
by

Ramsay Eaton Beveridge

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Graduate Department of Chemistry
University of Toronto

© Copyright by Ramsay Beveridge, 2014

Ramsay Eaton Beveridge

Doctor of Philosophy

Graduate Department of Chemistry
University of Toronto

2014

Abstract

This thesis is presented in two parts and summarizes work carried out in the laboratory of Professor Robert A. Batey at the University of Toronto from September 2010 through July 2014. Part 1 of this thesis covers the development and synthetic utility of new ynamide reagents toward nitrogen heterocycle generation and natural product synthetic applications (Chapters 1-4). Part 2 of this thesis outlines work related to the synthesis of new organo-allyl trifluoroborate reagents and their application in the synthesis of biologically active depsipeptide natural products (Chapters 5-7).

Part 1 begins with an introductory chapter (Chapter 1) to familiarize the reader with previous important ynamide reagent scientific contributions. Next, Chapter 2 describes our discovery of a previously unexplored ynehydrazide alkyne class including their application in the synthesis of pharmaceutically relevant nitrogen heterocycles.
Chapter 3 then describes an ynehydrazide approach to the total synthesis of the hydrazide natural product geralcin A and Z-enehydrazides. Also presented is the discovery of a Boc-carbazate epoxide ring opening/Peterson olefination sequence to stereospecifically prepare Z-enehydrazides. Importantly, this methodology was used to prepare the structurally unique Z-enehydrazide containing natural products hydrazidomycins A-B and elaiomycin B.

In Chapter 4, our synthetic studies using a terminal N,N-di-Boc ynimide as an aminoethylating reagent and precursor for regioselective synthesis of imide-functionalized heterocycles is outlined. Included are new examples of ynamide-acetylide reactivity and an ynimide approach to the total synthesis of pyrrolidinoindoline alkaloids (±)-CPC-1 and (±)-Alline.

Part 2 of this thesis begins with an introduction to allyl trifluoroborates and their synthetic utility (Chapter 5). Chapter 6 then describes our results concerning the synthesis of a prenyltrifluoroborate reagent and its use to γ-prenylate aldehydes and ketones. In particular, a diastereoselective prenyltrifluoroborate addition to the N-Boc-L-leucinal is featured as a strategy to install the key di-methyl-β-keto-ester fragment in the total synthesis of the potent cancer cell growth inhibitory depsipeptides kitastatin and respirantin.

Finally, Chapter 7 details the total synthesis of the potent cytokine inhibitory natural product splenocin-B. The chapter features a Z-benzyl-allyltrifluoroborate approach to construct the key stereotriad as well as studies on a new Wittig approach to synthesize Z-allyl-functionalized organotrifluoroborates.
Acknowledgments

Working in the Batey lab has been a lot of fun and I want to thank everybody over the past four years that I’ve worked with for being such a great group of enthusiastic and fun colleagues. Thanks are definitely also extended to the amazing research support staff in the chemistry department in particular Dimitry Pichugin (NMR), Darcy Burns (NMR), and Matt Forbes (MS); without whom the data in this thesis would not be possible. I want to also thank Anna Liza Villavelez as well as my supervisory committee members Prof. Lautens and Prof. Yudin for all their help throughout my tenure here.

In particular, I would like to formally acknowledge my supervisor Rob Batey for his guidance and tutelage over the past four years. Not only did I learn a lot about how to disconnect molecules and think analytically about organic synthesis, but Rob’s excellent teaching style has helped improve my own pedagogistic abilities and presentation skills. I am especially grateful to Rob for his patience and acceptance of me pursuing the many (sometimes crazy and not always project related) synthetic curiosities I have.

Most importantly, I want to thank my wife for being so supportive of my (unwise?) decision to resign an industrial position and become a graduate student (again!). This thesis is dedicated to you Rach.
# Table of Contents

List of Tables ............................................................................................................................. vi

List of Figures ............................................................................................................................. vii

List of Schemes ........................................................................................................................... ix

List of Appendices ....................................................................................................................... xvi

List of Abbreviations .................................................................................................................... xvii

Chapter 1: Synthetic Utility of 1-Amido-Alkynes (Ynamides) .................................................. 1

Chapter 2: Discovery and Development of a New Ynehydrazide Alkyne Class ...................... 29

Chapter 3: Total Synthesis of the N‒N Bond Containing Natural Products Geralcin A, Elaiomycin B, and Hydrazidomycins A-B ................................................................................. 81

Chapter 4: An Ynimide Approach to Pyrrolidinoindoline Alkaloids (±)-CPC-1 and (±)-Alline and Imide Functionalized Heterocycles .................................................................................. 130

Chapter 5: Synthetic Utility of Allyltrifluoroborate Reagents ..................................................... 182

Chapter 6: A Convergent Organotrifluoroborate-Based Total Synthesis of the Potent Cancer Cell Growth Inhibitory Depsipeptide Natural Products Kitastatin and Respirantin ............. 207

Chapter 7: An Organotrifluoroborate-Based Total Synthesis of the Potent Naturally Occuring Interleukin Inhibitor Splenocin-B and Studies Toward a Wittig-Olefination Approach to Z-Allyltrifluoroborates ........................................................................................................ 246
List of Tables

Table 3.1 Hydrazide ring-opening of syn silyl-epoxide 3.23 ................................................................. 88
Table 3.2 Synthetic vs. Natural $^{13}$C NMR data for Hydrazidomycins A and B (3.1-3.2) .......... 94
Table 3.3 Synthetic vs. Natural $^{13}$C NMR data for Elaiomycin B (3.3) ........................................ 95
Table 6.1 Synthetic vs. Natural $^{13}$C NMR data for Kitastatin (6.1) and Respirantin (6.2) .... 221
Table 7.1 Synthetic vs. Natural $^{13}$C NMR data for splenocin-B (7.6) ................................. 262
List of Figures

Fig. 1.1 Ynamides as stable yet polarized variants of highly reactive ynamines .......................... 2

Fig. 2.1 Amide and hydrazide-substituted alkynes................................................................. 29

Fig. 2.2 Proposed orthogonol ring-forming strategy using ynehydrazides to generate poly-
heterocyclic structures........................................................................................................... 30

Fig. 3.1 Biologically active enehydrazide natural products 3.1-3.6 .......................................... 82

Fig. 3.2 Proposed stereoselective ynehydrazide reduction approach to Z-enehydrazide natural
product hydrazidomycin A.................................................................................................. 83

Fig. 4.1 General concept of ynamide acetylides as ethyleneamine building blocks ............... 131

Fig. 4.2 Representative natural product and pharmaceutical molecules containing an
ethyleneamine fragment potentially accessible via ynamide carbonyl or epoxide addition. 131

Fig. 5.1 Synthetic utility of an aldehyde allylboration homoallylic alcohol product .............. 183

Fig. 5.2 Stereospecific and stereodivergent nature of the type-I class of allyl-metalloid
crotylboronates in additions to aldehydes via Zimmerman-Traxler transition states ....... 184

Fig. 5.3 Examples of common allylboron reagents in order of their stability/reactivity .......... 185

Fig. 6.1 Examples of cytotoxic natural products containing gem-dimethyl fragments
potentially accessible via carbonyl prenylation ................................................................... 207

Fig. 6.2 Representative biologically active antimycin/neo-antimycin natural products......... 208

Fig. 6.3 Anti-tumoral activity of neo-antimycin cyclic depsipeptides kitastatin 6.1 and
respirantin 6.2 and structural relationship to the (+)-antimycin A natural product family ... 209

Fig. 6.4 Summary of the Pettit synthesis of respirantin 6.2 and the decarboxylation issue
associated with the β-keto-ester fragment ...................................................................... 210

Fig. 7.1 The (+)-antimycin A family of 9-membered depsipeptides ........................................ 248

Fig. 7.2 Example neo-antimycin depsipeptide natural products prunustatin A (7.1) and
kitastatin (7.2) ....................................................................................................................... 249

Fig. 7.3 (+)-Antimycin A₃ (Fintrol™) and OMe BcL-2 inhibitory analog 7.4 ......................... 250

Fig. 7.4 The cytokine inhibitory depsipeptides splenocins A-D and the related weakly
cytotoxic UK-2A analog 7.9 .......................................................................................... 251

Fig. 7.5 Generalized Wittig olefination strategy for the one-step synthesis of Z-allylboronates
from aldehydes .................................................................................................................. 253
Fig. 7.6 Alternative Z-allylboronate disconnection via phosphorous ylide reaction with a methylene linked α-boryl aldehyde ................................................................. 256

Fig. 7.7 Proposed synthesis of unsubstituted methylene-linked α-boryl aldehydes via oxidative cleavage of allylboronates toward Z-allylboronates ......................................................... 256
List of Schemes

Chapter 1:

Scheme 1.1 Common generalized C\textsubscript{sp}-N bond formation methods................................................................. 2

Scheme 1.2 Selected alternative C\textsubscript{sp}-N synthesis strategies not based on alkynylidonium salts or metal-catalyzed amidation ........................................................................................................... 3

Scheme 1.3 Diastereoselective ynamide lithium-acetylide addition to a chiral sulfonyl-imine and proposed transition state ......................................................................................................................... 4

Scheme 1.4 Catalytic enantioselective terminal N-alkyne addition to aldehydes ................................................................. 5

Scheme 1.5 Stereodivergent intramolecular keteniminium cyclizations .................................................................................... 6

Scheme 1.6 Ynamide keteniminium cyclization approach to the total synthesis of (±)-desbromoarborescidines A and C ......................................................................................................................... 7

Scheme 1.7 Intermolecular hydroarylation of ynamides via keteniminium ion formation .......................................................... 8

Scheme 1.8 Asymmetric Ficini-Claisen and Saucy-Marbet [3,3]-sigmatropic rearrangements of ynamides via keteniminium trapping with allylic and propargylic alcohols .................................................. 9

Scheme 1.9 Select generalized intramolecular alkyne cyclizations to generate benzo-fused heterocycles from ynamides .................................................................................................................. 10

Scheme 1.10 Intramolecular ynamide carbo-palladation approach to the total synthesis of (±)-lennoxamine .................................................................................................................................................. 11

Scheme 1.11 Example of a platinum-catalyzed ene-ynamide cycloisomerization and proposed mechanism .................................................................................................................................................. 11

Scheme 1.12 Example of a ruthenium-catalyzed ene-ynamide RCM reaction and subsequent Diels-Alder reaction .................................................................................................................................................. 12

Scheme 1.13 Example of a Ruthenium-catalyzed enantioselective Ficini formal ynamide [2+2] cycloaddition .................................................................................................................................................. 13

Scheme 1.14 Ynamide [2+2] ketene cycloaddition and electrocyclization cascade route to (+)-FR900482 .................................................................................................................................................. 14

Scheme 1.15 Example of an asymmetric ynamide Kinugasa [3+2] reaction and deprotection to a synthetically useful syn-amino-β-lactam .................................................................................................. 15
Scheme 1.16 Example of a Bergmann-type ynamide [4+2] cycloaddition to generate a carbazole ring system ................................................................. 16

Scheme 1.17 Examples of 4-amide quinolines synthesized in Movassaghi’s ynamide [4+2] reaction and proposed ionic reaction intermediate ................................................................. 16

Scheme 1.18 Generalized example of alkene tethered ynamides in intramolecular [2+2+1] cycloadditions ........................................................................................................... 17

Scheme 1.19 Total synthesis of lavendamycin using an ynamide [2+2+2] cycloaddition approach ............................................................................................................... 18

Scheme 1.20 Total synthesis of herbindole C using an ynamide [2+2+2] cycloaddition approach ............................................................................................................... 18

Scheme 1.21 Rhodium-catalyzed ynamide carbometallation approach to the antifungal natural product (+)-tanikolide ........................................................................................................... 19

Scheme 1.22 Asymmetric ynamide-based carbometallation/allylation sequence to all-carbon quaternary stereocentres ........................................................................................................... 20

Scheme 1.23 Asymmetric ynamide-based carbo-metallation/enolate trapping sequence approach to chiral quaternary aldol products ........................................................................................................... 21

Chapter 2:

Scheme 2.1 Previous examples of ynehydrazine and ynehydrazide synthesis ........................................... 30

Scheme 2.2 A copper-promoted C$_{sp}$–N cross-coupling approach to ynehydrazides ................. 31

Scheme 2.3 Direct formation of ynehydrazide C$_{sp}$–N bonds via lithium-acetylide addition to diazodicarboxylates ........................................................................................................... 31

Scheme 2.4 Scope of ynehydrazide synthesis ........................................................................................................... 33

Scheme 2.5 Synthesis of terminal and carbonyl substituted ynehydrazides ........................................... 34

Scheme 2.6 Copper-catalyzed azide and terminal ynehydrazide [3+2] cycloadditions ............... 35

Scheme 2.7 Copper-catalyzed nitrile oxide and terminal ynehydrazide [3+2] cycloaddition ..... 35

Scheme 2.8 Synthesis of a 2-hydrazide substituted indole via palladium-catalyzed terminal ynehydrazide heterocyclization ........................................................................................................... 36

Scheme 2.9 Ruthenium-catalyzed ynehydrazide and azide [3+2] cycloadditions ............... 36

Scheme 2.10 Ruthenium-catalyzed ynehydrazide and nitrile oxide [3+2] cycloadditions ...... 37
Scheme 2.11 Attempted Povarov [4+2] reaction with ynehydrazides ........................................... 37
Scheme 2.12 Ynehydrazide [4+2] approach to N-functionalized quinolines................................. 38
Scheme 2.13 Unsuccessful [4+2] ynehydrazide cycloadditions with a 1,3,5-triazine and a coumalate ................................................................. 38
Scheme 2.14 Attempted [2+2+1], [2+2+2] and Bergman cycloaddition reactions with ynehydrazides................................................................................................. 39
Scheme 2.15 N-functionalized ynehydrazide synthesis and application in phthalizinone formation .................................................................................................................. 40
Scheme 2.16 Synthesis of N-amino oxazolones via Au-catalyzed intramolecular ynehydrazide cyclization............................................................................................................. 40
Scheme 2.17 N-functionalization and deprotection of an N-amino oxazolone............................... 41
Scheme 2.18 Hydrogenation of 2.56 to give N-amino oxazolidinone 2.61 ................................. 41
Scheme 2.19 Diels-Alder reaction of N-amino oxazolone 2.59..................................................... 41
Scheme 2.20 One-pot N-heterocycle functionalized pyrazole synthesis from ynehydrazide derived heterocycles ........................................................................................................ 42
Scheme 2.21 One-pot N-heterocycle functionalized 1,2,4-triazole synthesis from ynehydrazide derived heterocycles ........................................................................................................ 42

Chapter 3:

Scheme 3.1 Synthesis of Z-enehydrazides via stereoselective Lindlar reduction of ynehydrazides......................................................................................................................... 83
Scheme 3.2 Ynehydrazide based approach to hydrazidomycin A analogs ................................. 84
Scheme 3.3 Total synthesis of geralcin A using an ynehydrazide approach.................................... 85
Scheme 3.4 Unsuccessful Pd or Cu catalyzed C–N bond forming approach to hydrazidomycin A ......................................................................................................................... 86
Scheme 3.5 Synthesis of a terminal ynehydrazide with correct hydrazidomycin functional group distribution ......................................................................................................... 86
Scheme 3.6 Synthesis of a syn silyl-epoxide for hydrazine ring-opening toward a Peterson olefination of hydrazidomycin A ......................................................................................... 87
Scheme 3.7 Base-mediated Peterson olefination total synthesis of hydrazidomycin A (3.1) .... 89
Scheme 3.8 Synthesis of an E-hydrazidomycin A analog via acid-mediated silanol elimination of 3.25 ................................................................. 89

Scheme 3.9 Synthesis of Peterson elimination precursors 3.35 and 3.36 for hydrazidomycin B (3.2) and elaiomycin B (3.3) synthesis ................................................................. 90

Scheme 3.10 Completion of the synthesis of hydrazidomycin B 3.2 via base mediated Peterson silanol elimination ................................................................. 91

Scheme 3.11 Completion of the synthesis of elaiomycin B 3.3 via base mediated Peterson silanol elimination ................................................................. 91

Chapter 4:

Scheme 4.1 Proposed ynehydrazide aminoethylation approach to pyrrolidinoindoline alkaloids .......................................................................................................................... 132

Scheme 4.2 Unsuccessful ynehydrazide approach to (±)-CPC-1 ...................................................... 133

Scheme 4.3 Conversion of compound 4.5 to ethylenepyrazoles ...................................................... 133

Scheme 4.4 Synthesis of N,N-di-Boc-ynimide reagent 4.12 from alkynyliodonium triflate reagents .......................................................................................................................... 134

Scheme 4.5 Synthesis of di-Boc-di-bromo-enamide 4.14 and its attempted Corey-Fuchs type conversion to ynimide 4.12 .......................................................................................................................... 135

Scheme 4.6 Regioselective cross-coupling of dibromo-enamide 4.14 and subsequent Diels-Alder reaction .......................................................................................................................... 136

Scheme 4.7 Formal synthesis of (±)-CPC-1 using an ynimide aminoethylation approach ...... 137

Scheme 4.8 Formal synthesis of (±)-Alline using an ynimide aminoethylation approach ...... 137

Scheme 4.9 Reaction of ynimide 4.12 with carbonyl electrophiles .................................................. 138

Scheme 4.10 Copper-catalyzed reaction of ynimide 4.12 with N-acyl pyridinium ions .......... 138

Scheme 4.11 Reaction of ynimide 4.12 with epoxides ........................................................................ 139

Scheme 4.12 Reaction of ynimide 4.12 with Michael acceptors ......................................................... 139

Scheme 4.13 Sonogoshira coupling with ynimide 4.12 ........................................................................ 139

Scheme 4.14 Ethyleneamines from internal ynimides derived from 4.12 ........................................ 140

Scheme 4.15 Cu-catalyzed synthesis of 4-imide-functionalized triazoles from ynimide 4.12 .. 141
Scheme 4.16 Ru-catalyzed synthesis of 5-imide functionalized triazoles from ynimide 4.12... 141
Scheme 4.17 Catalytic synthesis of imide-functionalized isoxazoles from ynimide 4.12 ........ 141
Scheme 4.18 Deprotection and reaction of Boc-imide functionalized triazoles ...................... 142

Chapter 5:

Scheme 5.1 Early work on preparing aryl-trifluoroborate potassium salts and their application in asymmetric enolate reactions of amino acids by Vedejs and co-workers.............................. 186
Scheme 5.2 Synthesis of potassium allyl trifluoroborate from in situ generated allylboronic acid ................................................................................................................. 186
Scheme 5.3 Synthesis of Z-crotyl and E-crotyl trifluoroborate potassium salts .................... 187
Scheme 5.4 Matteson homologation approach to a γ-functionalized E-allyl trifluoroborate ..... 188
Scheme 5.5 Matteson homologation approach to a γ-functionalized Z-allyl trifluoroborate ..... 188
Scheme 5.6 Selected examples of γ-E-functionalized allyl trifluoroborate salts prepared via a palladium-catalyzed allylic-borylation approach ........................................................................... 189
Scheme 5.7 Synthesis of a chiral α-substituted allyl trifluoroborate salt............................... 189
Scheme 5.8 Common conditions for aldehyde and ketone allylation with allyl trifluoroborate salts......................................................................................................................... 190
Scheme 5.9 Allylation and crotylation of sulfonyl and sulfinyl imines using trifluoroborate reagents and BF₃·OEt₂ promoter ........................................................................................................ 191
Scheme 5.10 Representative Lewis-acid promoted C-2 allylation and crotylation of indoles using organotrifluoroborate salts .................................................................................................. 192
Scheme 5.11 Representative products of rhodium-catalyzed enantioselective allyl trifluoroborate additions to cyclic imines .................................................................................................................. 193
Scheme 5.12 Diastereoselective allyl- and crotyl-BF₃K additions to TBS protected α-hydroxy aldehydes .......................................................................................................................... 194
Scheme 5.13 Diastereoselective allyl- and crotyl-BF₃K additions to TBS protected β-hydroxy aldehydes .......................................................................................................................... 194
Scheme 5.14 Total synthesis of the anti-obesity agent (-)-tetrahydrolipstatin using a diastereoselective β-hydroxy aldehyde E-allyl trifluoroborate addition approach ................ 195
Scheme 5.15 Total synthesis of the depsipeptide respiratory inhibitor (+)-antimycin A1b using a diastereoselective α-hydroxy aldehyde Z-allyltrifluoroborate addition approach..... 195

Scheme 5.16 Diastereoselective allyltrifluoroborate additions to chiral α-amino aldehydes and application to the synthesis of the statine amino acid residue component of dolastatin 10 ................................................................................................................................. 196

Scheme 5.17 Diastereoselective crotyl-BF3K aldehyde addition in the total synthesis of polyketide natural product zincophorin methyl ester.......................................................... 197

Scheme 5.18 Diastereoselective crotyl-BF3K additions to chiral α-dithiane aldehydes .......... 197

Scheme 5.19 Representative products of indium-mediated allyltrifluoroborate addition to α,β-epoxy ketones ........................................................................................................ 198

Scheme 5.20 Enantioselective carbonyl allylation using a chiral α-substituted allyltrifluoroborate ...................................................................................................................... 198

Scheme 5.21 Palladium-catalyzed regio- and enantioselective synthesis of α-substituted allyl products using γ-functionalized allyltrifluoroborates ................................................ 199

Scheme 5.22 Palladium-catalyzed coupling of aroyl chlorides and allyl/crotyl-trifluoroborates .................................................................................................................... 200

Scheme 5.23 Allyltrifluoroborate approach to synthesize 1,2-azaborine 5.75 ................. 201

Scheme 5.24 Functionalization of 1,2-azaborine 5.74 toward unexplored 1,2-azaborane products .................................................................................................................. 201

Scheme 5.25 Cu-mediated chemoselective oxidation of an allyltrifluoroborate salt ............. 202

Scheme 5.26 Dihydroxylation of potassium allyltrifluoroborate ..................................... 202

Chapter 6:

Scheme 6.1 Proposed synthetic strategy to compounds 6.1 and 6.2 .......................... 211

Scheme 6.2 Synthesis of potassium prenyltrifluoroborate reagent 6.18 ..................... 212

Scheme 6.3 Prenylation of N-Boc-L-leucinal with prenyl-BF3K 6.18 ......................... 213

Scheme 6.4 Alternative prenylations of N-Boc-L-leucinal 6.17 .................................. 214

Scheme 6.5 Carbonyl prenylation using prenyl-BF3K reagent 3.18 under Mont. K10 clay-catalyzed conditions .......................................................... 215

Scheme 6.6 Synthesis of the southern fragment 6.13 ............................................... 215
Scheme 6.7 Synthesis of northern fragment 6.12 .................................................................216

Scheme 6.8 Synthesis of the core macrocycle 6.10 .................................................................217

Scheme 6.9 Completion of the synthesis of kitastatin 3.1 and respirantin 3.2 ................. 218

Chapter 7:

Scheme 7.1 Proposed synthetic strategy to splenocin-B (7.6) using a Z-benzyl allyltrifluoroborate aldehyde addition ................................................................. 252

Scheme 7.2 Reported 3,4-hydroboration approach to borono-phosphonate 7.18 and presumed actual reaction products 7.19 and 7.20 via 1,4-hydroboration ............................................................................. 254

Scheme 7.3 Successful synthesis of borono-phosphonate 7.18 via copper-catalyzed 1,4-borylation of diethyl vinylphosphonate and conversion to its stable trifluoroborate 7.21 .... 254

Scheme 7.4 Synthesis of tetrabutylammonium trifluoroboronophosphonate 7.22 and its reaction with benzaldehyde to give stable β-hydroxyphosphonate 7.23 ....................... 255

Scheme 7.5 Synthesis of MIDA-borane α-boryl aldehydes ................................................................................. 256

Scheme 7.6 Attempted Z-selective olefin cross-metathesis approach to Z-benzylallyl trifluoroborate 7.17 ................................................................................ 258

Scheme 7.7 Matteson homologation synthesis of Z-benzyl allyltrifluoroborate 7.17 ........ 258

Scheme 7.8 Stereoselective reaction of allyl-BF$_3$K 7.17 with aldehyde 7.16 and proposed transition state model ....................................................................................... 259

Scheme 7.9 Elaboration of 7.15 to TBS protected splenocin-B seco-acid 7.11 ................. 259

Scheme 7.10 Completing the total synthesis of splenocin-B 7.6 ............................................. 260
List of Appendices

Appendix 1 \(^1\)H and \(^{13}\)C NMR Spectra for Chapter 2 .........................................................278

Appendix 2 \(^1\)H and \(^{13}\)C NMR Spectra for Chapter 3 .........................................................337

Appendix 3 \(^1\)H and \(^{13}\)C NMR Spectra for Chapter 4 .........................................................378

Appendix 4 Crystallographic Material for Compound 6.20 in Chapter 6 ...............................427

Appendix 5 \(^1\)H and \(^{13}\)C NMR Spectra for Chapter 6 .........................................................443

Appendix 6 \(^1\)H and \(^{13}\)C NMR Spectra for Chapter 7 .........................................................475
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ</td>
<td>chemical shift</td>
</tr>
<tr>
<td>Ac</td>
<td>acyl</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2′-bis(diphenylphosphino)-1,1′-binaphthyl</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1′-bi-2-napthol</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butylcarbamate</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>Chx</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>cod</td>
<td>cyclooctadiene</td>
</tr>
<tr>
<td>d</td>
<td>days or doublet</td>
</tr>
<tr>
<td>DART</td>
<td>direct analysis in real time</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>N,N-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMB</td>
<td>2,4-dimethoxybenzyl</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Et₂O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HFIP</td>
<td>1,1,1,3,3,3-hexafluoroisopropanol</td>
</tr>
<tr>
<td>HMDS</td>
<td>hexamethyldisilazide</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high-resolution mass spectrometry</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>i-Pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>infrared spectroscopy</td>
</tr>
<tr>
<td>J</td>
<td>scalar coupling constant</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LRMS</td>
<td>low-resolution mass spectrometry</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mL</td>
<td>millilitre(s)</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole(s)</td>
</tr>
<tr>
<td>mol</td>
<td>mole(s)</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl ether</td>
</tr>
<tr>
<td>M.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>MS</td>
<td>molecular sieves or mass spectroscopy</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>ORTEP</td>
<td>Oak Ridge thermal ellipsoid plot</td>
</tr>
<tr>
<td>pin</td>
<td>pinacol</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PhMe</td>
<td>toluene</td>
</tr>
<tr>
<td>quant.</td>
<td>quantitative</td>
</tr>
<tr>
<td>R</td>
<td>alkyl, alkenyl, or alkynyl</td>
</tr>
<tr>
<td>rac</td>
<td>racemic</td>
</tr>
<tr>
<td>$R_f$</td>
<td>retention factor</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>S$_{N}$2</td>
<td>bimolecular nucleophilic substitution</td>
</tr>
<tr>
<td>S$_{N}$Ar</td>
<td>nucleophilic aromatic substitution</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butylidiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TCE</td>
<td>1,1,2,2-tetrachloroethane</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethansulfonyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl or tetramethylsilane</td>
</tr>
<tr>
<td>Ts</td>
<td>$p$-toluenesulfonyl</td>
</tr>
<tr>
<td>TS</td>
<td>transition state</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>$\mu$wave</td>
<td>microwave</td>
</tr>
</tbody>
</table>
Chapter 1: Synthetic Utility of 1-Amido-Alkynes (Ynamides)

1.1 Introduction

This chapter describes important prior work in the ynamide reagent field as background for the work described in chapters 2-4 of this thesis concerning the development of ynehydrazide and ynimide reagents. Since several excellent reviews already exist on the preparation and synthetic use of N-linked alkyne species, this chapter will be a general overview of important reactions and is not intended to be an all inclusive ynamide reference work. Specifically, this chapter will focus on common modes of generating Csp–N bonds and highlight synthetically important applications of these N-alkynyl species with a concentration on nitrogen heterocycle and natural product syntheses. An attempt has been made, however, to include examples of more recent (post 2010) ynamide chemistry which is not covered in prior comprehensive reviews.

1.2 Synthesis of Ynamides

The ynamine class of highly reactive and polarized heteroatom-linked alkynes have a rich chemical history of unique N-alkynyl based synthetic transformations after becoming popularized in the 1960’s. Although valuable, these 1-amino-alkynes are very hydrolytically sensitive and unstable to storage (sometimes termed “expensive amides”). The corresponding ynamide class of reagents (Fig. 1.1), however, balance this important reactive polarization with improved handling characteristics resulting in N-alkynyl species which can be column purified and stored on the bench-top. In addition to imparting stability by reducing the nitrogen lone-pair donation into the alkyne, the ynamide electron-withdrawing “amide” has additional utility as a functional handle to control in some cases the regiochemistry and stereochemistry of ynamide reactions.
Figure 1.1 Ynamides as stable yet polarized variants of highly reactive ynamines

Although first synthesized in 1972 by Viehe, the ynamide functional group did not find significant usage until the advent of practical and general preparatory methods appearing nearly three decades later. Pioneering work to build alkynyl-amides by the groups of Feldman and Witulski using alkynylidonium salts, and the groups of Hsung and Danheiser regarding copper-based cross-coupling strategies, laid the groundwork for the explosion of ynamide usage seen in the new millennium. These two complimentary ynamide synthesis protocols are the most common and important strategies to form C–N bonds as they can provide access to almost any desired ynamide structure (Scheme 1.1).

Amide addition to alkynylidonium triflate salts ("Witulski Protocol"): 

Copper-mediated alkynyl-bromide amidation ("Hsung Protocol"): 

Scheme 1.1 Common generalized C–N bond formation methods
In addition to various extensions and modifications of these “Witulski” and “Hsung” strategies,\(^1\) some other useful ynamide synthesis protocols are shown in Scheme 1.2. Before their discovery of a copper-mediated amidation route to ynamides, the Hsung lab made a number of ynamide compounds via isomerization of propargylamides\(^8\) or elimination of β-bromo-enamides.\(^9\) Alternatively, a powerful and flexible formamide-based route to prepare ynamides via a Corey-Fuchs type rearrangement of β,β-dichloroenamides was reported by Bruckner\(^10\) in 2000. The intermediate N-alkynyl acetylides generated from dichloroenamides can undergo direct electrophilic trapping or be further functionalized via Sonogashira coupling to generate internal ynamide structures.\(^10,11\) Dichloroenamides can also provide ynamides via the reverse pathway involving initial Suzuki-Miyaura cross-coupling followed by chloro-enamide elimination to generate aryl-substituted ynamides.\(^12\)

Scheme 1.2 Selected alternative C\(_{sp^2}-\)N synthesis strategies not based on alkynyliodonium salts or metal-catalyzed amidation

While the above strategies focus on generating the crucial nitrogen-alkyne bond, the functionalization of terminal ynamides via metal-acetylide reactivity with common electrophiles is largely unexplored. Until recently, and before our work described in chapter 4, reactions of terminal ynamides in this fashion were limited to examples of
indirect N-alkynyl acetylide functionalization\textsuperscript{13} and a few reports of Sonogoshira coupling.\textsuperscript{14} Of late, however, the groups of Hsung and Wolf have independently started to recognize the potential of using a pre-formed C\textsubscript{sp}-N containing terminal ynamide as a practical starting point to access other internally functionalized alkynyl-amides. In this area, Hsung and co-workers prepared chiral amide-substituted propargylamines via diastereoselective additions of sulfonamide protected N-alkynyl-acetylides to chiral “Ellman-Davis” sulfonyl-imines in 2013 (Scheme 1.3).\textsuperscript{15}

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.3.png}
\end{center}

\textbf{Scheme 1.3} Diastereoselective ynamide lithium-acetylide addition to a chiral sulfonyle-imine and proposed transition state\textsuperscript{15}

Shortly thereafter, the Wolf lab used Carreira-type conditions to execute catalytic enantioselective additions of terminal ynamides to aldehydes (Scheme 1.4).\textsuperscript{16} More recently, this group has also reported a copper-catalyzed ynamide-acetylide addition to N-acyl pyridinium salts.\textsuperscript{17} One draw-back to the enantioselective carbonyl ynamide addition work reported by Wolf and Cook is the unfortunate circumstance that high levels of asymmetry are only observed with N-alkynyl heterocycles (e.g., compound 1.6, Scheme 1.4) which limits the synthetic utility of the product propargyl-alcohols. In this regard, there remains room for growth in this general terminal ynamide reactivity area, specifically in the development and use of ynamide species which would be more flexible toward further product manipulation than sulfonamide or indole protected N-alkynes. Additionally, it would be useful to expand the scope of terminal ynamide reactivity to include other common electrophiles such as epoxides and Michael acceptors.
Scheme 1.4 Catalytic enantioselective terminal N-alkyne addition to aldehydes\textsuperscript{16}

1.3 Reaction of ynamides via keteniminium formation

Although ynamides are stable N-linked alkynes, they are still polarized and capable of participating in reactions via their keteniminium form. This type of polarization can be very useful as keteniminium generation usually results in highly regioselective reactivity. For example, the Hsung group has explored intramolecular keteniminium trapping by an ynamide appended aryl system under both Brønsted and Lewis acid conditions which give rise to useful isoquinoline or isoindoline heterocycle cores.\textsuperscript{18} Interestingly, the reaction is stereodivergent resulting in preferred formation of the Z-enamide with Brønsted acid, but predominantly E-enamide formation using a platinum Lewis-acid (Scheme 1.5). These results were rationalized by the relative stabilities of the proposed ionic intermediates due to contrasting steric interactions of the aryl ring with the keteniminium substituents.
Scheme 1.5 Stereodivergent intramolecular keteniminium cyclizations\textsuperscript{18}

This Pictet-Spengler type of reactivity was also extended to indole systems which provide cyclic enamide hydrocarboline-like structures 1.9 and 1.11 (Scheme 1.6). These examples demonstrate the practical utility of this approach as they were further elaborated in the total synthesis of the indole alkaloid natural products 10-desbromoarborescine A and 11-desbromoarborescine C.\textsuperscript{18} Although the ynamide keteniminium cyclizations in these examples were followed immediately by simple reductive transformations, there is perhaps potential in this area to use the indole-enamide structures generated in this approach toward other more complex alkaloid targets.
Scheme 1.6 Ynamide keteniminium cyclization approach to the total synthesis of (±)-desbromoarborescindines A and C

In addition to these intramolecular examples, ynamide keteniminium ions can be trapped in an intermolecular fashion by electron rich aromatic systems such as furans, pyrroles, and indoles using catalytic Brønsted acid (Scheme 1.7). The regioselectivity of this overall hydroarylation reaction is once again dictated by the alkyne polarization as a result of the nitrogen triple bond substitution. In agreement with the intramolecular variant of this reaction, this intermolecular keteniminium trapping is also selective for exclusive formation of the Z-enamide via nucleophilic approach anti to the alkyne substituent.
Scheme 1.7 Intermolecular hydroarylation of ynamides via keteniminium ion formation

This alkyne polarization leading to keteniminium ions has also been exploited with nucleophilic trapping by heteroatom species such as halides, amines/amides, thiols, and alcohols. This strategy is particularly useful with allylic and propargylic alcohol nucleophiles as these reactions generate enol-ether intermediates which rapidly undergo [3,3]-sigmatropic rearrangements (Scheme 1.8). Importantly, because chiral ynamides are used, these sigmatropic reactions provide asymmetric access to valuable chiral alkene and allene building blocks via Ficini-Claisen and Saucy-Marbet rearrangements. The rationale for the observed stereoselectivity in these reactions is a transition state with heteroatoms in an anti-relationship to minimize dipole formation. In the Saucy-Marbet rearrangements, a matched/mis-matched stereochemical issue was also observed depending on the chirality of the starting propargyl alcohol. The matched case with (S)-configured propargyl alcohols is proposed to provide better stereochemical ratios due to a more favourable transition state in which the propargyl alcohol substituent adopts a pseudo-equatorial position (Scheme 1.8).
Scheme 1.8 Asymmetric Ficini-Claisen and Saucy-Marbet [3,3]-sigmatropic rearrangements of ynamides via keteniminium trapping with allylic and propargylic alcohols

In addition to the above examples, a number of ynamide keteniminium intramolecular trapping reactions providing overall a formal [2+2] cycloaddition are also known, however, these examples will be discussed later (Section 1.5) in connection with a discussion of ynamide cycloadditions.

1.4 Intramolecular Ynamide Cyclizations

Taking advantage of well-known alkyne transformations, ynamides have been shown to be valuable precursors to a variety of nitrogen heterocycle structures through intramolecular alkyne cyclizations. Instructive examples of this type of reaction are shown in Scheme 1.9 which highlight participation of ynamides in Larock-type indole and benzoxazole formations, as well as a radical cyclization approach to isoindoles.
Scheme 1.9 Select generalized intramolecular alkyne cyclizations to generate benzo-fused heterocycles from ynamides.\textsuperscript{24-26}

In addition to the above general examples, a flexible intramolecular carbo-palladation strategy to access benzo-fused heterocycle products from ynamides was reported from the Cossy lab.\textsuperscript{27} The carbo-palladated intermediate in this reaction can be hydrogenated with NH\textsubscript{4}CO\textsubscript{2}H or used in a Suzuki-Miyaura coupling to provide an overall domino Heck/Suzuki sequence to create additional molecular complexity. For example, this isoindole-forming carbo-palladation Suzuki coupling strategy was used as a key step in their total synthesis of (\textpm)-lennoxamine (Scheme 1.10).\textsuperscript{27b-c}
Scheme 1.10 Intramolecular ynamide carbo-palladation approach to the total synthesis of (+)-lennoxamine\textsuperscript{27b-c}

In addition to benzo-fused heterocycles, small semi-saturated nitrogen containing ring systems can also be formed via intramolecular ene-ynamide metal-catalyzed cyclizations. In particular, ynamides with a tethered alkene can participate in either a platinum catalyzed cycloisomerization\textsuperscript{28} (Scheme 1.11) or an eneyne ring-closing metathesis (RCM) reaction\textsuperscript{29} (Scheme 1.12) to provide alkene substituted pyrrolidine or piperidine ring systems respectively. Notably, the products of these reactions contain a 1-amino-diene moiety which the Hsung group has shown in the case of compound 1.22 can participate in a Diels-Alder reaction to further generate structural complexity from an overall easily prepared ynamide starting point (Scheme 1.12). In addition to the 5 and 6-membered ring systems shown below, these ynamide reactions can also be tuned to provide access to other ring sizes depending on the tether length and alkene substituents.

Scheme 1.11 Example of a platinum-catalyzed ene-ynamide cycloisomerization and proposed mechanism\textsuperscript{28}
Scheme 1.12 Example of a ruthenium-catalyzed ene-ynamide RCM reaction and subsequent Diels-Alder reaction\textsuperscript{20a}

1.5 Cycloaddition reactions with ynamides

The participation of ynamide species in classical alkyne cycloaddition reactions is perhaps the most important type of N-alkynyl reactivity due to their ability to rapidly build molecular complexity by creating multiple bonds in a single step. Moreover, ynamide cycloadditions generally lead to highly regioselective introduction of amine functionality which can be used to access valuable heterocycle and natural product structures difficult to construct by alternative means.

As mentioned in Section 1.3 on keteniminium reactivity, many reports of ynamide [2+2] cycloadditions proceed via non-pericyclic step-wise pathways. For example, the formal [2+2] reaction of ynamides with carbonyl groups in the presence of BF$_3$·OEt$_2$\textsuperscript{30} was an unexpected consequence of intramolecular heteroatom trapping of a keteniminium intermediate. Other reactions that proceed via a step-wise intramolecular keteniminium based [2+2] cycloaddition include the metal-catalyzed reaction of ynamides with enones (Ficini cycloaddition) and related nitro-olefins. Ficini previously reported the thermal formal [2+2] cycloadditions of ynamines with enones in the 1970’s,\textsuperscript{2} however, it wasn’t until 2010 that the corresponding ynamide version which required a copper-catalyst was reported by Hsung and co-workers.\textsuperscript{31} This work was closely followed by publication of a useful Ru-catalyzed enantioselective version of this reaction by Mezzetti and co-workers (Scheme 1.13).\textsuperscript{32} The bicyclic amino-cyclobutenes such as 1.24 accessed by these Ficini ynamide [2+2] technologies are interesting structures whose reactivity is largely unexplored and worthy of further study. Similar types of structures can also be formed in
a complimentary but mechanistically different Ru-catalyzed [2+2] ynamide/alkene cycloadditions reported by the Tam group at the University of Guelph.\textsuperscript{33}

\begin{center}
\textbf{Scheme 1.13} Example of a Ruthenium-catalyzed enantioselective Ficini formal ynamide [2+2] cycloaddition\textsuperscript{32}
\end{center}

In contrast to the above stepwise reactions, the Danheiser group has explored the pericyclic [2+2] reaction of ynamides with ketenes to provide aminocyclobutene structures.\textsuperscript{34} Recently, the Danheiser group has extended this ketene/ynamide reactivity to build highly functionalized aryl and heteroaryl ring systems through a pericyclic ynamide [2+2] cycloaddition/electrocyclization cascade pathway.\textsuperscript{35} The utility of this approach to build complex aryl-rings was demonstrated in a formal total synthesis of the potent antitumor agent (+)-FR900482 from their laboratory (Scheme 1.14).\textsuperscript{35a}
Scheme 1.14 Ynamide [2+2] ketene cycloaddition and electrocyclization cascade route to (+)-FR900482\(^{35a}\)

Regarding ynamide [3+2] reactivity, terminal ynamides are effective participants in the most common terminal alkyne cycloaddition reaction: the “click” copper-catalyzed alkyne-azide cycloaddition (CuAAc).\(^{36}\) The products of these reactions are amino-functionalized 1,2,3-triazoles, and as is typically observed, the copper-catalyzed variant provides exclusively the 1,4-triazole isomer. Alternatively, under Fokin’s ruthenium catalyzed conditions (RuAAC)\(^{37}\) a complete regioselectivity switch is observed providing solely the 1,5-amide substituted triazole products. Similarly, terminal ynamides are also reported to undergo related [3+2] reaction with nitrile oxides\(^{38}\) and diazoacetates\(^{38a}\) giving amide-substituted isoxazole and pyrazole structures respectively.

One particularly useful ynamide [3+2] reaction that is somewhat disguised because it yields 4-membered ring amino-β-lactams, is the Kinugasa reaction between terminal alkynyl-amides and nitrones (Scheme 1.15).\(^{39}\) Use of chiral ynamides such as 1.28 in this reaction provides important asymmetric access to syn-functionalized β-lactams which are
the core structural element of the penicillin class of antibiotics. The rationale for the observed initial [3+2] stereoselectivity is not fully understood, however, the final relative syn relationship of the β-lactam substituents is proposed to be the result of a facially selective protonation anti to the phenyl groups of the auxiliary. Finally, a very recent contribution to ynamide [3+2] reactivity is a Lewis-acid catalyzed cycloaddition of ynamides with donor-acceptor cyclopropanes to give amide-linked cyclopentenes in generally very good yield.40

Scheme 1.15 Example of an asymmetric ynamide Kinugasa [3+2] reaction and deprotection to a synthetically useful syn-amino-β-lactam39

Most ynamide [4+2] cycloadditions proceed in an ionic stepwise fashion, but these processes still possess great synthetic utility to construct nitrogen-heterocycle products via one-pot dual carbon-carbon bond-formation. Early examples of ynamide [4+2] reactivity used rhodium-catalysis to facilitate both intermolecular and intramolecular cycloadditions providing cyclic enamides or aromatic aniline products depending on the reaction conditions.41 In contrast, more interesting indole and carbazole heterocyclic ring systems can be generated via intramolecular Bergmann-type [4+2] ynamide cycloadditions (Scheme 1.16).42
Scheme 1.16 Example of a Bergmann-type ynamide formal [4+2] cycloaddition to generate a carbazole ring system\textsuperscript{42b}

A significant contribution to ynamide \([4+2]\) cycloadditions comes from the Movassaghi group enabling synthesis of highly functionalized amide-substituted quinoline heterocycles in an inverse electron demand stepwise ynamide \([4+2]\) reaction (Scheme 1.17).\textsuperscript{43} This reaction is highly regioselective due to the natural polarity of the ynamide alkyne, and is powerfully flexible and divergent considering that simple aniline amides are used as cycloaddition precursors. In addition to quinoline heterocycles, 4-amide functionalized pyridines can be prepared under these conditions via enamide activation with Tf\(_2\)O and 2-chloropyridine.

Scheme 1.17 Examples of 4-amide quinolines synthesized in Movassaghi’s ynamide \([4+2]\) reaction and proposed ionic reaction intermediate\textsuperscript{43}
In the area of multicomponent cycloadditions, a number of groups have explored the application of ynamides in the synthesis of cyclopentenones via a Pauson-Khand [2+2+1] strategy.\textsuperscript{5,44} One unique advantage of using N-alkynyl species in this reaction is that the nitrogen heteroatom creates opportunity for easy attachment of the alkene component toward intramolecular cycloadditions resulting in fused 5/5 heterocycle ring systems (Scheme 1.18).\textsuperscript{5a}

\textbf{Scheme 1.18} Generalized example of alkene tethered ynamides in intramolecular [2+2+1] cycloadditions\textsuperscript{5a}

The corresponding multicomponent 3-bond forming ynamide [2+2+2] reaction initially developed by the Witulski group\textsuperscript{45} is likely the most useful cycloaddition application of N-linked alkynes. For example, the [2+2+2] ynamide cycloaddition reaction has proved very useful to rapidly construct highly functionalized aromatic ring systems as key steps in the total synthesis of carbazole and indole containing natural products.\textsuperscript{45,46} Two illustrative examples of this strategy are the total syntheses of the antitumor antibiotic lavendamycin\textsuperscript{46a} and herbindole C\textsuperscript{46b} (Schemes 1.19 and 1.20).
Scheme 1.19 Total synthesis of lavendamycin using an ynamide [2+2+2] cycloaddition approach$^{46a}$

Scheme 1.20 Total synthesis of herbindole C using an ynamide [2+2+2] cycloaddition approach$^{46b}$
1.6 Hydro- and carbometallation reactions of ynamides

Previously in Section 1.3, it was shown how ynamides can serve as precursors to enamides via their keteniminium form. In a complimentary fashion, highly functionalized valuable enamides can also be prepared via addition of metalloid species across the ynamide alkyne. Cintrat has, for example, explored palladium-catalyzed ynamide hydro-stannylation followed by Stille coupling to regioselectively prepare enamide structures. The corresponding boron-based ynamide hydroboration/Suzuki coupling approach to provide regio- and stereo-defined access to functionalized enamides has also been reported. In addition to these classical modes of alkyne hydrometallation, a highly flexible ynamide-based approach to enamides has been developed by Lam and co-workers using a rhodium-catalyzed carbometallation strategy. This powerful process combines ynamides with organozinc or organoboron reagents to generate various tri- and tetra-functionalized enamides with complete control of substituent site attachment. Notably, this ynamide-based enamide-synthesis strategy was used to prepare an α-chiral aldehyde with a quaternary stereocentre as the key step in the total synthesis of the antifungal natural product (+)-tanikolide (Scheme 1.21).

**Scheme 1.21** Rhodium-catalyzed ynamide carbometallation approach to the antifungal natural product (+)-tanikolide
The Marek lab has developed a similar type of ynamide carbometallation which they combine with aldehyde or imine allylation in a cascade process to provide products with a reversed α-substituted enamide regioselectivity compared to Lam’s rhodium-catalyzed system.\(^{50}\) Importantly, the use of alkynyl-amides with chiral urethane groups leads to asymmetric induction in these reactions to generate previously difficult to access all-carbon quaternary stereocentres with high levels of asymmetric control (Scheme 1.22). In this initial reaction development, removal of the enamide auxiliary was accomplished by conversion to the imine followed by hydrolysis to give chiral quaternary ketone aldol products such as compound 1.53.

Scheme 1.22 Asymmetric ynamide-based carbometallation/allylation sequence to all-carbon quaternary stereocentres\(^{50b}\)

More recently, the Marek group has further extended this ynamide carbo-metallation approach to quaternary stereocentre generation to directly provide chiral aldol products from ynamides (Scheme 1.23). This new development involves oxidation of the intermediate enamide followed by enolate electrophilic trapping to give readily deprotected α-chiral amide products. From a strategic standpoint, these new ynamide-based asymmetric bond-forming reactions are a useful new tool for disconnecting important all-carbon stereodefined aldol products.
Scheme 1.23 Asymmetric ynamide-based carbo-metallation/enolate trapping sequence approach to chiral quaternary aldol products\textsuperscript{50c}

1.7 Summary

Overall, alkynyl-amides have forever changed the way the N-linked alkyne functionality is viewed. Ynamine species were once considered impractical lab curiosities, but now, with the simple addition of electron-withdrawing nitrogen protecting groups, the ynamide research field has morphed into a popular and important organic synthesis research area. As outlined in the above sections, these easy-to-prepare stable polarized alkynes have inspired development of a number of transformations wherein the ynamide functional group offers unique synthetic opportunities and advantages.

Attracted by a general interest in nitrogen heterocycles and alkaloid natural products, we saw opportunity in this area to develop new alkynyl-nitrogen reagents and make some useful contributions. Specifically, we hoped to expand the scope of the nitrogen functionality attached to the alkyne group which we believed could open-up new modes of reactivity and improve further nitrogen functional group manipulations. To this end, Chapters 2-4 of this thesis summarize our contributions to this field involving the development of new hydrazide-linked alkynes (ynehydrazides) and N,N-di-Boc ynimide species including their general synthetic utility.
1.8 References


Chapter 2: Discovery and Development of a New Ynehydrazide Alkyne Class

2.1 Introduction

As summarized in Chapter 1, N-functionalized ynamide alkyne derivatives (Figure 2.1) have gained popularity as building blocks for selective introduction of nitrogen functionality in organic molecules.\(^1\) Important features of these reagents include their stability, ease of preparation,\(^2,3,4\) and predictable reaction regioselectivity due to the nitrogen-atom polarization of the alkyne bond. As a result, these amide-linked alkynes have been used in a variety of reactions for the synthesis of nitrogen-heterocycles and amide-functionalized molecules\(^1,5\) including application in natural product total syntheses.\(^6\)

![Figure 2.1 Amide and hydrazide-substituted alkynes](image)

Despite the wealth of knowledge in this area, the related dinitrogen ynehydrazine or ynehydrazide alkyne variants are virtually unknown. The utility of hydrazines as masked amines and the overall significance of N–N bonds in drug discovery research\(^7\) including the use of hydrazines\(^8\) and alkynes\(^9\) as precursors to heterocycles, suggested that development of the ynehydrazide functional group may be a useful contribution to the ynamide field. In connection with our interest in nitrogen heterocycles, alkaloids, and related enamides,\(^10\) we were attracted to developing a robust and general synthesis of ynehydrazides to study this unexplored class of hydrazide-linked alkynes as N–N bond building blocks. Specifically, we hoped to explore the use of ynehydrazides as precursors to medicinally relevant heterocycles and potentially apply these species in orthogonol ring-forming reactions to generate heterocycles using both the alkyne and hydrazine functionalities (Figure 2.2).
Prior work in this area is limited to a few reports on the synthesis of tri-methyl substituted ynehydrazines\textsuperscript{11} which are not amenable to providing differentially substituted hydrazine derived functionalities (e.g., N–N bond containing heterocycles) and a single example of an ynehydrazide (Scheme 2.1).\textsuperscript{12} This chapter describes the discovery of a previously unexplored hydrazide-substituted alkyne class of reagents as well as preliminary investigations regarding their use in cycloaddition and cyclization reactions. A convenient new method to form C\textsubscript{sp}–N bonds was developed to rapidly prepare a variety of stable 1-hyrazido-alkynes via addition of \textit{in situ} generated lithium-acetylides to hindered diazodicarboxylates. These hydrazide-linked alkynes were found to be useful new ynamide-type reagents in the construction of hydrazine-functionalized heterocycles including synthesis of a new class of N-amino oxazolidines. A significant portion of this chapter has been published,\textsuperscript{13} and this work was the starting point for the research described in chapters 3–4 concerning the attempted use of ynehydrazides in total synthesis applications.

\textbf{Scheme 2.1} Previous examples of ynehydrazine and ynehydrazide synthesis
2.2 Results and Discussion

Based on the successful copper-promoted $^2$ $C_{sp}$–N cross-coupling approaches to generate ynamides, a general ynehydrazide synthesis was initially envisaged via coupling of a suitably tri-protected hydrazide with alkynyl bromides (Scheme 2.2). In this regard, hydrazide 2.1 was chosen as a model coupling species since it could be readily generated from phthalic anhydride in gram-scale quantities; however, unsatisfactory yields of ynehydrazide products 2.2 were observed under typical ynamide copper-amidation conditions (Scheme 2.2).

Scheme 2.2 A copper-promoted $C_{sp}$–N cross-coupling approach to ynehydrazides

An alternative approach was therefore considered through which formation of the $C_{sp}$–N bond could be achieved via addition of terminal acetylide nucleophiles to readily available diazodicarboxylates (Scheme 2.3). Despite the known examples of organometallic addition to these electrophilic nitrogen sources, reaction of alkynyl nucleophiles across the N=N bond of these species has not been reported as a strategy to generate $C_{sp}$–N bonds. Such an approach is a potentially attractive one given its generality, the availability of the reagents, and the stabilizing effects of the electron-withdrawing carbamate group on the product ynehydrazides.

Scheme 2.3 Direct formation of ynehydrazide $C_{sp}$–N bonds via lithium-acetylide addition to diazodicarboxylates
Initial results toward generating ynehydrazides using *in situ* generated lithium-acetylides with commercially available diethyl azodicarboxylate (DEAD) and dibenzyl azodicarboxylate (DBnAD) resulted in complex reaction mixtures and generated only trace amounts of ynehydrazide products. In these cases, acetylide addition to the carbamate functionality instead of across the desired N=N bond was observed as a major side product. To avoid this competitive carbamate addition, more sterically hindered diazodicarboxylate esters were employed. Thus, reaction of diisopropyl azodicarboxylate (DIAD) with TMS-acetylide led to isolation of ynehydrazide 2.3 in moderate yield, and optimally, use of the more sterically hindered di-t-butylazodicarboxylate (DBAD) led to high yield formation of Boc-ynehydrazide 2.4 (Scheme 2.3).

The scope of this protocol was then investigated and a wide range of alkynes were found to undergo addition to DBAD and DIAD via the corresponding lithiated intermediates to provide novel hydrazide-substituted alkynes (Scheme 2.4). The reaction scope includes formation of aryl, heteroaryl, alkyl, benzyl and alkenyl substituted ynehydrazides with isolated yields of these compounds being generally good for addition to DBAD (Compounds 2.8-2.19) and lower observed yields in additions to DIAD (Compounds 2.5-2.7). Limitations include the incompatibility of ethyl propiolate, and the inability to produce terminal ynehydrazides directly from commercially available terminal organometallic acetylides (e.g., ethynylmagnesium bromide).
**(a)** General procedure: 1.2 mmol *n*-BuLi added to 1.0 mmol alkyne in 5 mL THF at -78 °C under N<sub>2</sub> followed by addition of 1.5 mmol DBAD dissolved in 3 mL THF and allowed to warm to rt over 30 mins. (b) 1.2 mmol LDA used in place of *n*-BuLi.

**Scheme 2.4** Scope of ynehydrazide synthesis

To overcome these drawbacks, TBAF mediated silyl group deprotection of the TMS-protected ynehydrazides 2.3 and 2.4 provided a rapid and convenient route to terminal ynehydrazides 2.20-2.21 in good yield (Scheme 2.5). In turn, terminal ynehydrazide 2.21 can be used to access other functionalized ynehydrazides such as the “push-pull” ester-substituted ynehydrazide 2.22 which was not directly accessible via ethyl propiolate acetylide addition to diazodicarboxylates.
Overall, ynehydrazides $2.3-2.22$ were observed to be generally quite stable to silica gel chromatography and storage and can conveniently be kept on the bench-top for months with little to no decomposition as monitored by TLC and $^1$H NMR. Exceptions include compounds $2.12$, $2.17$, and $2.18$ which were observed to decompose at room temperature after two days. However, storage of these compounds in a -15 °C freezer enhanced their lifespan to several months.

Because ynehydrazides are an unexplored compound class, a study of their properties and synthetic utility was next undertaken, with a focus on using the alkyne and hydrazide functionalities to form heterocycles using metal catalyzed transformations. Initial studies focused on the terminal ynehydrazides $2.20-2.21$ which were found to participate in room temperature copper-catalyzed “click-type” [3+2] cycloadditions with azides (Scheme 2.6) and a nitrile oxide (Scheme 2.7). To supply material for these studies, batch preparation (2 x 3 mmol scale) of Boc-carbamate protected terminal ynehydrazide $2.21$ was undertaken to provide 770 mg of this alkyne in an overall yield of 65% for two steps (see experimental section). Consistent with prior work on CuAAC reactions, these terminal ynehydrazide examples were completely regioselective to give 4-hydrazide-1,2,3-triazoles $2.23-2.28$ and 3-hydrazide isoxazole $2.29$ respectively.
Terminal ynehydrazide 2.20 also participated in a palladium-catalyzed Larock-type heterocyclization with 2-iodoaniline to provide 2-hydrazide functionalized indole 2.29 in moderate yield (Scheme 2.8). Unfortunately, this Larock-indole synthesis was only successful in the terminal ynehydrazide case, and attempts to generate 3-substituted indoles from internal ynehydrazides were entirely unsatisfactory under these conditions. Similarly, this reaction failed to provide a 2-hydrazide functionalized benzoxazole with a 2-bromo-phenol. Despite this, the reactions shown in Schemes 2.6-2.8 provided proof-of-concept examples of how ynehydrazides can function as hydrazide building blocks and represent new hydrazide substituted heterocycles. Nitrogen-substituted heterocycles 2.22-2.29 would be difficult to prepare under alternative conditions (e.g., cross-coupling of hydrazides or a nitration/reduction/diazotization sequence) and inspired us to further explore the utility of ynehydrazides with a focus on using internal substituted hydrazide-alkynes.
Scheme 2.8 Synthesis of a 2-hydrazide substituted indole via palladium-catalyzed terminal ynehydrazide heterocyclization

In this regard, attempted [3+2] reaction of internal ynehydrazides with azides under copper-catalysis or thermally in the absence of catalyst failed to produce triazoles. In contrast, internal ynehydrazides were found to undergo regioselective room-temperature ruthenium-catalyzed azide/alkyne cycloadditions (RuAAC)$^{16}$ to yield highly functionalized 1,2,3-triazoles (Scheme 2.9). In agreement with Fokin’s previous observations of ruthenium catalyzed 1,3-dipolar cycloadditions of this type, a complete regioselectivity switch is observed providing exclusively the 5-hydrazide isomers shown. The 1,5-selectivity observed using ruthenium catalysis in these [3+2] reactions is presumed to occur via an electronically controlled mechanism.$^{16}$

Scheme 2.9 Ruthenium-catalyzed ynehydrazide and azide [3+2] cycloadditions

Similarly, internal ynehydrazides also participated in [3+2] reactions with a nitrile oxide under Fokin’s Cp*RuCl(cod) catalyzed conditions for isoxazole generation (Scheme 2.10). Again, a complete regioselectivity switch is observed for this Ru-catalyzed
reaction versus the Cu-catalyzed variant and provides exclusively the 4-hydrazone isoxazole products shown.

Scheme 2.10 Ruthenium-catalyzed ynehydrazide and nitrile oxide [3+2] cycloadditions

As a result of our long-standing interest in the Povarov reaction,\textsuperscript{17,18} we became interested in whether ynehydrazides could participate as the electron rich $2\pi$ fragment to generate hydrazide-functionalized dihydroquinolines (Scheme 2.11). Although we observed dihydroquinoline formation using our multicomponent Povarov [4+2] conditions\textsuperscript{17e,f} with ynehydrazide 2.14 by ESI-MS analysis of the crude reaction mixture, $^1$H NMR analysis indicated poor conversion and no dihydroquinoline product 2.41 was cleanly isolated.

Scheme 2.11 Attempted Povarov [4+2] reaction with ynehydrazides

Alternatively, the Movassaghi group has reported a similar type of step-wise inverse electron demand [4+2] reaction which generates pyridines and quinolines from convenient amide starting materials (see Chapter 1 section 1.5). A significant advantage of this strategy is the direct formation of aromatic quinolines with electron rich alkynes versus traditional Povarov reactions which produce tetrahydroquinolines with olefins and dihydroquinolines with alkynes. Considering that ynamides participate in Movassaghi’s [4+2] reaction we were interested in exploring ynehydrazides under these conditions as a
route to regioselectively generate hydrazide-functionalized quinolines. Our first attempt in this area used Boc-protected DBAD derived ynehydrazide 2.14 (R³= C₆H₁₃, R⁴= t-Bu) which did not lead to a productive reaction presumably due to the presence of triflic acid which could deprotect the carbamate groups and lead to ynehydrazide decomposition (Scheme 2.12). Based on this assumption, we switched to DIAD derived ynehydrazides 2.5 – 2.7 which possess more robust isopropyl carbmates and we were pleased to observe successful cycloaddition with these hydrazide-alkynes to regioselectively generate quinolines 2.42 - 2.44 (Scheme 2.12).

**Scheme 2.12** Ynehydrazide [4+2] approach to N-functionalized quinolines

Based on this success, other ynehydrazide [4+2] reactions with electron-poor dienes such as a 1,3,5-triazine and a coumalate were attempted (Scheme 2.13). Despite the known use of these dienes in cycloaddition reactions with electron-rich ynamines, it appears that ynehydrazides may be too stable to efficiently react as only trace product was detected in these reactions.

**Scheme 2.13** Unsuccessful [4+2] ynehydrazide cycloadditions with a 1,3,5-triazine and a coumalate
We next turned our attention to intramolecular ynehydrazide cyclization strategies to access heterocycles. In this regard, we functionalized the ynehydrazide nitrogen with allyl and propargyl groups toward possible hydrazide-alkyne Pauson-Khand [2+2+1], Bergman [4+2] cyclization or rhodium-catalyzed [2+2+2] cycloaddition reactivity (Scheme 2.14). These conditions were unfortunately unsatisfactory, however, reaction optimization was not aggressively pursued and it is reasonable to assume that further experimentation in these areas could enable an ynehydrazide approach to interesting pyrazoline or indolazine heterocycles.

![Scheme 2.14 Attempted [2+2+1], [2+2+2] and Bergman cycloaddition reactions with ynehydrazides](image_url)

In contrast, N-functionalized ynehydrazide 2.50 was accessed in a single pot via acetylide addition to DBAD followed by in situ capping of the intermediate lithium amide with an acyl chloride (Scheme 2.15). Participation of this compound in a 6-exo-dig radical cyclization gave compound 2.51 as a mixture of olefin isomers. The alkene geometry in this example is inconsequential since acidic Boc-carbamate deprotection led to isolation of the more useful phthalizinone heterocycle 2.52 (Scheme 2.15).
Scheme 2.15 N-functionalized ynehydrazide synthesis and application in phthalizinone formation

Furthermore, an interesting gold-catalyzed intramolecular cyclization of Boc-protected ynehydrazides provided access to a variety of previously unknown N-amino oxazolone heterocycles (Scheme 2.16). One potential application of these new 5-membered nitrogen-heterocycles could be as peptide surrogates since hydrazide heterocycles have recently attracted attention in this regard.\textsuperscript{19} As an illustration, compound 2.53 was acylated to give an imide which was Boc-deprotected with catalytic Mg(ClO\textsubscript{4})\textsubscript{2} to give benzamide oxazolone 2.60 (Scheme 2.17).

Scheme 2.16 Synthesis of N-amino oxazolones via Au-catalyzed intramolecular ynehydrazide cyclization
Scheme 2.17 N-functionalization and deprotection of an N-amino oxazolone

Other synthetic manipulations of these new N-amino heterocycles are shown below in Schemes 2.18 and 2.19. For example, these ynehydrazide derived N-amino oxazolones can serve as precursors to other related heterocycles such as the corresponding N-amino-oxazolidinone 2.61 via hydrogenation of 2.56 (Scheme 2.18). Interestingly, amino-oxazolidinone 2.59 contains a 1-amino-diene component and as a result was found to participate in a Diels-Alder reaction with N-phenyl maleimide (Scheme 2.19). This reaction provided a single isomer which is presumed to be the endo adduct 2.62 and demonstrates how this previously unexplored class of ynehydrazide-derived heterocycles may be synthetically useful.

Scheme 2.18 Hydrogenation of 2.56 to give N-amino oxazolidinone 2.61

Scheme 2.19 Diels-Alder reaction of N-amino oxazolone 2.59

Significantly, ynehydrazide derived Boc-hydrazide functionalized heterocycles can be readily deprotected to reveal and apply hydrazine reactivity toward our original goal of exploiting both alkyne and hydrazine units in orthogonal ring-forming reactions. For example, $N,N'$-di-Boc hydrazide functionalized heterocycles such as 2.23 and 2.28 were
rapidly transformed into N-triazole and N-isoxazole functionalized pyrazoles 2.63 and 2.64 via simple addition of 1,3-dicarboxyls and anhydrous HCl (Scheme 2.20). In a related fashion, 1,2,3-triazole 2.32 and isoxazole 2.39 were directly converted in one-pot to N-functionalized 1,2,4-triazoles 2.65-2.66 via treatment with formamide and anhydrous HCl (Scheme 2.21). Overall, these heterocycle targets would be difficult to disconnect via alternative chemistry and demonstrate the significant promise of ynehydrazides for use in heterocycle synthesis.

**Scheme 2.20** One-pot N-heterocycle functionalized pyrazole synthesis from ynehydrazide derived heterocycles

**Scheme 2.21** One-pot N-heterocycle functionalized 1,2,4-triazole synthesis from ynehydrazide derived heterocycles
2.3 Conclusion

In summary, we have developed a convenient new method of generating \( \text{C}_v \text{N} \) bonds from commercially available terminal alkynes and diazodicarboxylates which provides rapid access to a previously unexplored class of ynehydrazide heteroatom-linked alkyne reagents. The ynehydrazide species thus formed were observed to be stable, storable compounds and preliminary results show that these di-nitrogen linked alkynes are useful reagents to selectively install hydrazine units into medicinally important heterocycles such as quinolines, triazoles and isoxazoles. Notably, introduction of hydrazide groups via ynehydrazide cycloaddition enabled hydrazine cyclocondensations to build N–N bond containing heterocycles such as pyrazoles.

Furthermore, intramolecular cyclizations with ynehydrazides furnished other interesting heterocycles including a phthalazinone and a new class of N-amino oxazolone 5-membered nitrogen heterocycles. In addition, there is further potential for using ynehydrazides in other cycloaddition/cyclization areas. Specifically, it would be valuable to develop \([2+2+2]\) and \([2+2+1]\) reactions using ynehydrazides toward pyrazoline and indazoline structures and future work in this regard should be pursued. Importantly, the work described above in this chapter provided inspiration for investigating N-substituted alkynes in natural product total synthesis as described in chapters 3 and 4 of this thesis.

2.4 Experimental Section

Copies of \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra for all new compounds listed above including select \(^1\text{D}\) NOESY’s for regioselectivity assignments can be found in Appendix 1. THF was dried over sodium benzophenone-ketyl and distilled fresh under nitrogen atmosphere before use and transferred via syringe using standard techniques unless otherwise stated. All reagents (unless otherwise stated below) including copper salts, \(\text{Cp}^*\text{RuCl(COD)}\), \(\text{PPh}_3\text{AuNTf}_2\), \(1,3\)-dicarboxyls, TBAF (tetrabutylammonium fluoride 1 M in THF), benzyl-azide, terminal alkynes, diazodicarboxylates, KHMDS (0.5 M in toluene) and \(n\)-BuLi (2.5 M in hexanes) were purchased from Aldrich or VWR and used as received.
iodo-N-methylaniline (Scheme 2.8) was prepared from 2-iodo-aniline (Aldrich) according to a literature protocol;\textsuperscript{20} and N-hydroxybenzimidoyl chloride (Schemes 2.7 \& 2.10) was prepared from syn-benzaldehyde oxime (Aldrich) according to a known procedure.\textsuperscript{21} LDA (lithium diisopropylamide) was prepared fresh according to a standard literature procedure.\textsuperscript{22} Aryl azides (Schemes 2.6 \& 2.9) were prepared by diazotization of anilines and substitution with sodium azide as per the literature procedure for preparation of phenyl-azide.\textsuperscript{23} Methyl 2-azidoacetate\textsuperscript{24} and tert-butyl (2-azidoethyl)carbamate\textsuperscript{25} were prepared by known protocols. NMR solvent (CDCl\textsubscript{3} with TMS internal standard) was purchased from Cambridge Isotopes Lab Inc. and used as received.

All products were characterized by \textsuperscript{1}H NMR and \textsuperscript{13}C NMR, IR and HRMS. Regioselectivity assignments for compounds 2.23-2.40 and 2.64 were determined by \textsuperscript{1}H-\textsuperscript{13}C HSQC, 1D NOESY, and 2D NOESY experiments. \textsuperscript{1}H NMR and \textsuperscript{13}C NMR were recorded on Varian Mercury 300 MHz, or 400 MHz spectrometers. \textsuperscript{1}H-\textsuperscript{13}C HSQC and 1D NOESY spectra were recorded on a Varian Mercury 400 MHz spectrometer and 2D-NOESY experiments were recorded on a Varian Mercury 300 MHz spectrometer. Chemical shifts are expressed in ppm values and \textsuperscript{1}H NMR spectra are referenced to 0.00 ppm for Me\textsubscript{4}Si (TMS) and \textsuperscript{13}C NMR spectra are referenced to 77.00 ppm for CDCl\textsubscript{3}. Peak multiplicities are designated by the following abbreviations: s, singlet; br.s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; r, rotomers; J, coupling constant in Hz rounded to 0.5 Hz. If a coupling pattern can be assigned as a combination of multiplicities, then the listed abbreviations are combined to provide an appropriate descriptor for the observed patterns (e.g., dt - doublet of triplets). IR spectra were obtained on a Shimadzu FTIR-8400S with samples loaded as thin films on NaCl plates neat or with CH\textsubscript{2}Cl\textsubscript{2} as indicated. Mass spectra were obtained by the University of Toronto mass spectral facility (AIMS); high resolution mass spectra (HRMS) were recorded on an AEI MS3074 spectrometer. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Flash column chromatography on silica gel (60 Å, 230-400 mesh, obtained from Silicycle Inc.) was performed with reagent grade ethyl acetate and hexanes as eluent. Analytical thin-layer chromatography (TLC)
was performed on pre-coated aluminum-backed silica gel plates (Alugram SIL G/UV254 purchased from Rose Scientific Limited or Silicycle Inc.) and visualized with a UV lamp (254 nm) or KMnO₄ stain and heating.

**Representative procedure for synthesis of ynehydrazides via addition of terminal alkynes to diazodicarboxylates (Schemes 2.3 & 2.4):**

In a nitrogen flushed 50 mL flask capped with a rubber septum was charged THF (5 mL) and ethynyltrimethylsilane (98 mg, 1.0 mmol, 1.0 eq.) under N₂ and cooled to -78 °C in a dry ice/acetone bath. A solution of n-BuLi (0.48 mL of a 2.5 M sol’n in hexanes, 1.2 mmol, 1.2 eq.) was then added dropwise over 1-2 mins and the resulting mixture stirred at -78 °C for 15 mins. A solution of DBAD (di-t-butyl-azodicarboxylate, 345 mg, 1.5 mmol, 1.5 eq.) in THF (3 mL) was then added dropwise over 1-2 mins and the cooling bath removed and the mixture allowed to warm to room temperature over 30 mins. The reaction mixture was then quenched by addition of sat’d NH₄Cl(aq) (10 mL) and diluted with ethyl acetate (100 mL) and water (10 mL) and the layers separated. The organic extract was dried (MgSO₄), filtered, and concentrated in vacuo. The resulting crude residue was purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0–100% EtOAc) providing 261 mg (80% yield) of Compound 2.4 (Scheme 2.3) as a clear oil.

**Diisopropyl-1-((trimethylsilyl)ethynyl)hydrazine-1,2-dicarboxylate (Compound 2.3, Scheme 2.3):**

Isolated yield= 124 mg (41%) as a pale yellow oil. Rf= 0.30 (20% EtOAc/hexanes); IR (neat, cm⁻¹) 3302 (br.), 2983, 2941, 2901, 2881, 2366, 2339, 2183, 1750-1712 (br.), 1688, 1635, 1469; ¹H NMR (300 MHz, CDCl₃) δ ppm 6.68 (1H, br. s.), 4.92 - 5.09 (2H, m), 1.31 (6H, d, J=6.0 Hz), 1.28 (6H, d, J=6.5 Hz), 0.19 (9H, s); ¹³C NMR (75 MHz, CDCl₃) δ ppm 154.6, 153.6, 72.9, 70.7, 69.9, 68.3, 22.0, 21.8, 0.00; HRMS (m/z): [M + H]⁺ for C₁₃H₂₇N₂O₄Si, calcd, 301.1578; found, 301.1580.
Di-tert-butyl 1-(((trimethylsilyl)ethynyl)hydrazine-1,2-dicarboxylate (Compound 2.4, Scheme 2.3):

Isolated yield= 261 mg (80%) as a clear oil. R_f = 0.42 (20% EtOAc/hexanes); IR (neat, cm⁻¹) 3310, 2981, 2935, 2902, 2182, 1755, 1724, 1477, 1457, 1395, 1370, 1326, 1250, 1151; ¹H NMR (400 MHz, CDCl₃) δ ppm 6.63 (1H, br.s.), 1.40 - 1.57 (18H, m), 0.18 (9H, s); ¹³C NMR (100 MHz, CDCl₃) δ ppm 153.8, 152.6, 94.3, 82.3, 73.3, 28.1, 27.8, -0.02; HRMS (m/z): [M + Na]⁺ for C₁₅H₂₈N₂O₄Si, calcd, 351.1713; found, 351.1710.

Diisopropyl 1-((4-fluorophenyl)ethynyl)hydrazine-1,2-dicarboxylate (Compound 2.5, Scheme 2.4):

Isolated yield= 75 mg (23%) as a clear oil. R_f = 0.22 (20% EtOAc/hexanes); IR (neat, cm⁻¹) 3296, 3109, 2982, 2935, 2902, 2182, 1755, 1724, 1477, 1457, 1395, 1370, 1326, 1250, 1151; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.40 (2H, dd, J=8.5, 5.5 Hz), 6.99 (2H, dd, J=8.5 Hz), 6.94 (1H, br. s.), 5.04 (2H, dq, J=12.5, 6.0 Hz), 1.34 (6H, d, J=6.0 Hz), 1.30 (6H, d, J=6.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ ppm 162.6 (d, J=248 Hz, C-F), 154.9, 153.8, 133.8, 118.8, 115.7 (d, J=22 Hz, C-C-F), 105.0, 81.5, 73.2, 71.0, 22.2, 22.0; ¹⁹F NMR (282 MHz, CDCl₃) δ ppm -111.84 (s, 1 F); HRMS (m/z): [M + H]⁺ for C₁₆H₁₉FN₂O₄, calcd, 313.2126; found, 313.2121.

