STUDIES AND SYNTHESIS OF SYRINGOLIN A, FUNCTIONALIZED THIADIAZINES, AND THIOL ADDITIONS TO ENONES

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STUDIES AND SYNTHESIS OF SYRINGOLIN A, FUNCTIONALIZED THIADIAZINES, AND THIOL ADDITIONS TO ENONES

Christopher Joseph Rosenker, PhD

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Part one of this dissertation describes the formal synthesis of syringolin A. Syringolin A contains a unique 12-membered dipeptide core and has been shown to be a potent irreversible proteasome inhibitor. Completion of the formal synthesis of syringolin A was facilitated by the rapid access to non-proteinogenic α,β-unsaturated-γ-amino acid and α-amino acid fragments with complete stereochemical control utilizing the stereoselective addition of alkenylorganometallic reagents to chiral *N*-*tert*-butanesulfinylimines.

Part two discusses the development of a robust strategy for the preparation and selective functionalization of heterocyclic thiadiazines with four points of diversity. Hydrolysis of the pendant C-4 ester and functionalization of the resulting acid provided access to a small library of highly substituted thiadiazine analogues that exhibit favorable physicochemical properties for drug-like compounds.

Part three describes the investigation of the equilibria of thiophenol conjugate additions to enone-containing indole scaffolds. Our studies indicate that mono-β-substituted enones form thermodynamically favorable adducts with thiophenol. We also found that thiol eliminations to form enones are favorable in the presence of DBU but not Et_3N. These experiments suggest that mono-β-substituted enones could be used as irreversible covalent protein modifiers.

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LIST OF ABBREVIATIONS

Ac.....acetyl

ATR.....attenuated total reflectance

aq.....aqueous

Bn.....benzyl

Boc .....*tert*-butyloxycarbonyl

BOP.....(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate

Bu.....butyl

calcd .....calculated

cat.....catalytic

conc .....concentrated

Cbz .....benzyloxycarbonyl

Cp.....cyclopentadienyl

DABCO.....1,4-diazabicyclo[2.2.2]octane

dba.....dibenzylideneacetone

DBAD .....di-*tert*-butyl azodicarboxylate

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

DCC .....dicyclohexylcarbodiimide

DEPC .....diethylphosphoryl cyanide

DFT .....density functional theory

DIPEA.....*N*,*N*-diisopropylethylamine

DMAD .....dimethyl acetylenedicarboxylate

DMAP 4-dimethylaminopyridine

DMSO .....dimethylsulfoxide

DME.....1,2-dimethoxyethane

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

DMP .....Dess-Martin periodinane

DPPA .....diphenylphosphoryl azide

dppp.....1,3-bis(diphenylphosphino)propane

dr .....diastereomeric ratio

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

ee .....enantiomeric excess

EI.....electron impact

EN .....electronegativity

ESI.....electrospray ionization

Et .....ethyl

eq.....equivalent(s)

er .....enantiomeric ratio

Fm 9-fluorenylmethyl

Fmoc 9-fluorenylmethoxycarbonyl

HFIP .....hexafluoroisopropanol

HOAt.....1-hydroxy-7-azabenzotriazole

HOBt 1-hydroxybenzotriazole

HPLC .....high performance liquid chromatography

HRMS .....high resolution mass spectroscopy

HWE .....Horner-Wadsworth-Emmons

IR.....infrared spectroscopy

kcal .....kilocalorie

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

LAH .....lithium aluminum hydride

LUMO.....lowest unoccupied molecular orbital

Me .....methyl

MOM.....methoxymethyl

mp .....melting point

NMR .....nuclear magnetic resonance

NMO .....*N*-methylmorpholine oxide

MWI.....microwave irradiation

NADPH.....nicotinamide adenine dinucleotide phosphate

NRPS.....non-ribosomal peptide synthetase

NOESY .....nuclear Overhauser enhancement spectroscopy

o-DCB .....*ortho*-dichlorobenzene

PG .....protecting group

PKS .....polyketide synthetase

PPE.....polyphosphate ester

PPTS .....pyridinium *para*-toluenesulfonate

Pss .....*Pseudomonas syringae* pv. *Syringae*

p-Tol.....*para*-toluene

PTSA.....*para*-toluene sulfonic acid

PyBOP.....(benzotriazole-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

RCM.....ring closing metathesis

ROS.....reactive oxygen species

rt .....room temperature

SAR.....structure-activity relationship

sat .....saturated

SFC .....supercritical fluid chromatography

SM.....starting material

TBAF .....tetrabutylammonium fluoride

TBAI .....tetrabutylammonium iodide

TBDPS .....*tert*-butyldiphenylsilyl

TBS .....*tert*-butyldimethylsilyl

TCI .....targeted covalent inhibitor

TEA.....triethylamine

TFA .....trifluoroacetic acid

THF .....tetrahydrofuran

TLC .....thin layer chromatography

TPAP.....tetrapropylammonium perruthenate

TPSA.....topological polar surface area

T.S.....transition state

Ts.....*p*-toluenesulfonyl

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1.0 FORMAL TOTAL SYNTHESIS OF SYRINGOLIN A

1.1 INTRODUCTION

1.1.1 Isolation and Structure

Syringolin A (**1-1**) was isolated from the bacterial plant pathogen *Pseudomonas syringae* pv. *syringae* (*Pss*) and initially shown to elicit the release of the defense-related *Pir7b* gene (encoding for an α/β hydrolase fold protein)[1] in rice plants.[2] The structure was deduced via mass spectrometry and 1D/2D homo- and hetero-nuclear NMR experiments. The central 12-membered ring contains two non-proteinogenic amino acids, 5-methyl-4-amino-2-hexenoic acid (an α,β-unsaturated-γ-amino acid) and 3,4-dehydrolysine (an α-amino acid), both containing (*E*)-olefins. The olefin configuration was assigned by ^{1}H NMR coupling constant analysis (J = 16 Hz). The α-amino acid is appended with a valine-urea-valine side chain. Further analysis of the *Pss* culture found structurally related natural products which differ from syringolin A by substitution of isoleucine for valine and lysine for 3,4-dehydrolysine (Figure 1).[3] Syringolin A accounts for over 60% of the relative abundance of the syringolins isolated from the culture broth. Interesting to note is that two expected minor variants of syringolin B (**1-2**), where the valine proximal to the core is replaced by isoleucine (syringolin H) and where both valines in the side chain are replaced by isoleucines (syringolin G), were not isolated. However, in 2012

Müller and coworkers cloned a syringolin biosynthetic gene (sylCDE) and expressed it in *E. coli*, which led to the discovery and isolation of the previously expected but not isolated natural products syringolin G and H.[4]

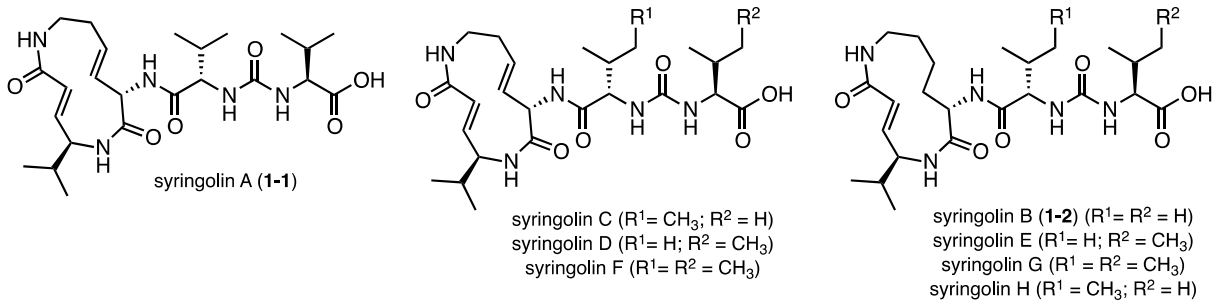


Figure 1. Structures of the syringolin family of natural products.

Syringolin A and a number of structurally similar, bioactive, peptide-based natural products have been collectively called syrbactins.[5] This family of natural products includes the glidobactins, isolated from bacterium *Polyangium brachysporum* sp. nov.,[6] cepafungins, isolated from the bacterium *Pseudomonas* sp.,[7] and luminmycin A, generated by heterologous expression of silent biosynthetic gene clusters in *Photorhabdus luminescens* (Figure 2).[8] The major differences between the glidobactins/luminmycin A and cepafungins are found in the fatty acid side chains; however, compared to syringolin A, they lack the 3,4-dehydrolysine moiety and contain either an alanine or serine based α,β-unsaturated-γ-amino acid.

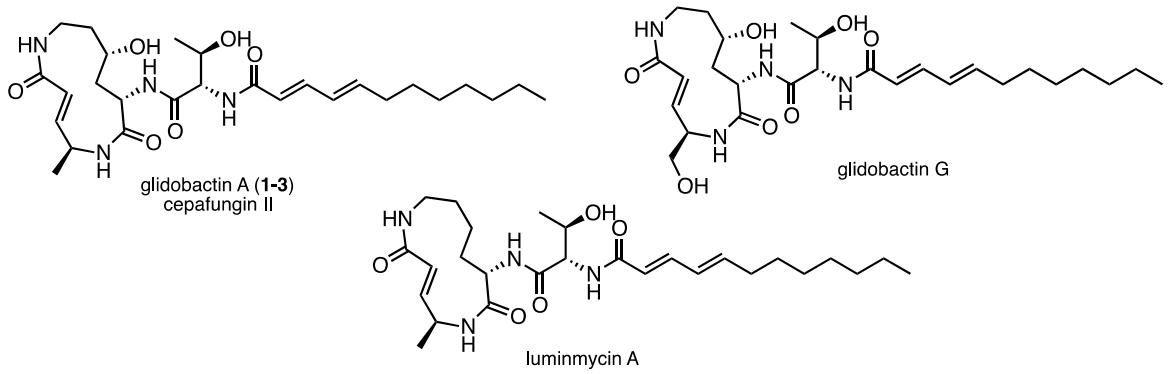


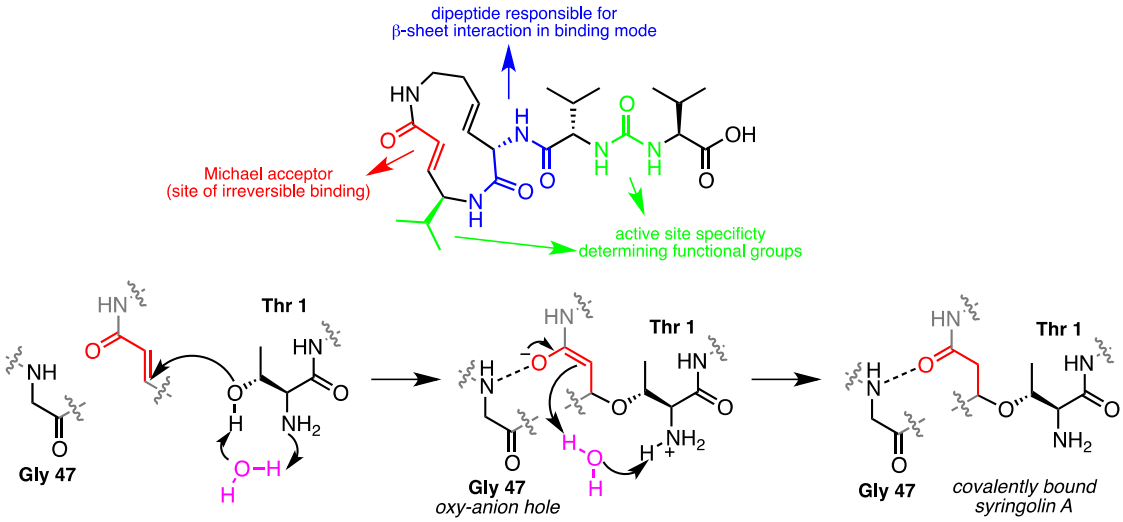
Figure 2. Structures of glidobactin A (**1-3**)/cepafungin II, glidobactin G, and luminmycin A of the syrbactin family of natural products.

1.1.2 Biological Activity

The initial discovery and isolation of syringolin A from the culture extracts of *Pss* was prompted by a marked increase of the defense-related *Pir7b* gene (encoding for an α/β hydrolase fold protein)[1] in rice plants inoculated with *Pss*.[2-3, 9] Later, it was found that syringolin A (**1-1**) completely eliminated powdery mildew in wheat plants, and, furthermore, protected wheat plants against future inoculation.[10] Interestingly, syringolin A, unlike the glidobactins and cepafungins, does not exhibit fungicidal activity, and therefore its mechanism of action against powdery mildew was hypothesized to be a result of an increase in pathogenesis-related gene transcripts which decline after an untreated infection.[10-11] In human neuroblastoma and ovarian cancer cell lines, syringolin A has been shown to induce apoptosis and increase the tumor suppressor protein p53 at μM concentrations.[12] In 2008, syrbactins syringolin A and glidobactin A (**1-3**) were shown to be potent irreversible proteasome inhibitors.[5] The proteasome plays a central role in the degradation of proteins via the ubiquitin-proteasome pathway and represents a significant regulatory checkpoint in many biological processes, including cell division, immune and inflammatory responses, embryonic development, and apoptosis.[13] Bortezomib (Velcade®, PS-

341), a reversible covalent proteasome inhibitor, is currently the only proteasome inhibitor approved by the FDA (since 2003) and is used for the treatment of relapsed multiple myeloma.[13h] The 20S proteasome is composed of three catalytic subunits, caspase-like (β1), trypsin-like (β2), and chymotrypsin-like (β5) proteolytic activities. Syringolin A exhibits inhibition (K_i) at high nM concentrations for the chymotrypsin-like subunit and at low μM concentrations for the trypsin-like subunit. Glidobactin A shows similar activity for the trypsin-like subunit; however, inhibition of the chymotrypsin-like subunit was seen at 49 nM.

In order to gain more understanding of the binding mode of syringolin A (**1-1**), a crystal structure of syringolin A bound to the yeast 20S proteasome was obtained.[5] This structure revealed a unique covalent binding mode resulting from a conjugate addition of the *N*-terminal threonine oxygen (Thr 1 O) onto the α,β-unsaturated-γ-amino acid, confirming that syringolin A was acting as an irreversible proteasome inhibitor (Scheme 1, Figure 3). Groll and coworkers proposed that the conjugate addition was facilitated, among other factors, by the stabilization of the enol intermediate by the oxyanion hole of a glycine adjacent to the binding site (Gly 47 N). Thermodynamically, conjugate addition releases some ring strain in the 12-membered ring by eliminating the two sp^2-hybridized carbons of the (*E*)-olefin. Additionally, the covalent binding is entropically favored, compared to more flexible ligands, based upon the initial rigidity of the 12-membered ring.[5] Furthermore, the dipeptide moiety containing the 3,4-dehydrolysine and proximal valine (blue in Scheme 1) creates an antiparallel β-sheet interaction in the substrate binding channel, thus effectively increasing binding pocket residence time and thereby facilitating covalent binding.



Scheme 1. Syringolin A and a schematic of the mechanism of irreversible proteasome binding (α,β-unsaturated carbonyl (red), active site specificity determinants (green), and dipeptide binding site stabilizing moiety (blue)).

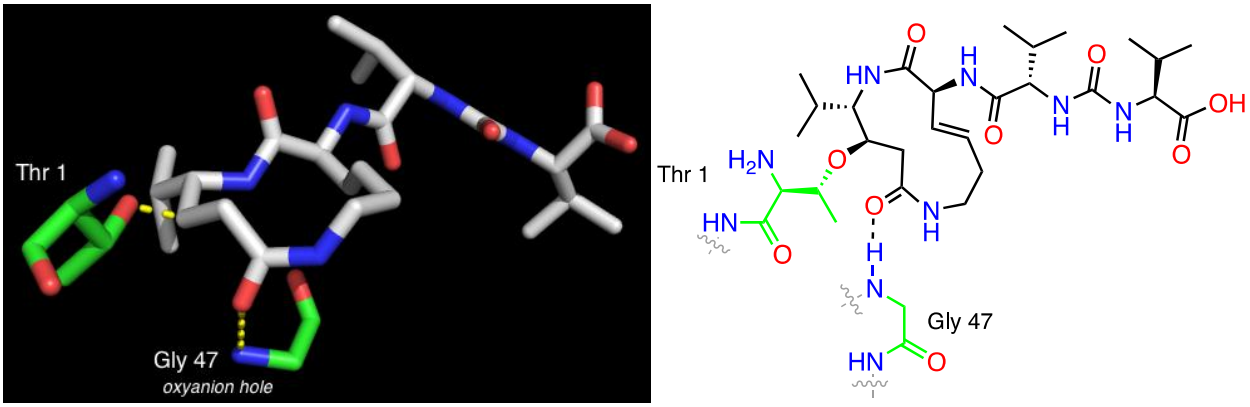


Figure 3. Details of the crystal structure of syringolin A (**1-1**) covalently bound to the proteasome via Thr 1 O (Figure was prepared in Pymol (Delano Scientific, Inc.) using PDB code 2ZCY).

1.1.3 Biosynthesis of Syringolin A

A model for the biosynthetic pathway of syringolin A was proposed after functional analysis of the genes in *Pss* which encode for proteins consisting of three distinct non-ribosomal peptide synthetase (NRPS) modules and one polyketide synthetase (PKS) module (Figure 4).[14] The NRPS are large modular enzymes that activate, condense and transfer amino acids according to the thiotemplate mechanism.[15] The exact biosynthetic pathway for formation of the valine-urea-valine side chain was initially unclear; however, isotopic labeling studies indicated that the carbon of the urea comes from bicarbonate/carbon dioxide.[16] Recent *in vitro* studies by Walsh and co-workers show that biosynthetic gene SlyC is responsible for the formation of the valine-urea-valine side chain.[17] Successive condensation/activation (C/A) of the valine fragment in module 1 provides the dehydrolysine fragment in module 2. The second non-proteinogenic amino acid is formed by coupling with valine (module 3), transfer to the polyketide synthetase (PKS)[18] module followed by condensation of malonate (β-ketoacyl synthase, KS), acyl transfer (acyl transferase, AT), dehydration (dehydratase, DH), and reduction (β-ketoreductase, KR). The acyl carrier protein (ACP) carries the natural product precursor to a cyclization step, presumably occurring via thioesterase (TE), to produce syringolin A (module 4).[14, 16, 19]

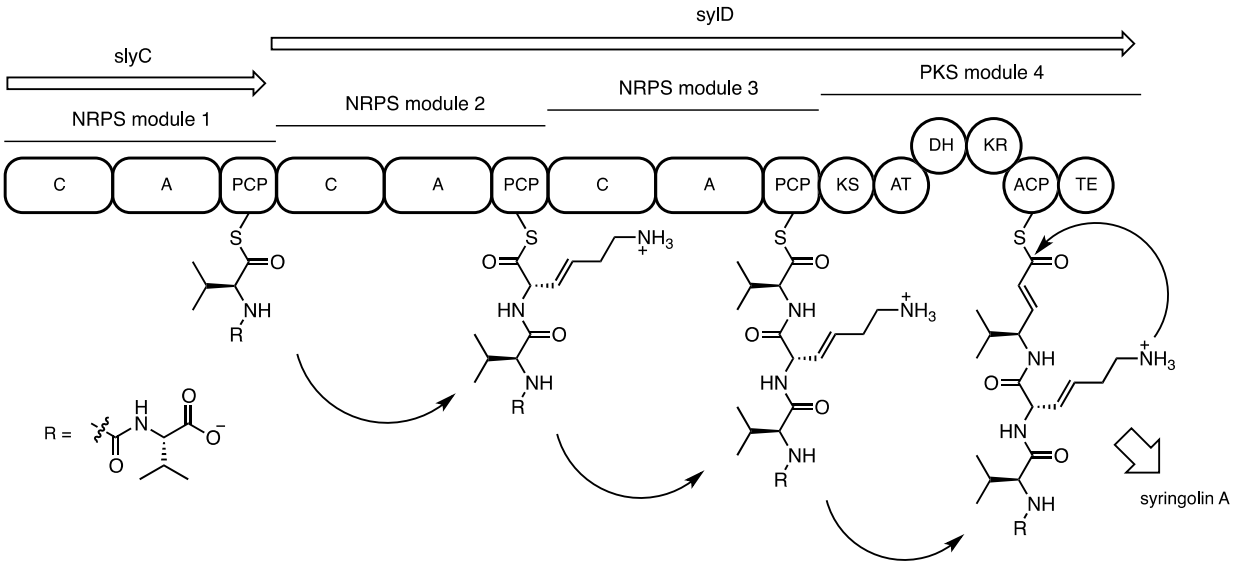


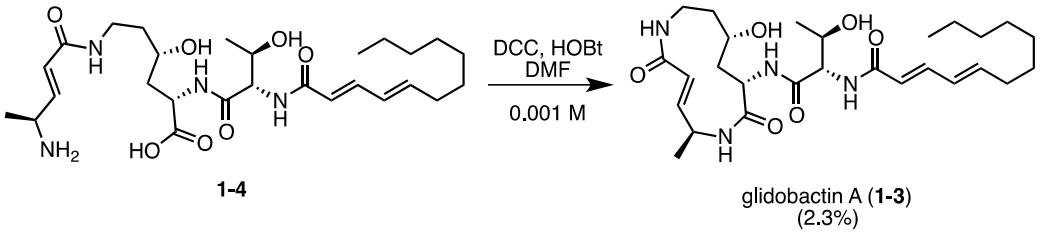
Figure 4. Biosynthetic gene cluster for the formation of syringolin A through NRPS modules 1-3 and PKS module 4. Condensation (C), activation (A), and peptide carrier protein (PCP) domains are indicated as boxes and the β-ketoacyl synthase (KS), acyl transferase (AT), dehydratase (DH), β-ketoreductase (KR), acryl carrier protein (ACP) and thioesterase (TE) domains are indicated as circles.[14, 16, 19]

1.1.4 Syntheses of Glidobactin A and Syringolin A

While Nature can complete the final macrolactamization to form syringolin A and similar members of the syrbactin family, synthetic endeavors towards members of the syrbactin family demonstrate that a macrolactamization approach is difficult to achieve. Several energetic factors need to be considered when performing a cyclization: Pitzer strain (imperfect staggering or overlapping torsional angles); Baeyer strain (deformation of ring bond angles); and transannular strain. The rate of cyclization can be estimated from two factors, activation energy and probability of end-to-end encounters. Activation energy is directly related to the thermodynamic factors noted above, because the transition state of the cyclization is product-like. The probability of end-to-end encounters is related to the entropy of the transition state, which is

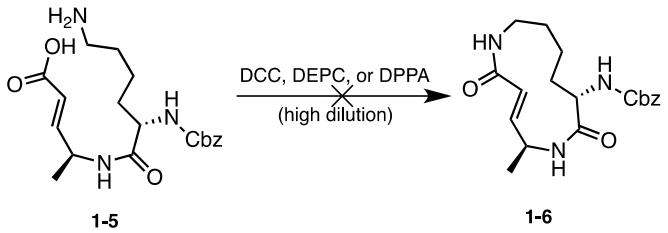
controlled by reducing the freedom of rotation (or ordering) around the single bonds during ring formation.

Synthetically, macrolactamization appears to be challenging due to the build up in transannular ring strain across the 12-membered macrocycle. While investigating the structure of glidobactin A, Oka and coworkers synthesized the natural product from the degradation fragments of the natural compound;[6c] however, cyclization of **1-4** using DCC and HOBt at high dilution afforded glidobactin A in only 2.3% yield as the only reported product (Scheme 2).



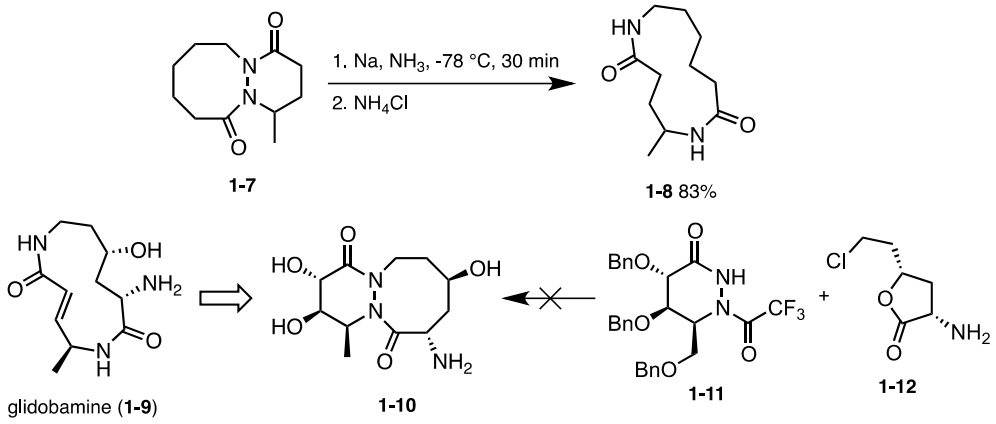
Scheme 2. Cyclization of amino acid **1-4** confirms the structure of glidobactin A (**1-3**).

Several years later, in 1991, Hesse and Meng attempted to synthesize the unfunctionalized core of glidobactin A, lacking the hydroxy group and the fatty acid side chain.[20] Their route differed from Oka and coworkers in that they chose to form the 12-membered ring using the lysine side chain amine; however, they were unable to close the ring using several different conditions,[21] even when employing high dilution conditions (Scheme 3). Failure to close the macrocyclic ring was rationalized by the absence of bulky substituents on the cyclization precursor. In general, the presence of bulky groups decreases the relative energy differences between the linear and bent conformations of an acyclic precursor, and thus facilitates cyclization.[20, 22]



Scheme 3. Failed cyclization of **1-5** to form the protected core scaffold of glidobactin A (**1-6**).

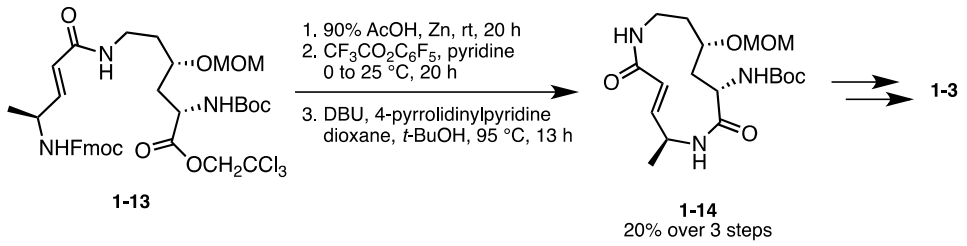
The inability to complete the macrolactamization led Hesse and Meng to develop another approach, which utilized a ring expansion strategy.[20-21, 23] This approach used the reductive cleavage of the N-N bond of the bicyclic hydrazide **1-7** to provide the unfunctionalized core **1-8** in promising yield (Scheme 4). Retrosynthetically, it was envisioned that glidobamine (**1-9**) could be synthesized from hydrazide **1-10**; however, the preparation of the desired hydrazinde **1-10** from **1-11** and lactone **1-12** was not described.[20-21]



Scheme 4. Reductive ring opening of bicyclic hydrazides as an approach to the core of glidobamine (**1-9**).

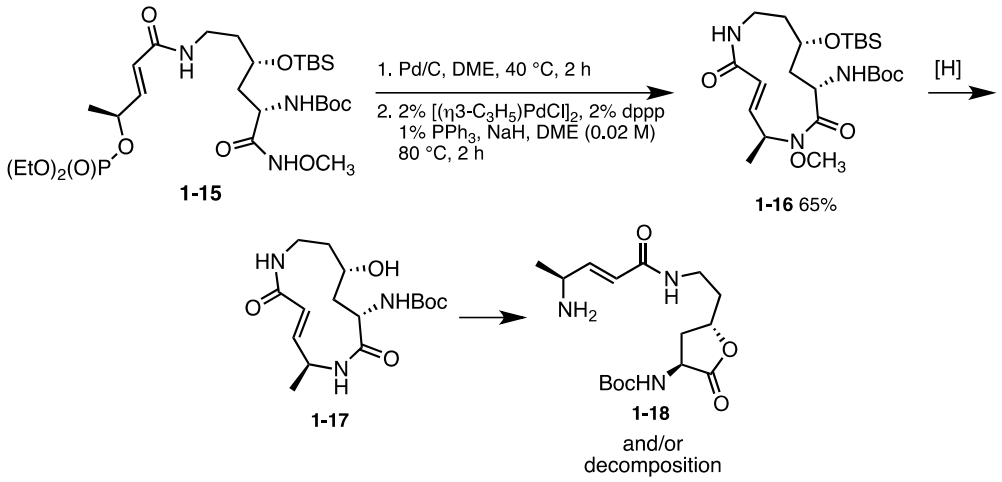
Meanwhile, Schmidt and coworkers utilized a similar approach to Oka and coworkers, forming the macrolactam from the free amine of the alanine-derived α,β-unsaturated-γ-amino acid fragment.[24] Macrolactamization was achieved in 20% yield over three steps using a

pentafluorophenyl ester as the activated intermediate. While this methodology eventually provided access to glidobactin A (**1-3**), the yield was also lower than desirable (Scheme 5).



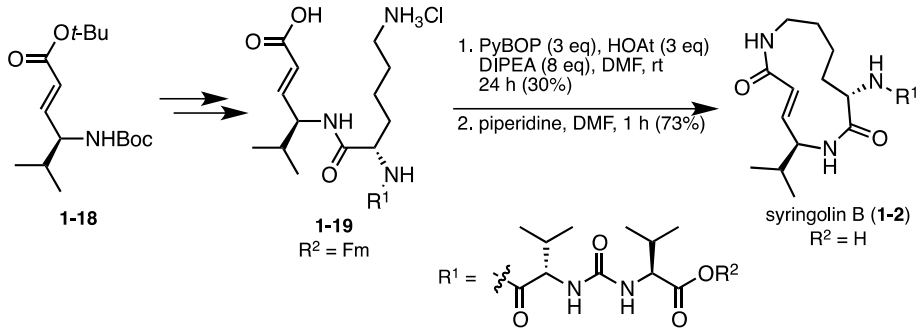
Scheme 5. Macrolactamization of **1-13** through an activated pentafluorophenyl ester towards the total synthesis of glidobactin A (**1-3**).

The apparent synthetic challenge to affect the desired macrolactamization in reasonable yields led Trost and Machajewski to investigate the application of a palladium catalyzed allylic alkylation.[25] After significant experimentation with activated amide pronucleophiles, allylic leaving groups, and cyclization conditions, a suitable substrate and reaction conditions were found. Treatment of **1-15** under the optimized Pd-conditions led to the formation of the desired macrocycle **1-16** in 65% yield (Scheme 6). The yield of the macrocyclization was irreproducible; however, Trost and Machajewski found that pretreatment of hydroxamate ester **1-15** with Pd/C before cyclization appeared to rectify the problem. Unfortunately, reduction of the hydroxamate ester **1-16** to the amide could not be optimized and led to deprotection of the silyl ether to give alcohol **1-17**, resulting in lactonization to provide **1-18**.[25]



Scheme 6. Palladium catalyzed allylic alkylation approach towards the core macrocycle **1-16** of glidobactin A.

In 2009, Kaiser and coworkers completed a synthesis of syringolin A (**1-1**) and B (**1-2**).[26] The valine-derived α,β-unsaturated-γ-amino acid **1-18** was prepared by a Wittig reaction of the corresponding α-amino aldehyde with the requisite ester. Formation of the linear dipeptide **1-19** occurred by coupling of the lysine- and valine-based α,β-unsaturated-γ-amino acid **1-18**. Subsequently, macrolactamization proceeded in 30% yield followed by deprotection of the valine-urea-valine side chain to provide syringolin B (**1-2**) in an overall 9 steps and 7.8% yield from *N*-Boc-valine methyl ester (Scheme 7).

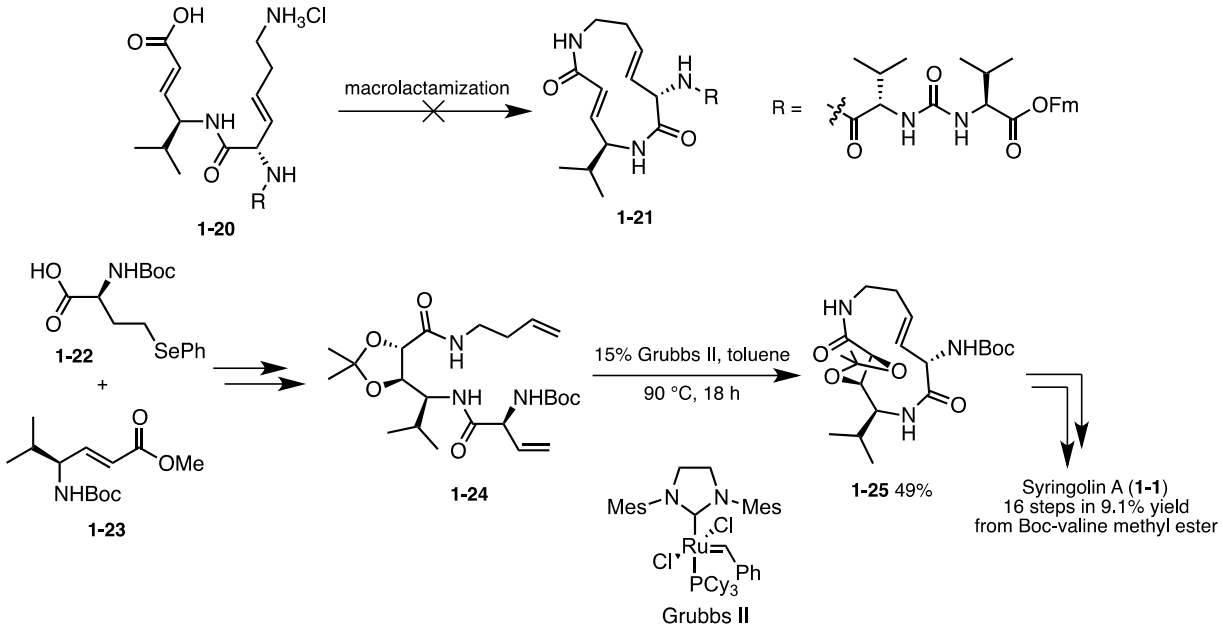


Scheme 7. Synthesis of syringolin B **(1-2**) by the macrolactamization of linear dipeptide **1-19**.

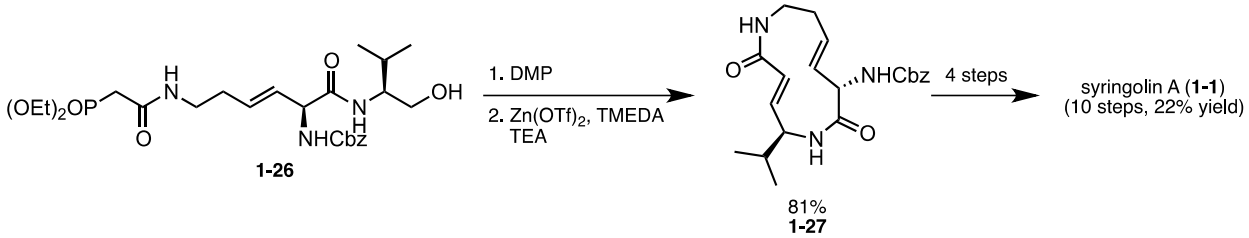
Kaiser and coworkers had hoped to use syringolin B as a model system for the synthesis of syringolin A; however, macrolactamization of the requisite linear dipeptide **1-20** afforded none of the desired product **1-21** (Scheme 8). Presumably, the failure in this step was due to the increase in strain energy associated with the macrolactam of syringolin A compared to syringolin B, stemming from the increased torsional strain and transannular interactions due to the presence of the second (*E*)-olefin. Thus, an alternate route to close the strained 12-membered ring utilized the RCM of **1-24** to provide the natural product precursor **1-25**. The RCM precursor could be obtained from valine-derived α,β-unsaturated-γ-amino acid **1-23**[27] and selenide **1-22**, generated by ring opening of homoserine lactone with phenylselenide. It should be noted that, although not explicitly stated, masking of the olefin in the α,β-unsaturated-γ-amino acid fragment **1-23** was necessary and eliminated the possibility of forming a smaller ring during the RCM process. Additionally, it also pre-organized the RCM transition state, biasing toward the geometry for localizing the reactive termini in proximity to one another (Thorpe-Ingold effect). Coupling to the side chain, deprotection of the diol and thiocarbonate formation, followed by a Corey-Winter reaction provided syringolin A in 16 steps and 9.1% yield from Boc-valine methyl ester.

During our synthetic endeavors in the total synthesis of syringolin A, both Pirrung and coworkers[28] and Stephenson and Dai[29] disclosed efficient syntheses of syringolin A. Pirrung and coworkers oxidized alcohol **1-26** with Dess-Martin periodinane (DMP) and cyclized the resulting aldehyde under Horner-Wadsworth-Emmons (HWE) olefination conditions developed by Helquist and Schauer[30] to provide **1-27**, the core of syringolin A, in good yield (Scheme 9). In four steps, the core **1-27** was functionalized to finish the total synthesis of syringolin A in a total of 10 steps and 22% overall yield.[28] Stephenson and Dai used a macrolactamization strategy to

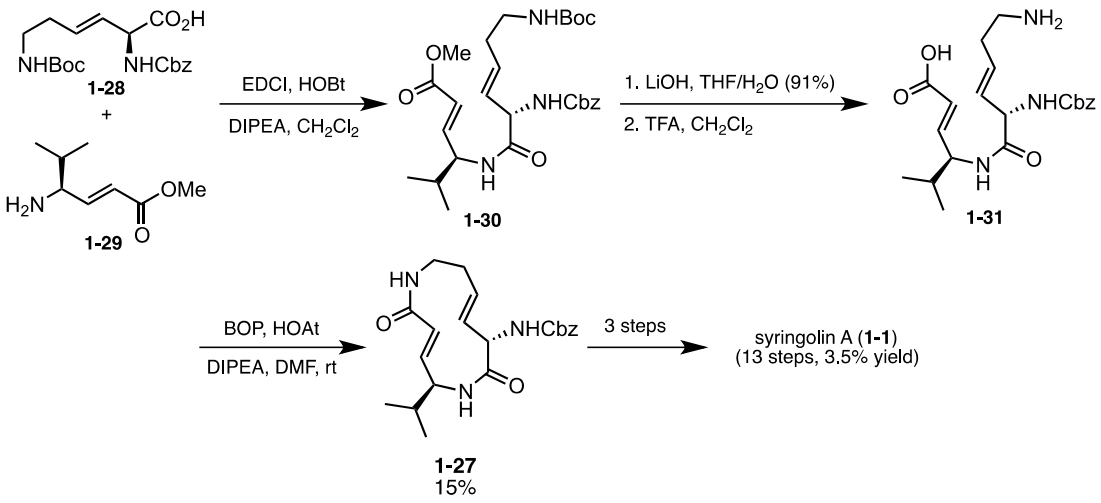
close the core of syringolin A (Scheme 10). Undeterred by reports describing the difficult nature of the macrolactamization,[26, 31] they were able to access the natural product core **1-27** by cyclization of the amino acid with BOP and HOAt, albeit in low yields. Using the macrolactamization strategy, the natural product could be obtained in 13 steps and a 3.5 % overall yield.[29]



Scheme 8. Failure of the macrolactamization approach led to the use of RCM to close **1-21**, forming the syringolin A precursor **1-22**.



Scheme 9. Pirrung and coworkers' synthetic strategy for the preparation of syringolin A.



Scheme 10. Synthesis of syringolin A by Stephenson and Dai.

1.1.5 Synthetic Analogues of Syringolin and Glidobactin

While completing the first total synthesis of syringolin A, Kaiser and coworkers prepared a lipophilic analogue of syringolin A, SylA-LIP (Figure 5).[26, 31] SylA-LIP exhibited 9 nM activity for chymotrypsin-like proteasome inhibition, which is two orders of magnitude more active than syringolin A. Encouraged by the increase in biological activity by appending a fatty acid side chain on syringolin A, Kaiser and coworkers prepared a hybrid of syringolin A and glidobactin A, SylA-GlbA (Figure 5).[32] The hybrid molecule contained the syringolin A core macrocycle with the glidobactin A fatty acid side chain. This hybrid exhibited increased proteasome inhibition compared to SylA-LIP and its parent natural products.[32] In 2012, the same group was able to obtain a crystal structure of SylA-GlbA covalently bound to the proteasome.[33] In addition, they found that the hybrid molecule exhibits proteasome inhibition on par with the approved drug bortezomib.

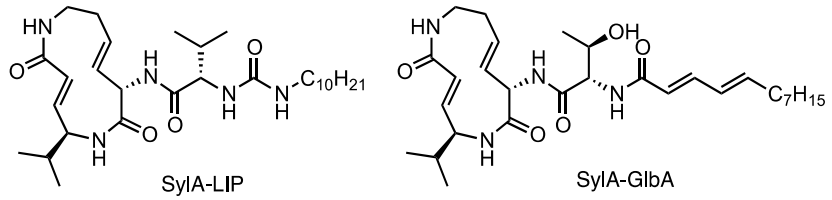


Figure 5. Structures of SylA-LIP and SylA-GibA, analogues of syringolin A.

SAR analysis of the syrbactins and syringolin A analogues revealed some key structural features that impacted the biological activity (Figure 6).[34] The macrocyclic core of syringolin A, R^1, and R^3 impact the proteasome subsite selectivity. The addition of a lipophilic group at R^4 increases the inhibitor activity. During the SAR it also became apparent that changes to the configuration of the amino acids were detrimental to the biological activity.

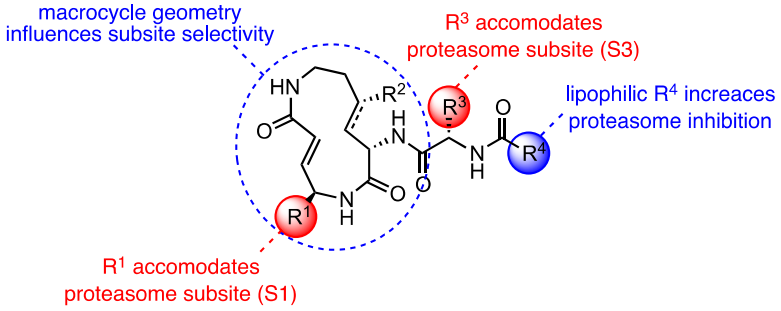
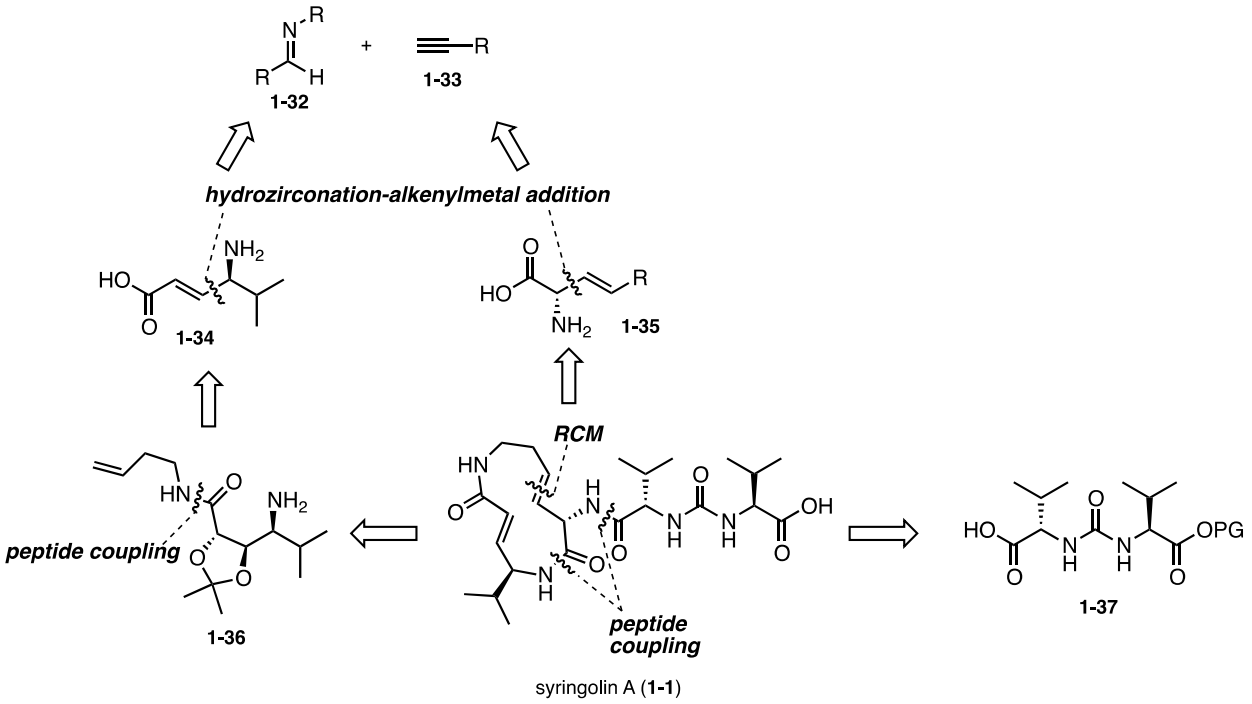


Figure 6. A summary of the SAR of syringolin A analogues.

1.1.6 Retrosynthetic Approach to Syringolin A

Initially, we were intrigued by syringolin A (**1-1**) not only because of its unique biological activity but also by its two (*E*)-alkenes, which we envisioned to be accessible using methodology previously developed in our group. A retrosynthetic analysis of **1-1** led us to the known protected valine-urea-valine **1-37**[26] and peptide fragments **1-35** and **1-36** that can be joined

together via peptide coupling and RCM to give the core structure. Fragment **1-36** can be further derived from allylic amine **1-34** which could be attained through protecting group and oxidation state adjustments followed by an amine coupling. Allylic amines **1-34** and **1-35** could be formed by utilizing our methodology involving hydrozirconation of an alkyne, transmetalation, and addition to a suitable imine electrophile (Scheme 11).[35]



Scheme 11. Retrosynthetic analysis of syringolin A (**1-1**).

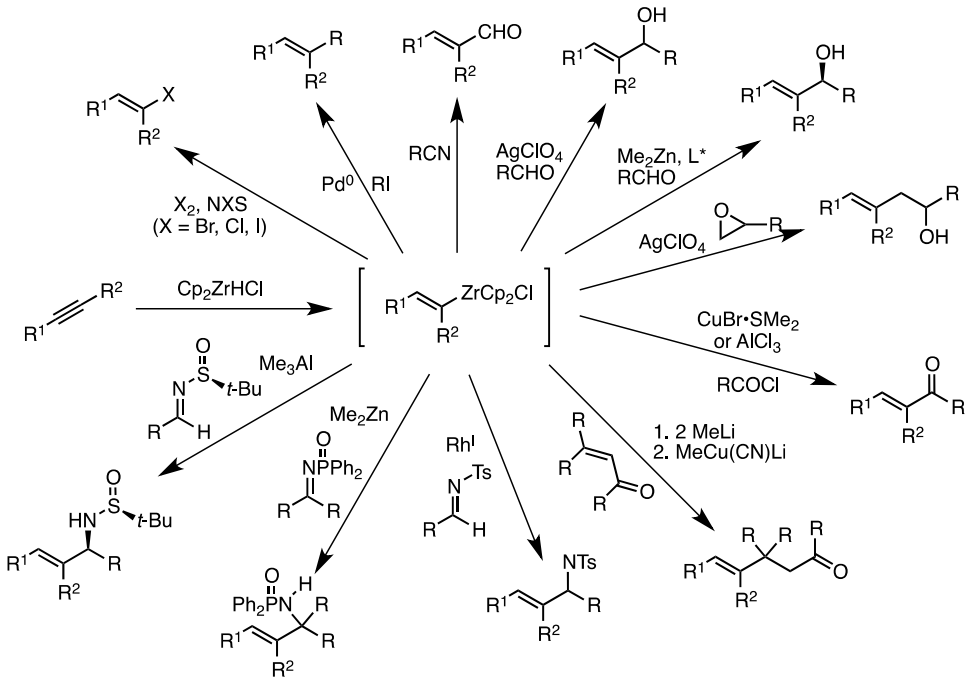
The endgame formation of the macrolactam core via RCM and coupling of the valine-urea-valine moiety are identical to the previously reported synthesis of syringolin A; however, as illustrated above in similar examples, macrolactamization appears to be quite low yielding and therefore this obvious disconnection was avoided.[26] Our proposed synthetic route differs from the other syntheses of glidobactin A and syringolin A in the generation of the non-proteinogenic amino acids. The core precursors, **1-34** and **1-35**, were synthesized from α-amino acids, valine

and homoserine, respectively.[26] We envisioned the synthesis of these fragments to showcase our methodology and expand its utility in the synthesis of non-proteinogenic α-amino- and α,β-unsaturated-γ-amino acids.

1.1.7 Hydrozirconation-Transmetalation Methodologies

Alkyl- and alkenylzirconocenes can be easily prepared by the hydrozirconation[36] of alkenes and alkynes using Schwartz reagent (Cp_2ZrHCl). In general, Schwartz reagent is moderately air-, moisture-, and light-sensitive, but can be conveniently prepared *in situ*[37] or on large scale[38] and stored for several months. Hydrozirconation has considerable functional group compatibility, greatly exceeding that of the preparation of lithium and magnesium reagents, and can therefore provide access to various functionalized organometallic compounds. However, the lack of reactivity of the resulting sterically shielded alkyl[39] and alkenyl[36e] zirconium species with organic electrophiles often necessitates transmetalation in order to gain utility for organic synthesis (Scheme 12).

In 1970, Wailes and Weigold first prepared zirconocene hydrochloride (Cp_2ZrHCl),[40] and later used it for the hydrozirconation of alkenes[41] and alkynes.[42] Thereafter, Schwartz and coworkers reacted alkyl-[43] and alkenylzirconocenes[44] with various halide electrophiles providing selective access to terminally halogenated alkanes and (*E*)-vinyl halides. Subsequently, Schwartz and Carr utilized transmetalation (from Zr to Al) to increase the reactivity of the resulting organometallic intermediates towards organic electrophiles.[45]



Scheme 12. Hydrozirconation of alkynes and addition to electrophiles provides access to various functionalized compounds.

The functional group tolerance to certain esters, carbamates, acetals, epoxides, ethers, halides and sulfides during the hydrozirconation process allows for the generation of relatively functionalized organometallic reagents, compared to the corresponding Mg or Li organometallic reagents. Amides, ketones, aldehydes, and nitriles are not compatible with hydrozirconation conditions due to the reducing ability of the hydride. Interestingly, alcohols undergo an acid-base reaction with one equivalent of Schwartz reagent, but subsequently do not interfere with hydrozirconation.

After hydrozirconation, the resulting C-Zr bond (EN = 1.33) has a similar ionic character to that of C-Mg (EN = 1.31); however, the zirconium organometallic species has a much lower propensity as a nucleophile. This is due to the steric shielding at the Zr metal center by the two cyclopentadienyl ligands. Some electrophiles, such as halogens, protons, dioxygen, CO, and

isocyanides, have been added directly into the C-Zr bond. The hydrozirconation of allenes results in the formation of highly reactive allylzirconocenes, which are the only class of organozirconium reagents that will react directly with organic electrophiles such as aldehydes.[46]

Two general strategies have been investigated to increase the nucleophilicity of alkyl- and alkenylzirconocenes towards synthetically useful and interesting organic electrophiles. One way to increase the nucleophilicity is to reduce the steric shielding around the zirconium by chloride abstraction. Treatment of alkenylzirconocenes with catalytic $AgClO_4$ has been used to generate a cationic zirconocene capable of rapidly reacting with aldehydes[46b, 47] and epoxides.[48] The oxophilic nature of the Ag salts activate the electrophiles and further promote nucleophilic attack of the cationic zirconocene. Alternatively transmetalation strategies[49] from Zr to Pd,[50] Ni,[51] Rh,[52] Cu, [53] Zn,[54] and Al[45, 55] have been used.

In general, the transmetalation approach provides access to a wide range of functionalized organometallic compounds from easily prepared organozirconocenes. To a first approximation, the relative electronegativity of an organometallic precursor can be used to predict the equilibrium of the ligand transfer process, which generally is shifted toward the more electronegative metal complex (EN for Pd = 2.20, Ni = 1.91, Rh = 2.28, Cu = 1.90, Zn = 1.65, Al = 1.61). The rate of ligand transfer is usually fastest for alkenyl groups followed by alkyl, methyl, and alkynyl groups; however, exceptions to this generalization can occur.

The transmetalation strategy from Zr to Pd[50a, b] and Ni[51] has been used for the cross-coupling of alkenylzirconocenes to aryl and alkenyl halides. In 2003, Fu and coworkers expanded the Pd-catalyzed coupling of alkenylzirconocenes to alkyl halides.[56]

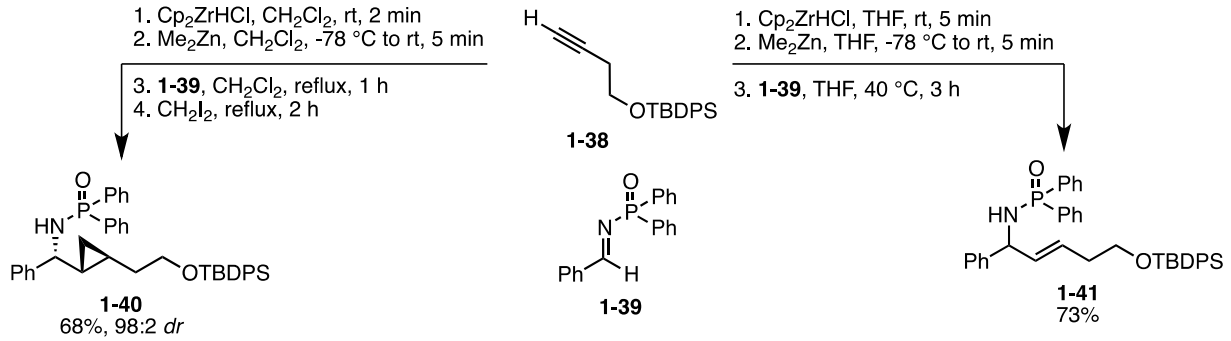
Hanzawa and coworkers demonstrated the Rh(I)-catalyzed addition of alkenylzirconium compounds to *N*-tosyl aldimines.[52b] Substrate scope included both aryl and alkyl aldimines. The

authors propose a transmetalation of the alkenylzirconium to an alkenylrhodium species that then adds into the *N*-tosyl aldimine. Additionally, Hanzawa and coworkers[52a] and Inoue and coworkers[57] were able to demonstrate the Rh(I)-catalyzed conjugate additions to various α,β-unsaturated carbonyl compounds.

