STUDIES TOWARD THE TOTAL SYNTHESIS AND STRUCTURE DETERMINATION OF LEIODELIDE A

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By

Mathieu François Chellat

Graduate Program in Chemistry

The Ohio State University

2011

Dissertation Committee:

Professor James P. Stambuli, Advisor

Professor Craig J. Forsyth

Professor Robert S. Coleman
ABSTRACT

Leiodelide A was isolated from the deep-water marine sponge *Leiodermatium* off the coast of Palau by Fenical and co-workers in 2006. Along with leiodelide B they form a new family of biologically active macrolides featuring an oxazole-containing 19-membered macrolide, seven stereocenters and a 10-carbon side chain with an α,α-disubstituted carboxylic acid terminus. Both currently have at least one unassigned stereogenic center. Biologically, leiodelide A exhibits cytotoxic activity against HCT-116 human colon carcinoma, HL-60 leukemia, NCI-H522 nonsmall cell lung cancer and OVCAR-3 ovarian cancer cell lines.

The combined factors of low natural supply, biological activity and unusual structure made it an attractive target for total synthesis. We therefore embarked on a quest to devise a strategy for the total synthesis and structure determination of leiodelide A.

Two different versions of the side chain have been synthesized in very efficient manners which will allow screening of conditions for the olefination reaction to attach the side chain to the macrolide as the penultimate step.

The polyoxygenated northern subunit was derived from D-xylose via opening of a fully protected lactone followed by Wittig olefination. This strategy allowed formation of both C13 epimers which will help in the determination of the absolute configuration of leiodelide A.
The C1-C7 southern subunit was rapidly assembled via an aldol reaction using Davies’ SuperQuat auxiliary followed by Horner-Wadsworth-Emmons olefination in a three-step protecting group free synthesis.

In order to obtain gram quantities of the required oxazole, a detailed mechanistic study of the halogen dance reaction was undertaken, which allowed a dramatic improvement in the yield of this reaction on iodooxazoles.

Finally, the macrolactone was closed using coupling chemistry developed in the Stambuli group. Although only an isomer of the assigned structure was synthesized, the overall strategy should be amenable to the synthesis of the required macrolide.
To Isabelle and Zoe.
ACKNOWLEDGMENTS

I would first like to thank my research advisor Professor James P. Stambuli for giving me the opportunity to work in his laboratory on a project far different from the rest of the group. Although total synthesis was not his area of expertise, James’ guidance, motivational speeches and sense of humor have helped me tremendously throughout my graduate studies. It has been an incredible privilege to be part of his research group and he will always be a reference for me throughout my career. I would also like to thank Professors Coleman and Forsyth for serving on my dissertation committee.

Secondly, I would like to thank the members of the Stambuli group whom I have worked with over the years. First and foremost, Dr. Nico Proust, who has been a tremendous source of knowledge and motivation throughout the project. Also, Dr. Chad Eichman and Dr. Carla Councill for their help early on and their work on the oxazole. Will Henderson deserves a special thank you for all the chemistry and non-chemistry related discussions we’ve had over the last 5 years.

Finally, I want to express my sincere love and gratitude to my wife Isabelle. Throughout all the stages of our relationship her unswerving support was always present inside and outside of the lab and I never could have made it without her.
VITA

March 21, 1983 .............................................Born – Villeurbanne, France
March 2007 .....................................................M.S. CPE Lyon, Villeurbanne, France
September 2006 – March 2011 .......................Graduate Teaching Associate, Department of Chemistry, The Ohio State University
March 2011 – September 2011 .........................Graduate Research Associate, Department of Chemistry, The Ohio State University

PUBLICATIONS


FIELDS OF STUDY

Major Field: Chemistry
# Table of Contents

Abstract ........................................................................................................................................... ii

Acknowledgments ............................................................................................................................. v

Vita .................................................................................................................................................. vi

List of Tables ................................................................................................................................... xi

List of Figures .................................................................................................................................. xiii

List of Schemes .............................................................................................................................. xv

List of Charts ................................................................................................................................... xix

List of Abbreviations ..................................................................................................................... xx

Chapter 1 Background .................................................................................................................... 1

1.1 Introduction ............................................................................................................................... 1

1.2 Isolation/Characterization Process ......................................................................................... 3

1.3 Fürstner’s Synthesis of Leiodelide B ..................................................................................... 5

Chapter 2 Retrosynthetic Analysis and Synthesis of the Side Chain ......................................... 12

2.1 Introduction ............................................................................................................................... 12

2.2 Retrosynthesis .......................................................................................................................... 13

2.3 Synthesis of the Side Chain ..................................................................................................... 16
2.3.1 Julia-Kocienski Version ................................................................. 16
2.3.2 Horner-Wadsworth-Emmons Version ............................................ 18

Chapter 3 Synthesis of the Northern Half ................................................. 22
3.1 Introduction ......................................................................................... 22
3.2 Synthesis of the Lactone ................................................................. 23
3.3 Synthesis of the Aldehyde ................................................................. 28
  3.3.1 PMB Protection ........................................................................... 29
  3.3.2 Silyl Protection and Reduction to the Aldehyde ......................... 30
3.4 Formation of the Olefin ................................................................. 31
  3.4.1 THP Protected Phosphonium Bromide Route ............................ 31
  3.4.2 Other Attempted Routes ............................................................. 35
  3.4.3 Benzyl Protected Phosphonium Bromide Route ......................... 40
3.5 Hydrogenation/Benzyl Ether Cleavage ............................................ 42
  3.5.1 Initial Solution ........................................................................... 42
  3.5.2 Optimized Solution .................................................................... 48
3.6 Completion and Characterization of the Northern Half .................... 53

Chapter 4 Synthesis of the Southern Half ................................................. 58
4.1 Introduction ......................................................................................... 58
4.2 First Generation Synthesis .............................................................. 59
4.3 Second generation synthesis of the southern half........................................ 61
4.4 Improved Synthesis of the Southern Half..................................................... 64
4.5 Optimized Synthesis of the Southern Half .................................................. 67

Chapter 5 Synthesis of the Oxazole .................................................................... 70
5.1 Introduction ...................................................................................................... 70
5.2 Synthesis of Oxazoles.................................................................................... 73
   5.2.1 Oxidation of Oxazolines ........................................................................... 74
   5.2.2 Direct Synthesis of Oxazoles ................................................................... 76
5.3 Initial Oxazole Attempts ................................................................................ 79
5.4 Oxazole Synthesis ........................................................................................ 84
5.5 Optimization of the Halogen Dance Reaction on Iodooxazoles ................. 87

Chapter 6 Formation of the Macrolide................................................................. 104
6.1 Introduction ..................................................................................................... 104
6.2 Southern Coupling ....................................................................................... 105
6.3 Formation of the Zinc Reagent .................................................................... 108
6.4 Northern Coupling ....................................................................................... 114
6.5 Formation of the seco-acid and Mitsunobu cyclization .............................. 115
6.6 Yamaguchi closing of the macrolide ............................................................. 124
6.7 Inversion of the C17 stereocenter .................................................................. 127
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.8 Future Work</td>
<td>131</td>
</tr>
<tr>
<td>6.9 Conclusion</td>
<td>135</td>
</tr>
<tr>
<td>Chapter 7 Experimental Details</td>
<td>136</td>
</tr>
<tr>
<td>References</td>
<td>231</td>
</tr>
<tr>
<td>Appendix A – $^1$H and Selected $^{13}$C Spectra</td>
<td>243</td>
</tr>
<tr>
<td>Appendix B – X-ray Data for 3.63</td>
<td>417</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Table 3.1. PMB protection of alcohol 3.16 ................................................................. 29
Table 3.2. Hydrogenation of olefin 3.23 ................................................................. 33
Table 3.3. Conversion of THP ether 3.24 into bromide 2.6 ................................. 35
Table 3.4. Screening of metals and solvents for the hydrogenation reaction .......... 45
Table 3.5. Screen of different palladium sources for the debenzylation of 3.60 ...... 49
Table 3.6. Initial hydrogenation solvent screen ...................................................... 51
Table 3.7. Second hydrogenation solvent screen .................................................... 52
Table 5.1. Formation of ditrifloyloxazole 5.11 ....................................................... 82
Table 5.2. Screening of bases for the halogen dance reaction ............................... 92
Table 5.3. Iodooxazole dance reaction results ......................................................... 96
Table 5.4. Scrambling reaction results ................................................................. 102
Table 6.1. Screening of zinc activation methods ...................................................... 111
Table 6.2. Effect of quench on zinc formation ....................................................... 112
Table 6.3. Effect of concentration and temperature ............................................. 113
Table 6.4. Effect of heating on activation of zinc .................................................. 113
Table 6.5. Reduction of ketone 6.42 ........................................................................ 130
Table B.1. Crystallographic details ...................................................................... 421
Table B.2. Atomic coordinates and equivalent isotropic displacement parameters 422
Table B.3. Bond lengths [Å] and angles [°] ........................................................... 423
Table B.4. Anisotropic displacement parameters ........................................... 427
Table B.5. Hydrogen coordinates and isotropic displacement parameters ............. 428
Table B.6. Torsion angles [°] .......................................................................... 429
Table B.7. Hydrogen bonds [Å and °] .................................................................. 430
LIST OF FIGURES

Figure 1.1. Structures of recently isolated macrolides.................................................. 2
Figure 1.2. Proposed structures of leiodelide A (1.1) and leiodelide B (1.2) .................. 3
Figure 1.3. Proposed biosynthetic relationship between the leiodelides. ....................... 5
Figure 1.4. Structures of the four diastereomeric products synthesized by Fürstner ... 6
Figure 1.5. Fürstner's retrosynthetic analysis of leiodelide B........................................ 7
Figure 2.1. Linear product derived from saponification of leiodelide A. .................... 12
Figure 2.2. Retrosynthetic analysis of leiodelide A...................................................... 15
Figure 2.3. Various possible side chains........................................................................ 21
Figure 3.1. Retrosynthetic analysis of the northern half of leiodelide A. .................... 23
Figure 3.2. Protecting group screening.......................................................................... 24
Figure 3.3. Viable lactone 2.9 and reported synthesis of its precursor 3.15..................... 26
Figure 3.4. Other attempted phosphonium bromides................................................... 36
Figure 4.1. Retrosynthetic analysis of the southern half............................................... 59
Figure 5.1. Structures of oxazole, thiazole and imidazole.......................................... 70
Figure 5.2. Other oxazole-containing natural products............................................... 72
Figure 5.3. Retrosynthetic plan for the attachment of the oxazole. ............................ 80
Figure 5.4. Other attempted oxazoles........................................................................... 83
Figure 6.1. Northern part and test model.................................................................... 109
Figure 6.2. Problematic system..................................................................................... 123
Figure 6.3. Similarities between Nicolaou’s, Leahy’s and our system. .......................... 124

Figure 6.4. Comparison of $^{13}$C NMR data between 1.1 and 6.37 in MeOH-$d_4$. .... 126

Figure 6.5. Proposed stereochemistry of the core of leiodelide A. .............................. 127
LIST OF SCHEMES

Scheme 1.1. Fürstner's synthesis of the northern half of leiodelide B. ...................... 8
Scheme 1.2. Fürstner's synthesis of the southern half of leiodelide B. ...................... 9
Scheme 1.3. Fürstner's synthesis of the side chain of leiodelide B. ......................... 9
Scheme 1.4. Fürstner's completion of the synthesis of leiodelide B. ...................... 10
Scheme 2.1. Synthesis of the Julia side chain 2.18 .............................................. 17
Scheme 2.2. Synthesis of the HWE side chain 2.26 ............................................ 19
Scheme 3.1. Differences between L-arabinose and D-xylose............................. 25
Scheme 3.2. Synthesis of lactone 2.9 ................................................................. 27
Scheme 3.3. Formation of Weinreb amide 3.16 .................................................... 28
Scheme 3.4. Synthesis of aldehyde 3.19 ........................................................... 31
Scheme 3.5. Formation of phosphonium bromide 3.22 ...................................... 32
Scheme 3.6. Synthesis of olefin 3.23 ................................................................. 32
Scheme 3.7. Synthesis of lactol 3.31 and attempted Wittig reaction. .................... 37
Scheme 3.8. Synthesis of phosphonium iodide 3.37 ...................................... 38
Scheme 3.9. Synthesis of sulfone 3.41 ............................................................... 39
Scheme 3.10. Synthesis of phosphonates for the northern half. ......................... 40
Scheme 3.11. Synthesis of phosphonium bromide 3.41 .................................. 41
Scheme 3.12. Synthesis of olefin 3.48 ............................................................... 42
Scheme 3.13. Initial results from hydrogenation of 3.48 .................................. 43
Scheme 3.14. Precedents of hydrogenation of homoallylic functionalities .......... 44
Scheme 3.15. Plausible mechanism for the formation of 3.50................................. 44
Scheme 3.16. Hydrogenation of 3.48 using Pt/C................................................. 47
Scheme 3.17. Removal of the benzyl ether to give alcohol 3.49............................. 47
Scheme 3.18. Two possible pathways from 3.48 to 3.49....................................... 50
Scheme 3.19. Optimized conditions for the one-pot hydrogenation.......................... 53
Scheme 3.20. Formation of bromides 2.6. .......................................................... 53
Scheme 3.21. Synthesis of p-nitrobenzoate esters 3.62 ......................................... 54
Scheme 3.22. Synthesis and X-ray structure of 3.63 ............................................. 55
Scheme 3.23. Synthesis of 3.65 ............................................................................ 56
Scheme 3.24. Synthesis of the northern half.......................................................... 57
Scheme 4.1. First generation synthesis of the southern half ..................................... 60
Scheme 4.2. Second generation synthesis of the southern part................................ 63
Scheme 4.3. Improved synthesis of the southern part............................................. 65
Scheme 4.4. Removal of the the TBS group of 4.10 ................................................. 66
Scheme 4.5. Optimized synthesis of the southern half ............................................ 68
Scheme 5.1. Biosynthetic pathway to oxazoles ...................................................... 73
Scheme 5.2. Synthesis of oxazolines from β-hydroxy amides ................................ 74
Scheme 5.3. Synthesis of oxazolines from nitriles ................................................ 75
Scheme 5.4. Oxidation of oxazolines to oxazoles .................................................. 75
Scheme 5.5. Metal mediated synthesis of oxazoles from nitriles ................................ 76
Scheme 5.6. Synthesis of oxazoles from α-substituted ketones.................................. 77

xvi
Scheme 5.7. Synthesis of oxazoles from propargylic amines.................................................. 78
Scheme 5.8. Synthesis of oxazoles from isocyanides............................................................... 78
Scheme 5.9. Robinson-Gabriel synthesis of oxazoles............................................................... 79
Scheme 5.10. Thiazole precedent............................................................................................... 81
Scheme 5.11. Synthesis of oxazolidinedione 5.10................................................................. 81
Scheme 5.12. Synthesis of 2,5-diaryloxazoles........................................................................... 84
Scheme 5.13. Synthesis of 2-thiobutyloxazole 5.22............................................................... 85
Scheme 5.14. Halogenation of 2-thiobutyloxazole................................................................. 86
Scheme 5.15. HD reaction on bromo- and iodooxazoles......................................................... 87
Scheme 5.16. Bromooxazole dance reaction mechanism....................................................... 88
Scheme 5.17. Iodoaxazole dance reaction mechanism........................................................... 90
Scheme 5.18. Kinetic study of the halogen dance reaction..................................................... 91
Scheme 5.19. Attempted synthesis of 5.26 from 5.25............................................................ 93
Scheme 5.20. Attempt to recycle the reduced oxazole............................................................ 94
Scheme 5.21. Conversion of the diiodo to the 4-iodooxazole.................................................. 95
Scheme 5.22. Attempted polyiodination of oxazole 5.22....................................................... 95
Scheme 5.23. Halogen dance reaction mechanism with catalytic 5.23................................. 97
Scheme 5.24. Scrambling experiment mechanism................................................................. 101
Scheme 6.1. Envisioned synthesis of the macrolide of leiodelide A......................................... 104
Scheme 6.2. Coupling of the TBS protected southern part..................................................... 105
Scheme 6.3. Effect of the TBS group on the southern coupling............................................. 106
Scheme 6.4. Coupling with 4-bromooxazole 5.25................................................................. 107
Scheme 6.5. Coupling of the southern half ................................................................. 108
Scheme 6.6. Attempted formation of the northern part zinc reagent 6.8 ............. 109
Scheme 6.7. Formation of the zinc reagent of the northern part .......................... 114
Scheme 6.8. Coupling of the northern and southern halves ................................. 115
Scheme 6.9. Formation of the seco-acid ................................................................. 116
Scheme 6.10. Attempted closing of the macrolide via Mitsunobu conditions ....... 117
Scheme 6.11. Mitsunobu lactonization in Nicolaou's synthesis of palmerolide A ... 118
Scheme 6.13. Mechanism of the Mitsunobu macrolactonization ....................... 120
Scheme 6.14. Formation of DIAD acylated product 6.31 ....................................... 121
Scheme 6.15. Possible formed product ................................................................. 122
Scheme 6.16. Closing of the ring via Yamaguchi conditions ............................... 125
Scheme 6.17. Deprotection of the TES group from 3.48 .................................... 127
Scheme 6.18. Mitsunobu inversion of C17 ............................................................ 128
Scheme 6.19. Oxidation of alcohol 6.39 ............................................................... 129
Scheme 6.20. Initial future work in the synthesis of leiodelide A ....................... 132
Scheme 6.21. Final future work on leiodelide A .................................................. 134
LIST OF CHARTS

Chart 5.1. HD reaction GC follow-up................................................................. 98
Chart 5.2. HD reaction GC follow-up (with 5 mol % 5-bromooxazole) ............... 99
Chart 5.3. HD reaction GC follow-up (with 10 mol % 5-bromooxazole) ............. 100
Chart 5.4. HD reaction GC follow-up for the scrambling reaction...................... 103
LIST OF ABBREVIATIONS

[α] specific rotation
Å ångström
Ac acetyl
aq aqueous
Ar aryl
BAIB [bis(acetoxy)iodo]benzene
Bn benzyl
br broad
BT benzothiazole
n-Bu normal-butyl
t-Bu tert-butyl
Bz benzoyl
°C degrees Celsius
calcd calculated
cat. catalytic
CSA camphorsulfonic acid
COSY correlation spectroscopy
Cy cyclohexyl

xx
\( \delta \) chemical shift in parts per million from tetramethylsilane

d day(s); doublet

DBU 1,8-diazabicyclo[5.4.0]undec-7-ene

DCC dicyclohexylcarbodiimide

DCE 1,2-dichloroethane

DCM dichloromethane

DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DEAD diethyl azodicarboxylate

DFT density functional theory

DHP 3,4-dihydro-2H-pyran

\((\text{DHQ})_2\text{PHAL}\) dihydroquinine 1,4-phthalazinediyl diether

\((\text{DHQD})_2\text{PHAL}\) dihydroquinidine 1,4-phthalazinediyl diether

DIAD diisopropyl azodicarboxylate

DIBAL diisobutylaluminum hydride

DIP-Cl \((-\)B-chlorodiisopinocampheylborane

DIPEA diisopropylethylamine

DMA dimethylacetamide

DMAP \(4-(N,N\text{-dimethylamino})\text{pyridine}\)

DMF \(N,N\text{-dimethylformamide}\)

DMP Dess-Martin periodinane

DMSO dimethylsulfoxide

dppe diphenylphosphinoethane
$E$ entgegen

eq equation

equiv equivalent(s)

Et ethyl

FID flame ionization detector

g gram(s)

GI$_{50}$ concentration required to inhibit growth by 50%

GC gas chromatography

h hour(s)

HD halogen dance

HMBC heteronuclear multiple bond correlation

HMQC heteronuclear multiple quantum correlation

HMPA hexamethylphosphoramide

HPLC high performance liquid chromatography

HRMS high resolution mass spectrometry

HWE Horner-Wadsworth-Emmons

IC$_{50}$ half maximal inhibitory concentration

imid imidazole

$i$ iso

IR infrared

$J$ coupling constant in Hz

k kilo
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>KHMDSD</td>
<td>potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>KDA</td>
<td>potassium diisopropylamide</td>
</tr>
<tr>
<td>L</td>
<td>liter(s)</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>lit.</td>
<td>literature value</td>
</tr>
<tr>
<td>lut</td>
<td>2,6-lutidine</td>
</tr>
<tr>
<td>m</td>
<td>meta</td>
</tr>
<tr>
<td>m</td>
<td>milli; multiplet</td>
</tr>
<tr>
<td>μ</td>
<td>micro</td>
</tr>
<tr>
<td>M</td>
<td>mega, moles per liter</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mol</td>
<td>mole(s)</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry; molecular sieves</td>
</tr>
<tr>
<td>m/z</td>
<td>mass to charge ratio</td>
</tr>
<tr>
<td>n</td>
<td>nano</td>
</tr>
<tr>
<td>n</td>
<td>normal</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>sodium hexamethyldisilazide</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>NR</td>
<td>no reaction</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>ORTEP</td>
<td>Oak Ridge thermal ellipsoid plot program</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>P#</td>
<td>protecting group</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzyl</td>
</tr>
<tr>
<td>PMP</td>
<td>para-metoxymethylphenyl</td>
</tr>
<tr>
<td>PPA</td>
<td>polyphosphoric acid</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium para-toluenesulfonate</td>
</tr>
<tr>
<td>psi</td>
<td>pounds per square inch</td>
</tr>
<tr>
<td>P.T.</td>
<td>proton transfer</td>
</tr>
<tr>
<td>p-TSA</td>
<td>para-toluenesulfonic acid</td>
</tr>
<tr>
<td>pyr</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
</tbody>
</table>

xxiv
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R$</td>
<td>rectus</td>
</tr>
<tr>
<td>rds</td>
<td>rate determining step</td>
</tr>
<tr>
<td>Red-Al®</td>
<td>sodium bis(2-methoxyethoxy)aluminum hydride</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>second(s); singlet</td>
</tr>
<tr>
<td>$s$/sec</td>
<td>sec (secondary)</td>
</tr>
<tr>
<td>$S$</td>
<td>sinister</td>
</tr>
<tr>
<td>SAR</td>
<td>structure-activity relationship</td>
</tr>
<tr>
<td>sat.</td>
<td>saturated</td>
</tr>
<tr>
<td>SM</td>
<td>starting material</td>
</tr>
<tr>
<td>$t$/tert</td>
<td>tert (tertiary)</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBAB</td>
<td>tetrabutylammonium bromide</td>
</tr>
<tr>
<td>TBAC</td>
<td>tetrabutylammonium chloride</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBAI</td>
<td>tetrabutylammonium iodide</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>TEMPO</td>
<td>(2,2,6,6-tetramethylpiperidin-1-yl)oxyl</td>
</tr>
<tr>
<td>Tf</td>
<td>triflyl (trifluoromethanesulfonyl)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoroacetic anhydride</td>
</tr>
<tr>
<td>TFP</td>
<td>tri-2-furylphosphine</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TMSE</td>
<td>2-(trimethylsilyl)ethyl</td>
</tr>
<tr>
<td>tol</td>
<td>tolyl</td>
</tr>
<tr>
<td>TosMIC</td>
<td>$p$-toluenesulfonylmethyl isocyanide</td>
</tr>
<tr>
<td>Tr</td>
<td>trityl (triphenylmethyl)</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl ($p$-toluenesulfonyl)</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>Z</td>
<td>zusammen</td>
</tr>
</tbody>
</table>
Chapter 1

BACKGROUND

1.1 Introduction

In the past 30 years, a great number of biologically active macrolide natural products have been isolated such as palmerolide A, dictyostatin, epothilone B, leucascandrolide A, rhizoxin D and peloruside A (Figure 1.1). These complex medium-size ring lactones all present some resemblance to leiodelide A.

All of these compounds have the potential to be extremely useful drugs, but the minuscule amounts in which they are usually isolated makes extensive testing very difficult. In most cases, total synthesis – the construction of natural products from simple molecules – is the only way to produce more of these compounds for further biological evaluation.
Figure 1.1. Structures of recently isolated macrolides.
1.2 Isolation/Characterization Process

In 2006, Fenical et al. reported the isolation of a novel family of macrolides from a new species of the deep-water marine sponge *Leiodermatium.* The sponges were collected off the coast of Palau in the Pacific Ocean via manned submersible at a depth of 220 m. The first two members of this family are 19-membered ring macrolides leiodelide A and B, which were tentatively assigned structures 1.1 and 1.2, respectively (Figure 1.2).  

![leiodelide A (1.1) and leiodelide B (1.2)](image)

*Figure 1.2. Proposed structures of leiodelide A (1.1) and leiodelide B (1.2).*

The leiodelides are comprised of several unique functional moieties such as a conjugated oxazole ring, a brominated tetrahydrofuran ring and an α-hydroxy-α-methyl carboxylic acid. Both are also significantly cytotoxic compounds against HCT-116 human colon carcinoma with IC<sub>50</sub> values of 2.5 µM and 5.6 µM for leiodelide A and B, respectively. Interestingly, the methyl ester of leiodelide A showed an IC<sub>50</sub> of 1.9 µM which would suggest that the carboxyl group is not required for activity. Leiodelide A also exhibits potent cytotoxic activity against a variety of cancer cell lines with GI<sub>50</sub>
values of 0.26 µM, 0.26 µM and 0.25 µM for HL-60 (leukemia), NCI-H522 (nonsmall cell lung cancer) and OVCAR-3 (ovarian cancer), respectively.

As is the case with many natural products – even more so with those coming from remote locations – the leiodelides were only isolated in minute quantities. In this case, after methanol extraction and two reversed-phase HPLC column purifications, 730 g of lyophilized sponge resulted in 8 mg of leiodelide A (1.1, 0.001% dry weight) and 0.8 mg of leiodelide B (1.2, 0.0001% dry weight).

Even with extensive spectroscopic studies and degradation experiments, the isolation team was not able to fully characterize the leiodelides and both have at least one unassigned stereogenic center. In both molecules the configuration of C13 remains unassigned. The authors were nevertheless able to propose a biosynthetic relationship between the two leiodelides that involves activation of the olefin by a bromonium ion followed by trapping of the electron poor olefin by the C16 hydroxyl group (Figure 1.3).
1.3 Fürstner’s Synthesis of Leiodelide B

In early 2011, Fürstner et al. published a paper entitled “The Leiodolide B Puzzle”. In this intriguingly titled paper, the synthesis of four different diastereomers of leiodelide B is presented (Figure 1.4). Indeed after synthesizing both the (13R) and (13S) epimers of the assigned structure and not finding a perfect match, the team made two more isomers with carbons 4 and 5 inverted (the assignment of the stereochemistry at those centers had been described as tenuous by Fenical et al.). Unfortunately none of the four diastereomers matched the published data enough to claim identity.
Fürstner’s retrosynthesis of leiodelide B involved synthesizing two main fragments: a northern and a southern unit along with a smaller piece that would contain the undefined C13 stereocenter (Figure 1.5). This strategy would allow them to easily bring up both epimers.

In the forward direction, the synthesis of leiodelide B started with Sonogashira coupling of alkyne 1.4 with vinyl bromide 1.3 (Scheme 1.1). The resulting allylic alcohol was epoxidized and the terminal alcohol protected as its TBS ether to give 1.5. Conjugate epoxide opening with methyl magnesium bromide in the presence of CuCN and P(OPh)₃ gave allenol 1.6 which was then converted to dihydrofuran 1.7 via Ag⁺-induced cyclization. From there, bromination and standard protecting-group manipulations yielded the desired aldehyde 1.8.
With the aldehyde in hand, chain extension with the C13-containing fragment was done with both enantiomers to give the corresponding alcohols 1.10. Finally, some more protecting group manipulations produced both epimers of the northern half 1.11. These compounds were made in 15 and 16 linear steps with an overall yield of 12%.

Figure 1.5. Fürstner's retrosynthetic analysis of leiodelide B.
Scheme 1.1. Fürstner's synthesis of the northern half of leiodelide B.

The southern half was made in a very short and efficient manner: Evans aldol reaction between oxazolidinone 1.12 and aldehyde 1.13 resulted in allylic alcohol 1.14 (Scheme 1.2). Removal of the auxiliary and PMP protection of the resulting 1,3-diol afforded alkenylstannane 1.15. The last step involved coupling of the vinyl tin with 2-methyloxazolyl triflate 1.16. Unfortunately this transformation failed under a variety of
standard reaction conditions and eventually needed close to stoichiometric amounts of 
Pd(PPh$_3$)$_4$ to work. Nevertheless the overall sequence was 4 steps and 73% yield.

![Scheme 1.2](image)

Scheme 1.2. Fürstner's synthesis of the southern half of leiodelide B.

The synthesis of the side chain is shown in Scheme 1.3 and started from l-malic acid in which the α-hydroxy acid was protected with pivaldehyde.

![Scheme 1.3](image)

Scheme 1.3. Fürstner's synthesis of the side chain of leiodelide B.
Diastereoselective methylation and reduction of the acid terminus afforded primary alcohol 1.18 which was converted to phosphonium iodide 1.19 in two steps. The overall sequence was 5 steps with an 18% overall yield.

The endgame involved coupling all the pieces together and is depicted in Scheme 1.4.

Scheme 1.4. Furstner's completion of the synthesis of leiodelide B.
Alkylation of southern fragment \textbf{1.17} with northern fragment \textbf{1.11} followed by protecting-group manipulations provided aldehyde \textbf{1.20}. Finally, attachment of the side chain and closing of the macrolide with adequate removal of protecting-groups, delivered the desired macrolide leiodelide B \textbf{1.2}. The overall synthesis has a longest linear sequence of 30 steps with an overall yield of 0.3%.

This long and linear synthesis of leiodelide B exemplifies the challenges and hurdles that researchers are faced with when trying to synthesize such a molecule and shows that the leiodelides are by no mean trivial targets. Furthermore, the fact that none of the four diastereomers synthesized matched the reported data makes these molecules even more intriguing and hopefully a total synthesis of the more carefully characterized sister compound leiodelide A will help solve “the leiodelide B puzzle”.
Chapter 2

RETSOSYNTHETIC ANALYSIS AND SYNTHESIS OF THE SIDE CHAIN

2.1 Introduction

Leiodelide A (1.1) is a 19-membered macrolide with a 10 carbon side-chain appended on C17. Saponification of the macrolide gives extended polyoxygenated unsaturated ester 2.1 (Figure 2.1).

Figure 2.1. Linear product derived from saponification of leiodelide A.
First and foremost the objective was to avoid a linear synthesis of the natural product. Due to their nature, macrolides such as leiodelide A are typically not assembled via intricate cascade reactions, but are usually synthesized in a linear fashion (cf. Furstner’s synthesis of leiodelide B,\textsuperscript{9} 30 steps longest linear). The goal was to divide the molecule into equal-size fragments that could then be combined to assemble the desired product in a very convergent manner. This strategy would not only allow scale up of the different fragments, leading to substantial amounts of the natural product, but would also ease the structure-activity relationship (SAR) studies. Furthermore, the C13 stereocenter problem would need to be accounted for by allowing the synthesis of both epimers. Finally, since the absolute configuration of carbons 4 and 5 was deemed tenuous by the isolation team, the ability to easily make the enantiomer of the southern half of the molecule was also of utmost importance.

2.2 Retrosynthesis

From the very beginning, certain key functionalities of leiodelide A had caught our attention as possible disconnections or evident precursors. For instance detaching the side chain from the macrolide at the $\Delta^{22,23}$ olefin seemed the most reasonable approach. Similarly, using the chiral pool for the three contiguous oxygenated chiral centers at C15-C17 would alleviate the need to set these up and avoid any possible mixtures of isomers. Carbohydrate chemistry would be an ideal starting point for these stereocenters. It was also recognized early on that the $\alpha,\beta$-unsaturated-\delta-hydroxy ester of the southern half could be obtained via aldol/HWE reaction. Finally, the oxazole ring would need to be the highlight of the synthesis. Appending the oxazole via two consecutive couplings at the 2
and the 4 positions would not only be highly convergent and allow easy access to derivatives, but would also only be the second example of this type of assembly in total synthesis.

As outlined in Figure 2.2, the retrosynthetic strategy started by disconnection at C22 to reveal side chain 2.2 and macrolide 2.3. The side chain could come from coupling of methallyl chloride 2.4 and benzoyl protected propargylic alcohol 2.5. The macrolide could be accessed from simplified fragments 2.6, 2.7, and 2.8. First, the northern subunit 2.6, with its three contiguous oxygenated chiral centers, was envisioned to originate from the opening of chiral lactone 2.9 (derived from D-xylose) followed by Wittig olefination with phosphonium bromide 2.10. Second, the α,β-unsaturated ester 2.8 could be generated from an Evans aldol reaction between acylated oxazolidinone 2.11 and aldehyde 1.13 followed by a Horner-Wadsworth-Emmons olefination reaction to install the ester moiety. Finally, oxazole 2.7 can be obtained in three steps from known 2-thiooxazole. The key steps of the synthesis would be the appending of the northern and southern fragments onto the oxazole via metal-catalyzed cross-coupling reactions. This highly convergent strategy would provide a great deal of flexibility when it comes to derivatization and SAR studies. It would also provide us with easy access to multiple diastereomers in the event of discrepancies between the synthetic and natural products.
Figure 2.2. Retrosynthetic analysis of leiodelide A.
2.3 Synthesis of the Side Chain

As shown in the retrosynthesis (Figure 2.2), attachment of the side chain to the macrolide had been anticipated to be the penultimate step in the synthesis. Originally the side chain was envisioned to be attached using Julia-Kocienski conditions which require a heteroarylsulfone to react with the aldehyde on the macrolide. After synthesizing the required substrate, it seemed that the E/Z ratio of the reaction would not be optimal\textsuperscript{11} and an alternative that would potentially give better stereoselectivity was needed. Examination of the chemical literature revealed that the Horner-Wadsworth-Emmons reaction seemed like a potentially more suitable option. Both versions of the side chain were therefore synthesized.

2.3.1 Julia-Kocienski Version

The synthesis of the Julia-Kocienski version of the side chain started from homopropargylic alcohol \textbf{2.12} (Scheme 2.1). Mitsunobu reaction with 2-mercaptobenzothiazole (BTSH) followed by \textit{m}-CPBA oxidation gave the sulfone in 86% yield over two steps. Following some known chemistry,\textsuperscript{12} copper mediated coupling of \textbf{2.13} with methallyl chloride gave the complete carbon skeleton of the side chain. In order to get to the correct oxidation state, a few more steps were required: Sharpless asymmetric dihydroxylation\textsuperscript{13} (85% yield, 90% ee by HPLC) followed by oxidation\textsuperscript{14} of the primary alcohol gave carboxylic acid \textbf{2.16}. Finally, protection of the acid as the 2-(trimethylsilyl)ethyl ester and palladium-catalyzed Z-selective reduction of the alkyne delivered the fully functionalized side chain \textbf{2.18}. 
The choice of the 2-(trimethylsilyl)ethyl ester as a protecting group for the acid terminus of the side chain was two-fold. Fürstner, in his synthesis of leiodelide B used a methyl ester which proved to be incredibly difficult to remove: “Unfortunately, selective cleavage of the methyl ester in the presence of the macrolactone was troublesome, despite exploring several enzymatic and chemical methods”.

Therefore such a protecting group...
needed to be avoided at all costs. Secondly, as shown in Figure 2.2, the three hydroxyl groups of leiodelide A would be protected as various silyl ethers until the final deprotection step. Using a silyl group on the acid would allow a one-step global deprotection of all the protecting groups liberating the desired natural product. Although this synthesis of the side chain was short and efficient (7 steps, 42% overall yield), we had reasons to believe that the $E/Z$ ratio of the Julia reaction would not be as good as desired. We therefore looked into other possible olefination methods and decided on the HWE alternative.

2.3.2 Horner-Wadsworth-Emmons Version

When developing the chemistry for the HWE side chain, a similar strategy as the one used for the Julia side chain was adopted. Unfortunately, the phosphonate moiety is not installed in the same straightforward manner as the sulfone and carrying such a highly polar compound through multiple steps is not optimal. Nevertheless most of the steps previously developed could be applied to this synthesis. Starting from benzoyl protected propargylic alcohol 2.5, the same three-step sequence involving coupling, asymmetric dihydroxylation and oxidation gave α-hydroxy acid 2.21 in 75% yield (Scheme 2.2).
From there, the acid was protected as its methyl ester \(2.22\) purely for economic reasons. Since the acid had to be protected earlier in the synthesis and \(2-\)
(trimethylsilyl)ethanol is relatively expensive, the much cheaper methyl ester was used to develop the chemistry. Once the chemistry was fully developed, either transesterification to the 2-(trimethylsilyl)ethyl ester or running the steps again with the adequate protecting group installed would yield the desired product. With the acid protected, the benzoyl group was removed and the resulting propargylic alcohol was converted to allylic bromide \(2.25\) in 89% yield by reduction and bromination. Finally, the phosphonate was made by treating the allylic bromide with diethyl ethylphosphonate in the presence of \(n\text{-BuLi}\) and protecting the tertiary alcohol as its TMS ether. The yield over these last two steps was somewhat low but the reactions were not optimized and only ran as a proof of principle that the desired phosphonate could be synthesized. With two different versions of the side chain in hand, the chance of getting good selectivity in the olefination reaction was increased but still not guaranteed. Although no definite method exists for making pure \((E)\) non-conjugated trisubstituted olefins, many methods exist and it is up to the researcher to find the most appropriate for their substrate. With gram quantities of \(2.25\) easily accessible, this strategy will allow to screen a variety of different olefination partners (Figure 2.3). Phosphonates such as \(2.26\) used in the Horner-Wadsworth-Emmons reaction have shown excellent selectivity in certain examples.\(^{15}\) Diphenylphosphine oxides such as \(2.27\) which are used in the Horner-Wittig reaction have also previously shown selectivity.\(^ {16}\) Phosphonamides such as \(2.28\), which are the amino equivalents of phosphonates, have also been used in olefination reactions with various degrees of selectivity.\(^ {17}\) Finally, even though phosphonium halides (Wittig reagents) such as \(2.29\) are
usually known to give predominantly the \((Z)\) isomer, examples where the \((E)\) isomer was the major product are reported.\(^{18}\)

Figure 2.3. Various possible side chains.
Chapter 3

SYNTHESIS OF THE NORTHERN HALF

3.1 Introduction

As mentioned earlier, the northern part of leiodelide A (C11-C17) was envisioned to be attached to the rest of the molecule by coupling reaction with the oxazole at C11, macrolactonization with the free hydroxyl group at C17 and olefination at C22 (Figure 3.1). With these initial disconnections made, it was evident that this northern part 3.1 has two very distinct halves. The left side, with its three differentiated contiguous oxygenated stereocenters (a methyl ether, a free hydroxyl and a lactone linkage) is completely different from the saturated unfunctionnalized alkyl fragment that composes the right side. Therefore it seemed logical to dissect the northern half between carbons 13 and 14. The assembly of these two halves should allow the synthesis of both epimers at C13 since it is the undefined stereocenter in leiodelide A. A Wittig reaction followed by hydrogenation would at first give us access to both epimers, which could eventually be
changed into a stereoselective hydrogenation to afford only the desired epimer once stereochemistry at C13 has been defined. Finally, the left half 3.3 seemed like it should be easily accessible from a sugar via a protected lactone. Careful identification of the required stereochemistry revealed d-xylose as the adequate starting material.

Figure 3.1. Retrosynthetic analysis of the northern half of leiodelide A.

### 3.2 Synthesis of the Lactone

Due to its more challenging aspect, the left half of the northern part was the first target. The choice of the protecting groups was really going to be the key aspect of its synthesis. Indeed as shown in Figure 3.1, the northern half would include up to four different protecting groups (P1-P4) on at once which would all need to be orthogonal to
allow selective removal. Figure 3.2 shows a number of different lactones or furanosides that were originally thought to be useful but were eventually abandoned due to low yielding synthesis or non-orthogonality of the protecting groups.

![Diagram of lactones and furanosides](image)

**Figure 3.2.** Protecting group screening.

Originally, the sugar used as starting material was L-arabinose which is very similar to D-xylose: the only difference is that L-arabinose is \(4S\) whereas D-xylose is \(4R\). As seen...
in Scheme 3.1, L-arabinose would have given the desired stereochemistry at C17 whereas D-xylose would give the opposite stereochemistry. This was not an issue though, as macrolactonizations can be done either with retention of configuration or inversion of configuration.\(^\text{19}\)

Scheme 3.1. Differences between L-arabinose and D-xylose.

Unfortunately the trans-junction in compound 3.5 (derived from L-arabinose) made the synthesis of this compound impossible due to the high strain of the system. When switching to an 8,5 bicycle (3.6) instead of a 6,5 the strain was much lower, but the low yield and exorbitant price of the di-silyl protecting group led to a rapid abandon of this route. At this point, switching to D-xylose was the only option, but initial attempts were met with various degrees of failure. Once again, the protecting group used for the synthesis of 3.7 was too expensive for use this early in the synthesis. Compounds such as 3.8 would not allow differentiation of the two benzyl protected alcohols later on in the
synthesis. Under a variety of conditions, the PMP acetal of 3.9 could not be selectively opened in the presence of the lactone. Once the primary alcohol of d-xylono-1,4-lactone was protected as a trityl ether, the two remaining secondary alcohols of 3.10 could not be differentiated. Finally, various acetal protected substrates (3.11-3.14) had selectivity problems when trying to remove the acetal in the presence of other acid sensitive protecting groups.

After realizing that installing different protecting groups on each hydroxyl group would be a more challenging task than originally thought, other alternatives were looked at. Eventually, we came up with compound 2.9 which was thought to be a suitable candidate for the synthesis of the northern part (Figure 3.3). Much to our delight a literature search on 2.9 revealed that the precursor alcohol 3.15 had been previously reported.\(^{20}\)

![Chemical structures](image)

**Figure 3.3.** Viable lactone 2.9 and reported synthesis of its precursor 3.15.

Unfortunately, the reported synthesis was not going to be of much use. In addition to starting from d-xylono-1,4-lactone which is only available from specialized suppliers at over $50/g, the process described yielded barely above 10% of the desired product. As
the first reaction of a multi-step synthesis, this was not going to be a viable option. After experimenting with different routes going through the methyl furanoside, we eventually settled on the synthesis shown in Scheme 3.2.

Scheme 3.2. Synthesis of lactone 2.9.

Bromine mediated oxidation of D-xylose afforded D-xylono-1,4-lactone.\textsuperscript{21} The cis 1,3-diol was then protected as the corresponding acetonide\textsuperscript{22} 3.15 and the remaining secondary alcohol was methylated with dimethyl sulfate\textsuperscript{23} to deliver lactone 2.9. Although bromine mediated oxidations of D-xylose and other pentoses are numerous in the chemical literature,\textsuperscript{21, 24} none of the procedures ever isolate the lactone and most of them dry the crude product with acetic acid before carrying it through the next step. In our case both water and acid were detrimental as the following step was the formation of an acid labile acetonide. Also, isolation was rendered extremely difficult by the very high

\[ \text{d-xylose} \xrightarrow{\text{Br}_2, K_2CO_3, H_2O} \text{d-xylono-1,4-lactone} \]

\[ \xrightarrow{\text{CSA, acetone, 25\% (2 steps)}} \text{3.15} \xrightarrow{\text{Me}_2\text{SO}_4, K_2CO_3, acetone, 82\%}} \text{2.9} \]
polarity of the triol and by the fact that the major contaminant KBr, has very similar solubility properties as the desired lactone. Nevertheless we were able to bring up hundreds of grams of lactone 3.15 due to the low cost of raw material and good scalability.

### 3.3 Synthesis of the Aldehyde

In order to convert the lactone into the desired aldehyde a three step sequence was envisioned comprised of opening of the lactone to the Weinreb amide, protection of the resulting secondary alcohol and reduction of the amide to the aldehyde. The first step, opening of the lactone with \( N,O \)-dimethylhydroxylamine hydrochloride and trimethyl aluminum,\(^{25}\) worked extremely well from the start to give Weinreb amide 3.16 (Scheme 3.3).