Diisopropyl 1-(thiophen-3-yethynyl)hydrazine-1,2-dicarboxylate (Compound 2.6, Scheme 2.4):

Isolated yield= 75 mg (24%) as a yellow solid. m.p.= 73-77 °C; R_f = 0.20 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3296, 3109, 2982, 2935, 2902, 2182, 1755, 1724, 1477, 1457, 1395, 1370, 1326, 1244, 1182, 1103; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.45 (1H, dd, J=3.0, 1.0 Hz), 7.21 - 7.29 (1H, m), 7.11 (1H, dd, J=5.0, 1.0 Hz), 6.92 (1H, br. S.), 5.03 (2H, m), 1.33 (6H, d, J=6.0 Hz), 1.29 (6H, d, J=6.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ ppm 154.7, 153.6, 130.2, 129.0, 125.1, 121.3, 81.0, 73.0, 70.7, 66.9, 22.0, 21.8; HRMS (m/z): [M + H]⁺ for C₁₄H₁₈N₂O₄S, calcd, 311.1055; found, 311.1060.
Diisopropyl 1-(oct-1-yn-1-yl)hydrazine-1,2-dicarboxylate (Compound 2.7, Scheme 2.4):

\[ \text{H}_3\text{C}_8\text{N} = \underbrace{\text{CO}_2\text{Pr}}_{\text{Pr}} \]

Isolated yield= 105 mg (34%) as a clear oil. \( R_f = 0.29 \) (20% EtOAc/hexanes); IR (neat, cm\(^{-1}\)) 3300, 2983, 2958, 2934, 2859, 2268, 1722, 1713, 1468, 1377, 1299, 1239, 1183, 1106, 1039; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 6.88 (1H, br. s.), 4.91 - 5.07 (2H, m), 2.30 (2H, t, \( J=7.0 \text{ Hz} \)), 1.47 - 1.56 (2H, m), 1.35 - 1.44 (2H, m), 1.29 - 1.34 (8H, m), 1.24 - 1.28 (8H, m), 0.89 (3H, t, \( J=7.0 \text{ Hz} \)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) ppm 155.0, 154.4, 73.1, 72.6, 71.6, 70.6, 31.5, 28.8, 28.6, 22.8, 22.1, 22.0, 18.6, 14.2; HRMS (m/z): [M + H]\(^+\) for C\(_{16}\)H\(_{18}\)N\(_2\)O\(_4\), calcd, 313.2126; found, 313.2121.

Di-tert-butyl 1-(phenylethynyl)hydrazine-1,2-dicarboxylate (Compound 2.8, Scheme 2.4):

\[ \text{Ph} = \underbrace{\text{N}}_{\text{Boc}} \]

Isolated yield= 216 mg (65%) as a yellow oil. \( R_f = 0.34 \) (20% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3054, 2987, 2686, 2411, 2306, 1741, 1738, 1421, 1151; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 7.35 - 7.42 (2H, m), 7.24 - 7.30 (3H, m), 6.84 (1H, br. s.), 1.53 (9H, s), 1.50 (9H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) ppm 154.3, 152.9, 131.3, 128.4, 127.9, 123.1, 84.5, 82.6, 82.5, 71.8, 28.4, 28.1; HRMS (m/z): [M + Na]\(^+\) for C\(_{18}\)H\(_{24}\)N\(_2\)O\(_4\), calcd, 355.1628; found, 355.1638.

Di-tert-butyl 1-(p-tolylethynyl)hydrazine-1,2-dicarboxylate (Compound 2.9, Scheme 2.4):

\[ \text{Me} = \underbrace{\text{N}}_{\text{Boc}} \]

Isolated yield= 222 mg (64%) as an off-white solid. m.p.= 91-94 °C; \( R_f = 0.32 \) (20% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3311 (br.), 3056, 3004, 2982, 2934, 2255, 1740, 1734, 1513, 1478, 1457, 1395, 1369, 1311, 1265, 1247, 1150; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) ppm 7.29 (2H, d, \( J=7.5 \text{ Hz} \)), 7.08 (2H, d, \( J=8.0 \text{ Hz} \)), 6.86 (1H, br. s.), 2.32 (3H, s), 1.52 (9H, s), 1.49 (9H, s); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) ppm 154.3, 153.0, 138.0, 131.4, 129.2, 120.0, 84.4, 82.5, 81.8, 71.6, 28.4, 28.1, 21.6; HRMS (m/z): [M + Na]\(^+\) for C\(_{19}\)H\(_{26}\)N\(_2\)O\(_4\), calcd, 369.1791; found, 369.1784.
Di-tert-butyl 1-((4-fluorophenyl)ethynyl)hydrazine-1,2-dicarboxylate (Compound 2.10, Scheme 2.4):

Isolated yield= 148 mg (42%) as a yellow wax. \( R_f = 0.32 \) (20% EtOAc/hexanes); IR (CH\textsubscript{2}Cl\textsubscript{2}, cm\textsuperscript{-1}) 3308 (br.), 3057, 2982, 2936, 2874, 2257, 1888, 1743, 1732, 1602, 1510, 1479, 1456, 1394, 1369, 1313, 1248, 1155; \(^1\text{H} \text{NMR} \) (400 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 7.39 (2H, m), 6.98 (2H, dd, \( J_1=9.0 \) Hz, \( J_2=9.0 \) Hz), 6.86 (1H, br. s.), 1.53 (9H, s), 1.51 (9H, s); \(^{13}\text{C} \text{NMR} \) (100 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 162.4 (d, \( J=248 \) Hz, C-F), 154.3, 152.6, 133.4, 119.1, 115.6 (d, \( J=22 \) Hz, C-C-F), 84.6, 82.6, 82.1, 70.7, 28.3, 28.1; \(^{19}\text{F} \text{NMR} \) (282 MHz, CDCl\textsubscript{3}) \( \delta \) ppm -112.37 (1F, s); HRMS \((m/z)\): [M + Na]\(^+\) for C\textsubscript{18}H\textsubscript{23}FN\textsubscript{2}O\textsubscript{4}, calcd, 373.1534; found, 373.1526.

Di-tert-butyl 1-((2-bromophenyl)ethynyl)hydrazine-1,2-dicarboxylate (Compound 2.11, Scheme 2.4):

1.2 eq. LDA used instead of \( \text{n-BuLi} \). Isolated yield= 120 mg (29%) as a yellow oil. \( R_f = 0.29 \) (20% EtOAc/hexanes); IR (neat, cm\textsuperscript{-1}) 3320 (br.), 3057, 2982, 2935, 2255, 1768-1698 (br., m), 1148, 1048, 1035; \(^1\text{H} \text{NMR} \) (300 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 7.54 (1H, dd, \( J=8.0, 1.0 \) Hz), 7.39 (1H, d, \( J=7.5 \) Hz), 7.21 (1H, td, \( J=7.5, 1.0 \) Hz), 7.04 - 7.13 (1H, m), 6.83 (1H, br. s.), 1.41 - 1.58 (18H, m); \(^{13}\text{C} \text{NMR} \) (75 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 154.2, 152.6, 132.6, 132.5, 128.8, 127.1, 125.5, 124.7, 86.9, 84.8, 82.7, 70.9, 28.4, 28.2; HRMS \((m/z)\): [M + NH\textsubscript{4}]\(^+\) for C\textsubscript{18}H\textsubscript{23}BrN\textsubscript{2}O\textsubscript{4}, calcd, 428.11849; found, 428.11903.

Di-tert-butyl 1-(pyridin-2-ylethynyl)hydrazine-1,2-dicarboxylate (Compound 2.12, Scheme 2.4):

Isolated yield= 100 mg (30%) as a yellow solid. m.p.= 142-146 °C; \( R_f = 0.12 \) (5% MeOH/CH\textsubscript{2}Cl\textsubscript{2}); IR (CH\textsubscript{2}Cl\textsubscript{2}, cm\textsuperscript{-1}) 3142, 3058, 2977, 2935, 2782, 2255, 1748, 1729, 1588, 1562, 1538, 1476, 1456, 1394, 1368, 1311, 1250, 1150; \(^1\text{H} \text{NMR} \) (400 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 8.54 (2H, d, \( J=4.5 \) Hz), 8.17 (1H, br. s.), 7.62 (1H, m), 7.38 (1H, br. s.), 7.17 (1H, m), 1.52 (9H, br. s.), 1.48 (9H, s); \(^{13}\text{C} \text{NMR} \) (100 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 154.3, 152.5, 149.8, 143.7, 136.3, 126.6, 122.3,
84.7, 83.0, 82.3, 71.7, 28.4, 28.1; HRMS (m/z): [M + H]^+ for C_{17}H_{23}N_{3}O_{4}, calcd, 334.1761; found, 334.1767.

Di-tert-butyl 1-(thiophen-3-ylethynyl)hydrazine-1,2-dicarboxylate (Compound 2.13, Scheme 2.4):

\[
\begin{align*}
&\text{Isolated yield= 185 mg (55%) as a yellow solid. m.p. = 88-95 °C; } \\
&R_f = 0.29 (20\% \text{ EtOAc/hexanes); IR (CH}_2\text{Cl}_2, \text{ cm}^{-1}) 3398, 3325, 3111, 3054, 2984, 1935, 2367, 2303, 2253, 1748, 1728, 1476, 1395, 1371, 1308, 1150; \\
&^1\text{H NMR (400 MHz, CDCl}_3\text{) } \delta \text{ ppm 7.38 (1H, br. s.), 7.21 (1H, m), 7.07 (1H, d, } J=5.0 \text{ Hz), 6.91 (1H, br. s.), 1.50 (9H, s), 1.48 (9H, s); } \\
&^13\text{C NMR (100 MHz, CDCl}_3\text{) } \delta \text{ ppm 154.3, 152.9, 130.3, 128.5, 125.2, 121.8, 84.5, 82.5, 81.8, 66.6, 28.4, 28.1; } \\
&\text{HRMS (m/z): [M + Na]^+ for C}_{16}H_{22}N_{2}O_{4}S, \text{ calcd, 361.1192; found, 361.1189.}
\end{align*}
\]

Di-tert-butyl 1-(oct-1-yn-1-yl)hydrazine-1,2-dicarboxylate (Compound 2.14, Scheme 2.4):

\[
\begin{align*}
&\text{Isolated yield= 255 mg (75%) as a yellow oil. R}_f = 0.38 (20\% \text{ EtOAc/hexanes); IR (neat, cm}^{-1}) 3312, 2980, 2959, 2934, 2860, 2266, 1744, 1717, 1479, 1456, 1395, 1370, 1306, 1248, 1151; \\
&^1\text{H NMR (300 MHz, CDCl}_3\text{) } \delta \text{ ppm 6.67 (1H, br. s.), 2.27 (2H, t, } J=7.0 \text{ Hz), 1.47 (9H, s), 1.46 (9H, s), 1.30 - } \\
&1.44 (4H, m), 1.20 - 1.30 (4H, m), 0.87 (3H, t, } J=7.0 \text{ Hz); } \\
&^13\text{C NMR (75 MHz, CDCl}_3\text{) } \delta \text{ ppm 154.3, 153.5, 83.8, 82.2, 73.5, 71.1, 31.6, 28.9, 28.7, 28.3, 28.1, 22.8, 18.7, 14.3; } \\
&\text{HRMS (m/z): [M + Na]^+ for C}_{18}H_{32}N_{2}O_{4}, \text{ calcd, 363.2254; found, 363.2251.}
\end{align*}
\]

Di-tert-butyl 1-(cyclohexylethynyl)hydrazine-1,2-dicarboxylate (Compound 2.15, Scheme 2.4):

\[
\begin{align*}
&\text{Isolated yield= 253 mg (75%) as a white waxy semi-solid. R}_f = 0.36 (20\% \text{ EtOAc/hexanes); IR (CH}_2\text{Cl}_2, \text{ cm}^{-1}) 3400, 3054, 2985, 2935, 2857, 2686, 2307, 2259, 1740, 1733, 1478, 1394, 1369, 1265, 1150; \\
&^1\text{H NMR (400 MHz, CDCl}_3\text{) } \delta \text{ ppm 6.69 (1H, br. s.), 2.48 - 2.57 (1H, m), 1.65 - 1.83 (4H, m), 1.50 (9H, s), } \\
&1.49 (9H, s), 1.43 - 1.46 (2H, m), 1.24 - 1.40 (4H, m); \\
&^13\text{C NMR (75 MHz, CDCl}_3\text{) } \delta \text{ ppm }
\end{align*}
\]
154.4, 153.5, 83.8, 82.2, 74.8, 74.0, 32.8, 28.9, 28.3, 28.1, 26.2, 24.8; HRMS (m/z): [M + Na]+ for C_{18}H_{30}N_{2}O_{4}, calcd, 361.2097; found, 361.2092.

**Di-tert-butyl 1-(4-((tert-butylidimethylsilyl)oxy)but-1-yn-1-yl)hydrazine-1,2-dicarboxylate (Compound 2.16, Scheme 2.4):**

\[ \text{TBSO} \quad \equiv \quad \begin{array}{c} \text{N} \\ \text{HN-Boc} \end{array} \]

Isolated yield= 270 mg (65%) as an orange oil. R_f = 0.40 (20% EtOAc/hexanes); IR (neat, cm\(^{-1}\)) 3311, 2979, 2931, 2858, 2268, 2245, 1742, 1711, 1472, 1464, 1394, 1354, 1313, 1267, 1151, 1106; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 6.69 (1H, br. s.), 3.73 (2H, t, \(J=7.5\) Hz), 2.52 (2H, t, \(J=7.5\) Hz), 1.36 - 1.63 (18H, m), 0.89 (9H, s), 0.07 (6H, s); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) ppm 159.3, 158.4, 89.1, 87.4, 79.5, 73.2, 67.3, 33.4, 33.2, 31.2, 28.1, 23.6, 0.00; HRMS (m/z): [M + NH\(_4\)]\(^+\) for C\(_{20}\)H\(_{38}\)N\(_2\)O\(_5\)Si, calcd, 432.28937; found, 432.28786.

**Di-tert-butyl 1-(3-phenylprop-1-yn-1-yl)hydrazine-1,2-dicarboxylate (Compound 2.17, Scheme 2.4):**

\[ \text{Ph} \quad \equiv \quad \begin{array}{c} \text{N} \\ \text{HN-Boc} \end{array} \]

Isolated yield= 183 mg (53%) as a yellow oil. R_f = 0.28 (20% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3319, 2981, 2935, 2286, 2212, 1742, 1729, 1496, 1479, 1456, 1394, 1369, 1313, 1249, 1151, 1051, 1022; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.33 - 7.39 (2H, m), 7.27 - 7.32 (2H, m), 7.22 (1H, m), 6.69 (1H, br. s.), 3.74 (2H, s), 1.51 (9H, s), 1.49 (9H, s); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 154.4, 153.3, 137.1, 128.6, 128.1, 126.7, 84.2, 82.4, 75.8, 68.5, 28.4, 28.2, 25.0; HRMS (m/z): [M + Na]+ for C\(_{19}\)H\(_{26}\)N\(_2\)O\(_4\), calcd, 369.1792; found, 369.1784.

**Di-tert-butyl 1-(cyclohex-1-en-1-ylethynyl)hydrazine-1,2-dicarboxylate (Compound 2.18, Scheme 2.4):**

\[ \equiv \quad \begin{array}{c} \text{N} \\ \text{HN-Boc} \end{array} \]

Isolated yield= 294 mg (87%) as a yellow oil. R_f = 0.36 (20% EtOAc/hexanes); IR (neat, cm\(^{-1}\)) 3313, 2980, 2935, 2253, 2210, 1752, 1707, 1478, 1456, 1394, 1358, 1313, 1247, 1150, 1049, 1019; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 6.69 (1H, br. s.), 5.96 - 6.09 (1H, br. s.), 2.05 - 2.16 (4H, m), 1.54 - 1.67 (4H, m), 1.51 (9H, s), 1.49 (9H, s); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\)
ppm 154.4, 153.0, 133.1, 120.1, 84.1, 82.3, 80.1, 72.9, 29.4, 28.3, 28.1, 25.8, 22.5, 21.7; HRMS (m/z): [M + Na]^+ for C_{18}H_{28}N_{2}O_{4}, calcd, 359.1941; found, 359.1928.

**Di-tert-butyl 1-(3-methylbut-3-en-1-yn-1-yl)hydrazine-1,2-dicarboxylate** (Compound 2.19, Scheme 2.4):

\[
\text{Me} \quad \overset{\text{Boc}}{\text{N}} \quad \overset{\text{Boc}}{\text{HN}}
\]

Isolated yield= 208 mg (70%) as a yellow oil. R_f = 0.38 (20% EtOAc/hexanes); IR (CHCl₃, cm⁻¹) 3310, 2980, 2934, 2875, 2243, 2209, 1739, 1707, 1474, 1369, 1248, 1150; \(^1\)H NMR (400 MHz, CDCl₃) δ ppm 6.67 (1H, br. s.), 5.03 - 5.28 (2H, m), 1.90 (3H, s), 1.35 - 1.62 (18H, m); \(^1^3\)C NMR (101 MHz, CDCl₃) δ ppm 154.0, 152.6, 126.1, 119.1, 84.2, 82.3, 81.6, 72.9, 28.1, 27.8, 23.3; HRMS (m/z): [M + NH₄]^+ for C_{15}H_{28}N_{3}O_{4}, calcd, 314.20798; found, 314.20726.

**Representative procedure for synthesis of terminal ynehydrazides** (Scheme 2.5):

In a nitrogen flushed 50 mL flask capped with a rubber septa was charged THF (5 mL) and di-tert-butyl 1-(((trimethylsilyl)ethynyl)hydrazine-1,2-dicarboxylate (Compound 2.4, 74 mg, 0.23 mmol, 1.0 eq.) under N₂ and cooled to between -15 and -20 °C in a dry ice/ethylene glycol bath. TBAF (tetrabutylammonium fluoride, 0.46 mL of a 1.0 M sol’n in THF, 0.46 mmol, 2.0 eq.) was then added dropwise over 30 seconds and the resulting mixture stirred in the cooling bath for 15 mins then sat’d NH₄Cl(aq) (3 mL) was added and the cooling bath removed. As soon as the reaction mixture reached room temperature (~15 mins) it was diluted with Et₂O (50 mL) and water (10 mL) and the layers separated. The aqueous layer was extracted a second time with Et₂O (30 mL) and the organic extracts were combined and dried (MgSO₄) and filtered through a pad of silica topped with celite flushing with ethyl acetate (3 x 50 mL). The filtrate was concentrated in vacuo to give 51 mg (86% yield) of ~90% pure desired product as a yellow oil as determined by \(^1\)H NMR. This material was further purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) giving 44 mg (76% yield) of Compound 2.21 (Scheme 2.5) as a yellow oil.
**Batch preparation (2 x 3 mmol) of terminal ynehydrazide 2.21:**

Two identical 3 mmol scale reactions were set-up side-by-side: In a nitrogen flushed 250 mL flask capped with a rubber septa was charged THF (15 mL) and ethynyltrimethylsilane (294 mg, 3.0 mmol, 1.0 eq.) under N₂ and cooled to -78 °C in a dry ice/acetone bath. A solution of n-BuLi (1.44 mL of a 2.5 M sol’n in hexanes, 3.6 mmol, 1.2 eq.) was then added dropwise over 1-2 mins and the resulting mixture stirred at -78 °C for 15 mins. A solution of DBAD (di-t-butyl-azodicarboxylate, 1.03 g, 4.5 mmol, 1.5 eq.) in THF (9 mL) was then added dropwise over 1-2 mins and the cooling bath removed and the mixture allowed to warm to room temperature over 30 mins. The two identical reaction mixtures were then quenched by addition of sat’d NH₄Cl(aq) (15 mL) and diluted with ethyl acetate (100 mL) and water (15 mL) and combined together in a separatory funnel and the layers separated. The organic extract was dried (MgSO₄), filtered through a short plug of silica (3 cm) topped with celite (0.5 cm) using 100 mL ethyl acetate to elute, and concentrated *in vacuo* to provide 1.54 g (78% yield) of 90% pure di-tert-butyl 1-((trimethylsilyl)ethynyl)hydrazine-1,2-dicarboxylate (Compound 2.4) as a yellow oil which was used without further purification.

Crude 2.4 obtained above (1.17 g, 3.57 mmol, 1eq.) was dissolved in 25 mL THF under N₂ and cooled to between -15 and -20 °C in a dry ice/ethylene glycol bath. TBAF (tetrabutylammonium fluoride, 7.14 mL of a 1.0 M sol’n in THF, 7.14 mmol, 2.0 eq.) was then added dropwise over 1 min and the resulting mixture stirred in the cooling bath for 15 mins then sat’d NH₄Cl(aq) (20 mL) was added and the cooling bath removed. As soon as the reaction mixture reached room temperature (~15 mins) it was diluted with Et₂O (200 mL) and water (50 mL) and the layers separated. The aqueous layer was extracted a second time with Et₂O (100 mL) and the organic extracts were combined and dried (MgSO₄) and filtered through a pad of silica topped with celite flushing with ethyl acetate (3 x 50 mL). The filtrate was concentrated *in vacuo* to give 880 mg (96% yield) of ~90% pure desired product as a yellow oil as determined by ¹H NMR. This material was further purified through silica gel using ethyl acetate in hexanes to elute (gradient
elution 0-100% EtOAc) giving 771 mg (84% yield) of Compound 2.21 (Scheme 2.5) as a yellow oil.

**Diisopropyl 1-ethynylhydrazine-1,2-dicarboxylate (Compound 2.20, Scheme 2.5):**

Isolated yield = 64 mg (56%) as a clear oil. $R_f = 0.23$ (20% EtOAc/hexanes); IR (neat, cm$^{-1}$) 3295, 2985, 2939, 2881, 2151, 1755-1716 (br., m.), 1496, 1468, 1377, 1314, 1243, 1183, 1104, 1037; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 6.96 (1H, br. s.), 5.02 (2H, dtd, $J=12.5$, 6.5, 6.5, 0.5 Hz), 3.04 (1H, s), 1.33 (6H, d, $J=6.0$ Hz), 1.29 (6H, d, $J=6.0$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 154.8, 153.8, 75.2, 73.3, 71.0, 60.6, 22.1, 22.0; HRMS ($m/z$): [M + Na]$^+$ for C$_{10}$H$_{16}$N$_2$O$_4$, calcd, 251.0997; found, 251.0997.

**Di-tert-butyl 1-ethynylhydrazine-1,2-dicarboxylate (Compound 2.21, Scheme 2.5):**

Isolated yield = 44 mg (76%) as a yellow oil. $R_f = 0.28$ (20% EtOAc/hexanes); IR (neat, cm$^{-1}$) 3311, 2980, 2936, 2149, 1748-1713 (br.), 1479, 1456, 1148; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 6.67 (1H, br.s.), 3.00 (1H, s), 1.50 (9H, s), 1.48 (9H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 152.9, 84.8, 82.7, 75.8, 60.1, 28.3, 28.1; HRMS ($m/z$): [M + Na]$^+$ for C$_{12}$H$_{20}$N$_2$O$_4$, calcd, 279.1328; found, 279.1315.

**Synthesis of carbonate functionalized ynehydrazide (Compound 2.22, Scheme 2.5):**

Di-tert-butyl 1-ethynylhydrazine-1,2-dicarboxylate (Compound 2.21, 128 mg, 0.5 mmol, 1.0 eq.) was dissolved in THF (3 mL) in a nitrogen flushed 50 mL flask capped with a rubber septa under N$_2$ and cooled to -78 °C in a dry ice/acetone bath. KHMSD (1.2 mL of a 0.5 M solution in toluene, 0.6 mmol, 1.2 eq.) was then added dropwise over 1-2 mins and the resulting mixture stirred at -78 °C for 10 mins. A solution of Boc$_2$O (120 mg, 0.55 mmol, 1.1 eq.) in THF (1 mL) was then added dropwise over 1-2 mins and the cooling bath removed and the mixture allowed to warm to room temperature and stirred at room temperature for 1 hr. The reaction mixture was then quenched by addition of sat’d NH$_4$Cl(aq) (10 mL) and
diluted with ethyl acetate (100 mL) and water (10 mL) and the layers separated. The organic extract was dried (MgSO₄), filtered through a short silica pad topped with celite, and the filtrate was concentrated in vacuo to give 171 mg (96% yield) of ~90% pure desired product as a yellow wax as determined by ¹H NMR. This material was further purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) giving 112 mg (63% yield) of tri-tert-butyl 2-ethynylhydrazine-1,1,2-tricarboxylate as a clear oil. R_f= 0.43 (20% EtOAc/hexanes); IR (neat, cm⁻¹) 3486, 3272, 2981, 2937, 2877, 2828, 2726, 2587, 2293, 2149, 1795-1695 (br.), 1480; ¹H NMR (400 MHz, CDCl₃) δ ppm 3.01 (1H, d, r, J=17.5 Hz), 1.42 - 1.60 (27H, m); ¹³C NMR (100 MHz, CDCl₃) δ ppm 151.6, 151.4, 149.2, 148.9, 84.68, 84.61, 74.54, 74.47, 61.0, 60.3, 28.1, 28.0; HRMS (m/z): [M + Na]^+ for C₁₇H₂₈N₂O₆, calcd, 379.1839; found, 379.1841.

Tri-tert-butyl 2-ethynylhydrazine-1,1,2-tricarboxylate prepared above (95 mg, 0.26 mmol, 1.0 eq.) dissolved in THF (2 mL) was added dropwise to a freshly prepared -78 °C cooled solution of LDA (0.31 mmol, 1.2 eq.) in 3 mL THF under N₂ and stirred at -78 °C for 15 mins then ethyl chloroformate (31 mg, 0.027 mL, 0.29 mmol, 1.1 eq.) was added and the cooling bath removed and warmed to room temperature over 30 mins. The reaction mixture was then quenched by addition of sat’d NH₄Cl(aq) (10 mL) and diluted with ethyl acetate (100 mL) and water (10 mL) and the layers separated. The organic extract was dried (MgSO₄), filtered, and concentrated in vacuo and the resulting crude residue was purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 53 mg (47% yield, 30% over 2 steps) of Compound 2.22 (Scheme 2.5) as an orange oil. R_f= 0.37 (20% EtOAc/hexanes); IR (neat, cm⁻¹) 3408, 3275, 2983, 2938, 2877, 2587, 2237, 2149, 1812-1695 (br.), 1456; ¹H NMR (400 MHz, CDCl₃) δ ppm 4.24 (2H, q, J=7.0 Hz), 1.52 (27H, s), 1.31 (3H, t, J=7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ ppm 154.4, 150.3, 148.7, 86.2, 85.2, 84.6, 80.2, 61.9, 28.1, 28.0, 14.3; HRMS (m/z): [M + NH₄]^+ for C₂₀H₃₂N₂O₈, calcd, 446.2524; found, 446.25235.
Representative procedure for synthesis of 1,2,3-triazoles by copper-catalyzed terminal ynehydrazide cycloaddition with azides (Scheme 2.6):

di-tert-butyl 1-ethynylhydrazine-1,2-dicarboxylate (Compound 2.21, 52 mg, 0.2 mmol, 1.0 eq.) was dissolved in water (2 mL) and t-BuOH (1 mL) in a 20-dram scintillation vial. Benzyl-azide (38 mg, 0.03 mL, 0.28 mmol, 1.4 eq.) was then added followed by addition of Cu(II)OAc-anhydrous (3.6 mg, 0.02 mmol, 0.1 eq.) and sodium-(L)-ascorbate (8 mg, 0.04 mmol, 0.2 eq.) and the resulting cloudy mixture stirred for 18 hrs at room temperature. Volatiles were removed under a stream of air and the resulting residue was partitioned between ethyl acetate (100 mL) and water (20 mL) and the layers were separated. The organic layer was washed with sat’d NaCl(aq) (20 mL), dried (MgSO₄), filtered and concentrated in vacuo and the crude residue purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 53 mg (68% yield) of Compound 2.24 (Scheme 2.6) as a white wax.

Diisopropyl 1-(1-benzyl-1H-1,2,3-triazol-4-yl)hydrazine-1,2-dicarboxylate (Compound 2.23, Scheme 2.6):

Isolated yield= 69 mg (73%) as a light yellow gum which foams under vacuum. Rf= 0.35 (5% MeOH/CH₂Cl₂); IR (CH₂Cl₂, cm⁻¹) 3301, 3178, 3034, 2983, 2939, 2879, 2312, 2254, 1750-1699 (br., m.), 1564, 1498, 1467, 1456, 1387, 1243, 1181, 1145, 1107, 1074, 1046, 990; ¹H NMR (300 MHz, CDCl₃) δ ppm 7.72 (1H, br. s.), 7.15 - 7.44 (5H, m), 7.01 (1H, br. s.), 5.47 (2H, s), 4.87 - 5.05 (2H, m), 1.27 (12H, d, J=5.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ ppm 155.4, 153.5, 146.6, 134.5, 129.3, 129.0, 128.4, 114.6, 71.6, 70.4, 54.9, 22.1, 22.1; HRMS (m/z); [M + H]⁺ for C₁₇H₂₅N₅O₄, calcd, 362.1822; found, 362.1821.

Di-tert-butyl 1-(1-benzyl-1H-1,2,3-triazol-4-yl)hydrazine-1,2-dicarboxylate (Compound 2.24, Scheme 2.6):

Isolated yield= 53 mg (68%) as a white wax. m.p.= 151-153 °C; Rf= 0.12 (20% EtOAc/hexanes); 0.27 (5% MeOH/CH₂Cl₂); IR (CH₂Cl₂, cm⁻¹) 3421, 3054, 2986, 2307, 1726, 1720, 1565; ¹H NMR (400 MHz,
CDCl₃) δ ppm 7.73 (1H, br.s.), 7.32 - 7.39 (3H, m), 7.24 - 7.30 (2H, m), 7.01 (1H, br.s.), 5.46 (2H, br.s.), 1.33 - 1.58 (18H, m); ¹³C NMR (100 MHz, CDCl₃) δ ppm 154.6, 152.7, 146.9, 134.5, 129.3, 129.0, 128.4, 114.4, 83.1, 82.0, 54.9, 28.4, 28.2; HRMS (m/z): [M + H]⁺ for C₁₉H₂₇N₅O₄, calcd, 390.2135; found, 390.2125.

**Di-tert-butyl 1-(1-phenyl-1H-1,2,3-triazol-4-yl)hydrazine-1,2-dicarboxylate (Compound 2.25, Scheme 2.6):**

Isolated yield= 52 mg (69%) as a white solid. m.p.= 65-68 °C; Rf= 0.18 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3408, 3054, 2985, 2934, 2685, 2305, 1745, 1729, 1570, 1371, 1152; ¹H NMR (300 MHz, CDCl₃) δ ppm 8.27 (1H, br. s.), 7.74 (2H, d, J=7.5 Hz), 7.35 - 7.57 (3H, m), 7.09 (1H, s), 1.39 - 1.66 (18H, m); ¹³C NMR (75 MHz, CDCl₃) δ ppm 154.5, 152.6, 147.1, 137.2, 129.7, 128.7, 120.4, 112.7, 83.4, 81.9, 28.2, 28.1; HRMS (m/z): [M + Na]⁺ for C₁₈H₂₅N₅O₄Na, calcd, 398.1798; found, 398.1813.

**Di-tert-butyl 1-(1-(2-methoxy-2-oxoethyl)-1H-1,2,3-triazol-4-yl)hydrazine-1,2-dicarboxylate (Compound 2.26, Scheme 2.6):**

Isolated yield= 34 mg (46%) as a light yellow solid. m.p.= 173-179 °C; Rf= 0.15 (40% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3176, 2981, 2935, 2366, 1756, 1722, 1700, 1367, 1152; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.93 (1H, br. s.), 7.05 (1H, s), 5.12 (2H, s), 3.80 (3H, s), 1.38 - 1.59 (18H, m); ¹³C NMR (75 MHz, CDCl₃) δ ppm 166.6, 154.6, 152.6, 147.0, 115.8, 83.2, 82.0, 53.2, 51.4, 28.4, 28.3; HRMS (m/z): [M + H]⁺ for C₁₅H₂₆N₅O₆, calcd, 372.18831; found, 372.18855.

**Di-tert-butyl 1-(1-(4-cyanophenyl)-1H-1,2,3-triazol-4-yl)hydrazine-1,2-dicarboxylate (Compound 2.27, Scheme 2.6):**

Isolated yield= 61 mg (76%) as a yellow wax. Rf= 0.41 (40% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3409, 3055, 2984, 2305, 2233, 1743, 1728, 1609, 1570, 1518, 1371, 1151, 1037; ¹H NMR
(400 MHz, CDCl₃) δ ppm 8.37 (1H, br. s.), 7.93 (2H, d, J=9.0 Hz), 7.77 - 7.87 (2H, m), 7.15 (1H, s), 1.41 - 1.63 (18H, m); ¹³C NMR (100 MHz, CDCl₃) δ ppm 154.4, 152.5, 147.7, 139.9, 133.9, 120.4, 117.7, 112.3, 111.8, 83.6, 82.1, 28.2, 28.1; HRMS (m/z): [M + H]⁺ for C₁₉H₂₅N₆O₄, calcd, 401.1931; found, 401.1933.

**Di-tert-butyl 1-(1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)hydrazine-1,2-dicarboxylate (Compound 2.28, Scheme 2.6):**

![Structure of the compound](image)

Isolated yield= 73 mg (81%) as a yellow solid. m.p. = 77-81 °C; Rᵣ = 0.24 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3410, 3054, 2984, 2305, 1745, 1727, 1568, 1498, 1370, 1152, 991; ¹H NMR (300 MHz, CDCl₃) δ ppm 8.25 (1H, br. s.), 7.64 (4H, s), 7.11 (1H, s), 1.38 - 1.65 (18H, m); ¹³C NMR (75 MHz, CDCl₃) δ ppm 154.4, 152.5, 147.3, 136.1, 132.8, 122.4, 121.7, 112.2, 83.3, 82.0, 28.2, 28.1; HRMS (m/z): [M + H]⁺ for C₁₈H₂₅BrN₅O₄, calcd, 454.1084; found, 454.1064.

**Copper-catalyzed synthesis of hydrazide functionalized isoxazole (Compound 2.29, Scheme 2.7):**

![Structure of the compound](image)

Di-tert-butyl 1-ethynylhydrazine-1,2-dicarboxylate (Compound 2.21, 43 mg, 0.17 mmol, 1.0 eq.) and N-hydroxybenzimidoyl chloride (37 mg, 0.24 mmol, 1.4 eq.) were combined in water (2 mL) and t-BuOH (1 mL) in a 20-dram scintillation vial. Sodium-(L)-ascorbate (3.4 mg, 0.017 mmol, 0.1 eq.) was then added followed by K₂CO₃ (51 mg, 0.37 mmol, 2.2 eq.) and Cu(II)SO₄-anhydrous (3 mg, 0.017 mmol, 0.1 eq.) and the resulting cloudy mixture stirred for 18 hrs at room temperature. Volatiles were removed under a stream of air and the resulting residue was partitioned between ethyl acetate (100 mL) and water (20 mL) and the layers were separated. The organic layer was washed with sat’d NaCl(aq) (10 mL), dried (MgSO₄), filtered and concentrated *in vacuo* and the crude residue purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 38 mg (60% yield) of Compound 2.29 (Scheme 2.7) as a white waxy semi-solid. Rᵣ = 0.24 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3398, 3054, 2986, 2305, 1751, 1711; ¹H NMR
(400 MHz, CDCl₃) δ ppm 7.71 - 7.84 (2H, m), 7.38 - 7.49 (3H, m), 6.89 (1H, br.s.), 6.47 (1H, br.s.), 1.42 - 1.60 (18H, m); ¹³C NMR (100 MHz, CDCl₃) δ ppm 164.0, 163.2, 154.3, 150.8, 130.2, 129.4, 129.0, 126.9, 88.5, 84.9, 82.7, 28.4, 28.2; HRMS (m/z): [M + H]^+ for C₁₉H₂₅N₃O₅, calcd, 376.18725; found, 376.18680.

**Palladium-catalyzed synthesis of 2-hydrazide functionalized indole (Compound 2.30, Scheme 2.8):**

\[
\text{Pd}^{2+}
\]

Di-tert-butyl 1-ethynylhydrazine-1,2-dicarboxylate (Compound 2.21, 153 mg, 0.6 mmol, 1.2 eq.) dissolved in DMF (3 mL) was added by syringe to a septa capped nitrogen purged MW vial containing 2-iodo-N-methylaniline (117 mg, 0.5 mmol, 1.0 eq.), tetrabutylammonium acetate (452 mg, 1.5 mmol, 3.0 eq.), triphenylphosphine (26 mg, 0.1 mmol, 0.2 eq.), and Pd(OAc)₂ (5.6 mg, 0.025 mmol, 0.05 eq.) and the vial was placed in a 65 °C oil bath under a blanket of N₂. After 18 hrs, the mixture was cooled to room temperature and diluted with ethyl acetate (100 mL) and washed with 50% sat’d NaCl(aq) (4 x 15 mL). The organic extract was dried (MgSO₄), filtered and concentrated *in vacuo* and the crude residue purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 64 mg (35% yield) of Compound 2.30 (Scheme 2.8) as an orange oil. Rₚ= 0.26 (20% EtOAc/hexanes); IR (neat, cm⁻¹) 3354 (br.), 3058, 2982, 2934, 2821, 2726, 2507, 2394, 2292, 2253, 1760-1682 (br.); ¹H NMR (400 MHz, CDCl₃) δ ppm 7.57 (1H, d, J=8.0 Hz), 7.26 - 7.32 (1H, m), 7.18 - 7.26 (1H, m), 7.05 - 7.14 (1H, m), 6.90 (1H, br.s.), 6.44 (1H, s), 3.73 (3H, br.s.), 1.47 (18H, br.s.); ¹³C NMR (100 MHz, CDCl₃) δ ppm 155.1, 154.3, 137.2, 135.0, 126.5, 122.2, 121.3, 119.9, 109.8, 97.1, 83.2, 81.9, 29.4, 28.3; HRMS (m/z): [M + H]^+ for C₁₉H₂₇N₃O₄, calcd, 362.2074; found, 362.2066.
Representative procedure for the synthesis of 1,2,3-triazoles via Ruthenium-catalyzed cycloaddition of ynehydrazides with azides (Scheme 2.9):

Cp*RuCl(COD) (1.5 mg, 0.004 mmol, 0.02 eq.) was charged to a MW vial capped with a septa and purged with nitrogen for 5 mins then charged with toluene (1 mL). di-tert-butyl 1-(p-tolylethynyl)hydrazine-1,2-dicarboxylate (Compound 2.9, 69 mg, 0.2 mmol, 1.0 eq.) in toluene (0.5 mL) was then added followed by addition of benzyl-azide (27 mg, 0.2 mmol, 1.0 eq.) in 0.5 mL toluene and the mixture stirred at room temperature. After 30 mins, TLC indicated the alkyne had been consumed and the reaction mixture was loaded directly onto silica gel and purified by flash column chromatography using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 50 mg (52% yield) of Compound 2.33 (Scheme 2.9) as a yellow solid.

Di-tert-butyl 1-(1-benzyl-1H-1,2,3-triazol-5-yl)hydrazine-1,2-dicarboxylate (Compound 2.31, Scheme 2.9):

Prepared according to the representative procedure for ruthenium-catalyzed ynehydrazide-azide cycloaddition except stirred for 16 hrs at room-temperature. Isolated yield= 44 mg (56%) as a white solid. m.p. = 169-175 °C; Rf= 0.32 (40% EtOAc/hexanes); IR (CH2Cl2, cm⁻¹) 3188, 3054, 2983, 2934, 2410, 2313, 1734, 1726, 1583, 1456, 1369, 1154, 1105, 976; ¹H NMR (400 MHz, CDCl3) δ ppm 7.69 (1H, br. s.), 7.11 - 7.45 (5H, m), 6.56 (1H, br. s.), 5.54 (2H, br. s.), 1.21 - 1.58 (18H, m); ¹³C NMR (100 MHz, CDCl3) δ ppm 155.0, 153.0, 137.1, 134.9, 130.6, 129.1, 128.6, 128.0, 84.3, 82.5, 51.7, 28.3, 28.0; HRMS (m/z): [M + H]⁺ for C₁₉H₂₈N₅O₄, calcd, 390.21413; found, 390.21443.

Di-tert-butyl 1-(1-benzyl-4-(2-bromophenyl)-1H-1,2,3-triazol-5-yl)hydrazine-1,2-dicarboxylate (Compound 2.32, Scheme 2.9):

Prepared according to the representative procedure for ruthenium-catalyzed ynehydrazide-azide cycloaddition except stirred for 18 hrs at room-temperature. Isolated yield= 30 mg (56%) as a tan solid. m.p. = 80-85 °C; Rf= 0.18 (20% EtOAc/hexanes); IR (CH2Cl2, cm⁻¹) 3407 (br.),
3054, 2987, 2686, 2411, 2315, 1753, 1737, 1464, 1425, 1371, 1326, 1149; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.66 (1H, d, \(J=8.0\) Hz), 7.24 - 7.53 (8H, m), 6.71 (1H, br. s.), 5.58 - 5.89 (2H, m), 1.01 - 1.53 (18H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 155.4, 152.4, 140.8, 135.4, 134.1, 133.4, 132.5, 131.7, 130.7, 128.8, 128.4, 128.2, 127.7, 123.3, 84.4, 82.7, 51.3, 28.3, 27.7; HRMS (m/z): [M + H]\(^+\) for C\(_{25}\)H\(_{30}\)BrN\(_5\)O\(_4\), calcd, 544.15594; found, 544.15530.

**Di-tert-butyl 1-(1-benzyl-4-(p-tolyl)-1H-1,2,3-triazol-5-yl)hydrazine-1,2-dicarboxylate (Compound 2.33, Scheme 2.9):**

![Di-tert-butyl 1-(1-benzyl-4-(p-tolyl)-1H-1,2,3-triazol-5-yl)hydrazine-1,2-dicarboxylate](image)

Isolated yield= 50 mg (52%) as a yellow solid. m.p.= 73-76 °C; \(R_f= 0.27\) (20% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3372, 2935, 1746, 1733, 1516, 1498, 1480, 1456, 1371, 1330; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.56 (2H, d, \(J=8.0\) Hz), 7.45 (2H, br. m), 7.27 - 7.37 (3H, m), 7.24 (2H, d, \(J=8.0\) Hz), 6.65 (1H, br. s.), 5.65 - 5.95 (2H, m), 2.38 (3H, s), 0.96 - 1.54 (18H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 155.3, 153.2, 140.7, 138.6, 135.4, 132.4, 129.9, 128.5, 128.8, 128.2, 127.4, 126.0, 84.4, 82.7, 51.2, 28.3, 27.6, 21.5; HRMS (m/z): [M + H]\(^+\) for C\(_{26}\)H\(_{33}\)N\(_5\)O\(_4\), calcd, 480.26108; found, 480.26086.

**Di-tert-butyl 1-(1-benzyl-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1H-1,2,3-triazol-5-yl)hydrazine-1,2-dicarboxylate (Compound 2.34, Scheme 2.9):**

![Di-tert-butyl 1-(1-benzyl-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1H-1,2,3-triazol-5-yl)hydrazine-1,2-dicarboxylate](image)

Prepared according to the representative procedure for ruthenium-catalyzed ynehydrazide-azide cycloaddition except stirred for 36 hrs at room-temperature and 0.36 mmol ynehydrazide and 0.36 mmol benzyl-azide and 0.007 mmol Cp*RuCl(COD) used. Isolated yield= 132 mg (55%) as a tan powder. m.p.= 50-54 °C; \(R_f= 0.26\) (20% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3376, 3054, 2985, 2931, 2685, 2320, 1733, 1600, 1421, 1371, 1151, 895; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.27 - 7.48 (5H, m), 7.15 (1H, br. s.), 5.50 - 5.82 (2H, m, r), 3.91 (2H, br.), 2.64 - 3.01 (2H, m), 1.07 - 1.65 (18H, m), 0.88 (9H, s), 0.09 (6H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 160.0, 158.0, 145.4, 140.5, 139.6, 133.8, 133.5, 133.2, 88.6, 86.9, 67.6, 56.2, 34.2, 33.4, 33.0, 31.4, 23.9, 0.01; HRMS (m/z): [M + H]\(^+\) for C\(_{27}\)H\(_{46}\)N\(_5\)O\(_5\)Si, calcd, 548.3262; found, 548.3275.
Di-tert-butyl 1-(1-(4-bromophenyl)-4-hexyl-1H-1,2,3-triazol-5-yl)hydrazine-1,2-dicarboxylate (Compound 2.35, Scheme 2.9):

Prepared according to the representative procedure for ruthenium-catalyzed ynehydrazide-azide cycloaddition except stirred for 16 hrs at room-temperature. Isolated yield = 74 mg (68%) as a yellow gum as a 9:1 mixture of regioisomers in favour of the one shown. Rf = 0.39 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3390, 3054, 2984, 2932, 2363, 1735, 1599, 1496, 1369, 1147, 1070; ¹H NMR (300 MHz, CDCl₃) δ ppm 7.67 (2H, d, J=9.0 Hz), 7.39 - 7.59 (2H, m), 6.43 (1H, br. s), 2.79 (2H, m), 1.69 - 1.83 (2H, m), 1.42 - 1.50 (15H, m), 1.26 - 1.36 (9H, m), 0.85 - 0.92 (3H, m); ¹³C NMR (100 MHz, CDCl₃) δ ppm 154.6, 152.5, 143.4, 135.1, 132.8, 126.0, 125.5, 123.4, 84.3, 82.5, 31.7, 29.1, 28.6, 28.1, 27.8, 24.6, 22.6, 14.1; HRMS (m/z): [M + H]⁺ for C₂₄H₃₇BrN₅O₄, calcd, 538.2023; found, 538.2015.

Di-tert-butyl 1-(1-(2-((tert-butoxycarbonyl)amino)ethyl)-4-(thiophen-3-yl)-1H-1,2,3-triazol-5-yl)hydrazine-1,2-dicarboxylate (Compound 2.36, Scheme 2.9):

Prepared according to the representative procedure for ruthenium-catalyzed ynehydrazide-azide cycloaddition except stirred for 18 hrs at room-temperature. Isolated yield = 67 mg (63%) as a white hygroscopic wax. Rf = 0.36 (40% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3363, 3244, 3109, 2980, 2933, 2301, 1737, 1712, 1681, 1606, 1506, 1456, 1392, 1367, 1323, 1249, 1151; ¹H NMR (300 MHz, CDCl₃) δ ppm 7.70 (1H, br. s.), 7.48 (1H, d, J=4.5 Hz), 7.38 - 7.45 (1H, m), 7.23 (1H, br. s.), 5.29 (1H, br. s.), 4.47 - 4.68 (2H, m), 3.62 - 3.79 (2H, m), 1.26 - 1.59 (27H, m); ¹³C NMR (75 MHz, CDCl₃) δ ppm 156.2, 155.5, 152.9, 137.7, 132.2, 130.8, 126.8, 126.0, 122.6, 84.9, 82.9, 79.9, 47.7, 39.9, 28.6, 28.3, 28.1; HRMS (m/z): [M + H]⁺ for C₂₃H₃₇N₆O₆Si, calcd, 525.2489; found, 525.2498.
Representative procedure for the synthesis of isoxazoles via Ruthenium-catalyzed cycloaddition of ynehydrazides with in situ generated phenylnitrile oxide (Scheme 2.10):

A MW vial was charged with di-tert-butyl 1-(p-tolylethynyl)hydrazine-1,2-dicarboxylate (Compound 2.9, 69 mg, 0.2 mmol, 1.0 eq.), N-hydroxybenzimidoyl chloride (34 mg, 0.22 mmol, 1.1 eq.), Cp*RuCl(COD) (3.8 mg, 0.01 mmol, 0.05 eq.). 1,2-dichloroethane (1 mL) was then added followed by addition of Et3N (25 mg, 0.034 mL, 0.25 mmol, 1.25 eq.) and the vial capped with a septa and purged with nitrogen for 5 mins then stirred at room temperature overnight. After 36 hours, the reaction mixture was loaded directly onto silica gel and purified by flash column chromatography using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 60 mg (65% yield) of Compound 2.40 (Scheme 2.10) as a white solid.

Di-tert-butyl 1-(3-phenylisoxazol-4-yl)hydrazine-1,2-dicarboxylate (Compound 2.37, Scheme 2.10):

Prepared according to the representative procedure for ruthenium-catalyzed ynehydrazide-nitrile oxide cycloaddition except stirred for 18 hrs at room-temperature. Isolated yield= 28 mg (37%) as a sticky yellow oil. Rf= 0.26 (20% EtOAc/hexanes); IR (neat, cm\(^{-1}\)) 3322, 2979, 2934, 2875, 2254, 1750, 1697, 1475, 1154; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 8.76 (1H, br. s.), 7.70 (2H, dd, \(J\=6.5, 3.0\) Hz), 7.38 - 7.55 (3H, m), 6.81 (1H, br. s.), 1.18 - 1.56 (18H, m); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) ppm 158.1, 155.5, 153.6, 151.7, 131.7, 130.0, 128.9, 128.1, 127.5, 83.3, 82.2, 28.1, 27.7; HRMS (m/z): [M + H]\(^+\) for C\(_{19}\)H\(_{25}\)N\(_3\)O\(_5\), calcd, 376.18725; found, 376.18616.

Di-tert-butyl 1-(5-benzyl-3-phenylisoxazol-4-yl)hydrazine-1,2-dicarboxylate (Compound 2.38, Scheme 2.10):

Isolated yield= 16 mg (29%) as a yellow solid. m.p.= 60-64 °C; Rf= 0.34 (20% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3272, 2979, 2933, 2363, 1729, 1711, 1458, 1367, 1247, 1151; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.56 -
7.69 (2H, m), 7.41 - 7.52 (3H, m), 7.19 - 7.40 (5H, m), 6.35 - 6.59 (1H, m), 4.36 (2H, br. s.), 1.13 - 1.56 (18H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 159.2, 155.4, 154.0, 135.8, 130.5, 130.2, 129.3, 129.0, 128.8, 128.6, 127.8, 127.5, 127.1, 83.3, 77.4, 31.5, 28.4, 28.0; HRMS (m/z): [M + H]$^+$ for C$_{26}$H$_{32}$N$_3$O$_5$, calcd, 466.23420; found, 466.23579.

**Di-tert-butyl 1-(5-hexyl-3-phenylisoxazol-4-yl)hydrazine-1,2-dicarboxylate (Compound 2.39, Scheme 2.10):**

Prepared according to the representative procedure for ruthenium-catalyzed ynehydrazide-nitrile oxide cycloaddition except stirred for 16 hrs at room-temperature. Isolated yield= 72 mg (78%) as a clear oil as a 9:1 mixture of regioisomers in favour of the one shown. R$_f$= 0.40 (20% EtOAc/hexanes); IR (neat, cm$^{-1}$) 3287, 2977, 2932, 2861, 2366, 1733, 1695, 1244, 1151, 1053; $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.62 (2H, dd, $J$=5.5, 3.5 Hz), 7.43 - 7.48 (3H, m), 6.37 - 6.60 (1H, m), 2.97 (2H, t, $J$=7.5 Hz), 1.69 - 1.83 (2H, m), 1.42 - 1.54 (15H, m), 1.27 - 1.35 (9H, m), 0.85 - 0.93 (3H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 158.8, 155.0, 153.9, 129.9, 129.1, 128.6, 127.5, 127.2, 117.6, 82.9, 81.8, 31.6, 29.0, 28.1, 27.9, 26.9, 25.4, 22.5, 14.1; HRMS (m/z): [M + H]$^+$ for C$_{26}$H$_{32}$N$_3$O$_5$, calcd, 460.28115; found, 460.28040.

**Di-tert-butyl 1-(3-phenyl-5-(p-tolyl)isoxazol-4-yl)hydrazine-1,2-dicarboxylate (Compound 2.40, Scheme 2.10):**

Isolated yield= 60 mg (65%) as a white solid. m.p.= 61-64 °C; R$_f$= 0.37 (20% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3289, 2980, 2932, 1728, 1708, 1453, 1367, 1426, 1150; $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.95 (2H, d, $J$=6.5 Hz), 7.74 (2H, br. m), 7.43 - 7.57 (3H, m), 7.32 (2H, d, $J$=8.0 Hz), 6.33 (1H, br. s.), 2.43 (3H, s), 1.12 - 1.51 (18H, m); $^{13}$C NMR (126 MHz, CDCl$_3$) δ ppm 163.5, 159.6, 154.6, 153.6, 140.7, 130.0, 129.5, 129.2, 128.6, 127.6, 126.8, 124.3, 116.8, 83.2, 81.8, 28.1, 27.7, 21.6; HRMS (m/z): [M + H]$^+$ for C$_{26}$H$_{32}$N$_3$O$_5$, calcd, 466.2336; found, 466.2359.
Representative procedure for the synthesis of hydrazide-substituted quinolines via [4+2] cycloaddition with ynehydrazides (Scheme 2.12):

N-phenylbenzamide (22 mg, 0.11 mmol, 1.0 eq.) and 2-chloropyridine (15 mg, 0.012 mL, 0.13 mmol, 1.2 eq.) were combined in CH₂Cl₂ (0.25 mL) in a MW vial and cooled to -78 °C in a dry ice/acetone bath. Tf₂O (0.12 mL of a 1 M sol’n in CH₂Cl₂, 0.12 mmol, 1.1 eq.) was then added and stirred at -78 °C for 5 mins then warmed to room temperature and diisopropyl 1-(oct-1-yn-1-yl)hydrazine-1,2-dicarboxylate (Compound 2.7, 37 mg, 0.12 mmol, 1.1 eq.) was added as a sol’n in CH₂Cl₂ (0.25 mL). The mixture was stirred for 1 hr at room temperature then heated at 120 °C in a μW reactor for 1 min and after cooling to room temperature the mixture was diluted with CH₂Cl₂ (50 mL) and sat’d NaHCO₃(aq) (10 mL). The layers were separated and the organic extract was dried (MgSO₄), filtered and concentrated in vacuo and the crude residue was purified by flash column chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 29 mg (54% yield) of Compound 2.42 (Scheme 2.12) as a yellow wax.

Diisopropyl 1-(3-hexyl-2-phenylquinolin-4-yl)hydrazine-1,2-dicarboxylate (Compound 2.42, Scheme 2.12):

Isolated yield= 29 mg (545%) as a as a yellow wax. Rf = 0.18 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3378, 3054, 2986, 2685, 2522, 2411, 2306, 1757, 1737, 1421, 1109, 895; ¹H NMR (300 MHz, CDCl₃) δ ppm 8.08 - 8.27 (2H, m), 7.63 - 7.73 (1H, m), 7.40 - 7.59 (6H, m), 6.91 (1H, s), 4.92 - 5.12 (2H, m), 2.67 - 2.96 (2H, m), 1.39 (3H, dd, J=13.5, 6.5 Hz), 1.22 - 1.32 (7H, m), 0.98 - 1.15 (10H, m), 0.77 (3H, t, J=7.0 Hz); ¹³C NMR (75 MHz, CDCl₃) δ ppm 162.5, 156.0, 155.7, 147.6, 143.9, 141.2, 129.8, 129.4, 128.8, 128.6, 128.5, 127.21, 127.16, 125.1, 123.6, 71.7, 70.7, 31.4, 29.6, 29.4, 29.0, 22.5, 22.2, 22.0, 21.9, 14.2; HRMS (m/z): [M + H]⁺ for C₂₉H₃₈N₃O₄, calcd, 492.2856; found, 492.2875.
Diisopropyl 1-(2-isopropyl-6-methoxy-3-(thiophen-3-yl)quinolin-4-yl)hydrazine-1,2-dicarboxylate (Compound 2.43, Scheme 2.12):

Isolated yield = 25 mg (47%) as a clear oil. $R_f = 0.27$ (20% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3371, 3294, 3097, 2980, 2933, 2870, 1751, 1724, 1622, 1585, 1492, 1467, 1375, 1315, 1228, 1180, 1161, 1105, 1035; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ ppm 8.01 - 8.12 (1H, m), 7.98 (1H, d, $J$=9.0 Hz), 7.55 (1H, br. s.), 7.26 - 7.40 (2H, m), 7.12 (1H, br. s.), 6.06 (1H, br. s.), 4.86 - 5.09 (2H, m), 3.97 (3H, s), 3.03 (1H, br. s.), 0.98 - 1.37 (18H, m); $^13$C NMR (126 MHz, CDCl$_3$) $\delta$ ppm 163.9, 157.8, 155.7, 155.3, 154.8, 145.2, 143.4, 136.1, 130.2, 128.3, 125.3, 123.5, 122.8, 102.2, 71.0, 70.0, 55.8, 32.6, 22.3, 22.0, 21.8; HRMS ($m/z$): [M + H]$^+$ for C$_{25}$H$_{32}$N$_3$O$_5$S, calcd, 486.20627; found, 486.20580.

Diisopropyl 1-(6-bromo-3-(4-fluorophenyl)-2-isopropylquinolin-4-yl)hydrazine-1,2-dicarboxylate (Compound 2.44, Scheme 2.12):

Isolated yield = 35 mg (59%) as a white solid. m.p. = 129-132 °C; $R_f = 0.41$ (20% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3383, 3282, 2980, 2935, 2872, 1737, 1712, 1604, 1581, 1512, 1471, 1373, 1317, 1228, 1105; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ ppm 8.36 - 8.92 (1H, m), 7.96 (1H, d, $J$=8.5 Hz), 7.77 (1H, d, $J$=9.0 Hz), 7.36 (1H, br. s.), 7.27 - 7.30 (1H, m), 7.17 (1H, t, $J$=8.5 Hz), 7.05 (1H, br. s.), 5.46 - 5.98 (1H, m), 4.78 - 5.09 (2H, m), 2.85 - 3.11 (1H, m), 0.97 - 1.41 (18H, m); $^13$C NMR (126 MHz, CDCl$_3$) $\delta$ ppm 167.1, 162.6 (1C, d [C-F], $J$= 248 Hz), 155.6, 154.4, 147.6, 147.4, 143.4, 143.1, 133.2, 131.7, 131.0, 130.0, 127.2, 125.1, 116.4, 71.6, 71.2, 32.7, 22.2, 21.9, 21.6; $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ ppm -112.2 (1F, s); HRMS ($m/z$): [M + H]$^+$ for C$_{26}$H$_{30}$BrFN$_3$O$_4$, calcd, 546.14037; found, 546.14064.
Synthesis of di-tert-butyl 1-(2-bromobenzoyl)-2-(p-tolylethynyl)hydrazine-1,2-dicarboxylate (Compound 2.50, Scheme 2.15):

In a nitrogen flushed 50 mL flask capped with a rubber septa was charged THF (5 mL) and p-tolyl-acetylene (116 mg, 0.13 mL, 1.0 mmol, 1.0 eq.) under N₂ and cooled to -78 °C in a dry ice/acetone bath. A solution of n-BuLi (0.48 mL of a 2.5 M sol’n in hexanes, 1.2 mmol, 1.2 eq.) was then added dropwise over 1-2 mins and the resulting mixture stirred at -78 °C for 15 mins. A solution of DBAD (di-t-butyl-azodicarboxylate, 345 mg, 1.5 mmol, 1.5 eq.) in THF (3 mL) was then added dropwise over 1-2 mins and the cooling bath removed and the mixture allowed to warm to room temperature over 30 mins. The reaction mixture was then re-cooled to -78 °C and 2-bromobenzoyl chloride (329 mg, 1.5 mmol, 1.5 eq.) added as a sol’n in THF (0.5 mL) and the cooling bath removed and the mixture allowed to warm to room temperature and stirred at room temperature for 1 hr then quenched by addition of sat’d NH₄Cl(aq) (10 mL) and diluted with ethyl acetate (100 mL) and water (10 mL) and the layers separated. The organic extract was dried (MgSO₄), filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 328 mg (62%) of Compound 2.50 (Scheme 2.15) as a yellow oil. Rf 0.34 (20% EtOAc/hexanes); IR (neat, cm⁻¹) 3061, 2981, 2959, 2934, 2873, 2731, 2266, 2235, 1774, 1713, 1695, 1589, 1456, 1142, 1065, 1025; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.53 - 7.62 (1H, m), 7.47 (1H, d, J=7.5 Hz), 7.28 - 7.39 (4H, m), 7.07 - 7.14 (2H, m), 2.34 (3H, s), 1.52 - 1.61 (9H, m), 1.26 - 1.34 (9H, m); ¹³C NMR (100 MHz, CDCl₃) δ ppm [rotomers, major listed] 166.2, 151.5, 149.1, 138.2, 133.0, 132.1, 131.6, 131.3, 129.2, 128.4, 128.0, 127.3, 119.3, 85.7, 85.0, 80.1, 72.9, 28.2, 27.7, 21.7; HRMS (m/z): [M + NH₄]⁺ for C₂₆H₃₃BrN₂O₅, calcd, 546.16036; found, 546.16098.
Synthesis of 4-(4-methylbenzyl)phthalazin-1(2H)-one via ynehydrazide radical cyclization (Compound 2.52, Scheme 2.15):

A 2-neck flask was charged with compound 2.50 (53 mg, 0.1 mmol, 1.0 eq.) and benzene (5 mL) and fitted with a reflux condenser and capped with rubber septa and degassed with argon for 3 mins and placed in a 80 °C oil bath. To this was then added a sol’n of AIBN (8.2 mg, 0.05 mmol, 0.5 eq.) and Bu3SnH (58 mg, 0.053 mL, 0.2 mmol, 2 eq.) in benzene (3 mL) degassed with argon for 3 mins at a rate of 0.2 mL every 10 mins. After 6 hrs total the reaction mixture was cooled to room temperature and 1 M NaOH (10 mL) was added and stirred for 15 mins before organics extracted with ethyl acetate (2 x 40 mL). The organic extracts were combined, dried (MgSO4), filtered and concentrated in vacuo and the crude residue was purified by flash column chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 26 mg (57% yield) of Compound 2.51 as a 2:1 mixture of olefin isomers. Rf = 0.27 (20% EtOAc/hexanes); HRMS (m/z): [M + H]+ for C26H31N2O5, calcd, 451.22330; found, 451.22236.

Compound 2.51 (26 mg, 0.0566 mmol, 1.0 eq.) was dissolved in ethyl acetate (3 mL) and 4 N HCl in dioxane (0.5 mL) was added and stirred at room temperature. After 16 hrs, mixture was diluted with ethyl acetate (40 mL) and washed with sat’d NaHCO3(aq) (10 mL). Organic extract was dried (MgSO4), filtered and concentrated in vacuo and the crude residue was purified by flash column chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 9.6 mg (68% yield) of Compound 2.52 (Scheme 2.15) as a white solid. m.p. = 191-195 °C; Rf= 0.19 (40% EtOAc/hexanes); IR (CH2Cl2, cm−1) 3167, 3071, 3007, 2950, 2904, 1675, 1635, 1346, 1153; 1H NMR (400 MHz, CDCl3) δ ppm 9.93 (1H, br. s.), 8.32 - 8.50 (1H, m), 7.62 - 7.85 (3H, m), 6.98 - 7.22 (4H, m), 4.25 (2H, s), 2.31 (3H, s); 13C NMR (101 MHz, CDCl3) δ ppm 160.1, 146.6, 136.4, 134.3, 133.5, 131.3, 129.8, 129.4, 128.41, 128.38, 127.0, 125.4, 38.4, 21.0; HRMS (m/z): [M + H]+ for C16H15N2O, calcd, 251.11844; found, 251.11771.
Representative procedure for the synthesis of N-amino oxazolones via ynehydrazide intramolecular gold-catalyzed cyclization (Scheme 2.16):

Ynehydrazide compound 2.14 (45 mg, 0.132 mmol, 1.0 eq.) was dissolved in CHCl₃ (0.5 mL) in a MW vial and PPh₃AuNTf₂ (10 mg of 2:1 complex with toluene, 0.0066 mmol, 0.05 eq.) added and stirred at room temperature. After 1 hr TLC shows complete consumption of ynehydrazide starting material and the reaction mixture loaded directly onto silica gel and purified by flash column chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 21 mg (56% yield) of Compound 2.54 (Scheme 2.16) as a white waxy solid.

Tert-butyl (2-oxo-5-phenyloxazol-3(2H)-yl)carbamate (Compound 2.53, Scheme 2.16):

Prepared according to the representative procedure for N-amino oxazolone synthesis using ynehydrazide 2.8 (105 mg, 0.316 mmol, 1.0 eq.) and PPh₃AuNTf₂ (25 mg of 2:1 complex with toluene, 0.0158 mmol, 0.05 eq.) in CHCl₃ (1 mL) stirring for 90 mins at room temperature. Isolated yield= 58 mg (66%) as a white solid. m.p.= 175-179 °C; Rₘ= 0.38 (40% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3219, 3121, 3002, 2981, 1763, 1733, 1454, 1369, 1248, 1156; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.27 - 7.54 (5H, m), 7.07 (1H, br. s.), 6.89 (1H, s), 1.50 (9H, s); ¹³C NMR (101 MHz, CDCl₃) δ ppm 153.8, 153.4, 137.9, 128.8, 128.6, 126.9, 123.1, 111.6, 83.5, 28.0; HRMS (m/z): [M + NH₄]⁺ for C₁₄H₂₀N₃O₄, calcd, 294.14538; found, 294.14596.

Tert-butyl (5-hexyl-2-oxooxazol-3(2H)-yl)carbamate (Compound 2.54, Scheme 2.16):

Isolated yield= 21 mg (56%) as a white waxy solid. m.p.= 72-75 °C; Rₘ= 0.50 (40% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3416 (br.), 2981, 2932, 2859, 2370, 2060, 1647, 1369, 1265, 1156; ¹H NMR (400 MHz, CDCl₃) δ ppm 6.77 (1H, br. s.), 6.28 (1H, s), 2.37 (2H, t, J=8.0 Hz), 1.53 - 1.58 (2H, m), 1.46 - 1.51 (9H, m), 1.22 - 1.39 (6H, m), 0.89 (3H, t, J=7.0 Hz); ¹³C NMR (101 MHz,
CDCl$_3$) δ ppm 154.1, 153.8, 139.9, 112.0, 83.2, 31.4, 28.5, 28.0, 26.2, 26.0, 22.5, 14.0; HRMS (m/z): [M + Na]$^+$ for C$_{14}$H$_{24}$N$_2$O$_4$Na, calcd, 307.1628; found, 307.1631.

**Tert-butyl (5-benzyl-2-oxooxazol-3(2H)-yl)carbamate (Compound 2.55, Scheme 2.16):**

Prepared according to the representative procedure for N-amino oxazolone synthesis using ynehydrazide 2.17 (59 mg, 0.17 mmol, 1.0 eq.) and PPh$_3$AuNTf$_2$ (13 mg of 2:1 complex with toluene, 0.0085 mmol, 0.05 eq.) in CHCl$_3$ (0.5 mL) stirring for 90 mins at room temperature. Isolated yield= 20 mg (40%) as a colourless solid. m.p.= 104-106 °C; R$_f$= 0.44 (40% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3406 (br.), 2982, 2934, 1776, 1736, 1652, 1369, 1252, 1159; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.15 - 7.39 (5H, m), 6.74 (1H, br. s.), 6.20 (1H, t, J=1.5 Hz), 3.71 (2H, s), 1.47 (9H, s); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 154.0, 153.7, 138.6, 134.8, 128.9, 128.7, 127.2, 113.2, 83.3, 32.6, 28.0; HRMS (m/z): [M + Na]$^+$ for C$_{15}$H$_{18}$N$_2$O$_4$Na, calcd, 313.1159; found, 313.1162.

**Tert-butyl (5-((2-(tert-butyldimethylsilyl)oxy)ethyl)-2-oxooxazol-3(2H)-yl)carbamate (Compound 2.56, Scheme 2.16):**

Prepared according to the representative procedure for N-amino oxazolone synthesis using ynehydrazide 2.16 (48 mg, 0.116 mmol, 1.0 eq.) and PPh$_3$AuNTf$_2$ (9 mg of 2:1 complex with toluene, 0.0058 mmol, 0.05 eq.) in CHCl$_3$ (0.5 mL) stirring for 90 mins at room temperature. Isolated yield= 29 mg (70%) as a white solid. m.p.= 69-72 °C; R$_f$= 0.52 (40% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3298, 3160, 2979, 2956, 2930, 2857, 1781, 1726, 1473, 1367, 1252, 1159, 1101; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 6.78 (1H, br. s.), 6.37 (1H, s), 3.79 (2H, t, J=6.5 Hz), 2.60 (2H, td, J=6.5, 1.5 Hz), 1.46 – 1.50 (9H, m), 0.88 (9H, s), 0.04 (6H, s); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 153.7, 137.1, 113.5, 83.2, 59.8, 29.9, 28.1, 28.0, 25.8, 18.2, -5.4; HRMS (m/z): [M + NH$_4$]$^+$ for C$_{16}$H$_{34}$N$_3$O$_5$Si, calcd, 376.22677; found, 376.22709.
Tert-butyl (5-cyclohexyl-2-oxooxazol-3(2H)-yl)carbamate (Compound 2.57, Scheme 2.16): Prepared according to the representative procedure for N-amino oxazolone synthesis using ynehydrazide 2.15 (38 mg, 0.112 mmol, 1.0 eq.) and PPh₃AuNTf₂ (9 mg of 2:1 complex with toluene, 0.0056 mmol, 0.05 eq.) in CHCl₃ (0.5 mL) stirring for 90 mins at room temperature. Isolated yield= 23 mg (72%) as a white solid. m.p. = 140-142 °C; Rₛ = 0.50 (40% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3308 (br.), 2978, 2931, 2855, 1781, 1728, 1482, 1452, 1536, 1249, 1159; ¹H NMR (400 MHz, CDCl₃) δ ppm 6.78 (1H, br. s.), 6.22 (1H, s), 2.29 - 2.47 (1H, m), 1.86 - 1.99 (2H, m), 1.74 - 1.84 (2H, m), 1.65 - 1.73 (1H, m), 1.44 - 1.52 (9H, m), 1.11 - 1.39 (4H, m); ¹³C NMR (101 MHz, CDCl₃) δ ppm 154.1, 153.9, 144.1, 110.6, 83.2, 35.2, 29.8, 28.2, 25.9, 25.4; HRMS (m/z): [M + NH₄]⁺ for C₁₄H₂₆N₂O₄, calcd, 300.19233; found, 300.19265.

Tert-butyl (2-oxo-5-(thiophen-3-yl)oxazol-3(2H)-yl)carbamate (Compound 2.58, Scheme 2.16): Prepared according to the representative procedure for N-amino oxazolone synthesis using ynehydrazide 2.13 (43 mg, 0.127 mmol, 1.0 eq.) and PPh₃AuNTf₂ (10 mg of 2:1 complex with toluene, 0.0063 mmol, 0.05 eq.) in CHCl₃ (0.5 mL) stirring for 60 mins at room temperature. Isolated yield= 26 mg (73%) as a yellow solid. m.p. = 111-114 °C; Rₛ = 0.38 (40% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3410 (br.), 2981, 2933, 1784, 1733, 1647, 1470, 1369, 1252, 1156; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.44 (1H, dd, J=3.0, 1.5 Hz), 7.35 (1H, dd, J=5.0, 3.0 Hz), 7.12 (1H, dd, J=5.0, 1.5 Hz), 6.90 (1H, br. s.), 6.74 (1H, s), 1.50 (9H, s); ¹³C NMR (101 MHz, CDCl₃) δ ppm 153.7, 153.1, 135.1, 135.3, 128.1, 127.1, 123.1, 120.8, 110.9, 83.6, 28.0; HRMS (m/z): [M + Na]⁺ for C₁₂H₁₄N₂O₄SNa, calcd, 305.0566; found, 305.0567.
Tert-butyl (5-(cyclohex-1-en-1-yl)-2-oxooxazol-3(2H)-yl)carbamate (Compound 2.59, Scheme 2.16):

Prepared according to the representative procedure for N-amino oxazolone synthesis using ynehydrazide 2.18 (116 mg, 0.345 mmol, 1.0 eq.) and PPh₃AuNTf₂ (27 mg of 2:1 complex with toluene0.017 mmol, 0.05 eq.) in CHCl₃ (2 mL) stirring for 2 hrs at room temperature. Isolated yield= 65 mg (67%) as a yellow solid. m.p. = 70-73 °C; Rf = 0.50 (40% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3303 (br.), 2980, 2934, 2866, 1774, 1729, 1495, 1393, 1367, 1248, 1157; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.03 (1H, br. s.), 6.36 (1H, s), 6.10 - 6.30 (1H, m), 2.12 - 2.22 (1H, m), 2.00 - 2.09 (1H, m), 1.60 - 1.73 (2H, m), 1.48 - 1.50 (4H, m), 1.47 (9H, s); ¹³C NMR (101 MHz, CDCl₃) δ ppm 155.8, 153.8, 139.2, 124.8, 123.2, 110.0, 83.2, 81.5, 28.1, 24.9, 23.2, 21.8; HRMS (m/z): [M + NH₄]⁺ for C₁₄H₂₄N₃O₄, calcd, 298.17668; found, 298.17671.

Synthesis of N-(2-oxo-5-phenyloxazol-3(2H)-yl)benzamide (Compound 2.60, Scheme 2.17):

N-amino oxazolone compound 2.53 (27.6 mg, 0.10 mmol, 1.0 eq.) was dissolved in THF (0.5 mL) in a N₂ purged MW vial and cooled to -78 °C a dry ice/acetone bath. KHMDS (0.22 mL of a 0.5 M sol’n in toluene, 0.11 mmol, 1.1 eq.) was added and the mixture stirred at -78 °C then benzoyl chloride (19.7 mg, 0.14 mmol, 1.4 eq.) as a sol’n in THF (0.5 mL) was added and the mixture removed from the cooling bath and stirred at room temperature. After 16 hrs, the mixture was diluted with ethyl acetate (50 mL) and sat’d NaHCO₃(aq) (10 mL) and phases separated. The organic extract was dried (MgSO₄), filtered through a 1 cm x 1 cm Si plug topped with celite using ethyl acetate (3 x 15 mL) to wash/elute. The filtrate was concentrated on the rotovap and the crude residue thus obtained was dissolved in MeCN (1 mL) and charged to a MW vial. Mg(ClO₄)₂ (2.2 mg, 0.01 mmol, 0.1 eq.) was added and the vial was capped and placed in a 55 °C oil bath and after 90 mins TLC showed complete consumption of the imide starting material. Volatiles were removed under an air stream and the crude material loaded directly onto silica gel using CH₂Cl₂ and purified by flash column chromatography through silica gel using ethyl acetate in hexanes to elute.
(gradient elution 0-100% EtOAc) providing 19.7 mg (70% yield) of Compound 2.60 (Scheme 2.17) as a white solid. m.p. = 172-175 °C; R\textsubscript{f} = 0.30 (40% EtOAc/hexanes); IR (CH\textsubscript{2}Cl\textsubscript{2}, cm\textsuperscript{-1}) 3249, 3146, 3062, 3007, 1776, 1762, 1680, 1517, 1487, 1274, 1121; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 7.95 (2H, dd, \(J=8.5, 1.5\) Hz), 7.62 - 7.69 (1H, m), 7.49 - 7.60 (6H, m), 7.43 (2H, t, \(J=7.5\) Hz), 7.30 - 7.37 (1H, m); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 169.0, 155.2, 139.7, 134.2, 132.5, 130.2, 130.1, 129.7, 129.0, 128.7, 124.2, 114.1; HRMS (m/z): [M + H]\textsuperscript{+} for C\textsubscript{16}H\textsubscript{13}N\textsubscript{2}O\textsubscript{3}, calcd, 281.0921; found, 281.0923.