Transmetalation from Zr to Cu blends the ease of formation of organozirconocenes with the vast chemistry performed by organocopper reagents.[58] Wipf and coworkers showed that the Cu-catalyzed addition of organozirconocenes to acid chlorides[59] and enones[36d, 60] provided access to ketones. Lipshutz and Kato showed that cyanocuprates generated from a hydrozirconation-transmetalation sequence could be added efficiently to activated (benzylic and allylic) halides, epoxides, and enol triflates[61] Lipshutz and Wood applied the Zr-Cu transmetalation methodology to the three-component coupling for the synthesis of prostaglandin-like compounds.[62] Additionally, in an interesting extension to heterocyclic chemistry, Hanzawa and coworkers utilized zirconium/copper transmetalation to perform asymmetric 1,2-additions of alkenylzirconocenes to 3,4-dihydroisoquinoline.[63]

Wipf and Xu reported the hydrozirconation of alkynes and transmetalation to alkenylzinc species using Me_2Zn and subsequent addition to aldehydes in 54-94% yield.[54] This methodology was developed into an enantioselective variant using chiral amino thiol catalyst[64] and has been used in various natural product total syntheses.[65] The methodology was expanded further by Wipf and coworkers by adding alkenylzinc reagents to *N*-diphenylphosphinoylimines.[35a, 35c] *N*-Diphenylphosphinoylimines are attractive electrophiles because they are almost as reactive as the corresponding *N*-tosylimines but can be easily deprotected under acidic conditions.[66] Performing the hydrozirconation-transmetalation protocol followed by imine addition in THF resulted in the formation of the expected allylic amine **1-41** (Scheme 13). However, performing the same

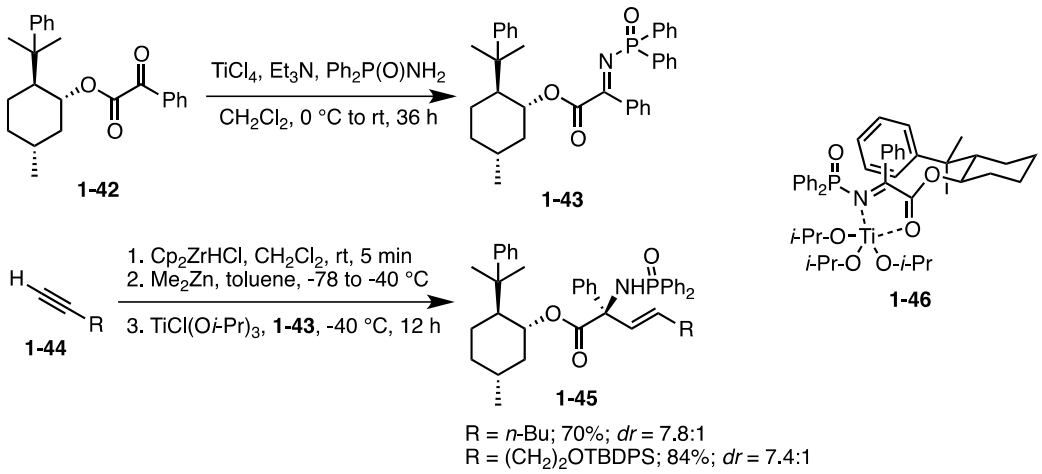
reaction in CH_2Cl_2 at reflux provided cyclopropane **1-40** with high diastereoselectivity. The cyclopropanation occurs through the formation of an *N*-bound zinc carbenoid that performs the Simmons-Smith cyclopropanation intramolecularly. Cyclopropanes of type **1-40** have been used as precursors to α,β-cyclopropyl-γ-amino acids.[67]



Scheme 13. Alkenylzinc addition to *N*-diphenylphosphinoylimine **1-39** to form cyclopropane **1-40** or allylic amide **1-41**.

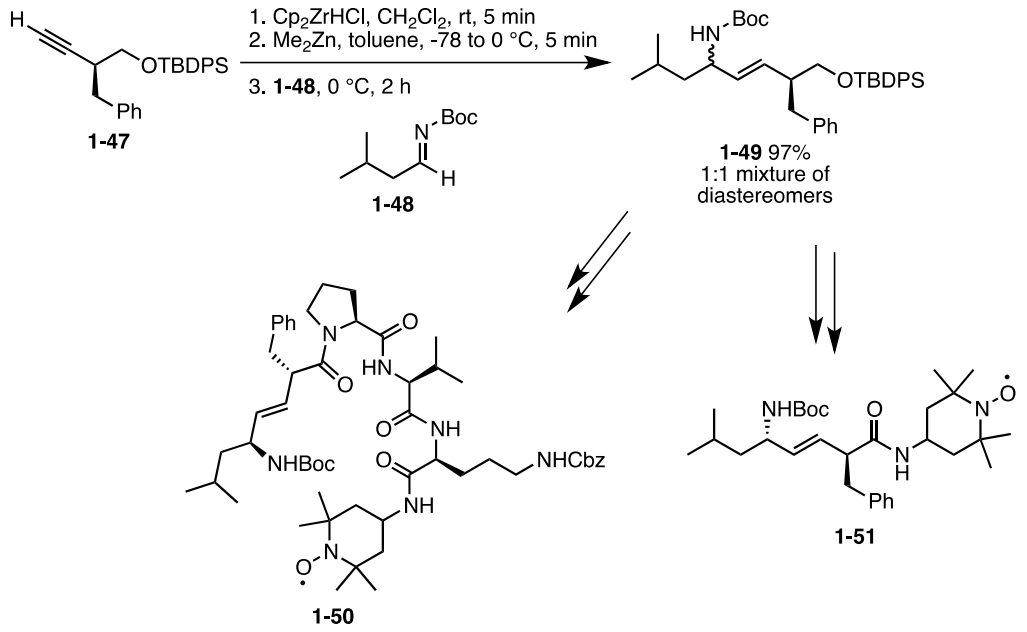
Initial attempts by Wipf and Stephenson to perform catalytic asymmetric additions of alkenylzinc reagents on α-ketoesters using chiral catalysts did not proceed to give enantiomerically enriched products; however, enantiomerically enriched products could be obtained by performing alkenylzinc additions to the 8-phenylmenthol derived α-ketoester **1-42**.[35d] In addition, Wipf and Stephenson expanded the hydrozirconation-transmetalation approach to the synthesis of enantiomerically enriched allylic amines via 1,2-additions to chiral α-*N*-diphenylphosphinoylimino esters. These imines could be synthesized in moderate yield by the condensation of *N*-diphenylphosphinamide with ketoester **1-42** in the presence of Et_3N and $TiCl_4$ (Scheme 14). Treatment of the pre-complexed mixture of α-imino ester **1-43** and $TiCl(O\text{-}i\text{-}Pr)_3$ with 1.5 equivalents of alkenylzinc species, generated by hydrozirconation of alkyne **1-44** followed by transmetalation with Me_2Zn, resulted in tertiary allylic amides **1-45** in

7-8:1 *dr*. The transition state model **1-46** provides a rational of the stereochemistry observed and the necessity of the Lewis acid.[68] This approach provided access to α,α-disubstituted α-amino acids.



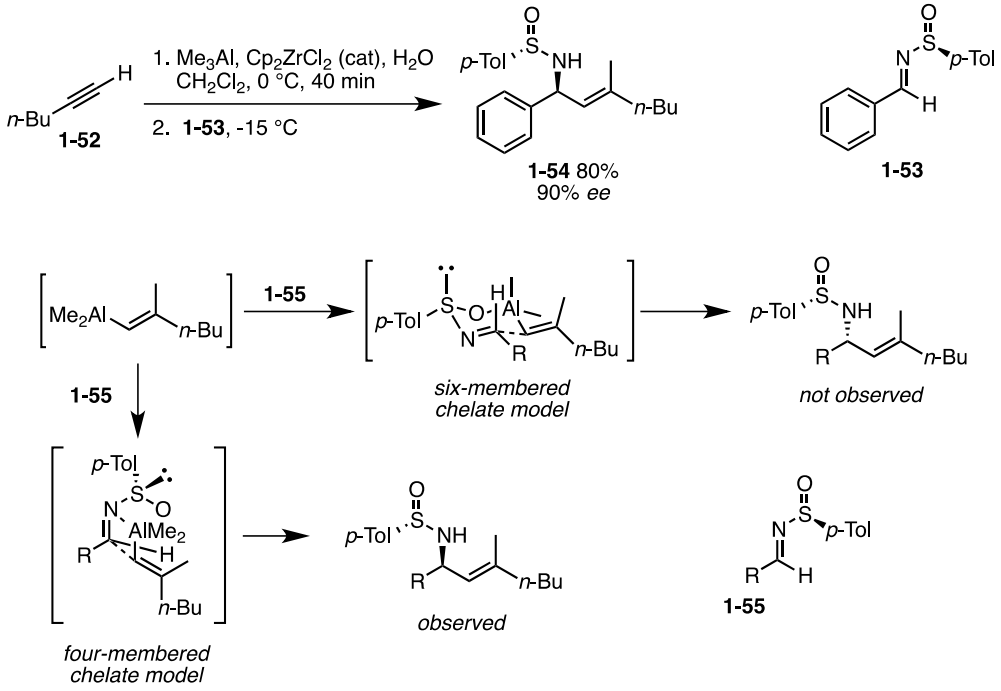
Scheme 14. Alkenylzinc addition to α-*N*-diphenylphosphinoylimino ester **1-43**.

Wipf and Xiao utilized the hydrozirconation-transmetalation-imine addition methodology in an approach to synthesize hemigramicidin conjugates as therapeutic agents to target reactive oxygen species (ROS).[69] Hydrozirconation of alkyne **1-47**, followed by transmetalation and addition to imine **1-48** afforded the allylic amide **1-49** as a 1:1 mixture of diastereomers (Scheme 15). The mixture of diastereomers could be separated after desilyation and oxidation to the acid. The desired diastereomer was further functionalized to provide nitroxides **1-50** and **1-51**.



Scheme 15. Application of hydrozirconation-transmetalation-imine addition in the synthesis of hemigramicidin conjugates by Xiao and Wipf.

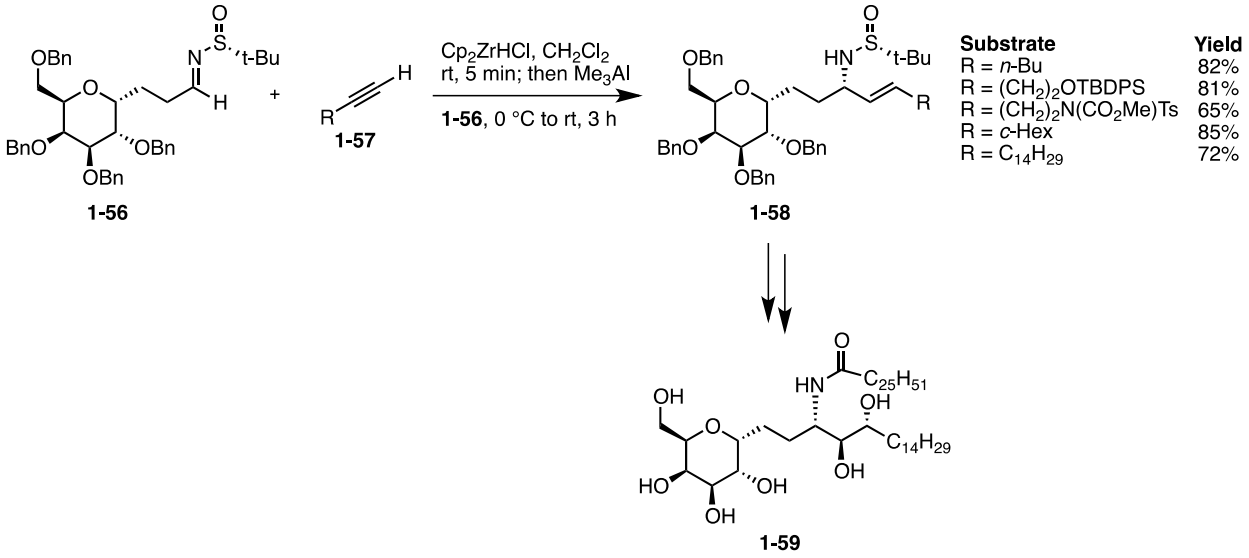
While alkenylzinc reagents have been used to generate allylic amides by the methodology described above, a general route to a variety of enantioenriched allylic amines has not been realized; however, work performed by Wipf and coworkers on the zirconium catalyzed carboalumination of alkynes provided alkenylalanes which were subsequently added with high diastereoselectivity to chiral *N*-tosylsulfinylimines (Scheme 16).[35b] Diastereoselective addition of the alkenylalane, obtained from the water-accelerated carboalumination[70] of 1-hexyne, to chiral *N*-tosylsulfinylimine **1-53** provided allylic amide **1-54**. The configuration can be explained by a four-membered chelate Felkin-Anh-type transition state model.[71] Interestingly, organolithium and -magnesium additions to similar sulfinylimines are thought to proceed through a six-membered chelate transition state in non-coordinating solvents.[72]



Scheme 16. Water accelerated carboaluminatation and addition to chiral sulfinylimine **1-56** to give allylic amide **1-54** in high diastereoselectivity.

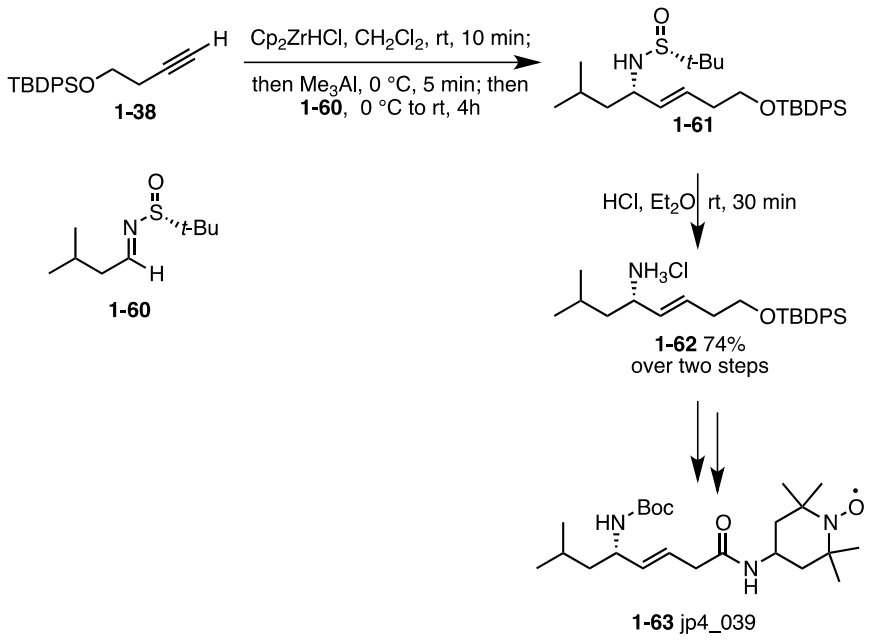
During the total synthesis of α-C-glycoside analogue **1-59** of the immunostimulant galactosylceramide (KRN7000) by Wipf and Pierce, a rapid and selective installation of the allylic amide was essential for a viable synthetic route.[35e] Initial attempts to apply the Zr-Zn transmetalation methodology did not provide the desired compound. However, inspired by the carboalumination/stereoselective addition to *N*-tosylsulfinylimines (Scheme 16),[35b] a hydrozirconation-transmetalation from Zr to Al[45] followed by addition to a chiral sulfinylimine electrophile was investigated. Fortunately, hydrozirconation of various alkynes **1-57** followed by transmetalation with Me_3Al and addition to *N-tert*-butanesulfinylimine **1-56** provided the desired allylic amides **1-58** in 65-82% yield and high diastereomeric ratios (Scheme 17).[73] The stereochemistry of the resulting additions could be rationalized using a four-membered chelate Felkin-Anh-type transition state model.[35b] Additionally, the *N-tert*-butanesulfinamides could be

easily deprotected under acidic conditions. The development of this new methodology contributed to the expedient (10 linear steps) synthesis of the α-C-glycoside **1-59**.



Scheme 17. Application of Zr-Al transmetalation to the diastereoselective addition of alkenylalanes to *N-tert*-butanesulfinylimine **1-56** in the synthesis of α-C-glycoside **1-59**.

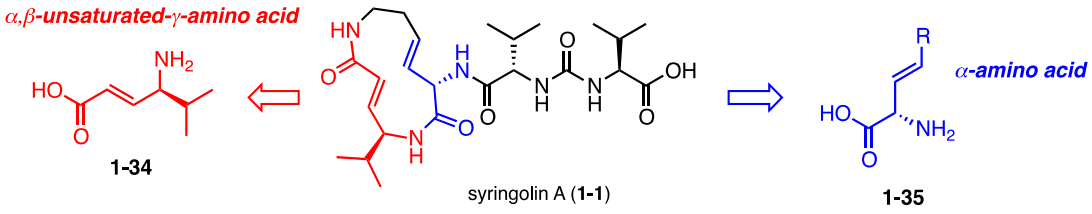
Wipf and Pierce utilized the Zr-Al transmetalation methodology again for the synthesis of the novel radioprotectant jp4_039 (**1-63**) (Scheme 17).[73-74] The hydrozirconation of alkyne **1-38**, transmetalation to form the alkenylalane, and addition to *N-tert*-butanesulfinylimine **1-60** yielded the expected allylic amide **1-61** in >95:5 *dr*. Subsequently, deprotection provided the amine hydrochloride **1-62** in 74% yield over the two steps. This amine could be further elaborated into jp4_039 (**1-63**).



Scheme 18. Application of the Zr-Al transmetalation/imine addition methodology in the synthesis of radioprotectant jp4_039 (**1-63**).

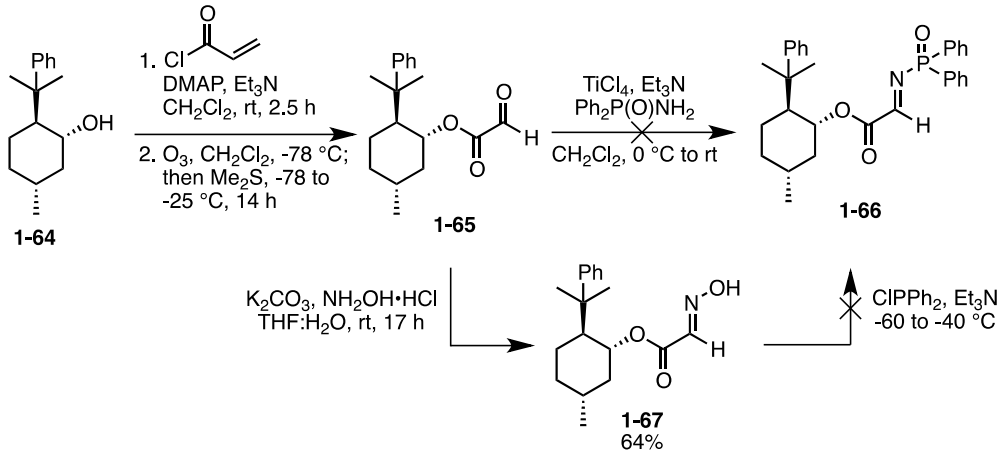
1.2 RESULTS AND DISCUSSION

1.2.1 Studies Towards the Preparation of α-Amino Acid Fragment 1-35



Scheme 19. Amino acid fragments **1-34** and **1-35** from the core dipeptide macrocycle of syringolin A (**1-1**).

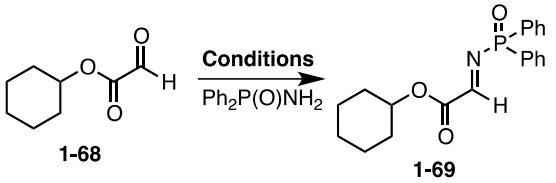
Our initial investigations into the synthesis of syringolin A began with the synthesis of the α-amino acid fragment **1-35** (Scheme 19), which will function as part of the dehydrolysine peptide fragment in the macrocyclic core. We were inspired by the diastereoselective addition of alkenylzinc reagents to menthol derivatives of α-iminoesters performed by Wipf and Stephenson (Scheme 14).[35d] This methodology had only been tested on α-ketoimino esters substituted with aryl groups; the analogous substrate for the synthesis of fragment **1-35** was *N*-diphenylphosphinoylimine **1-66** (Scheme 20). Preparation of the desired imine **1-66** began with the acylation of 8-phenylmenthol (**1-64**)[75] with acryloyl chloride followed by ozonolysis of the α,β-unsaturated ester to give glyoxylate **1-65**.[76] With this known glyoxylate in hand, imine formation was attempted under conditions used previously to generate the α-ketimino esters; however, none of the desired product could be isolated. *N*-Diphenylphosphinoylimines have also been synthesized in a more general fashion from their corresponding oximes by treatment with chlorodiphenylphosphine and Et_3N.[77] Work by Hudson and coworkers indicated that this reaction proceeds through a homolytic dissociation to a radical pair upon warming, followed by recombination to give the imine.[78] The oxime **1-67**[79] was prepared; however, the radical rearrangement did not provide the desired product.



Scheme 20. Attempted preparation of chiral *N*-diphenylphosphinoylimine **1-66**.

In order to investigate other conditions for the formation of the *N*-diphenylphosphinoylimine, we decided to substitute the 8-phenylmenthol glyoxylate for a more easily prepared cyclohexanol glyoxylate **1-68**. This glyoxylate was obtained by oxidative cleavage of the corresponding tartrate.[80] Several conditions for imine formation from **1-68** (Entries 1-5) resulted in either partial decomposition and/or formation of complex mixtures where no product could be observed (Table 1). Heating the glyoxylate **1-68** in benzene with 4 Å molecular sieves provided the desired *N*-diphenylphosphinoylimine **1-69** but only in a 3:1 (**1-69**:**1-68**) mixture of starting material and product as measured by ^{1}H NMR (decrease of the glyoxylate peak at δ 9.56 (s) and formation of the characteristic diphenylphosphinoylimine peak at δ 9.20 (d, J = 31.5 Hz)). Attempts to push the reaction to completion by adding more molecular sieves and extending the reaction time were not successful, and we therefore shifted focus towards the *in situ* preparation of the imine.

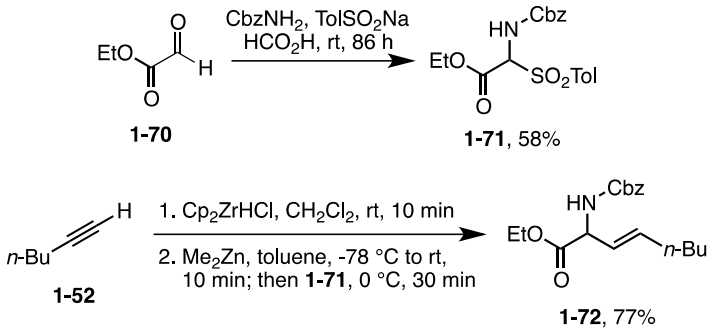
Table 1. Attempted condensation reactions to afford *N*-diphenylphosphinoyl imine **1-69**.



Entry	Conditions	Result[a]
1	$TiCl_4$, DIPEA, rt, 24 h	Prod. not observed
2	Dean-Stark, PTSA, toluene, reflux, 17 h	Prod. not observed
3	$MgSO_4$, PPTS, toluene, reflux, 4 h	Prod. not observed
4	$CuSO_4$, CH_2Cl_2, rt, 23 h	Prod. not observed
5	$Ti(EtO)_4$, THF, reflux, 6 h	Prod. not observed
6	4Å MS, benzene, reflux, 17 h	3:1 mixture of **1-69** and **1-68**

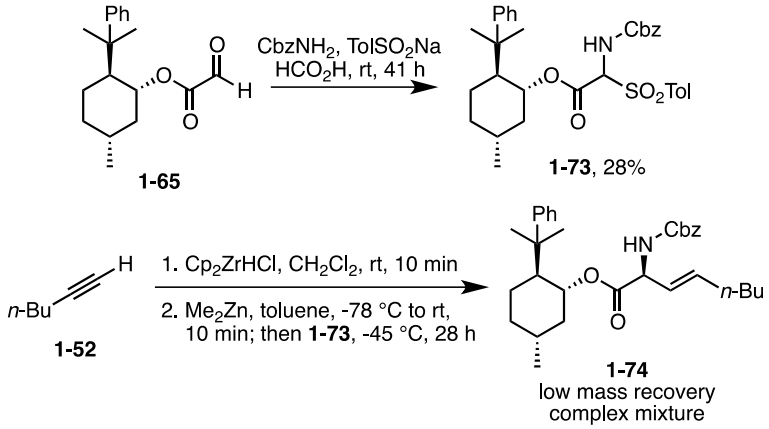
[a]determined by ^{1}H NMR of an aliquot of the reaction mixture monitoring **1-68** δ 9.56 (s) and **1-69** δ 9.20 (d, *J* = 31.5 Hz)

Inspired by work of Charette and coworkers,[66a] we set out to form the sulfinyl adducts of *N*-diphenylphosphinoyl imines, which would provide stable precursors that could undergo *in situ* elimination and formation of the desired imine.[66a, 81] Even more encouraging was that Charette and coworkers subsequently added dialkylzinc reagents to these *in situ* generated imines. Unfortunately, a direct application of their conditions for the preparation of sulfinyl adducts on glyoxylates **1-65**, **1-68**, and **1-70** gave none of the desired compounds. Further literature searching showed that sulfinyl adducts of the *N*-Cbz and *N*-Boc imines (**1-71**) have been synthesized and used as imine precursors.[82] Hydrozirconation of two equivalents of 1-hexyne (**1-52**), solvent swap and transmetalation followed by addition of one equivalent of sulfinyl adduct **1-71** resulted in deprotonation and *in situ* generation of the imine (Scheme 21). The second equivalent of alkenylzinc reagent added to the *in situ* generated acceptor to provide the allylic amide **1-72** in 77% yield.



Scheme 21. Alkenylzinc addition to sulfinyl adduct **1-71** to access allylic amide **1-72**.

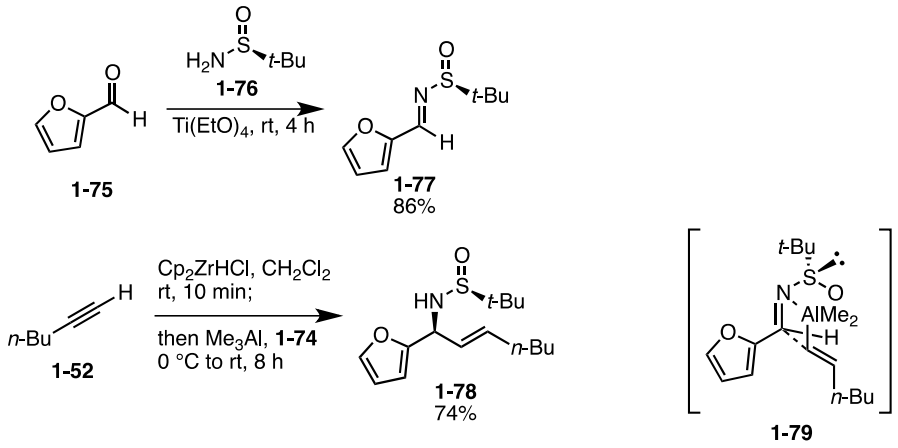
After the promising result obtained with the model system **1-72**, we attempted to apply the analogous approach to glyoxylate **1-65** and perform a diastereoselective addition of alkenylzinc reagent to the *in situ* generated imine from sulfinyl adduct **1-73** (Scheme 22). The addition of two equivalents of alkenyl zinc reagent and *in situ* imine generation followed by addition resulted in a complex mixture and low mass recovery.



Scheme 22. Alkenylzinc addition to sulfinyl aminal **1-73**.

After being met with limited success in the Zr-Zn transmetalation-alkenylzinc addition to imines, we turned our attention towards the Zr-Al transmetalation-alkenylalane addition to chiral

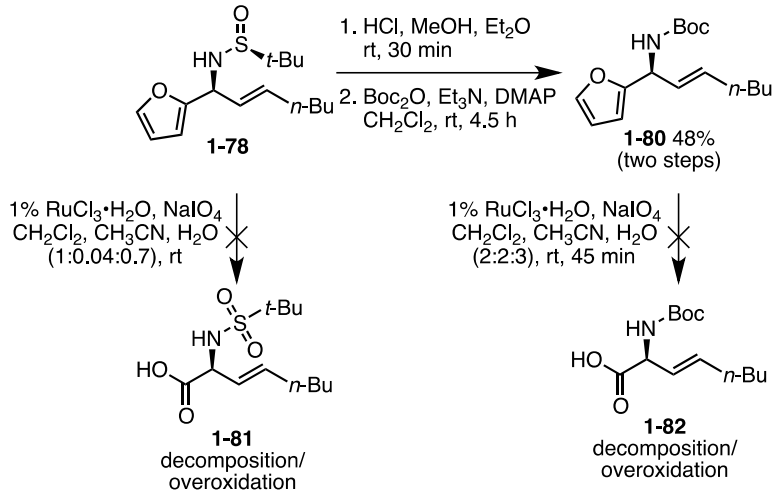
N-tert-butanesulfinylimines developed by Wipf and Pierce.[35e, 83] We had envisioned that the carboxylic acid moiety of α-amino acid fragment **1-35** could be brought in as a furan and later unmasked by oxidation.[84] *N-tert*-butanesulfinylimine **1-77**[85] could be synthesized from 2-furfural (**1-75**) and *S-tert*-butanesulfinamide (**1-76**) in good yield by stirring with titanium(IV) ethoxide (Scheme 23). Hydrozirconation of 1.2 equivalents of 1-hexyne (**1-53**) followed by transmetalation with trimethylaluminum and addition to *N-tert*-butanesulfinylimine **1-77** resulted in the desired allylic amide **1-78** as a single diastereomer (^{1}H NMR), however, the yield was only 45%. Increasing the amount of the alkenylalane to 2.3 equivalents provided **1-78** in 75% yield. In order to decrease the amount of Schwartz reagent and alkyne used, the *N-tert*-butanesulfinylimine **1-77** was pre-complexed with 1.1 equivalents of trimethylaluminum for five minutes at room temperature, before being added to the alkenylalane. This approach resulted in virtually identical yield. The configuration shown in **1-78** is based on the four-membered chelate Felkin-Anh-type transition state model **1-79**.[35b]



Scheme 23. Zr-Al transmetalation-alkenylalane addition to *N-tert*-butanesulfinylimine (**1-77**).

With the desired allylic amide **1-78** in hand, we attempted the unmasking of the furan moiety to give a protected amino acid (Scheme 24). We had realized that selective oxidation of

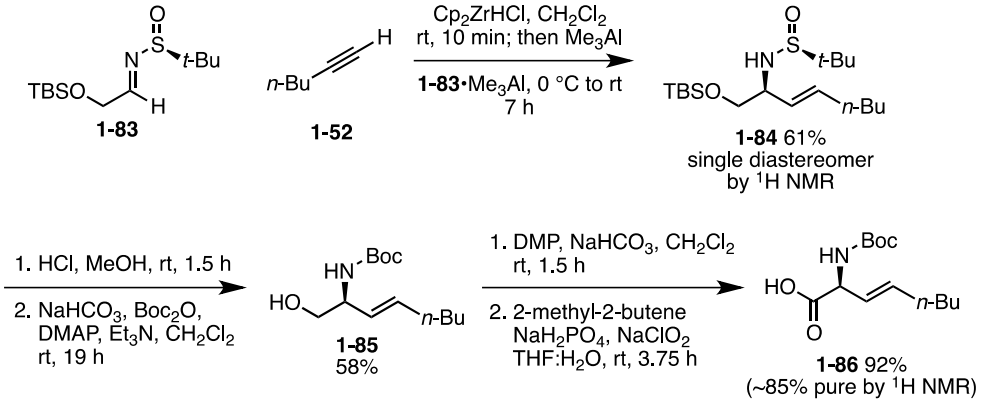
the furan in the presence of the olefin could be challenging. Oxidation under catalytic $RuCl_3$ and stoichiometric $NaIO_4$ conditions did not provide **1-81** but resulted in over oxidation.[84a] The oxidation conditions were also tested on the Boc-protected compound **1-80**, obtained through acid hydrolysis of the *N-tert*-butane sulfinamide and protection using Boc-anhydride. This reaction proceeded more slowly; however, ^{1}H NMR analysis of aliquots from the reaction mixture indicated that the oxidative cleavage of the olefin was occurring before the furan. Presumably, the olefin could have been masked via the protected diol, then the furan could be selectively oxidized and the diol eliminated by a Corey-Winter reaction; however, because this strategy would result in an excessive number of steps for this segment, an alternative imine substrate was investigated.



Scheme 24. Attempted oxidations of furans **1-78** and **1-80** to the corresponding protected α-amino acids.

In a different approach, hydrozirconation of 1-hexyne, transmetalation with trimethylaluminum, and addition to *N-tert*-butane sulfinyl imine **1-83**[86] pre-complexed with trimethylaluminum provided the allylic amide **1-84** in 61% yield as a single diastereomer (^{1}H NMR) (Scheme 25). Simultaneous deprotection of the *tert*-butanesulfinamide and silyl ether

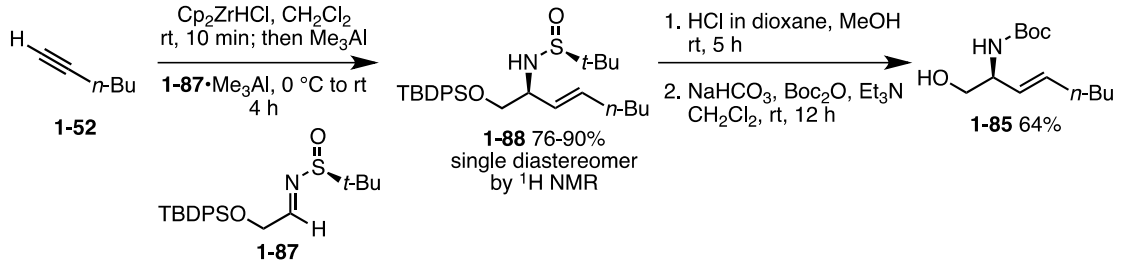
moieties in acidic methanol followed by Boc protection of the crude amine hydrochloride resulted in the *N*-Boc protected amino alcohol **1-85** in 58% yield from *N*-*tert*-butanesulfinamide **1-84**. Pretreating the crude amine hydrochloride with $NaHCO_3$, to neutralize the excess HCl from the deprotection step, was essential to reproducibly obtain the Boc-protected compound. Furthermore, two step conversion of the alcohol to the corresponding carboxylic acid by DMP[87] and Pinnick oxidation[88] provided the crude α-amino acid fragment **1-86** in high yield. The Jones oxidation was also used to oxidize **1-85** to the corresponding α-amino acid **1-86**, but the yield was only 35%. These results provided a proof of concept that the Zr-Al transmetalation methodology could be used to synthesize **1-86**; however, there was still opportunity for improvement in the alkenylalane addition to *N*-*tert*-butanesulfinylimine.



Scheme 25. Alkenylalane addition to *N*-*tert*-butanesulfinyl imine **1-83** and functional group manipulation to provide α-amino acid fragment **1-86**.

After changing the silyl protecting group from TBS to TBDPS, the yield of the alkenylalane addition increased to 76-90% and still resulted in the formation of a single diastereomer, **1-88**, as determined by ^{1}H NMR of the crude reaction mixture (Scheme 26). Furthermore, the silyl ether and *N*-*tert*-butanesulfinamide of **1-88** could be deprotected

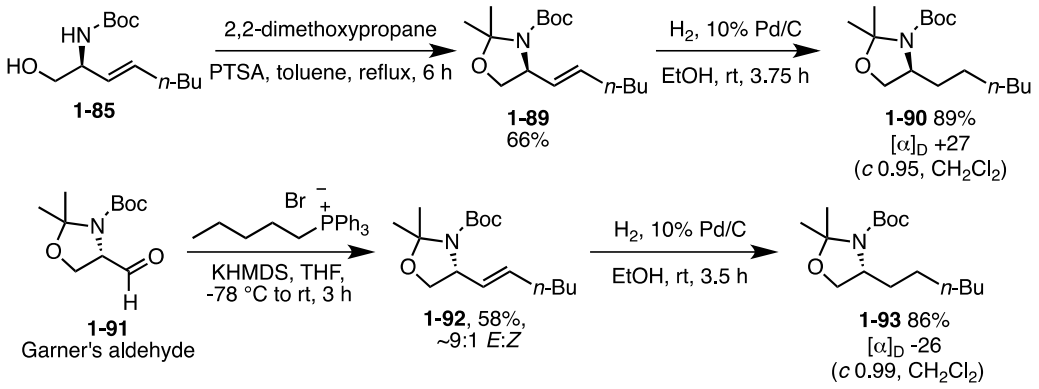
simultaneously resulting in the crude amine hydrochloride. The amine was protected and the *N*-Boc amino alcohol **1-85** was isolated in 64% yield over the two steps. Similar amino alcohols have been prepared by aminopalladation of trichloroacetimidates[89] and Wittig reactions on α-amino aldehydes.[90]



Scheme 26. Alkenylalane addition to *N*-*tert*-butansulfinylimine **1-87** and subsequent protective group switch to give *N*-Boc amino alcohol **1-85**.

At this point, it was considered necessary to support the stereochemical assignment from the alkenylalane addition to *N*-*tert*-butanesulfinylimines **1-83** and **1-87**, since the substrate is significantly different than the usual alkyl or aryl sulfinylimines previously investigated in the Wipf group. We thought that *N*-Boc amino alcohol **1-85** could be converted to a derivative of Garner's aldehyde **1-90** (Scheme 27). The *N*-Boc protected amino alcohol **1-85** was protected as the acetonide **1-89** and subsequent reduction of the olefin resulted in alkane **1-90**. For comparison, commercially available Garner's aldehyde was homologated by a Wittig reaction,[91] providing **1-92** as mixture of (*E*)- and (*Z*)-olefin isomers, which were reduced to arrive at **1-93**. All spectroscopic data for **1-90** and **1-93** were identical; however, their optical rotations were of equal value and opposite sign, thus supporting the initial stereochemical assignment based on the four-membered chelate model.[35b] Attempts to separate **1-90** and **1-93** by chiral SFC and chiral HPLC to determine the *er* of **1-90** were unsuccessful. With the α-amino acid fragment **1-86** in

hand, we set out to continue our synthetic efforts towards syringolin A by synthesizing the valine-derived α,β-unsaturated-γ-amino acid fragment **1-35**.

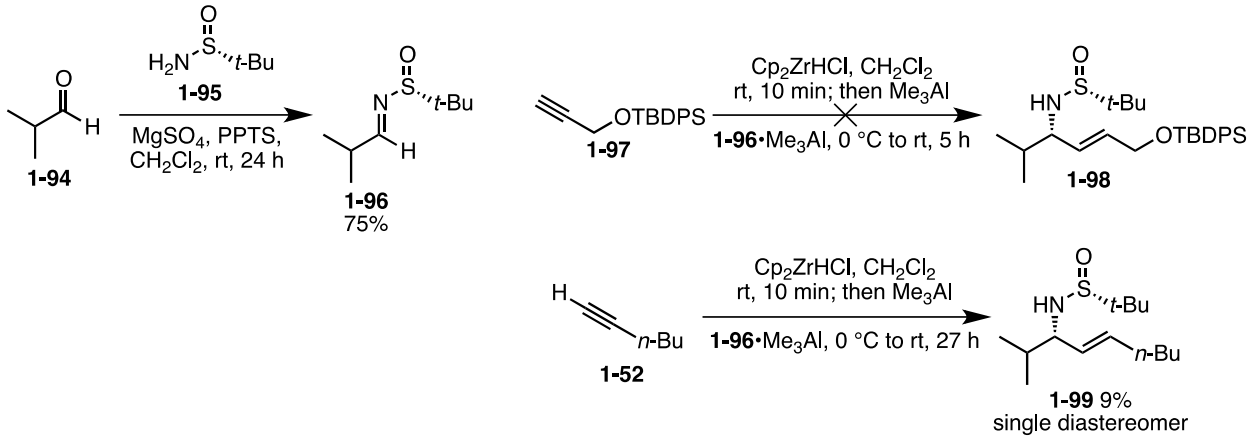


Scheme 27. Synthesis of **1-90** and **1-93** to support the stereochemical assignment of *N*-Boc amino alcohol **1-85**.

1.2.2 Synthesis of α,β-Unsaturated-γ-Amino Acid Fragment 1-35

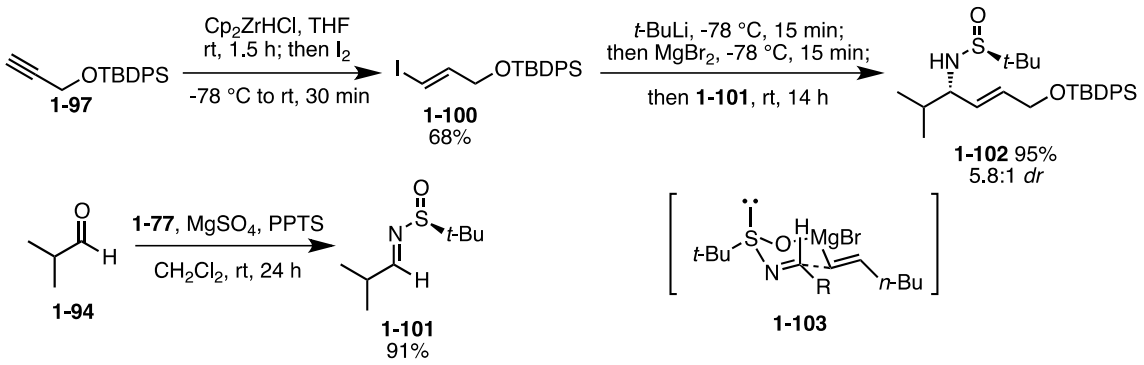
Encouraged by the high yield and high diastereocontrol of the alkenylalane addition to *N-tert*-butansulfinylimine **1-88** in the synthesis of the α-amino acid fragment **1-86**, we had hoped to apply the same approach for the synthesis of the α,β-unsaturated-γ-amino acid **1-35**, the second fragment of the dipeptide macrolactam core of syringolin A. The synthesis of *N-tert*-butane sulfinylimine **1-96** proceeded smoothly;[92] however, hydrozirconation of alkyne **1-97**, transmetalation with trimethylaluminum, and addition to the imine pre-complexed with trimethylaluminum showed no product **1-98** after 5 h (Scheme 28). A model reaction with 1-hexyne was allowed to proceed for 27 h, after which time it resulted in only 9% of the desired product. These results were quite unexpected based on the success of the methodology in the synthesis of jp4_039 (**1-63**) shown in Scheme 18. The major difference between the two

substrates is the lack of a methylene group in **1-96** compared to **1-60**, which perhaps creates enough steric bulk to block the alkenylalane-zirconium metal complex from performing the addition. Alkenylzinc additions to the corresponding sulfinyl adducts of *N*-diphenylphosphinoylimines were also attempted, but met with little success.



Scheme 28. Alkenylalane additions to *N-tert*-butanesulfinylimine **1-96**.

At this point, we foresaw the possibility to expand the substrate scope of the methodology developed by Ellman and coworkers in which vinyl Grignard reagents are added diastereoselectively to *N-tert*-butansulfinylimines to arrive at allylic amides with predictable stereochemistry following the six-membered chelate transition state model **1-103** (Scheme 29).[84b, 93] Thus, the opposite *N-tert*-butanesulfinyl imine enantiomer **1-101** had to be prepared. Preparation of the requisite vinyl iodide **1-100** was achieved by hydrozirconation of alkyne **1-97**[94] and quenching with iodine.[95] With vinyl iodide **1-100** in hand, lithium-halogen exchange followed by transmetalation to magnesium and addition to *N-tert*-butanesulfinylimine **1-101** provided the desired allylic *N-tert*-butanesulfinamide **1-102** as a mixture of diastereomers in 95% yield. Fortunately, these diastereomers were easily separable by chromatography on SiO_2.

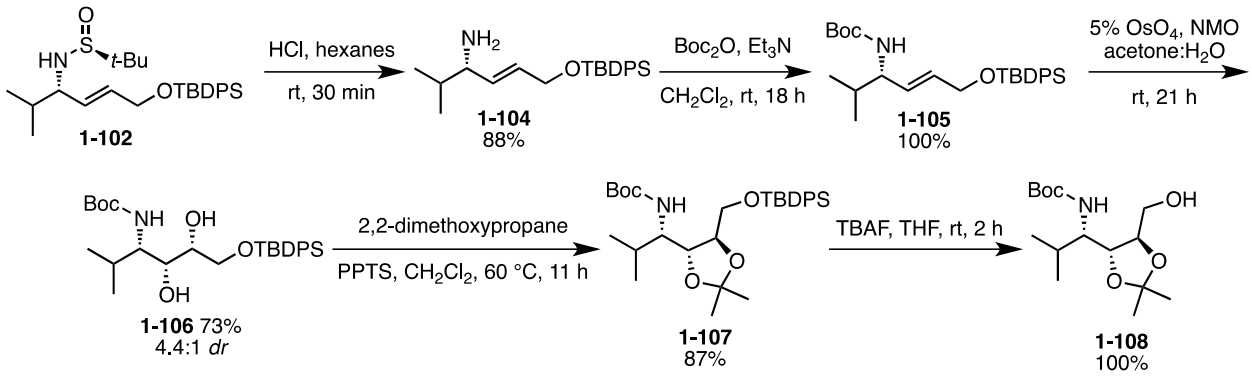


Scheme 29. Grignard reagent formation from vinyl iodide **1-100** followed by addition to *N*-*tert*-butanesulfinylimine **1-101** to produce *N*-*tert*-butansulfinamide **1-102** via six-membered chelate transition state model **1-103**.

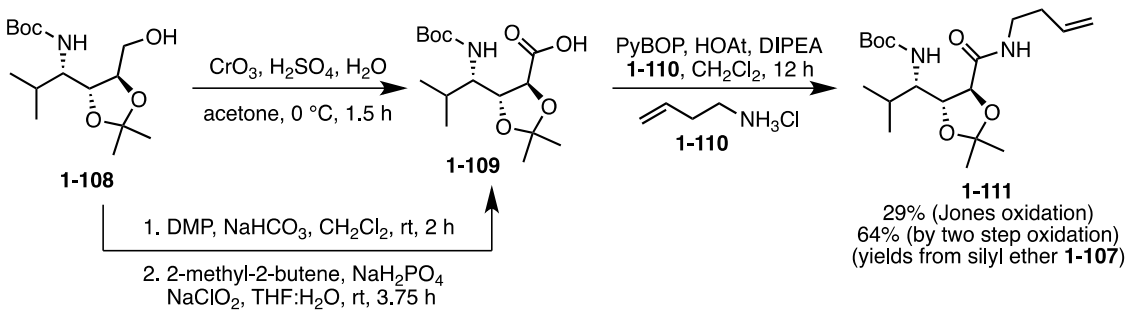
With *N*-*tert*-butanesulfinamide **1-102** in hand, deprotection in acidic hexanes allowed for the selective removal of the sulfinamide in the presence of the silyl ether and afforded the amine hydrochloride **1-104** as a colorless solid (Scheme 30). *N*-Boc protection of the amine went smoothly, followed by diastereoselective dihydroxylation of **1-105** to provide diol **1-106** as a 4.4:1 mixture of diastereomers that were conveniently separable by chromatography on SiO_2. In *N*-Boc amide **1-105**, the conformation minimizing $A^{1,3}$-strain has the *iso*-propyl group shielding the top face of the olefin, inducing high a *dr* for the diol **1-106** *syn* to the *N*-Boc amide. Protection of the diol as the acetonide **1-107** and subsequent cleavage of the silyl ether provided alcohol **1-108** in 87% yield over two steps.

Initially, the Jones oxidation and coupling of amine **1-110** using PyBOP and HOAt provided the desired coupling product **1-111** in 29% yield from silyl ether **1-107** (Scheme 31). However, application of a two step oxidation of the alcohol to the corresponding carboxylic acid by DMP[87] and Pinnick oxidation[88] followed by the same PyBOP conditions provided terminal

olefin **1-111** in a much improved 64% yield over the four steps. At this point, our route intersects with the previous synthesis of syringolin A by Kaiser and coworkers.[26]

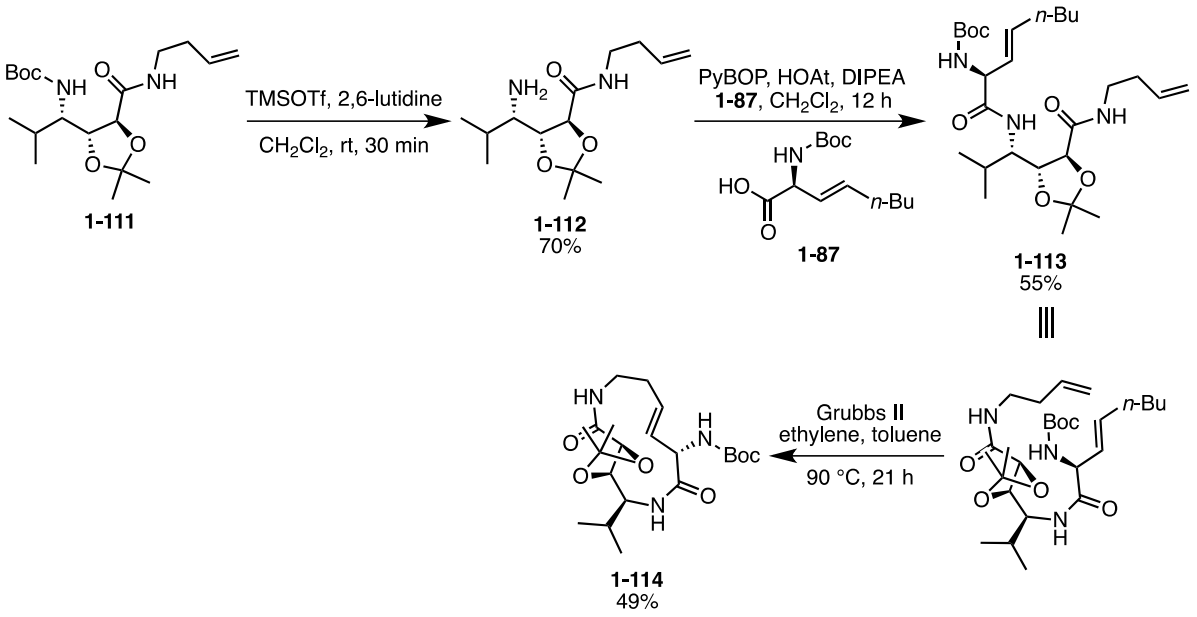


Scheme 30. Preparation of alcohol **1-108** from sulfinamide **1-102**.



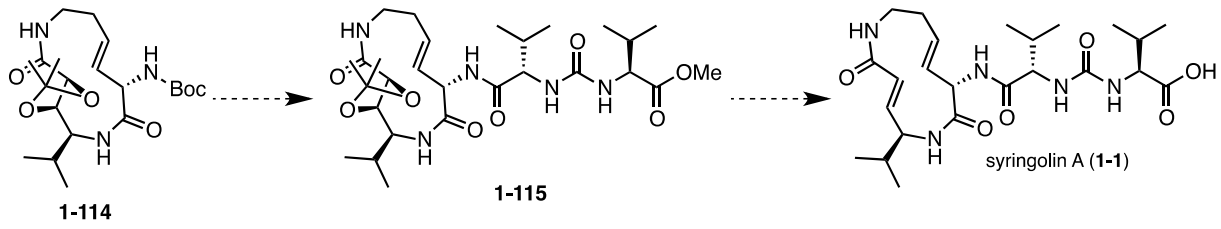
Scheme 31. Oxidation of alcohol **1-108** to the acid and coupling to provide terminal olefin **1-111**.

Mild deprotection of **1-111** with TMSOTf and 2,6-lutidine gave amine **1-112**, which was coupled with the *N*-Boc amino acid **1-88** in moderate yield (Scheme 32). RCM using modified conditions compared to those described by Kaiser and coworkers provided the 12-membered core **1-114** in comparable yield, successfully completing the formal synthesis of syringolin A. The spectral data obtained for carbamate **1-111** and the protected core **1-114** are consistent with the data published for the common intermediates in the synthesis by Kaiser and coworkers.[26]



Scheme 32. Synthesis of RCM precursor **1-113** and subsequent RCM to arrive at the protected core of syringolin A **1-114**.

In order to complete the total synthesis of syringolin A (**1-1**), deprotection of **1-114** and coupling of the valine-urea-valine fragment would provide intermediate **1-115** (Scheme 33). Hydrolysis of the acetonide, thiocarbonate formation, and subsequent Corey-Winter reaction, followed by methyl ester cleavage will provide syringolin A (**1-1**).



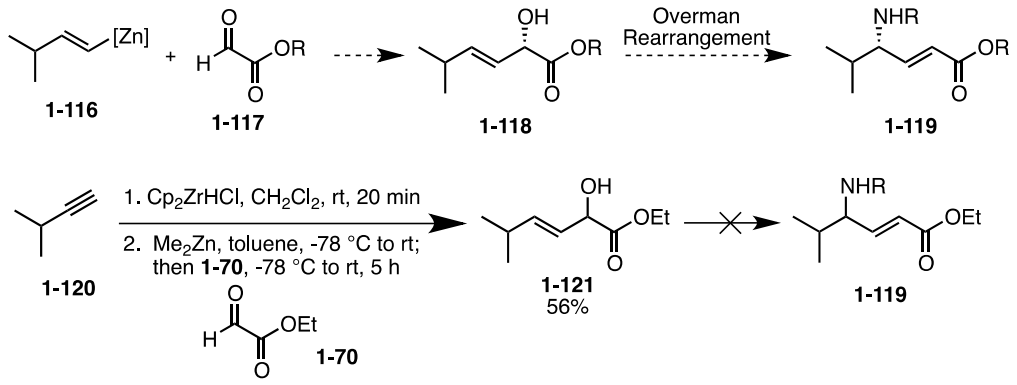
Scheme 33. Steps to complete the total synthesis of syringolin A (**1-1**).

The synthesis of macrocycle **1-111** was accomplished in 14 steps (longest linear sequence) from propargyl alcohol. Following the route described by Kaiser and coworkers[26, 31] from the macrocyclic core **1-111** to syringolin A (**1-1**) would provide the natural product in 20 steps. These routes to syringolin A are significantly longer than the 13 step synthesis performed

by Stephenson and Dai[29] in 3.5% overall yield and the 10 step synthesis executed by Pirrung and coworkers in 22% overall yield.[28] The routes used by Kaiser, Stephenson, and Pirrung rely on the chiral pool for the preparation of the amino acid fragments. While our approach is longer in comparison to the other reported syntheses, we successfully demonstrated the application of stereoselective additions of alkenylorganometallic reagents to *N*-*tert*-butanesulfinylimine, and this methodology provided enantiomerically pure α-amino acids and α,β-unsaturated-γ-amino acids in a manner not dependent on the chiral pool. In addition, our approach is amenable to the preparation of syringolin A analogues by using different aldehyde or alkyne starting materials.

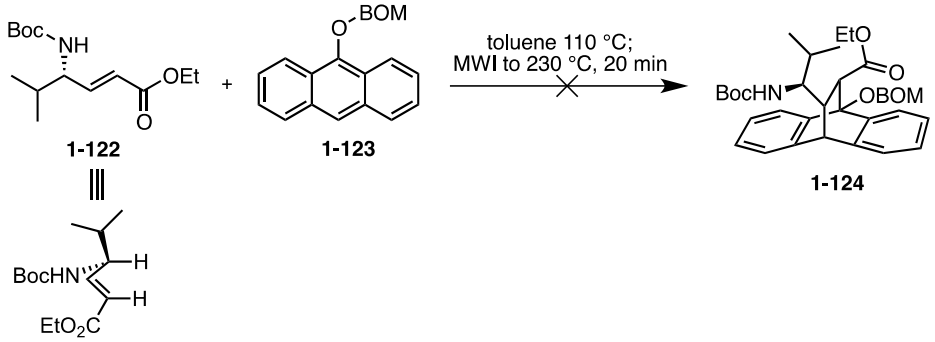
1.2.3 Attempts to Streamline the Synthesis of Syringolin A

After competing the formal total synthesis of syringolin A, we became interested in improving the efficiency of our current route. Upon retrospective analysis of our synthesis we realized that the synthesis of the α,β-unsaturated amino acid fragment, particularly the masking/unmasking strategy of the double bond, could be improved. We envisioned that a stereoselective alkenylzinc addition to glyoxylate **1-67** followed by an Overman rearrangement[96] would rapidly provide the desired α,β-unsaturated-γ-amino acid fragment **1-116** (Scheme 34). Preparation of racemic alcohol **1-118** was accomplished by hydrozirconation of alkyne **1-117**, transmetalation to zinc, and addition to ethyl glyoxylate **1-67**. Unfortunately, attempts to reach the amino acid fragment **1-116** using this strategy failed, presumably due to the steric bulk of the *iso*-propyl group.



