Regioselective, Asymmetric α,α-Bisalkylation of Ketones via N-Amino Cyclic Carbamate
Chiral Auxiliaries: Methodology Development and Application to the Total Synthesis of
both (+)- and (-)-Stigmolone and Apratoxin D

by

Sarah Elizabeth Wengryniuk

Department of Chemistry
Duke University

Date:_______________________
Approved:

________________________________
Don M. Coltart, Supervisor

________________________________
Steven W. Baldwin

________________________________
Eric J. Toone

________________________________
Patrick Charbonneau

Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor of Philosophy in the Department of
Chemistry in the Graduate School
of Duke University

2012
ABSTRACT

Regioselective, Asymmetric α,α-Bisalkylation of Ketones via N-Amino Cyclic Carbamate Chiral Auxiliaries: Methodology Development and Application to the Total Synthesis of both (+) and (-)-Stigmolone and Apratoxin D

by

Sarah Elizabeth Wengryniuk

Department of Chemistry
Duke University

Date:_______________________

Approved:

___________________________
Don M. Coltart, Supervisor

___________________________
Steven W. Baldwin

___________________________
Eric J. Toone

___________________________
Patrick Charbonneau

An abstract of a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry in the Graduate School of Duke University

2012
Abstract

The α-alkylation of ketones is a transformation of central importance to organic synthesis. Our lab recently introduced the N-amino cyclic carbamate (ACC) chiral auxiliaries for asymmetric ketone α-alkylation. ACCs provide significant advantages over existing asymmetric ketone alkylation methods as they are easy to introduce, both deprotonation and alkylation can be run at relatively mild temperatures, stereoselectivity of alkylation is excellent and auxiliary removal is facile. A unique feature of ACCs is their ability to control the regioselectivity of deprotonation through what we have termed Complex Induced Syn-Deprotonation. In what follows, we describe several projects relating to the development and synthetic application of ACCs.

An optimized synthesis of our most successful ACC auxiliary was developed, including an improved method for the formation of the key N-N hydrazide bond.

A detailed mechanistic investigation of four ACC auxiliaries was conducted, examining the regio- and stereoselectivity of the alkylations at the level of the ACC hydrazone. This work culminated in a theoretical study of ACC auxiliaries, conducted through a collaboration with the Houk Group at UCLA.
We also describe the use of ACCs in the development of the first method for the regiocontrolled asymmetric $\alpha,\alpha$-bisalkylation of ketones. The method proceeds in excellent yield and with $>99:1$ diastereoselectivity. This method was also extended to the asymmetric $\alpha,\alpha,\alpha',\alpha'$-tetraalkylation of ketones, enabled by the development of a mild, epimerization-free LDA-mediated isomerization of the $\alpha,\alpha$-bisalkylated ACC hydrazones.

**Asymmetric $\alpha,\alpha$-Bisalkylation**

\[
\text{ACC} \xrightarrow{1. \text{LDA; } RX} \text{ACC} \xrightarrow{2. \text{LDA; } R'X} \xrightarrow{\text{Hydrolysis}} \text{R}^1
\]

**Asymmetric $\alpha,\alpha,\alpha',\alpha'$-Tetraalkylation**

\[
\text{ACC} \xrightarrow{\text{LDA}} \text{ACC} \xrightarrow{1. \text{LDA; } R^2X} \xrightarrow{2. \text{LDA; } R^3X} \text{ACC}
\]

Additionally, we discuss three synthetic applications of the ACC $\alpha,\alpha$-bisalkylation methodology. We report an asymmetric formal synthesis of (+)- and (−)-stigmolone, as well as two approaches to the polyketide fragment of the novel cyclic
depsipeptide apratoxin D, which have led to the completion of the first asymmetric total synthesis of apratoxin D.
To my Family and friends
Contents

Abstract ........................................................................................................................................ iv

List of Tables ................................................................................................................................ xiii

List of Figures ............................................................................................................................... xv

List of Schemes ............................................................................................................................ xvii

Acknowledgements ...................................................................................................................... xxii

1. N-Amino Cyclic Carbamate Chiral Auxiliaries ........................................................................ 1
   1.1 Background and Introduction ............................................................................................. 1
       1.1.1 Asymmetric Ketone Alkylation ................................................................................... 1
           1.1.1.2 SAMP/RAMP .................................................................................................... 11
       1.1.2 N-Amino Cyclic Carbamate Chiral Auxiliaries ............................................................ 20

2. Synthesis of ACC 1.72 ........................................................................................................... 23
   1.2.1 Formation of N-N bond ................................................................................................. 25

3. Mechanistic Investigation ...................................................................................................... 29
   1.3.1 Theoretical Studies on ACC Hydrazones ................................................................... 29
   1.3.2 Examination of ACC Stereoselectivity in 3-Pentanone ............................................... 37
       1.3.2.1 Analysis of ACC Alkylations Prior to Hydrolysis .................................................. 37
       1.3.2.2 Temperature Screen .............................................................................................. 39
   1.3.3 ACC 1.73 in Alkylation of Systems with Increased Steric Bulk .................................... 41
   1.3.4 Development of New Hydrolysis Conditions ............................................................... 42

4. Conclusion ............................................................................................................................... 44
1.5 Experimental Section ........................................................................................................ 45

1.5.1 Auxiliary Synthesis ......................................................................................................... 45

1.5.1.2 Oxidation/Reduction Approach to N-Amination ...................................................... 49

1.5.1.2 Direct N-Amination with Chloramine ........................................................................ 50

1.5.2 Mechanistic Investigation ............................................................................................... 52

1.5.2.1 Synthesis of racemic 2-allyl-3-pentanone .................................................................. 52

1.5.2.2 Analysis of Alkylated Hydrazones of ACCs 1.72-1.75 ............................................. 54

1.5.2.3 Determination of Diastereoselectivity of the Allylation of Hydrazones 1.76-1.79 ................................................................. 60

1.5.2.3. Development of New Hydrolysis Conditions ....................................................... 66

1.5.2.4 Use of ACC 1.73 in Systems with Steric Bulk at the $\alpha'$-Position ...................... 78

2. Regioselective Asymmetric $\alpha,\alpha$-Bisalkylation, $\alpha,\alpha,\alpha',\alpha'$-Tetraalkylation of Ketones via ACCs .................................................................................................................... 83

2.1 Background and Introduction ........................................................................................... 83

2.2 Results and Discussion ...................................................................................................... 86

2.2.1 Preliminary Results ...................................................................................................... 86

2.2.2 Development of Monoalkylation .................................................................................. 88

2.2.3 Asymmetric $\alpha,\alpha$-Bisalkylation ................................................................................ 91

2.2.3 Attempt at $\alpha,\alpha,\alpha'$-Trisalkylation to Generate Quaternary Center ...................... 95

2.2.4 Hydrolysis of Bisalkylated Hydrazones ..................................................................... 97

2.2.5 $\alpha,\alpha$-Bisalkylation of $\alpha'$-Activated Hydrazones .................................................... 99

2.3 Regioselective Asymmetric $\alpha,\alpha,\alpha',\alpha'$-Tetraalkylation .......................................... 103

2.3.1 Background and Introduction ...................................................................................... 103
2.3.2 Results and Discussion ................................................................. 106
  2.3.2.1 Isomerization ........................................................................ 106
  2.3.2.2 Tetraalkylation ..................................................................... 110
  2.3.2.3 Hydrolysis ........................................................................... 113
  2.4 Conclusion .................................................................................. 116
  2.5 Experimental Section ................................................................ 117
    2.5.1 Regioselective Asymmetric α,α-Bisalkylation ............................. 118
      2.5.1.1 Monoalkylation ................................................................ 118
      2.5.1.2 α,α-Bisalkylation ................................................................. 133
      2.5.1.3 Hydrolysis of Bisalkylated Hydrazones ............................... 144
      2.5.1.4 α,α-Bisalkylation of α'-Activated Hydrazones ...................... 150
    2.5.2 Regioselective Asymmetric α,α,α',α'-Tetraalkylation .................. 158
      2.5.2.1 Synthesis of Bisalkylated Hydrazones 2.121 and 2.122 .......... 158
      2.5.2.2 Isomerization of Bisalkylated Hydrazones ......................... 161
      2.5.2.3 α,α,α',α'-Tetraalkylation ..................................................... 167
      2.5.2.4 Synthesis of Tetraalkylation Hydrolysis Model Systems ........ 187
  3. Synthetic Applications of ACC α,α-Bisalkylation ................................ 201
    3.1 Asymmetric Formal Synthesis of (+)- and (-) Stigmolone .............. 201
      3.1.1 Background and Introduction ............................................... 201
      3.1.2 Results and Discussion ......................................................... 204
      3.1.3 Conclusion ......................................................................... 206
    3.2 Asymmetric Total Synthesis of Apratoxin D ................................. 206
3.2.1 Background and Introduction ................................................................. 206
  3.2.1.1 Isolation and Biological Activity......................................................... 206
  3.2.1.2 Prior Synthetic Work ........................................................................ 209
3.2.2 Retrosynthetic Analysis ............................................................................ 221
  3.2.2.1 Retrosynthesis of Polyketide 3.99 Involving Chiral Aldehyde 3.102 ...... 222
  3.2.2.2 Retrosynthesis of Polyketide 3.99 with Key Late Stage α,α-Bisalkylation ................................................................................................. 223
3.2.3 Synthesis of Chiral Aldehyde 3.102 .......................................................... 225
  3.2.3.1 ACC α,α-Bisalkylation ...................................................................... 225
  3.2.3.2 Hydrazine Removal ......................................................................... 226
  3.2.3.3 Deoxygenation .................................................................................. 228
  3.2.3.4 Synthesis Completion ...................................................................... 232
3.2.4 Synthesis of Polyketide 3.99 via Advanced Ketone 3.107 ....................... 234
  3.2.4.1 Asymmetric α,α-Bisalkylation ............................................................. 234
  3.2.4.2 Hydrolysis .......................................................................................... 238
  3.2.4.3 Protecting Group Investigation .......................................................... 239
  3.2.4.4 Examination of Alkylating Agents ..................................................... 244
  3.2.4.5 Removal of Benzyl Group .................................................................. 246
  3.2.4.5 Esterification and Synthesis Completion ........................................... 250
3.2.5 Conclusion ............................................................................................... 253
3.3 Experimental Section .................................................................................. 254
  3.3.1 Asymmetric Formal Synthesis of (R)- and (S)-Stigmolone..................... 254
3.3.2 Asymmetric Synthesis of Chiral Aldehyde Intermediate 3.102 to be used for the Asymmetric Total Synthesis of Apratoxin D ................................................................. 262

3.3.3 Asymmetric Synthesis of Apratoxin D Polyketide 3.100 via Late Stage α,α-Bisalkylation .................................................................................................................. 269

References .......................................................................................................................................................... 291

Biography .......................................................................................................................................................... 303
List of Tables

Table 1. First Report of Imine-Based Asymmetric Alkylation ................................................. 6
Table 2. Koga’s use of t-Leucine Derived Imine in Cyclic Ketones ........................................ 7
Table 3. Meyers’ use of an Acyclic Amine with Chelating Methoxy Group ......................... 8
Table 4. Effect of Heating on Selectivity in Acyclic Ketones .................................................. 11
Table 5. Representative Alkylations of Ketone-Derived SAMP Hydrazones ....................... 15
Table 6. Representative Alkylations of Aldehyde-Derived SAMP Hydrazones ................. 15
Table 7. Alkylation of 3-Pentanone with ACC Auxiliaries 1.72-1.75 ............................... 21
Table 8. Screening of Conditions for Reduction of N-Nitroso 1.100 ............................... 27
Table 9. Regio- and Stereoselectivities of Alkylation of ACC Hydrazones 1.76-1.79 ....... 38
Table 10. Temperature Screen of both the Deprotonation and Alkylation of 1.76 ........... 40
Table 11. Hydrolysis of ACC Model System 1.118 ............................................................... 44
Table 12. Survey of Conditions for the Regioselective Allylation of 2.20 .......................... 89
Table 13. Regioselective Methylation of ACC Hydrazones 2.20,2.26-2.28 ....................... 90
Table 14. Scope of the Regioselective α-Alkylation of 2.20 via CIS-D .............................. 91
Table 15. Screen of Reaction Time for Methylation of 2.33 at –78 °C .............................. 94
Table 16. Regioselective Asymmetric α,α-Bisalkylation ..................................................... 95
Table 17. Hydrolysis of Bisalkylated Hydrazones .............................................................. 97
Table 18. Effect of Temperature on Isomerization of Monoalkylated Hydrazone 2.33 .. 108
Table 19. α,α-Bisalkyated Hydrazones after LDA-Mediated Isomerization ................. 110
Table 20. Attempted Hydrolysis of α,α,α’,α’-Tetraalkylated Hydrazones ..................... 113
Table 21. Screen of Hydrolysis Conditions for Tetraalkylated Hydrazone 2.115............. 114
Table 22. Screen of Hydrolysis Conditions for Tetraalkylated Hydrazone 2.119.......... 116
Table 23. Attempted Dithiane Reduction of 3.109..................................................228
Table 24. Removal of Tin Residues from 3.108 .....................................................231
Table 25. Attempts at Hydrolysis of PMB-Protected Hydrazone 3.127 ....................239
Table 26. Screening Conditions for Deprotection of PMB-Hydroxyl .......................241
Table 27. Attempted Hydrolysis of Bn-Protected Hydrazone 3.42............................244
Table 28. Attempted Reaction of 3.141 with Protected Hydroxyl Alkylating Agents .... 245
Table 29. Screening of Additional Alkylating Agents for Masked Aldehyde .............246
Table 30. Temperature Screen of BCl₃ Deprotection of 3.142.................................249
List of Figures

Figure 1. First Stereochemical Model for Asymmetric Ketone Alkylation .......................... 4
Figure 2. The SAMP and RAMP auxiliaries ........................................................................ 12
Figure 3. Four Possible Diastereomers of SAMP Hydrazone Alkylation ............................. 15
Figure 4. Stereochemical Model for SAMP Hydrazone Alkylation .................................... 17
Figure 5. Alkylated Hydrazones 1.85 and 1.86 and their Corresponding Crystal Structures 1.87 and 1.88 ........................................................................................................... 22
Figure 6. Study of Achiral Oxazolidinone 1.103 .................................................................... 29
Figure 7. Study of ACC 1.72 .................................................................................................. 31
Figure 8. Newman Projections of 1.104-syn-front and 1.104-syn-back ................................. 32
Figure 9. Examination of Deprotonation Transition State with an Achiral ACC ............... 33
Figure 10. Examination of Deprotonation Transition State with ACC 1.72 ......................... 33
Figure 11. Examination of Azaenolates Derived from 1.104 and Subsequent Alkylation with MeCl................................................................................................................................. 34
Figure 12. Transition States Leading to $E_{cc}$ or $Z_{cc}$ Azaenolate ....................................... 36
Figure 13. Four Possible Diastereomers Formed from ACC Hydrazone Alkylation ....... 39
Figure 14. Representative Structures Obtained from $\alpha$,$\alpha$-Bisalkylation of ACC Acetone-Derived Hydrazone .............................................................................................................. 84
Figure 15. Representative Structures Resulting from the $\alpha\alpha\alpha\alpha'$-Trisalkylation and $\alpha\alpha\alpha\alpha'$-Tetraalkylation of Acetone ......................................................................................... 105
Figure 16. Natural Products which could be Synthesized via an Asymmetric $\alpha\alpha\alpha\alpha'$-Tetraalkylation Strategy ..................................................................................................................... 106
Figure 17. X-Ray Crystal Structure of $\alpha\alpha\alpha\alpha'$-Tetraalkylated Hydrazone 2.104 .......... 111
Figure 18. Synthesis of Four Diastereomers, 2.105-2.108 of Tetraalkylated Hydrazone 111

Figure 19. (–)-(R)- and (+)-(S)-Stigmolone ................................................................. 201

Figure 20. Structures of Apratoxins A-E ................................................................. 207
List of Schemes

Scheme 1. Yamada’s Asymmetric Alkylation of Cyclohexanone with t-Bu-Proline Ester Auxiliary ................................................................................................................................. 3

Scheme 2. Asymmetric Allylation of Cyclohexanone via Initial N-Alkylation ..................... 5

Scheme 3. First Report of an Asymmetric Quaternary Center ........................................... 5

Scheme 4. Direct Formation of All-Carbon Quaternary Stereocenter ................................ 7

Scheme 5. Whitesell’s Asymmetric Methylation of Cyclohexanone .................................... 9

Scheme 6. Use of Cz-Symmetric Auxiliary in Asymmetric Enamine Alkylation ............... 9

Scheme 7. Alkylation of Tin-Enolates ................................................................................ 10

Scheme 8. Synthesis of A. SAMP and B. RAMP chiral auxiliaries .................................... 13

Scheme 9. SAMP hydrazone formation ......................................................................... 14

Scheme 10. Removal of SAMP/RAMP Auxiliaries .......................................................... 18

Scheme 11. Direct Transformations of Aldehyde-Derived SAMP Hydrazones .............. 19

Scheme 12. Stereochemical Model for ACC Hydrazone Alkylation ............................... 23

Scheme 13. First generation synthesis of camphor derived ACC 1.72 ............................ 24

Scheme 14. Optimized Synthesis of Oxazolidinone 1.98 ............................................... 25

Scheme 15. Two-Step Oxidation/Reduction Sequence for Formation of N-N Bond ....... 26

Scheme 16. Direct Amination of ACCs with Chloramine ................................................... 28

Scheme 17. Hydrolysis of Alkylated ACC Hydrazones .................................................... 37

Scheme 18. Alkylation with ACC 1.73 in System with Increased α’-Steric Bulk ............... 41

Scheme 19. Use of ACC 1.73 in Asymmetric Total Synthesis of (+)-Clusianone ............ 42

Scheme 20. Previous Hydrolysis Conditions for ACC Hydrazones ............................... 43
Scheme 21. Regioselectivity of Bisalkylation of A. Ketones B. SAMP/RAMP Dialkyl Hydrazones ................................................................. 83

Scheme 22. A. Syn-Dianion Effect in Sulfonyl Hydrazones B. α,α-Bisalkylation via Complex Induced syn-Deprotonation (CIS-D) (S = small substituent; L = large substituents) ........................................................................................................ 85

Scheme 23. Preliminary Studies on Regioselective, Asymmetric αα-Bisalkylation .......... 87

Scheme 24. Studies on Regioselective Asymmetric α,α-Bisalkylation ............................ 92

Scheme 25. Potential α,α,α-Trisalkylation to Generate All-Carbon Quaternary Stereocenter ........................................................................................................................................ 96

Scheme 26. Attempted α,α,α-Trisalkylation of Hydrazon 2.41 ........................................ 96

Scheme 27. α,α-Bisalkylation of ACC Hydrazon Possessing α’-Activating Group ....... 99

Scheme 28. A. Alkylation of via ACC 2.67 B. Alkylation via SAMP Hydrazon 2.64 .... 101

Scheme 29. Regioselective Enolization Towards Oxygen in α’-Alkoxyketones .......... 102

Scheme 30. α,α-Bisalkylation of Benzyloxyacetone-Derived Hydrazon 2.84 ............. 103

Scheme 31. Asymmetric, Regioselective Tetraalkylation of Acetone ......................... 104

Scheme 32. Proposed α,α,α’,α’-Tetraalkylation Sequence ........................................ 104

Scheme 33. Observation of Isomerization during α,α-Bisalkylation of 2.34 .............. 107

Scheme 34. Proposed LDA-mediated Isomerization of ACC Hydrazon .................... 107

Scheme 35. LDA-Mediated Isomerization of 2.44 and 2.41 with no Epimerization ...... 109

Scheme 36. α,α,α’,α’-Tetraalkylated Hydrazon 2.104 ................................................. 110

Scheme 37. α,α,α’,α’-Tetraalkylated Hydrazones Synthesized to Date .................... 112

Scheme 38. Synthesis of Model System for Tetraalkylated Hydrazon Hydrolysis .... 114

Scheme 39. Synthesis of Less Sterically Hindered Model System for Tetraalkylated Hydrazon Hydrolysis ........................................................................................................ 115
Scheme 40. Plaga’s Racemic Synthesis of (+/-)-Stigmolone .................................................. 202

Scheme 41. Synthesis of (S)- and (R)-Stigmolone Starting from (S)- or (R)-Citronellol .. 202

Scheme 42. Enders’ Asymmetric Total Synthesis of (S)- and (R)-Stigmolone via SAMP/RAMP ........................................................................................................... 203

Scheme 43. Asymmetric Formal Synthesis of both (R)- and (S)-Stigmolone via ACC \(\alpha,\alpha\)-Bisalkylation ........................................................................................................... 205

Scheme 44. Retrosynthetic Analysis of Apratoxin A ................................................................. 211

Scheme 45. Thiazoline Formation via Staudinger Reduction/Intramolecular Aza-Wittig ......................................................................................................................... 212

Scheme 46. Synthesis of Compound 3.50 ................................................................................ 213

Scheme 47. Synthesis of Tripeptide 3.35 ................................................................................ 213

Scheme 48. Convergent Synthesis of Apratoxin A ................................................................. 215

Scheme 49. Thiazoline Formation via Tandem Deprotection/Cyclodehydration ............ 216

Scheme 50. Takahashi Synthesis of Compound 3.50 ............................................................. 217

Scheme 51. Synthesis of Modified Cysteine 3.78 ................................................................. 217

Scheme 52. Takahashi Synthesis of 3.83 ................................................................................ 218

Scheme 53. Takahashi Synthesis of Apratoxin A ................................................................. 219

Scheme 54. Ma Synthesis of Fragment 3.93 ........................................................................... 220

Scheme 55. Ma Synthesis of Thiazoline 3.96 ...................................................................... 221

Scheme 56. Ma Synthesis of Apratoxin A ........................................................................... 221

Scheme 57. Retrosynthetic Analysis of Apratoxin D ............................................................ 222

Scheme 58. Retrosynthesis of Apratoxin D Leading to Chiral Aldehyde 3.102 .............. 223

xix
Scheme 59. Retrosynthetic Analysis of Apratoxin D Employing Late Stage ACC $\alpha,\alpha$-Bisalkylation of 3.107 .......................................................... 224

Scheme 60. $\alpha,\alpha$-Bisalkylation of Benzylxoy Acetone via ACC 1.72 ................................. 225

Scheme 61. Required Reduction of 2.87 with C38 Hydrazone to 3.108 with C38 Methylene................................................................. 226

Scheme 62. Attempted Direct Formation of Dithiane from 2.87 ........................................ 227

Scheme 63. BF$_3$$\cdot$OEt$_2$ Mediated Hydrolysis of Hydrazone 2.87 ................................. 227

Scheme 64. Attempted Direct Deoxygenation of 3.110.................................................... 229

Scheme 65. Attempted Deoxygenation via Super-Hydride Reduction............................. 230

Scheme 66. Barton-McCombie Deoxygenation of 3.111 via Xanthate 3.114.................... 231

Scheme 67. A. Completed Synthesis of Fragment 3.102 B. Use of 3.102 in Evans’ Aldol 233

Scheme 68. Synthesis of Advanced Ketone 3.123 with PMB-Protected Alcohol ............. 235

Scheme 69. Use of ACC 1.73 in Systems with Two $\alpha'$-Substituents.............................. 235

Scheme 70. Formation of Hydrazone 3.124 ........................................................................ 236

Scheme 71. Methylation of Hydrazone 3.124 ..................................................................... 237

Scheme 72. Asymmetric $\alpha,\alpha$-Bisalkylation of Hydrazone 3.125 ............................... 238

Scheme 73. DDQ Deprotection and Concomitant Hydrolysis of Model ACC Hydrazone 3.129 ........................................................................ 240

Scheme 74. Attempted DDQ Deprotection of 3.127 ......................................................... 240

Scheme 75. Synthesis of Bn-Protected Hydrazone 3.140 .................................................. 243

Scheme 76. Alkylation of 3-Pentanone Hydrazone 1.76 with Alkylating Agents Possessing Protected Hydroxyls ........................................ 245

Scheme 77. Hydrogenolysis of 3.142 and Subsequent Hydrolysis ...................................... 247
Scheme 78. Deprotection of Benzyl Ether 3.154 with BCl₃ ....................................................... 248
Scheme 79. Deprotection of Bn-Protected Hydrazone 3.142 with BCl₃ ................................. 248
Scheme 80. Hydrolysis of α-Hydroxy Hydrazone 3.134 ......................................................... 250
Scheme 81. Esterification of 3.156 via A. Yamaguchi Esterification B. EDCI Coupling 251
Scheme 82. Conversion of Alcohol 3.160 to Xanthate 3.161 ................................................... 252
Scheme 83. Completion of Aldehyde 3.163 .......................................................................... 252
Scheme 84. Completion of the Synthesis of Apratoxin D (3.31) .............................................. 253
Acknowledgements

First, and most importantly, I want to extend my thanks to my advisor, Professor Don Coltart, for his support, encouragement and patience throughout my graduate career. Don has always pushed me to do better, and to find abilities within myself that I did not even know I had. It is thanks to him, and his belief in me, that I have developed into the chemist that I am today and I am truly grateful for having had the opportunity to work with him.

I would also like to thank the members of my dissertation committee, Professors Steven Baldwin, Eric Toone, and Patrick Charbonneau, for their help and guidance throughout my graduate career.

I am also grateful to the members of the Coltart Lab, both past and present for their friendship and support throughout this journey. In particular, a special thanks to Michelle Garnsey, for sharing a hood row with me for five whole years, for our countless talks about our research, and for laughing with me through the days when we thought we might not make it.

Finally, I want to thank my Family, and in particular my mom, for their love and support throughout my entire academic career and for always encouraging me to chase my dreams. Also, thank you to Justin Torosian, for putting up with my frustrations, venting, and stress over the past few months, and whose constant support has helped me reach this day.
1. **N-Amino Cyclic Carbamate Chiral Auxiliaries**

1.1 **Background and Introduction**

1.1.1 **Asymmetric Ketone Alkylation**

The ketone is one of the most highly utilized functional groups in organic synthesis. As a result, some of the most important types of organic reactions are those based on enolate chemistry, leading to formation of carbon-carbon bonds $\alpha$ to a carbonyl. These are typically conducted through treatment of the parent ketone with a strong base such as LDA, followed by addition of an appropriate electrophile. Due to the wide prevalence of ketones in natural products, the desire to perform such transformations asymmetrically has been of long standing interest.

From the beginning it was clear that there were several challenges in attempting to develop asymmetric ketone $\alpha$-alkylation methods. A general and widely applicable asymmetric method would have to control numerous aspects of the reaction including the geometry about the C-C bond of the enolate and the facial approach of the electrophile to it. The situation becomes more complex in the case of non-symmetrical ketones, where one must also account for regioselectivity of deprotonation. As a result, early methods suffered from low enantioselectivities and yields, as well as being limited in both the substrate and electrophile. However, building upon those pioneering efforts, researchers in the field have made significant advancements and today a wide range of
methods are available that impart high stereoselectivity across a broad scope of substrates.

The majority of auxiliary-based asymmetric α-alkylation methods employ amines, either through derived enamines, imines or hydrazones. The large pool of naturally occurring chiral amines makes this approach particularly attractive. In order to be a viable method, the target auxiliary must be reasonably easy to synthesize, produce high levels of stereoselectivity, be easy to introduce and remove and be able to be recycled effectively and efficiently. If these criteria can be met, then methods utilizing auxiliaries possess the additional advantage of generating diastereomeric products, which allows for separation of the minor stereoisomer prior to auxiliary removal in cases of imperfect stereoselectivity, thus enhancing the optical purity.

The use of azacarbonyl compounds for the functionalization of ketones and aldehydes was introduced by Stork in 1963 in the context of imines.1 The ease of formation and cleavage of imines, as well as their increased reactivity upon deprotonation relative to ketones, made them attractive substrates for a wide array of transformations. These factors, in conjunction with the large pool of naturally occurring chiral amines, made the use of azacarboxyls appealing as a means of achieving enantioselective transformations. As a result of these attributes, the use of azacarbonyls has been the primary focus in the development of new asymmetric methods and is by far the most common approach.
The first report of an enantioselective ketone alkylation came from Horeau in 1968. This approach used isobornylamine to achieve the asymmetric methylation of cyclohexanone with methyl iodide. While it gave rise to the 2-methylcyclohexanone in 72% ee, the use of other alkyl halides gave significantly lower enantioselectivities. In the years following Horeau’s study, a more general approach was developed by Yamada through the use of proline derived enamines. Condensation of an (S)-proline t-butyl ester with cyclohexanone yielded the chiral nonracemic enamine (1.1). This method was restricted to the use of activated olefins as electrophiles, such as methacrylate and acrylonitrile, and gave low to moderate yields (17-55%) and ees from 43-59% (Scheme 1). However, this work was one of the first examples of asymmetric ketone alkylation, and as such it was a landmark achievement that laid the foundation for future developments.

Scheme 1. Yamada’s Asymmetric Alkylation of Cyclohexanone with t-Bu-Proline Ester Auxiliary

In addition, it provided the first stereochemical model for such asymmetric alkylations (Figure 1). Using a cyclohexene transition state model, it was proposed that the proline moiety would exist parallel to the double bond due to the conjugation of the nitrogen lone pair with the pi-system. This conformation would lead to competing steric
interactions between the ester and either the vinyl proton or the $\alpha$-proton highlighted in red. Conformers 1.3 and 1.5 were preferred over 1.4 and 1.6, with 1.3 presenting the fewest steric interactions. Axial attack of the approaching electrophile in this conformation would give the observed (S)-alkylated product. This model accounts for the low level of stereoselectivity since the conformers placing the stereocenter on the auxiliary closer to the reactive site were disfavored, leading to a lower degree of facial selectivity during alkylation.

**Figure 1. First Stereochemical Model for Asymmetric Ketone Alkylation**

Further studies by Yamada on similar cyclic enamine systems attempted to expand the electrophile scope, while providing more mechanistic insights. The use of allyl bromide, benzyl bromide and ethyl bromoacetate, were all examined, yet yields never exceeded 25%. The highest $ee$ was 30%, for the in the allylation reaction. In the allylation of cyclohexanone enamine with allyl bromide, Yamada proposed that carbon alkylation was preceded by nitrogen-alkylation and subsequent rearrangement (Scheme 2).
Scheme 2. Asymmetric Allylation of Cyclohexanone via Initial N-Alkylation

Yamada noted that an additional challenge in the synthesis of optically active 2-alkylcyclohexanones was that they are prone to racemization. This observation led to the first attempts at generating a quaternary $\alpha$-stereocenters, where no acidic $\alpha$-proton would be present for racemization. 2-Phenylpropanal was successfully alkylated via the L-proline pyrrolidine with methyl vinyl ketone in alcoholic solvent (e.g. methanol, ethanol) (Scheme 3). The alkylated product was subjected to hydrolysis and cyclization to give 4-methyl-4-phenyl-2-cyclohexenone (1.11) in 48% yield and 49% optical yield. Because the keto-aldehyde product underwent facile cyclization and dehydration to give the cyclohexenone derivative, attempts at isolating the keto-aldehyde were not made. The low optical yields in this case could be largely attributed to the alkylation of an acyclic aldehyde, wherein azaenolate geometry must also be controlled.

Scheme 3. First Report of an Asymmetric Quaternary Center

The low yields and limited electrophile scope that persisted through the above examples was due to the low reactivity of the *neutral* enamine nucleophile. In order to
circumvent the need to use a highly reactive electrophile, research began to shift towards the alkylation of chiral imines via metallation with a strong base such as LDA. The first reports by Yamada showed marked improvement over his imine alkylations in electrophile scope, allowing for the use of a wide range of alkyl halides with yields ranging from 26-51% and ees from 26-33% (Table 1).²

Table 1. First Report of Imine-Based Asymmetric Alkylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>RX</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeI</td>
<td>26</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>EtI</td>
<td>n.d.</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>n-PrI</td>
<td>37</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>i-PrI</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>AllyBr</td>
<td>33</td>
<td>51</td>
</tr>
</tbody>
</table>

Building on these initial studies, improved methods were introduced in the late 1970’s by both Koga⁷ and Meyers⁸. Utilizing a similar auxiliary to those in the above enamine studies, Koga employed imine 1.16, derived from the t-butyl ester of tert-leucine, in the methylation of cyclohexanone. This method offered comparable yields (57-75%) but consistently higher ees (84-98%) and a wider range of electrophiles than previous reports (Table 2).
Table 2. Koga’s use of t-Leucine Derived Imine in Cyclic Ketones

![Diagram of chemical reactions](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹X</th>
<th>Isolated Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me₂SO₄</td>
<td>65</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>MeI</td>
<td>57</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>AllylBr</td>
<td>75</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>n-PrI</td>
<td>70</td>
<td>97</td>
</tr>
</tbody>
</table>

Koga also provided the first example of direct α-alkylation of a ketone to successfully generate an asymmetric quaternary center (Scheme 4). This was conducted through the methylation of both α-phenyl cyclopent- and cyclohexanone to generate α-methyl-α-phenyl cyclic ketones with 94% ee. Typically, alkylation of 2-substituted cyclohexanone derivatives results in 2,6-disubstituted products, but, in this case, the presence of the phenyl group at the 2-position provided an enhanced acidity necessary for the desired quaternary center formation.

Scheme 4. Direct Formation of All-Carbon Quaternary Stereocenter

Meyers studied a chiral imine (1.19) in asymmetric alkylations, again using cyclohexanone (Table 3). This auxiliary produced yields of 50-80% with a wide variety of electrophiles and good to excellent ees (82->95%). The higher selectivities were
accounted for by the presence of the methoxy group, which, along with the nitrogen lone pair, is able to tightly chelate the lithium cation forming a rigid 5-membered ring, resulting in better control of the electrophile approach (1.22). The presence of a chelating group on the chiral auxiliary proved to be a significant advancement that continued to be a theme in the further development of amine based asymmetric methods.

**Table 3. Meyers' use of an Acyclic Amine with Chelating Methoxy Group**

<table>
<thead>
<tr>
<th>Entry</th>
<th>RX</th>
<th>Isolated Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me$_2$SO$_4$</td>
<td>72</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>EtI</td>
<td>56</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>n-PrI</td>
<td>50</td>
<td>&gt;95</td>
</tr>
<tr>
<td>4</td>
<td>AllylBr</td>
<td>80</td>
<td>&gt;90</td>
</tr>
<tr>
<td>5</td>
<td>BnBr</td>
<td>56</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

Whitesell reported the formation of chiral imines from cyclohexanone and the O-n-butyl derivative of (R)-2-amino-1-butanol (Scheme 5). Along the lines indicated above, key to the design of the auxiliary was incorporation of an oxygen moiety to participate in intramolecular chelation of the metal ion to inhibit rotation about the C-N bond. Treatment of the imines with isopropylmagnesium bromide gave rise to the metallated imines, which could form a 5-membered chelate (1.24). Subsequent treatment with methyl iodide at -78 °C, followed by hydrolysis with 2M HCl gave rise to α-methylated cyclohexanone (1.25) with an ee of 81%. Reducing the alkylation
temperature to \(-100\, ^\circ\text{C}\) increased the \(ee\) to 85\%. The alkylation was also attempted at reflux, which reduced the \(ee\) to 20\%.

![Scheme 5](image)

**Scheme 5. Whitesell’s Asymmetric Methylation of Cyclohexanone**

A subsequent report by Whitesell focused on the use of \(C_2\)-symmetric auxiliaries (Scheme 6).\(^{12}\) These auxiliaries were developed based on the hypothesis that, in the above systems, free rotation about the C-N bond of the enamine resulted in decreased proximity between the chiral center on the auxiliary and the center undergoing alkylation, thus giving rise to the lower \(ees\). Indeed, the \(C_2\)-symmetric auxiliaries did produce improved \(ees\) of 82-93\% relative to their non-\(C_2\) symmetric counterparts (43-59\%).

![Scheme 6](image)

**Scheme 6. Use of \(C_2\)-Symmetric Auxiliary in Asymmetric Enamine Alkylation**

The use of chiral organotin compounds derived from various amino acids was studied by De Jeso and offered comparable \(ees\) but significantly higher yields than the analogous lithium enolates (Scheme 7).\(^{13}\)
While the works discussed thus far provided significant advancements in terms of electrophile scope, yields and optical purities, it is noteworthy that all of the approaches were restricted to cyclic systems. Cyclic ketones are inherently easier to work with due to the double bond geometry of the enamine or derived azaenolate being locked in the \(E\)-configuration. As mentioned in the introduction, one of the difficulties in the \(\alpha\)-alkylation of acyclic ketones lies in the possibility of generating two possible isomers [(\(E\)) or (\(Z\))] about the \(\text{CC}\) bond of the azaenolate. The first to clearly address this problem was Meyers with his work utilizing chiral methoxyamine auxiliaries to achieve the first asymmetric \(\alpha\)-alkylation of an acyclic ketone (Table 4).\(^{14}\) Meyers’ initial attempts suffered from low \(ees\) (<50%), where deprotonation and alkylation were performed at low temperatures. It was hypothesized that these results were a reflection of the kinetic ratio of \(E:Z\) \(\text{CC}\)-bond geometries formed upon deprotonation. Indeed, when the lithio enamines were refluxed, allowing for equilibration of the \(E:Z\) mixture to the thermodynamically favored isomer (typically \(E\)), considerably higher \(ees\) (generally 50-98%) were obtained with a wide range of ketones and electrophiles (Table 4).
Table 4. Effect of Heating on Selectivity in Acyclic Ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R¹</th>
<th>R²X</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>ee prior to heating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Bu</td>
<td>n-Pr</td>
<td>Mel</td>
<td>75</td>
<td>88</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>n-Pr</td>
<td>Et</td>
<td>Mel</td>
<td>84</td>
<td>98</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>Me</td>
<td>EtI</td>
<td>48</td>
<td>76</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Et</td>
<td>Mel</td>
<td>77</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>Me</td>
<td>EtI</td>
<td>80</td>
<td>53</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>PhCH₂</td>
<td>Ph</td>
<td>Mel</td>
<td>90</td>
<td>41</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>Ph</td>
<td>Mel</td>
<td>88</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

1.1.1.2 SAMP/RAMP

The next significant advance in asymmetric ketone alkylation came in the form of N,N-dialkylhydrazones. In 1976, azaenolates derived from N,N-dialkyl hydrazones were studied as an alternative to direct ketone and aldehyde enolate alkylations. These species were found to exhibit higher reactivity towards electrophiles, as well as better regioselectivity for C-alkylation than their parent carbonyl compounds. N,N-dialkyl hydrazones are stable and are relatively easy to prepare, making them appealing from a practical point of view in comparison to imines and enamines, which can be difficult to form quantitatively and are hydrolytically unstable. Given these desirable attributes, Enders undertook the development of chiral non-racemic N,N-dialkyl hydrazine auxiliaries for the asymmetric α-alkylation of ketones. The result of his efforts were (S)- and (R)-1-amino-2-methoxypyrrolidine hydrazine (1.34 and 1.35, respectively) now commonly known as the SAMP and RAMP auxiliaries, respectively.
(Figure 2). Over the years, the SAMP/RAMP method has come to be considered the state of the art approach to asymmetric ketone α-alkylation, and as a result several comprehensive reviews concerning the SAMP/RAMP method are available.\textsuperscript{16-17}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figures/SAMP_RAMP_auxiliaries.png}
\caption{The SAMP and RAMP auxiliaries}
\end{figure}

**Auxiliary Synthesis**

Synthesis of the SAMP chiral auxiliary can be achieved in six steps, and in 57% overall yield, beginning with (S)-proline (1.36) using the procedure outlined in Scheme 8A.\textsuperscript{18-19} The RAMP auxiliary, on the other hand, may be obtained in six steps and 35% overall yield starting from (R)-glutamic acid (1.41, Scheme 8B).\textsuperscript{17} Purification of each auxiliary is achieved by distillation, and the enantiomeric purity can be established by either optical rotation or by chiral GC measurement.
Scheme 8. Synthesis of A. SAMP and B. RAMP chiral auxiliaries

Hydrazone Formation

The formation of SAMP/RAMP hydrazones is generally straightforward and proceeds in good to excellent yield (75-95%). For aldehydes, hydrazone formation may be conducted neat at 0 °C (Scheme 9A). In the case of ketones, however, somewhat more forcing conditions are usually required (Scheme 9B). In such situations, refluxing the auxiliary and ketone in benzene using a Dean Stark trap is required for high conversion to the desired hydrazone. As expected, with non-symmetrical ketones the resulting hydrazones are obtained as a mixture of $E$- and $Z$-diastereomers in a ratio that is dependent on the nature of the ketone. However, the alkylation may be conducted using the diastereomeric mixture without compromising the stereochemical outcome (see below).
Alkylation

The alkylation of SAMP/RAMP hydrazones derived from both ketones and aldehydes usually proceeds with very good to excellent levels of asymmetric induction and in good to very good yield (Table 5). In a typical reaction, the hydrazone is added to a solution of LDA (−78 °C) and then stirred at 0 °C for 2-10 h. The resulting azaenolate solution is then cooled to −110 °C, the alkylating agent is added, and stirring is continued at low temperature for 1-3 h, depending on the nature of the system. In certain cases, the stereoselectivity of the alkylation reaction can be determined by ¹H-NMR by comparison of the methoxy-singlet ratios for the four possible diastereomers (Figure 3, 1.49-1.52), using the chiral shift reagent Eu(fod)₃ or Eu(hfc)₃.²⁰
As indicated above, the SAMP/RAMP asymmetric alkylation method is unique in comparison to other ketone alkylation strategies in that it is also applicable to the asymmetric α-alkylation of aldehydes (Table 6). Alkylation yields and levels of asymmetric induction are consistent with those obtained for ketones.

Table 6. Representative Alkylations of Aldehyde-Derived SAMP Hydrazones
Mechanistic Aspects

Treatment of a SAMP/RAMP hydrazone with LDA at −110 °C typically results in kinetic removal of the least sterically-hindered proton. However, the opposite regioselectivity results for hydrazones having electronically activating groups (e.g., phenyl, ester).\textsuperscript{17, 20} Deprotonation is followed by equilibration of the azaenolate to a species having the $E$-configuration at the CC bond and the $Z$-configuration at the CN bond. The azaenolate geometry has been studied extensively, and its configuration has been verified by trapping experiments,\textsuperscript{20-24} MNDO calculations,\textsuperscript{25} spectroscopic studies, and X-ray analysis.\textsuperscript{26}

Enders has proposed a model for the stereoselectivity of the alkylation, which has proven highly successful in predicting the reaction outcome (Figure 4). Central to his model is a six-membered chelate between the nitrogen, Li\textsuperscript{+}, and the methoxy group of the auxiliary.\textsuperscript{16, 25} In this form, the top ($si$) face of the azaenolate is blocked and alkylation occurs at the more accessible bottom ($re$) face.
Auxiliary Removal

Removal of the auxiliary from alkylated SAMP/RAMP hydrazones is most often achieved using one of two approaches; ozonolysis or quaternization with Mel followed by hydrolysis with 3–4 M HCl. Both methods are reported to produce the α-alkyl ketones from the hydrazones without epimerization. In addition to the inherent functional group incompatibility, a notable limitation of each of these methods is that the auxiliary is liberated in an altered form. For instance, when ozonolysis is employed the auxiliary is recovered as its N-nitroso derivative (1.61). Reduction of this compound with LiAlH₄ produces the parent auxiliary, allowing it to be recovered from a typical alkylation in about 70% to 80% yield. In situations where quaternization/hydrolysis is employed for auxiliary removal, recycling of the auxiliary is much less efficient. Here, the auxiliary is recovered in the form of salts 1.62 and 1.63, which correspond to methylation of the endo- and exocyclic nitrogens, respectively. Neutralization allows 1.64 to be recovered, which then air oxidizes to formaldehyde hydrazone 1.65. Subsequent hydrolysis of 1.65 ultimately provides the recovered auxiliary (1.34) in approximately 40% yield.
A variety of other methods have been employed on a case-by-case basis to effect auxiliary cleavage, and a detailed account of these methods is available.\textsuperscript{28} In addition to hydrolytic approaches, for aldehyde hydrazones, a number of convenient direct methods are available that allow the auxiliary to be cleaved in such a way that a functional group other than an aldehyde is generated. For instance, aldehyde-derived SAMP/RAMP hydrazones can be directly converted to the corresponding nitriles,\textsuperscript{29} amines,\textsuperscript{30} or dithianes,\textsuperscript{31} thereby enabling subsequent reactively not immediately available from the aldehyde itself.
Despite the wide use of SAMP/RAMP over the past 30 years, these auxiliaries are not without limitations. The auxiliaries are based on a proline core, limiting structural variation and their synthesis is non-trivial making them cumbersome to make and expensive to buy (e.g., in 2012 SAMP = $171.00/g; RAMP = $192.00/g).\textsuperscript{28}

As discussed above, introduction of the auxiliaries often requires relatively harsh refluxing conditions, deprotonation requires lengthy (2-10 h) exposure to LDA, and subsequent alkylation must be performed at -110 °C to achieve high selectivity, therefore making large scale applications impractical. Finally, removal of the auxiliary is challenging, most commonly requiring either ozonolysis, which limits functional group compatibility, or quaternization/hydrolysis which prevents recycling of the auxiliaries.\textsuperscript{28} Additionally, the hydrolysis conditions (discussed above) often vary on a case to case basis, making synthetic planning and managing functional group compatibilities difficult. As a result, while there is no question that the SAMP/RAMP auxiliaries...
represent a valuable contribution to asymmetric ketone alkylation, there was room for significant improvement in this field.

1.1.2 N-Amino Cyclic Carbamate Chiral Auxiliaries

In 2008, our group introduced the N-amino cyclic carbamate (ACC) chiral auxiliaries for asymmetric ketone α-alkylation.\textsuperscript{32} In contrast to previous methods, the auxiliaries are both easily introduced and removed from ketones, and the auxiliary can be nearly quantitatively recycled. Furthermore, deprotonation is rapid and alkylation can be performed at relatively mild temperatures (\textasciitilde 20 °C to rt), and proceeds with excellent stereoselectivity and high yield.

In our initial publication, we reported the use of four different auxiliaries in the asymmetric alkylation of 3-pentanone (Table 7).\textsuperscript{32} At the time, the stereoselectivities of the alkylations were determined following hydrolysis of the alkylated hydrazones to the corresponding ketones, using 2 equivalents of \textit{p}-TsOH in acetone.
Table 7. Alkylation of 3-Pentanone with ACC Auxiliaries 1.72-1.75

<table>
<thead>
<tr>
<th>Entry</th>
<th>ACC</th>
<th>Hydrazone</th>
<th>Alkylated Hydrazone</th>
<th>β/α*</th>
<th>yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.72</td>
<td>1.76</td>
<td>1.80</td>
<td>96:4</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>1.73</td>
<td>1.77</td>
<td>1.81</td>
<td>76:24</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>1.74</td>
<td>1.78</td>
<td>1.82</td>
<td>91:9</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>1.75</td>
<td>1.79</td>
<td>1.83</td>
<td>86:14</td>
<td>82</td>
</tr>
</tbody>
</table>

* Determined by chiral GC

Of the ACCs screened, camphor-derived ACC 1.72 gave the highest selectivity ($er$ = 96:4) at the level of the hydrolyzed ketone. In order to further understand the origins of the stereoselectivity in the alkylation step, we wished to determine the stereochemistry of the azaenolate that we were forming. In order to do this, ACC hydrazones 1.76 and 1.84, derived from 3-pentanone and cyclohexanone, were alkylated with $p$-bromobenzyl bromide and allyl bromide respectively, and crystal structures of the products were obtained (1.87, 1.88 Figure 5).
Examination of crystal structures of the products resulting from these reactions (1.87 and 1.88, respectively; Figure 5) showed that both alkylations gave the same configuration at the newly formed stereocenter. Since the cyclohexyl system is constrained to the E\text{cc} azaenolate geometry, it was reasoned that the 3-pentanone azaenolate must also be adopting the same geometry in order to produce the same configuration at the new stereogenic center.

The crystal structures also revealed that both alkylations had occurred in a regioselective fashion, exclusively on the same side of the carbon–nitrogen double bond as the auxiliary. We believed that this must have occurred through generation of a configurationally stable $Z_{CN}$ azaenolate, formed as the result of a directed deprotonation event, which we have termed Complex Induced Syn-Deprotonation (CIS-D). CIS-D functions through coordination of the carbonyl oxygen of the auxiliary and LDA,
directing the deprotonation to the same side of the CN double bond as the auxiliary (cf. 1.90, Scheme 12).

Scheme 12. Stereochemical Model for ACC Hydrazine Alkylation

The resulting azaenolate (1.91) is configurationally stable and forms a tight 5-membered chelate involving the nitrogen-centered anion, the auxiliary carbonyl, and Li⁺. In this form, the bottom (re) face of the azaenolate is blocked, causing the electrophile to approach from the top (si) face, giving the α-alkylated hydrazone (1.92) (Scheme 12). This stereochemical model has proven very successful in predicting the outcome of ACC alkylation reactions to date and has been confirmed by subsequent theoretical studies (see Section 1.3.1).

1.2 Synthesis of ACC 1.72

In order to further explore the utility of ACC 1.72, which produced the highest selectivities in our initial studies, an optimized synthesis was required which both maximized yield and minimized cost, such that the auxiliary could be produced on a large scale. While 1.72 had been previously synthesized in our laboratory (Scheme 13),
there were several steps that required further optimization (Scheme 14), most notably the final step, formation of the N-N hydrazide bond.

Scheme 13. First generation synthesis of camphor derived ACC 1.72

The synthesis of (S)-1.72 begins with commercially available, and relatively inexpensive (S)-(+)‐camphor sulfonic acid (Note: The corresponding (R)-1.72 can be synthesized in an analogous manner simply by starting with the (R)-(−)-camphor sulfonic acid), which is converted to the camphor sulfonyl chloride 1.94. Previously, phosphorus pentachloride was used for this transformation (Scheme 13, 1.93 → 1.94), however, this method gave inconsistent yields and the reaction work-up left the resulting sulfonyl chloride moist and prone to degradation. As an alternative, we prepared it using SOCl₂ (Scheme 13), which proved to be a vastly superior method, and enabled the large-scale production (~275 g) of 1.94. With this compound in hand, we followed a known synthesis reported by Haslanger to obtain the (+)-ketopinic acid chloride (1.96). Thus, 1.94 was heated to reflux in the presence of p-TsCl to give the chlorosulfine 1.95. While the original conditions for this reaction were not altered, we
eliminated an unnecessary purification, thus increasing the reaction yield from 50 to 75%. 1.95 was subsequently ozonolyzed and the crude reaction mixture treated with SOCl₂ to give the ketopinic acid chloride 1.96. While Haslanger uses oxalyl chloride for this final transformation, we found SOCl₂ to be an equally effective and more affordable alternative. The acid chloride (1.96) was then treated with sodium azide and refluxed in toluene to give isocyanate 1.97, which was then subjected to a Luche-type reduction to yield the oxazolidinone 1.98.