**Synthesis of tert-butyl (5-(2-((tert-butyl dimethylsilyl)oxy)ethyl)-2-oxooxazolidin-3-yl)carbamate (Compound 2.61, Scheme 2.18):**

N-amino oxazolone compound 2.56 (23.0 mg, 0.064 mmol, 1.0 eq.) was dissolved in ethyl acetate (3 mL) and 10% w/w Pd/C (14 mg, ~ 0.2 eq. Pd) added and capped with a rubber septa and N\textsubscript{2} purged 3 mins then attached a H\textsubscript{2} balloon and purged 5 mins before fresh H\textsubscript{2} balloon attached and stirred at room temperature overnight. After 15 hrs, filtered through celite using ethyl acetate to wash/elute (40 mL) and concentrated in vacuo to give ~ 3:1 ratio of starting material:product. The crude material was re-subjected to the reaction conditions as described above and after a further 22 hrs (37 hrs total) was filtered through celite as above and concentrated in vacuo. The crude residue was purified by flash column chromatography through silica gel using ethyl acetate in hexanes (gradient elution 0-100% EtOAc) to elute providing 9.0 mg (39% yield) of Compound 2.61 (Scheme 2.18) as a clear oil. R\textsubscript{f} = 0.49 (40% EtOAc/hexanes); IR (CH\textsubscript{2}Cl\textsubscript{2}, cm\textsuperscript{-1}) 3363, 2980, 2931, 2858, 1708, 1653, 1479, 1392, 1367, 1249, 1157; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 6.47 (1H, br. s.), 6.22 (1H, br. s.), 4.57 - 4.85 (1H, m), 3.80 - 3.86 (1H, m), 3.73 - 3.79 (1H, m), 3.54 (1H, t, \(J=8.0\) Hz), 1.97 - 2.07 (1H, m), 1.84 - 1.95 (1H, m), 1.43 - 1.50 (9H, m), 0.88 (9H, s), 0.05 (6H, s); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 155.7, 154.1, 82.4, 81.6, 71.3, 58.5, 51.8, 37.6, 28.1, 25.8, -5.50; HRMS (m/z): [M + NH\textsubscript{4}]\textsuperscript{+} for C\textsubscript{16}H\textsubscript{36}N\textsubscript{5}O\textsubscript{5}Si, calcd, 378.24242; found, 378.24233.
Synthesis of tert-butyl ((3aS,3bS,6aS,6bR)-2,4,6-trioxo-5-phenyl-4,5,6,6a,7,8,9,10-octahydro-2H-benzo[e]oxazolo[5,4-g]isoindol-3(3aH,3bH,6bH)-yl)carbamate (Compound 2.62, Scheme 2.19):

N-amino oxazolone compound 2.59 (17.0 mg, 0.0606 mmol, 1.0 eq.) and N-phenyl maleimide (10.5 mg, 0.0606 mmol, 1.0 eq.) were combined in a MW vial. The vial was capped and N₂ purged for 5 mins before addition of toluene (0.5 mL) and placed in a 80 °C oil bath. After 3.5 hrs, TLC shows full conversion of cpd. 2.59. Volatiles were removed under air stream and ¹H NMR indicates a single [4+2] isomer has been formed. This residue was then loaded directly onto silica gel using CH₂Cl₂ and purified by flash column chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 15.5 mg (56% yield) Compound 2.62 (Scheme 2.19) as a clear wax. Rf= 0.31 (40% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3334, 3064, 2978, 2938, 2867, 1809, 1709, 1510, 1385, 1248, 1160, 1103; ¹H NMR (500 MHz, CDCl₃) δ ppm 7.42 - 7.48 (2H, m), 7.36 - 7.42 (1H, m), 7.10 - 7.16 (2H, m), 6.98 (1H, br. s.), 4.74 (1H, d, J=5.0 Hz), 3.62 (1H, t, J=8.5 Hz), 3.23 (1H, dd, J=8.5, 5.0 Hz), 2.36 - 2.48 (3H, m), 2.24 - 2.34 (1H, m), 1.90 - 1.97 (1H, m), 1.80 - 1.90 (1H, m), 1.59 - 1.64 (1H, m), 1.54 - 1.58 (1H, m), 1.50 (9H, s), 1.30 - 1.44 (1H, m); ¹³C NMR (126 MHz, CDCl₃) δ ppm 175.5, 173.7, 153.9, 153.7, 135.8, 131.2, 129.2, 129.0, 126.4, 111.8, 82.7, 54.6, 43.1, 42.2, 35.0, 28.2, 24.0, 22.1, 20.9, 20.3; HRMS (m/z): [M + Na]⁺ for C₂₄H₂₇N₅O₆Na, calcd, 476.1792; found, 476.1794.

Representative procedure for synthesis of N-heterocycle functionalized pyrazoles (Compounds 2.63 & 2.64, Scheme 2.20):

di-tert-butyl 1-(1-benzyl-1H-1,2,3-triazol-4-yl)hydrazine-1,2-dicarboxylate (Compound 2.23, 53 mg, 0.136 mmol, 1.0 eq.) was dissolved in 1.0 mL MeOH in a MW vial. 2,4-pentane dione (19 mg, 0.02 mL, 0.19 mmol, 1.4 eq.) was added followed by addition of 4N HCl in dioxane (0.5 mL). The mixture was stirred for 10 mins at room temperature then placed in a 80 °C oil bath for 15 mins. The reaction mixture was cooled to room
temperature and volatiles removed under a stream of air and crude residue partitioned between CH₂Cl₂ (75 mL) and sat’d NaHCO₃(aq) (15 mL) and the organic phase was separated and washed with sat’d NaCl(aq) (10 mL). The organic extract was dried (MgSO₄), filtered and concentrated in vacuo and the crude residue purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 18 mg (51% yield) of Compound 2.63 (Scheme 2.20) as a white solid.

1-Benzyl-4-(3,5-dimethyl-1H-pyrazol-1-yl)-1H-1,2,3-triazole (Compound 2.63, Scheme 2.20):

\[ \text{Isolated yield = 18 mg (51%) as a white solid. m.p. = 94-97 °C; Rf = 0.35 (5% MeOH/CH₂Cl₂); IR (CH₂Cl₂, cm}^{-1}) 3120, 3052, 2926, 2364, 2342, 1593, 1562, 1418, 1395, 1384; } \]
\[ \text{¹H NMR (300 MHz, CDCl₃) } \delta \text{ ppm 7.65 (1H, s), 7.29 - 7.44 (5H, m), 5.94 (1H, s), 5.53 (2H, s), 2.55 (3H, s), 2.23 (3H, s), } \]
\[ \text{¹³C NMR (75 MHz, CDCl₃) } \delta \text{ ppm 150.4, 141.4, 134.2, 129.4, 129.2, 128.6, 115.2, 107.6, 55.1, 13.6, 12.9; HRMS (m/z): } [M + H]^+ \text{ for C}_{14}H_{13}N₅, \text{ calcd, 254.1400; found, 254.1390.} \]

5-(5-Methyl-3-phenyl-1H-pyrazol-1-yl)-3-phenylisoxazole (Compound 2.64, Scheme 2.20):

\[ \text{Isolated yield = 24 mg (84%) of a combined 3:1 yield of both pyrazole regioisomers in favour of the one shown. Only the major isomer shown was fully characterized: 18 mg (64%) as a rose coloured solid. m.p. = 87-91 °C; Rf = 0.30 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm}^{-1}) 3360 (br.), 3053, 2988, 2930, 2364, 2307, 1624, 1578, 1414, 1114; } \]
\[ \text{¹H NMR (400 MHz, CDCl₃) } \delta \text{ ppm 7.74 (2H, m), 7.34 - 7.48 (8H, m), 6.34 (1H, s), 6.31 (1H, s), 2.41 (3H, s), } \]
\[ \text{¹³C NMR (100 MHz, CDCl₃) } \delta \text{ ppm 163.3, 162.3, 152.6, 145.8, 130.3, 129.3, 129.2, 128.9, 128.7, 128.62, 128.60, 126.7, 109.6, 91.8, 13.6; HRMS (m/z): } [M + H]^+ \text{ for C}_{19}H_{15}N₃O, \text{ calcd, 302.1287; found, 302.1302.} \]
Representative procedure for synthesis of N-functionalized 1,2,4-triazoles (Compounds 2.65 & 2.66, Scheme 2.21):

To di-tert-butyl 1-(1-benzyl-4-(p-tolyl)-1H-1,2,3-triazol-5-yl)hydrazine-1,2-dicarboxylate (Compound 2.32, 53 mg, 0.136 mmol, 1.0 eq.) in a MW vial was added formamide (0.5 mL, 567 mg, 12.6 mmol, 93 eq.) followed by 4N HCl in dioxane (0.25 mL) and the vial was capped and placed in a 120 °C heating block. After 12 hrs, the mixture was cooled to room temperature, vial was un-capped and volatiles removed under a stream of air. The crude residue was partitioned between CH$_2$Cl$_2$ (75 mL) and sat’d NaHCO$_3$(aq) (20 mL) and the organic phase was separated, dried (MgSO$_4$), filtered and concentrated in vacuo and the crude residue purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 15 mg (54% yield) of Compound 2.65 (Scheme 2.21) as a tan solid.

1-Benzyl-4-(p-tolyl)-5-(1H-1,2,4-triazol-1-yl)-1H-1,2,3-triazole (Compound 2.65, Scheme 2.21):

Isolated yield= 15 mg (54%) as a tan solid. m.p.= 172-174 °C; R$_f$= 0.28 (40% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3119, 3054, 2984, 2926, 2856, 2316, 1625, 1607, 1536, 1501, 1458, 1443, 1367, 1338; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 8.29 (1H, s), 7.73 (1H, s), 7.20 - 7.37 (5H, m), 7.14 (2H, d, $J$=8.0 Hz), 7.04 (2H, d, $J$=6.0 Hz), 5.49 (2H, s), 2.33 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 154.4, 146.2, 142.5, 139.6, 133.6, 130.0, 129.33, 129.19, 127.8, 127.2, 126.4, 125.4, 52.9, 21.5; HRMS (m/z): [M + H]$^+$ for C$_{18}$H$_{16}$N$_6$, calcd, 317.15147; found, 317.15241.

3-Phenyl-5-(p-tolyl)-4-(1H-1,2,4-triazol-1-yl)isoxazole (Compound 2.66, Scheme 2.21):

Performed as per the representative procedure using compound 2.39 (30 mg, 0.060 mmol, 1.0 eq.). Isolated yield= 11 mg (61%) as a tan solid. m.p.= 162-164 °C; R$_f$= 0.40 (40% EtOAc/hexanes); IR
(CH\textsubscript{2}Cl\textsubscript{2}, cm\textsuperscript{-1}) 3099, 2916, 2848, 1705, 1635, 1504, 1464, 1213, 1132; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 8.31 (1H, s), 8.12 (1H, s), 7.35 - 7.48 (5H, m), 7.30 - 7.34 (2H, m), 7.19 - 7.24 (2H, m), 2.38 (3H, s); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 166.7, 159.9, 154.0, 146.4, 142.5, 130.9, 130.2, 129.3, 127.6, 126.6, 126.5, 122.5, 112.1, 21.8; HRMS (m/z): [M + H]\textsuperscript{+} for C\textsubscript{18}H\textsubscript{14}N\textsubscript{4}O, calcd, 303.12459; found, 303.12420.

2.5 References


[23] Kwok, S. W.; Fotsing, J. R.; Fraser, R. J.; Rodionov, V. O.; Fokin, V. V. Org. Lett. 2010, 12, 4217-4219.

Chapter 3: Total Synthesis of the N–N Bond Containing Natural Products Geralcin A, Elaiomycin B and Hydrazidomycins A-B

3.1 Introduction

In contrast to their common incorporation in synthetic pharmaceutical molecules,\(^1\) hydrazine and hydrazide functional groups rarely occur in natural products.\(^2,3,4\) Although unusual, natural products containing a hydrazine functionality can exhibit impressive biological activities, as demonstrated by the potent broad spectrum antibiotic (\(+)\)-negamycin\(^3\) and the piperazic acid containing\(^4\) cytotoxic agents chloptosin, himastatin, and piperazimycin. In addition to these, a number of unusual enehydrazide compounds have recently been isolated from *Streptomyces* species including hydrazidomycins A-C,\(^5\) elaiomycins B and C,\(^6\) and geralcin B and C\(^7\) 3.1-3.6 (Figure 3.1). These compounds constitute a new family of N–N bond containing biologically active natural products, which include cytotoxic properties. In particular, hydrazidomycin A displays average *in vitro* IC\(_{50}\) cytotoxicity of 370 nM across a panel of 12 human cancer cell lines with specific values approaching clinical relevance (e.g., prostate PC-3M = 105 nM, stomach GXF 251L = 144 nM, colon CXF 269L = 222 nM).\(^5\)

The unprecedented Z-enehydrazide structure of the hydrazidomycins and the nano-molar anticancer activity of 3.1 prompted us to investigate this new enehydrazide antineoplastic pharmacophore and target these compounds for synthesis. The main synthetic challenges presented by structures 3.1-3.3 include the central *cis*-enehydrazide moiety, differentiation of the nitrogen atoms by two different acyl groups, and positional/geometric control of the additional *cis*-alkene in 3.2 and 3.3. Compared to the structurally similar and highly studied enamides,\(^8,9\) there are surprisingly very few reports concerning enehydrazide synthesis\(^10\) and to the best of our knowledge there are no examples of stereocontrolled *cis*-enehydrazide generation. In addition, although synthetic strategies to access enamides should in principle be applicable to target molecules 3.1–3.3, the synthesis of highly substituted hydrazide derivatives possessing
three or more distinct functional groups is not trivial. As a result, the combined task of developing a route to access the synthetically unexplored core \( Z \)-enehydrazide functionality, with the correct N–N bond substituent distribution posed unique synthetic challenges.

In Chapter 2 of this thesis, we described the discovery of a new class of 1-hydrazide-alkynes (ynehydrazides) and demonstrated their synthetic utility in the context of nitrogen heterocycle synthesis. In this chapter, we describe the attempted extension of these new hydrazide alkyne reagents toward the synthesis of natural products which contain an N–N bond fragment. The hydrazidomycins, for example, appeared to be only two hydrogen atoms away from a hypothetical ynehydrazide precursor and we were thus intrigued to explore a potential ynehydrazide approach to these \( Z \)-enehydrazide natural products via a stereoselective ynehydrazide reduction (Figure 3.2). This chapter describes our results in this area including an ynehydrazide approach to the total synthesis of geralcin A and a Peterson olefination route to construct the enehydrazide.

**Figure 3.1** Biologically active enehydrazide natural products 3.1-3.6
natural products hydrazidomycins A-B and elaionycin B. Importantly, this Peterson elimination approach represents the first highly stereocontrolled synthesis of previously unexplored Z-eneyhydrazide functional groups and a large portion of this chapter has been previously published.  

Figure 3.2 Proposed stereoselective enhydrazide reduction approach to Z-eneyhydrazide natural product hydrazidomycin A

3.3 Results and Discussion

Based on the analysis outlined in Figure 3.2, model reactions on simple eneyhydrazides provided proof-of-concept for selective synthesis of Z-eneyhydrazides via Lindlar reduction with good cis to trans stereochemistry as determined by $^1$H NMR (Scheme 3.1).

Scheme 3.1 Synthesis of Z-eneyhydrazides via stereoselective Lindlar reduction of eneyhydrazides

However, synthesis of the multi-substituted eneyhydrazide precursor 3.7 required for the synthesis of 3.1 proved difficult. For example, reaction of the lithium-acetylide of tetradehydye with DBAD (di-t-butyl-azodicarboxylate) and in situ capping with methoxyacetyl chloride furnished eneyhydrazide 3.10 (Scheme 3.2). Selective conversion of the N-Boc protected alkynyl-linked group to the required decanoyl amide was not
possible, due to the acid-lability of the ynehydrazide component. Nevertheless, the structural analogs 3.11 and 3.13 were readily accessible from 3.10, demonstrating the utility of an ynehydrazide-based strategy for the synthesis of congeners of 3.1 to test for cytotoxic activity.

**Scheme 3.2** Ynehydrazide based approach to hydrazidomycin A analogs

In addition, this ynehydrazide approach to regioselectively prepare multiply substituted hydrazides such as compound 3.13 inspired us to investigate an ynehydrazide strategy to prepare the related alkyl-hydrazide natural product geralcin A (Scheme 3.3). Geralcin A (3.16) was isolated with the structurally similar enehydrazide geralcin B natural product 3.5 but was not observed to possess any cytotoxic activity. At the outset of our study, 3.16 had not previously been synthesized, however, a total synthesis of this compound has recently been reported. In our approach, we were pleased to observe that formation of ynehydrazide 3.14 successfully enabled the total synthesis of this hydrazide natural product and further demonstrates the utility of using ynehydrazides to generate multiply functionalized hydrazide compounds (Scheme 3.3).
Scheme 3.3 Total synthesis of geralcin A using an ynehydrazide approach

Returning to our initial goal of preparing the Z-enehydrazide hydrazidomycins, the problems encountered in the ynehydrazide approach prompted the investigation of other routes toward the stereocontrolled formation of enehydrazides. In this area, one obvious strategy involved potential formation of ynehydrazide 3.7 or Z-enehydrazide 3.20 using palladium or copper mediated C–N bond formation with alkynyl or Z-alkenyl-bromides respectively (Scheme 3.4). Toward this goal, a deceptively simple tri-substituted hydrazide coupling partner with the correct placement of hydrazidomycin amide functionality was required. To accomplish this task, the primary amine portion of Boc-carbazate was di-blocked via hydrazone formation followed by an acylation/deprotection/acylation sequence to give hydrazide 3.19 as C–N coupling precursor (Scheme 3.4). Unfortunately, despite numerous attempts to facilitate alkynyl or Z-alkenyl group transfer under Cu or Pd catalyzed conditions, these reactions resulted in near complete recovery of hydrazide 3.19 with only a trace amount of C–N coupled products as indicated by LR-MS.
Scheme 3.4 Unsuccessful Pd or Cu catalyzed C–N bond forming approach to hydrazidomycin A

Interestingly, an alternative ynehydrazide synthesis using 3.19 was accomplished via reaction with a TMS-alkynyl iodonium triflate reagent (Scheme 3.5). Deprotection with TBAF provided terminal ynehydrazide 3.21 which we presumed could serve as a common intermediate to access multiple members of the hydrazidomycin family via acetylide alkylation. In the event, however, alkylation was not observed due to apparent hydrazide decomposition via possible imide de-acylation pathways.

Scheme 3.5 Synthesis of a terminal ynehydrazide with correct hydrazidomycin functional group distribution

Frustrated by the above failures, a comprehensive review of literature concerning Z-enamide formation revealed an interesting Peterson elimination\textsuperscript{14,15,16} based approach to construct either \textit{cis} or \textit{trans} enamides in a highly stereocontrolled fashion. Notably, this Peterson silanol elimination strategy has precedent in total synthesis applications having been used to install the central Z-enamide moiety of the biologically active crocacin natural products.\textsuperscript{16} We thus became interested in pursuing a similar type of Peterson olefination approach to construct the troublesome core \textit{cis}-enehydrazide of the
hydrazidomycins. Furthermore, an attractive feature of such an approach is the possibility of achieving highly stereocontrolled formation of either Z- or E-enehydrazides by appropriate substrate choice or elimination conditions.

To investigate a Peterson disconnection to enehydrazide natural products 3.1-3.3, development of regio- and stereoselective access to previously unknown hydrazine functionalized vicinal silanol derivatives was first required. In this regard, prior work on Z-enamides\(^{15-16}\) suggested that the key \textit{anti}-\(\beta\)-silyl-\(\beta\)-hydrazidoalcohols, needed for a base mediated Peterson elimination to Z-enehydrazides, might be accessible by silyl-directed ring-opening of a \textit{cis}-silylepoxide with a hydrazine nucleophile. Surprisingly, even though sodium azide is known to regioselectively ring-open silylepoxides, there are very few examples of such a reaction with other less nucleophilic heteroatom nucleophiles\(^{15d-e}\) and none using hydrazines.

To probe a hydrazine silyl epoxide ring opening toward hydrazidomycin A via silanol elimination, syn-epoxide 3.23 was prepared from tetradecyne in three steps using a hydroalumination reaction to set the important cis-geometry with excellent stereocontrol (Scheme 3.6). Initial attempts to then ring-open epoxide 3.23 with hydrazine or MeOH\(\cdot\)CONHNH\(\_2\) in the presence of either \(\text{NH}_4\text{Cl}\)\(^{15a-b,16}\) or \(\text{BF}_3\cdot\text{OEt}_2\)^{15d-e} catalysis were unsuccessful (Table 3.1). However, reaction of an excess of Boc-carbazate with 3.23 at 45 °C under \(\text{BF}_3\cdot\text{OEt}_2\) catalysis (10 mol %) allowed for the regioselective and stereospecific opening of the silyl-epoxide to give 3.24.

\[
\begin{align*}
\text{H} & \quad \text{C}_{12}\text{H}_{25} \quad \text{1. } \text{n-BuLi, TMS-Cl} \quad \text{THF, -78 °C to rt} \quad \text{TMS} \quad \text{C}_{12}\text{H}_{25} \\
& \quad \text{2. DIBAL-H, NMM} \quad \text{Et}_2\text{O, rt, 18 h} \quad \text{mCPBA} \quad \text{CH}_2\text{Cl}_2, \text{rt, 18 h} \quad \text{TMS} \quad \text{C}_{12}\text{H}_{25}
\end{align*}
\]

\textbf{Scheme 3.6} Synthesis of a \textit{syn} silyl-epoxide for hydrazine ring-opening toward a Peterson olefination of hydrazidomycin A
Table 3.1 Hydrazide ring-opening of syn silyl-epoxide 3.23

<table>
<thead>
<tr>
<th>R^1</th>
<th>conditions</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>H^b</td>
<td>NH_4Cl (2 equiv), MeOH/H_2O, 16 h, 65 °C</td>
<td>3%</td>
</tr>
<tr>
<td>Boc</td>
<td>NH_4Cl (2 equiv), MeOH/H_2O, 16 h, 65 °C</td>
<td></td>
</tr>
<tr>
<td>H^b</td>
<td>BF_3·OEt_2 (10 mol %), THF, 16 h, rt</td>
<td></td>
</tr>
<tr>
<td>MeOCH_2C(O)</td>
<td>BF_3·OEt_2 (10 mol %), THF, 16 h, 45 °C</td>
<td>30%</td>
</tr>
<tr>
<td>Boc</td>
<td>BF_3·OEt_2 (10 mol %), THF, 16 h, rt</td>
<td>75%</td>
</tr>
<tr>
<td>Boc</td>
<td>BF_3·OEt_2 (10 mol %), THF, 16 h, 45 °C</td>
<td></td>
</tr>
</tbody>
</table>

a) 2.0 equiv of R^1NHNH_2 used. b) Hydrazine monohydrate used. c) Near quantitative recovery of 3.23. d) Decomposition of 3.23. e) Decomposition of hydrazide. f) 4.0 equiv of R^1NHNH_2 used.

This represents the first example of a silyl-epoxide ring-opening reaction with a hydrazine nucleophile and conveniently, the use of Boc-carbazate in this ring-opening reaction provides suitably differentiated hydrazine nitrogens for site selective functionalization. Subsequently, acylation of hydrazide derivative 3.24 provided tri-substituted hydrazide intermediate 3.25 which was then successfully converted to the natural product target 3.1 in only three additional steps (Scheme 3.7). For convenience, and to limit silica gel exposure of the potentially labile Z-enehydrazide moiety, a telescoped three-step protocol proved optimal, utilizing a KOtBu mediated Peterson elimination followed immediately by Boc-carbamate acylation and catalytic Mg(II) imide-Boc deprotection. The total synthesis of hydrazidomycin A was thus achieved with complete control of Z-olefin geometry, in an overall yield of 16% over 8 steps.
Scheme 3.7 Base-mediated Peterson olefination total synthesis of hydrazidomycin A (3.1)

As mentioned previously, an attractive aspect of the Peterson based strategy to enehydrazides is the stereospecific and stereodivergent nature of acid or base mediated silanol elimination. Thus, a complimentary acid mediated silanol elimination sequence of 3.25 conveniently furnished the corresponding isomeric trans-hydrazidomycin A analog 3.26 in 50% yield over three steps (Scheme 3.8). Comparison of olefin coupling constants for 3.1 ($J = 9.0$ Hz) with 3.26 ($J = 14.0$ Hz) confirms the cis-stereochemical assignment for 3.1.

Scheme 3.8 Synthesis of an $E$-hydrazidomycin A analog via acid-mediated silanol elimination of 3.25
Adaptation of this Peterson olefination sequence toward the total synthesis of 3.2 and 3.3 was then undertaken using a similar alkyne hydroalumination based route to access the required hydrazino silanol precursors (Scheme 3.9). Reaction of 3.27 and 3.28 with a slight excess of DIBAL-H resulted in mixtures of the expected Z-alkenyl TBS protected alcohols and the corresponding O-deprotected products\textsuperscript{18} 3.29 and 3.30. This observation led to the development of a direct one-pot conversion of 3.27 / 3.28 into 3.29 / 3.30 using an excess amount of DIBAL-H to accomplish a highly stereoselective hydroalumination and TBS group deprotection. After epoxidation, the internal Z-olefins of these two enehydrazide natural products were then successfully installed using an oxidation/Wittig olefination sequence to provide 3.33 and 3.34, followed by Boc-carbazate epoxide ring opening to afford the key enehydrazide precursors 3.35 and 3.36. The observation of a single set of olefin carbons in the $^{13}$C NMR of 3.33-3.36 combined with alkene $^1$H NMR vicinal coupling constants of ~5.5–6.0 Hz support a cis-alkene stereochemical assignment.

Scheme 3.9 Synthesis of Peterson elimination precursors 3.35 and 3.36 for hydrazidomycin B (3.2) and elaiomycin B (3.3) synthesis

Completion of the total syntheses of hydrazidomycin B 3.2 and elaiomycin B 3.3 from 3.35 and 3.36 was then accomplished in four steps in an analogous manner to the previously described hydrazidomycin A synthesis. Thus, compounds 3.2 and 3.3 were
prepared in 7.3% and 6.7% overall yields respectively in a stereocontrolled fashion over 11 steps (Schemes 3.10 & 3.11).

Scheme 3.10 Completion of the synthesis of hydrazidomycin B 3.2 via base mediated Peterson silanol elimination

Scheme 3.11 Completion of the synthesis of elaiomycin B 3.3 via base mediated Peterson silanol elimination

3.3 Conclusions

In conclusion, we have demonstrated two distinct modes of preparing previously unexplored Z-enehydrazides via either stereoselective reduction of ynehydrazides or through a carbazate ring-opening/Peterson olefination sequence. Importantly, the Peterson elimination strategy enabled the first total synthesis of three structurally unique
Z-enehydrazide containing natural products in a stereocontrolled fashion. Moreover, because silanol elimination is stereodivergent, we have demonstrated that our carbazate epoxide opening can also be used to access E-enehydrazides in a complimentary acid-mediated protocol. Overall, these results should be amenable toward preparation of a variety of hydrazidomycin analogs to investigate this novel anti-tumoral pharmacophore class.

In addition to enehydrazides, we have also demonstrated that ynehydrazides can be useful precursors to regioselectively prepare highly substituted alkyl-hydrazides. This strategy was demonstrated in the preparation of an alkyl hydrazidomycin A analog as well as the total synthesis of the alkyl hydrazide natural product geralcin A.

3.4 Experimental Section

Copies of $^1$H and $^{13}$C NMR spectra for all new compounds and synthesized natural products listed above can be found in Appendix 2. THF and Et$_2$O were dried over sodium benzophenone-ketyl and toluene and acetonitrile were dried over calcium hydride and solvents distilled fresh under nitrogen atmosphere before use and transferred via syringe using standard techniques unless otherwise stated. All chemical manipulations were performed under a N$_2$ atmosphere unless otherwise stated. All reagents including tetradecyne, 3-octyn-1-ol, Lindlar’s catalyst, Boc-carbazate, KHMDS (0.5M in toluene), Et$_3$N, acid chlorides, KOTBu, TBS-Cl, TBAF (1M in THF), DIBAL (1M in hexanes), Mg(ClO$_4$)$_2$, BF$_3$·OEt$_2$ were purchased from Aldrich or VWR and used as received unless otherwise stated. 6-heptyn-1-ol was purchased from Matrix Scientific. TMS-Cl was distilled from calcium hydride before use. 7-octyn-1-ol was prepared according to a modified literature procedure. Ynehydrazide starting materials for synthesis of compounds 3.8 & 3.9 (Scheme 3.1) were prepared as described previously. Carboxylic acid 3-(2-oxo-2,5-dihydrofuran-3-yl)propanoic acid used in the synthesis of geralcin A (Compound 3.16, Scheme 3.3) was prepared according to a literature procedure. NMR solvents (CDCl$_3$ with TMS internal standard, d$_6$-DMSO, d$_4$-MeOH) were purchased from Cambridge Isotopes Lab Inc. and used as received.
All products were characterized by $^1$H NMR and $^{13}$C NMR, IR and HRMS. $^1$H NMR and $^{13}$C NMR were recorded on Varian Mercury 300 MHz, 400 MHz, 500 MHz or Bruker 400 MHz spectrometers. Chemical shifts are expressed in ppm values and $^1$H NMR spectra are referenced to Me$_4$Si internal standard of 0.00 ppm for CDCl$_3$ and to residual solvent peaks for d$_6$-DMSO, d$_4$-MeOH, d$_7$-DMF (2.50, 3.31, and 8.03 respectively). $^{13}$C NMR spectra are referenced to residual solvent peaks: 77.00 ppm for CDCl$_3$, 39.52 for d$_6$-DMSO, 49.00 for d$_4$-MeOH, and 34.89 for d$_7$-DMF. $^{13}$C NMR spectrum for elaiomycin B (compound 3.3) was referenced to a residual d$_6$-DMSO solvent peak of 39.7 for direct comparison with the isolation paper of the natural material.\textsuperscript{6a} $^{13}$C NMR spectra for hydrazidomycin B and elaiomycin B (compounds 3.2-3.3) were run on an Agilent DD2 500 MHz spectrometer with a HC 5-mm XSens cryogenically cooled probed. Peak multiplicities are designated by the following abbreviations: s, singlet; br.s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; r, rotomers; J, coupling constant in Hz. The coupling constant $J$ (Hz) has been rounded to 0.5 Hz for all compounds except hydrazidomycins A-B and elaiomycin B (compounds 3.1-3.3) where coupling constants are rounded to 0.1 Hz. If a coupling pattern can be assigned as a combination of multiplicities, then the listed abbreviations are combined to provide an appropriate descriptor for the observed patterns (e.g., dt - doublet of triplets). IR spectra were obtained on a Shimadzu FTIR-8400S with samples loaded as thin films on NaCl plates neat or with CH$_2$Cl$_2$ as indicated. Mass spectra were obtained by the University of Toronto mass spectral facility (AIMS); high resolution mass spectra (HRMS) were recorded on an AEI MS3074 spectrometer. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Flash column chromatography on silica gel (60 Å, 230-400 mesh, obtained from Silicycle Inc.) was performed with reagent grade ethyl acetate and hexanes as eluents. Analytical thin-layer chromatography (TLC) was performed on pre-coated aluminum-backed silica gel plates (Alugram SIL G/UV254 purchased from Rose Scientific Limited or Silicycle Inc.) and visualized using KMnO$_4$, or ninhydrin and heating.
Table 3.2. Synthetic vs. Natural $^{13}$C NMR data for Hydrazidomycins A and B (3.1-3.2)$^a$

<table>
<thead>
<tr>
<th></th>
<th>Hydrazidomycin A</th>
<th></th>
<th>Hydrazidomycin B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Natural$^5$</td>
<td>Synthetic</td>
<td>Natural$^5$</td>
</tr>
<tr>
<td>173.3</td>
<td>173.2</td>
<td>173.2</td>
<td>173.1</td>
</tr>
<tr>
<td>167.8</td>
<td>167.6</td>
<td>167.7</td>
<td>167.6</td>
</tr>
<tr>
<td>124.3</td>
<td>124.3</td>
<td>129.6 (2 C’s)</td>
<td>129.62, 129.55</td>
</tr>
<tr>
<td>117.2</td>
<td>117.3</td>
<td>124.3</td>
<td>124.3</td>
</tr>
<tr>
<td>70.7</td>
<td>70.7</td>
<td>117.1</td>
<td>117.1</td>
</tr>
<tr>
<td>59.0</td>
<td>58.9</td>
<td>70.7</td>
<td>70.7</td>
</tr>
<tr>
<td>31.4</td>
<td>31.3</td>
<td>59.0</td>
<td>58.9</td>
</tr>
<tr>
<td>31.2</td>
<td>31.2</td>
<td>31.3</td>
<td>31.3</td>
</tr>
<tr>
<td>29.2, 29.1 (5C’s)</td>
<td>29.07, 29.03 (5C’s)</td>
<td>31.2 (2C’s)</td>
<td>31.27, 31.15</td>
</tr>
<tr>
<td>29.0 (2C’s)</td>
<td>29.0, 28.87</td>
<td>29.1 (2C’s)</td>
<td>29.12, 28.99</td>
</tr>
<tr>
<td>28.8 (2C’s)</td>
<td>28.84, 28.80</td>
<td>28.9 (2C’s)</td>
<td>28.89 (2C’s)</td>
</tr>
<tr>
<td>28.7 (2C’s)</td>
<td>28.69 (2C’s)</td>
<td>28.8 (2C’s)</td>
<td>28.82 (2C’s)</td>
</tr>
<tr>
<td>28.6 (2C’s)</td>
<td>28.65, 28.57</td>
<td>28.7</td>
<td>28.67</td>
</tr>
<tr>
<td>25.9</td>
<td>25.8</td>
<td>28.6 (3C’s)</td>
<td>28.57, 28.54, 28.46</td>
</tr>
<tr>
<td>23.9</td>
<td>23.8</td>
<td>26.6 (2C’s)</td>
<td>26.62, 26.58</td>
</tr>
<tr>
<td>22.2 (2C’s)</td>
<td>22.1 (2C’s)</td>
<td>25.9</td>
<td>25.8</td>
</tr>
<tr>
<td>14.1 (2C’s)</td>
<td>13.9 (2C’s)</td>
<td>23.9</td>
<td>23.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22.1 (2C’s)</td>
<td>22.09, 22.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.9 (2C’s)</td>
<td>13.93, 13.92</td>
</tr>
</tbody>
</table>

a) δ in ppm; d6-DMSO at 25 °C relative to 39.52 solvent residual peak$^5$
Table 3.3 Synthetic vs. Natural $^{13}$C NMR data for Elaiomyacin B (3.3)a

<table>
<thead>
<tr>
<th>Natural$^{6a}$</th>
<th>Synthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>173.4</td>
<td>173.4</td>
</tr>
<tr>
<td>167.8</td>
<td>167.8</td>
</tr>
<tr>
<td>129.8</td>
<td>129.87</td>
</tr>
<tr>
<td>129.7</td>
<td>129.67</td>
</tr>
<tr>
<td>124.4</td>
<td>124.5</td>
</tr>
<tr>
<td>117.4</td>
<td>117.2</td>
</tr>
<tr>
<td>70.9</td>
<td>70.9</td>
</tr>
<tr>
<td>58.5</td>
<td>59.1</td>
</tr>
<tr>
<td>31.4</td>
<td>31.4</td>
</tr>
<tr>
<td>31.3, 31.2</td>
<td>31.3 (2C’s)</td>
</tr>
<tr>
<td>29.3</td>
<td>29.3</td>
</tr>
<tr>
<td>29.2-28.6</td>
<td>29.12, 29.06, 29.04, 28.99, 28.91, (9C’s)</td>
</tr>
<tr>
<td>26.8</td>
<td>26.8</td>
</tr>
<tr>
<td>26.7</td>
<td>26.7</td>
</tr>
<tr>
<td>26.0</td>
<td>25.9</td>
</tr>
<tr>
<td>23.9</td>
<td>24.0</td>
</tr>
<tr>
<td>22.3 (2C’s)</td>
<td>22.27, 22.26</td>
</tr>
<tr>
<td>14.1 (2C’s)</td>
<td>14.12, 14.12</td>
</tr>
</tbody>
</table>

a) $\delta$ in ppm; d6-DMSO at 25 °C relative to 39.7 solvent residual peak$^{6a}$

Synthesis of (Z)-di-tert-butyl 1-(oct-1-en-1-yl)hydrazine-1,2-dicarboxylate
(Compound 3.8, Scheme 3.1):

Di-tert-butyl 1-(oct-1-yn-1-yl)hydrazine-1,2-dicarboxylate ynehydrazide prepared according to the previously disclosed procedure$^{20}$ (68 mg, 0.2 mmol) in CH$_2$Cl$_2$ (20 mL) was charged with Lindlar’s catalyst (22 mg 5 wt% Pd on CaCO$_3$ poisoned with Pb) and the flask was sealed with a rubber septum and purged with nitrogen then a balloon of hydrogen attached and purged for 5 mins, then a fresh hydrogen balloon attached and stirred at room temperature. When complete by TLC (26 hours) the flask was purged with nitrogen for 5 mins then diluted with CH$_2$Cl$_2$ (40 mL) and filtered through a short celite plug and concentrated in vacuo. The crude material thus obtained was purified by flash column chromatography using ethyl acetate
in hexanes to elute (gradient elution 0-100% EtOAc) providing 52 mg (76% yield) of Compound 3.8 (Scheme 3.1) as a clear oil with ≥ 10:1 Z:E olefin geometry by $^1$H NMR (only peaks for the Z isomer are listed). $R_f = 0.42$ (20% EtOAc/hexanes); IR (neat, cm$^{-1}$) 3308 (br), 2978, 2922, 2857, 1751-1655 (br m), 1506, 1381, 1323, 1249, 1165; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 6.46 (1H, br. s.), 6.08 - 6.36 (1H, m), 4.80 (1H, d, $J$=8.0 Hz), 2.15 (2H, app q, $J$=6.0 Hz), 1.41 - 1.56 (18H, m), 1.19 - 1.38 (8H, m), 0.88 (3H, t, $J$=6.0 Hz); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 6.46 (1H, br. s.), 6.08 - 6.36 (1H, m), 4.80 (1H, d, $J$=8.0 Hz), 2.15 (2H, app q, $J$=6.0 Hz), 1.41 - 1.56 (18H, m), 1.19 - 1.38 (8H, m), 0.88 (3H, t, $J$=6.0 Hz); $^1$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 154.9, 153.6, 125.3, 117.5, 82.0, 81.4, 31.7, 29.7, 29.1, 28.2, 28.1, 26.4, 22.6, 14.1; HRMS (m/z): [M + H]$^+$ for C$_{18}$H$_{35}$N$_2$O$_4$, calcd, 343.2591; found, 343.2607.

**Synthesis of (Z)-di-tert-butyldi-(4-fluorostyryl)hydrazine-1,2-dicarboxylate** (Compound 3.9, Scheme 3.1):

Di-tert-butyldi-(4-fluorophenylethynyl)hydrazine-1,2-dicarboxylate ynehydrazide prepared according to the previously disclosed procedure$^{20}$ (44 mg, 0.12 mmol) in CH$_2$Cl$_2$ (12 mL) was charged with Lindlar’s catalyst (13 mg 5 wt% Pd on CaCO$_3$ poisoned with Pb) and the flask was sealed with a rubber septum and purged with nitrogen then a balloon of hydrogen attached and purged for 5 mins, then a fresh hydrogen balloon attached and stirred at room temperature. When complete by TLC (2 hours) the flask was purged with nitrogen for 5 mins then diluted with CH$_2$Cl$_2$ (40 mL) and filtered through a short celite plug and concentrated in vacuo. The crude material thus obtained was purified by flash column chromatography using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 52 mg (76% yield) of Compound 3.9 (Scheme 3.1) as a clear oil with ≥ 10:1 Z:E olefin geometry by $^1$H NMR (only peaks for the Z isomer are listed). $R_f = 0.45$ (20% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3313, 2979, 2935, 1888, 1722, 1656, 1603, 1511, 1368, 1316, 1155, 1052, 1023, 873, 849; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.24 (2H, m), 6.98 (2H, dd, $J$= 9.0, 9.0 Hz), 6.41-6.86 (1H, m), 6.17 (1H, br. s.), 5.79 (1H, d, $J$=9.5 Hz), 1.22 - 1.52 (18H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 161.8 (1C, d, $J = 245$ Hz), 154.1, 153.5, 132.5, 130.3, 127.1, 115.1 (1C, d, $J = 21$ Hz), 112.4, 83.0, 81.8, 28.3, 28.2; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ ppm -116.29 (1F, s, major cis isomer), -115.69 (1F,
s, minor trans isomer); HRMS ($m/z$): [M + H]$^+$ for C_{18}H_{26}FN_{2}O_{4}, calcd, 353.18766; found, 353.18869.

**Synthesis of di-tert-butyl 1-(2-methoxyacetyl)-2-(tetradec-1-yn-1-yl)hydrazine-1,2-dicarboxylate (Compound 3.10, Scheme 3.2):**

A solution of 1-tetradecyne (389 mg, 0.49 mL, 2.0 mmol, 1.0 eq.) in THF (8 mL) was cooled to 0 °C and treated with n-BuLi (0.96 mL of a 2.5 M sol’n in hexanes, 2.4 mmol, 1.2 eq.) and stirred for 10 mins. The mixture was then cooled to -78 °C and a solution of di-tert-butyl-diazodicarboxylate (690 mg, 3.0 mmol, 1.5 eq.) in THF (4 mL) was added quickly by syringe and the mixture removed from the cooling bath and warmed to room temperature. After stirring for 30 mins at room temperature, the mixture was re-cooled to -78 °C and a solution of methoxyacetyl chloride (326 mg, 0.27 mL, 3.0 mmol, 1.5 eq.) in THF (2 mL) was added and the cooling bath removed and warmed to room temperature. After stirring at room temperature for 14 hours the mixture was diluted with sat’d NH$_4$Cl(aq) (10 mL) and water (10 mL) and ethyl acetate (100 mL) and the phases were separated. The organic phase was dried (MgSO$_4$), filtered and concentrated *in vacuo* and the crude material thus obtained was purified by flash column chromatography using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 616 mg (62% yield) of Compound 3.10 (Scheme 3.2) as a yellow oil. $R_f$ = 0.35 (20% EtOAc/hexanes); IR (neat, cm$^{-1}$) 2980, 2926, 2855, 2830, 2266, 1802, 1740, 1456, 1395, 1371, 1151, 1130, 849; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 4.42 – 4.56 (2H, m, r), 3.48 (3H, s), 2.23 – 2.35 (2H, m, r), 1.42 - 1.62 (20H, m), 1.18 - 1.41 (18H, m), 0.83 - 0.92 (3H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm (major rotomer) 169.0, 151.7, 150.4, 85.1, 84.1, 73.0, 72.0, 71.6, 59.4, 31.9, 29.7, 29.6, 29.4, 29.2, 28.9, 28.8, 28.7, 27.89, 27.86, 27.8, 22.7, 18.4, 14.1; HRMS ($m/z$): [M + Na]$^+$ for C$_{27}$H$_{48}$N$_2$O$_6$Na, calcd, 519.3404; found, 519.3425.
Synthesis of (Z)-tert-butyl-2-(2-methoxyacetyl)-1-(tetradec-1-en-1-yl)hydrazinecarboxylate (Compound 3.11, Scheme 3.2):

To compound 3.10 (0.207 mmol, 1.0 eq., 103 mg) dissolved in MeCN (5 mL) was added Mg(ClO$_4$)$_2$ (4.6 mg, 0.0207 mmol, .1 eq.) and the mixture placed in a 55 °C oil bath with a reflux condenser. After 2 hours the mixture was cooled to room temperature and concentrated in vacuo and the crude material thus obtained was purified by flash column chromatography using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 64 mg (78% yield) of Boc deprotected compound as a clear oil. R$_f$ = 0.11 (20% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3299, 2979, 2925, 2855, 2264, 1748, 1714, 1489, 1370, 1318, 1253, 1156, 1117; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 8.38 (1H, s), 4.04 (2H, s), 3.44 (3H, s), 2.28 (2H, t, $J$=7.0 Hz), 1.43 - 1.57 (11H, m), 1.33 - 1.41 (2H, m), 1.22 - 1.30 (16H, m), 0.88 (3H, t, $J$=7.0 Hz); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 167.6, 152.5, 84.0, 72.6, 71.6, 71.1, 59.5, 31.9, 29.63, 29.61, 29.60, 29.5, 29.3, 29.1, 28.8, 28.7, 27.8, 22.6, 18.4, 14.1; HRMS (m/z): [M + H]$^+$ for C$_{22}$H$_{41}$N$_2$O$_4$, calcd, 397.30663; found, 397.30757.

Boc deprotected ynehydrazide compound prepared above (38 mg, 0.096 mmol, 1.0 eq.) was dissolved in CH$_2$Cl$_2$ (10 mL) and Lindlar’s catalyst (11 mg 5 wt% Pd on CaCO$_3$ poisoned with Pb) was added. The flask was sealed with a rubber septum and purged with nitrogen then a balloon of hydrogen attached and purged for 5 mins, then a fresh hydrogen balloon attached and stirred at room temperature. When complete by $^1$H NMR (17 hours) the flask was purged with nitrogen for 5 mins then diluted with CH$_2$Cl$_2$ (40 mL) and filtered through a short celite plug and concentrated in vacuo. The crude material thus obtained was purified by flash column chromatography using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 29 mg (76% yield, 59% over 2 steps) of Compound 3.11 (Scheme 3.2) as a clear oil with $\geq$ 10:1 Z:E olefin geometry by $^1$H NMR. R$_f$ = 0.48 (40% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3298, 2925, 2854, 1722, 1693, 1504, 1456, 1368, 1456, 1368, 1316, 1255, 1168, 1118; $^1$H NMR (300
MHz, CDCl₃) δ ppm 8.21 (1H, s), 6.22 - 6.51 (1H, m), 4.87 (1H, ddd, J=8.50, 7.50, 7.50 Hz), 4.01 (2H, s), 3.45 (3H, s), 2.08 (2H, qd, J=7.0, 1.5 Hz), 1.48 (9H, s), 1.19 - 1.38 (20H, m), 0.88 (3H, t, J=7.0 Hz); ¹³C NMR (126 MHz, CDCl₃) δ ppm 167.8, 153.0, 125.4, 119.4, 82.6, 71.8, 59.5, 31.9, 29.66, 29.64, 29.62, 29.61, 29.50, 29.39, 29.33, 28.1, 26.5, 22.7, 14.1; HRMS (m/z): [M + Na]⁺ for C₄₂H₄₂N₂O₄Na, calcd, 421.3036; found, 421.3038.

**Synthesis of di-tert-butyl 1-(2-methoxycetyl)-2-(tetradecyl)hydrazine-1,2-dicarboxylate (Compound 3.12, Scheme 3.2):**

Compound 3.11 (95 mg, 0.191 mmol, 1.0 eq.) was dissolved in ethyl acetate (5 mL) and Pd/C (21 mg 10 wt% dry Pd/C) was added. The flask was sealed with a rubber septum and purged with nitrogen then a balloon of hydrogen attached and purged for 5 mins, then a fresh hydrogen balloon attached and stirred at room temperature. After 18 hours the flask was purged with nitrogen for 5 mins then diluted with ethyl acetate (40 mL) and filtered through a short celite plug and concentrated in vacuo. The crude material thus obtained was purified by flash column chromatography using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 69 mg (72% yield) of Compound 3.12 (Scheme 3.2) as a clear oil. Rf = 0.44 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3379, 2977, 2925, 2855, 1739, 1721, 1460, 1394, 1369, 1322, 1254, 1151, 1128, 849; ¹H NMR (400 MHz, CDCl₃) δ ppm 4.46 - 4.56 (2H, m), 3.46 - 3.57 (1H, m), 3.44 - 3.46 (3H, m), 3.23 - 3.36 (1H, m), 1.37 - 1.53 (21H, m), 1.21 - 1.30 (21H, m), 0.86 (3H, t, J=7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ ppm (major rotomer) 170.5, 153.6, 152.2, 84.3, 81.1, 73.4, 59.2, 49.0, 31.9, 29.61, 29.56, 29.39, 29.32, 28.19, 28.12, 28.04, 27.87, 27.82, 27.49, 26.9, 22.6, 14.1; HRMS (m/z): [M + NH₄]⁺ for C₂₂H₄₂N₂O₄Na, calcd, 418.3036; found, 418.3038.

**N’-(2-methoxycetyl)-N-tetradecyldecanehydrazide (Compound 3.13, Scheme 3.2):**

Compound 3.12 (67 mg, 0.133 mmol, 1.0 eq.) dissolved in CH₂Cl₂ (3 mL) was cooled to 0 °C and treated with TFA (0.20
mL) and stirred for 3 hours allowing to warm to room temperature. A further portion of TFA (0.60 mL) was then added and stirred at room temperature until complete by TLC (4 hours, 7 hours total). The mixture was diluted with CH$_2$Cl$_2$ (50 mL) and washed with sat’d NaHCO$_3$(aq) (10 mL), and the organic phase was separated, dried (MgSO$_4$), filtered concentrated in vacuo to provide 35 mg (88% yield) of crude Boc deprotected intermediate as a white solid.

The deprotected hydrazide prepared above (35 mg, 0.116 mmol, 1.0 eq.) was dissolved in CH$_2$Cl$_2$ (2 mL) and cooled to 0 ºC before addition of Et$_3$N (16 mg, 0.162 mmol, 1.4 eq.) as a solution in CH$_2$Cl$_2$ (0.5 mL) followed by addition of decanoyl chloride (24 mg, 0.128 mmol, 1.1 eq.) as a solution in CH$_2$Cl$_2$ (0.5 mL). The mixture was stirred overnight allowing to warm to room temperature. After 16 hours the mixture was diluted with CH$_2$Cl$_2$ (50 mL) and washed with sat’d NaHCO$_3$(aq) (10 mL), and the organic phase was separated, dried (MgSO$_4$), filtered concentrated in vacuo. The crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 41 mg (78% yield, 68% over 2 steps) of N’-(2-methoxyacetyl)-N-tetradecyldecanehydrazide (Compound 3.13, Scheme 3.2) as a white solid. m.p. = 51-54 ºC (EtOAc/hexanes); R$_f$ = 0.48 (40% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3256, 2917, 2850, 1674, 1658, 1504, 1200, 1115, 989; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 8.19 (1H, s), 4.04 (2H, s), 3.57 (2H, t, $J$=8.0 Hz), 3.48 (3H, s), 2.26 (2H, t, $J$=8.0 Hz), 1.47 - 1.65 (4H, m), 1.17 - 1.34 (34H, m), 0.88 (6H, td, $J$=7.0, 2.0 Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ ppm 174.6, 167.7, 71.7, 59.5, 47.6, 32.2, 31.91, 31.87, 29.68, 29.66, 29.64, 29.57, 29.55, 29.44, 29.35, 29.32, 29.28, 27.0, 26.8, 24.6, 22.68, 22.66, 14.11, 14.10; [M + H]$^+$ for C$_{27}$H$_{55}$N$_2$O$_3$, calcd, 455.42127; found, 455.42142.

**Di-tert-butyl 1-(2-acetoxyacetyl)-2-(hex-1-yn-1-yl)hydrazine-1,2-dicarboxylate**

(Compound 3.14, Scheme 3.3):

A solution of 1-hexyne (82 mg, 0.115 mL, 1.0 mmol, 1.0 eq.) in THF (5 mL) was cooled to -78 ºC and treated with n-BuLi (0.48 mL of a 2.5 M
sol’n in hexanes, 1.2 mmol, 1.2 eq.) and stirred for 10 mins. A solution of di-tert-butyl-diazodicarboxylate (345 mg, 1.5 mmol, 1.5 eq.) in THF (3 mL) was added quickly by syringe and the mixture removed from the cooling bath and warmed to room temperature. After stirring for 30 mins at room temperature, the mixture was re-cooled to -78 ºC and a solution of 2-chloro-2-oxoethyl acetate (205 mg, 0.16 mL, 1.5 mmol, 1.5 eq.) in THF (0.5 mL) was added and the cooling bath removed and warmed to room temperature. After stirring at room temperature for 1 hour the mixture was diluted with sat’d NH₄Cl(aq) (10 mL) and water (10 mL) and ethyl acetate (75 mL) and the phases were separated. The organic phase was dried (MgSO₄), filtered and concentrated in vacuo and the crude material thus obtained was purified by flash column chromatography using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 269 mg (65% yield) of Compound 3.14 (Scheme 3.3) as a yellow oil. Rf = 0.32 (20% EtOAc/hexanes); IR (neat, cm⁻¹) 3497, 2977, 2932, 2875, 2367, 2266, 1790, 1733, 1681, 899; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 4.98 - 5.19 (2H, m), 2.23 - 2.33 (2H, m), 2.06 - 2.15 (3H, m), 1.44 - 1.54 (13H, m), 1.30 - 1.43 (9H, m), 0.81 - 0.92 (3H, m); ¹³C NMR (101 MHz, DMSO-d₆) δ ppm (major rotomer) 169.8, 166.1, 151.0, 149.5, 85.9, 84.2, 71.8, 70.8, 63.3, 30.2, 27.3, 27.1, 21.0, 20.2, 17.2, 13.3; HRMS (m/z): [M + NH₄]⁺ for C₂₀H₃₆N₃O₇, calcd, 430.25532; found, 430.25721.

**N’-hexyl-2-hydroxyacetohydrazide (Compound 3.15, Scheme 3.3):**

Compound 3.14 (98 mg, 0.238 mmol, 1.0 eq.) was dissolved in ethyl acetate (5 mL) and Pd/C (26 mg 10 wt% dry Pd/C) was added. The flask was sealed with a rubber septum and purged with nitrogen then a balloon of hydrogen attached and purged for 5 mins, then a fresh hydrogen balloon attached and stirred at room temperature. After 17 hours the flask was purged with nitrogen for 5 mins then diluted with ethyl acetate (40 mL) and filtered through a short celite plug and concentrated in vacuo. The crude material thus obtained was re-dissolved in CH₂Cl₂ (3 mL) and treated with TFA (0.5 mL) and stirred at room temperature overnight. After 14 hrs the reaction mixture was diluted with CH₂Cl₂ (40 mL) and sat’d NaHCO₃(aq) (20 mL) and the phases separated and aq. phase extracted
again with CH₂Cl₂ (20 mL). The organic extracts were combined, dried (MgSO₄), filtered and concentrated in vacuo to give 49 mg of crude Boc deprotected material. This was dissolved in MeOH (3 mL) and treated with sat’d K₂CO₃(aq) (0.5 mL) and stirred at room temperature vigorously for 5 hrs. The reaction mixture was then diluted with sat’d NH₄Cl(aq) (10 mL) and water (10 mL) and organics extracted with ethyl acetate (2 x 40 mL). The organic extracts were combined and dried (MgSO₄), filtered and concentrated in vacuo to give 23 mg (60% yield over 3 steps) of Compound 3.15 (Scheme 3.3) as a light yellow waxy paste. R_f = 0.22 (2% MeOH/EtOAc); IR (CH₂Cl₂, cm⁻¹) 3278, 3241, 3099, 2956, 2855, 2828, 2673, 1641, 1337, 1081; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.13 (1H, s), 5.29 (1H, t, J=6.0 Hz), 5.03 (1H, br. s), 3.82 (2H, d, J=5.0 Hz), 2.67 (2H, t, J=7.0 Hz), 1.19 - 1.43 (8H, m), 0.86 (3H, t, J=7.0 Hz); ¹³C NMR (101 MHz, DMSO-d₆) δ ppm 170.1, 60.8, 51.1, 31.2, 27.3, 26.2, 22.0, 13.9; HRMS (m/z): [M + H]^+ for C₈H₁₉N₂O₂, calcd, 175.1441; found, 175.1439.

**Geralcin A (Compound 3.16, Scheme 3.3):**

Compound 3.15 (12.2 mg, 0.070 mmol, 1.0 eq.) and 3-(2-oxo-2,5-dihydrofuran-3-yl)propanoic acid (13.1 mg, 0.0839 mmol, 1.2 eq.) prepared according to a known protocol were combined in CH₂Cl₂ (0.5 mL) and DMF (0.2 mL) and cooled to 0 °C. To this was then added HATU (29 mg, 0.077 mmol, 1.1 eq.) and Et₃N (10 mg, 0.098 mmol, 1.4 eq.) as a sol’n in CH₂Cl₂ (0.5 mL) and after 1 hr TLC indicated consumption of compound 3.15. The reaction mixture was diluted with CH₂Cl₂ (50 mL) and washed with 50% sat’d NaHCO₃(aq) (2 x 10 mL) then with 50% sat’d NaCl(aq) (2 x 10 mL), dried (MgSO₄), filtered and concentrated in vacuo. This crude material was purified by flash chromatography through silica gel using 5% MeOH in ethyl acetate to elute to give 12.1 mg (55% yield) of geraldin A (Compound 3.16, Scheme 3.3) as a white waxy paste. R_f = 0.24 (2% MeOH/EtOAc); IR (CH₂Cl₂, cm⁻¹) 3454 (br.), 3233 (br.), 2953, 2925, 2874, 2855, 1742, 1657, 1444, 1348, 1282, 1207, 1086; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.32 (1H, s), 7.30 - 7.47 (1H, m), 5.62 (1H, t, J=6.0 Hz), 4.79 - 4.82 (2H, m), 3.98 (2H, d, J=6.0 Hz), 3.35 - 3.62 (2H, m), 2.31 - 2.47 (4H, m), 1.36 - 1.46
(2H, m), 1.18 - 1.30 (6H, m), 0.85 (3H, t, J=7.0 Hz); $^1$H NMR (500 MHz, d$_7$-DMF) δ ppm 10.42 (1H, s), 7.47 (1H, dd, J=2.0 Hz), 5.77 (1H, br. s.), 4.85 (2H, dddd, J=2.0, 2.0, 2.0, 2.0 Hz), 4.15 (2H, s), 3.45 - 3.65 (2H, m), 2.53 - 2.67 (2H, m), 2.43 - 2.51 (2H, m), 1.52 (2H, app quin, J=7.5 Hz), 1.20 - 1.34 (6H, m), 0.87 (3H, t, J=7.0 Hz); $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 173.96, 172.38, 171.10, 147.08, 131.28, 70.41, 60.97, 46.76, 31.01, 29.17, 26.42, 25.83, 22.01, 20.03, 13.89; $^{13}$C NMR (126 MHz, d$_7$-DMF) δ ppm 174.40, 173.15, 171.76, 146.99, 132.34, 70.85, 62.08, 47.40, 31.78, 29.80, 27.17, 26.62, 22.71, 20.73, 13.89; HRMS (m/z): [M + H]$^+$ for C$_{15}$H$_{25}$N$_2$O$_6$, calcd, 313.17635; found, 313.17660.

**Tert-butyl 1-(2-methoxyacetyl)hydrazinecarboxylate (Compound 3.18, Scheme 3.4):**

![Hydrazone structure](image)

Hydrazone compound 3.17 was prepared according to a literature protocol:$^{22}$ Boc-carbazate (2.03 g, 15.36 mmol) was dissolved in acetone (15 mL, ACS reagent grade) and anhydrous MgSO$_4$ (400 mg) and 2 pipette drops of glacial acetic acid were added. The mixture was heated at 60 °C for 3 hours then cooled to room temperature and filtered through a celite pad to remove MgSO$_4$ using additional acetone (50 mL) to wash/elute. The filtrate was concentrated in vacuo on the rotovap to provide 2.70 g (quant. yield) of pure hydrazone product 3.17 as a white solid.

A N$_2$ flushed flask fitted with a rubber septa containing hydrazone compound 3.17 (1.60 g, 9.29 mmol, 1.0 eq.) was charged with THF (40 mL) and cooled to -78 °C. KHMDS (20.0 mL of 0.5 M sol’n in toluene, 10.2 mmol, 1.1 eq.) was added and stirred 15 minutes at -78 °C followed by addition of 2-methoxyacetyl chloride (1.20 g, 1.01 mL, 11.1 mmol, 1.2 eq.) and the mixture was stirred overnight in the cooling bath allowing to slowly warm to room temperature. After 18 hours the mixture was diluted with CH$_2$Cl$_2$ (150 mL) and washed with sat’d NaHCO$_3$(aq) (40 mL). The organic phase was dried (MgSO$_4$), then filtered and concentrated in vacuo on the rotovap to provide a crude yellow oil. The crude oil was dissolved in THF (90 mL) and H$_2$O (10 mL) and silica gel (14.0 g, 230-400 mesh) was added and the mixture was stirred vigorously at room
temperature for 4 hours then concentrated in vacuo on the rotovap. The resulting dry loaded silica gel thus obtained was loaded to the top of a silica gel column and subjected to flash column chromatography eluting with ethyl acetate in hexanes (gradient elution 0-100% EtOAc) to provide 1.15 g (60% yield for 2 steps) of Compound 3.18 (Scheme 3.4) as a clear oil. \( R_f = 0.26 \) (60% EtOAc/hexanes); IR (neat, cm\(^{-1}\)) 3580, 3341, 3230, 2981, 2935, 2827, 1780, 1711 (br), 1625, 1458, 1369, 1232, 1152, 987, 929, 851, 771; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 4.52 (2H, s), 4.50 (2H, br. s), 3.48 (3H, s), 1.57 (9H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) ppm 171.4, 152.0, 84.7, 73.4, 59.4, 28.0; HRMS (m/z): [M + H\(^+\)] for C\(_{8}\)H\(_{17}\)N\(_2\)O\(_4\), calcd, 205.11883; found, 205.11954.

**Tert-butyl 2-decanoyl-1-(2-methoxyacetyl)hydrazinecarboxylate (Compound 3.19, Scheme 3.4):**

tert-butyl 1-(2-methoxyacetyl)hydrazinecarboxylate (Compound 3.18, 820 mg, 4.0 mmol, 1.0 eq.) dissolved in CH\(_2\)Cl\(_2\) (30 mL) and cooled to 0 °C was treated with triethylamine (567 mg, 0.78 mL, 5.6 mmol, 1.4 eq.) then decanoyl chloride (839 mg, 0.91 mL, 4.4 mmol, 1.1 eq.) and stirred overnight allowing to slowly warm to room temperature. After 16 hours the mixture was diluted with CH\(_2\)Cl\(_2\) (150 mL) and washed with sat’d NaHCO\(_3\) (aq) (40 mL), dried (MgSO\(_4\)), filtered, and concentrated in vacuo on the rotovap. The crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 1.33 g (93% yield) of Compound 3.19 (Scheme 3.4) as a clear oil. \( R_f = 0.24 \) (40% EtOAc/hexanes); IR (neat, cm\(^{-1}\)) 3272 (br), 2977, 2956, 2925, 2856, 1788, 1733 (br), 1679 (br), 1504, 1456, 1370, 1332, 1254, 1155, 1044, 1005, 955, 851, 772; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 7.42 (1H, s), 4.59 (2H, s), 3.47 (3H, s), 2.28 (2H, \( J=7.5 \) Hz), 1.67 (3H, m), 1.50 (9H, s), 1.22 - 1.32 (11H, m), 0.88 (3H, \( J=8.0 \) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) ppm 171.6, 171.0, 151.2, 85.0, 73.3, 59.4, 34.1, 31.9, 29.40, 29.27, 29.17, 29.09, 27.8, 25.3, 22.7, 14.1; HRMS (m/z): [M + Na\(^+\)] for C\(_{18}\)H\(_{34}\)N\(_2\)O\(_5\)Na, calcd, 381.2359; found, 381.2367.
**Tert-butyl-2-decanoyl-2-ethynyl-1-(2-methoxyacetyl)hydrazinecarboxylate**

(Compound 3.21, Scheme 3.5):

TMS-phenylalkynyliodonium triflate was prepared according to a literature procedure;\(^{23}\) the following is representative: A suspension of PhI(OAc)\(_2\) (3.22 g, 10.0 mmol, 1.0 eq.) in CH\(_2\)Cl\(_2\) (5 mL) at 0 °C was treated with Tf\(_2\)O (5.0 mL of a 1.0 M sol’n in CH\(_2\)Cl\(_2\)), 5.0 mmol, 0.5 eq.) under N\(_2\). This mixture was stirred for 30 minutes in the ice bath then bis-trimethylsilylacetylene (1.70 g, 2.27 mL, 10.0 mmol, 1.0 eq.) was added by syringe and stirred for 2 hours in the cooling bath then volatiles were removed on the rotovap followed by brief vacuum line drying (5 minutes). The residue thus obtained was slurried in Et\(_2\)O (5 mL) and the solid filtered off using Et\(_2\)O (25 mL) to wash yielding the alkynyl-iodonium salt as a white solid (3.45 g, 77%).

A solution of tert-butyl 2-decanoyl-1-(2-methoxyacetyl)hydrazinecarboxylate (Compound 3.19, 179 mg, 0.5 mmol, 1.0 eq.) in toluene (15 mL) was cooled to 0 °C and treated with KHMDS (1.1 mL of a 0.5 M sol’n in toluene, 0.55 mmol, 1.1 eq.) and stirred for 30 minutes before addition of freshly prepared TMS-phenylalkynyliodonium triflate (405 mg, 0.9 mmol, 1.8 eq.) and the mixture was stirred overnight allowing to warm to room temperature. After 16 hours the solution was diluted with toluene (75 mL) and filtered through celite and concentrated *in vacuo* on the rotovap. The crude material obtained was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 168 mg (74% yield) of TMS-protected ynehydrazides tert-butyl 2-decanoyl-1-(2-methoxyacetyl)-2-((trimethylsilyl)ethynyl)hydrazinecarboxylate as a yellow oil. \(R_f= 0.40\) (20% EtOAc/hexanes); IR (neat, cm\(^{-1}\)) 2958, 2927, 2856, 2180, 1750, 1729, 1466, 1371, 1312, 1250, 1152, 1133, 845; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 4.57 (2H, m, r), 3.47 (3H, s), 2.67 (2H, \(J=8.0\) Hz), 1.65 - 1.77 (2H, m), 1.44 - 1.54 (9H, m, r), 1.20 - 1.34 (12H, m), 0.88 (3H, \(t, J=8.0\) Hz), 0.12 - 0.25 (9H, m, r); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 171.3, 168.6, 150.0, 93.2, 85.6, 77.7, 73.2, 59.6, 33.3, 32.0, 29.53, 29.38, 29.37, 29.28, 27.9,
24.7, 22.8, 14.2, 0.0; HRMS (m/z): [M + Na]^+ for C_{23}H_{42}N_{2}O_{5}Na, calcd, 477.2755; found, 477.2747.

A solution of the TMS ynehydrazide tert-butyl 2-decanoyl-1-(2-methoxyacetyl)-2-(((trimethylsilyl)ethynyl)hydrazinecarboxylate prepared above (229 mg, 0.5 mmol, 1.0 eq.) in THF (5 mL) was cooled to 0 °C and treated with TBAF (n-tetraethylammonium fluoride, 1.0 mL of a 1M sol’n in THF, 1.0 mmol, 1.0 eq.) and stirred until complete by TLC (30 minutes). The solution was then diluted with H_{2}O (25 mL) and organics extracted with Et_{2}O (2 x 50 mL), dried (MgSO_{4}), filtered, and concentrated in vacuo on the rotovap. The crude material obtained was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 144 mg (75% yield, 55% over 2 steps from 3.19) of Compound 3.21 (Scheme 3.5) as a yellow oil. R_{f} = 0.32 (20% EtOAc/hexanes); IR (neat, cm\(^{-1}\)) 3285, 2956, 2926, 2856, 2145, 1751, 1730, 1700, 1459, 1371, 1313, 1253, 1154; \(^1\)H NMR (400 MHz, CDCl_{3}) \(\delta\) ppm 4.57 (2H, s), 3.47 (3H, s), 3.23 (1H s), 2.70 (2H, m, r), 1.65 - 1.74 (2H, m), 1.46 - 1.54 (9H, m, r), 1.21 - 1.33 (12H, m), 0.88 (3H, t, J=8.0 Hz); \(^{13}\)C NMR (100 MHz, CDCl_{3}) \(\delta\) ppm 171.1, 168.7, 149.8, 85.7, 74.6, 73.1, 63.6, 59.5, 32.9, 31.9, 29.4, 29.2, 29.0, 28.2, 27.8, 24.4, 22.7, 14.1; HRMS (m/z): [M + NH_{4}]^+ for C_{20}H_{38}N_{3}O_{5}, calcd, 400.28115; found, 400.28119.

(\(Z\))-trimethyl(tetradec-1-en-1-yl)silane (Compound 3.22, Scheme 3.6):

A solution of 1-tetradecyne (972 mg, 1.23 mL, 5.0 mmol, 1.0 eq.) in THF (5 mL) was cooled to 0 °C and treated with n-BuLi (2.20 mL of a 2.5 M sol’n in hexanes, 5.5 mmol, 1.1 eq.) and stirred for 10 minutes before addition of distilled TMS-Cl (598 mg, 0.70 mL, 5.5 mmol, 1.1 eq.). The mixture was removed from the cooling bath and stirred at room temperature for 1 hour then quenched by addition of sat’d NH_{4}Cl(aq.) (10 mL) and water (10 mL) and organics extracted with ethyl acetate (75 mL). The organic extract was dried (MgSO_{4}), filtered through a silica plug (3 cm x 3 cm) using ethyl acetate (2 x 20 mL) to wash/elute and concentrated in vacuo on the rotovap to give 1.30 g (98% yield) of 95% pure TMS-tetradecyne as a clear oil. R_{f} = 0.33
(100% hexanes); IR (neat, cm\(^{-1}\)) 3316, 2957, 2926, 2855, 2176, 1468, 1248, 843; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 2.21 (2H, t, \(J=7.0\) Hz), 1.45 - 1.56 (2H, m), 1.21 - 1.41 (18H, m), 0.88 (3H, t, \(J=7.0\) Hz), 0.14 (9H, s); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 107.8, 84.2, 31.9, 29.67, 29.65, 29.60, 29.50, 29.36, 29.09, 28.8, 28.6, 22.7, 19.9, 14.1, 0.18; HRMS (m/z): \([M + H]^+\) for C\(_{17}\)H\(_{35}\)Si, calcd, 267.25080; found, 267.25060.

A solution of TMS-tetradecyne prepared above (1.30 g, 4.89 mmol, 1.0 eq.) and N-Me-Morpholine (594 mg, 0.65 mL, 5.87 mmol, 1.2 eq.) in Et\(_2\)O (10 mL) was treated with DIBAL (5.87 mL of a 1M sol’n in hexanes, 5.87 mmol, 1.2 eq.) at room temperature and stirred overnight. After 16 hours the mixture was diluted with Et\(_2\)O (75 mL) and poured slowly into a sep. funnel containing ice and 10% HCl(aq.) (10 mL). The organic phase was separated, washed with sat’d NaCl(aq) (10 mL), dried (MgSO\(_4\)), filtered through a celite plug and concentrated in vacuo on the rotovap. The resulting crude material was purified by flash chromatography through silica gel using hexanes to elute to provide 710 mg (53% yield over 2 steps) of Compound 3.22, Scheme 3.6, \(\geq\) 15:1 Z:E as determined by \(^1\)H NMR) as a clear oil. \(R_f\) = 0.72 (100% hexanes); IR (neat, cm\(^{-1}\)) 2957, 2926, 2855, 1607, 1468, 1377, 1248, 858, 837, 762; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 6.01 - 6.43 (1H, dt, \(J_1=14.0\) Hz, \(J_2=7.0\) Hz), 5.46 (1H, d, \(J=14.0\) Hz), 2.10 (2H, m), 1.19 - 1.40 (20H, m), 0.78 - 0.95 (3H, t, \(J=6.0\) Hz), 0.10 (9H, s); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 149.4, 128.7, 33.6, 31.9, 29.78, 29.69, 29.67, 29.65, 29.61, 29.59, 29.38, 29.36, 22.7, 14.1, 0.24; HRMS EI (m/z): \([M]\) for C\(_{17}\)H\(_{36}\)Si, calcd, 268.2586; found, 268.2590.

**Syn-(3-dodecyl-2-yl)trimethylsilane (Compound 3.23, Scheme 3.6):**

A solution of (Z)-trimethyl(tetradec-1-en-1-yl)silane (Compound 3.22, TMS\(_{C_{12}H_{25}}\) 549 mg, 2.05 mmol, 1.0 eq.) in CH\(_2\)Cl\(_2\) (10 mL) was treated with Na\(_2\)HPO\(_4\) (553 mg, 3.90 mmol, 1.9 eq.) followed by addition of \(m\)-CPBA (600 mg of 70% pure reagent, 3.48 mmol, 1.7 eq.) and stirred at room temperature overnight. After 18 hours the mixture was diluted with Et\(_2\)O (75 mL) and sat’d NaHCO\(_3\)(aq) (30 mL) and stirred at room temperature for 30 minutes before transferring to a sep. funnel and separating the phases. The organic extract was dried (MgSO\(_4\)), filtered and concentrated
in vacuo on the rotovap and the resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 493 mg (85% yield) of Compound 3.23 (Scheme 3.6) as a clear oil. Rf = 0.56 (20% EtOAc/hexanes); IR (neat, cm\(^{-1}\)) 2957, 2926, 2855, 1468, 1418, 1250, 841, 754; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 2.98 - 3.16 (1H, m), 2.19 (1H, d, \(J=5.0\) Hz), 1.40 - 1.55 (4H, m), 1.18 - 1.34 (18H, m), 0.81 - 0.94 (3H, t, \(J=6.0\) Hz), 0.13 (9H, s); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) ppm 57.7, 50.6, 31.9, 31.6, 29.67, 29.64, 29.58, 29.56 (2C, s), 29.35 (2C, s), 27.1, 22.7, 14.1, -1.7; HRMS (\(m/z\)): [M + H]\(^+\) for C\(_{17}\)H\(_{37}\)OSi, calcd, 285.26137; found, 285.26052.

**Tert-butyl 2-\((\text{anti})-2\)-hydroxy-1-(trimethylsilyl)tetradecyl)hydrazinecarboxylate (Compound 3.24, Table 3.1):**

A 5 mL Biotage\(^\text{TM}\) microwave vial was charged with syn-(3-dodecylxiran-2-yl)trimethylsilane (Compound 3.23, 118 mg, 0.41 mmol, 1.0 eq.) and Boc-carbazate (216 mg, 1.66 mmol, 4.0 eq.) and the vial was capped with a rubber septa and purged with N\(_2\) for 5 minutes before addition of THF (2 mL). The mixture was cooled to 0 °C and BF\(_3\)·OEt\(_2\) added (5.0 µL, 0.041 mmol, 0.1 eq.) then cooling bath removed and after warming to room temperature (20 minutes) the vial was placed in a 45 °C oil bath sealed (no N\(_2\) bubbler) overnight. After 14 hours the reaction mixture was cooled to room temperature and sat’d NH\(_4\)Cl(aq) (10 mL) added followed by water (10 mL) and organics extracted with ethyl acetate (2 x 40 mL). The organic phase was dried (Na\(_2\)SO\(_4\)), filtered and concentrated in vacuo on the rotovap and the resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 127 mg (75% yield) of Compound 3.24 (Table 3.1) as a clear oil. Rf = 0.11 (20% EtOAc/hexanes); IR (neat, cm\(^{-1}\)) 3445, 3308, 2953, 2922, 2855, 1709, 1456, 1367, 1250, 1165, 1045, 1017, 839; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 6.02 (1H, br. s.), 4.22 (1H, br. s.), 3.50 - 3.78 (2H, m), 2.41 (1H, d, \(J=5.0\) Hz), 1.40 - 1.49 (11H, m), 1.21 - 1.36 (19H, m), 0.88 (3H, t, \(J=7.0\) Hz) 0.12 (9H, s); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) ppm 157.7,
80.8, 70.8, 57.4, 36.7, 31.9, 29.6 (6C), 29.3, 28.3, 26.4, 22.7, 14.1, -1.8; HRMS (m/z): [M + H]^+ for C_{22}H_{49}N_2O_3Si, calcd, 417.35124; found, 417.34925.

