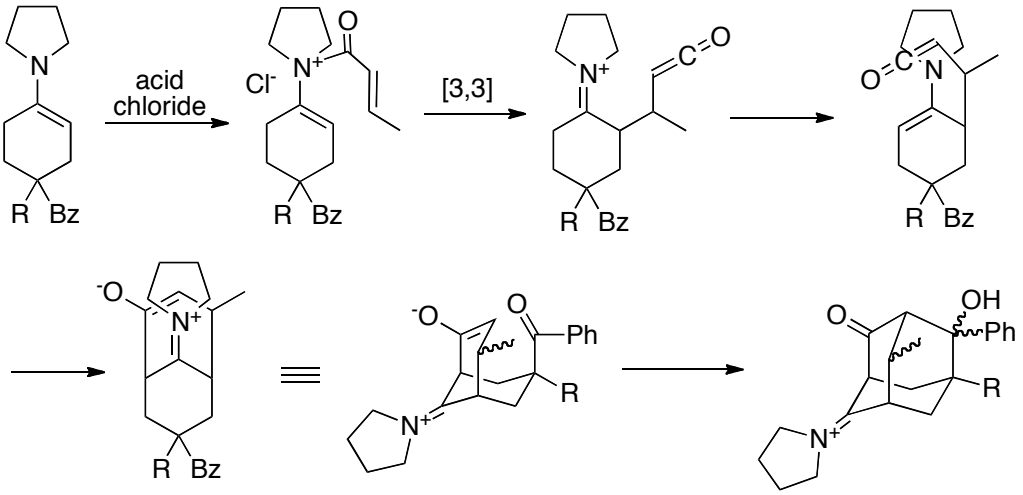
Scheme 2-18. SmI_2-mediated allylation of a ketene



Palladium π-allyl complexes,[74] silyl enol ethers,[75] and allyl-SmI_3 also exhibit nucleophilicity towards ketenes (Scheme 2-16, Scheme 2-17, Scheme 2-18).[76] Typically, a palladium π-allyl complex acts as an electrophile (Tsuji-Trost reaction), but in the presence of a ketene, it serves as a nucleophile due to the strong electrophilicity of ketene.

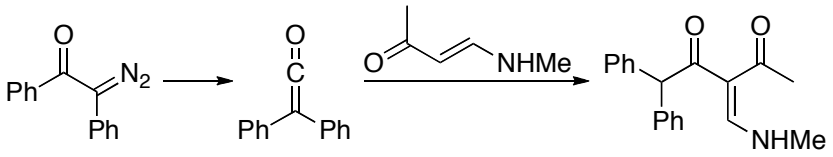
Enamines and enaminones, non-metallic neutral nucleophiles, have been exploited as well in a few reports. Hickmott generated the ketene from the [3,3] sigmatropic rearrangement of an *N*-acylated cationic enamine (Scheme 2-19). The enamine underwent nucleophilic addition to this ketene, followed by intramolecular aldol condensation to afford the tricyclic final product.[77]

Scheme 2-19. Nucleophilic addition of an enamine to a ketene

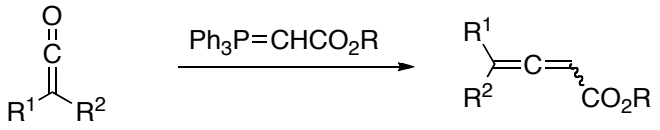


Although an enaminone is less nucleophilic than an enamine, it is still sufficiently reactive to a ketene, and the acyclic enaminone is found to react with diphenyl ketene (Scheme 2-20).[78] This reaction is a rare example where a ketene was generated from a diazoketone without any catalyst, presumably due to the stabilization from two phenyl substituents. Lastly, not surprisingly, Wittig and HWE reagents can convert ketenes to allenes (Scheme 2-21).[79] Similarly, ketenimines can be obtained in the aza-Wittig reaction.[80]

Scheme 2-20. Nucleophilic addition of an enaminone to a ketene



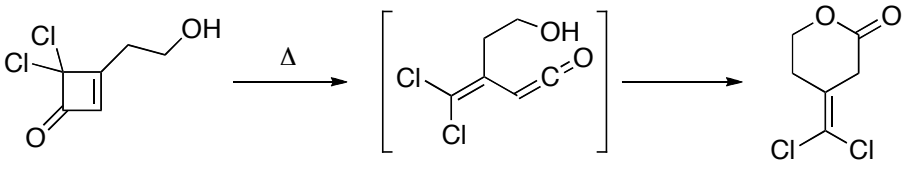
Scheme 2-21. Olefination of a ketene to an allene



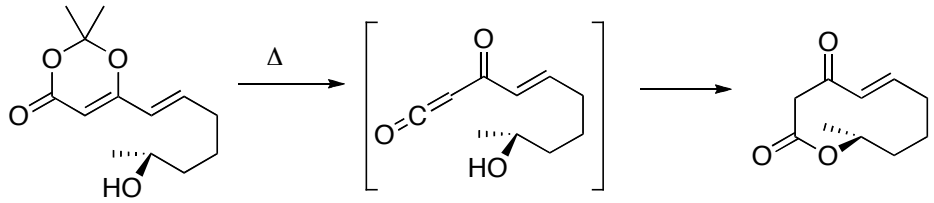
2.2.2.3 Ketene cyclization

Due to its superb electrophilicity, ketenes have been used for many cyclizations to construct medium to large ring systems (Scheme 2-22).[81] By virtue of its hard character, ketenes derived from Meldrum's acid derivatives are often used to form medium-sized lactone (Scheme 2-23).[82]

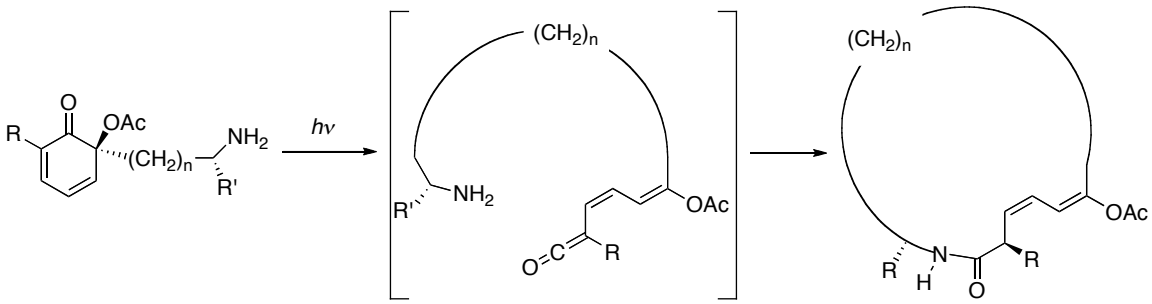
Scheme 2-22. Lactone construction via a ketene intermediate



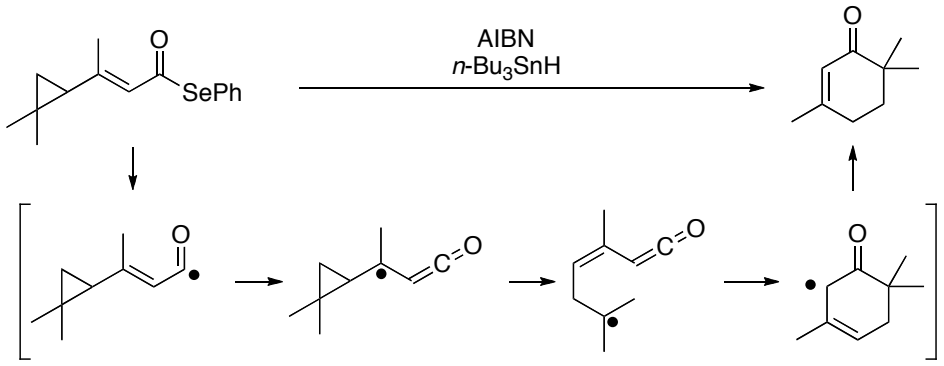
Scheme 2-23. Macrolactonization via a ketene intermediate



Scheme 2-24. Photolactamization via a ketene intermediate



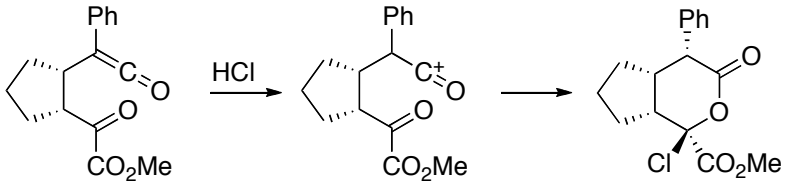
Scheme 2-25. Radical ketene cyclization and its proposed mechanism



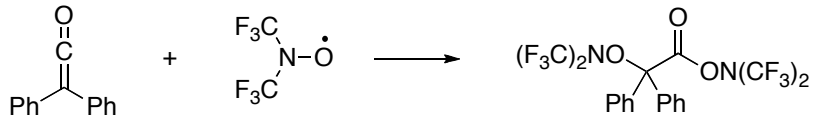
Quinkert has made seminal contributions to photolactamization to construct large ring systems via ketene intermediates (Scheme 2-24).[83] Upon irradiation, cyclohexadienone was converted to a ketene, which was trapped by a pendant primary amine to provide a lactam. Pattenden reported a radical ketene cyclization to construct a cyclohexeone (Scheme 2-25).[84] In this method, an initial acyl radical triggered the generation of a ketene and the opening of the cyclopropane, and the resulting isopropyl radical reacted with the ketene to form the six-membered ring.

2.2.2.4 Other types of reactions

Scheme 2-26. Lactonization via a protonation of a ketene



Scheme 2-27. Radical reaction of a ketene



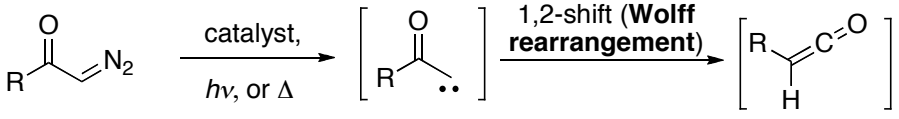
One of only a few electrophilic ketene reactions is the protonation of the ketene using acid, generating a carbocationic species (Scheme 2-26).[85]

Ketenes are also prone to undergo radical reactions, although synthetic application has not been fully explored (Scheme 2-27).[86]

2.3 Wolff rearrangement

Since Ludwig Wolff reported the first examples of the rearrangement of diazoketones in 1902, this transformation, the so-called Wolff rearrangement, has been extensively utilized in organic synthesis (Scheme 2-28).[87] Under certain conditions, a carbene intermediate is generated from a diazoketone, which is followed by 1,2-shift to give a ketene. With a limited number of exceptions, ketenes generated from Ag catalysts have only one substitution.[87a]

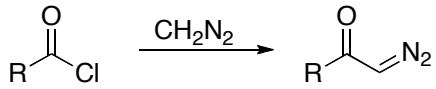
Scheme 2-28. Conversion of a diazoketone to a ketene



2.3.1 Preparation of diazoketones

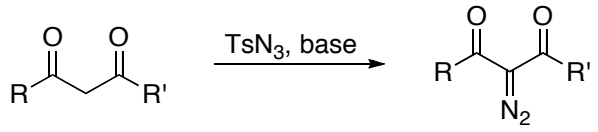
The Wolff rearrangement had not been used effectively in synthesis until a convenient method of preparing diazoketones was discovered by Arndt and Eistert (Scheme 2-29). The key for this method was to add an acid chloride into the solution of diazomethane so that liberated HCl could be trapped by another equivalent of diazomethane.[88] Although the yield of this reaction is nearly quantitative, it suffers from one drawback. That is the use of diazomethane, which is known as a hazardous and explosive reagent.[89]

Scheme 2-29. Preparation of a diazoketone by the Arndt-Eistert method

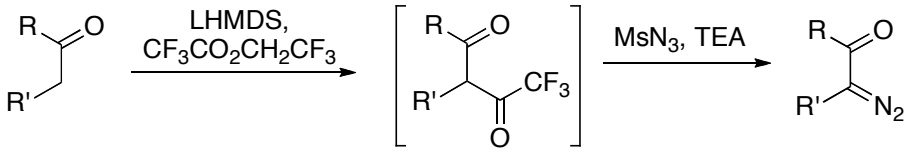


Efforts to circumvent the use of diazomethane realized a few practical methods that can be complimentary to the Arndt-Eistert diazoketone synthesis. Regitz found that an acidic methylene could react with TsN_3 under basic conditions to give a diazodiketone (Scheme 2-30).[90] Later, this approach was modified by Danheiser, enabling the use a simple ketone via *in situ* formation of *α*-trifluorocarbonyl ketone, followed by diazo transfer and liberation of CF_3CO_2H (Scheme 2-31).[91]

Scheme 2-30. Regitz diazo transfer reaction

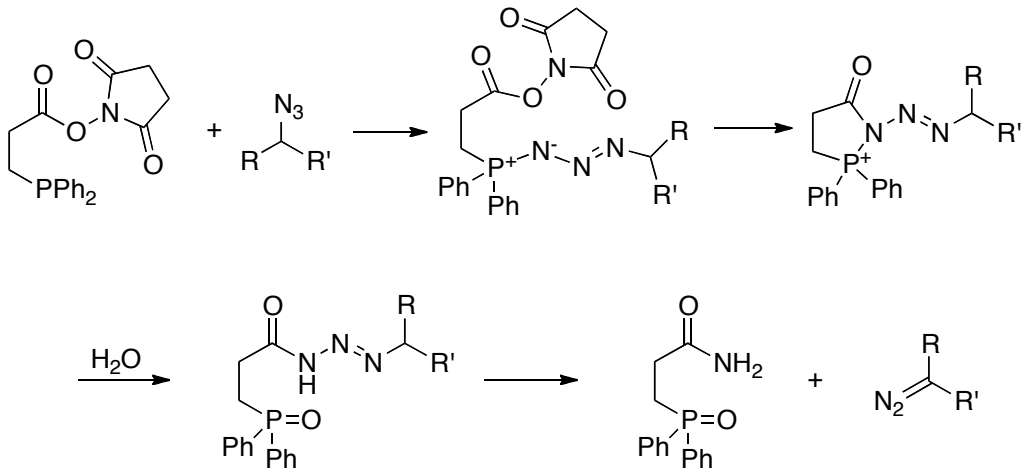


Scheme 2-31. Danheiser's modification



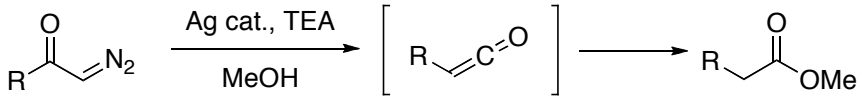
Most recently, Raines reported the conversion of azides into diazo compounds (Scheme 2-32).[92] The initial step is a Staudinger reaction, in which phosphine reacts with an azide. In the next step, however, the intermediate of the Staudinger reaction (phosphazide) is trapped by the activated ester in an intramolecular fashion, which leads to the formation of an acyl triazenophosphonium salt. Upon hydrolysis, an acyl triazene is generated, and liberation of the amide affords the diazo compound.

Scheme 2-32. Phosphine-mediated diazo synthesis from an azide



2.3.2 Conditions for the Wolff rearrangement

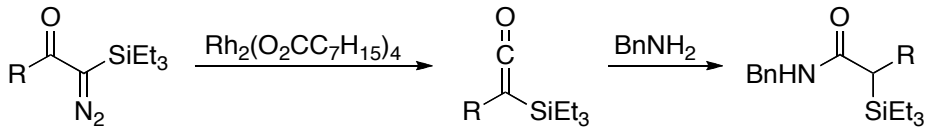
Scheme 2-33. Ag-catalyzed Wolff rearragement



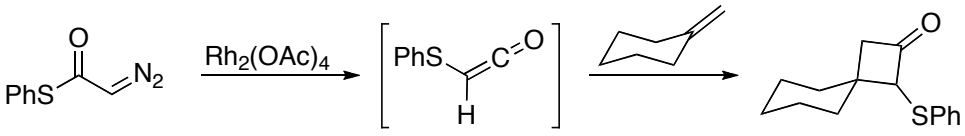
Among the several known conditions to induce the Wolff rearrangement, Ag catalysts have been the first choice (Scheme 2-33). Ag catalysts such as $PhCO_2Ag$, Ag_2O, and $AgNO_3$ have been utilized, with the occasional aid of sonication.[93] Also, tertiary amines are often used as additives. It is suggested that amine additives donate electrons to the silver catalyst and cause the formation of silver nanoclusters, which presumably catalyze the Wolff rearrangement effectively.[94]

In the presence of diazoketones, Rh catalysts are most commonly used to generate carbene intermediates that could insert into σ-bonds. However, a few reports show that some Rh catalysts could indeed induce the Wolff rearrangement, generating a ketene (Scheme 2-34, Scheme 2-35).[95] CuI is also known to catalyze the Wolff rearrangement.[93a]

Scheme 2-34. Rh-catalyzed Wolff rearrangement of silyl diazoketone



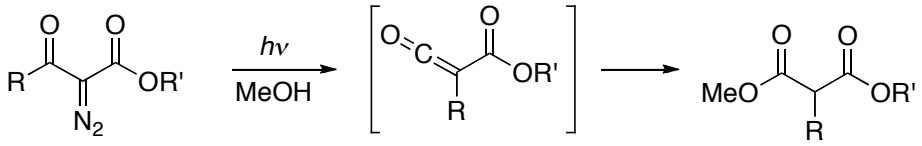
Scheme 2-35. Rh-catalyzed Wolff rearrangement of diazo thioester



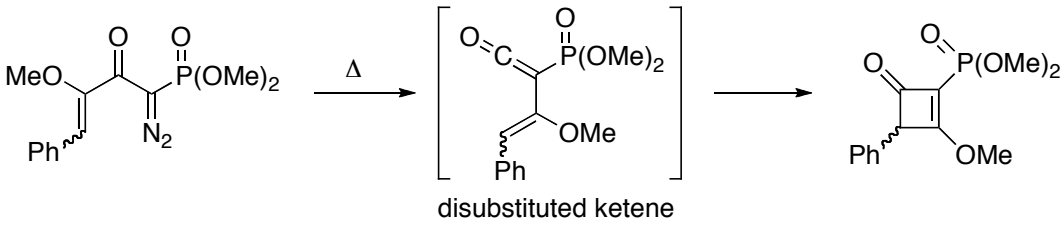
In general, disubstituted diazo compounds do not undergo Wolff rearrangement with the aid of Ag catalysts. However, under photolytic or thermal conditions, some diazo compounds undergo Wolff rearrangement to generate

disubstituted ketenes (Scheme 2-36, Scheme 2-37).[96] In this regard, the Regitz diazotransfer serves as a beneficial method to synthesize disubsituted diazo compounds.

Scheme 2-36. Photo-catalyzed Wolff rearrangement



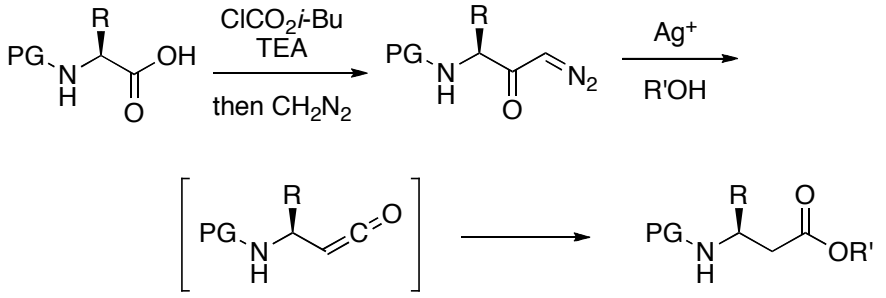
Scheme 2-37. Thermally catalyzed Wolff rearrangement



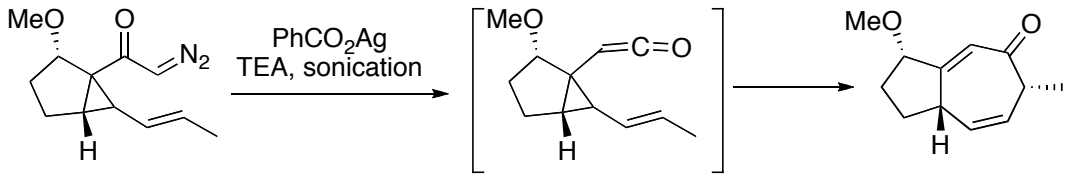
2.3.3 Application of the Wolff rearrangement

The most well-known application of the Wolff rearrangement is the Arndt-Eistert homologation. In particular, the homologation of amino acids was shown to be exceptionally useful in organic synthesis (Scheme 2-38).[97] In some cases, racemization was observed during acid chloride formation, which can be circumvented by forming mixed anhydride instead of an acid chloride. The homologated amino acids are obtained after nucleophilic addition of an alcohol or water to the ketene intermediates.

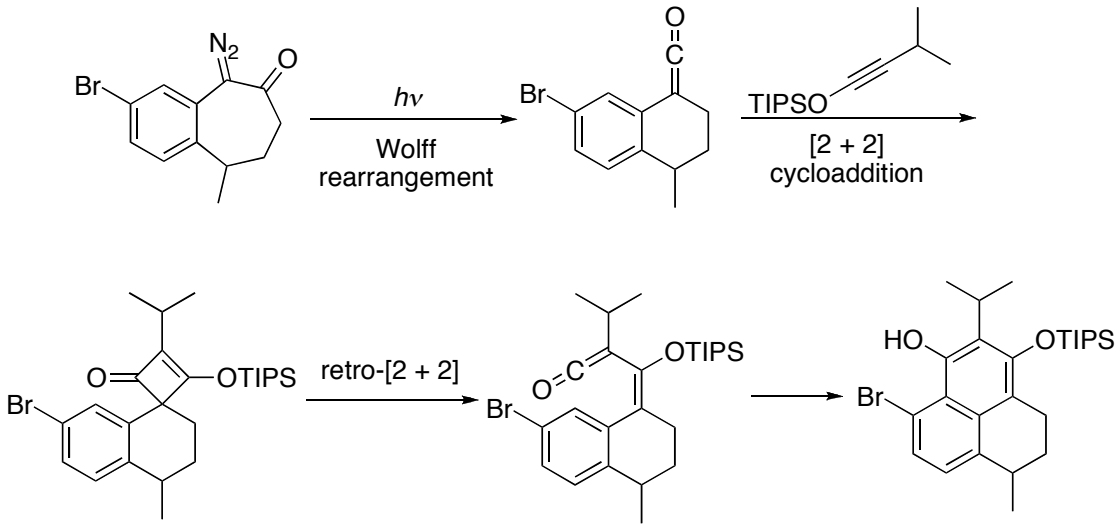
Scheme 2-38. Arndt-Eistert homologation of an *α*-amino acid



Scheme 2-39. Tandem Wolff-Cope reaction



Scheme 2-40. Danheiser benzannulation in the synthesis of salvilenone

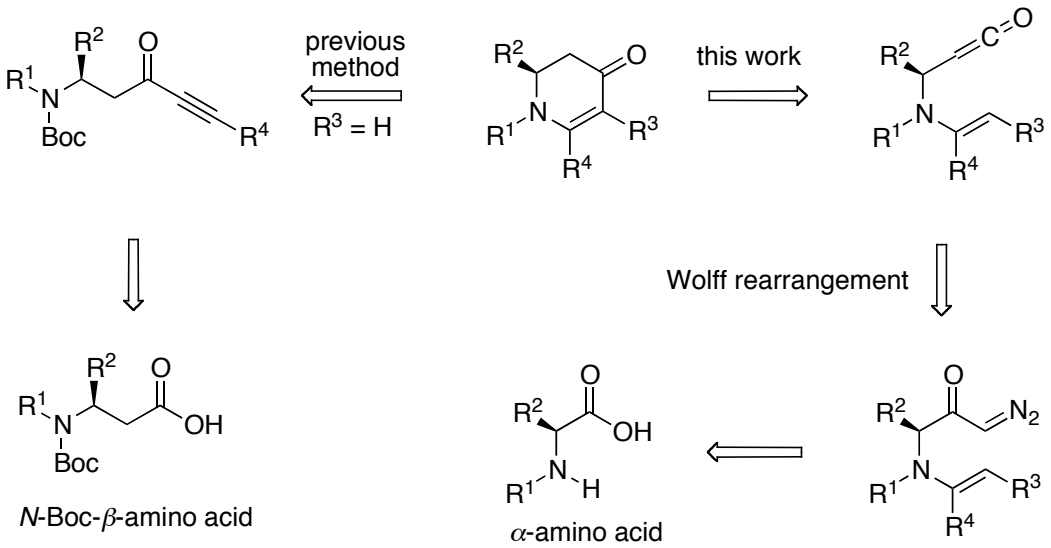


Stoltz's tandem Wolff-Cope reaction is worth noting (Scheme 2-39).[98] The diazoketone with a pendant vinyl cyclopropane underwent a Wolff rearrangement using $PhCO_2Ag$ and TEA, and the resulting ketene subsequently underwent a Cope rearrangement to furnish a seven-membered ring. This method allows rapid access to complex bicyclic enones, which can be seen in many natural products such as guanacastepene A.

Danheiser demonstrated the utility of a ketene generated from the Wolff rearrangement in the synthesis of salvilenone (Scheme 2-40).[99] Under photochemical conditions, a ketene was generated from a functionalized diazoketone, followed by [2 + 2] cycloaddition with an alkyne to give a cyclobutenone intermediate. This intermediate underwent electrocyclic cleavage to regenerate a ketene, which then participated in aromatization to give a functionalized arene system.

2.4 Retrosynthetic analysis

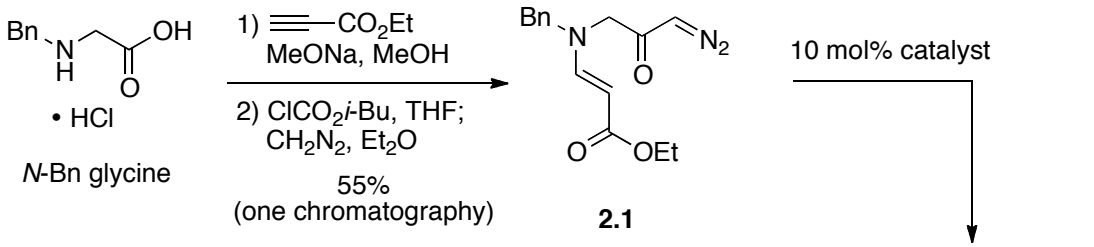
Scheme 2-41. Retrosynthetic analysis



With the knowledge of ketene chemistry and the Wolff rearrangement in mind, a new retrosynthetic disconnection of enaminones was sought. In the ynone cyclization, a retrosynthetic disconnection was made at a C–N bond of the enaminone (Scheme 2-41). As an alternative approach, our focus was drawn to the *α*-C−C bond of the enaminone. We hypothesized that for a pendant enamine, a ketene would be an excellent electrophile, which could be generated by the Wolff rearrangement of the corresponding diazoketone. The conversion of an *α*-amino acid to a diazoketone has a strong precedent, as seen in Arndt-Eistert homologation.

2.5 Optimization of reaction conditions[100]

Scheme 2-42. Optimization of reaction conditions



run[a]	catalyst	isolated yield (%)
1	Ag_2O	90
2	CF_3CO_2Ag	82
3	$AcOAg$[b]	97
4	**$PhCO_2Ag$**	**99**

[a] Reaction conditions: diazoketone in CH_2Cl_2 (0.2 M), 24 h, dark
[b] Sonication was used.

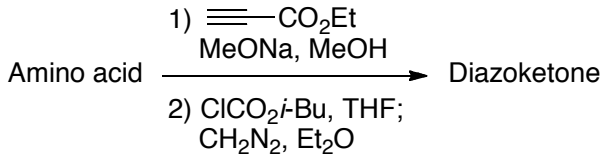
Our effort was initiated with the synthesis of diazoketone **2.1** as a starting material for the reaction in order to test the feasibility of our hypothesis (Scheme 2-42). First, *N*-Bn glycine hydrochloride was treated with ethyl propiolate under basic conditions, affording a vinylogous carbamate. In the same flask, upon evaporation of the solvent, the acid functionality was subsequently converted to a diazoketone. This process only requires one column chromatography.

With the desired diazoketone **2.1** in hand, a variety of silver salts, known to induce the Wolff rearrangement, as well as other reaction conditions were screened. To our delight, we found a few Ag catalysts that furnished the desired enaminone **2.11**. Also, halogenated solvents, especially dichloromethane, were found to be the best solvent for this transformation. The presence of triethylamine, which is often used in Arnde-Eistert homologations as an additive, diminished the yield. As a result of this study, $PhCO_2Ag$ and dichloromethane were selected as our choice of reagents.

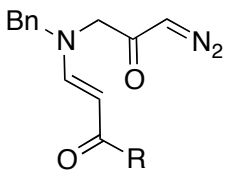
2.6 Scope and limitations

With optimized conditions in hand, the scope of the reaction was investigated employing several different alkynes and amino acids (Table 2-1). First, diazoketone **2.2**, **2.3**, and **2.4** were synthesized from *N*-Bn glycine and the corresponding alkynes. The *α*-substituted diazoketone **2.5** and **2.6** were prepared from *N*-methylalanine and *N*-methylleucine respectively. Diazoketone **2.8**, **2.9**, and **2.10** were derived from cyclic amino acids.

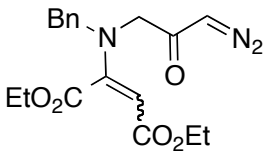
Table 2-1. Synthesized diazoketones



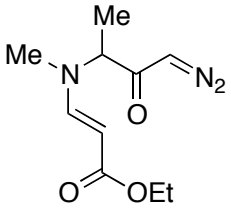
products & yields



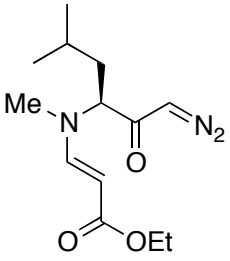
R = OEt **2.1** (55%)
= Ph **2.2** (46%)
= Me **2.3** (33%)



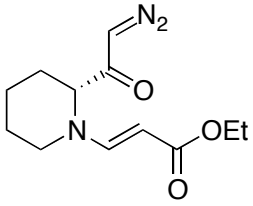
2.4 (53%)



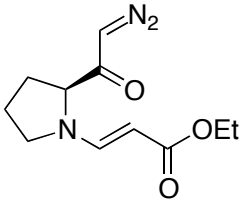
2.5 (31%)



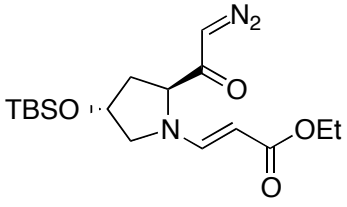
2.6 (45%)



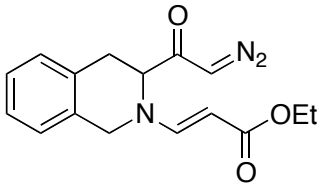
2.7 (42%)



2.8 (52%)

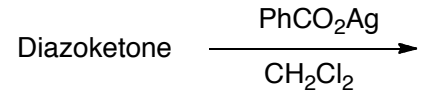


2.9 (40%)

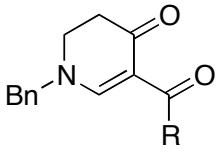


2.10 (48%)

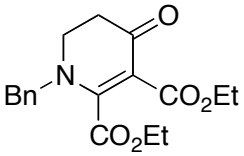
Table 2-2. Synthesized enaminones



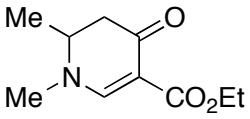
products & yields[a]



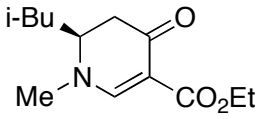
R = OEt **2.11** (99%)
= Ph **2.12** (88%)
= Me[b] **2.13** (93%)



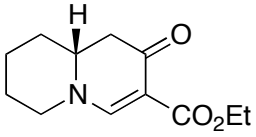
2.14 (80%)



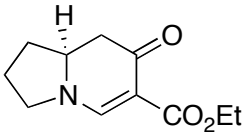
2.15 (93%)



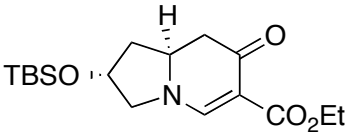
2.16 (76%)[c]



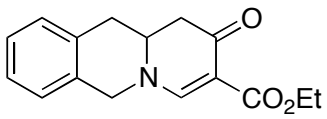
2.17 (93%)[c]



2.18 (86%)[c,d]



2.19 (79%)[e]



2.20 (81%)

Reaction condition: diazoketone and $PhCO_2Ag$ (10 mol%) in CH_2Cl_2 (0.2 M). [a] Isolated yield [b] 20 mol% of $PhCO_2Ag$ was used. [c] *ee* was ditermined by ^{19}FNMR (Mosher ester derivatives); only one isomer was observed. [d] Ag_2O (10 mol%) and $C_2H_4Cl_2$ (0.2 M) were used. [e] dr was determined by ^{1}HNMR; one isomer was observed.

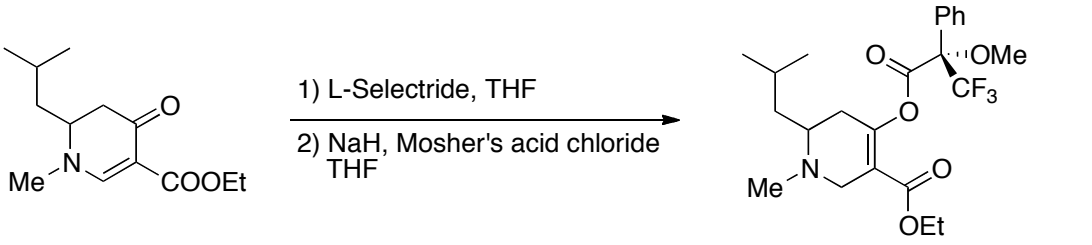
Each diazoketone was subjected to the conditions of the Wolff rearrangement (Table 2-2). A wide variety of piperidine, indolizidine, and quinolizidine ring systems were obtained in high yields.

2.7 Determination of enantiomeric ratio

Due to the relatively flat molecular shape, it was quite challenging to determine the enantiomeric ratios of the products. For example, the separation of enantiomers using a chiral HPLC or a chiral shift reagent was not successful. However, since only one diastereomer of enaminone **2.19** was observed by ^{1}H-NMR, at least its *dr* is > 95:5.

The other chiral enaminones were derivatized using Mosher's acid chloride (Scheme 2-43). First, enaminone **2.16** was treated with L-Selectride for 1,4 reduction. The resulting *β*-ketoester was *O*-acylated with Mosher's acid chloride, affording piperidine **2.21**. The racemic enaminone was derivatized similarly. The diastereomers were analyzed by HPLC, and only one enantiomer was observed.

Scheme 2-43. Derivatization of chiral/racemic enaminones



2.16 (chiral)
2.16' (racemic)

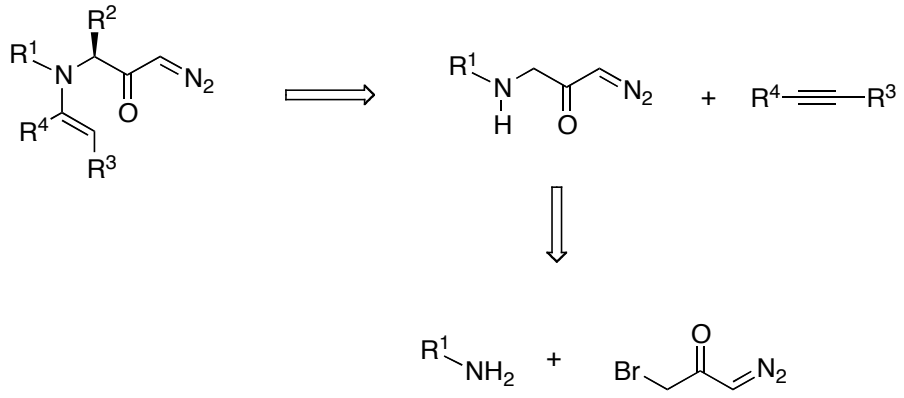
2.21 (single diastereomer)
2.21' (diastereomeric mixture)

Although one cannot rule out the possibility of chiral resolution, in other words, a major enantiomer selectively reacting with the acid chloride, these results together with ^{1}H-NMR observation of enaminone **2.19** led us to the conclusion that the cyclization proceeds without racemization.

2.8 Alternative approach: three-component synthesis of cyclic enaminones[101]

In our ketene cyclization, the diazoketone precursors were obtained from amino acids using diazomethane. Although the incorporation of chirality derived from an amino acid into the enaminone is advantageous, the use of diazomethane as well as the limited solubility of amino acids in organic solvents diminished the scale and scope of this method. For instance, *N*-methylglycine could not be used due to its insufficient solubility in MeOH. To address these issues, an alternative approach to synthesize the diazoketones was sought. We envisioned that the diazoketones could be derived from three components: a primary amine, an alkyne, and bromodiazoacetone (Scheme 2-44).

Scheme 2-44. Retrosynthetic analysis of the diazoketone

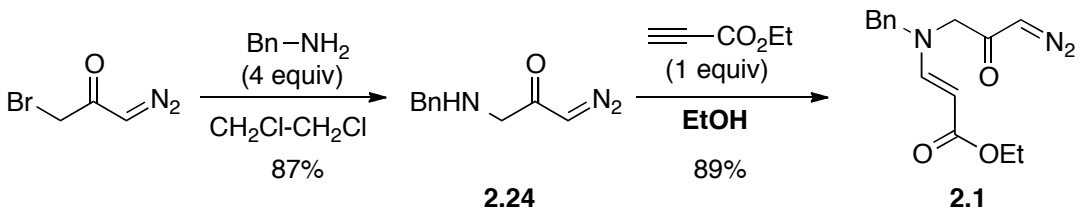


This disconnection could enable us to vary the substituents on the enaminone structure in a convergent fashion and to limit the use of diazomethane to the preparation of the common diazoacetone intermediate.

2.9 Optimization of reaction conditions

To test our hypothesis, we first investigated the synthesis of known diazoketone **2.1** (Scheme 2-45). We found that the desired product could be readily synthesized by an aza-Michael addition of benzylamino diazoacetone to ethyl propiolate. EtOH was found to be the best solvent for this Michael addition. Benzylamino diazoacetone was prepared by the treatment of readily available bromodiazoacetone with an excess of benzylamine.

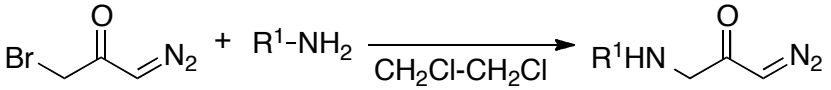
Scheme 2-45. Synthesis of diazoketone **2.1**

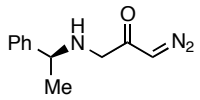
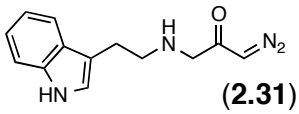


2.10 Synthesis of amino diazoketones

Encouraged by the successful synthesis of diazoketone **2.1**, several amino diazoketones were prepared in the same fashion using bromodizoacetone and alkyl amines. A variety of primary alkyl amines as well as a chiral amine and an amino acid derived-amine, afforded the corresponding amino diazoketones in good yields (Table 2-3).

Table 2-3. Synthesis of amino diazoketones



entry[a]	product	yield
1	R^1 = Bn (**2.24**)	87%
2	R^1 = Et (**2.25**)	65%
3	R^1 = *n*-Pr (**2.26**)	63%
4	R^1 = Allyl (**2.27**)	72%
5	R^1 = *n*-Bu (**2.28**)	80%
6	R^1 = -CH_2Cy (**2.29**)	81%
7	 (**2.30**)	93%
8[b]	 (**2.31**)	73%

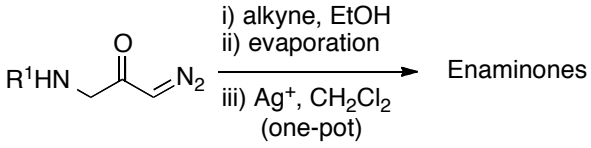
[a] Reaction conditions: bromodiazoacetone was treated with the amine (4 equiv) in dichloroethane (0.25 M) at 50 °C. [b] Bromodiazoacetone was treated with tryptamine HCl (2 equiv) in a 0.5 M MeONa/MeOH solution (0.25 M) at 50 °C.

2.11 Scope and limitation

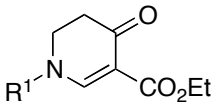
With amino diazoketones in hand, instead of isolating each diazoketone, we carried out the aza-Michael addition to the alkynes and subsequent Wolff rearrangement in a one-flask procedure. In order to obtain optimal yields, the use of two different solvents was necessary. Ethanol was employed for the aza-Michael addition, and dichloromethane for the Wolff rearrangement. Under these

reaction conditions, the enaminones were obtained in good to excellent yields (Scheme 2-46).

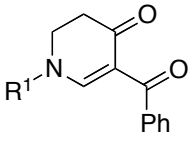
Scheme 2-46. Synthesis of an enaminone library via the sequence of aza-Michael addition, Wolff rearrangement, and ketene cyclization



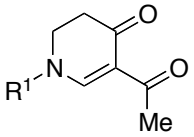
products & yields



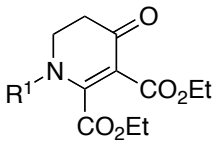
2.32 (R^1= Et) 85%
2.33 (R^1= *n*-Pr) 67%
2.34 (R^1= Allyl) 76%
2.35 (R^1= *n*-Bu) 78%
2.36 (R^1= -CH_2Cy) 88%
2.11(R^1= Bn) 82%



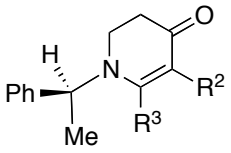
2.37 (R^1= Et) 81%
2.38 (R^1= Allyl) 63%
2.39 (R^1= *n*-Bu) 71%
2.40 (R^1= -CH_2Cy) 88%
2.12 (R^1= Bn) 68%



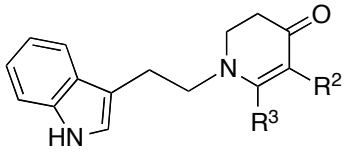
2.41 (R^1= Et) 94%
2.42 (R^1= *n*-Pr) 84%
2.43 (R^1= Allyl) 90%
2.44 (R^1= *n*-Bu) 81%
2.45 (R^1= -CH_2Cy) 92%
2.13 (R^1= Bn) 85%



2.46 (R^1= Et) 90%
2.47 (R^1= *n*-Pr) 60%
2.48 (R^1= Allyl) quant.
2.49 (R^1= *n*-Bu) 93%
2.50 (R^1= -CH_2Cy) 86%
2.14 (R^1= Bn) 92%



2.51 (R^2=CO_2Et, R^3 = H) 86%
2.52 (R^2=CO_2Et, R^3 = CO_2Et) 67%
2.53 (R^2=C(O)Me, R^3 = H) 75%
2.54 (R^2=C(O)Ph, R^3 = H) 81%



2.55 (R^2=CO_2Et, R^3 = H) 76%
2.56 (R^2=CO_2Et, R^3 = CO_2Et) 73%
2.57(R^2=C(O)Me, R^3 = H) 61%

Reaction conditions: The amino diazoketone was reacted with an alkyne (1.2 equiv) in EtOH (0.2 M). Upon evaporation, the reaction mixture was treated with the Ag catalyst (20 mol%, $PhCO_2Ag$, underline: Ag_2O) in dichloromethane (0.2 M) in the dark.

2.12 Mode of cyclization: 6-*exo*-*dig* or 6-*endo*-*dig*

This section is to analyze our novel cyclization from the perspective of Baldwin's rules. Baldwin's rules, reported first in 1976, are used to classify the formation of three- to seven-membered rings as *exo* or *endo*, involving *sp* (*dig*), sp^2 (*trig*), and sp^3 (*tet*) hybridized atoms.[102] These empirical rules are used to predict which ring-closure is favored when there are competing ring closure pathways possible. The carbon center of a ketene is an *sp* center, thus the mode of our cyclization is thought to be either 6-*exo*-*dig* or 6-*endo*-*dig*. From the context of the methodology, the main focus of discussion here is Ag-mediated cyclizations with an *sp* centers (alkyne and allene).[103]

2.12.1 Precedent 6-*exo*-*dig* cyclization

In *6-exo-dig* cyclization, a C−N or C−O bond can often be constructed by taking advantage of the nucleophilic character of heteroatoms (Figure 2-1). [104] Several transition metals, especially Au, are known to facilitate the bond formations. C−C bond formation, on the other hand, is attainable by mainly three methods: radical cyclizations,[105] metal-mediated cyclizations (M = Au, Pt, Pd, etc),[106] and anionic cyclizations.[107]

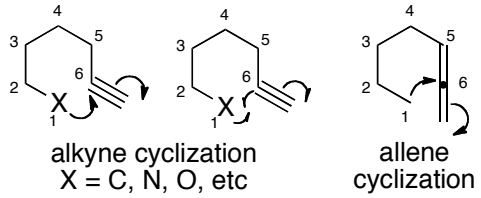
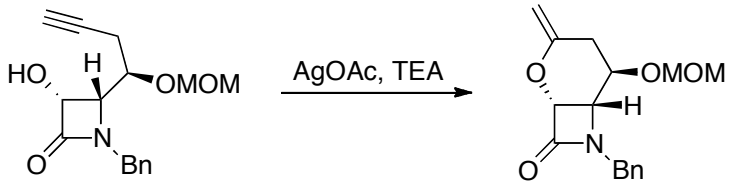


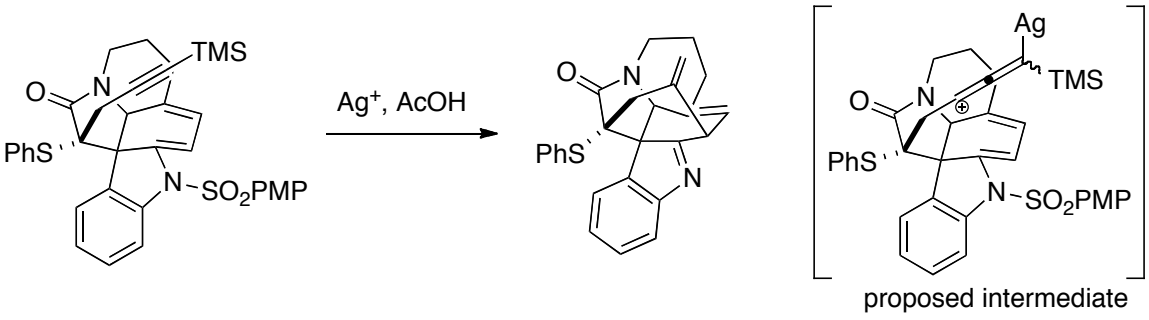
Figure 2-1. Various 6-*exo*-*dig* cyclizations.

In most cases, Ag is used as a co-catalyst for Au or other metals for its halogenophilicity, which is the tendency to form salt with halides. This event facilitates a reaction process by excluding halides from the reaction mixture, which would otherwise coordinate to metals or substrates. However, there are a few reactions where Ag acts as a Lewis acid to activate alkynes (Scheme 2-47, Scheme 2-48).[108] In the latter case, a cationic Ag-allene was proposed as the intermediate.

