Applications of titanium-mediated reductive coupling and cyclocarbonylation reactions toward natural product synthesis

Maria A. Appeaning
Louisiana State University and Agricultural and Mechanical College

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APPLICATIONS OF TITANIUM-MEDIATED REDUCTIVE COUPLING AND
CYCLOCARBONYLATION REACTIONS TOWARD NATURAL PRODUCT
SYNTHESIS

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
Maria A. Appeaning
B.S., Southern University and A&M College, 2000
December, 2006
DEDICATION

To my lovely mother,

Zoya G. Appeaning
ACKNOWLEDGMENTS

First of all, I would like to express my thanks and deepest gratitude to Professor William Crowe for providing me the opportunity to conduct my research in his group, for the interesting research theme, valuable discussion and guidance.

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# TABLE OF CONTENTS

DEDICATION .................................................................................................................. ii

ACKNOWLEDGMENTS ................................................................................................. iii

LIST OF TABLES ......................................................................................................... vii

LIST OF FIGURES ...................................................................................................... viii

LIST OF SCHEMES .................................................................................................... xii

LIST OF ABBREVIATIONS ............................................................................................. xviii

ABSTRACT .................................................................................................................. xx

## CHAPTER 1

AN OVERVIEW OF THE HETERO PAUSON-KHAND REACTION ......................... 1

1.1 Introduction to the Pauson-Khand Reaction ..................................................... 1

1.2 Intramolecular Pauson-Khand Reaction ....................................................... 2

1.3 Promoters .......................................................................................................... 3

1.4 Mechanism of the Pauson-Khand Reaction ..................................................... 3

1.5 Cobalt Catalyzed Pauson-Khand Reaction ..................................................... 5

1.6 Other Transition Metal Catalysts .................................................................... 6

1.7 γ-Butyrolactone Synthesis via the Hetero Pauson-Khand Reaction .............. 9

1.8 Catalytic Hetero Pauson-Khand Reaction ..................................................... 10

1.9 Ruthenium-Catalyzed Hetero Pauson-Khand Reaction ............................. 11

1.10 Research Overview ......................................................................................... 12

1.11 References ........................................................................................................ 12

## CHAPTER 2

APPLICATIONS OF THE HETERO PAUSON-KHAND REACTION: CONSTRUCTION OF COMPOUNDS RELEVANT TO THE SYNTHESSES OF PROSTAGLANDINS AND METHYL JASMONATE ........................................ 15

2.1 An Introduction to Prostaglandins (PG’s) ....................................................... 15

2.2 Synthesis of Prostaglandins ........................................................................... 18

2.3 Research Interests ............................................................................................. 19

2.4 Natural Product Target – Prostaglandins ...................................................... 22

2.5 Proposed Synthesis .......................................................................................... 23

2.6 Selectivity .......................................................................................................... 24

2.7 Preparation of Prostaglandin Precursors ....................................................... 26

2.8 The Challenge ................................................................................................... 31

2.9 Synthesis of the Trityl-Protected Prostaglandin Precursor ........................... 35

2.10 Switching from Hydroxyl to Silyl Functionality ......................................... 40

2.11 Other Synthetic Applications ........................................................................ 42

2.12 Synthesis Towards Methyl Jasmonate ....................................................... 42
4.8.2 Preparative Procedures ................................................................. 211
4.8.3 Spectral Data ............................................................................ 215
4.9 References .................................................................................... 215

VITA ........................................................................................................ 224
LIST OF TABLES

Table 2.1 Previously Reported Substrates ................................................................. 21
Table 3.1 Cycloadditions of Monosubstituted Allenynes........................................... 127
Table 3.2 Cycloadditions of 1,3-Disubstituted Allenynes.......................................... 128
Table 3.3 3,3-Disubstituted Allenynes ..................................................................... 129
Table 3.4 Cycloadditions of Trisubstituted Allenynes ............................................... 130
Table 3.5 Ru-Catalyzed [2+2+1] Cycloadditions of Allenyl Carbonyls ...................... 134
Table 3.6 Mo-Mediated Cyclocarbonylation of Allenyl Carbonyls ............................. 135
Table 3.7 Yields and Metallacyclic Products formed via Reductive Coupling .......... 146
Table 4.1 Attempted Titanium Mediated Cross-Metathesis Conditions .................... 209
Table 4.2 Attempted Reductive Coupling Conditions for Imine 4.2c ....................... 210
LIST OF FIGURES

Figure 2.1 Corey’s Lactone ........................................................................................................... 18
Figure 2.2 ORTEP Plot of Co-Crystallized Metallacycles 2.1s and 2.1t ............................... 30
Figure 2.3 ORTEP Plot of Metallacycle 2.2j ............................................................................. 34
Figure 2.4 ORTEP Plot of Co-Crystallized Metallacycles 2.3n and 2.3o ......................... 39
Figure 2.5 Similarities between Methyl Jasmonate 2.5g and PGE2 2.5h ............................. 42
Figure 2.6 Proposed Structures 2.6a and 2.7a ........................................................................ 45
Figure 2.7 1H NMR and 13C NMR of Penta-1,4-dien-3-ol 2.1j ........................................... 75
Figure 2.8 1H NMR and 13C NMR of Bromide 2.1k .............................................................. 76
Figure 2.9 1H NMR and 13C NMR of 2-Phenyl-1,3-dioxane 2.1c ......................................... 77
Figure 2.10 1H NMR and 13C NMR of 3-(Benzylxyloxy)propan-1-ol 2.1d ....................... 78
Figure 2.11 1H NMR and 13C NMR of 3-(Benzylxyloxy)propanal 2.1f ............................. 79
Figure 2.12 1H NMR and 13C NMR of Benzyl Protected 1° Alcohol 2.1l ......................... 80
Figure 2.13 1H NMR and 13C NMR of Acetal 2.1p ............................................................... 81
Figure 2.14 1H NMR and 13C NMR of Benzyl Protected 2° Alcohol 2.1q ....................... 82
Figure 2.15 1H NMR and 13C NMR of Benzyl Protected Aldehyde 2.1r .......................... 83
Figure 2.16 1H NMR and 13C NMR of Metallacycles 2.1s and 2.1t ................................. 84
Figure 2.17 1H NMR and 13C NMR of Lactone 2.1u ........................................................... 85
Figure 2.18 1H NMR and 13C NMR of Lactone 2.1v ........................................................... 86
Figure 2.19 1H NMR and 13C NMR of 2-(4-Methoxyphenyl)-1,3-dioxane 2.2b ............ 87
Figure 2.20 1H NMR and 13C NMR of 3-(4-Methoxybenzyloxy)propan-1-ol 2.2c .......... 88
Figure 2.21 1H NMR and 13C NMR of 3-(4-Methoxybenzyloxy)propanal 2.2d .......... .... 89
Figure 2.22 1H NMR and 13C NMR of PMB Protected 1° Alcohol 2.2e ........................... 90
Figure 2.23 $^1$H NMR and $^{13}$C NMR of TBDPS Ether 2.2f................................. 91
Figure 2.24 $^1$H NMR and $^{13}$C NMR of TBDPS Protected $^2$0 Alcohol 2.2g ................. 92
Figure 2.25 $^1$H NMR and $^{13}$C NMR of TBDPS Protected Aldehyde 2.2h........................ 93
Figure 2.26 $^1$H NMR and $^{13}$C NMR of Metallacycles 2.2i and 2.2j.......................... 94
Figure 2.27 $^1$H NMR and $^{13}$C NMR of Lactone 2.2k......................................... 95
Figure 2.28 $^1$H NMR and $^{13}$C NMR of Lactone 2.2l........................................ 96
Figure 2.29 $^1$H NMR and $^{13}$C NMR of Aldehyde 2.3i.................................... 97
Figure 2.30 $^1$H NMR and $^{13}$C NMR of TBDMS Protected $^1$0 Alcohol 2.3j................ 98
Figure 2.31 $^1$H NMR and $^{13}$C NMR of Trityl Ether 2.3k.................................... 99
Figure 2.32 $^1$H NMR and $^{13}$C NMR of Trityl Protected $^1$0 Alcohol 2.3d............... 100
Figure 2.33 $^1$H NMR and $^{13}$C NMR of Trityl Protected Aldehyde 2.3l..................... 101
Figure 2.34 $^1$H NMR and $^{13}$C NMR of Lactone 2.3m............................... 102
Figure 2.35 $^1$H NMR and $^{13}$C NMR of Lactones 2.3n and 2.3o......................... 103
Figure 2.36 $^1$H NMR and $^{13}$C NMR of Mesylated Alcohol 2.5a............................. 104
Figure 2.37 $^1$H NMR and $^{13}$C NMR of Alcohol 2.5b........................................ 105
Figure 2.38 $^1$H NMR and $^{13}$C NMR of Aldehyde 2.5c.................................... 106
Figure 2.39 $^1$H NMR and $^{13}$C NMR of Metallacycle 2.5d................................. 107
Figure 2.40 $^1$H NMR and $^{13}$C NMR of Lactone 2.5e.................................... 108
Figure 2.41 $^1$H NMR and $^{13}$C NMR of (E)-Pent-2-en-4-yn-1-ol 2.6d......................... 109
Figure 2.42 $^1$H NMR and $^{13}$C NMR of Alcohol 2.6d'.................................... 110
Figure 2.43 $^1$H NMR and $^{13}$C NMR of Bromide 2.6e.................................... 111
Figure 2.44 $^1$H NMR and $^{13}$C NMR of $^2$0 Alcohols 2.6h and 2.6h'........................ 112
Figure 2.45 $^1$H NMR and $^{13}$C NMR of Complexed Alcohols 2.6i and 2.6i'................ 113
Figure 2.46 $^1$H NMR and $^{13}$C NMR of Mesylated Complexes 2.6j and 2.6j' .......... 114
Figure 2.47 $^1$H NMR and $^{13}$C NMR of Decomplexed Alcohols 2.6k and 2.6k' .......... 115
Figure 2.48 $^1$H NMR and $^{13}$C NMR of Alcohol 2.6l .................................................. 116
Figure 2.49 $^1$H NMR and $^{13}$C NMR of Aldehyde 2.6a .................................................. 117
Figure 3.1 Examples of Allenic Prostaglandins .............................................................. 121
Figure 3.2 Structures of 15-Deoxy-$\Delta^{12,14}$-PGJ$_2$, crinipellin A, and hydroxymethylacylfulvene .......................................................... 124
Figure 3.3 Biologically Active $\alpha$-Methylene-$\gamma$-Butyrolactone Compounds .......... 132
Figure 3.4 Structures of Allenyl Carbonyls 3.1a-f .......................................................... 137
Figure 3.5 $^{13}$C-NMR Chemical Shifts $\delta$ (ppm) of Simple Allenes ................................. 137
Figure 3.6 ORTEP Plot of Metallacycle 3.6a ................................................................. 145
Figure 3.7 $^1$H NMR and $^{13}$C NMR of Iodide 3.3a ......................................................... 164
Figure 3.8 $^1$H NMR and $^{13}$C NMR of Allene 3.4a ......................................................... 165
Figure 3.9 $^1$H NMR and $^{13}$C NMR of Allenic Alcohol 3.5a ........................................... 166
Figure 3.10 $^1$H NMR and $^{13}$C NMR of Allenic Aldehyde 3.1a ...................................... 167
Figure 3.11 $^1$H NMR and $^{13}$C NMR of Iodide 3.3b ....................................................... 168
Figure 3.12 $^1$H NMR and $^{13}$C NMR of Allene 3.4b ....................................................... 169
Figure 3.13 $^1$H NMR and $^{13}$C NMR of Allenic Alcohol 3.5b ........................................ 170
Figure 3.14 $^1$H NMR and $^{13}$C NMR of Allenic Ketone 3.1b .......................................... 171
Figure 3.15 $^1$H NMR and $^{13}$C NMR of Alkyne 3.3c ...................................................... 172
Figure 3.16 $^1$H NMR and $^{13}$C NMR of 3,3-Disubstituted Allene 3.4c ........................... 173
Figure 3.17 $^1$H NMR and $^{13}$C NMR of 3,3-Disubstituted Allenic Alcohol 3.5c ........... 174
Figure 3.18 $^1$H NMR and $^{13}$C NMR of 3,3-Disubstituted Allenic Aldehyde 3.1c .......... 175
Figure 3.19 $^1$H NMR and $^{13}$C NMR of 3,3-Disubstituted Allene 3.4d .......................... 176
Figure 3.20 ¹H NMR and ¹³C NMR of 3,3-Disubstituted Allenic Alcohol 3.5d ........ 177
Figure 3.21 ¹H NMR and ¹³C NMR of 3,3-Disubstituted Allenic Aldehyde 3.1d .... 178
Figure 3.22 ¹H NMR and ¹³C NMR of Mesylate 3.2e′ ........................................... 179
Figure 3.23 ¹H NMR and ¹³C NMR of 1,3-Disubstituted Allene 3.3e .................. 180
Figure 3.24 ¹H NMR and ¹³C NMR of 1,3-Disubstituted Allenic Alcohol 3.4e .... 181
Figure 3.25 ¹H NMR and ¹³C NMR of 1,3-Disubstituted Allenic Aldehyde 3.1e .... 182
Figure 3.26 ¹H NMR and ¹³C NMR of Allene 3.3f ................................................. 183
Figure 3.27 ¹H NMR and ¹³C NMR of Allenic Alcohol 3.4f .................................. 184
Figure 3.28 ¹H NMR and ¹³C NMR of Allenic Aldehyde 3.1f............................... 185
Figure 3.29 ¹H NMR and ¹³C NMR of Metallacycle 3.6a ....................................... 186
Figure 3.30 ¹H NMR and ¹³C NMR of Metallacycle 3.6b ..................................... 187
Figure 3.31 ¹H NMR and ¹³C NMR of Metallacycle 3.6c ..................................... 188
Figure 3.32 ¹H NMR and ¹³C NMR of Metallacies 3.5e and 3.6e ......................... 189
Figure 4.1 Various Structural Alkaloids ............................................................... 193
Figure 4.2 Different Izidine Alkaloid Skeletons .................................................... 193
Figure 4.3 ¹H NMR and ¹³C NMR of Phthalamide 4.3a ....................................... 216
Figure 4.4 ¹H NMR and ¹³C NMR of Chloride 4.2b ............................................ 217
Figure 4.5 ¹H NMR and ¹³C NMR of Alcohol 4.3b ............................................. 218
Figure 4.6 ¹H NMR and ¹³C NMR of Amine 4.4a .............................................. 219
Figure 4.7 ¹H NMR and ¹³C NMR of Imine 4.2c ............................................... 220
LIST OF SCHEMES

Scheme 1.1 Pauson-Khand Reaction ................................................................. 1
Scheme 1.2 First Intramolecular Pauson-Khand Reaction ................................. 2
Scheme 1.3 Utilizing Tertiary N-Oxides .......................................................... 3
Scheme 1.4 Proposed Mechanism of the Pauson-Khand Reaction ..................... 4
Scheme 1.5 Rautenstrauch’s Catalytic Intermolecular Pauson-Khand Reaction .... 5
Scheme 1.6 Livinghouse’s and Krafft’s Intramolecular Pauson-Khand Reaction ... 6
Scheme 1.7 Jeong’s Catalytic Pauson-Khand Reaction with (S)-BINAP .......... 6
Scheme 1.8 Jeong’s Mo-Mediated Pauson-Khand Reaction .............................. 7
Scheme 1.9 Negishi’s Zr-Mediated Pauson-Khand Reaction ............................. 7
Scheme 1.10 Narasaka’s Rh-Catalyzed Pauson-Khand Reaction ....................... 7
Scheme 1.11 Fe-Mediated Pauson-Khand Reaction ....................................... 8
Scheme 1.12 Murai’s Ru-Catalyzed Intramolecular Pauson-Khand Reaction ...... 8
Scheme 1.13 Buchwald’s Ti-Catalyzed Pauson-Khand Reaction with Isonitriles . 8
Scheme 1.14 Hetero Pauson-Khand Reaction ................................................. 9
Scheme 1.15 Mechanism of the Hetero Pauson-Khand Reaction ...................... 10
Scheme 1.16 Buchwald’s Ti-Catalyzed Hetero Pauson-Khand Reaction ............ 10
Scheme 1.17 Crowe’s Catalytic Asymmetric Cyclocarbonylation .................... 11
Scheme 1.18 Ru-Catalyzed Intramolecular Hetero Pauson-Khand Reaction ...... 11
Scheme 1.19 Murai’s Ru-Catalyzed Intermolecular Cyclization ....................... 11
Scheme 2.1 Prostaglandin Nomenclature ..................................................... 15
Scheme 2.2 Biosynthesis of Prostaglandins ................................................... 16
Scheme 2.3 Corey’s Retrosynthetic Synthesis of PGF$_{2\alpha}$ ................................ 18
Scheme 2.27 Retrosynthetic Analysis of Primary Alcohol \(2.3d\) ........................................... 37
Scheme 2.28 Synthesis of Trityl Protected Aldehyde \(2.3l\) ............................................. 38
Scheme 2.29 Reductive Coupling and Carbonylation of \(2.3l\) ........................................... 38
Scheme 2.30 Retrosynthetic Analysis Outlining the Synthesis of \(2.4a\) ......................... 40
Scheme 2.31 Proposed Oxidative Cleavage of Silicon-Carbon Bond ......................... 41
Scheme 2.32 Attempted Substitution of Tosylate \(2.4f\) ...................................................... 41
Scheme 2.33 Retrosynthetic Analysis of Methyl Jasmonate \(2.5g\) ......................... 43
Scheme 2.34 Synthesis of Aldehyde \(2.5c\) ................................................................. 43
Scheme 2.35 Synthesis of Lactone \(2.5e\) ................................................................. 44
Scheme 2.36 Route towards 11-deoxy PGF\(_{1\alpha}\) \(2.5f\) Synthesis .............................. 44
Scheme 2.37 Proposed Synthesis of Methyl Jasmonate \(2.5g\) ........................................ 45
Scheme 2.38 Initial Proposed Synthesis of Aldehyde \(2.6a\) .............................. 46
Scheme 2.39 Synthesis towards Aldehyde \(2.6a\) ..................................................... 47
Scheme 2.40 Synthesis of Aldehyde \(2.6a\) ................................................................. 48
Scheme 3.1 Different Substitution Patterns of Allenes ................................................. 122
Scheme 3.2 Selectivity Problems of Unsaturated Substrates ........................................ 123
Scheme 3.3 Positional Selectivity: Competing Pathways of the Allenic Pauson-Khand Reaction ................................................................. 123
Scheme 3.4 General Pattern of the Pauson-Khand Reaction ........................................ 124
Scheme 3.5 Cazes’ Intermolecular Allenic Pauson-Khand Reaction ......................... 125
Scheme 3.6 Cazes’ Intramolecular Allenic Pauson-Khand Reaction ............................. 126
Scheme 3.7 General Hetero Pauson-Khand Reaction ................................................. 131
Scheme 3.8 Substrates under Investigation ................................................................. 131
Scheme 3.9 Allenic Hetero-Pauson-Khand Reaction ................................................. 132
Scheme 3.10 Ru-Catalyzed [2+2+1] Cycloadditions of Allenyl Carboxyls ...................... 133

Scheme 3.11 Proposed Mechanistic Route for Ru-Catalyzed [2+2+1] Cycloaddition of Allenyl Carboxyls .................................................................................................................. 133

Scheme 3.12 Possible Mo-Mediated Cyclocarbonylation Mechanism of Allenyl Carboxyls .................................................................................................................. 136

Scheme 3.13 Synthesis of Iodide 3.3a ......................................................................... 137

Scheme 3.14 S_2'-Type Substitution .......................................................................... 138

Scheme 3.15 Synthesis of Allene 3.4a ....................................................................... 138

Scheme 3.16 Synthesis of 3.4a via the Rieke Zinc Procedure ...................................... 139

Scheme 3.17 Synthesis of Allenic Alcohol 3.5a .......................................................... 140

Scheme 3.18 Synthesis of Allenic Aldehyde 3.1a ....................................................... 140

Scheme 3.19 Synthesis of Allenic Ketone 3.1b ........................................................... 140

Scheme 3.20 Synthesis of Alkyne 3.3c ...................................................................... 141

Scheme 3.21 Improved Synthesis of Alkyne 3.3c .................................................................. 141

Scheme 3.22 Synthesis of 3,3-Disubstituted Allene 3.4c .......................................... 141

Scheme 3.23 Synthesis of 3,3-Disubstituted Allenic Aldehyde 3.1c ............................ 141

Scheme 3.24 Synthesis of 3,3-Disubstituted Allene 3.1d ............................................ 142

Scheme 3.25 Synthesis of 1,3-Disubstituted Allene 3.3e ........................................... 142

Scheme 3.26 Synthesis of 1,3-Disubstituted Allenic Aldehyde 3.1e ............................ 143

Scheme 3.27 Possible π-Bond Selectivity Products from Allenic Aldehyde 3.1f ........ 143

Scheme 3.28 Synthesis of Allenic Aldehyde 3.1f ....................................................... 143

Scheme 3.29 Synthesis of 3.6a .................................................................................. 144

Scheme 4.1 Three General Metathesis Reactions ....................................................... 195

Scheme 4.2 Metathesis Mechanism ........................................................................ 196
Scheme 4.3 Formation of Carbene Complex [Cp₂Ti=CH₂] ........................................... 196
Scheme 4.4 Methylenation of Various Carbonyl Compounds .................................... 196
Scheme 4.5 Methylenation of γ-Butyrolactone .............................................................. 197
Scheme 4.6 Cp₂TiMe₂-Catalyzed ROMP of Norbornene ............................................. 197
Scheme 4.7 Olefin Metathesis ...................................................................................... 197
Scheme 4.8 Zirconium Carbene Complex Metathesis .................................................. 198
Scheme 4.9 Formation of an Titanium-imido Complex .............................................. 198
Scheme 4.10 Formation of Titanacyclobutenes ............................................................ 198
Scheme 4.11 Investigating Ti-N Bond Strength and Reduced Ring Strain ..................... 199
Scheme 4.12 Cp₂TiMe₂-Catalyzed Intermolecular Hydroamination ............................. 199
Scheme 4.13 Postulated Imine-Alkyne Metathesis Mechanism .................................... 200
Scheme 4.14 Alternative Imine-Alkyne Insertion Mechanism ...................................... 201
Scheme 4.15 Evidence of Insertion Mechanism .......................................................... 201
Scheme 4.16 Performing Aza-Diels-Alder Reactions .................................................. 202
Scheme 4.17 Hetero-Pauson-Khand Reaction ............................................................... 202
Scheme 4.18 Reductive Coupling .................................................................................. 203
Scheme 4.19 Reductive Coupling of δ-Alkynyl Imines .................................................. 203
Scheme 4.20 Ru₃(CO)₁₂-Catalyzed Reaction of Yne-Imines ........................................... 204
Scheme 4.21 Proposed Synthesis of the Pyrrolizidine Moiety ....................................... 204
Scheme 4.22 Modified Gabriel Synthesis of Amines .................................................... 205
Scheme 4.23 Synthesis of Phthalamide 4.3a .................................................................. 205
Scheme 4.24 Synthesis of Amine 4.4a (Method A) ..................................................... 206
Scheme 4.25 Alternative Synthesis of Amines ............................................................. 206
Scheme 4.26 Takano’s Route ................................................................. 207
Scheme 4.27 Synthesis of Alcohol 4.3b ...................................................... 207
Scheme 4.28 Synthesis of Amine 4.4a (Method B) ........................................ 208
Scheme 4.29 Iminophosphorane Formation ............................................... 208
Scheme 4.30 Synthesis of Imine 4.2c .......................................................... 208
Scheme 4.31 Attempted Synthesis of Metallacycle 4.4c .............................. 210
LIST OF ABBREVIATIONS

Vacant site or labile ligand
Å Angstrom
aq aqueous
9-BBN 9-borabicyclo[3.3.1]nonane
BINAP 2,2-bis(diphenylphosphino)-1,1-binaphthyl
Bn benzyl
t-Bu tert-butyl
n-BuLi n-butyllithium
C carbon
°C degrees Celsius
ca. approximately
calcd calculated
CDCl₃ chloroform-d
¹³C NMR Carbon-13 Nuclear Magnetic Resonance
Cp cyclopentadienyl
CO carbon monoxide
δ chemical shift in ppm downfield from Me₄Si
DCM dichloromethane
DIBAL diisobutylaluminum hydride
DMAP 4-(dimethylamino)pyridine
DMF dimethyl formamide
ee enantiometric excess
equiv. equivalent
Et ethyl
g gram(s)
h hour(s)
Hz hertz
¹H NMR Proton Nuclear Magnetic Resonance
J coupling constant
L liter(s)
m multiplet (NMR)
M moles per liter
Me methyl
MeCN acetonitrile
MHz megahertz
min minute(s)
mL milliliter
mol mole(s)
NBS N-bromosuccinimide
NMO 4-methylmorpholine-N-oxide
NMR nuclear magnetic resonance
ORTEP Oak Ridge Thermal Ellipsoid Plot
p para
PCC pyridinium chlorochromate
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Ph₃P</td>
<td>triphenylphosphine</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>psi</td>
<td>pounds per square inch</td>
</tr>
<tr>
<td>Rf</td>
<td>retention factor</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>sat</td>
<td>saturated</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDMS</td>
<td>t-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td>t-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>t-butyldimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMANO</td>
<td>trimethylamine-N-oxide</td>
</tr>
<tr>
<td>TMS</td>
<td>tetramethylsilane</td>
</tr>
<tr>
<td>TsCl</td>
<td>p-toluenesulfonyl chloride</td>
</tr>
</tbody>
</table>
ABSTRACT

Previous work in our laboratory has demonstrated not only a synthetic value of tandem reductive cyclization – carbonylation reactions in the preparation of complex molecules but also the interesting stereoselectivity observed therein.

The first part of this work employs the titanium-mediated cyclocarbonylation of tethered dienals for the synthesis of prostaglandin analogues, in particular PGF$_{2\alpha}$ and methyl jasmonate. Based on this hetero Pauson-Khand strategy, we have established an efficient racemic route to both the prostaglandin and the methyl jasmonate core skeletons. Moderate to excellent selectivities with regard to the hetero Pauson-Khand reaction were observed in both cases.

The second part of our study leads towards the novel synthesis of the biologically active $\alpha$-methylene-$\gamma$-butyrolactone moiety via titanium mediated hetero Pauson-Khand reaction of allenic aldehyde/ketone substrates. This substructure is embodied in many natural products such as Sarkomycin and Frullanolide which have excellent antibacterial and anticancer activities.

The final part of this study describes the development of the titanium-mediated reductive cyclocarbonylation and an imino-alkyne cross-metathesis strategy towards the synthesis of pyrrolizidine and indolizidine alkaloids respectively. The same substrates were employed in both reaction pathways.
CHAPTER 1

AN OVERVIEW OF THE HETERO PAUSON-KHAND REACTION

1.1 Introduction to the Pauson-Khand Reaction

Metal mediated and catalyzed reactions have made significant contributions to organic synthesis over the past decades. The growing interest in the development of organic reactions mediated and catalyzed by organotransition metals stems from the ability to assemble complex molecules from simple starting materials in a convergent and atom-economical manner.\(^\text{1.1}\) An important area of investigation toward this end has involved metal-mediated and -catalyzed cycloaddition reactions between carbonyl and unsaturated bonds as a means to find a practical way for the construction of cyclic frameworks. The Pauson-Khand reaction\(^\text{1.2}\) is one such intriguing reaction that exemplifies this concept. It is a three-component formal metal-mediated (or catalyzed) \([2 + 2 + 1]\)-cycloaddition of an alkyne \(\pi\)-bond, an alkene \(\pi\)-bond, and carbon monoxide to produce a cyclopentenone (Scheme 1.1).

![Scheme 1.1 Pauson-Khand Reaction](image_url)

The Pauson-Khand reaction was first discovered in 1971,\(^\text{1.3}\) and at that time, this cycloaddition process was accomplished with high temperatures using a stoichiometric
amount of dicobalt octacarbonyl (\(\text{Co}_2\text{CO}_8\)). The generation of the moderately air stable Co-acetylene complexes is the key property of this reagent. These complexes are formed at ambient temperature by stirring solutions of \(\text{Co}_2\text{(CO)}_8\) and the alkyne. The Pauson-Khand reaction has seen a remarkable growth in popularity and has become nowadays one of the most convergent and versatile methods for the synthesis of cyclopentenones. The Pauson-Khand reaction is compatible with a wide variety of functionalities such as alcohols, ethers, esters, tertiary amines and amides, nitriles, aromatic and hetero-aromatic rings. Initially, the scope of the reaction was limited to the use of strained olefins with the exception of ethylene itself. Harsh conditions were employed to effect the transformation and this sometimes led to the decomposition of starting materials and products. Also, regioselectivity was a problem.