**Tert-butyl-2-decanoyl-2-(anti)-2-hydroxy-1-(trimethylsilyl)tetradecyl)hydrazinecarboxylate (Compound 3.25, Scheme 3.7):**

A solution of tert-butyl 2-(anti)-2-hydroxy-1-(trimethylsilyl)tetradecyl)hydrazinecarboxylate (Compound 3.24, 160 mg, 0.38 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (5 mL) was cooled to 0 °C and treated with Et$_3$N (54 mg, 0.074 mL, 0.53 mmol, 1.4 eq.) followed by addition of decanoyl-chloride (83 mg, 0.43 mmol, 1.15 eq.) and the mixture was stirred overnight allowing to warm to room temperature. After 18 hours the mixture was diluted with CH$_2$Cl$_2$ (75 mL) and washed with sat’d NaHCO$_3$(aq) (20 mL) and the phases separated. The organic phase was dried (Na$_2$SO$_4$), filtered and concentrated in vacuo on the rotovap and the resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 191 mg (88% yield) of Compound 3.25 (Scheme 3.7) as a clear oil. R$_f$ = 0.42 (20% EtOAc/hexanes); IR (neat, cm$^{-1}$) 3428, 3250, 2955, 2926, 2855, 1742, 1713, 1643, 1456, 1368, 1250, 1161, 843; $^1$H NMR (400 MHz, DMSO-$d_6$, 55 °C) δ ppm 8.82 - 9.03 (1H, br.s), 4.37 - 4.53 (1H, m), 3.67 - 3.83 (1H, m), 3.38 - 3.55 (1H, m), 2.14 - 2.34 (4H, m), 1.45 (13H, m), 1.25 (30H, m), 0.86 (6H, t, J=7.0 Hz), 0.06 (9H, s); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ ppm 174.9, 155.5, 81.1, 70.1, 69.3, 34.9, 34.5, 32.0, 31.7, 29.43 (3 C), 29.38, 29.33, 29.22, 29.12 (2 C), 28.42 (2 C), 25.85, 25.71, 24.7, 24.6, 22.5, 14.39 (2 C), -0.40; HRMS (m/z): [M + Na]$^+$ for C$_{32}$H$_{66}$N$_2$O$_4$SiNa, calcd, 593.4695; found, 593.4701.
Hydrazidomycin A (Compound 3.1, Scheme 3.7):

A solution of tert-butyl 2-decanoyl-2-((anti)-2-hydroxy-1-(trimethylsilyl)tetradecyl)hydrazinecarboxylate (Compound 3.25, 87 mg, 0.15 mmol, 1.0 eq.) in THF (5 mL) was charged with KOrBu (43 mg, 0.38 mmol, 2.5 eq.) at room temperature then fitted with a reflux condenser and placed in a 45 °C oil bath overnight. After 16 hours the mixture was cooled to room temperature and diluted with ethyl acetate (75 mL) and washed with a mixture of water (5 mL) and sat’d NaHCO₃(aq) (10 mL) and the phases separated. The organic phase was dried (Na₂SO₄), filtered through a short plug of basic Al₂O₃ (2 cm tall x 1 cm wide) using ethyl acetate (25 mL) to wash/elute and concentrated in vacuo on the rotovap to give 69 mg (96% yield) of crude Boc-Z-enehydrazide as a clear oil.

Crude Boc-Z-enehydrazide prepared above (69 mg, 0.14 mmol, 1.0 eq.) was dissolved in THF (5 mL) and cooled to -78 °C and treated with KHMDS (0.30 mL of a 0.5 M sol’n in toluene, 0.15 mmol, 1.1 eq.) and stirred at -78 °C for 15 minutes. To this was then added 2-methoxyacetyl chloride (18 mg, 0.17 mmol, 1.2 eq.) as a solution in THF (0.5 mL) and the cooling bath was removed and warmed to room temperature and stirred 1 hour then partitioned between ethyl acetate (75 mL) and sat’d NaHCO₃(aq) (20 mL) and the phases were separated. The organic phase was dried (Na₂SO₄), filtered through a short plug of basic Al₂O₃ (1 cm tall x 1 cm wide) using ethyl acetate (25 mL) to wash/elute and concentrated in vacuo on the rotovap to give 78 mg (100% yield) of crude Boc-imide-Z-enehydrazide as a clear oil.

Crude Boc-imide-Z-enehydrazide prepared above (78 mg, 0.14 mmol, 1.0 eq.) was dissolved in MeCN (5 mL) and Mg(ClO₄)₂ (3.0 mg, 0.014 mmol, 0.1 eq.) was added and the flask equipped with a reflux condenser and placed in a 55 °C oil bath overnight. After 16 hours the mixture was cooled to room temperature and volatiles were removed in vacuo on the rotovap and the resulting crude residue was purified by flash chromatography through silica gel (pre-conditioned with 1% Et₃N in hexanes) using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 36 mg (53% yield
over 3 steps) of hydrazidomycin A (Compound 3.1, Scheme 3.7) as a white solid. m.p. = 38 – 40 °C (CH₂Cl₂); Rf = 0.52 (40% EtOAc/hexanes); IR (CH₂Cl₂ thin film, cm⁻¹) 3276, 2955, 2924, 2854, 1692, 1495, 1467, 1401, 1378, 1199, 1118; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.67 (1H, s), 6.40 (1H, dt, J=9.2, 1.6 Hz), 4.77 (1H, dt, J=9.2, 7.2 Hz), 3.97 (2H, s), 3.35 (3H, s), 1.94 - 2.38 (4H, m), 1.41 - 1.52 (2H, m), 1.19 - 1.31 (32H, m), 0.85 (6H, t, J=6.8 Hz); ¹³C NMR (100 MHz, DMSO-d₆) δ ppm 173.18, 167.64, 124.26, 117.31, 70.67, 58.94, 31.28, 31.16, 29.07 (2 C’s), 29.03 (3 C’s), 29.00, 28.87, 28.84, 28.80, 28.69 (2 C’s), 28.65, 28.57, 25.82, 23.84, 22.08 (2 C’s), 13.94 (2 C’s); HRMS (m/z): [M + H]⁺ for C₂₇H₅₃N₂O₃, calcd, 453.4061; found, 453.4043.

**E-Hydrazidomycin A (Compound 3.26, Scheme 3.8):**

![Chemical Structure](image)

A solution of tert-butyl 2-decanoyl-2-((anti)-2-hydroxy-1-(trimethylsilyl)tetradecyl)hydrazinecarboxylate (Compound 3.25, 24 mg, 0.042 mmol, 1.0 eq.) in THF (3 mL) was treated with BF₃·OEt₂ (12.5 mg, 0.01 µL, 0.0882 mmol, 2.1 eq.) at room temperature for 24 hours then fitted with a reflux condenser and placed in a 45 °C oil bath for 16 hours. The mixture was then cooled to room temperature and diluted with ethyl acetate (50 mL) and washed with sat’d NaHCO₃(aq) (10 mL) and the phases separated. The organic phase was dried (MgSO₄), filtered and concentrated *in vacuo* on the rotovap to give 23 mg (quantitative yield) of crude Boc-E-enehydrazide as a clear oil.

Crude Boc-E-enehydrazide prepared above (20 mg, 0.042 mmol, 1.0 eq.) was dissolved in THF (2 mL) and cooled to -78 °C and treated with KHMDS (0.09 mL of a 0.5 M sol’n in toluene, 0.0462 mmol, 1.1 eq.) and stirred at -78 °C for 15 minutes. To this was then added 2-methoxyacetyl chloride (5.5 mg, 0.0504 mmol, 1.2 eq.) as a solution in THF (0.5 mL) and the cooling bath was removed and warmed to room temperature and stirred 1 hour then partitioned between CH₂Cl₂ (50 mL) and sat’d NaHCO₃(aq) (10 mL) and the phases were separated. The organic phase was dried (MgSO₄), filtered through a short plug of silica gel (1 cm tall x 1 cm wide) using CH₂Cl₂ (10 mL) to wash/elute and
concentrated *in vacuo* on the rotovap to give crude Boc-imide-*E*-enehydrazide as a clear oil.

Crude Boc-imide-*E*-enehydrazide prepared above was dissolved in MeCN (3 mL) and Mg(ClO₄)₂ (1.0 mg, 0.0042 mmol, 0.1 eq.) was added and the flask equipped with a reflux condenser and placed in a 55 °C oil bath overnight. After 16 hours the mixture was cooled to room temperature and volatiles were removed *in vacuo* on the rotovap and the resulting crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 9.5 mg (50% yield over 3 steps) of *E*-hydrazidomycin A (Compound 3.26, Scheme 3.8) as a white solid. m.p. = 31 – 33 °C (EtOAc/hexanes); Rf = 0.19 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3269, 2955, 2925, 2854, 1697, 1677, 1456, 1397, 1116; ¹H NMR (500 MHz, DMSO-d₆) δ ppm 10.48 (1H, s), 7.02 (1H, d, J=14.0 Hz), 4.93 (1H, dt, J=14.0, 7.0 Hz), 4.04 (2H, s), 3.37 (3H, s), 2.33 (1H, dt, J=16.5, 7.5 Hz), 2.11 (1H, dt, J=16.5, 7.5 Hz), 1.99 (2H, q, J=7.0 Hz), 1.41 - 1.51 (2H, m), 1.18 - 1.31 (32H, m), 0.85 (6H, t, J=7.0 Hz); ¹³C NMR (126 MHz, DMSO-d₆) δ ppm 171.46, 168.06, 123.73, 109.66, 70.65, 58.92, 31.56, 31.29, 31.26, 29.44, 29.05, 29.02, 29.01, 28.85, 28.83, 28.78, 28.73, 28.70, 28.64, 28.57, 28.38, 23.80, 22.08, 13.94; HRMS (m/z): [M + H]⁺ for C₂₇H₅₃N₂O₃, calcd, 453.40562; found, 453.40463.

**Tert-butyldimethyl((7-(trimethylsilyl)hept-6-yn-1-yl)oxy)silane (Compound 3.27, Scheme 3.9):**

To a solution of 6-heptyn-1-ol (302 mg, 2.70 mmol, 1.0 eq.) in DMF (3 mL) was added imidazole (260 mg, 3.78 mmol, 1.4 eq.) followed by TBS-Cl (448 mg, 2.97 mmol, 1.1 eq.) and the mixture stirred at room temperature overnight. After 16 hours the mixture was diluted with ethyl acetate (75 mL) and washed with sat’d NaHCO₃(aq) (15 mL) then with water (10 mL) and finally with 50% sat’d NaCl(aq) (4 x 10 mL). The organic phase was dried (MgSO₄), filtered through a silica plug (3 cm tall x 2 cm wide) topped with celite using ethyl acetate (2 x 20 mL) to wash/elute and concentrated *in vacuo* on the rotovap to provide 602 mg (98%) of the OTBS terminal alkyne as a clear oil.
The protected alcohol intermediate obtained above (590 mg, 2.60 mmol, 1.0 eq.) was dissolved in THF (15 mL) and cooled to -78 ºC and treated with n-BuLi (1.25 mL of a 2.5 M sol’n in hexanes, 3.12 mmol, 1.2 eq.) and stirred 10 minutes before addition of TMS-Cl (395 mg, 0.46 mL, 3.64 mmol, 1.4 eq.). The cooling bath was removed and warmed to room temperature and stirred for 45 minutes before addition of sat’d NH₄Cl(aq) (5 mL) and water (10 mL). Organics were extracted with ethyl acetate (75 mL), dried (MgSO₄), filtered through a silica plug (3 cm tall x 2 cm wide) topped with celite using ethyl acetate (2 x 20 mL) to wash/elute and concentrated in vacuo on the rotovap. This provided 688 mg (89% yield, 87% over 2 steps) of Compound 3.27 (Scheme 3.9) as a clear oil of sufficient purity to use without further purification. Rf = 0.30 (5% EtOAc/hexanes); IR (neat, cm⁻¹) 2957, 2930, 2899, 2859, 2176, 1472, 1250, 1109, 841; ¹H NMR (400 MHz, CDCl₃) δ ppm 3.61 (2H, t, J=6.5 Hz), 2.22 (2H, t, J=7.0 Hz), 1.48 - 1.57 (4H, m), 1.37 - 1.46 (2H, m), 0.89 (9H, s), 0.14 (9H, s), 0.05 (6H, s); ¹³C NMR (100 MHz, CDCl₃) δ ppm 107.5, 84.3, 63.1, 32.4, 28.5, 26.0, 25.1, 20.0, 18.4, 0.17, -5.3; HRMS (m/z): [M + H]+ for C₁₆H₃₅OSi₂, calcd, 299.2220; found, 299.2220.

Tert-butyldimethyl((8-(trimethylsilyl)oct-7-yn-1-yl)oxy)silane (Compound 3.28, Scheme 3.9):

7-octyn-1-ol was prepared according to a modified literature procedure:¹⁹ Ethylene diamine (9 mL) in a 3-neck flask fitted with a reflux condenser and rubber septa was cooled to 0 ºC and charged with NaH in one portion (800 mg of a 60% dispersion in mineral oil, 20.0 mmol, 4.0 eq.). The mixture was stirred at 0 ºC for 5 minutes then 1 hour at room temperature before being transferred to a 65 ºC bath for 1 hour. The mixture was then cooled to 45 ºC before addition of 3-octyn-1-ol (631 mg, 0.72 mL, 5.0 mmol, 1.0 eq.) dropwise over 2 minutes. After warming back to 65 ºC the mixture was stirred at that temperature for 1 hour then cooled to 0 ºC and water (7.5 mL) was slowly added followed by slow addition of 1N HCl(aq) (7.5 mL). A further portion of 1N HCl(aq) (10 mL) was then added and organics were extracted with Et₂O (3 x 25 mL) and washed with 1N HCl(aq) (10 mL), sat’d NaCl(aq) (5 mL), dried (MgSO₄), filtered through a silica
plug (3 cm tall x 2 cm wide) topped with celite using Et₂O (2 x 20 mL) to wash/elute and concentrated *in vacuo* on the rotovap to provide 631 mg (100%) of 7-octyn-1-ol as a yellow oil in sufficient purity (>90% by ¹H NMR) to advance without further purification.

To a solution of 7-octyn-1-ol (630 mg, 5.0 mmol, 1.0 eq.) in DMF (8 mL) was added imidazole (476 mg, 7.0 mmol, 1.4 eq.) followed by TBS-Cl (829 mg, 5.5 mmol, 1.1 eq.) and the mixture stirred at room temperature overnight. After 16 hours the mixture was diluted with ethyl acetate (75 mL) and washed with water (10 mL) then with 50% sat’d NaCl(aq) (4 x 10 mL). The organic phase was dried (MgSO₄), filtered through a silica plug (3 cm tall x 2 cm wide) topped with celite using ethyl acetate (2 x 20 mL) to wash/elute and concentrated *in vacuo* on the rotovap to provide 1.25 g (100%) of the OTBS terminal alkyne as a yellow oil.

The protected alcohol intermediate thus obtained (1.25 g, 5.0 mmol, 1.0 eq.) was dissolved in THF (40 mL) and cooled to -78 °C and treated with n-BuLi (2.4 mL of a 2.5 M sol’n in hexanes, 6.0 mmol, 1.2 eq.) and stirred 15 minutes before addition of TMS-Cl (760 mg, 0.88 mL, 7.0 mmol, 1.4 eq.). The cooling bath was removed and warmed to room temperature and stirred for 1 hour before addition of sat’d NH₄Cl(aq) (10 mL) and water (10 mL). Organics were extracted with ethyl acetate (100 mL), dried (MgSO₄), filtered through a silica plug (3 cm tall x 2 cm wide) topped with celite using ethyl acetate (2 x 25 mL) to wash/elute and concentrated *in vacuo* on the rotovap. This provided 1.40 g (89% yield, 89% over 3 steps) of Compound 3.28 (Scheme 3.9) as a slightly yellow oil of sufficient purity to use without further purification. \( R_f = 0.42 \) (5% EtOAc/hexanes); IR (neat, cm⁻¹) 2957, 2930, 2857, 2176, 1464, 1387, 1362, 1250, 1101, 839, 775, 760; ¹H NMR (400 MHz, CDCl₃) δ ppm 3.61 (2H, t, \( J=6.5 \) Hz), 2.22 (2H, t, \( J=7.0 \) Hz), 1.47 - 1.59 (4H, m), 1.31 - 1.44 (4H, m), 0.90 (9H, s), 0.15 (9H, s), 0.06 (6H, s); ¹³C NMR (100 MHz, CDCl₃) δ ppm 107.6, 84.3, 63.2, 32.7, 29.7, 28.6, 26.0, 25.3, 19.8, 18.4, 0.18, -5.3; HRMS (m/z): [M + H]⁺ for C₁₇H₃₇OSi₂, calcd, 313.23829; found, 313.23830.
(Z)-7-(trimethylsilyl)hept-6-en-1-ol (Compound 3.29, Scheme 3.9):

A solution of compound 3.27 (550 mg, 1.84 mmol, 1.0 eq.) and N-Me-Morpholine (1.30 g, 1.41 mL, 12.9 mmol, 7.0 eq.) in Et₂O (25 mL) was treated with DIBAL (12.9 mL of a 1M sol’n in hexanes, 12.9 mmol, 7.0 eq.) at room temperature and stirred overnight. After 16 hours the mixture was diluted with Et₂O (75 mL) and poured slowly into a sep. funnel containing ice (~25 g) and 10% HCl(aq.) (15 mL). The organic phase was separated, dried (MgSO₄), filtered through a celite plug and concentrated in vacuo on the rotovap. The resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 215 mg (63% yield) of Compound 3.29 (Scheme 3.9) as a clear oil. R_f = 0.23 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3331, 2955, 2934, 2858, 1607, 1248, 1074, 1053, 858, 837, 762; ¹H NMR (400 MHz, CDCl₃) δ ppm 6.21 - 6.38 (1H, m), 5.48 (1H, dt, J=14.0, 1.0 Hz), 3.65 (2H, t, J=6.5 Hz), 2.05 - 2.22 (2H, m), 1.51 - 1.63 (2H, m), 1.36 - 1.47 (4H, m), 1.33 (1H, br. s.), 0.11 (9H, s); ¹³C NMR (101 MHz, CDCl₃) δ ppm 148.9, 129.1, 62.9, 33.4, 32.7, 29.5, 25.4, 0.21; HRMS (m/z): [M + H]+ for C₁₀H₂₃OSi, calcd, 187.15182; found, 187.15100.

(Z)-8-(trimethylsilyl)oct-7-en-1-ol (Compound 3.30, Scheme 3.9):

A solution of compound 3.28 (530 mg, 1.69 mmol, 1.0 eq.) and N-Me-Morpholine (1.20 g, 1.30 mL, 11.8 mmol, 7.0 eq.) in Et₂O (25 mL) was treated with DIBAL (11.8 mL of a 1M sol’n in hexanes, 11.8 mmol, 7.0 eq.) at room temperature and stirred overnight. After 16 hours the mixture was diluted with Et₂O (100 mL) and poured slowly into a sep. funnel containing ice (~25 g) and 10% HCl(aq.) (20 mL). The organic phase was separated, dried (MgSO₄), filtered through a celite plug and concentrated in vacuo on the rotovap. The resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 184 mg (54% yield) of Compound 3.30 (Scheme 3.9) as a clear oil. R_f = 0.23 (20%
EtOAc/hexanes); IR (neat, cm\(^{-1}\)) 3331 (br), 2955, 2929, 2857, 1744, 1724, 1607, 1248, 1057; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 6.22 - 6.35 (1H, m), 5.47 (1H, dt, \(J=14.0, 1.0\) Hz), 3.64 (2H, t, \(J=6.5\) Hz), 2.07 - 2.16 (2H, m), 1.53 – 1.62 (2H, m), 1.30 - 1.44 (7H, m), 0.11 (9H, s); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 149.1, 128.9, 63.0, 33.4, 32.7, 29.7, 29.1, 25.7, 0.23; HRMS (m/z): [M + H]\(^+\) for C\(_{11}\)H\(_{25}\)OSi, calcd, 201.16747; found, 201.16690.

**Syn-5-(3-(trimethylsilyl)oxiran-2-yl)pentan-1-ol (Compound 3.31, Scheme 3.9):**

Compound 3.29 (200 mg, 1.07 mmol, 1.0 eq.) was dissolved in CH\(_2\)Cl\(_2\) (10 mL) and Na\(_2\)HPO\(_4\) (289 mg, 2.03 mmol, 1.9 eq.) was added followed by addition of m-CPBA (406 mg of 70% pure reagent, 1.82 mmol, 1.7 eq.) and the mixture was stirred at room temperature overnight. After 14 hours the solution was partitioned between CH\(_2\)Cl\(_2\) (75 mL) and sat’d NaHCO\(_3\) (aq) (10 mL) and the phases were separated. The organic phase was dried (MgSO\(_4\)), filtered and concentrated *in vacuo* on the rotovap. The resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 200 mg (92% yield) of Compound 3.31 (Scheme 3.9) as a clear oil. \(R_f= 0.32\) (40% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3402, 2955, 2934, 2860, 1719, 1456, 1418, 1250, 1055, 843, 754; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 3.66 (2H, t, \(J=6.5\) Hz), 3.01 - 3.18 (1H, m), 2.20 (1H, d, \(J=5.0\) Hz), 1.53 - 1.66 (4H, m), 1.37 - 1.51 (5H, m), 0.13 (9H, s); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 62.9, 57.6, 50.6, 32.6, 31.5, 26.9, 25.6, -1.7; HRMS (m/z): [M + NH\(_4\)]\(^+\) for C\(_{10}\)H\(_{26}\)O\(_2\)NSi, calcd, 220.17328; found, 220.17315.

**Syn-6-(3-(trimethylsilyl)oxiran-2-yl)hexan-1-ol (Compound 3.32, Scheme 3.9):**

Compound 3.30 (154 mg, 0.77 mmol, 1.0 eq.) was dissolved in CH\(_2\)Cl\(_2\) (10 mL) and Na\(_2\)HPO\(_4\) (208 mg, 1.46 mmol, 1.9 eq.) was added followed by addition of m-CPBA (292 mg of 70% pure reagent, 1.31 mmol, 1.7 eq.) and the mixture was stirred at room temperature overnight. After 14 hours the solution was partitioned between CH\(_2\)Cl\(_2\) (75 mL) and sat’d NaHCO\(_3\) (aq) (10 mL) and the phases were separated. The organic phase was dried (MgSO\(_4\)), filtered and concentrated *in vacuo* on the rotovap. The resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 154 mg (86% yield) of Compound 3.32 (Scheme 3.9) as a clear oil. \(R_f= 0.32\) (40% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3324, 2955, 2931, 2857, 1719, 1456, 1418, 1250, 1055, 843, 754; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 3.65 (2H, t, \(J=6.5\) Hz), 3.01 - 3.18 (1H, m), 2.20 (1H, d, \(J=5.0\) Hz), 1.53 - 1.66 (4H, m), 1.43 - 1.51 (5H, m), 0.14 (9H, s); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 57.6, 50.6, 32.6, 31.5, 26.9, 25.6, -1.6; HRMS (m/z): [M + NH\(_4\)]\(^+\) for C\(_{10}\)H\(_{26}\)O\(_2\)NSi, calcd, 220.17328; found, 220.17315.
temperature overnight. After 16 hours the solution was partitioned between CH₂Cl₂ (50 mL) and sat’d NaHCO₃(aq) (10 mL) and the phases were separated. The organic phase was dried (MgSO₄), filtered and concentrated in vacuo on the rotovap. The resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 146 mg (88% yield) of Compound 3.32 (Scheme 3.9) as a clear oil. R_f = 0.26 (40% EtOAc/hexanes); IR (neat, cm⁻¹) 3393 (br), 2951, 2859, 1717, 1464, 1420, 1250, 841; ¹H NMR (400 MHz, CDCl₃) δ ppm 3.66 (2H, t, J=6.5 Hz), 3.05 - 3.13 (1H, m), 2.19 (1H, d, J=5.5 Hz), 1.51 - 1.63 (4H, m), 1.36 - 1.49 (7H, m), 0.13 (9H, s); ¹³C NMR (101 MHz, CDCl₃) δ ppm 62.9, 57.6, 50.6, 32.6, 31.4, 29.2, 27.1, 25.6, -1.7; HRMS (m/z): [M + H]⁺ for C₁₁H₂₅O₂Si, calcd, 217.16238; found, 217.16293.

(Z)-trimethyl(syn-3-(tetradec-5-en-1-yl)oxiran-2-yl)silane (Compound 3.33, Scheme 3.9):

Compound 3.31 (80 mg, 0.40 mmol, 1.0 eq.) and pyridine (32 mg, 0.40 mmol, 1.0 eq.) were combined in un-distilled CH₂Cl₂ (5 mL) and Dess-Martin periodinane reagent (212 mg, 0.48 mmol, 1.2 eq.) was added and the mixture stirred at room temperature until complete by TLC (90 minutes). The mixture was then diluted with ethyl acetate (75 mL) and washed with water (10 mL) followed by 1N NaOH(aq) (2 x 10 mL). The organic phase was dried (MgSO₄), filtered through a silica plug (1 cm tall x 1 cm wide) using ethyl acetate (2 x 5 mL) to wash/elute and concentrated in vacuo on the rotovap to give 75 mg (95%) of crude aldehyde intermediate which was used immediately in the next step without further purification. R_f = 0.57 (40% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ ppm 9.78 (1H, t, J=2.0 Hz), 2.96 - 3.18 (1H, m), 2.19 (1H, d, J=5.5 Hz), 1.51 - 1.63 (4H, m), 1.36 - 1.49 (7H, m), 0.13 (9H, s).

A solution of 1-nonyl-triphenylphosphonium bromide (193 mg, 0.412 mmol, 1.1 eq.) in THF (5 mL) was cooled to 0 ºC and LiHMDS (0.41 mL of a 1M sol’n in THF, 0.412 mmol, 1.1 eq.) was added and stirred at 0 ºC for 20 minutes. The solution was then
cooled to -78 °C and a solution of the aldehyde intermediate prepared above (75 mg, 0.375 mmol, 1.0 eq.) in THF (3 mL) was added dropwise in 0.3 mL portions every 5 minutes. After complete addition, the mixture was stirred for 30 minutes at -78 °C then warmed to room temperature and stirred for 30 minutes at which time TLC indicated complete conversion. The reaction mixture was treated with sat’d NH₄Cl(aq) (5 mL) and water (5mL) and organics extracted with 50 mL ethyl acetate. The organic phase was dried (MgSO₄), filtered, and concentrated in vacuo on the rotovap. The resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 69 mg (59% yield over 2 steps) of Compound 3.33 (Scheme 3.9) as a clear oil. Regardless of olefination conditions, this material always contained a single set of olefin peaks but was contaminated with an unknown impurity having a characteristic doublet at 3.36 ppm with a coupling constant J= 3.1 Hz. This peak correlates well with that of a trans epoxide, however, such a species is not observed in the previous starting materials. 

R_f= 0.61 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 2955, 2926, 2855, 1462, 1250, 841; ¹H NMR (300 MHz, CDCl₃) δ ppm 5.30 - 5.43 (2H, m), 2.98 - 3.18 (1H, m), 2.19 (1H, d, J=5.0 Hz), 1.92 - 2.11 (4H, m), 1.16 - 1.48 (18H, m), 0.88 (3H, t, J=7.0 Hz), 0.13 (9H, s); ¹³C NMR (126 MHz, CDCl₃) δ ppm 130.3, 129.4, 57.6, 50.6, 31.9, 31.5, 29.75, 29.64, 29.52, 29.33, 29.31, 27.24, 27.11, 26.7, 22.7, 14.1, -1.7; HRMS (m/z): [M + H]⁺ for C₁₉H₃₉OSi, calcd, 311.27702; found, 311.27693.

(Z)-trimethyl(syn-3-(tetradec-6-en-1-yl)oxiran-2-yl)silane (Compound 3.34, Scheme 3.9):

Compound 3.32 (58 mg, 0.268 mmol, 1.0 eq.) and pyridine (21 mg, 0.268 mmol, 1.0 eq.) were combined in un-distilled CH₂Cl₂ (5 mL) and Dess-Martin periodinane reagent (136 mg, 0.321 mmol, 1.2 eq.) was added and the mixture stirred at room temperature until complete by TLC (90 minutes). The mixture was then diluted with ethyl acetate (50 mL) and washed with water (5 mL) followed by 1N NaOH(aq) (2 x 5 mL). The organic phase was dried (MgSO₄), filtered through a silica plug (1 cm tall x 1 cm wide) using ethyl acetate (2 x 5 mL) to wash/elute and concentrated in vacuo on the rotovap to give 56 mg (98%) of
crude aldehyde intermediate which was used immediately in the next step without further purification.  \( R_f = 0.60 \) (40% EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 9.77 (1H, t, \( J=2.0 \) Hz), 3.08 (1H, dt, \( J=7.5, 5.0 \) Hz), 2.45 (2H, td, \( J=7.5, 2.0 \) Hz), 2.20 (1H, d, \( J=5.0 \) Hz), 1.66 (2H, quin, \( J=7.5 \) Hz), 1.51 - 1.61 (2H, m), 1.36 - 1.50 (4H, m), 0.13 (9H, s).

A solution of 1-octyl-triphenylphosphonium bromide (131 mg, 0.288 mmol, 1.1 eq.) in THF (5 mL) was cooled to 0 °C and n-BuLi (0.11 mL of a 2.5M sol’n in hexanes, 0.288 mmol, 1.1 eq.) was added and stirred at 0 °C for 20 minutes. The solution was then cooled to -78 °C and a solution of the aldehyde intermediate prepared above (56 mg, 0.261 mmol, 1.0 eq.) in THF (2 mL) was added dropwise in 0.2 mL portions every 5 minutes. After complete addition, the mixture was stirred for 30 minutes at -78 °C then warmed to room temperature and stirred for 30 minutes at which time TLC indicated complete conversion. The reaction mixture was treated with sat’d NH\(_4\)Cl(aq) (5 mL) and water (5mL) and organics extracted with 50 mL ethyl acetate. The organic phase was dried (MgSO\(_4\)), filtered, and concentrated in vacuo on the rotovap. The resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 42 mg (51% yield over 2 steps) of Compound 3.34 (Scheme 3.9) as a clear oil. Regardless of olefination conditions, this material always contained a single set of olefin peaks but was contaminated with an unknown impurity having a characteristic doublet at 3.36 ppm with a coupling constant \( J=3.1 \) Hz. This peak correlates well with that of a trans epoxide, however, such a species is not observed in the previous starting materials. \( R_f = 0.59 \) (20% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\) thin film, cm\(^{-1}\)) 3003, 2955, 2926, 2855, 1722, 1464, 1417, 1250, 841; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 5.35 (2H, appdt, \( J=6.0, 3.5 \) Hz), 3.03 - 3.13 (1H, m), 2.19 (1H, d, \( J=5.5 \) Hz), 1.96 - 2.08 (4H, m), 1.41 - 1.49 (2H, m), 1.20 - 1.40 (16H, m), 0.88 (3H, t, \( J=7.0 \) Hz), 0.14 (9H, s); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) ppm 130.1, 129.6, 57.7, 50.6, 31.9, 31.6, 29.76, 29.69, 29.28, 29.22, 29.21, 27.23, 27.11, 27.00, 22.7, 14.1, -1.7; HRMS (m/z): [M + H]\(^+\) for C\(_{19}\)H\(_{39}\)OSi, calcd, 311.27702; found, 311.27698.
(Z)-tert-butyl-2-anti-(2-hydroxy-1-(trimethylsilyl)hexadec-7-en-1-yl)hydrazinecarboxylate (Compound 3.35, Scheme 3.9):

A 5 mL Biotage™ microwave vial was charged with compound 3.33 (31 mg, 0.10 mmol, 1.0 eq.) and Boc-carbazate (52 mg, 0.4 mmol, 4.0 eq.) and the vial was capped with a rubber septa and purged with N₂ for 5 minutes before addition of THF (0.5 mL). The mixture was cooled to 0 °C and BF₃·OEt₂ added (1.2 µL, 0.01 mmol, 0.1 eq.) then cooling bath removed and after warming to room temperature (20 minutes) the vial was placed in a 45 °C oil bath sealed (no N₂ bubbler) overnight. After 20 hours the reaction mixture was cooled to room temperature and sat’d NH₄Cl(aq) (5 mL) added followed by water (10 mL) and organics extracted with ethyl acetate (2 x 30 mL). The organic phase was dried (Na₂SO₄), filtered and concentrated in vacuo on the rotovap and the resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 32 mg (73% yield) of Compound 3.35 (Scheme 3.9) as a clear oil. Rᵥ= 0.24 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3445, 3287, 3003, 2957, 2926, 2855, 1713, 1537, 1456, 1393, 1368, 1250, 1169, 839; ¹H NMR (400 MHz, CDCl₃) δ ppm 6.00 (1H, br. s.), 5.26 - 5.44 (2H, m), 4.22 (1H, br. s.), 3.55 - 3.75 (2H, m), 2.37 - 2.43 (1H, m), 1.96 - 2.07 (4H, m), 1.42 - 1.52 (13H, m), 1.23 - 1.38 (14H, m), 0.88 (3H, t, J=7.0 Hz), 0.12 (9H, s); ¹³C NMR (126 MHz, CDCl₃) δ ppm 157.8, 130.1, 129.6, 80.9, 70.7, 57.5, 36.6, 31.9, 29.80, 29.78, 29.52, 29.34, 29.31, 28.3, 27.25, 27.24, 26.1, 22.7, 14.1, 1.7; HRMS (m/z): [M + H]⁺ for C₂₄H₅₁N₂O₃Si, calcd, 443.36689; found, 443.36801.

(Z)-tert-butyl-2-anti-(2-hydroxy-1-(trimethylsilyl)hexadec-8-en-1-yl)hydrazinecarboxylate (Compound 3.36, Scheme 3.9):

A 5 mL Biotage™ microwave vial was charged with compound 3.34 (43 mg, 0.138 mmol, 1.0 eq.) and Boc-carbazate (72 mg, 0.552 mmol, 4.0 eq.) and the vial was capped with a rubber septa and purged with N₂ for 5 minutes before addition of THF (0.5 mL)....
mL). The mixture was cooled to 0 °C and BF₃·OEt₂ added (1.7 µL, 0.0138 mmol, 0.1 eq.) then cooling bath removed and after warming to room temperature (20 minutes) the vial was placed in a 45 °C oil bath sealed (no N₂ bubbler) overnight. After 14 hours the reaction mixture was cooled to room temperature and sat’d NH₄Cl(aq) (5 mL) added followed by water (10 mL) and organics extracted with ethyl acetate (2 x 30 mL). The organic phase was dried (Na₂SO₄), filtered and concentrated in vacuo on the rotovap and the resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 48 mg (79% yield) of Compound 3.36 (Scheme 3.9) as a clear oil. R_f = 0.18 (20% EtOAc/hexanes); IR (CH₂Cl₂ thin film, cm⁻¹) 3400, 3285 (br), 3005, 2926, 2855, 1709, 1456, 1368, 1250, 1167, 1047, 1022, 839; ¹H NMR (500 MHz, CDCl₃) δ ppm 6.03 (1H, br. s.), 5.34 (2H, ddd, J = 6.0, 3.5, 2.5 Hz), 4.22 (1H, br. s.), 3.70 (1H, br. s.), 3.57 - 3.65 (1H, m), 2.40 (1H, d, J = 5.0 Hz), 1.97 - 2.05 (4H, m), 1.42 - 1.48 (11H, m), 1.22 - 1.39 (16H, m), 0.88 (3H, t, J = 7.0 Hz), 0.11 (9H, s); ¹³C NMR (126 MHz, CDCl₃) δ ppm 157.8, 130.0, 129.7, 80.9, 70.7, 57.5, 36.7, 31.9, 29.77 (2C overlap), 29.31, 29.28, 29.22, 28.3, 27.21, 27.19, 26.3, 22.7, 14.1, -1.8; HRMS (m/z): [M + H]⁺ for C₂₄H₅₁N₂O₅Si, calcd, 443.36689; found, 443.36654.

Tert-butyl 2-decanoyl-2-((anti)-2-hydroxy-1-(trimethylsilyl)hexadec-8-(Z)-en-1-yl)hydrazinecarboxylate (Compound 3.37, Scheme 3.10):

A solution of compound 3.36 (40 mg, 0.0903 mmol, 1.0 eq.) in CH₂Cl₂ (2 mL) was cooled to 0 °C and treated with Et₃N (13 mg, 0.126 mmol, 1.4 eq.) in CH₂Cl₂ (0.5 mL) followed by addition of decanoyl-chloride (19 mg, 0.0994 mmol, 1.1 eq.) in CH₂Cl₂ (0.5 mL) and the mixture was stirred overnight allowing to warm to room temperature. After 14 hours the mixture was diluted with CH₂Cl₂ (50 mL) and washed with sat’d NaHCO₃(aq) (10 mL) and the phases separated. The organic phase was dried (Na₂SO₄), filtered and concentrated in vacuo on the rotovap and the resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) to provide 43 mg (80% yield) of
Compound 3.37 (Scheme 3.10) as a clear oil. Rf = 0.39 (20% EtOAc/hexanes); IR (CH2Cl2, cm⁻¹) 3455, 3361, 3227, 3004, 2956, 2925, 2855, 1715, 1717, 1635, 1451, 1367, 1249, 1160, 842; ¹H NMR (400 MHz, DMSO-d₆, 55 °C) δ ppm 8.87 (1H, br. s.), 5.24 - 5.42 (2H, m), 4.34 - 4.49 (1H, m), 3.68 - 3.81 (1H, m), 3.37 - 3.53 (1H, m), 2.12 - 2.35 (2H, m), 1.89 - 2.07 (4H, m), 1.37 - 1.57 (13H, m), 1.13 - 1.36 (28H, m), 0.86 (6H, t, J=7.0 Hz), 0.07 (9H, s); ¹³C NMR (126 MHz, DMSO-d₆) δ ppm 174.4, 155.1, 129.61, 129.58, 80.6, 80.4, 69.5, 68.9, 34.5, 34.1, 31.3, 31.2, 29.1, 28.86, 28.64 (2 C’s), 28.55, 28.52, 28.46, 27.95 (2 C’s), 26.59, 26.56, 25.2, 24.2, 22.08, 22.07, 13.92 (2 C’s), -0.86; HRMS (m/z): [M + H]+ for C₃₄H₆₉N₂O₄Si, calcd, 597.50266; found, 597.50529.

Hydrazidomycin B (Compound 3.2, Scheme 3.10):

A solution of compound 3.37 (54 mg, 0.0905 mmol, 1.0 eq.) in THF (3 mL) was charged with KOrBu (25 mg, 0.226 mmol, 2.5 eq.) at room temperature then fitted with a reflux condenser and placed in a 45 °C oil bath overnight. After 16 hours the mixture was cooled to room temperature and diluted with ethyl acetate (50 mL) and washed with a mixture of water (5 mL) and sat’d NaHCO₃(aq) (5 mL) and the phases separated. The organic phase was dried (Na₂SO₄), filtered through a short plug of basic Al₂O₃ (2 cm tall x 1 cm wide) using ethyl acetate (25 mL) to wash/elute and concentrated in vacuo on the rotovap to give 40 mg (87% yield) of crude Boc-Z-enehydrazide as a clear oil.

Crude Boc-Z-enehydrazide prepared above (40 mg, 0.079 mmol, 1.0 eq.) was dissolved in THF (3 mL) and cooled to -78 °C and treated with KHMDS (0.17 mL of a 0.5 M sol’n in toluene, 0.0869 mmol, 1.1 eq.) and stirred at -78 °C for 15 minutes. To this was then added 2-methoxyacetyl chloride (10 mg, 0.0948 mmol, 1.2 eq.) as a solution in THF (0.5 mL) and the cooling bath was removed and warmed to room temperature and stirred 1 hour then partitioned between ethyl acetate (50 mL) and sat’d NaHCO₃(aq) (10 mL) and the phases were separated. The organic phase was dried (Na₂SO₄), filtered through a short plug of basic Al₂O₃ (1 cm tall x 1 cm wide) using ethyl acetate (2 x 10 mL) to
wash/elute and concentrated in vacuo on the rotovap to give crude Boc-imide-Z-enehydrazide as a clear oil.

Crude Boc-imide-Z-enehydrazide prepared above was dissolved in MeCN (3 mL) and Mg(ClO$_4$)$_2$ (2.1 mg, 0.00948 mmol, 0.12 eq.) was added and the flask equipped with a reflux condenser and placed in a 55 ºC oil bath overnight. After 18 hours the mixture was cooled to room temperature and volatiles were removed in vacuo on the rotovap and the resulting crude residue was purified by flash chromatography through silica gel (pre-conditioned with 1% Et$_3$N in hexanes) using ethyl acetate in hexanes to elute (0-100% EtOAc) to provide 21.2 mg (49% yield over 3 steps) of hydrazidomycin B (Compound 3.2, Scheme 3.10) as a clear oil at room temperature and a white solid in a -15 ºC freezer. R$_f$ = 0.48 (40% EtOAc/hexanes); IR (CH$_2$Cl$_2$ thin film, cm$^{-1}$) 3265, 3003, 2955, 2925, 2855, 1692, 1680, 1498, 1466, 1401, 1378, 1284, 1245, 1199, 1160, 1118; $^1$H NMR (500 MHz, DMSO-d$_6$) δ ppm 10.66 (1H, s), 6.41 (1H, dt, J=9.3, 1.6 Hz), 5.32 (2H, app t, J=5.0 Hz), 4.76 (1H, dt, J=9.3, 7.3 Hz), 3.97 (2H, s), 3.36 (3H, s), 2.31 (1H, t, J=7.3 Hz), 2.01 - 2.15 (3H, m), 1.92 - 2.01 (4H, m), 1.40 - 1.54 (2H, m), 1.14 - 1.36 (28H, m), 0.85 (6H, t, J=6.9 Hz); $^{13}$C NMR (126 MHz, DMSO-d$_6$) δ ppm 173.14, 167.60, 129.62, 129.55, 124.26, 117.09, 70.68, 58.94, 31.29, 31.27, 31.15, 29.12, 28.99, 28.89 (2 C’s), 28.82 (2 C’s), 28.67, 28.57, 28.54, 28.46, 26.62, 26.58, 25.81, 23.84, 22.09, 22.07, 13.93, 13.92; HRMS (m/z): [M + H]$^+$ for C$_{29}$H$_{55}$N$_2$O$_3$, calcd, 479.42127; found, 479.42290.

Tert-butyl-2-decanoyl-2-((anti)-2-hydroxy-1-(trimethylsilyl)hexadec-7-(Z)-en-1-yl)hydrazinecarboxylate (Compound 3.38, Scheme 3.11):

A solution of compound 3.35 (38 mg, 0.0858 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (2 mL) was cooled to 0 ºC and treated with Et$_3$N (12 mg, 0.12 mmol, 1.4 eq.) in CH$_2$Cl$_2$ (0.5 mL) followed by addition of decanoyl-chloride (18 mg, 0.0944 mmol, 1.1 eq.) in CH$_2$Cl$_2$ (0.5 mL) and the mixture was stirred overnight allowing to warm to room temperature. After 16 hours the mixture was diluted with CH$_2$Cl$_2$ (50 mL) and washed with sat’d NaHCO$_3$(aq) (10 mL) and the phases separated. The organic
phase was dried (\(\text{Na}_2\text{SO}_4\)), filtered and concentrated \textit{in vacuo} on the rotovap and the resulting crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 42 mg (82% yield) of Compound \textbf{3.38} (Scheme 3.11) as a clear oil. \(R_f= 0.34\) (20% EtOAc/hexanes); IR (\(\text{CH}_2\text{Cl}_2\), cm\(^{-1}\)) 3460, 3252, 3003, 2955, 2926, 2855, 1743-1640 (m), 1368, 1250, 1159, 841; \(^1\text{H} \text{NMR} \) (400 MHz, DMSO-\(d_6\), 55 °C) \(\delta\) ppm 8.90 (1H, br. s), 5.26 - 5.39 (2H, m), 4.38 - 4.48 (1H, m), 3.68 - 3.81 (1H, m), 3.36 - 3.53 (1H, m), 2.10 - 2.40 (2H, m), 1.90 - 2.06 (4H, m), 1.37 - 1.59 (13H, m), 1.17 - 1.36 (28H, m), 0.87 (6H, t, \(J=7.0\) Hz), 0.07 (9H, s); \(^{13}\text{C} \text{NMR} \) (126 MHz, DMSO-\(d_6\)) \(\delta\) ppm 174.4, 155.1, 129.58, 129.55, 80.6, 69.4, 68.9, 34.3, 34.0, 31.9, 31.5, 31.3, 29.1, 28.86, 28.83, 28.67, 28.64, 28.61, 27.95, 27.68, 26.61, 26.58, 25.0, 24.2, 22.07 (2C), 13.9, 13.5, -0.86; HRMS (m/z): \([\text{M} + \text{H}]^+\) for \(\text{C}_{34}\text{H}_{69}\text{N}_2\text{O}_4\text{Si}\), calcd, 597.50266; found, 597.50165.

\textbf{Elaioomycin B (Compound 3.3, Scheme 3.11):}

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

A solution of compound \textbf{3.38} (60 mg, 0.10 mmol, 1.0 eq.) in THF (3 mL) was charged with K\(\text{OEt}_2\) (28 mg, 0.25 mmol, 2.5 eq.) at room temperature then fitted with a reflux condenser and placed in a 45 °C oil bath overnight. After 13 hours the mixture was cooled to room temperature and diluted with ethyl acetate (50 mL) and washed with a mixture of water (5 mL) and sat’d \(\text{NaHCO}_3\) (aq) (5 mL) and the phases separated. The organic phase was dried (\(\text{Na}_2\text{SO}_4\)), filtered through a short plug of basic \(\text{Al}_2\text{O}_3\) (2 cm tall x 1 cm wide) using ethyl acetate (25 mL) to wash/elute and concentrated \textit{in vacuo} on the rotovap to give 40 mg (80% yield) of the crude Boc-Z-enehydrazide intermediate as a clear oil.

Crude Boc-Z-enehydrazide prepared above (40 mg, 0.079 mmol, 1.0 eq.) was dissolved in THF (3 mL) and cooled to -78 °C and treated with KHMDS (0.17 mL of a 0.5 M sol’n in toluene, 0.0869 mmol, 1.1 eq.) and stirred at -78 °C for 15 minutes. To this was then added 2-methoxyacetyl chloride (10 mg, 0.0948 mmol, 1.2 eq.) as a solution in THF (0.5 mL) and the cooling bath was removed and warmed to room temperature and stirred 1
hour then partitioned between ethyl acetate (75 mL) and sat’d NaHCO₃(aq) (20 mL) and the phases were separated. The organic phase was dried (Na₂SO₄), filtered through a short plug of basic Al₂O₃ (1 cm tall x 1 cm wide) using ethyl acetate (25 mL) to wash/elute and concentrated in vacuo on the rotovap to give crude Boc-imide-Z-enehydrazide as a clear oil.

Crude Boc-imide-Z-enehydrazide was dissolved in MeCN (3 mL) and Mg(ClO₄)₂ (2.3 mg, 0.010 mmol, 0.13 eq.) was added and the flask equipped with a reflux condenser and placed in a 55 ºC oil bath overnight. After 19 hours the mixture was cooled to room temperature and volatiles were removed in vacuo on the rotovap and the resulting crude residue was purified by flash chromatography through silica gel (pre-conditioned with 1% Et₃N in hexanes) using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) to provide 19.1 mg (40% yield over 3 steps) of elaiomycin B (Compound 3.3, Scheme 3.11) as a clear oil at room temperature and a white solid in a -15 ºC freezer. Rf = 0.45 (40% EtOAc/hexanes); IR (CH₂Cl₂ thin film, cm⁻¹) 3271, 3003, 2955, 2922, 2855, 1710, 1663, 1495, 1456, 1402, 1379, 1283, 1252, 1233, 1198, 1117; ¹H NMR (500 MHz, DMSO-d₆) δ ppm 10.66 (1H, s), 6.40 (1H, dt, J=9.3, 1.6 Hz), 5.31 (2H, app t, J=5.4 Hz), 4.75 (1H, dt, J=9.3, 7.2 Hz), 3.97 (2H, s), 3.34 (3H, s), 2.30 (2H, t, J=7.3 Hz), 2.01 - 2.11 (2H, m), 1.96 (4H, dt, J=6.1, 6.4 Hz), 1.38 - 1.53 (2H, m), 1.19 - 1.31 (28H, m), 0.84 (6H, t, J=7.0 Hz); ¹³C NMR (126 MHz, DMSO-d₆) δ ppm 173.35, 167.80, 129.87, 129.67, 124.51, 117.25, 70.86, 59.13, 31.45, 31.34 (2 C’s), 29.31, 29.12, 29.06, 29.04, 28.99, 28.91, 28.86, 28.84, 28.80, 28.75, 28.77, 26.68, 25.89, 24.02, 22.27, 22.26, 14.12, 14.12; HRMS (m/z): [M + H]⁺ for C₂₉H₅₅N₂O₃, calcd, 479.42127; found, 479.42176.
3.5 References


Chapter 4: An Ynimide Approach to Pyrrolidinoindoline Alkaloids (±)-CPC-1 and (±)-Alline and Imide-Functionalized Heterocycles

4.1 Introduction

Ynamides\(^1\) are stable N-substituted alkynes which have seen considerable use as convenient reagents for selectively incorporating amine functional groups in organic molecules. The synthetic utility of these polarized 1-amido-alkynes is best exemplified by their use in natural product total synthesis typically via N-alkynyl cyclization or cycloaddition reactions.\(^2\) Despite the popular use of ynamide reagents in alkyne ring-forming reactions, terminal ynamide species remain surprisingly under-utilized as acetylide nucleophiles in additions to common organic electrophiles. For example, there are limited reports on ynamide Sonogoshira coupling,\(^3\) two examples of direct ynamide-acetylide addition to carbonyl groups,\(^4\)\(^,\)\(^5\) and one recent report on copper-catalyzed ynamide addition to acid-chlorides and pyridinium salts.\(^6\) While useful, these examples are limited by the use of N-linked alkynes possessing urethane, sulfonamide or indole groups on nitrogen which are not easily deprotected and transformed into other useful amine functional groups (e.g., primary amines). There are also, to the best of our knowledge, no examples of terminal ynamide nucleophiles reacting with other common electrophiles such as epoxides and Michael acceptors. We became intrigued with this overall type of terminal ynamide-acetylide reactivity since it would provide an alternative approach to generate functionalized ynamides complimentary to the typical ynamide synthesis strategies which focus on C\(_{sp^2}\)–N bond formation. Furthermore, such a general internal ynamide disconnection could potentially be coupled with alkyne hydrogenation as a route to install ethyleneamine groups and could thus be valuable for aminoethylation purposes (Figure 4.1).
For example, we were particularly attracted to this type of ynamide-based ethyleneamine installation since it could be used to access valuable ethyleneamine containing structures such as alkaloids and pharmaceutical agents (Figure 4.2). In addition, this ynamide aminoethylation would be a useful alternative to current aminoethylation strategies that generally only provide access to phenethylamine groups using boronate or organozinc reagents.

In this regard, our recent discovery of a new easily prepared ynehydrazide alkynre class outlined in Chapter 2 led us to consider whether these species could function as masked ynamides through N–N bond cleavage. We thus set-out to investigate the reactivity of a terminal ynehydrazide reagent with various electrophiles as a route to install ethyleneamine units. As shown below, this eventually led us to develop a more useful imide-linked alkyne approach to aminoethylation. Some experiments and results described herein were performed by undergraduate students Yiwei Hu and Bruce Gregoire and include ynimide [3+2] cycloadditions (Y. Hu) and synthesis and reactivity of di-Boc-di-bromo-enamide 4.14 (B. Gregoire).
4.2 Results and Discussion

To test a terminal ynehydrazide approach to aminoethylation, we disconnected the simple pyrrolidinoindoline alkaloids\(^1\) (±)-CPC-1\(^{11,12}\) and (±)-alline\(^{13,14}\) via ynehydrazide lithium-acetylide addition to N-protected isatins (Scheme 4.1). The resulting internal isatin-functionalized ynehydrazides were envisioned to provide access to the target alkaloids in only a few additional steps including alkyne reduction, hydrazine bond cleavage and reductive cyclization.

Scheme 4.1 Proposed ynehydrazide aminoethylation approach to pyrrolidinoindoline alkaloids

Toward this goal, we were pleased to observe that tri-Boc protected terminal ynehydrazide 4.3 was readily prepared in gram-scale quantities and underwent addition to the ketone of N-Me isatin via its lithium acetylide (Scheme 4.2). Although the alkyne of internal ynehydrazide 4.4 could be reduced to reveal ethylenehydrazide species 4.5 we unfortunately were unable to cleave the N–N bond under a variety of conventional conditions to generate the required ethylenecarbamate 4.6 to complete the total syntheses of (±)-CPC-1 4.1. A major side product observed in many of the reduction reactions attempted was the undesired reductive cleavage of the methyl ether α to the isatin amide.
Although unsuccessful in the synthesis of the target alkaloid, these results provide a proof-of-concept for using ynehydrazide 4.3 as a reagent for hydrazinoethylation which may be valuable for other applications including heterocycle generation. To illustrate this concept, compound 4.5 was directly elaborated in a single pot to pyrazole structures 4.7 and 4.8 demonstrating how reagent 4.3 can function as an ethylenepyrazole building block (Scheme 4.3).

Returning to our original N-linked acetylide aminating concept, we revisited our pyrrolidinoindoline synthetic strategy with the goal of using an alternative ynamide derivative for the key aminoethylation. Drawing a parallel with Gabriel amination strategies which utilize phthalimide or di-Boc-imide nucleophiles as masked amines, our efforts focused on investigating imide functionalized alkynes as ethyleneamine synthons. In this regard, we were particularly attracted to the previously reported N,N-di-Boc
terminal ynimide 4.12\(^{17}\) because it appeared straightforward to prepare and possessed flexible Boc carbamate protecting groups which should be easy to remove or manipulate.\(^{18}\) Thus, ynimide 4.12 was prepared via modification of previously described conditions\(^{17}\) involving addition of di-tert-butyl-iminodicarboxylate to alkynyliodonium triflate reagents with mild heating at higher dilution (Scheme 4.4).

**Scheme 4.4** Synthesis of N,N-di-Boc-ynamide reagent 4.12 from alkynyliodonium triflate reagents

Although successful, the preparation of 4.12 via alkynyliodonium triflates use expensive reagents in a multi-step process limiting scalability. For these reasons, we explored an alternative Corey-Fuchs type approach to prepare 4.12 which would instead use cheap readily available reagents and could potentially yield multiple grams of the terminal ynimide reagent in a single sequence (Scheme 4.5). In this regard, Corey-Fuchs precursor di-bromo-di-Boc enamide compound 4.14 was easily prepared in two steps on multi-gram scale starting from simple formamide. However, subsequent treatment of 4.14 with BuLi to facilitate \(\alpha\)-elimination and carbene rearrangement toward 4.12 was not observed to proceed. Instead, a possible \(\beta\)-elimination is presumed to operate in this case as di-Boc-imide 4.11 was observed to be formed.

Despite not being able to generate ynimide 4.12 via enamide 4.14, its simple preparation and sp²–Br bonds suggested that this compound may be useful as an organic building block in other applications. For example, regioselective palladium catalyzed Suzuki-Miyaura cross-coupling of 4.14 with vinyl-BF₃K gave 1-amino-diene 4.15 as a potential Diels-Alder 4π-diene participant (Scheme 4.6). However, attempted [4+2] cycloaddition using 1-imido-diene 4.15 did not yield appreciable amounts of the desired Diels-Alder adducts presumably due to poor nitrogen lone pair donation into the π-system. Based on this assumption, Mg(ClO₄)₂ catalyzed removal of one Boc-carbamate was used to provide the more electron-rich unstable amido-diene 4.16. This modification proved successful as amino-diene 4.16 was a competent participant in the Diels-Alder reaction with N-phenyl maleimide to give exclusively endo cycloadduct 4.17. This reaction is interesting as it stereoselectively installs amino-functionality and results in a 6-membered ring possessing an alkenyl-bromide component for future elaboration. These preliminary results indicate that further studies on enamide 4.14 are warranted.
Scheme 4.6 Regioselective cross-coupling of dibromo-enamide 4.14 and subsequent Diels-Alder reaction

Returning to the topic of the present study regarding proposed use of Boc-imide substituted terminal alkyne 4.12 as an aminoethylating synthon, we next examined its reaction with protected isatins toward alkaloids (±)-CPC-1 and (±)-alline. In contrast to our prior ynehydrazide results in this area, attempts to generate the lithium-acetylide of 4.12 with n-BuLi or LDA followed by trapping with N-Me-isatin resulted in unsatisfactory carbonyl addition. Ultimately, a slight modification of literature conditions for room temperature formation of Zn-acetylides using a Et₂Zn/HMPA mixture¹⁹ was found to mediate clean ketone addition with 4.12 to provide functionalized ynimide species 4.18 after tertiary alcohol methylation (Scheme 4.7). Notably, this ynimide strategy was successful in completing the formal total synthesis of pyrrolidinoidolone (±)-CPC-1 4.1 via hydrogenation and Mg(ClO₄)₂ catalyzed imide mono-Boc deprotection²⁰ to provide ethyleneamine compound 4.19 which is known to undergo reductive cyclization to the target alkaloid.¹²b
Scheme 4.7 Formal synthesis of (±)-CPC-1 using an ynimide aminoethylation approach

The related alkaloid (±)-alline 4.2 was then successfully accessed in a similar fashion via ynimide 4.12 Zn-acetylide addition to N-benzyl isatin followed by a hydrogenation/deprotection sequence to generate intermediate 4.20 (Scheme 4.8). The formal synthesis was completed by reductive cyclization with LiAlH₄ to provide compound 4.21 which is known to undergo benzyl deprotection to provide the target pyrrolidinoindoline.¹²ᵇ

Scheme 4.8 Formal synthesis of (±)-Alline using an ynimide aminoethylation approach

These results clearly illustrate how the N,N-di-boc imide group is flexible toward deprotection or conversion to other amine functional groups. As a result, we investigated the generality of this ynimide based aminoethylation strategy using 4.12 as an acetylide nucleophile with a variety of common electrophiles. Under conditions used for addition of this ynimide to isatins, the Zn-acetylide of 4.12 was also found to undergo reaction
with other carbonyl species including aldehydes, ketones and imines (Scheme 4.9). In this area, only activated N-sulfonyl imines were found to be reactive with the Zn-acetylide of 4.12 and attempts to alkynylate aldehydes with 4.12 under Carreira’s catalytic conditions\textsuperscript{21} were unsuccessful.

\[
\begin{align*}
\text{Boc} & \quad \text{N} \equiv \text{H} \\
& \quad \text{4.12} \quad \text{(2.0 eq.)}
\end{align*}
\]

\[
\begin{align*}
\text{HMPA (2.0 eq.)} & \quad \text{Et}_2\text{Zn (2.0 eq.)} \\
& \quad \text{toluene} \\
& \quad \text{rt, 16 h}
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
& \quad \text{(1.0 eq.)}
\end{align*}
\]

\[
\text{X} = \text{O, NTs}
\]

\[
\begin{align*}
\text{N} & \equiv \text{N} \quad \text{Boc}_{2} \\
& \quad \text{4.23 - 4.4.27}
\end{align*}
\]

\[
\begin{align*}
\text{NHTs} & \quad \text{Ph} \\
& \quad \text{4.23, 64\% N(Boc)}_{2}
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{Ph} \\
& \quad \text{4.24, 63\% N(Boc)}_{2}
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{Chx} \\
& \quad \text{4.25, 65\% N(Boc)}_{2}
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{CO}_2\text{Me} \\
& \quad \text{Ph} \\
& \quad \text{4.26, 60\% N(Boc)}_{2}
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{Ph} \\
& \quad \text{4.27, 65\% N(Boc)}_{2}
\end{align*}
\]

Scheme 4.9 Reaction of ynimide 4.12 with carbonyl electrophiles

In a somewhat related fashion, ynimide 4.12 participated in a copper-catalyzed multicomponent N-acyl pyridinium salt addition reaction\textsuperscript{22} (Scheme 4.10). The products of these reactions are interesting ynimide functionalized dihydroquinoline and dihydroisoquinoline compounds 4.28 and 4.29. In the quinoline case, although two regioisomeric addition sites exist, consistent with previous observations with other alkynes in this reaction only the 1,2-addition product 4.28 was observed.\textsuperscript{22}

\[
\begin{align*}
\text{Ph} & \quad \text{N} \quad \text{Boc} \\
& \quad \text{4.12} \quad \text{(1.0 equiv.)}
\end{align*}
\]

\[
\begin{align*}
\text{Boc} & \quad \text{N} \equiv \text{H} \\
& \quad \text{4.12} \quad \text{(1.2 eq.)}
\end{align*}
\]

\[
\begin{align*}
\text{EtCO}_2\text{Cl (1.1 eq.)} & \quad \text{iPr}_2\text{NEt (1.4 equiv.)} \\
& \quad \text{Cul (10 mol\%)} \\
& \quad \text{MeCN, rt}
\end{align*}
\]

\[
\begin{align*}
\text{C} \quad \text{N} \quad \text{CO}_2\text{Et} \\
& \quad \text{N(Boc)}_{2} \\
& \quad \text{4.28, 62\%}
\end{align*}
\]

\[
\begin{align*}
\text{N} \quad \text{C} \quad \text{CO}_2\text{Et} \\
& \quad \text{N(Boc)}_{2} \\
& \quad \text{4.29, 58\%}
\end{align*}
\]

Scheme 4.10 Copper-catalyzed reaction of ynimide 4.12 with N-acyl pyridinium ions

Additionally, the successful reaction of ynimide 4.12 with epoxide and Michael acceptor electrophiles can also be achieved (Schemes 4.11 and 4.12). For epoxide opening, we found the Yamaguchi conditions\textsuperscript{23} to be generally optimal, however, poor regioselectivity (~1:1) was observed with styrene oxide which did not improve using alternative conditions (result not shown). Furthermore, rhodium catalyzed attempts to facilitate a Michael addition of ynimide 4.12 failed due to competing decomposition pathways of
this electron rich alkyne in the presence of rhodium. Alternatively, we found that 1,4-addition of this alkyne could be achieved through Zn-acetylide formation in combination with silyl-triflate activation of the Michael acceptor. In order to reveal the desired ketone products 4.33-4.44 tetrabutylammonium fluoride was used to cleave the silyl-enol ether intermediates due to the acidic sensitivity of the ynimide fragment.

Scheme 4.11 Reaction of ynimide 4.12 with epoxides

Scheme 4.12 Reaction of ynimide 4.12 with Michael acceptors

Finally, reagent 4.12 was found to provide access to acyl and aryl ynimides under metal-catalyzed Sonogoshira conditions (Scheme 4.13). Ynimide arylation could be achieved only with aryl iodides as coupling partners since reaction of less active aryl bromides generated low amounts of desired aryl-coupled ynimide product due to possible competing metal facilitated oxazolinone cyclization of N-Boc alkyne 4.12.

Scheme 4.13 Sonogoshira coupling with ynimide 4.12

In agreement with our pyrrolidinoindoline alkaloid syntheses, simple Pd/C hydrogenation conditions efficiently converted a variety of the internal alkynyl-imides prepared above to the corresponding ethyleneamine functionalized products 4.38-4.43 (Scheme 4.14).
Importantly, expanded access to aminoethyl structures including valuable diamine and amino-alcohol product structures demonstrates how this ynimide reaction sequence is differentiated from other aminoethylating strategies which typically only provide access to aryl-functionalized ethyleneamines.\(^7,^8\)

Scheme 4.14 Ethyleneamines from internal ynimides derived from 4.12

In addition to aminoethylation, we also became interested in using ynimide reagent 4.12 in other synthetically useful modes such as [3+2] cycloadditions. Toward this goal, we first investigated its use in one of the simplest and most exploited terminal alkyne reactions: the copper-catalyzed [3+2] cycloaddition with azides.\(^25\) In this regard, a variety of 1,2,3-triazoles functionalized with the easily de-blocked di-Boc imide group were regioselectively generated from ynimide 4.12 (Scheme 4.15). Furthermore, when Fokin’s ruthenium catalyzed conditions\(^26\) were applied, a complete regioselectivity switch was observed providing 5-imide substituted 1,2,3-triazoles (Scheme 4.16). This interesting regioselectivity switch with ruthenium is consistent with Fokin’s observations and other related [3+2] results.\(^9a\)
Scheme 4.15 Cu-catalyzed synthesis of 4-imide-functionalized triazoles from ynimide 4.12

Scheme 4.16 Ru-catalyzed synthesis of 5-imide functionalized triazoles from ynimide 4.12

In a related fashion, di-Boc ynimide 4.12 can also be used to generate imide functionalized isoxazoles (Scheme 4.17). Again, a complete regioselectivity switch in isoxazole formation was observed using Fokin’s ruthenium catalyzed conditions versus more conventional copper-catalysis.

Scheme 4.17 Catalytic synthesis of imide-functionalized isoxazoles from ynimide 4.12
Moreover, as a proof-of-concept illustration of the simplicity with which these di-Boc imide functionalized heterocycles can be deprotected to reveal and exploit primary amine reactivity, we have prepared amide and amine functionalized triazoles (Scheme 4.18). In this regard, ynimide 4.12 is shown to be a more flexible reagent for heterocycle amine-functionalization via introduction of the di-Boc imide group versus conventional ynamide cycloadducts which result in sulfonamide or urethane nitrogen-functionality.

![Scheme 4.18 Deprotection and reaction of Boc-imide functionalized triazoles](image)

**Scheme 4.18** Deprotection and reaction of Boc-imide functionalized triazoles

### 4.3 Conclusions

In this study, we have demonstrated that ynimide reagent 4.12 is a useful building block to generate functionalized internal ynimides as well as di-Boc imide functionalized triazole and isoxazole heterocycles. The ynimide products included in this report were constructed using new examples of ynamide acetylide reactivity with common electrophiles including carbonyl groups, imines, epoxides, Michael acceptors, and pyridinium ions. Importantly, our results also demonstrate how ynimide 4.12 can function as an ethyleneamine building block via simple hydrogenation of internal ynimide products resulting in straightforward access to useful aminoethylated structures including alkaloid natural products. Future work in this area includes the investigation of catalyst controlled enantioselective ynimide carbonyl alkynylations, as well as using reagent 4.12 to prepare other alkaloids through possible epoxide opening or 1,4-addition strategies. In addition, further studies on the reactivity of di-Boc-di-bromo-enamide 4.14
including additional examples of Diels-Alder reactivity is warranted and should be pursued.

4.4 Experimental Section

Copies of $^1$H and $^{13}$C NMR spectra for all compounds can be found in Appendix 3. THF was dried over sodium benzophenone-ketyl and toluene and acetonitrile were dried over calcium hydride and distilled fresh under nitrogen atmosphere before use and transferred via syringe using standard techniques unless otherwise stated. Toluene and acetonitrile were dried over calcium hydride and distilled fresh under nitrogen atmosphere before use and transferred via syringe using standard techniques unless otherwise stated. The following non-commercial reagents were prepared according to previously reported literature conditions: N-hydroxybenzimidoyl chloride,$^{28}$ N-Me$^{29}$ and N-Bn-isatins,$^{30}$ 1-oxaspiro[2.5]octane,$^{31}$ (E)-N-benzylidene-4-methylbenzenesulfonamide,$^{32}$ methyl 2-azidoacetate,$^{33}$ tert-butyl (2-azidoethyl)carbamate$^{34}$ and aryl-azides.$^{35}$ All other reagents including catalysts, LiHMDS (1.0 M in THF), KHMDS (0.5 M in toluene), Tf$_2$O (1.0 M in CH$_2$Cl$_2$), Et$_2$Zn (1.0 M in hexanes), alkynes, di-tert-butyl-azodicarboxylate, epoxides, Michael acceptors, benzoyl-chloride, aryl-halides, aldehydes (passed through short plug of basic Al$_2$O$_3$ immediately prior to use), ketones and benzyl-azide were purchased from Aldrich or VWR and used as received unless otherwise stated. NMR solvent (CDCl$_3$ with TMS internal standard) was purchased from Cambridge Isotopes Lab Inc. and used as received.

All products were characterized by $^1$H NMR and $^{13}$C NMR, IR and HRMS. $^1$H NMR and $^{13}$C NMR were recorded on Varian Mercury 300 MHz, or 400 MHz spectrometers. Chemical shifts are expressed in ppm values and $^1$H NMR spectra are referenced to 0.00 ppm for Me$_4$Si (TMS) and solvent residual peak of 2.50 ppm for d$_6$-DMSO. $^{13}$C NMR spectra are referenced to 77.00 ppm for CDCl$_3$ and 39.52 ppm for d$_6$-DMSO. Peak multiplicities are designated by the following abbreviations: s, singlet; br.s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; r, rotomers; $J$, coupling constant in Hz. If a
coupling pattern can be assigned as a combination of multiplicities, then the listed abbreviations are combined to provide an appropriate descriptor for the observed patterns (e.g., dt - doublet of triplets). IR spectra were obtained on a Shimadzu FTIR-8400S with samples loaded as thin films on NaCl plates neat or with CH$_2$Cl$_2$ as indicated. Mass spectra were obtained by the University of Toronto mass spectral facility (AIMS); high resolution mass spectra (HRMS) were recorded on an AEI MS3074 spectrometer. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Flash column chromatography on silica gel (60 Å, 230-400 mesh, obtained from Silicycle Inc.) was performed with reagent grade ethyl acetate and hexanes as eluent. Analytical thin-layer chromatography (TLC) was performed on pre-coated aluminum-backed silica gel plates (Alugram SIL G/UV254 purchased from Rose Scientific Limited or Silicycle Inc.) and visualized with a UV lamp (254 nm) or KMnO$_4$ stain and heating.

**Synthesis of tri-tert-butyl 2-ethynylhydrazine-1,1,2-tricarboxylate (Compound 4.3, Scheme 4.2):**

```
H≡N(Boc)$_2$                         \( \text{N(Boc)$_2$} \)
\( \text{Boc} \)                        \( \text{N} \)
```

In a nitrogen flushed 250 mL flask capped with a rubber septa was charged THF (30 mL) and ethynyltrimethylsilane (982 mg, 1.42 mL, 10.0 mmol, 1.0 eq.) under N$_2$ and cooled to -78 °C in a dry ice/acetone bath. A solution of n-BuLi (4.80 mL of a 2.5 M sol’n in hexanes, 12.0 mmol, 1.2 eq.) was then added dropwise over 1-2 mins and the resulting mixture stirred at -78 °C for 15 mins. A solution of DBAD (di-t-butyl-azodicarboxylate, 3.45 g, 15.0 mmol, 1.5 eq.) in THF (15 mL) was then added over 1-2 mins and the cooling bath removed and the mixture allowed to warm to room temperature and stirred at room temperature for 30 mins. The reaction mixture was then re-cooled to -78 °C and Boc$_2$O (1.83 g, 15.0 mmol, 1.5 eq.) in THF (6 mL) added and the cooling bath removed and the mixture allowed to warm to room temperature and stirred at room temperature for 30 mins. The reaction mixture was then quenched by addition of sat’d NH$_4$Cl(aq) (30 mL) and diluted with ethyl acetate (100 mL) and water (20 mL) and the layers separated. The organic extract was dried (MgSO$_4$), filtered through a Si plug topped with celite (2” tall x 1” wide) using 50 mL ethyl acetate to wash/elute and the filtrate concentrated in vacuo to provide 3.90 g of a
yellow oil. The resulting crude residue thus obtained was dissolved in THF (20 mL) and cooled to 0 °C and treated with tetra-n-butyl-ammonium fluoride (TBAF, 18.2 mL of a 1M sol’n in THF, 18.2 mmol, ~2.0 eq.) and stirred for 45 minutes in the ice/water bath. The reaction mixture was then diluted with water (100 mL) and extracted with Et$_2$O (2 x 300 mL). The organic extracts were combined, washed with water (50 mL) then sat’d NaClaq. (25 mL), dried (MgSO$_4$), filtered and concentrated in vacuo. The crude residue was then purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 1.80 g (51% yield over 2 steps) of Compound 4.3 (Scheme 4.2) as a yellow oil. $R_f$ = 0.37 (20% EtOAc/hexanes); IR (neat, cm$^{-1}$) 3272, 2981, 2936, 2148, 1807, 1478, 1456, 1393, 1146, 1002, 847; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 3.01 (1H, r, app d, $J=16.0$ Hz), 1.43 - 1.60 (27H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 149.0, 148.7, 84.4, 74.3, 60.7, 60.1, 27.90, 27.84; HRMS (m/z): [M + Na]$^+$ for C$_{17}$H$_{28}$N$_2$O$_6$Na, calcd, 379.1839; found, 379.1852.

**Synthesis of tri-tert-butyl 2-((3-methoxy-1-methyl-2-oxoindolin-3-yl)ethyl)hydrazine-1,1,2-tricarboxylate (Compound 4.4, Scheme 4.2):**

Terminal ynehydrazide (Compound 4.3, 535 mg, 1.5 mmol, 1.5 eq.) was dissolved in THF (5 mL) and cooled to -78 °C in a dry ice/acetone bath. A solution of $n$-BuLi (0.60 mL of a 2.5 M sol’n in hexanes, 1.5 mmol, 1.5 eq.) was then added dropwise over 1-2 mins and the resulting mixture stirred at -78 °C for 15 mins. A solution of N-Me isatin (161 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was then added and the cooling bath removed and the mixture allowed to warm to room temperature. After stirring for 1 hr at room temperature dimethylsulfate (315 mg, 0.24 mL, 2.5 mmol, 2.5 eq.) was added and the mixture stirred at room temperature for a further 3 hours. The reaction mixture was then diluted with water (25 mL) and ethyl acetate (75 mL) and the phases separated. The aqueous phase was extracted again with ethyl acetate (50 mL) and the organic extracts combined and washed with sat’d NaClaq. (10 mL), dried (MgSO$_4$), filtered and concentrated in vacuo. The crude residue was then purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 407 mg (76%
yield over 2 steps) of Compound 4.4 (Scheme 4.2) as an orange oil after vacuum line drying to remove residual dimethylsulfate. \( R_f = 0.38 \) (40% EtOAc/hexanes); IR (neat, cm\(^{-1}\)) 3059, 2981, 2935, 1801, 1730, 1700, 1622, 1478; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 7.38 - 7.50 (1H, m), 7.29 - 7.37 (1H, m), 7.02 - 7.12 (1H, m), 6.78 - 6.85 (1H, m), 3.58 - 3.66 (3H, r, m), 3.12 - 3.23 (3H, r, m), 1.40 - 1.55 (27H, m); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) ppm 171.3, 151.0, 148.86, 148.79, 143.1, 130.4, 128.0, 124.8, 123.1, 108.6, 84.7, 84.51, 84.46, 80.3, 74.3, 67.5, 52.9, 28.1, 27.9, 27.8, 26.3; HRMS (m/z): [M + \(\text{NH}_4\)]\(^+\) for C\(_{27}\)H\(_{41}\)N\(_4\)O\(_8\), calcd, 549.29244; found, 549.29098.

**Synthesis of di-tert-butyl 1-(2-(3-methoxy-1-methyl-2-oxoindolin-3-yl)ethyl)hydrazine-1,2-dicarboxylate (Compound 4.5, Scheme 4.2):**

Compound 4.4 (215 mg, 0.405 mmol, 1.0 eq.) was dissolved in MeCN (5 mL) and Mg(ClO\(_4\))\(_2\) (9 mg, 0.0405 mmol, 0.1 eq.) was added and the flask fitted with a reflux condenser and placed in a 55 °C oil bath. After 4 hrs, an NMR aliquot shows conversion to the imide mono-Boc deprotected product. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude residue was dissolved in ethyl acetate (40 mL) and filtered through a celite pad and concentrated *in vacuo* again to provide 180 mg (quant. yield) of the mono imide-Boc deprotected intermediate. The crude residue thus obtained was dissolved in ethyl acetate (10 mL) and Pd/C added (90 mg 10% w/w, ~0.2 eq. Pd). The flask was capped with a rubber septa and purged with N\(_2\) for 2 minutes then a balloon of H\(_2\) attached and purged for 5 minutes before a fresh H\(_2\) balloon attached and the mixture stirred at room temperature overnight. After 24 hours, the reaction mixture was filtered through celite using 40 mL ethyl acetate to wash/elute and concentrated *in vacuo*. The crude residue was then purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 94 mg (53% yield over 2 steps) of Compound 4.5 (Scheme 4.2) as a yellow oil. \( R_f = 0.36 \) (40% EtOAc/hexanes); IR (neat, cm\(^{-1}\)) 3322, 3057, 3001, 2938, 2828, 2253, 1743, 1662, 1603, 1476; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 7.25 - 7.44 (2H, m), 7.00 - 7.21 (1H, m), 6.84 (1H, d, \( J=6.0 \) Hz), 6.28 - 6.58 (1H, m), 3.26 - 3.65 (2H, m), 3.18 (3H, s), 2.99 (3H, s), 1.40 - 1.55 (27H, m); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) ppm 171.3, 151.0, 148.86, 148.79, 143.1, 130.4, 128.0, 124.8, 123.1, 108.6, 84.7, 84.51, 84.46, 80.3, 74.3, 67.5, 52.9, 28.1, 27.9, 27.8, 26.3; HRMS (m/z): [M + \(\text{NH}_4\)]\(^+\) for C\(_{27}\)H\(_{41}\)N\(_4\)O\(_8\), calcd, 549.29244; found, 549.29098.
2.28 - 2.48 (1H, m), 2.07 - 2.26 (1H, m), 1.28 - 1.52 (18H, m); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 176.1, 155.0, 154.6, 144.2, 130.1, 128.0, 124.2, 123.2, 108.5, 81.7, 80.8, 77.2, 52.5, 43.4, 34.3, 28.2, 28.1, 26.1; HRMS (m/z): \([M + H]^+\) for C\(_{22}\)H\(_{34}\)N\(_3\)O\(_6\), calcd, 436.24476; found, 436.24411.