![Scheme 14. Optimized Synthesis of Oxazolidinone 1.98](image)

**1.2.1 Formation of N-N bond**

At this point we were faced with generating the nitrogen-nitrogen bond. The method employed in the first generation synthesis involved treatment of the anion obtained by deprotonation (n-BuLi) of 1.98 with the electrophilic aminating reagent Ph₂PO₂NH₂ (Scheme 13, 1.98 → 1.72).³⁴⁻³⁵ Despite the fact that this reagent facilitated direct incorporation of the required amino functionality, we found that there were several notable disadvantages to its use. For instance, the reagent itself had to be synthesized, it was difficult to handle, and the amination reaction generally gave
incomplete conversion. In the case of Ph₂PO₂NH₂, yields for the reagent synthesis never exceeded 40%, and the subsequent amination yields were never greater than 60%. Although another member of our group conducted an investigation of other commonly used aminating agents, better results were not achieved.

Given the difficulties associated with this form of amination, an alternative two-step oxidation/reduction process was explored, using 3-benzyl oxazolidinone (1.99) as a model system. Oxidation of the oxazolidinone to the corresponding N-nitroso compound and subsequent reduction would yield the desired hydrazide (Scheme 15).

Scheme 15. Two-Step Oxidation/Reduction Sequence for Formation of N-N Bond

Based on a literature precedent, the formation of the N-nitroso compound was first attempted using nitric acid, however, this proceeded in only 70% yield. Therefore, we explored the use of nitrosonium tetrafluoroborate. Gratifyingly, this reaction proceeded with nearly quantitative yield and purification was not required.
At this stage, reduction of the nitroso compound to the hydrazide was required, a transformation that, in a general sense, is often problematic as it can result in over-reductive cleavage of the N-N bond to regenerate the oxazolidinone.\textsuperscript{40} The most common approach to performing this reduction is to use zinc in glacial acetic acid.\textsuperscript{39, 41} However, in our system we found that this method gave no better than a 60:40 mixture of hydrazide to oxazolidinone, despite modifications to the reaction conditions, including dilution of the acetic acid, and variations in reaction time and temperature (Table 8). In an effort to improve the reduction, the use of a Ti(II) complex, generated \textit{in situ} by the reaction of TiCl\textsubscript{4} and Mg\textsuperscript{0}, was explored,\textsuperscript{40} and was found to give an 85:15 ratio of desired hydrazide to oxazolidinone (Table 8). Purification of the auxiliary from this mixture proved extremely difficult using either flash chromatography or recrystallization, however, we found that the hydrazide could be isolated as the HCl salt by treating an ethereal solution of the crude reduction mixture with HCl gas.

Table 8. Screening of Conditions for Reduction of N-Nitroso 1.100

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
<th>1.73:1.99</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zn, HOAc</td>
<td>None</td>
<td>10</td>
<td>40</td>
<td>50:50</td>
</tr>
<tr>
<td>2</td>
<td>Zn, HOAc</td>
<td>None</td>
<td>10</td>
<td>15</td>
<td>60:40</td>
</tr>
<tr>
<td>3</td>
<td>Zn, HOAc</td>
<td>Et\textsubscript{2}O</td>
<td>0</td>
<td>15</td>
<td>60:40</td>
</tr>
<tr>
<td>4</td>
<td>Zn, HOAc</td>
<td>Et\textsubscript{2}O</td>
<td>0</td>
<td>15</td>
<td>60:40</td>
</tr>
<tr>
<td>5</td>
<td>TiCl\textsubscript{4}, Mg</td>
<td>DCM:Et\textsubscript{2}O</td>
<td>rt</td>
<td>10</td>
<td>85:15</td>
</tr>
</tbody>
</table>
Unfortunately, despite the initially promising results with the TiCl$_4$/Mg$^0$ reduction, the reaction proved extremely inconsistent and often resulted in complete over-reduction of the $N$-nitroso compound back to the oxazolidinone. Therefore, we explored another approach to $N$-$N$ bond formation through the use of chloramine (NH$_2$Cl) (Scheme 16). Using a procedure recently reported by Hynes$^{42}$, NH$_2$Cl could be generated by combining NH$_3$, NH$_3$, and NaOCl (i.e. commercial bleach) in Et$_2$O (see Experimental). Treatment of the oxazolidinone with base followed by addition of the chloramine solution would give the desired hydrazide. The initial procedure called for the use of a nitrogen sparge during the amination step. We found this sparge to be problematic, due to solvent evaporation that led to inconsistent results. Upon further inquiry, it was found that the nitrogen sparge was used by the authors for removal of an impurity and was superfluous in our system. Removal of the nitrogen sparge and running the reaction under inert atmosphere led to consistently increased conversions.

Scheme 16. Direct Amination of ACCs with Chloramine

We found that deprotonation of the oxazolidinone with KO-tBu in THF, followed by addition of NH$_2$Cl gave rise to the desired $N$-aminated hydrazide in 95%
yield. This procedure has proven to be extremely reliable, consistently producing the hydrazide in >90% yield for numerous oxazolidinones (Scheme 16).

1.3 Mechanistic Investigation

1.3.1 Theoretical Studies on ACC Hydrazones

We wished to conduct a computational study on our ACC hydrazones in order to gain more insight into the conformations and transition states associated with both the ACC hydrazones and derived azaenolates, to lend support for our proposed stereochemical model for alkylation. Additionally, we had proposed a unique directed deprotonation event, CIS-D, as a key step in the alkylation process, and we hoped to be able to confirm and further understand this new type of reactivity. To this end, we established a collaboration with the Houk group at UCLA.

The Houk group began their studies with the simple ACC hydrazone 1.103, derived from an unsubstituted achiral oxazolidinone.\textsuperscript{43} Using B3LYP/6-31G(d),\textsuperscript{44,45} two isomers were observed, 1.103-\textit{syn} and 1.103-\textit{anti} (Figure 6).

![Figure 6. Study of Achiral Oxazolidinone 1.103](image-url)

1.103-syn, has a synclinal arrangement of the N–C\(_\infty\) bond and the N=C bond, with a dihedral angle of 71°. In contrast, 1.103-anti has the anti arrangement of these bonds (dihedral angle of 150°). Interestingly, 1.103-syn, which has the carbonyl ideally oriented to facilitate our proposed directed deprotonation event (CIS-D), was found to be the most stable isomer by 4.7 kcal/mol due to repulsive interactions between the C=N and C=O lone pairs in the 1.103-anti isomer. In both hydrazones, the ring nitrogen is pyramidal with an average bond angle of 114°, which is rather unexpected as typical carbamates have an average bond angle of 120° in order to maximize orbital overlap with the adjacent carbonyl. Our ACCs more closely resemble N,N-dialkylhydrazones in this regard, with the NR\(_2\) lone pair lying in the same plane as the C=N bond due to steric effects.\(^{46}\) When our camphor-derived ACC 1.72 was examined in the same manner, it was found that it could only adopt a syn conformation, due to steric crowding between the rigid bicycloalkane unit and the α-methyl of the hydrazone in the anti-conformer (Figure 7).
The two possible syn-isomers, 1.104-syn-front and 1.104-syn-back (with “front” and “back” referring to the orientation of the carbonyl group), correspond to and 1.89 and 1.90 respectively in Scheme 12, of which we had previously predicted that the “front” isomer would be favored due to steric interactions between the auxiliary and the methyl of the hydrazone. This prediction was confirmed, as it was found that the 1.104-syn-front isomer was 3.5 kcal/mol more stable than the 1.104-syn-back isomer. The destabilization of the “back” isomer can be attributed to the conformation about the N-C₄ bond in the oxazolidinone ring. The interconversion between the two isomers via rotation about the N-N bond induces a change in the configuration at the ring nitrogen.

By examining Newman projections along with N-C₄ isomer of both conformations we can see that 1.104-syn-back has substantial eclipsing interactions, with CNCC and NNCC dihedral angles of 12° and 22° respectively (Figure 8). In contrast, the smallest
dihedral angles about the same bonds in the 1.104-\textit{syn}-front isomer are 29° and 56°, making this isomer 2.2 kcal/mol lower in energy.

![Newman Projections of 1.104-\textit{syn}-front and 1.104-\textit{syn}-back]

**Figure 8. Newman Projections of 1.104-\textit{syn}-front and 1.104-\textit{syn}-back**

To study the key directed deprotonation event, the simple hydrazone 1.103 was again used, with Li(NMe$_2$)THF as a model for LDA in THF solution. Two transition states, corresponding to the 1.103-\textit{syn} and 1.103-\textit{anti} isomers were modeled undergoing intramolecular directed deprotonation (Figure 9), with TS-1.103-\textit{syn} corresponding to our proposed model of CIS-D and resulting in formation of the carbanion \textit{syn} to the ACC. Gratifyingly, the \textit{syn} transition state was found to be 1.4 kcal/mol more stable than TS-1.103-\textit{anti}, further supporting our hypothesized directed deprotonation event.
Figure 9. Examination of Deprotonation Transition State with an Achiral ACC

Again, this study was next applied in the context of ACC 1.72 (Figure 10). The transition states TS-1.104-syn-front and TS-1.104-syn-back possess the same barriers and eclipsing interactions as their corresponding hydrazones (1.104-syn-front and 1.104-syn-back, Figure 7). Additionally, TS-1.104-syn-back also has a destabilizing interaction between the hydrazone α-methyl group and the methyl group on the auxiliary. ACC 1.72 effectively blocks anti-deprotonation and makes the “front” deprotonation considerably easier than the “back”.

Figure 10. Examination of Deprotonation Transition State with ACC 1.72
At this stage, the geometry of the lithium azaenolate derived from 1.104 (1.105-front, 1.105-back) as well as the transition states corresponding to its reaction with MeCl were examined (Figure 11).

**Figure 11. Examination of Azaenolates Derived from 1.104 and Subsequent Alkylation with MeCl**

During alkylation of the azaenolate, the ACC can either be oriented with its carbonyl group in front of or behind the plane of the azaenolate, and MeCl can add either from the front or back face, giving rise to four possible alkylation transition states. With regard to the ACC orientation, the same factors that impacted both the hydrazone as well as the deprotonation TS still prevail, with the carbonyl “back” possessing
increased steric interactions with the α-methyl group as well as eclipsing interactions along the C-N\textsubscript{4} bond, making the carbonyl “front” azaenolate 5 kcal/mol more stable relative to the “back”. When the reaction of the azaenolate with MeCl is considered, the difference between the two TSs increases to 7 kcal/mol in favor of the carbonyl “front”. Moreover, addition of MeCl to the front face where the carbonyl is located (coordinated to Li\textsuperscript{+}) is favored by 7 kcal/mol. Addition to the “back” face is disfavored by steric repulsion between the MeCl and the bicycloalkane group. Therefore, the alkylation of 1.105 occurs exclusively through the lower-energy conformer 1.105-front and MeCl adds to the front side, which creates a large stereochemical preference as a result of both steric effects and Li\textsuperscript{+} •• Cl\textsuperscript{-} attraction in TS-1.105-A.

Having examined all of the above factors in the context of an unsubstituted azaenolate terminus, the Ecc/Zcc-geometry of azaenolate could not be examined. We had proposed that the Ecc-azaenolate was formed preferentially based on steric interactions between the auxiliary and the azaenolate methyl-group\textsuperscript{32}. Experimental support for this hypothesis was found in the alkylation of both 3-pentanone and cyclohexanone derived hydrazones, which led to ketones with the same configuration at the newly formed stereocenter (See Figure 4, Section 1.1.2). Examination of the transition states for the deprotonation of unsymmetrical hydrazone 1.106 by Li(NMe\textsubscript{2})(THF) led to calculated barriers which confirm the Ecc selectivity (Figure 12).
Figure 12. Transition States Leading to E<sub>cc</sub> or Z<sub>cc</sub> Azaenolate

The TS leading to 1.107-<i>E</i> is favored by 2.9 kcal/mol over 1.107-<i>Z</i>, in accordance with similar studies on SAMP/RAMP hydrazones.<sup>25</sup> Once formed, 1.107-<i>E</i> is unlikely to undergo conversion to the <i>Z</i> isomer. The C=C rotational barrier was calculated to be 43 kcal/mol for the azaenolate derived from 1.106 and the barrier for the more-hindered azaenolate 1.107-<i>E</i> is likely much higher. Reaction of 1.107-<i>E</i> with MeCl is calculated to have stereoselectivity similar to that of 1.105, with front side addition of MeCl favored by 6.9 kcal/mol over back-side addition.

Finally, while the B3LYP gas phase calculations for the alkylation of 1.105 correctly predicted the major products, they also predicted a higher selectivity than we
had originally reported.\textsuperscript{32} Our original report had shown that the alkylation of 3-pentanone with ACC 1.72 gave 96:4 \textit{er} for the alkylation of 3-pentanone (Table 7, Section 1.1.2). However, the gas-phase activation energies for reactions of the azaenolates 1.105 or 1.107-\textit{E}\textsubscript{CC} with MeCl predict that the 1.70-\textbeta product should be formed exclusively. This prompted us to conduct a thorough mechanistic examination of our ACCs, reexamining the stereoselectivities of the alkylation of 3-pentanone with ACCs 1.72-1.75 at the level of the alkylated hydrazones.

1.3.2 Examination of ACC Stereoselectivity in 3-Pentanone

1.3.2.1 Analysis of ACC Alkylations Prior to Hydrolysis

As a result of the computational study conducted by Houk, wherein it was predicted that asymmetric alkylation via ACCs should produce only a single diastereomeric product, we wanted to reexamine the stereoselectivities of our ACC alkylations of 3-pentanone. We had previously reported an \textit{er} of 96:4 for our camphor-derived ACC 1.72. However, as discussed previously, our initial report examined the stereoselectivity of ACC alkylations after hydrolysis to the ketones using 2 equivalents \textit{p}-TsOH in acetone (Scheme 17).

![Scheme 17. Hydrolysis of Alkylated ACC Hydrazones](image-url)
Due to this method of analysis, however, we were unable to definitively determine the cause of the imperfect selectivity of our auxiliaries. In principle, it could have resulted from 1) epimerization during the auxiliary removal step, 2) a lack of perfect facial selectivity during addition to the azaenolate, 3) competing α'-alkylation, or some combination of the above. We therefore wished to conduct an investigation of the stereoselectivities at the level of the alkylated hydrazones. To achieve this, 3-pentanone derived hydrazones 1.76-1.79 were allylated under the same conditions reported in our original publication (Table 9).32

Table 9. Regio- and Stereoselectivities of Alkylation of ACC Hydrazones 1.76-1.79

<table>
<thead>
<tr>
<th>Entry</th>
<th>ACC hydrazone</th>
<th>alkylated hydrazone</th>
<th>Previous er</th>
<th>dr</th>
<th>α:α' yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.72 1.76</td>
<td>1.80</td>
<td>96:4</td>
<td>&gt;99:1</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>2</td>
<td>1.73 1.77</td>
<td>1.81</td>
<td>76:24</td>
<td>95:5</td>
<td>96:4</td>
</tr>
<tr>
<td>3</td>
<td>1.74 1.78</td>
<td>1.82</td>
<td>91:9</td>
<td>98:2</td>
<td>97:3</td>
</tr>
<tr>
<td>4</td>
<td>1.75 1.79</td>
<td>1.83</td>
<td>86:14</td>
<td>&gt;99:1</td>
<td>94:6</td>
</tr>
</tbody>
</table>

a Determined by chiral HPLC

The products of each of these reactions were then examined by chiral HPLC against an independently prepared mixture of all four possible diastereomers (Figure 13) (see Experimental).
We found that, in fact, ACC 1.62, which had previously been found to give an er of 96:4, actually produced perfect levels of both regio- and stereoselectivity (Table 9, entry 1). This is in accordance with the Houk group’s computational study, wherein it was predicted that the ACC 1.72 should give rise to a single alkylated product. The three other ACCs (1.73-1.75) were also found to impart much higher levels of stereocontrol than originally reported, and high regioselectivity as well, albeit slightly lower than 1.72.

This union of the Houk computational studies and our subsequent experimental results represents an interesting melding of both experimental and theoretical studies, an approach which could prove valuable to the efficient design of chiral auxiliaries in the future.

1.3.2.2 Temperature Screen

Next, we wanted to examine how effective our ACCs were at imparting high levels of stereoselectivity at more elevated temperatures. The requirement of temperatures as low as –78 °C prohibits the application of our auxiliaries to large scale industrial applications. In order to maintain the high levels of selectivity, the rigid 5-
membered chelate that allows for facial selectivity during alkylation would have to remain intact as the temperature increases. We hoped that the presence of the coordinating carbonyl group on our ACCs would lend increased stability to the 5-membered chelate, allowing it to persist at higher temperatures. Indeed, after conducting a temperature screen of both the deprotonation and alkylation temperatures, we found that ACC 1.72 imparts equally high levels of regio- and stereoselectivity at temperatures up to –20 °C for both deprotonation and alkylation (Table 10).

**Table 10. Temperature Screen of both the Deprotonation and Alkylation of 1.76**

| Entry | Deprotonation Temperature (°C) | Alkylation Temperature (°C) | dr ([|x|:α) | α:α’ |
|-------|-------------------------------|----------------------------|----------|------|
| 1     | –78                           | –78 to rt                  | >99:1    | >99:1 |
| 2     | –40                           | –40 to rt                  | >99:1    | >99:1 |
| 3     | –20                           | –20 to rt                  | >99:1    | >99:1 |
| 4     | 0                             | 0 to rt                    | 97:3     | 98:2 |

\( \text{dr} = \frac{[|x|]}{[α]} \)

This result is significant as –20 °C is the typical threshold for industrial applications of low temperature reactions, making ACCs potentially viable options for pharmaceutical applications. It compares favorably to the SAMP/RAMP hydrazone method, which requires a temperature of –110 °C in order to achieve high levels of
stereocontrol,\textsuperscript{20} one of the factors that has limited SAMP/RAMP to academic scale applications.

1.3.3 ACC 1.73 in Alkylation of Systems with Increased Steric Bulk

During the course of the mechanistic investigation, we attempted the use of ACC 1.73, in the alkylation of 2-methyl-3-pentanone. This required condensation of ACC 1.73 with 3-methyl-2-butanone, followed by a methylation/allylation sequence (Scheme 18). Using this approach the opposite diastereomer, required for HPLC analysis, could easily be generated simply by reversing the order of alkylation. Originally this study was conducted with the hypothesis that a lack of perfect regioselectivity was the cause of the lower \( er \) values in the use 1.73 in the alkylation of 3-pentanone (Table 7, Entry 2, Section 1.1.2). While our study revealed that this was not the case, we found that in this system, possessing an additional substituent at the \( \alpha' \)-position, the simpler phenylalanine-derived ACC (1.73) was able to produce \( dr > 99:1 \).

![Scheme 18. Alkylation with ACC 1.73 in System with Increased \( \alpha' \)-Steric Bulk](image)
While we have yet to establish the basis for this enhanced selectivity, there appears to be a correlation between high selectivity and increasing steric bulk at the α'-position of the ketone, in comparison to 3-pentanone. As a result, this structurally simpler and more easily accessible auxiliary can be employed for certain synthetic applications. In our lab’s asymmetric synthesis of both (-)- and (+)-clusianone (1.114), ACC 1.73 was employed to set the C7 stereocenter (Scheme 19), as well as in the asymmetric total synthesis of apratoxin D (see later).

Scheme 19. Use of ACC 1.73 in Asymmetric Total Synthesis of (+)-CLUSIANONE

1.3.4 Development of New Hydrolysis Conditions

As a result of the mechanistic investigation, it was concluded that the previously reported hydrolysis conditions must have been causing epimerization. The previous conditions were an exchange-based process, employing 2 equivalents of p-TsOH in acetone, and producing the ketone as well as acetone derived hydrazone 1.115 (Scheme
20A). The auxiliary (1.116) could then be recovered in high yield by treatment of 1.115 with NH₂OH•HCl (Scheme 20B).

![Scheme 20. Previous Hydrolysis Conditions for ACC Hydrazones](image)

We hoped to find new hydrolysis conditions that would eliminate epimerization, while still allowing for efficient recovery of the auxiliary. To do this, model system hydrazone 1.118 was synthesized by condensation of ACC 1.72 with 3-methyl-2-butanone, followed by a methylation/benzylation sequence. Again, this approach allowed access to both diastereomers, simply by altering the order of alkylation, which would be necessary for HPLC analysis of the ketones following hydrolysis (see Experimental Section 1.4.2.3). This particular system, with increased steric bulk at the α'-position was chosen in hopes that the hydrolysis conditions we discovered would prove broadly applicable, even when employing our ACC chemistry in more complex and sterically hindered systems. After only a brief study we found that simply adding water to the previously reported conditions, resulted in completed hydrolysis after 40 h with no epimerization at the α-center (Table 11, entry 6).
We hypothesize that the addition of water converts all of the p-TsOH•H₂O (pKₐ ~2.8) to H₃O⁺ (pKₐ ~1.6), creating milder reaction conditions, which lengthened the reaction time but also eliminated epimerization. These hydrolysis conditions have proven to be widely applicable and have been successful in the context of multiple natural products syntheses.

1.4 Conclusion

In conclusion, we have developed an improved synthesis of camphor-derived ACC 1.72, which allows access to the auxiliary on a multi-gram scale. A key step in the synthesis is the formation of the N-N bond, which has been achieved through the use of

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time</th>
<th>β:α</th>
<th>yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 equiv. p-TsOH, acetone</td>
<td>12 h</td>
<td>96:4</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>CuCl₂, THF</td>
<td>15 h</td>
<td>n.d.</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>2 equiv. PPTS, acetone-H₂O (4:1)</td>
<td>7 h</td>
<td>n.d.</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>2 equiv. p-TsOH, acetone-H₂O (4:1)</td>
<td>5 h</td>
<td>&gt;99:1</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>2 equiv. p-TsOH, acetone-H₂O (4:1)</td>
<td>24 h</td>
<td>&gt;99:1</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>2 equiv. p-TsOH, acetone-H₂O (4:1)</td>
<td>40 h</td>
<td>&gt;99:1</td>
<td>95</td>
</tr>
</tbody>
</table>

*a Determined by HPLC
chloramine (NH₂Cl). This amination procedure has been applied to numerous ACCs, and in all cases the aminated products are obtained in high yield.

A theoretical study of our ACC hydrazones and their associated transition states was conducted through a collaboration with the Houk group at UCLA. Using B3LYP/6-31G(d) calculations, the Houk group was able to lend support to both our stereochemical model for alkylation as well as our proposed directed deprotonation event. Additionally, their calculations predicted that the selectivity of the alkylation using ACC 1.72 should produce a single regio- and stereoisomer, prompting us to conduct a more thorough mechanistic investigation into the selectivities of our various ACC auxiliaries. This mechanistic study found that in fact each of our previously investigated ACCs (1.72-1.75) produced significantly higher stereoselectivities than we had previously reported, with 1.72 producing only a single regio- and stereoisomer. As a result, we concluded that our previous hydrolysis conditions must have been causing epimerization during auxiliary removal, leading to the development of new epimerization-free hydrolysis conditions, which have been successful in a wide range of substrates.

1.5 Experimental Section

1.5.1 Auxiliary Synthesis
(+)-Camphorsulfonyl chloride (1.94). To a flask containing l-10-camphor sulfonic acid (2.01g, 8.61mmol), thionyl chloride (4.10g, 34.4mmol) was added dropwise with vigorous stirring. The reaction was refluxed for 30 min then allowed to cool and poured onto ice. The ice slurry was then partitioned and extracted with EtO (2x), dried (MgSO₄) and concentrated in vacuo to yield 1.94 as a white solid (2.00g; 92%). Spectroscopic data was identical to that reported previously.33, 47-50

(+)-10-Chlorocamphor-10-sulfine (1.95). A solution of tosyl chloride (186.2 g, 975 mol) in pyridine (216 mL, 2.66 mol) was heated to 100 °C (oil bath) and a solution of l-10-camphor sulfonyl chloride (222.2 g, .89 mol) in 1,2-dichloroethane (250 mL) was added dropwise over a period of 30 minutes. Upon completion of addition, the reaction was refluxed for 45 minutes then allowed to cool before being poured into EtO (2L). The resulting dark brown precipitate was then isolated (EtO solution saved) and washed with EtO. The combined organic solutions were then concentrated in vacuo to yield a dark brown oil. Recrystallization from hexanes yielded 1.95 as tan crystals (157.5 g; 75 %). Spectroscopic data was identical to that reported previously. Spectroscopic data was identical to that reported previously.33, 47-50
**(+)-Ketopinic acid chloride (1.96).** A solution of l-10-chlorocamphor-10-sulfine (49.8 g, 211 mmol) in CH₂Cl₂ (625 mL) with pyridine (22.0 mL, 221 mmol) was cooled to −78 °C (dry ice/acetone) and treated with ozone until a pale blue solution was observed. Reaction was then poured into pentanes (3 L) and the resulting precipitate filtered off. The filtrate was concentrated *in vacuo* to yield a brown oil. Thionyl chloride (15.4 mL, 211 mmol) and pyridine (0.3 mL, 4 mmol) were then added and the reaction refluxed for 2h. It was then allowed to cool before benzene was added and the solution concentrated *in vacuo* to yield (+)-ketopinic acid chloride 1.96 as a brown solid (38.32 g; 91%). Spectroscopic data was identical to that previously reported.33, 47-50

**(+)-1-isocyanato-7,7-dimethylbicyclo[2.2.1]heptan-2-one (1.97).** To a stirring solution of sodium azide (4.684 g, 72.1 mmol) in water (100 mL) cooled to 0 °C (ice/water) a solution of (+)-ketopinic acid chloride (4.832g, 24.1 mmol) in acetone (100 mL) was added dropwise over a 60 min period. After addition was complete, the reaction was warmed to room temperature and stirred for 3 hrs. The solution was then partially concentrated in vacuo, diluted with H₂O, and extracted with Et₂O (3 x 50 mL).
The combined organic layers are then washed twice with 5% NaHCO₃, dried (MgSO₄) and concentrated in vacuo to yield the crude acid azide. The azide was then dissolved in toluene, refluxed for 3 hrs then concentrated to yield 1.97 as a brown solid (4.32 g; 100%). ¹H NMR (400 MHz, CDCl₃): δ 2.49 (d, 1H, J = 18.7 Hz), 2.17-1.95 (m, 4H), 1.74-1.65 (m, 1H), 1.56-1.45 (m, 1H), 1.06 (s, 3H), 0.90 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 211.6, 128.6, 76.2, 47.3, 41.6, 40.2, 28.5, 26.8, 18.9, 18.7; IR (neat/NaCl) : 2963, 2241, 1753; LRMS (m/z, (relative intensity)) : 179 (M+, 8), 135 (100), 110 (48); HRMS calculated for C₁₀H₁₃O₂N: 179.0946, found: 179.0950. Spectroscopic data was identical to that reported previously.⁵¹

Oxazolidinone of (+)–Ketopinic acid (1.98). CeCl₃·7H₂O (0.898 g, 2.41 mmol) was added to a solution of isocyanate 1.97 (4.32 g, 24.1 mmol) in MeOH (125 mL) cooled to 0 °C. The solution was stirred at 0 °C for 10 min, then cooled to -78 °C. NaBH₄ (1.28 g, 33.7 mmol) was then added in four aliquots over a period of 20 min. The reaction was then warmed to -40 °C and stirred for 2.5 hr. After warming to room temperature, the solvent was then evaporated to remove majority of MeOH then diluted with H₂O (150 mL), extracted with EtOAc (3 x 300 mL), dried (MgSO₄), filtered and concentrated in vacuo to yield a tan powder. Recrystallization from EtOAc/hexanes yielded 1.98 as tan crystals (3.49 g; 80%). ¹H NMR (CDCl₃, 400 MHz): δ 6.85 (bs, 1H), 4.31 (apparent dd, J
=8.1 Hz, 4.2 Hz, 1H), 2.30-2.25 (m, 1H), 2.01-1.96 (m, 1H), 1.87-1.82 (m, 3H), 1.32-1.21 (m, 2H), 1.03 (s, 3H), 0.97 s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 161.5, 86.8, 69.7, 47.2, 42.2, 35.6, 27.3, 25.6, 19.3, 19.2; ESI-MS m/z [M + H]$^+$ calculated for C$_{10}$H$_{15}$O$_2$N: 181.11, found 181.1. Spectroscopic data was identical to that reported previously.$^{33,47-50}$

1.5.1.2 Oxidation/Reduction Approach to N-Amination

![](image)

$\text{N-Nitroso Oxazolidinone 1.100.}$ NOBF$_4$ (7.48 g, 63.5 mmol) was added to a stirring solution of oxazolidinone 1.99 (2.00 g, 11.3 mmol) and pyridine (4.46 mL, 55.2 mmol) in CH$_3$CN (350 mL) cooled to −30 °C. The reaction was stirred at −30 °C for 30 min then warmed to 0 °C and stirred for 2 h. Upon completion, the reaction mixture was poured onto CH$_2$Cl$_2$/ice, extracted with CH$_2$Cl$_2$ (3 x 100 mL), dried (MgSO$_4$), filtered, and concentrated in vacuo to yield 1.100 as a bright yellow solid (2.33 g; 100 %). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.37-7.28 (m, 3 H), 7.13 (d, 2 H, J= 6.8 Hz), 4.74-4.68 (m, 1 H), 4.37-4.27 (m, 2 H), 3.12 (dd, 1 H, J= 3.2, 14.0 Hz), 2.73 (dd, 1 H, J= 8.8, 14.0 Hz).

![](image)

$\text{N-ACC Hydrazide 1.73.}$ Magnesium powder (2.70 g, 0.110 mol) was added to a stirring solution of TiCl$_4$ (110.4 mL, 0.110 mol) in DCM/Et$_2$O (350 mL/90 mL) and the
reaction stirred for 2 hr. N-nitroso compound **1.100** (5.70 g, 27.6 mmol) was then added and stirred for 10 min. Dilute HCl (40:1, H₂O:conc HCl) was then added and stirred for 1 hr. The solution was then neutralized with 10 % NaOH, extracted with EtOAc (3 x 100 mL), dried (MgSO₄), filtered and concentrated in vacuo to yield the crude hydrazide as a brown solid. The crude material was then dissolved in Et₂O (10 mL) and cooled to −78 °C. HCl gas was then bubbled through the solution for 2 min to yield a white solid upon warming. The solid was isolated via vacuum filtration to yield the hydrazide•HCl salt (5.78 g, 90 %) as a white solid. Spectroscopic data was identical to that reported previously.⁶

### 1.5.1.2 Direct N-Amination with Chloramine

**N-ACC Hydrazide (1.72).** Aqueous NH₂OH (15 M, 12.12 mL, 0.182 mol) was added dropwise (ca. 10 min) to a stirred and cooled (−5 °C) suspension of NH₄Cl (8.22 g, 0.154 mol) in Et₂O (300 mL). Bleach (216 mL, 6.0% NaOCl) was then added dropwise (ca. 10 min) and the mixture was stirred for an additional 15 min. The organic layer was dried over CaCl₂ for 1 h at −20 °C. The solution was filtered immediately prior to use to yield an ethereal solution of NH₂Cl (approx. 0.15 M).
KOT-Bu (2.48 g, 22.1 mmol) was added to a solution of 1.98 (2.0 g, 11.0 mmol) in THF (75 mL) (Ar atmosphere), and the resulting suspension was stirred for 3 hr. A vigorous nitrogen sparge was then initiated and the previously prepared ethereal solution of NH₂Cl (110 mL, 16.5 mmol) was added dropwise (ca. 15 min). The mixture was stirred for 1.5 h, with periodic addition of Et₂O to account for solvent loss due to evaporation. The mixture was then quenched with 1 M aqueous Na₂SO₃ (50 mL). The aqueous phase was extracted with Et₂O (twice), and the combined organic layers were dried (MgSO₄), filtered, and concentrated under reduced pressure to yield a yellow oil (1.98 g) (~ 9:1 1.72:1.98). The crude material (1.98 g, 9.78 mmol) was dissolved in acetone (30 mL) and p-TsOH·H₂O (~ 25 mg) was added. The mixture was stirred for 12 h then partitioned between saturated aqueous NaHCO₃ and Et₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic layers were dried (MgSO₄), filtered, and concentrated under reduced pressure to give a pure, white solid (2.17 g, 94%). ¹H NMR (CDCl₃, 400 MHz): δ 4.16 (dd, J = 8.2, 4.1 Hz, 1H), 3.91 (s, 2H), 2.30-2.10 (m, 2H), 2.05-1.70 (m, 3H), 1.36-1.24 (m, 1H), 1.18 (s, 3H), 1.0 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 160.2, 83.2, 72.1, 47.3, 42.7, 35.1, 25.8, 25.4, 20.7, 19.5; ESI-MS m/z [M + H]⁺ calcd for C₁₀H₁₇N₂O₂: 197.26, found 197.1.
1.5.2 Mechanistic Investigation

1.5.2.1 Synthesis of racemic 2-allyl-3-pentanone

Methyl-2-methyl-3-oxopentanoate (1.120). K$_2$CO$_3$ (25.8 g, 0.187 mol) was added to a solution of methyl-3-oxopentanoate (25 mL, 0.200 mol) in acetone (250 mL) and the mixture was stirred for 5 min. Methyl iodide (58.1 mL, 0.935 mol) was added dropwise over ca. 5 min, and stirring was continued for 10 min. The reaction mixture was refluxed for 12 h and allowed to cool to rt. Et$_2$O (250 mL) was added, the mixture was filtered, dried (MgSO$_4$), and evaporated under reduced pressure to give a yellow liquid (26 g, 96%). The crude material was used directly in the next transformation. Spectroscopic data was consistent with that previously reported.$^{52}$

Methyl-2-methyl-2-allyl-3-oxopentanoate (1.121). NaH (200 mg, 8.33 mmol) was added to a cooled (ice-H$_2$O bath) solution of 1.120 (1.03 g, 6.94 mmol) in THF (8 mL) (Ar atmosphere), and stirring was continued for 10 min. Allyl bromide (0.755 mL, 8.67 mmol) was added dropwise over ca. 2 min. Stirring was continued for 3 h, the cold bath
was removed, and stirring was continued for an additional 12 h. The reaction mixture was then partitioned between saturated aqueous NH₄Cl and Et₂O. The aqueous phase was extracted with Et₂O (2x) and the combined organic extracts were washed with brine, dried (MgSO₄), filtered, and evaporated under reduced pressure to give 1.121 as a colorless liquid (1.22 g, 95%). The crude material was used without further purification. Spectroscopic data was consistent with that reported previously for the purified compound.⁵³

\[
\begin{align*}
1.122
\end{align*}
\]

2-Allyl-3-pentanone (1.122). LiOH (504 mg, 21 mmol) was added to a stirred solution of 1.121 (1.29 g, 7.0 mmol) in 3:1 THF-H₂O (32.5 mL). The resulting suspension was stirred at reflux temperature for 12 h, and then allowed to cool to rt before acidifying with 1.0 M HCl to pH ~1–2. The mixture was then extracted with Et₂O (2x), dried (MgSO₄), filtered, and concentrated under reduced pressure to give a pale yellow liquid. Flash chromatography over silica gel using 2:98 Et₂O-pentane gave 1.122 as a colorless liquid (800 mg, 90%). Spectroscopic data was identical to that reported previously.⁵⁴
1.5.2.2 Analysis of Alkylated Hydrazones of ACCs 1.72-1.75

The following procedure is representative of the synthesis of diastereomeric mixtures of allylated 3-pentanone hydrazones derived from ACCs 1.72-1.75

Synthesis of Diastereomeric Mixture (1.80-β-CN, 1.80-α-CN, 1.80-β-CN, 1.80-α-CN)

*p*-TsOH·H₂O (ca. 20 mg) was added to a stirred solution of 1.122 (0.406 g, 2.1 mmol) and 1.72 (328 mg, 2.6 mmol) in CH₂Cl₂ (11.0 mL) (Ar atmosphere). The mixture was refluxed for 18 h, cooled to rt, and then partitioned between CH₂Cl₂ (50 mL) and saturated aqueous NaHCO₃ (20 mL). The organic phase was washed with brine (20 mL), dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave a mixture of four diastereomers, 1.80-β-CN, 1.80-α-CN, 1.80-β-CN, 1.80-α-CN (0.562 g, 88%). ¹H NMR (CDCl₃, 400 MHz): δ 5.89-5.51 (m, 1H), 5.08-4.91 (m, 2H), 4.27-4.22 (m, 1H), 3.20-2.58 (m, 1H), 2.58-1.74 (m, 10H), 1.30-0.94 (m, 11H); ¹³C NMR (CDCl₃, 100 MHz): δ 184.2, 183.7, 183.4, 182.2, 155.4, 155.2, 154.9, 154.7, 154.9, 136.9, 136.5, 136.4, 135.9, 116.5, 116.3, 116.2, 116.0, 82.8, 82.7, 73.2, 73.16, 73.13, 47.8, 47.7, 42.9, 42.84, 42.8, 39.6, 39.5, 39.3, 39.1, 38.1, 37.4, 35.6, 35.4, 35.3, 34.9, 29.7, 26.7, 26.5, 26.4, 25.7, 25.65, 25.6, 24.7, 24.6, 24.5, 24.1, 21.4, 21.32,
21.3, 19.2, 19.13, 19.1, 17.7, 17.14, 17.1, 10.6, 10.4, 10.2, 10.0; \textbf{ESI-MS} \textit{m/z} [M + H]\textsuperscript{+} \text{calcd for C}_{18}H_{29}N_{2}O_{2}: 305.44, found 305.1.

Chiral HPLC analysis (0.5:99.5 \textit{i}-PrOH-hexanes; 0.5 mL/min) gave resolution of the previously synthesized four diastereomers (\textbf{1.80-\textit{\textbeta}-ZCN}, \textbf{1.80-\textalpha-ECN}, \textbf{1.80-\textbeta-ZCN}, \textbf{1.80-\textalpha-ECN}). Based on the anticipated thermodynamic preferences for hydrazone formation, we assume that the two major peaks (14.698 min, 18.811 min) represent the two \textit{E}_{CN} diastereomers, and the two minor peaks (15.830 min, 17.467 min) represent the two \textit{Z}_{CN} diastereomers. To ensure that these four peaks did indeed correspond to the four disatereomers, fractions from the HPLC corresponding to each peak were collected and ESI-MS was performed for each peak individually. The mass found for each peak matched that of the hydrazone, confirming that these were the four compounds of interest. \textbf{ESI-MS} \textbf{14.698}, found 305.1; \textbf{15.830}, found 305.1; \textbf{17.467}, found 305.1; \textbf{18.811}, found 305.1.
Diastereomeric Mixture (1.81-β-ZCN, 1.81-α-Ecn, 1.81-β-ZCN, 1.81-α-Ecn)

Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave a mixture of four diastereomers, 1.81-β-ZCN, 1.81-α-Ecn, 1.81-β-ZCN, 1.81-α-Ecn (0.562 g, 88%). ¹H NMR (CDCl₃, 400 MHz): δ 7.32-7.12 (m, 5 H), 5.89-5.60 (m, 1 H), 5.11-4.98 (m, 2 H), 4.36-4.22 (m, 1 H), 4.18-4.02 (m, 2 H), 3.22-3.08 (m, 2H), 2.76-2.60 (m, 1H), 2.58-2.30 (m, 4H), 1.29-1.11 (m, 6H); ESI-MS m/z [M + H]+ calcd for C₁₈H₂₇N₂O₂: 301.05, found 301.1.

Chiral HPLC analysis (1.0:99.0 i-PrOH-hexanes; 1.0 mL/min) gave resolution of the four diastereomers. Based on the anticipated thermodynamic preferences for hydrazone formation, we assume that the two major peaks (17.820 min, 18.624 min) represent the two Ecn diastereomers, and the two minor peaks (12.012 min, 21.706 min) represent the two ZCN diastereomers.
Diastereomeric Mixture (1.82-β-ZCN, 1.82-α-ECN, 1.82-β-ZCN, 1.82-α-ECN)

Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave a mixture of four diastereomers, 1.82-β-ZCN, 1.82-α-ECN, 1.82-β-ZCN, 1.82-α-ECN (22 mg, 72%). 

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.49-7.10 (m, 13 H), 6.90-6.86 (m, 2 H), 5.79-5.49 (m, 1 H), 5.08-4.88 (m, 3 H), 3.49-3.47 (m, 1 H), 2.88-2.78 (m, 2 H), 2.48-1.88 (m, 4 H), 1.24-0.87 (m, 7 H)

ESI-MS m/z [M + H]\(^+\) calcd for C\(_{18}\)H\(_{20}\)N\(_2\)O\(_2\): 305.44, found 305.1. ESI-MS m/z [M + H]\(^+\) calcd for C\(_{30}\)H\(_{33}\)N\(_2\)O\(_2\): 453.60, found 453.1.
Chiral HPLC analysis (7.0:93.0 i-PrOH-hexanes; 0.4 mL/min) gave resolution of the four diastereomers. Based on the anticipated thermodynamic preferences for hydrazone formation, we assume that the two major peaks (9.479 min, 28.642 min) represent the two $E_{CN}$ diastereomers, and the two minor peaks (16.966 min, 19.450 min) represent the two $Z_{CN}$ diastereomers.

Diastereomeric Mixture ($1.83-\beta-Z_{CN}$, $1.83-\alpha-E_{CN}$, $1.83-\beta-Z_{CN}$, $1.83-\alpha-E_{CN}$)

Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave a mixture of four diastereomers, $1.83-\beta-Z_{CN}$, $1.83-\alpha-E_{CN}$, $1.83-\beta-Z_{CN}$, $1.83-\alpha-E_{CN}$ (0.562 g, 88%).
NMR (CDCl$_3$, 400 MHz): $\delta$ 7.40-7.20 (m, 4H), 5.46-5.30 (m, 2H), 5.10-4.90 (m, 1H), 4.80-4.60 (m, 2H), 3.60-3.20 (m, 2H), 2.90-2.76 (m, 1H), 2.50-2.20 (m, 2H), 1.84 (t, $J = 7.3$ Hz, 2H), 1.22 (t, $J = 7.2$ Hz, 3H), 1.09 (d, $J = 6.8$ Hz, 3H); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.51-7.20 (m, 4H), 5.91-5.64 (m, 1H), 5.42-5.29 (m, 2H), 5.13-4.97 (m, 2H), 3.58-3.29 (m, 2H), 3.03-2.58 (m, 1H), 2.57-2.17 (m, 4H), 1.25-1.19 (m, 3H), 0.86-0.78 (m, 3H); ESI-MS m/z [M + H]$^+$ calcld for C$_{18}$H$_{23}$N$_2$O$_2$: 299.39, found 299.1.

Chiral HPLC analysis (5.0:95.0 i-PrOH-hexanes; 0.5 mL/min) gave resolution of the four diastereomers. Based on the anticipated thermodynamic preferences for hydrazone formation, we assume that the two major peaks (18.004 min, 19.860 min) represent the two $E$CN diastereomers, and the two minor peaks (26.853 min, 31.728 min) represent the two $Z$CN diastereomers.
1.5.2.3 Determination of Diastereoselectivity of the Allylation of Hydrazones 1.76-1.79

The following procedure of is representative of the diastereoselective alkylation of 3-pentanone derived hydrazones 1.76-1.79. The diastereoselectivity of each reaction was analyzed via chiral HPLC against a trace of the previously synthesized diastereomeric mixture.

General Procedure for Hydrazone Alkylation (Preparation of 1.80):

\[ n\text{-BuLi} \text{ (2.5 M in hexanes, 11.65 mL, 29.13 mmol)} \text{ was added dropwise over ca. 2 min to a stirred and cooled (−78 °C) solution of diisopropylamine (4.45 mL, 31.77 mmol) in THF (0.6 mL) (Ar atmosphere). The mixture was transferred to an ice-H}\_2\text{O bath, stirred for 30 min, and then cooled to −40 °C. A solution of 1.76 (7.002 g, 26.48 mmol) in THF (260 mL) was added by cannula, with additional THF (2 x 2.0 mL) as a rinse, and the mixture was stirred for 45 min. Allyl bromide (2.52 mL, 29.13 mmol) was then added and stirring was continued for 5 min. The cold bath was removed and the mixture was stirred for an additional 40 min and then partitioned between Et\_2O and H\_2O. The aqueous phase was extracted with Et\_2O (twice) and the combined organic extracts were washed with brine, dried (MgSO\textsubscript{4}), filtered and evaporated under reduced pressure to afford 1.80. \]
pressure to give a yellow oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 1.70 (7.899 g, 98%) as a pure, light-yellow oil.  

$^1$H NMR (CDCl$_3$, 400 MHz):

$\delta$ 5.90-5.70 (m, 1H), 5.18-4.94 (m, 2H), 4.25 (dd, $J = 8.1$, 4.1 Hz, 1H), 3.18-3.04 (m, 1H), 2.50-2.24 (m, 4H), 2.14-1.80 (m, 4H), 1.76 (t, $J = 4.4$ Hz, 1H), 1.26-1.32 (m, 2H), 1.23 (s, 3H), 1.16 (s, 3H), 1.13 (t, $J = 7.2$ Hz, 3H), 0.94 (d, $J = 7.0$ Hz, 3H);  

$^{13}$C NMR (CDCl$_3$, 400 MHz): $\delta$

184.4, 155.5, 136.6, 116.7, 82.9, 73.4, 47.9, 43.1, 37.6, 35.6, 35.1, 26.7, 25.8, 24.8, 21.5, 19.3, 17.3, 10.4;  

ESI-MS m/z [M + H]$^+$ calcd for C$_{18}$H$_{29}$N$_2$O$_2$: 305.44, found 305.1.

a) HPLC trace of diastereomeric mixture (0.5:99.5 i-PrOH-hexanes; 0.5 mL/min)

![HPLC trace of diastereomeric mixture](image)

b) Chiral HPLC analysis of crude 1.80 (0.5:99.5 i-PrOH-hexanes; 0.5 mL/min)
c) Chiral HPLC analysis of pure 1.80 (0.5:99.5 i-PrOH-hexanes; 0.5 mL/min)

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.706</td>
<td>89.4574</td>
</tr>
<tr>
<td>18.849</td>
<td>0.6583</td>
</tr>
</tbody>
</table>

Only peak 15.642

Synthesis and HPLC Analysis of 1.81

Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave 1.81 (0.088 g, 90%) as a pure, yellow oil. \( ^1H \) NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.38-7.30 (m 5H), 5.18-5.15 (m, 1H), 4.66 (t, \( J=8.6 \) Hz, 1H), 4.8-4.13 (m, 1H), 3.13-3.05 (m, 1H), 2.36-2.04 (m, 3H), 1.18 (d, \( J=6.7 \), 3H), 1.10 (t, \( J=7.3 \), 3H); \( ^{13}C \) NMR (CDCl\(_3\), 100 MHz): \( \delta \) 182.9, 155.6, 137.1, 136.1,
129.5, 129.1, 128.9, 127.3, 116.1, 69.2, 64.4, 28.5, 25.4, 11.1, 10.6; **ESI-MS** m/z [M + H]⁺ calcd for C₁₇H₂₃N₂O₂: 287.18, found 287.1.

a) HPLC trace of diastereomeric mixture (1.0:99.0 i-PrOH-hexanes; 1.0 mL/min)

\[
\begin{align*}
\text{1.81-} & \text{Z}_\text{CN} + \text{1.81-} \alpha_- \text{Z}_\text{CN} + \text{1.81-} \beta_- \text{E}_\text{CN} + \text{1.81-} \alpha_- \text{E}_\text{CN} \\
& \text{12.012} \quad 17.820 \\
& 21.706 \quad 18.624
\end{align*}
\]

b) Chiral HPLC analysis of 1.81 (1.0:99.0 i-PrOH-hexanes; 1.0 mL/min)

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.044</td>
<td>5.4160</td>
</tr>
<tr>
<td>18.169</td>
<td>0.6256</td>
</tr>
<tr>
<td>18.972</td>
<td>0.6065</td>
</tr>
<tr>
<td>21.190</td>
<td>92.9546</td>
</tr>
</tbody>
</table>

**Synthesis and HPLC Analysis of 1.82**
Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave 1.82 (0.102 g, 93%) as a pure, yellow oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.40-7.10 (m, 13H), 7.00-6.80 (m, 2H), 5.70-5.50 (m, 1H), 5.08 (t, $J = 6.0$ Hz, 1H), 5.40-4.90 (m, 2H), 3.48 (q, $J = 7.0$ Hz, 1H), 3.14-2.99 (m, 1H), 2.78 (d, $J = 6.0$ Hz, 1H), 2.40-1.90 (m, 4H), 1.21 (t, $J = 7.0$ Hz, 1H), 1.13 (d, $J = 6.8$ Hz, 3H), 0.95 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 183.6, 153.9, 142.2, 139.8, 137.6, 136.1, 129.5, 128.5, 128.4, 128.3, 128.2, 127.6, 126.6, 126.5, 116.9, 87.1, 69.4, 66.1, 39.5, 36.9, 36.8, 24.7, 16.9, 15.5, 10.3; ESI-MS m/z [M + H]$^+$ calcd for C$_{30}$H$_{33}$N$_2$O$_2$: 453.60, found 453.1.

a) HPLC trace of diastereomeric mixture (7.0:93.0 i-PrOH-hexanes; 0.4 mL/min)
b) Chiral HPLC analysis of **1.82** (7.0:93.0 i-PrOH-hexanes; 0.4 mL/min)

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.848</td>
<td>0.6062</td>
</tr>
<tr>
<td>16.958</td>
<td>2.4745</td>
</tr>
<tr>
<td>19.426</td>
<td>83.5465</td>
</tr>
<tr>
<td>28.607</td>
<td>8.8158</td>
</tr>
</tbody>
</table>

Synthesis and HPLC Analysis of **1.83**

Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave **1.83** (0.102 g, 93%) as a pure, yellow oil. **¹H NMR** (CDCl₃, 400 MHz): δ 7.40-7.20 (m, 4H), 5.46-5.30 (m, 2H), 5.10-4.90 (m, 1H), 4.80-4.60 (m, 2H), 3.60-3.20 m, 2H), 2.90-2.76 (m,1H), 2.50-2.20 (m, 2H), 1.84 (t, J = 7.3 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H); **¹³C NMR** (CDCl₃, 100 MHz): δ 184.8, 154.0, 140.9, 138.6, 135.8, 129.8, 127.4, 126.4, 125.5, 116.4, 77.2, 67.8, 39.6, 39.5, 36.6, 24.6, 16.9, 11.0; **ESI-MS** m/z [M + H]+ calcd for C₁₈H₂₃N₃O₂: 299.39, found 299.1.

a) HPLC trace of diastereomeric mixture **1.83** (5.0:95.0 i-PrOH-hexanes; 0.5 mL/min)
b) Chiral HPLC analysis of 1.83 (5.0:95.0 i-PrOH-hexanes; 0.5 mL/min)

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.981</td>
<td>0.9876</td>
</tr>
<tr>
<td>19.770</td>
<td>1.9033</td>
</tr>
<tr>
<td>26.831</td>
<td>1.3418</td>
</tr>
<tr>
<td>31.775</td>
<td>95.7673</td>
</tr>
</tbody>
</table>

1.5.2.3. Development of New Hydrolysis Conditions

Synthesis of Model System 1.118
Hydrazone 1.123. To a solution of 3-methyl-2-butanone (3 mL, 28.0 mmol) in CH₂Cl₂ (50 mL) was added 1.72 (370 mg, 1.90 mmol) followed by p-TsOH (36 mg, 0.190 mmol) and the solution stirred for 16 h. The reaction was then quenched by addition of NaHCO₃ (sat. aq.) and the aqueous layer extracted with CH₂Cl₂ (2x20 mL). The organic layers were combined and dried over MgSO₄, filtered and concentrated in vacuo to yield a yellow oil. Flash chromatography over silica gel (20:80 EtOAc:Hex) gave 1.123 as a white solid (452 mg, 90%). ¹H NMR (CDCl₃, 400 MHz): δ 4.23 (dd, 1 H, J= 4.0, 8.0 Hz), 2.63-2.53 (m, 1 H), 2.33-2.27 (m, 1 H), 2.01-1.98 (m, 2 H), 1.92 (s, 3 H), 1.87-1.82 (m, 1 H), 1.77-1.75 (m, 1 H), 1.23 (s, 3 H), 1.17-1.14 (m, 11 H, containing a s at δ 1.14 for 3 H).