![Scheme 3.3. Formation of Weinreb amide 3.16.](image)

Unfortunately the product would tend to recyclize when submitted to flash column chromatography and therefore had to be used crude in the following protection step. Once again the choice of protecting group was crucial here.
3.3.1 PMB Protection

Although this protecting group would be the first removed once the seco-acid was made, it would need to remain intact up to that point and also need to be removed in a mild and selective manner. The PMB group is known to be a resistant group that can be removed under specific conditions that do not affect benzyl or silyl ethers and was therefore the first choice. Unfortunately after screening a number of different methods to install a PMB ether, it seemed that the PMB group was not going to be a viable option (Table 3.1).

![Diagram](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PMBBR, Ag₂O, CH₂Cl₂</td>
<td>decomp.</td>
</tr>
<tr>
<td>2</td>
<td>PMB trichloroacetimidate, CSA, CH₂Cl₂</td>
<td>16-34%</td>
</tr>
<tr>
<td>3</td>
<td>PMBBR, TBAI, NaH, THF</td>
<td>decomp.</td>
</tr>
<tr>
<td>4</td>
<td>PMBBR, TBAI, DIPEA, CH₂Cl₂</td>
<td>no rxn</td>
</tr>
<tr>
<td>5</td>
<td>PMBO-lepidine, CSA, CH₂Cl₂</td>
<td>11%</td>
</tr>
<tr>
<td>6</td>
<td>PMBBR, n-BuLi, THF</td>
<td>decomp.</td>
</tr>
</tbody>
</table>

Table 3.1. PMB protection of alcohol 3.16.

Denmark in his synthesis of (+)-brasilenyne had a very similar sequence of lactone opening to the Weinreb amide and protection of the resulting alcohol in which he had to use PMBBR and Ag₂O to tolerate a vinyl iodide moiety. Unfortunately these neutral...
conditions (entry 1) seemed to decompose the starting material and did not yield any product. Switching to the very commonly used PMB trichloroacetimidate\textsuperscript{27} under acidic conditions (entry 2) the desired product \textbf{3.17} was obtained, albeit in low and non-reproducible yields (16-34\%). Standard conditions using a base such as NaH\textsuperscript{28} (entry 3) or DIPEA (entry 4) and PMBB\textsubscript{r} with TBAI either led to decomposition or no reaction was observed. The use of PMBO-lepidine\textsuperscript{29} (entry 5), an easier to handle and shelf-stable version of PMB trichloroacetimidate, afforded very low yields of the desired product \textbf{3.17}. Finally, under strongly basic conditions\textsuperscript{30} (entry 6), only decomposition of the SM was observed. Although other methods for PMB protection of alcohols are known\textsuperscript{31} it was reasoned that the alcohol was most certainly too hindered or strongly hydrogen-bonded and therefore a more reactive protecting group would be needed.

\textbf{3.3.2 Silyl Protection and Reduction to the Aldehyde}

Silyl triflates are extremely reactive molecules that when combined with alcohols in the presence of base give rise to the corresponding silyl ether in usually high yields\textsuperscript{32}. Although a silyl group that would need to remain intact until the very end of the synthesis was going to be present on the southern part, the ability to modulate the lability of silyl ethers by changing the size of their substituents allowed this protection\textsuperscript{33}. Since the other silyl protecting group was going to be a \textit{tert}-butyldimethylsilyl (TBS), the triethylsilyl (TES) ether which is more labile than the TBS ether was chosen.
Protection of crude alcohol 3.16 with TESOTf in the presence of 2,6-lutidine gave the desired silyl ether 3.18 which was then reduced to the corresponding aldehyde 3.19 using DIBAL.\textsuperscript{34} To our delight, the aldehyde was stable enough to survive flash column chromatography on regular silica gel and could be stored for months in the freezer.

### 3.4 Formation of the Olefin

With multi-gram quantities of aldehyde 3.19 in hand, we started looking at ways to make the right half of the northern part along with the assembly of the two halves.

#### 3.4.1 THP Protected Phosphonium Bromide Route

The initial approach was to make the phosphonium bromide of THP protected 3-bromobutan-1-ol 3.22. This known product\textsuperscript{35} has the desired carbon skeleton along with a THP protected alcohol that could theoretically be converted in one step to the requisite bromide.\textsuperscript{36} Following the literature procedure the phosphonium bromide was prepared in 66% yield from commercially available 2-bromoethanol via THP protection and reaction with ethyltriphenyl phosphonium bromide in the presence of \textit{n}-BuLi (Scheme 3.5).
Scheme 3.5. Formation of phosphonium bromide 3.22.

From there, coupling of aldehyde 3.19 with the phosphonium bromide using \( n\text{-BuLi} \)\textsuperscript{37} provided the desired olefin 3.23 (Scheme 3.6) in an inconsequential 1:1 (\( E \):(\( Z \)) ratio, albeit in low yield and always contaminated with an unknown product (\textit{vide infra}). Nevertheless, the northern part was close to completion and the material was pushed forward through the last two steps.


The last two steps involved reduction of the olefin and conversion of the THP protected alcohol to the corresponding bromide. While reduction of alkenes to alkanes is usually a trivial step, this substrate had two particularities. First, the double bond was trisubstituted, which usually requires higher pressures/temperatures or more active
catalysts. Secondly, the survival of the triethylsilyl protecting group was questionable. Indeed silyl groups, and most notably TES groups, have been shown to fall off during hydrogenation reactions depending on the commercial source of the catalyst and the solvent.\textsuperscript{38}

At first, hydrogenations in CH\textsubscript{3}CN or toluene under 1 atm of H\textsubscript{2} (balloon) gave the desired products only in low yields (Table 3.2, entry 1-2). Fortunately switching to EtOAc and raising the pressure to 50 psi (entry 3) led to a 92\% yield of the two resulting epimers. When the pressure was lowered back down to 1 atm, the reaction still went in 87\% yield (entry 4).

\begin{table}[h]
\centering
\begin{tabular}{cccc}
\hline
entry & solvent & pressure & yield \\
\hline
1 & CH\textsubscript{3}CN & 1 atm & 18\% \\
2 & PhMe & 1 atm & 22\% \\
3 & EtOAc & 50 psi & 92\% \\
4 & EtOAc & 1 atm & 87\% \\
\hline
\end{tabular}
\caption{Hydrogenation of olefin 3.23.}
\end{table}

The two newly formed epimers could be separated by flash column chromatography for identification purposes but were otherwise carried on as a mixture into the final step. The conversion of THP ethers into bromides is well documented in the literature and has
numerous sets of conditions that usually give high yields of the halide. Unfortunately as seen in Table 3.3 we were not met with such success. The standard PPh$_3$Br$_2$ conditions in CH$_2$Cl$_2$$^{36, 39}$ (entry 1) led to removal of the TES group along with that of the THP. Buffering with an insoluble base such as NaHCO$_3$ had no effect (entry 2), whereas buffering with a soluble amine base like pyridine$^{40}$ (entry 3) completely shut down the reaction. Switching to a bidentate phosphine like dppe$^{41}$ (entry 4) had no influence and gave the same result as PPh$_3$. Switching the bromide source to 2,4,4,6-tetabromocyclohexa-2,5-dienone$^{42}$ (entry 5), NBS (entry 6) or CBr$_4$$^{43}$ (entry 7) gave exactly the same results. Once again buffering the CBr$_4$ reaction with either pyridine (entry 8) or Et$_3$N (entry 9) shut the reaction down completely. Finally, using Viehe’s salt (N,N-dimethylphosgeniminium chloride) in combination with TBAB$^{44}$ still led to loss of the TES group. From these results and the accepted mechanism, it seems that this reaction requires an acidic media that is too harsh for the triethylsilyl group. At this point the TES group could have been put back on and the synthesis pushed forward, but instead the protecting group strategy was revised and a closer attention was paid to the low yields and side products that were formed during the Wittig reaction.
Table 3.3. Conversion of THP ether 3.24 into bromide 2.6.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{PPh}_3, \text{Br}_2, \text{CH}_2\text{Cl}_2$</td>
<td>lost TES</td>
</tr>
<tr>
<td>2</td>
<td>$\text{PPh}_3, \text{Br}_2, \text{NaHCO}_3, \text{CH}_2\text{Cl}_2$</td>
<td>lost TES</td>
</tr>
<tr>
<td>3</td>
<td>$\text{PPh}_3, \text{Br}_2, \text{pyridine, CH}_2\text{Cl}_2$</td>
<td>no rxn</td>
</tr>
<tr>
<td>4</td>
<td>dppe, $\text{Br}_2, \text{CH}_2\text{Cl}_2$</td>
<td>lost TES</td>
</tr>
<tr>
<td>5</td>
<td>$\text{PPh}_3, 2,4,4,6$-tetabromocyclohexa-2,5-diene, CH$_2$Cl$_2$</td>
<td>lost TES</td>
</tr>
<tr>
<td>6</td>
<td>$\text{PPh}_3$, NBS, CH$_2$Cl$_2$</td>
<td>lost TES</td>
</tr>
<tr>
<td>7</td>
<td>$\text{PPh}_3$, CBr$_4$, CH$_2$Cl$_2$</td>
<td>lost TES</td>
</tr>
<tr>
<td>8</td>
<td>$\text{PPh}_3$, CBr$_4$, pyridine, CH$_2$Cl$_2$</td>
<td>no rxn</td>
</tr>
<tr>
<td>9</td>
<td>$\text{PPh}_3$, CBr$_4$, Et$_3$N, CH$_2$Cl$_2$</td>
<td>no rxn</td>
</tr>
<tr>
<td>10</td>
<td>$N,N$-dimethylphosgeniminium chloride, TBAB, CH$_2$Cl$_2$</td>
<td>lost TES</td>
</tr>
</tbody>
</table>

3.4.2 Other Attempted Routes

With the failure of the THP protected version of the phosphonium bromide we started looking at other ways to install the right half of the northern fragment. Figure 3.4 shows some of the other phosphonium bromides that were attempted. Deprotection of the THP ether on 3.22 with PPTS to give alcohol 3.25 was not successful. In the same manner, conversion of the THP ether to bromide 3.26 failed using standard conditions. Starting from ethyltriphenyl phosphonium bromide, addition of either commercially available 1,2-dibromoethane 3.28 or bromide 3.29 gave none of the desired products 3.26 and 3.30 respectively.
Since the olefination reaction was working well on the aldehyde, running the reaction on the lactol instead of having to go through the Weinreb amide then the aldehyde was looked into. Synthesis of lactol 3.31 from the parent lactone using DIBAL\textsuperscript{45} was uneventful, but unfortunately attempts at doing the Wittig reaction on the lactol did not generate any of the desired olefin (Scheme 3.7). Although examples of Wittig reactions on lactols are reported in the literature\textsuperscript{46} very rarely is the phosphonium salt disubstituted and to the best of our knowledge substituted isopropyl ones are not known.
At this point in time, simultaneous screening of different coupling partners was undertaken in order to find a way that would allow to bring up material efficiently. Phosphonium iodide 3.37 was synthesized according to a literature procedure (Scheme 3.8).\textsuperscript{35} Starting from crotonic acid 3.33, reacting with HBr in acetic acid under 254 nm UV light\textsuperscript{47} gave the desired brominated acid 3.34. From there, conversion to the phosphonium bromide 3.35 was followed by esterification to the methyl ester along with counter ion exchange. Finally, DIBAL reduction of the ester to the primary alcohol delivered the fully functionalized product 3.37.

Scheme 3.7. Synthesis of lactol 3.31 and attempted Wittig reaction.
Although Wittig reactions with phosphonium salts containing free hydroxyl groups are known in the literature\(^{48}\), in this case reaction of phosphonium salt 3.37 with aldehyde 3.19 was low yielding usually giving 50% or less of the desired olefin. At the same time other methods of attaching the two parts were looked into such as via Julia-Kocienski olefination or Horner-Wadsworth-Emmons olefination. Therefore sulfone 3.41 (Scheme 3.9) along with phosphonate 3.46 (Scheme 3.10) were prepared.

Starting from commercially available 1,3-butandiol 3.38, selective benzoyl protection of the primary alcohol gave benzoate 3.39 (Scheme 3.9).\(^{49}\) The remaining alcohol was converted to the benzothiazole sulfide and oxidized to the sulfone using \(m\)-CPBA.\(^{50}\)
At the same time, attempts were made to synthesize the phosphonate version of sulfone 3.41 (Scheme 3.10). Unfortunately reacting ethyl diethylphosphonate 3.42 with 2-bromoethyl benzoate 3.29 (synthesized from commercially available 2-bromoethanol) never afforded desired phosphonate 3.43 but instead led to the formation of phosphonate 3.44. This product is presumably formed by attack of the deprotonated phosphonate onto the carbonyl of the benzoyl group, regenerating 2-bromoethanol, instead of on the primary bromide. Eventually when replacing the benzoyl group with a benzyl group, the reaction was found to work and afforded the desired product 3.46 in 47% yield. Unfortunately, by this time another route had been developed, and these last two substrates were never carried on to their respective olefination steps.
3.4.3 Benzyl Protected Phosphonium Bromide Route

After having experienced problems with both the THP and the Bz protecting groups, our attention was moved to the Bn group. Indeed the reasoning was that the double bond formed during the olefination reaction would need to be reduced to the alkane via hydrogenation. These reactions are usually run with catalytic Pd/C under an atmosphere of hydrogen, conditions which are also used to remove a benzyl ether. Therefore two transformations could theoretically be accomplished in a single one-pot reaction.

Synthesis of the benzyl protected phosphonium bromide 2.10 commenced with formation of the required bromide 3.45 from commercially available 2-(benzyloxy)ethanol 3.47 with NBS (Scheme 3.11). Treatment of this bromide with ethyltriphenyl phosphonium bromide 3.27 in the presence of n-BuLi delivered the desired phosphonium salt 2.10.
Unfortunately at first the product was never isolated in its pure form and was always contaminated with 5 to 20% of the starting phosphonium salt. Considering the starting phosphonium is monosubstituted and therefore much more reactive, running Wittig reactions with this mixture always led to huge losses of the precious aldehyde. This was a very problematic result for us as purification of the phosphonium by flash chromatography was definitely not an option nor was sublimation. Recrystallization was attempted with numerous solvent (EtOAc, acetone, CH₂Cl₂, PhMe, MeOH...) but none proved selective for one phosphonium over the other. Eventually after extensive screening of solvents it was found that a trituration with water allowed removal of the monosubstituted phosphonium salt from the disubstituted phosphonium salt. Although with hindsight water was probably a logical choice, it had been pushed aside at first due to the high hygroscopy of the phosphonium salts and the challenge it is to dry them.

With a solid procedure to synthesize 2.10, tens of grams of this phosphonium could easily be brought up. Coupling with aldehyde 3.19 via Wittig reaction gave the expected
mixture of olefins 3.48 in a consistent 1:1 ratio (Scheme 3.12). Although the olefins could be separated by flash column chromatography for characterization, they were usually carried on as a mixture in the following hydrogenation step.


3.5 Hydrogenation/Benzyl Ether Cleavage

3.5.1 Initial Solution

With olefin 3.48 in hand and the previous experience on hydrogenation of 3.23 we were fairly confident that the following step would be trivial. This made our surprise even greater when after treating the mixture of alkenes with Pd/C in EtOAc under and atmosphere of H₂, not only was the yield not as high as expected, but the desired product was contaminated with an unknown side product. After careful purification of the product mixture and extensive characterization by NMR, IR and HRMS this side product was determined to be the fully saturated alkane 3.50 (Scheme 3.13). As this result was completely unexpected, a thorough investigation of the mechanism was done along with a literature search of any precedence.
To the best of our knowledge, this specific reaction, going from a homoallylic benzyl ether to the corresponding fully reduced hydrogenolysed alkane has not been reported, but other similar substrates have been shown to go through this type of transformation. Indeed, Cocker has shown that car-3-ene 3.52 when treated with Pd and H₂ would give the ring expanded product 3.54 instead of the desired carane 3.51 (Scheme 3.14). This product is formed by migration of the double bond from the homoallylic position (with respect to the cyclopropane) to the allylic position (3.52 → 3.53) followed by opening of the ring. Interestingly, when running the same reaction with platinum instead of palladium, only the desired carane was observed.

Similarly, Nishimura showed that depending on the metal used for hydrogenation of 4-ethoxy-1-methylcyclohex-1-ene 3.55 the amount of methylcyclohexane 3.57 formed varied significantly. Palladium, which is the metal with the highest isomerization activity, was the one that gave the most undesired product. Once again the side product was formed by olefin migration from the Δ¹,² to the Δ²,³ position.
From these precedents, it was established that the mechanism for this transformation had to imply migration of the double bond to give trisubstituted olefin 3.58 followed by formation of palladium π-allyl intermediate 3.59 which upon elimination delivers alkane 3.50 (Scheme 3.15).
Further evidence for this mechanism was obtained when regioisomer 3.58 was isolated as a product of the hydrogenation and characterized by NMR spectroscopy.

A screening of different combinations of metals and solvents was therefore undertaken to see if the hydrogenolysis product could be suppressed (Table 3.4).

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>metal</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd/C</td>
<td>Rate of hydrogenolysis increases with polarity of solvent:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EtOH &gt;&gt; THF ~ EtOAc &gt; PhMe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rate of hydrogenolysis seems proportional to rate of reaction.</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OH)$_2$/C</td>
<td>Mainly hydrogenolysis product formed in EtOAc.</td>
</tr>
<tr>
<td>3</td>
<td>Rh/Al$_2$O$_3$</td>
<td>No rxn at 1 atm in EtOAc or Et$_2$O.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At 500 psi, Bn ring gets hydrogenated.</td>
</tr>
<tr>
<td>4</td>
<td>Rh/C</td>
<td>Hydrogenation of Bn ring happens at 1 atm.</td>
</tr>
<tr>
<td>5</td>
<td>Rh[PPh$_3$]$_3$Cl</td>
<td>No rxn in EtOAc at 1 atm.</td>
</tr>
<tr>
<td>6</td>
<td>Pt/C</td>
<td>Double bond reduced at 1 atm, Bn ring starts getting reduced at 1 atm.</td>
</tr>
</tbody>
</table>

Table 3.4. Screening of metals and solvents for the hydrogenation reaction.
Pd/C (entry 1) seemed to always give the undesired alkane product. Increasing the polarity of the solvent (EtOH) accelerated the rate of the reaction, but also that of the hydrogenolysis. Similarly when the polarity was decreased (PhMe) both reaction rates were decreased. Pd(OH)$_2$/C (entry 2) was very similar to Pd/C also giving the hydrogenolysis product. At this point it seemed that changing metal would be the only way to avoid this side reaction. Rhodium, the first choice, was not very convincing. When supported on Al$_2$O$_3$ (entry 3), at 1 atmosphere, there was no discernable reaction. When raising the pressure to 500 psi, the aromatic ring would start getting hydrogenated to the cyclohexyl. When using Rh/C (entry 4) the aromatic ring would start getting reduced even at 1 atmosphere. Wilkinson’s catalyst (entry 5) gave no reaction which is not surprising for a trisubstituted double bond. Finally, platinum (entry 6) gave similar results to rhodium but seemed slightly slower to reduce the aromatic ring. The completely qualitative aspect of this study is mainly due to the fact that the various metals used were from extremely old sources and not 100% reliable. On top of that, these reactions were run using catalytic amounts of supported metal which itself is catalytic in metal. Therefore, combined with the fact that these are heterogeneous reactions, reproducibility was often an issue on such small scales. Nevertheless with the trends obtained from this first screen the use of platinum warranted further investigation. What was found was that in non-polar solvents under one atmosphere of hydrogen and with careful monitoring of the reaction by GC, the olefin could be cleanly reduced and the reaction stopped before the aromatic ring started getting reduced (Scheme 3.16).
With the double bond reduced, all that was left was to remove the protecting group on the primary alcohol. At this point, since the benzyl ether was not homoallylic anymore treating it with Pd/C under H$_2$ was successful at cleaving it. Unfortunately high pressures of hydrogen had to be used to get complete removal in a reasonable time, once again possibly due to the age of the palladium catalyst. Nevertheless the two epimeric alcohols were obtained in good yield and could be separated by flash column chromatography.

While this two step route was good enough for us at first to bring up material in reasonable quantities, the fact that two different metals, solvents and pressures were needed to accomplish what seemed like a very trivial transformation was not ideal. We therefore set out on a quest to optimize this sequence.
3.5.2 Optimized Solution

Back to back hydrogenation/debenzylation sequences run in two subsequent steps have been previously done in the literature.\textsuperscript{55} Still, it seemed that in this case a one-pot sequence should be feasible. As mentioned earlier the quality of the metal catalysts used hitherto was questionable at best, therefore the first step was to acquire a variety of brand new catalysts. During the search for potential catalysts, it seemed that along with the choice of the metal, the choice of the support and wetness was as important. If the number of metals is relatively limited (Pd, Pt, Rh, Ir, Ru) the combination of support (carbon, activated carbon, carbon powder, peat carbon, wood carbon, charcoal, activated charcoal, alumina, barium carbonate, barium sulfate, calcium carbonate, titanium silicate…) and wetness (dry powder, wet support, moistened, wet paste, wetted powder…) seemed endless. Nevertheless this search was started with four different types of palladium all acquired from Aldrich.

Table 3.5 summarizes the initial screen of debenzylation conditions. Running the four new catalysts in both THF and EtOH revealed how important every parameter (metal, support, solvent) was. The first very obvious trend was that EtOH (entries 5-8), which is much more polar than THF (entries 1-4), dramatically accelerates the reaction rates including that of the TES removal side reaction.\textsuperscript{38} The next important observation was that no matter the metal, the support had a great influence on the outcome of the reaction (entries 1-2 and 3-4). With these results, conditions in entry 2 which gave fast and clean removal of the benzyl ether without any loss of the TES ether were deemed the best conditions.
These very encouraging results led us to try the two step sequence with only Pd(OH)$_2$ present, but unfortunately only the benzyl ether was removed and the trisubstituted double bond was left untouched after the reaction. Nevertheless, these results proved that not only could the benzyl ether be cleaved in 3 hours under 1 atm of hydrogen, but it was also possible to first remove the homoallylic benzyl ether without seeing any double bond migration. The resulting homoallylic alcohol could then be reduced to the alkane using the same conditions as described earlier (Pt/C, H$_2$ 1 atm, PhMe). With these two orthogonal pathways developed (Scheme 3.18) all that was left to do, was find a one-pot
sequence to go from 3.48 directly to 3.49. It seemed like a mixture of Pd(OH)$_2$/C and Pt/C should work as long as the correct ratio and solvent was used.

Scheme 3.18. Two possible pathways from 3.48 to 3.49.

With the current chemistry developed, in order for this one-pot sequence to be efficient a few objectives had to be attained. First and foremost, both metals had to be in the reaction mixture from the start. Having to add a second metal after a certain amount of time involved steps such as opening the reaction vessel, flushing with inert gas and replacing under hydrogen, which completely defeated the purpose of the one-pot reaction. The reaction also had to be run at room temperature and under one atmosphere of hydrogen gas (balloon). Not only does this make for an easier setup, but potentially
makes the methodology usable by research groups who don’t have access to high-pressure hydrogenators. Finally, having the reaction go to completion in less than 24 hours would be an advantage as the current two-step sequence can be done in 12 hours or less. With all these constraints in mind a screening of ratios of metals in different solvents was accomplished. The initial screen used a 1:1 ratio of both catalysts and tested a variety of solvents (Table 3.6).

Table 3.6. Initial hydrogenation solvent screen.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>Product</th>
<th>Cy</th>
<th>SM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>17%</td>
<td>-</td>
<td>83%</td>
</tr>
<tr>
<td>2</td>
<td>EtOAc</td>
<td>75%</td>
<td>25%</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>20%</td>
<td>-</td>
<td>80%</td>
</tr>
<tr>
<td>4</td>
<td>Pentane</td>
<td>40%</td>
<td>18%</td>
<td>42%</td>
</tr>
<tr>
<td>5</td>
<td>Et₂O</td>
<td>45%</td>
<td>16%</td>
<td>39%</td>
</tr>
<tr>
<td>6</td>
<td>CH₃CN</td>
<td>1%</td>
<td>-</td>
<td>80%a</td>
</tr>
<tr>
<td>7</td>
<td>CH₂Cl₂</td>
<td>74%</td>
<td>26%</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>s-BuOH</td>
<td>82%</td>
<td>-</td>
<td>18%</td>
</tr>
</tbody>
</table>

*a19% unknown peaks by GC.

What came out of these results was that EtOAc, CH₂Cl₂ and s-BuOH (entries 2, 7 and 8) seemed like decent solvents. On the other hand, ethers (entries 1 and 5), hydrocarbon
solvents (entries 3 and 4) and CH$_3$CN (entry 6) were deemed poor solvents for this transformation. It was also evident that platinum was much more reactive than palladium and in order to avoid hydrogenation of the aromatic ring palladium had to be used in excess. A second screen was therefore run with solvents similar to the best three and with a 4:1 ratio of palladium to platinum (Table 3.7).

![Chemical structure](image)

**Table 3.7.** Second hydrogenation solvent screen.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>SM 3.48</th>
<th>reduced</th>
<th>deprotected</th>
<th>product 3.49</th>
<th>alkane 3.50</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOAc</td>
<td>-</td>
<td>11%</td>
<td>-</td>
<td>81%</td>
<td>8%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Acetone</td>
<td>5%</td>
<td>10%</td>
<td>30%</td>
<td>45%</td>
<td>10%</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>CH$_2$Cl$_2$</td>
<td>-</td>
<td>-</td>
<td>65%</td>
<td>12%</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>4</td>
<td>CHCl$_3$</td>
<td>51%</td>
<td>-</td>
<td>49%</td>
<td>-</td>
<td>1%</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>CCl$_4$</td>
<td>-</td>
<td>1%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>99%</td>
</tr>
<tr>
<td>6</td>
<td>DCE</td>
<td>53%</td>
<td>15%</td>
<td>19%</td>
<td>11%</td>
<td>2%</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>s-BuOH</td>
<td>-</td>
<td>-</td>
<td>28%</td>
<td>42%</td>
<td>30%</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>t-BuOH</td>
<td>-</td>
<td>-</td>
<td>21%</td>
<td>51%</td>
<td>28%</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>i-PrOH</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>66%</td>
<td>33%</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>Me$_3$COH</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>71%</td>
<td>29%</td>
<td>-</td>
</tr>
</tbody>
</table>

After analysis of all the different solvents run, EtOAc (entry 1) came out as a clear choice. The ratio was then further optimized and eventually set at a 2:1 ratio for optimal conversion (Scheme 3.19).
The reduction/deprotection sequence had therefore been successfully accomplished in a one-pot fashion. Although all the initial goals had not been completely met (the reaction needed a little over 24 hours to reach completion) it was still very rewarding to have solved this problem.

### 3.6 Completion and Characterization of the Northern Half

With both epimers of the alcohol in hand, all that was left to do was make the corresponding bromides and determine the absolute C13 configuration of each epimer. The bromides were made via standard bromination using PPh₃/CBr₄ in CH₂Cl₂ in almost quantitative yields (Scheme 3.20).

Scheme 3.19. Optimized conditions for the one-pot hydrogenation.

Scheme 3.20. Formation of bromides 2.6.
In order to obtain the absolute C13 stereochemistry, an X-ray needed to be obtained. Unfortunately neither epimers of alcohol 3.49 nor bromide 2.6 were solids. In order to obtain crystalline solids from oily material, it is commonplace in synthetic organic chemistry to make the corresponding bromo- or nitrobenzoate ester. The resulting products are usually solids and more amenable to recrystallization.

Therefore, the p-nitrobenzoate ester of both epimers of alcohols 3.49 were originally synthesized (Scheme 3.21).

![Scheme 3.21. Synthesis of p-nitrobenzoate esters 3.62.](image)

Unfortunately, none of the two esters were solids and both turned out to be clear oils. When looking closer at the molecule, it became obvious that the “crystallizing group” was installed at the complete end of the molecule, essentially leaving the rest of the molecule unchanged. Considering the lack of functionality on the other end it was reasoned that this was the issue preventing the product from being a solid. The triethylsilyl group in particular seemed like the greasiest moiety of the left half. Upon removal of the TES group on both epimers of 3.49, one of the two epimers, 3.63 turned out to be a solid that was successfully recrystallized from Et2O to obtain an X-ray
structure (Scheme 3.22). Not only did this attribute the stereochemistry at the unknown C13 stereocenter, but also confirmed the stereochemistry at the other three stereogenic centers.

![Scheme 3.22. Synthesis and X-ray structure of 3.63.](image)

While the other diol epimer 3.64 was still an oil, it was possible to turn it into a solid by converting it to the bis-dinitrobenzoate 3.65 (Scheme 3.23). Unfortunately all attempts to obtain crystalline material from it were unfruitful and eventually getting X-ray data on this epimer was abandoned.
In conclusion, the northern half of the molecule has been synthesized in 8 steps from known lactone 3.15 (Scheme 3.24).
The overall yield of this sequence is 42% which has allowed us to bring up gram quantities of material. Moreover, both epimers can be synthesized and absolute stereochemistry has been attributed for each of them. Eventually the hydrogenation step could be done asymmetrically in order to obtain only the desired epimer.\textsuperscript{58}
4.1 Introduction

The southern half of leiodelide A (C1-C7) is characterized by an α,β-unsaturated carbonyl moiety along with an allylic alcohol which is conjugated with the oxazole ring (Figure 4.1). Attaching the southern part of the molecule to the northern half and the oxazole was envisioned from the start to be done via macrolactonization and metal-catalyzed cross-coupling reaction respectively. Therefore the left half would need to be brought up as an ester which could be saponified to the acid when needed, and the right half would need to be an alkenyl metal species to allow metal-mediated coupling to the oxazole. This led us to a molecule such as 4.1 in which the metal would be attached via hydrometallation of the alkyne precursor, the ester would be appended via Horner-Wadsworth-Emmons reaction and the two halves of the molecule would be combined by an Evans aldol reaction.
With the general retrosynthesis devised, the order in which the steps were going to be run was the only unknown left. The very first approach was to keep the hydrometallation step for last. This strategy was two-fold: first it eliminated the need to push a possibly labile vinylic metal species over multiple steps, and it would also allow to screen different metals such as zinc, boron or tin for the coupling reaction without having to go back multiple steps.

The synthesis commenced with oxidation of propargylic alcohol 4.2 to the corresponding aldehyde 4.3 (Scheme 4.1). This aldehyde was unstable and very volatile and had to be used without purification in the following step. Evans aldol reaction with acylated oxazolidinone 4.4 gave the desired aldol product 4.5. From there a series of protection, reduction and oxidation yielded aldehyde 4.8. Horner-Wadsworth-Emmons reaction with triethyl phosphonoacetate and Ba(OH)\textsubscript{2} delivered the desired alkyne 4.9.
Scheme 4.1. First generation synthesis of the southern half.

With ester 4.9 in hand, all that was left was to hydrometallate the alkyne to the vinylic metal species. Unfortunately what seemed like a fairly straightforward reaction turned out to be much more complicated than expected. Hydroboration either with catecholborane$^{62}$
or pinacolborane\textsuperscript{63} did not afford any product. Hydrozirconation\textsuperscript{64} would always lead to reduction of the conjugated ester to the allylic alcohol. Finally, hydrostannylation using $n$-Bu$_3$SnH with various sources of palladium (Pd(PPh$_3$)$_2$Cl$_2$, Pd(PPh$_3$)$_4$, Pd(dba)$_2$, Pd(OAc)$_2$) would constantly give low yields of an inseparable mixture of desired product along with regio- and stereoisomers.\textsuperscript{65} These results therefore led us to devise a new strategy where the metal would be attached prior to the installation of the conjugated ester.

4.3 Second generation synthesis of the southern half

From the results of the first synthesis, a new route in which the metal would be installed earlier in the synthesis was devised. The alkenylstannane moiety seemed to have the greatest chances of success both stability and reactivity wise and was therefore chosen. The synthesis commenced in the same manner as the first generation approach by formation of aldol product \textsuperscript{4.5} (Scheme 4.2). At this point the chiral auxiliary was cleaved by reduction to diol \textsuperscript{4.11}. Hydrostannylation of the alkyne using $n$-Bu$_3$SnH, CuCN and $n$-BuLi was very efficient and gave \textsuperscript{4.12} as a single regioisomer.\textsuperscript{66} The oxidation step was less straightforward and required some optimization. Among other methods, oxidation of a primary alcohol in the presence of a secondary alcohol can be achieved using BAIB in the presence of catalytic TEMPO.\textsuperscript{67} While these conditions are relatively mild, acetic acid is generated in the reaction. The $\beta$-hydroxyaldehyde formed was extremely reactive and trace amounts of acid are enough for it to dehydrate, resulting in the corresponding fully conjugated aldehyde. In order to prevent this side reaction, the reaction was buffered with solid NaHCO$_3$. Unfortunately aldehyde \textsuperscript{4.13} was also
sensitive to basic conditions and a retro-aldol reaction took place, liberating the conjugated aldehyde. Eventually, it was found that careful adjusting of pH afforded the desired product. Any attempts to isolate or purify aldehyde 4.13 always led to decomposition and eventually the crude product was carried on to the Horner-Wadsworth-Emmons reaction resulting in conjugated ester 2.8 albeit in low and difficultly reproducible yields. Finally, the secondary alcohol was protected as its TBS ether in nearly quantitative yield to give the fully functionalized southern half 4.10.
Although the desired product was obtained, this route suffered some major drawbacks that made it impractical for scale-up. Aldehyde 4.3 was both unstable and very volatile and its synthesis was not always reproducible. Aldehyde 4.13 was even more unstable and if not handled correctly would decompose instantaneously. Such a sensitive reaction

Scheme 4.2. Second generation synthesis of the southern part.
made this route not amenable to gram scale synthesis and an improved synthesis was therefore devised.

### 4.4 Improved Synthesis of the Southern Half

The goals set for this third generation synthesis of the southern half were to avoid going through either of the aforementioned unstable aldehydes (4.3 and 4.13). In order to do so, the synthesis had to be completely revised as aldehyde 4.3 was the first intermediate formed. Looking through the literature, known aldehyde 1.13 seemed like a perfect starting point for this synthesis.\(^{66, 68}\) Not only was the volatility issue solved due to the presence of the tin, but it was also very stable and easily amenable to gram-scale synthesis. Therefore starting from the same propargylic alcohol 4.2, hydrostannylation followed by MnO\(_2\) oxidation of the allylic alcohol afforded known aldehyde 1.13 (Scheme 4.3). From there, Evans aldol using the same chiral oxazolidinone as previously lead to alcohol 4.15 in quantitative yield which was protected as its TBS ether 4.16. The protection at this stage of the synthesis allowed the subsequent reduction/oxidation sequence without having to worry about possible elimination or retro-aldol side reactions. Stable aldehyde 4.18 was finally converted to the desired conjugated ester 4.10 via HWE olefination.
With this improved synthesis in place, decent amounts of organostannane 4.10 could be brought up and a screening of coupling conditions for the attachment of the oxazole onto the southern part was performed. Unfortunately, after an extensive screening of conditions (catalysts, additives, solvents) and obtaining yields that were modest at best,
alternatives were clearly needed. During a model study of the system it came to our attention that the TBS group on the alcohol $\gamma$ to the tin was the culprit in this reaction and once it was removed yields jumped significantly. Unfortunately, with the current designed synthesis, the TBS group was absolutely necessary to avoid the previous issues that arose with oxidation of the $\beta$-hydroxyalcohol (vide supra).

Instead of redesigning the synthesis once more, a possible deprotection/reprotection sequence adjoining the coupling was envisioned. Although the deprotection might seem trivial at first glance, it turned out to be much more challenging than originally thought. First, the alcohol is secondary and relatively hindered which makes it less susceptible to easy removal. Second, the presence of the vinyl tin makes the use of strong acids very delicate as protodestannylation would certainly be a concomitant reaction. Finally, the desired product, upon dehydration, would generate a trisubstituted double bond fully conjugated throughout the southern part. Therefore dehydration would be something to be concerned about.

With these observations made, a screening of conditions for the selective removal of the TBS group was undertaken (Scheme 4.4). As expected, acids (HCOOH,\textsuperscript{69} PPTS, Dowex, pTSA, CSA, AcOH, HCl, TFA) all led to some degree of protodestannylation.

![Scheme 4.4. Removal of the the TBS group of 4.10.](image-url)
While weak acids or catalytically used strong acids showed product formation starting before protodestannylation, strong acids used in stoichiometric amounts immediately led to the undesired alkene.

Using fluoride sources did not prove much more convincing. Hexafluorosilicic acid in either \( t\)-BuOH\(^{70}\) or CH\(_3\)CN\(^{71}\) gave mainly destannylation. Using milder HF•Et\(_3\)N, the reaction would not go when buffered with Et\(_3\)N and was extremely slow when not buffered.\(^{72}\) HF•pyr resulted in mainly destannylated product when used alone\(^{73}\) but far less when buffered with pyridine.\(^{74}\) Finally, whereas TBAF completely decomposed the molecule,\(^{75}\) AcOH buffered TBAF gave us the best results leading to a 70% yield of alcohol.\(^{76}\)

Although the original problem was once again solved, matters were only made worse by adding low yielding steps to an already long synthesis. A more optimal route that would not only cut down the number of steps but also avoid unattractive oxidation/reduction and protection/deprotection sequences was sought.

4.5 Optimized Synthesis of the Southern Half

In order to avoid both the redox and protection steps, the optimized synthesis needed to go through the highly reactive β-hydroxyalcohol 4.13. Ideally, removing the chiral auxiliary from the aldol product under neutral conditions should allow carrying the crude product through to the next reaction. Although going from the aldol product to the corresponding aldehyde when Evans’ auxiliary is used is not reported in the literature, Davies has developed an alternate auxiliary for this very purpose.\(^{77}\) A new synthesis using this synthon was therefore immediately devised (Scheme 4.5).
The synthesis commenced in the same manner as the previous by formation of known aldehyde 1.13, but instead of running the aldol reaction using Evans’ auxiliary, Davies’ SuperQuat oxazolidinone 2.11 was used. The desired product 4.19 was obtained in quantitative yield as a single enantiomer. At this point the desired southern half was theoretically only two steps away. Although cleavage of the chiral auxiliary with DIBAL worked extremely well and produced only the aldehyde, the work-up was very sensitive and required some optimization to obtain the highest possible yield. Eventually it was
found that filtration over Celite and concentration offered a good balance between purity and decomposition. Indeed even trivial steps like drying the organic layer would promote decomposition of the product. The crude aldehyde was then immediately subjected to HWE conditions and the fully functionalized southern part 2.8 was obtained in 76% yield over two steps.

With this optimized synthesis the complete carbon skeleton of the southern part could be constructed in a three-step protecting group-free synthesis from known starting materials. Also, this synthesis is easily amenable to making the enantiomer as the stereochemistry is set by the chiral auxiliary. This could prove to be useful since the assignment of the stereochemistry at carbons 4 and 5 was deemed tenuous by Fenical.7
Chapter 5

SYNTHESIS OF THE OXAZOLE

5.1 Introduction

The oxazole ring is a five-membered aromatic heterocycle that contains both oxygen and nitrogen (Figure 5.1). It belongs to the family of azoles along with its sister compounds thiazole and imidazole.

![Structures of oxazole, thiazole and imidazole.](image)

Figure 5.1. Structures of oxazole, thiazole and imidazole.

In the past 30 years, isolation of natural products containing oxazole rings have increased dramatically and are nowadays very frequent. Oxazoles can be found in
numerous types of natural products such as macrolides, polyols, peptides, alkaloids and polyketides. Also, the number of oxazoles, their location, and their substitution pattern can vary tremendously from one compound to another. Compounds such as leucascandrolide A$^4$ and rhizoxin D$^5$ (Figure 1.1) have only one 2,4-disubstituted oxazole ring located in the side chain of the molecule. In contrast, leiodelide A (1.1) possesses an oxazole ring with the same 2,4-disubstitution pattern, but present inside the macrolactone (Figure 1.2). More complex molecules such as phorboxazole A$^78$ (Figure 5.2) have two oxazole rings, one in the macrolactone and one in the side chain. Other bisoxazoles include muscoride A,$^79$ hennoxazole A,$^80$ bengazole A$^{81}$ and the structurally complex diazonamide A.$^82$ Ulapualide A$^83$ with its three contiguous 2,4-disubstituted oxazoles belongs to a family of trisoxazole-containing natural products that includes mycalolides, kabiramides, halichondramides and jaspiramides. Finally, both heptaoxazole-containing products telomestatin$^84$ and plantazolicin A$^{85}$ show how prevalent oxazole rings can be.
Figure 5.2. Other oxazole-containing natural products.
The proposed biosynthetic pathway to form oxazoles is shown in Scheme 5.1. Starting from serines (R’ = H) or threonines (R’ = Me) side chains 5.1, deprotonation of the hydroxyl group followed by heterocyclization onto the preceding carbonyl results in five-membered saturated heterocycle 5.2. After dehydration and two electron oxidation of the oxazoline 5.3 these compounds result in heteroaromatic oxazole 5.4.

Scheme 5.1. Biosynthetic pathway to oxazoles.

5.2 Synthesis of Oxazoles

The diversity and complexity of oxazoles occurring in natural products has led the synthetic community into a search for mild, efficient and selective formation of oxazoles in the presence of other functional groups.
5.2.1 Oxidation of Oxazolines

To date, the most common method for making oxazoles in natural product synthesis is to follow the biosynthetic pathway, which means first generating the oxazoline and then oxidizing it to the heteroaromatic oxazole. Of the numerous methods that exist to make oxazolines the two most common are to either start from the β-hydroxy amides (Scheme 5.2) or from nitriles (Scheme 5.3).

![Diagram of oxazoline synthesis from β-hydroxy amides.]

Scheme 5.2. Synthesis of oxazolines from β-hydroxy amides.

The β-hydroxy amide method to prepare oxazolines is certainly the most popular and involves a two-step mechanism where the hydroxyl group is activated as a leaving group followed by intramolecular cyclization. The requisite β-hydroxy amides are commonly prepared via acylation of the appropriate amino alcohol with acid chlorides or anhydrides, or via classical peptide coupling methodology. Some of the most commonly used reagents to affect this cyclodehydration are thionyl chloride, the Vilsmeier reagent, strong acids, the Burgess reagent or DAST. Converting the hydroxyl group to a mesylate or triflate permits the use of a Lewis acid to form the oxazoline.

Another widespread method for preparing oxazolines involves the Lewis acid catalyzed reaction of nitriles with amino alcohols (Scheme 5.3). The most common Lewis acids employed include ZnCl$_2$, CuCl$_2$, and kaolinitic clay.
With the oxazoline in hand, to obtain the aromatic oxazole, the oxazoline needs to be oxidized (Scheme 5.4). A wide variety of reagents have been evaluated for this transformation, but unfortunately none have come out as a general and high-yielding option. The most common oxidants used nowadays are nickel peroxide, manganese dioxide, copper salts and the Kharasch-Sosnovsky reaction. Other oxidants which avoid the use of metals are also employed such as BrCCl$_3$ or CCl$_4$ with DBU, I$_2$ or NBS/AIBN.

Along with this two step procedure many other direct syntheses of oxazoles have been developed.
5.2.2 Direct Synthesis of Oxazoles

While there are dozens of methods to synthesize oxazoles in the chemical literature, only a few of the most widely used ones will be presented here.\textsuperscript{102}

Oxazoles can be prepared by reacting nitriles with diazocarbonyl compounds in the presence of catalytic transition metals. Moody\textsuperscript{103} and Helquist\textsuperscript{104} have both extensively studied this reaction and found that Rh\textsubscript{2}(OAc)\textsubscript{4} was the most effective catalyst for this transformation (Scheme 5.5). Organotellurium reagents have also been used to prepare oxazoles from nitriles and acetylenes.\textsuperscript{105}

\begin{center}
\begin{align*}
\text{R}^1\text{-CN} + \text{N}_2\text{Z} \xrightarrow{\text{Rh}_2\text{(OAc)}_4} \text{R}^1\text{N}_2\text{Z} \\
\text{R}^1\text{-CN} + \text{R}^2\text{C} = \text{R}^3 \xrightarrow{\text{PhTeOTf}} \text{R}^1\text{N}\text{R}^2\text{R}^3
\end{align*}
\end{center}

Scheme 5.5. Metal mediated synthesis of oxazoles from nitriles.