**Synthesis of 3-(2-(3,5-dimethyl-1H-pyrazol-1-yl)ethyl)-3-methoxy-1-methylindolin-2-one (Compound 4.7, Scheme 4.3):**

Compound 4.5 (45 mg, 0.103 mmol, 1.0 eq.) was dissolved in MeOH (1 mL) in a \(\mu\)W vial and 2,4-pentanedione added (15.5 mg, 0.016 mL, 0.154 mmol, 1.5 eq.) followed by addition of 4N HCl in dioxane (0.5 mL). The reaction mixture was stirred at room temperature for 30 minutes then placed in a 80 °C oil bath sealed for 30 minutes. The reaction was cooled to room temperature and volatiles removed under an air stream. The crude residue was then partitioned between CH\(_2\)Cl\(_2\) (40 mL) and sat’d NaHCO\(_3\)aq. (10 mL) and the phases separated. The organic phase was dried (MgSO\(_4\)), filtered and concentrated \(\textit{in vacuo}\) and the crude residue purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 16.2 mg (52% yield) of 3-(2-(3,5-dimethyl-1H-pyrazol-1-yl)ethyl)-3-methoxy-1-methylindolin-2-one (Compound 4.7, Scheme 4.3) as a yellow oil. \(R_f = 0.09\) (60% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3091, 2981, 2930, 2827, 1720, 1612, 1553, 1471, 1372, 1347, 1121, 1094, 754; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.34 (1H, tt, \(J=7.5, 1.0\) Hz), 7.28 (1H, d, \(J=7.0\) Hz), 7.10 (1H, t, \(J=7.5\) Hz), 6.84 (1H, d, \(J=8.0\) Hz), 5.71 (1H, s), 4.10 - 4.30 (2H, m), 3.21 (3H, s), 3.03 (3H, s), 2.40 (1H, ddd, \(J=14.0, 10.5, 6.0\) Hz), 2.27 (1H, ddd, \(J=14.0, 10.0, 5.5\) Hz), 2.20 (3H, s), 2.15 (3H, s); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 175.4, 147.2, 143.7, 138.8, 130.0, 126.7, 124.3, 123.1, 108.4, 104.8, 81.0, 53.0, 42.8, 37.8, 26.1, 13.4, 10.9; HRMS (m/z): \([M + H]^+\) for C\(_{17}\)H\(_{22}\)N\(_3\)O\(_2\), calcd, 300.17120; found, 300.17107.
Synthesis of 3-(2-(4-chloro-3,5-dimethyl-1H-pyrazol-1-yl)ethyl)-3-methoxy-1-methylindolin-2-one (Compound 4.8, Scheme 4.3):

Identical procedure used for the preparation of compound 4.7 using compound 4.5 (39 mg, 0.0905 mmol, 1.0 eq.) and 3-chloro-2,4-pentanedione (17 mg, 0.014 mL, 0.127 mmol, 1.4 eq.) providing 9.2 mg (30% yield) of Compound 4.8 (Scheme 4.3) as a yellow wax. Rf = 0.17 (60% EtOAc/hexanes); IR (CH2Cl2, cm\(^{-1}\)) 3080, 2931, 2828, 1722, 1612, 1471, 1373, 1348, 1124, 1092, 753; \(^1\)H NMR (400 MHz, CDCl3) \(\delta\) ppm 7.35 (1H, td, \(J=7.5, 1.5\) Hz), 7.26 - 7.29 (1H, m), 7.10 (1H, td, \(J=7.5, 1.0\) Hz), 6.84 (1H, d, \(J=8.0\) Hz), 4.11 - 4.31 (2H, m), 3.21 (3H, s), 3.02 (3H, s), 2.39 (1H, ddd, \(J=14.0, 10.0, 6.0\) Hz), 2.24 (1H, ddd, \(J=14.0, 10.0, 6.0\) Hz), 2.18 (3H, s), 2.13 (3H, s); \(^1\)C NMR (101 MHz, CDCl3) \(\delta\) ppm 175.3, 144.2, 143.7, 135.1, 130.1, 126.6, 124.2 (2C), 123.1, 108.5, 80.8, 53.0, 43.9, 37.7, 26.2, 11.2, 9.2; HRMS (m/z): [M + H]\(^+\) for C\(_{17}\)H\(_{21}\)ClN\(_3\)O\(_2\), calcd, 334.13223; found, 334.13271.

Synthesis of di-tert-butyl-iminodicarboxylate (Compound 4.11, Scheme 4.4):

Di-tert-butyl-iminodicarboxylate is commercially available but can also be prepared according to the following adaptation of a literature protocol:\(^{36}\) NH\(_4\)Cl (1.07 g, 20.0 mmol, 1.0 eq.) was added to a 0 °C solution of Boc\(_2\)O (18.70 g, 85.78 mmol, 4.29 eq.) in 20 mL MeCN and a solution of DMAP (4.90 g, 40.0 mmol, 2.0 eq.) in 65 mL MeCN was added dropwise by addition funnel over 30 minutes under N\(_2\) and the mixture was allowed to stir overnight warming to room temperature. After 18 hours, the reaction mixture was concentrated in vacuo (rotovap) and the resulting residue was partitioned between Et\(_2\)O (150 mL) and 5% aqueous citric acid solution (50 mL) and separated. The organic extract was washed again with 5% aqueous citric acid (50 mL) then with sat’d NaHCO\(_3\) (aq) (2 x 50 mL) followed by sat’d NaCl (aq) (25 mL), dried (MgSO\(_4\)), filtered and concentrated in vacuo (rotovap) to provide 4.98 g (79% yield) of N,N,N-tri-tert-butyl iminotricarboxylate as a waxy solid. N,N,N-tri-tert-butyl iminocarboxylate prepared above (4.90 g, 15.46 mmol, 1.0 eq.) was dissolved in 20 mL MeOH and hydrazine-monohydrate (3.09 g, 3.0 mL, 61.8 mmol, 4.0 eq.) was added under N\(_2\) at room
temperature. The reaction mixture was stirred for 4 hours at room temperature then
diluted with Et₂O (100 mL) and washed with 10% HCl(aq) (2 x 25 mL) followed by sat’d
NaHCO₃(aq) (2 x 25 mL), dried (MgSO₄), filtered and concentrated in vacuo (rotovap) to
provide 3.05 g (91% yield) of Compoun 4.11 (Scheme 4.4) as a white solid.

**Synthesis of di-tert-butyl ethynylimidodicarbonate using terminal-alkynyliodonium triflate 4.9 (Compound 4.12, Scheme 4.4):**

A suspension of PhI(OAc)₂ (5.96 g, 18.5 mmol, 1.0 eq.) in 10 mL CH₂Cl₂
at 0 ºC was treated with Tf₂O (9.25 mL of a 1.0 M sol’n in CH₂Cl₂, 9.25
mmol, 0.5 eq.) under N₂. This mixture was stirred for 30 minutes in the ice bath then
tributyl(ethynyl)stannane (5.80 g, 18.5 mmol, 1.0 eq.) was added by syringe and stirred
for 90 minutes in the cooling bath then volatiles were removed on the rotovap followed
by brief vacuum line drying (5 minutes). The residue thus obtained was slurried in Et₂O
(5 mL) and the solid filtered off using Et₂O (25 mL) to wash yielding the terminal
alkynyl-iodonium salt 4.9 as a white solid (6.19 g, 88%).

Di-tert-butyl-iminodicarboxylate 4.11 (868 mg, 4.0 mmol, 1.0 eq.) in N₂ flushed flask
was dissolved in toluene (118 mL) and cooled to 0 ºC and KHMDS (8.40 mL of a 0.5 M
sol’n in toluene, 4.20 mmol, 1.05 eq.) was added. After stirring for 30 minutes, freshly
prepared terminal alkynyl-iodonium salt 4.9 (2.72 g, 7.20 mmol, 1.8 eq.) was added in
one portion and the mixture was removed from the cooling bath and after warming to
room temperature (20 minutes) the flask was placed in a 45 ºC oil bath with a reflux
condenser. After 16 hours, the reaction mixture was cooled to room temperature and
filtered through a short plug of celite using 75 mL of toluene to wash and the filtrate was
concentrated in vacuo (rotovap). The resulting crude residue was purified through silica
gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing
525 mg (55%) of Compound 4.12 (Scheme 4.4) as a yellow oil. Rᵣ= 0.45 (20%
EtOAc/hexanes); IR (neat, cm⁻¹) 3281, 2982, 2937, 2156, 1805, 1766, 1479, 1456, 1396,
1371, 1348, 1309, 1244, 1138, 846; ¹H NMR (300 MHz, CDCl₃) δ ppm 3.00 (1H, s),
1.55 (18H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 149.6, 85.0, 71.6, 62.6, 27.7; HRMS ($m/z$): [M + NH$_4$]$^+$ for C$_{12}$H$_{23}$N$_2$O$_4$, calcd, 259.16578; found, 259.16546.

**Preparation of di-tert-butyl ethynylimidodicarbonate using TMS-alkynylphenyliodonium triflate 4.10 (Compound 4.12, Scheme 4.4):**

TMS-alkynyl-phenyliodonium triflate was prepared following a literature protocol,$^{37}$ the following is representative: A suspension of PhI(OAc)$_2$ (12.9 g, 40.0 mmol, 1.0 eq.) in 20 mL CH$_2$Cl$_2$ at 0 ºC was treated with Tf$_2$O (20.0 mL of a 1.0 M sol’n in CH$_2$Cl$_2$, 20.0 mmol, 0.5 eq.) under N$_2$. This mixture was stirred for 30 minutes in the ice bath then bis-trimethylsilylacetylene (6.8 g, 9.08 mL, 40.0 mmol, 1.0 eq.) was added by syringe and stirred for 1 hour in the cooling bath then volatiles were removed on the rotovap followed by brief vacuum line drying (5 minutes). The residue thus obtained was slurried in Et$_2$O (20 mL) and the solids filtered off using Et$_2$O (25 mL) to wash yielding the alkynyl-iodonium salt 4.10 as a white solid (14.8 g, 82%).

Di-tert-butyl-iminodicarboxylate 4.11 (2.65 g, 12.21 mmol, 1.0 eq.) in N$_2$ flushed 1-L flask was dissolved in toluene (400 mL) and cooled to 0 ºC and KHMDS (25.6 mL of a 0.5 M sol’n in toluene, 12.82 mmol, 1.05 eq.) was added. After stirring for 30 minutes, TMS-alkynylphenyl-iodonium salt 4.10 (13.74 g, 30.5 mmol, 2.5 eq.) was added in two equal portions over 30 minutes and the mixture was removed from the cooling bath and after warming to room temperature (20 minutes) the flask was placed in a 65 ºC oil bath with a reflux condenser. After 15 hours, the reaction mixture was cooled to room temperature and filtered through a short plug of celite and the filtrate was concentrated *in vacuo* (rotovap). The resulting crude residue was dissolved in THF (10 mL) and cooled to 0 ºC and treated with tetra-$n$-butyl-ammonium fluoride (TBAF, 24.4 mL of a 1M sol’n in THF, 24.4 mmol, ~2eq.) and stirred 15 minutes in the cooling bath then stirred 1 hr at room temperature. The reaction mixture was then diluted with water (100 mL) and extracted with Et$_2$O (2 x 200 mL). The organic extracts were combined, washed with water (3 x 50 mL) then sat’d NaClaq. (25 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo*. The crude residue was then purified through silica gel using ethyl acetate in
hexanes to elute (gradient elution 0-100 % EtOAc) providing 1.52 g (51%) of Compound 4.12 (Scheme 4.4) as a yellow oil.

**Synthesis of di-tert-butyl-N-(2,2-dibromovinyl)-imidocarbonate (Compound 4.14, Scheme 4.5):**

![Chemical structure]

DMAP (244 mg, 2.0 mmol, 0.1 eq.) was dissolved in MeCN (5 mL) and formamide (901 mg, 0.79 mL, 20 mmol, 1.0 eq.) was added followed by addition of Boc$_2$O (9.17 g, 42 mmol, 2.1 eq.) as a solution in MeCN (10 mL). The reaction mixture was stirred at room temperature for 4 hrs then MeCN removed on the rotovap and the crude mixture diluted with ethyl acetate (75 mL) and washed with sat’d NaHCO$_3$(aq) (2 x 25 mL), dried (MgSO$_4$), filtered and concentrated in vacuo to give 4.34 g (88%) of di-Boc-formamide intermediate 4.13 as a slightly yellow oil.

PPh$_3$ (18.6 g, 70.8 mmol, 4.0 eq.) was suspended in CH$_2$Cl$_2$ (30 mL) and cooled to 0 °C before addition of CBr$_4$ (11.7 g, 35.4 mmol, 2.0 eq.). After stirring at 0 °C for 10 mins a solution of formamide 4.13 (4.34 g, 17.7 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (10 mL) was added and cooling bath removed and the mixture stirred at room temperature overnight. After 15 hrs, the reaction mixture was filtered through a 1” tall x 3” wide silica plug topped with celite using CH$_2$Cl$_2$ (200 mL) to wash/elute and the filtrate concentrated in vacuo. The crude residue was then purified by flash chromatography through silica gel using 20% ethyl acetate in hexanes to elute to provide 3.19 g (40% over 2 steps) of Compound 4.14 (Scheme 4.5) as a clear oil. R$_f$ = 0.42 (20% EtOAc/hexanes); IR (neat, cm$^{-1}$) 3433, 3308, 3055, 2980, 2935, 1805, 1716, 1651, 1471, 1035; $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 6.85 (1H, s) 1.51 (18H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 149.2, 130.6, 94.9, 83.7, 27.9; HRMS (m/z): [M + NH$_4$]$^+$ for C$_{12}$H$_{23}$Br$_2$N$_2$O$_4$, calcd, 417.00246; found, 417.00413.
Synthesis of (Z)-di-tert-butyl-N-(2-bromobuta-1,3-dien-1-yl)-imidocarbonate (Compound 4.15, Scheme 4.6):

A mixture of di-bromo-enamide compound 4.14 (1.99 g, 5.0 mmol, 1.0 eq.), vinyl-BF$_3$K (736 mg, 5.5 mmol, 1.1 eq.), Pd(OAc)$_2$ (56 mg, 0.25 mmol, 0.05 eq.), PPh$_3$ (131 mg, 0.5 mmol, 0.1 eq.) and Cs$_2$CO$_3$ (4.89 g, 15 mmol, 3.0 eq.) were combined in THF (20 mL) and H$_2$O (2 mL) in a flask fitted with a reflux condenser. The flask was purged with N$_2$ for 5 mins then placed in a 45 °C oil bath overnight. After 18 hrs, the reaction mixture was partitioned between ethyl acetate (100 mL) and H$_2$O (50 mL) and the phases separated. The organic extract was washed with sat’d NaCl(aq) (10 mL), dried (MgSO$_4$), filtered and concentrated in vacuo. The crude material was then purified by flash chromatography through silica gel using ethyl acetate in hexanes (gradient elution 0-100% EtOAc) to elute to provide 984 mg (56%) of Compound 4.15 (Scheme 4.6) as a clear oil. R$_f$ = 0.54 (20% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 2981, 2935, 1804, 1756, 1722, 1636, 1480, 1458, 1393, 1370, 1286, 1259, 1155, 1109, 850; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 6.60 (1H, s), 6.41 (1H, dd, $J$=16.0, 10.5 Hz), 5.68 (1H, d, $J$=16.0 Hz), 5.32 (1H, d, $J$=10.5 Hz), 1.48 - 1.54 (18H, m); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 150.1, 148.9, 132.5, 127.7, 124.9, 119.9, 83.9, 83.3, 27.9, 27.7; HRMS (m/z): [M + Na]$^+$ for C$_{14}$H$_{22}$BrNO$_4$Na, calcd, 370.1000; found, 370.1000.

Synthesis of tert-butyl ((3aS,4S,7aS)-5-bromo-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isooindol-4-yl)carbamate (Compound 4.17, Scheme 4.6):

1-amino-diene 4.15 (186 mg, 0.454 mmol, 1.0 eq.) was dissolved in MeCN (5 mL) and Mg(ClO$_4$)$_2$ (10.0 mg, 0.0454 mmol, 0.1 eq.) was added and the flask was placed in a 55 °C oil bath with a reflux condenser. After 1 hr, TLC indicated complete conversion and volatiles removed on the rotovap. The crude residue was re-dissolved in ethyl acetate (30 mL) and filtered through a 1 cm tall x 1 cm wide basic Al$_2$O$_3$ plug using ethyl acetate (3 x 10 mL) to wash/elute and the filtrate concentrated in vacuo to provide 88 mg (78%) of
>90% pure (1H NMR) mono-Boc intermediate 4.16 as a clear oil (not stable to storage or characterization, used within 5 hrs of preparation).

N-phenyl maleimide (10.0 mg, 0.0564 mmol, 1.0 eq.) and freshly prepared Boc-dibromo-enamide 4.16 (14.0 mg, 0.0564 mmol, 1.0 eq.) were combined in toluene (0.5 mL) and the flask was sealed and placed in a 80 °C oil bath for 2 hrs. Volatiles were then removed under a stream of air and the crude product shows no 4.16 starting material and a single cycloadduct isomer by 1H NMR (maleimide starting material is still present suggesting decomposition of 4.16). The crude material was purified by flash chromatography through silica gel using ethyl acetate in hexanes (gradient elution 0-100% EtOAc) to elute to provide 12.0 mg (50%) of Compound 4.17 (Scheme 4.6) as a colourless waxy gum. Rf = 0.44 (40% EtOAc/hexanes); IR (CH2Cl2, cm−1); 1H NMR (400 MHz, CDCl3) δ ppm 7.44 - 7.52 (2H, m), 7.37 - 7.43 (1H, m), 7.17 - 7.23 (2H, m), 6.32 - 6.39 (2H, m), 4.63 - 4.70 (1H, m), 3.53 (1H, dd, J=9.0, 5.5 Hz), 3.37 (1H, ddd, J=9.0, 7.5, 1.5 Hz), 2.86 (1H, ddd, J=15.5, 8.0, 1.5 Hz), 2.30 - 2.40 (1H, m), 1.49 (9H, s); 13C NMR (101 MHz, CDCl3) δ ppm 177.6, 176.8, 155.3, 131.3, 129.2, 129.0, 127.5, 126.3, 126.0, 80.3, 49.8, 43.9, 39.4, 28.3, 26.9; HRMS (m/z): [M + Na]+ for C19H21BrN2O4Na, calcd, 443.0577; found, 443.0573.

Synthesis of di-tert-butyl-((3-methoxy-1-methyl-2-oxoindolin-3-yl)ethynyl)-imidocarbonate (Compound 4.18, Scheme 4.7)

A N2 purged flask containing di-tert-butyl ethynylimidodicarbonate (Compound 4.12, 96 mg, 0.40 mmol, 2.0 eq.) and HMPA (72 mg, 0.07 mL, 0.40 mmol, 2.0 eq.) in toluene (1.0 mL) was treated with Et2Zn (0.40 mL of a 1 M sol’n in hexanes, 0.40 mmol, 2.0 eq.) at room temperature and after 2 hours N-Me-Isatin (32 mg, 0.20 mmol, 1.0 eq.) in toluene (1.0 mL) was added and the reaction mixture was stirred at room temperature overnight. After 14 hours dimethyl sulfate (50 mg, 0.038 mL, 0.40 mmol, 2.0 eq.) was added and stirred at room temperature for 3 hours then added sat’d NH4Cl(aq) (5 mL) and H2O (5 mL) and organics extracted with ethyl acetate (50 mL). Organic extract was washed with
1M NaOH (3 x 10 mL), dried (MgSO₄), filtered and concentrated in vacuo (rotovap). The crude residue was purified through silica gel (pre-treated with 1% Et₃N in hexanes) using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) providing 45 mg (54%) of Compound 4.18 (Scheme 4.7) as a yellow oil. Rf = 0.48 (40% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 2982, 2938, 2829, 2268, 1809, 1770, 1728, 1614, 1471, 1371, 1238, 1136, 1105, 1018, 845; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.41 - 7.46 (1H, m), 7.34 (1H, td, J=7.8, 1.2 Hz), 7.05 - 7.11 (1H, m), 6.82 (1H, d, J=7.8 Hz), 3.64 (3H, s), 3.19 (3H, s), 1.49 (18H, s); ¹³C NMR (126 MHz, CDCl₃) δ ppm 171.3, 148.8, 143.1, 130.4, 127.8, 124.7, 123.1, 108.6, 85.0, 76.9, 74.2, 69.5, 53.2, 27.7, 26.2; HRMS (m/z): [M + Na]⁺ for C₂₂H₂₈N₂O₆Na, calcd, 439.1839; found, 439.1846.

**Synthesis of tert-butyl (2-(3-methoxy-1-methyl-2-oxoindolin-3-yl)ethyl)carbamate (Compound 4.19, Scheme 4.7):**

To di-tert-butyl ((3-methoxy-1-methyl-2-oxoindolin-3-yl)ethynyl)-imidocarbonate (compound 4.18, 18 mg, 0.043 mmol, 1.0 eq.) dissolved in EtOAc (5 mL) was added Pd/C (9.0 mg of 10% w/w dry) and the flask was capped with a rubber septa and purged with N₂ then purged with a balloon of H₂ (5 min) and stirred at room temperature under a balloon of H₂ for 12 hours. The reaction flask was purged with N₂ and the reaction mixture filtered through celite using EtOAc (40 mL) to wash and the filtrate concentrated in vacuo. The resulting crude residue (18 mg) was dissolved in MeCN (3 mL) and Mg(ClO₄)_2 (2.1 mg, 0.0086 mmol, 0.2 eq.) was added and the flask was placed in a 55 °C oil bath with a reflux condenser under N₂ for 2.5 hours. The reaction mixture was cooled to room temperature and volatiles removed in vacuo (rotovap) and the crude residue was purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 10.8 mg (78%) of Compound 4.19 (Scheme 4.7) as a gum. Rf = 0.31 (40% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3364, 2976, 2933, 2828, 1713, 1614, 1500, 1472, 1367, 1348, 1250, 1173; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.30 - 7.39 (2H, m), 7.10 - 7.15 (1H, m), 6.85 (1H, d, J=7.8 Hz), 4.92 (1H, br. s.), 3.23 - 3.33 (2H, m), 3.21 (3H, s), 3.01 (3H, s), 2.08 (2H, t, J=6.6 Hz), 1.41 (9H, s); ¹³C NMR (101 MHz, CDCl₃) δ ppm 175.8, 155.8, 143.7,
Synthesis of di-tert-butyl (3-hydroxy-1-benzyl-2-oxoindolin-3-yl)ethynyl)imidocarbonate (Compound 4.20, Scheme 4.8):

A N$_2$ purged flask containing di-tert-butyl ethynylimidodicarbonate (Compound 4.12, 96 mg, 0.40 mmol, 2.0 eq.) and HMPA (72 mg, 0.07 mL, 0.40 mmol, 2.0 eq.) in toluene (1.0 mL) was treated with Et$_2$Zn (0.40 mL of a 1 M sol’n in hexanes, 0.40 mmol, 2.0 eq.) at room temperature and after 2 hours N-Bn-Isatin (47 mg, 0.20 mmol, 1.0 eq.) in toluene (1.0 mL) was added and the reaction mixture was stirred at room temperature overnight. After 16 hours sat’d NH$_4$Cl(aq) (5 mL) and H$_2$O (5 mL) was added and organics extracted with ethyl acetate (50 mL), dried (MgSO$_4$), filtered and concentrated in vacuo (rotovap). The crude residue was purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 59 mg (61%) of Compound 4.20 (Scheme 4.8) as a yellow oil. R$_f$ = 0.37 (40% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3379, 3063, 2982, 2933, 2268, 1809, 1778, 1738, 1614, 1489, 1468, 1373, 1267, 1240, 1170, 1138, 1109, 982; $^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.51 (1H, dd, $J$=7.6, 1.0 Hz), 7.27 - 7.36 (5H, m), 7.22 (1H, td, $J$=7.8, 1.2 Hz), 7.03 - 7.11 (1H, m), 6.71 (1H, d, $J$=7.8 Hz), 4.80 - 4.98 (2H, m), 3.60 (1H, s), 1.49 (18H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 173.7, 148.8, 142.0, 135.1, 130.3, 128.84, 128.80, 127.8, 127.1, 124.6, 123.5, 109.8, 85.1, 75.6, 71.8, 69.3, 44.0, 27.7; HRMS (m/z): [M + NH$_4$]$^+$ for C$_{27}$H$_{34}$N$_3$O$_6$, calcd, 496.24476; found, 496.24531.

Synthesis of tert-butyl (2-(1-benzyl-3-hydroxy-2-oxoindolin-3-yl)ethyl)carbamate (Compound 4.21, Scheme 4.8):

To di-tert-butyl ((3-hydroxy-1-benzyl-2-oxoindolin-3-yl)ethynyl)imidocarbonate (Compound 4.20, 35 mg, 0.073 mmol, 1.0 eq.) dissolved in EtOAc (5 mL) was added Pd/C (16 mg of 10% w/w dry) and the flask was capped with a rubber septa and purged with N$_2$ then purged with a
balloon of H\(_2\) (5 min) and stirred at room temperature under a balloon of H\(_2\) for 32 hours. The reaction flask was purged with N\(_2\) and the reaction mixture filtered through celite using EtOAc (40 mL) to wash and the filtrate concentrated in vacuo. The resulting crude residue (29 mg) was dissolved in 3 mL MeCN and Mg(ClO\(_4\))\(_2\) (1.3 mg, 0.006 mmol, 0.1 eq.) was added and the flask was placed in a 55 °C oil bath with a reflux condenser under N\(_2\) for 3 hours then a further portion of Mg(ClO\(_4\))\(_2\) (1.3 mg, 0.006 mmol, 0.1 eq.) was added and continued heating for 2 hours. The reaction mixture was then cooled to room temperature and volatiles removed in vacuo (rotovap) and the crude residue was purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 17.2 mg (62%) of Compound 4.21 (Scheme 4.8) as a white wax. R\(_f\)= 0.27 (40% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3366, 3061, 2976, 2930, 1720, 1614, 1489, 1468, 1367, 1251, 1175; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.41 (1H, dd, \(J=7.4, 0.8\) Hz), 7.26 - 7.35 (5H, m), 7.21 (1H, td, \(J=7.8, 1.2\) Hz), 7.02 - 7.11 (1H, m), 6.73 (1H, d, \(J=7.8\) Hz), 4.74 - 5.01 (3H, m), 3.26 - 3.38 (2H, m), 3.22 (1H, br. s.), 2.08 - 2.26 (2H, m), 1.43 (9H, s); \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) ppm 177.8, 156.0, 142.2, 135.4, 129.8, 128.9, 127.8, 127.3, 127.2, 124.1, 123.3, 109.7, 79.4, 75.4, 43.8, 38.3, 35.6, 28.4; HRMS (m/z): [M + Na]\(^{+}\) for C\(_{22}\)H\(_{26}\)N\(_2\)O\(_4\)Na, calcd, 405.1784; found, 405.1785.

**Synthesis of 8-benzyl-1-methyl-1,2,3,3a,8a-hexahydropyrrolo[2,3-b]indol-3a-ol (Compound 4.22, Scheme 4.8):**

Tert-butyl (2-(1-benzyl-3-hydroxy-2-oxoindolin-3-yl)ethyl)carbamate (compound 4.21, 15.5 mg, 0.0406 mmol, 1.0 eq.) was charged to a flask and N\(_2\) purged for 5 minutes then dissolved in THF (3 mL) and cooled to 0 °C in an ice/water bath. LiAlH\(_4\) was then added under N\(_2\) (0.14 mL of a 2.0 M sol’n in THF, 0.28 mmol, 7.0 eq.) and stirred 15 minutes then placed in a 65 °C oil bath with a reflux condenser under N\(_2\) for 14 hours. The mixture was then cooled to room temperature and quenched by addition of MeOH (1.0 mL) with stirring for 30 minutes followed by addition of H\(_2\)O (1.0 mL) and stirring for 30 minutes. The resulting slurry was diluted with ethyl acetate (30 mL) and filtered through celite using ethyl acetate (50 mL) to wash/elute and concentrated in vacuo (rotovap). The resulting crude residue was
purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) followed by elution with 5% MeOH in ethyl acetate to provide 7.1 mg (62%) of Compound 4.22 (Scheme 4.8) as a yellow oil. $R_f= 0.18$ (2% MeOH/EtOAc); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3354 (br), 2930, 2870, 1610, 1495, 1159, 1053; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ ppm 7.27 - 7.36 (6H, m), 7.12 (1H, td, $J=7.7, 1.2$ Hz), 6.76 (1H, td, $J=7.5, 0.5$ Hz), 6.40 (1H, d, $J=8.1$ Hz), 4.59 (1H, s), 4.55 (1H, s), 4.40 - 4.47 (2H, m), 2.83 - 2.90 (1H, m), 2.76 - 2.82 (1H, m), 2.47 (3H, s), 2.32 - 2.40 (1H, m), 2.22 - 2.29 (1H, m); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ ppm 151.4, 138.6, 132.2, 129.9, 128.6, 127.0, 126.9, 123.2, 118.4, 108.3, 96.8, 88.5, 53.4, 53.1, 40.2, 38.8; HRMS (m/z): [M + Na]$^+$ for C$_{22}$H$_{26}$N$_2$O$_4$Na, calcd, 405.1784; found, 405.1785.

Representative procedure for carbonyl addition with ynimide 4.12 (Scheme 4.9):

A N$_2$ purged flask containing di-tert-butyl ethynylimidodicarbonate (Compound 4.12, 48 mg, 0.20 mmol, 2.0 eq.) and HMPA (36 mg, 0.035 mL, 0.20 mmol, 2.0 eq.) in toluene (0.5 mL) was treated with Et$_2$Zn (0.20 mL of a 1 M sol’n in hexanes, 0.20 mmol, 2.0 eq.) at room temperature and after 2 hours (E)-N-benzylidene-4-methylbenzenesulfonamide$^{[2]}$ (26 mg, 0.10 mmol, 1.0 eq.) in toluene (0.5 mL) was added and the reaction mixture was stirred at room temperature overnight. After 14 hours sat’d NH$_4$Cl(aq) (5 mL) and H$_2$O (5 mL) was added and organics extracted with ethyl acetate (50 mL), dried (MgSO$_4$), filtered and concentrated in vacuo (rotovap). The crude residue was purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 32 mg (64%) of Compound 4.23 (Scheme 4.9) as a white solid.

(3-(4-methylphenylsulfonamido)-3-phenylprop-1-yn-1-yl)imidocarbonate

(Compound 4.23, Scheme 4.9):

![Chemical Structure](image-url)  
Isolated yield= 32 mg (64%) as a white solid. m.p. 123-126 ºC; $R_f= 0.51$ (40% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3273, 3064, 3032, 2982, 2933, 2274, 1809, 1740, 1599, 1456, 1371, 1329, 1242, 1138, 1045; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.77 (2H, d, $J=8.5$ Hz), 7.43 -7.51 (2H, m), 7.24 - 7.33 (5H, m), 5.50 (1H, d, $J=8.5$ Hz), 4.89 (1H, d, $J=8.0$ Hz), 2.41 (3H, s), 1.51
(18H, s); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 149.1, 143.4, 137.7, 137.6, 129.4, 128.6, 128.4, 127.35 (2C), 85.0, 75.7, 71.2, 49.6, 27.8, 21.5; HRMS ($m/z$): [M + Na]$^+$ for C$_{26}$H$_{32}$N$_2$O$_6$Na, calcd, 523.1873; found, 523.1887.

**Di-tert-butyl (3-hydroxy-3-phenylprop-1-yn-1-yl)imidocarbonate (Compound 4.24, Scheme 4.9):**

Prepared following the representative procedure using benzaldehyde (11 mg, 0.10 mmol, 1.0 eq.) in 0.5 mL toluene. Isolated yield = 22 mg (63%) as a yellow oil. R$_f$ = 0.49 (40% EtOAc/hexanes); IR (neat, cm$^{-1}$) 3450 (br), 2982, 2935, 2272, 2227, 1805, 1774, 1494, 1456, 1371, 1240, 1138, 844; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.54 - 7.64 (2H, m), 7.29 - 7.43 (3H, m), 5.65 (1H, d, $J$=6.0 Hz), 2.32 (1H, d, $J$=6.5 Hz), 1.53 (18H, s); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 149.5, 140.7, 128.5, 128.4, 126.8, 85.0, 76.1, 74.1, 64.9, 27.8; HRMS ($m/z$): [M + Na]$^+$ for C$_{19}$H$_{25}$NO$_5$Na, calcd, 370.1624; found, 370.1633.

**Di-tert-butyl (3-cyclohexyl-3-hydroxyprop-1-yn-1-yl)imidocarbonate (Compound 4.25, Scheme 4.9):**

Prepared following the representative procedure using cyclohexane carboxaldehyde (11 mg, 0.10 mmol, 1.0 eq.) in 0.5 mL toluene. Isolated yield = 23 mg (65%) as a clear oil. R$_f$ = 0.21 (40% EtOAc/hexanes); IR (neat, cm$^{-1}$) 3470 (br), 2982, 2930, 2852, 2272, 1805, 1767, 1460, 1394, 1371, 1240, 1140, 1034; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 4.33 (1H, dd, $J_1$=5.5 Hz, $J_2$=5.5 Hz), 1.88 (2H, d, $J$=11.5 Hz), 1.74 - 1.81 (2H, m), 1.65 - 1.71 (1H, m), 1.59 - 1.62 (1H, m), 1.46 - 1.56 (18H, m), 1.06 - 1.30 (6H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 149.6, 84.8, 82.0, 74.2, 67.4, 44.2, 28.5, 27.8, 26.3, 25.8; HRMS ($m/z$): [M + Na]$^+$ for C$_{19}$H$_{31}$NO$_5$Na, calcd, 376.2094; found, 376.2108.
Methyl-4-(di-tert-butoxycarbonylamino)-2-hydroxy-2-phenylbut-3-ynoate  
(Compound 4.26, Scheme 4.9):

Prepared following the representative procedure using methyl 2-oxo-2-phenylacetate (16 mg, 0.10 mmol, 1.0 eq.) in 0.5 mL toluene. Isolated yield = 24 mg (60%) as a yellow oil. Rf = 0.17 (20% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3474, 2955, 2276, 1809, 1767, 1734, 1371, 1240, 1138, 844; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.65 - 7.73 (2H, m), 7.32 - 7.39 (3H, m), 4.17 (1H, s), 3.78 (3H, s), 1.54 (18H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 172.4, 148.9, 139.2, 128.7, 128.3, 126.4, 85.0, 75.8, 73.2, 72.8, 54.1, 27.8; HRMS (m/z): [M + NH$_4$]$^+$ for C$_{21}$H$_{31}$N$_2$O$_7$, calcd, 423.21313; found, 423.21340.

Di-tert-butyl ((1-hydroxycyclohexyl)ethynyl)imidocarbonate  (Compound 4.27, Scheme 4.9):

Prepared following the representative procedure using cyclohexanone (10 mg, 0.10 mmol, 1.0 eq.) in 0.5 mL toluene. Isolated yield = 22 mg (65%) as a clear oil. Rf = 0.14 (20% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3447, 2980, 2936, 2858, 2270, 1805, 1770, 1456, 1371, 1244, 1140, 966, 847; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 2.00 - 2.06 (1H, m), 1.89 - 1.97 (2H, m), 1.65 - 1.74 (2H, m), 1.56 - 1.64 (4H, m), 1.53 (18H, s), 1.46 - 1.50 (1H, m), 1.17 - 1.31 (1H, m); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 149.6, 84.5, 73.9, 71.7, 69.1, 39.9, 27.8, 25.2, 23.4; HRMS (m/z): [M + Na]$^+$ for C$_{18}$H$_{29}$NO$_5$Na, calcd, 362.1937; found, 362.1941.

Representative procedure for addition of ynimide 4.12 to pyridinium salts (Scheme 4.10):

Quinoline (25.8 mg, 0.20 mmol, 1.0 eq.) in MeCN (0.5 mL) and EtCO$_2$Cl (24 mg, 0.22 mmol, 1.1 eq.) in MeCN (0.5 mL) were combined and treated with di-tert-butyl ethynylimidodicarbonate (Compound 4.12, 54 mg, 0.24 mmol, 1.2 eq.) in MeCN (0.5 mL) and this mixture was added by pipette to a pre-stirring mixture of CuI (3.8 mg, 0.02 mmol, 0.1 eq.) and (iPr)$_2$NEt (36 mg, 0.28 mmol, 1.4 eq.) in MeCN (1.0 mL) using MeCN (0.5 mL) to complete the transfer and stirred at room temperature for 14 hours.
then volatiles removed under an air stream and the crude residue purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 55 mg (62%) of Compound 4.28 (Scheme 4.10) as a yellow oil.

**Ethyl-2-(di-tert-butyl ethynylimidocarbonate) quinoline-1(2H)-carboxylate**  
(Compound 4.28, Scheme 4.10):

![Chemical Structure](image)

Isolated yield= 55 mg (62%) as a yellow oil. Rf= 0.23 (20% EtOAc/hexanes); IR (CH2Cl2, cm⁻¹) 3057, 2983, 2936, 2258, 1809, 1774, 1705, 1371, 1265, 1138; ¹H NMR (400 MHz, CDCl3) δ ppm 7.66 (1H, d, J=6.5 Hz), 7.19 - 7.26 (1H, m), 7.00 - 7.12 (2H, m), 6.48 - 6.54 (1H, m), 5.98 - 6.09 (2H, m), 4.16 - 4.40 (2H, m, r), 1.39 (18H, s), 1.34 (3H, t, J=7.0 Hz); ¹³C NMR (101 MHz, CDCl3) δ ppm 153.7, 149.3, 134.4, 127.8, 126.6, 126.5, 125.6, 125.1, 124.4, 124.3, 84.5, 72.7, 70.9, 62.5, 44.2, 27.6, 14.5; HRMS (m/z): [M + H]⁺ for C24H31N2O6, calcd, 443.21821; found, 443.21865.

**Ethyl-1-(di-tert-butyl-ethynylimidocarbonate)isoquinoline-2(1H)-carboxylate**  
(Compound 4.29, Scheme 4.10):

![Chemical Structure](image)

Prepared according to the representative procedure using isoquinoline (25.8 mg, 0.20 mmol, 1.0 eq.). Isolated yield= 51 mg (58%) as a yellow oil. Rf= 0.30 (20% EtOAc/hexanes); IR (CH2Cl2, cm⁻¹) 2982, 2935, 2270, 1809, 1770, 1712, 1635, 1456, 1371, 1325, 1242, 1138, 846; ¹H NMR (400 MHz, CDCl3) δ ppm 7.15 - 7.25 (3H, m), 7.07 (1H, d, J=6.5 Hz), 6.79 - 7.01 (1H, m), 6.15 - 6.39 (1H, m), 5.83 - 6.00 (1H, m), 4.21 - 4.38 (2H, m), 1.37 - 1.44 (18H, m), 1.30 - 1.37 (3H, m); ¹³C NMR (126 MHz, CDCl3) δ ppm 152.6, 149.1, 129.9, 129.6, 128.2, 127.2, 126.0, 124.9, 124.3, 108.3, 84.3, 72.8, 72.5, 62.6, 47.2 - 46.6 (1C, r), 27.6, 14.5; HRMS (m/z): [M + H]⁺ for C24H31N2O6, calcd, 443.21821; found, 443.21854.
Representative procedure for epoxide ring-opening with ynimide 4.12 (Scheme 4.11):

A N₂ purged flask containing di-tert-butyl ethynylimidodicarbonate (Compound 4.12, 36 mg, 0.15 mmol, 1.5 eq.) in THF (1 mL) was cooled to -78 °C in a dry ice/acetone bath and LiHMDS (0.15 mL of a 1.0 M sol’n in THF, 0.15 mmol, 1.5 eq.) was added and stirred for 5 minutes then cyclohexene oxide (10 mg, 0.10 mmol, 1.0 eq.) in THF (0.5 mL) was added followed immediately by BF₃·OEt₂ (21 mg, 0.018 mL, 0.15 mmol, 1.5 eq.). The reaction mixture was removed from the dry ice/acetone bath and placed in a 0 °C ice/water bath and stirred for 3 hours then diluted with sat’d NH₄Cl(aq) (5 mL), ethyl acetate (50 mL) and H₂O (5 mL) and separated. The organic extract was dried (MgSO₄), filtered, concentrated in vacuo (rotovap) and the crude residue obtained was purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 27 mg (79%) of Compound 4.30 (Scheme 4.11) as a white solid.

Di-tert-butyl 2-(anti-(2-hydroxycyclohexyl) ethynyl)imidocarbonate (Compound 4.30, Scheme 4.11):

Isolated yield= 27 mg (79%) as a white solid. m.p. 68-72 °C; Rf= 0.17 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3493(br), 2980, 2933, 2860, 2274, 2232, 1809, 1737, 1456, 1371, 1240, 1114, 1016, 1037, 848; ¹H NMR (400 MHz, CDCl₃) δ ppm 3.46 (1H, td, J=9.5, 4.0 Hz), 2.55 (1H, s), 2.37 (1H, ddd, J=11.5, 9.5, 3.5 Hz), 1.92 - 2.09 (2H, m), 1.73 - 1.83 (1H, m), 1.65 - 1.71 (1H, m), 1.53 (18H, s), 1.21 - 1.44 (4H, m); ¹³C NMR (100 MHz, CDCl₃) δ ppm 149.8, 84.7, 75.0, 73.9, 71.8, 39.0, 32.7, 30.5, 27.8, 24.8, 24.2; HRMS (m/z): [M + NH₄]⁺ for C₁₈H₃₃N₂O₅, calcd, 357.23895; found, 357.23933.
Di-tert-butyl (5-(benzyloxy)-4-hydroxypent-1-yn-1-yl)imidocarbonate (Compound 4.31, Scheme 4.11):

Prepared according to the representative procedure using 2-((benzyloxy)methyl)oxirane (16 mg, 0.10 mmol, 1.0 eq.) and stirring for 90 minutes at 0 °C. Isolated yield= 33 mg (82%) of a 94:6 ratio of regioisomers in favour of the one shown as a clear oil. Rf= 0.38 (40% EtOAc/hexanes); IR (CH2Cl2, cm⁻¹) 3470(br), 2980, 2934, 2868, 2280, 1805, 1766, 1738, 1456, 1371, 1240, 1140, 848; ¹H NMR (400 MHz, CDCl3) δ ppm 7.27 - 7.40 (5H, m), 4.58 (2H, s), 3.90 - 4.06 (1H, m), 3.63 (1H, dd, J=9.5, 4.5 Hz), 3.53 (1H, dd, J=9.5, 6.5 Hz), 2.60 (2H, dd, J=6.5, 2.0 Hz), 2.50 (1H, d, J=4.5 Hz), 1.52 (18H, s); ¹³C NMR (101 MHz, CDCl3) δ ppm 150.0, 137.9, 128.4, 127.8, 127.7, 84.6, 73.4, 73.0, 71.7, 69.6, 69.0, 27.8, 23.8; HRMS (m/z): [M + NH4]⁺ for C22H35N2O6, calcd, 423.24951; found, 423.25102.

Di-tert-butyl (3-(1-hydroxycyclohexyl)prop-1-yn-1-yl)imidocarbonate (Compound 4.32, Scheme 4.11):

Prepared according to the representative procedure using 1-oxaspiro[2.5]octane (11 mg, 0.10 mmol, 1.0 eq.) and stirring for 90 minutes at 0 °C. Isolated yield= 24 mg (69%) as a clear oil. Rf= 0.25 (20% EtOAc/hexanes); IR (CH2Cl2, cm⁻¹) 3516(br), 2982, 2933, 2860, 2276, 1805, 1766, 1456, 1371, 1240, 1140, 982, 848; ¹H NMR (400 MHz, CDCl3) δ ppm 2.49 (2H, s), 1.96 (1H, s), 1.55 - 1.73 (6H, m), 1.53 (18H, s), 1.42 - 1.51 (4H, m); ¹³C NMR (101 MHz, CDCl3) δ ppm 150.0, 84.6, 72.4, 70.7, 70.0, 36.9, 32.9, 27.8, 25.6, 22.2; HRMS (m/z): [M + H]⁺ for C19H32NO5, calcd, 354.22805; found, 354.22770.

Representative procedure for 1,4-addition of ynimide 4.12 to cyclic Michael acceptors (Scheme 4.12):

A N₂ purged flask containing di-tert-butyl ethynylimidodicarbonate (Compound 4.12, 36 mg, 0.15 mmol, 1.5 eq.) in Et₂O (0.5 mL) was cooled to -78 °C in a dry ice/acetone bath and LiHMDS (0.15 mL of a 1.0 M sol’n in THF, 0.15 mmol, 1.5 eq.) was added and
stirred for 5 minutes then ZnBr$_2$ (34 mg, 0.15 mmol, 1.5 eq.) in THF (0.5 mL) was added and the reaction mixture transferred to a -44 ºC dry ice/MeCN bath. After 20 minutes, cyclopent-2-enone (9.0 mg, 0.1 mmol, 1.0 eq.) in THF (0.5 mL) was added followed immediately by addition of TBSOTf (40 mg, 0.035 mL, 0.15 mmol, 1.5 eq.) and stirred in the dry ice/MeCN bath. After 2 hours, the reaction mixture was treated with sat’d NH$_4$Cl(aq) (5 mL) and warmed to room temperature and diluted with H$_2$O (5 mL) and ethyl acetate (50 mL) and the layers were separated. The organic phase was dried (MgSO$_4$), filtered through a celite plug and concentrated in vacuo (rotovap). The crude silyl-enol ether product thus obtained was dissolved in THF (3 mL) and treated with TBAF (tetrabutylammonium fluoride, 0.20 mL of a 1 M sol’n in THF, 0.2 mmol, 2.0 eq.) at room temperature under N$_2$. After 15 minutes H$_2$O (20 mL) was added and extracted with Et$_2$O (2 x 40 mL). The organic extracts were combined and washed with H$_2$O (4 x 10 mL) then with sat’d NaCl(aq) (10 mL), dried (MgSO$_4$), filtered, concentrated in vacuo (rotovap) and purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 20 mg (62%) of Compound 4.33 (Scheme 4.12) as a clear oil.

Di-tert-butyl 2-((3-oxocyclopentyl)ethynyl)imidocarbonate (Compound 4.33, Scheme 4.12):

Isolated yield= 20 mg (61%) as a clear oil. R$_f$= 0.20 (20% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 2980, 2935, 2276, 1805, 1768, 1743, 1371, 1240, 1138, 848; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 3.23 (1H, quin, $J$=7.0 Hz), 2.36 - 2.57 (2H, m), 2.14 - 2.34 (3H, m), 1.99 - 2.12 (1H, m), 1.52 (18H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 217.1, 149.9, 84.6, 74.9, 70.9, 45.1, 37.2, 30.2, 27.8, 27.4; HRMS (m/z): [M + Na]$^+$ for C$_{17}$H$_{25}$NO$_2$Na, calcd, 346.1624; found, 346.1627.
**Di-tert-butyl 2-((3-oxocyclohexyl)ethynyl)imidocarbonate (Compound 4.34, Scheme 4.12):**

Prepared according to the representative procedure using cyclohexenone (9.6 mg, 0.1 mmol, 1.0 eq.) and stirring 1 hr in dry ice/MeCN bath. Isolated yield = 19.3 mg (57%) as a clear oil. Rf = 0.18 (20% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 2980, 2939, 2272, 1805, 1770, 1716, 1456, 1371, 1242, 1140, 1105, 847; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 3.04 - 3.12 (1H, m), 2.58 (1H, dd, $J$=14.5, 5.0 Hz), 2.44 (1H, dd, $J$=14.5, 8.0 Hz), 2.34 (2H, t, $J$=6.5 Hz), 2.09 - 2.20 (1H, m), 1.98 - 2.06 (1H, m), 1.73 - 1.90 (2H, m), 1.52 (18H, s); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 209.0, 149.8, 84.5, 74.5, 71.8, 46.9, 41.2, 30.8, 29.9, 27.8, 23.8; HRMS (m/z): [M + NH$_4$]$^+$ for C$_{18}$H$_{31}$N$_2$O$_5$, calcd, 355.22330; found, 355.22305.

**Synthesis of di-tert-butyl 2-(3-oxo-3-phenylprop-1-yn-1-yl)imidocarbonate (Compound 4.35, Scheme 4.13):**

A flask charged with Pd(PPh$_3$)$_4$ (8.7 mg, 0.0075 mmol, 0.05 eq.) and CuI (1.4 mg, 0.0075 mmol, 0.05 eq.) was sealed with a rubber septum and purged with N$_2$ for 5 minutes. This was then charged with benzoyl-chloride (21 mg, 0.15 mmol, 1.0 eq.) in THF (0.5 mL), followed by addition of Et$_3$N (21.3 mg, 0.029 mL, 0.21 mmol, 1.4 eq.) then di-tert-butyl ethynylimidodicarbonate (Compound 4.12, 36 mg, 0.15 mmol, 1.0 eq.) in THF (0.5 mL) was added. The reaction mixture was stirred at room temperature under N$_2$ for 2 hours then diluted with ethyl acetate (50 mL) and washed with sat’d NaHCO$_3$(aq) (10 mL). The organic extract was dried (MgSO$_4$), filtered through a celite pad and concentrated in vacuo (rotovap) and the crude residue obtained was purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 32 mg (61%) Compound 4.35 (Scheme 4.13) as a light yellow oil. Rf = 0.37 (20% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3055, 2987, 2227, 1813, 1782, 1643, 1421, 1373, 1265, 1132, 896; $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 8.17 (2H, dd, $J$=8.5, 1.5 Hz), 7.55 - 7.64 (1H, m), 7.42 - 7.53 (2H, m), 1.58 - 1.66 (18H, m);
\[ \text{13C NMR (101 MHz, CDCl}_3 \text{)} \delta \text{ ppm 177.2, 148.3, 136.9, 133.8, 129.4, 128.4, 86.4, 84.0, 77.2, 27.8;} \text{ HRMS (m/z): } [\text{M + H}]^+ \text{ for } \text{C}_{19}\text{H}_{24}\text{NO}_5, \text{ calcd, 346.16545; found, 346.16506.} \]

**Synthesis of di-tert-butyl 2-((3-nitrophenyl)ethynyl)imidocarbonate (Compound 4.36, Scheme 4.13):**

A flask was charged with Pd(PPh\(_3\))\(_4\) (5.7 mg, 0.005 mmol, 0.05 eq.) and CuI (1.0 mg, 0.005 mmol, 0.05 eq.) was sealed with a rubber septum and purged with N\(_2\) for 5 minutes. This was then charged with 1-iodo-3-nitrobenzene (25 mg, 0.10 mmol, 1.0 eq.) in THF (0.5 mL), followed by addition of Et\(_3\)N (14.2 mg, 0.020 mL, 0.14 mmol, 1.4 eq.) then di-tert-butyl ethynylimidodicarbonate (Compound 4.12, 24 mg, 0.10 mmol, 1.0 eq.) in THF (0.5 mL) was added. The reaction mixture was stirred at room temperature under N\(_2\) for 24 hours then diluted with ethyl acetate (50 mL) and washed with sat’d NaHCO\(_3\) (aq) (10 mL). The organic extract was dried (MgSO\(_4\)), filtered through a celite pad and concentrated in vacuo (rotovap) and the crude residue obtained was purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 23 mg (64%) of Compound 4.36 (Scheme 4.13) as a brown solid. m.p. > 220 °C; R\(_f\) = 0.45 (20% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 2980, 2935, 2260, 1813, 1780, 1740, 1533, 1370, 1238, 1134; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \delta ppm 8.22 (1H, dd, \(J_1=2.0 \text{ Hz}, J_2=2.0 \text{ Hz}\)), 8.13 (1H, ddd, \(J=8.5, 2.0, 1.0 \text{ Hz}\)), 7.49 (1H, dd, \(J_1=8.0 \text{ Hz}, J_2=8.0 \text{ Hz}\)), 7.68 (1H, m), 1.59 (18H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \delta ppm 149.1, 136.4, 129.3, 128.5, 125.5, 125.0, 122.4, 85.3, 81.1, 72.7, 27.8; HRMS (m/z): [M + Na\(^+\)] for C\(_{18}\)H\(_{22}\)N\(_2\)O\(_6\)Na, calcd, 385.1370; found, 385.1379.

**Synthesis of di-tert-butyl 2-((3-pyridinyl)ethynyl)imidocarbonate (Compound 4.37, Scheme 4.13):**

A flask was charged with Pd(PPh\(_3\))\(_4\) (5.7 mg, 0.005 mmol, 0.05 eq.) and CuI (1.0 mg, 0.005 mmol, 0.05 eq.) was sealed with a rubber septum and purged with N\(_2\) for 5 minutes. This was then charged with 3-iodo-pyridine (20 mg, 0.10 mmol, 1.0 eq.) in THF (0.5 mL), followed by addition of Et\(_3\)N (14.2 mg, 0.020 mL, 0.14 mmol, 1.4 eq.) then di-tert-butyl ethynylimidodicarbonate (Compound 4.12, 24 mg, 0.10 mmol, 1.0 eq.) in THF (0.5 mL) was added. The reaction mixture was stirred at room temperature under N\(_2\) for 24 hours then diluted with ethyl acetate (50 mL) and washed with sat’d NaHCO\(_3\) (aq) (10 mL). The organic extract was dried (MgSO\(_4\)), filtered through a celite pad and concentrated in vacuo (rotovap) and the crude residue obtained was purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 23 mg (64%) of Compound 4.36 (Scheme 4.13) as a brown solid. m.p. > 220 °C; R\(_f\) = 0.45 (20% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 2980, 2935, 2260, 1813, 1780, 1740, 1533, 1370, 1238, 1134; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \delta ppm 8.22 (1H, dd, \(J_1=2.0 \text{ Hz}, J_2=2.0 \text{ Hz}\)), 8.13 (1H, ddd, \(J=8.5, 2.0, 1.0 \text{ Hz}\)), 7.49 (1H, dd, \(J_1=8.0 \text{ Hz}, J_2=8.0 \text{ Hz}\)), 7.68 (1H, m), 1.59 (18H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \delta ppm 149.1, 136.4, 129.3, 128.5, 125.5, 125.0, 122.4, 85.3, 81.1, 72.7, 27.8; HRMS (m/z): [M + Na\(^+\)] for C\(_{18}\)H\(_{22}\)N\(_2\)O\(_6\)Na, calcd, 385.1370; found, 385.1379.
0.020 mL, 0.14 mmol, 1.4 eq.) then di-tert-butyl ethynylimidodicarbonate (Compound 4.12, 24 mg, 0.10 mmol, 1.0 eq.) in THF (0.5 mL) was added. The reaction mixture was stirred at room temperature under N₂ for 16 hours then diluted with ethyl acetate (50 mL) and washed with sat’d NaHCO₃(aq) (10 mL). The organic extract was dried (MgSO₄), filtered through a celite pad and concentrated in vacuo (rotovap) and the crude residue obtained was purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 21 mg (66%) of Compound 4.37 (Scheme 4.13) as a yellow solid. m.p.= 62-67 ºC; Rᵋ= 0.08 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 2976, 2932, 2264, 1801, 1774, 1564, 1456, 1369, 1238, 1134, 1103, 845; ¹H NMR (400 MHz, CDCl₃) δ ppm 8.38 - 8.82 (2H, m), 7.68 (1H, d, J=8.0 Hz), 7.15 - 7.35 (1H, m), 1.57 (18H, s); ¹³C NMR (126 MHz, CDCl₃) δ ppm 151.5, 149.2, 148.1, 137.6, 132.1, 128.4, 85.1, 81.6, 71.5, 27.8; HRMS (m/z): [M + H]⁺ for C₁₇H₂₃N₂O₄, calcd, 319.16578; found, 319.16668.

**Representative procedure for reduction of internal ynimides to ethyleneamines (Scheme 4.14):**

To di-tert-butyl (3-(4-methylphenylsulfonamido)-3-phenylprop-1-yn-1-yl)imidocarbonate (Compound 4.23, 15 mg, 0.03 mmol, 1.0 eq.) dissolved in EtOAc (3 mL) was added Pd/C (3.0 mg of 10% w/w dry) and the flask was capped with a rubber septa and purged with N₂ then purged with a balloon of H₂ (5 min) and stirred at room temperature under a balloon of H₂ for 18 hours. The reaction flask was purged with N₂ and the reaction mixture was filtered through celite using EtOAc (40 mL) to wash and the filtrate concentrated in vacuo. The resulting crude residue was purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 11.7 mg (78%) of Compound 4.38 (Scheme 4.14) as a white solid.
Di-tert-butyl-(3-(4-methylphenylsulfonamido)-3-phenylpropyl)-imidocarbonate
(Compound 4.38, Scheme 4.14):

\[
\begin{align*}
\text{Ph} & \text{N}^\text{Hts} \text{NH}^\text{Boc} \\
\text{Ph} & \text{N}^\text{H}^\text{Boc}
\end{align*}
\]

Isolated yield= 11.7 mg (78%) as a yellow solid. m.p.= 118-121 °C; R\(_f\)= 0.12 (20% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3273, 2980, 2932, 1778, 1747, 1693, 1599, 1456, 1367, 1161, 1116; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 7.57 (2H, d, \(J=8.5\) Hz), 7.10 - 7.20 (5H, m), 7.03 - 7.09 (2H, m), 5.25 (1H, d, \(J=7.0\) Hz), 4.32 (1H, dt, \(J_1=7.0\) Hz, \(J_2=7.0\) Hz), 3.32 - 3.59 (2H, m), 2.36 (3H, s), 1.91 - 2.12 (2H, m), 1.46 (18H, s); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) ppm 152.4, 143.0, 140.4, 137.7, 129.3, 128.5, 127.4, 127.0, 126.3, 82.6, 56.2, 43.2, 36.2, 28.0, 21.4; HRMS (m/z): [M + NH\(_4\)]\(^+\) for C\(_{26}\)H\(_{40}\)N\(_3\)O\(_6\)S, calcd, 522.26378; found, 522.26464.

Di-tert-butyl (3-hydroxy-3-phenylpropyl)-imidocarbonate (Compound 4.39, Scheme 4.14):

\[
\begin{align*}
\text{Ph} & \text{N(Boc)}_2 \\
\text{OH}
\end{align*}
\]

Prepared according to the representative procedure using di-tert-butyl (3-hydroxy-3-phenylprop-1-yn-1-yl)imidocarbonate (Compound 4.24, 14 mg, 0.04 mmol, 1.0 eq.) and Pd/C (3.0 mg of 10% w/w dry) in EtOAc (3 mL) and stirring under a balloon of H\(_2\) for 16 hours. Isolated yield= 10.0 mg (71%) as a clear oil. R\(_f\)= 0.23 (20% EtOAc/hexanes); IR (neat, cm\(^{-1}\)) 3466(br), 3063, 2980, 2933, 1737, 1674, 1456, 1352, 1140; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 7.29 - 7.44 (5H, m), 4.68 (1H, dt, \(J=9.5, 3.5\) Hz), 3.67 - 3.90 (2H, m), 3.28 (1H, d, \(J=3.5\) Hz), 1.96 - 2.11 (1H, m), 1.81 - 1.95 (1H, m), 1.51 (18H, s); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) ppm 153.2, 144.0, 128.4, 127.3, 125.6, 82.8, 70.8, 43.2, 38.5, 28.0; HRMS (m/z): [M + Na\(^+\)] for C\(_{19}\)H\(_{29}\)NO\(_5\)Na, calcd, 374.1937; found, 374.1943.

Methyl-4-((di-tert-butoxycarbonylamino)-2-hydroxy-2-phenylbutanoate
(Compound 4.40, Scheme 4.14):

\[
\begin{align*}
\text{Ph} & \text{O(CO)}_2\text{Me} \\
\text{N(Boc)}_2
\end{align*}
\]

Prepared according to the representative procedure using methyl 4-((di-tert-butoxycarbonylamino)-2-hydroxy-2-phenylbut-3-ynoate (Compound 4.26, 24 mg, 0.059 mmol, 1.0 eq.) and Pd/C (7.0 mg of 10% w/w dry) in
EtOAc (3 mL) and stirring under a balloon of H₂ for 18 hours. Isolated yield= 16.3 mg (68%) as a yellow oil. R₉= 0.22 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3500(br), 2980, 2933, 1790, 1732, 1699, 1448, 1394, 1367, 1222, 1155, 1128, 856; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.56 - 7.65 (2H, m), 7.27 - 7.40 (3H, m), 4.17 (1H, s), 3.72 - 3.83 (4H, m), 3.62 (1H, ddd, J=14.0, 9.0, 4.5 Hz), 2.54 (1H, ddd, J=13.5, 8.5, 6.5 Hz), 2.30 (1H, ddd, J=13.5, 8.5, 4.5 Hz), 1.50 (18H, s); ¹³C NMR (101 MHz, CDCl₃) δ ppm 175.1, 152.6, 141.3, 128.3, 127.8, 125.4, 82.5, 76.8, 53.3, 42.0, 38.3, 28.1; HRMS (m/z): [M + Na]⁺ for C₂₁H₃₁NO₇Na, calcd, 432.1992; found, 432.1987.

**Ethyl-2-(2-(di-tert-butyl-imidocarbonate)ethyl)-3,4-dihydroquinoline-1(2H)-carboxylate (Compound 4.41, Scheme 4.14):**

Prepared according to the representative procedure using ethyl 2-(di-tert-butyl ethynylimidocarbonate) quinoline-1(2H)-carboxylate (Compound 4.28, 22 mg, 0.05 mmol, 1.0 eq.) and Pd/C (6.0 mg of 10% w/w dry) in EtOAc (5 mL) and stirring under a balloon of H₂ for 36 hours. Isolated yield= 14.8 mg (67%) as a yellow oil. R₉= 0.30 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3435, 2980, 2933, 1790, 1747, 1699, 1492, 1456, 1394, 1367, 1315, 1122, 855; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.54 (1H, d, J=8.0 Hz), 7.12 - 7.19 (1H, m), 7.05 - 7.11 (1H, m), 6.98 - 7.05 (1H, m), 4.60 (1H, quin, J=6.5 Hz), 4.10 - 4.33 (2H, m), 3.50 - 3.69 (2H, m), 2.61 - 2.81 (2H, m), 2.13 - 2.27 (1H, m), 1.76 - 1.88 (1H, m), 1.63 - 1.75 (2H, m), 1.37 - 1.52 (18H, m), 1.30 (3H, t, J=7.0 Hz); ¹³C NMR (126 MHz, CDCl₃) δ ppm 154.8, 152.3, 136.5, 130.8, 128.0, 126.0, 125.6, 124.1, 82.1, 61.8, 51.1, 43.8, 32.2, 28.3, 28.0, 24.5, 14.5; HRMS (m/z): [M + Na]⁺ for C₂₄H₃₆N₂O₆Na, calcd, 471.2465; found, 471.2466.

**Di-tert-butyl (2-(3-oxocyclohexyl)ethyl)imidocarbonate (Compound 4.42, Scheme 4.14):**

Prepared according to the representative procedure using di-tert-butyl 2-((3-oxocyclohexyl)ethynyl)imidocarbonate (Compound 4.34, 14 mg, 0.0415 mmol, 1.0 eq.) and Pd/C (9.0 mg of 10% w/w dry) in EtOAc (3
mL) and stirring under a balloon of H₂ for 20 hours. Isolated yield= 11.3 mg (80%) as a clear oil. R_f= 0.19 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 2978, 2933, 2866, 1791, 1747, 1716, 1695, 1456, 1394, 1367, 1294, 1257, 1228, 1176, 1141, 1120; ¹H NMR (400 MHz, CDCl₃) δ ppm 3.59 (2H, t, J=8.0 Hz), 2.41 - 2.48 (1H, m), 2.32 - 2.40 (1H, m), 2.19 - 2.31 (1H, m), 2.00 - 2.11 (2H, m), 1.90 - 1.99 (1H, m), 1.73 - 1.85 (1H, m), 1.58 - 1.68 (2H, m), 1.49 (18H, s), 1.23 - 1.43 (2H, m); ¹³C NMR (101 MHz, CDCl₃) δ ppm 211.2, 152.5, 82.3, 48.0, 44.1, 41.4, 36.9, 35.6, 31.1, 28.1, 25.2; HRMS (m/z): [M + NH₄]⁺ for C₁₈H₃₅N₂O₅, calcd, 359.25460; found, 359.25449.

**Di-tert-butyl (3-(1-hydroxycyclohexyl)propyl)imidocarbonate (Compound 4.43, Scheme 4.14):**

Prepared according to the representative procedure using di-tert-butyl (3-(1-hydroxycyclohexyl)prop-1-yn-1-yl)imidocarbonate (Compound 4.32, 21 mg, 0.0594 mmol, 1.0 eq.) and Pd/C (14 mg of 10% w/w dry) in EtOAc (3 mL) and stirring under a balloon of H₂ for 21 hours. Isolated yield= 17.8 mg (83%) as a clear oil. R_f= 0.16 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3520(br), 2980, 2933, 2862, 1784, 1734, 1695, 1456, 1394, 1367, 1174, 1134; ¹H NMR (400 MHz, CDCl₃) δ ppm 3.58 (2H, t, J=7.0 Hz), 1.62 - 1.72 (2H, m), 1.54 - 1.61 (4H, m), 1.47 - 1.53 (21H, m), 1.38 - 1.46 (4H, m), 1.22 - 1.31 (2H, m); ¹³C NMR (101 MHz, CDCl₃) δ ppm 152.8, 82.1, 71.2, 46.8, 39.1, 37.4, 28.1, 25.8, 22.7, 22.2; HRMS (m/z): [M + Na]⁺ for C₁₉H₃₅NO₅Na, calcd, 380.2407; found, 380.2412.

**Representative procedure for the copper-catalyzed cycloaddition of 4.12 with azides (Scheme 4.15):**

di-tert-butyl ethynylimidodicarbonate (Compound 4.12, 48 mg, 0.2 mmol, 1.0 eq.) was dissolved in water (2 mL) and t-BuOH (1 mL) in a 20-dram scintillation vial. Benzyl-azide (38 mg, 0.03 mL, 0.28 mmol, 1.4 eq.) was then added followed by addition of Cu(II)OAc-anhydrous (3.6 mg, 0.02 mmol, 0.1 eq.) and sodium-(L)-ascorbate (8 mg, 0.04 mmol, 0.2 eq.) and the resulting cloudy mixture stirred for 16 hrs at room temperature. Volatiles were removed under a stream of air and the resulting residue was
partitioned between ethyl acetate (100 mL) and water (20 mL) and the layers were separated. The organic layer was washed with sat’d NaCl(aq) (20 mL), dried (MgSO$_4$), filtered and concentrated in vacuo and the crude residue purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 62 mg (83% yield) of Compound 4.44 (Scheme 4.15) as a beige solid.

**Di-tert-butyl (1-benzyl-1H-1,2,3-triazol-4-yl)imidocarbonate (Compound 4.44, Scheme 4.15):**

![Diagram](Bn\-N\-N\-N\-N\-Boc\_2)

Isolated yield= 62 mg (83%) as a beige solid. m.p. = 97-100 °C; R$_f$ = 0.17 (10% MeOH/CH$_2$Cl$_2$); IR (CDCl$_3$, cm$^{-1}$) 3155, 2984, 2934, 2253, 1794, 1751, 1717, 1564, 1456, 1371, 1275, 1252, 1151, 1121, 1105, 908; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.30 - 7.42 (4H, m) 7.15 - 7.26 (2H, m) 5.54 (2H, s) 1.42 (18H, s); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 150.6; 143.5; 134.6; 129.1; 128.8; 127.7; 119.9; 83.5; 54.6; 27.8; HRMS (m/z): [M + H]$^+$ for C$_{19}$H$_{27}$N$_4$O$_4$, calcd, 375.2026; found, 375.2039.

**Di-tert-butyl (1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)imidocarbonate (Compound 4.45, Scheme 4.15):**

![Diagram](Br\-N\-N\-N\-Boc\_2)

Prepared according to the representative procedure using 1-azido-4-bromobenzene (55 mg, 0.28 mmol, 1.4 eq.). Isolated yield= 86 mg (98% yield) as a yellow solid. m.p. = 196-199 °C; R$_f$ = 0.53 (40% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3055, 2986, 2305, 1798, 1740, 1724, 1501, 1421, 1369, 1150, 1120, 897; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.92 (1H, s) 7.60 - 7.70 (4H, m) 1.49 (18H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 150.7; 143.9; 136.0; 132.9; 122.6; 121.7; 117.7; 84.0; 27.9; HRMS (m/z): [M + H]$^+$ for C$_{18}$H$_{24}$BrN$_4$O$_4$, calcd, 439.09809; found, 439.09703.
Methyl-2-(4-((di-tert-butoxycarbonyl)amino)-1H-1,2,3-triazol-1-yl)acetate
(Compound 4.46, Scheme 4.15):

Prepared according to the representative procedure using di-tert-butyl ethynylimidodicarbonate (Compound 4.12, 43 mg, 0.18 mmol, 1.0 eq.) and methyl 2-azidoacetate (29 mg, 0.25 mmol, 1.4 eq.). Isolated yield= 36.2 mg (63% yield) as a white solid. m.p.= 76-79 °C; Rf= 0.06 (20% EtOAc/hexanes); IR (CH2Cl2, cm⁻¹) 3055, 2986, 2306, 1784, 1759, 1720, 1566, 1518, 1421, 1369, 1151, 1115, 1040, 897; ¹H NMR (400 MHz, CDCl3) δ ppm 7.63 (1H, s), 5.17 (2H, s), 3.81 (3H, s), 1.44 (18H, s); ¹³C NMR (101 MHz, CDCl3) δ ppm 166.4, 150.5, 143.4, 121.4, 83.6, 53.1, 51.2, 28.2, 27.8; HRMS (m/z): [M + H]⁺ for C15H25N4O6, calcd, 357.17741; found, 357.17788.

Di-tert-butyl (1-(4-cyanophenyl)-1H-1,2,3-triazol-4-yl)imidocarbonate (Compound 4.47, Scheme 4.15):

Prepared according to the representative procedure using 1-azido-4-cyanobenzene (40 mg, 0.28 mmol, 1.4 eq.). Isolated yield= 53 mg (69% yield) as a yellow solid. m.p.= 170-175 °C; Rf= 0.54 (10% MeOH/CH2Cl2); IR (CH2Cl2, cm⁻¹) 3055, 2986, 2306, 2234, 1798, 1759, 1713, 1610, 1518, 1421, 1369, 1150, 1024, 843; ¹H NMR (300 MHz, CDCl3) δ ppm 8.02 - 7.96 (2H, m), 7.79 - 7.88 (2H, m), 1.50 (18H, s); ¹³C NMR (101 MHz, CDCl3) δ ppm 150.6, 144.4, 139.8, 134.0, 120.4, 117.6, 117.5, 112.6, 84.2, 27.9; HRMS (m/z): [M + H]⁺ for C19H24N5O4, calcd, 386.18283; found, 386.18325.

Tert-butyl-(2-(4-di-tert-butylimidocarbonate-1H-1,2,3-triazol-1-yl)ethyl)carbamate
(Compound 4.48, Scheme 4.15):

Prepared according to the representative procedure using tert-butyl (2-azidoethyl)carbamate (52 mg, 0.28 mmol, 1.4 eq.). Isolated yield= 39 mg (45% yield) as a white solid. m.p.= 135-138 °C; Rf= 0.30 (40% EtOAc/hexanes); IR (CH2Cl2, cm⁻¹) 3362, 3150, 3005, 2982, 2934, 2225, 1790, 1753, 1691, 1369, 1251, 1151, 1115, 854; ¹H NMR (400 MHz,
CDCl$_3$) $\delta$ ppm 7.50 (1H, s), 4.89 (1H, br. s), 4.48 (2H, $t$, $J$ = 5.5 Hz), 3.64 (2H, dt, app q, $J$ = 6.0 Hz), 1.46-1.44 (18H, m); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 155.8, 150.7, 143.0, 120.6, 83.6, 80.0, 50.2, 40.4, 28.3, 27.8; HRMS ($m/z$): [M + H]$^+$ for C$_{19}$H$_{24}$N$_5$O$_6$, calcd, 428.25091; found, 428.25174.

**Di-tert-butyl-(1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl)imidocarbonate**

(Compound 4.49, Scheme 4.15):

Prepared according to the representative procedure using 1-azido-3-methoxybenzene (42 mg, 0.28 mmol, 1.4 eq.). Isolated yield= 49 mg (63% yield) as a white solid. m.p.= 153-155 °C; $R_f$= 0.36 (20% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3055, 2984, 2938, 2225, 1794, 1759, 1720, 1610, 1369, 1265, 1151, 1121; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.92 (1H, s), 7.42 (1H, $t$, $J$ = 8.0 Hz), 7.36 (1H, $t$, $J$ = 2.0 Hz), 7.27-7.25 (1H, m), 6.98 (1H, dd, $J$ = 8.5, 2.5 Hz), 3.89 (3H, s), 1.49 (18H, s); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 160.6, 150.7, 143.7, 138.1, 130.6, 118.0, 114.8, 112.2, 106.2, 83.8, 55.7, 27.9; HRMS ($m/z$): [M + H]$^+$ for C$_{19}$H$_{27}$N$_4$O$_5$, calcd, 391.19814; found, 391.19921.

**Methyl-2-((di-tert-butoxycarbonyl)amino)-1H-1,2,3-triazol-1-yl)benzoate**

(Compound 4.50, Scheme 4.15):

Prepared according to the representative procedure using methyl 2-azidobenzoate (50 mg, 0.28 mmol, 1.4 eq.). Isolated yield= 58 mg (69% yield) as a yellow oil. $R_f$= 0.33 (40% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3055, 2986, 2306, 1792, 1759, 1732, 1421, 1369, 1150, 1122, 1103; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 8.02 (1H, dd, $J$=8.0, 1.5 Hz), 7.78 (1H, s), 7.46 - 7.54 (1H, m), 7.46 - 7.54 (1H, m), 3.75 (3H, s), 1.50 (18H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 165.4, 150.8, 142.9, 136.1, 132.7, 131.3, 130.0, 127.5, 126.8, 122.1, 83.6, 52.6, 27.9; HRMS ($m/z$): [M + H]$^+$ for C$_{20}$H$_{27}$N$_4$O$_6$, calcd, 419.19306; found, 419.19265.
**Representative procedure for the ruthenium-catalyzed cycloaddition of ynimide 4.12 with azides (Scheme 4.16):**

Cp*RuCl(COD) (1.5 mg, 0.004 mmol, 0.02 eq.) was charged to a µW vial capped with a septa and purged with nitrogen for 5 mins then di-tert-butyl ethynylimidodicarbonate (Compound 4.12, 48 mg, 0.2 mmol, 1.0 eq.) in toluene (0.5 mL) was added followed by addition of benzyl-azide (27 mg, 0.2 mmol, 1.0 eq.) in toluene (0.5 mL) and the mixture stirred at room temperature. After 16 hours, the reaction mixture was loaded directly onto silica gel and purified by flash column chromatography using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 54 mg (52% yield) of Compound 4.51 (Scheme 4.16) as a white solid.