Scheme 2-47. Ag-catalyzed C-O bond forming cyclization



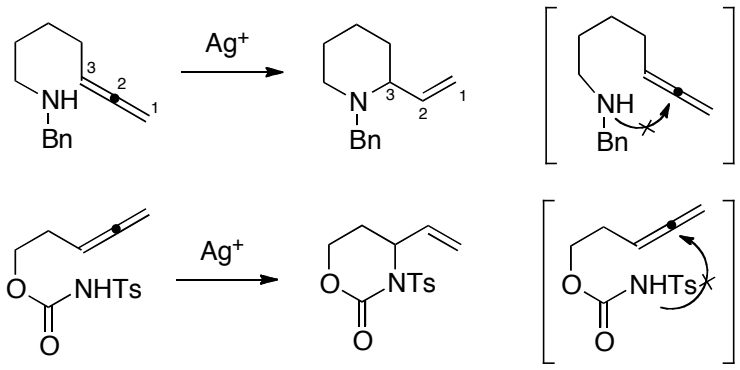
Scheme 2-48. Ag-catalyzed C−C bond forming cyclization



As for the Ag-mediated allene cyclization, we were not able to find an example where cyclization occurs at the *sp* center of an allene (C2) (Scheme

2-49). Instead, many of Ag-mediated cyclizations take place at the sp^2 center of the allene (C3), presumably leaving Ag on the C2 position.[109]

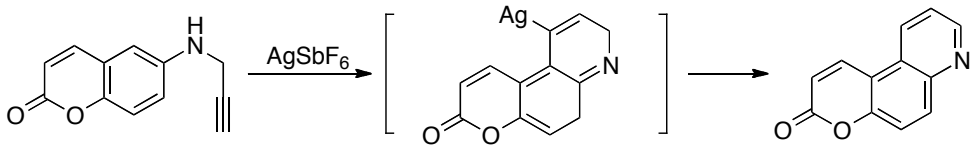
Scheme 2-49. Ag-mediated allene cyclizations



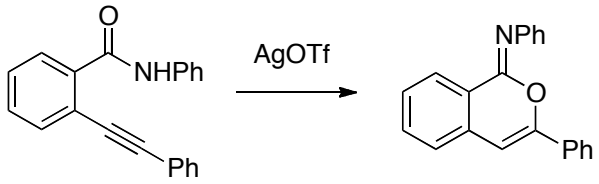
2.12.2 Precedent 6-*endo*-*dig* cyclizations

Along with several miscellaneous reactions such as radical cyclizations, a number of transition-metal catalyzed 6-*endo*-*dig* cyclizations have been reported (M = Au, Ag, Cu, Pd, etc).[110] For the same reason as discussed above, the use of Ag catalyst is mostly used as a co-catalyst for other metals. However, its ability to activate an alkyne is also known in the 6-*endo*-*dig* mode (Scheme 2-50, Scheme 2-51).[111] In the latter case, *O*-cyclization is dominant over *N*-cyclization.

Scheme 2-50. Ag-catalyzed alkyne cyclization

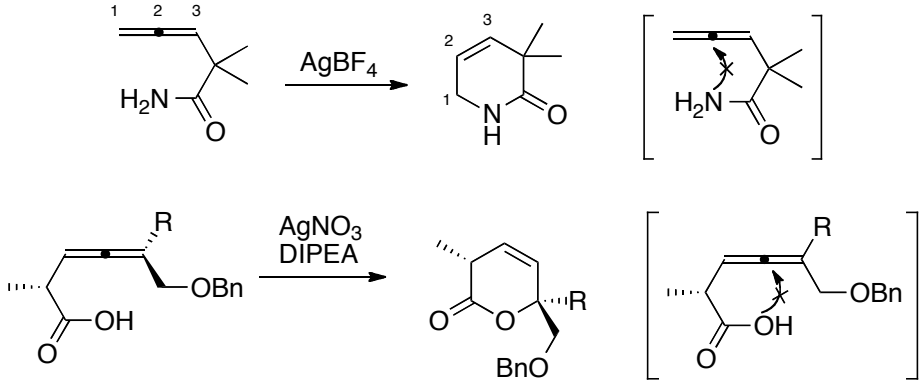


Scheme 2-51. Ag-catalyzed alkyne cyclization



As for the Ag-mediated allene cyclization, we were again unable to find a reaction where cyclization occurs at the *sp* center of an allene (C2) (Scheme 2-52). Instead, many of the Ag-mediated cyclizations take place at the sp^2 center of an allene (C1), affording internal olefin systems.[112]

Scheme 2-52. Ag-mediated allene cyclizations



2.12.3 Speculated cyclization mode of our methodology

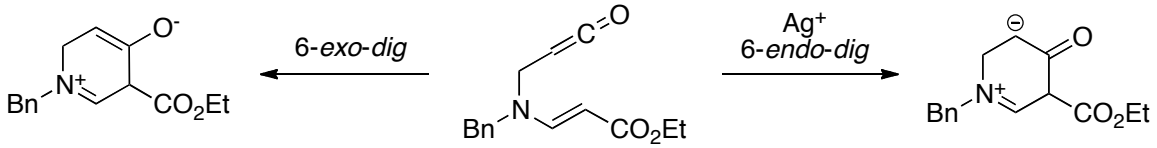
As shown above, the *sp* center of an allene was found to be unreactive toward nucleophiles upon activation by the Ag catalyst. This tendency clearly

differs from that of ketene, where the *sp* center is a predominant place of reaction, even though the allene has the same hybridization as a ketene. One can assume that this is attributed to the stability of resulting anionic intermediate. A ketene has an oxygen center to stabilize the anion, whereas an allene does not. As we have seen from many examples above, from the perspective of the cyclization mode, our cyclization represents a rare example of either a 6-*exo*-*dig* or a 6-*endo*-*dig* cyclization, in which a ketene was used as an electrophile and a carbon nucleophile was used as a nucleophile.

Ag^+ is a soft Lewis acid, and typically this indicates carbophilicity. This carbophilicity of Ag could lead us to the speculation that the mode of the cyclization might be a 6-*endo*-*dig*, if Ag was involved in not only the formation of the ketene from diazoketone but also in the cyclization itself (Scheme 2-53).

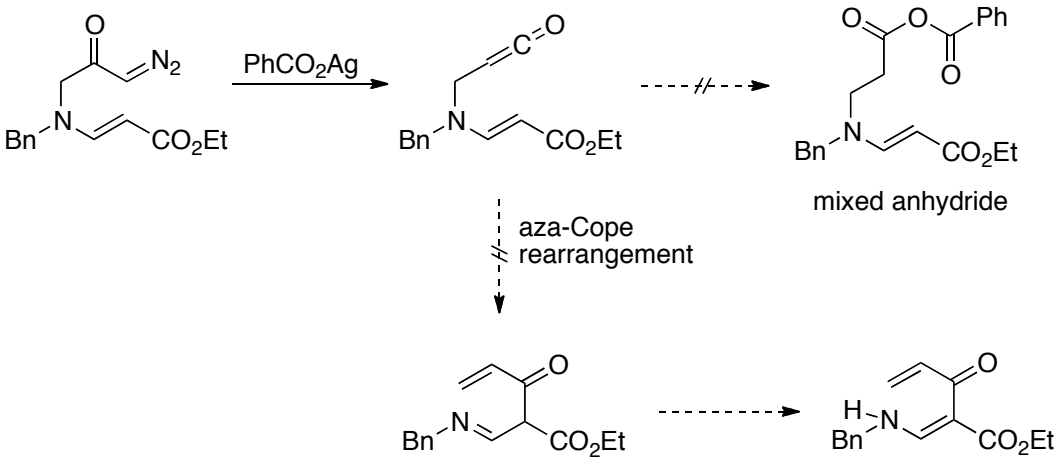
In the event that there is no involvement of Ag in the cyclization, one can suspect that the intermediate would most likely be in enolate form, which would make the cyclization a 6-*exo*-*dig* mode.

Scheme 2-53. Possible modes of our cyclization



One could also hypothesize the formation of a mixed anhydride intermediate, which could be derived from the addition of benzoate to the ketene (Scheme 2-54). However, the cyclization takes place with Ag_2O as well, which makes this hypothesis unlikely. Although one can imagine the aza-Cope pathway as the intermediate after ketene formation, this mechanism can be easily ruled out due to the lack of racemization in this methodology.[113]

Scheme 2-54. Unlikely pathways



2.13 Summary

We have developed a novel methodology to synthesize cyclic enaminones from diazoketones via the Wolff rearrangement. With this approach, it is possible to access the enaminone scaffold in two steps from commercially available starting materials without any protecting groups. One way to prepare the diazoketones is to utilize amino acids. In this case, monocyclic, bicyclic and tricyclic enaminones were obtained in an enantiospecific manner without racemization. Alternatively, the diazoketones can be prepared from bromodiazoacetone, primary amines, and alkynes. An aza-Michael addition, a Wolff rearrangement, and nucleophilic ketene cyclization were carried out sequentially in one flask, providing facile access to an enaminone library. This approach is more convergent, and limits the use of diazomethane for the preparation of bromodiazoacetone.

The ketene cyclization pathway represents a rare example of a 6-*exo*-*dig* or 6-*endo*-*dig* cyclization where a ketene is used as an electrophile. Although we

cannot determine at this point whether the cyclization takes a 6-*exo*-*dig* or 6-*endo*-*dig* mode, both are favorable transformations according to Baldwin's rule. Also, from the perspective of ketene chemistry, it is less common to observe a C−C bond formation in a nucleophilic addition reaction to ketene, whereas a C−C bond construction is a preferred process in the cycloaddition of ketene.

CHAPTER 3. ENANTIOSPECIFIC SYNTHESIS OF A NUPHAR ALKALOID

3.1 Introduction

This chapter describes the synthesis of (–)-(5*S*,8*R*,9*S*)-5-(3-furyl)-8-methyl-octahydroindolizin and its C8-epimer. Although these alkaloids contain only three stereocenters and their molecular weights are approximately 200 g/mol, we encountered a number of challenges. In particular, those challenges centered on the contradictions with prior publications, which made our research extremely difficult. Ultimately, our chemistry was validated unambiguously by X-ray analysis. Herein, we would like to share our synthesis of Nuphar alkaloids and their biological activities.

3.2 Nuphar alkaloids

Alkaloids have been isolated from a number of plants, and some of them come from traditional medicinal plants in Asia, especially from Japan and China. In this respect, Nuphar alkaloids are no exception. In 1931, Arima and Takahashi isolated an alkaloid from the rhizome of Nuphar japonicum DC., known as Kawahone or Senkotsu in Japan, which was traditionally used for medicinal purposes.[114] They named this alkaloid nupharidine as the very first Nuphar alkaloid (Figure 3-1). The structures of nupharidine and other constituents in the rhizome were studied later by Arata and coworkers using chemical derivatizations such as exhaustive methylation and ozonolysis.[115] Their study was reported in over 20 communications, ultimately leading to the structure determination of three Nuphar alkaloids: nupharidine,

desoxynupharidine, and nupharamine. Typically, those alkaloids possess 3-furan groups attached to quinolizidine, indolizidine, and the piperidine systems, and synthesis of those compounds also supported the validity of their structures.[116]

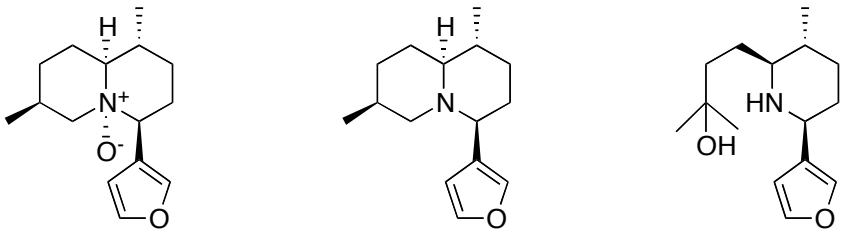


Figure 3-1. Nuphar alkaloids isolated first.

In 1962, Achmatowicz isolated a sulfur-containing alkaloid from Nuphar luteum, the yellow water lily, that is a species different from Kawahone.[117] Its structure was later elucidated by Acmatowicz and Wróbel (Figure 3-2).[118] A structurally-related alkaloid was isolated by LaLonde later.[119] These alkaloids have been a focus of chemical and biomedical research due to their interesting biological activities.[120] They were found to possess apoptosis-inducing, anti-metastatic, and immunosuppressive activities.[121]

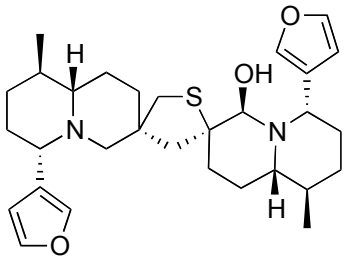


Figure 3-2. An example of a biologically active Nuphar alkaloid.

3.3 Castoreum

Plants are not the only source of Nuphar alkaloids. In fact, they were also discovered in the extract of the dried scent glands of beavers, known as Castoreum.[122] Castoreum is a strong-smelling secretion produced in the anal castor sacs of beavers. Beavers are large rodents that live in family units, and are considered territorial. It is believed that beavers use their secretion to mark territory as well as to attract the opposite sex.

Although it is unclear at what point people started using Castoreum for any purpose, its history can be traced back to ancient Greek and Rome. In the Hippocratic corpus, Castoreum seems to be used in gynecological context for women.[123] Herodotus noted that it was used to cure the womb. Also, it is said that Julius Caesar used Castoreum in his "Caesar's antidote" for the treatment of headache, heart palpitation, and delayed mense.[124] In recent years, Castoreum has been extensively used in perfumery for over 80 years, and has been approved by the FDA as a food additive, especially in vanilla flavored foods.[125] In 1976, B. Maurer and G. Ohloff reported the isolation of fourteen nitrogen-containing compounds from Castoreum, and eight of them were (−)-castoramin and closely related analogs (Figure 3-3).[126]

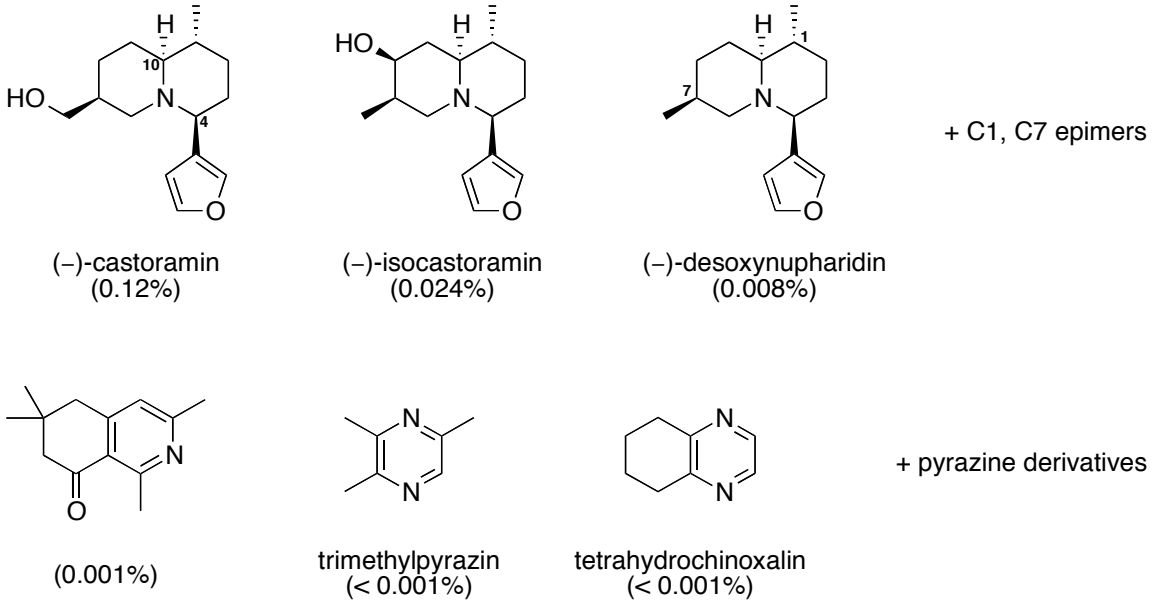
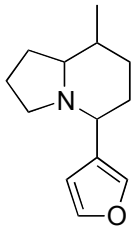


Figure 3-3. Selected components in Castoreum.

3.4 5-(3-Furyl)-8-methyl-octahydroindolizins and their prior syntheses

3.4.1 Background



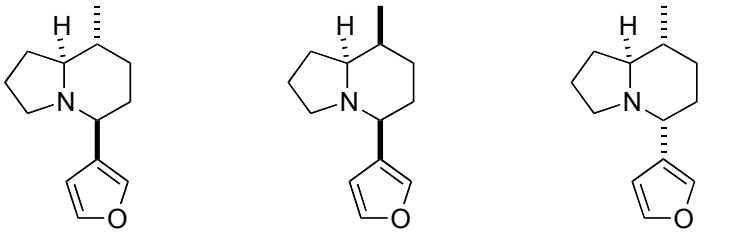
3

Figure 3-4. 5-(3-Furyl)-8-methyl-octahydroindolizin (**3**).

5-(3-Furyl)-8-methyl-octahydroindolizin (**3**) is a minor component (<0.0002%) in Castoreum (Figure 3-4). Due to insufficient quantities from natural sources, its structure was assigned based on mass fragmentation analysis. The relative and absolute stereochemistry remained ambiguous at that time. No biological activity of the compound has been reported to date.

3.4.2 Racemic syntheses

Three isomers of alkaloid **3** have been synthesized in racemic form (Figure 3-5).[127] Among the reported racemic syntheses, Ban's approach is worth noting (Scheme 3-1).[127b] His approach started with a diketone having a protected amine. Upon deprotection of the amine functionality under basic conditions, the intermediate **B** underwent cyclization to form a hemiaminal **C**, which was subsequently converted into an enol amide **D** via retro-aldol reaction. Upon acidic treatment, the ketoamide underwent a transannular cyclization to form the indolizidine system **E**, followed by dehydration to furnish **F**.



rac-**3.1**

LaLonde (1980)
Tufariello (1987)
Bates (2010)

rac-**3.2**

Ban (1983)

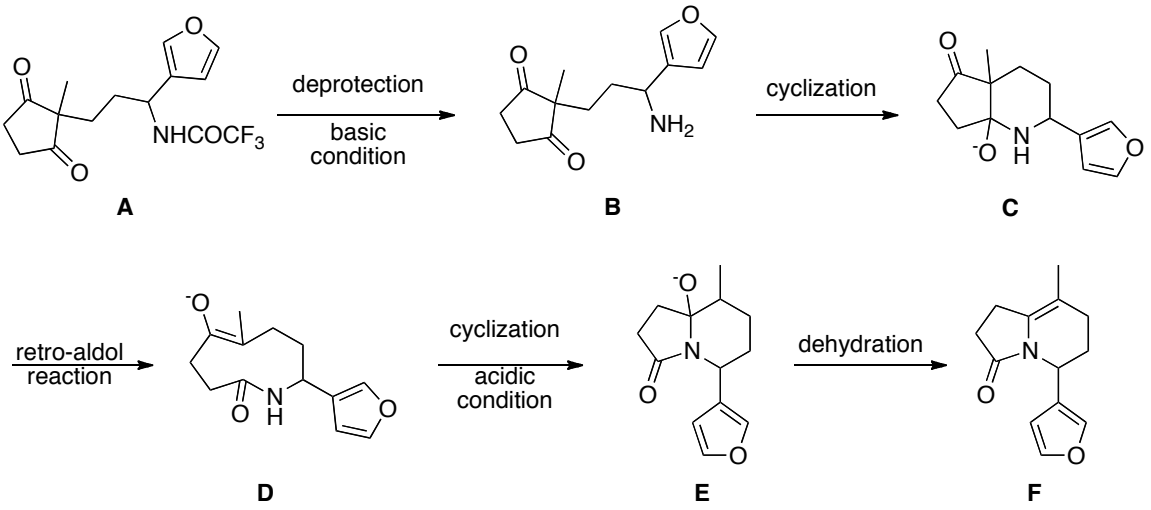
rac-**3.3**

Ban (1983)
Kurihara (1990)
Clive (1991)

Figure 3-5. Structures of synthesized compounds in racemic form.

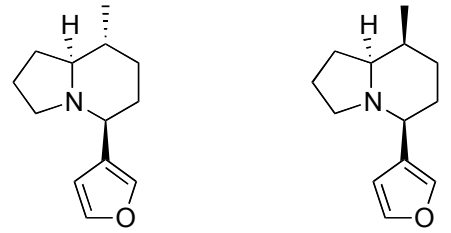
In pursuit of structural determination of the natural product, four groups analyzed their final products by GCMS. Lalonde and Tufariello independently analyzed *rac*-**3.1** and observed an identical fragmentation spectrum to that of the natural product. Ban noted in his paper that the GCMS spectra of his compounds (*rac*- **3.2** and **3.3**) were almost identical to that of the natural product. Kurihara also observed in his synthesis of rac-**3.3** that the spectrum of his final compound was identical to that of the natural product. This leads to the speculation that the stereochemical difference of compounds might not be reflected in GCMS fragmentation, which is somewhat understandable considering the structural similarity of the alkaloids (*rac*- **3.1**, **3.2**, and **3.3**).

Scheme 3-1. Ban's synthesis of the indolizidine system via retro-aldol reaction



3.4.3 Asymmetric/Enantiospecific syntheses

To date, three different groups have reported enantiospecific syntheses of alkaloid **3.1** and **3.2** (Figure 3-6).[128]



3.1 **3.2**

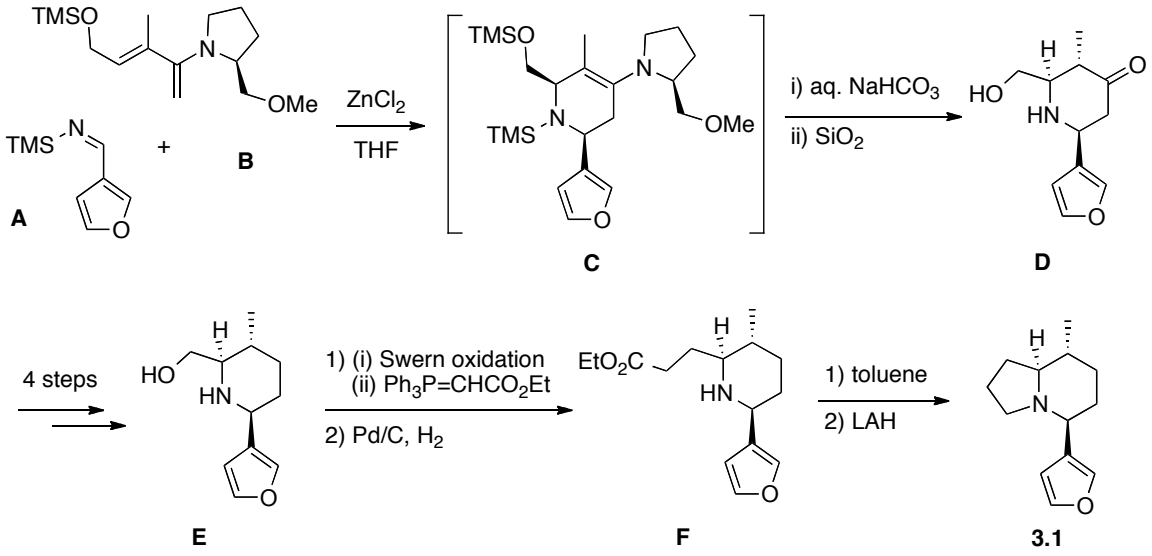
Barluenga (1999)
Davis (2006)
Kunz (2009)

Kunz (2009)

Figure 3-6. Structures of synthesized compounds in enantioenriched form.

3.4.3.1 First synthesis by Barluenga (1999)

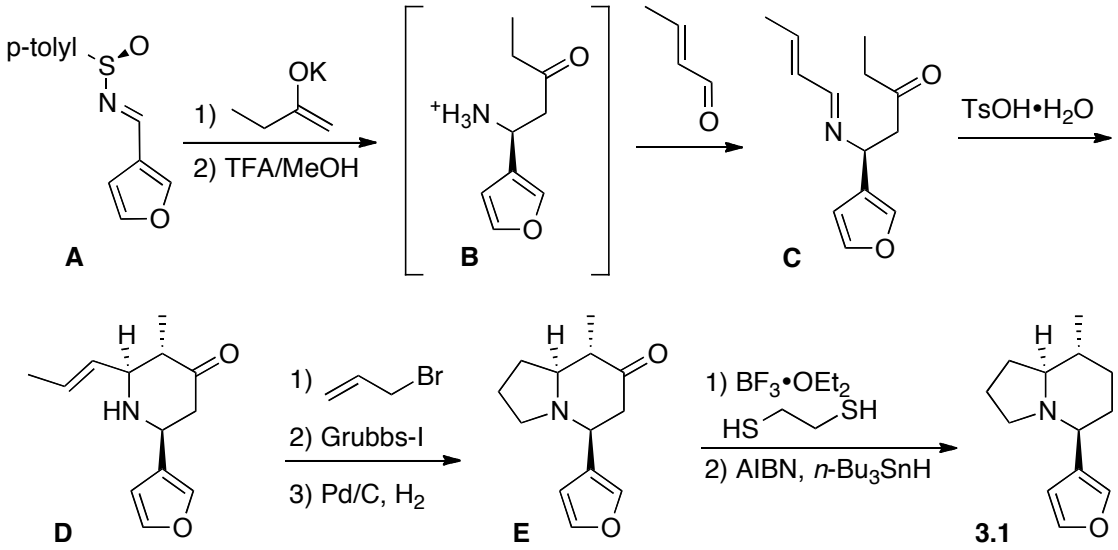
Scheme 3-2. Barluenga's synthetic route



Barluenga reported the first enantiospecific synthesis of **3.1** in 1999 (Scheme 3-2). The key step in the synthesis is the hetero Diels-Alder reaction between functionalized diene **A** and imine **B**, which was derived respectively from the hydroamination of the proline derivative to a terminal alkyne using $HgCl_2$ and the condensation between 3-furancarboxaldehyde and the amine.[129] The hetero Diels-Alder reaction afforded a piperidine structure **C** in 51% yield with > 99% *ee*, which was deoxygenated in four steps. The hydroxyl group was oxidized to an aldehyde and treated with a Wittig reagent, followed by the hydrogenation of the resulting olefin to furnish amino ester **F**. Upon heating, the amino ester underwent cyclization, and the resulting amide was reduced by LAH to give the final product.

3.4.3.2 Second synthesis by Davis (2006)

Scheme 3-3. Davis' synthetic route



Davis reported the second enantiospecific synthesis of **3.1** in 2006. The starting imine **A** was synthesized by the condensation of 3-furancarboxaldehyde and toluenesulfinamide, which underwent a Mannich reaction, followed by the deprotection of the sulfonamide to give amino ketone **B** (Scheme 3-3). After the formation of the imine using butenal, the intermediate underwent an intramolecular Mannich reaction to furnish a piperidine structure. After *N*-alkylation with allyl bromide, the RCM precursor was treated with Grubbs-I catalyst, and the resulting olefin was hydrogenated to afford an indolizidine. Lastly, the ketone functionality was removed by the formation of a thiolketal, followed by radical desulfurization using *n*-Bu_3SnH.

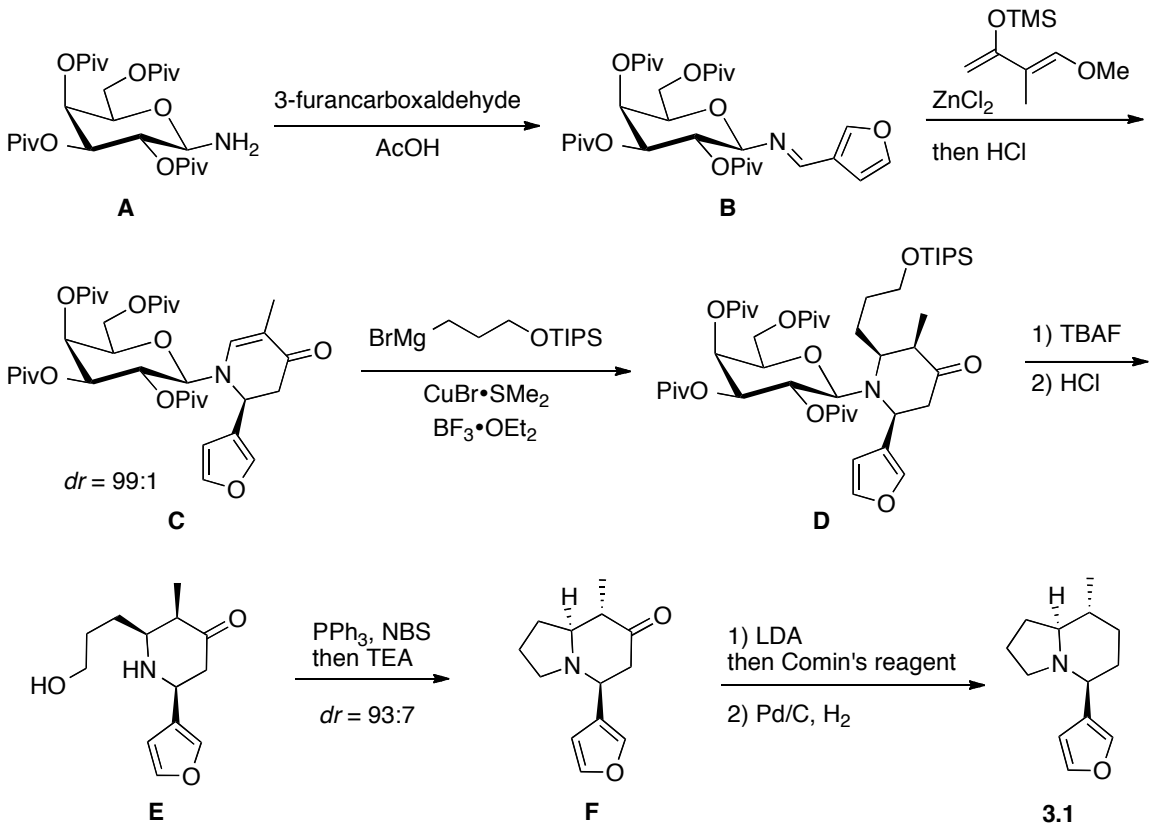
3.4.3.3 Third synthesis by Kunz (2009)

Kunz reported the third enantiospecific synthesis of **3.1** and the first enantiospecific synthesis of **3.2**. He stated in his paper that all known quinolizidines in Castoreum have the *S* configurations at C4 and C10 positions including the major component, (−)-castoramin (Figure 3-3). Assuming that the biosynthetic pathways of the compounds in Castoreum are similar to each other, he suggested that either alkaloid **3.1** or **3.2** is the natural product, and embarked on the synthesis of both alkaloids to determine the structure of the natural product.

Kunz utilized galactosylamine **A** as a chiral auxiliary (Scheme 3-4). After the condensation with 3-furancarboxaldehyde, the resulting imine **B** underwent hetero Diels-Alder reaction with a substituted Danishefsky's diene to afford the enaminone **C**. The enaminone was funcionalized by the Michael addition of a cuprate, followed by the cleavage of the TIPS group and the chiral auxiliary to provide the amino alcohol **E**. The amino alcohol underwent cyclization using PPh_3 and NBS to form **F**. During this reaction, the methyl group was isomerized to the thermodynamically more stable configuration with a diastereomeric ratio of

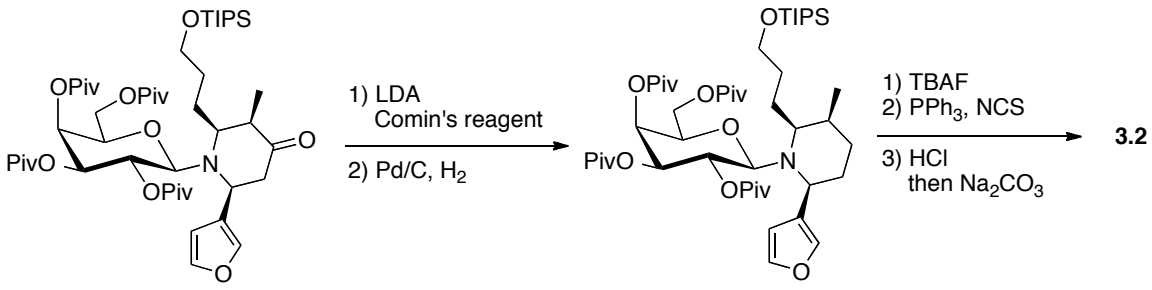
93:7. Lastly, the ketone functionality was removed by the formation of a triflate, followed by Pd-catalyzed reduction to give the final product **3.1**.

Scheme 3-4. Kunz's synthetic route for alkaloid **3.1**



The synthesis of compound **3.2** was achieved in a similar fashion (Scheme 3-5). After the Michael addition, instead of deprotecting the chiral auxiliary, deoxygenation was implemented to retain the stereochemistry of the methyl group. Then, upon deprotection of the chiral auxiliary, the indolizidine system was constructed to give the final product **3.2**.

Scheme 3-5. Kunz's synthetic route for alkaloid **3.2**



With both alkaloids in hand, Kunz analyzed **3.1** and **3.2** using GCMS, and observed that the fragmentation of **3.2** was in agreement with that of the natural product, whereas the fragmentation of **3.1** has several missing peaks in comparison.

3.4.4 Contradictions among the prior publications

As indicated in **3.4.2**, all three isomers **3.1**, **3.2**, and **3.3** might have exactly the same GCMS fragmentation pattern based on prior publications from LaLonde, Tufariello, Ban, and Kurihara. However, this contradicts Kunz's observation where **3.1** has several missing peaks in its fragmentation spectrum.

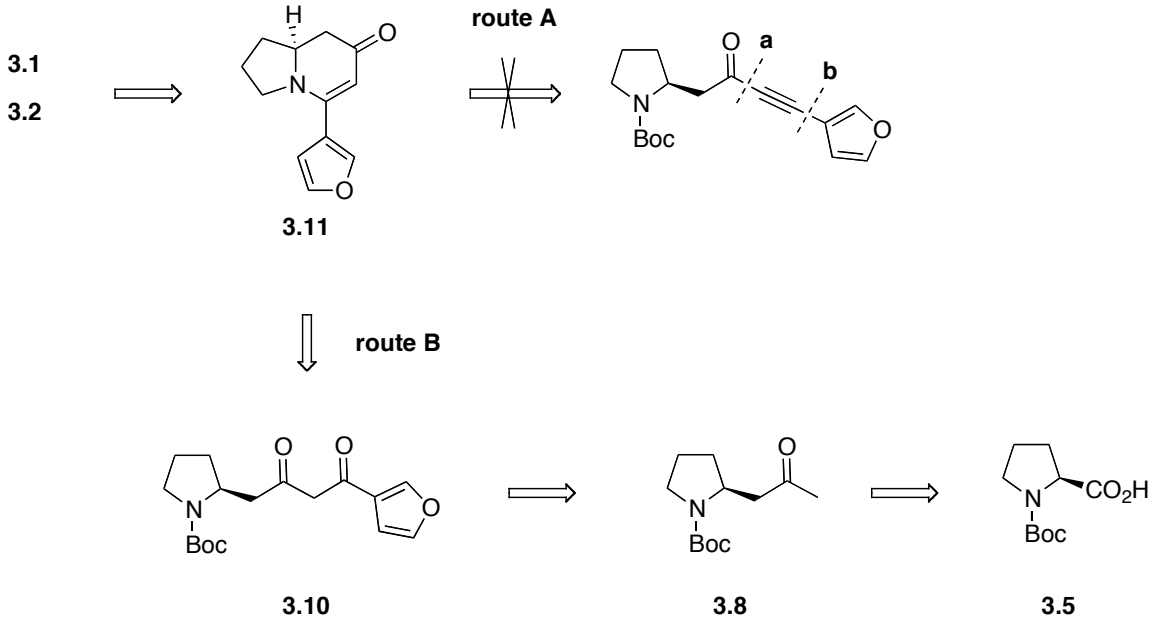
Upon close inspection of the supporting information of prior publications, we found that the ^{1}H-NMR data of compound **3.1** reported by LaLonde or Tufariello is significantly different from the ones by Barluenga or Davis. Also, the ^{1}HNMR data of Barluenga or Davis' reports is slightly different from the one by Kunz. Interestingly, the ^{13}C-NMR data reported by Kunz, Barluenga, and LaLonde all matched well. We also observed that the ^{1}H-NMR data of compound **3.2** reported by Ban differs from the one by Kunz. Considering the relatively simple structure of the target compound, this inconsistency of the ^{1}H-NMR spectra is quite surprising. In order to resolve this existing contradiction,

we expect that our synthetic approach must have a way to determine the structures in an unambiguous manner.

3.5 Synthetic strategy

We envision that our target could be synthesized from the enaminone intermediate **3.11** (Scheme 3-6). Initially our plan to synthesize this enaminone was to utilize an ynone cyclization strategy, which was developed in our group (**route A**). However, none of the attempts to synthesize the ynone either from ethynylfuran (**disconnection a**) or the coupling with the furan moiety (**disconnection b**) gave any promising results. Thus, **route B** was explored instead of **route A**. Diketone **3.10** was obtained via aldol condensation of methylketone **3.8**, which could be synthesized from *N*-Boc-(L)-proline **3.5**.

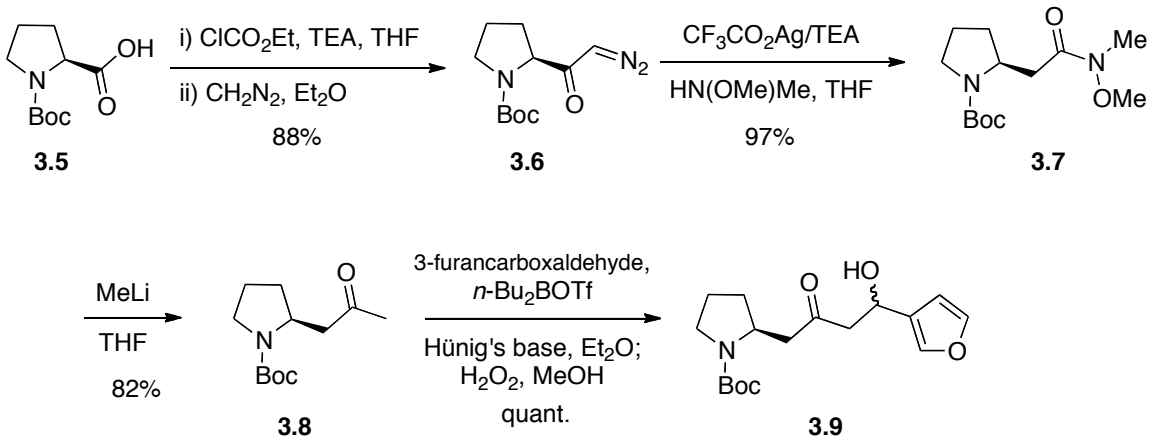
Scheme 3-6. Retrosynthetic analysis



3.6 Enantiospecific synthesis of (–)-(5*S*,8*R*,9*S*)-5-(3-furyl)-8-methyl-octahydroindolizin and its C8-epimer

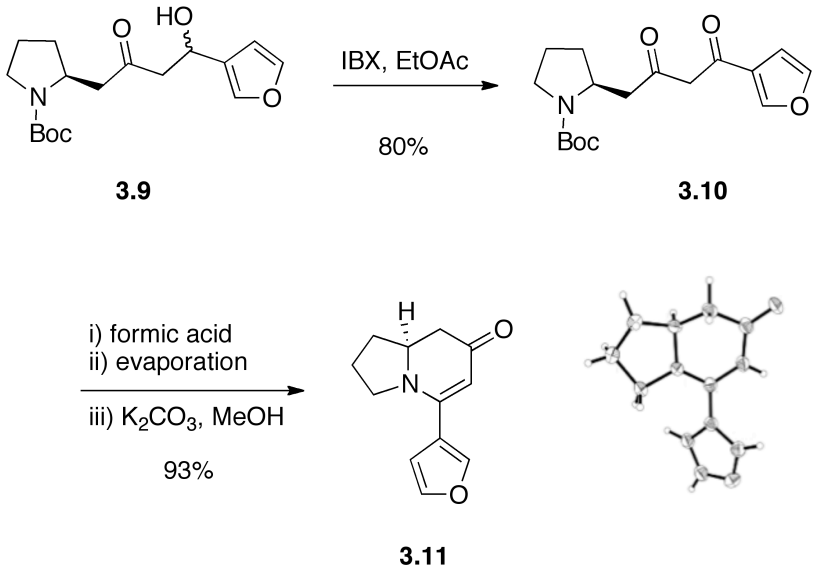
The synthesis started from *N*-Boc-(L)-proline **3.5**, which was converted to diazoketone **3.6** using diazomethane (Scheme 3-7). This diazoketone was first treated with a Ag catalyst to generate the ketene intermediate *in situ*. The nucleophilic addition of *N,O*-dimethylhydroxylamine to the ketene furnished the homologated Weinreb amide **3.7**. The Weinreb amide was reacted with MeLi to give methylketone **3.8**.[130] Next, this ketone underwent a boron-aldol reaction with 3-furancarboxaldehyde, providing β-hydroxyketone **3.9**.

Scheme 3-7. Synthesis of β-hydroxyketone **3.9**

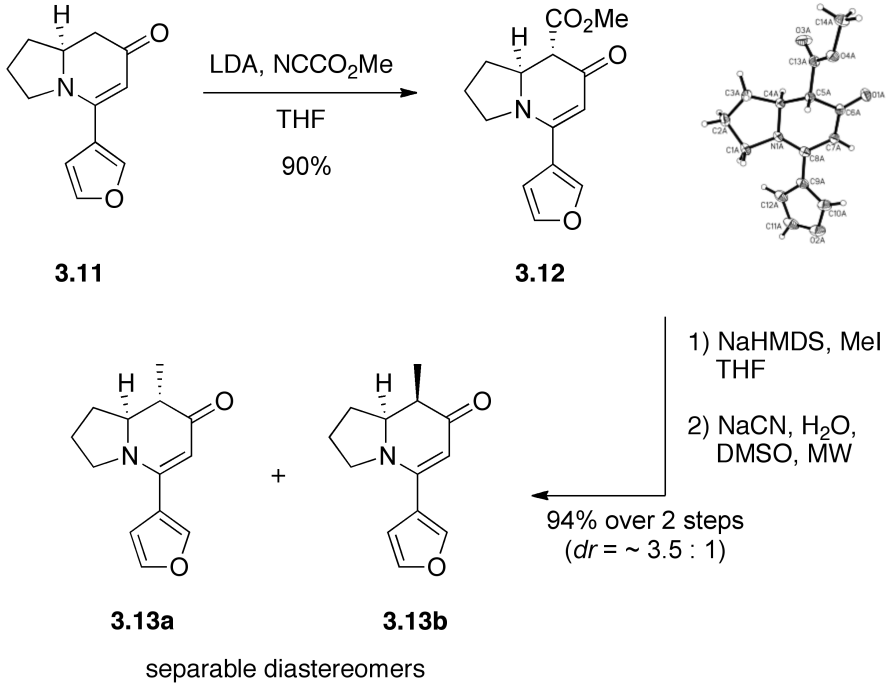


The hydroxyl group of β-hydroxyketone **3.9** was oxidized by IBX to give diketone **3.10** (Scheme 3-8). This diketone was first treated with formic acid to deprotect the Boc group. Upon evaporation of the acid, the reaction mixture was treated with K_2CO_3 in MeOH, which led to a spontaneous cyclization of the amino ketone, affording the desired enaminone **3.11**. The structure of the enaminone was confirmed by X-ray analysis.

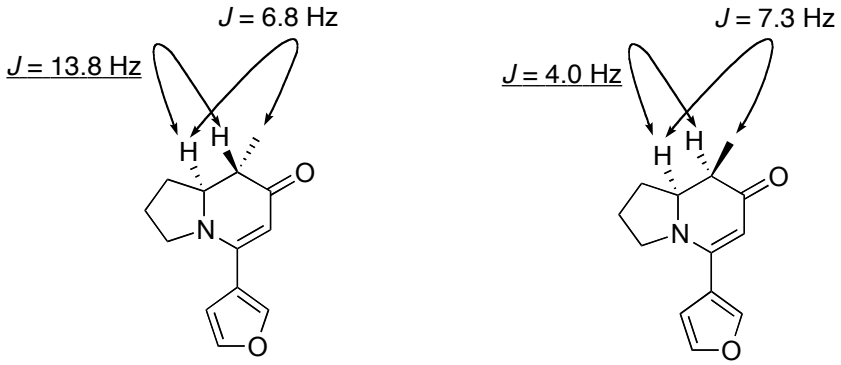
Scheme 3-8. Synthesis of the enaminone **3.11**



Scheme 3-9. Synthesis of α-methyl enaminones **3.13a** and **3.13b**



The α-alkylation of the enaminone was found to be somewhat challenging (Scheme 3-9). After screening several electrophiles, an ester group was successfully installed on enaminone **3.11** using Mander's reagent, affording the β-ketoester **3.12**. The structure of **3.12** was again confirmed by X-ray analysis. Next, the α-tertiary center of **3.12** was alkylated using MeI. The resulting diastereomeric mixture of β-ketoesters were subjected to Krapcho decarboxylation using a microwave. The α-methylated enaminones **3.13a** and **3.13b** were obtained in a thermodynamic ratio, and were separated by column chromatography. The coupling constants in ^{1}H-NMR spectra clearly indicated the relative stereochemistry of the two stereocenters (Figure 3-7). In the spectrum of **3.13a**, a large coupling constant 13.8 Hz was observed between two adjacent hydrogens, whereas 4.0 Hz was found for the corresponding coupling constant for **3.13b**. These results were further supported by the X-ray analysis of a derivative of **3.13a**, which will be discussed later.



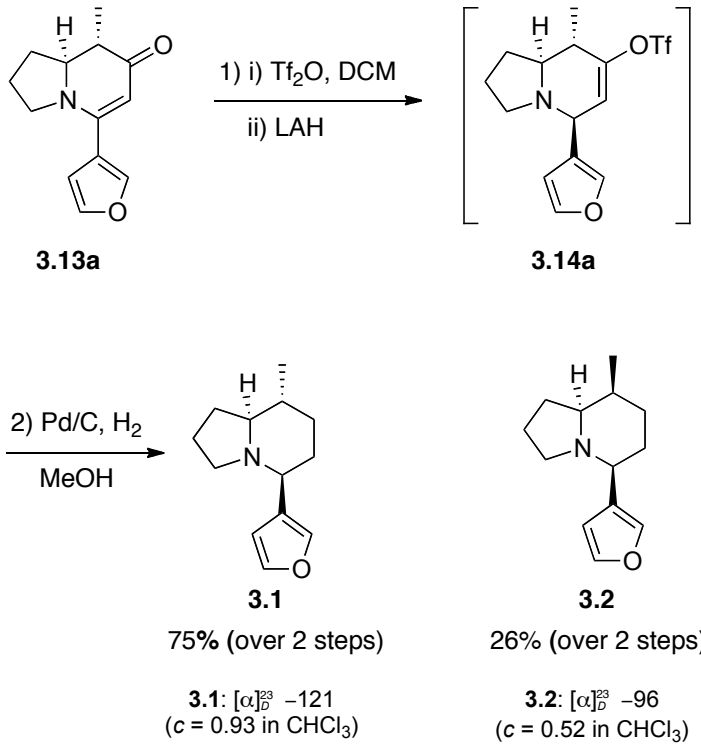
3.13a **3.13b**

Figure 3-7. Difference of the coupling constants.

The major diastereomer **3.13a** was first reacted with Tf_2O, and the resulting iminium enol triflate was reduced by LAH to give triflate **3.14a** (Scheme

3-10).[131] This crude triflate was directly subjected to Pd-catalyzed reduction to afford the final product **3.1**. The minor diastereomer **3.13b** was subjected to similar conditions, furnishing the C8-epimer **3.2**. ^{1}H- and ^{13}C-NMR data of both alkaloids were identical to those reported by Kunz.[128c] The optical rotations of alkaloid **3.1** and **3.2** were –121 and –96 respectively. Although the magnitude of the rotations was slightly different, the negative sign of the rotation was consistent with the data from Kunz, Barluenga, and Davis.[128] Given the precedent inconsistency of the ^{1}H-NMR data, however, we decided to further investigate our compounds.