Methylated Hydrazone 1.124. n-BuLi (2.5 M in hexanes, 0.488 mL, 1.22 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (0.188 mL, 1.34 mmol) in THF (5.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (1.81 mL, 0.443 mmol) was transferred via syringe to a pre-cooled (−78 °C) flask (Ar atmosphere). A solution of 1.123 (97.5 mg, 0.369 mmol) in THF (0.8 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was stirred for 45
min. MeI (0.230 mL, 3.69 mmol) was then added and the mixture removed from the cold bath and stirred at room temperature for 30 min. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice), and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave 1.124 (97.6 mg, 95%) as a pure, white solid. ¹H NMR (CDCl₃, 400 MHz): δ 4.24 (dd, J = 4.0, 8.0 Hz, 1 H), 2.70-2.63 (m, 1 H), 2.53-2.43 (m, 1 H), 2.33-1.20 (m, 2 H), 2.03-1.90 (m, 2 H), 1.84 (dd, 1 H, J= 8.4, 13.6 Hz), 1.76 (t, 1 H, J = 4.4 Hz), 1.31-1.20 (m, 5 H, containing a s at δ 1.23 for 3 H), 1.19-1.14 (m, 9 H, containing a s at δ 1.14 for 3 H), 1.06 (t, 3 H, J = 7.6 Hz).

Benzylated Hydrazone 1.125. n-BuLi (2.5 M in hexanes, 0.488 mL, 1.22 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (0.188 mL, 1.34 mmol) in THF (5.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (1.81 mL, 0.443 mmol) was transferred via syringe to a pre-cooled (−78 °C) flask (Ar atmosphere). A solution of 1.123 (97.5 mg, 0.369 mmol) in THF (0.8 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was stirred for 45
BnBr (52.2 µL, 0.443 mmol) was then added and the mixture removed from the cold bath and stirred at room temperature for 16 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice), and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 7.5:92.5 EtOAc-hexanes gave 1.125 (111 mg, 85%) as a pure, white solid. 

**¹H NMR** (CDCl₃, 400 MHz): δ 7.41-7.19 (m, 5 H), 4.24 (dd, J = 4.0, 8.0 Hz, 1 H), 2.87-2.76 (m, 3 H), 2.66-2.47 (m, 2 H), 2.33-2.27 (m, 1 H), 1.96-1.82 (m, 3 H), 1.77-1.75 (m, 1 H), 1.28-1.12 (m, 12 H, containing a s at δ 1.23 for 3 H and a s at δ1.14 for 3 H).

**Hydrazone 1.118-β.** n-BuLi (2.5 M in hexanes, 0.488 mL, 1.22 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (0.188 mL, 1.34 mmol) in THF (5.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (1.30 mL, 0.317 mmol) was transferred via syringe to a pre-cooled (−78 °C) flask (Ar atmosphere). A solution of 1.124 (73.5 mg, 0.264 mmol) in THF (0.8 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, the mixture transferred to an ice-H₂O and stirred
for 45 min. The mixture was then recooled to −78 °C, BnBr (37.7 µL, 0.317 mmol) was then added, the mixture stirred at −78 °C for 2 h, then removed from the cold bath and stirred at room temperature for 45 min. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice), and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 1.118-β (95 mg, 98%) as a pure, white solid. ¹H NMR (CDCl₃, 400 MHz): δ 7.30-7.17 (m, 5 H), 4.23 (dd, J = 4.0, 8.0 Hz, 1 H), 3.26-3.12 (m, 2 H), 2.83-2.74 (m, 1 H), 2.46-2.40 (m, 1 H), 2.34-2.28 (m, 1 H), 1.26-1.20 (m, 15 H, containing a s at δ 1.26 for 3 H), 1.17 (s, 3 H), 0.85 (d, 3 H, J = 6.8 Hz); ¹³C NMR (CDCl₃, 100 MHz): δ 187.3, 155.0, 139.9, 129.7, 128.2, 125.9, 82.7, 73.2, 47.8, 42.9, 38.3, 35.4, 30.2, 26.4, 25.6, 23.3, 22.8, 21.5, 19.2, 15.6. ESI/MS m/z calcd for C₂₃H₃₂N₃O₂ (M + H): 369.3, found: 369.3.

Hydrazone 1.118-α. n-BuLi (2.5 M in hexanes, 0.488 mL, 1.22 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (0.188 mL, 1.34 mmol) in THF (5.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (1.30 mL, 0.317 mmol) was transferred via syringe to a pre-cooled (−78 °C) flask (Ar atmosphere).
A solution of **1.125** (81.5 mg, 0.230 mmol) in THF (0.8 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H$_2$O bath and stirred for 45 min. The solution was then recooled to −78 °C, MeI (0.143 mL, 2.30 mmol) was then added and the mixture stirred at −78 °C for 2 h then removed from the cold bath and stirred at room temperature for 45 min. The mixture was then partitioned between Et$_2$O and H$_2$O. The aqueous phase was extracted with Et$_2$O (twice), and the combined organic extracts were dried (MgSO$_4$), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave **1.118-α** (95 mg, 98%) as a pure, white solid. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.26-7.08 (m, 5 H), 4.16 (dd, $J$ = 4.0, 8.0 Hz, 1 H), 3.43-3.34 (m, 1 H), 2.83-2.73 (m, 1 H), 2.65 (d, 2 H, $J$ = 7.6 Hz), 2.30-2.24 (m, 1 H), 1.85-1.78 (m, 2 H), 1.71-1.69 (m, 1 H), 1.65-1.58 (m, 1 H), 1.26-1.06 (m, 18 H, containing a d at δ 1.25 (3 H, $J$ = 6.8 Hz), a d at δ 1.21 (3 H, $J$ = 6.4 Hz), a s at δ 1.16 (3 H), a d at δ 1.10 (3 H, $J$ = 6.8 Hz), and a s at δ 1.08 (3 H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 185.7, 154.9, 139.7, 128.8, 128.2, 126.1, 82.6, 73.2, 47.8, 42.8, 40.7, 38.0, 35.3, 29.9, 26.3, 25.6, 24.3, 21.7, 21.4, 19.1, 17.0. ESI/MS m/z calcd for C$_{23}$H$_{32}$N$_2$O$_2$ (M + H): 369.3, found: 369.3.

a) HPLC trace of diastereomeric mixture (0.5:99.5 i-PrOH-hexanes; 0.5 mL/min)
b) Chiral HPLC analysis of **1.118-β** (0.5:99.5 i-PrOH-hexanes; 0.5 mL/min)

Single Peak at 11.946

c) Chiral HPLC analysis of **1.118-α** (0.5:99.5 i-PrOH-hexanes; 0.5 mL/min)
Ketone 1.119-β. To a solution of hydrazone 1.118-β (20 mg, 0.054 mg) in acetone (1 mL) was added p-TsOH•H₂O (20.5 mg, 0.108 mmol) and the solution stirred 12 h. The reaction was then quenched by addition of NaHCO₃ (sat. aq., 1 mL), diluted with Et₂O (10 mL), and the aqueous layer extracted with Et₂O (2x10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo to give a yellow oil. Flash chromatography over silica gel using 2.5:97.5 EtOAc-hexanes gave 1.119-β (9.3 mg, 91%) as a clear, colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 7.28-7.13 (m, 5 H), 3.02-2.92 (m, 2 H), 2.58-2.48 (m, 2 H), 1.08 (d, 3 H, J= 6.8 Hz), 1.01 (d, 3 H, J= 7.2 Hz), 0.87 (d, 3 H, J= 6.8 Hz); ESI/MS m/z calcd for C₁₃H₁₈O (M + H): 191.1, found: 191.1.
Ketone 1.119-α. To a solution of hydrazone 1.118-α (20 mg, 0.054 mg) in acetone (1 mL) was added p-TsOH•H₂O (20.5 mg, 0.108 mmol) and the solution stirred 12 h. The reaction was then quenched by addition of NaHCO₃ (sat. aq., 1 mL), diluted with Et₂O (10 mL), and the aqueous layer extracted with Et₂O (2x10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo to give a yellow oil. Flash chromatography over silica gel using 2.5:97.5 EtOAc-hexanes gave 1.119-α (9.3 mg, 91%) as a clear, colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 7.28-7.13 (m, 5 H), 3.02-2.92 (m, 2 H), 2.58-2.48 (m, 2 H), 1.08 (d, 3 H, J= 6.8 Hz), 1.01 (d, 3 H, J= 7.2 Hz), 0.87 (d, 3 H, J= 6.8 Hz); ESI/MS m/z calcd for C₁₃H₁₈O (M + H): 191.1, found: 191.1.

a) HPLC trace of enantiomeric mixture (0.2:99.8 i-PrOH-hexanes; 0.5 mL/min)
b) Chiral HPLC analysis of 1.119-β post hydrolysis with 2 equiv. p-TsOH in acetone (0.2:99.8 i-PrOH-hexanes; 0.5 mL/min)

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.829</td>
<td>3.8929</td>
</tr>
<tr>
<td>22.801</td>
<td>95.4717</td>
</tr>
</tbody>
</table>


c) Chiral HPLC analysis of 1.119-α post hydrolysis with 2 equiv. p-TsOH in acetone (0.2:99.8 i-PrOH-hexanes; 0.5 mL/min)
Ketone 1.119-β. To a solution of hydrazone 1.118-β (20 mg, 0.054 mg) in 4:1 acetone-H₂O (1 mL) was added p-TsOH•H₂O (20.5 mg, 0.108 mmol) and the solution stirred 40 h. The reaction was then quenched by addition of NaHCO₃ (sat. aq., 1 mL), diluted with Et₂O (10 mL), and the aqueous layer extracted with Et₂O (2x10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo to give a yellow oil. Flash chromatography over silica gel using 2.5:97.5 EtOAc-hexanes gave 1.119-β (9.3 mg, 91%) as a clear, colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 7.28-7.13 (m, 5 H), 3.02-2.92 (m, 2 H), 2.58-2.48 (m, 2 H), 1.08 (d, 3 H, J= 6.8 Hz), 1.01 (d, 3 H, J= 7.2 Hz), 0.87 (d, 3 H, J= 6.8 Hz); ESI/MS m/z calcd for C₁₃H₁₈O (M + H): 191.1, found:
a) HPLC trace of enantiomeric mixture (0.2:99.8 i-PrOH-hexanes; 0.5 mL/min)

\[
\begin{align*}
1.119-\alpha & \quad 21.190 \\
1.119-\beta & \quad 22.815
\end{align*}
\]

b) Chiral HPLC analysis of 1.119-\(\beta\) post hydrolysis with 2 equiv. \(p\)-TsOH in acetone-H\(_2\)O (4:1) (0.2:99.8 i-PrOH-hexanes; 0.5 mL/min)

Single peak at 21.866
1.5.2.4 Use of ACC 1.73 in Systems with Steric Bulk at the α′-Position

Hydrazone 1.108. To a solution of 3-methyl-2-butanone (3 mL, 28.0 mmol) in CH₂Cl₂ (50 mL) was added 1.73 (288 mg, 1.50 mmol) followed by p-TsOH (28.6 mg, 0.150 mmol) and the solution stirred for 16 h. The reaction was then quenched by addition of NaHCO₃ (sat. aq.) and the aqueous layer extracted with CH₂Cl₂ (2x20 mL). The organic layers were combined and dried over MgSO₄, filtered and concentrated in vacuo to yield a yellow oil. Flash chromatography over silica gel (15:85 EtOAc:Hex) gave 1.108 as a white solid (344 mg, 88%). ¹H NMR (CDCl₃, 400 MHz): δ 7.32-7.25 (m, 2 H), 7.14 (d, 2 H, 6.8 Hz), 4.38-4.31 (m, 1 H), 4.29-4.25 (m, 1 H), 4.06-4.02 (m, 1 H), 3.11 (dd, 1 H, 4.0, 13.6 Hz), 2.75 (dd, 1 H, J= 8.8, 13.6 Hz), 2.67-2.61 (m, 1 H), 1.96 (s, 3 H), 1.28-1.24 (m, 6 H).

Methylated Hydrazone 1.126. n-BuLi (2.5 M in hexanes, 0.369 mL, 0.923 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (0.142 mL, 1.01 mmol) in THF (4.0 mL) (Ar atmosphere). The mixture was transferred to
an ice-H₂O bath, stirred for 30 min, and then cooled to –78 °C. A solution of **1.108** (218.3 mg, 0.839 mmol) in THF (3.0 mL) was added by syringe, with additional THF (2 x 0.5 mL) as a rinse, and the mixture was stirred for 45 min. MeI (0.522 mL, 8.39 mmol) was then added and the mixture removed from the cold bath and stirred at room temperature for 30 min. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice), and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave **1.126** (186 mg, 81%) as a pure, white solid. **¹H NMR** (CDCl₃, 400 MHz): δ 7.33-7.23 (m, 3 H), 7.18-7.15 (m, 2 H), 4.35-4.24 (m, 2 H), 4.06-4.01 (m, 1 H), 3.14-3.09 (m, 1 H), 2.75-2.65 (m, 2 H), 2.56-2.45 (m, 1 H), 2.41-2.32 (m, 1 H), 1.19-1.11 (m, 9 H).

**Allylated Hydrazone 1.127.** n-BuLi (2.5 M in hexanes, 0.123 mL, 0.317 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (~78 °C) solution of i-Pr₂NH (48.5 µL, 0.346 mmol) in THF (1.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to –78 °C. A solution of **1.108** (75.0 mg, 0.288 mmol) in THF (1.0 mL) was added by syringe, with additional THF (2 x 0.2 mL) as
a rinse, and the mixture was stirred for 45 min. AllylBr (30.1 µL, 0.346 mmol) was then added and the mixture removed from the cold bath and stirred at room temperature for 12 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice), and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 1.127 (72 mg, 83%) as a pure, colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 7.33-7.23 (m, 3 H), 7.16 (m, 2 H), 5.85-5.75 (m, 1 H), 5.09-4.99 (m, 2 H), 4.34-4.23 (m, 2 H), 3.13 (dd, 1 H, J= 4.0, 13.6 Hz), 2.75-2.56 (m, 3 H), 2.47-2.37 (m, 1 H), 2.36-2.28 (m, 2 H), 1.19-1.15 (m, 6 H).

**Bisalkylated Hydrazone 1.109-β.** n-BuLi (2.5 M in hexanes, 81.1 µL, 0.193 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (29.5 µL, 0.210 mmol) in THF (1.5 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A solution of 1.126 (48.0 mg, 0.175 mmol) in THF (1.5 mL) was added by syringe, with additional THF (2 x 0.5 mL) as a rinse, and the mixture was stirred for 45 min. MeI (0.522 mL, 8.39 mmol) was then added and the mixture removed from the cold bath and stirred at room temperature for
12 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice), and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 1.109-β (51 mg, 93%) as a pure, white solid. 

**¹H NMR** (CDCl₃, 400 MHz): δ 7.33-7.25 (m, 3 H), 7.17 (d, 2 H, J = 7.2 Hz), 5.72-5.62 (m, 1 H), 5.09-4.98 (m, 2 H), 4.37-4.29 (m, 1 H), 4.25-4.21 (m, 1 H), 4.03-3.99 (m, 1 H), 3.22-3.10 (m, 2 H), 2.76-2.68 (m, 1 H), 2.59 (dd, 1 H, J = 10.0, 13.6 Hz), 2.26-2.09 (m, 2 H), 1.24-1.18 (m, 9 H).

**Bisalkylated Hydrazone 1.109-α.** n-BuLi (2.5 M in hexanes, 54.8 µL, 0.131 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (20.0 µL, 0.143 mmol) in THF (1.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A solution of 1.127 (35.9 mg, 0.120 mmol) in THF (1.0 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was stirred for 45 min. MeI (74.7 µL, 1.20 mmol) was then added and the mixture removed from the cold bath and stirred at room temperature for 12 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was
extracted with Et₂O (twice), and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 1.109-α (29 mg, 76%) as a pure, white solid. ¹H NMR (CDCl₃, 400 MHz): δ 7.33-7.23 (m, 3 H), 7.17 (d, 2 H, J= 6.8 Hz), 5.79-5.68 (m, 1 H), 5.09-5.02 (m, 2 H), 4.28-4.21 (m, 2 H), 4.08-4.02 (m, 1 H), 3.16-3.06 (m, 2 H), 2.75-2.66 (m, 1 H), 2.55-2.49 (m, 1 H), 2.10-2.02 (m, 1 H), 1.19 (t, 6 H, J= 6.8 Hz), 1.06 (d, 3 H, J= 6.8 Hz).

a) Chiral HPLC analysis of 1.109-α (1.0:99.0 i-PrOH-hexanes; 1.0 mL/min)

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.236</td>
<td>95.2440</td>
</tr>
<tr>
<td>22.569</td>
<td>0.7974</td>
</tr>
</tbody>
</table>

b) Chiral HPLC analysis of 1.109-β (1.0:99.0 i-PrOH-hexanes; 1.0 mL/min)

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.527</td>
<td>1.3091</td>
</tr>
<tr>
<td>22.173</td>
<td>97.6092</td>
</tr>
</tbody>
</table>
2. Regioselective Asymmetric $\alpha,\alpha$-Bisalkylation, $\alpha,\alpha,\alpha',\alpha'$-Tetraalkylation of Ketones via ACCs

2.1 Background and Introduction

In the $\alpha$-alkylation of ketones with LDA, the regiochemical outcome of the reaction is generally controlled by the kinetic preference of LDA for the removal of the least sterically hindered proton. For asymmetric ketone alkylation via the derived SAMP/RAMP hydrazones, the same is true, with LDA removing the most sterically accessible proton.\textsuperscript{16-17, 20} Therefore, in the case of equally substituted, non-symmetrical ketones (or their derived SAMP/RAMP hydrazones), possessing both $\alpha$- and $\alpha'$-protons, deprotonation with LDA results in mixtures of products (Scheme 21). Furthermore, attempted bisalkylation of both ketones and SAMP/RAMP hydrazones via successive treatment with LDA and alkyling agents results in exclusive formation of the $\alpha,\alpha'$-bisalkylated products.

![Scheme 21. Regioselectivity of Bisalkylation of A. Ketones B. SAMP/RAMP Dialkyl Hydrazones](image)

83
Therefore, the direct regiocontrolled asymmetric α,α-bisalkylation of ketone derivatives having indistinguishable α- and α'-protons has never before been possible (cf. 2.2 → 2.3 + 2.4, Scheme 21). However, if such a transformation could be achieved then, given the expansive body of literature on ketone manipulation, the bisalkylated products would provide access to an unusually wide array of chiral, non-racemic intermediates for use in asymmetric synthesis (Figure 14).

![Figure 14. Representative Structures Obtained from α,α-Bisalkylation of ACC Acetone-Derived Hydrazone](image)

In contrast to the aforementioned systems, alkylation of ACC chiral hydrazones proceeds via a directing effect termed Complex Induced Syn-Deprotonation, or CIS-D (2.15, Scheme 22B). It has been shown that CIS-D results in the regioselective monoalkylation of symmetrical ACC hydrazones on exclusively the same side of the CN-double bond as the auxiliary. This directing effect is enabled by coordination of the incoming base to the carbonyl oxygen of the auxiliary via the counterion, thus controlling the regiochemistry of the deprotonation event (Scheme 22, 2.15→2.16). While proven successful in the context of the monoalkylation of simple, symmetrical ketones we envisioned that this directed deprotonation event could enable the regioselective asymmetric α,α-bisalkylation of ketones having both α- and α’-protons.
Our inspiration for this regiocontrolled deprotonation event was the *syn*-dianion effect of *N*-sulfonyl hydrazones.\textsuperscript{55-57} In the *syn*-dianion effect (Scheme 22A), an *N*-centered monoanion (2.11), obtained from deprotonation of a sulfonyl hydrazone, directs an incoming base to remove a proton on the same side of the C=N bond as the anion, resulting in the formation of a configurationally stable dianion that can be alkylated (2.12 → 2.13). The process may then be repeated (2.13 → 2.14), again in a configurationally controlled manner with regard to the hydrazone C=N bond geometry.

*Scheme 22. A. Syn-Dianion Effect in Sulfonyl Hydrazones B. α,α-Bisalkylation via Complex Induced *syn*-Deprotonation (CIS-D) (S = small substituent; L = large substituents)*

We reasoned that a similar directed deprotonation might be possible by simply utilizing the carbonyl lone pair\textsuperscript{58} of an ACC hydrazone via CIS-D. Here, the carbonyl oxygen electrons would coordinate with the base, directing deprotonation to the same
side of the carbon–nitrogen double bond (2.15 → 2.16, 2.17 → 2.18). If such a directed deprotonation could be achieved then, providing the azaenolates involved (2.16, 2.18) were configurationally stable, and that the monoalkylation product (2.17) did not isomerize once formed, asymmetric α,α-bisalkylation would be possible.

2.2 Results and Discussion

2.2.1 Preliminary Results

Given the novelty of the proposed transformation, at the outset of our studies we did not know if the intended CIS-D would occur or, if it did, whether the resulting azaenolate intermediates (2.16, 2.18) would be configurationally stable about the original carbon-nitrogen double bond. This would be essential for the proposed asymmetric α,α-bisalkylation process for two reasons. First, since the monoalkylated hydrazone (2.17, Scheme 21B) would have to undergo a second directed deprotonation for regiocontrolled access to the second azaenolate (2.17 → 2.18), it would be critical that isomerization of the hydrazone double bond did not occur during the first alkylation (2.15 → 2.17), so that the auxiliary carbonyl could again direct deprotonation to the α-position. Second, since addition of the second electrophile would have to occur in a diastereoselective fashion, the auxiliary would need to be positioned on the same side of the carbon-nitrogen double bond that the electrophile was approaching from to ensure high facial selectivity.
Scheme 23. Preliminary Studies on Regioselective, Asymmetric αα-Bisalkylation

As an initial test, a previous member of the lab attempted the α,α-bisalkylation sequence starting from acetone-derived hydrazone 2.20 (Scheme 23).32 To do so, allyl bromide was added to a −78 °C solution of the lithium azaenolate derived from 2.20 in THF. The cold bath was removed immediately following addition, and the mixture was allowed to stir for 20 minutes, before quenching with H2O. This gave exclusively α-regioisomer 2.21 in excellent yield. In the key part of this bisalkylation study, 2.21 was subjected to a second alkylation reaction using p-bromobenzyl bromide as the alkylation agent. As hoped, the major product was indeed the α,α-bisalkylated compound (2.23), which was confirmed by X-ray crystallography (2.25, Scheme 23). Once again alkylation had occurred on the same side of the C=N bond as the auxiliary carbonyl. The diastereoselectivity of the transformation leading to 2.23 was also excellent (dr = 97:3).
To our knowledge, this was the first instance of asymmetric $\alpha,\alpha$-bisalkylation of a ketone having both $\alpha$- and $\alpha'$-protons.

With proof of concept established, we began a further investigation into this new asymmetric alkylation method. Unfortunately, our attempts to prepare more of compound 2.21 using the procedure describe above resulted in variable yields of product, and at times led to the formation of 2.22 as well, the latter presumably obtained via in situ isomerization of 2.21. We therefore undertook a study to develop reliable conditions to effect the monoalkylation of hydrazone 2.20.

### 2.2.2 Development of Monoalkylation

We began our study of the monoalkylation by conducting a survey of both reaction temperature and time, as outlined in Table 12. We eventually found that by holding the alkylation temperature constant at 4 °C and allowing the reaction to proceed for 1.5 h, an excellent yield of 2.21 could reliably be produced in a fully regiocontrolled manner. In order to confirm that this monoalkylation product was indeed the desired syn-isomer, we independently prepared a 15:85 mixture of 2.21 and 2.22, respectively, via acid catalyzed condensation of 5-hexene-2-one and auxiliary 1.72 (See Experimental). The NMR data of the minor, thermodynamically less favored isomer of this reaction matched the NMR data of the allylation product obtained from 2.20, strongly suggesting this compound to be 2.21. Using these conditions, we were able to prepare compound 2.21 starting with up to 5 g of 2.20, without compromising the outcome of the reaction.
This does not represent the upper limit of the reaction, but simply the largest scale we have conducted it on to date.

Table 12. Survey of Conditions for the Regioselective Allylation of 2.20

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time (min)</th>
<th>2.21:2.22</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–78</td>
<td>30</td>
<td>n.d.</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>–20</td>
<td>30</td>
<td>&gt; 99:1</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>–20</td>
<td>60</td>
<td>&gt; 99:1</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>60</td>
<td>&gt; 99:1</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>90</td>
<td>&gt; 99:1</td>
<td>99</td>
</tr>
</tbody>
</table>

*a n.d. = not determined

Next, we tested other ACC auxiliaries (1.73–1.75) for their ability to effect regioselective α-alkylation, in the hopes of providing increased flexibility in our later investigations on the second, asymmetric alkylation step. To do so, acetone-derived hydrazones 2.26–2.28 were prepared and each of these compounds, in addition to 2.20, was treated successively with LDA and then MeI using the conditions established above. Using a similar strategy to that for 2.21, the regioselectivity of each methylation was determined by HPLC against an independently prepared E:Z mixture of 2.29–2.32, prepared by acid catalyzed condensation of each auxiliary with 2-butanone (See
Experimental). As shown in Table 13, under these conditions all four of the hydrazones tested underwent regioselective alkylation strongly favoring formation of the $\alpha$-product. However, of these, hydrazone 2.20, formed from ACC auxiliary 1.72, gave the best result providing a single regioisomer, which was consistent with the results of our previous mechanistic studies. Consequently, auxiliary 1.72 was used for the remainder of our studies.

**Table 13. Regioselective Methylation of ACC Hydrazones 2.20,2.26-2.28**

<table>
<thead>
<tr>
<th>Entry</th>
<th>ACC</th>
<th>acetone hydrazone</th>
<th>methylated hydrazone</th>
<th>$\alpha:\alpha'$</th>
<th>yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.72</td>
<td>2.20</td>
<td>2.29</td>
<td>&gt;99:1</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>1.73</td>
<td>2.26</td>
<td>2.30</td>
<td>91:9</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>1.74</td>
<td>2.27</td>
<td>2.31</td>
<td>98:2</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>1.75</td>
<td>2.28</td>
<td>2.32</td>
<td>91:9</td>
<td>93</td>
</tr>
</tbody>
</table>

$^a$Determined by HPLC

At this stage, the scope of the monoalkylation was examined using hydrazone 2.20 and a variety of alkyl halides (Table 14). In each case the alkylation proceeded with excellent yield, and gave only the $\alpha$-regioisomer. The transformations proved highly reliable and were very easy to carry out. These results provided further evidence of CIS-
D occurring during azaenolate formation. Moreover, they supported the notion that the azaenolate intermediate was configurationally stable under the reaction conditions, and that isomerization of the hydrazone did not occur in situ following alkylation.

Table 14. Scope of the Regioselective α-Alkylation of 2.20 via CIS-D

<table>
<thead>
<tr>
<th></th>
<th>2.29</th>
<th>2.33</th>
<th>2.34</th>
<th>2.35</th>
<th>2.21</th>
</tr>
</thead>
<tbody>
<tr>
<td>R¹X</td>
<td>Mel</td>
<td>BnBr</td>
<td>Etl</td>
<td>PrI</td>
<td>Br</td>
</tr>
<tr>
<td>R²</td>
<td>Cl</td>
<td>CO₂Me</td>
<td>Br</td>
<td>Br</td>
<td>Br</td>
</tr>
<tr>
<td>Y</td>
<td>97%</td>
<td>91%</td>
<td>94%</td>
<td>94%</td>
<td>92%</td>
</tr>
</tbody>
</table>

2.2.3 Asymmetric α,α-Bisalkylation

With a highly effective regioselective, isomerization-free monoalkylation procedure established, we began a further investigation of the regio- and stereocontrolled incorporation of the second alkyl group at the α-position. This second alkylation requires an even more demanding application of CIS-D than the first, in that the ACC auxiliary in this instance must completely reverse the inherent preference of LDA for removal of the most sterically accessible α′-methyl protons of the monoalkylated...
compounds (cf. Table 3), and instead direct the removal of the less accessible α-methylene protons. Moreover, since a stereogenic center is formed, the auxiliary must also provide high levels of asymmetric induction. While the result of our preliminary test of this transformation described above (\(2.21 \rightarrow 2.23\), Scheme 23) was very promising, there was clearly room for improvement with regard to both the regio- and stereochemical outcome.

To investigate the possibility of such improvement, we chose to study the methylation of hydrazone 2.33. We began by using the conditions employed above for the \(p\)-bromobenzylation of 2.21 (Scheme 23), which had produced a 92:8 mixture of 2.23 and 2.24, respectively. We were pleased to find that under these conditions the methylation of 2.33 produced only the \(\alpha,\alpha\)-bisalkylation product 2.41 (Scheme 24), reproducibly and in excellent yield.

Scheme 24. Studies on Regioselective Asymmetric \(\alpha,\alpha\)-Bisalkylation
Inspired by this result, we next tried the allylation of 2.34 under the same conditions (Scheme 24). Unfortunately, in stark contrast to the methylation of 2.33, this reaction was extremely problematic providing variable yields and mixtures of products that appeared to include the desired product 2.42, as well as undesired (E)-isomer (2.43). With regard to the formation of 2.43, while it was possible that isomerization had occurred subsequent to the allylation, in which case it would have no bearing on the overall level of asymmetric induction (assuming no epimerization occurred during isomerization), we could neither be certain of that, nor could we assume that if that were the case, the same scenario would apply for other alkylation reactions. We therefore decided to focus on developing conditions that would enable regiocontrolled α,α-bisalkylation, without isomerization occurring. We suspected that this might be possible simply by holding the reaction temperature at –78 °C for the entire course of the alkylation, although we were concerned that the alkylation might not proceed appreciably at such a low temperature. To test this hypothesis, we reverted to the methylation of 2.33, which had previously worked extremely well, and studied the time course of this reaction at –78 °C. We found the reaction to be complete within 24 h, and also determined that no regioisomeric products had formed (Table 15). Moreover, we were extremely pleased to find that the diastereomer ratio for this reaction was >99:1. An
initial test of the scale-up of this reaction was conducted beginning with 4 g of 2.33, and proceeded without compromising the outcome of the transformation.

**Table 15. Screen of Reaction Time for Methylation of 2.33 at −78 °C**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>$d$&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−78</td>
<td>1</td>
<td>n.d.&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>−78</td>
<td>6</td>
<td>n.d.&lt;sup&gt;b&lt;/sup&gt;</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>−78</td>
<td>12</td>
<td>&gt; 99:1</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>−78</td>
<td>24</td>
<td>&gt; 99:1</td>
<td>98</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by HPLC  <sup>b</sup>n.d. = not determined

Gratifyingly, we found that the use of these conditions with a range of hydrazones and alkylating agents gave the desired α,α-bisalkylated products in excellent yield, with both complete regio- and stereochemical control (Table 16). The absolute configuration of the products was inferred by analogy to our previous experimental work, and the theoretical studies conducted by Houk (Section 1.3.1). An additional convenience of this bisalkylation procedure is that either enantiomeric ketone can be formed using the same auxiliary, following its cleavage, by simply changing the alkylation sequence. To highlight this, the alkylations in Table 16 were conducted in a pair-wise fashion. In all cases, the α,α-bisalkylated product was formed with essentially
complete regio- and stereochemical control, and in excellent yield, and the transformations were independent of the alkylation order.

Table 16. Regioselective Asymmetric \( \alpha,\alpha \)-Bisalkylation

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Yield</th>
<th>Diastereomeric Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.44</td>
<td>93%</td>
<td>dr &gt; 99:1</td>
</tr>
<tr>
<td>2.41</td>
<td>97%</td>
<td>dr &gt; 99:1</td>
</tr>
<tr>
<td>2.45</td>
<td>91%</td>
<td>dr &gt; 99:1</td>
</tr>
<tr>
<td>2.23</td>
<td>92%</td>
<td>dr &gt; 99:1</td>
</tr>
<tr>
<td>2.42</td>
<td>91%</td>
<td>dr &gt; 99:1</td>
</tr>
<tr>
<td>2.46</td>
<td>94%</td>
<td>dr &gt; 99:1</td>
</tr>
<tr>
<td>2.47</td>
<td>89%</td>
<td>dr &gt; 99:1</td>
</tr>
<tr>
<td>2.48</td>
<td>87%</td>
<td>dr &gt; 99:1</td>
</tr>
</tbody>
</table>

2.2.3 Attempt at \( \alpha,\alpha,\alpha \)-Trisalkylation to Generate Quaternary Center

Having proven the effectiveness of CIS-D in facilitating regioselective \( \alpha,\alpha \)-bisalkylation, we were curious if we could effect a third regioselective alkylation in order to form an all carbon quaternary stereocenter (Scheme 25). There were several aspects of this reaction that would prove challenging. First, we would have to be able to direct the deprotonation event for a considerably more challenging third time, and if it were successful, we would then have to be able to control the geometry of the resulting non-symmetrically trisubstituted azaenolate (2.50 vs. 2.51). Finally, if those could be
achieved, we would still have to be able to alkylate at the terminus of a sterically hindered disubstituted azaenolate.

![Scheme 25. Potential α,α,α-Trisalkylation to Generate All-Carbon Quaternary Stereocenter](image)

In order to test this, hydrazone 2.41 was treated with LDA and ethyl iodide under our standard bisalkylation conditions (Scheme 26). Somewhat disappointingly, this reaction repeatedly yielded only starting material. In order to examine if this were due to a lack of deprotonation or a lack of alkylation, we reran a sample of recovered 2.41 on the HPLC and found that the $dr$ was still $>99:1$.

![Scheme 26. Attempted α,α,α-Trisalkylation of Hydrazone 2.41](image)

Had directed deprotonation occurred, this would have lead to epimerization at the α-stereocenter, and thus we were able to conclude that we were not able to deprotonate at the tertiary α-center. We believed that the hydrazone was unable to
undergo a third deprotonation at the now tertiary carbon due to the developing steric interactions between the auxiliary and the $Z_{cc}$ azaenolate substituent, and thereby preventing epimerization during an LDA mediated isomerization. While this was disappointing from the perspective of the trisalkylation project, the lack of epimerization was encouraging for our hopes of achieving $\alpha,\alpha,\alpha',\alpha'$-tetraalkylation (see Secton 2.3), as we believed this meant we could avoid epimerization while attempting to further functionalize at the $\alpha'$-methyl group (see Section 2.2.7).

### 2.2.4 Hydrolysis of Bisalkylated Hydrazones

At this point we turned our attention to the removal and recovery of the auxiliary from the bisalkylated products. Thus, each of the $\alpha,\alpha$-bisalkylated hydrazones prepared (Table 16) were individually treated with $p$-TsOH·H$_2$O in acetone/H$_2$O (4:1) (conditions discussed in the previous section) and in each case the desired ketone and 2.20 were obtained in excellent yield, the latter conveniently set for a second round of asymmetric $\alpha,\alpha$-bisalkylation (Table 17). The stereochemical integrity of the resulting ketones was determined via chiral HPLC, by reference to a mixture of enantiomers for which baseline separation conditions had been established (see Experimental). From these experiments it was determined that no epimerization occurred during auxiliary removal.

**Table 17. Hydrolysis of Bisalkylated Hydrazones**
<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydrazine</th>
<th>Hydrazine $d^e$</th>
<th>Ketone</th>
<th>Ketone $e^e$</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Hydrazine" /></td>
<td>&gt;99:1</td>
<td><img src="image2" alt="Ketone" /></td>
<td>&gt;99:1</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Hydrazine" /></td>
<td>&gt;99:1</td>
<td><img src="image4" alt="Ketone" /></td>
<td>&gt;99:1</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Hydrazine" /></td>
<td>&gt;99:1</td>
<td><img src="image6" alt="Ketone" /></td>
<td>&gt;99:1</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Hydrazine" /></td>
<td>&gt;99:1</td>
<td><img src="image8" alt="Ketone" /></td>
<td>&gt;99:1</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Hydrazine" /></td>
<td>&gt;99:1</td>
<td><img src="image10" alt="Ketone" /></td>
<td>&gt;99:1</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Hydrazine" /></td>
<td>&gt;99:1</td>
<td><img src="image12" alt="Ketone" /></td>
<td>&gt;99:1</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Hydrazine" /></td>
<td>&gt;99:1</td>
<td><img src="image14" alt="Ketone" /></td>
<td>&gt;99:1</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15" alt="Hydrazine" /></td>
<td>&gt;99:1</td>
<td><img src="image16" alt="Ketone" /></td>
<td>&gt;99:1</td>
<td>98</td>
</tr>
</tbody>
</table>

$^e$Determined by HPLC
In conclusion, we have developed the first general method for the asymmetric $\alpha, \alpha$-bisalkylation of ketones having both $\alpha$- and $\alpha'$-protons, via CIS-D of ACC hydrazones. The transformation is efficient, and proceeds with both excellent regio- and stereo-selectivity. Significantly, CIS-D completely reverses the inherent preference of LDA to remove the least sterically hindered of two similarly acidic protons. It also overrides the normal tendency of LDA to remove the more strongly acidic proton in a substrate having protons differing significantly in their acidity. Consequently, the regiochemical outcome of this method is the opposite of that normally obtained for kinetic LDA-mediated deprotonation of ketones and SAMP/RAMP hydrazones.

### 2.2.5 $\alpha, \alpha$-Bisalkylation of $\alpha'$-Activated Hydrazones

To further probe the effectiveness of CIS-D, we wanted to explore the $\alpha, \alpha$-bisalkylation of hydrazones possessing $\alpha'$-activating groups (Scheme 27). During the monoalkylation, this would require that CIS-D be able to completely reverse the normal preference of LDA for removal of the significantly more acidic $\alpha'$-protons in these systems. This would also be true of the second alkylation. However, an additional challenge arises in this case as there would no longer be a steric preference for $\alpha$-deprotonation, since both the $\alpha$ and $\alpha'$ acidic sites would now be methylene groups.

![Scheme 27. $\alpha, \alpha$-Bisalkylation of ACC Hydrazone Possessing $\alpha'$-Activating Group](image-url)
As a first example, we explored the α,α-bisalkylation of phenylacetone-derived hydrazone 2.68 (Scheme 28A). In this case, the α'-protons are benzylic, making them ~6–7 pK\textsubscript{a} units more acidic than the α-methyl protons. Compound 2.68 was prepared and then subjected to the first alkylation reaction using MeI as the electrophile. We were very pleased to find that only the α-product was formed (2.69), thus indicating that CIS-D was indeed able to completely overcome the normal pK\textsubscript{a} bias favoring α’ deprotonation. Even more impressively, the second alkylation (2.69 → 2.70) also gave only α-alkylation, and with excellent (>99:1) diastereoselectivity. The α,α-bisalkylation was also conducted in the opposite order of alkylation (2.68 → 2.71 → 2.72), and was equally effective. Significantly, in contrast to these results, it has been established that the SAMP hydrazone of ketone 2.67 (i.e., 2.73) undergoes alkylation preferentially at the α’-position (2.73 → 2.74), not the α-position (2.75), and with low diastereoselectivity (Scheme 28B).\textsuperscript{20} As such, alkylation via our ACCs provides a convenient complimentary strategy to the Enders method for the asymmetric alkylation of ketones possessing activating substituents.
As a second example of this methodology, we explored the bisalkylation of benzyloxyacetone. This was of particular interest to us as we had hoped to employ the \(\alpha,\alpha\)-bisalkylation of (2.83, Scheme 30) as a key step in the synthesis of a chiral aldehyde in the synthesis of apratoxin D (see Section 3.2.3). It has been shown in the literature that deprotonation of \(\alpha'\)-methoxyacetone (2.76), as well as other \(\alpha'\)-alkoxyketones (2.79, 2.81), with a strong base, leads to almost exclusive regioselective deprotonation towards the oxygen substituent (Scheme 29).

Scheme 28. A. Alkylation of via ACC 2.67 B. Alkylation via SAMP Hydrazone 2.64
Scheme 29. Regioselective Enolization Towards Oxygen in $\alpha'$-Alkoxyketones

To see if our ACCs could once again reverse the regiochemical preference of LDA, hydrazone 2.84 was prepared, and treated with LDA and MeI. Gratifyingly, this gave rise to exclusively the $\alpha$-alkylated product (2.85) in high yield, with no evidence of the $\alpha'$-alkylated product. The second, and more challenging, alkylation, was then attempted using LDA and allyl bromide. As in the case of phenylacetone, this gave exclusively the desired $\alpha,\alpha$-bisalkylated product (2.87) in excellent yield and with a $dr > 99:1$ (determined by chiral HPLC, see Experimental).
In order to obtain the opposite configuration at the α-stereocenter, the alkylation sequence was also performed using the opposite order of alkylation (2.84 → 2.86), which proceeded with equally high levels of stereoselectivity and yield. With this result, we were confident that we would be able to employ this methodology for the synthesis of a key intermediate in the total synthesis of apratoxin D (Section 3.2.3).

2.3 Regioselective Asymmetric α,α,α’,α’-Tetraalkylation

2.3.1 Background and Introduction

Having developed a method for the regioselective, asymmetric α,α-bisalkylation of ketones employing our ACC auxiliaries, we wanted to try and extend the methodology to the α,α,α’,α’-tetraalkylation of ketones.
Scheme 31. Asymmetric, Regioselective Tetraalkylation of Acetone

The development of the tetraalkylation method would present a number of additional challenges beyond those present in the $\alpha,\alpha$-bisalkylation work. Starting from acetone hydrazone 2.20, the $\alpha,\alpha$-bisalkylation would be performed as described above (Scheme 32). In order to further functionalize at the $\alpha'$-carbon, we would then have to isomerize the auxiliary, while not causing any epimerization at the already formed $\alpha$-stereocenter ($2.88 \rightarrow 2.89$).

Scheme 32. Proposed $\alpha,\alpha,\alpha',\alpha'$-Tetraalkylation Sequence

While there are known methods for performing such isomerizations on $N,N$-dialkylhydrazones and oximes, employing both protic$^{59}$ and Lewis acids,$^{60}$ photoirradiation,$^{61}$ and heat,$^{62}$ we were unsure if any of those methods would be compatible with our auxiliaries or the presence of an $\alpha$-stereocenter. Another option would be to hydrolytically remove the auxiliary and reinstall it, which should give rise to the thermodynamically favored $E$-hydrazone. However, this would also require the
use of acidic conditions, potentially compromising the α-center, as well as adding additional steps to the overall process.

Once we were able to successfully obtain the necessary E-hydrazone, we would need to effect a second bisalkylation sequence (2.89→2.90). This alkylation sequence would have to proceed with high levels of stereoselectivity despite the presence of a nearby stereogenic center, overcoming any potential match/mismatch of chirality. Additionally, it would have to not cause any epimerization at pre-existing α'-stereocenter. Finally, if all of these steps could be achieved, we would have to be able to remove the auxiliary from a very sterically hindered, tetrasubstituted hydrazone without epimerization (2.90→2.91). However, despite the numerous challenges, if such a sequence could be affected, it would provide access to numerous useful synthetic intermediates (Figure 15).

Figure 15. Representative Structures Resulting from the αα,α'-Trisalkylation and α,α,α',α'-Tetraalkylation of Acetone

Additionally, the ability to rapidly incorporate high levels of structural and stereochemical complexity starting from a simple molecule such as acetone, in a completely regio- and stereochemically controlled fashion, could provide a novel
approach to the synthesis of complex molecules. Several examples of molecules whose key stereogenic centers could be constructed via a tetraalkylation sequence, including apratoxin D, which will be discussed later, are shown in Figure 16.

Figure 16. Natural Products which could be Synthesized via an Asymmetric $\alpha,\alpha,\alpha',\alpha'$-Tetraalkylation Strategy

2.3.2 Results and Discussion

2.3.2.1 Isomerization

Having learned from our work on the $\alpha,\alpha$-bisalkylation project, we thought that we might be able to effect isomerization to the thermodynamically favored $E$-hydrazone through the use of LDA. This was based on the observation of isomerization occurring during the bisalkylation of 2.34 when the temperature was raised above $-78 \, ^\circ C$ (Scheme 33). In this case, the reaction was warmed to room temperature after addition of the alkylating agent in order to promote the reaction, which yielded a mixture of the $E$ and $Z$ bisalkylated hydrazone isomers as well as other byproducts.
Scheme 33. Observation of Isomerization during α,α-Bisalkylation of 2.34

While we have not definitively proven this, we hypothesized that this isomerization was occurring via rotation about the CN-bond after the bisalkylation had occurred. With the α-carbon now possessing two alkyl substituents, a third deprotonation by LDA would occur at the sterically less hindered methyl group, rather than undergoing another directed deprotonation event, to give azaenolate 2.95, which can undergo rotation about the CN-bond to give 2.96, giving the more thermodynamically favored E-hydrazone (2.97) upon protonation (Scheme 34).

Scheme 34. Proposed LDA-mediated Isomerization of ACC Hydrazone

We hypothesized that it might be possible to facilitate complete isomerization through prolonged exposure of the bisalkylated compounds to LDA at higher temperatures. As an initial test of this hypothesis, monobenzylated hydrazone 2.33 was treated with 2 equivalents of LDA for 1 h at various temperatures (Table 18).
Table 18. Effect of Temperature on Isomerization of Monoalkylated Hydrazone 2.33

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Z:E</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-78</td>
<td>100:0</td>
</tr>
<tr>
<td>2</td>
<td>-40</td>
<td>75:25</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>40:60</td>
</tr>
<tr>
<td>4</td>
<td>r.t</td>
<td>15:85</td>
</tr>
</tbody>
</table>

Initial studies were conducted on the monoalkylated compound in order to eliminate any complicating issues with epimerization that could result in the bisalkylated systems. Indeed, it was found that stirring at room temperature for 1 h produced near quantitative isomerization to the E-hydrazone. With this promising result, we moved to bisalkylated hydrazone 2.44 (Scheme 35). In these bisalkylated systems, the increased steric bulk at the α-position would lead to an increased thermodynamic bias favoring isomerization to the E-hydrazone. However, we had the additional concern of possible epimerization at the α-stereocenter. As shown in Scheme 34, we proposed that deprotonation would occur at the methyl group rather than the system undergoing another directed deprotonation at the α-carbon, thus avoiding epimerization. This hypothesis was based on our earlier attempts at trisalkylation to generate a quaternary carbon center, which resulted in the recovery of starting material
with uncompromised *dr* (Scheme 26, Section 2.2.3). Treatment of 2.44 with two equivalent amounts of LDA at rt for 5 h led to quantitative isomerization to the *E*-hydrazone.

![Scheme 35. LDA-Mediated Isomerization of 2.44 and 2.41 with no Epimerization](image)

In order to examine the possibility of epimerization, hydrazone 2.41, possessing the opposite configuration at the α-center to 2.44, was subjected to the same isomerization conditions and the two compounds examined by HPLC. Gratifyingly, it was found that no epimerization had occurred in either hydrazone, with 2.98 and 2.99 both having *dr >* 99:1. In order to confirm that this isomerization method was applicable to variably substituted hydrazones, as well as gain more substrates for the subsequent tetraalkylation, a variety of differently substituted α,α-bisalkylated hydrazones were tested with equally positive results (Table 19).
2.3.2.2 Tetraalkylation

In an initial test of the tetraalkylation, 2.44 was treated with 1.5 equivalents of LDA at –78 °C, followed by addition of methyl iodide and warming to rt for 2 h (Scheme 36). Gratifyingly, this gave the desired α,α,α′-trisalkylated hydrazone in 80% yield. In order to complete the tetraalkylation, this hydrazone was treated with LDA and p-Br-BnBr under the same conditions as the trisalkylation, giving the tetraalkylated compound in 60% yield as a single diastereomer, as judged by 1H-NMR and 13C-NMR. To confirm the stereochemistry of 2.104, a crystal structure was obtained and revealed that we had indeed produced the predicted stereochemical configuration at each of the newly formed stereocenters (Figure 17).

Scheme 36. α,α,α′,α″-Tetraalkylated Hydrazone 2.104
Figure 17. X-Ray Crystal Structure of $\alpha,\alpha,\alpha$,\,$\alpha'$-Tetraalkylated Hydrazone 2.104

With this promising result in hand, we wished to further examine the stereoselectivity of the tetraalkylation. In order to evaluate potential issues of match/mismatch of chirality during the alkylation, we needed to examine the $dr$ of the products via HPLC. This required synthesis of all four possible diastereomers for each alkylation sequence. Therefore, isomerized hydrazones 2.100 and 2.101 were isomerized and subsequently subjected to both orders of alkylation using methyl iodide and prenyl bromide, generating all four possible diastereomers (Figure 18).

![Figure 18. Synthesis of Four Diastereomers, 2.105-2.108 of Tetraalkylated Hydrazone](image)

We assumed that the $dr$ of the $\alpha'$-center would not be compromised in this process since we had shown that no epimerization had occurred during the LDA-mediated isomerization (Scheme 35). Therefore, it was only necessary to resolve a
mixture of 2.105 and 2.106, separately from 2.107 and 2.108 on the HPLC, followed by each of the pure compounds, to determine the selectivity at the newly formed stereocenter (see Experimental). Each alkylation sequence proceeded with extremely high levels of diastereoselectivity, ranging from 96:4 to 99:1. We did observe some erosion of selectivity in the cases of 2.105 and 2.107, which we attribute to a mismatch of chirality with the α’-center. It is possible that the reaction conditions could be optimized in order to achieve complete selectivity in all cases, however attempts have not been made to do so at this point.