**Di-tert-butyl (1-benzyl-1H-1,2,3-triazol-5-yl)imidocarbonate (Compound 4.51, Scheme 4.16):**

Isolated yield= 54 mg (52 %) as a white solid. m.p. = 123-125 ºC; Rf = 0.38 (20% EtOAc/hexanes); IR (CH2Cl2, cm⁻¹) 3055, 2986, 2306, 1801, 1769, 1456, 1421, 1371, 1148, 1103, 897; ¹H NMR (300 MHz, CDCl3) δ ppm 7.54 (1H, s), 7.28 - 7.40 (5H, m), 5.36 (2H, s), 1.30 (18H, s); ¹³C NMR (101 MHz, CDCl3) δ ppm 148.9; 133.8; 133.4; 131.2; 129.0; 128.6; 128.1; 84.6; 51.5; 27.6; HRMS (m/z): [M + H]+ for C19H27N4O4, calcd, 375.2026; found, 375.2038.

**Methyl-2-(5-((di-tert-butoxycarbonyl)amino)-1H-1,2,3-triazol-1-yl)acetate (Compound 4.52, Scheme 4.16):**

Prepared according to the representative procedure using methyl 2-azidoacetate (23 mg, 0.2 mmol, 1.0 eq.). Isolated yield= 36 mg (51% yield) as a yellow solid. m.p. = 111-113 ºC; Rf = 0.31 (40% EtOAc/hexanes); IR (CH2Cl2, cm⁻¹) 3055, 2986, 2306, 1801, 1767, 1728, 1574, 1460, 1439, 1371, 1267, 1146, 1105; ¹H NMR (300 MHz, CDCl3) δ ppm 7.61 (1H, s), 5.01 (2H, s), 3.78 (3H, s), 1.44 (18H, s); ¹³C NMR (75 MHz, CDCl3) δ ppm 165.8, 149.0, 133.9, 131.2, 85.0, 52.9, 48.2, 27.7; HRMS (m/z): [M + H]+ for C15H25N4O6, calcd, 357.17741; found, 357.17767.
Synthesis of 5-(di-tert-butylimidocarbonate)-3-phenylisoxazole (Compound 4.53, Scheme 4.17):

\[
\begin{align*}
\text{Ph} & \quad \text{N} = \text{O} \\
& \quad \text{N(Boc)}_2
\end{align*}
\]

di-tert-butyl ethynylimidodicarbonate (Compound 4.12, 48 mg, 0.2 mmol, 1.0 eq.) and N-hydroxybenzimidoyl chloride (44 mg, 0.28 mmol, 1.4 eq.) were combined in water (2 mL) and t-BuOH (1 mL) in a 20-dram scintillation vial. Sodium-(L)-ascorbate (4.0 mg, 0.02 mmol, 0.1 eq.) was then added followed by K₂CO₃ (61 mg, 0.44 mmol, 2.2 eq.) and Cu(II)SO₄-anhydrous (3.0 mg, 0.02 mmol, 0.1 eq.) and the resulting cloudy mixture stirred for 16 hrs at room temperature. Volatiles were removed under a stream of air and the resulting residue was partitioned between ethyl acetate (75 mL) and water (25 mL) and the layers were separated. The organic layer was washed with sat’d NaCl(aq) (10 mL), dried (MgSO₄), filtered and concentrated in vacuo and the crude residue purified through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 28 mg (39% yield) of Compound 4.53 (Scheme 4.17) as a slightly yellow solid. m.p.= 147-150 °C; R_f= 0.28 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3055, 2988, 2305, 1801, 1653, 1636, 1421, 739; ¹H NMR (300 MHz, CDCl₃) δ ppm 7.73 - 7.89 (2H, m), 7.40 - 7.52 (3H, m), 6.43 (1H, s), 1.48 (18H, s); ¹³C NMR (75 MHz, CDCl₃) δ ppm 163.3, 161.4, 148.8, 130.2, 129.0, 128.9, 126.5, 97.3, 84.7, 27.8; HRMS (m/z): [M + H]⁺ for C₁₉H₂₅N₂O₅, calcd, 361.1757; found, 361.1762.

Synthesis of 4-(di-tert-butylimidocarbonate)-3-phenylisoxazole (Compound 4.54, Scheme 4.17):

\[
\begin{align*}
\text{Ph} & \quad \text{N} = \text{O} \\
& \quad \text{N(Boc)}_2
\end{align*}
\]

di-tert-butyl ethynylimidodicarbonate (Compound 4.12, 48 mg, 0.2 mmol, 1.0 eq.) and N-hydroxybenzimidoyl chloride (34 mg, 0.22 mmol, 1.1 eq.) and Cp*RuCl(COD) (3.8 mg, 0.01 mmol, 0.05 eq.) and Et₃N (25 mg, 0.034 mL, 0.25 mmol, 1.25 eq.) were combined in 1,2-dichloroethane (1.0 mL). The reaction vial was sealed and purged with N₂ for 5 mins then stirred at room temperature for 16 hours and the reaction mixture was loaded directly onto silica gel and purified by flash column chromatography using ethyl acetate in hexanes to elute (gradient elution 0-
100 % EtOAc) providing 50 mg (69% yield) of Compound 4.54 (Scheme 4.17) as a grey solid. m.p. = 57-59 °C; Rf = 0.27 (20% EtOAc/hexanes); IR (neat, cm\(^{-1}\)) 3111, 3068, 2982, 2342, 1798, 1755, 1713, 1622, 1464, 1362, 1246, 1159, 1116; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 8.45 (1H, s), 7.62 - 7.68 (2H, m), 7.44 - 7.49 (3H, m), 1.30 (18H, s); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) ppm 158.8, 155.2, 150.2, 130.1, 129.0, 127.8, 127.2, 119.2, 83.8, 27.6; HRMS (m/z): [M + H]\(^+\) for C\(_{19}\)H\(_{25}\)N\(_2\)O\(_5\), calcd, 361.17635; found, 361.17762.

**Synthesis of N-(1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)benzamide (Compound 4.55, Scheme 4.18):**

Compound 4.45 (35 mg, 0.08 mmol, 1.0 eq.) was suspended in EtOAc (4 mL) and treated with 4N HCl in dioxanes sol’n (0.5 mL) and stirred at room temperature. After 1 hr, a further 1.0 mL of 4N HCl in dioxanes sol’n and after a further 1 hr another 1.0 mL of 4N HCl in dioxanes sol’n added and stirred at room temperature overnight. After 16 hours, volatiles were removed on the rotovap and the resulting crude residue was re-dissolved in CH\(_2\)Cl\(_2\) (1 mL) and pyridine (1 mL) and cooled to 0 °C in an ice/water bath. A solution of benzoyl-chloride (13 mg, 0.096 mmol, 1.2 eq.) in CH\(_2\)Cl\(_2\) (0.5 mL) was then added and stirred for 4 hours then partitioned reaction mixture between CH\(_2\)Cl\(_2\) (50 mL) and sat’d NaHCO\(_3\)aq (15 mL) and the phases were separated. The organic phase was dried (MgSO\(_4\)), filtered and concentrated in vacuo and the crude material purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) to provide 13 mg (48% yield over 2 steps) of Compound 4.55 (Scheme 4.18) as a brown solid. m.p > 200 °C; Rf = 0.18 (40% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3252, 2955, 2924, 2852, 2228, 1720, 1659, 1593, 1497, 1402, 1159; \(^1\)H NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) ppm 11.49 (1H, s), 8.92 (1H, s), 8.02 - 8.11 (2H, m), 7.91 - 7.99 (2H, m), 7.74 - 7.82 (2H, m), 7.46 - 7.64 (3H, m); \(^{13}\)C NMR (126 MHz, DMSO-d\(_6\)) \(\delta\) ppm 164.8, 145.2, 136.4, 133.5, 133.2, 132.5, 129.0, 128.4, 122.4, 121.7, 112.8; HRMS (m/z): [M + H]\(^+\) for C\(_{15}\)H\(_{12}\)BrNaO, calcd, 343.0188; found, 343.0191.
Synthesis of 1-(3-methoxyphenyl)-N-(quinolin-2-ylmethyl)-1H-1,2,3-triazol-4-amine (Compound 4.56, Scheme 4.18):

Compound **4.49** (30 mg, 0.077 mmol, 1.0 eq.) dissolved in MeOH (1 mL) and treated with 4N HCl in dioxanes sol’n (0.5 mL) and stirred at room temperature overnight. After 18 hours, volatiles were removed under an air stream and the crude residue partitioned between CH$_2$Cl$_2$ (40 mL) and sat’d NaHCO$_3$(aq) (15 mL) and the organic phase separated, dried (MgSO$_4$), filtered and concentrated in vacuo to give 13 mg (89%) of crude deprotected material. The resulting crude free amine (13 mg, 0.068 mmol, 1.0 eq.) was re-dissolved in CH$_2$Cl$_2$ (3 mL) and 2-quinoline carboxaldehyde (10.8 mg, 0.068 mmol, 1.0 eq.) was added followed by MgSO$_4$ (25 mg) and the mixture stirred at room temperature overnight. After 16 hours, the reaction mixture was diluted with CH$_2$Cl$_2$ (40 mL) and filtered through celite and concentrated in vacuo. The resulting crude imine was re-dissolved in MeOH (3 mL) and treated with NaBH$_4$ (5.3 mg, 0.14 mmol, 2.0 eq.) and stirred at room temperature for 45 mins then volatiles removed on the rotovap and 5 mL MeOH added and volatiles removed again on the rotovap. The crude residue was then partitioned between CH$_2$Cl$_2$ (30 mL) and sat’d NaHCO$_3$aq (15 mL) and the phases were separated and the aq. phase was extracted again with CH$_2$Cl$_2$ (30 mL). The organic extracts were combined, dried (MgSO$_4$), filtered and concentrated in vacuo and the residue purified by flash chromatography through silica gel using 10% MeOH in ethyl acetate to elute to provide 14 mg (55% over 2 steps) of Compound **4.56** (Scheme 4.18) as a yellow waxy semi-solid. 

$R_f$= 0.34 (60% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3344, 3142, 3063, 2959, 2926, 2855, 1747, 1589, 1263, 1163, 1038; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 8.15 (1H, d, $J$=8.5 Hz), 8.09 (1H, d, $J$=8.0 Hz), 7.82 (1H, d, $J$=8.5 Hz), 7.73 (1H, ddd, $J$=8.5, 7.0, 1.5 Hz), 7.47 - 7.58 (2H, m), 7.15 - 7.39 (4H, m), 6.86 - 6.94 (1H, m), 5.27 (1H, br.s.), 4.71 (2H, s), 3.85 (3H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 160.5; 158.1; 154.8; 147.5; 138.4; 136.9; 130.3; 129.8; 128.8; 127.6; 127.4; 126.4; 119.7; 114.1; 111.8; 105.7; 103.7; 55.6; 51.2; HRMS (m/z): [M + H]$^+$ for C$_{19}$H$_{18}$N$_5$O, calcd, 332.15113; found, 332.15072.
4.5 References


[35] Kwok, S. W.; Fotsing, J. R.; Fraser, R. J.; Rodionov, V. O.; Fokin, V. V. Org. Lett. 2010, 12, 4217-4219.


Chapter 5: Synthetic Utility of Allyltrifluoroborate Reagents

5.1 Introduction

Trifluoroborate salts are a synthetically practical class of organoboron reagents with strong B–F bonds which protect against common deborylation pathways resulting in superior handling characteristics versus many other organoboron species. Within this sub-group, the trifluoro-derivates of allylboron compounds have emerged as generally useful alternatives to other allyl-metalloid species in reactions such as carbonyl allylation and palladium-catalyzed cross-couplings (vide infra). Specifically, because allyltrifluoroborate salts are isolated as air and water stable white solids, they are generally easier to purify and handle versus other types of allylmetal and allylboron reagents. This chapter will review this relatively new area of research including the synthesis of allyltrifluoroborate reagents and their use to install allyl groups with a focus on carbonyl allylations. Our group has had a long-standing interest in these stable allylboron reagents, and the following summary will provide context for the original work presented in Chapters 6-7 of this thesis concerning synthesis of biologically active antimycin/neoantimycin depsipeptide natural products using organotrifluoroborate-based allylations.

5.2 Comparison of allylboron and allylmetaloid carbonyl addition reagents

Generally, the most important application of allylboron reagents is their use to generate homoallylic alcohols and homoallylic amines through allyl group addition to aldehydes, ketones and imines.¹ The importance of such a transformation is depicted in Figure 5.1 which shows how the resulting homoallylic alcohol olefin functionality can be divergently manipulated to produce a variety of other important organic structures.
Typically, allylmetalloid species are grouped into three sub-types depending on their carbonyl allylation mechanism (i.e., open vs. closed transition state), and the stereochemical outcome of their aldehyde crotylation products.\textsuperscript{1,2} Due to their reaction with carbonyl groups in a closed Zimmerman-Traxler transition state, and the stereospecific nature of their aldehyde crotylations, allylboronates are members of the type-I class. Typical of type-I allyl-reagents, Z-crotylboronates always provide the 1,2-\textit{syn} alcohol product, while the corresponding \textit{E}-crotylboronate species always produce the opposite 1,2-\textit{anti} alcohol product (Figure 5.2). The stereospecificity observed in these reactions is proposed to be the result of the aldehyde substituent occupying a preferred pseudo-equatorial position in a closed 6-membered chair-like transition state. Thus, to reduce unfavourable 1,3-diaxial like interactions, transition state 5.2 is favoured for reaction of \textit{Z}-crotylboronates to provide 1,2-\textit{syn} products, and conversely, transition state 5.4 is favoured for generation of 1,2-\textit{anti} products with \textit{E}-crotylboronates.
Figure 5.2 Stereospecific and stereodivergent nature of the type-I class of allyl-metalloid crotylboronates in additions to aldehydes via Zimmerman-Traxler transition states

In contrast, other common allylmetalloids such as allylsilicon and allylstannane species transfer their allyl group in a non-stereospecific manner to carbonyl compounds through an open transition state and are thus differentiated as type-II allyl reagents. Type-III reagents are allylmetalloid compounds generated *in situ* from allyllic halides and transition metals such as titanium, aluminum, indium and zinc and whose carbonyl crotylation reactions are also not stereospecific.

As a result, type-I allylboronates are important chemical tools to diastereoselectively construct C–C bonds due to their unique ability amongst allylmetalloids to introduce an olefin functional handle via reliable and predictable 1,2-relative carbonyl addition stereochemistry. There are numerous known allylboron compounds with variable properties depending on the type of boron ligands used. The reagents shown in Figure 5.3 represent the most common allylboron compounds which can differ substantially in their stability and reactivity. For example, triallylboranones such as 5.9 are very reactive and don’t require additives to promote their instantaneous allyl group transfer to aldehydes, but have the disadvantage of instantly igniting in air. Allylboron species which possess electron-donating heteroatom ligands such as boronic esters typified by the
allyl pinacol boronic acid ester 5.6 have improved stability characteristics but can suffer from poor reactivity requiring higher temperatures and Lewis-acid additives to promote carbonyl allylation. In contrast, the trifluoroborate salt derivatives 5.5 hold a special place as stable allylboron reagents which can also be persuaded to react very quickly with carbonyl groups under mild conditions. Importantly, because trifluoroborate salts are free-flowing easy-to-weigh white solids that are isolated in pure form via simple precipitation or recrystallization, they offer superior handling properties compared to other organoboron allylating reagents of similar stability such as boronic esters. Due to the above characteristics, allyl trifluoroborates have gained a reputation as convenient reagents for allyl group transfer to carbonyl compounds. The following sections will focus on the synthesis and reactivity of allyl trifluoroborate salts with specific emphasis on their carbonyl addition reactivity.

![Diagram](image)

**Figure 5.3** Examples of common allylboron reagents in order of their stability/reactivity

### 5.3 Synthesis of allyl trifluoroborate salts

Compounds containing boron–fluorine bonds have long been known. However, practical synthesis of the specific trifluoroborate complexes was only first explored by Vedejs in the 1990’s. In connection with their studies on borate-mediated asymmetric amino acid reactions, the Vedejs lab identified a straight-forward route to easily prepare various aryl-trifluoroborate potassium salts via treatment of boronic acids with KHF$_2$ as a means to purify boron containing compounds and access the corresponding difluoroboronates via *in situ* fluorine atom abstraction (Scheme 5.1). Following this, a number of laboratories realized the utility of organoboron trifluoro-salts as stable precursors to their reactive sp$^2$ difluoroboron form, and they have since been applied as organic group transfer reagents.
in a number of well-known boron reactions such as the Suzuki-Miyaura cross-coupling.\textsuperscript{4}

In this regard, the Molander group has studied the synthesis and Pd-catalyzed cross-coupling reactivity of aryl- and alkyl-trifluoroborates so extensively\textsuperscript{4a,b} that these salts are sometimes referred to as “Molander-ites”.

\begin{equation}
\begin{array}{c}
\text{Ar}^-\overset{\text{KHF}_2}{\text{MeOH}}\text{Ar}^+\text{BF}_3\text{K} + \\
\text{Me}_2\text{N}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{NaO}\overset{\text{TMS-Cl}}{\text{Me}_2\text{N}}\overset{\text{TMS-F}}{\text{KCl}}\overset{\text{NaCl}}{\text{KHMDS}}
\end{array}
\end{equation}

\textbf{Scheme 5.1} Early work on preparing aryl-trifluoroborate potassium salts and their application in asymmetric enolate reactions of amino acids by Vedejs and co-workers\textsuperscript{3}

In general, trifluoroborate salts including allylboron variants, are prepared by the Vedejs method of treating organoboronic acids and esters with aqueous KHF\textsubscript{2} to give potassium salts which for brevity should be assumed as the counter-ion for the remainder of this review unless otherwise stated. Thus, the synthesis of allyltrifluoroborate salts hinges upon initial preparation of the corresponding allylboronic acids or esters.

In this area, the Batey lab was the first to prepare the parent potassium allyltrifluoroborate 5.10 via KHF\textsubscript{2} addition to the unstable allylboronic acid generated in situ via allyl-Grignard addition to trimethylborate (Scheme 5.2).\textsuperscript{5} Allyltrifluoroborate 5.10 has also recently been prepared from commercially available allylpinacolboronic ester in 75\% isolated yield under “non-etching” conditions using KF and tartaric acid to generate B–F bonds as an alternative to the use of KHF\textsubscript{2}.\textsuperscript{6}

\begin{equation}
\begin{array}{c}
\overset{\text{OH}}{\text{MgBr}} \overset{1.\text{B(OMe)}}{2.\text{2N HCl}} \overset{\text{KHFM}}{\text{5.10}}
\end{array}
\end{equation}

\textbf{Scheme 5.2} Synthesis of potassium allyltrifluoroborate from \textit{in situ} generated allylboronic acid\textsuperscript{5}
Similar to the parent allyltrifluoroborate 5.10, the corresponding crotyl potassiumtrifluoroborate salts 5.11 and 5.12 were prepared by the Batey group using the known Schlosser’s base protocol to stereospecifically prepare each intermediate crotylboronic acid diastereomer from geometrically pure 2-butenes (Scheme 5.3). The resulting salts 5.11 and 5.12 were observed to be free-flowing white solids which were easily separated from the reaction mixture in pure form by filtration. This can be practically advantageous since the corresponding allylboronic acids are unstable to storage and the allylboronic esters are oils which are not stable to silica gel chromatography and require distillation for purification.

![Scheme 5.3 Synthesis of Z-crotyl and E-crotyl trifluoroborate potassium salts](image)

The diastereospecific nature of the allylic anion trapping in the synthesis of 5.11 and 5.12 is presumed to be a function of the resulting allylpotassium ion’s resistance to isomerization and results in formation of the corresponding crotyl boronates with complete retention of starting butene geometric purity. This allyl-anion approach to allylboronates and their trifluoroborate salts is unfortunately only practical for preparing these γ-methyl-substituted crotylboron compounds. This is due to problems related to the regiochemistry of electrophile trapping when unsymmetrically substituted non-butene allylic anions are used which result in formation of undesirable mixtures of α- and γ-substituted allylboronates. As a result, access to stereopure γ-functionalized allyltrifluoroborates requires alternative stereoccontrolled methods to γ-functionalized allylboronic acids and esters. In this regard, Batey and co-workers have demonstrated a Matteson homologation sequence to prepare either E-substituted (Scheme 5.4) or Z-substituted (Scheme 5.5) allyltrifluoroborates with well-defined olefin geometry. In both examples, a hydroboration reaction is used to set the desired alkene stereochemistry to generate either trans 5.14 or cis 5.17 beginning from the same terminal alkyne starting.
point. A Matteson 1,2-boron group migration homologation with LiCH₂Cl was then used to install the methylene group with complete retention of starting olefin stereopurity and a final KHF₂ trapping provided the target allyltrifluoroborates 5.14 and 5.17.

\[
\text{Scheme 5.4 Matteson homologation approach to a } \gamma\text{-functionalized } E\text{-allyltrifluoroborate}^8
\]

In addition, palladium-catalyzed allylic borylation has emerged as a general approach to prepare a variety of substituted γ-functionalized allyltrifluoroborates (Scheme 5.6).¹⁰ This is a powerful approach to prepare various anti-functionalized allylboron trifluorosalts due to the availability of the allylic starting materials and the direct one-pot conversion to E-allyltrifluoroborates. This approach suffers, however, from an inability to generate the corresponding Z-functionalized allyltrifluoroborates due to the reversible nature of the intermediate allyl palladium species which always selects for reductive elimination of the more stable E-allylboronates regardless of starting allyl alkene stereochemistry (e.g., compound 5.21). It would therefore be advantageous to develop a
similarly simple and general protocol to access the corresponding Z-allyl trifluoroborates as an alternative to the Matteson homologation approach.

\[
\begin{align*}
R^1\text{R}^2\text{R}^3\text{OH} + \text{HO}\text{B} & \rightarrow \text{HO}\text{BF}_3\text{K} \\
Pd. \text{cat.} (5 \text{ mol } \%) & \text{DMSO/MeOH} \\
20-60 ^\circ \text{C}, 7-24 \text{ h} & \text{then} \\
\text{KHF}_2
\end{align*}
\]

**Scheme 5.6** Selected examples of $\gamma$-$E$-functionalized allyl trifluoroborate salts prepared via a palladium-catalyzed allylic-borylation approach\(^\text{10}\)

Finally, one example of preparing an optically pure $\alpha$-substituted allyl trifluoroborate salt has been reported by Hall and Carosi via copper-catalyzed alkylation of a $\gamma$-chboro alkenyl boronate using a chiral phosphoramidite ligand (Scheme 5.7).\(^\text{11}\)

\[
\begin{align*}
\text{Cl} & \rightarrow \text{EtMgBr} \\
\text{CuTC (2 mol %)} & \text{L}^\star (2.5 \text{ mol } \%) \\
\text{CH}_2\text{Cl}_2 & -78 ^\circ \text{C} \\
\text{Et} & \rightarrow \text{KHF}_2 \\
(6.0 \text{ equiv}) & \text{acetone/H}_2\text{O} \\
\text{rt, 2 h} & \text{5.22, 64\%} \\
(\text{ee} = 91\%) \\
\text{L}^\star = \begin{array}{c}
\text{OMe} \\
\text{Me} \\
\text{Me} \\
\text{OMe}
\end{array}
\]

**Scheme 5.7** Synthesis of a chiral $\alpha$-substituted allyl trifluoroborate salt\(^\text{11}\)
5.4 Additions of allyltrifluoroborate salts to carbonyl groups

To facilitate allylboration using a protected sp\(^3\)-trifluoroboron species, initial conversion to a di-valent sp\(^2\)-allylboron intermediate with an empty boron p-orbital is required. In this regard, the first examples of using an allyltrifluoroborate salt as an allyl transfer reagent with carbonyl groups was reported by the Batey lab using BF\(_3\)·OEt\(_2\) as promoter (Scheme 5.8).\(^5\) Presumably, the BF\(_3\)·OEt\(_2\) acts to remove a fluoride atom to generate KBF\(_4\) and releases a difluoro-allylboronate intermediate which is postulated to be the reactive allylating species.

Since then, the Batey group has also reported conditions for carbonyl allylation with allyltrifluoroborate salts using mild phase-transfer catalysis\(^8,12\) or heterogeneous Montmorillonite K10 clay-catalysis (Scheme 5.8).\(^13\) In both examples, water is crucial to reactivity and presumably these conditions generate allylboronic acid in situ as the active allylating species. Regardless of which of the above conditions are used, reaction of crotyltrifluoroborates with aldehydes provides reliable transfer of alkene geometry with complete diastereocontrol suggesting 6-membered Zimmerman-Traxler transition states and the intermediacy of di-valent crotylboron species. Other conditions which facilitate carbonyl allylation with allyl-BF\(_3\)K salts include the use of TsOH,\(^14\) lanthanide salts,\(^15\) O-glycosides,\(^16\) 18-crown-6 ether,\(^17\) palladium catalysis,\(^18\) and photochemical activation.\(^19\) However, the Batey conditions shown in Scheme 5.8 remain the most common including BF\(_3\)·OEt\(_2\) mediated addition to aldehydes generated in situ from oxiranes,\(^20\) and a recently reported Mont. K10 promoted aldehyde allyltrifluoroborate addition followed by oxidation and base mediated isomerization to give α,β-unsaturated ketones.\(^21\)

\[
\begin{align*}
\text{conditions:} & \quad \text{BF}_3\cdot\text{OEt}_2, \text{CH}_2\text{Cl}_2, -78 \text{°C} \text{ to rt} \\
& \quad \text{Bu}_3\text{Ni} (10 \text{ mol} \% \), \text{CH}_2\text{Cl}_2/\text{H}_2\text{O}, \text{rt} \\
& \quad \text{Mont. K10, CH}_2\text{Cl}_2/\text{H}_2\text{O, rt} \\
\text{X} & \quad \text{F, OH} \\
\text{allyl} & \quad R^3 = R^4 = \text{H} \\
\text{Z-crotyl} & \quad R^3 = \text{Me}, R^4 = \text{H} \\
\text{E-crotyl} & \quad R^3 = \text{H}, R^4 = \text{Me}
\end{align*}
\]

**Scheme 5.8** Common conditions for aldehyde and ketone allylation with allyltrifluoroborate salts\(^5,12,13\)
Batey and co-workers have also shown that allyltrifluoroborate salts can similarly undergo addition to imines and other carbon-nitrogen π-bonds to generate homoallylic amines using BF$_3$·OEt$_2$ as a promoter. For example, allylation and diastereoselective syn or anti crotylation of sulfonylimines was reported using allylboron trifluoro salts using Lewis-acid promoted conditions (Scheme 5.9).\textsuperscript{22} Notably, use of a chiral sulfinyl “Davis-Ellman” type imine resulted in a highly diastereoselective allyl addition to provide 5.23 which was easily deprotected to enantiomerically enriched primary homoallylic amine 5.24.

Scheme 5.9 Allylation and crotylation of sulfonyl and sulfinyl imines using trifluoroborate reagents and BF$_3$·OEt$_2$ promoter.\textsuperscript{22}

This type of C–N reactivity has also been extended to reaction with nitriles in an overall double-allylboration approach generating di-allylated homoallylic amine products.\textsuperscript{23} More significantly, the Batey group has also shown that these stable allyl-boron salts can react with indoles via their C=N 3H-indole tautomer in a one-pot BF$_3$·OEt$_2$ promoted indole isomerization and imine allylation (Scheme 5.10).\textsuperscript{24} The products of this reaction are interesting allyl-substituted indolines which are not easily generated under alternative conditions. Moreover, crotyl- and prenyltrifluoroborates are also reactive and may be specifically useful toward indole-derived alkaloid natural product structures.
Scheme 5.10 Representative Lewis-acid promoted C-2 allylation and crotylation of indoles using organotrifluoroborate salts$^{24}$

Perhaps the most important development regarding allyltrifluoroborate imine reactivity concern palladium$^{25}$ or rhodium$^{26}$ catalyzed enantioselective imine allylations. While the palladium-catalyzed variant is only modestly enantioselective, the rhodium-catalyzed cyclic imine allylation recently developed by the Lam group provides superb yields and enantioselectivities with allyl-, crotyl-, and prenyltrifluoroborates (Scheme 5.11). Because $E$- and $Z$-crotyltrifluoroborates in this rhodium-catalyzed reaction provide anti- and syn-allylation products respectively, a catalytic cycle involving a cyclic chair-like transition state with a configurationally stable allyl-rhodium boronate was proposed. Overall, these approaches constitute a fascinating development due to the catalyst-controlled stereoinduction which does not depend on stoichiometric use of chirality sources on the substrate (e.g., Davis-Ellman sulfinylimines) or the allylboron complex (e.g., Brown or Roush chiral allylboronates). Hopefully, this reaction-type can be extended to the catalytic enantioselective allylation of aldehydes and ketones using these easy-to-handle allyltrifluoroborate salts.
Although catalytic enantioselective carbonyl allylation with allyl-BF$_3$K species is currently unknown, stereoselective allylboration of carbonyl groups with allyltrifluoroborate salts can be performed under substrate-control for additions to α- and β-substituted aldehydes. For example, the Batey lab has shown that good levels of 1,2-anti diastereoinduction is observed in additions to OTBS protected α-hydroxy aldehydes (Scheme 5.12).$^{5,8}$ Additionally, modest levels of 1,3-anti diastereomeric ratios were also observed in additions to OTBS protected β-hydroxy aldehydes (Scheme 5.13).$^{5,8}$ Importantly, 1,2,3-stereotriads 5.40-5.41 (Scheme 5.12) and 1,3,4-stereotriads 5.43-5.44 (Scheme 5.13) can be generated with good overall levels of diastereocontrol in additions to these aldehydes with crotyltrifluoroborate reagents.
Scheme 5.12 Diastereoselective allyl- and crotyl-BF$_3$K additions to TBS protected α-hydroxy aldehydes$^{5,8}$

Scheme 5.13 Diastereoselective allyl- and crotyl-BF$_3$K additions to TBS protected β-hydroxy aldehydes$^{5,8}$

This type of 1,3,4-stereotriad diastereoselectivity was used by Batey and Thadani in the total synthesis of (-)-tetrahydrolipstatin using addition of E-allyltrifluoroborate 5.14 (prepared in Scheme 5.4) to a chiral β-hydroxy aldehyde to generate key intermediate 5.45 (Scheme 5.14).$^{8}$ In this synthesis, the allyl group functions as a synthetic equivalent of a carbonyl group and is used to generate the 4-membered lactone ring of the anti-obesity natural product.
Scheme 5.14 Total synthesis of the anti-obesity agent (-)-tetrahydrolipstatin using a diastereoselective β-hydroxy aldehyde E-allyltrifluoroborate addition approach\(^8\)

Similarly, Batey and Janetzko have used Z-allyltrifluoroborate reagent 5.17 (prepared in Scheme 5.5) to diastereoselectively prepare 1,2,3-stereotriad 5.48 via addition to a (+)-lactic acid derived α-hydroxy aldehyde in their synthesis of the depsipeptide natural product (+)-antimycin A\(_{1b}\) (Scheme 5.15).\(^9\) Again, the allyl group installation serves as an aldol type surrogate and is oxidatively transformed to a carboxylic acid for 9-membered lactone ring closure.

Scheme 5.15 Total synthesis of the depsipeptide respiratory inhibitor (+)-antimycin A\(_{1b}\) using a diastereoselective α-hydroxy aldehyde Z-allyltrifluoroborate addition approach\(^9\)
Allyl- and crotyltrifluoroborate salts have also been used by the Stefani group in diastereoselective additions to chiral \(\alpha\)-amino aldehydes (Scheme 5.16). The reactions provided good yields and high levels of 1,2- and 1,2,3-diastereoccontrol as a route to allyl-functionalized 1,2-aminoalcohol compounds. Specifically, this approach provided access to the non-ribosomal amino acid residue statine 5.57 which is a key component of the anti-tumoral natural product dolastatin 10.

**Scheme 5.16** Diastereoselective allyl trifluoroborate additions to chiral \(\alpha\)-amino aldehydes and application to the synthesis of the statine amino acid residue component of dolastatin 10

In addition to the above examples related to stereocontrolled access to peptidic structures, crotyltrifluoroborate salts have been demonstrated to be easy to use reagents to generate polyketide-type 1,2,3-stereotriads. In this area, the Leighton group used \(E\)-crotyltrifluoroborate en route to completing the total synthesis of zincophorin methyl ester (Scheme 5.17). Superb diastereoselectivity (>20:1 dr) was observed in this example, and the authors also noted superior handling and reactivity of \(E\)-crotyltrifluoroborate compared to other crotylmetalloids for their synthesis of compound
Polyketide stereotriads with dithiane handles were also generated using crotyltrifluoroborate additions to chiral $\alpha$-alkyl aldehydes (Scheme 5.18).\(^2^9\)

Scheme 5.17 Diastereoselective crotyl-BF$_3$K aldehyde addition in the total synthesis of polyketide natural product zincophorin methyl ester\(^2^8\)

Scheme 5.18 Diastereoselective crotyl-BF$_3$K additions to chiral $\alpha$-dithiane aldehydes\(^2^9\)

Substrate controlled diastereoselective additions of allyl-BF$_3$K reagents to $\alpha,\beta$-epoxy ketones has also been reported which provides access to epoxy homoallylic alcohol species in good yield and high stereoselectivity (Scheme 5.19).\(^3^0\) Interestingly, metallic indium was used to promote allyl group transfer in these reactions as an alternative to Lewis-acid based conditions which can lead to decomposition of the sensitive epoxy-ketone starting materials (and epoxy-alcohol products). In addition, the indium metal was also observed to provide good chemoselective control for reaction of the ketone functionality over the epoxide group. It is not clear, however, how the indium metal is functioning in these additions but it was noted that use of water co-solvent is necessary.
Scheme 5.19 Representative products of indium-mediated allyltrifluoroborate addition to \( \alpha,\beta \)-epoxy ketones\(^{30}\)

In addition to the above substrate-controlled stereoselective allylations, Hall and Carosi have reported a reagent controlled enantioselective allylation using chiral \( \alpha \)-substituted allyltrifluoroborate \( 5.22 \) (Scheme 5.20).\(^{11}\) Currently, this approach to chiral homoallylic alcohols is limited only to the two examples shown using \( 5.22 \) (prepared in Scheme 5.7), but hopefully will be fully explored as a general enantioselective method.

Scheme 5.20 Enantioselective carbonyl allylation using a chiral \( \alpha \)-substituted allyltrifluoroborate\(^{11}\)

5.5 Metal-catalyzed cross-couplings with allyltrifluoroborate salts

Carbonyl allylations are by-far the most common application of allyltrifluoroborate species, however, boron to palladium transmetallation with these compounds can also be used in Pd-catalyzed allyl group coupling reactions. The Miyaura group was the first to explore this type of Pd-catalyzed allyl-BF\(_3\)K reactivity with aryl and alkenyl-halides giving allylated cross-coupled products.\(^{31}\) Interestingly, although both \( \alpha \) and \( \gamma \)-regioisomers can result in reaction of \( \gamma \)-substituted allyltrifluoroborates, the use of ferrocenyl-phosphine derived ligands was found to provide excellent regiocontrolled synthesis of exclusively \( \alpha \)-substituted allyl products. This result was further extended to
provide regioselective synthesis of enantioenriched \( \alpha \)-allylated products using the Josiphos chiral ligand (Scheme 5.21).\(^{31c}\)

**Scheme 5.21** Palladium-catalyzed regio- and enantioselective synthesis of \( \alpha \)-substituted allyl products using \( \gamma \)-functionalized allyltrifluoroborates\(^{31}\)

Similarly, Pd-catalyzed cross-coupling of \( E \)-crotyltrifluoroborate with aroyl chlorides was also found to selectively provide \( \alpha \)-allylated ketones such as 5.70 (Scheme 5.22).\(^{32}\) Conversely, use of allyltrifluoroborate in this reaction directly provided instead \( \alpha,\beta \)-unsaturated ketone products via allyl ketone isomerization as exemplified by compound 5.71. This type of allyl group isomerization was also observed under similar reaction conditions between allyltrifluoroborates and aryl halides to give alkenyl instead of allyl-functionalized aromatic species.\(^{33}\)
Scheme 5.22 Palladium-catalyzed coupling of aroyl chlorides and allyl/crotyl-trifluoroborates\textsuperscript{32}

In addition to the reports described above, there is also a single example of allyl-BF\textsubscript{3}K participating in a copper-catalyzed oxidative Heck reaction with 1,1-diphenylethylene\textsuperscript{34} and one low-yielding palladium-catalyzed allyl-allyl coupling between allyl-BF\textsubscript{3}K and an allyl alcohol.\textsuperscript{35} Considering the superior handling characteristics of potassium allyltrifluoroborate over other allylmatalloid species such as allyltributylstannane, these boronate allyl salts should find more use in metal-catalyzed cross-couplings.

5.6 Miscellaneous allyltrifluoroborate reactions

Some notable reactions of allyltrifluoroborate salts that do not fit in the above general sections on carbonyl additions or cross-coupling applications are outlined below. For example, a heteroatom group transfer reaction of potassium allyltrifluoroborate with allylamine has been reported en route to interesting aza-boron heterocycle products (Scheme 5.23).\textsuperscript{36} Presumably, use of TMS-Cl generates a dichloroallylborane \textit{in situ} which undergoes substitution by the allylamine nucleophiles to give 5.72 which is then subjected to ring-closing metathesis to give cyclic boronate 5.73. Boron ligand-exchange of 5.73 followed by ring-oxidation and boron-reduction gave the target aromatic 1,2-azaborine compound 5.75 on a synthetically useful 1.8 gram scale. Interest in these structures stems from the apparent ability of cyclic B–N bonds to behave as isosteric replacements for aromatic carbon–carbon bonds and as a result these new arene compounds could be useful in areas such as drug-design and materials development.
Thus, this work is an important development in this boron-heterocycle area since 5.74 is a versatile intermediate for further synthesis of other unexplored azaborane structures (Scheme 5.24).

\[
\text{BF}_3\text{K} + \text{NH}_2\text{H} \quad \text{(excess)} \quad \xrightarrow{\text{TMS-Cl, MeCN, 80 °C, 57%}} \quad \text{HN} \quad 5.72 \quad \xrightarrow{\text{Schrock cat., (3 mol %), } \text{CH}_2\text{Cl}_2, \text{rt}, 94\%} \quad \text{NH} \quad 5.73
\]

1. n-BuOH  
2. Pd/C (10 mol %) cyclohexene, 60 °C  

\[
5.74 \quad \xrightarrow{\text{R}^1\text{-MgCl, then } E^+} \quad 5.76 \quad 62\% \quad 5.77 \quad 49\% \quad 5.78 \quad 63\%
\]

\[
5.74 \quad \xrightarrow{\text{BCl}_3 \text{ (0.6 equiv.)}} \quad \begin{cases} 5.79 \quad 63\% \\ 5.80 \quad 66\% \end{cases}
\]

**Scheme 5.23** Allyltifluoroborate approach to synthesize 1,2-azaborine 5.75

**Scheme 5.24** Functionalization of 1,2-azaborine 5.74 toward unexplored 1,2-azaborane products

Other miscellaneous reactions with allyl-BF₃K salts include a copper-mediated oxidation to give compound 5.81 (Scheme 5.25) and a dihydroxylation to give trifluoroborate diol 5.82 (Scheme 5.26). In the dihydroxylation example, the authors converted the organic insoluble potassium trifluoroborate product into the more organic soluble tetra-butyl ammonium salt. This facilitated extraction into dichloromethane to perform aqueous washes as a strategy to separate and purify the desired diol product from other reaction species such as osmium salts. This dihydroxylation reaction is interesting because typically β-hydroxy boron containing compounds are not stable, however, the protecting ability of the tetracoordinate trifluoroborate allows isolation of this unique example of a β-heteroatom functionalized boronate.
Scheme 5.25 Cu-mediated chemoselective oxidation of an allyltrifluoroborate salt\textsuperscript{37}

Scheme 5.26 Dihydroxylation of potassium allyltrifluoroborate\textsuperscript{38}

5.7 Summary

The preceding sections have outlined important reactions and preparations of the relatively new allyltrifluoroborate class of stable allylboron reagents. These species provide easy purification of functionalized allyl-boronates via filtration or recrystallization and are isolated as stable and storable white solids which provide superior handling characteristics versus other allylmetalloids. Importantly, despite their superb ability to protect the boron atom toward undesired protodeboronation, allyl-BF\textsubscript{3}K species can be easily transformed in the reaction flask into tricoordinate allylboron compounds capable of undergoing carbonyl allylation. This contrasts drastically with other stabilized tetracoordinate boron compounds such as MIDA-boronates which require elevated temperature and super-stoichiometric aqueous base to deprotect the organoboronate into a reactive tricoordinate form. The following chapters describe new contributions to this area including synthesis of new allyltrifluoroborate salts and their utility in the total synthesis of biologically active depsipeptide natural products.
5.8 References


Chapter 6: A Convergent Organotrifluoroborate-based
Total Synthesis of the Potent Cancer Cell Growth Inhibitory
Depsipeptide Natural Products Kitastatin and Respirantin

6.1 Introduction

As outlined in Chapter 5, our lab has had a long-standing interest in the use of allyl-BF₃K reagents as conveniently storable and easy-to-handle air and moisture stable reagents for allylation of carbonyl groups¹ and related π-electrophiles (e.g., imines,² nitriles,³ and anhydrides⁴). Despite extensive work in this area, including synthesis and use of crotyl-BF₃K species² and related Z⁴ and E-substituted⁵ allyltrifluoroborates, a corresponding prenyltrifluoroborate has not been explored as a carbonyl prenylation reagent.

We were interested in the development of such a prenyl-BF₃K reagent since it should display similarly attractive handling and stability characteristics of organotrifluoroborates and could be used to stereoselectively generate gem-dimethyl functionality commonly found in cytotoxic natural products via γ-carbonyl prenylation (Figure 6.1).

**Figure 6.1** Examples of cytotoxic natural products containing gem-dimethyl fragments potentially accessible via carbonyl prenylation
Among the natural products shown above, we are particularly interested in the antitumoral neo-antimycin \(^6\) depsipeptides kitastain 6.1 and respirantin 6.2. This is due to a general research goal of our laboratory to synthetically study members of the antimycin family to understand the structural basis of their various biological activities (Figure 6.2). Specifically, the neo-antimycin macrocycles 6.1 and 6.2 isolated by Pettit and co-workers in 2007 appeared attractive to study due to their reportedly impressive potent ng/mL cancer cell growth inhibitory activity (Figure 6.3).\(^7\)

**Figure 6.2** Representative biologically active antimycin/neo-antimycin natural products
Figure 6.3 Anti-tumoral activity of neo-antimycin cyclic depsipeptides kitastatin 6.1 and respirantin 6.2 and structural relationship to the (+)-antimycin A natural product family

Structurally, kitastatin and respirantin are related to the well-known (+)-antimycins through a shared threonine connected 3-amino-salicylic acid group, but are differentiated by their larger macrocycle component which contains an unusually high number of ester linkages and a rare gem-dimethyl-β-keto-ester fragment. Kitastatin 6.1 is particularly interesting since it appears to have preferential cytotoxic activity against pancreatic tumor cells, and is one of only two members\(^8\) of the antimycin/neo-antimycin class to contain a des-formamide amino-salicylic acid fragment. The potent anti-tumor activity of 6.1 and 6.2 combined with the potential selectivity of kitastatin for growth inhibition of high-mortality pancreatic tumor cells makes these compounds attractive potential cancer treatment candidates. Unfortunately, further pre-clinical testing on compounds 6.1 and 6.2, including elucidation of their tumor-killing mechanism, is limited by the small quantities that can be obtained via extraction from the natural bacterial source (e.g., 380 L of fermentation broth was required to obtain 2.6 mg of kitastatin).\(^8\) This supply issue, as well as the synthetic challenge presented by this 18-membered ester rich macrocycle have prompted us to target these compounds for synthesis.

Previously, a linear total synthesis of respirantin 6.2\(^9\) by Pettit and co-workers has been reported but the total synthesis of kitastatin 6.1 had not been accomplished.\(^10\) The Pettit
synthesis of 6.2 is also non-ideal considering the lengthy non-convergent step-count, and overall poor yield which includes a low yielding (28%) late-stage β-keto-ester dialkylolation route to the gem-dimethyl-β-keto-ester group (Scheme 6.4). The problems encountered regarding decarboxylation of the β-keto-ester fragment in the Pettit approach inspired us to examine alternative modes to construct this key fragment. Additionally, we considered that a more convergent non-linear strategy to construct the core depsipeptide macrocycle would be advantageous to minimize the overall step-count and thus improve the yield and scalability of these interesting cytotoxic targets.

**Figure 6.4** Summary of the Pettit synthesis of respirantin 6.2 and the decarboxylation issue associated with the β-keto-ester fragment

As a result, our overall synthetic strategy to these natural products was designed as shown in Scheme 6.1. To overcome the decarboxylation issue associated with the β-keto-ester fragment, an alternative strategy was envisaged in which the ketone portion of this moiety would be protected in a reduced alcohol oxidation state and generated after ester bond formation. In this regard, prenylation of aldehyde 6.17 using prenyl-BF₃K reagent 6.18, followed by an oxidative cleavage of the resultant terminal alkene to a gem-dimethyl-β-hydroxy carboxylic acid, could ultimately provide access to the gem-dimethyl-β-keto-ester functionality found in the target natural products. Additionally, a ring-disconnection through the only amide bond in the depsipeptide structure appeared as a logical choice for macrocyclization. To streamline late-stage deprotections, the
resulting linear cyclization precursor 6.11 was designed to allow for possible simultaneous removal of both the C- and N- termini protecting groups using simple acidic conditions prior to macrolactamization. Finally, a convergent approach to 6.11 was envisaged through disconnection of the central ester linkage to give northern and southern fragments 6.12 and 6.13 as synthetic targets.

Scheme 6.1 Proposed synthetic strategy to compounds 6.1 and 6.2
Described below are our results toward development of a potassium prenyltrifluoroborate compound as an easy to handle prenylboron reagent for carbonyl \( \gamma \)-prenylation with specific application to the total synthesis of cytotoxic depsipeptides 6.1 and 6.2. Most of the key results presented herein have been previously published.\(^{11}\)

### 6.2 Results and Discussion

To examine the planned aldehyde prenyl-addition strategy outlined above, a simple and scalable synthesis of prenyltrifluoroborate reagent 6.18 was required (Scheme 6.2). To accomplish this, a slight modification of Miyaura’s palladium catalyzed \( \mathrm{B}_2\mathrm{pin}_2 \) borylation\(^ {12} \) of 1,1-dimethylallyl acetate was used to generate prenylpinacolboronate. Treatment of this crude boryl-ester with KHF\(_2\) resulted in isolation of four grams of reagent 6.18 as a stable, free-flowing white solid.

![Scheme 6.2 Synthesis of potassium prenyltrifluoroborate reagent 6.18](image)

Reaction of 6.18 with \( \text{N-Boc-L-Leucinal} \)\(^{13} \) 6.17 was then evaluated under conditions previously reported for potassium allyl- and crotyltrifluoroborate additions to carbonyl groups (Scheme 6.3). Use of BF\(_3\)·OEt\(_2\)\(^{2a,b} \) proved too acidic and product formation was not observed due to possible N-Boc carbamate deprotection. In contrast, phase-transfer catalyzed conditions\(^ {2c} \) facilitated prenylation of this \( \alpha\)-chiral aldehyde in a 5:1 ratio of diastereomers (crude \(^1\)H NMR) and resulted in a 59% isolated yield of the major \textit{syn} isomer 6.20. Optimal conditions were established on multi-gram scale using a convenient montmorillonite K10 catalyzed protocol\(^ {2d} \) to provide the major \textit{syn} amino-alcohol isomer 6.20 in 74% isolated yield. The observed 85:15 reaction dr was established by \(^1\)H NMR of the crude reaction mixture\(^ {14} \) and the major isomer 6.20 was determined to be \textit{syn} by x-ray crystallography (see Appendix 4). These results represent the first example of an aldehyde prenylation using a prenyltrifluoroborate reagent, and to the best of our
knowledge, is also the only example of a prenylboron reagent addition to a protected \( \alpha \)-aminoaldehyde.\(^{15}\)

\[ \text{Scheme 6.3} \quad \text{Prenylation of N-Boc-L-leucinal with prenyl-BF}_3\text{K 6.18 and possible transition states} \]

Ignoring boat-like structures, four closed chair-like transition states representing Felkin-Ahn and Cornforth aldehyde conformations can be used to rationalize the observed modest \( \text{syn} \) selectivity of prenyltrifluoroborate addition to 6.17 (Scheme 6.3). Overall, the results are most consistent with prenyl addition occurring \( \text{anti} \) to the iso-butyl group in a closed transition state with the aldehyde in a non-polar Felkin-Ahn conformation (transition state 6.22, Scheme 6.3). In contrast, the closed Cornforth \( \text{syn} \) transition state model 6.24 suffers from eclipsing interactions of both the iso-butyl and NHBoc groups and is thus quite unlikely. Alternatively, both polar Felkin-Ahn transition state 6.23 and Cornforth transition state 6.25 predict \( \text{anti} \) stereochemistry. Transition state 6.23 is presumed not to be a major conformation as it suffers from additional eclipsing prenyl methyl group strain of the larger (by relative A-values) iso-butyl group compared to NHBoc in 6.22. Thus, Cornforth transition state 6.25 is presumed to be the reason why \( \text{anti} \) isomer 6.21 is observed in such appreciable quantities. Interestingly, although aldehydes with \( \alpha \)-heteroatom substituents are generally supposed to favour dipole minimized transition states such as 6.23 and 6.25, the observed \( \text{syn} \) preference of this
reaction suggests that this is not a major factor in this reaction. Potentially, this could be due to NHBoc being less electron withdrawing compared to α-chloro or α-hydroxy substituted aldehydes, and suggests that the competing iso-butyl steric factor has a slightly greater impact to produce modest syn control.

Interestingly, an alternative Barbier prenylation of aldehyde 6.17 using prenly-bromide and zinc dust also provided the syn isomer 6.20 as the major product (Scheme 6.4). Although these Barbier conditions are operationally convenient, they result in a lower yield and stereoselectivity versus the prenyltrifluoroborate addition. In contrast, attempted prenylation of N-Boc-L-leucinal with prenlypinacolboronate using lanthanide salt catalysis resulted in poor conversion (Scheme 6.4).

**Scheme 6.4 Alternative prenylations of N-Boc-L-leucinal 6.17**

Thus, a brief survey of the convenient clay-catalyzed reactivity of prenylboron compound 6.18 with other carbonyl containing compounds indicates that this prenyl reagent may be generally useful for γ-prenylations (Scheme 6.5). For example, both ketones and aldehydes are efficiently prenylated under these conditions including good observed levels of substrate controlled diastereoselectivity. Notably, reagent 6.18 has desirable preparation, stability, storage, and handling properties compared to alternative alkyl prenylboron derivatives, and readily reacts with carbonyl groups under mild conditions versus the elevated temperature and long reaction times typically required for prenlypinacolboronate reagent addition.
Scheme 6.5 Carbonyl prenylation using prenyl-BF$_3$K reagent 6.18 under Mont. K10 clay-catalyzed conditions

Importantly, the leucinal aldehyde prenylation strategy was successful in circumventing decarboxylation and enabled synthesis of the southern fragment 6.13 (Scheme 6.6). Thus, acetonide protection of 6.20 and oxidative olefin cleavage gave stable carboxylic acid 6.32 which was coupled using MNBA promoted esterification with 6.19 to give ester 6.33. The ketone group of the southern fragment was then revealed via acid-mediated acetonide deprotection and DMP oxidation of the neo-pentylic alcohol of 6.34 to provide compound 6.13 in an overall 8 steps and 29% yield from N-Boc-L-Leucinal.

Scheme 6.6 Synthesis of the southern fragment 6.13
Synthesis of northern fragment 6.12 began with a large-scale diazotization and acetate ion substitution of L-isoleucine to generate α-acetoxy-acid compound 6.35 (Scheme 6.7). Protection of 6.35 as the tert-butyl ester using Boc-anhydride and DMAP,19 followed by acetate deprotection furnished α-hydroxy ester 6.14. Reaction of 6.14 with acid chloride 6.15 provided ester 6.37 which after deprotection with TBAF was coupled with protected threonine 6.16 under MNBA20 conditions to provide O-TBS protected western fragment 6.39. TBAF induced desilylation provided the desired northern fragment 6.12 in 18% overall yield in 7 steps from L-isoleucine.

Scheme 6.7 Synthesis of northern fragment 6.12

With the northern and southern fragments in hand, deprotection of 6.13 under hydrogenolysis conditions and MNBA promoted coupling with 6.12 provided the linear cyclization precursor 6.11 in 63% yield for two steps (Scheme 6.8). As planned, deprotection of both the Boc-carbamate and t-Bu-ester of compound 6.11 was accomplished using TFA and the resulting crude deprotected TFA salt used directly in the macrocyclization. Under optimized conditions, the key macrolactamization was performed by dual syringe pump addition of crude deprotected TFA salt and Hünig’s base to a stirring room temperature solution of HATU and HOAt with an overall final concentration of 0.005 M. The core macrocyclic depsipeptide 6.10 was thus obtained in
71% yield over 2 steps utilizing a convenient C- and N-terminus bis-deprotection strategy.

**Scheme 6.8 Synthesis of the core macrocycle 6.10**

With the macrocycle secured, our attention turned to attaching the amino-salicylic acid component to complete the synthesis of 6.1 and 6.2 in a step-minimized manner (Scheme 6.9). Deprotection of 6.10 by hydrogenolysis and reaction of the resulting amino-macrocycle intermediate with the acid chloride of commercially available 3-nitrosalicylic acid gave nitroaryl compound 6.40 in 74% yield over 2 steps. Conveniently, 6.40 serves as a single intermediate for completing the synthesis of both natural product targets enabling an alternative approach to install amino-salicylic acid components characteristic of this natural product class. Hydrogenation of the nitro-group of 6.40 afforded 6.1 in 83% yield, thus completing the first total synthesis of the cytotoxic natural product kitastatin 6.1 in 7.9% overall yield in 12 linear steps and only 9 chromatographic purifications from N-Boc-L-leucinal. Finally, reaction of 6.1 under neutral conditions with the recently disclosed N-formylsaccharin reagent\(^\text{21}\) converted the aniline of kitastatin into the target formamide of 6.2 to complete the total synthesis of respirantin in 5.9% yield over 13 linear steps and 10 chromatographic purifications.
6.3 Conclusion

In conclusion, we have completed the total synthesis of the potent depsipeptide neo-antimycin cytotoxic agents kitastatin 6.1 and respirantin 6.2 in a convergent and scaleable manner. Importantly, the application of a prenylation strategy solved the issues associated with decarboxylation of gem-dimethyl-β-keto-acids, and validated the use of prenyltrifluoroborate aldehyde additions to α-chiral gem-dimethyl-β-keto-ester units and the preparation of related prenyl-alcohol derivatives. Overall, our synthesis of these compounds is superior to that of the previous Pettit respirantin synthesis in terms of step-count, yield, and convergency and meets our initial goals in this regard.

In addition, we have initiated a collaboration with Prof. Aaron Schimmer’s laboratory at the Princess Margaret hospital to evaluate our synthetic kitastatin and respirantin compounds against leukemia cancer cell lines previously unexplored with these natural products. The results of these assays show that our synthetic depsipeptides are potent growth inhibitors of these leukemia cells and corroborate the observations of the Pettit
group that these compounds are highly active cytotoxic agents. As a result, we are currently generating synthetic analogs of both the amino-salicylic acid and macrocycle components of these compounds to explore the structural basis of their activity and to evaluate the clinical potential of this class of compounds. Currently, we have obtained some promising results in this area, however, due to confidentiality concerns these data will have to be released at a later time.

6.4 Experimental Section

Copies of $^1$H and $^{13}$C NMR spectra for all compounds prepared above including ROESY, HSQC, and HMBC spectra for kitastatin (6.1) can be found in Appendix 5. Crystallographic information for compound 6.20 can be found in Appendix 4. Solvents distilled fresh under nitrogen atmosphere before use and transferred via syringe using standard techniques unless otherwise stated. THF and Et$_2$O were dried over sodium benzophenone-ketyl before use. Toluene, acetonitrile, and dichloromethane were dried over calcium hydride before use. All chemical manipulations were performed under a N$_2$ atmosphere unless otherwise stated. Bispinacolotodiboron (B$_2$pin$_2$) reagent was generously donated by Frontier Scientific Inc.. All other reagents were purchased from Aldrich or VWR and used as received unless otherwise stated. NMR solvent (CDCl$_3$ with TMS internal standard and CD$_2$Cl$_2$) were purchased from Cambridge Isotopes Lab Inc. and used as received.

All products were characterized by $^1$H NMR and $^{13}$C NMR, IR and HRMS. $^1$H NMR and $^{13}$C NMR were recorded on Varian Mercury 300 MHz, Varian Mercury 400 MHz, Bruker 400 MHz or Agilent 500 MHz spectrometers. Chemical shifts are expressed in ppm values and $^1$H NMR spectra are referenced to Me$_4$Si internal standard of 0.00 ppm for CDCl$_3$ and solvent residual peak of 5.32 for CD$_2$Cl$_2$. $^{13}$C NMR spectra are referenced to residual solvent peak of 77.00 ppm for CDCl$_3$ and a solvent residual peak of 54.00 for CD$_2$Cl$_2$. $^{13}$C NMR spectra for kitastatin (6.1) and respirantin (6.2) were run on an Agilent DD2 500 MHz spectrometer with a HC 5-mm XSens cryogenically cooled probed. Peak multiplicities are designated by the following abbreviations: s, singlet; br.s,
broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; r, rotomers; $J$, coupling constant in Hz. The coupling constant $J$ (Hz) has been rounded to 0.5 Hz for all compounds. If a coupling pattern can be assigned as a combination of multiplicities, then the listed abbreviations are combined to provide an appropriate descriptor for the observed patterns (e.g., dt - doublet of triplets). IR spectra were obtained on a Shimadzu FTIR-8400S with samples loaded as thin films on NaCl plates neat or with CH$_2$Cl$_2$ as indicated. Mass spectra were obtained by the University of Toronto mass spectral facility (AIMS); high resolution mass spectra (HRMS) were recorded on an AEI MS3074 spectrometer. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Flash column chromatography on silica gel (60 Å, 230-400 mesh, obtained from Silicycle Inc.) was performed with reagent grade ethyl acetate and hexanes as eluents. Analytical thin-layer chromatography (TLC) was performed on pre-coated aluminum-backed silica gel plates (Alugram SIL G/UV254 purchased from Rose Scientific Limited or Silicycle Inc.) and visualized using KMnO$_4$, or ninhydrin, or Hannesian’s Stain and heating.
Table 6.1. Synthetic vs. Natural $^{13}$C NMR data for Kitastatin (6.1) and Respirantin (6.2)$^a$

<table>
<thead>
<tr>
<th>Natural$^7$ Kitastatin (1)</th>
<th>Synthetic Kitastatin (1)</th>
<th>Natural$^7$ Respirantin (2)</th>
<th>Synthetic Respirantin (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>208.5</td>
<td>208.7</td>
<td>208.0</td>
<td>208.6</td>
</tr>
<tr>
<td>173.7</td>
<td>173.9</td>
<td>173.7</td>
<td>174.0</td>
</tr>
<tr>
<td>172.3</td>
<td>172.4</td>
<td>172.3</td>
<td>172.4</td>
</tr>
<tr>
<td>171.3</td>
<td>171.5</td>
<td>170.7</td>
<td>171.0</td>
</tr>
<tr>
<td>170.4</td>
<td>170.6</td>
<td>170.4</td>
<td>170.6</td>
</tr>
<tr>
<td>170.2</td>
<td>170.4</td>
<td>170.1</td>
<td>170.3</td>
</tr>
<tr>
<td>168.0</td>
<td>168.2</td>
<td>167.8</td>
<td>168.0</td>
</tr>
<tr>
<td>150.9</td>
<td>150.1</td>
<td>159.3</td>
<td>159.5</td>
</tr>
<tr>
<td>137.0</td>
<td>137.6</td>
<td>150.9</td>
<td>151.2</td>
</tr>
<tr>
<td>119.3</td>
<td>119.5</td>
<td>127.9</td>
<td>128.0</td>
</tr>
<tr>
<td>118.5</td>
<td>118.9</td>
<td>125.0</td>
<td>125.2</td>
</tr>
<tr>
<td>114.6</td>
<td>114.8</td>
<td>120.7</td>
<td>120.9</td>
</tr>
<tr>
<td>113.3</td>
<td>113.3</td>
<td>119.2</td>
<td>119.4</td>
</tr>
<tr>
<td>81.4</td>
<td>81.6</td>
<td>113.3</td>
<td>113.5</td>
</tr>
<tr>
<td>72.9</td>
<td>73.1</td>
<td>81.4</td>
<td>81.6</td>
</tr>
<tr>
<td>72.6</td>
<td>72.8</td>
<td>72.7</td>
<td>72.9</td>
</tr>
<tr>
<td>71.6</td>
<td>71.8</td>
<td>72.6</td>
<td>72.8</td>
</tr>
<tr>
<td>56.0</td>
<td>57.0</td>
<td>71.7</td>
<td>71.9</td>
</tr>
<tr>
<td>55.8</td>
<td>56.0</td>
<td>56.8</td>
<td>57.0</td>
</tr>
<tr>
<td>53.7</td>
<td>53.5</td>
<td>56.0</td>
<td>56.2</td>
</tr>
<tr>
<td>43.3</td>
<td>43.5</td>
<td>54.2</td>
<td>53.5</td>
</tr>
<tr>
<td>39.8</td>
<td>40.0</td>
<td>43.3</td>
<td>43.6</td>
</tr>
<tr>
<td>36.9</td>
<td>37.1</td>
<td>39.7</td>
<td>40.0</td>
</tr>
<tr>
<td>25.7</td>
<td>25.9</td>
<td>36.8</td>
<td>37.1</td>
</tr>
<tr>
<td>25.0</td>
<td>25.13</td>
<td>25.7</td>
<td>25.9</td>
</tr>
<tr>
<td>24.9</td>
<td>25.06</td>
<td>24.9</td>
<td>25.14</td>
</tr>
<tr>
<td>24.3</td>
<td>24.5</td>
<td>24.8</td>
<td>25.07</td>
</tr>
<tr>
<td>23.6</td>
<td>23.8</td>
<td>24.3</td>
<td>24.5</td>
</tr>
<tr>
<td>22.9</td>
<td>23.2</td>
<td>23.6</td>
<td>23.8</td>
</tr>
<tr>
<td>21.6</td>
<td>21.8</td>
<td>23.0</td>
<td>23.2</td>
</tr>
<tr>
<td>21.1</td>
<td>21.3</td>
<td>21.5</td>
<td>21.8</td>
</tr>
<tr>
<td>20.0</td>
<td>20.2</td>
<td>21.0</td>
<td>21.3</td>
</tr>
<tr>
<td>18.3</td>
<td>18.5</td>
<td>20.0</td>
<td>20.2</td>
</tr>
<tr>
<td>16.6</td>
<td>16.8</td>
<td>18.3</td>
<td>18.5</td>
</tr>
<tr>
<td>14.7</td>
<td>14.8</td>
<td>16.6</td>
<td>16.8</td>
</tr>
<tr>
<td>10.6</td>
<td>10.8</td>
<td>14.5</td>
<td>14.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.6</td>
<td>10.8</td>
</tr>
</tbody>
</table>

$^a$ $\delta$ in ppm; CD$_2$Cl$_2$ at 25 °C relative to CH$_2$Cl$_2$ solvent residual peak (54.00)
Potassium-trifluoro(3-methylbut-2-en-1-yl)borate (Compound 6.18, Scheme 6.2):

An argon-flushed flask was charged with Pd(dba)$_2$ monomer (256 mg, 0.445 mmol, 0.01 eq.) and bispinacolotodiboron (12.43 g, 49.0 mmol, 1.1 eq.) and the flask was sealed with a rubber septa and purged with an argon balloon for 5 minutes. Freshly prepared (according to a literature protocol) 2,1,1-dimethylallyl acetate (5.70 g, 44.5 mmol, 1.0 eq.) in DMSO (50 mL) was then added and the flask was purged with an argon balloon for 5 minutes before being placed in a 50 ºC oil bath sealed with an argon balloon. After 24 hours the reaction mixture was cooled to room temperature and diluted with toluene (100 mL) and washed with 50% sat’d NaCl(aq) (4 x 50 mL). The organic layer was dried (MgSO$_4$), filtered through a celite pad and concentrated in vacuo. The crude residue was then dissolved in a solution of 5% ethyl acetate in hexanes (40 mL) and filtered through a plug of silica gel (1.5” tall x 1” wide) topped with celite using a solution of 5% ethyl acetate in hexanes (60 mL) to wash/elute. The filtrate was concentrated in vacuo to provide 8.7 g (99%) of crude prenyl pinacolboronate as a yellow oil (~80% pure by $^1$H NMR).

KHF$_2$ (20.8 g, 266 mmol, 6.0 eq.) was dissolved in water (90 mL) and added to a solution of prenyl pinacolboronate prepared above (8.7 g, 44.4 mmol, 1.0 eq.) in acetone (400 mL) and the mixture was stirred vigorously at room temperature for 2 hours. The mixture was then repeatedly concentrated on a rotovap using additional acetone (4 x 50 mL) until a light yellow solid was obtained. The resulting crude solid was extracted with 50 ºC acetone (6 x 40 mL) with each extract being filtered through a celite pad just thin enough to cover the plug surface and the resulting filtrate was concentrated in vacuo and dried on the vacuum line (20 mins). The residue was then slurried in Et$_2$O (60 mL) with sonication and the solids were filtered off using Et$_2$O (3 x 20 mL) to wash/elute. The collected solids were slurried in hexanes (20 mL) and placed in a 60 ºC oil bath with vigorous stirring for 10 minutes and solids filtered off using room temperature hexanes (10 mL) to wash/elute and the collected powder was dried on a vacuum line (20 minutes) to give 4.0 g (51% yield over 2 steps) of potassium prenyltrifluoroborate reagent 6.18 as a white solid. $^{19}$F NMR (377 MHz, CD$_3$CN) $\delta$ ppm -140.40 (s); $^{11}$B NMR (128 MHz,
CD$_3$CN) δ ppm 4.59 (q, $J$=192.00 Hz); $^1$H NMR (400 MHz, CD$_3$CN) δ ppm 5.22 (1H, tt, $J$=8.0, 1.4 Hz), 1.62 (3H, s), 1.52 (3H, s), 0.89 (2H, br. s.); $^{13}$C NMR (101 MHz, CD$_3$CN) δ ppm 128.34, 126.13, 26.46, 21.67 (br. m), 17.93; HRMS ($m/z$): [M - H]$^-$ for C$_5$H$_9$BF$_3$, calcd, 137.0754; found, 137.0759.

**Tert-butyl ((4S)-5-hydroxy-2,6,6-trimethylocot-7-en-4-yl)carbamate (Compound 6.20, Scheme 6.3):**

Aldehyde 6.17 was prepared according to a literature protocol: L-Leucine-OMe (3.68 g, 15.0 mmol, 1.0 eq.) was dissolved in toluene (55 mL) and cooled to -78 ºC. To this was then added Dibal-H (37.5 mL of a 1M sol’n in hexanes, 37.5 mmol, 2.5 eq.) dropwise over 6 minutes and stirred an additional 5 minutes at -78 ºC before addition of MeOH (4 mL) then sat’d Rochelle’s salt (15 mL) and the mixture removed from the cooling bath. After reaching room temperature the gel-like mixture was diluted with Et$_2$O (600 mL) and sonicated to loosen particulates before addition of water (400 mL) and separation of the phases. The organic layer was dried (MgSO$_4$), filtered through a plug of silica gel (2” tall x 3” wide) topped with celite and concentrated in vacuo to give 2.90 g (90%) of aldehyde 6.17 as a clear oil which was used directly in the next step without further purification within 3 hours of its preparation.

Aldehyde 6.17 (2.90 g, 13.5 mmol, 1.0 eq.) was dissolved in CH$_2$Cl$_2$ (60 mL) and water (15 mL) and montmorrolonite K10 (3.43 g) were added and the mixture cooled to 0 ºC before addition of prenyl-trifluoroborate reagent 6.18 (3.26 g, 18.5 mmol, 1.37 eq.) in a single portion. The reaction mixture was stirred vigorously overnight allowing to warm to room temperature and after 20 hours was filtered through a celite plug (1.5” tall x 1” wide) using CH$_2$Cl$_2$ (150 mL) to wash/elute and the filtrate concentrated in vacuo and crude $^1$H NMR shows no trace of aldehyde starting material 6.17 and an 85:15 ratio of diastereomers. The crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 2.86 g (74%) of the major diastereomer Compound 6.20 (Scheme 6.3) as a colourless
crystalline solid. \([\alpha]_D = -34.8\) (c 0.40, CH\(_2\)Cl\(_2\)); m.p. = 64 - 66 °C (EtOAc/hex); \(R_f = 0.38\) (20% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3446, 3054, 2961, 2871, 1695, 1505, 1367, 1265, 1168; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 5.85 (1H, dd, \(J = 17.5, 11.0\) Hz), 4.95 - 5.17 (2H, m), 4.75 - 5.17 (1H, d, \(J = 9.0\) Hz), 3.89 (1H, td, \(J = 9.0, 6.0\) Hz), 3.20 (1H, d, \(J = 5.0\) Hz), 1.93 (1H, d, \(J = 5.5\) Hz), 1.57 - 1.65 (1H, m), 1.49 - 1.55 (1H, m), 1.43 (9H, s), 1.20 - 1.31 (1H, m), 1.06 (6H, s), 0.87 - 0.97 (6H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 155.4, 144.9, 113.5, 79.0, 78.8, 47.6, 44.9, 41.6, 28.5, 24.7, 24.1, 22.9, 22.4, 22.0; HRMS \((m/z)\): \([M + Na]^+\) for C\(_{16}\)H\(_{31}\)NO\(_3\)Na, calcd, 308.2196; found, 308.2185.

**Barbier prenylation preparation of tert-butyl ((4S)-5-hydroxy-2,6,6-trimethylloct-7-en-4-yl)carbamate (Compound 6.20, Scheme 6.4):**

Aldehyde 6.17 was prepared according to a literature protocol:\(^{13}\) L-Leucine-OMe (3.21 g, 14.9 mmol, 1.0 eq.) was dissolved in DMF (40 mL) and cooled to 0 °C. To this was then added Zn dust (2.92 g, 44.7 mmol, 3.0 eq.) followed by addition of prenyl-bromide (5.72 g, 4.5 mL, 38.4 mmol, 2.58 eq.). Water (13 mL) was then added and the mixture stirred for 16 hours then diluted with ethyl acetate (150 mL) and water (50 mL) and the phases separated. The organic extract was washed with 50% sat’d NaCl(aq) (3 x 25 mL), dried (Na\(_2\)SO\(_4\)), filtered, and the filtrate concentrated \textit{in vacuo} and crude \(^1\)H NMR shows no trace of aldehyde starting material 6.17 and 75:25 ratio of diastereomers. The crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 2.68 g (63%) of the major diastereomer Compound 6.20 (Scheme 6.4) as a colourless crystalline solid.

**\((E)-3,4,4\)-trimethyl-1-phenylhexa-1,5-dien-3-ol (Compound 6.26, Scheme 6.5):**

\((E)-4\)-phenylbut-3-en-2-one (73 mg, 0.5 mmol, 1.0 eq.) was dissolved in CH\(_2\)Cl\(_2\) (1.4 mL) and water (0.1 mL) and montmorrolonite K10 (100 mg) was added followed by addition of prenyl-trifluoroborate reagent 6.18 (176 mg, 1.0 mmol, 2.0 eq.) in a single portion. The reaction mixture was stirred
vigorously overnight at room temperature and after 14 hours was filtered through a celite plug (1 cm tall x 1 cm wide) using CH₂Cl₂ (30 mL) to wash/elute and the filtrate concentrated in vacuo and the crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) to provide 98 mg (90%) of Compound 6.26 (Scheme 6.5) as a clear oil. Rf = 0.42 (20% EtOAc/hexanes); IR (neat, cm⁻¹) 3482(br), 3082, 3060, 3025, 2976, 2938, 2875, 1636, 1599, 1495, 1447, 1369, 1098, 1071, 973, 913; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.35 - 7.43 (2H, m), 7.28 - 7.34 (2H, m), 7.18 - 7.25 (1H, m), 6.59 (1H, d, J=16.0 Hz), 6.41 (1H, d, J=16.0 Hz), 6.03 (1H, dd, J=17.5, 11.0 Hz), 5.03 - 5.20 (2H, m), 1.66 (1H, s), 1.34 (3H, s), 1.11 (6H, s); ¹³C NMR (101 MHz, CDCl₃) δ ppm 144.9, 137.2, 134.5, 128.6, 128.1, 127.3, 126.4, 114.0, 76.4, 44.3, 23.8, 22.6, 21.9; HRMS (m/z): [M – H₂O + H]⁺ for C₁₅H₁₉, calcd, 199.14868; found, 199.14825.

1-(2-methylbut-3-en-2-yl)cyclohexanol (Compound 6.27, Scheme 6.5):

Cyclohexanone (49 mg, 0.5 mmol, 1.0 eq.) was dissolved in CH₂Cl₂ (1.4 mL) and water (0.1 mL) and montmorrolonite K10 (100 mg) was added followed by addition of prenyl-trifluoroborate reagent 6.18 (176 mg, 1.0 mmol, 2.0 eq.) in a single portion. The reaction mixture was stirred vigorously overnight at room temperature and after 16 hours was filtered through a celite plug (1 cm tall x 1 cm wide) using CH₂Cl₂ (30 mL) to wash/elute and the filtrate concentrated in vacuo and the crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) to provide 66 mg (78%) of Compound 6.27 (Scheme 6.5) as a clear oil. Rf = 0.52 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3499, 3081, 2935, 2857, 1476, 1381, 1360, 1258, 1142, 936, 910; ¹H NMR (400 MHz, CDCl₃) δ ppm 6.00 (1H, dd, J=17.5, 11.0 Hz), 5.07 (1H, dd, J=11.0, 1.5 Hz), 5.03 (1H, dd, J=17.5, 1.5 Hz), 1.49 - 1.71 (8H, m), 1.33 - 1.45 (2H, m), 1.20 - 1.26 (1H, m), 1.03 (6H, s); ¹³C NMR (100 MHz, CDCl₃) δ ppm 145.5, 113.3, 74.4, 44.2, 31.3, 25.8, 24.7, 21.9, 21.8; HRMS (m/z): [M – H₂O + H]⁺ for C₁₁H₁₉, calcd, 151.14868; found, 151.14864.
(±)-anti-3-methyl-1-(2-methylbut-3-en-2-yl)cyclohexanol (Compound 6.28, Scheme 6.5):

3-Me-cyclohexanone (56 mg, 0.5 mmol, 1.0 eq.) was dissolved in CH₂Cl₂ (1.4 mL) and water (0.1 mL) and montmorillonite K10 (100 mg) was added followed by addition of prenyl-trifluoroborate reagent 6.18 (176 mg, 1.0 mmol, 2.0 eq.) in a single portion. The reaction mixture was stirred vigorously overnight at room temperature and after 16 hours was filtered through a celite plug (1 cm tall x 1 cm wide) using CH₂Cl₂ (30 mL) to wash/elute and the filtrate concentrated in vacuo and crude ¹H NMR shows a 9:1 ratio of diastereomers. The crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) to provide 76 mg (83%) of Compound 6.28 (Scheme 6.5) as a clear oil. R₉= 0.53 (20% EtOAc/hexanes); IR (neat, cm⁻¹) 3479, 3081, 2948, 2927, 2866, 2843, 1636, 1456, 1414, 1367, 1263, 1146, 1007, 983; ¹H NMR (400 MHz, CDCl₃) δ ppm 6.00 (1H, dd, J=17.5, 11.0 Hz), 5.07 (1H, dd, J=11.0, 1.5 Hz), 5.02 (1H, dd, J=17.5, 1.5 Hz), 1.51 - 1.75 (6H, m), 1.24 - 1.38 (2H, m), 1.23 (1H, s), 1.03 (6H, s), 0.86 (3H, d, J=6.5 Hz), 0.66 - 0.79 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ ppm 145.5, 113.4, 75.1, 44.1, 40.2, 34.5, 30.9, 28.0, 24.7, 22.8, 21.8, 21.7; HRMS (m/z): [M + NH₄]⁺ for C₁₂H₂₆NO, calcd, 200.20144; found, 200.20250.