Scheme 3-10. Synthesis of the final compounds



Optical rotations:

Kunz
3.1: $[\alpha]_D^{23}$ –95 (*c* = 0.35 in $CHCl_3$)
3.2: $[\alpha]_D^{25}$ –58 (*c* = 1.0 in $CHCl_3$)

Davis
3.1: $[\alpha]_D^{20}$ –98 (*c* = 1.1 in CH_2Cl_2)

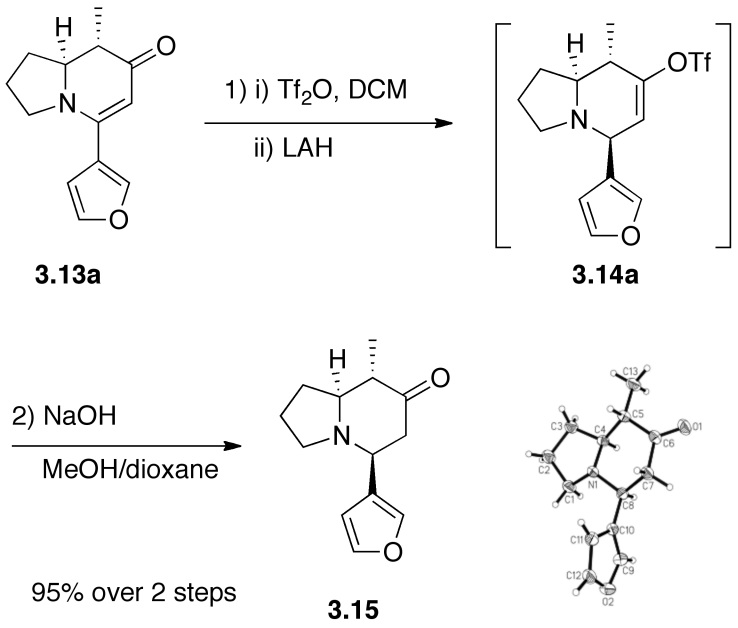
Barluenga
3.1: $[\alpha]_D^{20}$ –99 (*c* = 1.3 in CH_2Cl_2)

To establish the stereochemistry of the methyl and furan substituents, the major diastereomer **3.13a** was again reacted with Tf_2O to give a crude triflate

3.14a (Scheme 3-11). Instead of reducing the triflate functionality with hydrogen, this triflate was hydrolyzed to aminoketone **3.15**, which is already reported by Davis.[128b] Although we observed a significant difference from the Dvais' ^{1}H-NMR, the structure of our compound was unambiguously confirmed by X-ray analysis, thus providing us definitive proof that our synthesis indeed produced the desired alkaloids.

Concerned that a trace amount of acid might be altering the spectrum of **3.1** in Barluenga and Davis' reports, a substoichiometric amount of TFA was added to our compound **3.1** in $CDCl_3$. However, the addition of acid only made the peaks in ^{1}H-NMR broader, and no major change of chemical shifts was observed (0.1 ppm shift for α-protons to N-center).

Scheme 3-11. Synthesis of a known ketone **3.15**



3.7 GCMS analysis of synthesized Nuphar alkaloids

Given the inconsistent GCMS information among the precedent reports, we analyzed our compounds **3.1** and **3.2** using EI-GCMS (70 eV). Unlike Kunz's results, however, the fragmentation of both of our compounds was exactly identical to that of the natural product, which suggests that the stereochemistry of the methyl group remains ambiguous (Figure 3-8, Figure 3-9, Figure 3-10).

Although we have little information to speculate why the fragmentation of Kunz's compound produced a different spectrum from the natural product, our results are not unreasonable considering LaLonde, Tufariello, and Ban's earlier observation, where their compounds **3.1**, **3.2** and **3.3** showed similar fragmentation to the natural product.

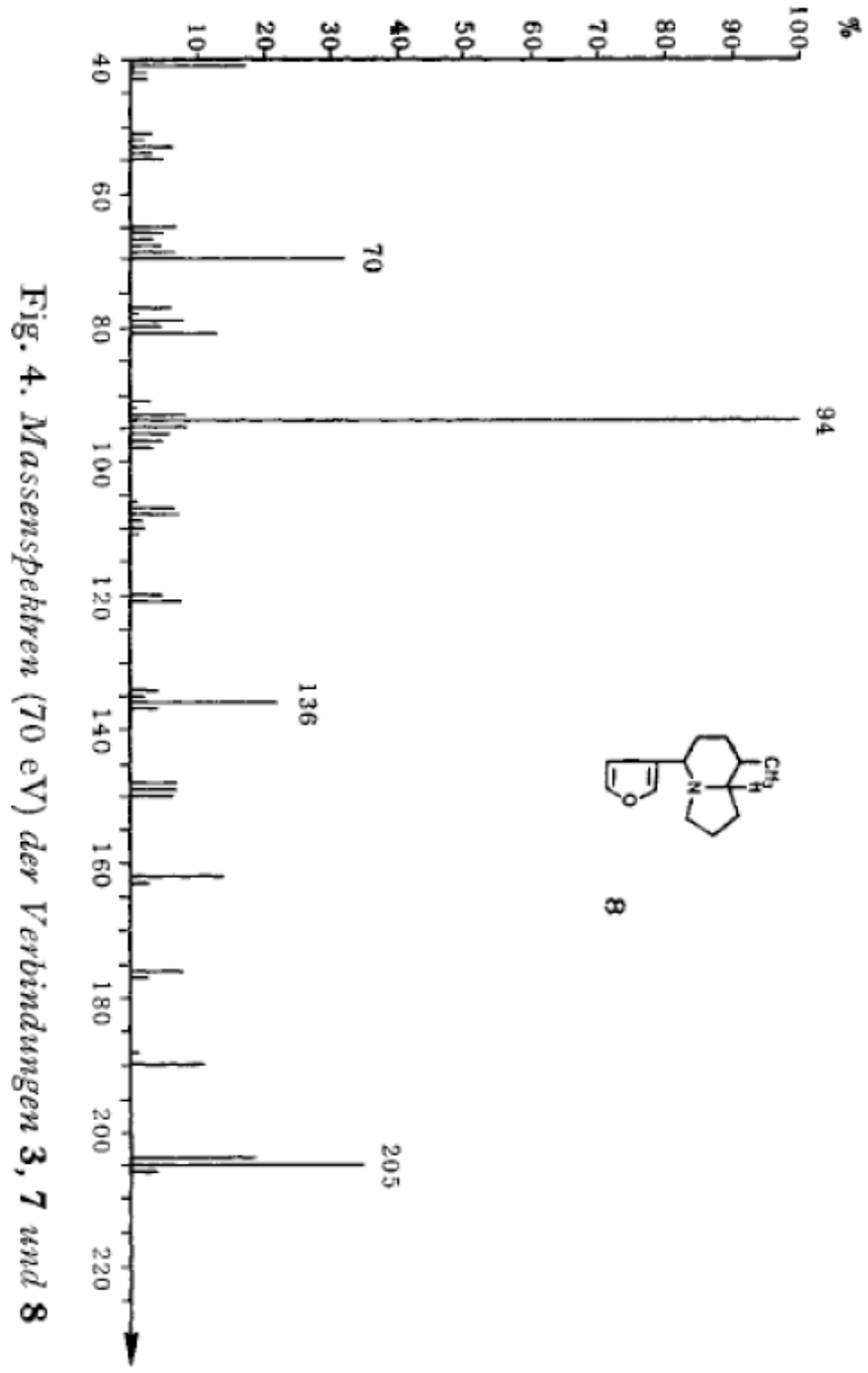


Fig. 4. *Massenspektren* (70 eV) *der Verbindungen* **3**, **7** *und* **8**

Figure 3-8. GCMS fragmentation of the natural product.[126, 132]

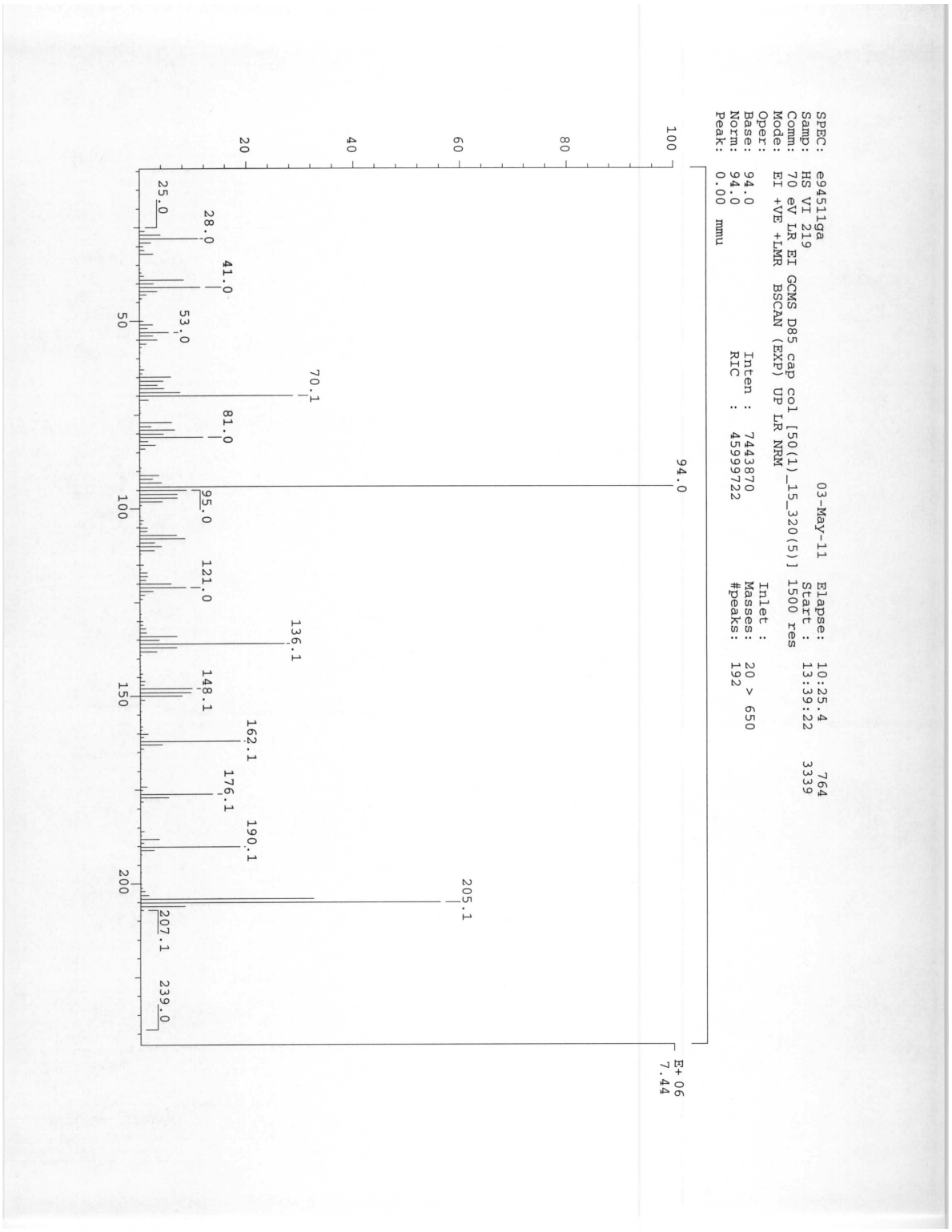


Figure 3-9. GCMS fragmentation of alkaloid **3.1**.

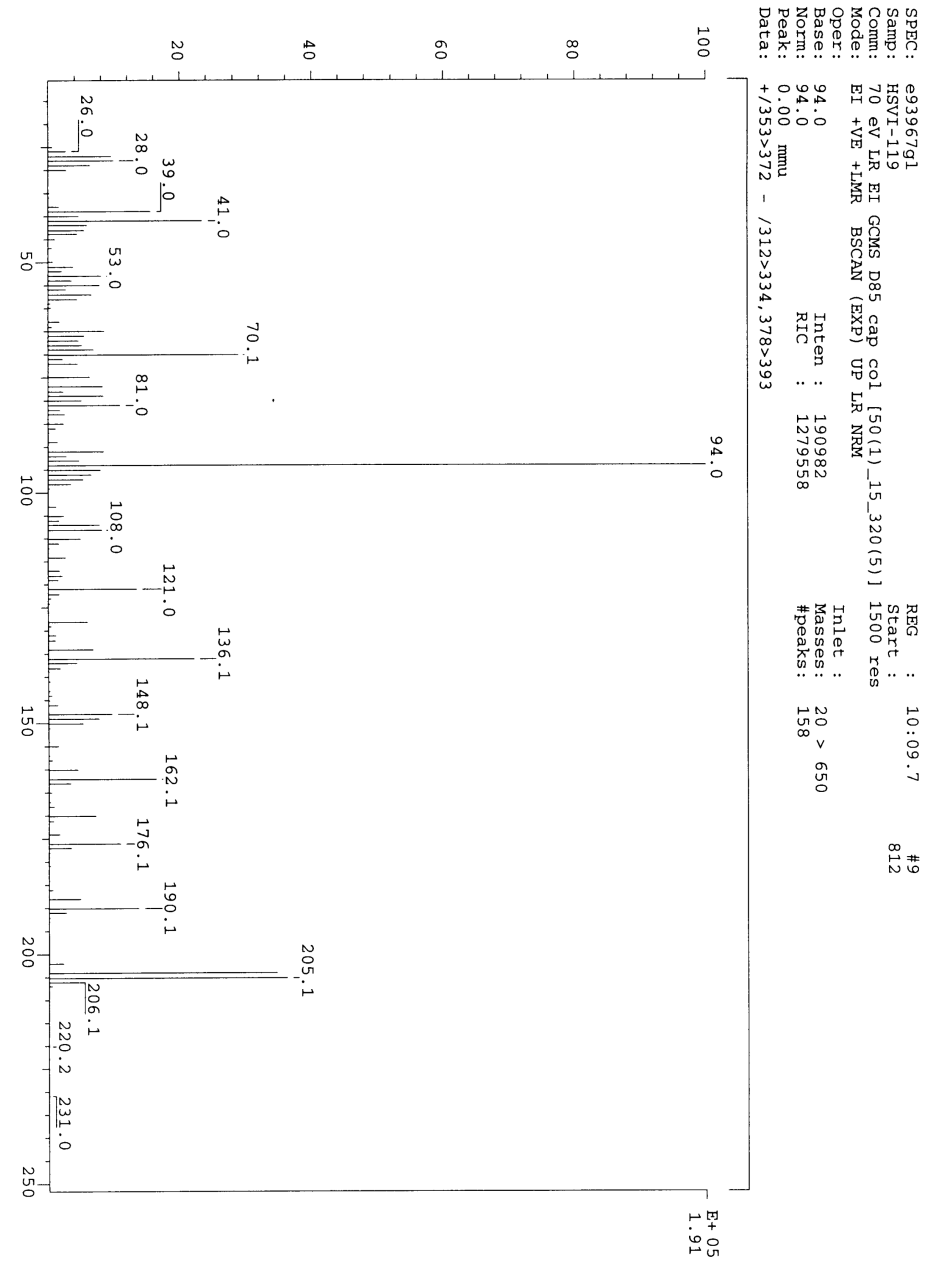


Figure 3-10. GCMS fragmentation of alkaloid **3.2**.

3.8 Biological investigation of (–)-(5*S*,8*R*,9*S*)-5-(3-furyl)-8-methyl-octahydroindolizin

3.8.1 Cytotoxic activity

The final compound **3.1** along with synthetic intermediates as well as a few derivatives were tested in the MCF-7 cancer cell line at 10 μM for their cytotoxic activity (Figure 3-11). As indicated from the approval of Castoreum by the FDA, no cytotoxicity was observed in any of the compounds.

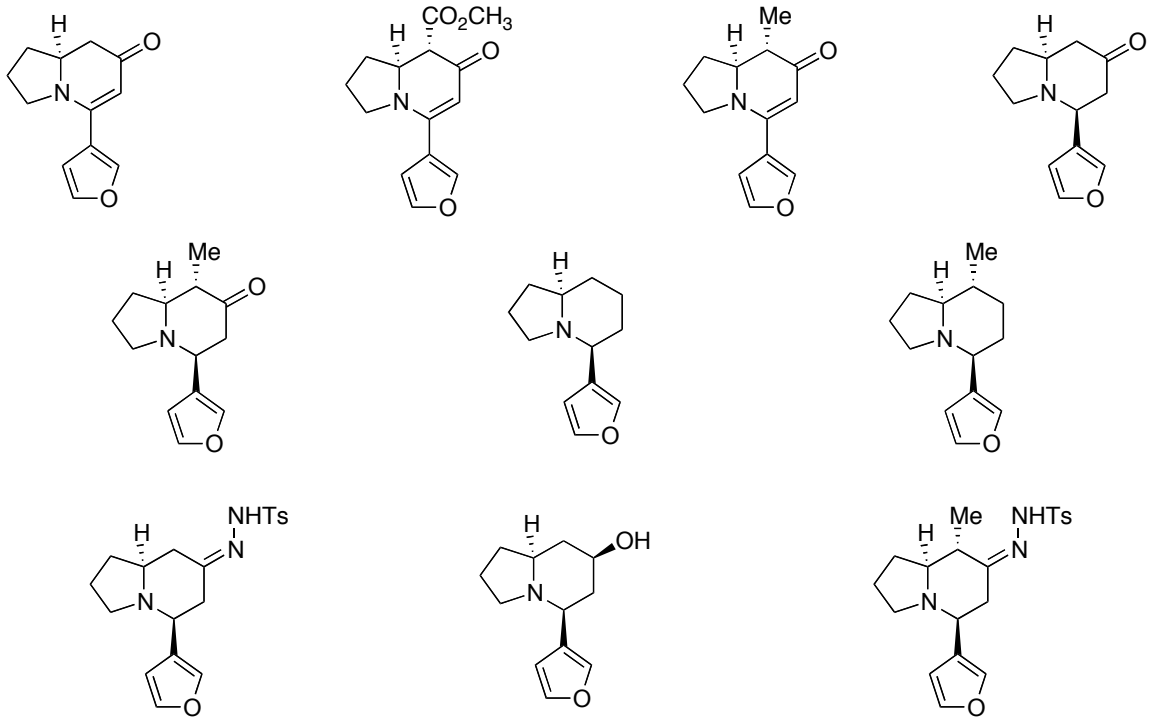


Figure 3-11. Compounds submitted to testing in a cancer cell line.

3.8.2 Binding to CNS receptors

A number of compounds having a basic amine are known to interact with CNS receptors. The tylocrebrin analogs synthesized in our group showed significant affinities to CNS receptors (see chapter 4). Since alkaloid **3.1** has a basic amine and indolizidine structure like tylocrebrin, we hypothesized that it could bind to CNS receptors. Thus, our final product **3.1** was submitted to the NIMH-Psychoactive Drug Screening Program at the University of North Carolina, and was tested for the activity in CNS receptors (Table 3-1). As indicated by the green color, the compound **3.1** was inactive in most of the receptors. However, we observed moderate bindings to the following three receptors: oxytocin, Sigma 1, and Sigma 2 receptors. Our compound was also found to be selective for the oxytocin receptor over vasopressin receptors, which have structural similarity with oxytocin receptors. It is quite intriguing that our non-peptide compound, which is as small as 200 g/mol, possesses a certain level of selectivity between those two receptors.

Oxytocin, known as a hormone or neuromodulator, is a nonapeptide agonist for the oxytocin receptor.[133] It can stimulate milk ejection and uterine contractions in the female body, and modulate mood and certain behaviors such as parental or sexual behaviors.[134] On the other hand, an oxytocin receptor antagonist (Atosiban) can halt premature labor, and has been used in several countries.[135] Thus, the affinity of **3.1** to oxytocin could explain its use in gynecology in ancient Greek.

As for the Sigma receptors, little is known despite the fact that it has been more than three decades since they were first discovered in 1976 by William Martin.[136] A number of synthetic ligands are known to bind to sigma receptors, most of which have basic amine functionalities, as seen in alkaloid **3.1** as well. However, the development of selective sigma receptor ligands over other receptors as well as subtype-selective ligands for sigma receptor is still a challenge, which renders the precise role of the receptor ambiguous. Currently, studies to use sigma receptor ligands for drug development are ongoing in many

therapeutic areas including oncology, immunology and psychiatry.[136] Also, sigma receptors have been suggested to regulate the cardiovascular systems.[137] This could be related to the use of **3.1** for the treatment of heart palpitation in ancient Greek.

Table 3-1. Results of comprehensive CNS target screening[a]

Assay <50%

Alpha1A	Alpha1B	Alpha1D	Alpha2A	Alpha2B	Alpha2C

D1	D2	D3	D4	D5	DAT	DOR

5-HT1A	5-HT1B	5-HT1D	5-ht1e	5-HT2A	5-HT2B	5-HT2C

5-HT3	H1	H2	5-ht5a	5-HT6	5-HT7

Beta1	Beta2	Beta3	BZP Rat Brain Site	MOR	NET

GABAA	KOR	M1	M2	M3	M4	M5

Oxytocin	SERT	Sigma 1	Sigma 2	V1A	V2
600		228	1,794.00	>10,000	>10,000

a) Unless otherwise indicated, data represent Ki (nM) values obtained from non-linear regression of radioligand competition binding isotherms. Ki values are calculated from best fit IC50 values using the Cheng-Prusoff equation.

Considering the small amounts of **3.1** in Castoreum and its binding affinities to the three receptors, it is unlikely that this alkaloid played a major role in Castoreum's therapeutic use. However, it is not unreasonable to speculate that the major component of Castoreum, castoramine, could have similar biological activities due to its structural similarity to **3.1**, thus constituting the therapeutic effects of Castoreum. In any case, it is quite exciting to see the correlation between our biological data and the use of Castoreum over 2000 years ago.

3.9 Speculated structure of the natural product

Since GCMS could not provide information for the structure of the natural product, we looked for clues elsewhere. Firstly, in our synthesis, we found that the alkaloid **3.2** is relatively unstable and volatile. Also, at 0 °C compound **3.1** formed white crystals whereas compound **3.2** was a clear oil.

Secondly, other components in Castoreum were taken into consideration (Figure 3-3). All three major alkaloids (castoramin and its epimers) share the configuration of the methyl group, which is in a *trans* relationship to the furan group. Although biosynthetic pathways of these compounds have not been reported, it is somewhat reasonable to speculate that our compound underwent a similar biosynthetic route to castoramin's, considering its considerably small amount from nature.

These two factors: 1) stability of the compound, and 2) the structure of castoramin, led us to the conclusion that the alkaloid **3.1** is likely to be the natural product.

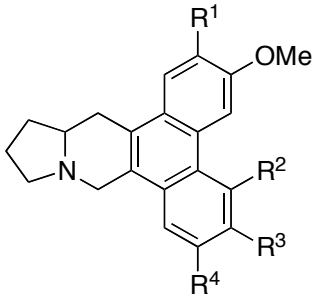
3.10 Summary

Enantiospecific syntheses of Nuphar alkaloids **3.1** and **3.2** were achieved using enaminone chemistry. The reactions employed were conventional but reliable and scalable. The final compounds were obtained in 9 steps from readily available *N*-Boc-(L)-proline, which renders our synthesis the shortest and most efficient to date. This work led to the correction of multiple prior publications, and it is the first time that any biological activity of the compound was revealed.

CHAPTER 4. EFFORTS TOWARD THE SYNTHESIS OF POLAR PHENANTHROPIPERIDINES

4.1 Background

Phenanthropiperidines are attractive drug leads primarily due to their potent cytotoxicity.[52, 138] Among over 60 phenanthropiperidines known to date, only one compound, tylocrebrine (**4.1**) has entered a clinical trial (Figure 4-1).[139] The clinical study was discontinued immediately, however, as a result of side effects such as ataxia and disorientation, which are clear signs of central nervous system (CNS) toxicity. Recently several phenanthropiperidines, including antofine (**4.3**) and tylophorine (**4.6**) were re-examined and it was revealed that they were promising anti-cancer agents with a broad spectrum and potent cytotoxicity.[140] Thus, despite tylocrebrine's side effects, interest to develop a phenanthropiperidine for chemotherapeutic use still persists.



Compound	R^1	R^2	R^3	R^4
tylocrebrine (**4.1**)	OMe	OMe	OMe	H
6-desmethoxytylocrebrine (**4.2**)	OMe	OMe	H	H
antofine (**4.3**)	OMe	H	OMe	H
7-desmethoxytylophorine (**4.4**)	OMe	H	H	OMe
deoxypergularinine (**4.5**)	H	H	OMe	OMe
tylophorine (**4.6**)	OMe	H	OMe	OMe

Figure 4-1. Phenanthropiperidines synthesized in the Georg group.

Having the development of safe phenanthropiperidines as an ultimate goal, the Georg group initiated the research by synthesizing tylocrebrine (**4.1**) and its several structural analogues with different substitution patterns on the phenanthroline core.[141] Six phenanthroindolizidines (**4.1**-**4.6**) were synthesized in the Georg group and tested in cancer cell lines (Table 4-1). Most of these alkaloids were very potent against COLO-205, MCF-7 and NCI/ADR-RES cell lines, and comparable with paclitaxel. It was shown that the removal or relocation of methoxy groups had little effect on the activity.

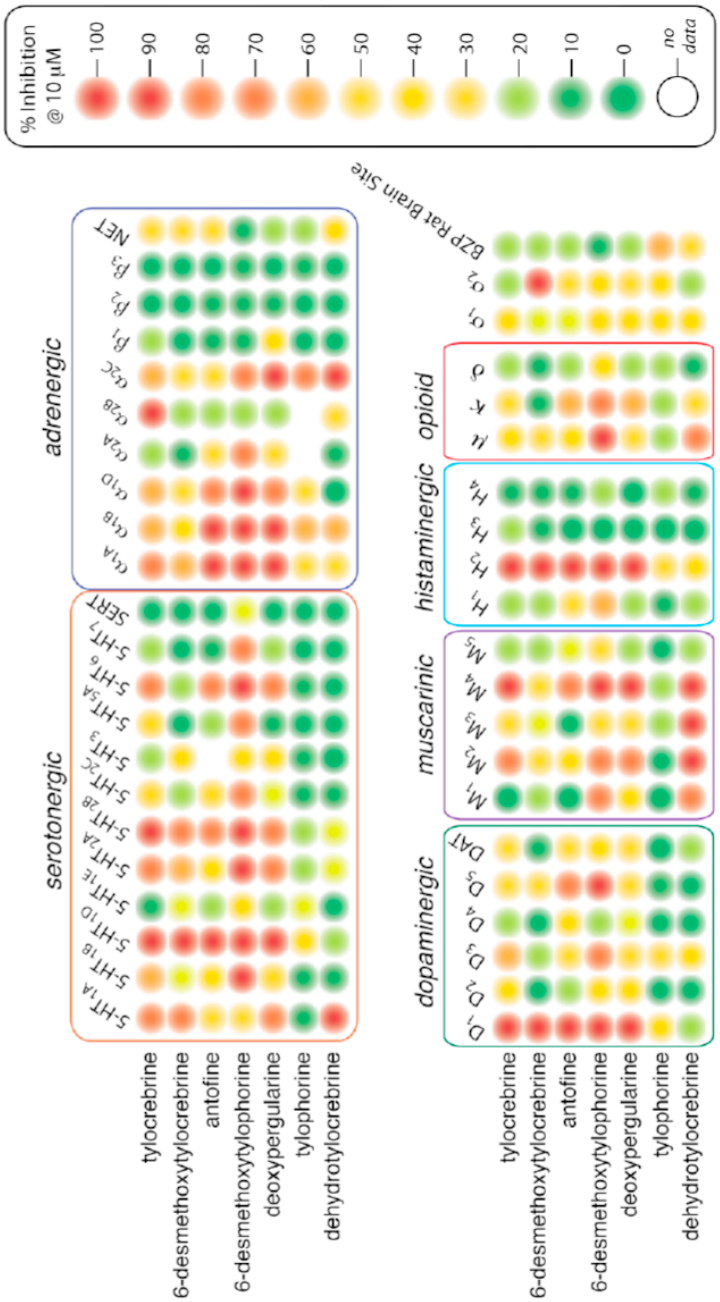
Table 4-1. Antiproliferative activity of phenanthropiperidine library

	Antiproliferative Activity		
	IC_{50} (nM)		
Compound[b]	COLO-205	MCF-7	NCI/ADR-RES
paclitaxel	5.3	2.3	>6400
(*R*)-**4.1**	1.3	15	26
4.1	12	39	46
4.2	9.5	22	16
4.3	2.8	21	23
4.4	270	530	1300
4.5	8.5	5.8	200
(*R*)-**4.6**	17	32	160
4.6	10	42	50

In collaboration with the NIHM-PDSP, the analogues were also submitted for a comprehensive CNS-target screen (Table 4-2). Not surprisingly, the compounds exhibited significant interactions with multiple CNS receptors, as indicated from tylocrebrine's clinical trial. However, relatively few affinities were observed with tylophorine (**4.6**), which makes this symmetrical (2,3,6,7-tetramethoxy) substitution appropriate for library development. Also, considering the precedent SAR studies of this class of compounds, we chose the E ring for

modification since little is known about this E ring, and alterations on the D ring were detrimental to the cytotoxic activity (Figure 4-2).[140b, 142]

Table 4-2. Comprehensive CNS target screen[142d]



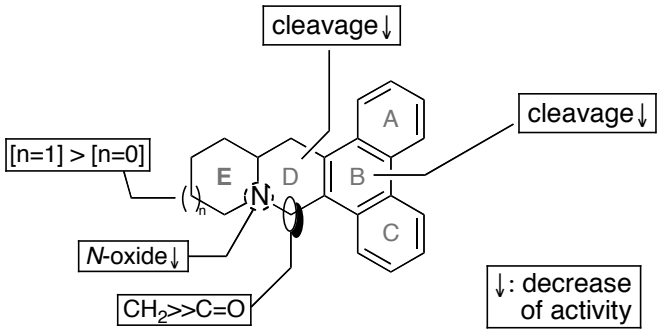
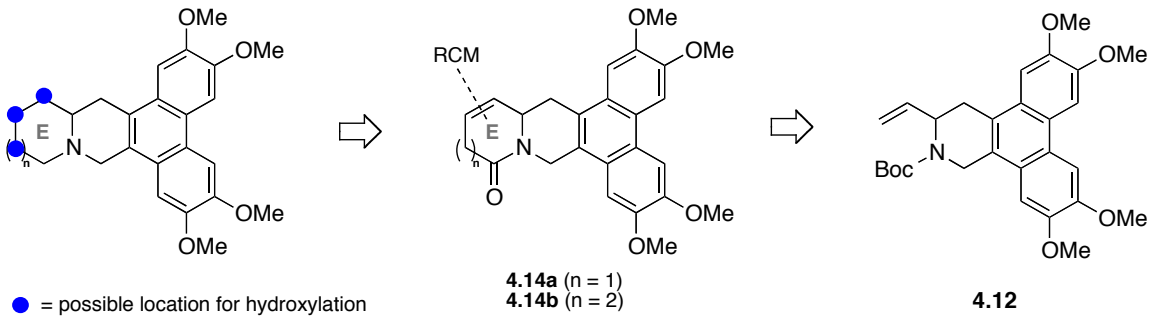


Figure 4-2. SAR studies of the phenanthropiperidine structure.

4.2 Synthesis of phenanthropiperidine analogs

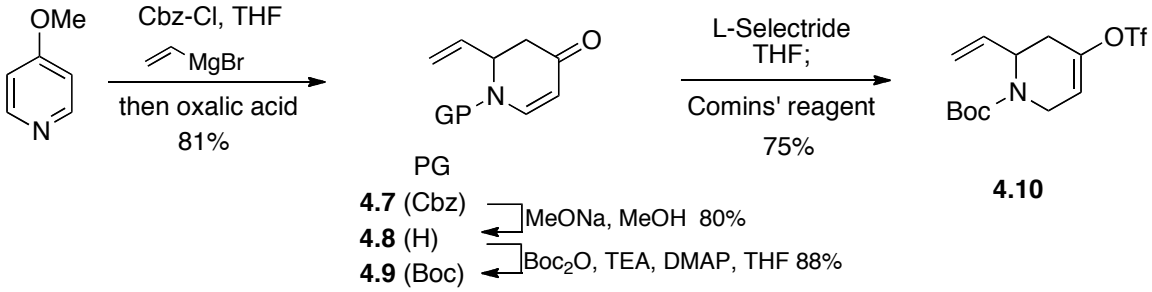
To begin our investigation, we decided to install a hydroxyl group on the E ring because 1) reliable synthetic methods have already been established; 2) the hydroxyl group can be a linker for further derivatization; 3) the hydroxyl group itself is a hydrophilic functional group as well as a hydrogen-bond donor which could reduce CNS-permeation (Scheme 4-1).[143]

Scheme 4-1. Derivatization plan

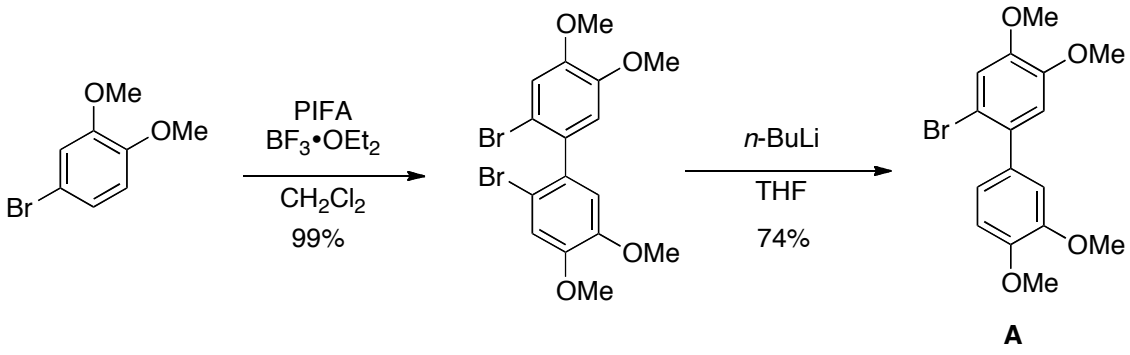


Given the contemporary synthetic methods of hydroxylation and dihydroxylation, amides **4.14a** and **4.14b** were selected as key intermediates, which could be derived from the RCM reaction. Assuming that an amide is easily constructed by amide ligation, the first key intermediate to synthesize is *N*-Boc phenanthropiperidine **4.12**.

Scheme 4-2. Synthesis of triflate **4.10**



Scheme 4-3. Synthesis of biaryl **A**

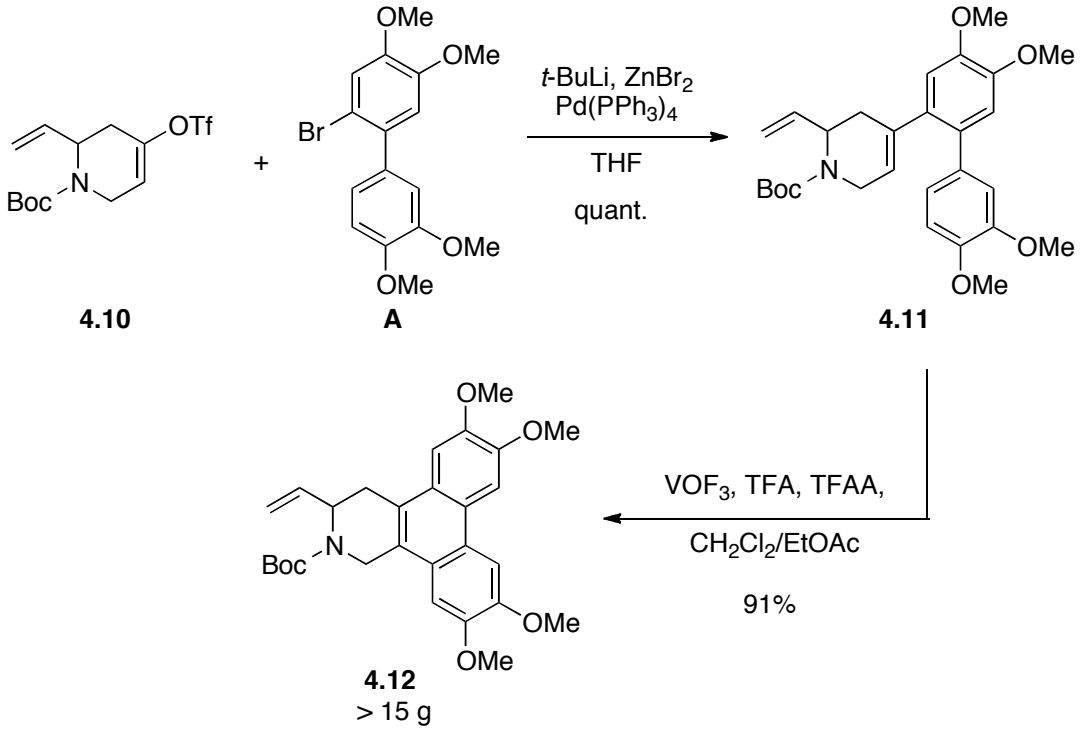


The synthesis was conducted by using the phenanthropiperidine synthesis developed in the Georg group.[51, 141] First, *N*-Boc-vinylenaminone **4.9** was

prepared from 4-methoxypyridine by the reported procedure and simple protecting-group manipulation (Scheme 4-2).[144] Then, the *N*-Boc enaminone was first reduced with L-Selectride, and the resulting boron enolate was trapped with Comins' reagent to afford triflate **4.10**.

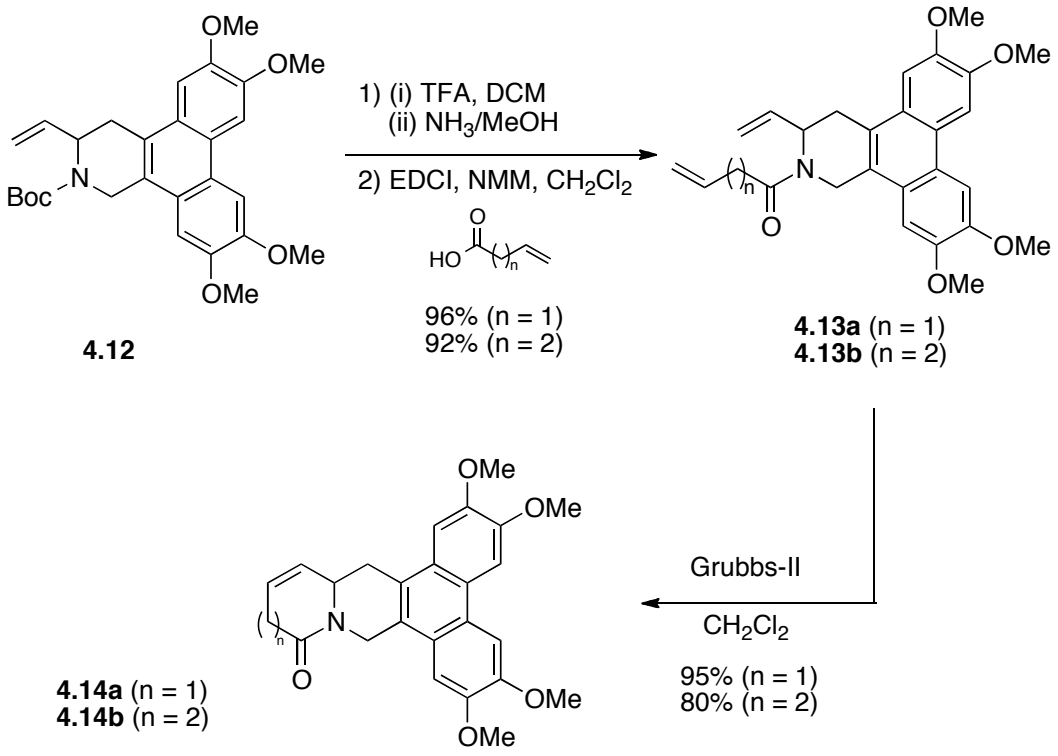
Next, 4-bromoveratrole was dimerized using PIFA, and the resulting dibromide was mono-lithiated by the addition of *n*-BuLi to give monobromide **A** (Scheme 4-3). With two fragments in hand, triflate **4.10** and biarylbromide **A** were connected employing a Negishi cross-coupling to afford biaryl **4.11** (Scheme 4-4). This biaryl **4.11** was oxidized to phenanthroline **4.12** using the protocol developed in the Georg group.

Scheme 4-4. Synthesis of N-Boc phenanthropiperidine **4.12**



Upon Boc deprotection with TFA, the free amine was reacted with two different acids to give amides **4.13a** and **4.13b** respectively (Scheme 4-5). Each amide was subjected to RCM conditions to afford the cyclized products **4.14a** and **4.14b**.

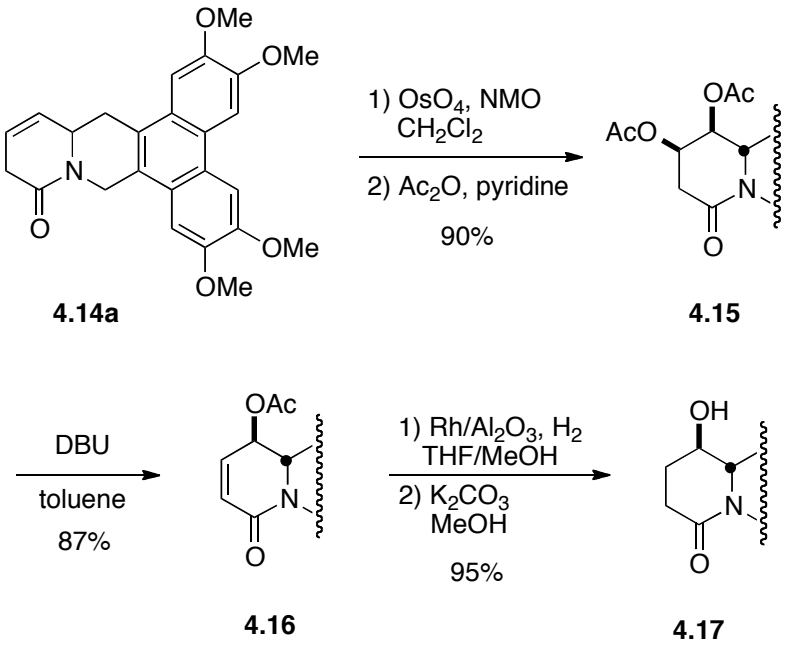
Scheme 4-5. Synthesis of RCM products **4.14a** & **4.14b**



The 6,6-RCM product **4.14a** was dihydroxylated using an osmium catalyst, and subsequently protected with acetyl groups to provide amide **4.15** (Scheme 4-6). One of the acetoxy groups was removed under basic conditions to provide a mono-acetoxy amide **4.16**. This amide was first hydrogenated using a Rh catalyst, and upon treatment with base, the acetyl group was deprotected. The use of a Pd or Pt catalyst for hydrogenation was unsuccessful due to the formation of a Pd/Pt π-allyl complex. 6,7-phenanthroline **4.14b** was similarly

dihydroxylated to give two diastereomers **4.18a** and **4.18b**, which were separated by chromatography (Scheme 4-7).

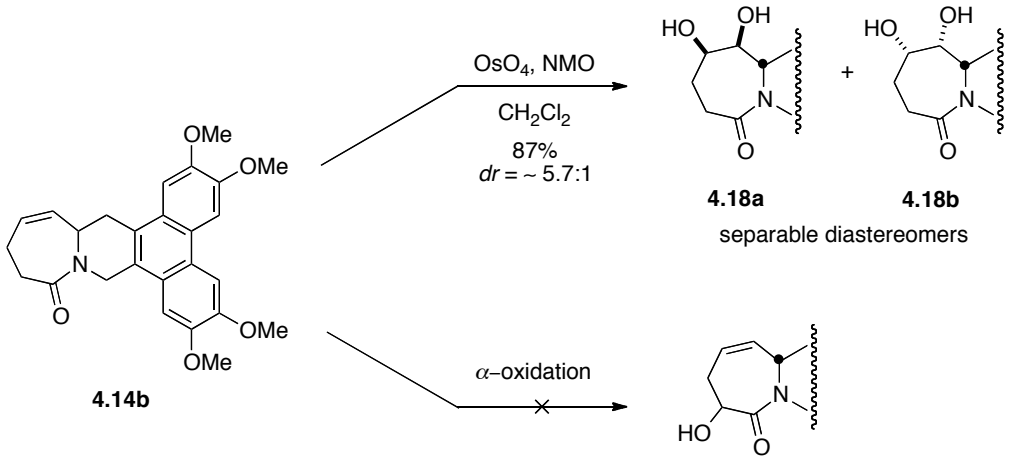
Scheme 4-6. Dihydroxylation of **4.14a** and further derivatizations



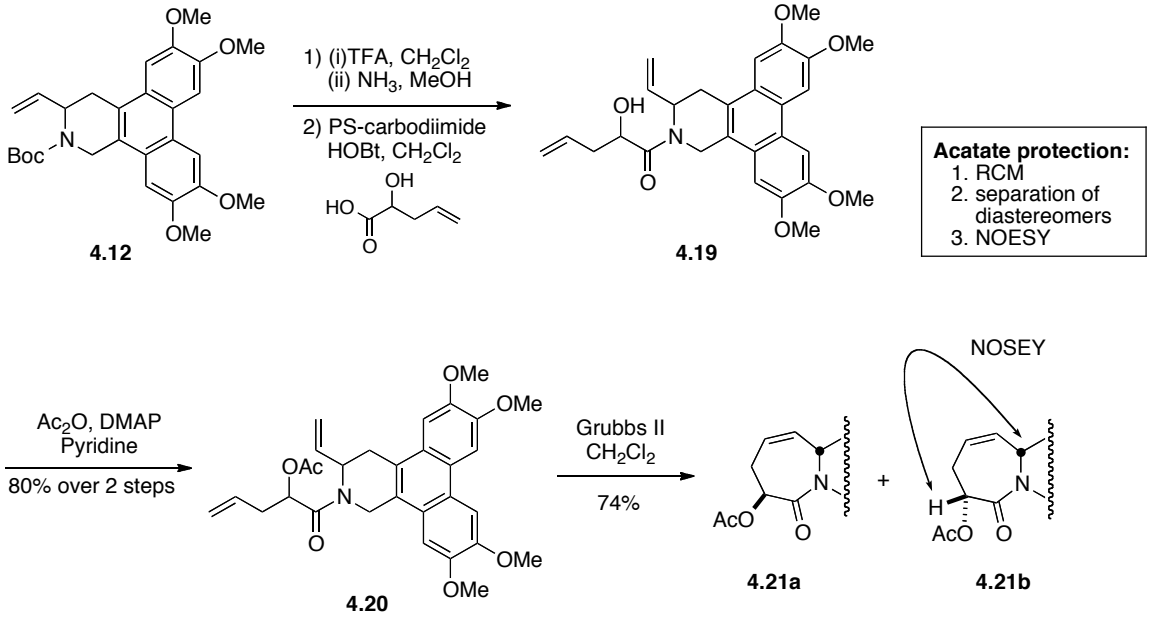
4.14a **4.15** **4.16** **4.17**

Mono-hydroxylation of **4.14b** was attempted using various conventional methods. However, poor solubility of the RCM product in most organic solvents impeded the generation of α-anion, thus leaving the substrate intact. The 6,6 RCM product **4.14a** was even more insoluble in organic solvents, evidently producing unsuccessful results for an *α*-oxidation. This peculiar solubility issue prompted us to install a hydroxyl group before the RCM.