Scheme 34. Proposed and attempted strategy to the α,β-unsaturated-γ-amino acid fragment **1-119**.

We also envisioned that masking the olefin **1-122** by a Diels-Alder/retro-Diels-Alder pathway[97] would reduce the number of steps used to mask the olefin in the current approach. Attempts to obtain the Diels-Alder adduct **1-124** from the cycloaddition reaction between α,β-unsaturated amino acid **1-122** and anthracene **1-123** were not met with success. The lack of reactivity between **1-122** and **1-123** could be due to steric interactions. In the $A^{1,3}$-minimized conformation, the olefin is sterically shielded on both faces by the *iso*-propyl group and the *tert*-butyl carbamate.



Scheme 35. Attempted Diels-Alder cycloaddition between **1-122** and **1-123** as an olefin masking strategy.

1.2.4 Work Towards a Cyclopropane Analogue of Syringolin A

In addition to streamlining the synthesis, we were also interested in investigating the synthesis of cyclopropane derivatives (**1-125** and **1-126**) of syringolin A (Figure 7). Cyclopropanes have been shown to function as geometric and electronic bioisosteres for (*E*)-alkenes, but unlike (*E*)-alkenes, they do not suffer from possible isomerization or oxidation pathways.[98] They are also less susceptible to Michael addition and unspecific alkylation processes. We envisioned that the cyclopropane analog could function as a more selective proteasome inhibitor and be less susceptible to degradation and off-target interactions, thereby limiting side effects. In addition, the biological activity may increase due to the release of ring strain upon covalent binding via a cyclopropane opening. Computational investigation of the core structures of syringolin A (**1-1**) and the cyclopropane analogs **1-125** and **1-126** revealed that the structures are nearly superimposable (Figure 8). The global minimum of the core structure of cyclopropane analog **1-125** contains two (*E*)-amide configurations causing the backbone to deviate from the other core structures.

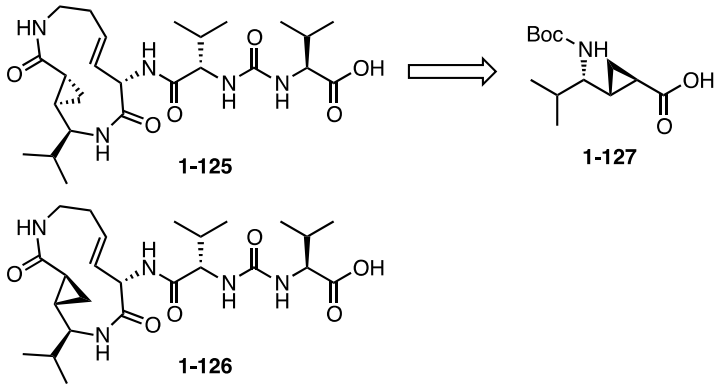


Figure 7. Cyclopropane analogs **1-125** and **1-126** of syringolin A (**1-1**) and precursor α,β-cyclopropane-γ-amino acid **1-127**.

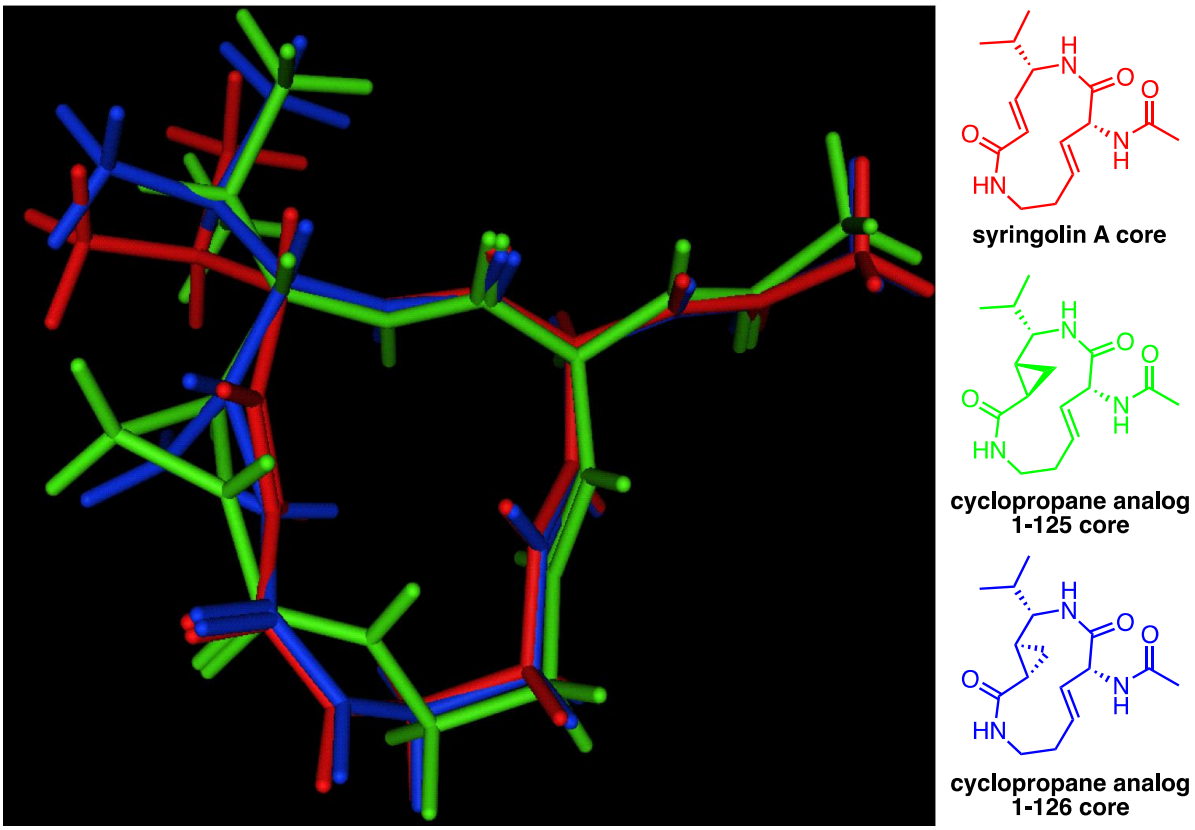
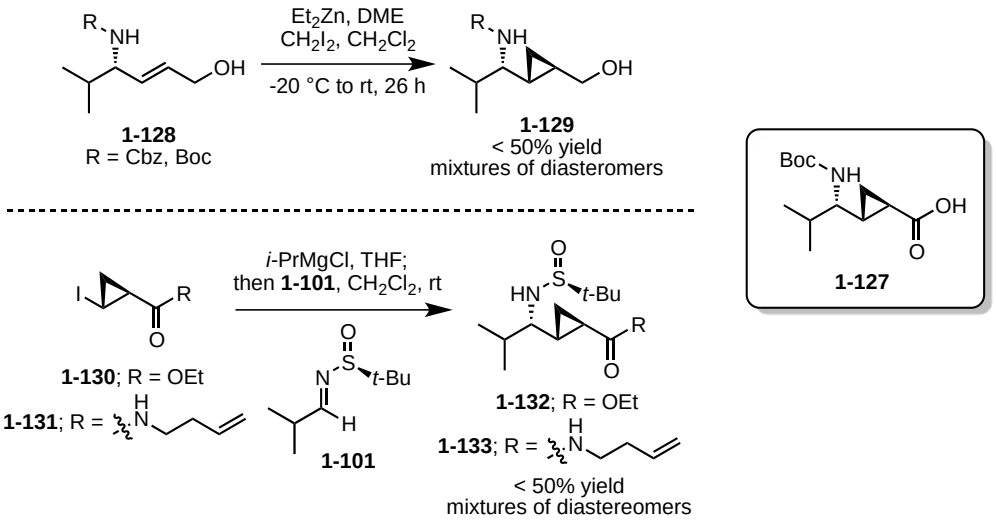


Figure 8. Superimposed structures of the core of syringolin A (**1-1**) and the core of cyclopropane analogs **1-125** and **1-126** in red, green, and blue respectively.*

Attempts to apply the addition of alkenylzinc reagents to *N*-diphenylphosphinoylimines and subsequent Simmons-Smith cyclopropanation[35a, 35c, d, 99] were plagued with low yields and diastereoselectivities. Unfortunately, attempts to prepare the cyclopropane containing building block **1-127** by a Simmons-Smith cyclopropanation of allylic alcohols **1-128** gave yields of less than 50% and poor diastereoselectivity (Scheme 36). We believe the low yield is a result of the steric hindrance around the olefin, as described previously (Scheme 35). A different approach using the addition of cyclopropyl magnesium bromides, derived from the corresponding

* Figure 8 was prepared using Molecular Operating Environment (MOE; Chemical Computing Group). The global minima shown were obtained using a stochastic conformer search with an MMFF94x force field, while fixing double bond geometry and allowing amide bond rotation.

iodocyclopropanes **1-130** and **1-131**, to *tert*-butanesulfinyl imine **1-101** also suffered from low yields and diastereoselectivities (Scheme 36). Due to the low yields and mixtures of diastereomers, this approach was abandoned.



Scheme 36. Attempts towards the synthesis of cyclopropane **1-127**.

1.2.5 Conclusion

The successful application of the Zr-Al transmetalation followed by the alkenylalane addition to *N*-*tert*-butanesulfinylimines provided a facile access to the α-amino acid fragment **1-86**. Methodology developed by Ellman and co-workers utilizing vinyl Grignard additions to *N*-*tert*-butanesulfinylimines proved useful for the synthesis of the α,β-unsaturated-γ-amino acid **1-109**. We were able to complete the formal synthesis of syringolin A (**1-1**) by synthesizing macrolactam **1-114** in a longest linear sequence of 14 steps (4.1% yield), compared to 10 steps (15% yield) obtained by Kaiser and coworkers.[26] Attempts to shorten our approach by incorporating an Overman rearrangement or an alternative olefin protecting group strategy were

unsuccessful. The preparation of fragment **1-127** for the synthesis of the cyclopropane derivative of syringolin A (**1-125**) suffered from low yields and diastereoselectivties. In our formal synthesis of syringolin A, we have demonstrated the addition of alkenylorganometallic reagents to *N-tert*-butanesulfinylimines to provide rapid access to non-proteinogenic amino acids similar to α,β-unsaturated-γ-amino acid **1-34** and α-amino acid **1-35** with complete stereochemical control.

2.0 SYNTHESIS AND SELECTIVE FUNCTIONALIZATION OF A HETEROCYCLIC THIADIAZINE SCAFFOLD

2.1 INTRODUCTION

2.1.1 Biological Importance of Sulfamide Containing Heterocycles

Sulfamide containing heterocycles are attractive synthetic targets[100] and have been shown to exhibit a wide variety of biological activities (Figure 9). These activities include anti-bacterial (**2-1**, **2-2**),[101] colony stimulating factor-1 inhibition (CSF-1, implied in rheumatoid arthritis and metastatic bone cancer, **2-3**),[102] opioid receptor-like 1 receptor inhibition (nociception receptor, NOP, **2-4**),[103] and 11β-HSD1 inhibition (a target for type 2 diabetes, **2-5**).[104] A subclass of sulfamide containing heterocycles, 1,2,6-thiadiazine 1,1-dioxides (Figure 10), have been shown to act as cannabinoid agonists and antagonists (**2-6**),[105] exhibit modest antimicrobial activity (**2-7**),[106] and display smooth muscle relaxation in rats and guinea pigs (**2-8** and **2-9**).[107] The structurally related 2,1,3-benzothiadiazine-2,2-dioxides have demonstrated herbicidal activity (commercial pesticide bentazon, **2-10**) and sedative effects.[108] In addition to the varied biological activity, the sulfamide unit has also been shown to function as a urea bioisostere in which the tetrahedral nature of the sulfamide can increase receptor recognition.[109]

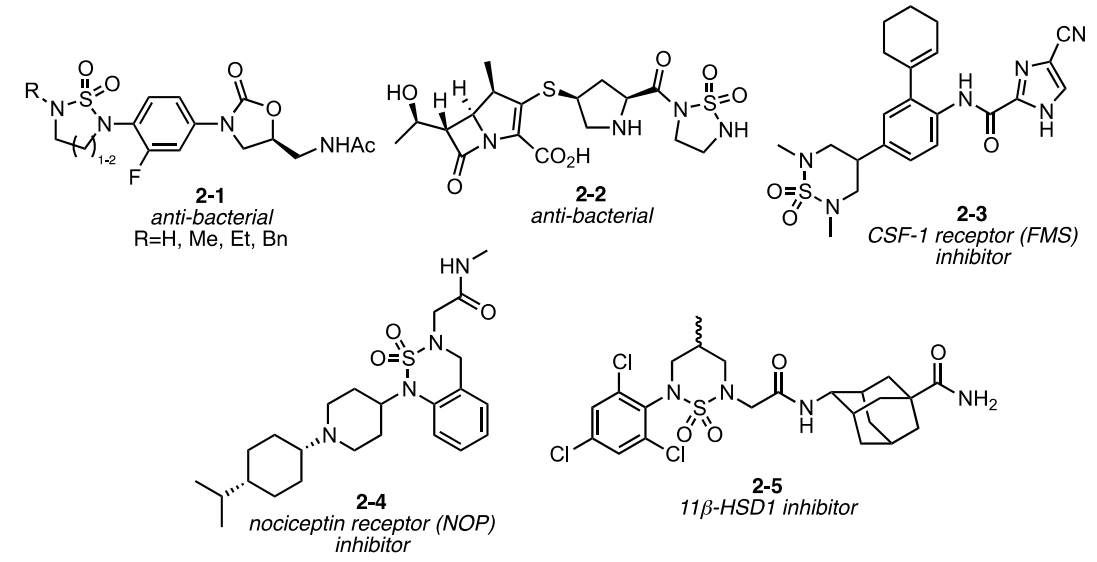


Figure 9. Examples of biologically active sulfamide containing molecules.

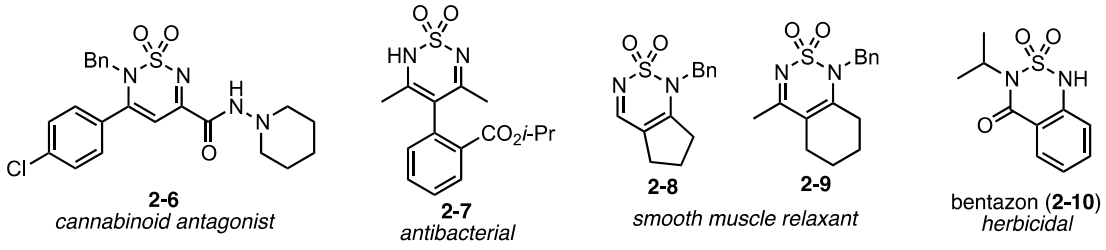
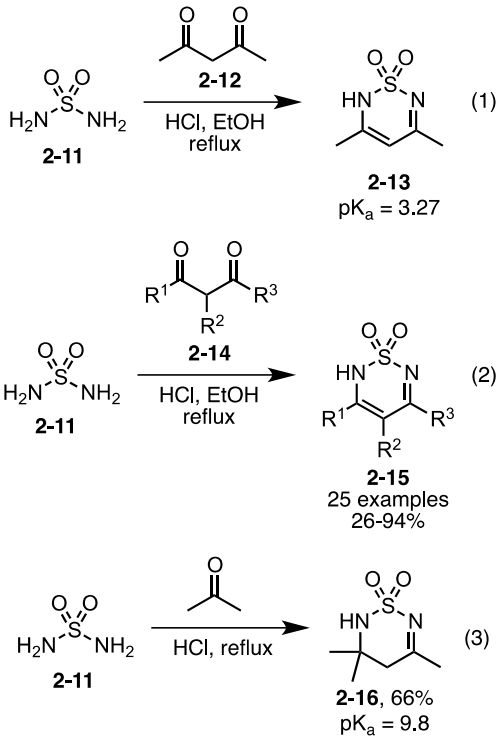


Figure 10. Examples of biologically active thiadiazine containing molecules.

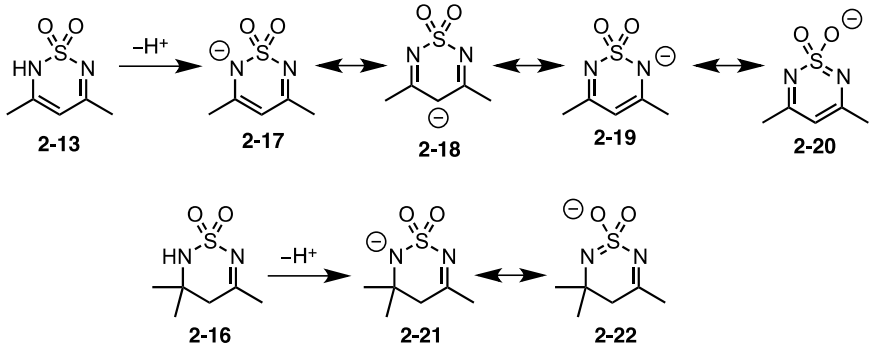
2.1.2 Methods for the Synthesis of Thiadiazines

The preparation of a 1,2,6-thiadiazine 1,1-dioxide (**2-13**) was first demonstrated in 1952, by Degering and Wilson. Sulfamide **2-11** was condensed with pentanedione **2-12** in the presence of catalytic hydrogen chloride (Scheme 37, Equation 1).[110] In order to expand upon the initial substrate scope of Degering and Wilson, Wright investigated the condensations of sulfamide **2-11** with β-diketones **2-14** to give thiadiazines **2-15** (Scheme 37, Equation 2).[111] At the same time, Moeller and Ouchi explored the preparation of thiadiazine **2-16** from sulfamide **2-11** and

monoketones (Scheme 37, Equation 3).[112] It is interesting to note that thiadiazine **2-13** is acidic (pK_a = 3.27) compared to **2-16** (pK_a= 9.8), which can be explained by the stability of the diazapentadienyl anion (Scheme 38).

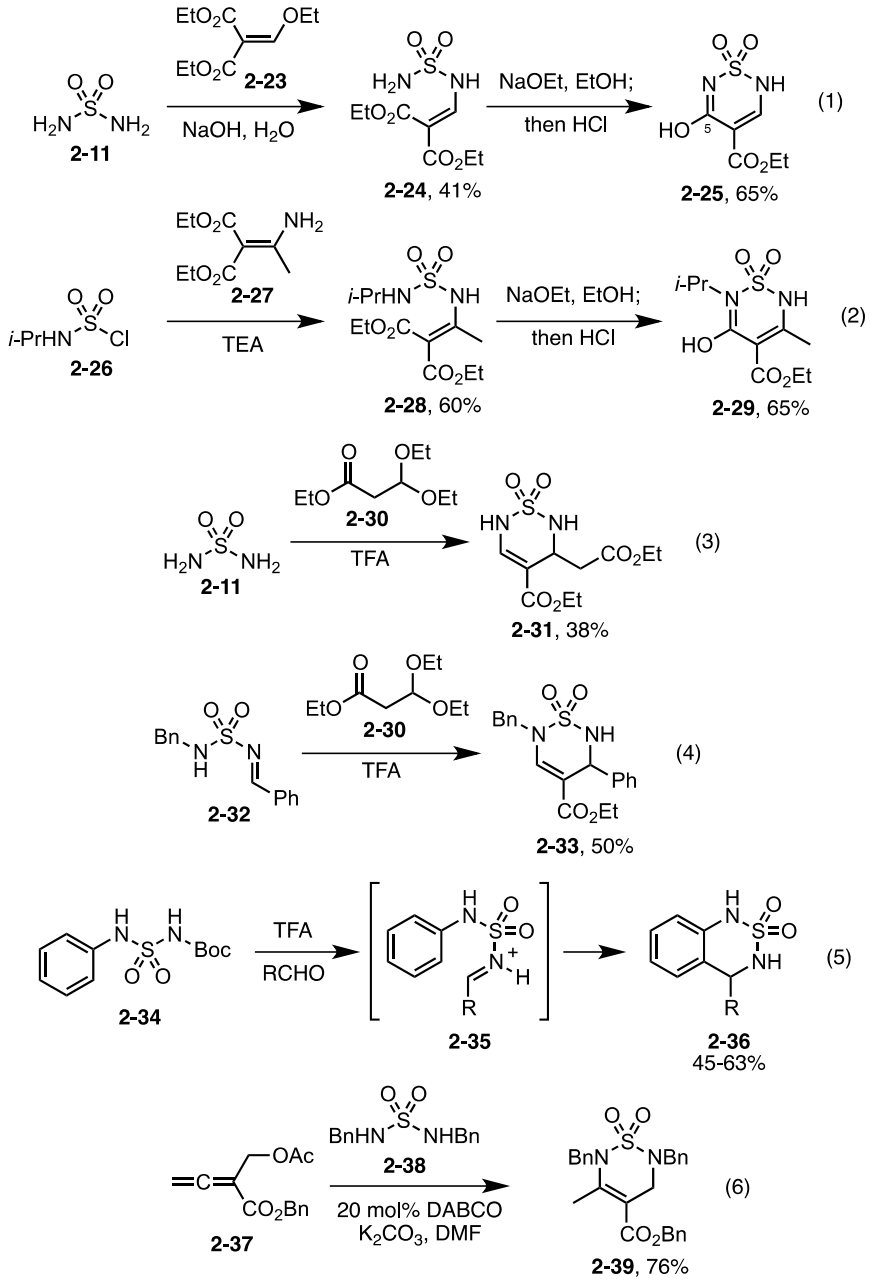


Scheme 37. Preparation of thiadiazines **2-13**, **2-15**, and **2-16**.



Scheme 38. Deprotonation of thiadiazines **2-13** and **2-16** and resonance structures of the conjugate bases.

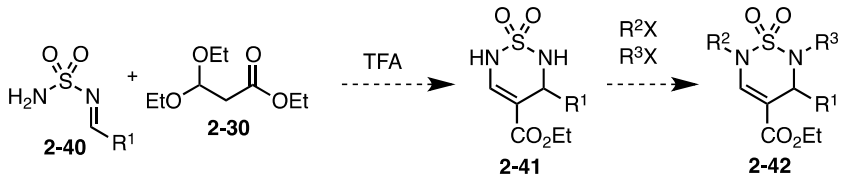
Building upon the initial reports, a number of methods have been developed to prepare functionalized thiadiazines. Access to the C-5 hydroxy thiadiazine **2-25** has been achieved by a base-mediated condensation of sulfamide **2-11** and ethoxy methylene **2-23**, followed by an intramolecular cyclization of sulfaminomethylene **2-24** (Scheme 39, Equation 1).[113] Using a modified strategy, a 6-*N*-alkylated thiadiazine **2-29** was prepared from a monoalkylated sulfamoyl chloride **2-26** and amino methylene **2-27** (Scheme 39, Equation 2).[114] Lee and Kohn generated thiadiazine **2-31** by treatment of sulfamide (**2-11**) and 3,3-diethoxypropane (**2-30**) with TFA (Scheme 39, Equation 3).[115] A variation of this approach by the same group used sulfamide imines **2-32**, prepared from sulfamide and the corresponding aldehyde, and acetal **2-30** to arrive at thiadiazine **2-33** (Scheme 39, Equation 4).[116] Recently, Kang and coworkers developed an intramolecular Friedel-Crafts acylation of sulfamide iminium species **2-35** to assemble benzo-fused thiadiazines **2-36** (Scheme 39, Equation 5).[117] In 2010, Tong and co-workers prepared *N*-benzylated thiadiazine **2-39** using a unique approach by joining substituted sulfamide **2-38** and allene **2-37** in the presence of catalytic DABCO (Scheme 39, Equation 6).[118]



Scheme 39. Methods for the synthesis of functionalized thiadiazines.

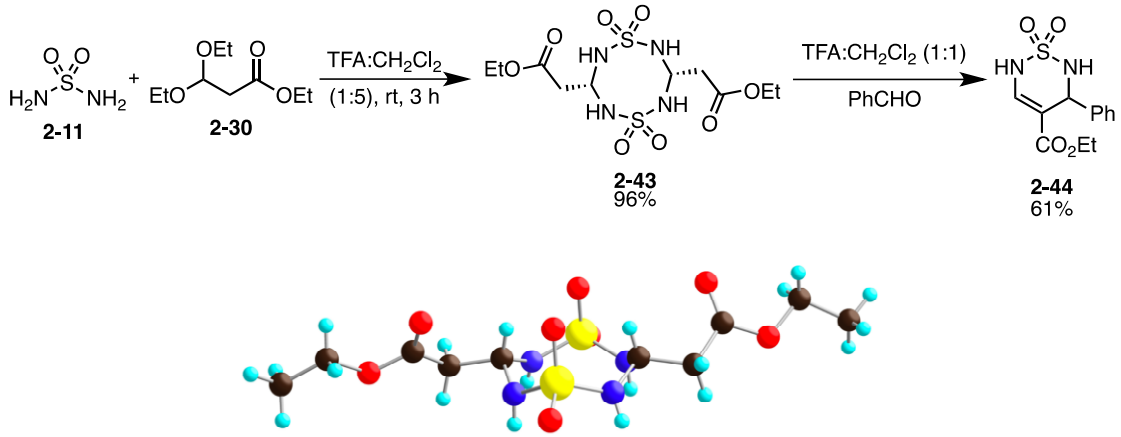
2.1.3 Wipf Group Methodology for Thiadiazine Preparation and Functionalization

As a part of our group's ongoing interest in heterocyclic compounds, Wipf and coworkers found 1,2,6-thiadiazine 1,1-dioxides to be interesting structures wherein the core heterocycle could be synthesized and functionalized utilizing a streamlined synthetic strategy outlined in Scheme 40. They envisioned that various thiadiazines **2-41** would be prepared from sulfamide imine **2-40** using conditions reported in the literature.[115-116] Thiadiazines **2-41** would then be selectively *N*-alkylated to give substituted thiadiazines **2-42**.[119] Unfortunately, initial attempts to access **2-41** in TFA required long reaction times and gave inconsistent yields.[120]



Scheme 40. Initial synthetic strategy to access functionalized thiadiazines **2-42**.

Access to alkylated thiadiazine **3-42** hinged on the successful and reliable preparation of the thiadiazine core **2-41**. After considerable experimentation, it was found that condensation of commercially available sulfamide **2-11** and **2-30** resulted in the formation of a stable 8-membered ring dimer, **2-43** (Scheme 41).[113, 121] Similar 8-membered sulfamide dimers have been reported.[122] The structure of **2-43** was confirmed by X-ray analysis.[123] Subsequent condensation of **2-43** with benzaldehyde in TFA:CH_2Cl_2 (1:1) provided the desired thiadiazine **2-44** in 61% yield.[121]

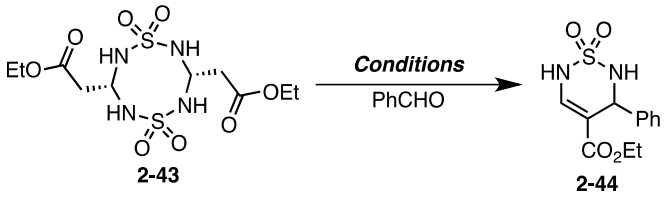


Scheme 41. Synthesis of thiadiazine **2-44** and X-ray structure of **2-43**.

After their initial success with the formation of thiadiazines in TFA:CH_2Cl_2 (1:1), an investigation began to find alternative acidic conditions that were milder and would provide **2-44** in a higher yield. Polyphosphate ester (PPE),[124] BF_3•Et_2O, triflamide, methanesulfonic acid, and TFA:CH_2Cl_2 (1:5) yielded thiadiazine **2-44** in lower or comparable yields (Table 2, Entry 2-6).[121] The amount of TFA could be reduced to 10 equivalents with no decrease in yield observed (Table 2, Entry 7).[123]

With a general method for thiadiazine formation conditions identified by Wipf and coworkers, the scope of compatible aldehydes was investigated. Alkyl (Table 3, Entry 1-2), electron deficient (Table 3, Entry 3-6), and electron rich (Table 3, Entry 7-8) aryl aldehydes were tolerated.[121] Heterocyclic thiophene-3-carboxaldeyde provided **2-53** in modest yield (Table 3, Entry 9); however, other heterocyclic aldehydes (furans, quinolines, and pyridines) resulted in formation of complex mixtures.

Table 2. Optimization of thiadiazine **2-44** formation.

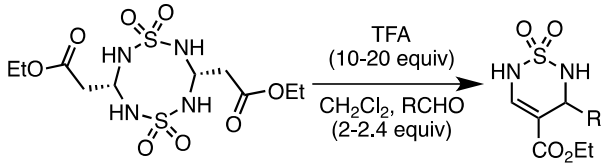


2-43 **2-44**

Entry	Conditions	Yield (%)[a]
1	TFA:CH_2Cl_2 (1:1), rt, 30 min	61
2	PPE, THF, reflux, 40 min	45
3	BF_3•OEt_2 (2 equiv), CH_2Cl_2, rt, 6 h	65
4	10% Tf_2NH, CH_2Cl_2, rt, 2.5 h	42
5	$MeSO_3H$ (5.7 equiv), CH_2Cl_2, 0 °C, 40 min	39
6	TFA:CH_2Cl_2 (1:5), rt, 3 h	61
7	TFA (10 equiv), CH_2Cl_2, rt, 60 h	59

[a]isolated yield after SiO_2 chromatography

Table 3. Substrate scope of thiadiazine formation.

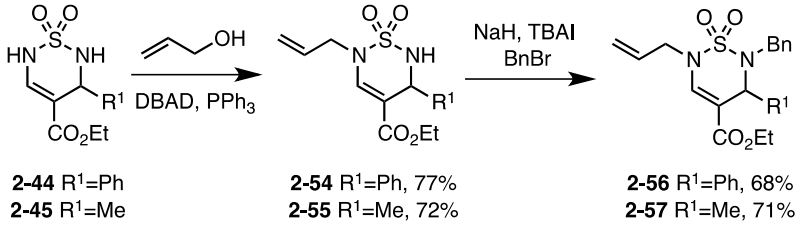


2-43 **2-45 - 2-53**

Entry	R	Product	Yield (%)[a]
1	Me	**2-45**	59
2	Et	**2-46**	56
3	4-CNC_6H_4	**2-47**	41
4	4-$CO_2MeC_6H_4$	**2-48**	57
5	4-$CF_3C_6H_4$	**2-49**	65
6	2-BrC_6H_4	**2-50**	45
7	4-$OAcC_6H_4$	**2-51**	48
8	3-$OMeC_6H_4$	**2-52**	62
9	3-thiophene	**2-53**	30

[a]isolated yield after SiO_2 chromatography

In order to complete the strategy to prepare functionalized thiadiazines, Wipf and coworkers explored the possibility of regioselective and sequential *N*-alkylation of the two sulfamide nitrogens by exploiting their inherent difference in acidity (sulfamide vs. vinylogous carbamate and sulfamide). Thiadiazines **2-44** and **2-45** were subjected to NaH followed by allyl iodide, which led to a mixture of mono- and di-alkylated products;[120] however, treatment of thiadiazines **2-44** and **2-45** with allyl alcohol under Mitsunobu[125] conditions using DBAD gave selective 6-*N*-mono-alkylation in good yields to provide **2-54** and **2-55** (Scheme 42).[121] The regiochemistry was determined by NOESY correlation between the methylene hydrogens of the allyl group and the hydrogen of the thiadiazine alkene. A second alkylation at *N*-2 was achieved using NaH, TBAI, and benzyl bromide to yield compounds **2-56** and **2-57** (Scheme 42). Alternatively, the *N*-2 alkylation was accomplished using alkyl halides and K_2CO_3.



Scheme 42. Mono- and di-alkylation of thiadiazines.

Using the strategy described above, Wipf and coworkers prepared an 87-membered library of functionalized thiadiazines that were submitted to the Molecular Libraries Small Molecule Repository (MLSMR). The library (UPCMLD24A) was tested in approximately 230 assays. Several compounds exhibited ~10 μM activity for DNA rereplication in normal MCF10A breast cells (implicated as an anti-cancer therapy)[126] and glucagon-like peptide-1

receptor inverse agonist activity (a potential target for diabetes and neurodegenerative disease).[127]

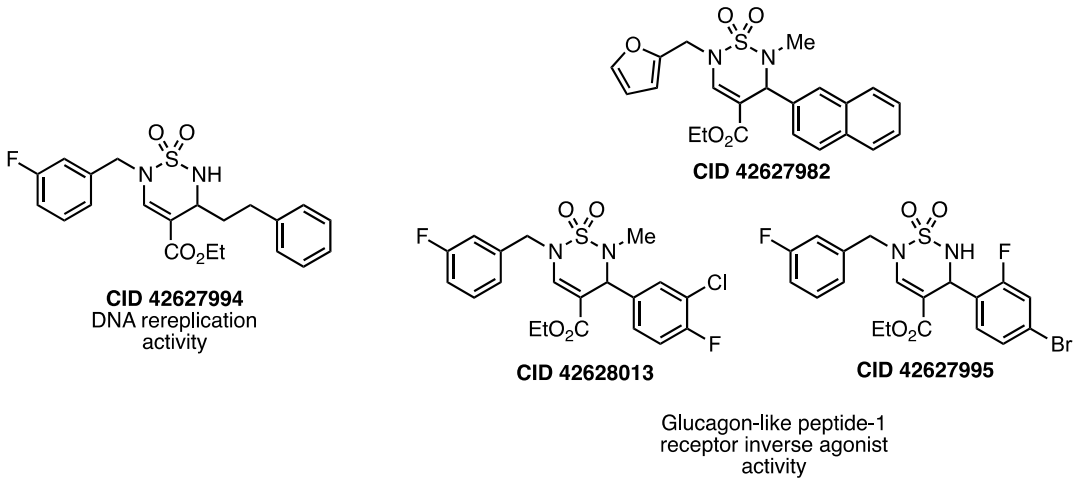


Figure 11. Structures of biologically active thiadiazine analogues from UPCMLD24A.

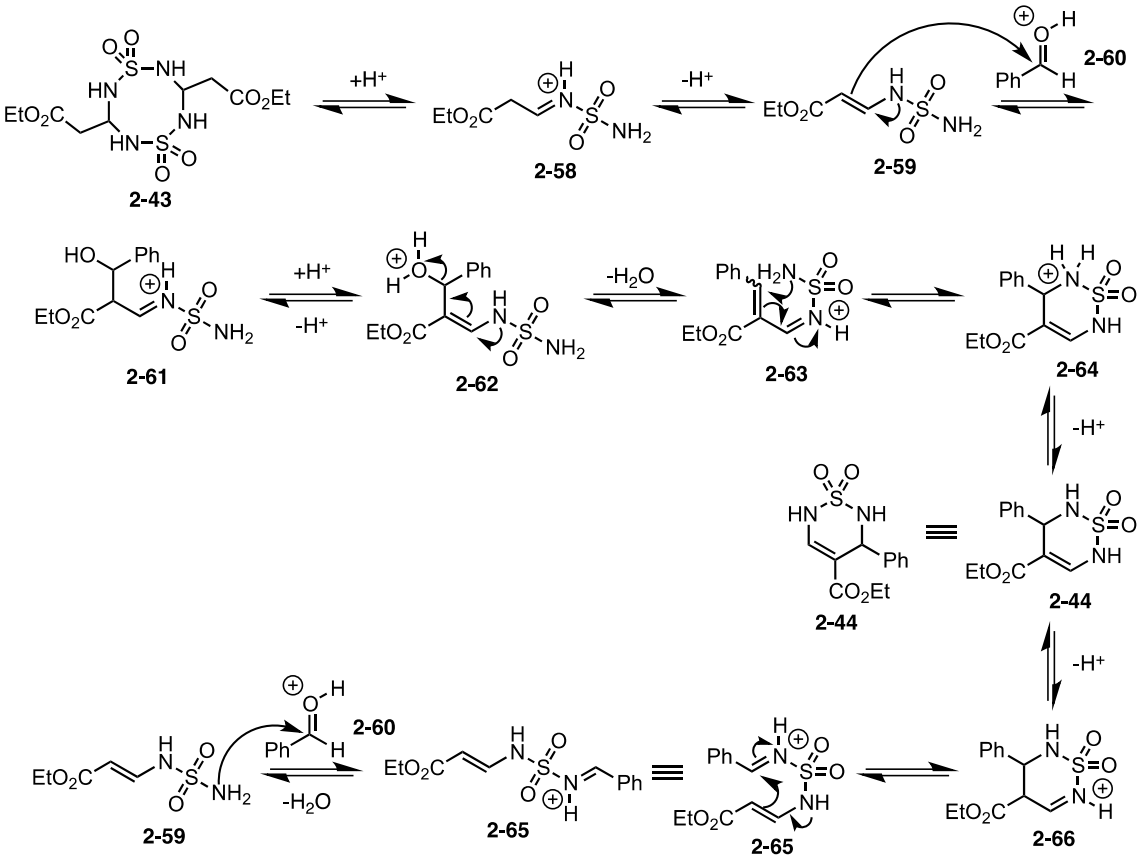
2.2 RESULTS AND DISSCUSSION

2.2.1 Optimization of Thiadiazine Formation

Previous results in the Wipf group from a brief optimization study for the preparation of thiadiazine **2-44** showed that a variety of acid mediated conditions facilitated the formation of the heterocycle (Table 2).[121] At the time, the optimal conditions used 10 equivalents of TFA at room temperature in CH_2Cl_2 to give **2-44** in 59% yield. We sought to improve the reaction conditions by (1) decreasing the amount of TFA needed to obtain the thiadiazine product and (2) reducing the reaction time.

Before tackling these problems, we felt it was important to consider a possible mechanism for the formation of **2-44**. We propose the mechanism begins with protonation and

cleavage of the sulfamide dimer **2-43** to give iminium **2-58**. Proton transfer provides **2-59** and Mannich reaction with aldehyde **2-60** yields **2-61**. Sequential proton transfer and β-elimination of water from **2-62** produces the α,β-unsaturated iminium **2-63**. Intramolecular Michael addition of the sulfamide nitrogen in **2-63** followed by proton transfer gives the observed thiadiazine **2-44**. Alternatively, a pathway that involves condensation of **2-59** and aldehyde **2-60** via the sulfamide nitrogen resulting in formation of iminium **2-65** could be envisioned. Intramolecular aza-Mannich reaction forms iminum **2-66** that after proton transfer provides thiadiazine **2-44**. Upon isolation of the desired product, specific byproducts could not be identified; however, oligomer formation via condensation of enamine **2-59** and iminium species **2-58**, **2-61**, **2-65**, and **2-66** are reasonable possibilities. From the proposed mechanism, we envisioned that the reaction could be improved by changing the acid and/or by changing the solvent in order to facilitate the formation of and/or stabilize the cationic intermediates. We suspected a slow step in the reaction sequence to be the break down of the sulfamide dimer **2-43**, because **2-43** exhibited limited solubility in CH_2Cl_2. This was further supported by the observation that the reaction mixture remained heterogeneous and became homogeneous only at the completion of the reaction.

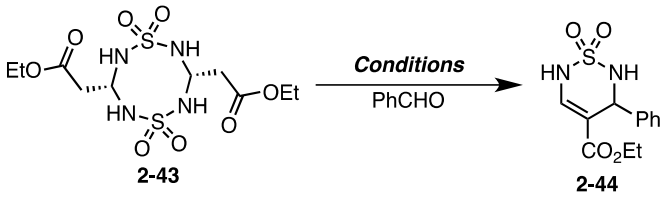


Scheme 43. Possible mechanisms for the acid mediated transformation of sulfamide dimer **2-43** to thiadiazine **2-44**.

In order find conditions to improve the formation of thiadiazine **2-44**, a brief screen of reaction conditions was undertaken. Changing the acid from TFA to anhydrous hydrogen chloride in 1,4-dioxane provided thiadiazine **2-44**, but it could not be obtained pure (Table 4, Entry 2). Increasing the concentration of the reaction mixture and decreasing the amount of TFA to 5 equivalents yielded no product at room temperature, but gave 55% of **2-44** upon heating to 40 °C (Table 4, Entry 3-4). Using 2.5 equivalents of TFA and increasing the concentration to 0.51 M in CH_2Cl_2 resulted in the same yield (Table 4, Entry 5). Due to the poor solubility of the sulfamide dimer **2-43** in CH_2Cl_2 coupled with our desire to increase the reaction rate and yield, the solvent was changed to hexafluoroisopropanol (HFIP). It was envisioned the non-

nucleophilic alcohol and hydrogen bond donor/acceptor capabilities of HFIP would provide an increase in reaction rate and yield by increasing the dissolution of **2-43** and stabilizing carbocation intermediates shown in Scheme 43. Unfortunately, the change in solvent provided a modest reduction of the reaction time and a comparable yield of **2-44** (Table 4, Entry 6). To explore if the relatively acidic HFIP (pKa = 9.3 in H_2O (17.9 in DMSO)) could promote the thiadiazine formation alone, a control reaction without TFA was performed and returned 81% of the sulfamide dimer starting material (**2-43**) (Table 4, Entry 7). The small optimization screen showed that a reduction in TFA and reaction time was accomplished by increasing the reaction concentration and heating the reaction mixture to achieve similar yields. The optimal conditions use 2.5 equivalents of TFA and HFIP as a solvent at 35-40 °C (Table 4, Entry 6).

Table 4. Optimization of conditions for the synthesis of thiadiazine **2-44**.



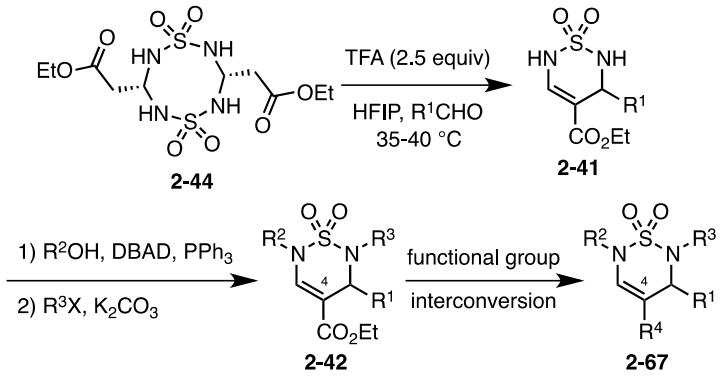
2-43 **2-44**

Entry	Conditions	Yield (%)[a]
1	TFA (10 equiv), CH_2Cl_2 (0.13 M), rt, 60 h	59
2	4 M HCl (10 equiv), 1,4-dioxane, rt, 14 h	47[b]
3	TFA (5 equiv), CH_2Cl_2 (0.25 M), rt, 17 h	SM
4	TFA (5 equiv), CH_2Cl_2 (0.25 M), 40 °C, 18 h	55
5	TFA (2.5 equiv), CH_2Cl_2 (0.51 M), 40 °C, 30 h	57
6	TFA (2.5 equiv), HFIP (0.50 M), 35-40 °C, 17 h	66
7	HFIP (0.51 M), 35-40 °C, 17 h	SM (81%)

[a]isolated yield after SiO_2 chromatography [b]isolated 85% pure.

2.2.2 Functionalization of Thiadiazines

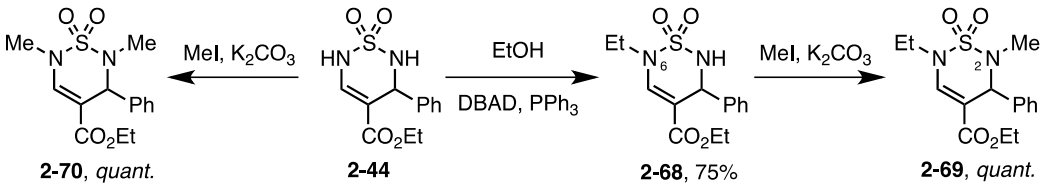
We desired to develop a strategy to access a thiadiazine scaffold with four points of diversity (Scheme 44, **2-67**). We envisioned that the methods developed by our group could be used to prepare thiadiazine **2-41** and differentially alkylated thiadiazine **2-42**, which in turn could be used to access compounds of type **2-67**. A conversion of the C-4 ester in **2-42** to the carboxylic acid would allow us to investigate Curtius rearrangements, amide bond formations, and reductive aminations.



Scheme 44. Approach to thiadiazines **2-67** with four points of diversity.

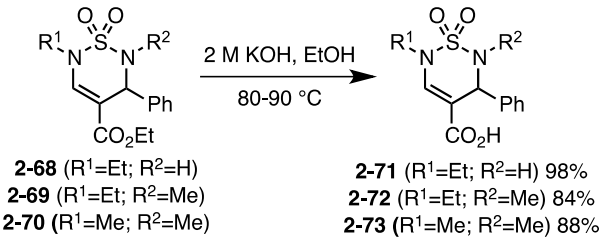
To begin the preparation of functionalized thiadiazines of type **2-67**, conditions to hydrolyze the C-4 ester to the carboxylic acid were needed. Initial saponification of thiadiazine **2-44** was attempted under a variety of conditions; however, the desired acid was not obtained. We envisioned this was due to the relatively acidic nature of the 6-*N*H as seen in Scheme 37 (**2-16**). Thus, we set out to explore hydrolysis conditions on alkylated thiadiazines. The alkylated thiadiazines would be prepared using the alkylation strategy previously developed in our group. Thiadiazine **2-44** was selectively 6-*N* alkylated using Mitsunobu conditions to provide **2-68**, which was subsequently treated with methyl iodide and K_2CO_3 to afford **2-69** in 75% over two

steps (Scheme 45). B*is*-alkylated thiadiazine **2-70** was also prepared quantitatively by treatment of **2-44** with excess methyl iodide and K_2CO_3.



Scheme 45. Alkylation of thiadiazine **2-44**.

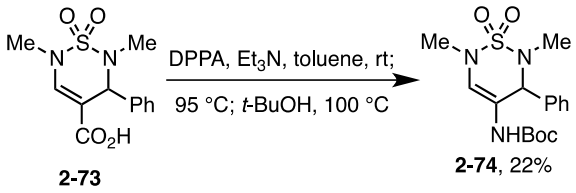
With the alkylated thiadiazines **2-68**, **2-69**, and **2-70** in hand, we explored Lewis acid-mediated transesterifications and mild hydrolysis with TMSOK or Bu_3SnOH. These transformations were not met with success, and we attributed the lack of reactivity under these mild conditions to the electron rich nature of the vinylogous carbamate at C-4. Gratifyingly, hydrolysis of **2-68**, **2-69**, and **2-70** was cleanly completed under more vigorous conditions using 2 M KOH in EtOH at elevated temperatures to give **2-71**, **2-72**, and **2-73**, respectively, in good yields (Scheme 46). The crude acids were stable at room temperature for weeks and could be used without purification.



Scheme 46. Saponification of esters **2-68**, **2-69**, and **2-70**.

Having developed reliable conditions to arrive at alkylated thiadiazines containing a carboxylic acid at C-4, we began to investigate transformations that could be used to introduce

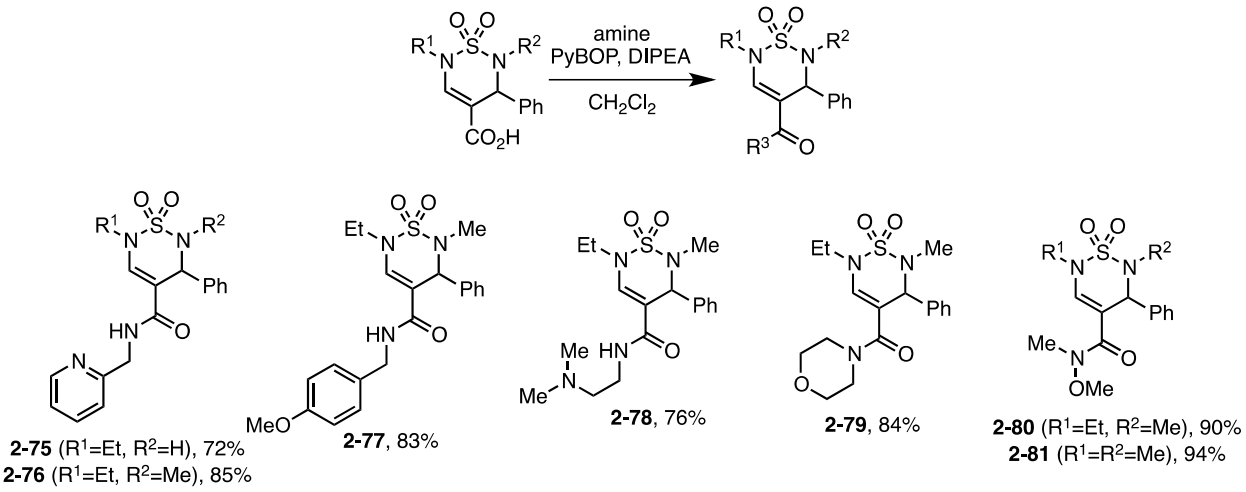
other functional groups at C-4. The first target we envisioned preparing was the *tert*-butyl carbamate.[128] Attempts at the Curtius rearrangement[129] of mono-alkylated thiadiazine **2-71** did not provide the desired product, presumably due to the presence of the free N-H. However, the dialkylated thiadiazine **2-73** was treated with DPPA[130] to evoke the Curtius rearrangement and afforded *tert*-butyl carbamate **2-74**, in modest yield (Scheme 47). In attempts to improve the yield, we performed a stepwise reaction to try to determine which step was responsible for the low yield. There was clean conversion to the acyl azide intermediate but decomposition products appeared after formation of the vinylisocyanate.



2-73 **2-74**, 22%

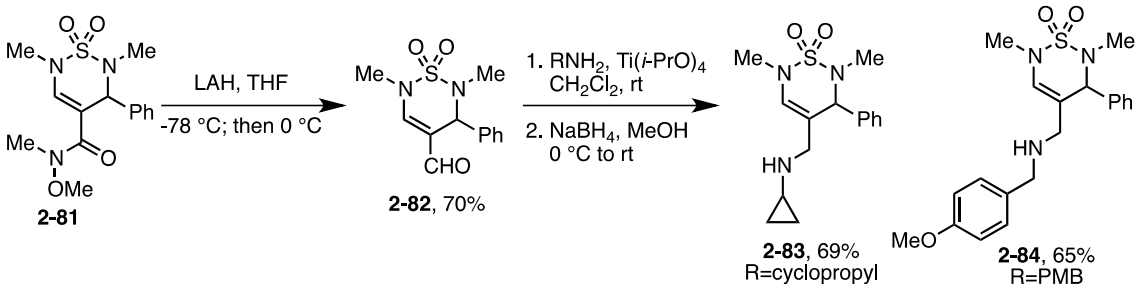
Scheme 47. Curtius rearrangement of acid **2-73** to provide **2-74**.

Another approach to functionalize the C-4 carboxylic acid was amide bond formation. EDCI coupling conditions with monoalkylated thiadiazine **2-75** and pyridinylmethanamine proceeded in good yield. PyBOP and DIPEA conditions were used to couple pyridylmethanamine, *p*-methoxybenzylamine, *N*,*N*-dimethylethylene diamine, and morpholine to give amides **2-76 – 2-79** (Scheme 48). These conditions were also used to obtain Weinreb amides[131] **2-80** and **2-81** in high yields, which provide a convenient handle for further functional group manipulation.



Scheme 48. Amidation of acids **2-71**, **2-72**, and **2-73** to give amides **2-75** – **2-81**.

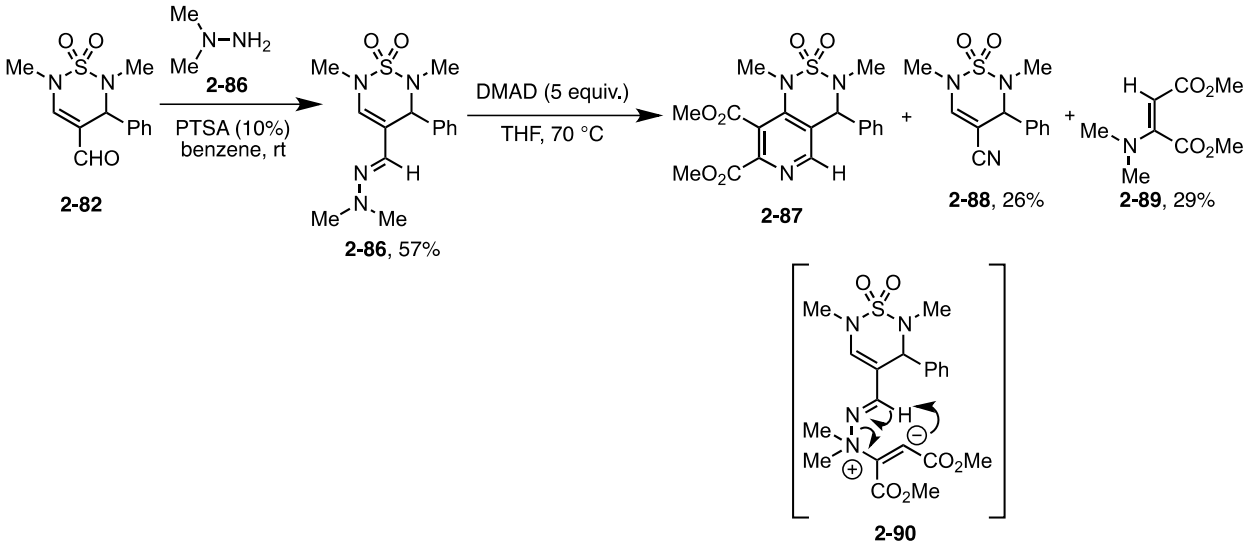
With the Weinreb amide **2-81** in hand, selective reduction to aldehyde **2-82** was accomplished with lithium aluminum hydride (LAH, Scheme 49). To avoid over reduction to the corresponding alcohol, the reaction was kept at -78 °C for two hours, warmed to 0 °C for 15 minutes, and quenched at 0 °C. Initial attempts to perform a reductive amination with aldehyde **2-82** using a one-pot imine formation-reduction strategy were not successful. Imine formation required aldehyde **2-82** to be treated with cyclopropylamine and *p*-methoxybenzylamine in the presence of Ti-Lewis acid. The resulting imines were reduced using $NaBH_4$ to provide amines **2-83** and **2-84**. $NaBH_3CN$ and Curran's *N*-heterocyclic carbene borane[132] were also explored as reducing agents, but amine formation was not observed. We attribute the lack of reactivity of the aldehyde **2-82** and imine to the electron rich nature of the vinylogous formamide and formimide. This low electrophilicity necessitated the use of Lewis acid to promote imine formation and $NaBH_4$ to afford the amine products.



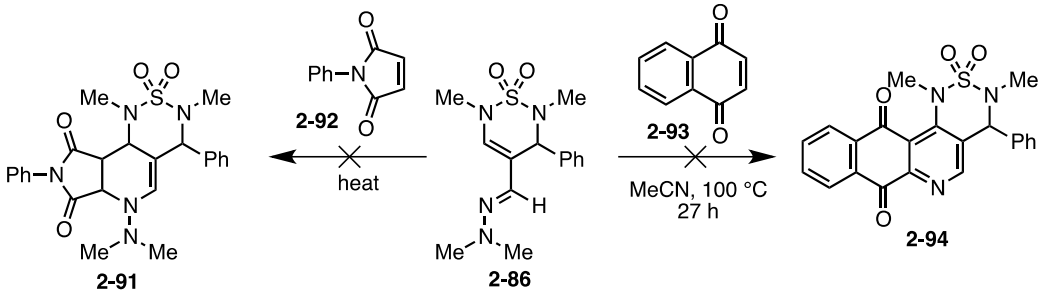
Scheme 49. Reduction of Weinreb amide **2-81** and reductive amination sequence to yield **2-83** and **2-84**.