Finally, the scope of the tetraalkylation was examined. Starting from acetone hydrazone 2.20, a variety of differently substituted hydrazones were generated, all with excellent diastereoselectivity and high yield. These initial examples have demonstrated the potential promise of this tetraalkylation method for the efficient and rapid elaboration of acetone into a highly functionalized compound possessing multiple stereogenic centers.

Scheme 37. α,α,α’,α’-Tetraalkylated Hydrazones Synthesized to Date
2.3.2.3 Hydrolysis

With a variety of \(\alpha,\alpha,\alpha',\alpha'\)-tetraalkylated compounds in hand, we turned our attention to the removal of the auxiliaries to regenerate the ketones. We initially attempted to use our previously developed conditions employing \(p\)-TsOH\(\cdot\)H\(_2\)O in acetone-H\(_2\)O (4:1),\(^{63}\) however this resulted in no hydrolysis. We then examined several alterations to those conditions, such as solvents and temperatures, but with no success (Table 20).

**Table 20. Attempted Hydrolysis of \(\alpha,\alpha,\alpha',\alpha'\)-Tetraalkylated Hydrazones**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Hydrazone</th>
<th>Time (h)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 equiv. (p)-TsOH, acetone-MeOH (4:1)</td>
<td>2.106</td>
<td>24</td>
<td>$&lt;5$</td>
</tr>
<tr>
<td>2</td>
<td>2 equiv. (p)-TsOH, acetone-MeOH-H(_2)O (4:1:1)</td>
<td>2.105</td>
<td>24</td>
<td>$&lt;5$</td>
</tr>
<tr>
<td>3</td>
<td>2 equiv. (p)-TsOH, acetone-H(_2)O (4:1), 35 °C</td>
<td>2.108</td>
<td>24</td>
<td>$&lt;5$</td>
</tr>
<tr>
<td>4</td>
<td>2 equiv. (p)-TsOH, acetone-H(_2)O (4:1), reflux</td>
<td>2.107</td>
<td>24</td>
<td>$&lt;5$</td>
</tr>
<tr>
<td>5</td>
<td>2 equiv. (p)-TsOH, acetone, H(_2)O(_2) in H(_2)O</td>
<td>2.108</td>
<td>24</td>
<td>$&lt;5$</td>
</tr>
</tbody>
</table>

In order to avoid wasting any more of the valuable tetraalkylated compounds, a model system was synthesized for further screening (Scheme 38). Dibenzylketone 2.112 was synthesized via bisalkylation of \(\beta\)-ketoester 2.111, followed by decarboxylation. Acid catalyzed condensation with ACC 1.72 gave the desired hydrazone (2.113), which was then subjected to both orders of alkylation with methyl iodide and prenyl bromide to give 2.114 and 2.115.
Scheme 38. Synthesis of Model System for Tetraalkylated Hydrazone Hydrolysis

After establishing the dr of each hydrazone was >99:1 (see Experimental), we screened a range of hydrolysis conditions using 2.115 (Table 21), however none were successful in producing considerable amounts of the desired ketone (Note: 2.114 was also hydrolyzed using the conditions in Entry 1 in order to generate a racemate).

Table 21. Screen of Hydrolysis Conditions for Tetraalkylated Hydrazone 2.115

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time (h)</th>
<th>α/β&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 equiv. p-TsOH, acetone</td>
<td>40</td>
<td>n.d.</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>2 equiv. p-TsOH, acetone-H&lt;sub&gt;2&lt;/sub&gt;O (4:1)</td>
<td>40</td>
<td>n.d.</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>2 equiv. p-TsOH, acetone, H&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
<td>40</td>
<td>n.d.</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>Oxalic Acid, Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>40</td>
<td>n.d.</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>O&lt;sub&gt;3&lt;/sub&gt;, Sudan Red; Me&lt;sub&gt;2&lt;/sub&gt;S</td>
<td>40</td>
<td>n.d.</td>
<td>&lt;5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>NH&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;PO&lt;sub&gt;4&lt;/sub&gt;, THF</td>
<td>40</td>
<td>n.d.</td>
<td>&lt;5</td>
</tr>
<tr>
<td>7</td>
<td>Ethanedithiol, BF&lt;sub&gt;3&lt;/sub&gt;·H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>40</td>
<td>n.d.</td>
<td>&lt;5</td>
</tr>
<tr>
<td>8</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;OH·HCl, THF·H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>40</td>
<td>n.d.</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

<sup>a</sup>n.d. = not determined  <sup>b</sup>Resulted only in oxidation of alkene
At this stage we believed that the model system was perhaps too hydrophobic due to the two phenyl rings, and as such was not a good representation of our tetraalkylated systems. Therefore, a new model system ketone, possessing two ethyl groups (2.117), was synthesized in an analogous manner to that of 2.112, and bisalkylated with methyl iodide and benzyl bromide using both order of alkylation to give 2.119 and 2.120 (Scheme 39).

Scheme 39. Synthesis of Less Sterically Hindered Model System for Tetraalkylated Hydrazone Hydrolysis

To date, we have only attempted the hydrolysis of 2.119 using p-TsOH in acetone-H₂O (4:1) (Table 22), which resulted in only 10% hydrolysis to the ketone. This result makes 2.119 seem like a promising model system, unlike 1.118 and 2.115, which were either possessed to little or too much steric bulk respectively, and we hope that it will prove to be an accurate model of our tetraalkylated hydrazones.
Table 22. Screen of Hydrolysis Conditions for Tetraalkylated Hydrazone 2.119

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time</th>
<th>β:α</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-TsOH+H₂O, acetone-H₂O (4:1)</td>
<td>14 h</td>
<td>n.d.</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>p-TsOH+H₂O, acetone</td>
<td>14 h</td>
<td>n.d.</td>
<td>25</td>
</tr>
</tbody>
</table>

*n.d.= not determined

2.4 Conclusion

In conclusion, the first method for the regioselective asymmetric α,α- bisalkylation of ketones using ACC chiral auxiliaries has been developed. The regioselective bisalkylation is enabled through a directed deprotonation event, which we have termed Complex Induced Syn-Deprotonation. The method produces the α,α- bisalkylated ketones in excellent yield and with complete regio- and stereoselectivity. In addition, this method has been extended to the α,α,α′,α′-tetraalkylation of ketones. A key step in this process was the development of a novel, epimerization-free, LDA-mediated isomerization of the α,α-bisalkylated ACC hydrazones. A second bisalkylation sequence gives the tetraalkylated hydrazones in high yield and excellent diastereoselectivity. Current work is focusing on the hydrolysis of the tetraalkylated hydrazone products to liberate the ketones without any epimerization at either of the newly formed stereogenic centers.
2.5 Experimental Section

General Considerations. Unless stated to the contrary, where applicable, the following conditions apply: Reactions were carried out using dried solvents (see below) and under a slight static pressure of Ar (pre-purified quality) that had been passed through a column (5 x 20 cm) of Drierite. Glassware was dried in an oven at 120 °C for at least 12 h prior to use and then either cooled in a desiccator cabinet over Drierite or assembled quickly while hot, sealed with rubber septa, and allowed to cool under a stream of Ar. Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 120 °C for at least 12 h prior to use then cooled in a desiccator cabinet over Drierite. Hamilton microsyringes were dried in an oven at 60 °C for at least 24 h prior to use and cooled in the same manner. Commercially available Norm-Ject disposable syringes were used. Dry benzene, toluene, Et₂O, CH₂Cl₂, THF, MeCN, and DME were obtained using an Innovative Technologies solvent purification system. All other dry solvents were of anhydrous quality purchased from Aldrich. Commercial grade solvents were used for routine purposes without further purification. Et₃N, pyridine, i-Pr₂NEt, 2,6-lutidine, i-Pr₂NH, and TMEDA were distilled from CaH₂ under a N₂ atmosphere prior to use. Flash column chromatography was performed on silica gel 60 (230–400 mesh). ¹H and ¹³C NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer or Varian INOVA 500 MHz spectrophotometer at ambient temperature. All ¹H chemical
shifts are reported in ppm (δ) relative to TMS; \(^{13}\)C shifts are reported in ppm (δ) relative to CDCl\(_3\) (77.16). MS data were obtained using an Agilent 1100 Series liquid chromatography-electrospray ionization mass spectrometer. Chiral HPLC was performed on a 4.6 x 250 mm Chiralcel OD-H column (Chiral Technologies) or a 4.6 mm x 250 mm Chiralpak AD-H column, using UV detection.

2.5.1 Regioselective Asymmetric α,α-Bisalkylation

2.5.1.1 Monoalkylation

*The following procedure is a representative of the preparation of hydrazones 2.20, 2.26-2.28:*

Hydrazone 2.20. Aqueous NH\(_4\)OH (15 M, 12.12 mL, 0.182 mol) was added dropwise (ca. 10 min) to a stirred and cooled (−5 °C) suspension of NH\(_4\)Cl (8.22 g, 0.154 mol) in Et\(_2\)O (300 mL). Bleach (216 mL, 6.0% NaOCl) was then added dropwise (ca. 10 min) and the mixture was stirred for an additional 15 min. The organic layer was dried over CaCl\(_2\) for 1 h at −20 °C. The solution was filtered immediately prior to use to yield an ethereal solution of NH\(_2\)Cl (approx. 0.15 M).

KOT-Bu (2.48 g, 22.1 mmol) was added to a solution of 1.98 (2.0 g, 11.0 mmol) in THF (75 mL) (Ar atmosphere), and the resulting suspension was stirred for 3 h. A vigorous nitrogen sparge was then initiated and the previously prepared ethereal solution of NH\(_2\)Cl (110 mL, 16.5 mmol) was added dropwise (ca. 15 min). The mixture
was stirred for 1.5 h, with periodic addition of Et₂O to account for solvent loss due to evaporation. The mixture was then quenched with 1 M aqueous Na₂SO₃ (50 mL). The aqueous phase was extracted with Et₂O (twice), and the combined organic layers were dried (MgSO₄), filtered, and concentrated under reduced pressure to yield a yellow oil (1.98 g) (~ 9:1 1.72-1.98). The crude material (1.98 g, 9.78 mmol) was dissolved in acetone (30 mL) and p-TsOH·H₂O (~ 25 mg) was added. The mixture was stirred for 12 h then partitioned between saturated aqueous NaHCO₃ and Et₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic layers were dried (MgSO₄), filtered, and concentrated under reduced pressure to give a pure, white solid (2.17 g, 94%). Spectroscopic data was identical to that previously reported.³²

Hydrazone 2.26. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave 2.26 (520 mg, 87%) as a pure, pale yellow solid. ¹H NMR (CDCl₃, 400 MHz): δ 7.33-7.23 (m, 3 H), 7.16-7.14 (m, 2 H), 4.36-4.29 (m, 1 H), 4.27-4.23 (m, 1 H), 4.06-4.02 (m, 1 H), 3.14 (A of AB₂, J = 4.0, 16.0 Hz, 1 H), 2.74 (B of AB₂, J = 8.0, 12.0 Hz, 1 H), 2.12 (s, 3 H), 2.02 (s, 3 H); ¹³C NMR (CDCl₃, 100 MHz): δ173.9, 154.8, 135.6, 129.2, 128.8, 127.1, 66.6, 60.7, 38.4, 25.3, 20.8; ESI/MS m/z calcd for C₁₅H₁₅N₂O₂ (M + H): 232.1, found: 232.1.
Hydrazone 2.27. Flash chromatography over silica gel using 30:70 EtOAc-hexanes gave 2.27 (415 mg, 86%) as a pure, white solid. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.44-7.41 (m, 2 H), 7.37-7.28 (m, 7 H), 7.20-7.15 (m, 5 H), 6.87-6.84 (m, 2 H), 5.00 (apparent t, $J = 6.4$ Hz), 2.82 (d, 2 H), 1.91 (s, 3 H), 1.89 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 174.1, 153.3, 142.4, 139.4, 137.3, 129.3, 128.6, 128.4, 128.2, 128.2, 127.2, 126.5, 126.2, 87.0, 68.6, 36.9, 25.1, 20.8; ESI/MS m/z calcd for C$_{25}$H$_{24}$N$_{2}$O$_2$ (M + H): 385.15, found: 385.2.

Hydrazone 2.28. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave 2.28 (614 mg, 89%) as a pure, white solid. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.45-7.43 (d, $J = 8.0$ Hz, 1 H), 7.35-7.22 (m, 3 H), 5.39 (dt, $J = 4.0$, 8.0 Hz, 1 H), 5.33-5.10 (m, 1 H), 3.49 (A of AB$_2$; $J = 7.0$, 17.8 Hz, 1 H), 3.34 (B of AB$_2$; $J = 3.0$, 17.8 Hz, 1 H), 2.15 (s, 3 H), 1.85 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 175.0, 153.4, 140.5, 138.7, 129.7, 127.6, 126.1, 125.5, 67.1, 39.2, 25.4, 20.7; ESI/MS m/z calcd for C$_{13}$H$_{14}$N$_{2}$O$_2$ (M + H): 231.1, found: 231.1.
Preparation of mixture of 2.21 and 2.22 via acid catalyzed condensation of 5-hexen-2-one and 1.72.

5-hexen-2-one (1.12 mL, 1.00 mmol) was added to a solution of crude 1.72 (see above) (454 mg, 0.500 mmol) in CH₂Cl₂ (10 mL) followed by catalytic p-toluenesulfonic acid (ca. 2 mg) (Ar atmosphere). The mixture was heated to reflux and stirred for 12 h then allowed to cool to rt before being partitioned between saturated aqueous NaHCO₃ and CH₂Cl₂. The aqueous phase was extracted with CH₂Cl₂ (twice) and the combined organic layers were dried (MgSO₄), filtered, and concentrated under reduced pressure to give a pale yellow oil. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave 2.21 and 2.22 as 15:85 E:Z mixture. ¹H NMR (CDCl₃, 400 MHz): δ 5.91-5.72 (m, 1H), 5.08-4.97 (m, 2 H), 4.26-4.24 (m, 1 H), 2.60-2.22 (m, 5 H), 2.071 and 1.939 (two s, 15:85 ratio, 3 H), 1.87-1.83 (m, 1 H), 1.31-1.23 (m, containing an apparent s at δ 1.23, 5 H), 1.16-1.11 (m, containing an apparent s at δ 1.14, 4 H); ¹³C NMR (CDCl₃, 100 MHz): δ 176.6, 174.1, 154.8, 137.8, 137.2, 115.4, 115.1, 83.1, 83.0, 73.2, 48.0, 43.0, 38.2, 35.5, 35.4, 31.8, 30.0, 29.8, 26.8, 25.8, 24.8, 22.9, 21.4, 21.4, 19.3, 19.3; ESI/MS m/z calcd for C₁₆H₂₄N₂O₂ (M + H): 277.2, found: 277.2.
**Procedure A:** Representative of the preparation of hydrazones 2.29-2.32, 2.34, 2.35, 2.36, and 2.40, which utilized alkyl iodides as the alkylation agents.

Hydrazone 2.29. n-BuLi (2.5 M in hexanes, 0.488 mL, 1.22 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 ºC) solution of i-Pr₂NH (0.188 mL, 1.34 mmol) in THF (5.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 ºC. A portion of this solution (1.04 mL, 0.254 mmol) was transferred via syringe to a pre-cooled (−78 ºC) flask (Ar atmosphere). A solution of 2.20 (50.0 mg, 0.212 mmol) in THF (0.8 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was stirred for 45 min. MeI (0.132 mL, 2.12 mmol) was then added and the mixture transferred to an ice-H₂O bath and stirred for 1.5 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice), and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.29 (53.9 mg, 92%) as a pure, colorless oil. HPLC analysis against a mixture of E:Z diastereomers prepared by acid
catalyzed dehydration of 1.72 and methyl ethyl ketone showed \( \alpha:\alpha' > 99:1 \). \(^1H\) NMR (CDCl\(_3\), 400 MHz): \( \delta \) 4.26-4.23 (dd, \( J = 4.0, 8.0 \) Hz, 1 H), 2.44-2.27 (m, 3 H), 2.07 (s, 3 H), 2.04-1.75 (m, 4 H), 1.31-1.12 (m, 7 H, containing a s at \( \delta 1.22 \) (3 H) and a s at \( \delta 1.15 \) (3 H)), 1.11-1.07 (apparent t, \( J = 8.0 \) Hz, 3 H); \(^{13}C\) NMR (CDCl\(_3\), 100 MHz): \( \delta \) 178.8, 155.4, 83.0, 73.2, 48.1, 43.0, 35.5, 26.7, 26.0, 25.8, 22.4, 21.4, 19.2, 10.7; ESI/MS m/z calcd for C\(_{14}\)H\(_{22}\)N\(_2\)O\(_2\) (M + H): 251.2, found: 251.2.

\( a \) HPLC trace of \( E:Z \) mixture of 2.29  

\( b \) HPLC trace of crude 2.29

Hydrazone 2.30. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et\(_3\)N and 5:95 EtOAc-hexanes) using 10:90 EtOAc-hexanes gave 2.30 (26.7 mg, 84%) as a 92:8 mixture of \( Z:E \) diastereomers. HPLC analysis against a mixture of \( E:Z \)
diastereomers prepared by acid catalyzed dehydration of 1.73 and methyl ethyl ketone showed $\alpha:\alpha' = 92:8$. H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.33-7.23 (m, 3 H), 7.16-7.14 (m, 2 H), 4.35-4.20 (m, 3 H), 4.04 (apparent t, $J = 8.0$ Hz, 1 H), 3.14 (dd, $J = 4.0$, 12.0 Hz, 1 H), 2.72 (dd, $J = 8.0$, 16.0 Hz, 1 H), 2.50-2.36 (m, 2 H), 2.11 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 177.6, 155.3, 82.9, 73.1, 47.9, 42.9, 35.4, 34.6, 26.6, 25.7, 21.4, 19.5, 19.2, 14.1; ESI/MS m/z calcd for C$_{16}$H$_{18}$N$_2$O$_2$ (M + H): 247.1, found: 247.2.

**Hydrazone 2.31.** Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et$_3$N and 5:95 EtOAc-hexanes) using 20:80 EtOAc-hexanes gave 2.31 (13.5 mg, 81%) as a 98:2 mixture of Z:E diastereomers. HPLC analysis against a mixture of $E:Z$
diastereomers prepared by acid catalyzed dehydration of 1.74 and methyl ethyl ketone showed $\alpha:\alpha' = 98:2$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.45-7.28 (m, 9 H), 7.20-7.14 (m, 4 H), 6.88-6.86 (m, 2 H), 4.99 (t, $J = 8.0$ Hz, 1 H), 2.86-2.74 (m, 2 H), 2.31 (q, $J = 8.0$ Hz, 2 H), 1.88 (s, 3 H), 1.02 (t, $J = 8.0$ Hz, 3 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 174.1, 153.3, 142.4, 139.4, 137.3, 129.3, 128.6, 128.4, 128.2, 127.2, 126.5, 126.2, 87.0, 68.6, 36.9, 25.1, 20.8; ESI/MS m/z calcd for C$_{26}$H$_{26}$N$_2$O$_2$ (M + H): 399.15, found: 399.1.

a) HPLC trace of E:Z mixture of 2.31

b) HPLC trace of crude 2.31

Hydrazone 2.32. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et$_3$N and 5:95 EtOAc-hexanes) using 10:90 EtOAc-hexanes gave 2.32 (25.1 mg, 79%) as a 91:9 mixture of Z:E diastereomers. HPLC analysis against a mixture of E:Z diastereomers prepared by acid catalyzed dehydration of 1.75 and methyl ethyl ketone
showed $\alpha:\alpha' = 92.8$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.41-7.21 (m, 4 H), 5.42-5.37 (m, 1 H), 5.33-5.29 (m, 1 H), 3.53-3.31 (m, 2 H), 2.25-2.18 (m, 2 H), 2.13 (s, 3 H), 0.91 (t, 3 H, $J = 8.0$ Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 174.1, 153.3, 142.4, 139.4, 137.3, 129.3, 128.6, 128.4, 128.2, 128.2, 127.2, 126.5, 126.2, 87.0, 68.6, 36.9, 25.1, 20.8; ESI/MS m/z calcd for C$_{14}$H$_{16}$N$_2$O$_2$ (M + H): 245.15, found: 245.2.

*a) HPLC trace of E:Z mixture of 2.32*  
*b) HPLC trace of crude 2.32*

Hydrazone 2.34. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et$_3$N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.34 (52.6 mg, 94%) as a pure, white solid. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 4.22 (dd, 1H, $J = 4.0$, 8.0 Hz), 2.43-2.35 (m, 1H), 2.29-2.15 (m, 2H), 2.03 (s, 3H), 1.98-1.89 (m, 3H), 1.81 (dd, $J = 8.0$, 12.0 Hz), 1.74-1.72 (m, 1H), 1.65-1.40 (m, 2H), 1.28-1.22 (m, 2H), 1.19 (s, 3H), 1.11 (s, 3H), 0.91 (t, 3H, $J = 8.0$ Hz).
0.87 (t, 3 H, J = 8.0 Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 177.6, 155.3, 82.9, 73.1, 47.9, 42.9, 35.4, 34.6, 26.6, 25.7, 22.7, 21.4, 19.5, 19.2, 14.1; \textbf{ESI/MS} m/z calcd for C\(_{15}\)H\(_{24}\)N\(_2\)O\(_2\) (M + H): 265.2, found: 265.1.

\begin{equation*}
\begin{array}{c}
\text{Hydrazone 2.35. Flash chromatography over silica gel (pre-treated with 1\% (v/v) solution of Et\(_3\)N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes yielded 2.35 (56.1 mg, 87\%) as a pure, white solid. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 4.25 (dd, \(J = 4.0, 8.0\) Hz, 1 H), 2.50-2.43 (m, 1 H), 2.33-2.18 (m, 2 H), 2.07 (s, 3 H), 2.04-1.93 (m, 3 H), 1.84 (dd, \(J = 8.0, 16.0\) Hz, 1 H), 1.77-1.75 (m, 1 H), 1.61-1.37 (m, 3 H), 1.33-1.25 (m, 4 H), 1.22 (s, 3 H), 1.15 (s, 3 H), 0.90 (t, \(J = 8.0\) Hz, 3 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 177.8, 155.3, 83.0, 73.1, 48.0, 42.9, 35.4, 33.4, 28.2, 26.6, 25.7, 22.8, 22.6, 21.4, 19.2, 13.9; \textbf{ESI/MS} m/z calcd for C\(_{16}\)H\(_{25}\)N\(_2\)O\(_2\) (M + H): 279.2, found: 279.2.
\end{array}
\end{equation*}
solution of Et₃N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.40 (57.3 mg, 85%) as a pure, colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 5.10-5.07 (m, 1 H), 4.24 (dd, J = 4.0, 8.0 Hz, 1 H), 2.49-2.41 (m, 1 H), 2.32-2.18 (m, 2 H), 2.07 (s, 3 H), 2.04-1.92 (m, 4 H), 1.84 (dd, J = 8.0, 12.0 Hz, 1 H), 1.77-1.75 (m, 1 H), 1.69 (s, 3 H), 1.66-1.62 (m, 1 H), 1.59 (s, 3 H), 1.51-1.41 (m, 1 H), 1.30-1.23 (m, 1 H), 1.22 (s, 3 H), 1.15 (s, 3 H); ¹³C NMR (CDCl₃, 100 MHz): δ 177.9, 155.4, 132.5, 123.8, 83.1, 73.2, 48.0, 42.9, 35.5, 32.5, 28.0, 26.7, 26.5, 25.8, 22.9, 21.4, 19.2, 17.9; ESI/MS m/z calcd for C₁₉H₃₀N₂O₂ (M + H): 319.2, found: 319.2.

Hydrazone 2.36. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 20:80 EtOAc-hexanes) using 20:80 EtOAc-hexanes gave 2.36 (25.1 mg, 95%) as a pure, white solid. ¹H NMR (CDCl₃, 400 MHz): δ 4.25 (dd, J = 2.8 Hz, 6.0 Hz, 1 H), 3.58-3.50 (m, 2 H), 2.50-2.44 (m, 1 H), 3.32-2.23 (m, 2 H), 2.08 (s, 3 H), 2.04-1.92 (m, 3 H), 1.87-1.70 (m, 4 H), 1.31-1.13 (m, 8 H, containing a s at δ 1.23 (3 H), and a s at δ 1.14 (3 H)); ¹³C NMR (CDCl₃ 100 MHz): δ 176.4, 155.3, 83.1, 73.2, 48.1, 44.6, 43.0, 35.4, 32.3, 31.9, 26.7, 25.8, 23.3, 22.8, 21.4, 19.2; ESI/MS m/z calcd for C₁₆H₂₈ClN₂O₂ (M + H): 313.1, found: 313.2.
Procedure B: Representative of the preparation of alkyl hydrazones 2.21, 2.33, 2.38, 2.39, and 2.37, which utilized alkyl bromides as the alkylation agents.

Hydrazone 2.21. n-BuLi (2.5 M in hexanes, 0.488 mL, 1.22 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NEt (0.188 mL, 1.34 mmol) in THF (5.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (1.04 mL, 0.254 mmol) was transferred via syringe to a pre-cooled (−78 °C) flask (Ar atmosphere). A solution of 2.20 (50.0 mg, 0.212 mmol) in THF (0.8 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was stirred for 45 min. Allyl bromide (22.1 µL, 0.254 mmol) was then added and the mixture transferred to an ice-H₂O bath and stirred for 1.5 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.21 (53.9 mg, 92%) as a pure, colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 5.88-5.70 (m, 1 H), 5.12-4.94 (m, 2 H),
4.25 (dd, J = 4.0, 8.0 Hz, 1 H), 2.74-2.12 (m, 5 H), 2.08 (s, 3 H), 2.06-1.70 (m, 4 H), 1.36-1.10 (m, 8 H, containing a s at δ 1.22 (3 H) and a s at δ 1.15 (3 H)), 0.89 (t, J = 7.4 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 176.6, 155.3, 137.2, 115.5, 83.1, 73.2, 48.1, 43.0, 35.5, 31.8, 29.9, 26.8, 25.8, 22.9, 21.5, 19.3; ESI/MS m/z calcd for C$_{16}$H$_{25}$N$_2$O$_2$ (M + H): 277.4, found: 277.4.

**Hydrazone 2.33.** Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et$_3$N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.33 (62.9 mg, 91%) as a pure, colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.29-7.25 (m, 2 H), 7.20-7.16 (m, 3 H), 4.22 (dd, J = 4.0, 8.0 Hz, 1 H), 2.98-2.0 (m, 1 H), 2.83-2.74 (m, 2 H), 2.61-2.53 (m, 2 H), 2.31-2.25 (m, 1 H), 2.07 (s, 3 H), 1.83 (dd, J = 8.0, 12.0 Hz, 1 H), 1.75 (m, 1 H), 1.32-1.24 (m, 2 H), 1.22 (s, 3 H), 1.14 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 176.1, 155.3, 140.8, 128.6, 128.3, 126.3, 83.0, 73.1, 48.1, 42.9, 35.4, 34.1, 32.0, 26.7, 25.7, 23.0, 21.4, 19.2; ESI/MS m/z calcd for C$_{20}$H$_{26}$N$_2$O$_2$ (M + H): 327.2, found: 327.2.
**Hydrazone 2.38.** Flash chromatography over silica gel pretreated (pre-treated with 1% (v/v) solution of Et₃N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.38 (82.2 mg, 96%) as a pure, white solid. **¹H NMR** (CDCl₃, 400 MHz): δ 7.39 (d, J = 8.0 Hz, 2 H), 7.05 (d, J = 8.0, 2 H), 4.23 (dd, J = 4.0, 8.0 Hz, 1 H), 2.96-2.82 (m, 1 H), 2.79-2.64 (m, 2 H), 2.62-2.52 (m, 1 H), 2.33-2.80 (m, 1 H), 2.06 (s, 3 H), 1.95-1.90 (m, 2 H), 1.85 (dd, J = 8.0, 12.0 Hz, 1 H), 1.77-1.74 (m, 1 H), 1.30-1.05 (m, 9 H, containing a s at δ 1.22 (3 H) and a s at δ 1.13 (3 H)); **¹³C NMR** (CDCl₃, 100 MHz): δ 175.3, 155.3, 139.8, 131.6, 130.0, 120.0, 83.1, 73.1, 48.0, 42.9, 35.4, 33.9, 31.4, 26.7, 25.7, 23.0, 21.4, 19.2; **ESI/MS** m/z calcd for C₂₀H₂₅BrN₂O₂ (M + H): 405.1, found: 405.1.

![Reaction scheme](image)

Hydrazone 2.39. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.39 (56.1 mg, 87%) as a pure, white solid. **¹H NMR** (CDCl₃, 400 MHz): δ 5.04-5.01 (m, 1 H), 4.24 (dd, J = 4.0, 8.0 Hz, 1 H), 2.52-2.44 (m, 1 H), 2.31-2.12 (m, 5 H), 2.07 (s, 3 H), 2.02-1.93 (m, 2 H), 1.84 (dd, J = 8.0, 16 Hz, 1 H), 1.77-1.75 (m, 1 H), 1.68 (s, 3 H), 1.61 (s, 3 H), 1.32-1.10 (m, 10 H, containing a s at δ 1.23 (3 H) and a s at δ 1.14 (3 H)); **¹³C NMR** (CDCl₃, 100 MHz): δ 177.3, 155.3, 132.8, 122.9, 83.0, 73.1, 47.9, 43.9, 35.4, 32.7, 26.7, 25.8, 25.7, 24.7, 22.9, 21.4,
19.2, 17.7; **ESI/MS** m/z calcd for C_{18}H_{28}N_{2}O_{2} (M + H): 305.2, found: 305.2.

**Hydrazone 2.37.** Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 15:85 EtOAc-hexanes) using 15:85 EtOAc-hexanes gave **2.37** (52.8 mg, 81%) as a pure, colorless oil. **¹H NMR** (CDCl₃, 400 MHz): δ 4.26 (dd, J = 4.0 Hz, 8.0 Hz, 1 H), 3.68 (s, 3 H), 2.73-2.50 (m, 4 H), 2.33-2.27 (m, 1 H), 2.07 (s, 3 H), 2.05-1.90 (m, 2 H), 1.851 (dd, J = 8.0 Hz, 13.6, 1 H), 1.32-1.11 (m, 6 H, containing a s at δ 1.23 (3 H) and a s at δ 1.13 (3 H)); **¹³C NMR** (CDCl₃, 100 MHz): δ 174.7, 173.0, 155.3, 83.2, 73.2, 51.9, 48.1, 43.0, 35.4, 30.4, 28.1, 26.7, 25.8, 22.8, 21.4, 19.2; **ESI/MS** m/z calcd for C_{16}H_{24}N_{2}O_{4} (M + H): 309.2, found: 309.2.

*Scale up experiment for the monoalkylation of hydrazone 2.20.*

**Hydrazone 2.37.** *n*-BuLi (2.5 M in hexanes, 10.18 mL, 25.4 mmol) was added
dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of \( i-\text{Pr}_2\text{NH} \) (3.86 mL, 27.5 mmol) in THF (50.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H\(_2\)O bath, stirred for 30 min, and then cooled to −78 °C. A solution of 2.20 (5.00 g, 21.2 mmol) in THF (45 mL) was added by syringe, with additional THF (2 x 2.5 mL) as a rinse, and the mixture was stirred for 45 min. Allyl bromide (2.21 mL, 25.4 mmol) was then added and the mixture transferred to an ice-H\(_2\)O bath and stirred for 1.5 h. The mixture was then partitioned between Et\(_2\)O and H\(_2\)O. The aqueous phase was extracted with Et\(_2\)O (twice) and the combined organic extracts were dried (MgSO\(_4\)), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (pretreated with 1% (v/v) solution of Et\(_3\)N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.37 (5.28 mg, 90%) as a pure, colorless oil. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 5.88-5.70 (m, 1 H), 5.12-4.94 (m, 2 H), 4.25 (dd, \( J = 4.0, 8.0 \) Hz, 1 H), 2.74-2.12 (m, 5 H), 2.08 (s, 3 H), 2.06-1.70 (m, 4 H), 1.36-1.10 (m, 8 H, containing a s at \( \delta \) 1.22 (3 H) and a s at \( \delta \) 1.15 (3 H)), 0.89 (t, \( J = 7.4 \) Hz); \(^13\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 176.6, 155.3, 137.2, 115.5, 83.1, 73.2, 48.1, 43.0, 35.5, 31.8, 29.9, 26.8, 25.8, 22.9, 21.5, 19.3; ESI/MS m/z calcd for C\(_{16}\)H\(_{25}\)N\(_2\)O\(_2\) (M + H): 277.4, found: 277.4.

2.5.1.2 \( \alpha,\alpha \)-Bisalkylation

\textit{Procedure C:} Representative of the alkylation of the monoalkylated hydrazones obtained above, where an alkyl bromide was used as the alkylating agent. Applicable to the preparation of 2.44,
2.23, 2.45, 2.42, 2.47, and 2.48.

Hydrazone 2.44. *n*-BuLi (2.5 M in hexanes, 0.488 mL, 1.22 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (–78 °C) solution of *i*-PrNH (0.188 mL, 1.34 mmol) in THF (5.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to –78 °C. A portion of this solution (1.14 mL, 0.278 mmol) was then transferred via syringe to a pre-cooled (–78 °C) flask (Ar atmosphere). A solution of 2.29 (58.0 mg, 0.232 mmol) in THF (1.0 mL) was added by syringe, with additional THF (2 x 0.25 mL) as a rinse, and the mixture was stirred for 45 min. Benzyl bromide (33.1 µL, 0.278 mmol) was then added and the mixture stirred at –78 °C for 24 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil.

Procedure D: Representative of the alkylation of the monoalkylated hydrazones obtained above, where an alkyl iodide was used as the alkylating agent. Applicable to the preparation of 2.41, 2.46, 2.72, and 2.86.
Hydrazone 2.41. n-BuLi (2.5 M in hexanes, 0.488 mL, 1.22 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (0.188 mL, 1.34 mmol) in THF (5.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (0.953 mL, 0.233 mmol) was then transferred via syringe to a pre-cooled (−78 °C) flask (Ar atmosphere). A solution of 2.33 (63.2 mg, 0.194 mmol) in THF (0.8 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was stirred for 45 min. MeI (0.119 mL, 1.94 mmol) was then added and the mixture stirred at −78 °C for 24 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil.

• Synthesis and stereochemical analysis of 2.44 and 2.41.
**Hydrazone 2.44.** Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et3N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.44 (78.5 mg, 97%) as a pure, colorless oil. HPLC analysis showed a $dr > 99:1$. $^1$H NMR (CDCl₃, 400 MHz): $\delta$ 7.30-7.17 (m, 5 H), 4.23 (dd, $J = 4.0, 8.0$ Hz, 1 H), 3.21-3.12 (m, 2 H), 2.45-2.39 (m, 1 H), 2.33-2.27 (m, 1 H), 2.07 (s, 3 H), 1.99-1.91 (m, 2 H), 1.84 (dd, $J = 8.0, 13.6, 1$ H), 1.77-1.75 (m, 1 H), 1.29-1.25 (m, 1 H), 1.23 (s, 3 H), 1.18 (s, 3 H), 1.16-1.07 (m, 2 H), 0.89 (d, $J = 6.8, 3$ H); $^{13}$C NMR (CDCl₃, 100 MHz): $\delta$ 181.3, 155.6, 139.9, 129.7, 128.3, 126.2, 83.0, 73.2, 47.9, 43.0, 39.3, 37.6, 35.4, 26.6, 25.7, 21.5, 19.2, 18.9, 16.3; ESI/MS m/z calcd for C₂₁H₂₈N₂O₂ (M + H): 341.2, found: 341.2.

![Reaction Scheme](image)

**Hydrazone 2.41.** Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et3N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.41 (65.6 mg, 91%) as a pure, white solid. HPLC analysis showed a $dr > 99:1$. $^1$H NMR (CDCl₃, 400 MHz): $\delta$ 7.27-7.16 (m, 3 H), 7.09-7.07 (m, 2 H), 4.14 (dd, $J = 4.0, 8.0$ Hz, 1 H), 3.37-3.28 (m, 1 H), 2.70-2.60 (m, 2 H), 2.28-2.21 (m, 1 H), 2.05 (s, 3 H), 1.87-1.76 (m, 2 H), 1.70-1.68 (m, 1 H), 1.53 (dt, $J = 4.0, 12.0$ Hz, 1 H), 1.23 (d, $J = 8.0$ Hz, 3 H), 1.21-1.14 (m, 2 H), 1.13 (s, 3 H), 1.09 (s, 3 H); $^{13}$C NMR (CDCl₃, 100 MHz): $\delta$ 179.5, 155.5, 139.6, 128.8, 128.5, 126.3, 82.9, 47.9, 43.0, 39.3, 37.6, 35.4, 26.6, 25.7, 21.5, 19.2, 18.9, 16.3; ESI/MS m/z calcd for C₂₁H₂₈N₂O₂ (M + H): 341.2, found: 341.2.
73.0, 48.0, 42.9, 40.9, 37.8, 35.4, 26.3, 25.7, 21.4, 19.1, 18.7, 17.4; **ESI/MS** m/z calcd for C_{21}H_{28}N_{2}O_{2} (M + H): 341.2, found: 341.2.

\[ a) \text{ HPLC trace of 2.44 and 2.41 } \]
\[ b) \text{ HPLC trace of 2.44 } \]
\[ b) \text{ HPLC trace of 2.41 } \]

- **Synthesis and stereochemical analysis of 2.42 and 2.46.**

\[ \text{Hydrazone 2.42.} \]

Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes yielded **2.42** (80.9 mg, 94%) as a pure white solid. HPLC analysis showed a \( dr > 99:1 \). ¹H NMR (CDCl₃, 400 MHz): \( \delta \) 5.87-5.76 (m, 1 H), 5.08-4.98 (m, 2 H), 4.25-4.22 (dd, \( j = 4.0, 8.0 \) Hz, 1 H), 2.90-2.82 (m, 1 H), 2.53-2.47 (m, 1 H), 2.33-2.26 (m, 1 H), 2.14-1.83 (m, 6 H, containing a s at \( \delta \) 1.96 (3 H)), 1.76-1.74 (m, 1 H), 1.60-1.55 (m, 1 H), 1.30-1.09 (m, 8 H, containing a s at \( \delta \) 1.24 (3 H) and a s at \( \delta \) 1.15 (3 H)), 0.76 (t, \( j = 8.0 \) Hz, 3 H); ¹³C NMR (CDCl₃, 100 MHz): \( \delta \) 179.6,
155.4, 136.9, 116.6, 82.9, 73.2, 48.0, 42.9, 42.3, 36.8, 35.4, 26.9, 25.8, 24.1, 21.5, 19.2, 18.7, 12.0; ESI/MS m/z calcd for C_{18}H_{28}N_{2}O_{2} (M + H): 305.2, found: 305.2.

**Hydrazone 2.46.** Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.46 (79.2 mg, 92%) as a pure, white solid. HPLC analysis showed a 

\[ \text{dr} > 99:1 \].

\[ \text{H NMR (CDCl}_3, 400 \text{ MHz)}: \delta 5.64-5.53 (m, 1 H), 5.09-4.89 (m, 2 H), 4.25-4.22 (dd, \text{ J} = 4.0 \text{ Hz, 8.0 Hz, 1 H}), 2.93-2.86 (m, 1 H), 2.33-2.26 (m, 2 H), 2.04-1.92 (m, 6 H, containing a s at \delta 1.97), 1.86-1.81 (dd, \text{ J} = 4.0, 12.0 \text{ Hz, 1 H}), 1.76-1.67 (m, 2 H), 1.47-1.40 (m, 1 H), 1.30-1.10 (m, 7 H, containing a s at \delta 1.21 (3 H) and a s at \delta 1.15 (3 H), 0.97 (t, \text{ J} = 8.0 \text{ Hz, 3 H})];

\[ \text{C NMR (CDCl}_3, 100 \text{ MHz)}: \delta 180.3, 155.5, 135.9, 116.3, 82.8, 73.2, 47.9, 42.8, 42.4, 36.1, 35.3, 26.8, 25.7, 24.8, 21.4, 19.1, 18.8, 12.3. \]

ESI/MS m/z calcd for C_{18}H_{28}N_{2}O_{2} (M + H): 305.2, found: 305.2.

\[ \text{a) HPLC trace of 2.42 and 2.46} \quad \text{b) HPLC trace of 2.42} \quad \text{b) HPLC trace of 2.46} \]
Synthesis and stereochemical analysis of 2.45 and 2.23.

Hydrazone 2.45. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et$_3$N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.45 (71.9 mg, 91%) as a pure, white solid. HPLC analysis showed a $dr > 99:1$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.37-7.35 (d, $J = 8.4$ Hz, 2 H), 6.96-6.94 (d, $J = 8.4$ Hz, 2 H), 5.91-5.81 (m, 1 H), 5.15-5.09 (m, 2 H), 4.08 (dd, $J = 4.0$ Hz, 8.0 Hz, 1 H), 3.19-3.12 (m, 1 H), 2.83 (dd, $J = 4.8$ Hz, 14.4 Hz, 1 H), 2.66-2.63 (m, 1 H), 2.48 (dd, $J = 10$ Hz, 14.0 Hz, 1 H), 2.25-2.21 (m, 1 H), 2.15-1.98 (m, 4 H, containing a s at $\delta$ 2.03 (3 H)), 1.86-1.75 (m, 3 H), 1.69-1.67 (m, 1 H), 1.48-1.41 (m, 1 H), 1.25-1.01 (m, 9 H, containing a s at $\delta$ 1.12 (3 H) and a s at $\delta$ 1.06 (3 H)); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 176.7, 155.3, 138.8, 136.6, 131.5, 130.6, 130.5, 120.2, 117.4, 82.9, 73.1, 48.1, 42.9, 42.8, 36.9, 36.5, 35.3, 26.2, 25.7, 21.5, 19.3, 19.2; ESI/MS m/z calcd for C$_{23}$H$_{28}$BrN$_2$O$_2$ (M + H): 445.2, found: 445.2.
Hydrazone 2.23. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes yielded 2.23 (72.7 mg, 92%) as a pure, white solid. HPLC analysis showed a $d_r > 99:1$. $^1$H NMR (CDCl₃, 400 MHz): δ 7.39 (d, $J = 8.0$ Hz, 2 H), 7.15 (d, $J = 8.0$ Hz, 2 H), 5.43-5.34 (m, 1 H), 4.95-4.87 (m, 2 H), 4.24 (dd, $J = 4.0$, 8.0 Hz, 1 H), 3.21-3.12 (m, 1 H), 3.13-3.03 (m, 1 H), 2.46-2.40 (m, 1 H), 2.34-2.29 (m, 1 H), 2.15-2.07 (m, 1 H), 2.03-1.91 (m, 6 H, containing a s at δ 2.03 (3 H)), 1.85 (dd, $J = 8.0$ Hz, 13.6 Hz, 1 H), 1.78-1.76 (m, 1 H), 1.31-1.07 (m, 9 H, containing a s at δ 1.25 (3 H) and a s at δ 1.15 (3 H)); $^{13}$C NMR (CDCl₃, 100 MHz): δ 177.3, 155.4, 138.8, 135.5, 131.6, 120.2, 116.7, 83.1, 73.2, 48.1, 43.3, 43.0, 37.7, 35.4, 35.0, 26.9, 25.8, 21.5, 19.2, 18.9; ESI/MS m/z calcd for C₂₃H₂₄BrN₂O₂ (M + H): 445.2, found 445.1.

a) HPLC trace of 2.23 and 2.45  
b) HPLC trace of 2.23  
c) HPLC trace of 2.45
• Synthesis and stereochemical analysis of 2.47 and 2.48

Hydrazone 2.47. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et$_3$N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.47 (36.9 mg, 92%) as a pure, white solid. HPLC analysis showed a $dr > 99:1$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.36-7.34 (d, $J = 8.0$ Hz, 2 H), 6.96-6.94 (d, $J = 8.0$ Hz, 2 H), 5.22-5.19 (m, 1 H), 4.09-4.06 (dd, $J = 4.0$, 8.0 Hz, 1 H), 3.15-3.07 (m, 1 H), 2.82-2.77 (dd, $J = 4.0$, 12.0 Hz, 1 H), 2.52-2.42 (m, 2 H, containing apparent dd, $J = 12.0$, 16.0 Hz (3 H)), 2.27-2.11 (m, 3 H), 2.03 (s, 3 H), 1.80-1.62 (m, 8 H, containing a s at $\delta$ 1.72 (3 H) and a s at $\delta$ 1.65 (3 H)), 1.46-1.38 (m, 2 H), 1.20-1.11 (m, 3 H), 1.11 (s, 3 H), 1.07 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 177.5, 155.4, 139.1, 133.8, 131.5, 130.6, 122.2, 120.1, 82.8, 73.1, 48.0, 43.7, 42.9, 37.0, 35.4, 37.0, 35.4, 30.7, 26.2, 26.0, 25.7, 21.5, 19.4, 19.2, 18.2; ESI/MS m/z calcd for C$_{25}$H$_{33}$BrN$_2$O$_2$ (M + H): 473.2, found: 473.2.
**Hydrazone 2.48.** Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes yielded 2.48 (34.9 mg, 87%) as a pure, white solid. HPLC analysis showed a $da > 99:1$. ¹H NMR (CDCl₃, 400 MHz): δ 7.39 (d, $J = 8.0$ Hz, 2 H), 7.15 (d, $J = 8.0$ Hz, 2 H), 4.73-4.70 (m, 1 H), 4.24 (dd, $J = 4.0, 8.0$ Hz, 1 H), 3.18 (dd, $J = 4.0, 12$ Hz, 1 H), 3.04-2.97 (m, 1 H), 2.42 (dd, $J = 12.0$ Hz, 1 H), 2.34-2.28 (m, 1 H), 2.01-1.94 (m, 6 H, containing s at δ 2.01 (3 H)), 1.85 (dd, $J = 8.0, 16.0$ Hz, 1 H), 1.78-1.76 (m, 1 H), 1.59 (s, 3 H), 1.47 (s, 3 H), 1.31-1.10 (m, 8 H, containing s at δ 1.26 (3 H) and a s at δ 1.16 (3 H)); ¹³C NMR (CDCl₃, 100 MHz): δ 178.1, 155.4, 139.1, 133.1, 131.6, 131.4, 121.1, 120.0, 83.1, 73.2, 48.1, 43.6, 43.0, 37.8, 35.4, 29.1, 26.9, 25.8, 21.5, 19.2, 18.9, 17.9; ESI/MS m/z calcd for C₂₅H₃₃BrN₂O₂ (M + H): 473.1, found 473.1.

*a) HPLC trace of 2.47 and 2.48  \  b) HPLC trace of 2.47  \  c) HPLC trace of 2.48*
Scale up experiment for the bisalkylation of hydrazone **2.33**.

![Reaction Scheme]

**Hydrazone 2.41.** $n$-BuLi (2.5 M in hexanes, 5.90 mL, 14.76 mmol) was added dropwise (ca. 2 min) to a stirred and cooled ($-78 \, ^\circ C$) solution of $i$-Pr$_2$NH (2.23 mL, 15.9 mmol) in THF (35.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H$_2$O bath, stirred for 30 min, and then cooled to $-78 \, ^\circ C$. A solution of **2.33** (4.00 g, 12.3 mmol) in THF (35 mL) was added by syringe, with additional THF (2 x 2.5 mL) as a rinse, and the mixture was stirred for 45 min. MeI (3.83 mL, 61.5 mmol) was then added and the mixture stirred at $-78 \, ^\circ C$ for 24 h. The mixture was then partitioned between Et$_2$O and H$_2$O. The aqueous phase was extracted with Et$_2$O (twice) and the combined organic extracts were dried (MgSO$_4$), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et$_3$N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave **2.41** (3.85 g, 92%) as a pure, white solid. HPLC analysis showed a $dr > 99:1$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.27-7.16 (m, 3 H), 7.09-7.07 (m, 2 H), 4.14 (dd, $J = 4.0, 8.0$ Hz, 1 H), 3.37-3.28 (m, 1 H), 2.70-2.60 (m, 2 H), 2.28-2.21 (m, 1 H), 2.05 (s, 3 H), 1.87-1.76 (m, 2 H), 1.70-1.68 (m, 1 H), 1.53 (dt, $J = 4.0, 12.0$ Hz, 1 H), 1.23 (d, $J = 8.0$ Hz, 3 H), 1.21-1.14 (m, 2 H), 1.13 (s, 3 H), 1.09 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 179.5, 155.5, 139.6, 128.8, 128.5, 126.3, 82.9, 73.0, 48.0, 42.9,
40.9, 37.8, 35.4, 26.3, 25.7, 21.4, 19.1, 18.7, 17.4; **ESI/MS** \( m/z \) calcd for \( \text{C}_{21}\text{H}_{28}\text{N}_{2}\text{O}_{2} \) (M + H): 341.2, found: 341.2.

2.5.1.3 Hydrolysis of Bisalkylated Hydrazones

*The following procedure is representative of the preparation of ketones 2.57-2.64 via acid catalyzed hydrolysis of hydrazones 2.23, 2.41-2.42, 2.44-2.48.*

Ketone 2.64. 2.48 (21.5 mg, 0.046 mmol) was dissolved in reagent grade acetone (1.12 mL) and then \( \text{H}_{2}\text{O} \) (0.28 mL) and \( p\)-TsOH·\( \text{H}_{2}\text{O} \) (17.4 mg, 0.091 mmol) were added. The mixture was stirred for 24 h and partitioned between saturated aqueous NaHCO\(_{3}\) and Et\(_{2}\)O. The aqueous phase was extracted with Et\(_{2}\)O (twice) and the combined organic extracts were dried (MgSO\(_{4}\)), filtered and evaporated under reduced pressure to give a yellow oil.

*Synthesis and stereochemical analysis of ketones 2.57 and 2.58.*
Ketone 2.57. Flash chromatography over silica gel 2.5:97.5 EtO-pentanes gave 2.57 (9.4 mg, 98%) as a pure, colorless oil, along with pure recovered 2.20 (6.15 mg, 98%) as a white solid. HPLC analysis showed an er > 99:1. Spectroscopic data was identical to that previously reported.64

Ketone 2.58. Flash chromatography over silica gel 2.5:97.5 EtO-pentanes gave 2.58 (9.4 mg, 98%) as a pure, colorless oil, along with pure recovered 2.20 (6.15 mg, 98%) as a white solid. HPLC analysis showed an er > 99:1. Spectroscopic data was identical to that previously reported.64

a) HPLC trace of 2.57 and 2.58  

b) HPLC trace of 2.57  

c) HPLC trace of 2.58
Synthesis of ketones 2.59 and 2.60.