Scheme 4-7. Derivatization of **4.14b**



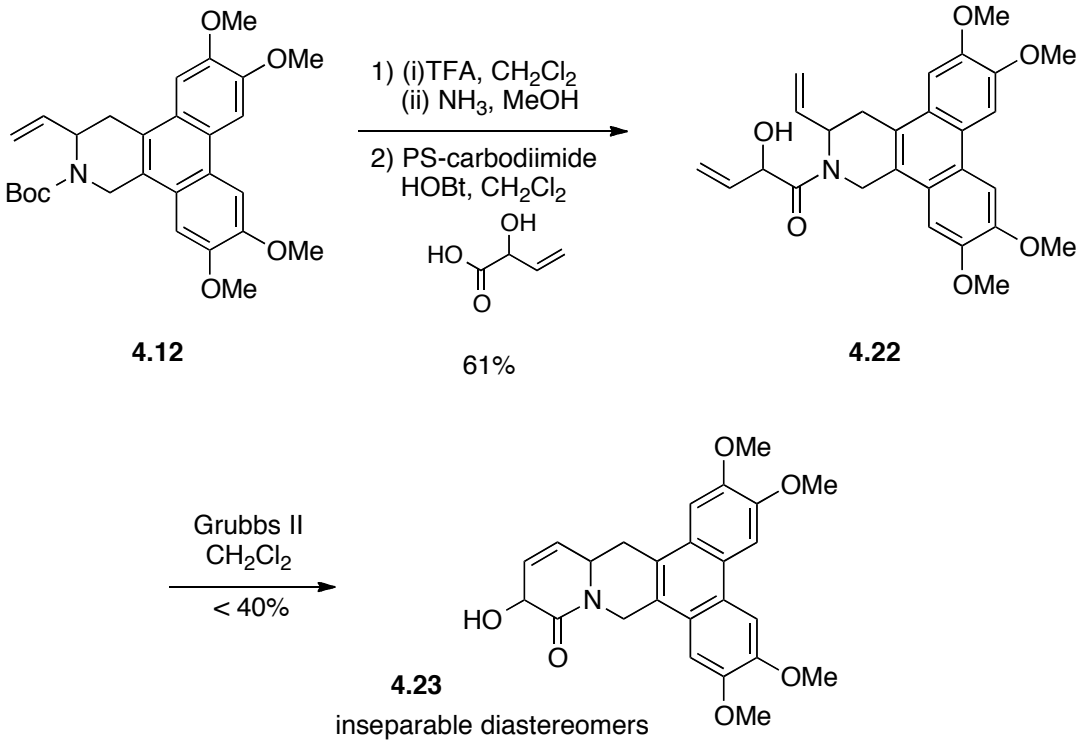
Scheme 4-8. Synthesis of monohydroxylated 6,7-system



The *N*-Boc intermediate **4.12** was deprotected, and its free amine was subjected to solid-phase amide ligation with an *α*-hydroxylated acid, affording *α*-

hydroxylated RCM precursor **4.19** (Scheme 4-8). The hydroxyl group was protected with acetate. This α-acetoxy amide **4.20** was subjected to RCM conditions to give the RCM product **4.21a** & **4.21b**. The acetate protection was necessary for the following three reasons. Firstly, we observe that the RCM reaction was much cleaner with acetate protection than with the free hydroxyl group. Secondly, RCM products were separable with the acetate group whereas RCM products with the free hydroxyl group were hard to separate. Lastly, the acetate group was used to determine the relative stereochemistry of the diastereomers by NOSEY.

Scheme 4-9. Synthesis of monohydroxylated 6,6-system



4.12 61% **4.22**

4.23
inseparable diastereomers

A similar strategy was pursued to synthesize an α-hydroxylated 6,6-phenanthroline. Upon Boc deprotection, the amine was subjected to solid-phase

amide ligation to give amide **4.22** (Scheme 4-9). Despite several attempts to protect the hydroxyl group of **4.22**, the protection was unsuccessful presumably due to the increased acidity of the hydroxyl group and coordination to the proximal amide group. Thus, the free hydroxyl amide was directly subjected to RCM conditions to provide RCM products **4.23**. Unfortunately, the diastereomers were inseparable and the yield of the RCM reaction was only modest.

4.3 Outlook

With several hydroxylated amides in hand, reduction using LAH was attempted. Unfortunately most of the compounds underwent decomposition during the reaction or purification process. Although we scarcely have evidence for why those compounds are unstable, we suspect air oxidation is responsible for the decomposition.

During the course of the synthesis, we encountered two major challenges: 1) solubility of the intermediates; and 2) reactivity of the phenanthroline moiety. It was found that the intermediates after the RCM reaction have very poor solubility in organic solvents such as THF and alcohols, in which most conventional reactions are conducted. Also, not many electrophilic reactions are applicable to functionalize the intermediate after RCM due to the nucleophilicity of the phenanthroline moiety. For example, all the attempts to epoxidize the olefin derived from RCM were unsuccessful presumably because the electron-rich phenanthroline reacted with an electrophilic oxygen source, leading to the decomposition of the entire molecule.

Considering the two challenges above, one strategy in the future is to install a polar functionality before the coupling with **4.12**, as seen in the synthesis of monohydroxylated products. Another strategy is to install -CH_2OH into the 6,6- or 6,7- systems. If hydroxyl groups directly attached to the ring system are inducing pyridinium formation, the addition of a methylene spacer could be a way to circumvent the decomposition of the product.

CHAPTER 5. EXPERIMENTAL DATA

5.1 Materials and methods

Unless specified, all reactions were performed under a nitrogen atmosphere in oven-dried glasswares. Dry THF and CH_2Cl_2 were dried before use over an activated alumina column (Innovative Technology, PS-400-5MD). Silica gel was purchased from SiliCycle (Silia Flash, R12030B). All reagents were used as received. The methods for analysis are as following.

1) TLC analysis was conducted using Analtech Uniplate (silica gel HLF 250 μm). All diazo ketones and enaminone products were UV-active. Diazoketones and enaminones were also detectible with ninhydrine and $KMnO_4$, respectively.
2) NMR data were recorded using a 400 MHz Bruker spectrometer. Chemical shifts are shown as ppm values relative to internal $CHCl_3$ (δ 7.26 for ^1H, δ 77.0 for ^{13}C).
3) Melting points are uncorrected (Barnstead electrothermal 9100).
4) FT-IR was taken by Perkin Elmer spectrometer (Spectrum 100).
5) High resolution mass was taken by Waters LCT-TOF mass spectrometer with acquity UPLC.
6) Optical rotation was measured by Rudolph polarimeter (Autopol V) at 22 °C.
7) HPLC analysis was conducted using Waters 1525 binary pump and 2996 PDA detector.

5.2 Chapter 2

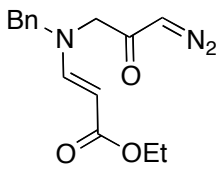
5.2.1 Preparation of diazo compounds

Preparation of substrates was carried out employing 2.0 mmol of amino acids. Generally diazoketones were synthesized from amino acids in one-flask.

Warning: Diazomethane was used for the following transformation. Even in a small scale, proper care should be taken when handling this highly explosive reagent. All glassware used was free of cracks, scratches or ground-glass joints and a blast shield was used.

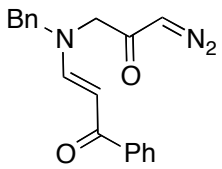
Procedure to synthesize diazoketones:

To a solution of the amino acid and NaOMe (1.0 equiv.) in MeOH (0.33 M), alkyne (1.0 equiv.) was added at 0 °C.[145] The consumption of alkyne was confirmed generally within 20 min. The solvent was evaporated under reduced pressure, affording the acid salt as a slightly yellow solid. The acid salt was re-dissolved in THF (0.2 M) at 0 °C, and ClCOO*i*-Bu (1.0 equiv.) was added. After 30 min, freshly distilled diazomethane (3 equiv), prepared from DIAZALD and KOH in Et_2O was carefully transferred into the solution at once. The reaction mixture was allowed to warm to room temperature, stirred overnight in the dark. The reaction was quenched with aq. AcOH (10 wt%, 1 mL) at 0 °C, followed by addition of water and EtOAc. The partitioned organic layer was washed with aq. 10 wt% H_3PO_4, sat. aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. The filtered organic phase was concentrated *in vacuo*, and subjected to silica gel column chromatography (EtOAc/hexane), furnishing the diazoketone.

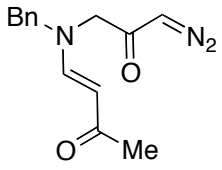


(*E*)-Ethyl 3-(Benzyl(3-diazo-2-oxopropyl)amino)acrylate (2.1):

yellow solid (55% yield); mp: 113.5-113.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25 (t, J = 7.2 Hz, 3H), 3.75 (s, 2H), 4.14 (q, J = 7.2 Hz, 2H), 4.42 (s, 2H), 4.72 (d, J = 13.1 Hz, 1H), 5.31 (s, 1H), 7.17-7.22 (m, 2H), 7.28-7.38 (m, 3H), 7.63 (d, J = 13.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 14.5, 53.8, 56.1 (determined by HMQC), 59.3, 59.5 (determined by HMQC), 87.8, 127.8, 128.3, 129.0, 135.3, 151.7, 169.1, 190.1; IR (neat, cm^{-1}): 1144, 1370, 1612, 1685, 2109; HRMS (ESI) calcd for $C_{15}H_{18}N_3O_3$ $(M + H)^+$ 288.1348, found 288.1353.

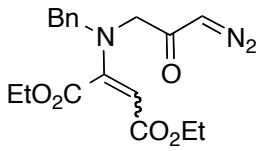


(*E*)-3-(Benzyl(3-diazo-2-oxopropyl)amino)-1-phenylprop-2-en-1-one (2.2):
yellow oil (46% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.89 (s, 2H), 4.55 (s, 2H), 5.34 (s, 1H), 5.70-6.20 (bs, 1H), 7.21-7.27 (m, 2H), 7.31-7.51 (m, 6H), 7.87 (d, J = 7.2 Hz, 2H), 7.91-8.12 (bs, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ:54.0, 55.2, 61.1, 94.4, 127.6, 127.9, 128.2, 128.4, 129.0, 131.4, 134.9, 139.7, 153.2, 189.2, 189.5; IR (neat, cm^{-1}): 1200, 1368, 1548, 1581, 1644, 2109; HRMS (ESI) calcd for $C_{19}H_{18}N_3O_2$ $(M + H)^+$ 320.1399, found 320.1393.



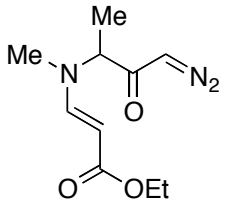
(*E*)-4-(Benzyl(3-diazo-2-oxopropyl)amino)but-3-en-2-one (2.3):
yellow oil (33% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.10 (s, 3H), 3.77 (s, 2H), 4.44 (s, 2H), 5.20 (bs, 1H), 5.30 (s, 1H), 7.16-7.21 (d, J = 7.2 Hz, 2H), 7.27-7.38 (m, 3H), 7.63 (d, J = 12.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ:28.5, 53.8, 54.9,

60.6, 98.9, 127.8, 128.3, 129.0, 135.0, 151.5, 189.4, 195.9; IR (neat, cm^{-1}): 1265, 1363, 1563, 1607, 1652, 2108; HRMS (ESI) calcd for $C_{14}H_{16}N_3O_2$ $(M + H)^+$ 258.1243, found 258.1240.



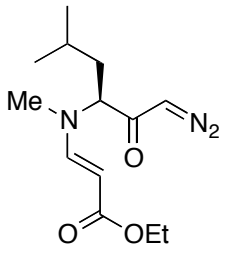
Diethyl 2-(Benzyl(3-diazo-2-oxopropyl)amino)but-2-enedioate (2.4):

yellow solid (53% yield); mp: 78.1-79.9 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.24 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H), 3.75 (s, 2H), 4.09 (q, J = 7.1 Hz, 2H), 4.37-4.44 (m, 4H), 4.75 (s, 1H), 5.49 (s, 1H), 7.23-7.28 (m, 2H), 7.28-7.39 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 13.8, 14.3, 54.0, 55.3, 56.1, 59.7, 62.5, 88.0, 127.8, 128.3, 129.0, 134.7, 153.9, 165.3, 167.0, 190.0; IR (neat, cm^{-1}): 1148, 1376, 1579, 1646, 1694, 1735, 2110; HRMS (ESI) calcd for $C_{18}H_{22}N_3O_5$ $(M + H)^+$ 360.1559, found 360.1566.



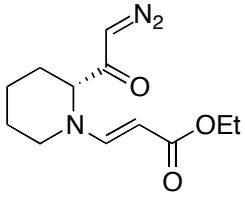
(*E*)-Ethyl 3-((4-Diazo-3-oxobutan-2-yl)(methyl)amino)acrylate (2.5):

yellow oil (31% yield); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.23 (t, J = 7.1 Hz, 3H), 1.38 (d, J = 7.1 Hz, 3H), 2.70 (s, 3H), 3.90 (dlike, J = 6.7 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 4.67 (d, J = 13.0 Hz, 1H), 5.35 (s, 1H), 7.46 (d, J = 13.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 14,4, 14.5, 33.5, 53.8, 59.1, 66.7, 87.2, 151.0, 169.1, 192.8; IR (neat, cm^{-1}): 1052, 1095, 1155, 1224, 1349, 1610, 1686, 2109, 2981; HRMS (ESI) calcd for $C_{10}H_{16}N_3O_3$ $(M + H)^+$ 226.1192, found 226.1182.



(*S*,*E*)-Ethyl 3-((1-Diazo-5-methyl-2-oxohexan-3-yl)(methyl)amino)acrylate (2.6):

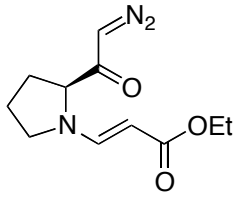
yellow oil (45% yield); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 0.88 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.43-1.57 (m, 1H), 1.61-1.77 (m, 2H), 2.70 (s, 3H), 3.79 (bs, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.68 (d, *J* = 13.0 Hz, 1H), 5.32 (s, 1H), 7.47 (d, *J* = 13.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 14.5, 21.4, 23.1, 24.4, 32.9, 36.8, 54.1, 59.1, 70.2, 86.9, 151.6, 169.2, 192.6; IR (neat, cm^{-1}): 1130, 1156, 1222, 1344, 1609, 1686, 2107, 2958; $[\alpha]_D$= −377 (*c* = 0.981 in $CHCl_3$); HRMS (ESI) calcd for $C_{13}H_{22}N_3O_3$ $(M + H)^+$ 268.1661, found 268.1662.



(*R*,*E*)-Ethyl 3-(2-(2-Diazoacetyl)piperidin-1-yl)acrylate (2.7):

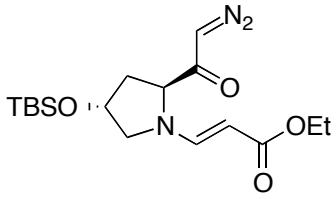
yellow oil (42% yield); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.25 (t, *J* = 7.1 Hz, 3H), 1.34-1.75 (m, 5H), 2.28-2.40 (dlike, *J* = 13.4 Hz,1H), 3.18 (bs, 1H), 3.36-3.44 (dlike, *J* = 12.9 Hz, 1H), 3.99 (d, *J* = 4.4 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.72 (d, *J* = 13.2 Hz, 1H), 5.42 (s, 1H) 7.43 (d, *J* = 13.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 14.5, 20.1, 24.6, 25.6, 48.0, 54.1, 59.2, 64.3, 86.0, 152.2, 169.4, 192.9;

IR (neat, cm^{-1}): 1144, 1369, 1607, 1686, 2106; $[\alpha]_D$= −402 (*c* = 1.02 in $CHCl_3$); HRMS (ESI) calcd for $C_{12}H_{18}N_3O_3$ $(M + H)^+$ 252.1348, found 252.1350.



(*S*,*E*)-Ethyl 3-(2-(2-Diazoacetyl)pyrrolidin-1-yl)acrylate (2.8):

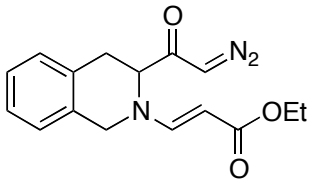
yellow oil (52% yield);^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.25 (t, *J* = 7.1 Hz, 3H), 1.90-2.01 (m, 2H), 2.08-2.28 (m, 2H), 3.15-3.60 (bm, 2H), 4.03 (bs, 1H), 4.08-4.17 (m, 2H), 4.63 (d, *J* = 13.1 Hz , 1H), 5.37 (s, 1H), 7.56 (d, *J* = 13.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 14.5, 23.7, 30.9, 49.2, 53.6, 59.1, 68.1, 88.5, 147.8, 168.9, 194.6; IR (neat, cm^{-1}): 1143, 1364, 1609, 1686, 2107; $[\alpha]_D$= −302 (*c* = 0.990 in $CHCl_3$); HRMS (ESI) calcd for $C_{11}H_{16}N_3O_3$ $(M + H)^+$ 238.1192, found 238.1186.



(*E*)-Ethyl 3-((2*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-(2-diazoacetyl)pyrrolidin-1-yl)acrylate (2.9):

yellow oil (40% yield); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 0.05 (d, *J* = 3.0 Hz, 6H), 0.85 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 2.06-2.16 (m, 1H), 2.17-2.29 (m, 1H), 3.18 (d, *J* = 10.2 Hz, 1H), 3.57 (dlike, *J* = 6.4 Hz, 1H), 4.07-4.20 (m, 3H), 4.40-4.48 (m, 1H), 4.61 (d, *J* = 13.2 Hz, 1H), 5.38 (s, 1H), 7.50 (d, *J* = 13.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: −4.9, −4.8, 14.5, 18.0, 25.7, 40.2, 53.5, 58.9, 59.2, 66.2, 70.0, 88.8, 148.4, 168.9, 194.0; IR (neat, cm^{-1}): 777, 838, 1145, 1252, 1363,

1616, 1685, 2108, 2857, 2930, 2955; $[\alpha]_D$= −134 (*c* = 1.02 in $CHCl_3$); HRMS(ESI) calcd for $C_{17}H_{30}N_3O_4Si$ $(M+H)^+$ 368.2006, found 368.2003.

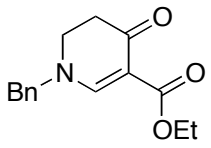


(*E*)-Ethyl 3-(3-(2-Diazoacetyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)acrylate (2.10): yellow syrup (48% yield)); ^1H NMR (400 MHz, $CDCl_3$) *δ*: 1.28 (t, *J* = 7.1 Hz, 3H), 3.09-3.18 (dd, *J* = 6.0, 15.5 Hz, 1H), 3.30-3.40 (dlike, *J* = 15.5 Hz, 1H), 4.10-4.25 (m, 3H), 4.38 (s, 2H), 4.84 (d, *J* = 13.2 Hz, 1H), 5.20 (s, 1H), 7.09-7.25 (m, 4H), 7.60 (d, *J* = 13.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 14.5, 31.1, 48.0, 54.3, 59.3, 64.8, 88.1, 126.0, 127.1, 127.5, 128.5, 131.2, 131.9, 150.9, 168.8, 193.2; IR (neat, cm^{-1}): 752, 795, 1048, 1152, 1352, 1609, 1683, 2109, 2980; HRMS (ESI) calcd for $C_{16}H_{18}N_3O_3$ $(M+H)^+$ 300.1348, found 300.1341.

5.2.2 Preparation of cyclic enaminones

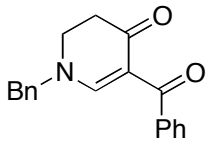
To a solution of the diazoketone (0.1 mmol) in CH_2Cl_2 (0.5 mL), $PhCO_2Ag$ (0.01 mmol) was added. Under air, the flask was sealed with a septum. The reaction was stirred for 24 h in the dark. Then the crude mixture was directly subjected to silica gel column chromatography (20% acetone/CH_2Cl_2 to 1-3%MeOH/CH_2Cl_2), affording the enaminone.

To synthesize enaminone **16**, Ag_2O and $C_2H_4Cl_2$ were used as catalyst and solvent respectively. For the synthesis of enaminone **8**, 20 mol% of $PhCO_2Ag$ was employed.



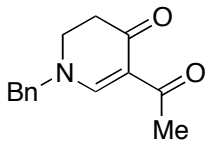
Ethyl 1-Benzyl-4-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (2.11):

clear oil (99% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (t, J = 7.1 Hz, 3H), 2.50 (dd, J = 7.6, 7.8 Hz, 2H), 3.45 (dd, J = 7.6, 7.8 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 4.55 (s, 2H), 7.25-7.29 (m, 2H), 7.35-7.44 (m, 3H), 8.32 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 14.5, 35.9, 46.0, 59.9, 61.0, 100.7, 127.7, 128.9, 129.3, 134.0, 159.4, 165.4, 186.4; IR (neat, cm^{-1}): 1053, 1152, 1600, 1659, 1716; HRMS (ESI) calcd for $C_{15}H_{18}NO_3$ $(M + H)^+$ 260.1287, found 260.1290.



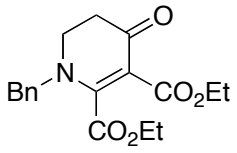
5-Benzoyl-1-benzyl-2,3-dihydropyridin-4(1*H*)-one (2.12):

white solid (88% yield); mp: 81.7-83.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.54 (t, J = 7.6 Hz, 2H), 3.45 (t, J = 7.6 Hz, 2H), 4.59 (s, 2H), 7.27-7.32 (d, J = 6.4 Hz, 2H), 7.34-7.49 (m, 6H), 7.65 (d, J = 7.0 Hz, 2H), 8.26 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 35.6, 46.2, 61.1, 110.2, 127.6, 127.8, 128.9, 129.0, 129.3, 131.2, 133.9, 140.1, 159.6, 186.7, 192.5; IR (neat, cm^{-1}): 1188, 1337, 1583, 1623, 1652; HRMS (ESI) calcd for $C_{19}H_{18}NO_2$ $(M + H)^+$ 292.1338, found 292.1332.



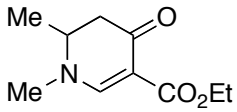
5-Acetyl-1-benzyl-2,3-dihydropyridin-4(1*H*)-one (2.13):

clear oil (93% yield); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 2.49 (m, 5H), 3.46 (dd, *J* = 7.6, 7.8 Hz , 2H), 4.57 (s, 2H), 7.24-7.28 (m, 2H), 7.35-7.45 (m, 3H), 8.44 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 30.5, 35.7, 46.2, 61.3, 110.0, 127.8, 129.0, 129.3, 133.8, 159.2, 188.0, 195.3; IR (neat, cm^{-1}): 1045, 1325, 1361, 1387, 1577, 1636, 2922; HRMS (ESI) calcd for $C_{14}H_{16}NO_2$ $(M + H)^+$ 230.1181, found 230.1183.



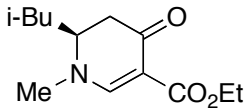
Diethyl 1-Benzyl-4-oxo-1,4,5,6-tetrahydropyridine-2,3-dicarboxylate (2.14):

clear oil (80% yield); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.27-1.36 (m, 6H), 2.46 (t, *J* = 7.6 Hz, 2H), 3.50 (t, *J* = 7.4 Hz , 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 4.48 (s, 2H), 7.31-7.43 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 13.8, 14.4, 35.5, 47.0, 57.2, 60.5, 62.8, 100.6, 127.9, 128.8, 129.2, 134.0, 160.2, 163.6, 165.3, 186.8; IR (neat, cm^{-1}): 1154, 1256, 1377, 1452, 1550, 1669, 1739, 2981; HRMS (ESI) calcd for $C_{18}H_{22}NO_5$ $(M + H)^+$ 332.1498, found 332.1494.



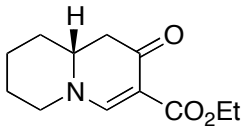
(*S*)-Ethyl 1,6-Dimethyl-4-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (2.15):

clear oil (93% yield); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.27 (m, 6H), 2.27 (dd, *J* = 3.7, 15.9 Hz , 1H), 2.79 (dd, *J* = 6.7, 15.9 Hz, 1H), 3.22 (s, 3H), 3.65 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 8.02 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 14.5, 15.5, 42.1, 42.7, 54.7, 59.8, 99.6, 158.5, 165.4, 185.9; IR (neat, cm^{-1}): 1055, 1173, 1279, 1303, 1332, 1383, 1426, 1606,1652, 1714, 2975; HRMS (ESI) calcd for $C_{10}H_{16}NO_3$ $(M + H)^+$ 198.1130, found 198.1128.



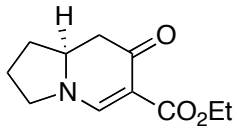
(*S*)-Ethyl 6-Isobutyl-1-methyl-4-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (2.16):

clear oil (76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86 (d, J = 6.4 Hz, 3H), 0.92 (d, J = 6.3 Hz , 3H), 1.26-1.42 (m, 4H), 1.59-1.72 (m, 2H), 2.36 (dd, J = 2.2, 15.9 Hz, 1H), 2.78 (dd, J = 6.7, 15.9 Hz, 1H), 3.23 (s, 3H), 3.46-3.55 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 8.03 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 14.5, 21.1, 23.4, 24.1, 37.1, 39.5, 42.6, 57.4, 59.8, 99.4, 158.6, 165.3, 185.7; IR (neat, cm^{-1}): 1047, 1061, 1174, 1296, 1330, 1396, 1603, 1655, 1716, 2957; $[\alpha]_D$= −38 (c = 0.95 in $CHCl_3$); HRMS (ESI) calcd for $C_{13}H_{22}NO_3$ $(M + H)^+$ 240.1600, found 240.1605.



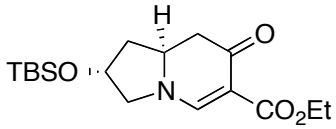
(*R*)-Ethyl 2-Oxo-2,6,7,8,9,9a-hexahydro-1*H*-quinolizine-3-carboxylate (2.17):

white solid (93% yield); mp: 55.8-57.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (t, J = 7.1 Hz, 3H), 1.40-1.79 (m, 3H), 1.79-1.95 (m, 3H), 2.41 (dd, J = 10.8, 16.2 Hz, 1H), 2.64 (dd, J = 6.2, 16.2 Hz, 1H), 3.27 (dt, J = 2.9, 12.8 Hz, 1H), 3.46-3.57 (m, 1H), 3.59-3.67 (m, 1H), 4.23 (q, J = 7.1 Hz, 2H), 8.02 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ:14.5, 22.9, 25.9, 31.8, 43.3, 54.4, 56.8, 59.8, 100.5, 159.1, 165.3, 186.7; IR (neat, cm^{-1}): 1153, 1306, 1595, 1663, 1719, 2937; $[\alpha]_D$= −16 (c = 0.96 in $CHCl_3$); HRMS (ESI) calcd for $C_{12}H_{18}NO_3$ $(M + H)^+$ 224.1287, found 224.1282.



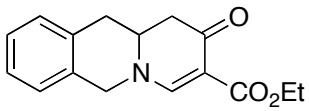
(*S*)-Ethyl 7-Oxo-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate (2.18):

yellow oil (86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.30 (t, *J* = 7.1 Hz, 3H), 1.64-1.78 (m, 1H), 1.91-2.06 (m, 1H), 2.12-2.22 (m, 1H), 2.30-2.42 (m, 2H), 2.56 (dd, *J* = 4.6, 15.6 Hz, 1H), 3.57-3.68 (m, 1H), 3.70-3.85 (m, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 8.30 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 14.5, 24.1, 32.6, 41.9, 50.5, 58.1, 59.6, 100.0, 155.7, 165.4, 187.2; IR (neat, cm^{-1}): 1056, 1145, 1190, 1288, 1599, 1651, 1716, 2977; $[\alpha]_D$= −574 (*c* = 1.01 in $CHCl_3$); HRMS (ESI) calcd for $C_{11}H_{16}NO_3$ $(M + H)^+$ 210.1130, found 210.1127.



(2*R*,8a*S*)-Ethyl 2-(*tert*-Butyldimethylsilyloxy)-7-oxo-1,2,3,7,8,8a-hexahydro indolizine-6-carboxylate (2.19):

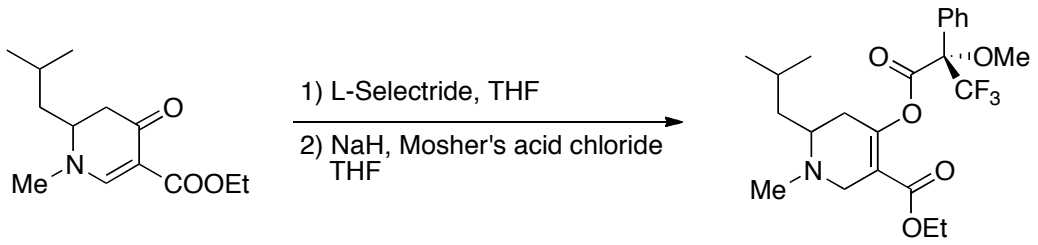
yellow oil (79% yield); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*:0.07 (d, *J* = 1.0 Hz, 6H), 0.86 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.72-1.82 (m, 1H), 2.22 (dd, *J* = 5.4, 12.7 Hz, 1H), 2.35 (t, *J* = 15.7 Hz, 1H), 2.56 (dd, *J* = 4.6, 15.6 Hz, 1H), 3.56 (d, *J* = 12.2 Hz, 1H), 3.78 (dd, *J* = 4.1, 12.1 Hz, 1H), 4.07-4.20 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.56 (t, *J* = 3.8 Hz, 1H), 8.26 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: −4.9, −4.8, 14.5, 17.9, 25.7, 29.7, 41.7, 42.2, 56.0, 59.7, 70.3, 100.4, 155.9, 165.4, 187.2; IR (neat, cm^{-1}): 1069, 1191, 1290, 1325, 1374, 1594, 1717, 2857, 2931, 2954; $[\alpha]_D$= −8.9 (*c* = 0.99 in $CHCl_3$); HRMS (ESI) calcd for $C_{17}H_{30}NO_4Si$ $(M + H)^+$ 340.1944, found 340.1933.



Ethyl 2-Oxo-2,6,11,11a-tetrahydro-1*H*-pyrido[1,2-*b*]isoquinoline-3-carboxylate (2.20):

clear oil (81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (t, J = 7.1, 3H), 2.57 (dd, J = 7.8, 16.3 Hz, 1H), 2.78-2.88 (m, 2H), 3.07-3.17 (dd, J = 12.1, 15.8 Hz, 1H), 3.86-3.96 (m, 1H), 4.24 (q, J = 7.1, 2H), 4.67 (d, J = 15.8, 1H), 4.78 (d, J = 15.8, 1H), 7.11-7.21 (m, 2H), 7.22-7.29 (m, 2H), 8.24 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 14.5, 33.2, 41.5, 54.3, 55.2, 59.9, 100.5, 125.7, 127.2, 127.9, 128.7, 131.8, 133.3, 158.2, 165.2, 186.0; IR (neat, cm^{-1}): 1052, 1152, 1189, 1304, 1348, 1393, 1456, 1595, 1657, 1715, 2979; HRMS (ESI) calcd for $C_{16}H_{18}NO_3$ $(M + H)^+$ 272.1287, found 272.1287.

5.2.3 Determination of enantiomeric ratio by derivatization using Mosher's acid chloride

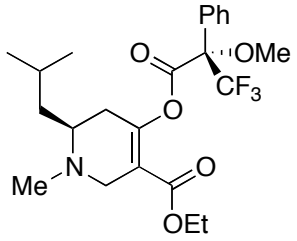


2.16 (chiral)
2.16' (racemic)

2.21 (single diastereomer)
2.21' (diastereomeric mixture)

First, racemic enaminone **2.16'** was prepared. Racemic and enantiopure enaminones were derivatized by the following procedure.

The enaminone (0.1 mmol) was dissolved in THF (1 mL) at − 78 °C. L-Selectride (1.0 M in THF, 1.1 equiv.) was added, and stirring was continued for 3 h at − 78 °C. Acetone (0.5 mL) was added and the solution was warmed to room temperature and evaporated under reduced pressure. The crude mixture was purified by preparative TLC, affording the corresponding enol. The enol was dissolved in THF (0.7 mL) and the solution was cooled to 0 °C. NaH (2 equiv.) was added to the solution, which was stirred for another 10 min. (*R*)-Mosher's acid chloride in THF (0.3 mL) was then added to the reaction mixture. The reaction was warmed to room temperature and left for 2 h with stirring. Water and EtOAc were added to the reaction mixture, and the partitioned organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The crude mixture was purified by preparative TLC, affording the desired Mosher's ester derivative. The diastereomeric mixture **2.21'** (3.3 mg) was dissolved in $CDCl_3$ (1.2 mL) and the ^{19}F NMR was taken. Slightly overlapping ^{19}F peaks were separated using Gaussian deconvolution. The ^{19}F NMR of compound **2.21** was also recorded at a similar concentration, and a single ^{19}F peak was observed.

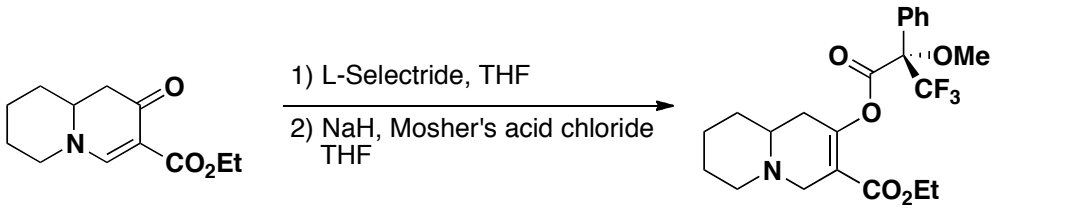


(*S*)-Ethyl 6-Isobutyl-1-methyl-4-((*S*)-3,3,3-trifluoro-2-methoxy-2-phenyl propanoyloxy)-1,2,5,6-tetrahydropyridine-3-carboxylate (2.21):

clear oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.87-0.94 (d, J = 6.6 Hz, 6H), 1.19 (t, J = 7.1 Hz, 3H), 1.21-1.27 (m, 1H), 1.40-1.50 (m, 1H), 1.57-1.71 (m, 1H), 2.00-2.11 (m, 1H), 2.22-2.32 (m, 1H), 2.35 (s, 3H), 2.78-2.89 (m, 1H), 3.42-3.57 (dt, J = 2.1, 17.2 Hz, 2H), 3.65 (s, 3H), 4.10 (q, J = 7.1 Hz, 2H), 7.40-7.47 (m, 3H), 7.63-7.69 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 14.1, 22.4, 23.0, 24.7, 29.8, 38.5, 40.3, 51.7, 55.3, 55.7, 60.7, 84.5, 84.8, 117.1, 121.6, 124.5, 127.7, 128.4, 129.8, 131.4,

151.2, 163.9, 164.0; IR (neat, cm^{-1}): 703, 1004, 1045, 1123, 1174, 1236, 1732, 1763, 2930, 2958; $[\alpha]_D$= −0.600 (*c* = 1.33 in $CHCl_3$); HRMS (ESI) calcd for $C_{23}H_{31}F_3NO_5$ $(M + H)^+$ 458.2154, found 458.2156.

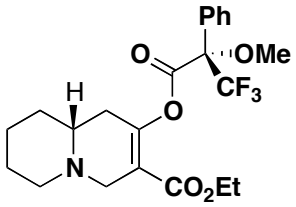
Enaminones **2.17** and **2.18** were derivatized similarly.



2.17 (chiral)
2.17' (racemic)

2.22 (single diastereomer)
2.22' (diastereomeric mixture)

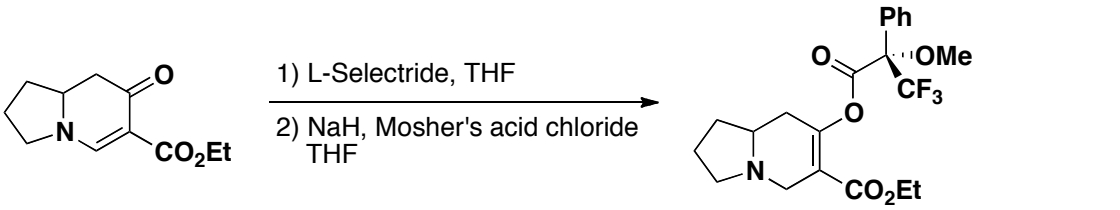
Enantiopurity of compound **2.22** was confirmed by HPLC analysis. Also, ^{19}FNMR of the compound **2.22** showed a single ^{19}F peak.



(*R*)-Ethyl 2-((*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyloxy)-4,6,7,8,9,9a-hexahydro-1*H*-quinolizine-3-carboxylate (2.22):

clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.17 (t, *J* = 7.1 Hz, 3H), 1.52-1.81 (m, 6H), 2.04-2.17 (m, 1H), 2.17-2.32 (m, 3H), 2.94-3.07 (m, 2H), 3.63 (s, 3H), 3.68 (d, *J* = 16.3 Hz, 1H), 4.03-4.16 (m, 2H), 7.41-7.46 (m, 3H), 7.60-7.66 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) *δ*:14.1, 23.5, 25.5, 32.7, 35.6, 54.0, 54.8, 55.6, 56.2, 60.8, 84.6, 84.9, 117.2, 121.6, 124.5, 127.8, 128.4, 129.8, 131.3, 151.2, 163.3, 163.7;

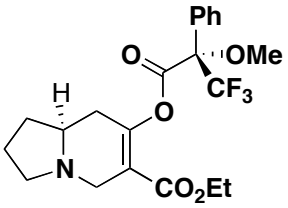
IR (neat, cm^{-1}): 1048, 1107, 1183, 1239, 1725, 1763, 2937; $[\alpha]_D$= −47 (*c* = 0.39 in $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{27}F_3NO_5$ $(M + H)^+$ 442.1841, found 442.1836.; HPLC analysis (Daicel CHIRACEL OD column) solvent system: Heptane/*i*-PrOH, 100/0 to 85/15 over 15 min; retention times: 10.5 min (**2.22**), 8.1 min (the other diastereomer).



2.18 (chiral)
2.18' (racemic)

2.23 (single diastereomer)
2.23' (diastereomeric mixture)

Enantiopurity of compound **2.23** was confirmed by HPLC analysis. Also, ^{19}FNMR of the compound **2.23** showed a single ^{19}F peak.



(*S*)-Ethyl 7-((*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyloxy)-1,2,3,5,8,8a hexahydroindolizine-6-carboxylate (2.23):

clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.17 (t, *J* = 7.1 Hz, 3H), 1.41-1.55 (m, 1H), 1.72-2.07 (m, 3H), 2.26 (q, *J* = 9.0 Hz, 1H), 2.30-2.42 (m, 3H), 3.01 (dt, *J* = 3.5, 16.1 Hz, 1H), 3.22 (dt, *J* = 2.2, 8.7 Hz, 1H), 3.63 (s, 3H), 3.91 (d, *J* = 16.1 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 7.41-7.47(m, 3H), 7.62-7.68 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) *δ*:14.1, 22.0, 30.5, 35.2, 50.9, 53.6, 55.8, 59.3, 60.9, 84.4, 84.7,

118.3, 121.6, 124.4, 127.7, 128.5, 129.9, 131.2, 153.1, 163.5, 164.0; IR (neat, cm^{-1}): 1002, 1056, 1108, 1172, 1234, 1733, 1767; $[\alpha]_D$= −46 (*c* = 0.76 in $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{25}F_3NO_5$ $(M + H)^+$ 428.1685, found 428.1688.; HPLC analysis (Daicel CHIRACEL OD column) solvent system: Hexane/*i*-PrOH, 100/0 to 85/15 over 15 min; retention times: 5.3 min (**2.23**), 9.6 min (the other diastereomer).

5.2.4 Preparation of amino diazoketones

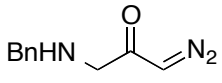
Synthesis of amino diazoketones 2.24-2.30:

To a solution of the amine (10 mmol, 4 equiv) in dichloroethane (9 mL), bromo diazoacetone (2.5 mmol) in dichloroethane (1 mL) was added dropwise.[146] The reaction mixture was heated to 50 °C for 3 h, then washed with aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was subjected to column chromatography ($MeOH/CH_2Cl_2$), affording the amino diazoketones as yellow oils.

Synthesis of amino diazoketone 2.31:

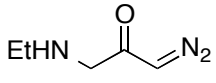
Bromo diazoacetone (2.5 mmol) and tryptamine hydrochloride (5 mmol, 2 equiv) were dissolved in MeONa/MeOH (0.5 M, 10mL). The solution was heated at 50 °C for 3 h, concentrated *in vacuo*, and re-dissolved in CH_2Cl_2. This organic solution was washed with aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and again concentrated *in vacuo*. The crude mixture was subjected to column chromatography ($NH_4OH/MeOH/CH_2Cl_2$), affording amino diazoketone **8** as a yellow oil.

All amino diazoketones were carried to the next reaction immediately after isolation because they are not stable over a long period of time.



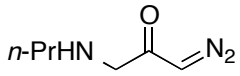
1-(Benzylamino)-3-diazopropan-2-one (2.24):

yellow oil (87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 5H), 5.63 (s, 1H), 3.79 (s, 2H), 3.40 (s, 2H), 1.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 139.6, 128.6, 128.3, 127.4, 56.3, 53.7, 53.1; IR (neat, cm^{-1}): 1143, 1343, 1638, 2105; HRMS (ESI) calcd for $C_{10}H_{12}N_3O$ $(M + H)^+$ 190.0980, found 190.0981.



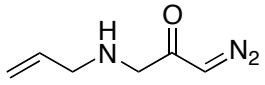
1-Diazo-3-(ethylamino)propan-2-one (2.25):

yellow oil (65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (s, 1H), 3.38 (s, 2H), 2.63 (q, *J* = 7.1 Hz, 2H), 1.60 (s, 1H), 1.10 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 57.1, 52.9, 44.3, 15.4; IR (neat, cm^{-1}): 1139, 1352, 1635, 2106, 2968; HRMS (ESI) calcd for $C_5H_{10}N_3O$ $(M + H)^+$ 128.0824, found 128.0817.



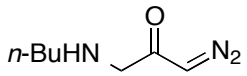
1-Diazo-3-(propylamino)propan-2-one (2.26):

yellow oil (63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (s, 1H), 3.38 (s, 2H), 2.55 (t, *J* = 7.1 Hz, 2H), 1.60 (s, 1H), 1.60 – 1.41 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 57.3, 52.9, 52.0, 23.4, 11.8; IR (neat, cm^{-1}): 1139, 1343, 1637, 2104, 2960; HRMS (ESI) calcd for $C_6H_{12}N_3O$ $(M + H)^+$ 142.0980, found 142.0979.



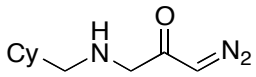
1-(Allylamino)-3-diazopropan-2-one (2.27):

yellow oil (72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.63 (s, 1H), 5.26 – 5.07 (m, 2H), 3.39 (s, 2H), 3.24 (d, *J* = 5.9 Hz, 2H), 1.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 136.3, 116.7, 56.2, 53.1, 52.2; IR (neat, cm^{-1}): 923, 1143, 1344, 1638, 2105, 3080; HRMS (ESI) calcd for $C_6H_{10}N_3O$ $(M + H)^+$ 140.0824, found 140.0811.



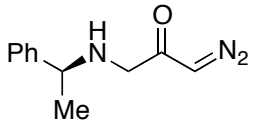
1-(Butylamino)-3-diazopropan-2-one (2.28):

yellow oil (80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 (s, 1H), 3.38 (s, 2H), 2.58 (t, *J* = 7.1 Hz, 2H), 1.78 (s, 1H), 1.46 (m, 2H), 1.35 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 57.3, 52.9, 49.9, 32.3, 20.5, 14.1; IR (neat, cm^{-1}): 927, 1141, 1344, 1639, 2105, 2930; HRMS (ESI) calcd for $C_7H_{14}N_3O$ $(M + H)^+$ 156.1137, found 156.1132.

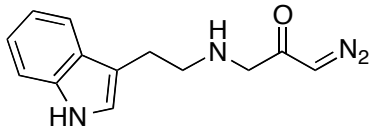


1-((Cyclohexylmethyl)amino)-3-diazopropan-2-one (2.29):

yellow oil (81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (s, 1H), 3.36 (s, 2H), 2.41 (d, *J* = 6.6 Hz, 2H), 1.78 – 1.55 (m, 6H), 1.41 (m, 1H), 1.29 – 1.08 (m, 3H), 0.98 – 0.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 57.5, 56.9, 52.9, 38.3, 31.5, 26.8, 26.2; IR (neat, cm^{-1}): 1140, 1340, 1638, 2102, 2923; HRMS (ESI) calcd for $C_{10}H_{18}N_3O$ $(M + H)^+$ 196.1450, found 196.1450.



(*S*)-1-Diazo-3-((1-phenylethyl)amino)propan-2-one (2.30):
yellow oil (93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.20 (m, 5H), 5.49 (s, 1H), 3.75 (q, *J* = 6.6 Hz, 1H), 3.25 (s, 2H), 1.90 (s, 1H), 1.37 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 144.8, 128.7, 127.4, 126.8, 58.2, 55.1, 53.2, 24.4; IR (neat, cm^{-1}): 1143, 1349, 1638, 2104, 2967; $[\alpha]_D$= −82.4 (*c* = 1.09 in $CHCl_3$); HRMS (ESI) calcd for $C_{11}H_{14}N_3O$ $(M + H)^+$ 204.1137, found 204.1132.



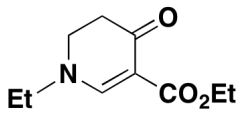
1-((2-(1*H*-Indol-3-yl)ethyl)amino)-3-diazopropan-2-one (2.31):
yellow oil (73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.30 – 7.08 (m, 2H), 7.04 (s, 1H), 5.60 (s, 1H), 3.39 (s, 2H), 3.27 – 2.91 (m, 4H), 1.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 136.5, 127.5, 122.2, 122.1, 119.4, 118.9, 113.7, 111.3, 57.2, 53.0, 50.0, 26.0; IR (neat, cm^{-1}): 1147, 1342, 1634, 2105, 2918; HRMS (ESI) calcd for $C_{13}H_{15}N_4O$ $(M + H)^+$ 243.1246, found 243.1239.

5.2.5 Preparation of cyclic enaminones

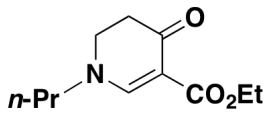
The amino diazoketone (0.20 mmol) was reacted with an alkyne (0.24 mmol, 1.2 equiv) in ethanol (1 mL) at ambient temperature overnight.[3,4] Upon evaporation, the reaction mixture was treated with the Ag catalyst (0.04 mmol, 20 mmol%) in

CH_2Cl_2 (1 mL) at ambient temperature overnight, during which the flask was covered with aluminum foil to exclude light. This mixture was then washed with aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was subjected to column chromatography ($MeOH/CH_2Cl_2$), affording a desired enaminone.

$PhCO_2Ag$ was used as a catalyst for the Wolff rearrangement in all cases except for the synthesis of enaminone **2.33**, **2.41**, **2.43**, **2.46** and **2.54-2.56**, where Ag_2O was used instead.

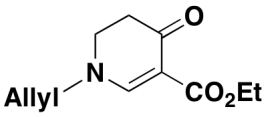


Ethyl 1-Ethyl-4-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (2.32):
white solid (85%); mp: 45.8-47.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.60 – 3.41 (t, *J* = 7.5 Hz, 2H), 3.49 – 3.43 (q, *J* = 7.3 Hz, 2H), 2.59 – 2.50 (t, *J* = 7.8 Hz, 2H), 1.32 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 165.6, 158.9, 100.5, 60.0, 52.1, 46.2, 36.1, 14.7, 14.0; IR (neat, cm^{-1}): 1053, 1159, 1246, 1303, 1335, 1398, 1605, 1714, 2978; HRMS (ESI) calcd for $C_{10}H_{16}N_1O_3$ $(M + H)^+$ 198.1130, found 198.1124.