1.2 Intramolecular Pauson-Khand Reaction

In the early eighties, Shore and co-workers demonstrated the considerable synthetic utility of this reaction by attaching the alkene to the alkyne via a carbon tether and introduced the first intramolecular version of the Pauson-Khand reaction (Scheme 1.2).\(^1\)\(^4\) As defined earlier, the intermolecular variant involves the reaction of three separate compounds: an alkyne, an alkene and CO. The intramolecular variant however, involves the reaction of an enyne and CO. Though tremendous attention has been devoted to the intermolecular reaction, much of the interest in the area today is due to the formation of bicyclic products from the intramolecular variant.

\[
\begin{align*}
\text{Co}_2\text{(CO)}_8 & \quad 95^\circ\text{C} \\
(31\%) & \\
\end{align*}
\]

Scheme 1.2 First Intramolecular Pauson-Khand Reaction
1.3 Promoters

As mentioned before, with the early intermolecular variants of the Pauson-Khand reactions, regioselectivity was a problem and strained olefins were necessary for the efficient conversion from starting materials to products. Now, with the establishment of the intramolecular Pauson-Khand reaction, strained alkenes are no longer necessary and regioselectivity is not a problem. With this discovery, came other improvements on the optimization of the reaction conditions. In the early nineties, Schreiber\textsuperscript{1.5} and Jeong\textsuperscript{1.6} independently reported the promotion of the Pauson-Khand reaction using tertiary amine N-oxides that generate free coordination sites at the cobalt metal center by oxidative removal of CO ligands. These promoters have since helped to circumvent the need for high temperatures and long reaction times and have allowed for a significant acceleration of the Pauson-Khand reaction at room temperature and in high yields (Scheme 1.3).

Other promoters such as silica gel\textsuperscript{1.7}, dimethyl sulfoxide (DMSO)\textsuperscript{1.8} and molecular sieves\textsuperscript{1.9} have also been reported but tertiary amine N-oxides like N-methyl morpholine-N-oxide (NMO)\textsuperscript{1.10} and trimethyl amine-N-oxide (TMANO)\textsuperscript{1.11} are still the most widely employed.

\begin{align*}
\text{(a) NMO, CH}_2\text{Cl}_2, \text{rt, 8 h} & \quad (87\%) \\
\text{(b) Me}_2\text{NO, O}_2, \text{CH}_2\text{Cl}_2, \text{rt, 3 h} & \quad (90\%)
\end{align*}

\textbf{Scheme 1.3 Utilizing Tertiary N-Oxides}

1.4 Mechanism of the Pauson-Khand Reaction

Beyond the fact that a hexacarbonyldicobalt-alkyne complex is involved, little is actually known about the mechanism of the Pauson-Khand reaction. The current level of
mechanistic understanding is inferred from observations of regio- and stereochemistry in a large number of examples. A working and widely accepted mechanistic pathway was first proposed by Magus\textsuperscript{1,10} and is outlined in Scheme 1.4.

\begin{equation}
\begin{align*}
R\equiv&-R' & \text{R} \equiv - \text{R}'
\end{align*}
\end{equation}

**Scheme 1.4 Proposed Mechanism of the Pauson-Khand Reaction**

The first step in the mechanistic sequence would be alkyne complexation, followed by dissociation of a CO ligand and coordination of the alkene. This ligand substitution step is presumably the rate-determining step while the following step, cobaltacycle formation, is the product-determining step, since (with adequately substituted substrates) it determines both the regiochemistry and the stereochemistry of the product cyclopentenone. Finally, the cobaltacycle that forms then proceeds to the final product by a standard sequence of steps beginning with CO insertion, reductive elimination and loss of the cobalt moiety or decomplexation.
1.5 Cobalt Catalyzed Pauson-Khand Reaction

In order to fulfill the criterion of atom economy, there has been a surge in the development of the catalytic version of the Pauson-Khand reaction. Ever since Pauson and co-workers reported in 1973, the first catalytic Co₂(CO)₈ cycloaddition, (0.023 equiv.) utilizing norbornene under one atmosphere of a 1:1 mixture of acetylene and CO in DME at 60-70 °C to provide a 62% yield of the cyclopentenone, there has been a growth in the utility of the original catalyst.

In 1990, Rautenstrauch and co-workers reported the synthesis of the dihydrojasmonate precursor 1.0a from ethylene and hept-1-yne. However, the major drawback of this protocol was the use of high pressures of CO (100 atm) and a continuous supply of ethyne (Scheme 1.5).

![Scheme 1.5 Rautenstrauch’s Catalytic Intermolecular Pauson-Khand Reaction](image)

The situation changed at the end of the decade, when a practical catalytic procedure involving photoactivation of Co₂(CO)₈ under low CO pressures (Scheme 1.6) was published by Livinghouse. Krafft and co-workers also reported high yielding catalytic Pauson-Khand reactions by using only 1 atm of CO. However, where Livinghouse put great emphasis on the use of highly pure catalysts, Krafft went further to enhance the efficiency of the reaction by addition of Lewis bases such as cyclohexylamine which act by stabilizing the reaction intermediates.
Scheme 1.6 Livinghouse’s and Krafft’s Intramolecular Pauson-Khand Reaction

Other compounds have been employed as additives to aid in the acceleration of the catalytic Pauson-Khand reaction. In 1994, Jeong and co-workers\textsuperscript{1.15} subsequently reported the addition of phosphines, phosphites and chiral phosphites such as (S)-BINAP in their reactions and delivered products with high enantiomeric excess (Scheme 1.7).

\[
\begin{align*}
\text{N} & \quad \text{Ts} \\
\text{N} & \quad \text{O} \\
\text{H} & \quad \text{Ts} \\
\text{Co}_2(\text{CO})_8 & \quad (0.2 \text{ equiv.}) \\
(\text{S})-\text{BINAP} & \quad (0.2 \text{ equiv.}) \\
\end{align*}
\]

\[80 \degree \text{C} \ 1 \text{ atm CO} \]

\[\text{Yield: 54\%} \]

\[\text{ee\%: 94\%} \]

Scheme 1.7 Jeong’s Catalytic Pauson-Khand Reaction with (S)-BINAP

1.6 Other Transition Metal Catalysts

In recent years, other transition metal complexes besides Co$_2$(CO)$_8$ have been used to catalyze/mediate the Pauson-Khand reaction. These various transition metal-complexes include molybdenum,\textsuperscript{1.16} zirconium,\textsuperscript{1.17} rhodium,\textsuperscript{1.18} iron,\textsuperscript{1.19} ruthenium,\textsuperscript{1.20} and titanium.\textsuperscript{1.21} Not only do some of these metal-complexes exhibit impressive catalytic ability, but based on their intrinsic design, asymmetric variants of the catalytic cycloaddition are now available.

Beginning with molybdenum metal, Jeong\textsuperscript{1.22} has reported that the cycloaddition can be mediated in good yield by the use of Mo(CO)$_6$ and DMSO (Scheme 1.8).
Scheme 1.8 Jeong’s Mo-Mediated Pauson-Khand Reaction

Negishi and co-workers\textsuperscript{1,17} have reported the zirconium metal-mediated Pauson-Khand reaction which directs the conversion of enynes into the corresponding metallacycles, followed by conversion into enones (Scheme 1.9).

Scheme 1.9 Negishi’s Zr-Mediated Pauson-Khand Reaction

Chloro-bridged rhodium dimers such as the ones established by Narasaka\textsuperscript{1,23} (Scheme 1.10) and Jeong\textsuperscript{1,18} have been shown to promote the catalytic cycloaddition process. In 1998, these two groups simultaneously published reports that showed that, rhodium-based catalysts could be used to effect these transformations under one atmosphere of CO.

Scheme 1.10 Narasaka’s Rh-Catalyzed Pauson-Khand Reaction

In 1994, Pearson and Dubbert reported the iron carbonyl promoted Pauson-Khand reaction (Scheme 1.11).\textsuperscript{1,19} The reaction with iron carbonyl is not catalytic and the iron carbonyl is actually used in excess. The efficiency of the reaction is improved when, in
place of Fe(CO)₅, a pre-made complex such as Fe(CO)₄(solvent) is used instead. Despite the form of the catalyst, high temperatures must be maintained regardless.

**Scheme 1.11 Fe-Mediated Pauson-Khand Reaction**

The scope of ruthenium carbonyl catalyzed reactions spans wide over a number of carbon-carbon bond forming reactions including the Pauson-Khand reaction. The first examples of the ruthenium-catalyzed Pauson-Khand reactions employing Ru₃(CO)₁₂ as the catalyst was discovered simultaneously by Mitsudo¹²⁴ and Murai¹²⁰ in 1997. These early reactions required high temperatures of about 140 °C to 180 °C and about 10-15 atm CO pressure (Scheme 1.12).

**Scheme 1.12 Murai’s Ru-Catalyzed Intramolecular Pauson-Khand Reaction**

In 1993, Buchwald and co-workers reported a titanium-based method for cyclopentenone synthesis (Scheme 1.13).¹²¹
This reaction proceeds as follows; the initial intermediate titanacyclopentene formed is captured by isocyanides and the resulting intermediate iminocyclopentene is subsequently hydrolyzed to the cyclopentenone. They have also been successful at avoiding the use of the air- and moisture-sensitive Cp₂Ti(PMe₃)₂ by utilizing a catalyst which is generated in situ from another titanocene, Cp₂TiCl₂.

1.7 γ-Butyrolactone Synthesis via the Hetero Pauson-Khand Reaction

In 1996, Dr. Crowe’s laboratory and others, were the first to report the Cp₂Ti(PMe₃)₂ mediated [2 + 2 + 1] cycloaddition of δ-unsaturated ketones and aldehydes with carbon monoxide into bicyclic γ-butyrolactones and coined the phrase “hetero Pauson-Khand reaction” (Scheme 1.14).¹²⁵

![Scheme 1.14 Hetero Pauson-Khand Reaction](image)

These reactions can be performed under mild conditions (low temperature and CO pressure) and high yield. The hetero Pauson-Khand reaction involves three key sequences. The first is the reductive coupling step of the pair of unsaturated organic fragments with the transition metal center to form a metallacycle. This is followed by carbonylation, which is the insertion of one equivalent of carbon monoxide into the Ti-C bond of the metallacycle, thus forming the carbonylated metallacycle. The final step, reductive elimination, is the loss of the titanium metal with ligands and leads to the formation of the cis-fused γ-butyrolactone. Reductive elimination can be induced thermally or by facile exposure to air. The mechanism of the hetero Pauson-Khand reaction as just described is shown in Scheme 1.15.
1.8 Catalytic Hetero Pauson-Khand Reaction

Soon after our first discovery of the general type hetero Pauson-Khand reactions, Buchwald reported a catalytic version of the reaction using Cp₂Ti(PMe₃)₂ or Cp₂Ti(CO)₂ to convert conjugated aromatic ketones to the corresponding γ-butyrolactones.¹,²⁶ However, this methodology had limited scope, since in general, the substrates feature only a keto moiety with an allyl group situated in an ortho-relationship on the aromatic ring (Scheme 1.16).

Scheme 1.16 Buchwald’s Ti-Catalyzed Hetero Pauson-Khand Reaction

Our group has recently published an asymmetric version of the hetero Pauson-Khand reaction.¹,²⁷ This asymmetric hetero Pauson-Khand cyclization involves the air stable chiral ansa-metallocene catalyst, (EBTHI)Ti(CO)₂, and enals or enones as the viable substrates (Scheme 1.17). The greater reactivity of (EBTHI)Ti(CO)₂, over the
unbridged counterpart, Cp₂Ti(CO)₂, towards carbonylation is the reason for its catalytic ability.

![Scheme 1.17 Crowe’s Catalytic Asymmetric Cyclocarbonylation](image)

**Scheme 1.17 Crowe’s Catalytic Asymmetric Cyclocarbonylation**

### 1.9 Ruthenium-Catalyzed Hetero Pauson-Khand Reaction

Murai and co-workers pioneered the first catalytic hetero Pauson-Khand reaction of substrates such as ketones and aldehydes in place of either an alkyne or an alkene. Below in Scheme 1.18, is an example of the an intramolecular [2+2+1] cycloaddition of yne-aldehydes with CO to give unsaturated γ-butenolides.

![Scheme 1.18 Ru-Catalyzed Intramolecular Hetero Pauson-Khand Reaction](image)

**Scheme 1.18 Ru-Catalyzed Intramolecular Hetero Pauson-Khand Reaction**

![Scheme 1.19 Murai’s Ru-Catalyzed Intermolecular Cyclization](image)

**Scheme 1.19 Murai’s Ru-Catalyzed Intermolecular Cyclization**
They also reported the intermolecular catalytic version of the hetero Pauson-Khand cyclization of ketones or aldehydes, ethylene, and CO in the presence of Ru₅(CO)₁₂ (Scheme 1.19).¹²⁹

1.10 Research Overview

The Pauson-Khand cycloaddition has been successfully used as a key step in the synthesis of biologically relevant natural products¹³⁰ and its high value will continue to be demonstrated in the formation of complex compounds from our laboratory and others. This introductory chapter, chapter 1, presents a brief summary and overview of the versatility of the hetero Pauson-Khand reaction. Chapter 2 demonstrates the utility of the hetero Pauson-Khand reaction as a synthetic approach towards the construction of intermediates relevant to the synthesis of prostaglandins and methyl jasmonate. Chapter 3 presents the titanium-mediated hetero Pauson-Khand methodology for the preparation of α-methylene-γ-butyrolactones from allenic carbonyl substrates. Finally, chapter 4 discusses an approach to the formation of the pyrrolizidine and indolizidine alkaloid skeletons via titanium-mediated synthesis.

1.11 References


CHAPTER 2

APPLICATIONS OF THE HETERO PAUSON-KHAND REACTION: CONSTRUCTION OF COMPOUNDS RELEVANT TO THE SYNTHESSES OF PROSTAGLANDINS AND METHYL JASMONATE

2.1 An Introduction to Prostaglandins (PG’s)

Prostaglandins are very important naturally-occurring physiologically potent substances which have been the subject of continuous attention by biologist, pharmacists and chemists since their discovery in the 1930s by the Swedish physiologist Ulf von Euler. The chemical structures of prostaglandins are based on the structure of prostanoic acid which comprises of a five-membered carbon ring with two side chains. The classification of prostaglandins into groups and subgroups depends on unsaturation and functional groups on both the ring and the side chains (Scheme 2.1).

Prostanoic acid

\[
\text{\begin{tabular}{c}
\hline
1 & COOH \\
2 & \alpha \text{ side chain} \\
3 & \omega \text{ side chain} \\
\hline
\end{tabular}}
\]

Divided into series A, B, C, D and F

\[
\text{\begin{tabular}{c}
A & B & C & D & E & F \\
\hline
1 & COOH & \alpha \text{ side chain} & \omega \text{ side chain} & \end{tabular}}
\]

Numerical subscripts represent different pairs of side chains

\[
\text{\begin{tabular}{c}
1 & 2 & 3 \\
\hline
R_\alpha & R_\omega & R_\alpha & R_\omega & R_\alpha & R_\omega \\
\end{tabular}}
\]

Scheme 2.1 Prostaglandin Nomenclature
The side chain with the acid functionality is called the \( \alpha \) side chain and the other the \( \omega \) side chain. Depending on the different substitution patterns of the five membered ring, alphabetical designations are made (A, B, C,…) and the different numerical subscripts represent the different pairs of side chains. The structure of PGF\(_{2\alpha}\) is indicated by the highlighted structural elements in Scheme 2.1. Prostaglandins belong to the family of eicosanoids. The \textit{in vivo} synthesis of eicosanoids starts from arachidonic acid, a 20 carbon unsaturated fatty acid, which is converted in the presence of oxygen by two cyclooxygenase enzyme systems widely distributed in mammalian tissue to endoperoxides.\(^2\)\(^2\) These intermediates are isomerized or reduced by various enzymes to several types of eicosanoids (Scheme 2.2).\(^2\)\(^3\)\(^4\) Other members of the eicosanoids are the prostacyclins and the thromboxanes.

\[ \text{C}_{20} \text{ unsaturated fatty acid} \]

\[ \text{(arachidonic acid)} \]

\[ \text{cyclooxygenase} \]

\[ \text{(enzyme)} \]

\[ \text{O}_2 \]

\[ \text{Endoperoxides} \]

\[ \text{(PGG}_2 \text{ or PGH}_2) \]

\[ \text{PGI}_2 \]

\[ \text{Prostacyclin} \]

\[ \text{PGF}_{2\alpha} \]

\[ \text{Prostaglandin} \]

\[ \text{TXA}_2 \]

\[ \text{Thromboxane} \]

\[ \text{Eicosanoids} \]

\textbf{Scheme 2.2 Biosynthesis of Prostaglandins}
All these eicosanoids play important regulatory roles in many normal cellular functions. They are found in the phospholipids of cell membranes. In contrast to hormones, they do not circulate nor are they stored in tissues. Rather they are synthesized locally on demand, perform a tissue-specific function and are rapidly inactivated by metabolic enzymes afterwards.

Pharmacological studies have shown that prostaglandins in particular, exhibit an extremely broad spectrum of activity and have a great impact, depending on the type and tissue. Prostaglandins can stimulate smooth-muscle contraction, affect the cardiovascular system (lower or raise blood pressure), the nervous system (increase body temperature), the reproductive system (fertility), stimulate inflammation and cause a general increase of hormone secretion.\(^2\)\(^5\)

Three major problems associated with the use of natural prostaglandins as drugs have been encountered: (1) chemical instability, (2) rapid metabolism, and (3) incidence of numerous side effects. These problems have created a need to synthesize prostaglandin analogs without such limitations. A large number of analogs have been synthesized during the last couple of decades and many of these are being marketed today. They are used as antihypertensive, antiulcer and antiglaucoma drugs and play an important role in the field of fertility control.\(^2\)\(^6\)

From the academic point of view, eicosanoids are still one of the most intensively studied class of natural products and every year hundreds of papers are published about these compounds in chemical, medicinal and biological journals like for example, Advances in Prostaglandin, Thromboxane and Leukotriene Research, and Prostaglandins & other Lipid Mediators.\(^2\)\(^4\)
2.2 Synthesis of Prostaglandins

The first main contributions in this field are those from E. J. Corey. In the late 1960s, Corey published a general route for the synthesis of several prostaglandins.\textsuperscript{2,7} This method has been extensively used in the synthesis of natural prostaglandins as well as many prostaglandins analogs. Also, although many precursors have been used for the synthesis of prostaglandins, Corey’s lactone, (Scheme 2.3) is one of the most successful building blocks which is also used for the industrial production of prostaglandin analogs.\textsuperscript{2,8-9}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{coreys_lactone.png}
\caption{Corey’s Lactone}
\end{figure}

In the classical approach, side chains 4 and 2 were introduced by the Wittig and Wittig-Horner reactions to lactol 3 and aldehyde 1 respectively (Scheme 2.4).\textsuperscript{2,10}

\begin{scheme}[h]
\centering
\includegraphics[width=\textwidth]{coreys_retrosynthetic.png}
\caption{Corey’s Retrosynthetic Synthesis of PGF\textsubscript{2α}}
\end{scheme}

A second very powerful synthesis of prostaglandin analogs is based on the two component coupling.\textsuperscript{2,11} The key step is a conjugate addition reaction of an \textit{in situ} formed cuprate from 5 to substituted enone 6 (Scheme 2.5). The optically pure precursor (\textit{R})-6
for the stereoselective synthesis can be obtained by an enzymatic resolution.\textsuperscript{2,12}

![Chemical structure](image)

**Scheme 2.4 Two Component Coupling**

Related is the three component coupling method developed by Noyori,\textsuperscript{2,13} which is one of the most elegant approaches because of the shortness of this convergent synthetic route. The key step of this method is the conjugate addition-aldol reaction connecting both side-chains in one step (Scheme 2.6).

![Chemical structure](image)

**Scheme 2.5 Three Component Coupling**

**2.3 Research Interests**

Major areas of interest in Dr. Crowe’s group at the present time include medicinal chemistry, synthetic organic/organometallic chemistry, and natural products chemistry. More specifically, we are interested in the synthesis of natural products with biological activity or related analogs with enhanced activity. Research of this type has led us into the alkaloid, \(g\)-butyrolactone, and \(\alpha\)-methylene-\(g\)-butyrolactone fields just to name a few. A central focal point that encompasses much of our research efforts is exploring the
scope of titanium mediated/catalyzed carbon-carbon bond-forming reactions. Metals of certain designs from across the periodic table may catalyze many C-C bond-forming reactions. However, titanium complexes have several advantages. First, titanium is the 2nd most abundant transition element in the earth’s crust (after iron) and is quite inexpensive relative to many of the later metals, e.g. palladium. Consequently, catalyst/reagent loadings are much less a concern. Second, titanium is readily removed from products by flushing through an alumina or silica plug. And as a final point, on hydrolysis the metal containing product is TiO2, a nontoxic compound found in many of the foods we buy and in toothpastes. In 1996, our laboratory provided the first examples of an intramolecular, titanium mediated hetero Pauson-Khand reaction of tethered enals 2a-h. This strategy has subsequently been developed as a generally useful synthetic method. The three component [2 + 2 + 1] cycloaddition which incorporates the ketone or the aldehyde π-bond, the alkene π-bond, and the carbon atom of CO into the five-membered ring represents an attractive route to γ-butyrolactones 2‴a-h (Scheme 2.7).

Scheme 2.6 Scope of the Hetero Pauson-Khand Reaction Outlined

The mechanistic scheme of this reaction is exposure of titanium metallacycles 2′a-h, obtained by the reaction of a stiochiometric amount of Cp2Ti(PMe3)2 with olefinic aldehydes or ketones 2a-h, with CO followed by an oxidatively induced reductive elimination to give γ-butyrolactones 2‴a-h (Scheme 2.7). All metallacycles and γ
-butyrolactone products possess a cis-fused ring junction. Below in Table 2.1 are some previously reported substrates 2a-h which underwent tandem reductive cyclization-carbonylation reactions. Diastereoselectivity ratios of product metallacycles and γ-butyrolactones are provided for substrates 2c, 2e, and 2f.

Table 2.1 Previously Reported Substrates

<table>
<thead>
<tr>
<th>Substrates 2a-h</th>
<th>Products (Yields)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2'a-h</td>
</tr>
<tr>
<td>2a</td>
<td>91</td>
</tr>
<tr>
<td>2b</td>
<td>84</td>
</tr>
<tr>
<td>2c&lt;sup&gt;a&lt;/sup&gt;</td>
<td>95&lt;sup&gt;(2.3:1)&lt;/sup&gt;</td>
</tr>
<tr>
<td>2d</td>
<td>90</td>
</tr>
<tr>
<td>2e&lt;sup&gt;a&lt;/sup&gt;</td>
<td>89&lt;sup&gt;(4.5:1)&lt;/sup&gt;</td>
</tr>
<tr>
<td>2f&lt;sup&gt;a&lt;/sup&gt;</td>
<td>88&lt;sup&gt;(1.8:1)&lt;/sup&gt;</td>
</tr>
<tr>
<td>2g</td>
<td>88</td>
</tr>
<tr>
<td>2h</td>
<td>84</td>
</tr>
</tbody>
</table>

(a) Diastereoselectivity values provided below yields
(b) A reasonably pure product could not be isolated from the reaction mixture by crystallization
2.4 Natural Product Target – Prostaglandins

In Scheme 2.8 below, we would like to emphasize the appeal of the hetero Pauson-Khand reaction. Three new bonds and two new asymmetric centers are formed in one step. It is clearly apparent to see the similarities between the product of the hetero Pauson-Khand reaction and the particular prostaglandin we are interested in synthesizing, which is PGF$_{2\alpha}$.

Similarly: Prostaglandins

F-type prostaglandins possess an additional center of asymmetry at C-9. Oxidation of F-type prostaglandins while the C-11 and C-15 sites are selectively protected provides a convenient access to PGEs. Since the E-type prostaglandins can, in turn, be readily converted to any other member of the same class, this makes the F-type prostaglandins highly attractive synthetic targets. Previous work (Table 2.1) in our laboratory has demonstrated not only a synthetic value of tandem reductive cyclization – carbonylation reactions in the preparation of complex molecules but also the interesting stereoselectivity observed therein. We now wish to feature PGF$_{2\alpha}$, as our representative
molecule to describe the exciting development of utilizing the hetero Pauson-Khand methodology as a convenient and flexible approach to the synthesis of prostaglandins and other structural analogs.

2.5 Proposed Synthesis

Our present goal for the hetero Pauson-Khand reaction would be to provide us with prostaglandin precursors using a stoichiometric equivalent of Cp₂Ti(PMe₃)₂, in combination with known trends in the diasteroselective features of this reaction.²,¹⁴ Based on this hetero Pauson-Khand strategy, we hope to be able to efficiently access the prostaglandin core and its substituents with the correct relative stereochemistry (Scheme 2.8).

Scheme 2.8 Retrosynthetic Cyclocarbonylation Route to Prostaglandins
Prior to the installment of the respective $\alpha$- and $\gamma$- side chains, $2.0h$ and $2.0i$, we plan to convert $2.0b$ to the aldehyde $2.0b'$ via ozonolysis in methanol at $-78$ °C followed by treatment with dimethyl sulfide.\textsuperscript{2.15} The aldehyde $2.0b'$, which is essentially Corey’s lactone, will then be transformed into PGF$_2\alpha$. $2.0a$ via the usual procedures common to many syntheses of prostaglandins; the Horner-Wadsworth-Emmons reaction to install the $\gamma$-side chain $2.0h$ and trans olefin followed by diastereoselective reduction of the conjugated ketone to give the allylic $\alpha$-oriented alcohol.\textsuperscript{2.10}

Protection of that alcohol followed by DIBAL opening of the lactone will provide us the ability to connect the $\alpha$-side chain $2.0i$ via a Wittig reaction.\textsuperscript{2.10} Subsequent deprotection steps should yield our desired product $2.0a$. Substrate $2.0c$ will be prepared to test this idea of using diastereotopic group selectivity to set the C-12 stereocenter. The chiral substrate $2.0c$, in an enantiomerically pure form, can be easily accessed using the method of Ito,\textsuperscript{2.16} which combines a five-carbon conjugated diene, $2.0f$, with an aldehyde $2.0d$ to give the pentadienylborane reagent $2.0g$ using the bromoborane reagent $2.0e$, the preparation of which is known.\textsuperscript{2.17}

It is hoped that, if the hetero Pauson-Khand cyclization of the deconjugated dienol $2.0c$ gives the expected diastereoselectivity, we would then be able to access it in high enantiomeric excess (ee) in order to achieve the synthesis enantiomerically.

2.6 Selectivity

From the outset, our endeavor seemed to have anticipated that the control of the absolute configuration of the three new stereogenic centers would be dictated by substrate $2.0c$ carrying a sterically-bulky protecting hydroxyl group of a fixed stereochemistry and nature of the stereoselection of the cycloaddition. This, however, is simply a hypothesis.
and is the basis of our inquiry into establishing a new and promising area of possibly highly diastereoselective hetero Pauson-Khand reactions. Metallcycles $2.0c'$ and $2.0c''$ modeled after the proposal outlined in Scheme 2.9 seem to provide hope that the correct diastereoselectivity would be observed in the cyclization event.

![Scheme 2.9 Group Selective Reactions](image)

The hetero Pauson-Khand reaction of $2.0c$ is expected to favor diastereomer $2.0b$, since both substituents can adopt preferred pseudoequatorial positions in the metallacycle intermediate $2.0c'$ leading to the desired product. The metallacycle diastereomer $2.0c''$ leading to the undesired product $2.0b''$ should be less favorable since the alkoxy substituent is forced to occupy a pseudoaxial position.

Again, it is important to emphasize that the crucial component of this strategy is clearly the diastereoselectivity of the hetero Pauson-Khand cyclization, so the initial goal was to test this, in racemic form prior to proceeding with construction of any enantiomerically pure substrates. We decided to use a tert-butyldimethylsilyl group (TBDMS) as our alcohol protecting group. This silyl protecting group is a commonly used hydroxyl protecting group in prostaglandin synthesis.
2.7 Preparation of Prostaglandin Precursors

In order to examine the influence of the alcohol protecting group on diastereotopic group selectivity, compound 2.1p was proposed. The retrosynthetic analysis is illustrated below in Scheme 2.10.

![Retrosynthetic Analysis of TBDMS Protected Aldehyde 2.1p](image)

Scheme 2.10 Retrosynthetic Analysis of TBDMS Protected Aldehyde 2.1p

Preparation of 2.1k\textsuperscript{2.18} commenced with the synthesis of 2.1j\textsuperscript{2.19} (Scheme 2.11). We initially prepared it from acrolein 2.1g and vinyl bromide 2.1h with an excess amount of magnesium in a 4:1 mixture of THF-Et\textsubscript{2}O. However, the yield of this reaction was low, 55%, hence we switched to using vinylmagnesium bromide 2.1i.

![Synthesis of Bromide 2.1k](image)

Scheme 2.11 Synthesis of Bromide 2.1k
Next, the synthesis of 2.1f\textsuperscript{2,20} was performed (Scheme 2.12). The acetal 2.1c, was derived from 1,3-propanediol 2.1a and benzaldehyde 2.1b by azeotropic removal of water via a Dean-Stark set-up. The acetal 2.1c was then reduced to the alcohol 2.1d with borane, followed by PCC oxidation to yield the desired aldehyde 2.1f.

