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Process Improvement of Rac-Progesterone and Other Synthetic Studies

Rimantas Slegeris
PROCESS IMPROVEMENT OF RAC-PROGESTERONE AND OTHER SYNTHETIC STUDIES

By

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# TABLE OF CONTENTS

LIST OF TABLES .......................................................................................................................... vi
LIST OF FIGURES ........................................................................................................................ vii
LIST OF ABBREVIATIONS ............................................................................................................. xi
ABSTRACT ...................................................................................................................................... xviii

CHAPTER ONE - SYNTHETIC APPROACH TOWARDS ALDINGENIN B: LITERATURE OVERVIEW, RETROSYNTHESIS, AND SIGNIFICANCE OF WORK ............................................................ 1

1.1. Literature Overview ........................................................................................................... 1

1.1.1. Marine Natural Products From Red Algae Genus *Laurencia* ........................................ 1
1.1.2. Isolation of Aldingenin B ............................................................................................. 3
1.1.3. Structural Determination of Aldingenin B .................................................................. 4
1.1.4. Biosynthesis of Aldingenin A ...................................................................................... 5

1.2. Retrosynthetic Analysis, Project Aims and Significance of Work ...................................... 6

1.2.1. Retrosynthetic Analysis ............................................................................................... 6
1.2.2. Strategic Analysis of Keto-ketalization Step, and Potential Road Blocks ..................... 7
1.2.3. Strategic Analysis of the Second Key Step - an Enantioselective Synthesis of *anti*-Homopropargylic Alcohol (HPA) ............................................................................................. 10
1.2.4. Summary / project aims .............................................................................................. 14

CHAPTER TWO - SYNTHETIC APPROACH TOWARDS ALDINGENIN B: RESULTS AND DISCUSSION .......................................................................................................................... 15

2.1. Synthesis of the Model Substrate 31 .................................................................................. 15
2.2. Keto-ketalization and Proposed Mechanism ..................................................................... 18
2.3. Alternative Conditions Investigated .................................................................................. 20
2.4. Attempted Incorporation of Fragmentation Chemistry .................................................... 20
2.5. Total Synthesis of Proposed Structure of Aldingenin B by Crimmins *et. al.*^25^ ............ 23
2.6. Structural Discrepancies, Reported by Crimmins *et. al.*, and Relationship of Their Intermediates to Our Intermediates ........................................................................................................ 26
2.7. Summary / Conclusion .................................................................................................... 29

CHAPTER THREE - EPIDEMIOLOGY OF TRAUMATIC BRAIN INJURY: A RATIONALE FOR THE IMPROVED SYNTHESIS OF *ent*-PROGESTERONE, AND OVERVIEW OF THE STRATEGY .......................................................................................................................... 30

3.1. Epidemiology of Traumatic Brain Injury (TBI) ................................................................ 30
3.2. Differences of Effects of Progesterone (PROG) and *ent*-Progesterone (*ent*-PROG) on Living Organisms ................................................................................................................................. 33
3.3. Literature Overview of Existing Syntheses of ent-Progesterone ................................................. 35
  3.3.1. Synthesis of ent-Progesterone by Auchus et. al. / Rychnovsky et. al. .......................... 35
  3.3.2. Synthesis of rac-Progesterone by Johnson42 .......................................................... 38
  3.3.3. Other Approaches to Tetracyclic Steroid Cores ......................................................... 40

3.4. The Strategy .......................................................................................................................... 45

CHAPTER FOUR - AN IMPROVED TOTAL SYNTHESIS OF RAC-PROGESTERONE ....... 47

4.1. The Improved Synthesis of Aldehyde 94 ............................................................ 47
  4.1.1. Aldehyde Synthesis, Gen. #1 .................................................................................. 48
  4.1.2. Aldehyde Synthesis, Gen. #2 .................................................................................. 49
  4.1.3. Aldehyde Synthesis, Gen. #3 .................................................................................. 51

4.2. Synthesis of trans-Central Double Bond ......................................................................... 54
  4.2.1. Investigation of the Synthesis of trans-Central Double Bond via Reductive 1,3-
         Transposition of α,β-Unsaturated Hydrazone .......................................................... 55
  4.2.2. Synthesis of trans-Central Double Bond via Julia-Kocienski Olefination .......... 58
  4.2.3. Investigation of the Synthesis of trans-Central Double Bond via Takai Olefination /
         Suzuki Coupling ......................................................................................................... 61
  4.2.4. Synthesis of trans-Central Double Bond via Cyclopropyl-homoallyl Rearrangement
                                                  ................................................................................................................................. 66

4.3. Summary / Conclusion ...................................................................................................... 72

CHAPTER FIVE - COST ANALYSIS OF THE ORIGINAL JOHNSON’S ROUTE VS. IMPROVED ROUTE ..................................................................................................................... 73

CHAPTER SIX - FUTURE DIRECTIONS: KINETIC RESOLUTION AND ENANTIOSELECTIVE CASCADE STUDIES ............................................................. 76

6.1. The Kinetic Resolution Strategies ...................................................................................... 76

6.2. The Enantioselective Cascade .......................................................................................... 78

APPENDIX A - BENZYLATION REACTIONS OF BENZYLOXYPYRIDINIUM TRIFLATE IN THE MICROWAVE ........................................................................................................................................ 83

APPENDIX B - EXPERIMENTAL CHAPTER II ........................................................................... 99

APPENDIX C - EXPERIMENTAL CHAPTER IV ..................................................................... 128

REFERENCES ............................................................................................................................ 162

BIOGRAPHICAL SKETCH ....................................................................................................... 175
LIST OF TABLES

Table 1.1: Spectral data, reported by Lago et al.6b .................................................................................. 4

Table 1.2: Known methods to oxidize dialkyl alkynes to diones .......................................................... 9

Table 2.1: Oxidative keto-ketalization results from our lab ................................................................. 23

Table 2.2: Crimmins group comparison of synthetic vs. natural sample data25 ....................................... 26

Table 4.1: Optimization of dual alkylation ......................................................................................... 52

Table 4.2: Optimization of Julia-Kocienski reaction of sulfone 147 ...................................................... 60

Table 4.2: Attempted Suzuki couplings of 157 .................................................................................... 64

Table 4.3: Attempted couplings of 157 with alkenyl bromides .............................................................. 65

Table 4.4: Ligand screen to reduce β-hydride elimination / reinsertion .................................................. 68

Table A.1: Benzyl-transfer reactions of 1 with various alcohols, carboxylic acids, and other substrates under MW heating ........................................................................................................ 87
LIST OF FIGURES

Figure 1.1: Several natural products from red algae genus *Laurencia*................................. 2

Figure 1.2: Originally proposed structures of aldingenins (image source *ref. 1d*) ................. 3

Figure 1.3: Proposed biosynthesis of aldingenin A .................................................................. 5

Figure 1.4: Our retrosynthetic analysis for aldingenin B........................................................... 7

Figure 1.5: Rationale for one step oxidation / ketalization.......................................................... 8

Figure 1.6: Homopropargylic alcohols .................................................................................... 10

Figure 1.7: Recently discovered useful transformations of homopropargylic alcohols ........... 11

Figure 1.8: Recent use of HPA’s in total synthesis (HPA fragment in final product highlighted in blue) ......................................................................................................................................... 12

Figure 1.9: Synthesis of HPA’s via addition of allenyl reagents to aldehydes............................ 12

Figure 1.10: Nucleophilic addition / fragmentation to give HPA’s............................................ 13

Figure 1.11: Synthesis of homopropargylic alcohol 30, envisioned for aldingenin B .......... 14

Figure 2.1: Initial target for oxidative keto-ketalization study .................................................. 15

Figure 2.2: Synthesis of diol 35 ................................................................................................. 16

Figure 2.3: Selectivity of hydroboration / oxidation in the synthesis of 38................................. 17

Figure 2.4: Synthesis of 41 ....................................................................................................... 18

Figure 2.5: Oxidative keto-ketalization and proposed mechanism............................................. 19

Figure 2.6: Retrosynthesis for incorporation of fragmentation chemistry................................. 20

Figure 2.7: Synthesis of α–bromoacid 51 .................................................................................... 21

Figure 2.8: Synthesis of keto-ketalization precursor 59 ............................................................. 22

Figure 2.9: Crimmins’s synthesis of aldehyde 68................................................................. 24

Figure 2.10: Crimmins’s synthesis of tricyclic core .................................................................. 24
Figure 2.11: Crimmins’s endgame strategy for aldingenin B ................................................................. 25

Figure 2.12: Comparision of tricyclic core 77: ours vs. Crimm’s .......................................................... 27

Figure 2.13: Originally proposed and revised structures of aldingenin C ............................................ 28

Figure 3.1: CDC statistics on TBI for years 2001-201028 (ED visits, hospitalizations - bar chart (values on the left); deaths - line chart (values on the right.). ................................................................. 31

Figure 3.2: Experimental treatments for TBI ......................................................................................... 32

Figure 3.3: Progesterone production and receptors in nervous system38a. Progesterone is produced from pregnenolone with the assistance of 3-β-hydroxysteroid dehydrogenase/Δ-5-4 isomerase and it can interact with membrane as well as nuclear receptors. ......................................................................................... 34

Figure 3.4: Rychnovsky’s synthesis of ent-testosterone ......................................................................... 36

Figure 3.5: Homologation of ent-testosterone to ent-progesterone. ..................................................... 37

Figure 3.6: Synthesis of 93 ..................................................................................................................... 38

Figure 3.7: Synthesis of tertiary alcohol 97 ............................................................................................ 39

Figure 3.8: The cascade reaction and the completion of synthesis .......................................................... 40

Figure 3.9: Cascade reactions to construct steroid cores ....................................................................... 41

Figure 3.10: Some examples of radical cascades to access steroid cores .............................................. 42

Figure 3.11: Cycloaddition reactions to access steroids .......................................................................... 42

Figure 3.12: Reactions to access steroid cores ....................................................................................... 44

Figure 3.13: Central objectives .............................................................................................................. 45

Figure 4.1: Synthesis of aldehyde 94 by Johnson .................................................................................. 47

Figure 4.2: First generation synthesis of aldehyde 94 ......................................................................... 48

Figure 4.3: Reactions of geraniol ........................................................................................................... 49

Figure 4.4: Second generation approach to aldehyde 94 ..................................................................... 50

Figure 4.5: Propyne dianion synthons ................................................................................................ 51

Figure 4.6: Optimal synthesis of aldehyde 94 ..................................................................................... 54
Figure 4.7: Strategies for the synthesis of trans-central alkene ................................................... 54
Figure 4.8: Reductive transposition of $\alpha,\beta$-unsaturated .......................................................... 55
Figure 4.9: Reductive transposition model .................................................................................. 56
Figure 4.10: Attempted alkylations ........................................................................................... 57
Figure 4.11: Attempted cross-metathesis .................................................................................. 57
Figure 4.12: The Julia olefination and Julia-Kocienski modification ........................................ 58
Figure 4.13: Synthesis of sulphone 147 ....................................................................................... 59
Figure 4.14: Synthesis of sulphones 150 and 152 ...................................................................... 61
Figure 4.15: Takai olefination / B-alkyl Suzuki coupling strategy .............................................. 61
Figure 4.16: Attempted diboron lynchpin strategy ...................................................................... 62
Figure 4.17: Takai olefination of aldehyde 94 ............................................................................. 62
Figure 4.18: Synthesis of potassium trifluoroborate reagent 157 ............................................ 63
Figure 4.19: Strategies for accessing 161 ................................................................................... 66
Figure 4.20: One-pot synthesis of homoallyl bromide 159 ....................................................... 67
Figure 4.21: Suzuki coupling to give 96 ....................................................................................... 69
Figure 4.22: Attempted borylations of 159 ................................................................................ 69
Figure 4.23: Completion of synthesis of 96 ............................................................................... 70
Figure 4.24: Completion of the synthesis of rac-progesterone .................................................. 71
Figure 5.1: Synthetic intermediates from the new route (top) and the Johnson’s route (bottom) 74
Figure 5.2: Tree analysis of the RMC for the new route an original Johnson’s route displaying: moles of reagent / price per mole of reagent / total price of reagent / reagent name / MW .... 75
Figure 6.1: Kinetic resolution strategies of tetracycle 99 ........................................................... 76
Figure 6.2: Kinetic resolution strategies of rac-progesterone ................................................... 77
Figure 6.3: Asymmetric epoxidation of $\alpha,\beta$-unsaturated ketones by List et. al. 67 .............. 77
Figure 6.4: Early reports of proton-induced enantioselective cascades to construct tetracyclic or larger cores.

Figure 6.5: Alternative enantioselective cascade reactions to access polycycles.

Figure 6.6: More recent enantioselective cascades.

Figure 6.7: Possible enantioselective cascade for the synthesis of ent-progesterone.

Figure A.1: 2-Benzyl oxy-1-methylpyridinium triflate (174), and benzyl ethers (OBn) optimally or uniquely prepared using 174 (yield in parentheses).

Figure A.2: Optimization of reaction for the microwave.
LIST OF ABBREVIATIONS

δ – chemical shift

µg – microgram

µM – micromolar

3β-HSD – 3-β-hydroxysteroid dehydrogenase/Δ-5-4 isomerase

Ac – acetyl

Ac₂O – acetic anhydride

Acetyl-CoA – acetyl coenzyme A

AD-mix α – asymmetric dihydroxylation mix α

AD-mix β – asymmetric dihydroxylation mix β

AIBN – azobisisobutyronitrile

app. – apparent

Aux* – chiral auxilliary

BBD – broadband decoupled

Bn – benzyl

Boc – tert-Butyloxycarbonyl

BT – benzothiazole

BuLi – n-butyllithium

calcd. – calculated

cat. – catalytic ammount

CDC – Centers for Disease Control and Prevention

Cl⁺ – chemical ionization
cm$^{-1}$ – wavenumber

COSY – correlated spectroscopy

Cy – cyclohexyl

Cy$_2$BOTf – dicyclohexyl boron triflate

DBU – 1,8-Diazabicycloundec-7-ene

DCC – $N,N'$-Dicyclohexylcarbodiimide

DCE – dichloroethane

DCM – dichloromethane

dd – doublet of doublets

ddd – doublet of doublets of doublets

DEAD – diethyl azodicarboxylate

DEGME – 2-(2-Methoxyethoxy) ethanol

DEPT135 – Distortionless Enhancement by Polarization 135

DEPT90 – Distortionless Enhancement by Polarization 90

DHP – 5,6-dihydro-2-pyrone

DIBAL-H – diisobutylaluminium hydride

DMAP – 4-Dimethylaminopyridine

DMF – dimethylformamide

DMP – Dess–Martin periodinane

DMPU – 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

DMSO – dimethyl sulfoxide

DNA – deoxyribonucleic acid

dppf – 1,1’-Bis(diphenylphosphino)ferrocene
$dr$ – diastereomeric ratio

$\text{ED}_{50}$ – effective dose 50 %

$ee$ – enantiomeric excess

$ent$ – enantiomer

$ent$-PROG – enantiomer of progesterone

equiv. – equivalents

$\text{ESI}^+$ – Electrospray Ionization

Et – ethyl

$et. al.$ – and others

EtOH – ethanol

$\text{FAB}^+$ – Fast Atom Bombardment

FDA – Food and Drug Administration

g – gram

$\text{GABA}_A$R – gamma-aminobutyric acid type A receptor

HMBC – Heteronuclear Multiple-Bond Correlation

HMPA – hexamethylphosphoramide

HMQC – Heteronuclear Multiple Quantum Coherence

HPA – homopropargylic alcohol

HPLC – High-Performance Liquid Chromatography

HREIMS – High Resolution Electron Ionization Mass Spectrometry

$\text{IC}_{50}$ – inhibitory concentration 50 %

IMDA – Intramolecular Diels-Alder Reaction

$i$-Pr – isopropyl
IR – infrared

$J$ – coupling constant

KHMDS – potassium bis(trimethylsilyl)amide

$L$ – ligand

L.A. – lewis acid

LDA – lithium diisopropylamide

LiHMDS – lithium bis(trimethylsilyl)amide

$M$ – moles per liter

$m$ – milli, multiplet

$mCPBA$ – meta-Chloroperoxybenzoic acid

$Me$ – methyl

$MeI$ – methyl iodide

$mg$ – milligram

$MHz$ – megahertz

$mL$ – milliliter

$mM$ – milimolar

$mmol$ – millimole

$mPR\alpha$ – membrane progestin receptor alpha

$MVA$ – mevalonic acid

$MW$ – microwave

$nAchR\sigma 1$ – Nicotinic acetylcholine receptor $\sigma 1$

$NBS$ – $N$-Bromosuccinimide

$ng$ – nanogram
NIS – N-Iodosuccinimide
nM – nanomolar
NMO – N-Methylmorpholine-N-Oxide
NMR – nuclear magnetic resonance
NOE – Nuclear overhauser effect
PCC – pyridinium chlorochromate
PG – protecting group
PGF2α – prostaglandin F2α
Ph – phenyl
PhCF3 – trifluorotoluene
pin – pinacol
piv – pivaloyl
PMB – 4-Methoxybenzyl
PP – Pyrophosphate
ppm – parts per million
PPTS – Pyridinium p-toluenesulfonate
PR – Progesterone receptor
PROG – Progesterone
PT – 5-Phenyltetrazole
PTSD – Posttraumatic stress disorder
pTsOH – p-Toluenesulfonic acid
py – pyridine
q – quartet
quint. – quintet

R – radical (functional group)

s – singlet

satd. – saturated

SEM – [2-(Trimethylsilyl)ethoxy]methyl acetal

t – triplet

TBAF – tetra-n-butylammonium fluoride

TBAI – tetra-n-butylammonium iodide

TBCO – 2,4,4,6-Tetrabromocyclohex-2,5-dien-1-one

TBDPS – tert-Butyldiphenylsilyl ether

TBI – traumatic brain injury

TBS – tert-butyldimethylsilyl

TBSCI – tert-butyldimethylsilyl chloride

TBSOTf – tert-butyldimethylsilyl triflate

TBT – 5-tert-butyltetrazole

t-Bu – tertiary butyl

t-BuOH – tertiary butyl alcohol

t-BuOK – potassium tert-butoxide

TEA – triethylamine

tert – tertiary

Tf – triflate

TFA – trifluoroacetic acid

THF – tetrahydrofuran
TMEDA – tetramethylethylenediamine

TMS – trimethylsilyl

TPAP – tetrapropylammonium perruthenate
ABSTRACT

This thesis describes the work performed by the author during PhD studies at FSU. The first two chapters present the summary of the studies done trying to accomplish the first total synthesis of aldingenin B – a natural product first isolated in 2003. While our studies were ongoing, some additional information on the structure of the natural product emerged, therefore our studies and their relationship with the literature available up to 2015 are discussed in detail.

Chapters 3 through 6 represent the main topic of the thesis. They focus on the studies directed towards the development of the efficient synthesis of ent-progesterone - a potential drug candidate for the treatment of traumatic brain injury. Chapter 3 introduces the problem and the necessity for such synthesis and reviews the literature relevant to the topic. Chapter 4 presents an improved synthesis of rac-progesterone - an important step in the synthesis of ent-progesterone. Chapter 5 compares the efficiency of the two approaches - an old one and the improved route.
CHAPTER ONE
SYNTHETIC APPROACH TOWARDS ALDINGENIN B: LITERATURE OVERVIEW, RETROSYNTHESIS, AND SIGNIFICANCE OF WORK

The first half of this chapter reviews the literature on isolation and structure of aldingenin B, and the second half of this chapter introduces our design of the synthesis and key steps.

1.1. Literature Overview

1.1.1. Marine Natural Products From Red Algae Genus Laurencia

*Laurencia* is a genus of around 430 species of red algae, which are typically found around islands in oceans all over the globe\(^{1a}\). These seaweeds are an abundant source of secondary metabolite natural products, with \(\sim 700\) natural products isolated up until 2014\(^{1b}\). The most commonly encountered structures within the family are terpenoids, while halogenated sesquiterpenes (C\(_{15}\)) constitute the largest group\(^1\). Elatol (1), thrysiferol (2a), cartilagineol (3) and isorigidol (4), represent a few examples of well studied *Laurencia* natural products (Figure 1.1).

These small molecules act as a chemical defense against other species that can harm the algae in their natural habitat\(^2\). This effect for *Laurencia* species was demonstrated in antibiofouling experiments done by Hay\(^{2a}\). The study showed that treatment of a fish food source with elatol, reduced feeding by up to 90 % for sea urchin *Diadema Antillarum*, and had lesser, but still significant inhibition towards other marine herbivores. Other *Laurencia* natural products used in the same study displayed similar effects.
The fact that the natural purpose of these secondary metabolites appears to be chemical defense against other species makes them attractive targets for the search of any beneficial biological activity. Several studies already produced promising results: thyrsiferol (2b) is one of the most promising anticancer drug candidates within marine natural products.\textsuperscript{3} It acts as a selective inhibitor for serine / threonine phosphatase 2A, and induces apoptosis in vitro in leukemia P338 cancer cell lines in very small doses (ED\textsubscript{50} = 10 ng/mL). Thyrsiferyl acetate (2a) is even more potent (ED\textsubscript{50} = 0.3 ng/mL). Obtusol (3), is an efficient agent in vitro against different strains of *Leishmania* parasites\textsuperscript{4} (IC\textsubscript{50} = 9.7 µg/mL, promastigotes; IC\textsubscript{50} = 4.5 µg/mL, amastigotes), isorigidol (4), is efficient in killing several species of worms in vitro\textsuperscript{5} with a moderate activity.

\textbf{Figure 1.1:} Several natural products from red algae genus *Laurencia*
(EC$_{50} < 100$ mM). Not all of these natural products are highly abundant, so chemical synthesis might be a useful way to access some of them for biological activity studies.

1.1.2. Isolation of Aldingenin B

Currently there are 4 natural products with proposed structures in the family of aldingenins (Figure 1.2). Aldingenin A (5, Figure 1.2), was the first of the family to be reported in 2003$^{6a}$, and aldingenins B, C and D were reported 3 years later by the same group$^{6b}$. All of them were isolated from the species Laurencia Aldingensis$^6$. In fact, the difficulties in taxonomy of red algae species led to the practice that these natural products are now used as taxonomic markers for the purposes of classification of these seaweeds.

The Lago group isolated aldingenin B via extraction of 153 g of dried algae with dichloromethane. Extracts were purified using a series of silica-gel and size exclusion chromatography steps. After purification only ~2.0 mg of pure aldingenin B was isolated, and no X-ray diffraction crystal structure was reported.

Figure 1.2: Originally proposed structures of aldingenins (image source ref. 1d)
1.1.3. Structural Determination of Aldingenin B

To determine the structure the Lago group collected HREIMS, $^{13}$C NMR (BBD, DEPT135, DEPT90), IR, $^1$H NMR, COSY, HMQC, HMBC spectral data. The brief overview of the main spectral data is displayed in Table 1.1. HREIMS data showed a mass of 346.0748, corresponding to molecular formula C$_{15}$H$_{23}$O$_4$Br. IR showed alcohol present, and no double or triple bonds, so a tetracyclic structure was proposed. The structure was consistent with NOE and HMBC correlation.

Table 1.1: Spectral data, reported by Lago et. al.$^{6b}$

<table>
<thead>
<tr>
<th>Carbon #</th>
<th>$^{13}$C NMR Chemical Shift</th>
<th>$^1$H NMR Chemical Shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31.3 (CH$_2$)</td>
<td>1.65 m</td>
</tr>
<tr>
<td>2</td>
<td>60.3 (CH)</td>
<td>3.99 dd (9.6, 6.3)</td>
</tr>
<tr>
<td>3</td>
<td>69.3 (C)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>44.3 (CH$_2$)</td>
<td>1.92 dd (14.5, 9.6); 2.16 dd (14.5, 4.7)</td>
</tr>
<tr>
<td>5</td>
<td>68.9 (CH)</td>
<td>3.86 dddd (9.6, 8.4, 4.7)</td>
</tr>
<tr>
<td>6</td>
<td>47.8 (CH)</td>
<td>1.44 dd (9.0, 8.4)</td>
</tr>
<tr>
<td>7</td>
<td>78.5 (C)</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>107.0 (C)</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>39.5 (CH$_2$)</td>
<td>2.19 t (13.5); 1.72 dd (13.5, 3.5)</td>
</tr>
<tr>
<td>10</td>
<td>52.7 (CH)</td>
<td>4.17 dd (13.5, 3.5)</td>
</tr>
<tr>
<td>11</td>
<td>76.2 (C)</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>29.6 (CH$_3$)</td>
<td>1.36 s</td>
</tr>
<tr>
<td>13</td>
<td>23.2 (CH$_3$)</td>
<td>1.49 s</td>
</tr>
<tr>
<td>14</td>
<td>22.2 (CH$_3$)</td>
<td>1.19 s</td>
</tr>
<tr>
<td>15</td>
<td>30.7 (CH$_3$)</td>
<td>1.57 s</td>
</tr>
</tbody>
</table>
data that the group collected. However, in 2012, the Crimmins group reported some evidence contradicting the reported structure\(^7\), which will be discussed later in this thesis.

1.1.4. Biosynthesis of Aldingenin A

In their original publication the Lago group proposed the pathway by which aldingenin A, and possibly other aldingenins could be formed\(^6\). The proposed biosynthesis starts with the

**Figure 1.3:** Proposed biosynthesis of aldingenin A
mevalonate (MVA) pathway, which is also observed in other Laurencia\textsuperscript{8}, as well as in most of other plant or animal species. MVA pathway starts from acetyl-CoA, which is an essential biosynthetic block in all living organisms. Via the series of enzymatic reactions, it produces farnesyl pyrophosphate (Figure 1.3). Farnesyl pyrophosphate then undergoes enzymatic cyclization to α-bisabolene (9). The pathway then diverges into the speculative one, more specific to Laurencia - the enzyme assisted oxidation and bromination to tetrabromo triol 10, followed by three consecutive etherifications are believed to produce aldingenin A.