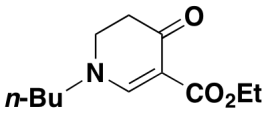


Ethyl 4-Oxo-1-propyl-1,4,5,6-tetrahydropyridine-3-carboxylate (2.33):
off-white solid (88%); mp: 55.8-57.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.59 – 3.48 (t, *J* = 7.5 Hz, 2H), 3.36 (t, *J* = 7.1 Hz, 2H), 2.60 – 2.47 (t, *J* = 7.5 Hz, 2H), 1.76 – 1.66 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.97

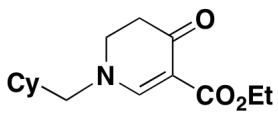
(t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 165.6, 159.5, 100.3, 60.0, 59.1, 46.5, 36.1, 21.7, 14.7, 11.0; IR (neat, cm^{-1}): 1054, 1157, 1240, 1301, 1333, 1384, 1459, 1602, 1658, 1719, 2966; HRMS (ESI) calcd for $C_{11}H_{18}N_1O_3$ $(M + H)^+$ 212.1287, found 212.1290.



Ethyl 1-Allyl-4-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (2.34):
yellow oil (76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 5.84 (dq, *J* = 10.8, 6.0 Hz, 1H), 5.36 (m, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.98 (d, *J* = 6.0 Hz, 2H), 3.53 (t, *J* = 7.7 Hz, 2H), 2.54 (t, *J* = 7.7 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 165.5, 159.4, 131.3, 120.7, 100.9, 60.00, 59.58, 46.4, 36.1, 14.7; IR (neat, cm^{-1}): 1053, 1152, 1241, 1303, 1338, 1397, 1602, 1645, 1715, 2978; HRMS (ESI) calcd for $C_{11}H_{16}N_1O_3$ $(M + H)^+$ 210.1130, found 210.1130.

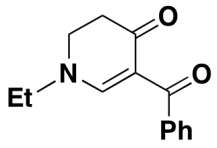


Ethyl 1-Butyl-4-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (2.35):
clear oil (78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.59 – 3.48 (t, *J* = 7.8 Hz, 2H), 3.39 (t, *J* = 7.2 Hz, 2H), 2.60 – 2.48 (t, *J* = 7.8 Hz, 2H), 1.71 – 1.57 (m, 2H), 1.42 – 1.29 (m, 5H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 165.7, 159.5, 100.4, 60.0, 57.2, 46.6, 36.2, 30.5, 20.0, 14.7, 13.7; IR (neat, cm^{-1}): 1054, 1158, 1245, 1302, 1335, 1395, 1462, 1603, 1659, 1714, 2960; HRMS (ESI) calcd for $C_{12}H_{20}N_1O_3$ $(M + H)^+$ 226.1443, found 226.1432.



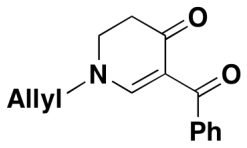
Ethyl 1-(Cyclohexylmethyl)-4-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (2.36):

off-white solid (88%); mp: 65.1-66.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.61 – 3.48 (t, *J* = 7.6 Hz, 2H), 3.20 (d, *J* = 6.9 Hz, 2H), 2.61 – 2.47 (t, *J* = 7.6 Hz, 2H), 1.83 – 1.61 (m, 7H), 1.36 – 1.11 (m, 5H), 0.94 (q, *J* = 11.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 165.67, 159.8, 100.1, 64.0, 60.0, 47.2, 36.8, 36.1, 30.6, 26.3, 25.7, 14.7; IR (neat, cm^{-1}): 1055, 1158, 1249, 1306, 1331, 1403, 1451, 1603, 1709, 2927; HRMS (ESI) calcd for $C_{15}H_{24}N_1O_3$ $(M + H)^+$ 266.1756, found 266.1766.



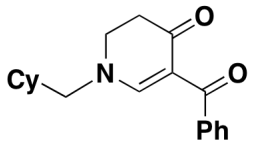
5-Benzoyl-1-ethyl-2,3-dihydropyridin-4(1*H*)-one (2.37):

off-white solid (81%); mp: 89.5-91.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.67 – 7.59 (m, 2H), 7.48 – 7.41 (m, 1H), 7.37 (t, *J* = 7.4 Hz, 2H), 3.69 – 3.61 (t, *J* = 7.7 Hz, 2H), 3.53 (q, *J* = 7.2 Hz, 2H), 2.64 – 2.53 (t, *J* = 7.7 Hz, 2H), 1.37 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 186.7, 159.1, 140.5, 131.3, 129.0, 127.7, 110.1, 52.2, 46.4, 35.9, 14.0; IR (neat, cm^{-1}): 1191, 1252, 1325, 1384, 1447, 1587, 1623, 2975; HRMS (ESI) calcd for $C_{14}H_{16}N_1O_2$ $(M + H)^+$ 230.1181, found 230.1179.



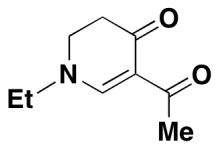
1-Allyl-5-benzoyl-2,3-dihydropyridin-4(1*H*)-one (2.38):

off-white solid (63%); mp: 88.1-89.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.63 (m, 2H), 7.49 – 7.42 (m, 1H), 7.37 (m, 2H), 5.89 (ddt, *J* = 16.4, 10.2, 6.1 Hz, 1H), 5.40 (m, 2H), 4.03 (d, *J* = 6.1 Hz, 2H), 3.62 (t, *J* = 7.7 Hz, 2H), 2.60 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 186.9, 159.6, 140.3, 131.4, 131.1, 129.0, 127.7, 121.0, 110.5, 59.8, 46.6, 35.8; IR (neat, cm^{-1}): 1190, 1239, 1323, 1385, 1585, 1623, 2923; HRMS (ESI) calcd for $C_{15}H_{16}N_1O_2$ $(M + H)^+$ 242.1181, found 242.1173.



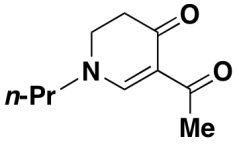
5-Benzoyl-1-(cyclohexylmethyl)-2,3-dihydropyridin-4(1*H*)-one (2.39):

off-white solid (88%); mp: 152.4-154.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.69 – 7.59 (m, 2H), 7.48 – 7.41 (m, 1H), 7.40 – 7.33 (m, 2H), 3.62 (t, *J* = 7.6 Hz, 2H), 3.26 (d, *J* = 6.9 Hz, 2H), 2.63 – 2.52 (t, *J* = 7.6 Hz, 2H), 1.86 – 1.64 (m, 6H), 1.35 – 1.12 (m, 3H), 1.04 – 0.89 (m, 2H);$^{1\,3}$C NMR (100 MHz, $CDCl_3$) δ 192.6, 186.8, 160.1, 140.5, 131.3, 129.0, 127.7, 109.7, 64.1, 47.5, 36.8, 35.9, 30.7, 26.3, 25.7; IR (neat, cm^{-1}): 1191, 1254, 1322, 1385, 1449, 1584, 1622, 2925; HRMS (ESI) calcd for $C_{19}H_{24}N_1O_2$ $(M + H)^+$ 298.1807, found 298.1804.



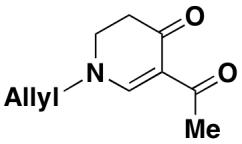
5-Acetyl-1-ethyl-2,3-dihydropyridin-4(1*H*)-one (2.40):

white solid (94%); mp: 55.0-57.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 3.61 – 3.55 (t, *J* = 7.7 Hz, 2H), 3.49 (q, *J* = 7.3 Hz, 2H), 2.59 – 2.52 (t, *J* = 7.7 Hz, 2H), 2.49 (s, 3H), 1.34 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 188.0, 158.7, 110.0, 52.3, 46.5, 36.0, 30.6, 13.9; IR (neat, cm^{-1}): 1150, 1248, 1324, 1360, 1388, 1586, 1634, 2975; HRMS (ESI) calcd for $C_9H_{14}N_1O_2$ $(M + H)^+$ 168.1025, found 168.1021.



5-Acetyl-1-propyl-2,3-dihydropyridin-4(1*H*)-one (2.41):

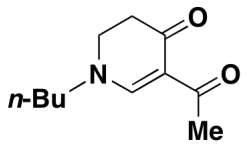
white solid (84%); mp: 81.3-83.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 3.62 – 3.51 (t, *J* = 7.7 Hz, 2H), 3.40 (t, *J* = 7.1 Hz, 2H), 2.58 – 2.52 (t, *J* = 7.7 Hz, 2H), 2.50 (s, 3H), 1.79 – 1.66 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 188.0, 159.3, 109.8, 59.2, 46.8, 36.0, 30.6, 21.7, 11.0; IR (neat, cm^{-1}): 1150, 1246, 1325, 1394, 1595, 1626, 2965; HRMS (ESI) calcd for $C_{10}H_{16}N_1O_2$ $(M + H)^+$ 182.1181, found 182.1174.



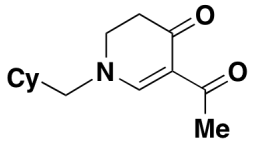
5-Acetyl-1-allyl-2,3-dihydropyridin-4(1*H*)-one (2.42):

white solid (90%); mp: 42.5-44.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 5.84 (ddt, *J* = 16.4, 10.2, 6.1 Hz, 1H), 5.43 – 5.30 (m, 2H), 4.01 (d, *J* = 6.1 Hz, 2H), 3.55 (t, *J* = 7.7 Hz, 2H), 2.58 – 2.52 (t, *J* = 7.7 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 188.1, 159.2, 131.0, 121.0, 110.3, 59.8, 46.6,

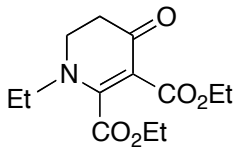
36.0, 30.6; IR (neat, cm^{-1}): 1148, 1237, 1323, 1361, 1388, 1583, 1635, 2922; HRMS (ESI) calcd for $C_{10}H_{14}N_1O_2$ $(M + H)^+$ 180.1025, found 180.1022.



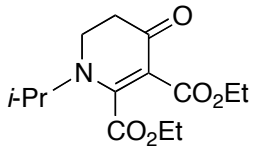
5-Acetyl-1-butyl-2,3-dihydropyridin-4(1*H*)-one (2.43):
off-white solid (81%); mp: 60.4-62.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 3.56 (t, *J* = 7.7 Hz, 2H), 3.42 (t, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 7.7 Hz, 2H), 2.49 (s, 3H), 1.75 – 1.53 (m, 2H), 1.36 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 188.0, 159.2, 109.8, 57.4, 46.8, 36.0, 30.6, 30.4, 19.8, 13.7; IR (neat, cm^{-1}): 1153, 1328, 1359, 1395, 1595, 1623, 2958; HRMS (ESI) calcd for $C_{11}H_{18}N_1O_2$ $(M + H)^+$ 196.1338, found 196.1331.



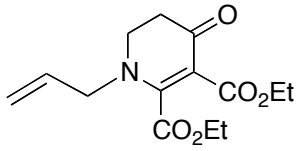
5-Acetyl-1-(cyclohexylmethyl)-2,3-dihydropyridin-4(1*H*)-one (2.44):
off-white solid (92%); mp: 124.8-126.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 3.61 – 3.51 (t, *J* = 7.7 Hz, 2H), 3.23 (d, *J* = 6.9 Hz, 2H), 2.57 – 2.51 (t, *J* = 7.7 Hz, 2H), 2.49 (s, 3H), 1.82 – 1.63 (m, 6H), 1.32 – 1.10 (m, 3H), 0.94 (q, *J* = 12.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 188.4, 159.6, 109.7, 64.1, 47.5, 36.7, 36.0, 30.6 (overlap of two non-equivalent carbons), 26.2, 25.7; IR (neat, cm^{-1}): 1152, 1249, 1324, 1362, 1388, 1451, 1584, 1634, 2925; HRMS (ESI) calcd for $C_{14}H_{22}N_1O_2$ $(M + H)^+$ 236.1651, found 236.1653.



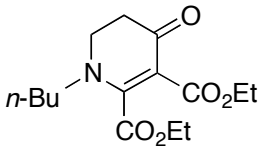
Diethyl 1-Ethyl-4-oxo-1,4,5,6-tetrahydropyridine-2,3-dicarboxylate (2.45): yellow oil (90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (q, *J* = 7.2 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.63 (t, *J* = 7.5 Hz, 2H), 3.39 (q, *J* = 7.1 Hz, 2H), 2.55 (t, *J* = 7.5 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.30 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9, 165.5, 163.6, 160.4, 100.3, 62.8, 60.6, 49.4, 47.5, 35.8, 14.5, 13.99, 13.96; IR (neat, cm^{-1}): 1050, 1157, 1256, 1379, 1449, 1555, 1666, 1740, 2982; HRMS (ESI) calcd for $C_{13}H_{20}N_1O_5$ $(M + H)^+$ 270.1341, found 270.1330.



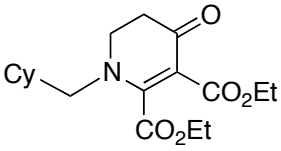
Diethyl 4-Oxo-1-propyl-1,4,5,6-tetrahydropyridine-2,3-dicarboxylate (2.46): clear oil (81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (q, *J* = 7.2 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.67 – 3.57 (t, *J* = 7.4 Hz, 2H), 3.31 – 3.22 (t, *J* = 7.6 Hz, 2H), 2.59 – 2.48 (t, *J* = 7.4 Hz, 2H), 1.77 – 1.65 (m, 2H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9, 165.5, 163.6, 160.6, 100.3, 62.8, 60.5, 55.9, 47.9, 35.8, 22.0, 14.5, 14.0, 11.06; IR (neat, cm^{-1}): 1023, 1071, 1175, 1254, 1299, 1378, 1448, 1552, 1668, 1740, 2978; HRMS (ESI) calcd for $C_{14}H_{22}N_1O_5$ $(M + H)^+$ 284.1498, found 284.1496.



Diethyl 1-Allyl-4-oxo-1,4,5,6-tetrahydropyridine-2,3-dicarboxylate (2.47):
yellow oil (quant.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 16.5, 10.4, 6.1 Hz, 1H), 5.38 – 5.29 (m, 2H), 4.39 (q, *J* = 7.2 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.90 (d, *J* = 6.1 Hz, 2H), 3.63 – 3.55 (t, *J* = 7.5 Hz, 2H), 2.58 – 2.51 (t, *J* = 7.5 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.0, 165.4, 163.6, 160.3, 131.2, 120.7, 100.2, 62.9, 60.7, 56.5, 47.6, 35.8, 14.5, 14.0; IR (neat, cm^{-1}): 1025, 1074, 1176, 1255, 1378, 1448, 1551, 1669, 1740, 2981; HRMS (ESI) calcd for $C_{14}H_{20}N_1O_5$ $(M + H)^+$ 282.1341, found 282.1349.

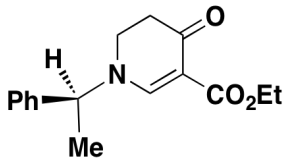


Diethyl 1-Butyl-4-oxo-1,4,5,6-tetrahydropyridine-2,3-dicarboxylate (2.48):
clear oil (93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (q, *J* = 7.2 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.68 – 3.58 (t, *J* = 7.5 Hz, 2H), 3.36 – 3.26 (t, *J* = 7.7 Hz, 2H), 2.58 – 2.49 (t, *J* = 7.5 Hz, 2H), 1.68 (m, 2H), 1.41 – 1.27 (m, 8H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9, 165.5, 163.6, 160.5, 100.4, 62.8, 60.6, 54.2, 48.0, 35.8, 30.8, 20.0, 14.5, 14.0, 13.8; IR (neat, cm^{-1}): 1025, 1072, 1175, 1254, 1378, 1459, 1554, 1668, 1741, 2961; HRMS (ESI) calcd for $C_{15}H_{24}N_1O_5$ $(M + H)^+$ 298.1654, found 298.1646.



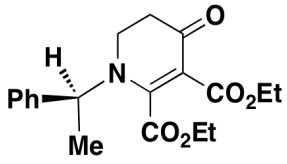
Diethyl 1-(Cyclohexylmethyl)-4-oxo-1,4,5,6-tetrahydropyridine-2,3-dicarboxylate (2.49):

yellow oil (86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (q, *J* = 7.2 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.68 – 3.57 (t, *J* = 7.4 Hz, 2H), 3.16 (d, *J* = 6.9 Hz, 2H), 2.57 – 2.48 (t, *J* = 7.4 Hz, 2H), 1.81 – 1.66 (m, 6H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.27 – 1.11 (m, 3H), 0.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.0, 165.6, 163.5, 160.7, 100.6, 62.8, 60.6, 60.2, 48.6, 37.5, 35.8, 30.9, 26.2, 25.8, 14.5, 14.0; IR (neat, cm^{-1}): 1154, 1246, 1378, 1449, 1547, 1668, 1740, 2927; HRMS (ESI) calcd for $C_{18}H_{28}N_1O_5$ $(M + H)^+$ 338.1967, found 338.1970.



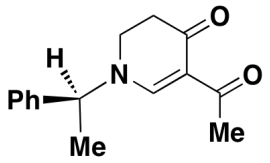
(*S*)-Ethyl 4-Oxo-1-(1-phenylethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate (2.50):

yellow oil (86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.45 – 7.33 (m, 3H), 7.30 – 7.26 (m, 2H), 4.71 (q, *J* = 7.0 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.48 – 3.36 (m, 1H), 3.35 – 3.26 (m, 1H), 2.43 (m, 2H), 1.72 (d, *J* = 7.0 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.7, 165.9, 157.3, 138.8, 129.4, 128.9, 126.5, 100.8, 64.6, 60.1, 44.6, 36.2, 19.2, 14.7; IR (neat, cm^{-1}): 1052, 1140, 1245, 1297, 1394, 1456, 1595, 1659, 1717, 2978; $[\alpha]_D$= −17 (*c* = 0.99 in $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{20}N_1O_3$ $(M + H)^+$ 274.1443, found 274.1435.

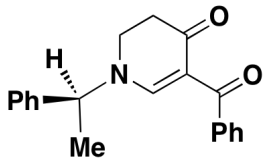


(*S*)-Diethyl 4-Oxo-1-(1-phenylethyl)-1,4,5,6-tetrahydropyridine-2,3-dicarboxylate (2.51):

yellow oil (67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.31 (m, 5H), 4.94 (q, *J* = 6.8 Hz, 1H), 4.54 – 4.41 (m, 2H), 4.32 – 4.20 (m, 2H), 3.40 (ddd, *J* = 13.6, 10.4, 5.8 Hz, 1H), 3.16 (ddd, *J* = 13.5, 7.5, 5.9 Hz, 1H), 2.40 – 2.21 (m, 2H), 1.70 (d, *J* = 6.9 Hz, 3H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.2, 165.7, 164.1, 160.2, 137.5, 129.2, 128.9, 127.3, 100.4, 63.0, 60.6, 60.0, 42.1, 35.8, 16.5, 14.5, 14.1; IR (neat, cm^{-1}): 1026, 1142, 1255, 1299, 1374, 1453, 1538, 1668, 1738, 2982; $[\alpha]_D$= −26 (*c* = 0.97 in $CHCl_3$); HRMS (ESI) calcd for $C_{19}H_{24}N_1O_5$ $(M + H)^+$ 346.1654, found 346.1642.

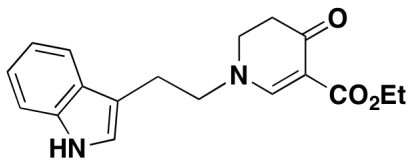


(*S*)-5-Acetyl-1-(1-Phenylethyl)-2,3-dihydropyridin-4(1*H*)-one (2.52):
yellow oil (75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.46 – 7.32 (m, 3H), 7.30 – 7.26 (m, 2H), 4.74 (q, *J* = 7.0 Hz, 1H), 3.51 – 3.37 (m, 1H), 3.37 – 3.24 (m, 1H), 2.52 (s, 3H), 2.43 (m, 2H), 1.72 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 188.3, 157.0, 138.6, 129.4, 128.9, 126.6, 110.2, 65.0, 44.8, 36.0, 30.7, 19.2; IR (neat, cm^{-1}): 1051, 1141, 1248, 1292, 1574, 1635, 2978; $[\alpha]_D$= −19 (*c* = 0.95 in $CHCl_3$); HRMS (ESI) calcd for $C_{15}H_{18}N_1O_2$ $(M + H)^+$ 244.1338, found 244.1338.



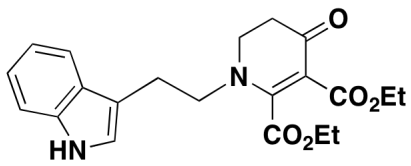
(*S*)-5-Benzoyl-1-(1-phenylethyl)-2,3-dihydropyridin-4(1*H*)-one (2.53):
yellow oil (81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.69 – 7.61 (m, 2H), 7.46 – 7.30 (m, 8H), 4.77 (q, *J* = 7.0 Hz, 1H), 3.55 – 3.45 (m, 1H), 3.45 – 3.35 (m,

1H), 2.48 (m, 2H), 1.75 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 187.1, 157.5, 140.4, 138.7, 131.4, 129.4, 129.0, 129.0, 127.7, 126.6, 110.3, 64.9, 44.8, 35.9, 19.2; IR (neat, cm^{-1}): 1080, 1186, 1252, 1296, 1345, 1378, 1455, 1581, 1622, 2980; $[\alpha]_D$= −13 (*c* = 0.98 in $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{20}N_1O_2$ $(M + H)^+$ 306.1494, found 306.1479.



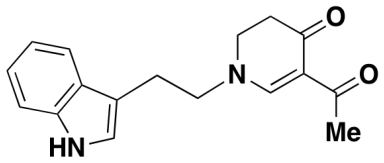
Ethyl 1-(2-(1*H*-Indol-3-yl)ethyl)-4-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (2.54):

white solid (76%); mp: 157.5-158.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.91 (s, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.23 (m, 1H), 7.15 (t, *J* = 7.1 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.72 (t, *J* = 6.7 Hz, 2H), 3.49 (t, *J* = 7.7 Hz, 2H), 3.14 (t, *J* = 6.7 Hz, 2H), 2.48 – 2.38 (t, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 186.7, 165.3, 159.5, 136.6, 126.7, 122.9, 122.7, 120.0, 118.2, 111.9, 110.8, 100.2, 60.0, 57.6, 47.2, 36.1, 25.3, 14.6; IR (neat, cm^{-1}): 1054, 1157, 1243, 1338, 1400, 1457, 1602, 1709, 3286; HRMS (ESI) calcd for $C_{18}H_{21}N_2O_3$ $(M + H)^+$ 313.1552, found 313.1541.



Diethyl 1-(2-(1*H*-Indol-3-yl)ethyl)-4-oxo-1,4,5,6-tetrahydropyridine-2,3-dicarboxylate (2.55):

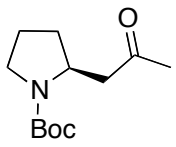
off-white solid (73%); mp: 46.9-48.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.16 (m, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.72 – 3.62 (m, 2H), 3.57 – 3.48 (t, *J* = 7.5 Hz, 2H), 3.16 (t, *J* = 7.3 Hz, 2H), 2.42 – 2.30 (m, 2H), 1.31 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.2, 165.5, 163.7, 160.4, 136.5, 127.0, 122.7, 122.6, 120.0, 118.4, 111.7, 111.3, 100.7, 62.9, 60.6, 54.9, 49.0, 35.7, 25.6, 14.5, 14.0; IR (neat, cm^{-1}): 1028, 1174, 1257, 1378, 1458, 1552, 1658, 1714, 1739, 3306; HRMS (ESI) calcd for $C_{21}H_{25}N_2O_5$ $(M + H)^+$ 385.1763, found 385.1747.



1-(2-(1*H*-Indol-3-yl)ethyl)-5-acetyl-2,3-dihydropyridin-4(1*H*)-one (2.56):
off-white solid (61%); mp: 183.7-184.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.15 (s, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.16 (m, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 3.73 (t, *J* = 7.0 Hz, 2H), 3.50 (t, *J* = 7.7 Hz, 2H), 3.15 (t, *J* = 6.9 Hz, 2H), 2.47 (s, 3H), 2.45 – 2.39 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 188.1, 159.2, 136.5, 126.8, 122.8, 122.5, 120.0, 118.2, 111.8, 111.0, 109.9, 57.8, 47.5, 36.0, 30.6, 25.4; IR (neat, cm^{-1}): 1151, 1323, 1361, 1583, 1629, 2924, 3282; HRMS (ESI) calcd for $C_{17}H_{19}N_2O_2$ $(M + H)^+$ 283.1447, found 283.1450.

5.3 Chapter 3

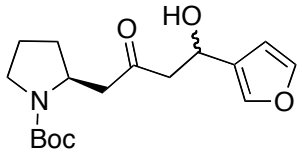
Unless specified, all reactions were conducted in oven-dried glassware under nitrogen atmosphere using anhydrous solvents. 3-furancarboxaldehyde was purified by distillation prior to use. IBX was prepared according to the literature procedure. Synthesis of **3.6** and **3.7** was conducted according to the literature procedure.[48]



(*S*)-tert-butyl 2-(2-oxopropyl)pyrrolidine-1-carboxylate (3.8):

To a solution of Weinreb amide (5.82 g, 21.4 mmol, 1 equiv) in THF (80 mL) was slowly added MeLi (1.6 M in THF, 33 mL, 53.5 mmol, 2.5 equiv) at –78 °C. After 5 h, additional MeLi (20 mL, 32.1 mmol, 1.5 equiv) was added to the reaction mixture. After 2 h, the reaction was quenched by the addition of 10% H_2O in THF (10 mL) and warmed to 0 °C, which was then treated with aq.HCl (3 M, 30 mL). The partitioned organic layer was washed with aq.NH_4Cl, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (EtOAc/Hexanes).

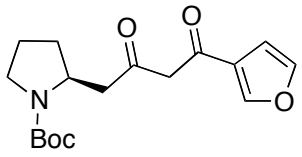
clear oil (3.96 g, 81%, rec.SM: 8%); ^{1}H NMR (400 MHz, $CDCl_3$, 333 K) δ; 4.14 (ddd, *J* = 11.2, 7.4, 3.5 Hz, 1H), 3.33 (dt, *J* = 10.2, 5.6 Hz, 2H), 3.00 (s, 1H), 2.41 (dd, *J* = 15.8, 9.4 Hz, 1H), 2.13 (d, *J* = 3.1 Hz, 3H), 2.10 – 2.01 (m, 1H), 1.85 – 1.74 (m, 2H), 1.68 – 1.60 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$, 333 K) δ 207.1, 154.5, 79.6, 53.8, 48.6, 46.6, 31.5, 30.5, 28.7, 23.5; IR (neat, cm^{-1}): 2974, 1692, 1397, 1170, 1103; $[\alpha]_D$= −36.9 (*c* = 1.39 in $CHCl_3$); HRMS (ESI) calcd for $C_{12}H_{22}N_1O_3$ $(M+H)^+$ 228.1600, found 228.1603.



(2*S*)-tert-butyl 2-(4-(furan-3-yl)-4-hydroxy-2-oxobutyl)pyrrolidine-1-carboxylate (3.9):

To a solution of methylketone **3.8** (4.00 g, 17.4 mmol, 1 equiv) and DIPEA (2.58 g, 20.0 mmol, 1.2 equiv) in Et_2O (140 mL) was slowly added *n*-Bu_2BOTf (1 M, 18.3 mL, 18.3 mmol, 1.1 equiv) via a syringe pump at –78 °C. After 1 h, 3-furancarboxaldehyde (1.92 g, 20.0 mmol, 1.2 equiv) in Et_2O (10 mL) was added dropwise again via a syringe pump over 1h. After 4 h, 7.2 buffer (20 mL) in MeOH (80 mL) was added to the reaction mixture, which was then warmed to 0 °C, followed by the addition of H_2O_2 (30%, 20 mL)/MeOH (40 mL). After stirring for 1 h at ambient temperature, organic layer of the reaction mixture was evaporated, and Et_2O/H_2O were added to the solution. The partitioned aqueous layer was extracted with Et_2O (×3), and the combined organic layers were washed with aq.$NaHCO_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc/Hexanes).

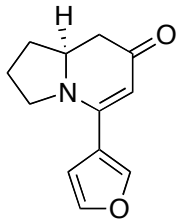
clear oil (5.60 g, quant.); ^{1}H NMR (400 MHz, $CDCl_3$, 333 K) δ; 7.38 (dd, *J* = 9.0, 1.1 Hz, 2H), 6.38 (s, 1H), 5.15 (s, 1H), 4.18 (s, 1H), 3.69 – 3.05 (m, 3H), 3.03 – 2.72 (m, 3H), 2.46 (dd, *J* = 15.6, 8.3 Hz, 1H), 2.08 (dq, *J* = 15.9, 8.0 Hz, 1H), 1.82 (d, *J* = 5.3 Hz, 2H), 1.65 (dt, *J* = 10.7, 4.9 Hz, 1H), 1.45 (dd, *J* = 5.0, 4.3 Hz, 9H) ; ^{13}C NMR (101 MHz, $CDCl_3$, 333 K) δ; 209.0, 154.8, 143.5, 139.2, 128.1, 108.7, 79.8, 63.4, 53.8, 50.9, 48.7, 46.6, 31.7, 28.7, 23.6; IR (neat, cm^{-1}): 3421, 2974, 1690, 1400, 1168, 1121, 1026, 875; $[\alpha]_D$= −25 (*c* = 1.1 in $CHCl_3$); HRMS (ESI) calcd for $C_{17}H_{26}N_1O_5$ $(M+H)^+$ 324.1811, found 324.1806.



(*S*)-tert-butyl 2-(4-(furan-3-yl)-2,4-dioxobutyl)pyrrolidine-1-carboxylate (3.10):

To a solution of hydroxyketone **3.9** (2.10 g, 6.5 mmol, 1 equiv) was added freshly prepared IBX (5.5 g, 19.5 mmol, 3 equiv). After heating at 60 °C for 3h, additional IBX (1.82 g, 6.5 mmol, 1equiv) was added to the reaction mixture, which was further stirred overnight. Upon Celite filtration, the crude mixture was purified by flash column chromatography (EtOAc/Hexanes).

clear oil (1.68 g, 80%); ^{1}H NMR (400 MHz, d^{4}-MeOD) δ; 8.23 (s, 1H), 7.61 (s, 1H), 6.81 (s, 1H), 6.07 (d, *J* = 14.5 Hz, 1H), 4.19 (s, 1H), 3.34 (d, *J* = 16.0 Hz, 3H), 2.83 (m, 1H), 2.41 (s, 1H), 1.95 (m, 4H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, d^{4}-MeOD, 333 K) δ; 191.7, 182.4, 156.2, 147.7, 145.9, 126.1, 109.0, 99.3, 81.1, 56.5, 47.4, 43.3, 31.5, 28.8, 24.0; IR (neat, cm^{-1}): 2974, 1690, 1619, 1396, 1160, 1119; $[\alpha]_D$= −4.7 (*c* = 1.1 in $CHCl_3$); HRMS (ESI) calcd for $C_{17}H_{24}N_1O_5$ $(M+H)^+$322.1654, found 322.1651.

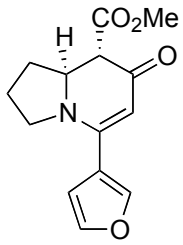


(*S*)-5-(furan-3-yl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3.11):

To a cold flask containing enol **3.10** (1.43 g, 4.46 mmol, 1 equiv) was added cold formic acid (45 mL). After stirring for 6 h at ambient temperature, the reaction mixture was concentrated *in vacuo*. K_2CO_3 (1.23 g, 8.91 mmol, 2 equiv) and MeOH (45 mL) were added to the reaction mixture at 0 °C, which was stirred

overnight. Upon evaporation of MeOH, resulting crude mixture was extracted with CH_2Cl_2 (×3). The extraction was concentrated and subjected to flash column chromatography (MeOH/ CH_2Cl_2).

white solid (845 mg, 93%); mp: 107.6-108.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.68 (s, 1H), 7.46 (d, *J* = 1.6 Hz, 1H), 6.53 (d, *J* = 1.0 Hz, 1H), 5.19 (s, 1H), 4.03 – 3.91 (m, 1H), 3.71 – 3.63 (m, 1H), 3.56 – 3.48 (m, 1H), 2.44 (s, 1H), 2.41 (d, *J* = 2.7 Hz, 1H), 2.31 (ddd, *J* = 18.9, 6.7, 4.5 Hz, 1H), 2.15 – 2.04 (m, 1H), 1.94 (tt, *J* = 12.7, 7.8 Hz, 1H), 1.77 (ddd, *J* = 16.5, 12.4, 8.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 333 K) δ; 192.0, 154.3, 143.6, 142.7, 121.9, 110.1, 98.9, 59.3, 49.6, 41.6, 32.0, 24.7; IR (neat, cm^{-1}): 3117, 2968, 2879, 1622, 1507, 1266, 1162, 1045; $[\alpha]_D$= −739 (*c* = 0.590 in $CHCl_3$); HRMS (ESI) calcd for $C_{12}H_{14}N_1O_2$ $(M+H)^+$ 204.1025, found 204.1020.

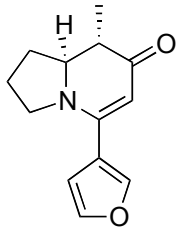


(8*S*,8a*S*)-methyl 5-(furan-3-yl)-7-oxo-1,2,3,7,8,8a-hexahydroindolizine-8-carboxylate (3.12):

To a solution of diisopropylamine (263mg, 2.6 mmol, 1.3 equiv) in THF (10 mL) at –78 °C was slowly added *n*-BuLi (1.6 M, 1.63 mL, 2.6 mmol, 1.3 equiv). The solution was warmed to 0 °C and stirred for 10 min to generate LDA, and cooled again to –78 °C. Enaminone **3.11** (408mg, 2.0 mmol, 1.0 equiv) in THF (5 mL) was added dropwise to the LDA solution, which was stirred for 1 h. Methyl cyanoformate (Mander's reagent, 272 mg, 3.2 mmol, 1.6 equiv) was added to the reaction mixture. After 1 h, the reaction mixture was poured into ice and extracted with EtOAc (×3). The combined organic layers were washed with brine,

dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by recrystallization (EtOAc/Hexanes, twice, 1st crop and 2nd crop were combined).

yellow solid (468 mg, 90%); mp: 140.2-141.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.69 (s, 1H), 7.47 (t, *J* = 1.6 Hz, 1H), 6.53 (d, *J* = 1.0 Hz, 1H), 5.25 (s, 1H), 4.29 (dt, *J* = 14.9, 7.3 Hz, 1H), 3.82 (s, 3H), 3.76 – 3.68 (m, 1H), 3.54 (dt, *J* = 10.6, 7.6 Hz, 1H), 3.41 (d, *J* = 15.2 Hz, 1H), 2.32 (ddd, *J* = 19.1, 6.8, 4.8 Hz, 1H), 2.16 – 2.04 (m, 1H), 1.96 (ddd, *J* = 14.8, 12.8, 8.3 Hz, 1H), 1.76 (ddd, *J* = 16.5, 12.5, 7.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ; 186.1, 170.1, 154.2, 143.8, 142.9, 121.5, 110.1, 98.5, 60.7, 56.7, 52.5, 50.0, 30.9, 24.5; IR (neat, cm^{-1}): 1737, 1624, 1510, 1255, 1160; $[\alpha]_D$= −729 (*c* = 0.650 in $CHCl_3$); HRMS (ESI) calcd for $C_{14}H_{16}N_1O_4$ $(M+H)^+$ 262.1079, found 262.1074.

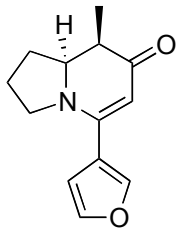


(8*S*,8a*S*)-5-(furan-3-yl)-8-methyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3.13a):

To a solution of enaminone **3.12** (501 mg, 1.92 mmol, 1.0 equiv) in THF (19 mL) at –78 °C was added NaHMDS (1.0 M, 2.10 mL, 2.1 mmol, 2.1 equiv). After 1 h, MeI (817 mg, 5.75 mmol, 3.0 equiv) was added to the reaction mixture. Again the reaction flask was stirred for 1 h, and warmed to 0 °C. After 1 h, the reaction was quenched with aq. $NaHCO_3$, which was extracted with EtOAc (×3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography ($MeOH/CH_2Cl_2$), and two inseparable diastereomers were obtained (yellow oil).

To the resulting diastereomeric mixtures in DMSO (19 mL) was added NaCN (466 mg, 9.5 mmol, 5.0 equiv) and H_2O (171 mg, 9.5 mmol, 5.0 equiv). This reaction mixture was heated to 160 °C using microwave for 1.5 h. EtOAc and water were added to the reaction mixture, which was extracted with EtOAc (×3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude products were purified by flash column chromatography (EtOAc/Hexanes) to give each diastereomer.

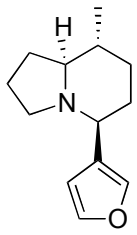
white solid (303 mg, 73%, major diastereomer); mp: 128.7-129.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.69 – 7.64 (m, 1H), 7.45 (t, *J* = 1.7 Hz, 1H), 6.53 (dd, *J* = 1.8, 0.8 Hz, 1H), 5.21 (s, 1H), 3.77 – 3.67 (m, 1H), 3.51 (ddd, *J* = 14.2, 13.8, 7.7 Hz, 2H), 2.33 (dtd, *J* = 12.6, 6.5, 3.2 Hz, 1H), 2.23 (dq, *J* = 13.7, 6.8 Hz, 1H), 2.09 (m, 1H), 1.99 – 1.87 (m, 1H), 1.84 – 1.73 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ; 194.2, 153.5, 143.5, 142.5, 121.8, 110.2, 98.6, 65.2, 49.8, 43.7, 31.7, 24.5, 11.8; IR (neat, cm^{-1}): 3117, 2967, 2869, 1613, 1538, 1302, 1231, 1027; $[\alpha]_D$= −688 (*c* = 0.590 in $CHCl_3$); HRMS (ESI) calcd for $C_{13}H_{16}N_1O_2$ $(M+H)^+$ 218.1181, found 218.1180.



(8*R*,8a*S*)-5-(furan-3-yl)-8-methyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3.13b):

white solid (88.2 mg, 21%, minor diastereomer); mp: 78.8-80.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.69 (s, 1H), 7.46 (t, *J* = 1.6 Hz, 1H), 6.57 – 6.52 (m, 1H), 5.12 (s, 1H), 4.04 (dd, *J* = 11.6, 7.4 Hz, 1H), 3.74 – 3.67 (m, 1H), 3.54 (dt, *J* = 10.7, 6.9 Hz, 1H), 2.31 – 2.23 (qd, *J* = 7.3, 4.0 Hz, 1H), 2.14 – 2.03 (m, 2H), 2.01 – 1.90 (m, 2H), 1.04 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ; 196.9, 153.3,

143.6, 142.6, 121.6, 110.1, 97.0, 62.4, 49.9, 42.5, 27.1, 25.0, 11.0; IR (neat, cm^{-1}): 2967, 1619, 1584, 1511, 1474, 1258, 1161; $[\alpha]_D$= − 455 (*c* = 0.840 in $CHCl_3$); HRMS (ESI) calcd for $C_{13}H_{16}N_1O_2$ $(M+H)^+$ 218.1181, found 218.1171.

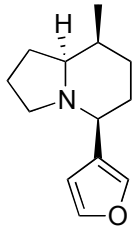


(5*S*,8*R*,8a*S*)-5-(furan-3-yl)-8-methyloctahydroindolizine (3.1):

To a solution of enaminone **3.13a** (150 mg, 0.692 mmol, 1.0 equiv) in CH_2Cl_2 (7 mL) at –78 °C was added Tf_2O (390 mg, 1.38 mmol, 2.0 equiv). The reaction mixture was warmed to ambient temperature and stirred for 3 h, which was then cooled to –78 °C. LAH (2.0 M, 0.69 mL, 1.38 mmol, 2.0 equiv) was added to the solution, which was warmed to ambient temperature. After 1 h, the reaction was quenched by the addition of sat. Rochelle salt solution (2 mL) at –78 °C. The partitioned aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was carried to the next step without further purification.

Pd/C (10%, 370 mg, 0.35 mmol, 0.5 equiv) was added to the crude triflate in MeOH (7 mL). H_2 was initially bubbled through a needle to the reaction mixture for 5 min, which was then stirred overnight under H_2 atmosphere using a balloon. Upon Celite filtration, MeOH was evaporated and the crude mixture was re-dissolved in CH_2Cl_2, which was washed with aq. $NaHCO_3$, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by Al_2O_3 (Et_2O/Hexanes). In concentration of eluent, only rotary evaporator (25 °C for the temperature of water bath) was used due to the low boiling point of the product.

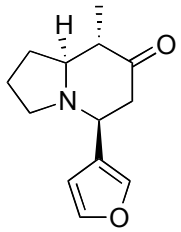
clear oil (106 mg, 75%, upon cooling at 0 °C, a title compound formed white crystals); ^{1}H NMR (400 MHz, $CDCl_3$, 333 K) δ; 7.34 (d, *J* = 0.9 Hz, 2H), 6.44 (s, 1H), 2.95 – 2.84 (m, 2H), 1.93 (ddd, *J* = 23.6, 12.8, 7.4 Hz, 2H), 1.83 – 1.36 (m, 9H), 1.14 – 1.00 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, 333 K) δ; 142.8, 139.5, 128.4, 109.9, 71.6, 59.9, 53.3, 36.6, 34.3, 34.1, 29.2, 20.3, 19.0; IR (neat, cm^{-1}): 2953, 2926, 2781, 1501, 1458, 1166, 1023; $[\alpha]_D$= −121 (*c* = 1.17 in $CHCl_3$); HRMS (ESI) calcd for $C_{13}H_{20}N_1O_1$ $(M+H)^+$ 206.1545, found 206.1541.



(5*S*,8*S*,8a*S*)-5-(furan-3-yl)-8-methyloctahydroindolizine (3.2):

To a solution of enaminone **3.13b** (31 mg, 0.14 mmol, 1.0 equiv) in CH_2Cl_2 (0.8 mL) at –78 °C was added Tf_2O (79 mg, 0.28 mmol, 2.0 equiv). The reaction mixture was warmed to 0 °C and stirred for 3 h, which was then cooled to –78 °C. LAH (2.0 M, 0.14 mL, 0.28 mmol, 2.0 equiv) was added to the solution, which was warmed to ambient temperature. The crude triflate as well as the title compound were obtained in the same protocol as described in a previous procedure.

clear oil (7.6 mg, 26%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H), 6.43 (s, 1H), 2.90 – 2.83 (m, 2H), 2.14 – 2.06 (m, 1H), 1.93 (td, *J* = 6.8, 2.8 Hz, 1H), 1.87 – 1.75 (m, 2H), 1.70 – 1.53 (m, 6H), 1.52 – 1.45 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 139.2, 129.0, 109.9, 67.7, 61.1, 53.6, 32.3, 29.6, 29.1, 27.0, 20.3, 12.4; IR (neat, cm^{-1}): 2925, 1459, 1158, 1023, 873, 784; $[\alpha]_D$= − 96 (*c* = 0.52 in $CHCl_3$); HRMS (ESI) calcd for $C_{13}H_{20}N_1O_1$ $(M+H)^+$ 206.1545, found 206.1535.

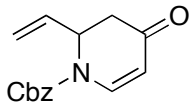


(5*S*,8*S*,8a*S*)-5-(furan-3-yl)-8-methylhexahydroindolizin-7(1*H*)-one (3.15):

To a solution of the crude triflate **3.14a** (175 mg, 0.5 mmol, 1 equiv) obtained from **3.13a** (109 mg, 0.5 mmol) in 1,4-dioxane (3 mL) and MeOH (1.5 mL) was added aq.NaOH solution (1 M, 1.5 mL, 1.5 mmol, 3 equiv). After 6 h, MeOH was evaporated and EtOAc, and water were added to the crude mixture. The partitioned aqueous layer was extracted with EtOAc (×3), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($MeOH/CH_2Cl_2$).

white solid (103 mg, 95%); mp: 94.8-95.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 333 K) δ; 7.42 – 7.32 (m, 2H), 6.47 (s, 1H), 3.34 (dd, *J* = 11.9, 3.2 Hz, 1H), 2.94 (dd, *J* = 12.4, 5.4 Hz, 1H), 2.76 – 2.65 (m, 1H), 2.50 – 2.39 (m, 2H), 2.09 – 1.97 (m, 3H), 1.92 – 1.58 (m, 3H), 1.04 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, 333 K) δ; 209.8, 143.6, 139.6, 126.8, 109.1, 70.5, 58.1, 52.2, 50.5, 48.6, 30.5, 21.5, 10.7; IR (neat, cm^{-1}): 3140, 2966, 2787, 1710, 1504, 1359, 1171, 1019; $[\alpha]_D$= −97.6 (*c* = 0.505 in $CHCl_3$); HRMS (ESI) calcd for $C_{13}H_{18}N_1O_2$ $(M+H)^+$ 220.1338, found 220.1341.

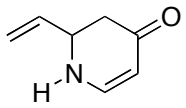
5.4 Chapter 4



Benzyl 4-Oxo-2-vinyl-3,4-dihydropyridine-1(2*H*)-carboxylate (4.7):

To a solution of 4- methoxypyridine (12.6 g, 115 mmol, 1.0 equiv) in 1.0 L of anhydrous THF at –23 °C was added dropwise benzyl chloroformate (21.8 g, 121 mmol, 1.05 equiv). The reaction mixture was stirred at –23 °C for 1.5 h. Vinylmagnesium bromide (197 mL, 138 mmol, 1.2 equiv, 0.7 M in THF) was transferred via a dropping funnel to the flask containing the *N*-acylpyridinium salt, and the mixture was stirred at –23 °C for 2 h. Saturated aqueous oxalic acid (400 mL) was added. The reaction mixture was warmed to room temperature and stirred for 2 h. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine and were dried over anhydrous Na_2SO_4. Filtration and concentration in vacuo gave the crude product. Purification by flash chromatography (silica gel, 30% EtOAc/hexanes) yielded of the title compound.

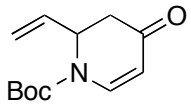
off-white solid (24.0 g, 81%): mp 47.5 – 50.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 1H), 7.41 – 7.34 (m, 6H), 5.80 (ddd, *J* = 17.5, 10.5, 5.0 Hz, 1H), 5.33 (d, *J* = 8.3 Hz, 1H), 5.27 (s, 1H), 5.27 (s, 1H), 5.22 (dd, *J* = 10.6, 1.0 Hz, 1H), 5.14 (d, *J* = 16.2 Hz, 1H), 5.17 – 5.10 (m, 1H), 2.90 (dd, *J* = 16.5, 6.8 Hz, 1H), 2.54 (d, *J* = 16.5 Hz, N Cbz1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 152.5, 141.5, 134.9, 132.7, 128.8, 128.8, 128.4, 117.5, 107.6, 69.2, 54.7, 39.9; IR (neat) 3089, 1727, 1671, 1606, 1387, 1190, 993, 764, 699 cm^{-1}; HRMS (ESI^+) *m/e* calc'd for $[M+H]^+$ $C_{15}H_{16}NO_3$: 258.1130, found 258.1128.