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
+ & \\
\text{ benzaldehyde} & \\
\text{cat. TsOH, PhCH}_3 & \xrightarrow{-H_2O} 96\% \\
\text{BH}_3 \text{THF} & \xrightarrow{99\%} \\
\text{DCM} & \rightarrow \\
\text{90\%} & \text{on Al}_2\text{O}_3 \text{ support, DCM} \\
\end{align*}
\]

Scheme 2.12 Synthesis of Aldehyde 2.1f

With substrates 2.1k and 2.1f at hand, we were now ready for our first convergency which is the pentadienylation reaction. A variety of convenient protocols exist for this transformation.\textsuperscript{2,21} We selected the indium mediated pentadienylation method.\textsuperscript{2,22} This reaction is actually quite unique in that we obtain exclusively the \(\gamma\)-pentadienylation product. We believe that this selectivity is obtained through a cyclic six-membered transition state, where an aldehyde coordinates with the indium metal center and reacts in a 1,2-addition manner to the \(\gamma\)-position of the pentadienylindium (Scheme 2.13).

\[
\begin{align*}
\text{InH} & \quad \text{Br} \\
\text{In Metal} & \rightarrow \\
\text{O} & \\
\text{H} & \\
\text{R} & \\
\end{align*}
\]

Scheme 2.13 Indium Mediated Pentadienylation
Therefore, following our pentadienylation reaction, (Scheme 2.14) we obtained the benzyl protected alcohol 2.1l which in turn underwent protection with TBDMS-Cl to yield the TBDMS-protected alcohol 2.1m.\textsuperscript{2,23}

\[ \text{TBDMSCl} + \text{Imidazole} \rightarrow \text{TBDMS-protected alcohol} \]

\[ \text{OTBDMS} \]

O

H

Br

[88%]

[Imidazole, DMF]

\[ \text{98%} \]

\[ \text{OTBDMS} \]

\[ \text{THF} \]

\[ \text{88\%Overall} \]

\[ \text{Na, liq. NH}_3 \rightarrow \text{1\textsuperscript{st} Alcohol} \]

\[ \text{1\textsuperscript{st} Alcohol} \]

\[ \text{TBDMS group undergoes 1,3-Migration} \]

\[ \text{Desired Product} \]

\[ \text{Silyl Group Transfer} \]

\[ \text{Product Ratio: 1\textsuperscript{st} : 2\textsuperscript{nd} alcohol} \]

\[ 1 : 5 \]

\textbf{Scheme 2.14 Observed Silyl Migration}

We next employed sodium-liquid ammonia reducing conditions\textsuperscript{2,24} to promote debenzylolation of 2.1m. Unfortunately, instead of a sole primary alcohol product, we obtained a mixture of 2.1o and 2.1n in a 1:5 ratio. The emergence of 2.1n is explained by 1,3-silyl migration\textsuperscript{2,25} which occurs during the debenzylolation of 2.1m as a result of the formation of an alkoxide intermediate. Hence, we decided to return to substrate 2.1l and utilize the already present benzyl protecting group. Accordingly, 2.1l was subjected to DDQ oxidation\textsuperscript{2,26} followed by selective DIBAL opening\textsuperscript{2,27} on the less hindered side of the acetal 2.1p. PCC oxidation in DCM furnished our new desired target 2.1r (Scheme 2.15). In addition, trace amounts of benzoate regioisomers 2.1p' and 2.1p'' (due to over
oxidation of the acetal 2.1p were also identified. With compound 2.1r at hand, we treated it with Cp₂Ti(PMe₃)₂ and formed two diastereomeric metallacyclic compounds 2.1s and 2.1t in a 1:1 ratio confirmed by ¹H NMR data (Scheme 2.16). To verify the correct stereochemistry, a solid sample mixture of these two new metallacycles was submitted for crystal X-ray analysis and the results indicated that both diastereomers had co-crystallized within a single crystal (Figure 2.2).
Scheme 2.16 Preparation of Metallacycles 2.1s and 2.1t

Figure 2.2 ORTEP Plot of Co-Crystallized Metallacycles 2.1s and 2.1t
The metallacycles were subjected to carbonylation conditions of 20 psi of CO at room
temperature in pentane and lactones 2.1u and 2.1v were obtained in the same 1:1 ratio
(Scheme 2.17).

Scheme 2.17 Synthesis of Lactones 2.1u and 2.1v

2.8 The Challenge

Scheme 2.18 Choice of Protecting Groups
Seeing that we are not achieving any sort of selectivity with the benzyl protecting group, we decided next to explore bulkier alcohol protecting groups (Scheme 2.18). The retrosynthetic analysis (Scheme 2.19) lays out a route where silyl group transfer is avoided due to the fact that deprotecting conditions for 2.2f do not generate an alkoxide intermediate. Synthesis of 2.2d was reminiscent to that of 2.1f (Scheme 2.20).

Scheme 2.19 Retrosynthetic Analysis of 2.2h

Scheme 2.20 Synthesis of Aldehyde 2.2d

Following indium mediated pentadienylation of 2.2d and 2.1k, the PMB protected secondary alcohol 2.2e was then protected with our second choice of alcohol protecting groups towards diastereoselective optimization: TBDPSCI. Next, the p-methoxy benzyl-protecting group was cleaved off by treating 2.2f with DDQ to furnish the alcohol 2.2g in excellent yield (Scheme 2.21).
We subsequently subjected the aldehyde $\text{2.2h}$ to reductive coupling conditions. While the coupling reaction in pentane yielded a mixture of two metallacyclic compounds $\text{2.2i}$ and $\text{2.2j}$ in a ratio of ca. 2:1, almost no selectivity was afforded in THF (Scheme 2.22). Initially, the complexity in the $^1$H-NMR of the mixture and relatively less crystalline property of $\text{2.2i}$ precluded us from formally deducing its structure. However, we were able to isolate a crystal structure of the undesired metallacycle $\text{2.2j}$ (Figure 2.3)(Entry 1). Henceforth, we then turned our attention to the subsequent carbonylation reaction whereby the corresponding products lead us to identify to the nature of $\text{2.2i}$.

**Scheme 2.21 Synthesis of TBDPS Protected Aldehyde 2.2h**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Ratio of Metallacycles $\text{2.2i}:\text{2.2j}$</th>
<th>Yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 equiv. $\text{Cp}_2\text{Ti}(\text{PMe}_3)_2$, Pentane</td>
<td>~ 2:1</td>
<td>88%</td>
</tr>
<tr>
<td>2</td>
<td>1.0 equiv. $\text{Cp}_2\text{Ti}(\text{PMe}_3)_2$, THF</td>
<td>~ 1:1</td>
<td>92%</td>
</tr>
</tbody>
</table>

(a) Ratios determined from $^1$H NMR data. (b) Overall Yield.

**Scheme 2.22 Results from Synthesis of Metallacycles 2.2i and 2.2j**
We were a little surprised at the change in metallacyclic ratios when going from pentane to THF. Unfortunately we do not have a firm explanation or hypothesis on this observed solvent effect on the metallacycle ratio at this point. Devising mechanistic studies in the future could lead to clarification of this outcome. The metallacyclic mixture of diastereomers 2.2i and 2.2j obtained from the reaction involving conditions in Entry 1
were subjected to varying carbonylation conditions and the results are summarized below in Scheme 2.23.

![Reaction Conditions Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Ratio of lactones$^a$</th>
<th>Yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pentane, 25 °C, 12 h</td>
<td>~ 1.25:1</td>
<td>39%:31%</td>
</tr>
<tr>
<td>2</td>
<td>Toluene, 70 °C, 3 h</td>
<td>~ 1.20:1</td>
<td>44%:37%</td>
</tr>
</tbody>
</table>

(a) Ratios determined from $^1$H NMR data. (b) Isolated Yields.

**Scheme 2.23 Results from Synthesis of Lactones 2.2k and 2.2l**

Here again, we observed that the lactone ratios changed from that of the metallacyclic ratio. Possible explanations for this are that the reductive coupling step is reversible or that one of the metallacycles is decomposing while the other reacts faster. These results however, definitely indicate that further investigation into the trityl group is required.

**2.9 Synthesis of the Trityl-Protected Prostaglandin Precursor**

Initial experiments to synthesize 2.3d were carried out with compound 2.2e. An attempted protection of the secondary alcohol with triphenylmethyl chloride$^{2,29}$ and DBU as base was unsuccessful. We then tried conditions utilizing triphenylmethylpyridinium tetrafluoroborate$^{2,30}$ in MeCN and the best yield obtainable was 10%, which was unacceptable. We recognized that a stronger tritylating reagent would have to be synthesized and to that respect we embarked on preparing a very powerful tritylating
reagent; triphenylmethyl perchlorate (Scheme 2.24). When we subjected compound 2.2e to the tritylating conditions described in Scheme 2.25, we obtained an alcohol product (tentatively assigned from $^1$H NMR data) with an unusually high Rf value. We believe that the trityl perchlorate reagent 2.3c oxidatively cleaved the PMB group, however we were not sure if it was the 1° or 2° alcohol product remaining. We therefore submitted the sample to PCC oxidation and verified the subsequent product as the ketone 2.3f which lead us to assign the alcohol as 2.3e.

Scheme 2.25 Tritylation of Alcohol 2.2e
It appeared to us that further investigations into tritylating \textbf{2.2e} would be futile, so instead, we decided to test compound \textbf{2.1l} along the lines of Scheme 2.25 (Scheme 2.26).

\[\text{Ph}_3\text{C}^+\text{ClO}_4^- \xrightarrow{\text{2,4,6-Collidine}} \text{DMAP} \xrightarrow{\text{DCM} \ 78\%} \text{Na, liq. NH}_3 \xrightarrow{\text{THF}} \]

\[\text{2.1l} \rightarrow \text{2.3g} \rightarrow \text{2.3d} \]

\textbf{Scheme 2.26 Attempted Synthesis of Primary Alcohol 2.3d}

The tritylation step to transform the secondary alcohol \textbf{2.1l} to \textbf{2.3g} went smoothly and uneventfully, but the next crucial step of debenzylation, however, did not yield the desired alcohol \textbf{2.3d}. Instead, the sodium-liquid ammonia conditions afforded a complex reaction mixture and in retrospect, this observation is understandable since it is known that some detritylation procedures employ reduction treatment with sodium in liquid ammonia.\textsuperscript{2.32}

We plotted out a retrosynthetic analysis, illustrated in Scheme 2.27 where the position originally occupied by the benzyl derived protecting groups would now be replaced with a silyl group.

\[\text{TBS Deprotection} \xrightarrow{TBS Protection} \]

\[\text{2.3d} \rightarrow \text{TBSO} \rightarrow \text{TBSO} \rightarrow \text{OH} \]

\textbf{Scheme 2.27 Retrosynthetic Analysis of Primary Alcohol 2.3d}

37
The synthesis of 2.3l proceeded without any difficulty starting with the commercially available mono TBS-protected propanediol 2.3h. Familiar reactions were repeated and much to our delight, TBAF deprotection of the silyl protecting group yielded compound 2.3d with the trityl protecting group intact (Scheme 2.28).

During PCC oxidation of 2.3d, we observed cleavage of the trityl group due to the slight acidic nature of the reaction solution. As a result, an equivalent amount of sodium acetate was added to buffer the reaction solution and cleanly afford enal 2.3l.

Reductive coupling of 2.3l commenced under the conditions employed in synthesizing metallacycles 2.1s and 2.1t, (1.0 equiv. of Cp2Ti(PMe3)2, pentane) (Scheme 2.29).

Scheme 2.28 Synthesis of Trityl Protected Aldehyde 2.3l

Scheme 2.29 Reductive Coupling and Carbonylation of 2.3l
A mixture of metallacycles was obtained. It proved difficult to isolate and characterize each metallacycle. Therefore, we followed through with the carbonylation step and obtained approximately a 2:1:1 (determined by crude $^1$H NMR data) mixture of the three diastereomeric lactones 2.3m, 2.3n and 2.3o.

Figure 2.4 ORTEP Plot of Co-Crystallized Metallacycles 2.3n and 2.3o
The two minor diastereomers \(2.3n\) and \(2.3o\) were not separable by TLC, but were individually visible by analytical HPLC. After subjecting the crude mixture to column chromatography, the major product lactone \(2.3m\) was separated and characterized. The identities of the minor products were ascertained by recrystallization and confirmed by X-ray crystallography (Figure 2.4). Both diastereomers co-crystallized within a single crystal structure. This study has established the difficulty in obtaining the desired diastereoselectivity based solely on the size of the protecting alcohol group. However, we decided to try one more idea which involved completely converting the alcohol functionality into a bulky silyl group. We believed that the shorter distance and increased steric bulk may contribute to enhancing the diastereoselectivity of the hetero Pauson-Khand reaction. If good selectivity could be achieved with this reaction, then the correct stereochemical relationship of the silyl group (\(2.4c\)) to the rest of the molecule would be easily achieved (Scheme 2.30).

Scheme 2.30 Retrosynthetic Analysis Outlining the Synthesis of \(2.4a\)

2.10 Switching from Hydroxyl to Silyl Functionality

First, the reaction of the silyllithium reagent should proceed with complete inversion of configuration. Afterward, following the hetero Pauson-Khand reaction, the
phenyl groups would be converted to alkylalkoxy groups.\textsuperscript{2,34a} This would be followed by oxidative cleavage of the carbon-silicon bond with trimethylamine-\(N\)-oxide where the alcohol would be regenerated with complete retention of configuration (Scheme 2.31).\textsuperscript{2,34b}

Scheme 2.31 Proposed Oxidative Cleavage of Silicon-Carbon Bond

To this end, we synthesized the triphenylsilyl lithium reagent \textbf{2.4e} by stirring a THF solution of triphenylsilyl chloride with lithium metal.\textsuperscript{2,35} We determined the molarity of the silyllithium solution \textbf{2.4e} by titration with standard BHT solution with 9,10-phenanthroline as indicator. Tosylation of compound \textbf{2.2e} provided compound \textbf{2.4f}. This was then reacted with the freshly prepared silyl lithium reagent \textbf{2.4e} via a normal \(S_N2\) reaction (Scheme 2.32).\textsuperscript{2,36}

Scheme 2.32 Attempted Substitution of Tosylate 2.4f
Unfortunately, no substitution occurred and we only obtained the eliminated product, 2.4g. We also prepared the silyl lithium reagent (Ph₂BuSiLi) and silyl cuprate reagent (Ph₂BuSi)₂CuLi, but these reagents still only afforded the eliminated product 2.4g.

2.11 Other Synthetic Applications

At this point, we decided to take a step back and take a broad look at the project and determine if there were any other potential lactones that could be formed based on the knowledge that we had just gleaned from all the reactions performed so far. Methyl jasmonate, 2.5g, a main component of jasmine oil, is structurally similar to that of medicinally important prostanoids, for example, PGE₂, 2.5h (Figure 2.5). Therefore, any knowledge that has been acquired in the synthesis towards prostaglandin analogs could be directly applied to prepare the perfume ingredient, methyl jasmonate 2.5g.

![Figure 2.5 Similarities between Methyl Jasmonate 2.5g and PGE₂ 2.5h](image)

2.12 Synthesis Towards Methyl Jasmonate

Methyl jasmonate belongs to the jasmonoid group, which are 2,3-disubstituted five-membered cyclic ketones. They are the most important representatives of natural jasmine fragrances which are isolated from jasmine flowers. Jasmonoids not only exhibit characteristic fragrance properties, but also play a key role in phytohormones in plants. This range of plant regulatory and pheromonal properties has attracted attention to methyl jasmonate as an important synthetic target.
We now wish to propose the preparation of methyl jasmonate as illustrated in the retrosynthetic analysis below (Scheme 2.33). The key step is the deoxygenation of 2.3j.

\[
\begin{align*}
2.5g & \quad \text{CO}_2\text{Me} \\
\quad & \quad \text{TBSO} \\
\quad & \quad \text{OH} \\
\quad & \quad \text{CO}_2\text{Me}
\end{align*}
\]

Methyl Jasmonate

Scheme 2.33 Retrosynthetic Analysis of Methyl Jasmonate 2.5g

Our synthesis starts with the already available 2.3j which was synthesized earlier for the preparation of the trityl-protected enal 2.3l. Mesylation of the secondary alcohol proceeded easily, as well as the LAH reduction\textsuperscript{2.41} of the mesyl function. Following the latter reaction, we encountered an unexpected surprise, evidenced by the loss of the TBDMS group, which actually then saved us a step (deprotection). We believe that the loss of the TBS group occurred during the aqueous work-up of compound 2.5a'. PCC oxidation in DCM furnished the desired aldehyde 2.5c (Scheme 2.34).

\[
\begin{align*}
\text{TBSO} & \quad \text{OH} \\
\quad & \quad \text{NCI} \\
\quad & \quad \text{NEt}_3 \\
\quad & \quad \text{DCM} \\
\quad & \quad 82\% \\
\quad & \quad \text{TBSO} \\
\quad & \quad \text{OMs} \\
\quad & \quad \text{LiAlH}_4 \\
\quad & \quad \text{Ether} \\
\quad & \quad 64\% \\
\quad & \quad \text{H}_2\text{O} \\
\quad & \quad \text{HO} \\
\quad & \quad \text{DCM} \\
\quad & \quad 61\% \\
\quad & \quad \text{PCC on Al}_2\text{O}_3 \\
\quad & \quad \text{support}
\end{align*}
\]

Scheme 2.34 Synthesis of Aldehyde 2.5c
Reductive coupling of \textbf{2.5c} with 1.0 equivalent of \( \text{Cp}_2\text{Ti(PMe}_3\text{)}_2 \) in pentane yielded the desired metallacyclic diastereomer \textbf{2.5d} exclusively. Carbonylation of metallacycle \textbf{2.5d} afforded the single \textit{cis}-fused \( \gamma \)-butyrolactone diastereomer \textbf{2.5e} (Scheme 2.35).

\begin{center}
\includegraphics[width=\textwidth]{scheme2_35.png}
\end{center}

\textbf{Scheme 2.35 Synthesis of Lactone 2.5e}

Other than just serving as a jasmonoid precursor, \textbf{2.5e} can also be converted to 11-deoxyprostaglandins, such as 11-deoxy PGF\textsubscript{1\alpha} (Scheme 2.36). This class of prostaglandins are known to inhibit gastric acid secretion and can cause uterine contractions.\textsuperscript{242}

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme2_36.png}
\end{center}

\textbf{Scheme 2.36 Route towards 11-deoxy PGF\textsubscript{1\alpha} 2.5f Synthesis}

We would however like to propose the total synthesis of methyl jasmonate \textbf{2.5g} in Scheme 2.37. The primary alcohol \textbf{2.5i} can be very easily obtained by hydroboration of \textbf{2.5e} with 9-BBN at \( 0 \) °C followed by \textit{in situ} oxidation of the intermediate alkylboron with \( \text{H}_2\text{O}_2 \). DIBAL reduction of the lactone to the corresponding lactol and a subsequent Wittig reaction would provide the skeletal framework \textbf{2.5k} for jasmonoid and prostanoid...
derivatives. Further oxidation to the carboxylic acid by using Jones’ reagent and esterification should afford the desired product, methyl jasmonate 2.5g.

![Scheme 2.37 Proposed Synthesis of Methyl Jasmonate 2.5g](image)

This proposed preparation constitutes a formal synthesis of the natural product, methyl jasmonate 2.5g in racemic form.

**2.13 More Possibilities!**

The exclusive diastereoselectivity exhibited by lactone 2.5e, stirred a curiosity in us to explore substrates 2.6a and 2.7a (Figure 2.6) which are structurally similar to aldehyde 2.5c.

![Figure 2.6 Proposed Structures 2.6a and 2.7a](image)
In the cases of aldehyde substrates 2.6a and 2.7a, we wondered what type of chemoselectivity the titanocene reagent [Cp₂Ti(PMe₃)₂] would exhibit in the hetero Pauson-Khand reaction. After coordinating with the aldehyde group, would the titanium center proceed to react with the alkyne selectively? or with the alkene? or both? This investigation will shed interesting light on the reactivity of alkyne versus alkene functionalities in titanium mediated reductive cyclizations. The racemic synthesis of 2.7a can be easily obtained from synthetic intermediates of 2.6a. Hence, we commenced this venture by proposing the racemic synthesis of 2.6a (Scheme 2.38). We began by treating excess sodium acetylide 2.6c with epichlorohydrin 2.6b in liquid ammonia at -33 °C.
for 3 h to afford alcohol 2.6d. Treatment of alcohol 2.6d with EtMgBr at 0 °C in THF, followed by the addition of TMSCl yielded the alcohol 2.6d'. Treatment of alcohol 2.6d' with 1.1 equiv. of NBS and 1.2 equiv. of PPh₃ in DCM at 0 °C yielded the bromide 2.6e. Indium mediated reaction analogous to the pentadienylation of 2.1k was used next to prepare the 1:1 mixture of diastereomers, 2.6f and 2.6f'. This lack of selectivity indicates that a more selective pentadienylation reaction would be necessary for the synthesis of 2.7a. Mesylation of the mixture of diastereomers unfortunately resulted in the elimination product 2.6g. We believe that this elimination which is absent when the alkyne is replaced with an alkene, is due to the overlap of the alkyne π-orbitals with that of the C-H bond thus facilitating elimination. At this point, we envisioned that the effect of the alkyne group could be diminished if complexed with Co₂CO₈ (Scheme 2.39).

Scheme 2.39 Synthesis towards Aldehyde 2.6a
We decided to test the idea by first synthesizing the 1:1 diastereomeric mixture of TBS protected alcohols 2.6i and 2.6i'. Next, we formed the hexacarbonyldicobalt-alkyne complexes 2.6j and 2.6j' by reacting with 1.0 equiv. of Co$_2$CO$_8$ in DCM.$^{2.45}$ Much to our delight, the much anticipated mesylation reaction of 2.6j and 2.6j' occurred smoothly to afford the mesylated products. Decomplexation of the mesylated Co-acetylene complexes 2.6k and 2.6k' with ceric ammonium nitrate (CAN) in anhydrous MeOH not only freed the alkyne, but also enabled the deprotection of the TBS protecting group.$^{2.46}$ LAH reduction of the mesyl function produced the alcohol 2.6l and PCC oxidation furnished the desired aldehyde 2.6a (Scheme 2.40).

Scheme 2.40 Synthesis of Aldehyde 2.6a

2.14 Conclusion

We are currently applying titanium mediated reductive coupling conditions to substrate 2.6a. We have also began to investigate exploitation of 2.5e as a synthon to synthesize methyl jasmonate 2.5g. Going back to our original hypothesis, changing the reaction conditions and protecting groups brought the ratio up to 1.25:1, but no higher. Hence, while the methodology described in this project appears to be reasonably versatile in that it allows for easy access to the prostaglandin lactone precursors, there is still the need to improve the selectivity. We will still continue to look into different conditions that may enhance the diastereoselectivity with respect to the hetero Pauson-Khand reaction.
2.15 Experimental Section

2.15.1 General Methods

All experiments were performed under a nitrogen atmosphere in oven- and/or flame-dried glassware using a Vacuum Atmospheres dry-box or by using standard Schlenk techniques. Solvents used as reaction media were distilled immediately before use: Et$_2$O, THF, benzene and toluene were distilled from Na/benzophenone ketyl. Pentane is distilled from Na/benzophenone ketyl/tetraglyme. DCM was distilled from calcium hydride. Carbon monoxide of 2.3 grade (99.3%) was purchased from BOC Gases, New Jersey. Cp$_2$Ti(PMe$_3$)$_2$ and PMe$_3$ were prepared as described in literature. Titanocene dichloride was purchased from Alfa Chemicals. Other reagents were purified by simple distillation or by passing through a short column of activated alumina or silica gel.

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker 250 and 300 MHz spectrometers in deuterated solvents using the solvent carbon or residual protons (CHCl$_3$: 7.27 ppm $^1$H, 77.23 ppm $^{13}$C, C$_6$D$_6$: 7.15 ppm $^1$H, 128.0 ppm $^{13}$C) as an internal reference. NMR solvents were dried over 4Å molecular sieves or by passing through a short column of activated alumina. Chemical shifts ($\delta$) are given in parts per million down from tetramethylsilane (TMS). Data for 1H NMR spectra are 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, m = multiplet), coupling constant (Hz), and integration. Elemental analyses (%C, %H) were determined by Huffman Laboratories, Inc., Golden, Colorado. Analytical thin layer chromatography (TLC) was performed on
Scientific Adsorbent Company Inc. silica gel plates. Components were visualized by illumination with long wave ultraviolet light, exposure to iodine vapor, or by standing with one of the following reagents (followed by heating): \( p \)-anisaldehyde (or vanillin) in ethanol/sulfuric acid and 7\% phosphomolybdic acid in ethanol. Solvents for extraction and chromatography were reagent grade and used as received. Flash column chromatography was performed using Scientific Adsorbent Company Inc. silica gel (32-63 m). Brine refers to a saturated aqueous solution of NaCl. NH\(_4\)Cl and NaHCO\(_3\) refer to saturated aqueous solutions unless otherwise specified.

### 2.15.2 Preparative Procedures

\[
\text{MgBr} + \text{O}_{\text{II}} \xrightarrow{\text{THF-Et}_2\text{O}} \text{OH}
\]

**Penta-1,4-dien-3-ol (2.1j).** 2.1j was prepared from vinylmagnesium bromide 2.1i (66.9 g, 510.0 mmol), and acrolein 2.1g (23.6, 420.0 mmol) in THF/ether (4:1) at -15 °C for 3 h. After quenching the reaction mixture with saturated ammonium chloride at 0 °C, followed by filtering off the inorganic precipitate on Celite. 2.1j was obtained by fractional distillation; 23.7 g (67\%), b.p. 116 °C/760 mm Hg. \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta\) 5.90-5.81 (m, 2H), 5.29-5.11 (m, 4H), 4.60 (m, 1H), 1.77 (br s, 1H); \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)): \(\delta\) 139.5, 115.7, 74.4.

\[
\text{OH} \xrightarrow{48\% \text{ HBr}} \text{Br}
\]

**\((E)\)-5-bromopenta-1,3-diene (2.1k).** 41.1 mL of a 48\% aqueous solution of HBr was added dropwise to a neat pre-cooled solution (0 °C) of 2.1j (20.4 g, 242.7 mmol). After the resulting yellow solution was stirred for 1 h, ether (100 mL) was added. The organic
layer was extracted and washed with NaHCO₃ (100 mL). The organic layer was dried with Na₂SO₄ and distilled (54-55 °C/34 mm Hg) to give 24.9 g (70 %) of 2.1k. ¹H NMR (300 MHz, CDCl₃): δ 6.37-6.32 (m, 2H), 5.95-5.87 (m, 1H), 5.39-5.19 (m, 2H), 4.08-4.05 (d, J = 7.78 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 135.6, 135.4, 129.5, 119.8, 33.2.

2-Phenyl-1,3-dioxane (2.1c). 1,3-Propanediol 2.1a (76.1 g, 1 mmol) was dissolved in toluene (250 mL) and treated with benzaldehyde 2.1b (106 g 1 mmol) and a catalytic amount of p-toluenesulfonic acid monohydrate (300 mg). The resulting solution was stirred at reflux under a Dean-Stark trap until the theoretical amount of water had separated (3 h). The acetal was extracted with ether (3 x 100 mL) and washed with NaHCO₃ (100 mL). It was then dried over MgSO₄, filtered and concentrated under reduced pressure to yield 157 g (96%) of 2.1c as a white crystalline solid. The crude acetal was used directly in the subsequent reduction. ¹H NMR (250 MHz, CDCl₃): δ 7.49-7.45 (m, 2H), 7.36-7.32 (m, 3H), 5.49 (s, 1H), 4.29-4.22 (dd, J = 11.9 Hz, J = 5.0 Hz, 2H), 4.03-3.92 (td, J = 12.3 Hz, J = 2.5 Hz, 2H), 2.36-2.10 (m, 1H), 1.46-1.39 (dt, J = 13.5 Hz, J = 1.35 Hz, 1H); ¹³C NMR (62.5 MHz, CDCl₃): δ 139.1, 129.2, 128.7, 126.4, 102.4, 67.8.
3-(Benzyloxy)propan-1-ol (2.1d). To a neat sample of 2.1c (6 g, 36.5 mmol) in a round-bottom flask, was added 219 mL, (219 mmol) of 1M BH₃·THF, while cooling the solution with an ice bath. The mixture was stirred overnight and then quenched slowly by adding 50 mL of water. The reaction mixture was then filtered through Celite and the combined filtrate and washings were concentrated to 6.0 g (99%). This was used without purification in the following step. ¹H NMR (250 MHz, CDCl₃): δ 7.36-.29 (m, 5H), 4.50 (s, 2H), 3.80-3.73 (q, J = 5.5 Hz, 2H), 3.67-3.62 (t, J = 11.5 Hz, 2H), 2.30-2.25 (t, J = 5.5 Hz, 1H), 1.81-1.80 (m, 2H); ¹³C NMR (62.5 MHz, CDCl₃): δ 138.4, 128.8, 128.1, 128.1, 73.7, 69.9, 62.4, 32.5.