(±)-syn-2-methoxy-1-(2-methylbut-3-en-2-yl)cyclohexanol (Compound 6.29, Scheme 6.5):

2-methoxy-cyclohexanone (64 mg, 0.5 mmol, 1.0 eq.) was dissolved in CH₂Cl₂ (1.4 mL) and water (0.1 mL) and montmorillonite K10 (100 mg) was added followed by addition of prenyl-trifluoroborate reagent 6.18 (176 mg, 1.0 mmol, 2.0 eq.) in a single portion. The reaction mixture was stirred vigorously overnight at room temperature and after 16 hours was filtered through a celite plug (1 cm tall x 1 cm wide) using CH₂Cl₂ (30 mL) to wash/elute and the filtrate concentrated in vacuo and crude ¹H NMR shows ~65% conversion and a 15:1 ratio of diastereomers. The crude residue was purified by flash chromatography through silica gel using ethyl
acetate in hexanes to elute (gradient elution 0-100 % EtOAc) to provide 48 mg (48%) of Compound 6.29 (Scheme 6.5) as a clear oil. Rf = 0.50 (20% EtOAc/hexanes); IR (neat, cm⁻¹) 3525, 3081, 2969, 2930, 2888, 2862, 2820, 1636, 1446, 1377, 1373, 1196, 1159, 1095, 1066, 981; ¹H NMR (400 MHz, CDCl₃) δ ppm 6.05 (1H, dd, J=17.5, 11.0 Hz), 4.91 - 5.17 (2H, m), 3.27 - 3.29 (1H, m), 3.26 (3H, s), 1.72 - 1.85 (2H, m), 1.56 - 1.70 (2H, m), 1.29 - 1.52 (4H, m), 1.24 (1H, s), 1.10 (6H, s); ¹³C NMR (100 MHz, CDCl₃) δ ppm 145.0, 111.8, 79.0, 73.4, 54.1, 43.1, 26.5, 22.6, 22.4, 20.6, 19.9, 17.8; HRMS (m/z): [M + NH₄]⁺ for C₁₂H₂₆NO₂, calcd, 216.19635; found, 216.19641.

(2S,3R)-2-((tert-butyldimethylsilyl)oxy)-4,4-dimethylhex-5-en-3-ol (Compound 6.30, Scheme 6.5):

Aldehyde derived from (S)-ethyl-lactate [(S)-2-((tert-butyldimethylsilyl)oxy)propanal] was prepared according to a literature protocol:²³ [(S)-2-((tert-butyldimethylsilyl)oxy)propanal (94 mg, 0.5 mmol, 1.0 eq.) was dissolved in CH₂Cl₂ (1.4 mL) and water (0.1 mL) and montmorrolonite K10 (100 mg) was added followed by addition of prenyl-trifluoroborate reagent 6.18 (114 mg, 0.65 mmol, 1.3 eq.) in a single portion. The reaction mixture was stirred vigorously overnight at room temperature and after 14 hours was filtered through a celite plug (1 cm tall x 1 cm wide) using CH₂Cl₂ (30 mL) to wash/elute and the filtrate concentrated in vacuo and crude ¹H NMR shows no trace of aldehyde starting material and an 82:18 ratio of diastereomers. The crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute to provide 99 mg (76%) of Compound 6.30 (Scheme 6.5) as an inseparable 5:1 mixture of diastereomers (clear oil). [α]D = -21.9 (c 0.064, CH₂Cl₂); Rf = 0.69 (40% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3584, 3082, 2957, 2930, 2858, 1636, 1472, 1388, 1078, 837; ¹H NMR (400 MHz, CDCl₃) δ ppm major isomer: 6.04 (1H, dd, J=18.0, 10.5 Hz), 4.99 - 5.04 (1H, m), 4.93 - 4.99 (1H, m), 3.91 (1H, qd, J=6.5, 2.5 Hz), 3.40 (1H, dd, J=2.5, 2.5 Hz), 2.31 (1H, d, J=2.0 Hz), 1.04 - 1.12 (9H, m), 0.89 (9H, s), 0.04 - 0.07 (6H, m); ¹³C NMR (101 MHz, CDCl₃) δ ppm major isomer: 145.0, 111.4, 82.0, 69.6, 39.7, 25.9, 25.8, 25.5, 23.8, 17.8, -4.5, -4.8; HRMS (m/z): [M + H]⁺ for C₁₄H₃₁O₂Si, calcd, 259.20933; found, 259.20877.
(4S)-tert-butyl 4-isobutyl-2,2-dimethyl-5-(2-methylbut-3-en-2-yl)oxazolidine-3-carboxylate (Compound 6.31, Scheme 6.6):

Amino-alcohol compound 6.20 (2.24 g, 7.84 mmol, 1.0 eq.) was dissolved in CH₂Cl₂ (65 mL) and anhydrous Na₂SO₄ (1.18 g) was added followed by addition of 2,2-dimethoxypropane (4.06 g, 4.79 mL, 39.0 mmol, 5.0 eq.) and p-TsOH·H₂O (149 mg, 0.78 mmol, 0.1 eq.). The reaction mixture was stirred at room temperature for 18 hours then diluted with CH₂Cl₂ (75 mL) and washed with sat’d NaHCO₃(aq) (50 mL). The organic extract was dried (MgSO₄), filtered through a plug of silica gel (1.5” tall x 1.5” wide) topped with celite using EtOAc (100 mL) to wash/elute and the filtrate concentrated in vacuo to give 2.38 g (93%) of Compound 6.31 (Scheme 6.6) as a clear oil. \([\alpha]_D= -2.0 (c 0.50, \text{CH}_2\text{Cl}_2); R_f= 0.66 \ (20\% \text{EtOAc/hexanes}); \text{IR} \ \ (\text{neat}, \ \text{cm}^{-1}) 3413, 3085, 2979, 2872, 1646, 1448, 1390, 1258, 1092, 1033; \ 1^H \text{NMR} \ (400 \text{MHz, CDCl}_3) \ \delta \ \text{ppm} \ 5.83 \ (1H, dd, \ J=17.5, 10.5 \text{ Hz}), 5.04 - 5.08 \ (1H, m), 5.02 - 5.03 \ (1H, m), 3.82 \ (1H, br. s.), 3.60 \ (1H, d, \ J=2.5 \text{ Hz}), 1.63 \ (3H, br. s.), 1.42 - 1.58 \ (15H, m), 1.03 \ (3H, s), 1.00 \ (3H, s), 0.90 - 0.95 \ (6H, m); \ 13^C \text{NMR} \ (100 \text{MHz, CDCl}_3) \ \delta \ \text{ppm} \ 151.4, 144.3, 113.0, 94.3, 89.0, 79.6, 56.4, 45.5, 40.7, 28.5, 24.7, 24.2, 24.0, 22.2, 21.3; \ \text{HRMS} \ (m/z): \ [M + H]^+ \ \text{for C}_{19}H_{36}NO_3, \ \text{calcd, 326.26952}; \ \text{found, 326.26850}.

2-((4S)-3-(tert-butoxycarbonyl)-4-isobutyl-2,2-dimethyloxazolidin-5-yl)-2-methylpropanoic acid (Compound 6.32, Scheme 6.6):

Acetonide compound 6.31 (2.17 g, 6.66 mmol, 1.0 eq.) was dissolved in CH₂Cl₂ (10 mL) and N-methylmorpholine-N-oxide (1.95 g, 16.66 mmol, 2.5 eq.) was added followed by addition of OsO₄ (0.90 mL of a 4 wt% sol’n in H₂O). The reaction mixture was stirred vigorously at room temperature for 18 hours then diluted with CH₂Cl₂ (100 mL) and washed with 50% sat’d Na₂S₂O₅(aq) (40 mL). The organic extract was dried (MgSO₄), filtered and concentrated in vacuo to give a quantitative yield of the crude intermediate diol as a clear oil. This crude diol was dissolved in acetone (30 mL) and water (8 mL) and NaIO₄ (2.0
eq., 13.32 mmol, 2.85 g) was added and the mixture stirred at room temperature for 30 minutes. The reaction mixture was then partitioned between EtOAc (100 mL) and water (50 mL) and the phases were separated. The aqueous phase was extracted again with EtOAc (50 mL) and the organic extracts were combined and washed with sat’d NaCl(aq) (20 mL), dried (MgSO₄), filtered and concentrated in vacuo to give 2.2 g (quant. yield) of crude aldehyde as a slightly yellow oil.

The aldehyde thus obtained above (2.2 g, 6.66 mmol, 1.0 eq.) was dissolved in t-BuOH (35 mL) and water (15 mL) and NaH₂PO₄·H₂O (3.68 g, 26.64 mmol, 4.0 eq.) was added followed by addition of 2-Me-2-Butene (3.74 g, 5.65 mL, 53.3 mmol, 8.0 eq.) and NaClO₂ (4.22 g of 80% pure reagent, 46.62 mmol, 7.0 eq.) in that order and the mixture was stirred at room temperature. After 18 hours t-BuOH was removed on the rotovap before addition of water (80 mL) and CH₂Cl₂ (100 mL) and the phases were separated. The aqueous phase was further extracted with CH₂Cl₂ (2 x 50 mL) and the organic extracts were combined and washed with sat’d NaCl(aq) (40 mL), dried (MgSO₄), filtered and concentrated in vacuo. The resulting crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) giving 1.73 g (75% yield) of Compound 6.32 (Scheme 6.6) as a light yellow solid. [α]D= + 6.2 (c 0.16, MeOH); m.p.= 82 – 84 ºC (CH₂Cl₂); Rf= 0.13 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3054, 2985, 2962, 2937, 2873, 2305, 1700, 1467, 1392, 1368, 1176, 1094; ¹H NMR (300 MHz, CDCl₃) δ ppm (missing RCO₂-H) 4.06 - 4.12 (1H, m), 3.98 (1H, d, J=8.0 Hz), 1.63 (3H, s), 1.49 - 1.59 (6H, m), 1.47 (9H, s), 1.21 (3H, s), 1.18 (3H, s), 0.89 - 0.98 (6H, m); ¹³C NMR (75 MHz, CDCl₃) δ ppm 181.8, 151.3, 94.8, 86.3, 80.0, 56.4, 46.5, 45.2, 28.5, 24.7, 24.1, 21.6, 21.3, 20.2; HRMS (m/z): [M + H]+ for C₁₈H₃₂NO₅, calcd, 344.24370; found, 344.24467, [M - H]- for C₁₈H₃₂NO₅, calcd, 342.22805; found, 342.22783.
(4S)-tert-butyl 5-(1-(((S)-1-(benzyloxy)-4-methyl-1-oxopentan-2-yl)oxy)-2-methyl-1-oxopropan-2-yl)-4-isobutyl-2,2-dimethylxazolidine-3-carboxylate (Compound 6.33, Scheme 6.6):

Compound 6.19 was prepared by benzylative alkylation of (S)-(-)-2-hydroxyisocaproic acid according to a literature protocol. Acid compound 6.32 (989 mg, 2.88 mmol, 1.0 eq.) was dissolved in CH₂Cl₂ (5 mL) and MNBA (1.39 g, 4.0 mmol, 1.4 eq.), DMAP (176 mg, 1.44 mmol, 0.5 eq.) and Et₃N (1.16 g, 1.60 mL, 11.5 mmol, 4.0 eq.) were added in that order and stirred together at room temperature for 15 minutes before addition of alcohol compound 6.19 (1.28 g, 5.76 mmol, 2.0 eq.) as a solution in CH₂Cl₂ (1 mL). The reaction mixture was stirred at room temperature for 40 hours then diluted with CH₂Cl₂ (75 mL) and washed with sat’d NaHCO₃(aq) (25 mL). The organic extract was dried (MgSO₄), filtered and concentrated in vacuo and the resulting crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc). This provided 1.47 g (93% yield) of Compound 6.33 (Scheme 6.6) as a yellow oil. [α]D= - 23.5 (c 0.23, CH₂Cl₂); Rf= 0.50 (20% EtOAc/hexanes); IR (neat, cm⁻¹) 2977, 2960, 2935, 2873, 1814, 1727, 1708, 1456, 1373, 1258; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.27 - 7.43 (5H, m), 5.10 - 5.22 (2H, m), 5.06 (1H, dd, J=9.0, 4.0 Hz), 4.13 (1H, d, J=2.5 Hz), 3.83 - 4.02 (1H, br.s), 1.70 - 1.87 (2H, m), 1.53 - 1.65 (6H, m), 1.43 - 1.50 (13H, m), 1.22 (3H, s), 1.13 (3H, s), 0.88 - 0.99 (12H, m); ¹³C NMR (100 MHz, CDCl₃) δ ppm 175.8, 170.4, 151.3, 135.4, 128.5, 128.3, 128.2, 94.6, 86.2, 79.8, 71.3, 66.8, 56.2, 48.2, 46.6, 45.4, 39.6, 28.5, 24.7, 24.6, 24.0, 23.0, 21.7, 21.6, 21.4, 19.4, 19.2; HRMS (m/z): [M + H]+ for C₃₁H₅₀NO₇, calcd, 548.3581; found, 548.3575.
(4S)-(S)-1-(benzyl oxy)-4-methyl-1-oxopentan-2-yl 4-((tert-butoxycarbonyl)amino)-3-hydroxy-2,2,6-trimethyl heptanoate (Compound 6.34, Scheme 6.6):

Acetonide ester compound 6.33 (616 mg, 1.12 mmol, 1.0 eq.) was dissolved in EtOAc (20 mL) and 3M HCl(aq) (10 mL) was added and the mixture stirred at room temperature overnight. After 18 hours, the reaction mixture was diluted with EtOAc (100 mL) and washed with water (20 mL) then washed with sat’d NaHCO₃(aq) (2 x 20 mL) and the organic extract was dried (Na₂SO₄), filtered and concentrated in vacuo. The resulting crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) to provide 412 mg (72% yield) of Compound 6.34 (Scheme 6.6) as a clear oil. [α]D = -40.9 (c 0.32, MeOH); Rp = 0.41 (20% EtOAc/hexanes); IR (neat, cm⁻¹) 3493 (br), 3445, 2959, 2934, 2872, 1738, 1862, 1653, 1506, 1471, 1456, 1368, 1271, 1253, 1215, 1169, 1126; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.30 - 7.46 (5H, m), 5.22 - 5.32 (2H, m), 5.09 - 5.15 (1H, m), 4.96 (1H, d, J=10.0 Hz), 3.82 - 3.92 (2H, m), 3.70 (1H, d, J=6.5 Hz), 1.76 - 1.85 (1H, m), 1.69 - 1.73 (1H, m), 1.63 - 1.67 (2H, m), 1.51 - 1.61 (2H, m), 1.42 (9H, s), 1.28 (3H, s), 1.21 (3H, s), 0.89 - 0.98 (12H, m); ¹⁳C NMR (100 MHz, CDCl₃) δ ppm 176.1, 172.0, 155.4, 134.7, 128.7 (s, 2C), 128.4, 78.8, 77.8, 70.3, 67.7, 47.4, 44.6, 39.7, 36.6, 28.4, 24.7, 24.6, 23.3, 23.0, 22.9, 22.5, 21.5, 18.7; HRMS (m/z): [M + H]⁺ for C₂₈H₄₆NO₇, calcd, 508.32743; found, 508.32815.

(S)-1-(benzyl oxy)-4-methyl-1-oxopentan-2-yl 4-((tert-butoxycarbonyl)amino)-2,2,6-trimethyl-3-oxo heptanoate (Compound 6.13, southern fragment, Scheme 6.6):

Amino-alcohol compound 6.34 (705 mg, 1.39 mmol, 1.0 eq.) was dissolved in CH₂Cl₂ (15 mL non-distilled reagent grade) and pyridine (121 mg, 0.12 mL, 1.53 mmol, 1.1 eq.) was added followed by addition of Dess-Martín Periodinane reagent (2.95 g, 6.95 mmol, 5.0 eq.) in 4 equal portions over 5 minutes. The reaction mixture was stirred at room temperature for 14 hours then diluted with CH₂Cl₂ (80 mL) and washed with sat’d NaHCO₃(aq) (2 x 20 mL) and the organic extract was dried (MgSO₄), filtered and
concentrated in vacuo. The resulting crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) to provide 583 mg (83% yield) of Compound 6.13 (Scheme 6.6) as a clear oil. \([\alpha]_D = -43.8 \, (c \, 0.55, \text{CH}_2\text{Cl}_2)\); \(R_f = 0.50 \, (20\% \text{EtOAc/hexanes})\); IR (\text{CH}_2\text{Cl}_2, \text{cm}^{-1}) 3343, 2959, 2936, 2872, 1744, 1720, 1709, 1520, 1472, 1456, 1391, 1368, 1252, 1169, 1140, 1126, 1078; \(^1\text{H NMR (400 MHz, CDCl}_3\) \(\delta \, \text{ppm} \, 7.29 - 7.45 (5\text{H, m}), 6.09 (1\text{H, d, }J=10.0 \, \text{Hz}), 5.15 - 5.28 (2\text{H, m}), 5.09 (1\text{H, dd, }J=10.0, 4.0 \, \text{Hz}), 4.53 (1\text{H, td, }J=10.0, 4.0 \, \text{Hz}), 1.64 - 1.81 (4\text{H, m}), 1.58 - 1.63 (1\text{H, m}), 1.45 - 1.48 (1\text{H, m}), 1.41 (9\text{H, s}), 1.40 (3\text{H, s}), 1.36 (3\text{H, s}), 0.83 - 0.96 (12\text{H, m}); \(^{13}\text{C NMR (100 MHz, CDCl}_3\) \(\delta \, \text{ppm} \, 209.2, 172.6, 171.4, 156.0, 135.0, 128.7, 128.6, 128.3, 79.5, 71.3, 67.3, 56.2, 53.4, 41.7, 39.8, 28.3, 24.6, 24.4, 23.7, 23.5, 23.0, 21.25, 21.22, 20.8; \)) HRMS (\(m/z\)): [M + Na]^+ \, \text{for} \, C_{28}H_{43}NO_7Na, \text{calcd}, 528.2931; \text{found}, 528.2953.

\((2S,3S)-2\text{-acetoxy-3-methylpentanoic acid (Compound 6.35, Scheme 6.7):}\)

L-isoleucine (11.79 g, 90.0 mmol, 1.0 eq.) and NaOAc (11.07 g, 135.0 mmol, 1.50 eq.) were suspended in glacial acetic acid (180 mL) and treated with solid NaNO\(_2\) (5.54 g, 68.0 mmol, 1.51 eq.) portion-wise over 50 minutes at room temperature in 12 equal portions allowing the resulting yellow gas to dissipate between additions. The mixture was then stirred at room temperature for a further 3 hours before dilution with ethyl acetate (400 mL) and water (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (300 mL) and the organic extracts were combined and washed with water (100 mL) then sat’d NaCl(aq) (50 mL), dried (MgSO\(_4\)), filtered and concentrated under an air stream to give 13.9 g of a yellow oil contaminated with residual acetic acid. This crude residue was treated with Et\(_2\)O (100 mL) to give a cloudy mixture which was filtered through a celite pad using Et\(_2\)O (50 mL) to wash/elute and the filtrate concentrated under an air stream to give 11.85 g (76% yield) of Compound 6.35 (Scheme 6.7) free of acetic acid as a yellow oil. \([\alpha]_D = -16.7 \, (c \, 0.27, \text{MeOH})\); \(R_f = 0.20 \, (5\% \text{MeOH/CH}_2\text{Cl}_2)\); IR (neat, cm\(^{-1}\)) 3122 (br.), 2969, 2939, 2881, 2642, 2562, 2368, 1745, 1720, 1648, 1465, 1424, 1374, 1231, 1046; \(^1\text{H NMR (400 MHz, CDCl}_3\) \(\delta \, \text{ppm} \, 11.51 (1\text{H, br. s.}), 4.95 (1\text{H, d, }J=4.5 \, \text{Hz}), 2.15 (3\text{H, s}), 1.95 - 2.07 (1\text{H, m}), 1.47 - 1.61 (1\text{H, m}), 1.27 - 1.41 (1\text{H, m}), 1.01 (3\text{H, d, }J=7.0 \, \text{Hz}).\)
Hz), 0.94 (3H, t, J=7.5 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 175.6, 170.9, 75.8, 36.4, 24.4, 20.4, 15.2, 11.4; HRMS ($m/z$): [M - H] for C$_8$H$_{13}$O$_4$, calcd, 173.0819; found, 173.0822.

**(2S,3S)-tert-butyl 2-acetoxy-3-methylpentanoate (Compound 6.36, Scheme 6.7):**

Compound 6.35 (3.56 g, 26.9 mmol, 1.0 eq.), Boc$_2$O (23.5 g, 108 mmol, 4.0 eq.) and DMAP (1.64 g, 13.4 mmol, 0.5 eq.) were combined in $t$-BuOH (8.0 mL) in that order and stirred at room temperature. After 72 hours, $t$-BuOH was removed on the rotovap and the crude residue partitioned between ethyl acetate (300 mL) and sat’d NaHCO$_3$(aq) and the phases were separated. The organic layer was washed with 5% aq. citric acid (75 mL), then with water (75 mL) and finally with sat’d NaCl(aq) (50 mL). The organic layer was then dried (MgSO$_4$) and filtered through a 2 cm tall x 3 cm wide silica plug topped with celite and concentrated in vacuo to provide 5.99 g (96% yield) of Compound 6.36 (Scheme 6.7) as an orange oil. [$\alpha$]$_D$ = -26.8 (c 0.8, MeOH); R$_f$ = 0.54 (20% EtOAc/ hexanes); IR (neat, cm$^{-1}$) 2969, 2939, 2980, 1739, 1467, 1456, 1370, 1233, 1162, 1045, 848; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 4.77 (1H, d, $J$=4.5 Hz), 2.12 (3H, s), 1.88 - 1.99 (1H, m), 1.47 (9H, s), 1.19 - 1.41 (2H, m), 0.89 - 1.00 (6H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 170.7, 168.7, 81.8, 76.6, 36.6, 28.0, 24.7, 20.7, 15.3, 11.6; LRMS ($m/z$): [M + H]$^+$ for C$_{12}$H$_{25}$O$_4$, calcd, 231.16; found, 231.2.

**(2S,3S)-tert-butyl 2-hydroxy-3-methylpentanoate (Compound 6.14, Scheme 6.7):**

K$_2$CO$_3$ (5.93 g, 43 mmol, 3.0 eq.) was dissolved in a solution of water (40 mL) and MeOH (30 mL) and added to (2S,3S)-tert-butyl 2-acetoxy-3-methylpentanoate (Compound 6.36, 3.30 g, 14.3 mmol, 1.0 eq.) and the mixture was stirred at room temperature overnight. After 18 hours MeOH was removed on the rotovap and the aqueous phase was extracted with CH$_2$Cl$_2$ (100 mL) then again with CH$_2$Cl$_2$ (50 mL) and the organic extracts were combined and dried (MgSO$_4$), filtered and concentrated in vacuo to give 2.39 g (89% yield) of Compound 6.14 (Scheme 6.7) as an orange oil. [$\alpha$]$_D$ = -10.3 (c 0.35, MeOH); R$_f$ = 0.36 (20% EtOAc/ hexanes); IR
(neat, cm$^{-1}$) 3519, 2968, 2937, 2878, 1726, 1646, 1459, 1395, 1369, 1276, 1249, 1164, 1149, 1074, 1045, 849; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 3.95 (1H, dd, $J$=6.0, 3.5 Hz), 2.78 (1H, d, $J$=5.5 Hz), 1.70 - 1.84 (1H, m), 1.49 (9H, s), 1.33 - 1.44 (1H, m), 1.21 - 1.31 (1H, m), 0.98 (3H, d, $J$=7.0 Hz), 0.91 (3H, t, $J$=7.5 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 174.2, 82.3, 74.7, 39.2, 28.1, 23.9, 15.3, 11.9; HRMS (m/z): [M + Na]$^+$ for C$_{10}$H$_{20}$O$_3$Na, calcd, 211.1328; found, 211.1310.

(2S,3S)-tert-butyl-2-(((S)-2-((tert-butyldimethylsilyl)oxy)propanoyloxy)-3-methylpentanoate (Compound 6.37, Scheme 6.7):

Compound 6.15 was prepared according to a literature procedure.$^{25}$ Lithium-(L)-Lactate (2.88 g, 30 mmol, 1.0 eq.) in DMF (30 mL) was treated with TBS-Cl (9.04 g, 60 mmol, 2.0 eq.) and imidazole (8.17 g, 120 mmol, 4.0 eq.) and the mixture was stirred at room temperature overnight.

After 18 hours the reaction mixture was diluted with ethyl acetate (150 mL) and washed with 50% sat’d NaCl(aq) (4 x 50 mL). The organic layer was dried (MgSO$_4$), filtered and concentrated in vacuo to give 8.56 g (90% yield) of di-TBS protected (L)-lactic acid as a clear oil with >90% $^1$H NMR purity. This material was used immediately in the next step without further purification.

Freshly prepared di-TBS protected (L)-lactic acid compound prepared above (7.10 g, 22.3 mmol, 1.4 eq.) was dissolved in CH$_2$Cl$_2$ (60 mL) and cooled to 0 °C before addition of DMF (325 mg, 0.35 mL, 4.45 mmol, 0.28 eq.) followed by addition of a solution of oxalyl chloride (3.03 g, 2.05 mL, 23.9 mmol, 1.5 eq.) in CH$_2$Cl$_2$ (15 mL) dropwise over 10 minutes. The mixture was stirred at 0 °C for 90 minutes then warmed to room temperature and stirred for an additional 1 hour before removal of volatiles on the rotovap followed by dissolution of the crude residue in CH$_2$Cl$_2$ (25 mL) and re-concentrating in vacuo to give compound 6.15. To this crude acid-chloride was then added a solution of (2S,3S)-tert-butyl 2-hydroxy-3-methylpentanoate (Compound 6.36, 3.0 g, 15.9 mmol, 1.0 eq.) as a solution in a mixture of CH$_2$Cl$_2$ (30 mL) and pyridine (40 mL) dropwise by addition funnel under N$_2$ at room temperature. After stirring for 14 hours the reaction mixture was diluted with THF (150 mL) and filtered through a celite
plug and the filtrate was concentrated in vacuo. The crude material was dissolved in ethyl acetate (200 mL) and washed with water (40 mL) then sat’d NaHCO\textsubscript{3}(aq) (40 mL) then sat’d NaCl(aq) (25 mL) and dried (MgSO\textsubscript{4}), filtered and concentrated in vacuo. The resulting crude material was purified by flash column chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) providing 4.18 g (70% yield) of Compound 6.37 (Scheme 6.7) as a yellow oil. [\(\alpha\)]\textsubscript{D}= -31.2 (c 0.25, CH\textsubscript{2}Cl\textsubscript{2}); R\textsubscript{f}= 0.62 (20% EtOAc/ hexanes); IR (neat, cm\textsuperscript{-1}) 2964, 2935, 2883, 2859, 1765, 1748, 1463, 1369, 1062, 977, 834, 779; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 4.80 (1H, d, \(J=5.0\) Hz), 4.40 (1H, q, \(J=7.0\) Hz), 1.89 - 2.04 (1H, m), 1.49 - 1.57 (1H, m), 1.45 - 1.47 (12H, m), 1.25 - 1.36 (1H, m), 0.97 (3H, d, \(J=7.0\) Hz), 0.92 - 0.95 (3H, m), 0.91 (9H, s), 0.12 (3H, s), 0.09 (3H, s); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 173.7, 168.3, 81.8, 76.7, 68.0, 36.6, 28.0, 25.7, 24.6, 21.4, 18.3, 15.3, 11.6, -4.9, -5.3; HRMS (m/z): [M + H]\textsuperscript{+} for C\textsubscript{19}H\textsubscript{39}O\textsubscript{5}Si, calcd, 375.2561; found, 375.2561.

**\((2S,3S)\text{-}\text{tert-bu}l y 2-\text{((S)\text{-}2\text{-}hydroxypropanoy}l)\text{oxy}}\text{-3\text{-}methylpentanoate (Compound 6.38, Scheme 6.7):**

A flask containing compound 6.37 (4.0 g, 10.68 mmol, 1.0 eq.) [neat] was cooled to 0 °C and TBAF (42.0 mL of a 1M sol’n in THF, 42.3 mmol, 3.93 eq.) was added by syringe over 2 minutes. After 1 hour at 0 °C the mixture was warmed to room temperature and stirred for 1 hour before addition of water (100 mL) and stirred for an additional 1 hour. The reaction mixture was then extracted with ethyl acetate (200 mL then again with 100 mL) and the organic extracts were combined and washed with water (40 mL) then sat’d NaCl(aq) (30 mL), dried (MgSO\textsubscript{4}), filtered and concentrated in vacuo. The crude residue thus obtained was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) to provide 1.67 g (62%) of Compound 6.38 (Scheme 6.7) as a yellow oil. [\(\alpha\)]\textsubscript{D}= + 2.9 (c 0.56, CH\textsubscript{2}Cl\textsubscript{2}); R\textsubscript{f}= 0.30 (20% EtOAc/hexanes); IR (neat, cm\textsuperscript{-1}) 3463 (br), 2977, 2938, 2880, 1740, 1735, 1457, 1369, 1291, 1257, 1206, 1162, 1129, 1048, 847; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 4.85 (1H, d, \(J=4.5\) Hz), 4.35 (1H, dq, \(J=7.0, 5.5\) Hz), 2.70 - 2.77 (1H, m), 1.92 - 2.06 (1H, m), 1.50 (3H, d, \(J=7.0\) Hz),
1.47 (9H, s), 1.24 - 1.42 (2H, m), 0.98 (3H, d, J=7.0 Hz), 0.94 (3H, t, J=7.5 Hz, 3 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 175.4, 168.0, 82.3, 77.4, 66.6, 36.6, 28.0, 24.5, 20.6, 15.3, 11.6; HRMS \((m/z)\): [M + NH\(_4\)]\(^+\) for C\(_{13}\)H\(_{28}\)NO\(_5\), calcld, 278.19675; found, 278.19601.

\((2S,3S)-\text{tert-butyl} \quad 2-(((S)-2-(((2S,3R)-2-(((\text{benzyloxy})\text{carbonyl})\text{amino})-3-((\text{tert-butyl dimethylsilyl})\text{oxy})\text{butanoyl})\text{oxy})\text{propanoyl})\text{oxy})-3\text{-methylpentanoate}\)

(Compound 6.39, Scheme 6.7): Compound 6.16 was prepared according to a literature procedure.\(^{26}\) L-CBz-Threonine-OH (3.80 g, 15.0 mmol, 1.0 eq.) was dissolved in DMF (20 mL) and treated with TBS-Cl (5.65 g, 37.5 mmol, 2.5 eq.), imidazole (3.06 g, 45 mmol, 3.0 eq.) and DMAP (183 mg, 1.5 mmol, 0.1 eq.) in that order and stirred at room temperature overnight. After 16 hours the mixture was partitioned between ethyl acetate (150 mL) and water (50 mL) and the phases were separated. The organic extract was washed with 50% sat’d NaCl(aq) (4 x 25 mL), dried (MgSO\(_4\)), filtered and concentrated \textit{in vacuo}. Purification of the crude residue by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) gave 2.59 g (47%) of 6.16 as a white solid. \(R_f = 0.26\) (5% MeOH/CH\(_2\)Cl\(_2\)).

Compound 6.16 (3.22 g, 8.75 mmol, 1.1 eq.) was dissolved in CH\(_2\)Cl\(_2\) (45 mL) and MNBA (3.01 g, 8.75 mmol, 1.1 eq.) was added followed by addition of DMAP (243 mg, 1.99 mmol, 0.25 eq.) and Et\(_3\)N (2.65 g, 3.65 mL, 26.2 mmol, 3.3 eq.). To this mixture was then added a solution of (2S,3S)-tert-butyl 2-(((S)-2-hydroxypropanoyl)oxy)-3-methylpentanoate (Compound 6.38, 2.07 g, 7.95 mmol, 1.0 eq.) in CH\(_2\)Cl\(_2\) (30 mL) by syringe and the reaction mixture was stirred at room temperature overnight. After 18 hours the mixture was diluted with ethyl acetate (300 mL) and washed with water (50 mL), 6% NaHCO\(_3\)(aq) (2 x 25 mL), 5% aqueous citric acid (2 x 25 mL), and sat’d NaCl(aq) (25 mL). The organic phase was then dried (MgSO\(_4\)), filtered and concentrated \textit{in vacuo} to give a crude residue which was purified by flash chromatography through
silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) to provide 3.42 g (71%) of Compound 6.39 (Scheme 6.7) as a clear oil. [α]D= -33.9 (c 0.62, CH2Cl2); Rf = 0.47 (20% EtOAc/hexanes); IR (neat, cm⁻¹) 3452, 3360, 3091, 3066, 3034, 2964, 2935, 2896, 2858, 2883, 1750, 1733, 1722, 1717, 1504, 1456, 1368, 840, 778; 1H NMR (300 MHz, CDCl3) δ ppm 7.29 - 7.47 (5H, m), 5.49 (1H, d, J=9.5 Hz), 5.25 (1H, q, J=7.0 Hz), 5.15 (2H, s), 4.84 (1H, d, J=4.0 Hz), 4.49 (1H, qd, J=6.0, 2.0 Hz), 4.32 (1H, dd, J=9.5, 2.0 Hz), 1.89 - 2.05 (1H, m), 1.59 (3H, d, J=7.0 Hz), 1.49 - 1.55 (1H, m), 1.47 (9H, s), 1.27 - 1.37 (1H, m), 1.25 (3H, d, J=6.0 Hz), 0.98 (3H, d, J=7.0 Hz), 0.89 - 0.96 (3H, m), 0.84 (9H, s), 0.06 (3H, s), 0.01 (3H, s); 13C NMR (75 MHz, CDCl3) δ ppm 170.3, 169.6, 168.0, 156.6, 136.3, 128.5, 128.2, 128.0, 82.1, 77.03, 68.8, 68.6, 67.1, 59.7, 36.5, 28.0, 25.7, 24.5, 21.2, 17.9, 17.2, 15.3, 11.6, -4.4, -5.4; HRMS (m/z): [M + H]⁺ for C31H52NO9Si, calcd, 610.3405; found, 610.3415.

(2S,3S)-tert-butyl 2-(((S)-2-((2S,3R)-3-hydroxy-2-((2-oxo-2-phenylethylidene)amino)butanoyl)oxy)propanoyl)oxy)-3-methylpentanoate

(northern fragment Compound 6.12, Scheme 6.7):

Compound 6.39 (1.25 g, 2.05 mmol, 1.0 eq.) was dissolved in THF (8 mL) and cooled to 0 °C and treated with TBAF (4.30 mL of a 1M sol’n in THF, 4.30 mmol, 2.1 eq.) and after stirring for 15 minutes the mixture was diluted with water (20 mL) and extracted with Et2O (2 x 50 mL). The organic extracts were then washed with water (2 x 20 mL) then sat’d NaCl(aq) (10 mL), dried (Na2SO4), filtered and concentrated in vacuo. Purification of the crude residue by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) gave 899 mg (88%) of Compound 6.12 (Scheme 6.7) as a clear oil. [α]D= - 49.7 (c 0.16, MeOH); Rf= 0.11 (20% EtOAc/hexanes); IR (neat, cm⁻¹) 3520, 3445, 3067, 3034, 2976, 2938, 2880, 1771, 1738, 1713, 1699, 1506, 1456, 1367, 1261, 1197, 1159, 1130, 1095, 1010, 845; 1H NMR (400 MHz, CDCl3) δ ppm 7.27 - 7.41 (5H, m), 5.57 (1H, d, J=10.0 Hz), 5.27 (1H, q, J=7.0 Hz), 5.07 - 5.19 (2H, m), 4.88 (1H, d, J=4.5 Hz), 4.53 - 4.63 (1H, m), 4.43 (1H, dd, J=9.5, 2.0 Hz), 3.30 (1H, d, J=4.5 Hz), 1.97 (1H, dqt, J=9.0, 7.0, 4.5 Hz), 1.62 (3H, d,
$J=7.5$ Hz), 1.48 - 1.54 (1H, m), 1.45 (9H, s), 1.29 - 1.33 (1H, m), 1.26 (3H, d, $J=6.5$ Hz), 0.97 (3H, d, $J=7.0$ Hz), 0.93 (3H, t, $J=7.5$ Hz); $^{13}$C NMR (101 MHz, CDCl$_3$) ppm 171.0, 170.8, 156.8, 168.0, 136.3, 128.5, 128.1, 127.9, 82.7, 77.4, 69.1, 67.7, 67.0, 59.4, 36.6, 28.0, 24.5, 19.0, 16.6, 15.2, 11.6; HRMS ($m/z$): [M + Na]$^+$ for C$_{25}$H$_{37}$NO$_9$Na, calcd, 518.2360; found, 518.2379.

(S)-(5S,8S,11S,12R,15S)-11-(((benzylloxycarbonyl)amino)-5-((S)-sec-butyl)-2,2,8,12,17-pentamethyl-4,7,10,14-tetraoxo-3,6,9,13-tetraoxaoctadecan-15-yl 4-((tert-butoxycarbonyl)amino)-2,2,6-trimethyl-3-oxoheptanoate (Compound 6.11, Scheme 6.8):

The southern fragment compound 6.13 (573 mg, 1.13 mmol, 1.0 eq.) was dissolved in EtOAc (20 mL) and Pd/C added (124 mg 5 wt% dry) and the flask sealed with a rubber septum and purged with N$_2$ for 5 minutes before attaching a balloon of H$_2$. The reaction flask was purged with the H$_2$ balloon for 5 minutes before a fresh H$_2$ balloon attached and the mixture was stirred at room temperature overnight. After 13 hours, the H$_2$ balloon was removed and the reaction flask was purged with N$_2$ before removal of the septa and filtration through a pad of celite using EtOAc (60 mL) to wash/elute. The filtrate was concentrated in vacuo to give 416 mg (88%) of pure acid compound as a clear oil which was used directly in the next step without further purification.

Southern fragment acid compound prepared above (410 mg, 0.987 mmol, 1.0 eq.) was dissolved in CH$_2$Cl$_2$ (2 mL) and MNBA (476 mg, 1.38 mmol, 1.4 eq.), DMAP (60 mg, 0.493 mmol, 0.5 eq.) and Et$_3$N (399 mg, 0.55 mL, 3.95 mmol, 4.0 eq.) were added in that order and stirred together at room temperature for 20 minutes before addition of northern fragment alcohol compound 6.12 (538 mg, 1.08 mmol, 1.1 eq.) as a solution in CH$_2$Cl$_2$ (1 mL). The reaction mixture was stirred at room temperature for 40 minutes (stirring too long results in threonine ester elimination decomposition to an enamide side product) then diluted with CH$_2$Cl$_2$ (75 mL) and washed with sat’d NaHCO$_3$(aq) (15 mL). The organic extract was dried (MgSO$_4$), filtered and concentrated in vacuo and the resulting
crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc). This provided 635 mg (72% yield, 63% over 2 steps from southern fragment 6.13) of Compound 6.11 (Scheme 6.8) as a clear oil. \([\alpha]_D = -50.7\) (c 0.14, MeOH); \(R_f = 0.25\) (20% EtOAc/hexanes); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3430, 3347, 2965, 2938, 2874, 1767, 1747, 1728, 1717, 1699, 1516, 1456, 1387, 1368, 1251, 1165, 1132, 1092, 1063, 1007; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.28 - 7.45 (5H, m), 6.08 (1H, d, \(J=9.0\) Hz), 5.60 (1H, d, \(J=9.5\) Hz), 5.40 - 5.51 (1H, m), 5.19 - 5.27 (1H, m), 5.08 - 5.18 (2H, m), 4.99 (1H, dd, \(J=10.0, 3.5\) Hz), 4.79 (1H, d, \(J=4.5\) Hz), 4.60 - 4.71 (1H, m), 4.56 (1H, dd, \(J=9.0, 3.5\) Hz), 1.96 (1H, dqt, \(J=9.0, 7.0, 4.5\) Hz), 1.61 - 1.79 (4H, m), 1.39 - 1.58 (29H, m), 1.38 (3H, d, \(J=6.5\) Hz), 1.23 - 1.36 (2H, m), 0.84 - 0.99 (18H, m); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 210.4, 172.2, 169.8, 169.2, 168.8, 167.9, 156.5, 155.7, 136.3, 128.5, 128.1, 128.0, 82.2, 79.7, 71.8, 69.5, 67.1, 57.6, 54.7, 54.1, 41.5, 39.5, 36.6, 28.3, 28.0, 24.7, 24.5, 23.5, 23.1, 22.6, 21.7, 21.3, 21.2, 16.8, 16.6, 15.2, 11.6; HRMS (m/z): [M + H]\(^+\) for C\(_{46}\)H\(_{73}\)N\(_2\)O\(_{15}\), calcd, 893.5005; found, 893.5015.

**Benzyl-((2S,5S,8S,13S,16R,17S)-5-(((S)-sec-butyl)-8,13-diisobutyl-2,10,10,16-tetramethyl-3,6,9,11,14,18-hexaoxo-1,4,12,15-tetraoxa-7-azacyclooctadecan-17-yl)carbamate (Compound 6.10, Scheme 6.8):**

Linear precursor compound 6.11 (264 mg, 0.296 mmol, 1.0 eq.) was dissolved in CH\(_2\)Cl\(_2\) (6 mL) and cooled to 0 °C before addition of TFA (2.02 g, 1.36 mL, 17.7 mmol, 60 eq.) and the mixture was stirred overnight allowing to slowly warm to room temperature. After 18 hours, ESI-MS showed complete deprotection and volatiles were removed under an air stream and the crude residue was re-dissolved in CH\(_2\)Cl\(_2\) (5 mL) and concentrated in vacuo on the rotovap. This was repeated 6 times before vacuum line drying to give 274 mg (108% yield) of the crude TFA salt intermediate as a yellow oil which was used immediately in the next step.
The crude TFA salt prepared above (274 mg, 0.296 mmol, 1.0 eq.) was dissolved in CH$_2$Cl$_2$ (18.5 mL) and added by syringe pump simultaneously with a separate solution of iPr$_2$NEt (191 mg, 1.48 mmol, 5.0 eq.) in CH$_2$Cl$_2$ (18.5 mL) at a rate of 1mL/hr to a stirring room temperature solution of HATU (157 mg, 0.414 mmol, 1.4 eq.) and HOAt (40 mg, 0.296 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (22 mL). The reaction mixture was stirred for a total of 48 hours then washed with sat’d NaHCO$_3$(aq). The organics were dried (MgSO$_4$), filtered and concentrated in vacuo and the crude residue purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc). This provided 151 mg (71% yield over 2 steps) of Compound 6.10 (Scheme 6.8) as a clear oil which solidified to a clear solid on standing. m.p. = 63 – 66 °C (CH$_2$Cl$_2$); [α]$_D$ = - 19.0 (c 0.41, CHCl$_3$) [lit.$^{10}$ -17.7 (c 0.90, CHCl$_3$); R$_f$= 0.64 (40% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3323, 2960, 2936, 2874, 1746, 1710, 1679, 1516, 1462, 1389, 1352, 1312, 1283, 1258, 1211, 1141, 1088, 1059, 1004; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.50 (1H, d, $J$=9.5 Hz), 7.31 - 7.43 (5H, m), 5.90 (1H, qd, $J$=6.5, 2.5 Hz), 5.80 (1H, q, $J$=6.5 Hz), 5.56 (1H, d, $J$=9.4 Hz), 5.09 - 5.25 (2H, m), 4.86 - 4.94 (1H, m), 4.83 (1H, d, $J$=9.5 Hz), 4.73 (1H, dd, $J$=9.0, 2.5 Hz), 4.59 (1H, dd, $J$=10.0, 4.0 Hz), 2.02 - 2.14 (1H, m), 1.60 - 1.89 (6H, m), 1.54 - 1.59 (3H, m), 1.42 - 1.51 (1H, m), 1.36 (3H, d, $J$=6.5 Hz), 1.28 - 1.34 (1H, m), 1.26 (3H, s), 1.13 (3H, s), 0.89 - 1.02 (15H, m), 0.87 (3H, d, $J$=6.5 Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) δ ppm 208.3, 173.1, 171.8, 170.0, 169.7, 167.8, 156.6, 135.8, 128.6, 128.5, 128.2, 80.8, 72.3, 71.9, 71.1, 67.6, 57.7, 56.4, 53.0, 43.0, 39.4, 36.6, 25.3, 24.6, 24.4, 24.0, 23.6, 22.9, 21.3, 21.0, 19.8, 18.2, 16.2, 14.4, 10.4; HRMS (m/z): [M + H]$^+$ for C$_{37}$H$_{55}$N$_2$O$_{12}$, calcd, 719.3749; found, 719.3731.
N-((2S,5S,8S,13S,16R,17S)-5-((S)-sec-butyl)-8,13-diisobutyl-2,10,16-tetramethyl-3,6,9,11,14,18-hexaoxo-1,4,12,15-tetraoxa-7-azaacyclooctadecan-17-yl)-2-hydroxy-3-nitrobenzamide (Compound 6.40, Scheme 6.9):

3-nitro-salicylic acid chloride was prepared according to a literature procedure from commercially available 3-nitro-salicylic acid: 3-nitro-salicylic acid (60 mg, 0.328 mmol, 1.0 eq.) was suspended in CH$_2$Cl$_2$ (5 mL) and oxalyl chloride (125 mg, 0.086 mL, 0.984 mmol, 3.0 eq.) was added followed by addition of DMF (3.6 mg, 0.0492 mmol, 0.15 eq.) as a solution in CH$_2$Cl$_2$ (0.5 mL). The reaction mixture was stirred at room temperature for 14 hours then concentrated in vacuo on the rotovap and vacuum line dried to give 70 mg (quant. yield) of 3-nitro-salicylic acid chloride as a waxy yellow solid which was used immediately as is.

Protected macrocycle compound 6.10 (70.0 mg, 0.0974 mmol, 1.0 eq.) was dissolved in EtOAc (5 mL) and Pd/C added (21 mg 10 wt% dry, ~20 mol % Pd) and the flask sealed with a rubber septum and purged with N$_2$ for 2 minutes before attaching a balloon of H$_2$. The reaction flask was purged with the H$_2$ balloon for 5 minutes before a fresh H$_2$ balloon attached and the mixture was stirred at room temperature overnight. After 16 hours, the H$_2$ balloon was removed and the reaction flask was purged with N$_2$ before removal of the septa and filtration through a pad of celite using EtOAc (50 mL) to wash/elute. The filtrate was concentrated in vacuo to give 60 mg (quant. yield) of 90-95% pure ($^1$H NMR) amine macrocycle as a waxy solid which was used directly in the next step within 6 hours of isolation without further purification.

Amine macrocycle compound prepared above (31.9 mg, 0.0538 mmol, 1.0 eq.) and iPr$_2$NEt (10.4 mg, 0.0807 mmol, 1.5 eq.) and DMAP (0.7 mg, 0.0054 mmol, 0.1 eq.) were dissolved in CH$_2$Cl$_2$ (1 mL) and added to a 0 °C cooled solution of 3-nitro-salicylic acid chloride (32 mg, 0.161 mmol, 3.0 eq.) in CH$_2$Cl$_2$ (1 mL) and the mixture was stirred
overnight allowing to slowly warm to room temperature. After 14 hours, the reaction mixture was diluted with CH$_2$Cl$_2$ (40 mL) and washed with an aqueous 0.1 M pH= 5.5 phosphate buffer sol’n (10 mL). The aqueous was extracted again with CH$_2$Cl$_2$ (10 mL) and the organic extracts were combined, dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100 % EtOAc) to provide 30.0 mg (74% yield over 2 steps) of Compound 6.40 (Scheme 6.9) as a yellow solid. m.p. = 93 - 96 °C (EtOAc/hexanes); [$\alpha$]$_D$= - 5.3 (c 0.34, CHCl$_3$); R$_f$= 0.32 (40% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3419, 3325, 2961, 2930, 2875, 1747, 1717, 1677, 1609, 1535, 1447, 1387, 1354, 1282, 1211, 1142, 1092; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 12.26 (1H, br. s), 8.50 - 8.69 (2H, m), 8.35 (1H, dd, J=8.5, 1.5 Hz), 7.50 (1H, d, J=10.0 Hz), 7.19 (1H, dd, J=8.0, 8.0 Hz), 6.04 (1H, qd, J=6.5, 2.5 Hz), 5.85 (1H, q, J=7.0 Hz), 5.33 (1H, dd, J=8.5, 2.5 Hz), 4.88 - 4.96 (1H, m), 4.85 (1H, d, J=9.5 Hz), 4.71 (1H, dd, J=9.5, 4.5 Hz), 2.06 - 2.15 (1H, m), 1.66 - 1.84 (5H, m), 1.58 (3H, d, J=7.0 Hz), 1.50 - 1.56 (2H, m), 1.41 (3H, d, J=6.5 Hz), 1.31 - 1.38 (1H, m), 1.28 (3H, s), 1.15 (3H, s), 0.86 - 1.04 (18H, m); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ ppm 208.2, 173.2, 171.9, 170.0, 169.8, 167.6, 163.9, 153.5, 140.5, 134.5, 129.2, 122.4, 120.2, 80.8, 72.4, 72.0, 71.2, 56.4, 56.3, 53.0, 43.0, 39.6, 36.6, 25.3, 24.6, 24.5, 24.0, 23.6, 22.7, 21.7, 21.0, 19.8, 18.2, 16.6, 14.4, 10.4; HRMS (m/z): [M + H]$^+$ for C$_{36}$H$_{52}$N$_{3}$O$_{14}$, calcd, 750.3444; found, 750.3439.

**Kitastatin (Compound 6.1, Scheme 6.9):**

Nitro-aryl compound 6.40 (45.0 mg, 0.060 mmol, 1.0 eq.) dissolved in EtOAc (3 mL) and Pd/C added (28 mg 5 wt% dry, 21 mol % Pd) and the flask sealed with a rubber septum and purged with N$_2$ for 2 minutes before attaching a balloon of H$_2$. The reaction flask was purged with the H$_2$ balloon for 5 minutes before a fresh H$_2$ balloon attached and the mixture was stirred at room temperature. After 3 hours, the H$_2$ balloon was removed and the reaction flask was purged with N$_2$ before removal of the septa and filtration through a pad of celite using
EtOAc (50 mL) to wash/elute. The filtrate was concentrated in vacuo and the crude residue purified by flash chromatography through silica gel using ethyl acetate in hexanes (gradient elution from 0-100% EtOAc) to elute to provide 36 mg (83% yield) of kitastatin Compound 6.1 as a light yellow amorphous solid. m.p. = 114 - 119 °C (CH2Cl2); [α]D = -7.3 (c 0.11, MeOH); Rf = 0.38 (40% EtOAc/hexanes); IR (CH2Cl2, cm⁻¹) 3460, 3392, 3325, 2961, 2932, 2874, 2856, 1756, 1729, 1717, 1679, 1641, 1593, 1516, 1467, 1387, 1316, 1284, 1259, 1240, 1211, 1141, 1092, 1019; 1H NMR (500 MHz, CD2Cl2) δ ppm 12.05 (1H, br. s.), 7.53 (1H, d, J=9.5 Hz), 7.08 (1H, d, J=9.0 Hz), 7.01 (1H, dd, J=8.0, 1.5 Hz), 6.88 (1H, dd, J=7.5, 1.5 Hz), 6.74 - 6.81 (1H, m), 6.03 (1H, qd, J=6.5, 2.5 Hz), 5.80 (1H, q, J=7.0 Hz), 5.25 (1H, dd, J=9.0, 2.5 Hz), 4.84 (1H, ddd, J=9.5, 7.5, 5.5 Hz), 4.67 - 4.75 (2H, m), 3.99 (2H, br. s.), 2.06 - 2.16 (1H, m), 1.81 (1H, dd, J=7.5, 7.5), 1.81 (1H, dd, J=7.5, 5.5), 1.57 - 1.78 (5H, m), 1.55 (3H, d, J=7.0 Hz), 1.37 (3H, d, J=6.5 Hz), 1.29 - 1.34 (1H, m), 1.27 (3H, s), 1.10 (3H, s), 0.83 - 1.02 (18H, m); 13C NMR (126 MHz, CD2Cl2) δ ppm 208.7, 173.9, 172.4, 171.5, 170.6, 170.4, 168.2, 150.1, 137.6, 119.5, 118.9, 114.8, 113.3, 81.6, 73.1, 72.8, 71.8, 57.0, 56.0, 53.5, 43.5, 40.0, 37.1, 25.9, 25.13, 25.06, 24.5, 23.8, 23.2, 21.8, 21.3, 20.2, 18.5, 16.8, 14.8, 10.8; HRMS (m/z): [M + H]+ for C36H54N3O12, calcd, 720.3702; found, 720.3701.

**Respirantin (Compound 6.2, Scheme 6.9):**

Kitastatin 6.1 (7.3 mg, 0.0101 mmol, 1.0 eq.) dissolved in THF (4 mL) and N-formyl-saccharin (2.3 mg, 0.0111 mmol, 1.1 eq.) added and stirred at room temperature. After 12 hours a further portion of N-formyl-saccharin (2.3 mg, 0.0111 mmol, 1.1 eq.) was added and continued stirring at room temperature. After a further 8 hours an additional portion of N-formyl-saccharin (2.3 mg, 0.0111 mmol, 1.1 eq.) was added. After stirring an additional 18 hours (38 hours total) TLC indicated complete consumption of compound 6.1. The reaction mixture was diluted with Et2O (40 mL) and washed with sat’d NaHCO3(aq) (10 mL), dried (Na2SO4), filtered and concentrated in vacuo. The resulting crude residue was
purified by flash chromatography through silica gel using ethyl acetate in hexanes (gradient elution from 0-100% EtOAc) to elute to provide 5.7 mg (75% yield) of 86% pure (HPLC-UV @ 254nm) respirantin Compound 6.2 as an off-white waxy solid. A portion of this was re-purified by semi-prep C-18 reverse phase HPLC [Eclipse XDB C18 9.4 x 250 mm (5μm) column, gradient elution 5% MeCN / 95% H2O to 95% MeCN / 5% H2O 0 - 40 mins then isocratic 95% MeCN / 5% H2O 40 mins – 70 mins, cpd. 6.2 eluted 42 – 44 mins] to provide an analytically pure sample of compound 6.2 as a white solid. m.p. = 122 – 126 °C (CH2Cl2); [α]D= - 4.2 (c 0.12, MeOH); Rf= 0.26 (40% EtOAc/hexanes); IR (CH2Cl2, cm−1) 3422 (br.), 2963, 2935, 2875, 1747, 1703, 1647, 1547, 1464, 1370, 1284, 1215, 1142, 1092, 1062; 1H NMR (500 MHz, CD2Cl2) δ ppm 12.63 (1H, s), 8.54 (1H, dd, J=8.0, 1.0 Hz), 8.48 (1H, d, J=1.5 Hz), 7.94 (1H, br. s.), 7.51 (1H, d, J=9.5 Hz), 7.41 (1H, dd, J=8.0, 1.5 Hz), 7.17 (1H, d, J=8.5 Hz), 6.98 (1H, t, J=8.0), 6.04 (1H, qd, J=6.5, 2.5 Hz), 5.81 (1H, q, J=7.0 Hz), 5.26 (1H, dd, J=9.0, 2.5 Hz), 4.79 - 4.89 (1H, m), 4.68 - 4.76 (2H, m), 2.06 - 2.15 (1H, m), 1.78 - 1.84 (2H, m), 1.61 - 1.78 (4H, m), 1.56 - 1.58 (1H, m), 1.55 (3H, d, J=7.0 Hz), 1.37 (3H, d, J=6.5 Hz), 1.30 - 1.36 (1H, m), 1.28 (3H, s), 1.10 (3H, s), 0.88 - 1.01 (18H, m); 13C NMR (126 MHz, CD2Cl2) δ ppm 208.6, 174.0, 172.4, 171.0, 170.6, 170.3, 168.0, 159.5, 151.2, 128.1, 125.2, 120.9, 119.4, 113.5, 81.6, 72.9, 72.8, 71.9, 57.0, 56.2, 53.5, 43.6, 40.0, 37.1, 25.9, 25.14, 25.07, 24.5, 23.8, 23.2, 21.8, 21.3, 20.2, 18.5, 16.8, 14.8, 10.8; HRMS (m/z): [M + H]+ for C37H54N3O13, calcd, 748.3651; found, 748.3636.

3.6 References


[10] The synthesis of kitastatin **6.1** is claimed in a patent, however, no experimental details or yields were included regarding its preparation. Pettit, G. R.; Smith, T. H.; Feng, S.; U.S. Pat. Appl. 065991, 2008.


[14] The major syn and minor anti diastereomers were separated by chromatography and the $^1$H NMR (CDCl$_3$) chemical shifts for the methine protons on the alcohol-bearing carbon appear at 3.44 ppm for the minor anti isomer and 3.21 ppm for the major syn isomer. The dr was calculated by the ratio of these peaks in the $^1$H NMR spectra of the crude reaction mixture before chromatography.


In the course of this work we have examined numerous coupling conditions for the various ester formations and have found MNBA (“Shiina’s Reagent”) to be generally optimal: (a) Shiina, I.; Miyao, R. *Heterocycles* **2008**, *76*, 1313-1328. (b) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822-1830.


[27] Khanskaya, I. V.; Sadeh, J. S.; Staudinger, H. W. PCT Int. Appl. 073683, **2009**.
Chapter 7: An Organotrifluoroborate-Based Total Synthesis of the Potent Naturally Occurring Interleukin Inhibitor Splenocin-B and Studies Toward a Wittig-Olefination Approach to Z-Allyltrifluoroborates

7.1 Introduction

Macrocyclic depsipeptides constitute an important class of synthetic targets due to their structural complexity and diverse range of biological activities. In this area, we have initiated a research program aimed at synthetically studying members of the antimycin and neo-antimycin depsipeptide families due to their ester-rich structural features and interesting medicinally relevant activities. Structurally, the (+)-antimycin A (AA) family of depsipeptides are characterized by a 9-membered lactone containing a threonine connected amino-salicylic acid with various members differentiated only by the ring-appended alkyl groups and exocyclic esters (Figure 7.1). The related neo-antimycin depsipeptide natural products similarly contain threonine connected amino salicylic acid structural features but are distinguished by their larger polyester lactone rings (Figure 7.2). These include the 15-membered macrocyclic GRP78 (glucose regulated protein 78) inhibitor 7.1 (Prunustatin A), and the potent 18-membered macrolactone cancer cell growth inhibitor 7.2 (kitastatin).

![Figure 7.1](image)

**Figure 7.1** The (+)-antimycin A family of 9-membered depsipeptides
Figure 7.2 Example neo-antimycin depsipeptide natural products prunustatin A (7.1) and kitastatin (7.2)

Biologically, the (+)-AA antimycin family are known to be potent inhibitors of cytochrome b-c reductase resulting in mitochondrial respiratory inhibition and cell death.\(^7\) As a result, antimycins display anti-fungal and cytotoxic effects including commercial use of (+)-antimycin A\(_3\) (Compound 7.3, Figure 7.3) as a piscicide (Fintrol\(^{TM}\)) in the catfish aquaculture industry. Unfortunately, the cytotoxic effects of the antimycins are non-selective and no known therapeutic window exists for their use to treat human antiproliferative disorders such as cancer.

However, Hockenbery and co-workers have shown that in addition to mitochondrial cytochrome inhibition, (+)-antimycin A\(_3\) induces cell death as a potent inhibitor of BcL-2 proteins (Figure 7.3).\(^8\) Since the BcL family of proteins govern mitochondrial membrane permeability and are involved in cell apoptosis,\(^9\) antimycin analogs may be useful toward a BcL-2 based cancer chemotherapy. Notably, these authors also showed that simple chemical modification of (+)-antimycin A\(_3\) can result in profoundly different behaviour. For example, conversion of the (+)-antimycin A\(_3\) phenol to a methoxy-group resulted in synthetic analog 7.4 which retained BcL-2 inhibitory activity and induced cell death via apoptosis but was not an inhibitor of cellular respiration (Figure 7.3).\(^8\) This result suggests that synthetic modifications of the amino-salicylic formamide of the antimycins may be a strategy to reduce or remove non-selective cytochrome inhibitory activity.
Figure 7.3 (+)-Antimycin A₃ (Fintrol™) and OMe BcL-2 inhibitory analog 7.4

There also appears to be an important structural component of the lactone that governs the activity of the antimycin class of cyclic esters. For example, the Fenical group has recently reported isolation of the splenocin depsipeptides which are only differentiated from the antimycins by a ring-appended benzyl group (Figure 7.4).¹⁰ Importantly, despite their near identical structure to the antimycins, members of the splenocin group display reduced cytotoxicity and are potent inhibitors of pro-inflammatory cytokines IL-3 and IL-5 (Figure 7.4). In particular, splenocin-B (Compound 7.6) displays low nanomolar cytokine inhibition and appears to possess a therapeutic window similar to dexamethasone for the potential treatment of anti-inflammatory disorders such as asthma. The decrease in cell toxicity observed for splenocin-B suggests that ring-appended groups should be tunable components of biological activity for this general class of depsipeptides. In addition, a splenocin-related synthetic analog¹¹ of the antimycin-like antibiotic UK-2A¹² (7.9)¹¹ᵃ was observed to be significantly less toxic than (+)-antimycin A₃ to the LLC-PK1 cell line (Figure 7.4). Since this UK-2A analog is only differentiated from splenocin-B by replacement of the threonine ring fragment with a serine residue, modification of the lactone ring of the splenocins could be used as a strategy to further reduce their cytotoxicity toward a potential splenocin-based anti-asthma treatment.
Considering the interesting properties of the antimycins and splenocins described above, it is clear that structural differences in both the amino-salicylic acid and lactone components contribute to their biological activities and selectivities. Despite this, there has been no systematic study to identify the structural basis for these potentially useful properties. To address this, we have initiated a research program aimed at synthesizing natural products of the antimycin/neo-antimycin class. Toward this goal, we have successfully completed total syntheses of the cytotoxic neo-antimycins kitastatin and respirantin (see Chapter 6) as well as one member of the antimycin family [(+)-antimycin A1b]. Notably, these syntheses feature stereoselective allyltrifluoroborate aldehyde allylations as key steps to demonstrate the use of organotrifluoroborate allylmetaloids in total synthesis applications.

As a further extension of this work, splenocin-B (7.6) appeared attractive to target for total synthesis due to the interesting reported anti-inflammatory activity of this natural product. In addition, synthetic access to the splenocins would enable analog generation to for the tuning these cyclic lactones to improve their pre-clinical profile and to better understand in general the cell toxicity components of the overall antimycin family.

Figure 7.4 The cytokine inhibitory depsipeptides splenocins A-D and the related weakly cytotoxic UK-2A analog 7.911a

<table>
<thead>
<tr>
<th>Compound</th>
<th>R¹</th>
<th>IC₅₀ (nM)</th>
<th>Cytotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>dexamethasone</td>
<td></td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Splenocin-A (7.5)</td>
<td>Me</td>
<td>3.1</td>
<td>53</td>
</tr>
<tr>
<td>Splenocin-B (7.6)</td>
<td>s-Pr</td>
<td>1.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Splenocin-C (7.7)</td>
<td>s-Bu</td>
<td>6.7</td>
<td>7.3</td>
</tr>
<tr>
<td>Splenocin-D (7.8)</td>
<td>Et</td>
<td>48</td>
<td>44</td>
</tr>
</tbody>
</table>

7.9, UK-2A analog
LLC-PK1 cytotoxicity IC₅₀= >100 mg/mL
Antimycin A₃ (7.3) LLC-PK1 cytotoxicity IC₅₀= <0.01 mg/mL.
Scheme 7.1 Proposed synthetic strategy to splenocin-B (7.6) using a Z-benzyl allyltrifluoroborate aldehyde addition

Prior synthetic studies on (+)-antimycin A\textsubscript{1b} from our laboratory\textsuperscript{3} suggested a nearly identical strategy to splenocin-B hinging upon a stereoselective allyltrifluoroborate aldehyde addition to secure the core stereotriad 7.15 (Scheme 7.1). Thus, the olefin of 7.12 would serve as a carbonyl surrogate and oxidative cleavage should provide carboxylic acid 7.11 for 9-membered lactonization. Similarly, analysis of the splenocin stereotriad 7.15 revealed that Z-benzyl allyltrifluoroborate reagent 7.17 would be needed to set the desired 2,3-\textit{syn} relative stereochemistry. Considering that all members of the antimycin/splenocin lactones contain this core triad, it would be useful toward analog synthesis to prepare various Z-functionalized allyltrifluoroborates to react with aldehyde 7.16. However, as mentioned in chapter 5, the synthesis of Z-allylboronates is not as straightforward as the corresponding E-allylboronates and generally requires a multi-step Matteson homologation (see Section 5.3, Chapter 5). As a result, we became interested with the potential of applying the famous Wittig olefination to develop a general approach to Z-allylboronates via the disconnection shown in Figure 7.5. Such a strategy would be useful considering the availability of the aldehyde starting materials and would directly provide \textit{cis}-allylboron compounds in a single step. Some early experiments
regarding this Wittig-olefination strategy were performed by undergraduate student Daniel Dalessandro.

\[
\begin{align*}
\text{R}^1\text{C}=\text{H} & \quad + \quad [\overset{\overset{\uparrow}{\text{P}}}{\text{P}}\cdots\text{B}] \\
\text{R}^1\text{C}=[\text{B}] & \quad \rightarrow
\end{align*}
\]

**Figure 7.5** Generalized Wittig olefination strategy for the one-step synthesis of Z-allylboronates from aldehydes

### 7.2 Results and Discussion

The key challenge associated with a phosphorous-ylide based olefination approach to allylboronates is the synthesis of an amphoteric ethylene linked borono-phosphine precursor. Although there is precedent for the preparation of small molecules containing both boron and phosphorous functional groups,\textsuperscript{13} and even some examples of the use of these in Wittig\textsuperscript{13b} or Horner-Wadsworth-Emmons reactions,\textsuperscript{13a} the ethylene spacer required in the present case could be problematic since it would position the boron and phosphorous atoms in close enough proximity that these complimentary Lewis acidic (boron) and Lewis basic (phosphorous) atoms can interact in a 5-membered ring. As a starting point, we were interested in the reported hydroboration of diethyl vinylphosphonate to prepare ethylene spaced borono-phosphonate 7.18 (Scheme 7.2).\textsuperscript{14}

In our hands, although near complete conversion of the vinyl phosphonate was observed by \textsuperscript{31}P NMR, we were not able to isolate compound 7.18 via vinylphosphonate reaction with pinacolborane under these conditions. Based on the known 1,4-reduction of \(\alpha,\beta\)-unsaturated esters with pinacolborane,\textsuperscript{15} we propose that this reaction proceeds similarly to generate intermediate 7.19 which upon work-up or chromatography decomposes to the volatile ethyl phosphonate 7.20 (Scheme 7.2).
Scheme 7.2 Reported 3,4-hydroboration approach to borono-phosphonate 7.18 and presumed actual reaction products 7.19 and 7.20 via 1,4-hydroboration

As an alternative for the preparation of 7.18, we were attracted to exploring a potential B2pin2 1,4-borylation of diethyl vinylphosphonate (Scheme 7.3). Although not known previously for this particular case, this type of reaction has been used in the borylation of other vinyl phosphonates.16 It should be noted, however, that these previous borono-phosphonate reactions only report GC yields and no ethylene spaced boronophosphonate species had been isolated as a stable compound. Of these borylations, we found the copper-catalyzed variant reported by Yun and co-workers gave optimal conversion to crude 7.18 by 1H NMR analysis. Attempted silica gel chromatographic purification of boronophosphonate 7.18 was, however, not successful. Subsequently, we established that treatment of 7.18 with KHF2 resulted in clean isolation of the trifluoroborate-phosphonate derivative 7.21 as a stable free-flowing white solid which enabled its full characterization.

Scheme 7.3 Successful synthesis of borono-phosphonate 7.18 via copper-catalyzed 1,4-borylation of diethyl vinylphosphonate and conversion to its stable trifluoroborate 7.21

Synthesis of ethylene linked trifluoro-boronophosphonate 7.21 thus enabled exploration of a Wittig-type olefination reaction with aldehydes toward Z-allylboronates. In this
regard, attempted deprotonation of 7.21 and reaction with benzaldehyde was not observed to proceed presumably due to the insolubility of this potassium organotrifluoroborate in ethereal solvents. Our lab has previously experienced this issue with other potassium trifluoroborates and developed a salt metathesis reaction with tetrabutylammonium hydroxide to generate organic soluble tetrabutylammonium organotrifluoroborates.\(^{17}\) Thus, compound 7.21 was converted to the organic soluble ammonium salt 7.22 under these conditions and this compound was observed to undergo addition to benzaldehyde to generate alcohol 7.23 by \(^1\)H NMR and mass spec analysis (Scheme 7.4). In contrast to phosphonates with \(\beta\)-electron withdrawing substituents which provide \(E\)-olefin geometries upon reaction with aldehydes, alkyl substituted phosphonate-ylides (e.g., 7.22) are known to instead provide \(Z\)-olefins from aldehydes.\(^{18}\) However, this is typically a two-step process as these species tend to give stable \(\beta\)-hydroxyphosphonate intermediates (e.g., 7.23) which must be further treated with NaH,\(^{18a,b}\) TBAF\(^{18c}\) or aqueous base\(^{18d}\) to form the desired alkenes. In this regard, we were disappointed to find that 7.23 did not convert to the desired allylboronate product(s) 7.24 under these conditions (Scheme 7.4).

Scheme 7.4 Synthesis of tetrabutylammonium trifluoroboronophosphonate 7.22 and its reaction with benzaldehyde to give stable \(\beta\)-hydroxyphosphonate 7.23

Fundamentally, another possible Wittig-olefination approach to allylboronates could involve a disconnection involving reaction of classical phosphorous ylides with an \(\alpha\)-boryl aldehyde compound (Figure 7.6). Until recently, \(\alpha\)-boryl aldehydes were an unknown compound class since these species preferred their more stable boron enolate
tautomer form. Work from both the Burke group\textsuperscript{19} and the Yudin group\textsuperscript{20} have independently shown, however, that tetracoordinate MIDA boronate derived $\alpha$-boryl aldehydes are stable and isolable species when prepared via a cation induced 1,2-shift of MIDA-boryl epoxides (Scheme 7.5).

![Scheme 7.5 Synthesis of MIDA-boronate $\alpha$-boryl aldehydes\textsuperscript{19,20}](image)

**Figure 7.6** Alternative Z-allylboronate disconnection via phosphorous ylide reaction with a methylene linked $\alpha$-boryl aldehyde

In this area, the unsubstituted methylene linked variant required for proposed Wittig-olefination has not been prepared. By analogy with classical aldehyde syntheses, one potential alternative preparation of a simple unsubstituted methylene linked $\alpha$-boryl aldehyde required for our proposed allylboronate synthesis could be formed via oxidative cleavage of an allylboronate (Figure 7.7). This approach was attractive since many allylboron species are commercially available including the stabilized tetracoordinate MIDA and BF$_3$K compounds. In addition, there exists some precedent in this area since Molander and Cooper have reported the ozone mediated olefin cleavage of alkenyltrifluoroborate salts.\textsuperscript{21}

![Figure 7.7 Proposed synthesis of unsubstituted methylene-linked $\alpha$-boryl aldehydes via oxidative cleavage of allylboronates toward Z-allylboronates](image)
Our attempts to oxidatively cleave MIDA-allylboronate and the potassium or tetrabutylammonium allyl-BF$_3$ salts using ozonolysis or a sequence of OsO$_4$ dihydroxylation and diol cleavage toward this goal were disappointingly unsatisfactory. A trace amount of $\alpha$-boryl aldehyde product was observed by crude $^1$H NMR analysis of these reactions. However, a complex mixture of unidentified products was predominant.

As a final attempt at developing a new synthetic route to functionalized allylboronates with challenging Z-alkene stereochemistry, we were attracted to recent developments in the area of Z-selective metal-catalyzed olefin cross-metathesis. Specifically, we were interested in commercially available ruthenium-based catalyst 7.24 developed by Grubbs and co-workers, and we thus briefly explored its use toward preparation of the splenocin allylboronate 7.17 (Scheme 7.6). Previously, catalyst 7.24 has been used to prepare a functionalized Z-allylboronate pinacol ester, however, in this example no boronate product was isolated. Instead, oxidation of the carbon-boron bond was effected to isolate the resulting Z-allyl alcohol presumably due to issues in allylboronate purification. A similar issue was encountered in our case when catalyst 7.24 was applied to the cross-metathesis reaction of allylpinacol boronate and allylbenzene (Scheme 7.6). Formation of Z-allylboronate intermediate 7.25 was observed by $^1$H NMR, however, attempted purification by silica gel chromatography led to its decomposition. In addition, treatment of crude allylboronate 7.25 with KHF$_2$ toward attempted purification by filtration resulted in a 1:1 mixture of desired 7.17 and allyltrifluoroborate 7.26 due to residual allylboronic ester present.
Scheme 7.6 Attempted Z-selective olefin cross-metathesis approach to Z-benzylallyltrifluoroborate 7.17

Although we believe that a Wittig-olefination approach to Z-allylboronates is still in principle possible, as a result of the problems encountered above, our attention turned to our primary goal of synthesizing splenocin-B 7.6. In this regard, a Matteson homologation synthetic sequence proved capable of preparing the Z-benzyl allyltrifluoroborate salt 7.17 required for the proposed stereoselective allylboration (Scheme 7.7). Thus, vinyl boronate 7.28 was stereoselectively generated via hydroboration and selective proto-deboronation of alkynyl boronate 7.27 and subsequently reacted with chloromethyl-lithium and KHF$_2$ to give geometrically pure 7.17.

Scheme 7.7 Matteson homologation synthesis of Z-benzyl allyltrifluoroborate 7.17

In agreement with our prior antimycin A$_{1b}$ synthesis,$^3$ reaction of 7.17 with α-chiral aldehyde 7.16 derived from OTBS protected (S)-ethyl lactate using montmorrolonite K10 clay-catalyzed conditions was highly stereoselective to provide key splenocin stereotriad
7.15 (Scheme 7.8). Prior work on aldehyde 7.16 suggests a Cornforth aldehyde conformation resulting in possible transition states 7.29 and 7.30 with the latter presumably being preferred to minimize \( \text{syn} \)-pentane like interaction with the allylboronate benzyl substituent.

![Scheme 7.8 Stereoselective reaction of allyl-BF\(_3\)K 7.17 with aldehyde 7.16 and proposed transition state model](image)

Elaboration of 7.15 was used to provide seco-acid precursor 7.11 as shown in Scheme 7.9. Esterification with isobutyryl chloride (7.14) followed by HF·pyridine silyl group deprotection provided alcohol 7.32 which was then esterified with protected threonine 7.13 to give 7.12 using MNBA coupling conditions. Ozonolysis of 7.12 followed by Pinnick oxidation thus provided splenocin-B seco-acid precursor 7.11.

![Scheme 7.9 Elaboration of 7.15 to TBS protected splenocin-B seco-acid 7.11](image)
Silyl-group deprotection of 7.11 using TBAF followed by MNBA promoted lactonization then provided the core challenging 9-membered lactone 7.10 in 25% yield for 2 steps (Scheme 7.10). Acidic Boc carbamate deprotection using TFA followed by direct reaction with unprotected 3-formamide-salicylic acid 7.33 using our previously described conditions thus provided the target antiinflammatory natural product splenocin-B 7.6.