2-vinyl-2,3-dihydropyridin-4(1*H*)-one (4.8):

To a solution of enaminone **4.7** (14.7 g, 57.3 mmol, 1.00 equiv) in MeOH (160 mL) was added sodium methoxide (9.3 g, 172 mmol, 3.00 equiv) and the reaction mixture brought to reflux. After 2 h, when the reaction was judged complete by TLC, the reaction mixture was cooled to room temperature and the solvent was evaporated *in vacuo*. The remaining residue was redissolved in CH_2Cl_2, filtered, and the filtrate was concentrated. This was repeated two more times. The crude product was purified by flash chromatography (silica gel, 80% acetone/hexanes) to yield the title compound.

off-white solid (5.62 g, 80%): mp 59 – 61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, *J* = 6.9 Hz, 1H), 6.55 – 6.45 (m, 1H), 5.91 (ddd, *J* = 16.9, 9.8, 7.0 Hz, 1H), 5.31 (d, *J* = 17.1 Hz, 1H), 5.22 (d, *J* = 10.3 Hz, 1H), 4.96 (d, *J* = 7.3 Hz, 1H), 4.26 – 4.16 (m, 1H), 2.53 – 2.39 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 151.9, 136.0, 117.3, 98.2, 55.7, 41.8; IR (neat) 3246, 3032, 1620, 1575, 1236, 931, 782 cm^{-1}; HRMS (ESI$^+$) *m/e* calc'd for $[M+H]^+$ $C_7H_{10}NO$: 124.0762, found 124.0757.

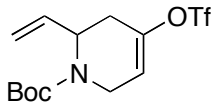


***tert*-Butyl 4-Oxo-2-vinyl-3,4-dihydropyridine-1(2*H*)-carboxylate (4.9):**

Enaminone **4.8** (5.62 g, 45.6 mmol, 1.00 equiv), TEA (6.92 g, 68.4 mmol, 1.5 equiv) and DMAP (557 mg, 4.56 mmol, 0.1 equiv) were dissolved in anhydrous THF (450 mL). To this solution was added Boc_2O (11.9 g, 54.7 mmol, 1.2 equiv) and the reaction mixture was stirred for 6 h at room temperature. The reaction was quenched with a saturated solution of $NaHCO_3$ (*aq.*) and added to a separatory funnel. The product was extracted with EtOAc (3x). The combined

organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The title compound was obtained after SiO_2 flash chromatography (20% EtOAc/hexanes).

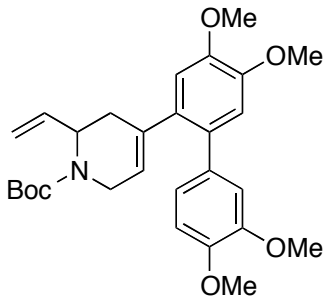
colorless oil (8.95 g, 88%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 1H), 5.80 (ddd, *J* = 17.1, 10.5, 5.4 Hz, 1H), 5.29 (d, *J* = 8.4 Hz, 1H), 5.21 (dd, *J* = 10.5, 1.0 Hz, 1H), 5.14 (ddd, *J* = 17.1, 1.6, 0.5 Hz, 1H), 5.09 – 5.02 (m,1H), 2.90 (dd, *J* = 16.5, 7.1 Hz, 1H), 2.53 (dt, *J* = 16.5, 1.4 Hz, 1H), 1.53 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5, 151.2, 142.1, 133.1, 117.0, 106.5, 83.6, 54.5, 39.9, 28.0; IR (neat) 2980, 1724, 1672, 1604 1336, 1156, 862, 767 cm^{-1}; HRMS (ESI^+) *m/e* calc'd for $[M+H]^+$ $C_{12}H_{18}NO_3$: 224.1287, found 224.1275.



tert-butyl 4-(((trifluoromethyl)sulfonyl)oxy)-6-vinyl-5,6-dihydropyridine-1(2*H*)-carboxylate (4.10):

Enaminone **4.9** (8.95 g, 40.1 mmol, 1.0 equiv.) was dissolved in anhydrous THF (400 mL) under a N_2 atmosphere. The solution was cooled to –78 °C at which point L-Selectride (44.1 mL, 44.1 mmol, 1.1 equiv, 1.0 M in THF) was added over 15 minutes. After stirring for 1 h, the reaction was slowly warmed to 0 °C over 1.5 h and stirred at room temperature for an additional hour. The reaction mixture was once again cooled to –78 °C and Comins' reagent (17.3 g, 44.1 mmol, 1.1 equiv) was added all at once. The mixture was stirred for another hour at –78 °C and then slowly warmed to 0 °C over 2 h. The reaction was quenched with a saturated solution of $NaHCO_3$ (*aq.*) and added to a separatory funnel. The product was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The title compound was obtained after SiO_2 flash chromatography (3% EtOAc/hexanes).

colorless oil (10.8 g, 75% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 – 5.70 (m, 2H), 5.25 – 5.16 (m, 2H), 5.09 – 5.01 (m, 1H), 4.39 (d, *J* = 18.4 Hz, 1H), 3.68 – 3.60 (m, 1H), 2.90 – 2.81 (m, 1H), 2.35 (d, *J* = 17.0 Hz, 1H), 1.48 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.8; ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.40, 145.22, 134.73, 118.50 (q, *J* = 320.3 Hz), 117.08, 114.96, 80.79, 50.53, 39.08, 31.45, 28.36; IR (neat) 2980, 1706, 1420, 1212, 1143, 1065, 875, 772 cm–1; HRMS (ESI^+) *m/e* calc'd for $[M+H]^+$ $C_{13}H_{18}F_3NNaO_5S$: 380.0755, found 380.0758.

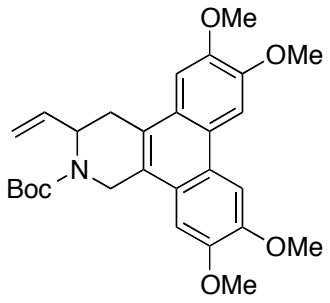


tert-Butyl 4-(3',4,4',5-tetramethoxy-[1,1'-biphenyl]-2-yl)-6-vinyl-5,6-dihydropyridine-1(2*H*)- carboxylate (4.11):

Preparation of organo zinc reagent. A dry RBF containing anhydrous $ZnBr_2$ (2.10 g, 9.23 mmol, 1.65 equiv) was heated with a heat gun under vacuum for 5 min. The flask was then cooled to 25 °C, and anhydrous THF (90 mL) was added. To a separate flask containing 120 mL of THF at –78 °C was added *tert*-butyllithium (10.4 mL, 17.6 mmol, 3.15 equiv, 1.7 M in THF), and then the biarylbromide (2.96 g, 8.39 mmol, 1.50 equiv) in a minimal amount of THF (~25 mL) was added dropwise. The mixture was stirred at –78 °C for 1 h, and the solution of $ZnBr_2$ in THF was transferred via a cannula. The resulting zinc reagent was let warm to room temperature. Triflate **4.10** (1.96 g, 5.48 mmol, 1.00 equiv) and $Pd(PPh_3)_4$ (129 mg, 0.11 mmol, 0.02 equiv) were added sequentially to the solution of zinc reagent. The resulting yellow mixture was stirred at room temperature until the triflate had been consumed (~30 min). The reaction was quenched with a saturated solution of NH_4Cl (*aq.*) and added to a separatory funnel. The product

was extracted with EtOAc (3x). The combined organic layers were concentrated *in vacuo*. Methanol (~50 mL) was added to the residue and the solution was heated to boiling. Upon cooling this solution, a white crystalline solid (3,3',4,4'-tetramethoxy-1,1'-biphenyl) formed and was subsequently filtered off. The filtrate was concentrated *in vacuo* and a minimal volume of methanol was added to the residue, and the recrystallization process repeated. After repeating the recrystallization one more time, the concentrated filtrate residue was purified by SiO_2 flash chromatography (25% EtOAc/hexanes) to yield the title compound.

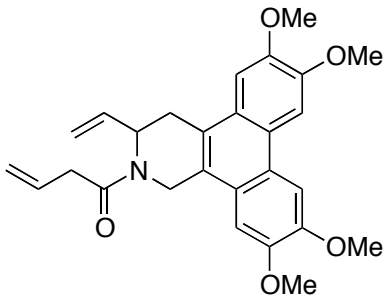
colorless foamy solid (2.7 g, quant.): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 2H), 6.87 (s, 1H), 6.80 (s, 1H), 6.73 (s, 1H), 5.68 (bs, 1H), 5.39 (ddd, *J* = 17.2, 10.4, 4.7 Hz, 1H), 5.01 (dt, *J* = 10.4, 1.5 Hz, 1H), 4.95 (d, *J* = 17.2 Hz, 1H), 4.71 (bs, 1H), 4.22 (d, *J* = 18.4 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.83 (s, 3H), 3.69 – 3.61 (m, 1H), 2.32 (d, *J* = 15.7 Hz, 1H), 1.87 (d, *J* = 16.6 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 147.4, 147.0, 146.9, 146.8, 135.9, 134.8, 133.3, 133.0, 131.3, 121.4, 120.4, 113.8, 112.4, 111.8, 111.7, 110.0, 78.7, 55.1, 55.0, 55.0, 54.8, 49.4, 39.8, 32.6, 27.4. IR (neat) 2934, 1692, 1504, 1250, 1151, 1028, 731 cm^{-1}; HRMS (ESI$^+$) *m/e* calc'd for $[M+H]^+$ $C_{28}H_{36}NO_6$: 482.2543, found 482.2560.



tert-butyl 6,7,10,11-tetramethoxy-3-vinyl-3,4 dihydrodibenzo [*f*,*h*]isoquinoline-2(1*H*)- carboxylate (4.12):

Piperidine **4.11** (5.87 g, 12.2 mmol, 1.00 equiv) was dissolved in anhydrous CH_2Cl_2 (800 mL) and cooled to –78 °C. In a separate flask containing VOF_3 (3.32 g, 26.8 mmol, 2.2 equiv) was added anhydrous CH_2Cl_2 (130 mL), anhydrous EtOAc (65 mL), TFA (6.4 mL) and TFAA (0.32 mL). The VOF_3 solution was then added over 20 minutes to the solution of indolizidine **4.11**. The reaction mixture was stirred for 1 h at –78 °C. To the reaction mixture was added 10% NaOH (500 mL) and the biphasic mixture was vigorously stirred for 1 h at room temperature. The product was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* gave the crude product. Purification by flash chromatography (80 % EtOAc/hexanes) provided the title compound.

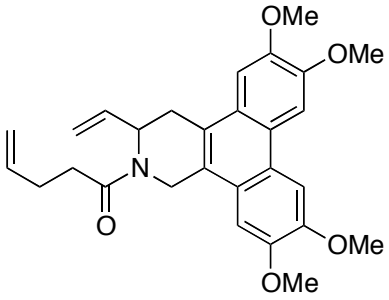
white crystalline solid (5.28 g, 91%): mp 203.0 – 204.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.84 (s, 1H), 7.32 (s, 1H), 7.20 (s, 1H), 5.82 (ddd, *J* = 17.2, 10.4, 5.3 Hz, 1H), 5.36 – 5.24 (m, 1H), 5.26 (d, *J* = 17.5 Hz, 1H), 5.15 (dt, *J* = 17.3, 1.4 Hz, 1H), 5.07 (dt, *J* = 10.4, 1.3 Hz, 1H), 4.57 (d, *J* = 17.1 Hz, 1H), 4.12 (s, 3H), 4.12 (s, 4H), 4.06 (s, 4H), 4.03 (s, 3H), 3.39 (dd, *J* = 16.3, 6.1 Hz, 1H), 3.30 (d, *J* = 16.2 Hz, 1H), 1.56 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 149.0, 148.9, 148.8, 148.7, 136.3, 125.4, 123.8, 123.7, 123.5, 116.5, 103.9, 103.5, 102.8, 80.2, 56.1, 55.9, 41.0, 29.8, 28.5; IR (neat) 2974, 1689, 1516, 1250, 1151, 1018, 840, 731 cm^{-1}; HRMS (ESI$^+$) *m/e* calc'd for $[M+H]^+$ $C_{28}H_{34}NO_6$: 480.2386, found 480.2365.



1-(6,7,10,11-Tetramethoxy-3-vinyl-3,4-dihydrodibenzo[*f,h*]isoquinolin-2(1*H*)-yl)but-3-en-1- one (4.13a):

Piperidine **4.12** (956 mg, 2.00 mmol, 1.00 equiv) was dissolved in anhydrous CH_2Cl_2 (20 mL). TFA (5 mL) was added to the solution. The reaction mixture immediately turned dark purple and slowly turned a light brown color. After the reaction was stirred for 1 h the solvent was removed by passing N_2 over it. To the remaining residue was added CH_2Cl_2 (50 mL) and NH_3 (5 mL, 2.0 M in MeOH). This solution was stirred for 30 min and then poured into a separatory funnel containing 10% NaOH (*aq.*). The product was extracted with CH_2Cl_2 (3x) and combined organic layers were dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* gave the crude product which was used without further purification. The deprotected amine from above was dissolved in anhydrous CH_2Cl_2 (100 mL) under argon atmosphere and cooled to 0 °C. To this solution was added vinylacetic acid (189 mg, 2.2 mmol, 1.1 equiv) and *N*-methylmorpholine (0.14 mL, 1.3 mmol, 1.1 equiv) followed by EDCI (422 mg, 2.2 mmol, 1.1 equiv). The reaction mixture was then allowed to come to room temperature. After 2 hours, the reaction was again cooled to 0 °C and quenched by the addition of an ice cold 10% HCl solution (50 mL) and was stirred at this temperature for 5 minutes. The reaction was diluted with water (100 mL) and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with saturated $NaHCO_3$ (x1), dried over Na_2SO_4, filtered and concentrated. The title compound was obtained after SiO_2 flash chromatography (70% EtOAc/Hexanes).

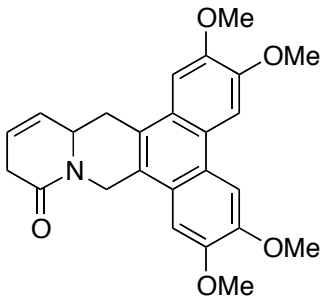
white solid (854 mg, 96%): mp 163 – 165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.83 (s, 1H), 7.33 – 7.08 (m, 2H), 6.09 (m, 1H), 5.92 (m, 0.35H), 5.81 (m, 1H), 5.62 (d, 0.65H), 5.27 – 5.02 (m, 5H), 4.80 (d, 0.35H), 4.54 (d, 0.65H), 4.12 (s, 6H), 4.06 (s, 6H), 3.45 – 3.30 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 149.06, 148.90, 148.82, 148.82, 135.8, 131.6, 125.0, 123.87, 123.58, 123.37, 122.7, 118.04, 117.2, 103.73, 103.54, 103.46, 103.0, 56.11, 56.11, 56.07, 55.92, 53.0, 39.9, 39.3, 30.6; IR (neat) 2938, 1646, 1516, 1424, 1250, 1151, 916, 730 cm^{-1}; HRMS (ESI^+) *m/e* calc'd for $[M+H]^+$ $C_{27}H_{30}NO_5$: 448.2124, found 448.2115.



1-(6,7,10,11-tetramethoxy-3-vinyl-3,4-dihydrodibenzo[*f*,*h*]isoquinolin-2(1*H*)-yl)pent-4-en-1- one (4.13b):

See above for procedure (0.52 mmol scale for **4.12**). 4-Pentenoic acid was used instead of vinylacetic acid. The title compound was obtained after SiO_2 flash chromatography (70% EtOAc/ Hexanes).

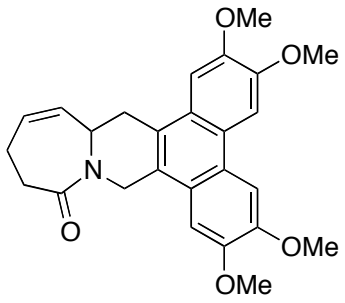
white solid (222 mg, 92%): mp 119.5 – 131.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.84 (s, 1H), 5.94 (m, 1H), 5.90 (m, 0.35H), 5.83 (m, 1H), 5.62 (d, 0.65H), 5.15 – 5.04 (m, 5H), 4.69 (d, 0.35H), 4.55 (d, 0.65H), 4.13 (s, 3H), 4.12 (s, 3H), 4.06 (s, 3H), 4.05 (s, 3H), 3.37 (m, 2H), 2.66 (m, 2H), 2.53 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 149.07, 148.91, 148.82, 148.82, 137.5, 135.9, 125.03, 123.87, 123.66, 123.58, 123.49, 122.6, 117.07, 115.04, 103.7, 103.6, 103.5, 103.0, 56.11, 56.11, 56.05, 55.93, 52.8, 39.9, 32.8, 30.8, 29.3; IR (neat) 2937, 1644, 1515, 1424, 1250, 1150, 916, 730 cm^{-1}; HRMS (ESI$^+$) *m/e* calc'd for $[M+H]^+$ $C_{28}H_{32}NO_5$: 462.2280, found 462.2268.



2,3,6,7-Tetramethoxy-14a,15-dihydro-9*H*-dibenzo[*f,h*]pyrido[1,2-*b*]isoquinolin-11(12*H*)- one (4.14a):

To a flame dried flask was added amide **4.13a** (826 mg, 1.84 mmol, 1.0 equiv) and anhydrous CH_2Cl_2 (100 mL). Grubbs 2nd generation catalyst (313 mg, 0.0370 mmol, 0.02 equiv) was added to the reaction flask, which was then heated to reflux for 3 h. After the addition of DMSO (0.4 mL), the reaction mixture was stirred overnight, which was then washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by SiO_2 flash chromatography (0-2.5% MeOH/CH_2Cl_2).

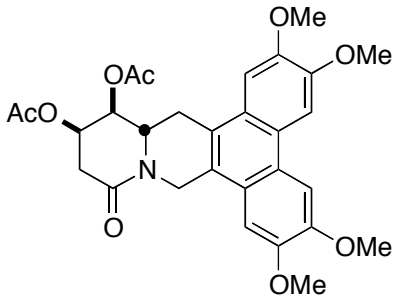
white solid (735 mg, 95%): mp: 259 – 262 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 2H), 7.20 (s, 2H), 6.04 – 5.97 (m, 2H), 5.96 – 5.90 (m, 1H), 4.44 (d, *J* = 17.3 Hz, 1H), 4.40 – 4.32 (m, 1H), 4.12 (s, 6H), 4.06 (s, 3H), 4.05 (s, 3H), 3.36 (dd, *J* = 15.9, 3.1 Hz, 1H), 3.17 – 3.10 (m, 2H), 3.05 – 2.94 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 149.0, 148.9, 148.8, 148.8, 124.9, 124.8, 124.4, 123.8, 123.7, 123.7, 123.6, 122.0, 103.7, 103.4, 103.4, 103.0, 56.1, 56.1, 55.9, 54.4, 42.7, 34.7, 32.0; IR (neat) 2937, 1638, 1515, 1249, 1150, 840, 770 cm^{-1}; HRMS (ESI$^+$) *m/e* calc'd for $[M+H]^+$ $C_{25}H_{26}NO_5$: 420.1811, found 420.1809.



2,3,6,7-Tetramethoxy-12,13,15a,16-tetrahydroazepino[1,2*b*]dibenzo[*f,h*] isoquinolin-11 (9*H*)-one (4.14b):

See above procedure (1.01 mmol scale for amid **4.13b**). The crude product was purified by SiO_2 flash chromatography (0-2.5% MeOH/CH_2Cl_2).

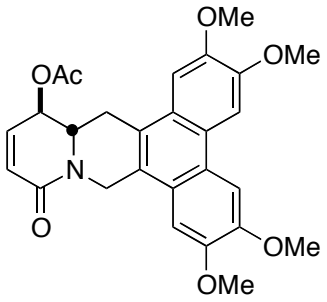
white solid (351 mg, 80%): mp: 160 – 167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.82 (s, 1H), 7.40 (s, 1H), 7.37 (s, 1H), 5.76 – 5.69 (m, 1H), 5.59 – 5.53 (m, 1H), 5.32 (d, *J* = 15.8 Hz, 1H), 4.95 – 4.87 (m, 1H), 4.92 (d, *J* = 15.7 Hz, 1H), 4.12 (s, 3H), 4.11 (s, 3H), 4.08 (s, 6H), 3.37 (dd, *J* = 15.3, 5.1 Hz, 1H), 3.28 (dd, *J* = 15.3, 7.7 Hz, 1H), 3.13 (dt, *J* = 13.4, 8.1 Hz, 1H), 2.57 (dt, *J* = 13.4, 4.5 Hz, 1H), 2.46 – 2.40 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 149.2, 149.1, 148.9, 131.5, 130.4, 127.3, 126.3, 124.5, 124.0, 123.6, 123.5, 103.6, 103.5, 103.4, 103.4, 56.1, 56.0, 51.4, 40.9, 34.9, 31.6, 25.1; IR (neat) 2937, 1635, 1515, 1251, 1151, 841, 790 cm^{-1}; HRMS (ESI$^+$) *m/e* calc'd for $[M+H]^+$ $C_{26}H_{28}NO_5$: 434.1967, found 434.1978.



(13*S,14*R**,14a*R**)-2,3,6,7-Tetramethoxy-11-oxo-11,12,13,14,14a,15-hexahydro-9*H*-dibenzo[*f,h*]pyrido[1,2-*b*]isoquinoline-13,14-diyl diacetate (4.15)**

To a solution of amide 4.14a (475 mg, 1.13 mmol, 1.0 equiv) in CH_2Cl_2 (45 mL) was added OsO4 (1.5 mL of 1% OsO_4 in *t*-BuOH, 0.057 mmol, 0.05 equiv) and NMO (292 mg, 2.50 mmol, 2.2 equiv.), and the reaction mixture was stirred overnight. Upon evaporation, pyridine (15 mL), Ac_2O (15 mL), and DMAP (1 crystal) were added to the reaction flask, which was stirred overnight. Upon evaporation, the crude mixture was purified by SiO_2 flash chromatography (5% MeOH/CH_2Cl_2).

white solid (551 mg, 90%): mp 238–241 ºC (decomp.); ^{1}H NMR (400 MHz, CDCl3) δ 7.82 (s, 2H), 7.18 (s, 1H), 7.18 (s, 1H), 5.89 (d, *J* = 17.1 Hz, 1H), 5.57 (s, 1H), 5.51 (ddd, *J* = 9.5, 6.1, 2.4 Hz, 1H), 4.46 (d, *J* = 17.3 Hz, 1H), 4.12 (s, 3H), 4.12 (s, 3H), 4.07 (s, 3H), 4.05 (s, 3H), 3.94 (dt, *J* = 12.2, 3.3 Hz, 1H), 3.41 (dd, *J* = 15.7, 3.1 Hz, 1H), 3.13 (dd, *J* = 14.5, 13.3 Hz, 1H), 2.94 (dd, *J* = 17.1, 9.6 Hz, 1H), 2.87 (dd, *J* = 17.2, 5.9 Hz, 1H), 2.18 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 170.3, 170.2, 165.7, 149.1, 149.0, 149.0, 124.7, 123.8, 123.8, 123.6, 123.4, 123.4, 103.6, 103.5, 103.0, 70.0, 65.2, 56.1, 56.1, 56.1, 55.9, 43.5, 33.5, 31.6, 21.0, 20.9; IR (neat) 2938, 1747, 1645, 1516, 1248, 1151, 1042, 916, 841 cm^{-1}; HRMS (ESI^{+}) *m/e* calc'd for [M+H]+ $C_{29}H_{32}NO_9$: 538.2077, found 538.2068.

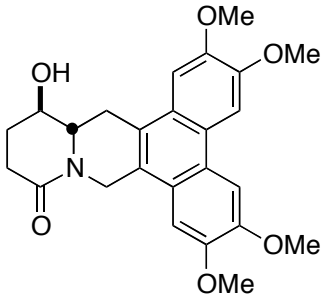


(14*S,14a*R**)-2,3,6,7-Tetramethoxy-11-oxo-11,14,14a,15-tetrahydro-9*H*-dibenzo[*f*,*h*]pyrido[1,2-*b*]isoquinolin-14-yl acetate (4.16)**

To a solution of amide **4.15** (551 mg, 1.03 mmol, 1.0 equiv) in toluene (50 mL) was added DBU (468 mg, 3.08 mmol, 3.0 equiv). The reaction mixture was heated to reflux for 2 h. Upon evaporation, the crude mixture was purified by SiO_2 flash chromatography (2% MeOH/CH_2Cl_2).

off-white solid (427 mg, 87%)mp 293–295 ºC (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 2H), 7.21 (s, 1H), 7.17 (s, 1H), 6.66 (ddd, *J* = 9.9, 5.4, 1.1 Hz, 1H), 6.29 (d, *J* = 9.9 Hz, 1H), 6.03 (d, *J* = 16.7 Hz, 1H), 5.52 (dd, *J* = 5.4, 1.2 Hz, 1H), 4.51 (d, *J* = 16.7 Hz, 1H), 4.13 – 4.10 (m, 1H), 4.12 (s, 6H), 4.06 (s, 3H),

4.04 (s, 3H), 3.28 – 3.14 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 161.0, 149.0, 149.0, 149.0, 148.9, 132.5, 129.3, 125.0, 124.4, 124.3, 123.8, 123.7, 123.6, 103.5, 103.4, 103.0, 66.6, 56.9, 56.1, 56.0, 55.9, 43.5, 30.5, 21.0; IR (neat) 2938, 1738, 1673, 1619, 1516, 1249, 1151, 1045, 841 cm^{-1}; HRMS (ESI$^+$) *m/e* calc'd for $[M+H]^+$ $C_{27}H_{28}NO_7$: 478.1866, found 478.1870.

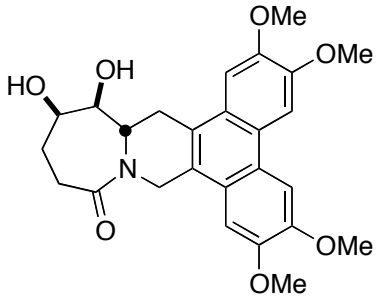


(14*R*, 14aS*)-14-hydroxy-2,3,6,7-tetramethoxy-13,14,14a,15-tetrahydro-9*H*-dibenzo[*f*,*h*]pyrido[1,2-*b*]isoquinolin-11(12*H*)-one (4.17)

To a solution of amide **4.16** (11.8 mg, 0.0247 mmol) in MeOH (0.5 mL) and THF (1 mL) was added Rh on Al_2O_3 (5%, 7.1 mg), and the reaction mixture was stirred for 7 h under hydrogen atmosphere (balloon). Upon filtration, the reaction mixture was concentrated. To this flask, K_2CO_3 (30 mg) and MeOH (1.5 mL) were added. After 3 h, the reaction mixture was concentrated and purified by SiO_2 flash chromatography (5% MeOH/CH_2Cl_2).

white solid (10.3 mg, 95%): mp: 114 – 116 °C; ^{1}H NMR [400 MHz, $CDCl_3$] δ 7.81 (s, 1H), 7.80 (s, 1H), 7.19 (s, 1H), 7.18 (s, 1H), 5.90 (d, *J* = 17.2 Hz, 1H), 4.41 (d, *J* = 17.4 Hz, 1H), 4.22 (s, 1H), 4.12 (m, 6H), 4.04 (s, 6H), 3.74 (dt, *J* = 11.8, 3.5 Hz, 1H), 3.41 – 3.33 (m, 1H), 3.02 – 2.91 (m, 1H), 2.86 – 2.74 (m, 1H), 2.52 (dt, *J* = 17.6, 5.6 Hz, 1H), 2.29 – 2.19 (m, 1H), 2.13 – 2.01 (m, 2H); ^{13}C NMR [101 MHz, $CDCl_3$] δ 168.7, 149.19, 149.01, 149.00, 148.94, 124.97, 124.20, 124.06, 123.89, 123.72, 103.80, 103.58, 103.55, 103.24, 68.9, 60.1, 56.26, 56.21, 56.21, 56.14, 43.6, 32.3, 28.0, 26.2; IR (neat) 3369, 2935, 1623, 1515, 1471, 1424, 1248, 1196,

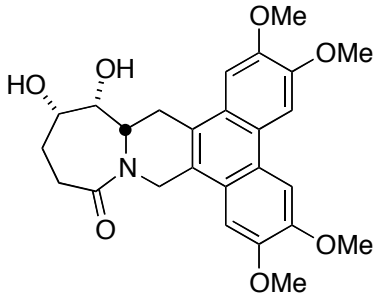
1149, 1046, 1016 cm^{-1}; HRMS (ESI^+) *m/e* calc'd for $[M+H]^+$ $C_{25}H_{28}NO_6$: 438.1917, found 438.1898.



(14*S,15*R**,15a*R**)-14,15-Dihydroxy-2,3,6,7-tetramethoxy-12,13,14,15,15a,16-hexahydroazepino[1,2-*b*]dibenzo[*f*,*h*]isoquinolin-11(9*H*)-one (4.18a)**

To a solution of amide **4.14b** (115 mg, 0.266 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added OsO_4 (338mg of 1% OsO_4 in *t*-BuOH, 0.013 mmol, 0.05 equiv) and NMO (68.5 mg, 0.584 mmol, 2.2 equiv.), and the reaction mixture was stirred overnight. Upon evaporation, the crude mixture was purified by SiO_2 flash chromatography ($MeOH/CH_2Cl_2$) to give two separable diastereomers.

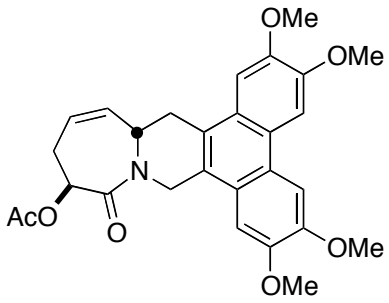
white solid (91.6 mg, 74%): mp 266–268 ºC (decomp.); ^1H NMR [400 MHz, $CDCl_3$:CD_3OD (1mL : 3 drops)] δ 7.78 (s, 1H), 7.78 (s, 1H), 7.46 (s, 1H), 7.35 (s, 1H), 5.30 (d, *J* = 16.3 Hz, 1H), 4.52 (d, *J* = 16.3 Hz, 1H), 4.53 – 4.47 (m, 1H), 4.05 (s, 3H), 4.05 (s, 3H), 4.01 (s, 3H), 4.00 (s, 3H), 3.89 – 3.77 (m, 2H), 3.16 – 3.03 (m, 2H), 2.31 (ddd, *J* = 14.5, 5.9, 3.0 Hz, 1H), 2.14 (s, 8H), 2.04 – 1.93 (m, 1H), 1.81 – 1.69 (m, 1H); ^{13}C NMR [101 MHz, $CDCl_3$:CD_3OD (1mL : 3 drops)] δ 175.9, 149.2, 149.0, 149.0, 148.9, 126.1, 125.6, 124.2, 124.1, 123.7, 123.3, 104.2, 103.5, 103.4, 103.2, 71.4, 70.2, 56.1, 56.0, 55.9, 51.8, 40.4, 29.7, 27.7, 26.1; IR (neat) 3464, 3017, 1604, 1519, 1428, 1252, 1085, 843 cm^{-1}; HRMS (ESI^+) *m/e* calc'd for $[M+H]^+$ $C_{26}H_{30}NO_7$: 468.2022, found 468.2009.



(14*R,15*S**,15a*R**)-14,15-Dihydroxy-2,3,6,7-tetramethoxy-12,13,14,15,15a,16-hexahydroazepino[1,2-*b*]dibenzo[*f*,*h*]isoquinolin-11(9*H*)-one (4.18b)**

This minor diastereomer was slightly unstable on SiO_2. After SiO_2 chromatography, the product was again purified by Al_2O_3 ($MeOH/CH_2Cl_2$) to obtain the clean spectra.

white solid (16.2 mg, 13%): mp 210–212 ºC (decomp.); ^{1}H NMR [400 MHz, $CDCl_3$:CD_3OD (1mL : 3 drops)] δ 7.83 (s, 1H), 7.80 (s, 1H), 7.45 (s, 1H), 7.38 (s, 1H), 5.94 (d, *J* = 15.2 Hz, 1H), 4.28 (d, *J* = 15.3 Hz, 1H), 4.10 (s, 3H), 4.08 (s, 3H), 4.06 (s, 6H), 4.01 (d, *J* = 2.9 Hz, 1H), 3.85 (dd, *J* = 9.7, 6.0 Hz, 1H), 3.72 – 3.65 (m, 1H), 3.56 (dd, *J* = 15.2, 5.8 Hz, 1H), 3.43 – 3.35 (m, 1H), 2.53 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.34 (t, *J* = 12.7 Hz, 1H), 1.95 – 1.78 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 149.39, 149.15, 149.07, 128.09, 126.86, 124.28, 123.89, 123.63, 123.22, 103.72, 103.61, 103.56, 103.48, 74.78, 74.33, 56.15, 56.10, 56.05, 53.75, 50.05, 49.8, 49.6, 49.4, 49.2, 40.3, 32.9, 30.0, 25.7; IR (neat) 3366, 3022, 1592, 1518, 1430, 1248, 1148, 843 cm^{-1}; HRMS (ESI^+) *m/e* calc'd for $[M+H]^+$ $C_{26}H_{30}NO_7$: 468.2022, found 468.2038.



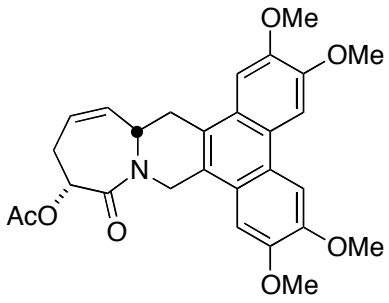
(12*S,15a*S**)-2,3,6,7-tetramethoxy-11-oxo-9,11,12,13,15a,16-hexahydroazepino[1,2-*b*]dibenzo[*f*,*h*]isoquinolin-12-yl acetate (4.21a)**

Amide **4.12** (480 mg, 1.00 mmol) was deprotected according to the procedure above. To a solution of free amine in CH_2Cl_2 (25 mL) was added acid (139 mg, 1.2 mmol, 1.2 equiv), HOBt (230 mg, 1.70 mmol, 1.7 equiv), and polymer-supported carbodiimide (1.47 g, 2.00 mmol, 2.0 equiv). The reaction was stirred overnight, and quenched by the addition of MP carbonate (1.5 g, 4.5 mmol, 4.5 equiv). After 2 h, the reaction mixture was filtered, washed with aq. $NaHCO_3$, dried over $MgSO_4$, and concentrated. To this crude mixture was added pyridine (5 mL), Ac_2O (5 mL), and DMAP (12.0 mg, 0.1 mmol, 0.1 equiv). The reaction mixture was stirred overnight. Upon evaporation, this mixture was re-dissolved in CH_2Cl_2, washed with aq. $NaHCO_3$, dried over $MgSO_4$, and concentrated. The crude mixture was carefully purified by combiflash (hexanes/EtOAc) to afford inseparable diastereomeric mixture (416 mg, 80% from **4.12**).

This diastereomeric mixture was subjected to RCM conditions in CH_2Cl_2 (40 mL) using Grubbs 2nd generation catalyst (13.6 mg, 0.016 mmol, 0.02 equiv). The reaction was stirred overnight, and then quenched by the addition of DMSO (0.5 mL). In 2h, the reaction mixture was washed with brine, dried over $MgSO_4$, and concentrated. The crude products were purified by combiflash ($MeOH/CH_2Cl_2$), and resulting diastereomeric mixture was separated by preparative TLC (the mixture was divided into 5 portions).

white solid (99.9 mg, 25%): mp: 133 – 135 ºC (decomp.); ^{1}H NMR [400 MHz, $CDCl_3$] δ 7.82 (s, 2H), 7.24 (d, *J* = 4.5 Hz, 2H), 6.11 – 5.92 (m, 2H), 5.83 (d, *J* = 12.1 Hz, 1H), 5.41 (dd, *J* = 10.6, 2.5 Hz, 1H), 4.70 – 4.47 (m, 2H), 4.17 – 3.95 (m, 12H), 3.37 (d, *J* = 11.1 Hz, 2H), 2.81 (ddd, *J* = 17.0, 10.7, 2.8 Hz, 1H), 2.55 (dd, *J* = 17.2, 7.3 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.4, 149.1, 149.1, 149.0, 149.0, 129.2, 126.2, 125.8, 125.7, 125.2, 124.0, 123.9, 123.8, 103.8, 103.5, 103.5, 103.3, 73.2, 56.9, 56.2, 56.2, 56.1, 56.1, 46.4, 33.5,

30.3, 21.0; IR (neat) 2934, 1744, 1659, 1620, 1515, 1473, 1425, 1250, 1150, 1043 cm^{-1}; HRMS (ESI^+) *m/e* calc'd for $[M+H]^+$ $C_{28}H_{30}NO_7$: 492.2022, found 492.2012.



(12*R,15a*S**)-2,3,6,7-tetramethoxy-11-oxo-9,11,12,13,15a,16-hexahydroazepino[1,2-*b*]dibenzo[*f*,*h*]isoquinolin-12-yl acetate (4.21b)**

white solid (49%. more polar diastereomer): mp 153 – 155 ºC (decomp.); ^1H NMR [400 MHz, $CDCl_3$] δ 7.86 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 3.1 Hz, 2H), 5.92 (t, *J* = 9.1 Hz, 1H), 5.61 – 5.51 (m, 2H), 5.46 (dd, *J* = 11.3, 3.2 Hz, 1H), 5.16 (s, 1H), 4.67 (d, *J* = 15.9 Hz, 1H), 4.10 (m, 12H), 3.49 (dd, *J* = 15.1, 4.3 Hz, 1H), 3.34 (dd, *J* = 15.1, 5.4 Hz, 1H), 2.62 – 2.47 (m, 2H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 169.7, 149.4, 149.3, 149.2, 149.2, 131.9, 129.2, 127.1, 125.9, 124.6, 124.3, 123.9, 123.4, 103.8, 103.6, 103.3, 69.6, 56.3, 56.2, 56.13, 56.07, 49.2, 39.8, 30.9, 30.4, 20.9; IR (neat): 2936, 1742, 1661, 1620, 1516, 1473, 1427, 1252, 1151, 1034 cm^{-1}; HRMS (ESI^+) *m/e* calc'd for $[M+H]^+$ $C_{28}H_{26}NO_7$: 492.2022, found 492.2034.

5.5 X-Ray crystallographic structure

5.5.1 Enaminone

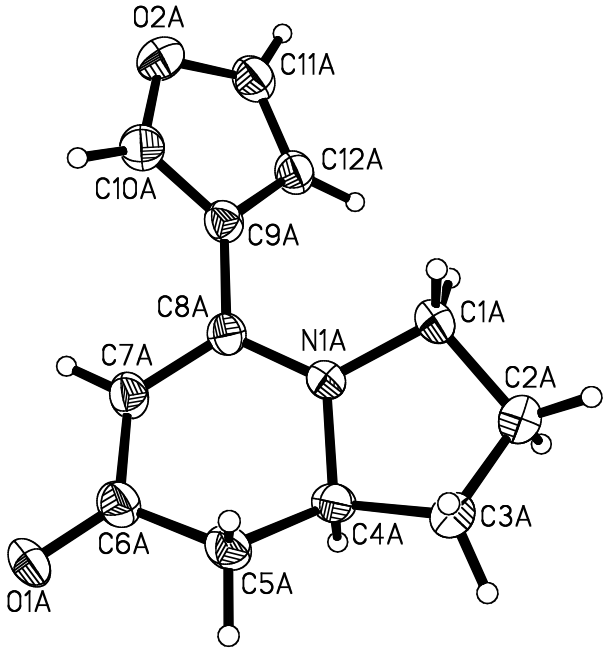
REFERENCE NUMBER: 10010a

CRYSTAL STRUCTURE REPORT

C_{12} H_{13} N O_2

Report prepared for: H. Seki / Prof. G. Georg

January 21, 2010



Victor G. Young, Jr.

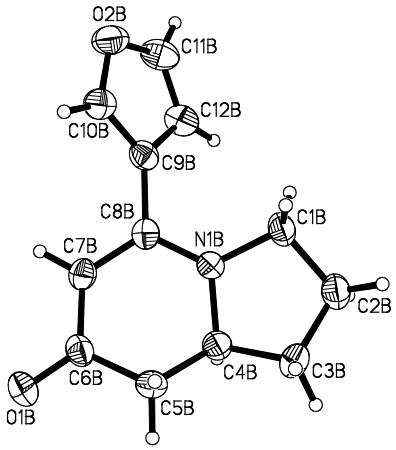
X-Ray Crystallographic Laboratory

Department of Chemistry

University of Minnesota

207 Pleasant St. S.E.

Minneapolis, MN 55455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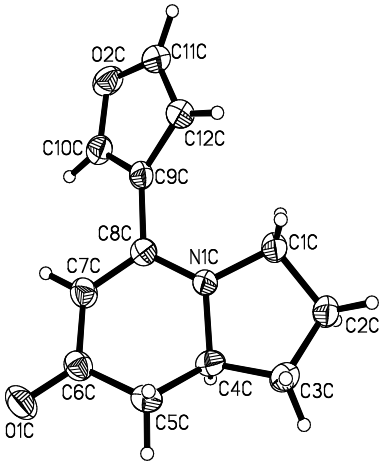
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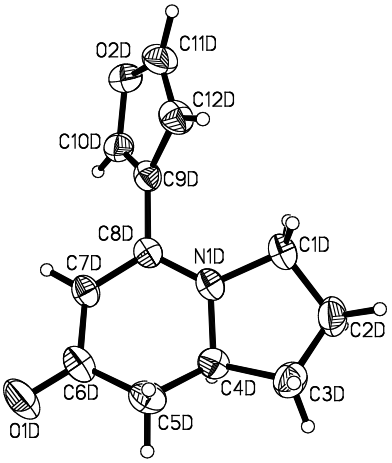
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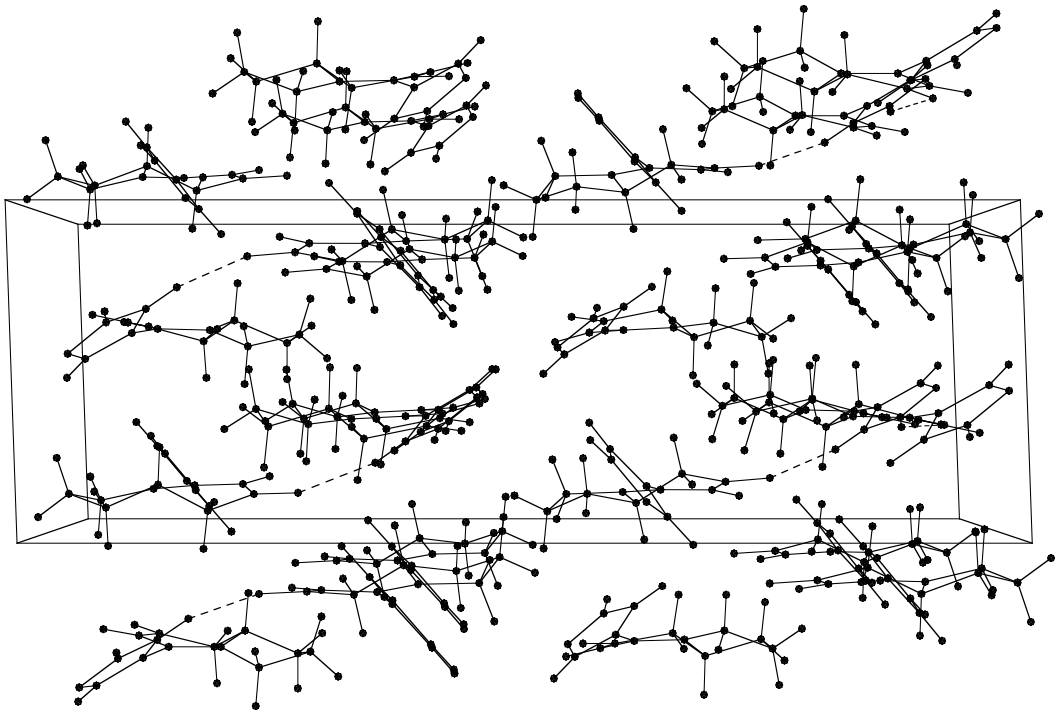

Data collection

A crystal (approximate dimensions 0.45x 0.40 x 0.35mm^3) was placed onto the tip of a 0.1 mm diameter glass capillary and mounted on a CCD area detector diffractometer for a data collection at173(2) K.[1] A preliminary set of cell constants was calculated from reflections harvested from three sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrices determined from 86 reflections. The data collection was carried out using MoKa radiation (graphite monochromator) with a frame time of 20 seconds and a detector distance of 4.8 cm. A randomly oriented region of reciprocal space was surveyed to the extent of one sphere and to a resolution of 0.77 Å. Four major sections of frames were collected with 0.30º steps in w at four different f settings and a detector position of -28º in2q. The intensity data were corrected for absorption and decay (SADABS).[2] Final cell constants were calculated from 2912 strong reflections from the actual data collection after integration (SAINT).[3] Please refer to Table 1 for additional crystal and refinement information.

Structure solution and refinement

The structure was solved using Bruker SHELXTL[4] and refined using Bruker SHELXTL.[4] The space group $P2_1$ was determined based on systematic absences and intensity statistics. A direct-methods solution was calculated which provided most non-hydrogen atoms from the E-map. Full-matrix least squares / difference Fourier cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. The final full matrix least squares refinement converged to $R1 = 0.0377$ and $wR2 = 0.0913$ (F^2, obs. data).

Structure description

The structure is the one suggested. There are four molecules in the asymmetric unit. The only obvious difference seen in the drawings is the difference in the torsion angles about the C8-C9 pairs. CHECKCIF warns that there is pseudo-symmetry approximating $P2_1/c$. A centrosymmetric space group is impossible since the S-enantiomer for all four molecules is found. Only relative stereochemistry can be assigned since no heavy atom is present. The Flack parameter is deemed meaningless in this instance. The crystals had sufficient quality to require refinement of extinction. Two short non-classical C-H···O hydrogen bonds are presented in Table 7 without attempting to normalize the H position.

Data collection and structure solution were conducted at the X-Ray Crystallographic Laboratory,

192 Kolthoff Hall, Department of Chemistry, University of Minnesota. All calculations were performed using Pentium computers using the current SHELXTL suite of programs. All publications arising from this report MUST either 1) include Victor G. Young, Jr. as a coauthor or 2) acknowledge Victor G. Young, Jr. and the X-Ray Crystallographic Laboratory.

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1 SMART V5.054, Bruker Analytical X-ray Systems, Madison, WI (2001).

2 An empirical correction for absorption anisotropy, R. Blessing, *Acta Cryst.* **A51**, 33-38(1995).

3 SAINT+ V7.34A, Bruker Analytical X-Ray Systems, Madison, WI (2003).

4 SHELXTL V6.14, Bruker Analytical X-Ray Systems, Madison, WI (2000).

Some equations of interest:

$R_{int} = S|F_o^2 - < F_o^2 >| / S|F_o^2|$

$R_1 = S||F_o| - |F_c|| / S|F_o|$

$wR2 = [S[w(F_o^2 - F_c^2)^2] / S[w(F_o^2)^2]]^{1/2}$

where $w = q / [s^2(F_o^2) + (a*P)^2 + b*P + d + e*\sin(q)]$

GooF = $S = [S[w(F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$

Table 1. Crystal data and structure refinement for 10010a.