1.2. **Retrosynthetic Analysis, Project Aims and Significance of Work**

1.2.1. **Retrosynthetic Analysis**

We started our work on aldingenin B, targeting the originally proposed structure 6. Our retrosynthetic plan with highlighted key steps is outlined in Figure 1.4. To construct the bromopyran ring, a bromoetherification reaction of alcohol 16 was envisioned. The double bond of 16 would come from elimination of tertiary alcohol, which would be incorporated into side-chain as an ether in 17. To construct the tricyclic core, a novel keto-ketalization reaction of alkyne-diol 18 had to be developed\textsuperscript{9}, which was the first key aim of our synthesis. We planned to prepare 18 from protected *anti*-homopropargylic alcohol 19, which would come from enantiomerically enriched 5,6-dihydro-2-pyrone (DHP) triflate 20, via nucleophilic addition / fragmentation methodology, recently developed in the Dudley lab\textsuperscript{10}. As a part of synthetic studies, a route towards enantiomerically enriched DHP triflates had to be developed. We believed that our strategy could be generalized for the synthesis of complex enantiomerically enriched *anti*-homopropargylic
alcohols. The most attractive pathway we envisioned for the synthesis of DHP triflate was via reductive cyclization of $\alpha$-bromo ester 21, which would come from coupling of $\alpha$-bromo carboxylic acid and anti-aldol piece 22.

1.2.2. Strategic Analysis of Keto-ketalization Step, and Potential Road Blocks

To construct the tricyclic core, the most direct method would be the oxidation of alkyne to dione, followed by acid-catalyzed ketalization. However, there are potential setbacks in applying this method to our system. Firstly, $\alpha$–1,2–diones generally are known to tautomerize to enol form\(^{11}\) (figure 1.5), and this could cause the scrambling of stereochemistry at the $\alpha$ – position of the dione at C6. Moreover, since there is a protected alcohol planned at C5, which would end up
next to intermediate enol, the reaction could be compromised by \( \beta \)-elimination, to give \( \alpha, \beta \)-unsaturated dione 26.

Therefore, to circumvent these issues in advance, we decided to focus on conditions that would avoid the dione intermediate 24, and would produce the core directly via oxidation / ketalization. The reagent of choice had to oxidize the alkyne, but not any of the alcohols. Also, the oxidant had to be efficient in oxidizing dialkyl substituted alkynes.

Table 1.2 reviews the currently known conditions to oxidize alkynes to diones, where dione was isolated as the major product. One of the earliest reports dates back to as early as 1867\textsuperscript{13a}, when oxidation with nitric acid was reported. This method, however, is not synthetically useful, due to the highly reactive nature of nitric acid. Alternatively, the Nikolaeva group in 1972 reported
another nitrogen-based oxidant, N$_2$O$_4$, which is milder$^{13b}$. Potassium permanganate is also known to oxidize alkynes to diones since as early as the first decade of 20$^{th}$ century$^{13c}$. This method was not optimized until 1983, when Snider buffered the reaction with NaHCO$_3$ / MgSO$_4$ to prevent overoxidation$^{13d}$. Other common methods for oxidation of alkynes include ruthenium (IV) oxide / NaIO$_4$$^{13e}$, originally reported in 1955 by Pappo, and few modern modifications of this protocol$^{13f}$-$^{13h}$, or ozone$^{13i}$. And finally few more recent, but less common methods include the modified Wacker oxidation$^{13j}$, a mixture of Ph$_2$Se$_2$ / (NH$_4$)$_2$S$_2$O$_8$$^{13k}$, a mixture of KClO$_3$ / OsO$_4$$^{13l}$, and molybdenum dioxide diperoxide in presence of Hg(II) salts$^{13m}$.

**Table 1.2: Known methods to oxidize dialkyl alkynes to diones**

<table>
<thead>
<tr>
<th>Entry #</th>
<th>Oxidants</th>
<th>Date of First Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HNO$_3$</td>
<td>1867</td>
</tr>
<tr>
<td>2</td>
<td>N$_2$O$_4$</td>
<td>1975</td>
</tr>
<tr>
<td>3</td>
<td>KMnO$_4$</td>
<td>1902</td>
</tr>
<tr>
<td>4</td>
<td>KMnO$_4$ / NaHCO$_3$ / MgSO$_4$</td>
<td>1983</td>
</tr>
<tr>
<td>5</td>
<td>RuO$_2$ / NaIO$_4$</td>
<td>1955</td>
</tr>
<tr>
<td>6</td>
<td>RuO$_2$ / Electrolysis</td>
<td>1987</td>
</tr>
<tr>
<td>7</td>
<td>[1,4,7-Me$_3$-1,4,7-triazacyclononane(CF$_3$CO$_2$)Ru$^{IV}$O$_2$]ClO / TFA</td>
<td>2000</td>
</tr>
<tr>
<td>8</td>
<td>t-BuOOH / [{RuCl$_2$(cymene)}$_2$] / I$_2$</td>
<td>2010</td>
</tr>
<tr>
<td>9</td>
<td>H$_2$O / O$_2$ / CuBr$_2$ / PdBr$_2$</td>
<td>2009</td>
</tr>
<tr>
<td>10</td>
<td>O$_3$</td>
<td>1953</td>
</tr>
<tr>
<td>11</td>
<td>Ph$_2$Se$_2$ / (NH$_4$)$_2$S$_2$O$_8$</td>
<td>1991</td>
</tr>
<tr>
<td>12</td>
<td>KClO$_3$ / OsO$_4$</td>
<td>2000</td>
</tr>
<tr>
<td>13</td>
<td>HMPA / Mo(VI)O$_4$ / Hg(OAc)$_2$</td>
<td>1986</td>
</tr>
</tbody>
</table>
Most of conditions displayed in Table 1.2 are clearly incompatible with alcohols (i.e. periodate would cleave diols, potassium chlorate or permanganate would oxidize alcohols), or substrates more complex than just a simple alkyne. Due to this fact, complemented by the fact that reaction displayed in entry 11 mechanistically is believed to go through $\alpha$-keto-ketal intermediate, Ph$_2$Se$_2$ / (NH$_4$)$_2$S$_2$O$_8$ oxidant mixture was selected for further study for our first key step.

1.2.3. Strategic Analysis of the Second Key Step - an Enantioselective Synthesis of anti-Homopropargylic Alcohol (HPA)

1.2.3.1. Synthetic value of homopropargylic alcohols. Homopropargylic alcohols (Figure 1.6) consist of alcohol and alkyne fragment separated by two sp$^3$ carbons. This dual functionality allows them to participate in chemical reactions as alcohols or alkynes individually, but additionally the proximity of these two groups allows for more complex reaction pathways where both functionalities are involved, making them highly useful intermediates in organic synthesis.

![Figure 1.6: Homopropargylic alcohols](image)

In recent years, many innovative transformations of HPA’s were discovered (Figure 1.7). Novel methods to prepare isoxazoles, trifluoromethyl carbonyls, substituted tetrahydrofurans, lactones, substituted furans, homopropargylic amines, 1,2-allenic ketones, pyrano[2,3-d]pyrimidine-2,5-dione nucleosides in one synthetic step with the assistance of transition metal catalysis have been reported recently. This high flexibility of HPA’s
means that they often end up as intermediates in organic synthesis\textsuperscript{15}, quite often in polypropionate-based natural products. Carolactom\textsuperscript{15a}, trichostatic acid\textsuperscript{15b}, callystatin A\textsuperscript{15c}, pilocarpine\textsuperscript{15c}, dictyostatin\textsuperscript{15d} are a few natural products that either have been synthesized or are in progress of being synthesized using HPA’s over the last 6 years (Figure 1.8).

\textbf{Figure 1.7:} Recently discovered useful transformations of homopropargylic alcohols

\begin{center}
\includegraphics[width=\textwidth]{figure1.png}
\end{center}
1.2.3.2. Synthetic methods to prepare homopropargylic alcohols. The most common method to prepare homopropargylic alcohols is the addition of allenyl nucleophiles to a carbonyl group. A wide range of metal and non-metal species have been reported to facilitate this transformation \(^{16}\) (Figure 1.9). Typically allenyl reagents are generated from propargylic halides in situ, or in some cases prepared separately. More recently, asymmetric versions of this reaction

\[
\text{addition of allenyl compounds to carbonyl group to give homopropargylic alcohols}
\]

\[
\begin{array}{c}
\text{M} \\
R_1 \quad \text{R}_2 \\
\end{array}
\begin{array}{c}
+ \\
\text{O} \\
\text{R}_4 \\
\end{array}
\begin{array}{c}
\xrightarrow{\text{R}_3 \text{R}_4} \\
\text{R}_1 \quad \text{R}_2 \quad \text{OH} \\
\end{array}
\]

\(M = \text{B, Si / Lewis acid, Cr, Li, Zn, Al, Sn, Cu, Pb, Ga, Ti, Zr, Te, Dy, In, Cd, Ba, Ce}\)

**Figure 1.8:** Recent use of HPA’s in total synthesis (HPA fragment in final product highlighted in blue)

**Figure 1.9:** Synthesis of HPA’s via addition of allenyl reagents to aldehydes
emerged\textsuperscript{17}, with James Marshall’s group pioneering the work by demonstrating the enantioselective additions of chiral allenylstananes\textsuperscript{17a}, allenylsilanes\textsuperscript{17b}, allenyl zinc\textsuperscript{17c}, allenylindium reagents\textsuperscript{17d}. The most novel, powerful catalytical methods using either chiral allenylboronates\textsuperscript{17e} or achiral allenylboronates combined with chiral Bronsted acids\textsuperscript{17f} or chiral copper complexes\textsuperscript{17g} are most powerful variations of this chemistry. Catalytic asymmetric versions of allenylchromium\textsuperscript{17h}, allenylzinc\textsuperscript{17i}, allenyltrichlorosilyl\textsuperscript{17j} species were also recently reported in the literature. There are limitations, however, with using this strategy in synthesis of more complex homopropargyl alcohols as the synthesis of allenyl-boronates is not always straightforward task, and it does not always give ideal stereoselectivity. Alternatively, HPA’s could be prepared via addition of acetylenes to epoxides.

Recently, a new method to prepare racemic HPA’s was developed in the Dudley lab\textsuperscript{10}. As part of ongoing larger research program on fragmentation reactions, it was discovered that the addition of methylmagnesium bromide to DHP triflates leads to fragmentation with carbonyl extrusion to give HPA’s. (Figure 1.10). Our initial report had only racemic substrates, however

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fragmentation_reaction.png}
\caption{Nucleophilic addition / fragmentation to give HPA’s}
\end{figure}
from the mechanistic point of view it is obvious that the reaction is stereospecific. Therefore, we
decided to target enantiomerically enriched triflate 29, which upon nucleophilic addition /
fragmentation would give enantiomerically enriched anti-homopropargylic alcohol 30 which we
planned to elaborate to aldingenin B. We planned to use reactions with well-established
enantioselectivity to prepare 29, therefore, the potential issues that could arise from the use of other
methods to prepare HPA’s could be avoided.

1.2.4. Summary / Project Aims

In conclusion, our goals for this project could be formulated into 3 specific aims:

AIM1: Develop oxidative keto-ketalization reaction

AIM2: Investigate fragmentation approach to aldingenin B

AIM3: Accomplish total synthesis of aldingenin B
CHAPTER TWO
SYNTHETIC APPROACH TOWARDS ALDINGENIN B: RESULTS AND DISCUSSION

This chapter discusses our synthetic efforts to accomplish the total synthesis of aldingenin B. The results presented in 2.1.1 and 2.2.2 and corresponding appendix stem from the work over my first 2 years of graduate program, and are reproduced with permission from Organic Letters\textsuperscript{9}. Copyright 2011, American Chemical Society. The authorship is shared with the authors as described in the reference, and the former graduate student Dr. J. Yang was the first author of this publication, although every experiment listed here was also reproduced by the author to advance the material to support development of synthesis.

2.1. Synthesis of the Model Substrate 31

We started investigating the synthesis of aldingenin B from oxidative keto-ketalization reaction\textsuperscript{9}, as described in the previous chapter. To test this reaction, an alkyne-diol 31 was selected as the initial target (Figure 2.1). We hypothesized that when subjected to a mixture of (NH\textsubscript{4})\textsubscript{2}S\textsubscript{2}O\textsubscript{8} and Ph\textsubscript{2}Se\textsubscript{2} or similar conditions, the tricyclic core structure, which is part of the natural product would be formed. We started synthesis from known 4-methyl-cyclohexa-1,4-dienecarboxylic

![Figure 2.1: Initial target for oxidative keto-ketalization study](image)

PG = protecting group  tricyclic core  ALDINGENIN B
acid\textsuperscript{18}, which was prepared from commercial propionic acid and isoprene via Diels-Alder reaction in 77 \% yield (figure 2.2). Carboxylic acid was then esterified using methanol and catalytic amounts of sulfuric acid in 95 \% yield. Ester was then subjected to Sharpless asymmetric dihydroxylation to give enantiomerically enriched diol 35. The absolute stereochemistry was assigned using Sharpless empirical induction model\textsuperscript{19} (Figure 2.2). Out of two alkenes present, only dihydroxylation on more electron rich alkene was observed. The reaction gave diol 35 in 83 \% yield (79 \% over 2 steps) even when performed on up to 10 g scale. Diol 35 was then protected as TBS ether in 93\% - 100\% yield (figure 2.3). Protection using TBSOTf was necessary, whereas
attempts to optimize the reaction using TBSCl did not give full conversion to the TBS diether. Ester 36 was then reduced, using LiAlH₄ in THF in quantitative yield. No purification was necessary for this step. Allylic alcohol 37 was then subjected to hydroboration / oxidation to produce diol 38 in up to 72 % yield. It is important to note here that bulky TBS protecting groups were necessary to direct hydroboration from one face, whereas the use of smaller protecting groups (such as acetonide), led to diminished yield and selectivity.® Diol 38, was then protected using anisaldehyde dimethyl acetal and PPTS, and then selectively reduced to primary alcohol using DIBAL-H, in 70 % yield over 2 steps to give alcohol 39 (Figure 2.4). Oxidation of primary

**Figure 2.3:** Selectivity of hydroboration / oxidation in the synthesis of 38
alcohol, using PCC / Celite, followed by Ohira-Bestman reaction\textsuperscript{20} gave terminal alkyne 40 in 63 % yield over 2 steps. DMP and Swern oxidation were also investigated as possible alternatives for oxidation, but they did not show any improvement over PCC. 40 was then alkylated using methyl iodide and deprotected using excess of TBAF to give alkyne-diol 41. With the substrate in hand, we then went on to study keto-ketalization step.

### 2.2. Keto-ketalization and Proposed Mechanism

We were pleased to see that when 41 was subjected to mixture of diphenyl diselenide and ammonium persulfate in mixture of water, methanol and acetonitrile and refluxed for 2 hours at 85 °C, it produced tricyclic core of aldingenin B (Figure 2.5). The envisioned mechanism for this novel transformation is depicted in Figure 2.5: first, the diphenyl selenide is oxidized to give phenyl selenyl sulfate, which is highly electrophilic and can add to the triple bond with the loss of
sulfate anion. This enables the attack of alcohol at C2 on selenyl cationic intermediate 44. It is unclear exactly what the conformation of 44 is during this process, however given the conformation of the product it is highly likely that it reacts from boat conformation, as having it in chair would require to put two relatively large substituents in diaxial position. Second equivalent of phenyl selenyl sulfate than coordinates with the double bond, which enables the attack of

Figure 2.5: Oxidative keto-ketalization and proposed mechanism
cationic intermediate by tertiary alcohol. The selenoketal 46 then is oxidized and hydrolysed to give the tricyclic core 42, at the same time regenerating phenyl selenyl sulfate.

2.3. Alternative Conditions Investigated

Motivated by the success of oxidative keto-ketalization studies, we looked into alternative conditions for this reaction. Various combinations of Ph₂Se₂ or Ph₂Te₂ with Na₂S₂O₈ or (NH₄)₂S₂O₈ were investigated, but the condition reported in 2.2 was the only one to induce the reaction. Also, since the proposed mechanism involves electrophilic attack on alkyne and then corresponding alkene, mixtures of Ph₂Se₂ or Ph₂Te₂ with other electrophiles NIS, NBS and persulfate oxidants were investigated. None of the alternative conditions gave satisfactory results – only complex mixtures of products were produced.

2.4. Attempted Incorporation of Fragmentation Chemistry

![Figure 2.6: Retrosynthesis for incorporation of fragmentation chemistry](image)

Having a method to assemble the core, we then focused studies on the second key step – incorporation of nucleophilic addition / fragmentation reaction. To achieve that, the side chain 51, which contains tertiary alcohol was prepared via the scheme, shown in Figure 2.7: first, MeLi was
added selectively to ethyl 5-oxohexanoate\textsuperscript{21}, then tertiary alcohol was protected as TBS ether to give 49 (the use of triethylamine as a base was crucial for efficient reaction), and the resulting ester was then subjected to $\alpha$–bromination and saponification to give 51.

The Masamune \textit{anti}-aldol\textsuperscript{22} reaction emerged as the best method to prepare \textit{anti}-aldol fragment 53, necessary for aldingenin B (Figure 2.8). The product was formed directly from 52 and aldehyde 60 in 74 % yield. Alternatively, the preparation of \textit{anti}-aldol fragment via Frater\textsuperscript{23} asymmetric alkylation, required more steps and gave lower overall yield. 53 was then subjected to ring closing metathesis. To perform metathesis at this early stage was essential, as carrying through 2 terminal alkenes, and closing the ring late later resulted in very low overall yield. 54 was then coupled with carboxylic acid 51, and after reductive cyclization and triflation, a triflate 56 was obtained in $\geq 31$ % yield over 4 steps. Fragmentation of 56, gave \textit{anti}-homopropargylic alcohol 57 in 81 % yield. At least 3.0 equivalents of methylmagnesium bromide were necessary for efficient fragmentation. Using our previously reported condition (2.0 equiv.), homopropargylic acetate was observed as a byproduct. Protection of 57 as benzyl bromide and Sharpless dihydroxylation gave substrate 59 – a precursor for keto-ketalization.
However, when 59 was subjected to keto-ketalization conditions, no tricyclic core product was observed. This result, combined with the results reported previously by Dr. J. Yang, a former graduate student in the laboratory (Table 2.1 entry 1-3), seem to follow a trend. The size of substituents at C8 roughly correlates with the yield of the reaction.

We were in progress of trying to prepare keto-ketalization substrates that have smaller substituent at C8, using the fragmentation route, but around this time we were contacted by Dr. Micharl Crimmins, as his group was independently working on the synthesis of aldingenin B at the University of North Carolina at Chapel Hill. During communications with Dr. Crimmins it was
indicated that there might be some concerns regarding the structure of the natural product. Therefore, in the next two subchapters Crimmins’s synthesis of aldingenin B\textsuperscript{25} will be discussed as well as relationship of their intermediates to our intermediates.

### Table 2.1: Oxidative keto-ketalization results from our lab

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Substrate" /></td>
<td>52%</td>
</tr>
<tr>
<td><img src="image2.png" alt="Substrate" /></td>
<td>37%</td>
</tr>
<tr>
<td><img src="image3.png" alt="Substrate" /></td>
<td>&lt; 20%</td>
</tr>
<tr>
<td><img src="image4.png" alt="Substrate" /></td>
<td>0%</td>
</tr>
</tbody>
</table>

#### 2.5. Total Synthesis of Proposed Structure of Aldingenin B by Crimmins et. al.\textsuperscript{25}

Crimmins’s total synthesis started with chiral auxiliary mediated aldol reaction of thiazolidinethione 61 with dibenzyl acetal of 3-methyl-3-butenal 64 (Figure 2.9). The *anti*-aldol fragment 20, was produced in 67% yield with the diastereomeric ratio of 94 : 6, preferring the desired isomer. Chiral auxiliary was then reduced using lithium borohydride and methanol in
diethyl ether to give primary alcohol 63 in 85% yield. Ring closing metathesis then gave cyclic alcohol 66 in 90% yield. Alcohol was then dihydroxylated using OsO₄/TMEDA complex to give triol 67 in 98% yield. Authors describe the use of TMEDA and stoichiometric amounts of osmium as being essential for efficient transformation, as the other more typical dihydroxylation conditions using catalytic amounts of osmium were not giving acceptable diastereomeric ratio. 67 was then protected as cyclopentylidene acetal and oxidized using TPAP/NMO in 85% yield.

**Figure 2.9:** Crimmins’ synthesis of aldehyde 68

**Figure 2.10:** Crimmins’s synthesis of tricyclo core
over 2 steps. To aldehyde 68 dithiane side chain 72 was then added (Figure 2.10) and dithiane was deprotected using mercuric perchlorate. The key deprotection-cyclization was then accomplished using perchloric acid and ultrasound, producing tricyclic core 71.

To finish the synthesis, diol 71 was first oxidized using Swern conditions (Figure 2.11), and aldehyde was selectively olefinated using Nysted reagent to terminal alkene, which was then subjected to cross-methatesis conditions to give prenyl side chain. The authors chose this two step process, because Wittig olefination using isopropylidene phosphonium ylide was giving irreproducible results, and the two step process worked reasonably well, giving trisubstituted alkene 16 in 54 % yield. To a resulting ketone, methyllithium was then added. The addition required presence of cerium trichloride, because otherwise the opening of the acetal was observed due to the basicity of resulting lithium alkoxide. The final bromoetherification was achieved using TBCO in nitromethane in only 21 % yield. Deprotection of benzyl group using standard conditions gave the proposed structure of aldingenin B.
2.6. **Structural Discrepancies, Reported by Crimmins *et. al.*, and Relationship of Their Intermediates to Our Intermediates

Interestingly, the structure synthesized by Crimmins group did not match the spectral data of natural sample. The comparison shown in Table 2.2 displays that every single $^1$H NMR signal for the synthetic sample was off from the natural sample, and some of them by rather significant margin (i.e. the difference of chemical shifts between hydrogens at C5 is 0.79 ppm.). In addition to that, the natural sample showed coupling between H5 and H6 whereas there is no such coupling reported in the natural sample. The Crimmins group did an extensive spectral study (HMBC, H # | Natural Sample, $C_6D_6$, 500 MHz | Synthetic Sample, $C_6D_6$, 600 MHz
---|---|---
$1\alpha$ | 1.65 m | 1.55 $ddd$ (15.0, 3.6, 1.8)
$1\beta$ | | 1.65 $ddd$ (15.0, 3.6, 1.8)
2 | 3.99 $dd$ (9.6, 6.3) | 3.62 $dd$ (3.6, 1.8)
$4\beta$ | 1.92 $dd$ (14.5, 9.6) | 1.10 $dd$ (13.8, 7.8)
$4\alpha$ | 2.16 $dd$ (14.5, 4.7) | 2.21 $dd$ (13.8, 7.8)
5 | 3.86 $ddd$ (9.6, 8.4, 4.7) | 4.65 $app. T$ (7.8)
6 | 1.44 $dd$ (9.0, 8.4) | 1.53 $app. S$
$9\alpha$ | 1.72 $dd$ (13.5, 3.5) | 2.25 $dd$ (13.2, 4.2)
$9\beta$ | 2.19 $t$ (13.5) | 2.50 $t$ (13.2, 4.2)
10 | 4.17 $dd$ (13.5, 3.5) | 4.55 $dd$ (13.2, 4.2)
12 | 1.36 $s$ | 1.40 $s$
13 | 1.49 $s$ | 1.39 $s$
14 | 1.19 $s$ | 1.24 $s$
15 | 1.57 $s$ | 1.00 $s$
COSY, NOESY, HMQC, DEPT) to confirm that they made the originally proposed structure, so there is little doubt that original structure was misassigned. The authors also synthesized a C5 epimer of the originally proposed structure, but it did not match the natural data either.

During communications with Dr. Crimmins, we disclosed that tricyclic core 77b was prepared in our lab previously, and their group had similar intermediate. To strengthen the evidence that they and we have the tricyclic core, the two structures were compared. The analysis of chemical shifts in key positions of the tricyclic core shows that they are nearly perfect match. The minor discrepancies could be attributed to the difference of PMB vs. Bn protecting groups. Therefore, the evidence suggests that Crimmins group and our group indeed has the same intermediate as depicted. That corroborates the fact that the originally proposed structure of aldingenin B was incorrect. There is no easy way of reassigning the real structure of aldingenin B without natural sample in hand, which we do not possess. Therefore at this point, there was little left to be gained from pursuing the synthesis of incorrect structure, and our plans to finish originally proposed structure of aldingenin B were abandoned.

![Comparison of key 1H chemical shifts of intermediates prepared by Crimmins group and in our lab.](image)

**Figure 2.12:** Comparision of tricyclic core 77: ours vs. Crimmins’
Recently, additional evidence refuting other structures reported by Lago et. al.\textsuperscript{6} in their original report emerged. In 2014, Hiroyuki Koshima group synthesized the proposed structure of aldingenin C\textsuperscript{26}. However, just as in case of Crimmins’ synthesis, the synthetic sample spectral data did not match the proposed structure data. Using NMR database search software developed by one of the co-authors, Koshima group did a thorough search of the $^{13}$C NMR spectral data, and found that there is another natural product already known that has identical carbon NMR spectral data - caspitol, and closely matching $^1$H NMR signals.