After developing a strategy to prepare the electron rich aldehyde **2-82**, we saw an opportunity to access the corresponding hydrazone and explore a hetero-Diels-Alder reaction to provide a structurally unique fused thiadiazine-pyridine heterocyclic scaffold. Hydrazone **2-86** was obtained from aldehyde **2-82** and *N*,*N*-dimethylhydrazine (**2-85**). The attempted cycloaddition reaction with DMAD did not produce the desired product **2-87**. However, nitrile **2-88** and enamine **2-89** were isolated from the reaction mixture. These by-products can be explained by the formation of intermediate **2-90** followed by intramolecular elimination.[133] To circumvent the elimination side reaction, and in turn promote the desired pyridine formation, the less electron rich *N*,*N*-methylphenylhydrazone was used. Unfortunately, pyridine **2-87** or cycloaddition intermediates were not observed.

Additional efforts to arrive at the thiadiazine-pyridine scaffold were attempted with less electrophilic dieneophiles. We believed that this strategy would avoid formation of intermediates of type **2-90**. Unfortunately, the cycloaddition reaction of hydrazone **2-86** with maleimide **2-92** and quinone **2-93** did not provide the desired products **2-91** and **2-94**, respectively.



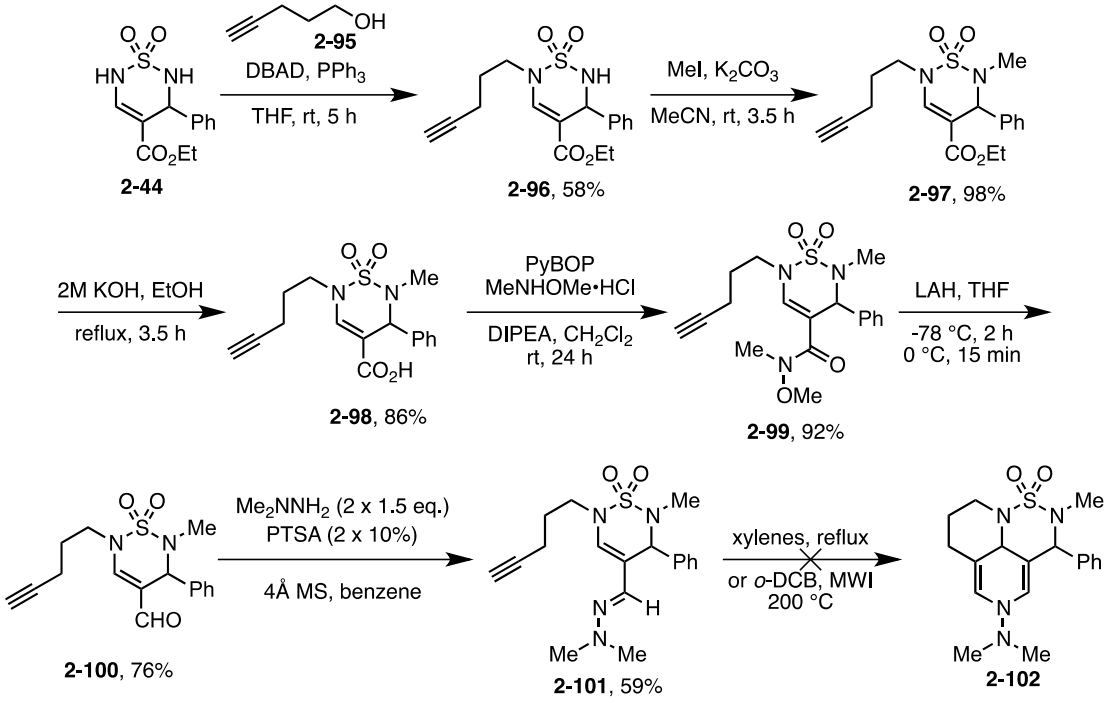
Scheme 50. Hydrazone **2-86** synthesis and attempted cycloaddition to form pyridine **2-87**.



Scheme 51. Attempted cycloaddition with hydrazone **2-86** and dienophilies **2-91** and **2-93**.

Since the intermolecular hetero-Diels-Alder reaction was not observed with substrate **2-86**, we set out to prepare thiadiazine **2-101**, which we envisioned could undergo an intramolecular hetero-Diels-Alder reaction to access a structurally unique scaffold containing three fused rings. We were encouraged to find that Markgraf and coworkers were able to perform an intramolecular cycloaddition on an electronically similar substrate to form pyridines.[134] The preparation of the intramolecular cycloaddition precursor **2-101** began with the selective alkylation strategy previously developed in our group[121] to give thiadiazine **2-97**.

Hydrolysis of ester **2-97** followed by Weinreb amide formation proceeded smoothly to provide **2-99**. Careful reduction of the Weinreb amide **2-99** using LAH was accomplished to give aldehyde **2-100** that was treated with *N*,*N*-dimethylhydrazine to afford hydrazone **2-101**. Conventional heating of hydrazone **2-101** in xylenes for several days or microwave irradiation in *o*-DCB did not yield the desired cycloaddition product **2-102**.



Scheme 52. Synthesis of intramolecular cycloaddition precursor **2-101** and attempted intramolecular cycloaddition reaction.

2.2.3 Analysis of the Physicochemical Properties of Thiadiazine Analogues

At this point, we have developed a robust strategy for the preparation of thiadiazines with four points of diversification. We prepared analogues that contained a *tert*-butyl carbamate, amides, and amines at the C-4 position of the thiadiazine core. With a small library of structurally unique

thiadiazines in hand, we were interested in evaluating their physicochemical properties. The physicochemical properties of C-4 functionalized thiadiazine analogues were calculated using Instant JChem[135] (Table 5). All of the compounds in Table 5 meet Lipinski's rules for drug like compounds[136] and Veber's rules for good bioavailability in rats.[137] The clogP and clogD for most of the compounds fall in the optimal range (0< log P <3); however, under physiological conditions (clogD) amines **2-78**, **2-83**, and **2-84** may suffer from poor lipid bilayer permeability. In general, the synthetic strategy allows for the strategic introduction of polar or lipophilic groups to achieve the desired physicochemical properties.

Table 5. Calculated physicochemical properties of thiadiazine analogues.

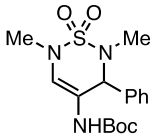
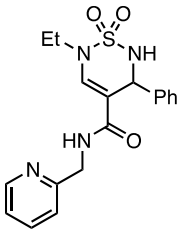
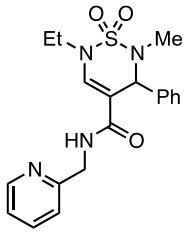
Compound	MW (g/mol)	Log P	Log D	TPSA (Å^2)	H-Bond Acceptors	H-Bond Donors	Rotatable Bonds
 **2-74**	353.44	1.0	-	79.0	4	1	4
 **2-75**	372.44	0.39	-	91.4	5	2	5
 **2-76**	386.47	0.61	-	82.6	5	1	5

Table 5 (continued). Calculated physicochemical properties of thiadiazine analogues.

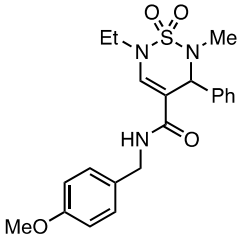
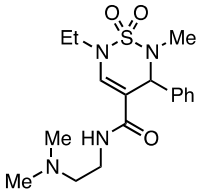
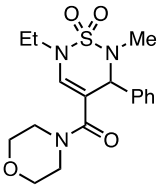
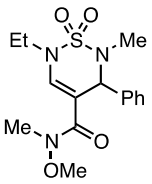
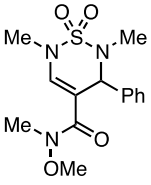
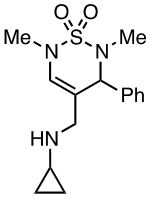
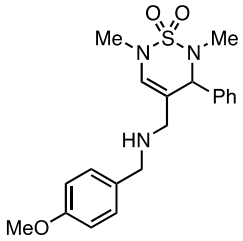
Compound	MW (g/mol)	Log P	Log D	TPSA (Å^2)	H-Bond Acceptors	H-Bond Donors	Rotatable Bonds
 **2-77**	415.51	1.59	-	79.0	5	1	5
 **2-78**	366.48	0.04	-1.10	73.0	5	1	6
 **2-79**	365.45	0.03	-	70.2	5	0	3
 **2-80**	339.41	0.40	-	70.2	5	0	4
 **2-81**	325.38	0.04	-	70.2	5	0	3
 **2-83**	307.41	0.57	-1.01	52.7	5	2	5

Table 5 (continued). Calculated physicochemical properties of thiadiazine analogues.

Compound	MW (g/mol)	Log P	Log D	TPSA (Å^2)	H-Bond Acceptors	H-Bond Donors	Rotatable Bonds
 **2-84**	387.50	1.67	0.18	61.9	5	1	6

2.3 CONCLUSION

We have developed a robust strategy for the preparation and selective functionalization of heterocyclic thiadiazines with four points of diversity. Original thiadiazine preparation conditions were optimized, and the amount of TFA was reduced from 10 to 2.5 equivalents. A method for the hydrolysis of the C-4 ester to install the requisite carboxylic acid was developed. The acid functional group handle was used to investigate Curtius rearrangements, amide bond formations, aldehyde formation, and reductive aminations, providing access to highly substituted thiadiazines. The formation of structurally unique thiadiazines though an inter- and intramolecular hetero Diels-Alder reaction was studied, but the desired heterocyclic scaffolds were not obtained. The prepared analogues exhibit favorable physicochemical properties for drug-like compounds and display some biological effects, including DNA rereplication, an anti-cancer target, and glucagon-like peptide 1 receptor inverse agonist activity, a potential target for diabetes and neurodegenerative disease.[126a, 127a]

3.0 INFLUENCE OF BASE AND STRUCTURE IN THE REVERSIBLE CONJUGATE ADDITION OF THIOLS TO INDOLE SCAFFOLDS

3.1 INTRODUCTION

3.1.1 Background of covalent protein inhibitors

Recently, a significant amount of research has focused on covalent protein inhibitors as potential therapeutics for a variety of diseases.[138] As we gain knowledge of the mechanism of action,[139] strategies can be developed to modulate the reactivity of the functional groups through which covalent attachment occurs. Many different functional groups and structural motifs have been used as the warhead for covalent protein modification in clinically approved drugs (Figure 12).[138a] Compounds such as Orlistat (**3-1**) and Amoxicillin (**3-2**) covalently bind via opening of their strained β-lactone and β-lactam core. The widely used drugs Aspirin (**3-4**),[140] for pain relief, and Warfarin (**3-5**),[141] an anticoagulant, function as acylation agents. Bortezomib (**3-3**), which is used to treat multiple myeloma and mantle cell lymphoma, behaves as a covalent proteasome inhibitor, forming a covalent link between the active site threonine and the pendant boronic acid.[142] The popular proton pump inhibitor, Omeprazole (**3-6**), behaves as a prodrug that upon exposure to the acidic conditions in the stomach rearranges to spirocycle **3-11** and forms a covalent disulfide enzyme adduct **3-13** (Scheme 53).[143] The hepatitis C virus NS3 serine protease

is inhibited by telaprevir (VX-950, **3-7**) through a reversible covalent hemiketal formation at the α-ketoamide.[144] Another widely used class of electrophiles for covalent inhibitors are Michael acceptors. Michael addition of a cysteine, of thymidylate synthase, to floxuridine (**3-8**) generates an enolate that subsequently reacts with the cofactor CH_2FAH_4 to give a covalently modified species.[145] A similar mechanism of action is followed by finasteride (**3-9**), which is used to treat prostatic hyperplasia.[146] PX-866 (**3-10**), an analogue of the natural product Wortmanin, functions as a covalent inhibitor of phosphoinositide-3-kinase (PI3K), and is in clinical trials as an anti-cancer therapeutic.[147]

A new approach to improve the selectivity or decrease off-target binding events of covalent inhibitors uses targeted covalent inhibitors (TCIs).[138b, 148] TCIs involve improving the binding of an optimized lead compound by appending a weakly electrophilic functional group in the direction of a potential nucleophile in the protein binding pocket. This approach can be very successful and has been used to develop the compounds shown in Figure 13. Acrylamides and α-keto-amides are commonly used electrophiles because they are weakly electrophilic, thereby modulating off-target effects, but will react rapidly when in close proximity to a nucleophile.[148b] Prominent examples of TCIs are carfilzomib (**3-14**), a proteasome inhibitor that reacts through the terminal epoxide, and boceprevir (**3-15**), an HCV protease inhibitor, which reversibly forms a hemiketal. A particularly useful strategy for TCI design is the use of a γ-amino-acrylamide functional group (as seen in neratinib (**3-16**) and Tovok (**3-17**)), which functions as an intramolecular catalyst of the nucleophilic addition of a cysteine via deprotonation. A potential drawback for widespread application of TCIs is that it is imperative to have protein structure information, substrate-binding orientation, and a nucleophilic group (such as cysteine or serine) near the binding site.

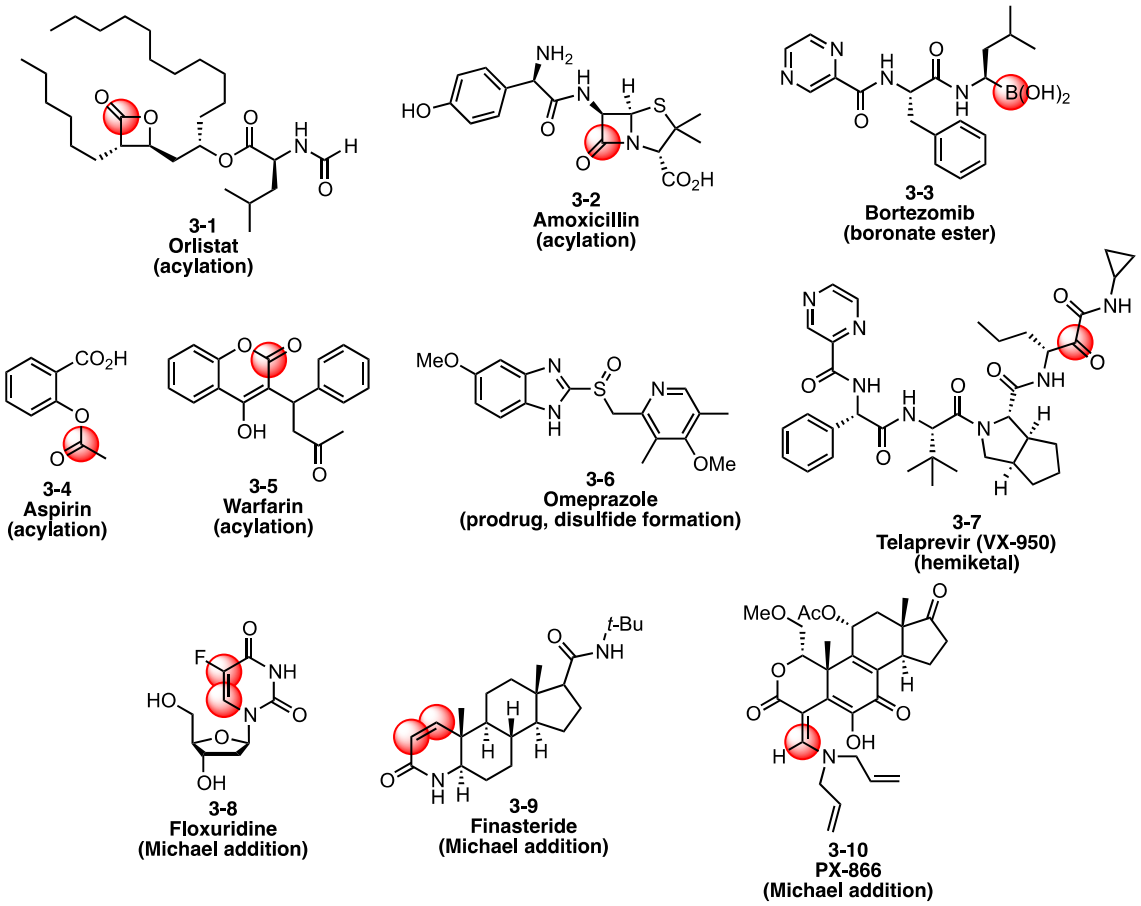
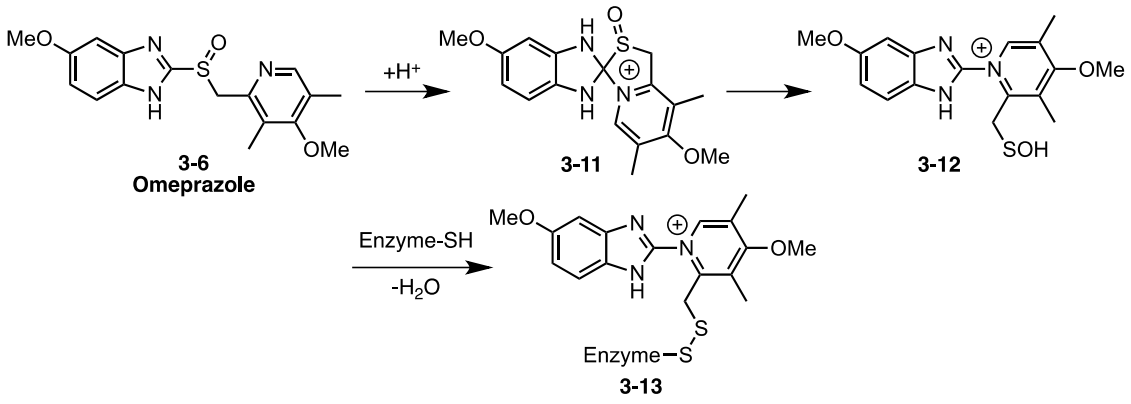


Figure 12. Clinically approved covalent inhibitors. Regions where covalent modification occurs are highlighted.



Scheme 53. Mechanism of covalent enzyme binding of Omeprazole (**3-6**).

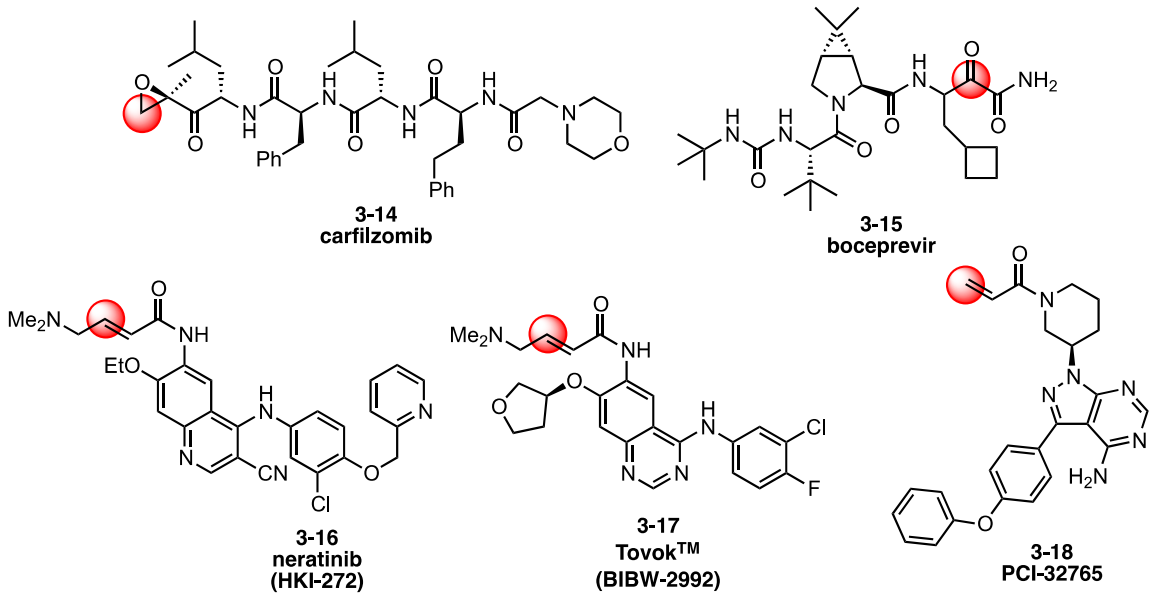
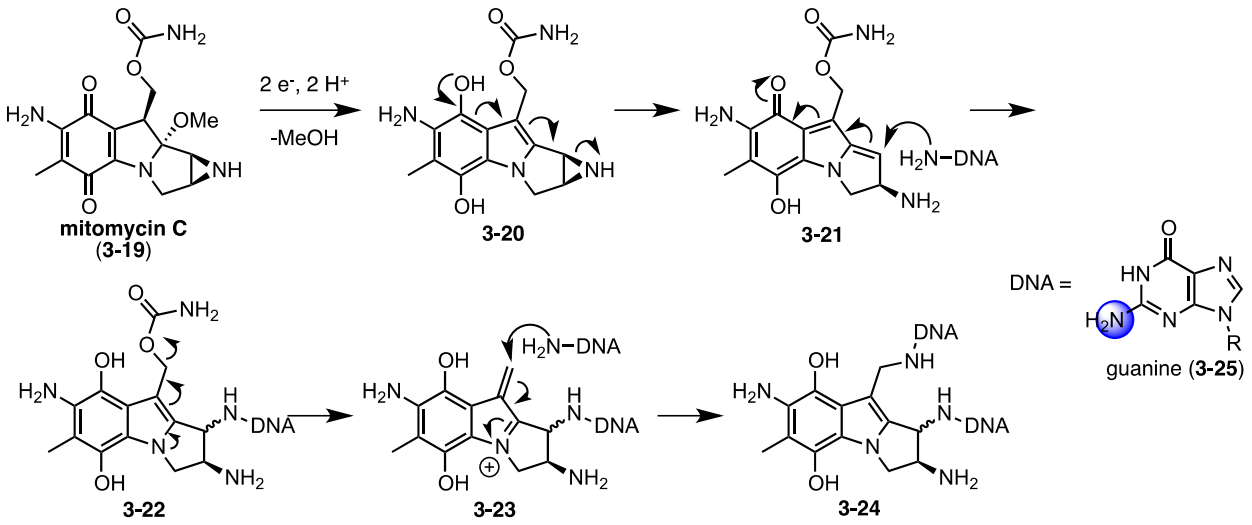


Figure 13. Approved drugs and candidate compounds that were developed using targeted covalent inhibitors (TCIs).

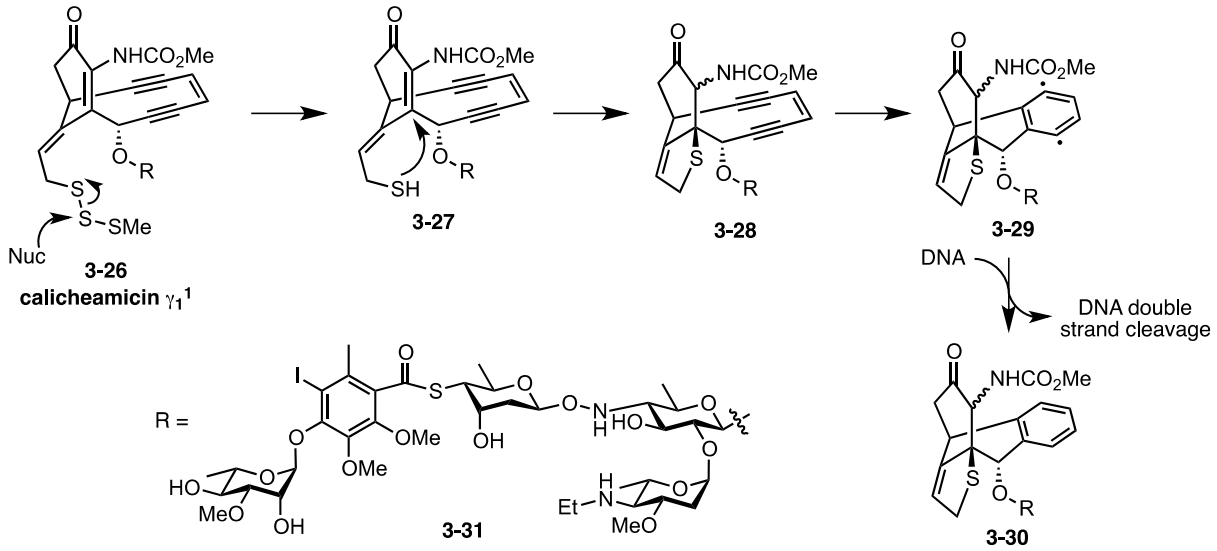
In addition to the synthetic covalent inhibitors mentioned above, many natural products have been shown to exhibit biological activity through a covalent mechanism.[139, 148b] Two classic examples are the mitomycins and enediyne antibiotics. Unlike many of the compounds that covalently modify proteins (Figure 12 and Figure 13), the biological activity of the mitomycins and enediyne natural products is a result of DNA modification. Mitomycin C (**3-19**) was isolated from the bacterium *Streptomyces lavendulae* in 1958[149] and has since proved to be a valuable anticancer therapeutic, especially for the treatment of bladder cancer.[150] The anticancer activity of mitomycin C comes from its ability to covalently alkylate and crosslink DNA.[151] Mechanistically, the natural product is activated by reduction of the quinone moiety leading to **3-20** (Scheme 54).[152] Opening of the aziridine forms the conjugated enone **3-21**, which is susceptible to nucleophilic attack from DNA (guanine (**3-25**)) to give **3-22**. Elimination of the

pendant carbamate gives iminum **3-23** which is attacked by DNA to give the dialkylated compound **3-24**.[151, 153]



Scheme 54. Mechanism of action of mitomycin C.

The enediyne family of natural products is characterized by a unique (*Z*)-1,5-diyne-3-ene structural unit and possesses nanomolar anticancer activities.[154] Their mechanism of action involves a Bergman cycloaromatization and formation of a 1,4-benzenoid diradical intermediate.[154c] The diradical abstracts a hydrogen from the ribose backbone of DNA, at C(5'), C(4'), or C(1'). The resulting radical leads to DNA strand cleavage via oxidation, reduction, and elimination.[154c] Specifically, enediyne natural product, calicheamicin γ_1^1 (**3-26**), accomplishes DNA double strand cleavage through the mechanism shown in Scheme 55.[154a, 154c] The trisulfide **3-26** is cleaved by nucleophilic displacement, postulated to occur with glutathione, to give thiol **3-27**. Conjugate addition of the thiol side chain provides **3-28**, which undergoes a structural change and leads to spontaneous cycloaromatization to relieve strain and form diradical **3-29**. The diradical induces DNA double strand cleavage to give **3-30**.



Scheme 55. Mechanism of action of calicheamicin γ_1[1] leading to DNA double strand cleavage.

Some more recent examples of covalently modifying natural products employ ring-strained scaffolds and Michael acceptors to accomplish covalent modification of a protein target. Duocarmycin SA (**3-32**) contains a strained cyclopropane and azinomycin A (**3-33**) contains a strained aziridine that function as electrophilic targets.[155] Syringolin A (**3-34**) inhibits the 20S proteasome by covalent attachment through a threonine residue (See Section 1.1.2). The Michael acceptor ability of the cross-conjugated enone zerumbone (**3-35**) has suggested uses as a chemopreventive and anticancer agent.[156] A biotinylated derivative of the anti-inflammatory natural product parthenolide (**3-36**) was revealed to be a covalent binder.[157] The anti-proliferative activity of leptomycin B (**3-50**) has been attributed to Michael addition into the α,β-unsaturated lactone.[158] Wortmannin (**3-37**) irreversibly inhibits PI 3-kinase by lysine addition into the activated furan.[159] Other electrophilic groups that function as effective Michael acceptors are vinyl sulfones (methyldambullin, **3-38**) and vinyl nitrones (avrainvillamide, **3-39**).[148b, 160]

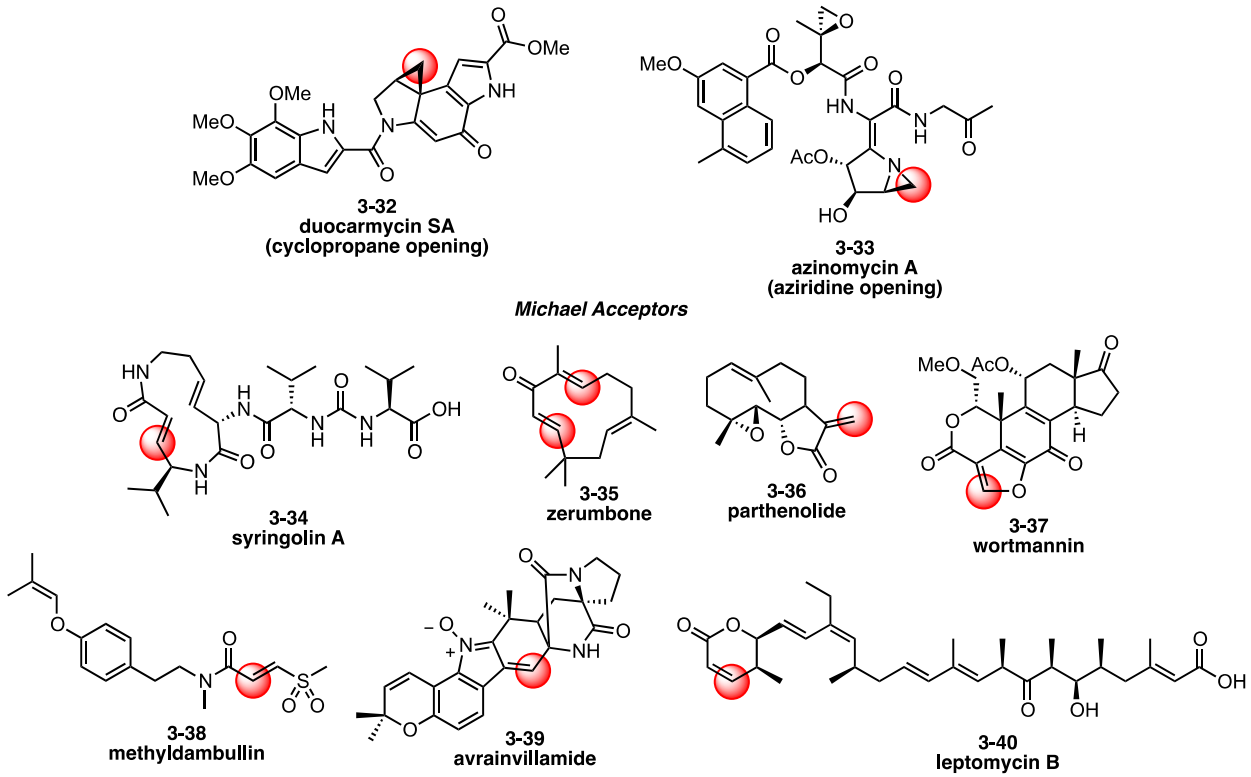
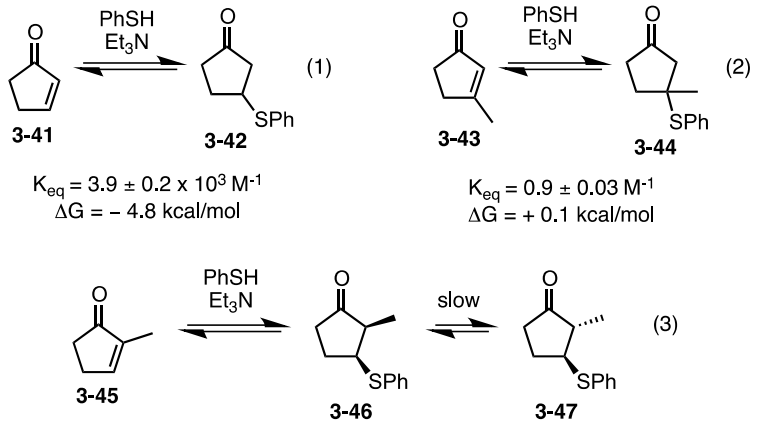


Figure 14. Biologically active natural products that inhibit though covalent inhibition.

3.1.2 Mechanistic Studies of Thiol Additions to Enones

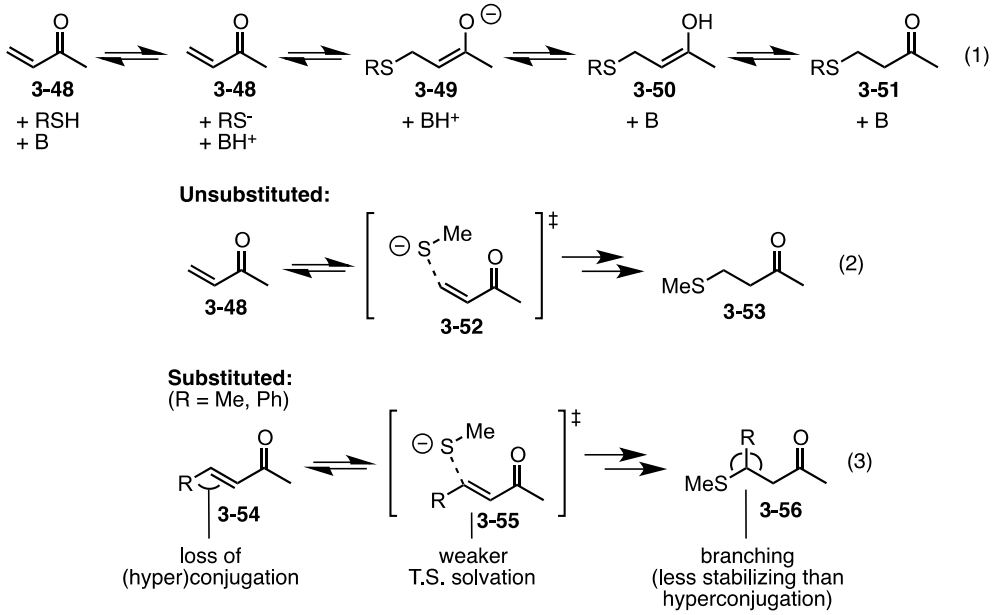
Understanding the mechanism and the influence of structural features on the rate and equilibrium of thiol additions to enones is paramount for the rational development of enones as covalent inhibitors. To this end, several research groups have investigated the addition of thiols to simple enones using experimental and computational methods. Bernardi and coworkers have investigated the kinetics and equilibria of the Et_3N-catalyzed addition of thiophenol to enones using ^1H NMR.[161] The concentrations of enone, thiophenol, and adduct were determined at equilibrium by integration of the appropriate ^1H NMR signals and used to calculate the equilibrium constant (K_{eq}). With the equilibrium constant known, ΔG ($RTlnK_{eq}$) was calculated. Thiophenol addition to cyclopentenone **3-41** gave thioether adduct **3-42**, which was favored by

−4.8 kcal/mol (Scheme 56, Equation 1). Thiophenol addition to β-substituted enone **3-43** was slightly unfavorable by +0.1 kcal/mol (Scheme 56, Equation 2). Interestingly, thiophenol addition to α-substituted enone **3-45** resulted in kinetic formation of the *cis*-substituted adduct **3-46** (Scheme 56, Equation 3). The *cis*-substituted adduct **3-46** is formed by rapid protonation of the intermediate enolate from the less sterically hindered face. The initial formation of the *cis*-substituted adduct **3-46** is −0.2 kcal/mol downhill in energy compared to enone **3-45**. Over 150 h, equilibration of the *cis*-adduct **3-46** to the *trans*-substituted adduct **3-47** was observed, which was found to be favored by −0.9 kcal/mol. The equilibration is thought to occur via enolization of ketones **3-46** and **3-47** followed by protonation give the more thermodynamic *trans* orientation between the thiophenyl and methyl group. Kinetic measurements indicated thiophenol addition to enone **3-41** is two orders of magnitude faster than addition to α-substituted enone **3-45** and three orders of magnitude faster than addition to β-substituted enone **3-43**. The authors propose that the decrease in product formation for the thiol addition to enones **3-43** and **3-45** is a result of both the electronic stabilizing effect of the methyl group on the π-bond and the increase of bond eclipsing interactions in the thiol adducts **3-44**, **3-46**, and **3-47**.



Scheme 56. Kinetic and equilibrium studies of thiophenol additions to cyclopentenones **3-41**, **3-43**, and **3-45**.

In 2011, Houk and coworkers investigated the transition states and thermodynamics of the addition of thiols to α,β-unsaturated ketones using density functional theory (DFT) calculations.[162] The general mechanism of thiol additions to enones begins with thiolate formation followed by addition to enone **3-48** (Scheme 57, Equation 1). The resulting enolate **3-49** is protonated to give enol **3-50** that tautomerizes to yield the ketone **3-51**. Transition states **3-52** and **3-55** were identified by DFT calculations† for the addition of a thiolate to an enone (Scheme 57, Equation 2 and 3). The energy of the unsubstituted enone transition state **3-52** is lower than the β-substituted enone transition state **3-55**. The authors propose this is due to the loss of hyperconjugation in the branched enone **3-54** and the weaker solvation of the more sterically crowded transition state **3-55** (Scheme 57, Equation 3).



Scheme 57. Computational evaluation of the mechanism of thiol additions to enones.

† Gas phase calculations using B3LYP/CBSB7 and solution phase calculations using CPCM water B3LYP/6-31+G(d) in Gaussian 03

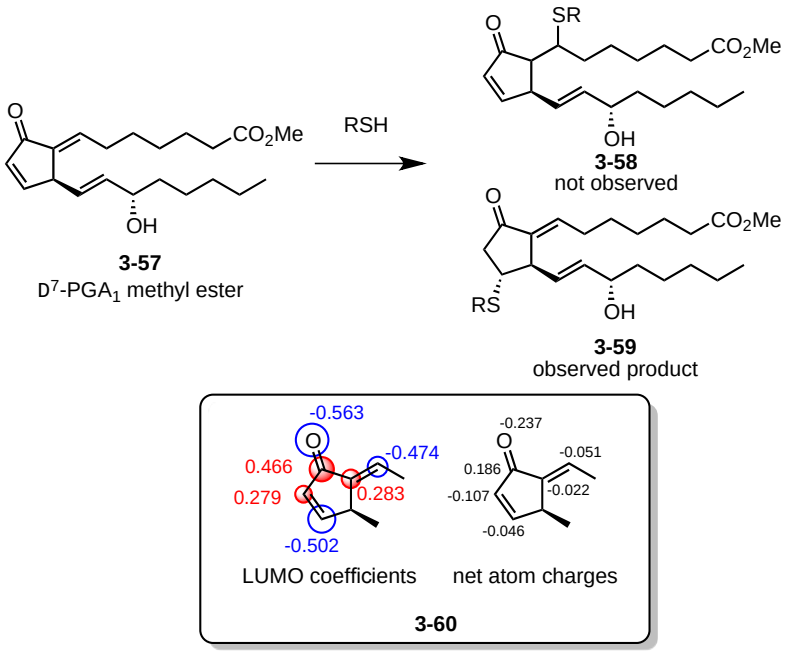
3.1.3 Spectroscopic and Computational Methods for the Identification and Classification of Thiol Acceptors

In order to better understand and use thiol acceptors as lead structures in drug discovery, several methods have been published to rapidly identify, classify, and predict the reactivity of thiol acceptor molecules. Suzuki and coworkers investigated the rates and equilibria of thiol additions to enone-containing prostaglandins.[163] Thiol addition to cross-conjugated enone **3-57** provided **3-59** as the only observed product (Scheme 58). They were able to rationalize the regiochemistry of the thiol addition to cross-conjugated enone **3-57** by calculating the LUMO orbital coefficients and atomic charges[‡] for enone **3-60**. The thiol addition occurs at the endocyclic β-position, which has a larger LUMO coefficient and a more positive atomic charge.

Cusack and coworkers investigated the β-carbon chemical shift of α,β-unsaturated carbonyl compounds to estimate the reactivity of drug-like molecules.[164] They examined small libraries of three scaffold families **3-61**, **3-62**, and **3-63** by ^{13}C-NMR (Figure 15) and found that the chemical shifts for the β-carbon fell into three distinct groups. Chemical shifts between 137-139 ppm were observed for compounds **3-61** that exhibited Michael acceptor properties, while compounds **3-62** with chemical shifts of 135-128 ppm showed redox activity and are reduced by NADPH. The chemical shift for scaffold **3-61** is slightly higher due to the presence of the conjugated indole, while the electron rich pyrrole in scaffold **3-62** causes the chemical shift to decrease slightly. Compounds from the scaffold **3-63** have a much lower chemical shift range, between 122-118 ppm, due to the increase in electron density of the enamide from the benzothiazinone ring. Enamide scaffold **3-63** was inactive as a Michael acceptor and an

[‡] Calulations performed using STO-3G in Monstergaus 81

NADPH substrate, but did show a lack of olefin geometry photostability. Compounds from scaffold **3-61** and **3-62** have better photostability of the olefin geometry due to the stabilizing nature of an intramolecular H-bond.



Scheme 58. Calculated LUMO coefficients and atomic charges used to rationalize regioselectivity of thiol additions to cross-conjugated enones.

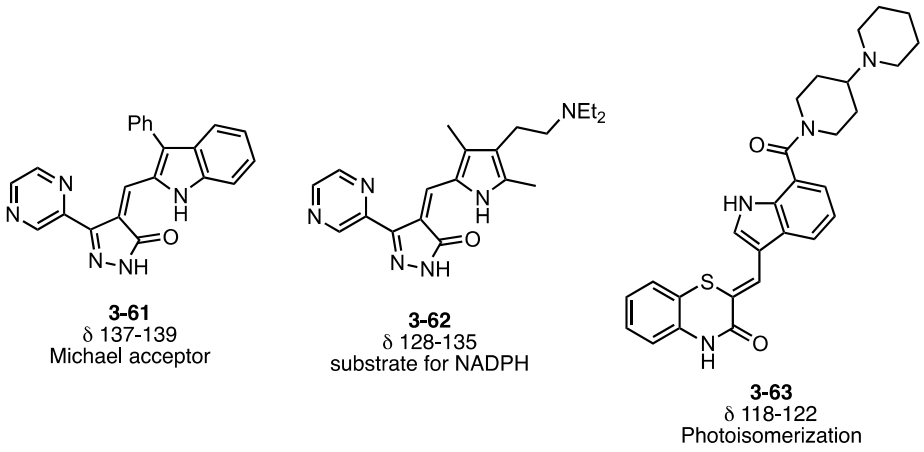
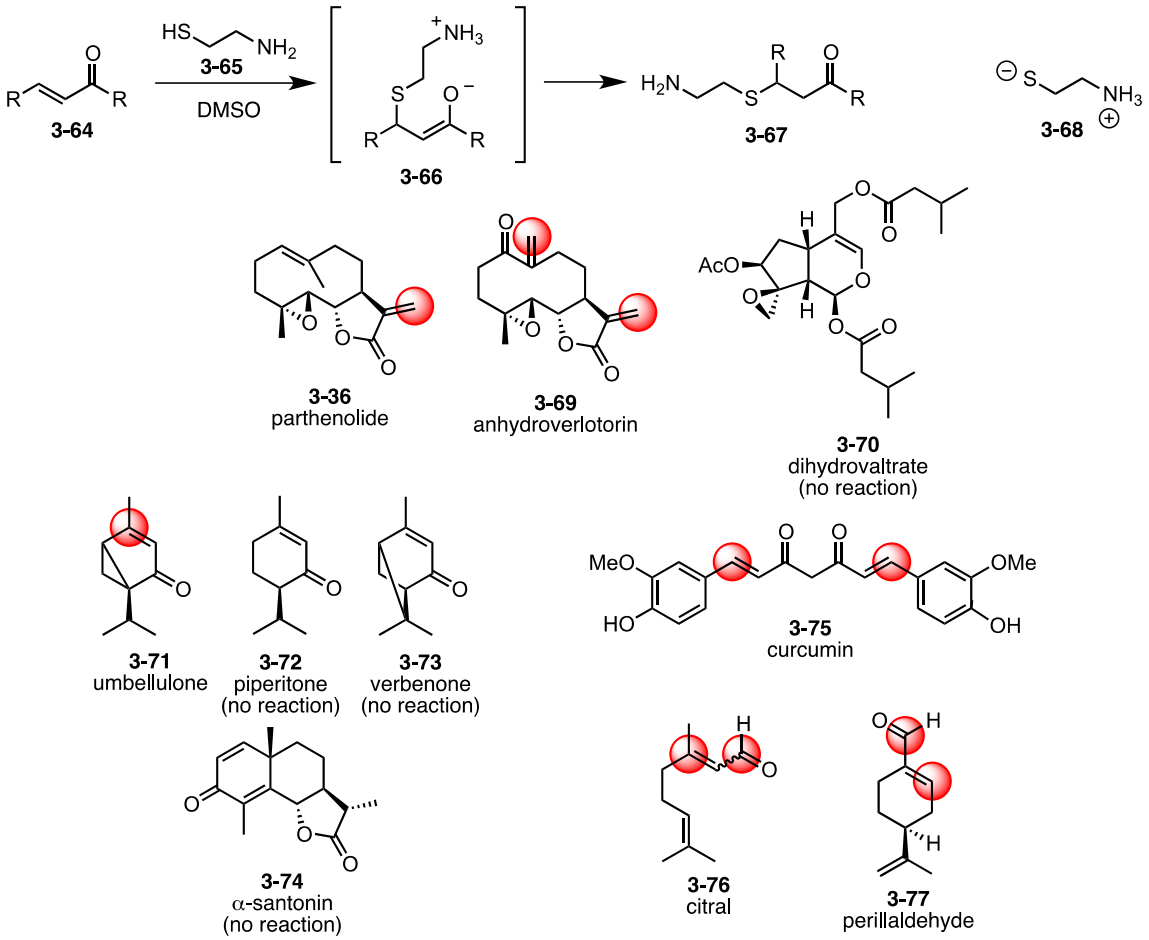


Figure 15. β-carbon enone chemical shifts used to predict enone reactivity.

In 2011, Appendino and coworkers developed a rapid NMR spectroscopic method to identify thiol acceptors.[165] A variety of α,β-unsaturated carbonyl compounds were treated with cysteamine **3-65** followed by ^{1}H NMR analysis to reveal if the thiol addition occurred. Initial attempts to use *N*-acylcysteamine showed a lack of reactivity with enones while cysteamine **3-65** performed much better. The authors suggest the increase in reactivity of cysteamine compared to *N*-acylcysteamine is because of the ability of the amine to catalyze the thiol addition reaction to enones through an intramolecular proton transfer, seen in intermediate **3-66** (Scheme 59). Additionally, the nucleophilicity of cysteamine **3-65** has been explained by the charge-separated tautomer **3-68**, which is stabilized by the polar aprotic solvent DMSO. This method was able to identify parthenolide **3-36** and anhydroverlotorin **3-69** as mono- and di-thiol acceptors, respectively. Dihydrovaltrate **3-70**, containing the reactive epoxide moiety, showed no reaction under the assay conditions. Structurally similar α,β-unsaturated ketones **3-71**, **3-72**, and **3-73** were treated with cysteamine, but only umbellone **3-71** gave a positive assay result. The authors speculate that **3-71** is reactive due to the cyclopropane of the cyclopentenone stabilizing a partial positive charge on the β-carbon. In addition to the electronic effects, the steric interactions in the thiol adduct of the bridged system **3-73** are unfavorable. Curcumin **3-75** reacted with two equivalents of cysteamine, while cross-conjugated enone **3-74** (α-santonin) gave no reaction. The lack of reactivity of **3-74** under the assay conditions could be due to the electron rich nature of the cross conjugated enone and the sterics of the quaternary center next to the β-carbon of the enone. α,β-Unsaturated aldehydes **3-76** and **3-77** were compatible with the assay conditions; however, 1,2-addition of cysteamine (kinetic product) into the carbonyl was observed.



Scheme 59. ^{1}H NMR assay for the identification of thiol acceptors.

In 2012, Taunton and coworkers explored the use of cyanoacrylates as reversible covalent inhibitors for non-catalytic cysteine residues.[166] Initial investigations found a rapid formation of thiol adducts when cyanoacrylamides in Figure 16 were treated with β-mercaptoethanol. Upon dilution of the adduct mixtures, rapid thiol dissociation occurred. These findings suggested that cyanoacrylamides could be used to reversibly target cysteine residues. Thus, a set of pyrrolopyrimidine-containing Michael acceptors (Figure 17) was tested *in vitro* and compound **3-86** exhibited nanomolar inhibition of p90 ribosomal protein S6 kinase RSK2, which has been implicated as a target to treat cancer.[167] Compound **3-86** showed long enzyme

residence time and was completely reversible over several hours. A co-crystal structure was obtained with derivative **3-87**, which showed that covalent attachment to RSK2 via Cys436 was stabilized by key hydrogen bonds to the pyrimidine core. The design and application of reversible covalent inhibitors could be a useful approach to maintain potency and mitigate off-target effects compared to traditional irreversible covalent inhibitors.[165]

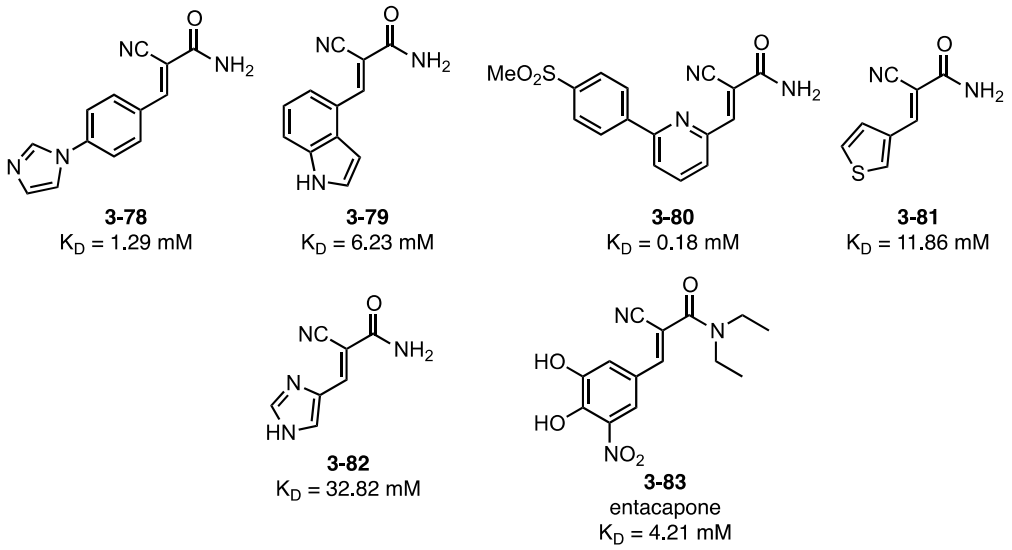


Figure 16. Cyanoacrylamide-based reversible thiol acceptors with reported thiol dissociation constants.

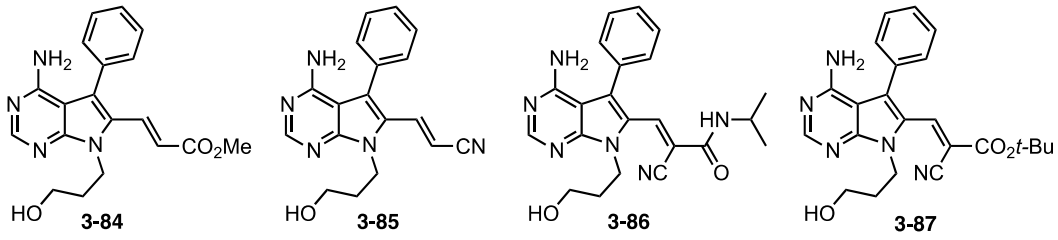
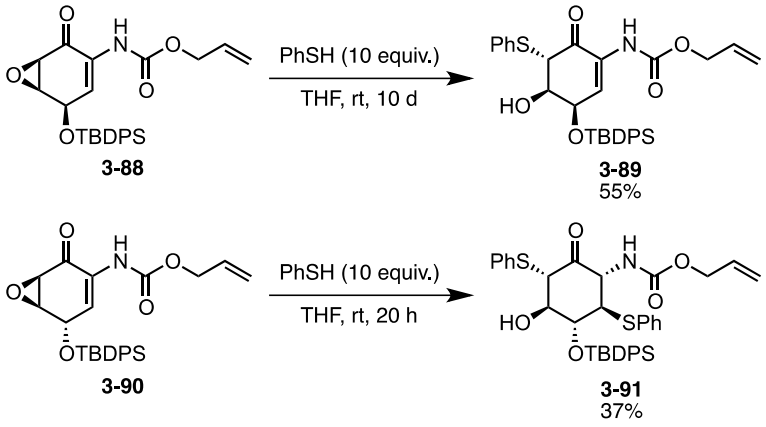


Figure 17. Rationally designed reversible covalent p90 ribosomal protein S6 kinase RSK2 inhibitors.

3.1.4 Thiol Addition Chemistry in the Wipf Group

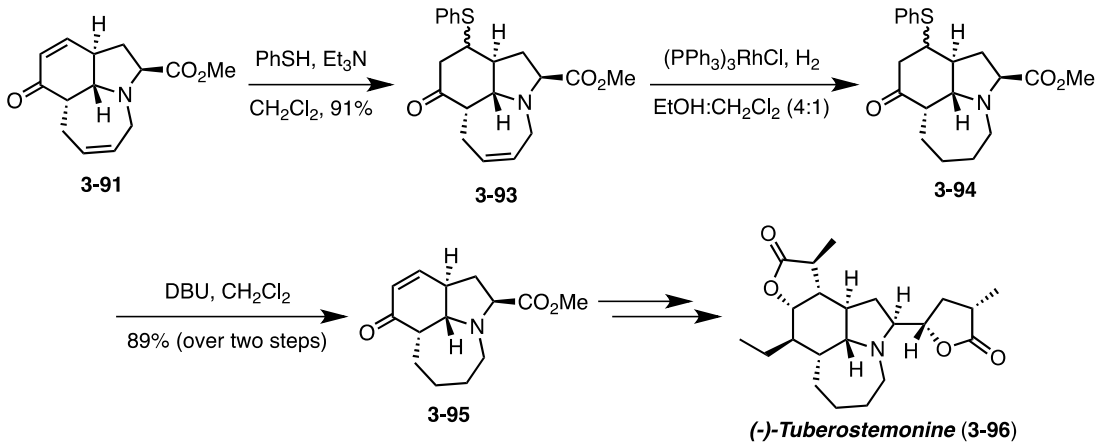
The Wipf group has investigated the fundamental alkylating properties of epoxyketone-containing natural products such as aranorosin, LL-C10037α, manumycin and dipoxin σ.[168] Of particular relevance is the thiol capture pathway of the manumycin A core **3-88** (Scheme 60).[168a] In the presence of excess thiophenol, regioselective epoxide opening was observed to give **3-89** with no Michael addition into the enone. Interestingly, they found that thiophenol addition to **3-90**, a diastereomer of **3-88**, provided **3-91** in which both epoxide opening and Michael addition was observed. Kinetically favored addition of thiophenol in to the enone would form a chair shaped intermediate but would give a thiol addition diastereomer that was not observed. Thus addition of the thiol to the enone must arise from equatorial attack and a boat shaped intermediate to arrive at a thermodynamically more stable diastereomer **3-91**.



Scheme 60. Thiophenol addition reactions to manumycin A core enone **3-88** and **3-90**.