Identification code	10010a	
Empirical formula	C_{12} H_{13} N O_2	
Formula weight	203.23	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	*a* = 8.2719(14) Å	a = 90°
	b = 10.0704(18) Å	b = 91.990(2)°
	c = 24.416(4) Å	g = 90°
Volume	2032.7(6) $Å^3$	
Z	8	
Density (calculated)	1.328 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	864	
Crystal color, morphology	Colorless, Block	
Crystal size	0.45 x 0.40 x 0.35 mm^3	
Theta range for data collection	1.67 to 27.51°	
Index ranges	-10 £*h* £ 10,0 £*k* £ 13,0 £*l* £ 31	
Reflections collected	19284	
Independent reflections	4902 [*R*(int) = 0.0317]	
Observed reflections	4150	
Completeness to theta = 27.51°	99.3%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9689 and 0.9603	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4902 / 1 / 542	
Goodness-of-fit on F^2	1.029	
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0377, *wR*2 = 0.0863	
R indices (all data)	*R*1 = 0.0497, *wR*2 = 0.0913	
Absolute structure parameter	0.3(10)	
Extinction coefficient	0.0056(6)	
Largest diff. peak and hole	0.196 and -0.181 e.$Å^{-3}$	

Table 2. Atomic coordinates(x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 10010a. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
N1A	6307(2)	4923(2)	1718(1)	26(1)
C1A	5782(3)	5808(2)	2157(1)	34(1)
C2A	6164(3)	5006(3)	2675(1)	39(1)
C3A	5918(3)	3576(3)	2487(1)	33(1)
C4A	6650(3)	3563(2)	1921(1)	26(1)
C5A	5990(3)	2530(2)	1525(1)	30(1)
C6A	6462(3)	2812(3)	939(1)	30(1)
O1A	6635(2)	1898(2)	612(1)	39(1)
C7A	6567(3)	4181(3)	801(1)	29(1)
C8A	6342(3)	5187(3)	1177(1)	24(1)
C9A	6184(3)	6569(3)	987(1)	26(1)
C10A	5387(3)	6943(3)	518(1)	32(1)
O2A	5531(2)	8268(2)	436(1)	37(1)
C11A	6463(3)	8746(3)	870(1)	36(1)
C12A	6895(3)	7766(3)	1214(1)	31(1)
N1B	1237(2)	3886(2)	996(1)	30(1)
C1B	858(3)	3677(3)	407(1)	36(1)
C2B	1146(4)	5026(3)	160(1)	44(1)
C3B	775(4)	5996(3)	615(1)	40(1)
C4B	1447(3)	5307(3)	1130(1)	32(1)
C5B	652(3)	5644(2)	1666(1)	32(1)
C6B	1115(3)	4668(3)	2115(1)	32(1)
O1B	1174(2)	5023(2)	2602(1)	46(1)
C7B	1361(3)	3335(3)	1941(1)	31(1)
C8B	1295(3)	2974(3)	1394(1)	28(1)
C9B	1367(3)	1556(3)	1232(1)	31(1)
C10B	468(3)	554(3)	1423(1)	36(1)
O2B	939(2)	-632(2)	1212(1)	43(1)
C11B	2199(3)	-356(3)	887(1)	44(1)
C12B	2507(3)	946(3)	878(1)	38(1)

N1C	3594(2)	8964(2)	3307(1)	26(1)
C1C	3415(3)	8047(3)	2842(1)	35(1)
C2C	3887(3)	8890(3)	2352(1)	38(1)
C3C	3406(3)	10291(3)	2526(1)	34(1)
C4C	3925(3)	10335(2)	3127(1)	28(1)
C5C	3086(3)	11315(2)	3486(1)	30(1)
C6C	3440(3)	11038(3)	4090(1)	30(1)
O1C	3326(2)	11949(2)	4434(1)	43(1)
C7C	3768(3)	9687(3)	4229(1)	32(1)
C8C	3669(3)	8682(3)	3845(1)	26(1)
C9C	3650(3)	7279(3)	4025(1)	27(1)
C10C	4436(3)	6830(3)	4484(1)	32(1)
O2C	4188(2)	5504(2)	4549(1)	38(1)
C11C	3198(3)	5114(3)	4122(1)	37(1)
C12C	2834(3)	6139(3)	3789(1)	33(1)
N1D	8802(2)	4(2)	3936(1)	33(1)
C1D	8853(4)	164(3)	4539(1)	48(1)
C2D	9487(4)	-1175(3)	4743(1)	49(1)
C3D	8982(3)	-2142(3)	4292(1)	43(1)
C4D	9232(3)	-1355(3)	3773(1)	33(1)
C5D	8309(3)	-1739(3)	3251(1)	40(1)
C6D	8516(3)	-705(3)	2813(1)	38(1)
O1D	8412(3)	-1006(3)	2322(1)	58(1)
C7D	8698(3)	636(3)	3002(1)	32(1)
C8D	8672(3)	949(3)	3553(1)	29(1)
C9D	8484(3)	2347(3)	3727(1)	31(1)
C10D	9344(3)	3391(3)	3548(1)	38(1)
O2D	8832(2)	4547(2)	3778(1)	43(1)
C11D	7600(3)	4202(3)	4108(1)	45(1)
C12D	7339(3)	2891(3)	4097(1)	41(1)

Table 3. Bond lengths [Å] and angles [°] for 10010a.

N(1A)-C(8A)	1.349(3)	C(1B)-H(1BB)	0.9900
N(1A)-C(1A)	1.472(3)	C(2B)-C(3B)	1.518(4)
N(1A)-C(4A)	1.480(3)	C(2B)-H(2BA)	0.9900
C(1A)-C(2A)	1.525(3)	C(2B)-H(2BB)	0.9900
C(1A)-H(1AA)	0.9900	C(3B)-C(4B)	1.524(4)
C(1A)-H(1AB)	0.9900	C(3B)-H(3BA)	0.9900
C(2A)-C(3A)	1.522(4)	C(3B)-H(3BB)	0.9900
C(2A)-H(2AA)	0.9900	C(4B)-C(5B)	1.522(3)
C(2A)-H(2AB)	0.9900	C(4B)-H(4BA)	1.0000
C(3A)-C(4A)	1.530(3)	C(5B)-C(6B)	1.513(4)
C(3A)-H(3AA)	0.9900	C(5B)-H(5BA)	0.9900
C(3A)-H(3AB)	0.9900	C(5B)-H(5BB)	0.9900
C(4A)-C(5A)	1.508(3)	C(6B)-O(1B)	1.240(3)
C(4A)-H(4AA)	1.0000	C(6B)-C(7B)	1.425(4)
C(5A)-C(6A)	1.524(3)	C(7B)-C(8B)	1.382(3)
C(5A)-H(5AA)	0.9900	C(7B)-H(7BA)	0.9500
C(5A)-H(5AB)	0.9900	C(8B)-C(9B)	1.483(4)
C(6A)-O(1A)	1.230(3)	C(9B)-C(10B)	1.346(4)
C(6A)-C(7A)	1.422(4)	C(9B)-C(12B)	1.439(4)
C(7A)-C(8A)	1.383(3)	C(10B)-O(2B)	1.362(3)
C(7A)-H(7AA)	0.9500	C(10B)-H(10B)	0.9500
C(8A)-C(9A)	1.471(4)	O(2B)-C(11B)	1.360(3)
C(9A)-C(10A)	1.354(3)	C(11B)-C(12B)	1.336(4)
C(9A)-C(12A)	1.443(4)	C(11B)-H(11B)	0.9500
C(10A)-O(2A)	1.355(3)	C(12B)-H(12B)	0.9500
C(10A)-H(10A)	0.9500	N(1C)-C(8C)	1.344(3)
O(2A)-C(11A)	1.375(3)	N(1C)-C(1C)	1.467(3)
C(11A)-C(12A)	1.336(4)	N(1C)-C(4C)	1.477(3)
C(11A)-H(11A)	0.9500	C(1C)-C(2C)	1.528(3)
C(12A)-H(12A)	0.9500	C(1C)-H(1CA)	0.9900
N(1B)-C(8B)	1.337(3)	C(1C)-H(1CB)	0.9900
N(1B)-C(1B)	1.476(3)	C(2C)-C(3C)	1.530(4)
N(1B)-C(4B)	1.478(3)	C(2C)-H(2CA)	0.9900
C(1B)-C(2B)	1.509(4)	C(2C)-H(2CB)	0.9900
C(1B)-H(1BA)	0.9900	C(3C)-C(4C)	1.515(3)

C(3C)-H(3CA)	0.9900	C(1D)-H(1DB)	0.9900
C(3C)-H(3CB)	0.9900	C(2D)-C(3D)	1.517(4)
C(4C)-C(5C)	1.506(3)	C(2D)-H(2DA)	0.9900
C(4C)-H(4CA)	1.0000	C(2D)-H(2DB)	0.9900
C(5C)-C(6C)	1.518(3)	C(3D)-C(4D)	1.516(4)
C(5C)-H(5CA)	0.9900	C(3D)-H(3DA)	0.9900
C(5C)-H(5CB)	0.9900	C(3D)-H(3DB)	0.9900
C(6C)-O(1C)	1.249(3)	C(4D)-C(5D)	1.512(4)
C(6C)-C(7C)	1.427(4)	C(4D)-H(4DA)	1.0000
C(7C)-C(8C)	1.381(3)	C(5D)-C(6D)	1.508(4)
C(7C)-H(7CA)	0.9500	C(5D)-H(5DA)	0.9900
C(8C)-C(9C)	1.479(4)	C(5D)-H(5DB)	0.9900
C(9C)-C(10C)	1.354(3)	C(6D)-O(1D)	1.235(3)
C(9C)-C(12C)	1.443(4)	C(6D)-C(7D)	1.434(4)
C(10C)-O(2C)	1.361(3)	C(7D)-C(8D)	1.382(3)
C(10C)-H(10C)	0.9500	C(7D)-H(7DA)	0.9500
O(2C)-C(11C)	1.361(3)	C(8D)-C(9D)	1.481(4)
C(11C)-C(12C)	1.342(4)	C(9D)-C(10D)	1.351(4)
C(11C)-H(11C)	0.9500	C(9D)-C(12D)	1.440(4)
C(12C)-H(12C)	0.9500	C(10D)-O(2D)	1.366(3)
N(1D)-C(8D)	1.337(3)	C(10D)-H(10D)	0.9500
N(1D)-C(4D)	1.472(4)	O(2D)-C(11D)	1.366(3)
N(1D)-C(1D)	1.480(3)	C(11D)-C(12D)	1.338(4)
C(1D)-C(2D)	1.524(5)	C(11D)-H(11D)	0.9500
C(1D)-H(1DA)	0.9900	C(12D)-H(12D)	0.9500

C(8A)-N(1A)-C(1A)	127.7(2)	C(1A)-C(2A)-H(2AA)	111.1
C(8A)-N(1A)-C(4A)	119.97(19)	C(3A)-C(2A)-H(2AB)	111.1
C(1A)-N(1A)-C(4A)	112.01(18)	C(1A)-C(2A)-H(2AB)	111.1
N(1A)-C(1A)-C(2A)	103.1(2)	H(2AA)-C(2A)-H(2AB)	109.1
N(1A)-C(1A)-H(1AA)	111.2	C(2A)-C(3A)-C(4A)	103.2(2)
C(2A)-C(1A)-H(1AA)	111.2	C(2A)-C(3A)-H(3AA)	111.1
N(1A)-C(1A)-H(1AB)	111.2	C(4A)-C(3A)-H(3AA)	111.1
C(2A)-C(1A)-H(1AB)	111.2	C(2A)-C(3A)-H(3AB)	111.1
H(1AA)-C(1A)-H(1AB)	109.1	C(4A)-C(3A)-H(3AB)	111.1
C(3A)-C(2A)-C(1A)	103.2(2)	H(3AA)-C(3A)-H(3AB)	109.1
C(3A)-C(2A)-H(2AA)	111.1	N(1A)-C(4A)-C(5A)	111.28(18)

N(1A)-C(4A)-C(3A)	102.52(19)	N(1B)-C(1B)-H(1BA)	111.1
C(5A)-C(4A)-C(3A)	116.1(2)	C(2B)-C(1B)-H(1BA)	111.1
N(1A)-C(4A)-H(4AA)	108.9	N(1B)-C(1B)-H(1BB)	111.1
C(5A)-C(4A)-H(4AA)	108.9	C(2B)-C(1B)-H(1BB)	111.1
C(3A)-C(4A)-H(4AA)	108.9	H(1BA)-C(1B)-H(1BB)	109.1
C(4A)-C(5A)-C(6A)	112.0(2)	C(1B)-C(2B)-C(3B)	104.3(2)
C(4A)-C(5A)-H(5AA)	109.2	C(1B)-C(2B)-H(2BA)	110.9
C(6A)-C(5A)-H(5AA)	109.2	C(3B)-C(2B)-H(2BA)	110.9
C(4A)-C(5A)-H(5AB)	109.2	C(1B)-C(2B)-H(2BB)	110.9
C(6A)-C(5A)-H(5AB)	109.2	C(3B)-C(2B)-H(2BB)	110.9
H(5AA)-C(5A)-H(5AB)	107.9	H(2BA)-C(2B)-H(2BB)	108.9
O(1A)-C(6A)-C(7A)	124.3(2)	C(2B)-C(3B)-C(4B)	103.5(2)
O(1A)-C(6A)-C(5A)	120.6(2)	C(2B)-C(3B)-H(3BA)	111.1
C(7A)-C(6A)-C(5A)	115.0(2)	C(4B)-C(3B)-H(3BA)	111.1
C(8A)-C(7A)-C(6A)	122.9(2)	C(2B)-C(3B)-H(3BB)	111.1
C(8A)-C(7A)-H(7AA)	118.6	C(4B)-C(3B)-H(3BB)	111.1
C(6A)-C(7A)-H(7AA)	118.6	H(3BA)-C(3B)-H(3BB)	109.0
N(1A)-C(8A)-C(7A)	120.8(2)	N(1B)-C(4B)-C(5B)	110.8(2)
N(1A)-C(8A)-C(9A)	119.3(2)	N(1B)-C(4B)-C(3B)	102.8(2)
C(7A)-C(8A)-C(9A)	119.8(2)	C(5B)-C(4B)-C(3B)	116.8(2)
C(10A)-C(9A)-C(12A)	105.8(2)	N(1B)-C(4B)-H(4BA)	108.7
C(10A)-C(9A)-C(8A)	124.4(2)	C(5B)-C(4B)-H(4BA)	108.7
C(12A)-C(9A)-C(8A)	129.7(2)	C(3B)-C(4B)-H(4BA)	108.7
C(9A)-C(10A)-O(2A)	110.9(2)	C(6B)-C(5B)-C(4B)	111.9(2)
C(9A)-C(10A)-H(10A)	124.6	C(6B)-C(5B)-H(5BA)	109.2
O(2A)-C(10A)-H(10A)	124.6	C(4B)-C(5B)-H(5BA)	109.2
C(10A)-O(2A)-C(11A)	106.3(2)	C(6B)-C(5B)-H(5BB)	109.2
C(12A)-C(11A)-O(2A)	110.9(2)	C(4B)-C(5B)-H(5BB)	109.2
C(12A)-C(11A)-H(11A)	124.6	H(5BA)-C(5B)-H(5BB)	107.9
O(2A)-C(11A)-H(11A)	124.6	O(1B)-C(6B)-C(7B)	123.9(3)
C(11A)-C(12A)-C(9A)	106.2(2)	O(1B)-C(6B)-C(5B)	120.6(2)
C(11A)-C(12A)-H(12A)	126.9	C(7B)-C(6B)-C(5B)	115.5(2)
C(9A)-C(12A)-H(12A)	126.9	C(8B)-C(7B)-C(6B)	122.4(2)
C(8B)-N(1B)-C(1B)	127.7(2)	C(8B)-C(7B)-H(7BA)	118.8
C(8B)-N(1B)-C(4B)	120.2(2)	C(6B)-C(7B)-H(7BA)	118.8
C(1B)-N(1B)-C(4B)	111.9(2)	N(1B)-C(8B)-C(7B)	121.4(2)
N(1B)-C(1B)-C(2B)	103.3(2)	N(1B)-C(8B)-C(9B)	117.9(2)

C(7B)-C(8B)-C(9B)	120.7(2)	C(5C)-C(4C)-C(3C)	117.5(2)
C(10B)-C(9B)-C(12B)	105.6(2)	N(1C)-C(4C)-H(4CA)	108.8
C(10B)-C(9B)-C(8B)	127.0(2)	C(5C)-C(4C)-H(4CA)	108.8
C(12B)-C(9B)-C(8B)	127.2(2)	C(3C)-C(4C)-H(4CA)	108.8
C(9B)-C(10B)-O(2B)	111.0(2)	C(4C)-C(5C)-C(6C)	111.6(2)
C(9B)-C(10B)-H(10B)	124.5	C(4C)-C(5C)-H(5CA)	109.3
O(2B)-C(10B)-H(10B)	124.5	C(6C)-C(5C)-H(5CA)	109.3
C(11B)-O(2B)-C(10B)	106.1(2)	C(4C)-C(5C)-H(5CB)	109.3
C(12B)-C(11B)-O(2B)	111.1(3)	C(6C)-C(5C)-H(5CB)	109.3
C(12B)-C(11B)-H(11B)	124.4	H(5CA)-C(5C)-H(5CB)	108.0
O(2B)-C(11B)-H(11B)	124.4	O(1C)-C(6C)-C(7C)	123.9(2)
C(11B)-C(12B)-C(9B)	106.3(3)	O(1C)-C(6C)-C(5C)	120.0(2)
C(11B)-C(12B)-H(12B)	126.9	C(7C)-C(6C)-C(5C)	115.8(2)
C(9B)-C(12B)-H(12B)	126.9	C(8C)-C(7C)-C(6C)	122.0(2)
C(8C)-N(1C)-C(1C)	128.6(2)	C(8C)-C(7C)-H(7CA)	119.0
C(8C)-N(1C)-C(4C)	119.0(2)	C(6C)-C(7C)-H(7CA)	119.0
C(1C)-N(1C)-C(4C)	111.91(18)	N(1C)-C(8C)-C(7C)	120.6(2)
N(1C)-C(1C)-C(2C)	103.6(2)	N(1C)-C(8C)-C(9C)	119.5(2)
N(1C)-C(1C)-H(1CA)	111.0	C(7C)-C(8C)-C(9C)	119.9(2)
C(2C)-C(1C)-H(1CA)	111.0	C(10C)-C(9C)-C(12C)	105.7(2)
N(1C)-C(1C)-H(1CB)	111.0	C(10C)-C(9C)-C(8C)	123.7(2)
C(2C)-C(1C)-H(1CB)	111.0	C(12C)-C(9C)-C(8C)	130.6(2)
H(1CA)-C(1C)-H(1CB)	109.0	C(9C)-C(10C)-O(2C)	110.7(2)
C(1C)-C(2C)-C(3C)	102.60(19)	C(9C)-C(10C)-H(10C)	124.6
C(1C)-C(2C)-H(2CA)	111.2	O(2C)-C(10C)-H(10C)	124.6
C(3C)-C(2C)-H(2CA)	111.2	C(10C)-O(2C)-C(11C)	106.5(2)
C(1C)-C(2C)-H(2CB)	111.2	C(12C)-C(11C)-O(2C)	111.0(2)
C(3C)-C(2C)-H(2CB)	111.2	C(12C)-C(11C)-H(11C)	124.5
H(2CA)-C(2C)-H(2CB)	109.2	O(2C)-C(11C)-H(11C)	124.5
C(4C)-C(3C)-C(2C)	103.2(2)	C(11C)-C(12C)-C(9C)	106.1(2)
C(4C)-C(3C)-H(3CA)	111.1	C(11C)-C(12C)-H(12C)	126.9
C(2C)-C(3C)-H(3CA)	111.1	C(9C)-C(12C)-H(12C)	126.9
C(4C)-C(3C)-H(3CB)	111.1	C(8D)-N(1D)-C(4D)	119.1(2)
C(2C)-C(3C)-H(3CB)	111.1	C(8D)-N(1D)-C(1D)	128.1(2)
H(3CA)-C(3C)-H(3CB)	109.1	C(4D)-N(1D)-C(1D)	111.8(2)
N(1C)-C(4C)-C(5C)	110.24(19)	N(1D)-C(1D)-C(2D)	103.1(2)
N(1C)-C(4C)-C(3C)	102.18(19)	N(1D)-C(1D)-H(1DA)	111.1

C(2D)-C(1D)-H(1DA)	111.1	C(6D)-C(5D)-H(5DB)	109.5
N(1D)-C(1D)-H(1DB)	111.1	C(4D)-C(5D)-H(5DB)	109.5
C(2D)-C(1D)-H(1DB)	111.1	H(5DA)-C(5D)-H(5DB)	108.1
H(1DA)-C(1D)-H(1DB)	109.1	O(1D)-C(6D)-C(7D)	123.1(3)
C(3D)-C(2D)-C(1D)	104.3(2)	O(1D)-C(6D)-C(5D)	120.9(3)
C(3D)-C(2D)-H(2DA)	110.9	C(7D)-C(6D)-C(5D)	115.7(2)
C(1D)-C(2D)-H(2DA)	110.9	C(8D)-C(7D)-C(6D)	121.6(3)
C(3D)-C(2D)-H(2DB)	110.9	C(8D)-C(7D)-H(7DA)	119.2
C(1D)-C(2D)-H(2DB)	110.9	C(6D)-C(7D)-H(7DA)	119.2
H(2DA)-C(2D)-H(2DB)	108.9	N(1D)-C(8D)-C(7D)	121.0(3)
C(4D)-C(3D)-C(2D)	103.2(2)	N(1D)-C(8D)-C(9D)	118.8(2)
C(4D)-C(3D)-H(3DA)	111.1	C(7D)-C(8D)-C(9D)	120.1(2)
C(2D)-C(3D)-H(3DA)	111.1	C(10D)-C(9D)-C(12D)	105.8(3)
C(4D)-C(3D)-H(3DB)	111.1	C(10D)-C(9D)-C(8D)	125.8(2)
C(2D)-C(3D)-H(3DB)	111.1	C(12D)-C(9D)-C(8D)	128.4(3)
H(3DA)-C(3D)-H(3DB)	109.1	C(9D)-C(10D)-O(2D)	110.8(2)
N(1D)-C(4D)-C(5D)	110.2(2)	C(9D)-C(10D)-H(10D)	124.6
N(1D)-C(4D)-C(3D)	102.6(2)	O(2D)-C(10D)-H(10D)	124.6
C(5D)-C(4D)-C(3D)	119.4(2)	C(11D)-O(2D)-C(10D)	105.9(2)
N(1D)-C(4D)-H(4DA)	108.0	C(12D)-C(11D)-O(2D)	111.3(3)
C(5D)-C(4D)-H(4DA)	108.0	C(12D)-C(11D)-H(11D)	124.4
C(3D)-C(4D)-H(4DA)	108.0	O(2D)-C(11D)-H(11D)	124.4
C(6D)-C(5D)-C(4D)	110.8(2)	C(11D)-C(12D)-C(9D)	106.2(3)
C(6D)-C(5D)-H(5DA)	109.5	C(11D)-C(12D)-H(12D)	126.9
C(4D)-C(5D)-H(5DA)	109.5	C(9D)-C(12D)-H(12D)	126.9

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters($Å^2$x 10^3)for 10010a. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2a^{*2}U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1A	35(1)	21(1)	24(1)	-2(1)	1(1)	2(1)
C1A	48(2)	26(1)	26(1)	-5(1)	4(1)	6(1)
C2A	54(2)	37(2)	26(1)	0(1)	0(1)	7(1)
C3A	41(1)	31(1)	26(1)	3(1)	1(1)	4(1)
C4A	28(1)	22(1)	29(1)	0(1)	0(1)	2(1)
C5A	37(1)	22(1)	31(1)	-2(1)	4(1)	-3(1)
C6A	33(1)	27(1)	31(1)	-5(1)	-2(1)	-1(1)
O1A	59(1)	25(1)	32(1)	-10(1)	2(1)	1(1)
C7A	35(1)	29(1)	24(1)	-3(1)	5(1)	-1(1)
C8A	24(1)	24(1)	24(1)	-2(1)	1(1)	-2(1)
C9A	28(1)	27(1)	24(1)	-1(1)	5(1)	0(1)
C10A	37(1)	28(1)	30(1)	1(1)	2(1)	-3(1)
O2A	45(1)	34(1)	32(1)	7(1)	-1(1)	3(1)
C11A	45(1)	29(1)	34(1)	-3(1)	7(1)	-1(1)
C12A	39(1)	27(1)	27(1)	-2(1)	4(1)	-1(1)
N1B	35(1)	28(1)	26(1)	-2(1)	2(1)	-2(1)
C1B	41(1)	42(2)	24(1)	-1(1)	2(1)	-2(1)
C2B	58(2)	46(2)	28(1)	3(1)	0(1)	-12(1)
C3B	52(2)	34(2)	34(1)	9(1)	2(1)	-3(1)
C4B	34(1)	31(1)	30(1)	-1(1)	2(1)	-6(1)
C5B	37(1)	27(1)	32(1)	-3(1)	1(1)	-4(1)
C6B	31(1)	38(2)	26(1)	-3(1)	3(1)	-7(1)
O1B	65(1)	45(1)	27(1)	-5(1)	2(1)	-5(1)
C7B	31(1)	33(2)	29(1)	5(1)	-1(1)	3(1)
C8B	21(1)	33(1)	28(1)	2(1)	2(1)	0(1)
C9B	29(1)	34(2)	29(1)	-2(1)	-4(1)	2(1)
C10B	36(1)	34(2)	37(1)	-2(1)	0(1)	0(1)
O2B	50(1)	30(1)	50(1)	-3(1)	-2(1)	-2(1)
C11B	38(1)	42(2)	53(2)	-12(2)	0(1)	4(1)
C12B	31(1)	42(2)	42(2)	-7(1)	4(1)	-1(1)

N1C	31(1)	22(1)	23(1)	0(1)	1(1)	1(1)
C1C	52(2)	28(1)	24(1)	-1(1)	2(1)	5(1)
C2C	56(2)	33(2)	26(1)	-1(1)	6(1)	5(1)
C3C	43(1)	31(1)	29(1)	5(1)	4(1)	4(1)
C4C	27(1)	25(1)	33(1)	4(1)	4(1)	0(1)
C5C	31(1)	24(1)	36(1)	1(1)	2(1)	1(1)
C6C	29(1)	30(1)	32(1)	-4(1)	0(1)	-3(1)
O1C	57(1)	32(1)	41(1)	-12(1)	-2(1)	2(1)
C7C	36(1)	31(1)	27(1)	-2(1)	-4(1)	0(1)
C8C	23(1)	26(1)	28(1)	0(1)	2(1)	3(1)
C9C	30(1)	28(1)	24(1)	-2(1)	4(1)	2(1)
C10C	33(1)	35(2)	29(1)	1(1)	4(1)	1(1)
O2C	45(1)	34(1)	36(1)	10(1)	6(1)	7(1)
C11C	48(2)	30(1)	34(1)	1(1)	8(1)	-3(1)
C12C	39(1)	28(1)	31(1)	-1(1)	3(1)	0(1)
N1D	34(1)	40(1)	26(1)	-2(1)	4(1)	-2(1)
C1D	66(2)	51(2)	27(1)	0(1)	8(1)	6(2)
C2D	58(2)	57(2)	31(1)	9(1)	7(1)	3(2)
C3D	45(2)	41(2)	44(2)	7(1)	8(1)	1(1)
C4D	31(1)	35(1)	34(1)	-1(1)	6(1)	-4(1)
C5D	38(1)	37(2)	45(2)	-7(1)	2(1)	-10(1)
C6D	34(1)	51(2)	31(1)	-7(1)	2(1)	-7(1)
O1D	77(1)	61(2)	34(1)	-14(1)	1(1)	-19(1)
C7D	31(1)	38(2)	26(1)	-1(1)	4(1)	-5(1)
C8D	23(1)	36(2)	29(1)	-2(1)	1(1)	-1(1)
C9D	26(1)	40(2)	28(1)	-2(1)	-1(1)	3(1)
C10D	38(1)	39(2)	36(1)	2(1)	5(1)	8(1)
O2D	45(1)	37(1)	46(1)	-1(1)	3(1)	7(1)
C11D	42(2)	50(2)	42(2)	-8(1)	6(1)	12(1)
C12D	32(1)	52(2)	39(2)	-4(1)	5(1)	4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 10010a.

	x	y	z	U(eq)
H1AA	4610	6003	2117	40
H1AB	6392	6653	2159	40
H2AA	7291	5157	2810	47
H2AB	5417	5236	2969	47
H3AA	4755	3344	2464	39
H3AB	6490	2949	2739	39
H4AA	7848	3445	1965	31
H5AA	4796	2509	1541	36
H5AB	6405	1645	1637	36
H7AA	6803	4415	436	35
H10A	4805	6356	280	38
H11A	6761	9650	918	43
H12A	7540	7842	1542	37
H1BA	-279	3394	345	43
H1BB	1581	3001	252	43
H2BA	419	5175	-165	53
H2BB	2282	5118	50	53
H3BA	-405	6145	635	48
H3BB	1317	6859	559	48
H4BA	2631	5504	1171	38
H5BA	979	6549	1782	39
H5BB	-538	5639	1606	39
H7BA	1578	2670	2210	37
H10B	-381	659	1671	43
H11B	2783	-1005	692	53
H12B	3316	1381	677	46
H1CA	2287	7728	2797	41
H1CB	4144	7273	2890	41
H2CA	3285	8614	2013	46

H2CB	5063	8832	2292	46
H3CA	3979	10973	2315	41
H3CB	2225	10428	2476	41
H4CA	5117	10497	3158	34
H5CA	1904	11268	3410	36
H5CB	3449	12225	3398	36
H7CA	4064	9471	4598	38
H10C	5073	7367	4728	38
H11C	2816	4233	4067	44
H12C	2171	6118	3463	39
H1DA	7762	346	4676	58
H1DB	9591	893	4655	58
H2DA	10678	-1156	4797	58
H2DB	8998	-1420	5093	58
H3DA	9668	-2948	4305	51
H3DB	7836	-2407	4322	51
H4DA	10412	-1368	3698	40
H5DA	8706	-2606	3121	48
H5DB	7146	-1834	3327	48
H7DA	8839	1326	2743	38
H10D	10190	3329	3295	45
H11D	7005	4814	4317	53
H12D	6555	2415	4294	49

Table 6. Torsion angles [°] for 10010a.

C8A-N1A-C1A-C2A	-175.0(2)	C4B-N1B-C1B-C2B	10.1(3)
C4A-N1A-C1A-C2A	11.9(3)	N1B-C1B-C2B-C3B	-29.6(3)
N1A-C1A-C2A-C3A	-32.0(3)	C1B-C2B-C3B-C4B	38.3(3)
C1A-C2A-C3A-C4A	40.5(2)	C8B-N1B-C4B-C5B	-37.0(3)
C8A-N1A-C4A-C5A	-36.1(3)	C1B-N1B-C4B-C5B	138.8(2)
C1A-N1A-C4A-C5A	137.7(2)	C8B-N1B-C4B-C3B	-162.5(2)
C8A-N1A-C4A-C3A	-160.8(2)	C1B-N1B-C4B-C3B	13.3(3)
C1A-N1A-C4A-C3A	12.9(2)	C2B-C3B-C4B-N1B	-31.1(3)
C2A-C3A-C4A-N1A	-32.5(2)	C2B-C3B-C4B-C5B	-152.6(2)
C2A-C3A-C4A-C5A	-154.0(2)	N1B-C4B-C5B-C6B	48.4(3)
N1A-C4A-C5A-C6A	48.7(3)	C3B-C4B-C5B-C6B	165.6(2)
C3A-C4A-C5A-C6A	165.5(2)	C4B-C5B-C6B-O1B	150.2(2)
C4A-C5A-C6A-O1A	150.3(2)	C4B-C5B-C6B-C7B	-33.7(3)
C4A-C5A-C6A-C7A	-33.8(3)	O1B-C6B-C7B-C8B	-179.7(2)
O1A-C6A-C7A-C8A	178.9(2)	C5B-C6B-C7B-C8B	4.4(3)
C5A-C6A-C7A-C8A	3.2(4)	C1B-N1B-C8B-C7B	-167.5(2)
C1A-N1A-C8A-C7A	-167.4(2)	C4B-N1B-C8B-C7B	7.6(3)
C4A-N1A-C8A-C7A	5.2(3)	C1B-N1B-C8B-C9B	15.5(3)
C1A-N1A-C8A-C9A	14.3(3)	C4B-N1B-C8B-C9B	-169.4(2)
C4A-N1A-C8A-C9A	-173.04(19)	C6B-C7B-C8B-N1B	10.2(4)
C6A-C7A-C8A-N1A	12.5(4)	C6B-C7B-C8B-C9B	-172.9(2)
C6A-C7A-C8A-C9A	-169.3(2)	N1B-C8B-C9B-C10B	-132.7(3)
N1A-C8A-C9A-C10A	-143.6(2)	C7B-C8B-C9B-C10B	50.3(4)
C7A-C8A-C9A-C10A	38.1(3)	N1B-C8B-C9B-C12B	53.4(3)
N1A-C8A-C9A-C12A	41.6(4)	C7B-C8B-C9B-C12B	-123.6(3)
C7A-C8A-C9A-C12A	-136.7(3)	C12B-C9B-C10B-O2B	-0.7(3)
C12A-C9A-C10A-O2A	-0.4(3)	C8B-C9B-C10B-O2B	-175.6(2)
C8A-C9A-C10A-O2A	-176.3(2)	C9B-C10B-O2B-C11B	1.2(3)
C9A-C10A-O2A-C11A	0.3(3)	C10B-O2B-C11B-C12B	-1.3(3)
C10A-O2A-C11A-C12A	0.0(3)	O2B-C11B-C12B-C9B	0.9(3)
O2A-C11A-C12A-C9A	-0.2(3)	C10B-C9B-C12B-C11B	-0.1(3)
C10A-C9A-C12A-C11A	0.4(3)	C8B-C9B-C12B-C11B	174.8(3)
C8A-C9A-C12A-C11A	175.9(2)	C8C-N1C-C1C-C2C	-164.4(2)
C8B-N1B-C1B-C2B	-174.5(2)	C4C-N1C-C1C-C2C	7.5(3)

N1C-C1C-C2C-C3C	-29.4(3)
C1C-C2C-C3C-C4C	40.7(3)
C8C-N1C-C4C-C5C	-43.8(3)
C1C-N1C-C4C-C5C	143.3(2)
C8C-N1C-C4C-C3C	-169.53(19)
C1C-N1C-C4C-C3C	17.6(2)
C2C-C3C-C4C-N1C	-35.5(2)
C2C-C3C-C4C-C5C	-156.3(2)
N1C-C4C-C5C-C6C	50.5(3)
C3C-C4C-C5C-C6C	167.0(2)
C4C-C5C-C6C-O1C	156.1(2)
C4C-C5C-C6C-C7C	-28.7(3)
O1C-C6C-C7C-C8C	171.1(2)
C5C-C6C-C7C-C8C	-3.9(4)
C1C-N1C-C8C-C7C	-177.1(2)
C4C-N1C-C8C-C7C	11.4(3)
C1C-N1C-C8C-C9C	3.1(3)
C4C-N1C-C8C-C9C	-168.4(2)
C6C-C7C-C8C-N1C	14.1(4)
C6C-C7C-C8C-C9C	-166.1(2)
N1C-C8C-C9C-C10C	147.7(2)
C7C-C8C-C9C-C10C	-32.1(4)
N1C-C8C-C9C-C12C	-34.0(4)
C7C-C8C-C9C-C12C	146.2(3)
C12C-C9C-C10C-O2C	0.7(3)
C8C-C9C-C10C-O2C	179.3(2)
C9C-C10C-O2C-C11C	-0.9(3)
C10C-O2C-C11C-C12C	0.8(3)
O2C-C11C-C12C-C9C	-0.4(3)
C10C-C9C-C12C-C11C	-0.2(3)
C8C-C9C-C12C-C11C	-178.7(3)
C8D-N1D-C1D-C2D	-164.3(2)
C4D-N1D-C1D-C2D	4.5(3)
N1D-C1D-C2D-C3D	-26.4(3)
C1D-C2D-C3D-C4D	38.6(3)
C8D-N1D-C4D-C5D	-42.7(3)
C1D-N1D-C4D-C5D	147.3(2)
C8D-N1D-C4D-C3D	-171.0(2)
C1D-N1D-C4D-C3D	19.1(3)
C2D-C3D-C4D-N1D	-34.8(3)
C2D-C3D-C4D-C5D	-157.0(2)
N1D-C4D-C5D-C6D	52.2(3)
C3D-C4D-C5D-C6D	170.6(2)
C4D-C5D-C6D-O1D	152.7(2)
C4D-C5D-C6D-C7D	-32.4(3)
O1D-C6D-C7D-C8D	174.4(2)
C5D-C6D-C7D-C8D	-0.4(4)
C4D-N1D-C8D-C7D	9.6(3)
C1D-N1D-C8D-C7D	177.7(2)
C4D-N1D-C8D-C9D	-170.9(2)
C1D-N1D-C8D-C9D	-2.8(4)
C6D-C7D-C8D-N1D	13.5(4)
C6D-C7D-C8D-C9D	-165.9(2)
N1D-C8D-C9D-C10D	131.3(3)
C7D-C8D-C9D-C10D	-49.2(4)
N1D-C8D-C9D-C12D	-51.4(4)
C7D-C8D-C9D-C12D	128.0(3)
C12D-C9D-C10D-O2D	0.3(3)
C8D-C9D-C10D-O2D	178.0(2)
C9D-C10D-O2D-C11D	-0.6(3)
C10D-O2D-C11D-C12D	0.7(3)
O2D-C11D-C12D-C9D	-0.5(3)
C10D-C9D-C12D-C11D	0.1(3)
C8D-C9D-C12D-C11D	-177.6(3)

Symmetry transformations used to generate equivalent atoms:

Table 7. The shortest **non-classical** hydrogen bonds for 10010a [Å and °]. H position is **not** normalized.

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C12A-H12A...O1D#1	0.95	2.32	3.193(3)	151.7
C11A-H11A...O1A#1	0.95	2.38	3.240(3)	149.6

Symmetry transformations used to generate equivalent atoms:
#1 x,y+1,z

5.5.2 Methoxycarbonyl enaminone

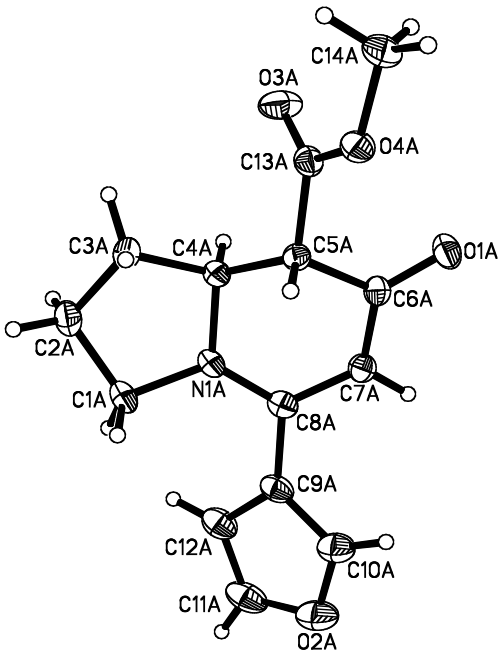
REFERENCE NUMBER: 10019a

CRYSTAL STRUCTURE REPORT

$C_{14}\,H_{15}\,N\,O4$

Report prepared for:
H. Seki / Prof. G. Georg

February 3, 2010



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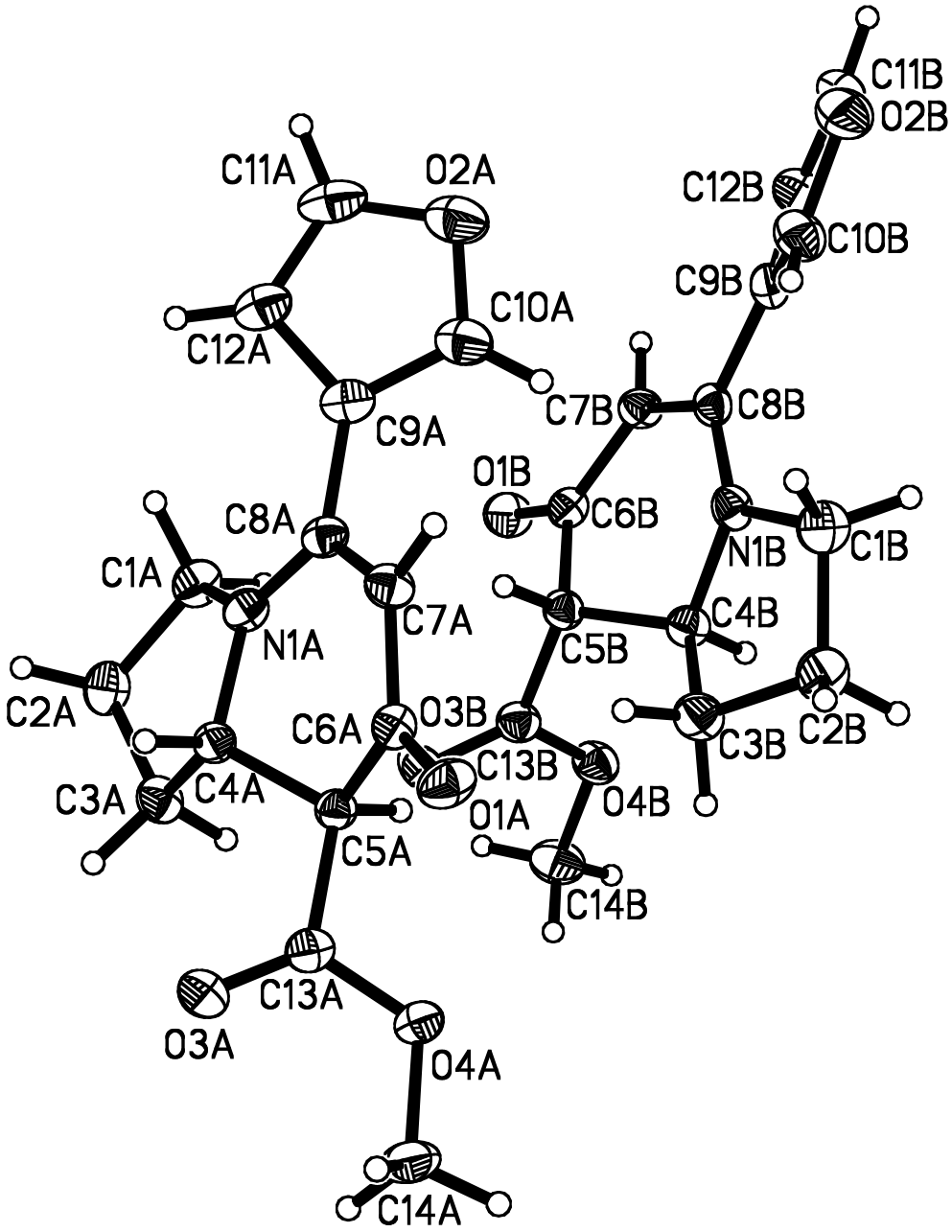
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O2B
C11A
O2A
C12B
C10B
C9B
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C7B
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C8A
C6B
N1B
C1B
C1A
C7A
C4B
N1A
C5B
C2A
C6A
O3B
C3B
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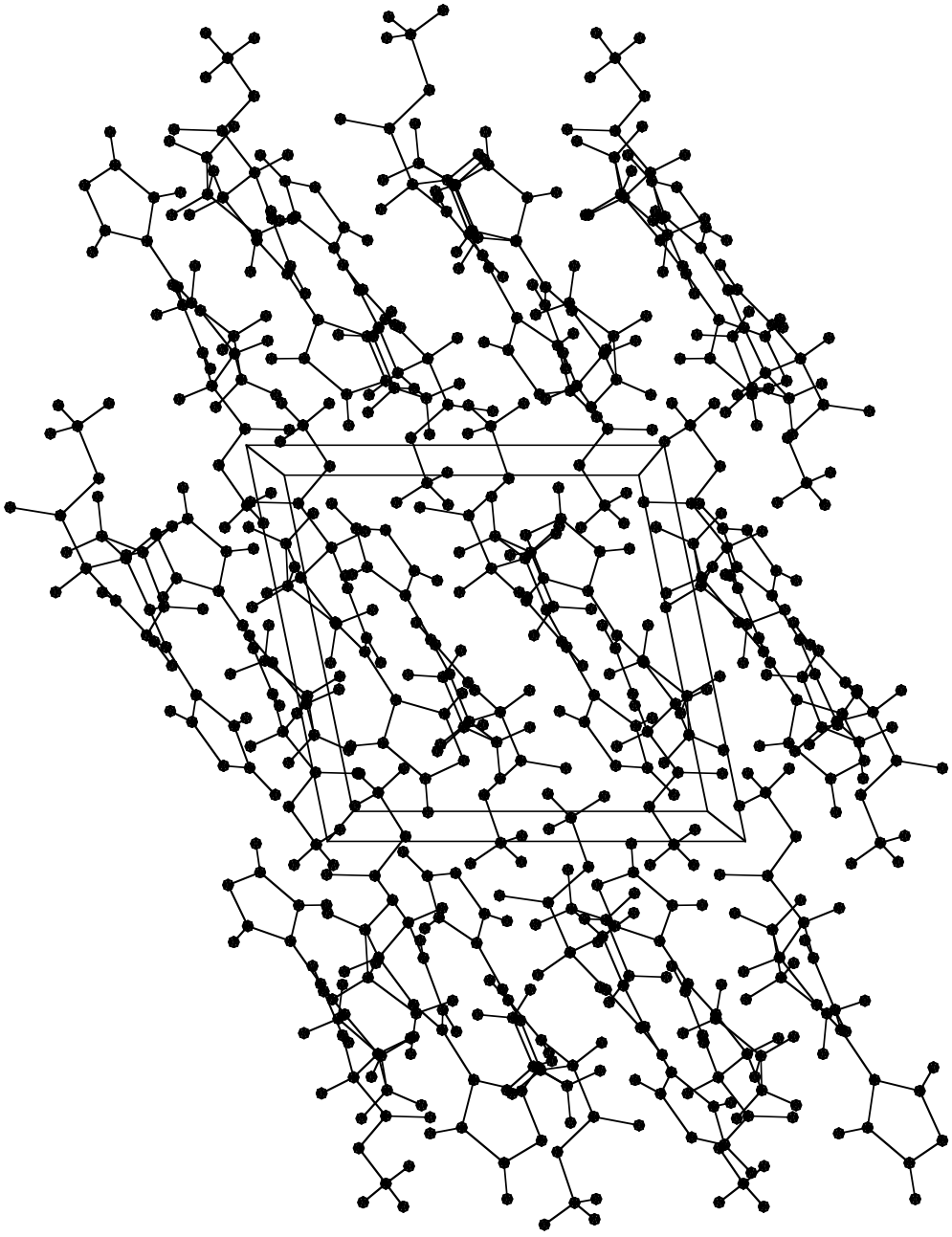
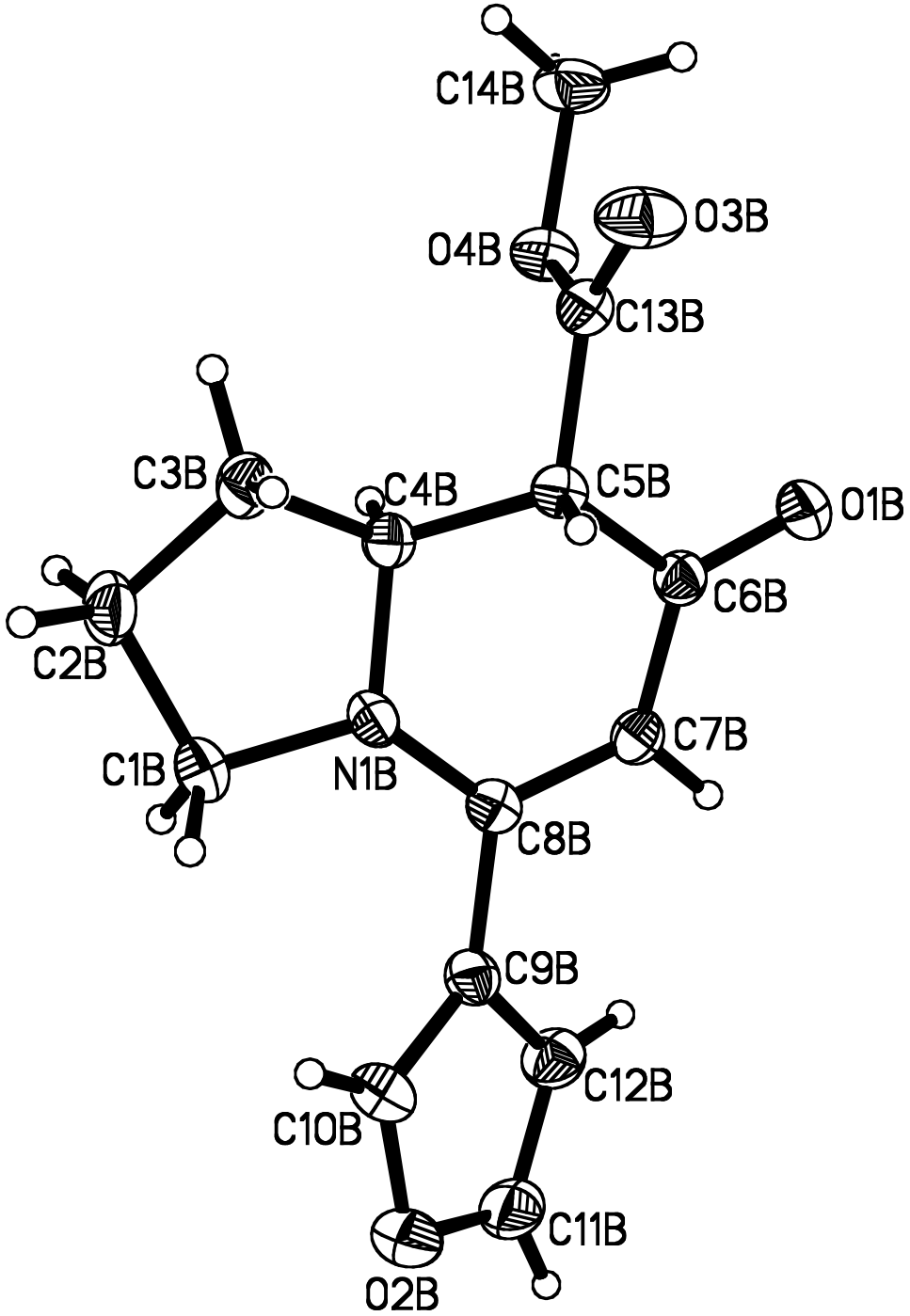
O4A
C14A




C14B
O3B
O4B
C13B
C3B
C4B
C5B
O1B
C6B
C2B
C7B
C1B
N1B
C8B
C9B
C12B
C10B
C11B
O2B

Data collection

A crystal (approximate dimensions 0.45x 0.35 x 0.30mm^3) was placed onto the tip of a 0.1 mm diameter glass capillary and mounted on a CCD area detector diffractometer for a data collection at 123(2) K.[1] A preliminary set of cell constants was calculated from reflections harvested from three sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrices determined from 76 reflections. The data collection was carried out using MoKa radiation (graphite monochromator) with a frame time of 10 seconds and a detector distance of 4.8 cm. A randomly oriented region of reciprocal space was surveyed to the extent of one sphere and to a resolution of 0.77 Å. Four major sections of frames were collected with 0.30º steps in w at four different f settings and a detector position of -28º in2q. The intensity data were corrected for absorption and decay (SADABS).[2] Final cell constants were calculated from 2925 strong reflections from the actual data collection after integration (SAINT).[3] Please refer to Table 1 for additional crystal and refinement information.

