Enantioselective Syntheses and Chemical Investigations of Plant-Derived Bioactive Volatile Compounds

Anne Marie Sauer

Louisiana State University and Agricultural and Mechanical College

Follow this and additional works at: https://repository.lsu.edu/gradschool_dissertations

Part of the Chemistry Commons

Recommended Citation
https://repository.lsu.edu/gradschool_dissertations/592

This Dissertation is brought to you for free and open access by the Graduate School at LSU Scholarly Repository. It has been accepted for inclusion in LSU Doctoral Dissertations by an authorized graduate school editor of LSU Scholarly Repository. For more information, please contact gradetd@lsu.edu.
ENANTIOSELECTIVE SYNTHESES AND CHEMICAL INVESTIGATIONS OF PLANT-DERIVED BIOACTIVE VOLATILE COMPOUNDS

A Dissertation

Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirements for the degree of Doctor of Philosophy

in

The Department of Chemistry

by

Anne Marie Sauer
B.S., Louisiana State University, 2000
August 2005
DEDICATION

To my parents,

Joe and Carolyn Sauer
ACKNOWLEDGEMENTS

“Love bears all things,
believes all things, hopes all things,
endures all things,
Love never ends.” 1 Corinthians 13:7-8

It is this love that has allowed me to persevere and become the person that I am today. I have been fortunate to have been surrounded by those who have offered sound guidance and unflagging support, no matter what they had to sacrifice. I am so blessed.

Mom and Dad, you have demonstrated what true love is. I could not have asked for better role models, friends, or parents. This is, in a very small way, my appreciation for all that you’ve done and all that you are.

Danny and Tricia, with faith untiring, your will and determination endless, you truly are an inspiration.

Maggie and Charlie, my aspiring scientists, your laughter and vision are refreshing... May you always view the world with wonder and never lose sight of your dreams.

Joshua, you’ve picked me up, calmed me down, lifted my spirits, held my hand, and loved me though it all. Thank you.

I would like to thank my extended family in Oklahoma. Your support and love was felt across hundreds of miles. I have cherished the time we spent together and look forward to our next party.

I would be remiss not to thank Dr. Crowe, who after realizing my enthusiasm for natural products, tailored his research to accommodate my interests. It was his flexibility that allowed me to work freely, inspiring ingenuity and heightening motivation.
Dr. Henderson and Dr. Laine, you made me realize that research is much bigger than dreams. You unlocked new avenues and created endless possibilities of exploration that I could never have imagined. It truly has been an honor.

I would like to extend my heartfelt appreciation to those members at Albemarle, past and present, who guided me through two eventful and wonderful summers. The experiences and relationships formed have proven instrumental to my scientific development.

I would like to recognize and thank the remaining members of my committee: Dr. Strongin, Dr. Spivak, Dr. Dyer, and Dr. Woodring. They serve as educators, not only in science, but in all facets of life. Sincere appreciation is extended to Dr. Dale Treleaven, Dr. Frank Zhou, and Mr. Guangyu Li for their knowledgeable assistance with 2D-NMR studies, Dr. Frank Fronczek for his expertise in X-ray crystallography, Mr. Rafael Cueto for his mentoring with respect to FT-IR and EPR instrumentation, Betty Zhu and members, past and present, of the Henderson group for their willingness to acclimate me to relevant termite “matters”.

Special thanks is extended to Caleb Clark, Dr. Alfonso Davila, Dr. Tamara Nauman, Ms. Sherry Wilkes, Ms. Dottye Melancon, and Mr. Benn Fowler for their encouragement and friendship. It is with the deepest gratitude that I also recognize Dr. Julia Chan, Dr. George Stanley, and Dr. Steve Watkins, who unselfishly sacrificed their time whenever I was in need. In addition, I will always remember the bonds formed with the members of the Crowe group.
In closing, I have found that the following passage provides guidance and strength when faced with a variety of tasks. I leave this message with my readers in hopes that they find solace and inspiration.

"Trust in the Lord with all of your heart and lean not on your own understanding; in all your ways acknowledge him, and he will make your paths straight." Proverbs 3:5-6
TABLE OF CONTENTS

DEDICATION........................................................................................................... ii
ACKNOWLEDGEMENTS.......................................................................................... iii
LIST OF TABLES....................................................................................................... xi
LIST OF FIGURES.................................................................................................... xiii
LIST OF SCHEMES.................................................................................................. xxiii
LIST OF ABBREVIATIONS...................................................................................... xxvi
ABSTRACT............................................................................................................... xxviii

CHAPTER 1: IMPORTANCE OF PLANT-DERIVED VOLATILE COMPOUNDS........................................... 1
  1.1 Overview......................................................................................................... 1
  1.2 Applications................................................................................................... 1
    1.2.1 Relevance in Medicinal Fields............................................................... 1
    1.2.2 Additives in Fragrances and Flavors.................................................... 2
    1.2.3 Applications in Plant-Insect Research................................................ 2
  1.3 Role of Organic Chemistry.......................................................................... 5
  1.4 Target Compounds Identified...................................................................... 7
  1.5 References................................................................................................... 7

PART I: SYNTHESES AND CHEMICAL INVESTIGATIONS OF VALENCENOIDS, EREMOPHILANES, AND EUDESMANES........ 11

CHAPTER 2: AN EFFICIENT AND ASYMMETRIC SYNTHESIS OF NOOTKATONE, TETRAHYDRONOOTKATONE, AND DERIVATIVES........................................................................ 11
  2.1 An Introduction to Termites....................................................................... 11
  2.2 Historical Overview of Termiticides: The Importance of Botanical Insecticides......................................................... 11
  2.3 Sesquiterpenes as Botanical Termiticides.................................................. 13
  2.4 Economical Concerns.................................................................................. 14
  2.5 Synthesis and Reactivity Considerations................................................... 15
    2.5.1 Yoshikoshi’s Route............................................................................... 17
    2.5.2 Synthetic Route to (+)-Nootkatone 2.2............................................... 18
  2.6 Conclusion.................................................................................................... 24
  2.7 Experimental............................................................................................... 24
    2.7.1 General Experimental......................................................................... 24
CHAPTER 5: DIENONE-PHENOL REARRANGEMENTS OF VARIOUS SESQUITERPENOID DIENONES
5.1 Introduction to the Dienone-Phenol Rearrangement................................. 148
5.2 History of the Dienone-Phenol Rearrangement....................................... 148
5.3 Reactivity Considerations....................................................................... 151
  5.3.1 Overview....................................................................................... 151
  5.3.2 Solvent and Substituent Effects................................................... 152
5.4 Sesquiterpenoid DPR Substrates......................................................... 153
  5.4.1 Synthesis of Sesquiterpenoid Dienones....................................... 154
5.5 DPR Experimental Findings.................................................................. 154
5.6 Explanation of Findings....................................................................... 157
5.7 Outlook / Conclusion.......................................................................... 161
5.8 Experimental...................................................................................... 162
  5.8.1 General Experimental................................................................. 162
  5.8.2 Preparative Procedures............................................................... 163
  5.8.3 Spectral Data............................................................................... 175
  5.8.4 X-ray Data.................................................................................. 175
5.9 References......................................................................................... 175

CHAPTER 6: STRUCTURE-ACTIVITY EVALUATIONS OF SYNTHETIC NORSESQUITERPENES AND SESQUITERPENOID DERIVATES OF (+)-NOOTKATONE TO THE FORMOSAN SUBTERRANEAN TERMITE
6.1 Introduction...................................................................................... 218
6.2 Methods and Materials....................................................................... 218
  6.2.1 Termites...................................................................................... 218
  6.2.2 Synthetic Derivatives................................................................. 219
  6.2.3 Repellency Test Against Formosan Subterranean Termites.......... 220
6.3 Experimental.................................................................................... 220
  6.3.1 General Experimental............................................................... 220
  6.3.2 Preparative Procedures............................................................... 221
  6.3.3 Spectral Data............................................................................... 222
6.4 References......................................................................................... 222

PART II: A FLEXIBLE ROUTE TO JASMONE AND STRUCTURAL ANALOGS VIA APPLICATIONS OF THE HETERO PAUSON-KHAND REACTION
CHAPTER 7: INTRODUCTION AND OVERVIEW........................................... 225
7.1 History and Economical Importance.................................................... 225
7.2 Chemical Composition of Jasmine Oil and Industrial Synthesis........... 225
7.3 Incorporation of Jasmine to Our Daily Lives....................................... 227
  7.3.1 Commercial Uses........................................................................ 227
  7.3.2 Plant – Insect Research............................................................... 227
CHAPTER 8: HETERO PAUSON-KHAND SUBSTRATES VIA [3,3]-SIGMATROPIC REARRANGEMENTS

8.1 Overview and Introduction
8.1.1 Claisen Rearrangements
8.1.2 Cope Rearrangements
8.1.3 Relevant Bond Dissociation Energies
8.1.4 HPK Substrates via [3,3]-Sigmatropic Rearrangements

8.2 Synthesis of HPK Substrates
8.2.1 Synthesis of HPK Substrate \(8.1a\) via Pivalate Route
8.2.2 Synthesis of HPK Substrate \(8.1b\) via TBDMS Route

8.2.3 Outlook

8.3 HPK Substrates \(8.1c\) and \(8.1d\) via AOC Rearrangements
8.3.1 Construction of Compulsory Octa-1, 5, 7-triene-3-ols via \(\varepsilon\)-Selective Pentadienylation to \(\alpha,\beta\)-unsaturated Aldehydes
8.3.2 AOC Rearrangements of Octa-1,5,7-triene-3-ols

8.3.3 Explanation of Findings
8.3.4 Alternative Approaches
8.3.5 Outlook

8.4 Conclusion
8.5 Experimental
8.5.1 General Experimental
8.5.2 Preparative Procedures
8.5.3 Spectral Data

8.6 References

CHAPTER 9: CONSTRUCTION OF JASMONE ANALOGS VIA TITANIUM MEDIATED HETERO PAUSON-KHAND REACTIONS OF TETHERED ENALS

9.1 Preface
9.2 HPK Substrates and Their Performance in the HPK Reaction
9.2.1 HPK Reaction of Tethered Enal \(9.1a\)
9.2.2 HPK Reaction of Tethered Dienals \(9.1b\) and \(9.1c\)

9.3 Outlook / Conclusion
9.4 Experimental

9.4.1 General Experimental
9.4.2 Preparative Procedures
9.4.3 X-ray Data
APPENDIX A: TERMITE BIOLOGY AND TERMITICIDE

BACKGROUND........................................................................................................ 343
A.1 Subterranean Termite Background................................................................ 343
A.2 Biogenesis of Eremophilanes........................................................................ 352
A.3 References..................................................................................................... 353

APPENDIX B: X-RAY DATA................................................................................. 354
B.1 Epoxide (4.6)................................................................................................. 354
B.2 Tetrahydronootkatone Acetal (4.8)................................................................. 358
B.3 Dibromide (4.9)............................................................................................. 362
B.4 Dienone-Phenol Acetate (5.X)....................................................................... 368
B.5 Titanocene Complex (9.2b)............................................................................ 373

APPENDIX C: LETTERS OF PERMISSION.......................................................... 377

VITA.......................................................................................................................... 379
LIST OF TABLES

Table 1.1 Plant-Derived Medicinal Compounds........................................................ 3
Table 1.2 Plant-Derived Sensory Compounds.......................................................... 4
Table 1.3 Plant-Derived Compounds and Plant Defense........................................... 6
Table 1.4 Plant-Derived Target Compounds............................................................ 8
Table 2.1 Formation of the Homoallylic Alcohol..................................................... 20
Table 3.1 Catalytic Hydrogenation of Bicyclic Enone 3.3....................................... 67
Table 3.2 Hydrogenation of 4a-Methyl Substituted Decalones............................... 68
Table 3.3 Catalytic Hydrogenation of Natural Product Derivates............................. 69
Table 3.4 Experimental Hydrogenations of Valencanes.......................................... 71
Table 4.1 Bromination of THN 4.7........................................................................ 112
Table 4.2 Variations in Dehydrohalogenation Reaction Conditions.......................... 116
Table 5.1 Influence of External Factors on the DPR................................................. 153
Table 8.1 Variants of the Claisen Rearrangement.................................................... 237
Table 8.2 Bond Dissociation Energies..................................................................... 239
Table 8.3 Protecting Group Studies......................................................................... 241
Table 8.4 Pentadienylation Investigations of Acrolein.............................................. 247
Table 8.5 One-Pot “In Situ” Pentadienylation Methodology.................................... 249
Table 8.6 AOC Rearrangement of 8.16d................................................................. 254
Table 8.7 Time / Temperature / Color Observations for AOC Rearrangement of 8.16d............................................................................................................ 256
Table 8.8 AOC Rearrangement Deuterium Labeling Experimentation..................... 257
Table 8.9 AOC Comparison Studies....................................................................... 258
Table A.1 Classification System the Formosan Subterranean Termite.................... 343
Table A.2 Termites -vs- Ants.................................................................................... 344
Table A.3 Termite Castes........................................................................................... 344
Table A.4 Types of Subterranean Termites............................................................... 345
Table A.5 Federally Banned Chlorinated Hydrocarbons........................................... 346
Table A.6 Wood Treatment Products........................................................................ 346
Table A.7 Repellent Chemical Barrier Treatments (Synthetic Pyrethroids).............. 347
Table A.8 Non-Repellent Liquid Treatments............................................................. 348
Table A.9 Termite Baits............................................................................................ 349
Table A.10 Botanical Termiticides............................................................................ 350
Table A.11 Comparison of Termite Treatment Methodology................................... 351

Table B.1 Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($\vec{A}^2$) for 4.6.......................................................... 355
Table B.2 Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($\vec{A}^2$) for 4.8.......................................................... 359
Table B.3 Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($\vec{A}^2$) for 4.9.......................................................... 363
Table B.4 Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($\vec{A}^2$) for 5.36.......................................................... 369
Table B.5 Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($\vec{A}^2$) for 9.2b.......................................................... 375
LIST OF FIGURES

Figure 2.1 Structures of (α)-Vetivone and (+)-Nootkatone........................................... 13
Figure 2.2 Nootkatone Derivatives and Termite Repellency........................................... 14
Figure 2.3 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.8........................................ 36
Figure 2.4 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.8........................................ 37
Figure 2.5 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.9......................................... 38
Figure 2.6 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.9......................................... 39
Figure 2.7 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.14a..................................... 40
Figure 2.8 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.14a..................................... 41
Figure 2.9 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.14b..................................... 42
Figure 2.10 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.14b.................................. 43
Figure 2.11 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.10a..................................... 44
Figure 2.12 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.10a..................................... 45
Figure 2.13 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.16a..................................... 46
Figure 2.14 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.16a..................................... 47
Figure 2.15 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.15a..................................... 48
Figure 2.16 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.15a..................................... 49
Figure 2.17 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.15b..................................... 50
Figure 2.18 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.15b..................................... 51
Figure 2.19 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.11a..................................... 52
Figure 2.20 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.11a..................................... 53
Figure 2.21 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 2.11a........... 54
Figure 2.22 $^1$H NMR (250 MHz, CDCl$_3$) of Compound **2.12** ........................................ 55

Figure 2.23 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound **2.12** ........................................ 56

Figure 2.24 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion
  of Compound **2.12** ........................................................................................................ 57

Figure 2.25 $^1$H NMR (250 MHz, CDCl$_3$) of (+)-Nootkatone **2.2** ........................................ 58

Figure 2.26 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of (+)-Nootkatone **2.2** ........................................ 59

Figure 3.1 *Cis* and *Trans* Decalin Ring Fusions ................................................................... 61

Figure 3.2 Commercially Available THN and Possible Stereoisomers ........................................ 62

Figure 3.3 COSY Spectra (400 MHz, d-Toluene) of THN
  (Aromor Inc., Israel) ........................................................................................................ 63

Figure 3.4 HSQC Spectra (400 MHz, d-Toluene) of THN
  (Aromor Inc., Israel) ........................................................................................................ 64

Figure 3.5 NOESY Spectra (400 MHz, d-Toluene) of THN
  (Aromor Inc., Israel) ........................................................................................................ 65

Figure 3.6 Structures of Chamaecynone **3.1** and Isochamaecynone **3.2** ......................... 66

Figure 3.7 Steric Model ........................................................................................................ 68

Figure 3.8 $^1$H NMR (250 MHz, CDCl$_3$) of Compound **3.8** ............................................. 84

Figure 3.9 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound **3.8** ............................................. 85

Figure 3.10 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion
  of Compound **3.8** ........................................................................................................ 86

Figure 3.11 $^1$H NMR (250 MHz, CDCl$_3$) of Compound **3.9** ............................................. 87

Figure 3.12 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound **3.9** ............................................. 88

Figure 3.13 $^1$H NMR (250 MHz, CDCl$_3$) of Compound **3.10** .......................................... 89

Figure 3.14 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound **3.10** .......................................... 90

Figure 3.15 $^1$H NMR (250 MHz, CDCl$_3$) of Compound **3.11** .......................................... 91
Figure 4.5 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 4.8........................................... 131
Figure 4.6 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 4.8................................. 132
Figure 4.7 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 4.9................................. 133
Figure 4.8 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 4.9................................. 134
Figure 4.9 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 4.9................................. 135
Figure 4.10 $^1$H NMR (250 MHz, d-toluene) of Compound 4.9................................. 136
Figure 4.11 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 4.10................................. 137
Figure 4.12 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 4.10................................. 138
Figure 4.13 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 4.10................................. 139
Figure 4.14 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 4.11................................. 140
Figure 4.15 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 4.11................................. 141
Figure 4.16 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 4.11................................. 142
Figure 4.17 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 4.12................................. 143
Figure 4.18 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 4.12................................. 144
Figure 4.19 $^1$H NMR (250 MHz, CDCl$_3$) of Compounds 4.13 and 4.14................... 145
Figure 4.20 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compounds 4.13 and 4.14................... 146
Figure 4.21 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compounds 4.13 and 4.14...................................................... 147
Figure 5.1 Sesquiterpenoid Dienones........................................................................... 155
Figure 5.2 Crystal Structure of 5.36........................................................................... 156
Figure 5.3 Calculations and Selectivity for Dienone 5.25 in the DPR.......................... 159
Figure 5.4 Calculations and Selectivity for Dienones **rac-5.26** and **5.27** in the DPR.................................................................................. 160

Figure 5.5 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of 4-Isopropylcyclohexanone............. 176

Figure 5.6 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound **A**.................................. 177

Figure 5.7 $^1$H NMR (250 MHz, CDCl$_3$) of **rac-5.30**.......................................... 178

Figure 5.8 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of **rac-5.30**.......................................... 179

Figure 5.9 $^1$H NMR (250 MHz, CDCl$_3$) of Dienone **rac-5.26**........................... 180

Figure 5.10 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Dienone **rac-5.26**........................... 181

Figure 5.11 $^1$H NMR (300 MHz, CDCl$_3$) of (R)-(+-)-Dihydrocarvone............... 182

Figure 5.12 $^{13}$C NMR (75 MHz, CDCl$_3$) of (R)-(+-)-Dihydrocarvone............... 183

Figure 5.13 $^1$H NMR (300 MHz, CDCl$_3$) of Chiral Imine **c**............................... 184

Figure 5.14 $^1$H NMR (300 MHz, CDCl$_3$) Upfield Expansion of Chiral Imine **c**.......................................................................................................... 185

Figure 5.15 $^{13}$C NMR (75 MHz, CDCl$_3$) of Chiral Imine **c**............................... 186

Figure 5.16 $^1$H NMR (300 MHz, CDCl$_3$) of Imino Intermediate.......................... 187

Figure 5.17 $^1$H NMR (300 MHz, CDCl$_3$) Upfield Expansion of Imino Intermediate............................................................................................................. 188

Figure 5.18 $^{13}$C NMR (75 MHz, CDCl$_3$) of Imino Intermediate.......................... 189

Figure 5.19 $^1$H NMR (300 MHz, CDCl$_3$) of Diketone **c**.................................... 190

Figure 5.20 $^{13}$C NMR (75 MHz, CDCl$_3$) of Diketone **c**.................................... 191

Figure 5.21 $^1$H NMR (300 MHz, CDCl$_3$) of Compound **5.32**......................... 192

Figure 5.22 $^{13}$C NMR (75 MHz, CDCl$_3$) of Compound **5.32**......................... 193

Figure 5.23 $^{13}$C NMR (75 MHz, CDCl$_3$) Upfield Expansion of Compound **5.32**............................................................................................................. 194

Figure 5.24 $^1$H NMR (300 MHz, CDCl$_3$) of Chiral Imine **b**............................... 195
Figure 5.25 $^{13}$C NMR (75 MHz, CDCl$_3$) of Chiral Imine $b$............................................. 196
Figure 5.26 $^1$H NMR (300 MHz, CDCl$_3$) of Diketone $b$.................................................. 197
Figure 5.27 $^{13}$C NMR (75 MHz, CDCl$_3$) of Diketone $b$.................................................. 198
Figure 5.28 $^1$H NMR (250 MHz, CDCl$_3$) of Compound $D$................................................ 199
Figure 5.29 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound $D$............................................. 200
Figure 5.30 $^1$H NMR (250 MHz, CDCl$_3$) of Compound $5.31$.......................................... 201
Figure 5.31 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound $5.31$.......................................... 202
Figure 5.32 $^1$H NMR (250 MHz, CDCl$_3$) of Compound $E$................................................ 203
Figure 5.33 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound $E$................................................ 204
Figure 5.34 $^1$H NMR (250 MHz, CDCl$_3$) of Compound $F$................................................ 205
Figure 5.35 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound $F$................................................ 206
Figure 5.36 $^1$H NMR (250 MHz, CDCl$_3$) of Dienone $5.27$............................................. 207
Figure 5.37 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Dienone $5.27$............................................. 208
Figure 5.38 $^1$H NMR (250 MHz, CDCl$_3$) of Phenol Acetate $5.36$..................................... 209
Figure 5.39 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Phenol Acetate $5.36$..................................... 210
Figure 5.40 $^1$H NMR (250 MHz, CDCl$_3$) of Phenol $G$...................................................... 211
Figure 5.41 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Phenol $G$...................................................... 212
Figure 5.42 $^1$H NMR (300 MHz, CDCl$_3$) of 1:1 Mixture of Phenolic Acetates $5.36 : 5.37$ .......................................................... 213
Figure 5.43 $^1$H NMR (300 MHz, CDCl$_3$) Upfield Expansion of 1:1 Mixture of Phenolic Acetates $5.36 : 5.37$.......................................................... 214
Figure 5.44 $^{13}$C NMR (75 MHz, CDCl$_3$) Downfield Region of 1:1 Mixture of Phenolic Acetates $5.36 : 5.37$.......................................................... 215
Figure 5.45 13C NMR (75 MHz, CDCl3) Upfield Region of 1:1 Mixture of Phenolic Acetates 5.36 : 5.37................................. 216

Figure 6.1 Synthetic Derivatives................................................................. 219

Figure 6.2 1H NMR (250 MHz, CDCl3) of Compound 6.18........................ 223

Figure 6.3 13C NMR (62.5 MHz, CDCl3) of Compound 6.18.................... 224

Figure 7.1 Natural and Synthetic Jasmine Odorants.................................... 225

Figure 7.2 Structural Comparison of Methyl Jasmonate 7.2 and PGE2 7.7........................ 228

Figure 8.1 1H NMR (CDCl3, 250 MHz) of (E)-8.1m.................................. 251

Figure 8.2 ROESY Spectra (CDCl3, 500 MHz) of 8.1m............................... 252

Figure 8.3 ROESY Spectra (CDCl3, 500 MHz) of 4:1 Inseparable Mixture of 8.1d: (Z)-8.1i.................................................. 255

Figure 8.4 NMR Analogy Used to Elucidate EPR Signal............................. 261

Figure 8.5 Future AOC Investigations........................................................ 265

Figure 8.6 1H NMR (250 MHz, d-Acetone) Downfield Expansion of Compound 8.3.......................................................... 285

Figure 8.7 1H NMR (250 MHz, d-Acetone) Upfield Expansion of Compound 8.3.......................................................... 286

Figure 8.8 1H NMR (250 MHz, CDCl3) of Compound 8.5c........................... 287

Figure 8.9 1H NMR (250 MHz, CDCl3) Expansion of Free -OH on Compound 8.5c.......................................................... 288

Figure 8.10 1H NMR (250 MHz, CDCl3) of Compound 8.5d............................ 289

Figure 8.11 13C NMR (62.5 MHz, CDCl3) of Compound 8.5d...................... 290

Figure 8.12 1H NMR (250 MHz, CDCl3) of Compound 8.7c............................ 291

Figure 8.13 13C NMR (62.5 MHz, CDCl3) Downfield Expansion of Compound 8.7c.......................................................... 292
Figure 8.14 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 8.7c................................................................................................................. 293

Figure 8.15 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.7d........................................... 294

Figure 8.16 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.7d........................................... 295

Figure 8.17 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.8c............................................. 296

Figure 8.18 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.8d............................................. 297

Figure 8.19 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.8d........................................... 298

Figure 8.20 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.11............................................ 299

Figure 8.21 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.11............................................ 300

Figure 8.22 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.10............................................. 301

Figure 8.23 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.10............................................. 302

Figure 8.24 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.1a............................................. 303

Figure 8.25 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.1a............................................. 304

Figure 8.26 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.15............................................. 305

Figure 8.27 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.15............................................. 306

Figure 8.28 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.16c............................................. 307

Figure 8.29 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.16c............................................. 308

Figure 8.30 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.16d............................................. 309

Figure 8.31 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.16d............................................. 310

Figure 8.32 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.16e............................................. 311

Figure 8.33 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.16e............................................. 312

Figure 8.34 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.16f............................................. 313

Figure 8.35 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.16f............................................. 314
Figure 8.36 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.16g .................. 315
Figure 8.37 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.16g ................. 316
Figure 8.38 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.17e .................. 317
Figure 8.39 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.17e ............... 318
Figure 8.40 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.17e .................. 319
Figure 8.41 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.17e ............... 320
Figure 8.42 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.17g .................. 321
Figure 8.43 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.17g ............... 322
Figure 8.44 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.1e .................... 323
Figure 8.45 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.1e ................. 324
Figure 8.46 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound ($E$)-8.1m .......... 325
Figure 8.47 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.19d .................. 326
Figure 8.48 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.19d ............... 327
Figure 8.49 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.21 ..................... 328
Figure 8.50 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.21 ................. 329
Figure 9.1 Synthesized HPK Substrates .................................................. 332
Figure 9.2 Crystal Structure of 9.2b ...................................................... 333
Figure 9.3 $^1$H NMR (250 MHz, C$_6$D$_6$) of Compound 9.1b ...................... 334
Figure 9.4 $^{13}$C NMR (62.5 MHz, C$_6$D$_6$) of Compound 9.1b .................... 335
Figure 9.5 $^1$H NMR (300 MHz, C$_6$D$_6$) of Compound 9.1c ...................... 336
Figure 9.6 $^{13}$C NMR (75 MHz, C$_6$D$_6$) of Compound 9.1c ...................... 337
Figure A.1 Map of US Termite Formosan Subterranean Infestations ......... 343
Figure A.2 Eudesmane, Eremophilane, and Valencane Sesquiterpenoid Skeleta.. 352
Figure B.1 Epoxide (4.6) Crystal Structure................................................................. 357
Figure B.2 Tetrahydronootkatone Acetal (4.8).......................................................... 361
Figure B.3 Dibromide (4.9) Packing........................................................................ 366
Figure B.4 Dibromide (4.9) Crystal Structure......................................................... 367
Figure B.5 Dienone-Phenol Acetate (5.36) Crystal Structure................................. 372
Figure B.6 Titanocene Complex (9.2b) Crystal Structure........................................ 374
# LIST OF SCHEMES

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Robinson Annulation Considerations</td>
<td>16</td>
</tr>
<tr>
<td>2.2</td>
<td>Yoshikoshi’s Route to (+)-Nootkatone</td>
<td>17</td>
</tr>
<tr>
<td>2.3</td>
<td>Synthetic Route to (+)-Nootkatone</td>
<td>18</td>
</tr>
<tr>
<td>2.4</td>
<td>Anionic Oxy-Cope Rearrangement</td>
<td>21</td>
</tr>
<tr>
<td>2.5</td>
<td>Anionic Oxy-Cope Rearrangement (R = Me)</td>
<td>22</td>
</tr>
<tr>
<td>2.6</td>
<td>Anionic Oxy-Cope Rearrangement (R = H)</td>
<td>23</td>
</tr>
<tr>
<td>3.1</td>
<td>Generation of cis-Hydrindanol</td>
<td>70</td>
</tr>
<tr>
<td>3.2</td>
<td>Mechanistic Consideration of Alkene Isomerization at Low Pressures</td>
<td>73</td>
</tr>
<tr>
<td>3.3</td>
<td>Summary of Schaffer’s Results</td>
<td>74</td>
</tr>
<tr>
<td>3.4</td>
<td>Kabbara’s Reported Result</td>
<td>74</td>
</tr>
<tr>
<td>3.5</td>
<td>Influence of the C4-Methyl Group on Hydrogenation Selectivity</td>
<td>75</td>
</tr>
<tr>
<td>3.6</td>
<td>Predicted Hydrogenation Result for Compound 3.16</td>
<td>76</td>
</tr>
<tr>
<td>4.1</td>
<td>Synthetic Derivatives of (+)-Nootkatone</td>
<td>111</td>
</tr>
<tr>
<td>4.2</td>
<td>Favorskii Rearrangement of 4.9</td>
<td>115</td>
</tr>
<tr>
<td>4.3</td>
<td>Demonstrated Enolization Preference in the Favorskii Rearrangement</td>
<td>116</td>
</tr>
<tr>
<td>5.1</td>
<td>Product Stability in Dienone-Phenol Rearrangements</td>
<td>148</td>
</tr>
<tr>
<td>5.2</td>
<td>Historical Dienone-Phenol Rearrangements</td>
<td>150</td>
</tr>
<tr>
<td>5.3</td>
<td>Woodward’s Mechanistic Proof</td>
<td>150</td>
</tr>
<tr>
<td>5.4</td>
<td>Bloom’s Bond Differentiation</td>
<td>151</td>
</tr>
<tr>
<td>5.5</td>
<td>Overview of the Dienone-Phenol Rearrangement</td>
<td>152</td>
</tr>
</tbody>
</table>
Scheme 8.9 HPK Substrate 8.1b via TBDMS Route

Scheme 8.10 Future Plans for the Synthesis of 8.1b

Scheme 8.11 Regiochemical Adducts from Pentadienylmetal Attack on Electrophiles

Scheme 8.12 Retrosynthetic Analysis to Substrates of Type 8.1c-g

Scheme 8.13 AOC Rearrangements of Octa-1, 5, 7-triene-3-ols

Scheme 8.14 Possible AOC Rearrangement Products from Triene Alcohols 8.16

Scheme 8.15 Influence of Enolate Geometry in the AOC Rearrangement

Scheme 8.16 Enolate Geometry and Stereochemical Considerations

Scheme 8.17 Proposed Mechanism for Crotonaldehyde’s Conjugated Diene Product

Scheme 8.18 Proposed Radical Mechanism for the Conversion to Conjugated Diene

Scheme 8.19 “Masked” Route to HPK Substrates 8.1c, 8.1d, and 8.1f

Scheme 8.20 Synthesis of β-Trimethylsilyl-Substituted Aldehydes

Scheme 8.21 AOC Rearrangement of Silylated Derivative 8.19d

Scheme 8.22 Thermal Rearrangement

Scheme 8.23 Predicted Outcome of the AOC Rearrangement on (Z)-Allylic Alcohol Substrate

Scheme 8.24 Diels-Alder Reactions to Separate Isomeric Aldehydes

Scheme 9.1 Designed Syntheses for Jasmone Analogs

Scheme A.1 Biogenesis of Valencane Framework
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>AOC</td>
<td>anionic oxy-Cope</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>BHT</td>
<td>2,6-di-tert-butyl-4-methylphenol</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-butyllithium</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celcius</td>
</tr>
<tr>
<td>ca.</td>
<td>approximately</td>
</tr>
<tr>
<td>cat</td>
<td>catalytic</td>
</tr>
<tr>
<td>calc’d</td>
<td>calculated</td>
</tr>
<tr>
<td>CDCl₃</td>
<td>deuterated chloroform</td>
</tr>
<tr>
<td>¹³C NMR</td>
<td>Carbon-13 Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadienyl</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift in ppm downfield from Me₄Si</td>
</tr>
<tr>
<td>Δ</td>
<td>heat</td>
</tr>
<tr>
<td>d</td>
<td>deuterated</td>
</tr>
<tr>
<td>DA</td>
<td>Diels-Alder</td>
</tr>
<tr>
<td>2D-NMR</td>
<td>two dimensional Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane, methylene chloride</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-cyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N’-dimethylformamide</td>
</tr>
<tr>
<td>DMPU</td>
<td>1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone</td>
</tr>
<tr>
<td>DPR</td>
<td>Dienone-Phenol Rearrangement</td>
</tr>
<tr>
<td>eq</td>
<td>equivalents</td>
</tr>
<tr>
<td>EPR</td>
<td>Electron Paramagnetic Resonance</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>EVE</td>
<td>ethyl vinyl ether</td>
</tr>
<tr>
<td>FT-IR</td>
<td>Fourier Transform Infrared Spectrometer</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
</tr>
<tr>
<td>GC-MS</td>
<td>gas chromatography – mass spectrometry</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>hv</td>
<td>light</td>
</tr>
<tr>
<td>H₂</td>
<td>hydrogen</td>
</tr>
<tr>
<td>H⁺</td>
<td>proton</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
</tbody>
</table>
\(^1\)H NMR Proton Nuclear Magnetic Resonance
HPK hetero Pauson-Khand
HRMS high resolution mass spectrum
IR infrared
\(J\) coupling constant
LAH lithium aluminum hydride
LDA lithium diisopropylamide
\(\mu\) micro
m milli, multiplet (NMR)
M moles per liter
Me methyl
MHz megahertz
min minute(s)
mol mole(s)
mp melting point
MVK methyl vinyl ketone
\(m/z\) mass to charge ratio
NMR Nuclear Magnetic Resonance
NOESY Nuclear Overhauser Effect Spectroscopy
OAc acetate
OEC orthoester Claisen
ORTEP Oak Ridge Thermal Ellipsoid Plot
\(p\) para
PCC pyridinium chlorochromate
PGs prostaglandins
Piv pivalate
ppm parts per million
\(p\)TSA \textit{para}-toluenesulfonic acid
Py pyridine
\(R_f\) frontal retention value
rac racemic
rt room temperature
sat’d saturated
TBAF tetrabutylammonium fluoride
TBDMS \textit{tert}-butyldimethylsilyl
TEA triethylamine
TES triethylsilyl
THF tetrahydrofuran
THN tetrahydronootkatone
THV tetrahydrovalencene
TLC thin layer chromatography
TMS trimethylsilyl, tetramethyldisilane
Ts tosyl = \textit{p}-toluenesulfonyl
ABSTRACT

Research, inspired by nature, provides ample opportunity for discovery, ingenuity, and creative endeavor. For these reasons, the work and accomplishments presented herein focus on the total syntheses and related investigations of a variety of natural product derivatives, specifically (+)-nootkatone and jasmone. While the former consists of several independent projects: (a) an enantioselective synthetic route to (+)-nootkatone and derivatives, (b) examination of the valencane ring system, (c) determination of the absolute configuration of (+)-nootkatone, and (d) rearrangements of various sesquiterpenoid derivatives; the latter focuses on the construction of δ,ε-unsaturated carbonyl compounds, hetero Pauson-Khand substrates, via [3,3]-sigmatropic rearrangements.
CHAPTER 1: IMPORTANCE OF PLANT-DERIVED VOLATILE COMPOUNDS

1.1 Overview

Though separated by the vast expanse of oceans, continents, impenetrable jungles, or deserts, the forbears of every race and land upon Earth possessed a remarkable knowledge of plants. They relied heavily on “Nature’s Gift” and incorporated plant components into every facet of their daily lives. Plants supplied early mankind with elements crucial for survival: shelter, food, medicine, and highly prized flavors and fragrances.\(^1\),\(^2\)

Even now, the potentiality of plant resources continues to be assessed. Exploration of plant uses has led to modern medical treatments via drug discoveries, new flavor and fragrance additives, and pest control by way of plant-insect research. Plant-derived natural products continue to find application in a wide variety of consumer wares and provide a foundation for many industrial settings.\(^3\)

1.2 Applications

1.2.1 Relevance in Medicinal Fields

Thousands of years ago, it was found that the employment of compounds extracted from the roots, leaves, bark, and seeds of plants aided in the remedy of various ailments. The relics of hundreds of Mesopotamian clay tablets (2600 BC), the Egyptian’s Papyrus Ebers pharmaceutical scroll (1500 BC), and the Chinese *Materia Medica* (1000 BC), represent three historical literature documents that confirm the use of plant-derived substances in medicinal treatments. As discovered in ancient times, extracts from cedars and cypress, licorice, myrrh, poppy juice, cumin, peppermint, and caraway were found to be effective for a wide variety of maladies and are still utilized in modern times.\(^1\),\(^2\),\(^4\)
Plant-derived natural products continue to provide the framework for traditional medical treatments. The World Health Organization (WHO) estimated that 80% of the world’s population relies heavily on active substances from plants for their primary health care. The remaining 20% are treated via prescription drugs, which utilize the natural product either as the immediate drug or as a synthetic precursor. There are thousands of medicines in our pharmacopoeia that were originally extracted from plants. Table 1.1 gives a few examples of drugs that have been used since ancient times.1.2, 1.5-1.7

1.2.2 Additives in Fragrances and Flavors

Since early stages of recorded history, volatile fragrances and flavors from plants have intrigued and captivated the senses of mankind. In addition to their pleasurable sensory properties, the rarity and expense of these fine specialty commodities rendered them useful as currencies and gifts among royalty.1.8

Through genuine interest, scientists were curious to identify the compounds responsible for the characteristic fragrances and flavors perceived. The 1800’s marked a dramatic turning point in the evolution of flavors and fragrances with the isolation and identification of principle natural products. Among those isolated were coumarin (tonka beans, 1868) and vanillin (vanilla beans, 1876). Continued progress has been made in these fields and today, the flavor and fragrance industry relies on extensive research of plant volatiles to discover new molecules. Table 1.2 contains examples of sensory compounds derived from plant resources.1.7, 1.9-1.11

1.2.3 Applications in Plant-Insect Research

Causing destruction to homes, personal health, and to farmers' livelihood, insects have long been responsible for drastic impacts and devastating losses to man. Since
<table>
<thead>
<tr>
<th>Chemical</th>
<th>Chemical Structure</th>
<th>History / Comments</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td><img src="image1" alt="Salicylic Acid" /> → <img src="image2" alt="Aspirin" /> (Acetylsalicylic Acid)</td>
<td>- salicylic acid, isolated from Willow Tree (<em>Salix</em> spp.), used in ancient times &lt;br&gt;- 1875: salicylic acid synthesized in laboratory &lt;br&gt;- this ancient form reported to cause stomach pain, bleeding, nausea &lt;br&gt;- 1893: the less acidic acetylsalicyclic acid derivative synthesized (Hoffman) and patented by Bayer &lt;br&gt;- 1915: aspirin tablets marketed</td>
<td>Ancient: pain, gout, fever, headaches &lt;br&gt;Modern: Arthritis, pain, fever, inflammation, prevention of strokes and heart attacks</td>
</tr>
<tr>
<td><strong>Taxol</strong></td>
<td><img src="image3" alt="Taxol" /></td>
<td>- bark of the Pacific Yew tree (<em>Taxus brevifolia</em>) in northwestern U.S. &lt;br&gt;- reported use in Julius Caesar’s time &lt;br&gt;- 1962: first isolated (Barclay) &lt;br&gt;- 1971: X-ray crystallographic data (<em>Wall et al.</em>.) &lt;br&gt;- 1994: synthesis reported (<em>Nicolaou et al.</em>.)</td>
<td>Ancient: Poison, cancer-healing folk medicine &lt;br&gt;Modern: ovarian and breast cancer, lung cancer, melanoma</td>
</tr>
<tr>
<td><strong>Reserpine</strong></td>
<td><img src="image4" alt="Reserpine" /></td>
<td>- alkaloid found in the Indian Snakeroot (<em>Rauvolfia serpentina</em>) &lt;br&gt;- 1952: first isolated (<em>Schlittler et al.</em>.) &lt;br&gt;- 1955: fully characterized (<em>Ciba et al.</em>.) &lt;br&gt;- 1957: &gt;1500 papers published on medical uses &lt;br&gt;- 1958: first synthesis disclosed (Woodward)</td>
<td>Ancient: Snake bites, mental illness &amp; insanity &lt;br&gt;Modern: Antihypertensive, nervous, and mental disorders</td>
</tr>
<tr>
<td>Compound</td>
<td>Structure</td>
<td>Plant Source</td>
<td>Comments</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------</td>
<td>-----------------------</td>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>Hydroxy-citronellal</td>
<td><img src="image" alt="Structure" /></td>
<td><em>Convallaria majalis</em> Lily of the Valley</td>
<td>Floral scent Fine fragrances, scented household items</td>
</tr>
<tr>
<td>Raspberry Ketone</td>
<td><img src="image" alt="Structure" /></td>
<td><em>Rubus idaeus</em></td>
<td>Fruit aroma and flavor</td>
</tr>
<tr>
<td>Menthol</td>
<td><img src="image" alt="Structure" /></td>
<td><em>Mentha arvensis</em></td>
<td>Confectionary, perfumes, liqueurs, cough drops, cigarettes, toothpaste, nasal inhalers</td>
</tr>
<tr>
<td>Capsaicin</td>
<td><img src="image" alt="Structure" /></td>
<td><em>Capsicum annuum</em></td>
<td>Sharp, pungent; Active principle of red peppers; component in Tabasco sauce</td>
</tr>
</tbody>
</table>
anciently, populations have tried to control insects through the use of various plant oils. Even now, natural ingredients, such as citronella oil, extracted from citronella grass, are included in formulations for insect repellents.\textsuperscript{1.12}

However, there is a constant and continual need for new ideas for pest management, and, regardless of the treatment, the material used should not have an adverse impact on the environment.\textsuperscript{1.13} Therefore, one such area of recent interest, plant-insect research, centers the investigation of insect repellents from those of natural origin. Correlating volatile compounds from plants to insect responses, such as attraction or repulsion, aids in the development of new control methods.\textsuperscript{1.3} Table 1.3 provides specific examples of plant chemicals that provide a defense against pests.\textsuperscript{1.12,1.14}

1.3 Role of Organic Chemistry

As illustrated, compounds derived from plants serve as an invaluable resource to man and has applications in diverse areas. However, there are some disadvantages. First, and foremost, is the location and accessibility man has to the natural supply. And secondly, once identified, the relative expense of the natural resource often renders it impractical for most applications. One, 100-year-old Pacific Yew tree, for example, is capable of supplying 300 milligrams of taxol, just enough anticancer medicine to provide one dose to one patient.\textsuperscript{1.7} It was, therefore, the combination of concerns that left scientists searching for alternative methods that would supply society with compounds possessing properties comparable to those obtained from the natural source.

It was not until the conclusion of World War II that the fusion of organic synthesis with the science of natural products began. This exciting new area of research, the total synthesis of compounds derived from natural products, flourished and provided a means
<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Chemical Structure</th>
<th>Plant Source</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnolol</td>
<td><img src="image1.png" alt="Magnolol Structure" /></td>
<td>Magnolia tree (Magnolia virginiana)</td>
<td>Toxic to silkworms (Callosomia promethean)</td>
</tr>
<tr>
<td>Limonene</td>
<td><img src="image2.png" alt="Limonene Structure" /></td>
<td>Pine Tree (Pinus ponderosa)</td>
<td>Feeding deterrent to pine bark beetle (Dendroctonus brevicomis)</td>
</tr>
<tr>
<td>Osajin</td>
<td><img src="image3.png" alt="Osajin Structure" /></td>
<td>Hedgeapple (Maclura pomifera)</td>
<td>Repellent to German cockroaches (Blattella germanica) and the maize weevil (Sitophilus zeamais)</td>
</tr>
</tbody>
</table>
for the deliverance of such specific compounds through synthetic technology. It is through this venue that chemists have been able to construct not only those compounds of interest, but also similar analogs, thereby granting ample opportunity for discovery and creative endeavor. Such research, inspired by nature, has served as a catalyst in the development of highly successful and novel systems.1.7

1.4 Target Compounds Identified

Research efforts, to date, have been aimed at the cyclopentanone natural product Jasmone and sesquiterpenoids possessing the skeletal framework characteristic of valencanes.1.15, 1.16 Several additional derivatives, useful intermediates to more biologically-active eudesmane1.17 and eremophilane1.18 systems, have also been explored. All of the aforementioned compounds are plant derived or synthetic precursors, have volatile uses (flavors and fragrances), medicinal impact, and demonstrate promise in plant-insect research (Table 1.4). The synthesis, studies, and applications of each are described herein.1.19

1.5 References


1.5 Sumner, J. The Natural History of Medicinal Plants; Timber Press: Portland, OR, 2000, pp 125-144.
<table>
<thead>
<tr>
<th>Class</th>
<th>Skeletal Framework</th>
<th>Specific Example</th>
<th>Occurrence</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valencane</td>
<td></td>
<td>Nootkatone</td>
<td><em>Chamaecyparis nootkatensis</em></td>
<td>-treatment of kidney ailments, mental illness, rheumatism, anticancer treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alaskan Yellow Cedar; <em>Citrus paradise</em> peel of grapefruit</td>
<td>-Grapefruit flavor and aroma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Repellent activity towards Formosan Subterranean Termite (<em>Coptotermes formosanus</em>) and other insects</td>
</tr>
<tr>
<td>Prostaglandin B</td>
<td></td>
<td>(Z)-Jasmone</td>
<td><em>Jasminium sp.</em> Cultivated in Grasse, France</td>
<td>-Treats ringworm &amp; arrest milk secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Structurally similar to prostaglandins</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Jasmine fragrance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Aphid repellent (<em>Coccinella septempunctata</em>) and (<em>Aphidius ervi</em>)</td>
</tr>
<tr>
<td>Eudesmane</td>
<td></td>
<td>β-eudesmol</td>
<td><em>Eucalyptus sp.</em> Gum trees Australia</td>
<td>-Treat colds, toothache, fever, diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Agent in perfumes, household products, and soaps</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Mosquito repellent</td>
</tr>
<tr>
<td>Eremophilane</td>
<td></td>
<td>Eremophilone</td>
<td><em>Eremophilia mitchelli</em> “Buddha wood” Queensland; Southern Australia</td>
<td>-characteristic sweet odor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-scenting perfumes and soaps</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-derivates possess insect antifeedant &amp; cell growth inhibitory properties</td>
</tr>
</tbody>
</table>


2.1 An Introduction to Termites

Since the time of the Romans, termites have been known to acquire nutritional value from cellulose, a structural polymer component of wood and plants.2.1 Because of this diet, termites play an essential role in nature by reducing and recycling fallen and decaying wood matter, thereby regenerating the soil with rich nutrients necessary for new growth. However, having a constant and steady supply of food, living protected and sheltered from Nature’s harsh elements, and hidden from predators, termites cause more destruction and therefore demand more attention than any other structural pest. Of particular interest is the destructive and aggressive foraging nature of Coptotermes formosanus Shiraki.