In 2014, Kutateladze et. al.\textsuperscript{27} did a computational studies on proposed structures of aldingenins A-C to predict coupling constants of these two natural products. The predicted NMR coupling constants did not match those reported for the natural samples of aldingens, but they did match the coupling constants obtained from synthetic sample of aldingenin B produced in Crimmins lab.

**Figure 2.13:** Originally proposed and revised structures of aldingenin C
2.7. Summary / Conclusion

In summary, a novel keto-ketalization method to access tricyclic core of aldingenin B was developed. A possibility of synthetic route towards aldingenin B, incorporating enantioselective synthesis of anti-homopropargylic alcohol was investigated. The evidence provided by Crimmins lab suggests that the real structure of aldingenin B is currently unknown, and the data obtained in our lab supports that claim. The structures of four aldingenins proposed by the Lago group should be reevaluated, preferably by X-ray crystallography.
CHAPTER THREE

EPIDEMIOLOGY OF TRAUMATIC BRAIN INJURY: A RATIONALE FOR THE IMPROVED SYNTHESIS OF ENT-PROGESTERONE, AND OVERVIEW OF THE STRATEGY

In this chapter, the biological activity of progesterone and ent-progesterone is reviewed, and the reasons why an improved synthesis of ent-progesterone is desirable are explored. The previous syntheses of progesterone, and general strategies for steroid synthesis are reviewed, and our approach is introduced at the end of the chapter.

3.1. Epidemiology of Traumatic Brain Injury (TBI)

Traumatic brain injury (TBI) is a severe health problem in the United States, as well as in the rest of the world. According to CDC report\textsuperscript{28}, between the years of 2000 and 2010, the incidence of TBI, that required medical attention was 500-800 cases per 100 000 of population on average, with 17-18 fatalities per 100 000 (Figure 3.1). Unfortunately, the incidence seems to be increasing, while there is no significant reduction in deaths. Within the general population, the most common causes are accidental falls, motor vehicle accidents and assaults\textsuperscript{29}, but some groups of people are more likely to suffer TBI than average people. This includes, but is not limited to professional athletes\textsuperscript{30a} and active military personnel\textsuperscript{30b}, so there has been interest from the army\textsuperscript{31a} and sports organizations\textsuperscript{31b} to find an effective treatment. Recent studies show that there might be a link between the pathophysiology of TBI and PTSD\textsuperscript{32a}, as well as a link between chronic mild TBI and uncontrollable mood swings leading to violent behavior, and reduced overall cognitive performance\textsuperscript{32b} as well as learning disorders\textsuperscript{32c}. TBI can be ranked by
degree of severity on a 15 point scale, known as Glasgow Coma Scale. Lower numbers indicate more severe injuries. The score of 13-15 indicates mild TBI, which does not cause loss of consciousness, however can still have some undesired aftereffects. The scale of 9-12 indicates moderate TBI, which includes loss of consciousness for short amount of time, which could cause long-term disability, and may require rehabilitation. And the scale 3-8 indicates severe TBI, which results in long-term comatose state.

There are currently no FDA approved drugs for the treatment of TBI, and in cases of severe brain injury there is little that could be done to improve the condition, as the brain is a critical poorly understood organ. Given the high impact of TBI to the general population, there is a significant effort in medical community to find an effective treatment. People are tackling this
problem on multiple fronts: small molecules\textsuperscript{a-d}, as well as proteins\textsuperscript{e} and gas therapies\textsuperscript{f,g}. Figure 3.2 shows some of prospective ways to treat TBI currently under investigation all over the world.

\textbf{Figure 3.2:} Experimental treatments for TBI

Physiologically there are different targets which are being investigated as a source for improvement after TBI. AL 88101\textsuperscript{a} is a known antagonist for prostaglandin receptor PGF2\(\alpha\), and the prostaglandins are overexpressed in damaged brain, so a recent study on this molecule has shown some positive outcomes. Epothilone D\textsuperscript{b} is a prescription drug that induces axonal sprouting - a growth of connections between neurons and cells of muscles, and in animal models
it proved to be useful in treatment of TBI that results in the loss of motor function. Ellagic acid, a natural antioxidant, targets the oxidative stress that is suffered during TBI\(^{35c}\). Some of the proteins naturally produced in the body can also have neuroprotective effects: erythropoietin, a natural cytokine has shown positive outcomes in animal models through the induction of cell signaling pathways, and derivatives of it have been designed to selectively exploit its neuroprotective effects\(^{35e}\).

One of the most promising, and very thoroughly studied drug candidates up until recently was the female pregnancy hormone – progesterone\(^ {36}\). A large number of studies displayed significant improvements of the key physiological functions in vitro as well as in animal models. However, the recent full-scale clinical trial, published in December of 2014 in New England Journal of Medicine\(^ {37}\), demonstrated that in case of moderate to severe TBI, there is no benefit of using progesterone with respect to placebo, and actually the outcome was slightly worse (although statistically insignificant), so the chase for the “wonder drug” is still on.

Another promising drug candidate is the enantiomer of progesterone (\textit{ent}-PROG), and its differences of effects on bodily functions with regards to natural progesterone will be discussed in more detail in the next subchapter.

3.2. \textbf{Differences of Effects of Progesterone (PROG) and \textit{ent}-Progesterone (\textit{ent}-PROG) on Living Organisms}

Progesterone is a hormone, naturally produced in human body, and its primary function is to regulate the female reproduction cycle by inducing DNA transcription through binding with nuclear progesterone receptors\(^ {38a}\) (nuclear PR, Figure 3.3). As a secondary function, it can act as a neuroprotective steroid. PROG receptors located in cell membranes having high distribution in
nervous system have been identified\textsuperscript{38}. It is believed that with the assistance of these receptors progesterone regulates water transport over cell membranes in the nervous system and thereby reduces inflammation in damaged brain cells after a concussion. Two major PROG-recognizing membrane receptors are mPR\textsubscript{α}, and 25 Dx receptor, while PROG can also interact with N-acetylcholine receptors and γ-acetylbutyrate receptors located in cell membranes.

In a recent study, it was demonstrated that \textit{ent}-PROG reduces excessive brain water content (which is an indication of reduced swelling and inflammation) after TBI in mice\textsuperscript{39} as efficiently as the natural PROG. The same study showed that \textit{ent}-PROG does not induce the nuclear PR receptor function, and actually can act as an inhibitor to nuclear PR. Additionally, \textit{ent}-PROG showed activation of glutathione reductase, which is responsible for fighting oxidative stress suffered during TBI, which natural progesterone does not induce. These features make it a superior drug candidate. The exact mechanism of action between different enantiomers is unknown, We speculate that while nuclear receptors recognize the whole structure of PROG, the membrane receptors recognize only the distance between two terminal ketones, which is the same in both

\textbf{Figure 3.3:} Progesterone production and receptors in nervous system\textsuperscript{38a}. Progesterone is produced from pregnenolone with the assistance of 3-β-hydroxysteroid dehydrogenase/Δ-5-4 isomerase and it can interact with membrane as well as nuclear receptors.
enantiomers. It was previously demonstrated that enantiomeric steroids can interact with membrane GABA\textsubscript{A} receptors\textsuperscript{40} in the same way as natural steroids do.

There is a limiting factor that prevents more thorough biological studies of the enantiomer of progesterone as a potential drug candidate - the accessibility of material. While natural progesterone is inexpensive and readily available for clinical trials in large quantities from natural sources, the only way the enantiomer can be accessed is through chemical synthesis. To address this issue of accessibility, we decided to develop a new synthetic route that would allow access larger amounts of enantiomer of ent-progesterone more easily, which in turn would enable more thorough medicinal studies of this molecule.

3.3. Literature Overview of Existing Syntheses of ent-Progesterone

Currently there is only one total synthesis of ent-progesterone reported in the literature\textsuperscript{41}, and one synthesis of racemic progesterone, reported by Johnson\textsuperscript{42}. Upon the latter, marginal improvements were made and enantiomer of progesterone was obtained by resolution via chiral prep HPLC as reported by Cran \textit{et. al.} in a patent application filed in 2014\textsuperscript{43}.

3.3.1. Synthesis of ent-Progesterone by Auchus \textit{et. al.} / Rychnovsky \textit{et. al.}

The synthesis of ent-progesterone that was used to support early studies of its biological activity, consists of two phases. First - the synthesis of ent-testosterone, reported by Rychnovsky in 1991\textsuperscript{41a}, followed by the homologation of ent-testosterone to ent-progesterone, reported by Auchus \textit{et. al.} in 2003\textsuperscript{41b}. 
Rychnovsky’s synthesis started from the synthesis of enantiomerically enriched Wieland-Miescher ketone 80, which was prepared from trione 79, via D-proline catalyzed Robinson anulation in 76 % yield and 87 % ee (Figure 3.4). 80 was then selectively reduced, and the resulting alcohol was protected using isobutylene and subsequently reacted with Stiles reagent to give carboxylic acid 81 in 68 % yield over 3 steps. Reduction of the double bond with H₂/Pd in 81
was used to establish trans-5,6-fused stereochemistry, and after subsequent decarboxylation / aldol reaction enone, 82 was obtained. Robinson anulation with β-keto ester 86, was used to establish the tricyclic core 83, which was lacking the methyl at C10. This methyl group was installed using dissolving metal reduction / alkylation sequence to give 84, which after tandem deprotection / aldol reaction produced ent-testosterone.

The second phase of synthesis of ent-progesterone was reported in 2003, and the product was used for the studies of its interaction with cytochrome P450. The synthesis involves the direct homologation of ent-testosterone (Figure 3.5) using straightforward reactions: first, the alcohol at C17 was protected as acetate, followed by protection of ketone at C3 as a ketal, and deprotection of alcohol to give intermediate 87, which was then oxidized and olefinated using ethyl Wittig
reagent to give ent-progesterone carbon framework \( \text{88} \). Hydroboration / oxidation was then performed on \( \text{88} \), and the resulting alcohol was oxidized, followed by deprotection of ketone at C3. This sequence gave the ent-Progesterone in overall 8 steps and 21 % yield from ent-testosterone, and 17 longest linear steps and \( \sim \)3 % yield from trione \( \text{79} \), which is not commercially available in high quantities and has to be prepared in 1 synthetic step from high-cost building block: 2-methyl-cyclopentane-1,3-dione.

3.3.2. Synthesis of rac-Progesterone by Johnson\(^{42}\)

Johnson’s synthesis of rac-progesterone\(^{42}\) was first published in 1971. It demonstrated the high synthetic utility of cation-\( \pi \) cascade reactions for the total synthesis of steroids. It started from alkylation of 2-methylfuran (Figure 2.5) with 1,4-dibromobutane, followed by opening of the furan ring, and Finkelstein reaction to give iodide \( \text{92} \), which was then reacted with triphenylphosphine to give Wittig reagent \( \text{93} \) in overall 4 steps and 49 % yield.

**Figure 3.6: Synthesis of \( \text{93} \)**
Wittig reagent 93 was then coupled with aldehyde 94, and deprotected to give dione 95 in 95 : 5 E : Z ratio at central alkene. 95 was subjected to aldol reaction, which generated the cyclopentenone ring and methyllithium was then added to give alcohol 97.

The alcohol 97 is a tertiary allylic alcohol, which ionized to a carbocation readily and selectively. Treating it with TFA allowed for cascade reaction to occur via intermediate 98 (Figure 3.8), which was terminated with ethylene carbonate, and after basic hydrolysis gave tetracyclic compound 99. The tetracycle was then subjected to ozonolysis and aldol reaction to give racemic progesterone, which contained two diastereomers with a ratio of 85 : 15.

In a recent patent, the alternative combinations of aldehydes and Wittig reagents were presented, as well as alternative methods for cleavage of the double bond (OsO₄ and RuCl₃), and Peterson olefination for the synthesis of the trans alkene. The patent also presented the resolution
of racemic mixture via chiral prep HPLC. However, it is not a feasible route for large scale production, as chiral prep HPLC is extremely expensive.

3.3.3. Other Approaches to Tetracyclic Steroid Cores

The syntheses described above are the only two total syntheses of progesterone that use simple starting materials, not including the semisyntheses. They represent two general strategies used to access steroids: a cation-π cascade and Robinson annulation, but many other novel strategies to access the tetracyclic steroid cores exist, which will be discussed further.
3.3.3.1. Cascade reactions. The cation-π cascade reaction is the most widely studied cascade reaction for the synthesis of steroids, but other types of cascades, albeit more rare, can be used to access tetracyclic cores (Figure 3.9). The Negishi group, as a part of their studies in transition metal catalysis, reported zipper type carbopalladation cascade of intermediate 101\textsuperscript{44a}, which gave tetracyclic product 102 in 76% yield when treated with Pd(PPh\textsubscript{3})\textsubscript{4} and triethylamine in refluxing acetonitrile. A transition-metal catalyzed cascade was reported by Grubbs\textsuperscript{44b}: the treatment of diene-triyne 103 with Grubbs I resulted in a tetracyclic steroid core 104. Anionic cascade was developed by Deslongchamps group\textsuperscript{44c} as a part of synthetic studies towards

**Figure 3.9:** Cascade reactions to construct steroid cores
Oubain\textsuperscript{44d}. Here intermediates 105 and 106 were converted to tetracycle 107 with the assistance of cesium carbonate.

Novel radical cascade reactions\textsuperscript{44e} were developed more recently: here radicals were generated from halide or selenide in intermediates 108 or 110 (Figure 3.10). Treating them with the radical conditions – tributyltin hydride / AIBN, resulted in generation of tetracycles, out of which intermediate 109 was later converted to estrone.

\textbf{3.3.3.2. Cycloaddition reactions.} Cycloaddition reactions are another powerful way to access steroid cores. Bimolecular Diels-Alder reactions were one of the earliest strategies used to access steroids. More recently, intramolecular Diels-Alder reactions (IMDA) emerged as another powerful method. In a report published in 1986, IMDA was used efficiently to prepare intermediates that were further transformed to testosterone and androsterone (Figure 3.11)\textsuperscript{44f}. High

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.10.png}
\caption{Some examples of radical cascades to access steroid cores}
\end{figure}
temperature and 4 days of reaction time were necessary for the IMDA reaction of 112 to occur to give testosterone carbon skeleton 113.

Alternatively, dienes which participate in Diels-Alder raction can be accessed from benzenecyclobutenic intermediates. Heating of intermediate 114 results in opening of cyclobutane ring to diene with the loss of aromaticity at benzene ring, and the subsequent IMDA regenerates the aromaticity and forms the steroid core 114\textsuperscript{44g}.

A cobalt catalyzed [2 + 2 + 2] cycloaddition reaction of 115 to produce (3S)-Hydroxyandrost-5,7-diene-17-ones (i.e. 116)\textsuperscript{44h} was reported by Groth \textit{et. al.} in 2006.. In this case, since the starting material was diastereomeric mixture, the product was also a mixture of diastereomers. Similar cobalt-mediated cyclizations were also reported by Vollhardt.\textsuperscript{44l}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure_3_11.png}
\caption{Cycloaddition reactions to access steroids}
\end{figure}
3.3.3.3. **Miscellaneous reactions.** Besides these approaches, alternative strategies that do not fall into these 2 general categories have been reported to produce steroid cores: Masataka et al.\(^{44i}\) in a 1999 reported ring expansion of cyclobutanolic intermediate 118 to construct C and D rings of steroid using catalytic palladium acetate (figure 3.12); a stereoslective dearomative cyclization approach recently appeared using palladium cinnamyl dichloride and P-chiral biaryl monophosphine ligands\(^{44j}\), when it was used to connect B and C rings of steroids (120 to 121); a tandem gold catalyzed process of aldehyde diyne was used to construct the B and C rings of steroids in tetracycle 123.

**Figure 3.12:** Reactions to access steroid cores
3.4. The Strategy

Since the existing synthesis of rac-PROG is relatively short, the decision was made to use the Johnson’s route as a template to access the enantiomer of progesterone. Therefore, we envisioned the development of kinetic resolution of racemic progesterone or tetracyclic intermediate 99, stemming from the synthesis of rac-PROG. To account for the loss of 50% of material during kinetic resolution step, we focused our efforts towards improving synthesis of rac-PROG first. Our initial goal was to target intermediate 96 (Figure 3.13), using highly efficient approaches, and to use known chemistry from there to access rac-PROG. The specific focus was in a devising synthesis of 96 that is shorter and higher yielding, uses inexpensive reagents and fewer column purifications and is potentially more scalable than original Johnson synthesis. As an alternative to kinetic resolution, we also considered an enenatoselective cation-π cascade

Figure 3.13: Central objectives
reaction. Therefore, the 4 central objectives could be formulated for the initial studies as displayed in Figure 3.13:

AIM1: Improvement of the synthesis of aldehyde 94.

AIM2: Investigation of alternative olefinations for the synthesis of trans-central alkene.

AIM3: Incorporation of more convergence to the synthesis through incorporation of commercially available 2-bromo-3-methyl-cyclopentenone (124).

AIM4: Development of kinetic resolution or stereoselective cascade reaction.
CHAPTER FOUR
AN IMPROVED TOTAL SYNTHESIS OF RAC-PROGESTERONE

This chapter presents the strategies explored, experimental results, and problems encountered during the process of devising the improved synthesis of rac-PROG, an important step in accessing ent-PROG in large quantities, and concludes with the final optimal route towards rac-PROG.

4.1. The Improved Synthesis of Aldehyde 94

We started synthetic studies with the development of the more efficient synthetic route towards aldehyde 94. The route, originally published by Johnson, after inclusion of currently available new procedures for preparation of intermediates\(^{45}\), is displayed in Figure 4.1. There are some drawbacks with this route: it uses 3-pentyn-1-ol, which is currently available for ~$7/g from Acros Organics\(^ {46}\) - a relatively high price for the first intermediate in the synthesis, and there is no

\[
\begin{array}{c}
\text{Issue:} \\
\text{Use of 4-pentyn-1-ol}
\end{array}
\]

57 / g

1. CBr\(_4\), PPh\(_3\), 89 % ref. 45

2. Mg, 125

HO

\[
\begin{array}{c}
\text{Johnson's route:} \\
37 \%, 5 \text{ steps}
\end{array}
\]

Figure 4.1: Synthesis of aldehyde 94 by Johnson
easy synthetic route in the reported literature that provides an efficient way to prepare this alcohol from readily available reagents. Three of the reported one-step methods are the addition of propyne anion to ethylene oxide\textsuperscript{47}, alkylation of dianion of 3-butyn-1-ol\textsuperscript{47b}, or addition of 1-bromo-2-butyne\textsuperscript{47c} to formaldehyde. The first method uses 2 gaseous reagents, so it is inconvenient on a lab scale, and in case of the second and third one, the starting materials are expensive.

4.1.1. Aldehyde Synthesis, Gen. #1

The first idea that we investigated was the incorporation of 4-pentyn-1-ol, which is a little less expensive\textsuperscript{48} than 3-pentyn-1-ol (125, Figure 4.2) into the synthesis. 125 was subjected to Swern oxidation, and to the crude product isopropyl-magnesium Gringard was added. The transformation proceeded in 57 % yield over 2 steps. Johnson’s synthesis was then intercepted via the alkylation of dianion, generated from 126 in 67 – 85 % yield. The reaction required the use of 5.0 equiv. of HMPA, and excess of methyl iodide, and precise temperature control. Warming up the dianion to 0 °C for the deprotonation step sometimes resulted in low yields, so the reaction had

\[
\begin{align*}
\text{126} & \quad \text{1. DMSO, } \text{COCl}_2, \text{Et}_3\text{N}, \text{DCM} \\
& \quad \text{2. isopropenyl-MgBr, THF} \\
& \quad \text{57 % Over 2 steps} \\
\text{127} & \quad \text{3. BuLi, MeI, THF, HMPA, THF} \\
& \quad \text{67-85 %} \\
\end{align*}
\]

\[
\begin{align*}
& \quad \text{4. CH}_3(\text{COEt})_2, \text{propionic a., heat} \\
& \quad \text{5. LiAlH}_4, \text{THF} \\
& \quad \text{6. PCC, Celite, DCM} \\
& \quad \text{78 %, 3 steps} \\
\end{align*}
\]

**Figure 4.2:** First generation synthesis of aldehyde 94
to be kept at -30 °C for the initial deprotonation step. From here, the next 3 steps parallel to Johnson’s synthesis: Claisen orthoester rearrangement, reduction with lithium aluminium hydride and PCC oxidation were used to obtain the aldehyde in overall 29-38 % yield. This route allowed us to produce aldehyde for the initial studies, however, it failed to deliver any significant improvements over original Johnson’s route, so a second generation route was developed.

4.1.2. Aldehyde Synthesis, Gen. #2

Geraniol and farnesol are important building blocks in natural product synthesis. Their high value comes from the fact that they are highly abundant natural products that can be extracted from several different plants in high quantities. Therefore, they are inexpensive and can provide a relatively complex carbon framework as a starting point for the synthesis of natural products. The current price for geraniol at Sigma-Aldrich catalog is less than $30 / Kg, and typically it is used to produce perfumes or cleaning products, so it is available at bulk quantities for even lower prices. Geraniol can be easily converted to geranyl chloride or geranyl bromide in nearly quantitative yields using inexpensive reagents49, therefore, the geranyl bromide was chosen as a starting material for the second generation approach to the aldehyde 94.

Figure 4.3: Reactions of geraniol
First, geranyl bromide was selectively oxidized to the epoxide using mCPBA. Trace of epoxidation of other double bond was observed in crude NMR, however material was used as is without purification, as it did not survive chromatography or distillation. The epoxide was then propargylated using lithiated trimethylsilylpropyne\textsuperscript{50a}, and the reaction was quenched with TBAF in a one-pot protocol to give terminal alkyn. This was the only column purification step necessary for this route. Epoxide 130 was then alkylated using methyl iodide in quantitative yield with the epoxide functionality remaining intact. The epoxide was then cleaved using HCl / NaIO\textsubscript{4} to give aldehyde 94. This four step protocol gave the aldehyde in 52\% overall yield from readily available geranyl bromide. However, there were still few inefficiencies with this route: the intermediate allylic bromide is unstable, and the price of trimethylsilyl propyne is high, so a few modifications were made based on this template for the 3\textsuperscript{rd} generation approach towards the aldehyde.

**Figure 4.4:** Second generation approach to aldehyde 94
4.1.3. Aldehyde Synthesis, Gen. #3

To address the issue of high cost of trimethylsilylpropyne, few options were considered: conceptually, lithiated trimethylsilyl propyne can be treated as a formal dianion of propyne. (Figure 4.5). The disadvantage is that several steps (deprotonation, deprotection, deprotonation) are required to use it, so the decision was made to incorporate both alkylations simultaneously, using alternative methods to generate the dianion of propyne. There are three general ways known to generate the dianion of propyne: the deprotonation of propyne\textsuperscript{50b} or allene\textsuperscript{50c} in presence of TMEDA, or halogen-metal exchange of propargyl bromide\textsuperscript{50d} with n-butyllithium. Due to the fact that propargyl bromide is liquid unlike propyne or allene, it was chosen as a source for the generation of dianion. Also, the geranyl bromide was exchanged to geranyl chloride, since its epoxidation product was more stable.

To optimize the dual alkylation reaction, \textsuperscript{1}HNMR integration analysis was used, and approximate ratios of products were determined. Three major products were identified in crude \textsuperscript{1}HNMR: starting material 132, monoalkylated product 130, dialkylated product 131 (Table 4.1), and the approximate product ratios were determined by comparing the integration values of vinylic and acetylenic hydrogens. Some of the optimization reactions for double alkylation are shown in

![Figure 4.5: Propyne dianion synthons](image-url)
Table 4.1: Optimization of dual alkylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. Dianion</th>
<th>Additives</th>
<th>Alkylating Agent</th>
<th>Temp. Profile</th>
<th>Approx. $^1$H NMR Product Ratio: $^d$</th>
<th>Isolated Yield:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>-</td>
<td>2.0 MeI</td>
<td>Stage 1: -78 °C, 20 min. Stage 2: -78 °C, 20 min.</td>
<td>132 only</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>-</td>
<td>2.0 MeI</td>
<td>Stage 1: 0 °C, 20 min. Stage 2: 0 °C, 60 min.</td>
<td>40(132) : 38(130) : 22(131)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>-</td>
<td>3.0 MeI</td>
<td>Stage 1: rt, 30 min. Stage 2: 0 °C, 60 min.</td>
<td>60(132) : 32(130) : 8(131)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>TBAI (10 %)</td>
<td>-</td>
<td>Stage 1: 0 °C, 30 min.</td>
<td>32(132) 68(130)</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>2.2</td>
<td>TBAI (10 %)</td>
<td>-</td>
<td>Stage 1: 0 °C, 30 min.</td>
<td>130 Only</td>
<td>81 % 130</td>
</tr>
<tr>
<td>6</td>
<td>2.2</td>
<td>TBAI (10 %) / 5.0 DMPU</td>
<td>5.0 MeI</td>
<td>Stage 1: 0 °C, 30 min. Stage 2: rt, 60 min.</td>
<td>36 % 132, 64 % 131</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>2.2</td>
<td>TBAI (10 %) / 5.0 DMPU</td>
<td>5.0 Me$_2$SO$_4$</td>
<td>Stage 1: 0 °C, 30 min. Stage 2: rt, 60 min.</td>
<td>131 only</td>
<td>74 % 131</td>
</tr>
<tr>
<td>7$^c$</td>
<td>2.2</td>
<td>TBAI (10 %) / 5.0 DMPU</td>
<td>5.0 Me$_2$SO$_4$</td>
<td>Stage 1: 0 °C, 30 min. Stage 2: rt, 60 min.</td>
<td>131 Only</td>
<td>76 % 131</td>
</tr>
<tr>
<td>9$^d$</td>
<td>2.2</td>
<td>TBAI (10 %) / 5.0 DMPU</td>
<td>5.0 Me$_2$SO$_4$</td>
<td>Stage 1: 0 °C, 30 min. Stage 2: rt, 60 min.</td>
<td>Mix of products</td>
<td>0-73 % 131 $^e$</td>
</tr>
<tr>
<td>10$^{abc}$</td>
<td>2.4</td>
<td>TBAI (10 %) / 6.0 DMPU</td>
<td>6.0 Me$_2$SO$_4$</td>
<td>Stage 1: 0 °C, 60 min. Stage 2: rt, 60 min.</td>
<td>131 only</td>
<td>$\geq$67 131</td>
</tr>
</tbody>
</table>

$^a$ 5 % NH$_3$ quench was used. $^b$ 8.33 mmol scale $^c$ THF was used as a cosolvent after stage 1 $^d$ 129 : 131 Ratio was estimated from crude $^1$H NMR product mixture by comparing integrations of vinylic hydrogens. 129 : 130 ratio was compared by integrating vinylic and acetylenic hydrogens. Crude mixtures contained trace amounts of unidentified products. $^e$ Stirling was complicated by formation of insoluble sludge, which resulted in reaction failing.
Table 4.1. It was observed that when less than 2.2 equiv. of dianion was used, the first alkylation did not proceed to completion. Also, it seems that 0 °C was the best temperature for first alkylation, whereas running it at -78 °C showed no conversion (entry 1), and at room temperature the reaction was less efficient than at 0 °C (entries 2 vs. 3) and more byproducts were observed in crude NMR. Eventually, when 2.2. equiv. of dianion was used, and the first alkylation was performed at 0 °C with TBAI as an additive and no alkylating agent in the second step, the full conversion to monoalkylated product 129 was observed (entry 5).