Another commonly used method is to start from \(\alpha\)-substituted ketones (Scheme 5.6). When \(\alpha\)-halo or \(\alpha\)-trifloylketones are reacted with amides or ureas the corresponding 2,4-disubstituted oxazoles are produced.\textsuperscript{106} Reactions with a nitrile most likely produces a nitrilium salt which subsequently cyclizes to the corresponding 2,5-disubstituted oxazole.\textsuperscript{107} Often, the \(\alpha\)-trifloylketone is generated \textit{in situ} from the ketone.\textsuperscript{108}
Yet another way to synthesize oxazoles is to start from propargylic amides (Scheme 5.7). Treatment of this class of molecules with bases such as NaH or K$_2$CO$_3$ results in clean conversion to the oxazole.$^{109}$ The proposed mechanism involves an isomerization to the allene followed by deprotonation and attack by the oxygen at the central allenic carbon.
Isocyanides can also be used as precursors to oxazoles (Scheme 5.8).\textsuperscript{110} Upon acylation of ethyl isocyanoacetate with an acid chloride, the resulting $\alpha$-ketoimidoyl chloride immediately cyclizes to afford the oxazole when treated with base.\textsuperscript{111}

Another example of this transformation is the Van Leusen reaction,\textsuperscript{112} where TosMIC is reacted with aromatic aldehydes to give the corresponding 5-substituted oxazole.
This method can be used to synthesize the parent heterocycle oxazole either by condensing ethyl isocyanoacetate with formic acid followed by hydrolysis and decarboxylation or by condensing with paraformaldehyde.

Finally, the Robinson-Gabriel reaction which is one of the oldest methods available to prepare a wide variety of oxazoles, involves dehydration of 2-acylamidoketones (Scheme 5.9). Some of the most commonly used dehydrating agents are POCl₃, SOCl₂, P₂O₅, PPA, pTSA, and TFAA.

Scheme 5.9. Robinson-Gabriel synthesis of oxazoles.

5.3 Initial Oxazole Attempts

As mentioned earlier, the installation of the oxazole needed to be a key step in the synthesis. The goal was to attach a preformed oxazole to the northern and southern halves, ideally in back to back reactions, to make the synthesis as convergent as possible. Also, coupling chemistry would be used at both ends of the oxazole (Figure 5.3).
As seen in the previous methods to synthesize oxazoles, most if not all result in alkyl or aryl substituted oxazoles, which was not applicable to the desired game plan as a halo or pseudohalo 2,4-disubstituted oxazole was needed.

The original idea was to use chemistry developed by Panek in which he takes 2,4-ditrifloylthiazole 5.6 (made from thiazolidinedione 5.5) and performs two consecutive couplings selectively to afford the 2,4-disubstituted thiazoles 5.7 (Scheme 5.10).123
Oxazole and thiazole only differ by one heteroatom (Figure 5.1), which are both from the same group, which led us to believe that the chemistry should be transferable to oxazoles.

Oxazolidinedione 5.10, which is not commercially available (whereas thiazolidinedione is) was synthesized from glycolamide 5.8 and diethyl carbonate 5.9 in the presence of sodium methoxide (Scheme 5.11).\textsuperscript{124}

Scheme 5.10. Thiazole precedent.

Scheme 5.11. Synthesis of oxazolidinedione 5.10.
Unfortunately, synthesizing ditrifloyloxazole 5.11 was not possible even under a large set of conditions (Table 5.1). Triflic anhydride in various solvents with or without bases gave either no reaction or resulted in decomposition of the material. When switching to Comins’ reagent,\textsuperscript{125} decomposition was all that was observed.

![Reaction Scheme](image)

Table 5.1. Formation of ditrifloyloxazole 5.11.

<table>
<thead>
<tr>
<th>entry</th>
<th>Tf source</th>
<th>base</th>
<th>solvent</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tf\textsubscript{2}O</td>
<td>Et\textsubscript{3}N</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>Tf\textsubscript{2}O</td>
<td>2,6-lutidine</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>Tf\textsubscript{2}O</td>
<td>Cs\textsubscript{2}CO\textsubscript{3}</td>
<td>THF</td>
<td>polymerized THF</td>
</tr>
<tr>
<td>4</td>
<td>Tf\textsubscript{2}O</td>
<td>-</td>
<td>Et\textsubscript{2}O</td>
<td>no rxn</td>
</tr>
<tr>
<td>5</td>
<td>Tf\textsubscript{2}O</td>
<td>Cs\textsubscript{2}CO\textsubscript{3}</td>
<td>Et\textsubscript{2}O</td>
<td>no rxn</td>
</tr>
<tr>
<td>6</td>
<td>Tf\textsubscript{2}O</td>
<td>Cs\textsubscript{2}CO\textsubscript{3}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>no rxn</td>
</tr>
<tr>
<td>7</td>
<td>Tf\textsubscript{2}O</td>
<td>DIPEA</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>decomposition</td>
</tr>
<tr>
<td>8</td>
<td>Tf\textsubscript{2}O</td>
<td>DBU</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>no rxn</td>
</tr>
<tr>
<td>9</td>
<td>Tf\textsubscript{2}O</td>
<td>NaH</td>
<td>Et\textsubscript{2}O</td>
<td>no rxn</td>
</tr>
<tr>
<td>10</td>
<td>Comins’ reagent</td>
<td>NaHMDS</td>
<td>THF</td>
<td>decomposition</td>
</tr>
<tr>
<td>11</td>
<td>Comins' reagent</td>
<td>DIPEA</td>
<td>THF</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

With this negative result in hand, similar oxazoles were attempted to be made (Figure 5.4). Using tosyl chloride instead of triflic anhydride, the ditosylate 5.12 was attempted, but once again depending on the base either no reaction was observed or the starting material (or product) was completely decomposed. 2-Trifloyloxazolinone 5.13 and 2-
tosyloxazolinone 5.14 were also attempted by quenching the oxazolidinedione formation reaction with either Tf$_2$O or TsCl but in both cases no desired product was obtained. Formation of both 2-trifloyl$^{126}$ and 4-trifloyl$^{127}$ oxazoles from the parent oxazolinones have been reported in the literature when the other position was substituted, but never has the 2,4-ditrifloyloxazole been reported, possibly due to high reactivity. This chemistry was most notably used by the Smith group for the synthesis of phorboxazole A.$^{128}$ Finally, protection of the amino group of oxazolidinedione either with a Bn or PMB group followed by mono triflation gave none of desired products 5.15 and 5.16.

Using halides instead of pseudohalides on the oxazole ring was also looked into, but was quickly abandoned following a result from the Greaney group in which 2,4-diiodoxazole was obtained from oxazole in 77% in 14 days.$^{129}$ Not only is oxazole outrageously expensive (>80/g) but the reaction required 2 weeks to get yields higher than 70%. Seeing that the original idea of a 2,4-halo or pseudohalo disubstituted oxazole was not going to work, other possible substrates were sought.
5.4 Oxazole Synthesis

In 2009, our group published a method for making 2,5-diarylsubstituted oxazoles 5.18 starting from 2,5-dithiomethyl oxazole 5.17 (Scheme 5.12).\textsuperscript{130} Thioalkyloxazoles had been previously synthesized by the groups of Molinski\textsuperscript{131} and Marino\textsuperscript{132} and had been shown to be stable even under harsh conditions. Moreover 2,5-dithiomethyl oxazole could give access to disubstituted oxazoles without the need for the parent oxazole. The coupling chemistry was based on established Fukuyama coupling reactions of thioesters\textsuperscript{133} along with other reports of oxidative addition of aryl sulfides.\textsuperscript{134}

![Scheme 5.12. Synthesis of 2,5-diaryloxazoles.](image)

While this chemistry showcased an efficient way to generate 2,5-disubstituted oxazoles, the specific need here was for the 2,4 pattern. Unfortunately, the route to 2,4-dialkylthiooxazole requires many steps, mainly due to the hydrogen at C5 being more acidic than the hydrogen at C4. This makes selective deprotonation of the oxazole at C4 impossible and therefore pushed us toward the halogen dance rearrangement of 2-butylthio-5-halooxazoles.
The halogen dance (HD) reaction involves a base mediated reaction of a haloaromatic compound in which the position of the halogen atom in the product differs from its position in the starting material.\textsuperscript{135} The migration of the halogen is coined as a “dance” from one position to the other.

The synthesis of the required 2-thiobutyloxazole is shown in Scheme 5.13. Reaction of potassium thiocyanate with the diethyl acetal of glycolaldehyde \textsuperscript{5.20} afforded 2-thiooxazole \textsuperscript{5.21} in almost quantitative yield.\textsuperscript{136} From there alkylation of the thiol with butyl iodide provided desired oxazole \textsuperscript{5.22}. Although the thiomethyl version\textsuperscript{131} works equally well in coupling reactions, the low boiling point of 2-thiomethyloxazole made it harder to work with. Therefore the higher molecular weight butyl compound was chosen for this reaction.

\begin{equation}
\text{KSCN} \quad \text{EtO} \quad \text{OH} \quad \text{HCl} \quad \text{KH} \quad \text{Bu} \quad \text{BuS}
\end{equation}

\begin{align}
5.19 & \quad 5.20 & \quad 5.21 & \quad 5.22
\end{align}

Scheme 5.13. Synthesis of 2-thiobutyloxazole \textsuperscript{5.22}.

Halogenation of the oxazole was easily done by deprotonation with \textit{n}-BuLi and quenching with either CBr\textsubscript{4} to give the 5-bromo \textsuperscript{5.23} or I\textsubscript{2} to give the 5-iodo \textsuperscript{5.24} (Scheme 5.14). When oxazole is substituted at the 2 position, the order of acidity is C5 > C4. Therefore halogenation is selectively done at the 5 position.
With gram quantities available of both halogenated oxazoles, the halogen dance reaction was the next hurdle. Using standard conditions (LDA, THF) the desired 4-bromooxazole 5.25 was obtained in high yields (Scheme 5.15). Surprisingly, under identical conditions, the 4-iodooxazole 2.7 was only obtained in poor and irreproducible yields. In fact, the desired product was only a minor product and the major product was always the reduced 2-thiobutyloxazole 5.22.
This unexpected result led to a detailed investigation of the iodooxazole dance reaction mechanism to understand where the side product was originating from as well as to find ways to reduce its formation and favor the desired product.

### 5.5 Optimization of the Halogen Dance Reaction on Iodooxazoles

In order to elucidate the current problem, a rigorous understanding of the mechanism of the halogen dance reaction was necessary. Based on accepted mechanisms along with our own observations the mechanism for the bromooxazole dance reaction is postulated to be that shown in Scheme 5.16.
Scheme 5.16. Bromooxazole dance reaction mechanism.

Starting from 5-bromooxazole 5.23, deprotonation with LDA gives lithiated species 5.26. This lithio compound can then react by lithium-halogen exchange with another molecule of 5-bromooxazole to generate dibromooxazole 5.27 along with lithiated species 5.28. These two molecules can then react together by another lithium-halogen exchange reaction to generate a molecule of 4-bromo-5-lithiooxazole 5.29, which upon quenching with water will provide the desired 4-bromooxazole 5.25, along with a molecule of 5-bromooxazole 5.23 that can enter the cycle again. While this mechanism
can explain the high yield for the bromooxazole, it fails to account for the dramatically lower yield seen with the iodooxazole along with the formation of reduced oxazole.

The reason behind the lower yield and formation of reduced oxazole can be explained by the propensity of aryl iodides to undergo lithium-halogen exchange much faster than aryl bromides. Indeed when looking at the mechanism for the iodooxazole dance (Scheme 5.17), the steps to get to the desired product are identical to the bromooxazole. The only difference is that when adding LDA to iodooxazole, along with the productive deprotonation step, a lithium-iodide exchange happens resulting in the unproductive 5-lithio oxazole 5.28 which remains unreactive until quenching of the reaction with water to give reduced oxazole 5.22.
With these results established, ways to diminish this side reaction were investigated. The first experiment was to determine the rate at which the reaction was proceeding. Taking bromooxazole as the test substrate, running it under standard halogen dance reaction conditions and immediately quenching with a source of deuterium such as D$_2$O should allow seeing how fast the reaction proceeds.

As seen in Scheme 5.18, when quenching a halogen dance reaction on bromooxazole 5.23 with D$_2$O after 30 seconds, the only isolated product was the 4-bromo-5-
deuteriooxazole 5.32 resulting from complete dance and quenching with deuterium. None of the possible intermediates were isolated in this reaction.

Scheme 5.18. Kinetic study of the halogen dance reaction.

With a better understanding of the rate of the reaction, suppressing the unproductive lithium-halogen exchange reaction was the next step. The initial idea was to switch from a lithium base to a non-lithium base (Table 5.2).
Table 5.2. Screening of bases for the halogen dance reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>equiv</th>
<th>solvent</th>
<th>temp</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>1.5</td>
<td>THF</td>
<td>-78 °C</td>
<td>2.7 (35%), 5.22 (31%)</td>
</tr>
<tr>
<td>2</td>
<td>KHMDS</td>
<td>1.5</td>
<td>THF</td>
<td>-78 °C</td>
<td>no rxn</td>
</tr>
<tr>
<td>3</td>
<td>NaNHMDS</td>
<td>1.5</td>
<td>THF</td>
<td>-78 °C</td>
<td>no rxn</td>
</tr>
<tr>
<td>4</td>
<td>NaNH₂</td>
<td>3.0</td>
<td>DMF</td>
<td>0 °C</td>
<td>no rxn</td>
</tr>
<tr>
<td>5</td>
<td>NaNH₂</td>
<td>1.5</td>
<td>NH₃</td>
<td>-78 °C</td>
<td>no rxn</td>
</tr>
<tr>
<td>6</td>
<td>KH</td>
<td>2.0</td>
<td>THF</td>
<td>0 °C</td>
<td>no rxn</td>
</tr>
<tr>
<td>7</td>
<td>KDA</td>
<td>1.5</td>
<td>THF</td>
<td>-78 °C</td>
<td>5.24 (46%), 5.22 (54%)</td>
</tr>
<tr>
<td>8</td>
<td>n-BuLi</td>
<td>1.0</td>
<td>THF</td>
<td>-78 °C</td>
<td>5.22 (98%)</td>
</tr>
</tbody>
</table>

Very quickly it was obvious that not any base could promote the halogen dance reaction. The various HMDS bases (entries 2 and 3) were not basic enough to deprotonate the oxazole and NaNH₂ either in DMF (entry 4) or liquid ammonia (entry 5) also failed to give any product. KH in THF (entry 6) gave no reaction either, possibly due to the insoluble nature of KH. It therefore seemed like LDA was the only base with the right pKa for this reaction. While LDA is the most used diisopropylamide, KDA can also be prepared. Unfortunately KDA is usually prepared in situ by mixing LDA and KOt-Bu also generating LiOt-Bu in the process. This could explain the disappointing result obtained with KDA. Finally, just to help prove the mechanism, the reaction was performed using n-BuLi, a strong lithium base, and the reduced oxazole 5.22 was obtained in quantitative yield.
Still trying to find a way to generate 4-iodooxazole in higher yields and seeing how efficient \(n\)-BuLi was at effecting lithium-halogen exchange, generating 4-iodooxazole 2.7 from easily accessible 4-bromooxazole 5.25 seemed plausible (Scheme 5.19). The reasoning was that treating 4-bromooxazole with \(n\)-BuLi should generate the 4-lithio species which could then be quenched with I\(_2\) to afford the desired 4-bromooxazole. Unfortunately, after running the reaction none of the desired 4-iodooxazole was isolated. Instead 5-iodooxazoles 5.24 and 5.35 were isolated in 42% and 39% respectively.

With hindsight, this result could have been predicted. Indeed after lithium-bromine exchange, the resulting 4-lithiooxazole will rapidly isomerize to the more stable 5-lithiooxazole. From there, quenching with iodine gives 5-iodooxazole 5.24. Oxazole 5.35 is obtained by simply deprotonation of the starting material at the C5 position followed by quenching with I\(_2\).

![Scheme 5.19. Attempted synthesis of 5.26 from 5.25.](image)

Upon searching for a more efficient way to make the 4-iodooxazole, we were still bringing up material using the low-yielding halogen dance. While large amounts of reduced oxazole were recovered and could be reused to make more desired product, it
was still a two-step process involving iodination followed by halogen dance reaction. One of the ideas was to try to quench the reaction with iodine in order to recover the 5-iodo instead of the fully reduced oxazole. Unfortunately, it was extremely hard to control regioselectivity and the amount of iodine to add. Moreover the 4-iodooxazole 2.7 and 4,5-diiodooxazole 5.31 were chromatographically very challenging to separate leading to mixtures of the two products. Therefore upon quenching the reaction with excess iodine both 5-iodooxazole 5.24 and 4,5-diiodooxazole 5.31 were isolated in an overall good yield (Scheme 5.20).

Scheme 5.20. Attempt to recycle the reduced oxazole.

With the diiodooxazole 5.31 in hand a direct conversion to the desired 4-iodooxazole 2.7 was attempted. To our delight, treatment of 5.31 with 1 equivalent of n-BuLi cleanly and quantitatively afforded the 4-iodooxazole 2.7. Indeed, removal of the iodide that gives the most stable anion takes place, as planned (Scheme 5.21).
Conversion of the diiodo to the 4-iodooxazole.

From this very encouraging result we set out to make diiodooxazole 5.31 in an efficient manner from the reduced oxazole. Unfortunately, using conditions known to polyiodinate imidazoles, the desired 4,5-diiodooxazole could not be synthesized. Indeed treating oxazole 5.22 with NIS in CH$_2$Cl$_2$ gave only 5-iodooxazole 5.24 (Scheme 5.22). While this was an interesting result as it gave a milder method of forming 5-iodooxazole, it did not produce the desired diiodinated product. To this date we have still not been able to produce 4,5-diiodooxazole from reduced oxazole.

During the search for a higher yielding halogen dance reaction, it became clear that 5-bromooxazole 5.23 underwent the rearrangement considerably faster and more selectively than 5-iodooxazole 5.24. From this observation, using 5.23 as a catalyst in the
HD reaction to avoid the undesired lithium-halogen exchange was attempted. Indeed when 5-bromooxazole 5.23 was added in 5 to 10 mol % (Table 5.3, entries 2-3) to the reaction, the jump in yield was dramatic, almost doubling when 10 mol % was used.

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>5.23 (mol %)</th>
<th>M</th>
<th>Add'n time (min)</th>
<th>2.7 (% yield)</th>
<th>5.25 (GC area %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.1</td>
<td>10</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>0.1</td>
<td>10</td>
<td>58</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>0.1</td>
<td>10</td>
<td>71</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0.05</td>
<td>45</td>
<td>64</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>0.05</td>
<td>45</td>
<td>79</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>0.05</td>
<td>45</td>
<td>85</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 5.3. Iodooxazole dance reaction results.

This dramatic difference can be explained by looking at the mechanism when bromooxazole is added in catalytic amount (Scheme 5.23). Since 5-bromooxazole 5.23 is far more reactive than 5-iodooxazole 5.24 with LDA, the deprotonation step should be selective for the bromooxazole (this implies that the 4 position of 5.23 is more acidic than the 4 position of 5.24). Indeed, upon slow addition of LDA to a mixture containing 10 mol % of 5.23, selective deprotonation occurs at the C4 position of 5.23 to generate lithio species 5.26. This molecule can then react with the much more abundant 5-
iodooxazole 5.24 via lithium-halogen exchange to provide 4-iodo-5-bromooxazole 5.37 along with lithio species 5.28. Finally, a second lithium-halogen exchange between the two newly formed species affords the desired 4-iodooxazole 2.7 and regenerates 5-bromooxazole 5.23. This molecule can then be deprotonated again and continue the reaction cycle until all of 5.24 is consumed.

Scheme 5.23. Halogen dance reaction mechanism with catalytic 5.23.

At this point 5.26 would react with another molecule of 5.23 to eventually give 10 mol % of 4-bromooxazole. In an attempt to further increase the yield of desired
product, the LDA solution was diluted twice and added over a much longer period of time (Table 5.3, entries 4-6). Once again the yields were greatly improved. Not only was the yield of the non-catalyzed reaction almost doubled, but the reaction with 10 mol % 5-bromo 5.23 saw its yield move up to 81% which is close to those obtained with 5-bromooxazole. GC follow-up of these three optimized sets of conditions allowed us to plot the amount of each species in solution over the time of the addition. Chart 5.1 shows the amount of all three molecules present during a standard HD reaction on 5-iodooxazole 5.24.

Chart 5.1. HD reaction GC follow-up.
Chart 5.2 and Chart 5.3 show the amount of all 5 molecules present during the HD reaction of 5-iodooxazole 5.24 with 5 and 10 mol % 5-bromooxazole 5.23 present respectively.

![Chart 5.2](image)

Chart 5.2. HD reaction GC follow-up (with 5 mol % 5-bromooxazole).
To better understand the role of 5-bromooxazole 5.23 in the reaction and further expand our knowledge of the mechanism, a scrambling experiment was designed (Scheme 5.24).

Oxazole 5.38 was prepared to be used as a labeled base in the HD reaction of 5.24. Upon treating a mixture of oxazoles 5.38 and 5.24 with LDA, 5.38 would react selectively to give the corresponding lithiated species which in turn would react with 5.24 to generate 5-lithiooxazole 5.28 and iodobromo 5.40. These two molecules would then further react together to afford the labeled 4-iodooxazole 5.42 along with a molecule of 5.23. Oxazole 5.23 would then enter the previously described cycle to afford 5.26. In the end, the reaction should produce oxazole 2.7 along with 10 mol % of 5.42 and 10 mol % of 5.25.
Scheme 5.24. Scrambling experiment mechanism.
After running the reaction with 10 mol % of 5.38 and carefully monitoring by GC, 7% of both 5.42 and 5.25 were obtained, which is in good agreement with the expected results (Table 5.4).

![Reaction Diagram]

Table 5.4. Scrambling reaction results.

<table>
<thead>
<tr>
<th></th>
<th>10%</th>
<th>9%</th>
<th>7%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected Yield</td>
<td>10%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Experimental GC Yield</td>
<td>7%</td>
<td></td>
<td>7%</td>
</tr>
</tbody>
</table>

The GC monitoring also allowed to see the amount of all the different molecules present during the scrambling experiment (Chart 5.4). The large amount of reduced oxazole formed in this reaction was due to the fact that the LDA was added over a much shorter period of time.
In summary, by an in-depth study of the reaction mechanism, the yield of the halogen dance reaction of 5-iodooxazole to 4-iodooxazole has been dramatically increased. The key aspects of this improvement were the use of catalytic amounts of 5-bromooxazole as an additive along with dilution and slow addition of the LDA solution to the reaction.
Chapter 6

FORMATION OF THE MACROLIDE

6.1 Introduction

With all the fragments of the macrolactone synthesized, all that was left was to assemble them into macrolide 6.1. The steps involved in this sequence were coupling at both the 2 and 4 positions of the oxazole and macrolactonization (Scheme 6.1).

Scheme 6.1. Envisioned synthesis of the macrolide of leiodelide A.
While coupling reactions, due to the use of catalytic amounts of transition metals, are usually run at higher concentrations, the closing of the macrolide, an intramolecular process, would need to be run at very high dilutions to avoid any possible competing intermolecular processes. With these observations in mind, it was clear that the northern and southern pieces would first be coupled to the oxazole and the esterification would be kept for the closing of the macrolide.

### 6.2 Southern Coupling

The 2-thiobutyl-4-halooxazole system allowed to do selective couplings, but the 4-halo position would always be more reactive and therefore needed to be coupled before any chemistry could be done at the 2 position. As mentioned earlier, quite some time was originally spent attempting to get the coupling to work on the TBS protected version of the southern half (Scheme 6.2).

![Scheme 6.2. Coupling of the TBS protected southern part.](image)

The conditions attempted involved a palladium catalyst (PdCl₂(PPh₃)₂, PdCl₂(CH₃CN)₂, PdCl₂(PhCN)₂, Pd(dba)₂ + P(2-furyl)₃) along with an additive (ZnCl₂, ...
LiCl, CuCl, KF, CsF) in various solvents (DMSO, DMF, PhMe). At first the reactions were run on the 4-bromooxazole **5.25** due to its easier and higher yielding synthesis. After seeing no reaction with all the conditions tried, the more reactive 4-iodooxazole **2.7** was used. Unfortunately, the reaction again yielded no product whatsoever. It was only once a model study was performed on a simplified substrate that the importance of not having the bulky TBS group present became evident (Scheme 6.3). Indeed, using TBS protected model **6.3**, under a wide variety of conditions, no product was obtained. When switching to the unprotected version **6.5**, product was immediately formed and eventually conditions were optimized to give the coupled product in 62% yield.

Scheme 6.3. Effect of the TBS group on the southern coupling.

With this positive result obtained we decided to return to the bromooxazole, reasoning that maybe the TBS group was also the culprit in the bromooxazole coupling.
Unfortunately, when submitting bromooxazole 5.25 to the two best set of conditions, none of the desired product 6.7 was obtained (Scheme 6.4).

![Scheme 6.4. Coupling with 4-bromooxazole 5.25.](image)

Eventually the southern part and the oxazole were successfully coupled by using the unprotected southern part 2.8 with 2-thiobutyl-4-iodooxazole 2.7 in 61% yield (Scheme 6.5). The reaction could be scaled up to 1 g without loss of yield. Finally, TBS protection of the secondary alcohol of 6.7 delivered the fully protected southern half of leiodelide A 6.2. Unfortunately the TBS protection of allylic alcohol 6.7 was much lower yielding than previously with related substrate 2.8 (Scheme 4.2). Menche, during his synthesis of etnangien, had similar problems on a comparable substrate.\textsuperscript{139} Switching from 2,6-lutidine to proton sponge allowed a jump in yield from 52% to 87%. Alternatively TBSCI, although less reactive might allow for higher yield as has been shown before.\textsuperscript{140} Unfortunately due to time constraints, these modified conditions were not attempted on this substrate.
With the coupling at the 4-position established attention was moved to the coupling at the 2 position.

### 6.3 Formation of the Zinc Reagent

The northern half primary bromide 2.6 needed to be converted into the corresponding alkyl zinc bromide reagent in order to be coupled to the oxazole. Organozinc reagents have been used extensively in organic chemistry in cross-coupling and conjugate addition reactions.\(^{141}\) They are considered a milder alternative to the more reactive Grignard reagents. Their high-yield preparation, functional group tolerance, high-yielding reactions and stereoselectivity when used with chiral catalysts make them reagents of choice in organic synthesis. While there are many methods for preparing zinc reagents, starting from an alkyl bromide left only two possible options: direct oxidative zincation or formation of the Grignard/lithium species followed by transmetallation. In this case, the direct oxidative zincation seemed to make more sense and was therefore the chosen method.
Considering the ease in which zinc reagents are usually made, standard conditions used in our group were initially followed to make the zinc reagent of the northern half. The zinc dust was activated using TMSCl and dibromoethane and following addition of the alkyl bromide and stirring overnight, no reaction was observed (Scheme 6.6). Realizing that this reaction would be less trivial than originally planned a simpler model was preferred in order to develop an efficient manner of making the zinc reagent.

Scheme 6.6. Attempted formation of the northern part zinc reagent 6.8.

The model chosen for this study was 1-bromodecane 6.9 (Figure 6.1). Not only was this molecule cheap and commercially available, but it was also similar enough to substrate 2.6 and easily monitored by GC. Indeed GC monitoring of this reaction was the only quantitative way to assess formation of the zinc reagents.

Figure 6.1. Northern part and test model.
Since the TMSCl/1,2-dibromoethane activation method had not worked on the northern part, alternatives for activating the zinc were looked at. The addition of iodine is another commonly used method for activating Zn before making organozinc reagents. In addition, Knochel has shown that LiCl can greatly accelerate the formation of organozinc compounds.\textsuperscript{142a} A screen of different possible activation methods was therefore undertaken (Table 6.1). Again, 1,2-dibromoethane/TMSCl gave only trace amounts of desired product (entry 1). Trying to activate the zinc by sonication (entry 2) was a complete failure. Adding LiCl (entry 3) showed a clear increase in formation of product, but it was only once I\textsubscript{2} was added (entry 4) that the yields became synthetically useful. Clearly LiCl is needed along with I\textsubscript{2} as once it is removed (entries 5-6) the yields immediately drop. Finally, it was found that the 1,2-dibromoethane and TMSCl were not needed and that using 1.1 equivalents of LiCl along with catalytic amounts of I\textsubscript{2} gave the best results (entry 7).
While screening zinc activation reactions, it became evident that the solvent used to quench the reactions had a huge impact on the outcome of the GC chromatogram. These reactions should be extremely clean resulting in either starting material (no reaction), decane (zinc formation followed by quenching) or mixtures thereof, but sometimes multiple unidentifiable peaks would be observed depending on the solvent used to quench the reaction (Table 6.2). Eventually it was found that MeOH (entry 3) was the only solvent that would give clean and reproducible yields of formed products. Water or aqueous solutions (entries 1-2) would form other minor products upon quenching, while CH$_2$Cl$_2$ would result in a majority of other peaks (entry 4).

### Table 6.1. Screening of zinc activation methods.

<table>
<thead>
<tr>
<th>entry</th>
<th>(BrCH$_2$)$_2$ (equiv)</th>
<th>TMSCl (equiv)</th>
<th>LiCl (equiv)</th>
<th>I$_2$ (equiv)</th>
<th>[THF]</th>
<th>yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.15</td>
<td>0.05</td>
<td>0</td>
<td>0</td>
<td>0.5 M</td>
<td>5%</td>
</tr>
<tr>
<td>2$^b$</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.5 M</td>
<td>no rxn</td>
</tr>
<tr>
<td>3</td>
<td>0.15</td>
<td>0.05</td>
<td>1.1</td>
<td>0</td>
<td>1 M</td>
<td>15%</td>
</tr>
<tr>
<td>4</td>
<td>0.15</td>
<td>0.05</td>
<td>1.1</td>
<td>0.1</td>
<td>1 M</td>
<td>75%</td>
</tr>
<tr>
<td>5</td>
<td>0.15</td>
<td>0.05</td>
<td>0</td>
<td>0.1</td>
<td>1 M</td>
<td>no rxn</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
<td>1 M</td>
<td>2%</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
<td>1.1</td>
<td>0.1</td>
<td>1 M</td>
<td>98%</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0</td>
<td>1.1</td>
<td>0</td>
<td>1 M</td>
<td>7%</td>
</tr>
</tbody>
</table>

$^a$GC % of decane after quenching in MeOH. $^b$Zn sonicated for 30 min.
Another aspect that needed to be improved on for the formation of the zinc reagent was the concentration at which the reaction is run. Indeed these reactions are usually run at relatively high concentrations such as 1-2 M. While this is not an issue when running the reaction on a large scale with low molecular weight, cheap, commercially available halides such as iodobenzene, it becomes more of a problem when the bromide requires more than 10 steps to synthesize and is only available in hundreds of milligram quantities. With this issue in mind, various combinations of concentrations and temperature were screened to find that the concentration could safely be lowered to a much more manageable 0.5 M without loss of yield as long as the temperature was raised to 65 °C (Table 6.3, entry 4).

Table 6.2. Effect of quench on zinc formation.

<table>
<thead>
<tr>
<th>entry</th>
<th>quenching agent</th>
<th>product</th>
<th>SM</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O</td>
<td>73%</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>2</td>
<td>sat. aq. NH₄Cl</td>
<td>73%</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>86%</td>
<td>14%</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>34%</td>
<td>13%</td>
<td>53%</td>
</tr>
</tbody>
</table>
Finally, the last aspect that needed improvement was the activation sequence. While the published procedure calls for a drying of the LiCl at 150 °C for 20 min followed by adding the Zn and redrying at 150 °C for 20 min and finally heating the reaction at 60 °C for 20 min once the THF and I₂ had been added, it was found that these tedious steps were superfluous. As long as the Zn and LiCl were dry and used from a glovebox, the yields obtained were identical when heated or not (Table 6.4).

Table 6.3. Effect of concentration and temperature.

<table>
<thead>
<tr>
<th>entry</th>
<th>[THF]</th>
<th>T</th>
<th>Product</th>
<th>SM</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 M</td>
<td>45 °C</td>
<td>91%</td>
<td>9%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>0.5 M</td>
<td>45 °C</td>
<td>87%</td>
<td>13%</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>1 M</td>
<td>65 °C</td>
<td>94%</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>4</td>
<td>0.5 M</td>
<td>65 °C</td>
<td>97%</td>
<td>3%</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 6.4. Effect of heating on activation of zinc.

<table>
<thead>
<tr>
<th>entry</th>
<th>Zn + LiCl heated</th>
<th>I₂ heated</th>
<th>Product</th>
<th>SM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>250 °C</td>
<td>60 °C</td>
<td>95%</td>
<td>5%</td>
</tr>
<tr>
<td>2</td>
<td>250 °C</td>
<td>-</td>
<td>96%</td>
<td>4%</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>60 °C</td>
<td>96%</td>
<td>4%</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-</td>
<td>95%</td>
<td>5%</td>
</tr>
</tbody>
</table>
With this careful study of the formation of an organozinc reagent an optimized set of conditions had been established. These conditions developed on 1-bromodecane were then applied to the desired substrate, the northern part 2.6. Delightfully, the method developed transferred extremely well to this substrate and showed >90% product by GC after 12 h (Scheme 6.7).

![Scheme 6.7. Formation of the zinc reagent of the northern part.](image)

### 6.4 Northern Coupling

With the organozinc reagent in hand we started looking at coupling of the northern and southern halves. After some initial failed attempts the two pieces were successfully attached together (Scheme 6.8).
Although the yield was low at first (13%) it was later improved to 37% by using more rigorously dry conditions. Unfortunately, due to lack of material no other sets of conditions were attempted for this reaction and only the conditions published in our group’s methodology paper were used.\textsuperscript{10} A variety of other conditions will be tested once more material is brought back up.\textsuperscript{143}

6.5 Formation of the seco-acid and Mitsunobu cyclization

The small amount of material of \textbf{6.11} obtained from the Negishi coupling was pushed forward. In order to get to the seco-acid, the TES group had to be removed and the ethyl ester saponified to the acid. To avoid having to carry a highly polar carboxylic acid over multiple steps, the deprotections were done in this order. To remove the secondary TES group in the presence of a secondary TBS group, HF•pyr buffered with pyridine had to be used (Scheme 6.9).\textsuperscript{144} Complete selectivity was observed and the TBS group remained
untouched. Finally, the hydroxy ester 6.12 was converted to the seco-acid 6.13 by saponification with LiOH•H₂O.

Scheme 6.9. Formation of the seco-acid.

With the seco-acid in hand, the closed macrolide was only one step away. The current configuration at C17 necessitated a closing of the macrolide with inversion of stereochemistry. This type of reaction, the Mitsunobu macrolactonization, is frequently done in natural product synthesis often resulting in high yields of the macrolactone.¹⁹,¹⁴⁵ The disappointment was therefore even greater when realizing that the product formed from submitting the seco-acid to standard Mitsunobu conditions (DIAD, PPh₃, PhMe)
was not the desired lactone. Instead, what is thought to be DIAD acylated product 6.15 was formed (Scheme 6.10).

![Scheme 6.10. Attempted closing of the macrocycle via Mitsunobu conditions.](image)

Examples of formation of this kind of product in the literature are actually numerous. Evans, in his synthesis of lonomycin A had similar problems that were solved by switching from DEAD in THF to DIAD in PhMe. Unfortunately these were already the conditions employed for our substrate. Looking further in the literature, two other examples clearly stood out to us. The first one comes from the synthesis of palmerolide A by the Nicolaou group (Scheme 6.11).
As seen in Scheme 6.11, after experimenting with numerous conditions the best result obtained by the Nicolaou group was a 31% yield accompanied with 34% of DEAD acylated dehydrated product 6.19. Although they were able to obtain the desired product, the yield in which it was obtained was obviously very disappointing. The second example is taken from the synthesis of rhizoxin D by the Leahy group (Scheme 6.12).
Here a 16-membered ring was again envisioned being closed with inversion of configuration via Mitsunobu macrolactonization, but unfortunately only amide formation was observed. The authors mention that a wide variety of solvents (benzene, toluene, THF), diazocarboxylates (DEAD, DIAD, ADDP) and order of addition of reagents was screened but product 6.21 was always the major product formed. Eventually significant revision of the synthesis had to be undertaken in order to close the ring without inversion.

The main problem about designing a synthesis with a Mitsunobu macrolactonization step is that in the event the reaction fails, very few alternatives are available. Moreover
stereochemistry is often set early on in the synthesis which usually means redesigning the synthesis over multiple steps.

In our case, before redesigning the synthesis to invert the alcohol at C17, we tried looking more in depth at the mechanism and if there was a way to obtain the desired product. The classical Mitsunobu macrolactonization mechanism is shown in Scheme 6.13.

![Scheme 6.13. Mechanism of the Mitsunobu macrolactonization.](image)

In the first reaction, the seco-acid had been added dropwise to a mixture of PPh₃ and DIAD. While this order of addition is well suited for intermolecular reactions, in the case of an intramolecular macrolactonization, this order is not ideal. Indeed as seen in Scheme
6.14 when PPh₃ and DIAD are premixed they form intermediate 6.23. Upon dropwise addition of the seco-acid, deprotonation takes place as in the regular Mitsunobu mechanism, but considering the abundance of 6.23 compared to the seco-acid, the carboxylate will attack the triphenylphosphonium moiety to afford intermediate 6.29. This reaction will be even more prominent when the alcohol is sterically hindered. Finally, the generated amide 6.30 will displace Ph₃PO providing side-product 6.31.

In order to avoid this type of mechanism the order of addition can be changed to addition of the azodicarboxylate dropwise last. With this order of addition, there is no accumulation of 6.23 and therefore should not be any formation of undesired 6.31. When
switching to these conditions, formation of the DIAD acylated product was completely suppressed, but unfortunately still none of the desired product was formed. What was isolated was a product whose mass was that of the seco-acid•PPh₃. The structure of this product was probably a mixture of 6.32 and 6.33, which have been shown to coexist in equilibrium.¹⁴⁹

![Scheme 6.15. Possible formed product.](image)

With this result, it seemed obvious that the alcohol was most certainly too hindered for the Mitsunobu reaction to take place. While the steric hindrance around the alcohol could not be reduced, switching to smaller phosphines in the hope that the carboxylate would now have enough room to displace the phosphine oxide was the other option. Unfortunately neither Pₙ-Bu₃ nor PMe₃ gave any product both in PhMe and THF.

The reasoning behind this absolute lack of reactivity is the steric hindrance around the alcohol. Not only is it a relatively sterically hindered secondary alcohol, but it is also part of a six membered ring in a 1,4 position with respect to the gem-dimethyl group. The molecule exists therefore in two major chair conformations (Figure 6.2). The first
conformation, 6.34 places one of the methyl groups along with the rest of the molecule both axial and 1,3 to each other, which will make it much less favorable. The other more favorable conformer 6.35 removes all 1,3-strain, but places a methyl group axial 1,4 anti to the leaving group which will certainly block the displacement by the carboxylate. Therefore it seems that this system is less than ideal for a Mitsunobu macrolactonization.

![Figure 6.2. Problematic system.](image)

Finally, the last observation that can be made is that when comparing both Nicolaou’s and Leahy’s systems to ours, in all cases the alcohol was secondary and sterically hindered and the carboxylic acid was conjugated (Figure 6.3).
6.6 **Yamaguchi closing of the macrolide**

After giving up on the Mitsunobu reaction, the small amount of material left was closed via Yamaguchi lactonization. Although the product formed would not have the required configuration, it would still give some valuable insight. Also, since the attribution of stereochemistry was not definitive and considering the problems Fürstner had with leiodelide B, it would just be more information for the leiodelide puzzle.⁹

Using standard conditions (2,4,6-trichlorobenzoyl chloride, Et₃N, DMAP) the desired product 6.37 was only obtained in 10% yield (Scheme 6.16).
While this result was very disappointing, lack of material prevented optimization. Nevertheless, full characterization of the obtained product allowed to conduct spectroscopic data comparison with the reported values of leiodelide A (Figure 6.4). Obviously the two compounds 1.1 and 6.37 are noticeably different and comparison of the two can only give qualitative ideas at best. When looking at the differences in chemical shifts between the two, some trends come out. First of all, the C1-C10 fragment, which corresponds to the southern half and the oxazole, correlates relatively well with the natural product ($\Delta \delta < 1.6$ ppm) with the exception of C2 which could arise from the inverted C17. This would tend to prove that the assignment of C4 and C5, even though deemed “tenuous” by Fenical, would be correct. Second, carbons 11 through 15 and 20, which encompass the undefined C13 stereocenter, are all very different ($1.6$ ppm $\leq \Delta \delta \leq 6.3$ ppm) from the natural product. This would tend to prove that the C13 stereochemistry is actually opposite to the epimer carried on. Finally, C16, C17 and C21 are all much different ($\Delta \delta > 2.5$ ppm) from the natural product which was expected due to C17 being inverted.
With these observations, the new target was defined to be macrolide 6.38 where C13 would be inverted and the macrolide would be closed with the correct stereochemistry (Figure 6.5).
In order to make macrolide 6.38, the C17 stereocenter needed to be inverted. To avoid a total redesign of the synthesis (the configuration at C17 is derived from D-xylose, the very first starting material) and to make use of the material brought up, it seemed that the latest intermediate on which the inversion could be made was the product of the Wittig reaction 3.48. The first step would be to unmask the alcohol in order to invert it. Removal of the TES group from 3.48 with HF•pyr delivered alcohol 6.39 in 79% yield (Scheme 6.17).

Scheme 6.17. Deprotection of the TES group from 3.48.
With the alcohol in hand, the first idea was to try an intermolecular Mitsunobu inversion. Even if the intramolecular reaction had been a failure we were hoping that forcing the intermolecular with a more reactive acid could solve the problem. Unfortunately, using $p$-nitrobenzoic acid with $\text{PPh}_3$ and DIAD, once again none of the epimeric ester was obtained (Scheme 6.18).


This negative result left us with an oxidation/reduction sequence as only other option. Oxidation of the secondary alcohol to the ketone was first tried using DMP conditions, but only trace amounts of the desired ketone were formed. Switching to PDC gave only marginally better results. Fortunately Swern oxidation afforded the desired ketone 6.42 in 85% yield (Scheme 6.19).
With the alcohol in hand all that was left was to find a suitable reducing agent that would afford the desired epimeric alcohol.
A screen of multiple reducing agent showed that NaBH₃CN was the best, affording almost a 3:1 ratio of desired to undesired epimer.¹⁵⁴
6.8 Future Work

Future work in the total synthesis of leiodelide A will begin by generating bromide 6.44 (Scheme 6.20). From alcohol 6.43 this bromide would be easily generated in 3 steps which have already been optimized on the diastereomer. From there, formation of the organozincate 6.45 using our developed conditions will allow screening of different sets of conditions to attach the southern and northern pieces together. With the alcohol in the correct configuration for the ring closing step in 6.46, many more options will now be available to us. The first route that will be attempted will be to use Otera’s catalyst 6.48 to close hydroxy ester 6.47 to the desired macrolide. This catalyst has been shown to affect macrocyclization of hydroxy-esters in decent yields and would allow to cut a step as well as avoid making the very polar seco-acid. In the event that this ambitious reaction failed, we would fall back onto more traditional methods involving saponification of the ester and macrolactonization using the Yamaguchi or related methods.
Scheme 6.20. Initial future work in the synthesis of leiodelide A.
With macrolide \textbf{6.38} in hand, the following step will involve removal of the acetonide to the diol \textbf{6.49} (Scheme 6.21). From this diol, two different routes to desired lactone \textbf{2.3} can be imagined. The first route will involve selective oxidation of the primary alcohol to the aldehyde,\textsuperscript{67} followed by TES protection of the remaining secondary alcohol. While this route seems relatively safe and straightforward, selectivity of the oxidation along with stability of the aldehyde could be potential problems. An alternate route will be to TES protect both alcohols followed by oxidation of the primary silyl ether to the aldehyde under Swern conditions. This sequence was first reported by Miftahkov\textsuperscript{157} on Corey aldehyde related compounds and later expanded by Spur\textsuperscript{158} on a wide variety of diols. It has since been applied to the synthesis of a multitude of natural products\textsuperscript{159} and most notably by the Wipf group during the synthesis of disorazole C1 in which the same three-step sequence (acetonide removal, TES protection, selective oxidation) was accomplished in high overall yield.\textsuperscript{160} Muzart also reviewed oxidative deprotections of silyl ethers.\textsuperscript{161} Finally, the side chain will be appended onto the macrolide on small scale using both sulfone \textbf{6.52} and phosphonate \textbf{6.53} derived from \textbf{2.18} and \textbf{2.26} respectively. Whichever affords the highest \((E):(Z)\) ratio will be used for scale up. An ultimate global deprotection step to remove all four silyl protecting groups will deliver leiodelide A \textbf{1.1}. 