In the USA, one Formosan subterranean termite colony, comprised of up to 10 million individuals, is capable of consuming one thousand pounds of wood per year. The estimated nationwide damage reaches an excess of one billion dollars. In Louisiana, the damage caused by this species is valued at $500 million; New Orleans, alone, accounts for $300 million.2.2 (Appendix A contains additional information on the identification and relative importance of subterranean termites.)

2.2 Historical Overview of Termiticides: The Importance of Botanical Insecticides

First introduced in 1952, cyclodienes, such as chlordane and heptachlor, served as the standard method of controlling termites. Capable of withstanding 30 years of intense environmental conditions, these chlorinated hydrocarbons were seemingly effective for
the prevention and control of termites. However, after nearly forty years of dominance, organochlorines were progressively banned due to the environmental and health concerns.\textsuperscript{2,3}

With the departure of chlorinated hydrocarbons, manufacturers were left in search of suitable and effective replacements for termite control. This sparked scientific interest and launched novel research programs in an effort to gain insight into the world of termite behavior and ecology. Soon, new products and applications were introduced and are currently incorporated in termite control (Appendix A). Synthetic pyrethroids, due to their repellent capabilities, have been utilized in soil barrier treatments. However, these compounds pose a threat to aquatic life and therefore have restricted use. Organophosphates, more toxic to vertebrates than chlorinated hydrocarbons, are reported to contribute to air pollution and the contamination of small ponds. For these reasons, the EPA will ultimately remove them from termite formulations. In addition, fipronil, the active ingredient in a newly registered non-repellent termiticide, has been reported to cause thyroid cancer.\textsuperscript{2,4} Therefore, the search for new, safe, and effective termiticides is essential.

It has been well documented that the highly active compounds plants exude are vital to the plants' maintenance, survival, and perseverance in their natural habitat (Chapter 1). Therefore, in an effort to implement Nature’s successful design for our own practicality, the introduction of these active compounds into “modern” termiticide formulations has received growing interest and attention in recent years. Although several botanical termiticides have been identified, nothing, to date, is available for commercial use (Appendix A).
2.3 Sesquiterpenes as Botanical Termiticides

In 1939, Pfau and Plattner isolated $\alpha$-vetivone 2.1 (Figure 2.1), a sesquiterpenoid and the essential odiferous constituent found in vetiver grass (*Vetiveria zizanioides* Stapf), from vetiver oil.\(^2\)\(^5\) This oil, reportedly repellent to flies and cockroaches, has recently been identified to serve as repellents to the Formosan subterranean termite, *Coptotermes formosanus* Shiraki.\(^2\)\(^4\) In an effort to identify additional termite-active sesquiterpenes, similar sesquiterpenoid compounds were targeted for investigation.

Although first isolated from the heartwood of Alaskan yellow cedar, *Chamaecyparis nootkatensis* (D. Don), (+)-nootkatone 2.2 (Figure 2.1), responsible for the odor of grapefruit, is also found to be present in the peel of *Citrus paradisi* Macfaden.\(^2\)\(^6\) This sesquiterpenoid has found applications not only in fine fragrances, but also in food and beverage confections. Zhu et al. discovered its termiticidal potential in 2001 through preliminary evaluations, and its success has prompted scientific endeavors and opened doors to novel botanical termiticides.\(^2\)\(^7\)

![Figure 2.1 Structures of (α)-Vetivone and (+)-Nootkatone](image)

Using 2.2 as a basis for comparison, several derivatives 2.3-2.7 possessing (+)-nootkatone’s valencane structural skeleton were acquired and tested for their repellency
against *C. formosanus* (Figure 2.2). Interpretation of the structure-activity results reveals several relationships. First, removal of the ketone group resulted in diminished activity, indicating that the carbonyl function group is essential for repellency. Also, as seen in 2.5, the reduction of the isopropylidene group does not significantly alter the repellency. Hydrogenation of the 1,10-olefin (2.6 and 2.7) produced intensely repellent compounds thereby rendering them attractive termiticidal targets.2.7

![Chemical structures](image)

**Figure 2.2 Nootkatone Derivatives and Termite Repellency** 2.7

**2.4 Economical Concerns**

As shown, nootkatone and its derivatives have capabilities to serve a prominent role in termite control methodology. In addition, a more eminent application of current interest involves the devastation imparted by a series of hurricanes to Florida’s grapefruit
The combination of demands leaves a pressing need for an economic and facile route to these compounds.

At the present time, nootkatone is prepared as an oxidation product of valencene ($700 / kilo) and is valued at $3,000 / kilo. Through the reduction of nootkatone, tetrahydronootkatone is obtained and can be purchased at a price of $3-6,000 / kilo (Aromor Inc.; Israel). However, the cost of these compounds renders them uneconomical and therefore inadequate for any industrial application.

Although several research groups have synthesized compounds from this family of sesquiterpenoids, none have been able to produce a viable scheme that would be appropriate for a large-scale production. Therefore, it was the purpose of this project to develop an efficient and economic asymmetric synthesis for nootkatone and analogs that could be applied to an industrial setting and utilized not only for termite (and other arthropods) control, but also as a grapefruit flavor and fragrance additive. The findings of this work are presented herein.

2.5 Synthesis and Reactivity Considerations

For nearly forty years, much effort has been devoted to the synthetic construction of compounds possessing the valencane skeletal framework. And, although they are found in nature, the synthetic construction of these irregular isoprenoid sesquiterpenes has challenged the ingenuity and technical skill of chemists. Most synthetic approaches to date have relied on Robinson annulation reactions. However, the stereospecific establishment of the vicinal cis-dimethyl substituents and their relative configuration to the isopropenyl group, has proven problematic. A discussion of these isoprenoids and their biogenesis can be found in Appendix A.
Bessière investigated the preparation of tricyclo[7.1.1.0]undecenones via Robinson annulation to nopinone (Scheme 2.1). Although the *trans*-fused diketone cyclized readily under the reaction conditions (basic media), the conversion of the *cis*-fused diketone to its corresponding aldol product, the (+)-nootkatone precursor, was impossible. The explanation, obtained through analysis of stereochemical considerations of the aldol intermediates A and B, was based on relative steric strain. In intermediate A, the severe interactions between the bridgehead substituents with the *gem*-dimethyls are minimized through the ability to adopt a chair conformation. Intermediate B suffers from a 1,3-interaction which it is unable to overcome.²,¹⁰

Scheme 2.1 Robinson Annulation Considerations²,¹⁰

In 1980, Yoshikoshi reported that acetic media would not only cyclize the *cis*-diketone but also simultaneously prompt the cyclobutane cleavage. With this, an enantioselective synthesis to (+)-nootkatone ².² was finally achieved (Scheme 2.2).²,⁶
2.5.1 Yoshikoshi’s Route

Yoshikoshi’s approach to (+)-nootkatone begins with nopinone 2.8 and focuses on the titanium tetrachloride catalyzed conjugate addition of allyltrimethylsilane to 2.9, as the stereoselective step (Scheme 2.1). The observed selectivity in this critical step, however, did not exceed a 4:1 inseparable diastereomeric mixture 2.10a : 2.10b, leaving room for improvement. Treatment of the dione 2.11 with gaseous hydrogen chloride produced the chloroenone 2.12 via concomitant cyclobutane cleavage – aldol cyclization process. The final step, a highly regioselective dehydrochlorination of 2.12, provided (+)-nootkatone 2.2 in ~14% overall yield.

\[ \text{Reagents: (a) acetaldehyde, KOH, EtOH, 5°C (72%); (b) H}_2\text{C=CCH}_2\text{SiMe}_3, \text{TiCl}_4, \text{DCM (89%); (c) NaNH}_2, \text{MeI, benzene (72%); (d) Hg(OAc)}_2, \text{CuCl}_2, \text{Li}_2\text{PdCl}_4, \text{MeOH (58%); (e) gaseous HCl, acetic acid (73%); (f) Al}_2\text{O}_3, \text{hexane, 60°C, 24 h (72%).} \]

**Scheme 2.2 Yoshikoshi’s Route to (+)-Nootkatone 2.2**
2.5.2 Synthetic Route to (+)-Nootkatone 2.2

Similar to Yoshikoshi’s route, my synthetic scheme takes advantage of the steric bias imparted by the gem-dimethyl bridge (Scheme 2.3). For economical and environmental purposes, natural product β-pinene 2.13, a GRAS (Generally Recognized As Safe) compound, was chosen as the starting material. And, while the conversion of β-pinene to nopinone 2.8 could be performed via ozonolysis methods, a safer and more cost-efficient alternative was required. Using a procedure previously reported by Lee,2.12 the oxidative cleavage of β-pinene was performed with mild reaction conditions and inexpensive reagents to provide 2.8 in excellent yields (95%).

As described by Yoshikoshi, 2.8 was converted to the mixed aldol product 2.9. Due to product loss via heat-induced polymerization of excess acetaldehyde, Yoshikoshi’s work-up conditions were altered to incorporate dry column chromatography (DCC) as a preliminary purification method. As a result, a 12% increase in the product yield was observed for this step.

![Scheme 2.3 Synthetic Route to (+)-Nootkatone 2.2](image)

Reagents: (a) KMnO₄, alumina, H₂O, DCM (95%); (b) acetaldehyde, KOH, EtOH, 5°C (84%); (c) Mg, THF, R = H: allyl chloride (98%) or Mg, THF, R = Me: methallyl chloride (92%); (d) KH, 18-crown-6, THF, (2.16a = 71%, page 46 / 2.10a = 81%, page 44); (e) NaN₃, Mel, benzene, (2.15a = 78% and 2.15b = 73%), page 21; (f) 2.11a from 2.15a: KMnO₄, alumina, H₂O, DCM (88%); from 2.15b: Hg(OAc)₂, CuCl₂, LiCl, PdCl₂, MeOH (73%); (g) gaseous HCl, acetic acid (Quantitative); (h) AcOH, NaOAc (93%).
With 2.9 in hand, attempts were made to locate conditions for the formation of the homoallylic alcohols 2.14 in high yield and selectivity (Table 2.1). Although the conditions utilized in Entry 1 provided the desired compound, only a 50% conversion was possible. In an attempt to drive the reaction to completion, the mixture was heated at reflux, only to produce 2,6-dimethyl-1,6-heptadien-4-ol as a major product (Entry 2). Following reported literature procedures, several additional experiments were tried, each unsuccessful (Entries 3-5). Grignard reactions finally proved to be the optimal way to synthesize the desired alcohols 2.14a and 2.14b in excellent yields and high selectivity (Entries 6 and 7). Achievement of the high selectivity is attributed to the steric bias of the isopropylene bridge, a latent isopropenyl group, which facilitates the control of bond formation to occur from the less hindered (opposite) face.

The acquired homoallylic alcohols 2.14 (R = H and R = Me) provide the framework compulsory for sigmatropic anionic Oxy-Cope rearrangements and readily undergo this electronic “reorganization” to afford the corresponding ketones 2.15. This process ultimately establishes the cis-vicinal stereochemical relationship characteristic of (+)-nootkatone (Scheme 2.4).

Several attempts were made to identify appropriate reaction conditions for this rearrangement (Scheme 2.5). When subjected to reflux conditions, a retro-Ene fragmentation product was produced (Entry 1). Milder temperatures were, therefore, warranted for latter experiments. Despite the fact that the KH proved to be an effective (Entry 2) deprotonating agent, O-alkylation occurred when iodomethane was incorporated into the reaction mixture. In addition, the desired rearrangement did not take place within the time span allotted. In order to provide a sufficient amount of time
Table 2.1 Formation of the Homoallylic Alcohol

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>X</th>
<th>Metal</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Br</td>
<td>Zn</td>
<td>DMF</td>
<td>23 °C</td>
<td>~50% conversion to desired product</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Br</td>
<td>Zn</td>
<td>DMF</td>
<td>Reflux</td>
<td>produced as a major product</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Br</td>
<td>Zn</td>
<td>Sat’d NH₄Cl / THF</td>
<td>23 °C</td>
<td>No Reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Starting Material Recovered</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Br</td>
<td>Zn</td>
<td>THF / DMPU</td>
<td>23 °C</td>
<td>No Reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Starting Material Recovered</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>Br</td>
<td>Zn</td>
<td>THF / DMPU</td>
<td>Reflux</td>
<td>Numerous Products Observed via NMR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>Cl</td>
<td>Mg</td>
<td>THF</td>
<td>-42 °C</td>
<td>Selectivity ~20:1 71% Yield</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>Cl</td>
<td>Mg</td>
<td>THF</td>
<td>-42 °C</td>
<td>Selectivity ~20:1 98% Yield</td>
</tr>
</tbody>
</table>
for the Oxy-Cope rearrangement to transpire, a third trial was carried out that would allow the reaction to proceed for 24 hours at room temperature before the addition of methyl iodide. Unfortunately, a $^1$H NMR spectrum of the crude sample revealed that a paraldehyde substance was present in copious amounts (Entry 3).
Efforts were then turned towards the Oxy-Cope Rearrangement of 2.14b (R = H) (Scheme 2.6). Keeping with the knowledge acquired from previous trials, the first experiment was performed at room temperature in order to avoid any retro-Ene decomposition. However, even at room temperature, the retro-Ene product was observable (equation 1) as a by-product. And, although this substrate underwent the Oxy-Cope Rearrangement with ease, the tendency for the potassium enolate to alkylate on the oxygen appeared to be a recurring theme. To enhance the desired C-alkylation, a smaller counter ion was required to coordinate to the oxygen site. Therefore, the K⁺ was replaced with a smaller Li⁺ and the reaction was rerun at 0 °C (Equation 2). Although the alkylation step did not transpire, the rearrangement itself was successful. The only
product observed from this reaction was compound 2.10a indicating that lower temperatures seem to be essential for the elimination of the retro-Ene fragmentation product. This experiment also produced higher selectivity when compared to Yoshikoshi’s previously reported 4:1 inseparable mixture. Precautions were taken to eliminate any possible sources of moisture in an effort to avoid protonation to form 2.10a. This process should reinforce the efforts for the system to undergo C-alkylation to form the desired product. Having taken these measures, the desired compound 2.15b can be produced with extreme care (Equation 3).

\[
\begin{align*}
\text{2.14b} & \quad \text{i) KH, 18-cr-6, THF, 3 hr, rt} \\
& \quad \text{ii) Mel, 0°C, 1 hour} \\
\text{ANHYDROUS} & \quad \text{low yielding} \\
\text{2.15b} & \quad \text{i) KH, 18-cr-6, THF, 5 hr, 0°C} \\
& \quad \text{ii) LiBr} \\
& \quad \text{iii) Mel, 0°C, 1 hour (81%)} \\
\text{2.10a} & \quad \text{i) KH, 18-cr-6, THF, 5 hr, 0°C} \\
& \quad \text{ii) LiBr} \\
& \quad \text{iii) Mel, 0°C, 1 hour (81%)} \\
\end{align*}
\]

\[\text{Equation 3}\]

\[\text{Scheme 2.6 Anionic Oxy-Cope Rearrangement (R = H)}\]

Due to the sensitivity encountered in the tandem anionic Oxy-Cope rearrangement-alkylation sequence, these steps were performed individually (Scheme 2.3). When done separately, the synthesis of 2.15 is successful, high yielding, and achieves remarkable
selectivity, regardless of the R group (Me or H). Subsequent Wacker Oxidation (R = H) or oxidative cleavage (R = Me) of 2.15 produces 2.11a, an intermediate in Yoshikoshi’s route. The remaining steps in Yoshikoshi’s synthesis, concurrent cyclobutane cleavage and aldol cyclization with subsequent dehydrochlorination, were then intercepted to provide an efficient and economic asymmetric synthesis of (+)-nootkatone 2.2. However, to optimize yields, an alternative procedure for the dehydrohalogenation of the chloroenone 2.12 was employed in lieu of Yoshikoshi’s ambiguous alumina prep. (+)-Nootkatone was thus prepared from its hydrochloride precursor utilizing the methodologies previously described by Caine.2.16 This modification ultimately resulted in a 21% yield increase in the last step of the reaction sequence.

2.6 Conclusion

The combination of the Grignard reaction and the anionic Oxy-Cope rearrangement resulted in a powerful tool that could be used to selectively generate two adjacent stereocenters, thereby providing a synthetic sequence to enantiomerically pure (+)-nootkatone. The overall yields for the eight-step syntheses were 31% (R = H) and 33% (R = Me), respectively. Due to the successful outcome, the route developed will prove to be invaluable for a variety of industrial applications. Not only can (+)-nootkatone be utilized for insect (termites, ticks, cockroaches, mole crickets, nematodes, ectoparasites, and red imported fire ants) control with applications in wood preservatives, but the compound synthesized also possesses substantial value in the flavors and fragrance world.2.17

2.7 Experimental

2.7.1 General Experimental
Unless otherwise stated, all experiments were performed under an atmosphere of nitrogen or argon in oven-dried glassware utilizing standard Schlenk techniques and/or a Vacuum Atmospheres dry box. Solvents used as reaction media were distilled immediately before use. Tetrahydrofuran (THF), toluene, and benzene were distilled from sodium benzophenone ketyl. Unless otherwise noted, reagents purchased from Aldrich were used without further purification. Authentic (+)-Nootkatone was purchased from Aromor Inc.; Israel.

Column chromatography was carried out with Standard Grade, 60 Å, 32-63µm, from Sorbent Technologies. Analytical thin layer chromatography (TLC) was performed on precoated silica gel plates (size: 2.5 × 7.5 cm; layer thickness: 250 µm). Components were visualized by illumination with long wave ultraviolet light or exposure to iodine vapor. Frontal retention values (Rf) are reported along with the solvent system used.

All yields and melting points were determined after purification. Melting points were obtained on an Electrothermal Melting Point apparatus. IR spectra were recorded utilizing a Nicolet Avatar 320 FT-IR instrument. GC / MS analyses were performed using a Varian Saturn 2200 equipped with a DB5 column (30m x 0.25 mm i.d. x 0.25 mm thickness) and E.I. (70 eV) capabilities. HRMS analyses were performed by Ohio State University. Compounds requiring elemental analysis were sent to Prevalere Life Sciences. NMR spectra (1H and 13C) were obtained on Bruker AC – 250 and Bruker AC-300 Spectrometers. Chemical shifts, δ, are reported in ppm relative to CDCl3 (7.27 ppm, 1H; 77.23 ppm, 13C) unless noted otherwise. 1H NMR data reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet,
dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets,
ddt = doublet of doublet of triplets, br = broadened, m = multiplet), integration, and
coupling constant (Hz).

### 2.7.2 Preparative Procedures

6,6-dimethyl-bicyclo [3.3.1]heptan-2-one, Nopinone (2.8). Following a method as
described by Lee,\textsuperscript{2,12} finely ground KMnO₄ (2.8 g, 17.8 mmol), acidic alumina
(Brockmann Activity 1, 11.2 g, 0.1098 mol) and water (2.79 g, 0.1552 mol) were mixed
together for five minutes in order to achieve a homogeneous mixture. (-)-β-Pinene 2.13
(0.5 g, 0.582 mL, 3.67 mmol), dissolved in DCM (100 mL), was placed in a round
bottom flask. The moistened permanganate / alumina mixture was added in small
portions over a 10 minute period with continual stirring. The mixture was allowed to
proceed at room temperature while the progress of the reaction was monitored by TLC
(90:10 / hexane: EtOAc). Once complete conversion of the starting material had
occurred, the crude mixture was filtered through a fritted glass funnel and the residue was
washed with DCM (2 x 50mL). The excess solvent was removed via rotary evaporator to
leave a yellow oil, which was further purified by column chromatography (90:10 /
hexane:EtOAc) to give colorless 2.8 (0.48 g, 95% yield). Spectroscopic data matches
that of an authentic sample of nopinone (Aldrich). \(^1\)H NMR: (250 MHz, CDCl₃), δ 2.7-
2.5 (m, 3H), 2.42-2.29 (m, 1H), 2.27-2.2 (m, 1H), 2.13-1.87 (m, 2H), 1.59 (d, 1H, \(J =

\[\text{KMnO}_4, \text{Alumina} \quad \xrightarrow{\text{H}_2\text{O, DCM}} \quad 6,6\text{-dimethyl-bicyclo [3.3.1]heptan-2-one, Nopinone (2.8).} \]

2.13

2.8
9.46), 1.33 (s, 3H), 0.86 (s, 3H). $^{13}$C NMR: (62.5 MHz, CDCl$_3$), $\delta$ 214.77, 57.94, 41.10, 40.30, 32.57, 25.88, 25.17, 22.10, 21.31.

(1$R,5R$)-6,6-dimethyl-3-(E)-ethylidenebicyclo[3.3.1]heptan-2-one (2.9).$^{2,6}$ A magnetic stir bar was placed in a clean, dry 3-neck jacketed RBF fitted with a constant addition funnel and two inlet valves. The apparatus was purged with Argon. A solution of starting material 2.8 (1 g, 1.0194 mL, 7.24 mmol), KOH (0.4872 g, 8.7 mmol) (NaOH may be used in lieu of KOH), and EtOH (17.2 mL) was cooled to 5°C to which a solution of acetaldehyde (0.609 mL, 0.4781 g, 10.9 mmol) in EtOH (4.3 mL) was added over 30 minutes under Argon. The reaction was allowed to proceed at 5°C. After four additional portions of acetaldehyde (0.609 mL) in EtOH (4.3 mL) had been added to the solution at intervals of 15h, stirring was continued for an additional 6h. $p$-Toluenesulfonic acid monohydrate (1.927 g, 10.1 mmol) in EtOH (5 mL) was added to the mixture and the resulting solution was stirred for 3h at room temperature. The solvent was removed via rotovap and the crude brown residue was dissolved in ether. The ethereal solution was passed through a series of dry columns (90:10 / Hexane:EtOAc) and subsequently subjected to a Kugelrohr distillation (85-95°C, 3mmHg) to give 2.9 (1 g, 84% yield) as a colorless liquid. Spectral information matches previously reported data.$^{2,6}$ $^1$H NMR: (250 MHz, CDCl$_3$), $\delta$ 6.89-6.86 (m, 1H), 2.59-2.56
(m, 4H), 2.21 (m, 1H), 1.81-1.77 (m, 3H), 1.46 (m, 1H), 1.35 (s, 3H), 0.86 (s, 3H). $^{13}$C NMR: (62.5 MHz, CDCl$_3$), δ 202.48, 134.76, 134.00, 55.5, 40.5, 38.98, 27.9, 27.8, 26.2, 21.6, 13.7.

**General Grignard Reaction Procedure (2.14).** A solution of the allyl chloride (9 mmol) in freshly distilled THF was added over 30 minutes to a suspension of flame-dried Mg metal turnings (14 mmol) in THF at 60 °C. The Grignard solution darkened while heating at reflux for an additional 20 minutes. The mixture was then cooled to -42°C (dry ice / chlorobenzene) where a solution of the enone 2.9 (3 mmol) in THF was added dropwise. After 5 minutes, the cooling bath was removed and the reaction stirred at room temperature for 1.5 hours. The mixture was decanted into ice-cold 0.1 N HCl and extracted with ether. The combined organic fractions were washed with water and brine, dried over Na$_2$SO$_4$, filtered, and concentrated to provide crude product.

**3-ethylidene-6,6-dimethyl-2-(2-methyl-allyl)-bicyclo[3.1.1]heptan-2-ol (2.14a).** Column chromatography (9:1 / Hexane:EtOAc) provided title compound (0.52 g, 92% yield) as a colorless liquid. $^1$H NMR (250 MHz, CDCl$_3$) δ 5.79-5.77 (m, 1H), 4.82-4.65 (m, 2H), 2.63-2.18 (m, 5H), 1.92 (s, 3H), 1.61 (s, 3H), 1.60-1.57 (dt, 3H), 1.21 (s, 3H), 1.05-1.01 (d, 1H), 0.973 (s, 3H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) δ 143.4, 143.2, 122.0,
114.4, 78.7, 49.8, 48.9, 38.7, 37.9, 31.6, 30.1, 27.3, 24.7, 22.4, 13.1; IR (neat, ν cm⁻¹) 3379, 2970, 2925, 1694, 1465.

**2-allyl-3-ethylidene-6,6-dimethyl-bicyclo[3.1.1]heptan-2-ol (2.14b).** Column chromatography (9:1 / Hexane:EtOAc) provided title compound (0.62 g, 98% yield) as a colorless liquid. ¹H NMR (250 MHz, CDCl₃) δ 5.79-5.83 (m, 2H), 4.97-5.07 (m, 2H), 2.27-2.67 (m, 5H), 1.95 (s, 1H), 1.92 (s, 1H), 1.82 (s, 1H), 1.58-1.61 (dt, 3H), 1.19 (s, 3H), 1.03 (s, 1H), 0.976 (s, 3H); ¹³C NMR (62.5 MHz, CDCl₃) δ 142.9, 134.8, 122.1, 117.7, 78.3, 49.1, 46.7, 38.8, 38.1, 31.5, 29.3, 27.2, 22.4, 13.1; IR (neat, ν cm⁻¹) 3466, 3073, 2914, 1637, 1468; HRMS (EI) m/z 206.1672 (calcd for C₁₄H₂₂O⁺, 206.166516).

![Diagram](image)

**General Procedure for the Oxy-Cope Rearrangement (2.16a and 2.10a).** Under an argon atmosphere, oil free KH (4.1 mmol) was placed in a RBF. Freshly distilled THF (35 mL) was cannulated to the flask and the contents were allowed to stir at 0 °C. Immediately after the addition of the alcohol 2.14 (2.4 mmol), a solution of 18-crown-6 in THF (2.4 mmol) was incorporated via cannulation. The reaction was allowed to proceed at 0-5 °C for ~ 6 hours. Upon completion, the resulting mixture was quenched with a phosphate buffer solution (pH = 7) and the contents were extracted with ether. The combined organic layers were washed with water and brine and dried over Na₂SO₄. After filtration, the excess solvent was removed in vacuo to provide crude product.
3-(1,3-dimethyl-but-3-enyl)-6,6-dimethyl-bicyclo[3.1.1]heptan-2-one (2.16a).

Pure 2.16a (0.49g, 71%) was obtained upon column chromatography (90:10 / Hexane:EtOAc). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 4.76 (s, 1H, C=CH$_2$), 4.72 (s, 1H, C=CH$_2$), 2.65-2.60 (m, 1H, -OH), 2.57-2.50 (m, 2H), 2.47-2.43 (m, 1H), 2.42-2.25 (m, 1H), 2.12-1.95 (m, 3H), 1.73-1.68 (s and q overlapping, 5H), 1.32 (s, 3H), 0.92 (d, 3H, $J$ = 6.84 Hz), 0.79 (s, 3H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 215.9, 144.0, 111.9, 57.9, 44.9, 43.5, 43.2, 40.6, 27.6, 26.8, 25.8, 21.8, 21.2, 15.3.

6,6-dimethyl-3-(1-methyl-but-3-enyl)-bicyclo[3.1.1]heptan-2-one (2.10a). Pure 2.10a (0.4g, 81%) was obtained upon column chromatography (90:10 / Hexane:EtOAc). Spectral information matches previously reported data. $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 5.71-5.60 (m, 1H), 4.99-4.90 (m, 2H), 2.73-2.61 (m, 1H, -OH), 2.45 (t, 1H), 2.38-2.19 (m, 3H), 2.09-1.96 (m, 3H), 1.65-1.61 (m, 2H), 1.22 (s, 3H), 0.85 (d, 3H, $J$ = 6.84 Hz), 0.70 (s, 3H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 215.8, 137.2, 116.1, 57.8, 45.0, 43.4, 40.5, 39.2, 30.2, 26.7, 25.7, 22.3, 21.3, 15.4.

![MethylationReaction](image)

**General Procedure for Methylation (2.15).** Sodium amide (3.64 mmol, assay 90%) was placed in a RBF fitted with a reflux condenser and evacuated and subsequently purged with nitrogen. Freshly distilled benzene was cannulated into the apparatus and
the mixture was allowed to warm via a heating mantle. The starting ketone (1.2 mmol) was then injected and the reaction mixture was allowed to reflux with continual stirring for 5 hours. After which time, the reaction was cooled to 45 °C (via a hot water bath) and iodomethane (2.9 mmol) (freshly dried and distilled from Drierite) was injected in one portion. An additional portion of methyl iodide (1.57 eq.) was injected after 2.5 hours and the solution was allowed to proceed at 45 °C for an additional 15 hours. Upon completion, saturated aqueous NH₄Cl was added to the cooled solution and the product was extracted with Et₂O. The organic layer was then washed with water and brine and dried over Na₂SO₄. Removal of excess solvent provided the crude product 2.15.

3-(1,3-dimethyl-but-3-enyl)-3,6,6-trimethyl-bicyclo[3.1.1]heptan-2-one (2.15a).

Pure 2.15a (0.25g, 78%) was obtained upon column chromatography (50:1 / Hexane:EtOAc). ¹H NMR (250 MHz, CDCl₃) δ 4.72 (s, 1H, C=CH₂), 4.67 (s, 1H, C=CH₂), 3.12-3.01 (br d, 1H), 2.59 (t, 1H), 2.49-2.36 (m, 1H), 2.30-2.22 (m, 1H), 2.13-1.89 (m, 3H), 1.80-1.73 (m, 2H), 1.70 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 0.89-0.87 (s and d overlapping, 6H); ¹³C NMR (62.5 MHz, CDCl₃) δ 219.2, 145.1, 111.3, 59.5, 45.9, 43.1, 41.7, 40.7, 38.1, 35.2, 26.6, 25.8, 22.3, 21.8, 14.7.

3,6,6-trimethyl-3-(1-methyl-but-3-enyl)bicycle[3.1.1]heptan-2-one (2.15b).

Pure 2.15b (0.19g, 73%) was obtained upon column chromatography (90:10 / Hexane:EtOAc). ¹H NMR (250 MHz, CDCl₃) δ 5.82-5.62 (m, 1H), 4.99-4.87 (m, 2H), 3.18-3.04 (m, 1H), 2.52 (t, 1H), 2.39-2.31 (m, 1H), 2.23-2.19 (m, 1H), 1.95-1.79 (m, 3H), 1.72-1.58 (m, 2H), 1.26 (s, 3H), 1.23 (s, 3H), 0.86 (d, 3H, J = 6.79 Hz), 0.79 (s, 3H); ¹³C NMR (62.5 MHz, CDCl₃) δ 219.3, 138.7, 115.1, 59.5, 45.9, 43.0, 41.6, 40.4, 36.9, 35.4, 26.5, 26.1, 25.8, 22.6, 14.7.
(1R, 3S, 5R)-3-[(1R)-1-Methyl-3-oxobutyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-one (2.11). \(^1\)H NMR: (250 MHz, CDCl\(_3\)), \(\delta\) 3.58-3.52 (m, 1H), 2.58-2.47 (m, 2H), 2.42-2.27 (m, 1H), 2.24-2.12 (m, 1H), 2.09 (s, 3H), 2.09-1.96 (m, 1H), 1.93-1.85 (2 br s, 1H), 1.78-1.72 (m, 2H), 1.24 (s, 3H), 1.17 (s, 3H), 0.85-0.82 (d and s overlapping, 6H); \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)) \(\delta\) 219.9, 208.2, 59.5, 47.3, 44.6, 42.7, 41.6, 36.9, 35.1, 30.4, 26.3, 25.7, 24.8, 22.6, 16.4.

Procedure A: Finely ground KMnO\(_4\) (400 mg, 2.5 mmol), acidic alumina (Brockmann Activity 1, 1.56 g, 15.3 mmol) and water (0.4 g, 22 mmol) were mixed together for five minutes in order to achieve a homogeneous mixture. The terminal olefin 2.15a (120 mg, 0.512 mmol), dissolved in DCM (20mL), was placed in a round bottom flask. The moistened permanganate / alumina mixture was added in small portions over a 10 minutes period with continual stirring. The mixture was allowed to proceed at room temperature while the progress of the reaction was monitored by TLC (90:10 / hexane: EtOAc). Once complete conversion of the starting material had occurred, the crude mixture was filtered through a fritted glass funnel and the residue was washed with DCM...
(2 x 50mL). The excess solvent was removed via rotary evaporator to leave a yellow oil, which was further purified by column chromatography (90:10 / hexane:EtOAc) to give colorless 2.11a (0.11 g, 89% yield). Spectral information matches previously reported data.

**Procedure B:** The terminal olefin 2.15b (220 mg, 1 mmol), mercuric acetate (320 mg, 1 mmol), and methanol (2 mL) were stirred under nitrogen at room temperature for 15 minutes. The mixture was then cannulated to a reaction flask containing a solution of LiCl (9 mg, 0.21 mmol), PdCl2 (18 mg, 0.1 mmol), and CuCl2 (40 mg, 3 mmol) in methanol (1 mL). The reaction was allowed to proceed at 55 °C for 1 hour after which time, aqueous NaHCO3 was added and the product was extracted with ether. The organic layer was washed with water, brine, dried (MgSO4), filtered, and concentrated via rotary evaporator to provide the crude material. Column chromatography (90:10 / Hexane:EtOAc) provided 2.11a in pure form (0.16 g, 73%). Spectral information matches previously reported data.

\[
\begin{align*}
\text{2.11a} & \quad \text{gaseous HCl} \quad \text{AcOH} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

*(4R,4aS,6R)-4,4a,5,6,7,8-hexahydro-4,4a-dimethyl-6-(1-chloro-1-methylethyl)-2(3H)-naphthalenone (2.12).* Under a steady stream of argon, a dry 3-neck RBF, fitted with a porous gas frit and two gas flow adapters, was charged with a solution of pure 2.11a in acetic acid (99.6%, Aldrich). Anhydrous gaseous HCl (lecture bottle,
Aldrich) was bubbled through the porous frit at room temperature until a saturated solution was acquired. After 21 hours of stirring at room temperature, the mixture was poured into ice and extracted with dichloromethane. The organic layer was subsequently washed with water and brine, dried (MgSO₄), filtered, and concentrated to provide the crude material in oil form. Recrystallization from hexane provided the nootkatone hydrochloride 2.12 as colorless needles. Spectral information matches previously reported data.² ²⁶ ¹H NMR (300 MHz, CDCl₃) δ 5.75 (s, 1H), 2.53-2.34 (m, 2H), 2.31-2.22 (m, 2H), 2.20-1.91 (m, 4H), 1.60 (s, 3H, CH₃), 1.59 (s, 3H, CH₃), 1.39-1.25 (m, 2H), 1.10 (s, 3H, CH₃), 1.00-0.97 (d, 3H, CH₃, J = 6.76 Hz); ¹³C NMR (62.5 MHz, CDCl₃) δ 199.7, 170.1, 124.9, 74.1, 45.8, 42.4, 40.8, 40.5, 39.5, 32.3, 30.9, 30.5, 28.5, 17.3, 15.3.

(±)-Nootkatone (2.2).² ¹⁶ Sodium acetate (trihydrate, 0.22 g, 1.6 mmol) was added to a single-neck RBF fitted with a reflux condenser. A solution of the chloroenone 2.12 (0.14 g, 0.54 mmol) in glacial acetic acid (4 mL) was injected and the mixture was heated to 100 °C for 2 hours. Upon completion, the reaction mixture was cooled to room temperature, poured into cold water, and extracted with chloroform. The organic layer was then washed with successive portions of 2% aqueous KOH, 2 N HCl, sat’d aqueous NaHCO₃, brine, and dried (MgSO₄). The excess solvent was removed via rotary evaporator to provide the desired compound 2.2 as a yellow oil (93%). The synthesized sample was identical with authentic (±)-Nootkatone in all aspects. ¹H NMR: (250 MHz,
CDCl₃), δ 5.77 (s, 1H, HC=C), 4.74 (s, 1H, C=CH₂), 4.72 (s, 1H, C=CH₂), 1.74 (s, 3H), 1.13 (s, 3H), 0.97 (d, 3H, J = 6.76 Hz). ¹³C NMR: (62.5 MHz, CDCl₃), δ 199.6, 170.5, 149.0, 124.7, 109.3, 43.9, 42.1, 40.5, 40.3, 39.3, 33.0, 31.6, 20.8, 16.8, 14.9.

2.7.3 Spectral Data

Spectral data are included on the following pages.

2.8 References


2.8 Henderson, G. Louisiana State University, Baton Rouge, LA; Bailo, M. Degussa Company. Personal communication, 2005.

Figure 2.3 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.8
Figure 2.4 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.8
Figure 2.5 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.9
Figure 2.6 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.9
Figure 2.7 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.14a

~20:1 selectivity
Figure 2.8 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.14a
Figure 2.9 \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}) of Compound 2.14b
Figure 2.10 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.14b
Figure 2.11 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.10a
Figure 2.12 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.10a
Figure 2.13 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.16a
Figure 2.14 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.16a
Figure 2.15 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.15a
Figure 2.16 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.15a
Figure 2.17 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.15b
Figure 2.18 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.15b
Figure 2.19 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.11a
Figure 2.20 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.11a
Figure 2.21 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 2.11a
Figure 2.22 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 2.12
Figure 2.23 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 2.12
Figure 2.24 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 2.12
Figure 2.25 $^1$H NMR (250 MHz, CDCl$_3$) of (+)-Nootkatone 2.2
Figure 2.26 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of (+)-Nootkatone 2.2


3.1 Cis and Trans Decalins

The two possible stereoisomers of the decalin (bicyclo[4.4.0]decane) ring system, cis and trans, arise from the relative configuration of the substituents located at the bridgehead ring junction. These two systems, therefore, assume drastically different conformations. trans-Fused decalins are linear in shape and are incapable of ring inversion, thereby considered “conformationally locked”. However, the cis-fused decalins are “cup-shaped” and conformationally mobile allowing for ring inversion. The cis-isomer also suffers from three unfavorable gauche interactions as illustrated (Figure 3.1). Thus, the more stable trans-isomer is favored by ~2.8 kcal/mol.  

![Figure 3.1 Cis and Trans Decalin Ring Fusions](image)

3.2 NMR Analysis of Commercially Available Tetrahydronootkatone (THN)

As mentioned in Chapter 2, nootkatone, a sesquiterpenoid ketone, served as a repellent and a feeding deterrent to Formosan subterranean termites, Coptotermes
formosanus Shiraki. Two derivatives of (+)-nootkatone, 1,10-dihydroneootkatone and tetrahydronootkatone (THN), were found to be extremely effective toxicants to Formosan subterranean termites, more so than (+)-nootkatone.3,2

Structure-activity studies performed thus far have been conducted utilizing commercially available THN (Aromor Inc., Israel) and derivatives thereof. However, there was some ambiguity as to the relative stereochemistry of the proton positioned on the ring junction of this compound (Figure 3.2). Considering the two possible stereoisomers of THN, cis and trans-fused, and understanding that conformational differences can often have a dramatic impact on activity, the elucidation of the commercially available THN was essential.

![Figure 3.2 Commercially Available THN and Possible Stereoisomers](image)

With the assistance of 2D-NMR, the assignments of protons, carbons, proton-carbon correlations, and long-range correlations were possible through COSY (Figure 3.3) and
Figure 3.3 COSY Spectra (400 MHz, d-Toluene) of THN (Aromor Inc., Israel)
Figure 3.4 HSQC Spectra (400 MHz, d-Toluene) of THN (Aromor Inc., Israel)
Figure 3.5 NOESY Spectra (400 MHz, d-Toluene) of THN (Aromor Inc., Israel)
HSQC (Figure 3.4) experiments. Through the presence (or absence) of NOE’s in the NOESY Spectra (Figure 3.5), THN was properly identified and it was ascertained that the relative stereochemistry was, in fact, trans-fused (Figure 3.6).

3.3 Cis-fused Systems and Termiticidal Activity

Ando recently studied the termiticidal activity of compounds isolated from Benihi wood, *Chamaecyparis formosensis* Matsum. Interestingly, both acetylenic norisquiterpenoids chamaecynone 3.1 and isochamaecynone 3.2, possess the cis-fused eudesmane framework and are reported to have demonstrated significant termiticidal activity against *Coptotermes formosanus* Shiraki.3.3

With Ando’s findings and recalling that tetrahydronootkatone (now known to be trans-fused and therefore, possesses a linear configuration) exhibits high toxicity and repellent activity towards Formosan subterranean termites, efforts were made to prepare the “cup-shaped” cis-fused tetrahydronootkatone counterpart. With contrasting geometries, important structure-termiticidal activity relationships could be acquired through the comparison of these two stereoisomers, further delineating the structural requirements necessary for biological activity.

![Figure 3.6 Structures of Chamaecynone 3.1 and Isochamaecynone 3.2](image)

3.4 Hydrogenations and Literature Precedence

3.4.1 The Work of Augustine
Augustine, a pioneer in this field of catalytic hydrogenation, carried out a series of experiments on bicyclic enone 3.3. He discovered that the product configuration was particularly influenced by the nature of the solvent and the relative acidity or basicity of the reaction mixture (Table 3.1). While neutral or basic conditions resulted in a lower degree of diastereoselectivity (entries 1-4), extremely high selectivity for the cis-decalone was observed in the presence of acidic media (entries 5, 6).3.4

Table 3.1 Catalytic Hydrogenation of Bicyclic Enone 3.3 3.4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Product Ratio (cis / trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂ (760 torr) / 5% Pd-C / CH₃CN</td>
<td>30 : 70</td>
</tr>
<tr>
<td>2</td>
<td>H₂ (760 torr) / 10% Pd-C / MeOH</td>
<td>41 : 59</td>
</tr>
<tr>
<td>3</td>
<td>H₂ (760 torr) / 5% Pd-C / EtOH</td>
<td>55 : 45</td>
</tr>
<tr>
<td>4</td>
<td>H₂ (760 torr) / 10% Pd-C / NaOH / EtOH</td>
<td>62 : 38</td>
</tr>
<tr>
<td>5</td>
<td>H₂ (760 torr) / 5% Pd-C / CCl₄</td>
<td>97 : 3</td>
</tr>
<tr>
<td>6</td>
<td>H₂ (760 torr) / 10% Pd-C / 3N HCl / EtOH</td>
<td>93 : 7</td>
</tr>
</tbody>
</table>

3.4.2 Hydrogenation of Angular-Substituted Decalones

Substituents positioned along the octalone backbone have been shown to have a strong directing effect on the hydrogenation of the α,β-unsaturated double bond. Such is the case of 3.5 when the angular substituent is a methyl group. Regardless of the hydrogenation method, conventional catalytic hydrogenation 3.4 (entry 1) or transfer hydrogenation 3.5 (entry 2), the corresponding cis-fused decalone is acquired in high selectivity.
Table 3.2 Hydrogenation of 4a-Methyl Substituted Decalones

![Diagram of hydrogenation reaction]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Product Ratio (cis / trans)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂ (760 torr) / 10% Pd-C / EtOH</td>
<td>80 : 20</td>
<td>3.4</td>
</tr>
<tr>
<td>2</td>
<td>HCOONH₄ / 10% Pd-C / MeOH</td>
<td>100 : 0</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>5 min.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The preference for cis-directed hydrogenation has been explained on the basis of the steric model presented in Figure 3.7. Provided that R is small, hydrogenation from the less hindered (top) face will predominate yielding the cis-fused product in high selectivity. When R becomes substantially large, adsorption from the top face is sterically hindered thereby promoting reduction from the bottom face to provide the trans-isomer.³⁶

There have also been several natural product derivatives possessing angular groups that have been subjected to catalytic hydrogenation. Similar to the unsubstituted octalones 3.3, the hydrogenation of these substrates greatly depends on the reaction media. However, in contrast to Augustine’s findings, cis-fused products are preferred under basic media (entries 2, 3, 5) and acidic media yields preferentially the trans-isomer (entry 4).³⁶⁻³⁸
<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Reaction Conditions</th>
<th>Product</th>
<th>Yield</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>H₂ (760 torr) / 10% Pd-C / EtOH</td>
<td><img src="image2.png" alt="Product" /></td>
<td>96</td>
<td>3.7</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>H₂ (760 torr) / 10% Pd-C / 0.3 N NaOH / EtOH</td>
<td><img src="image4.png" alt="Product" /></td>
<td>97</td>
<td>3.8</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>H₂ (760 torr) / 10% Pd-C / KOH / EtOH</td>
<td><img src="image6.png" alt="Product" /></td>
<td>Not Reported</td>
<td>3.6</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Structure" /></td>
<td>H₂ (760 torr) / PtO₂ / HOAc</td>
<td><img src="image8.png" alt="Product" /></td>
<td>90</td>
<td>3.7</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Structure" /></td>
<td>H₂ (760 torr) / Pt / NaOH / H₂O</td>
<td><img src="image10.png" alt="Product" /></td>
<td>65</td>
<td>3.7</td>
</tr>
</tbody>
</table>
3.4.3 Crabtree’s Hydroxyl-Directed Hydrogenations

In the early 1980’s, Crabtree demonstrated that the iridium catalyst, [Ir(cod)py(PCy3)]PF₆, was effective in the stereoselective hydrogenation of cyclic allylic alcohols.³⁹ It is precedent that the absorption of hydrogen to the neighboring alkene occurs syn to that of the directing hydroxyl group. With this, Corey published an example of the stereocontrolled synthesis of cis-hydindanol, incorporating Crabtree’s catalyst (Scheme 3.1).³¹⁰

![Scheme 3.1 Generation of cis-Hydrindanol](image)

3.5 Experimental Findings

With the methodology demonstrated in the aforementioned literature results, efforts were turned towards the hydrogenation of nootkatone and derivatives in hopes to obtain the cis-isomer of tetrahydronootkatone. The results are summarized in Table 3.4.