3-(Benzyloxy)propanal (2.1f). To a suspension of PCC (11.7 g, 54.6 mmol) in CH₂Cl₂ was added neutral Al₂O₃ (11.7 g) at room temperature. After 30 min stirring, the alcohol 2.1d (4.5 g, 27.3 mmol) was added, and then further stirring for 2 h during which time the reaction mixture turned a dark black in color. The reaction mixture was diluted with ether and filtered through a plug of dry silica gel. The solvent was evaporated under reduced pressure. Purification by column chromatography (silica gel, pentane/ethyl ether, 80/20) yielded the product 2.1f (4.03 g, 90%) as a colorless liquid. ¹H NMR (250 MHz, CDCl₃): δ 9.79-9.77 (t, J = 1.77 Hz, 1H), 7.33-7.24 (m, 5H), 4.51 (s, 2H), 3.82-3.77 (t, J = 6.1 Hz, 2H), 2.71-2.65 (td, J = 6.0 Hz, J = 1.8 Hz, 2H); ¹³C NMR (62.5 MHz, CDCl₃): δ 201.6, 138.2, 128.8, 128.2, 128.1, 73.6, 64.24, 44.3.
1-(Benzyloxy)-4-vinylhex-5-en-3-ol (2.1l). Indium powder, (100 mesh, 4.26 g, 37.1 mmol) was added to a solution of 2.1k (10.9 g, 74.2 mmol) in DMF (60 mL). The solution was cooled to 0 °C and the carbonyl compound 2.1f (6.1 g, 37.1 mmol) in DMF (30 mL) was added. The reaction was stirred for 3 h at 0 °C, then diluted with water (50 mL) and extracted with ether (3 x 50 mL). The organic extracts were washed with a saturated solution of CuSO₄ (100 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (silica gel, hexanes/EtOAc, 95:05) yielded the product 2.1l (8.45 g, 98%) as a colorless oil. ¹H NMR (250 MHz, CDCl₃): δ 7.39-7.33 (m, 5H), 5.90-5.80 (m, 2H), 5.20-5.09 (m, 4H), 4.52 (s, 2H), 3.81-3.65 (m, 3H), 2.85-2.80 (m, 2H), 1.81-1.74 (m, 2H); ¹³C NMR (62.5 MHz, CDCl₃): δ 138.3, 138.0, 137.5, 128.8, 128.1, 117.4, 117.1, 73.7, 73.2, 69.4, 55.2, 34.2.

4-(Penta-1,4-dien-3-yl)-2-phenyl-1,3-dioxane (2.1p). In a 50 mL round-bottom flask, DDQ (4.77 g, 21.0 mmol) and Na₂SO₄ (5 g) were suspended in DCM (100 mL) and stirred for 1 h. Alcohol 2.1l (4.887 g, 21.0 mmol) in DCM (10 mL) was cannulated into the DDQ mixture. The reaction mixture immediately turned greenish-black, then faded to a chocolate brown after about 10 min. The reaction was quenched after 3 h with the
addition of sat. Na$_2$SO$_3$ (50 mL). The mixture was stirred until the solution became yellow. The slurry was then filtered through a Celite pad and rinsed multiple times with ether (50 mL total) and sat. NaHCO$_3$ (50 mL total). The aqueous layer was reextracted with ether (3 x 20 mL). The combined ethereal layers were washed with sat. NaHCO$_3$ (30 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Column chromatography (silica gel, hexanes/EtOAc, 95:05) yielded the purified product 2.1p (1.45 g, 30%) as a colorless oil. $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 7.51-7.34 (m, 5H), 6.05-5.80 (m, 2H), 5.51 (s, 1H), 5.18-5.10 (m, 4H), 4.27-4.20 (m, 1H), 4.01-3.84 (m, 2H), 3.01-2.95 (m, 1H), 1.92-1.82 (m, 2H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 139.2, 137.3, 137.2, 129.0, 128.5, 126.4, 117.3, 117.0, 101.4, 67.4, 53.5, 29.3. Anal. Calcd for C$_{15}$H$_{18}$O$_2$: C, 78.23; H, 7.88; Found: C, 78.21; H, 7.84.

3-(Benzyloxy)-4-vinylhex-5-en-1-ol (2.1q). To a solution of 2.1p (2.0 g, 8.68 mmol) in DCM (50 mL) at -78 °C was added dropwise a solution of DIBAL (52.1 mL, 1.0 M solution in hexanes, 52.1 mmol). After 3 h at -78 °C, the cold reaction mixture was poured into a saturated aqueous solution of Rochelle’s salt (20 mL). The mixture was diluted with DCM (20 mL) and after 2 h of stirring at room temperature, the two phases were separated. The aqueous layer was extracted with more DCM (20 mL) and the combined organic extracts were washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. Column chromatography (silica gel,
hexanes/EtOAc, 70:30) yielded the purified product 2.1q (1.99 g, 99%) as a colorless oil.

\[ ^1H \text{ NMR (250 MHz, CDCl}_3\]: } \delta 9.78-9.77 (t, J = 1.67 Hz, 1H), 7.32 (s, 5H), 5.91-5.82 (m, 2H), 5.21-5.11 (m, 4H), 4.66-4.53 (q, J = 11.3 Hz, 2H), 4.05-4.02 (m, 1H), 3.14-3.11 (m, 1H), 2.70-2.60 (m, 2H);

\[ ^{13}C \text{ NMR (62.5 MHz, CDCl}_3\]: } \delta 138.5, 137.5, 137.3, 128.9, 128.3, 128.2, 117.3, 117.2, 81.1, 72.3, 61.0, 51.4, 34.0. Anal. Calcd for C\textsubscript{15}H\textsubscript{20}O\textsubscript{2}: C, 77.55; H, 8.68; Found: C, 77.22; H, 8.69.

3-(Benzyloxy)-4-vinylhex-5-enal (2.1r). The procedure analogous to that used for 2.1f afforded the product 2.1r (1.42 g, 90% yield from the alcohol 2.1q on a 6.86 mmol scale) as a colorless oil. Column chromatography (silica gel, hexanes/EtOAc, 90:10). \(^1\)H NMR (250 MHz, CDCl_3): \(\delta 7.35\) (s, 5H), 6.05-5.79 (m, 2H), 5.19-5.09 (m, 4H), 4.72-4.50 (m, 2H), 3.76-3.69 (m, 3H), 3.10-3.25 (m, 1H), 1.81-1.74 (q, \(J = 6.23\) Hz, 2H); \(^{13}C\) NMR (62.5 MHz, CDCl_3): \(\delta 201.5, 138.4, 137.0, 136.8, 128.8, 128.2, 128.1, 117.9, 117.8, 77.3, 72.6, 52.0, 46.6.

**Metallacycles (2.1s) and (2.1t).** To a solution of \(\text{Cp}_2\text{Ti(PMe}_3)_2\) (0.43 g, 1.3 mmol) in THF (5 mL) was added enal 2.1r (0.3 g, 1.3 mmol) inside an argon filled glove box.
After stirring for 2 h at room temperature, the reaction mixture was filtered through a pad of Celite and rinsed with pentane to give a reddish-brown solution. THF was removed under reduced pressure and the reddish-brown solid residue was obtained as the inseparable 1:1 mixture of compound 2.1s and 2.1t (0.329 g, 91%). H NMR (300 MHz, C₆D₆): δ 7.53-7.46 (m, 4H), 7.34-7.28 (m, 4H), 7.25-7.21 (m, 2H), 6.42-6.32 (m, 1H), 5.98 (s, 10H), 5.93 (s, 5H), 5.92 (s, 5H) 5.44-5.26 (m, 5H), 4.93-4.90 (m, 1H), 4.67-4.58 (m, 2H), 4.54-4.38 (m, 2H), 4.02-3.93 (m, 2H), 3.42-3.35 (m, 2H), 3.01-2.85 (m, 2H), 2.76-2.70 (m, 1H), 2.30-2.24 (m, 2H), 2.98-2.89 (m, 1H), 2.80-2.70 (m, 1H), 1.37-1.26 (m, 2H), 1.28-1.20 (m, 2H); ¹³C NMR (75 MHz, C₆D₆): δ 141.4, 139.9, 139.8, 139.4, 132.6, 114.3, 114.0, 112.4, 112.3, 83.9, 82.1, 81.9, 81.1, 71.6, 71.0, 68.5, 68.4, 63.4, 62.7, 54.5, 53.8, 41.9, 41.6, 34.5, 22.6, 14.2.

(3aS,4S,5S,6aR)-5-(benzyloxy)-4-vinyl-hexahydrocyclopenta[b]furan-2-one (2.1u) and 3aR,4R,5S,6aS)-5-(benzyloxy)-4-vinyl-hexahydrocyclopenta[b]furan-2-one (2.1v). A glass (max. pressure: 70 psi) high pressure reactor was charged with the metallacyclic compounds 2.1s and 2.1t (0.25 g, 0.898 mmol) and pentane (20 ml), inside an argon filled glove box. After removing the reactor from the glove box, CO (20 psi) was introduced into the reactor. The reaction mixture was stirred for 12 h at room temperature, and then CO pressure was cautiously released inside a fume hood. The reaction mixture was filtered through a pad of silica gel, washed with Et₂O (25 ml). A solution of the product in Et₂O was stirred for 1h, and then concentrated under reduced
pressure. The crude residue was chromatographed on silica gel (hexanes/EtOAc, 80:20) yielded the titled lactones 2.1u (0.073 g, 41%) and 2.1v (0.072 g, 40%) in a 1:1 ratio as oils. Lactone 2.1u: $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.34-7.25 (m, 5H), 6.06-5.94 (m, 1H), 5.18-5.11 (m, 2H), 5.06-5.02 (m, 1H), 4.55-4.41 (m, 2H), 4.05-4.02 (m, 1H), 2.94-2.87 (m, 1H), 2.78-2.29 (m, 2H), 2.54-2.46 (m, 1H), 2.32-1.96 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 178.5, 139.7, 136.8, 129.9, 129.2, 118.2, 85.3, 84.8, 72.9, 57.0, 43.6, 38.5, 36.4. Lactone 2.1v: $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.40-7.30 (m, 5H), 5.78-5.67 (m, 1H), 5.31-5.12 (m, 2H), 5.00-4.95 (m, 1H), 4.62-4.48 (m, 2H), 3.88-3.82 (m, 1H), 2.83-2.49 (m, 4H), 2.35-2.14 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 178.5, 139.5, 139.2, 129.2, 118.2, 85.3, 84.8, 72.9, 57.0, 43.6, 38.5, 36.4.

2-(4-Methoxyphenyl)-1,3-dioxane (2.2b). The procedure analogous to that used for 2.1c afforded the product 2.2b (118 g, 92% yield from 2.2a on a 661 mmol scale) as white crystals. Recrystallization (hexanes/EtOAc, 70:30). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 7.44-7.40 (d, $J = 7.10$ Hz, 2H), 6.91-6.88 (d, $J = 7.10$ Hz, 2H), 5.46 (s, 1H), 4.29-4.22 (dd, $J = 13.0$ Hz, $J = 4.9$ Hz, 2H), 4.03-3.92 (td, $J = 12.3$ Hz, $J = 2.5$ Hz, 2H), 3.80 (s, 3H), 2.25-2.19 (m, 1H), 1.47-1.40 (m, 1H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 160.3, 131.7, 127.7, 114.0, 101.9, 67.8, 55.7, 26.2.
3-(4-Methoxybenzyloxy)propan-1-ol (2.2c). The procedure analogous to that used for 2.1d afforded the product 2.2c (70.5 g, 98% yield from 2.2b on a 367 mmol scale) as colorless oil. Column chromatography (silica gel, hexanes/EtOAc, 55:45). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 7.26-7.21 (d, $J = 11.4$ Hz, 2H), 6.89-6.84 (d, $J = 11.4$ Hz, 2H), 4.43 (s, 2H), 3.78 (s, 3H), 3.75-3.70 (t, $J = 5.7$ Hz, 2H), 3.63-3.58 (t, $J = 5.8$ Hz, 2H), 1.87-1.78 (m, 2H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 159.6, 130.6, 129.7, 114.1, 73.3, 69.2, 61.8, 55.6, 32.6.

3-(4-Methoxybenzyloxy)propanal (2.2d). The procedure analogous to that used for 2.1f afforded the product 2.2d (10.0 g, 92% yield from the alcohol 2.2c on a 56 mmol scale) as a colorless oil. Column chromatography (silica gel, hexanes/EtOAc, 70:30). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 9.79-9.78 (t, $J = 1.8$ Hz, 1H), 7.27-7.23 (d, $J = 11.4$ Hz, 2H), 6.91-6.86 (d, $J = 11.4$ Hz, 2H), 4.46 (s, 2H), 3.81 (s, 3H), 3.81-3.76 (m, 2H), 2.71-2.66 (m, 2H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 201.6, 159.7, 130.3, 129.7, 114.3, 73.3, 63.9, 55.7, 44.3.
**1-(4-Methoxybenzyloxy)-4-vinylhex-5-en-3-ol (2.2e).** The procedure analogous to that used for 2.1l afforded the product 2.2e (7.93 g, 96% yield from the aldehyde 2.2d on a 31.4 mmol scale) as a colorless oil. Column chromatography (silica gel, hexanes/EtOAc, 80:20). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 7.26-7.23 (d, $J = 8.7$ Hz, 2H), 6.89-6.85 (d, $J = 8.7$ Hz, 2H), 5.97-5.75 (m, 2H), 5.18-5.06 (m, 4H), 4.45 (s, 2H), 3.80 (s, 3H), 3.70-3.61 (m, 3H), 2.86-2.85 (d, $J = 2.9$ Hz, 1H), 2.90-2.70 (m, 1H), 1.82-1.65 (m, 2H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 159.6, 138.0, 137.6, 130.4, 129.7, 117.4, 117.1, 114.2, 73.3, 69.1, 55.6, 55.1, 34.3.

**tert-Butyl(1-(4-methoxybenzyloxy)-4-vinylhex-5-en-3-yloxy)diphenylsilane (2.2f).** To a solution of 2.2e (3.62 g, 13.7 mmol) in dry DCM (30 mL) was added imidazole (1.87 g, 27.5 mmol) followed by the addition of TBDPSCI (4.93 g, 17.9 mmol). The reaction mixture was stirred at room temperature for 12 h under an atmosphere of nitrogen. The reaction mixture was diluted with DCM (25 mL) and washed successively with water, brine and dried over Na$_2$SO$_4$. The organic layer was evaporated under reduced pressure. Column chromatography (silica gel, hexanes/EtOAc, 95:05) yielded the purified product 2.2f (6.42 g, 93%) as a colorless oil. $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 7.66-7.63 (m, 4H), 7.37-7.32 (m, 6H), 7.10-7.06 (d, $J = 8.6$ Hz, 2H), 6.82-6.79 (d, $J = 8.6$ Hz, 2H), 5.94-5.81
(m, 2H), 5.06-4.83 (m, 4H), 4.14 (s, 2H), 3.92-3.90 (m, 1H), 3.78 (s, 3H), 3.33-3.22 (m, 2H), 2.89-2.79 (m, 1H), 1.77-1.69 (m, 2H), 1.03 (s, 9H); $^1$C NMR (62.5 MHz, CDCl$_3$): \( \delta 159.4, 138.6, 137.2, 136.5, 136.4, 134.9, 134.3, 131.0, 130.0, 129.9, 129.5, 127.9, 127.8, 117.4, 116.4, 114.0, 74.3, 72.6, 67.2, 55.6, 53.6, 34.5, 27.5, 20.0. 

3-(tert-Butyldiphenylsilyloxy)-4-vinylhex-5-en-1-ol (2.2g). To a solution of 2.2f (4.89 g, 9.7 mmol) in a mixture of DCM and water (20:1, 68 mL) was added DDQ (3.32 g, 14.6 mmol) and the reaction mixture stirred at room temperature for 5 h. The reaction mixture was then diluted with DCM (30 mL) and washed successively with aqueous NaHCO$_3$, water, brine and dried over Na$_2$SO$_4$. The organic layer was evaporated under reduced pressure to yield the crude product mixture which was purified by silica gel chromatography using (hexanes/EtOAc, 90:10) to yield 3.32 g (90%) of 2.2g. $^1$H NMR (250 MHz, CDCl$_3$): \( \delta 7.72-7.67 \) (m, 4H), 7.41-7.36 (m, 6H), 6.05-5.67 (m, 2H), 5.27-4.92 (m, 4H), 3.98-3.91 (m, 1H), 3.53-3.46 (m, 2H), 2.93-2.87 (m, 1H), 1.72-1.63 (m, 2H), 1.07 (s, 9H); $^1$C NMR (62.5 MHz, CDCl$_3$): \( \delta 138.1, 137.3, 136.5, 136.4, 134.5, 134.1, 130.2, 130.1, 128.0, 117.5, 116.7, 74.3, 60.0, 53.6, 36.8, 27.5, 19.9, 14.6. 

3-(tert-Butyldiphenylsilyloxy)-4-vinylhex-5-enal (2.2h). The procedure analogous to that used for 2.1f afforded the product 2.2h (1.22 g, 88% yield from the alcohol 2.2g on a 3.67 mmol scale) as a colorless oil. Column chromatography (silica gel, hexanes/EtOAc,
95:05). \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta\) 9.53-9.51 (t, \(J = 2.1\) Hz, 1H), 7.72-7.63 (m, 4H), 7.45-7.36 (m, 6H), 6.01-5.70 (m, 2H), 5.16-4.90 (m, 4H), 4.32-4.28 (m, 1H), 2.92-2.90 (m, 1H), 2.51-2.47 (m, 2H), 1.06 (s, 9H); \(^1\)C NMR (62.5 MHz, CDCl\(_3\)): \(\delta\) 201.5, 137.3, 136.5, 136.3, 134.1, 133.6, 130.3, 128.0, 118.3, 117.6, 72.0, 54.1, 48.6, 27.4, 19.8.

\[
\begin{array}{c}
\text{TBDPSO} - \text{Cp}_2\text{Ti(PMe}_3\text{)}_2 \\
\downarrow \quad \downarrow \\
\text{Pentane} \\
\quad \quad \quad 25^\circ \text{C}
\end{array}
\]  

2.2h → 2.2i + 2.2j

**Metallacycles (2.2i and 2.2j).** The procedure analogous to that used for (2.1s) and (2.1t) afforded the reddish-brown solid residue as a 2:1 mixture of compounds 2.2i and 2.2j (0.322 g, 88% combined yield from 2.2h on a 0.86 mmol scale). \(^1\)H NMR (250 MHz, C\(_6\)D\(_6\)): \(\delta\) 7.92-7.88 (m, 6H), 7.32-7.28 (m, 4H), 6.20-6.40 (m, 1H), 5.88 (s, 5H), 5.87 (s, 5H), 5.81 (s, 5H), 5.76 (s, 5H), 5.76-5.68 (m, 1H), 5.40-5.17 (m, 4H), 4.54-4.52 (m, 1H), 3.92-3.89 (m, 1H), 3.64-3.60 (m, 1H), 3.36-3.27 (m, 1H), 2.90-2.86 (m, 1H), 2.76-2.68 (m, 1H), 2.48-2.47 (m, 1H), 1.96-1.87 (m, 2H), 1.54-1.47 (m, 1H), 1.22-1.04 (m, 6H), 1.33 (s, 9H), 0.95 (s, 9H); \(^1\)C NMR (75 MHz, C\(_6\)D\(_6\)): \(\delta\) 142.5, 141.2, 138.0, 137.7, 136.5, 131.2, 116.4, 115.8, 115.5, 115.3, 113.6, 85.2, 82.7, 77.9, 76.9, 69.7, 69.1, 67.8, 65.0, 55.7, 55.4, 46.6, 46.4, 28.7, 24.1, 23.3, 21.0, 20.8.

\[
\begin{array}{c}
2.2i + 2.2j \\
\text{24 h} \\
\quad \quad \quad 25^\circ \text{C}
\end{array}
\]  

\[
\begin{array}{c}
\text{TBDPSO} \\
\quad \quad \quad 25^\circ \text{C}
\end{array}
\]  

2.2i + 2.2j → 2.2k + 2.2l

1.25:1
(3aS,4S,5S,6aR)-5-(tert-butylidiphenylsilyloxy)-4-vinyl-hexahydrocyclopenta[b]furan-2-one (2.2k) and (3aR,4R,5S,6aS)-5-(tert-butylidiphenylsilyloxy)-4-vinyl-hexahydrocyclopenta[b]furan-2-one (2.2l). The procedure analogous to that used for 2.1u and 2.1v afforded the clear oils 2.2k (0.089 g, 39%) and 2.2l (0.071 g, 31%) in a 1.25:1 ratio from the metallacycles 2.2i and 2.2j on a 0.70 mmol scale. Column chromatography (silica gel, hexanes/EtOAc, 90:10). Lactone 2.2k: \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta\) 7.60-7.58 (m, 4H), 7.44-7.35 (m, 6H), 5.12-4.94 (m, 1H), 5.12-4.94 (m, 3H), 4.41 (m, 1H), 3.04-2.94 (m, 1H), 2.77-2.26 (m, 2H), 2.15-2.04 (m, 2H), 1.78-1.69 (m, 1H), 1.04 (s, 9H); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 177.0, 137.4, 137.3, 137.2, 135.6, 134.7, 131.4, 131.3, 129.3, 129.2, 119.0, 79.2, 57.4, 43.1, 43.8, 34.8, 28.5, 20.9, 0.9. Lactone 2.2l: \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta\) 7.65-7.62 (m, 4H), 7.43-7.32 (m, 6H), 5.45-5.34 (m, 1H), 4.99-4.91 (m, 2H), 4.83-4.77 (m, 1H), 3.99-3.92 (m, 1H), 2.75-2.67 (m, 1H), 2.59-2.45 (m, 3H), 2.02-1.97 (m, 2H), 1.02 (s, 9H); \(^1^3\)C NMR (62.5 MHz, CDCl\(_3\)): \(\delta\) 177.39, 137.8, 136.4, 136.3, 134.0, 133.7, 130.2, 128.0, 117.2, 83.7, 78.8, 77.6, 58.4, 42.0, 40.7, 35.2, 27.2, 19.4, 0.39.

![TBSOOH](image)

3-(tert-Butyldimethylsilyloxy)propanal (2.3i). The procedure analogous to that used for 2.1f afforded the product 2.3i (8.71 g, 89% yield from the alcohol 2.3h on a 52.5 mmol scale) as a colorless oil. Column chromatography (silica gel, Pentane/ethyl ether, 95:05). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 9.81-9.80 (d, \(J=2.0\) Hz, 1H), 4.01-3.97 (t, \(J=12.0\) Hz,
2H), 2.62-2.58 (m, 2H), 0.88 (s, 9H), 0.07 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 203.6, 58.9, 48.1, 27.4, 19.7, -3.8.

**1-((tert-Butyldimethylsilyloxy)-4-vinylhex-5-en-3-ol (2.3j).** The procedure analogous to that used for 2.11 afforded the product 2.3j (5.00 g, 92% yield from the aldehyde 2.3i on a 21.2 mmol scale) as a colorless oil. Column chromatography (silica gel, hexanes/EtOAc, 95:05). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.98-5.82 (m, 2H), 5.19-5.10 (m, 4H), 3.93-3.80 (m, 3H), 3.29 (br s, 1H), 2.87-2.80 (m, 1H), 1.75-1.64 (m, 2H), 0.92 (s, 9H), 0.09 (s, 6H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 138.2, 137.7, 117.1, 116.9, 74.0, 62.9, 55.1, 36.3, 26.2, 18.5, -5.1.

**Triphenylmethylium perchlorate (2.3c).** Triphenylcarinol 2.3b (10 g, 38.4 mmol) was reacted with 70% HClO$_4$ (12.92 mL) in 100 mL of acetic anhydride. The acid was added drop-wise from an addition funnel to the alcohol, which had been dissolved in the anhydride by gentle warming with a heat gun. The mixture was stirred rapidly with a magnetic stirrer and cooled in ice water during the addition to maintain the reaction temperature between 10 and 20 °C. After addition was complete, the mixture was stirred for an additional 1 h in the ice bath to assure complete precipitation of the product. The
stirring was ended, and the product was allowed to settle. The supernatant liquid was
drawn off with a pipet, and the yellow solid was washed with 20 mL portions of
anhydrous diethyl ether until the ether washing was colorless. After each washing, the
ether was decanted. The remaining solid was then placed under high vacuum for 24 h to
rid the solid of residual ether, acetic anhydride, and acetic acid. The product 2.3c (12.39 g
91%) was stored in a light-tight flask under nitrogen atmosphere in the refrigerator as
bright yellow powder.

\[
\begin{align*}
\text{TBSO} & - \text{OH} \quad \text{Ph}_3\text{C}^\ominus \text{ClO}_4^\ominus \\
& \quad \text{Collidine} \\
& \quad \text{DMAP} \\
& \quad \text{DCM} \\
\end{align*}
\]

\[
\begin{align*}
2.3c & \quad \text{TBSO} - \text{OCPh}_3 \\
& \quad \text{TBSO} - \text{OCPh}_3
\end{align*}
\]

*tert*-Butyldimethyl(3-(trityloxy)-4-vinylhex-5-enyloxy)silane (2.3k). A solution of 2.3j
(1.92 g, 7.5 mmol), 2.3c (8.00 g, 22.5 mmol) and DMAP (0.84 g, 7.5 mmol) in DCM (30
mL) and 2,4,6-collidine (4.55 g, 37.5 mmol) was kept for 24 h at ambient temperature.
Then ether (100 mL) was added and the precipitate that crushed out was filtered through
Celite. The organic filtrate was washed with a saturated solution of CuSO₄ (3 x 100 mL),
dried with Na₂SO₄, filtered and concentrated under reduced pressure. Column
chromatography (silica gel, hexanes/EtOAc, 97:03) yielded the purified product 2.3k
(2.69 g, 72%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 7.53-7.51 (m, 6H), 7.34-
7.25 (m, 9H), 6.05-5.82 (m, 2H), 5.18-4.85 (m, 4H), 3.52-3.42 (m, 2H), 3.37-3.29 (m,
1H), 2.62-2.59 (m, 1H), 1.78-1.73 (m, 2H), 0.83 (s, 9H), -0.03 (s, 6H); ¹³C NMR (75
MHz, C₆D₆): δ 147.1, 140.2, 139.1, 130.9, 129.3, 128.7, 118.5, 117.7, 88.4, 76.5, 62.3,
53.1, 37.3, 27.7, 19.9, -3.5.
3-(Trityloxy)-4-vinylhex-5-en-1-ol (2.3d). Into a 50 mL round-bottom flask was placed 2.3k (2.0 g, 4.0 mmol) and THF (20 mL). To this stirred solution was added TBAF (4.81 mL of 1.0 M solution in THF, 4.81 mmol). The solution was stirred for 4 h at room temperature before quenching the reaction with saturated ammonium chloride. The mixture was poured into a separatory funnel containing 10 mL of water and 10 mL of diethyl ether. The organic layer was extracted twice more with 10 mL portions of water. The combined aqueous layers were then back extracted with 20 mL of diethyl ether. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Column chromatography (silica gel, hexanes/EtOAc, 85:15) yielded the purified product 3.5a (1.30 g, 85%) as a colorless liquid. 

\[
\begin{align*}
\text{H NMR (250 MHz, CDCl₃): } & \delta 7.55-7.52 (m, 6H), 7.34-7.25 (m, 9H), 6.12-5.69 (m, 2H), 5.18-4.84 (m, 4H), 3.52-3.45 (m, 3H), 2.71-2.68 (m, 1H), 1.77-1.67 (m, 2H); \\
\text{C NMR (62.5 MHz, CDCl₃): } & \delta 145.5, 138.1, 137.7, 129.7, 128.1, 127.5, 117.3, 116.9, 87.4, 75.1, 60.8, 51.5, 35.3.
\end{align*}
\]

3-(Trityloxy)-4-vinylhex-5-en-1-ol (2.3d). The procedure modified (NaOAc, equivalent in weight to PCC) to that used for 2.1f afforded the product 2.3l (0.23 g, 83% yield from the alcohol 2.3d on a 0.861 mmol scale) as a colorless oil. Column chromatography (silica gel, hexanes/EtOAc, 95:05). 

\[
\begin{align*}
\text{H NMR (250 MHz, CDCl₃): } & \delta 9.46-9.44 (m, 1H), 7.49-7.46
\end{align*}
\]
(m, 6H), 7.32-7.24 (m, 9H), 5.99-5.57 (m, 2H), 5.18-4.83 (m, 4H), 4.05-4.00 (m, 1H), 2.68-2.60 (m, 1H), 2.45-2.29 (m, 2H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): δ 201.6, 144.9, 137.0, 136.7, 129.4, 128.2, 127.7, 118.2, 117.9, 87.7, 72.3, 52.5, 46.8.