Structure solution and refinement

The structure was solved using Bruker SHELXTL[4] and refined using Bruker SHELXTL.[4] The space group $P2_1$ was determined based on systematic absences and intensity statistics. A direct-methods solution was calculated which provided most non-hydrogen atoms from the E-map. Full-matrix least squares / difference Fourier cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. The final full matrix least squares refinement converged to $R1 = 0.0329$ and $wR2 = 0.0894$ (F^2, obs. data).

Structure description

The structure is the one suggested. There are two molecules per asymmetric unit. The absolute configuration is selected based on known reference materials. The atom labeling scheme is based on 10010. The data were treated as though it were centrosymmetric since no heavy atom is present. The Flack X parameter is considered meaningless.

Data collection and structure solution were conducted at the X-Ray Crystallographic Laboratory, 192 Kolthoff Hall, Department of Chemistry, University of Minnesota. All calculations were performed using Pentium computers using the current SHELXTL suite of programs. All publications arising from this report MUST either 1) include Victor G. Young, Jr. as a coauthor or 2) acknowledge Victor G. Young, Jr. and the X-Ray Crystallographic Laboratory.

1 SMART V5.054, Bruker Analytical X-ray Systems, Madison, WI (2001).

2 An empirical correction for absorption anisotropy, R. Blessing, *Acta Cryst.* **A51**, 33-38(1995).

3 SAINT+ V7.34A, Bruker Analytical X-Ray Systems, Madison, WI (2003).

4 SHELXTL V6.14, Bruker Analytical X-Ray Systems, Madison, WI (2000).

Some equations of interest:

$R_{int} = S|F_o^2 - \langle F_o^2 \rangle| / S|F_o^2|$

$R_1 = S||F_o| - |F_c|| / S|F_o|$

$wR2 = [S[w(F_o^2 - F_c^2)^2] / S[w(F_o^2)^2]]^{1/2}$

where $w = q / [s^2(F_o^2) + (a*P)^2 + b*P + d + e*\sin(q)]$

GooF = $S = [S[w(F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$

Table 1. Crystal data and structure refinement for 10019a.

Identification code	10019a	
Empirical formula	C_{14} H_{15} N O_4	
Formula weight	261.27	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	*a* = 9.5071(12) Å	a = 90°
	b = 13.8272(18) Å	b = 101.595(2)°
	c = 9.8419(13) Å	g = 90°
Volume	1267.4(3) Å^3	
Z	4	
Density (calculated)	1.369 Mg/m^3	
Absorption coefficient	0.101 mm^{-1}	
F(000)	552	
Crystal color, morphology	Yellow, Block	
Crystal size	0.45 x 0.35 x 0.30 mm^3	
Theta range for data collection	2.11 to 27.51°	
Index ranges	-12 £*h* £ 12,0 £*k* £ 17,0 £*l* £ 12	
Reflections collected	15225	
Independent reflections	3019 [*R*(int) = 0.0282]	
Observed reflections	2808	
Completeness to theta = 27.51°	99.6%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9703 and 0.9560	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3019 / 1 / 345	
Goodness-of-fit on F^2	1.032	
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0329, *wR*2 = 0.0856	
R indices (all data)	*R*1 = 0.0371, *wR*2 = 0.0894	
Absolute structure parameter	0.1(9)	
Largest diff. peak and hole	0.301 and -0.172 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 10019a. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
O1A	6851(2)	5155(1)	1450(2)	28(1)
O2A	1908(2)	7601(2)	3597(2)	37(1)
O3A	8789(2)	6473(2)	-510(2)	34(1)
O4A	9783(2)	6059(1)	1674(2)	25(1)
N1A	5545(2)	7969(1)	1121(2)	21(1)
C1A	5491(2)	9031(2)	1212(2)	25(1)
C2A	6466(3)	9364(2)	248(2)	28(1)
C3A	7582(2)	8560(2)	349(2)	25(1)
C4A	6730(2)	7637(2)	471(2)	19(1)
C5A	7554(2)	6832(1)	1337(2)	18(1)
C6A	6488(2)	6012(2)	1488(2)	20(1)
C7A	5142(2)	6344(2)	1731(2)	22(1)
C8A	4777(2)	7316(2)	1668(2)	20(1)
C9A	3509(2)	7627(2)	2216(2)	24(1)
C10A	3134(2)	7210(2)	3344(2)	30(1)
C11A	1477(2)	8273(2)	2575(3)	35(1)
C12A	2406(2)	8325(2)	1714(2)	30(1)
C13A	8759(2)	6445(2)	707(2)	22(1)
C14A	10937(2)	5585(2)	1173(3)	32(1)
O1B	6293(2)	9849(1)	5810(2)	29(1)
O2B	1701(2)	6306(1)	7414(2)	39(1)
O3B	8501(2)	8862(2)	3824(2)	37(1)
O4B	9244(2)	8879(1)	6138(2)	26(1)
N1B	5889(2)	6954(1)	6442(2)	22(1)
C1B	5991(2)	5896(2)	6667(3)	29(1)
C2B	7475(3)	5628(2)	6377(3)	31(1)
C3B	7875(2)	6481(2)	5538(2)	28(1)
C4B	7245(2)	7344(1)	6164(2)	22(1)
C5B	6947(2)	8238(2)	5265(2)	21(1)
C6B	6095(2)	8976(2)	5952(2)	21(1)

C7B	5045(2)	8559(2)	6623(2)	22(1)
C8B	4899(2)	7566(2)	6746(2)	20(1)
C9B	3625(2)	7184(2)	7201(2)	23(1)
C10B	2884(2)	6343(2)	6845(2)	31(1)
C11B	1696(3)	7151(2)	8168(3)	36(1)
C12B	2827(2)	7706(2)	8060(2)	30(1)
C13B	8300(2)	8691(2)	4977(2)	23(1)
C14B	10548(2)	9357(2)	5951(3)	34(1)

Table 3. Bond lengths [Å] and angles [°] for 10019a.

O(1A)-C(6A)	1.236(3)	C(14A)-H(14C)	0.9800
O(2A)-C(10A)	1.353(3)	O(1B)-C(6B)	1.234(3)
O(2A)-C(11A)	1.371(3)	O(2B)-C(10B)	1.354(3)
O(3A)-C(13A)	1.204(3)	O(2B)-C(11B)	1.386(4)
O(4A)-C(13A)	1.329(2)	O(3B)-C(13B)	1.212(3)
O(4A)-C(14A)	1.447(3)	O(4B)-C(13B)	1.329(3)
N(1A)-C(8A)	1.340(3)	O(4B)-C(14B)	1.449(3)
N(1A)-C(1A)	1.473(3)	N(1B)-C(8B)	1.343(3)
N(1A)-C(4A)	1.476(2)	N(1B)-C(4B)	1.473(3)
C(1A)-C(2A)	1.525(3)	N(1B)-C(1B)	1.480(3)
C(1A)-H(1AA)	0.9900	C(1B)-C(2B)	1.540(3)
C(1A)-H(1AB)	0.9900	C(1B)-H(1BA)	0.9900
C(2A)-C(3A)	1.526(3)	C(1B)-H(1BB)	0.9900
C(2A)-H(2AA)	0.9900	C(2B)-C(3B)	1.530(3)
C(2A)-H(2AB)	0.9900	C(2B)-H(2BA)	0.9900
C(3A)-C(4A)	1.529(3)	C(2B)-H(2BB)	0.9900
C(3A)-H(3AA)	0.9900	C(3B)-C(4B)	1.520(3)
C(3A)-H(3AB)	0.9900	C(3B)-H(3BA)	0.9900
C(4A)-C(5A)	1.520(3)	C(3B)-H(3BB)	0.9900
C(4A)-H(4AA)	1.0000	C(4B)-C(5B)	1.514(3)
C(5A)-C(13A)	1.507(3)	C(4B)-H(4BA)	1.0000
C(5A)-C(6A)	1.548(3)	C(5B)-C(13B)	1.507(3)
C(5A)-H(5AA)	1.0000	C(5B)-C(6B)	1.541(3)
C(6A)-C(7A)	1.424(3)	C(5B)-H(5BA)	1.0000
C(7A)-C(8A)	1.386(3)	C(6B)-C(7B)	1.425(3)
C(7A)-H(7AA)	0.9500	C(7B)-C(8B)	1.387(3)
C(8A)-C(9A)	1.480(3)	C(7B)-H(7BA)	0.9500
C(9A)-C(10A)	1.361(3)	C(8B)-C(9B)	1.472(3)
C(9A)-C(12A)	1.439(3)	C(9B)-C(10B)	1.368(3)
C(10A)-H(10A)	0.9500	C(9B)-C(12B)	1.438(3)
C(11A)-C(12A)	1.343(3)	C(10B)-H(10B)	0.9500
C(11A)-H(11A)	0.9500	C(11B)-C(12B)	1.342(3)
C(12A)-H(12A)	0.9500	C(11B)-H(11B)	0.9500
C(14A)-H(14A)	0.9800	C(12B)-H(12B)	0.9500
C(14A)-H(14B)	0.9800	C(14B)-H(14D)	0.9800

C(14B)-H(14E)	0.9800	C(14B)-H(14F)	0.9800

C(10A)-O(2A)-C(11A)	106.08(18)	O(1A)-C(6A)-C(7A)	125.45(19)
C(13A)-O(4A)-C(14A)	115.73(16)	O(1A)-C(6A)-C(5A)	120.45(18)
C(8A)-N(1A)-C(1A)	128.24(18)	C(7A)-C(6A)-C(5A)	114.03(18)
C(8A)-N(1A)-C(4A)	119.31(17)	C(8A)-C(7A)-C(6A)	122.04(19)
C(1A)-N(1A)-C(4A)	112.04(17)	C(8A)-C(7A)-H(7AA)	119.0
N(1A)-C(1A)-C(2A)	103.30(18)	C(6A)-C(7A)-H(7AA)	119.0
N(1A)-C(1A)-H(1AA)	111.1	N(1A)-C(8A)-C(7A)	121.30(18)
C(2A)-C(1A)-H(1AA)	111.1	N(1A)-C(8A)-C(9A)	119.99(19)
N(1A)-C(1A)-H(1AB)	111.1	C(7A)-C(8A)-C(9A)	118.70(19)
C(2A)-C(1A)-H(1AB)	111.1	C(10A)-C(9A)-C(12A)	105.7(2)
H(1AA)-C(1A)-H(1AB)	109.1	C(10A)-C(9A)-C(8A)	122.8(2)
C(1A)-C(2A)-C(3A)	103.96(17)	C(12A)-C(9A)-C(8A)	131.4(2)
C(1A)-C(2A)-H(2AA)	111.0	O(2A)-C(10A)-C(9A)	111.0(2)
C(3A)-C(2A)-H(2AA)	111.0	O(2A)-C(10A)-H(10A)	124.5
C(1A)-C(2A)-H(2AB)	111.0	C(9A)-C(10A)-H(10A)	124.5
C(3A)-C(2A)-H(2AB)	111.0	C(12A)-C(11A)-O(2A)	111.2(2)
H(2AA)-C(2A)-H(2AB)	109.0	C(12A)-C(11A)-H(11A)	124.4
C(2A)-C(3A)-C(4A)	103.90(16)	O(2A)-C(11A)-H(11A)	124.4
C(2A)-C(3A)-H(3AA)	111.0	C(11A)-C(12A)-C(9A)	105.9(2)
C(4A)-C(3A)-H(3AA)	111.0	C(11A)-C(12A)-H(12A)	127.0
C(2A)-C(3A)-H(3AB)	111.0	C(9A)-C(12A)-H(12A)	127.0
C(4A)-C(3A)-H(3AB)	111.0	O(3A)-C(13A)-O(4A)	124.37(19)
H(3AA)-C(3A)-H(3AB)	109.0	O(3A)-C(13A)-C(5A)	124.78(19)
N(1A)-C(4A)-C(5A)	109.65(16)	O(4A)-C(13A)-C(5A)	110.85(16)
N(1A)-C(4A)-C(3A)	103.73(16)	O(4A)-C(14A)-H(14A)	109.5
C(5A)-C(4A)-C(3A)	115.68(16)	O(4A)-C(14A)-H(14B)	109.5
N(1A)-C(4A)-H(4AA)	109.2	H(14A)-C(14A)-H(14B)	109.5
C(5A)-C(4A)-H(4AA)	109.2	O(4A)-C(14A)-H(14C)	109.5
C(3A)-C(4A)-H(4AA)	109.2	H(14A)-C(14A)-H(14C)	109.5
C(13A)-C(5A)-C(4A)	112.21(16)	H(14B)-C(14A)-H(14C)	109.5
C(13A)-C(5A)-C(6A)	110.22(16)	C(10B)-O(2B)-C(11B)	106.37(19)
C(4A)-C(5A)-C(6A)	108.47(15)	C(13B)-O(4B)-C(14B)	115.29(16)
C(13A)-C(5A)-H(5AA)	108.6	C(8B)-N(1B)-C(4B)	119.31(17)
C(4A)-C(5A)-H(5AA)	108.6	C(8B)-N(1B)-C(1B)	128.09(19)
C(6A)-C(5A)-H(5AA)	108.6	C(4B)-N(1B)-C(1B)	110.88(17)

N(1B)-C(1B)-C(2B)	104.16(18)	O(1B)-C(6B)-C(7B)	125.8(2)
N(1B)-C(1B)-H(1BA)	110.9	O(1B)-C(6B)-C(5B)	119.49(19)
C(2B)-C(1B)-H(1BA)	110.9	C(7B)-C(6B)-C(5B)	114.51(18)
N(1B)-C(1B)-H(1BB)	110.9	C(8B)-C(7B)-C(6B)	122.16(19)
C(2B)-C(1B)-H(1BB)	110.9	C(8B)-C(7B)-H(7BA)	118.9
H(1BA)-C(1B)-H(1BB)	108.9	C(6B)-C(7B)-H(7BA)	118.9
C(3B)-C(2B)-C(1B)	104.55(18)	N(1B)-C(8B)-C(7B)	121.12(19)
C(3B)-C(2B)-H(2BA)	110.8	N(1B)-C(8B)-C(9B)	119.88(19)
C(1B)-C(2B)-H(2BA)	110.8	C(7B)-C(8B)-C(9B)	118.99(19)
C(3B)-C(2B)-H(2BB)	110.8	C(10B)-C(9B)-C(12B)	105.75(19)
C(1B)-C(2B)-H(2BB)	110.8	C(10B)-C(9B)-C(8B)	129.8(2)
H(2BA)-C(2B)-H(2BB)	108.9	C(12B)-C(9B)-C(8B)	124.3(2)
C(4B)-C(3B)-C(2B)	103.03(16)	O(2B)-C(10B)-C(9B)	110.8(2)
C(4B)-C(3B)-H(3BA)	111.2	O(2B)-C(10B)-H(10B)	124.6
C(2B)-C(3B)-H(3BA)	111.2	C(9B)-C(10B)-H(10B)	124.6
C(4B)-C(3B)-H(3BB)	111.2	C(12B)-C(11B)-O(2B)	110.5(2)
C(2B)-C(3B)-H(3BB)	111.2	C(12B)-C(11B)-H(11B)	124.7
H(3BA)-C(3B)-H(3BB)	109.1	O(2B)-C(11B)-H(11B)	124.7
N(1B)-C(4B)-C(5B)	109.85(16)	C(11B)-C(12B)-C(9B)	106.6(2)
N(1B)-C(4B)-C(3B)	102.63(17)	C(11B)-C(12B)-H(12B)	126.7
C(5B)-C(4B)-C(3B)	116.54(18)	C(9B)-C(12B)-H(12B)	126.7
N(1B)-C(4B)-H(4BA)	109.2	O(3B)-C(13B)-O(4B)	124.1(2)
C(5B)-C(4B)-H(4BA)	109.2	O(3B)-C(13B)-C(5B)	123.93(19)
C(3B)-C(4B)-H(4BA)	109.2	O(4B)-C(13B)-C(5B)	111.98(16)
C(13B)-C(5B)-C(4B)	112.48(17)	O(4B)-C(14B)-H(14D)	109.5
C(13B)-C(5B)-C(6B)	110.56(17)	O(4B)-C(14B)-H(14E)	109.5
C(4B)-C(5B)-C(6B)	109.67(16)	H(14D)-C(14B)-H(14E)	109.5
C(13B)-C(5B)-H(5BA)	108.0	O(4B)-C(14B)-H(14F)	109.5
C(4B)-C(5B)-H(5BA)	108.0	H(14D)-C(14B)-H(14F)	109.5
C(6B)-C(5B)-H(5BA)	108.0	H(14E)-C(14B)-H(14F)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for 10019a. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1A	23(1)	19(1)	40(1)	2(1)	5(1)	2(1)
O2A	29(1)	47(1)	38(1)	-9(1)	13(1)	-2(1)
O3A	32(1)	49(1)	24(1)	2(1)	11(1)	10(1)
O4A	21(1)	27(1)	29(1)	3(1)	6(1)	5(1)
N1A	22(1)	16(1)	24(1)	-1(1)	4(1)	3(1)
C1A	28(1)	16(1)	31(1)	-2(1)	5(1)	3(1)
C2A	34(1)	18(1)	29(1)	2(1)	5(1)	0(1)
C3A	28(1)	20(1)	28(1)	3(1)	9(1)	-2(1)
C4A	20(1)	18(1)	20(1)	0(1)	5(1)	2(1)
C5A	17(1)	18(1)	20(1)	0(1)	4(1)	0(1)
C6A	20(1)	18(1)	21(1)	0(1)	3(1)	-2(1)
C7A	21(1)	19(1)	26(1)	-1(1)	7(1)	-3(1)
C8A	17(1)	22(1)	21(1)	-4(1)	2(1)	0(1)
C9A	21(1)	24(1)	27(1)	-9(1)	4(1)	-1(1)
C10A	25(1)	36(1)	31(1)	-6(1)	9(1)	-1(1)
C11A	20(1)	38(1)	45(1)	-16(1)	5(1)	3(1)
C12A	23(1)	30(1)	35(1)	-7(1)	2(1)	4(1)
C13A	20(1)	19(1)	28(1)	0(1)	5(1)	0(1)
C14A	23(1)	33(1)	43(1)	3(1)	10(1)	9(1)
O1B	30(1)	19(1)	41(1)	4(1)	11(1)	0(1)
O2B	30(1)	38(1)	51(1)	10(1)	11(1)	-5(1)
O3B	30(1)	56(1)	26(1)	2(1)	10(1)	-7(1)
O4B	23(1)	30(1)	26(1)	-2(1)	6(1)	-6(1)
N1B	25(1)	17(1)	23(1)	1(1)	7(1)	-1(1)
C1B	32(1)	18(1)	39(1)	1(1)	8(1)	-1(1)
C2B	39(1)	20(1)	36(1)	0(1)	11(1)	6(1)
C3B	32(1)	22(1)	32(1)	-1(1)	12(1)	4(1)
C4B	22(1)	19(1)	25(1)	-1(1)	6(1)	0(1)
C5B	20(1)	22(1)	20(1)	0(1)	4(1)	-1(1)
C6B	20(1)	21(1)	23(1)	0(1)	2(1)	0(1)

C7B	23(1)	21(1)	25(1)	-2(1)	8(1)	3(1)
C8B	22(1)	22(1)	17(1)	0(1)	3(1)	-1(1)
C9B	24(1)	24(1)	21(1)	5(1)	5(1)	-1(1)
C10B	30(1)	28(1)	37(1)	4(1)	10(1)	-6(1)
C11B	29(1)	43(1)	41(1)	14(1)	17(1)	5(1)
C12B	29(1)	34(1)	28(1)	1(1)	10(1)	2(1)
C13B	23(1)	22(1)	26(1)	0(1)	7(1)	1(1)
C14B	24(1)	36(1)	41(1)	-3(1)	8(1)	-10(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 10019a.

	x	y	z	U(eq)
H1AA	5857	9254	2174	30
H1AB	4499	9272	893	30
H2AA	6926	9989	559	33
H2AB	5919	9434	-715	33
H3AA	8359	8648	1176	30
H3AB	8008	8543	-489	30
H4AA	6323	7385	-480	23
H5AA	7969	7093	2280	22
H7AA	4474	5885	1942	26
H10A	3662	6711	3882	36
H11A	631	8653	2486	42
H12A	2346	8738	934	36
H14A	11569	5259	1946	49
H14B	11487	6068	770	49
H14C	10534	5108	464	49
H1BA	5216	5555	6022	35
H1BB	5928	5731	7632	35
H2BA	8187	5548	7254	37
H2BB	7424	5020	5837	37
H3BA	8930	6541	5651	33
H3BB	7444	6410	4540	33
H4BA	7890	7520	7063	26
H5BA	6336	8043	4357	25
H7BA	4424	8975	6998	27
H10B	3162	5853	6277	37
H11B	990	7315	8689	43
H12B	3056	8322	8471	36
H14D	11103	9560	6855	50
H14E	10302	9925	5356	50

H14F	11122	8908	5515	50

Table 6. Torsion angles [°] for 10019a.

C8A-N1A-C1A-C2A	-173.37(19)
C4A-N1A-C1A-C2A	14.1(2)
N1A-C1A-C2A-C3A	-30.9(2)
C1A-C2A-C3A-C4A	36.6(2)
C8A-N1A-C4A-C5A	-40.7(2)
C1A-N1A-C4A-C5A	132.52(18)
C8A-N1A-C4A-C3A	-164.83(17)
C1A-N1A-C4A-C3A	8.4(2)
C2A-C3A-C4A-N1A	-27.5(2)
C2A-C3A-C4A-C5A	-147.62(17)
N1A-C4A-C5A-C13A	178.61(16)
C3A-C4A-C5A-C13A	-64.6(2)
N1A-C4A-C5A-C6A	56.6(2)
C3A-C4A-C5A-C6A	173.43(16)
C13A-C5A-C6A-O1A	18.2(3)
C4A-C5A-C6A-O1A	141.44(19)
C13A-C5A-C6A-C7A	-164.59(17)
C4A-C5A-C6A-C7A	-41.4(2)
O1A-C6A-C7A-C8A	-175.7(2)
C5A-C6A-C7A-C8A	7.3(3)
C1A-N1A-C8A-C7A	-167.0(2)
C4A-N1A-C8A-C7A	5.0(3)
C1A-N1A-C8A-C9A	13.2(3)
C4A-N1A-C8A-C9A	-174.77(17)
C6A-C7A-C8A-N1A	13.0(3)
C6A-C7A-C8A-C9A	-167.24(18)
N1A-C8A-C9A-C10A	-144.9(2)
C7A-C8A-C9A-C10A	35.3(3)
N1A-C8A-C9A-C12A	39.3(3)
C7A-C8A-C9A-C12A	-140.5(2)
C11A-O2A-C10A-C9A	1.3(3)
C12A-C9A-C10A-O2A	-1.0(3)
C8A-C9A-C10A-O2A	-177.70(19)
C10A-O2A-C11A-C12A	-1.2(3)
O2A-C11A-C12A-C9A	0.5(3)
C10A-C9A-C12A-C11A	0.3(3)
C8A-C9A-C12A-C11A	176.6(2)

C14A-O4A-C13A-O3A	-4.8(3)
C14A-O4A-C13A-C5A	174.63(17)
C4A-C5A-C13A-O3A	-25.9(3)
C6A-C5A-C13A-O3A	95.1(3)
C4A-C5A-C13A-O4A	154.66(17)
C6A-C5A-C13A-O4A	-84.3(2)
C8B-N1B-C1B-C2B	-169.8(2)
C4B-N1B-C1B-C2B	-5.1(2)
N1B-C1B-C2B-C3B	-18.9(2)
C1B-C2B-C3B-C4B	35.2(2)
C8B-N1B-C4B-C5B	-42.2(2)
C1B-N1B-C4B-C5B	151.56(17)
C8B-N1B-C4B-C3B	-166.79(17)
C1B-N1B-C4B-C3B	27.0(2)
C2B-C3B-C4B-N1B	-37.6(2)
C2B-C3B-C4B-C5B	-157.66(19)
N1B-C4B-C5B-C13B	178.27(16)
C3B-C4B-C5B-C13B	-65.6(2)
N1B-C4B-C5B-C6B	54.8(2)
C3B-C4B-C5B-C6B	170.91(18)
C13B-C5B-C6B-O1B	22.0(3)
C4B-C5B-C6B-O1B	146.6(2)
C13B-C5B-C6B-C7B	-162.64(17)
C4B-C5B-C6B-C7B	-38.1(2)
O1B-C6B-C7B-C8B	-179.6(2)
C5B-C6B-C7B-C8B	5.4(3)
C4B-N1B-C8B-C7B	8.6(3)
C1B-N1B-C8B-C7B	172.2(2)
C4B-N1B-C8B-C9B	-172.11(17)
C1B-N1B-C8B-C9B	-8.5(3)
C6B-C7B-C8B-N1B	11.0(3)
C6B-C7B-C8B-C9B	-168.21(18)
N1B-C8B-C9B-C10B	-32.2(3)
C7B-C8B-C9B-C10B	147.0(2)
N1B-C8B-C9B-C12B	153.7(2)
C7B-C8B-C9B-C12B	-27.1(3)
C11B-O2B-C10B-C9B	-0.5(3)

C12B-C9B-C10B-O2B	0.0(3)
C8B-C9B-C10B-O2B	-175.0(2)
C10B-O2B-C11B-C12B	0.8(3)
O2B-C11B-C12B-C9B	-0.8(3)
C10B-C9B-C12B-C11B	0.5(3)
C8B-C9B-C12B-C11B	175.8(2)
C14B-O4B-C13B-O3B	2.7(3)
C14B-O4B-C13B-C5B	-177.27(18)
C4B-C5B-C13B-O3B	125.8(2)
C6B-C5B-C13B-O3B	-111.3(2)
C4B-C5B-C13B-O4B	-54.3(2)
C6B-C5B-C13B-O4B	68.7(2)

Symmetry transformations used to generate equivalent atoms:

5.5.3 Aminoketone

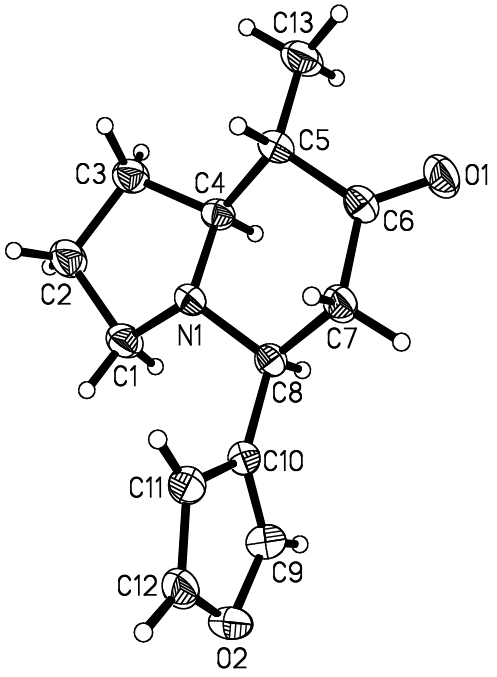
REFERENCE NUMBER: 10071a

CRYSTAL STRUCTURE REPORT

C_{13} H_{17} N O_2

Report prepared for: H. Seki / Prof. G. Georg

June 2, 2010



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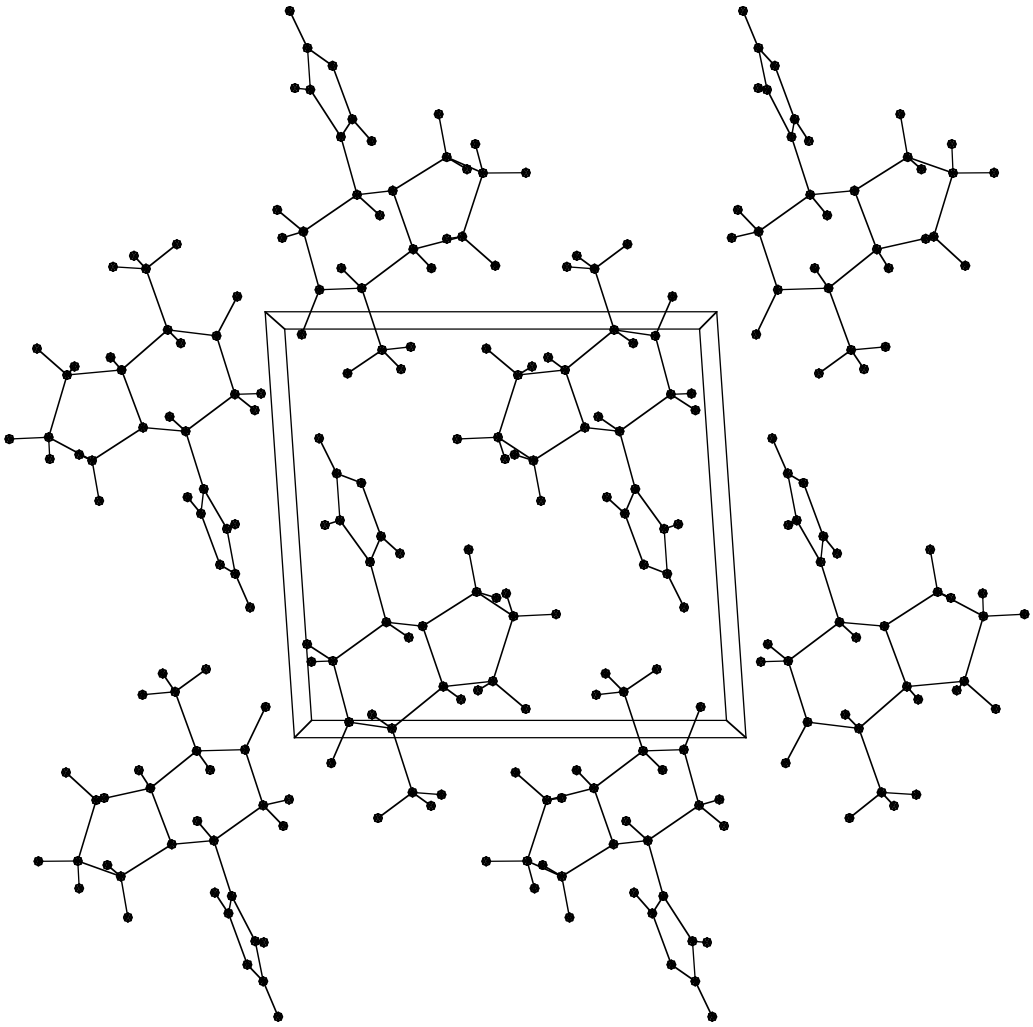
Minneapolis, MN 55455



Data collection

A crystal (approximate dimensions 0.45x 0.20 x 0.09mm^3) was placed onto the tip of a 0.1 mm diameter glass capillary and mounted on a CCD area detector diffractometer for a data collection at173(2) K.[1] A preliminary set of cell constants was calculated from reflections harvested from three sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrices determined from 110 reflections. The data collection was carried out using MoKa radiation (graphite monochromator) with a frame time of 45 seconds and a detector distance of 4.8 cm. A randomly oriented region of reciprocal space was surveyed to the extent of one sphere and to a resolution of 0.77 Å. Four major sections of frames were collected with 0.30º steps in w at four different f settings and a detector position of -28º in2q. The intensity data were corrected for absorption and decay (SADABS).[2] Final cell constants were calculated from 2449 strong reflections from the actual data collection after integration (SAINT).[3] Please refer to Table 1 for additional crystal and refinement information.

Structure solution and refinement

The structure was solved using Bruker SHELXTL[4] and refined using Bruker SHELXTL.[4] The space group $P2_1$ was determined based on systematic absences and intensity statistics. A direct-methods solution was calculated which provided most non-hydrogen atoms from the E-map. Full-matrix least squares / difference Fourier cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. The final full matrix least squares refinement converged to $R1 = 0.0361$ and $wR2 = 0.0935$ (F^2, obs. data).

Structure description

The structure is the one suggested. Both C4 and C5 are known to be S, so the correct enantiomorph was chosen. C8 is found to be S. The correct stereoisomer has all three chiral centers as S.

The data were merged as though the structure was centrosymmetric since no heavy atom was present according to the IUCr guidelines. The Flack parameter is considered meaningless in this situation.

Data collection and structure solution were conducted at the X-Ray Crystallographic Laboratory, 192 Kolthoff Hall, Department of Chemistry, University of Minnesota. All calculations were

performed using Pentium computers using the current SHELXTL suite of programs. All publications arising from this report MUST either 1) include Victor G. Young, Jr. as a coauthor or 2) acknowledge Victor G. Young, Jr. and the X-Ray Crystallographic Laboratory.

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1 SMART V5.054, Bruker Analytical X-raySystems, Madison, WI (2001).

2 An empirical correction for absorption anisotropy,R. Blessing, *Acta Cryst.* **A51**, 33-38(1995).

3 SAINT+ V7.34A, Bruker Analytical X-Ray Systems,Madison, WI (2003).

4 SHELXTL V6.14, Bruker Analytical X-Ray Systems,Madison, WI (2000).

Some equations of interest:

$R_{int} = S|F_o^2 - < F_o^2 >| / S|F_o^2|$

$R_1 = S||F_o| - |F_c|| / S|F_o|$

$wR2 = [S[w(F_o^2 - F_c^2)^2] / S[w(F_o^2)^2]]^{1/2}$

where $w = q / [s^2(F_o^2) + (a*P)^2 + b*P + d + e*\sin(q)]$

GooF = $S = [S[w(F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$

Table 1. Crystal data and structure refinement for 10071a.

Identification code	10071a	
Empirical formula	C_{13} H_{17} N O_2	
Formula weight	219.28	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	*a* = 9.9993(19) Å	a = 90°
	b = 5.5242(10) Å	b = 93.929(2)°
	c = 10.570(2) Å	g = 90°
Volume	582.47(19) Å^3	
Z	2	
Density (calculated)	1.250 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	236	
Crystal color, morphology	Colorless, Plate	
Crystal size	0.45 x 0.20 x 0.09 mm^3	
Theta range for data collection	1.93 to 27.50°	
Index ranges	-12 £*h* £ 12,0 £*k* £ 7,0 £*l* £ 13	
Reflections collected	3611	
Independent reflections	1446 [*R*(int) = 0.0231]	
Observed reflections	1299	
Completeness to theta = 27.50°	97.8%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.995 and 0.980	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1446 / 1 / 146	
Goodness-of-fit on F^2	1.064	
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0361, *wR*2 = 0.0891	
R indices (all data)	*R*1 = 0.0428, *wR*2 = 0.0935	
Absolute structure parameter	-0.6(17)	
Largest diff. peak and hole	0.254 and -0.145 e.Å^{-3}	

Table 2. Atomic coordinates(x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 10071a. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
O1	-562(1)	709(3)	803(1)	37(1)
O2	6001(1)	-2394(3)	1802(1)	37(1)
N1	2669(1)	2495(3)	3052(1)	22(1)
C1	3456(2)	2292(5)	4271(2)	31(1)
C2	2936(2)	4406(5)	5034(2)	38(1)
C3	1479(2)	4756(4)	4501(2)	29(1)
C4	1300(2)	2928(4)	3417(2)	23(1)
C5	372(2)	3692(4)	2266(2)	26(1)
C6	435(2)	1685(4)	1292(2)	26(1)
C7	1828(2)	905(4)	1002(2)	28(1)
C8	2719(2)	384(4)	2223(2)	24(1)
C9	4720(2)	-2390(5)	2167(2)	32(1)
C10	4124(2)	-248(4)	1936(2)	24(1)
C11	5101(2)	1246(4)	1380(2)	30(1)
C12	6204(2)	-129(5)	1334(2)	34(1)
C13	-1050(2)	4231(5)	2623(2)	38(1)

Table 3. Bond lengths [Å] and angles [°] for 10071a.

O(1)-C(6)	1.217(2)	C(5)-C(13)	1.525(3)
O(2)-C(9)	1.363(2)	C(5)-H(5A)	1.0000
O(2)-C(12)	1.366(3)	C(6)-C(7)	1.510(3)
N(1)-C(8)	1.462(2)	C(7)-C(8)	1.544(3)
N(1)-C(4)	1.467(2)	C(7)-H(7A)	0.9900
N(1)-C(1)	1.468(2)	C(7)-H(7B)	0.9900
C(1)-C(2)	1.531(3)	C(8)-C(10)	1.499(2)
C(1)-H(1A)	0.9900	C(8)-H(8A)	1.0000
C(1)-H(1B)	0.9900	C(9)-C(10)	1.340(3)
C(2)-C(3)	1.538(3)	C(9)-H(9A)	0.9500
C(2)-H(2A)	0.9900	C(10)-C(11)	1.435(3)
C(2)-H(2B)	0.9900	C(11)-C(12)	1.343(3)
C(3)-C(4)	1.529(3)	C(11)-H(11A)	0.9500
C(3)-H(3A)	0.9900	C(12)-H(12A)	0.9500
C(3)-H(3B)	0.9900	C(13)-H(13A)	0.9800
C(4)-C(5)	1.537(3)	C(13)-H(13B)	0.9800
C(4)-H(4A)	1.0000	C(13)-H(13C)	0.9800
C(5)-C(6)	1.517(3)		

C(9)-O(2)-C(12)	105.50(18)	C(4)-C(3)-C(2)	104.55(17)
C(8)-N(1)-C(4)	111.01(14)	C(4)-C(3)-H(3A)	110.8
C(8)-N(1)-C(1)	115.26(16)	C(2)-C(3)-H(3A)	110.8
C(4)-N(1)-C(1)	103.64(14)	C(4)-C(3)-H(3B)	110.8
N(1)-C(1)-C(2)	102.89(17)	C(2)-C(3)-H(3B)	110.8
N(1)-C(1)-H(1A)	111.2	H(3A)-C(3)-H(3B)	108.9
C(2)-C(1)-H(1A)	111.2	N(1)-C(4)-C(3)	103.94(15)
N(1)-C(1)-H(1B)	111.2	N(1)-C(4)-C(5)	111.10(14)
C(2)-C(1)-H(1B)	111.2	C(3)-C(4)-C(5)	116.42(18)
H(1A)-C(1)-H(1B)	109.1	N(1)-C(4)-H(4A)	108.4
C(1)-C(2)-C(3)	104.50(18)	C(3)-C(4)-H(4A)	108.4
C(1)-C(2)-H(2A)	110.9	C(5)-C(4)-H(4A)	108.4
C(3)-C(2)-H(2A)	110.9	C(6)-C(5)-C(13)	113.15(17)
C(1)-C(2)-H(2B)	110.9	C(6)-C(5)-C(4)	106.60(17)
C(3)-C(2)-H(2B)	110.9	C(13)-C(5)-C(4)	112.34(16)
H(2A)-C(2)-H(2B)	108.9	C(6)-C(5)-H(5A)	108.2

C(13)-C(5)-H(5A)	108.2
C(4)-C(5)-H(5A)	108.2
O(1)-C(6)-C(7)	121.9(2)
O(1)-C(6)-C(5)	122.76(18)
C(7)-C(6)-C(5)	115.34(17)
C(6)-C(7)-C(8)	111.78(15)
C(6)-C(7)-H(7A)	109.3
C(8)-C(7)-H(7A)	109.3
C(6)-C(7)-H(7B)	109.3
C(8)-C(7)-H(7B)	109.3
H(7A)-C(7)-H(7B)	107.9
N(1)-C(8)-C(10)	112.24(16)
N(1)-C(8)-C(7)	108.11(15)
C(10)-C(8)-C(7)	111.68(15)
N(1)-C(8)-H(8A)	108.2
C(10)-C(8)-H(8A)	108.2
C(7)-C(8)-H(8A)	108.2
C(10)-C(9)-O(2)	111.4(2)
C(10)-C(9)-H(9A)	124.3
O(2)-C(9)-H(9A)	124.3
C(9)-C(10)-C(11)	106.02(18)
C(9)-C(10)-C(8)	125.5(2)
C(11)-C(10)-C(8)	128.5(2)
C(12)-C(11)-C(10)	105.9(2)
C(12)-C(11)-H(11A)	127.1
C(10)-C(11)-H(11A)	127.1
C(11)-C(12)-O(2)	111.22(19)
C(11)-C(12)-H(12A)	124.4
O(2)-C(12)-H(12A)	124.4
C(5)-C(13)-H(13A)	109.5
C(5)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(5)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 10071a. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	21(1)	48(1)	43(1)	-10(1)	-1(1)	-5(1)
O2	26(1)	41(1)	44(1)	-7(1)	3(1)	11(1)
N1	17(1)	25(1)	25(1)	0(1)	0(1)	0(1)
C1	26(1)	38(1)	29(1)	-2(1)	-4(1)	6(1)
C2	29(1)	50(2)	34(1)	-14(1)	-5(1)	6(1)
C3	25(1)	34(1)	29(1)	-2(1)	3(1)	4(1)
C4	19(1)	24(1)	25(1)	2(1)	3(1)	1(1)
C5	20(1)	29(1)	29(1)	1(1)	1(1)	3(1)
C6	20(1)	32(1)	26(1)	1(1)	1(1)	-2(1)
C7	20(1)	36(1)	29(1)	-7(1)	2(1)	-1(1)
C8	18(1)	24(1)	29(1)	-1(1)	4(1)	-2(1)
C9	29(1)	30(1)	36(1)	-3(1)	3(1)	5(1)
C10	22(1)	26(1)	25(1)	-4(1)	1(1)	0(1)
C11	24(1)	30(1)	36(1)	-6(1)	6(1)	-2(1)
C12	21(1)	43(1)	38(1)	-13(1)	6(1)	-4(1)
C13	24(1)	52(2)	38(1)	-8(1)	-2(1)	11(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 10071a.

	x	y	z	U(eq)
H1A	4427	2460	4161	37
H1B	3292	723	4686	37
H2A	3471	5886	4914	46
H2B	2972	4011	5949	46
H3A	844	4423	5159	35
H3B	1332	6428	4184	35
H4A	948	1386	3762	28
H5A	746	5198	1902	31
H7A	2247	2195	513	34
H7B	1768	-571	470	34
H8A	2329	-1027	2662	28
H9A	4303	-3735	2538	38
H11A	4991	2874	1102	36
H12A	7020	405	1017	41
H13A	-1026	5523	3259	58
H13B	-1439	2768	2972	58
H13C	-1597	4747	1867	58

Table 6. Torsion angles [°] for 10071a.

C8-N1-C1-C2	-166.29(16)
C4-N1-C1-C2	-44.8(2)
N1-C1-C2-C3	29.1(2)
C1-C2-C3-C4	-3.5(2)
C8-N1-C4-C3	167.05(15)
C1-N1-C4-C3	42.7(2)
C8-N1-C4-C5	-67.0(2)
C1-N1-C4-C5	168.71(19)
C2-C3-C4-N1	-23.4(2)

C2-C3-C4-C5	-145.90(18)
N1-C4-C5-C6	57.3(2)
C3-C4-C5-C6	176.00(16)
N1-C4-C5-C13	-178.22(18)
C3-C4-C5-C13	-59.5(3)
C13-C5-C6-O1	3.6(3)
C4-C5-C6-O1	127.6(2)
C13-C5-C6-C7	-174.10(19)
C4-C5-C6-C7	-50.1(2)
O1-C6-C7-C8	-127.9(2)
C5-C6-C7-C8	49.8(3)
C4-N1-C8-C10	-174.44(16)
C1-N1-C8-C10	-57.0(2)
C4-N1-C8-C7	61.95(18)
C1-N1-C8-C7	179.37(16)
C6-C7-C8-N1	-52.7(2)
C6-C7-C8-C10	-176.65(19)
C12-O2-C9-C10	0.6(2)
O2-C9-C10-C11	-0.1(2)
O2-C9-C10-C8	-179.81(17)
N1-C8-C10-C9	122.8(2)
C7-C8-C10-C9	-115.6(2)
N1-C8-C10-C11	-56.8(2)
C7-C8-C10-C11	64.8(3)
C9-C10-C11-C12	-0.4(2)
C8-C10-C11-C12	179.27(19)
C10-C11-C12-O2	0.8(2)
C9-O2-C12-C11	-0.9(2)

Symmetry transformations used to generate equivalent atoms:

CHAPTER 6. Bibliography

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