The Wipf group has also used a thiol addition to an enone as a protecting group strategy to differentiate the two olefins in **3-92** *en route* to the natural product tuberostemonine **3-96** (Scheme 61).[169] Conjugate addition of thiophenol in the presence of catalytic Et_3N gave

thiophenol adduct **3-93**.[170] Reduction of the azepine was accomplished with Wilkinson's catalyst under an atmosphere of H_2 to afford **3-94**, and the enone was regenerated by a DBU-mediated thiophenol elimination to provide **3-95**.[171] Enone **3-95** was then used to complete the synthesis of tuberostemonine **3-96**.



Scheme 61. Thiol addition/elimination strategy used in the synthesis of tuberostemonine (**3-96**).

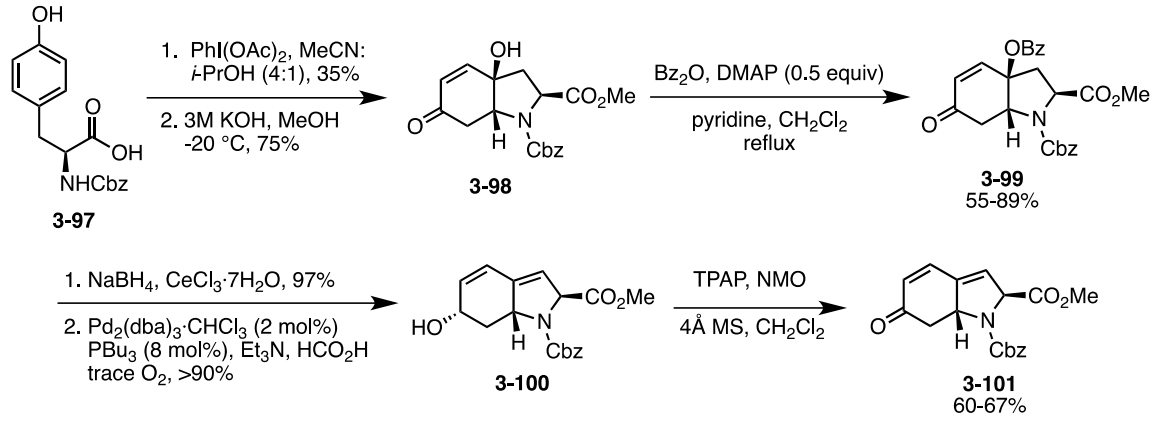
3.2 RESULTS AND DISCUSSION

3.2.1 Investigation of the Thermodynamics of Thiol Additions to Enones

The ability to shift the equilibrium from **3-92** to **3-93** and **3-94** to **3-95** by changing the base was noteworthy; however we could only speculate how the equilibrium was affected by conformational changes of the tricycle (azepine (**3-92**) *vs.* azepane (**3-95**)) or base strength (Et_3N *vs.* DBU). As discussed previously, the ability to predictably influence the electrophilicity of Michael acceptors has a profound effect on their use in drug discovery. It is also apparent that substitution, sterics, and electrophilicity of the Michael acceptor effect the kinetics and

thermodynamics of thiol additions. Accordingly, we experimentally explored the equilibria of thiophenol addition and elimination reactions of several indole containing enones.

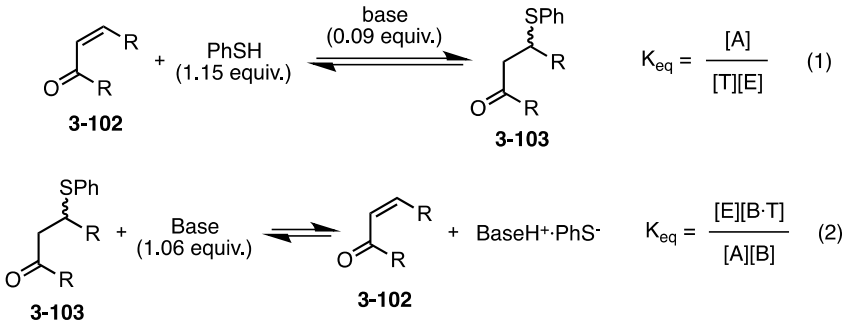
We began our investigation of the equilibria of the thiol addition/elimination reactions using enone containing indole scaffolds that were reported in the synthesis of tuberostemonine.[169] The enones **3-98** and **3-99** were prepared according to reported methods starting from Cbz-protected tyrosine (Scheme 62).[169, 172] The enone **3-101** was obtained from a Ley oxidation[173] of known alcohol **3-100**.



Scheme 62. Preparation of enones **3-98**, **3-99**, and **3-101**.

In order to measure the equilibrium of the thiophenol addition reaction and investigate the effects of enone structure and base strength, NMR experiments were performed in the presence of an excess of thiophenol (1.15 equivalents) and catalytic base (0.09 equivalents of Et_3N and DBU, Scheme 63, Equation 1). The experiments for the measurement of the thiol elimination reactions equilibria were performed using stoichiometric base (1.06 equivalents of Et_3N and DBU, Scheme 63, Equation 2). The ratio of starting material to product was measured by the integration of diagnostic peaks in the ^1H NMR and used to determine the equilibrium

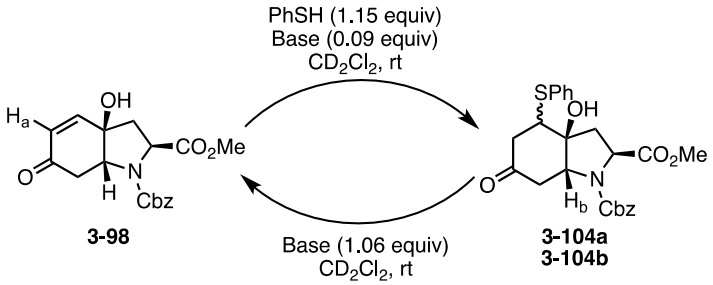
constant (K_{eq}). In turn, the K_{eq} was used to calculate the ΔG of the thiol addition/elimination reactions (Scheme 63). From these observations, we expected the catalytic base to have no influence on the thiol addition reaction and thus measure the equilibrium between the enone **3-102** and thiol adduct **3-103**. Although, in the thiol elimination reactions we expected to see a difference in the equilibrium constant with respect to the base because of the stoichiometric formation of a base-thiol ion pair complex (Scheme 63, Equation 2). By comparing equilibrium constants from the thiol elimination reactions using Et_3N and DBU we expected to calculate the difference in energy between the two base-thiol complexes ($DBUH^+PhS^-$ *vs.* $Et_3NH^+PhS^-$). The pK_a values of thiophenol, $DBUH^+$, and $TEAH^+$ (pK_a values in DMSO of 10.3, 12, and 9, respectively)[174] suggest that the formation of the $DBUH^+PhS^-$ ion pair complex will be favored over the $TEAH^+PhS^-$ ion pair complex.



Scheme 63. General reaction schemes for the (1) thiol addition and (2) thiol elimination reactions accompanied by equations for equilibrium constants. [A]=thiol addition adduct; [T]=thiol; [E]=enone; [B•T]=base thiol complex; [B]=base.

With the enones in hand, we began investigating the equilibria of the thiol addition and elimination reactions. The addition of thiophenol to enone **3-98** with either Et_3N and DBU gave a ratio of **3-104**:**3-98** of ≥50:1 by ^1H NMR (beyond the limit of detection by ^1H NMR) and a ΔG

of ≤ −4.6 kcal/mol (Figure 18). The equilibrium constant was determined by integration of the peaks for **3-98** (H_a δ 5.95 (dd)) and **3-104** (H_b δ 4.29 (app. t, minor diastereomer); 4.22 (app. t) and 4.17 (dd, major diastereomer)). Thiol elimination of thioether **3-104** in the presence of Et_3N resulted in a ΔG of +1.8 kcal/mol, while the thiol elimination of **3-104** using DBU yielded a ratio of **3-98**:**3-104** of ≥50:1 by ^{1}H NMR and a ΔG of ≤ −3.8 kcal/mol.



Reaction	Base	ΔG
3-98 to **3-104**	Et_3N	≤ −4.6 kcal/mol
3-98 to **3-104**	DBU	≤ −4.6 kcal/mol
3-104 to **3-98**	Et_3N	+1.8 ± 0.03 kcal/mol
3-104 to **3-98**	DBU	≤ −3.8 kcal/mol

Figure 18. Thiol addition/elimination reactions with enone **3-98** using Et_3N and DBU.

On preparative scale, thiol adducts **3-104a** and **3-104b** were isolated in 79% yield as an inseparable ~2.3:1 mixture of diastereomers. In the major diastereomer, coupling constant analysis of the methine proton highlighted in Figure 19 indicated the presence of a large and a

small coupling constant, which suggests an equatorial thiophenyl group. Simple MMFF calculations[§] agreed with the assignment of the major diastereomer to **3-104a**.

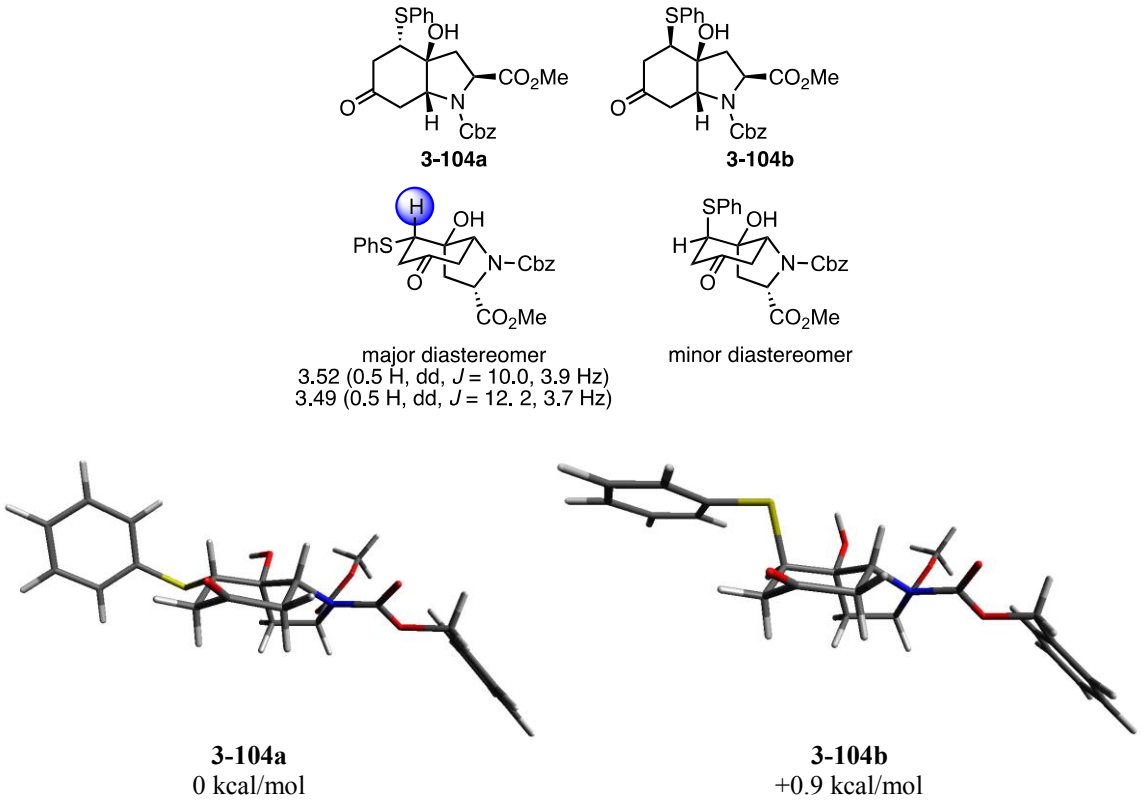
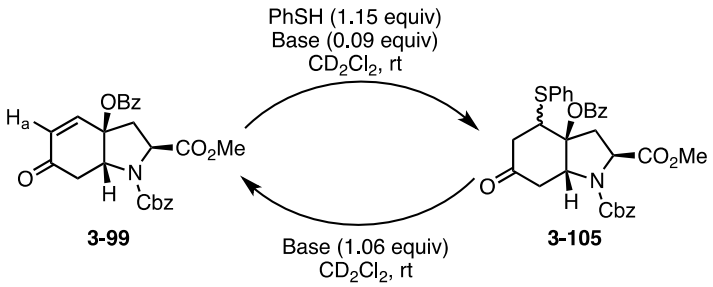


Figure 19. Assignment of diastereomers of thiol addition products **3-104a** and **3-104b**.

Next, we investigated the thiol addition reaction to *O*-benzoyl protected enone **3-99**. The equilibrium constant was determined by integration of the peaks for **3-99** (H_a δ 6.10 (app. t)) and **3-105** (H *o*-OBz, δ 7.99-7.95 (m, 2 H, minor diastereomer) and 7.71-7.67 (m, 2 H, major diastereomer)). The reaction was favored by a ΔG of −4.1 and −4.0 kcal/mol using catalytic Et_3N and DBU, respectively (Figure 20). Additionally, thiol elimination of the major diastereomer **3-105** to afford **3-99** was unfavorable by +1.0 kcal/mol using Et_3N but favorable by ≤ −3.8 kcal/mol in the presence DBU. On preparative scale, the thiophenol addition to enone **3-**

[§] Calculations performed using MMFF conformational search with Spartan 10'

99 yielded adduct **3-105** as a separable ~2:1 mixture of diastereomers in 92% yield. Unfortunately, the relative configuration at C-4 could not be determined; however, MMFF calculations[§] and analogy to **3-104** suggest the α-epimer to be the major diastereomer.



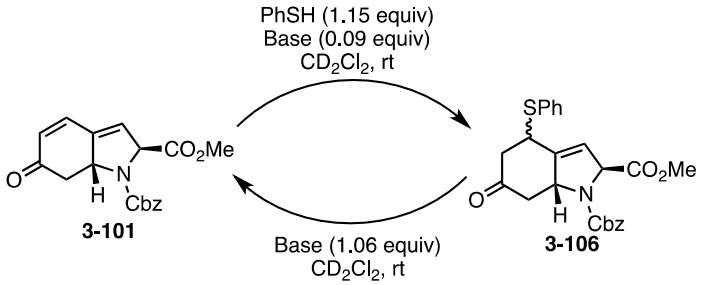
Reaction	Base	ΔG
3-99 to **3-105**	Et_3N	−4.1 ± 0.06 kcal/mol
3-105 to **3-105**	DBU	−4.0 ± 0.02 kcal/mol
3-105 to **3-105**	Et_3N	+1.0 ± 0.001 kcal/mol
3-105 to **3-99**	DBU	≤ −3.8 kcal/mol

Figure 20. Thiol addition/elimination reactions with enone **3-99** using Et_3N and DBU.

Although the ΔG of the base-catalyzed thiol addition reaction to enones should be independent with respect to the identity of the base catalyst, initial experiments for the thiophenol addition to enone **3-99** resulted in deviations of 0.4 kcal/mol when Et_3N or DBU were used. This deviation was initially attributed to the inherent basicity of DBU and the stability of the $DBUH^+PhS$ complex, both of which shift equilibrium toward enone **3-99**. However, upon close inspection of the data we realized that the diastereomers of **3-105** were observed in 1.9:1 ratio in Et_3N and a 2.3:1 ratio in DBU after 23 h. This observation suggested that while the equilibration between enone **3-99** and **3-105** appeared to be complete, equilibration of the

diastereomers of **3-105** was comparably slower. Literature precedent[161a] and repeating the enone addition reactions indicated that equilibration between the diastereomers occurs over 150 hours, however during the extended reaction only minor changes in the ΔG (0.3 kcal/mol) were observed to give a ΔG −4.0 to −4.1 kcal/mol for the thiol addition reaction.

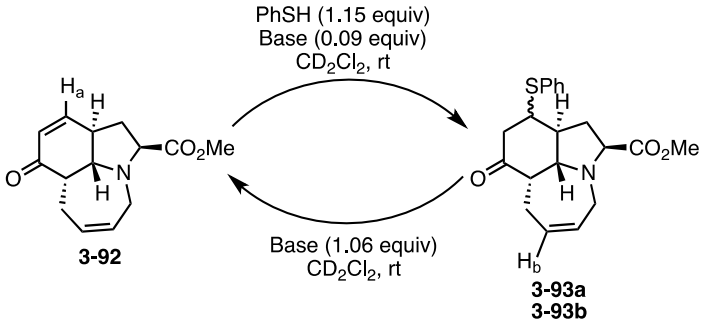
Enone **3-101** could be accessed via oxidation of an undesired byproduct in the synthesis of tuberostemonine. We thought that the additional alkene could impact the equilibria of the thiol addition/elimination reactions due to the increase in conjugation and elimination of steric influence at the γ-carbon of the enone **3-101**. Base-catalyzed thiol addition to enone **3-101** and thiol mediated elimination of adduct **3-106** gave significant quantities of unidentifiable byproducts during the equilibration (Scheme 64); therefore, proper thermodynamic analysis of this substrate could not be completed. We imagine a mixture of β- and δ-conjugate addition products could form in addition to epimerization or isomerization reactions.



Scheme 64. Attempted thiol addition to enone **3-101** and thiol elimination with adduct **3-106**.

After performing a preliminary analysis on simplified enones **3-98** and **3-99**, we were poised to explore the equilibrium of the thiol addition reaction of tricyclic enone **3-92**. Enone **3-92** was prepared in 8 steps from enone **3-99** following the literature procedure.[169] The equilibrium constant was determined by integration of the peaks for **3-92** (H_a δ 6.96 (d)) and **3-**

93 (H_b δ 5.70-5.62 (m)). Addition of thiophenol to enone **3-92** was favorable beyond the limits of detection for NMR (≤ −4.6 kcal/mol) using either catalytic Et_3N or DBU (Figure 21). Thiol elimination of thioether **3-93b** was unfavorable by +3.4 kcal/mol in the presence of Et_3N; however, the thiol elimination was favorable by −2.6 kcal/mol in the presence of DBU.



Reaction	Base	ΔG
3-92 to **3-93**	Et_3N	≤ −4.6 kcal/mol
3-92 to **3-93**	DBU	≤ −4.6 kcal/mol
3-93b to **3-92**	Et_3N	+3.4 ± 0.1 kcal/mol
3-93b to **3-92**	DBU	≤ −2.6 kcal/mol

Figure 21. Thiol addition/elimination reactions with enone **3-92** using Et_3N and DBU.

Preparation of thiol adducts **3-93a** and **3-93b** was accomplished in 86% yield as a separable ~2.7:1 mixture of diastereomers. In the minor diastereomer, coupling constant analysis of the methine proton highlighted in Figure 22 indicated the presence of two large and one small coupling constant, which suggests an equatorial thiophenyl group. MMFF calculations[§] indicate a 1.1 kcal/mol preference for **3-93b**, with the equatorial thiophenyl group,

however the parameters in the low level calculations may not properly account for the 6,7,6-ring system.

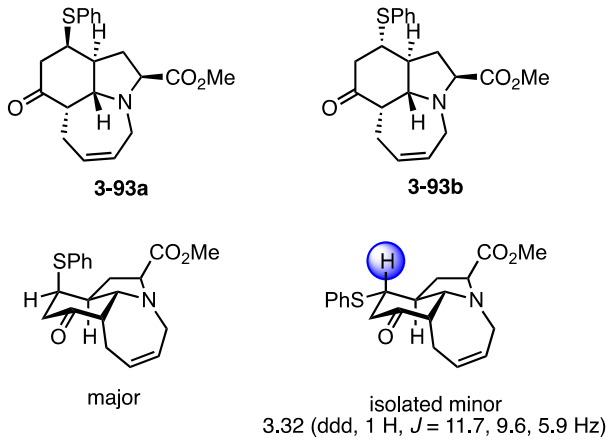
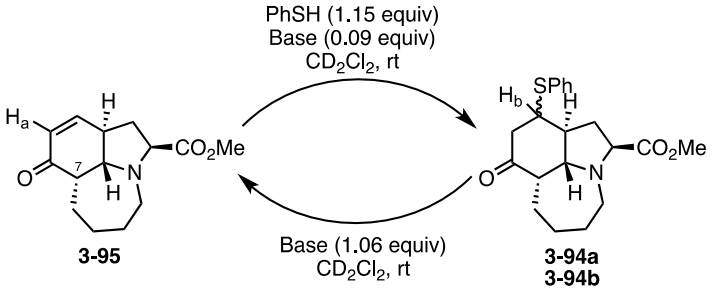


Figure 22. Assignment of diastereomers of thiol addition products **3-93a** and **3-93b**.

After hydrogenation of the azepine **3-93a**, the thiophenol addition/elimination reaction was performed with enone **3-95**. The equilibrium constant was determined by integration of the peaks for **3-95** (H_a δ 5.91 (dd)) and **3-94** (H_b δ 4.02 (dd, major diastereomer) and 3.98 (dd, minor diastereomer). Et_3N- and DBU-catalyzed thiophenol addition to enone **3-95** was favorable with a ΔG of ≤ −4.8 kcal/mol (Figure 23). The thiol elimination reaction of **3-94a** (major) was unfavorable by +2.3 kcal/mol using Et_3N. The thiol elimination reaction of **3-94b** using DBU was favorable by −2.9 kcal/mol, although enone **3-95** was epimerized to a 2.5:1 (*S*:*R*) mixture of epimers at C-7 during the reaction. It could not be determined if epimerization occurred in **3-94** because of the small amount present at equilibrium.



Reaction	Base	ΔG
3-95 to **3-94**	Et_3N	≤ −4.6 kcal/mol
3-95to **3-94**	DBU	≤ −4.6 kcal/mol
3-94a to **3-95**	Et_3N	+2.3 ± 0.03 kcal/mol
3-94b to **3-95**	DBU	−2.9 ± 0.2 kcal/mol[a]

[a]during reaction **3-94b** to **3-95** with DBU enone **3-95** is observed as a 2.5:1 mixture of diastereomers (epimerization α to ketone).

Figure 23. Thiol addition/elimination reactions with enone **3-95** using Et_3N and DBU.

During our investigations, our data showed that Michael additions of thiophenol to enones are highly energetically favorable (≤ −4.6 kcal/mol) for enones **3-92**, **3-95**, and **3-98**. The thiol addition to enone **3-99** is slightly less favorable, −4.1 to −4.0 kcal/mol, which may be a result of the increased steric bulk of the benzoyl group on the tertiary alcohol. The ΔG of the thiol additions to our enones compares well with the ΔG of −4.8 kcal/mol calculated for the addition of thiophenol to cyclopentenone by Bernardi and coworkers.[161a] Our results suggest that these enone containing indole scaffolds could function as covalent inhibitors through a thiol addition pathway.

The thiol elimination reactions of thioethers in the presence of DBU were favored by ≤ −2.6 kcal/mol; however, in the presence of Et_3N the thiol elimination reactions were unfavored by ≥ +1.0 kcal/mol. The difference in ΔG between the thiol elimination reactions using Et_3N and

DBU provides the difference in energy of the two base-thiol complexes ($DBUH^+PhS^-$ vs. $Et_3NH^+PhS^-$). The difference in ΔG between the thiol elimination reactions employing Et_3N and DBU shows that the $DBUH^+PHS^-$ is ≥ 4.8 kcal/mol lower in energy than $Et_3NH^+PHS^-$. The stability of the $DBUH^+PhS^-$ can be explained by the intrinsic basicity of DBU compared to Et_3N ($DBUH^+$ pKa 12.0 (DMSO) vs. Et_3NH^+ pK_a 9.0 (DMSO)). This trend correlates with the acidity of PhSH (pK_a 10.3 (DMSO)), which thermodynamically should be deprontated to a greater extent by DBU compared to TEA. These thiol elimination experiments indicate that in the absence of strong base, equilibrium between the enone and thiol adduct favors the thiol adduct. This suggests that these enones would function as irreversible thiol trapping agents.

3.3 CONCLUSIONS

Our investigations of the equilibria of thiophenol additions to enones and base-mediated thiol eliminations reveal that the formation of thiol adducts is energetically favorable and that the elimination of thiophenol is dependent on the strength of the base used in the elimination reaction. The difference in ΔG of the base-thiol ion pair complexes ($DBUH^+PhS^-$ vs. $Et_3NH^+PhS^-$) acts as a ≥ 4.8 kcal/mol driving force for the thiol eliminations using DBU. Our results show that structure and base strength are two factors that play an important role in the equilibrium between enone and thiol adducts. In agreement with the literature, mono-β-substituted enones form energetically favorable adducts with thiol nucleophiles, which suggests they could be used as covalent protein modifiers. The thiol elimination reactions indicate that strongly basic conditions are required to reverse the equilibrium to favor the enone, which implies that these enones would function as irreversible covalent inhibitors. The effect of base

on the thiol adduct and enone equilibrium should be considered when covalent protein modification occurs in the presence of basic amino acids, such as histidine, lysine, or arginine. The potential impact of these basic residues in the enone binding site may cause a shift in the equilibrium favoring the unbound enone over the thiol adduct.

4.0 EXPERIMENTAL

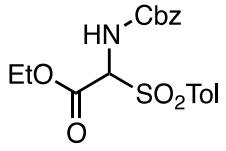
4.1 GENERAL EXPERIMENTAL

All glassware was flame dried and cooled under dry N_2 or Ar prior to use. All moisture sensitive reactions were performed under an atmosphere of dry N_2 or Ar. Reactions carried out below 0 °C employed an acetone/dry ice bath or a cyrocool and an isopropanol/ethanol bath. Reagents obtained from commercial sources were used as received unless otherwise specified. THF, Et_2O, and 1,4-dioxane were distilled from sodium/benzophenone ketyl; DIPEA and Et_3N were distilled from CaH_2 and stored over KOH; *t*-BuOH was distilled over CaH_2; HFIP was distilled from 4Å MS and stored over 4Å MS; and CH_2Cl_2 and toluene were purified by passage through an activated alumina filtration system or by distillation from CaH_2. Concentrating under reduced pressure refers to the use of a rotary evaporator connected to a membrane vacuum pump or a PIAB Lab Vac H40 to remove solvent.

Melting points were determined using a Laboratory Devices Mel-Temp II in open capillary tubes and are uncorrected. Infrared spectra were determined as neat solids or oils on a Smiths Detection IdentifyIR FT-IR spectrometer. Mass spectra were obtained on a Micromass Autospec UK Limited double focusing instrument or a Q-TOF Ultima API a Thermo Scientific Exactive Orbitrap LC-MS. Optical rotations were determined using a Perkin-Elmer 241 polarimeter at 23 °C. Microwave reactions were performed using a Biotage Initiator microwave

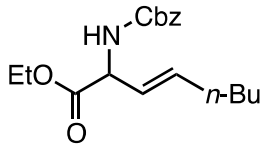
reactor. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz, 400 MHz, 500 MHz, or 600 MHz instruments. Chemical shifts (δ) were reported in parts per million with the residual solvent peak used as an internal standard δ ^{1}H / ^{13}C (Solvent); 7.26 / 77.16 ($CDCl_3$); 2.50 / 39.52 (DMSO-d_6); 5.32 / 53.84 (CD_2Cl_2); 2.05 / 29.84 (acetone-d_6) and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet), number of protons, and coupling constant(s). ^{13}C NMR spectra were obtained using a proton-decoupled pulse sequence and are tabulated by observed peak. Thin-layer chromatography was performed using pre-coated silica gel 60 F_{254} plates (EMD, 250 μm thickness) and visualization was accomplished with a 254 nm UV light and by staining with a *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution), or Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}$•4 H_2O and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution). Flash chromatography on SiO_2 (Silicycle, Silia-P Flash Silica Gel or SiliaFlash® P60, 40-63 μm) was used to purify crude reaction mixtures. All desired products were placed under high vacuum (0.5-4 mmHg) to remove trace solvent.

4.2 CHAPTER 1 EXPERIMENTAL PART



1-71

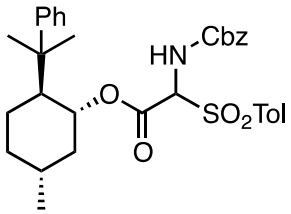
Ethyl 2-(((benzyloxy)carbonyl)amino)-2-((*p*-tolylsulfinyl)oxy)acetate (1-71).[82] To a solution of ethyl glyoxylate **1-70** (2.02 g, 9.89 mmol, 50% in toluene, freshly depolymerized by heating at ~50 °C for 1 min) in formic acid (4.85 mL, 128 mmol) was added benzylcarbamate (1.48 g, 9.79 mmol) and sodium *p*-toluensulfinate (2.62 g, 14.7 mmol). The resulting slurry turned into a solution after 2 min and was stirred vigorously for 86 h at rt. The mixture was poured onto ice water (50 mL) and the resulting colorless precipitate was filtered, washed with water and dried to give **1-71** (2.24 g, 58%) as a colorless solid of 90% purity that was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 2 H, J = 8.2 Hz), 7.39-7.26 (m, 5 H), 7.31 (d, 2 H, J = 8.2 Hz), 6.00 (d, 1 H, J = 10.0 Hz), 5.61 (d, 1 H, J = 10 Hz), 5.03 (s, 2 H), 4.31 (q, 2 H, J = 7.1 Hz), 2.44 (s, 3 H), 1.31 (t, 3 H, J = 7.1 Hz).



1-72

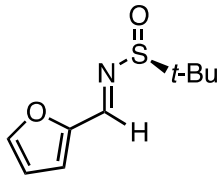
(*E*)-Ethyl 2-(((benzyloxy)carbonyl)amino)oct-3-enoate (1-72). To a suspension of Cp_2ZrHCl (0.172 g, 0.667 mmol) in CH_2Cl_2 (2 mL) was immediately added 1-hexyne **1-52** (65.0 μL, 0.566 mmol). The suspension was stirred for 10 min at rt and the solvent was removed *in vacuo*. The residue was dissolved in toluene (2 mL), cooled to -78 °C, Me_2Zn (280 μL, 0.532 mmol, 1.90 M toluene) was added and the mixture was allowed to warm to rt. The vinyl zinc reagent was added to a suspension of sulfinyl adduct **1-71** (0.100 g, 0.255 mmol) in toluene (2 mL) at 0 °C and allowed to stir for 30 min, quenched with sat. aq. NH_4Cl (1 mL), washed with 1 M HCl (1 x 10 mL) and brine (1 x 10 mL), the organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on

SiO_2 (1:4; EtOAc:hexanes) to give **1-72** (0.0625 g, 77%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.30 (m, 5 H), 5.77 (dt, 1 H, *J* = 15.3, 6.7 Hz), 5.48-5.42 (m, 2 H), 5.12 (s, 2 H), 4.83 (bt, 1 H, *J* = 6.5 Hz), 4.20 (q, 2 H, *J* = 7.1 Hz), 2.04 (aq, 2 H, *J* = 7.0 Hz), 1.37-1.25 (m, 7 H), 0.88 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz) δ 171.2, 155.6, 136.4, 135.1, 128.6, 128.2, 124.1, 67.1, 61.8, 55.8, 31.9, 31.0, 22.2, 14.2, 14.0; MS (EI) *m/z* 319 (M^+, 9), 246 (94), 228 (14), 91 (70); HRMS (EI) *m/z* calcd for $C_{18}H_{25}NO_4$ M^+ 319.1784, found 319.1777.



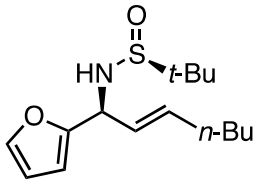
1-73

(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-(((benzyloxy)carbonyl) amino)-2-((*p*-tolylsulfinyl)oxy)acetate (1-73). To a solution of 8-phenylmethol glyoxylate **1-65** (1.67 g, 5.77 mmol) in formic acid (4.50 mL) was added benzylcarbamate (0.874 g, 5.78 mmol), and sodium *p*-toluenesulfinate (1.61 g, 9.02 mmol). The solution was stirred rapidly for 16 h upon which the mixture became gel like. The mixture was allowed to stand for 25 h then diluted with water (5 mL), cooled on ice, filtered, and washed with water (2 x 50 mL). The crude solid was recrystallized from Et_2O (75 mL) and MeOH (5-10 mL) to give **1-73** (0.918 g, 28%) as a colorless solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.79 (d, 1 H, *J* = 10.0 Hz), 7.61 (d, 2 H, *J* = 8.0 Hz), 7.48 (d, 2 H, *J* = 8.0 Hz), 7.41-7.34 (m, 5 H), 7.08-6.98 (m, 5 H), 5.06 (d of AB, 1 H, *J* = 13.0 Hz), 5.03 (d of AB, 1 H, *J* = 13.0 Hz), 4.74 (td, 1 H, *J* = 10.8, 4.3 Hz), 4.67 (d, 1 H, *J* = 10.2 Hz), 2.45 (s, 3 H), 1.91-1.86 (m, 1 H), 1.73-1.58 (m, 3 H), 1.41-1.39 (m, 1 H), 1.08 (s, 6 H), 0.98-0.86 (m, 3 H), 0.87 (d, 3 H, *J* = 6.5 Hz); MS (EI) *m/z* 577 (M^+, 0.1), 422 (88), 156 (100); HRMS (ESI^+) *m/z* calcd for $C_{33}H_{39}NO_6SNa$ $[M+Na]^+$ 600.2396, found 600.2417.



1-77

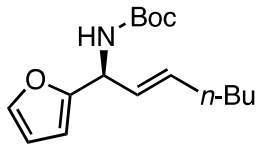
(*S*,*E*)-*N*-(Furan-2-ylmethylene)-2-methylpropane-2-sulfinamide (1-77).[85] To a mixture of *S*-*N*-*tert*-butanesulfinamide (**1-73**) (0.637 g, 5.15 mmol) and furfural (**1-75**) (0.435 mL, 5.20 mmol, freshly distilled from Na_2CO_3 and passed through basic alumina) was added $Ti(EtO)_4$ (3.20 mL, 10.3 mmol) and the solution was stirred rapidly for 4 h at rt. The resulting slurry was poured into a flask and diluted with CH_2Cl_2 (20 mL) and brine (10 mL), filtered through a pad of Celite®, and the filter cake was washed with CH_2Cl_2 (3 x 50 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were concentrated under reduced pressure and purified by chromatography on SiO_2 (2:8; EtOAc:hexanes) to give **1-77** (0.895 g, 86%) as a yellow solid (upon refrigeration): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.35 (s, 1 H), 7.61-7.60 (m, 1 H), 6.97 (dd, 1 H, *J* = 3.5, 0.6 Hz), 6.53 (dd, 1 H, *J* = 3.5, 1.8 Hz), 1.21 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.9, 149.9, 146.9, 118.8, 112.3, 57.9, 22.6.



1-78

(*S*)-*N*-((*S*,*E*)-1-(Furan-2-yl)hept-2-en-1-yl)-2-methylpropane-2-sulfinamide (1-78). A solution of 1-hexyne (**1-52**) (70.0 μL, 0.609 mmol) in CH_2Cl_2 (1.5 mL) was treated with

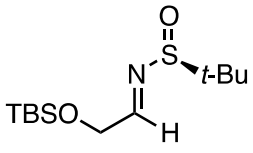
Cp_2ZrHCl (0.187 g, 0.725 mmol) and allowed to stir for 10 min at rt. A solution of imine **1-77** (0.100 g, 0.502 mmol) in CH_2Cl_2 (1 mL) was treated with Me_3Al (276 μL, 0.552 mmol, 2.0 M in CH_2Cl_2) and allowed to stir for 5 min at 0 °C. The vinyl zirconium species was cooled to 0 °C, then Me_3Al (301 μL, 0.602 mmol, 2.0 M in CH_2Cl_2) and the pre-complexed imine **1-77** were added. The reaction mixture was allowed to warm to rt and stirred for 8 h, quenched with sat. aq. NH_4Cl (1 mL), diluted with Et_2O (50 mL) and stirred vigorously with sat. aq. Rochelle's salt (100 mL) for 30 min. The mixture was filtered through a short pad of Celite®, and the organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude mixture was purified by chromatography on SiO_2 (1:5 to 2:3; EtOAc:hexanes) to give **1-78** (0.106 g, 74%) as yellow oil and a single diastereomer by ^1H NMR: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34 (d, 1 H, *J* = 1.2 Hz), 6.28 (dd, 1 H, *J* = 1.8, 3.3 Hz), 6.19 (d, 1 H, *J* = 3.0 Hz), 5.76 (dt, 1 H, *J* = 6.9, 15.3), 5.52 (ddt, 1 H, *J* = 1.2, 7.5, 15.3 Hz), 4.94 (dd, 1 H, *J* = 3.6, 7.5 Hz), 3.53 (d, 1 H, *J* = 3.3 Hz), 2.06 (app q, 2 H, *J* = 6.6 Hz), 1.41-1.22 (m, 4 H), 1.19 (s, 9 H), 0.86 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.4, 142.3, 135.7, 127.1, 110.3, 106.8, 55.7, 55.0, 31.9, 31.1, 22.6, 22.2, 13.9; MS (EI) *m/z* 283 (M^+, 0.3), 163 (100), 107 (87), 57 (88); HRMS (EI) *m/z* calcd for $C_{15}H_{25}NO_2S$ $M^{+\bullet}$ 283.1606, found 283.1600.



1-80

(*S*,*E*)-*tert*-Butyl (1-(furan-2-yl)hept-2-enyl)carbamate (1-80). To a solution of sulfinamide **1-78** (0.475 g, 1.68 mmol) in MeOH (2.0 mL) was added HCl (2.00 mL, 4.00 mmol, 2.0 M in Et_2O). The reaction mixture was allowed to stir for 30 min at rt and concentrated *in*

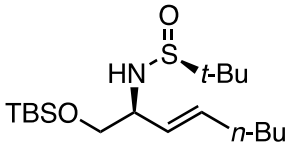
vacuo to give the crude amine hydrochloride (0.361 g, 100%) as a orange-red colored oil that was taken on without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.87 (bs, 3 H), 7.41 (d, 1 H, *J* = 1.5 Hz), 6.48 (d, 1 H, *J* = 3.3 Hz), 6.33 (dd, 1 H, *J* = 1.8, 3.3 Hz), 5.95 (dt, 1 H, *J* = 6.9, 15.3 Hz), 5.74 (dd, 1 H, *J* = 7.5, 15.6 Hz), 4.90 (app t, 1 H, *J* = 5.7 Hz), 2.09 (app q, 2 H, *J* = 6.9 Hz), 1.40-1.26 (m, 4 H), 0.88 (t, 3 H, *J* = 6.9 Hz); To a solution of the crude amine hydrochloride in CH_2Cl_2 (4.0 mL) was added Boc_2O (0.427 g, 1.94 mmol), DMAP (0.203 g, 1.66 mmol), and Et_3N (0.500 mL, 3.56 mmol). The reaction mixture was allowed to stir a rt. After 3.5 h, Boc_2O (0.464 g, 2.13 mmol) was added and the solution was allowed to stir for 1 h at rt, then concentrated under reduced pressure and purified by chromatography on SiO_2 (1:9; EtOAc:hexanes) to give **1-80** (0.225 g, 48%) as a yellow oil: $[\alpha]_D$ -17.3 (*c* 0.77, CH_2Cl_2); IR (ATR) 3338, 2956, 2926, 2870, 1696, 1165, 1006, 967, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (dd, 1 H, *J* = 0.6, 1.2 Hz), 6.30 (dd, 1 H, *J* = 1.8, 3.3 Hz), 6.15 (d, 1 H, *J* = 3.3 Hz), 5.66 (dt, 1 H, *J* = 5.7, 15.3 Hz), 5.56 (dd, 1 H, *J* = 5.7, 15.5 Hz), 5.28 (bs, 1 H), 4.87 (bs, 1 H), 2.05 (app q, 2 H, *J* = 6.9 Hz), 1.44 (s, 9 H), 1.38-1.25 (m, 4 H), 0.88 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.0, 154.4, 142.1, 133.3, 127.2, 110.3, 106.3, 79.9, 77.4, 32.0, 31.3, 28.5, 22.3, 14.1; MS (EI) *m/z* 279 (M^+, 0.7), 223 (49), 178 (17), 163 (28), 57 (59); HRMS (EI) *m/z* calcd for $C_{16}H_{25}NO_3$ M^+ 279.1834, found 279.1830.



1-83

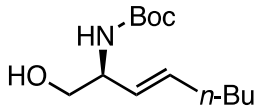
(*S*,*E*)-*N*-(2-((*tert*-Butyldimethylsilyl)oxy)ethylidene)-2-methylpropane-2-sulfinamide (1-83).[86b, 175] To a solution of but-2-ene-1,4-diol (2.00 g, 1.87 mL, 22.0 mmol), imidazole (3.04

g, 44.2 mol) and DMAP (0.151 g, 1.22 mmol) in CH_2Cl_2 (46 mL) was added TBSCl (6.86 g, 44.6 mmol). The reaction mixture was stirred for 13.5 h at rt, concentrated, dissolved in Et_2O (50 mL), washed with 1M HCl (1 x 50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the protected diol as a crude mixture. To a solution of the crude diol (6.67 g, 22.0 mmol) in CH_2Cl_2 (44 mL) was bubbled ozone at -78 °C until a blue color persisted (~25 min). Nitrogen was bubbled through the solution until the blue color disappeared. Me_2S (9.25 mL, 123 mmol) was then slowly added at -78 °C. The reaction mixture was slowly warmed to rt, stirred for 16 h, and concentrated under reduced pressure. The residue was redissolved in Et_2O (50 mL), washed with water (50 mL), and the organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the crude aldehyde as a colorless oil. To a solution of the aldehyde (1.50 g, 8.61 mmol) in CH_2Cl_2 (15 mL) was added anhydrous copper sulfate (4.27 g, 26.8 mmol) followed by the *S*-*N*-*tert*-butanesulfinamide (**1-76**) (0.852 g, 7.03 mmol). The heterogeneous mixture was stirred rapidly for 14 h at rt and filtered through a pad of Celite®. The filter cake was washed with CH_2Cl_2, and the filtrate was concentrated under reduced pressure. The resulting oil was purified by chromatography on SiO_2 (15:85; EtOAc:hexanes) to give **1-83** (0.818 g, 34% from *cis*-butene-1,4-diol) as a light yellow oil containing ~15% of a silyl impurity (could be stored under dry N_2 at -20 °C for several weeks, decomposition occurred at rt over several days): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (t, 1 H, J = 3.1 Hz), 4.54 (d, 2 H, J = 3.1 Hz), 1.20 (s , 9 H), 0.91 (s, 9 H), 0.09 (s, 6 H).



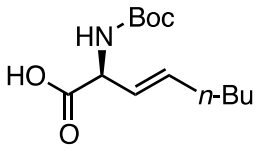
1-84

(*S*)-*N*-((*S*,*E*)-1-((*tert*-Butyldimethylsilyl)oxy)oct-3-en-2-yl)-2-methylpropane-2-sulfinamide (1-84). To a solution of 1-hexyne (**1-52**) (0.602 mL, 5.24 mmol) in CH_2Cl_2 (7.0 mL) at 0 °C was added Cp_2ZrHCl (1.48 g, 5.73 mmol). The reaction mixture was warmed to rt, stirred for 10 min, cooled to 0 °C, and treated with Me_3Al (2.20 mL, 4.04 mmol, 2.02 M in CH_2Cl_2). To a separate flask containing imine **1-83** (1.12 g, 4.03 mmol) in CH_2Cl_2 (7.0 mL) cooled to 0 °C was added Me_3Al (2.20 mL, 4.04 mmol, 2.02 M in CH_2Cl_2) and then this solution was cannulated into the solution of the vinyl alane and stirred at rt for 9 h. The reaction mixture was transferred to a larger flask and diluted with Et_2O (100 mL), quenched with sat. aq. NH_4Cl (2 mL), and stirred vigorously with sat. aq. Rochelle's salt (100 mL) for 30 min. The mixture was filtered though a pad of Celite®, and the organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (15:85; EtOAc:hexanes) to give **1-84** (0.884 g, 61%) as a light yellow oil: $[\alpha]_D$ +111 (*c* 0.99, CH_2Cl_2); IR (ATR) 3202, 3282, 2952, 2926, 2855, 1470, 1463, 1251, 1060, 833 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.73 (dt, 1 H, J = 6.8, 15.3 Hz), 5.12 (ddt, 1 H, J = 1.2, 7.8, 15.3 Hz), 3.90-3.82 (m, 2 H), 3.61 (AB dd, 1 H, J_{AB} = 4.2, 9.9 Hz), 3.41 (AB dd, 1 H, J_{AB} = 8.7, 9.6 Hz), 2.00 (app q, 2 H, J = 6.6 Hz), 1.37-1.26 (m, 4 H), 1.17 (s, 9 H), 0.86 (s, 12 H), 0.03 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.2, 126.7, 66.5, 57.8, 55.1, 32.1, 31.2, 25.9, 22.7, 22.1, 18.2, 13.9, -5.3, -5.4; MS (EI) *m/z* 361 (M^+, 7), 304 (43), 241 (30), 185 (92), 142 (73); HRMS (ESI^+) *m/z* calcd for $C_{18}H_{39}NO_2SiS$ M^+ 361.2471, found 361.2463.



1-85

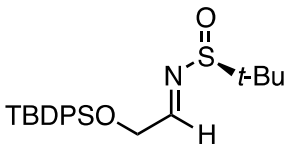
(*S*,*E*)-*tert*-Butyl (1-hydroxyoct-3-en-2-yl)carbamate (1-85).[176] To a solution of sulfinamide **1-84** (0.644 g, 1.78 mmol) in MeOH (2.0 mL) cooled to 0 °C was added HCl (9.00 mL, 18.0 mmol, 2.0 M in Et_2O). The mixture was warmed to rt and stirred for 1.5 h then concentrated *in vacuo* and to yield the crude amino alcohol hydrochloride. To a solution of the crude amino alcohol hydrochloride in CH_2Cl_2 (6.0 mL) was added $NaHCO_3$ (0.747 g, 8.89 mmol) and stirred rapidly for 5 min. Et_3N (0.750 mL, 5.34 mmol), DMAP (0.0423 g, 0.346 mmol), and Boc_2O (0.253 g, 2.71 mmol) were added and the mixture was allowed to stir for 19 h at rt, quenched with water (3 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with brine (1 x 7 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified by chromatography on SiO_2 (1:9 to 2:8; EtOAc:hexanes) to give **1-85** (0.433 g, 58%) as a light yellow oil: $[\alpha]_D$ +4.2 (*c* 1.02, CH_2Cl_2); IR (ATR) 3332, 2956, 2924, 1685, 1165, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.66 (ddt, 1 H, *J* = 1.2, 6.9, 15.3 Hz), 5.35 (dd, 1 H, *J* = 6.3, 15.3 Hz), 4.88 (d, 1 H, *J* = 7.5 Hz), 4.15 (bs, 1 H), 3.67-3.52 (m, 2 H), 2.02 (app q, 2 H, *J* = 6.9 Hz), 1.43 (s, 9 H), 1.36-1.29 (m, 4 H), 0.87 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.3, 133.7, 126.8, 79.9, 66.6, 54.5, 32.1, 31.3, 28.5, 22.3, 14.0; MS (EI) *m/z* 212 ($[M\text{-}CH_3O]^+$, 60), 156 (100), 112 (96), 96 (65); HRMS (EI) *m/z* calcd for $C_{12}H_{22}NO_2$ $[M\text{-}CH_3O]^+$ 212.1651, found 212.1648.



1-86

(*S*,*E*)-2-((*tert*-Butoxycarbonyl)amino)oct-3-enoic acid (1-86).[176] To a solution of **1-85** (0.219 g, 0.900 mmol) in CH_2Cl_2 (8.0 mL) was added $NaHCO_3$ (0.232 g, 2.76 mmol) and DMP

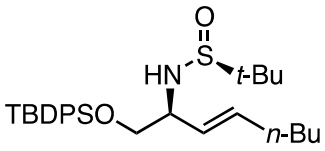
(0.575 g, 1.36 mmol). The reaction mixture was allowed to stir at rt for 1.5 h, quenched with sat. aq. $Na_2S_2O_3$ (3 mL) and sat. aq. $NaHCO_3$ (3 mL), diluted with Et_2O (5 mL), and stirred rapidly until the solids dissolved. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. To a solution of the crude aldehyde in THF (4.0 mL) and water (2.0 mL) was added $NaH_2PO_4 \bullet H_2O$ (0.376 g, 2.72 mmol), 2-methyl-2-butene (0.950 mL, 8.97 mmol), followed by $NaClO_2$ (0.243 g, 2.69 mmol). The mixture was allowed to stir at rt for 3.75 h, extracted with EtOAc (3 x 10 mL), washed with brine (1 x 10 mL), and concentrated under reduced pressure. The oily residue was dissolved in CH_2Cl_2, filtered through a pad of Celite®, washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give **1-86** (0.214 g, 92%) as a crude yellow oil of approximately 85% purity based on ^{1}H NMR analysis: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.25 (bs, 1 H), 7.18 (bs, 1 H), 5.83-5.76 (m, 1 H), 5.49-5.44 (m, 1 H), 5.19 (d, 1 H, J = 6.9 Hz), 2.04 (app q, 2 H, J = 6.6 Hz), 1.42 (s, 9 H), 1.38-1.25 (m, 4 H), 0.87 (t, 3 H, J = 6.6 Hz).



1-87

(*S*,*E*)-*N*-(2-((*tert*-Butyldiphenylsilyl)oxy)ethylidene)-2-methylpropane-2-sulfinamide (1-87).[177] To a solution of 2-*cis*-1,4-butenediol (1.00 mL, 12.2 mL), in CH_2Cl_2 (30 mL) was added TBDPSCl (6.32 mL, 24.3 mmol), imidazole (2.51 g, 36.5 mmol) and DMAP (0.0743 g, 0.608 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 15 h, concentrated, redissolved in Et_2O (30 mL) and washed with 1 M HCl (30 mL). The organic layer was dried

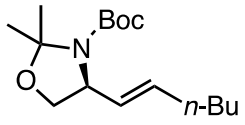
($MgSO_4$), filtered, and concentrated under reduced pressure. To a solution of the crude protected diol (6.87 g, 12.17 mmol) in CH_2Cl_2 (30 mL) was bubbled ozone at -78 °C until a blue color persisted (~20 min). Nitrogen was bubbled through the blue solution until it turned colorless and Me_2S (32.0 mL, 433 mmol) was then slowly added. The reaction mixture was slowly warmed to rt, stirred for 17 h, and concentrated under reduced pressure. The residue was partitioned between Et_2O (30 mL) and water (30 mL). The organic layer was washed with water (1 x 30 mL) and brine (1 x 30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. To a solution of the crude aldehyde (1.06 g, 3.55 mmol) in THF (6 mL) was added *S*-*N*-*tert*-butanesulfinamide (**1-76**) (0.485 g, 4.00 mmol) and $Ti(EtO)_4$ (1.50 mL, 7.15 mmol). The mixture was stirred for 20 h at rt. The resulting slurry was diluted with EtOAc (10 mL), quenched with brine (5 mL), stirred for 5 min, and filtered through a pad of Celite®. The filtrate was washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered and concentrated. The crude oil was purified by chromatography on SiO_2 (1:9, EtOAc:hexanes) to give **1-87** (0.680 g, 48% from 2-cis-1,4-butenediol) as a light yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (t, 1 H, J = 2.9 Hz), 7.72-7.67 (m, 4 H), 7.45-7.37 (m, 6 H), 4.57 (d, 2 H, J = 2.9 Hz), 1.20 (s, 9 H), 1.10 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.3, 135.6, 132.9, 130.1, 127.9, 66.2, 56.9, 26.8, 22.4, 19.3.



1-88

(*S*)-*N*-((*S*,*E*)-1-((*tert*-Butyldiphenylsilyl)oxy)oct-3-en-2-yl)-2-methylpropane-2-sulfinamide (1-88). To a solution of 1-hexyne (**1-52**) (0.205 mL, 1.78 mmol) in CH_2Cl_2 (2.25 mL) was adde Cp_2ZrHCl (0.498 g, 1.93 mmol) and the suspension was stirred at rt for 10 min,

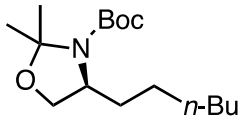
cooled to 0 °C and treated with Me_3Al (0.750 mL, 1.50 mmol, 2.0 M in CH_2Cl_2). To a solution of imine **1-87** (0.549 g, 1.37 mmol) in CH_2Cl_2 (2.25 mL) in a separate flask at 0 °C was added Me_3Al (0.750 mL, 1.50 mmol, 2.0 M in CH_2Cl_2). The mixture was stirred for 5 min and the vinyl alane was added via cannula. The reaction mixture was warmed to rt, stirred for 4 h, diluted with Et_2O (50 mL), quenched with sat. aq. NH_4Cl (5 mL), and stirred rapidly with sat. aq. Rochelle's salt (100 mL) for 10 min. The mixture was filtered through a pad of Celite®, separated, the aqueous layer was extracted with Et_2O (2 x 10 mL), and the organic layers were combined, washed with brine (1 x 20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Analysis of the crude mixture by ^1H NMR showed a single diastereomer before purification by chromatography on SiO_2 (2:8; EtOAc:hexanes) to give **1-88** (0.503 g, 76%) as a colorless oil: $[\alpha]_D$ +68.3 (*c* 1.03, CH_2Cl_2); IR (ATR) 3280, 2952, 2926, 1109, 1073, 969 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.69-7.65 (m, 4 H), 7.47-7.36 (m, 6 H), 5.72 (dt, 1 H, *J* = 15.4, 6.7 Hz), 5.10 (dd, 1 H, *J* = 15.4, 8.0 Hz), 4.10 (bs, 1 H), 4.04-3.97 (m, 1 H), 3.67 (dd, 1 H, *J* = 9.9, 4.2 Hz), 3.53 (app t, 1 H, *J* = 9.6 Hz), 1.99 (app q, 2 H, *J* = 6.7 Hz), 1.36-1.26 (m, 4 H), 1.24 (s, 9 H), 1.06 (s, 9 H), 0.86 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.7, 135.7, 135.7, 133.2, 133.0, 130.0, 130.0, 127.9, 127.9, 126.4, 67.2, 57.8, 55.2, 32.2, 31.2, 26.9, 22.8, 22.2, 19.3, 14.0; MS (ESI^+) *m/z* 508 ($[M+Na]^+$, 100), 486 ($[M+H]^+$, 4), 387 (48); HRMS (ESI^+) *m/z* calcd for $C_{28}H_{44}NO_2SSi$ $[M+H]^+$ 486.2862, found 486.2870.



1-89

(*S*,*E*)-*tert*-Butyl 4-(hex-1-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (1-89). To a solution of **1-85** (0.036 g, 0.15 mmol) in toluene (0.5 mL) was added 2,2-dimethoxypropane

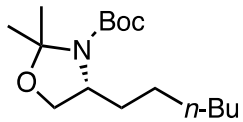
(0.037 mL, 0.30 mmol) and PTSA (0.0010 g, 0.0058 mmol). The reaction mixture was stirred at reflux for 6 h, cooled to rt, quenched with sat. aq. $NaHCO_3$ (5 mL) and extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was purified by chromatography on SiO_2 (5:95; EtOAc:hexanes) to give **1-89** (0.027 g, 66%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.55 (bs, 1 H), 5.40 (dd, 1 H, J = 7.8, 15.3 Hz), 4.33-4.21 (m, 1 H), 4.00 (AB dd, 1 H, J_{AB} = 6.0, 8.7 Hz), 3.70 (AB dd, 1 H, J_{AB} = 2.1, 8.7 Hz), 2.02 (app q, 2 H, J = 6.6 Hz), 1.59 (bs, 3 H), 1.49 (s, 3 H), 1.43 (bs, 9 H), 1.36-1.24 (m, 4 H), 0.88 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.1, 132.8, 129.2, 93.8, 79.5, 68.7, 59.4, 31.9, 31.5, 28.6, 26.8, 23.9, 22.3, 14.0; MS (EI) *m/z* 268 ([M-CH_3]$^+$, 73), 212 (20), 168 (80), 57 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{26}NO_3$ [M-CH_3]$^+$ 268.1913, found 268.1910.