Hydrogenation of nootkatone 3.7 and valencene 3.9 provided the trans-product, regardless of the conditions and reaction media generated (entries 1-6 & 10).³⁴,³⁵ Suspicion was aimed at the isopropylidene group of nootkatone. Due to its accessibility, it would be the first to undergo hydrogenation. It was thought that this isopropylidene group could coordinate to the metal catalyst and direct the second addition of hydrogen to add from the top face, thereby providing the trans-fused isomer almost exclusively.
Table 3.4 Experimental Hydrogenations of Valencanes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Reaction Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.7</td>
<td>H₂ (760 torr) / 5% Pd-C / EtOH / 2 hr</td>
<td>trans - 3.11</td>
</tr>
<tr>
<td>2</td>
<td>3.7</td>
<td>H₂ (50 psi) / 5% Pd-C / CCl₄ / 2 hr</td>
<td>3.7</td>
</tr>
<tr>
<td>3</td>
<td>3.7</td>
<td>H₂ (760 torr) / 10% Pd-C / 3N HCl / EtOH / 2 hr</td>
<td>trans - 3.11</td>
</tr>
<tr>
<td>4</td>
<td>3.7</td>
<td>H₂ (760 torr) / 10% Pd-C / 0.3 N NaOH / EtOH</td>
<td>trans - 3.12</td>
</tr>
<tr>
<td>5</td>
<td>3.7</td>
<td>HCOONH₄ / 10% Pd-C / MeOH / 20 min.</td>
<td>3.7</td>
</tr>
<tr>
<td>6</td>
<td>3.7</td>
<td>HCOONH₄ / 10% Pd-C / MeOH / 1 hr</td>
<td>Inseparable</td>
</tr>
<tr>
<td>7</td>
<td>3.7</td>
<td>H₂ / [(C₆H₅)₃P]₃RhCl / Benzene / 8 hr</td>
<td>3.8</td>
</tr>
<tr>
<td>8</td>
<td>3.8</td>
<td>H₂ (760 torr) / 10% Pd-C / 3N HCl / EtOH / 2 hr</td>
<td>trans - 3.11</td>
</tr>
<tr>
<td>9</td>
<td>3.8</td>
<td>HCOONH₄ / 10% Pd-C / MeOH</td>
<td>trans - 3.11</td>
</tr>
<tr>
<td>10</td>
<td>3.9</td>
<td>H₂ (760 torr) / 5% Pd-C / EtOH / 2 hr</td>
<td>trans - 3.13</td>
</tr>
<tr>
<td>11</td>
<td>3.10</td>
<td>H₂ / [Ir(cod)py(PCy₃)]PF₆ (20 mol %) / DCM / 2hr</td>
<td>trans - 3.11</td>
</tr>
<tr>
<td>12</td>
<td>3.14</td>
<td>H₂ (50 psi) / 5% Pd-C / CCl₄ / 2 hr</td>
<td>3.14 &amp; 3.8</td>
</tr>
<tr>
<td>13</td>
<td>3.14</td>
<td>NaBH₄ / BF₃ / EtCO₂H</td>
<td>Inseparable</td>
</tr>
<tr>
<td>14</td>
<td>3.15</td>
<td>H₂ (760 torr) / 5% Pd-C / EtOH / (3, 6, &amp; 15 hrs)</td>
<td>3.14</td>
</tr>
<tr>
<td>15</td>
<td>3.15</td>
<td>9-BBN, HOAc</td>
<td>3.14</td>
</tr>
</tbody>
</table>

3.7: X = O; R = isopropylidene
3.8: X = O; R = isopropyl
3.9: X = H,H; R = isopropylidene
3.10: X = equatorial OH, axial H; R = isopropylidene
3.11: X = O; R = isopropyl
3.12: X = O; R = isopropylidene
3.13: X = H,H; R = isopropyl
3.14: R = isopropyl
3.15: R = isopropylidene

---

71
Therefore, the terminal olefinic group of nootkatone was selectively reduced utilizing Wilkinson’s catalyst (entry 7). The hydrogenation product, 11,12-dihydronootkatone 3.8, was subjected to both catalytic hydrogenation (entry 8) and transfer hydrogenation (entry 9) conditions. Unfortunately, both methods provided the trans-isomer exclusively indicating that this recurring result was actually due to the steric impact imparted by the C-4 methyl substituent.

To test this hypothesis, 11,12-dihydronootkatone 3.8 was converted to its corresponding β,γ-unsaturated ketal 3.14. Through this process, the steric effects between the incoming reagent and the C-4 methyl group would be reduced, opening the possibility for a cis-fused ring junction upon the adsorption of hydrogen. Hydrogenation in acidic media (entry 12) did not occur to an appreciable extent and the isomerization and regeneration of 3.8 became the competing and predominant reaction. Hydroboration with subsequent protonation resulted in a complex and inseparable mixture (entry 13). Regardless of the reaction conditions or the duration of exposure to the hydrogen source, the β,γ olefin of nootkatone’s deconjugated acetal 3.15 was not reduced, resulting in the generation of 3.14 as the exclusive product (entries 14 & 15).

Efforts were then turned to the hydroxyl-directed hydrogenation of 3.10, implementing Crabtree’s iridium catalyst. Unfortunately, this transformation was plagued with olefin isomerization and produced trans-THN as the exclusive product.

Alkene isomerization to ketonic products has been reported in various other systems and surprisingly, the catalysts (iridium and rhodium) prove ineffective in these stereoselective reductions. It is postulated that at low pressures, oxidative addition of hydrogen to the catalyst-substrate complex is rate determining, resulting in the competitive alkene
isomerization pathway (Scheme 3.2). Although this problem can be circumvented in rhodium-catalyzed hydrogenations by increasing the hydrogen pressure (>600 psi), no such improvements are observed with iridium catalysts. (At high pressure, substrate-catalyst complexation becomes rate determining, thereby attenuating isomerization.)

\[
\begin{align*}
\text{HO-} & + \text{L} + \text{ML}_2 \xrightleftharpoons[\text{rate determining step}]{K_{eq}} \text{HO-} + \text{ML}_2 \\
& \xrightarrow{k_1} \text{HO-} + \text{ML}_2 \\
& \xrightarrow{k_2} \text{HO-} + \text{ML}_2
\end{align*}
\]

**Scheme 3.2 Mechanistic Consideration of Alkene Isomerization at Low Pressures**

### 3.6 Published Reactions of Valencanes

It is worthy of note that Schaffer published a series of experiments focusing on the oxidations of valencene. And, as illustrated in Scheme 3.3, the trans-isomer was obtained as the major product in all reactions attempted. These results parallel those of our own.

In contrast to our work and the work of Schaffer, Kabbara implies that a cis-fused derivative of nootkatone was obtained (14:1 diastereomeric ratio by $^1$H 300 MHz NMR) during his studies on the conjugate addition of organoaluminium reagents to sterically hindered enones (Scheme 3.4). However, he only reports $^1$H NMR data for the major compound and does not appear to have additional supporting information (2D NMR, X-ray characterization, etc.) to validate his claimed stereochemical result.
Scheme 3.3 Summary of Schaffer’s Results

Scheme 3.4 Kabbara’s Reported Result
3.7 Discussion and Postulated Theory

One of the more interesting aspects of the valencane framework, from a synthetic point of view, is the underestimated steric influence imparted by the C4-methyl substituent. As alluded to earlier, this methyl group provides enough steric congestion to hinder the coordination of the hydrogen-carrying species to the β-face thus deterring an otherwise straight-forward and well-documented chemical transformation from occurring (Scheme 3.5).

Scheme 3.5 Influence of the C4-Methyl Group on Hydrogenation Selectivity

A simple experiment, the hydrogenation of 3.16, would help to substantiate this claim. As illustrated in Scheme 3.6, the axial C4-methyl group, positioned away from the hydrogen-delivery vehicle, should not have a steric impact on the course of the reaction and not impede the generation of the cis-fused isomer.

In 1974, Piers was investigating lithium-ammonia reductions of various octalone systems. These reactions generated the isomeric cis and trans-products in unequal
proportions. Therefore, he required access to pure and authentic samples of each stereoisomer in order to properly evaluate his results. Compound 3.16 was synthesized and subjected to hydrogenation conditions (Table 3.3, entry 2). His results validate and support our postulated theory.

### 3.8 Conclusion

It has been well-demonstrated that systems possessing a non-hydrogen substituent at the C4 position play a definitive role in the steric determination of the reaction. To date, compounds possessing the characteristic valancene skeleta have yet to be selectively reduced to their corresponding cis-isomer in our lab. Perhaps continued experimentation will identify reaction conditions that will be capable of this transformation.

### 3.9 Experimental

#### 3.9.1 General Experimental

Unless otherwise stated, all experiments were performed under an atmosphere of nitrogen or argon in oven-dried glassware utilizing standard Schlenk techniques and / or a
Vacuum Atmospheres dry box. Solvents used as reaction media were distilled immediately before use. Tetrahydrofuran (THF), diethyl ether, toluene, and benzene were distilled from sodium benzophenone ketyl. Dichloromethane (DCM) was dried and distilled from calcium hydride. Unless otherwise noted, reagents purchased from Aldrich were used without further purification.

Hydrogenation products were analyzed via NMR techniques and compared to authentic samples. Tetrahydronootkatone (THN) 3.11, nootkatone 3.7, and 1,10-dihydrnnootkatone 3.12 were purchased from Aromor Inc., (Israel). While THN and nootkatone were used without further purification, 1,10-dihydrnnootkatone was purified via Kugelrohr distillation (162°C / 3mm Hg) before use. Wilkinson’s catalyst was obtained from Pressure Chemical Company (Pittsburgh, PA). Crabtree’s catalyst ([Ir(cod)py(PCy3)]PF6) was purchased from Strem Chemicals.

Column chromatography was carried out with Standard Grade, 60 Å, 32-63μm, from Sorbent Technologies. Analytical thin layer chromatography (TLC) was performed on precoated silica gel plates (size: 2.5 × 7.5 cm; layer thickness: 250 μm). Components were visualized by illumination with long wave ultraviolet light or exposure to iodine vapor. Frontal retention values (Rf) are reported along with the solvent system used.

All yields and melting points were determined after purification. Melting points were obtained on an Electrothermal Melting Point apparatus. IR spectra were recorded utilizing a Nicolet Avatar 320 FT-IR instrument. GC / MS analyses were performed using a Varian Saturn 2200 equipped with a DB5 column (30m x 0.25 mm i.d. x 0.25 mm thickness) and E.I. (70 eV) capabilities. HRMS analyses were performed by Ohio State University. Compounds requiring elemental analysis were sent to Prevalere Life.
Sciences. NMR spectra ($^1$H and $^{13}$C) were obtained on Bruker AC – 250 and Bruker AC-300 Spectrometers. Chemical shifts, $\delta$, are reported in ppm relative to CDCl$_3$ (7.27 ppm, $^1$H; 77.23 ppm, $^{13}$C) unless noted otherwise. $^1$H NMR data reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, br = broadened, m = multiplet), integration, and coupling constant (Hz).

### 3.9.2 Preparative Procedures

**11,12-dihyronootkatone (3.8).** A mixture of nootkatone 3.7 (1 g, 0.46 mmol) and Wilkinson’s catalyst 3.11 ([(PPh$_3$)$_3$RhCl], Pressure Chemical Company, Pittsburgh) (0.686 g, 0.74 mmol) was placed in an oven-dried round bottom flask. The flask was placed under vacuum and purged with argon. Dry benzene (150 mL) was added via syringe. The flask was then flushed with hydrogen gas to expel the argon. The reaction was allowed to proceed at room temperature under a constant flow of hydrogen for 8 h. Upon completion, the mixture was passed through an alumina column and concentrated. To purify, the compound was chromatographed on silica gel eluting with 90:10 hexane:EtOAc, $R_f$ 0.31. Evaporation of solvent gave 3.8 (0.97 g, 96% yield) as a colorless liquid. $^1$H NMR: (250 MHz, CDCl$_3$) $\delta$ 5.50 (s, 1H), 2.47-2.10 (m, 4H), 2.0-1.78
(m, 3H), 1.40 (m, 2H), 1.12-1.10 (m, 1H), 0.99 (s, 3H), 0.91-0.80 (3d and m obscured, 10H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 199.60, 171.49, 124.18, 42.34, 41.97, 40.41, 39.09, 38.80, 33.06, 32.36, 29.50, 19.87, 19.34, 16.85, 14.84.

**Nootkatol (3.10).** To a solution of nootkatone 3.7 (3 g, 13.7 mmol) in dry diethyl ether (50 mL) was added dropwise a 1M solution of LAH (1.1 equivalent, 15.1 mL) in Et$_2$O with continual stirring at 0°C. The reaction stirred at room temperature for four hours and subsequently cooled in an ice bath where it was quenched by the slow addition (caution: vigorous gas evolution) of 1M aqueous sodium potassium tartrate solution. Hexane was incorporated and the heterogeneous solution was warmed to room temperature and stirred for an additional hour, resulting in clear layers. The layers were then separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried (Na$_2$S$_2$O$_4$), filtered, and concentrated to provide the desired alcohol 3.10 (2 g, 66%) in ~96% purity (~4% is the minor diastereomeric alcohol). Analytical results match previously reported data.$^{3,17}$ $^{1}$H NMR: (250 MHz, CDCl$_3$) $\delta$ 5.36 (s, 1H, =$\text{CH}$-), 4.67 (m, 2H, =$\text{CH}_2$), 4.30-4.20 (m, 1H, CH-O-), 2.62 (br s, 1H, -OH), 2.36-2.01 (m, 3H), 1.86-1.77 (m, 3H), 1.70 (s, 3H, =$\text{CCH}_3$), 1.54-1.29 (m, 2H), 0.99 (s, 3H, quaternary Me), 0.89 (d, 3H, $J = 6.61$ Hz, C4 Me), $^{13}$C NMR (62.5 MHz, CDCl$_3$)
δ 149.9, 145.1, 124.4, 108.3, 67.4, 44.3, 40.5, 39.0, 37.9, 36.8, 32.7, 32.1, 20.6, 17.9, 15.1.

**General Hydrogenation Procedure.** To a solution of the substrate in solvent, the transition metal catalyst was added. The mixture was agitated at room temperature under a flow of hydrogen at indicated pressure (Refer to Experimental Table 3.4 for more detail). Once complete, the solution was filtered through a Celite cake and the excess solvent was removed with the aid of a rotary evaporator. Products isolated from reaction mixtures were compared to authentic samples and the identity was established via $^1$H and $^{13}$C NMR.

**General Ammonium Formate Procedure for Transfer Hydrogenation (Table 3.4: Entries 5, 6, and 9).** A mixture of α,β-unsaturated ketone (1 mmol), ammonium formate (5 mmol) and 10% Pd-C (5% of the unsaturated ketone by weight) in redistilled MeOH (20 mL) was refluxed for 5 minutes. Once complete (monitor via TLC), the catalyst was removed by filtration through a Celite cake and the product was isolated by standard workup.

**General Procedure for Hydroboration (NaBH₄ / BF₃) / Protonation (Entry 13, Table 3.4).** To a stirred solution of the alkene in diglyme under nitrogen was added boron trifluoride etherate in diglyme over 1.5 hours. Propionic acid was added and the reaction was heated and maintained at the boiling point as ethyl ether and product distilled. The product was washed with bicarbonate solution, water, dried, filtered, and concentrated via rotary evaporator. The crude oil was characterized via NMR methodologies.
General Procedure for Hydroboration (9-BBN) / Protonation (Entry 15, Table 3.4). The olefin in THF was treated with solid 9-BBN dimer (2.8 equivalents) at 23 °C and was stirred 4 h. The solution, cooled to 0°C, was then treated with glacial acetic acid (3 mL) and the reaction was warmed to 23 °C and stirred for an additional 1.5 h. Upon completion, the mixture was extracted with Et₂O (2 x 50 mL) and the combined organic layers were washed with water (10 mL), dried over MgSO₄, filtered and concentrated in vacuo. The crude oil was characterized via NMR methodologies.

Tetrahydronootkatone (3.11; Table 3.4: Entries 1, 3, 8, 9, 11). The product isolated from reaction mixture matched an authentic sample of commercially available THN (Aromor Inc., Israel). ¹H NMR (250 MHz, d-toluene), δ 2.00-1.88 (m, 1H), 1.85-1.51 (m, 3H), 1.42-1.31 (m, 2H), 1.25-0.72 (m, 6H), 0.71 and 0.60 (2d, 3H each), 0.5 (d, 3H, J = 6.74 Hz), 0.39 (s, 3H); ¹³C NMR (62.5 MHz, CDCl₃), δ 211.0, 46.5, 45.8, 45.0, 44.0, 41.6, 38.6, 35.9, 32.8, 29.4, 28.9, 19.9, 19.5, 14.9, 10.6.
Tetrahydrovalencene (3.13; Entry 10, Table 3.4). To a solution of valencene 3.9 (3 g, 14.7 mmol) (110°C / 3mm Hg) in absolute ethanol (45 mL) was added 150 mg of palladium (5 wt. % on activated carbon). The reaction was allowed to stir under a constant flow of hydrogen gas. Upon completion (monitored via NMR), the reaction mixture was filtered through a Celite cake and the excess solvent removed under vacuo. Kugelrohr distillation (90°C / 3mm Hg) was employed for further purification of the title compound 3.13 (2.6 g, 85%). Analytical results match previously reported data.\textsuperscript{3,18} ¹³C NMR: (62.5 MHz, CDCl₃) δ 46.7, 43.5, 42.5, 38.9, 36.7, 33.2, 30.9, 30.0, 29.2, 29.1, 26.8, 20.0, 19.6, 15.2, 11.3.

General Procedure for Preparation of Deconjugated Acetals (3.14, 3.15).\textsuperscript{3,12} To a solution of the α,β-unsaturated ketone in benzene was added ethylene glycol (3.5 equivalents) and p-toluenesulfonic acid monohydrate (0.02 equivalents). The contents were heated with continuous azeotropic removal of water and excess ethylene glycol via a Dean-Stark trap. Once the theoretical amount of water had been collected, the cooled mixture was diluted with ether, washed with brine and sat’d aqueous NaHCO₃, dried (Na₂SO₄), and concentrated.

\[
\text{Deconjugated acetal of 11,12-dihydonootkatone (3.14). The crude material was purified by column chromatography (90:10 / Hexane:EtOAc) to give compound 3.14 (77%) as a colorless oil, } R_f \ 0.47. \quad ^1H \text{ NMR: (250 MHz, CDCl}_3\text{) δ 5.39-5.28 (m, 1H),}
\]
3.92-3.84 (m, 4H), 2.45-2.31 (m, 1H), 2.19-2.08 (m, 1H), 1.95-1.80 (m, 1H), 1.81-1.6 (m, 2H), 1.56-1.50 (m, 2H), 1.49-1.33 (m, 2H), 0.97-0.78 (m, 14H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 140.51, 122.38, 108.97, 64.33, 63.95, 41.50, 40.82, 40.32, 39.59, 37.50, 36.25, 32.27, 29.09, 19.90, 19.23, 17.19, 15.10. IR (film, $\nu$ cm$^{-1}$) 2970, 1661, 1160, 1105, 950; MS ($m/z$) 264.

Deconjugated Acetal of (+)-Nootkatone (3.15). Product 3.15 was isolated as a thick yellow oil (99%). $^1$H NMR: (250 MHz, CDCl$_3$) $\delta$ 5.50-5.28 (m, 1H, -C=CHC-), 4.71 (m, 2H, C=CH$_2$), 3.94 (m, 4H, -OCH$_2$CH$_2$O-), 2.50-2.34 (m, 1H), 2.25-1.75 (m, 3H), 1.73 (s, 3H), 1.68-1.50 (m, 4H), 1.32-1.12 (m, 2H), 0.98 (s, 3H), 0.88 (d, 3H, $J$ = 6.28 Hz); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 150.1, 140.5, 122.0, 108.9, 108.6, 64.4, 64.2, 42.4, 41.6, 40.3, 39.6, 37.8, 31.1, 20.7, 17.3, 15.1; IR (film, $\nu$ cm$^{-1}$) 2968, 2877, 1674, 1149, 1092; HRMS (EI) $m/z$ 262.1935 (M$^+$, 262.1927 calcd for C$_{17}$H$_{26}$O$_2$).

3.9.3 Spectral Data

Spectral data are included on the following pages. NMR spectra for Nootkatone 3.7 are located in Chapter 2 (Figures 2.25 and 2.26).

3.10 References

Figure 3.8 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 3.8
11, 12-dihyronootkatone

Figure 3.9 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 3.8
Figure 3.10 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 3.8
Figure 3.11 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 3.9
Figure 3.12 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 3.9
Figure 3.13 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 3.10
Figure 3.14 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 3.10
Figure 3.15 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 3.11

Tetrahydronootkatone (THN)

3.11
Figure 3.16 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 3.11
Figure 3.17 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 3.11
Figure 3.18 $^1$H NMR (250 MHz, d-Toluene) of Compound 3.11
Figure 3.19 $^{13}$C NMR (62.5 MHz, d-Toluene) of Compound 3.11

Tetrahydronootkatone (THN)  
3.11
Figure 3.20 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 3.12
Figure 3.21 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 3.12
Figure 3.22 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 3.12
Figure 3.23 ¹H NMR (250 MHz, CDCl₃) of Compound 3.13
Figure 3.24 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 3.13
Figure 3.25 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 3.14
Figure 3.26 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 3.14
Figure 3.27 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 3.14
Figure 3.28 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 3.15
Figure 3.29 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Downfield Expansion of Compound 3.15
Figure 3.30 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 3.15
Figure 3.31 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 3.15


4.1 Overview

As a member of the valencane family, (+)-nootkatone 4.1, recognized for its odor-profile and non-toxic nature, is currently added to juices and fragrances to impart a grapefruit essence. Of particular interest, however, is its potent and seemingly receptor-specific activity towards the Formosan subterranean termite, Coptotermes formosanus Shiraki. In an effort to further delineate the structural requirements that are necessary to elicit such termital response, several (+)-nootkatone-based derivatives have been synthesized and tested for activity. (The results of the biological-activity studies will be discussed later in Chapter 6.) In addition, since structure is usually an important factor controlling biological activity, it was necessary to establish the absolute configuration of this naturally occurring sesquiterpenoid through X-ray analysis of a heavy-atom derivative.

4.2 Synthetic Derivatives of (+)-Nootkatone

(+)-Nootkatone 4.1 was subjected to a variety of reagents to yield an assortment of compounds possessing different functionalities. These functional groups encompass: acetals (4.2, 4.4, 4.8), alcohols (4.5), epoxides (4.6), amides (4.13, 4.14), alkyl bromides (4.9, 4.10), ketones (4.3, 4.7, 4.11), and dienes (4.12) (Scheme 4.1). The heavy-atom derivative, α,α’-dibromoketone 4.9, was not only used to establish the absolute configuration of (+)-nootkatone, but it was also an invaluable precursor to several sesquiterpenoid analogs.

Scheme 4.1 Synthetic Derivatives of (+)-Nootkatone 4.1
4.3 Synthesis and Structure Determination of a Heavy-Atom Derivative

In 1965, MacLeod reported the generation of the monobrominated derivative 4.15 from tetrahydronootkatone (THN) 4.7.\(^1\) Using a standard experimental procedure for the \(\alpha\)-halogenation of a carbonyl containing compound, it was surprising that with one equivalent of bromine, the crude mixture contained enriched amounts of an unexpected dibromo product 4.9 (entry 2, Table 4.1).\(^2\) Although the isolation of MacLeod’s monobromide was not achieved in our hands, under optimal conditions, the reaction was driven to the exclusive production of this dibromide species (entry 3, Table 4.1) where both bromine substituents are oriented equatorial, thereby minimizing steric strain. (Alternative axial placement would have resulted in unfavorable 1,3-interactions with the angular methyl group.)

![Table 4.1 Bromination of THN 4.7]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents of Bromine</th>
<th>Monobromide : Dibromide ((^1)H NMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>1.2 : 1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1 : 1.7</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>4.9 exclusive</td>
</tr>
</tbody>
</table>

\[^1\]HOAc

\[^2\]m.p. = 80-81°C

\[^3\]m.p. = 133-135°C
This heavy-atom dibromide, derivative 4.9, recrystallized with ease and was sufficient for the determination of the absolute configuration via X-ray crystallography (Figure 4.2).\(^4,3\)

### 4.4 Reactivity Consideration of 2-Decalones

According to Huffman, 5α-3-keto steroids 4.15 enolize away from the bridgehead predominately towards C-2 to afford the 2-bromo-3-ketone 4.16. On the basis of torsional and vector-analysis calculations, this phenomenon has been extended to include 2-decalone systems. Calculations also indicate that 2,3-olefins of trans-octalin systems have increasing stability as the angular substituent increases in size (Figure 4.1).\(^4,4\)

![Diagram of regiochemical preference for 2-Decalones](image_url)

**Figure 4.1 Regiochemical Preference for 2-Decalones** \(^4,4\)
Figure 4.2 Crystal Structure of 4.9
4.5 α,α’-Dibromoketone 4.9 as a Precursor to Various Sesquiterpenoid Analogs

4.5.1 Favorskii Rearrangement

By subjecting 4.9 to tert-butyl amine, entries into 5/6 ring fused systems were accessed through a ring-contracted Favorskii rearrangement. Both cyclopentenecarboxylic amides 4.13 and 4.14 were acquired in a 3:1 inseparable mixture (characterized via $^1$H NMR of olefinic proton), respectively (Scheme 4.2). The preference for 4.13 was determined on the basis of the aforementioned regiochemical considerations of 2-decalones.

![Scheme 4.2 Favorskii Rearrangement of 4.9](image)

Under the influence of base, α,α’-dibromoketone 4.9 tautomerizes away from the bridgehead into its preferred enol form. While it is this enol that is responsible for the formation of the major amide product 4.13, the minor amide, 4.14, is generated from the alternative regio-enol form (Scheme 4.3).

4.5.2 Dehydrohalogenation Reactions

The dibromide was also subjected to dehydrohalogenation conditions in order to obtain a cyclohexadienone compound. While monitoring the reaction progress, it became evident that the reaction proceeds through a stable intermediate, which could easily be separated and isolated via column chromatography. Based on the noted
Scheme 4.3 Demonstrated Enolization Preference in the Favorskii Rearrangment

Table 4.2 Variations in Dehydrohalogenation Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents (Li₂CO₃)</th>
<th>Equivalents (LiBr)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.1</td>
<td>5.9</td>
<td>~50% conversion; 4.10 isolated</td>
</tr>
<tr>
<td>2</td>
<td>12.2</td>
<td>11.8</td>
<td>Complete conversion to 4.12; 70% Yield</td>
</tr>
</tbody>
</table>
regiochemical enolization preference, and the fact that a singlet (δ 1.90 ppm), corresponding to a vinylic methyl substituent (-C=CH\textsubscript{3}), was observed in the \textsuperscript{1}H NMR spectrum, the intermediate was elucidated to be \textbf{4.10}. By modifying the reaction conditions, the reaction was effectively driven to the double elimination product and dienone-phenol substrate \textbf{4.12} (Table 4.2). (An in-depth discussion on the reactivity and selectivity of sesquiterpenoid dienones, such as \textbf{4.12}, in dienone-phenol rearrangements will be addressed in Chapter 5.) Reduction of α-bromo ketone \textbf{4.10} (Zn / acetic acid) into the parent ketone \textbf{4.11} also provided an additional (+)-nootkatone sesquiterpenoid derivative (Scheme 4.1, 68\%).

\textbf{4.6 Conclusion}

Through the synthesis and characterization of various sesquiterpenoids, the absolute configuration of (+)-nootkatone was established and an assortment of valencenoid derivatives were constructed. The series of compounds generated demonstrated the innate preference 2-decalone systems have with respect to enolization. These compounds, tested for repellent activity, will also aid in the elucidation of structure-activity relationships.

\textbf{4.7 Experimental}

\textbf{4.7.1 General Experimental}

Unless otherwise stated, all experiments were performed under an atmosphere of nitrogen or argon in oven-dried glassware utilizing standard Schlenk techniques and / or a Vacuum Atmospheres dry box. Solvents used as reaction media were distilled immediately before use. Diethyl ether and benzene were distilled from sodium benzophenone ketyl. Chloroform and DMF (N,N-dimethylformamide) were dried and
distilled from 4A Linde molecular sieves. Unless otherwise noted, reagents purchased from Aldrich were used without further purification.

Hydrogenation products were analyzed via NMR techniques and compared to authentic samples. Authentic samples of tetrahydronootkatone (THN) 4.7 and nootkatone 4.1 were purchased from Aromor Inc., (Israel) and used without further purification. Wilkinson’s catalyst was obtained from Pressure Chemical Company (Pittsburgh, PA).

Column chromatography was carried out with Standard Grade, 60 Å, 32-63μm, from Sorbent Technologies. Analytical thin layer chromatography (TLC) was performed on precoated silica gel plates (size: 2.5 × 7.5 cm; layer thickness: 250 μm). Components were visualized by illumination with long wave ultraviolet light or exposure to iodine vapor. Frontal retention values (Rf) are reported along with the solvent system used.

All yields and melting points were determined after purification. Melting points were obtained on an Electrothermal Melting Point apparatus. IR spectra were recorded utilizing a Nicolet Avatar 320 FT-IR instrument. GC / MS analyses were performed using a Varian Saturn 2200 equipped with a DB5 column (30m x 0.25 mm i.d. x 0.25 mm thickness) and E.I. (70 eV) capabilities. HRMS analyses were performed by Ohio State University. Compounds requiring elemental analysis were sent to Prevalere Life Sciences. NMR spectra (1H and 13C) were obtained on Bruker AC – 250 and Bruker AC-300 Spectrometers. Chemical shifts, δ, are reported in ppm relative to CDCl3 (7.27 ppm, 1H; 77.23 ppm, 13C) unless noted otherwise. 1H NMR data reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets,
ddt = doublet of doublet of triplets, br = broadened, m = multiplet), integration, and coupling constant (Hz).

4.7.2 Preparative Procedures

**General Procedure for Preparation of Deconjugated Acetals.** To a solution of the α,β-unsaturated ketone in benzene was added ethylene glycol (3.5 equivalents) and p-toluenesulfonic acid monohydrate (0.02 equivalents). The contents were heated with continuous azeotropic removal of water and excess ethylene glycol via a Dean-Stark trap. Once the theoretical amount of water had been collected, the cooled mixture was diluted with ether, washed with brine and sat’d aqueous NaHCO₃, dried (Na₂SO₄), and concentrated.

Deconjugated Acetal of (+)-Nootkatone (4.2). Product 4.2 was isolated as a thick yellow oil (99%). ¹H NMR: (250 MHz, CDCl₃) δ 5.50-5.28 (m, 1H, -C=CHC-), 4.71 (m, 2H, C=CH₂), 3.94 (m, 4H, -OCH₂CH₂O-), 2.50-2.34 (m, 1H), 2.25-1.75 (m, 3H), 1.73 (s, 3H), 1.68-1.50 (m, 4H), 1.32-1.12 (m, 2H), 0.98 (s, 3H), 0.88 (d, 3H, J = 6.28 Hz); ¹³C NMR (62.5 MHz, CDCl₃) δ 150.1, 140.5, 122.0, 108.9, 108.6, 64.4, 64.2, 42.4, 41.6, 40.3, 39.6, 37.8, 31.1, 20.7, 17.3, 15.1; IR (film, ν cm⁻¹) 2968, 2877, 1674, 1149, 1092; HRMS (EI) m/z 262.1935 (M⁺, 262.1927 calcd for C₁₇H₂₆O₂). Anal. Calcd for C₁₇H₂₆O₂: C, 77.82; H, 9.99. Found: C, 77.58; H, 9.90.
Deconjugated Acetal of 11,12-dihyronootkatone (4.4). Product 4.4 was isolated in pure form as a colorless oil (77.2%). $^1$H NMR: (250 MHz, CDCl$_3$) $\delta$ 5.39-5.28 (m, 1H, -C=CH-), 3.92-3.84 (m, 4H, -OCH$_2$CH$_2$O-), 2.45-2.31 (m, 1H), 2.19-2.08 (m, 1H), 1.95-1.80 (m, 1H), 1.81-1.6 (m, 2H), 1.56-1.50 (m, 2H), 1.49-1.33 (m, 2H), 0.97-0.78 (m, 14H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 140.51, 122.38, 108.97, 64.33, 63.95, 41.50, 40.82, 40.32, 39.59, 37.50, 36.25, 32.27, 29.09, 19.90, 19.23, 17.19, 15.10; IR (film, $\nu$ cm$^{-1}$) 2970, 1661, 1160, 1105, 950; MS ($m/z$) 264.

Acetal of Tetrahyronootkatone (4.8). Following the procedure for the preparation of deconjugated acetals, 4.8 was isolated as a colorless oil (98%), mp 37-39 °C. $^1$H NMR: (250 MHz, CDCl$_3$) $\delta$ 3.93 (s, 4H, -OCH$_2$CH$_2$O-), 1.74-1.61 (m, 2H), 1.58-1.44 (m, 2H), 1.42-1.19 (m, 7H), 0.85 (d, 3H, $J = 6.64$ Hz), 0.84 (d, 3H, $J = 6.64$ Hz), 0.80 (d, 3H, $J = 6.24$ Hz), 0.69 (s, 3H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 109.2, 64.1, 64.0, 43.0, 41.7, 40.7, 39.8, 38.7, 38.0, 35.9, 33.0, 29.5, 28.6, 19.9, 19.5, 15.7, 10.3; IR (film, $\nu$ cm$^{-1}$) 2935, 2873, 1717, 1455, 1111, 1073; HRMS (EI) $m/z$ 266.2209 ($M^+$, 266.224031 calcd for C$_{17}$H$_{30}$O$_2$).
11,12-dihyronootkatone (4.3). A mixture of nootkatone 4.1 (1 g, 0.46 mmol) and Wilkinson’s catalyst $^4$9 [(PPh$_3$)$_3$RhCl], Pressure Chemical Company, Pittsburgh) (0.686 g, 0.74 mmol) was placed in an oven-dried round bottom flask. The flask was placed under vacuum and purged with argon. Dry benzene (150 mL) was added via syringe. The flask was then flushed with hydrogen gas to expel the argon. The reaction was allowed to proceed at room temperature under a constant flow of hydrogen for 8 h. Upon completion, the mixture was passed through an alumina column and concentrated. To purify, the compound was chromatographed on silica gel eluting with 90:10 hexane:EtOAc, $R_f$ 0.31. Evaporation of solvent gave 4.3 (0.97 g, 96% yield) as a colorless liquid. $^1$H NMR: (250 MHz, CDCl$_3$) $\delta$ 5.50 (s, 1H), 2.47-2.10 (m, 4H), 2.0-1.78 (m, 3H), 1.40 (m, 2H), 1.12-1.10 (m, 1H), 0.99 (s, 3H), 0.91-0.80 (3d and m obscured, 10H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 199.60, 171.49, 124.18, 42.34, 41.97, 40.41, 39.09, 38.80, 33.06, 32.36, 29.50, 19.87, 19.34, 16.85, 14.84.

Nootkatol (4.5). To a solution of nootkatone 4.1 (3 g, 13.7 mmol) in dry diethyl ether (50 mL) was added dropwise a 1M solution of LAH (1.1 equivalent, 15.1 mL) in
Et₂O with continual stirring at 0°C. The reaction stirred at room temperature for four hours and subsequently cooled in an ice bath where it was quenched by the slow addition (caution: vigorous gas evolution) of 1M aqueous sodium potassium tartrate solution. Hexane was incorporated and the heterogeneous solution was warmed to room temperature and stirred for an additional hour, resulting in clear layers. The layers were then separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried (Na₂S₂O₄), filtered, and concentrated to provide the desired alcohol 4.5 (2 g, 66%) in ~96% purity (~4% is the minor diastereomeric alcohol).

Analytical results matches previously reported data. ¹H NMR: (250 MHz, CDCl₃) δ 5.36 (s, 1H, =CH-), 4.67 (m, 2H, =CH₂), 4.30-4.20 (m, 1H, CH-O-), 2.62 (br s, 1H, -OH), 2.36-2.01 (m, 3H), 1.86-1.77 (m, 3H), 1.70 (s, 3H, =CCH₃), 1.54-1.29 (m, 2H), 0.99 (s, 3H, quaternary Me), 0.88 (d, 3H, J = 6.61 Hz, C₄ Me); ¹³C NMR (62.5 MHz, CDCl₃) δ 149.9, 145.1, 124.4, 108.3, 67.4, 44.3, 40.5, 39.0, 37.9, 36.8, 32.7, 32.1, 20.6, 17.9, 15.1.

11,12-epoxy-11,12-dihydroneootkatone (4.6). (+)-Nootkatone (0.5 g, 2.3 mmol) in dry chloroform (15 mL) was placed in a three-neck jacketed flask fitted with a constant addition funnel. A solution of m-chloroperbenzoic acid (2.7 mmol, 70-75%) in chloroform was charged to the funnel and slowly added to the cooled reaction solution (5°C). The reaction was maintained at this temperature overnight and subsequently
diluted with ether, washed with aq. NaOH and brine, dried (Na₂SO₄), filtered, and concentrated. Upon Kugelrohr distillation (180°C / 3mm Hg), the epoxy-ketone 4.6 solidified in a diastereomeric mixture and was ultimately recrystallized as thick needles (0.49 g, 91%) from light petroleum, mp 90-92 °C. Analytical data match those previously reported.⁴.⁵b ¹H NMR (250 MHz, CDCl₃), δ 5.76 (s, 1H, -HC=C-), 1.21 (d, 3H, J = 2.49 Hz), 1.02 (s, 3H), 0.98 and 0.97 (2d, 3H, J = 6.74 Hz); ¹³C NMR (62.5 MHz, CDCl₃), δ 199.3, 169.8, 124.8, 59.1, 53.3, 42.0, 40.7, 40.4, 39.4, 39.0, 32.4, 28.4, 18.0, 16.7, 14.9; IR (film, ν cm⁻¹) 2943, 1666, 1613, 1284. X-ray data available in Appendix B.

**Tetrahydronootkatone (4.7).** To a solution of (+)-nootkatone 4.1 in ethanol, 5% palladium on carbon was added. The mixture was agitated at room temperature under a steady flow of hydrogen for two hours. Once complete, the solution was filtered through a Celite cake and the excess solvent was removed with the aid of a rotary evaporator. The product isolated from reaction mixture matched an authentic sample of commercially available THN (Aromor Inc., Israel). ¹H NMR (250 MHz, d-toluene), δ 2.00-1.88 (m, 1H), 1.85-1.51 (m, 3H), 1.42-1.31 (m, 2H), 1.25-0.72 (m, 6H), 0.71-0.60 (2d, 3H each), 0.5 (d, 3H, J = 6.74 Hz), 0.39 (s, 3H); ¹³C NMR (62.5 MHz, CDCl₃), δ 211.0, 46.5, 45.8, 45.0, 44.0, 41.6, 38.6, 35.9, 32.8, 29.4, 28.9, 19.9, 19.5, 14.9, 10.6.
1,3-dibromo-6-isopropyl-4,4a-dimethyl-octahydro-naphthalen-2-one (4.9). To a solution of THN 4.7 (0.5 g, 2.25 mmol) in glacial acetic acid (11.2 mL) was slowly added a 1M solution of Br₂ (0.23 mL) in acetic acid (5 mL). The solution was allowed to stir at room temperature for 15 h under a positive pressure of N₂. The reaction mixture was then poured over ice where it remained for 1 h. The mixture was filtered on a fritted funnel to isolate a tan solid. This solid material can easily be recrystallized from ethanol to provide the title compound 4.9 as colorless crystals, 0.53 g (33%), mp 133-135 °C. ¹H NMR (250 MHz, CDCl₃), δ 4.59 (s, 1H, α-H), 4.54 (s, 1H, α-H), 2.27-2.16 (m, 1H), 1.92-1.67 (m, 3H), 1.55-1.24 (m, 4H), 1.22 (d, J = 6.62 Hz, 3H), 0.98 (s, 3H), 0.91-68 (m, 8H); ¹³C NMR (62.5 MHz, CDCl₃), δ 193.18, 61.75, 60.70, 53.69, 53.37, 43.47, 41.10, 38.58, 32.92, 29.50, 28.69, 20.41, 19.91, 15.64, 12.72; [α]D = +0.28°; IR (KBr pellet, ν cm⁻¹) 2942, 2868, 1735; MS (m/z) 380; Anal. Calcd for C₁₅H₂₄OBr₂: C, 47.39; H, 6.36. Found: C, 47.35; H, 6.10. X-ray data available in Appendix B.

1-bromo-6-isopropyl-4.4a-dimethyl-4a,5,6,7,8,8a-hexahydro-1H-naphthalen-2-one (4.10). The crude dibromide 4.9 (0.1 g, 0.26 mmol) was placed in a flask,
evacuated, and subsequently purged with N₂. Dry DMF was cannulated and the solution was allowed to stir. Lithium bromide (0.13 g, 1.6 mmol) and lithium carbonate (0.12 g, 1.6 mmol) were weighed and added to the solution in one portion. The mixture was allowed to heat at 85 °C for 16 h under an inert atmosphere. Once complete, the solution was cooled and decanted into ice-cold 1.5 N HCl and extracted with Et₂O. The organic layer was washed with water, dried over sodium sulfate, filtered, and concentrated. The crude material was purified by column chromatography (75:25 / hexane:EtOAc), Rf 0.59 of the pure single elimination product 4.10 (40 mg, 50%). ¹H NMR: (250 MHz, CDCl₃) δ 5.81 (m, 1H), 4.49 (d, 1H, J = 13 Hz), 2.19-2.06 (m, 1H), 2.0-1.91 (m, 1H), 1.89 (s, 3H), 1.85-1.73 (m, 2H), 1.46-1.13 (m, 4H), 1.08 (s, 3H), 1.01-0.97 (2d and 1m overlapping, 9H); ¹³C NMR: (62.5 MHz, CDCl₃), δ 191.1, 172.0, 124.4, 58.67, 50.97, 41.91, 38.88, 38.31, 32.57, 28.59, 27.33, 19.88, 19.39, 19.29, 17.95; IR (film, ν cm⁻¹) 2953, 1677, 1616; MS (m/z) 300. Anal. Calcd for C₁₅H₂₃OBr: C, 60.20; H, 7.75. Found: C, 60.05; H, 7.60.

Reactive Debromination of 4.10.⁴⁷ To a solution of the α-brominated compound 4.10 (0.1 g, 0.33 mmol) in acetic acid (5 mL) was added activated Zn dust ⁴.¹¹ in one portion. The reaction mixture was stirred magnetically under an atmosphere of argon for three hours. Upon completion, the reaction mixture was poured into water (50 mL) and
filtered through a Celite cake. The filtrate was then extracted with ethyl acetate, washed successively with water, sat’d aqueous NaHCO₃, and water again. The organic layer was dried (Na₂SO₄), filtered, and concentrated in vacuo to provide 4.11 in crude form.

Column chromatography (9:1 / hexane:ethyl acetate), Rₙ 0.30, provided 50 mg of pure 4.11 (68%). ¹H NMR: (250 MHz, CDCl₃) δ 5.71 (s, 1H), 1.89 (s, 3H, -C=CCH₃), 1.05 (s, 3H), 1.04-0.89 (m, 3H), 0.86 and 0.85 (2d, 3H each, J = 6.45 Hz); ¹³C NMR: (62.5 MHz, CDCl₃) δ 201.0, 173.8, 127.6, 44.5, 42.4, 40.6, 40.1, 39.9, 34.4, 30.4, 29.5, 21.4, 20.9, 20.8, 18.3.

6-isopropyl-4,4a-dimethyl-5,6,7,8-tetrahydro-4aH-naphthalen-2-one (4.12). The crude dibromide 4.9 (1 g, 2.6 mmol) was placed in a round bottom flask, evacuated, and subsequently purged with N₂. Dry DMF was cannulated and the solution was allowed to stir. Lithium bromide (2.7 g, 31 mmol) and lithium carbonate (2.37 g, 32 mmol) were weighed and added to the solution in one portion. The mixture was allowed to heat at 85 °C for 16 h under an inert atmosphere. Once complete, the solution was cooled and decanted into ice-cold 1.5 N HCl and extracted with Et₂O. The organic layer was washed with water, dried over sodium sulfate, filtered, and concentrated. The crude material was purified by column chromatography (75:25 / hexane:EtOAc), Rₙ 0.44 to give 0.4 g (70%) of the pure dienone 4.12. ¹H NMR: (250 MHz, CDCl₃) δ 6.03-6.01 (m,
2H), 2.58-2.38 (tdd, 1H), 2.37-2.28 (ddd, 1H), 1.95-1.94 (d and br m obscured, 4H), 1.93-
1.88 (m, 1H), 1.72-1.33 (m, 2H), 1.24 (s, 3H), 1.16-0.88 (m, 2H), 0.83 (2d overlapping,
6H); $^{13}$C NMR: (62.5 MHz, CDCl$_3$), $\delta$ 186.4, 168.4, 166.2, 126.5, 123.9, 43.31, 40.70,
38.44, 32.75, 32.09, 31.26, 23.33, 20.00, 19.43, 18.79; IR (film, $\nu$ cm$^{-1}$) 2955, 2871, 1660,
1627; MS (m/z) 218.