133
Scheme 6.21. Final future work on leiodelide A.
6.9 Conclusion

The synthesis of an isomer of the leiodelide A macrolide has been completed along with two different versions of the side chain.

Both a Julia-Kocienski and a Horner-Wadsworth-Emmons version of the side chain have been synthesized in seven and nine steps respectively with good overall yields. These two substrates will allow screening of conditions in order to get the best \((E):(Z)\) ratio possible in a crucial penultimate olefination step.

The C1-C7 southern fragment of leiodelide A has been synthesized in a very efficient and high yielding three-step protecting-group free synthesis from known starting material after four distinct syntheses.

The synthesis of the C11-C17 northern fragment has been accomplished in nine steps from cheap and abundant D-xylose. Along the way a difficult hydrogenation/benzyl deprotection sequence was solved by careful observations and logical reasoning.

In order to produce sufficient quantities of required 4-iodo-2-thiobutyloxazole from the corresponding 5-iodo analog, the halogen dance reaction mechanism was thoroughly investigated and resulted in a dramatic increase in yield.

Finally, all the aforementioned pieces were combined and carried on to an isomer of the macrolide of leiodelide A. The spectroscopic data obtained from it nevertheless gave us insightful knowledge with respect to the structure of leiodelide A. Efforts toward the total synthesis and absolute configuration determination of leiodelide A are currently ongoing in the Stambuli research group.
Chapter 7

Experimental Details

Materials and Methods. Unless stated otherwise, reactions were conducted in oven-dried glassware under an atmosphere of nitrogen using anhydrous solvents. Dichloromethane, diethyl ether, toluene and tetrahydrofuran were obtained from a dry solvent system (activated alumina columns) and used without further drying. Triethylamine and diisopropylamine were freshly distilled over calcium hydride prior to use. $n$-Butyllithium was purchased from Acros and standardized by titration with menthol/2,2'-bipyridine. All other commercially obtained reagents and solvents were used as received. Thin-layer chromatography (TLC) was conducted with SiliCycle glass backed 60 Å UV254 plates (0.25 mm) and visualized using UV lamps and KMnO$_4$ or ceric ammonium molybdate (CAM) stain followed by heating. Flash chromatography was performed using normal phase Aldrich 40-63 μm 60 Å silica gel. $^1$H and $^{13}$C spectra were taken in CDCl$_3$ on 400 or 500 MHz Bruker spectrometers. Chemical shifts are
reported in parts per million relative to TMS (\(\delta 0.00\)) for \(^1\)H and relative to CDCl\(_3\) (\(\delta 77.16\)) for \(^{13}\)C. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, sep = septet, m = multiplet, br = broad), coupling constant, integration. Melting points were recorded on a Laboratory Devices Inc. Mel-Temp II capillary melting point apparatus and are uncorrected. Optical rotations were recorded on a PerkinElmer 241 polarimeter at the sodium D line (589 nm) and reported as follows: concentration (\(c\) in g/100 mL), solvent. IR spectra were recorded on a PerkinElmer Spectrum RX1 FTIR spectrometer. High-resolution mass spectra were obtained on a Bruker MicrOTOF II instrument from the mass spectrometry facility at The Ohio State University.
2-(pent-4-yn-2-ylthio)benzo[d]thiazole (2.12′)

To a solution of **2.12** (0.5 g, 5.95 mmol) in THF (50 mL) were added **PPh₃** (2.2 g, 8.33 mmol, 1.4 equiv) and **BTSH** (1.3 g, 7.74 mmol, 1.3 equiv) at rt. The reaction mixture was then cooled to 0 °C and **DIAD** (1.9 g, 9.52 mmol, 1.6 equiv) was added dropwise (formation of a yellow precipitate) The resultant mixture was warmed to rt and stirred 4 h then concentrated *in vacuo*. Purification by flash chromatography (silica gel, 15% EtOAc/hexanes) gave **2.12′** (1.36 g, 98%) as a pale yellow oil.

**1H NMR** (400 MHz, CDCl₃, δ): 1.59 (d, *J* = 7.0 Hz, 3H), 2.10 (t, *J* = 2.8 Hz, 1H), 2.78 (m, 2H), 4.19 (m, 1H), 7.28 (dt, *J* = 8.0, 1.3 Hz, 1H), 7.40 (dt, *J* = 7.3, 1.3 Hz, 1H), 7.73 (d, *J* = 7.0 Hz, 1H), 7.87 (dd, *J* = 8.8, 0.8 Hz, 1H); **13C NMR** (100 MHz, CDCl₃, δ): 19.7, 26.5, 42.0, 71.0, 80.6, 120.9, 121.6, 124.3, 125.9, 135.2, 153.2, 165.4; **IR** (thin film) ν<sub>max</sub> (cm<sup>-1</sup>): 3285, 3062, 2975, 2930, 2120, 1469; **HRMS** (ESI): calcd for C₁₂H₁₁NS₂ [M+Na]<sup>+</sup>: 256.0231, found 256.0238.

**2-(pent-4-yn-2-ylsulfonyl)benzo[d]thiazole (2.13)**

---

138
To a solution of 2.12' (1.3 g, 5.57 mmol) in CH₂Cl₂ (50 mL) at 0 °C were successively added NaHCO₃ (2.3 g, 27.86 mmol, 5.0 equiv) and m-CPBA (3.0 g, 12.26 mmol, 2.2 equiv). The resulting suspension was maintained 2 h at 0 °C then was left to warm to rt overnight (14 h). The reaction was quenched by addition of sat. aq. NaHCO₃ and extracted with CH₂Cl₂. The organic layer was separated, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 2% EtOAc/hexanes) gave 2.13 (1.3 g, 88%) as a white powder.

¹H NMR (400 MHz, CDCl₃, δ): 1.60 (d, J = 7.2 Hz, 3H), 2.01 (t, J = 2.4 Hz, 1H), 2.65 (ddd, J = 16.8, 10.0, 2.8 Hz, 1H), 3.01 (ddd, J = 16.8, 4.0, 2.8 Hz, 1H), 3.77 (m, 1H), 7.63 (m, 2H), 8.03 (m, 1H), 8.24 (m, 1H); ¹³C NMR (100 MHZ, CDCl₃, δ): 12.6, 19.9, 58.5, 71.6, 78.3, 122.2, 125.6, 127.7, 128.1, 136.9, 152.9, 164.2; IR (thin film) ν max (cm⁻¹): 3288, 3059, 2976, 2933, 2121, 1470, 1324, 1146; HRMS (ESI): calcd for C₁₂H₁₁NO₂S₂ [M+Na]⁺: 288.0129, found 288.0134.

2-((7-methyloct-7-en-4-yn-2-yl)sulfonyl)benzo[d]thiazole (2.14)

A solution of CuI (933 mg, 4.9 mmol, 1.0 equiv) in DMF (40 mL) was prepared in the glovebox. K₂CO₃ (3.4 g, 24.5 mmol, 5.0 equiv), 2.13 (1.3 g, 4.9 mmol) and β-methallyl chloride (2.7 g, 29.4 mmol, 6.0 equiv) were successively added to the stirring mixture at
rt. A color change from white suspension to yellow to green was observed over a few hours. The reaction mixture was stirred overnight (13 h) at rt then was poured into water. The mixture was extracted with Et₂O then the combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 3% EtOAc/hexanes) gave 2.14 (1.28 g, 82%) as a pale yellow oil.

¹H NMR (400 MHz, CDCl₃, δ): 1.60 (d, J = 7.2 Hz, 3H), 1.70 (s, 3H), 2.66 (m, 3H), 2.99 (m, 1H), 3.75 (m, 1H), 4.76 (t, J = 1.2 Hz, 1H), 4.87 (d, J = 0.8 Hz, 1H), 7.62 (m, 2H), 8.02 (m, 1H), 8.22 (m, 1H); ¹³C NMR (100 MHz, CDCl₃, δ): 12.6, 20.2, 21.8, 27.1, 58.9, 76.2, 80.6, 111.4, 122.1, 125.4, 127.5, 127.9, 136.9, 140.2, 152.8, 164.4; IR (thin film) νmax (cm⁻¹): 3444, 3081, 2979, 2937, 2254, 1657, 1553, 1470, 1324, 1147; HRMS (ESI): calcd for C₁₆H₁₇NO₂S₂ [M+Na]⁺: 342.0598, found 342.0583.

(2S)-7-(benzo[d]thiazol-2-ylsulfonyl)-2-methyloct-4-yne-1,2-diol (2.15)

To a 1:1 t-BuOH:H₂O mixture (20 mL) was added K₃Fe(CN)₆ (1.2 g, 3.61 mmol, 2.4 equiv), K₂CO₃ (498 mg, 3.61 mmol, 2.4 equiv), (DHQ)₂PHAL (35 mg, 0.045 mmol, 3 mol %) and K₂OsO₄•2H₂O (3 mg, 0.007 mmol, 0.5 mol %). The suspension was cooled to 0 °C and a solution of 2.14 (480 mg, 1.50 mmol) in THF (2 mL) was added dropwise.
The reaction mixture was kept at 0 °C for 6 h then was left to warm to rt overnight (13 h). The reaction mixture was cooled to 0 °C and Na$_2$SO$_3$ (2.25 g) was added. The resulting slurry was stirred for 30 min and extracted with EtOAc. The combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 66% EtOAc/hexanes) gave 2.15 (451 mg, 85%, 90% ee) as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$, δ): 1.22 (s, 3H), 1.58 (d, $J = 6.8$ Hz, 3H), 2.26 (dd, $J = 16.4$, 2.4 Hz, 1H), 2.37 (d, $J = 16.4$ Hz, 1H), 2.44 (br s, 1H), 2.76 (m, 1H), 2.90 (m, 1H), 3.46 (d, $J = 11.2$ Hz, 1H), 3.52 (dd, $J = 11.2$, 1.2 Hz, 1H), 3.79 (m, 1H), 7.63 (m, 2H), 8.03 (d, $J = 7.2$ Hz, 1H), 8.23 (d, $J = 7.2$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 13.0, 20.2, 23.4, 29.2, 58.4, 68.9, 72.0, 76.9, 79.9, 122.3, 125.6, 127.7, 128.1, 136.9, 152.8, 164.5; IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$): 3360, 2975, 2252, 1470, 1325, 1251, 1150, 1060; HRMS (ESI): calcd for C$_{16}$H$_{19}$NO$_4$S$_2$ [M+Na]$^+$: 376.0648, found 376.0629.

(2S)-7-(benzo[d]thiazol-2-ylsulfonyl)-2-hydroxy-2-methyloct-4-ynoic acid (2.16)

A mixture of 2.15 (300 mg, 0.85 mmol), TEMPO (66 mg, 0.42 mmol, 0.5 equiv), phosphate buffer (pH = 6.7, 6 mL), MeCN (15 mL), H$_2$O (3.5 mL) and NaClO$_2$ (80%, 1.04 g, 9.17 mmol, 6.0 equiv) was heated to 35 °C. A solution of NaClO (6.15% in H$_2$O,
1.1 mL, 0.09 mmol, 0.1 equiv) in H₂O (3 mL) was slowly added to the reaction over 1 h. After 15 h, the mixture was cooled to rt, diluted with CH₂Cl₂ and acidified to pH = 1 with 2 N HCl. Sat. aq. Na₂SO₃ was added, then the organic layer was separated, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 5% MeOH/CH₂Cl₂) gave 2.16 (280 mg, 90% yield) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃, δ): 1.47 (d, J = 1.6 Hz, 3H), 1.55 (d, J = 7.2 Hz, 3H), 2.46 (m, 1H), 2.66 (m, 2H), 2.90 (m, 1H), 3.76 (m, 1H), 7.63 (m, 2H), 8.22 (d, J = 7.6 Hz, 1H), 13C NMR (100 MHz, CDCl₃, δ): 12.7, 20.0, 24.7, 30.8, 58.5, 73.8, 77.7, 78.1, 122.2, 125.4, 127.7, 128.1, 136.8, 152.7, 164.2, 178.7; IR (thin film) ν max (cm⁻¹): 3405, 2936, 2254, 1715, 1472, 1319, 1146; HRMS (ESI): calcd for C₁₆H₁₇NO₅S₂ [M+Na]⁺: 390.0440, found 390.0441.

(2S)-2-(trimethylsilyl)ethyl 7-(benzo[d]thiazol-2-ylsulfonyl)-2-hydroxy-2-methyloct-4-ynoate (2.17)

To a cold solution of 2.16 (100 mg, 0.27 mmol) in TMS-ethanol (3 mL) was slowly added SOCl₂ (60 μL, 0.82 mmol, 3.0 equiv). The resulting mixture was allowed to warm to rt overnight (13 h) and concentrated in vacuo. Purification by flash chromatography (silica gel, 33% EtOAc/hexanes) gave 2.17 (101 mg, 79%) as a pale yellow oil.
\(^1\)H NMR (400 MHz, CDCl\(_3\), \(\delta\)): 0.02 (s, 9H), 0.99 (m, 2H), 1.37 (s, 3H), 1.54 (d, \(J = 7.2\) Hz, 3H), 2.38 (m, 1H), 2.51 (m, 1H), 2.61 (m, 1H), 2.91 (m, 1H), 3.41 (s, 1H), 3.69 (m, 1H), 4.22 (m, 2H), 7.59 (m, 2H), 7.98 (d, \(J = 8.8\) Hz, 1H), 8.19 (d, \(J = 8.8\) Hz, 1H); 
\(^{13}\)C NMR (100 MHz, CDCl\(_3\), \(\delta\)): -1.7, 12.6, 17.3, 20.1, 24.8, 31.0, 58.7, 64.5, 73.5, 77.1, 78.4, 122.2, 125.5, 127.6, 128.0, 136.9, 152.8, 164.3, 175.3; IR (thin film) \(\nu_{\text{max}}\) (cm\(^{-1}\)): 3510, 2955, 2253, 1725, 1470, 1335, 1251, 1150; HRMS (ESI): calcd for C\(_{21}\)H\(_{29}\)NO\(_5\)S\(_2\)Si \([\text{M+Na}]^+\): 490.1149, found 490.1164.

**(2S,Z)-2-(trimethylsilyl)ethyl 7-(benzo[d]thiazol-2-ylsulfonyl)-2-hydroxy-2-methyloct-4-enoate (2.18)**

![Chemical Structure](image)

To a solution of 2.17 (150 mg, 0.32 mmol) in CH\(_2\)Cl\(_2\) (5 mL) was added Pd/BaSO\(_4\) (75 mg, 50 wt %). The heterogeneous solution was placed under 1 atm of H\(_2\) (balloon) and was stirred for 24 h. The reaction mixture was filtered over Celite, washed with CH\(_2\)Cl\(_2\) and the filtrate was concentrated \textit{in vacuo} to afford 2.18 (149 mg, 99%) as a colorless oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\), \(\delta\)): 0.04 (s, 9H), 0.99 (q, \(J = 8.8\) Hz, 2H), 1.35 (d, \(J = 12.4\) Hz, 3H), 1.40 (m, 3H), 2.41 (m, 3H), 2.81 (m, 1H), 3.18 (d, \(J = 16.4\) Hz, 1H), 3.63 (m, 1H), 4.21 (m, 2H), 5.51 (m, 2H), 7.60 (m, 2H), 8.00 (d, \(J = 8.4\) Hz, 1H), 8.21 (d, \(J = 143\))
A solution of CuI (5.9 g, 31 mmol, 1.0 equiv) in DMF (150 mL) was prepared in the glovebox. K$_2$CO$_3$ (21.6 g, 156 mmol, 5.0 equiv), 2.5 (5.0 g, 31 mmol), and β-methallyl chloride (16.9 g, 187.0 mmol, 6 equiv) were added to the mixture at rt. A color change from white suspension to yellow to green was observed over a few hours. The reaction mixture was stirred overnight at rt (13 h) then was poured into water. The mixture was extracted with Et$_2$O then the combined organic layers were washed with brine, dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 5% Et$_2$O/hexanes) gave 2.19 (6.0 g, 90%) as a pale yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$, δ): 1.78 (s, 3H), 2.95 (s, 2H), 4.85 (m, 1H), 4.95 (t, $J = 2.4$ Hz, 2H), 5.01 (t, $J = 0.8$ Hz, 1H), 7.42 (m, 2H), 7.54 (m, 1H), 8.07 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 22.0, 27.4, 53.1, 76.4, 84.5, 111.9, 113.4, 128.3, 129.7, 133.1, 139.9, 165.9; HRMS (ESI): calcd for C$_{14}$H$_{14}$O$_2$ [M+Na]$^+$: 237.0891, found 237.0885.
(S)-5,6-dihydroxy-5-methylhex-2-yn-1-yl benzoate (2.20)

To a 1:1 t-BuOH:H₂O mixture (200 mL) was added K₃Fe(CN)₆ (18.4 g, 56.0 mmol, 2.4 equiv), K₂CO₃ (7.74 mg, 56.0 mmol, 2.4 equiv), (DHQ)₂PHAL (555 mg, 0.7 mmol, 3 mol %), and K₂OsO₄•2H₂O (43 mg, 0.12 mmol, 0.5 mol %). The suspension was cooled to 0 °C and 2.19 (5.0 g, 23.3 mmol) in THF (5 mL) was added dropwise. The reaction mixture was kept for 6 h at 0 °C then was warmed to rt overnight (12 h). The reaction mixture was cooled to 0 °C and Na₂SO₃ (35 g) was added. The resulting slurry was stirred for 30 min, extracted with EtOAc, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 5% MeOH/CH₂Cl₂) gave 2.20 (5.59 g, 97%, 80%ee by HPLC: OD-H column, hexanes:i-PrOH, 90:10, 1.0 mL/min) as a pale yellow oil.

¹H NMR (400 MHz, CDCl₃, δ): 1.27 (s, 3H), 2.52 (m, 2H), 2.94 (s, 2H), 3.49 (d, J = 10.8 Hz, 1H), 3.59 (d, J = 11.2 Hz, 1H), 4.91 (t, J = 2.4 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.57 (m, 1H), 8.05 (dd, J = 8.0, 0.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃, δ): 23.3, 29.2, 53.1, 68.7, 72.2, 76.9, 83.6, 128.4, 129.5, 129.7, 133.2, 166.1; HRMS (ESI): caled for C₁₄H₁₆O₄ [M+Na]⁺: 271.0946, found 271.0953.
(S)-6-(benzoyloxy)-2-hydroxy-2-methylhex-4-ynoic acid (2.21)

A mixture of 2.20 (1.00 g, 4.03 mmol), TEMPO (315 mg, 2.02 mmol, 0.5 equiv), phosphate buffer (pH = 6.7, 25 mL), MeCN (50 mL), H$_2$O (15 mL) and NaClO$_2$ (80%, 2.73 g, 24.16 mmol, 6.0 equiv) was heated to 35 °C. A solution of NaClO (6.15% in H$_2$O, 7.3 mL, 0.63 mmol, 0.15 equiv) in H$_2$O (10 mL) was slowly added over 90 min. After 15 h, the mixture was diluted with CH$_2$Cl$_2$ and acidified to pH = 1 with 2 N HCl. Sat. aqueous Na$_2$SO$_3$ was added and the organic layer was separated, dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 66% EtOAc/hexanes) gave 2.21 (0.91 g, 86% yield) as a white powder.

$^1$H NMR (400 MHz, CDCl$_3$, δ): 1.53 (s, 3H), 2.67 (m, 1H), 2.77 (m, 1H), 4.90 (t, $J = 2.0$ Hz, 2H), 7.43 (m, 2H), 7.56 (m, 1H), 8.04 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 24.8, 31.1, 53.0, 73.7, 78.0, 81.6, 128.4, 129.5, 129.8, 133.3, 166.1, 179.0; HRMS (ESI): calcd for C$_{14}$H$_{14}$O$_5$ [M+Na]$^+$: 285.0739, found 285.0728.
(S)-5-hydroxy-6-methoxy-5-methyl-6-oxohex-2-yn-1-yl benzoate (2.22)

To a solution of 2.21 (500 mg, 1.91 mmol) in methanol (10 mL) at 0 °C was slowly added AcCl (176 μL, 2.48 mmol, 1.3 equiv). The resulting mixture was allowed to warm to rt overnight (13 h) and was subsequently concentrated in vacuo. Purification by flash chromatography (silica gel, 33% EtOAc/hexanes) gave 2.22 (495 mg, 94%) as a colorless oil.

\[^1\text{H}\ \text{NMR (400 MHz, CDCl}_3, \delta): 1.46\ (m, 3H), 2.60\ (m, 1H), 2.71\ (m, 1H), 3.75\ (s, 3H), 4.88\ (t, J = 2.0 Hz, 2H), 7.42\ (m, 2H), 7.55\ (m, 1H), 8.04\ (m, 2H); \[^{13}\text{C}\ \text{NMR (100 MHz, CDCl}_3, \delta): 24.9, 31.2, 52.9, 73.8, 77.3, 81.9, 128.3, 129.6, 129.7, 133.1, 165.8, 175.5; HRMS (ESI): calcd for C\text{15}H_{16}O_5\ [M+Na]^+: 299.0895, found 299.0903.\]

(S)-methyl 2,6-dihydroxy-2-methylhex-4-ynoate (2.23)

To a solution of 2.22 (495 mg, 1.79 mmol) in MeOH (10 mL) at 0 °C was added K\textsubscript{2}CO\textsubscript{3} (149 mg, 1.08 mmol, 0.6 equiv) in one portion. After 2 h the reaction mixture was
filtered through Celite and concentrated \textit{in vacuo}. Purification by flash chromatography (silica gel, 33\% EtOAc/hexanes) gave \textbf{2.23} (233 mg, 76\%) as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 1.48 (s, 3H), 2.57-2.63 (m, 1H), 2.69-2.74 (m, 1H), 3.06 (br s, OH), 3.81 (s, 3H), 3.86 (br s, OH), 4.24 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 24.8, 31.1, 50.8, 53.0, 74.0, 80.3, 81.9, 175.8; HRMS (ESI): calcd for C$_8$H$_{12}$O$_4$ [M+Na]$^+$: 195.0633, found 195.0628.

\textit{(S,Z)-methyl 2,6-dihydroxy-2-methylhex-4-enoate} (2.24)

![Diagram of the reaction](image)

To a solution of \textbf{2.23} (233 mg, 1.35 mmol) in CH$_2$Cl$_2$ (20 mL) was added Pd/CaCO$_3$ (Lindlar) (160 mg, 70 wt \%). The heterogeneous solution was placed under 1 atmosphere of H$_2$ (balloon) and was stirred for 2 h. The flask was then flushed with N$_2$ and the reaction mixture was filtered through Celite. The reaction was concentrated \textit{in vacuo} to afford \textbf{2.24} (227 mg, 96\%) as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 1.45 (s, 3H), 2.51 (m, 2H), 2.68 (br s, OH), 3.65 (s, OH), 3.79 (s, 3H), 4.12 (m, 2H), 5.52 (m, 1H), 5.85 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 25.7, 37.6, 52.8, 57.8, 74.2, 125.8, 132.8, 176.7; HRMS (ESI): calcd for C$_8$H$_{14}$O$_4$ [M+Na]$^+$: 197.0790, found 197.0778.
(S,Z)-methyl 6-bromo-2-hydroxy-2-methylhex-4-enoate (2.25)

To a solution of 2.24 (50 mg, 0.29 mmol) in CH₂Cl₂ (3 mL) at 0 °C were added successively PPh₃ (99 mg, 0.37 mmol, 1.3 equiv) and CBr₄ (143 mg, 0.43 mmol, 1.5 equiv). After 30 min the reaction mixture was quenched by addition of sat. aq. NaHCO₃ and H₂O. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with water, brine, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 25\% EtOAc/hexanes) gave 2.25 (63 mg, 93\%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃, δ): 1.44 (s, 3H), 2.47 (ddd, \(J = 14.4, 7.6, 1.6\) Hz, 1H), 2.59 (ddd, \(J = 14.4, 4.0, 0.8\) Hz, 1H), 3.21 (s, OH), 3.78 (s, 3H), 3.96 (dd, \(J = 8.4, 3.2\) Hz, 2H), 5.55-5.61 (m, 1H), 5.83-5.91 (m, 1H); ¹³C NMR (100 MHz, CDCl₃, δ): 25.9, 26.7, 37.4, 53.0, 74.6, 128.3, 129.0, 176.5; HRMS (ESI): calcd for C₈H₁₃BrO₃ [M+Na]⁺: 258.9946, found 258.9940.

(2S,Z)-methyl 7-(diethoxyphosphoryl)-2-hydroxy-2-methyloct-4-enoate (2.25')
To a solution of diethyl ethylphosphonate (41 \( \mu \)L, 42 mg, 0.253 mmol, 2.0 equiv) in THF (4 mL) at -78 °C was added \( n \)-BuLi (1.45 M in hexanes, 170 \( \mu \)L, 0.247 mmol, 1.95 equiv) dropwise. After 10 min, a solution of 2.25 (30 mg, 0.127 mmol) in THF (3 mL) was added in one portion to the reaction mixture. After 1 h, the reaction was quenched with sat. aq. NH\(_4\)Cl, warmed to rt and extracted with CH\(_2\)Cl\(_2\). The combined organic layers were washed with brine, dried (Na\(_2\)SO\(_4\)), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, EtOAc) gave 2.25\(^*\) (30 mg) contaminated with diethyl ethylphosphonate. The mixture was used as is in the following step.

(2S,\( Z \))-methyl 7-(diethoxyphosphoryl)-2-methyl-2-((trimethylsilyl)oxy)oct-4-enoate (2.26)

To a solution of 2.25\(^*\) (30 mg, 0.09 mmol) in CH\(_2\)Cl\(_2\) (5 mL) at 0 °C was added pyridine (12 \( \mu \)L, 12 mg, 0.15 mmol, 1.6 equiv) and TMSOTf (24 \( \mu \)L, 29 mg, 0.13 mmol, 1.4 equiv). The mixture was left to warm to rt overnight (12 h) then more pyridine (12 \( \mu \)L, 12 mg, 0.15 mmol, 1.6 equiv) and TMSOTf (24 \( \mu \)L, 29 mg, 0.13 mmol, 1.4 equiv) were added. After 20 min, the reaction was quenched with sat. aq. CuSO\(_4\) and extracted with CH\(_2\)Cl\(_2\). The combined organic layers were washed with sat. aq. NaHCO\(_3\), brine, dried (Na\(_2\)SO\(_4\)), filtered and concentrated in vacuo. Purification by flash...
chromatography (silica gel, 5% MeOH/CH₂Cl₂) gave 2.26 (28 mg, 55% over two steps) as a colorless oil.

¹H NMR (400 MHz, CDCl₃, δ): 0.11 (s, 9H), 1.15 (m, 3H), 1.31 (m, 6H), 1.41 (s, 3H), 1.82 (m, 1H), 2.11 (m, 1H), 2.43 (m, 3H), 3.68 (s, 3H), 4.10 (m, 4H), 5.49 (m, 2H).

**d-xylono-1,4-lactone**

The lactone was prepared by slight modification of a literature procedure.²¹ A 250-mL three-neck round bottom flask was equipped with a magnetic stirrer, thermometer, addition funnel and left open to air. d-xylose (50 g, 333 mmol) and distilled water (150 mL) were charged into the reaction flask, stirred 5 min at rt, and the resulting clear colorless solution was cooled in an ice-water bath in the dark. Potassium carbonate (58 g, 420 mmol, 1.26 equiv) was then added in portions while maintaining the internal temperature below 10 °C. The mixture was then cooled to below 0 °C with a salt-ice bath and bromine (62.2 g, 20 mL, 389 mmol, 1.17 equiv) was added dropwise via the addition funnel over 1 h, while keeping the temperature below 5 °C. After the addition was complete, the reaction was brought back to rt and stirred for 1 h. The bright orange reaction was then cooled back in an ice-water bath and quenched by careful addition of sat. aq. NaHSO₃ to give a cloudy white solution. The solution was concentrated in vacuo at 50 °C to give a white slurry. The solids were filtered off, washed with acetone...
(500 mL) and the filtrate was concentrated. Toluene was added and the water was removed by distilling the toluene–water azeotrope and leaving overnight on a high vacuum line to yield crude D-xylono-1,4-lactone as a colorless oil which was used in the next step without further purification.

3.5-O-isopropylidene-D-xylono-1,4-lactone (3.15)

To a solution of the crude D-xylono-1,4-lactone (assumed 49.8 g, 333 mmol) and CSA (1.4 g, 6 mmol, 0.02 equiv) in acetone (700 mL) at 0 °C was slowly added 2-methoxypropene (38 mL, 28.6 g, 396 mmol, 1.2 equiv). The resulting solution was stirred at 0 °C for 30 min then warmed back to rt. After 4 h the reaction was neutralized by addition of potassium carbonate (5 g), stirred for 30 min and concentrated in vacuo. Ether was added, the salts were filtered off and the solvent was evaporated. The crude product was recrystallized from EtOAc/hexanes (3:1) to afford 3.15 (15.2 g, 25% over two steps) as a white crystalline solid.

Rf (50% EtOAc/hexanes, CAM stain): 0.41; mp 105-107 °C (lit.20 mp 90-92 °C); 
$[\alpha]_D^{22} + 83.6$ (c 1.10, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 1.38 (s, 3H), 1.48 (s, 3H), 3.01 (br s, 1H), 4.11 (dd, $J = 13.6$, 2.8 Hz, 1H), 4.16 (dd, $J = 13.6$, 2.8 Hz, 1H), 4.22 (s, 1H), 4.42 (d, $J = 2.8$ Hz, 1H), 4.56 (q, $J = 2.8$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 19.6, 28.3, 59.6, 71.5, 73.9, 74.1, 98.3, 176.0; IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$): 3372, 2996,
2948, 1782, 1383, 1184, 1110, 1057; HRMS (ESI): calcd for $\text{C}_8\text{H}_{12}\text{O}_5$ [M+Na]$^+$: 211.0577, found 211.0587.

### 3,5-**O**-isopropylidene-2-**O**-methyl-**D**-xylono-1,4-lactone (2.9)

![Chemical reaction](image)

To a solution of **3.15** (1.21 g, 6.43 mmol) and $\text{K}_2\text{CO}_3$ (1.44 g, 10.4 mmol, 1.60 equiv) in acetone (13 mL) at 0 °C was slowly added dimethyl sulfate (953 µL, 1.27 g, 10.1 mmol, 1.55 equiv). The resulting reaction was stirred 30 min at 0 °C then warmed to rt and stirred overnight (14 h). The reaction was diluted with brine (40 mL), and extracted with CH$_2$Cl$_2$. The combined organic layers were dried ($\text{Na}_2\text{SO}_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 10 to 40% EtOAc/hexanes) gave **2.9** (1.06 g, 82%) as a colorless oil.

$R_f$ (25% EtOAc/hexanes, CAM stain): 0.27; $\left[\alpha\right]_D^{22} + 69.4$ (c 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$, δ): 1.37 (s, 3H), 1.47 (s, 3H), 3.55 (s, 3H), 3.74 (s, 1H), 4.09 (dd, $J = 13.6$, 2.4 Hz, 1H), 4.13 (dd, $J = 13.6$, 2.4 Hz, 1H), 4.37 (d, $J = 2.8$ Hz, 1H), 4.45 (q, $J = 2.8$ Hz, 1H); $^1$C NMR (100 MHz, CDCl$_3$, δ): 19.5, 28.3, 58.6, 59.6, 70.4, 73.4, 81.5, 98.1, 172.7; IR (thin film) $v_{\text{max}}$ (cm$^{-1}$): 2994, 2940, 1785, 1381, 1185, 1126, 1063; HRMS (ESI): calcd for $\text{C}_9\text{H}_{14}\text{O}_5$ [M+Na]$^+$: 225.0733, found 225.0743.
(R)-2-((4S,5S)-5-hydroxy-2,2-dimethyl-1,3-dioxan-4-yl)-N,2-dimethoxy-N-methylacetamide (3.16)

![Chemical structure]

To a suspension of N,O-dimethylhydroxylamine hydrochloride salt (1.89 g, 19.4 mmol, 2.0 equiv) in THF (40 mL) at 0 °C was slowly added AlMe₃ (9.69 mL, 19.4 mmol, 2.0 equiv, 2.0 M in hexanes) via syringe. The resulting solution was stirred 30 min at rt and then cooled to -15 °C in an ice/salt bath. A solution of 2.9 (1.96 g, 9.69 mmol) in THF (40 mL) at 0 °C was slowly added via cannula and the resulting solution was stirred 30 min at 0 °C and 90 min at rt. The mixture was then cooled to 0 °C, diluted with diethyl ether, and quenched by careful addition of sat. aq. sodium potassium tartrate. The resulting suspension was allowed to warm to rt over 2 h, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo to yield 3.16 as a colorless oil which was used in the next step without further purification.

Rᵣ (EtOAc, CAM stain): 0.24; [α]ᵢ₂² = 25.2 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃, δ): 1.48 (s, 3H), 1.51 (s, 3H), 2.97 (d, J = 10.4 Hz, 1H), 3.24 (br s, 3H), 3.45 (s, 3H), 3.46 (d, J = 8 Hz, 1H), 3.76 (dd, J = 12.4, 2.4 Hz, 1H), 3.81 (s, 3H), 4.06 (dd, J = 12.4, 1.6 Hz, 1H), 4.31 (d, J = 8 Hz, 1H), 4.54 (br d, J = 7.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, δ): 18.6, 29.7, 32.0, 58.1, 61.8, 63.6, 65.8, 73.0, 76.5, 99.5, 170.1; IR
(thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 3454, 2990, 2941, 2829, 1655, 1458, 1382, 1277, 1242, 1199, 1160, 1068; HRMS (ESI): calcd for C\(_{11}\)H\(_{21}\)NO\(_6\) [M+Na]\(^+\): 286.1261, found 286.1255.

\((R)-N,2\text{-dimethoxy-2-}((4S,5R)-5-((4\text{-methoxybenzyl})oxy)\text{-2,2-dimethyl-1,3-dioxan-4-yl})\text{-N-methylacetamide (3.17)}\)

\[
\begin{align*}
3.16 & \quad \text{Cl}_3\text{COPMB} & \quad \text{CSA} & \quad \text{CH}_2\text{Cl}_2 \\
\rightarrow & & \rightarrow \\
3.17 & 
\end{align*}
\]

To a solution of 3.16 (44 mg, 0.17 mmol) in CH\(_2\text{Cl}_2\) (1.7 mL) was added PMB trichloroacetimidate (96 mg, 0.34 mmol, 2.0 equiv) followed by CSA (4 mg, 0.017 mmol, 0.1 equiv). Every 12 h, more PMB trichloroacetimidate (96 mg, 0.34 mmol, 2.0 equiv) and CSA (4 mg, 0.017 mmol, 0.1 equiv) were added over 48 h. The reaction was diluted with Et\(_2\text{O}\), washed with sat. aq. NaHCO\(_3\), brine, dried (MgSO\(_4\)), filtered and concentrated \textit{in vacuo}. Purification by flash chromatography (silica gel, 20 to 50\% EtOAc/hexanes) gave 3.17 (22 mg, 34\%) as a yellow oil.

\( R_f \) (20\% EtOAc/hexanes, CAM stain): 0.29; \([\alpha]^{22}_D = -17.7\) (c 1.00, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\), \( \delta \)): 1.47 (s, 3H), 1.48 (s, 3H), 3.16 (s, 3H), 3.48 (s, 3H), 3.52 (br s, 1H), 3.58 (s, 3H), 3.79 (s, 3H), 3.88 (ddd, \( J = 20.4, 12.8, 2.8 \text{ Hz, 1H} \)), 4.28 (d, \( J = 11.2 \text{ Hz, 1H} \)), 4.39 (dd, \( J = 8, 2.4 \text{ Hz, 1H} \)), 4.48 (d, \( J = 11.2 \text{ Hz, 1H} \)), 4.57 (br d, \( J = 8 \text{ Hz, 1H} \)), 6.84 (d, \( J = 8.4 \text{ Hz, 2H} \)), 7.22 (d, \( J = 8.4 \text{ Hz, 2H} \)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\), \( \delta \)): 19.9, 28.5, 31.9, 55.4, 58.6, 61.0, 61.5, 70.9, 71.0, 72.5, 76.0, 99.2, 113.8 (2C), 129.8 (2C), 130.3, 159.4, 169.8; IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 2989, 2938, 2835, 1661, 1614, 1514,
HRMS (ESI): calcd for C_{17}H_{35}NO_{6}Si [M+H]^+: 406.1836, found 406.1842.

(R)-2-((4R,5S)-2,2-dimethyl-5-(triethylsilyloxy)-1,3-dioxan-4-yl)-N,2-dimethoxy-N-methyl-acetamide (3.18)

To a solution of 3.16 (assumed 2.55 g, 9.69 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (50 mL) at -78 °C was added 2,6-lutidine (1.46 mL, 1.35 g, 12.6 mmol, 1.3 equiv) followed by dropwise addition of TESOTf (2.41 mL, 2.82 g, 10.66 mmol, 1.1 equiv). The reaction was stirred for 2 h at -78 °C, quenched with sat. aq. NaHCO\textsubscript{3}, brought back to rt and diluted with CH\textsubscript{2}Cl\textsubscript{2}. The layers were separated and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic layers were washed with brine, dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 10 to 25% EtOAc/hexanes) gave 3.18 (3.03 g, 83% over two steps) as a colorless oil.

R\textsubscript{f} (50% EtOAc/hexanes, CAM stain): 0.68; [α]_{D}^{22} = 2.0 (c 0.90, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}, δ): 0.56 (q, J = 8 Hz, 6H), 0.94 (t, J = 8 Hz, 9H), 1.45 (s, 3H), 1.46 (s, 3H), 3.20 (br s, 3H), 3.47 (s, 3H), 3.67 (dd, J = 12.4, 3.6 Hz, 1H), 3.77 (s, 3H), 3.85 (s, 1H), 3.96 (dd, J = 12.4, 3.2 Hz, 1H), 4.35 (d, J = 8.4 Hz, 1H), 4.60 (d, J = 8 Hz, 1H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}, δ): 5.1, 6.7, 20.0, 28.1, 31.7, 57.2, 61.6, 65.0, 65.6, 71.6, 75.2, 98.9, 169.7; IR (thin film) ν\textsubscript{max} (cm\textsuperscript{-1}): 2988, 2953, 2877, 1668, 1458, 1380, 1275, 1239,
1199, 1179, 1152, 1108, 1073; HRMS (ESI): calcd for C$_{17}$H$_{35}$NO$_6$Si [M+H]$^+$: 378.2306, found 378.2310.

**(R)-2-((4R,5S)-2,2-dimethyl-5-(triethylsilyloxy)-1,3-dioxan-4-yl)-2-methoxyacetalddehyde (3.19)**

![Chemical Structure](image)

To a solution of **3.18** (2.0 g, 5.3 mmol) in THF (30 mL) at -78 °C was added DIBAL (20 wt % in toluene, 13.5 mL, 16 mmol, 3.0 equiv) dropwise. After 1 h, the reaction was quenched by careful addition of sat. aq. Rochelle Salt, brought back to rt and stirred 1 h. The layers were separated and the aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with water, brine, dried (MgSO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 10 to 30% EtOAc/hexanes) gave **3.19** (1.40 g, 83%) as a clear oil.

R$_f$ (20% EtOAc/hexanes, CAM stain): 0.51; [α]$^22_D$ = 60.4 (c 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$, δ): 0.60 (q, $J = 8$ Hz, 6H), 0.96 (t, $J = 8$ Hz, 9H), 1.44 (s, 3H), 1.45 (s, 3H), 3.55 (s, 3H), 3.62 (d, $J = 6$ Hz, 1H), 3.74 (dd, $J = 11.6$, 2.4 Hz, 1H), 3.76 (s, 1H), 3.94 (dd, $J = 13.6$, 3.2 Hz, 1H), 4.21 (dd, $J = 6$, 1.2 Hz, 1H), 9.77 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 4.9, 6.8, 19.4, 28.7, 59.8, 64.2, 65.0, 72.9, 83.8, 99.0, 199.7; IR (thin film) ν$_{max}$ (cm$^{-1}$): 2991, 2954, 2877, 1733, 1460, 1380, 1274, 1235, 1147, 1132, 1094, 1020; HRMS (ESI): calcd for C$_{13}$H$_{30}$O$_5$Si [M+Na]$^+$: 341.1755, found 341.1741.
2-(2-bromoethoxy)tetrahydro-2H-pyran (3.21)

\[
\begin{align*}
\text{Br} & \quad \text{OH} \\
\text{3.20} & \quad \text{DHP, PPTS} \\
\text{CH}_2\text{Cl}_2 & \quad \text{Br} \\
\text{3.21} & \quad \text{THP}
\end{align*}
\]

The ether was prepared following a literature procedure.\textsuperscript{35} To a solution of DHP (103 mL, 100 g, 1213 mmol, 1.5 equiv) and PPTS (410 mg, 1.63 mmol, 0.002 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (400 mL) at 0 °C was added freshly distilled 3.20 (56.7 mL, 100 g, 807 mmol) dropwise. The mixture was stirred for 1 h at rt then K\textsubscript{2}CO\textsubscript{3} (150 g) was added and the mixture was filtered and concentrated \textit{in vacuo}. Purification by fractional distillation gave 3.21 (131 g, 78%) as a clear liquid.

bp 49-52°C at 0.3 mmHg (lit.\textsuperscript{35} bp 70-75°C at 20 mmHg); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, \(\delta\)): 1.50-1.88 (m, 6H), 3.48-3.55 (m, 3H), 3.77 (dt, \(J = 11.4, 6.3\) Hz, 1H), 3.89 (m, 1H), 4.02 (dt, \(J = 11.4, 6.3\) Hz, 1H), 4.68 (t, \(J = 3.3\) Hz, 1H); IR (thin film) \(\nu_{\text{max}}\) (cm\textsuperscript{-1}): 3010, 2945, 2875, 2850, 1132, 1122, 1090, 1032; HRMS (ESI): calcd for C\textsubscript{7}H\textsubscript{13}BrO\textsubscript{2} [M+Na\textsuperscript{+}]: calcd: 230.9991; found 230.9983.

triphenyl(4-((tetrahydro-2H-pyran-2-yl)oxy)butan-2-yl)phosphonium bromide (3.22)

\[
\begin{align*}
\text{Br}^+ & \quad \text{Ph}_3\text{P} \quad + \\
\text{3.27} & \quad \text{Br} \\
\text{3.21} & \quad \text{THP} \\
\text{n-BuLi} & \quad \text{THF} \\
\text{3.22} & \quad \text{Br}^+ \\
& \quad \text{Ph}_3\text{P}
\end{align*}
\]

The phosphonium was prepared following a literature procedure.\textsuperscript{35} n-BuLi (1.96 M in hexanes, 11.84 mL, 23.2 mmol, 1.0 equiv) was added dropwise to a stirred suspension of 3.27 (8.6 g, 23.2 mmol) in THF (400 mL) at -78 °C. The reaction mixture was brought
back to rt and stirred until the solution became dark red (~1 h). The reaction was then cooled to 0 °C and 3.21 (7.3 g, 34.9 mmol, 1.5 equiv) was added dropwise. The reaction was then warmed to rt and stirred at that temperature for 48 h. The white solid formed was filtered and rinsed with THF to afford 3.22 (7.8 g, 80%) as a white solid. In the event of contamination with starting phosphonium bromide, the product was trituated with water, filtered, suspended in toluene and the residual water was removed by distilling the toluene–water azeotrope and leaving overnight on a high vacuum line.

mp 194-196 °C (lit.\textsuperscript{35} mp 197-198 °C); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, δ): 1.36-1.56 (m, 8H), 1.73-1.88 (m, 2H), 2.23-2.30 (m, 1H), 3.47-3.54 (m, 1H), 3.72-3.91 (m, 2H), 4.06-4.14 (m, 1H), 4.59-4.61 (m, 1H), 4.66-4.80 (m, 1H), 7.70-7.96 (m, 15H); \textsuperscript{13}C NMR (62.5 MHz, CDCl\textsubscript{3}, δ): 14.0, 20.6, 23.5, 24.3, 25.4, 31.0 (2C), 64.0, 64.8, 65.0, 100.2, 116.9, 130.6, 130.7, 130.8 (2C), 133.9, 134.1, 135.0, 135.1; IR (thin film) ν\textsubscript{max} (cm\textsuperscript{-1}): 3010, 2940, 1440, 1240, 1115, 1080; HRMS (ESI): calcd for C\textsubscript{27}H\textsubscript{32}\textsuperscript{79}BrO\textsubscript{2}P [M-\textsuperscript{79}Br]\textsuperscript{+}: 419.2134, found 419.2139.

triethyl(((4\textit{R},5\textit{R})-4-((1\textit{S},\textit{Z})-1-methoxy-3-methyl-5-((tetrahydro-2\textit{H}-pyran-2-yl)oxy)pent-2-en-1-yl)-2,2-dimethyl-1,3-dioxan-5-yl)oxy)silane (\textit{Z})-3.23) and triethyl(((4\textit{R},5\textit{R})-4-((1\textit{S},\textit{E})-1-methoxy-3-methyl-5-((tetrahydro-2\textit{H}-pyran-2-yl)oxy)pent-2-en-1-yl)-2,2-dimethyl-1,3-dioxan-5-yl)oxy)silane (\textit{E})-3.23)
To a stirred suspension of 3.22 (dried over P$_2$O$_5$ in a vacuum oven at 70 °C for 48 h) (837 mg, 1.99 mmol, 2.2 equiv) at -78 °C in THF (5 mL) was added n-BuLi (1.6 M in hexanes, 1.08 mL, 1.73 mmol, 1.9 equiv). The resulting thick orange solution was warmed back to 0 °C and stirred 30 min during which it turned dark red. A solution of 3.19 (290 mg, 0.91 mmol) in THF (5 mL) was then slowly added at 0 °C. After 1 h, the reaction was quenched by addition of sat. aq. NH$_4$Cl until the reaction turned colorless and was then extracted with Et$_2$O. The combined organic layers were dried (MgSO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 5 to 25% EtOAc/hexanes) gave 3.23 (250 mg, 60%) as a mixture of olefins (~1:1 E:Z NMR ratio) as a colorless oil. For identification purposes, a sample was purified to give the E and Z olefins as clear oils.