Ketone 2.59. Flash chromatography over silica gel 2.5:97.5 Et₂O-pentanes gave 2.59 (5.2 mg, 95%) as a pure, colorless oil, along with pure recovered 2.20 (6.15 mg, 98%) as a white solid. Spectroscopic data was identical to that previously reported.⁶⁵

Ketone 2.60. Flash chromatography over silica gel 2.5:97.5 Et₂O-pentanes gave 2.60 (5.3 mg, 96%) as a pure, colorless oil, along with pure recovered 2.20 (6.15 mg, 98%) as a white solid. Spectroscopic data was identical to that previously reported.⁶⁵
Synthesis and stereochemical analysis of ketones 2.62 and 2.61.

**Ketone 2.62.** Flash chromatography over silica gel 2.5:97.5 Et\(_2\)O-pentanes gave 2.62 (11.6 mg, 97%) as a pure, colorless oil, along with pure recovered 2.20 (6.15 mg, 98%) as a white solid. HPLC analysis showed an er > 99:1. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 7.39\) (d, \(J = 6.8\) Hz, 2 H), 7.02 (d, \(J = 6.4\) Hz, 2 H), 5.75-5.67 (m, 1 H), 5.08-5.05 (m, 2H), 2.89-2.83 (m, 2 H), 2.68-2.63 (m, 1 H), 2.38-2.29 (m, 1 H), 2.24-2.20 (m, 1 H), 2.01 (s, 3 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta 206.8, 136.2, 132.9, 130.0, 129.0, 119.1, 116.2, 55.7, 38.3, 37.8, 33.1\); ESI/MS m/z calcld for C\(_{13}\)H\(_{15}\)BrO (M + H): 267.0, found: 267.1.

**Ketone 2.61.** Flash chromatography over silica gel 2.5:97.5 Et\(_2\)O-pentanes gave 2.61 (11.2 mg, 98%) as a pure, colorless oil, along with pure recovered 2.20 (6.15 mg, 98%) as a white solid. HPLC analysis showed an er > 99:1. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 7.39\) (d, \(J = 6.8\) Hz, 2 H), 7.02 (d, \(J = 6.4\) Hz, 2 H), 5.75-5.67 (m, 1 H), 5.08-5.05 (m, 2H),
2.89-2.83 (m, 2 H), 2.68-2.63 (m, 1 H), 2.38-2.29 (m, 1 H), 2.24-2.20 (m, 1 H), 2.01 (s, 3 H).

$^1$C NMR (CDCl$_3$, 125 MHz): $\delta$ 206.8, 136.2, 132.9, 130.0, 129.0, 119.1, 116.2, 55.7, 38.3, 37.8, 33.1; ESI/MS m/z calcd for C$_{13}$H$_{15}$BrO (M + H): 267.0, found: 267.1.

*a) HPLC trace of 2.62 and 2.6  
*b) HPLC trace of 2.62  
*c) HPLC trace of 2.61

Synthesis and stereochemical analysis of ketones 2.63 and 2.64

Ketone 2.63. Flash chromatography over silica gel 2.5:97.5 Et$_2$O-pentanes gave 2.63 (12.1 mg, 98%) as a pure, colorless oil, along with pure recovered 2.20 (6.48 mg, 99%) as a white solid. HPLC analysis showed an $er > 99:1$. 

$^1$H NMR (CDCl$_3$, 400 MHz):

$\delta$ 7.38 (d, $J = 8.4$ Hz, 2 H), 7.01 (d, $J = 8.0$ Hz, 2 H), 5.06-5.02 (m, 1 H), 2.87-2.76 (m, 2 H), 148
2.63 (ABq, $J = 12.4$ Hz, 1 H), 2.32-2.11 (m, 2 H), 1.99 (s, 3 H), 1.69 (s, 3 H), 1.57 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 211.8, 139.0, 134.5, 131.6, 130.8, 120.7, 120.2, 54.7, 36.6, 30.7, 30.4, 29.8, 25.9, 18.0; ESI/MS m/z calcd for C$_{15}$H$_{18}$BrN$_2$O$_2$ (M + H): 295.1, found: 295.2.

Ketone 2.64. Flash chromatography over silica gel 2.5:97.5 Et$_2$O-pentanes gave 2.64 (11.2 mg, 99%) as a pure, colorless oil, along with pure recovered 2.20 (6.15 mg, 98%) as a white solid. HPLC analysis showed an $er > 99:1$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.38 (d, $J = 8.4$ Hz, 2 H), 7.01 (d, $J = 8.0$ Hz, 2 H), 5.06-5.02 (m, 1 H), 2.87-2.76 (m, 2 H), 2.63 (m, 1 H), 2.32-2.11 (m, 2 H), 1.99 (s, 3 H), 1.69 (s, 3 H), 1.57 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 211.8, 139.0, 134.5, 131.6, 130.8, 120.7, 120.2, 54.7, 36.6, 30.7, 30.4, 29.8, 25.9, 18.0; ESI/MS m/z calcd for C$_{15}$H$_{22}$N$_2$O$_2$ (M + H): 295.1, found: 295.2.

a) HPLC trace of 2.63 and 2.64  

b) HPLC trace of 2.63  

c) HPLC trace of 2.64
2.5.1.4 α,α'-Bisalkylation of α'-Activated Hydrazones

**Hydrazone 2.68.** 2.67 (342 mg, 2.55 mmol) was added to a solution of crude 1.72 (see above) (1.00 g, 5.10 mmol) in CH₂Cl₂ (25 mL) followed by catalytic p-toluenesulfonic acid (ca. 5 mg) (Ar atmosphere). The mixture was heated to reflux and stirred for 12 h then allowed to cool to rt before being partitioned between saturated aquesous NaHCO₃ and CH₂Cl₂. The aqueous phase was extracted with CH₂Cl₂ (twice) and the combined organic layers were dried (MgSO₄), filtered, and concentrated under reduced pressure to give a pale yellow oil. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave 2.68 as an 85:15 E:Z mixture. Recrystallization from hot hexanes yielded pure (E)-2.68 (418.4 mg, 53 %) as a white solid. ¹H NMR (CDCl₃, 400 MHz): δ 7.33-7.22 (m, 5 H), 4.25 (dd, J = 4.0, 8.0 Hz, 1 H), 3.71 (A of ABq, J = 14.4 Hz, 1 H), 3.61 (B of ABq, J = 14.4 Hz, 1 H), 2.33-2.27 (m, 1 H), 2.06-1.82 (m, 7 H containing a s at δ 1.88 (3 H)), 1.78-1.76 (m, 1 H), 1.22 (s, 3 H), 1.16 (s, 3 H); ¹³C NMR (CDCl₃, 100 MHz): δ 174.6, 154.8, 136.8, 129.2, 128.6, 126.8, 83.1, 73.2, 48.0, 45.4, 42.9, 35.4, 26.8, 25.7, 21.3, 19.2, 18.4; ESI/MS m/z calcd for C₁₉H₂₅N₂O₂ (M + H): 311.2, found: 311.2.
Hydrazone 2.69. 2.69 was prepared according to Procedure A (Section 2.4.1.1). Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.68 (21.8 mg, 91%) as a pure, white solid. ¹H NMR (CDCl₃, 400 MHz): δ 7.34-7.20 (m, 5 H), 4.25 (dd, J = 4.0 Hz, 8.0 Hz, 1 H), 3.72 (apparent q, J = 12 Hz, 2 H), 2.41-2.23 (m, 4 H), 2.04-1.91 (m, 2 H), 1.84 (dd, J = 8.0 Hz, 12.0 Hz, 1 H), 1.76 (t, J = 4.0 Hz, 1 H), 1.31-1.19 (m, 2 H), 1.17 (s, 3 H), 1.15 (s, 3 H), 1.03 (t, J = 8.0 Hz, 3 H); ¹³C NMR (CDCl₃ 100 MHz): δ 177.9, 155.1, 137.1, 136.7, 129.2, 128.6, 126.7, 115.4, 83.1, 73.3, 48.0, 43.0, 42.9, 35.4, 30.4, 29.9, 26.7, 25.8, 21.3, 19.2; ESI/MS m/z calcd for C₂₀H₂₆N₂O₂ (M + H): 327.2, found: 327.2.

Hydrazone 2.71. 2.71 was prepared according to Procedure B (Section 2.4.1.1). Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.71 (21.1 mg, 81%) as a pure, white solid. ¹H NMR (CDCl₃, 400 MHz): δ 7.34-7.20 (m, 5 H), 5.74-5.66 (m, 1 H), 5.00-4.94
(m, 2 H), 4.26 (dd, $J = 4.0$ Hz, 8.0 Hz, 1 H), 3.70 (apparent s, 2 H), 2.57-2.50 (m, 1 H), 2.33-2.19 (m, 5 H), 2.05-1.91 (m, 3 H), 1.85 (dd, $J = 8.0$, 12.0 Hz, 1 H), 1.77-1.75 (m, 1 H), 1.31-1.14 (m, 12 H), containing a s at $\delta$ 1.15 (3 H) and a s at $\delta$ 1.14 (3 H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 182.6, 155.3, 137.3, 136.5, 129.6, 128.3, 126.4, 116.9, 83.1, 73.4, 47.9, 43.1, 38.9, 37.6, 35.5, 26.7, 25.8, 21.0, 19.1, 17.5; ESI/MS m/z calcd for C$_{22}$H$_{30}$N$_2$O$_2$ (M + H): 353.8, found: 353.7.

- Synthesis and stereochemical analysis of 2.70 and 2.72.

Hydrazone 2.70. 2.70 was prepared according to Procedure C (Section 2.4.1.2). Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et$_3$N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.70 (61.7 mg, 80%) as a pure, white solid. HPLC analysis showed a $dr > 99:1$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.33-7.18 (m, 5 H), 5.82-5.72 (m, 1 H), 5.10-5.02 (m, 2 H), 4.25 (dd, $J = 4.0$, 8.0 Hz, 1 H), 3.68 (apparent s, 2 H), 3.19-3.10 (m, 1 H), 2.52-2.46 (m, 1 H), 2.31-2.25 (m, 1 H), 2.07-2.02 (m, 1 H), 1.93-1.80 (m, 3 H), 1.72-1.70 (m, 1 H), 1.27-1.09 (m, 4 H), 1.07 (s, 3 H), 0.92-0.91 (m, 6 H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 182.6, 155.3, 137.3, 136.5, 129.6, 128.3, 126.4, 116.9, 83.1, 73.4, 47.9, 43.1, 38.9, 37.6, 35.5, 26.7, 25.8, 21.0, 19.1, 17.5; ESI/MS m/z calcd for C$_{23}$H$_{30}$N$_2$O$_2$ (M + H): 367.3, found: 367.3
Hydrazone 2.72. 2.72 was prepared according to Procedure D (Section 2.4.1.2).

Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.72 (21.9 mg, 84%) as a white solid, containing trace amounts of starting material. HPLC analysis showed a $dr > 99:1$.

$^1$H NMR (CDCl₃, 400 MHz): $\delta$ 7.35-7.29 (m, 2 H), 7.24-7.17 (m, 3 H), 5.61-5.50 (m, 1 H), 5.00-4.94 (m, 2 H), 4.22 (dd, $J = 4.0$, 8.0 Hz, 1 H), 3.64 (apparent s, 2 H), 2.32-2.20 (m, 2 H), 2.17-2.12 (m, 3 H), 2.02-1.79 (m, 5 H), 1.70-1.68 (m, 1 H), 1.25-1.14 (m, 6 H, containing an apparent d at $\delta$ 1.17 (3 H)), 1.02 (s, 3 H), 0.87 (s, 3 H); $^{13}$C NMR (CDCl₃, 100 MHz): $\delta$ 180.4, 155.2, 137.3, 135.9, 129.7, 128.2, 126.3, 116.6, 83.0, 73.3, 47.9, 43.0, 39.3, 38.2, 36.1, 35.5, 26.9, 25.8, 20.9, 19.1; ESI/MS m/z calcd for C₂₃H₃₀N₂O₂ (M + H): 367.3, found: 367.3.

a) HPLC trace of 2.70 and 2.72  

b) HPLC trace of 2.70  

c) HPLC trace of 2.72
Hydrazone 2.84. 1.72 was dissolved in dichloromethane (130 mL) followed by 2.83 (2.74 mL, 26.0 mmol) and p-TsOH·H₂O (490 mg, 2.60 mmol) and the mixture heated to reflux for 12 h. The mixture was allowed to cool to room temperature before it was quenched with NaHCO₃ and the aqueous layer extracted with dichloromethane (twice). The combined organic extracts were dried (MgSO₄), filtered, and concentrated under reduced pressure to yield 2.84 as an 85:15 mixture of E:Z diastereomers. Flash chromatography over silica gel (5:95 → 20:80 EtOAc:Hexanes) gave pure 2.84 as exclusively the E diastereomer and a colorless oil (7.12 g, 80 %). ¹H NMR (CDCl₃, 400 MHz): δ 7.36-7.28 (m, 5H), 4.55 (s, 2 H), 4.28 (dd, J= 3.6 Hz, 8.0 Hz, 1 H), 4.17 (s, 2 H), 2.34-2.28 (m, 1 H), 2.09-1.91 (m, 5 H, containing a s at δ 2.03 for 3 H), 1.86 (dd, 1 H, J= 8.0 Hz, 13.6 Hz), 1.79-1.77 (m, 1 H), 1.33-1.13 (m, 7 H, containing a s at δ 1.24 for 3 H and a s at δ 1.13 for 3 H); ¹³C NMR (CDCl₃, 125 MHz): δ 172.0, 154.2, 137.6, 128.4, 128.0, 127.8, 83.0, 73.2, 73.0, 72.2, 47.9, 42.8, 35.3, 26.7, 25.6, 21.3, 19.1, 16.5; ESI/MS m/z calcd for C₂₀H₂₆N₂O₃ (M + H): 343.2, found: 343.3.
Hydrazone 2.85. 2.85 was prepared according to Procedure A (Section 2.4.1.1).

Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 7.5:92.5 EtOAc-hexanes) using 7.5:92.5 EtOAc-hexanes gave 2.85 (2.81 g, 90%) as a pure, colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 7.38-7.27 (m, 5 H), 4.56 (d, J = 2.4 Hz, 2 H), 4.29-4.19 (m, 3 H), 2.54-2.39 (m, 2 H), 2.34-2.28 (m, 1 H), 2.07-1.91 (m, 2 H), 1.89-1.84 (dd, J = 8.4 Hz, 14 Hz, 1 H), 1.78 (t, J = 4.4 Hz, 1 H), 1.33-1.12 (m, 12 H, containing a s at δ 1.23 for 3 H); ¹³C NMR (CDCl₃, 125 MHz): δ 177.3, 154.7, 137.7, 128.4, 128.0, 127.8, 83.0, 73.1, 72.2, 71.2, 47.9, 42.9, 35.3, 26.6, 25.6, 23.2, 21.3, 19.1, 10.2; ESI/MS m/z calcd for C₂₁H₂₈N₂O₃ (M + H): 357.2, found: 357.3.

Hydrazone 2.135. 2.135 was prepared according to Procedure B (Section 2.4.1.1).

Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 7.5:92.5 EtOAc-hexanes) using 7.5:92.5 EtOAc-hexanes gave 2.135 (160 mg, 95%) as a pure, colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 7.37-7.26 (m, 5 H), 5.82-5.72 (m, 1 H),
5.03-4.95 (m, 2 H), 4.55 (ABq, 1 H, J_{AB}= 12.0, 28.8 Hz), 4.30-4.25 (m, 2 H), 4.15 (d, 1 H, J = 12.8 Hz), 2.67-2.60 (m, 1 H), 2.53-2.46 (m, 1 H), 2.43-2.25 (m, 4 H), 2.04 (dt, 1 H, J = 4.4, 11.6 Hz), 1.99-1.91 (m, 1 H), 1.86 (dd, 1 H, J = 8.0, 13.5 Hz), 1.79-1.77 (m, 1 H), 1.31-1.26 (m, 1 H), 1.22 (s, 3 H), 1.19-1.16 (m, 1 H), 1.14 (s, 3 H); ^{13}C NMR (CDCl\textsubscript{3}, 125 MHz): δ 175.5, 154.8, 137.7, 137.4, 128.5, 128.2, 127.9, 115.3, 83.1, 73.2, 72.2, 71.6, 48.0, 43.0, 35.4, 29.5, 29.1, 26.7, 25.7, 21.4, 19.2; ESI/MS m/z calcd for C\textsubscript{23}H\textsubscript{30}N\textsubscript{2}O\textsubscript{3} (M + H): 383.2, found: 383.2.

Hydrazone 2.87. 2.87 was prepared according to Procedure C (Section 2.4.1.2).

Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et\textsubscript{3}N and 7.5:92.5 EtOAc-hexanes) using 7.5:92.5 EtOAc-hexanes gave 2.87 (2.84 g, 91 %) as a pure, colorless oil. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): δ 7.36-7.25 (m, 5 H), 5.83-5.75 (m, 1 H), 5.08-5.01 (m, 2 H), 4.59, 4.54 (ABq, J_{AB}= 9.2 Hz, 2 H), 4.33, 4.23 (ABq, J_{AB}= 10.4 Hz, 2 H), 4.29 (dd, J= 3.2 Hz, 6.8 Hz, 1 H), 3.17-3.09 (m, 2 H), 2.60-2.55 (m, 1 H), 2.34-2.29 (m, 1 H), 2.21-2.15 (m, 1 H), 2.08-2.02 (m, 1 H), 1.99-1.92 (m, 1 H), 1.85 (dd, J= 6.8 Hz, 11.2 Hz, 1 H), 1.79-1.77 (m, 1 H), 1.31-1.13 (m, 7 H, containing a s at δ 1.24 for 3 H and a s at δ 1.16 for 3 H), 1.07 (d, J= 6.0 Hz, 3 H); ^{13}C NMR (CDCl\textsubscript{3}, 125 MHz): δ 179.4, 155.0, 137.9, 136.7,
Hydrazine 2.86. 2.86 was prepared according to Procedure C (Section 2.4.1.2). Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 7.5:92.5 EtOAc-hexanes) using 7.5:92.5 EtOAc-hexanes gave 2.86 (83.4 mg, 87%) as a pure, colorless oil. ^1H NMR (CDCl₃, 400 MHz): δ 7.37-7.27 (m, 5 H), 5.67-5.57 (m, 1 H), 5.01-4.93 (m, 2 H), 4.58 (d, 2 H, J= 3.6 Hz), 4.30-4.25 (m, 3 H), 3.21-3.12 (m, 1 H), 2.34-2.23 (m, 2 H), 2.21-2.14 (m, 1 H), 2.05 (dt, 1 H, J= 4.4, 11.2 Hz), 1.99-1.91 (m, 1 H), 1.89-1.84 (m, 1 H), 1.79-1.77 (m, 1 H), 1.33-1.29 (m, 1 H), 1.26 (d, 3 H, J= 7.2 Hz), 1.24 (s, 3 H), 1.23-1.18 (m, 1 H), 1.15 (s, 3 H); ^13C NMR (CDCl₃, 125 MHz): δ 177.5, 154.9, 138.0, 136.2, 128.4, 128.0, 127.7, 116.5, 83.1, 73.2, 72.3, 69.9, 48.0, 43.0, 39.0, 35.5, 35.4, 26.8, 25.8, 21.5, 19.2, 16.7; ESI/MS m/z calcd for C₂₁H₂₈N₂O₃ (M + H): 397.2, found: 397.3.
2.5.2 Regioselective Asymmetric $\alpha,\alpha,\alpha',\alpha'$-Tetraalkylation

2.5.2.1 Synthesis of Bisalkylated Hydrazones 2.121 and 2.122

Hydrazone 2.21. $n$-BuLi (2.5 M in hexanes, 0.326 mL, 0.820 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of $i$-Pr$_2$NH (0.124 mL, 0.880 mmol) in THF (3.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H$_2$O bath, stirred for 30 min, and then cooled to −78 °C. A solution of 2.21 (184.6 mg, 0.680 mmol) in THF (2.0 mL) was added by syringe, with additional THF (2 x 0.5 mL) as a rinse, and the mixture was stirred for 1 h. Benzyl bromide (97.0 µL, 0.820 mmol) was then added and the mixture stirred at −78 °C for 24 h. The mixture was then partitioned between Et$_2$O and H$_2$O. The aqueous phase was extracted with Et$_2$O (twice) and the combined organic extracts were dried (MgSO$_4$), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et$_3$N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.121 (204 mg, 82%) as a pure, colorless oil. $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.31-7.19 (m, 5 H), 5.44-5.36 (m, 1 H), 4.95-4.86 (m, 2 H), 4.22 (dd, $J = 4.0, 8.0$ Hz, 1 H), 3.25 (d, 1 H, $J = 13$ Hz), 3.17-3.12 (m, 1 H), 2.49-2.44 (m, 1 H), 2.32-2.28 (m, 1 H), 2.20-2.15 (m, 1 H), 2.02-1.90 (m, 3
1H, 1.84 (dd, 1 H, J= 8.0, 11.5 Hz), 1.76-1.75 (m, 1 H), 1.28-1.20 (m, 6 H, containing a s at δ 1.25 for 3 H), 1.16 (s, 3 H), 1.11-1.07 (m, 1 H); 13C NMR (CDCl3, 125 MHz): δ 177.9, 155.4, 139.7, 135.7, 129.8, 128.3, 126.2, 116.4, 82.9, 73.1, 48.0, 43.3, 43.9, 38.2, 35.4, 35.0, 26.8, 25.7, 21.5, 19.1, 18.9; ESI/MS m/z calcd for C33H30N2O2 (M + H): 367.2, found: 367.3.

**Hydrazone 2.122.** n-BuLi (2.5 M in hexanes, 0.326 mL, 0.820 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr2NH (0.124 mL, 0.880 mmol) in THF (3.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H2O bath, stirred for 30 min, and then cooled to −78 °C. A solution of 2.33 (221.5 mg, 0.680 mmol) in THF (2.0 mL) was added by syringe, with additional THF (2 x 0.5 mL) as a rinse, and the mixture was stirred for 1 h. Allyl bromide (71.0 µL, 0.816 mmol) was then added and the mixture stirred at −78 °C for 24 h. The mixture was then partitioned between Et2O and H2O. The aqueous phase was extracted with Et2O (twice) and the combined organic extracts were dried (MgSO4), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et3N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.122 (205 mg, 82%) as a pure, colorless oil. 1H NMR (CDCl3, 500 MHz): δ 7.24-7.15 (m, 3 H),
7.06 (d, 2 H, J= 7.5 Hz), 5.91-5.83 (m, 1 H), 5.15-5.07 (m, 2 H), 4.08 (dd, J= 4.0, 8.0 Hz, 1 H), 3.26-3.20 (m, 1 H), 2.85 (dd, 1 H, J= 5.0, 14.0 Hz), 2.64-2.59 (m, 1 H), 2.54 (dd, 1 H, J= 9.5, 27.5 Hz), 2.24-2.20 (m, 1 H), 2.16-2.08 (m, 1 H), 2.0 (s, 3 H), 1.15-1.03 (m, 7 H, with a s at δ 1.10 for 3 H and a s at δ 1.07 for 3 H), 0.57 (t, 1 H, J= 9.0 Hz); 13C NMR (CDCl3, 125 MHz): δ 177.7, 155.3, 139.6, 136.7, 128.8, 128.4, 126.3, 177.1, 82.8, 73.1, 47.9, 42.8, 42.7, 37.6, 36.6, 35.3, 26.1, 25.6, 21.4, 19.3, 19.1; ESI/MS m/z calcd for C23H30N2O2 (M + H): 367.2, found: 367.3.

a) HPLC trace of diastereomeric mixture of 2.121, 2.122 (2.0:98.0 i-PrOH-hexanes; 0.5 mL/min)

![HPLC trace](image1)

b) Chiral HPLC analysis of 2.122 (2.0:98.0 i-PrOH-hexanes; 0.5 mL/min)
c) Chiral HPLC analysis of 2.121 (2.0:98.0 i-PrOH-hexanes; 0.5 mL/min)

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.332</td>
<td>99.4161</td>
</tr>
<tr>
<td>18.894</td>
<td>0.5839</td>
</tr>
</tbody>
</table>

2.5.2.2 Isomerization of Bisalkylated Hydrazones

The following procedure is representative of the isomerization of bisalkylated hydrazones 2.41, 2.42, 2.44, 2.46, 2.121, and 2.122.

**E-Hydrazone 2.101.** n-BuLi (2.5 M in hexanes, 1.0 mL, 2.5 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr2NH (0.385 mL, 2.75
mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H$_2$O bath, stirred for 30 min, and then cooled to –78 °C. A portion of this solution (0.410 mL, 0.102 mL) was then transferred to a pre-cooled (–78 °C) flask (Ar Atmosphere). A solution of 2.121 (25 mg, 0.068 mmol) in THF (0.5 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was removed from the cold bath and stirred at rt for 5 h. The mixture was then partitioned between Et$_2$O and H$_2$O. The aqueous phase was extracted with Et$_2$O (twice) and the combined organic extracts were dried (MgSO$_4$), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et$_3$N and 10:90 EtOAc-hexanes) using 10:90 EtOAc-hexanes gave 2.101 (23 mg, 92%) as a pure, colorless oil. ¹H NMR (CDCl$_3$, 400 MHz): δ 7.26-7.23 (m, 2 H), 7.18-7.15 (m, 3 H), 5.86-5.78 (m, 1 H), 5.08-5.00 (m, 2 H), 4.17 (dd, J = 4.0, 8.0 Hz, 1 H), 2.87-2.78 (m, 3 H), 2.44-2.40 (m, 1 H), 2.29-2.24 (m, 2 H), 1.91-1.78 (m, 5 H, containing a s at δ 1.87 for 3 H), 1.73-1.70 (m, 1 H), 1.64 (dt, 1 H, J= 5.0, 11.5 Hz), 1.23-1.18 (m, 1 H), 1.13-1.04 (m, 6 H, containing a s at δ 1.09 for 3 H and a s at δ 1.08 for 3 H), 0.98-0.93 (m, 3 H); ¹³C NMR (CDCl$_3$, 100 MHz): δ 176.9, 154.4, 139.8, 136.0, 135.8, 129.3, 129.1, 128.4, 128.2, 126.2, 125.9, 116.9, 116.7, 116.4, 83.0, 82.8, 73.1, 49.8, 49.7, 42.9, 42.8, 39.1, 38.9, 38.7, 36.7, 36.4, 35.5, 35.3, 26.5, 26.4, 25.7, 25.6, 21.3, 19.2, 17.4, 17.3; ESI/MS m/z calcd for C$_{23}$H$_{30}$N$_2$O$_2$ (M + H): 367.2, found: 367.3.
**E-Hydrazone 2.100.** Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 2.100 (21 mg, 88%) as a pure, colorless oil. ¹H NMR (CDCl₃, 500 MHz): δ 7.27-7.17 (m, 5 H), 5.85-5.76 (m, 1 H), 5.06-4.98 (m, 2 H), 4.22 (dd, 4.0, 8.0 Hz, 1 H), 3.01-2.96 (m, 1 H), 2.80-2.73 (m, 2 H), 2.37-2.25 (m, 3 H), 1.94-1.90 (m, 2 H), 1.86 (s, 3 H), 1.84-1.81 (m, 2 H), 1.76-1.74 (m, 1 H), 1.27-1.24 (m, 1 H), 1.20 (s, 3 H), 1.12-1.09 (m, 4 H, containing a s at δ 1.11 for 3 H); ¹³C NMR (CDCl₃, 125 MHz): δ 176.7, 154.4, 140.1, 136.1, 129.2, 128.3, 126.1, 116.7, 82.9, 73.1, 49.6, 47.9, 42.9, 38.4, 36.9, 35.4, 26.7, 25.8, 21.5, 19.2, 18.9; ESI/MS m/z calcd for C₂₃H₃₀N₂O₂ (M + H): 367.2, found: 367.3.

a) HPLC trace of diastereomeric mixture 2.100, 2.101 (2.0:98.0 i-PrOH-hexanes; 0.5 mL/min)
b) Chiral HPLC analysis of **2.100** (0.5:99.5 i-PrOH-hexanes; 0.5 mL/min)

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.174</td>
<td>99.4506</td>
</tr>
<tr>
<td>21.099</td>
<td>0.5494</td>
</tr>
</tbody>
</table>

c) Chiral HPLC analysis of **2.101** (2.0:98.0 i-PrOH-hexanes; 0.5 mL/min)

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.303</td>
<td>0.7398</td>
</tr>
<tr>
<td>20.941</td>
<td>99.2502</td>
</tr>
</tbody>
</table>
**E-Hydrazine 2.98.** Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 2.98 (21 mg, 92%) as a pure, colorless oil. **^1H NMR** (CDCl₃, 400 MHz): δ 7.28-7.16 (m, 5 H), 4.19 (dd, J = 4.0, 8.0 Hz, 1 H), 2.95-2.80 (m, 2 H), 2.70 (dd, 1 H, J = 7.2, 13.2, Hz), 2.30-2.24 (m, 1 H), 1.91 (s, 3 H), 1.88-1.78 (m, 5 H), 1.73-1.70 (m, 1 H), 1.68-1.64 (m, 1 H), 1.16 (d, 3 H, J = 6.4 Hz), 1.10 (s, 6 H); **ESI/MS** m/z calcd for C₂₁H₂₆N₂O₂ (M + H): 341.2, found: 341.2.

![Diagram of reaction](image)

**E-Hydrazine 2.99.** Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 2.99 (29 mg, 91%) as a pure, colorless oil. **^1H NMR** (CDCl₃, 400 MHz): δ 7.28-7.25 (m, 3 H), 7.20-7.17 (m, 2 H), 4.23 (dd, J = 4.0, 8.0 Hz, 1 H), 3.07 (dd, 1 H, J = 5.6, 13.6 Hz), 2.78-2.70 (m, 1 H), 2.64 (dd, 1 H, J = 8.4, 13.2 Hz), 2.32-2.26 (m, 1 H), 1.97-1.94 (m, 2 H), 1.93 (s, 3 H), 1.84 (dd, 1 H, J = 8.0, 13.6 Hz), 1.29-1.22 (m, 2 H), 1.20 (s, 3 H), 1.15-1.10 (m, 7 H); **ESI/MS** m/z calcd for C₂₁H₂₆N₂O₂ (M + H): 341.2, found: 341.2.
a) HPLC trace of diastereomeric mixture of 2.98, 2.99 (0.5:99.5 i-PrOH-hexanes; 0.5 mL/min)

![HPLC trace of diastereomeric mixture of 2.98, 2.99](image)

b) Chiral HPLC analysis of 2.99 (0.5:99.5 i-PrOH-hexanes; 0.5 mL/min)

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>68.079</td>
<td>99.4228</td>
</tr>
</tbody>
</table>
**E-Hydrazone 2.43.** Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave \(2.43\) (48.1 mg, 98%) as a pure, colorless oil. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 5.81-5.71 (m, 1 H), 5.04-4.97 (m, 2 H), 4.24 (dd, \(J = 4.0, 8.0\) Hz, 1 H), 2.45-2.39 (m, 1 H), 2.32-2.25 (m, 3 H), 2.03-1.91 (m, 2 H), 1.86 (s, 3 H), 1.85-1.81 (m, 1 H), 1.77-1.75 (m, 1 H), 1.64-1.50 (m, 1 H), 1.30-1.25 (m, 3 H), 1.23 (s, 3 H), 1.14 (s, 3 H), 0.92 (t, 3 H, \(J = 7.2\) Hz); ESI/MS m/z calcd for C\(_{18}\)H\(_{28}\)N\(_2\)O\(_2\) (M + H): 305.2, found: 305.2.

**2.5.2.3 \(\alpha,\alpha,\alpha',\alpha'\)-Tetraalkylation**

**Hydrazone 2.103.** \(n\)-BuLi (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (\(-78 \, ^\circ\)C) solution of \(i\)-Pr\(_2\)NH (0.385 mL, 2.75 mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H\(_2\)O bath, stirred for 30 min, and then cooled to \(-78 \, ^\circ\)C. A portion of this solution (0.668 mL, 0.167 mmol) was transferred to a pre-cooled (\(-78 \, ^\circ\)C) flask (Ar Atmosphere). A solution
of 2.98 (47.3 mg, 0.139 mmol) in THF (1.0 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H₂O bath and stirred for 1 h. The solution was recooled to −78 °C, methyl iodide (86.5 µL, 1.39 mmol) was then added and the solution removed from the cold bath and stirred at rt for 1 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 7.5:92.5 EtOAc-hexanes gave 2.103 (29 mg, 57%) as a pure, colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 7.28-7.18 (m, 5 H), 4.23 (dd, J = 4.0, 8.0 Hz, 1 H), 3.08 (dd, 1 H, J = 6.8, 13.6, Hz), 2.84-2.76 (m, 1 H), 2.67 (dd, 1 H, J = 7.6, 13.2 Hz), 2.45-2.35 (m, 1 H), 2.32-2.26 (m, 1 H), 2.24-2.17 (m, 1 H), 2.05-1.91 (m, 2 H), 1.84 (dd, 1 H, J = 8.4, 13.2 Hz), 1.78-1.76 (m, 1 H), 1.31-1.28 (m, 1 H), 1.26 (s, 3 H), 1.18-1.13 (m, 7 H), 0.96 (t, 3 H, J = 7.6 Hz); ESI/MS m/z calcd for C₂₂H₃₀N₂O₂ (M + H): 355.2, found: 355.2.

**Hydrazone 2.104.** n-BuLi (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (0.385 mL, 2.75 mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O
bath, stirred for 30 min, and then cooled to –78 °C. A portion of this solution (0.412 mL, 0.103 mmol) was transferred to a pre-cooled (–78 °C) flask (Ar Atmosphere). A solution of 2.103 (30.4 mg, 0.086 mmol) in THF (1.0 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H2O bath and stirred for 1 h. The solution was recooled to –78 °C, p-bromobenzyl bromide (25.7 mg, 0.103 mmol, in 0.5 mL THF) was then added and after 5 min the solution removed from the cold bath and stirred at rt for 1 h. The mixture was then partitioned between Et2O and H2O. The aqueous phase was extracted with Et2O (twice) and the combined organic extracts were dried (MgSO4), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave 2.104 (27 mg, 60%) as a pure, white solid. 1H NMR (CDCl3, 400 MHz): δ 7.36 (d, 2 H, J= 8.8 Hz), 7.29-7.18 (m, 5 H), 7.07 (d, 2 H, J= 8.4 Hz), 4.25 (dd, J = 4.0, 8.0 Hz, 1 H), 3.23 (dd, 1 H, J= 2.8, 12.4 Hz), 3.05 (dd, 1 H, J= 6.8, 12.4 Hz), 3.01-2.96 (m, 1 H), 2.86-2.74 (m, 2 H), 2.36-2.26 (m, 2 H), 2.10 (dt, 1 H, J= 4.4, 11.6 Hz), 1.88 (dd, 1 H, J= 8.0, 14.0 Hz), 1.83-1.81 (m, 1 H), 1.40 (s, 3 H), 1.35-1.31 (m, 3 H), 1.27 (d, 3 H, J= 6.4 Hz), 1.19 (s, 3 H), 0.38 (d, 3 H, J= 6.8 Hz); 13C NMR (CDCl3, 100 MHz): δ 184.7, 141.0, 139.1, 131.6, 131.4, 129.5, 128.3, 126.3, 120.0, 82.9, 73.5, 48.2, 43.1, 42.4, 38.6, 38.4, 37.9, 35.5, 26.8, 25.9, 22.4, 22.0, 19.3, 14.6; ESI/MS m/z calcd for C29H35BrN2O2 (M + H): 523.2, found: 523.2.
Hydrazone 2.123. n-BuLi (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (0.385 mL, 2.75 mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (1.05 mL, 0.262 mmol) was transferred to a pre-cooled (−78 °C) flask (Ar Atmosphere). A solution of 2.101 (80.0 mg, 0.218 mmol) in THF (1.5 mL) was added by syringe, with additional THF (2 x 0.5 mL) as a rinse, and the mixture was transferred to an ice-H₂O bath and stirred for 1 h. The solution was recooled to −78 °C, prenyl bromide (30.3 µL, 0.262 mmol) was then added and the mixture stirred at 4 °C for 1 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 5:95 EtOAc-hexanes) using 5:95 EtOAc-hexanes gave 2.123 (59 mg, 62%) as a pure, colorless oil. ¹H NMR (CDCl₃, 500 MHz): δ 7.32-7.17 (m, 5 H), 5.80-5.72 (m, 1 H), 5.06-4.95 (m, 2 H), 4.23 (dd, J = 4.0, 8.0 Hz, 1 H), 3.01-2.96 (m, 1 H), 2.78-2.72 (m, 2 H), 2.50-2.42 (m, 2 H), 2.33-2.28 (m, 1 H), 2.23-2.18 (m, 1 H), 2.09-1.76 (m, 7 H), 1.64 (s, 3 H), 1.55 (s, 3 H), 1.32-1.22 (m, 1 H), 1.21 (s, 3 H), 1.19-1.15 (m, 1 H), 1.14 (s, 3 H).
\(^{13}\)C NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta\) 180.8, 154.5, 139.7, 136.7, 132.5, 129.5, 128.2, 126.1, 123.1, 116.2, 82.8, 73.2, 47.8, 47.6, 42.9, 40.5, 36.0, 35.4, 26.6, 25.6, 24.1, 21.5, 19.1, 17.7, ;

ESI/MS m/z calcd for C\textsubscript{26}H\textsubscript{38}N\textsubscript{2}O\textsubscript{2} (M + H): 435.3, found: 435.3.

Hydrazone 2.124. \(n\)-BuLi (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (–78 °C) solution of \(i\)-Pr\textsubscript{2}NH (0.385 mL, 2.75 mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H\textsubscript{2}O bath, stirred for 30 min, and then cooled to –78 °C. A portion of this solution (1.05 mL, 0.262 mmol) was transferred to a pre-cooled (–78 °C) flask (Ar Atmosphere). A solution of 2.101 (80.0 mg, 0.218 mmol) in THF (1.0 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H\textsubscript{2}O bath and stirred for 1 h. The solution was recooled to –78 °C, methyl iodide (0.135 mL, 2.18 mmol) was then added and after 5 min the solution was removed from the cold bath and stirred at rt for 2 h. The mixture was then partitioned between Et\textsubscript{2}O and H\textsubscript{2}O. The aqueous phase was extracted with Et\textsubscript{2}O (twice) and the combined organic extracts were dried (MgSO\textsubscript{4}), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 7.5:92.5 EtOAc-hexanes gave 2.124 (42.1 mg,
68%) as a pure, colorless oil. $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.30-7.17 (m, 5 H), 5.79-5.72 (m, 1 H), 5.03-4.96 (m, 2 H), 4.87-4.84 (m, 1 H), 4.24 (dd, $J= 4.0$, 8.0 Hz, 1 H), 3.17-2.98 (m, 1 H), 2.79-2.72 (m, 2 H), 2.49-2.37 (m, 2 H), 2.32-2.29 (m, 1 H), 2.24-2.19 (m, 1 H), 2.12-2.05 (m, 1 H), 1.97-1.89 (m, 2 H), 1.84 (dd, 1 H, $J=8.0$, 13.0 Hz), 1.77-1.75 (m, 1 H), 1.28-1.26 (m, 1 H), 1.21 (s, 3 H), 1.15 (s, 3 H), 1.14-1.11 (m, 1 H), 0.95 (t, 3 H, $J= 9.0$ Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 182.1, 154.7, 139.9, 136.5, 129.5, 129.3, 128.3, 126.1, 116.3, 82.9, 82.8, 73.2, 47.9, 47.2, 42.9, 40.4, 36.2, 35.5, 26.5, 25.8, 25.7, 21.5, 19.2, 10.1; ESI/MS m/z calcd for C$_{24}$H$_{32}$N$_2$O$_2$ (M + H): 381.2, found: 381.3.

Hydrazone 2.125. n-BuLi (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr$_2$NH (0.385 mL, 2.75 mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H$_2$O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (0.60 mL, 0.150 mmol) was transferred to a pre-cooled (−78 °C) flask (Ar Atmosphere). A solution of 2.100 (41.8 mg, 0.137 mmol) in THF (1.0 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H$_2$O bath and stirred for 1 h. The solution was recooled to −78 °C, methyl iodide (0.135 mL, 2.18
mmol) was then added and after 5 min the solution was removed from the cold bath and stirred at rt for 2 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 7.5:92.5 EtOAc-hexanes gave **2.125** (14.3 mg, 21%) as a pure, colorless oil. ¹H NMR (CDCl₃, 500 MHz): δ 7.28-7.15 (m, 5 H), 5.96-5.87 (m, 1 H), 5.10-5.02 (m, 2 H), 4.87-4.84 (m, 1 H), 4.23 (dd, J = 4.0, 8.0 Hz, 1 H), 3.03-2.98 (m, 1 H), 2.81-2.76 (m, 2 H), 2.45-2.37 (m, 2 H), 2.33-2.25 (m, 2 H), 2.11-1.91 (m, 4 H), 1.87-1.77 (m, 3 H), 1.61 (s, 3 H), 1.50 (s, 3 H), 1.30 (s, 3 H), 1.28-1.26 (m, 1 H), 1.15 (s, 3 H), 1.14-1.11 (m, 1 H); ¹³C NMR (CDCl₃, 125 MHz): δ 180.4, 154.7, 140.9, 136.0, 132.6, 129.3, 128.3, 126.1, 123.2, 117.1, 82.9, 82.8, 73.3, 48.1, 47.5, 38.7, 37.9, 35.5, 33.1, 26.7, 25.9, 25.7, 24.1, 21.9, 19.3, 17.7; ESI/MS m/z calcd for C₂₃H₄₂N₄O₂ (M + H): 381.3, found: 381.3.

**Hydrazone 2.126.** n-BuLi (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (0.385 mL, 2.75 mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (0.357 mL,
0.089 mmol) was transferred to a pre-cooled (−78 °C) flask (Ar Atmosphere). A solution of 2.100 (27.2 mg, 0.074 mmol) in THF (0.5 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H2O bath and stirred for 1 h. The solution was recooled to −78 °C, methyl iodide (0.146 mL, 0.740 mmol) was then added and after 5 min the solution was removed from the cold bath and stirred at rt for 2 h. The mixture was then partitioned between Et2O and H2O. The aqueous phase was extracted with Et2O (twice) and the combined organic extracts were dried (MgSO4), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 7.5:92.5 EtOAc-hexanes gave 2.126 (21.3 mg, 78%) as a pure, colorless oil. 1H NMR (CDCl3, 500 MHz): δ 7.27-7.16 (m, 5 H), 5.95-5.87 (m, 1 H), 5.10-5.04 (m, 2 H), 4.23 (dd, J = 4.0, 8.0 Hz, 1 H), 3.02-2.97 (m, 1 H), 2.83-2.76 (m, 2 H), 2.45-2.40 (m, 1 H), 2.33-2.25 (m, 3 H), 2.17-2.09 (m, 1 H), 2.04-1.91 (m, 2 H), 1.87-1.83 (m, 2 H), 1.78-1.76 (m, 1 H), 1.30 (s, 3 H), 1.28-1.26 (m, 1 H), 1.15 (s, 3 H), 1.14-1.11 (m, 1 H), 0.81 (t, 3 H, J= 8.0 Hz); 13C NMR (CDCl3, 125 MHz): δ 181.7, 154.5, 140.7, 136.1, 129.9, 128.6, 126.1, 116.9, 82.9, 73.3, 48.1, 46.9, 43.0, 38.7, 38.4, 35.5, 26.7, 26.3, 25.9, 21.8, 19.3, 9.9; ESI/MS m/z calcd for C24H32N2O2 (M + H): 381.3, found: 381.3.
Hydrazone 2.107. *n*-BuLi (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (–78 °C) solution of *i*-Pr₂NH (0.385 mL, 2.75 mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to –78 °C. A portion of this solution (1.08 mL, 0.270 mmol) was transferred to a pre-cooled (–78 °C) flask (Ar Atmosphere). A solution of 2.123 (58.5 mg, 0.135 mmol) in THF (1.0 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H₂O bath and stirred for 1 h. The solution was recooled to –78 °C, methyl iodide (84.0 µL, 1.35 mmol) was then added and the mixture stirred at 4 °C for 1 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 7.5:92.5 EtOAc-hexanes gave 2.107 (52.9 mg, 88%) as a pure, colorless oil. ¹H NMR (CDCl₃, 500 MHz): δ 7.28-7.17 (m, 5 H), 5.78-5.69 (m, 1 H), 5.01-4.92 (m, 3 H), 4.24 (dd, J = 4.0, 8.0 Hz, 1 H), 3.09-3.01 (m, 2 H), 2.76-2.66 (m, 2 H), 2.44-2.38 (m, 1 H), 2.33-2.30 (m, 1 H), 2.24-2.19 (m, 1 H), 2.06-2.01 (m, 1 H), 1.98-1.93 (m, 3 H), 1.85 (dd, 1 H, J = 8.0, 13.5 Hz), 1.79-1.77 (m, 1 H), 1.65 (s, 3 H), 1.55 (s, 3 H), 1.31-1.28 (m, 1 H), 1.27 (s, 3 H), 1.21-1.17 (m, 1 H), 1.16 (s, 3 H), 0.98 (d, 3 H, J = 7.0 Hz); ¹³C NMR (CDCl₃, 125 MHz): δ 183.6, 154.9, 140.2, 137.3, 137.2, 132.9, 129.9, 128.4, 126.3, 121.2, 121.1, 116.4, 82.9, 73.4, 48.1, 43.1, 40.2, 37.7, 36.8, 35.6, 32.6, 27.0, 25.9, 25.8, 21.9, 19.5, 18.2, 16.2; ESI/MS m/z calcd for
C_{29}H_{40}N_{2}O_{2} (M + H): 449.3, found: 449.3.