Cyclopentenecarboxylic amides (4.13, 4.14).\(^{4.5}\) To a stirred solution of the
dibromide 4.9 (0.2 g, 0.53 mmol) in freshly distilled Et$_2$O (3 mL) was added $t$-butyl
amine (0.19 g, 2.6 mmol) dropwise. The reaction was allowed to proceed at room
temperature for 22 h after which time pentane (1 mL) was added. The precipitate was
filtered through a short pad of Celite and rinsed with ethyl acetate. The crude material
was purified by column chromatography (hexane:EtOAc / 9:1) to give 0.122 g (80%) of
4.13 and 4.14 in a 3:1 ratio, respectively. $^1$H NMR (250 MHz, CDCl$_3$), $\delta$ 5.98 (m, 1H, -
C=CH), 5.98 (m, 1H, -C=CH), 5.33 (br s, 1H, NH), 1.31 (s, 9H, $t$Bu), 1.2-1.02 (m, 7H),
0.94-0.91 (d and br m overlapping, 4H), 0.88-0.71 (2d and m overlapping, each 3H), 0.63
(s, 3H); $^{13}$C NMR (62.5 MHz, CDCl$_3$), $\delta$ 167.2, 142.1, 140.5, 54.1, 50.9, 49.59, 48.86,
38.97, 38.12, 33.13, 29.98, 28.78, 22.51, 20.02, 19.87, 13.1, 11.2. IR (neat, $\nu$ cm$^{-1}$) 2975-
2865, 1695. Anal. Calcd for C$_{19}$H$_{33}$NO: C, 78.29; H, 11.41; N, 4.81. Found: C, 78.15;
H, 11.38; N, 4.68.
4.7.3 Spectral Data

NMR spectra for Nootkatone 4.1 are located in Chapter 2 (Figures 2.25 and 2.26). NMR spectra for 11,12-dihydronootkatone 4.3, (+)-nootkatol 4.5, tetrahydronootkatone 4.7, and deconjugated acetals (4.2, 4.4) were presented in Chapter 3. Spectral data for the remaining compounds are included on the following pages.

4.7.4 X-ray Data

X-ray data for compounds 4.6, 4.8 and 4.9 are included in Appendix B.

4.8 References


4.11 To activate zinc dust, wash well with successive portions of: 5% HCl, water, methanol, and ether. Remove excess solvent *in vacuo* with slight heating.
Figure 4.3 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 4.6
Figure 4.4 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 4.6
Figure 4.5 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 4.8
Figure 4.6 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 4.8
Figure 4.7 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 4.9
Figure 4.8 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 4.9
Figure 4.9 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 4.9
Figure 4.10 $^1$H NMR (250 MHz, d-toluene) of Compound 4.9
Figure 4.11 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 4.10
Figure 4.12 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 4.10
Figure 4.13 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 4.10
Figure 4.14 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 4.11
Figure 4.15 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 4.11
Figure 4.16 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 4.11
Figure 4.17 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 4.12
Figure 4.18 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 4.12
Figure 4.19 $^1$H NMR (250 MHz, CDCl$_3$) of Compounds 4.13 and 4.14
Figure 4.20 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compounds 4.13 and 4.14
Figure 4.21 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compounds 4.13 and 4.14
5.1 Introduction to the Dienone-Phenol Rearrangement

Cyclohexadienones, or “blocked aromatic molecules”, are commonly embedded in natural and biologically active products and possess a single quaternary carbon in their framework, preventing them from acquiring the stability of an aromatic system. The conversion from the cyclohexadienone tautomer to its corresponding aromatic system is a facile reaction, favored by approximately 18 kcal / mol, and is classified as a dienone-phenol rearrangement (DPR).\textsuperscript{5.1}

Because there is such a dramatic driving force in dienone-phenol reactions, there exists a plethora of rearrangements for cyclohexadienone ring systems. For our purposes, acid-catalyzed rearrangements, in which migrations of alkyl groups convert these non-aromatic molecules to their aromatic counterparts, are of particular interest (Scheme 5.1).

5.2 History of the Dienone-Phenol Rearrangement

In 1893, Androecchi reported the first example of a dienone-phenol rearrangement during his experimentation with the terpenoid, santonin.\textsuperscript{5.1} It was this rearrangement
of santonin to desmotroposantonin 5.2 that led steroid scientists Inhoffen and Huang-Minlon to establish an unfortunate analogy and precedent for the interpretation of steroidal systems. 5.3 Dienone-phenol rearrangement of steroid 5.3 represents one such example and for many years, the products derived from dienone-phenol rearrangement of steroid para-dienones were incorrectly identified. It was not until 1950, that Woodward and Singh provided the first structural study of the dienone-phenol rearrangement with their evaluations of model dienone 5.6. 5.4 Rearrangement of 5.6 provided the para-substituted phenol 5.7, rather than Inhoffen’s anticipated meta-substituted isomer 5.8 (Scheme 5.2).

In light of this ramification, several proofs were supplied to further elucidate the mechanistic pathway demonstrated in dienone-phenol rearrangements. 5.5-5.7 Woodward, in 1956, reported that the acid-catalyzed DPR on optically active dienone 5.9 afforded an optically inactive product 5.11 (Scheme 5.3). 5.5 This transformation had to have proceeded through a symmetrical intermediate, identified as spirocyclic carbonium ion 5.10, where both methylene groups are equally likely to migrate. The result led him to propose that dienone-phenol rearrangements actually proceed via a spirocyclic intermediate by way of a more complicated pathway comprised of a succession of [1,2]-shifts, rather than the seemingly simplistic approach of a [1,3]-migration.

In accordance to Woodward’s findings, Bloom studied the dienone-phenol rearrangement of 5.12 and established that these successive [1,2]-shifts also exhibited selective bond differentiation, in favor of the migrating group that could best stabilize the positive charge (Scheme 5.4). 5.6 In this case, while phenol 5.14 is formed exclusively via [1,2]-migration of the 2º alkyl group, production of aromatic isomer 5.15 is not observed.
Scheme 5.2 Historical Dienone-Phenol Rearrangements

Scheme 5.3 Woodward’s Mechanistic Proof
**5.3 Reactivity Considerations**

**5.3.1 Overview**

As previously noted, dienone-phenol rearrangements (DPR), in which dienones of type 5.16 undergo isomerization to phenolic products upon treatment with acidic media, have been extensively studied. A mixture of two phenols are generally obtained, which result from two separate pathways, A and B. While the former proceeds via a 1,2-migration of the bridgehead substituent (R₁) with subsequent deprotonation of intermediate 5.18 to afford the m-cresol product 5.19, the latter intercepts spirocyclic intermediate 5.20 which provides the p-cresol product 5.22, as determined by Bloom’s preference for bond differentiation. Although there are a number of cases where either m-cresol 5.19 or p-cresol 5.22 may be formed with high selectivity, formation of the alternative p-cresol product 5.24 via cationic intermediate 5.23 is never a major pathway.
5.3.2 Solvent and Substituent Effects

The significance of external factors in controlling the DPR is dramatically demonstrated by the difference in reaction pathways, influenced not only by the choice of reaction media, but also the nature of the angular substituent R<sub>1</sub>. In 1972, Shine published on a series of experiments investigating these effects. Because DPR reactions are highly exothermic, they can take place in moderately strong acids such as solutions of acetic anhydride with a trace amount of sulfuric acid. It is hypothesized that these conditions, classified as “anhydrous”, result in the migration of the most stable carbonium ion (Table 5.1). Thus, according to Shine, when R<sub>1</sub> is a small methyl group, the ring itself, a methylene group, will preferentially migrate, yielding a para-substituted aromatic. To contradict these findings, Hirakura demonstrated that the DPR of the cis-
isomer of 5.41 (Scheme 5.10) unexpectedly provided the *meta*-product under anhydrous conditions.\textsuperscript{5.13} Shine further theorizes that when R\textsubscript{1} is at least two carbons in length (entries 2-4), it takes priority and will undergo a [1,2]-shift, affording the *meta*-product. However, when in the presence of aqueous sulfuric acid, the *meta*-phenol always predominated, regardless of the size of R\textsubscript{1} (entries 5-8). Needless to say, the factors that govern selectivity in the DPR are still ambiguous and remain open for experimental investigations and interpretation.

Table 5.1 Influence of External Factors on the DPR\textsuperscript{5.8}

![DPR Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>R\textsubscript{1}</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>anhydrous methyl</td>
<td>84</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>anhydrous ethyl</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>anhydrous propyl</td>
<td>7</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>anhydrous butyl</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>aqueous methyl</td>
<td>14</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>aqueous ethyl</td>
<td>23</td>
<td>77</td>
</tr>
<tr>
<td>7</td>
<td>aqueous propyl</td>
<td>2</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>aqueous butyl</td>
<td>8</td>
<td>92</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>anhydrous aqueous</td>
</tr>
<tr>
<td>Ac\textsubscript{2}O / H\textsubscript{2}SO\textsubscript{4} 20.6 N H\textsubscript{2}SO\textsubscript{4}</td>
</tr>
<tr>
<td>R = Ac</td>
</tr>
<tr>
<td>R = H</td>
</tr>
</tbody>
</table>

5.4 Sesquiterpenoid DPR Substrates

In conjunction with other studies involving the preparation and biological testing of valencane-type sesquiterpenes and simple derivatives, we had occasion to examine the dienone-phenol rearrangement of nootkatone-derived dienone 5.25. The unexpected
selectivity of this reaction prompted us to examine the DPR of eremophilane and eudesmane-like isomeric compounds rac-5.26 and 5.27 (Figure 5.1). Herein, we report the synthesis and performance of these compounds in the dienone-phenol rearrangement and reveal hitherto unexplored conformational factors that serve to influence the regiochemical outcome of the reaction.

5.4.1 Synthesis of Sesquiterpenoid Dienones

Dienone 5.25 was prepared by dehydrohalogenation of the dibromide 5.29, which has been described previously in Chapter 4. Sesquiterpenoid rac-5.26 was generated from Robinson annulation product rac-5.30 5.9 followed by a DDQ oxidation 5.10 (Scheme 5.6). Norsesquiterpenoids 5.31 and 5.32 were both constructed via Pfau’s enantioselective chiral imine chemistry. 5.11 However, only 5.31 could be successfully transformed into the corresponding sesquiterpenoid dienone 5.27. Homochiral octalone 5.32, along with previously reported eudesmane analogs, prove to be poor substrates for dehydrogenation with DDQ. 5.12 It has been speculated that the steric bulk imparted by the isopropyl group hinders the approach of the DDQ reagent, thereby impeding the abstraction of the axial β-hydrogen.

5.5 DPR Experimental Findings

Dienone-phenol rearrangement of 5.25 under anhydrous conditions produced, instead of the expected mixture of regioisomers 5.36 and 5.37, a single phenol acetate product (Scheme 5.7). The identity of this product, established by X-ray analysis, was shown to be 5.36 (Figure 5.2) indicating that the isopropyl group elicits a marked influence on the relative rate of C-5 vs. C-8 bond migration in the spirocyclic intermediate 5.33.
Figure 5.1 Sesquiterpenoid Dienones

Scheme 5.6 Preparation of Sesquiterpenoid Dienones
Scheme 5.7 Dienone-Phenol Rearrangement of Nootkatone-Derived Substrate 5.25

Figure 5.2 Crystal Structure of 5.36
In contrast, under identical reaction conditions, the DPR of dienones rac-5.26 and 5.27 were found to be unselective, providing a 1:1 mixture of phenolic acetates 5.36 and 5.37. Here, the isopropyl substituent in the diastereomeric spirocyclic intermediate 5.38, with respect to 5.33, does not seemingly impart any influence on the relative rate of bond migration (Scheme 5.8).

Scheme 5.8 Dienone-Phenol Rearrangement of Isomeric Substrates rac-5.26 and 5.27

5.6 Explanation of Findings

Selectivity of the DPR, proceeding through spirocyclic diastereomeric intermediates 5.33 and 5.38, roughly parallels the relative conformational stability adopted by the cationic intermediates, generated as a result of the C-5 or C-8 bond migration (Scheme 5.9). The exclusive formation of phenol acetate 5.36 from dienone 5.25 correlates with the enhanced stability of cationic intermediate 5.34, when compared to intermediate 5.35, obtained from the spirocyclic intermediate 5.33. Where the former cationic species
possesses an equatorial isopropyl group, the latter competing intermediate suffers from a pair of unfavorable 1,3-diaxial interactions and has, therefore, a higher energy associated with it (Figure 5.3). Using this analogy, the less selective rearrangement results of dienones rac-5.26 and 5.27 can be explained. Although cationic intermediate 5.39, generated from migration of the C-8 bond, suffers 1,3-diaxial interactions through axial orientation of the isopropyl group, calculations indicate that there is actually no appreciable difference in energy (~0.9 kcal / mol) between competing intermediates 5.40 and 5.39 (Figure 5.4). As a result, a 1:1 mixture of products is observed.

In accordance with our findings, Hirakura reported that under anhydrous conditions, the dienone-phenol rearrangement of trans-dienoneacetic acid 5.41 provided the p-type cresol 5.46, exclusively. Through the examination of the conformational stability of cationic intermediate 5.43, one can see that this system suffers from a pair of debilitating 1,3-diaxial interactions, like that of previous dienone 5.25. The alternative pathway, proceeding via reaction intermediate 5.44, orients the carboxylic acid in the more stable,
Figure 5.3 Calculations and Selectivity for Dienone 5.25 in the DPR

Energy Difference
~1.7 kcal / mol

equatorial orientation

axial placement: pair of unfavorable 1,3-diaxial interactions
Figure 5.4 Calculations and Selectivity for Dienones rac-5.26 and 5.27 in the DPR
equatorial position, thereby providing a favorable route to the exclusive production of the phenolic acetate (Scheme 5.10). One could, therefore, assume that under the same conditions, subjection of dienone 5.47 would provide the analogous result (Scheme 5.11).

Scheme 5.10 Hirakura’s DPR on 5.41

Scheme 5.11 Prediction of Sesquiterpenoid Dienone 5.47 in the DPR

5.7 Outlook / Conclusion

In the history of the dienone-phenol rearrangement, there have been no known cases of bond differentiation of a dienone substrate that possessed two “primary” substituents. With this series of investigations, we have now provided a basis for the prediction of
reaction selectivity of such substrates through examination of conformational stability of the reaction intermediates.

The synthesis of sesquiterpenoid dienone 5.47 and investigation of its DPR should be conducted in an effort to provide validation of our proposed model. Future studies should also entail a thorough examination of the DPR under aqueous conditions.

5.8 Experimental

5.8.1 General Experimental

Unless otherwise stated, all experiments were performed under an atmosphere of nitrogen or argon in oven-dried glassware utilizing standard Schlenk techniques and / or a Vacuum Atmospheres dry box. Solvents used as reaction media were distilled immediately before use. Tetrahydrofuran (THF), 1,4-dioxane, toluene, 1,2-dimethoxyethane (DME), and benzene were distilled from sodium benzophenone ketyl. N,N-Dimethylformamide (DMF) was dried and stored over 4Å molecular sieves under an argon atmosphere. Unless otherwise noted, reagents purchased from Aldrich were used without further purification. 4-isopropylcyclohexanone (Lancaster) was bought and used without further purification.

Column chromatography was carried out with Standard Grade, 60 Å, 32-63μm, from Sorbent Technologies. Analytical thin layer chromatography (TLC) was performed on precoated silica gel plates (size: 2.5 × 7.5 cm; layer thickness: 250 μm). Components were visualized by illumination with long wave ultraviolet light or exposure to iodine vapor. Frontal retention values (Rf) are reported along with the solvent system used.

All yields and melting points were determined after purification. Melting points were obtained on an Electrothermal Melting Point apparatus. IR spectra were recorded
utilizing a Nicolet Avatar 320 FT-IR instrument. GC / MS analyses were performed using a Varian Saturn 2200 equipped with a DB5 column (30m x 0.25 mm i.d. x 0.25 mm thickness) and E.I. (70 eV) capabilities. HRMS analyses were performed by Ohio State University. Compounds requiring elemental analysis were sent to Prevalere Life Sciences. NMR spectra ($^1$H and $^{13}$C) were obtained on Bruker AC – 250 and Bruker AC-300 Spectrometers. Chemical shifts, $\delta$, are reported in ppm relative to CDCl$_3$ (7.27 ppm, $^1$H; 77.23 ppm, $^{13}$C) unless noted otherwise. $^1$H NMR data reported as follows: chemical shift ($\delta$ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, br = broadened, m = multiplet), integration, and coupling constant (Hz).

### 5.8.2 Preparative Procedures

**6-isopropyl-4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-3H-naphthalen-2-one (rac-5.30).** Sodium amide (1.5 g, 37.4 mmol, assay 90%) was placed in a RBF fitted with a reflux condenser, evacuated and subsequently purged with nitrogen. Freshly distilled benzene (200 mL) was cannulated into the apparatus and the mixture was allowed to warm to reflux via a heating mantle. The starting ketone, 4-isopropylcyclohexanone (5 g, 36 mmol), was injected and the reaction mixture was allowed to reflux with continual stirring for 5 hours. After which time, the reaction was cooled to 45 °C (via a hot water
bath) and iodomethane (dried and distilled from Drierite, 2.22 mL, 36 mmol) was injected in one portion. An additional portion of methyl iodide (3.5 mL, 1.57 eq.) was injected after 2.5 hours and the solution was allowed to proceed at 45 °C for an additional 15 hours. Upon completion, saturated aqueous NH₄Cl was added to the cooled solution and the product was extracted with Et₂O. The organic layer was then washed with water and brine and dried (Na₂SO₄). Removal of excess solvent via fractional distillation provided the crude product. Column chromatography (9:1 / hexane:EtOAc), Rf 0.55 afforded the methylated product A, 2.75 g (50% yield) in pure form. ¹³C NMR (62.5 MHz, CDCl₃) δ 213.3, 44.3, 43.0, 41.3, 39.3, 32.0, 30.7, 19.9, 14.6. The sodium amide was generated utilizing the method previously described by Cope and Hancock.5.14 The apparatus, consisting of a three-neck, 250-mL round bottom flask, equipped with a Dewar-type condenser, a constant addition funnel, and a gas inlet valve is cooled to -78°C and charged with anhydrous ammonia (150 mL). A catalytic amount of hydrated ferric nitrate is added. Under a steady stream of nitrogen, freshly cut sodium (0.7 g, 30 mmol) is quickly introduced to the apparatus via one of the inlet valves. The solution is stirred until a blue color disappears and a grey hue is observed. Following a similar procedure,5.9a the Robinson annulation of 2-penten-3-one with methylated ketone A (4 g, 26 mmol) was performed. A solution of dry DME containing 10 mg of triphenylmethane indicator was added over a 30 minute period to the sodium amide solution. Upon completion, observed by the disappearance of the red color, the reaction mixture was allowed to stir for an additional 30 minutes. Anhydrous DME (30 mL) was added through the constant addition funnel and the excess liquid ammonia was allowed to evaporate under a nitrogen stream. A solution of 2-penten-3-one in DME (2.6 g, 30
mmol in 20 mL) is added slowly while keeping the temperature between -30 and -35°C. The resulting solution was allowed to stir overnight at -5°C. Aqueous workup provided a material consisting of ketol intermediate (1 g, 16% yield) and recovered starting material (1.8 g). To a solution of 5% KOH in MeOH (3 mL solution) was added the ketol (300 mg) mixture. The reaction was allowed to heat at reflux for 10h. The dark brown solution was then poured into water and extracted with ether. The combined ether extracts were dried (MgSO₄), filtered, and concentrated to provide the desired product in crude form. Column chromatography (50:50 / hexane:ether), Rₖ 0.48 employed for further purification, provided the desired compound **rac-5.30** as a yellow liquid (26 mg, 94% yield). ¹H and ¹³C NMR spectra reveal a 6:1 ratio of products. ¹H NMR (250 MHz, CDCl₃) δ 5.79 (s, 1H), 2.51-2.38 (m, 1H), 2.30-2.08 (m, 4H), 2.81-1.49 (m, 4H), 1.30-1.12 (m, 2H), 1.05 (s, 3H), 0.98-0.96 (d, 3H, J = 6.24 Hz), 0.88 and 0.85 (d, 3H, J = 6.71 Hz), 0.87 and 0.84 (d, 3H, J = 6.69 Hz); ¹³C NMR (62.5 MHz, CDCl₃) δ 199.1, 175.1, 124.9, 42.2, 39.9, 37.1, 35.6, 31.6, 29.1, 27.5, 19.9, 19.5, 19.1, 15.3.

**Dienone (rac-5.26).** To a magnetically stirred solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 403 mg, 1.8 mmol) in anhydrous 1,4-dioxane (15 mL) was added the purified Robinson annulation product **rac-5.30** (280 mg, 1.3 mmol). The mixture was refluxed for 24h. The dark brown reaction mixture was allowed to come to room temperature and gravity filtration was employed to remove the tan DDHQ
precipitate. The solvent was removed via rotary evaporator to provide a dark brown residue. This residue was dissolved in acetone and purified on a column (50:50 / hexane:ether) to recover starting material (R\text{f} 0.46, 66 mg) and provide the dienone rac-5.26 (R\text{f} 0.26, 30 mg, 11% yield). \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}) δ 6.14 (s, 1H), 6.06 (s, 1H), 2.75-2.59 (m, 1H), 2.46-2.26 (m, 1H), 2.03 (s, 3H), 1.34 (s, 3H), 0.94 and 0.92 (d, 3H, J = 6.72 Hz), 0.91 and 0.88 (d, 3H, J = 6.68 Hz); \textsuperscript{13}C NMR (62.5 MHz, CDCl\textsubscript{3}) δ 186.3, 169.4, 166.2, 125.9, 124.8, 43.7, 40.1, 38.4, 30.6, 29.4, 27.7, 27.0, 20.6, 20.4, 18.9.

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

**Generation of Chiral Imine** b. A magnetically stirred solution of (R)-(+)\-dihydrocarvone (31.4 g, 0.21 mol), (R)-(+)\-phenylethylamine (25 g, 0.21 mol), and toluene (25 mL) was refluxed overnight under a nitrogen atmosphere with continuous
azeotropic removal of water via a Dean-Stark trap. Upon collection of the theoretical amount of water, the reaction was cooled to room temperature. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.52-7.09 (m, 5H, Ph), 4.75-4.69 (m, 3H, vinylic protons and benzylic H overlapped), 1.73 (s, 3H, =CCH\(_3\)), 1.36 (d, 3H, CH\(_3\) on chiral group, \(J = 6.59\) Hz), 1.17 (d, 3H, Me, \(J = 6.34\) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 171.6, 149.0, 147.3, 128.5, 126.8, 126.4, 109.5, 57.8, 47.3, 41.9, 36.1, 34.4, 31.7, 26.1, 20.7, 17.0.

**Generation of Chiral Imine c.** Imine c was prepared following the same procedure, by reaction of \((R)-(+)\)-dihydrocarvone with \((S)-(+)\)-phenylethylamine.

**Diketone b.** Methyl vinyl ketone (acquired from Aldrich; dried over anhydrous potassium carbonate for 30 minutes and distilled at reduced pressure to give a colorless liquid; caution: lacrymator) (0.87 g, 12.3 mmol) is added via syringe to the crude imine b solution with continuous stirring under a nitrogen atmosphere. For the Michael addition to occur, the reaction is allowed to proceed at 45°C for 3 days. The light yellow solution is then cooled in an ice bath and a 10% aqueous acetic acid solution (1.15 equivalents) is added. Hydrolysis is achieved by stirring the heterogeneous mixture at room temperature for 2 hours. The solution is then poured into a separatory funnel containing brine (20 mL) and water (32 mL) and extracted with a 50:50 mixture of hexane:ether. The organic phase is washed with 10% HCl, water, brine, dried (MgSO\(_4\)), filtered, and concentrated via rotary evaporator to provide a mixture of diketone products (\textit{cis:trans} = 5:1). The crude material was found pure enough for the next step. (The phenylethylamine chiral auxiliary can be recovered from the aqueous layer.) \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.82 (s, 1H, C=CH\(_2\)), 4.71 (s, 1H, C=CH\(_2\)), 2.50-2.40 (m, 3H), 2.12 (s, 3H, methyl ketone), 1.82-1.73 (m, 4H), 1.72 (s, 3H, =CCH\(_3\)), 1.69-1.55 (m, 2H), 1.11 (s, 3H, methyl of
quaternary carbon); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 214.7, 208.6, 147.3, 137.8, 46.9, 46.1, 43.3, 38.7, 36.7, 31.6, 29.9, 25.9, 23.1, 20.7.

**Diketone c.** Diketone c was obtained in a similar manner, by reaction with methyl vinyl ketone for 2 days at 45 °C to provide the imino intermediate. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.72 (m, 3H, vinylic protons and benzylic H overlapped), 2.07 (s, 3H, methyl ketone), 1.67 (s, 3H, =CCH$_3$), 1.35 (d, 3H, CH$_3$ on chiral group, $J = 6.58$ Hz), 1.11 (s, 3H, methyl of quaternary carbon); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 209.1, 172.9, 148.8, 147.3, 140.2, 128.4, 127.9, 125.7, 109.3, 57.9, 45.9, 42.9, 39.9, 38.5, 31.1, 30.2, 26.7, 25.9, 24.9, 20.7. Workup, as described above, provided the crude diketone c. The crude material was found pure enough for the next step. (The phenylethylamine chiral auxiliary can be recovered from the aqueous layer.) $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.75 (s, 1H, C=CH$_2$), 4.62 (s, 1H, C=CH$_2$), 2.03 (s, 3H, methyl ketone), 1.72 (s, 3H, =CCH$_3$), 0.97 (s, 3H, methyl of quaternary carbon); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 214.5, 207.5, 147.3, 137.7, 47.0, 46.1, 43.4, 38.5, 37.9, 30.6, 29.8, 25.9, 22.1, 20.5.

![Chemical diagram](image-url)
Catalytic Hydrogenation of Isopropylidene (D). According to the method of Brown\textsuperscript{5,15}, the crude unsaturated diketone solution and (PPh\textsubscript{3})\textsubscript{3}RhCl (Wilkinson’s catalyst, 0.1 equiv.) was placed in an oven-dried 1-L flask. Freshly distilled benzene was added and hydrogen gas was bubbled through the solution for 10 hours via a porous frit. The solution was then filtered through a Celite cake and concentrated to provide the reduced diketone product. The crude was found pure enough for the next step. Reduced diketone D: \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}) \( \delta \) 2.49-2.39 (m, 1H), 2.31-2.25 (m, 2H), 2.12 (s, 3H, methyl ketone), 1.10 (s, 3H, quaternary Me), 0.90-0.87 (2 d, 6H, isopropyl Me); \textsuperscript{13}C NMR (62.5 MHz, CDCl\textsubscript{3}) \( \delta \) 215.8, 208.8, 46.8, 45.6, 41.9, 38.7, 36.9, 32.2, 31.6, 29.7, 24.2, 23.0, 19.4, 19.3.

Robinson Annulation Product (5.31). Robinson annulation product 5.31 was obtained through careful cyclization and selective dehydration of reduced diketone D. An ice-cold solution of the starting diketone (1 g, 4.5 mmol) in KOH (0.23 g, 0.9 eq.) / EtOH (50 mL) was allowed to stir for one hour. Upon conclusion, the reaction was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na\textsubscript{2}SO\textsubscript{4}), filtered, and concentrated. Column chromatography (50:50 hexane / ether) gave 5.31 (R\textsubscript{f} 0.54) in pure form (39.8% overall yield from starting (R)-(+)-dihydrocarvone). \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}) \( \delta \) 5.72 (s, 1H, C=CH), 2.68-2.03 (m, 4H), 1.98-1.78 (m, 2H), 1.75-1.61 (m, 2H), 1.60-1.29 (m, 4H), 1.22 (s, 3H, methyl of quaternary carbon), 0.94-0.90 (2 d, 6H, isopropyl Me); \textsuperscript{13}C NMR (62.5 MHz, CDCl\textsubscript{3}) \( \delta \) 199.0, 170.4, 123.9, 45.0, 41.0, 37.5, 36.1, 35.5, 33.6, 32.5, 24.5, 21.8, 19.4, 19.3. Spectroscopic data is identical with those reported in the literature.\textsuperscript{5,16
Robinson Annulation Product (5.32). The diketone c is placed in a 100-mL flask and a rubber septum is fitted. The flask is evacuated and subsequently purged with nitrogen to eliminate traces of oxygen; dry methanol is added. A 25 wt. % solution of sodium methoxide in methanol (available from Aldrich) is introduced via syringe. When a basic pH is achieved, the reaction is allowed to proceed at 60 °C for 10 hours. The solution is then cooled and neutralized with glacial acetic acid. The thick paste that precipitates is taken up in water and the mixture is poured into a separatory funnel. Extraction is carried out using a 50:50 mixture of hexane:ether. The organic phase is washed with water and brine and subsequently dried (MgSO₄). The filtrate is concentrated in rotovap to afford crude 5.32 as an orange liquid. Purification was carried out via Kugelrohr distillation (135 °C / 3mm Hg) to provide the desired compound as a white crystalline material. ¹H NMR (300 MHz, CDCl₃) δ 5.86 (s, 1H, C=CH), 4.85 and 4.68 (2s, 2H, C=CH₂), 2.66-2.61 (m, 1H), 2.55-2.48 (m, 3H), 2.38-2.34 (m, 1H), 1.97-1.79 (m, 3H), 1.75 (m, 1H), 1.71 (s, 3H, C=CCH₃), 1.48-1.32 (m, 2H), 1.27 (s, 3H, methyl of quaternary carbon); ¹³C NMR (75 MHz, CDCl₃) δ 199.2, 170.5, 146.7, 125.7, 112.4, 40.4, 37.9, 35.9, 35.8, 35.5, 34.1, 23.5, 22.7, 22.5.

7-isopropyl-4a-methyl-5,6,7,8-tetrahydro-4aH-naphthalen-2-one (E). To a magnetically stirred solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 1.77 g, 7.8 mmol) in anhydrous 1,4-dioxane (50 mL) was added the purified Robinson
annulation product **5.31** (1.15 g, 5.6 mmol). The mixture was refluxed for 24h. The dark brown reaction mixture was allowed to come to room temperature and gravity filtration was employed to remove the tan DDHQ precipitate. The solvent was removed via rotary evaporator to provide a dark brown residue. This residue was dissolved in acetone and purified on a column (75:25 / hexane:EtOAc) to provide the dienone **E** (R$_f$ 0.37, 0.82 g, 72% yield). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 6.79 (d, 1H, $J = 9.87$ Hz), 6.23 (d, 1H), 6.12 (s, 1H), 2.39-2.31 (m, 1H), 2.26-2.13 (m, 1H), 1.89-1.82 (m, 1H), 1.77-1.28 (m, 5H), 1.24 (s, 3H, quaternary Me), 0.95 (d, 3H, isopropyl Me, $J = 6.79$ Hz), 0.94 (d, 3H, isopropyl Me, $J = 6.78$ Hz); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 186.9, 167.9, 157.2, 126.6, 124.2, 46.5, 40.6, 37.6, 36.2, 32.5, 23.9, 22.8, 19.6, 19.5. HRMS (EI) m/z 204.1498 (M$^+$, 204.150866 calcd for C$_{14}$H$_{20}$O).

[![Diagram of reaction](image.png)]

**7-isopropyl-4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-3$H$-naphthalen-2-one (F).**

Following the methods of Marshall $^{5,17}$ and House $^{5,18}$, a solution of lithium dimethyl copper was prepared under nitrogen by the addition of 6.12 mL of 1.6 M ethereal methyllithium (10 mmol) to an ice-cold suspension of copper iodide (0.93 g, 5 mmol) in dry ether (23 mL). [When one equivalent of methyllithium is added to CuI, a yellow precipitate of methyl copper separated. The second equivalent of methyllithium dissolved the yellow precipitate (1 hour) to give a colorless to pale tan solution.] When a
homogeneous solution was achieved, the starting dienone E (0.5 g, 2.5 mmol) was injected in a solution of anhydrous ether (23 mL). After 1 hour at 0°C, the solution is poured into sat’d aqueous NH₄Cl and concentrated ammonium hydroxide is added (enough to dissolve copper salts). Ether extraction provides the desired methylated product F in quantitative yield (0.54 g) and in pure form. ¹H NMR (250 MHz, CDCl₃) δ 5.75 (s, 1H), 2.58-2.47 (m, 1H), 2.26-2.13 (m, 3H), 2.03-1.89 (m, 1H), 1.75-1.38 (m, 6H), 1.25 (s, 3H, quaternary Me), 0.99 (d, 3H, Me, J = 6.96 Hz), 0.93-0.90 (2d, 6H, isopropyl Me); ¹³C NMR (62.5 MHz, CDCl₃) δ 199.3, 169.7, 123.2, 46.5, 42.2, 39.3, 38.4, 36.6, 33.3, 32.7, 24.6, 23.5, 19.6, 19.4, 15.6. HRMS (EI) m/z 220.1826 (M⁺, 220.182166 calcd for C₁₅H₂₄O).

**Dienone (5.27).** To a magnetically stirred solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 0.58 g, 2.5 mmol) in anhydrous 1,4-dioxane (17 mL) was added the crude methylated product F (0.4 g, 1.8 mmol). The mixture was refluxed for 24h. The dark brown reaction mixture was allowed to come to room temperature and gravity filtration was employed to remove the tan DDHQ precipitate. The solvent was removed via rotary evaporator to provide a dark brown residue. This residue was dissolved in acetone and purified on a column (50:50 / hexane:ether) to provide the dienone 5.27 (Rᶠ 0.22, 0.21 g, 53% yield). ¹H NMR (250 MHz, CDCl₃) δ 6.08 (s, 2H), 2.38-2.17 (m, 2H),
2.15-2.06 (m, 1H), 2.00 (s, 3H, Me), 1.77-1.16 (m, 5H), 1.27 (s, 3H, quaternary Me), 0.94 (d, 3H, isopropyl Me, $J = 6.75$ Hz), 0.94 (d, 3H, isopropyl Me, $J = 6.77$ Hz); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 186.4, 168.2, 165.9, 126.6, 124.4, 46.9, 43.1, 36.8, 36.4, 32.5, 24.4, 22.4, 19.6, 19.5, 18.8. HRMS (EI) m/z 218.1651 (M$^+$, 218.166516 calcd for C$_{15}$H$_{22}$O).

DPR of Sesquiterpenoid Dienone 5.25; 6-isopropyl-3,4-dimethyl-5,6,7,8-tetrahydro-naphthalen-1-ol (G). Using the method described by Woodward,$^{5,4}$ a solution of the dienone 5.25 (0.1 g, 0.45 mmol) in acetic anhydride (4.7 g, 45.8 mmol) was placed in a round bottom flask and cooled to 0 °C. A trace amount of concentrated sulfuric acid (46 mg, 0.47 mmol) in acetic anhydride (1.5 mL) was added dropwise with continual stirring. Upon completion, the reaction was allowed to warm to room temperature where it was maintained for 5 h. The reaction mixture was then shaken with water until all of the excess acetic anhydride had been hydrolyzed. Extraction with EtOAc and subsequent concentration of the organic layer provided the acetate intermediate as a crystalline material, mp 103-105 °C, which could easily be recrystallized into needles of the acetate intermediate 5.36 (0.147 g, 62% yield) using EtOAc as a solvent. $^1$H NMR: (250 MHz, CDCl$_3$) $\delta$ 6.66 (s, aromatic 1H), 2.67-2.56 (m, 2H), 2.48-2.23 (2s and 1m overlapped, 8H), 2.09 (s, 3H), 1.92-1.84 (m, 1H), 1.69-1.54 (oct, 1H), 1.51-1.36 (m, 1H), 1.31-1.18 (m, 1H), 0.97-0.93 (2d, each 3H); $^{13}$C NMR:
The phenolic acetate \textbf{5.36} (60 mg, 0.23 mmol) in absolute ethanol (4.7 mL) was heated under reflux for 6 h with \textit{conc.} hydrochloric acid (0.4 mL), after which time the excess solvent was removed via rotary evaporator to leave a white, powdery residue. This solid material was washed with water, extracted in \text{Et}_2\text{O}, dried (\text{Na}_2\text{SO}_4), filtered, and concentrated by the slow evaporation of solvent to provide the pure phenol \textbf{G} as shining needles, mp 107-109°C, (40 mg, 75.8% yield). \textsuperscript{1}H NMR: (250 MHz, CDCl\textsubscript{3}) \(\delta\) 6.49 (s, aromatic 1H), 4.23-3.91 (br s, OH), 2.82-2.69 (m, 2H), 2.52-2.44 (m, 1H), 2.33-2.27 (m, 1H), 2.23 (s, 3H), 2.09 (s, 3H), 1.99-1.94 (m, 1H), 1.74-1.55 (septet, 1H), 1.53-1.42 (m, 1H), 1.37-1.19 (m and s overlapped, 2H), 1.01 (d, \(J = 2.62\) Hz, 3H), 0.99 (d, \(J = 2.56\) Hz, 3H); \textsuperscript{13}C NMR: (62.5 MHz, CDCl\textsubscript{3}), \(\delta\) 152.2, 138.4, 135.7, 128.3, 122.2, 114.9, 41.98, 33.84, 32.95, 26.74, 25.20, 21.87, 21.26, 21.14, 15.67. HRMS (EI) \textit{m/z} 218.1651 (M\textsuperscript{+}, 218.166516 calcd for C\textsubscript{13}H\textsubscript{22}O).

\begin{center}
\begin{tikzpicture}
\draw (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
\draw (1,0) -- (2,1) -- (1,2) -- (0,1) -- cycle;
\draw (0,0) -- (0,1) -- (0,1.5) -- (0.5,1.5) -- (0.5,2) -- (2,2) -- (2,2.5) -- (1.5,2.5) -- (1.5,3) -- (0,3) -- cycle;
\draw (1,0) -- (1,0.5) -- (1.5,0.5) -- (1.5,1) -- (2,1) -- (2,1.5) -- (1.5,1.5) -- (1.5,2) -- (1,2) -- cycle;
\draw (0.25,0.5) -- (0.25,1) -- (0,1) -- (0,0.5) -- cycle;
\draw (1.25,0.5) -- (1.25,1) -- (1,1) -- (1,0.5) -- cycle;
\draw (0.75,0.5) -- (0.75,1) -- (0.5,1) -- (0.5,0.5) -- cycle;
\draw (1.75,0.5) -- (1.75,1) -- (1.5,1) -- (1.5,0.5) -- cycle;
\draw (0.25,1.5) -- (0.25,2) -- (0,2) -- (0,1.5) -- cycle;
\draw (1.25,1.5) -- (1.25,2) -- (1,2) -- (1,1.5) -- cycle;
\draw (0.75,1.5) -- (0.75,2) -- (0.5,2) -- (0.5,1.5) -- cycle;
\draw (1.75,1.5) -- (1.75,2) -- (1.5,2) -- (1.5,1.5) -- cycle;
\node at (0.5,0.5) {\textbf{rac-5.26:} \(R_1 = \text{i-Pr}, \ R_2 = \text{H}\)};
\node at (1.5,0.5) {\textbf{5.27:} \(R_1 = \text{H}, \ R_2 = \text{i-Pr}\)};
\node at (0.5,2.5) {AcO};
\node at (1.5,2.5) {AcO};
\begin{scope}[xshift=3cm]
\draw (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
\draw (1,0) -- (2,1) -- (1,2) -- (0,1) -- cycle;
\draw (0,0) -- (0,1) -- (0,1.5) -- (0.5,1.5) -- (0.5,2) -- (2,2) -- (2,2.5) -- (1.5,2.5) -- (1.5,3) -- (0,3) -- cycle;
\draw (1,0) -- (1,0.5) -- (1.5,0.5) -- (1.5,1) -- (2,1) -- (2,1.5) -- (1.5,1.5) -- (1.5,2) -- (1,2) -- cycle;
\draw (0.25,0.5) -- (0.25,1) -- (0,1) -- (0,0.5) -- cycle;
\draw (1.25,0.5) -- (1.25,1) -- (1,1) -- (1,0.5) -- cycle;
\draw (0.75,0.5) -- (0.75,1) -- (0.5,1) -- (0.5,0.5) -- cycle;
\draw (1.75,0.5) -- (1.75,1) -- (1.5,1) -- (1.5,0.5) -- cycle;
\draw (0.25,1.5) -- (0.25,2) -- (0,2) -- (0,1.5) -- cycle;
\draw (1.25,1.5) -- (1.25,2) -- (1,2) -- (1,1.5) -- cycle;
\draw (0.75,1.5) -- (0.75,2) -- (0.5,2) -- (0.5,1.5) -- cycle;
\draw (1.75,1.5) -- (1.75,2) -- (1.5,2) -- (1.5,1.5) -- cycle;
\node at (0.5,0.5) {5.36};
\node at (1.5,0.5) {5.37};
\node at (0.5,2.5) {\text{AcO}};
\node at (1.5,2.5) {\text{AcO}};
\draw[->] (0.5,0.5) -- (0.5,1.5);\node at (0.5,1) {Ac_2O};\node at (0.5,1.25) {H_2SO_4};
\end{scope}
\end{tikzpicture}
\end{center}

**DPR of Dienones rac-5.26 and 5.27.** A solution of the dienone (0.1 g, 0.45 mmol) in acetic anhydride (4.7 g, 45.8 mmol) was placed in a round bottom flask and cooled to
0 °C. A trace amount of concentrated sulfuric acid (46 mg, 0.47 mmol) in acetic anhydride (1.5 mL) was added dropwise with continual stirring. Upon completion, the reaction was allowed to warm to room temperature where it was maintained for 5 h. The reaction mixture was then shaken with water until all of the excess acetic anhydride had been hydrolyzed. Extraction with EtOAc and subsequent concentration of the organic layer provided a crude material which was characterized via NMR. $^1$H NMR: (250 MHz, CDCl$_3$) $\delta$ 2.30 (d, 3H), 2.17 (s, 3H), 0.96-0.94 (2d, each 3H); $^{13}$C NMR: (62.5 MHz, CDCl$_3$), $\delta$ 167.6, 146.6, 134.3, 132.4, 126.6, 120.0, 39.3, 31.9, 28.1, 27.2, 26.1, 20.3, 19.8, 19.7, 14.6.

5.8.3 Spectral Data

NMR spectra for dienone 5.25 via dibromide 5.29 were presented in Chapter 4. Spectral data for the remaining compounds are included on the following pages.

5.8.4 X-ray Data

X-ray data for compound 5.36 is included in Appendix B.

5.9 References


Figure 5.5 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of 4-Isopropylcyclohexanone
Figure 5.6 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound A
Figure 5.7 $^1$H NMR (250 MHz, CDCl$_3$) of rac-5.30
Figure 5.8 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of rac-5.30
Figure 5.9 $^1$H NMR (250 MHz, CDCl$_3$) of Dienone rac-5.26
181

Figure 5.10 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Dienone rac-5.26
(R)-(+) -dihydrocarvone

Figure 5.11 $^1$H NMR (300 MHz, CDCl$_3$) of (R)-(+) -Dihydrocarvone
Figure 5.12 $^{13}$C NMR (75 MHz, CDCl$_3$) of (R)-(+) Dihydrocarvone
Figure 5.13 $^1$H NMR (300 MHz, CDCl$_3$) of Chiral Imine c
Figure 5.14 $^1$H NMR (300 MHz, CDCl$_3$) Upfield Expansion of Chiral Imine c
Figure 5.15 $^{13}$C NMR (75 MHz, CDCl$_3$) of Chiral Imine c
Figure 5.16 $^1$H NMR (300 MHz, CDCl$_3$) of Imino Intermediate
Figure 5.17 $^1$H NMR (300 MHz, CDCl$_3$) Upfield Expansion of Imino Intermediate
Figure 5.18 $^{13}$C NMR (75 MHz, CDCl$_3$) of Imino Intermediate
Figure 5.19 $^1$H NMR (300 MHz, CDCl$_3$) of Diketone c
Figure 5.20 $^{13}$C NMR (75 MHz, CDCl$_3$) of Diketone c
Figure 5.21 $^1$H NMR (300 MHz, CDCl$_3$) of Compound 5.32
Figure 5.22 $^{13}$C NMR (75 MHz, CDCl$_3$) of Compound 5.32
Figure 5.23 $^{13}$C NMR (75 MHz, CDCl$_3$) Upfield Expansion of Compound 5.32
Figure 5.24 $^1$H NMR (300 MHz, CDCl$_3$) of Chiral Imine b
Figure 5.25 $^{13}$C NMR (75 MHz, CDCl$_3$) of Chiral Imine b
Figure 5.26 $^1$H NMR (300 MHz, CDCl$_3$) of Diketone b
Figure 5.27 $^{13}$C NMR (75 MHz, CDCl$_3$) of Diketone b
Figure 5.28 $^1$H NMR (250 MHz, CDCl$_3$) of Compound D
Figure 5.29 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound D
Figure 5.30 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 5.31
Figure 5.31 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 5.31
Figure 5.32 $^1$H NMR (250 MHz, CDCl$_3$) of Compound E
Figure 5.33 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound E
Figure 5.34 $^1$H NMR (250 MHz, CDCl$_3$) of Compound F
Figure 5.36 $^1$H NMR (250 MHz, CDCl$_3$) of Dienone 5.27
Figure 5.37 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Dienone 5.27
Figure 5.38 $^1$H NMR (250 MHz, CDCl$_3$) of Phenol Acetate 5.36
Figure 5.39 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Phenol Acetate 5.36
Figure 5.40 $^1$H NMR (250 MHz, CDCl$_3$) of Phenol G
Figure 5.41 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Phenol G
Figure 5.42 $^1$H NMR (300 MHz, CDCl$_3$) of 1:1 Mixture of Phenolic Acetates 5.36 : 5.37
Figure 5.43 $^1$H NMR (300 MHz, CDCl$_3$) Upfield Expansion of 1:1 Mixture of Phenolic Acetates 5.36 : 5.37

* = 5.36
(as determined by $^1$H NMR)
Figure 5.44 $^{13}$C NMR (75 MHz, CDCl$_3$) Downfield Region of 1:1 Mixture of Phenolic Acetates 5.36 : 5.37

doubling of peaks
Figure 5.45 $^{13}$C NMR (75 MHz, CDCl$_3$) Upfield Region of 1:1 Mixture of Phenolic Acetates 5.36 : 5.37

* = 5.36
(as determined by $^{13}$C NMR)


CHAPTER 6: STRUCTURE-ACTIVITY EVALUATIONS OF SYNTHETIC NORSESQUITERPENES AND SESQUITERPENOID DERIVATES OF (+)-NOOTKATONE TO THE FORMOSAN SUBTERRANEAN TERMITE

6.1 Introduction

Plant-derived natural products have received increasing investigation for their potential role as insect repellents, fumigants, and feeding deterrents. Of particular interest was the seemingly receptor-specific activity of (+)-nootkatone, a sesquiterpenoid ketone, isolated from Alaskan yellow cedar (*Chamaecyparis nootkatensis*) and found in the peel of grapefruit (*Citrus paradise*).\(^1\) Of the (+)-nootkatone derivatives evaluated thus far, 1,10-dihydronootkatone and tetrahydronootkatone (THN) exhibited the highest toxicity, more so than starting (+)-nootkatone.\(^2\) Through structure-activity studies, continued efforts are underway to elucidate the mode of action these naturally occurring insect repellents have on sensory chemoreceptors. Herein, we report several synthetic norsesquiterpenoids and sesquiterpenoids derivates, of the valencane and eremophilane family that are currently being evaluated for their repellent activity against Formosan subterranean termites, *Coptotermes formosanus* Shiraki.