(3aR,4R,5R,6aS)-5-(trityloxy)-4-vinyl-hexahydrocyclopenta[b]furan-2-one (2.3m) and (3aS,4S,5R,6aR)-5-(trityloxy)-4-vinyl-hexahydrocyclopenta[b]furan-2-one (2.3n) and (3aS,4R,5R,6aR)-5-(trityloxy)-4-vinyl-hexahydrocyclopenta[b]furan-2-one (2.3o). The first part of this procedure is analogous to that used for 2.1s and 2.1t afforded metallacycles (0.58 g, 81% combined yield from the enal 2.3l on a 1.6 mmol scale) as a red solid. We then used the red solid directly in the next step. The second procedure is analogous to that used for 2.1u and 2.1v afforded the white solids 2.3m (0.155 g, 37%), 2.3n and 2.3o (0.15 g, 37%) in a 2:1:1 ratio from the metallacycles mixture on a 1.3 mmol scale. Column chromatography (silica gel, hexanes/EtOAc, 80:20). Lactone 2.3m: $^1$H NMR (250 MHz, CDCl$_3$): δ 7.51-7.47 (m, 6H), 7.30-7.21 (m, 9H), 5.48-5.30 (m, 1H), 4.98-4.82 (m, 3H), 3.99-3.96 (m, 1H), 2.73-2.47 (m, 3H), 2.08-1.60 (m, 3H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): δ 171.6, 144.86, 138.4, 129.3, 128.3, 127.5, 116.5, 88.2, 84.7, 80.3, 56.6, 42.0, 39.2, 35.5. Mixture of lactones 2.3n and 2.3o: $^1$H NMR (250 MHz, CDCl$_3$): δ 7.47-7.43 (m, 12H), 7.30-7.25 (m, 18H), 6.18-6.04 (m, 1H), 5.43-4.78 (m, 7H), 4.24-4.17 (m, 1H), 4.07-4.02 (m, 1H), 3.13-1.52 (m, 12H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): δ 177.6, 177.4, 144.8, 137.0, 135.3, 129.3, 129.2, 128.3, 127.7,
1-(tert-Butyldimethylsilyloxy)-4-vinylhex-5-en-3-yl methanesulfonate (2.5a). To a solution of 2.3j (5.0 g, 19.4 mmol) and Et₃N (6.79 mL, 48.7 mmol) in DCM (50 mL) was added MsCl (3.34 g, 29.2 mmol) at 0 °C. The reaction mixture was stirred for 3 h, and ether added (50 mL). The precipitate formed was filtered through Celite and the filtrate was washed with a saturated solution of CuSO₄ (2 x 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, hexanes/EtOAc, 90:10) yielded the purified product 2.3k (5.21 g, 82%) as a colorless oil. \(^{1}H\) NMR (250 MHz, CDCl₃): \(\delta\) 5.84-5.68 (m, 2H), 5.21-5.11 (m, 4H), 4.90-4.87 (m, 1H), 3.71-3.66 (m, 2H), 3.26-3.18 (m, 1H), 2.99 (s, 3H), 1.88-1.79 (m, 2H), 0.86 (s, 9H), 0.03 (s, 6H); \(^{13}C\) NMR (62.5 MHz, CDCl₃): \(\delta\) 135.9, 135.4, 118.8, 118.5, 82.5, 59.0, 52.2, 38.8, 34.9, 26.4, 18.5, -4.9.

4-Vinylhex-5-en-1-ol (2.5b). To an ice-cooled and stirred suspension of LAH (1.57 g, 41 mmol) in diethyl ether (50 mL) was added dropwise a solution of 2.5a (2.31 g, 6.9 mmol) in diethyl ether (15 mL). This mixture was allowed to warm to room temperature and stirring was continued for 1.5 h. It was then cooled to 0 °C again, quenched with water, filtered through Celite and the filtrate was concentrated in vacuo. Purification by
column chromatography (silica gel, hexanes/EtOAc, 90:10) yielded the purified product 2.5b (0.557 g, 64%) as a colorless oil. $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 5.79-5.65 (m, 2H), 5.06-4.99 (m, 4H), 3.68-3.61 (m, 2H), 2.74-2.68 (m, 1H), 1.63-1.46 (m, 4H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 141.4, 114.8, 77.6, 63.3, 48.0, 30.8.

4-Vinylhex-5-enal (2.5c). The procedure analogous to that used for 2.1f afforded the product 2.5c (0.977 g, 61% yield from the alcohol 2.5b on a 12.9 mmol scale) as a colorless oil. Column chromatography (silica gel, pentane/ethyl ether, 90:10). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 9.78-9.77 (t, $J$ = 1.1 Hz, 1H), 5.77-5.63 (m, 2H), 5.08-5.01 (m, 4H), 2.78-2.69 (m, 1H), 2.50-2.44 (m, 2H), 1.80-1.71 (m, 2H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 202.6, 140.5, 115.6, 47.5, 42.0, 26.7.

Metallacycle 2.5d. The procedure analogous to that used for metallacycles 2.1s and 2.1t afforded the sole product 2.5d (0.49 g, 87% yield from enal 2.5c on a 3.3 mmol scale) as a red solid. $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 5.95 (s, 5H), 5.91 (s, 5H), 5.24-5.09 (m, 2H), 5.05-4.97 (m, 1H), 3.39-3.32 (m, 1H), 2.89-2.81 (m, 1H), 2.56-2.51 (m, 1H), 1.93-1.86 (m, 2H), 1.64-1.10 (m, 4H); $^{13}$C NMR (62.5 MHz, C$_6$D$_6$): $\delta$ 143.4, 114.2, 112.5, 85.7, 70.8, 58.6, 54.6, 36.8, 30.2.
(3aR,4R,6aS)-4-vinyl-hexahydrocyclopenta[b]furan-2-one (2.5e). The procedure analogous to that used for lactones 2.1u and 2.1v afforded the sole product 2.5e (0.24 g, 68% yield from metallacycle 2.5d on a 2.3 mmol scale) as an oil. Column chromatography was (silica gel, pentane/ethyl ether, 80:20). \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta\) 5.79-5.65 (m, 1H), 5.11-4.94 (m, 2H), 2.80-1.48 (m, 8H); \(^1\)C NMR (62.5 MHz, C\(_6\)D\(_6\)): \(\delta\) 177.4, 139.7, 115.6, 86.6, 50.4, 45.4, 34.5, 32.3, 31.8.

(E)-Pent-2-en-4-yn-1-ol (2.6d). To a suspension of 2.6c (6.0 g, 124.9 mmol) in 100 mL of liquid ammonia was added slowly epichlorohydrin 2.6b (5.78 g, 62.4 mmol) as an ethereal solution. After stirring at -33 °C for 3 h, ether (100 mL) and ammonium chloride (10 mL) were added. The ammonia was allowed to evaporate and the aqueous phase was extracted with (2 x 30 mL) of ether. The combined extracts were dried over MgSO\(_4\), filtered and the ether removed in vacuo. Distillation (68-69 °C at 19 mm Hg yielded the purified product 2.6d (2.45 g, 48%) as a yellow liquid. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 6.44-6.35 (dt, \(J = 15.9\) Hz, \(J = 4.9\) Hz, 1H), 5.82-5.76 (d, \(J = 15.9\) Hz, 1H), 4.27-4.19 (m, 2H), 2.93 (s, 1H); \(^1\)C NMR (62.5 MHz, CDCl\(_3\)): \(\delta\) 144.2, 109.4, 82.0, 78.4, 78.4, 62.7.
(E)-5-(Trimethylsilyl)pent-2-en-4-yn-1-ol (2.6d'). To a cooled (0 °C) THF solution of ethylmagnesium bromide (182 mL, 1.0 M solution in THF, 182 mmol) was added a solution of alcohol 2.6d (5 g, 60.9 mmol) in THF (50 mL). The suspension was stirred overnight at room temperature. The resulting solution was cooled to 0 °C and trimethyl silyl chloride (13.3 g, 121.8 mmol) was added dropwise. After complete addition, the mixture was heated to 50 °C for 2 h. After being cooled to 20 °C, 1N H2SO4 (20 mL) was cautiously added to the suspension. After stirring for 10 min, the reaction mixture was partitioned between ether and a saturated solution of NaHCO3. The organic layer was washed with brine, dried over Na2SO4, filtered and concentrated. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 80:20) yielded the purified product 2.6d' (8.55 g, 91%) as a colorless oil. 1H NMR (250 MHz, CDCl3): δ 6.31-6.21 (dt, J = 15.9 Hz, J = 5.0 Hz, 1H), 5.76-5.69 (d, J = 15.9 Hz, 1H), 4.16-4.14 (m, 2H), 2.36 (br s, 1H), 0.16 (s, 9H); 13C NMR (62.5 MHz, CDCl3): δ 143.3, 110.6, 103.4, 95.5, 63.0, 0.26.

(E)-(5-Bromopent-3-en-1-ynyl)trimethylsilane (2.6e). The alcohol 2.6d' (10 g, 64.8 mmol) was dissolved in dry DCM (100 mL) and cooled to -30 °C under nitrogen. To this stirred solution was added triphenylphosphine (20.4 g, 77 mmol) followed by recrystallized NBS (13.8 g, 77 mmol). The reaction was run for 5 h after which the organic phase was washed with NaHCO3 (2 x 30 mL) and the organic layer was dried (MgSO4), filtered and concentrated. The crude was then treated with hexane (100 mL) which helped to precipitate out triphenylphosphine oxide and succinimide which were
filtered off. Column chromatography was dry-packed (silica gel, hexanes/EtOAc, 80:20) and yielded the purified product 2.6e (12.10 g, 86%) as a colorless oil. \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta\) 6.36-6.24 (m, 1H), 5.78-5.72 (d, \(J = 15.5\) Hz, 1H), 3.98-3.95 (m, 2H), 0.19 (s, 9H); \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)): \(\delta\) 139.3, 114.8, 102.3, 98.0, 31.7, 0.19.

\[
\begin{align*}
\text{TMS} & \quad \text{Br} \\
2.6e & \quad \text{In Powder} \\
& \quad \text{DMF} \\
2.3h & \quad \text{OH} \\
& \quad \text{TBSO} \\
\text{O} & \quad \text{OTBS} \\
& \quad \text{OH} \\
& \quad \text{TBSO} \\
& \quad \text{TMS} \\
2.6h & \quad 1:1 \\
& \quad \text{TMS} \\
2.6h' &
\end{align*}
\]

(3R,4S)-1-(\textit{tert}-Butyldimethylsilyloxy)-4-((\textit{trimethylsilyl})ethynyl)hex-5-en-3-ol (2.6h) and (3R,4R)-1-(\textit{tert}-butyldimethylsilyloxy)-4-((\textit{trimethylsilyl})ethynyl)hex-5-en-3-ol (2.6h'). The procedure analogous to that used for 2.1l afforded the diastereomeric products 2.6h and 2.6h' in a 1:1 ratio (3.5 g, 79% yield from the aldehyde 2.3h on a 13.6 mmol scale) as a colorless oil. The diastereomers were not separable by column chromatography (silica gel, hexanes/EtOAc, 95:05). \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta\) 5.96-5.82 (m, 2H), 5.47-5.36 (m, 2H), 5.27-5.19 (m, 2H), 3.94-3.81 (m, 6H), 3.45-3.23 (d, \(J = 3.25\) Hz, 1H), 3.20-3.15 (m, 2H), 3.04-3.02 (d, \(J = 3.65\) Hz, 1H), 1.86-1.72 (m, 4H), 0.90 (s, 18H), 0.18 (s, 18H), 0.08 (s, 12H); \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)): \(\delta\) 134.8, 134.4, 117.8, 117.6, 104.6, 104.0, 90.4, 90.0, 74.0, 72.8, 62.5, 62.1, 44.3, 43.19, 36.2, 35.9, 26.2, 18.5, 0.48, -5.1.
Co-acetylene complexes 2.6i and 2.6i'. A mixture of 2.6h and 2.6h' (2.75 g, 8.4 mmol) was added to a solution of Co\(_2\)(CO)\(_8\) (3.4 g, 10.0 mmol) in DCM at 0 °C. This black-reddish solution was stirred at room temperature for 2 h. The solvent was then removed under vacuo. The product diastereomers were in a 1:1 ratio, and not separable by column chromatography (silica gel, pentane/ethyl ether, 99:01) yielded the purified products 2.6i and 2.6i' (4.49 g, 94%) as a dark reddish oil. \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta \) 6.12-5.95 (m, 1H), 5.82-5.65 (m, 1H), 5.22-5.08 (m, 4H), 4.09-3.67 (m, 7H), 3.59-3.42 (m, 1H), 4.01-3.23 (m, 1H), 3.18 (s, 1H), 2.01-1.51 (m, 4H), 0.89 (s, 18H), 0.31 (s, 18H), 0.08 (s, 12H); \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)): \(\delta \) 201.0, 138.8, 138.0, 118.0, 113.2, 77.5, 75.6, 75.2, 63.1, 62.9, 57.0, 56.1, 41.9, 37.8, 36.2, 26.1, 22.0, 18.4, 1.21, -5.25.

Mesylated Co-acetylene complexes 2.6j and 2.6j'. The procedure analogous to that used for 2.5a afforded the products 2.6j and 2.6j' in an inseparable 1:1 mixture (4.87 g, 86% yield from the alcohol mixture 2.6i and 2.6i' on a 8.7 mmol scale) as a dark reddish oil. Column chromatography (silica gel, pentane/ethyl ether, 95:05). \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta \) 5.91-5.70 (m, 2H), 5.39-5.23 (m, 4H), 5.03-4.93 (m, 2H), 4.17-4.11 (m, 2H), 3.83-3.68 (m, 4H), 3.06 (s, 6H), 2.10-1.92 (m, 4H) 0.89 (s, 18H), 0.35 (s, 18H), 0.04 (s, 12H); \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)): \(\delta \) 200.4, 137.9, 120.1, 119.3, 107.9, 107.2, 82.1, 81.9, 80.6, 80.4, 59.4, 58.9, 54.8, 54.3, 53.7, 38.8, 38.7, 34.6, 32.9, 29.6, 26.3, 26.2, 18.7, 18.5, 1.55, 1.33, -5.07, -5.15.
(3R,4S)-1-hydroxy-4-((trimethylsilyl)ethynyl)hex-5-en-3-yl methanesulfonate (2.6k) and (3R,4R)-1-hydroxy-4-((trimethylsilyl)ethynyl)hex-5-en-3-yl methanesulfonate (2.6k'). A solution of 2.6i and 2.6i' (1.23 g, 1.9 mmol) and ceric ammonium nitrate (4.18 g, 7.6 mmol) in anhydrous methanol (30 mL) was stirred under nitrogen for 1 h. The reaction was quenched by addition of sat. NaCl solution. Extraction with DCM (2 x 30 mL) drying with MgSO₄, filtering and solvent removal afforded alcohol mixture 2.6k and 2.6k' as an inseparable 1:1 mixture (0.37 g, 68% yield) after column chromatography (silica gel, hexanes/EtOAc, 60:40). ¹H NMR (250 MHz, CDCl₃): δ 5.94-5.72 (m, 2H), 5.54-5.27 (m, 4H), 4.98-4.88 (m, 2H), 3.81-3.77 (m, 4H), 3.65-3.58 (m, 2H), 3.12 (s, 3H), 3.09 (s, 3H), 2.07-1.83 (m, 4H), 1.70-1.50 (m, 2H), 0.18 (s, 18H); ¹³C NMR (62.5 MHz, CDCl₃): δ 132.5, 132.2, 119.7, 102.3, 101.8, 91.8, 91.4, 80.3, 80.2, 58.4, 58.3, 42.5, 41.9, 39.1, 38.9, 34.8, 34.6, 0.32.

4-(Trimethylsilyl)ethynyl)hex-5-en-1-ol (2.6l). The procedure analogous to that used for 2.5b afforded the product 2.6l (0.125 g, 62% yield from the alcohols 2.6k and 2.6k' on a 1.03 mmol scale) as a colorless oil. Column chromatography (silica gel, pentane/ethyl ether, 90:10). ¹H NMR (250 MHz, CDCl₃): δ 5.83-5.69 (m, 1H), 5.35-5.08 (m, 2H), 3.71-
3.66 (m, 2H), 3.17-3.09 (m, 1H), 1.81-1.52 (m, 4H), 1.35 (br s, 1H), 0.18 (s, 9H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 137.8, 115.7, 107.4, 88.2, 62.7, 36.5, 31.7, 30.3, 0.53.

![Reaction Diagram]

4-((Trimethylsilyl)ethynyl)hex-5-enal (2.6a). The procedure analogous to that used for 2.1f afforded the product 2.6a (1.34 g, 74% yield from the alcohol 2.6l on a 9.3 mmol scale) as a colorless oil. Column chromatography (silica gel, pentane/ethyl ether, 90:10).

$^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 9.80 (s, 1H), 5.7-5.65 (m, 1H), 5.36-5.10 (m, 2H), 3.19-3.16 (m, 1H), 2.61-2.55 (m, 2H), 1.95-1.90 (m, 2H), 0.16 (s, 9H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 202.1, 137.0, 116.4, 106.1, 89.2, 41.4, 35.9, 27.5, 0.58.

2.15.3 Spectral Data

Spectral data for the experimental details discussed above are shown on the next page.

2.16 References


(References are continued on page 118)
Figure 2.7 $^1$H NMR and $^{13}$C NMR of Penta-1,4-dien-3-ol 2.1j
Figure 2.8 $^1$H NMR and $^{13}$C NMR of Bromide 2.1k
Figure 2.9 $^1$H NMR and $^{13}$C NMR of 2-Phenyl-1,3-dioxane 2.1c
Figure 2.10 $^1$H NMR and $^{13}$C NMR of 3-(Benzyloxy)propan-1-ol 2.1d
Figure 2.11 $^1$H NMR and $^{13}$C NMR of 3-(Benzyloxy)propanal 2.1f
Figure 2.12 $^1$H NMR and $^{13}$C NMR of Benzyl Protected $^1$° Alcohol 2.1I
Figure 2.13 $^1$H NMR and $^{13}$C NMR of Acetal 2.1p
Figure 2.14 $^1$H NMR and $^{13}$C NMR of Benzyl Protected $2^\circ$ Alcohol 2.1q
Figure 2.15 $^1$H NMR and $^{13}$C NMR of Benzyl Protected Aldehyde 2.1r
Figure 2.16 $^1$H NMR and $^{13}$C NMR of Metallacycles 2.1s and 2.1t
Figure 2.17 $^1$H NMR and $^{13}$C NMR of Lactone 2.1u
Figure 2.18 $^1$H NMR and $^{13}$C NMR of Lactone 2.1v
Figure 2.19 $^1$H NMR and $^{13}$C NMR of 2-(4-Methoxyphenyl)-1,3-dioxane 2.2b
Figure 2.20 $^1$H NMR and $^{13}$C NMR of 3-(4-Methoxybenzyloxy)propan-1-ol 2.2c
Figure 2.21 $^1$H NMR and $^{13}$C NMR of 3-(4-Methoxybenzyl)oxypropanal 2.2d
Figure 2.22 $^1$H NMR and $^{13}$C NMR of PMB Protected $^1$º Alcohol 2.2e
Figure 2.23 $^1$H NMR and $^{13}$C NMR of TBDPS Ether 2.2f
Figure 2.24 $^1$H NMR and $^{13}$C NMR of TBDPS Protected 2º Alcohol 2.2g
Figure 2.25 $^1$H NMR and $^{13}$C NMR of TBDPS Protected Aldehyde 2.2h
Figure 2.26 $^1$H NMR and $^{13}$C NMR of Metallacycles 2.2i and 2.2j
Figure 2.27 $^1$H NMR and $^{13}$C NMR of Lactone 2.2k
Figure 2.28 $^1$H NMR and $^{13}$C NMR of Lactone 2.2l
Figure 2.29 $^1$H NMR and $^{13}$C NMR of Aldehyde 2.3i
Figure 2.30 $^1$H NMR and $^{13}$C NMR of TBDMS Protected $^1$° Alcohol 2.3j
Figure 2.31 $^1$H NMR and $^{13}$C NMR of Trityl Ether 2.3k
Figure 2.32 $^1$H NMR and $^{13}$C NMR of Trityl Protected 1$^o$ Alcohol 2.3d
Figure 2.33 $^1$H NMR and $^{13}$C NMR of Trityl Protected Aldehyde 2.3l
Figure 2.34 $^1$H NMR and $^{13}$C NMR of Lactone 2.3m
Figure 2.35 ¹H NMR and ¹³C NMR of Lactones 2.3n and 2.3o
Figure 2.36 $^1$H NMR and $^{13}$C NMR of Mesylated Alcohol 2.5a
Figure 2.37 $^1$H NMR and $^{13}$C NMR of Alcohol 2.5b
Figure 2.38 $^1$H NMR and $^{13}$C NMR of Aldehyde 2.5c
Figure 2.39 $^1$H NMR and $^{13}$C NMR of Metallacycle 2.5d
Figure 2.40 $^1$H NMR and $^{13}$C NMR of Lactone 2.5e
Figure 2.41 $^1$H NMR and $^{13}$C NMR of (E)-Pent-2-en-4-yn-1-ol 2.6d
Figure 2.42 $^1$H NMR and $^{13}$C NMR of Alcohol 2.6d'}
Figure 2.43 $^1$H NMR and $^{13}$C NMR of Bromide 2.6e
Figure 2.44 $^1$H NMR and $^{13}$C NMR of $^2$o Alcohols 2.6h and 2.6h'
Figure 2.45 $^1$H NMR and $^{13}$C NMR of Complexed Alcohols 2.6i and 2.6i'
Figure 2.46 $^1$H NMR and $^{13}$C NMR of Mesylated Complexes 2.6j and 2.6$j'$

114
Figure 2.47 $^1$H NMR and $^{13}$C NMR of Decomplexed Alcohols 2.6k and 2.6k'
Figure 2.48 $^1$H NMR and $^{13}$C NMR of Alcohol 2.6l
Figure 2.49 $^1$H NMR and $^{13}$C NMR of Aldehyde 2.6a


3.1 An Introduction to Allenes

The simplest cumulated diene is 1,2-propadiene, \( \text{CH}_2=\text{C}=\text{CH}_2 \), also known as an allene. Indeed, cumulated dienes are often called allenes. In this present day, about 150 natural products comprising of an allenic or cumulenic structure are known. A substantial number of these allenic natural products possess biological and pharmacological properties. Several compounds with an allenic moiety incorporated into the existing backbone of the molecule, have been developed and marketed (Figure 3.1), with the most noted example being enprostil, a PGE\(_2\)-analogue that strongly inhibits gastric acid secretion. Enprostil is usually administered as a racemic mixture of diastereomers with regard to the allenic axis of chirality. The allenic PGF\(_{2\alpha}\)-analogues fenprostalene and prostalene are closely related to enprostil and are used in veterinary medicine.

![Figure 3.1 Examples of Allenic Prostaglandins](image_url)
Allenes can be mono-, di-, tri- or tetra-substituted (Scheme 3.1). The central carbon of an allene is \( sp \)-hybridized and as a result, the double bond array is linear as a result. Since the \( \pi \)-bonds of allenes are orthogonal, an interesting consequence of this configuration is that allenes having two different substituents on each of the terminal carbon atoms are chiral. During the 1800’s, proving the existence of this class of compounds proved difficult.\(^3\)\(^4\) At the time, a lack of modern analytical techniques made it really difficult to distinguish allenes from the corresponding alkynes. However, with the introduction of IR and Raman Spectroscopy (allenes show a characteristic C-C vibration at about 1950 cm\(^{-1}\)) and other sophisticated methods, it became possible to prove their existence irrefutably. Spurred by intent chemical curiosity, the chemistry of allenes has grown into an attractive and prolific area of interest. Reactions such as cycloadditions\(^3\)\(^5\) and electrocyclizations\(^3\)\(^6\) are among a few that have taken advantage of this versatile entity. In the field of transition metal catalysis, allenes have reemerged as highly interesting compounds in the past decade. Their slow rise from obscurity, as compared to the more popular alkenes and alkynes, is simply due to the increasing selectivity problems as we proceed from A to C (Scheme 3.2).\(^3\)\(^7\)
Scheme 3.2 Selectivity Problems of Unsaturated Substrates

As with alkynes, regio-, and stereoselectivity issues are significant, but with allenes, we furthermore face the question of positional selectivity – which of the two orthogonal double bonds will react in the case of a single addition?

3.2 Obtaining Cyclopentenones via Allenic Precursors

In early investigations, reactions of allenes with transition metals proceeded quite unselectively and this led to the neglect of allenes as viable substrates. However, with the intramolecularization of reactions and other factors such as introducing substituents which impart steric hindrance and electronic differentiation, most of the positional selectivity problems were automatically solved. A key transition metal-mediated/catalyzed reaction where allenes have been used in place of olefins and produced cycloadduct products intramolecularly is the allenic Pauson-Khand reaction (Scheme 3.3).3,13

Scheme 3.3 Positional Selectivity: Competing Pathways of the Allenic Pauson-Khand Reaction
The Pauson-Khand reaction,\textsuperscript{3,8} or three component cyclopentenone synthesis (Scheme 3.4), has been used extensively in the synthesis of natural products.\textsuperscript{3,9} Dicobalt octacarbonyl, [Co\textsubscript{2}(CO)\textsubscript{8}],\textsuperscript{3,10} is the most well-known and the most highly utilized reagent in the Pauson-Khand process.

![Scheme 3.4 General Pattern of the Pauson-Khand Reaction](image)

When alkynyl allenes are used as potential substrates for the intramolecular Pauson-Khand reaction as seen in Scheme 3.3, two different cycloadducts are produced (positional selectivity). If the external $\pi$-system of the allene reacts, then this affords the 4-alkylidene cyclopentenone (B), and if the internal $\pi$-system of the allene reacts, then this route affords the $\alpha$-methylene cyclopentenone (A). Either resulting cycloadduct gives interesting substructures which are present in many biologically important compounds (Figure 3.2).\textsuperscript{3,11}

![Figure 3.2 Structures of 15-Deoxy-$\Delta^{12,14}$-PGJ\textsubscript{2}, crinipellin A, and hydroxymethylacylfulvene](image)
The *exo*-α-methylene cyclopentenone is an especially exciting substitution pattern in synthesis and is often a major structural feature in the synthesis of biologically active natural products.

There are a number of natural products that possess the α-methylene cyclopentenone moiety, including the prostaglandin 15-Deoxy-Δ^{12,14}-PGJ₂. PGJ₂ represents the first natural ligand for any isoform of the peroxisome proliferators activated receptor (PPAR), which has been shown to be an active intermediate in diseases such as hypertension, obesity, non-insulin dependent diabetes mellitus (NIDDM) and coronary artery disease.³.¹²

3.3 Allenic Pauson-Khand Reaction

Cazes and co-workers have largely investigated the cobalt mediated intermolecular allenic Pauson-Khand reaction using dicobalt octacarbonyl and N-methylmorpholine-N-Oxide (NMO) (Scheme 3.5).³.¹³ The reaction proceeds at very low temperatures (-78 °C to 20 °C) and occurs selectively with the less substituted π-bond of the allene.

![Scheme 3.5 Cazes’ Intermolecular Allenic Pauson-Khand Reaction](image)

Cazes and co-workers have also shown that medium rings can be formed in the intramolecular variant of the cobalt/NMO promoted allenic Pauson-Khand reaction (Scheme 3.6).³.¹³ These are the first reported examples of seven-membered rings formed via an intramolecular Pauson-Khand reaction.

125
In these reactions, however, di- or trisubstituted allenes must be employed, because less substituted allenes tend to polymerize in the presence of \( \text{Co}_2(\text{CO})_8 \).\textsuperscript{3.14}

Kay M. Brummond and co-workers have been at the forefront in extensively investigating the intermolecular allenic Pauson-Khand reaction. Her work has established the allenic Pauson-Khand reaction as the new and regioselective method for the preparation of \( \alpha \)-methylene and 4-alkylidene cyclopentenones.\textsuperscript{3.15} The standard conditions used to effect the intramolecular allenic Pauson-Khand reactions are molybdenum hexacarbonyl \([\text{Mo(CO)}_6]\), dimethylsulfoxide (DMSO) and toluene at 100 °C.\textsuperscript{3.15} Brummond’s work has yielded results which have ranged from obtaining the target compound stereoselectively in good yields, to obtaining the target compounds as mixtures. She has demonstrated that the formation of either the \( \alpha \)-methylene or 4-alkylidene cyclopentenone can be controlled by either the allene structure or reaction conditions.

In the next four sections, a summary of Brummond’s work outlining the allenic Pauson-Khand reaction with different substitution patterns on the allenes will be reviewed.\textsuperscript{3.15} This overview will provide a helpful insight into our study which shares similar features such as positional selectivity of allenic substrates.
3.4 Cycloadditions of Monosubstituted Allenynes

As shown in Table 3.1, all monosubstituted allenynes studied afforded the α-methylene cyclopentenones as the only cycloadduct.