For the second stage of the reaction, when MeI was used as an alkylating agent, the reaction did not go to completion even when 5.0 equiv. of additive (DMPU), was used (entry 6). Therefore, a more reactive alkylating agent - dimethyl sulfate (Me₂SO₄) was chosen as an alternative, and when 5.0 equiv. of Me₂SO₄ was used together with 5.0 equiv. of DMPU, it produced only the desired product in 74 % yield (entry 7). The crude product had significant amount of unreacted Me₂SO₄, which is highly toxic, so to quench it, the reaction was stirred for 1 h with 5 % NH₃ solution before extraction without any significant effect on the yield (entry 8). When the reaction was scaled up to 8.33 mmol scale, some problems emerged: after addition of Me₂SO₄, the reaction formed an insoluble sludge, which complicated stirring, and resulted in highly variable yields, with few runs producing no desired product at all. To avoid the insoluble sludge, THF was added after the stage 1, which reduced the formation of precipitate (entries 9-10). In a regular multiple runs, the condition 10 provided the dialkylated product in ≥67% yield.

For the final step – a periodate cleavage of epoxide, the reaction conditions were switched to HIO₄ / NaIO₄ instead of HCl / NaIO₄ for optimum performance. The crude aldehyde was used in the further reactions without any further purification. This was the final optimal route towards aldehyde 94. The aldehyde now can be accessed from geranyl chloride in 3 steps, 1 column
purification and ≥67 % overall yield (Figure 4.6), which is far superior to what has been reported up until today.

### 4.2. Synthesis of trans-Central Double Bond

The second key aspect crucial for the synthesis of rac-PROG is the formation of disubstituted trans-central double bond. Originally, Johnson constructed this bond by E-selective Wittig reaction. This reaction requires precise temperature control at low temperatures (which could be problematic to achieve upon scale-up) and has low atom economy. We decided to investigate the alternative methods (Figure 4.7) for the formation of trans-central double bond and

**Johnson:**
E - selective Wittig

**Our investigations:**
1,3-transposition
Julia-Kocienski Olefination
Takai Olefination
Cyclopropyl-homoallyl rearrangement

**Figure 4.7:** Strategies for the synthesis of trans-central alkene

---

1. m-CPBA, CHCl₃, 0°C, 30 min.
2. a) Propargyl-Br, BuLi, TMEDA, Et₂O, 20 min.
b) Epoxide, TBAI, 0°C, 60 min.
c) Me₂SO₄/DMPU, Et₂O/THF, r.t., 60 min.
3. HIO₄, NaIO₄,
THF : H₂O, 0 °C to r.t, 4 h.

**Figure 4.6:** Optimal synthesis of aldehyde 94
try to improve the overall proces. While it might seem like a simple problem at a first glance, the synthesis of dialkyl substituted trans-alkenes is not trivial, as typically olefinations often give mixtures of E : Z isomers when performed on substrates with no \( \alpha \)-branching on the resulting double bond.

4.2.1. Investigation of the Synthesis of trans-Central Double Bond via Reductive 1,3-Transposition of \( \alpha,\beta \)-Unsaturated Hydrazone

The first strategy we investigated for the synthesis of trans-central alkene was the reduction of \( \alpha,\beta \)-unsaturated hydrazones with a transposition of the double bond. Tosyl hydrazones and semicarbazones can be reduced using soft reducing agents, such as NaCNBH\(_3\) or catecholborane to give trans-substituted double bonds\(^{51}\) in high E : Z ratios (Figure 4.8).

First, a simple model system 136a was examined (Figure 4.9). Attempts to form ketone via redox isomerization\(^{52}\) of alcohol 133 were unsuccessful, so the ketone was prepared via addition of anion generated from trans-1-iodo-hexene to the aldehyde 94 and PCC oxidation of...
resulting alcohol. Hydrazone 135 was then formed by reacting 134 with tosyl hydrazide in methanol, which produced a mixture of isomers in 73% overall yield over 3 steps. A few literature conditions for the reductive transposition were investigated, and the reduction with catecholborane in presence of sodium acetate was successful, giving predominantly trans alkene in 70% yield and ~15:1 E:Z ratio was observed by $^1$H NMR analysis, therefore the possibility of incorporating the real substrate similar to 136b into this route was investigated.

The most attractive way for this purpose found in the literature was reported by Smith et al.\textsuperscript{53} (Figure 4.10). The Smith group reported alkylation of the anion generated from bromide 137
using iodopentane in 60 % yield. The reaction required very forcing conditions (the use of HMPA). The efforts to apply this method for other alkylating agents: propargyl bromide, 1,3-dibromopropene or trimethylsilylpropargyl bromide, were unsuccessful. The reaction only produced decomposition, and in some cases the debrominated product 140 was isolated.

To circumvent this issue, attempts to access ketone 135b via cross-metathesis of ketone 140, which was prepared in 3 steps (addition of allyl Gringard, PCC oxidation and isomerization of the resulting double bond) in 29 % unoptimized yield from aldehyde 94 (Figure 4.11), with

**Figure 4.10:** Attempted alkylatyon

**Figure 4.11:** Attempted cross-metathesis
ketal 143, which was prepared by protection of known ketone 142 with ethylene glycol in 22% yield, were investigated as well as few other simple alkenes. All attempts to perform cross-metathesis resulted in decomposition of ketone 141, as observed in crude $^1$H NMR. This reaction might be complicated by the other alkene in 140, which could interfere with the reaction. After these dissatisfying results, alternative methods to prepare the trans-central alkene were investigated.

4.2.2. Synthesis of trans-Central Double Bond via Julia-Kocienski Olefination

One of the common methods to make double bonds is Julia-olefination. Original version of this reaction involves either 2 or 3 step process: addition of sulfones to aldehydes, followed by esterification of $\alpha$-sulfonyl alcohols and radical reduction of resulting $\alpha$-sulfonyl esters using

\[ R^1 = p\text{-tolyl} \]

\[ \text{R} \]

\[ \text{S} \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{R}_1 \]

\[ \text{R}_2 \]

\[ \text{Na (Hg)} \]

\[ \text{or} \]

\[ \text{SmI}_2 \]

---

**Figure 4.12:** The Julia olefination and Julia-Kocienski modification
either Na / Hg amalgam or SmI2 (Figure 4.12)\textsuperscript{54a-c}. More recent modifications of this reaction, known as Julia-Kocienski reaction\textsuperscript{54d-e}, offer the advantage of the reduction of number of steps to one. These improvements are achieved by using more elaborate sulfones, such as phenyl tetrazole (PT), tert-butyltetrazole (TBT) or benzothiazole (BT), as well as some others.

For this purpose, sulfone 147, was prepared from known diol\textsuperscript{55} 144 (Figure 4.13). The diol was protected using TBSCl and imidazole in DCM, followed by hydroboration / oxidation to give primary alcohol 145, which was then converted to sulfide 146 using Mitsunobu reaction with 1-Phenyl-1H-tetrazole-5-thiol thiol (PTSH). 146 was then oxidized using H\textsubscript{2}O\textsubscript{2} / (NH\textsubscript{4})\textsubscript{6}Mo\textsubscript{7}O\textsubscript{24} catalytic system to give sulfone 147 in 34% overall yield. Julia-Kocienski coupling reactions with aldehyde 94 were then investigated (Table 4.2). Using LiHMDS as a base in THF, the reaction gave E : Z selectivity of 3 : 1, which was not a satisfactory result (entry 1). When base was switched to KHMDS, the ratio improved to 5 : 1. When 18-crown-6 was used, applying the procedure, reported by Pospíšil\textsuperscript{56}, the ratio slightly improved and deviated to anywhere between 7 : 1 to 9 : 1. In this case, the product 148 was obtained in 67% yield. 148 could be converted to our desired

![Figure 4.13: Synthesis of sulfone 147](image-url)
target compound 96 by deprotecting TBS, oxidizing diol using PCC and performing the aldol reaction to generate the cyclopentenone ring in 61 % overall yield. However that did not provide

Table 4.2: Optimization of Julia-Kocienski reaction of sulfone 147

<table>
<thead>
<tr>
<th>Entry</th>
<th>Condition</th>
<th>E : Z</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiHMDS / THF</td>
<td>3 : 1</td>
<td>n. d.</td>
</tr>
<tr>
<td>2</td>
<td>KHMDS / THF</td>
<td>5 : 1</td>
<td>n. d.</td>
</tr>
<tr>
<td>3</td>
<td>KHMDS / 18-C-6 / THF</td>
<td>7 : 1</td>
<td>67 %</td>
</tr>
</tbody>
</table>

the desired improvements for the synthesis in reducing the number of steps, so the sulfones 150 and 152 were prepared. Julia coupling reactions of 150 and 152 (Figure 4.14) were then investigated with the aldehyde 94, however no evidence of coupled products was observed. Even though selective Julia-Kocienski olefination between aldehydes and ketones is known, the intramolecular ketone probably makes the coupling problematic. The issue could potentially be solved by protecting the ketone, but that would add 2 more synthetic steps to overall sequence, and combined with the fact that the Julia-Kocienski coupling of the linear sulfone with 147 was giving relatively low E : Z selectivity, it would not provide the desired improvements for the synthesis.
4.2.3. Investigation of the Synthesis of *trans*-Central Double Bond via Takai Olefination / Suzuki Coupling

Takai olefination\textsuperscript{57a} in combination with B-alkyl Suzuki coupling reaction is often used in synthesis\textsuperscript{57b-c} to construct trans alkenes (Figure 4.15). In Takai olefination, an aldehyde is treated with chloroform, bromoform or iodoform in the presence of chromium dichloride to give predominantly E alkenyl halides with moderate E : Z selectivity. When aldehyde 94 was subjected to Takai olefination, the corresponding *trans* alkenyl iodide 153 was obtained in 51 % yield with \(~5 : 1\) E : Z ratio.

![Figure 4.15: Takai olefination / B-alkyl Suzuki coupling strategy](image)

---

**Figure 4.14:** Synthesis of sulfones 150 and 152

---

**Figure 4.15:** Takai olefination / B-alkyl Suzuki coupling strategy
Recently, Molander group reported diboron lynchpin strategy to couple two halides with two carbon lynchpin reagent (Figure 4.17). They treated potassium vinyltrifluoroborate with 9-BBN, and used the resulting diboronate in cross-coupling reactions with two different electrophiles. The method is based on a specific design: the fluoride base can activate 9-BBN terminus of the lynchpin reagent, while keeping trifluoroborate terminus protected, therefore monocoupling of the diboronate to alkenyl halide is achieved. The second set of conditions then uses aqueous base, to hydrolyze trifluoroborate and induce the coupling.

Unfortunately, coupling did not give the desired product when a few conditions from the original report were used, so the next logical step was to investigate the cross-coupling reactions.
of individual pieces. For this purpose, a trifluoroborate reagent 157 was prepared from bromide 124 in 3 steps: first, Suzuki coupling with potassium vinyltrifluoroborate, then selective borylation on terminal alkene, using CuCl / BDPB (bisdiphenylphosphino benzene) catalytic system and treatment of the resulting bispinacolato ester with potassium hydrogen difluoride. This 3 reaction sequence provided the product in up to 52 % overall yield. Suzuki coupling reactions of 157 were then investigated and the results are summarized in Table 4.2. Typically the best solvent system for Suzuki coupling with potassium trifluoroborates is toluene : water mixture with 3 : 1 or 10 : 1 ratio, and cesium carbonate or potassium carbonate as a base. Under these conditions, different ligands were screened with a few different iodide substrates. However under all conditions only decomposition of iodide or no reaction was observed. However, when 3-bromo-anisole was used as a substrate, the reaction gave coupling product in ~87 % yield. Motivated by success of this coupling with the alkenyl bromide, the couplings of trifluoroborate 156 with bromides were investigated. The screening of different conditions was, however again, unsuccessful. All conditions examined gave either $\beta$-hydride elimination products or hydrolysis of trifluoroborate with no transmetallation taking place. While the bromides were not
Table 4.2: Attempted Suzuki couplings of 157

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst System</th>
<th>Temp. Profile</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="" /></td>
<td>Pd(dppf)C(_2)</td>
<td>80 °C</td>
<td>Decomp. + SM</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="" /></td>
<td>Pd(dppf)Cl(_2)</td>
<td>80 °C</td>
<td>Decomp. + SM</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="" /></td>
<td>Pd(OAc)(_2) / XPhos</td>
<td>80 °C to 95 °C</td>
<td>Decomp.</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Pd(OAc)(_2) / RuPhos</td>
<td>80 °C to 95 °C</td>
<td>Decomp.</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Pd(PPh(_3))Cl(_2)</td>
<td>80 °C</td>
<td>Decomp.</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Pd(PPh(_3))(_4)</td>
<td>80 °C</td>
<td>Decomp. + SM</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>Pd(P(o-tollyl)(_3))Cl(_2)</td>
<td>80 °C</td>
<td>Decomp. + SM</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>Pd(OAc)(_2) / PC(_3)</td>
<td>80 °C</td>
<td>N. R.</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>Pd(OAc)(_2) / SPhos</td>
<td>80 °C</td>
<td>N. R.</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>Pd(Pr-Bu(_3))[N,N-dimethyl-4-aminobiphenyl]Cl(_2)</td>
<td>80 °C</td>
<td>Decomp. + SM</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>Pd(dppf)Cl(_2) / PAs(_3)</td>
<td>80 °C</td>
<td>Decomp.</td>
</tr>
<tr>
<td>12(^a)</td>
<td></td>
<td>Pd(OAc)(_2) / RuPhos</td>
<td>80 °C</td>
<td>Decomp.</td>
</tr>
<tr>
<td>13(^a)</td>
<td>![image]</td>
<td>Pd(OAc)(_2) / RuPhos</td>
<td>80 °C</td>
<td>87 % Yield</td>
</tr>
</tbody>
</table>

\(^a\) K\(_2\)CO\(_3\) as a base and 10 : 1 Tol : H\(_2\)O was used
Table 4.3: Attempted couplings of 157 with alkenyl bromides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image1" alt="Substrate" /></td>
<td>Pd(dppf)Cl&lt;sub&gt;2&lt;/sub&gt;, 80 °C</td>
<td>boronic a.</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image2" alt="Substrate" /></td>
<td>154&lt;sup&gt;d&lt;/sup&gt;, 80 °C</td>
<td>boronic a. + unknown P</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image3" alt="Substrate" /></td>
<td>Pd(dppf)Cl&lt;sub&gt;2&lt;/sub&gt;, 80 °C</td>
<td>β-hyd. Elimination</td>
</tr>
<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image4" alt="Substrate" /></td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;, 80 °C</td>
<td>β-hyd. Elimination</td>
</tr>
<tr>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td><img src="image5" alt="Substrate" /></td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;, 80 °C</td>
<td>β-hyd. Elimination</td>
</tr>
<tr>
<td>6&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image6" alt="Substrate" /></td>
<td>154&lt;sup&gt;c&lt;/sup&gt;, 100 °C</td>
<td>~5-10 % unknown mix of products</td>
</tr>
<tr>
<td>7&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image7" alt="Substrate" /></td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;, 80 °C</td>
<td>β-hydride elimination</td>
</tr>
<tr>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image8" alt="Substrate" /></td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;, PPh&lt;sub&gt;3&lt;/sub&gt;, NaOAc,</td>
<td>boronic a.</td>
</tr>
<tr>
<td>9&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image9" alt="Substrate" /></td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;), 110 °C</td>
<td>β-hydride elimination</td>
</tr>
<tr>
<td>10&lt;sup&gt;b&lt;/sup&gt;</td>
<td><img src="image10" alt="Substrate" /></td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;, RuPhos, 110 °C</td>
<td>β-hydride elimination</td>
</tr>
<tr>
<td>11&lt;sup&gt;b&lt;/sup&gt;</td>
<td><img src="image11" alt="Substrate" /></td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;, RuPhos, 80 °C</td>
<td>N. R.</td>
</tr>
<tr>
<td>12&lt;sup&gt;bc&lt;/sup&gt;</td>
<td><img src="image12" alt="Substrate" /></td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;, RuPhos, 80 °C</td>
<td>N. R.</td>
</tr>
<tr>
<td>13&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image13" alt="Substrate" /></td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;, RuPhos, KOH, 80 °C, Tol : H&lt;sub&gt;2&lt;/sub&gt;O 10 : 1</td>
<td>N. R.</td>
</tr>
<tr>
<td>14&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image14" alt="Substrate" /></td>
<td>i-Pr-PEPPSI Pd MeOH, K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, 60 °C</td>
<td>Only boronic a.</td>
</tr>
<tr>
<td>15&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image15" alt="Substrate" /></td>
<td>i-Pr-PEPPSI Pd 80 °C</td>
<td>Only boronic a.</td>
</tr>
<tr>
<td>16&lt;sup&gt;b&lt;/sup&gt;</td>
<td><img src="image16" alt="Substrate" /></td>
<td>i-Pr-PEPPSI Pd 80 °C</td>
<td>Only boronic a.</td>
</tr>
<tr>
<td>17&lt;sup&gt;b&lt;/sup&gt;</td>
<td><img src="image17" alt="Substrate" /></td>
<td>i-PEPPSI Pd 120 °C</td>
<td>boronic a. + β-hydride elimination</td>
</tr>
</tbody>
</table>

<sup>a</sup> Cs<sub>2</sub>CO<sub>3</sub>, toluene : H<sub>2</sub>O; <sup>b</sup>K<sub>2</sub>CO<sub>3</sub>. Toluene : H<sub>2</sub>O 10 : 1 <sup>c</sup>c = 0.5 M <sup>d</sup>Pd(Pt-Bu<sub>2</sub>[N,N-dimethyl-4-aminobiphenyl])<sub>2</sub>Cl<sub>2</sub>

Decomposing like iodide, no coupled products were observed in any of these reactions - only β-hydride elimination or hydrolysis of trifluoroborate reagent. The rationale for the fact that 157...
does react with aryl halide, but not alkenyl halides is unclear, but there might be an interaction from the electrons on the free ketone to the boron, which could complicate the reaction under typical Suzuki coupling conditions. Since these couplings were unsuccessful, the decision was made to approach problem from the different angle.

4.2.4. Synthesis of trans-Central Double Bond via Cyclopropyl-homoallyl Rearrangement

4.2.4.1. The optimization of rearrangement. For the alternative strategy for Suzuki coupling, a boron reagent 161 was necessary. Conceptually, it could be prepared from bromide 159 or diene 160. The bromide 159 was selected as a starting point due to the fact that there are methods to prepare the trans-homoallyl halides with high selectivity via cyclopropyl-homoallyl rearrangement. The original cyclopropyl-homoallyl rearrangement was reported by Julia in 1960’s \(^{60a}\) using HBr as an acid with 90-95+ % E : Z selectivity. The further modifications include the use of magnesium halides \(^{60b}\) or other sources of HBr such as TMSBr \(^{60c}\). This cyclopropyl-homoallyl strategy was used previously in systems other than progesterone by several groups \(^{61}\).

![Figure 4.19: Strategies for accessing 161](image-url)
During the initial process of optimization, an alcohol 158 was prepared and isolated, and several literature conditions were screened to look for the most effective one. It was found that 5.0 equiv. of magnesium bromide in refluxing diethyl ether was the best condition to induce the rearrangement. This, however, required two steps from the aldehyde to perform. To streamline the process, one pot approach was developed (Figure 4.20). First, a cyclopropylmagnesium bromide (freshly prepared in ether, commercial solutions in other solvents do not work) was added to the aldehyde 94, and then the reaction was diluted with ether and quenched with 1 % (by volume with respect to Et₂O) of H₂O. Magnesium bromide was then added and reaction was heated at reflux for overnight. The addition of 1 % of water was essential, because if magnesium bromide was added directly, decomposition was observed by TLC, and if more water was used the Gringard addition product with no rearrangement was isolated. This reaction sequence gave rearranged product 158 in 45-62 % yield and >20 : 1 E : Z ratio.

4.2.4.2. Synthesis of 97 via Suzuki coupling. With the way to prepare bromide in hand, the Suzuki coupling of corresponding boronate with bromide 124 had to be investigated. First, however, one issue had to be resolved: it was previously reported that Suzuki cross-coupling reaction of 124 with homobenzyl trifluoroborate reagent gives a mixture of two isomeric products\textsuperscript{58}: direct coupling product and \(\beta\)-hydride elimination / reinsertion / coupling product. To
address this issue, a ligand screening between 124 and commercial potassium 3-buteryl trifluoroborate was performed (Table 4.4). Out of the ligands screened, 2 ligands emerged as the ones favoring the desired product 163: XantPhos and RuPhos (entries 2 and 5). Reaction using RuPhos proceeded faster than XantPhos as observed by crude NMR, so it was selected for further base optimization. The base screen revealed that the reaction using potassium phosphate as a base proceeded the fastest with no 124 remaining after 12h.

**Table 4.4: Ligand screening to reduce $\beta$-hydride elimination / reinsertion**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Base</th>
<th>approx. $^1$H NMR Product Ratio $163 : 164 : 124$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>dppe</td>
<td>Cs$_2$CO$_3$</td>
<td>1 : 1.4 : 4</td>
</tr>
<tr>
<td>2</td>
<td>XantPhos</td>
<td>Cs$_2$CO$_3$</td>
<td>1 : 0.2 : 4</td>
</tr>
<tr>
<td>3</td>
<td>dppb</td>
<td>Cs$_2$CO$_3$</td>
<td>0 : 1 : 2.5</td>
</tr>
<tr>
<td>4</td>
<td>dppp</td>
<td>Cs$_2$CO$_3$</td>
<td>1 : 1.8 : 9</td>
</tr>
<tr>
<td>5</td>
<td>BINAP</td>
<td>Cs$_2$CO$_3$</td>
<td>1 : 2.7 : 6</td>
</tr>
<tr>
<td>6</td>
<td>RuPhos</td>
<td>Cs$_2$CO$_3$</td>
<td>1 : 0.15 : 0.6</td>
</tr>
<tr>
<td>7</td>
<td>RuPhos</td>
<td>K$_3$PO$_4$</td>
<td>1 : 0.17 : 0</td>
</tr>
</tbody>
</table>

When applied to real system, the condition did provide the coupled product in low yields with high variability (9-45 %) (Figure 4.21). The issues with this reaction lie most likely with the first step.
Usually when trifluoroborate reagents are prepared, they crystalize as white solids from acetone / ether mixture. In the case of reagent, prepared from 159, the crystalline product never formed after several crystallization attempts, and a mixture of products was observed in crude NMR, with –CH₂-BF₃ signal present at ~0 ppm in variable quantities. This mixture was used in Suzuki coupling directly, since column chromatography is not feasible here. To address this issue, alternative borylation conditions were investigated. In general there are 3 ways to prepare trifluoroborate reagents: reaction of trialkoxyboranes, boronic acids or bispinacolato boronic esters with KHF₂, so a metal catalyzed borylation of bromide 159 were investigated using several copper, iron and palladium catalysts with the hope to access the trifluoroborate reagent from bispinacolato ester, however none of the conditions give the selective borylation at the halide. In all attempts to use copper catalysis, borylation of the alkyne was always observed as a byproduct in a mixture of inseparable products as evident by the appearance of a new vinylic peak at ~6.3 ppm. When iron catalysts were used, decomposition of starting material was observed, and in case of palladium catalysis, the elimination of bromide was observed, because those condition reaquire strong base.

Figure 4.21: Suzuki coupling to give 96

Figure 4.22: Attempted borylations of 159
in protic solvents. There are currently no methods reported in the literature to selectively borylate sp³ halide in presence of alkynes.