6.2 Methods and Materials

6.2.1 Termites

A carton nest of Formosan subterranean termites, *Coptotermes formosanus* Shiraki, were collected in May, 2004 from Brechtel Park, New Orleans. Under the care of Zhu, termites were held in 250-L cans with pine used as a food source and kept at 24-26 °C. Moistened corrugated cardboard rolls were used to retrieve termites from the cans. Termites were gently knocked from the cardboard rolls into clean, plastic trays (40 cm × 50 cm) and isolated from debris by allowing them to climb on moistened paper towels.
6.2.2 Synthetic Derivatives

The compounds synthesized are represented in Figure 6.1. Their synthesis has been described previously (Chapters 3, 4, and 5). Although structure-activity evaluations are ongoing, the methods of such testing processes are described below.

Figure 6.1 Synthetic Derivatives
6.2.3 Repellency Test Against Formosan Subterranean Termites

Repellency tests were performed by Betty Zhu, as described by Lewis\textsuperscript{3} and Zhu\textsuperscript{4}. A petri dish (5 cm diameter $\times$ 1 cm high) was coated evenly with a hot agar solution (1 mL, 1.5 g agar / 100 mL H\textsubscript{2}O) and allowed to cool to room temperature. This ensures adequate moisture for the termites and provides a foundation for a layer of blasting sand (fine, #4, autoclaved for 30 minutes and oven dried). The synthesized compounds (6.1-6.19) were dissolved in ethanol and prepared in a series of dilutions for testing. Seven concentrations (2.5, 5, 12.5, 25, 50, 100, and 200 $\mu$g / dish) of each chemical were used to evaluate the repellent activity. While one half of the petri dish was covered with untreated sand (1 g), the other half was covered with treated sand (1 g).

To record termite behavior, 10 worker termites were added to each petri dish, and the number of termites observed on the untreated sand was recorded every hour for 3 hours. Five replicates were used for each test, including the control (untreated sand). The repellency threshold was defined as the lowest concentration of the chemicals which showed a repellent effect.

6.3 Experimental

6.3.1 General Experimental

Unless otherwise stated, all experiments were performed under an atmosphere of nitrogen or argon in oven-dried glassware utilizing standard Schlenk techniques and / or a Vacuum Atmospheres dry box. Solvents used as reaction media were distilled immediately before use. Diethyl ether was distilled from sodium benzophenone ketyl. Unless otherwise noted, reagents purchased from Aldrich were used without further purification. Authentic samples of tetrahydronootkatone (THN), 1,10-dihydronootkatone
and nootkatone were purchased from Aromor Inc., (Israel) and used without further purification.

IR spectra were recorded utilizing a Nicolet Avatar 320 FT-IR instrument. GC / MS analyses were performed using a Varian Saturn 2200 equipped with a DB5 column (30m x 0.25 mm i.d. x 0.25 mm thickness) and E.I. (70 eV) capabilities. HRMS analyses were performed by Ohio State University. Compounds requiring elemental analysis were sent to Prevalere Life Sciences. NMR spectra (\(^1\)H and \(^{13}\)C) were obtained on Bruker AC – 250 and Bruker AC-300 Spectrometers. Chemical shifts, \(\delta\), are reported in ppm relative to CDCl\(_3\) (7.27 ppm, \(^1\)H; 77.23 ppm, \(^{13}\)C) unless noted otherwise. \(^1\)H NMR data reported as follows: chemical shift (\(\delta\) ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplet, br = broadened, m = multiplet), integration, and coupling constant (Hz).

6.3.2 Preparative Procedures

\[ \text{\textbf{1,10-dihydronootkatone}} \xrightarrow{\text{LAH Et}_2\text{O}} \text{\textbf{6.18}} \]

1,10-dihydronootkatol (6.18). To a solution of 1,10-dihydronootkatone (3 g, 13.6 mmol) in dry diethyl ether (50 mL) was added dropwise a 1\(M\) solution of LAH (1.1 equivalent, 15.0 mL) in Et\(_2\)O with continual stirring at 0°C. The reaction was stirred at room temperature for four hours and subsequently cooled in an ice bath where it was quenched by the slow addition (caution: vigorous gas evolution) of 1\(M\) aqueous sodium
potassium tartrate solution. Hexane was incorporated and the heterogeneous solution was warmed to room temperature and stirred for an additional hour, resulting in clear layers. The layers were then separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried (Na$_2$S$_2$O$_4$), filtered, and concentrated to provide the desired alcohol **6.18** (2.9 g, 96%) in ~96% purity (~4% is the minor diastereomeric alcohol). $^1$H NMR: (250 MHz, CDCl$_3$) $\delta$ 4.67 (m, 2H, =CH$_2$), 3.73-3.51 (m, 1H, CH-O-), 2.52 (br s, 1H, =CH$_3$), 2.36-2.01 (m, 1H), 1.69 (s and m obscured, 4H, =CCH$_3$), 0.81 (d, 3H, $J$ = 6.24 Hz, -CH$_3$), 0.74 (s, 3H, quaternary Me); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 150.8, 108.1, 70.2, 43.8, 43.7, 41.5, 40.3, 39.9, 37.7, 35.9, 31.9, 28.6, 20.9, 14.7, 11.3. HRMS (EI) $m/z$ 222.1971 (M$^+$, 222.197816 calcd for C$_{15}$H$_{26}$O).

6.3.3 Spectral Data

NMR spectra for dienone **6.18** are presented on the following pages.

6.4 References


Figure 6.2 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 6.18
Figure 6.3 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 6.18
CHAPTER 7: INTRODUCTION AND OVERVIEW

7.1 History and Economical Importance

Originating from the lower valleys of the Indian Himalayas, jasmine was brought to North Africa and Spain by the conquering Moors. During the 16th century, it rapidly spread over the Mediterranean basin. Soon after, its potential in the fragrance industry was realized and large-scale field cultivations began in Grasse, southern France, in 1860. However, because of the local climatic conditions, a frost-resisting jasmine variety was required and obtained by grafting Jasminium grandiflorum onto Jasminium officinale. One kilogram of harvested jasmine absolute, extracted from ~8 million individual flowers weighing 1000 kg, is valued at $15,000 / kg. With 5,000-6,000 kilograms of jasmine absolute produced worldwide annually, it is easy to understand why a great deal of scientific interest was placed on the chemical aspects of jasmine and its derivatives.7.1

7.2 Chemical Composition of Jasmine Oil and Industrial Synthesis

There are more than 100 components present in jasmine oil. (Z)-Jasmonone 7.1, methyl-(−)-trans-(Z)-jasmonate 7.2, and (−)-(R)-(Z)-dec-7-en-5-olide 7.3, constitute ~4% of jasmine absolute and are identified as the specific carriers of the true natural jasmine essence (Figure 7.1).7.1

![Figure 7.1 Natural and Synthetic Jasmine Odorants](image-url)
Over one hundred syntheses of jasmine-type odorants have been published. Even though there was an abundance of routes available, none were economically feasible and therefore, could not be applied to an industrial setting. For some time, structurally simpler and cheaper synthetic substitutes such as 2-benzylideneoctanal 7.4, were employed to minimize cost.\(^7.1\) Finally, in 1974, Descotes reported that the spiro compound 7.5 undergoes a 1,5-thermal rearrangement to yield compound 7.6, a well-known intermediate for (Z)-jasmone 7.1 and methyl jasmonate 7.2.\(^7.2\) Requiring 7 steps to get to the spiral system, Descotes’ route proved to be too lengthy and low yielding. However, in 1978, Decorzant improved on the earlier work of Descotes by utilizing inexpensive starting materials, cyclopentanone and piperylene, in the synthesis.\(^7.3\) This enabled for a cost efficient and economical synthesis (4 steps) of methyl jasmonate and (Z)-jasmone that could be applied to an industrial process (Scheme 7.1).

Scheme 7.1 Industrial Synthesis of (Z)-Jasmone 7.1 and Methyl Jasmonate 7.2 \(^7.2, 7.3\)
7.3 Incorporation of Jasmine to Our Daily Lives

Jasmine has reigned for centuries as an emblem of good luck and prosperity. For this reason, its flowers have been incorporated into many cherished and ceremonial traditions and its scent has served as a staple in thousands of commercially available products today. While its involvement in medicinal and healthcare practices has spanned the world since antiquity, recent discoveries with respect to its promising role in insect control provides an additional realm of utility.

7.3.1 Commercial Uses

The exotic floral character of jasmine absolute renders it a foundation for fine fragrances such as *Arpege de Lanvin* (1927), *Joy of Patou* (1938), and *Miss Dior* (1947); as a common ingredient in feminine perfumes (*Anaïs Anaïs*, 1979; *Charlie*, 1973; *Diorella*, 1972; *Joy*, 1935; *First*, 1976; *Shalimar*, 1925) and, at lower dosages, in masculine fragrances (*Eau Sauvage*, 1966).7.1

Originating in Asia during the 13th century under the Sung Dynasty, jasmine has also been used to flavor tea and scent desserts. These practices have persisted through time, and today, one can find the essence of jasmine in thousands of commercial products ranging from lotions, massage oil, and base creams to candles, bath products and cleaning agents.

7.3.2 Plant – Insect Research

It is well known that plants emit volatiles for survival purposes and as a defense mechanism. Recently, scientists at Britain’s Institute for Arable Crops have discovered that the components responsible for the fragrance of jasmine, namely *(Z)-jasmone* 7.1, serve not only as a repellent to a variety of insect herbivores (aphids), but also as an
attractant to insect predators (seven-spot ladybird). The results of this study provide hope and a new remedy for the drastic devastation aphids impart on farmers' crops. 

7.3.3 Biological Importance

As noted by the Swedish botanist, Carolus Linnaeus (1707-1778), the natives of India used the jasmine plant to treat scabies. It has also been reported to be of considerable use to aid in the relief of fever, congestion, headaches, insomnia, pain, and it has also been implemented as an antidepressant and a cough suppressant. Today’s vapor therapy provides help for asthmatics and reduces stress, nervousness, and tension. In modern medicine, jasmine has been used to treat gallstones, diabetes mellitus, venereal disease, and even cancerous tumors.

Notably, methyl jasmonate is also structurally similar to that of medicinally important, type E prostaglandins (PGs). PGE\textsubscript{2}, biological compounds found in animals and humans, have been reported and examined in a variety of clinical indications, and are primarily used for treatment of cardiovascular diseases and peptic ulcers (Figure 7.2). 

\[
\text{Figure 7.2 Structural Comparison of Methyl Jasmonate 7.2 and PGE}_2 7.7
\]
Therefore, it is the hope that any knowledge acquired in the synthesis towards jasmone and its derivatives could be directly applied to manufacture biologically active analogs.

7.4 Proposed Jasmone Syntheses

7.4.1 Introduction to the Hetero Pauson-Khand (HPK) Reaction

The heteroatom variant of the Pauson-Khand reaction, first reported in our laboratories, is an atom-efficient, formal [2 + 2 + 1] cycloaddition of an alkene or alkyne, a carbonyl, and carbon monoxide (Scheme 7.2), mediated by Cp₂Ti(PMe₃)₂. The result of this convergent method is the formation of cis-fused bicyclic γ-butyrolactones (a) or fused butenolides (b), each ubiquitous in the infrastructure of biologically active natural compounds. These reactions can be performed under ambient temperatures and pressures.⁷ ⁷

The mechanism for the generation of the bicyclic γ-butyrolactones is shown in Scheme 7.3 and 7.4. As illustrated, the starting eighteen-electron titanocene complex, Cp₂Ti(PMe₃)₂, undergoes ligand substitution to coordinate the δ,ε-unsaturated carbonyl substrate 7.8. Formation of the metallacycle 7.9, followed by CO insertion into the Ti-C bond with subsequent reductive elimination affords the cis-fused bicyclic γ-butyrolactone 7.10.

![Scheme 7.2 Hetero Pauson-Khand (HPK) Reaction](image)
Scheme 7.3 Generation of Oxatitanabicyclopentane Intermediate 7.9
Scheme 7.4 Generation of Fused Bicyclic $\gamma$-Butyrolactones 7.10
Soon after the discovery of HPK reactions, Buchwald reported a catalytic version that could be mediated by either Cp$_2$Ti(PMe$_3$)$_2$ or Cp$_2$Ti(CO)$_2$. However, his method was limited only to aryl ketones and did not accommodate δ,ε-unsaturated substrates (Scheme 7.5). Therefore, a generalized catalytic protocol and asymmetric version of the HPK reaction was required. In 2001, Crowe demonstrated the first series of asymmetric HPK syntheses of γ-butyrolactones from enones or enals via a chiral titanocene catalyst, (EBTHI)Ti(CO)$_2$ (Scheme 7.6). Not only is the bridged ansa-metallocene complex 7.11 more reactive toward cyclocarbonylation substrates than the Cp$_2$Ti(CO)$_2$ counterpart, this catalyst can easily be prepared on the chemists' bench, with no provisions to exclude moisture or oxygen.

![Scheme 7.5 Buchwald’s Titanocene-Catalyzed Cyclocarbonylation 7.8](image)

**Scheme 7.5 Buchwald’s Titanocene-Catalyzed Cyclocarbonylation**

### 7.4.2 Application of the HPK Reaction: A Flexible Route to Jasmone and Analogs

My synthesis efforts were centered on the formation of bicyclic γ-butyrolactone intermediates 7.10 from δ,ε-unsaturated carbonyl compounds 7.8 via the Hetero Pauson-Khand (HPK) reaction (Scheme 7.7). Once the bicyclic γ-butyrolactone 7.10 is obtained, reduction of the ketone to the corresponding alcohol and a subsequent Wittig reaction provides the skeletal framework for Jasmone and PGE derivates. The synthesis of a variety of δ,ε-unsaturated carbonyl precursors 7.8 as well as their performance in the HPK reaction will be discussed in Chapters 8 and 9, respectively.
Scheme 7.6 Crowe’s Catalytic Asymmetric Cyclocarbonylation

Scheme 7.7 Overview of Cyclocarbonylation
7.5 References


8.1 Overview and Introduction

Pericyclic, or “around the circle”, reactions are characterized by the concerted cyclic shift of electrons. Electrocyclic (Scheme 8.1a), cycloaddition (Scheme 8.1b), and sigmatropic reactions (Scheme 8.1c), the three main types of concerted pericyclic reactions, all adhere to the rules of orbital symmetry, as described by Woodward and Hoffmann. However, of these three concerted transformations, only sigmatropic rearrangements, in which the thermally allowed migration of an allylic σ-bond across a π-electron system to the terminus of an adjacent π-electron system will be discussed.\(^8\)

\[ \text{Scheme 8.1 Concerted Pericyclic Reactions} \]

There are several different classifications of sigmatropic rearrangements, each denoted with a corresponding \([i,j]\), indicating the number of atoms over which a σ-bond appears to traverse. Some examples are given in Scheme 8.2.
[1,7]-sigmatropic shift of hydrogen

[3,3]-sigmatropic rearrangement of 1,5-hexadiene

[1,3]-sigmatropic shift of an alkyl group

[3,3]-sigmatropic rearrangement of an allyl vinyl ether

Scheme 8.2 Examples of Sigmatropic Rearrangements

Among these “reorganizations”, [3,3]-sigmatropic rearrangements, such as the Claisen or Cope rearrangement, represent some of the most powerful methods for stereoselective C-C bond formation. The numerical positions within the pericyclic system are generally marked as indicated (Scheme 8.3).

Scheme 8.3 [3,3]-Sigmatropic Rearrangements

8.1.1 Claisen Rearrangements

In addition to the classical allyl vinyl ether rearrangement, several variations have been developed that broadened the utility and scope through the generation of products.
with diverse functionalities. A sampling of these variants, identified in Table 8.1, ultimately improve the synthetic value of the Claisen rearrangement.8.1

### Table 8.1 Variants of the Claisen Rearrangement

<table>
<thead>
<tr>
<th>X</th>
<th>Product Functionality</th>
<th>Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkyl, H</td>
<td>Ketone, Aldehyde</td>
<td>Simple Claisen</td>
</tr>
<tr>
<td>OR</td>
<td>Ester</td>
<td>Johnson Orthoester</td>
</tr>
<tr>
<td>NR₂</td>
<td>Carboxylic Amide</td>
<td>Eschenmoser (Ficini)</td>
</tr>
<tr>
<td>OSiR₃</td>
<td>Carboxylic Acid</td>
<td>Ireland</td>
</tr>
<tr>
<td>OZnBr₂</td>
<td>Zinc Carboxylate</td>
<td>Reformatsky-Claisen</td>
</tr>
</tbody>
</table>

Of particular interest, however, is Johnson’s orthoester Claisen (OEC). Discovered in 1970, Johnson reported the use of orthoesters as Claisen reagents for the transformation of allylic alcohols into the corresponding $\gamma,\delta$-unsaturated esters. This process, catalyzed by a weak (e.g., propionic) acid, is driven to completion through the generation and subsequent elimination and distillation of a volatile alcohol byproduct at relatively low temperatures and with a minimum amount of decomposition.8.2

### 8.1.2 Cope Rearrangements

The Cope rearrangement, a [3,3]-sigmatropic shift in 1,5-hexadienes, was first discovered in 1940. It is the simplest form, constituting an all-carbon skeletal framework, as denoted in Scheme 8.3. Like its hetero-atom counterpart, the Claisen rearrangement, variations on this reaction have been reported over the years. The oxy-Cope and anionic
oxy-Cope rearrangements, in which a donating hydroxyl group is positioned at C-3, are two such variations that are widely used today.\textsuperscript{8,3}

Utilizing 1,5-diene potassium alkoxides as substrates coupled with a complexing agent (e.g., 18-crown-6) in the anionic oxy-Cope (AOC) rearrangement, greatly facilitates the overall rate at which the reaction transpires ($10^{10}$-$10^{17}$). The resulting enol readily tautomerizes to its more stable keto-form, yielding in the process, the desired $\delta,\varepsilon$-unsaturated carbonyl compounds necessary for the HPK (Scheme 8.4). For this reason, this particular Cope rearrangement is of considerable interest.

\begin{center}
\textbf{Scheme 8.4 AOC Rearrangement}
\end{center}

8.1.3 Relevant Bond Dissociation Energies

In Claisen rearrangements, the formation of a carbonyl (C=O) group at the expense of a C=C bond yields products that are highly favored (by $\sim25$ kcal / mol), thereby leading to an overall irreversible transformation. Although a diminished value is affiliated with Cope rearrangements, which suffers from equilibria (reversibility), variations of this process (oxy-Cope, anionic oxy-Cope) provide carbonyl functionalities
through enol tautomerization. The net result of these Cope rearrangement variants parallels the irreversibility observed in Claisen rearrangements.

Table 8.2 Bond Dissociation Energies

<table>
<thead>
<tr>
<th>Bond</th>
<th>Energy (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-C</td>
<td>~80</td>
</tr>
<tr>
<td>C=C</td>
<td>~145</td>
</tr>
<tr>
<td>C-O</td>
<td>~80</td>
</tr>
<tr>
<td>C=O</td>
<td>~170</td>
</tr>
</tbody>
</table>

8.1.4 HPK Substrates via [3,3]-Sigmatropic Rearrangements

Two [3,3]-sigmatropic rearrangements, the orthoester Claisen (OEC) and the anionic oxy-Cope (AOC), have been implemented in the construction of a variety of δ,ε-unsaturated carbonyl HPK substrates 8.1 (Scheme 8.5). The syntheses of substrates 8.1 will be discussed herein.

Scheme 8.5 Retrosynthetic Analysis
8.2 Synthesis of HPK Substrates 8.1a and 8.1b via OEC Rearrangements

The first attempt to synthesize 8.1a was centered around a tandem OEC reaction of 1,2-diol 8.3 to provide a diester (Scheme 8.6). Isomerization of cis-2-butene-1,4-diol 8.2 to 3-butene-1,2-diol 8.3 was accomplished utilizing a procedure described by Rao. However, upon subjecting 8.3 to conditions prescribed for an OEC, a diastereomeric pair 8.4 was acquired instead of the desired diester.

Scheme 8.6 Tandem OEC Approach

Failure of the OEC to produce the diester in a concerted fashion prompted a step-wise alternative that would rely on the utility of protecting groups. The chosen protecting group should react preferentially with the primary alcohol of 8.3, leaving the secondary allylic alcohol free for an OEC rearrangement. This conversion should not only be performed in good yields and be easily isolable from possible byproducts, but should also provide a substrate that could withstand subsequent reaction conditions (Table 8.3).

Following Masamune’s procedure, the first attempt at converting the 1,2-diol to a primary protected substrate utilized benzyl bromide as the protecting agent to obtain a
benzyl ether in the product (Table 8.3, entry a). This reaction was accompanied not only by low yields but also resulted in an inseparable mixture of primary : secondary (2.4:1) protected products.

Buono, working on the same diol system, also encountered difficulties with this benzyl protection and resorted to employing a tosyl group as the protecting agent.\textsuperscript{8.7} This lead was followed and the 1,2-diol \textbf{8.3} was subjected to \textit{p}-toluenesulfonyl chloride in pyridine and dichloromethane (Table 8.3, entry b). Although this reaction was selective for the exclusive protection of the primary alcohol, the yield was not optimal. Furthermore, the tosyl protected substrate, when subjected to the heat associated with the OEC rearrangement, decomposed (Scheme 8.7).

It was then found that \textbf{8.3} could be selectively silylated at the primary position using \textit{t}-butyldimethylsilyl chloride (TBDMSCl).\textsuperscript{8.8} This process provided \textbf{8.5c} as the exclusive

\begin{center}
\textbf{Table 8.3 Protecting Group Studies}
\end{center}

\begin{tabular}{|c|c|c|c|}
\hline
\textbf{R} & \textbf{Reaction Conditions} & \textbf{Product} & \textbf{Yield} \\
& & \textbf{8.5 : 8.6} & \\
\hline
\textbf{a}: Bn & NaH, DMF, Benzyl Bromide, -70°C, 40 min. & 2.37 : 1 & 52 \\
\textbf{b}: Ts & TSCl, DCM, rt, 2 days & \textbf{8.5b} only & 59 \\
\textbf{c}: TBDMS & TBDMSCl, DMAP, TEA, DCM, rt, 1 day & \textbf{8.5c} only & 89 \\
\textbf{d}: Piv & Pivaloyl chloride, pyridine, DCM, rt, 14h & \textbf{8.5d} only & 90 \\
\hline
\end{tabular}
Scheme 8.7 TBDMS and Pivalate Routes toward HPK Substrates 8.1
product and in high yields. In addition, subjection of 8.3 to pivaloyl chloride in methylene chloride and pyridine afforded the primary protected pivaloyl ester 8.5d in excellent yield.8.9

Unlike the fragile tosyl group, both the silyl and pivalyl protecting groups of 8.7c and 8.7d withstood the heat affiliated with the OEC reaction, resulting in the successful transformation to their corresponding \( \gamma,\delta \)-unsaturated esters.

Desilylation of 8.7c via tetrabutylammonium fluoride (TBAF) supplied the allylic alcohol 8.8c. Alternatively, a one step conversion, lithium aluminum hydride reduction of the ester groups that flank 8.7d, provided the corresponding diol 8.8d in moderate yields. Both allylic alcohol products, 8.8c and 8.8d, serve as intermediates toward the synthesis of HPK substrates 8.1a and 8.1b, respectively.

8.2.1 Synthesis of HPK Substrate 8.1a via Pivalate Route

Surprisingly, the OEC on compound 8.8d did not proceed according to plan. The triethyl orthoacetate reacted with both alcoholic substituents of 8.8d to produce the mixed orthoester 8.9 (Scheme 8.8). In order to obtain the desired substrate 8.1a, crude 8.9 was refluxed in dry ethanol and camphor sulfonic acid to provide the free alcohol 8.10 which, in turn, underwent PCC oxidation to yield the desired HPK \( \delta,\varepsilon \)-unsaturated carbonyl substrate 8.1a.

8.2.2 Synthesis of HPK Substrate 8.1b via TBDMS Route

The allylic alcohol 8.8c was treated with ethyl vinyl ether (EVE) to produce compound 8.11 in low yields. In addition, numerous aldehyde products resulted in the subsequent thermal rearrangement, thereby concluding this particular route (Scheme 8.9).
8.2.3 Outlook

An alternative route towards the synthesis of HPK substrate 8.1b has been established (Scheme 8.10). This path intercepts the unanticipated orthoester 8.9 intermediate constructed in the pivalate scheme. Under anhydrous conditions, the orthoester can be regarded as a protecting group, thereby allowing the conversion of the ester moiety to a benzyl ether. Successive hydrolysis and PCC oxidation of the mixed orthoester produces the desired δ,ε-unsaturated carbonyl HPK substrate 8.1b.
Scheme 8.10 Future Plans for the Synthesis of 8.1b

8.3 HPK Substrates 8.1c and 8.1d via AOC Rearrangements

8.3.1 Construction of Compulsory Octa-1, 5, 7-triene-3-ols via ε-Selective Pentadienylations to α,β-unsaturated Aldehydes

Penta-2,4-dienylmetals, obtained by transmetalation of the corresponding pentadienyllithium reagents, react with various electrophiles in two possible regiochemical modes: reaction at the terminal ε- and / or α-position(s) to provide a conjugated 1,3-pentadiene or attack of the internal γ-position to yield a non-conjugated 1,4-pentadiene (Scheme 8.11). The delocalized anion may react at either site, as dictated

\[ \text{pentadienylmetal} + \text{electrophile} \rightarrow \text{ε / α-adduct} + \text{γ-adduct} \]

Scheme 8.11 Regiochemical Adducts from Pentadienylmetal Attack on Electrophiles
by the metal counterion selected. While ε (or α) adducts generally arise from pentadienyl congeners of tins and silanes, metals such as indium, zirconium, zinc, and titanium have been employed for the generation of the skipped diene (γ) product.

For the synthesis of jasmone and structural analogs, we require the mode of attack to occur at primarily at the ε-terminus of the pentadienyl moiety and the preferential 1,2-addition to α,β-unsaturated aldehydes. Subsequent oxy-Cope rearrangement would provide direct access to δ,ε-unsaturated carbonyl HPK substrates of skeletal types (Scheme 8.12). However, α,β-unsaturated aldehydes lacking β-substituents, including acrolein (R = R1 = R2 = H) and methacrolein (R = Me; R1 = R2 = H), are plagued with polymerization, and have not reportedly been the subject of any pentadienylation methodologies.

Scheme 8.12 Retrosynthetic Analysis to Substrates of Type 8.1c-g
Table 8.4 Pentadienylation Investigations of Acrolein

![Diagram of reaction]

<table>
<thead>
<tr>
<th>Method</th>
<th>Lewis Acid / Reaction Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt;•OEt&lt;sub&gt;2&lt;/sub&gt; / 1 hour</td>
<td>Polymerization</td>
</tr>
<tr>
<td>(2) A</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt;•OEt&lt;sub&gt;2&lt;/sub&gt; / 30 min.</td>
<td>Desired product forming in small amounts; isolation difficult due to polymerization</td>
</tr>
<tr>
<td>(3) A</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt;•OEt&lt;sub&gt;2&lt;/sub&gt; / 10 min.</td>
<td>Starting material present; polymerization occurring</td>
</tr>
<tr>
<td>(4) A</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt;•OEt&lt;sub&gt;2&lt;/sub&gt; / 30 min. &lt;sup&gt;b&lt;/sup&gt;</td>
<td>Polymerization</td>
</tr>
<tr>
<td>(5) A</td>
<td>TiCl&lt;sub&gt;4&lt;/sub&gt; / 3 min.</td>
<td>Polymerization</td>
</tr>
<tr>
<td>(6) B&lt;sup&gt;c&lt;/sup&gt;</td>
<td>None / 1.5 hours</td>
<td>8.16c, 48%</td>
</tr>
</tbody>
</table>

<sup>a</sup> General Procedure: A flame-dried flask, evacuated and purged with nitrogen, was charged with freshly distilled dichloromethane. The apparatus, cooled to -78°C, was injected with the α,β-unsaturated aldehyde, followed by a successive addition of the Lewis acid (2 equiv) and the organostannane (1.2 equiv). The reaction was maintained at this temperature until completion. At which time, it was quenched by the slow addition of sodium bicarbonate solution, followed by the usual aqueous workup.

<sup>b</sup> Order of addition reversed (acrolein injected last).

<sup>c</sup> General Procedure: To a flame dried flask, evacuated and purged with nitrogen, was placed 1,4-pentadiene (14.7 mmol) and charged with freshly distilled THF (80 mL). The flask was cooled to -60 °C (dry ice / chloroform bath) and butyllithium (1.6 M solution in hexanes, 73 mmol) was injected. The solution was allowed to warm to 0 °C over a thirty minute period and subsequently stirred for 1 hour at 5-10 °C. The resulting red-orange solution was cooled to -70 °C (dry ice / acetone bath) and quenched with the aldehyde (15 mmol). The reaction mixture (now colorless) was poured into sat’d aq. NH<sub>4</sub>Cl, diluted with water, and extracted with hexanes. The combined organic fractions were washed with water, brine, and dried (MgSO<sub>4</sub>). Solvent removal provided a crude oil which was then purified by column chromatography.
Following a previously described procedure for the generation of $\varepsilon$-linear alcohols (Method A), polymerization-prone acrolein was investigated in a series of pentadienylation experiments.\textsuperscript{8,15} In all cases where the organostannane was employed, (Table 8.4, entries 1-5), polymerization was evident, rendering isolation of pure product an extremely difficult and laborious task. Luckily, and much to my surprise, manipulation of the experimental procedure to allow for the pentadienylation to occur “in situ” (Method B), resulted in the successful production of target compound 8.16c without the adverse effects of acrolein polymerization (Table 8.4, entry 6). The corresponding branched ($\gamma$-adduct) alcohol was also produced as a minor product.

The scope and generality of this new pentadienylation method was tested utilizing a variety of $\alpha,\beta$-unsaturated aldehydes. The results of this study are organized in Table 8.5. As indicated, this novel, one-pot, “in situ” pentadienylation appears to be universal and supplies the linear and branched alcohol products in moderate yields. In all instances, $\varepsilon$-electrophilic attack of the carbonyl carbon is predominant (elucidation via $^1$H NMR spectroscopy) and separation of the respective alcohols was easily done by means of column chromatography. While Fallis has studied AOC rearrangements on the branched, $\gamma$-adduct 8.17e,\textsuperscript{8,11} AOC rearrangements of conjugated dienes 8.16, generated from $\varepsilon$-attack, have yet to be investigated.

### 8.3.2 AOC Rearrangements of Octa-1,5,7-triene-3-ols

The first AOC rearrangement, from the family of octa-1,5,7-triene-3-ols (Scheme 8.13), was performed on senecialdehyde derivative 8.16e. After forty minutes, the AOC rearrangement of this $\varepsilon$-pentadienylation adduct proved successful with complete conversion to the desired $\delta,\varepsilon$-unsaturated carbonyl HPK substrate 8.1e in a 42% yield.
Table 8.5 One-Pot “In Situ” Pentadienylation Methodology

![Chemical Reaction Diagram]

c: R = R1 = R2 = H
d: R1 = Me; R = R2 = H
e: R1 = R2 = Me; R = H
f: R1 = Ph; R = R2 = H
g: R = Me; R1 = R2 = H

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde 8.14</th>
<th>Product Ratio</th>
<th>Isolated 8.16, %</th>
<th>Isolated 8.17, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>c</td>
<td>2.7 : 1</td>
<td>48%</td>
<td>19%</td>
</tr>
<tr>
<td>2</td>
<td>d</td>
<td>1.8 : 1</td>
<td>52%</td>
<td>28%</td>
</tr>
<tr>
<td>3</td>
<td>e</td>
<td>3.5 : 1</td>
<td>63%</td>
<td>22%</td>
</tr>
<tr>
<td>4</td>
<td>f</td>
<td>2.6 : 1</td>
<td>62%</td>
<td>24%</td>
</tr>
<tr>
<td>5</td>
<td>g</td>
<td>2.6 : 1</td>
<td>43%</td>
<td>17%</td>
</tr>
</tbody>
</table>

The AOC rearrangement of methacrolein derived linear alcohol 8.16g was also investigated. After forty minutes of reaction time and a solution green in color, only one aldehyde species was present, and surprisingly, it was not attributed to the formation of skipped diene 8.1g. To aid in structure elucidation, the product was subjected to a series of NMR studies. While $^1$H NMR established the presence of a terminal methyl group,
more sophisticated through-space techniques (2D NMR) were implemented to elucidate the geometry (E or Z) of the trisubstituted olefin. Through the evaluation of cross-peaks in the ROESY, it was determined that the aldehyde formed resembles that of the conjugated system (E)-8.1m (Figures 8.1-8.2).

By reducing the reaction time and temperature in half (20 min. / 0-10°C), it was the goal to isolate and identify any intermediates. However, only ~30% conversion to the conjugated diene (E)-8.1m was observed, with the majority of the reaction mixture comprised of unreacted starting material and only trace amounts of 8.1g, thereby indicating that the rearrangement of 8.1g to (E)-8.1m is immediate.
Figure 8.1 $^1$H NMR (CDCl$_3$, 250 MHz) of (E)-8.1m
Figure 8.2 ROESY Spectra (CDCl₃, 500 MHz) of 8.1m
In an attempt to delineate the mechanistic pathway of these AOC rearrangements, crotonaldehyde derived ε-alcohol 8.16d was subjected to a variety of experimentation sequences including: time / temperature evaluations (Table 8.6), modification of reaction parameters (radical inhibitors, phase transfer agents (PTA), metal hydrides, concentration), color progression annotations (Table 8.7), deuterium labeling studies (Table 8.8), 2D NMR (Figure 8.3) and EPR (Table 8.7) evaluations.

In summation, reaction conditions were never identified for the clean conversion to pure HPK substrate 8.1d or its conjugated aldehyde product(s) 8.1i and, reactions resulting in mixed amounts of these products were inseparable by purification methodologies. 2D-NMR evaluations (COSY and ROESY) were conducted on an inseparable mixture of isomeric aldehydes (4:1) to identify and characterize the components. While the major aldehyde was confirmed to be 8.1d, the minor component in the reaction mixture was attributed to (Z)-8.1i. The knowledge acquired from these stereochemical assignments was used to interpret spectral data obtained from subsequent experiments.

The marked color transformations observed in the reaction progress is not understood. Although it was believed that the exuberant colors displayed signified that the reaction proceeded via a radical process, inclusion of a radical scavenger (Table 8.6, entry 3) did not alter the outcome or the color progression observed during the course of the reaction. Trials also indicate that for this AOC to occur, a phase transfer agent is essential, and KH is, in fact, the metal hydride of choice (Table 8.6, entries 10-12).

Maintaining the temperature at 5°C, the AOC rearrangement was monitored over a period of three hours of which extracted aliquots were quenched with d-MeOH. 1H NMR
Table 8.6 AOC Rearrangement of 8.16d

| Entry | Reaction Time (min) | Temp. | Modifications | 
|-------|---------------------|-------|---------------|-------|
| 1     | 40                  | 0-18°C| 1.5 eq KH     | 8.1d  |
| 2     | 20                  | 0-18°C| 1 eq 18-cr-6  | 8.1d  |
| 3     | 20                  | 0-18°C| 0.1 equiv BHT | 8.1d  |
| 4     | 10                  | 0-18°C| 1 eq 18-cr-6  | 8.1d  |
| 5     | 120                 | 0-18°C| 1 eq 18-cr-6  | 8.1d  |
| 6     | 20                  | 8°C   | 2× volume THF | 8.1d  |
| 7     | 20                  | 0-18°C| 2× volume THF | 8.1d  |
| 8     | 20                  | 0-18°C| 1.5 equiv NaH | 8.1d  |
| 9     | 20                  | 5°C   | No 18-cr-6    | 8.1d  |
| 10    | 60                  | 23°C  | No 18-cr-6    | 8.1d  |
| 11    | 30                  | reflux| No 18-cr-6    | 8.1d  |
| 12    | 30                  | reflux| No 18-cr-6;   | 8.1d  |

**Conversion**

- **(Z)-8.1i**
- **(E)-8.1i**

**1H NMR**

- 8.1d: 9.75 ppm
- (Z)-8.1i: 9.70 ppm
- (E)-8.1i: 9.65 ppm

**Conversion**

- Complete conversion
- 60% conversion of SM
- 20% conversion to d
- 15% conversion to d
- Complete conversion
Figure 8.3 ROESY Spectra (CDCl₃, 500 MHz) of 4:1 Inseparable Mixture of 8.1d : (Z)-8.1i
**Table 8.7 Time / Temperature / Color Observations for AOC Rearrangement of 8.16d**

<table>
<thead>
<tr>
<th>Reaction Time (min)</th>
<th>Temp. (°C)</th>
<th>Reaction Color</th>
<th>Reaction Time (min)</th>
<th>Temp. (°C)</th>
<th>Reaction Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>initial</td>
<td>0°C</td>
<td><img src="image" alt="Yellow Bottle" /></td>
<td>60</td>
<td>10°C</td>
<td><img src="image" alt="Purple Bottle" /></td>
</tr>
<tr>
<td>10</td>
<td>4°C</td>
<td><img src="image" alt="Brown Bottle" /></td>
<td>90</td>
<td>15°C</td>
<td><img src="image" alt="Blue Bottle" /></td>
</tr>
<tr>
<td>35</td>
<td>8°C</td>
<td><img src="image" alt="Red Bottle" /></td>
<td>120&lt;sup&gt;d&lt;/sup&gt;</td>
<td>18°C</td>
<td><img src="image" alt="Blue Bottle" /></td>
</tr>
</tbody>
</table>

<sup>d</sup> Excess solvent removed “*en vacuo*” to provide a dark blue solid. Reaction vessel placed in dry box for manipulations and evaluations (EPR).
Table 8.8 AOC Rearrangement Deuterium Labeling Experimentation

<table>
<thead>
<tr>
<th>Reaction Time (min)</th>
<th>Reaction Color</th>
<th>$^1$H NMR 8.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>initial</td>
<td>SM</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>20% conversion to d</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>d : (Z)-i : (E)-i : 5 : 1 : 0</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>d : (Z)-i : (E)-i : 2 : 1 : 0</td>
<td></td>
</tr>
<tr>
<td>180</td>
<td>d : (Z)-i : (E)-i : 1.6 : 5.6 : 1</td>
<td>MeOD quench at 3 hours</td>
</tr>
</tbody>
</table>

α-carbon picked up deuterium upon quench
spectra reveal that the \( \alpha \)-carbon was the recipient of the deuterium label (Table 8.8), indicating that this enolate carbon is the only carbon in the system where negative charge resides to an appreciable extent.

With noticeable isomerization occurring with the linear alcohol of crotonaldehyde \( 8.16d \), a comparison study to the \( \varepsilon \)-alcohol adduct of senecialdehyde \( 8.16e \) was engineered (Table 8.9). With all variables equal, \( 8.16e \) did not succumb to isomerization.

### Table 8.9 AOC Comparison Studies

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Reaction Time</th>
<th>Reaction Temp.</th>
<th>Final Color</th>
<th>Products</th>
<th>Isomerization</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 8.16d )</td>
<td>2 hours</td>
<td>5°C</td>
<td>Purple</td>
<td>( 8.1d ), (Z)-8.1i, (E)-8.1i</td>
<td>YES</td>
</tr>
<tr>
<td>( 8.16e )</td>
<td>2 hours</td>
<td>5°C</td>
<td>Green</td>
<td>( 8.1e )</td>
<td>NO</td>
</tr>
</tbody>
</table>

Like the crotonaldehyde linear alcohol \( 8.16d \), similar observations were obtained from the AOC rearrangement of \( 8.16f \) (cinnamaldehyde precursor, \( R_1 = \text{Ph} \)). After 20 minutes of reaction time at 0°C, an inseparable 4 : 1 mixture of HPK substrates \( 8.1f \) and (Z)-\( 8.1k \) were obtained, respectively.
8.3.3 Explanation of Findings

Like others, we have demonstrated that the stereochemistry associated with AOC rearrangements of acyclic systems is a reflection of the orientation preference assumed by the alkoxide substituent. The data presented clearly indicate that these substrates prefer to undergo the [3,3]-sigmatropic rearrangement through a cyclic chair transition state in order to diminish steric strain. While in the case of senecialdehyde, axial positioning of the oxido functionality induces unfavorable 1,3-diaxial interactions, methacrolein, however, suffers from 1,2-interactions through equatorial orientation of the alkoxy group.

Both are forced to operate from their alternative chair transition state, thus providing a sole aldehyde product (Scheme 8.15). Alternatively, in the cases of crotonaldehyde and cinnamaldehyde, substrates lacking a vicinyl and cis-substituent, both the alkoxide and hydrogen atom vie for equatorial orientation (Scheme 8.15), each providing acceptable pathways for the reaction to proceed.

Unexpectedly, AOC routes that proceeded via a (Z)-enolate were accompanied by a series of hydrogen transfers (Scheme 8.16). These rearrangements proceeded through accessible 6 and expanded 8-membered cyclic transition states which ultimately resulted in a conjugated diene system. Coupled with the knowledge acquired from these AOC processes, the 2D-NMR evaluations and deuterium labeling experiments help to substantiate the proposed mechanism (Scheme 8.17).

However, the drastic color progression observed, coupled with the acquired EPR signal, seems to be indicative of a radical pathway. Analogous to $^1$H NMR, the quintet observed in the EPR spectrum indicates that the reaction mixture contains a radical species and is split by 4 equivalent spin +1/2 (Figure 8.4). To account for these
Scheme 8.15 Influence of Enolate Geometry in the AOC Rearrangement
Scheme 8.16 Enolate Geometry and Stereochemical Considerations

Scheme 8.17 Proposed Mechanism for Crotonaldehyde’s Conjugated Diene Product

Figure 8.4 NMR Analogy Used to Elucidate EPR Signal
facts, an alternative radical process, initiated through catalytic oxidation of the enol, undertakes a series of hydrogen transfers to form the conjugated diene and ultimately regenerates the enol through a subsequent reduction (Scheme 8.18).

8.3.4 Alternative Approaches

The synthesis of β-trimethylsilyl-substituted, α,β-unsaturated aldehydes 8.18 with subsequent “in situ” pentadienylation provides access into the corresponding protected linear alcohols 8.19. It was the hope that the outcome of the AOC rearrangement of these protected alcohols would be reminiscent of the substrate derived from senecialdehyde. If successful, desilylation would afford direct access to HPK targets of type 8.1c, 8.1d, and 8.1f, circumventing the aforementioned isomerization issue (Scheme 8.19).
Utilizing the methodology of Otera, crotonaldehyde was transformed into β-TMS-substituted 8.18d in a 25% overall yield over a 5-step reaction sequence (Scheme 8.20).

The pentadienylation product, 8.19d, obtained in 72% yield, was subjected to the same

Scheme 8.19 “Masked” Route to HPK Substrates 8.1c, 8.1d, and 8.1f

Reagents: (a) AcOH, benzenesulfonic acid (Na salt), rt, 12h; (b) benzene, ethylene glycol, pTSA; (c) HMPA, n-BuLi; (d) acetone, 5N HCl, rt, 6h; (e) DBU, DCM, reflux, 2h

Scheme 8.20 Synthesis of β-Trimethylsilyl-Substituted Aldehydes

Scheme 8.21 AOC Rearrangement of Silylated Derivative 8.19d
AOC reaction conditions that proved successful for the ε-adduct of senecialdehyde (40 min, 0-18°C). It was found that the silyl group of 8.19d imparted too much steric impact for the AOC rearrangement to be effective and, as a result, only starting material was recovered (Scheme 8.21).

Another alternative approach, the thermal rearrangement of TES (triethylsilyl)8.19 protected alcohol 8.21 from 8.16d, was also tried (Scheme 8.22). Unfortunately, while starting material was apparent in the crude 1H NMR, there was no evidence of 8.22. It was clear that the heat associated with this method led to decomposition, thereby concluding this route.

\[
\begin{align*}
\text{OH} & \hspace{1cm} 8.16d \\
& \begin{array}{c}
\text{OTES} \\
\text{TESCl} \\
\text{Imidazole} \\
\text{DMF, 8h, rt} \\
\text{95%}
\end{array} \\
& \begin{array}{c}
\text{OTES} \\
150°C \\
6h
\end{array} \\
& \text{not obtained}
\end{align*}
\]

Scheme 8.22 Thermal Rearrangement

8.3.5 Outlook

Synthesis and investigations of a Z-allylic alcohol is a top priority in order to substantiate the isomerization theory and validate the influential role that the enolate geometry appears to evoke (Scheme 8.23). The AOC rearrangement of α-substituted trimethylsilyl-α,β-unsaturated aldehydes would also be of considerable interest (Figure 8.5, entry a) as an alternate route to ε-selective adducts derived from acrolein. Syntheses of deuterium labeled alcohols, such as those identified in entries (b) and (c), would also provide additional substrates to examine in this AOC process and furthermore, EPR
evaluations of isolated intermediates should be conducted in order to delineate a radical mechanism, in applicable. To determine if methacrolein would eventually succumb to isomerization, an additional AOC study, implementing prolonged reaction times as listed in Table 8.9, should also be performed.

Another experiment is the employment of Diels-Alder (DA) reactions to resolve the isomeric and inseparable AOC aldehyde products obtained. The highlighted reactive diene would provide a Diels-Alder adduct, allowing for further separation (Scheme 8.24).