Table 3.1 Cycloadditions of Monosubstituted Allenynes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allenyne</th>
<th>Cyclopentenone</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td>A</td>
<td>68%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td>A</td>
<td>47%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td>A</td>
<td>54%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td>A</td>
<td>30%</td>
</tr>
</tbody>
</table>

Possessing substituents on C4 and C5 of the tethers of the alkynyl allenes 3 and 5 did not affect the outcome of the cyclization pathway. Also, lengthening the tether, as in alkynyl allene 7, still yielded the α-methylene cycloadduct, albeit in low yield.

3.5 Cycloadditions of 1,3-Disubstituted Allenynes

Next, Brummond and co-workers varied the substitution pattern on the allenes and explored the 1,3-disubstituted pattern (Table 3.2).
Table 3.2 Cycloadditions of 1,3-Disubstituted Allenynes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allenyne</th>
<th>Cyclopentenone</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="" /></td>
<td>![image2]</td>
<td>A</td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td>![image3]</td>
<td>![image4]</td>
<td>A</td>
<td>70%</td>
</tr>
<tr>
<td>3</td>
<td>![image5]</td>
<td>![image6]</td>
<td>![image7]</td>
<td>62%</td>
</tr>
<tr>
<td>4</td>
<td>![image8]</td>
<td>![image9]</td>
<td>![image10]</td>
<td>48%</td>
</tr>
<tr>
<td>5</td>
<td>![image11]</td>
<td>![image12]</td>
<td>![image13]</td>
<td>33%</td>
</tr>
<tr>
<td>6</td>
<td>![image14]</td>
<td>![image15]</td>
<td>![image16]</td>
<td>48%</td>
</tr>
</tbody>
</table>

| Conditions: A: Mo(CO)₆/DMSO/toluene/Ar/100 °C/10 h B: DMSO/air/CH₂Cl₂ 40 °C/22 h C: Me₃NO/CH₂Cl₂/Ar/1.3 h D: DMSO/air/benzene/40 °C/26 h E: 1. Cp₂ZrCl₂/n-BuLi, 2. CO/2 h |

These results indicate that the cycloaddition of 1,3-disubstituted allenynes generally affords mixtures of several possible cycloadducts. Different reaction conditions were studied and it appears that there is good control over the product ratio depending
upon the metal used (see entry 4 and 6). Essentially, contingent on the metal used, the regioselectivity can be directed to the internal $\pi$-bond (Path A in Scheme 3.3).

### 3.6 Cycloadditions of 3,3-Disubstituted Allenynes

Next, Brummond’s research group has shown that 3,3-disubstituted allenynes undergo cycloaddition with the least substituted $\pi$-bond of the allene and that the cycloaddition affords the bicyclo[4.3.0] nonane ring system (entries 1-3) and a bicyclo[3.3.0] octane ring system (entry 4), selectively (Table 3.3).

#### Table 3.3 3,3-Disubstituted Allenynes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allenyne</th>
<th>Cyclopentenone</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td>60%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
<td>59%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td>42%a</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td>66%</td>
</tr>
</tbody>
</table>

Reaction Conditions: Mo(CO)$_6$/DMSO/toluene/Ar/100 °C

$^a$ Yield based upon recovered starting material

This result demonstrates a dependence of $\pi$-bond selectivity of the allenic [2+2+1] cycloaddition upon the substrate structures. To date, there are only a few examples of this type of substrate dependence in [2+2+1] cycloaddition reactions.$^{3,16}$
3.7 Cycloadditions of Trisubstituted Allenynes

Finally, Brummond and co-workers have shown that trisubstituted allenynes undergo cyclization exclusively with the less substituted π-bond of the allene as evidenced by entries 1 and 2 in Table 3.4.

Table 3.4 Cycloadditions of Trisubstituted Allenynes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allenyne</th>
<th>Cyclopentenone</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td>59%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td>58%</td>
</tr>
</tbody>
</table>

Reaction Conditions: Mo(CO)$_6$/DMSO/toluene/Ar/100 °C

Other groups have also shown that allenes can be used in these types of cycloadditions using catalytic cobalt and metals other than cobalt and molybdenum.$^{3,17}$

3.8 Goal of this Study

At the initiation of our project, no examples using aldehydes in place of the alkyne component in the allenic Pauson-Khand reaction had been reported. We felt that it would be interesting to investigate the overall utility of this methodology by exploring the possibility of an allenic hetero Pauson-Khand reaction.

In 1996, our research group discovered a new, titanium-mediated reaction which can be used for the synthesis of fused, bicyclic γ-butyrolactones from δ,ε-unsaturated carbonyls (Scheme 3.7).$^{3,18}$
This reaction has since been termed the hetero Pauson-Khand (HPK) reaction and we have also since developed an asymmetric catalytic version of this reaction based on chiral ansa-bridged titanocene catalysts. A detailed review can be found in chapter 1 of this dissertation. Syntheses of new substrates play a very important role in the development of the hetero Pauson-Khand reaction. A variety of new substrates have been investigated, with the choice of a particular substrate often motivated by the desire to develop an efficient synthetic route to a particular class of natural products or to molecules which have potential to exhibit useful biological or medicinal properties. A brief survey of investigated substrates is depicted in Scheme 3.8 below.

Scheme 3.8 Substrates under Investigation
This chapter adds allenyl aldehydes and allenyl ketones (section 3.13) to the list of new substrates studied by our group.

3.9 Synthesis of $\alpha$-Methylene-$\gamma$-Butyrolactones

The structure of an $\alpha$-methylene-$\gamma$-butyrolactone is not only an integral building block in organic synthesis, but can also be found in many natural compounds having biological activity. Sarkomycin, frullanolide and vernolepin are representative substances having the $\alpha$-methylene-$\gamma$-butyrolactone structure. This moiety constitutes about 10% of natural substances having excellent antibacterial and anticancer activity (Figure 3.3).^{3,20}

![Figure 3.3 Biologically Active $\alpha$-Methylene-$\gamma$-Butyrolactone Compounds](image)

Not only are $\alpha$-methylene-$\gamma$-butyrolactones present in a large number of natural products, but the $\alpha$-methylene-$\gamma$-butyrolactone unit is a good Michael acceptor and often plays a central role in biological activity. In our continued synthetic efforts to utilize the titanium-mediated cyclocarbonylation, we reasoned that the $\alpha$-methylene-$\gamma$-butyrolactone moiety can be obtained from tethered allenyl aldehydes and allenyl ketones via path A under the established reaction conditions developed in our group (Scheme 3.9), while path B is expected to give the minor product.

![Scheme 3.9 Allenic Hetero-Pauson-Khand Reaction](image)
While this project was underway, two procedures for the synthesis of cis-fused bicyclic α-methylene-γ-butyrolactones from allenyl carbonyl substrates were published independently by the Kang\textsuperscript{3.21} and Yu\textsuperscript{3.22} laboratories respectively.

**3.10 Ru-Catalyzed Cyclocarbonylation of Allenyl Carbonyls**

Kang and co-workers have utilized the late transition metal ruthenium in the form of Ru\textsubscript{3}(CO)\textsubscript{12} and have demonstrated the catalytic ability of this late transition metal to efficiently afford α-methylene-γ-butyrolactones directly (Scheme 3.10).\textsuperscript{3.21}

\[
\text{Scheme 3.10 Ru-Catalyzed [2+2+1] Cycloadditions of Allenyl Carbonyls}
\]

The proposed mechanistic pathway for this catalytic process most likely involves first, a metallacyclopentene A, followed by insertion of CO to form the carbonylated metallacycle B, and then finally reductive elimination to yield the bicyclic α-methylene-γ-butyrolactone product (Scheme 3.11). The key active species in the catalysis is generally believed to be the unsaturated 16 electron complex, Ru(CO)\textsubscript{4}, which is generated \textit{in situ} from the stable 18 electron Ru\textsubscript{3}(CO)\textsubscript{12} complex.

\[
\text{Scheme 3.11 Proposed Mechanistic Route for Ru-Catalyzed [2+2+1] Cycloaddition of Allenyl Carbonyls}
\]
A table illustrating the results obtained from the ruthenium-catalyzed cyclocarbonylation of allenyl carbonyls is seen below in Table 3.5. The optimum reaction conditions for catalyzed cyclocarbonylation was found to be 1 mol % of Ru$_3$(CO)$_{12}$ in dioxane and 20 atm of CO pressure at 120 °C for 12 h. This ruthenium cyclocarbonylation methodology was also found to be applicable to the conversion of ε-allenyl carbonyls into corresponding six-membered cis-fused α-methylene-γ-butyrolactone (Entry 2 and 5).

Table 3.5 Ru-Catalyzed [2+2+1] Cycloadditions of Allenyl Carbonyls

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TsN</td>
<td>TsN</td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td>tBocN</td>
<td>tBocN</td>
<td>70%</td>
</tr>
<tr>
<td>3</td>
<td>EtO$_2$C</td>
<td>EtO$_2$C</td>
<td>58%$^a$</td>
</tr>
<tr>
<td>4</td>
<td>tBocN</td>
<td>tBocN</td>
<td>72%</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>O</td>
<td>61%</td>
</tr>
</tbody>
</table>

The reactions were carried out with [Ru$_3$(CO)$_{12}$] (1 mol %) and allenyl aldehyde or ketone (1.0 equiv.) in dioxane under CO (20 atm) at 120 °C for 12 h. (a) For 17 h.
3.11 Mo-Mediated Cyclocarbonylation of Allenyl Carbonyls

More recently, Yu and co-workers also obtained α-methylene-γ-butyrolactones directly from allenyl carbonyls by utilizing stiochiometric amounts of Mo(CO)$_6$ with DMSO (Table 3.6). The ideal reaction conditions for this system were determined to be 1.2 equiv. of Mo(CO)$_6$ and 10 equiv. of DMSO in toluene.$^{3,22}$

**Table 3.6 Mo-Mediated Cyclocarbonylation of Allenyl Carbonyls**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{TsN}$</td>
<td>$\text{TsNO}$</td>
<td>5 h</td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td>$\text{TsN}$</td>
<td>$\text{Et}$</td>
<td>6 h</td>
<td>82%</td>
</tr>
<tr>
<td>3</td>
<td>$\text{TsN}$</td>
<td>$\text{Ph}$</td>
<td>6 h</td>
<td>83%</td>
</tr>
<tr>
<td>4</td>
<td>$\text{EtO}_2\text{C}$</td>
<td>$\text{EtO}_2\text{C}$</td>
<td>6 h</td>
<td>58%</td>
</tr>
<tr>
<td>5</td>
<td>$\text{Bu}$</td>
<td>$\text{TsN}$</td>
<td>6 h</td>
<td>59%</td>
</tr>
</tbody>
</table>

The reactions were carried out with Mo(CO)$_6$ (1.2 equiv.) and DMSO (10 equiv.) at 100 °C in toluene.
The plausible mechanistic pathway can be interpreted as follows: DMSO undergoes ligand exchange with CO on molybdenum and this results in a vacant orbital that can accommodate the allenic moiety and form A. Cyclization followed by migratory insertion of the vinyl group into the Mo-complex to yield C then undergoes reductive elimination, and product 1 is obtained (Scheme 3.12).

Scheme 3.12 Possible Mo-Mediated Cyclocarbonylation Mechanism of Allenyl Carbonyls

3.12 Research Aims

The characteristic features of these recently established protocols emphasize the chemical efficiency of the three-component coupling process. This has encouraged us to keep carrying out our investigations in screening titanium metal-mediated cyclocarbonylations. This research endeavor will definitely provide further insight into expanding the scope and utility of these reactions. Ultimately, an underlying motive for this investigation is the eventual application of this method to natural product synthesis. Hence, described herein, are the results of our strategy aimed at adapting a practical titanium metal-mediated cyclocarbonylation to allenyl functionalities. In the next
section, we will discuss the design and synthesis of six allenyl carbonyl substrates, where the substitution patterns are varied in an effort to observe the regiochemical outcome of the Cp₂Ti(PMe₃)₂ mediated allenic Pauson-Khand reaction.

### 3.13 Substrate Synthesis

In order to explore the range of allenyl carbonyls that may be cyclized via the titanium-mediated cyclocarbonylation reaction, we synthesized the desired allenyl carbonyls 3.1a-f (Figure 3.4) by a number of methods.

![Figure 3.4 Structures of Allenyl Carbonyls 3.1a-f](image)

13C NMR provides an excellent method for the structural analysis of allenes. In general, the central sp-hybridized carbon has a chemical shift of ca. 210 ppm and the terminal carbons have chemical shifts in the 75-100 ppm range, leading to a very distinctive spectroscopic ‘fingerprint’ for the allene moiety (Figure 3.5).

![Figure 3.5 13C-NMR Chemical Shifts δ (ppm) of Simple Allenes](image)

The terminal allenyl aldehyde 3.1a was synthesized by the cleavage of THF (3.2a) by t-butyldimethylsilyl iodide which was generated (in situ) by reaction of TBSCI (Scheme 3.13 Synthesis of Iodide 3.3a).
with NaI in MeCN to give the corresponding 4-iodobutanol 3.3a (Scheme 3.13). This regioselective reaction occurred in high yield (91%) and required no purification. Our next objective was to obtain the allenic moiety. Standard methods of allene synthesis are based on the $S_N2'$-type substitution of propargylic compounds (Scheme 3.14).

Scheme 3.14 $S_N2'$-Type Substitution

This led us to develop the organozinc reagent 3.3a'. This intermediate was generated from the iodide 3.3a using zinc dust in DMF. The zinc dust was then activated by the addition of some TMSCl; the mechanism of this activation is still unclear. The excess zinc dust was allowed to settle and the supernatant was then cannulated into a pre-mixed DMF solution of a catalytic amount of CuBr·SMe₂ and propargyl chloride at -10 °C (Scheme 3.15).

Scheme 3.15 Synthesis of Allene 3.4a

Unfortunately, as evidenced by NMR, during subsequent chromatography, the starting material 3.3a was co-eluted with the product 3.4a and further separation was
necessary. We decided to react the mixture of starting iodide 3.3a and product allene 3.4a with excess NEt3 in DMF at 60 °C for 3 hours.\textsuperscript{3.26}

The iodide starting material 3.3a formed a quaternary ammonium salt and was easily trapped on silica gel during purification. However, this led to further loss of product allene 3.4a and our overall yield was unsatisfactory. We then turned to a more efficient method of forming the organozinc intermediate 3.3a'.

One of the most highly activated forms of zinc is known as Rieke zinc.\textsuperscript{3.27} We adopted this method and prepared the Rieke zinc by the reduction of ZnCl2 in THF with lithium naphtalenide. This reagent readily underwent oxidative addition with the iodide 3.3a to yield the corresponding organozinc reagent 3.3a'. This procedure afforded the TBS-protected allene 3.4a as the sole product after purification (Scheme 3.16).

\begin{center}
\includegraphics[width=\textwidth]{scheme3.16.png}
\end{center}

\textbf{Scheme 3.16 Synthesis of 3.4a via the Rieke Zinc Procedure}

Next, we used a HF solution in MeCN to cleave the silyl protecting group.\textsuperscript{3.28} This reaction was performed in a polyethylene flask. However, the yield of this reaction was low (47%), hence we switched to TBAF as the silyl deprotecting reagent (Scheme 3.17). PCC oxidation then furnished aldehyde 3.1a (Scheme 3.18).
Scheme 3.17 Synthesis of Allenic Alcohol 3.5a

Scheme 3.18 Synthesis of Allenic Aldehyde 3.1a

Allenyl ketone 3.1b was produced in a similar fashion to allenyl aldehyde 3.1a from cleavage of 2-methyl-tetrahydrofuran 3.2b (Scheme 3.19). The opening of 3.2b is highly regioselective, however, trace amounts of tert-butyl(4-iodopentyloxy)dimethylsilane3.28b 3.3b' was present but subsequently removed by column chromatography.

Scheme 3.19 Synthesis of Allenic Ketone 3.1b

In order to obtain the 3,3-disubstituted allenyl aldehyde 3.1c, alkylation of the lithium salt of methyl propargyl ether 3.2c with the iodide 3.3a was attempted (Scheme 3.20).3.29
Scheme 3.20 Synthesis of Alkyne 3.3c

Unfortunately, this reaction yielded the desired product 3.3c as the minor product. We decided to follow a different procedure which utilizes NaNH₂ as the base and DMPU as co-solvent.³³⁰ This method afforded the desired product 3.3c in 82% yield (Scheme 3.21).

Scheme 3.21 Improved Synthesis of Alkyne 3.3c

Product 3.3c was then treated with methylmagnesium bromide, CuBr and refluxed to produce 3.4c (71%) (Scheme 3.22).³²⁹

Scheme 3.22 Synthesis of 3,3-Disubstituted Allene 3.4c

The final aldehyde 3.1c was obtained by subsequent deprotection and oxidation steps (Scheme 3.23).

Scheme 3.23 Synthesis of 3,3-Disubstituted Allenic Aldehyde 3.1c
Allenyl aldehyde 3.1d was obtained in a likewise fashion to compound 3.1c where phenylmagnesium bromide was used instead of methymagnesium bromide (Scheme 3.24).

Both the methyl and phenyl substituents on products 3.1c and 3.1d will afford us the opportunity to study whether steric effects of substituents have an influence on the outcome of the titanium-mediated cyclocarbonylation.

The initial step to obtaining the 1,3-disubstituted allenyl aldehyde 3.1e was by mesylation of 3-butyn-2-ol 3.2e,\(^{3,31}\) followed by a reaction with iodide 3.3a via the Rieke method to produce the 1,3-substituted allene 3.3e (Scheme 3.25). TBAF treatment and PCC oxidation provided the final product 3.1e (Scheme 3.26). Finally, allenyl aldehyde 3.1f was prepared. This compound possesses a tether that is one carbon
shorter than the other allenyl carbonyls synthesized. It is speculated as to which of the π-bonds of the allene will react during the reductive coupling step. If the internal π-bond reacts, then 3.6f will be formed and if the external π-bond reacts, then 3.5f will be formed (Scheme 3.27).

Scheme 3.27 Possible π-Bond Selectivity Products from Allenic Aldehyde 3.1f

The synthesis of compound 3.1f began with commercially available (3-bromopropoxy)(tert-butyl)dimethylsilane, 3.2f and proceeded through the familiar reaction sequence (Scheme 3.28).
With the functionalized allenyl carbonyls 3.1a-f, in hand, we then pursued their use in the titanium-mediated Hetero Pauson-Khand reaction.

### 3.14 Metallacycle Formation

In our study of the reactions of the allenyl carbonyls 3.1a-f towards carbonylation, we first set out to isolate the initial reductive cyclization products. The first reductive cyclization reaction was run with allenyl aldehyde 3.1a with a stoichiometric amount of CpTi(PMe₃)₂ in pentane (Scheme 3.29). This resulted in very low yields of product formation. During the reaction, the formation of an insoluble by-product was also noticed. This prompted the need to carry out the reaction in other solvents. The next solvent tried was diethyl ether. The yield was higher but there was still insoluble by-product present. Finally, the reaction was carried out in THF resulting in a dark reddish brown solution with no presence of insoluble by-product and in high yield.

![Scheme 3.29 Synthesis of 3.6a](image)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentane</td>
<td>10%</td>
</tr>
<tr>
<td>Et₂O</td>
<td>30%</td>
</tr>
<tr>
<td>THF</td>
<td>94%</td>
</tr>
</tbody>
</table>

**Scheme 3.29 Synthesis of 3.6a**

Obtaining crystals of 3.6a via slow evaporation of THF was difficult but we were able obtain a few from the reaction of 3.1a in pentane. On the following page is an ORTEP representation confirming the presence of metallacycle 3.6a following a single crystal X-ray structure determination (Figure 3.6).
Figure 3.6 ORTEP Plot of Metallacycle 3.6a
The other allenyl carbonyls 3.1b-f were also subjected to reductive coupling and the results of these reactions are summarized in Table 3.7.

Table 3.7 Yields and Metallacyclic Products formed via Reductive Coupling

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allenyl Carbonyl</th>
<th>Metallacyclic Product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.1a</td>
<td><img src="3.6a.png" alt="Image" /></td>
<td>94%</td>
</tr>
<tr>
<td>2</td>
<td>3.1b</td>
<td><img src="3.6b.png" alt="Image" /></td>
<td>89%</td>
</tr>
<tr>
<td>3</td>
<td>3.1c</td>
<td><img src="3.6c.png" alt="Image" /></td>
<td>85%</td>
</tr>
<tr>
<td>4</td>
<td>3.1d</td>
<td><img src="3.5e.png" alt="Image" /></td>
<td>- - - c</td>
</tr>
<tr>
<td>5</td>
<td>3.1e</td>
<td><img src="3.5e.png" alt="Image" /> <img src="3.6e.png" alt="Image" /></td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>3.1f</td>
<td>- - - c</td>
<td></td>
</tr>
</tbody>
</table>

All reactions were carried out with Cp₂Ti(PEt₃)₂ (1.0 equiv.) for 2 h at room temperature in THF. (a) Chemical shifts of significant signals in ppm. (b) All yields are overall isolated yields starting from allenyl carbonyls. (c) Decomposition was detected by NMR.
The results shown in Table 3.7 indicate that in general, allenyl carbonyls undergo reductive coupling with $\text{Cp}_2\text{Ti(PMe}_3\text{)}_2$. Entries 1 and 2 show that both allenic aldehydes and allenic ketones undergo reductive coupling on the substituted $\pi$-bond of the allenic moiety with ease. These findings are consistent with the selectivity pattern seen with ruthenium-catalyzed$^{3.21}$ and molybdenum-mediated$^{3.22}$ couplings earlier. Entry 3 indicates the preference of titanium-mediated reductive coupling on the more substituted $\pi$-bond of the allenic moiety. This selectivity is in direct contrast to the findings observed by Brummond and co-workers$^{3.17}$ where 3,3-disubstituted allenynes underwent cycloaddition on the least substituted $\pi$-bond of the allenic moiety (Table 3.3). Entry 5 shows that titanium-mediated reductive coupling of 1,3-disubstituted allenyl carbonyls result in a mixture of two possible cycloadducts. However, further studies will have to be performed to determine how much the ratio of the two cycloadducts is changed when more sterically substituted substrates are employed. Finally, entries 4 and 6 indicate that possible metallacycles formed from the reductive cyclization of $3.1d$ and $3.1f$ decomposed into unidentifiable products. $^{13}$C NMR for both compounds show the existence of cyclopentadienyl carbons ranging from 114.4 ppm to 113.9 ppm and their $^1$H NMRs show the chemical shift signals characteristic for cyclopentadienyl protons in the range of 5.87 ppm to 5.67 ppm. It is likely that the bulkiness of the phenyl substituent in $3.1d$ and the ring strain of the possible metallacycle $3.6f$ from allenyl aldehyde $3.1f$ lead to the decomposition observed. Chemical shifts of significant protons are denoted in Table 3.7. There is a clear pattern in the values of similar protons on the different metallacycles. Knowledge of these chemical shift values can aid in future assignment of such metallacycles.
3.15 Future Goals

The progress made in this titanium-mediated allenic hetero Pauson-Khand methodology is encouraging and informative. Further studies into reductive cyclization remain, in order to establish a general trend. Carbonylation studies are also currently underway to afford the desired α-methylene-γ-butyrolactones.

3.16 Experimental Section

3.16.1 General Methods

All experiments were performed under a nitrogen or argon atmosphere in oven-dried glassware using a Vacuum Atmospheres dry box, or by using standard Schlenk techniques. Solvents used as reaction media were distilled immediately before use. Et₂O, pentane, and THF were distilled from Na/benzophenone ketyl. CH₂Cl₂ was distilled from calcium hydride. Cp₂Ti(PMe₃)₂ and PMe₃ were prepared as described in literature. Other reagents were purified by simple distillation or by passing through a short column of activated alumina or silica gel. ¹H and ¹³C NMR spectra were recorded on Bruker 250 and 300 MHz spectrometers in deuterated solvents using the solvent carbon or residual protons (CHCl₃: 7.27 ppm ¹H, 77.23 ppm ¹³C, C₆D₆: 7.15 ppm ¹H, 128.0 ppm ¹³C) as an internal reference unless otherwise stated. Chemical shifts (δ) are given in parts per million down from tetramethylsilane (TMS). Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, qd = quartet of doublets, m = multiplet), coupling constant (Hz), and integration.

Analytical thin layer chromatography (TLC) was performed on Scientific Adsorbent Company Inc. silica gel plates. Components were visualized by illumination
with long wave ultraviolet light, exposure to iodine vapor, or by staining with \( p \)-anisaldehyde in ethanol/sulfuric acid. Flash column chromatography was performed using silica gel (Scientific Adsorbent Company Inc. 32-63 \( \mu \)m particle size, 60 Å pore size).

### 3.16.2 Preparative Procedures

**tert-Butyl(4-iodobutoxy)dimethylsilane (3.3a).** To a solution of TBSCl (10 g, 66.34 mmol) in MeCN (150 mL) was added NaI (19.9 g, 132.69 mmol) and THF (17.5 mL, 242.17 mmol). The reaction mixture was left to stir overnight at 60 °C. After the reaction mixture was cooled to room temperature, it was poured into a separatory funnel containing water. The reaction mixture was extracted with pentane/ether (9 : 1, 3 x 500 mL), and the combined organic layer was washed with saturated aqueous NaHCO₃. After drying over MgSO₄, the solvent was removed under reduced pressure. The product 3.3a (18.95 g, 91%). 3.3a must be foiled during storage to avoid light decomposition and was used in the next step without purification. \(^1\)H NMR (250 MHz, CDCl₃): \( \delta \) 3.63 (t, \( J = 6.2 \) Hz, 2H), 3.22 (t, \( J = 7.0 \) Hz, 2H), 1.91 (m, 2H), 1.61 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H); \(^{13}\)C NMR (62.5 MHz, CDCl₃): \( \delta \) 62.4, 33.9, 30.6, 26.3, 18.7, 7.6, 4.9.
**tert-Butyl-hepta-5,6-dienyloxy-dimethyl-silane (3.4a).** Procedure A: Zinc dust (10.8 g, 47.7 mmol), was weighed into a 50 mL round-bottom flask with a side arm, which was repeatedly evacuated (with heating using a hot air gun) and flushed with nitrogen. Dry DMF (20 mL) and trimethylsilyl chloride (0.146 g, 0.975 mmol) were added, and the resultant mixture was stirred for 30 min at room temperature. The iodide 3.3a (5g, 15.9 mmol) was dissolved in dry DMF (20 mL) under nitrogen. The iodide solution was cannulated into the zinc suspension and stirred at 0 °C. After stirring for 2 h at 0 °C, the organozinc intermediate 3.3a′ was formed and the excess zinc dust was allowed to settle. The supernatant was cannulated under nitrogen to a pre-mixed solution of CuBr·SMe₂ (0.16 g, 5 mol%) and propargyl chloride (1.54 g, 20.7 mmol) in DMF (25 mL) at -10 °C (ice-salt). The solution was then allowed to warm slowly to room temperature and stirred for a further 14 h. The reaction mixture was diluted with ethyl acetate (60 mL) and washed successively with water (40 mL), a saturated aqueous solution of CuSO₄ solution (40 mL) and finally brine (40 mL). The combined organic extracts were dried with MgSO₄, filtered and the solvent removed under reduced pressure. Unfortunately, this procedure yielded a mixture of product 3.4a and the starting iodide 3.3a which proved impossible to separate via chromatography.