**Scheme 7.10** Completing the total synthesis of splenocin-B 7.6

### 7.3 Conclusions

In Chapter 6 of this thesis we described a prenyltrifluoroborate approach to the total synthesis of the cytotoxic neo-antimycin depsipeptides kitastatin and respirantin. This chapter has similarly described an organotrifluoroborate-based approach to prepare the previously un-synthesized non-steroidal antimycin family cytokine inhibitor natural product splenocin-B. The synthesis relies upon a stereoselective aldehyde allylboration using a Z-benzyl allyltrifluoroborate prepared using a Matteson homologation sequence as well as an MNBA mediated lactonization to close the 9-membered ring. Also included in this chapter were experiments directed toward a new Z-allyltrifluoroborate synthesis using a Wittig-olefination strategy. Although currently unsuccessful, this approach did lead to the synthesis of an interesting ethylene-linked trifluoroborate-phosphonate species as a unique example of a stable compound which contains both Lewis acidic and Lewis basic functionality. Future work should include optimization of the splenocin-B
lactonization and subsequent amino-salicylic acid amide coupling as well as considering alternative reaction sequences toward an ylide-based allylboronation synthesis.

7.4 Experimental Section

Copies of $^1$H and $^{13}$C NMR spectra for synthesized compounds in this chapter can be found in Appendix 5. Solvents distilled fresh under nitrogen atmosphere before use and transferred via syringe using standard techniques unless otherwise stated. THF and Et$_2$O were dried over sodium benzophenone-ketyl before use. Toluene, acetonitrile, and dichloromethane were dried over calcium hydride before use. All chemical manipulations were performed under a N$_2$ atmosphere unless otherwise stated. All reagents were purchased from Aldrich or VWR and used as received unless otherwise stated. NMR solvent (CDCl$_3$ with TMS internal standard and CD$_2$Cl$_2$) were purchased from Cambridge Isotopes Lab Inc. and used as received.

All products were characterized by $^1$H NMR and $^{13}$C NMR, IR and HRMS. $^1$H NMR and $^{13}$C NMR were recorded on Varian Mercury 300 MHz, Varian Mercury 400 MHz, Bruker 400 MHz or Agilent 500 MHz spectrometers. Chemical shifts are expressed in ppm values and $^1$H NMR spectra are referenced to Me$_4$Si internal standard of 0.00 ppm for CDCl$_3$ and residual solvent peak of 1.94 for CD$_2$CN. $^{13}$C NMR spectra are referenced to residual solvent peak of 77.00 ppm for CDCl$_3$ and residual solvent peak of 118.26 for CD$_2$CN. $^{13}$C NMR spectra for splenocin-B (7.6) was recorded on an Agilent DD2 500 MHz spectrometer with a HC 5-mm XSens cryogenically cooled probe. Peak multiplicities are designated by the following abbreviations: s, singlet; br.s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; r, rotomers; J, coupling constant in Hz. The coupling constant $J$ (Hz) has been rounded to 0.5 Hz for all compounds. If a coupling pattern can be assigned as a combination of multiplicities, then the listed abbreviations are combined to provide an appropriate descriptor for the observed patterns (e.g., dt - doublet of triplets). IR spectra were obtained on a Shimadzu FTIR-8400S with samples loaded as thin films on NaCl plates neat or with CH$_2$Cl$_2$ as indicated. Mass spectra were obtained by the University of Toronto mass spectral facility (AIMS); high resolution
mass spectra (HRMS) were recorded on an AEI MS3074 spectrometer. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Flash column chromatography on silica gel (60 Å, 230-400 mesh, obtained from Silicycle Inc.) was performed with reagent grade ethyl acetate and hexanes as eluents. Analytical thin-layer chromatography (TLC) was performed on pre-coated aluminum-backed silica gel plates (Alugram SIL G/UV254 purchased from Rose Scientific Limited or Silicycle Inc.) and visualized using KMnO₄, or ninhydrin, or Hannesian’s Stain and heating.

Table 7.1. Synthetic vs. Natural¹³C NMR data for splenocin-B (7.6)ᵃ

<table>
<thead>
<tr>
<th>Natural Splenocin-B (7.6)¹³</th>
<th>Synthetic Splenocin-B (7.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>175.7</td>
<td>175.6</td>
</tr>
<tr>
<td>171.9</td>
<td>171.9</td>
</tr>
<tr>
<td>170.1</td>
<td>170.0</td>
</tr>
<tr>
<td>169.3</td>
<td>169.3</td>
</tr>
<tr>
<td>159.1</td>
<td>158.9</td>
</tr>
<tr>
<td>150.7</td>
<td>150.6</td>
</tr>
<tr>
<td>137.9</td>
<td>137.9</td>
</tr>
<tr>
<td>128.7</td>
<td>128.7</td>
</tr>
<tr>
<td>128.5</td>
<td>128.6</td>
</tr>
<tr>
<td>127.4</td>
<td>127.4</td>
</tr>
<tr>
<td>126.6</td>
<td>126.6</td>
</tr>
<tr>
<td>124.8</td>
<td>124.8</td>
</tr>
<tr>
<td>120.3</td>
<td>120.0</td>
</tr>
<tr>
<td>118.8</td>
<td>119.0</td>
</tr>
<tr>
<td>112.6</td>
<td>112.5</td>
</tr>
<tr>
<td>75.0</td>
<td>75.1</td>
</tr>
<tr>
<td>74.7</td>
<td>74.8</td>
</tr>
<tr>
<td>70.9</td>
<td>70.9</td>
</tr>
<tr>
<td>53.4</td>
<td>53.5</td>
</tr>
<tr>
<td>51.9</td>
<td>51.9</td>
</tr>
<tr>
<td>34.5</td>
<td>34.5</td>
</tr>
<tr>
<td>34.1</td>
<td>34.1</td>
</tr>
<tr>
<td>18.9</td>
<td>19.0</td>
</tr>
<tr>
<td>17.8</td>
<td>17.9</td>
</tr>
<tr>
<td>14.7</td>
<td>14.7</td>
</tr>
</tbody>
</table>

ᵃ) δ in ppm; CD₂Cl₂ at 25 °C relative to CHCl₃ solvent residual peak (77.00)
Preparation of potassium diethyl(2-(trifluoroborate)ethyl)phosphonate (Compound 7.21, Scheme 7.3):

A flask containing Cu(I)Cl (30 mg, 0.30 mmol, 0.03 eq.) and DPEphos (160 mg, 0.30 mmol, 0.03 eq.) and NaOtBu (96 mg, 1.0 mmol, 0.1 equiv.) was sealed with a rubber septa and purged with an argon balloon for 10 minutes. THF (8 mL) was then added to this mixture and stirred for 30 mins at room temperature before addition of B\textsubscript{2}pin\textsubscript{2} (2.79 g, 11.0 mmol, 1.1 equiv.) as a solution in THF (8 mL). After stirring for 10 mins, diethyl vinylphosphonate (1.64 g, 1.54 mL, 10.0 mmol, 1.0 equiv.) as a sol’n in THF (8 mL) was then added followed immediately by MeOH (1.28 g, 1.62 mL, 40.0 mmol, 4.0 equiv.) and the mixture stirred at room temperature overnight under Argon. After 18 hrs, the mixture was diluted with ethyl acetate (100 mL) and H\textsubscript{2}O (25 mL) and the phases separated and organic extract washed with 1M HCl (25 mL) then sat’d NaCl(aq) (15 mL). The organic extract was then dried (MgSO\textsubscript{4}), filtered through a 1” tall x 3” wide silica plug topped with celite using ethyl acetate (100 mL) to wash/elute and the filtrate concentrated in vacuo to provide 2.30 g (79% yield, ~80-90% pure by \textsuperscript{1}H NMR) crude pinacolboronate 7.18 as a slightly yellow oil.

KHF\textsubscript{2} (3.69 g, 47.2 mmol, 6.0 eq.) was dissolved in water (9 mL) and added to a solution of pinacolboronate 7.18 prepared above (2.30 g, 7.87 mmol, 1.0 eq.) in acetone (10 mL) and the mixture was stirred vigorously at room temperature for 2 hours. The mixture was then repeatedly concentrated on a rotovap using additional acetone (4 x 10 mL) until a white solid was obtained which was vacuum line dried to give 862 mg (27% yield over 2 steps) of 7.21 as a white solid. \textsuperscript{19}F NMR (377 MHz, CD\textsubscript{3}CN) δ ppm -143.2; \textsuperscript{11}B NMR (128 MHz, CD\textsubscript{3}CN) δ ppm 0.43 – 9.42 (1B, m); \textsuperscript{31}P NMR (162 MHz, CD\textsubscript{3}CN) δ ppm 38.1 (1P, s); \textsuperscript{1}H NMR (400 MHz, CD\textsubscript{3}CN) δ ppm 3.70-3.81 (4H, m), 1.45-1.64 (2H, m), 1.24 (6H, t, J= 7.0 Hz), 0.23 (2H, br.m.); \textsuperscript{13}C NMR (101 MHz, CD\textsubscript{3}CN) δ ppm 62.2, 22.5, 21.2, 17.2; HRMS (m/z): [M - H\textsuperscript{-}]\textsuperscript{+} for C\textsubscript{6}H\textsubscript{14}BO\textsubscript{3}F\textsubscript{3}P, calcd, 233.0731; found, 233.0726.
**Preparation of tetrabutylammonium diethyl(2-(trifluoroborate)ethyl)phosphonate**  
(Compound 7.22, Scheme 7.4):

Trifluoroborophosphonate 7.21 (100 mg, 0.367 mmol, 1.0 eq.) was suspended in CH₂Cl₂ (3 mL) and Bu₄NOH (0.24 mL of a 40 wt % [1.54 M] aqueous sol’n, 0.367 mmol, 1.0 eq.) was added and the mixture stirred vigorously at room temperature for 30 mins. The mixture was then transferred to a sep. funnel using H₂O (0.5 mL) and CH₂Cl₂ (0.5 mL) and the phases were separated and the organic extract was dried (MgSO₄), filtered and concentrated in vacuo to give 167 mg (95% yield) of Compound 7.22 (Scheme 7.4) as a clear oil.

- **¹⁹F NMR** (377 MHz, CDCl₃) δ ppm -151.51 (1F, s), -142.67 (1F, s), -78.23 (1F, s);
- **¹¹B NMR** (128 MHz, CDCl₃) δ ppm 5.0 (1B, s);
- **³¹P NMR** (162 MHz, CDCl₃) δ ppm 38.8 (1P, s);
- **¹H NMR** (400 MHz, CDCl₃) δ ppm 3.92 - 4.12 (4H, m), 3.14 - 3.30 (8H, m), 1.69 - 1.84 (2H, m), 1.55 - 1.68 (8H, m), 1.44 (8H, sxt, J=7.5 Hz), 1.28 (6H, t, J=7.0 Hz), 1.01 (12H, t, J=7.5 Hz), 0.37 - 0.53 (2H, m);
- **¹³C NMR** (101 MHz, CDCl₃) δ ppm 60.8, 58.5, 23.8, 21.6, 20.9 (C-P, d, J=135 Hz), 16.4, 13.5, 10.1; HRMS (m/z): [M - H]⁻ for C₆H₁₄BO₃F₃P, calcd, 233.0731; found, 233.0732.

**Preparation of (Z)-4,4,5,5-tetramethyl-2-(3-phenylprop-1-en-1-yl)-1,3,2-dioxaborolane** (Compound 7.28, Scheme 7.7):

A nitrogen-flushed flask was charged with Et₂O (50 mL) and 3-phenyl-1-acetylene (1.0 g, 1.07 mL, 8.61 mmol, 1.0 eq.) and cooled to -78 °C in a dry ice/acetone bath and n-BuLi (3.44 mL of a 2.5 M sol’n in hexanes, 8.61 mmol, 1.0 eq.) was added dropwise. Upon complete addition, the mixture was stirred 15 mins in the cooling bath then HBpin (1.10 g, 1.25 mL, 8.61 mmol, 1.0 eq.) was added and stirred 1 hr at -78 °C then warmed to 0 °C. Anhydrous HCl (2.15 mL of a 4N HCl in dioxanes sol’n, 8.61 mmol, 1.0 eq.) was then added and stirred 30 mins at 0 °C then directly filtered through a 1” tall x 3” wide celite plug using Et₂O (3 x 50 mL) to wash/elute and the filtrate concentrated in vacuo to give 2.26 g (108% yield) of ~90%
pure alkynylboronate 7.27 as a yellow oil which was used within 3 hrs of preparing without further purification.

A nitrogen-flushed flask was charged with Et₂O (20 mL) and cooled to 0 °C. BH₃·THF (10.3 mL of a 1M sol’n in THF, 10.3 mmol, 1.2 eq.) was then added followed by addition of cyclohexene (1.70 g, 2.1 mL, 20.66 mmol, 2.4 eq.) and stirred for 30 mins in the ice/water bath. A solution of alkynylboronate 7.27 prepared above (2.08 g, 8.61 mmol, 1.0 eq.) in Et₂O (15 mL) was then added and the cooling bath removed. After stirring at room temperature for 2 hrs, the mixture was re-cooled to 0 °C and HOAc (618 mg, 0.59 mL, 10.3 mmol, 1.2 eq.) was added and stirred 20 mins before addition of ethanolamine (1.26 g, 1.25 mL, 20.66 mmol, 2.4 eq.) and the cooling bath was removed. After 10 mins, the reaction mixture was diluted with hexanes (40 mL) and filtered through 1” tall x 3” wide celite plug using hexanes (3 x 40 mL) to wash/elute then this filtrate was filtered through a 1” tall x 1” wide silica plug topped with celite using hexanes (3 x 20 mL) to wash/elute and the filtrate concentrated in vacuo. The resulting crude residue was purified by flash chromatography through silica gel using 10% EtOAc in hexanes to elute to provide 982 mg (47% yield over 2 steps) of Compound 7.28 (Scheme 7.7) as a clear oil with ≥ 15:1 cis:trans olefin geometry as determined by ¹H NMR. Rᵣ= 0.23 (5% EtOAc/hexanes); IR (neat, cm⁻¹) 3062, 3027, 2857, 2978, 1627, 1495, 1453, 1379, 1260, 1140; ¹¹B NMR (128 MHz, CDCl₃) δ ppm 29.75 (1B, s); ¹H NMR (400 MHz, CDCl₃) δ ppm 7.11 - 7.37 (5H, m), 6.43 - 6.64 (1H, m), 5.43 (1H, d, J=13.5 Hz), 3.76 (2H, d, J=8.0 Hz), 1.30 (12H, s); ¹³C NMR (101 MHz, CDCl₃) δ ppm [missing C-B peak] 152.7, 140.7, 128.6, 128.4, 125.9, 83.0, 38.7, 24.9; HRMS (m/z): [M + H]⁺ for C₁₅H₂₁BO₂, calcd, 245.17129; found, 245.17072.
Preparation of potassium (Z)-2-(4-phenylbut-2-en-1-yl)-1-trifluoroborate (Compound 7.17, Scheme 7.7):

A nitrogen-flushed flask containing alkenylboronate 7.28 (925 mg, 3.79 mmol, 1.0 eq.) was charged with Et₂O (10 mL) followed by ClCH₂I (736 mL, 0.30 mL, 4.17 mmol, 1.1 eq.) and wrapped in aluminum foil and cooled to -78 °C in a dry ice/acetone bath with the fumehood overhead light turned off. To this was then added n-BuLi (1.67 mL of a 2.5 M sol’n in hexanes, 4.17 mmol, 1.1 eq.) dropwise over 3 mins and the mixture stirred 1 hr at -78 °C then cooling bath removed and stirred overnight. After stirring 13 hrs at room temperature the mixture was diluted with Et₂O (75 mL) and H₂O (25 mL) and phases separated and the organic extract was dried (MgSO₄), filtered and concentrated in vacuo to give 986 mg (quant. yield) of crude allylboronate 7.25 as a yellow oil which was used directly without further purification (~75% pure by ¹H NMR).

KHF₂ (1.77 g, 22.7 mmol, 6.0 eq.) was dissolved in water (8 mL) and added to a solution of allylboronate 7.25 prepared above (978 mg, 3.79 mmol, 1.0 eq.) in acetone (8 mL) and the mixture was stirred vigorously at room temperature for 3 hours. The mixture was then repeatedly concentrated on a rotovap using additional acetone (4 x 10 mL) until a white solid was obtained. The resulting solid was extracted using 55 °C acetone (3 x 10 mL) filtering each extract through a frit and the filtrate was concentrated in vacuo and the resulting crude residue was sonicated with Et₂O (10 mL) and the white solids collected to give 412 mg (46 % over 2 steps) Compound 7.17 (Scheme 7.7) as a white solid. ¹⁹F NMR (377 MHz, CD₃CN) δ ppm -140.09 - -138.76 (3F, m); ¹¹B NMR (128 MHz, CD₃CN) δ ppm 4.33 (1B, q, J= 62.0 Hz); ¹H NMR (400 MHz, CD₃CN) δ ppm 7.19 - 7.41 (4H, m), 7.10 - 7.18 (1H, m), 5.64 (1H, dt, J=10.5, 8.5 Hz), 5.15 - 5.26 (1H, m), 3.37 (2H, dd, J=7.4, 1.6 Hz), 1.04 - 1.16 (2H, m); ¹³C NMR (101 MHz, CD₃CN) δ ppm [missing C-B peak] 144.39, 134.98, 129.84, 129.52, 126.66, 124.14, 34.34; HRMS (m/z): [M - H]⁻ for C₁₀H₁₁BF₃, calcd, 199.0911; found, 199.0419.
Preparation of (2S,3R,4S)-4-benzyl-2-((tert-butyldimethylsilyl)oxy)hex-5-en-3-ol (Compound 7.15, Scheme 7.8):

Aldehyde 7.16 derived from (S)-ethyl-lactate [(S)-2-((tert-butyldimethylsilyl)oxy)propanal] was prepared according to a literature protocol:23 (S)-2-((tert-butyldimethylsilyl)oxy)propanal (684 mg, 3.63 mmol, 1.0 eq.) and Z-benzyl allyltrifluoroborate 7.17 (1.04 g, 4.36 mmol, 1.2 eq.) were combined in CH$_2$Cl$_2$ (9 mL) and water (1 mL) and montmorrolonite K10 (700 mg) was added and the reaction mixture was stirred vigorously overnight at room temperature. After 14 hours, the mixture was filtered through a celite plug (1 cm tall x 1 cm wide) using CH$_2$Cl$_2$ (30 mL) to wash/elute and the filtrate concentrated in vacuo and crude $^1$H NMR shows no trace of aldehyde starting material and 88:9 ratio of 1,2-anti:1,2-syn diastereomers and 97:3 ratio of 2,3-syn:2,3-anti diastereomers. The crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 892 mg (77%) of Compound 7.15 (Scheme 7.8) as a clear oil as an inseparable 10:1 mixture of diastereomers. \([\alpha]_D^{25} = -3.6\) (c 0.28, CHCl$_3$); R$_f$ = 0.53 (20% EtOAc/hexanes); IR (neat, cm$^{-1}$) 3573, 3083, 3028, 2955, 2898, 2857, 1641, 1604, 1471, 1463, 1454, 1383, 1257, 1094, 996; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm major isomer: 7.21 - 7.26 (2H, m), 7.10 - 7.19 (3H, m), 5.44 (1H, dt, $J$=17.0, 10.0 Hz), 4.95 (1H, dd, $J$=10.5, 2.0 Hz), 4.76 (1H, dd, $J$=17.0, 2.5 Hz), 3.84 (1H, qd, $J$=6.5, 3.0 Hz), 3.51 (1H, ddd, $J$=10.0, 3.0, 1.0 Hz), 3.26 (1H, dd, $J$=13.5, 3.5 Hz), 2.47 - 2.58 (2H, m), 2.29 (1H, dddd, $J$=9.5, 9.5, 9.5, 3.0 Hz), 1.07 (3H, d, $J$=6.5 Hz), 0.89 (9H, s), 0.07 – 0.04 (6H, m); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm major isomer: 140.00, 137.09, 129.73, 127.86, 125.67, 117.28, 69.67, 48.50, 37.90, 25.81, 18.02, 15.15, -4.53, -4.87; HRMS (m/z): [M + H]$^+$ for C$_{19}$H$_{33}$O$_2$Si, calcd, 321.22498; found, 321.22589.
Preparation of (2S,3R,4S)-4-benzyl-2-((tert-butyldimethylsilyl)oxy)hex-5-en-3-yl isobutyrate (Compound 7.31, Scheme 7.9):

Homo-allylic alcohol 7.15 prepared above (410 mg, 1.28 mmol, 1.0 eq.) was dissolved in CH_{2}Cl_{2} (10 mL) and cooled to 0 °C. Pyridine (505 mg, 0.51 mL, 6.39 mmol, 5.0 eq.) was then added followed by DMAP (16 mg, 0.128 mmol, 0.1 eq.) then isobutyryl chloride (681 mg, 0.67 mL, 6.39 mmol, 5.0 eq.) and the mixture stirred overnight allowed to warm to room temperature. After 16 hrs, the mixture was diluted with CH_{2}Cl_{2} (75 mL) and sat’d NaHCO_{3}(aq) (20 mL) and the phases were separated. The organic extract was dried (MgSO_{4}), filtered and concentrated in vacuo and the crude residue thus obtained was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 443 mg (88%) of Compound 7.31 (Scheme 7.9) as a clear oil. [α]_{D}^{25} = -9.1 (c 0.60, CHCl_{3}); R_{f} = 0.56 (20% EtOAc/hexanes); IR (CH_{2}Cl_{2}, cm\(^{-1}\)) 3084, 3064, 3028, 2975, 2956, 2929, 2894, 2857, 1738, 1471, 1454, 1385, 1256, 1190, 1156, 1109, 1070, 1031, 833; \(^1\)H NMR (400 MHz, CDCl_{3}) δ ppm 7.23 (2H, d, J =7.5 Hz), 7.06 - 7.18 (3H, m), 5.53 (1H, dt, J =17.0, 9.5 Hz), 4.91 - 5.02 (2H, m), 4.72 - 4.81 (1H, m), 3.97 (1H, qd, J =6.5, 3.5 Hz), 2.90 (1H, dd, J =13.5, 3.5 Hz), 2.51 - 2.64 (2H, m), 2.40 - 2.49 (1H, m), 1.21 (6H, d, J =7.0 Hz), 1.13 (3H, d, J =6.5 Hz, 3 H), 0.87 (9H, s), 0.01 - 0.06 (6H, m); \(^1\)C NMR (101 MHz, CDCl_{3}) δ ppm 176.5, 139.9, 137.2, 129.3, 128.0, 125.8, 117.5, 78.0, 68.3, 47.2, 36.9, 34.4, 25.8, 19.2, 18.0, 17.4, -4.6, -4.9; HRMS (m/z): [M + H]^+ for C_{23}H_{39}O_{3}Si, calcd, 391.26685; found, 391.26597.

Preparation of (2S,3R,4S)-4-benzyl-2-hydroxyhex-5-en-3-yl isobutyrate (Compound 7.32, Scheme 7.9):

Compound 7.31 (322 mg, 0.824 mmol, 1.0 eq.) was dissolved in THF (5 mL) and pyridine (1 mL) in a scintillation vial and ~70% HF-pyridine (3.0 mL) was then added and stirred vigorously at room temperature overnight. After 16 hrs, the reaction mixture was carefully diluted with sat’d NaHCO_{3}(aq) (10 mL) and CH_{2}Cl_{2} (50 mL) and the phases were separated. The
aqueous phase was extracted again with CH$_2$Cl$_2$ (50 mL) and the organic extracts combined, dried (MgSO$_4$), filtered and concentrated in vacuo. The crude residue thus obtained was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 160 mg (70%) of Compound 7.32 (Scheme 7.9) as a clear oil. [α]$_D^{25}$ = -29.0 (c 0.10, CH$_2$Cl$_2$); R$_f$ = 0.53 (40% EtOAc/hexanes); IR (neat, cm$^{-1}$): 3476, 3085, 3064, 3028, 2977, 2934, 2876, 1727, 1709, 1603, 1497, 1468, 1454, 1386, 1262, 1197, 1156, 1070, 917; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.22 - 7.29 (2H, m), 7.14 - 7.21 (1H, m), 7.06 - 7.13 (2H, m), 5.56 (1H, dt, J=17.0, 9.5 Hz), 4.93 - 5.03 (2H, m), 4.83 (1H, d, J=17.0 Hz), 3.93 - 4.08 (1H, m), 2.93 (1H, dd, J=13.5, 3.5 Hz), 2.54 - 2.70 (2H, m), 2.42 - 2.53 (1H, m), 2.06 (1H, d, J=5.5 Hz), 1.24 (6H, d, J=7.0 Hz), 1.15 (3H, d, J=6.5 Hz); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 177.8, 139.4, 136.8, 129.4, 128.1, 126.0, 117.8, 78.7, 68.2, 47.7, 37.3, 34.4, 19.14, 19.10, 16.8; HRMS (m/z): [M + H]$^+$ for C$_{17}$H$_{25}$O$_3$, calcd, 277.18037; found, 277.18052.

Preparation of (2S,3R)-(2S,3R,4S)-4-benzyl-3-(isobutyrolyoxy)hex-5-en-2-yl 2-((tert-butoxycarbonyl)amino)-3-((tert-butyldimethylsilyl)oxy)butanoate (Compound 7.12, Scheme 7.9):

Protected threonine compound 7.13 [(2S,3R)-2-((tert-butoxycarbonyl)amino)-3-((tert-butyldimethylsilyl)oxy)butanoic acid] was prepared according to a literature procedure from N-Boc-L-threonine.$^{24}$ To OTBS-NBoc-L-threonine acid 7.13 (263 mg, 0.788 mmol, 2.0 eq.) dissolved in CH$_2$Cl$_2$ (1 mL) was added MNBA (271 mg, 0.788 mmol, 2.0 eq.), DMAP (24 mg, 0.197 mmol, 0.5 eq.) and Et$_3$N (159 mg, 0.22 mL, 1.58 mmol, 4.0 eq.) in that order. This mixture was stirred at room temperature for 20 mins before addition of alcohol 7.31 (109 mg, 0.394 mmol, 1.0 eq.) as a solution in CH$_2$Cl$_2$ (1 mL) and stirred at room temperature overnight. After 18 hrs, the reaction mixture was diluted with CH$_2$Cl$_2$ (100 mL) and sat’d NaHCO$_3$(aq) (15 mL) and the phases were separated. The organic extract was dried (MgSO$_4$), filtered, concentrated in vacuo and the crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 194
mg (83%) of Compound 7.12 (Scheme 7.9) as a clear oil. \([\alpha]_D^{24} = -11.4 \text{ (c 0.29, CH}_2\text{Cl}_2); \text{R}_{f} = 0.73 \text{ (40% EtOAc/hexanes); IR (CH}_2\text{Cl}_2, \text{ cm}^{-1}) 3459, 3085, 3029, 2977, 2957, 2930, 2857, 1738, 1720, 1495, 1366, 1156, 1098, 1070; \text{^1H NMR (400 MHz, CDCl}_3) \delta \text{ ppm 7.20 - 7.28 (2H, m), 7.13 - 7.19 (1H, m), 7.04 - 7.11 (2H, m), 5.46 (1H, dt, J=17.0, 10.0 Hz), 5.12 - 5.24 (2H, m), 4.96 - 5.07 (2H, m), 4.77 - 4.89 (1H, m), 4.32 - 4.44 (1H, m), 4.09 (1H, dd, J=10.0, 1.5 Hz), 2.85 (1H, dd, J=13.0, 3.5 Hz), 2.63 (1H, dt, J=14.0, 7.0 Hz), 2.38 - 2.54 (2H, m), 1.46 (9H, s), 1.26 (3H, d, J=6.3 Hz), 1.23 (6H, d, J=7.0 Hz), 1.17 (3H, d, J=6.0 Hz), 0.85 (9H, s), 0.03 - 0.10 (6H, m); \text{^13C NMR (101 MHz, CDCl}_3) \delta \text{ ppm 176.4, 170.1, 156.1, 139.0, 135.8, 129.4, 128.1, 126.0, 118.6, 79.7, 74.6, 71.7, 68.7, 59.4, 47.4, 37.3, 34.3, 28.3, 25.7, 21.0, 19.2, 19.1, 17.9, 13.1, -4.3, -5.2; HRMS (m/z): [M + H]^+ \text{ for C}_{32}\text{H}_{54}\text{NO}_7\text{Si, calcd, 592.36695; found, 592.36726.}

Preparation of (2R,3R,4S)-2-benzyl-4-(((2S,3R)-2-((tert-butoxycarbonyl)amino)-3-((tert-butyldimethylsilyl)oxy)butanoyl)oxy)-3-(isobutyryloxy)pentanoic-acid (Compound 7.11, Scheme 7.9):

Compound 7.12 (138 mg, 0.233 mmol, 1.0 eq.) was dissolved in CH₂Cl₂ (10 mL) and ~5-6 Sudan III crystals were added to colour the solution pink. After cooling this solution to to -78 °C in a dry ice/acetone bath, ozone was bubbled through the solution until colourless (15 mins) and the ozone flow stopped. Argon was then bubbled through the solution (5 mins) to remove residual ozone then Me₂S (72 mg, 0.085 mL, 1.16 mmol, 5.0 eq.) was added and mixture warmed to room temperature and stirred 2 hrs. The mixture was then diluted with CH₂Cl₂ (40 mL) and H₂O (10 mL) and the phases separated and aqueous extracted again with CH₂Cl₂ (20 mL). Organic extracts were combined, dried (MgSO₄), filtered and concentrated in vacuo to give 141 mg (quant. yield) of crude aldehyde intermediate which was used immediately in the next step without further purification.

The aldehyde obtained above (138 mg, 0.233 mmol, 1.0 eq.) was dissolved in rBuOH (4 mL) and H₂O (2 mL) and NaH₂PO₄·H₂O (129 mg, 0.932 mmol, 4.0 eq.) was then added
followed by addition of NaClO₂ (147 mg 1.63 mmol, 7.0 eq.) and 2-Me-2-butene (130 mg, 0.20 mL, 1.86 mmol, 8.0 eq.) in that order. The reaction mixture was then stirred at room temperature for 18 hrs then volatiles removed on the rotovap and the crude residue was partitioned between CH₂Cl₂ (40 mL) and H₂O (10 mL) and the phases were separated. The organic extract was dried (Na₂SO₄), filtered and concentrated in vacuo and the crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 82 mg (58% over 2 steps) of Compound 7.11 (Scheme 7.9) as a light yellow oil. \([\alpha]_D^{25} = +5.8 \text{ (c 0.26, CH₂Cl₂); } R_f = 0.42 \text{ [streaks] (60% EtOAc/hexanes); IR (CH₂Cl₂, cm}^{-1}) 3455, 2977, 2956, 2930, 2857, 1750, 1714, 1505, 1367, 1316, 1252, 1164, 1100, 1070; ^1H NMR (400 MHz, CDCl₃) δ ppm (missing COOH peak) 7.12 - 7.25 (5H, m), 5.39 (1H, t, J=7.5 Hz), 5.25 (1H, d, J=10.0 Hz), 5.08 (1H, dq [app quin], J=6.5 Hz), 4.51 (1H, qd, J=6.0, 1.0 Hz), 4.11 (1H, dd, J=10.0, 1.5 Hz), 2.81 - 2.89 (3H, m), 2.59 (1H, spt, J=7.0 Hz), 1.48 (9H, s), 1.24 (3H, d, J=6.5 Hz), 1.21 (6H, dd, J= 7.0, 2.5 Hz), 1.15 (3H, d, J=6.0 Hz), 0.84 (9H, s), 0.07 (3H, s), 0.02 (3H, s); ^13C NMR (126 MHz, CDCl₃) δ ppm 175.8, 173.9, 170.1, 157.2, 137.9, 128.8, 128.5, 126.6, 80.8, 73.4, 71.6, 68.5, 59.8, 49.5, 34.5, 34.2, 28.4, 25.7, 20.8, 19.05, 18.97, 17.9, 16.2, -4.3, -5.1; HRMS (m/z): [M + Na]+ for C₃₁H₅₁NO₅SiNa, calcd, 632.3225; found, 632.3224, [M - H]- for C₃₁H₅₀NO₅Si, calcd, 608.3260; found, 608.3251.

**Preparation of the splenocin N-Boc-lactone (Compound 7.10, Scheme 7.10):**

Compound 7.11 (60 mg, 0.0984 mmol, 1.0 eq.) was dissolved in THF (3 mL) and TBAF (0.20 mL of a 1M sol’n in THF, 0.20 mmol, 2.0 eq.) was added and stirred at room temperature. After 2 hrs, TLC appeared to indicate complete conversion. The mixture was partitioned between Et₂O (50 mL) and H₂O (20 mL) and the phases were separated and the aqueous was extracted again with Et₂O (50 mL). Organic extracts were combined and washed with 1M HCl (2 x 10 mL) then with sat’d NaCl(aq) (10 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude residue thus obtained was observed to be only ~3:1 deprotected product:starting material by ^1H NMR. As a result,
this material was re-dissolved in THF (3 mL) and TBAF (0.40 mL of a 1M sol’n in THF, 0.40 mmol, 4.0 eq.) was added and stirred at room temperature. After 1 hr, the reaction was subjected to the same work-up as described above to give 40 mg (82% yield) of ~90% deprotected material as a clear oil which was used immediately in the next step without further purification.

The seco-acid obtained above (40 mg, 0.0807 mmol, 1.0 eq.) was dissolved in toluene (15 mL) and added by syringe pump at a rate of 1.0 mL/hr to a stirring room temperature solution of MNBA (42 mg, 0.121 mmol, 1.5 eq.) and DMAP (59 mg, 0.484 mmol, 6.0 eq.) and powdered 4 Å mol. Sieves (500 mg) in toluene (25 mL) [total final conc. = 0.002 M]. After complete addition of seco-acid (15 hrs) the mixture was stirred a further 29 hrs at room temperature (44 hrs total) then filtered through a celite pad to remove mol. sieves using ethyl acetate (20 mL) to wash/elute. The filtrate was then partitioned between ethyl acetate (50 mL) and sat’d NaHCO₃(aq) (20 mL) and the organic phase was extracted, washed with sat’d NaCl(aq) (5 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 11.8 mg (25% over 2 steps) of Compound 7.10 (Scheme 7.10) as a white waxy semi-solid. [α]D²⁴ = +54.8 (c 0.21, CH₂Cl₂); Rf= 0.35 (20% EtOAc/hexanes); IR (CH₂Cl₂, cm⁻¹) 3390, 2977, 2937, 2875, 1750, 1715, 1497, 1367, 1245, 1150, 1065; ¹H NMR (500 MHz, CDCl₃) δ ppm 7.21 - 7.25 (2H, m), 7.15 - 7.20 (1H, m), 7.08 - 7.13 (2H, m), 5.39 - 5.47 (1H, m), 5.13 - 5.21 (2H, m), 4.91 - 4.99 (1H, m), 4.87 (1H, t, J=8.0 Hz), 2.97 (1H, dd, J= 13.5, 11.5 Hz), 2.81 - 2.89 (1H, m), 2.66 (1H, dd, J=13.5, 3.5 Hz), 2.58 (1H, spt, J=7.0 Hz), 1.43 (9H, s), 1.28 (3H, d, J=6.0 Hz), 1.22 (3H, d, J=3.0 Hz), 1.22 (6H, dd, J=7.0, 3.0 Hz), 1.14 (3H, d, J=6.5 Hz); ¹³C NMR (126 MHz, CDCl₃) δ ppm 175.6, 171.9, 170.6, 154.7, 138.1, 128.7, 128.5, 126.5, 80.4, 75.2, 74.0, 71.3, 54.3, 51.8, 34.5, 34.1, 28.2, 19.0, 17.9, 14.6; HRMS (m/z): [M + Na]⁺ for C₂₅H₃₅NO₈Na, calcd, 500.2255; found, 500.2243.
Preparation of splenocin-B (Compound 7.6, Scheme 7.10):

Compound 7.10 (11.8 mg, 0.0247 mmol, 1.0 eq.) was dissolved in CH$_2$Cl$_2$ (2 mL) and treated with TFA (0.25 mL) and stirred at room temperature overnight. After 20 hrs, TLC indicated complete consumption of starting material and volatiles were removed under an air stream. The residue was re-dissolved in CH$_2$Cl$_2$ (3 mL) and volatiles removed again under an air stream to give 12.4 mg (quant. yield) of the crude Boc deprotected TFA salt as a white solid which was used immediately in the next step without further purification.

The splenocin lactone TFA salt obtained above (12.1 mg, 0.0247 mmol, 1.0 eq.) and 3-formamide salicyclic acid 7.33 (5.4 mg, 0.0296 mmol, 1.2 eq.) [prepared as previously described] and HOBT (3.8 mg, 0.0247 mmol, 1.0 eq.) and EDCI (5.2 mg, 0.0272 mmol, 1.1 eq.) were combined. Then a solution of N-Me-morpholine (12.5 mg, 0.124 mmol, 5.0 eq.) in DMF (1 mL) was added and the mixture stirred at room temperature overnight. After 20 hrs, the mixture was diluted with ethyl acetate (40 mL) and washed with pH=5.5 phosphate buffer (10 mL) followed by 50% sat’d NaCl(aq) (4 x 10 mL). The organic extract was then dried (MgSO$_4$), filtered and concentrated in vacuo and the crude residue was purified by flash chromatography through silica gel using ethyl acetate in hexanes to elute (gradient elution 0-100% EtOAc) to provide 3.2 mg (24% over 2 steps) of splenocin-B (Compound 7.6, Scheme 7.10) as a white waxy semi-solid. [$\alpha$]$_D^{25} = +58.9$ (c 0.056, MeOH); [lit.$^{10}$ [$\alpha$]$_D = +68.0$ (c 0.1, MeOH); R$_f$ = 0.18 (40% EtOAc/hexanes); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3379, 2985, 2935, 1747, 1651, 1616, 1533, 1365, 1253, 1180, 1149, 1062; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ ppm 12.60 (1H, s), 8.54 (1H, dd, $J$=8.0, 1.5 Hz), 8.50 (1H, d, $J$=2.0 Hz), 7.89 (1H, br. s.), 7.24 - 7.25 (1H, m), 7.16 - 7.23 (3H, m), 7.13 (2H, dd, $J$=8.0, 1.5 Hz), 6.99 (1H, d, $J$=7.5 Hz), 6.91 (1H, dd, $J$=8.0 Hz), 5.62 (1H, dq[app quin], $J$=7.0 Hz), 5.27 (1H, dd, $J$=7.5 Hz), 5.22 (1H, dd, $J$=10.0 Hz), 5.03 (1H, dq, $J$=10.0, 6.5 Hz), 3.00 (1H, dd, $J$=13.5, 11.5 Hz), 2.87 - 2.94 (1H, m), 2.70 (1H, dd, $J$=13.5, 3.0 Hz), 2.61 (1H, spt, $J$=7.0 Hz), 1.33 (3H, d, $J$=6.0 Hz), 1.24 (6H, dd, $J$=7.0, 3.5 Hz), 1.17 (3H, d, $J$=6.5 Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ ppm 175.6, 171.9, 170.0, 169.3, 158.9,
150.6, 137.9, 128.7, 128.6, 127.4, 126.6, 124.8, 120.0, 119.0, 112.5, 75.1, 74.8, 70.9, 53.5, 51.9, 34.5, 34.1, 19.0, 17.9, 14.7; HRMS (m/z): [M + H]^+ for C_{28}H_{33}N_{2}O_{9}, calcd, 541.21860; found, 541.21806.

3.5 References


Appendix 1:

$^1$H and $^{13}$C NMR Spectra for Chapter 2
20110722-reb_3_1_f23_Proton-002

TMS $\equiv \equiv N$ $\equiv N$ $\equiv N$

\begin{align*}
\text{CO}_2\text{-Pr} & \quad \text{CO}_2\text{-Pr} \\
2.3 & \quad 2.3
\end{align*}

20110126-reb_1_127_f23_Carbon-001

TMS $\equiv \equiv N$ $\equiv N$ $\equiv N$

\begin{align*}
\text{CO}_2\text{-Pr} & \quad \text{CO}_2\text{-Pr} \\
2.3 & \quad 2.3
\end{align*}
Boc  
\text{Ph} \equiv \equiv \text{N}  
\text{HN-Boc} 
\text{2.8} 

\text{Chemical Shift (ppm)} 

18.00 \quad 1.06 \quad 2.67 \quad 1.88 

\text{Chemical Shift (ppm)} 

154.30 \quad 152.88 \quad 131.33 \quad 128.38 \quad 127.90 \quad 123.13 \quad 84.54 \quad 82.58 \quad 82.53 \quad 71.59 \quad 28.36 \quad 28.13
\text{HN-Boc}

\text{2.14}

\text{HN-Boc}

\text{2.14}
Chemical Shift (ppm)

2.26

Chemical Shift (ppm)

166.37
154.32
152.39
146.79
115.57
82.98 81.74
52.97 51.15
28.12 27.75
20110903-reb_3_83_c2f21_Proton-001

Chemical Shift (ppm)
3.48 9.52 15.01 1.83 1.88 1.16 1.91 2.09

20110905-reb_3_83_c2_f21_Carbon-002

Chemical Shift (ppm)
154.64 152.46 143.39 135.09 132.80 126.04 125.47 123.42 84.28 82.51 31.72 29.11 28.58 28.08 27.85 24.64 22.59 14.10
Chemical Shift (ppm)

- 9.00
- 1.58
- 0.77
- 0.76
- 4.78

Chemical Shift (ppm)

- 153.97
- 153.73
- 138.63
- 134.81
- 128.87
- 128.73
- 127.23
- 113.22
- 83.31
- 32.59
- 28.02
Chemical Shift (ppm)

- 3.35
- 3.32
- 2.27
- 1.00
- 4.98
- 0.96

Chemical Shift (ppm)

- 150.45
- 141.44
- 134.15
- 129.44
- 128.62
- 115.26
- 107.64
- 55.11
- 13.64
- 12.90
Representative 1D NOE Spectra:
Appendix 2:

$^1$H and $^{13}$C NMR Spectra for Chapter 3
Hydrazidomycin A

(Compound 3.1, $^1$H NMR @ rm. temp. d6-DMso)
Hydrazidomycin A

(Compound 3.1, $^1$H NMR @ 55 °C d6-DMSO)
Hydrazidomycin A
(Compound 3.1)
Hydrazidomycin B
(Compound 3.2, $^1$H NMR @ RT in $d_6$-DMSO)
Hydrazidomycin B
(Compound 3.2, $^1$H NMR @ 55 °C in d6-DMSO)
Hydrazidomycin B
(Compound 3.2)
Elaiomycin B
(Compound 3.3, $^1$H NMR @ RT in $d$-DMSO)
Elaiomycin B
(Compound 3.3, $^1$H NMR @ 55 °C in $d_6$-DMSO)
Elaiomycin B
(Compound 3.3)
(Compound 3.16, d$_7$-DMF)
20130612-reb-10-92-c3-fs6-8-1.bkr.esp

Chemical Shift (ppm)
3.00 6.15 2.07 3.54 1.52 1.93 1.95 0.97 0.93 0.90

20130614-reb-10-92-fs6-8-1.bkr.esp

Chemical Shift (ppm)
173.96 172.38 171.10 147.08 131.28 70.41 60.97 46.76 31.01 26.42 25.83 22.01 20.03 13.89
20111012-reb_3_159_fs34_41_Proton-002

Boc - O
\[ \text{NH}_2 \]

3.18

20111012-reb_3_159_fs34_41_Carbon-001

Boc - O
\[ \text{NH}_2 \]

3.18

Chemical Shift (ppm)
20111020-reb_3_167_fs15_16_Proton-002

Chemical Shift (ppm)
3.50 11.93 10.27 2.09 1.80 0.85 2.44 1.69

20111021-reb_3_167_fs15_16_Carbon-002

Chemical Shift (ppm)
171.11
168.68
149.81
85.74
74.58 73.09
63.55
59.48
32.92 31.86
29.37
27.80
24.43 22.67
14.11
**Chemical Shift (ppm)**

- 8.52
- 6.00
- 29.98
- 12.43
- 2.54
- 1.14
- 1.47
- 1.46
- 1.56

**Chemical Shift (ppm)**

- 174.92
- 155.48
- 81.14
- 70.10
- 69.34
- 34.91
- 31.98
- 31.73
- 29.43
- 29.12
- 28.42
- 24.61
- 22.54
- 14.39
- -0.40
3.26 (E-Hydrazidomycin A)

Chemical Shift (ppm)

3.26 (E-Hydrazidomycin A)

Chemical Shift (ppm)
reb-9-40-f16-55deg

Chemical Shift (ppm)
8.21  6.50  27.27  13.36  4.19  2.59  1.39  1.17  1.18  2.37  1.46

Chemical Shift (ppm)
174.91  155.55  130.04  81.10  69.89  69.37  34.78  34.49  31.96  31.71  29.29  29.11  28.41  27.05  24.61  22.53  14.37  14.00 -0.40
Appendix 3:

$^1$H and $^{13}$C NMR Spectra for Chapter 4
Chemical Shift (ppm)

8.44 0.96 0.97 0.93 0.94 0.90 1.53 1.68 0.87 1.76

Chemical Shift (ppm)

177.63 176.76 155.48 131.30 129.22 126.34 126.04 80.31 49.77 43.86 39.36 28.33 26.91

[Diagram of chemical structures]

[Diagram of chemical structures]
Chemical Shift (ppm)
20120924_mercury_400_reb-7-149-fs19-20-PROTON_01

\[
\text{OH} \quad 4.25 \quad \text{N(Boc)}_2
\]

20120924_mercury_400_reb-7-149-fs19-20-CARBON_01

\[
\text{OH} \quad 4.25 \quad \text{N(Boc)}_2
\]
Chemical Shift (ppm)

20120724_mercury_300_yh-1-72-f11-12-PROTON_01

Bn–N–N–N

4.44 N(Boc)$_2$

Chemical Shift (ppm)

20120725-yhu-72-f11-12-1.bkr.esp

Bn–N–N–N

4.44 N(Boc)$_2$

Chemical Shift (ppm)
Chemical Shift (ppm)

155.78
150.71
142.99
120.64
83.58
80.00
50.25
40.38
28.26 27.82
**PROTON Spectrum**

- Chemical Shift (ppm): 18.16, 3.02, 1.80, 0.79

**CARBON Spectrum**

- Chemical Shift (ppm): 158.77, 155.21, 150.16, 130.08, 129.02, 127.21, 119.24, 83.80, 27.59
Appendix 4:

X-Ray Crystal Structure Data for Compound 6.20 in Chapter 6

(Compound 6.20, Chapter 6)
Table 1. Crystal data and structure refinement for d13127.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>d13127</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C16 H31 N O3</td>
</tr>
<tr>
<td>Formula weight</td>
<td>285.42</td>
</tr>
<tr>
<td>Temperature</td>
<td>147(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>P 2 1 2 1 21</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 10.1293(9) Å, α = 90°.</td>
</tr>
<tr>
<td></td>
<td>b = 10.9916(10) Å, β = 90°.</td>
</tr>
<tr>
<td></td>
<td>c = 16.0690(15) Å, γ = 90°.</td>
</tr>
<tr>
<td>Volume</td>
<td>1789.1(3) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.060 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.072 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>632</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.540 x 0.200 x 0.130 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.245 to 27.598°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-13&lt;=h&lt;=13, -11&lt;=k&lt;=14, -20&lt;=l&lt;=20</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>25826</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>4138 [R(int) = 0.0375]</td>
</tr>
<tr>
<td>Completeness to theta = 25.242°</td>
<td>99.9 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.7456 and 0.6719</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>4138 / 0 / 196</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.045</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0341, wR2 = 0.0784</td>
</tr>
<tr>
<td></td>
<td>R1 = 0.0421, wR2 = 0.0825</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>-0.2(3)</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>n/a</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.196 and -0.152 e.Å⁻³</td>
</tr>
</tbody>
</table>
Table 2. Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($\AA^2 \times 10^3$) for d13127. $U_{eq}$ is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>$U_{eq}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>6336(1)</td>
<td>5585(1)</td>
<td>7673(1)</td>
<td>33(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>4020(1)</td>
<td>8732(1)</td>
<td>6231(1)</td>
<td>31(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>5118(1)</td>
<td>7430(1)</td>
<td>5372(1)</td>
<td>28(1)</td>
</tr>
<tr>
<td>N(1)</td>
<td>5214(1)</td>
<td>7145(1)</td>
<td>6727(1)</td>
<td>25(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>4733(2)</td>
<td>7189(1)</td>
<td>7586(1)</td>
<td>23(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>5730(2)</td>
<td>6524(1)</td>
<td>8152(1)</td>
<td>25(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>6775(2)</td>
<td>7353(2)</td>
<td>8570(1)</td>
<td>28(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>7690(2)</td>
<td>6544(2)</td>
<td>9097(1)</td>
<td>42(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>7587(2)</td>
<td>8042(2)</td>
<td>7922(1)</td>
<td>39(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>6038(2)</td>
<td>8183(2)</td>
<td>9160(1)</td>
<td>32(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>6027(2)</td>
<td>9377(2)</td>
<td>9172(1)</td>
<td>45(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>3364(2)</td>
<td>6598(2)</td>
<td>7644(1)</td>
<td>28(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>2562(2)</td>
<td>6886(2)</td>
<td>8424(1)</td>
<td>31(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>2096(2)</td>
<td>8202(2)</td>
<td>8434(1)</td>
<td>44(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>1390(2)</td>
<td>6018(2)</td>
<td>8476(1)</td>
<td>48(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>4727(2)</td>
<td>7844(1)</td>
<td>6123(1)</td>
<td>23(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>4867(2)</td>
<td>8130(2)</td>
<td>4607(1)</td>
<td>30(1)</td>
</tr>
<tr>
<td>C(14)</td>
<td>3398(2)</td>
<td>8269(2)</td>
<td>4450(1)</td>
<td>41(1)</td>
</tr>
<tr>
<td>C(15)</td>
<td>5480(2)</td>
<td>7321(2)</td>
<td>3946(1)</td>
<td>44(1)</td>
</tr>
<tr>
<td>C(16)</td>
<td>5562(2)</td>
<td>9348(2)</td>
<td>4659(1)</td>
<td>48(1)</td>
</tr>
</tbody>
</table>
Table 3. Bond lengths [Å] and angles [°] for d13127.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)-C(2)</td>
<td>1.427(2)</td>
</tr>
<tr>
<td>O(1)-H(1O)</td>
<td>0.77(2)</td>
</tr>
<tr>
<td>O(2)-C(12)</td>
<td>1.223(2)</td>
</tr>
<tr>
<td>O(3)-C(12)</td>
<td>1.3483(19)</td>
</tr>
<tr>
<td>O(3)-C(13)</td>
<td>1.4723(19)</td>
</tr>
<tr>
<td>N(1)-C(12)</td>
<td>1.334(2)</td>
</tr>
<tr>
<td>N(1)-C(1)</td>
<td>1.464(2)</td>
</tr>
<tr>
<td>N(1)-H(1N)</td>
<td>0.85(2)</td>
</tr>
<tr>
<td>C(1)-C(8)</td>
<td>1.534(2)</td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.544(2)</td>
</tr>
<tr>
<td>C(1)-H(1A)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.549(2)</td>
</tr>
<tr>
<td>C(2)-H(2A)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(3)-C(6)</td>
<td>1.513(2)</td>
</tr>
<tr>
<td>C(3)-C(5)</td>
<td>1.527(2)</td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.539(3)</td>
</tr>
<tr>
<td>C(4)-H(4A)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(4)-H(4B)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(4)-H(4C)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(5)-H(5A)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(5)-H(5B)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(5)-H(5C)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(6)-C(7)</td>
<td>1.313(3)</td>
</tr>
<tr>
<td>C(6)-H(6A)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(7)-H(7A)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(7)-H(7B)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(8)-C(9)</td>
<td>1.527(2)</td>
</tr>
<tr>
<td>C(8)-H(8A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(8)-H(8B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(9)-C(10)</td>
<td>1.522(3)</td>
</tr>
<tr>
<td>C(9)-C(11)</td>
<td>1.525(3)</td>
</tr>
<tr>
<td>C(9)-H(9A)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(10)-H(10A)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(10)-H(10B)</td>
<td>0.9800</td>
</tr>
</tbody>
</table>
C(10)-H(10C)  0.9800
C(11)-H(11A)  0.9800
C(11)-H(11B)  0.9800
C(11)-H(11C)  0.9800
C(13)-C(16)  1.515(3)
C(13)-C(14)  1.517(3)
C(13)-C(15)  1.518(3)
C(14)-H(14A)  0.9800
C(14)-H(14B)  0.9800
C(14)-H(14C)  0.9800
C(15)-H(15A)  0.9800
C(15)-H(15B)  0.9800
C(15)-H(15C)  0.9800
C(16)-H(16A)  0.9800
C(16)-H(16B)  0.9800
C(16)-H(16C)  0.9800

C(2)-O(1)-H(1O)  108.8(18)
C(12)-O(3)-C(13)  121.33(13)
C(12)-N(1)-C(1)  122.96(14)
C(12)-N(1)-H(1N)  118.0(14)
C(1)-N(1)-H(1N)  117.1(13)
N(1)-C(1)-C(8)  110.14(12)
N(1)-C(1)-C(2)  108.79(13)
C(8)-C(1)-C(2)  110.77(13)
N(1)-C(1)-H(1A)  109.0
C(8)-C(1)-H(1A)  109.0
C(2)-C(1)-H(1A)  109.0
O(1)-C(2)-C(1)  107.79(13)
O(1)-C(2)-C(3)  111.43(14)
C(1)-C(2)-C(3)  115.07(13)
O(1)-C(2)-H(2A)  107.4
C(1)-C(2)-H(2A)  107.4
C(3)-C(2)-H(2A)  107.4
C(6)-C(3)-C(5)  113.20(15)
C(6)-C(3)-C(4)  107.51(14)
<table>
<thead>
<tr>
<th>Bond</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(5)-C(3)-C(4)</td>
<td>109.68(16)</td>
</tr>
<tr>
<td>C(6)-C(3)-C(2)</td>
<td>106.81(14)</td>
</tr>
<tr>
<td>C(5)-C(3)-C(2)</td>
<td>111.37(13)</td>
</tr>
<tr>
<td>C(4)-C(3)-C(2)</td>
<td>108.06(14)</td>
</tr>
<tr>
<td>C(3)-C(4)-H(4A)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(3)-C(4)-H(4B)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(4A)-C(4)-H(4B)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(3)-C(4)-H(4C)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(4A)-C(4)-H(4C)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(4B)-C(4)-H(4C)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(3)-C(5)-H(5A)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(3)-C(5)-H(5B)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(5A)-C(5)-H(5B)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(3)-C(5)-H(5C)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(5A)-C(5)-H(5C)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(5B)-C(5)-H(5C)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(7)-C(6)-C(3)</td>
<td>128.03(18)</td>
</tr>
<tr>
<td>C(7)-C(6)-H(6A)</td>
<td>116.0</td>
</tr>
<tr>
<td>C(3)-C(6)-H(6A)</td>
<td>116.0</td>
</tr>
<tr>
<td>C(6)-C(7)-H(7A)</td>
<td>120.0</td>
</tr>
<tr>
<td>C(6)-C(7)-H(7B)</td>
<td>120.0</td>
</tr>
<tr>
<td>H(7A)-C(7)-H(7B)</td>
<td>120.0</td>
</tr>
<tr>
<td>C(9)-C(8)-C(1)</td>
<td>116.32(13)</td>
</tr>
<tr>
<td>C(9)-C(8)-H(8A)</td>
<td>108.2</td>
</tr>
<tr>
<td>C(1)-C(8)-H(8A)</td>
<td>108.2</td>
</tr>
<tr>
<td>C(9)-C(8)-H(8B)</td>
<td>108.2</td>
</tr>
<tr>
<td>C(1)-C(8)-H(8B)</td>
<td>108.2</td>
</tr>
<tr>
<td>H(8A)-C(8)-H(8B)</td>
<td>107.4</td>
</tr>
<tr>
<td>C(10)-C(9)-C(11)</td>
<td>110.62(17)</td>
</tr>
<tr>
<td>C(10)-C(9)-C(8)</td>
<td>111.73(15)</td>
</tr>
<tr>
<td>C(11)-C(9)-C(8)</td>
<td>109.23(15)</td>
</tr>
<tr>
<td>C(10)-C(9)-H(9A)</td>
<td>108.4</td>
</tr>
<tr>
<td>C(11)-C(9)-H(9A)</td>
<td>108.4</td>
</tr>
<tr>
<td>C(8)-C(9)-H(9A)</td>
<td>108.4</td>
</tr>
<tr>
<td>C(9)-C(10)-H(10A)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(9)-C(10)-H(10B)</td>
<td>109.5</td>
</tr>
</tbody>
</table>
H(10A)-C(10)-H(10B) 109.5
C(9)-C(10)-H(10C) 109.5
H(10A)-C(10)-H(10C) 109.5
H(10B)-C(10)-H(10C) 109.5
C(9)-C(11)-H(11A) 109.5
C(9)-C(11)-H(11B) 109.5
H(11A)-C(11)-H(11B) 109.5
C(9)-C(11)-H(11C) 109.5
H(11A)-C(11)-H(11C) 109.5
H(11B)-C(11)-H(11C) 109.5
O(2)-C(12)-N(1) 124.98(15)
O(2)-C(12)-O(3) 124.65(14)
N(1)-C(12)-O(3) 110.38(14)
O(3)-C(13)-C(16) 109.58(14)
O(3)-C(13)-C(14) 111.20(14)
C(16)-C(13)-C(14) 112.08(17)
O(3)-C(13)-C(15) 102.00(14)
C(16)-C(13)-C(15) 111.44(16)
C(14)-C(13)-C(15) 110.12(15)
C(13)-C(14)-H(14A) 109.5
C(13)-C(14)-H(14B) 109.5
H(14A)-C(14)-H(14B) 109.5
C(13)-C(14)-H(14C) 109.5
H(14A)-C(14)-H(14C) 109.5
H(14B)-C(14)-H(14C) 109.5
C(13)-C(15)-H(15A) 109.5
C(13)-C(15)-H(15B) 109.5
H(15A)-C(15)-H(15B) 109.5
C(13)-C(15)-H(15C) 109.5
H(15A)-C(15)-H(15C) 109.5
H(15B)-C(15)-H(15C) 109.5
C(13)-C(16)-H(16A) 109.5
C(13)-C(16)-H(16B) 109.5
H(16A)-C(16)-H(16B) 109.5
C(13)-C(16)-H(16C) 109.5
H(16A)-C(16)-H(16C) 109.5
H(16B)-C(16)-H(16C)  109.5

Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å²x 10³) for d13127. The anisotropic displacement factor exponent takes the form: \(-2\pi²\left[ h² a^{*2} U^{11} + \ldots + 2 h k a^{*} b^{*} U^{12} \right]\)

<table>
<thead>
<tr>
<th></th>
<th>U^{11}</th>
<th>U^{22}</th>
<th>U^{33}</th>
<th>U^{23}</th>
<th>U^{13}</th>
<th>U^{12}</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>50(1)</td>
<td>25(1)</td>
<td>23(1)</td>
<td>1(1)</td>
<td>2(1)</td>
<td>9(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>42(1)</td>
<td>27(1)</td>
<td>23(1)</td>
<td>1(1)</td>
<td>-1(1)</td>
<td>6(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>35(1)</td>
<td>32(1)</td>
<td>16(1)</td>
<td>3(1)</td>
<td>3(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>N(1)</td>
<td>32(1)</td>
<td>27(1)</td>
<td>18(1)</td>
<td>1(1)</td>
<td>5(1)</td>
<td>4(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>31(1)</td>
<td>24(1)</td>
<td>14(1)</td>
<td>-1(1)</td>
<td>2(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>34(1)</td>
<td>23(1)</td>
<td>19(1)</td>
<td>1(1)</td>
<td>1(1)</td>
<td>2(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>31(1)</td>
<td>32(1)</td>
<td>22(1)</td>
<td>1(1)</td>
<td>-1(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>40(1)</td>
<td>49(1)</td>
<td>36(1)</td>
<td>1(1)</td>
<td>-11(1)</td>
<td>6(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>39(1)</td>
<td>46(1)</td>
<td>33(1)</td>
<td>-2(1)</td>
<td>4(1)</td>
<td>-12(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>40(1)</td>
<td>35(1)</td>
<td>20(1)</td>
<td>-3(1)</td>
<td>-3(1)</td>
<td>-2(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>69(2)</td>
<td>38(1)</td>
<td>27(1)</td>
<td>-4(1)</td>
<td>-7(1)</td>
<td>5(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>31(1)</td>
<td>33(1)</td>
<td>18(1)</td>
<td>-3(1)</td>
<td>0(1)</td>
<td>-3(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>31(1)</td>
<td>42(1)</td>
<td>20(1)</td>
<td>0(1)</td>
<td>3(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>47(1)</td>
<td>50(1)</td>
<td>35(1)</td>
<td>-2(1)</td>
<td>13(1)</td>
<td>10(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>45(1)</td>
<td>63(1)</td>
<td>36(1)</td>
<td>-2(1)</td>
<td>13(1)</td>
<td>-15(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>26(1)</td>
<td>24(1)</td>
<td>18(1)</td>
<td>0(1)</td>
<td>1(1)</td>
<td>-6(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>30(1)</td>
<td>43(1)</td>
<td>17(1)</td>
<td>8(1)</td>
<td>0(1)</td>
<td>-5(1)</td>
</tr>
<tr>
<td>C(14)</td>
<td>32(1)</td>
<td>67(1)</td>
<td>24(1)</td>
<td>3(1)</td>
<td>-3(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>C(15)</td>
<td>40(1)</td>
<td>73(1)</td>
<td>19(1)</td>
<td>4(1)</td>
<td>5(1)</td>
<td>5(1)</td>
</tr>
<tr>
<td>C(16)</td>
<td>52(1)</td>
<td>51(1)</td>
<td>39(1)</td>
<td>19(1)</td>
<td>-2(1)</td>
<td>-16(1)</td>
</tr>
</tbody>
</table>
Table 5. Hydrogen coordinates (× 10^4) and isotropic displacement parameters (Å^2 x 10^3) for d13127.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(1A)</td>
<td>4667</td>
<td>8058</td>
<td>7766</td>
<td>28</td>
</tr>
<tr>
<td>H(2A)</td>
<td>5216</td>
<td>6123</td>
<td>8607</td>
<td>30</td>
</tr>
<tr>
<td>H(4A)</td>
<td>8321</td>
<td>7056</td>
<td>9399</td>
<td>63</td>
</tr>
<tr>
<td>H(4B)</td>
<td>8172</td>
<td>5984</td>
<td>8731</td>
<td>63</td>
</tr>
<tr>
<td>H(4C)</td>
<td>7162</td>
<td>6076</td>
<td>9495</td>
<td>63</td>
</tr>
<tr>
<td>H(5A)</td>
<td>8249</td>
<td>8545</td>
<td>8204</td>
<td>59</td>
</tr>
<tr>
<td>H(5B)</td>
<td>7002</td>
<td>8564</td>
<td>7592</td>
<td>59</td>
</tr>
<tr>
<td>H(5C)</td>
<td>8030</td>
<td>7459</td>
<td>7555</td>
<td>59</td>
</tr>
<tr>
<td>H(6A)</td>
<td>5520</td>
<td>7792</td>
<td>9574</td>
<td>38</td>
</tr>
<tr>
<td>H(7A)</td>
<td>6525</td>
<td>9822</td>
<td>8774</td>
<td>54</td>
</tr>
<tr>
<td>H(7B)</td>
<td>5520</td>
<td>9797</td>
<td>9578</td>
<td>54</td>
</tr>
<tr>
<td>H(8A)</td>
<td>2844</td>
<td>7153</td>
<td>6854</td>
<td>33</td>
</tr>
<tr>
<td>H(8B)</td>
<td>3477</td>
<td>5705</td>
<td>7610</td>
<td>33</td>
</tr>
<tr>
<td>H(9A)</td>
<td>3137</td>
<td>6748</td>
<td>8922</td>
<td>37</td>
</tr>
<tr>
<td>H(10A)</td>
<td>2863</td>
<td>8517</td>
<td>8453</td>
<td>65</td>
</tr>
<tr>
<td>H(10B)</td>
<td>1544</td>
<td>8341</td>
<td>8926</td>
<td>65</td>
</tr>
<tr>
<td>H(10C)</td>
<td>1582</td>
<td>8368</td>
<td>7930</td>
<td>65</td>
</tr>
<tr>
<td>H(11A)</td>
<td>872</td>
<td>6201</td>
<td>8975</td>
<td>72</td>
</tr>
<tr>
<td>H(11B)</td>
<td>1711</td>
<td>5178</td>
<td>8503</td>
<td>72</td>
</tr>
<tr>
<td>H(11C)</td>
<td>834</td>
<td>6119</td>
<td>7981</td>
<td>72</td>
</tr>
<tr>
<td>H(14A)</td>
<td>2975</td>
<td>7468</td>
<td>4464</td>
<td>61</td>
</tr>
<tr>
<td>H(14B)</td>
<td>3258</td>
<td>8640</td>
<td>3902</td>
<td>61</td>
</tr>
<tr>
<td>H(14C)</td>
<td>3011</td>
<td>8790</td>
<td>4880</td>
<td>61</td>
</tr>
<tr>
<td>H(15A)</td>
<td>5062</td>
<td>6517</td>
<td>3961</td>
<td>66</td>
</tr>
<tr>
<td>H(15B)</td>
<td>6428</td>
<td>7236</td>
<td>4054</td>
<td>66</td>
</tr>
<tr>
<td>H(15C)</td>
<td>5347</td>
<td>7688</td>
<td>3396</td>
<td>66</td>
</tr>
<tr>
<td>H(16A)</td>
<td>6497</td>
<td>9219</td>
<td>4790</td>
<td>71</td>
</tr>
<tr>
<td>H(16B)</td>
<td>5154</td>
<td>9842</td>
<td>5096</td>
<td>71</td>
</tr>
<tr>
<td>H(16C)</td>
<td>5486</td>
<td>9769</td>
<td>4124</td>
<td>71</td>
</tr>
<tr>
<td>H(1N)</td>
<td>5673(19)</td>
<td>6528(18)</td>
<td>6588(12)</td>
<td>28(5)</td>
</tr>
<tr>
<td>H(1O)</td>
<td>6310(20)</td>
<td>4980(20)</td>
<td>7923(15)</td>
<td>45(7)</td>
</tr>
<tr>
<td>---------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>-------</td>
</tr>
</tbody>
</table>

Table 6. Torsion angles [°] for d13127.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Torsion Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(12)-N(1)-C(1)-C(8)</td>
<td>72.77(19)</td>
</tr>
<tr>
<td>C(12)-N(1)-C(1)-C(2)</td>
<td>-165.64(14)</td>
</tr>
<tr>
<td>N(1)-C(1)-C(2)-O(1)</td>
<td>-30.75(17)</td>
</tr>
<tr>
<td>C(8)-C(1)-C(2)-O(1)</td>
<td>90.45(15)</td>
</tr>
<tr>
<td>N(1)-C(1)-C(2)-C(3)</td>
<td>94.26(16)</td>
</tr>
<tr>
<td>C(8)-C(1)-C(2)-C(3)</td>
<td>-144.54(13)</td>
</tr>
<tr>
<td>O(1)-C(2)-C(3)-C(6)</td>
<td>-171.51(13)</td>
</tr>
<tr>
<td>C(1)-C(2)-C(3)-C(6)</td>
<td>65.40(17)</td>
</tr>
<tr>
<td>O(1)-C(2)-C(3)-C(5)</td>
<td>64.42(18)</td>
</tr>
<tr>
<td>C(1)-C(2)-C(3)-C(5)</td>
<td>-58.67(19)</td>
</tr>
<tr>
<td>O(1)-C(2)-C(3)-C(4)</td>
<td>-56.10(18)</td>
</tr>
<tr>
<td>C(1)-C(2)-C(3)-C(4)</td>
<td>-179.19(14)</td>
</tr>
<tr>
<td>C(5)-C(3)-C(6)-C(7)</td>
<td>0.0(3)</td>
</tr>
<tr>
<td>C(4)-C(3)-C(6)-C(7)</td>
<td>121.3(2)</td>
</tr>
<tr>
<td>C(2)-C(3)-C(6)-C(7)</td>
<td>-122.9(2)</td>
</tr>
<tr>
<td>N(1)-C(1)-C(8)-C(9)</td>
<td>-163.07(14)</td>
</tr>
<tr>
<td>C(2)-C(1)-C(8)-C(9)</td>
<td>76.53(18)</td>
</tr>
<tr>
<td>C(1)-C(8)-C(9)-C(10)</td>
<td>69.9(2)</td>
</tr>
<tr>
<td>C(1)-C(8)-C(9)-C(11)</td>
<td>-167.37(16)</td>
</tr>
<tr>
<td>C(1)-N(1)-C(12)-O(2)</td>
<td>13.9(3)</td>
</tr>
<tr>
<td>C(1)-N(1)-C(12)-O(3)</td>
<td>-165.76(14)</td>
</tr>
<tr>
<td>C(13)-O(3)-C(12)-O(2)</td>
<td>8.6(2)</td>
</tr>
<tr>
<td>C(13)-O(3)-C(12)-N(1)</td>
<td>-171.66(13)</td>
</tr>
<tr>
<td>C(12)-O(3)-C(13)-C(16)</td>
<td>61.4(2)</td>
</tr>
<tr>
<td>C(12)-O(3)-C(13)-C(14)</td>
<td>-63.0(2)</td>
</tr>
<tr>
<td>C(12)-O(3)-C(13)-C(15)</td>
<td>179.60(15)</td>
</tr>
</tbody>
</table>

Symmetry transformations used to generate equivalent atoms:
Table 7. Hydrogen bonds for d13127 [Å and °].

<table>
<thead>
<tr>
<th>D-H...A</th>
<th>d(D-H)</th>
<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)-H(1O)...O(2)#1</td>
<td>0.77(2)</td>
<td>1.96(2)</td>
<td>2.7170(17)</td>
<td>165(3)</td>
</tr>
<tr>
<td>N(1)-H(1N)...O(1)</td>
<td>0.85(2)</td>
<td>2.136(19)</td>
<td>2.5571(19)</td>
<td>110.0(16)</td>
</tr>
</tbody>
</table>

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y-1/2,-z+3/2
Appendix 5:

$^1$H and $^{13}$C Spectra for Chapter 6
kitastatin (6,1)
Chemical Shift (ppm)

- 208.68
- 173.92
- 172.45
- 171.52
- 170.61
- 170.39
- 168.18
- 158.07
- 150.07
- 144.82
- 123.29
- 119.50
- 118.86
- 114.82
- 81.57
- 73.08
- 72.82
- 71.77
- 67.01
- 56.04
- 53.50
- 43.53
- 39.95
- 37.08
- 25.13
- 25.06
- 23.85
- 21.77
- 21.28
- 20.24
- 14.76
- 10.76
Chemical Shift (ppm)
18.00  2.87  3.17  0.94  3.14  3.70  4.01  1.89  0.98  2.01  1.04  1.00  1.03  1.05  1.02  1.01  0.96  1.02  0.85  0.83  0.80  0.62

respirantin (6.2)
respirantin (6.2)
$\text{BF}_3K$

**$6.18 \ [^1H \text{NMR}]$**

---

$\text{BF}_3K$

**$6.18 \ [^{13}\text{C NMR}]$**
BF$_3$K

6.18 [${}^{11}$B NMR]

BF$_3$K

6.18 [${}^{19}$F NMR]
20131005_mercury_400_reb-11-98-fs33-34-PROTON_01

Chemical Shift (ppm)
6.49  1.44  2.00  7.49  0.95  0.88  0.90

20131005_mercury_400_reb-11-98-fs33-34-CARBON_01

Chemical Shift (ppm)
145.52  113.32  74.37  44.20  31.33  25.76  21.90  21.76
**Chemical Shift (ppm)**

- 3.17
- 2.82
- 3.20
- 0.75
- 9.04
- 0.66
- 3.04
- 1.00
- 0.86
- 0.87
- 0.95
- 0.90
- 2.00
- 0.94
- 0.87
- 4.34

20121116-reb-8-93-fs23-24-3.bkr.esp

**Chemical Shift (ppm)**

- 171.03
- 170.81
- 167.98
- 156.78
- 136.26
- 128.46
- 127.88
- 82.69
- 77.41
- 69.13
- 67.68
- 67.02
- 59.40
- 36.63
- 27.97
- 24.52
- 18.95
- 16.65
- 15.18
- 11.55

20121116-reb-8-93-fs23-24-1.bkr.esp

**20121116-reb-8-93-fs23-24-3.bkr.esp**

**Chemical Shift (ppm)**

0.94
0.87
0.95
0.90
2.00
0.94
0.87
4.34

**Chemical Shift (ppm)**

0.87
0.85
0.90
0.95
1.00
0.86
0.87
0.95
0.90
2.00
0.94
0.87
4.34

**20121116-reb-8-93-fs23-24-1.bkr.esp**

**Chemical Shift (ppm)**

0.94
0.87
0.95
0.90
2.00
0.94
0.87
4.34
Appendix 6:

$^1$H and $^{13}$C NMR Spectra for Chapter 7
7.21

$^1$H NMR

7.21

$^{13}$C NMR
$^{11}$B NMR

$^{19}$F NMR
Chemical Shift (ppm)

1.63
12.00
5.86
8.12
9.71
2.50
7.81
3.35

1H NMR

Chemical Shift (ppm)

3.35
7.81
5.5
1.63

13C NMR
\((\text{Bu}_4\text{N})\text{F}_3\text{B}\) 

\begin{align*}
\text{O} & \\
\text{P} & \\
\text{OEt} & \\
\text{OEt} & \\
\end{align*}

7.22 

\text{\textsuperscript{11}B NMR}

---

\((\text{Bu}_4\text{N})\text{F}_3\text{B}\) 

\begin{align*}
\text{O} & \\
\text{P} & \\
\text{OEt} & \\
\end{align*}

7.22 

\text{\textsuperscript{31}P NMR}
Chemical Shift (ppm):

- $1^H$ NMR:
  - 7.17

- $^{13}C$ NMR:
  - 144.39
  - 134.98
  - 129.84
  - 126.66
  - 124.14
  - 34.34
Chemical Shift (ppm)

-139.13  -139.28  -139.45  -139.60

\[ \text{Chemical Shift (ppm)} \]

-50  -100  -150  -200

\[ \text{Chemical Shift (ppm)} \]

-140  -120  0  20  40  60  80  100  120  140

\[ \text{Chemical Shift (ppm)} \]
20131217-reb-12-54-pdt-fracs-1.bkr.esp

TBSO
Me

O

BocHN
Me

O

7.12

iPr

Chemical Shift (ppm)
5.07
9.01
2.75
5.54
2.78
8.57
1.79
1.00
0.85
0.69
0.76
0.93
1.74
1.73
0.83
1.89
1.03
2.14

20131217-reb-12-54-pdt-fracs-3.bkr.esp

180 160 140 120 100 80 60 40 20 0

Chemical Shift (ppm)
176.37
170.13
156.06
143.03
139.02
135.78
129.35
128.06
126.01
118.62
79.68
74.58
71.70
68.67
59.39
47.43
37.43
34.33
28.31
25.70
20.99
19.23
19.07
17.87
13.11
-4.30
-5.20

20131217-reb-12-54-pdt-fracs-3.bkr.esp

TBSO
Me

O

BocHN
Me

O

7.12

iPr

Chemical Shift (ppm)
176.37
170.13
156.06
143.03
139.02
135.78
129.35
128.06
126.01
118.62
79.68
74.58
71.70
68.67
59.39
47.43
37.43
34.33
28.31
25.70
20.99
19.23
19.07
17.87
13.11
-4.30
-5.20