Figure 8.5 Future AOC Investigations
Scheme 8.24 Diels-Alder Reactions to Separate Isomeric Aldehydes

8.4 Conclusion

In short, through the use of [3,3]-sigmatropic rearrangements, the synthesis of HPK substrates 8.1a, 8.1e, and 8.1m was achieved. An original, one-step, “in situ”, pentadienylation process was developed and, taken in conjunction with novel acyclic AOC rearrangements of conjugated $\pi$-systems, this tandem sequence aided in the construction of the latter two HPK substrates. The respective performance of these substrates in the HPK reaction will be discussed in Chapter 9.

8.5 Experimental

8.5.1 General Experimental

Unless otherwise stated, all experiments were performed under an atmosphere of nitrogen or argon in oven-dried glassware utilizing standard Schlenk techniques and/or a Vacuum Atmospheres dry box. Solvents used as reaction media were distilled immediately before use. Tetrahydrofuran (THF), diethyl ether, pentane, and benzene were distilled from sodium benzophenone ketyl. Dichloromethane (DCM) was dried and distilled from calcium hydride. DMF ($N,N$-dimethylformamide) was dried over activated Linde type 4A molecular sieves. Unless otherwise noted, reagents purchased from Aldrich were used without further purification.
Column chromatography was carried out with Standard Grade, 60 Å, 32-63μm, from Sorbent Technologies. Analytical thin layer chromatography (TLC) was performed on precoated silica gel plates (size: 2.5 × 7.5 cm; layer thickness: 250 μm). Components were visualized by illumination with long wave ultraviolet light or exposure to iodine vapor. Frontal retention values (R_f) are reported along with the solvent system used. All yields and melting points were determined after purification. Melting points were obtained on an Electrothermal Melting Point apparatus. IR spectra were recorded utilizing a Nicolet Avatar 320 FT-IR instrument. GC / MS analyses were performed using a Varian Saturn 2200 equipped with a DB5 column (30m x 0.25 mm i.d. x 0.25 mm thickness) and E.I. (70 eV) capabilities. HRMS analyses were performed by Ohio State University. Compounds requiring elemental analysis were sent to Prevalere Life Sciences. EPR spectra were recorded at room temperature on a Bruker EMX-20/2.7 ESR spectrometer (Bruker Instruments, Billerica MA), X-band, 100 kHz. The instrument also has a frequency counter. The spectra were taken using a ER 4105DR double resonator and the following parameters: microwave frequency, 9.740 GHz; center field, 3471.610 Gauss; sweep width, 25.000 Gauss; power, 1.270 mW; receiver gain, 3.99e+005; modulation amplitude, 1.00 Gauss; time constant, 10.240 ms; 10 scans. NMR spectra (^1H and ^13C) were obtained on Bruker AC – 250 and Bruker AC-300 Spectrometers. Chemical shifts, δ, are reported in ppm relative to CDCl₃ (7.27 ppm, ^1H; 77.23 ppm, ^13C) unless noted otherwise. ^1H NMR data reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of
doublet of triplets, br = broadened, m = multiplet), integration, and coupling constant (Hz).

8.5.2 Preparative Procedures

But-3-ene-1,2-diol (8.3). To a solution of water (25 mL), mercuric sulfate (250 mg, 0.84 mmol), and conc. sulfuric acid (644 mg, 6.6 mmol) was added freshly distilled starting 1,4-diol 8.2 (60 g, 0.68 mol). The contents were heated under reflux for 1.5 h and then neutralized to a pH of 7. Pure compound 8.3 was isolated as a thick, colorless oil through fractional distillation, bp 85-92 °C (3 mm Hg). Spectroscopic data matches those previously reported.1H NMR: (250 MHz, d-acetone) δ 5.99-5.86 (m, 1H, J = 5.2 Hz), 5.37 and 5.30 (2t, 1H), 5.14 and 5.09 (2t, 1H), 4.19-4.14 (m, 1H), 4.06-4.04 (d, 1H, -OH), 3.84 (t, 1H, -OH), 3.60-3.39 (m, 2H).

TBDMS Protection, 1-(tert-butyl-dimethyl-silanyloxy)but-3-en-2-ol, (8.5c). To a solution of DMAP (5 mg, 0.4 mmol), TBDMSCl (5.62 g, 37.3 mmol), TEA (3.76 g, 37.2 mmol) and freshly distilled DCM (30 mL), the starting diol 8.3 (3.13 g, 35.5 mmol) in DCM (20 mL) was added in one portion. The solution should stir at ambient temperature for 24 h. Once complete (monitored via TLC), 2M HCl (50 mL) was added and the
solution was mixed via a separatory funnel. The organic layer was washed with water (50 mL), brine (50 mL), dry over Na2SO4, filter, and concentrated. The crude material can be isolated via flash chromatography (8:1 / hexane:EtOAc), Rf 0.38 to give 6.37 g (88.6 % yield) of pure 1° TBDMS-protected product 8.5c, bp 73-81 °C. Spectroscopic data match those previously reported.8.8 1H NMR: (250 MHz, CDCl3) δ 5.8-5.67 (ddd, 1H, -CH=CH2), 5.3-5.22 (m, 1H, -CH=CH2), 5.13-5.08 (m, 1H, -CH=CH2), 4.19-4.01 (m, 1H), 3.62-3.25 (m, 2H, -OCH2-), 2.50 (br s, 1H, -OH), 0.84 (s, 9H, tBu), 0.01 (s, 6H, 2 -CH3).

Pivalate Protection, 2,2-dimethyl-propionic acid 2-hydroxy-but-3-enyl ester, (8.5d). A solution of the diol 8.3 (3.13 g, 35.5 mmol) in dry pyridine (37 mL) and freshly distilled DCM (40 mL) was cooled to 0 ºC. Pivaloyl chloride (4.3 g, 35.5 mmol) was added dropwise with continual stirring over a thirty minute period. Upon completion, the reaction was allowed to proceed at room temperature for 14 h. Concentration followed by azeotropic removal of pyridine (toluene:pyridine / 5:1) gives a syrup which was further purified via column chromatography (75:25 / hexane:EtOAc), Rf 0.56 to give 8.5d (5.48 g, 89.7% yield) as a colorless oil, bp 73-86 ºC (3 mm Hg). Spectroscopic data match those previously reported.8.9 1H NMR: (250 MHz, CDCl3) δ 5.89-5.67 (m, 1H), 5.41-5.20 (m, 2H), 4.44-4.27 (m, 1H), 4.13-4.08 (m, 2H), 2.82 (br s, -OH), 1.22 (s, 9H); 13C NMR: (62.5 MHz, CDCl3), δ 178.6, 136.4, 116.6, 70.84, 67.48, 38.69, 26.85.
General Procedure for OEC.\textsuperscript{8,20} To the allylic alcohol was added the triethyl orthoacetate (5.74 eq.) and the propionic acid (0.1 eq.) in catalytic amounts. The contents were heated until the theoretical amount of ethanol had distilled from the mixture. After cooling, the excess orthoacetate and propionic acid were removed under reduced pressure to provide a yellow liquid which could be purified via column chromatography.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {8.5c};
  \node (b) at (1,0) {OEC};
  \node (c) at (2,0) {8.7c};
  \node (d) at (0,-1) {TBDMOSO\_OH};
  \node (e) at (2,-1) {EtO\_O\_TBDMS};
  \node (f) at (2,1) {\text{8.7c}};
\end{tikzpicture}
\end{center}

6-\textit{(}tert\text{-}butyl\text{-}dimethyl\text{-}silanyloxy\text{)}\textendash;hex\textendash;4\textendash;enoic acid ethyl ester (8.7c). The general procedure for the OEC was followed to provide crude 8.7c, which was purified via column chromatography (8:1 / hexane:EtOAc), R\textsubscript{f} 0.58 to afford pure product (0.65 g, 96.7% yield) as a colorless liquid, bp 132-145 °C. \textsuperscript{1}H NMR: (250 MHz, CDCl\textsubscript{3}) δ 5.61-5.54 (m, 2H), 4.08-4.04 (m, -OCH\textsubscript{2}- and -CH\textsubscript{2}- of Et overlapping, 4H), 2.31-2.30 (br s, -CH\textsubscript{2}CH\textsubscript{2}-, 4H), 1.21 (t, 3H, -CH\textsubscript{3}), 0.85 (s, 9H, tBu), 0.01 (s, 6H, 2 –CH\textsubscript{3}); \textsuperscript{13}C NMR: (62.5 MHz, CDCl\textsubscript{3}), δ 173.4, 130.8, 129.2, 64.10, 60.68, 34.31, 27.86, 26.35, 18.79, 14.64, -4.77.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {8.5d};
  \node (b) at (1,0) {OEC};
  \node (c) at (2,0) {8.7d};
  \node (d) at (0,-1) {PivO\_OH};
  \node (e) at (2,-1) {EtO\_OPiv};
  \node (f) at (2,1) {\text{8.7d}};
\end{tikzpicture}
\end{center}

6-\textit{(}2,2\text{-}dimethyl\text{-}propionyloxy\text{)}\textendash;hex\textendash;4\textendash;enoic acid ethyl ester (8.7d). The general procedure for the OEC was followed to provide crude 8.7d, which was purified on a column (9:1 / hexane:EtOAc), R\textsubscript{f} 0.53 to afford pure diester (2.42 g, 86.1% yield) as a
colorless liquid. $^1$H NMR: (250 MHz, CDCl$_3$) δ 5.89-5.57 (m, 2H, H=$\text{C}=$CH), 4.50 (d, 2H, $J$ = 5.2 Hz, -OCH$_2$C=C-), 4.13 (q, 2H, CH$_2$ of Et), 2.40-2.38 (2s overlapping, 4H, -CH$_2$CH$_2$), 1.25 (t, 3H), 1.19 (s, 9H); $^{13}$C NMR: (62.5 MHz, CDCl$_3$), δ 177.9, 172.6, 132.8, 125.2, 64.44, 60.16, 38.59, 33.43, 27.33, 27.21, 14.08; IR cm$^{-1}$ 2976, 1729, 1397, 1152; MS (m/z) 242.

**TBDMS Deprotection, 6-hydroxy-hex-4-enoic acid ethyl ester, (8.8c).** A solution of the TBDMS protected alcohol 8.7c (0.2 g, 0.73 mmol) in freshly distilled THF (5 mL) was cooled to 0 °C. TBAF (1M soln in THF) (0.25 g, 0.95 mmol) was added dropwise with continual stirring. The progress of the reaction was monitored by TLC (8:1 / hexane:EtOAc). Upon complete conversion, the reaction mixture was quenched with sat’d aqueous NH$_4$Cl (15 mL), extracted with Et$_2$O, and subsequently washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated via rotary evaporator. The crude material was purified by column chromatography (50:50 / hexane:EtOAc), $R_f$ 0.43 to give 0.082 g (70.6% yield) of pure 8.8c. $^1$H NMR: (250 MHz, CDCl$_3$) δ 5.69 (br m, 2H, -CH=$\text{C}=$CH-), 4.19-4.09 (q and br s overlapped, 4H, -OCH$_2$-), 2.39 (2s overlapping, 4H, -CH$_2$CH$_2$-), 1.66 (br s, 1H, -OH), 1.26 (t, 3H, -CH$_3$ of Et).
Diester Reduction, *trans*-2-hexene-1,6-diol, (8.8d). A 250 mL RBF, fitted with a magnetic stirring bar, septum, and a nitrogen inlet was charged with the diester 8.7d (2 g, 8.25 mmol) and freshly distilled THF (65 mL). After cooling the contents to 0 ºC, LAH (1M solution in Et₂O) (16.5 mmol) was added dropwise. Stirring continued at this temperature for 1 h and was subsequently quenched by the slow addition (caution: vigorous gas evolution) of 100 mL of 1M aqueous sodium potassium tartrate. Hexane (100 mL) was then added and the mixture was warmed to room temperature and stirred to give two clear layers. The layers were then separated and the aqueous phase was extracted with EtOAc (2x40 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The crude material was purified by Kugelrohr distillation, bp 120-130 ºC (3 mm Hg) to provide the desired compound 8.8d as a thick, colorless oil (0.73 g, 76.3% yield). ¹H NMR: (250 MHz, CDCl₃) δ 5.89-5.55 (m, 2H), 4.09-4.07 (m, 2H), 3.65 (t, 2H), 2.29-2.12 (m, 2H), 2.06-1.98 (m, 2H), 1.66 (p, 2H); ¹³C NMR: (62.5 MHz, CDCl₃), δ 132.3, 129.5, 63.47, 62.15, 31.87, 28.48.

![Chemical structure](image)

6-vinloxy-hex-4-enoic acid ethyl ester (8.11). A solution of the starting allylic alcohol 8.8c (0.12 g, 0.76 mmol), ethyl vinyl ether (EVE, 0.55 g, 7.6 mmol), and a catalytic amount of mercuric acetate (0.1 eq) was heated under reflux for 16 hours. Upon disappearance of the alcohol, the excess EVE was removed *en vacuo*. The remaining residue was purified via column chromatography (9:1 / hexane : EtOAc), R₅ 0.5 to afford
pure 8.11 (150 mg, 10%). $^1$H NMR: (250 MHz, CDCl$_3$) $\delta$ 6.45-6.36 (dd, 1H), 5.83-5.57 (m, 2H), 4.20-3.95 (m, 6H), 2.36 (2s overlapping, 4H, -CH$_2$CH$_2$-), 1.22 (t, 3H, CH$_3$ of Et); $^{13}$C NMR: (62.5 MHz, CDCl$_3$), $\delta$ 172.8, 151.3, 132.8, 126.0, 86.9, 68.5, 60.3, 33.6, 27.5, 14.2.

HPK Substrate, 6-oxo-3-vinyl-hexanoic acid ethyl ester, (8.1a). Conversion of 8.8d, using the general procedure for the OEC, provides the mixed orthoester 8.9. Crude 8.9 was combined with freshly distilled, anhydrous EtOH, and camphor sulfonic acid in a RBF fitted with a reflux condenser. The contents were heated for 1 h. After cooling to room temperature, the acidic reaction mixture was neutralized with solid NaHCO$_3$. The solution was then washed with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), filtered, and concentrated to provide crude 8.10, which could be purified via column chromatography (9:1 / hexane:EtOAc), R$_f$ 0.45. In a RBF fitted with a reflux condenser, pyridinium chlorochromate$^{8.22}$ (52 mg, 0.24 mmol) was suspended in anhydrous DCM (0.32 mL). The alcohol 8.10 (30 mg, 0.16 mmol) in DCM (0.03 mL) was then added in one portion to the magnetically stirred suspension. After 1.5 h, dry Et$_2$O was added and the supernatant liquid was decanted from a black gum. The insoluble residue was washed with Et$_2$O and DCM and subsequently passed through a pad of Florisil. The excess solvent was removed via rotary evaporator to leave a crude product which was purified via column chromatography (9:1 / hexane:EtOAc), R$_f$ 0.28 to give 19.5 mg (65.7% yield) of the pure
δ,ε-unsaturated aldehyde 8.1a.  

\[ ^1 \text{H NMR: (250 MHz, CDCl}_3) \delta 9.72 (s, 1H), 5.66-5.43 (m, 1H), 5.04-4.98 (m, 2H), 4.09 (q, 2H), 2.67-2.22 (m, 5H), 1.99 (s, 1H), 1.87-1.34 (m, 2H), 0.84 (t, 3H); \]

\[ ^{13} \text{C NMR: (62.5 MHz, CDCl}_3), \delta 201.7, 171.8, 139.6, 116.3, 60.2, 41.4, 39.8, 31.4, 26.1, 25.08, 20.81, 14.05. \]

\[ \text{Generation of 2,4-pentadienylstannane (8.15).} \]

To a flame dried round bottom flask, evacuated and subsequently purged with nitrogen, was placed the 1,4-pentadiene (73 mmol) and charged with freshly distilled THF (200 mL). The flask was cooled to -60 °C (dry ice / chloroform bath) and butyllithium (1.6 N solution in hexanes, 73 mmol) was injected. The solution was allowed to warm to 0 °C over a thirty minute period and subsequently stirred for 1 h at 5-10 °C. The resulting red-orange solution was cooled to -70 °C and quenched with trimethyltin chloride (1.0 M solution in THF, 75 mmol). The reaction mixture (now colorless) was poured into sat’d aqueous NH₄Cl, diluted with water, and extracted with hexanes. The combined organic fractions were washed with water, brine, and dried (MgSO₄). Solvent removal provided a crude oil which was then purified by Kugelrohr distillation (bp 55-65 °C / 3 mm Hg). The by-product, hexamethylditin, was precipitated at -30 °C. NMR data for 8.15 match those reported in literature.  

\[ ^1 \text{H NMR: (250 MHz, CDCl}_3) \delta 6.28 (ddd, 1H), 5.91 (dd, 1H), 5.84 (dt, 1H), 4.94 (dd, 1H), 4.79 (dd, 1H), 1.81 (d, 1H), 0.11 (dd, 9H); \]

\[ ^{13} \text{C NMR: (62.5 MHz, CDCl}_3), \delta 137.5, 135.1, 132.0, 111.7, 19.4, -10.2. \]
Maruyama’s Pentadienylation Procedure. A flame-dried flask, evacuated and purged with nitrogen, was charged with freshly distilled dichloromethane. The apparatus, cooled to -78°C, was injected with the \( \alpha,\beta \)-unsaturated aldehyde, followed by a successive addition of the Lewis acid (2 equiv) and the organostannane (1.2 equiv). The reaction was maintained at this temperature until completion, then quenched by the slow addition of sodium bicarbonate solution, followed by the usual aqueous workup. This procedure was used to synthesize pure 8.16d and 8.16f. The spectroscopic data, reported below, match previously reported data.

General Procedure “in situ” Pentadienylation. To a flame dried flask, evacuated and purged with nitrogen, was placed 1,4-pentadiene (14.7 mmol) and charged with freshly distilled THF (80 mL). The flask was cooled to -60 °C (dry ice / chloroform bath) and butyllithium (1.6N solution in hexanes, 73 mmol) was injected. The solution was allowed to warm to 0 °C over a thirty minute period and subsequently stirred for 1
hour at 5-10 °C. The resulting red-orange solution was cooled to -70 °C (dry ice / acetone bath) and quenched with the aldehyde (15 mmol). The reaction mixture (now colorless) was poured into sat’d aqueous NH₄Cl, diluted with water, and extracted with hexanes. The combined organic fractions were washed with water, brine, and dried (MgSO₄). Solvent removal provided a crude oil comprised of sweet-smelling linear 8.16 and branched (pungent odor) 8.17 alcohols, which were then purified by column chromatography.

**(8.16c):** Pure 8.16c was obtained from column chromatography (9:1 / hexane:EtOAc), Rf 0.09 as a colorless oil (48%). $^1$H NMR (250 MHz, CDCl₃) δ 6.38-6.07 (m, 2H), 5.91-5.75 (m, 1H), 5.73-5.58 (m, 1H), 5.25-4.91 (m, 4H), 4.12-4.09 (m, 1H), 2.50-2.25 (m, 3H); $^{13}$C NMR (62.5 MHz, CDCl₃) δ 140.2, 136.6, 134.0, 129.7, 115.8, 114.8, 72.0, 40.2.

**(8.16d):** Pure 8.16d was obtained from column chromatography (75:25 / hexane:EtOAc), Rf 0.53 as a colorless oil (52%). $^1$H NMR (250 MHz, CDCl₃) δ 6.35-6.07 (m, 2H), 5.74-5.63 (m, 2H), 5.54-5.43 (m, 1H), 5.16-4.98 (m, 2H), 4.28-4.05 (m, 1H), 2.27 (t, 2H), 2.02 (br s, 1H), 1.65 (d, 3H, $J = 6.34$ Hz); $^{13}$C NMR (62.5 MHz, CDCl₃) δ 136.8, 133.8, 133.4, 131.6, 126.7, 115.7, 72.2, 40.6, 17.7.

**(8.16e):** Pure 8.16e (63%) was obtained upon column chromatography (75:25 / hexane:EtOAc), Rf 0.55. $^1$H NMR (250 MHz, CDCl₃) δ 6.33-6.09 (m 2H), 5.69 (p, 1H), 5.19-4.95 (m, 3H), 4.39-4.32 (dd, 1H), 2.37-2.24 (m, 3H), 1.71 (s, 3H), 1.66 (s, 3H); $^{13}$C NMR (62.5 MHz, CDCl₃) δ 136.8, 134.8, 133.3, 130.3, 127.3, 115.3, 68.0, 40.6, 25.7, 17.9. IR (neat, $\nu$ cm⁻¹) 3344, 2971-2913, 1675-1602, 1002. HRMS (ESI) m/z 191.10415 (MNa⁺, 191.104248 calcd for C$_{10}$H$_{16}$O).
(8.16f): Column chromatography (75:25 / hexane:EtOAc) afforded pure 8.16f as a colorless oil (62%). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.41-7.22 (m, 5H, Ph), 6.55 (d, 1H, $J$ = 15.9 Hz), 6.39-6.15 (m, 3H), 5.78-5.68 (m, 1H), 5.17-5.00 (m, 2H), 4.34 (q, 1H, OCH), 2.44-2.38 (m, 2H, CCH$_2$C), 2.06 (br s, 1H, OH); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 137.7, 137.5, 135.3, 132.5, 131.3, 130.7, 129.5, 128.6, 127.5, 117.1, 72.9, 41.7.

(8.16g): Column chromatography (75:25 / hexane:EtOAc), $R_f$ 0.58 yielded the linear allylic alcohol (43%) 8.16g in pure form as a colorless oil. $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 6.31-6.13 (m, 2H), 5.73-5.59 (m, 1H), 5.15-4.84 (m, 4H), 4.09 (q, 1H, OCH), 2.45-2.33 (m, 2H, -CH$_2$-), 2.20 (d, 1H, OH), 1.73 (s, 3H, CH$_3$); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 146.6, 136.7, 133.7, 130.3, 115.7, 110.9, 74.9, 38.4, 17.7. IR (neat, $\nu$ cm$^{-1}$) 3365, 3084-2917, 1650-1602, 1002. HRMS (El) $m/z$ 138.1044 (M$^+$, 138.103916 calcd for C$_9$H$_{14}$O).

(8.17c): Pure 8.17c was obtained from column chromatography (9:1 / hexane:EtOAc), $R_f$ 0.09 as a colorless oil (19%). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 5.94-5.69 (m, 3H), 5.22-5.05 (m, 6H), 4.10-4.03 (m, 1H), 2.89 (q, 1H), 1.93 (br s, 1H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 138.0, 136.4, 136.3, 117.6, 117.3, 116.0, 74.4, 54.3.

(8.17e): Pure 8.17e (22%) was obtained upon column chromatography (75:25 / hexane:EtOAc). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 5.74-5.82 (m, 2H), 5.06-5.19 (m, 5H), 4.24 (dd, $J$ = 9.0, 6.9 Hz, 1H), 2.80-2.85 (m, 1H), 1.71 (s, 3H), 1.66 (s, 3H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 137.1, 137.0, 136.6, 125.1, 117.7, 116.7, 70.1, 55.0, 25.8, 18.5.

(8.17g): Pure 8.17g (17%) was obtained upon column chromatography (75:25 / hexane:EtOAc). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 5.88-5.70 (m, 2H, C=CHC), 5.22-4.85.
(m, 6H, C=CH₂), 3.98-3.94 (dd, J = 3.0, 7.2 Hz, 1H, CHOH), 2.97-2.89 (q, 1H), 2.10 (d, 1H, -OH), 1.76 (s, 3H, CH₃); ¹³C NMR (62.5 MHz, CDCl₃) δ 145.3, 137.6, 137.3, 118.1, 116.7, 113.6, 77.9, 52.5, 18.1. IR (neat, v cm⁻¹) 3412, 3077-2918, 1643, 1076. HRMS (El) m/z 138.1044 (M⁺, 138.103916 calcd for C₉H₁₄O).

**General Procedure for the AOC Rearrangement.** To a cooled suspension of oil free KH (2 mmol) in freshly distilled THF (14 mL) was added the allylic alcohol (1.3 mmol). Immediately after, a solution of 18-crown-6 (1.3 mmol) in THF was cannulated. After desired temperature and time requirements were achieved, the reaction mixture was cooled to -78 °C, where it was quenched with methanol. The reaction was treated with sat’d aqueous NH₄Cl solution at 0 °C and subsequently extracted with diethyl ether. The usual workup provided a crude oil which could be purified via column chromatography (95:5 / pentane:ether) and ultimately subjected to NMR data collection.

![HPK Substrate, 3,3-dimethyl-4-vinyl-hex-5-enal, (8.1e).](image)

**HPK Substrate, 3,3-dimethyl-4-vinyl-hex-5-enal, (8.1e).** To a cooled suspension of oil free KH (80 mg, 2 mmol) in freshly distilled THF (14 mL) was added the allylic alcohol (0.2 g, 1.3 mmol) **8.16e**. Immediately after, a solution of 18-cr-6 (35 mg, 1.3 mmol) in THF was cannulated. The reaction was allowed to warm to 20 °C over a 40 minute period. Upon completion, the reaction mixture was cooled to -78 °C, where it was quenched with methanol. The reaction was treated with sat’d aqueous NH₄Cl.
solution at 0 °C and subsequently extracted with diethyl ether. The usual workup provided an oil which could easily be purified via column chromatography (95:5 / pentane:ether), R_f 0.52, to provide the desired aldehyde **8.1e** (84 mg, 42%). Losses in yield are attributed to the extreme volatility of the aldehyde product. ^1H NMR (250 MHz, CDCl₃) δ 9.84 (t, 1H, CHO), 5.96-5.79 (ddd, 2H, H₂C=CH), 5.24-5.01 (m, 4H, HC=CH₂), 2.65 (t, 1H, =CCHC=), 2.31 (d, 2H, J = 2.90 Hz, CH₂), 1.06 (s, 6H, CH₃); ^13C NMR (62.5 MHz, CDCl₃) δ 203.7, 137.3, 117.5, 58.8, 54.0, 36.4, 25.4. IR (neat, ν cm⁻¹) 2968, 1720, 1469-1372.

**HPK Substrate, 2-methyl-4-vinyl-hex-4-enal, (8.1m).** To a cooled suspension of oil free KH (36 mg, 0.9 mmol) in freshly distilled THF (7 mL) was added the allylic alcohol (80 mg, 0.58 mmol) **8.16g**. Immediately after, a solution of 18-cr-6 (150 mg, 0.58 mmol) in THF was cannulated. The reaction was allowed to warm to 20 °C over a 40 minute period. Upon completion, the reaction mixture was cooled to -78 °C, where it was quenched with methanol. The reaction was treated with sat’d aqueous NH₄Cl solution at 0 °C and subsequently extracted with diethyl ether. The usual workup provided an oil which could easily be purified via column chromatography (95:5 / pentane:ether), R_f 0.39, to provide the conjugated aldehyde (**E**-**8.1m** (46 mg, 57%). Losses in yield are attributed to the extreme volatility of the aldehyde product. ^1H NMR (250 MHz, CDCl₃) δ 9.68 (d, 1H, CHO), 6.34-6.23 (dd, 1H, H₂C=CH), 5.72 (q, 1H, ...
3-benzensulfonyl-butyraldehyde. To an acetic acid solution (140 mL) of benzensulfinic acid, Na salt (21 g, 129 mmol) was added crotonaldehyde (5 g, 5.91 mL, 71.4 mmol). The reaction was allowed to proceed overnight at room temperature. Upon completion, the mixture was shaken with aqueous NaHCO₃ and extracted with benzene (caution: vigorous gas evolution!!). After successive washing with water, the benzene layer was dried (MgSO₄) and concentration via rotary evaporator provided the sulfone (9.89 g, 66%) as an oil. The product was found pure enough for further use. Data match those previously reported.\(^ {8,18} \) \(^ 1 \)H NMR (250 MHz, CDCl₃) δ 9.74 (t, 1H, CHO), 7.90-7.86 and 7.74-7.52 (m, 5H, Ph), 3.76-3.62 (m, 1H, CHSO₂Ph), 3.22-3.13 (m, 1H, CH₂CO), 2.70-2.59 (m, 1H, CH₂CO), 1.28 (d, 3H, CH₃, \( J = 6.85 \) Hz); \(^ {13} \)C NMR (62.5 MHz, CDCl₃) δ 197.3, 136.4, 133.9, 129.3, 128.8, 54.3, 43.0, 14.1.

2-(2-benzensulfonyl-propyl)-[1,3]dioxolane. A benzene solution containing starting aldehyde (9.8 g, 46 mmol), ethylene glycol (28.7 g, 460 mmol), and \( p- \)
toluenesulfonic acid monohydrate (0.18 g, 0.92 mmol) was refluxed with continuous azeotropic removal of water via a Dean-Stark trap. When the theoretical yield of water had been collected (~6 hours), the cooled mixture was poured into aqueous NaHCO₃ and extracted with benzene. The organic layer was washed with water and subsequently dried over MgSO₄. Concentration provided protected acetal (10.8 g, 91%) in pure form. The product was found pure enough for further use. Data match those previously reported.

\[ ^1H \text{ NMR (250 MHz, CDCl}_3\] \( \delta \) 7.91-7.82 and 7.64-7.47 (m, 5H, Ph), 4.95-4.91 (dd, 1H, CH, \( J = 5.275 \text{ Hz} \)), 3.91-3.70 (m, 4H, -OCH₂CH₂O-), 3.39-3.23 (m, 1H, CHSO₂Ph), 2.34-2.25 (m, 1H, CCH₂C), 1.81-1.67 (m, 1H, CCH₂C), 1.33 (d, 3H, CH₃, \( J = 6.905 \text{ Hz} \)); \[ ^13C \text{ NMR (62.5 MHz, CDCl}_3\] \( \delta \) 136.8, 133.6, 129.1, 128.9, 101.9, 64.9, 64.4, 56.4, 33.4, 13.9.

(1-benzenesulfonyl-2-[1,3]dioxolan-2-yl-1-methyl-ethyl-trimethyl-silane. To a cooled solution (-78 °C) of the ketalized sulfone (10.9 g, 43 mmol) and hexamethylphosphoramide (22.9 g, 128 mmol) in THF was added dropwise a solution of \( n \)-Butyllithium (1.6 \( M \) in hexanes, 51 mmol). The temperature was maintained for 1 hour, after which time chlorotrimethylsilylane (9.24 g, 85 mmol) was injected. After an additional hour at -78 °C, the reaction was allowed to warm to room temperature, where it remained for 60 minutes. Extraction with benzene – water provided crude product as a thick oil. Pure material was collected upon recrystallization from hexane as a white solid. The product was found pure enough for further use. Data match those previously
3-benzenesulfonyl-3-trimethylsilanyl-butyraldehyde. A solution of acetone (100 mL), 5N HCl (100 mL), and starting acetal (4.25 g) was allowed to stir at room temperature for 6 hours. Upon completion, the reaction mixture was poured into aqueous NaHCO₃ and extracted with benzene. After successive washings with water and brine, the organic layer was dried (Na₂SO₄) and concentrated to provide the product as a thick oil. The compound was allowed to crystallize at -30° C overnight after which time, the solid mass was crushed into a fine powder and washed with successive portions of 90:10 (hexane : EtOAc) to provide pure product (2.4 g, 65%) as a white solid. The product was found pure enough for further use. Data match those previously reported.¹⁸ ¹H NMR (250 MHz, CDCl₃) δ 9.46 (t, 1H, CHO, J = 2.74 Hz), 7.44-7.40 and 7.32-7.18 (m, 5H, Ph), 2.10 (d, 2H, CH₂CO, J = 2.80 Hz), 0.93 (s, 3H, CH₃), 0.00 (s, 9H, SiMe₃); ¹³C NMR (62.5 MHz, CDCl₃) δ 200.1, 136.8, 134.8, 131.0, 130.2, 56.7, 49.2, 20.9, -0.11.
**3-trimethylsilanyl-but-2-enal.** A solution of starting aldehyde (8.2 g, 29 mmol) and DBU (8.8 g, 58 mmol) in freshly distilled DCM (280 mL) was refluxed for 2 hours under an atmosphere of nitrogen. The cool solution was washed with water and extracted with ether. The organic layer was then dried (MgSO₄), filtered, and concentrated via rotary evaporator (cold water) to provide 8.18d (5.05 g, 25% overall yield from crotonaldehyde) as a dark brown as a mixture of Z/E isomers (1:4). The crude was used without further purification. The product was found pure enough for further use. Data match those previously reported.⁸¹ H NMR (250 MHz, CDCl₃) δ 9.97 (d, 1H, CHO, J = 7.92 Hz), 9.72 (d, 1H, CHO, J = 8.54 Hz), 6.35-6.28 (dq, 1H, CH=C, J = 7.6, 1.6 Hz), 6.09-6.01 (dq, 1H, CH=C, J = 7.92, 1.73 Hz), 2.11 (d, 3H, CH₃, J = 1.72 Hz), 1.93 (d, 3H, CH₃, J = 1.58), 0.131 (s, 9H, SiMe₃), 0.00 (s, 9H, SiMe₃); ¹³C NMR (62.5 MHz, CDCl₃) δ 193.7, 191.2, 170.7, 166.8, 143.2, 138.5, 27.4, 16.6, 1.50, -1.78.

Pentadienylation, 2-trimethylsilanyl-nona-2,6,8-trien-4-ol, (8.19d). A flame-dried flask, evacuated and purged with nitrogen, was charged with freshly distilled dichloromethane. The apparatus, cooled to -78°C, was injected with the α,β-unsaturated aldehyde 8.18d, followed by a successive addition of the Lewis acid (2 equiv) and the organostannane (1.2 equiv). The reaction was maintained at this temperature until completion. At which time, it was quenched by the slow addition of sodium bicarbonate solution, followed by the usual aqueous workup. A 4:1 mixture (E:Z) of 8.19d was
obtained upon column chromatography (75:25 / hexane / EtOAc), Rf 0.57, (72%).  $^1$H NMR (250 MHz, CDCl$_3$) δ 6.35-6.02 (m, 2H), 5.67-5.55 (m, 2H), 5.10-4.92 (m, 2H), 4.49 (m, 1H), 2.26-2.20 (m, 2H), 1.65 (d, 3H, CH$_3$, $J = 1.75$), 0.00 (s, 9H, SiMe$_3$); $^{13}$C NMR (62.5 MHz, CDCl$_3$) δ 140.3, 136.8, 134.0, 130.0, 115.8, 67.4, 40.4, 14.8, -0.02, -2.42.

![Chemical Structure](image)

**Triethyl-(1-propenyl-hexa-3,5-dienyloxy)-silane (8.21).** The allylic alcohol (0.25 g, 1.8 mmol) in dry DMF (0.3 mL) was slowly added to a mixture of TESCl (chlorotriethylsilane, 0.3 g, 2 mmol) and imidazole (0.14 g, 2 mmol) in DMF (5 mL) at 0°C. Upon completion, the reaction mixture was stirred for 10 hours at room temperature. It was then poured into water and extracted with hexanes. The organic layer was dried (MgSO$_4$), filtered, and concentrated under reduced pressure. Column chromatography (9:1 / hexane:EtOAc), Rf 0.87 yielded the product (0.35 g, 95%) as a colorless oil. $^1$H NMR (250 MHz, CDCl$_3$) δ 6.41-6.22 (m, 1H), 6.11-6.01 (m, 1H), 5.75-5.35 (m, 3H), 5.12-4.93 (m, 2H), 4.07 (q, 1H), 2.27 (br q, 2H), 1.66 (d, 3H, $J = 5.98$ Hz), 0.94 (t, 9H, CH$_3$ of TES), 0.59-0.47 (m, 6H, CH$_2$ of TES); $^{13}$C NMR (62.5 MHz, CDCl$_3$) δ 137.1, 134.1, 132.8, 131.2, 125.3, 114.9, 73.3, 41.7, 17.4, 6.64, 4.82.

**8.5.3 Spectral Data**

Spectral data are included on the following pages.
Figure 8.6 $^1$H NMR (250 MHz, d-Acetone) Downfield Expansion of Compound 8.3
Figure 8.7 $^1$H NMR (250 MHz, d-Acetone) Upfield Expansion of Compound 8.3
Figure 8.8 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.5c
Figure 8.9 $^1H$ NMR (250 MHz, CDCl$_3$) Expansion of Free -OH on Compound 8.5c
Figure 8.10 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.5d
Figure 8.11 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.5d
Figure 8.12 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.7c
Figure 8.13 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Downfield Expansion of Compound 8.7c
Figure 8.14 $^{13}$C NMR (62.5 MHz, CDCl$_3$) Upfield Expansion of Compound 8.7c
Figure 8.15 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.7d
Figure 8.16 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.7d
Figure 8.17 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.8c
Figure 8.18 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.8d
Figure 8.19 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.8d
Figure 8.20 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.11
Figure 8.21 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.11
Figure 8.22 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.10
Figure 8.23 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.10
Figure 8.24 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.1a
Figure 8.25 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.1a
Figure 8.26 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.15
Figure 8.27 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.15
Figure 8.28 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.16c
Figure 8.29 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.16c
Figure 8.30 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.16d
Figure 8.31 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.16d
Figure 8.32 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.16e
Figure 8.33 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.16e
Figure 8.34 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.16f
Figure 8.35 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.16f
Figure 8.36 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.16g
Figure 8.37 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.16g
Figure 8.38 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.17c
Figure 8.39 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.17c
Figure 8.40 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.17e
Figure 8.41 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.17e
Figure 8.42 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.17g
Figure 8.43 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.17g
Figure 8.44 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.1e
Figure 8.45 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.1e
Figure 8.46 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound $(E)$-8.1m
Figure 8.47 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.19d
Figure 8.48 $^{13}$C NMR (62.5 MHz, CDCl₃) of Compound 8.19d
Figure 8.49 $^1$H NMR (250 MHz, CDCl$_3$) of Compound 8.21
Figure 8.50 $^{13}$C NMR (62.5 MHz, CDCl$_3$) of Compound 8.21
8.6 References


8.19 Because of its higher boiling point, triethylsilyl (TES) was chosen over trimethylsilyl (TMS).


CHAPTER 9: CONSTRUCTION OF JASMONE ANALOGS VIA TITANIUM MEDIATED HETERO PAUSON-KHAND REACTIONS OF TETHERED ENALS

9.1 Preface

The relative importance of jasmonic natural products and the syntheses of several analogs have been the focus of the latter portion of this dissertation (Chapters 7 & 8, respectively). Through vast efforts, the development of several tethered enals was achieved. Now, the hetero Pauson-Khand reaction will assume the pivotal role in the construction of such biologically active targets (Figure 9.1).

![Figure 9.1 Synthesized HPK Substrates]

9.2 HPK Substrates and Their Performance in the HPK Reaction

9.2.1 HPK Reaction of Tethered Enal 9.1a

Unfortunately, treatment of 9.1a with Cp₂Ti(PMe₃)₂ proved unsuccessful in the HPK reaction. The failure to generate the titanium oxametallacycle could possibly be attributed to the oxophilic nature associated with early transition metals. Early transition metal complexes, including HPK titanocene Cp₂Ti(PMe₃)₂, are highly oxophilic and will, therefore, favor any ligand that has an accessible oxygen atom that can donate one (or
more) lone pairs to the metal center. The two carbonyl functionalities in the skeletal framework of HPK substrate 9.1a, the ester and aldehyde moiety, compete for coordination and subsequent engagement in favorable π-backbonding to the electron-rich Ti(+2) metal center. Such competition hindered the ability for the reaction to proceed and resulted in the recovery of starting material.

9.2.2 HPK Reaction of Tethered Dienals 9.1b and 9.1c

In contrast, conversion of dienals 9.1b and 9.1c to their respective bicyclic titanium oxametallacycles, occurred with ease, as indicated through the generation of a characteristic red precipitate. In both cases, excellent selectivity was achieved and pure products were easily isolable from the reaction mixture via crystallization (Figures 9.2-9.6).

Figure 9.2 Crystal Structure of 9.2b
Figure 9.3 $^1$H NMR (250 MHz, C$_6$D$_6$) of Compound 9.1b
Figure 9.4 $^{13}$C NMR (62.5 MHz, C$_6$D$_6$) of Compound 9.1b
Figure 9.5 $^1$H NMR (300 MHz, C$_6$D$_6$) of Compound 9.1c
Figure 9.6 $^{13}$C NMR (75 MHz, C$_6$D$_6$) of Compound 9.1c
9.3 Outlook / Conclusion

The net result of the novel, “in situ”, ε-selective pentadienylation of 1,4-pentadiene and α,β-unsaturated carbonyl systems with subsequent AOC rearrangement provides a facile entry into elaborate tethered dienal HPK substrates in only two steps. Of the substrates investigated, both dienals proved highly effective in this titanium mediated cyclization process to afford 9.2 in high yields (9.2b = 87% and 9.2c = 82%) and excellent selectivity. Formation of the corresponding carbonylated metallacycles with successive reductive elimination should supply direct access to fused, bicyclic γ-butyrolactones 9.3. With 9.3 in hand, reduction of the ketone to the corresponding alcohol, followed by a Wittig reaction, provides the skeletal framework for Jasmone and PGE derivatives 9.4 (Scheme 9.1).

\[ \text{Scheme 9.1 Designed Syntheses for Jasmone Analogs} \]

9.4 Experimental

9.4.1 General Experimental

Unless otherwise stated, all experiments were performed under an atmosphere of nitrogen or argon in oven-dried glassware utilizing standard Schlenk techniques and / or a Vacuum Atmospheres dry box. Solvents used as reaction media were distilled immediately before use. Tetrahydrofuran (THF) and pentane were distilled from sodium.
benzophenone ketyl. Iodomethane was distilled (42-45°C) before use and stored under nitrogen in a -30°C fridge until needed. Magnesium (powder, ~50 mesh, 99+% ) was oven-dried 24 hours before use. P(OPh)₃ was distilled under reduced pressure at high temperatures.

NMR spectra (¹H and ¹³C) were obtained on Bruker AC – 250 and Bruker AC-300 Spectrometers. Chemical shifts, δ, are reported in ppm relative to CDCl₃ (7.27 ppm, ¹H; 77.23 ppm, ¹³C) unless noted otherwise. ¹H NMR data is reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, br = broadened, m = multiplet), integration, and coupling constant (Hz).

9.4.2 Preparative Procedures

\[
\text{MeI } + \text{ Mg } + \text{ P(OPh)₃ } \rightarrow \text{ PMe₃}
\]

Trimethylphosphine (PMe₃). To a 3-neck, 2L RBF, installed with a mechanical stirrer, a 1L addition funnel, and a vacuum / nitrogen manifold, was added dried Mg mesh (~50, 99+% ) (51.1 g, 2.1 mol). The entire apparatus was flame dried under vacuum along with the Mg mesh. The apparatus was then filled with nitrogen, cooled to room temperature, and charged with \( n \)-Bu₂O (650 mL) via cannulation. After cooling to 0 °C in an ice bath, MeI (300 g, 2.1 mol) and an equal volume of \( n \)-Bu₂O was added dropwise to avoid evolution of gas (over 2 h). After 20 minutes, the reaction mixture began to turn blue, and was allowed to stir overnight (the temperature should be kept at 0 °C for at least the first 4 h). Additional MeI may be added to consume all Mg, if necessary. After
cooling to 0 °C, P(OPh)₃ (142.3 mL, 0.54 mol) in equal volume of n-Bu₂O was added dropwise over a period of 3 h. A fractional distillation apparatus was then required. The 3-neck RBF was adapted and fitted with a 16”-long 24/40 Vigreaux column and a 24/40 water cooled condenser. Carefully, the temperature of the heating mantle was adjusted to allow the PMe₃ to be fractionally distilled under a stream of nitrogen and collected in a cooled (-78 °C) receiving flask as a colorless liquid. If n-Bu₂O is still present, it can be eliminated after a second fractional distillation. ¹H NMR: (250 MHz, CDCl₃) δ 0.93 (d, J = 1.7 Hz, 9H); ¹³C NMR: (62.5 MHz, CDCl₃), δ 16.16, 16.31.

\[
\text{Cp₂TiCl₂ + Mg + PMe₃ } \rightarrow \text{Cp₂Ti(PMe₃)₂}
\]

Bis(cyclopentadienyl)titanium bis(trimethylphosphine), [Cp₂Ti(PMe₃)₂]. In the drybox, cold PMe₃ (15.2 g, 0.2 mol) was added to a mixture of Mg powder (4.3 g, 0.177 mol), Cp₂TiCl₂ (10 g, 40 mmol), and freshly distilled THF (250 mL) in a 500 mL RBF. The reaction mixture was purged with argon, sealed, and stirred for 20 h. THF was then removed from the reaction mixture under vacuo and the residual solid chunks were crushed into fine powder and extracted with pentane (200 mL). The pentane extract was filtered through a pad of celite (vacuum dried for 1 day) into a 500 mL side arm flask. The frit was rinsed with more pentane to avoid clogging. The reaction flask and the frit were rinsed with additional pentane until the celite became white. Pentane was then removed under vacuo until the volume was ~100 mL. The flask was cooled to -33 °C overnight to allow crystals (black needles) to form. The next day, the pentane was decanted and the crystals were collected, placed in a vial, and dried under vacuo. The pentane filtrate was then concentrated to dryness to produce a second batch of needles.
$^1$H NMR: (250 MHz, C$_6$D$_6$) δ 4.57 (s, 10H, Cp-H), 0.84 (s, 18H, PMe$_3$-H).