4.2.4.3. Completion of the Synthesis of 97 via Alkylation of β-Ketoester 165. As the Suzuki coupling was giving low yields, the decision was made to look for an alternative solution. The plans to incorporate 2-bromo-3-methylcyclopentenone were abandoned, and a solution previously used by several groups in synthesis of other steroids⁶¹ was implemented for the synthesis of progesterone. A known β-keto ester 165⁶³ was prepared in 2 steps from commercial

![Reaction diagram](image)

**Figure 4.23:** Completion of synthesis of 96

and readily available 2, 5-hexanедione. 165 was alkylated with 159, using cesium carbonate in acetone, which resulted in rapid alkylation. Only 8h were necessary for the reaction to go to completion (reports in literature using other bases in similar systems indicate reaction time necessary as days). Some elimination product (less by 10 % by NMR) was observed in crude NMR. A one-pot procedure decarboxylation / deprotection / aldol reaction of 166 was then
attempted, but the reaction did not give the desired product, and only decarboxylated product was observed, so the decarboxylation had to be performed separately, and only deprotection / aldol was performed as one-pot process. The overall yield for the 2 steps from 166 to 96 was 71 %.

4.2.4.4. The Completion of the Synthesis.

The synthesis was completed using Johnson’s chemistry with minor changes. The yield for cation-π cascade, however did not match the originally reported yields. The reaction gave the tetracycle 99 in 38-55 % yield, which is significantly lower than originally reported in the literature. Therefore, the reaction has to be optimized further before the synthesis could be scaled up. For the ozonolysis step, a deviation from the original protocol was used: dimethyl sulfide, instead of Zn / AcOH for the workup, and heat was used in the final reaction to give racemic progesterone in 57 % yield over 2 steps.
4.3. Summary / Conclusion

A synthetic route to rac-progesterone, which cuts out 3 synthetic steps from the original Johnson’s route was developed. This was achieved by implementing the dual alkylation of the dianion of propyne and investigating the various approaches for the synthesis of trans-central double bond. Cyclopropyl-homoallyl rearrangement, combined with alkylation was identified as the best way to prepare trans-central double bond for the synthesis of rac-progesterone. The route uses readily available reagents, which can be purchased in bulk, therefore the synthesis has high potential to be scaled up.
CHAPTER FIVE
COST ANALYSIS OF THE ORIGINAL JOHNSON’S ROUTE VS. IMPROVED ROUTE

To estimate the benefits of using the new route vs. original route, a tree analysis was used to calculate raw material cost (RMC) for the two approaches towards intermediate 97 (P), since the completion of the synthesis follows the same path. Current prices (May 2015) at Sigma-Aldrich catalog were used after converting them to the price per mole for the largest available volume of reagent. The amount and purity, giving the lowest price per mole was used. Figures 5.1 and 5.2 display synthesis trees of the original synthesis and improved synthesis with the cost of reagents embedded into figure 5.2. To estimate amounts of I5* and I1, literature yields were used, and for the other steps, equivalents described in procedures in appendix C of the thesis were used to calculate the amounts. The estimated RMC per mole of product P using improved route is $11,432.14 / mole, while the RMC for the original route is $17,465.80 / mole. The improved route as it stands provides 35% reduction in RMC.

The majority of materials costs of the original route comes from the synthesis of aldehyde I5a (same intermediate as I4), while the material costs of the original route for the steps from I5a to P is actually lower using original route. However, the new route does not use cryogenic reactions in the steps from I4 to P, which could make it more feasible for larger scale synthesis.
Figure 5.1: Synthetic intermediates from the new route (top) and the Johnson’s route (bottom)
Figure 5.2: Tree analysis of the RMC for the new route and an original Johnson's route displaying:

- moles of reagent
- price per mole of reagent
- total price of reagent
- reagent name
- MW

Approach presented in thesis.
CHAPTER SIX
FUTURE DIRECTIONS: KINETIC RESOLUTION AND ENANTIOSELECTIVE CASCADE STUDIES

This chapter presents the discussion of studies that still have to be done in the future to solve the ent-progesterone supply problem. Discussion of possible solutions and literature review on these solutions is presented. This work is currently in progress and only preliminary work, which is not reported in this thesis was done on these systems.

6.1. The Kinetic Resolution Strategies

The synthesis of racemic progesterone proceeds through tetracyclic intermediate 99. The ketone functionality in tetracycle can serve as a functional handle for kinetic resolution to give

Figure 6.1: Kinetic resolution strategies of tetracycle 99
enantiomerically enriched 99 (Figure 6.1). In general, any reaction that is stereoselective could serve for the purposes of kinetic resolution. One of possibilities is to do a stereoselective reduction of ketone. Alternatively, selective crystallization of diastereomeric intermediates could be employed: 99 could be converted into diastereomeric ketal or imine, which then can be selectively crystallized. Another possibility is to use acidic or basic hydrazines, which then could be co-crystalized with chiral bases or acids.

**Figure 6.2:** Kinetic resolution strategies of rac-progesterone

Alternatively, rac-progesterone can also be used for kinetic resolution. Selective reduction to progesterone diol is known and the diol could be subjected to Sharpless epoxidation, and then be reoxidized to give ent-progesterone. This strategy, however would be very inefficient, as

**Figure 6.3:** Asymmetric epoxidation of α,β-unsaturated ketones by List et. al.
it would add 3 more synthetic steps to already 11 step process, so direct resolution of rac-
progesterone is highly desirable. This could be achieved by employing a recently reported
enantiososelective epoxidation of α,β-unsaturated trisubstituted cyclohexenones by List. et. al.\textsuperscript{67}
(Figure 5.2).

6.2. The Enantioselective Cascade

One of the challenges in achieving efficient synthesis of ent-progesterone is the development
of enantioselective cascade reaction. As a part of the studies of the synthesis of ent-PROG, some
time was spent by the author of this thesis trying to develop an enantioselective cascade that could
be implemented for the synthesis of ent-progesterone with no success, and thus the results are not
reported in this thesis.

There are a few reports in the literature that offer some insight on what the possible solution
might be, but all of them produce steroid cores that are far off from the desirable one. The
enantioselective cation-π cascade chemistry was pioneered by Ishihara and Yamamoto\textsuperscript{68a-c} when
they demonstrated the enantioselective cascades using alcohols derived from BINOL, complexed
with tin chloride. The complex releases H\textsuperscript{+} and acts as a chiral acid equivalent to deliver proton
that initiates the cascade reaction (Figure 5.4). These reactions usually take several days and
require very low temperatures to control enantioselectivity, and sometimes it is necessary to add
co-acids to achieve full conversion (the process is not fully concerted), as demonstrated in the
examples. While this reaction is pretty powerful in constructing the tetracyclic or larger cores, the
enantioselectivity is not perfect and the yields can be modest. Also, there is no general catalyst,
which works in every case, and for every slightly different structure some modification of BINOL
-derived catalyst is necessary to achieve optimum selectivity. More recently, Corey group reported
modification of original protocol\textsuperscript{68d}: the tin chloride was substituted with antimony chloride, which gives the improved yield and enantioselectivity.

\textbf{Figure 6.4}: Early reports of proton-induced enantioselective cascades to construct tetracyclic or larger cores.
Besides these examples, using acids as an electrophiles, some other strategies were used to access the polycyclic cores enantioselectively: Ishihara et al. reported the chiral halonium ion induced enantioselective cationic cascade using NIS complexed with chiral phosphonium catalyst, which is derived from BINOL. (Figure 6.5, top)\textsuperscript{68e}; Gagne et al. reported palladium catalyzed cascade reaction to produce tricyclic cores, but this method has not yet been elaborated into larger
polycycles. In this process, a palladium coordination to the alkene induces the cascade and the final product is formed by β-hydride elimination\(^{68f}\), McMillan group\(^{68g}\), and Toste group\(^{68h}\) have also elaborated their methodologies previously used in their catalysis of other reactions to the synthesis of polycyclic hydrocarbons.

A few of the most recent methods include the ene-reaction type of process to construct tetracyclic cores\(^{68i}\) and iridium transition metal catalyzed cascade reaction reported by Carreira\(^{68j}\) in 2012 (Figure 6.6).

**Figure 6.6:** More recent enantioselective cascades

---

**Figure 6.7:** Possible enantioselective cascade for the synthesis of *ent*-progesterone
While all of these methods reported here are meritorious, it is not clear exactly how to elaborate them into the synthesis of *ent*-progesterone. It seems that each different deviation of enantioselective cascade requires different chiral acid to achieve reasonable yield and selectivity. One of the possible solutions is presented in Figure 6.7. Assuming that the intermediate 174 can be protonated (or halogenated) selectively at the cyclopentadiene, to give intermediate 175 (similar to Ishihara, Yamamoto or Corey) group reports, it would generate tetracycle 176 enantioselectively, which then could be elaborated to *ent*-progesterone. The group R here can be incorporated to enhance the enantioselectivity, which would address the issues encountered in the previous reports of similar systems. The most rational choice would be the high throughput screening of different chiral BINOL-derived acids and halonium ions, combined with the computational modelling of the R group for enhanced selectivity.
APPENDIX A

BENZYLATION REACTIONS OF BENZYLOXYPYRIDINIUM TRIFLATE IN THE MICROWAVE

As a part of PhD work at FSU, I was managing a total of 7 undergraduate project students over the years. This chapter presents results from one of these projects with undergraduate students, which was published in Organic and Biomolecular Chemistry. 2 undergraduate students (Teng-wei Wang and Tanit Intrakulit) that worked under my direct supervision are the first authors of this publication. The text is reformatted from original publication to fit the format of the thesis.

The project focuses on adaptation of the use of benzyloxypyridinium triflate in the microwave reactors, and it concluded with improved conditions that allows fast benzylation of alcohols, carboxylic acids and aromatic rings. Copyright permission was obtained from OBC editorial to use the text from the article in this appendix of the thesis and permission letter is shown in A.4.

ABSTRACT

Benzylation of alcohols and other substrates under thermal conditions translates smoothly from conventional heating into MW-assisted organic synthesis (MAOS). Reactions times are decreased from hours to minutes while good to excellent yields are maintained. MW heating should be considered for benzylation of high-value substrates using the title reagent.
A.1. Microwave-assisted Benzyl-transfer Reactions of Commercially Available 2-benzyloxy-1-methylpyridinium Triflate

A.1.1. Introduction

Benzyl ethers and esters are ubiquitous for the protection of alcohols and carboxylic acids in chemical synthesis\textsuperscript{70}. The benzyl group is inert to most common reaction conditions, yet it is susceptible to cleavage on command using a variety of mild protocols. The synthesis of benzyl ethers from alcohols has traditionally been accomplished under basic or acidic conditions (using benzyl bromide or trichloroacetimidate, respectively). We recently offered 2-benzyloxy-1-methylpyridinium triflate (174) as a complementary option using neutral, thermal conditions\textsuperscript{71}.

\textbf{Figure A.1:} 2-Benzyloxy-1-methylpyridinium triflate (174), and benzyl ethers (O\textsubscript{Bn}) optimally or uniquely prepared using 174 (yield in parentheses).
The advantage of using 174\textsuperscript{72} for the benzylation of acid- and/or base-sensitive alcohols is clear from literature reports in which its unique effectiveness has been noted (figure A.1).\textsuperscript{73} As this reagent gains popularity, we considered it worthwhile to revisit our reagent development efforts in order to minimize certain disadvantages. Namely, the prolonged heating needed to activate the reagent can be detrimental to sensitive substrates, and the standard use of excess reagent increases costs and can increase the formation of by-products, most notably dibenzyl ether.\textsuperscript{72b} We reasoned that these disadvantages could possibly be attenuated using rapid and efficient microwave (MW) heating;\textsuperscript{74} reports of MW heating of ionic liquids\textsuperscript{75} fuelled our optimism with respect to reactions involving 174, an ionic reagent.

MW heating of organic reactions has been associated with reduced reaction times and, in many cases, higher chemical yields and fewer by-products, typically based on the ability of dedicated MW reactors to produce (and reproduce) heating profiles that are difficult to generate using conventional heating methods. The benefits of MW heating are most commonly observed in systems involving polar solvents and/or solutes, which convert incident MW radiation into heat more effectively than nonpolar solutes owing to higher loss tangents (\text{tan} \delta) for polar molecules. Benzyl transfer reactions of 174 meet these criteria, so we investigated a representative sample of diverse substrates using MW heating that we had previously examined using conventional heating. Specifically, we looked at primary and secondary alcohols, carboxylic acids, and electron-rich aromatic systems, all of which are good substrates for benzylation using 174. We also tested the benzylation of tertiary alcohols and phenols, which have been problematic substrates. In all cases, MW-assisted benzylations were accomplished in comparable yield with dramatic reductions in reaction times, as described in the following paragraphs.
A.1.2. Results and Discussion

We first examined the benzylation of diethylene glycol, monomethyl ether (DEGME, 175a, Figure A.2). Our original protocol, developed for maximum generality, involves heating at ca. 83 °C for 24 h in the presence of magnesium oxide (MgO, an acid scavenger). The sealed vessel capabilities of dedicated MW reactors make it convenient to heat reaction mixtures above the boiling point of the solvent (PhCF₃, b.p. 102 °C). After screening multiple sets of conditions, we settled on heating at 120 °C for 20 min. DEGME, like other primary alcohols, is an excellent substrate for benzylation, so one can reduce the stoichiometry of 174 and omit MgO as shown in figure A.2.

MW benzylation of diverse substrates is recounted in Table 1. Primary alcohols DEGME (175a) and the Roche ester (175b, a core building block for polypropionate synthesis) are shown in entries 1 and 2. Roche esters 175b and 175b are prone to elimination under non-neutral conditions, so the high yield in entry 2 is noteworthy. For substrates other than primary alcohols, it was necessary to use two equivalents of 174 to achieve full conversion (entries 3-9).

Thus, MW-promoted benzylation of other substrate types - secondary and tertiary alcohol, phenol, carboxylic acid, and arene - occurred with yields comparable to previous reports but...
Table A.1: Benzyl-transfer reactions of 1 with various alcohols, carboxylic acids, and other substrates under MW heating

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield&lt;sup&gt;b,h&lt;/sup&gt;</th>
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<td>&lt;225x255&gt;175a&lt;/225&gt;</td>
<td>A</td>
<td>&lt;225x255&gt;176a&lt;/225&gt;</td>
<td>98% (93%)</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;225x255&gt;MeO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;OH&lt;/225&gt;</td>
<td>A</td>
<td>&lt;225x255&gt;MeO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;Bn&lt;/225&gt;</td>
<td>98% (85%)</td>
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<tr>
<td>3</td>
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<td>A</td>
<td>&lt;225x255&gt;Ph&lt;sub&gt;2&lt;/sub&gt;Bn&lt;/225&gt;</td>
<td>70%&lt;sup&gt;d&lt;/sup&gt; (83%)</td>
</tr>
<tr>
<td>4</td>
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<td>A</td>
<td>&lt;225x255&gt;176d&lt;/225&gt;</td>
<td>70%&lt;sup&gt;d&lt;/sup&gt;, 82%&lt;sup&gt;d,e&lt;/sup&gt; (88%)</td>
</tr>
<tr>
<td>5&lt;sup&gt;f&lt;/sup&gt;</td>
<td>&lt;225x255&gt;Ph&lt;sub&gt;2&lt;/sub&gt;OH&lt;/225&gt;</td>
<td>A</td>
<td>&lt;225x255&gt;176e&lt;/225&gt;</td>
<td>56%&lt;sup&gt;d&lt;/sup&gt; (65%)</td>
</tr>
<tr>
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<td>&lt;225x255&gt;175f&lt;/225&gt;</td>
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<td>B</td>
<td>&lt;225x255&gt;176h&lt;/225&gt;</td>
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<td>9</td>
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<td>B</td>
<td>&lt;225x255&gt;BocNH&lt;sub&gt;2&lt;/sub&gt;Bn&lt;/225&gt;</td>
<td>98% (91%)</td>
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<tr>
<td>10</td>
<td>&lt;225x255&gt;175j&lt;/225&gt;</td>
<td>C</td>
<td>&lt;225x255&gt;176j&lt;/225&gt;</td>
<td>91%&lt;sup&gt;g&lt;/sup&gt; (90%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions A: 2.0 equiv 174, 120 °C (MW), 20 min. Conditions B: 2.0 equiv 1, 2.0 equiv Et<sub>3</sub>N, 120 °C (MW), 20 min. Conditions C: 5.0 equiv 175j, 1.0equiv 1, 120 °C (MW), 20 min. <sup>b</sup> Refers to isolated yield of pure products, unless otherwise indicated. <sup>c</sup> 1.2 equiv of 174. <sup>d</sup> Yield estimated by <sup>1</sup>H NMR spectroscopy; product could not be separated from Bn<sub>2</sub>O by-product. <sup>e</sup> 1.0 equiv of diethylene glycol, dimethyl ether (diglyme) added. <sup>f</sup> 2.0 equiv of MgO added. <sup>g</sup> ca. 60 : 40 mixture of regioisomers. <sup>h</sup> Yields in parentheses refer to benzylation using conditions reported earlier (ref. 2).
all within the shortened reaction time (entries 3–10). Note the selectivity for benzylolation of a carboxylic acid in the presence of an alcohol (entry 9), as reported previously.\textsuperscript{71c} Selective esterification using \textbf{174} provides a convenient alternative to the use of diazomethane for making alkyl esters. Non-polar benzyl ethers \textbf{176a–f} could not be separated from dibenzyl ether (Bn\textsubscript{2}O, a common by-product in these reactions\textsuperscript{71}), so the reaction yields are estimated by analysis of the \textsuperscript{1}H NMR spectrum after silica gel chromatography (entries 3–6). Interestingly, the yield of \textbf{176d} was improved by including 1.0 equiv of diethylene glycol, dimethyl ether (entry 4). This additive had no effect on other experiments; the rationale behind the improved yield in entry 4 is unclear.

Considering the cost and high molecular weight of \textbf{174} compared to, for example, benzyl bromide, \textbf{1} is perhaps most attractive for the benzylation of complex, high-value substrates, such as key intermediates in multi-step synthesis research (cf. Figure A.1). Such efforts typically involve lab-scale experimentation, which coincidentally is also the arena in which MAOS has had the most impact (as opposed to chemical process or manufacturing scale activities). Thus, MW heating protocols should be widely applicable for activating the title reagent (\textbf{174}).

\textbf{A.1.3. Conclusions}

Thus, MW heating protocols should be widely applicable for activating the MW-assisted benzylolation reactions using 2-benzylxy-1-methylpyridinium triflate (\textbf{174}) are reported. Representative substrates are benzylolated upon heating either in an oil bath\textsuperscript{71} or MW reactor, but MW experiments can be conducted conveniently at higher temperatures and at dramatically reduced reaction times. For those considering installing benzyl ethers onto high-value alcohols or carboxylic acids, we recommend using MW technology in the development of the optimal protocol.
A.2. Experimental

A.2.1. Experimental Procedures

General procedure (Alcohols and arene). An oven-dried 10 mL microwave reaction vessel equipped with a magnetic stir bar was charged with 2-benzyloxy-1-methylpyridinium trifluoromethanesulfonate (174) (1.2–2.0 mmol, 1.2–2.0 equiv, see table A.1), \(a,a,a\)-trifluorotoluene (2 mL), and alcohol 175\(^a\) (1.0 mmol, 1.0 equiv).\(^b\) The mixture was irradiated in an Anton Paar Monowave 300 microwave synthesis reactor at a constant temperature of 120 °C. After 20 minutes at 120 °C, the reaction vessel was cooled using a stream of compressed air, and the reaction mixture was suction-filtered through a pad of Celite. The Celite was washed with diethyl ether (2 x 10 mL). The filtrate was concentrated by rotary evaporation, and the resulting light brown oil was purified by flash column chromatography on silica gel to obtain the benzylated products as described in table A.1.

Notes: \(^a\)Used 5 equiv. of 175i. \(^b\) 2 equiv. of MgO included with alcohols 175e and 175f; see Table A.1.

General procedure (Carboxylic Acid). An oven-dried 10 mL microwave reaction vessel equipped with a magnetic stir bar was charged with carboxylic acid (1.0 mmol, 1.0 equiv.), 2-benzyloxy-1-methylpyridinium trifluoromethanesulfonate (174) (2.0 mmol, 2.0 equiv.), \(a,a,a\)-trifluorotoluene (2 mL) and trimethylamine (2.0 mmol, 2.0 equiv.). The mixture was irradiated in an Anton Paar Monowave 300 microwave synthesis reactor at a constant temperature of 120 °C. After 20 minutes at 120 °C, the reaction vessel was cooled using a stream of compressed air. The sample was then diluted with water (5 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The
crude residue was purified by flash column chromatography on silica gel to provide the benzyl ester products as described in Table A.1.

A.2.2. Characterization (Analytical) Data

**Diethylene glycol benzyl methyl ether (176a):**

\[
\begin{align*}
\text{MeO} & \quad \text{O} & \quad \text{OBn} \\
\end{align*}
\]


**Methyl (2R)-3-(benzyloxy)-2-methylpropionate (176b):**

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{O} & \quad \text{OBn} \\
\end{align*}
\]


**Benzyl α-methylbenzylether (176c):**

\[
\begin{align*}
\text{Ph} & \quad \text{O} & \quad \text{OBn} \\
\end{align*}
\]


**(1R,2S,5R)-(-)-O-Benzylmenthol (176d):**

\[
\begin{align*}
\text{O} & \quad \text{OBn} \\
\end{align*}
\]


**4-Benzyloxybiphenyl (176e):**

\[
\begin{align*}
\text{Ph} & \quad \text{O} & \quad \text{OBn} \\
\end{align*}
\]

2-Phenyl-2 Benzyloxy butane (176f*):

\[
\begin{align*}
&\text{HNMR (400MHz, CDCl}_3\text{) }\delta \text{ 7.26-7.23 (m, 10H), 4.32-4.29(d, } J = 12 \text{ Hz, 1H), 4.21-} \\
&\text{4.18 (d, } J = 12\text{Hz), 1.91-1.86 (q, } J = 7.4 \text{ Hz, 2H), 1.61 (s, 3H), 0.84-0.80(t, } J = 7.4 \text{ Hz,} \\
&\text{3H). C NMR (100 MHz, CDCl}_3\text{) }\delta \text{ 145.38, 139.60, 128.42, 128.27, 128.12, 127.80,} \\
&\text{127.68, 127.24, 127.09, 126.79, 126.32, 79.65, 72.13, 64.50, 35.51, 23.15, 8.44. IR cm}^{-1}\text{; 3062.36,} \\
&\text{3029.89, 2936.10, 2878.42, 1602.71, 1494.87, 1446.73, 1381.34, 1295.97, 1229.74,} \\
&\text{1156.91, 1130.84, 1088.65, 1063.32, 1027.25, 986.71, 892.06, 759.75, 732.12, 694.58} \\
&\text{*NMR signals associated with the dibenzyl ether by-product have been omitted.}
\end{align*}
\]

3-benzyloxy-3-methyl-butyne (176g):

\[
\begin{align*}
&\text{HNMR (400MHz, CDCl}_3\text{) }\delta \text{ 7.39-7.26 (m, 5H), 4.64 (s, 2H), 2.48 (s, 1H), 1.56 (s,} \\
&\text{6H). C NMR (100 MHz, CDCl}_3\text{) }\delta \text{ 138.85, 128.30, 127.73, 127.38, 86.08, 72.23,} \\
&\text{70.47, 66.52, 28.84. IR 3032.22, 2985.75, 2936.01, 2867.77, 1605.69, 1497.72, 1454.38, 1380.38,} \\
&\text{1360.84, 1227.10, 1186.83, 1157.05, 1085.15, 1052.00, 1028.56, 1002.92, 942.42, 883.03, 734.45,} \\
&\text{710.56, 694.47}
\end{align*}
\]

Benzoic acid benzyl ester (176h):

Complete characterization data from Tummatorn, J.; Albiniak, P. A.; Dudley, G. B.


2-tert-Butoxycarboanoamino-3-hydroxy-propionic acid benzyl ester (176i):

2-Benzyl anisole + 4-Benzyl anisole (176j):

A.3. $^1$H NMR Spectra

![A.3. $^1$H NMR Spectra](image-url)
A.4. Permission to reproduce paper as an appendix

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APPENDIX B

EXPERIMENTAL CHAPTER II

$^1$H-NMR and $^{13}$C-NMR spectra were recorded on a Bruker 400 MHz or 600 MHz spectrometer using CDCl$_3$ as the deuterated solvent. The chemical shifts (δ) are reported in parts per million (ppm) relative to internal TMS (0 ppm for $^1$H NMR) or the residual CDCl$_3$ peak (7.26 ppm for $^1$H NMR, 77.0 ppm for $^{13}$C NMR). The coupling constants (J) are reported in Hertz (Hz). IR spectra were recorded on an FT-IR spectrometer. Mass spectra were recorded using electrospray ionization (ESI), electron ionization (EI), chemical ionization (CI) or fast atom bombardment (FAB) techniques. All chemicals were used as received unless otherwise stated. Tetrahydrofuran (THF) was purified by passing over a column of dry alumina. Methylene chloride (CH$_2$Cl$_2$) was distilled from calcium hydride (CaH$_2$). Other solvents were used without any purification. Glassware, NMR tubes, stir bars, needles, and syringes were dried overnight in an oven heated at 120 °C. All reactions were performed under nitrogen atmosphere unless otherwise noted. Neutral organic compounds were purified by flash column chromatography using silica gel F-254 (230-499 mesh particle size). Yields refer to isolated material judged to be >95% pure by $^1$H NMR spectroscopy unless otherwise indicated in the text.

B.1. Experimental 2.1 & 2.2

4-Methycyclohexa-1,4-dienecarboxylic acid (34):

A toluene (50 mL) solution of 5.0 g (68 mmol, 1.0 equiv.) of propiolic acid, 13.6 mL (136 mmol, 2.0 equiv.) of isoprene and 60 mg (0.55 mmol, 0.008 equiv.) of hydroquinone was heated in a sealed tube at 120 °C for 24 hours. The reaction mixture was then
cooled to room temperature, during which time a white crystalline precipitate formed. The white crystals were then collected by filtration to provide title compound in 77% yield. The $^1$H NMR of product matched the data reported in reference 17\textsuperscript{17}.