**tert-Butyl-hepta-5,6-dienyloxy-dimethyl-silane (3.4a).** Procedure B: Typical preparation of Rieke zinc: Finely cut lithium wire (99.9% pure, ∼0.01% Na, 0.29 g, 42.5 mmol) and naphthalene (2.04 g, 1.6 mmol) were weighed into a 100 mL, two-neck round-bottom flask equipped with an addition funnel. Similarly, in an argon drybox, ZnCl₂ (2.79 g, 20.5 mmol) was weighed into a 50 mL round-bottom flask. The flasks were then transferred to the Schlenk line. THF (15 mL) was added to the flask with
lithium and naphthalene while ZnCl₂ was dissolved in 20 mL of THF. After 1 h of stirring, the resulting dark green lithium napthalenide was ready. The dissolved THF solution of ZnCl₂ was transferred via cannula into the addition funnel of the lithium naphtalenide flask. Next, the THF solution of ZnCl₂ was added dropwise into the lithium naphtalenide taking care to maintain the green color. After the transfer was complete, the Rieke zinc was stirred for 30 min (to further ensure that all of the lithium was consumed) and the resulting black suspension of active zinc was allowed to settle. The supernatant was cannulated off and the remaining solvent was removed under vacuum. Iodide 3.3a (5 g, 15.9 mmol) in 14 mL of dry DMF was added via syringe and stirred at 0 °C for 1 h before the excess zinc was allowed to settle. Once the organozinc intermediate 3.3a' was generated, the supernatant was transferred carefully, under nitrogen via cannula into a pre-mixed solution of CuBr·SMe₂ (0.16 g, 5 mol%) and propargyl chloride (1.54 g, 20.7 mmol) in DMF (10 mL) at -10 °C (ice-salt). The solution was then allowed to warm slowly to room temperature and stirred for a further 14 h. The reaction mixture was diluted with ethyl acetate (80 mL) and washed successively with water (60 mL), a saturated aqueous solution of CuSO₄ solution (60 mL) and finally brine (60 mL). The combined organic extracts were dried with MgSO₄, filtered and the solvent removed under reduced pressure. Column chromatography (silica gel, hexanes/EtOAc, 90:10) yielded the purified product 3.4a (2.3g, 60%) as a yellow oil. ¹H NMR (250 MHz, CDCl₃): δ 5.07 (quin, J = 6.7 Hz, 1H), 4.63 (m, 2H), 3.59 (t, J = 6.2 Hz, 2H), 2.00 (m, 2H), 1.57-1.24 (m, 4H), 0.87 (s, 9H), 0.03 (s, 6H). ¹³C NMR (62.5 MHz, CDCl₃): δ 208.9, 90.4, 75.1, 63.4, 32.7, 28.4, 26.4, 25.8, 18.8, -4.9.
Hepta-5,6-dien-1-ol (3.5a). Procedure A: The TBS ether 3.4a (0.914 g, 4.03 mmol) was treated with 40 mL of 48% HF in acetonitrile (v/v 1/20) at room temperature for 2 h. Water was added (20 mL) and the mixture was extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic solutions were washed successively with water (15 mL) and brine (15 mL), dried over MgSO$_4$, filtered and concentrated under reduced pressure. Column chromatography (silica gel, hexanes/EtOAc, 80:20) yielded the purified product 3.5a (0.21 g, 47%) as a colorless liquid.

Hepta-5,6-dien-1-ol (3.5a). Procedure B: Into a 50 mL round-bottom flask was placed 3.4a (0.914 g, 4.03 mmol) and THF (20 mL). To this stirred solution was added TBAF (4.84 mL of 1.0 M solution in THF, 4.84 mmol). The solution was stirred for 4 h at room temperature before quenching the reaction with saturated ammonium chloride. The mixture was poured into a separatory funnel containing 10 mL of water and 10 mL of diethyl ether. The organic layer was extracted twice more with 10 mL portions of water. The combined aqueous layers were then back extracted with 20 mL of diethyl ether. The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. Column chromatography (silica gel, hexanes/EtOAc, 80:20) yielded the purified product 3.5a (0.38 g, 84%) as a colorless liquid. $^1$H NMR (250 MHz, CDCl$_3$): δ 5.11 (quin, $J = 6.7$, 1H), 4.66 (m, 2H), 3.67 (t, $J =$
6.3 Hz, 2H), 2.04 (m, 2H), 1.65-1.46 (m, 4H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 208.9, 90.1, 75.2, 63.2, 32.6, 28.3, 25.6.

Hepta-5,6-dienal (3.1a). To a suspension of PCC (2 g, 9.48 mmol) in CH$_2$Cl$_2$ was added neutral Al$_2$O$_3$ (2 g) at room temperature. After 30 min stirring, the alcohol 3.5a (0.532 g, 4.74 mmol) was added, and then further stirring for 2 h during which time the reaction mixture turned dark brown in color. The reaction mixture was diluted with ether and filtered through a plug of dry silica gel. The solvent was evaporated under reduced pressure. Purification by column chromatography (silica gel, pentane/ethyl ether, 95:05) yielded the product 3.1a (0.428 g, 82%) as a colorless liquid. $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 9.75 (t, $J$ = 1.7 Hz, 1H), 5.05 (quin, $J$ = 6.7 Hz, 1H), 4.66 (m, 2H), 2.46 (m, 2H), 2.03 (m, 2H), 1.74 (m, 2H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 209.1, 202.9, 89.4, 75.7, 43.6, 27.9, 21.7.

$^{t}$ert-Butyl(5-iodopentan-2-yloxy)dimethylsilane (3.3b). 3.3b was prepared on a 66.34 mmol scale using the procedure described above for 3.3a and utilizing 3.2b. Column chromatography (silica gel, 100% hexanes) yielded 3.3b (18.6 g, 85%) as a yellow liquid. $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 3.81 (m, 1H), 3.20 (t, $J$ = 7.0 Hz, 2H), 1.89 (m, 2H), 1.52 (m, 2H), 1.13 (d, $J$ = 6.0 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 67.9, 40.7, 30.3, 26.2, 24.2, 18.4, 7.6, -4.3. (A trace amount of tert-butyl(4-iodopentyloxy)dimethylsilane 3.3b' was also removed chromatographically).
**tert-Butyldimethyl(octa-6,7-dien-2-yloxy)silane (3.4b).** The procedure analogous to that used for 3.4a (Procedure B) afforded the product 3.4b (2.5 g, 65% yield from the iodide 3.3b on a 15.9 mmol scale) as a colorless oil. Column chromatography (silica gel, hexanes/EtOAc, 98:02). $^1$H NMR (300 MHz, CDCl$_3$): δ 5.10 (quin, $J = 6.7$ Hz, 1H), 4.67 (m, 2H), 3.80 (q, $J = 5.5$ Hz, 1H), 2.00 (m, 2H), 1.17-1.40 (m, 4H), 1.13 (d, $J = 6.1$ Hz, 3H), 0.87 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): δ 208.9, 90.4, 75.0, 68.6, 39.5, 28.6, 26.3, 25.7, 24.2, 18.5, -4.3.

**Octa-6,7-dien-2-ol (3.5b).** The procedure analogous to that used for 3.5a (Procedure B) afforded the product 3.5b (1.2 g, 84% yield from the TBS ether 3.4b on a 11.5 mmol scale) as a colorless oil. Column chromatography (silica gel, hexanes/EtOAc, 80:20). $^1$H NMR (300 MHz, CDCl$_3$): δ 5.13 (quin, $J = 6.7$ Hz, 1H), 4.70 (m, 2H), 3.85 (q, $J = 5.6$ Hz, 1H), 2.06 (m, 2H), 1.55-1.49 (m, 4H), 1.24 (d, $J = 6.2$ Hz, 3H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): δ 208.9, 96.1, 75.2, 68.3, 39.0, 28.5, 25.6, 23.9.

**Octa-6,7-dien-2-one (3.1b).** The procedure analogous to that used for 3.1a afforded the product 3.1b (0.75 g, 69% yield from the alcohol 3.5b on a 8.79 mmol scale) as a
colorless oil. Column chromatography (silica gel, pentane/ethyl ether 95:05). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 5.07 (quin, \(J = 6.7\) Hz, 1H), 4.68 (m, 2H), 2.48 (m, 2H), 2.14 (s, 3H), 2.01 (m, 2H), 1.71 (m, 2H); \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)): \(\delta\) 209.1, 206.3, 89.9, 75.2, 41.8, 29.5, 28.0, 23.5.

\[
\begin{align*}
   &\text{BuLi, THF} \quad \text{reflux} \quad 3.3c \\
   &\text{NaNH}, \text{DMPU} \quad \text{THF} \quad 3.3c
\end{align*}
\]

**tert-Butyl(7-methoxyhep-5-ynyloxy)dimethysilane (3.3c).** Procedure A: BuLi (33.7 mL of 2.0 M solution in hexanes, 69.4 mmol) was added over 40 min to a solution of methyl propargyl ether 3.2c (5 g, 71.3 mmol) in 200 mL of anhydrous THF at 0 °C. The TBS ether of 4-iodobutanol 3.3a (11.2 g, 35.6 mmol) was added via syringe over 5 min. The reaction mixture was heated at reflux for 4 days, cooled to room temperature, and quenched by the addition of 100 mL of water. Most of the THF was removed under reduced pressure and the residue was extracted with 5 x 50 mL of ether. The combined organic extracts were dried over MgSO\(_4\), filtered and concentrated under reduced pressure. Purification by column chromatography (silica gel, hexanes/EtOAc, 90/10) yielded the product 3.3c (1.34 g, 15%) as a yellow oil.

**tert-Butyl(7-methoxyhep-5-ynyloxy)dimethysilane (3.3c).** Procedure B: Into a 100 mL round-bottom flask sodium amide (1.65 g, 42.3 mmol) was added and the powder suspended in 30 mL of THF. The flask was cooled to -78 °C and methyl propargyl ether 3.2c (2.30 g, 32.8 mmol) was added, via syringe, as a solution in THF. The suspension was stirred at -78 °C for 1 h and then warmed to room temperature for 1 h to ensure formation of the acetylide. The suspension was cooled to -78 °C and 7.54 mL (62.3
mmol) of DMPU was added. 12.3 g, (39 mmol) of iodide 3.3a, was added via syringe, as a solution in THF and the reaction was allowed to warm up to room temperature. After 12 h, the reaction was quenched with saturated ammonium chloride and the mixture poured into a separatory funnel containing 80 mL of water and 80 mL of diethyl ether. The organic portion was extracted twice more with 50 mL portions of water and the combined aqueous layers back extracted with 100 mL of diethyl ether. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes/EtOAc, 90/10) to yield 3.3c (7.3 g, 82%) as a clear colorless liquid.

$^1$H NMR (300 MHz, CDCl₃): δ 4.07 (t, J = 2.1 Hz, 2H), 3.62 (t, J = 5.9 Hz, 2H), 3.36 (s, 3H), 2.26 (m, 2H), 1.60 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H); $^{13}$C NMR (75 MHz, CDCl₃): δ 88.5, 77.4, 64.1, 61.7, 58.9, 33.5, 27.5, 26.6, 20.1, 19.9, -3.7.

**tert-Butyldimethyl(5-methylhepta-5,6-dienyloxy)silane (3.4c).** Methylmagnesium bromide (7.8 mL of 3.0 M solution in ether, 23.3 mmol) was added to a solution of 3.3c (3.0 g, 11.7 mmol) and CuBr (0.5 g, 3.5 mmol) in 100 mL of anhydrous ether. The resulting black solution was heated at reflux for 60 h. The reaction was cooled, quenched with water, and the mixture transferred into separatory flask. The product was extracted with ethyl ether (3 x 50 mL). The combined extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. Column chromatography (silica gel, hexanes/EtOAc, 90:10) yielded the purified product 3.4c (1.86 g, 71%) as a colorless liquid. $^1$H NMR (300 MHz, CDCl₃): δ 4.59 (m, 2H), 3.64 (m, 2H), 1.95 (m, 2H), 1.67 (m,
3H), 1.57-1.47 (m, 4H), 0.90 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 207.7, 99.8, 75.4, 64.6, 34.7, 33.9, 27.5, 25.2, 20.2, 19.9, -3.7.

5-Methylhepta-5,6-dien-1-ol (3.5c). The procedure analogous to that used for 3.5a (Procedure B) afforded the product 3.5c (0.52 g, 86% yield from the TBS ether 3.4c on a 4.7 mmol scale) as a colorless oil. Column chromatography (silica gel, hexanes/EtOAc, 80:20). $^1$H NMR (300 MHz, CDCl$_3$): δ 4.60 (m, 2H), 3.66 (t, $J = 6.2$ Hz, 2H), 1.97 (m, 2H), 1.68 (m, 3H), 1.61-1.50 (m, 4H), 0.05 (s, 6H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): δ 206.5, 98.5, 74.5, 63.2, 33.5, 32.7, 23.9, 19.1.

5-Methylhepta-5,6-dienal (3.1c). The procedure analogous to that used for 3.1a afforded the product 3.1c (0.41 g, 85% yield from the alcohol 3.5c on a 3.96 mmol scale) as a colorless oil. Column chromatography (silica gel, pentane/ethyl ether, 95:05). $^1$H NMR (300 MHz, CDCl$_3$): δ 9.77 (s, 1H), 4.62 (m, 2H), 2.45 (m, 2H), 1.97 (m, 2H), 1.79 (m, 2H), 1.68 (m, 3H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): δ 206.5, 202.9, 97.8, 74.9, 43.7, 33.0, 20.2, 19.0.

Butyldimethyl(5-phenylhepta-5,6-dienyloxy)silane (3.4d). The procedure analogous to that used for 3.4c utilizing phenylmagnesium bromide afforded the product 3.4d (3.8 g, 89% yield from 3.3c on a 14 mmol scale) as a colorless oil. Column chromatography (silica gel, hexanes/EtOAc, 90:10). $^1$H NMR (300 MHz, CDCl$_3$): δ 7.46-7.23 (m, 5H),
5.11 (m, 2H), 3.66 (m, 2H), 2.47 (m, 2H), 1.67-1.60 (m, 4H), 0.90 (s, 9H), 0.09 (s, 6H);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 210.2, 138.0, 129.9, 128.1, 127.5, 106.5, 79.7, 64.6, 34.1, 30.8, 27.5, 25.7, 19.9, -3.6.

5-Phenylhepta-5,6-dien-1-ol (3.5d). The procedure analogous to that used for 3.5a (Procedure B) afforded the product 3.5d (1.5 g, 71% yield from the TBS ether 3.4d on a 11.3 mmol scale) as a colorless oil. Column chromatography (silica gel, hexanes/EtOAc, 80:20). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.46-7.22 (m, 5H), 5.12 (m, 2H), 3.72 (m, 2H), 2.15 (m, 2H), 1.74-1.65 (m, 4H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 208.9, 136.7, 128.8, 127.7, 126.8, 105.2, 78.7, 63.0, 32.7, 29.5, 25.3.

5-Phenylhepta-5,6-dienal (3.1d). The procedure analogous to that used for 3.1a afforded the product 3.1d (0.9 g, 59% yield from the alcohol 3.5d on a 8.17 mmol scale) as a colorless oil. Column chromatography (silica gel, Pentane/ethyl ether, 95:05). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.79 (s, 1H), 7.42-7.26 (m, 5H), 5.11 (m, 2H), 2.55-2.49 (m, 4H), 1.94 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 210.1, 203.9, 137.5, 130.0, 128.4, 127.5, 105.7, 80.3, 44.9, 30.3, 21.8.

But-3-yn-2-yl methanesulfonate (3.2e'). Methanesulfonyl chloride (8.28 mL, 107 mmol) was added dropwise at 0 °C to a solution of but-3-yn-2-ol 3.2e, (5 g, 71 mmol) in
CH₂Cl₂ (150 mL), containing NEt₃ (24.85 mL, 178 mmol). The reaction was over within 2 h, as determined by TLC; the mixture was then allowed to warm to room temperature, and diethyl ether (100 mL) and water (50 mL) were added. The aqueous phase was extracted twice with 100 mL of diethyl ether; the combined organic phases were washed copiously with a saturated aqueous solution of CuSO₄ and finally, brine. The combined organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure. Column chromatography (silica gel, hexanes/EtOAc, 95:05) yielded the purified product 3.2e' (8.76 g, 83%) as a yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 5.29 (qd, J = 6.7 Hz, J = 2.1 Hz, 1H), 3.13 (s, 3H), 2.71 (d, J = 2.0 Hz, 1H), 1.68 (d, J = 6.7 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 81.7, 77.9, 69.0, 40.6, 23.9.

**tert-Butyldimethyl(octa-5,6-dienyloxy)silane (3.3e).** The procedure analogous to that used for 3.4a (Procedure B) utilizing 3.2e' afforded the product 3.3e (2.7 g, 71% yield from the iodide 3.3a on a 15.9 mmol scale) as a colorless oil. Column chromatography (silica gel, hexanes/EtOAc, 98:02). ¹H NMR (300 MHz, CDCl₃): δ 5.08 (m, 2H), 3.65 (t, J = 6.3 Hz, 2H), 2.20 (m, 2H), 1.68 (m, 3H), 1.62-1.44 (m, 4H), 0.93 (s, 9H), 0.08 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 206.3, 91.7, 87.0, 64.6, 33.8, 30.2, 27.5, 26.9, 19.9, 16.1, -3.7.
Octa-5,6-dien-1-ol (3.4e). The procedure analogous to that used for 3.5a (Procedure B) afforded the product 3.4e (0.42 g, 67% yield from the TBS ether 3.3e on a 4.99 mmol scale) as an oil. Column chromatography (silica gel, hexanes/EtOAc, 80:20). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.08 (m, 2H), 3.66 (m, 2H), 2.02 (m, 2H), 1.64 (m, 3H) 1.60-1.48 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 206.3, 91.5, 87.2, 64.2, 33.6, 30.1, 26.7, 16.1.

Octa-5,6-dienal (3.1e). The procedure analogous to that used for 3.1a afforded the product 3.1e (0.3 g, 73% yield from the alcohol 3.4e on a 3.33 mmol scale) as a colorless oil. Column chromatography (silica gel, pentane/ethyl ether, 95:05). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.78 (s, 1H), 5.05 (m, 2H), 2.47 (m, 2H), 2.02 (m, 2H), 1.75 (m, 2H), 1.65 (dd, $J = 6.8$ Hz, $J = 3.3$ Hz, 3H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 206.2, 202.8, 90.0, 86.3, 43.4, 29.3, 21.7, 14.8.

** tert-Butyl(hexa-4,5-dienyloxy)dimethylsilane (3.3f).** The procedure analogous to that used for 3.4a (Procedure B) utilizing 3.2f afforded the product 3.3f (2.6 g, 77% yield from the bromide 3.2f on a 15.9 mmol scale) as a colorless oil. Column chromatography (silica gel, hexanes/EtOAc, 98:02). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.12 (quin, $J = 6.7$ Hz, 1H), 4.65 (m, 2H), 3.63 (t, $J = 4.0$, 2H), 2.07 (m, 2H), 1.67 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 208.9, 90.1, 75.2, 62.7, 32.5, 26.2, 24.8, 18.7, -5.0.
**Hexa-4,5-dien-1-ol (3.4f).** The procedure analogous to that used for 3.5a (Procedure B) afforded the product 3.5f (0.5 g, 67% yield from the TBS ether 3.4f on a 7.72 mmol scale) as a colorless oil. Column chromatography (silica gel, hexanes/EtOAc, 80:20). $^1$H NMR (300 MHz, CDCl$_3$): δ 5.13 (quin, $J = 6.7$ Hz, 1H), 4.69 (m, 2H), 3.71 (q, $J = 6.0$ Hz, 2H), 2.11 (m, 2H), 1.70 (m, 2H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): δ 208.9, 89.8, 75.5, 62.6, 32.2, 24.8.

**Hexa-4,5-dienal (3.1f).** The procedure analogous to that used for 3.1a afforded the product 3.1f (0.31 g, 74% yield from the alcohol 3.4f on a 4.36 mmol scale) as a colorless oil. Column chromatography (silica gel, pentane/ethyl ether, 95:05). $^1$H NMR (300 MHz, CDCl$_3$): δ 9.80 (s, 1H), 5.20 (m, 1H), 4.74 (m, 2H), 2.59 (m, 2H), 2.34 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 210.0, 203.4, 90.2, 78.1, 43.9, 22.1.

**Metallacycle (3.6a).** To a solution of Cp$_2$Ti(PMe$_3$)$_2$ (0.209 g, 0.63 mmol) in THF (5 mL) was added aldehyde 3.1a (0.07 g, 0.63 mmol) inside an argon filled glove box. After stirring for 2 h at room temperature, the reaction mixture was filtered through a pad of Celite and rinsed with pentane to give a reddish-brown solution. THF was removed under reduced pressure and the reddish-brown solid residue was obtained as the titled compound 3.6a (0.172 g, 94%). $^1$H NMR (300 MHz, C$_6$D$_6$): δ 5.97 (s, 5H), 5.89 (s, 5H),
5.71 (s, 1H), 5.03 (m, 1H), 4.15 (m, 1H), 3.78-3.71 (m, 1H), 2.22-2.15 (m, 2H), 1.94-1.84 (m, 2H), 1.53-1.35 (m, 2H); $^{13}$C NMR (62.5 MHz, C$_6$D$_6$): δ 204.2, 115.9, 115.1, 114.1, 85.5, 79.1, 37.5, 36.1, 24.8.

Metallacycle (3.6b). The procedure analogous to that used for 3.6a afforded the product 3.6b (0.155 g, 89% yield from the aldehyde 3.1b on a 0.57 mmol scale) as a reddish-brown solid. $^1$H NMR (300 MHz, C$_6$D$_6$): δ 5.96 (s, 5H), 5.95 (s, 5H), 5.74 (s, 1H), 4.21 (s, 1H), 3.93-3.89 (m, 1H), 2.20-1.35 (m, 6H), 1.29 (s, 3H); $^{13}$C NMR (62.5 MHz, C$_6$D$_6$): δ 203.9, 115.6, 115.1, 114.6, 94.2, 81.9, 42.8, 34.6, 27.8, 24.7.

Metallacycle (3.6c). The procedure analogous to that used for 3.6a afforded the product 3.6c (0.148 g, 85% yield from the aldehyde 3.1c on a 0.57 mmol scale) as a reddish-brown solid. $^1$H NMR (250 MHz, C$_6$D$_6$): δ 6.09 (s, 5H), 5.98 (s, 5H), 5.84 (s, 1H), 4.09 (s, 1H), 4.82 (m, 1H), 1.71-1.47 (m, 6H), 1.26 (s, 3H); $^{13}$C NMR (62.5 MHz, C$_6$D$_6$): δ 207.7, 114.9, 114.1, 113.7, 92.0, 82.5, 42.3, 34.9, 26.5, 23.7.
Mixture of metallacycles (3.5e) and (3.6e). The procedure analogous to that used for 3.6a afforded the mixture of products 3.5e and 3.6e in a 4:1 ratio (0.14 g, 80% yield from the aldehyde 3.1e on a 0.58 mmol scale) as a reddish-brown solid. Major product 3.5e: $^1$H NMR (300 MHz, C$_6$D$_6$): δ 6.11 (s, 5H), 6.02 (s, 5H), 5.22 (m, 1H), 4.29 (m, 1H), 3.89 (m, 1H), 2.18-1.35 (m, 6H), 1.74 (d, $J = 6.4$, 3H); $^{13}$C NMR (75 MHz, C$_6$D$_6$): δ 191.5, 124.9, 116.2, 115.4, 86.2, 76.1, 38.5, 34.9, 26.2, 17.7. Minor product 3.6e: $^1$H NMR (300 MHz, C$_6$D$_6$): δ 6.18 (s, 5H), 6.08 (s, 5H), 5.96 (m, 1H), 5.15 (m, 1H), 3.70 (m, 1H), 1.66-1.35 (m, 6H), 1.22 (d, $J = 6.4$, 3H); $^{13}$C NMR (75 MHz, C$_6$D$_6$): δ 192.4, 124.0, 115.5, 114.4, 85.6, 80.9, 38.7, 37.6, 25.7, 20.7.

3.16.3 Spectral Data

Spectral data for the experimental details discussed above are shown on the next page.

3.17 References


(References are continued on page 190)
Figure 3.7 $^1$H NMR and $^{13}$C NMR of Iodide 3.3a
Figure 3.8 $^1$H NMR and $^{13}$C NMR of Allene 3.4a
Figure 3.9 $^1$H NMR and $^{13}$C NMR of Allenic Alcohol 3.5a
Figure 3.10 $^1$H NMR and $^{13}$C NMR of Allenic Aldehyde 3.1a
Figure 3.11 $^1$H NMR and $^{13}$C NMR of Iodide 3.3b
Figure 3.12 $^1$H NMR and $^{13}$C NMR of Allene 3.4b
Figure 3.13 $^1$H NMR and $^{13}$C NMR of Allenic Alcohol 3.5b
Figure 3.14 $^1$H NMR and $^{13}$C NMR of Allenic Ketone 3.1b
Figure 3.15 $^1$H NMR and $^{13}$C NMR of Alkyne 3.3c
Figure 3.16 $^1$H NMR and $^{13}$C NMR of 3,3-Disubstituted Allene 3.4c
Figure 3.17 $^1$H NMR and $^{13}$C NMR of 3,3-Disubstituted Allenic Alcohol 3.5c
Figure 3.18 $^1$H NMR and $^{13}$C NMR of 3,3-Disubstituted Allenic Aldehyde 3.1c
Figure 3.19 $^1$H NMR and $^{13}$C NMR of 3,3-Disubstituted Allene 3.4d
Figure 3.20 $^1$H NMR and $^{13}$C NMR of 3,3-Disubstituted Allenic Alcohol 3.5d
Figure 3.21 $^1$H NMR and $^{13}$C NMR of 3,3-Disubstituted Allenic Aldehyde 3.1d
Figure 3.22 $^1$H NMR and $^{13}$C NMR of Mesylate 3.2e'
Figure 3.23 $^1$H NMR and $^{13}$C NMR of 1,3-Disubstituted Allene 3.3e
Figure 3.24 $^1$H NMR and $^{13}$C NMR of 1,3-Disubstituted Allenic Alcohol 3.4e
Figure 3.25 $^1$H NMR and $^{13}$C NMR of 1,3-Disubstituted Allenic Aldehyde 3.1e
Figure 3.26 $^1$H NMR and $^{13}$C NMR of Allene 3.3f
Figure 3.27 $^1$H NMR and $^{13}$C NMR of Allenic Alcohol 3.4f
Figure 3.28 $^1$H NMR and $^{13}$C NMR of Allenic Aldehyde 3.1f
Figure 3.29 $^1$H NMR and $^{13}$C NMR of Metallacycle 3.6a
Figure 3.30 $^1$H NMR and $^{13}$C NMR of Metallacycle 3.6b
Figure 3.31 $^1$H NMR and $^{13}$C NMR of Metallacycle 3.6c
Figure 3.32 $^1$H NMR and $^{13}$C NMR of Metallacycles 3.5e and 3.6e


3.30. Ginn, J. D. *Titanium Mediated Reductive Cyclization of δ-Alkynyl Aldehydes; Catalytic Carbocyclization and Carbonylation Reactions*, M.S. Department of Chemistry, Emory University, 1996.


4.1 Introduction to Alkaloids

Synthetic chemists have always marveled at Nature’s ability to elaborate a fantastic variety of structurally diverse and frequently very complex substances from a few relatively simple starting materials. Alkaloids, derived from plants or animals, are the picture perfect model of this phenomenon. The term alkaloid was originally coined by Meissner in 1818 to cover alkali-like compounds that contain nitrogen either in a heterocyclic ring or as part of an acyclic chain. Many alkaloids are not, however, notably basic in character and certain nitrogen containing heterocyclic compounds, such the purines and pyrimidines in DNA and RNA, are not considered to be alkaloids.

Medicinally, the alkaloids have played a key role for millennia, and even today some 25% of commercial drugs are either alkaloids or their structural modifications or analogues.

At present, some 6000 natural alkaloids are known. These can be subdivided according to their chemical structures. Typical structural groups are indole alkaloids (e.g. reserpine, which possesses blood pressure reducing properties), pyrrolidine alkaloids (e.g. mesembrine, a potent serotonin uptake inhibitor), tropane alkaloids (cocaine and its relatives, such as atropine and scopolamine; these are anticholinergic agents), quinoline alkaloids (the malaria drug quinine and morphine for pain relief and the izidine alkaloids (securinine, a CNS stimulant, is an indolizidine). Also pilocarpine, a histidine derivative
which is used for the treatment of glaucoma, belongs to this broad class of natural products (Figure 4.1).

![Reserpine, Mesembrine, Pilocarpine, Cocaine, Morphine, Quinine, Securine](Image)

**Figure 4.1 Various Structural Alkaloids**

We are currently directing our interest at the alkaloid family known as izidine alkaloids. These alkaloids include some 500 compounds containing a pyrrolizidine, indolizidine or quinolizidine skeleton (Figure 4.2).

![Pyrrolizidine, Indolizidine, Quinolizidine](Image)

**Figure 4.2 Different Izidine Alkaloid Skeletons**

Several of them have interesting physiological and pharmacological activities. Stirring further interest, some compounds in this class also bear a close resemblance to the amino sugars.4.1
4.2 Research Focus

We shall now further pinpoint our focus on pyrrolizidines and indolizidines. The syntheses of pyrrolizidines have been reviewed. Although many of these compounds occur as mono or bisesters or lactones, the vast majority of efforts have been expended on devising ways to assemble the core necine bases also called 1-hydroxymethylpyrrolizidines with control of the extent and stereochemistry of oxygenation about the ring. The highlight in this very broad area must be the ongoing contribution made by Denmark and his group.

As with the pyrrolizidines, interest in the indolizidines has led to a wide array of new synthetic methodology being developed, but the more useful biological activity profile of certain members of this class has tended to focus efforts, and a host of syntheses of certain individual compounds have been recorded. For example, there have been at least 20 syntheses of monomorine in both racemic and enantiomerically pure forms, but those by Livinghouse and Mori are amongst the most interesting.

Hence, in view of their potent and various biological activities, pyrrolizidine and indolizidine alkaloids as well as structurally related unnatural compounds are continuously stimulating new synthetic approaches. An exhaustive coverage of the literature dealing with pyrrolizidine and indolizidines is currently assured by specialist periodicals.