Z isomer: R$_f$ (20% EtOAc/hexanes, CAM stain) 0.29; $^1$H NMR (400 MHz, CDCl$_3$, δ): 0.61 (q, $J$ = 8 Hz, 6H), 0.97 (t, $J$ = 8 Hz, 9H), 1.45 (s, 3H), 1.47 (s, 3H), 1.51-1.76 (m, 6H), 1.81 (s, 3H), 2.21 (m, 1H), 2.82 (m, 1H), 3.33 (s, 3H), 3.47-3.51 (m, 2H), 3.57 (s, 1H), 3.74-3.77 (m, 1H), 3.77-3.80 (m, 1H), 3.83-3.87 (m, 2H), 3.92 (dd, $J$ = 12.8, 2 Hz, 1H), 4.15 (t, $J$ = 8.8 Hz, 1H), 4.60 (m, 1H), 5.08 (d, $J$ = 8.8 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 5.5, 7.0, 19.3, 19.6, 24.0, 25.6, 29.1, 30.8, 33.2, 56.5, 62.1, 65.4, 65.8, 66.0, 75.4, 76.5, 98.7, 98.9, 123.3, 140.4; IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$): 2952, 2876, 1456, 1380, 1122, 1080, 1034; HRMS (ESI): calcd for C$_{24}$H$_{46}$O$_6$Si [M+Na]$^+$: 481.2956, found 481.2974.

E isomer: R$_f$ (20% EtOAc/hexanes, CAM stain) 0.17; $^1$H NMR (400 MHz, CDCl$_3$, δ): 0.60 (q, $J$ = 8 Hz, 6H), 0.96 (t, $J$ = 8 Hz, 9H), 1.45 (s, 3H), 1.48 (s, 3H), 1.50-1.74 (m,
6H), 1.81 (s, 3H), 2.36 (m, 2H), 3.27 (s, 3H), 3.49-3.54 (m, 2H), 3.55 (s, 1H), 3.73 (dd, J = 8.4, 1.6 Hz, 1H), 3.78 (dd, J = 12.4, 2 Hz, 1H), 3.85 (m, 2H), 3.92 (dd, J = 12.4, 2 Hz), 4.18 (t, J = 9 Hz, 1H), 4.59 (m, 1H), 5.01 (d, J = 9.6 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 5.6, 7.0, 17.9, 19.2, 19.7, 25.6, 29.2, 30.8, 40.0, 55.8, 62.4, 65.4, 65.8, 66.1, 75.4, 76.4, 98.8, 98.9, 122.3, 140.5; IR (thin film) ν$_{\text{max}}$ (cm$^{-1}$): 2940, 2876, 1458, 1380, 1122, 1079, 1034; HRMS (ESI): calcd for C$_{24}$H$_{46}$O$_6$Si [M+Na]$^+$: 481.2956, found 481.2974.

triethyl(((4R,5R)-4-((1S,3S)-1-methoxy-3-methyl-5-((tetrahydro-2H-pyran-2-yl)oxy)pentyl)-2,2-dimethyl-1,3-dioxan-5-yl)oxy)silane ((S)-3.24) and triethyl(((4R,5R)-4-((1S,3R)-1-methoxy-3-methyl-5-((tetrahydro-2H-pyran-2-yl)oxy)pentyl)-2,2-dimethyl-1,3-dioxan-5-yl)oxy)silane ((R)-3.24)

A mixture of the E and Z 3.23 (1.43 g, 3.11 mmol) and 10% Pd/C (143 mg, 10 wt %) in EtOAc (15 mL) was hydrogenated under 50 psi of H$_2$ at rt for 14 h. The reaction mixture was filtered over Celite, washed with EtOAc and the filtrate was concentrated in vacuo to afford 3.24 (1.32 g, 92%) as a clear oil which was used in the next step without further purification. For identification purposes, a sample was purified to give the (R) and (S) epimers as clear oils.

(R) isomer: R$_{f}$ (20% EtOAc/hexanes, CAM stain) 0.39; $^1$H NMR (400 MHz, CDCl$_3$, δ): 0.64 (q, J = 8 Hz, 6H), 0.96 (d, J = 8 Hz, 3H), 0.99 (t, J = 8 Hz, 9H), 1.22-1.28 (m, 2H), 1.35-1.38 (m, 1H), 1.42 (s, 3H), 1.43 (s, 3H), 1.50-1.61 (m, 3H), 1.67-1.75 (m, 1H), 161
1.81-1.93 (m, 3H), 3.38-3.42 (m, 1H), 3.50 (s, 3H), 3.48-3.52 (m, 2H), 3.60 (s, 1H), 3.68 (dd, $J = 8, 1.2$ Hz, 1H), 3.75 (dd, $J = 12.4, 2.4$ Hz, 1H), 3.80-3.88 (m, 2H), 3.93 (dd, $J = 12.4, 2.4$ Hz, 1H), 4.59 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 5.4, 7.0, 19.5, 19.6, 20.9, 25.6, 26.4, 28.7, 30.8, 35.5, 35.8, 38.2, 59.9, 62.0, 65.5, 65.6, 66.0, 77.1, 78.4, 98.2, 98.5, 98.9; IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$): 2952, 2876, 1457, 1380, 1366, 1275, 1200, 1148, 1078; HRMS (ESI): calcd for C$_{24}$H$_{48}$O$_6$Si [M+Na]$^+$: 483.3112, found 483.3112.

(S) isomer: $R_f$ (20% EtOAc/hexanes, CAM stain) 0.47; $^1$H NMR (400 MHz, CDCl$_3$, δ): 0.63 (q, $J = 8$ Hz, 6H), 0.95 (d, $J = 6.4$ Hz, 3H), 0.99 (t, $J = 8$ Hz, 9H), 1.20-1.27 (m, 1H), 1.35-1.41 (m, 1H), 1.42 (s, 3H), 1.43 (s, 3H), 1.48-1.53 (m, 5H), 1.60-1.74 (m, 1H), 1.80-1.91 (m, 2H), 3.39-3.58 (m, 3H), 3.48 (s, 3H), 3.59 (s, 1H), 3.68 (dd, $J = 8, 2$ Hz, 1H), 3.75 (dd, $J = 12.4, 2.8$ Hz, 1H), 4.57 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 5.5, 6.9, 19.0, 19.5, 19.7, 25.5, 26.1, 28.7, 30.8, 37.4, 38.0, 59.6, 62.3, 65.6, 65.8, 65.9, 77.2, 77.8, 98.5, 98.8; IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$): 2952, 2876, 1457, 1380, 1366, 1275, 1238, 1200, 1148, 1078; HRMS (ESI): calcd for C$_{24}$H$_{48}$O$_6$Si [M+Na]$^+$: 483.3112, found 483.3112.

2-bromoethyl benzoate

![Diagram of 2-bromoethyl benzoate reaction](image)

To a solution of DMAP (1.98 g, 16.2 mmol, 0.2 equiv) in CH$_2$Cl$_2$ (160 mL) at 0 °C was added 3.20 (5.67 mL, 10 g, 81 mmol) and Et$_3$N (22.6 mL, 16.4 g, 162 mmol, 2.0 equiv). After 1 h, BzCl (11.3 mL, 13.66 g, 97.2 mmol, 1.2 equiv) was added slowly
and the reaction was left to warm to rt overnight (14 h) before being quenched with sat. aq. NaHCO₃ and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 1 to 10% EtOAc/hexanes) gave 3.29 (14 g, 76%) as a clear oil.

¹H NMR (500 MHz, CDCl₃, δ): 3.65 (t, J = 6.25 Hz, 2H), 4.63 (t, J = 6.25 Hz, 2H), 7.46 (t, J = 8 Hz, 2H), 7.58 (t, J = 8 Hz, 1H), 8.07 (dd, J = 8.25, 1.25 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃, δ): 28.9, 64.2, 128.5, 129.7, 129.8, 133.3, 166; IR (thin film) νmax (cm⁻¹): 3062, 2966, 1721, 1601, 1451, 1378, 1270, 1114, 1070, 1026; HRMS (ESI): calcd for C₉H₇BrO₂ [M+Na]⁺: 250.9678, found 250.9667.

3,5-O-isopropylidene-2-O-methyl-d-xylono-1,4-lactol (3.31)

To a solution of 2.9 (500 mg, 2.47 mmol, 1.0 equiv) in CH₂Cl₂ at -78 °C under N₂ was slowly added DIBAL (20 wt % in PhMe, 6.19 mL, 5.25 g, 7.41 mmol, 3.0 equiv) over 15 min. After 30 min the reaction was quenched with sat. aq. Rochelle Salt, warmed to rt and extracted with CH₂Cl₂. The combined organic layers were washed with water, brine, dried (MgSO₄), filtered and concentrated in vacuo to give a 1:2 mixture of α and β anomers 3.31 (463 mg, 92%) as a clear oil that was used in the following step without further purification.
α anomer: \(^1\)H NMR (400 MHz, CDCl\(_3\), δ): 1.38 (s, 3H), 1.45 (s, 3H), 3.53 (s, 3H), 3.66 (d, \(J = 4\) Hz, 1H), 3.93 (d, \(J = 10.8\) Hz, OH), 4.00 (s, 1H), 4.09 (m, 2H), 4.30 (m, 1H), 5.61 (dd, \(J = 10.8, 4\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), δ): 19.4, 28.5, 59.1, 60.6, 70.8, 72.2, 84.8, 97.3, 97.6; IR (thin film) \(v_{\text{max}}\) (cm\(^{-1}\)): 3514, 3438, 2990, 2939, 1381, 1198, 1125, 1099, 1074; HRMS (ESI): calcd for C\(_9\)H\(_{16}\)O\(_5\) [M+Na]\(^+\): 227.0890, found 227.0898.

β anomer: \(^1\)H NMR (400 MHz, CDCl\(_3\), δ): 1.41 (s, 3H), 1.47 (s, 3H), 3.44 (s, 3H), 3.62 (d, \(J = 16\) Hz, OH), 3.71 (s, 1H), 3.98 (s, 1H), 4.09 (m, 2H), 4.30 (m, 1H), 5.24 (d, \(J = 15.5\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), δ): 18.7, 28.9, 57.8, 61.0, 71.8, 73.2, 85.6, 97.8, 101.1; IR (thin film) \(v_{\text{max}}\) (cm\(^{-1}\)): 3514, 3438, 2990, 2939, 1381, 1198, 1125, 1099, 1074; HRMS (ESI): calcd for C\(_9\)H\(_{16}\)O\(_5\) [M+Na]\(^+\): 227.0890, found 227.0898.

3-bromobutanoic acid (3.34)

\[
\begin{align*}
\text{HBr} \quad \text{UV (254 nm)} \\
\text{AcOH} \\
\text{3.33} & \text{3.34}
\end{align*}
\]

The acid was prepared following a literature procedure.\(^{47a}\) A solution of 3.33 (10 g, 116.2 mmol) was dissolved in AcOH (300 mL) and HBr (30% w/w AcOH, 5.1 M, 100 mL, 510 mmol, 4.4 equiv) was added. The resulting solution was stirred under a 254 nm UV lamp for 8 h, poured over crushed ice and diluted with CH\(_2\)Cl\(_2\). The organic layer was washed with water, dried (Na\(_2\)SO\(_4\)), filtered and concentrated \textit{in vacuo} to give 3.34 (12.6 g, 65%) as an orange oil which was used in the next step without further purification.
\[ ^1H \text{NMR} (400 \text{ MHz}, \text{CDCl}_3, \delta): 1.78 \text{ (d, } J = 6.5 \text{ Hz, 3H), 2.92 \text{ (dd, } J = 16.5, 6 \text{ Hz, 1H), 2.99 \text{ (dd, } J = 16.5, 8 \text{ Hz, 1H), 4.44 \text{ (sext, } J = 6.5 \text{ Hz, 1H), 11.64 \text{ (br s, 1H); } ^{13}\text{C NMR} (100 \text{ MHz, CDCl}_3, \delta): 26.2, 42.4, 45.8, 176.6; \text{ IR (thin film) } \nu_{\text{max}} \text{ (cm}^{-1}): 2986, 2924, 1714, 1427, 1302, 1244, 1170, 1010; \text{ HRMS (ESI): calcd for } C_4H_7^{^{79}}\text{BrO}_2 [M+Na]^+: 188.9522, \text{ found } 188.9523. \]

(1-carboxypropan-2-yl)triphenylphosphonium bromide (3.35)

\[
\begin{array}{c}
\text{Br} \\
\text{CO}_2H
\end{array} \rightarrow \begin{array}{c}
\text{Br} \\
\text{PPh}_3
\end{array} \rightarrow \begin{array}{c}
\text{PPh}_3 \\
\text{CO}_2H
\end{array}
\]

The phosphonium was prepared following a literature procedure.\textsuperscript{35} To a solution of \textbf{3.34} (6 g, 36 mmol) in PhMe (100 mL) was added PPh\textsubscript{3} (9.5 g, 36 mmol, 1.0 equiv). The resulting solution was heated at reflux for 48 h and cooled to rt where the product solidified out. The solvent was decanted and the crude \textbf{3.35} was used in the next step without further purification.

\[ ^1H \text{NMR} (400 \text{ MHz, CDCl}_3, \delta): 1.43 \text{ (dd, } J = 19, 7 \text{ Hz, 3H), 2.96-3.03 \text{ (m, 1H), 3.11-3.18 \text{ (m, 1H), 4.54-4.60 \text{ (m, 1H), 7.73-7.77 \text{ (m, 6H), 7.80-7.86 \text{ (m, 9H), 10.8 \text{ (br s, 1H); } ^{13}\text{C NMR} (100 MHz, CDCl}_3, \delta): 14.7, 25.0, 37.0, 116.4, 117.1, 131.0, 131.1, 133.8, 133.9, 135.5, 135.6, 170.2; \text{ IR (thin film) } \nu_{\text{max}} \text{ (cm}^{-1}): 2878, 2198, 1731, 1438, 1390, 1321, 1222, 1165, 1111, 996, 920; \text{ HRMS (ESI): calcd for } C_{22}H_{22}^{^{79}}\text{BrO}_2P [M-^{79}\text{Br}]^+: 349.1352, \text{ found } 349.1336. \]
The phosphonium was prepared following a literature procedure.\(^{35}\) To a solution of crude 3.35 (assumed 16 g, 37.3 mmol) in acetone (400 mL) was sequentially added NaI (8.4 g, 56.0 mmol, 1.5 equiv), Na\(_2\)CO\(_3\) (3.9 g, 36.8 mmol, 1.0 equiv) and MeI (5 mL, 11.4 g, 80.3 mmol, 2.1 equiv). The mixture was heated at reflux for 20 h, concentrated in vacuo and the residue was dissolved in CH\(_2\)Cl\(_2\). Filtration and evaporation of the solvent, gave 3.36 (17.05 g, 93% over two steps) as a yellow meringue.

\(^1\)H NMR (400 MHz, CDCl\(_3\), \(\delta\)): 1.52 (dd, \(J = 18.5, 7\) Hz, 3H), 2.29-2.45 (m, 1H), 2.93 (td, \(J = 15.5, 2.5, 1\)H), 3.72 (s, 3H), 4.64-4.69 (m, 1H), 7.79-7.82 (m, 6H), 7.86-7.90 (m, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), \(\delta\)): 14.7, 24.8, 35.3, 52.6, 115.9, 116.6, 130.8, 130.9, 133.6 (2C), 135.3 (2C), 169.3; IR (thin film) \(\nu_{\text{max}}\) (cm\(^{-1}\))\: 3054, 3006, 2951, 2845, 2187, 1738, 1437, 1233, 1111, 996, 919; HRMS (ESI): calcd for C\(_{23}\)H\(_{24}\)O\(_2\)P [M-I]\(^+\): 363.1508, found 363.1523.

(4-hydroxybutan-2-yl)triphenylphosphonium (3.37)
The phosphonium was prepared following a literature procedure. DIBAL (20 wt % in PhMe, 35 mL, 58 mmol, 4.3 equiv) was slowly added to a solution of 3.36 (6.6 g, 13.46 mmol) in CH₂Cl₂ (150 mL) at 0 °C. After 45 min at the same temperature, the reaction was quenched by addition of Na₂SO₄•10H₂O and left to warm to rt overnight (12 h). The reaction was dried (Na₂SO₄), filtered and concentrated in vacuo to give 3.37 (5.25 g, 84%) as a white solid.

mp 221-222 °C (lit. mp 219-221 °C); ¹H NMR (400 MHz, CDCl₃, δ): 1.15 (tt, J = 11, 3 Hz, 1H), 1.42 (dd, J = 19.5, 8.5 Hz, 3H), 2.24 (qd, J = 13, 4 Hz, 1H), 3.75, 3.80 (m, 1H), 3.93-3.99 (m, 1H), 4.42 (t, J = 7 Hz, OH), 4.87-4.93 (m, 1H), 7.70-7.76 (m, 6H), 7.78-7.81 (m, 3H), 7.89-7.93 (m, 6H); ¹³C NMR (100 MHz, CDCl₃, δ): 14.0, 22.5, 33.9, 56.8, 117.4, 118.0, 130.6, 130.7, 133.8 (2C), 134.9 (2C); IR (thin film) ν_max (cm⁻¹): 3356, 3054, 2944, 2875, 2194, 1587, 1485, 1438, 1384, 1111, 1051, 996, 918; HRMS (ESI): calcd for C₂₂H₂₄IOP [M-I]⁺: 335.1559, found 335.1559.

3-hydroxybutyl benzoate (3.39)

The benzoate was prepared following a literature procedure. To a solution of DMAP (1.36 g, 11.1 mmol, 0.2 equiv) in CH₂Cl₂ (111 mL) at 0 °C was added 3.38 (4.97 mL, 5 g, 55.5 mmol) and Et₃N (15.5 mL, 11.23 g, 111 mmol, 2.0 equiv). After 1 h, BzCl (6.64 mL, 8.03 g, 57.1 mmol, 1.03 equiv) was added slowly and the reaction was left to warm to rt overnight (14 h) before being quenched with sat. aq. NaHCO₃ and
extracted with EtOAc. The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 10 to 20% EtOAc/hexanes) gave 3.29 (9.4 g, 87%) as a clear oil.

$^1$H NMR (500 MHz, CDCl$_3$, δ): 1.27 (d, $J = 6.5$ Hz, 3H), 1.82-1.88 (m, 1H), 1.91-1.94 (m, 1H), 2.04 (d, $J = 5$ Hz, OH), 3.97-4.00 (m, 1H), 4.37-4.41 (m, 1H), 4.58-4.63 (m, 1H), 7.44 (td, $J = 7$, 1.5 Hz, 2H), 7.56 (tt, $J = 7$, 1.5 Hz, 1H), 8.04 (dt, $J = 7$, 1.5 Hz, 2H);

$^{13}$C NMR (125 MHz, CDCl$_3$, δ): 23.7, 38.4, 62.3, 65.0, 128.5, 129.7, 130.3, 133.2, 166.9; IR (thin film) $\nu_{max}$ (cm$^{-1}$): 3423, 2967, 1717, 1452, 1381, 1279, 1114; HRMS (ESI): calcd for C$_{11}$H$_{14}$O$_3$ [M+Na$^+$]: 217.0835, found 217.0826.

3-(benzo[d]thiazol-2-ylthio)butyl benzoate (3.40)

![Chemical Structure]

To a solution of BTSH (2.07 g, 12.4 mmol, 1.2 equiv), PPh$_3$ (3.50 g, 13.3 mmol, 1.3 equiv) and 3.39 (2 g, 10.3 mmol) in THF (100 mL) at 0 °C was slowly added DIAD (3.24 mL, 3.33 g, 16.5 mmol, 1.6 equiv). The resulting milky yellowish solution was left to warm to rt overnight (14 h) and concentrated in vacuo. Purification by flash chromatography (silica gel, 1 to 15% EtOAc/hexanes) gave 3.40 (2.9 g, 82%) as an oil.

$^1$H NMR (500 MHz, CDCl$_3$, δ): 1.61 (d, $J = 5$ Hz, 3H), 2.20-2.24 (m, 1H), 2.31-2.35 (m, 1H), 4.25 (q, $J = 7$ Hz, 1H), 4.52 (t, $J = 6$ Hz, 2H), 7.28 (t, $J = 7$ Hz, 1H), 7.38 (t, $J = 7$ Hz, 1H), 7.43 (t, $J = 7$ Hz, 1H), 7.55 (t, $J = 7$ Hz, 1H), 7.73 (d, $J = 8$ Hz, 1H), 7.79 (d, $J = 8$ Hz, 1H), 8.06 (d, $J = 7$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$, δ): 21.5, 36.1, 41.4,
62.6, 121.1, 121.8, 124.5, 126.1, 128.5, 129.8, 130.4, 133.1, 135.5, 153.5, 165.8; IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 3060, 2962, 1719, 1452, 1426, 1312, 1273, 1112, 992; HRMS (ESI): calcd for C\(_{18}\)H\(_{17}\)NO\(_2\)S\(_2\) [M+Na]\(^+\): 366.0593, found 366.0600.

3-(benzo[d]thiazol-2-ylsulfonyl)butyl benzoate (3.41)

To a solution of 3.40 (1.7 g, 4.95 mmol) and NaHCO\(_3\) (2.08 g, 24.8 mmol, 5 equiv) at 0 °C, was added portionwise \( m \)-CPBA (70%, 3.05 g, 12.4 mmol, 2.5 equiv). The resulting white suspension was left to warm to rt overnight (14 h), quenched with sat. aq. NaHCO\(_3\) and extracted with CH\(_2\)Cl\(_2\). The combined organic layers were washed with brine, dried (MgSO\(_4\)), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 10 to 25% EtOAc/hexanes) gave 3.41 (1.52 g, 82%) as a colorless oil that turned into a solid under high vacuum.

\(^1\)H NMR (500 MHz, CDCl\(_3\), \( \delta \)): 1.56 (d, \( J = 7 \text{ Hz} \), 3H), 2.05-2.12 (m, 1H), 2.63-2.68 (m, 1H), 3.85-3.89 (m, 1H), 4.42-4.46 (m, 1H), 4.47-4.53 (m, 1H), 7.43 (t, \( J = 7 \text{ Hz} \), 2H), 7.56-7.64 (m, 3H), 7.98 (d, \( J = 8 \text{ Hz} \), 2H), 8.02 (d, \( J = 8 \text{ Hz} \), 1H), 8.17 (d, \( J = 8 \text{ Hz} \), 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\), \( \delta \)): 13.16, 28.9, 57.2, 61.3, 122.4, 125.6, 127.8, 128.2, 128.5, 129.7 (2C), 133.3, 137.0, 153.0, 164.7, 166.3; IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 3064, 2978, 1719. 1470, 1324, 1273, 1149, 1070, 1025; HRMS (ESI): calcd for C\(_{18}\)H\(_{17}\)NO\(_4\)S\(_2\) [M+Na]\(^+\): 398.0491, found 398.0509.
2-bromoethyl benzyl ether (3.45)

\[
\begin{align*}
\text{HO} & \quad \text{O} & \text{Bn} \\
\text{NBS, PPh}_3 & \quad \text{DCM} & \text{Br} & \quad \text{O} & \text{Bn} \\
\text{3.47} & \quad & \text{3.45}
\end{align*}
\]

The bromide was prepared following a literature procedure.\textsuperscript{51a} To a stirred suspension of NBS (41 g, 231 mmol, 1.17 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (500 mL) in the dark at -78 °C was added dropwise a solution of PPh\textsubscript{3} (60 g, 231 mmol, 1.17 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (300 mL). Stirring was continued until all the NBS had dissolved. A solution of 3.47 (30 g, 28 mL, 197 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (200 mL) was then added dropwise. The cooling bath was removed and the reaction was stirred 1 h at rt during which it turned orange. The reaction was quenched by addition of MeOH (20 mL) and PhMe (300 mL) and concentrated in vacuo to a brown semi-solid. Purification by flash chromatography (silica gel, 0 to 10% EtOAc/hexanes) gave 3.45 (41.4 g, 98%) as a clear liquid.

\(^1\)H NMR (500 MHz, CDCl\textsubscript{3}, δ): 3.49 (t, \(J = 6\) Hz, 2H), 3.79 (t, \(J = 6\) Hz, 2H), 4.59 (s, 2H), 7.30 (m, 1H), 7.35 (m, 4H); \(^1\)C NMR (125 MHz, CDCl\textsubscript{3}, δ): 30.6, 70.1, 73.3, 127.9 (Ar), 128.0 (Ar), 128.6 (Ar), 137.9 (Ar); IR (thin film) \(v_{\text{max}}\) (cm\textsuperscript{-1}): 3063, 3029, 2859, 1496, 1453, 1361, 1276, 1205, 1108, 1040, 1027; HRMS (ESI): calcd for C\textsubscript{9}H\textsubscript{11}BrO\textsuperscript{[M+Na]}\textsuperscript{+}: 238.9866, found 238.9838.

diethyl (4-(benzyloxy)butan-2-yl)phosphonate (3.46)

\[
\begin{align*}
\text{O} & \quad \text{)} & \text{P} & \quad \text{O} \\
\text{EtO}_2 & \quad \text{P} & \quad \text{O} & \quad \text{Bn} \\
\text{3.42} & \quad \text{3.45} & \quad \text{3.46}
\end{align*}
\]
To a solution of 3.42 (1.95 mL, 2 g, 12.04 mmol) in THF (60 mL) under N₂ at -78 °C was slowly added n-BuLi (1.5 M, 9.63 mL, 14.45 mmol, 1.2 equiv) over 30 min. The resulting light gold solution was then warmed to -45 °C and kept at that temperature for 30 min. 3.45 (3.88 g, 18.06 mmol, 1.5 equiv) was then added. The reaction was kept at -45 °C for 3 h then left to warm to rt overnight (14 h). The reaction was quenched with water and extracted with Et₂O. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 25 to 100% EtOAc/hexanes) gave 3.46 (1.70 g, 47%) as a clear oil.

¹H NMR (400 MHz, CDCl₃, δ): 1.17 (dd, J = 18.5, 7 Hz, 3H), 1.32 (t, J = 7 Hz, 6H), 1.57-1.65 (m, 1H), 2.03-2.19 (m, 1H), 3.55-3.60 (m, 1H), 4.06-4.13 (m, 1H), 4.50 (dd, J = 29, 12 Hz, 2H), 7.26-7.36 (m, 5H); ¹³C NMR (100 MHz, CDCl₃, δ): 13.3, 16.6, 27.1, 28.2, 30.3, 61.6, 67.6, 73.0, 127.7 (2C), 128.5, 137.8; IR (thin film) νₘₐₓ (cm⁻¹): 3467, 3030, 2979, 2933, 2868, 1454, 1391, 1366, 1240, 1098, 1057, 1026, 959; HRMS (ESI): calcd for C₁₅H₂₅O₄P [M+Na⁺]: 323.1383, found 323.1374.

(4-(benzyloxy)butan-2-yl)triphenylphosphonium bromide (2.10)

\[
\begin{align*}
\text{Br}^- & \quad \text{Ph}_3\text{P}^+ & \quad \text{Br}^- & \quad \text{Ph}_3\text{P}^+ \\
\text{3.27} & \quad \text{3.45} & \quad n\text{-BuLi} & \quad \text{THF} & \quad \text{2.10}
\end{align*}
\]

n-BuLi (1.6 M in hexanes, 58 mL, 93 mmol, 1.15 equiv) was added dropwise to a mechanically stirred suspension of 3.27 (30 g, 80.8 mmol) in THF (400 mL) at -78 °C. The reaction mixture was brought back to rt and stirred until the solution became dark red
(~1 h). The reaction was then cooled to 0 °C and 3.45 (25 g, 116 mmol, 1.44 equiv) was added dropwise. The reaction was then warmed to rt and stirred at that temperature for 48 h. The white solid formed was filtered and rinsed with THF to afford 2.10 (29.7 g, 73%) as a white crystalline solid. In the event of contamination with starting phosphonium bromide, the product was triturated with water, filtered, suspended in toluene and the residual water was removed by distilling the toluene–water azeotrope and leaving overnight on a high vacuum line.

mp 104-106 °C; 1H NMR (500 MHz, CDCl₃, δ): 1.42 (dd, J = 20, 7 Hz, 3H), 1.46 (m, 1H), 2.23 (m, 1H), 3.85 (m, 1H), 4.04 (m, 1H), 4.54 (dd, J = 34, 11 Hz, 2H), 5.26 (m, 1H), 7.33 (m, 5H), 7.68 (m, 6H), 7.76 (m, 3H), 7.96 (m, 6H); 13C NMR (125 MHz, CDCl₃, δ): 13.9, 23.5, 23.9, 31.1, 66.9, 67.1, 73.4, 117.1 (Ar), 117.8 (Ar), 127.8 (Ar), 128.0 (Ar), 128.4 (Ar), 130.6 (Ar), 130.7 (Ar), 133.8 (Ar), 133.9 (Ar), 134.9 (Ar), 135.0 (Ar), 138.0 (Ar); IR (thin film) ν max (cm⁻¹): 3392, 3055, 2936, 2854, 2177, 1484, 1438, 1365, 1111, 996, 923; HRMS (ESI): calcd for C₂₉H₅₀^⁻BrOP [M⁻Br]^⁺: 425.2029, found 425.2039.

(((4R,5R)-4-((S,Z)-5-(benzyloxy)-1-methoxy-3-methylpent-2-en-1-yl)-2,2-dimethyl-1,3-dioxan-5-yl)oxy)triethylsilane ((Z)-3.48) and (((4R,5R)-4-((S,E)-5-(benzyloxy)-1-methoxy-3-methylpent-2-en-1-yl)-2,2-dimethyl-1,3-dioxan-5-yl)oxy)triethylsilane ((E)-3.48)
To a stirred suspension of 2.10 (dried over P₂O₅ in a vacuum oven at 70 °C for 48 h) (3.65 g, 7.22 mmol, 2.3 equiv) at -78 °C in THF (25 mL) was added n-BuLi (1.6 M in hexanes, 4.12 mL, 6.59 mmol, 2.1 equiv). The resulting thick orange solution was warmed back to 0 °C and stirred 30 min during which it turned dark red. A solution of 3.19 (1 g, 3.14 mmol) in THF (5 mL) was then slowly added at 0 °C. After 1 h, the reaction was quenched by addition of sat. aq. NH₄Cl until the reaction turned colorless and was then extracted with Et₂O. The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 10 to 30% EtOAc/hexanes) gave 3.48 (1.26 g, 87%) as a mixture of olefins (~1:1 E:Z NMR ratio) as a colorless oil. For identification purposes, a sample was purified to give the E and Z olefins as clear oils.

**Z isomer:** Rₕ (20% EtOAc/hexanes, CAM stain) 0.30; [α]D²² − 0.4 (c 2.00, CHCl₃); ¹H NMR (500 MHz, CDCl₃, δ): 0.60 (q, J = 8 Hz, 6H), 0.96 (t, J = 8 Hz, 9H), 1.43 (s, 3H), 1.46 (s, 3H), 1.79 (s, 3H), 2.33 (m, 1H), 2.85 (m, 1H), 3.27 (s, 3H), 3.57 (m, 3H), 3.73 (m, 1H), 3.74 (dd, J = 12.5, 2.5 Hz, 1H), 3.85 (dd, J = 12.5, 2.5 Hz, 1H), 4.12 (t, J = 9 Hz, 1H), 4.50 (s, 2H), 5.10 (d, J = 9 Hz, 1H), 7.32 (m, 5H); ¹³C NMR (125 MHz, CDCl₃, δ): 5.5, 7.0, 19.4, 24.1, 29.1, 33.3, 56.5, 65.4, 65.8, 68.9, 73.1, 75.5, 76.7, 98.9, 123.4, 127.7 (Ar), 128.5 (Ar), 138.6, 140.3; IR (thin film) νₘₐₓ (cm⁻¹): 3030, 2953, 2876, 1454, 1380, 1242, 1149, 1079, 1004; HRMS (ESI): calcd for C₂₆H₄₄O₅Si [M+Na]⁺: 487.2850, found 487.2868.

**E isomer:** Rₕ (20% EtOAc/hexanes, CAM stain) 0.21; [α]D²² − 32.7 (c 1.54, CHCl₃); ¹H NMR (500 MHz, CDCl₃, δ): 0.58 (q, J = 8 Hz, 6H), 0.95 (t, J = 8 Hz, 9H), 1.45 (s, 3H),
1.47 (s, 3H), 1.80 (s, 3H), 2.38 (q, $J = 6$ Hz, 2H), 3.27 (s, 3H), 3.51 (d, $J = 1.5$ Hz, 1H), 3.59 (td, $J = 7$, 2.5 Hz, 2H), 3.71 (dd, $J = 5.6$, 1.5 Hz, 1H), 3.75 (dd, $J = 12.5$, 1.6 Hz, 1H), 3.87 (dd, $J = 1.6$, 12.5 Hz, 1H), 4.17 (t, $J = 9$ Hz, 1H), 4.50 (s, 2H), 5.01 (d, $J = 9$ Hz, 1H), 7.30 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$, $\delta$): 5.6, 7.0, 17.9, 19.2, 29.3, 40.1, 56.0, 65.3, 65.8, 68.9, 73.0, 75.4, 76.4, 98.9, 122.4, 127.7 (Ar), 128.5 (Ar), 138.5, 140.4; IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$): 3030, 2953, 2876, 1454, 1380, 1241, 1123, 1079, 1004; HRMS (ESI): calcd for C$_{26}$H$_{44}$O$_5$Si [M+Na]$^+$: 487.2850, found 487.2873.

$$\left((4R,5R)-4-((1S,3R)-5-\text{(Benzyloxy)}-1-\text{methoxy-3-methylpentyl)}-2,2-\text{dimethyl-1,3-dioxan-5-yl)oxy}\right)\text{triethylsilane ((R)-3.60) and }\left((4R,5R)-4-((1S,3S)-5-\text{(Benzyloxy)}-1-\text{methoxy-3-methylpentyl)}-2,2-\text{dimethyl-1,3-dioxan-5-yl)oxy}\right)\text{triethylsilane ((S)-3.60)}$$

A mixture of the $E$ and $Z$ olefins **3.48** (380 mg, 0.82 mmol) and 10% Pt/C (38 mg, 10 wt %) in PhMe (4 mL) was hydrogenated under 1 atm of H$_2$ (balloon) at rt for 7 h. The reaction mixture was filtered over Celite, washed with EtOAc and the filtrate was concentrated in vacuo to afford **3.60** as a clear oil which was used in the next step without further purification. For identification purposes, a sample was purified to give the ($R$) and ($S$) olefins as clear oils.

($R$) isomer: $R_f$ (20% EtOAc/hexanes, CAM stain) 0.42; $[\alpha]_{D}^{22} 38.4$ (c 1.03, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$, $\delta$): 0.62 (qd, $J = 8$, 1.5 Hz, 6H), 0.94 (d, $J = 6.5$ Hz, 3H), 0.98 (t, $J = 8$ Hz, 9H), 1.22 (m, 1H), 1.38 (m, 1H), 1.42 (s, 3H), 1.43 (s, 3H), 1.53 (m,
1H), 1.62 (m, 1H), 1.90 (m, 1H), 3.48 (s, 3H), 3.52 (m, 3H), 3.58 (q, \( J = 2 \) Hz, 1H), 3.67 (dd, \( J = 8, 2 \) Hz, 1H), 3.74 (dd, \( J = 12.5, 2.5 \) Hz, 1H), 3.92 (dd, \( J = 12.5, 2.5 \) Hz, 1H), 4.49 (d, \( J = 3 \) Hz, 2H), 7.26 (m, 1H), 7.33 (m, 4H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\), \( \delta \)): 5.6, 7.1, 19.2, 19.7, 26.3, 28.8, 37.5, 38.2, 59.8, 65.7, 65.7 (2C), 69.0, 73.0, 77.3, 77.9, 98.7, 127.6 (Ar), 127.7 (Ar), 128.4 (Ar), 138.8; IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 3029, 2953, 2876, 1455, 1379, 1366, 1275, 1232, 1200, 1149, 1103, 1004; HRMS (ESI): calcd for C\(_{26}\)H\(_{46}\)O\(_5\)Si [M+Na]\(^{+}\):489.3007, found 489.2999.

(S) isomer: \( R_f \) (20\% EtOAc/hexanes, CAM stain) 0.45; \([\alpha]_D^{22} = -43.1 \) (c 0.63, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\), \( \delta \)): 0.62 (qd, \( J = 8, 1.5 \) Hz, 6H), 0.94 (d, \( J = 6.5 \) Hz, 3H), 0.99 (t, \( J = 8 \) Hz, 9H), 1.28 (m, 3H), 1.40 (m, 1H), 1.41 (s, 3H), 1.43 (s, 3H), 1.89 (m, 2H), 3.47 (s, 3H), 3.53 (m, 3H), 3.60 (q, \( J = 2.5 \) Hz, 1H), 3.68 (dd, \( J = 8, 1.5 \) Hz, 1H), 3.75 (dd, \( J = 13, 3 \) Hz, 1H), 3.92 (dd, \( J = 13, 3 \) Hz, 1H), 4.50 (dd, \( J = 22.5, 12 \) Hz, 2H), 7.26 (m, 1H), 7.33 (m, 4H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\), \( \delta \)): 5.6, 7.1, 19.7, 21.1, 26.7, 28.8, 35.8, 38.3, 59.9, 65.7, 65.8, 69.1, 72.8, 78.6, 98.7, 127.5 (Ar), 127.6 (Ar), 128.4 (Ar), 139.0; IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 2952, 2875, 1456, 1365, 1237, 1199, 1148, 1102, 1004; HRMS (ESI): calcd for C\(_{26}\)H\(_{46}\)O\(_5\)Si [M+Na]\(^{+}\):489.3007, found 489.3006.

(3R,5S)-5-((4R,5R)-2,2-dimethyl-5-((triethylsilyl)oxy)-1,3-dioxan-4-yl)-5-methoxy-3-methylpentan-1-ol ((R)-3.49) and (3S,5S)-5-((4R,5R)-2,2-dimethyl-5-((triethylsilyl)oxy)-1,3-dioxan-4-yl)-5-methoxy-3-methylpentan-1-ol ((S)-3.49)

\[
\begin{align*}
\text{OTES} & \quad \text{H}_2, \text{Pd(OH)}_2/\text{C} \quad \text{THF} \\
3.60 & \quad \text{OTES} & \quad \text{OH} \\
& \quad *(3.49)
\end{align*}
\]
A mixture of the (R) and (S) 3.60 (assumed 381 mg, 0.82 mmol) and 10% Pd(OH)$_2$/C (38 mg, 10 wt %) in THF (4 mL) was hydrogenated under 1 atm of H$_2$ at rt for 3 h. The reaction mixture was filtered over Celite, washed with EtOAc and the filtrate was concentrated in vacuo. Purification by flash chromatography (silica gel, 25 to 75% EtOAc/hexanes) gave 3.49 ((R) epimer: 111 mg, (S) epimer: 121 mg, 75% combined yield) as clear oils.

(R) isomer: R$_f$ (50% EtOAc/hexanes, CAM stain) 0.30; $[\alpha]^{22}_D$ – 70.4 (c 0.47, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$, δ): 0.63 (qd, $J = 8$, 1.5 Hz, 6H), 0.96 (d, $J = 6.5$ Hz, 3H), 0.99 (t, $J = 8$ Hz, 9H), 1.25 (m, 1H), 1.38 (m, 1H), 1.42 (s, 3H), 1.43 (s, 3H), 1.52 (q, $J = 7$ Hz, 2H), 1.68 (br s, 2H), 1.89 (m, 1H), 3.51 (s, 3H), 3.53 (m, 1H), 3.59 (q, $J = 2$ Hz, 1H), 3.69 (m, 3H), 3.75 (dd, $J = 12.5$, 2 Hz, 1H), 3.93 (dd, $J = 12.5$, 2 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$, δ): 5.5, 6.7, 19.5 (2C), 25.8, 28.6, 37.0, 40.9, 60.1, 60.9, 65.5, 65.6, 77.3, 78.4, 98.6; IR (thin film) ν$_{max}$ (cm$^{-1}$): 3406, 2955, 2877, 1461, 1380, 1153, 1100, 1005; HRMS (ESI): calcd for C$_{19}$H$_{40}$O$_5$Si [M+Na]$^+$: 399.2537, found 399.2519.

(S) isomer: R$_f$ (50% EtOAc/hexanes, CAM stain) 0.45; $[\alpha]^{22}_D$ – 43.3 (c 0.33, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$, δ): 0.64 (qd, $J = 8$, 2 Hz, 6H), 0.97 (d, $J = 8$ Hz, 3H), 0.99 (t, $J = 8$ Hz, 9H), 1.32 (m, 3H), 1.42 (s, 3H), 1.43 (s, 3H), 1.44 (m, 1H), 1.61 (br s, 1H), 1.77 (m, 1H), 1.87 (m, 1H), 3.48 (s, 3H), 3.55 (m, 1H), 3.61 (q, $J = 2$ Hz, 1H), 3.67 (m, 1H), 3.71 (dd, $J = 8$, 2 Hz, 1H), 3.73 (m, 1H), 3.75 (dd, $J = 12.5$, 3 Hz, 1H), 3.93 (dd, $J = 12.5$, 2.5 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$, δ): 5.6, 7.1, 19.7, 21.3, 26.3, 28.8, 37.7, 39.0, 59.6, 61.5, 65.7, 65.8, 76.9, 78.5, 98.8; IR (thin film) ν$_{max}$ (cm$^{-1}$): 3414, 2954, 2877, 1461,
A mixture of the E and Z 3.48 (1 g, 2.15 mmol) and 10% Pd(OH)$_2$/C (100 mg, 10 wt %) in THF (10 mL) was hydrogenated under 1 atm of H$_2$ (balloon) at rt for 4 h. The reaction mixture was filtered over Celite, washed with EtOAc and the filtrate was concentrated in vacuo to afford 3.61 as a clear oil which was used in the next step without further purification. For identification purposes, a sample was purified to give the E and Z olefins as clear oils.