White Crystals: $^1$H NMR (400 MHz, CDCl$_3$) \emph{d} 7.14-7.08 (m, 1H), 5.53-5.47 (m, 1H), 2.98-2.87 (m, 2H), 2.86-2.76 (m, 2H), 1.74-1.64 (s, 3H).

**Methyl 4-methylcyclohexa-1,4-diene-1-carboxylate (34):**

\[
\begin{align*}
\text{3.0 g (22 mmol, 1.0 equiv.) of 4-Methylcyclohexa-1,4-dienecarboxylic acid was}
\end{align*}
\]

refluexed in 30 mL of dry methanol with 3 drops of sulfuric acid until all the starting material was consumed. The reaction mixture was then diluted with saturated sodium bicarbonate solution (10 mL) and water (20 mL), and then extracted with ethyl acetate (3 x 30 mL). The combined organics were then washed with saturated aqueous sodium chloride solution (30 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give a crude colorless oil. Crude product was used in the next step.

Colorless oil: $^1$H NMR (600 MHz, CDCl$_3$) \emph{d} 6.98-6.95 (m, 1H), 5.49-5.45 (m, 1H), 3.77-3.73 (s, 3H), 2.93-2.86 (m, 2H), 2.80-2.74 (m, 2H), 1.71-1.68 (s, 3H).

**Methyl (4S,5R)-4,5-dihydroxy-4-methylcyclohex-1-ene-1-carboxylate (35):**

To crude ester from previous step was added to a 250-mL round-bottom flask, which was equipped with a magnetic stirrer, a mixture of 200 mL \textit{t}-BuOH : H$_2$O (1 : 1) was then added. Solution was then cooled to 0 \textdegree C, and then 30 g (10 equiv. by mass from \textbf{34}) of AD-mix-$\beta$ and 2.1 g (22 mmol, 1.0 equiv.) of methanesulfonamide was added. The heterogeneous slurry was stirred vigorously at 0 \textdegree C for 60 h. While the mixture was still at 0 \textdegree C, solid sodium sulfite (32 g) was added and the mixture was allowed to warm to room temperature and was kept for 60 minutes with stirring. The reaction mixture was then
extracted with ethyl acetate (4 x 50 mL). The combined organics were washed with 2 M KOH solution (50 mL), water (50 mL), saturated aqueous sodium chloride (50 mL), and then dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a white solid. The crude product was purified by chromatography on silica gel (elution with 80 % EtOAc / Hexanes) to provide 3.17 g of title compound (79% yield over two steps).

White Solid: m.p. 85-86 °C; ¹H NMR (400 MHz, CDCl₃) δ 6.88 (m, 1H), 7.74 (s, 7H), 7.11 (s, 7H), 2.60-2.31 (m, 4H), 2.07-1.89 (app br s, 2H), 1.24 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 167.2, 137.0, 126.5, 72.2, 70.5, 51.7, 37.1, 30.8, 24.8; IR (cm⁻¹) 3386, 2952, 1701, 1652, 1438, 1321, 1257, 1132, 1049; HRMS (Cl⁺) Calcd. for C₉H₁₅O₄: 187.0970, found: 187.0961.

**Methyl (4S,5R)-4,5-bis((tert-butyldimethylsilyl)oxy)-4-methylcyclohex-1-ene-1-carboxylate (36):**

To a solution of 186 mg (1.00 mmol, 1.0 equiv.) of diol 35 and 0.46 mL, (4.0 mmol, 4.0 equiv.) of 2,6-lutidine in 2 mL of DCM was added 0.69 mL (3.0 mmol, 3.0 equiv.) of TBSOTf dropwise at room temperature. The reaction mixture was stirred at room temperature for 30 min, and then quenched with H₂O (10 mL). The reaction mixture was extracted with dichloromethane (3 x 10 mL). The combined organics were washed with saturated aqueous sodium chloride (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 5% EtOAc/Hexanes) to provide provide 410 mg of TBS ether 36 in quantitative yield.

Colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 6.75 (m, 1H), 7.75 (s, 7H), 3.52 (t, 1H, J=7.6 Hz), 2.44-2.35 (m, 3H), 2.26-2.19 (m, 1H), 1.26 (s, 3H), 0.91 (s, 9H), 0.81 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.4, 136.5, 128.6, 74.3, 73.1,
51.6, 41.0, 31.0, 26.0, 25.9, 25.8, 18.3, 18.1, -2.0, -2.3, -4.2, -4.8; **IR** (cm\(^{-1}\)) 2954, 2929, 2887, 2857, 1719, 1655, 1472, 1463, 1388, 1361, 1325, 1291, 1249, 1180, 1137, 1100, 1088, 1063, 1042, 1026, 1005; **HRMS** (FAB\(^+\)) Calcd. for C\(_{21}\)H\(_{42}\)O\(_4\)Si\(_2\)Na: 437.2519, found: 437.2540.

**(4S,5R)-4, 5 – bis ((tert-butyldimethylsilyl)oxy)-4-methylcyclohex-1-en-1-yl)methanol (37):**

To a solution of 415 mg (1.00 mmol, 1.0 equiv.) of TBS ether 36 in THF (5 mL), was added 88 mg (2.2 mmol, 2.2 equiv.) of lithium aluminum hydride powder (95%), in small portions over 5 min at 0 °C. The reaction mixture was then warmed up to room temperature, stirred for 1 hour and then quenched with ice-cold H\(_2\)O (10 mL). The reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined organics were washed with saturated aqueous sodium chloride (10 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure to give a colorless oil. The crude product was purified by chromatography on silica gel (elution with 15% EtOAc / Hexanes) to provide 387 mg of alcohol 37 in quantitative yield as colorless oil.

Colorless oil: **\(^1\)H NMR** (400 MHz, CDCl\(_3\)) \(\delta\) 5.44 (s, 1H), 3.98 (s, 2H), 3.56 (dd, 1H, \(J\)=9.4, 5.6 Hz), 2.31-2.04 (m, 4H), 1.24 (s, 1H), 0.90 (s, 9H), 0.82 (s, 9H), 0.09-0.02 (m, 12H); **\(^13\)C NMR** (100 MHz, CDCl\(_3\)) \(\delta\) 136.1, 119.8, 74.6, 73.7, 66.9, 40.3, 32.8, 26.3, 25.9, 25.8, 18.4, 18.1, -2.0, -2.4, -4.2, -4.8; **IR** (cm\(^{-1}\)) 3322, 2955, 2929, 2886, 2856, 1472, 1463, 1427, 1407, 1388, 1361, 1322, 1294, 1251, 1179, 1146, 1116, 1095, 1053, 1030, 1005; **HRMS** (EI\(^+\)) Calcd for C\(_{20}\)H\(_{42}\)O\(_3\)Si\(_2\): 386.2673, found: 386.2658.

**(1S,2R,4R,5S)-4,5-bis((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl) -5-methylcyclohexan-1-ol (38):**

387 mg (1.00 mmol, 1.0 equiv.) of alcohol 37 was dissolved in THF (5 mL) in a 25-mL round bottom flask at room temperature. To this solution was added 1.5 mL (1.5 mmol, 1.5 equiv.) 1.0
M in THF BH$_3$·THF complex solution dropwise (exothermic reaction was observed), and the resulting solution was stirred for 2 hours at room temperature. Then 2.8 mL of 3 M NaOH solution and 1.2 mL of H$_2$O$_2$ (30 % in H$_2$O) were added to the reaction mixture and stirred for another 2 hours. The resulting mixture was extracted with EtOAc (4 x 10 mL). The combined organic extracts were then washed with water, saturated aqueous sodium chloride (2 x 10mL), dried under Na$_2$SO$_4$, filtered, concentrated under vacuum, and purified on silica gel (30% EtOAc / Hexanes) to give diol 38 in 72% yield as a white solid,

White solid: mp. 140-141 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.91 (td, 1H, $J$=10.5, 4.5 Hz), 3.68-3.64 (app. br. m, 2H, $J$=11.0, 4.5 Hz), 2.94-2.87 (app. br. m, 2H), 1.97 (dd, 1H, $J$=13.0, 4.5 Hz), 1.65-1.60 (m, 1H), 1.50 (q, 1H, $J$=12.2 Hz), 1.38-1.29 (m, 2H), 1.22 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.10-0.04(m, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) 76.4, 75.6, 72.5, 68.6, 47.8, 44.4, 31.1, 26.8, 26.0, 25.9, 18.5, 18.1, -1.9, -2.1, -4.4, -4.6; IR (cm$^{-1}$) 3431, 2951, 2927, 2892, 1472, 1462, 1407, 1386, 1361, 1330, 1251, 1191, 1141, 1108, 1050, 1014; HRMS (FAB$^+$) Calcd. for C$_{20}$H$_{44}$O$_4$Si$_2$Na: 427.2676, found: 427.2673.

(1R,2S,4S,5R)-4,5-bis((tert-butyldimethylsilyl)oxy)-2-((4-methoxybenzyl)oxy)-4-methyl cyclohexyl)methanol (39):

To a solution of 405 mg (1.00 mmol, 1.0 equiv.) of diol 38 and 25 mg (0.1 mmol, 0.1 equiv.) of pyridinium p-toluenesulfonate in DCM (5 mL) was added 0.34 mL (2.0 mmol, 2.0 equiv.) of anisaldehyde dimethyl acetal at room temperature. The reaction mixture was stirred for 2 hours and then diluted with H$_2$O (10 mL). The reaction mixture was extracted with DCM (3 x 10 mL). The combined organics were washed with saturated aqueous sodium chloride (2 x 10 mL), dried over Na$_2$SO$_4$, filtered and concentrated
under reduced pressure to give a colorless oil. This crude product was then dissolved in DCM (5 mL) in a 25-mL round bottom flask at room temperature. To this solution was added 2.4 mL (2.4 mmol, 2.4 equiv.) of diisobutylaluminium hydride (1.0 M in toluene) solution dropwise, and the resulting solution was stirred for 4 hours and then quenched with H₂O (10 mL). The reaction mixture was extracted with DCM (3 x 10 mL). The combined organics were washed with saturated aqueous sodium chloride (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a colorless oil. The crude product mixture was purified by chromatography on silica gel (elution with 15% EtOAc / Hexanes) to provide 367 mg of primary alcohol 39 (70% yield over 2 steps) as colorless oil.

Colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, 2H, J=8.6 Hz), 6.87 (d, 2H, J=8.6 Hz), 4.57 (d, A part of ABX, 1H, J=11.1 Hz), 4.33 (d, B part of ABX, 1H, J=11.1 Hz), 3.79 (s, 3H), 3.73-3.61 (m, 2H), 3.56-3.49 (m, 1H), 3.36 (dd, 1H, J=11.0, 4.6 Hz), 3.02 (app. br. d, 1H, J=7.9 Hz), 2.20 (dd, 1H, J=12.9, 4.2 Hz), 1.76-1.68 (app. br. s, 1H), 1.54 (q, 1H, J=11.4 Hz), 1.47-1.42 (m, 1H), 1.29-1.22 (m, 4H), 0.89 (s, 9H), 0.86 (s, 9H), 0.11-0.04 (m, 12 H); ¹³C NMR (100 MHz, CDCl₃) δ 159.9, 150.1, 129.4, 114.0, 79.3, 76.5, 75.7, 70.2, 67.9, 55.3, 43.8, 43.5, 31.8, 27.0, 26.0, 25.9, 18.5, 18.1, -1.9, -2.0, -4.4, -4.6; IR (cm⁻¹) 3468, 2953, 2929, 2884, 2856, 1613, 1587, 1514, 1471, 1463, 1388, 1361, 1337, 1302, 1248, 1190, 1173, 1161, 1137, 1062, 1038, 1013; HRMS (FAB⁺) Calcd. for C₂₈H₅₂O₅Si₂Na: 547.3251, found: 547.3241.

(((1S,2R,4R,5S)-4-ethynyl-5-((4-methoxybenzyl)oxy)-1-methylcyclohexane-1,2-diyl)bis(oxy))bis(tert-butyldimethylsilane) (40):

A suspension of 525 mg (1.00 mmol, 1.0 equiv.) of primary alcohol 39, 525 mg of Celite and 431 mg (2.00 mmol, 2.0 equiv.) of pyridinium chlorochromate in DCM (5 mL) was stirred at room temperature until starting material was gone.
by TLC. The reaction mixture was then filtered through a short column of SiO$_2$ / Celite and the filtrate was concentrated under reduced pressure to give a white solid. This crude product was added to a 25-mL round-bottomed flask, which was equipped with a magnetic stirrer, charged with 480 mg (2.50 mmol, 2.50 equiv.) of Ohira-Bestmann reagent 42 and 415 mg (3.0 mmol, 3.0 equiv.) of K$_2$CO$_3$ in a solution of methanol (5 mL) at room temperature. The resulting solution was stirred for 5 hours and then diluted with H$_2$O (10 mL). The reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined organics were washed with saturated aqueous sodium chloride (2 x 10 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give a white solid. The crude product mixture was purified by chromatography on silica gel (elution with 10% EtOAc/Hexanes) to provide 327 mg of alkyne 40 (63% yield over 2 steps) as a white crystal.

White crystals: mp. 140-141°C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31 (d, 2H, $J$=8.5 Hz), 6.86 (d, 2H, $J$=8.6 Hz), 4.64, 4.60 (ABq, 2H, $J$=11.4 Hz), 3.80 (s, 3H), 3.68 (td, 1H, $J$=10.8, 4.3 Hz), 3.24 (dd, 1H, $J$=11.2, 4.3 Hz), 2.39 (tm, 1H, $J$=10.9 Hz), 2.12 (d, 1H, $J$=2.2 Hz), 2.04-1.95 (m, 2H), 1.83-1.77 (m, 1H), 1.23-1.17 (m, 4H), 0.89 (s, 9H), 0.85 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.1, 1γ0.9, 1β9.4, 11γ.7, 86.2, 76.6, 75.7, 75.5, 71.8, 68.9, 55.3, 44.6, 35.4, 35.1, 26.8, 26.0, 25.9, 18.5, 18.1, -1.9, -2.2, -4.4, -4.7; IR (cm$^{-1}$) 3313, 2955, 2930, 2886, 2857, 2857, 1581, 1513, 1472, 1463, 1388, 1361, 1316, 1302, 1249, 1191, 1172, 1158, 1132, 1109, 1081, 1052; HRMS (FAB$^+$) Calcd, for C$_{29}$H$_{50}$O$_4$Si$_2$Na: 541.3145, found: 541.3147.

(((1S,2R,4R,5S)-5-((4-methoxybenzyl)oxy)-1-methyl-4-(prop-1-yn-1-yl)cyclohexane-1,2-diy1)bis(oxy))bis(tert-butyldimethylsilane):

To a solution of 104 mg (0.2 mmol, 1.0 equiv.) alkyne 40 in THF (1 mL), was added 0.1 mL (0.22 mmol, 1.0 equiv.) of n-butyllithium (2.25 M in
hexanes) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 10 minutes. 0.02 mL (3.0 mmol, 1.5 equiv.) of CH$_3$I was then added to the reaction mixture and the solution was warmed up to room temperature and stirred overnight. The reaction was quenched with H$_2$O (5 mL), extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with saturated aqueous sodium chloride (5 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 10% EtOAc / Hexanes) to provide title compound in quantitative yield as colorless oil.

Colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.31 (d, 2H, $J$=8.5 Hz), 6.86 (d, 2H, $J$=8.6 Hz), 4.63, 4.60 (ABq, 2H, $J$=11.8 Hz), 3.80 (s, 3H), 3.58 (td, 1H, $J$=10.7, 4.3 Hz), 3.23 (dd, 1H, $J$=11.2, 4.3 Hz), 2.32 (tm, 1H, $J$=10.8 Hz), 2.00 (dd, 1H, $J$=13.3, 4.3 Hz), 1.93-1.83 (m, 4H), 1.77-1.71 (m, 1H), 1.21-1.15 (m, 4H), 0.89 (s, 9H), 0.84 (s, 9H), 0.07-0.03 (m, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 159.1, 131.1, 129.4, 113.7, 80.9, 76.2, 75.9, 75.6, 71.6, 55.3, 44.7, 35.8, 35.4, 26.9, 26.0, 25.9, 18.5, 18.1, 3.7, -1.9, -2.2, -4.4, -4.6; IR (cm$^{-1}$) 2955, 2929, 2857, 1613, 1587, 1513, 1472, 1463, 1366, 1301, 1248, 1190, 1170, 1153, 1078, 1056, 1039, 1005; HRMS (FAB$^+$) Calcd for C$_{30}$H$_{52}$O$_4$Si$_2$Na: 555.3302, found: 555.3300.

(1S,2R,4R,5S)-5-((4-methoxybenzyl)oxy)-1-methyl-4-(prop-1-yn-1-yl)cyclohexane-1,2-diol (41): A 107 mg (0.200 mmol, 1.0 equiv.) solution of alkyne from previous section solvent THF (2 mL) solution of alkyne and 1.0 mL (1.0 mmol, 5.0 equiv.) solution of tetrabutylammonium fluoride (1.0 M in THF) was heated at reflux for 3 hours. The resulting mixture was cooled to room temperature, then diluted with H$_2$O (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with saturated aqueous sodium chloride (5 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give a
colorless oil. The crude product was purified by chromatography on silica gel (elution with 50% EtOAc/Hexanes) to provide diol 41 in 88% yield over 2 steps as a colorless oil.

\[ ^1H \text{NMR} (400 \text{ MHz, } CDCl_3) \delta 7.32 (d, 2H, J=8.5 \text{ Hz}), 6.87 (d, 2H, J=8.5 \text{ Hz}), 4.66, 4.59 (ABq, 2H, J=11.2 \text{ Hz}), 3.80 (s, 3H), 3.61 (td, 1H, J=10.4, 4.2 Hz), 3.39 (dd, 1H, J=10.9, 4.5 Hz), 2.38 (tm, 1H, J=10.3 Hz), 2.14 (dd, 1H, J=13.9, 4.2 Hz), 1.99-1.95 (app br m, 3H), 1.84-1.78 (m, 4H), 1.32 (dd, 1H, J=13.76, 10.80 Hz), 1.25 (s, 3H); \]

\[ ^13C \text{NMR} (100 \text{ MHz, } CDCl_3) \delta 159.1, 1\gamma0.9, 129.4, 113.7, 80.3, 76.92, 76.89, 73.4, 71.90, 71.88, 55.3, 41.8, 35.2, 34.5, 27.1, 3.6; \]

IR (cm\(^{-1}\)) 3421, 2932, 1613, 1586, 1514, 1455, 1367, 1302, 1247, 1173, 1145, 1060, 1036; HRMS (EI\(^+\)) Calcd for C\(_{18}\)H\(_{24}\)O\(_4\): 304.1675, found: 304.1679.

(2R,3aR,5S)-6-(((4-methoxybenzyl)oxy)-2,7a-dimethylhexahydro-2,5-methanobenzo[d][1,3]dioxol-8-one (42, tricyclic core of aldingenin B):

A solution of 20.5 mg (0.066 mmol, 1.0 equiv.) of diphenyl diselenide and 30 mg (0.13 mmol, 2.0 equiv.) of ammonium persulfate in CH\(_3\)CN (1 mL) and H\(_2\)O (0.4 mL) was heated to 85 °C for 15 minutes. To this reaction mixture was added a solution of 20.0 mg (0.066 mmol, 1.0 equiv.) of 41 in acetonitrile (3 mL). The resulting mixture was heated at 85 °C for 2 hours and cooled to room temperature. The reaction mixture was then diluted with H\(_2\)O (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with saturated aqueous sodium chloride (5 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 15%-20% EtOAc/Hexanes) to provide keto-ketal 42 in 52% yield as colorless oil. \[ ^1H \text{NMR} (400 \text{ MHz, } CDCl_3) \delta 7.25 (d, 2H, J=8.4 \text{ Hz}), 6.89 (d, 2H, J=8.5 \text{ Hz}), 4.53 (d, A part of ABX, 1H, J=11.4 \text{ Hz}), 4.39 (d, B part of ABX, 1H, J=11.4 \text{ Hz}), 4.26 (app. s, 1H), 3.82-3.80 (m, 4H), 2.95 (app. s, 1H), 2.51 (dd, 1H, J=14.4, 7.9 Hz), 2.34-2.20 (m, 2H), 1.73 (dd,
\( ^1\text{H, } J=14.4, 7.4 \text{ Hz,} \) 1.44 (s, 3H), 1.41 (s, 3H); \( ^{13}\text{C NMR (100 MHz, CDCl}_3) \delta 200.3, 159.3, 129.8, \) 129.3, 113.9, 107.3, 80.0, 79.8, 73.8, 70.6, 55.3, 47.9, 37.2, 29.3, 27.0, 16.4; \( \text{IR (cm}^{-1}) \) 2945, 1729, \) 1613, 1514, 1458, 1388, 1302, 1249, 1177, 1154, 1093, 1050, 1012; \( \text{HRMS (ESI)}^+ \) Calcd. for \( \text{C}_{18}\text{H}_{22}\text{O}_5\text{Na}: 341.1365, \) found: 341.1371.
B.2. $^1$H and $^{13}$C NMR spectra for 2.1 and 2.2
B.3. Experimental 2.3-2.6

For part 2.4, the structures were confirmed by $^1$HNMR, as the experiments were exploratory. The $^1$HNMR was consistent with the structures we were expecting to see, and compounds were advanced without full characterization.

**Ethyl 5-hydroxy-5-methylhexanoate (48):**

![Chemical structure of ethyl 5-hydroxy-5-methylhexanoate (48)](image)

To a solution of 2.4 g (12.64 mmol, 1.0 equiv.) of TiCl$_4$ in 60 mL of Et$_2$O, precooled to -78 °C was added 8.9 mL (12.64 mmol, 1.0 equiv.) of MeLi in Et$_2$O (1.42 M in Et$_2$O) over 3 min. Solution was then brought to -30°C over 27 min. 2.0 g (12.64 mmol, 1.0 equiv.) of ethyl 5-oxo-hexanoate was then added over 2 min. and solution was then stirred for additional 4 h 55 min., while allowing the reaction to slowly warm up to -10°C. Ice-cold H$_2$O was then added and reaction was extracted 3 times with Et$_2$O. Organic layers were washed with water, brine, dried under Na$_2$SO$_4$ and concentrated to give 2.1 g (95 % yield) of title compound which was pure by $^1$HNMR.

Slightly yellow oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 4.18-4.11 (q, 2H, $J=7.2$), 2.37-2.30 (t, 2H, $J=8$), 1.76-1.67 (m, 2H), 1.64-1.60 (broad s, 1H), 1.53-1.47 (m, 2H), 1.29-1.24 (t, 3H), 1.24 (s, 3H).

**ethyl 5-((tert-butyldimethylsilyl)oxy)-5-methylhexanoate (49):**

![Chemical structure of ethyl 5-((tert-butyldimethylsilyl)oxy)-5-methylhexanoate (49)](image)

To a solution of 1.55 g (8.9 mmol, 1.0 equiv.) of 48 in DCM, precooled to -20°C was added 4.1 mL (17.8 mmol, 2.0 equiv.) of TBSOTf dropwise. Reaction was then stirred for 5 min. and then 3.7 mL (26.7 mmol, 3.0 equiv.) of Et$_3$N was added and the solution was kept overnight. Water was then added to reaction mixture and reaction was extracted 3 times with ethyl acetate. Organic extracts were washed with water, brine, dried under sodium sulfate and concentrated to give crude product, which was purified using
column chromatography (gradient elution hexans to 1 % EtOAc / Hexanes to 2 % EtOAc / Hexanes) to give 2.1 g (82 % yield) of title compound.

Colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.17-4.10 (q, 2H, $J=7.2$), 2.31-2.26 (t, 2H, $J=7.2$), 1.76-1.66 (m, 2H), 1.47-1.40 (m, 2H), 1.30-1.22 (t, 3H, $J=7.2$), 1.20 (s, 3H), 0.86 (s, 9H), 0.07 (s, 6H).

**ethyl 2-bromo-5-((tert-butyldimethylsilyl)oxy)-5-methylhexanoate(50):**

![ester structure]

To a solution of 1.6 g (5.54 mmol, 1.0 equiv.) of ester 49, and 1.2 g (11.1 mmol, 2.0 equiv.) of dry TMSCl, dissolved in THF at -78°C, 2.2 equiv. of freshly prepared LDA (~0.6 M in THF) was added dropwise. Reaction then was placed in 0°C ice bath and kept for 15 min. and then recooled to -78°C. 4.9 g (27.7 mmol, 5.0 equiv.) of NBS in 30 mL THF / 2 mL HMPA was then added dropwise and reaction was stirred for 3 h 45 min. at 0°C. Reaction was then diluted with ammonium chloride and extracted with 3 portions of EtOAc. Organic layers were washed with 3 portions of ammonium chloride, water, brined, dried under sodium sulfate and concentrated to give crude product, which was purified using column chromatography (1 % to 2 % EtOAc / Hexanes) to give 1.53 g (75 % yield) of title compound.

Colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.29-4.19 (qd, 2H, $J=7.4, 1.1$), 2.26-2.03 (m, 2H), 1.64-1.54 (td, $J=4.8$), 1.34-1.29 (t, 3H, $J=6.8$), 1.23 + 1.24 (s, s, 6H), 0.88 (s, 9H), 0.09 (s, 6H).