4.3 Metathesis

Our interest in the diverse applications of these structurally intricate ring systems has propelled us into investigating two proposed ideas. The first concept describes a short and versatile synthesis of indolizidine tailored derivatives, in a process, which constitutes
the first performance of metathesis reactions of the complex \([\text{Cp}_2\text{Ti}=\text{CH}_2]\) with iminoalkyne substrates starting from \(\text{Cp}_2\text{TiMe}_2\).\(^{4,10}\) The blossoming field of metathesis, now encompasses milestone reactions such as olefin metathesis,\(^{4,11}\) enyne metathesis,\(^{4,12}\) and imine metathesis.\(^{4,13}\) Olefin metathesis reactions are very popular and useful reactions, which often occur under very mild conditions in the presence of an active catalytic species. The overall conversion of the reaction proceeds by a series of \([2+2]\) cycloadditions and retrocycloadditions. There are three closely related types of olefin metathesis:\(^{4,14}\) ring opening metathesis polymerization (ROMP), ring closing metathesis (RCM) and exchange metathesis which may yield both self-metathesis and cross-metathesis products (Scheme 4.1). Metathesis catalysts are primarily transition metal complexes of Mo, W, Re, some Group 4 and 5 metals and Ru. Two very important ruthenium catalysts which show remarkable reactivity, selectivity and tolerance against various functional groups are the second generation Grubbs catalyst and the Hoveyda catalyst.\(^{4,15}\) The currently accepted mechanism\(^ {4,16}\) was established by Chauvin and co-workers and involves a cycloaddition reaction between a catalytic amount of metal carbene complex and an olefin to form a metallacyclobutane derivative. The four-membered ring breaks apart in a retrocycloaddition to expel the new olefin and regenerate the metal carbene which continues the cycle (Scheme 4.2).
4.4 Dimethyltitanocene [Cp₂Ti=CH₂]

Dimethyltitanocene, a reasonably stable compound, first synthesized in 1956 by Clauss and Bestian, is readily prepared from methyllithium and titanocene dichloride (Cp₂TiCl₂). It has been extensively used as a reagent for stoichiometric transformations and more recently as a catalyst for some modern applications.⁴.¹⁷-¹⁸ The active species utilized for these reactions is the reactive titanium carbene complex [Cp₂Ti=CH₂]⁴.¹⁹ formed via α–elimination of methane (Scheme 4.3).

Scheme 4.3 Formation of Carbene Complex [Cp₂Ti=CH₂]

Probably one of the most important applications of Cp₂TiMe₂ as a reagent is the methylenation of carbonyl compounds such as aldehydes, ketones, esters, etc, (Scheme 4.4).⁴.¹⁷ The mechanism of the reaction involves a [2+2] cycloaddition between [Cp₂Ti=CH₂] and the carbonyl compound with a final loss of Cp₂TiO (Scheme 4.5).

Scheme 4.4 Methylenation of Various Carbonyl Compounds
Scheme 4.5 Methylenation of γ-Butyrolactone

It is known that [Cp₂Ti=CH₂] is able to initiate the ring-opening metathesis polymerization (ROMP) of Norbornene (Scheme 4.6).⁴¹⁸

Scheme 4.6 Cp₂TiMe₂-Catalyzed ROMP of Norbornene

In combination with tungsten compounds (WOCl₄, WCl₆), Cp₂TiMe₂ further acts as a catalyst for olefin metathesis (Scheme 4.7).⁴²⁰

Scheme 4.7 Olefin Metathesis

4.5 Research Interests

As of yet, there are no reported results on metathesis products between imines and methylidenetitanocene. However, Group 4 carbene complexes are clearly known to react with a range of substrates, including imines, to give olefins. Schwartz and co-workers, discovered that not only does metathesis between zirconium carbene complexes and imines occur, but probed further into an existent correlation between the E/Z selectivity of the olefins formed and the size of the substituent group on the imine nitrogen (Scheme 4.8).⁴²¹ Also, we believe that imine metathesis with carbenes should be analogous to the methylenation reactions of carbonyl compounds.
Thus, based on these findings, we believe that the titanocene carbene complex \([\text{Cp}_2\text{Ti}=\text{CH}_2]\), will likewise perform a [2+2] followed by a retro-[2+2] to form a catalytically active titanium-imido complex (Scheme 4.9).

![Scheme 4.9 Formation of a Titanium-imido Complex](image)

Although it is well known that \([\text{Cp}_2\text{Ti}=\text{CH}_2]\) undergoes facile [2+2] cycloaddition with alkynes to yield titanacyclobutene intermediates (Scheme 4.10),\(^{4,22}\) we believe that the product azatitanocyclobutane formed from the carbene reacting with the imine would be more favorable as compared to the competing titanacyclobutene formation.

![Scheme 4.10 Formation of Titanacyclobutenes](image)

The basis of this assumption is that the Ti-N bond formed is more stable than the Ti-C bond. The ring strain in the intermediate of these two reactions can, moreover, be accounted as one of the reasons for the preference of imine-carbene metathesis over
alkyne-carbene metathesis. The angle difference in titanacyclobutene is approximately 30 degrees, whereas in azatitanocyclobutane, its 19.5 degrees (Scheme 4.11).

Scheme 4.11 Investigating Ti-N Bond Strength and Reduced Ring Strain

Thus, the activation energy towards the formation of the titanacyclobutene is therefore, expected to be higher.

Inspired by the work of Bergman et al. and Livinghouse et al., work done by Doye and co-workers on the recently developed dimethyltitanocene-catalyzed inter- and intra-molecular hydroamination of alkynes also represents another important application of Cp₂TiMe₂ as a catalyst (Scheme 4.12).

Scheme 4.12 Cp₂TiMe₂-Catalyzed Intermolecular Hydroamination
It is assumed that Cp₂TiMe₂ reacts with an amine under loss of methane to form a catalytically active titanium-imido complex which undergoes a [2+2] cycloaddition with the alkyne. The resulting azatitanacyclobutene is then irreversibly protonated by further amine to form a titanocene bisamide, which is thermally cleaved into an enamine and the catalytically active titanium-imido complex. Finally, the enamine is converted into the imine under reaction conditions.

With exactly the same intermediate at hand, we expect our titanium-imido complex to undergo an intramolecular [2+2] cycloaddition with the alkyne end on the substrate followed by a retro [2+2] to generate a carbene complex which could further react with the starting material to form the desired product (Scheme 4.13).

\[ \text{N} \quad \text{H} \quad \text{R} \]
\[ \text{N} \quad \text{H} \quad \text{R} \]
\[ \text{Cp}_2\text{Ti} \quad \text{N} \quad \text{H} \quad \text{R} \]

\( \text{Cp}_2\text{Ti}=\text{CH}_2 \)

\[ 1\text{st Cycle} \]

\[ \text{Cp}_2\text{Ti} \quad \text{N} \quad \text{H} \quad \text{R} \]
\[ \text{N} \quad \text{H} \quad \text{R} \]

\[ 2\text{nd Cycle} \]

\( \text{R} = \text{Phenyl} \)

**Scheme 4.13 Postulated Imine-Alkyne Metathesis Mechanism**

Alternatively, a possible imine insertion may occur into the titanium-vinyl bond of the azatitanacyclobutene. The corresponding 6-membered diazatitanacycloclohexene derivative may then undergo subsequent retro [4+2]
cycloaddition to afford the desired product and regenerate the active titanium-imido complex (Scheme 4.14).

![Scheme 4.14 Alternative Imine-Alkyne Insertion Mechanism](image)

**Scheme 4.14 Alternative Imine-Alkyne Insertion Mechanism**

Evidence for this proposed imine insertion mechanism comes from Doxsee et al.\textsuperscript{4,26} They previously reported unprecedented reactions of titanacyclobutenes, in which nitriles preferentially insert first into the titanium-vinyl bond of the titanacycle, then into the titanium-alkyl bond. They then, more recently reported that ketones and aldehydes undergo analogous preferential insertions into the titanium-vinyl bond of titanacyclobutenes (Scheme 4.15).

![Scheme 4.15 Evidence of Insertion Mechanism](image)
This insertion is followed not by a second insertion, as observed for the nitrile reactions, but rather by facile thermal decomposition of the metallocyclic insertion product, apparently via a retro [4+2] reaction, to afford conjugated dienes in synthetically useful yields.

As a result, we believe that existent literature provides evidence which suggests that dimethyltitanocene may react with imino-alkynes via dual pathways depending on reaction conditions, one via the titanium carbene and one via an insertion mechanism. The scope of our study will involve investigating the behavior of the new catalytically active titanium-imido complexes and determining if the resulting conjugated azadiene species can further undergo a possible inverse electron demand aza-Diels-Alder reaction to form indolizidine alkaloid derivatives (Scheme 4.16).

\[
\begin{align*}
\text{N} & \quad \text{A} & \quad \text{B} \\
\text{R}_1 & \quad \text{Cp}_2\text{M}=\text{CH}_2 & \quad \text{A} & \equiv \text{B} & \quad [4+2] \\
\text{R}_2 & \quad \text{N} & \quad \text{R}_1 & \quad \text{R}_2 & \quad \text{R}_1 & \quad \text{R}_2
\end{align*}
\]

**Scheme 4.16 Performing Aza-Diels-Alder Reactions**

The second proposal is a novel, efficient synthetic route to pyrrolizidine alkaloids. Our research group recently reported the formal [2+2+1] cycloaddition of an alkene, a carbonyl and carbon monoxide towards the catalytic asymmetric carbonylation of \(\gamma\)-butyrolactone ring skeleton (Scheme 4.17).\(^{4.27}\)

\[
\begin{align*}
\text{R} & \quad \text{Y} & \equiv \text{O} & \quad \text{X} & \quad \text{O} & \quad \text{C} & \equiv \text{O} \\
\text{R} & \quad \text{Y} & \equiv \text{H} & \quad \text{X} & \equiv \text{Y} & \quad \text{X} & \equiv \text{O} & \quad \text{H} & \equiv \text{H} \\
\text{R} & \equiv \text{Ph} \text{ or } X & \equiv Y & \equiv \text{o-phenylene}
\end{align*}
\]

**Scheme 4.17 Hetero-Pauson-Khand Reaction**
This reaction is more commonly known as the Hetero-Pauson-Khand reaction.\textsuperscript{4.28} The initial step of this reaction involves reductive coupling (Scheme 4.18).

\[ \text{L}_n\text{M} + \text{A} = \text{B} \xrightarrow{\text{Reductive Coupling}} \text{L}_n\text{M} \]

\[ M = \text{Ti, Zr, Hf, Nb, Ta}..... \]
\[ A, B = \text{C, N, O} \]
\[ \text{L}_n = \text{ligand} \]

\textbf{Scheme 4.18 Reductive Coupling}

Transition metal-mediated intramolecular reductive coupling refers to the coupling of a pair of linked unsaturated organic bonds to a metallacene with concomitant formation of a new carbon-carbon bond.\textsuperscript{4.29} The unsaturated organic fragments can be either alkenes, alkynes, carbonyls or imines. \((\text{Cp}_2\text{Zr})\) and synthetic equivalents of \(\text{Ti(II)}\) are used frequently to affect reductive coupling and the \(\text{Cp}_2\text{M}\) complexes formed are referred to as metallacycles.

In 1996, Sato and co-workers reported a protocol for the synthesis of substituted pyrroles (Scheme 4.19).\textsuperscript{4.30} Hence, azatitanacyclopentenes formed by reductive coupling of \(\delta\)-alkynyl imines using \(\text{Ti(O-i-Pr)}_4/2\ i\text{-PrMgCl}\), could be carbynolated under standard atmospheric pressure of CO to afford bicyclic pyrroles in good yields.

\[ \begin{array}{c}
\text{R}_1\text{N=CH} \xrightarrow{\text{Ti(O-i-Pr)}_4/2\ i\text{-PrMgX}} \text{N} = \text{CHR} \xrightarrow{\text{CO}} \text{N} = \text{CHR} \\
\text{R}_2 \end{array} \]

\[ n = 1, 2 \]

\textbf{Scheme 4.19 Reductive Coupling of \(\delta\)-Alkynyl Imines}
In 1999, Murai and co-workers reported the Ru$_3$(CO)$_{12}$-catalyzed cyclocarbonylation of yne-imines (Scheme 4.20).$^{4,31}$ The reaction is an intramolecular [2+2+1] cycloaddition incorporating the acetylenic π-bond, the imine π-bond and the carbon atom of CO. The product of these reactions is a γ-lactam.

We, on the other hand, are interested in exploring this reaction with Cp$_2$Ti(PMe$_3$)$_2$,$^{4,32}$ a stable and isolable titanocene equivalent. We plan to coupling it with an imino-alkyne substrate, followed by carbonylation (Scheme 4.21). This route should directly lead toward the formation of the pyrrolizidine building block.

Thus, described in this study are the development of titanium-mediated reductive cyclocarbonylation and an imino-alkyne cross-metathesis strategy towards the synthesis of pyrrolizidine and indolizidine alkaloids respectively. The same substrates are employed for both reaction pathways.
4.6 Discussion

To obtain the imino-alkyne substrate we decided to first synthesize the aminoalkyne precursor and then react it with an appropriate aldehyde to form the desired imine bond. We first synthesized the aminoalkyne based on the technique known as the Ing-Mnske procedure (Method A). This method is a modification of the Gabriel synthesis in which the reaction of hydrazine with phthalimide or its N-substituted derivatives is used in the preparation of primary amines (Scheme 4.22).

Scheme 4.22 Modified Gabriel Synthesis of Amines

To obtain our target aminoalkyne, we began with commercially available 5-chloro-1-pentyne, 4.1a. This was reacted with sodium iodide and potassium phthalimide 4.2a at 100 °C in dimethylformide (DMF) (Scheme 4.23) to afford N-4-pentynylphthalimide 4.3a quantitatively.

Scheme 4.23 Synthesis of Phthalamide 4.3a

N-4-pentynylphthalimide 4.3a and hydrazine monohydrate were then allowed to react at 60 °C, overnight, followed by addition of concentrated hydrochloric acid. After workup, distillation afforded a 30% yield of 4-pentyn-1-amine 4.4a (Scheme 4.24).
The low yield obtained by this method geared us into exploring one other possible route. This alternative route to obtaining 4-pentyn-1-amine 4.4a (Method B) was by an innovative method in which 4-pentyn-1-ol 4.3b was utilized as a key synthon and was converted into 4-pentyn-1-amine 4.4a using NaN₃ and PPh₃ in CCl₄-DMF (1:4). This reaction occurs in one step to yield the desired amine and a general scheme of this convenient and efficient one pot sequence is shown below (Scheme 4.25).

**Scheme 4.25 Alternative Synthesis of Amines**

4-pentyn-1-ol 4.3b can be derived from the inexpensive, commercially available tetrahydrofurfuryl alcohol 4.1b \textit{via} the chloride; tetrahydrofurfuryl chloride 4.2b (Scheme 4.26). One of the most convenient methods for converting alcohols to chlorides is based on \textit{in situ} generation of chlorophosphonium ions\textsuperscript{4.36} by reactions of triphenylphosphine with various chlorine compounds such as carbon tetrachloride\textsuperscript{4.37}. In order to obtain the chloride, 4.2b which will be converted into the amine 4.4a as described in the preceding paragraph, we decided to follow the procedure developed by Takano et al\textsuperscript{4.38-39}. In Takano’s paper, this route is applied to the construction of optically active 3-hydroxyalkyne functionalities using optically active α,β-epoxy alcohols\textsuperscript{4.40} (Scheme 4.26).
Scheme 4.26 Takano’s Route

Starting from tetrahydrofurfuryl alcohol 4.1b, we applied the same set of conditions (Ph₃P, 1.2 equiv.) for chlorination. Tetrahydrofurfuryl alcohol 4.1b and triphenylphosphine in excess carbon tetrachloride were refluxed for 4.5 h, during which time the chlorophosphonium ion reacted with the alcohol to give an alkoxyphosphonium ion, which was then converted to tetrahydrofurfuryl chloride 4.2b. Exposure of the chloride to butyllithium (3 equiv.) in tetrahydrofuran (THF) at -35 °C provided 4-pentyn-1-ol 4.3b in 85% yield, presumably via a sequence triggered by initial generation of an α-chlorocarbanion (Scheme 4.27).

Scheme 4.27 Synthesis of Alcohol 4.3b

As mentioned earlier, to obtain the aminoalkyne 4.4a, we followed the convenient and efficient one-pot sequence developed by Reddy et al.⁴.³⁵ for the transformation of alcohols to amines using sodium azide and triphenylphosphine in CCl₄-DMF (Scheme 4.28).
Scheme 4.28 Synthesis of Amine 4.4a (Method B)

Formation of the aminoalkyne may be visualized as the initial azide formed would react with the second equivalent of triphenylphosphine giving the iminophosphorane, which in turn converts into the aminoalkyne upon treatment with water (Scheme 4.29).

Scheme 4.29 Iminophosphorane Formation

In summary, this alternative sequence of reactions provides an advantageous preparation of 4-pentyn-1-amine 4.4a over the Gabriel route based on higher yields and shorter number of steps. We next synthesized the desired imino-alkyne substrate 4.2c by a simple equimolecular condensation reaction\(^4\) between 4-pentyn-1-amine 4.4a and benzaldehyde 4.1c (Scheme 4.30). Anhydrous magnesium sulfate was successively added during the course of the reaction to remove the water formed during imine formation.

Scheme 4.30 Synthesis of Imine 4.2c
After the reaction was complete, the mixture was filtered, and the volatiles evaporated to obtain 4.2c as a bright yellow syrup (90% yield). Having our desired substrate at hand, we now focused on the proposed reactions.

### 4.7 Results

Our cross-metathesis and cyclocarbonylation precursor 4.2c has been synthesized. We next undertook the titanium catalyzed/mediated cross-metathesis of 4.2c to produce the azadiene moiety.

In order accomplish this, we synthesized the dimethyltitanocene reagent following a published literature procedure. Several reactions were carried out under a variety of reaction conditions, summarized in Table 4.1.

**Table 4.1 Attempted Titanium Mediated Cross-Metathesis Conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20 mol % Cp₂TiMe₂, 60-65 °C, 48 h, Toluene</td>
<td>No Reaction</td>
</tr>
<tr>
<td>2</td>
<td>20 mol % Cp₂TiMe₂, 110 °C, 48 h, Toluene</td>
<td>No Reaction</td>
</tr>
<tr>
<td>3</td>
<td>0.5 equiv. Cp₂TiMe₂, 110 °C, 48 h, Toluene</td>
<td>No Reaction</td>
</tr>
<tr>
<td>4</td>
<td>0.5 equiv. Cp₂TiMe₂, 60-65 °C, 48 h, THF</td>
<td>No Reaction</td>
</tr>
<tr>
<td>5</td>
<td>1.0 equiv. Cp₂TiMe₂, 110 °C, 48 h, THF</td>
<td>No Reaction</td>
</tr>
</tbody>
</table>

Under the conditions described no titanium mediated cross metathesis was observed. The imino-alkyne starting material could be recovered.

We also attempted the synthesis of the pyrrolizidine alkaloid skeleton 4.5c *via* titanium mediated cyclocarbonylation of 4.2c (Scheme 4.31).
Scheme 4.31 Attempted Synthesis of Metallacycle 4.4c

Cp₂Ti(PMe₃)₂ was synthesized following a published literature procedure.⁴.⁴³ The reaction conditions and results for the reductive coupling step is as follows in Table 4.2.

**Table 4.2 Attempted Reductive Coupling Conditions for Imine 4.2c**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 equiv. Cp₂Ti(PMe₃)₂, rt, 2 h, Pentane</td>
<td>Green Oil, Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>1.0 equiv. Cp₂Ti(PMe₃)₂, rt, 2 h, Ether</td>
<td>Green Oil, Decomposition</td>
</tr>
</tbody>
</table>

The first reductive cyclization reaction was run with a stochiometric amount of Cp₂Ti(PMe₃)₂ utilizing pentane as the reaction solvent. This resulted in a green color in the reaction and subsequently a green oil which simply showed decomposition of both reagent and 4.2c via NMR. The next solvent tried was diethyl ether. Identical observations were made. Work done by Negishi⁴.⁴⁴ has shown that terminal acetylenes undergo reductive cyclizations very poorly or not at all presumably due to the reaction of the acidic acetylenic hydrogen with the basic metallacene. In concluding, a different strategy will have to be invented for the synthesis of such interesting alkaloids and will be the topic of future accounts from this laboratory.

**4.8 Experimental Section**

**4.8.1 General Methods**

All the experiments were performed under a nitrogen or argon atmosphere in oven dried glassware. Solvents used as reaction media were distilled immediately before use. Diethyl ether, THF, pentane, and toluene were distilled from Na/benzophenone ketyl.
Methylene chloride was distilled from calcium hydride. Other reagents were purified by simple distillation or passed through a short column of activated alumina or silica gel.

$^1$H spectra and $^{13}$C NMR spectra were recorded on a Bruker 250 MHz spectrometer in deuterated chloroform (CHCl$_3$: 7.27 ppm $^1$H, 77.23 ppm $^{13}$C). Chemical shifts (δ) are given in parts per million down from tetramethylsilane (TMS); multiplicities are indicated as br (broadened), s (singlet), t (triplet), q, quintet, td (triplet of doublets), m (multiplet), coupling constant (Hz), and intergration.

Analytical TLC was performed on Scientific Adsorbent Company Inc. silica gel plates. Components were visualized by illumination with long wave ultraviolet light, exposure to iodine vapor, or by standing with p-anisaldehyde in ethanol/sulfuric acid. Flash column chromatography was performed using silica gel (Scientific Adsorbent Company Inc. 32-63 μm particle size, 60 Å pore size).

### 4.8.2 Preparative Procedures

N-4-Pentynylphthalimide (4.3a). A suspension of 5-chloro-1-pentyne 4.1a (2.5 g, 24 mmol), potassium phthalimide (5.4 g, 29 mmol), and NaI (15.3 mg) in DMF (16 mL) was refluxed, with stirring, under inert atmosphere, at 100 °C overnight. The solution was allowed to warm to room temperature and treated with water (16 mL). N-4-entynylphthalimide 4.3a crystals immediately precipitated. The product was then washed with copious amounts of water to remove any residual DMF. The pure yellow crystals
(5.16 g) were then dried under high vacuum and used in the next step without further purification. Yield (99%). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 7.84-7.81 (m, 2H), 7.71-7.68 (m, 2H), 3.78 (t, $J = 6.6$ Hz, 2H), 2.27-2.23 (m, 2H), 1.94-1.85 (m, 3H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 168.7, 134.3, 132.5, 123.6, 83.4, 69.4, 37.5, 27.7, 16.6.

4-pentyn-1-amine (4.4a) (Method A). N-4-pentynylphthalimide 4.3a (4.0 g, 19.0 mmol) and hydrazine monohydrate (2.557 g, 51.0 mmol) in MeOH (170 mL) were heated with stirring at 60 °C overnight. After the mixture was cooled to room temperature, followed by the addition of concentrated HCl, (3.5 mL) the solution was heated at 60 °C for an additional 4 h. The mixture was then cooled and filtered, and the white precipitate washed with EtOH (50 mL). Removal of solvent from the combined filtrates at reduced pressure gave a white precipitate. The white solid was then treated with a mixture of KOH (2N, 18 mL) and diethyl ether (15 mL). After separation, the organic phase was extracted with diethyl ether (3x10 mL). The ether phase was then washed with brine (5 mL) and dried over Na$_2$SO$_4$. After filtration and removal of solvent from the filtrate by rotary evaporation, distillation (124-125 °C) afforded 4-pentyn-1-amine (0.466 g). Yield (30%). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 2.62 (t, $J = 13.7$ Hz, 2H), 2.09 (td, $J = 7.0$ Hz, $J = 2.6$ Hz, 2H), 1.82 (t, $J = 2.6$ Hz, 1H), 1.51-1.42 (m, 2H), 1.40 (br s, 2H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 84.2, 68.9, 41.2, 32.2, 16.1.
Tetrahydrofurfuryl chloride (4.2b). A solution of tetrahydrofurfuryl alcohol (13 g, 127 mmol) and triphenylphosphine (40 g, 150 mmol) in CCl₄ (115 mL) was refluxed for 4 h. After the solution was cooled to room temperature, Et₂O (60 mL) was added to the mixture, and the solid that separated was removed by filtration. The filtrate was concentrated to give an oil (11.5 g), which was used without further purification. Yield (75%). ¹H NMR (250 MHz, CDCl₃): δ 4.17-4.12 (m, 1H), 3.94-3.83 (m, 2H), 3.58-3.52 (m, 2H), 2.09-1.92 (m, 3H), 1.80-1.70 (m, 1H); ¹³C NMR (62.5 MHz, CDCl₃): δ 78.7, 69.1, 47.2, 29.6, 26.1.

4-pentyn-1-ol (4.3b). To a -35 °C, stirred solution of tetrahydrofurfuryl chloride (2.48 g, 21 mmol) in THF (23 mL) was added drop-wise BuLi (37.2 mL in a 1.66 M solution in hexane, 62 mmol) under N₂. The mixture was stirred at the same temperature for 4 h, quenched with water (20 mL), and extracted with Et₂O (20 mL). The extracts were washed with brine (15 mL), dried (MgSO₄), and concentrated. Column chromatography (silica gel, hexanes/Et₂O, 2:1) yielded the purified residual oil. Yield (85%). ¹H NMR (250 MHz, CDCl₃): δ 3.58 (m, 2H), 2.17 (m, 2H), 1.89 (t, J = 2.6 Hz, 1H), 1.64 (q, J = 6.6 Hz, 2H); ¹³C NMR (62.5 MHz, CDCl₃): δ 84.2, 69.2, 61.2, 31.3, 15.1.
4-pentyn-1-amine (4.4a) (Method B). A mixture of alcohol (0.73 g, 0.868 mmol), sodium azide (0.68 g, 10 mmol) and triphenylphosphine (4.78 g, 18 mmol) in CCl₄-DMF (1:4) (44 mL) was warmed at 90 °C with stirring. After total disappearance of starting material (monitored by TLC: 2:1 (Hexane: Et₂O)), reaction mixture was brought to room temperature and quenched by adding water (21 mL). After stirring for 10 min, the reaction mixture was diluted with ether (30 mL) and washed thoroughly with water. By tituration of the ether fraction at 0 °C, triphenylphosphine oxide was crystallized out and ether was filtered off. After drying over anhydrous Na₂SO₄, filtration and concentration of solvent afforded the amine in pure form (0.58 g) as a yellow liquid. Yield (90%). ¹H NMR (250 MHz, CDCl₃): δ 2.62 (t, J = 13.7 Hz, 2H), 2.09 (td, J = 7.0 Hz, J = 2.6 Hz, 2H), 1.82 (t, J = 2.6 Hz, 1H), 1.51-1.42 (m, 2H), 1.40 (br s, 2H); ¹³C NMR (62.5 MHz, CDCl₃): δ 84.2, 68.9, 41.2, 32.2, 16.1.

Imino-Alkyne substrate (4.2c). 4-pentyn-1-amine 4.4a (1.00 g, 12 mmol) and benzaldehyde 4.1c (1.28 g, 12 mmol) were allowed to react overnight in methylene chloride (30 mL) at room temperature in the presence of anhydrous MgSO₄ (3.0 g). After filtration, the solvent was removed and the product isolated in pure form (1.85 g). Yield (90%). ¹H NMR (250 MHz, CDCl₃): δ 8.30 (s, 1H), 7.75-7.72 (m, 2H), 7.41-7.39 (m,
3H), 3.74-3.69 (m, 2H), 2.32-2.25 (m, 2H), 2.00-1.91 (m, 3H); $^{13}$C NMR (62.5 MHz, CDCl$_3$): δ 161.9, 136.6, 131.0, 129.0, 128.5, 84.3, 69.2, 60.2, 29.8, 16.5.

4.8.3 Spectral Data

Spectral data for the experimental details discussed above are shown on the next page.

4.9 References


(References are continued on page 221)
Figure 4.3 $^1$H NMR and $^{13}$C NMR of Phthalamide 4.3a
Figure 4.4 $^1$H NMR and $^{13}$C NMR of Chloride 4.2b
Figure 4.5 $^1$H NMR and $^{13}$C NMR of Alcohol 4.3b
Figure 4.6 $^1$H NMR and $^{13}$C NMR of Amine 4.4a
Figure 4.7 $^1$H NMR and $^{13}$C NMR of Imine 4.2c


VITA

Maria Appeaning was born on September 7, 1979 to a Ghanian father and Ukranian mother, Mr. and Mrs. Appeaning. She was born and raised in Ghana. Upon graduation from high school, she enrolled at Southern University A&M College in August 1996. Throughout her matriculation at Southern University, she maintained a 4.0 GPA. She belonged to a number of national and professional honor societies that include, Golden Key National Honor Society and the American Chemical Society (ACS). She earned her bachelor’s degree in chemistry in 2000. In the fall of 2000, she started her studies towards a doctoral degree in chemistry at Louisiana State University and joined Dr. William Crowe’s research group. Her dissertation work focused on the titanium-mediated Hetero Pauson-Khand reaction of different funtionalized substrates. The degree of Doctor of Philosophy will be conferred on Maria at the December 2006 Commencement.