**Hydrazone 2.108.** n-BuLi (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (0.385 mL, 2.75 mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (0.730 mL, 0.183 mmol) was transferred to a pre-cooled (−78 °C) flask (Ar Atmosphere). A solution of 2.124 (34.9 mg, 0.092 mmol) in THF (1.0 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H₂O bath and stirred for 1 h. The solution was recooled to −78 °C, prenyl bromide (13.0 µL, 0.110 mmol) and after 5 min the solution was removed from the cold bath and stirred at rt for 2 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 7.5:92.5 EtOAc-hexanes gave 2.108 (38 mg, 92%) as a pure, colorless oil. ¹H NMR (CDCl₃, 500 MHz): δ 7.29-7.17 (m, 5 H), 5.76-5.68 (m, 1 H), 5.08-4.92 (m, 3 H), 4.25 (dd, J = 4.0, 8.0 Hz, 1 H), 3.11 (dd, 1 H, J = 5.5, 14.0 Hz), 3.02-2.95
(m, 1 H), 2.80-2.66 (m, 2 H), 2.46-2.40 (m, 1 H), 2.33-2.30 (m, 1 H), 2.26-2.21 (m, 1 H), 2.17-2.15 (m, 1 H), 2.00-1.91 (m, 2 H), 1.87-1.80 (m, 2 H, (1.78-1.76 (m, 1 H), 1.67 (s, 3 H), 1.56 (s, 3 H), 1.26 (s, 3 H), 1.97-1.93 (m, 3 H), 1.85 (dd, 1 H, $J = 8.0, 13.5$ Hz), 1.79-1.77 (m, 1 H), 1.65 (s, 3 H), 1.55 (s, 3 H), 1.31-1.26 (m, 1 H), 1.25 (s, 3 H), 1.18 (s, 3 H), 1.15-1.10 (m, 3 H), 0.87 (d, 3 H, $J = 7.0$ Hz); **ESI/MS** m/z calcd for C$_{29}$H$_{40}$N$_2$O$_2$ (M + H): 449.3, found: 449.4.

a) HPLC trace of diastereomeric mixture of 2.108, 2.107 (2.0:98.0 i-PrOH-hexanes; 0.5 mL/min)

![Structures of 2.108 and 2.107](image)

b) Chiral HPLC analysis of 2.108 (2.0:98.0 i-PrOH-hexanes; 0.5 mL/min)
c) Chiral HPLC analysis of **2.107** (2.0:98.0 i-PrOH-hexanes; 0.5 mL/min)

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.442</td>
<td>86.4670</td>
</tr>
<tr>
<td>13.789</td>
<td>0.9249</td>
</tr>
</tbody>
</table>

Hydrazone **2.106**. **n-BuLi** (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (0.385 mL, 2.75 mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (0.400 mL,
0.100 mmol) was transferred to a pre-cooled (−78 °C) flask (Ar Atmosphere). A solution of 2.125 (21.7 mg, 0.050 mmol) in THF (0.5 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H₂O bath and stirred for 1 h. The solution was recooled to −78 °C, methyl iodide (31.1 µL, 0.500 mmol) was then added and the mixture stirred at 4 °C for 1 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 6:94 EtOAc-hexanes gave 2.106 (15.3 mg, 68%) as a pure, colorless oil. ¹H NMR (CDCl₃, 500 MHz): δ 7.27-7.15 (m, 5 H), 5.96-5.87 (m, 1 H), 5.09-5.02 (m, 2 H), 4.61-4.58 (m, 1 H), 4.22 (dd, J = 4.0, 8.0 Hz, 1 H), 3.01-2.92 (m, 2 H), 2.85-2.75 (m, 2 H), 2.48-2.42 (m, 1 H), 2.34-2.29 (m, 1 H), 2.23-2.15 (m, 1 H), 2.12 (dt, 1 H, J = 4.5, 11.0 Hz), 2.05-1.98 (m, 1 H), 1.88-1.78 (m, 2 H), 1.68-1.57 (m, 2 H), 1.68-1.59 (m, 2 H), 1.55 (s, 3 H), 1.50-1.43 (m, 1 H), 1.43 (s, 3 H), 1.40 (s, 3 H), 1.36-1.25 (m, 2 H), 1.17 (s, 3 H), 1.12 (d, 3 H, J = 7.0 Hz); ¹³C NMR (CDCl₃, 125 MHz): δ 183.1, 154.9, 141.0, 136.3, 132.6, 129.5, 128.3, 126.2, 121.8, 116.9, 82.8, 73.4, 48.1, 43.1, 40.1, 39.1, 36.7, 35.5, 32.0, 26.9, 25.9, 25.8, 22.0, 19.3, 17.9, 16.2; ESI/MS m/z calcd for C₂₀H₄₀N₂O₂ (M + H): 449.3, found: 449.3.
Hydrazone 2.105. $n$-BuLi (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of $i$-Pr$_2$NH (0.385 mL, 2.75 mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H$_2$O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (0.450 mL, 0.112 mmol) was transferred to a pre-cooled (−78 °C) flask (Ar Atmosphere). A solution of 2.126 (21.3 mg, 0.056 mmol) in THF (0.5 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H$_2$O bath and stirred for 1 h. The solution was recooled to −78 °C, methyl iodide (88.0 µL, 0.067 mmol) was then added and the mixture stirred at 4 °C for 1 h. The mixture was then partitioned between Et$_2$O and H$_2$O. The aqueous phase was extracted with Et$_2$O (twice) and the combined organic extracts were dried (MgSO$_4$), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 6:94 EtOAc-hexanes gave 2.105 (16.9 mg, 71%) as a pure, colorless oil. $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.26-7.16 (m, 5 H), 5.97-5.89 (m, 1 H), 5.09-5.05 (m, 3 H), 4.61-4.58 (m, 1 H), 4.23 (dd, $J$ = 4.0, 8.0 Hz, 1 H), 2.99-2.94 (m, 1 H), 2.90-2.83 (m, 2 H), 2.79-2.72 (m, 1 H), 2.52-2.48 (m, 1 H), 2.43-2.29 (m, 1 H), 2.25-2.19 (m, 1 H), 2.13-2.07 (m, 1 H), 2.04-1.98 (m, 1 H), 1.92-1.84 (m, 2 H), 1.81-1.79 (m, 1 H), 1.66 (s, 3 H), 1.59 (s, 3 H), 1.38 (s, 3 H), 1.34-1.25 (m, 2
H), 1.18 (s, 3 H), 1.16-1.14 (m, 1 H), 0.38 (d, 3 H, J= 7.0 Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$

184.5, 155.0, 141.0, 136.6, 133.2, 129.5, 128.2, 126.2, 122.2, 116.9, 82.8, 73.4, 48.1, 43.9, 43.1, 40.0, 39.6, 36.4, 35.5, 30.6, 26.8, 25.9, 22.1, 19.3, 18.1, 15.2; ESI/MS m/z calcd for C$_{29}$H$_{40}$N$_2$O$_2$ (M + H): 449.3, found: 449.3.

a) HPLC trace of diastereomeric mixture of 2.105, 2.106 (2.0:98.0 i-PrOH-hexanes; 0.5 mL/min)

b) Chiral HPLC analysis of 2.105 (2.0:98.0 i-PrOH-hexanes; 0.5 mL/min)
c) Chiral HPLC analysis of **2.106** (2.0:98.0 i-PrOH-hexanes; 0.5 mL/min)

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.526</td>
<td>95.5376</td>
</tr>
<tr>
<td>12.496</td>
<td>4.4624</td>
</tr>
</tbody>
</table>

Hydrazone **2.127**. *n*-BuLi (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (–78 °C) solution of *i*-Pr₂NH (0.385 mL, 2.75 mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to –78 °C. A portion of this solution (0.446 mL,
0.109 mmol) was transferred to a pre-cooled (–78 °C) flask (Ar Atmosphere). A solution of 2.43 (27.6 mg, 0.091 mmol) in THF (0.5 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H₂O bath and stirred for 1 h. The solution was recooled to –78 °C, methyl iodide (56.3 µL, 0.910 mmol) was then added and the mixture was then removed from the cold bath and stirred at rt for 2 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 6:94 EtOAc-hexanes gave 2.127 (27.5 mg, 96%) as a pure, colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 5.90-5.80 (m, 1 H), 5.08-4.99 (m, 2 H), 4.25 (dd, J = 4.0, 8.0 Hz, 1 H), 2.52-2.35 (m, 3 H), 2.34-2.28 (m, 1 H), 2.26-2.13 (m, 2 H), 2.03-1.90 (m, 2 H), 1.85 (dd, 1 H, J= 8.4, 13.6 Hz), 1.77-1.75 (m, 1 H), 1.72-1.67 (m, 1 H), 1.58-1.49 (m, 1 H), 1.31-1.24 (m, 1 H), 1.22 (s, 3 H), 1.19-1.16 (m, 1 H), 1.14 (s, 3 H), 1.04 (t, 3 H, J= 7.6 Hz), 0.88 (t, 3 H, J= 7.6 Hz); ¹³C NMR (CDCl₃, 100 MHz): δ 182.5, 154.9, 136.7, 116.4, 82.9, 82.8, 73.3, 47.9, 46.9, 43.0, 38.0, 35.5, 26.7, 25.8, 25.2, 24.6, 21.5, 19.3, 11.7, 10.5; ESI/MS m/z calcd for C₁₉H₂₉N₂O₂ (M + H): 319.2, found: 319.3.
**Hydrazone 2.128.** *n*-BuLi (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of *i*-Pr₂NH (0.385 mL, 2.75 mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (0.379 mL, 0.092 mmol) was transferred to a pre-cooled (−78 °C) flask (Ar Atmosphere). A solution of 2.43 (23.4 mg, 0.077 mmol) in THF (0.5 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H₂O bath and stirred for 1 h. The solution was recooled to −78 °C, *p*-Br-BnBr (23.0 mg, 0.092 mmol) was then added and the mixture was then removed from the cold bath and stirred at rt for 2 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 8:92 EtOAc-hexanes gave 2.128 (26.0 mg, 71%) as a pure, white solid. **¹H NMR** (CDCl₃, 400 MHz): δ 7.38 (d, 2 H, J= 8.4 Hz), 7.04 (d, 2 H, J= 8.0 Hz), 5.88-5.78 (m, 1 H), 5.09-5.01 (m, 2 H), 4.25 (dd, J = 4.0, 8.0 Hz, 1 H), 2.84-2.68 (m, 3 H), 2.50-2.22 (m, 3 H), 1.98-1.91 (m, 2 H), 1.89-1.83 (m, 2 H), 1.79-1.75 (m, 1 H), 1.70-1.65 (m, 1 H), 1.29-1.23 (m, 1 H), 1.22 (s, 3 H), 1.14 (s, 3 H), 0.83 (t, 3 H, J= 7.6 Hz); **ESI/MS** m/z calcd for C₂₅H₃₃BrN₂O₂ (M + H): 473.2, found: 472.3.
**Hydrazone 2.109.** n-BuLi (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (0.385 mL, 2.75 mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (0.541 mL, 0.132 mmol) was transferred to a pre-cooled (−78 °C) flask (Ar Atmosphere). A solution of 2.127 (21.0 mg, 0.066 mmol) in THF (0.5 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H₂O bath and stirred for 1 h. The solution was recooled to −78 °C, p-Br-BnBr (19.8 mg, 0.079 mmol) was then added and the mixture was then removed from the cold bath and stirred at rt for 3 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 3:97 EtOAc-hexanes gave **2.109** (27.8 mg, 87%) as a pure, white solid. **¹H NMR** (CDCl₃, 400 MHz): δ 7.39 (d, 2 H, J= 8.4 Hz), 7.11 (d, 2 H, J= 8.0 Hz), 5.96-5.85 (m, 1 H), 5.09-5.01 (m, 2 H), 4.26 (dd, J = 4.0, 8.0 Hz, 1 H), 3.23 (dd, 1 H, J= 2.4, 12.4 Hz), 3.14-3.08 (m, 1 H), 2.51-2.47 (m, 1 H), 2.34-2.20 (m, 3 H), 2.01-1.92 (m, 2 H), 1.88 (dd, 1 H, J= 8.0, 13.6 Hz), 1.79-1.77 (m, 1 H), 1.73 (t, 1 H, J= 6.8 Hz), 1.69-1.58 (m,
2 H), 1.31-1.25 (m, 2 H), 1.24 (s, 3 H), 1.16 (s, 3 H), 1.12 (m, 1 H), 0.90 (t, 3 H, J= 7.6 Hz),
0.80 (d, 3 H, 6.8 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 183.2, 155.1, 139.1, 136.7, 131.7, 131.3,
120.0, 116.6, 82.9, 82.8, 73.4, 47.9, 43.1, 42.6, 39.9, 38.0, 35.5, 26.7, 26.5, 25.8, 21.5, 19.3, 15.6,
12.2; ESI/MS m/z calcd for C$_{25}$H$_{33}$BrN$_2$O$_2$ (M + H): 473.2, found: 472.3.

Hydrazone 2.110. n-BuLi (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added
dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of $i$-Pr$_2$NH (0.385 mL, 2.75
mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H$_2$O
bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (0.355 mL,
0.086 mmol) was transferred to a pre-cooled (−78 °C) flask (Ar Atmosphere). A solution
of 2.128 (20.7 mg, 0.043 mmol) in THF (0.5 mL) was added by syringe, with additional
THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H$_2$O bath and
stirred for 1 h. The solution was recooled to −78 °C, methyl iodide (26.6 µL, 0.430 mmol)
was then added and the mixture was then removed form the cold bath and stirred at rt
for 3 h. The mixture was then partitioned between Et$_2$O and H$_2$O. The aqueous phase
was extracted with Et$_2$O (twice) and the combined organic extracts were dried (MgSO$_4$),
filtered, and evaporated under reduced pressure to give a yellow oil. Flash
chromatography over silica gel using 3:97 EtOAc-hexanes gave 2.110 (13.2 mg, 62%) as a pure, white solid.  

$^1$H NMR (CDCl$_3$, 400 MHz): δ 7.37 (d, 2 H, $J$= 8.0 Hz), 6.97 (d, 2 H, $J$= 8.4 Hz), 5.93-5.83 (m, 1 H), 5.07-5.00 (m, 2 H), 4.26 (dd, $J$= 4.0, 8.0 Hz, 1 H), 3.37 (m, 1 H), 2.64-2.60 (m, 1 H), 2.51-2.45 (m, 3 H), 2.33-2.21 (m, 2 H), 1.90-1.84 (m, 4 H), 1.77-1.75 (m, 1 H), 1.28-1.20 (m, 2 H), 1.19 (s, 3 H), 1.14 (d, 3 H, $J$= 6.8 Hz), 1.12 (s, 3 H), 0.87 (t, 3 H, $J$= 7.2 Hz); ESI/MS m/z calcd for C$_{26}$H$_{35}$BrN$_2$O$_2$ (M + H): 487.2, found: 487.3.

2.5.2.4 Synthesis of Tetraalkylation Hydrolysis Model Systems

Hydrazone 2.113. To a solution of dibenzyl methyl ketone 2.112 (746 mg, 3.13 mmol) in CH$_2$Cl$_2$ (16 mL) was added 1.72 (700 mg, 3.56 mmol) and $p$-TsOH•H$_2$O (119 mg, 0.626 mmol). The solution was refluxed for 14 h, allowed to cool and the reaction quenched by addition of NaHCO$_3$ (sat. aq., 15 mL). The aqueous phase was then extracted with CH$_2$Cl$_2$ (2x25 mL) and the combined organic layers dried over MgSO$_4$, filtered and concentrated in vacuo to yield a yellow oil. Flash chromatography over silica gel (10:90 EtOAc-Hex) gave 2.113 (662 mg, 51%) as a pure, colorless oil.  

$^1$H NMR (CDCl$_3$, 500 MHz): δ 7.28-7.15 (m, 10 H), 4.16 (dd, 1 H, $J$= 4.0, 8.0 Hz), 3.06-3.01 (m, 2 H), 2.91-2.77 (m, 3 H), 2.28-2.23 (m, 1 H), 1.88-1.59 (m, 6 H), 1.29-1.18 (m, 2 H), 1.09 (s, 3 H), 1.09 (s, 3 H).
1.08 (s, 3 H), 0.96-0.86 (m, 2 H); $^1$C NMR (CDCl$_3$, 125 MHz): δ 176.9, 154.3, 139.9, 129.2, 128.4, 126.2, 126.1, 82.9, 73.1, 51.7, 47.9, 42.9, 39.3, 38.8, 35.4, 31.7, 26.5, 25.7, 22.8, 21.5, 19.2, 18.5; ESI/MS m/z calcd for C$_{27}$H$_{32}$N$_2$O$_2$ (M + H): 417.2, found: 417.2.

**Prenylated Hydrazone 2.129.** $n$-BuLi (2.5 M in hexanes, 1.0 mL, 2.5 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr$_2$NH (0.385 mL, 2.75 mmol) in THF (10 mL) (Ar atmosphere). The mixture was transferred to an ice-H$_2$O bath, stirred for 30 min, and then cooled to −78 °C. A solution of 2.113 (600 mg, 1.44 mmol) in THF (10 mL) was added by syringe, with additional THF (2 x 1.0 mL) as a rinse, and the mixture transferred to an ice-H$_2$O bath and stirred for 1 h. The mixture was then recooled to −78 °C, prenyl bromide (0.20 mL, 1.73 mmol) added and the mixture transferred to an ice-H$_2$O bath and stirred for 2 h. The mixture was then partitioned between Et$_2$O and H$_2$O. The aqueous phase was extracted with Et$_2$O (twice) and the combined organic extracts were dried (MgSO$_4$), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (15:85 EtOAc-hexanes) gave 2.129 (611 mg, 87%) as a pure, colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.30-7.15 (m, 10 H), 4.78-4.76 (m, 1 H), 4.21 (dd, $J$ = 4.0, 8.0 Hz, 1 H), 3.05-2.97 (m,
3 H), 2.79-2.74 (m, 2 H), 2.33-2.27 (m, 2 H), 2.01-1.89 (m, 3 H), 1.86-1.78 (m, 3 H), 1.71-1.65 (m, 1 H), 1.58 (s, 3 H), 1.48 (s, 3 H), 1.31 (s, 3 H), 1.30-1.27 (m, 1 H), 1.18 (s, 3 H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 181.0, 154.6, 140.8, 139.9, 132.5, 129.6, 129.5, 128.4, 128.2, 126.2, 123.2, 123.1, 82.9, 82.8, 73.4, 49.1, 48.1, 43.1, 41.5, 38.2, 35.5, 33.4, 26.7, 25.8, 25.7, 25.6, 23.8, 21.9, 19.4, 17.7; ESI/MS m/z calcd for C\(_{32}\)H\(_{40}\)N\(_2\)O\(_2\) (M + H): 485.3, found: 485.2.

**Hydrazone 2.130.** n-BuLi (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr\(\text{NH}\) (0.385 mL, 2.75 mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H\(_2\)O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (0.763 mL, 0.191 mmol) was then transferred to a pre-cooled (−78 °C) flask (Ar Atmosphere). A solution of 2.113 (66.2 mg, 0.159 mmol) in THF (1 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H\(_2\)O bath and stirred for 1 h. The mixture was then recooled to −78 °C, MeI (0.100 mL, 1.59 mmol) added, and the mixture was removed from the cold bath and stirred at rt for 2 h. The mixture was then partitioned between Et\(_2\)O and H\(_2\)O. The aqueous phase was extracted with Et\(_2\)O (twice) and the combined organic extracts were dried (MgSO\(_4\)),
filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (7.5:92.5 EtOAc-hexanes) gave 2.130 (629 mg, 87%) as a pure, colorless oil.  ^1H NMR (CDCl$_3$, 400 MHz): δ 7.30-7.14 (m, 10 H), 4.55-4.53 (m, 1 H), 4.22 (dd, $J$ = 4.0, 8.0 Hz, 1 H), 3.14-3.10 (m, 1 H), 3.01-2.89 (m, 3 H), 2.79-2.74 (m, 1 H), 2.65 (dd, 1 H, $J$ = 3.0, 9.0 Hz), 2.36-2.31 (m, 1 H), 2.14 (dt, 1 H, $J$ = 5.0, 11.0 Hz), 2.05-1.99 (m, 1 H), 1.88-1.81 (m, 2 H), 1.53 (s, 3 H), 1.44 (s, 3 H), 1.38 (s, 3 H), 1.37-1.27 (m, 4 H), 1.22 (s, 3 H), 0.93 (d, 3 H, $J$ = 6.5 Hz); ^13C NMR (CDCl$_3$, 125 MHz): δ 183.6, 154.9, 140.9, 140.2, 132.6, 129.8, 129.6, 129.5, 129.4, 128.4, 126.2, 121.7, 82.9, 82.8, 73.4, 48.1, 45.9, 43.1, 43.0, 42.6, 39.1, 36.8, 36.7, 35.5, 31.8, 26.9, 25.9, 25.8, 22.2, 19.5, 17.9, 15.8; ESI/MS m/z calcd for C$_{33}$H$_{42}$N$_2$O$_2$ (M + H): 431.2, found: 431.2.

**Hydrazone 2.115.** $n$-BuLi (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of $i$-Pr$_2$NH (0.385 mL, 2.75 mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H$_2$O bath, stirred for 30 min, and then cooled to −78 °C. A solution of 2.129 (611 mg, 1.26 mmol) in THF (5 mL) was added by syringe, with additional THF (2 x 1.0 mL) as a rinse, and the mixture was transferred to an ice-H$_2$O bath and stirred for 1 h. The mixture was
then recooled to –78 °C, MeI (0.784 mL, 12.6 mmol) added, and the mixture was removed from the cold bath and stirred at rt for 2 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (7.5:92.5 EtOAc-hexanes) gave 2.115 (629 mg, 87%) as a pure, colorless oil. Chiral HPLC Analysis against a prepared diastereomeric mixture of 2.114 and 2.115 showed a dr of 96:4. ¹H NMR (CDCl₃, 400 MHz): δ 7.30-7.14 (m, 10 H), 4.55-4.53 (m, 1 H), 4.22 (dd, J = 4.0, 8.0 Hz, 1 H), 3.14-3.10 (m, 1 H), 3.01-2.89 (m, 3 H), 2.79-2.74 (m, 1 H), 2.65 (dd, 1 H, J = 3.0, 9.0 Hz), 2.36-2.31 (m, 1 H), 2.14 (dt, 1 H, J = 5.0, 11.0 Hz), 2.05-1.99 (m, 1 H), 1.88-1.81 (m, 2 H), 1.53 (s, 3 H), 1.44 (s, 3 H), 1.38 (s, 3 H), 1.37-1.27 (m, 4 H), 1.22 (s, 3 H), 0.93 (d, 3 H, J = 6.5 Hz); ¹³C NMR (CDCl₃, 125 MHz): δ 183.6, 154.9, 140.9, 140.2, 132.6, 129.8, 129.6, 129.5, 129.4, 128.4, 126.2, 121.7, 82.9, 82.8, 73.4, 48.1, 45.9, 43.1, 43.0, 42.6, 39.1, 36.8, 36.7, 35.5, 31.8, 26.9, 25.9, 25.8, 22.2, 19.5, 17.9, 15.8; ESI/MS m/z calcd for C₃₃H₄₂N₂O₂ (M + H): 499.3, found: 499.2.

Bisalkylated Hydrazone 2.114. n-BuLi (2.5 M in hexanes, 1.0 mL, 2.50 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (–78 °C) solution of i-Pr₂NH (0.385
mL, 2.75 mmol) in THF (10.0 mL) (Ar atmosphere). The mixture was transferred to an ice-
H2O bath, stirred for 30 min, and then cooled to –78 °C. A portion of this solution
(0.580 mL, 0.145 mL) was then transferred to a pre-cooled (–78 °C) flask (Ar
Atmosphere). A solution of 2.130 (52.0 mg, 0.121 mmol) in THF (1 mL) was added by
syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to
an ice-
H2O bath and stirred for 1 h. The mixture was then recooled to –78 °C, prenylBr
(16.8 µL, 0.145 mmol) added, and the mixture was removed from the cold bath and
stirred at rt for 2 h. The mixture was then partitioned between Et2O and H2O. The
aqueous phase was extracted with Et2O (twice) and the combined organic extracts were
dried (MgSO4), filtered, and evaporated under reduced pressure to give a yellow oil.
Flash chromatography over silica gel (15:85 EtOAc-hexanes) gave 2.114 (33 mg, 56%) as
a pure, colorless oil. Chiral HPLC Analysis against a prepared diastereomeric mixture
of 2.114 and 2.115 showed a dr of 97:3. 1H NMR (CDCl3, 500 MHz): δ 7.31-7.12 (m, 10 H),
5.00-4.97 (m, 1 H), 4.24 (dd, 1 H, J = 4.0, 8.5 Hz), 3.16 (dd, 1 H, J= 5.0, 24.0 Hz), 3.01-2.92
(m, 2 H), 2.88-2.83 (m, 1 H), 2.77 (dd, 1 H, J= 4.5, 12 Hz), 2.67 (dd, 1 H, J= 7.5 Hz, 13.5 Hz),
2.36-2.31 (m, 1 H), 2.14-2.09 (m, 2 H), 2.05-1.99 (m, 1 H), 1.87 (dd, 1 H, J= 8.0, 14.0 Hz),
1.83-1.81 (m, 1 H), 1.63 (s, 3 H), 1.53 (s, 3 H), 1.42 (s, 3 H), 1.36-1.16 (m, 5 H, containing a s
at δ 1.23 for 3 H), 0.34 (d, 3 H, J= 7.0 Hz); 13C NMR (CDCl3, 125 MHz): δ 185.1, 155.0,
140.9, 140.4, 133.2, 129.7, 129.6, 129.4, 128.5, 128.4, 128.3, 126.3, 122.1, 121.9, 82.3, 82.8,
73.5, 48.1, 46.5, 43.1, 42.2, 39.6, 36.4, 35.6, 30.3, 26.8, 25.9, 22.2, 19.5, 18.1, 15.1; ESI/MS m/z
calcd for C_{33}H_{42}N_{2}O_{2} (M + H): 499.3, found: 499.2.

a) HPLC trace of diastereomeric mixture of 2.114, 2.115 (2.0:98.0 i-PrOH-hexanes; 0.5 mL/min)

![HPLC trace of diastereomeric mixture of 2.114, 2.115](image)

b) Chiral HPLC analysis of 2.115 (0.5:99.5 i-PrOH-hexanes; 0.5 mL/min)

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.916</td>
<td>96.0525</td>
</tr>
<tr>
<td>20.717</td>
<td>3.9475</td>
</tr>
</tbody>
</table>
c) Chiral HPLC analysis of 2.114 (2.0:98.0 i-PrOH-hexanes; 0.5 mL/min)

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.959</td>
<td>3.2444</td>
</tr>
<tr>
<td>20.661</td>
<td>96.7556</td>
</tr>
</tbody>
</table>

Hydrazone 2.118. To a solution of diethyl methyl ketone 2.117 (589 mg, 5.16 mmol) in CH₂Cl₂ (16 mL) was added 1.72 (1.82 g, 6.19 mmol) and p-TsOH•H₂O (98.2 mg, 0.516 mmol). The solution was stirred for 14 h and the reaction quenched by addition of NaHCO₃ (sat. aq., 15 mL). The aqueous phase was then extracted with CH₂Cl₂ (2x25 mL) and the combined organic layers dried over MgSO₄, filtered and concentrated in vacuo to yield a yellow oil. Flash chromatography over silica gel (5:95 EtOAc-Hex) gave 2.118 (860 mg, 56%) as a pure, colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 4.24 (dd, 1 H, J = 4.4, 8.8 Hz), 2.33-2.20 (m, 2 H), 2.03-1.89 (m, 3 H), 1.87-1.80 (m, 4 H, containing a s at δ 1.85 for 3 H), 1.77-1.75 (m, 1 H), 1.62-1.44 (m, 5 H), 1.31-1.23 (m, 4 H, containing a s at δ
1.23 for 3 H), 1.17-1.12 (m, 4 H, containing a s at δ 1.14 for 3 H), 0.91 (t, 3 H, J= 7.6 Hz), 0.86 (t, 3 H, J= 7.6 Hz); ESI/MS m/z calcd for C_{17}H_{28}N_{2}O_{2} (M + H): 293.4, found: 293.4.

Methylated Hydrazone 2.131. n-BuLi (2.5 M in hexanes, 0.884 mL, 2.21 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (0.330 mL, 2.35 mmol) in THF (6.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A solution of 2.118 (430 mg, 1.47 mmol) in THF (5 mL) was added by syringe, with additional THF (2 x 0.5 mL) as a rinse, and the mixture was transferred to an ice-H₂O bath and stirred for 1 h. The mixture was then recooled to −78 °C, MeI (0.458 mL, 7.35 mmol) added, and the mixture was removed from the cold bath and stirred at rt for 2 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (10:90 EtOAc-hexanes) gave 2.131 (450 mg, 97%) as a pure, colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 4.24 (dd, 1 H, J = 4.0, 8.0 Hz), 2.53-2.44 (m, 1 H), 2.34-2.25 (m, 2 H), 2.19-2.10 (m, 1 H), 2.03-1.94 (m, 2 H), 1.84 (dd, 1 H, J= 8.0, 9.2 Hz), 1.77-1.75 (m, 1 H), 1.72-1.46 (m, 6
H, 1.22 (s, 3 H), 1.14 (s, 3 H), 1.04 (t, 3 H, J= 7.6 Hz), 0.93 (t, 3 H, J= 7.6 Hz), 0.89 (t, 3 H, J=
7.2 Hz); **ESI/MS** m/z calcd for C_{18}H_{30}N_{2}O_{2} (M + H): 306.2, found: 306.2.

**Benzylated Hydrazone 2.132.** n-BuLi (2.5 M in hexanes, 0.884 mL, 2.21 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr_{2}NH (0.330 mL, 2.35 mmol) in THF (6.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H_{2}O bath, stirred for 30 min, and then cooled to −78 °C. A solution of 2.118 (430 mg, 1.47 mmol) in THF (5 mL) was added by syringe, with additional THF (2 x 0.5 mL) as a rinse, and the mixture was transferred to an ice-H_{2}O bath and stirred for 1 h. The mixture was then recooled to −78 °C, BnBr (0.192 mL, 1.61 mmol) added, and the mixture was removed from the cold bath and stirred at rt for 2 h. The mixture was then partitioned between Et_{2}O and H_{2}O. The aqueous phase was extracted with Et_{2}O (twice) and the combined organic extracts were dried (MgSO_{4}), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (10:90 EtOAc-hexanes) gave 2.132 (497 mg, 88%) as a pure, colorless oil. **^{1}H NMR** (CDCl_{3}, 400 MHz): δ 7.29-7.14 (m, 5 H), 4.25 (dd, 1 H, J = 4.0, 8.0 Hz), 2.86-2.74 (m, 3 H), 2.49-2.40 (m, 1 H), 2.33-2.28 (m, 2 H), 1.98-1.93 (m, 2 H), 1.88-1.83 (m, 1 H), 1.77-1.75 (m, 1 H), 1.73-1.46
(m, 6 H), 1.31-1.24 (m, 2 H), 1.22 (s, 3 H), 1.14 (s, 3 H), 0.94 (t, 3 H, \( J = 7.6 \) Hz), 0.84 (t, 3 H, \( J = 7.2 \) Hz); \textbf{ESI/MS} m/z calcd for C\textsubscript{2}H\textsubscript{3}N\textsubscript{2}O\textsubscript{2} (M + H): 382.3, found: 382.3.

\textbf{Bisalkylated Hydrazone 2.119-\( \beta \)}. \( n \)-BuLi (2.5 M in hexanes, 0.856 mL, 2.14 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (\(-78 ^\circ \text{C}\)) solution of \( i \)-Pr\( _2 \)NH (0.321 mL, 2.29 mmol) in THF (6.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H\( _2 \)O bath, stirred for 30 min, and then cooled to \(-78 ^\circ \text{C}\). A solution of 2.131 (437 mg, 1.43 mmol) in THF (5 mL) was added by syringe, with additional THF (2 x 0.5 mL) as a rinse, and the mixture was transferred to an ice-H\( _2 \)O bath and stirred for 1 h. The mixture was then recooled to \(-78 ^\circ \text{C}\), BnBr (0.254 mL, 2.14 mmol) added, and the mixture was removed from the cold bath and stirred at rt for 2 h. The mixture was then partitioned between Et\( _2 \)O and H\( _2 \)O. The aqueous phase was extracted with Et\( _2 \)O (twice) and the combined organic extracts were dried (MgSO\( _4 \)), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (8:92 EtOAc-hexanes) gave 2.119-\( \beta \) (567 mg, 70\%) as a pure, colorless, viscous oil. Chiral HPLC Analysis against a prepared diastereomeric mixture of 2.119-\( \beta \) and 2.119-\( \alpha \) showed a \( dr \) of 96:4. \( ^1 \text{H NMR} \) (CDCl\( _3 \), 400 MHz): \( \delta \) 7.30-7.19 (m, 5 H), 4.24 (dd, 1 H, \( J = 4.0, 8.0 \) Hz),
3.25 (dd, 1 H, \( J = 2.8, 12.4 \) Hz), 3.20-3.14 (m, 1 H), 2.43-2.30 (m, 3 H), 1.97-1.92 (2 H), 1.85 (dd, 1 H, \( J = 8.0, 13.6 \) Hz), 1.78-1.71 (m, 3 H), 1.63-1.52 (m, 4 H), 1.29-1.19 (m, 4 H, containing a s at \( \delta = 1.24 \) for 3 H), 1.16 (s, 3 H), 0.99 (t, 3 H, \( J = 7.2 \) Hz), 0.91 (t, 3 H, \( J = 7.6 \) Hz), 0.81 (d, 3 H, \( J = 6.8 \) Hz); **ESI/MS** m/z calcd for C\(_{25}\)H\(_{36}\)N\(_2\)O\(_2\) (M + H): 383.3, found: 383.3.

**Hydrazone 2.119-α.** \( n \)-ButLi (2.5 M in hexanes, 0.318 mL, 0.796 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of \( i \)-Pr\(_2\)NH (0.119 mL, 0.850 mmol) in THF (3.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H\(_2\)O bath, stirred for 30 min, and then cooled to −78 °C. A solution of 2.132 (203 mg, 0.531 mmol) in THF (2 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was transferred to an ice-H\(_2\)O bath and stirred for 1 h. The mixture was then recooled to −78 °C, MeI (0.165 mL, 2.66 mmol) added, and the mixture was removed from the cold bath and stirred at rt for 2 h. The mixture was then partitioned between Et\(_2\)O and H\(_2\)O. The aqueous phase was extracted with Et\(_2\)O (twice) and the combined organic extracts were dried (MgSO\(_4\)), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (10:90 EtOAc-
hexanes) gave **2.119-α** (211 mg, 71%) as a pure, white solid. Chiral HPLC Analysis against a prepared diastereomeric mixture of **2.119-β** and **2.119-α** showed a *dr* of 98:2.

**1H NMR** (CDCl₃, 400 MHz): δ 7.28-7.23 (m, 2 H), 7.20-7.17 (m, 1 H), 7.10 (d, 2 H, *J* = 7.2 Hz), 4.26 (dd, 1 H, *J* = 4.0, 8.0 Hz), 3.40-3.33 (m, 1 H), 2.67 (dd, 1 H, *J* = 5.6, 17.6 Hz), 2.47 (dd, 1 H, *J* = 4.8, 13.6 Hz), 2.43-2.36 (m, 1 H), 2.32-2.29 (m, 1 H), 1.93-1.76 (m, 3 H), 1.75-1.50 (m, 5 H, containing a s at δ 1.57 for 3 H), 1.30-1.22 (m, 1 H), 1.20 (s, 3 H), 1.13-1.11 (m, 6 H), 0.95 (t, 3 H, *J* = 7.2 Hz), 0.89 (t, 3 H, *J* = 7.2 Hz); **ESI/MS** m/z calcd for C₃₆H₅₆N₂O₂ (M + H): 397.2, found: 397.3.

a) HPLC trace of diastereomeric mixture of **2.119-α**, **2.119-β** (10:90 *i*-PrOH-hexanes; 1.0 mL/min)

![Diastereomeric mixture HPLC trace](image)

b) Chiral HPLC analysis of **2.119-α** (10:90 *i*-PrOH-hexanes; 1.0 mL/min)
c) Chiral HPLC analysis of **2.119-β** (2.0:98.0 i-PrOH-hexanes; 0.5 mL/min)

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.471</td>
<td>1.3810</td>
</tr>
<tr>
<td>5.058</td>
<td>96.5962</td>
</tr>
</tbody>
</table>
3. Synthetic Applications of ACC $\alpha,\alpha$-Bisalkylation

3.1 Asymmetric Formal Synthesis of (+)- and (-) Stigmolone

3.1.1 Background and Introduction

Stigmolone is a highly potent pheromone that induces the formation of fruiting bodies in the myxobacterium *Stigmatella aurantica* (Figure 19).

![Figure 19. (-)-(R)- and (+)-(S)-Stigmolone](image)

Myxobacteria are Gram-negative soil bacteria that live on soluble polymer surfaces such as rotten wood. Like most myxobacteria, *S. aurantiaca* exists in two different life cycles. In the vegetative growth cycle, the population grows through normal cellular division. However under starvation conditions, the bacteria enter a developmental cycle and form multicellular fruiting bodies, tree-like structures that contain dormant cells called myxospores. The switch from the vegetative to developmental life cycle is induced by the aggregation of the pheromone $8$-hydroxy-$2,5,8$-trimethylnonan-$4$-one, or stigmolone.

Stigmolone was first isolated and its structure elucidated by Plaga in 1998. It was found to possess a C5 stereogenic center $\alpha$ to the C4 carbonyl, as well as a tertiary alcohol at C8. Plaga also reported the first racemic synthesis (3.7, Scheme 40) and conducted studies on its biological activity.\textsuperscript{66-67}
The active concentration necessary for fruiting body formation was found to be only 1.0 nM, making stigmolone one of the most effective, non-peptidic bacterical pheromones to date. Mori reported the first synthesis of both (S)- and (R)-stigmolone by drawing from the chiral pool, starting with either (S)- or (R)-citronellol (Scheme 41). Bioassays of each enantiomer showed equivalent biological activity, and as such the naturally occurring compound was presumed to exist as a racemate.

Scheme 40. Plaga’s Racemic Synthesis of (+/-)-Stigmolone

Scheme 41. Synthesis of (S)- and (R)-Stigmolone Starting from (S)- or (R)-Citronellol
The only asymmetric synthesis was completed by Enders in 2000. In this synthesis, Enders employed his SAMP/RAMP auxiliaries to set the C5 stereocenter through an asymmetric bisalkylation sequence starting from 4-methyl-2-pentanone (Scheme 42). Alkylation of RAMP hydrazone 3.17 with prenyl bromide proceeded in high yield, however, subsequent methylation gave only 48% yield of the desired C5 bisalkylated compound (3.19). Hydrolysis promoted by CuCl₂ yielded the ketone (3.20) in moderate yield, and this could undergo epimerization-free oxidation at C8 using Co(tfa)₂ and O₂ to give (S)-stigmolone (3.2) in 20% overall yield and 93% ee. A similar sequence was conducted using SAMP hydrazone 3.21 to give (R)-stigmolone in 6.4% overall yield and 89% ee (Scheme 42B).

Scheme 42. Enders' Asymmetric Total Synthesis of (S)- and (R)-Stigmolone via SAMP/RAMP
We believed that the low yield in the second alkylation was due to a lack of regioselectivity, since 3.18 (and the corresponding SAMP-derived hydrazone) possesses largely indistinguishable α and α’-protons. Therefore, we felt that our ACC α,α-bisalkylation methodology would be ideally suited for setting the C5 stereocenter, proceeding in high yield and with complete regioselectivity. We also planned to generate both (R)- and (S)-stigmolone using only (S)-ACC 1.62, simply by altering the order of α,α-bisalkylation sequence.

3.1.2 Results and Discussion

The synthesis of both (R)- and (S)-stigmolone began with the formation of the common intermediate 3.23, by acid catalyzed condensation of ACC 1.62 and 4-methyl-2-pentanone (Scheme 43A). 3.23 then underwent regioselective monoalkylation with LDA and prenyl bromide to give 3.24 as a single regioisomer in excellent yield. The regioselective, asymmetric α,α-bisalkylation was then attempted by treatment with LDA and methyl iodide. As anticipated, this gave rise to the desired α,α-bisalkylated product (3.25) in both excellent overall yield and diastereoselectivity (dr > 99:1). Auxiliary cleavage proceeded efficiently using p-TsOH•H₂O in acetone-H₂O (4:1) to produce ketone 3.20 (er = 99:1). As shown in Enders’ synthesis, 3.20 undergoes cobalt-mediated oxidation to give (S)-stigmolone (3.2) in 75% yield, without epimerization occurring.⁷¹
Scheme 43. Asymmetric Formal Synthesis of both (R)- and (S)-Stigmolone via ACC α,α-Bisalkylation

Access to the ketone precursor needed for the preparation of (R)-stigmolone simply entailed switching the order of alkylation of hydrazone 3.23 (Scheme 43B). Therefore, 3.23 was treated with LDA and methyl iodide, followed by prenyl bromide to give 3.26 also with excellent yield and diastereoselectivity (dr > 99:1). Hydrolysis of the bisalkylated product (3.26) produced ketone 3.27 (er = 99:1, which has previously been converted to (R)-stigmolone (3.1) without epimerization occurring. Utilizing our α,α-bisalkylation method, ketones 3.20 and 3.27 were prepared from ketone 3.16 in an overall yield of 89% and 87%, respectively, and with excellent enantioselectivity (er = 99:1). This compares favorably to the only other reported asymmetric synthesis of these ketones using the SAMP and RAMP auxiliaries, shown above (Scheme 42).
3.1.3 Conclusion

In conclusion, we completed the asymmetric formal synthesis of both (R)- and (S)-stigmolone employing our ACC mediated α,α-bisalkylation method to set the C5 stereogenic center. The precursors to (R)- and (S)-stimolone were synthesized in 87% and 89% overall yield respectively and each with a enantioselectivity $er >99:1$. Both of these compounds have been shown to undergo cobalt-mediated oxidation to give either (R)- or (S)-stigmolone. This synthesis compares favorably to the only other reported asymmetric synthesis of these compounds, using the SAMP/RAMP chiral auxiliaries which gave (R)-stigmolone in 6.4% overall yield and 89% ee and (S)-stigmolone in 20% overall yield and 93% ee.

3.2 Asymmetric Total Synthesis of Apratoxin D

3.2.1 Background and Introduction

3.2.1.1 Isolation and Biological Activity

Apratoxins A-E (3.28-3.32, Figure 20) are a family of cyclic depsipeptides isolated from the *Lyngbya* species of cyanobacteria. Not only do these natural products possess novel and synthetically challenging structural motifs, but they are also compelling targets to study on the basis of their biological activity. It has been shown that apratoxin A exhibits a potent (low nanomolar) inhibition of cancer cell growth by inducing G1 phase cell cycle arrest and apoptosis. The apratoxins are of mixed biogenetic origin, containing both polyketide and polypeptide fragments.
Apratoxin A (3.28) was isolated from the marine cyanobacterium *Lyngbya majuscula* in Guam by Moore, Paul, and co-workers. Apratoxins B and C, were isolated one year later from further collections of the cyanobacteria. These naturally occurring analogues differ only slightly from apratoxin A, with apratoxin B lacking a N-methyl group on the isoleucine residue and apratoxin C containing an isopropyl group in place of the tert-butyl group at C39. Apratoxin A shows potent in vitro cytotoxicity against both KB (0.52 nM) and LoVo (0.36 nM) cell lines, but was poorly tolerated in mice, mainly due to lack of selectivity. Apratoxins B (3.29) and C (3.30) both displayed weaker cytotoxicity than A; however, while C closely approached the IC₅₀ value of apratoxin A, apratoxin B showed significantly less activity. These differences in activity
indicate that the tert-butyl group is not essential for cytotoxicity, as replacing it with the somewhat less sterically demanding isopropyl group has a minimal effect on activity.\textsuperscript{73} In addition, the substantial difference in activity exhibited by apratoxin B indicates that the N-methyl group at the isoleucine residue might be necessary for cytotoxic activity.

Apratoxin E (3.32) was isolated from the marine cyanobacterium \textit{Lyngbya bouillonii} in 2008.\textsuperscript{75} Like apratoxin A, this compound contains the N-methylated isoleucine as well as the tert-butyl group at C39. However, compared to A, apratoxin E is unsaturated at the C34–C35 bond alpha to the thiazoline moiety and lacking a methyl group at C34. In addition, the modified cysteine residue is fully saturated at C28–C29 and lacks a C28 methyl group. When tested for activity against several human cancer cell lines including HT29 colon adenocarcinoma, HeLa cervical carcinoma, and U2OS osteosarcoma cells, apratoxin E exhibited strong cytotoxicity (21-72 nM); however, this was 5- to 15-fold less active than apratoxin A (1.4-10 nM).\textsuperscript{75}

Apratoxin D (3.31) was isolated from two species of cyanobacteria, \textit{L. majuscula} and \textit{L. sordida} in 2008.\textsuperscript{74} Structural analysis revealed that apratoxin D has the same sequence of amino acid residues as A and C, but its polyketide moiety is longer than that of the other apratoxins. Apratoxin D showed potent in vitro cytotoxicity against H-460 human lung cancer cells with an IC\textsubscript{50} value of 2.6 nM. This activity is nearly the same as apratoxin A, indicating that the activity of the compound is not negatively impacted by the longer alkyl group at C39. This suggests that the C39 alkyl chain can potentially be
varied in the design of structural analogues to improve activity or provide insight into
the mechanism of action of this family of compounds. Significantly, the H-460 cell line is
representative of non-small cell lung cancer (NSCLC), which is a class that is relatively
unresponsive to current chemotherapeutics, making the study and development of new
potential therapeutics of the utmost importance.

The extremely promising biological activity of the apratoxins, as well as the small
amounts available via isolation from natural sources, make them very compelling lead
compounds for the development of anti-tumor drugs via asymmetric total synthesis. By
developing synthetic routes to these newly isolated compounds (apratoxins D and E), as
well as structurally modified versions, we can probe the mechanism of action to fully
develop their biomedical potential. The following project focuses on the total synthesis
of apratoxin D via two different approaches, both of which employ an ACC mediated,
asymmetric α,α-bisalkylation to set the insulated C37 stereocenter.

3.2.1.2 Prior Synthetic Work

Three total syntheses of apratoxin A have been reported, one each by Forsyth,77-78
Takahashi,79 and Ma.80 As outlined in Scheme 44, apratoxin A could logically be
disconnected to yield tetrapeptide 3.33 and the thiazoline containing polyketide (3.34).
However, one strategy common to all three syntheses for merging the peptide and
polyketide domains is the early incorporation of the proline residue as the C39 ester
(3.36). This strategy was utilized in anticipation of a higher yielding amide formation
between the isoleucine carboxylate of tripeptide 3.35 and proline amine moieties in comparison to the condensation between the proline carboxylate of 3.33 and the hindered C39 hydroxyl of 3.34. Also common to the three prior syntheses is the late stage assembly of the thiazoline moiety, which is oxidatively sensitive and potentially prone to unwanted side reactions. While the tripeptide (3.35) can theoretically be accessed in a relatively straightforward way using standard peptide synthesis procedures, the polyketide and thiazoline portions of the molecule present a significant synthetic challenge, necessitating the development of new strategies for their synthesis.
Forsyth’s strategy for constructing the sensitive thiazoline moiety was a one-pot Staudinger reduction/intramolecular aza-Wittig of an α-azido thioester (Scheme 45). Exposure to Ph₃P generated the phosphinimine from the azide in situ, which could then undergo the aza-Wittig with the adjacent carbonyl of the thioester to generate the thiazoline.⁷⁸,⁸¹-⁸²

Scheme 44. Retrosynthetic Analysis of Apratoxin A
This strategy for thiazoline formation required an advanced intermediate containing the essential α-azido thioester (Scheme 45, compound 3.37). Advanced intermediate 3.37 was constructed from triamide 3.39 and polyketide 3.38 (see below).

As outlined in Scheme 46, the synthesis of 3.38 began with acylation of compound 3.40 with acrylic acid yielding diene 3.41. Ring closing metathesis of 60 gave an α,β-unsaturated δ-valeryl lactone, which upon methyl cuprate addition provided the C37 methyl group in 3.42. The lactone was then reductively opened and the primary alcohol was TBS-protected to give secondary alcohol 3.43. The hydroxyl group was then esterified with N-Boc-L-proline under Yamaguchi conditions followed by TBS group removal and oxidation of the resulting primary alcohol (3.45) to the aldehyde (3.46). An anti-selective aldol reaction of aldehyde 3.46 with (R)-2-benzoyloxy-3-pentanone (3.47) provided β-hydroxy ketone 3.48. Compound 3.48 was TBS protected.
and the benzoyloxy-containing functionality was removed to give the target compound (3.50), the TBS protected version of fragment 3.38.

Scheme 46. Synthesis of Compound 3.50

The triamide (3.35) was assembled in a C→N fashion beginning with isoleucine derivative 3.51 (Scheme 47). Compound 3.51 was deprotected and coupled with Boc-protected N-methyl-L-alanine to yield compound 3.53. Boc removal followed by a second PyAOP-mediated condensation with tyrosine derivative 3.54 gave triamide 3.35.

Scheme 47. Synthesis of Tripeptide 3.35
To carry out the intended Staudinger reduction/aza-Wittig strategy for thiazoline formation, triamide 3.35 had to be joined with modified cysteine surrogate 3.55 to form 3.56, which was converted to thiol 3.39 in a stepwise fashion (Scheme 48). Thioester formation between 3.39 and 3.50 followed by deprotection of the C30 hydroxyl and treatment with diphenyl phosphoryl azide under Mitsunobu conditions yielded azido thioester 3.60. Because their attempts to remove the C35 TBS group at the ultimate stage of the total synthesis were unsuccessful, this protecting group was switched to a TES group at the stage of compound 3.60 to give 3.61. Thiazoline formation was then carried out using Ph₃P giving compound 3.62. Conversion of N-Boc protected compound 3.62 to the silyl carbamate followed by selective desilylation gave compound 3.64. Saponification of the isoleucine methyl ester and macrolactam formation afforded cyclic depsipeptide 3.64. TES group removal yielded apratoxin A (3.28).
Scheme 48. Convergent Synthesis of Apratoxin A

Both Takahashi and Ma assembled the thiazoline unit using a tandem deprotection/cyclodehydration strategy (Scheme 49). This strategy required the coupling of carboxylic acid 3.38 with modified cysteine 3.69 to form the trityl protected thiol amide 3.68.
Scheme 49. Thiazoline Formation via Tandem Deprotection/Cyclodehydration

Takahashi approached the synthesis of fragment 3.38 starting with compound 3.70, the product of a proline-catalyzed aldol reaction between acetone and pivaldehyde (Scheme 50). MPM protection followed by subsequent allylation and acetylation provided 3.71. Palladium(II)-catalyzed isomerization of allylic acetate 3.71 and removal of the acetyl group gave alcohol 3.72, which was asymmetrically hydrogenated to set the C37 stereocenter (compound 3.73). Alcohol 3.73 was then oxidized to the aldehyde and subjected to a Paterson\textsuperscript{88} anti-aldol reaction to set stereocenters C34 and C35, as Forsyth did. The resulting aldol product was TBS protected to give 3.75. Removal of the MPM group followed by Yamaguchi coupling\textsuperscript{86} with N-Boc-Pro-OH provided compound 3.75. As with Forsyth’s method, removal of the benzoate and oxidative cleavage of the resulting α-hydroxy ketone provided acid 3.49, as previously reported.\textsuperscript{77}
To prepare the modified cysteine residue (3.78), Takahashi converted the corresponding S-Trt-N-Boc-D-cysteine to its aldehyde via the Weinreb amide and then Wittig olefination was carried out on the aldehyde. Hydrolysis of the ethyl ester, allyl ester formation, and selective deprotection of the N-Boc group provided modified cysteine residue (3.78).

Scheme 50. Takahashi Synthesis of Comound 3.50

Condensation of modified cysteine residue 3.78 and acid 3.50 was followed by stepwise conversion of 3.79 into the corresponding 2,2,2-trichloroethoxycarbonyl (Troc) ester 3.80. Thiazoline formation was then carried out via treatment of 3.80 with Ph3P(O)/TfO. The
Troc group was then removed followed by conversion of the allyl ester to the acid to afford compound 3.83 (Scheme 52).

Scheme 52. Takahashi Synthesis of 3.83

Tripeptide 3.84, prepared by sequential coupling of N-methylisoleucine allyl ester with N-Boc-N-methylalanine and N-Fmoc-O-methyltyrosine by repeated treatment with HATU-DIEA and ultimately Et$_2$NH in acetonitrile, was coupled to fragment 3.83 providing compound 3.85 (Scheme 53). Cleavage of the allyl ester and removal of the Fmoc group afforded compound 3.86, which was treated with HATU/DIEA to promote macrolactamization yielding apratoxin A (3.28).
Scheme 53. Takahashi Synthesis of Apratoxin A

Because Ma’s synthesis of apratoxin A employed the same strategy for thiazoline formation as Takahashi’s synthesis, the initial target was fragment 3.93 (Scheme 54). Their synthesis of fragment 3.93 began with the same proline-catalyzed aldol product (3.69) as used by Takahashi. This compound was TBS protected, reduced, and eliminated via its mesylate to give allyl ether 3.87. This compound was then converted to $\alpha,\beta$-unsaturated lactone 3.88, which was treated with a methyl cuprate to form 3.42, setting the C37 stereocenter as Foryth did.$^{77}$ The lactone was reduced and protected as the diester with acetyl chloride, which was selectively deprotected to form the primary alcohol. The alcohol was oxidized to aldehyde 3.89, which was subjected to an anti-aldol using Oppolzer’s sultam methodology to give 3.90.$^{69}$ Treatment with LAH removed both the auxiliary and the acyl group yielding a triol, which was protected with DMP to provide alcohol 3.91. The Boc-protected proline was installed via Yamaguchi esterification,$^{86}$ as with the other two syntheses, giving 3.92. The diol was liberated, and the primary alcohol was selectively oxidized using the bulky chloro oxammonium salt
generated from TEMPO/NaClO to give an aldehyde, which was subsequently oxidized to acid 3.93.

Scheme 54. Ma Synthesis of Fragment 3.93

The modified cysteine unit (3.94) was prepared using the same conditions as outlined in Takahashi’s synthesis, but starting with Fmoc protected cysteine as opposed to the Boc-protected cysteine and generating the prenyl ester rather than the allyl ester. This modified cysteine (3.94) was coupled to the carboxylic acid (3.93), and the thiazoline was formed under the same conditions employed by Takahashi.
Scheme 55. Ma Synthesis of Thiazoline

Fragment 3.96 was then coupled with tripeptide 3.97. Subsequent cleavage of the Fmoc and TMSE protecting groups yielded the cyclization precursor 3.98. Macrolactamization followed by acyl group removal resulted in Apratoxin A (3.28) (Scheme 56).

Scheme 56. Ma Synthesis of Apratoxin A

3.2.2 Retrosynthetic Analysis

We planned to synthesize apratoxin D (3.31) in a convergent manner as outlined in Scheme 57. Based on the prior synthetic work on apratoxin A, we intended to incorporate the proline residue in the polyketide fragment (3.99) and carry out the macrolactamization between the proline amine and the isoleucine carboxylate. By analogy to earlier work, this strategy would presumably be advantageous over
macrolactone formation involving the proline carboxylate and sterically hindered C39 hydroxyl. Since tripeptide 3.35 is known, our target becomes fragment 3.99. We envisioned disconnecting polyketide 3.99 into fragment 3.100 and cysteine-derived intermediate 3.101, which could later be joined via Kelly’s thiazoline formation procedure, recently utilized in the synthesis of apratoxin A.

Scheme 57. Retrosynthetic Analysis of Apratoxin D

The focus of the work that follows will be two different approaches to the synthesis of polyketide 3.100, both employing an asymmetric α,α-bisalkylation via our ACC auxiliaries to set the key C37 stereocenter.