3-bis(cyclopentadienyl)-7,7-dimethyl-2-oxa-6-vinyl-3-titanabicyclo[3.3.0]octane (9.2b). To a solution of the aldehyde 9.1b (170 mg, 1.1 mmol) in dry pentane was added directly the titanium catalyst Cp$_2$Ti(PMe$_3$)$_2$ (0.37 g, 1.1 mmol). After stirring for 4 hours at room temperature, the reaction mixture was filtered through a pad of Celite and rinsed with dry pentane to provide a reddish solution. Pentane was removed under vacuo and the red solid residue was recrystallized from a small amount of pentane overnight at -33 °C. The solid product was obtained by decantation and the mother liquor was concentrated under vacuo and subsequently cooled to -33 °C overnight to provide additional product. Overall yield 320 mg (87%). $^1$H NMR (250 MHz, CDCl$_3$) δ 5.85 (s, 5H, Cp), 5.84 (s, 5H, Cp), 5.82-5.56 (ddd, 1H), 5.23-5.09 (m, 3H), 3.56 (p, 1H, $J$ = 8.75 Hz), 2.80 (t, 1H, $J$ = 9.27 Hz), 2.20 (t, 1H, $J$ = 8.89 Hz), 1.78-1.71 (dd, 1H, $J$ = 6.98, 12.15 Hz), 1.54-1.46 (dd, 1H, $J$ = 8.26, 12.10 Hz), 1.13-1.08 (dd, 1H), 1.02 (s, 3H), 0.72 (s, 3H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) δ 139.3, 115.2, 114.0, 112.2, 83.95, 69.3, 69.1, 55.3, 52.3, 40.1, 28.1, 22.8.
3-bis(cyclopentadienyl)-8-methyl-2-oxa-6-ethylidene-3-
titanabicyclo[3.3.0]octane (9.2c). To a solution of the aldehyde 9.1c (150 mg, 1.1 mmol) in dry pentane was added directly the titanium catalyst Cp2Ti(PMe3)2 (0.36 g, 1.1 mmol). After stirring for 4 hours at room temperature, the reaction mixture was filtered through a pad of Celite and rinsed with dry pentane to provide a reddish solution. Pentane was removed under vacuo and the red solid residue was recrystallized from a small amount of pentane overnight at -33 °C. The solid product was obtained by decantation and the mother liquor was concentrated under vacuo and subsequently cooled to -33 °C overnight to provide additional product. Overall yield 280 mg (82%). "H NMR (300 MHz, CDCl3) δ 5.84 (s, 5H, Cp), 5.83 (s, 5H, Cp), 5.27-5.24 (m, 1H), 4.23-4.20 (m, 2H), 2.99 (t, 1H, J = 10.3 Hz), 2.56-2.49 (dd, 1H, J = 7.26, 15.5 Hz), 2.04-1.96 (m, 1H), 1.70 (d, 3H, J = 6.62 Hz, CH3), 1.57-1.52 (m, 1H), 1.26-1.20 (m, 2H), 1.01 (d, 3H, J = 6.63 Hz, CH3); "C NMR (75 MHz, CDCl3) δ 152.0, 114.6, 113.4, 113.2, 93.1, 66.5, 57.9, 41.9, 34.4, 18.6, 14.9.

9.4.3 X-ray Data

X-ray data for compound 9.2b is included in Appendix B.
APPENDIX A: TERMITE BIOLOGY AND TERMITICIDE BACKGROUND

A.1 Subterranean Termite Background

Figure A.1 Map of US Termite Formosan Subterranean Infestations

Table A.1 Classification System the Formosan Subterranean Termite

<table>
<thead>
<tr>
<th>Kingdom</th>
<th>Anamalia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phylum</td>
<td>Arthropoda</td>
</tr>
<tr>
<td>Class</td>
<td>Insecta</td>
</tr>
<tr>
<td>Order</td>
<td>Isoptera</td>
</tr>
<tr>
<td>Family</td>
<td>Rhinotermidae</td>
</tr>
<tr>
<td>Genus</td>
<td>Coptotermes</td>
</tr>
<tr>
<td>Species</td>
<td>Formosanus</td>
</tr>
</tbody>
</table>
### Table A.2 Termites -vs- Ants

<table>
<thead>
<tr>
<th>Termite</th>
<th>Ant</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Illustration" /></td>
<td><img src="image2" alt="Illustration" /></td>
</tr>
<tr>
<td>Waist</td>
<td>Broad</td>
</tr>
<tr>
<td>Antenna</td>
<td>Antenna</td>
</tr>
<tr>
<td>Broad</td>
<td>Constricted</td>
</tr>
<tr>
<td>Alate Wings</td>
<td>Alate Wings</td>
</tr>
<tr>
<td>Antenna Straight &amp; Beadlike</td>
<td>Elbowed</td>
</tr>
<tr>
<td>Alate Wings Equal sized</td>
<td>Front wings larger than hind wings</td>
</tr>
</tbody>
</table>

### Table A.3 Termite Castes

<table>
<thead>
<tr>
<th>Immature / Worker</th>
<th>Soldier</th>
<th>Reproductive</th>
<th>Winged Reproductive</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3" alt="Figure" /></td>
<td><img src="image4" alt="Figure" /></td>
<td><img src="image5" alt="Figure" /></td>
<td><img src="image6" alt="Figure" /></td>
</tr>
<tr>
<td>Role</td>
<td>Role</td>
<td>Role</td>
<td>Role</td>
</tr>
<tr>
<td>-forage for food (damage)</td>
<td>-defend colony</td>
<td>-largest termites in colony</td>
<td>-alates</td>
</tr>
<tr>
<td>-housekeeping duties</td>
<td>-larger than workers</td>
<td>-at least one present</td>
<td>-most commonly seen by</td>
</tr>
<tr>
<td>-feed other members of colony</td>
<td>-mandibles adapted for fighting</td>
<td>(queen)</td>
<td>individuals</td>
</tr>
<tr>
<td>-care for young</td>
<td>-fed by workers</td>
<td>-produces eggs</td>
<td>-swarm to start a new</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-regulates pheromones</td>
<td>colony</td>
</tr>
<tr>
<td>Characteristic Feature of Soldier</td>
<td>Rectangular head</td>
<td>Teardrop-shaped head</td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------</td>
<td>----------------------</td>
<td></td>
</tr>
<tr>
<td>Distinguishing Habits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-go back to ground for water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-only 2% comprised of soldiers</td>
<td>-hold water source</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-alates fly during day</td>
<td>-nearly ¼ of colony population are soldiers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-attraction to light not obvious</td>
<td>-fly at night</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-hairless alates avoid water areas</td>
<td>-collect at bright lights as night falls</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-infest water-bound trees (aids floatation)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table A.5 Federally Banned Chlorinated Hydrocarbons^A.4^  

<table>
<thead>
<tr>
<th>Chlorinated Hydrocarbon</th>
<th>Chlorinated Hydrocarbon</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Aldrin" /></td>
<td><img src="image" alt="Dieldrin" /></td>
</tr>
<tr>
<td><strong>Aldrin</strong></td>
<td><strong>Dieldrin</strong></td>
</tr>
<tr>
<td>40% remaining after 14 years</td>
<td>15% remaining after 14 years</td>
</tr>
<tr>
<td><img src="image" alt="Chlordane" /></td>
<td><img src="image" alt="Heptachlor" /></td>
</tr>
<tr>
<td><strong>Chlordane</strong></td>
<td><strong>Heptachlor</strong></td>
</tr>
<tr>
<td>40% remaining after 14 years</td>
<td>16% remaining after 14 years</td>
</tr>
</tbody>
</table>

### Table A.6 Wood Treatment Products^A.5-A.7^  

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Brand Name / Manufacturer</th>
<th>Structure</th>
<th>Action on Termites / Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>disodium octaborate tetrahydrate</td>
<td>Bora-Care (liquid) / Nisus Corporation</td>
<td>Na$_2$B$<em>8$O$</em>{13}$$\cdot$4H$_2$O</td>
<td>Stomach Poison</td>
</tr>
<tr>
<td></td>
<td>Tim-bor (powder) / U.S. Borax</td>
<td></td>
<td>Feeding Deterrent / Borate</td>
</tr>
<tr>
<td></td>
<td>Jecta (gel) / Nisus Corporation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Ingredient</td>
<td>Brand Name / Manufacturer</td>
<td>Structure</td>
<td>Action on Termites</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------</td>
<td>-----------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Fenvalerate</td>
<td>Tribute® / AgrEvo</td>
<td><img src="image1" alt="Structure" /></td>
<td>Axonic Poison&lt;br&gt;Sodium Channel Blocker</td>
</tr>
<tr>
<td>Permethrin</td>
<td>Prelude® / Syngenta</td>
<td><img src="image2" alt="Structure" /></td>
<td>Axonic Poison&lt;br&gt;Sodium Channel Blocker</td>
</tr>
<tr>
<td></td>
<td>Permethrin Pro / MicroFlo, Co.</td>
<td><img src="image3" alt="Structure" /></td>
<td>Axonic Poison&lt;br&gt;Sodium Channel Blocker</td>
</tr>
<tr>
<td></td>
<td>Permethrin TC / Speckoz, Inc.</td>
<td><img src="image4" alt="Structure" /></td>
<td>Axonic Poison&lt;br&gt;Sodium Channel Blocker</td>
</tr>
<tr>
<td>Cypermethrin</td>
<td>Demon® TC / Syngenta</td>
<td><img src="image5" alt="Structure" /></td>
<td>Axonic Poison&lt;br&gt;Sodium Channel Blocker</td>
</tr>
<tr>
<td></td>
<td>Prevail® / FMC Corporation</td>
<td><img src="image6" alt="Structure" /></td>
<td>Axonic Poison&lt;br&gt;Sodium Channel Blocker</td>
</tr>
<tr>
<td>Bifenthrin</td>
<td>Talstar One® / FMC Corporation</td>
<td><img src="image7" alt="Structure" /></td>
<td>Axonic Poison&lt;br&gt;Sodium Channel Blocker</td>
</tr>
<tr>
<td>Active Ingredient</td>
<td>Brand Name / Manufacturer</td>
<td>Structure</td>
<td>Action on Termites / Class</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------</td>
<td>-----------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Imidacloprid</td>
<td>Premise ® 75 / Bayer</td>
<td><img src="structure1.png" alt="Structure" /></td>
<td>Chloride Channel Blocker / Chloronicotinyl</td>
</tr>
<tr>
<td>Fipronil</td>
<td>Termidor ® / BASF</td>
<td><img src="structure2.png" alt="Structure" /></td>
<td>Chloride Channel Blocker / Phenyl Pyrazole</td>
</tr>
<tr>
<td>Chlorfenapyr</td>
<td>Phantom ® / BASF</td>
<td><img src="structure3.png" alt="Structure" /></td>
<td>Stomach Insecticide Uncoupling Oxidative Phosphorylation / Pyrrole</td>
</tr>
<tr>
<td>Chlorpyrifos</td>
<td>Cyren ® TC / Cheminova</td>
<td><img src="structure4.png" alt="Structure" /></td>
<td>Cholinesterase inhibitor / Organophosphate</td>
</tr>
<tr>
<td></td>
<td>Dursban ™ TC / Dow AgroSciences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Ingredient</td>
<td>Brand Name / Manufacturer</td>
<td>Structure</td>
<td>Action on Termites / Class</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------</td>
<td>-----------</td>
<td>---------------------------</td>
</tr>
</tbody>
</table>
| Sulfluramid      | FirstLine™ / FMC Corporation  
                   | Terminate™ / Spectracide Corporation | ![Structure](image1) | Stomach Poison / Fluoroaliphatic Sulfonamide |
| Hydramethylnon   | Subterfuge™ / BASF | ![Structure](image2) | Stomach Poison / Trifluoromethyl Aminohydrazones |
| Hexaflumuron     | Sentricon® / Dow AgroSciences | ![Structure](image3) | Insect Growth Regulator  
                   | Chitin Inhibitor / Benzoylurea |
| Diflubenzuron    | Labyrinth™ / Ensystex | ![Structure](image4) | Insect Growth Regulator  
<pre><code>               | Chitin Inhibitor / Benzoylurea |
</code></pre>
<table>
<thead>
<tr>
<th>Natural Source / Active Component</th>
<th>Natural Source / Active Component</th>
<th>Natural Source / Active Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco Leaves (Nicotiana tabacum)</td>
<td>Catnip / “Catmint” (Nepeta cataria)</td>
<td>Red Peppers (Capsicum annuum)</td>
</tr>
<tr>
<td>Nicotine Highly toxic alkaloid  Cancelled</td>
<td>Nepetalactone</td>
<td>Capsaicin</td>
</tr>
<tr>
<td>Sesame Oil (Sesamum indicum)</td>
<td>Corn Bud Oil (Zea mays)</td>
<td>Alaskan Yellow Cedar (Chamaecyparisp nootkatensis)</td>
</tr>
<tr>
<td>Sesamol</td>
<td>2'-acetonaphthone</td>
<td>Nootkatone</td>
</tr>
</tbody>
</table>
Table A.11 Comparison of Termite Treatment Methodology A.2, A.6-A.7

<table>
<thead>
<tr>
<th>Repellent Chemical Barrier Treatments</th>
<th>Wood Treatment Products</th>
<th>Non-Repellent Chemical Barrier Treatments</th>
<th>Termite Baiting Systems</th>
<th>Botanical Termiticides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual Life of Treatment</td>
<td>After 5 years, &lt; 10% remains</td>
<td>Mostly lifetime, but variable with type of application</td>
<td>After 5 years, &lt; 10% remains*</td>
<td>Continuous process; applied as necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*Fipronil &gt; 5 years</td>
<td>Relatively short: &lt; 2 years</td>
</tr>
<tr>
<td>Relative Cost</td>
<td>Least expensive</td>
<td></td>
<td>Most expensive</td>
<td></td>
</tr>
<tr>
<td>Advantages</td>
<td>-immediate protection</td>
<td>-low toxicity</td>
<td>-require little active ingredient</td>
<td>-environmentally friendly</td>
</tr>
<tr>
<td></td>
<td>-less expensive</td>
<td>-no necessity for soil treatments</td>
<td>-immediate protection</td>
<td>-fewer health risks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-kills foraging termites</td>
<td>-less disruptive and intrusive (no drilling)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-more effective than repellent treatments</td>
<td>-natural</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>-must be applied carefully to ensure proper barrier</td>
<td>-more suitable as a preconstruction treatment or as a supplement to other treatments</td>
<td>-must be applied carefully to ensure proper barrier</td>
<td>-more expensive</td>
</tr>
<tr>
<td></td>
<td>-barriers may fail</td>
<td></td>
<td>-barriers may fail</td>
<td>-continual monitoring</td>
</tr>
<tr>
<td></td>
<td>-termiticides break down in soil</td>
<td></td>
<td>-termiticides break down in soil</td>
<td>-longer to take effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-passive control</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-must be reapplied</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-not</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-commercialized</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-volatiles may</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>be of concern</td>
</tr>
</tbody>
</table>

351
A.2 Biogenesis of Eremophilanes

Although eudesmane and eremophilane sesquiterpenoid skeleta are a recurring theme in nature, the latter does not conform to Ruzicka’s well-established isoprene rule (Figure A.2). In 1939, Robinson hypothesized that these irregular isoprenoids were generated by sequential 1,2-hydride and methyl migrations of the corresponding eudesmane precursor (Scheme A.1). Robinson’s biogenesis theory was later verified through both in vivo and in vitro experimentation.

Figure A.2 Eudesmane, Eremophilane, and Valencane Sesquiterpenoid Skeleta

Scheme A.1 Biogenesis of Valencane Framework
A.3 References


A.2 Henderson, G. Louisiana State University, Baton Rouge, LA. Personal communication, 2005.


APPENDIX B: X-RAY DATA

B.1 Epoxide (4.6)

Experimental

Crystal data
C\textsubscript{15}H\textsubscript{22}O\textsubscript{2}
M\textsubscript{r} = 234.33
Monoclinic
P\textsubscript{2}1
\(a = 12.235\) (3) Å
\(b = 8.958\) (3) Å
\(c = 13.196\) (5) Å
\(\beta = 115.100\) (13)\(^\circ\)
\(V = 1309.7\) (7) Å\textsuperscript{3}
\(Z = 4\)
\(D_x = 1.188\) Mg m\textsuperscript{-3}
\(D_m\) not measured

Mo \(K\alpha\) radiation
\(\lambda = 0.71073\) Å
Cell parameters from 3987 reflections
\(\theta = 2.5–30.5^\circ\)
\(\mu = 0.077\) mm\textsuperscript{-1}
\(T = 110\) K
Lath
Colorless
0.40 × 0.18 × 0.07 mm
Crystal source: local laboratory

Data collection
KappaCCD (with Oxford Cryostream) diffractometer
\(\omega\) scans with \(\kappa\) offsets
Absorption correction: none
25783 measured reflections
4182 independent reflections

2372 reflections with \(I > 2\sigma(I)\)
\(R_{int} = 0.068\)
\(\theta_{max} = 30.6^\circ\)
h = −17 → 17
k = −12 → 12
l = −18 → 18
intensity decay: <2%

Refinement
Refinement on \(F^2\)
\(R[F^2 > 2\sigma(F^2)] = 0.070\)
\(wR(F^2) = 0.192\)
S = 1.049
4182 reflections
313 parameters
H-atom parameters constrained

\(w=1/|\sigma^2(F_o^2) + (0.0850P)^2 + 0.2326P|\)
\((\Delta/\sigma)_{max} = 0.000\)
\(\Delta\rho_{max} = 0.49\) e Å\textsuperscript{-3}
\(\Delta\rho_{min} = -0.35\) e Å\textsuperscript{-3}
Extinction correction: none
Scattering factors from \textit{International Tables for Crystallography} (Vol. C)
Table B.1 Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters (Å²) for 4.6

\[ U_{eq} = (1/3) \sum_{ij} a_i^* a_j^* a_i \cdot a_j. \]

<table>
<thead>
<tr>
<th></th>
<th>( x )</th>
<th>( y )</th>
<th>( z )</th>
<th>( U_{eq} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1A</td>
<td>0.5985 (3)</td>
<td>0.4062 (4)</td>
<td>-0.1482 (3)</td>
<td>0.0403 (9)</td>
</tr>
<tr>
<td>O2A</td>
<td>0.8852 (4)</td>
<td>0.2011 (4)</td>
<td>0.5733 (3)</td>
<td>0.0636 (12)</td>
</tr>
<tr>
<td>C1A</td>
<td>0.6561 (3)</td>
<td>0.2855 (4)</td>
<td>0.0249 (3)</td>
<td>0.0225 (9)</td>
</tr>
<tr>
<td>H1A</td>
<td>0.6865</td>
<td>0.1933</td>
<td>-0.0055</td>
<td>0.027</td>
</tr>
<tr>
<td>C2A</td>
<td>0.6203 (4)</td>
<td>0.4157 (4)</td>
<td>-0.0480 (4)</td>
<td>0.0255 (10)</td>
</tr>
<tr>
<td>C3A</td>
<td>0.6074 (4)</td>
<td>0.5584 (4)</td>
<td>0.0042 (3)</td>
<td>0.0254 (9)</td>
</tr>
<tr>
<td>H3A1</td>
<td>0.5228</td>
<td>0.5684</td>
<td>-0.0059</td>
<td>0.030</td>
</tr>
<tr>
<td>H3A2</td>
<td>0.6247</td>
<td>0.6429</td>
<td>-0.0351</td>
<td>0.030</td>
</tr>
<tr>
<td>C4A</td>
<td>0.6911 (3)</td>
<td>0.5684 (4)</td>
<td>0.1289 (3)</td>
<td>0.0196 (8)</td>
</tr>
<tr>
<td>H4A</td>
<td>0.7755</td>
<td>0.5621</td>
<td>0.1355</td>
<td>0.024</td>
</tr>
<tr>
<td>C5A</td>
<td>0.6739 (3)</td>
<td>0.4334 (4)</td>
<td>0.1940 (3)</td>
<td>0.0159 (8)</td>
</tr>
<tr>
<td>C6A</td>
<td>0.7798 (4)</td>
<td>0.4334 (4)</td>
<td>0.3123 (3)</td>
<td>0.0204 (8)</td>
</tr>
<tr>
<td>H6A1</td>
<td>0.8559</td>
<td>0.4506</td>
<td>0.3047</td>
<td>0.024</td>
</tr>
<tr>
<td>H6A2</td>
<td>0.7688</td>
<td>0.5180</td>
<td>0.3553</td>
<td>0.024</td>
</tr>
<tr>
<td>C7A</td>
<td>0.7927 (3)</td>
<td>0.2899 (4)</td>
<td>0.3791 (3)</td>
<td>0.0238 (8)</td>
</tr>
<tr>
<td>H7A</td>
<td>0.7163</td>
<td>0.2751</td>
<td>0.3882</td>
<td>0.029</td>
</tr>
<tr>
<td>C8A</td>
<td>0.8073 (4)</td>
<td>0.1570 (4)</td>
<td>0.3125 (3)</td>
<td>0.0279 (9)</td>
</tr>
<tr>
<td>H8A1</td>
<td>0.8814</td>
<td>0.1700</td>
<td>0.3007</td>
<td>0.033</td>
</tr>
<tr>
<td>H8A2</td>
<td>0.8155</td>
<td>0.0637</td>
<td>0.3553</td>
<td>0.033</td>
</tr>
<tr>
<td>C9A</td>
<td>0.6979 (4)</td>
<td>0.1450 (4)</td>
<td>0.1995 (3)</td>
<td>0.0266 (9)</td>
</tr>
<tr>
<td>H9A</td>
<td>0.7108</td>
<td>0.0637</td>
<td>0.1556</td>
<td>0.032</td>
</tr>
<tr>
<td>H9A2</td>
<td>0.6256</td>
<td>0.1213</td>
<td>0.2119</td>
<td>0.032</td>
</tr>
<tr>
<td>C10A</td>
<td>0.6754 (3)</td>
<td>0.2886 (4)</td>
<td>0.1334 (3)</td>
<td>0.0193 (8)</td>
</tr>
<tr>
<td>C11A</td>
<td>0.8958 (4)</td>
<td>0.3014 (4)</td>
<td>0.4950 (4)</td>
<td>0.0331 (10)</td>
</tr>
<tr>
<td>C12A</td>
<td>0.8714 (5)</td>
<td>0.3730 (6)</td>
<td>0.5816 (4)</td>
<td>0.0531 (14)</td>
</tr>
<tr>
<td>H12A</td>
<td>0.7896</td>
<td>0.4137</td>
<td>0.5612</td>
<td>0.064</td>
</tr>
<tr>
<td>H12B</td>
<td>0.9379</td>
<td>0.4281</td>
<td>0.6411</td>
<td>0.064</td>
</tr>
<tr>
<td>C13A</td>
<td>1.0238 (4)</td>
<td>0.2962 (6)</td>
<td>0.5051 (5)</td>
<td>0.0559 (14)</td>
</tr>
<tr>
<td>H13A</td>
<td>1.0808</td>
<td>0.3067</td>
<td>0.5839</td>
<td>0.084</td>
</tr>
<tr>
<td>H13B</td>
<td>1.0360</td>
<td>0.3781</td>
<td>0.4616</td>
<td>0.084</td>
</tr>
<tr>
<td>H13C</td>
<td>1.0376</td>
<td>0.2007</td>
<td>0.4762</td>
<td>0.084</td>
</tr>
<tr>
<td>C14A</td>
<td>0.5519 (4)</td>
<td>0.4410 (4)</td>
<td>0.2034 (3)</td>
<td>0.0234 (8)</td>
</tr>
<tr>
<td>H14A</td>
<td>0.4858</td>
<td>0.4502</td>
<td>0.1284</td>
<td>0.035</td>
</tr>
<tr>
<td>H14B</td>
<td>0.5518</td>
<td>0.5278</td>
<td>0.2485</td>
<td>0.035</td>
</tr>
<tr>
<td>H14C</td>
<td>0.5410</td>
<td>0.3498</td>
<td>0.2391</td>
<td>0.035</td>
</tr>
<tr>
<td>C15A</td>
<td>0.6792 (4)</td>
<td>0.7210 (4)</td>
<td>0.1756 (4)</td>
<td>0.0288 (9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>H15A</td>
<td>0.6958</td>
<td>0.8000</td>
<td>0.1827</td>
<td>0.043</td>
</tr>
<tr>
<td>H15B</td>
<td>0.7372</td>
<td>0.7279</td>
<td>0.2543</td>
<td>0.043</td>
</tr>
<tr>
<td>H15C</td>
<td>0.5971</td>
<td>0.7328</td>
<td>0.1697</td>
<td>0.043</td>
</tr>
<tr>
<td>O1B</td>
<td>0.0940 (3)</td>
<td>0.4596 (4)</td>
<td>-0.1454 (2)</td>
<td>0.0376 (8)</td>
</tr>
<tr>
<td>O2B</td>
<td>0.3857 (4)</td>
<td>0.1673 (4)</td>
<td>0.5626 (3)</td>
<td>0.0711 (13)</td>
</tr>
<tr>
<td>C1B</td>
<td>0.1581 (3)</td>
<td>0.3163 (4)</td>
<td>0.0200 (3)</td>
<td>0.0238 (9)</td>
</tr>
<tr>
<td>H1B</td>
<td>0.1691</td>
<td>0.2305</td>
<td>-0.0169</td>
<td>0.029</td>
</tr>
<tr>
<td>C2B</td>
<td>0.1185 (4)</td>
<td>0.4551 (5)</td>
<td>-0.0440 (3)</td>
<td>0.0245 (9)</td>
</tr>
<tr>
<td>C3B</td>
<td>0.1042 (4)</td>
<td>0.5884 (4)</td>
<td>0.0174 (3)</td>
<td>0.0247 (9)</td>
</tr>
<tr>
<td>H3B1</td>
<td>0.0198</td>
<td>0.5931</td>
<td>0.0085</td>
<td>0.030</td>
</tr>
<tr>
<td>H3B2</td>
<td>0.1201</td>
<td>0.6798</td>
<td>-0.01642</td>
<td>0.030</td>
</tr>
<tr>
<td>C4B</td>
<td>0.1888 (3)</td>
<td>0.5851 (4)</td>
<td>0.1417 (3)</td>
<td>0.0196 (8)</td>
</tr>
<tr>
<td>H4B</td>
<td>0.2732</td>
<td>0.5866</td>
<td>0.1480</td>
<td>0.024</td>
</tr>
<tr>
<td>C5B</td>
<td>0.1739 (3)</td>
<td>0.4383 (4)</td>
<td>0.1977 (3)</td>
<td>0.0166 (8)</td>
</tr>
<tr>
<td>C6B</td>
<td>0.2793 (4)</td>
<td>0.4292 (4)</td>
<td>0.3164 (3)</td>
<td>0.0188 (8)</td>
</tr>
<tr>
<td>H6B1</td>
<td>0.3553</td>
<td>0.4555</td>
<td>0.3111</td>
<td>0.023</td>
</tr>
<tr>
<td>H6B2</td>
<td>0.2658</td>
<td>0.5046</td>
<td>0.3647</td>
<td>0.023</td>
</tr>
<tr>
<td>C7B</td>
<td>0.2950 (3)</td>
<td>0.2764 (4)</td>
<td>0.3727 (3)</td>
<td>0.0224 (8)</td>
</tr>
<tr>
<td>H7B</td>
<td>0.2182</td>
<td>0.2532</td>
<td>0.3790</td>
<td>0.027</td>
</tr>
<tr>
<td>C8B</td>
<td>0.3123 (3)</td>
<td>0.1568 (4)</td>
<td>0.2988 (3)</td>
<td>0.0246 (8)</td>
</tr>
<tr>
<td>H8B1</td>
<td>0.3210</td>
<td>0.0580</td>
<td>0.3350</td>
<td>0.030</td>
</tr>
<tr>
<td>H8B2</td>
<td>0.3870</td>
<td>0.1774</td>
<td>0.2894</td>
<td>0.030</td>
</tr>
<tr>
<td>C9B</td>
<td>0.2043 (3)</td>
<td>0.1548 (4)</td>
<td>0.1845 (3)</td>
<td>0.0226 (8)</td>
</tr>
<tr>
<td>H9B1</td>
<td>0.2195</td>
<td>0.0814</td>
<td>0.1359</td>
<td>0.027</td>
</tr>
<tr>
<td>H9B2</td>
<td>0.1319</td>
<td>0.1218</td>
<td>0.1939</td>
<td>0.027</td>
</tr>
<tr>
<td>C10B</td>
<td>0.1796 (3)</td>
<td>0.3046 (4)</td>
<td>0.1282 (3)</td>
<td>0.0188 (8)</td>
</tr>
<tr>
<td>C11B</td>
<td>0.3958 (4)</td>
<td>0.2793 (4)</td>
<td>0.4909 (3)</td>
<td>0.0306 (9)</td>
</tr>
<tr>
<td>C12B</td>
<td>0.3692 (5)</td>
<td>0.3366 (7)</td>
<td>0.5808 (4)</td>
<td>0.0530 (15)</td>
</tr>
<tr>
<td>H12C</td>
<td>0.2866</td>
<td>0.3737</td>
<td>0.5619</td>
<td>0.064</td>
</tr>
<tr>
<td>H12D</td>
<td>0.4345</td>
<td>0.3882</td>
<td>0.6439</td>
<td>0.064</td>
</tr>
<tr>
<td>C13B</td>
<td>0.5248 (4)</td>
<td>0.2837 (6)</td>
<td>0.5036 (4)</td>
<td>0.0509 (13)</td>
</tr>
<tr>
<td>H13D</td>
<td>0.5802</td>
<td>0.2855</td>
<td>0.5833</td>
<td>0.076</td>
</tr>
<tr>
<td>H13E</td>
<td>0.5368</td>
<td>0.3736</td>
<td>0.4672</td>
<td>0.076</td>
</tr>
<tr>
<td>H13F</td>
<td>0.5408</td>
<td>0.1950</td>
<td>0.4686</td>
<td>0.076</td>
</tr>
<tr>
<td>C14B</td>
<td>0.0524 (3)</td>
<td>0.4336 (4)</td>
<td>0.2070 (3)</td>
<td>0.0211 (8)</td>
</tr>
<tr>
<td>H14D</td>
<td>-0.0134</td>
<td>0.4559</td>
<td>0.1339</td>
<td>0.032</td>
</tr>
<tr>
<td>H14E</td>
<td>0.0530</td>
<td>0.5079</td>
<td>0.2617</td>
<td>0.032</td>
</tr>
<tr>
<td>H14F</td>
<td>0.0405</td>
<td>0.3340</td>
<td>0.2313</td>
<td>0.032</td>
</tr>
<tr>
<td>C15B</td>
<td>0.1717 (4)</td>
<td>0.7270 (4)</td>
<td>0.1972 (4)</td>
<td>0.0301 (9)</td>
</tr>
<tr>
<td>H15D</td>
<td>0.1802</td>
<td>0.8144</td>
<td>0.1600</td>
<td>0.045</td>
</tr>
<tr>
<td>H15E</td>
<td>0.2289</td>
<td>0.7273</td>
<td>0.2764</td>
<td>0.045</td>
</tr>
<tr>
<td>H15F</td>
<td>0.0890</td>
<td>0.7305</td>
<td>0.1911</td>
<td>0.045</td>
</tr>
</tbody>
</table>
Figure B.1 Epoxide (4.6) Crystal Structure
B.2 Tetrahydronootkatone Acetal (4.8)

Experimental

Crystal data

C_{17}H_{30}O_{2}

\( M_r = 266.41 \)

Orthorhombic

\( P2_12_12_1 \)

\( a = 5.879 \) Å

\( b = 13.177 \) (5) Å

\( c = 19.677 \) (8) Å

\( V = 1524.3 \) (10) Å³

\( Z = 4 \)

\( D_x = 1.161 \) Mg m⁻³

\( D_m \) not measured

Mo Kα radiation

\( \lambda = 0.71073 \) Å

Cell parameters from 2007 reflections

\( \theta = 2.5\text{–}27.5^\circ \)

\( \mu = 0.073 \) mm⁻¹

\( T = 110 \) K

Needle

Colorless

0.30 × 0.10 × 0.07 mm

Crystal source: local laboratory

Data collection

KappaCCD (with Oxford Cryostream) diffractometer

\( \omega \) scans with \( \kappa \) offsets

Absorption correction: none

11104 measured reflections

2034 independent reflections

1532 reflections with

\( I > 2\sigma(I) \)

\( R_{int} = 0.042 \)

\( \theta_{\text{max}} = 27.5^\circ \)

\( h = -7 \rightarrow 7 \)

\( k = -16 \rightarrow 17 \)

\( l = -25 \rightarrow 25 \)

intensity decay: <2%

Refinement

Refinement on \( F^2 \)

\( R[F^2 > 2\sigma(F^2)] = 0.043 \)

\( wR(F^2) = 0.102 \)

\( S = 1.027 \)

2034 reflections

177 parameters

H-atom parameters constrained

\( w = 1/\sigma^2(F_o^2) + (0.0543P)^2 \)

where \( P = (F_o^2 + 2F_c^2)/3 \)

\( (\Delta/\sigma)_{\text{max}} = 0.000 \)

\( \Delta \rho_{\text{max}} = 0.19 \) e Å⁻³

\( \Delta \rho_{\text{min}} = -0.21 \) e Å⁻³

Extinction correction: SHELXL

Extinction coefficient: 0.012 (2)

Scattering factors from International Tables for Crystallography (Vol. C)


Flack parameter = 3.3 (17)
Table B.2 Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($\AA^2$) for 4.8

\[ U_{eq} = \frac{1}{3} \sum_{ij} a_i^2 U_{ij} \]

<table>
<thead>
<tr>
<th></th>
<th>$x$</th>
<th>$y$</th>
<th>$z$</th>
<th>$U_{eq}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1</td>
<td>0.2547(2)</td>
<td>0.70027(12)</td>
<td>0.09011 (7)</td>
<td>0.0252(4)</td>
</tr>
<tr>
<td>O2</td>
<td>0.5669(2)</td>
<td>0.69030 (12)</td>
<td>0.16000 (7)</td>
<td>0.0243 (4)</td>
</tr>
<tr>
<td>C1</td>
<td>0.2289(4)</td>
<td>0.59502 (16)</td>
<td>0.19014 (10)</td>
<td>0.0218 (5)</td>
</tr>
<tr>
<td>H1A</td>
<td>0.2937</td>
<td>0.5363</td>
<td>0.1654</td>
<td>0.026</td>
</tr>
<tr>
<td>H1B</td>
<td>0.0617</td>
<td>0.5935</td>
<td>0.1843</td>
<td>0.026</td>
</tr>
<tr>
<td>C2</td>
<td>0.3218 (3)</td>
<td>0.69214 (18)</td>
<td>0.16037 (10)</td>
<td>0.0206 (5)</td>
</tr>
<tr>
<td>C3</td>
<td>0.2469 (4)</td>
<td>0.78406 (16)</td>
<td>0.20025 (10)</td>
<td>0.0212 (5)</td>
</tr>
<tr>
<td>H3A</td>
<td>0.0806</td>
<td>0.7928</td>
<td>0.1950</td>
<td>0.025</td>
</tr>
<tr>
<td>H3B</td>
<td>0.3219</td>
<td>0.8451</td>
<td>0.1814</td>
<td>0.025</td>
</tr>
<tr>
<td>C4</td>
<td>0.3045 (4)</td>
<td>0.77537 (16)</td>
<td>0.27606 (10)</td>
<td>0.0190 (5)</td>
</tr>
<tr>
<td>H4</td>
<td>0.4734</td>
<td>0.7676</td>
<td>0.2792</td>
<td>0.023</td>
</tr>
<tr>
<td>C5</td>
<td>0.1993 (3)</td>
<td>0.67804 (16)</td>
<td>0.30772 (10)</td>
<td>0.0175 (4)</td>
</tr>
<tr>
<td>C6</td>
<td>0.2864 (4)</td>
<td>0.66481 (15)</td>
<td>0.38130 (10)</td>
<td>0.0184 (5)</td>
</tr>
<tr>
<td>H6A</td>
<td>0.4543</td>
<td>0.6705</td>
<td>0.3812</td>
<td>0.022</td>
</tr>
<tr>
<td>H6B</td>
<td>0.2259</td>
<td>0.7209</td>
<td>0.4094</td>
<td>0.022</td>
</tr>
<tr>
<td>C7</td>
<td>0.2199 (4)</td>
<td>0.56369 (15)</td>
<td>0.41433 (10)</td>
<td>0.0208 (5)</td>
</tr>
<tr>
<td>H7</td>
<td>0.0499</td>
<td>0.5616</td>
<td>0.4157</td>
<td>0.025</td>
</tr>
<tr>
<td>C8</td>
<td>0.2971 (4)</td>
<td>0.47508 (16)</td>
<td>0.36975 (10)</td>
<td>0.0251 (5)</td>
</tr>
<tr>
<td>H8A</td>
<td>0.4653</td>
<td>0.4716</td>
<td>0.3701</td>
<td>0.030</td>
</tr>
<tr>
<td>H8B</td>
<td>0.2383</td>
<td>0.4109</td>
<td>0.3891</td>
<td>0.030</td>
</tr>
<tr>
<td>C9</td>
<td>0.2144 (4)</td>
<td>0.48536 (17)</td>
<td>0.29653 (10)</td>
<td>0.0246 (5)</td>
</tr>
<tr>
<td>H9A</td>
<td>0.2772</td>
<td>0.4291</td>
<td>0.2690</td>
<td>0.030</td>
</tr>
<tr>
<td>H9B</td>
<td>0.0465</td>
<td>0.4801</td>
<td>0.2955</td>
<td>0.030</td>
</tr>
<tr>
<td>C10</td>
<td>0.2868 (4)</td>
<td>0.58621 (16)</td>
<td>0.26558 (9)</td>
<td>0.0194 (5)</td>
</tr>
<tr>
<td>H10</td>
<td>0.4565</td>
<td>0.5882</td>
<td>0.2686</td>
<td>0.023</td>
</tr>
<tr>
<td>C11</td>
<td>0.3033 (4)</td>
<td>0.55203 (17)</td>
<td>0.48818 (10)</td>
<td>0.0235 (5)</td>
</tr>
<tr>
<td>H11</td>
<td>0.2459</td>
<td>0.4851</td>
<td>0.3049</td>
<td>0.028</td>
</tr>
<tr>
<td>C12</td>
<td>0.2033 (4)</td>
<td>0.63332 (18)</td>
<td>0.53513 (11)</td>
<td>0.0291 (6)</td>
</tr>
<tr>
<td>H12A</td>
<td>0.2322</td>
<td>0.6147</td>
<td>0.5826</td>
<td>0.044</td>
</tr>
<tr>
<td>H12B</td>
<td>0.0390</td>
<td>0.6383</td>
<td>0.5275</td>
<td>0.044</td>
</tr>
<tr>
<td>H12C</td>
<td>0.2748</td>
<td>0.6989</td>
<td>0.5253</td>
<td>0.044</td>
</tr>
<tr>
<td>C13</td>
<td>0.5624 (4)</td>
<td>0.55026 (19)</td>
<td>0.49583 (11)</td>
<td>0.0317 (6)</td>
</tr>
<tr>
<td>H13A</td>
<td>0.6261</td>
<td>0.6140</td>
<td>0.4787</td>
<td>0.047</td>
</tr>
<tr>
<td>H13B</td>
<td>0.6249</td>
<td>0.4933</td>
<td>0.4698</td>
<td>0.047</td>
</tr>
<tr>
<td>H13C</td>
<td>0.6021</td>
<td>0.5423</td>
<td>0.5439</td>
<td>0.047</td>
</tr>
<tr>
<td>C14</td>
<td>-0.0618 (3)</td>
<td>0.68394 (18)</td>
<td>0.30795 (10)</td>
<td>0.0228 (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>H14A</td>
<td>-0.1246</td>
<td>0.6201</td>
<td>0.3254</td>
<td>0.034</td>
</tr>
<tr>
<td>H14B</td>
<td>-0.1167</td>
<td>0.6953</td>
<td>0.2615</td>
<td>0.034</td>
</tr>
<tr>
<td>H14C</td>
<td>-0.1108</td>
<td>0.7401</td>
<td>0.3371</td>
<td>0.034</td>
</tr>
<tr>
<td>C15</td>
<td>0.2443 (4)</td>
<td>0.87394 (16)</td>
<td>0.31325 (10)</td>
<td>0.0235 (5)</td>
</tr>
<tr>
<td>H15A</td>
<td>0.3184</td>
<td>0.9313</td>
<td>0.2905</td>
<td>0.035</td>
</tr>
<tr>
<td>H15B</td>
<td>0.2971</td>
<td>0.8699</td>
<td>0.3604</td>
<td>0.035</td>
</tr>
<tr>
<td>H15C</td>
<td>0.0791</td>
<td>0.8837</td>
<td>0.3126</td>
<td>0.035</td>
</tr>
<tr>
<td>C16</td>
<td>0.4560 (4)</td>
<td>0.71365 (18)</td>
<td>0.04994 (11)</td>
<td>0.0266 (5)</td>
</tr>
<tr>
<td>H16A</td>
<td>0.4907</td>
<td>0.7865</td>
<td>0.0432</td>
<td>0.032</td>
</tr>
<tr>
<td>H16B</td>
<td>0.4411</td>
<td>0.6803</td>
<td>0.0051</td>
<td>0.032</td>
</tr>
<tr>
<td>C17</td>
<td>0.6347 (4)</td>
<td>0.66268 (19)</td>
<td>0.09287 (11)</td>
<td>0.0280 (6)</td>
</tr>
<tr>
<td>H17A</td>
<td>0.6325</td>
<td>0.5881</td>
<td>0.0866</td>
<td>0.034</td>
</tr>
<tr>
<td>H17B</td>
<td>0.7886</td>
<td>0.6887</td>
<td>0.0822</td>
<td>0.034</td>
</tr>
</tbody>
</table>
Figure B.2 Tetrahydronootkatone Acetal (4.8)
B.3 Dibromide (4.9)

Experimental

Crystal data
C_{12}H_{24}Br_{2}O
M_r = 380.16

Monoclinic
P\bar{2}_1
a = 13.500 (3) Å
b = 6.1403 (10) Å
c = 18.909 (5) Å
\beta = 92.145 (7)°
V = 1566.3 (6) Å³
Z = 4
D_x = 1.612 Mg m⁻³
D_m not measured

Data collection
KappaCCD (with Oxford Cryostream) diffractometer
\omega scans with \kappa offsets
Absorption correction:
    multi-scan HKL Scalepack (Otwinowski & Minor 1997)
T_{\text{min}} = 0.385, T_{\text{max}} = 0.902
19375 measured reflections
9388 independent reflections
7482 reflections with
    I > 2\sigma(I)
R_{\text{int}} = 0.063
\theta_{\text{max}} = 30.5°
h = -19 → 19
k = -8 → 8
l = -27 → 26
intensity decay: <2%

Refinement
Refinement on F²
R[F² > 2\sigma(F²)] = 0.053
wR(F²) = 0.095
S = 1.101
9388 reflections
333 parameters
H-atom parameters constrained
\quad w = 1/[\sigma²(F_h²) + 4.9110P]
\quad \text{where } P = (P_o² + 2P_c²)/3
\quad (\Delta/\sigma)_{\text{max}} = 0.001
\quad \Delta\rho_{\text{max}} = 1.09 e Å⁻³
\quad \Delta\rho_{\text{min}} = -0.66 e Å⁻³
Extinction correction: none
Scattering factors from International Tables
    for Crystallography (Vol. C)
Absolute structure: Flack H D (1983), Acta
    Cryst. A39, 876-881
Flack parameter = 0.019 (11)
Table B.3 Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($A^2$) for 4.9

\[ U_{eq} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j. \]