Z isomer: R$_f$ (20% EtOAc/hexanes, CAM stain) 0.39; \([\alpha]^{22}_D\) – 14.0 (c 1.01, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$, $\delta$): 0.61 (q, $J$ = 8 Hz, 6H), 0.96 (t, $J$ = 8 Hz, 9H), 1.44 (s, 6H), 1.81 (s, 3H), 2.29-2.36 (m, 1H), 2.47-2.55 (m, 1H), 2.81 (br s, OH), 3.36 (s, 3H), 3.68-3.76 (m, 4H), 3.91-4.18 (m, 2H), 4.20 (t, $J$ = 8.5 Hz, 1H), 5.45 (d, $J$ = 9 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$, $\delta$): 5.4, 6.9, 19.5, 23.7, 28.7, 35.9, 56.4, 59.8, 65.2, 66.0, 74.5, 75.9, 99.0, 124.9, 140.1; IR (thin film) $\nu_{max}$ (cm$^{-1}$): 3459, 2954, 2877, 1668, 1668, 1456, 1380, 1242, 1149, 1079, 1005, 906, 856, 744; HRMS (ESI): calcd for C$_{19}$H$_{38}$O$_5$Si [M+Na]$^+$: 397.2381, found 397.2392.
$E$ isomer: $R_f$ (20% EtOAc/hexanes, CAM stain) 0.21; $[\alpha]^2_D = 30.6$ (c 1.06, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$, $\delta$): 0.61 (q, $J = 8$ Hz, 6H), 0.97 (t, $J = 8$ Hz, 9H), 1.45 (s, 3H), 1.46 (s, 3H), 1.79 (s, 3H), 2.32 (t, $J = 6.5$ Hz, 2H), 3.30 (s, 3H), 3.58 (d, $J = 1.5$ Hz, 1H), 3.70-3.73 (m, 1H), 3.77-3.79 (m, 2H), 3.93 (dd, $J = 13$, 2 Hz, 1H), 4.19 (t, $J = 9$ Hz, 1H), 5.12 (dd, $J = 9.5$, 1 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$, $\delta$): 5.3, 7.0, 17.4, 19.3, 29.2, 43.2, 56.2, 60.4, 65.4, 65.8, 75.1, 76.6, 98.9, 123.8, 139.5; IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$): 3461, 2953, 2877, 1458, 1381, 1241, 1150, 1078, 1005, 906, 857, 742; HRMS (ESI): calcd for C$_{19}$H$_{38}$O$_5$Si [M+Na]$^+$: 397.2381, found 397.2365.

(3R,5S)-5-((4R,5R)-2,2-dimethyl-5-((triethylsilyl)oxy)-1,3-dioxan-4-yl)-5-methoxy-3-methylpentan-1-ol ((R)-3.49) and (3S,5S)-5-((4R,5R)-2,2-dimethyl-5-((triethylsilyl)oxy)-1,3-dioxan-4-yl)-5-methoxy-3-methylpentan-1-ol ((S)-3.49)

A mixture of the $E$ and $Z$ olefins 3.61 (assumed 800 mg, 2.13 mmol) and 10% Pt/C (80 mg, 10 wt %) in PhMe (8 mL) was hydrogenated under 1 atm of H$_2$ (balloon) at rt for 7 h. The reaction mixture was filtered over Celite, washed with EtOAc and the filtrate was concentrated in vacuo. Purification by flash chromatography (silica gel, 35 to 75% EtOAc/hexanes) gave 3.49 ((R) epimer: 385 mg, (S) epimer: 310 mg, 86% combined yield) as clear oils.
(3R,5S)-5-((4R,5R)-2,2-dimethyl-5-((triethylsilyl)oxy)-1,3-dioxan-4-yl)-5-methoxy-3-methylpentan-1-ol ((R)-3.49) and (3S,5S)-5-((4R,5R)-2,2-dimethyl-5-((triethylsilyl)oxy)-1,3-dioxan-4-yl)-5-methoxy-3-methylpentan-1-ol ((S)-3.49)

A mixture of the E and Z 3.48 (1 g, 2.15 mmol), 10% Pd(OH)$_2$/C (100 mg, 10 wt %) and 10% Pt/C (50 mg, 5 wt %) in EtOAc (10 mL) was hydrogenated under 1 atm of H$_2$ (balloon) at rt for 29 h. The reaction mixture was filtered over Celite, washed with EtOAc and the filtrate was concentrated in vacuo. Purification by flash chromatography (silica gel, 35 to 75% EtOAc/hexanes) gave 3.49 ((R) epimer: 320 mg, (S) epimer: 310 mg, 78% combined yield) as clear oils.

(((4R,5R)-4-((1S,3R)-5-bromo-1-methoxy-3-methylpentyl)-2,2-dimethyl-1,3-dioxan-5-yl)oxy)triethylsilane ((R)-2.6)

To a solution of (S)-3.49 (843 mg, 2.24 mmol) in CH$_2$Cl$_2$ (25 mL) at 0 °C was sequentially added Et$_3$N (2.26 g, 3.11 mL, 22.4 mmol, 10 equiv), PPh$_3$ (1.17 g, 4.48 mmol, 2 equiv) and CBr$_4$ (1.48 g, 4.48 mmol, 2 equiv). After stirring 2 h at 0 °C, the reaction was quenched by addition of sat. aq. NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo.
Purification by flash chromatography (silica gel, 10% EtOAc/hexanes) gave \((R)-2.6\) (898 mg, 91%) as a colorless oil.

\[ \text{R}_f \text{ (20% EtOAc/hexanes, CAM stain) 0.60}; \ \left[ \alpha \right]_D^{22} = 50.2 \text{ (c 0.89, CHCl}_3\right); \ \text{^1H NMR} \]

(500 MHz, CDCl\(_3\), \(\delta\)): 0.63 (qd, \(J = 8, 2 \text{ Hz}, 6\text{H}\)), 0.95 (d, \(J = 6.5 \text{ Hz}, 3\text{H}\)), 0.99 (t, \(J = 8 \text{ Hz}, 9\text{H}\)), 1.29 (m, 1H), 1.40 (m, 1H), 1.42 (s, 3H), 1.43 (s, 3H), 1.60 (m, 1H), 1.95 (m, 1H), 2.08 (m, 1H), 3.40 (m, 1H), 3.50 (s, 3H), 3.51 (m, 2H), 3.60 (q, \(J = 2 \text{ Hz}, 1\text{H}\)), 3.70 (dd, \(J = 2, 8 \text{ Hz}, 1\text{H}\)), 3.75 (dd, \(J = 3, 12.5 \text{ Hz}, 1\text{H}\)), 3.93 (dd, \(J = 3, 12.5 \text{ Hz}, 1\text{H}\)); \text{^13C NMR} \]

(125 MHz, CDCl\(_3\), \(\delta\)): 5.6, 7.1, 19.7, 20.3, 28.4, 28.8, 32.2, 37.7, 39.3, 60.0, 65.7, 65.8, 77.1, 78.4, 98.8; IR (thin film) \(\nu_{\text{max}} \text{ (cm}^{-1}\text{)}\): 2954, 2877, 1150, 1081, 1004; HRMS (ESI): calcd for C\(_{19}\)H\(_{39}\)O\(_4\)BrSi [M+Na\(^+\)]: 461.1693, found 461.1671.

(((4R,5R)-4-((1S,3S)-5-bromo-1-methoxy-3-methylpentyl)-2,2-dimethyl-1,3-dioxan-5-yl)oxy)triethylsilane ((S)-2.6)

\[ \text{To a solution of } (R)-3.49 \text{ (619 mg, 1.64 mmol) in CH}_2\text{Cl}_2 \text{ (16 mL) at 0 °C was sequentially added Et}_3\text{N (1.66 g, 2.29 mL, 16.4 mmol, 10 equiv), PPh}_3 \text{ (860 mg, 3.28 mmol, 2 equiv) and CBr}_4 \text{ (1.09 g, 3.28 mmol, 2 equiv). After stirring 2 h at 0 °C, the reaction was quenched by addition of sat. aq. NaHCO}_3 \text{ and extracted with CH}_2\text{Cl}_2. \text{ The combined organic layers were dried (Na}_2\text{SO}_4\text{), filtered, and concentrated in vacuo.} \]
Purification by flash chromatography (silica gel, 10% EtOAc/hexanes) gave (S)-2.6 (636 mg, 88%) as a colorless oil.

R_f (20% EtOAc/hexanes, CAM stain) 0.58; [α]_D^{22} – 38.1 (c 1.54, CHCl₃); ¹H NMR (500 MHz, CDCl₃, δ): 0.63 (qd, J = 8, 2 Hz, 6H), 0.95 (d, J = 6.5 Hz, 3H), 0.99 (t, J = 8 Hz, 9H), 1.25 (m, 1H), 1.36 (m, 1H), 1.42 (s, 3H), 1.43 (s, 3H), 1.77 (m, 1H), 1.87 (m, 1H), 1.95 (m, 1H), 3.42 (m, 2H), 3.49 (s, 3H), 3.53 (m, 1H), 3.59 (q, J = 2 Hz, 1H), 3.70 (dd, J = 8, 2 Hz, 1H), 3.75 (dd, J = 12.5, 3 Hz, 1H), 3.93 (dd, J = 12.5, 3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃, δ): 5.6, 7.1, 18.6, 19.7, 28.3, 28.8, 31.7, 37.0, 41.5, 60.0, 65.7 (2C), 77.2, 78.0, 98.8; IR (thin film) ν_max (cm⁻¹): 2955, 2877, 1153, 1100, 1004; HRMS (ESI): calcd for C₁₉H₃₉O₄BrSi [M+Na]⁺: 463.1675, found 463.1681.

(4S,5R)-4-((1S,3S)-5-hydroxy-1-methoxy-3-methylpentyl)-2,2-dimethyl-1,3-dioxan-5-ol (3.63)

To a stirred solution of 3.49 (115 mg, 0.30 mmol) in THF (3 mL) at 0 °C under N₂ was added Et₃N (369 μL, 269 mg, 2.66 mmol, 8.7 equiv) followed by dropwise addition of HF•Et₃N (37%, 289 μL, 286 mg, 5.3 mmol, 17.4 equiv). After 24 h, more HF•Et₃N (37%, 100 μL, 99 mg, 1.83 mmol, 6.1 equiv) was added. After 36 h, the reaction was diluted with CH₂Cl₂ and carefully quenched with sat. aq. NaHCO₃. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers
were washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 50% EtOAc/hexanes) gave 3.63 (69 mg, 88% yield) as a white solid. X-ray quality crystals were obtained by recrystallization from Et₂O.

mp 74-75 °C; Rᵣ (EtOAc, CAM stain) 0.38; [α]ᵣ²⁰ – 24.2 (c 0.70, CHCl₃); ¹H NMR (400 MHz, CDCl₃, δ): 0.97 (d, J = 6.8 Hz, 3H), 1.32 (m, 1H), 1.45 (m, 1H), 1.46 (s, 6H), 1.56 (m, 1H), 1.68 (m, 1H), 1.83 (m, 1H), 2.31 (br s, 1H), 3.47 (s, 3H), 3.50 (m, 3H), 3.69 (m, 2H), 3.81 (m, 2H), 4.02 (d, J = 12.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, δ): 18.5, 20.9, 26.2, 29.6, 36.8, 38.9, 59.0, 60.6, 64.7, 66.1, 75.2, 79.7, 99.0; IR (thin film) νₘₐₓ (cm⁻¹): 3417, 2933, 1454, 1384, 1276, 1201, 1138, 1059, 981, 913, 858, 733; HRMS (ESI): calcd for C₁₃H₂₆O₅ [M+Na]⁺: 285.1672, found 285.1661.

(4S,5R)-4-((1S,3R)-5-hydroxy-1-methoxy-3-methylpentyl)-2,2-dimethyl-1,3-dioxan-5-ol (3.64)

To a stirred solution of the (R)-3.49 (150 mg, 0.40 mmol) in THF (4 mL) at 0 °C under N₂ was added pyridine (803 μL, 790 mg, 10 mmol, 25 equiv) followed by dropwise addition of HF•pyr (70%, 415 μL, 460 mg, 16 mmol, 40 equiv). After 1 h the reaction was diluted with CH₂Cl₂ and carefully quenched with sat. aq. NaHCO₃. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash
chromatography (silica gel, 50 to 100% EtOAc/hexanes) gave 3.64 (102 mg, 97% yield) as a clear oil.

Rf (EtOAc, CAM stain) 0.31; [α]$_D^{22}$ - 32.9 (c 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$, δ): 0.97 (d, J = 6.8 Hz, 3H), 1.32 (m, 1H), 1.46 (s, 3H), 1.47 (s, 3H), 1.51 (m, 3H), 1.85 (m, 1H), 2.52 (br s, 1H), 3.16 (br s, 1H), 3.42 (s, 1H), 3.48 (s, 3H), 3.50 (m, 1H), 3.67 (m, 2H), 3.80 (m, 2H), 4.02 (dd, J = 12.4, 1.6 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 18.5, 19.6, 25.8, 29.7, 36.8, 40.6, 59.7, 60.6, 64.3, 66.1, 76.4, 79.2, 99.0; IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$): 3417, 2934, 1462, 1384, 1276, 1201, 1151, 1060, 981, 912, 857; HRMS (ESI): calcd for C$_{13}$H$_{26}$O$_5$ [M+Na]$^+$: 285.1672, found 285.1675.

(4R,5R)-4-((1S,3R)-5-((3,5-dinitrobenzoyl)oxy)-1-methoxy-3-methylpentyl)-2,2-dimethyl-1,3-dioxan-5-yl 3,5-dinitrobenzoate (3.65)

![Diagram](image_url)

To a solution of 3.64 (50 mg, 0.19 mmol) in CH$_2$Cl$_2$ (1 mL) at 0 °C under N$_2$ was sequentially added DMAP (5 mg, 0.04 mmol, 0.2 equiv), Et$_3$N (106 µL, 77 mg, 0.76 mmol, 4.0 equiv), and 3,5-dinitrobenzoyl chloride (132 mg, 0.57 mmol, 3.0 equiv). The resulting cloudy pale brown reaction was left to warm to rt overnight (13 h), quenched with sat. aq. NH$_4$Cl, diluted with Et$_2$O and the organics were washed with sat.
aq. NH₄Cl, sat. aq. NaHCO₃, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 20 to 50% EtOAc/hexanes) gave 3.65 (102 mg, 83%) as an off-white meringue.

^{1}H NMR (400 MHz, CDCl₃, δ): 0.86 (d, J = 6.8 Hz, 3H), 1.45-1.62 (m, 2 H), 1.54 (s, 3H), 1.56 (s, 3H), 1.68-1.82 (m, 2H), 1.90-2.00 (m, 1H), 3.54 (s, 3H), 3.54-3.60 (m, 1H), 4.05 (dd, J = 13.6, 1.6 Hz, 1H), 4.16 (d, J = 7.6 Hz, 1H), 4.23 (dd, J = 13.6, 1.6 Hz, 1H), 4.45 (t, J = 6.8 Hz, 2H), 5.03 (s, 1H), 9.10 (m, 2H), 9.20 (m. 3H), 9.26 (s, 1H); ^{13}C NMR (100 MHz, CDCl₃, δ): 18.8, 19.2, 26.4, 29.3, 36.3, 37.6, 60.2, 62.8, 65.1, 68.9, 73.9, 78.3, 99.3, 122.4, 122.9, 129.4, 129.6, 133.7, 134.1, 148.8, 148.9, 162.3, 162.5; IR (thin film) ν_{max} (cm⁻¹): 3103, 2937, 1732, 1630, 1548, 1462, 1346, 1282, 1169, 1077, 920, 730; HRMS (ESI): calcd for C_{27}H_{30}N_{4}O_{15}[M+Na]^+: 673.1600, found 673.1568.

but-2-ynal (4.3)

The aldehyde was prepared by slight modification of a literature procedure.⁵⁹ To a rapidly stirring solution of 4.2 (2.30 mL, 30.8 mmol) in CH₂Cl₂ (70 mL) and aqueous 0.5 M NaHCO₃/0.05 M K₂CO₃ (64 mL) was added TBAC (894 mg, 3.22 mmol, 0.1 equiv), TEMPO (0.508 g, 3.26 mmol, 0.1 equiv), and NCS (6.86 g, 51.4 mmol, 1.67 equiv). After stirring for 6 h the aqueous layer was separated and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried (MgSO₄) and
filtered. The CH$_2$Cl$_2$ was carefully distilled off to give 4.3 as a yellow oil which used in the following step without further purification.

(R)-4-benzyl-3-((2R,3R)-3-hydroxy-2-methylhex-4-ynoyl)oxazolidin-2-one (4.5)

To a solution of 4.4 (3.6 g, 15.4 mmol) in CH$_2$Cl$_2$ (40 mL) at -5 °C was added Bu$_2$BOTf (1 M in CH$_2$Cl$_2$, 18.4 mL, 18.4 mmol, 1.2 equiv) dropwise, followed by freshly distilled Et$_3$N (2.80 mL, 20.0 mmol, 1.3 equiv) (internal temperature should remain below 3 °C). The reaction mixture turned orange after the addition of Bu$_2$BOTf then yellow after the addition of Et$_3$N. The reaction mixture was then cooled to -78 °C and a solution of 4.3 (assumed 2.10 g, 30.8 mmol, 2.0 equiv) in CH$_2$Cl$_2$ (~5 mL) was added dropwise. The mixture became orange again. The reaction mixture was stirred 30 min at -78 °C and 2 h at 0 °C then phosphate buffer (22 mL), MeOH (66 mL) and a MeOH/H$_2$O$_2$ mix (2:1, 66 mL) was added while keeping the internal temperature under 10 °C. After 1 h, the reaction mixture was concentrated in vacuo and taken up into Et$_2$O. The aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with 5% aq. NaHCO$_3$, brine, dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 25% EtOAc/hexanes) gave 4.5 (3.12 g, 83%) as a clear oil which crystallized under high vacuum to give a white crystalline solid.
$[\alpha]_D^{22} = 69.1 \text{ (c 1.00, CHCl}_3$); $^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 1.41 (d, $J = 8.0$ Hz, 3H), 1.85 (d, $J = 2.0$ Hz, 3H), 2.80 (dd, $J = 12.0$ Hz, 8.0 Hz, 1H), 2.87 (br s, 1H), 3.25 (dd, $J = 4.0$ Hz, 12.0 Hz, 1H), 3.92 (m, 1H), 4.18-4.25 (m, 2H), 4.70-4.74 (m, 2H), 7.19-7.35 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 3.9, 12.4, 38.1, 44.2, 55.4, 63.8, 66.6, 77.9, 82.4, 127.7, 129.3, 129.7, 135.3, 153.3, 175.9; IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 3484, 3030, 2974, 2928, 2371, 2233, 1777, 1678, 1454, 1381, 1260, 1212, 1184, 1033, 1005, 971, 763, 694, 596; HRMS (ESI): calcd for C$_{17}$H$_{19}$O$_4$N [M+Na]$^+$: 324.1206, found 324.1212.

(R)-4-benzyl-3-((2R,3R)-3-((tert-butyldimethylsilyl)oxy)-2-methylhex-4-ynoyl)oxazolidin-2-one (4.6)

![Diagram](image)

To a solution of 4.5 (2.45 g, 8.12 mmol) and imidazole (1.40 g, 20.6 mmol, 2.5 equiv) in CH$_2$Cl$_2$ (30 mL) at 0 °C was added TBSCl (1.61 g, 10.65 mmol, 1.3 equiv). The cloudy white reaction was left to warm to rt overnight (20 h) and diluted with CH$_2$Cl$_2$. The combined organic layers were washed with water, brine, dried (MgSO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 25% EtOAc/hexanes) gave 4.6 (3.03 g, 90%) as a light yellow oil which solidified to a white solid under high vacuum.

$[\alpha]_D^{22} = 15.7 \text{ (c 1.00, CHCl}_3$); $^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 0.10 (s, 3H), 0.13 (s, 3H), 0.89 (s, 9H), 1.30 (d, $J = 6.8$ Hz, 3H), 1.81 (d, $J = 2.4$ Hz, 3H), 2.77 (dd, $J = 13.2$, 2.4 Hz, 2H), 2.80 (dd, $J = 12.0$ Hz, 8.0 Hz, 1H), 2.87 (br s, 1H), 3.25 (dd, $J = 4.0$ Hz, 12.0 Hz, 1H), 4.18-4.25 (m, 2H), 4.70-4.74 (m, 2H), 7.19-7.35 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 3.9, 12.4, 38.1, 44.2, 55.4, 63.8, 66.6, 77.9, 82.4, 127.7, 129.3, 129.7, 135.3, 153.3, 175.9; IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 3484, 3030, 2974, 2928, 2371, 2233, 1777, 1678, 1454, 1381, 1260, 1212, 1184, 1033, 1005, 971, 763, 694, 596; HRMS (ESI): calcd for C$_{17}$H$_{19}$O$_4$N [M+Na]$^+$: 324.1206, found 324.1212.
10 Hz, 1H), 3.30 (dd, \( J = 13.2, 3.2 \) Hz, 1H), 4.08 (p, \( J = 7.2 \) Hz, 1H), 4.16 (m, 2H), 4.54 (dd, \( J = 7.6, 2.4 \) Hz, 1H), 4.66 (m, 1H), 7.35-7.21 (m, 5H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), \( \delta \)): -5.0, -4.4, 3.8, 13.7, 18.4, 26.0, 38.1, 45.3, 55.8, 64.9, 66.3, 79.2, 81.6, 127.6, 129.2, 129.7, 135.6, 153.3, 174.3; IR (KBr) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 2935, 2854, 2345, 2275, 2234, 1764, 1698, 1393, 1352, 1252, 1071, 1007, 974, 870, 836, 779, 704.

HRMS (ESI): calcd for C\(_{23}\)H\(_{33}\)NO\(_4\)Si [M+Na]\(^+\): 438.2071, found 438.2080.

(2S,3R)-3-(tert-butyldimethylsilyl)oxy)-2-methylhex-4-yn-1-ol (4.7)

To a solution of 4.6 (613 mg, 1.48 mmol) in THF (12 mL) at 0 \( ^\circ \)C was added a freshly prepared solution of NaBH\(_4\) (129 mg, 3.42 mmol, 2.3 equiv) in H\(_2\)O (1.8 mL) dropwise. The reaction mixture was left to warm to rt overnight (20 h). The bulk of the THF was evaporated off and the reaction was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO\(_4\)), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 75\% CH\(_2\)Cl\(_2\)/hexanes) gave 4.7 (251 mg, 70\%) as a clear oil. (R)-4-benzylloxazolidin-2-one can be recovered upon elution of the column with 30\% EtOAc in hexanes.

\([\alpha]_D^{22} + 45.1 \ (c \ 1.00, \ \text{CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\), \( \delta \)): 0.10 (s, 3H), 0.13 (s, 3H), 0.87 (d, 3H), 0.87 (s, 9H), 1.97-2.00 (m, 1H), 2.83 (br s, 1H), 3.50-3.53 (m, 1H), 3.81-3.77 (m, 1H), 4.44 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), \( \delta \)): -5.4, -4.6, 3.4, 12.6, 187.
18.1, 25.7, 41.4, 65.7, 67.6, 78.2, 82.1; IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 3360, 2929, 2857, 2236, 1472, 1361, 1252, 1144, 1034, 837, 776; HRMS (ESI): calcd for C\(_{13}\)H\(_{26}\)O\(_2\)Si [M+Na]\(^{+}\): 265.1594, found 265.1601.

\((2R,3R)-3-((\text{tert-butylimethylsilyl})oxy)-2\text{-methylhex-4-ynal} \ (4.8)\)

\[
\begin{align*}
\text{HO} & \quad \xrightarrow{(\text{COCl})_2, \text{DMSO, Et}_3\text{N}} \quad \text{O} \\
\text{OTBS} & \quad \xrightarrow{\text{CH}_2\text{Cl}_2} \quad \text{OTBS}
\end{align*}
\]

To a stirring solution of oxalyl chloride (330 \( \mu \text{L}, 488 \text{ mg}, 3.84 \text{ mmol}, 1.5 \text{ equiv}) in CH\(_2\)Cl\(_2\) (14 mL) at -78 °C was slowly added DMSO (710 \( \mu \text{L}, 781 \text{ mg}, 10.0 \text{ mmol}, 4.0 \text{ equiv). The reaction mixture was stirred for 15 min before a solution of 4.7 (610 mg, 2.51 mmol) in CH\(_2\)Cl\(_2\) (1.5 mL) was added. The reaction mixture was stirred for an additional 30 min followed by the addition of Et\(_3\)N (1.75 mL, 1.27 g, 12.6 mmol, 5.0 equiv). The reaction mixture was stirred for 30 min at -78 °C and for an additional 60 min at 0 °C. To the reaction mixture was added sat. aq. NaHCO\(_3\). The aqueous layer is then extracted with CH\(_2\)Cl\(_2\). The combined organic layers were washed with brine, dried (MgSO\(_4\)), filtered and concentrated \textit{in vacuo}. Purification by flash chromatography (silica gel, 2\% EtOAc/hexanes) gave 4.8 (493 mg, 82\%) as a light yellow oil.

\[\alpha\]\(\text{D}\)^2 + 23.2 (c 1.00, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\), \( \delta \)): 0.10 (s, 3H), 0.14 (s, 3H), 0.87 (s, 9H), 1.15 (d, \( J = 6.8 \) Hz, 3H), 1.82 (d, \( J = 2.0 \) Hz, 3H), 2.49-2.52 (m, 1H), 4.64-4.67 (m, 1H), 9.79 (d, \( J = 1.6 \) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), \( \delta \)): -5.2, -4.5, 3.4, 9.3, 18.1, 25.7, 52.8, 63.5, 78.2, 82.7, 204.0; IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 2956, 2930,
2957, 2711, 2423, 1728, 1463, 1390, 1362, 1342, 1252, 1144, 1077, 1031, 1006, 939, 838, 778, 671; HRMS (ESI): calcd for C_{13}H_{24}O_{2}Si [M+Na]^+: 263.1438, found 263.1445.

(4S,5R,E)-ethyl 5-((tert-butyldimethylsilyl)oxy)-4-methyloct-2-en-6-ynoate (4.9)

To a suspension of Ba(OH)$_2$•8H$_2$O (321 mg, 1.87 mmol, 1.1 equiv; dried at 110 °C for 20 h) in THF (5 mL) was added ethyl diethylphosphonoacetate (410 μL, 459 mg, 2.05 mmol, 1.2 equiv). The mixture was stirred for 20 min before a solution of 4.8 (408 mg, 1.70 mmol) in THF (5 mL) and water (0.12 mL) was added. The reaction mixture was stirred for 3 h, diluted with CH$_2$Cl$_2$, washed with sat. aq. NaHCO$_3$, brine, dried (MgSO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 3% EtOAc/hexanes) gave 4.9 (475 mg, 90%) as a light yellow oil.

\[ \alpha \]$_D$ $^2$ + 23.3 ($c$ 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$, δ): 0.08 (s, 3H), 0.12 (s, 3H), 0.89 (s, 9H), 1.12 (d, $J = 3.6$ Hz, 3H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.82 (d, $J = 2.0$ Hz, 3H), 2.49-2.54 (m, 1H), 4.19 (q, $J = 7.2$ Hz, 2H), 4.24-4.27 (m, 1H), 5.84 (dd, $J = 15.6$, 1.2 Hz, 1H), 7.01 (dd, $J = 15.6$, 7.2 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, δ): -4.6, -4.5, 3.4, 14.2, 14.5, 18.2, 25.7, 43.8, 60.1, 66.4, 78.8, 81.7, 121.6, 150.3, 166.6. IR (thin film) ν$_\text{max}$ (cm$^{-1}$): 2957, 2929, 2893, 2858, 2233, 1723, 1652, 1471, 1463, 1368, 1310, 1258, 1181, 1140, 1096, 1070, 1031, 1006, 984, 940, 838, 777, 720, 668; HRMS (ESI): calcd for C$_{17}$H$_{30}$O$_3$Si [M+Na]$^+$: 333.1856, found 333.1845.
(2S,3R)-2-methylhex-4-yn-1,3-diol (4.11)

To a solution of 4.5 (1.70 g, 5.6 mmol) in THF (50 mL) at 0 °C was added a freshly prepared solution of NaBH₄ (854 mg, 22.6 mmol, 4.0 equiv) in H₂O (8 mL). The reaction mixture was maintained 3 h at 0 °C then was warmed to rt and quenched with H₂O (5 mL). The bulk of the THF was then removed and the reaction was diluted with CH₂Cl₂. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 10 to 50% EtOAc/hexanes) gave 4.11 (627 mg, 87%) as a clear oil and the oxazolidinone (910 mg, 91%) as a white crystalline solid.

¹H NMR (400 MHz, CDCl₃, δ): 0.93 (d, J = 4.0 Hz, 3H), 1.88 (d, J = 1.0 Hz, 3H), 2.40-2.10 (m, 1H), 2.53 (t, J = 4.0 Hz, 1H), 3.10 (d, J = 4.0 Hz, 1H), 3.65-3.70 (m, 1H), 3.83-3.88 (m, 1H), 4.48 (t, J = 1.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, δ): 3.5, 12.3, 40.3, 65.6, 66.6, 78.1, 82.3; HRMS (ESI): calcd for C₇H₁₂O₂ [M+Na]⁺: 151.0730, found 151.0727.
(2S,3R,E)-2-methyl-5-(tributylstannyl)hex-4-ene-1,3-diol (4.12)

CuCN (91 mg, 1.01 mmol, 1.3 equiv) was loaded and dried under high vacuum with a heat gun (color: pale green → cream). THF (3 mL) was then added and the suspension was cooled to -78 °C where n-BuLi (2.36 M in hexanes, 860 μL, 2.03 mmol, 2.6 equiv) was added dropwise. After 15 min, the reaction mixture turned clear and pale yellow. n-Bu₃SnH (554 μL, 599 mg, 2.03 mmol, 2.6 equiv) was then added dropwise to the reaction mixture at -78 °C, which progressively turned bright yellow. The mixture was maintained 30 min at -78 °C then a solution of 4.11 (100 mg, 0.78 mmol) in THF (1 mL) was added (reaction mixture turned dark red). After 3 h at -78 °C, MTBE (3 mL) was added followed by sat. aq. NH₄Cl (containing 1% NH₄OH) (3 mL). The mixture was allowed to warm to rt overnight (14 h) then was extracted with MTBE. The combined organic layers were dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 20 to 30% EtOAc/hexanes) gave 4.12 (164 mg, 50%) as a clear oil along with 4.11 (46 mg, 93% brsm)

¹H NMR (400 MHz, CDCl₃, δ): 0.86-0.94 (m, 18 H), 1.26-1.36 (m, 6H), 1.44-1.56 (m, 6H), 1.91 (d, J = 1.6 Hz, 3H), 1.93-1.99 (m, 1H), 2.23 (s, 1H), 2.54 (br s, 1H), 3.61-3.63 (m, 1H), 3.72 (t, J = 8.3 Hz, 1H), 4.73 (m, 1H), 5.66 (dq, J = 8.4, 2.0 Hz, 1H), ¹³C NMR (100 MHz, CDCl₃, δ): 9.2, 11.6, 13.7, 19.8, 27.3, 29.2, 40.4, 66.4, 70.4, 140.5, 142.8; HRMS (ESI): calcd for C₁₉H₄₀O₂Sn [M+Na]⁺: 443.1942, found 443.1962.
(2R,3R,E)-3-hydroxy-2-methyl-5-(tributylstannyl)hex-4-enal (4.13)

To a solution of 4.12 (100 mg, 0.24 mmol) in CH₂Cl₂ (1.0 mL) was added TEMPO (3.7 mg, 0.024 mmol, 0.1 equiv) and NaHCO₃ (100 mg, 1.2 mmol, 5.0 equiv). A solution of BAIB (84.5 mg, 0.26 mmol, 1.1 equiv) and NaHCO₃ (100 mg, 1.2 mmol, 5.0 equiv) in CH₂Cl₂ (0.5 mL) was then added dropwise to the reaction. After 90 min, the reaction mixture was diluted with CH₂Cl₂ and washed with sat. aq. NaHCO₃ and sat. aq. Na₂S₂O₃. The combined aqueous layer was extracted twice with CH₂Cl₂. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo to give a yellow oil, which was dissolved immediately in wet THF (0.6 mL + 1 drop of H₂O) and used in the next step without further purification.

(2E,4S,5R,6E)-ethyl 5-hydroxy-4-methyl-7-(tributylstannyl)octa-2,6-dienoate (2.8)

To a suspension of Ba(OH)₂•8H₂O (83 mg, 0.264 mmol, 1.1 equiv; dried at 110 °C for 20 h) in THF (0.6 mL) was added the ester-phosphonate (54 mg, 0.24 mmol, 1.0 equiv). The heterogeneous mixture was stirred at rt for 30 min then was cooled to 0 °C and crude 4.13 in wet THF (0.6 mL) was added dropwise. The reaction mixture turned yellow but
remained heterogeneous. After 3 h at 0 °C, the mixture was diluted with CH₂Cl₂, washed with sat. aq. NaHCO₃, brine, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 10 to 15% EtOAc/hexanes) gave 2.8 (68 mg, 59% over 2 steps) as a colorless oil.

¹H NMR (400 MHz, CDCl₃, δ): 0.87-0.91 (m, 15H), 1.10 (d, J = 6.8 Hz, 3H), 1.26-1.35 (m, 9H), 1.44-1.52 (m, 6H), 1.69 (br s, 1H), 1.90 (d, J = 2.0 Hz, 3H), 2.52 (q, J = 6.8 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.50 (dd, J = 8.4, 6.0 Hz, 1H), 5.50 (dd, J = 8.4, 1.2 Hz, 1H), 5.84 (dd, J = 16.0, 1.2 Hz, 1H), 6.97 (dd, J = 16.0, 7.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, δ): 9.2, 13.6, 14.2, 14.4, 19.9, 27.3, 29.1, 42.7, 60.2, 69.9, 121.7, 140.1, 144.0, 150.2, 166.5; HRMS (ESI): calcd for C₂₃H₄₄O₃Sn [M+Na]⁺: 511.2205, found 511.2215.

(2E,4S,5R,6E)-ethyl 5-((tert-butyldimethylsilyl)oxy)-4-methyl-7-(tributylstannyloxy)octa-2,6-dienoate (4.10)

![Chemical structure of 4.10](image)

To a solution of 2.8 (125 mg, 0.26 mmol) in CH₂Cl₂ (5 mL) at 0 °C were added dropwise 2,6-lutidine (149 μL, 1.28 mmol, 5.0 equiv) and TBSOTf (77 μL, 0.33 mmol, 1.3 equiv). The reaction mixture was stirred at 0 °C for 2 h then was allowed to warm to rt overnight (12 h) and diluted with CH₂Cl₂. The reaction was washed with sat. aq. NaHCO₃, brine, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel) gave 4.10 (151 mg, 98%) as a colorless oil.
\(^1\)H NMR (400 MHz, CDCl\(_3\), δ): 0.01 (s, 3H), 0.02 (s, 3H), 0.83-0.91 (m, 24H), 1.07 (d, \(J = 11.2\) Hz, 3H), 1.24-1.38 (m, 9H), 1.41-1.51 (m, 6H), 1.82-1.84 (m, 3H), 2.36-2.41 (m, 1H), 4.16 (q, \(J = 11.2\) Hz, 2H), 4.41 (dd, \(J = 13.2, 9.2\) Hz, 1H), 5.44 (dd, \(J = 13.2, 2.8\) Hz, 1H), 5.75 (dd, \(J = 25.2, 2.0\) Hz, 1H), 6.98 (dd, \(J = 25.2, 11.6\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), δ): -5.0, -4.3, 9.1, 13.7, 14.3, 18.2, 19.8, 25.8, 27.3, 29.1, 43.6, 60.0, 71.1, 120.8, 139.4, 142.4, 151.5, 166.7; HRMS (ESI): calcd for C\(_{29}\)H\(_{58}\)O\(_3\)SiSn [M+Na]\(^+\): 625.3069, found 625.3054.

\((E)\)-3-(tributylstannyl)but-2-en-1-ol (4.14)

\[
\text{HO} \quad \text{CuCN, n-BuLi, n-Bu}_3\text{SnH} \quad \text{THF} \quad \text{HO} \quad \text{SnBu}_3
\]

CuCN (4.6 g, 51.4 mmol, 1.2 equiv) was dried under high vacuum with a heat gun (color: pale green to cream). THF (100 mL) was then added, the suspension was cooled to -78 °C and \(n\)-BuLi (1.6 M in hexanes, 64 mL, 102.7 mmol, 2.4 equiv) was added dropwise. After 20 min, the reaction mixture turned clear and pale yellow. \(n\)-Bu\(_3\)SnH (28.1 mL, 102.7 mmol, 2.4 equiv) was then added dropwise to the reaction mixture at -78 °C, which progressively turned bright yellow. The mixture was maintained 30 min at -78 °C then a solution of 4.2 (3.0 g, 42.8 mmol) in THF (50 mL) was slowly added (reaction mixture turned dark red). After 2 h at -78 °C MTBE (10 mL) was added followed by sat. aq. NH\(_4\)Cl (containing 1% NH\(_4\)OH) (10 mL). The mixture was allowed to warm to rt overnight (14 h) and was diluted with MTBE (200 mL). The organic layer was dried (Na\(_2\)SO\(_4\)), filtered and concentrated \textit{in vacuo}. Purification by flash
chromatography (silica gel, 5% EtOAc/hexanes) gave **4.14** (12.4 g, 80%) as a colorless oil.

R_f (10% EtOAc/hexanes, KMnO_4 stain): 0.30; \(^1\)H NMR (500 MHz, CDCl_3, \(\delta\)): 0.92 (m, 15H), 1.31 (m, 7H), 1.49 (m, 6H), 1.93 (s, 3H), 4.25 (d, \(J = 5.5\) Hz, 2H), 5.75 (m, 1H); \(^{13}\)C NMR (125 MHz CDCl_3, \(\delta\)): 9.3, 13.8, 19.5, 27.5, 29.3, 59.1, 139.4, 142.7; IR (thin film) \(\nu_{\text{max}}\) (cm\(^{-1}\)): 3307, 2955, 2923, 2870, 2851, 1463, 1375, 1058, 1003; HRMS (ESI): calcd for C\(_{16}\)H\(_{34}\)OSn [M+Na]^+: 385.1527, found 385.1532.

**(E)-3-(tributylstannyl)but-2-enal (1.13)**

![Chemical Structure](image)

To a solution of **4.14** (12.3 g, 34.1 mmol) in CH\(_2\)Cl\(_2\) (500 mL) at rt were added Na\(_2\)CO\(_3\) (72.0 g, 680.0 mmol, 20 equiv) and activated MnO\(_2\) (59.0 g, 680.0 mmol, 20 equiv) in one portion. The resultant mixture was stirred at rt overnight (16 h) then was filtered through Celite, washed with CH\(_2\)Cl\(_2\) and the filtrate was concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% EtOAc/hexanes) gave **1.13** (11.4 g, 93%) as a yellow oil.

R_f (5% EtOAc/hexanes, KMnO\(_4\) stain): 0.34; \(^1\)H NMR (500 MHz, CDCl_3, \(\delta\)): 0.90 (t, \(J = 7.0\) Hz, 9H), 0.99 (m, 6H), 1.32 (sext, \(J = 7.0\) Hz, 6H), 1.50 (m, 6H), 2.45 (d, \(J = 1.5\) Hz, 3H), 6.21 (dq, \(J = 1.5, 8.0\) Hz, 1H), 10.06 (d, \(J = 8.0\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl_3, \(\delta\)): 9.6, 13.8, 20.9, 27.5, 29.1, 140.1, 174.4, 187.6; IR (thin film) \(\nu_{\text{max}}\)
(cm\(^{-1}\)): 2958, 2927, 2871, 2851, 1665, 1463, 1420, 1146, 1071, 934; HRMS (ESI): calcd for C\(_{16}\)H\(_{32}\)OSn [M+Na\(^+\)]: 383.1370, found 383.1386.

\((R)-4\text{-}\text{benzyl-3-)((2R,3R,E)-3-hydroxy-2-methyl-5-(tributylstannyl)hex-4-enoyl})\text{oxazolidin-2-one} \ (4.15)\)

To a solution of 4.4 (331 mg, 1.42 mmol) in CH\(_2\)Cl\(_2\) (5 mL) at -10 °C was added Bu\(_2\)BOTf (1 M in CH\(_2\)Cl\(_2\), 1.85 mL, 1.85 mmol, 1.3 equiv) dropwise followed by freshly distilled Et\(_3\)N (277 μL, 2.0 mmol, 1.4 equiv) (internal temperature should remain below +3 °C). The reaction mixture turned orange after the addition of Bu\(_2\)BOTf then yellow after the addition of Et\(_3\)N. The reaction mixture was then cooled to -78 °C and a solution of 1.13 (560 mg, 1.56 mmol, 1.1 equiv) in CH\(_2\)Cl\(_2\) (~1 mL) was added dropwise. The mixture became orange again. The reaction mixture was stirred 30 min at -78 °C and 2 h at 0 °C then phosphate buffer (2 mL), MeOH (6 mL) and a 2:1 MeOH/H\(_2\)O\(_2\) mix (6 mL) were added while keeping the internal temperature under 10 °C. After 1 h, the reaction mixture was concentrated and taken up into Et\(_2\)O. The aqueous layer was extracted twice with Et\(_2\)O. The combined organic layers were washed with 5% aqueous NaHCO\(_3\), brine, dried (Na\(_2\)SO\(_4\)), filtered and concentrated \textit{in vacuo}. Purification by flash chromatography (silica gel, 10% EtOAc/hexanes) gave 4.15 (675 mg, 80%) as a clear oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\), δ): 0.87-0.92 (m, 15H), 1.24-1.36 (m, 9H), 1.46-1.53 (m, 6H), 1.91 (d, \(J = 1.6 \text{ Hz}, \text{3H}\)), 2.73 (br s, OH), 2.80 (dd, \(J = 13.6, 9.6 \text{ Hz}, \text{1H}\)), 3.25 (dd, 2958, 2927, 2871, 2851, 1665, 1463, 1420, 1146, 1071, 934; HRMS (ESI): calcd for C\(_{16}\)H\(_{32}\)OSn [M+Na\(^+\)]: 383.1370, found 383.1386.