**2-bromo-5-((tert-butyldimethylsilyl)oxy)-5-methylhexanoic acid(51):**

![acid structure]

1.53 g (4.13 mmol, 1.0 equiv.) of 50 was dissolved in 60 mL of 3 : 1 mix of THF : MeOH and then 12.4 mL (12.4 mol, 3.0 equiv.) of LiOH (1.0 M in H$_2$O was added to the reaction. Reaction was then stirred for 30 min., diluted with 3 : 1 CHCl$_3$ : 1.0 M HCl, extracted 3 x 25 mL of CHCl$_3$, dried under MgSO$_4$ and concentrated to give 1.43 g
of crude title compound in quantitative yield (>95 % pure by $^1$HNMR) which was used in the next step without any purification.

Colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.27 (t, 1H, $J=7.2$), 2.28-2.04 (m, 2H), 1.61 (td, 1H, $J=13.0$, 4.6), 1.48 (td, 1H, $J=13.0$, 4.6), 1.23 (2x s, 6H), 0.86 (s, 9H), 0.083 (s, 6H).

**Compound 53 (anti-aldol piece):**

To a solution of 2.76 g (6.0 mmol, 1.0 equiv.) of ester 52 (prepared according to reference XX) in DCM (60 mL), precooled to -78°C, 3.16 mL (21 mmol, 4.0 equiv.) of TEA was added, followed by dropwise addition of 16.8 mL (16.8 mmol, 2.8 equiv.) of Cy$_2$BOTf (1.0 M in hexanes, prepared according to reference 77) over 10 min. Reaction was then stirred for 1h 20 min. at -78°C and then 1.53 g (18 mmol, 3.0 equiv.) of aldehyde 60 (solution in DCM, prepared according to reference 78) was added dropwise over 10 min. Reaction was then warmed up to 0°C over 1h 20 min. To a reaction 25 mL of pH = 7.0 phosphate buffer (1.0 M) was added carefully, followed by the addition of 70 mL of methanol. 7 mL of H$_2$O$_2$ (30 % in H$_2$O) was added slowly (reaction highly exothermic) and reaction was stirred overnight. Reaction then was concentrated using rotary evaporator until only water remained and water layer was then extracted 3 times with ethyl acetate. Extracts then were washed with water, brine, dried under sodium sulfate and concentrated to give crude mixture, which was purified using column chromatography (1 : 1 : 9 DCM : EtOAc : Hexanes) to give 2.05 g (74 % yield) of compound 53 as a white amorphous solid.
White solid: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.32 (d, 2H, $J$=6.8), 7.27-7.17 (m, 5H), 7.13 (t, 2H, $J$=7.7), 6.87 (s, 2H), 6.80 (d, 2H, $J$=7.5), 5.79 (d, 1H, $J$=5.3), 5.60-5.48 (m, 1H), 4.97-4.73 (m, 5H), 4.54 (d, 2H, $J$=16.5), 4.10 (quin., 1H, $J$=5.5), 3.86 (sext., 1H, $J$=3.8), 2.56-2.49 (m, 1H), 2.44 (s, 6H), 2.39-2.22 (m, 7H), 2.18-2.07 (m, 1H), 1.73 (s, 3H), 1.20 (d, $J$=6.9).

(4aR,8aR)-3-(3-((tert-butyldimethylsilyl)oxy)-3-methylbutyl)-7-methyl-2-oxo-4a,5,8,8a-tetrahydro-2H-chromen-4-yl trifluoromethanesulfonate (56):

Stage A: To a 193 mg (0.36 mmol) of compound 53 in DCM (10 mL), 15 mg of Grubbs II was added. Reaction was then stirred for 4 h at reflux and filtered on short silica pad (elution with 20 % ethyl acetate / 20 % DCM / hexanes) and concentrated using rotary evaporator to give crude product, which was all used in next reaction (100 % yield assumed).

Stage B: In a separate vial, carboxylic acid 51 was diddolved in 0.9 mL of THF, and then 147 mg of DCC was added and reaction was stirred for 20 min. Product, described in paragraph 1 was then dissolved in 0.9 mL of THF, together with 18 mg of DMAP, and this mixture was added to the reaction and the reaction was stirred for additional 3h 40 min., after which it was filtered on SiO$_2$, and used in the next reaction without further characterization.

Stage C: To a 15 mL 2-necked flask, fitted with reflux condenser, 2 mL of THF was added and the flask was then heated to 60°C. All product from step B was then dissolved in 2 mL of THF and was added dropwise via syringe simultaneously with another syringe containing 1.1 mL of t-BuMgCl (1.0 M in THF) to the reaction over 10 min. Reaction was then stirred for additional 1h 50 min. at 60°C and 1.0 mL of citric acid (1.0 M in water) was then added to the reaction and it was stirred for 10 min. Reaction was then diluted with 1.0 M HCl and extracted 3 times with ethyl
acetate. Organic layers were then washed with 1.0 M HCl, concentrated to give crude product, which was purified using 10 % ethyl acetate / hexanes. The mixture contained significant amount of co-eluting impurities, but was used in the next step as is.

Stage D: All product from step C was dissolved in 6 mL of DCM and was cooled to -78 °C. 135 mg of Tf₂O and 65 mg of triethyl amine were then added dropwise via syringe and reaction was stirred for 30 min at -78 °C. 1.0 mL of water was then carefully added and reaction was diluted with more water and extracted 3 times with ethyl acetate. Organic layers were washed with water, brine, dried under sodium sulfate and concentrated to give crude product, which was purified using 2 % ethyl acetate / hexanes to give 162 mg (31 % yield over 4 steps) of the title compound.

White solid: **¹H NMR** (400 MHz, CDCl₃) δ 5.42 (s, 1H), 4.34-4.26 (m, 1H), 2.96 (td, 1H, J=11.6, 5.8), 2.62-2.57 (t + m, 3H, J(triplet)=7.2), 2.47-2.32 (m, 2H), 2.15-2.04 (m, 1H), 1.74 (s, 3H), 1.72-1.60 (m, 1H), 1.52-1.40 (m, 1H), 1.23 (s, 6H), 0.86 (s, 9H), 0.08 (s, 6H).

**{(1R,6S)-6-((tert-butyldimethylsilyl)oxy)-5-methylhex-1-yn-1-yl)-3-methylcyclohex-3-en-1-ol (57):}**

57 mg of triflate 56 was dissolved in 2 mL of toluene in 10 mL round bottom flask, fitted with reflux condenser. Flask was then cooled down to -78 °C and 0.11 mL of methylmagnesium bromide (3.0 M in diethyl ether) was added dropwise. Reaction was then kept at -78 °C for 20 min, then cooling bath was removed and reaction was stirred for 30 min., after which the flask was immersed into oil-bath preheated to 60 °C and stirred overnight. Reaction was then quenched with the careful addition of saturated ammonium chloride, extracted with 3 portions of ethyl acetate, washed with water, brine, dried under sodium sulfate and concentrated to give crude product, which was
purified using 10 % ethyl acetate / hexanes to give 30 mg (81 % yield) of pure product that had $^1$H NMR consistent with the title structure.

Colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 5.28 (s, 1H), 3.69 (q, 1H, J=9.8), 2.48-2.21 (m, 5H), 2.15-2.02 (m, 1H), 2.03-1.91 (m, 1H), 1.69-1.63 (m, 5H), 1.20 (s, 6H), 0.85 (s, 9H), 0.06 (s, 6H).

**(1R,2S,4S,5R)-5-(benzyloxy)-4-(5-((tert-butyldimethylsilyl)oxy)-5-methylhex-1-yn-1-yl)-1-methylcyclohexane-1,2-diol:**

![Chemical Structure](image)

**Stage A:** To a 118 mg (0.35 mmol, 1.0 equiv.) of alcohol 57, precooled to 0 °C in acetonitrile (8 mL), was added 28 mg (0.70 mmol, 2.0 equiv.) of NaH (60 % in oil), and reaction was stirred for 15 min. 300 mg (1.75 mmol, 5.9 equiv.) of BnBr and 13 mg (0.035 mmol, 0.1 equiv.) of TBAI. Reaction was then stirred until complete consumption of starting material by TLC was observed and then was quenched with satd. ammonium chloride. Reaction was then extracted 3 times with ethyl acetate, washed with water, brine, dried under sodium sulfate and concentrated to give crude product, which was purified using 3 % ethyl acetate / hexanes. To give benzylation product that had moderate purity by NMR (yield est. ~66 %)

**Stage B:** 47 mg (0.15 mmol, 1.0 equiv.) of product was then dissolved in 2 ml ice-cold 1 : 1 H$_2$O : t-BuOH and 235 mg (5.0 mass equiv.) of AD-mix-α was added to the reaction, followed by the addition of 15 mg (0.15 mmol, 1.0 equiv.) of methanesulfonylamine. Reaction was then stirred for 24h overnight at 0 °C and then 330 mg of solid sodium sulfite was added and reaction was allowed to warm to r.t. over 1h. Reaction was then diluted with 1M KOH, extracted 3 times with ethyl acetate, washed with water, brine, and was concentrated to give crude product, which was purified using column chromatography to give 20.3 mg of product that had $^1$H NMR consistent with the title structure.
B.4. Select $^1$H NMR Spectra for part 2.4

![NMR Spectra for 2-25-p](image-url)

![NMR Spectra for 279-c1](image-url)
APPENDIX C

EXPERIMENTAL CHAPTER IV

$^1$H-NMR and $^{13}$C-NMR spectra were recorded on a Bruker 400 MHz or 600 MHz spectrometer using CDCl$_3$ as the deuterated solvent, unless otherwise stated in the text. The chemical shifts (δ) are reported in parts per million (ppm) relative to internal TMS (0 ppm for $^1$H NMR) or the residual CDCl$_3$ peak (7.26 ppm for $^1$H NMR, 77.0 ppm for $^{13}$C NMR). The coupling constants ($J$) are reported in Hertz (Hz). Mass spectra were recorded using electrospray ionization (ESI), electron ionization (EI), chemical ionization (CI) or fast atom bombardment (FAB) techniques. All chemicals were used as received unless otherwise stated. THF, DCM, Diethyl Ether, DMF and toluene were purified using solvent purification system. Other solvents were used as received from Sigma-Aldrich. Glassware, NMR tubes, stir bars, needles, and syringes were dried overnight in an oven heated at 120 °C. All reactions were performed under nitrogen atmosphere unless otherwise noted. Neutral organic compounds were purified by flash column chromatography using silica gel F-254 (230-499 mesh particle size), where purification was necessary. Yields refer to isolated material judged to be >95% pure by $^1$H NMR spectroscopy unless otherwise indicated in the text.

C.1. Experimental procedures

Preparation procedures for compounds in the order they appear in the text. Full characterization was obtained for the compounds leading to the desired intermediates for the final synthesis. Compounds for exploratory studies were characterized by $^1$H NMR.

2-methylhept-1-en-6-yn-3-ol (127):

**Stage A:** To a precooled to -78 °C solution of 3.32 g (26.2 mmol, 1.1 equiv) oxallyl chloride in 50 mL of DCM, was added 3.7 mL (52.3 mmol, 2.2 equiv.)
of DMSO in 10 mL of DCM over 20 min. Solution was then stirred for additional 20 min at -78 °C, and then 2.0 g (23.8 mmol, 1.0 equiv.) of 4-pentyn-1-ol in 20 mL of DCM was added over 10 min. Solution was then stirred for additional 30 min and 16.57 mL (119 mmol, 5.0 equiv.) of TEA was added dropwise. Solution was then kept at -78 °C for 10 min and warmed up to 0 °C and stirred for additional 1 h. Solution was then poured into solution of of brine, acidified with 1 % HCl and DCM, and was extracted 3 times with DCM. Organic layers were then washed 3 times with brine / 1% HCl solution and aqueous layers were extracted additional 3 times with DCM. Combined organic layers were then washed with brine, dried under sodium sulfate and concentrated using rotary evaporator. Aldehyde was used immediately for the next step:

**Stage B:** All aldehyde was dissolved in 40 mL of THF, cooled down to -78 °C, and then 2.2 equiv. (105 mL) of isopropenyl-magnesium bromide (0.5 M in THF) was added, and reaction was warmed to r.t. and stirred until complete consumption of starting material (~ 2 h). Reaction was then quenched with satd. ammonium chloride, extracted 3 times with ethyl acetate, washed with satd. ammonium chloride, water, brine, dried under sodium sulfate and concentrated using rotary evaporator. Crude product was then purified using 10 % ethyl acetate / hexanes to give 1.67 g (57 % yield) of alcohol 127.

Colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 5.01 (s, 1H), 4.88 (s, 1H), 4.22 (t, 1H, J = 6.8), 2.30 (q, 2H, J = 5.6), 1.98 (t, 1H, J = 2.6), 1.78 (q + s, 5H, J = 7.6).

2-methyloct-1-en-6-yn-3-ol (128):

1.0 g (8.2 mmol, 1.0 equiv.) of 2-methylhept-1-en-6-yn-3-ol was dissolved in 120 mL of THF, and cooled down to -78 °C. 11.1 mL (17.7 mmol, 2.2 equiv.) of BuLi (1.6 M in hexanes) was then added dropwise. Solution was then stirred for 10 min at -78°C, then 20 min at -30 °C, and cooled to -78 °C again. 2.5 mL (40.3 mmol, 5.0 equiv.) of MeI in 3.0 mL (40.3 mmol, 5.0 equiv.) of HMPA was then added dropwise and reaction was warmed to 0°C and stirred for 1 h. Ammonium chloride was then carefully added to reaction mixture and reaction was extracted 3 times with ethyl acetate. Organic layers were washed with water, brine, dried with sodium sulfate and concentrated using rotary evaporators. Product was then purified using column chromatography using 10 % ethyl acetate / hexanes to give 758 mg (67 % yield) of the title compound.

Colorless oil: \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 4.98 (s, 1H), 4.86 (s, 1H), 4.18 (t, \(J=5.6\)), 2.33-2.12 (m, 2H), 1.84-1.65 (m, 9H, sharp s at 1.78, 1.73).


(E)-2,2-dimethyl-3-(3-methyloct-3-en-7-yn-1-yl)oxirane (130):
Stage A: 1.6 g (6.86 mmol) scale, prepared following the procedure for chloro analog 132. Contained some impurities and isomeric epoxidation product, and was used as is in the next step. Highly unstable.

Light brown oil: $^1$H NMR* (400 MHz, CDCl$_3$) $\delta$ 5.62-5.54 (td, 2H, $J$=8.4, 1.2), 4.07-3.98 (d, 2H, $J$=8.4), 2.73-2.67 (t, 1H, $J$=6.2), 2.30-2.17 (m, 2H), 1.75 (s, 3H), 1.70-1.61 (q, 2H, $J$=7.8), 1.31 (s, 3H), 1.27 (s, 3H) *Peaks representing impurities and other isomer omitted.

Stage B: To a flask, containing 35 mL of dry THF, precooled to 0 °C was added 3.16 mL (1.15 equiv., 7.89 mmol) of BuLi (2.5M in hexanes), followed by the dropwise addition of 1.0 g of 1-(trimethylsilyl)propyne. Reaction was then stirred for 1 h. and 129a (1.0 equiv., 1.6 g, 6.86 mmol) in 15 mL of THF was added dropwise. Reaction was then kept for 2 h. at -78 °C and then 10.3 mL (1.5 equiv., 10.3 mmol) of TBAF (1.0 M in THF) was added and reaction was allowed to warm to r.t. Reaction was then diluted with satd. ammonium chloride. Extracted 3 times with ethyl acetate. Washed with water, brine, dried under sodium sulfate and concentrated to give crude product which was purified using column chromatography 2 % ethyl acetate / hexanes to give 686 mg (52 % yield) of title compound.

Colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.24 (t, 1H, $J$=5.6), 2.71 (t, 1H, $J$=6.2), 2.28-2.04 (m, 6H), 1.93 (t, 1H, $J$=2.4), 1.7-1.54 (m, 5H), 1.3 (s, 3H), 1.26 (s, 3H) $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 135.85, 123.07, 84.37, 68.23, 64.08, 58.35, 36.27, 27.32, 27.10, 24.88, 18.84, 18.74, 16.12

(E)-3-(5-chloro-3-methylpent-3-en-1-yl)-2,2-dimethyloxirane (132):

5.8 g (33.6 mmol, 1.0 equiv.) of geranyl chloride was dissolved in 336 mL of chloroform. Solution was then cooled to 0°C and then 7.9 g (35.3 mmol, 1.05 equiv.) of mCPBA (77 % purity) was added in small portions over 30 min. After addition, solution was stirred for additional 30 minutes at 0°C.
Solution was then extracted 5 times with 1M NaHCO₃. Organic layer was washed with water, brine, dried under Na₂SO₄ and concentrated to give 6.34 g (100 % yield, c.a. 90-95 % pure by ¹H NMR) of title compound, which was used in the next step as is without further purification.

Colorless liquid: ¹H NMR (400 MHz, CDCl₃) δ 5.50 (td, 1H, J=7.9, 1.1), 4.10 (d, 2H, J=8.0), 2.69 (t, 1H, J=6.2), 2.29-2.11 (m, 2H), 1.74 (s, 3H), 1.66 (q, 2H, J= 7.5), 1.30 (s, 3H), 1.27 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 141.7, 1β0.8, 6γ.8, 58.4, 40.8, 40.8, 36.1, 26.9, 24.8, 18.7, 16.0


**(E)-2,2-dimethyl-3-(3-methylnon-3-en-7-yn-1-yl)oxirane (131)** (Method A):

![Chemical structure](image)

To a 686 mg of 129 in 17 mL of THF, precooled to -78 °C, 2.67 mL of BuLi (1.6 M in hexanes) was added and reaction was stirred for 30 min. 760 mg of MeI was then added and reaction was warmed to r.t. and left for 1 h with stirring. Reaction was the quenched with ammonium chloride and extracted 3 times with ethyl acetate. Organic layers were then washed with water, brine, dried under sodium sulfate and concentrated to give 710 mg (quant. yield) of title compound.

**(E)-2,2-dimethyl-3-(non-3-en-7-yn-1-yl)oxirane (131)** (Method B):

![Chemical structure](image)

To a 250 mL round-bottom flask at -78 °C. 25 mL of Et₂O was added under inert atmosphere. Then 25 mL (40 mmol, 4.8 equiv.) of BuLi (1.6 M in hexanes) was added and solution was stirred for 5 minutes to equilibrate the temperature. Then 1.162 g (10 mmol, 1.5 mL, 1.2 equiv.) of TMEDA was added dropwise, and solution was stirred for 1 min. 2.97 g (20 mmol, 2.15 mL, 2.4 equiv.) of propargyl bromide (80 wt % in toluene) was then added dropwise over few minutes and solution was stirred for 20 min. at -78 °C. In a separate vial, a
solution of 1.572 g (8.33 mmol, 1.0 equiv.) (E)-3-(5-chloro-3-methylpent-3-en-1-yl)-2,2-dimethyloxirane and 303 mg (0.833 mmol, 0.1 equiv.) of TBAI was prepared in 5 mL of Et₂O. Solution was then added to the flask containing dianion dropwise via canulla and the remaining solids in a vial were washed out with 2 5mL fractions of 5 mL Et₂O. Dry ice bath was then replaced with ice bath and reaction was stirred for 1h. at 0 °C. At this stage solution contained white/yellowish precipitate. Reaction was then diluted with 50 mL of THF and and 6.41 g of DMPU (50 mmol, 6.03 mL, 6.0 equiv) was then added dropwise, followed by the dropwise addition of 6.30 g (50 mmol, 4.78 mL, 6.0 equic.) of dimetyl sulfate. Ice bath was then removed and reaction was then stirred vigorously for 1 h at r.t. Reaction was then cooled to 0 °C and 25 mL of 5 % NH₃ solution was added to quench the unreacted dimethyl sulfate and reaction was stirred for 1 h at r.t. Reaction was then diluted with water and extracted 3 times with ethyl acetate. Organic extracts were then washed twice with 2 fractions of ammonium chloride, 2 fractions of water and one fraction of brine. Organic layer was then dried with Na₂SO₄, concentrated under rotary evaporator and subjected to column chromatography using 3 % ethyl acetate / hexanes to afford 1.14 g (67 % yield) of the title compound.

Colorless liquid: ¹H NMR (400 MHz, CDCl₃) δ 5.21 (t, 1H, J=5.6), 2.71 (t, 1H, J=6.3), 2.25-2.05 (m, 6H), 1.77 (t, 3H), 1.72-1.56 (m, 5H), 1.31 (s, 3H), 1.27 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 135.4, 123.6, 79.1, 75.4, 64.1, 58.4, 36.3, 27.7, 27.4, 24.9, 19.1, 18.7, 16.1, 3.5

(E)-4-methyldec-4-en-8-ynal (94):

540 mg (2.62 mmol, 1.0 equiv.) of Compound 130 was dissolved in 10.5 mL of 1 : 1 THF : H₂O. Solution was then cooled to 0 °C in an ice bath and 1.35 g (6.28 mmol, 2.4 equiv.) of sodium periodate was then added to reaction mixture, followed by the addition of 59.7 mg (0.262 mmol, 0.1 equiv.) of periodic acid. Reaction
was then stirred for 3 h. at 0°C and for additional hour at r.t. Reaction was then poured into 1 M NaHCO₃ : EtOAc (precooled to 0 °C). Layers were then separated and aqueous layer was extracted with 3 portions of ethyl acetate. Organic layers were then combined and washed twice with water, brine and dried under sodium sulfate. Reaction mixture was then concentrated using rotary evaporator and crude mixture was used as is without purification in the next step. Aldehyde has very strong irritating odor, which is felt even outside fume hood.

Colorless liquid: $^1$H NMR (400 MHz, CDCl₃) δ 9.80-9.74 (t, 1H, $J=1.2$), 5.21 (t, 1H, $J=5.7$), 2.52 (tq, 2H, $J=8, 1.2$), 2.33 (t, 2H, $J=8$), 2.2-2.07 (m, 4H), 1.76 (t, 3H, $J=2.4$), 1.62 (s, 3H). $^{13}$C NMR (100 MHz, CDCl₃) δ 202.6, 134.3, 124.1, 78.9, 75.6, 42.1, 31.8, 27.6, 19.0, 16.2.


**{(6E,10E)-7-methylhexadeca-6,10-dien-2-yne (136a, model for reductive transposition):}**

Stage A: To a solution of 315 mg of *trans*-iodo hexane, in THF (15 mL), precooled to -78 °C, 1.76 mL of t-BuLi (1.7 M in pentane) was added dropwise. Reaction was then stirred for 15 min. and 165 mg of aldehyde 94 in 3 mL of THF was added dropwise. Reaction was then allowed to warm to 0 °C and then was quenched with ammonium chloride. Reaction was then extracted 3 times with ethyl acetate, washed with water, brine, dried under sodium sulfate and concentrated to give crude product, which was used in the next step without further purification.
**Stage B:** All product from the previous step was dissolved in 15 mL of DCM, and then Celite (322 mg) and PCC (322 mg) were added to reaction and it was stirred overnight. Reaction was then filtered on celite pad and all used in the next step.

**Stage C:** To all ketone from step B, dissolved in 1 mL of anhydrous ethanol 224 mg of tosylhydrazine was added and the reaction was stirred until no more starting ketone was visible by TLC. Reaction was then concentrated and purified using column chromatography to give 302 mg of 55 : 45 isomeric mixture of hydrazones which was used in the next step.

**Stage D:** In a vial, 42 mg of hydrazine from step C was dissolved in 1 mL of CHCl$_3$ and the vial was cooled to 0 °C. 0.14 mL of catecholborane (1.0 M in THF) was then added dropwise to the reaction dropwise and it was stirred for 1 h. Then 32 mg of NaOAc*3H$_2$O was added to the reaction and it was allowed to warm to r.t. and then it was heated overnight. Reaction was then filtered on SiO$_2$/celite pad (elution with 10 % ethyl acetate / hexanes) and concentrated to give crude product, which was purified using column chromatography (hexane to 1 % ethyl acetate / hexanes) to give 19.5 mg (70 % yield) of title compound.

Colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 5.47-5.31 (m, 2H), 5.16 (t, $J$=6.2), 2.26-1.90 (m, 10 H), 1.78 (t, 3H, $J$=2.4), 1.59 (s, 3H), 1.77-1.22 (m, 6H), 0.88 (t, 3H, $J$=6.7); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 136.5, 130.6, 129.8, 123.0, 79.6, 75.6, 39.8, 32.6, 31.4, 31.2, 29.3, 27.8, 22.6, 19.2, 16.1, 14.1, 3.5.

**2E,7E)-7-methyltrideca-2,7-dien-11-yn-4-one (141):**

Stage A: To a 330 mg solution aldehyde 94, in 8 mL of THF, precooled to 0 °C 3.0 mL of allylmagnesium bromide (1.0 M in diethyl ether) was added dropwise and reaction was stirred for 30 min. at 0°C and for additional 30 min. at r.t. Reaction was then cooled to 0°C
and quenched with careful addition of water, and diluted with water (10 mL). Reaction was then extracted 3 times with ethyl acetate, washed with water, brine, dried under sodium sulfate and concentrated to give crude product, which was used in the next reaction as is without further purification.

**Stage B:** All above product was dissolved in 20 mL of DCM and then 646 mg of PCC and 646 mg of celite was added to the reaction and it was stirred for 4 h. The reaction was then filtered on SiO2 / celite pad (elution 20 % ethyl acetate / hexanes and used as is in next step.