3.2.2.1 Retrosynthesis of Polyketide 3.99 Involving Chiral Aldehyde 3.102

In the first approach, fragment 3.100 would be synthesized via a syn-selective aldol addition to set the C39–C40 stereochemistry, followed by an anti-aldol to set the C34 and C35 stereogenic centers. We also looked to utilize the first aldol addition as a
means to introduce the challenging C41 t-butyl group via the recently developed Terao-Kambe coupling, following conversion of the C41 carboxylate moiety into a tosylate.

![Scheme 58. Retrosynthesis of Apratoxin D Leading to Chiral Aldehyde 3.102](image)

At this stage we were faced with the synthesis of aldehyde 3.102 and needed to consider setting the insulated C37 stereocenter, which we believed could be achieved using our ACC α,α-bisalkylation methodology. In addition to serving as an interesting synthetic application of our method, this approach would allow for the introduction of a variety of substituents at the C37 position, setting the stage for future SAR studies.

### 3.2.2.2 Retrosynthesis of Polyketide 3.99 with Key Late Stage α,α-Bisalkylation

In our second approach, we again planned to employ the Terao-Kambe coupling to introduce the C41 t-butyl moiety, as well as an anti-aldol to set the C34 and C35 stereochemistry, giving 3.105 (Scheme 59). At this stage, we again focused on the setting of the C37 stereocenter, this time using a late stage ACC α,α-bisalkylation of hydrazone 3.106, derived from advanced ketone 3.107. In order for this approach to be successful,
we would have to select an alkylating agent that could serve as the masked C35 aldehyde, as well as a protecting group for the C39 hydroxyl that would be compatible with the alkylation sequence, while at the same time being able to be removed orthogonally to the masked aldehyde moiety.

Scheme 59. Retrosynthetic Analysis of Apratoxin D Employing Late Stage ACC α,α-Bisalkylation of 3.107

This approach would be particularly challenging as it would require the ACC auxiliary be able to impart high levels of stereoselectivity in the alkylation of a ketone possessing multiple stereogenic centers, including an α'-hydroxyl group. Additionally, we would have to be able to remove the auxiliary from the sterically hindered, tetrasubstituted hydrazone after the bisalkylation, without causing epimerization at the α-, or the even more sensitive α'-stereocenter.
3.2.3 Synthesis of Chiral Aldehyde 3.102

3.2.3.1 ACC α,α-Bisalkylation

To begin the synthesis of chiral aldehyde 3.102, ACC 1.72 was condensed with benzyloxyacetone to give the desired hydrazone (2.84) as an 85:15 mixture of E:Z diastereomers (Scheme 60). The diastereomers were separable via column chromatography to yield exclusively the E-diastereomer (See Experimental). At this stage, regioselective α,α-bisalkylation of 2.84 was required, setting the C37 stereocenter and introducing our masked C35 aldehyde moiety. This was a particularly challenging application of our ACCs and CIS-D, as regioselective alkylation would require that CIS-D completely override the inherent selectivity for LDA to deprotonate at the considerably more acidic α’-protons. However, as discussed previously in Section 2.2.5, we had successfully demonstrated that our ACC auxiliaries were able to override this preference of LDA and facilitate the α,α-bisalkylation of 2.84 in high yield and diastereoselectivity (Scheme 60). We were able to repeat this bisalkylation sequence using methyl iodide and allyl bromide, producing upwards of 1g of 2.87, wherein the allyl moiety could later be oxidized to the necessary C35 aldehyde.

Scheme 60. α,α-Bisalkylation of Benzyloxy Acetone via ACC 1.72
3.2.3.2 Hydrazone Removal

With bisalkylated hydrazone 2.87 in hand, we were faced with the challenge of removing the auxiliary to eventually gain access to compound 3.108, possessing a methylene at C38 (Scheme 61).

**Scheme 61. Required Reduction of 2.87 with C38 Hydrazone to 3.108 with C38 Methylene**

Our first approach focused on the formation of dithiane 3.109, which could then be reduced to give 3.108. Reduction with Raney Ni was possible, but competing alkene reduction was a concern. Based on literature precedent, we hoped to be able to tune the reactivity of our Raney Ni in order to effect reduction of the dithiane while not affecting the allyl group.\(^{90-91}\) Alternative methods for dithiane reduction, which could be more compatible with the allyl moiety, include radical mediated cleavage with Bu₃SnH/AIBN,\(^ {92-93}\) as well as hydride reduction involving LiAlH₄, ZnCl₂ and CuCl₂.\(^ {94}\)

Based on previous success in our lab involving the direct conversion of ACC hydrazones to dithianes,\(^ {31, 95}\) we initially attempted to form the dithiane directly from hydrazone 2.87. Unfortunately, treatment of 2.87 with ethanedithiol and BF₃•OEt₂ was never successful in giving a high yield of 3.109, and gave only recovered starting material in addition to the formation of unidentified byproducts (Scheme 62).
Scheme 62. Attempted Direct Formation of Dithiane from 2.87

We therefore turned our attention to hydrolysis of 2.87 to the ketone, which could then be transformed to the dithiane. Due to a related study on Lewis acid promoted deprotection of a benzyl ether that we were conducting, we were prompted to try BF$_3$•OEt$_2$, rather than our standard p-TsOH•H$_2$O, for the hydrolysis of 2.87. We hypothesized that, due to the presence of the proximal hydroxyl group, the BF$_3$•OEt$_2$ would form a 5-membered chelate with the α'-hydroxyl as well as the lone pair on sp$^2$-N of the hydrazone, thus promoting attack of H$_2$O at the hydrazone carbon (Scheme 63).

Scheme 63. BF$_3$•OEt$_2$ Mediated Hydrolysis of Hydrazone 2.87

Gratifyingly, treatment of 2.87 with BF$_3$•OEt$_2$ in acetone-H$_2$O (4:1) gave 96% yield of the desired ketone with no epimerization at the α-stereocenter. These conditions have also been applied in the context a simple 3-pentanone derived hydrazone, however the reaction time is significantly longer (24 h), likely due to the lack of an α’-oxygen as a second coordinating group.
3.110 could then be converted to dithiane 3.109 under standard conditions in high yield (Table 23). However, it is worth noting that if the dithiane formation proceeded overnight, reduction of the allyl group to the alkane was also observed. Unfortunately, all attempts to remove the dithiane via the aforementioned methods were unsuccessful (Table 23). As a result, we turned our attention to other possible methods of deoxygenation.

![Chemical structure](image)

**Table 23. Attempted Dithiane Reduction of 3.109**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time (h)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Raney Ni, EtOH&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14</td>
<td>Recovered SM</td>
</tr>
<tr>
<td>2</td>
<td>Bu₃SnH, AIBN, 80 °C</td>
<td>2</td>
<td>Recovered SM</td>
</tr>
<tr>
<td>3</td>
<td>CuCl₂, ZnCl₂, LiAlH₄</td>
<td>6</td>
<td>Recovered SM</td>
</tr>
</tbody>
</table>

<sup>a</sup>Same result with multiple sources of Raney Ni

### 3.2.3.3 Deoxygenation

Due to the unsuccessful attempts at dithiane reduction, we turned our attention to other deoxygenation methods. Several such methods are known, primarily involving conversion of the ketone to the tosyl hydrazone followed by NaCNBH₃ reduction,<sup>96-98</sup> Wolff-Kishner reduction,<sup>99</sup> or Clemmenson reduction.<sup>100-101</sup> The Clemmenson was ruled out due to the harshly acidic conditions required. Both the Wolff-Kishner and the use of NaCNBH₃ were not viable options, as both proceed via formation of a carbanion at the carbonyl carbon, which could potentially eliminate the α‘-hydroxyl group.
Therefore, we first looked at a direct deoxygenation method employing ZnI₂ and Et₃SiH, however, this yielded only starting material despite several attempts (Scheme 64).

Scheme 64. Attempted Direct Deoxygenation of 3.110

Next, we explored hydride reduction of the ketone to the alcohol followed by derivatization. There are numerous methods for the deoxygenation of secondary alcohols, including the radical-based Barton-McCombie deoxygenation,¹⁰²⁻¹⁰³ involving derivatization as the xanthate followed by treatment with a tin hydride, or Super-Hydride reduction following transformation to the tosylate or mesylate.¹⁰⁴⁻¹⁰⁶ Due to the well-established issues associated with purification of tin-mediated reactions,¹⁰⁷ we decided to first explore the Super-Hydride methods.

Treatment of 3.110 with LiAlH₄ for 1 h gave alcohol (3.111), as a mixture of diastereomers, in 89% yield (Scheme 65). Conversion to either the tosylate (3.112) or mesylate (3.113) under standard conditions proceeded in moderate yield, setting the stage for Super-Hydride reduction. Unfortunately, treatment of either 3.112 or 3.113 with LiEt₃BH in THF gave only recovered starting material.
Scheme 65. Attempted Deoxygenation via Super-Hydride Reduction

We then turned our attention to the radical-mediated Barton-McCombie deoxygenation. This requires prior transformation of the alcohol to the xanthate via the Chugaev Reaction, involving sequential treatment of the alcohol with NaH, followed by excess carbon disulfide, and finally methyl iodide. Upon treatment with $n$-Bu$_3$SnH in the presence of a radical initiator such as AIBN, the xanthate$^{108}$ can be used to deoxygenate the alcohol via the aforementioned Barton-McCombie reaction. This radical based method is very useful in the context of sterically hindered secondary alcohols as the carbon-oxygen bond is cleaved homolytically and avoids the rearrangements associated with carbocation intermediates. Additionally, the reaction is run under relatively neutral conditions, thus avoiding any potential epimerization.

Alcohol 3.111 was subjected to the Chugaev conditions, giving xanthate 3.114 in near quantitative yield (Scheme 66). Gratifyingly, treatment of 3.114 with Bu$_3$SnH and AIBN in refluxing toluene for 14 h resulted in complete conversion to 3.108.
Scheme 66. Barton-McCombie Deoxygenation of 3.111 via Xanthate 3.114

Unfortunately, 3.108 was contaminated with a large amount of tin residues, which as mentioned previously, are extremely challenging to remove via standard purification methods. Numerous approaches to tin purification have been introduced, including polymer-supported,\(^{109-111}\) flourinated tin reagents,\(^{112-113}\) a range of functionalized tin compounds which can hydrolyzed and removed upon work up,\(^{107,114-115}\) and modified silica gel preparations\(^{116-117}\) which aid in their removal chromatographically. Rather than spend additional time synthesizing any of the functionalized tin compounds, many of which require numerous steps, we began with the silica gel preparations in order to attempt to remove the tin chromatographically (Table 24, entries 1, 2).

Table 24. Removal of Tin Residues from 3.108

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10% w/w powdered KF in silica gel</td>
<td>No removal of tin residues</td>
</tr>
<tr>
<td>2</td>
<td>10% w/w powdered K(_2)CO(_3) in silica gel</td>
<td>No removal of tin residues</td>
</tr>
<tr>
<td>3</td>
<td>NaCNBH(_3), MeOH, (\Delta) prior to purification</td>
<td>Complete removal of tin upon silica gel chromatography</td>
</tr>
</tbody>
</table>
Using powdered KF as an additive to the silica gel in a 10% w/w ratio resulted in no improvement in separation.\textsuperscript{117} Alternatively, powdered K$_2$CO$_3$ was added, also in a 10% w/w ratio, again with no change in the separation upon chromatography.\textsuperscript{116} At this time we discovered a procedure reporting that subsequent treatment of Bu$_3$SnH reactions with NaCNBH$_3$ prior to purification leads to facile removal of any tin contaminants.\textsuperscript{118} This is due to the fact that the tin impurities that are difficult to remove are in fact byproducts of the reduction reaction, and converting them back to Bu$_3$SnH with NaCNBH$_3$ drastically simplifies purification. Gratifyingly, treatment of the crude deoxygenation reaction with NaCNBH$_3$ in MeOH and refluxing for 3 h, followed by silica gel chromatography (Hexanes → 10% EtOAc/Hex) led to 3.108, free of any tin contaminants.

\textbf{3.2.3.4 Synthesis Completion}

Having successfully synthesized 3.108, the final step required oxidation of the allyl moiety to the required aldehyde. The most common approaches to this type of oxidation are either ozonolysis or Lemieux-Johnson oxidation. We chose to avoid ozonolysis as it can also facilitate oxidation at the benzylic position of benzyl ethers. The Lemieux-Johnson oxidation involves treatment of the alkene with catalytic osmium tetroxide and stoichiometric $N$-methyl morpholine oxide to generate the diol, followed by treatment with sodium periodate to cleave the diol and give the desired carbonyl moiety. Happily, subjecting 3.108 to the Lemieux-Johnson oxidation resulted in
complete conversion to 3.102 in good yield, completing the synthesis of aldehyde 3.102 (Scheme 67A). In order to establish that we indeed had the desired configuration at the C37 stereocenter, optical rotation data was acquired. 3.102 was found to have an optical rotation of $-4.55$ in CHCl$_3$ at 25.3 °C and 1.073 mg/mL, compared to a literature value of $-4.5$ in CHCl$_3$ at 25 °C and 1.00 mg/mL,$^{119}$ confirming that not only did we have the correct enantiomer, but we had synthesized it with an extremely high level of enantiopurity.

Scheme 67. A. Completed Synthesis of Fragment 3.102. Use of 3.102 in Evans’ Aldol

Working with another member of the lab, this aldehyde was then used in the asymmetric Evans’ syn-aldol reaction to generate 3.116 in 83% yield, which could be transformed to fragment 3.100 in 11 steps (Scheme 67B).
3.2.4 Synthesis of Polyketide 3.99 via Advanced Ketone 3.107

3.2.4.1 Asymmetric $\alpha,\alpha$-Bisalkylation

As a second approach to polyketide 3.100, we planned to utilize an ACC asymmetric $\alpha,\alpha$-bisalkylation of advanced ketone 3.107 possessing numerous stereogenic centers. The synthesis of this ketone had already been established by several previous members of the lab, resulting in PMB-protected $\alpha'$-hydroxy ketone 3.123 (Scheme 68).

The synthesis of 3.123 begins with acyl oxazolidinone 3.115, which is subjected to an Evans' syn-aldol to yield 3.117, followed by treatment with LiBH$_4$ to yield diol 3.118. Chemoselective PMB-protection of the secondary alcohol was achieved via a two-step process, requiring formation of acetal 3.119 and subsequent DIBAL-H reduction to give 3.120. In order to achieve the challenging incorporation of the $t$-butyl moiety we employed the Terao-Kambe cross-coupling reaction, which required prior formation of tosylate 3.121, followed by copper-catalyzed addition of $t$-BuMgCl in the presence of catalytic (10 mol%) 1-phenyl-1-propyne ($3.121 \rightarrow 3.122$). Finally, Lemieux-Johnson oxidation of 3.122 yielded the desired PMB-protected ketone 3.123. For the purposes of this work, a small amount of the advanced ketone (3.123) had already been synthesized and that material was sufficient to complete the portion of this work focusing on the PMB-derivative.
Scheme 68. Synthesis of Advanced Ketone 3.123 with PMB-Protected Alcohol

With the necessary ketone in hand, we needed to effect hydrazone formation with ACC 1.73. During the course of our mechanistic investigation into the ACC auxiliaries (Section 1.3.2), we had found that in systems possessing at least two substituents at the α'-position, that the simpler phenylalanine derived ACC 1.73 gave $dr > 99:1$ (Scheme 69). Therefore, we felt that 1.73 could be applied in the context of this synthesis.

Scheme 69. Use of ACC 1.73 in Systems with Two α'-Substituents
Due to the ketone (3.123) possessing a stereogenic center at the α'-position, an added challenge was introducing the ACC auxiliary without causing epimerization at that center. Fortunately, a prior member of our group had already conducted a thorough screening of conditions to facilitate hydrazone formation without epimerization, finding that catalytic p-TsOH•H₂O (5 mol%) and 5 equiv. of MgSO₄ in CH₂Cl₂ gave the desired hydrazone in 87% yield (Scheme 70).

![Scheme 70. Formation of Hydrazone 3.124](image)

**Scheme 70. Formation of Hydrazone 3.124**

We were now able to explore the α,α-bisalkylation sequence of hydrazone 3.124. In the context of the monoalkylation, there was the potential issue of epimerization at the α'-center, as well as potentially low conversion in such a sterically hindered system. To address these issues we pulled from our work on the α,α,α',α'-tetraalkylation of acetone (Section 2.4). In those systems, an α'-stereocenter was also present, albeit consisting of only alkyl substituents, and no epimerization was observed. Additionally, we knew that in order to facilitate complete formation of the azaenolate in systems with two α'-substituents, warming to 0 °C during deprotonation is necessary. Therefore, as a first test, we utilized 3 equiv. of LDA, with warming at 0 °C for 1 h, followed by the additional of 5 equiv. of MeI (Scheme 71). While these conditions did produce the desired product (3.125), they also resulted in a large amount of bismethylated material.
(3.126), resulting in only a 70% yield. Therefore, both the amounts of LDA and of MeI were reduced (2 equiv. and 3 equiv. respectively), which gave an increased yield of 85% for the monomethylated compound 3.125.

**Scheme 71. Methylation of Hydrazone 3.124**

It is worth noting, however, that further lowering of either the amounts of LDA or MeI results in residual starting material, which is inseparable from the desired product using chromatography. We were able to determine that no detectable epimerization at the $\alpha'$-carbon was occurring, as judged by $^1$H-NMR.

Next, the $\alpha,\alpha$-bisalkylation was attempted. The additional challenge in this transformation was the need to impart high levels of stereoselectivity in the presence of the $\alpha'$-stereocenter. Additionally, in this step, we had to incorporate what would serve as the masked C35 aldehyde moiety. Initially, we looked at the use of allyl bromide, which had proven successful in other ACC-mediated alkylations and could later be converted to the aldehyde via a Lemieux-Johnson oxidation. Treatment of the hydrazone with 2 equiv. of LDA and warming to 0 °C for 1 h gave the azaenolate, followed by recooling to −78 °C and addition of 3 equiv. of allyl bromide (Scheme 72).
This solution was then stirred at room temperature for 2 h to give the desired \( \alpha,\alpha \)-bisalkylated compound in 80% yield.

![Scheme 72. Asymmetric \( \alpha,\alpha \)-Bisalkylation of Hydrazone 3.125](image)

As mentioned earlier, the diastereoselectivity of the alkylation was a concern, as there was a potential for a match/mismatch relationship between the configuration at the \( \alpha' \)-stereocenter and that of the auxiliary. However, examination of both the \( ^1\text{H}\text{-NMR} \) and \( ^{13}\text{C}\text{-NMR} \) of the bisalkylated compound showed a single diastereomer.

### 3.2.4.2 Hydrolysis

With the desired \( \alpha,\alpha \)-bisalkylated hydrazone in hand, we needed to hydrolyze the hydrazone to liberate the ketone. The challenge here was the presence of both \( \alpha \)- and \( \alpha' \)-stereocenters, as well as high steric bulk, which had proven problematic in the hydrolysis of other tetraalkylated ACC hydrazones. An initial attempt using our original hydrolysis conditions, 2 equivalents \( p\text{-TsOH}\cdot\text{H}_2\text{O} \) in acetone, gave 40% conversion to the desired ketone after 40 h, but with a significant amount of epimerization (Table 25).
We therefore looked to our modified conditions, \( p\)-TsOH\( \cdot \)H\(_2\)O in acetone-H\(_2\)O (4:1) but unfortunately no conversion to the ketone was observed. We therefore examined the possibility of removing the protecting group on the \( \alpha' \)-hydroxyl in order to reduce the steric bulk of the hydrazone.

### 3.2.4.3 Protecting Group Investigation

Prior work in the lab had reported that removal of the PMB-group with DDQ in a simple model system (3.129) resulted in both deprotection of the alcohol and hydrolysis of the ketone via the mechanism proposed in Scheme 73.\(^{95}\) It has been found that the presence of a proximal hydroxyl group to the site of DDQ deprotection can lead to attack of the alcohol lone pair on the intermediate oxonium ion to generate an acetal.\(^{120}\)
Scheme 73. DDQ Deprotection and Concomitant Hydrolysis of Model ACC Hydrazone 3.129

In the case of ACC hydrazone 3.129, we had hypothesized that the nitrogen lone pair of the ACC hydrazone was acting in an analogous fashion, leading to a 5-membered cyclic intermediate which could break down to liberate the hydrolyzed ketone as well as anisaldehyde-derived hydrazone 3.133. However, in the context of the advanced hydrazone 3.127, it was found that only deprotection of the hydroxyl occurred with no hydrolysis (Scheme 74A).

**A. Preliminary Result of DDQ Deprotection of 3.127**

3.127 \[ \text{ACC} \] \[ \text{PMB} \] \[ \text{DDQ, DCM-H}_2\text{O (10:1)} \] \[ 80\% \text{ yield} \] \[ 3.134 \]

**B. Attempts to Repeat DDQ Deprotection of 3.127**

3.127 \[ \text{ACC} \] \[ \text{PMB} \] \[ \text{DDQ, DCM-H}_2\text{O (10:1)} \] \[ 15\% \text{ yield} \] \[ 3.134 \] + Unidentified Byproducts

Scheme 74. Attempted DDQ Deprotection of 3.127
Unfortunately, attempts to repeat these results in the context of hydrazone 3.127 were not successful, resulting in significant losses of material and only minimal desired product (Scheme 73B). As a result, we turned to model system hydrazone 3.135 and screened PMB-removal conditions (Table 26). While we were able to repeat the previously observed deprotection and hydrolysis result using a variety of DDQ conditions, this result was not useful, as we knew it would not translate to the advanced hydrazone. Unfortunately, despite screening a variety of other conditions including I$_2$ in MeOH,$^{121}$ CAN,$^{122}$ and TMSCl and SnCl$_2$ with anisole,$^{123}$ no deprotection of the alcohol was observed.

**Table 26. Screening Conditions for Deprotection of PMB-Hydroxyl**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DDQ, DCM:H$_2$O</td>
<td>0 to rt</td>
<td>16</td>
<td>Deprotection and Hydrolysis$^a$</td>
</tr>
<tr>
<td>2</td>
<td>DDQ, DCM: pH 7 phosphate buffer</td>
<td>0 to rt</td>
<td>16</td>
<td>Deprotection and Hydrolysis$^a$</td>
</tr>
<tr>
<td>3</td>
<td>I$_2$(1%), MeOH</td>
<td>reflux</td>
<td>16</td>
<td>Multiple Compounds</td>
</tr>
<tr>
<td>4</td>
<td>CAN, CH$_3$CN:H$_2$O</td>
<td>rt</td>
<td>2</td>
<td>SM and Unknown Byproduct</td>
</tr>
<tr>
<td>5</td>
<td>TMSCl, SnCl$_2$, Anisole, DCM</td>
<td>rt</td>
<td>2</td>
<td>SM and Unknown Byproduct</td>
</tr>
<tr>
<td>3</td>
<td>DDQ, LiCl, DCM: pH 7 phosphate buffer</td>
<td>0</td>
<td>16</td>
<td>Deprotection and Hydrolysis$^a$</td>
</tr>
</tbody>
</table>

$^a$This result does not translate to hydrazone 3.127

It was therefore determined that we would need to alter the ketone synthesis to introduce a different protecting group. Silyl protecting groups such as TBS or TES were
not viable options as prior work had already established that in those systems, the hydrazone alkylations did not proceed in high yield.\textsuperscript{95} We therefore turned to the use of the benzyl protecting group, which could be introduced in an analogous manner to that used for the PMB-group, and possessed similar steric bulk so it was likely to not interfere with the hydrazone alkylations. While we note that the most common method for benzyl group removal is hydrogenolysis, which would be incompatible with our allyl moiety, we felt that, based on the variety of other benzyl removal conditions available, as well as the diversity of alkylating agents which could fill the role of our masked aldehyde, that we would be able to find an agreeable combination that would allow us to advance in our synthesis.

In order to alter the protecting group from \textit{p}-methoxybenzyl to benzyl, the synthesis of the advanced ketone \textbf{3.123} needed to only be slightly modified. At the stage of the acetal formation and subsequent reduction, the use of a benzylidene acetal allowed for facile introduction of the desired benzyl group (Scheme 75). This synthesis has been completed to give \textasciitilde{}3 g of Bn-protected ketone \textbf{3.139}. Hydrazone formation to give \textbf{3.140} and subsequent methylation went smoothly under the same conditions as used for PMB-ketone \textbf{3.123} to give \textbf{3.141}. 
Scheme 75. Synthesis of Bn-Protected Hydrazone 3.140

Before screening alternative alkylating agents or benzyl removal conditions, we hoped that perhaps upon changing protecting groups, hydrolysis of 3.142 without deprotection may be possible. 3.141 was therefore allylated, which went smoothly to produce 3.142 in 83% yield (Scheme 75). Unfortunately, as with the p-methoxybenzyl system, no conversion to the ketone was observed using p-TsOH•H₂O, acetone/H₂O (4:1) (Table 27). However, we also tried our recently discovered BF₃•OEt conditions, and while the conversion was not optimal, we did observe 30% conversion to the ketone after 40 h.
3.2.4.4 Examination of Alkylating Agents

As our first approach to addressing the issue of compatibility between the benzyl protecting group and our masked aldehyde moiety, we chose to re-examine our choice for the second alkylating agent. Previously, we had used allyl bromide, however the allyl moiety would undoubtedly be reduced during hydrogenolysis of the benzyl protecting group prior to auxiliary removal. We were intrigued by the use of alkyl halides possessing protected hydroxyl groups, which could subsequently be deprotected and oxidized. Concurrently in the lab, successful alkylation of 3-pentanone derived hydrazone 1.76 with alkyl iodides possessing TBS- and Bn-protected hydroxyl moieties (Scheme 76), had been achieved and, as a result, we attempted the alkylation of 3.141 with these reagents.

Table 27. Attempted Hydrolysis of Bn-Protected Hydrazone 3.42

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 equiv. p-TsOH, acetone-H₂O (4:1)</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>BF₃•OEt₂, acetone-H₂O (4:1)</td>
<td>40</td>
<td>30</td>
</tr>
</tbody>
</table>
Scheme 76. Alkylation of 3-Pentanone Hydrazone 1.76 with Alkylating Agents Possessing Protected Hydroxyls

Unfortunately, in the context of the more complex hydrazone 3.141, despite alterations in equivalents of both LDA and alkylating agent, as well as deprotonation and alkylation temperature, we were unable to obtain any of the desired bisalkylated compounds.

Table 28. Attempted Reaction of 3.141 with Protected Hydroxyl Alkylating Agents

<table>
<thead>
<tr>
<th>Entry</th>
<th>RX</th>
<th>RX Equiv</th>
<th>LDA Equiv</th>
<th>RX Temp</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>3</td>
<td>2</td>
<td>-78 to 0</td>
<td>Recovered SM</td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>5</td>
<td>1.5</td>
<td>0 to rt</td>
<td>Recovered SM</td>
</tr>
<tr>
<td>3</td>
<td>OMe</td>
<td>3</td>
<td>3</td>
<td>-78 to rt</td>
<td>Recovered SM</td>
</tr>
<tr>
<td>4</td>
<td>OMe</td>
<td>10</td>
<td>5</td>
<td>0 to rt</td>
<td>Recovered SM</td>
</tr>
</tbody>
</table>

At this stage, in order to avoid using more of the valuable advanced hydrazone, we continued our screening in the context of model system 3.146. We examined the use of methyl α-bromoacetate, epi-bromohydrin, and propylene oxide, all under our standard alkylation conditions (Table 29). Unfortunately, only in the case of methyl α-bromoacetate was any product formed, and only in 30% yield.
Due to some of our previous work with heteroatom-containing alkylating agents in the context of monoalkylations, we hypothesize that the addition of HMPA to the reaction mixture could lead to increased conversion. We were hesitant to explore this, as it would potentially erode the stereoselectivity of the alkylation by disrupting the Li-chelate. However, recent discoveries in the lab suggest that addition of HMPA into ACC alkylations after the deprotonation step does not lead to a decrease in selectivity. Therefore, we may look into the use of HMPA in the future but have not done so to this point.

### 3.2.4.5 Removal of Benzyl Group

With minimal success in the alteration of the alkylation agent, we focused our attention on finding conditions for removal of the benzyl group that would be compatible with our allyl moiety. As an initial test, we took bisalkylated hydrazone

**Table 29. Screening of Additional Alkylating Agents for Masked Aldehyde**

<table>
<thead>
<tr>
<th>Entry</th>
<th>RX</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Recovered SM</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Recovered SM</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Recovered SM</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>30 %</td>
</tr>
</tbody>
</table>

3.146 LDA, 0 °C, 1h; RX, –78 °C → rt, 2h

3.147
3.142 and subjected it to hydrogenolysis with H\textsubscript{2}, Pd/C in EtOH. Unfortunately, hydrogenation of the benzyl ether was not observed, and in fact even the allyl group remained intact. Alterations in catalyst (Pd/alumina), solvent (EtOH, MeOH) and reaction time (6-24 h) did not improve results. Gratifyingly, when we increased the pressure of the hydrogenation to 60 psi, we obtained full hydrogenolysis of the benzyl ether (Scheme 77). Unfortunately, and rather expectedly, this also resulted in hydrogenation of the allyl group, thus destroying our masked aldehyde. However, we decided that this compound could now serve as a model system to test the hydrolysis of the hydrazone with the free hydroxyl. Therefore, 3.148 was treated with p-TsOH•H\textsubscript{2}O in acetone-H\textsubscript{2}O (4:1) for 20 h, resulting in full conversion to the hydrolyzed ketone, with no apparent epimerization. With this promising result, we focused on finding conditions for deprotection of the benzyl ether without reduction of the allyl moiety.

Scheme 77. Hydrogenolysis of 3.142 and Subsequent Hydrolysis

We were intrigued by Lewis acid mediated deprotection of the benzyl moiety, and found several examples of the use of BCl\textsubscript{3} in the context of complex molecules.\textsuperscript{120} Attack on BCl\textsubscript{3} by oxygen leads to 3.151, which activates the benzylic position for attack by chlorine, generating benzyl chloride and liberating the free hydroxyl (Scheme 78A).
We felt that this approach might be ideally suited for our system as additional coordination of the boron to the hydrazone nitrogen, in a manner analogous to the mechanism for PMB-deprotection discussed earlier, would further activate the system for deprotection (Scheme 78B).

To test this, 10 mg of 3.142 was treated with BCl₃ in CH₂Cl₂ at –78 °C followed by warming to room temperature over 12 h resulted in full conversion to the desired product (Scheme 79).

However, attempts to scale up the reaction (~400 mg) resulted in the formation of multiple compounds and low yields. It was hypothesized that perhaps we were
observing a mixture of E/Z hydrazone diastereomers, which would resolve after hydrolysis. Unfortunately, attempts to hydrolyze the mixture of compounds were unsuccessful. We were therefore forced to reexamine the reaction conditions in order to come up with a more reproducible result.

Initially, the reaction was conducted by addition of BCl₃ at −78 °C, followed by slow warming of the solution to room temperature over a period of 16 h. This introduced a wide variability in the rate of warming, especially upon scale-up of the reaction, possibly leading to mixtures of products and unreliable outcomes. Therefore, we conducted a temperature screen of the reaction (Table 30) and found that holding the reaction temperature at −20 °C for 16 h resulted in full conversion to the desired product in a repeatable fashion.

Table 30. Temperature Screen of BCl₃ Deprotection of 3.142

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−78</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>−40</td>
<td>16</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>−20</td>
<td>16</td>
<td>100</td>
</tr>
</tbody>
</table>

However, even in this case, a small amount of what was determined to be isomerized hydrazone was present, which became one compound upon hydrolysis to the ketone (Scheme 80). It is worth noting that although more reliable results were
obtained using this procedure, the BCl₃ degrades quickly after the first use (even when stored under inert atmosphere and handled in a glove box) and the reaction yield steadily declines over the period of a week if the same bottle is used repeatedly.

![Scheme 80. Hydrolysis of α-Hydroxy Hydrazone 3.134](image)

3.2.4.5 Esterification and Synthesis Completion

Having established conditions to successfully obtain α,α-bisalkylated α’-hydroxy ketone 3.156, we turned our attention to the installation of the proline ester moiety. In Forsyth’s work on apratoxin A, he employs the Yamaguchi esterification to conduct this coupling with the Boc-protected proline ester 3.158. Unfortunately, despite multiple attempts, only 30-40% yield of the coupling product was ever observed (Scheme 81A). We therefore attempted the use of EDCI, DMAP, and N-Boc-L-proline (3.159), with first purifying both 3.159, as well as 3.156, via benzene azeotrope. Gratifyingly, this resulted in quantitative esterification in only 1 h (Scheme 81B).
Scheme 81. Esterification of 3.156 via A. Yamaguchi Esterification B. EDCI Coupling

Next we were faced with deoxygenation of the ketone moiety to the corresponding methylene, followed by final oxidation of the allyl moiety to the desired aldehyde. In our earlier work toward the synthesis of chiral aldehyde 3.102, we had employed the Barton-McCombie deoxygenation for an analogous transformation. This required that we first reduce the ketone to the corresponding alcohol (3.160) with NaBH₄, followed by derivatization as the xanthate (Scheme 82). While the reduction went smoothly to give a high yield of a mixture of diastereomeric alcohols (3.160), attempts at subsequent xanthate formation using standard conditions (NaH, CS₂, MeI) resulted in a mixture of compounds (Scheme 82). We hypothesized that the mixture of compounds was arising from undesired side reactions (e.g. transesterification) resulting from prior generation of the anion. Therefore, we attempted formation of the xanthate under neutral conditions using 1,1′-thiocarboxyldiimidazole, which unfortunately did not lead to any desired product. We then attempted reversing the order of addition of CS₂ and NaH in the Chugaev reaction, with the hope that the carbon disulfide would
immediately react with the anion as it was generated, thus preventing any possible transesterification. Gratifyingly, this resulted in conversion to the desired product in high yield, with none of the previously observed byproducts.

Scheme 82. Conversion of Alcohol 3.160 to Xanthate 3.161

With the necessary xanthate in hand, we treated 3.161 with Bu₃SnH and AIBN, resulting in complete deoxygenation to give 3.162. As in our prior synthesis of chiral aldehyde 3.102, we treated this crude reaction mixture with NaCNBH₃ in order to facilitate removal of the tin residues during purification, allowing for the isolation of pure 3.162 after chromatography (Scheme 83). The final step in the synthesis of aldehyde 3.163 required oxidation of the allyl moiety to give the C35 aldehyde. Lemieux-Johnson oxidation of 3.163 gave the desired aldehyde in good yield.

Scheme 83. Completion of Aldehyde 3.163
At this stage, in collaboration with another member of the lab, aldehyde 3.163 was taken on to generate fragment 3.100, which could then undergo peptide coupling and macrocyclization to complete the synthesis of apratoxin D (Scheme 84).

Scheme 84. Completion of the Synthesis of Apratoxin D (3.31)

3.2.5 Conclusion

In conclusion, we have completed the synthesis of the polyketide fragment of apratoxin D (3.100) via two separate approaches, both employing an ACC mediated asymmetric α,α-bisalkylation to set the insulated C37 stereocenter. The first approach required the α,α-bisalkylation of a benzylxoy acetone-derived hydrazone, possessing an
electron withdrawing group at the α’-position, testing the limits of CIS-D. This approach resulted in the synthesis of chiral aldehyde 3.102, which was then successfully elaborated into polyketide 3.100. In the second approach, we employed a simpler ACC auxiliary (1.73) in the α,α-bisalkylation of an advanced ketone intermediate possessing multiple stereogenic centers. This approach resulted in the synthesis of advanced intermediate 3.163, which was also taken on to generate polyketide 3.100. In collaboration with another lab member, both of these approaches to the apratoxin D polyketide have been employed in completing the first asymmetric total synthesis of apratoxin D.

3.3 Experimental Section

3.3.1 Asymmetric Formal Synthesis of (R)- and (S)-Stigmolone

Hydrazone 3.23. 4-methyl-2-pentanone (3.20 mL, 25.5 mmol) was added to a solution of 1.72 (1.00 g, 5.10 mmol) in CH₂Cl₂ (25 mL) followed by catalytic p-toluenesulfonic acid (ca. 5 mg) (Ar atmosphere). The mixture was heated to reflux and stirred for 12 h then allowed to cool to rt before being partitioned between saturated aqueous NaHCO₃ and CH₂Cl₂. The aqueous phase was extracted with CH₂Cl₂ (twice) and the combined organic layers were dried (MgSO₄), filtered, and concentrated under
reduced pressure to give a pale yellow oil. Flash chromatography over silica gel using 15:85 EtOAc-hexanes gave 3.23 as a white solid (1.22 g, 96%). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 4.25 (dd, 1 H, \(J = 4.0\) Hz, 8.0 Hz), 2.33-2.26 (m, 1 H), 2.25-2.20 (m, 1 H), 2.07-1.95 (m, 4 H), 1.92 (s, 3 H), 1.88-1.81 (m, 1 H), 1.78-1.75 (m, 1 H), 1.31-1.24 (m, 1 H); \(^1^3\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 174.9, 154.7, 82.9, 72.9, 47.8, 42.8, 35.3, 26.7, 25.7, 25.6, 22.5, 22.3, 21.2, 19.1, 19.0; ESI/MS m/z calcd for C\(_{16}\)H\(_{26}\)N\(_2\)O\(_2\) (2M + Na): 579.4, found: 579.4.

Hydrazone 3.24. \(n\)-BuLi (2.5 M in hexanes, 0.488 mL, 1.22 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of \(i\)-Pr\(_2\)NH (0.188 mL, 1.34 mmol) in THF (5.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H\(_2\)O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (1.55 mL, 0.378 mmol) was transferred via syringe to a pre-cooled (−78 °C) flask (Ar atmosphere). A solution of 3.23 (87.3 mg, 0.315 mmol) in THF (0.8 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was stirred for 45 min. Prenyl bromide (43.7 µL, 0.378 mmol) was then added and the mixture transferred to an ice-H\(_2\)O bath and stirred for 1.5 h. The mixture was then partitioned between Et\(_2\)O and H\(_2\)O. The aqueous phase was extracted with Et\(_2\)O (twice) and the combined organic extracts were dried (MgSO\(_4\)), filtered, and evaporated under reduced pressure to give a
yellow oil. Flash chromatography over silica gel using 15:85 EtOAc-hexanes gave 3.24 (107 mg, 98%) as a pure, colorless oil. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 5.04-5.01 (m, 1 H), 4.24 (dd, \(J = 4.0\) Hz, 8.0 Hz, 1 H), 3.70 (apparent s, 2 H), 2.52-2.42 (m, 1 H), 2.33-2.28 (m, 2 H), 2.52-2.44 (m, 1 H), 2.33-2.26 (m, 2 H), 2.23-1.92 (m, 7 H), 1.84 (dd, \(J = 8.0\) Hz, 13.6 Hz), 1.77-1.75 (m, 1 H), 1.67 (s, 3 H), 1.60 (s, 3 H), 1.32-1.14 (m, 8 H, containing a s at \(\delta\) 1.23 (3 H) and a s at \(\delta\) 1.14 (3 H)), 0.96 (apparent t, \(J = 6.4\) Hz, 6 H); \(^13\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 178.5, 155.0, 132.5, 122.9, 82.8, 73.0, 47.9, 45.1, 42.8, 35.3, 32.0, 26.6, 25.6, 25.4, 24.6, 22.8, 22.2, 21.3, 19.1, 17.7; ESI/MS m/z calcd for C\(_{21}\)H\(_{34}\)N\(_2\)O\(_2\) (M + H): 346.4, found: 346.6.

**Hydrazone 3.169.** \(n\)-BuLi (2.5 M in hexanes, 0.488 mL, 1.22 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of \(i\)Pr\(_2\)NH (0.188 mL, 1.34 mmol) in THF (5.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H\(_2\)O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (1.04 mL, 0.254 mmol) was transferred via syringe to a pre-cooled (−78 °C) flask (Ar atmosphere). A solution of 3.23 (50.0 mg, 0.212 mmol) in THF (0.8 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was stirred for 45 min. MeI (0.132 mL, 2.12 mmol) was then added and the mixture transferred to an ice-H\(_2\)O bath.
and stirred for 1.5 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice), and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil.

Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 3.169 (149 mg, 94%) as a pure, white solid. ¹H NMR (CDCl₃, 400 MHz): δ 4.25 (dd, J = 4.0 Hz, 8.4 Hz, 1 H), 2.45-1.89 (m, 8 H), 2.04-1.91 (m, 2 H), 1.86 (dd, J = 8.0 Hz, 13.6 Hz, 1 H), 1.76 (t, J = 4.0 Hz, 1 H), 1.32-1.24 (m, 1 H), 1.23 (s, 3 H), 1.14 (s, 3 H), 1.07 (t, J = 7.2 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H); ¹³C NMR (CDCl₃ 100 MHz): δ 180.0, 155.0, 82.8, 73.0, 47.8, 44.5, 42.8, 35.3, 26.5, 25.6, 25.3, 25.2, 22.7, 22.3, 21.3, 19.1, 10.5; ESI/MS m/z calcd for C₁₇H₂₈N₂O₂ (M + H): 292.2, found: 292.3.

Hydrazone 3.25. n-BuLi (2.5 M in hexanes, 0.488 mL, 1.22 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (0.188 mL, 1.34 mmol) in THF (5.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (0.857 mL, 0.209 mmol) was transferred via syringe to a pre-cooled (−78 °C) flask (Ar atmosphere). A solution of 3.24 (60.2 mg, 0.174 mmol) in THF (0.8 mL) was added by syringe, with
additional THF (2 x 0.2 mL) as a rinse, and the mixture was stirred for 45 min. MeI (0.102 mL, 1.74 mmol) was then added and the mixture stirred at −78 °C for 24 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 15:85 EtOAc-hexanes gave 3.25 (62.1 mg, 98%) as a pure, colorless oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 3.25 (60.7 mg, 97%) as a pure, white solid. HPLC analysis showed a \( dr > 99:1 \). \(^1\)H NMR (CDCl₃, 400 MHz): \( \delta \) 4.92-4.89 (m, 1 H), 4.24 (dd, \( J = 4.0, 8.0 \) Hz, 1 H), 3.10-3.01 (m, 1 H), 2.34-2.21 (m, 3 H), 2.06-1.90 (m, 5 H), 1.88-1.81 (m, 1 H), 1.78-1.75 (m, 1 H), 1.70-1.58 (m, 8 H, containing s at \( \delta \) 1.64 (3 H), and a s at \( \delta \) 1.58 (3 H)), 1.32-1.13 (m, 11 H, containing a s at \( \delta \) 1.23 (3 H)), 0.97 (d, \( J = 6.4 \) Hz, 3 H), 0.91 (d, \( J = 6.8 \) Hz, 3 H); \(^{13}\)C NMR (CDCl₃, 100 MHz): \( \delta \) 180.1, 155.2, 132.8, 121.9, 82.9, 73.3, 48.0, 43.0, 39.9, 35.3, 32.7, 27.0, 25.9, 24.5, 23.2, 22.4, 21.5, 19.3, 18.0, 16.9; ESI/MS m/z calcd for C₂₂H₃₆N₂O₂ (M + H): 361.3, found: 361.3.

**Hydrazone 3.26.** \( n \)-BuLi (2.5 M in hexanes, 0.488 mL, 1.22 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of \( i \)-Pr₂NH (0.188 mL, 1.34
mmol) in THF (5.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H2O bath, stirred for 30 min, and then cooled to −78 °C. A portion of this solution (1.55 mL, 0.378 mmol) was transferred via syringe to a pre-cooled (−78 °C) flask (Ar atmosphere). A solution of 3.169 (91.8 mg, 0.315 mmol) in THF (0.8 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was stirred for 45 min. Prenyl bromide (43.7 µL, 0.378 mmol) was then added and the mixture stirred at −78 °C for 24 h. The mixture was then partitioned between Et2O and H2O. The aqueous phase was extracted with Et2O (twice) and the combined organic extracts were dried (MgSO4), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 15:85 EtOAc-hexanes gave 3.25 (62.1 mg, 98%) as a pure, colorless oil. Flash chromatography over silica gel using 5:95 EtOAc-hexanes gave 3.26 (109 mg, 96%) as a white solid. HPLC analysis showed a dr > 99:1. 1H NMR (CDCl3, 400 MHz): δ 5.15-5.12 (m, 1 H), 4.25 (dd, J = 4.0, 7.6 Hz, 1 H), 3.06-2.98 (m, 1 H), 2.34-2.22 (m, 4 H), 2.14-2.06 (m, 1 H), 2.04-1.92 (3 H), 1.88-1.81 (m, 1 H), 1.76-1.74 (m, 1 H), 1.69 (s, 3 H), 1.62 (s, 3 H), 1.31-1.14 (m, 8 H, containing a s at δ 1.21 (3 H)), 0.98 (d, J = 6.4 Hz, 3 H), 0.92-0.90 (m, 6 H); 13C NMR (CDCl3, 100 MHz): δ 183.3, 155.3, 133.2, 122.2, 82.9, 73.3, 47.9, 43.1, 40.7, 35.8, 35.6, 31.2, 26.8, 25.9, 25.8, 24.5, 23.1, 22.4, 21.5, 19.3, 18.1, 16.8; ESI/MS m/z calcd for C22H36N2O2 (M + H): 361.3, found: 361.4.

a) HPLC trace of 3.25 and 3.26    b) HPLC trace of 3.25    c) HPLC trace of 3.26
Ketone 3.2. 3.25 (58.0 mg, 0.161 mmol) was dissolved in reagent grade acetone (1.6 mL) and then H₂O (0.4 mL) and p-TsOH·H₂O (61.2 mg, 0.322 mmol) were added. The mixture was stirred for 24 h and partitioned between saturated aqueous NaHCO₃ and Et₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel 2.5:97.5 Et₂O-pentanes gave 3.2 (17.9 mg, 98%) as a pure, colorless oil, along with pure recovered 2.20 (29 mg, 99%) as a white solid. HPLC analysis showed an er of 99:1. Spectroscopic data was identical to that previously reported.⁷¹
Ketone 77. 3.26 (40.0 mg, 0.111 mmol) was dissolved in reagent grade acetone (0.880 mL) and then H₂O (0.220 mL) and p-TsOH·H₂O (42.4 mg, 0.222 mmol) were added. The mixture was stirred for 24 h and partitioned between saturated aqueous NaHCO₃ and Et₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel 2.5:97.5 Et₂O-pentanes gave 3.1 (20.0 mg, 97%) as a pure, colorless oil, along with pure recovered 2.20 (25.7 mg, 98%) as a white solid. HPLC analysis showed an er 99:1. Spectroscopic data was identical to that previously reported.

a) HPLC trace of 3.1 and 3.2  b) HPLC trace of 3.1  c) HPLC trace of 3.2
3.3.2 Asymmetric Synthesis of Chiral Aldehyde Intermediate 3.102 to be used for the Asymmetric Total Synthesis of Apratoxin D

Hydrazone 2.84. 1.72 was dissolved in dichloromethane (130 mL) followed by 2.83 (2.74 mL, 26.0 mmol) and p-TsOH·H2O (490 mg, 2.60 mmol) and the mixture heated to reflux for 12 h. The mixture was allowed to cool to room temperature before it was quenched with NaHCO3 and the aqueous layer extracted with dichloromethane (twice). The combined organic extracts were dried (MgSO4), filtered, and concentrated under reduced pressure to yield 2.84 as an 85:15 mixture of E:Z diastereomers. Flash chromatography over silica gel (5:95 → 20:80 EtOAc:Hexanes) gave pure 2.84 as exclusively the E diastereomer and a colorless oil (7.12 g, 80 %). \(^1\)H NMR (CDCl3, 400 MHz): \(\delta\) 7.36-7.28 (m, 5H), 4.55 (s, 2 H), 4.28 (dd, \(J = 3.6\) Hz, \(8.0\) Hz, 1 H), 4.17 (s, 2 H), 2.34-2.28 (m, 1 H), 2.09-1.91 (m, 5 H, containing a s at \(\delta\) 2.03 for 3 H), 1.86 (dd, 1 H, \(J = 8.0\) Hz, \(13.6\) Hz), 1.79-1.77 (m, 1 H), 1.33-1.13 (m, 7 H, containing a s at \(\delta\) 1.24 for 3 H and a s at \(\delta\) 1.13 for 3 H); \(^13\)C NMR (CDCl3, 125 MHz): \(\delta\) 172.0, 154.2, 137.6, 128.4, 128.0, 127.8, 83.0, 73.2, 73.0, 72.2, 47.9, 42.8, 35.3, 26.7, 25.6, 21.3, 19.1, 16.5; ESI/MS m/z calcd for C20H26N2O3 (M + H): 343.2, found: 343.3.
Hydrazone 2.85. *n*-BuLi (2.5 M in hexanes, 4.20 mL, 10.51 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 ºC) solution of *i*-Pr₂NH (1.60 mL, 11.41 mmol) in THF (30.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 ºC. A solution of 2.84 (3.0 g, 8.76 mmol) in THF (25 mL) was added by syringe, with additional THF (2 x 2.5 mL) as a rinse, and the mixture was stirred for 45 min. MeI (2.73 mL, 43.8 mmol) was then added and the mixture transferred to an ice-H₂O bath and stirred for 1.5 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice), and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 7.5:92.5 EtOAc-hexanes) using 7.5:92.5 EtOAc-hexanes gave 2.85 (2.81 g, 90 %) as a pure, colorless oil. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et₃N and 7.5:92.5 EtOAc-hexanes) using 7.5:92.5 EtOAc-hexanes gave 2.85 (2.81 g, 90 %) as a pure, colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 7.38-7.27 (m, 5 H), 4.56 (d, *J* = 2.4 Hz, 2 H), 4.29-4.19 (m, 3 H), 2.54-2.39 (m, 2 H), 2.34-2.28 (m, 1 H), 2.07-1.91 (m, 2 H), 1.89-1.84 (dd, *J* = 8.4 Hz, 14 Hz, 1 H), 1.78 (t, *J* = 4.4 Hz, 1 H), 1.33-1.12 (m, 12 H, containing a s at δ 1.23 for 3 H); ¹³C NMR (CDCl₃, 125
MHz): δ 177.3, 154.7, 137.7, 128.4, 128.0, 127.8, 83.0, 73.1, 72.2, 47.9, 42.9, 35.3, 26.6, 25.6, 23.2, 21.3, 19.1, 10.2; ESI/MS m/z calcd for C_{21}H_{28}N_{2}O_{3} (M + H): 357.2, found: 357.3.