\((R)-4\text{-}\text{benzyl-3-)((2R,3R,E)-3-hydroxy-2-methyl-5-(tributylstannyl)hex-4-enoyl})\text{oxazolidin-2-one} \ (4.15)\)

To a solution of 4.4 (331 mg, 1.42 mmol) in CH\(_2\)Cl\(_2\) (5 mL) at -10 °C was added Bu\(_2\)BOTf (1 M in CH\(_2\)Cl\(_2\), 1.85 mL, 1.85 mmol, 1.3 equiv) dropwise followed by freshly distilled Et\(_3\)N (277 μL, 2.0 mmol, 1.4 equiv) (internal temperature should remain below +3 °C). The reaction mixture turned orange after the addition of Bu\(_2\)BOTf then yellow after the addition of Et\(_3\)N. The reaction mixture was then cooled to -78 °C and a solution of 1.13 (560 mg, 1.56 mmol, 1.1 equiv) in CH\(_2\)Cl\(_2\) (~1 mL) was added dropwise. The mixture became orange again. The reaction mixture was stirred 30 min at -78 °C and 2 h at 0 °C then phosphate buffer (2 mL), MeOH (6 mL) and a 2:1 MeOH/H\(_2\)O\(_2\) mix (6 mL) were added while keeping the internal temperature under 10 °C. After 1 h, the reaction mixture was concentrated and taken up into Et\(_2\)O. The aqueous layer was extracted twice with Et\(_2\)O. The combined organic layers were washed with 5% aqueous NaHCO\(_3\), brine, dried (Na\(_2\)SO\(_4\)), filtered and concentrated \textit{in vacuo}. Purification by flash chromatography (silica gel, 10% EtOAc/hexanes) gave 4.15 (675 mg, 80%) as a clear oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\), δ): 0.87-0.92 (m, 15H), 1.24-1.36 (m, 9H), 1.46-1.53 (m, 6H), 1.91 (d, \(J = 1.6 \text{ Hz}, \text{3H}\)), 2.73 (br s, OH), 2.80 (dd, \(J = 13.6, 9.6 \text{ Hz}, \text{1H}\)), 3.25 (dd,
\[ J = 13.6, 3.2 \text{ Hz, 1H}, 3.88-3.91 \text{ (m, 1H)}, 4.13-4.23 \text{ (m, 2H)}, 4.66-4.71 \text{ (m, 1H)}, 4.88 \text{ (d, } J = 4.0 \text{ Hz, 1H)}, 5.60-5.63 \text{ (m, 1H)}, 7.19-7.35 \text{ (m, 5H)}. \]

**(R)-4-benzyl-3-((2R,3R,E)-3-((tert-butyldimethylsilyl)oxy)-2-methyl-5-(tributylstanny)hex-4-enoyl)oxazolidin-2-one (4.16)**

![Diagram](image)

To a solution of **4.15** (15.1 g, 25.4 mmol) in CH\(_2\)Cl\(_2\) (400 mL) at 0 °C under N\(_2\) were added dropwise 2,6-lutidine (14.7 mL, 127.0 mmol, 5.0 equiv) and TBSOTf (7.6 mL, 33.0 mmol, 1.3 equiv). The reaction mixture was stirred at 0 °C for 2 h then was allowed to warm to rt overnight (14 h). The mixture was then diluted with CH\(_2\)Cl\(_2\), washed with sat. aq. NaHCO\(_3\), brine, dried (MgSO\(_4\)), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% EtOAc/hexanes) gave **4.16** (17.3 g, 96%) as a clear oil.

\(^1^H\) NMR (400 MHz, CDCl\(_3\), \(\delta\)): 0.09 (m, 6H), 0.87-0.92 (m, 24H), 1.27-1.37 (m, 9H), 1.46-1.54 (m, 6H), 1.92 (d, \(J = 1.6\) Hz, 3H), 2.80 (dd, \(J = 13.2, 9.6\) Hz, 1H), 3.30 (dd, \(J = 13.2, 3.2\) Hz, 1H), 4.02-4.18 (m, 3H), 4.54-4.60 (m, 1H), 4.76-4.80 (m, 1H), 5.48-5.55 (m, 1H), 7.22-7.37 (m, 5H); \(^{13}C\) NMR (100 MHz, CDCl\(_3\), \(\delta\)): -5.0, -4.4, 9.3, 13.1, 13.7, 18.1, 19.8, 25.8, 27.4, 29.1, 37.8, 44.1, 55.6, 65.8, 69.3, 127.3, 128.9, 129.5, 135.4, 140.4, 141.8, 153.0, 174.6; HRMS (ESI): calcd for C\(_{35}\)H\(_{61}\)NO\(_4\)SiSn [M+Na]\(^+\): 730.3284, found 730.3300.
(2S,3R,E)-3-((tert-butyldimethylsilyl)oxy)-2-methyl-5-(tributylstanny1)hex-4-en-1-ol (4.17)

To a solution of 4.16 (5.4 g, 7.6 mmol) in THF (100 mL) at rt was added a freshly prepared solution of NaBH₄ (2.9 g, 76.4 mmol, 10.0 equiv) in H₂O (15 mL). After 2 h, LiCl (1.6 g, 5 equiv) was added in one portion at 0 °C then the mixture was left to warm to rt overnight (14 h). The reaction was diluted with EtOAc and H₂O. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 5% EtOAc/hexanes) gave 4.17 (3.2 g, 78%) as a clear oil.

¹H NMR (400 MHz, CDCl₃, δ): 0.04 (s, 3H), 0.07 (s, 3H), 0.80 (d, J = 8.2 Hz, 3H), 0.87-0.92 (m, 24H), 1.27-1.36 (m, 6H), 1.46-1.53 (m, 6H), 1.81-1.92 (m, 3H), 1.99-2.03 (m, 1H), 3.02 (br s, OH), 3.47-3.49 (m, 1H), 3.68-3.73 (m, 1H), 4.69 (q, J = 4.3 Hz, 1H), 5.63 (dd, J = 7.0, 1.5 Hz, 1H), ¹³C NMR (100 MHz, CDCl₃, δ): -5.0, -4.49.2, 12.3, 13.7, 15.7, 19.9, 25.8, 27.4, 29.2, 41.4, 66.2, 71.9, 140.0, 141.0; HRMS (ESI): calcd for C₂₅H₅₄O₂SiSn [M+Na]⁺: 557.2807, found 557.2818.
(2R,3R,E)-3-((tert-butyldimethylsilyl)oxy)-2-methyl-5-(tributylstannyl)hex-4-enal (4.18)

To a solution of 4.17 (1.3 g, 2.44 mmol) in CH$_2$Cl$_2$ (6.0 mL) was sequentially added TEMPO (57 mg, 0.37 mmol, 0.15 equiv), NaHCO$_3$ (1.0 g, 12.18 mmol, 5.0 equiv) and BAIB (1.6 g, 4.87 mmol, 2.0 equiv). After 3 h, the reaction mixture was diluted with CH$_2$Cl$_2$ and washed with sat. aq. NaHCO$_3$ and sat. aq. Na$_2$S$_2$O$_3$. The combined aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 5% EtOAc/hexanes) gave 4.18 (1.30 g, 97%) as a clear oil.

$^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 0.04 (s, 3H), 0.07 (s, 3H), 0.87-0.91 (m, 24H), 1.08 (d, $J = 7.2$ Hz, 3H), 1.26-1.33 (m, 6H), 1.44-1.51 (m, 6H), 1.88 (d, $J = 1.6$ Hz, 3H), 2.43-2.49 (m, 1H), 4.90-4.93 (m, 1H), 5.53 (dq, $J = 8.4$, 1.6 Hz, 1H), 9.77 (d, $J = 1.2$ Hz, 1H); 29.1, $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): -5.1, -4.3, 8.5, 9.2, 13.7, 18.1, 19.6, 25.7, 27.3, 53.0, 68.2, 140.5, 141.4, 204.8; HRMS (ESI): calcd for C$_{25}$H$_{52}$O$_2$SiSn [M+Na]$^+$: 555.2651, found 555.2560.
(2E,4S,5R,6E)-ethyl 5-((tert-butylidimethylsilyl)oxy)-4-methyl-7-(tributylstannyl)octa-2,6-dienoate (4.10)

To a suspension of Ba(OH)$_2•$8H$_2$O (2.7 g, 8.67 mmol, 1.4 equiv; dried at 110 °C for 20 h) in THF (25 mL) was added the ester-phosphonate (1.67 g, 7.43 mmol, 1.2 equiv). The white heterogeneous mixture was stirred at rt for 30 min then was cooled to 0 °C and a solution of 4.18 (3.29 g, 6.19 mmol) in wet THF (20 mL + ~25 drops of H$_2$O) was added dropwise. The reaction mixture turned very pale yellow but remained heterogeneous. After 3 h at 0 °C, the mixture was diluted with CH$_2$Cl$_2$, washed with sat. aq. NaHCO$_3$, brine, dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 5% EtOAc/hexanes) gave 4.10 (3.30 g, 89%) as a colorless oil.

(R)-4-benzyl-3-((2R,3R,E)-3-hydroxy-2-methyl-5-(tributylstannyl)hex-4-enoyl)-5,5-dimethyloxazolidin-2-one (4.19)

To a solution of 2.11 (9.5 g, 36.4 mmol) in CH$_2$Cl$_2$ (140 mL) at -10 °C was added Bu$_2$BOTf (1 M in CH$_2$Cl$_2$, 40.0 mL, 40.0 mmol, 1.10 equiv) dropwise followed by
freshly distilled Et$_3$N (6.3 mL, 45.5 mmol, 1.25 equiv) while maintaining the internal temperature below 0 °C. The reaction mixture turned orange after the addition of Bu$_2$BOTf then yellow after the addition of Et$_3$N. The reaction mixture was then cooled to -78 °C and a solution of 1.13 (14.4 g, 40.0 mmol, 1.10 equiv) in CH$_2$Cl$_2$ (40 mL) was added dropwise. The mixture became orange again. The reaction mixture was stirred 30 min at -78 °C and 2 h at 0 °C then phosphate buffer (60 mL), MeOH (200 mL) and a MeOH/H$_2$O$_2$ mix (2:1 200 mL) were sequentially added while keeping the internal temperature under 10 °C. After 1 h, the reaction mixture was concentrated in vacuo and taken up into Et$_2$O (500 mL). The aqueous layer was extracted with Et$_2$O and the combined organic layers were washed with 5% aqueous NaHCO$_3$, brine, dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 10% EtOAc/hexanes) gave 4.19 (22.2 g, 99%) as a colorless oil.

R$_f$ (CH$_2$Cl$_2$, KMnO$_4$ stain): 0.43; [α]$^2_{D}$ + 11.7 (c 1.10, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$, δ): 0.89 (t, $J$ = 7.5 Hz, 15H), 1.20 (d, $J$ = 7 Hz, 3H), 1.31 (q, $J$ = 7.5 Hz, 6H), 1.38 (s, 3H), 1.39 (s, 3H), 1.49 (m, 6H), 1.91 (d, $J$ = 1.5 Hz, 3H), 2.58 (br s, 1H), 2.9 (dd, $J$ = 14.5, 9.5 Hz, 1H), 3.08 (dd, $J$ = 14.5, 4.5 Hz, 1H), 3.89 (m, 1H), 4.53 (m, 1H), 4.85 (m, 1H), 5.58 (m, 1H), 7.27 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$, δ): 9.3, 11.8, 13.8, 20.0, 22.3, 27.5, 28.6, 29.2, 35.5, 43.1, 63.5, 67.8, 82.3, 127.0 (Ar), 128.8 (Ar), 129.2 (Ar), 136.8, 139.5, 143.5, 152.5, 176.9; IR (thin film) $\nu_{max}$ (cm$^{-1}$): 3500, 2955, 2925, 1778, 1693, 1454, 1354, 1276, 1234, 1101; HRMS (ESI): calcd for C$_{31}$H$_{51}$N$_1$O$_4$Sn [M+Na]$^+$: 644.2739, found 644.2757.
To a solution of 4.19 (1.00 g, 1.61 mmol) in THF (50 mL) at -78 °C was slowly added DIBAL (1 M in THF, 4.8 mL, 4.84 mmol, 3.0 equiv). After 1 h, the reaction was quenched by the addition of aqueous phosphate buffer (pH = 7.2). The mixture was diluted with CH₂Cl₂, warmed to rt and transferred into a separatory funnel. The content of the funnel was then slowly poured and filtered through a pad of Celite (this method allows the easy filtration of the organic layer first, then the aqueous layer. The aqueous layer contains all the salts and can easily clog the filter). The Celite was washed with CH₂Cl₂ and the whole filtrate was reloaded into the separatory funnel (the separation of the two phases was then clear. If not, the mixture was filtered through Celite one more time). The organic layer was separated, NOT dried, and concentrated in vacuo to give 4.13 as a pale yellow oil that was used in the following step without further purification.
A solution of diethylphosphonoacetic acid ethyl ester (384 μL, 1.94 mmol, 1.20 equiv) and Ba(OH)₂•8H₂O (712 mg, 2.26 mmol, 1.40 equiv; dried at 110 °C for 20 h) in THF (6 mL) was stirred at rt for 30 min then cooled to 0 °C. A solution of crude 4.13 (assumed 671 mg, 1.61 mmol) in wet THF (6 mL + 0.1 mL of H₂O) was then added to the phosphonate. The reaction mixture was maintained at 0 °C for 3 h then sat. aq. NaHCO₃ and CH₂Cl₂ were added. The organic layer was separated, washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 25% EtOAc/hexanes) gave 2.8 (600 mg, 76% over two steps) as a pale yellow oil.

Rf (CH₂Cl₂, KMnO₄ stain): 0.33; [α]₂⁺² + 2.6 (c 1.00, CHCl₃); ¹H NMR (500 MHz, CDCl₃, δ): 0.88 (t, J = 7.5 Hz, 15H), 1.10 (d, J = 7.0 Hz, 3H), 1.30 (m, 9H), 1.48 (m, 6H), 1.56 (br s, 1H), 1.90 (d, J = 1.5 Hz, 3H), 2.52 (q, J = 7.0 Hz, 1H), 4.18 (q, J = 7.0 Hz, 2H), 4.50 (dd, J = 6.0, 8.5 Hz, 1H), 5.50 (dq, J = 2.0, 8.5 Hz, 1H), 5.85 (dd, J = 1.0, 16.0 Hz, 1H), 6.97 (dd, J = 7.5, 15.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃, δ): 9.2, 13.7, 14.3, 14.5, 19.9, 27.4, 29.2, 42.8, 60.2, 70.0, 121.7, 140.4, 143.6, 150.4, 166.6; IR (thin film) νmax (cm⁻¹): 3434, 2956, 2926, 2871, 2852, 1721, 1651, 1456, 1374, 1272, 1179, 1020; HRMS (ESI): calcd for C₂₃H₄₄O₃Sn [M+Na]^+: 511.2209, found: 511.2219.

oxazolidine-2,4-dione (5.10)
To a solution of 5.8 (100 mg, 1.33 mmol) and NaOMe (76 mg, 1.41 mmol, 1.06 equiv) in MeOH (1 mL) was added 5.9 (186 μL, 181 mg, 1.54 mmol, 1.15 equiv) and the reaction was heated at reflux overnight (12 h). The reaction was cooled to rt, quenched with water, extracted with Et₂O, and the aqueous layer was acidified to pH = 1 with 2 N HCl. The resulting solution was extracted with EtOAc and the combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo. The resulting white solid was suspended in benzene and the residual water was removed by distilling the benzene–water azeotrope and leaving overnight on a high vacuum line to give 5.10 (110 mg, 82%) as a white solid.

Rᵣ (10:10:1 MeOH:CHCl₃:NH₄OH, CAM stain): 0.16; ¹H NMR (400 MHz, acetone-d₆, δ): 4.80 (s, 2H); ¹³C NMR (100 MHz, CDCl₃, δ): 70.0, 156.6, 173.0; IR (thin film) ν ᵐᵝ (cm⁻¹): 3216, 3010, 2961, 1814, 1760, 1434, 1387, 1171, 1057, 1006, 960, 906.

oxazole-2-thiol (5.21)

\[
\text{KSCN} + \text{EtOH}_2\text{O} \xrightarrow{\text{HCl}} \text{EtOH}_2\text{O} \xrightarrow{\text{HCl}} \text{HSCN} \xrightarrow{\text{CH}_3\text{CN}} \text{5.21}
\]

To a suspension of 5.19 (27 g, 279 mmol, 1.5 equiv) in MeCN (450 mL) was added concentrated HCl (24.8 mL, 29.3 g, 298 mmol, 1.6 equiv). After stirring the resulting milky white solution at rt for 30 min, the precipitates were removed by filtration through Celite (previously washed with 10% HCl/CH₃CN) and washed with CH₃CN. To the resulting pale yellow solution of HSCN was added 5.20 (25 g, 186 mmol) and the mixture was refluxed for 4 h. After being cooled to rt, the reaction mixture was filtered...
and the filtrate concentrated *in vacuo*. The crude brown residue was taken in cold acetone, filtered and rinsed with cold acetone. The filtrate was dried (Drierite), filtered and concentrated *in vacuo* to give 5.21 (18.4 g, 98%) as a brown solid. Spectroscopic data for this compound matched the previously reported literature values.  

\(^1\)H NMR (250 MHz, CDCl\(_3\), δ): 6.92 (d, \(J = 1.7\) Hz, 1H), 7.33 (d, \(J = 1.8\) Hz, 1H); \(^13\)C NMR (62.5 MHz, CDCl\(_3\), δ): 116.0, 137.4; IR (thin film) \(\nu_{max}\) (cm\(^{-1}\)): 3119, 2925, 1588, 1472, 1255, 1166, 1091, 1034.

\( \text{2-(butylthio)oxazole (5.22)} \)

![Chemical reaction diagram](image)

A solution of 5.21 (3.60 g, 35.6 mmol) in THF (90 mL) was slowly added to pentane-washed KH (1.70 g, 42.7 mmol, 1.20 equiv) in THF (90 mL) at -78 °C, and allowed to stir 30 min. 1-Iodobutane (7.30 mL, 64.1 mmol, 1.80 equiv) was then added slowly and the reaction was allowed to warm to rt overnight (14 h). The reaction was then quenched with sat. aq. NH\(_4\)Cl (60 mL) and was diluted with H\(_2\)O (100 mL). The layers were separated and the aqueous layer was extracted with Et\(_2\)O. The combined organic layers were washed with brine, dried (MgSO\(_4\)), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5 to 20% Et\(_2\)O/pentane) gave 5.22 (5.20 g, 93%) as a yellow oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\), δ): 0.94 (t, \(J = 7.5\) Hz, 3H), 1.44-1.49 (m, 2H), 1.71-1.77 (m, 2H), 3.17 (t, \(J = 7.5\) Hz, 2H), 7.09 (s, 1H), 7.64 (s, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\), 205
δ): 13.7, 21.8, 31.8, 32.5, 128.5, 140.0, 161.1; IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 2959, 2872, 1534, 1489; HRMS (ESI): calcd for C\(_7\)H\(_{11}\)NOS \([\text{M+Na}]^+\): 180.0454, found: 180.0449.

5-bromo-2-(butylthio)oxazole (5.23)

![Chemical structure diagram]

To a solution of 5.22 (1.00 g, 6.36 mmol) in THF (60 mL) at \(-78\) °C was added \( n\)-BuLi (1.61 M in hexanes, 3.75 mL, 6.04 mmol, 0.95 equiv) dropwise. The reaction mixture was stirred for 30 min at \(-78\) °C then a solution of CBr\(_4\) (2.53 g, 7.63 mmol, 1.20 equiv) in THF (2 mL) was added. The dark green reaction mixture was stirred for 1 h at \(-78\) °C then was allowed to warm to rt over 2 h. The reaction was quenched with sat. aq. NH\(_4\)Cl then diluted with water. The layers were separated and the aqueous layer was extracted with Et\(_2\)O. The combined organic layers were washed with brine, dried (MgSO\(_4\)), filtered and concentrated \textit{in vacuo}. Purification by flash chromatography (silica gel, 10% Et\(_2\)O/pentane) gave 5.23 (1.10 g, 73%) as a yellow oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\), δ): 0.94 (t, \( J = 7.5 \) Hz, 3H), 1.42-1.49 (m, 2H), 1.69-1.75 (m, 2H), 3.15 (t, \( J = 7.5 \) Hz, 2H), 6.94 (s, 1H); \(^13\)C NMR (125 MHz, CDCl\(_3\), δ): 13.7, 21.9, 31.6, 32.6, 121.4, 128.7, 162.2; IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 2959, 2872, 1540, 1483; HRMS (ESI): calcd for C\(_7\)H\(_{10}\)BrNOS \([\text{M+Na}]^+\): 257.9559, found 257.9554.
2-(butylthio)-5-iodooxazole (5.24)

To a solution of 5.22 (5.40 g, 34.3 mmol) in THF (200 mL) at −78 °C was slowly added n-BuLi (1.65 M in hexanes, 19.8 mL, 32.6 mmol, 0.95 equiv) dropwise. The orange reaction mixture was stirred for 30 min at −78 °C then a solution of I₂ (10.7 g, 42.0 mmol, 1.20 equiv) in THF (50 mL) was added. The dark red reaction mixture was stirred for 3 h at −78 °C then 1 h at 0 °C. EtOAc was added and the solution was washed with sat. aq. NaHSO₃. The organic layer was separated, dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 10% CH₂Cl₂/hexanes) gave 5.24 (9.18 g, 94%) as a light orange oil.

¹H NMR (500 MHz, CDCl₃, δ): 0.94 (t, J = 7.5 Hz, 3H), 1.44-1.48 (m, 2H), 1.69-1.75 (m, 2H), 3.16 (t, J = 7.5 Hz, 2H), 7.09 (s, 1H); ¹³C NMR (125 MHz, CDCl₃, δ): 13.7, 21.9, 31.6, 32.6, 85.8, 137.0, 165.0; IR (thin film) νmax (cm⁻¹): 2950, 2926, 1521, 1468; HRMS (ESI): calcd for C₇H₁₀INOS [M+Na]⁺: 305.9420, found: 305.9405.

4-bromo-2-(butylthio)oxazole (5.25)


\[ i-\text{Pr}_2\text{NH} \text{ (447 } \mu\text{L, 3.19 mmol, 1.60 equiv) was dissolved in THF (10 mL) and cooled to 0 } ^\circ\text{C then } n-\text{BuLi (1.4 M in hexanes, 2.00 mL, 3.00 mmol, 1.50 equiv) was added slowly. The reaction was allowed to stir for 5 min at 0 } ^\circ\text{C then was cooled to } -78 \ ^\circ\text{C. A solution of 5.23 (470 mg, 1.99 mmol) in THF (5 mL) was quickly added in one portion. The reaction was allowed to stir for 5 min at -78 } ^\circ\text{C then was poured into water. The layers were separated and the aqueous layer was extracted with Et}_2\text{O. The combined organic layers were washed with brine, dried (MgSO}_4\text{), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 5% Et}_2\text{O/hexanes) gave 5.25 (419 mg, 89%) as a light yellow oil.} \]

\[ ^1\text{H NMR (500 MHz, CDCl}_3, \delta) : 0.94 (t, J = 7.5 Hz, 3H), 1.42-1.50 (m, 2H), 1.70-1.76 (m, 2H), 3.20 (t, J = 7.5 Hz, 2H), 7.60 (s, 1H); ^1\text{C NMR (125 MHz, CDCl}_3, \delta) : 13.7, 21.9, 31.5, 32.5, 116.5, 137.94, 162.2; IR (thin film) \nu_{\text{max}} (\text{cm}^{-1}) : 3164, 2959, 2871, 1537, 1478, 1265; \text{HRMS (ESI): calcld for C}_7\text{H}_{10}\text{BrNOS [M+Na]}^+: 257.9559, \text{found: 257.9555.} \]

\[ \text{2-(butylthio)-4-iodooxazole (2.7)} \]

\[ \begin{align*}
\text{5.24} & \quad + \quad \text{5.23} \\
\xrightarrow{\text{LDA, THF}} & \quad \rightarrow \\
\text{2.7}
\end{align*} \]

\[ i-\text{Pr}_2\text{NH} \text{ (280 } \mu\text{L, 2.00 mmol, 2.00 equiv) was dissolved in THF (6 mL), cooled to 0 } ^\circ\text{C then } n-\text{BuLi (1.3 M in hexanes, 1.38 mL, 1.80 mmol, 1.80 equiv) was added slowly. The reaction was allowed to stir for 5 min at 0 } ^\circ\text{C then was cooled to } -78 \ ^\circ\text{C. A solution of 5.24 (283 mg, 1.00 mmol) and 5.23 (24 mg, 0.10 mmol, 0.10 equiv) in THF (4 mL) } \]
was prepared and cooled to -78 °C. The LDA solution was then transferred via cannula into the oxazole mixture by slow dropwise addition over 10 min. The reaction was allowed to stir for 2 min at -78 °C then was quickly cannula transferred into water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated \textit{in vacuo}. Purification by flash chromatography (silica gel, 3\% EtOAc/hexanes) gave \textbf{2.7} (201 mg, 71\%) as a light yellow oil.

\(^1\)H NMR (500 MHz, CDCl₃, δ): 0.94 (t, \(J = 7.5\) Hz, 3H), 1.42-1.48 (m, 2H), 1.69-1.74 (m, 2H), 3.18 (t, \(J = 7.5\) Hz, 2H), 7.64 (s, 1H); \(^{13}\)C NMR (125 MHz, CDCl₃, δ): 13.7, 21.9, 31.4, 32.5, 82.3, 143.7, 162.7; IR (thin film) \(\nu_{\max}\) (cm\(^{-1}\)): 2959, 2872, 1503, 1405; HRMS (ESI): calcd for C\(_7\)H\(_{10}\)INOS [M+Na]\(^+\): 305.9402, found: 305.9408.

When 5 mol \% 5-bromo-2-thiobutyl oxazole \textbf{5.23} was used, the desired 4-iodo-2-thiobutyl oxazole \textbf{2.7} was obtained in 58\% yield (166 mg, addition time of LDA: 8 min 40 s). When no \textbf{5.23} was used, the desired 4-iodo-2-thiobutyl oxazole \textbf{2.7} was obtained in 43\% yield (124 mg, addition time of LDA: 9 min 54 s).

\textbf{General procedure for halogen dance of \textbf{5.24} with higher dilution.}

\(i\)-Pr\(_2\)NH (280 μL, 2.00 mmol, 2.00 equiv) was dissolved in THF (12 mL), cooled to 0 °C then \(n\)-BuLi (1.3 M in hexanes, 1.38 mL, 1.80 mmol, 1.80 equiv) was added slowly. The reaction was allowed to stir for 5 min at 0 °C then was cooled to –78 °C. A solution of \textbf{5.24} (283 mg, 1.00 mmol) and \textbf{5.23} (24 mg, 0.10 mmol, 0.10 equiv) in THF (6 mL) was prepared and cooled to -78 °C. The LDA solution was then transferred via cannula into the oxazole mixture by slow dropwise addition over 50 min. The reaction was
allowed to stir for 2 min at -78 °C then was quickly transferred via cannula into water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 3% EtOAc/hexanes) gave 2.7 (241 mg, 85%) as a light yellow oil.

When 5 mol % 5-bromo-2-thiobutyl oxazole 5.23 was used, the desired 4-iodo-2-thiobutyl oxazole 2.7 was obtained in 79% yield (226 mg, addition time of LDA: 60 min). When no 5.23 was used, the desired 4-iodo-2-thiobutyl oxazole 2.7 was obtained in 64% yield (181 mg, addition time of LDA: 50 min). When the reaction was performed on a 10 mmol scale (2.83 g) with no 5.23 and only 1.6 equiv of LDA, the desired 4-iodo-2-thiobutyl oxazole 2.7 was obtained in 65% yield (1.85 g, addition time of LDA: 140 min).

2-(butylthio)-4,5-diiiodooxazole (5.31)

\[
\begin{align*}
\text{LDA, I₂} & \quad \text{THF} \\
5.24 & \quad \rightarrow \\
5.31 & 
\end{align*}
\]

To a solution of i-Pr₂NH (112 μL, 0.80 mmol, 1.60 equiv) in THF (4 mL) at 0 °C was added n-BuLi dropwise (1.5 M in hexanes, 0.5 mL, 0.75 mmol, 1.50 equiv). After 5 min at 0 °C, the mixture was cooled to -78 °C and a solution of 5.24 (142 mg, 0.50 mmol, 1.00 equiv) in THF (2 mL) was quickly added. After 5 min at -78 °C, a solution of I₂ (127 mg, 0.50 mmol, 1.00 equiv) in THF (2 mL) was added giving rise to a dark red
reaction mixture. The mixture was maintained at -78 °C for 5 min then quenched with sat. aq. NaHSO₃ and diluted with H₂O. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 5% Et₂O/hexanes) gave 5.31 (59 mg, 29%) as a colorless oil along with 5.24 (66 mg, 47%) as a colorless oil in 76% overall yield.

¹H NMR (500 MHz, CDCl₃, δ): 0.94 (t, J = 7.5 Hz, 3H), 1.46 (sext, J = 7.5 Hz, 2H), 1.72 (p, J = 7.5 Hz, 2H), 3.17 (t, J = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃, δ): 13.5, 21.6, 31.1, 32.5, 96.0, 96.4, 166.3; IR (thin film) νmax (cm⁻¹): 2957, 2929, 2870, 1470, 1191, 1149, 1075, 972; HRMS (ESI): calcd for C₇H₉I₂NOS [M+Na]⁺: 431.8386, found: 431.8379.

2-(butylthio)-4-iodooxazole (2.7)

To a solution of 5.31 (59 mg, 0.14 mmol) in THF (5 mL) at -78 °C was added n-BuLi (1.5 M in hexanes, 0.10 mL, 0.14 mmol, 1.00 equiv) dropwise. After 3 min at -78 °C, H₂O (10 mL) was added and the reaction mixture was warmed to rt. The bulk of the THF was removed under vacuum and the resulting mixture was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo to give 2.7 (40 mg, 98%) as a pale yellow oil.
^{1}H NMR (500 MHz, CDCl$_3$, $\delta$): 0.94 (t, $J = 7.5$ Hz, 3H), 1.42-1.48 (m, 2H), 1.69-1.74 (m, 2H), 3.18 (t, $J = 7.5$ Hz, 2H), 7.64 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$, $\delta$): 13.7, 21.9, 31.4, 32.5, 82.3, 143.7, 162.7; IR (thin film) $v_{\text{max}}$ (cm$^{-1}$): 2959, 2872, 1503, 1405; HRMS (ESI): calcd for C$_7$H$_{10}$INO$_5$ [M+Na]$^+$: 305.9402, found: 305.9408.

4-bromo-2-(butylthio)-5-iodooxazole (5.35)

![Chemical Structure]

To a solution of 5.25 (237 mg, 1.00 mmol) in THF (20 mL) at -78 °C was added $n$-BuLi (1.35 M in hexanes, 0.78 mL, 1.05 mmol, 1.05 equiv) dropwise. After 5 min at -78 °C, I$_2$ (279 mg, 1.10 mmol, 1.10 equiv) in THF (3 mL) was added. The dark red reaction was then quenched with sat. aq. NaHSO$_3$ and water, and was warmed to rt. The bulk of the THF was removed under vacuum and the resulting mixture was extracted with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 3% EtOAc/hexanes) gave 5.35 (140 mg, 39%) as a pale yellow oil.

^{1}H NMR (500 MHz, CDCl$_3$, $\delta$): 0.94 (t, $J = 7.5$ Hz, 3H), 1.45 (sext, $J = 7.5$ Hz, 2H), 1.72 (p, $J = 7.5$ Hz, 2H), 3.18 (t, $J = 7.5$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$, $\delta$): 13.5, 21.7, 31.1, 32.5, 87.9, 126.6, 165.7; IR (thin film) $v_{\text{max}}$ (cm$^{-1}$): 2958, 2929, 2871, 1519, 1470, 1200, 1084, 986; HRMS (ESI): calcd for C$_7$H$_9$BrINO$_5$ [M+Na]$^+$: 385.8504, found: 385.8531.
5-bromo-2-(isopropylthio)oxazole (5.38)

To a solution of 5.43 (775 mg, 5.41 mmol) in THF (25 mL), at –78 °C under N₂ was slowly added n-BuLi (1.5 M in hexanes, 3.8 mL, 5.70 mmol, 1.05 equiv) dropwise. The reaction mixture was stirred for 30 min at –78 °C then a solution of CBr₄ (1.80 g, 5.44 mmol, 1.01 equiv) in THF (5 mL) was added. The dark reaction mixture was stirred for 1 h at –78 °C then was allowed to warm to rt over 2 h. The reaction was quenched with sat. aq. NH₄Cl then was diluted with water. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 10% Et₂O/hexanes) gave 5.38 (1.09 g, 91%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃, δ): 1.43 (d, J = 6.5 Hz, 6H), 3.75-3.80 (m, 1H), 6.97 (s, 1H); ¹³C NMR (100 MHz, CDCl₃, δ): 23.3, 38.9, 121.4, 128.5, 161.3; IR (thin film) νₘₐₓ (cm⁻¹): 3140, 2967, 2927, 2866, 1540, 1483, 1368, 1246, 1152, 1106, 1058, 950; HRMS (ESI): calcd for C₆H₈BrNOS [M+Na]⁺: 243.9402, found 243.9404.
4-iodo-2-(isopropylthio)oxazole (5.42)

\[
\text{5.44} \quad \xrightarrow{\text{LDA, THF}} \quad \text{5.42}
\]

\(i\)-Pr\(_2\)NH (1.6 mL, 11.30 mmol, 1.54 equiv) was dissolved in THF (30 mL) and cooled to 0 °C then \(n\)-BuLi (1.45 M in hexanes, 7.6 mL, 11.02 mmol, 1.50 equiv) was slowly added. The reaction was allowed to stir for 5 min at 0 °C then was cooled to –78 °C. A solution of 5.44 (1.98 g, 7.30 mmol) in THF (10 mL) was prepared at -78 °C. The LDA solution was cooled to -78 °C and was slowly added dropwise to the oxazole solution. The reaction was allowed to stir for 30 min at -78 °C then was poured into water. The layers were separated and the aqueous layer was extracted with Et\(_2\)O. The combined organic layers were washed with brine, dried (MgSO\(_4\)), filtered and concentrated \textit{in vacuo}. Purification by flash chromatography (silica gel, 5% Et\(_2\)O/hexanes) gave 5.42 (615 mg, 31%) as a light yellow oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\), \(\delta\)): 1.43 (d, \(J = 7.0\) Hz, 6H), 3.81-3.86 (m, 1H), 7.66 (s, 1H); \(^13\)C NMR (125 MHz, CDCl\(_3\), \(\delta\)): 23.3, 38.8, 82.2, 143.5, 161.9; IR (thin film) \(\nu_{\text{max}}\) (cm\(^{-1}\)): 3157, 2966, 2926, 2865, 1470, 1368, 1259, 1151, 1118, 1075, 936; HRMS (ESI): calcd for C\(_6\)H\(_8\)INOS [M+Na\(^+\): 291.9263, found: 291.9249.
2-(isopropylthio)oxazole (5.43)

A solution of 5.21 (922 mg, 9.11 mmol) in THF (20 mL) was added to pentane-washed KH (439 mg, 10.94 mmol, 1.20 equiv) in THF (25 mL) at -78 °C, and allowed to stir 30 min. 2-Iodopropane (2.80 mL, 28.10 mmol, 3.00 equiv) was added to the reaction at -78 °C then the reaction mixture was stirred at rt for 3 h and at 40 °C overnight (14 h). The reaction was then quenched with sat. aq. NH₄Cl and was diluted with H₂O. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 5% Et₂O/hexanes) gave 5.43 (716 mg, 55%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃, δ): 1.42 (d, J = 6.8 Hz, 6H), 3.79 (sept, J = 6.8 Hz, 1H), 7.10 (s, 1H), 7.64 (s, 1H); ¹³C NMR (100 MHz, CDCl₃, δ): 23.4, 38.6, 128.4, 139.9, 160.3; IR (thin film) νmax (cm⁻¹): 3217, 2968, 2928, 1534, 1488, 1318, 1246, 1151, 1095, 1058; HRMS (ESI): calcd for C₆H₉NOS [M+Na]⁺: 166.0297, found: 166.0289.

5-iodo-2-(isopropylthio)oxazole (5.44)
To a solution of 5.43 (629 mg, 4.40 mmol) in THF (20 mL) at –78 °C under N₂ was added n-BuLi (1.6 M in hexanes, 2.9 mL, 4.64 mmol, 1.05 equiv) dropwise. The orange reaction mixture was stirred for 30 min at –78 °C then a solution of I₂ (1.21 g, 4.75 mmol, 1.08 equiv) in THF (5 mL) was added. The dark red reaction mixture was stirred for 3 h at –78 °C then 1 h at 0 °C. EtOAc was added and the solution was washed with sat. aq. NaHSO₃. The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 5% Et₂O/hexanes) gave 5.44 (574 mg, 49%) as a light orange oil.

¹H NMR (500 MHz, CDCl₃, δ): 1.42 (d, J = 7.0 Hz, 6H), 3.76-3.82 (m, 1H), 7.11 (s, 1H); ¹³C NMR (125 MHz, CDCl₃, δ): 23.3, 39.0, 86.0, 136.9, 164.2; IR (thin film) ν max (cm⁻¹): 3133, 2966, 2926, 2865, 1525, 1470, 1368, 1244, 1150, 1106, 1072, 944; HRMS (ESI): calcd for C₆H₈INO₂ [M+Na]+: 291.9263, found: 291.9256.

Scrambling Experiment

\[ \text{i-Pr₂NH (280 µL, 2.00 mmol, 2.00 equiv) was diluted with THF (8 mL) and cooled to 0 °C then n-BuLi (1.3 M in hexanes, 1.38 mL, 1.80 mmol, 1.80 equiv) was added slowly. The reaction was allowed to stir for 5 min at 0 °C then was cooled to –78 °C. A solution of 5.24 (283 mg, 1.00 mmol) and 5.38 (22 mg, 0.10 mmol, 0.10 equiv) in THF (6 mL) was prepared and cooled to -78 °C. The LDA solution was then transferred via cannula} \]
into the oxazole mixture by slow dropwise addition over 12 min. The reaction was monitored by GC every minute for the first five minutes then every 2 min until the end of the addition. At the end of the addition, the reaction mixture was allowed to stir for 2 min at -78 °C then was quickly transferred via cannula into water. Due to the large number of products, the reaction mixture was not purified further.

\((E)-2\text{-methyl-5-(tributylstannyl)hex-4-en-3-ol} (6.5)\)

To a solution of 1.13 (1.823 g, 5.08 mmol) in THF (25 mL) at 0 ºC was slowly added \(\text{-PrMgCl} \) (2.0 M, 3.05 mL, 6.10 mmol, 1.2 equiv). The solution was allowed to warm to rt then was stirred for 1 h and quenched with sat. aq. \(\text{NH}_4\text{Cl}\). The layers were separated and the aqueous layer was extracted with \(\text{Et}_2\text{O}\). The combined organic layers were washed with brine, dried (\(\text{MgSO}_4\)), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 10\% EtOAc/hexanes) gave 6.5 (983 mg, 48\%) as a clear oil.

\(^1\text{H NMR} \text{ (400 MHz, CDCl}_3\text{, }\delta)\): 0.85-0.91 (m, 18H), 0.96 (d, \(J = 6.4 \text{ Hz}\), 3H), 1.26-1.36 (m, 6H), 1.45-1.55 (m, 6H), 1.69 (d, \(J = 1.6 \text{ Hz}\), 3H), 4.23-4.27 (m, 1H), 5.52-5.55 (m, 1H); \(^{13}\text{C NMR} \text{ (100 MHz, CDCl}_3\text{, }\delta)\): 9.2, 13.7, 18.1, 18.3, 27.4, 29.2, 34.3, 72.1, 141.8, 142.2; \(\text{IR} \text{ (thin film) } \nu_{\text{max}} \text{ (cm}^{-1})\): 3367, 2956, 2926, 1464; Anal. calcd for \(\text{C}_{19}\text{H}_{40}\text{OSn}\): C, 56.59; H, 10.00, found C, 56.74; H, 9.91.
*(E)-5-(2-(butylthio)oxazol-4-yl)-2-methylhex-4-en-3-ol (6.6)*

In the glovebox, PdCl$_2$(CH$_3$CN)$_2$ (11.0 mg, 0.042 mmol, 4 mol %) and LiCl (151 mg, 3.56 mmol, 3.56 equiv) were placed in a 15 mL round bottom flask. The flask was removed from the glovebox and DMF (6 mL) was added, followed by 2.7 (283 mg, 1.00 mmol) and 6.5 (403.3 mg, 1.00 mmol, 1.0 equiv) then the reaction was stirred at 90 °C for 20 h. After this time, the reaction was allowed to cool to rt then 5% aq. HCl and Et$_2$O were added. The layers were separated and the aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with water, brine, dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 20% EtOAc/hexanes) gave 6.6 (167 mg, 62%) as a light yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$, δ): 0.90 (d, $J$ = 6.8 Hz, 3H), 0.94 (t, $J$ = 7.2 Hz, 3H), 1.00 (d, $J$ = 6.8 Hz, 3H), 1.46 (m, 2H), 1.54 (br s, 1H), 1.69-1.84 (m, 3H), 1.93 (d, $J$ = 1.2 Hz, 3H), 3.17 (t, $J$ = 7.6 Hz, 2H), 4.21 (dd, $J$ = 9.2, 6.8 Hz, 1H), 6.32 (dd, $J$ = 9.2, 1.2 Hz, 1H), 7.51 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 13.7, 14.3, 18.4, 21.9, 31.8, 32.4, 34.7, 73.4, 127.1, 129.1, 135.0, 143.8, 160.9; IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$): 3367, 2958, 2930, 2872, 1504; HRMS (ESI): calcd for C$_{14}$H$_{23}$NO$_2$S [M+Na]$^+$: 292.1342, found: 292.1328.
In the glovebox, Pd(dba)$_2$ (59 mg, 0.10 mmol, 0.05 equiv), P(2-furyl)$_3$ (71 mg, 0.31 mmol, 0.15 equiv) and CuI (664 mg, 3.49 mmol, 1.70 equiv) were placed in a 250 mL flask. The flask was removed from the box, placed under N$_2$ and equipped with a reflux condenser. A solution of 2.8 (1.00 g, 2.05 mmol) and 2.7 (639 mg, 2.26 mmol, 1.10 equiv) in DMSO (70 mL) was added and the reaction was heated to 65 °C for 48 h. The mixture was cooled to rt, diluted with EtOAc and washed with small volumes of water. The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 20% EtOAc/hexanes) gave 6.7 (444 mg, 61%) as a yellow oil.

R$_f$ (25% EtOAc/hexanes, KMnO$_4$ stain): 0.28; $[\alpha]_{D}^{22} = -20.4$ (c 1.50, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$, δ): 0.95 (t, $J$ = 7.5 Hz, 3H), 1.15 (d, $J$ = 7 Hz, 3H), 1.28 (t, $J$ = 7 Hz, 3H), 1.47 (sext, $J$ = 7 Hz, 2H), 1.74 (p, $J$ = 7.5 Hz, 2H), 1.94 (s, 3H), 2.61 (sext, $J$ = 7 Hz, 1H), 3.18 (t, $J$ = 7.5 Hz, 2H), 4.18 (q, $J$ = 7 Hz, 2H), 4.46-4.49 (m, 1H), 5.88 (dd, $J$ = 16, 1.5 Hz, 1H), 6.30 (dd, $J$ = 9, 1.5 Hz, 1H), 7.00 (dd, $J$ = 15.5, 1.5 Hz, 1H), 7.53 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$, δ): 13.6, 14.3 (2C), 14.6, 21.8, 31.7, 32.3, 42.9, 60.3, 71.1, 122.0, 127.6, 127.9, 135.3, 143.4, 150.1, 161.0, 166.7; IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$): 3332,
2960, 2930, 2873, 1714, 1455, 1370, 1274, 1183; HRMS (ESI): calcd for C_{18}H_{27}NO_{4}S [M+Na]^+: 376.1553, found 376.1540.

(2E,4S,5R,6E)-ethyl 5-((tert-butyldimethylsilyl)oxy)-7-(2-(butylthio)oxazol-4-yl)-4-methylocta-2,6-dienoate (6.2)

To a solution of 6.7 (670 mg, 1.90 mmol) in CH_{2}Cl_{2} (30 mL) at 0 °C under N\textsubscript{2} were added 2,6-lutidine (1.1 mL, 9.48 mmol, 5.00 equiv) and TBSOTf (566 μL, 2.46 mmol, 1.3 equiv) dropwise. The reaction mixture was stirred at 0 °C for 2 h then was allowed to warm to rt overnight (14 h). The mixture was diluted with CH_{2}Cl_{2} then washed with sat. aq. NaHCO\textsubscript{3} and brine. The organic layer was dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and concentrated \textit{in vacuo}. Purification by flash chromatography (silica gel, 10% EtOAc/hexanes) gave 6.2 (578 mg, 65%) as a yellow oil.