1-90

(*S*)-*tert*-Butyl 4-hexyl-2,2-dimethyloxazolidine-3-carboxylate (1-90). To a solution of olefin **1-89** (0.020 g, 0.072 mmol) in EtOH (0.42 mL) was added 10% Pd/C (0.012 g, 0.011 mmol) and H_2 was bubbled through the reaction mixture at rt for 3.75 h. The mixture was filtered through a pad of Celite®, washed with CH_2Cl_2, and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (3:97; EtOAc:hexanes) to give **1-90** (0.018 g, 89%) as a colorless oil: $[\alpha]_D$ +27 (*c* 0.95, CH_2Cl_2); IR (ATR) 2928, 2857, 1694, 1385, 1375 cm^{-1}; ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 3.90 (ddd, 1 H, J = 8.7, 5.9, 0.6 Hz), 3.77 (dddd, 1 H, J = 8.8, 5.7, 3.8, 1.8 Hz), 3.67 (dd, 1 H, J = 8.7, 1.8 Hz), 1.69-1.56 (m, 1 H), 1.48 (s, 3 H), 1.43 (s, 9 H), 1.41 (s, 3 H), 1.28 (bs, 9 H), 0.88 (t, 3 H, J = 6.7 Hz); ^{13}C NMR (DMSO-d_6,

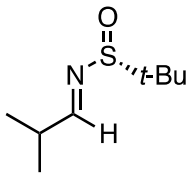
60 °C, 75 MHz) δ 150.9, 92.3, 66.2, 56.5, 32.6, 30.7, 28.1, 27.7, 26.5, 24.9, 23.4, 21.5, 13.3; MS (EI) *m/z* 285 (M^+, 0.5), 270 (75); HRMS (EI) *m/z* calcd for $C_{16}H_{31}NO_3$ M^+ 285.2304, found 285.2312.



1-93

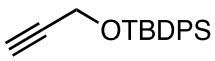
(*R*)-*tert*-Butyl 4-hexyl-2,2-dimethyloxazolidine-3-carboxylate (1-93). To a solution of pentylphosphoniumbromide (0.136 g, 0.330 mmol) in THF (1.0 mL) cooled to -78 °C was added dropwise KHMDS (0.610 mL, 0.305 mmol, 0.5 M in toluene). The solution was warmed to rt, stirred for 5 min, cooled to -78 °C and treated dropwise with a solution of Garner's aldehyde **1-91** (0.051 g, 0.22 mmol) in THF (0.6 mL). After dropwise addition of MeOH (1.6 mL), the mixture was warmed to rt, stirred for 3 h, diluted with $CHCl_3$, washed with water, dried ($MgSO_4$), filtered through a pad of Celite®, and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (5:95; EtOAc:hexanes) to give **1-92** (0.0365 g, 58%) as a colorless oil and ~92:8 *E*:*Z* mixture of olefin isomers. Major isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.54 (bs, 1 H), 5.39 (dd, 1 H, *J* = 15.3, 7.5 Hz), 4.32-4.21 (m, 1 H), 3.99 (dd of AB, 1 H, *J* = 8.7, 6.0 Hz), 3.69 (dd of AB, 1 H, *J* = 8.7, 2.1 Hz), 2.01 (app q, 2 H, *J* = 6.6 Hz), 1.58 (bs, 3 H), 1.48 (s, 3 H), 1.42 (bs, 9 H), 1.36-1.24 (m, 4 H), 0.87 (t, 3 H, *J* = 6.9 Hz). To a solution of the olefin mixture **1-92** (0.0365 g, 0.129 mmol) in EtOH (0.75 mL) was added 10% Pd/C (0.0186 g, 0.0175 mmol) and H_2 was bubbled through at rt for 3.5 h. The reaction mixture was filtered through a pad of Celite®, washed with CH_2Cl_2, concentrated under reduced pressure, and the crude residue was purified by chromatography on SiO_2 (3:97; EtOAc:hexanes) to give **1-93** (0.0317 g, 86%) as a colorless oil: $[\alpha]_D$ -26 (*c* 0.99, CH_2Cl_2); IR (ATR) 2924, 2857,

1692, 1385, 1374 cm^{-1}; ^1H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 3.90 (dd of AB, 1 H, *J* = 8.7, 5.7, Hz), 3.78-3.72 (m, 1 H), 3.67 (dd of AB, 1 H, *J* = 8.7, 1.8 Hz), 1.69-1.56 (m, 2 H), 1.56 (s, 3 H), 1.43 (s, 9 H), 1.41 (s, 3 H), 1.28 (bs, 8 H), 0.87 (t, 3 H, *J* = 6.6 Hz); ^{13}C NMR (DMSO-d_6, 60 °C, 75 MHz) δ 150.9, 92.3, 78.4, 66.2, 56.5, 32.6, 30.8, 28.1, 27.8, 26.5, 24.9, 23.4, 21.5, 13.3; MS (EI) *m/z* 285 (M^+, 0.6), 214 (55); HRMS (EI) *m/z* calcd for $C_{16}H_{31}NO_3$ M^+ 285.2304, found 285.2312.



1-96

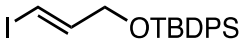
(*R*,*E*)-2-Methyl-*N*-(2-methylpropylidene)propane-2-sulfinamide (1-96).[92] To a solution of isobutyraldehyde (**1-94**) (1.20 mL, 13.0 mmol) in CH_2Cl_2 (40 mL) was added $MgSO_4$ (3.66 g, 30.4 mmol), (*R*)-*tert*-butanesulfinamide (**1-95**) (0.753 g, 6.09 mmol), and PPTS (0.0813 g, 0.324 mmol). The resulting suspension was stirred for 20 h at rt, filtered through a pad of Celite®, washed with CH_2Cl_2 (50 mL), and concentrated under reduced pressure to give **1-96** (0.800 g, 75%) as a light yellow oil that was used without purification: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.97 (d, 1 H, *J* = 4.4 Hz), 2.70 (dqq, 1 H, *J* = 6.9, 6.9, 4.4 Hz), 1.17 (s, 9 H), 1.16 (d, 3 H, *J* = 6.9 Hz), 1.15 (d, 3 H, *J* = 6.9 Hz).



1-97

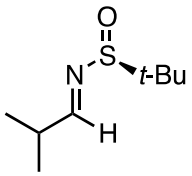
***tert*-Butyldiphenyl(prop-2-ynyloxy)silane (1-97).**[94] To a solution of propargyl alcohol (10.3 mL, 178 mmol) in CH_2Cl_2 (100 mL) was added TBDPSCl (52.5 mL, 197 mmol) and

imidazole (13.5 g, 196 mmol). The reaction mixture was stirred for 16 h at rt, diluted with Et_2O (100 mL), washed with brine (2 x 50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting oil was cooled in the freezer (-20 °C) then placed under high vacuum, resulting in a light yellow solid that was recrystallized (Et_2O:hexanes) to give **1-97** (42.1 g, 80 %) as a light yellow crystalline solid. The filtrate was concentrated and purified by chromatography (1:99; Et_2O:hexanes) to give **1-97** (10.9 g, 21%) as a colorless solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76-7.74 (m, 4 H), 7.50-7.40 (m, 6 H), 4.34 (d, 2 H, *J* = 2.3 Hz), 2.41 (t, 1 H, *J* = 2.3 Hz) 1.10 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.7, 133.1, 130.0, 127.9, 82.1, 73.2, 52.6, 26.8, 19.3.



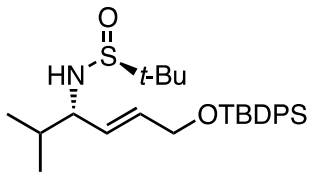
1-100

(*E*)-*tert*-Butyl((3-iodoallyl)oxy)diphenylsilane (1-100).[95] To a suspension of Cp_2ZrHCl (5.25 g, 20.4 mmol) in THF (48 mL) at 0 °C was added **1-97** (5.00 g, 17.0 mmol). The reaction mixture was warmed to rt, stirred for 1.5 h while protected from light, cooled to -78 °C, and treated with iodine (5.33 g, 21.0 mmol). The mixture was warmed to rt and stirred for 30 min, then quenched with 1 M HCl (50 mL). The mixture was extracted with Et_2O (3 x 25 mL), and the combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (2 x 20 mL), sat. aq. $NaHCO_3$ (1 x 20 mL), and brine (1 x 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude oil was purified by chromatography on SiO_2 (hexanes) to give 1.17 g (68%) of **1-100** as light orange oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67-7.65 (m, 4 H), 7.48-7.37 (m, 6 H), 6.60 (dt, 1 H, *J* = 4.5, 14.4 Hz), 6.36 (dt, 1 H, *J* = 1.8, 14.4 Hz), 4.13 (dd, 2 H, *J* = 1.8, 4.5 Hz), 1.07 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.6, 135.6, 133.2, 130.0, 127.9, 76.1, 66.2, 26.9, 19.4.



1-101

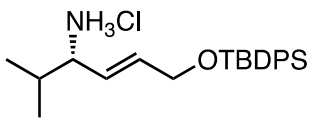
(*S*,*E*)-2-Methyl-*N*-(2-methylpropylidene)propane-2-sulfinamide (1-101).[92] To a slurry of (*S*)-*tert*-butanesulfinamide (**1-77**) (3.00 g, 24.8 mmol), $MgSO_4$ (14.9 g, 123 mmol), and PPTS (0.314 g, 1.25 mmol) in CH_2Cl_2 (90 mL) was added isobutyraldehyde (4.75 mL, 52.0 mmol). The reaction mixture was stirred for 24 h at rt, filtered through a pad of Celite®, washed thoroughly with CH_2Cl_2, and concentrated under reduced pressure. The resulting oil was purified by chromatography on SiO_2 (1:9; EtOAc:hexanes) to give **1-101** (3.96 g, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98 (d, 1 H, *J* = 4.4 Hz), 2.71 (dqq, 1 H, *J* = 6.9, 6.9, 4.4 Hz), 1.18 (s, 9 H), 1.16 (d, 3 H, *J* = 7.1 Hz), 1.16 (d, 3 H, *J* = 6.9 Hz).



1-102

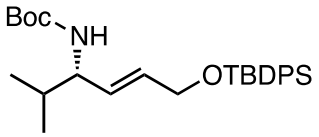
(*S*)-*N*-((*S*,*E*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2-methylhex-4-en-3-yl)-2-methylpropane-2-sulfinamide (1-102). To a solution of **1-100** (1.78 g, 4.21 mmol) in Et_2O (4.0 mL) cooled to -78 °C was added *t*-BuLi (5.00 mL, 8.45 mmol, 1.69 M in pentane) dropwise. The reaction mixture was allowed to stir for 15 min, treated dropwise with $MgBr_2$ (4.21 mL, 4.21 mmol, 1.0 M in benzene:Et_2O; 1:4), and stirred for 15 min. A solution of imine **1-101** (0.568 g, 3.24 mmol) in CH_2Cl_2 (5 mL) was added via cannula. The mixture was warmed to rt, and stirred for 14 h, quenched with sat. aq. NH_4Cl (5 mL) and water (5 mL), and extracted with CH_2Cl_2 (3 x

10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (2:8 to 4:6; EtOAc:hexanes) to give **1-102** (1.24 g, 81%) as a light yellow oil along with a minor diastereomer (0.208 g, 14%). Major diastereomer: $[\alpha]_D$ +38.7 (*c* 1.00, CH_2Cl_2); IR (ATR) 3211, 2956, 2930, 2855, 1470, 1428, 1109, 1057, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.70-7.66 (m, 4 H), 7.45-7.34 (m, 6 H), 5.82 (dt, 1 H, *J* = 15.6, 3.6 Hz), 5.75 (ddt, 1 H, *J* = 15.6, 6.3, 0.9 Hz), 4.24 (d, 2 H, *J* = 3.0 Hz), 3.67 (app q, 1 H, *J* = 5.7 Hz), 3.05 (d, 1 H, *J* = 5.7 Hz), 1.95 (dqq, 1 H, *J* = 6.6, 6.6, 4.8 Hz), 1.23 (s, 9 H), 1.06 (s, 9 H), 0.90 (d, 3 H, *J* = 6.6 Hz), 0.89 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.6, 133.8, 133.8, 132.6, 129.8, 128.7, 127.8, 63.9, 62.9, 56.0, 32.3, 26.9, 22.8, 19.4, 18.8, 17.5; MS (EI) *m/z* 472 ($[M+H]^+$, 30), 394 (22), 351 (47), 337 (63), 295 (37), 280 (51), 121 (23), 77 (35); HRMS (EI) *m/z* calcd for $C_{27}H_{42}NO_2SSi$ $[M+H]^+$ 472.2706, found 472.2695. Minor diastereomer: $[\alpha]_D$ +45.8 (*c* 1.00, CH_2Cl_2); IR (ATR) 3209, 2953, 2928, 1470, 1105, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.70-7.67 (m, 4 H), 7.45-7.34 (m, 6 H), 5.77 (dt, 1 H, *J* = 15.3, 4.2 Hz), 5.62 (ddt, 1 H, *J* = 15.3, 8.1, 1.8 Hz), 4.24 (dd, 2 H, *J* = 3.9, 1.5 Hz), 3.70 (ddd, 1 H, *J* = 8.1, 4.8, 3.0 Hz), 3.15 (d, 1 H, *J* = 2.7 Hz), 1.79 (dqq, 1 H, *J* = 6.6, 6.6, 4.8 Hz), 1.21 (s, 9 H), 1.05 (s, 9 H), 0.94 (d, 3 H, *J* = 6.6 Hz), 0.92 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.6, 135.6, 133.9, 133.8, 133.2, 129.8, 127.8, 127.7, 63.8, 62.1, 55.5, 33.8, 26.9, 22.8, 19.4, 19.1, 17.6; MS (EI) *m/z* 472 ($[M+H]^+$, 3), 351 (24), 337 (28), 295 (21), 280 (94), 121 (34); HRMS (EI) *m/z* calcd for $C_{27}H_{42}NO_2SSi$ $[M+H]^+$ 472.2706, found 472.2722.



1-104

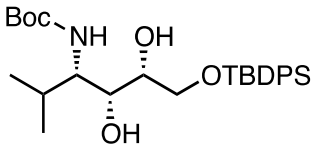
(*S*,*E*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2-methylhex-4-en-3-amine hydrochloride (1-104). To a solution of sulfinamide **1-102** (0.187 g, 0.396 mmol) in hexanes (1.8 mL) was added HCl (2 M in Et_2O, 0.400 mL, 0.800 mmol). The resulting slurry was stirred at rt for 30 min, filtered, and washed with hexanes (2 x 5 mL) to give amine hydrochloride **1-104** (0.140 g, 88%) as a colorless solid: Mp 171.3-172.1 °C (hexanes); $[\alpha]_D$ -2.84 (*c* 1.00, CH_2Cl_2); IR (ATR) 3008, 2954, 2889, 1599, 1109, 971 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.59 (bs, 3 H), 7.66-7.63 (m, 4 H), 7.38-7.37 (m, 6 H), 5.95 (dt, 1 H, *J* = 15.5, 3.6 Hz), 5.83 (dd, 1 H, *J* = 15.5, 7.2 Hz), 4.20 (d, 1 H, *J* = 2.5 Hz), 3.56-3.55 (m, 1 H), 2.13 (app sext., 1 H, *J* = 6.4 Hz), 1.05 (s, 9 H), 0.98 (d, 3 H, *J* = 6.4 Hz), 0.96 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.8, 135.6, 133.5, 133.5, 129.8, 127.9, 127.9, 122.3, 63.3, 59.0, 31.4, 26.9, 19.4, 19.3, 17.5; MS (EI) *m/z* 324 ($[M-C_3H_7]^+$, 13), 310 (18), 199 (100); HRMS (EI) *m/z* calcd for $C_{20}H_{26}NOSi$ $[M-C_3H_7]^+$ 324.1784, found 324.1780.



1-105

(*S*,*E*)-*tert*-butyl (6-((*tert*-butyldiphenylsilyl)oxy)-2-methylhex-4-en-3-yl)carbamate (1-105). To a solution of amine hydrochloride **1-104** (0.150 g, 0.371 mmol) in CH_2Cl_2 (2.5 mL) was added Boc_2O (0.100 mL, 0.435 mL) and Et_3N (0.155 mL, 1.10 mmol). The reaction mixture was stirred at rt for 17.75 h, quenched with sat. aq. NH_4Cl (5 mL) and water (5 mL), separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 (1:9; EtOAc:hexanes) to give 0.180 g (100%) of **1-105** as a colorless oil: $[\alpha]_D$ -12.2 (*c* 1.00, CH_2Cl_2); IR (ATR) 3338, 2959, 2930, 1700, 1497,

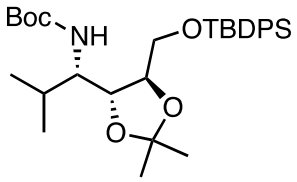
1111 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.69-7.66 (m, 4 H), 7.45-7.34 (m, 6 H), 5.72-5.59 (m, 2 H), 4.50-4.46 (m, 1 H), 4.21 (dd, 2 H, *J* = 2.3, 0.9 Hz), 4.00 (bs, 1 H), 1.77 (app sext., 1 H, *J* = 6.6 Hz), 1.45 (s, 9 H), 1.06 (s, 9 H), 0.89 (d, 3 H, *J* = 6.8 Hz), 0.88 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.8, 135.8, 134.2, 130.3, 129.8, 129.5, 127.8, 79.3, 64.3, 32.8, 28.7, 27.7, 27.1, 19.5, 18.7, 18.4; MS (ESI^+) *m/z* 490 ($[M+Na]^+$, 100), 351 (15); HRMS (ESI^+) *m/z* calcd for $C_{28}H_{41}NO_3SiNa$ $[M+Na]^+$ 490.2753, found 490.2744.



1-106

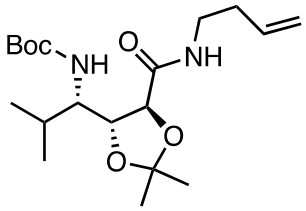
***tert*-Butyl ((3*S*,4*R*,5*R*)-6-((*tert*-butyldiphenylsilyl)oxy)-4,5-dihydroxy-2-methylhexan-3-yl)carbamate (1-106)**. To a biphasic solution of carbamate **1-105** (1.86 g, 3.98 mmol) in acetone (17 mL) and water (8 mL) was added NMO (0.806 g, 5.96 mmol) and OsO_4 (2.50 mL, 0.200 mmol, 0.08 M in *n*-BuOH). The reaction mixture was vigorously stirred for 20.5 h, quenched with sat. aq. $NaHSO_3$ (20 mL), and the acetone was removed under reduced pressure. The aqueous mixture was diluted with water (10 mL) and EtOAc (15 mL), separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered through a pad of Celite®, and concentrated. The crude residue was composed of a 4:1 mixture of diastereomers that were purified by chromatography on SiO_2 (10:90 to 15:85; EtOAc:hexanes) to give the major diastereomer **1-106** (1.18 g, 59%) as a colorless solid: Mp 45.6-47.9 °C ($CHCl_3$); $[\alpha]_D$ -2.5 (*c* 1.00, CH_2Cl_2); IR (ATR) 3360, 2956, 2928, 1679, 1170, 1111 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.70-7.66 (m, 4 H), 7.45-7.37 (m, 6 H), 4.59 (d, 1 H, *J* = 9.3 Hz), 3.81-3.80 (m, 2 H), 3.73 (app q, 1 H, *J* = 5.0 Hz), 3.59-3.54 (m, 2 H), 3.51 (dt, 1 H, *J* = 9.2,

3.9 Hz), 2.56 (d, 1 H, *J* = 7.9 Hz), 2.24 (dqq, 1 H, *J* = 6.9, 6.9, 4.3 Hz), 1.45 (s, 9 H), 1.07 (s, 9 H), 0.96 (d, 3 H, *J* = 6.9 Hz), 0.89 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7, 135.7, 135.7, 133.4, 133.2, 129.9, 127.9, 80.2, 70.8, 70.1, 65.4, 57.0, 28.5, 27.1, 27.0, 20.4, 19.3, 16.1; MS (ESI$^+$) *m/z* 524 ([M+Na]$^+$, 55), 387 (100); HRMS (ESI$^+$) *m/z* calcd for $C_{28}H_{45}NO_5SiNa$ [M+Na]$^+$ 524.2808, found 524.2825.



1-107

***tert*-Butyl ((*S*)-1-((4*R*,5*R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropyl)carbamate (1-107)**. To a solution of diol **1-106** (0.031 g, 0.061 mmol) in CH_2Cl_2 (0.25 mL) was added 2,2-dimethoxypropane (0.25 mL, 2.0 mmol) and PPTS (0.0010 g, 0.0040 mmol). The reaction vessel was sealed and heated at 60 °C for 10.5 h, concentrated under reduced pressure, and purified by chromatography on SiO_2 to give dioxolane **1-107** (0.029 g, 87%) as a colorless oil: $[\alpha]_D$ -27.3 (*c* 1.00, CH_2Cl_2); IR (ATR) 2958, 2930, 1716, 1700, 1167, 1111 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72-7.68 (m, 4 H), 7.47-7.36 (m, 6 H), 4.17 (d, 1 H, *J* = 10.4 Hz), 4.08 (dt, 1 H, *J* = 6.7, 3.5 Hz), 3.97 (dd, 1 H, *J* = 9.4, 6.8 Hz), 3.88 (dd, 1 H *J* = 11.1, 3.7 Hz), 3.70 (dd, 1 H, *J* = 10.0, 3.1 Hz), 3.63 (dd, 1 H, *J* = 11.2, 3.3 Hz), 2.11 (dqq, 1 H, *J* = 6.8, 6.8, 3.2 Hz), 1.41 (s, 3 H), 1.36 (s, 9 H), 1.08 (s, 9 H), 0.93 (d, 3 H, *J* = 6.9 Hz), 0.83 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 135.8, 133.5, 133.4, 129.9, 129.8, 127.9, 127.9, 109.3, 80.6, 79.4, 64.1, 57.6, 28.7, 28.4, 27.6, 27.5, 27.0, 20.0, 19.4, 15.7; MS (ESI$^+$) *m/z* 564 ([M+Na]$^+$ (100); HRMS (ESI$^+$) *m/z* calcd for $C_{31}H_{47}NO_5SiNa$ [M+Na]$^+$ 564.3121, found 564.3119.



1-111

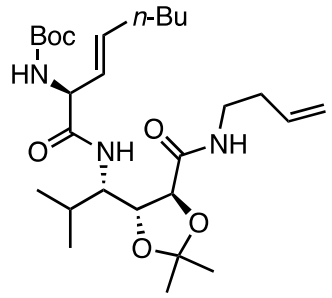
***tert*-Butyl ((*S*)-1-((4*R*,5*S*)-5-(but-3-en-1-ylcarbamoyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropyl)carbamate (1-111)**.[26] To a solution of silyl ether **1-107** (1.20 g, 2.21 mmol) in THF (19 mL) was added TBAF (3.00 mL, 3.00 mmol, 1.0 M in THF). The resulting yellow solution was stirred at rt for 2 h, quenched with sat. aq. NH_4Cl (5 mL) and water (2 mL), separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered through a pad of Celite®, concentrated under reduced pressure and purified by chromatography (3:7; EtOAc:hexanes) to give **1-108** (0.674 g, 101%) as a colorless oil.

To a solution of alcohol **1-108** (0.0923 g, 0.304 mmol) in CH_2Cl_2 (3.0 mL) was added $NaHCO_3$ (0.0790 g, 0.940 mmol) followed by Dess-Martin periodinane (0.197 g, 0.460 mmol). The resulting colorless slurry was stirred at rt for 2 h, quenched with sat. aq. $Na_2S_2O_3$ (2 mL) and sat. aq. $NaHCO_3$ (2 mL), and diluted with Et_2O (5 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give crude aldehyde as a colorless oil that was taken on without further purification.

To a solution of the crude aldehyde partitioned between THF (1.33 mL) and water (0.67 mL) was added $NaH_2PO_4 \bullet H_2O$ (0.125 g, 0.909 mmol), 2-methyl-2-butene (0.290 mL, 2.74 mmol), followed by $NaClO_2$ (0.0802 g, 0.887 mmol). The reaction mixture was allowed to stir at rt for 3.75 h, extracted with EtOAc (3 x 10 mL), washed with brine (1 x 10 mL), and

concentrated under reduced pressure. The oily residue was dissolved in CH_2Cl_2 (10 mL), filtered through a pad of Celite®, washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give **1-109** as a colorless oil that was used without further purification.

To a slurry of crude acid **1-109**, PyBOP (0.238 g, 0.457 mmol), HOAt (0.105 g, 0.464 mmol), and amine **1-110** (0.0398 g, 0.370 mmol) in CH_2Cl_2 (0.350 mL) at 0 °C was added dropwise DIPEA (0.106 mL, 0.609 mmol). The resulting yellow solution was warmed to rt and stirred for 13 h, quenched with 1 M citric acid (5 mL), and diluted with $CHCl_3$ (5 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 x 5 mL). The combined organic layers were dried (Na_2SO_4), decanted, and concentrated. The crude residue was purified by chromatography on SiO_2 (2:8; EtOAc:hexanes) to give **1-111** (0.0718 g, 64% over 4 steps) as colorless solid: Mp 90.3-91.0 °C (EtOAc); $[\alpha]_D$ -25.5 (*c* 1.00, CH_2Cl_2); IR (ATR) 3314, 2972, 2961, 1700, 1662 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.63 (bs, 1 H), 5.74 (ddt, 1 H, *J* = 16.9, 10.4, 6.8 Hz), 5.20 (d, 1 H, *J* = 9.5 Hz), 5.12-5.05 (m, 2 H), 4.28 (d, 1 H, *J* = 6.0 Hz), 4.05 (dd, 1 H, *J* = 9.2, 6.0 Hz), 3.67 (dt, 1 H, *J* = 9.4, 3.2 Hz), 3.40 (dq, 1 H, *J* = 13.3, 6.6 Hz), 3.27 (dq, 1 H, *J* = 13.1, 6.7 Hz), 2.26 (app q, 2 H, *J* = 6.8 Hz), 2.05 (dqq, 1 H, *J* = 6.9, 6.9, 3.6 Hz) 1.44 (s, 3 H), 1.41 (s, 9 H), 1.34 (s, 3 H), 0.94 (d, 3 H, *J* = 6.9 Hz), 0.85 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.4, 156.6, 135.1, 117.6, 111.4, 79.2, 79.1, 78.3, 58.1, 38.0, 33.8, 29.6, 28.5, 27.3, 26.3, 19.8, 16.2; MS (ESI^+) *m/z* 393 ($[M+Na]^+$, 100); HRMS (ESI^+) *m/z* calcd for $C_{19}H_{34}N_2O_5Na$ $[M+Na]^+$ 393.2365, found 393.2338.

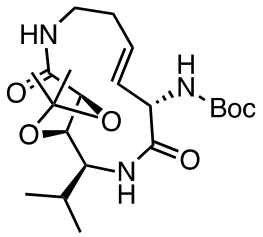


1-113

***tert*-Butyl ((*S*,*E*)-1-(((*S*)-1-((4*R*,5*S*)-5-(but-3-en-1-ylcarbamoyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropyl)amino)-1-oxooct-3-en-2-yl)carbamate (1-113)**. To a solution of amide **1-111** (5.1 mg, 14 μmol) in CH_2Cl_2 (0.1 mL) was added 2,6-lutidine (3.2 μL, 28 μmol) followed by freshly distilled TMSOTf (3.7 μL, 21 μmol). The solution was stirred for 30 min at rt and quenched with sat. aq. NH_4Cl (1 mL). The aqueous phase was basified (pH 9) by addition of 2 M KOH (3 drops) and the aqueous phase was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give free amine **1-102** (2.6 mg, 70%) as a yellow oil.[26]

To a suspension of amine **1-102** (2.6 mg, 9.6 μmol), acid **1-87** (3.8 mg, 14 μmol), PyBOP (8.1 mg, 15 μmol), and HOAt (2.3 mg, 17 μmol) in CH_2Cl_2 (0.075 mL) was added DIPEA (3.4 μL, 19 μmol). The suspension became a yellow solution and was stirred at rt for 12 h. The reaction was quenched with 1 M citric acid (2 mL) and the mixture was extracted with $CHCl_3$ (3 x 3 mL). The combined organic layers were dried (Na_2SO_4), decanted, concentrated, and purified by chromatography on SiO_2 (1:4; EtOAc:hexanes) to give **1-113** (2.7 mg, 55%) as colorless film: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.93 (d, 1 H, *J* = 8.8 Hz), 6.66 (t, 1 H, *J* = 5.4 Hz), 5.81-5.71 (m, 2 H), 5.48 (dd, 1 H, *J* = 15.3, 6.8 Hz), 5.41 (bs, 1 H), 5.12 (dq, 1 H, *J* = 6.0, 1.5 Hz), 5.09 (t, 1 H, *J* = 1.2 Hz), 4.58 (bs, 1 H), 4.14 (d, 1 H, *J* = 6.7 Hz), 4.07 (dd, 1 H, *J* = 9.0, 6.8 Hz), 3.98 (dt, 1 H, *J* = 9.0, 3.5 Hz), 3.43 (dq, 1 H, *J* = 13.4, 6.7 Hz), 3.26 (dq, 1 H, *J* = 13.1, 6.6

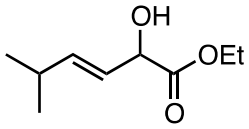
Hz) 2.28 (dq, 2 H, *J* = 6.8, 1.0 Hz), 2.08 (dqq, 1 H, *J* = 6.9, 6.9, 3.5 Hz), 2.01 (app q, 2 H, *J* = 6.7 Hz), 1.45 (s, 3 H), 1.43 (s, 9 H), 1.36 (s, 3 H), 1.35-1.27 (m, 4 H), 0.94 (d, 3 H, *J* = 6.9 Hz), 0.89 (d, 3 H, *J* = 6.9 Hz), 0.86 (t, 3 H, *J* = 7.1 Hz).



1-114

***tert*-Butyl ((3a*R*,4*S*,7*S*,13a*S*,*E*)-4-isopropyl-2,2-dimethyl-6,13-dioxo-3a,4,5,6,7,10,11,12,13,13a-decahydro-[1,3]dioxolo[4,5-*c*][1,6]diazacyclododecin-7-yl)carbamate (1-114)**.[26] To a solution of **1-113** (3 mg, 5 μmol) in degassed toluene (5.0 mL) was added Grubbs 2nd generation catalyst (0.7 mg, 0.8 μmol). The reaction flask was evacuated and back filled with ethylene gas (6 x), then heated at 90 °C under an atmosphere of ethylene. After 14.5 h, a second batch of Grubbs 2nd generation catalyst (0.8 mg, 0.8 μmol) was added and the reaction flask was purged with ethylene (3 x). The reaction mixture was heated at 90 °C for 6 h, cooled to rt, and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (1:1; EtOAc:hexanes) to give of **1-114** (1.1 mg, 49%) as a light brown solid in about 90% purity. A second purification was needed to eliminate traces of impurities, providing **1-114** (0.5 mg, 22%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.79-5.68 (m, 2 H), 5.59-5.55 (m, 2 H), 5.17 (dd, 1 H, *J* = 15.0, 9.7 Hz), 4.53 (app t, 1 H, *J* = 9.1 Hz), 4.41 (t, 1 H, *J* = 7.9 Hz), 4.00-3.91 (m, 2 H), 3.75 (d, 1 H, *J* = 8.3 Hz), 2.93 (app d, 1 H, *J* = 13.8 Hz), 2.47 (app d, 1 H, *J* = 13.1 Hz), 2.07 (dqq, 1 H, *J* = 6.9, 6.9, 3.3 Hz), 1.98-1.90 (m, 1 H), 1.42 (s, 9 H), 1.41 (s, 3 H),

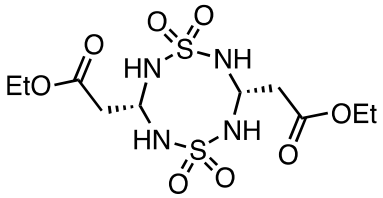
1.40 (s, 3 H), 0.95 (d, 3 H, J = 6.9 Hz), 0.93 (d, 3 H, J = 6.9 Hz); MS (EI) *m/z* 425 (M^+, 1), 369 (23), 325 (5); HRMS (EI) *m/z* calcd for $C_{21}H_{35}N_3O_6$ M^+ 425.2526, found 425.2538.



1-121

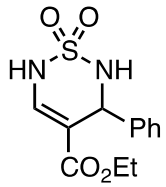
(*E*)-Ethyl 2-hydroxy-5-methylhex-3-enoate (1-121). To a solution of alkyne **1-120** (0.150 mL, 1.47 mmol) in CH_2Cl_2 (3.5 mL) was added Cp_2ZrHCl (0.347 g, 1.72 mmol). The reaction mixture was stirred for 20 min at rt. The solvent was removed *in vacuo* and the resulting light yellow oil was dissolved in toluene (3.0 mL), cooled to -78 °C for 5 min, and treated with Me_2Zn (1.54 mL, 3.08 mmol, 2 M in toluene). The solution was warmed to rt, stirred for 10 min, then cooled to -78 °C for 5 min. Freshly cracked ethyl glyoxylate (0.270 mL, 1.23 mmol, 45% in toluene by ^{1}H NMR) was added to the vinyl zinc reagent at -78 °C, warmed to rt, and stirred for 5 h. The reaction was quenched with sat. aq. NH_4Cl (5 mL) at rt, stirred for 30 min, diluted with EtOAc (25 mL), filtered though a pad of Celite®, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (1 x 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. The crude residue was purified by chromatography on SiO_2 (1:9; EtOAc:hexanes) to give **1-121** (0.118 g, 56%) as a yellow oil: IR (ATR) 3468, 2956, 1729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.86 (ddd, 1 H, J = 15.5, 6.6, 1.5 Hz), 5.45 (ddd, 1 H, J = 15.5, 5.9, 1.4 Hz), 4.58 (d, 1 H, J = 5.6 Hz), 4.25 (q, 2 H, J = 7.1 Hz), 2.90 (s, 1 H), 2.32 (app. sext, 1 H, J = 6.7 Hz), 1.29 (t, 3 H, J = 7.1 Hz), 1.00 (d, 6 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.1, 141.5, 123.5, 71.5, 62.0, 30.8, 22.2, 22.1, 14.3; MS (ESI^+) *m/z* 195 ($[M+Na]^+$, 100); HRMS (ESI^+) *m/z* calcd for $C_9H_{16}O_3Na$ $[M+Na]^+$195.0997, found 195.0992.

4.3 CHAPTER 2 EXPERIMENTAL PART



2-43

Diethyl 2,2'-(1,1,5,5-tetraoxido-1,5,2,4,6,8-dithiatetrazocane-3,7-diyl)diacetate (2-43).[113] To a suspension of sulfamide (**2-11**) (11.00 g, 113.3 mmol) in CH_2Cl_2 (217 mL) and TFA (44.0 mL, 586 mmol) was added diethyoxypropionate (**2-30**) (25.5 mL, 125 mmol) over 5 min. The solution was stirred for 4 h at rt, filtered through a medium glass fritted funnel, washed with CH_2Cl_2 (~60 mL), MeOH (~50 mL), and Et_2O (~50 mL), and dried under high vacuum to give **2-43** (21.2 g, 96%) as a colorless solid: Mp 182.9-183.4 °C (CH_2Cl_2); IR (ATR) 3318, 2990, 1717, 1348, 1335, 1048 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.52 (d, 4 H, J = 9.4 Hz), 5.18 (ddt, 2 H, J = 9.2, 9.2, 7.3 Hz), 4.06 (q, 4 H, J = 7.1 Hz), 2.64 (d, 4 H, J = 7.2 Hz), 1.18 (t, 6 H, J = 7.1 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 168.5, 62.1, 60.2, 41.1, 14.0; HRMS (ESI^+) *m/z* calcd for $C_{10}H_{21}N_4O_8S_2$ $[M+H]^+$ 389.0801, found 389.0779.

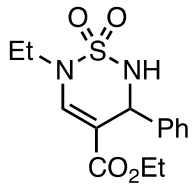


2-44

Ethyl 3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (2-44).[116] To a suspension of sulfamide **2-43** (9.76 g, 25.1 mmol) and benzaldehyde (5.20 mL, 51.2 mmol)

in HFIP (100 mL) was added dropwise TFA (9.65 mL, 126 mmol). The solution was stirred between 35-40 °C in a round bottom flask capped with a glass stopper for 17 h. The solvent was evaporated under reduced pressure to give a yellow oil that was purified by chromatography on SiO_2 (2:8 to 4:6; EtOAc:hexanes) to give the thiadiazine **2-44** (9.33 g, 66%) as a colorless solid: Mp 143.8-144.9 °C ($CHCl_3$); IR (ATR) 3269, 3176, 2980, 1655, 1150, 1100 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.82 (s, 1 H), 7.93 (d, 1 H, J = 7.2 Hz), 7.49 (s, 1 H), 7.31-7.21 (m, 5 H), 5.33 (d, 1 H, J = 7.2 Hz), 4.01, 3.96 (AB dq, 2 H, J_{AB} = 10.9, 7.1 Hz), 1.04 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.2, 139.0, 138.8, 127.9, 127.8, 127.3, 102.8, 59.6, 57.5, 14.0; HRMS (ESI^+) *m/z* calcd for $C_{12}H_{14}N_2O_4S$ $[M+H]^+$ 283.0753, found 283.0786.

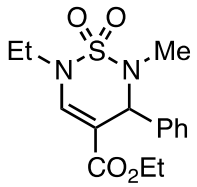
SFC Separation: Chiralpak IA (250 mm x 4.6 mm), run time 6.08 min; Peak A: 2.57 min $[\alpha]_D$ -8.1 (*c* = 0.16, CH_2Cl_2); Peak B: 3.08 min $[\alpha]_D$ +9.0 (c = 0.13, CH_2Cl_2).



2-68

Ethyl 6-ethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (2-68). To a solution of thiadiazine **2-44** (0.871 g, 3.09 mmol) and ethanol (0.213 mL, 3.70 mmol) in THF (20 mL) was added PPh_3 (0.984 g, 3.72 mmol) and DBAD (0.853 g, 3.63 mmol). The reaction mixture was stirred at rt for 4.5 h, concentrated under reduced pressure, and purified by chromatography on SiO_2 (15:85 to 3:7; EtOAc:hexanes) to give **2-68** (0.723 g, 75%) as a colorless solid: Mp 98.9-101.3°C (CH_2Cl_2); IR (ATR) 3197, 1661, 1609, 1171 cm^{-1}; ^1H NMR

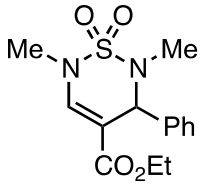
(acetone-*d6*, 400 MHz) δ 7.63 (s, 1 H), 7.39-7.35 (m, 2 H), 7.34-7.23 (m, 3 H), 6.95 (d, 1 H, J = 7.6 Hz), 5.55 (d, 1 H, J = 7.7 Hz), 4.03, 3.97 (AB dq, 2 H, J_{AB} = 10.8, 7.1 Hz), 3.73, 3.68 (AB dq, 2 H, J_{AB} = 14.5, 7.2 Hz), 1.32 (t, 3 H, J = 7.2 Hz), 1.03 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (acetone-*d6*, 100 MHz) δ 165.8, 142.6, 139.9, 129.0, 128.8, 128.4, 106.3, 60.4, 59.5, 45.6, 15.6, 14.4; HRMS (ESI$^+$) *m/z* calcd for $C_{14}H_{19}N_2O_4S$ $[M+H]^+$ 311.1066, found 311.1069.



2-69

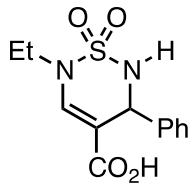
Ethyl 6-ethyl-2-methyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (2-69). To a suspension of thiadiazine **2-68** (0.741 g, 2.39 mmol) and K_2CO_3 (1.01 g, 7.27 mmol) in MeCN (24 mL) was added iodomethane (0.372 mL, 5.98 mmol). The solution was stirred at rt for 2.5 h, then diluted with water (20 mL) and EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with sat. aq. Na_2SO_3 (1 x 15 mL) and brine (1 x 15 mL), dried (Na_2SO_4), decanted, and concentrated under reduced pressure to give a yellow colored crude oil. The crude mixture was purified by chromatography on SiO_2 (15:85 to 2:8; EtOAc:hexanes) to give the dialkylated thiadiazine **2-69** (0.782 g, 100%) as a light yellow viscous oil: IR (ATR) 2977, 1692, 1141, 1038 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.70 (s, 1 H), 7.34-7.17 (m, 5 H), 5.52 (s, 1 H), 4.10, 4.06 (AB dq, 2 H, J_{AB} = 10.8, 7.1 Hz), 3.73 (q, 2 H, J = 7.2 Hz), 2.95 (s, 3 H), 1.32 (t, 3 H, J = 7.2 Hz), 1.12 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (acetone-

d_6, 100 MHz) δ 166.3, 141.6, 140.0, 128.8, 128.4, 128.1, 102.7, 67.0, 60.7, 46.0, 40.1, 15.8, 14.5; HRMS (ESI^+) *m/z* calcd for $C_{15}H_{21}N_2O_4S$ $[M+H]^+$ 325.1222, found 325.1236.



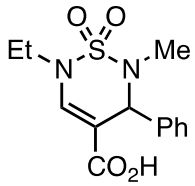
2-70

Ethyl 2,6-dimethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (2-70). To a suspension of thiadiazine **2-44** (2.390 g, 8.465 mmol) and K_2CO_3 (7.00 g, 50.7 mmol) in MeCN (40 mL) was added iodomethane (2.65 mL, 42.6 mmol). The solution was stirred at rt for 2.25 h, then diluted with water (50 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with sat. aq. Na_2SO_3 (1 x 25 mL), sat. aq. $NaHCO_3$ (1 x 25 mL), and brine (1 x 25 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light yellow sticky oil. The crude mixture was purified by chromatography on SiO_2 (1:9 to 2:8; EtOAc:hexanes) to give **2-70** (2.620 g, 100%) as a light yellow oil: IR (ATR) 2977, 2932, 1691, 1366 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.45 (s, 1 H), 7.34-7.25 (m, 5 H), 5.46 (s, 1 H), 4.15, 4.11 (AB dq, 2 H, J_{AB} = 10.9, 7.1 Hz), 3.28 (s, 3 H), 2.93 (s, 3 H), 1.15 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.0, 142.1, 138.0, 128.1, 128.0, 127.8, 102.4, 66.4, 60.7, 39.8, 36.8, 14.3; HRMS (ESI^+) *m/z* calcd for $C_{14}H_{19}N_2O_4S$ $[M+H]^+$ 311.1066, found 311.1103.



2-71

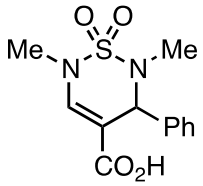
6-Ethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylic acid 1,1-dioxide (2-71). To a suspension of ester **2-68** (0.250 g, 0.805 mmol) in EtOH (1.0 mL) was added in one portion 2 M KOH (4.0 mL, 8.0 mmol). The reaction mixture was stirred at 80 °C for 4 h then cooled to rt, diluted with EtOAc (5 mL), and acidified with 5 M HCl (~ 2 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried (Na_2SO_4), decanted, and concentrated under reduced pressure to give acid **2-71** (0.222 g, 98%) as a yellow-orange solid: Mp 170.1-175.3 °C (dec, CH_2Cl_2); IR (ATR) 3245, 2922, 1661, 1152 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 10.53 (bs, 1 H), 7.66 (s, 1 H), 7.40-7.37 (m, 2 H), 7.32-7.22 (m, 3 H), 7.01 (d, 1 H, J = 7.5 Hz), 5.56 (d, 1 H, J = 7.5 Hz), 3.74, 3.69 (AB dq, 2 H, J_{AB} = 14.4, 7.1 Hz), 1.33 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (acetone-d_6, 100 MHz) δ 167.0, 143.1, 139.9, 129.0, 128.7, 128.3, 105.6, 59.2, 45.6, 15.6; HRMS (ESI^-) *m/z* calcd for $C_{12}H_{13}N_2O_4S$ $[M-H]^-$ 281.0596, found 281.0609.



2-72

6-Ethyl-2-methyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylic acid 1,1-dioxide (2-72). To a solution of dialkylated thiadiazine **2-69** (2.69 g, 8.29 mmol) in EtOH (10

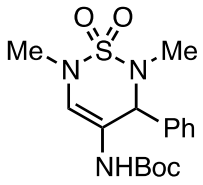
mL) was added in one portion 2 M KOH (43 mL, 85 mmol). The reaction mixture was warmed to 90 °C and stirred for 5 h, cooled to rt, diluted with EtOAc (50 mL), cooled to 0 °C, and acidified with 5 M HCl (~ 17 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with water (1 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), decanted, and concentrated under reduced pressure. The crude product contained AcOH that was removed by evaporating with hexanes and $CHCl_3$ to give the acid **2-72** (2.06 g, 84%) as a light yellow powder: Mp 156.7-158.6 °C (dec, CH_2Cl_2); IR (ATR) 2969, 2563, 1668, 1655, 1169, 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 10.96 (bs, 1 H), 7.63 (s, 1 H), 7.37-7.26 (m, 5 H), 5.41 (s, 1 H), 3.62 (q, 2 H, J = 7.2 Hz), 2.91 (s, 3 H), 1.33 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 142.9, 137.8, 128.1, 128.0, 127.7, 100.1, 66.1, 45.9, 40.1, 15.5; MS (ESI^-) *m/z* 295 ($[M-1]^-$, 100), 231 ($-SO_2$, 85); HRMS (ESI^-) *m/z* calcd for $C_{13}H_{15}N_2O_4S$ $[M-H]^-$ 295.0753, found 295.0795.



2-73

2,6-Dimethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylic acid 1,1-dioxide (2-73). To a solution of dialkylated thiadiazine **2-70** (2.589 g, 8.343 mmol) in EtOH (10 mL) was added in one portion 2 M KOH (41.5 mL, 83.0 mmol). The reaction mixture was heated to 75 °C and stirred for 3.5 h. The reaction mixture was cooled to rt, diluted with water (10 mL), and acidified with conc. aq. HCl (~5 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL), dried ($MgSO_4$),

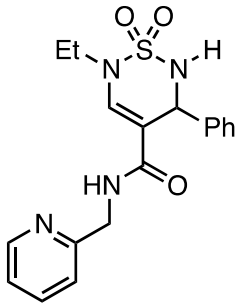
filtered, and concentrated under reduced pressure. The crude oil was placed under high vacuum for 6 h to give the desired acid **2-73** (2.063 g, 88%) as a light yellow solid: Mp 158.2-160.9 °C (dec, Et_2O); IR (ATR) 3062, 2951, 2626, 2561, 1663, 1279, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.70 (bs, 1 H), 7.56 (s, 1 H), 7.37-7.27 (m, 5 H), 5.42 (s, 1 H), 3.26 (s, 1 H), 2.95 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 144.4, 137.7, 128.2, 127.7, 100.2, 66.1, 40.3, 37.0; HRMS (ESI⁻) *m/z* calcd for $C_{12}H_{13}N_2O_4S$ $[M-H]^-$ 281.0596, found 281.0632.



2-74

***tert*-Butyl (2,6-dimethyl-1,1-dioxido-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazin-4-yl)carbamate (2-74)**. To a suspension of dimethyl thiadiazine carboxylate **2-73** (0.0770 g, 0.273 mmol) in toluene (0.6 mL) was added Et_3N (0.0840 mL, 0.598 mmol). The mixture was degassed by FPT (3 x), backfilled with Ar, and treated with DPPA (0.0640 mL, 0.297 mmol). The reaction mixture was stirred at rt for 2 h, and heated to 95 °C for 1 h (during which time bubbling occurred for 30 min). The mixture was then cooled to rt, treated with *t*-BuOH (0.200 mL, 2.10 mmol) and heated to 100 °C for 3 h. The reaction mixture was cooled to rt, diluted with EtOAc (5 mL), and washed with 1 M NaOH (1 x 5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified by chromatography on SiO_2 (1:9 to 2:8; EtOAc:hexanes), dissolved in $CHCl_3$ and concentrated under reduced pressure (3 x) to remove

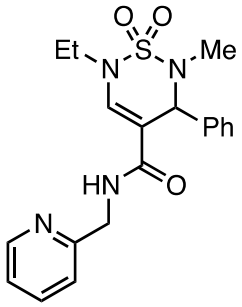
trace EtOAc to give *N*-Boc amine **2-74** (21.5 mg, 22%) as a colorless solid: Mp 124.7-126.6 °C ($CHCl_3$); IR (ATR) 3336, 2973, 1722 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.45-7.37 (m, 5 H), 6.69 (bs, 1 H), 5.08 (s, 1 H), 4.77 (s, 1 H), 3.10 (s, 3 H), 2.56 (s, 3 H), 1.36 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.9, 135.2, 129.6, 129.5, 129.3, 122.2, 119.3, 81.0, 68.7, 38.7, 34.8, 28.3; HRMS (ESI^+) *m/z* calcd for $C_{16}H_{23}N_3O_4SNa$ $[M+Na]^+$ 376.1307, found 376.1346.



2-75

6-Ethyl-3-phenyl-*N*-(pyridin-2-ylmethyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxamide 1,1-dioxide (2-75). To a solution of monoalkylated thiadiazine **2-71** (0.101 g, 0.357 mmol), 2-pyridylmethylamine (0.445 mL, 0.428 mmol), EDCI (0.0756 g, 0.394 mmol), and DMAP (0.0267 g, 0.219 mmol) in CH_2Cl_2 (0.5 mL) was added DIPEA (0.0445 mL, 0.432 mmol). The reaction mixture was sealed under an atmosphere of Ar in a screw cap vial, stirred at rt for 15 h, quenched with sat. aq. NH_4Cl (2 mL), diluted with EtOAc (5 mL), and separated. The aqueous layer was extracted with EtOAc (3 x 5 mL). The organic layers were combined, washed with sat. aq. $NaHCO_3$ (1 x 5 mL), water (1 x 5 mL), and brine (1 x 5 mL), dried (Na_2SO_4), decanted, and concentrated under reduced. The crude solid was purified by chromatography on SiO_2 (6:94; MeOH:CH_2Cl_2) to give amide **2-75** (0.0950 g, 72%) as a colorless solid: Mp 157.5-157.8 °C ($CHCl_3$); IR (ATR) 3333, 3314, 3066, 1644, 1171 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 8.41 (ddd, 1 H, *J* = 4.8, 1.8, 0.9 Hz), 7.57 (td, 1 H, *J* = 7.6, 1.8

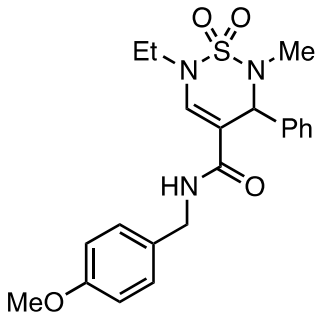
Hz), 7.53-7.48 (m, 1 H), 7.48-7.44 (m, 2 H), 7.41-7.40 (m, 1 H), 7.34-7.26 (m, 3 H), 7.15 (ddd, 1 H, J = 7.4, 4.8, 0.8 Hz), 6.98 (d, 1 H, J = 7.6 Hz), 6.92 (d, 1 H, J = 7.8 Hz), 5.77 (d, 1 H, J = 7.4 Hz), 4.45, 4.36 (AB dd, 2 H, J_{AB} = 16.2, 5.7 Hz), 3.64, 3.59 (AB dq, 2 H, J_{AB} = 10.9, 7.2 Hz), 1.30 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (acetone-d_6, 100 MHz) δ 166.5, 159.5, 149.6, 139.5, 137.8, 137.2, 129.4, 128.9, 128.7, 122.7, 121.7, 111.6, 59.7, 45.3, 45.2, 15.3; HRMS (ESI$^+$) *m/z* calcd for $C_{18}H_{21}N_4O_3S$ $[M+H]^+$ 373.1334, found 373.1348.



2-76

6-Ethyl-2-methyl-3-phenyl-*N*-(pyridin-2-ylmethyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxamide 1,1-dioxide (2-76). To a vial containing acid **2-72** (0.0900 g, 0.304 mmol) in CH_2Cl_2 (0.85 mL) was added PyBOP (0.173 g, 0.333 mmol), 2-pyrididylmethylamine (34.0 μL, 0.330 mmol), and DIPEA (0.110 mL, 0.632 mmol). The reaction mixture was sealed under an atmosphere of Ar and stirred for 23 h at rt. The reaction mixture was diluted with EtOAc (15 mL) and washed with sat. aq. NH_4Cl (1 x 10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by chromatography on SiO_2 (6:4; EtOAc:hexanes to 100% EtOAc) to give the amide **2-76** (0.100 g, 85%) as a colorless foam: IR (ATR) 3307, 1638, 1357, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.34 (d, 1 H, J = 4.8 Hz), 7.59 (dt, 1 H, J = 7.7, 1.8

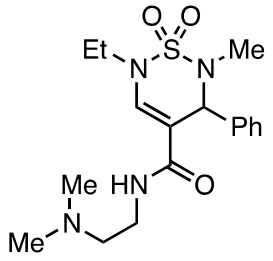
Hz), 7.42-7.40 (m, 3 H), 7.34-7.26 (m, 3 H), 7.15-7.09 (m, 2 H), 6.62 (bs, 1 H), 5.52 (s, 1 H), 4.51, 4.46 (AB dd, 2 H, J_{AB} = 16.5, 4.7 Hz), 3.64 (dq, 2 H, J = 7.3, 1.8 Hz), 2.84 (s, 3 H), 1.35 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.9, 156.0, 148.9, 137.5, 136.8, 136.7, 128.9, 128.7, 128.5, 122.3, 122.0, 106.0, 66.5, 45.3, 44.6, 39.0, 15.5; HRMS (ESI$^+$) *m/z* calcd for $C_{19}H_{23}N_4O_3S$ $[M+H]^+$ 387.1491, found 387.1466.



2-77

6-Ethyl-*N*-(4-methoxybenzyl)-2-methyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxamide 1,1-dioxide (2-77). To a solution of acid **2-72** (0.0974 g, 0.329 mmol), PyBOP (0.2052 g, 0.3944 mmol), and *p*-methoxybenzylamine (0.0520 mL, 0.398 mmol) in CH_2Cl_2 (0.9 mL) was added DIPEA (0.125 mL, 0.718 mmol). The reaction mixture was sealed under and atmosphere of Ar, stirred at rt for 23 h, concentrated under reduced pressure, and partitioned between EtOAc (10 mL) and water (10 mL). The organic layer was washed with 1 M $NaHSO_4$ (2 x 5 mL), sat. aq. $NaHCO_3$ (1 x 5 mL), and brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (2:8 to 1:1; EtOAc:hexanes) to give a light yellow oil that was dissolved in $CHCl_3$ (3 x 10 mL) and concentrated under reduced pressure to remove trace EtOAc to give amide **2-77** (0.114 g, 83%) as a light yellow sticky foam: IR (ATR) 3405, 3297, 2973, 2931, 1637, 1357, 1338 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (d, 1 H, J = 0.7 Hz), 7.39-7.32 (m, 5 H), 6.90 (d, 2 H, J =

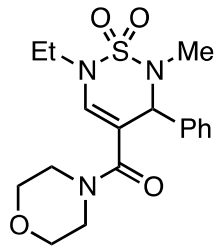
8.7 Hz), 6.76-6.74 (m, 2 H), 5.41 (s, 1 H), 5.30 (t, 1 H, J = 5.1 Hz), 4.32, 4.23 (AB dd, 2 H, J_{AB} = 14.7, 5.8 Hz), 3.77 (s, 3 H), 3.62 (q, 2 H, J = 7.2 Hz), 2.77 (s, 3 H), 1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.6, 159.1, 137.9, 136.4, 130.1, 128.98, 128.96, 128.9, 128.7, 114.1, 105.8, 66.2, 55.4, 45.4, 43.4, 38.4, 15.5; HRMS (ESI^+) *m/z* calcd for $C_{21}H_{26}N_3O_4S$ $[M+H]^+$ 416.1644, found 416.1648.