**Hydrazone 2.87.** n-BuLi (2.5 M in hexanes, 3.78 mL, 9.46 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr_2NH (1.44 mL, 10.24 mmol) in THF (25.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H_2O bath, stirred for 30 min, and then cooled to −78 °C. A solution of 2.85 (2.81 g, 7.88 mmol) in THF (20 mL) was added by syringe, with additional THF (2 x 2.5 mL) as a rinse, and the mixture was stirred for 45 min. AllylBr (0.823 mL, 9.46 mmol) was then added and the mixture stirred at -78 °C for 18h. The mixture was then partitioned between Et_2O and H_2O. The aqueous phase was extracted with Et_2O (twice), and the combined organic extracts were dried (MgSO_4), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et_3N and 7.5:92.5 EtOAc-hexanes) using 7.5:92.5 EtOAc-hexanes gave 2.87 (2.84 g, 91 %) as a pure, colorless oil. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et_3N and 7.5:92.5 EtOAc-hexanes) using 7.5:92.5 EtOAc-hexanes gave 2.87 (2.84 g, 91 %) as a pure, colorless oil. ^1H NMR (CDCl_3, 400 MHz): δ 7.36-7.25 (m, 5 H),
5.83-5.75 (m, 1 H), 5.08-5.01 (m, 2 H), 4.59, 4.54 (ABq, \(J_{AB} = 9.2\) Hz, 2 H), 4.33, 4.23 (ABq, \(J_{AB} = 10.4\) Hz, 2 H), 4.29 (dd, \(J = 3.2\) Hz, 6.8 Hz, 1 H), 3.17-3.09 (m, 2 H), 2.60-2.55 (m, 1 H), 2.34-2.29 (m, 1 H), 2.21-2.15 (m, 1 H), 2.08-2.02 (m, 1 H), 1.99-1.92 (m, 1 H), 1.85 (dd, \(J = 6.8\) Hz, 11.2 Hz, 1 H), 1.79-1.77 (m, 1 H), 1.31-1.13 (m, 7 H, containing a s at \(\delta = 1.24\) for 3 H and a s at \(\delta = 1.16\) for 3 H), 1.07 (d, \(J = 6.0\) Hz, 3 H); \(^{13}\mathrm{C}\) NMR (CDCl\(_3\), 125 MHz): \(\delta = 179.4, 155.0, 137.9, 136.7, 128.5, 128.1, 127.9, 116.8, 83.2, 73.4, 72.5, 70.6, 48.0, 46.6, 43.1, 36.9, 35.5, 34.8, 26.8, 25.8, 21.5, 19.3, 17.5, 8.8; ESI/MS m/z calcd for C\(_{21}\)H\(_{28}\)N\(_2\)O\(_3\) (M + H): 397.2, found: 397.3.

Ketone 3.110. 3.25 (2.75 g, 6.94 mmol) was dissolved in reagent grade acetone (56 mL) and then H\(_2\)O (14 mL) and BF\(_3\)•OEt\(_2\) (1.74 mL, 13.9 mmol) were added. The mixture was stirred for 12 h and partitioned between saturated aqueous 1M NaOH and Et\(_2\)O. The aqueous phase was extracted with Et\(_2\)O (twice) and the combined organic extracts were dried (MgSO\(_4\)), filtered and evaporated under reduced pressure to give a colorless oil. Flash chromatography over silica gel (pre-treated with 1% (v/v) solution of Et\(_3\)N and 5.0:95.0 EtOAc-hexanes) gave 3.110 as a colorless oil (1.41 g, 93%). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 7.37-7.30\) (m, 5 H), 5.76-5.65 (m, 1 H), 5.06-5.00 (m, 2 H), 2.82-2.73 (m, 1 H), 2.43-
2.36 (m, 1 H), 2.14-2.07 (m, 1 H), 1.08 (d, J= 7.2 Hz); $^1$C NMR (CDCl$_3$, 100 MHz): $\delta$ 211.4, 137.3, 135.5, 128.6, 128.1, 117.2, 74.3, 73.4, 42.1, 36.7, 15.9; ESI/MS m/z calcd for C$_{14}$H$_{18}$O$_2$ (M + Na): 241.1, found: 241.1.

**Alcohol 3.111.** To a solution of 3.110 in THF, cooled to 0 °C in an ice/H$_2$O bath, LiAlH$_4$ was added (Ar atmosphere) and the mixture stirred for 2h. The mixture was then quenched by slow addition of H$_2$O and diluted with Et$_2$O. The aqueous layer was extracted with Et$_2$O (twice) and the combined organic extracts were dried (MgSO$_4$), filtered, and concentrated under reduced pressure to yield 3.111 as a mixture of diastereomers and a colorless oil. Crude material was used in subsequent reactions without purification. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.37-7.28 (m, 5 H), 5.83-5.73 (m, 1 H), 5.04-5.00 (m, 2 H), 4.56 (s, 2 H), 3.77-3.40 (m, 3 H), 2.36-2.21 (m, 2 H), 1.99-1.89 (m, 1 H), 1.73-1.65 (m, 1 H), 0.93-0.85 (m, containing a d at $\delta$ 0.92, $J$= 5.6 Hz, and a d at $\delta$ 0.86, $J$= 5.6 Hz, 3 H); $^1$C NMR (CDCl$_3$, 125 MHz): $\delta$ 138.1, 137.2, 128.6, 127.9, 127.8, 116.3, 74.0, 73.5, 73.0, 72.6, 37.6, 37.1, 35.9, 35.6, 15.3, 14.4; ESI/MS m/z calcd for C$_{14}$H$_{20}$O$_2$ (M + Na): 243.2, found: 243.1.
Xanthate 3.114. To a solution of 3.111 (1.41 g, 6.45 mmol) in THF, was added NaH (60% dispersion in mineral oil, 770 mg, 19.4 mmol) and the mixture stirred at rt for 30 mins (Ar atmosphere). CS$_2$ (1.95 mL, 32.25 mmol) was then added dropwise and the mixture stirred 1h. Finally, MeI (2.01 mL, 32.25 mmol) was added dropwise and the mixture stirred an additional 1h. The mixture was then quenched by addition of H$_2$O and diluted with Et$_2$O. The aqueous layer was extracted with Et$_2$O (twice) and the combined organic extracts were dried (MgSO$_4$), filtered, and concentrated under reduced pressure to yield 3.114 as a mixture of diastereomers and a yellow oil. Flash chromatography over silica gel (10:90 EtOAc:Hex) gave 3.114 as a yellow oil which contained a 50:50 mixture of diastereomers (1.81 g, 86%). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.33-7.24 (m, 5 H), 5.87 (q, 0.5 H, $J$ = 4.8 Hz), 5.81-5.71 (m, 1.5 H), 5.04-5.00 (m, 2 H), 4.60-4.48 (m, 2 H), 3.76-3.64 (m, 2 H), 2.56 (s, 3 H), 2.29 (m, 2 H), 1.99-1.92 (m, 1 H), 0.96 (dd, 3 H, $J$ = 6.0, 16.8 Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 216.2, 138.1, 136.3, 128.5, 127.8, 116.9, 85.9, 85.8, 84.9, 84.8, 73.3, 68.5, 68.4, 37.4, 37.0, 34.2, 33.9, 29.8, 19.1, 15.2, 14.7; ESI/MS m/z calcd for C$_{16}$H$_{22}$O$_2$S$_2$ (M + Na): 333.1, found: 333.1.

Benzyl ether 3.108. To a solution of xanthate 3.114 (1.81 g, 5.54 mmol) in toluene (50 mL) was added Bu$_3$SnH (4.32 mL, 16.6 mmol) followed by AIBN (182 mg, 1.11 mmol)
(Ar atmosphere) and the mixture was heated to reflux for 12 h. The mixture was then allowed to cool to rt and concentrated under reduced pressure to yield a brown oil which was then dissolved in t-BuOH (50 mL) and NaCNBH$_3$ added (2.09 g, 33.2 mmol) and was again heated to reflux for 1h (see note). Mixture was then concentrated, diluted in DCM (100 mL), washed with H$_2$O, the aqueous layer extracted with DCM (twice) and the combined organic extracts dried (MgSO$_4$), filtered and concentrated under reduced pressure to yield a pale yellow oil. Flash chromatography over silica gel using 500 mL hexanes followed by 4:96 EtOAc-hexanes gave 3.108 (0.996 g, 88%) as a pure, colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.34-7.25 (m, 5 H), 5.83-5.72 (m, 1 H), 5.04-4.97 (m, 2 H), 4.50 (s, 2 H), 3.55-3.47 (m, 2 H), 2.11-2.05 (m, 1 H), 1.95-1.88 (m, 1 H), 1.74-1.64 (m, 2 H), 1.47-1.38 (m, 1 H), 0.89 (d, $J$= 6.8 Hz, 3 H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 138.8, 137.5, 128.6, 127.7, 116.0, 73.0, 68.7, 41.6, 36.4, 30.0, 19.6; ESI/MS m/z calcd for C$_{14}$H$_{20}$O (M + Na): 227.1, found: 227.1.

Note: NaCNBH$_3$ was added exclusively to expedite purification of desired product away from tin residues by reducing all tin compounds to Bu$_3$SnH.$^{118}$

Aldehyde 3.102. Benzyl ether 3.108 (0.996 g, 4.88 mmol) was dissolved in THF/t-BuOH/H$_2$O (1:1:0.25, 90 mL). Nmo (1.14 g, 9.76 mmol) was added followed by OsO$_4$ (2.5
wt% in t-BuOH, (0.306 mL, 0.244 mmol) and the mixture stirred for 12h. Na₂SO₃ (approx. 8g) was added followed by 100 mL H₂O and the mixture stirred 30 mins. The mixture was diluted with Et₂O, the aqueous layer extracted with Et₂O (twice) and the combined organic layers dried (MgSO₄), filtered and concentrated under reduced pressure to yield a colorless oil. The oil was then dissolved in MeOH:H₂O (2:1, 90 mL) and cooled to 0 °C in an ice/H₂O bath before NaIO₄ (2.09 g, 9.76 mmol) was added, forming a white suspension. The mixture was allowed to warm slowly to rt over a period of 3h, at which point it was diluted with Et₂O and H₂O, the aqueous layer extracted with Et₂O (twice), and the combined organic layers dried (MgSO₄), filtered and concentrated under reduced pressure to yield a colorless oil. Flash chromatography over silica gel using 4:96 EtOAc:Hexanes gave 3.102 as a pure colorless oil (852 mg, 3.90 mmol). 

\[^1\text{H NMR} (\text{CDCl}_3, 500 \text{ MHz}): \delta 9.74 (s, 1 \text{ H}), 7.36-7.26 (m, 5 \text{ H}), 4.49 (s, 2 \text{ H}), 3.52 (t, J = 5.5 \text{ Hz}, 2 \text{ H}), 2.46-2.42 (m, 1 \text{ H}), 2.32-2.22 (m, 1 \text{ H}), 1.70-1.51 (m, 4 \text{ H}), 0.98 (d, J = 6.0 \text{ Hz}, 3 \text{ H}); \[^{13}\text{C NMR} (\text{CDCl}_3, 125 \text{ MHz}): \delta 202.9, 138.5, 128.5, 127.8, 127.7, 73.1, 68.1, 51.1, 36.7, 25.5, 20.2; \text{ESI/MS} \text{ m/z calcd for C}_{13}\text{H}_{18}\text{O}_2 (\text{M} + \text{Na}): 229.1, \text{found: 229.2.}\]

3.3.3 Asymmetric Synthesis of Apratoxin D Polyketide 3.100 via Late Stage \(\alpha,\alpha\)-Bisalkylation

**General Considerations.** Unless stated to the contrary, where applicable, the following conditions apply: Reactions were carried out using dried solvents (see below) and under a slight static pressure of Ar (pre-purified quality) that had been passed
through a column (5 x 20 cm) of Drierite. Glassware was dried in an oven at 120 °C for at least 12 h prior to use and then either cooled in a desiccator cabinet over Drierite or assembled quickly while hot, sealed with rubber septa, and allowed to cool under a stream of Ar. Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 120 °C for at least 12 h prior to use then cooled in a desiccator cabinet over Drierite. Hamilton microsyringes were dried in an oven at 60 °C for at least 24 h prior to use and cooled in the same manner. Commercially available Norm-Ject disposable syringes were used. Dry benzene, toluene, Et₂O, CH₂Cl₂, THF, MeCN, and DME were obtained using an Innovative Technologies solvent purification system. All other dry solvents were of anhydrous quality purchased from Aldrich. Commercial grade solvents were used for routine purposes without further purification. Et₃N, pyridine, i-Pr₂NEt, 2,6-lutidine, i-Pr₂NH, and TMEDA were distilled from CaH₂ under a N₂ atmosphere prior to use. Flash column chromatography was performed on silica gel 60 (230–400 mesh). ¹H and ¹³C NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer or Varian INOVA 500 MHz spectrophotometer at ambient temperature. All ¹H chemical shifts are reported in ppm (δ) relative to TMS; ¹³C shifts are reported in ppm (δ) relative to CDCl₃ (77.16). MS data were obtained using an Agilent 1100 Series liquid chromatography-electrospray ionization mass spectrometer. Chiral HPLC was
performed on a 4.6 X 250 mm Chiralcel OD-H column (Chiral Technologies) or a 4.6 mm x 250 mm Chiralpak AD-H column, using UV detection.

The following procedures are relating to studies of PMB-hyrazones 3.124, 3.125, 3.127.

Hydrazone 3.124. To a solution of ketone 3.123 (105 mg, 0.359 mmol) in CH2Cl2 (5 mL) was added (R)-1.73 (90% mixture, 264 mg, 1.24 mmol) followed by p-TsOH•H2O (3.41 mg, 0.018 mmol) and MgSO4 (216 mg, 1.80 mmol) and the mixture was allowed to stir for 16 h. The solution was then filtered to remove MgSO4, diluted with CH2Cl2 (15 mL), washed with NaHCO3 (10 mL, sat. aq.), the organic layer dried over MgSO4, filtered and concentrated in vacuo to yield a yellow oil. Flash chromatography over silca gel (15:85 EtOAc:Hex) yielded 3.124 as a colorless, viscous oil (152 mg, 91%). 1H NMR (CDCl3, 400 MHz): δ 6.85-7.31 (m, 9H), 4.61 (d, J = 12.0 Hz, 1H), 4.36-4.44 (m, 1H), 4.24-4.34 (m, 2H), 4.08 (app, t, J = 9.3, 1H), 3.81 (s, 3H), 3.64 (d, J = 8.0 Hz, 1H), 3.16-3.21 (m, 1H), 2.72 (dd, J = 9.0, 13.0 Hz, 1H), 2.04 (s, 3H), 1.35 (m, 1H), 1.84-1.92 (m, 1H), 1.21 (d, J = 6.0 Hz, 3H), 1.02-1.08 (m, 1H), 0.90 (s, 9H).
Methylated PMB-Protected Hydrazone 3.125. n-BuLi (2.5 M in hexanes, 0.167 mL, 0.418 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr:NH (61.5 µL, 0.439 mmol) in THF (1.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A solution of 3.124 (97.5 mg, 0.209 mmol) in THF (0.5 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was stirred at 4 °C in an ice-H₂O bath for 1 h. The solution was then recooled to −78 °C, MeI (39.0 µL, 0.627 mmol) was added dropwise and the solution removed from the cold bath and allowed to stir at room temperature for 2 h. The mixture was then partitioned between Et₂O and H₂O. The aqueous phase was extracted with Et₂O (twice), and the combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 25:75 EtOAc-hexanes gave 3.125 (85.4 mg, 85%) as a colorless, viscous oil. \(^1\)H NMR (CDCl₃, 400 MHz): δ 7.19-7.42 (m, 10H), 4.74 (d, \(J = 12.0\) Hz, 1H), 4.20-4.41 (m, 1H), 4.36 (d, \(J = 12.0\) Hz, 1H), 4.29 (app t., \(J = 8.0\) Hz, 1H), 4.90 (app t., \(J = 8.0\) Hz, 1H), 3.99 (d, \(J = 4.8\) Hz, 1H), 3.21 (dd, \(J =4.0, 13.3\) Hz, 1H), 2.76 (dd, \(J = 9.3, 13.3\) Hz, 1H), 2.62-2.71 (m, 1H), 2.31-2.41 (m, 1H), 1.95-2.03 (m, 1H), 1.39-1.49 (m, 1H), 1.28 (t, \(J = 8.0\) Hz, 3H), 1.13-1.16 (m, 1H), 1.11 (d, \(J = 7.0\) Hz, 3H), 9.01 (s,
$^{13}$C NMR (CDCl$_3$, 125 MHz): δ 179.6, 159.3, 154.6, 135.6, 130.3, 129.9, 129.1, 129.0, 127.3, 113.8, 85.5, 71.3, 67.2, 61.2 55.4, 47.4, 38.9, 32.4, 31.1, 30.3, 23.8, 17.3, 10.8; ESI/MS

m/z calcd for C$_{29}$H$_{40}$N$_2$O$_4$ (M + H): 481.3, found: 481.3.

Bisalkylated PMB-Protected Hydrazone 3.127. $n$-BuLi (2.5 M in hexanes, 0.128 mL, 0.320 mmol) was added dropwise (ca. 2 min) to a stirred and cooled ($-78$ °C) solution of $i$-Pr$_2$NH (47.1 µL, 0.336 mmol) in THF (1.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H$_2$O bath, stirred for 30 min, and then cooled to $-78$ °C. A solution of 3.125 (76.9 mg, 0.160 mmol) in THF (1 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was stirred at 4 °C in an ice-H$_2$O bath for 1 h. The solution was then recooled to $-78$ °C, allylBr (41.6 µL, 0.480 mmol) was added dropwise and the mixture removed from the cold bath and allowed to stir at room temperature for 2 h. The mixture was then partitioned between Et$_2$O and H$_2$O. The aqueous phase was extracted with Et$_2$O (twice), and the combined organic extracts were dried (MgSO$_4$), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 25:75 EtOAc-hexanes gave 3.127 (67.5 mg, 81%) as a colorless, viscous oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 6.85-7.30 (m, 9H), 5.67-
5.80 (m, 1H), 5.03-5.14 (m, 2H), 4.62 (d, J = 11.2 Hz, 1H), 4.42-4.49 (m, 1H), 4.20-4.31 (m, 2H), 4.32 (d, J = 4.0 Hz, 1H), 4.12-4.19 (m, 1H), 3.80 (s, 3H), 3.24-3.18 (m, 2H), 2.66 (dd, J = 9.6, 12.8 Hz, 1H), 2.31-2.38 (m, 1H), 2.06-2.21 (m, 2H), 1.48-1.51 (m, 1H), 1.24 (d, J = 13.0 Hz, 3H), 1.07 (d, J = 12.0 Hz, 3H), 0.90 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 179.6, 159.3, 155.2, 136.1, 135.6, 130.7, 129.3, 129.0, 128.9, 127.3, 117.3, 113.8, 82.3, 70.5, 67.4, 61.5, 55.4, 49.1, 39.6, 39.2, 36.0, 32.6, 31.2, 30.3, 16.9, 16.1; ESI/MS m/z calcd for C₃₂H₄₄N₂O₃ (M + H): 521.3, found: 521.4.

**PMB-Hydrazone Model System 3.135.** ACC auxiliary 1.73 (1.3 g, 3.74 mmol) was added to a stirred solution of the PMB-ketone (0.59g, 2.88 mmol) and MgSO₄ (1.73g, 19.4 mmol) in DCM (15 ml). PPTS (0.03g, 0.014 mmol) was added and stirring was continued 24 h at rt. The reaction was filtered, diluted with diethyl ether (20 ml), and washed with NaHCO₃ (10 mL) and brine (10 mL). The organic layer was dried over MgSO₄, filtered, evaporated under reduced pressure. Flash chromatography over silica gel, using 10:90 EtOAc/Hexane gave 3.135 (0.99g, 93%) as a pure, clear oil. ¹H NMR (CDCl₃, 400 MHz): δ 6.85 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H), 7.22-7.38 (m, 5H), 4.54 (app. d, J = 12.0 Hz, 1H), 4.28-4.42 (m, 3H), 4.16 (q, J = 6.4 Hz, 1H), 4.81 (app. t, J = 8.0 Hz, 1H), 3.80 (s,
3H) 3.12 (dd, $J = 4.0, 14.0$ Hz, 1H), 2.77 (dd, $J = 8.0, 14.0$ Hz, 1H), 2.03 (s, 3H), 1.36 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): $\delta$ 177.3, 159.3, 154.4, 135.6, 130.1, 129.8, 129.3, 128.9, 127.2, 113.9, 70.6, 66.8, 60.9, 55.4, 38.2, 19.3, 14.4.

The following procedures are related to the synthesis of Bn-protected Ketone 3.142

Acyl Oxazolidinone 3.115. Oxazolidinone 1.99 (5.00 g, 28.2 mmol) was acylated with propionyl chloride according to a literature procedure.$^{124}$ Purification over silica gel (25:75, EtOAc:Hex) gave 3.115 as a colorless oil (6.06 g, 92 %). Spectroscopic data was identical to that previously reported.$^{124}$

Aldol Adduct 3.117. Aldol adduct 3.117 was prepared according to a literature procedure. Purification over silica gel (20:80 EtOAc:Hex $\rightarrow$ 25:75 EtOAc:Hex $\rightarrow$ 30:70 EtOAc:Hex) gave 3.117 as a pale yellow oil (9.46 g, 83%). Spectroscopic data was identical to that previously reported.$^{125}$
**Diol 3.118.** To a solution of 3.117 (1.31 g, 4.32 mmol) in diethyl ether (20 mL) was added H₂O (85.6 µL, 4.75 mmol) and the solution cooled to 0 °C. LiBH₄ was added dropwise and the mixture was allowed to warm to room temperature slowly over a period of 5 h. The mixture was then recooled to 0 °C, quenched by the addition of 1M NaOH and stirred for 5 minutes. The mixture was then diluted with H₂O, extracted twice with Et₂O, and the organic layers were combined and dried over MgSO₄. Concentration in vacuo gave a yellow oil. ¹H-NMR of the crude reaction confirmed the formation of 3.118 and the crude material was used in the next reaction without purification.

**Benzylidene Acetal 3.137.** To a solution of diol 3.118 (570.0 mg, 4.38 mmol) in CH₂Cl₂ (25 mL), was added benzylidene dimethyl acetal (733 mg, 4.82 mmol) followed by camphor sulfonic acid (30.5 mg, 0.131 mmol) and the solution stirred 16 h. The solution was then quenched by addition of NaHCO₃ (sat. aq.), the aqueous layer extracted twice with CH₂Cl₂, the organic layers combined, dried over MgSO₄ and concentrated in vacuo to yield a yellow oil. Purification over silica gel (10:90,
EtOAc:Hex) gave acetal 3.137 as a colorless oil (765 mg, 80% from 3.117). Spectroscopic data was identical to that previously reported.\textsuperscript{126}

**Diol 3.138.** To a solution of acetal 3.137 (4.50 g, 20.6 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (100 mL) (under an Ar atmosphere) and cooled to 0 °C, DIBAL-H (1.0 M in toluene, 51.5 mL, 51.5 mmol) was added dropwise (ca. 5 min.) and the mixture was stirred at 0 °C for 1 h. The ice bath was then removed and stirring continued for 2 h at room temperature. The mixture was then diluted with CH\textsubscript{2}Cl\textsubscript{2}, 10% HCl (50 mL, cooled to 0 °C) was added dropwide and the mixture stirred an additional 30 min. The aqueous layer was then extracted twice with CH\textsubscript{2}Cl\textsubscript{2}, and the organic layers combined, dried over MgSO\textsubscript{4} and concentrated in vacuo to yield a colorless oil. Flash chromatography over silica gel (20:80 EtOAC:Hexanes) yielded 3.138 (3.51 g, 79%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 7.37-7.25 (m, 5 H), 5.06 (s, 1 H), 5.01 (s, 1 H), 4.57, 4.25 (ABq, 2 H, \(J_{AB}\) = 12 Hz), 3.72 (d, \(J\) = 6.4 Hz), 3.57 (dd, 1 H, \(J\) = 6.0, 11.2 Hz), 3.49 (dd, 1 H, \(J\) = 4.8, 10.8 Hz), 1.95-1.89 (m, 1 H), 1.736 (s, 3 H), 0.98 (d, \(J\) = 6.8 Hz); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta\) 143.4, 138.6, 128.4, 127.9, 127.6, 113.9, 84.8, 70.4, 65.8, 37.9, 18.3, 12.4; ESI/MS m/z calcd for C\textsubscript{14}H\textsubscript{20}O\textsubscript{2} (M + Na): 243.1, found: 243.1.
**Tosylate 3.170.** To a solution of alcohol 3.138 (2.97 g, 13.5 mmol) in CH$_2$Cl$_2$ (75 mL) cooled to 4 °C was added Et$_3$N (2.82 mL, 20.2 mmol), TsCl (3.85 g, 20.2 mmol), and DMAP (165 mg, 1.35 mmol) in that order. The mixture was allowed to stir for 16 hrs while warming slowly to room temperature. Reaction was then quenched with 10% HCl (30 mL), the organic layers washed twice with 10% HCl (2x20 mL), followed by NaHCO$_3$ (sat. aq.) (20 mL) and finally NaCl (sat. aq.) (20 mL). The organic layers were combined, dried over MgSO$_4$, and concentrated in vacuo to yield a white solid. Purification over silica gel (15:85 EtOAc/Hexanes) gave 3.170 as a white solid (4.3 g, 87%).

**$^1$H NMR** (CDCl$_3$, 400 MHz): δ 7.76 (d, 2 H, J = 8.0 Hz), 7.33-7.24 (m, 7 H), 4.98 (s, 1 H), 4.91 (s, 1 H), 4.47, 4.13 (AB$_q$, 2 H, $J_{AB}$ = 11.6), 3.97 (dd, 1 H, J = 6.0, 9.2 Hz), 3.81 (dd, 1 H, J = 6.0, 9.6 Hz), 3.63 (d, J = 6.4 Hz), 2.43 (s, 3 H), 2.05-1.99 (m, 1 H), 1.62 (s, 3 H), 0.94 (d, J = 6.8 Hz);

**$^{13}$C NMR** (CDCl$_3$, 125 MHz): δ 144.8, 142.0, 138.5, 133.1, 129.9, 128.4, 127.7, 127.6, 114.6, 82.8, 72.6, 70.6, 35.5, 21.7, 17.9, 12.2; ESI/MS m/z calcd for C$_{21}$H$_{26}$O$_4$S (M + Na): 397.1, found: 397.2.
3.171. To a solution of tosylate 3.170 (3.24 g, 8.65 mmol) in THF (45 mL) was added CuCl₂ (116 mg, 0.865 mmol) followed by 1-phenyl-1-propyne (0.270 mL, 2.16 mmol). The mixture was stirred at room temperature for 30 mins, then heated to reflux for 30 h. The mixture was allowed to cool, then quenched by the slow addition of NH₄Cl (sat. aq.) and stirred for 10 min. The mixture was then diluted with Et₂O and H₂O, the organic layers extracted twice with Et₂O, combined, dried over MgSO₄, and concentrated in vacuo to yield a yellow oil. Purification over silica gel (5:95 EtOAc/Hexanes) gave 3.171 as a colorless oil (1.02 g, 65%). Further elution gave recovered starting material 3.170 (1.71 g, 4.6 mmol). ¹H NMR (CDCl₃, 400 MHz): δ 7.35-7.25 (m, 5 H), 5.04 (s, 1 H), 4.91 (s, 1 H), 4.52, 4.22 (ABq, 2 H, J_AB= 12 Hz), 3.34 (d, 1 H, J= 7.6 Hz), 1.69 (s, 3 H), 1.32 (dd, 1 H, J= 2.4 Hz, 14 Hz), 1.02 (d, 3 H, J= 6.4 Hz), 0.95-0.89 (m, 2 H), 0.86 (s, 9 H); ¹³C NMR (CDCl₃, 101 MHz): δ 139.2, 128.4, 128.0, 127.4, 114.9, 88.8, 70.6, 47.1, 31.9, 31.0, 30.3, 18.7, 17.8; ESI/MS m/z calcd for C₁₈H₂₈O (M + Na): 283.2, found: 283.1.

3.171

3.139. Alkene 3.171 (1.02 g, 3.92 mmol) was dissolved in THF/t-BuOH/H₂O (1:1:0.25, 68 mL). N-methyl morpholine oxide (918 mg, 7.84 mmol) was added followed by OsO₄ (2.5 wt% in t-BuOH, 2.46 mL, 0.196 mmol) and the mixture stirred for 12 h.
Na₂SO₃ (approx. 8 g) was added followed by 50 mL H₂O and the mixture stirred 30 mins. The mixture was diluted with Et₂O, the aqueous layer extracted with Et₂O (twice) and the combined organic layers dried (MgSO₄), filtered and concentrated under reduced pressure to yield a colorless oil. The oil was then dissolved in MeOH:H₂O (2:1, 75 mL) and cooled to 0 °C in an ice/H₂O bath before NaIO₄ (1.68 g, 7.84 mmol) was added, forming a white suspension. The mixture was allowed to warm slowly to rt over a period of 3 h, at which point it was diluted with Et₂O and H₂O, the aqueous layer extracted with Et₂O (twice), and the combined organic layers dried (MgSO₄), filtered and concentrated under reduced pressure to yield a colorless oil. Flash chromatography over silica gel using 4:96 EtOAc:Hexanes gave 3.139 as a pure colorless oil (874 mg, 85%).

**¹H NMR** (CDCl₃, 400 MHz): δ 7.36-7.27 (m, 5 H), 4.62, 4.36 (ABq, 2 H, J<sub>AB</sub>= 13.2 Hz), 3.55 (d, 1 H, J= 5.2 Hz), 2.17 (s, 3 H), 1.98-1.92 (m, 1 H), 1.36 (dd, 1 H, J= 3.2, 14.4 Hz), 1.07-1.02 (m, 1 H), 0.98 (d, 3 H, J= 6.8 Hz), 0.86 (s, 9 H); **¹³C NMR** (CDCl₃, 125 MHz): δ 211.7, 137.8, 128.5, 128.0, 127.9, 90.0, 73.0, 46.8, 32.5, 31.0, 29.9, 26.7, 17.9; **ESI/MS** m/z calcd for C₁₇H₂₆O₂ (M + Na): 285.2, found: 285.2.

**Hydrazone 3.140.** To a solution of ketone 3.139 (250 mg, 0.953 mmol) in CH₂Cl₂ (5 mL) was added *(R)-1.63* (90% mixture, 264 mg, 1.24 mmol) followed by p-TsOH•H₂O
(9.1 mg, 0.048 mmol) and MgSO₄ (574 mg, 4.76 mmol) and the mixture was allowed to stir for 16 h. The solution was then filtered to remove MgSO₄, diluted with CH₂Cl₂ (15 mL), washed with NaHCO₃ (10 mL, sat. aq.), the organic layer dried over MgSO₄, filtered and concentrated in vacuo to yield a yellow oil. Flash chromatography over silica gel (15:85 EtOAc:Hex) yielded 3.140 as a colorless, viscous oil (387 mg, 93%). ¹H NMR (CDCl₃, 500 MHz): δ 7.48-7.26 (m, 10 H), 4.78, 4.49 (ABq, 2 H, J_AB = 11.5 Hz), 4.49-4.45 (m, 1 H), 4.37 (t, 1 H, J = 9.0 Hz), 3.79 (d, 1 H, J = 10 Hz), 3.30 (A of ABq, J = 4.0, 14.0 Hz, 1 H), 2.84 (B of ABq, J = 9.5, 13.5 Hz, 1 H), 2.15 (s, 3 H), 2.05-2.01 (m, 1 H), 1.53 (d, 1 H, J = 14 Hz), 1.24 (d, 1 H, J = 7 Hz), 1.17 (dd, 1 H, J = 8.5, 14.5 Hz), 0.99 (s, 9 H); ¹³C NMR (CDCl₃, 125 MHz): δ 176.2, 154.4, 138.2, 135.5, [129.2, 128.3, 127.8, 127.4; aromatic carbons, appear jagged and split, 2:2:1:1 ratio], 87.7, 71.6, 67.0, 61.1, 46.4, 38.8, 32.4, 31.0, 30.3, 19.0, 15.9; ESI/MS m/z calcd for C₂₇H₃₆N₂O₃ (M + H): 437.1, found: 437.3.

Methylated Benzyl-Protected Hydrazone 3.141. n-BuLi (2.5 M in hexanes, 0.643 mL, 1.61 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (−78 °C) solution of i-Pr₂NH (0.237 mL, 1.68 mmol) in THF (4.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H₂O bath, stirred for 30 min, and then cooled to −78 °C. A solution
of 3.140 (350.8 mg, 0.804 mmol) in THF (3 mL) was added by syringe, with additional
THF (2 x 0.5 mL) as a rinse, and the mixture was stirred at 4 °C in an ice-H₂O bath for 1
h. The solution was then recooled to −78 °C, MeI (0.150 mL, 2.41 mmol) was added
dropwise and the solution removed from the cold bath and allowed to stir at room
temperature for 2 h. The mixture was then partitioned between Et₂O and H₂O. The
aqueous phase was extracted with Et₂O (twice), and the combined organic extracts were
dried (MgSO₄), filtered, and evaporated under reduced pressure to give a yellow oil.
Flash chromatography over silica gel using 10:90 EtOAc-hexanes gave 3.141 (308 mg,
85%) as a colorless, viscous oil. ¹H NMR (CDCl₃, 500 MHz): δ 7.39-7.24 (m, 8 H), 7.15 (d,
2 H, J= 7.5 Hz), 4.72, 4.35 (ABq, 2 H, J_AB= 11.5 Hz), 4.49-4.39 (m, 1 H), 4.26 (t, 1 H, J= 8.0
Hz), 4.06 (t, 1 H, J= 9.0 Hz), 3.88-3.87 (m, 1 H), 3.19 (dd, 1 H, J= 3.5, 13.5 Hz), 2.77-2.73 (m,
1 H), 2.69-2.62 (m, 1 H), 2.38-2.31 (m, 1 H), 1.97 (broad s, 1 H), 1.45 (dd, 1 H, J= 3.0, 15
Hz), 1.19-1.56 (m, 3 H), 1.10-1.09 (m, 3 H), 0.88 (s, 9 H; ¹³C NMR (CDCl₃, 125 MHz): δ
179.3, 154.5, 138.2, 135.6, 129.1, 128.9, 128.4, 128.3, 127.7, 127.3, 85.9, 71.7, 67.1, 61.1, 47.4,
38.9, 32.5, 31.0, 30.2, 23.8, 17.3, 10.7; ESI/MS m/z calcd for C₂₈H₃₈N₂O₃ (M + H): 451.3,
found: 451.3.
Bisalkylated Benzyl-Protected Hydrazone 3.142. n-BuLi (2.5 M in hexanes, 0.178 mL, 0.444 mmol) was added dropwise (ca. 2 min) to a stirred and cooled (–78 °C) solution of i-PrNH (65.3 µL, 0.466 mmol) in THF (1.0 mL) (Ar atmosphere). The mixture was transferred to an ice-H2O bath, stirred for 30 min, and then cooled to –78 °C. A solution of 3.141 (100 mg, 0.222 mmol) in THF (1 mL) was added by syringe, with additional THF (2 x 0.2 mL) as a rinse, and the mixture was stirred at 4 °C in an ice-H2O bath for 1 h. The solution was then recooled to –78 °C, allylBr (57.9 µL, 0.666 mmol) was added dropwise and the mixture removed from the cold bath and allowed to stir at room temperature for 2 h. The mixture was then partitioned between Et2O and H2O. The aqueous phase was extracted with Et2O (twice), and the combined organic extracts were dried (MgSO4), filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using 20:80 EtOAc-hexanes gave 3.142 (87 mg, 80%) as a colorless, viscous oil. 1H NMR (CDCl3, 400 MHz): δ 7.41-7.25 (m, 8 H), 7.11 (d, 2 H, J= 8.4 Hz), 5.80-5.70 (m, 1 H), 5.13-5.06 (m, 2 H), 4.69 (d, 1 H, J= 11.6 Hz), 4.49-4.41 (m, 1 H), 4.35 (d, 1 H, J= 11.6 Hz), 4.26-4.22 (m, 1 H), 4.15 (d, 1 H, J= 4.0 Hz), 4.08-4.04 (m, 1 H), 3.26-3.18 (m, 2 H), 2.66 (dd, 1 H, J= 10.4, 13.2 Hz), 2.39-2.32 (m, 1 H), 2.21-2.09 (m, 2 H), 1.53-1.49 (m, 1 H), 1.32-1.28 (m, 1 H), 1.25 (d, 3 H, J= 7.2 Hz), 1.08 (d, 3 H, J= 6.8 Hz), 0.91-0.90 (m, 9 H); 13C NMR (CDCl3, 125 MHz): δ 179.5, 155.2, 138.6, 136.1, 135.6, 129.1, 128.4, 127.8, 127.7, 127.3, 117.4, 82.6, 82.5, 70.9, 67.4, 61.6, 49.2, 39.7, 39.3, 36.1, 32.7, 31.3, 30.3, 16.9, 16.1; ESI/MS m/z calcd for C31H42N2O3 (M + Na): 513.3, found: 513.4.
**α-Hydroxy Hydrazine 3.134.** Hydrazone 3.142 (20.0 mg, 0.041 mmol) was dissolved in CH$_2$Cl$_2$ (1 mL) and cooled to −20 °C (Ar Atmosphere). BCl$_3$ (1.0 M in toluene, 0.410 mL, 0.410 mmol) was then added dropwise (ca. 1 min) and the solution stirred for 16 h. The solution was then quenched by slow addition of H$_2$O (1 mL), diluted with CH$_2$Cl$_2$ (10 mL), the aqueous layer extracted with CH$_2$Cl$_2$ (1x10 mL), the organic layers combined and dried over MgSO$_4$, filtered and concentrated in vacuo to yield a yellow liquid. Flash chromatography over silica gel (25:75 EtOAc:Hex) gave 3.134 as a pale yellow oil and a mixture of $E/Z$ (~10:90) hydrazine diastereomers (13.1 mg, 80%).

**$^1$H NMR (CDCl$_3$, 400 MHz):** δ 7.35-7.23 (m, 3 H), 7.18-7.16 (m, 2 H), 5.92-5.62 (m, 1 H), 5.13-5.03 (m, 2 H), 4.42-4.34 (m, 2 H), 4.31-4.24 (m, 1 H), 4.07 (dd, 1 H, $J$ = 8.8, 10.4 Hz), 3.49 (d, 1 H, $J$ = 7.2 Hz), 3.24-3.16 (m, 1 H), 3.11 (dd, 1 H, $J$ = 4.4, 13.6 Hz), 2.64 (dd, 1 H, $J$ = 9.6, 13.6 Hz), 2.32-2.17 (m, 2 H), 2.01-1.96 (m, 1 H), 1.67 (dd, 1 H, $J$ = 3.6, 14.4 Hz), 1.31-1.21 (m, 2 H), 0.96 (s, 9 H), 0.89 (d, 3 H, $J$ = 6.8 Hz);

**$^{13}$C NMR (CDCl$_3$, 125 MHz):** δ 181.7, 155.2, 135.4, 129.1, 127.4, 117.6, 75.0, 67.6, 61.8, 49.2, 39.6, 36.4, 33.5, 31.3, 30.6, 30.2, 17.0, 14.9. **ESI/MS** m/z calcd for C$_{24}$H$_{36}$N$_2$O$_3$ (M + H): 401.4, found: 401.3.
α-Hydroxy Ketone 3.156. Hydrazone 3.134 (50.0 mg, 0.124 mmol) was dissolved in reagent grade acetone (1.12 mL) and then H₂O (0.28 mL) and p-TsOH·H₂O (47.2 mg, 0.248 mmol) were added. The mixture was stirred for 20 h and partitioned between saturated aqueous NaHCO₃ and Et₂O. The aqueous phase was extracted with Et₂O (twice) and the combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel (15:85 EtOAc:Hex) gave 3.156 as a colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 5.79-5.68 (m, 1 H), 5.12-5.02 (m, 2 H), 4.30 (dd, 1 H, J= 2.4, 5.6 Hz), 3.35 (d, 1 H, J= 5.6 Hz), 2.85-2.75 (m, 1 H), 2.51-2.44 (m, 1 H), 2.18-2.02 (m, 2 H), 1.66 (dd, 1 H, J= 4.8, 14.4 Hz), 1.20 (dd, 1 H, J= 5.6, 14.4 Hz), 1.14 (d, 3 H, J= 7.2 Hz), 0.97 (s, 9 H), 0.71 (d, 3 H, J= 6.8 Hz); ¹³C NMR (CDCl₃, 125 MHz): δ 215.0, 135.5, 117.4, 79.7, 48.3, 41.8, 36.1, 35.9, 32.1, 31.3, 30.5, 30.0, 17.9, 15.6; ESI/MS m/z calcd for C₁₄H₂₆O₂ (M + Na): 249.2, found: 249.1.

N-Boc-Proline Ester 3.158. Prior to the reaction, both N-Boc-L-proline and 3.156 were azeotropically dried in benzene. Once complete, 3.156 (10 mg, 0.044 mmol) was
dissolved in CH₂Cl₂ (1 mL) followed by EDCI (12.7 mg, 0.066 mmol), DMAP (7.5 mg, 0.062 mmol), and N-Boc-L-proline (14.2 mg, 0.066 mmol) in 0.5 mL CH₂Cl₂ (Ar Atmosphere). The solution as stirred for 1 h, then partitioned between Et₂O and H₂O, and the aqueous layer extracted with Et₂O (2x10 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated in vacuo to yield a pale yellow oil. Flash chromatography over silica gel (20:80 EtOAc:Hex) gave 3.158 as a colorless oil (18.1 mg, 97%). **¹H NMR** (CDCl₃, 400 MHz): δ 5.75-5.65 (m, 1 H), 5.14-4.99 (m, 3 H), 4.37-4.31 (m, 1 H), 3.59-3.39 (m, 2 H), 2.80-2.70 (m, 1 H), 2.46-2.89 (m, 1 H), 2.27-2.03 (m, 6 H), 1.94-1.88 (m, 1 H), 1.47, 1.44 (two apparent singlets, 9 H), 1.39-1.16 (m, 4 H), 0.94, 0.92 (two apparent singlets, 9 H), 0.86-0.83 (m, 3 H); **¹³C NMR** (CDCl₃, 200 MHz): δ 209.6, 208.5, 172.8, 154.3, 153.9, 135.8, 135.6, 117.3, 117.2, 82.5, 82.1, 80.1, 79.7, 59.6, 59.5, 48.4, 47.9, 46.7, 46.4, 43.0, 42.7, 36.5, 36.4, 31.3, 31.1, 30.4, 30.3, 29.9, 29.8, 29.5, 29.2, 28.7, 28.6, 24.4, 23.4, 17.7, 17.5, 16.7, 16.5; **ESI/MS** m/z calcd for C₂₃H₄₁NO₅ (M + Na): 446.3, found: 446.3.

**Alcohol 3.160.** Ketone 3.158 (20 mg, 0.047 mmol) was dissolved in MeOH, and the solution cooled to 4 °C in an ice-H₂O bath. NaBH₄ (9 mg, 0.236 mmol) was then added, the solution capped and allowed to warm to room temperature slowly over 14 h. The reaction was then quenched with slow addition of H₂O, diluted with Et₂O (10 mL),
and the aqueous layer extracted twice with EtO (2×10 mL). The organic layers were then combined, dried over MgSO₄, and concentrated in vacuo to yield a yellow oil. Flash chromatography over silica gel (20:80 EtOAc:Hex → 100% EtOAc) gave 3.160 (15 mg, 75%). ¹H NMR (CDCl₃, 400 MHz): δ 5.87-7.75 (m, 1 H), 5.09-4.92 (m, 3 H), 4.35-4.22 (m, 1 H), 3.68-3.36 (3 H), 2.29-1.86 (m, 5 H), 1.46-1.41 (m, 10 H, containing a s at 1.45 for 9 H), 1.38-0.83 (m, 16 H, containing a s at 0.905 for 9 H); ESI/MS m/z calcd for C₂₅H₄₄NO₅ (M + Na): 448.3, found: 448.3.

Xanthate 3.158. Alcohol 3.157 (9.0 mg, 0.021 mmol) was dissolved in THF (Ar Atmosphere) followed by CS₂ (6.5 µL, 0.105 mmol) and NaH (2.5 mg, 0.063 mmol) in that order, and the solution allowed to stir for 30 mins. MeI (6.6 µL, 0.105 mmol) was then added and the solution stirred for 1 h. The reaction was quenched by slow addition of H₂O, diluted with EtO (10 mL), and the aqueous layer extracted with EtO (2×10 mL). The organic layers were combined, dried over MgSO₄, filtered and concentrated in vacuo to yield a yellow oil. Flash chromatography over silica gel (8:92 EtOAc:Hex → 15:85 EtOAc:Hex) yielded 3.158 (10.1 mg, 78%). ¹H NMR (CDCl₃, 400 MHz): δ 6.42-6.31 (m, 1 H), 5.87-5.72 (m, 1 H), 5.38-5.42 (m, 1 H), 5.15-5.02 (m, 2 H), 4.40-4.34 (m, 1 H), 3.35-3.33 (m, 2 H), 2.52 (s, 3 H), 2.21-1.78 (m, 5 H), 1.60-1.22 (m, 13 H, containing a s at δ 1.45
for 9 H), 1.08-0.87 (m, 16 H, containing a s at δ 0.90 for 9 H); ESI/MS m/z calcd for C_{26}H_{45}NO_5S_2 (M + Na): 538.3, found: 538.2.

Alkene 3.162. Xanthate 3.161 (2.6 mg, 0.005 mmol) was dissolved in toluene (0.5 mL), followed by Bu_3SnH (2.7 µL, 0.010 mmol) and AIBN (0.3 mg, 0.0005 mmol). The solution was heated to reflux for 16 h. The solution was allowed to cool to rt, then concentrated in vacuo to yield a cloudy white oil. Flash chromatography over silica gel (Hexanes → 10:90 EtOAc:Hex) gave 3.162 (1.5 mg, 74%). ^1H NMR (CDCl_3, 400 MHz): δ 5.79-5.70 (m, 1 H), 5.07-4.94 (m, 3 H), 4.32 (dd, 0.4 H, J= 3.2 Hz, 8.8 Hz), 4.27 (dd, 0.6 H, J= 3.2 Hz, 8.8 Hz), 3.58-3.35 (m, 2 H), 2.23-2.10 (m, 2 H), 2.03-1.85 (m, 4 H), 1.72-1.66 (1 H), 1.52-1.33 (m, 11 H, with two apparent singlets at 1.46 and 1.43 for a total of 9 H), 1.03-0.83, m, 18 H, with two apparent singlets at 0.89 and 0.88 for a total of 9 H); ESI/MS m/z calcd for C_{26}H_{43}NO_4 (M + Na): 432.3, found: 432.3.
Aldehyde 3.162. Alkene 3.162 (1.5 mg, 0.004 mmol) was dissolved in THF/t-BuOH/H$_2$O (1:1:0.25, 0.5 mL). N-methyl morpholine oxide (1 mg, 0.008 mmol) was added followed by OsO$_4$ (2.5 wt% in t-BuOH, 2.5 µL, 0.0002 mmol) and the mixture stirred for 12 h. Na$_2$SO$_3$(approx. 8g) was added followed by 50 mL H$_2$O and the mixture stirred 30 mins. The mixture was diluted with Et$_2$O, the aqueous layer extracted with Et$_2$O (twice) and the combined organic layers dried (MgSO$_4$), filtered and concentrated under reduced pressure to yield a colorless oil. The oil was then dissolved in MeOH:H$_2$O (2:1, 0.75 mL) and cooled to 0 °C in an ice/H$_2$O bath before NaIO$_4$ (1.8 mg, 0.008 mmol) was added. The mixture was allowed to warm slowly to rt over a period of 3 h, at which point it was diluted with Et$_2$O and H$_2$O, the aqueous layer extracted with Et$_2$O (twice), and the combined organic layers dried (MgSO$_4$), filtered and concentrated under reduced pressure to yield a colorless oil. Flash chromatography over silica gel using 10:90 EtOAc:Hexanes gave 3.163 as a mixture of rotomers and a pure colorless oil (1.4 mg, 82%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 9.73 (s, 0.4 H), 9.67 (d, 0.6 H, J= 3.2 Hz), 4.96-4.88 (m, 1 H), 4.28 (apparent d, 1 H, J= 9.2 Hz), 3.57-3.36 (m, 2 H), 2.64 (dd, 0.6 H, J= 4.0, 15.2 Hz), 2.57 (dd, 0.4 H, J= 5.2 Hz, 16.8 Hz), 2.27-2.17 (m, 2 H), 2.09-1.88 (m, 5 H), 1.75-1.70 (m, 1 H), 1.44, 1.43 (2 s, for a total of 9 H), 1.35-1.25 (m, 2 H), 1.01-0.94 (m, 7 H), 0.89, 0.88 (2 s, for a total of 9 H); $^{13}$C NMR (CDCl$_3$, 200 MHz): δ 203.9, 202.1, 173.5, 79.8, 59.3, 59.2, 50.4, 49.8, 47.4, 46.8, 46.7, 46.4, 38.7, 38.3, 32.9, 32.5, 31.1, 31.0, 29.9, 28.6, 25.1.
24.6, 24.5, 23.4, 20.9, 20.6, 17.5, 16.9; **ESI/MS** m/z calcd for C_{23}H_{41}NO_5 (M + Na): 434.3, found: 434.3.
References


104. Arai, H.; Watanabe, B.; Nakagawa, Y.; Miyagawa, H., Synthesis of ponasterone A derivatives with various steroid skeleton moieties and evaluation of their binding to the ecdysone receptor of Kc cells. *Steroids* **2008**, *73* (14), 1452-1464.


Biography

Sarah Wengryniuk was born August 9, 1985 in Frederick, Maryland. She graduated *summa cum laude* from Winthrop University with a B. S. in Chemistry and a B. S. in Biology in 2007. At Winthrop, she conducted undergraduate research in the laboratory of Professor Aaron Hartel studying the synthesis of β-hydroxy carbonyl compounds through the selective reduction of α,β-epoxyketones with silyllithium reagents. Sarah also competed on both the Winthrop track and cross-country teams for all four years of her college career. While at Winthrop she received several honors and awards, including being named a Winthrop Scholar, which included a full academic scholarship, numerous Presidential and Big South Scholar Athlete awards (2003-2007), was named the NCAA Track Scholar-Athlete of the Year in 2004, the Rudisill-Hamm Scholarship for Outstanding Performance in the Sciences, the Mamie G. Harley Scholarship from the College of Arts and Sciences, and a Winthrop Summer Research Fellowship. Upon graduation she also received one of the inaugural Merck Inc. Women in Chemistry Fellowships.

In the Fall of 2007, she began her Ph.D. studies in the Department of Chemistry at Duke University under the supervision of Professor Don M. Coltart. In 2007 she was named an NSF Graduate Research Fellow, which provided her with funding for three years of her graduate career. In the final year of her graduate studies she received the Duke University Kathleen Zielek Fellowship. A list of her current published articles