R\textsubscript{f} (10% EtOAc/hexanes, KMnO\textsubscript{4} stain): 0.42; \([\alpha]_{D}^{22} = 33.0\) (c 1.00, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}, δ): -0.01 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 0.94 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 6.5 Hz, 3H), 1.27 (t, J = 7 Hz, 3H), 1.46 (sext, J = 7.5 Hz, 2H), 1.75 (p, J = 7 Hz, 2H), 1.87 (s, 3H), 2.49 (q, J = 7 Hz, 1H), 3.12-3.21 (m, 2H), 4.17 (qd, J = 7, 1.5 Hz, 2H), 4.42 (dd, J = 9, 5.5 Hz, 1H), 5.80 (dd, J = 16.0, 1.0 Hz, 1H), 6.24 (dd, J = 9.0, 1.0 Hz, 1H), 7.00 (dd, J = 16.0, 7.5 MHz, 1H), 7.49 (s, 1H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3},
δ): -4.9, -4.1, 13.6, 14.3 (2C), 14.4, 18.3, 21.8, 25.9, 31.8, 32.3, 43.8, 60.2, 72.4, 121.2, 124.9, 129.7, 134.8, 143.7, 151.3, 160.6, 166.8; IR (thin film) ν\(_{\text{max}}\) (cm\(^{-1}\)):\ 2957, 2929, 2857, 1722, 1651, 1511, 1463, 1367, 1265, 1180, 1057, 837, 776; HRMS (ESI): calcd for C\(_{24}\)H\(_{41}\)NO\(_4\)SSi [M+Na]\(^+\): 490.2418, found 490.2433.

(2\(E\),4\(S\),5\(R\),6\(E\))-ethyl 5-((tert-butyldimethylsilyl)oxy)-7-((3\(S\),5\(S\))-5-((4\(R\),5\(R\))-2,2-dimethyl-5-((triethylsilyl)oxy)-1,3-dioxan-4-yl)-5-methoxy-3-methylpentyl)oxazol-4-yl)-4-methylocta-2,6-dienoate (6.11)

![Reaction Scheme]

In the glovebox, a suspension of Zn (88 mg, 1.34 mmol, 1.5 equiv), LiCl (38 mg, 0.89 mmol, 1.0 equiv) and I\(_2\) (23 mg, 0.09 mmol, 0.1 equiv) in THF (0.5 mL) was prepared in an oven dried Schlenk tube with a stir bar. The reaction was stirred until the red color had fully dissipated (~1 min). A solution of 2.6 (392 mg, 0.89 mmol) in THF (0.1 mL) was then added dropwise and rinsed (2 x 0.2 mL). The Schlenk tube was sealed and parafilmed, taken out of the box and stirred at 60 °C overnight (12 h). GC of an aliquot quenched in MeOH showed >90% conversion, and HRMS of an aliquot quenched
in D$_2$O shows ~2:1 D:H. The Schlenk tube was cooled to rt and brought back into the box.

In the glovebox, Pd(PPh$_3$)$_4$ (100 mg, 0.086 mmol, 20 mol %) and ZnBr$_2$ (240 mg, 1.1 mmol, 2.5 equiv) were weighed in a small vial with a stir bar. A solution of 6.2 (200 mg, 0.43 mmol) in THF (1 mL) was added to the reaction followed by the Zn reagent (assumed 0.89 M, 1 mL, 0.89 mmol, 2.0 equiv). The vial was capped, taken out of the glovebox and stirred at 60 °C overnight (12 h). The reaction was diluted with Et$_2$O and quenched with sat. aq. NaHCO$_3$. The layers were separated and the aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 5 to 20% EtOAc/hexanes) gave 6.11 (116 mg, 37%) as an orange oil.

$R_f$ (20% EtOAc/hexanes, CAM stain): 0.42; $[\alpha]_{D}^{22}$ $\approx$ -39.6 (c 1.55, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$, $\delta$): -0.02 (s, 3H), 0.03 (s, 3H), 0.61 (qd, $J$ = 8.5, 1.5 Hz, 6H), 0.88 (s, 9H), 0.97 (m, 12H), 1.10 (d, $J$ = 6.5 Hz, 3H), 1.27 (t, $J$ = 7 Hz, 3H), 1.30 (m, 1H), 1.41 (s, 3H), 1.42 (3H), 1.37-1.48 (m, 2H), 1.73-1.80 (m, 1H), 1.88 (s, 3H), 1.96-2.06 (m, 1H), 2.46-2.51 (m, 1H), 2.68-2.75 (m, 1H), 2.82-2.89 (m, 1H), 3.45 (s, 3H), 3.49-3.54 (m, 1H), 3.59-3.61 (m, 1H), 3.67 (dd, $J$ = 7.5, 2 Hz, 1H), 3.75 (dd, $J$ = 12.5, 6 Hz, 1H), 3.92 (dd, $J$ = 12.5, 6 Hz, 1H), 4.17 (qd, $J$ = 7, 2.5 Hz, 2H), 4.43 (dd, $J$ = 9, 5.5 Hz, 1H), 5.80 (dd, $J$ = 16, 1.5 Hz, 1H), 6.19 (dd, $J$ = 9, 1.5 Hz, 1H), 7.01 (dd, $J$ = 15.5, 7.5 Hz, 1H), 7.40 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): -4.9, -4.0, 5.6, 7.1, 14.3, 14.4, 14.6, 18.3, 19.7, 20.6, 26.0, 26.4, 28.8, 29.0, 33.2, 38.1, 43.9, 60.0, 60.2, 65.7, 65.8, 72.3, 77.3, 78.5, 98.7, 121.2, 125.5, 128.9, 133.2, 142.5, 151.5, 165.0, 166.8; IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$):
2955, 2880, 1721, 1587, 1462, 1367, 1255, 1180, 1096, 837, 744; HRMS (ESI): calc'd for C_{39}H_{71}NO_{8}Si_{2} [M+Na]^+: 760.4610, found 760.4641.

(2E,4S,5R,6E)-ethyl 5-((tert-butyldimethylsilyl)oxy)-7-(2-((3S,5S)-5-((4S,5R)-5-hydroxy-2,2-dimethyl-1,3-dioxan-4-yl)-5-methoxy-3-methypentyl)oxazol-4-yl)-4-methylocta-2,6-dienoate (6.12)

To a solution of 6.11 (105 mg, 0.14 mmol) and pyridine (270 μL, 265 mg, 3.35 mmol, 24 equiv) in THF (3 mL) at 0 °C was added HF-pyr (70%, 140 μL, 154 mg, 5.39 mmol, 39 equiv) dropwise. After 1 h, the reaction was quenched with sat. aq. NaHCO_3 and diluted with Et_2O. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 20 to 40% EtOAc/hexanes) gave 6.12 (75 mg, 86%) as an orange oil.

R_f (40% EtOAc/hexanes, CAM stain): 0.37; [α]_{D}^{22} = -27.4 (c 1.10, CHCl_3); ^1H NMR (500 MHz, CDCl_3, δ): -0.01 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 0.99 (d, J = 7 Hz, 3H), 1.10 (d, J = 7 Hz, 3H), 1.27 (t, J = 7 Hz, 3H), 1.31-1.37 (m, 1H), 1.44 (s, 3H), 1.45 (s, 3H), 1.54-1.62 (m, 2H), 1.68-1.75 (m, 1H), 1.89 (s, 3H), 1.90-1.96 (m, 1H), 2.48-2.52 (m, 1H), 2.72-2.78 (m, 1H), 2.79-2.85 (m, 1H), 3.21 (d, J = 11 Hz, 1H), 3.44 (s, 3H),
3.45-3.51 (m, 2H), 3.77-3.81 (m, 2H), 4.00 (dd, \( J = 12, 1.5 \) Hz, 1H), 4.17 (qd, \( J = 7.0, 2.0 \) Hz, 2H), 4.43 (dd, \( J = 9, 5.5 \) Hz, 1H), 5.80 (dd, \( J = 16, 1 \) Hz, 1H), 6.18 (dd, \( J = 9.0, 1.0 \) Hz, 1H), 7.01 (dd, \( J = 16, 7.5 \) Hz, 1H), 7.41 (s, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\), \( \delta \)): -4.9, -4.1, 14.3, 14.4, 14.6, 18.3, 18.5, 20.3, 25.9, 26.0, 28.8, 29.7, 33.4, 36.8, 43.8, 59.2, 60.2, 65.0, 66.2, 72.3, 75.1, 79.9, 99.1, 121.2, 125.5, 128.9, 133.3, 142.5, 151.4, 164.9, 166.8; IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1} \)): 3453, 2954, 2930, 2858, 1716, 1652, 1586, 1462, 1380, 1258, 1181, 1096, 1056, 837, 776; HRMS (ESI): calcd for C\(_{33}\)H\(_{57}\)NO\(_8\)Si [M+Na]\(^{+}\): 646.3746, found 646.3753.

(2E,4S,5R,6E)-5-((tert-butyldimethylsilyl)oxy)-7-(2-((3S,5S)-5-((4S,5R)-5-hydroxy-2,2-dimethyl-1,3-dioxan-4-yl)-5-methoxy-3-methylpentyl)oxazol-4-yl)-4-methylocta-2,6-dienoic acid (6.13)

![Chemical Structure](image)

To a solution of 6.12 (75 mg, 0.12 mmol) in a 2:2:1 THF:MeOH:H\(_2\)O (5 mL) mixture was added LiOH•H\(_2\)O (101 mg, 2.40 mmol, 20 equiv). The resulting solution was stirred at rt overnight (16 h), quenched with 0.2 N HCl until pH ~2-3 and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na\(_2\)SO\(_4\)), filtered and concentrated \textit{in vacuo} to give crude 6.13 (65 mg, 91%) as an orange oil.
Rf (EtOAc, CAM stain): 0.31; $[\alpha]_D^{22} = 26.5$ (c 1.35, CHCl3); $^1$H NMR (500 MHz, CDCl3, $\delta$): 0.04 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 0.98 (d, $J = 6.5$ Hz, 3H), 1.10 (d, $J = 7$ Hz, 3H), 1.26 (br s, 1H), 1.31-1.37 (m, 1H), 1.45 (s, 3H), 1.46 (s, 3H), 1.52-1.60 (m, 2H), 1.68-1.77 (m, 1H), 1.89 (s, 3H), 1.90-1.95 (m, 1H), 2.54 (q, $J = 6.5$ Hz, 1H), 2.72-2.78 (m, 1H), 2.82-2.87 (m, 1H), 3.44 (s, 3H), 3.47-3.52 (m, 2H), 3.78-3.82 (m, 2H), 4.00 (d, $J = 12$ Hz, 1H), 4.43 (dd, $J = 9$, 5.5 Hz, 1H), 5.80 (d, $J = 16$ Hz, 1H), 6.11 (d, $J = 9.5$ Hz, 1H), 7.10 (dd, $J = 16$, 7 Hz, 1H), 7.41 (s, 1H); $^{13}$C NMR (100 MHz, CDCl3, $\delta$): 4.9, -4.1, 14.4, 14.6, 18.3, 18.6, 20.3, 25.8, 26.0, 28.8, 29.6, 33.4, 36.9, 44.0, 59.3, 64.9, 66.2, 72.3, 75.2, 79.8, 99.2, 120.8, 125.5, 128.8, 133.3, 142.3, 153.5, 165.1, 170.9; IR (thin film) $\nu_{\max}$ (cm$^{-1}$): 3416, 3155, 2954, 2932, 2857, 2247, 1714, 1698, 1651, 1583, 1462, 1383, 1258, 1059, 912, 837, 777, 733; HRMS (ESI): calcd for $C_{31}H_{53}NO_8Si$ [M+Na]$^+$: 618.3433, found 618.3445.

diisopropyl 1-((2E,4S,5R,6E)-5-((tert-butyldimethylsilyl)oxy)-7-(2-((3S,5S)-5-((4S)-5-hydroxy-2,2-dimethyl-1,3-dioxan-4-yl)-5-methoxy-3-methylpentyl)oxazol-4-yl)-4-methylocta-2,6-dienoyl)hydrazine-1,2-dicarboxylate (6.15)

To a solution of PPh$_3$ (5.9 mg, 0.022 mmol, 4.0 equiv) in PhMe (5 mL) at 0 °C under N$_2$, was added DIAD (4.4 μL, 4.5 mg, 0.022 mmol, 4.0 equiv). The resulting solution was
stirred 15 min and then a solution of 6.13 (3.3 mg, 0.0056 mmol) in PhMe (1 mL) was added over 1 h via syringe pump. After 2 h, the reaction was concentrated in vacuo. Purification by flash chromatography (silica gel, 20 to 100% EtOAc/hexanes) gave 6.15 (1.1 mg, 14%) as a yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$, δ): -0.01 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 0.98 (d, $J$ = 6.5 Hz, 3H), 1.13 (d, $J$ = 7 Hz, 3H), 1.27-1.34 (m, 13H), 1.44 (s, 3H), 1.44 (s, 3H), 1.52-1.60 (m, 2H), 1.68-1.73 (m, 1H), 1.88 (s, 3H), 1.90-1.95 (m, 1H), 2.56 (q, $J$ = 6.5 Hz, 1H), 2.70-2.76 (m, 1H), 2.78-2.85 (m, 1H), 3.42 (s, 3H), 3.43-3.50 (m, 2H), 3.76-3.82 (m, 2H), 4.00 (d, $J$ = 12 Hz, 1H), 4.43 (dd, $J$ = 9, 5.5 Hz, 1H), 4.97 (p, $J$ = 6 Hz, 1H), 5.04 (p, $J$ = 6 Hz, 1H), 6.17 (d, $J$ = 8 Hz, 1H), 6.85 (m, 1H), 7.11 (dd, $J$ = 15.5, 7.5 Hz, 1H), 7.41 (s, 1H); HRMS (ESI): calcd for C$_{39}$H$_{67}$N$_3$O$_{11}$Si [M+Na]$^+$: 804.4437, found 804.4587.

macrolide (6.37)

To a solution of 6.13 (43 mg, 0.0722 mmol) in PhMe (2 mL) under N$_2$ was added Et$_3$N (60 μL, 44 mg, 0.433 mmol, 6.0 equiv) followed by a solution of 6.36 (17 μL, 26 mg, 0.108 mmol, 1.5 equiv) in PhMe (1 mL). The resulting pale yellow solution was
stirred at rt for 3 h then diluted with PhMe (5 mL) and added to a separate solution of DMAP (176 mg, 1.44 mmol, 20 equiv) in PhMe (90 mL) at 45 °C over 5 h via syringe pump. The resulting solution was stirred for 18 h, cooled to rt, diluted with EtOAc, washed with sat. aq. NaHCO₃, 0.1 M CuSO₄, sat. aq. NaHCO₃, brine, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 10 to 100% EtOAc/hexanes) gave 6.37 (4.2 mg, 10%) as a yellow oil.

\[ \alpha^{22}_{D} = -27.5 \ (c \ 0.40, \ CHCl_3); \]

\(^1\)H NMR (500 MHz, MeOD, δ): 0.04 (s, 3H), 0.13 (s, 3H), 0.93 (s, 9H), 1.00 (d, J = 6.5 Hz, 3H), 1.04 (d, J = 6.5 Hz), 1.15-1.22 (m, 1H), 1.27-1.32 (m, 2H), 1.36-1.43 (m, 1H), 1.41 (s, 3H), 1.49 (s, 3H), 1.85-1.91 (m, 1H), 1.92 (s, 3H), 2.68-2.75 (m, 3H), 3.49 (s, 3H), 3.55 (m, 1H), 3.84 (dd, J = 13.5, 2 Hz, 1H), 3.96 (dd, J = 8.5, 1.5 Hz, 1H), 4.12 (dd, J = 13, 2 Hz, 1H), 4.53 (dd, J = 10, 5 Hz, 1H), 4.61 (d, J = 1.5 Hz, 1H), 5.75 (dd, J = 16, 1.7 Hz, 1H), 6.23 (dd, J = 10.5, 1 Hz, 1H), 7.38 (dd, J = 16, 5.5 Hz, 1H); \(^{13}\)C NMR (125 MHz, MeOD, δ): -4.7, -3.8, 14.1, 14.7, 18.9, 19.0, 19.9, 25.1, 26.4, 29.7, 31.6, 36.3, 40.2, 45.6, 60.9, 63.7, 67.4, 73.3, 75.9, 82.9, 99.9, 121.7, 127.1, 130.1, 134.5, 143.4, 152.8, 166.0, 167.4; IR (thin film) \(\nu_{\text{max}}\) (cm\(^{-1}\)): 2929, 2857, 1716, 1654, 1458, 1380, 1250, 1088, 990, 838, 777; HRMS (ESI): calcd for C\(_{31}\)H\(_{51}\)NO\(_7\)Si [M+Na]\(^+\): 600.3327, found 600.3308.
(4S,5R)-4-((S)-5-(benzyloxy)-1-methoxy-3-methylpent-2-en-1-yl)-2,2-dimethyl-1,3-dioxan-5-ol (6.39)

To a solution of 3.48 (200 mg, 0.43 mmol) and pyridine (347 μL, 340 mg, 4.30 mmol, 10 equiv) in THF (4.3 mL) at 0 °C under N₂ was added HF•pyr (70%, 223 μL, 246 mg, 8.61 mmol, 20 equiv) dropwise. After 1 h, the reaction was quenched with sat. aq. NaHCO₃ and diluted with Et₂O. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 25 to 50% EtOAc/hexanes) gave 6.39 (mixture of E and Z) (118 mg, 79%) as a clear oil.

¹H NMR (500 MHz, CDCl₃, δ): 1.43-1.44 (m, 3H), 1.49 (s, 3H), 1.78-1.80 (m, 3H), 2.26-2.46 (m, 1.5H), 2.75-2.82 (m, 1H), 3.26-3.37 (m, 4H), 3.58-3.75 (m, 5H), 3.88 (dd, J = 12, 1.5 Hz, 1H), 4.14-4.20 (m, 1H), 4.45-4.54 (m, 2H), 5.02-5.09 (m, 1H), 7.27-7.35 (m, 5H); HRMS (ESI): calcd for C₂₀H₃₀O₅ [M+Na]⁺: 373.1985, found 373.2183.
To a solution of (COCl)$_2$ (40 mg, 0.114 mmol, 9.0 equiv) and 3 Å MS in CH$_2$Cl$_2$ (0.3 mL) at -78 °C under N$_2$ was added a solution of DMSO (114 µL, 125 mg, 1.60 mmol, 14.0 equiv) in CH$_2$Cl$_2$ (0.3 mL) dropwise. After 20 min, a solution of 6.39 (40 mg, 0.114 mmol) in CH$_2$Cl$_2$ (0.4 mL) was added dropwise. After 30 min at -78 °C, the mixture was warmed to -40 °C and stirred for 30 min. The reaction was then cooled back down to -78 °C and Et$_3$N (430 µL, 311 mg, 3.08 mmol, 27.0 equiv) was added. After 10 min, the reaction was warmed to -10 °C, diluted with PhMe and warmed to rt. The reaction was filtered over Celite, rinsed with PhMe and concentrated in vacuo. Purification by flash chromatography (silica gel, 20 to 40% EtOAc/hexanes) gave 6.42 (mixture of E and Z) (36 mg, 90%) as a clear oil.

$^1$H NMR (500 MHz, CDCl$_3$, δ): 1.31-1.37 (m, 3H), 1.48-1.50 (m, 3H), 1.77-1.81 (m, 3H), 2.25-2.31 (m, 0.5H), 2.37-2.42 (m, 1H), 2.58-2.65 (m, 0.5H), 3.20-3.22 (m, 3H), 3.50-3.60 (m, 2H), 3.86-3.97 (m, 1H), 4.10-4.12 (m, 1H), 4.24-4.33 (m, 1H), 4.44-4.53 (m, 3H), 5.37-5.42 (m, 1H), 7.30-7.33 (m, 5H); HRMS (ESI): calcd for C$_{20}$H$_{28}$O$_5$ [M+Na]$^+$: 371.1829, found 371.1820.
(4S,5S)-4-((S)-5-(benzyl oxy)-1-methoxy-3-methylpent-2-en-1-yl)-2,2-dimethyl-1,3-dioxan-5-ol (6.42)

To a solution of 6.42 (9 mg, 0.026 mmol) in CH$_2$Cl$_2$ (220 μL) at -23 °C under N$_2$ was added AcOH (40 μL) and NaBH$_3$CN (3.3 mg, 0.052 mmol, 2.0 equiv). After 1 h, the reaction was quenched with sat. aq. NaHCO$_3$ and diluted with EtOAc. GC of the reaction mixture shows 72:28 desired:undesired.
REFERENCES


(8) Although the isolation publication used both the terms "leiodelide" and "leiodolide", we chose the leiodelide spelling shown in the original abstract.


231


234


235


APPENDIX A – $^1$H AND SELECTED $^{13}$C SPECTRA
APPENDIX B – X-RAY DATA FOR 3.63
The data collection crystal was a colorless chunk. Examination of the diffraction pattern on a Nonius Kappa CCD diffractometer indicated a monoclinic crystal system. All work was done at 180 K using an Oxford Cryosystems Cryostream Cooler. The data collection strategy was set up to measure a quadrant of reciprocal space with a redundancy factor of 3.8, which means that 90% of the reflections were measured at least 3.8 times. Phi and omega scans with a frame width of 1.0° were used. Data integration was done with Denzo,¹ and scaling and merging of the data was done with Scalepack.¹ Merging the data and averaging the symmetry equivalent reflections resulted in an Rint value of 0.032.

The structure was solved by direct methods in SHELXS-97.² Full-matrix least-squares refinements based on $F^2$ were performed in SHELXL-97,³ as incorporated in the WinGX package.⁴ Because of the space group, P2₁, only one enantiomer is present in the crystal. The enantiomer was chosen based on the line drawing provided by N. Proust.

For each methyl group, the hydrogen atoms were added at calculated positions using a riding model with $U(H) = 1.5 \times U_{eq}(\text{bonded carbon atom})$. The torsion angle, which defines the orientation of the methyl group about the C-C or O-C bond, was refined. The hydroxyl hydrogen atoms bonded to O(3) and O(5) were isotropically refined. The rest of the hydrogen atoms were included in the model at calculated positions using a riding model with $U(H) = 1.2 \times U_{eq}(\text{bonded atom})$. 

418
The final refinement cycle was based on 3363 intensities, 1 restraint, and 175 variables and resulted in agreement factors of R1(F) = 0.044 and wR2(F^2) = 0.086. For the subset of data with I > 2*sigma(I), the R1(F) value is 0.036 for 2934 reflections. The final difference electron density map contains maximum and minimum peak heights of 0.13 and -0.16 e/Å^3. Neutral atom scattering factors were used and include terms for anomalous dispersion.\(^5\)

Both hydroxyl groups are involved in intermolecular hydrogen bonding as shown in Table 7.


Table B.1. Crystallographic details

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>C_{13}H_{26}O_{5}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>262.34</td>
</tr>
<tr>
<td>Temperature</td>
<td>180(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2₁</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 8.9146(1) Å</td>
</tr>
<tr>
<td></td>
<td>b = 8.5388(2) Å</td>
</tr>
<tr>
<td></td>
<td>c = 10.1252(2) Å</td>
</tr>
<tr>
<td></td>
<td>β = 106.470(1)°</td>
</tr>
<tr>
<td>Volume</td>
<td>739.11(2) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.179 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.089 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>288</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.12 x 0.27 x 0.27 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.38 to 27.44°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-11≤h≤11, -11≤k≤11, -13≤l≤13</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>13726</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>3363 [R(int) = 0.032]</td>
</tr>
<tr>
<td>Completeness to theta = 27.44°</td>
<td>99.8 %</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>3363 / 1 / 175</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.063</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0358, wR2 = 0.0820</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0443, wR2 = 0.0865</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.126 and -0.164 e/Å³</td>
</tr>
</tbody>
</table>
Atomic coordinates (x10^4) and equivalent isotropic displacement parameters (Å^2x10^3).

U(eq) is defined as one third of the trace of the orthogonalized U_ij tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)</td>
<td>-190(2)</td>
<td>6375(2)</td>
<td>6778(1)</td>
<td>29(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>2349(2)</td>
<td>7607(2)</td>
<td>7287(2)</td>
<td>28(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>2532(2)</td>
<td>7038(2)</td>
<td>5916(2)</td>
<td>30(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>1528(2)</td>
<td>5593(2)</td>
<td>5453(2)</td>
<td>33(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>298(2)</td>
<td>5093(2)</td>
<td>7859(2)</td>
<td>37(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>-1880(2)</td>
<td>6840(2)</td>
<td>6543(2)</td>
<td>35(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>3079(2)</td>
<td>9200(2)</td>
<td>7732(2)</td>
<td>29(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>4809(2)</td>
<td>9257(2)</td>
<td>7803(2)</td>
<td>32(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>5579(2)</td>
<td>10861(2)</td>
<td>8190(1)</td>
<td>31(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>4964(2)</td>
<td>12051(2)</td>
<td>7041(2)</td>
<td>35(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>5439(2)</td>
<td>13732(2)</td>
<td>7417(2)</td>
<td>41(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>1864(2)</td>
<td>10753(3)</td>
<td>9124(2)</td>
<td>63(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>7355(2)</td>
<td>10698(2)</td>
<td>8532(2)</td>
<td>44(1)</td>
</tr>
<tr>
<td>O(1)</td>
<td>-62(1)</td>
<td>5851(1)</td>
<td>5467(1)</td>
<td>32(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>702(1)</td>
<td>7769(1)</td>
<td>7166(1)</td>
<td>29(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>2183(1)</td>
<td>8222(1)</td>
<td>4887(1)</td>
<td>36(1)</td>
</tr>
<tr>
<td>O(4)</td>
<td>2943(1)</td>
<td>9541(1)</td>
<td>9089(1)</td>
<td>37(1)</td>
</tr>
<tr>
<td>O(5)</td>
<td>4688(2)</td>
<td>14352(2)</td>
<td>8364(2)</td>
<td>52(1)</td>
</tr>
</tbody>
</table>
Table B.3. Bond lengths [Å] and angles [°]

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length [Å]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)-O(2)</td>
<td>1.4235(17)</td>
</tr>
<tr>
<td>C(1)-O(1)</td>
<td>1.4361(16)</td>
</tr>
<tr>
<td>C(1)-C(6)</td>
<td>1.510(2)</td>
</tr>
<tr>
<td>C(1)-C(5)</td>
<td>1.522(2)</td>
</tr>
<tr>
<td>C(2)-O(2)</td>
<td>1.4454(15)</td>
</tr>
<tr>
<td>C(2)-C(7)</td>
<td>1.520(2)</td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.5227(19)</td>
</tr>
<tr>
<td>C(3)-H(2)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(3)-O(3)</td>
<td>1.4218(18)</td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.519(2)</td>
</tr>
<tr>
<td>C(3)-H(3)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(4)-O(1)</td>
<td>1.4378(17)</td>
</tr>
<tr>
<td>C(4)-H(4A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(4)-H(4B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(5)-H(5A)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(5)-H(5B)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(5)-H(5C)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(6)-H(6A)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(6)-H(6B)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(6)-H(6C)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(7)-O(4)</td>
<td>1.4427(17)</td>
</tr>
<tr>
<td>C(7)-C(8)</td>
<td>1.5248(17)</td>
</tr>
<tr>
<td>C(7)-H(7)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(8)-C(9)</td>
<td>1.532(2)</td>
</tr>
<tr>
<td>C(8)-H(8A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(8)-H(8B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(9)-C(10)</td>
<td>1.525(2)</td>
</tr>
<tr>
<td>C(9)-C(13)</td>
<td>1.5283(19)</td>
</tr>
<tr>
<td>C(9)-H(9)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(10)-C(11)</td>
<td>1.514(2)</td>
</tr>
<tr>
<td>Bond</td>
<td>Distance (Å)</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>C(10)-H(10A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(10)-H(10B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(11)-O(5)</td>
<td>1.418(2)</td>
</tr>
<tr>
<td>C(11)-H(11A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(11)-H(11B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(12)-O(4)</td>
<td>1.420(2)</td>
</tr>
<tr>
<td>C(12)-H(12A)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(12)-H(12B)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(12)-H(12C)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(13)-H(13A)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(13)-H(13B)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(13)-H(13C)</td>
<td>0.9800</td>
</tr>
<tr>
<td>O(3)-H(1O3)</td>
<td>0.87(2)</td>
</tr>
<tr>
<td>O(5)-H(1O5)</td>
<td>0.81(2)</td>
</tr>
<tr>
<td>O(2)-C(1)-O(1)</td>
<td>109.32(10)</td>
</tr>
<tr>
<td>O(2)-C(1)-C(6)</td>
<td>106.13(11)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(6)</td>
<td>105.87(11)</td>
</tr>
<tr>
<td>O(2)-C(1)-C(5)</td>
<td>112.33(11)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(5)</td>
<td>111.08(12)</td>
</tr>
<tr>
<td>C(6)-C(1)-C(5)</td>
<td>111.80(12)</td>
</tr>
<tr>
<td>O(2)-C(2)-C(7)</td>
<td>106.16(10)</td>
</tr>
<tr>
<td>O(2)-C(2)-C(3)</td>
<td>108.80(11)</td>
</tr>
<tr>
<td>C(7)-C(2)-C(3)</td>
<td>114.08(11)</td>
</tr>
<tr>
<td>O(2)-C(2)-H(2)</td>
<td>109.2</td>
</tr>
<tr>
<td>C(7)-C(2)-H(2)</td>
<td>109.2</td>
</tr>
<tr>
<td>C(3)-C(2)-H(2)</td>
<td>109.2</td>
</tr>
<tr>
<td>O(3)-C(3)-C(4)</td>
<td>111.38(12)</td>
</tr>
<tr>
<td>O(3)-C(3)-C(2)</td>
<td>112.56(12)</td>
</tr>
<tr>
<td>C(4)-C(3)-C(2)</td>
<td>109.52(11)</td>
</tr>
<tr>
<td>O(3)-C(3)-H(3)</td>
<td>107.7</td>
</tr>
<tr>
<td>C(4)-C(3)-H(3)</td>
<td>107.7</td>
</tr>
<tr>
<td>C(2)-C(3)-H(3)</td>
<td>107.7</td>
</tr>
<tr>
<td>O(1)-C(4)-C(3)</td>
<td>111.65(11)</td>
</tr>
</tbody>
</table>
O(1)-C(4)-H(4A)  109.3
C(3)-C(4)-H(4A)  109.3
O(1)-C(4)-H(4B)  109.3
C(3)-C(4)-H(4B)  109.3
H(4A)-C(4)-H(4B)  108.0
C(1)-C(5)-H(5A)  109.5
C(1)-C(5)-H(5B)  109.5
H(5A)-C(5)-H(5B)  109.5
C(1)-C(5)-H(5C)  109.5
H(5A)-C(5)-H(5C)  109.5
H(5B)-C(5)-H(5C)  109.5
C(1)-C(6)-H(6A)  109.5
C(1)-C(6)-H(6B)  109.5
H(6A)-C(6)-H(6B)  109.5
C(1)-C(6)-H(6C)  109.5
H(6A)-C(6)-H(6C)  109.5
H(6B)-C(6)-H(6C)  109.5
O(4)-C(7)-C(2)  108.53(11)
O(4)-C(7)-C(8)  107.80(11)
C(2)-C(7)-C(8)  112.61(11)
O(4)-C(7)-H(7)  109.3
C(2)-C(7)-H(7)  109.3
C(8)-C(7)-H(7)  109.3
C(7)-C(8)-C(9)  114.46(11)
C(7)-C(8)-H(8A)  108.6
C(9)-C(8)-H(8A)  108.6
C(7)-C(8)-H(8B)  108.6
C(9)-C(8)-H(8B)  108.6
H(8A)-C(8)-H(8B)  107.6
C(10)-C(9)-C(13)  111.05(12)
C(10)-C(9)-C(8)  111.24(11)
C(13)-C(9)-C(8)  109.65(12)
C(10)-C(9)-H(9)  108.3
C(13)-C(9)-H(9)  108.3
C(8)-C(9)-H(9)  108.3
C(11)-C(10)-C(9)  115.15(13)
C(11)-C(10)-H(10A)  108.5
C(9)-C(10)-H(10A)  108.5
C(11)-C(10)-H(10B)  108.5
C(9)-C(10)-H(10B)  108.5
H(10A)-C(10)-H(10B)  107.5
O(5)-C(11)-C(10)  111.85(14)
O(5)-C(11)-H(11A)  109.2
C(10)-C(11)-H(11A)  109.2
O(5)-C(11)-H(11B)  109.2
C(10)-C(11)-H(11B)  109.2
H(11A)-C(11)-H(11B)  107.9
O(4)-C(12)-H(12A)  109.5
O(4)-C(12)-H(12B)  109.5
H(12A)-C(12)-H(12B)  109.5
O(4)-C(12)-H(12C)  109.5
H(12A)-C(12)-H(12C)  109.5
H(12B)-C(12)-H(12C)  109.5
C(9)-C(13)-H(13A)  109.5
C(9)-C(13)-H(13B)  109.5
H(13A)-C(13)-H(13B)  109.5
C(9)-C(13)-H(13C)  109.5
H(13A)-C(13)-H(13C)  109.5
H(13B)-C(13)-H(13C)  109.5
C(1)-O(1)-C(4)  113.18(10)
C(1)-O(2)-C(2)  114.69(10)
C(3)-O(3)-H(1O3)  111.4(14)
C(12)-O(4)-C(7)  114.26(13)
C(11)-O(5)-H(1O5)  108.5(14)
Anisotropic displacement parameters (Å² x 10³). The anisotropic displacement factor exponent takes the form: -2\pi²[ h²a*²U_{11} + ... + 2 h k a* b* U_{12} ]

<table>
<thead>
<tr>
<th></th>
<th>U¹¹</th>
<th>U²²</th>
<th>U³³</th>
<th>U²³</th>
<th>U¹³</th>
<th>U¹²</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)</td>
<td>30(1)</td>
<td>28(1)</td>
<td>29(1)</td>
<td>-2(1)</td>
<td>10(1)</td>
<td>-4(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>25(1)</td>
<td>28(1)</td>
<td>32(1)</td>
<td>1(1)</td>
<td>9(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>29(1)</td>
<td>27(1)</td>
<td>35(1)</td>
<td>1(1)</td>
<td>13(1)</td>
<td>3(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>36(1)</td>
<td>30(1)</td>
<td>36(1)</td>
<td>-5(1)</td>
<td>16(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>40(1)</td>
<td>35(1)</td>
<td>35(1)</td>
<td>4(1)</td>
<td>12(1)</td>
<td>-4(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>32(1)</td>
<td>34(1)</td>
<td>40(1)</td>
<td>-2(1)</td>
<td>13(1)</td>
<td>-6(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>28(1)</td>
<td>29(1)</td>
<td>31(1)</td>
<td>-3(1)</td>
<td>10(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>26(1)</td>
<td>32(1)</td>
<td>39(1)</td>
<td>-2(1)</td>
<td>10(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>27(1)</td>
<td>34(1)</td>
<td>31(1)</td>
<td>-1(1)</td>
<td>8(1)</td>
<td>-2(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>31(1)</td>
<td>40(1)</td>
<td>33(1)</td>
<td>3(1)</td>
<td>8(1)</td>
<td>-3(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>34(1)</td>
<td>35(1)</td>
<td>54(1)</td>
<td>6(1)</td>
<td>11(1)</td>
<td>-2(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>56(1)</td>
<td>76(1)</td>
<td>62(1)</td>
<td>-20(1)</td>
<td>25(1)</td>
<td>19(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>27(1)</td>
<td>46(1)</td>
<td>53(1)</td>
<td>1(1)</td>
<td>4(1)</td>
<td>-3(1)</td>
</tr>
<tr>
<td>O(1)</td>
<td>34(1)</td>
<td>35(1)</td>
<td>29(1)</td>
<td>-5(1)</td>
<td>11(1)</td>
<td>-5(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>25(1)</td>
<td>27(1)</td>
<td>36(1)</td>
<td>-4(1)</td>
<td>11(1)</td>
<td>-2(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>40(1)</td>
<td>34(1)</td>
<td>39(1)</td>
<td>6(1)</td>
<td>19(1)</td>
<td>5(1)</td>
</tr>
<tr>
<td>O(4)</td>
<td>35(1)</td>
<td>41(1)</td>
<td>36(1)</td>
<td>-8(1)</td>
<td>14(1)</td>
<td>-3(1)</td>
</tr>
<tr>
<td>O(5)</td>
<td>42(1)</td>
<td>50(1)</td>
<td>58(1)</td>
<td>-11(1)</td>
<td>3(1)</td>
<td>11(1)</td>
</tr>
</tbody>
</table>
Table B.5. Hydrogen coordinates and isotropic displacement parameters

Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3).

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(2)</td>
<td>2818</td>
<td>6818</td>
<td>8018</td>
<td>33</td>
</tr>
<tr>
<td>H(3)</td>
<td>3649</td>
<td>6725</td>
<td>6068</td>
<td>36</td>
</tr>
<tr>
<td>H(4A)</td>
<td>1543</td>
<td>5306</td>
<td>4510</td>
<td>39</td>
</tr>
<tr>
<td>H(4B)</td>
<td>1972</td>
<td>4707</td>
<td>6071</td>
<td>39</td>
</tr>
<tr>
<td>H(5A)</td>
<td>1380</td>
<td>4782</td>
<td>7947</td>
<td>55</td>
</tr>
<tr>
<td>H(5B)</td>
<td>-393</td>
<td>4185</td>
<td>7580</td>
<td>55</td>
</tr>
<tr>
<td>H(5C)</td>
<td>220</td>
<td>5486</td>
<td>8747</td>
<td>55</td>
</tr>
<tr>
<td>H(6A)</td>
<td>-2038</td>
<td>7209</td>
<td>7410</td>
<td>52</td>
</tr>
<tr>
<td>H(6B)</td>
<td>-2554</td>
<td>5933</td>
<td>6209</td>
<td>52</td>
</tr>
<tr>
<td>H(6C)</td>
<td>-2145</td>
<td>7680</td>
<td>5857</td>
<td>52</td>
</tr>
<tr>
<td>H(7)</td>
<td>2503</td>
<td>10016</td>
<td>7072</td>
<td>34</td>
</tr>
<tr>
<td>H(8A)</td>
<td>4927</td>
<td>8946</td>
<td>6895</td>
<td>39</td>
</tr>
<tr>
<td>H(8B)</td>
<td>5375</td>
<td>8477</td>
<td>8487</td>
<td>39</td>
</tr>
<tr>
<td>H(9)</td>
<td>5318</td>
<td>11242</td>
<td>9032</td>
<td>37</td>
</tr>
<tr>
<td>H(10A)</td>
<td>5337</td>
<td>11749</td>
<td>6244</td>
<td>42</td>
</tr>
<tr>
<td>H(10B)</td>
<td>3807</td>
<td>11993</td>
<td>6744</td>
<td>42</td>
</tr>
<tr>
<td>H(11A)</td>
<td>6586</td>
<td>13783</td>
<td>7827</td>
<td>50</td>
</tr>
<tr>
<td>H(11B)</td>
<td>5167</td>
<td>14380</td>
<td>6572</td>
<td>50</td>
</tr>
<tr>
<td>H(12A)</td>
<td>2186</td>
<td>11721</td>
<td>8760</td>
<td>95</td>
</tr>
<tr>
<td>H(12B)</td>
<td>1845</td>
<td>10923</td>
<td>10076</td>
<td>95</td>
</tr>
<tr>
<td>H(12C)</td>
<td>818</td>
<td>10452</td>
<td>8559</td>
<td>95</td>
</tr>
<tr>
<td>H(13A)</td>
<td>7641</td>
<td>10420</td>
<td>7696</td>
<td>65</td>
</tr>
<tr>
<td>H(13B)</td>
<td>7713</td>
<td>9875</td>
<td>9225</td>
<td>65</td>
</tr>
<tr>
<td>H(13C)</td>
<td>7850</td>
<td>11693</td>
<td>8894</td>
<td>65</td>
</tr>
<tr>
<td>H(1O3)</td>
<td>1370(30)</td>
<td>8770(30)</td>
<td>4920(20)</td>
<td>71(7)*</td>
</tr>
<tr>
<td>H(1O5)</td>
<td>5280(20)</td>
<td>14290(30)</td>
<td>9130(20)</td>
<td>53(6)*</td>
</tr>
</tbody>
</table>

*Refined isotropically
Table B.6. Torsion angles [°]

<table>
<thead>
<tr>
<th>Bond Sequence</th>
<th>Torsion Angle [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(2)-C(2)-C(3)-O(3)</td>
<td>72.70(14)</td>
</tr>
<tr>
<td>C(7)-C(2)-C(3)-O(3)</td>
<td>-45.60(16)</td>
</tr>
<tr>
<td>O(2)-C(2)-C(3)-C(4)</td>
<td>-51.78(15)</td>
</tr>
<tr>
<td>C(7)-C(2)-C(3)-C(4)</td>
<td>-170.08(11)</td>
</tr>
<tr>
<td>O(3)-C(3)-C(4)-O(1)</td>
<td>-73.34(14)</td>
</tr>
<tr>
<td>C(2)-C(3)-C(4)-O(1)</td>
<td>51.83(15)</td>
</tr>
<tr>
<td>O(2)-C(2)-C(7)-O(4)</td>
<td>65.03(12)</td>
</tr>
<tr>
<td>C(3)-C(2)-C(7)-O(4)</td>
<td>-175.18(11)</td>
</tr>
<tr>
<td>O(2)-C(2)-C(7)-C(8)</td>
<td>-175.71(11)</td>
</tr>
<tr>
<td>C(3)-C(2)-C(7)-C(8)</td>
<td>-55.91(15)</td>
</tr>
<tr>
<td>O(4)-C(7)-C(8)-C(9)</td>
<td>-62.67(15)</td>
</tr>
<tr>
<td>C(2)-C(7)-C(8)-C(9)</td>
<td>177.64(12)</td>
</tr>
<tr>
<td>C(7)-C(8)-C(9)-C(10)</td>
<td>-68.92(15)</td>
</tr>
<tr>
<td>C(7)-C(8)-C(9)-C(13)</td>
<td>167.86(12)</td>
</tr>
<tr>
<td>C(13)-C(9)-C(10)-C(11)</td>
<td>-67.66(18)</td>
</tr>
<tr>
<td>C(8)-C(9)-C(10)-C(11)</td>
<td>169.92(12)</td>
</tr>
<tr>
<td>C(9)-C(10)-C(11)-O(5)</td>
<td>-69.91(17)</td>
</tr>
<tr>
<td>O(2)-C(1)-O(1)-C(4)</td>
<td>56.89(15)</td>
</tr>
<tr>
<td>C(6)-C(1)-O(1)-C(4)</td>
<td>170.82(11)</td>
</tr>
<tr>
<td>C(5)-C(1)-O(1)-C(4)</td>
<td>-67.62(15)</td>
</tr>
<tr>
<td>C(3)-C(4)-O(1)-C(1)</td>
<td>-55.11(16)</td>
</tr>
<tr>
<td>O(1)-C(1)-O(2)-C(2)</td>
<td>-59.52(13)</td>
</tr>
<tr>
<td>C(6)-C(1)-O(2)-C(2)</td>
<td>-173.28(10)</td>
</tr>
<tr>
<td>C(5)-C(1)-O(2)-C(2)</td>
<td>64.26(15)</td>
</tr>
<tr>
<td>C(7)-C(2)-O(2)-C(1)</td>
<td>-178.92(11)</td>
</tr>
<tr>
<td>C(3)-C(2)-O(2)-C(1)</td>
<td>57.90(14)</td>
</tr>
<tr>
<td>C(2)-C(7)-O(4)-C(12)</td>
<td>-109.85(15)</td>
</tr>
<tr>
<td>C(8)-C(7)-O(4)-C(12)</td>
<td>127.90(15)</td>
</tr>
</tbody>
</table>
Table B.7. Hydrogen bonds [Å and °]

<table>
<thead>
<tr>
<th>D-H...A</th>
<th>d(D-H)</th>
<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(3)-H(1O3)...O(1)#1</td>
<td>0.87(2)</td>
<td>2.10(2)</td>
<td>2.8916(15)</td>
<td>151(2)</td>
</tr>
<tr>
<td>O(5)-H(1O5)...O(4)#2</td>
<td>0.81(2)</td>
<td>2.05(2)</td>
<td>2.8369(18)</td>
<td>167(2)</td>
</tr>
</tbody>
</table>

Symmetry transformations used to generate equivalent atoms:

#1 -x,y+1/2,-z+1    #2 -x+1,y+1/2,-z+2