2-78

***N*-(2-(Dimethylamino)ethyl)-6-ethyl-2-methyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxamide 1,1-dioxide (2-78)**. To a vial containing acid **2-72** (0.0900 g, 0.304 mmol) in CH_2Cl_2 (0.85 mL) was added PyBOP (0.173 g, 0.333 mmol), *N*,*N*-dimethylethylene diamine (36.0 μL, 0.330 mmol), and DIPEA (0.110 mL, 0.632 mmol). The reaction mixture was sealed under an atmosphere of Ar and stirred for 23 h at rt. The reaction mixture was diluted with EtOAc (15 mL) and washed with sat. aq. NH_4Cl (1 x 10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified by chromatography on SiO_2 (1:99 to 1:9; MeOH:$CHCl_3$) to give amide **2-78** (0.0847 g, 76%) as a light yellow foam: IR (ATR) 3420, 3307, 2975, 1638, 1357, 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41-7.29 (m, 5 H), 7.37 (s, 1 H), 6.04 (bs, 1 H), 5.45 (s, 1 H), 3.64 (q, 2 H, J = 7.3 Hz), 3.27-3.18 (m, 2 H), 2.79 (s, 3 H), 2.39,

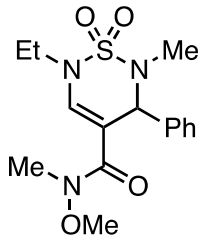
2.52 (AB ddd, 2 H, J_{AB} = 12.1, 6.6, 4.9 Hz), 2.06 (s, 6 H), 1.35 (3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.5, 137.7, 136.8, 128.9, 128.7, 128.5, 105.9, 66.3, 57.7, 45.4, 44.7, 38.5, 37.0, 15.5; HRMS (ESI^+) *m/z* calcd for $C_{17}H_{27}N_4O_3S$ $[M+H]^+$ 367.1804, found 367.1797.



2-79

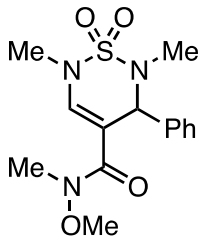
(6-Ethyl-2-methyl-1,1-dioxido-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazin-4-yl)(morpholino)methanone (2-79). To a vial containing acid **2-72** (0.0900 g, 0.304 mmol) in CH_2Cl_2 (0.85 mL) was added PyBOP (0.173 g, 0.333 mmol), morpholine (29.0 uL, 0.332 mmol), and DIPEA (0.110 mL, 0.632 mmol). The reaction mixture was sealed under and atmosphere of Ar and stirred for 23 h at rt. The reaction mixture was diluted with EtOAc (15 mL) and washed with sat. aq. NH_4Cl (1 x 10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by chromatography on SiO_2 (3:7 to 1:1; EtOAc:hexanes) to give amide **2-79** (0.0933 g, 84%) as a colorless colorless powder: Mp 115.7-116.8 °C ($CHCl_3$); IR (ATR) 2969, 2923, 2852, 1623, 1610, 1357 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37-7.32 (m, 5 H), 6.56 (d, 1 H, J = 1.6 Hz), 5.68 (d, 1 H, J = 1.5 Hz), 3.62, 3.58 (AB dq, 2 H, J_{AB} = 14.5, 7.2 Hz), 3.54-3.47 (m, 2 H), 3.43-3.34 (m, 4 H), 3.34-3.27 (m, 2 H), 2.54 (s, 3 H), 1.34 (t, 3 H, J = 7.2

Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6, 135.4, 134.2, 129.2, 129.1, 128.7, 109.8, 66.6, 66.5, 45.2, 34.5, 15.3; HRMS (ESI^+) *m/z* calcd for $C_{17}H_{24}N_3O_4S$ $[M+H]^+$ 388.1307, found 388.1314.



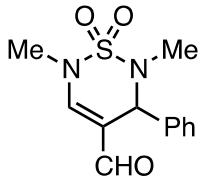
2-80

6-Ethyl-*N*-methoxy-*N*,2-dimethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxamide 1,1-dioxide (2-80). To a round bottom flask containing acid **2-72** (0.9985 g, 3.369 mmol), dimethylhydroxylamine hydrochloride (0.4413 g, 4.524 mmol), and PyBOP (2.073 g, 3.984 mmol) was added CH_2Cl_2 (9.9 mL). The solution was cooled to 0 °C and treated with DIPEA (2.05 mL, 11.8 mmol), slowly warmed to rt, and stirred for 23 h. The reaction mixture was concentrated under reduced pressure and partitioned between EtOAc (40 mL) and water (20 mL). The organic layer was washed with 1 M $NaHSO_4$ (2 x 20 mL), sat. aq. $NaHCO_3$ (1 x 20 mL), and brine (1 x 20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (2:8 to 1:1; EtOAc:hexanes) to give a light yellow oil. The oil was dissolved in $CHCl_3$ (3 x 10 mL) and concentrated under reduced pressure to remove trace EtOAc to give **2-80** (1.026 g, 90%) as a light yellow sticky oil: IR (ATR) 2977, 2936, 1627, 1163 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36-7.31 (m, 5 H), 7.05 (d, 1 H, J = 1.8 Hz), 5.92 (d, 1 H, J = 1.8 Hz), 3.65, 3.61 (AB dq, 2 H, J_{AB} = 14.4, 7.2 Hz), 3.54 (s, 3 H), 2.99 (s, 3 H), 2.43 (s, 3 H), 1.36 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 137.7, 136.1, 129.2, 128.7, 128.6, 108.4, 65.7, 61.1, 45.1, 34.0, 33.2, 15.5; HRMS (ESI^+) *m/z* calcd for $C_{15}H_{22}N_3O_4S$ $[M+H]^+$ 340.1331, found 340.1330.



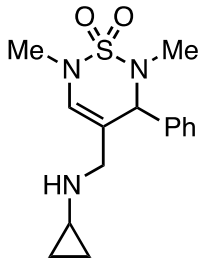
2-81

***N*-Methoxy-*N*,2,6-trimethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxamide 1,1-dioxide (2-81)**. To a solution of acid **2-73** (5.0772 g, 17.984 mmol), dimethylhydroxylamine hydrochloride (2.330 g, 23.89 mmol), PyBOP (11.306 g, 21.730 mmol) was added CH_2Cl_2 (51 mL) and stirred at rt for 5 min then cooled to 0 °C for 10 min. The cooled solution was treated dropwise over 5 min with DIPEA (10.95 mL, 62.92 mmol) and slowly warmed to rt and stirred for 24.25 h. The reaction mixture was diluted with EtOAc (150 mL) and water (100 mL). The organic layer was separated and washed with 1 M $NaHSO_4$ (2 x 50 mL), sat. aq. $NaHCO_3$ (1 x 50 mL), and brine (1 x 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified by chromatography on SiO_2 (2:8 to 1:1; EtOAc:hexanes) to give a light yellow oil that was dissolved in $CHCl_3$ (100 mL) and washed with 1 M $NaHSO_4$ (2 x 50 mL), $NaHCO_3$ (1 x 50 mL), and brine (1 x 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the amide **2-81** (5.500 g, 94%) a light yellow oil: IR (ATR) 2936, 1629, 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.29 (m, 5 H), 6.96 (d, 1 H, J = 1.8 Hz), 5.91 (d, 1 H, J = 1.8 Hz), 3.53 (s, 3 H), 3.25 (s, 3 H), 2.97 (s, 3 H), 2.46 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.6, 139.2, 135.9, 129.2, 128.7, 128.6, 108.7, 65.7, 61.1, 36.4, 34.0, 33.2; HRMS (ESI^+) *m/z* calcd for $C_{14}H_{20}N_3O_4S$ $[M+H]^+$ 326.1175, found 326.1186.



2-82

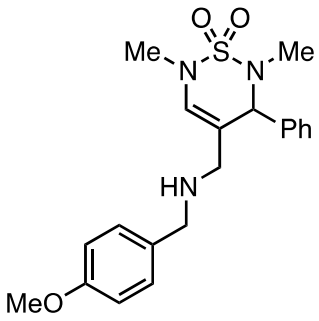
2,6-Dimethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carbaldehyde 1,1-dioxide (2-82). To a solution of Weinreb amide **2-81** (1.2654 g, 3.8890 mmol) in THF (26 mL) cooled to -78 °C was added dropwise $LiAlH_4$ (1 M in Et_2O, 7.80 mL, 7.80 mmol) over 5 min. The reaction mixture was stirred for 2 h at -78 °C, warmed to 0 °C, stirred for 15 min, diluted with Et_2O (80 mL), quenched with water (100 mL), and 1 M HCl (40 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with brine (1 x 50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light yellow oil. The crude material was purified by chromatography on SiO_2 (4:6 to 6:4; EtOAc:hexanes) to give the aldehyde **2-82** (0.7267 g, 70%) as a colorless foam: IR (ATR) 1659, 1610, 1363, 1307, 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.38 (s, 1 H), 7.34-7.26 (m, 5 H), 7.13 (s, 1 H), 5.51 (s, 1 H), 3.35 (s, 3 H), 2.93 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.7, 150.3, 136.4, 128.3, 127.7, 113.9, 64.8, 39.9, 37.2; HRMS (ESI^+) *m/z* calcd for $C_{12}H_{14}N_2O_3S$ $[M+H]^+$ 267.0803, found 267.0815.



2-83

4-((Cyclopropylamino)methyl)-2,6-dimethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxide (2-83). To a solution of aldehyde **2-82** (0.0603 g, 0.226 mmol) in CH_2Cl_2 (0.28 mL) was added cyclopropylamine (0.0170 mL, 0.245 mmol) and Ti(*i*-PrO)$_4$ (0.200 mL, 0.676 mmol). The reaction mixture was sealed under an atmosphere of Ar and stirred at rt for 21 h. The reaction mixture was diluted with EtOAc (10 mL), quenched with brine (10 mL), and filtered through a pad of Celite®. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The oil was dried under high vacuum overnight to give the imine, isolated as a colorless foam, was taken on without purification.

To a solution of imine (0.0691 g, 0.226 mmol) in MeOH (0.4 mL) and THF (0.4 mL) cooled to 0 °C was slowly added $NaBH_4$ (0.0261 g, 0.690 mmol). The reaction mixture was stirred at 0 °C for 15 min then warmed to rt. After 1.5 h the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with 5% aq. K_2CO_3 (2 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by chromatography through a short plug of SiO_2 (2:8 to 1:1; EtOAc:hexanes w/ 2% Et_3N) to give the amine **2-83** (0.0455 g, 65%) as a colorless solid: Mp 87.2-88.2 °C ($CHCl_3$); IR (ATR) 3308, 2839, 1338, 1158, 755, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.30 (m, 5 H), 6.03 (s, 1 H), 4.74 (s, 1 H), 3.08 (s, 3 H), 2.94, 2.86 (AB d, 2 H, J_{AB} = 13.7 Hz), 2.55 (s, 3 H), 2.00 (m, 1 H), 1.41 (bs, 1 H), 0.41-0.32 (m, 1 H), 0.32-0.24 (m, 2 H), 0.12-0.02 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.0, 129.1, 128.8, 128.1, 122.1, 69.1, 50.4, 38.0, 34.5, 29.8, 6.7, 6.0; HRMS (ESI$^+$) *m/z* calcd for $C_{12}H_{15}N_2O_2S$ [M-C_3H_6N]$^+$ 251.0849, found 251.0841.

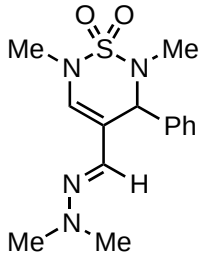


2-84

4-(((4-Methoxybenzyl)amino)methyl)-2,6-dimethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxide (2-84). To a solution of aldehyde **2-82** (0.0603 g, 0.226 mmol) in CH_2Cl_2 (0.28 mL) was added 4-methoxybenzylamine (0.0320 mL, 0.245 mmol) and Ti(*i*-PrO)$_4$ (0.205 mL, 0.676 mmol). The reaction mixture was sealed under an atmosphere of Ar and stirred at rt for 24 h. The reaction mixture was diluted with EtOAc (10 mL), quenched with water (10 mL), stirred at rt for 5 min, and filtered through a pad of Celite®. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined and washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, concentrated under reduced pressure to give a light yellow oil that was dried under high vacuum for several hours to give the imine that was taken on without further purification.

To a solution of imine in MeOH (0.9 mL) cooled to 0 °C was slowly added $NaBH_4$ (0.0261 g, 0.690 mmol). The reaction mixture was stirred at 0 °C for 30 min and warmed to rt and stirred for 3.5 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with 5% aq. K_2CO_3 (2 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by chromatography through a short plug of SiO_2 (4:6 to 1:1; EtOAc:hexanes w/ 2% Et_3N) to give the amine **2-84** (0.0604 mg, 69%) as a light yellow oil: IR (ATR) 3329, 2900, 2831, 1510, 1241, 1158 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.30 (m, 5 H), 7.12 (d, 2 H, *J* = 8.2 Hz), 6.82 (d, 2 H, *J* = 8.2 Hz), 6.04 (s, 1 H), 4.80 (s, 1

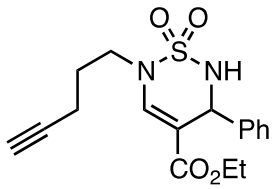
H), 3.79 (s, 3 H), 3.61, 3.51 (AB d, 2 H, J_{AB} = 13.0 Hz), 3.09 (s, 3 H), 2.89, 2.85 (AB d, 2 H, J_{AB} = 14.6 Hz), 2.58 (s, 3 H), 1.42 (bs, 1 H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.8, 137.1, 132.2, 129.4, 129.1, 128.82, 128.77, 128.3, 121.8, 113.9, 69.1, 55.4, 52.2, 49.8, 38.0, 34.7; HRMS (ESI$^+$) *m/z* calcd for $C_{20}H_{26}N_3O_3S$ $[M+H]^+$ 388.1695, found 388.1707.



2-86

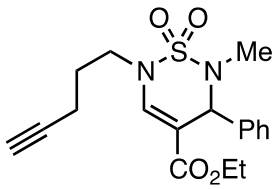
(*E*)-4-((2,2-Dimethylhydrazono)methyl)-2,6-dimethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxide (2-86). To a solution of aldehyde **2-82** (0.5240 g, 1.968 mmol) and PTS (0.0398 g, 0.209) in benzene (4.9 mL) was added 1,1-dimethylhydrazine (0.230 mL, 3.02 mmol). The reaction mixture was stirred at rt for 14 h, heated to 65 °C for 2 h, heated to reflux for 1.5 h, treated with powdered 4Å MS (125 mg), heated at 75 °C for 1 h, cooled to rt, diluted with CH_2Cl_2 (15 mL), and washed with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude mixture was purified by chromatography on SiO_2 (2:8 to 4:6; EtOAc:hexanes) to give the hydrazone **2-86** (0.320 g, 53%) as a light yellow foam: IR (ATR) 1627, 1355, 1165, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35-7.20 (m, 5 H), 6.89 (s, 1 H), 6.31 (s, 1 H), 5.41 (s, 1 H), 3.16 (s, 3 H), 2.89 (s, 3 H), 2.65 (s, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.4, 131.8, 131.7, 128.6, 127.7,

127.4, 114.2, 66.9, 43.0, 38.9, 36.5; HRMS (ASAP$^+$) *m/z* calcd for $C_{14}H_{21}N_4O_2S$ $[M+H]^+$ 309.1385, found 309.1369.



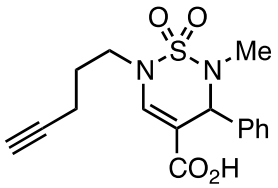
2-96

Ethyl 6-(pent-4-yn-1-yl)-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (2-96). To a solution of thiadiazine **2-44** (1.446 g, 5.120 mmol) and pentyn-1-ol (**2-95**) (0.572 mL, 6.15 mmol) in THF (30 mL) was added PPh_3 (1.463 g, 5.523 mmol) and DBAD (1.304 g, 5.551 mmol). The reaction mixture was stirred at rt for 5.3 h, concentrated under reduced pressure, and purified by chromatography on SiO_2 (1:9 to 1:1; EtOAc:hexanes) to give **2-96** (1.033 g, 58%) as a colorless oil: IR (ATR) 3439, 3282, 1685, 1618, 1165, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.50 (d, 1 H, J = 0.9 Hz), 7.38-7.30 (m, 5 H), 5.55 (d, 1 H, J = 8.5 Hz), 4.55 (d, 1 H, J = 8.5 Hz), 4.03, 3.96 (AB dq, 2 H, J_{AB} = 10.9, 7.2 Hz), 3.73 (dt, 2 H, J = 14.5, 7.1 Hz), 2.34 (td, 2 H, J = 6.8, 2.7 Hz), 2.06 (t, 1 H, J = 2.7 Hz), 1.97 (quint., 2 H, J = 6.9 Hz), 1.00 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.2, 142.3, 138.3, 128.9, 128.7, 127.6, 106.7, 82.6, 70.2, 60.5, 59.8, 49.2, 28.1, 15.6, 14.0; HRMS (ESI$^+$) *m/z* calcd for $C_{14}H_{19}N_2O_4S$ $[M+H]^+$ 311.1066, found 311.1069.



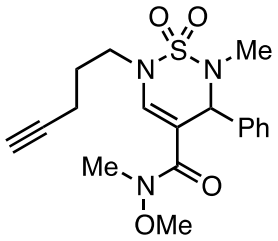
2-97

Ethyl 2-methyl-6-(pent-4-yn-1-yl)-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (2-97). To a suspension of thiadiazine **2-96** (1.009 g, 2.895 mmol) and K_2CO_3 (1.208 g, 8.738 mmol) in MeCN (14 mL) was added iodomethane (0.450 mL, 7.23 mmol) over 5 min. The solution was stirred at rt for 3.5 h. The reaction mixture was diluted with water (25 mL) and EtOAc (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with sat. aq. Na_2SO_3 (1 x 20 mL), sat. aq. $NaHCO_3$ (1 x 20 mL), and brine (1 x 20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude mixture was purified by chromatography on SiO_2 (1:9 to 2:8; EtOAc:hexanes) to give **2-97** (1.027 g, 98%) as a colorless oil: IR (ATR) 3286, 1692, 1622, 1366, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.57 (s, 1 H), 7.33-7.26 (m, 5 H), 5.46 (s, 1 H), 4.16, 4.10 (AB dq, 2 H, J_{AB} = 10.9, 7.2 Hz), 3.77, 3.70 (AB dt, 2 H, J_{AB} = 14.7, 6.3 Hz), 2.32 (dt, 2 H, J = 6.7, 2.6 Hz), 2.07 (t, 1 H, J = 2.4 Hz), 2.01-1.88 (m, 2 H), 1.15 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.0, 141.3, 138.0, 128.1, 128.0, 127.8, 102.2, 82.4, 70.2, 66.4, 60.7, 49.5, 39.6, 28.5, 15.5, 14.3; HRMS (ESI^+) *m/z* calcd for $C_{18}H_{23}N_2O_4S$ $[M+H]^+$ 363.1379, found 363.1400.



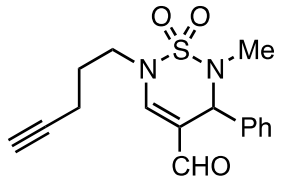
2-98

2-Methyl-6-(pent-4-yn-1-yl)-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylic acid 1,1-dioxide (2-98). To a solution of dialkylated thiadiazine **2-97** (0.9339 g, 2.577 mmol) in EtOH (3.5 mL) and THF (3 mL) was added in one portion 2 M KOH (13.0 mL, 26.0 mmol). The reaction mixture was warmed to 85 °C and stirred for 3.5 h. The reaction mixture was cooled to rt and extracted with Et_2O (1 x 20 mL). The organic layer was extracted with 2 M KOH (1 x 20 mL). The aqueous layer was cooled in an ice bath and acidified with conc. aq. HCl (~6 mL). A colorless precipitate formed and the slurry was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give acid **2-98** (0.7386, 86%) as a light yellow solid: Mp 152.5-153.8 °C (dec., Et_2O); IR (ATR) 3292, 2930, 2554, 1663, 1616, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.69 (s, 1 H), 7.34-7.26 (m, 5 H), 5.41 (s, 1 H), 3.82-3.75 (m, 1 H), 3.74-3.67 (m, 1 H), 2.94 (s, 3 H), 2.30 (dt, 2 H, J = 6.8, 2.6 Hz), 2.07 (t, 1 H, J = 2.6 Hz), 1.99-1.85 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 143.7, 137.7, 128.2, 128.1, 127.7, 99.9, 82.2, 70.5, 66.1, 49.9, 40.2, 28.4, 15.4; HRMS (ESI^+) *m/z* calcd for $C_{16}H_{19}N_2O_4S$ $[M+H]^+$ 335.1066, found 335.1064.



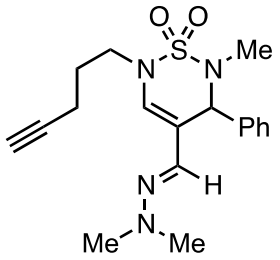
2-99

***N*-Methoxy-*N*,2-dimethyl-6-(pent-4-yn-1-yl)-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxamide 1,1-dioxide (2-99)**. To a solution of acid **2-98** (0.3432 g, 1.026 mmol), dimethylhydroxylamine hydrochloride (0.1326 g, 1.359 mmol), PyBOP (0.6440 g, 1.238 mmol) in CH_2Cl_2 (2.9 mL) cooled to 0 °C was added DIPEA (0.625 mL, 3.59 mmol). The reaction mixture was slowly warmed to rt, stirred for 23 h, and diluted with EtOAc (15 mL) and water (15 mL). The aqueous layer was separated and extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with 1 M $NaHSO_4$ (2 x 10 mL), sat. aq. $NaHCO_3$ (1 x 20 mL), and brine (1 x 20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (2:8 to 1:1; EtOAc:hexanes) to give a light yellow oil. The oil was dissolved in $CHCl_3$ and concentrated under reduced pressure (3 x 10 mL) to give the Weinreb amide **2-99** (0.3548 g, 92%) as a light yellow oil: IR (ATR) 3284, 2934, 1635, 1631, 1359, 1158 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.37-7.29 (m, 5 H), 7.10 (d, 1 H, J = 1.6 Hz), 5.91 (d, 1 H, J = 1.5 Hz), 3.73, 3.68 (AB dt, 2 H, J_{AB} = 14.5, 7.1 Hz), 356 (s, 3 H), 2.99 (s, 3 H), 2.46 (s, 3 H), 2.32 (dt, 2 H, J = 6.8, 2.6 Hz), 2.03 (t, 1 H, J = 2.6 Hz), 1.95 (pentet, 2 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6, 138.3, 136.1, 129.1, 128.6, 128.5, 107.9, 82.5, 70.1, 65.8, 61.1, 49.2, 34.3, 33.3, 28.6, 15.5; HRMS (ESI^+) *m/z* calcd for $C_{18}H_{24}N_3O_4S$ $[M+H]^+$ 378.1488, found 378.1501.



2-100

2-Methyl-6-(pent-4-yn-1-yl)-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carbaldehyde 1,1-dioxide (2-100). To a solution of Weinreb amide **2-99** (0.7689 g, 2.037 mmol) in THF (13.5 mL) cooled to -78 °C was added dropwise $LiAlH_4$ (1 M in Et_2O, 4.20 mL, 4.20 mmol) over 5 min. The reaction mixture was stirred for 2 h at -78 °C. The reaction mixture was warmed to 0 °C for 15 min, diluted with Et_2O (20 mL), and quenched with water (5 mL). The aqueous layer was diluted with water (30 mL), acidified with 1 M HCl (~10 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (2 x 20 mL), CH_2Cl_2 (1 x 20 mL), and EtOAc (1 x 20 mL). The combined organic layers were washed with brine (1 x 10 mL), diluted with EtOAc (~40 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude solid was purified by chromatography on SiO_2 (2:8 to 6:4; EtOAc:hexanes) to give the desired aldehyde **2-100** (0.4899 g, 76%) as a colorless foam: IR (ATR) 3239, 2936, 1663, 1618, 1353, 1338, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.39 (s, 1 H), 7.34-7.25 (m, 6 H), 5.51 (s, 1 H), 3.88, 3.79 (AB dt, 2 H, J_{AB} = 14.6, 7.3 Hz), 2.91 (s, 3 H), 2.35 (dt, 2 H, J = 6.4, 2.6 Hz), 2.10 (t, 1 H, J = 2.6 Hz), 2.04-1.91 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.8, 149.8, 136.4, 128.27, 128.25, 127.7, 113.6, 82.3, 70.7, 64.8, 50.0, 39.8, 28.2, 15.3; HRMS ($ASAP^+$) *m/z* calcd for $C_{16}H_{19}N_2O_3S$ $[M+H]^+$ 319.1119, found 319.1117.



2-101

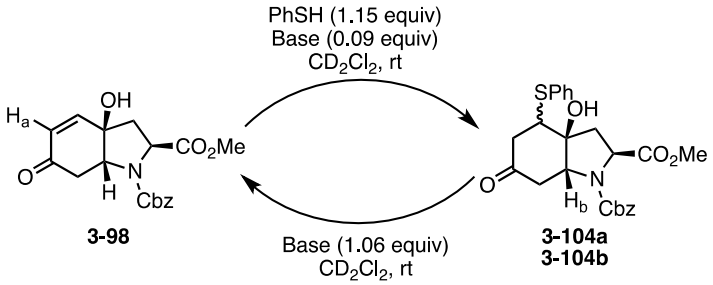
(*E*)-4-((2,2-Dimethylhydrazono)methyl)-2-methyl-6-(pent-4-yn-1-yl)-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxide (2-101). To a suspension of aldehyde **2-100** (0.3040 g, 0.9548 mmol) in benzene (2.35 mL) was added PTS (0.0186 g, 0.0978 mmol) and 1,1-dimethylhydrazine (0.110 mL, 1.45 mmol). The aldehyde did not dissolve and CH_2Cl_2 (1 mL) was added to increase solubility. The reaction mixture was stirred at rt for 14 h, heated to 65 °C for 2 h, then the reaction flask was equipped with a dean-stark trap, heated at reflux for 1.5 h, treated with powdered 4A MS (200 mg), and stirred for 2.5 h at 85 °C. The reaction was incomplete and treated with PTS (0.0228 g, 1.20 mmol) and 1,1-dimethylhydrazine (0.110 mL, 1.45 mmol), heated to 80 °C for 3 h, cooled to rt, diluted with CH_2Cl_2 (10 mL), filtered, and washed with water (1 x 10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give hydrazone **2-101** (0.2020 g, 59%) as a light yellow oil: IR (ATR) 3284, 2952, 1631, 1448, 1351, 1161, 1016 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34-7.20 (m, 5 H), 6.92 (s, 1 H), 6.43 (s, 1 H), 5.42 (s, 1 H), 3.63 (t, 2 H, J = 6.9 Hz), 2.87 (s, 3 H), 2.65 (s, 6 H), 2.32 (dt, 2 H, J = 6.8, 2.5 Hz), 2.04 (t, 1 H, J = 2.6 Hz), 1.93 (pentet, 2 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.4, 132.2, 130.7, 128.5, 127.7, 127.3, 113.1, 83.0, 69.8, 66.7, 48.7, 43.0, 39.1, 28.3, 15.6; HRMS (ESI^+) *m/z* calcd for $C_{18}H_{24}N_4O_2S$ $[M+H]^+$ 361.1698, found 361.1722.

4.4 CHAPTER 3 EXPERIMENTAL PART

General Notes for Equilibrium Experiments by ^{1}H NMR:

All experiments were performed with a delay time (d1) of 5 s and the spin off on a Bruker Avance 500 mHz NMR. Samples were auto tuned and matched (atma), auto shimmed (topshim), and calibrated to CD_2Cl_2 (δ 5.32). Each sample was analyzed three consecutive times at each time point to account for variations due to manual integration.

Experimental set up for equilibrium study for enone 3-98 and thiophenyl adduct 3-104.



Reaction	Base	ΔG
3-98 to **3-104**	Et_3N	≤ −4.6 kcal/mol
3-98 to **3-104**	DBU	≤ −4.6 kcal/mol
3-104to **3-98**	Et_3N	+1.8 ± 0.03 kcal/mol
3-104to **3-98**	DBU	≤ −3.8 kcal/mol

For **3-98** to **3-104** using Et_3N as a base:

To a solution of enone **3-98** (0.0290 g, 0.0840 mmol) in CD_2Cl_2 (0.75 mL) was added thiophenol (10.0 μL, 96.6 μmol) and Et_3N (1.0 μL, 8.5 μmol). The solution was transferred to an

NMR tube, flushed with argon, capped, and sealed with parafilm. The solution was analyzed by ^{1}H NMR at 12, 23, and 38 h while monitoring the ratio of **3-98** (δ 5.95 (dd)) and **3-104** (minor diastereomer: δ 4.29 (app. t); 4.22 (app. t), major diastereomer: δ 4.17 (dd)). The ratio of **3-104**:**3-98** was > 50:1. K_{eq} = ≥ 2.6 x 10^3 and ΔG = ≤ −4.6 kcal/mol. The *dr* of **3-104** was observed to be 2.7 to 1 (**3-104a** to 3-104**b**) from the peaks for minor diastereomer: δ 4.29 (app. t, 0.5 H); 4.22 (app. t, 0.5 H), major diastereomer: δ 4.17 (dd, 1 H).

For **3-98** to **3-104** using DBU as a base:

To a solution of enone **3-98** (0.0290 g, 0.0840 mmol) in CD_2Cl_2 (0.75 mL) was added thiophenol (10.0 μL, 96.6 μmol) and Et_3N (1.0 μL, 6.7 μmol). The solution was transferred to an NMR tube, flushed with argon, capped, and sealed with parafilm. The solution was analyzed by ^{1}H NMR at 10 and 23 h while monitoring the ratio of **3-98** (δ 5.95 (dd)) and **3-104** (minor diastereomer: δ 4.30 (app. t); 4.23 (app. t), major diastereomer: δ 4.18 (m)). The ratio of **3-104**:**3-98** was > 50:1. K_{eq} = ≥ 2.6 x 10^3 and ΔG = ≤ −4.6 kcal/mol. The *dr* of **6** was observed to be 1.6 to 1 (**3-104a** to **3-104b**) from the peaks for minor diastereomer: δ 4.30 (app. t, 0.5 H); 4.23 (app. t, 0.5 H), major diastereomer: δ 4.18 (m, 1 H).

For **3-104** to **3-98** using Et_3N as a base:

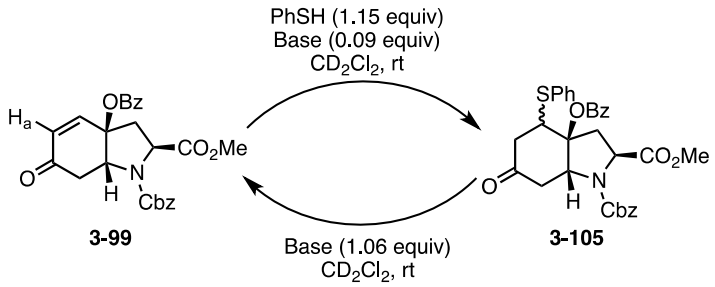
To a solution of thiophenol adduct **3-104** (0.0128 g, 0.0281 mmol) in CD_2Cl_2 (0.75 mL) was added Et_3N (4.2 μL, 3.0 μmol). The solution was transferred to an NMR tube, flushed with argon, capped, and sealed with parafilm. The solution was analyzed by ^{1}H NMR at 10, 24, and 30 h while monitoring the ratio of **3-104** (minor diastereomer: δ 4.29 (app. t); 4.22 (app. t), major diastereomer: δ 4.17 (dd)) to **3-98** (δ 5.95 (dd)). The ratio of **3-98**:**3-104** was 1:4.3. K_{eq} = 5.0 ±

0.2 x 10^{-2} and $\Delta G = 1.8 \pm 0.03$ kcal/mol. The *dr* of **3-104** was observed to be 1.8 to 1 (**3-104a** to **3-104b**) from the peaks for minor diastereomer: δ 4.29 (app. t, 0.5 H); 4.22 (app. t, 0.5 H), major diastereomer: δ 4.17 (dd, 1 H).

For **3-104** to **3-98** using DBU as a base:

To a solution of thiophenol adduct **3-104** (0.0128 g, 0.0281 mmol) in CD_2Cl_2 (0.75 mL) was added DBU (4.5 μL, 3.0 μmol). The solution was transferred to an NMR tube, flushed with argon, capped, and sealed with parafilm. The solution was analyzed by ^{1}H NMR at 10, 24, and 30 h while monitoring the ratio of **3-104** (minor diastereomer: δ 4.30 (app. t); 4.23 (app. t), major diastereomer: δ 4.18 (m)) to **3-98** (δ 5.95 (dd)). The ratio of **3-98**:**3-104** was > 50:1. $K_{eq} = \geq 6.3$ x 10^2 and $\Delta G = \leq -3.8$ kcal/mol.

Experimental set up for equilibrium study for enone 3-99 and thiophenyl adduct 3-105.



Reaction	Base	ΔG
3-99 to **3-105**	Et_3N	−4.1 ± 0.06 kcal/mol
3-99 to **3-105**	DBU	−4.0 ± 0.02 kcal/mol
3-105 to **3-99**	Et_3N	+1.0 ± 0.001 kcal/mol
3-105 to **3-99**	DBU	≤ −3.8 kcal/mol

For **3-99** to **3-105** using Et_3N as a base:

To a solution of enone **3-99** (0.0247 g, 0.0550 mmol) in CD_2Cl_2 (0.3 mL) was added thiophenol (0.100 mL, 0.0633 mmol, 0.633 M in CD_2Cl_2) and Et_3N (0.10 mL, 5.0 μmol, 0.050 M in CD_2Cl_2). The solution was transferred to a J-Young NMR tube, flushed with argon, and sealed. The solution was analyzed by ^1H NMR for 13 d while monitoring the ratio of **3-99** (δ 6.10 (app t, 1 H)) and **3-105** (minor diastereomer: δ 7.99-7.95 (m, 2 H); major diastereomer: 7.71-7.67 (m, 2 H)). After 150 h the ratio of **3-105**:**3-99** was 22:1. $K_{eq} = 1.0 \pm 0.09 \times 10^3$ and ΔG = −4.1 ± 0.06 kcal/mol. The *dr* of **3-105** was observed to be 2.6 to 1 from the peaks for minor diastereomer: δ 7.99-7.95 (m, 2 H), major diastereomer: δ 7.71-7.67 (m, 2 H). The relative stereochemistry of the diastereomers could not be determined.

For **3-99** to **3-105** using DBU as a base:

To a solution of enone **3-99** (0.0247 g, 0.0550 mmol) in CD_2Cl_2 (0.3 mL) was added thiophenol (0.100 mL, 0.0633 mmol, 0.633 M in CD_2Cl_2) and DBU (0.10 mL, 5.0 μmol, 0.050 M in CD_2Cl_2). The solution was transferred to a J-Young NMR tube, flushed with argon, and sealed. The solution was analyzed by ^{1}H NMR for 14 d while monitoring the ratio of **7** (δ 6.10 (app t, 1 H)) and **3-105** (minor diastereomer: δ 7.99-7.95 (m, 2 H); major diastereomer: 7.71-7.67 (m, 2 H)). After 150 h the ratio of **3-105**:**3-99** was 21:1. $K_{eq} = 9.1 \pm 0.3 \times 10^2$ and $\Delta G = -4.0 \pm 0.02$ kcal/mol. The *dr* of **3-105** was observed to be 2.1 to 1 from the peaks for minor diastereomer: δ 7.99-7.95 (m, 2 H), major diastereomer: δ 7.71-7.67 (m, 2 H). The relative stereochemistry of the diastereomers could not be determined.

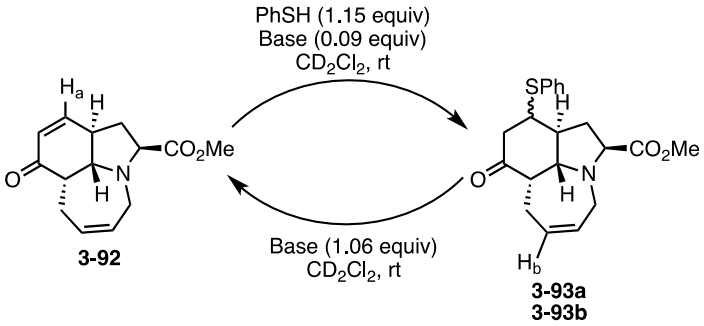
For **3-105** to **3-99** using Et_3N as a base:

To a solution of the major diastereomer of the thiophenol adduct **3-105** (0.0157 g, 0.0280 mmol) in CD_2Cl_2 (0.75 mL) was added Et_3N (4.2 μL, 3.0 μmol). The solution was transferred to an NMR tube, flushed with argon, capped, and sealed with parafilm. The solution was analyzed by ^{1}H NMR at 24 h while monitoring the ratio of **3-105** (minor diastereomer: δ 7.98-7.94 (m, 2 H); major diastereomer: 7.71-7.67 (m, 2 H)) to **7** (δ 6.10 (app. t)). The ratio of **3-99**:**3-105** was 1:2.3. $K_{eq} = 1.8 \pm 0.004 \times 10^{-1}$ and $\Delta G = 1.0 \pm 0.001$ kcal/mol. The *dr* of **3-105** was observed to be 6.7:1 from the peaks for minor diastereomer: δ 7.98-7.94 (m, 2 H); major diastereomer: 7.71-7.67 (m, 2 H).

For **3-105** to **3-99** using DBU as a base:

To a solution of the major diastereomer of the thiophenol adduct **3-105** (0.0126 g, 0.0225 mmol) in CD_2Cl_2 (0.6 mL) was added DBU (3.5 μL, 2.4 μmol). The solution was transferred to an NMR tube, flushed with argon, capped, and sealed with parafilm. The solution was analyzed by ^1H NMR at 8 and 22 h while monitoring the ratio of **3-105** (minor diastereomer: δ 7.98-7.94 (m, 2 H); major diastereomer: 7.71-7.67 (m, 2 H)) to **7** (δ 6.10 (app. t)). The ratio of **3-99**:**3-105** was ≥ 50:1. $K_{eq} = \geq 6.1 \times 10^2$ and $\Delta G = \leq -3.8$ kcal/mol.

Experimental set up for equilibrium study for enone 3-92 and thiophenyl adduct 3-93.



Reaction	Base	ΔG
3-92 to **3-93**	Et_3N	≤ −4.6 kcal/mol
3-92 to **3-93**	DBU	≤ −4.6 kcal/mol
3-93b to **3-92**	Et_3N	+3.4 ± 0.1 kcal/mol
3-93b to **3-92**	DBU	≤ −2.6 kcal/mol

For **3-92** to **3-93** using Et_3N as a base:

To a solution of enone **3-92** (0.012 g, 0.0485 mmol) in CD_2Cl_2 (0.45 mL) was added thiophenol (5.7 μL, 55.8 μmol) and Et_3N (0.61 μL, 4.4 μmol). The solution was transferred to an

NMR tube, flushed with argon, capped, and sealed with parafilm. The solution was analyzed by ^{1}H NMR at 6, 10, and 22 h while monitoring the ratio of **3-92** (δ 6.96 (d)) and **3-93** (δ 5.70-5.62 (m)). The ratio of **3-93**:**3-92**was > 50:1. $K_{eq} = \geq 2.8 \times 10^3$ and $\Delta G = \leq -4.6$ kcal/mol. The *dr* of **3-93** was observed to be 3.8 to 1 (**3-93a** to **3-93b**) from the methyl ester peaks at δ 3.70 (s) and 3.68 (s).

For **3-92** to **3-93** using DBU as a base:

To a solution of enone **3-92** (0.0120 g, 0.0485 mmol) in CD_2Cl_2 (0.45 mL) was added thiophenol (5.7 μL, 55.8 μmol) and DBU (0.65 μL, 4.4 μmol). The solution was transferred to an NMR tube, flushed with argon, capped, and sealed with parafilm. The solution was analyzed by ^{1}H NMR at 6, 10, and 22 h while monitoring the ratio of **3-92** (δ 6.96 (d)) and **3-93** (δ 5.70-5.62 (m)). The ratio of **3-93**:**3-92**was < 50:1. $K_{eq} = \geq 2.8 \times 10^3$ and $\Delta G = \leq -4.6$ kcal/mol. The *dr* of **3-93** was observed to be 2.7 to 1 (**3-93a** to **3-93b**) from the methyl ester peaks at δ 3.70 (s) and 3.68 (s).

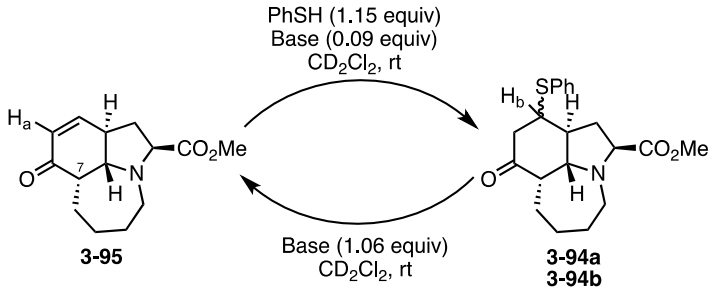
For **3-93b** to **3-92** using Et_3N as a base:

To a solution of ketone **3-93b** (0.0060 g, 0.017 mmol, minor diastereomer **3-93b**) in CD_2Cl_2 (0.45 mL) was added Et_3N (2.5 μL, 0.018 mmol). The solution was transferred to an NMR tube, flushed with argon, capped, and sealed with parafilm. The solution was analyzed by ^{1}H NMR at 19 and 24 h while monitoring the ratio of **3-93b** (δ 5.70-5.62 (m)) and **3-92** (δ 6.98 (dd)). The ratio of **3-92**: **3-93b** was 1:17.1. $K_{eq} = 3.3 \pm 0.7 \times 10^{-3}$ and $\Delta G = +3.4 \pm 0.1$ kcal/mol. The *dr* of **3-93** was observed as a single diastereomer (**3-93b**).

For **3-93b** to **3-92** using DBU as a base:

To a solution of ketone **3-93b** (0.0083 g, 0.023 mmol, minor diastereomer **3-93b**) in CD_2Cl_2 (0.620 mL) was added DBU (3.7 μL, 0.025 mmol). The solution was transferred to an NMR tube, flushed with argon, capped, and sealed with parafilm. The solution was analyzed by ^1H NMR at 19 and 24 h while monitoring the ratio of **3-93b** (δ 5.70-5.62 (m)) and **3-92** (δ 5.76-5.71 (m)). The ratio of **3-92**:**3-93b** was >12.4:1. $K_{eq} = \geq 84$ and $\Delta G = \leq -2.6$ kcal/mol.

Experimental set up for equilibrium study for enone 3-95 and thiophenyl adduct 3-94.



Reaction	Base	ΔG
3-95 to **3-94**	Et_3N	≤ −4.6 kcal/mol
3-95 to **3-94**	DBU	≤ −4.6 kcal/mol
3-94a to **3-95**	Et_3N	+2.3 ± 0.03 kcal/mol
3-94b to **3-95**	DBU	−2.9 ± 0.2 kcal/mol[a]

[a]during reaction **3-94** to **3-95** with DBU enone **3-95** is observed as a 2.5:1 mixture of diastereomers (epimerization α to ketone).

For **3-95** to **3-94** using Et_3N as a base:

To a solution of enone **3-95** (0.0133 g, 0.0533 mmol) in CD_2Cl_2 (0.3 mL) was added thiophenol (0.100 mL, 61.3 μmol, 0.613 M in CD_2Cl_2) and Et_3N (0.100 mL, 4.80 μmol, 0.0480 M in CD_2Cl_2). The solution was transferred to an NMR tube, flushed with argon, capped, and sealed with parafilm. The solution was analyzed by ^1H NMR at 9 and 22 h while monitoring the ratio of **3-95** (δ 5.91 (dd)) and **3-94** (δ 4.02 (dd, major diastereomer) and 3.98 (dd, minor diastereomer). The ratio of **3-94**:**3-95** was > 50:1. $K_{eq} = \geq 2.8 \times 10^3$ and $\Delta G = \leq -4.6$ kcal/mol. The *dr* of **3-94** was observed to be 3.6 to 1 from the peaks at δ 4.02 (dd) and 3.98 (dd).

For **3-95** to **3-94** using DBU as a base:

To a solution of enone **3-95** (0.0133 g, 0.0533 mmol) in CD_2Cl_2 (0.3 mL) was added thiophenol (0.100 mL, 61.3 μmol, 0.613 M in CD_2Cl_2) and DBU (0.100 mL, 4.80 μmol, 0.0480 M in CD_2Cl_2). The solution was transferred to an NMR tube, flushed with argon, capped, and sealed with parafilm. The solution was analyzed by ^1H NMR at 12 and 22 h while monitoring the ratio of **3-95** (δ 5.91 (dd)) and **3-94** (δ 4.02 (dd, major diastereomer) and 3.98 (dd, minor diastereomer). The ratio of **3-94**:**3-95** was > 50:1. $K_{eq} = \geq 2.8 \times 10^3$ and $\Delta G = \leq -4.6$ kcal/mol. The *dr* of **3-94** was observed to be 3.5 to 1 from the peaks at δ 4.02 (dd) and 3.98 (dd).

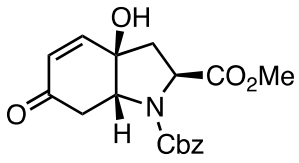
For **3-94** to **3-95** using Et_3N as a base:

To a solution of ketone **3-94** (0.0083 g, 0.023 mmol, major diastereomer) in CD_2Cl_2 (0.6 mL) was added Et_3N (3.4 μL, 0.025 mmol). The solution was transferred to an NMR tube, flushed with argon, capped, and sealed with parafilm. The solution was analyzed by ^1H NMR at 23 h while monitoring the ratio of **3-94** (δ 4.02 (dd, major diastereomer) and 3.98 (dd, minor

diastereomer) and **3-95** (δ 3.89 (app. t)). The ratio of **3-95: 3-94** was 1:6.7. $K_{eq} = 2.1 \pm 0.1 \times 10^{-2}$ and $\Delta G = +2.3 \pm 0.03$ kcal/mol. The *dr* of **3-94** shifted from a single isomer to a ratio of 3.1:1.

For **3-94** to **3-95** using DBU as a base:

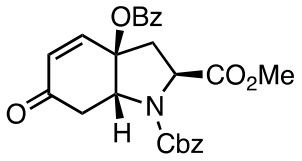
To a solution of ketone **3-94** (0.0069 g, 0.019 mmol, minor diastereomer) in CD_2Cl_2 (0.45 mL) was added DBU (3.0 μL, 0.020 mmol). The solution was transferred to an NMR tube, flushed with argon, capped, and sealed with parafilm. The solution was analyzed by ^{1}H NMR at 23 h while monitoring the ratio of **3-94** (δ 3.98 (app. t)) and **3-95** (δ 5.95 (dd) and 5.91 (dd) epimers). The ratio of **3-95:3-94** was 15.8:1. $K_{eq} = 140 \pm 40$ and $\Delta G = -2.9 \pm 0.2$ kcal/mol. During the reaction enone **3-95** was epimerized to a 2.5:1 mixture of diastereomers and the position alpha to the ester.



3-98

(2*S*,3a*R*,7a*R*)-1-Benzyl 2-methyl 3a-hydroxy-6-oxo-3,3a,7,7a-tetrahydro-1*H*-indole-1,2(2*H*,6*H*)-dicarboxylate (3-98).[169, 172] The enone **3-98** was prepared according to the literature to give **3-98** (11.04 g, 71%) as a pale orange foam: ^{1}H NMR ($CDCl_3$, 400 MHz, 1:2 mixture of rotamers) δ 7.39-7.26 (m, 5 H), 6.82 (d, 0.66 H, *J* = 10.3 Hz), 6.80 (d, 0.33 H, *J* = 10.3 Hz), 6.02 (d, 0.33 H, *J* = 10.3 Hz), 6.01 (d, 0.66 H, *J* = 10.3 Hz), 5.21 (d, 1 H, *J* = 12.2 Hz), 5.10 (d, 0.66 H, *J* = 12.2 Hz), 5.01 (d, 0.33 H, *J* = 12.1 Hz), 4.58-4.51 (m, 1.33 H), 4.48-4.42 (m, 0.66 H), 3.85 (s, 2 H), 3.56 (s, 1 H), 3.27 (dd, 0.33 H, *J* = 16.6, 6.4 Hz), 3.05 (dd, 0.66 H, *J* = 16.6, 6.4

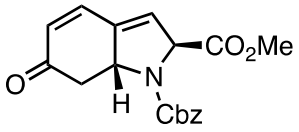
Hz), 2.60-2.50 (m, 1 H), 2.31 (d, 0.33 H, J = 14.2 Hz), 2.29 (d, 0.66 H, J = 14.3 Hz), 2.19 (d, 0.66 H, J = 16.6 Hz), 2.16 (d, 0.33 H, J = 16.6 Hz).



3-99

(2*S*,3a*R*,7a*R*)-1-Benzyl 2-methyl 3a-(benzoyloxy)-6-oxo-3,3a,7,7a-tetrahydro-1*H*-indole-1,2(2*H*,6*H*)-dicarboxylate (3-99).[169] To solution of alcohol **3-98** (1.000 g, 2.896 mmol), benzoic anhydride (1.021 g, 4.513 mmol), and DMAP (0.0367 g, 0.300 mmol) in CH_2Cl_2 (14 mL) was added pyridine (1.15 mL, 14.22 mmol). The light yellow solution was heated to reflux for 17 h, treated with DMAP (44.3 mg, 0.363 mmol), and heated for 26 h. The reaction was not complete yet and more DMAP (101.2 mg, 0.828 mmol) was added, the reaction was stirred at reflux for an additional 21 h, quenched with 10% aq. HCl (50 mL), and extracted with $CHCl_3$ (3 x 20 mL). The combined organic layers were washed with 1 M HCl (2 x 50 mL), sat. aq. $NaHCO_3$ (1 x 50 mL) and brine (1 x 50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude oil was purified by chromatography on SiO_2 (1:4 to 2:3; EtOAc:hexanes) to give benzyolated compound **3-99** (0.9027 g, 69 %) as a colorless foam: ^{1}H NMR (CD_2Cl_2, 500 MHz, 1:1 mixture of rotamers) δ 7.94-7.91 (m, 2 H), 7.63-7.58 (m, 1 H), 7.48-7.44 (m, 2 H), 7.38-7.36 (m, 2 H), 7.36-7.39 (m, 3 H), 7.05 (d, 0.5 H, J = 10.5 Hz), 7.01 (d, 0.5 H, J = 10.4 Hz), 6.10 (app t, 1 H, J = 10.6 Hz), 5.20 (AB d, 0.5 H, J_{AB} = 12.3 Hz), 5.16 (AB d, 0.5 H, J_{AB} = 12.4 Hz), 5.11 (AB d, 0.5 H, J_{AB} = 12.4 Hz), 5.03 (AB d, 0.5 H, J_{AB} = 12.7 Hz), 5.01 (dt, 1 H, J = 10.1, 1.1 Hz), 4.72 (dd, 0.5 H, J = 9.8, 1.4 Hz), 4.66 (dd, 0.5 H, J = 9.5, 1.9 Hz), 3.59 (s, 1.5 H), 3.40 (s, 1.5 H), 3.83 (ddd, 0.5 H, J = 16.8, 6.7, 0.6 Hz), 3.22 (ddd, 0.5 H, J =

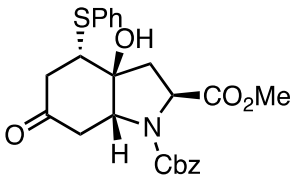
16.7, 6.7, 0.7 Hz), 3.08 (dt, 0.5 H, *J* = 6.2, 1.5 Hz), 3.05 (dt, 0.5 H, *J* = 6.3, 1.6 Hz), 2.75 (dd, 0.5 H, *J* = 14.3, 9.5 Hz), 2.69 (dd, 0.5 H, *J* = 14.5, 9.9 Hz), 2.50 (dd, 0.5 H, *J* = 16.7, 9.9 Hz), 2.42 (dd, 0.5 H, *J* = 16.7, 10.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, 1:1 mixture of rotamers) δ 195.0, 194.9, 171.4, 170.8, 165.5, 165.3, 154.2, 153.9, 145.0, 144.1, 136.1, 135.9, 133.9, 133.8, 130.3, 130.0, 129.9, 129.8, 129.39, 129.36, 128.8, 128.6, 128.53, 128.45, 128.4, 128.3, 84.0, 82.8, 68.0, 67.6, 62.0, 61.4, 58.6, 58.4, 52.7, 52.5, 42.9, 41.6, 39.6, 38.8.



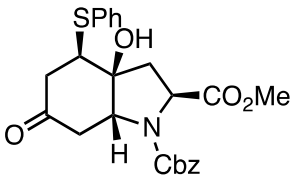
3-101

(2*S*,7a*R*)-1-Benzyl 2-methyl 6-oxo-7,7a-dihydro-1*H*-indole-1,2(2*H*,6*H*)-dicarboxylate (3-101). To a suspension of diene **3-84** (0.8048 g, 2.444 mmol) and activated 4Å MS (0.850 g) in CH_2Cl_2 (10.4 mL) cooled to 0 °C was added NMO (0.4069 g, 3.011 mmol) and TPAP (0.0275 g, 0.0783 mmol). The black suspension was warmed to rt and stirred for 17.5 h. By TLC the reaction was incomplete so NMO (0.0917 g, 0.678 mmol) was added, the reaction was stirred at rt for 26 h, filtered through a pad of SiO_2, washed with EtOAc, and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (1:4 to 1:3: EtOAc:hexanes) to give ketone **3-101** (0.5636 g, 67%) as a light yellow oil: IR (ATR) 2952, 1745, 1705, 1670, 1405, 1348, 1204 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, 1:1 mixture of rotamers) δ 7.37-7.29 (m, 5 H), 7.20 (d, 1 H, *J* = 9.8 Hz), 7.19 (d, 1 H, *J* = 9.8 Hz), 6.09 (d, 0.5 H, *J* = 9.2 Hz), 6.07 (d, 0.5 H, *J* = 9.2 Hz), 5.28-5.15 (m, 2.5 H), 5.12-4.98 (m, 1.5 Hz), 3.75 (s, 1.5 H), 3.65 (dd, 0.5 H, *J* = 15.8, 5.7 Hz), 3.52 (s, 1.5 H), 3.40 (dd, 0.5 H, *J* = 15.8, 5.6 Hz), 2.49 (dd, 0.5 H, *J* = 12.5, 3.1 Hz), 2.45 (dd, 0.5 H, *J* = 12.6, 3.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, 1:1 mixture of rotamers) δ 196.8, 196.7, 169.8, 169.6, 154.8, 154.0, 138.5, 138.4, 137.4, 136.9, 136.04,

135.99, 135.9, 131.5, 131.1, 128.7, 128.6, 128.5, 128.4, 128.32, 128.27, 122.8, 122.4, 68.7, 68.3, 67.9, 67.4, 62.2, 61.4, 52.8, 52.6, 45.8, 44.9; HRMS (ESI^+) *m/z* calcd for $C_{18}H_{17}NO_5Na$ $[M+Na]^+$ 350.1004, found 350.0992.