<table>
<thead>
<tr>
<th>Atom</th>
<th>$x$</th>
<th>$y$</th>
<th>$z$</th>
<th>$U_{eq}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br1A</td>
<td>0.31</td>
<td>0.634</td>
<td>0.3873</td>
<td>0.0253</td>
</tr>
<tr>
<td>Br2A</td>
<td>0.72</td>
<td>0.65</td>
<td>0.4693</td>
<td>0.0233</td>
</tr>
<tr>
<td>O1A</td>
<td>0.50</td>
<td>0.70</td>
<td>0.4713</td>
<td>0.0210</td>
</tr>
<tr>
<td>C1A</td>
<td>0.44</td>
<td>0.45</td>
<td>0.3845</td>
<td>0.0161</td>
</tr>
<tr>
<td>H1A</td>
<td>0.42</td>
<td>0.31</td>
<td>0.4064</td>
<td>0.019</td>
</tr>
<tr>
<td>C2A</td>
<td>0.52</td>
<td>0.56</td>
<td>0.4236</td>
<td>0.0145</td>
</tr>
<tr>
<td>C3A</td>
<td>0.62</td>
<td>0.46</td>
<td>0.4519</td>
<td>0.017</td>
</tr>
<tr>
<td>C4A</td>
<td>0.65</td>
<td>0.39</td>
<td>0.3483</td>
<td>0.0153</td>
</tr>
<tr>
<td>H4A</td>
<td>0.66</td>
<td>0.53</td>
<td>0.3213</td>
<td>0.018</td>
</tr>
<tr>
<td>C5A</td>
<td>0.57</td>
<td>0.26</td>
<td>0.3104</td>
<td>0.0135</td>
</tr>
<tr>
<td>C6A</td>
<td>0.59</td>
<td>0.22</td>
<td>0.2334</td>
<td>0.0196</td>
</tr>
<tr>
<td>C6A</td>
<td>0.61</td>
<td>0.26</td>
<td>0.2117</td>
<td>0.024</td>
</tr>
<tr>
<td>C7A</td>
<td>0.66</td>
<td>0.12</td>
<td>0.2339</td>
<td>0.024</td>
</tr>
<tr>
<td>C7A</td>
<td>0.56</td>
<td>0.11</td>
<td>0.1864</td>
<td>0.0190</td>
</tr>
<tr>
<td>C8A</td>
<td>0.49</td>
<td>-0.02</td>
<td>0.2087</td>
<td>0.023</td>
</tr>
<tr>
<td>C8A</td>
<td>0.42</td>
<td>0.26</td>
<td>0.1875</td>
<td>0.0233</td>
</tr>
<tr>
<td>H8A1</td>
<td>0.43</td>
<td>0.40</td>
<td>0.1648</td>
<td>0.028</td>
</tr>
<tr>
<td>H8A2</td>
<td>0.36</td>
<td>0.19</td>
<td>0.1597</td>
<td>0.028</td>
</tr>
<tr>
<td>C9A</td>
<td>0.39</td>
<td>0.30</td>
<td>0.2625</td>
<td>0.0186</td>
</tr>
<tr>
<td>H9A1</td>
<td>0.37</td>
<td>0.18</td>
<td>0.2837</td>
<td>0.022</td>
</tr>
<tr>
<td>C10A</td>
<td>0.47</td>
<td>0.40</td>
<td>0.2009</td>
<td>0.022</td>
</tr>
<tr>
<td>C11A</td>
<td>0.55</td>
<td>0.06</td>
<td>0.1117</td>
<td>0.0241</td>
</tr>
<tr>
<td>C11A</td>
<td>0.57</td>
<td>0.20</td>
<td>0.0928</td>
<td>0.029</td>
</tr>
<tr>
<td>C12A</td>
<td>0.62</td>
<td>-0.11</td>
<td>0.1140</td>
<td>0.0372</td>
</tr>
<tr>
<td>C12A</td>
<td>0.59</td>
<td>-0.24</td>
<td>0.1369</td>
<td>0.056</td>
</tr>
<tr>
<td>C12B</td>
<td>0.68</td>
<td>-0.05</td>
<td>0.1409</td>
<td>0.056</td>
</tr>
<tr>
<td>C12C</td>
<td>0.64</td>
<td>-0.15</td>
<td>0.0657</td>
<td>0.056</td>
</tr>
<tr>
<td>C13A</td>
<td>0.46</td>
<td>-0.0035</td>
<td>0.0597</td>
<td>0.0337</td>
</tr>
<tr>
<td>C13A</td>
<td>0.49</td>
<td>-0.0319</td>
<td>0.0132</td>
<td>0.050</td>
</tr>
<tr>
<td>C13B</td>
<td>0.41</td>
<td>0.1136</td>
<td>0.0556</td>
<td>0.050</td>
</tr>
<tr>
<td>C13C</td>
<td>0.42</td>
<td>-0.1359</td>
<td>0.0770</td>
<td>0.050</td>
</tr>
<tr>
<td>C14A</td>
<td>0.54</td>
<td>0.04</td>
<td>0.3484</td>
<td>0.0180</td>
</tr>
<tr>
<td>C14A</td>
<td>0.49</td>
<td>-0.0281</td>
<td>0.3275</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>H14B</td>
<td>0.5393</td>
<td>0.0762</td>
<td>0.3988</td>
<td>0.027</td>
</tr>
<tr>
<td>H14C</td>
<td>0.6968</td>
<td>-0.0493</td>
<td>0.3428</td>
<td>0.027</td>
</tr>
<tr>
<td>C15A</td>
<td>0.7499 (4)</td>
<td>0.2750 (9)</td>
<td>0.3515 (3)</td>
<td>0.0220 (10)</td>
</tr>
<tr>
<td>H15A</td>
<td>0.7428</td>
<td>0.1355</td>
<td>0.3760</td>
<td>0.033</td>
</tr>
<tr>
<td>H15B</td>
<td>0.7993</td>
<td>0.5648</td>
<td>0.3772</td>
<td>0.033</td>
</tr>
<tr>
<td>H15C</td>
<td>0.7715</td>
<td>0.2487</td>
<td>0.3033</td>
<td>0.033</td>
</tr>
<tr>
<td>Br1B</td>
<td>-0.18748 (3)</td>
<td>0.40480 (9)</td>
<td>0.09903 (3)</td>
<td>0.02568 (11)</td>
</tr>
<tr>
<td>Br2B</td>
<td>0.21533 (3)</td>
<td>0.40263 (11)</td>
<td>0.04876 (3)</td>
<td>0.02671 (12)</td>
</tr>
<tr>
<td>O3B</td>
<td>0.0012 (3)</td>
<td>0.3464 (5)</td>
<td>0.02916 (19)</td>
<td>0.02216 (8)</td>
</tr>
<tr>
<td>C1B</td>
<td>-0.0709 (3)</td>
<td>0.5832 (7)</td>
<td>0.1113 (3)</td>
<td>0.0159 (10)</td>
</tr>
<tr>
<td>H1B</td>
<td>-0.0871</td>
<td>0.7364</td>
<td>0.0866</td>
<td>0.019</td>
</tr>
<tr>
<td>C2B</td>
<td>0.0149 (4)</td>
<td>0.4910 (7)</td>
<td>0.0716 (3)</td>
<td>0.0161 (9)</td>
</tr>
<tr>
<td>C3B</td>
<td>0.1152 (3)</td>
<td>0.5842 (7)</td>
<td>0.0865 (2)</td>
<td>0.0145 (9)</td>
</tr>
<tr>
<td>H3B</td>
<td>0.1167</td>
<td>0.7319</td>
<td>0.0581</td>
<td>0.011</td>
</tr>
<tr>
<td>C4B</td>
<td>0.1396 (3)</td>
<td>0.6571 (9)</td>
<td>0.1641 (2)</td>
<td>0.0149 (8)</td>
</tr>
<tr>
<td>H4B</td>
<td>0.1477</td>
<td>0.5193</td>
<td>0.1019</td>
<td>0.018</td>
</tr>
<tr>
<td>C5B</td>
<td>0.0514 (3)</td>
<td>0.7568 (7)</td>
<td>0.1950 (3)</td>
<td>0.0140 (9)</td>
</tr>
<tr>
<td>C6B</td>
<td>0.0746 (3)</td>
<td>0.8319 (7)</td>
<td>0.2737 (3)</td>
<td>0.0160 (9)</td>
</tr>
<tr>
<td>H6B1</td>
<td>0.1320</td>
<td>0.9312</td>
<td>0.2780</td>
<td>0.019</td>
</tr>
<tr>
<td>H6B2</td>
<td>0.0938</td>
<td>0.6935</td>
<td>0.2073</td>
<td>0.019</td>
</tr>
<tr>
<td>C7B</td>
<td>-0.0126 (3)</td>
<td>0.9326 (8)</td>
<td>0.3124 (2)</td>
<td>0.0183 (10)</td>
</tr>
<tr>
<td>H7B</td>
<td>-0.0332</td>
<td>1.0662</td>
<td>0.2854</td>
<td>0.022</td>
</tr>
<tr>
<td>C8B</td>
<td>-0.0995 (4)</td>
<td>0.7742 (8)</td>
<td>0.3068 (3)</td>
<td>0.0216 (10)</td>
</tr>
<tr>
<td>H8B1</td>
<td>0.0807</td>
<td>0.6354</td>
<td>0.3304</td>
<td>0.026</td>
</tr>
<tr>
<td>H8B2</td>
<td>-0.1566</td>
<td>0.8359</td>
<td>0.3314</td>
<td>0.026</td>
</tr>
<tr>
<td>C9B</td>
<td>-0.1293 (4)</td>
<td>0.7307 (8)</td>
<td>0.2207 (3)</td>
<td>0.0204 (10)</td>
</tr>
<tr>
<td>H9B1</td>
<td>-0.1515</td>
<td>0.6684</td>
<td>0.2069</td>
<td>0.024</td>
</tr>
<tr>
<td>H9B2</td>
<td>-0.1857</td>
<td>0.6274</td>
<td>0.2273</td>
<td>0.024</td>
</tr>
<tr>
<td>C10B</td>
<td>0.0433 (3)</td>
<td>0.6350 (9)</td>
<td>0.1803 (2)</td>
<td>0.0148 (8)</td>
</tr>
<tr>
<td>H10B</td>
<td>-0.0262</td>
<td>0.4030</td>
<td>0.2115</td>
<td>0.018</td>
</tr>
<tr>
<td>C11B</td>
<td>0.0138 (4)</td>
<td>1.0057 (8)</td>
<td>0.3891 (3)</td>
<td>0.0215 (11)</td>
</tr>
<tr>
<td>H11B</td>
<td>-0.0490</td>
<td>1.0596</td>
<td>0.4093</td>
<td>0.026</td>
</tr>
<tr>
<td>C12B</td>
<td>0.0518 (4)</td>
<td>0.8221 (8)</td>
<td>0.4373 (3)</td>
<td>0.0236 (11)</td>
</tr>
<tr>
<td>H12D</td>
<td>0.1155</td>
<td>0.7696</td>
<td>0.4268</td>
<td>0.035</td>
</tr>
<tr>
<td>H12E</td>
<td>0.0038</td>
<td>0.7023</td>
<td>0.4362</td>
<td>0.035</td>
</tr>
<tr>
<td>H12F</td>
<td>0.0666</td>
<td>0.8766</td>
<td>0.4858</td>
<td>0.035</td>
</tr>
<tr>
<td>C13B</td>
<td>0.0860 (4)</td>
<td>1.1991 (9)</td>
<td>0.3898 (3)</td>
<td>0.0314 (13)</td>
</tr>
<tr>
<td>H13D</td>
<td>0.0954</td>
<td>1.2537</td>
<td>0.4383</td>
<td>0.047</td>
</tr>
<tr>
<td>H13E</td>
<td>0.0587</td>
<td>1.3153</td>
<td>0.3594</td>
<td>0.047</td>
</tr>
<tr>
<td>H13F</td>
<td>0.1499</td>
<td>1.1517</td>
<td>0.3723</td>
<td>0.047</td>
</tr>
<tr>
<td>C14B</td>
<td>0.0340 (4)</td>
<td>1.0032 (7)</td>
<td>0.1551 (3)</td>
<td>0.0185 (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>H14B</td>
<td>0.5393</td>
<td>0.0702</td>
<td>0.3988</td>
<td>0.027</td>
</tr>
<tr>
<td>H14C</td>
<td>0.6068</td>
<td>-0.0493</td>
<td>0.3428</td>
<td>0.027</td>
</tr>
<tr>
<td>C15A</td>
<td>0.7499 (4)</td>
<td>0.2760 (9)</td>
<td>0.3515 (3)</td>
<td>0.0220 (10)</td>
</tr>
<tr>
<td>H15A</td>
<td>0.7428</td>
<td>0.1355</td>
<td>0.3760</td>
<td>0.033</td>
</tr>
<tr>
<td>H15B</td>
<td>0.7993</td>
<td>0.3648</td>
<td>0.3772</td>
<td>0.033</td>
</tr>
<tr>
<td>H15C</td>
<td>0.7715</td>
<td>0.2487</td>
<td>0.3033</td>
<td>0.033</td>
</tr>
<tr>
<td>Br1B</td>
<td>-0.18748 (3)</td>
<td>0.40480 (9)</td>
<td>0.09903 (3)</td>
<td>0.02568 (11)</td>
</tr>
<tr>
<td>Br2B</td>
<td>0.21533 (3)</td>
<td>0.40203 (11)</td>
<td>0.04876 (5)</td>
<td>0.02671 (12)</td>
</tr>
<tr>
<td>O1B</td>
<td>0.0012 (3)</td>
<td>0.3464 (5)</td>
<td>0.02916 (19)</td>
<td>0.0216 (8)</td>
</tr>
<tr>
<td>C1B</td>
<td>-0.0709 (3)</td>
<td>0.5932 (7)</td>
<td>0.1113 (3)</td>
<td>0.0159 (10)</td>
</tr>
<tr>
<td>H1B</td>
<td>-0.0871</td>
<td>0.7364</td>
<td>0.0886</td>
<td>0.019</td>
</tr>
<tr>
<td>C2B</td>
<td>0.0140 (4)</td>
<td>0.4910 (7)</td>
<td>0.0715 (3)</td>
<td>0.0161 (9)</td>
</tr>
<tr>
<td>C3B</td>
<td>0.1152 (3)</td>
<td>0.5943 (7)</td>
<td>0.0805 (2)</td>
<td>0.0145 (9)</td>
</tr>
<tr>
<td>H3B</td>
<td>0.1167</td>
<td>0.7319</td>
<td>0.0583</td>
<td>0.017</td>
</tr>
<tr>
<td>C4B</td>
<td>0.1396 (3)</td>
<td>0.6571 (9)</td>
<td>0.1641 (2)</td>
<td>0.0149 (8)</td>
</tr>
<tr>
<td>H4B</td>
<td>0.1477</td>
<td>0.5193</td>
<td>0.1919</td>
<td>0.018</td>
</tr>
<tr>
<td>C5B</td>
<td>0.0514 (3)</td>
<td>0.7868 (7)</td>
<td>0.1950 (3)</td>
<td>0.0149 (9)</td>
</tr>
<tr>
<td>C6B</td>
<td>0.0746 (3)</td>
<td>0.8319 (7)</td>
<td>0.2737 (3)</td>
<td>0.0160 (9)</td>
</tr>
<tr>
<td>H6B1</td>
<td>0.1320</td>
<td>0.9318</td>
<td>0.2780</td>
<td>0.019</td>
</tr>
<tr>
<td>H6B2</td>
<td>0.0938</td>
<td>0.6935</td>
<td>0.2973</td>
<td>0.019</td>
</tr>
<tr>
<td>C7B</td>
<td>-0.0126 (3)</td>
<td>0.9326 (8)</td>
<td>0.5124 (2)</td>
<td>0.0183 (10)</td>
</tr>
<tr>
<td>H7B</td>
<td>-0.0332</td>
<td>1.0662</td>
<td>0.2854</td>
<td>0.022</td>
</tr>
<tr>
<td>C8B</td>
<td>-0.0995 (4)</td>
<td>0.7742 (8)</td>
<td>0.3068 (3)</td>
<td>0.0216 (10)</td>
</tr>
<tr>
<td>H8B1</td>
<td>-0.0807</td>
<td>0.6354</td>
<td>0.3304</td>
<td>0.026</td>
</tr>
<tr>
<td>H8B2</td>
<td>-0.1666</td>
<td>0.8359</td>
<td>0.3314</td>
<td>0.026</td>
</tr>
<tr>
<td>C9B</td>
<td>-0.1293 (4)</td>
<td>0.7307 (8)</td>
<td>0.2297 (3)</td>
<td>0.0204 (10)</td>
</tr>
<tr>
<td>H9B1</td>
<td>-0.1515</td>
<td>0.8884</td>
<td>0.2069</td>
<td>0.024</td>
</tr>
<tr>
<td>H9B2</td>
<td>-0.1857</td>
<td>0.8274</td>
<td>0.2273</td>
<td>0.024</td>
</tr>
<tr>
<td>C10B</td>
<td>-0.0433 (3)</td>
<td>0.6359 (9)</td>
<td>0.1893 (2)</td>
<td>0.0148 (8)</td>
</tr>
<tr>
<td>H10B</td>
<td>-0.0262</td>
<td>0.4930</td>
<td>0.2115</td>
<td>0.018</td>
</tr>
<tr>
<td>C11B</td>
<td>0.0138 (4)</td>
<td>1.0007 (8)</td>
<td>0.3891 (3)</td>
<td>0.0213 (11)</td>
</tr>
<tr>
<td>H11B</td>
<td>-0.0499</td>
<td>1.0596</td>
<td>0.4093</td>
<td>0.026</td>
</tr>
<tr>
<td>C12B</td>
<td>0.0518 (4)</td>
<td>0.8221 (8)</td>
<td>0.4373 (3)</td>
<td>0.0236 (11)</td>
</tr>
<tr>
<td>H12D</td>
<td>0.1155</td>
<td>0.7096</td>
<td>0.4208</td>
<td>0.035</td>
</tr>
<tr>
<td>H12E</td>
<td>0.0038</td>
<td>0.7023</td>
<td>0.4362</td>
<td>0.035</td>
</tr>
<tr>
<td>H12F</td>
<td>0.0666</td>
<td>0.8766</td>
<td>0.4858</td>
<td>0.035</td>
</tr>
<tr>
<td>C13B</td>
<td>0.0860 (4)</td>
<td>1.1991 (9)</td>
<td>0.3898 (3)</td>
<td>0.0314 (13)</td>
</tr>
<tr>
<td>H13D</td>
<td>0.0964</td>
<td>1.2537</td>
<td>0.4383</td>
<td>0.047</td>
</tr>
<tr>
<td>H13E</td>
<td>0.0587</td>
<td>1.3153</td>
<td>0.3594</td>
<td>0.047</td>
</tr>
<tr>
<td>H13F</td>
<td>0.1499</td>
<td>1.1517</td>
<td>0.3723</td>
<td>0.047</td>
</tr>
<tr>
<td>C14B</td>
<td>0.0340 (4)</td>
<td>1.0032 (7)</td>
<td>0.1551 (3)</td>
<td>0.0185 (10)</td>
</tr>
<tr>
<td></td>
<td>x</td>
<td>y</td>
<td>z</td>
<td>U</td>
</tr>
<tr>
<td>-----</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>----</td>
</tr>
<tr>
<td>H14D</td>
<td>-0.0296</td>
<td>1.0649</td>
<td>0.1678</td>
<td>0.028</td>
</tr>
<tr>
<td>H14E</td>
<td>0.0337</td>
<td>0.9765</td>
<td>0.1040</td>
<td>0.028</td>
</tr>
<tr>
<td>H14F</td>
<td>0.0873</td>
<td>1.1056</td>
<td>0.1683</td>
<td>0.028</td>
</tr>
<tr>
<td>C15B</td>
<td>0.2377 (4)</td>
<td>0.7796 (9)</td>
<td>0.1696 (3)</td>
<td>0.0207 (10)</td>
</tr>
<tr>
<td>H15D</td>
<td>0.2806</td>
<td>0.6021</td>
<td>0.1483</td>
<td>0.031</td>
</tr>
<tr>
<td>H15E</td>
<td>0.2558</td>
<td>0.8065</td>
<td>0.2195</td>
<td>0.031</td>
</tr>
<tr>
<td>H15F</td>
<td>0.2310</td>
<td>0.9188</td>
<td>0.1446</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Figure B.3 Dibromide (4.9) Packing
Figure B.4 Dibromide (4.9) Crystal Structure
**B.4 Dienone-Phenol Acetate (5.36)**

**Experimental**

*Crystal data*

C$_{17}$H$_{24}$O$_2$

$M_r = 290.36$

Monoclinic

$P2_1$

$a = 8.4058$ (10) Å

$b = 11.136$ (2) Å

$c = 15.720$ (3) Å

$\beta = 100.261$ (7)$^\circ$

$V = 1448.0$ (4) Å$^3$

$Z = 4$

$D_x = 1.194$ Mg m$^{-3}$

$D_m$ not measured

*Cell parameters from 4295 reflections*

$\theta = 2.5$–$30.5^\circ$

$\mu = 0.076$ mm$^{-1}$

Needle

Colorless

$0.43 \times 0.12 \times 0.10$ mm

Crystal source: local laboratory

*KappaCCD (with Oxford Cryostream) diffractometer*

$\omega$ scans with $\kappa$ offsets

Absorption correction: none

28919 measured reflections

4556 independent reflections

3945 reflections with $I > 2\sigma(I)$

$R_{int} = 0.028$

$\theta_{\text{max}} = 30.5^\circ$

$h = -11$ to $11$

$k = -15$ to $15$

$l = -22$ to $22$

Intensity decay: $<2\%$

**Refinement**

Refinement on $F^2$

$R(F^2 > 2\sigma(F^2)) = 0.043$

$wR(F^2) = 0.104$

$S = 1.028$

4556 reflections

353 parameters

H atoms treated by a mixture of independent and constrained refinement

Scattering factors from *International Tables for Crystallography* (Vol. C)
Table B.4 Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($A^2$) for 5.36

\[
U_{eq} = \left(\frac{1}{3}\right)\sum_{j} \sum_{i} u_{ij} a_i \cdot a_j.
\]

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U_{eq}</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1A</td>
<td>0.87950 (16)</td>
<td>0.07231 (13)</td>
<td>0.30026 (9)</td>
<td>0.0175 (3)</td>
</tr>
<tr>
<td>O2A</td>
<td>1.14528 (17)</td>
<td>0.08268 (14)</td>
<td>0.29315 (11)</td>
<td>0.0249 (3)</td>
</tr>
<tr>
<td>C1A</td>
<td>0.8515 (2)</td>
<td>0.43579 (18)</td>
<td>0.36062 (13)</td>
<td>0.0154 (4)</td>
</tr>
<tr>
<td>C2A</td>
<td>0.8621 (2)</td>
<td>0.34579 (19)</td>
<td>0.42565 (12)</td>
<td>0.0174 (4)</td>
</tr>
<tr>
<td>C3A</td>
<td>0.8745 (2)</td>
<td>0.22765 (19)</td>
<td>0.40476 (13)</td>
<td>0.0181 (4)</td>
</tr>
<tr>
<td>H3A</td>
<td>0.8803</td>
<td>0.1677</td>
<td>0.4482</td>
<td>0.022</td>
</tr>
<tr>
<td>C4A</td>
<td>0.8782 (2)</td>
<td>0.19011 (18)</td>
<td>0.32049 (13)</td>
<td>0.0159 (4)</td>
</tr>
<tr>
<td>C5A</td>
<td>0.8707 (2)</td>
<td>0.27663 (18)</td>
<td>0.25405 (12)</td>
<td>0.0149 (3)</td>
</tr>
<tr>
<td>C6A</td>
<td>0.8766 (2)</td>
<td>0.23892 (18)</td>
<td>0.16531 (12)</td>
<td>0.0170 (4)</td>
</tr>
<tr>
<td>H6A1</td>
<td>0.8143</td>
<td>0.1650</td>
<td>0.1502</td>
<td>0.020</td>
</tr>
<tr>
<td>H6A2</td>
<td>0.9531</td>
<td>0.2190</td>
<td>0.1600</td>
<td>0.020</td>
</tr>
<tr>
<td>C7A</td>
<td>0.8187 (2)</td>
<td>0.33374 (18)</td>
<td>0.09571 (12)</td>
<td>0.0165 (4)</td>
</tr>
<tr>
<td>H7A1</td>
<td>0.7001</td>
<td>0.3422</td>
<td>0.0903</td>
<td>0.020</td>
</tr>
<tr>
<td>H7A2</td>
<td>0.8424</td>
<td>0.3083</td>
<td>0.0389</td>
<td>0.020</td>
</tr>
<tr>
<td>C8A</td>
<td>0.9000 (2)</td>
<td>0.45459 (17)</td>
<td>0.12113 (13)</td>
<td>0.0145 (3)</td>
</tr>
<tr>
<td>H8A</td>
<td>1.0198</td>
<td>0.4421</td>
<td>0.1321</td>
<td>0.017</td>
</tr>
<tr>
<td>C9A</td>
<td>0.8507 (2)</td>
<td>0.49719 (18)</td>
<td>0.20566 (12)</td>
<td>0.0161 (4)</td>
</tr>
<tr>
<td>H9A1</td>
<td>0.9224</td>
<td>0.5643</td>
<td>0.2293</td>
<td>0.019</td>
</tr>
<tr>
<td>H9A2</td>
<td>0.7390</td>
<td>0.5289</td>
<td>0.1922</td>
<td>0.019</td>
</tr>
<tr>
<td>C10A</td>
<td>0.8577 (2)</td>
<td>0.40119 (18)</td>
<td>0.27485 (12)</td>
<td>0.0143 (3)</td>
</tr>
<tr>
<td>C11A</td>
<td>0.8582 (2)</td>
<td>0.54872 (17)</td>
<td>0.04831 (12)</td>
<td>0.0160 (4)</td>
</tr>
<tr>
<td>H11A</td>
<td>0.7377</td>
<td>0.5546</td>
<td>0.0332</td>
<td>0.019</td>
</tr>
<tr>
<td>C12A</td>
<td>0.9239 (3)</td>
<td>0.67343 (19)</td>
<td>0.07699 (15)</td>
<td>0.0223 (4)</td>
</tr>
<tr>
<td>H12A</td>
<td>1.0397</td>
<td>0.6676</td>
<td>0.1006</td>
<td>0.033</td>
</tr>
<tr>
<td>H12B</td>
<td>0.8668</td>
<td>0.7945</td>
<td>0.1215</td>
<td>0.023</td>
</tr>
<tr>
<td>H12C</td>
<td>0.9073</td>
<td>0.7279</td>
<td>0.0272</td>
<td>0.033</td>
</tr>
<tr>
<td>C13A</td>
<td>0.9214 (3)</td>
<td>0.5106 (2)</td>
<td>-0.03315 (13)</td>
<td>0.0239 (4)</td>
</tr>
<tr>
<td>H13A</td>
<td>0.8907</td>
<td>0.5708</td>
<td>-0.0785</td>
<td>0.036</td>
</tr>
<tr>
<td>H13B</td>
<td>0.8744</td>
<td>0.4328</td>
<td>-0.0531</td>
<td>0.030</td>
</tr>
<tr>
<td>H13C</td>
<td>1.0394</td>
<td>0.5036</td>
<td>-0.0199</td>
<td>0.036</td>
</tr>
<tr>
<td>C14A</td>
<td>0.8355 (2)</td>
<td>0.56772 (19)</td>
<td>0.38100 (13)</td>
<td>0.0192 (4)</td>
</tr>
<tr>
<td>H14A</td>
<td>0.8071</td>
<td>0.5701</td>
<td>0.4385</td>
<td>0.029</td>
</tr>
<tr>
<td>H14B</td>
<td>0.7507</td>
<td>0.6039</td>
<td>0.3378</td>
<td>0.029</td>
</tr>
<tr>
<td>H14C</td>
<td>0.9383</td>
<td>0.6084</td>
<td>0.3799</td>
<td>0.029</td>
</tr>
<tr>
<td>C15A</td>
<td>0.8635 (3)</td>
<td>0.3819 (2)</td>
<td>0.51944 (13)</td>
<td>0.0240 (4)</td>
</tr>
<tr>
<td>H15A</td>
<td>0.9578</td>
<td>0.4324</td>
<td>0.5405</td>
<td>0.036</td>
</tr>
<tr>
<td>H15B</td>
<td>0.8090</td>
<td>0.3086</td>
<td>0.5544</td>
<td>0.036</td>
</tr>
<tr>
<td>H15C</td>
<td>0.7645</td>
<td>0.4261</td>
<td>0.5240</td>
<td>0.036</td>
</tr>
<tr>
<td>C16A</td>
<td>1.0214 (2)</td>
<td>0.02647 (18)</td>
<td>0.26334 (12)</td>
<td>0.0168 (4)</td>
</tr>
<tr>
<td>C17A</td>
<td>0.9974 (3)</td>
<td>−0.09599 (19)</td>
<td>0.24999 (14)</td>
<td>0.0222 (4)</td>
</tr>
<tr>
<td>H17A</td>
<td>0.9436</td>
<td>−0.0978</td>
<td>0.1853</td>
<td>0.033</td>
</tr>
<tr>
<td>H17B</td>
<td>0.9302</td>
<td>−0.1437</td>
<td>0.2843</td>
<td>0.023</td>
</tr>
<tr>
<td>H17C</td>
<td>1.1026</td>
<td>−0.1391</td>
<td>0.2546</td>
<td>0.033</td>
</tr>
<tr>
<td>O1B</td>
<td>0.36761 (16)</td>
<td>0.77257 (12)</td>
<td>0.17527 (9)</td>
<td>0.0177 (3)</td>
</tr>
<tr>
<td>O2B</td>
<td>0.63269 (17)</td>
<td>0.77827 (14)</td>
<td>0.23299 (11)</td>
<td>0.0290 (3)</td>
</tr>
<tr>
<td>C1B</td>
<td>0.3589 (2)</td>
<td>0.40264 (18)</td>
<td>0.13495 (13)</td>
<td>0.0153 (4)</td>
</tr>
<tr>
<td>C2B</td>
<td>0.3921 (2)</td>
<td>0.48211 (18)</td>
<td>0.06626 (13)</td>
<td>0.0158 (4)</td>
</tr>
<tr>
<td>C3B</td>
<td>0.3891 (2)</td>
<td>0.60573 (18)</td>
<td>0.05192 (13)</td>
<td>0.0164 (4)</td>
</tr>
<tr>
<td>H3B</td>
<td>0.2933</td>
<td>0.6611</td>
<td>0.0364</td>
<td>0.020</td>
</tr>
<tr>
<td>C4B</td>
<td>0.3801 (2)</td>
<td>0.64767 (17)</td>
<td>0.16341 (13)</td>
<td>0.0156 (4)</td>
</tr>
<tr>
<td>C5B</td>
<td>0.3729 (2)</td>
<td>0.57085 (18)</td>
<td>0.23203 (12)</td>
<td>0.0147 (3)</td>
</tr>
<tr>
<td>C6B</td>
<td>0.3506 (2)</td>
<td>0.62069 (17)</td>
<td>0.31922 (13)</td>
<td>0.0172 (4)</td>
</tr>
<tr>
<td>H6B1</td>
<td>0.2752</td>
<td>0.6809</td>
<td>0.3100</td>
<td>0.021</td>
</tr>
<tr>
<td>H6B2</td>
<td>0.4561</td>
<td>0.6504</td>
<td>0.3505</td>
<td>0.021</td>
</tr>
<tr>
<td>C7B</td>
<td>0.2849 (2)</td>
<td>0.52602 (19)</td>
<td>0.37426 (12)</td>
<td>0.0165 (4)</td>
</tr>
<tr>
<td>H7B1</td>
<td>0.1722</td>
<td>0.5005</td>
<td>0.3478</td>
<td>0.020</td>
</tr>
<tr>
<td>H7B2</td>
<td>0.2643</td>
<td>0.5595</td>
<td>0.4327</td>
<td>0.029</td>
</tr>
<tr>
<td>C8B</td>
<td>0.3883 (2)</td>
<td>0.41319 (18)</td>
<td>0.38150 (12)</td>
<td>0.0152 (4)</td>
</tr>
<tr>
<td>H8B</td>
<td>0.5033</td>
<td>0.4368</td>
<td>0.4029</td>
<td>0.018</td>
</tr>
<tr>
<td>C9B</td>
<td>0.3774 (2)</td>
<td>0.35832 (17)</td>
<td>0.29113 (12)</td>
<td>0.0190 (4)</td>
</tr>
<tr>
<td>H9B1</td>
<td>0.4685</td>
<td>0.5016</td>
<td>0.2926</td>
<td>0.019</td>
</tr>
<tr>
<td>H9B2</td>
<td>0.2762</td>
<td>0.3111</td>
<td>0.2779</td>
<td>0.019</td>
</tr>
<tr>
<td>C10B</td>
<td>0.3803 (2)</td>
<td>0.44652 (17)</td>
<td>0.21813 (12)</td>
<td>0.0148 (3)</td>
</tr>
<tr>
<td>C11B</td>
<td>0.3392 (2)</td>
<td>0.3210 (2)</td>
<td>0.44540 (13)</td>
<td>0.0188 (4)</td>
</tr>
<tr>
<td>H11B</td>
<td>0.2231</td>
<td>0.2998</td>
<td>0.4250</td>
<td>0.023</td>
</tr>
<tr>
<td>C12B</td>
<td>0.4389 (3)</td>
<td>0.20539 (19)</td>
<td>0.44804 (14)</td>
<td>0.0206 (4)</td>
</tr>
<tr>
<td>H12D</td>
<td>0.4165</td>
<td>0.1658</td>
<td>0.3915</td>
<td>0.031</td>
</tr>
<tr>
<td>H12E</td>
<td>0.4106</td>
<td>0.1515</td>
<td>0.4923</td>
<td>0.031</td>
</tr>
<tr>
<td>H12F</td>
<td>0.5543</td>
<td>0.2250</td>
<td>0.4620</td>
<td>0.031</td>
</tr>
<tr>
<td>C13B</td>
<td>0.3556 (3)</td>
<td>0.3716 (2)</td>
<td>0.53722 (14)</td>
<td>0.0286 (5)</td>
</tr>
<tr>
<td>H13D</td>
<td>0.3219</td>
<td>0.3107</td>
<td>0.5753</td>
<td>0.043</td>
</tr>
<tr>
<td>H13E</td>
<td>0.2869</td>
<td>0.4428</td>
<td>0.5365</td>
<td>0.043</td>
</tr>
<tr>
<td>H13F</td>
<td>0.4685</td>
<td>0.2904</td>
<td>0.5585</td>
<td>0.043</td>
</tr>
<tr>
<td>C14B</td>
<td>0.3043 (3)</td>
<td>0.26763 (18)</td>
<td>0.12214 (14)</td>
<td>0.0191 (4)</td>
</tr>
<tr>
<td>H14D</td>
<td>0.2825</td>
<td>0.2497</td>
<td>0.0603</td>
<td>0.029</td>
</tr>
<tr>
<td>H14E</td>
<td>0.3059</td>
<td>0.2298</td>
<td>0.1454</td>
<td>0.029</td>
</tr>
<tr>
<td>H14F</td>
<td>0.4980</td>
<td>0.2363</td>
<td>0.1524</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>C15B</td>
<td>0.3974 (3)</td>
<td>0.4401 (2)</td>
<td>-0.02468 (13)</td>
<td>0.0201 (4)</td>
</tr>
<tr>
<td>H15D</td>
<td>0.3921</td>
<td>0.5097</td>
<td>-0.0632</td>
<td>0.030</td>
</tr>
<tr>
<td>H15E</td>
<td>0.3052</td>
<td>0.3871</td>
<td>-0.0446</td>
<td>0.030</td>
</tr>
<tr>
<td>H15F</td>
<td>0.4983</td>
<td>0.4962</td>
<td>-0.0252</td>
<td>0.030</td>
</tr>
<tr>
<td>C16B</td>
<td>0.5055 (2)</td>
<td>0.82934 (18)</td>
<td>0.21460 (12)</td>
<td>0.0172 (4)</td>
</tr>
<tr>
<td>C17B</td>
<td>0.4730 (3)</td>
<td>0.96850 (19)</td>
<td>0.23064 (15)</td>
<td>0.0225 (4)</td>
</tr>
<tr>
<td>H17D</td>
<td>0.5798</td>
<td>1.0013</td>
<td>0.2469</td>
<td>0.034</td>
</tr>
<tr>
<td>H17E</td>
<td>0.4108</td>
<td>0.9647</td>
<td>0.2776</td>
<td>0.034</td>
</tr>
<tr>
<td>H17F</td>
<td>0.4112</td>
<td>0.9942</td>
<td>0.1780</td>
<td>0.034</td>
</tr>
</tbody>
</table>
Figure B.5 Dienone-Phenol Acetate (5.36) Crystal Structure
B.5 Titanocene Complex (9.2b)

Experimental

Crystal data
C$_{20}$H$_{26}$OTi
$M_r$ = 330.31
Monoclinic
$P2_1/c$

$\begin{align*}
a &= 10.442 (6) \text{ Å} \\
b &= 11.005 (7) \text{ Å} \\
c &= 14.671 (11) \text{ Å} \\
\beta &= 92.12 (3)^\circ \\
V &= 1684.8 (19) \text{ Å}^3 \\
Z &= 4 \\
D_x &= 1.302 \text{ Mg m}^{-3} \\
D_m \text{ not measured}
\end{align*}$

Mo K$\alpha$ radiation
$\lambda = 0.71073 \text{ Å}$
Cell parameters from 3047 reflections
$\theta = 2.5-25.0^\circ$
$\mu = 0.508 \text{ mm}^{-1}$
$T = 105 \text{ K}$
Fragment
Orange
$0.10 \times 0.07 \times 0.05 \text{ mm}$
Crystal source: local laboratory

Data collection
KappaCCD (with Oxford Cryostream) diffractometer
$\omega$ scans with $\kappa$ offsets
Absorption correction:
multi-scan HKL Scalepack (Otwinowski & Minor 1997)
$T_{\text{min}} = 0.908$, $T_{\text{max}} = 0.975$
13150 measured reflections
2928 independent reflections

$1846$ reflections with $I > 2\sigma(I)$
$R_{\text{int}} = 0.072$
$\theta_{\text{max}} = 25.0^\circ$
$h = -12 \rightarrow 12$
$k = -13 \rightarrow 11$
$l = -17 \rightarrow 17$

Intensity decay: <2%

Refinement
Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)] = 0.070$
$wR(F^2) = 0.168$
$S = 1.038$
2928 reflections
201 parameters
H-atom parameters constrained

$w=1/[\sigma^2(F_o^2) + (0.0471P)^2 + 4.2486P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\text{max}} = 0.000$
$\Delta\rho_{\text{max}} = 0.75 \text{ e Å}^{-3}$
$\Delta\rho_{\text{min}} = -0.30 \text{ e Å}^{-3}$
Extinction correction: none
Scattering factors from International Tables for Crystallography (Vol. C)
Figure B.6 Titanocene Complex (9.2b) Crystal Structure
Table B.5 Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($U^e$) for 9.2b

\[
U_{eq} = \frac{1}{3} \Sigma_i \Sigma_j U^{ij} a_i \cdot a_j.
\]

<table>
<thead>
<tr>
<th></th>
<th>(x)</th>
<th>(y)</th>
<th>(z)</th>
<th>(U_{eq})</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>0.27006 (9)</td>
<td>0.40206 (8)</td>
<td>0.37833 (6)</td>
<td>0.0299 (3)</td>
</tr>
<tr>
<td>O1</td>
<td>0.1471 (3)</td>
<td>0.5015 (3)</td>
<td>0.3288 (3)</td>
<td>0.0381 (9)</td>
</tr>
<tr>
<td>C1</td>
<td>0.1751 (5)</td>
<td>0.6156 (5)</td>
<td>0.2970 (4)</td>
<td>0.06 (15)</td>
</tr>
<tr>
<td>H1</td>
<td>0.2052</td>
<td>0.6065</td>
<td>0.2335</td>
<td>0.056</td>
</tr>
<tr>
<td>C2</td>
<td>0.2873 (6)</td>
<td>0.6746 (5)</td>
<td>0.3562 (4)</td>
<td>0.0464 (15)</td>
</tr>
<tr>
<td>H2</td>
<td>0.3557</td>
<td>0.7000</td>
<td>0.3142</td>
<td>0.056</td>
</tr>
<tr>
<td>C3</td>
<td>0.2306 (5)</td>
<td>0.7871 (4)</td>
<td>0.3960 (4)</td>
<td>0.0391 (13)</td>
</tr>
<tr>
<td>H3</td>
<td>0.1829</td>
<td>0.7576</td>
<td>0.4495</td>
<td>0.047</td>
</tr>
<tr>
<td>C4</td>
<td>0.1241 (5)</td>
<td>0.8292 (4)</td>
<td>0.3258 (4)</td>
<td>0.0351 (12)</td>
</tr>
<tr>
<td>C5</td>
<td>0.0682 (6)</td>
<td>0.7062 (5)</td>
<td>0.2944 (4)</td>
<td>0.0485 (15)</td>
</tr>
<tr>
<td>H5A</td>
<td>0.0001</td>
<td>0.6804</td>
<td>0.3354</td>
<td>0.058</td>
</tr>
<tr>
<td>H5B</td>
<td>0.0306</td>
<td>0.7131</td>
<td>0.2317</td>
<td>0.058</td>
</tr>
<tr>
<td>C6</td>
<td>0.3454 (5)</td>
<td>0.5831 (4)</td>
<td>0.4238 (3)</td>
<td>0.0319 (11)</td>
</tr>
<tr>
<td>H6A</td>
<td>0.3174</td>
<td>0.6007</td>
<td>0.4862</td>
<td>0.058</td>
</tr>
<tr>
<td>H6B</td>
<td>0.4401</td>
<td>0.5865</td>
<td>0.4229</td>
<td>0.038</td>
</tr>
<tr>
<td>C7</td>
<td>0.3189 (5)</td>
<td>0.8787 (4)</td>
<td>0.4337 (4)</td>
<td>0.0422 (14)</td>
</tr>
<tr>
<td>H7</td>
<td>0.3728</td>
<td>0.9158</td>
<td>0.3910</td>
<td>0.051</td>
</tr>
<tr>
<td>C8</td>
<td>0.3341 (7)</td>
<td>0.9161 (6)</td>
<td>0.5162 (5)</td>
<td>0.0666 (19)</td>
</tr>
<tr>
<td>H8A</td>
<td>0.2835</td>
<td>0.8820</td>
<td>0.5626</td>
<td>0.059</td>
</tr>
<tr>
<td>H8B</td>
<td>0.3960</td>
<td>0.9769</td>
<td>0.5309</td>
<td>0.080</td>
</tr>
<tr>
<td>C9</td>
<td>0.1783 (5)</td>
<td>0.9098 (5)</td>
<td>0.2473 (4)</td>
<td>0.0439 (13)</td>
</tr>
<tr>
<td>H9A</td>
<td>0.2408</td>
<td>0.8507</td>
<td>0.2163</td>
<td>0.065</td>
</tr>
<tr>
<td>H9B</td>
<td>0.2203</td>
<td>0.9745</td>
<td>0.2711</td>
<td>0.065</td>
</tr>
<tr>
<td>H9C</td>
<td>0.1086</td>
<td>0.9234</td>
<td>0.2040</td>
<td>0.065</td>
</tr>
<tr>
<td>C10</td>
<td>0.0933 (5)</td>
<td>0.9063 (5)</td>
<td>0.3704 (4)</td>
<td>0.0445 (13)</td>
</tr>
<tr>
<td>H10A</td>
<td>-0.0447</td>
<td>0.9266</td>
<td>0.3253</td>
<td>0.067</td>
</tr>
<tr>
<td>H10B</td>
<td>0.0631</td>
<td>0.9812</td>
<td>0.3941</td>
<td>0.067</td>
</tr>
<tr>
<td>H10C</td>
<td>-0.0128</td>
<td>0.8608</td>
<td>0.4208</td>
<td>0.067</td>
</tr>
<tr>
<td>C11</td>
<td>0.2725 (5)</td>
<td>0.3771 (5)</td>
<td>0.5415 (4)</td>
<td>0.0421 (14)</td>
</tr>
<tr>
<td>H11</td>
<td>0.3273</td>
<td>0.4257</td>
<td>0.5796</td>
<td>0.051</td>
</tr>
<tr>
<td>C12</td>
<td>0.3033 (6)</td>
<td>0.2657 (5)</td>
<td>0.5057 (4)</td>
<td>0.0437 (15)</td>
</tr>
<tr>
<td>H12</td>
<td>0.3820</td>
<td>0.2236</td>
<td>0.5161</td>
<td>0.052</td>
</tr>
<tr>
<td>C13</td>
<td>0.2003 (6)</td>
<td>0.2265 (5)</td>
<td>0.4521 (4)</td>
<td>0.0475 (15)</td>
</tr>
<tr>
<td>H13</td>
<td>0.1962</td>
<td>0.1518</td>
<td>0.4184</td>
<td>0.057</td>
</tr>
<tr>
<td>C14</td>
<td>0.1025 (5)</td>
<td>0.3132 (5)</td>
<td>0.4562 (4)</td>
<td>0.0441 (14)</td>
</tr>
<tr>
<td>H14</td>
<td>0.0204</td>
<td>0.3095</td>
<td>0.4262</td>
<td>0.053</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>C15</td>
<td>0.1400 (5)</td>
<td>0.4067 (5)</td>
<td>0.5129 (3)</td>
<td>0.0384 (12)</td>
</tr>
<tr>
<td>H15</td>
<td>0.1037</td>
<td>0.4780</td>
<td>0.5289</td>
<td>0.046</td>
</tr>
<tr>
<td>C16</td>
<td>0.3407 (6)</td>
<td>0.3863 (6)</td>
<td>0.2236 (4)</td>
<td>0.0483 (15)</td>
</tr>
<tr>
<td>H16</td>
<td>0.2901</td>
<td>0.4223</td>
<td>0.1757</td>
<td>0.058</td>
</tr>
<tr>
<td>C17</td>
<td>0.3271 (6)</td>
<td>0.2691 (5)</td>
<td>0.2568 (4)</td>
<td>0.0487 (15)</td>
</tr>
<tr>
<td>H17</td>
<td>0.2639</td>
<td>0.2121</td>
<td>0.2367</td>
<td>0.058</td>
</tr>
<tr>
<td>C18</td>
<td>0.4204 (6)</td>
<td>0.2496 (5)</td>
<td>0.3234 (4)</td>
<td>0.0477 (16)</td>
</tr>
<tr>
<td>H18</td>
<td>0.4351</td>
<td>0.1756</td>
<td>0.3555</td>
<td>0.057</td>
</tr>
<tr>
<td>C19</td>
<td>0.4893 (6)</td>
<td>0.3556 (6)</td>
<td>0.3359 (4)</td>
<td>0.0529 (17)</td>
</tr>
<tr>
<td>H19</td>
<td>0.5575</td>
<td>0.3686</td>
<td>0.3795</td>
<td>0.064</td>
</tr>
<tr>
<td>C20</td>
<td>0.4398 (6)</td>
<td>0.4415 (5)</td>
<td>0.2718 (4)</td>
<td>0.0521 (16)</td>
</tr>
<tr>
<td>H20</td>
<td>0.4696</td>
<td>0.5222</td>
<td>0.2637</td>
<td>0.063</td>
</tr>
</tbody>
</table>
Dear Anne

Permission granted.

Best wishes

Mike Dacombe

Anne M Sauer wrote:

> Hello!
> I am writing to obtain permission for inclusion of results in my doctoral dissertation. Please see the attached PDF file. Thank you for your time and consideration on this matter.
> Regards,
> Anne Sauer

--

************************
Michael H. Dacombe
Executive Secretary
IUCr
2 Abbey Square
Chester CH1 2HU
UK

Telephone 44 1244 345 431
Fax 44 1244 344 843
Email execsec@iucr.org
International Union of Crystallography

To Whom It May Concern:

I am a graduate student in the Department of Chemistry at Louisiana State University and I am writing to obtain permission for the use of my contributions published in Acta Crystallogr., Sect. C. I am the first author of “The Sesquiterpenoid Nootkatone and the Absolute Configuration of a Dibromo Derivative” (2003, Vol. 59, pp. o254-o256; ISSN: 0108-2701) and would like to include this information in my doctoral dissertation.

Thank you for your consideration of this request.

Sincerely,

Anne Sauer
Phone: (225) 753-1647
Fax: (225) 756-0521
E-mail: asauer@lsu.edu
VITA

Anne Marie Sauer was welcomed into the world June 14, 1978, by parents Joe and Carolyn and brother Daniel. A native to Baton Rouge, Louisiana, she attended local public schools and was an active participant in soccer, dance, and piano. In May 1996, she graduated from Baton Rouge Magnet High School with honors. Four years later, she graduated *cum laude* from Louisiana State University, receiving her bachelor’s degree in chemistry, coupled with a minor in psychology. Upon completion of her undergraduate degree, Anne returned to LSU in the doctoral program under the direction of Professor William E. Crowe. Her research focus, the synthesis of plant-derived natural products, allowed her to work with world renowned authorities Dr. Gregg Henderson (entomology) and Dr. Roger A. Laine (biochemistry). During her graduate career, she amassed multiple honors and awards including: the Procter and Gamble Research Fellowship, a Troy H. Middleton Scholarship, Louisiana State University’s Outstanding Teaching Award, and a Procter and Gamble award for Most Distinguished Graduate Student. In addition to being co-owner of a patent, her research has also culminated in several professional publications. Awarded the degree of Doctor of Philosophy in August 2005, she then embarked on the next stage of her life... the working world.