**Stage C:** All product from step B was dissolved in 8 mL of toluene and DBU (365 mh, 2.4 equiv.) was added and reaction was heated at 70 °C for 4 h. Reaction was then filtered on short silica pad (elution with 20 % ethyl acetate / hexanes), concentrated to give crude product, which was purified using column chromatography (3 % ethyl acetate / hexanes) to give 118 mg (29 % yield) of compound that had NMR spectra consistent with the title compound.

Colorless oil: **1H NMR** (400 MHz, CDCl3) δ 6.93-6.79 (m, 1H), 6.12 (dq, 1H, J=16, 1.6), 5.18 (t, 1H, J=6.8), 2.62 (t, 2H, J=8), 2.28 (t, 2H, J=7.2), 2.24-2.08 (m, 4H), 1.90 (dd, 3H, J=6.8, 1.6), 1.77 (t, 3H, J=2.4), 1.62 (s, 3H).

**6-allyl-7-methyl-1,4-dioxaspiro[4.4]non-6-ene (143):**

To a 1.1 g (8.08 mmol, 1.0 equiv.) of ketone 142, prepared according to reference 55 in 32 mL of toluene, was added pTsOH*H2O (0.24 mmol, 0.03 equiv.) reaction then was refluxed for 2 days with dean-stark trap to remove water. After 2 days reaction was diluted with ethyl acetate, washed with water, brine, dried under sodium sulfate and concentrated to give crude product, which was purified using column chromatography (10 % ethyl acetate hexanes) to give 330 mg of product, which had 1H NMR consistent with the 143.*
Slightly brown oil: **\(^1\text{H NMR}\)** (400 MHz, CDCl\(_3\)) \(\delta\) 5.88-5.76 (m, 1H), 5.01 (dq, 1J, \(J=17, 1.8\)), 4.93 (dq, \(J=11.7, 1.8\)), 2.80 (d, 2H \(J=6.5\)), 2.28 (t, 2H, \(J=5.6\)), 1.98 (t, \(J=6.2\)), 1.71 (s, 3H).

* NMR contained small amount of deprotected hydrolysis product as evident by trace ethylene glycol and starting material peaks.

**5,8-bis((tert-butyldimethylsilyl)oxy)nonan-1-ol (145):**

**Stage A:** To a solution of 2.0 g (1.0 equiv., 12.64 mmol) of non-8-ene-2,5-diol, prepared according to reference 55 as a mixture of diastereomers in DMF (40 mL), was added 3.87 g (4.5 equiv., 56.9 mmol) of imidazole and 5.72 g (3.0 equiv., 37.9 mmol) of TBSCl. Reaction was then stirred overnight and diluted with ethyl acetate, washed 3 times with 1M HCl, water, brine, dried under sodium sulfate and concentrated under rotary evaporator (bath temp. 70 °C).

Colorless oil: **\(^1\text{H NMR}\)** (400 MHz, CDCl\(_3\)) \(\delta\) 5.88-5.74 (m, 1H), 5.04-4.96 (dd, 1H, \(J=1.6, 17.1\)), 4.96-4.90, (dd, 1H, \(J=1.2, 10.2\)), 3.80-3.70 (quint., 1H, \(J=6.0\)), 3.70-3.60 (quint., 1H, \(J=5.6\)), 2.18-1.97 (m, 2 H), 1.64-1.21 (m, 10 H), 1.14-1.08 (d, 3H, \(J=6.0\)), 0.88 (s, 18 H), 0.03 (s, 12 H)

**Stage B:** All product, obtained in the previous stage was dissolved in 25 mL of THF, and then 18.96 mL (1.5 equiv., 18.96 mmol) of BH\(_3\)*THF was added. Reaction was then stirred for 3 h and then 13.0 mL of 3M NaOH and 5.0 mL of H\(_2\)O\(_2\) (30 % in H\(_2\)O) were added to the reaction and it was stirred for 3 hours. Reaction was then diluted with saturated ammonium chloride, extracted 3 times with EtOAc, washed with water, brine, dried with sodium sulfate and concentrated to give crude product, which contained some impurities, and was used as is in the next step. For characterization purposes it was purified using column chromatography.

Colorless oil (mixture of diastereomers): **\(^1\text{H NMR}\)** (400 MHz, CDCl\(_3\)) \(\delta\) 3.79-3.70 (quint., 1H \(J=5.8\)), 3.68-3.58 (broad s, 3H), 1.65-1.29 (m, 10H), 1.15-1.08 (d, 3H, \(J=6.0\)), 0.88 (s, 18H), 0.03
(s, 12 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 72.4, 68.9, 63.0, 36.7, 35.2, 35.2, 33.0, 33.0, 33.0, 25.9, 23.8, 21.5, 18.1, 4.4, 4.4, 4.7, 4.7

5-((5,8-bis((tert-butyldimethylsilyl)oxy)nonyl)sulfonyl)-1-phenyl-1H-tetrazole (147):

**Stage A:** All product from previous step was dissolved in 100 mL of THF. Solution was cooled to 0°C and then 4.97 g (18.96 mmol, 1.5 equiv.) of triphenylphosphine and 3.38 g (18.96 mmol, 1.5 equiv.) of 1-penyl-1H-tetrazole-5-thiol were added, followed by dropwise addition of 9 mL (22.75 mmol, 1.8 equiv.) of DEAD (40 wt % in toluene). Ice bath was then removed and reaction was stirred for 20 min. Reaction was quenched by the addition of sat. NaHCO$_3$ and then extracted 3 times with ethyl acetate. Reaction was concentrated and passed over short silica plug and was used as is.

**Stage B:** All product from stage A was dissolved in absolute ethanol (250 mL) at 0 °C and then (NH$_4$)$_6$Mo$_7$O$_{24}$ *4H$_2$O (1.56 g, 1.26 mmol, 0.1 equiv.) was added to the flask, followed by the slow addition of 14.2 mL (11 equiv., 126 mmol) of dihydrogen peroxide (30 wt % in H$_2$O). Reaction was then stirred at rt for 3 h and was quenched with the slow addition of 50 mL of saturated sodium thiosulfate (reaction highly exothermic). Reaction was then concentrated using rotary evaporator and remaining water was extracted 3 times with ethyl acetate. Organic extracts were washed with water, brine, dried under sodium sulfate and were concentrated to give crude product, which was purified using column chromatography (5 % ethyl acetate / hexanes).

Colorless oil (mixture of diastereomers): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71-7.67 (m, 2H), 7.64-7.58 (m, 2H), 3.79-3.67 (m, 3H), 3.64 (broad s, 1H), 1.60-1.64 (m, 10H), 1.12, 1.11 (2xd, 2H total, J=6.0), 0.88, 0.87 (2xs, 18H total), 0.03 (s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 153.5, 133.1,
General procedure for Suzuki coupling of 124:

To a scintillation vial or round-bottomed flask (depending on the scale of the reaction), fitted with rubber septa were added potassium trifluoroborate reagent, 124, catalyst (or Pd(OAc)$_2$ and ligand) and base. Air was removed by evacuating the flask and backfilling it with nitrogen 3 times. Degassed solvent was then added and reaction was heated until starting material was consumed. Reactions on 0.1 mmol or smaller scale were then filtered on SiO$_2$ and concentrated to give crude products, which were purified using column chromatography. Larger scale reactions were diluted with satd. ammonium chloride, extracted 3 times with ethyl acetate, washed with water, brine, dried under sodium sulfate and concentrated to give crude products, which were purified using column chromatography.

3-methyl-2-(3-((1-phenyl-1H-tetrazol-5-yl)sulfonyl)propyl)cyclopent-2-en-1-one (150):

Stage A: Prepared using general procedure for Suzuki coupling: 1 mmol scale, 5 mol % Pd(dppfCl)$_2$, 3 equiv. Cs$_2$CO$_3$, 1.2 equiv. of 149, 2 days at 80 °C. 88 mg (57 % yield).
White solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.49 (t, 2H, $J$=6.0), 2.56-2.49 (m, 2H), 2.42-2.37 (m, 2H), 2.31 (t, 2H, $J$=7.0), 2.08 (s, 3H), 1.62 (quint. 2H, $J$=6.3).

Stages B / C: Prepared following the procedure for preparation of 147, 0.53 mmol scale, 116 mg (59 %) of product, that had the $^1$H NMR matching the title structure isolated.

White solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.77-7.52 (m, 5H), 3.69 (t, 2H, $J$=7.9), 2.59-2.53 (m, 2H), 2.44-2.36 (m, 4H), 2.15-2.02 (m, (-CH$_3$ singlet at 2.09), 5H).

3-methyl-2-(3-(phenylsulfonyl)propyl)cyclopent-2-en-1-one (152):

Stage A: Prepared according to general Suzuki coupling procedure: 1 mmol scale, 10 mol % Pd(PPh$_3$)$_4$, 3.0 equiv. of Cs$_2$CO$_3$, 1.2 equiv. of 151. 12 h at 0 °C. 240 mg of product, 83 % yield.

Stage B: Prepared adapting the procedure from preparation of 147 stage C. 0.183 mmol scale, 36 mg of product (71 % yield).

White solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.92-7.85 (m, 2H), 7.65 (t, 1H, $J$=7.5), 7.76 (t, 2H, $J$=7.3), 3.08-3.03 (m, 2H), 2.53-2.47 (m, 2H), 2.34 (t, 2H, $J$=4.6), 2.27 (t, 2H, $J$=7.5), 2.06 (s, 3H), 1.86-1.76 (m, 2H).

(1E,5E)-1-iodo-5-methylundeca-1,5-dien-9-yne (153, ~5:1 E : Z mixture):

To 1.3 g (6.0 equiv., 10.6 mmol) of CrCl$_2$ in 5.4 mL was added 5.4 mL of p-dioxane and reaction was cooled to 0 °C. 290 mg (1.77 mmol, 1.0 equiv) of aldehyde 94 in 1 mL of p-dioxane was then added to the reaction, followed
by the dropwise addition of 1.39 g (3.53 mmol, 2.0 equiv.) iodoform in 3 mL of THF dropwise. Reaction was then stirred for 2h at 0 °C and then was diluted with water and extracted 3 times with diethyl ether. Organic layers were then washed with 1.0 M sodium thiosulfate solution, water, brine, dried under sodium sulfate and concentrated to give crude product, which was purified using column chromatography (1% ethyl acetate / hexanes) to give 260 mg (51 %) of products, that had $^1$H NMR spectra matching the title compound and had an E : Z ratio of 51 %.

Colorless oil: $^1$H NMR (E isomer) (400 MHz, CDCl$_3$) $\delta$ 6.55-5.44 (m, 1H), 5.99 (dt, 1H, $J=14.4, 1.2$), 5.18 (t, 1H, $J=5.8$), 2.25-2.02 (m, 8H), 1.79 (t, 3H, $J=2.3$), 1.60 (s, 3H).

3-methyl-2-(2-(trifluoro-l4-boranyl)ethyl)cyclopent-2-en-1-one, potassium salt (157):

Stage A: Prepared using general procedure for Suzuki coupling: 4.46 mmol scale, 1.5 equiv. potassium vinyltrifluoroborate, 3 equiv. Cs$_2$CO$_3$, 0.1 M in 3 : 1 toluene : water. 2d. at 80 °C. Product is slightly volatile using regular rotary evaporator, so care must be taken to minimize loss of the product.


Stage B: All product from step A was dissolved in 1 mL of THF and 286 mg of anhydrous methanol. Is a separate vial, 100 mg of 1,2-bis(diphenylphosphino)benzene, 22 mg of copper(I) chloride, 1.7 g of B$_2$Pin$_2$ were added, followed by the addition of 4.5 mL of THF. Mixture was cooled to 0 °C and then 25 mg of t-BuOK was added quickly and the reaction was stirred for 10
min. Mixture containing product A in the first vial was then added dropwise and reaction was stirred until no more starting material was visible by TLC and reaction was filtered on short silica pad. Reaction was then concentrated and dissolved in 22 mL of acetonitrile. Flask was cooled down to 0 °C and 1.39 g (17.9 mmol, 4.0 equiv.) of KHF$_2$ was added in one portion. 0.6 mL of H$_2$O was then added slowly over 1h and reaction was allowed to warm up to r.t. over 2.5 h. Reaction was then diluted with 20 mL of acetone, organic layers were decanted and solids were extracted with 3*20 mL portions of methanol. Organic layers were filtered on cotton and concentrated. Solids were dissolved in 20 mL of H$_2$O and aqueous layer was extracted 3 times with ethyl acetate. Aqueous layer was then concentrated and extracted 3 times with hot acetone. Extracts were filtered and concentrated to give product, which had $^1$H NMR spectra matching the structure of 157, which was used in the coupling reactions.

White solid: $^1$H NMR (400 MHz, DMSO-D$_6$) δ 2.37 (broad s, 2H), 2.19-2.15 (m, 2H), 1.96 (s, 3H), 1.93-1.85 (m, 2H), -0.06 (broad s, 2H).

(6E,10E)-13-bromo-6-methyltrideca-6,10-dien-2-yne (159):

All crude product 94, prepared using procedure above was added to 10 mL of dry Et$_2$O under N$_2$ atmosphere. Solution was then cooled down to 0 °C. And 7.82 mL (3.91 mmol, 1.5 equiv.) of cyclopropylmagnesium bromide (0.5 M solution in Et$_2$O) was added dropwise and reaction was stirred for 30 min at 0 °C, followed by 30 min at r.t. 0.29 mL of H$_2$O was then carefully added at 0 °C and reaction was stirred for 5 minutes and the diluted with 12 mL of Et$_2$O. 3.35 g (13.1 mmol, 5.0 equiv.) of MgBr$_2$*Et$_2$O was then introduced to flask and reaction was stirred at reflux overnight. Reaction was then diluted with ethyl acetate and 1.0 M solution of NaHCO$_3$, 2 layers were separated and aqueous layer was extracted 2 times with EtOAc. Organic
layer was then washed with NaHCO$_3$ (1.0 M), water, brine, dried with sodium sulfate and concentrated using rotary evaporator. Reaction was then purified using column chromatography (gradient elution hexanes to 1% ethyl acetate / hexanes) to give 435 mg (62% yield) of the title compound (c.a. ~90% pure by NMR).

Colorless liquid: $^1$H NMR (400 MHz, CDCl$_3$) δ 5.53 (dt, 1H, J=14.8, 8), 5.40 (dt, 1H, J=14.8, 8), 5.18 (t, 1H, J=5.2), 3.36 (t, 2H, J=8), 2.54 (q, 2H, J=8), 2.23-2.00 (m, 8H), 1.78 (t, 3H, J=2.8), 1.6 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 135.6, 133.4, 126.5, 123.3, 79.1, 75.4, 39.3, 36.0, 32.8, 30.9, 27.7, 19.2, 16.0, 3.45;

**(5E,9E)-methyl 9-methyl-2-(3-(2-methyl-1,3-dioxolan-2-yl)propanoyl)pentadeca-5,9-dien-13-ynoate (166):**

To a solution of 430 mg (1.99 mmol, 1.5 equiv.) of methyl 5-(2-methyl-1,3-dioxolan-2-yl)-3-oxopentanoate (prepared according to reference 63) in 5.3 mL of acetone was added 562 mg (1.73 mmol, 1.3 equiv.) of cesium carbonate, followed by addition of 357 mg (1.33 mmol, 1.0 equiv.) of bromide. Vial was then capped and solution was heated at 70 °C for 8 h, after which the solution was diluted with ethyl acetate and quenched with satd. ammonium chloride. Reaction was then diluted with water and aqueous layer was then extracted 3 times with ethyl acetate, washed with water, brine, dried under sodium sulfate and concentrated using rotary evaporator. Crude product was then purified using column chromatography with 15% Ethyl Acetate / Hexanes to give 357 mg (73% yield) of the title compound.

Colorless liquid: $^1$H NMR (400 MHz, CDCl$_3$) δ 5.48-5.26 (m, 2H), 5.16 (t, 1H, J=6.5), 3.97-3.86 (m, 4H), 3.71 (s, 3H), 3.49 (t, 3H, J=7.2), 2.68-2.62 (m, 2H), 2.22-1.84 (m, 14H), 1.77 (t, 3H,
J=2.9), 1.59 (s, 3H), 1.30 (s, 3H) **^13C NMR** (100 MHz, CDCl$_3$) δ 204.7, 170.3, 135.89, 131.8, 128.4, 123.2, 109.1, 79.2, 75.4, 64.7, 64.6, 58.0, 52.3, 39.5, 36.7, 32.5, 31.1, 30.3, 28.0, 27.7, 23.9, 19.2, 16.0, 3.5 **HRMS** (ESI$^+$) Calcd. for C$_{24}$H$_{36}$O$_5$Na: 427.24604, found: 427.24571.

**Preparation of 5-(2-methyl-1,3-dioxolan-2-yl)-3-oxopentanoate:**


**3-methyl-2-((3E,7E)-7-methyltrideca-3,7-dien-11-yn-1-yl)cyclopent-2-enone (Method A):**

![Chemical structure](image)

**Stage A:** 173 mg (3.0 equiv., 7.13 mmol) of magnesium was added to a 10 mL round-bottomed flask, fitted with reflux condenser. 3 mL of THF and small crystal of iodine was then added. Solution was then brought to reflux and 640 mg (1.0 equiv., 2.38 mmol) of bromide 159, dissolved in 3 mL of THF was added dropwise and the reaction was stirred for additional hour at reflux. In a separate flask, 296 mg (1.2 equiv., 2.85 mmol) of trimethyl borate in 3 mL of THF was added. The flask was then cooled to -78 °C and gringard reagent was added dropwise and reaction was stirred for 20 min and then was allowed to warm to rt over 1 h. Flask was then cooled to 0 °C and 928 mg (5.0 equiv., 11.9 mmol) of KHF$_2$ was added. 1.3 mL of H$_2$O was then added over 1 h and the reaction was concentrated under rotary evaporator. Solids were then extracted 3 times with acetone and concentrated to give crude product, which was used in the Suzuki coupling as is.

**Stage B:** Prepared using general procedure of Suzuki coupling: 1.0 equiv of crude trifluoroborate reagent from stage A, 1.5 equiv. 124, 10 % Pd(OAc)$_2$, 20 % RuPhos, 3.0 equiv. K$_3$PO$_4$, 12 h. 9-46 % yield.
3-methyl-2-((3E,7E)-7-methyltrideca-3,7-dien-11-yn-1-yl)cyclopent-2-enone (Method B):

To a 310 mg (1.0 equiv., 0.77 mmol) of compound 166, was added 2 mL of methanol, 2 mL of THF and 2 mL of 2M KOH. The reaction was refluxed for 3 h (bath temp. 75 °C) and then poured into mixture of ethyl acetate and satd. ammonium chloride. Aqueous layers were extracted with 3 portions of ethyl acetate, washed with water, brine, dried with sodium sulfate and concentrated under rotary evaporator. Product was then dissolved in 3.0 mL of methanol and 0.5 mL of 2 M HCl was then added. Reaction was stirred for 3 h, then 2.5 mL of 2M KOH and 3 mL of THF were added and reaction was stirred at reflux overnight. After completion, the reaction was poured into mixture of satd. ammonium chloride and ethyl acetate, extracted 3 times with ethyl acetate, washed with water, brine and dried under sodium sulfate to give crude product, which was purified using column chromatography (10 % ethyl acetate / hexanes) to give 155 mg of title compound.

Colorless Oil: \( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 5.47-5.30 (m, 2H), 5.16 (t, 1H, \( J=6.1 \)), 2.48 (d, 2H, \( J=4.2 \)), 2.36 (t, 2H, \( J=4.2 \)), 2.32-1.92 (m, 15 H), 1.78 (t, \( J=2.3 \)), 1.60 (s, 3H); \( ^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)) \( \delta \) 209.6, 170.6, 140.0, 136.0, 130.7, 129.4, 123.1, 79.2, 75.4, 29.6, 34.3, 31.5, 31.2, 31.1, 27.7, 23.2, 19.2, 17.3, 16.1, 3.5. \( \text{HRMS (ESI}^+\text{)} \) Calcd. for C\(_{24}\)H\(_{36}\)O\(_5\)Na: 427.24604, found: 427.24571. \( \text{HRMS (ESI}^+\text{)} \) Calcd. for C\(_{20}\)H\(_{28}\)ONa: 307.20378, found: 307.20299

1-((1S,3aS,3bS,8aR,8bS,10aS)-6,8a,10a-trimethyl-1,2,3,3a,3b,4,5,7,8,8a,8b,9,10,10a-ttradecahydrodicyclopenta[a,f]naphthalen-1-yl)ethanone (99):

Stage A: To a 100 mg (1.0 equiv., 0.35 mmol) solution of compound 96b in diethyl ether (2 mL) at 0 °C, was added 0.33 mL (0.53 mmol, 1.5 equiv.) of MeLi (1.6 M in Et\(_2\)O). Reaction was then stirred until no more starting material was observed by TLC (~10 min.), and 0.5 mL of water was then
carefully added. Reaction was then diluted with water, extracted 3 times with ethyl acetate, washed with water, brine, dried under sodium sulfate and concentrated to give crude product, which was used immediately (unstable) in the next stage.

**Stage B:** All product was dissolved in 1 mL of DCE and was added to a mixture, containing 1.04 g of ethylene carbonate and 8 mL of DCE. Reaction was then cooled down to 0 °C and 0.47 mL of trifluoroacetic acid was added dropwise. Reaction was then stirred for 1.5 h and another 0.47 mL fraction of trifluoroacetic acid was added dropwise. Reaction was then stirred for additional 1.5 h and then 18 mL of 1 : 1 mixture of 10 % Na$_2$CO$_3$ and methanol was added dropwise and reaction was allowed to warm to r.t. and stir for 1h. Reaction was then concentrated under rotary evaporator and extracted 3 times with ethyl acetate. Organic layers were then washed with water, brine, dried under sodium sulfate and concentrated to give crude product, which was purified using column chromatography (1 % ethyl acetate / hexanes) to give 39 mg (38 % yield) of title compound.

Colorless Oil (83:17 mixture of diastereomes): $^1$H NMR (400 MHz, CDCl$_3$) δ 3.11 (t, 0.17 H, J=9.4), 2.55 (t, 0.83 H, J=9.1), -CH$_3$ singlets (2.14, 1.59, 0.91, 0.65; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 209.8, 141.4, 126.2, 63.8, 56.3, 55.0, 49.7, 44.5, 39.0, 38.1, 36.0, 35.5, 32.0, 31.6, 29.7, 24.6, 22.8, 22.7, 22.6, 18.0, 13.6, 13.4

**rac-progesterone:**

10 mg of 99 was dissolved in 2 mL of 10 : 1 mixture DCM : MeOH. Reaction was cooled down to -78 °C and then ozone was bubbled through the reaction mixture until reaction turned blue, followed by the bubbling of air until it got clear again. 0.2 mL of dimethyl sulfide was then added and the reaction was stirred for 2 h at -78 °C, and then was left in cooling bath to slowly warm to rt overnight. Solvent was then removed using rotary evaporator and 2 mL of H₂O and 0.4 mL of 2M KOH was added to reaction and reaction was heated for 1 h at 70 °C. White solid precipitate formed and reaction was then quenched with 2 mL of 1M HCl, diluted with water, extracted 3 times with ethyl acetate, washed with water, brine, dried under sodium sulfate and concentrated to give crude product, which was purified using column chromatography to give 5.9 mg (57 % yield) of pure rac-progesterone, that contained trace ammounts of C₁₇ epimer. ¹H NMR and ¹³C NMR matched the data for natural progesterone.

C.2. Select $^1$H NMR and $^{13}$C NMR spectra
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12 www.reaxys.com database search, performed on January 2015, provided significantly larger number of literature sources available on oxidation of electron deficient alkynes, while only a few examples were available for oxidation of dialkyl substituted alkynes.


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**76 One can reproduce these conditions under conventional heating by immersing a resealable reaction vessel in a pre-heated oil bath, but this protocol provides lower yield (89%) and is less convenient than using the dedicated MW reactor.**
BIOGRAPHICAL SKETCH

Educational Background:
2009 - 2015  PhD in Organic Chemistry (expected Summer 2015)
   GPA: 3.97 / 4.0
   Department of Chemistry and Biochemistry
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2005 - 2009  BSc in Biochemistry
   GPA 8.0 / 10.0
   Department of Chemistry
   Vilnius University, Vilnius, Lithuania
   Thesis Title: “Synthesis and Analysis of Optically Active bionanetwork”

Research Internships:
Summer 2008    Vilnius University, Institute of Biochemistry
   Research Area: Kinetic resolution of bicyclic alcohols using lipases.

Summer 2007    Vilnius University, Institute of Immunology
   Research Area: Synthesis and functionalization of polypyrrole nanoparticles

Publications


Teaching Experience
2009 - 2012    Florida State University, Tallahassee, FL, USA
   Teaching Assistant:
   Organic Chemistry Recitation (CHM2210, CHM2211, CHM2200)
   General Chemistry Recitation (CHM1046)
   Organic Chemistry Laboratory (CHM2211L, CHM2210L)

Conference Presentations:
1. Slegeris, R., Dudley G. Synthetic efforts toward efficient synthesis of ent-progesterone 247th ACS National Meeting & Exposition, Dallas, TX, United States, March 16-20, 2014 (2014), ORGN-551
Skills
Analytical techniques: $^1$H NMR, $^{13}$C NMR, IR, HPLC, SERS, AFM
Design and execution of multi-step synthesis
Management of undergraduate projects
Computer literacy: MS Office, Python, Delphi, Gaussian

Awards
* Deans Scholarship, FSU, 2009
* Pharma Algorithms Scholarship, Vilnius University, Fall 2005
* Bronze medal. International Chemistry Olympiad for High School Students. Taipei, Taiwan, 2005

Languages:
* English – fluent
* Lithuanian – fluent (native)
* Russian - basic