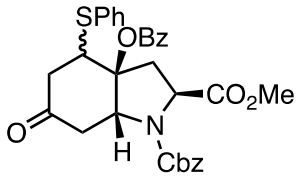
3-104a



3-104b

(2*S*,3a*S*,4*S*,7a*R*)-1-Benzyl 2-methyl 3a-hydroxy-6-oxo-4-(phenylthio)octahydro-1*H*-indole-1,2-dicarboxylate (3-104a) and (2*S*,3a*S*,4*R*,7a*R*)-1-benzyl 2-methyl 3a-hydroxy-6-oxo-4-(phenylthio)octahydro-1*H*-indole-1,2-dicarboxylate (3-104b). To a round bottom flask was added enone **3-98** (0.150 g, 0.434 mmol) in CH_2Cl_2 (3.9 mL) was added thiophenol (0.051 mL, 0.50 mmol) and Et_3N (0.005 mL, 0.04 mmol) and stirred at rt for 16.5 h. The crude reaction mixture was concentrated under reduced pressure and purified by chromatography on SiO_2 (1:4 to 1:2; EtOAc:hexanes) to give the thiol addition product **3-104a** and **3-104b** (0.1544 g, 79%) as a colorless foam and an inseparable 2.3:1 (**3-104a**:**3-104b**) mixture of diastereomers: IR (ATR) 3433, 3057, 2951, 1702, 1404, 1346, 1113, 736, 693 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz, 1:1 mixture of rotamers, peaks for major diastereomer **3-104a**) δ 7.52-7.45 (m, 2 H), 7.38-7.27 (m, 8 H), 5.19 (m, 2 H), 5.01 (app d, 1 H, *J* = 12.3 Hz), 4.54-4.47 (m, 1 H), 4.16 (dd, 1 H, *J* = 11.8, 5.3 Hz), 3.78 (s, 1.5 H), 3.61 (s, 1.5 H), 3.50 (dt, 1 H, *J* = 11.4, 4.2 Hz), 3.17 (dd, 0.5 H, *J* = 16.4, 5.3 Hz), 3.00 (dd, 0.5 H, *J* = 16.4, 5.2 Hz), 2.71-2.45 (m, 3 H), 2.45-2.14 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz, 1:1 mixture of rotamers, mixture of diastereomers) δ 206.9, 206.7, 205.6, 204.8, 175.1, 174.7, 174.5, 174.2, 155.25, 154.86, 136.8, 136.7, 134.1, 134.0, 133.62, 133.51, 133.3, 129.9, 129.7, 129.0, 128.9, 128.7, 128.50, 128.48, 81.2, 80.5, 80.1, 68.0, 67.9, 67.8, 65.9,

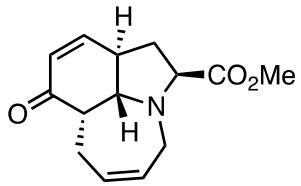
65.6, 65.2, 64.6, 60.8, 59.7, 59.6, 58.4, 58.3, 53.3, 53.1, 51.65, 51.4, 45.0, 44.9, 44.6, 44.0, 43.8, 43.0, 42.9, 42.8, 42.2, 40.9, 37.2, 36.7; HRMS (ESI^+) *m/z* calcd for $C_{24}H_{26}NO_6S$ $[M+H]^+$ 456.1475, found 456.1568.



3-105

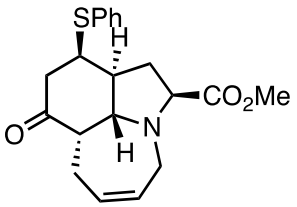
(2*S*,3a*S*,7a*R*)-1-Benzyl 2-methyl 3a-(benzoyloxy)-6-oxo-4-(phenylthio)octahydro-1*H*-indole-1,2-dicarboxylate (3-105). To a solution of enone **3-99** (0.0762 g, 0.170 mmol) and thiophenol (0.020 mL, 0.20 mmol) was added Et_3N (0.0035 mL, 0.025 mmol) and stirred at rt for 10 h. The reaction mixture was concentrated under reduced pressure and purified by chromatography on SiO_2 (1:4; 1:2; 2:3; EtOAc:hexanes) to give thiol addition product **3-105** as an unassigned mixture of diastereomers. Major diastereomer (0.0597 g, 63 %) and minor diastereomer (0.0273 g, 29%, containing trace **3-99**): Major diastereomer: IR (ATR) 2951, 1746, 1705, 1282, 1094 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 3:1 mixture of rotamers) δ 7.72-7.67 (m, 2 H), 7.55-7.48 (m, 1 H), 7.38-7.27 (m, 9 H), 7.04-6.94 (m, 3 H), 5.18 (d, 0.75 H, *J* = 12.3 Hz), 5.15 (d, 0.25 H, *J* = 14.4 Hz), 5.07 (dd, 0.75 H, *J* = 12.2, 6.2 Hz), 5.00-4.85 (m, 2.25 H), 4.68 (d, 0.25 H, *J* = 8.9 Hz), 4.59 (d, 0.75 H, *J* = 9.0 Hz), 3.58, (s, 0.75 H), 3.30 (s, 2.25 H), 3.24 (app d, 1.5 H, *J* = 4.5 Hz), 3.18 (dd, 0.25 H, *J* = 15.6, 6.5 Hz), 2.97 (app d, 0.25 H, *J* = 15.5 Hz), 2.92-2.82 (m, 2 H), 2.67-2.57 (m, 1 H), 2.48-2.37 (m, 1 H); ^{13}C NMR (CD_2Cl_2, 100 MHz, major rotamer) δ 206.0, 172.4, 166.2, 155.5, 136.8, 134.0, 133.9, 130.1, 129.6, 129.1, 129.0, 128.7, 128.5, 90.4, 67.8, 63.9, 59.0, 52.8, 46.2, 43.4, 43.1, 37.1; HRMS (ESI^+) *m/z* calcd for $C_{31}H_{29}NO_7SNa$ $[M+Na]^+$ 582.1557, found 582.1551. Minor diastereomer: IR (ATR) 2951,

1752, 1705, 1702, 1405, 1277, 1245, 1094 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 3:2 mixture of rotamers) δ 7.99-7.94 (m, 2 H), 7.60-7.55 (m, 1 H), 7.47-7.34 (m, 7 H), 7.34-7.23 (m, 5 H), 5.27-5.17 (m, 1.6 H), 5.06 (d, 0.4 H, *J* = 12.1 Hz), 4.96 (t, 0.6 H, *J* = 6.4 Hz), 4.86 (t, 0.4 H, *J* = 7.8 Hz), 4.66-4.62 (m, 1.4 H), 4.57 (d, 0.6 H, *J* = 9.0 Hz), 4.49 (dd, 0.6 H, *J* = 16.8, 7.6 Hz), 3.33 (s, 1.2 H), 3.30-3.25 (m, 1.4 H), 3.14 (s, 1.8 H), 2.87-2.78 (m, 1 H), 2.70-2.57 (m, 2.6 H), 2.40 (dd, 0.4 H, *J* = 16.6, 7.4 Hz); ^{13}C NMR (CD_2Cl_2, 100 MHz, 3:2 mixture of rotamers) δ 205.6, 204.9, 171.9, 171.3, 166.1, 166.0, 154.8, 154.7, 136.9, 134.5, 134.4, 134.1, 133.0, 132.7, 130.5, 130.4, 130.3, 129.9, 129.1, 129.0, 128.8, 128.63, 128.57, 89.0, 88.2, 68.1, 67.8, 62.4, 61.6, 58.6, 58.4, 52.7, 49.5, 49.3, 45.1, 43.8, 42.5, 38.3, 37.0; HRMS (ESI^+) *m/z* calcd for $C_{31}H_{29}NO_7SNa$ $[M+Na]^+$ 582.1557, found 582.1553.

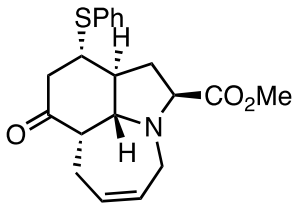


3-92

(2*S*,3^1*S*,7a*S*,10a*R*)-Methyl 8-oxo-1,2,3^1,4,7,7a,8,10a-octahydroazepino[3,2,1-*hi*]indole-2-carboxylate (3-92).[169] The enone **3-92** was prepared according to the literature to give enone **3-92** as a light yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.98 (dd, 1 H, *J* = 9.8, 1.9 Hz), 5.99 (dd, 1 H, *J* = 9.8, 2.9 Hz), 5.80-5.74 (m, 1 H), 5.59 (ddd, 1 H, *J* = 8.4, 5.2, 2.3 Hz), 4.01 (dd, 1 H, *J* = 8.4, 6.0 Hz), 3.71 (s, 3 H), 3.62-3.55 (m, 2 H), 3.30 (dd, 1 H, *J* = 17.6, 6.0 Hz), 2.94 (ddd, 1 H, *J* = 12.4, 7.2, 2.0 Hz), 2.78-2.69 (m, 1 H), 2.60 (dt, 1 H, *J* = 12.3, 8.3 Hz), 2.59-2.51 (m, 1 H), 2.18 (dd, 1 H, *J* = 16.2, 8.1 Hz), 1.81 (td, 1 H, *J* = 11.8, 5.9 Hz); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 200.7, 174.4, 148.5, 130.5, 129.5, 128.6, 65.2, 63.2, 51.4, 50.4, 47.4, 37.2, 32.2, 24.2.



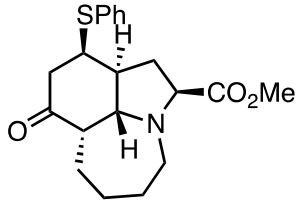
3-93a



3-93b

(2*S*,3^1*R*,7a*S*,10*R*,10a*S*)-Methyl 8-oxo-10-(phenylthio)-1,2,3^1,4,7,7a,8,9,10,10a-decahydroazepino[3,2,1-*hi*]indole-2-carboxylate (3-93a) and (2*S*,3^1*R*,7a*S*,10*S*,10a*S*)-methyl 8-oxo-10-(phenylthio)-1,2,3^1,4,7,7a,8,9,10,10a-decahydroazepino[3,2,1-*hi*]indole-2-carboxylate (3-93b). To a solution of enone **3-92** (0.0604 g, 0.244 mmol) in CH_2Cl_2 (2.2 mL) was added thiophenol (29.0 μL, 0.283 mmol) and Et_3N (5.5 μL, 39 μmol). The solution was stirred at rt for 3 h, concentrated under reduced pressure and purified by chromatography on SiO_2 (0:1; 5:95; 1:9; 1:4; to 1:1; EtOAc:hexanes) to the major diastereomer **3-93a** (0.0553 g, 63%) as a colorless solid and the minor diastereomer **3-93b** (0.0198 g, 23%) as a light yellow oil: Major diastereomer **3-93a**: Mp 142.5-143.6 °C (dec., $CHCl_3$); IR (ATR) 3014, 2962, 2898, 2811, 1728, 1694, 1193, 1152, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39-7.36 (m, 2 H), 7.31-7.28 (m, 2 H), 7.26-7.23 (m, 1 H), 5.72-5.66 (m, 1 H), 5.57-5.52 (m, 1 H), 4.04 (dd, 1 H, *J* = 8.9, 5.1 Hz), 3.83 (dd, 1 H, *J* = 10.8, 7.4 Hz), 3.78-3.70 (m, 1 H), 3.74 (s, 3 H), 3.62-3.55 (m, 1 H), 3.32 (ddt, 1 H, *J* = 17.8, 5.8, 1.8 Hz), 2.95 (dd, 1 H, *J* = 11.6, 7.4 Hz), 2.69 (ddd, 1 H, *J* = 16.2, 3.3, 0.9 Hz), 2.65-2.58 (m, 1 H), 2.61 (dd, 1 H, *J* = 16.1 , 5.7 Hz), 2.52 (tdd, 1 H, *J* = 10.4, 8.4, 3.9 Hz), 2.41 (dt, 1 H *J* = 12.9, 8.7 Hz), 2.24 (ddd, 1 H, *J* = 12.9, 10.2, 5.0 Hz), 2.03 (dd, 1 H, *J* = 15.6, 8.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.8, 174.5, 134.6, 132.3, 129.7, 129.3, 127.9, 127.5, 63.9, 61.2, 54.4, 51.7, 48.5, 46.0, 44.7, 42.3, 30.5, 25.9; HRMS (ESI$^+$) *m/z* calcd for $C_{20}H_{24}NO_3S$ $[M+H]^+$ 358.1471, found 358.1461. Minor diastereomer **3-93b**: IR (ATR) 3018, 2947, 2915, 1728, 1702, 1437, 1199 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.44 (dd, 2 H, *J* = 8.1, 1.6 Hz),

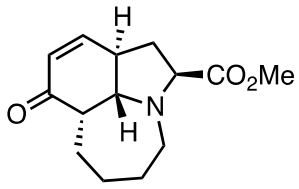
7.36-7.29 (m, 3 H), 5.65 (ddd, 1 H, *J* = 10.1, 10.1, 1.1 Hz), 5.52 (m, 1 H), 3.98 (dd, 1 H, *J* = 8.9, 5.4 Hz), 3.68 (s, 3 H), 3.51 (m, 1 H), 3.47 (dd, 1 H, *J* = 10.1, 7.6 Hz), 3.34-3.24 (m, 2 H), 2.80 (dd, 1 H, *J* = 11.7, 7.6 Hz), 2.75 (dd, 1 H, *J* = 16.5, 5.9 Hz), 2.64 (dt, 1 H, *J* = 13.2, 8.3 Hz), 2.53-2.44 (m, 1 H), 2.33 (dd, 1 H, *J* = 16.4, 9.5 Hz), 2.05-1.94 (m, 2 H), 1.74 (ddd, 1 H, *J* = 13.1, 10.3, 5.3 Hz); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 200.1, 164.5, 123.4, 122.6, 119.5, 119.1, 117.9, 117.8, 54.8, 53.4, 43.6, 41.4, 38.2, 36.9, 35.4, 33.6, 23.0, 15.7; HRMS (ESI$^+$) *m/z* calcd for $C_{20}H_{24}NO_3S$ $[M+H]^+$ 358.1471, found 358.1459.



3-94a

(2*S*,3^1*R*,7a*S*,10*R*,10a*S*)-Methyl 8-oxo-10-(phenylthio)dodecahydroazepino[3,2,1-*hi*]indole-2-carboxylate (3-94a).[169] To a solution of thioether **3-93a** (0.0553 g, 0.155 mmol) in CH_2Cl_2:EtOH (1:4; 4.3 mL) was added Wilkinson's catalyst (0.0317 g, 0.0343 mmol). The suspension was stirred under an atmosphere of H_2 (Balloon) at rt for 14 h and concentrated under reduced pressure to give red oil. The crude oil was purified by chromatography on SiO_2 (0:1; 5:95; 1:9: 15:85; 1:4; EtOAc:hexanes) to give **3-94a** (34.2 mg, 62%) as a light red-orange solid: Mp 135.3-136.4 °C (dec., $CHCl_3$); IR (ATR) 2917, 2902, 2820, 2848, 1726, 1689, 1431, 1202, 1167, 749, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (d, 2 H, *J* = 7.4 Hz), 7.28 (d, 2 H, *J* = 7.2 Hz), 7.22 (app. t, 1 H, *J* = 7.3 Hz), 4.03 (dd, 1 H, *J* = 8.1, 6.5 Hz), 3.79 (dd, 1 H, *J* = 10.9, 7.4 Hz), 3.72 (s, 3 H), 3.74-3.68 (m, 1 H), 2.85 (dt, 1 H, *J* = 14.7, 3.2 Hz), 2.81-2.76 (m, 1 H), 2.66 (dd, 1 H, *J* = 11.3, 7.8 Hz), 2.63-2.57 (m, 2 H), 2.42 (ddt, 1 H, *J* = 11.0, 7.8, 3.8 Hz), 2.33 (dt, 1 H, *J* = 12.5, 8.0 Hz), 2.15 (ddd, 1 H, *J* = 12.3, 10.8, 6.3 Hz), 1.96-1.89 (m, 1 H), 1.79-1.70 (m, 1

H), 1.67-1.57 (m, 2 H), 1.46-1.37 (m, 1 H), 1.32-1.22 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 211.7, 175.4, 134.7, 132.2, 129.2, 127.4, 63.7, 61.2, 56.4, 51.7, 47.5, 45.8, 45.0, 42.6, 30.9, 30.41, 3.38, 27.0, ; HRMS (ESI$^+$) *m/z* calcd for $C_{20}H_{26}NO_3S$ $[M+H]^+$ 360.1628, found 360.1612.



3-95

(2*S*,3^1*S*,7a*S*,10a*R*)-Methyl 8-oxo-1,2,3^1,4,5,6,7,7a,8,10a-decahydroazepino[3,2,1-*hi*]indole-2-carboxylate (3-95).[169] To a solution of ketone **3-94a** (0.0219 g, 0.0610 mmol) in CH_2Cl_2 (1.85 mL) was added DBU (10.0 μL, 0.0669 mmol). The solution placed under an Ar atmosphere, stirred at rt for 2 h, concentrated under reduced pressure, and purified by chromatography on SiO_2 (1:9 to 2:3; EtOAc:hexanes) to give enone **3-95 (**9.5 mg, 63%) as a light yellow oil: ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 6.96 (d, 1 H, *J* = 9.7 Hz), 5.91 (dd, 1 H, *J* = 9.7, 2.2 Hz), 3.89 (app. t, 1 H, *J* = 7.9 Hz), 3.68 (s, 3 H), 3.50 (dd, 1 H, *J* = 10.0, 6.1 Hz), 2.94-2.78 (m, 2 H), 2.72-2.63 (m, 2 H), 2.52 (dt, 1 H, *J* = 11.8, 7.2 Hz), 1.97-1.91 (m, 1 H), 1.79-1.66 (m, 3 H), 1.64-1.56 (m, 1 H), 1.52-1.40 (m, 1 H), 1.39-1.27 (m, 1 H).

BIBLIOGRAPHY

1. Wäspi, U.; Misteli, B.; Hasslacher, M.; Jandrositz, A.; Kohlwein, S. D.; Schwab, H.; Dudler, R. *Eur. J. Biochem.* **1998**, *254*, 32.

2. Wäspi, U.; Blanc, C.; Winkler, T.; Rüedi, P.; Dudler, R. *Mol. Plant-Microbe Interact.* **1998**, *11*, 727.

3. Wäspi, U.; Hassa, P.; Staempfli, A. A.; Molleyres, L.-P.; Winkler, T.; Dudler, R. *Microbiol. Res.* **1999**, *154*, 89.

4. Bian, X.; Huang, F.; Stewart, F. A.; Xia, L.; Zhang, Y.; Müller, R. *ChemBioChem* **2012**, *13*, 1946.

5. Groll, M.; Schellenberg, B.; Bachmann, A.; Archer, C.; Huber, R.; Powell, T.; Lindow, S.; Kaiser, M.; Dudler, R. *Nature* **2008**, *452*, 755.

6. (a) Oka, M.; Nishiyama, Y.; Ohta, S.; Kamei, H.; Konishi, M.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1988**, *41*, 1331. (b) Oka, M.; Ohkuma, H.; Kamei, H.; Konishi, M.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1988**, *41*, 1906. (c) Oka, M.; Yaginuma, K.; Numata, K.; Konishi, M.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1988**, *41*, 1338.

7. (a) Shoji, J.-i.; Hinoo, H.; Kato, T.; Hattori, T.; Hirooka, K.; Tawara, K.; Shiratori, O.; Terui, Y. *J. Antibiot.* **1990**, *43*, 783. (b) Terui, Y.; Nishikawa, J.; Hinoo, H.; Kato, T.; Shoji, J.-i. *J. Antibiot.* **1990**, *43*, 788.

8. (a) Fu, J.; Bian, X.; Hu, S.; Wang, H.; Huang, F.; Seibert, P. M.; Plaza, A.; Xia, L.; Stewart, A. F.; ller, R. M. u.; Zhang, Y. *Nat. Biotechnol.* **2012**, *30*, 440. (b) Bian, X.; Plaza, A.; Zhang, Y.; Müller, R. *J. Nat. Prod.* **2012**, *75*, 1652.

9. Hassa, P.; Granado, J.; Freydl, E.; Wäspi, U.; Dudler, R. *Mol. Plant-Microbe Interact.* **2000**, *13*, 342.

10. Wäspi, U.; Schweizer, P.; Dudler, R. *Plant Cell* **2001**, *13*, 153.

11. (a) Michel, K.; Abderhalden, O.; Bruggmann, R.; Dudler, R. *Plant Mol. Biol.* **2006**, *62*, 561. (b) Schellenberg, B.; Ramel, C.; Dudler, R., Syringolin A: Action on Plants, Regulation of Biosynthesis, and Phylogenetic Occurrence of Structurally Related Compounds. In *Pseudomonas Syringae Pathovars and Related Pathogens* -

Identification, Epidemiology and Genomics, Fatmi, M.; Collmer, A.; Iacobellis, N. S.; Mansfield, J. W.; Murrillo, J.; Schaad, N. W.; Ullrich, M., Eds. Springer: Dordrecht, NL, 2008; pp 249.

12. Coleman, C. S.; Rocetes, J. P.; Park, D. J.; Wallick, C. J.; Warn-Cramer, B. J.; Michel, K.; Dudler, R.; Bachmann, A. S. *Cell Proliferat.* **2006**, *39*, 599.

13. (a) Adams, J. *Curr. Opin. Oncol.* **2002**, *14*, 628. (b) Hershko, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5932. (c) Voorhees, P. M.; Orlowski, R. Z. *Annu. Rev. Pharmacol. Toxicol.* **2006**, *46*, 189. (d) Naujokat, C.; Fuchs, D.; Berges, C. *Biochim. Biophys. Acta* **2007**, *1773*, 1389. (e) Borissenko, L.; Groll, M. *Chem. Rev.* **2007**, *107*, 687. (f) Moore, B. S.; Eustáquio, A. S.; McGlinchey, R. P. *Curr. Opin. Chem. Biol.* **2008**, *12*, 434. (g) Sterz, J.; von Metzler, I.; Hahne, J.-C.; Lamottke, B.; Rademacher, J.; Heider, U.; Terpos, E.; Sezer, O. *Expert Opin. Invest. Drugs* **2008**, *17*, 879. (h) Kisselev, A. *Chem. Biol.* **2008**, *15*, 419. (i) Tsukamoto, S.; Yokosawa, H. *Expert Opin. Ther. Targets* **2009**, *13*, 605.

14. Amrein, H.; Makart, S.; Granado, J.; Shakya, R.; Schneider-Pokorny, J.; Dudler, R. *Mol. Plant-Microbe Interact.* **2004**, *17*, 90.

15. (a) Marahiel, M. A.; Stachelhaus, T.; Mootz, H. D. *Chem. Rev.* **1997**, *97*, 2651 . (b) von Dohren, H.; Dieckmann, R.; Pavela-Vrancic, M. *Chem. Biol.* **1999**, *6*, R273 . (c) Finking, R.; Marahiel, M. A. *Annu. Rev. Microbiol.* **2004**, *58*, 453

16. Ramel, C.; Tobler, M.; Meyer, M.; Bigler, L.; Ebert, M.-O.; Schellenberg, B.; Dudler, R. *BMC Biochem.* **2009**, *10*, 26.

17. Imker, H.; Walsh, C.; Wuest, W. *J. Am. Chem. Soc.* **2009**, *131*, 18263.

18. (a) Hopwood, D. A. *Chem. Rev.* **1997**, *97*, 2465 . (b) Fischbach, M. A.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3468

19. Wuest, W. M.; Krahn, D.; Kaiser, M.; Walsh, C. T. *Org. Lett.* **2011**, *13*, 4518.

20. Meng, Q.; Hesse, M. *Tetrahedron* **1991**, *47*, 6251.

21. Meng, Q. Synthetic Studies Toward Glidobamine and Novel Diterpenoids from *Pygmaeopremna herbacea*. Ph.D., University of Zurich, Zurich, 1991.

22. Lipshutz, B. H.; Huff, B. E.; McCarthy, K. E.; Miller, T. A.; Mukarram, S. M. J.; Siahaan, T. J.; Vaccaro, W. D.; Webb, H.; Falick, A. M. *J. Am. Chem. Soc.* **1990**, *112*, 7032.

23. Meng, Q.; Hesse, M. *Synlett* **1990**, 148.

24. Schmidt, U.; Kleefeldt, A.; Mangold, R. *J. Chem. Soc., Chem. Commun.* **1992**, 1687.

25. Machajewski, T. D. Palladium Catalyzed Cyclization Strategies Toward Natural Products. Standford University, Stanford, 1997.

26. Clerc, J.; Groll, M.; Illich, D. J.; Bachmann, A. S.; Huber, R.; Schellenberg, B.; Dudler, R.; Kaiser, M. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 6507.

27. (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (b) Reetz, M. T.; Griebenow, N.; Goddard, R. *J. Chem. Soc., Chem. Commun.* **1995**, 1605.

28. Pirrung, M. C.; Biswas, G.; Ibarra-Rivera, T. R. *Org. Lett.* **2010**, *12*, 2402.

29. Dai, C.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 3453.

30. Schauer, D.; Helquist, P. *Synthesis* **2006**, *2006*, 3654.

31. Clerc, J.; Schellenberg, B.; Groll, M.; Bachmann, A. S.; Huber, R.; Dudler, R.; Kaiser, M. *Eur. J. Org. Chem.* **2010**, *2010*, 3991.

32. Clerc, J.; Li, N.; Krahn, D.; Groll, M.; Bachmann, A. S.; Florea, B. I.; Overkleeft, H. S.; Kaiser, M. *Chem. Commun.* **2010**, *47*, 385.

33. Archer, C. R.; Groll, M.; Stein, M. L.; Schellenberg, B.; Clerc, J.; Kaiser, M.; Kondratyuk, T. P.; Pezzuto, J. M.; Dudler, R.; Bachmann, A. S. *Biochemistry* **2012**, *51*, 6880.

34. Krahn, D.; Ottmann, C.; Kaiser, M. *Nat. Prod. Rep.* **2011**, *28*, 1854.

35. (a) Wipf, P.; Kendall, C.; Stephenson, C. R. *J. Am. Chem. Soc.* **2001**, *123*, 5122. (b) Wipf, P.; Nunes, R. L.; Ribe, S. *Helv. Chim. Acta* **2002**, *85*, 3478. (c) Wipf, P.; Kendall, C.; Stephenson, C. R. *J. Am. Chem. Soc.* **2003**, *125*, 761. (d) Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2003**, *5*, 2449. (e) Wipf, P.; Pierce, J. G. *Org. Lett.* **2006**, *8*, 3375.

36. (a) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333. (b) Labinger, J. A., Hydrozirconation of the Alkenes and Alkynes and Hydrometallation by Other Metals. In *Comprehensive Organic Synthesis*, Trost, B. M.; Flemming, I., Eds. Pergamon Press: Oxford, 1991; Vol. 8, pp 667. (c) Endo, J.; Koga, N.; Morokuma, K. *Organometallics* **1993**, *12*, 2777. (d) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853. (e) Wipf, P.; Nunes, R. L. *Tetrahedron* **2004**, *60*, 1269. (f) Wipf, P.; Kendall, C. *Top. Organomet. Chem.* **2004**, *8*, 1.

37. (a) Negishi, E.; Miller, J. A.; Yoshida, T. *Tetrahedron Lett.* **1984**, *25*, 3407. (b) Lipshutz, B. H.; Keil, R.; Ellsworth, E. L. *Tetrahedron Lett.* **1990**, *31*, 7257. (c) Swanson, D. R.; Thinh, N.; Noda, Y.; Negishi, E. *J. Org. Chem.* **1991**, *56*, 2590.

38. (a) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895. (b) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Org. Synth.* **1993**, *71*, 77.

39. (a) Annby, U.; Karlsson, S.; Gronowitz, S.; Hallberg, A.; Alvhäll, J.; Svenson, R. *Acta Chem. Scand.* **1993**, *47*, 425. (b) Chirik, P. J.; Day, M. W.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **1999**, *121*, 10308.

40. Wailes, P. C.; Weigold, H. *J. Organomet. Chem.* **1970**, *24*, 405.

41. Wailes, P. C.; Weigold, H.; Bell, A. P. *J. Organomet. Chem.* **1972**, *43*, C32.

42. Wailes, P. C.; Weigold, H.; Bell, A. P. *J. Organomet. Chem.* **1971**, *27*, 373.

43. Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115.

44. Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679.

45. (a) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 638. (b) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1979**, *101*, 3521.

46. (a) Chino, M.; Matsumoto, T.; Suzuki, K. *Synlett* **1994**, *1994*, 359. (b) Suzuki, K.; Hasegawa, T.; Imai, T.; Maeta, H.; Ohba, S. *Tetrahedron* **1995**, *51*, 4483. (c) Yamanoi, S.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1999**, *40*, 2793. (d) Wipf, P.; Pierce, J. G. *Org. Lett.* **2005**, *7*, 3537.

47. (a) Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K. *Tetrahedron Lett.* **1992**, *33*, 5965. (b) Richter, F.; Bauer, M.; Perez, C.; Maichle-Mossmer, C.; Maier, M. E. *J. Org. Chem.* **2002**, *67*, 2474.

48. (a) Wipf, P.; Xu, W. *J. Org. Chem.* **1993**, *58*, 825. (b) Wipf, P.; Xu, W. *J. Org. Chem.* **1993**, *58*, 5880. (c) Wipf, P.; Methot, J.-L. *Org. Lett.* **1999**, *1*, 1253.

49. Lipshutz, B. H.; Pfeiffer, S. S.; Noson, K.; Tomioka, T., Hydrozirconation and Further Transmetalation Reactions. In *Titanium and Zirconium in Organic Synthesis*, Marek, I., Ed. Wiley-VCH: Weinheim, 2002; pp 110.

50. (a) Okukado, N.; Van Horn, D. E.; Klima, W. L.; Negishi, E.-i. *Tetrahedron Lett.* **1978**, *19*, 1027. (b) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393. (c) Barrett, A. G. M.; Pena, M.; Willardsen, J. A. *J. Org. Chem.* **1996**, *61*, 1082.

51. Negishi, E.; Van Horn, D. E. *J. Am. Chem. Soc.* **1977**, *99*, 3168.

52. (a) Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Tetrahedron* **2004**, *60*, 1293. (b) Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **2003**, *44*, 923.

53. (a) Yoshifuji, M.; Loots, M. J.; Schwartz, J. *Tetrahedron Lett.* **1977**, *18*, 1303. (b) Wipf, P.; Smitrovich, J. H. *J. Org. Chem.* **1991**, *56*, 6494. (c) Wipf, P.; Smitrovich, J. H.; Moon, C.-W. *J. Org. Chem.* **1992**, *57*, 3178. (d) Wipf, P.; Xu, W.; Smitrovich, J. H.; Lehmann, R.; Venanzi, L. M. *Tetrahedron* **1994**, *50*, 1935.

54. (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Wipf, P.; Xu, W. *Org. Synth.* **1997**, *74*, 205.

55. (a) Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *100*, 2252. (b) Yoshida, T.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 4985.

56. Wiskur, S. L.; Korte, A.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *126*, 82.

57. Oi, S.; Sato, T.; Inoue, Y. *Tetrahedron Lett.* **2004**, *45*, 5051.

58. (a) Wipf, P. *Synthesis* **1993**, 537. (b) Rosenker, C. J.; Wipf, P., Transmetalation Reactions Producing Organocopper Compounds. In *Patai's Chemistry of Functional Groups: The Chemistry of Organocopper Compounds*, Rappoport, Z.; Marek, I., Eds. John Wiley & Sons: Chichester, 2009; pp 443.

59. Wipf, P.; Xu, W. J. *Synlett* **1992**, 718.

60. Wipf, P.; Xu, W. J.; Smitrovich, J.; Lehmann, R.; Venanzi, L. M. *Tetrahedron* **1994**, *50*, 1935.

61. Lipshutz, B. H.; Kato, K. *Tetrahedron Lett.* **1991**, *32*, 5657.

62. Lipshutz, B. H.; Wood, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 11689.

63. Saito, A.; Iimura, K.; Hayashi, M.; Hanzawa, Y. *Tetrahedron Lett.* **2009**, *50*, 587.

64. (a) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454. (b) Wipf, P.; Jayasuriya, N.; Ribe, S. *Chirality* **2003**, *15*, 208. (c) Wipf, P.; Jayasuriya, N. *Chirality* **2008**, *20*, 425.

65. (a) Trauner, D.; Schwarz, J.; Danishefsky, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542. (b) Wipf, P.; Reeves, J. T. *Chem. Commun.* **2002**, 2066. (c) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 7889. (d) Su, Q.; Dakin, L. A.; Panek, J. S. *J. Org. Chem.* **2006**, *72*, 2. (e) Moslin, R. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 15106. (f) Moslin, R. M.; Jamison, T. F. *J. Org. Chem.* **2007**, *72*, 9736. (g) Evans, P. A.; William, J. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 5426.

66. (a) Côté, A.; Boezio, A. A.; Charette, A. B. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5405. (b) Weinreb, S.; Orr, R. *Synthesis* **2005**, 1205.

67. Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2005**, *7*, 1137.

68. (a) Whitesell, J. K.; Bhattacharya, A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 988. (b) Basavaiah, D.; Bharathi, T. K. *Tetrahedron Lett.* **1991**, *32*, 3417. (c) Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953.

69. (a) Wipf, P.; Xiao, J.; Jiang, J.; Belikova, N. A.; Tyurin, V. A.; Fink, M. P.; Kagan, V. E. *J. Am. Chem. Soc.* **2005**, *127*, 12460. (b) Hoye, A. T.; Davoren, J. E.; Wipf, P.; Fink, M. P.; Kagan, V. E. *Acc. Chem. Res.* **2008**, *41*, 87.

70. Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068.

71. (a) Shaw, A. W.; deSolms, S. J. *Tetrahedron Lett.* **2001**, *42*, 7173. (b) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303. (c) Fujisawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881.

72. (a) Fujisawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881. (b) Cogan, D.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883. (c) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303.

73. Pierce, J. G. Applications of Allyl and Alkenyl Zirconocenes and Progress Toward the Total Synthesis of Tuberostemonone. University of Pittsburgh, Pittsburgh, 2008.

74. (a) Kagan, V. E.; Wipf, P.; Stoyanovsky, D.; Greenberger, J. S.; Borisenko, G.; Belikova, N. A.; Yanamala, N.; Arias, A. K. S.; Tungekar, M. A.; Jiang, J.; Tyurina, Y. Y.; Ji, J.; Klein-Seetharaman, J.; Pitt, B. R.; Shvedova, A. A.; Bayır, H. *Adv. Drug Delivery Rev.* **2009**, *61*, 1375. (b) Frantz, M.-C. l.; Pierce, J. G.; Pierce, J. M.; Kangying, L.; Qingwei, W.; Johnson, M.; Wipf, P. *Org. Lett.* **2011**, *13*, 2318. (c) Skoda, E. M.; Davis, G. C.; Wipf, P. *Org. Process Res. Dev.* **2012**, *16*, 26.

75. Ort, O. *Org. Synth.* **1987**, *65*, 203.

76. Whitesell, J. K.; Bhattacharya, A.; Buchanan, C. M.; Chen, H. H.; Deyo, D.; James, D.; Liu, C.; Minton, M. A. *Tetrahedron* **1986**, *42*, 2993.

77. Kruglyak, Y. L.; Leibovskaya, G. A.; Sretenskaya, I. I.; Sheluchenko, V. V.; Martynov, I. V. *J. Gen. Chem. USSR (Engl. Transl.)* **1968**, *38*, 908.

78. (a) Brown, C.; Hudson, R. F.; Maron, A.; Record, K. *J. Chem. Soc., Chem. Commun.* **1976**, 663. (b) Robert, F. H.; Charles, B.; Maron, A. *Chem. Ber.* **1982**, *115*, 2560.

79. Kudyba, I.; Jozwik, J.; Romanski, J.; Raczko, J.; Jurczak, J. *Tetrahedron: Asymmetry* **2005**, *16*, 2257.

80. Lautens, M.; Tayama, E.; Herse, C. *J. Am. Chem. Soc.* **2005**, *127*, 72.

81. Petrini, M. *Chem. Rev.* **2005**, *105*, 3949.

82. Nagano, T.; Kinoshita, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1605.

83. Pierce, J.; Waller, D.; Wipf, P. *J. Organomet. Chem.* **2007**, *692*, 4618.

84. (a) Sasaki, S.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1997**, *38*, 3013. (b) Borg, G.; Chino, M.; Ellman, J. A. *Tetrahedron Lett.* **2001**, *42*, 1433.

85. Owens, T. D.; Souers, A. J.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 3.

86. (a) Tang, T. P.; Volkman, S.; Ellman, J. A. *J. Org. Chem.* **2001**, *66*, 8772. (b) Rech, J. C.; Yato, M.; Duckett, D.; Ember, B.; LoGrasso, P. V.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 490.

87. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

88. (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888. (b) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825. (c) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175. (d) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

89. Maleckis, A.; Jaunzeme, I.; Jirgensons, A. *Eur. J. Org. Chem.* **2009**, *2009*, 6407.

90. (a) Craig, D.; Hyland, C. J. T.; Ward, S. E. *Chem. Commun.* **2005**, 3439. (b) Sellanes, D.; Scarone, L.; Mahler, G.; Manta, E.; Baz, A.; Dematteis, S.; Saldaña, J.; Domínguez, L.; Wipf, P.; Serra, G. *Lett. Drug Des. Discovery* **2006**, *3*, 34.

91. Oh, J. S.; Kim, B. H.; Kim, Y. G. *Tetrahedron Lett.* **2004**, *45*, 3925.

92. Liu, G. C.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.

93. Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.

94. Larrosa, I.; Da Silva, M. I.; Gómez, P. M.; Hannen, P.; Ko, E.; Lenger, S. R.; Linke, S. R.; White, A. J. P.; Wilton, D.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2006**, *128*, 14042.

95. Gagnon, D.; Lauzon, S.; Godbout, C.; Spino, C. *Org. Lett.* **2005**, *7*, 4769.

96. Overman, L. *Acc. Chem. Res.* **1980**, *13*, 218.

97. (a) Bunnage, M.; Nicolaou. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1110. (b) Bunnage, M.; Nicolaou. *Chem.: Eur. J.* **1997**, *3*, 187. (c) Wipf, P.; Jung, J. *J. Org. Chem.* **2000**, *65*, 6319.

98. (a) Wipf, P.; Reeves, J.; Balachandran, R.; Day, B. W. *J. Med. Chem.* **2002**, *45*, 1901. (b) Wipf, P.; Coleman, C. M.; Janjic, J. M.; Iyer, P. S.; Fodor, M. D.; Shafer, Y. A.; Stephenson, C. R.; Kendall, C.; Day, B. W. *J. Comb. Chem.* **2005**, *7*, 322. (c) Wipf, P.; Xiao, J.; Geib, S. *Adv. Synth. Catal.* **2005**, *347*, 1605. (d) Wipf, P.; Xiao, J. *Org. Lett.* **2005**, *7*, 103.

99. Wipf, P.; Janjic, J.; Stephenson, C. R. *Org. Biomol. Chem.* **2004**, *2*, 443.

100. (a) Petersen, H. *Synthesis* **1973**, *1973*, 243. (b) Lawson, A.; Tinkler, R. B. *Chem. Rev.* **1970**, *70*, 593. (c) McDermott, S. D.; Spillane, W. J. *Org. Prep. Proced. Int.* **1984**, *16*, 49. (d) Arán, V. J.; Goya, P.; Ochoa, C. *Adv. Heterocycl. Chem.* **1988**, *44*, 81. (e) Gazieva, G. A.; Kravchenko, A. N.; Lebedev, O. V. *Russ. Chem. Rev.* **2000**, *69*, 221.

101. (a) Kim, S. J.; Jung, M.-H.; Yoo, K. H.; Cho, J.-H.; Oh, C.-H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5815. (b) Kim, S. J.; Cho, J.-H.; Oh, C.-H. *Arch. Pharm. Chem. Life Sci.* **2009**, *342*, 528.

102. Wilson, K. J.; Illig, C. R.; Chen, J.; Wall, M. J.; Ballentine, S. K.; DesJarlais, R. L.; Chen, Y.; Schubert, C.; Donatelli, R.; Petrounia, I.; Crysler, C. S.; Molloy, C. J.; Chaikin, M. A.; Manthey, C. L.; Player, M. R.; Tomczuk, B. E.; Meegalla, S. K. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3925.

103. Palin, R.; Clark, J. K.; Evans, L.; Feilden, H.; Fletcher, D.; Hamilton, N. M.; Houghton, A. K.; Jones, P. S.; McArthur, D.; Montgomery, B.; Ratcliffe, P. D.; Smith, A. R. C.; Sutherland, A.; Weston, M. A.; Wishart, G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6441.

104. Kim, S. H.; Bok, J. H.; Lee, J. H.; Kim, I. H.; Kwon, S. W.; Lee, G. B.; Kang, S. K.; Park, J. S.; Jung, W. H.; Kim, H. Y.; Rhee, S. D.; Ahn, S. H.; Bae, M. A.; Ha, D. C.; Kim, K. Y.; Ahn, J. H. *ACS Med. Chem. Lett.* **2012**, *3*, 88.

105. Cano, C.; Goya, P.; Paez, J. A.; Girón, R.; Sánchez, E.; Martín, M. I. *Bioorg. Med. Chem.* **2007**, *15*, 7480.

106. Bhatt, N.; Vyas, K.; Joshi, K.; Nimavat, K. *Asian J. Biochem. Pharm. Res.* **2011**, *1*, 464.

107. Castro, A.; Martínez, A.; Cardelús, I.; Llenas, J. *Bioorg. Med. Chem.* **1995**, *3*, 179.

108. Houlihan, W. J. Dioxybenzothiadiazines. US 3 278 532, October 11, 1966.

109. (a) Ax, A.; Schaal, W.; Vrang, L.; Samuelsson, B.; Hallberg, A.; Karlén, A. *Bioorg. Med. Chem.* **2005**, *13*, 755. (b) Sevilla, S.; Forns, P.; Fernàndez, J.-C.; de la Figuera, N.; Eastwood, P.; Albericio, F. *Tetrahedron Lett.* **2006**, *47*, 8603. (c) Reitz, A. B.; Smith, G. R.; Parker, M. H. *Expert Opin. Ther. Pat.* **2009**, *19*, 1449. (d) Ghosh, A. K.; Anderson, D. D. *Future Med. Chem.* **2011**, *3*, 1181.

110. Degering, E. F.; Wilson, J. E. *J. Org. Chem.* **1952**, *17*, 339.

111. Wright, J. *J. Org. Chem.* **1964**, *29*, 1905.

112. Ouchi, A.; Moeller, T. *J. Org. Chem.* **1964**, *29*, 1865.

113. Goya, P.; Stud, M. *J. Heterocycl. Chem.* **1978**, *15*, 253.

114. Hansen, H.; König, K.-H.; Rohr, W. *Liebigs Ann. Chem.* **1979**, *1979*, 950.

115. Lee, C.-H.; Kohn, H. *J. Heterocycl. Chem.* **1990**, *27*, 2107.

116. Lee, C.-H.; Lee, Y. H.; Choi, W. S.; Chung, B. Y. *Bull. Korean Chem. Soc.* **1992**, *13*, 462.

117. Lee, C.-H.; Jin, G. F.; Lim, H. W.; Yang, E. H.; Lee, J.-D.; Nakamura, H.; Ban, H. S.; Kang, S. O. *Heteroat. Chem.* **2011**, *22*, 192.

118. Li, C.; Zhang, Q.; Tong, X. *Chem. Commun.* **2010**, *46*, 7828.

119. Goya, P.; Martinez, P.; Ochoa, C.; Stud, M. *J. Heterocycl. Chem.* **1981**, *18*, 459.

120. Johnstone, L.; Wipf, P. *Unpublished Work*.

121. Johnstone, L.; Zhang, L.; Miller, B.; Wipf, P. *Unpublished Work*.

122. (a) Dusemund, J. *Arch. Pharm.* **1974**, *307*, 883. (b) Lee, C.-H.; Kohn, H. *Heterocycles* **1988**, *27*, 2581. (c) Lee, C.; Kohn, H. *J. Org. Chem.* **1990**, *55*, 6098.

123. Zhang, L.; Miller, B.; Wipf, P. *Unpublished Work*.

124. Cava, M. P.; Lakshmikantham, M. V.; Mitchell, M. J. *J. Org. Chem.* **1969**, *34*, 2665.

125. Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.

126. (a) National Center for Biotechnology Information. PubChem BioAssay Database: AID=624296, Source=NCGC, http://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi?aid=624296 (accessed Nov. 13, 2012). (b) National Center for Biotechnology Information. PubChem Compound Database; CID=4267994, http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=42627994 (accessed Nov. 13, 2012).

127. (a) National Center for Biotechnology Information. PubChem BioAssay Database: AID=624417, Source=NCGC, http://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi?aid=624417 (accessed Nov. 13, 2012). (b) National Center for Biotechnology Information. PubChem Compound Database; CID=42627982, http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=42627982 (accessed Nov. 13, 2012). (c) National Center for Biotechnology Information. PubChem Compound Database; CID=42627995, http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=42627995 (accessed Nov. 13, 2012). (d) National Center for Biotechnology Information. PubChem Compound Database; CID=42628013, http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=42628013 (accessed Nov. 13, 2012).

128. Shioiri, T.; Ninomiya, K.; Yamada, S.-i. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

129. Curtius, T. *Chem. Ber.* **1890**, *23*, 3023.

130. Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

131. Nahm, S.; Weinreb, S. *Tetrahedron Lett.* **1981**, *22*, 3815.

132. Horn, M.; Mayr, H.; Lacôte, E.; Merling, E.; Deaner, J.; Wells, S.; McFadden, T.; Curran, D. P. *Org. Lett.* **2012**, *14*, 82.

133. Chakrabarty, M.; Sarkar, S.; Khasnobis, S.; Harigaya, Y.; Sato, N.; Arima, S. *Synth. Commun.* **2002**, *32*, 2295.

134. Snyder, S. A.; Vosburg, D. A.; Jarvis, M. G.; Markgraf, J. H. *Tetrahedron* **2000**, *56*, 5329.

135. Instant JChem was used for structure prediction, Instant JChem 5.9.4, ChemAxon (http://www.chemaxon.com), 2012.

136. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **1997**, *23*, 3.

137. Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. *J. Med. Chem.* **2002**, *45*, 2615.

138. (a) Potashman, M. H.; Duggan, M. E. *J. Med. Chem.* **2009**, *52*, 1231. (b) Singh, J.; Petter, R. C.; Baillie, T. A.; Whitty, A. *Nat. Rev. Drug Discovery* **2011**, *10*, 307.

139. Drahl, C.; Cravatt, B. F.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5788.

140. Van Der Ouderaa, F. J.; Buytenhek, M.; Nugteren, D. H.; Van Dorp, D. A. *Eur. J. Biochem.* **1980**, *109*, 1.

141. Silverman, R. B. *J. Am. Chem. Soc.* **1981**, *103*, 3910.

142. Groll, M.; Berkers, C. R.; Ploegh, H. L.; Ovaa, H. *Structure* **2006**, *14*, 451.

143. Shin, J. M.; Cho, Y. M.; Sachs, G. *J. Am. Chem. Soc.* **2004**, *126*, 7800.

144. Lin, C.; Lin, K.; Luong, Y. P.; Rao, G.; Wei, Y. Y.; Brennan, D. L.; Fulghum, J. R.; Hsiao, H. M.; Ma, S.; Maxwell, J. P.; Cottrell, K. M.; Perni, R. B.; Gates, C. A.; Kwong, A. D. *J. Biol. Chem.* **2004**, *279*, 17508.

145. Santi, D. V.; McHenry, C. S.; Sommer, H. *Biochemistry* **1974**, *13*, 471.

146. Herbert, G.; Garcia-Calvo, M.; Andersson, S.; Baginsky, W. F.; Chan, H. K.; Ellsworth, D. E.; Miller, R. R.; Stearns, R. A.; Bakshi, R. K.; Rasmusson, G. H. *J. Am. Chem. Soc.* **1996**, *118*, 2359.

147. (a) Wipf, P.; Minion, D. J.; Halter, R. J.; Berggren, M. I.; Ho, C. B.; Chiang, G. G.; Kirkpatrick, L.; Abraham, R.; Powis, G. *Org. Biomol. Chem.* **2004**, *2*, 1911. (b) Ihle, N. T.; Williams, R.; Chow, S.; Chew, W.; Berggren, M. I.; Paine-Murrieta, G.; Minion, D. J.; Halter, R. J.; Wipf, P.; Abraham, R.; Kirkpatrick, L.; Powis, G. *Mol. Cancer Ther.* **2004**, *3*, 763.

148. (a) Singh, J.; Dobrusin, E. M.; Fry, D. W.; Haske, T.; Whitty, A.; McNamara, D. J. *J. Med. Chem.* **1997**, *40*, 1130. (b) Gersch, M.; Kreuzer, J.; Sieber, S. A. *Nat. Prod. Rep.* **2012**, *29*, 659.

149. Kudo, S.; Marumo, T.; Tomioka, T.; Kato, H.; Fujimoto, Y. *Antibiot. Chemother.* **1958**, *8*, 228.

150. (a) Doll, D. C.; Weiss, R. B.; Issell, B. F. *J. Clin. Oncol.* **1985**, *3*, 276. (b) Bradner, W. T. *Cancer Treat. Rev.* **2001**, *27*, 35.

151. Andrez, J.-C. *Beilstein J. Org. Chem.* **2009**, *5*.

152. (a) Cera, C.; Egbertson, M.; Teng, S. P.; Crothers, D. M.; Danishefsky, S. J. *Biochemistry* **1989**, *28*, 5665. (b) Penketh, P. G. *J. Biol. Chem.* **2001**, *276*, 34445.

153. Tomasz, M.; Lipman, R.; Chowdary, D.; Pawlak, J.; Verdine, G. L.; Nakanishi, K. *Science* **1987**, *235*, 1204.

154. (a) Nicolaou, K. C.; Smith, A. L.; Yue, E. W. *Proc. Natl. Acad. Sci. U. S. A.* **1993**, *90*, 5881. (b) Murphy, J. A.; Griffiths, J. *Nat. Prod. Rep.* **1993**, *10*, 551. (c) Smith, A. L.; Nicolaou, K. C. *J. Med. Chem.* **1996**, *39*, 2103. (d) Shao, R. G. *Curr. Mol. Pharmacol.* **2008**, *1*, 50.

155. (a) Wolkenberg, S. E.; Boger, D. L. *Chem. Rev.* **2002**, *102*, 2477. (b) LePla, R. C.; Landreau, C. A. S.; Shipman, M.; Jones, G. D. D. *Org. Biomol. Chem.* **2005**, *3*, 1174.

156. (a) Murakami, A.; Takahashi, M.; Jiwajinda, S.; Koshimizu, K.; Ohigashi, H. *Biosci., Biotechnol., Biochem.* **1999**, *63*, 1811. (b) Takada, Y.; Murakami, A.; Aggarwal, B. B. *Oncogene* **2005**, *24*, 6957. (c) Holland, R.; Fishbein, J. C. *Antioxid. Redox Signaling* **2010**, *13*, 1749. (d) Shin, J. W.; Ohnishi, K.; Murakami, A.; Lee, J. S.; Kundu, J. K.; Na, H. K.; Ohigashi, H.; Surh, Y. J. *Cancer Prev. Res.* **2011**, *4*, 860.

157. (a) Kwok, B. H.; Koh, B.; Ndubuisi, M. K. I.; Elofsson, M.; Crews, C. M. *Chem. Biol.* **2001**, *8*, 759. (b) Kunzmann, M. H.; Staub, I.; Böttcher, T.; Sieber, S. A. *Biochemistry* **2011**, *50*, 910.

158. Kudo, N.; Matsumori, N.; Taoka, H.; Fujiwara, D.; Schreiner, E. P.; Wolff, B.; Yoshida, M.; Horinouchi, S. *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 9112.

159. Wipf, P.; Halter, R. J. *Org. Biomol. Chem.* **2005**, *3*, 2053.

160. Wulff, J. E.; Siegrist, R.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 14444.

161. (a) van Axel Castelli, V.; Bernardi, F.; Dalla Cort, A.; Mandolini, L.; Rossi, I.; Schiaffino, L. *J. Org. Chem.* **1999**, *64*, 8122. (b) van Axel Castelli, V.; Dalla Cort, A.; Mandolini, L.; Reinhoudt, D. N.; Schiaffino, L. *Eur. J. Org. Chem.* **2003**, 627.

162. Krenske, E. H.; Petter, R. C.; Zhu, Z.; Houk, K. N. *J. Org. Chem.* **2011**, *76*, 5074.

163. Suzuki, M.; Mori, M.; Niwa, T.; Hirata, R.; Furuta, K.; Ishikawa, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 2376.

164. Cusack, K. P.; Arnold, L. D.; Barberis, C. E.; Chen, H.; Ericsson, A. M.; Gaza-Bulseco, G. S.; Gordon, T. D.; Grinnell, C. M.; Harsch, A.; Pellegrini, M.; Tarcsa, E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5503.

165. Avonto, C.; Taglialatela-Scafati, O.; Pollastro, F.; Minassi, A.; Di Marzo, V.; De Petrocellis, L.; Appendino, G. *Angew. Chem., Int. Ed.* **2010**, *50*, 467.

166. Serafimova, I. M.; Pufall, M. A.; Krishnan, S.; Duda, K.; Cohen, M. S.; Maglathlin, R. L.; McFarland, J. M.; Miller, R. M.; Frödin, M.; Taunton, J. *Nat. Chem. Biol.* **2012**, *8*, 471.

167. Nguyen, T. L. *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 710.

168. (a) Wipf, P.; Jeger, P.; Kim, Y. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 351. (b) Hammill, J. T.; Contreras-García, J.; Virshup, A. M.; Beratan, D. N.; Yang, W.; Wipf, P. *Tetrahedron* **2010**, *66*, 5852.

169. (a) Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848. (b) Wipf, P.; Spencer, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 225.

170. de Groot, A.; Peperzak, R. M.; Vader, J. *Synth. Commun.* **1987**, *17*, 1607.

171. Asaoka, M.; Shima, K.; Fujii, N.; Takei, H. *Tetrahedron* **1988**, *44*, 4757.

172. Pierce, J. G.; Kasi, D.; Fushimi, M.; Cuzzupe, A.; Wipf, P. *J. Org. Chem.* **2008**, *73*, 7807.

173. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, *1994*, 639.

174. Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

175. Abraham, E.; Cooke, J. W. B.; Davies, S. G.; Naylor, A.; Nicholson, R. L.; Price, P. D.; Smith, A. D. *Tetrahedron* **2007**, *63*, 5855.

176. Mehmandoust, M.; Petit, Y.; Larchevêque, M. *Tetrahedron Lett.* **1992**, *33*, 4313.

177. (a) Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655. (b) Beenen, M.; An, C.; Ellman, J. *J. Am. Chem. Soc.* **2008**, *130*, 6910.