Efforts Toward the Synthesis of Maoecrystal V and Atropurpuran with the Discovery of Novel Skeletal Rearrangements

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Abstract

Synthetic strategies and efforts towards two complex diterpene natural products, maocryystal V and atropurpuran are described. Novel skeletal rearrangements that were observed during the travails of the latter are reported.

The first chapter describes efforts to synthesize the bioactive diterpenoid, maocryystal V in enantiopure fashion starting from (+)-limonene oxide. An intramolecular Rh(II)-catalyzed C-H insertion reaction installed the tetrahydrofuran ring with requisite stereochemistry. The chemistry culminated with the installation of all desired atoms albeit with unsuccessful attempts to install the desired δ-lactone.

The last chapter presents efforts to make the fused double bicyclo[2.2.2]octane containing diterpene, atropurpuran. Initial attempts to forge the skeletal core of the system were proposed to use cascading [4+2] cycloaddition chemistry. After it became apparent that the first strategy would unlikely be successful, a slightly reworked strategy provided the first synthetically made fused double bicyclo[2.2.2]octane molecule in low yield. Then a major strategy shift to attempt to make desired ring system via cascading radicals generated from arylsulfonyl hydrazones, led to an unexpected skeletal rearrangement under neutral conditions. A few examples of this novel reaction are presented. A second unexpected reaction forming a tricyclic-azo-compound occurred when attempting to expand the scope of the first C-C insertion reaction.
This thesis is dedicated to

the memory of my dad,

Edgar J. Smith.
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# Table of Contents

Abstract.................................................................iii
Dedication.................................................................iv
Acknowledgements..................................................v
Table of contents.....................................................ix
List of Figures..........................................................x
List of Schemes..........................................................x
List of Tables...........................................................xv
List of Spectra..........................................................xv
List of Abbreviations................................................xxiv
General Methods.....................................................xxix

## Chapter 1

1.1 Discovery and identification of maocrystal V..........................2
1.2 Proposed biosynthesis...................................................4
1.3 Previous synthetic efforts-Literature....................................5
1.4 Previous synthetic efforts-Sorensen Lab................................20
1.5 Results and Discussion..................................................31
1.6 Conclusions.............................................................56
1.7 Experimental Details...................................................58
1.8 Spectroscopic Data.....................................................93
1.9 References.............................................................145

## Chapter 2

2.1 Discovery and identification of atropurpuran.........................149
2.2 Proposed biogenic synthesis...........................................150
2.3 Literature efforts to make atropurpuran...........................151
2.4 Results and Discussion................................................153
2.5 Conclusions.............................................................173
2.6 Experimental Details...................................................175
2.7 Spectroscopic Data.....................................................217
2.8 References.............................................................277

## Appendix

Appendix: X-ray Crystallographic Data for Compound 2.92........279
List of Figures

Figure 1.1: Core skeletal framework for ent-kauranes with and without numbering. Bicyclo[3.2.1]octane highlighted in blue.................................................................2

Figure 1.2: Representative ent-kauranoids with antitumor (1.1, 1.2) and antibacterial activity (1.3, 1.4).........................................................................................................................2

Figure 1.3: Structure of maoecrystal V with carbon numbering.................................3

Figure 1.4: X-ray crystal structure of 1.161 indicating undesired stereochemistry at C8.................................................................................................................................40

Figure 1.5: 1,3-diaxial steric interactions that may prevent alkylation......................52

Figure 2.1: Structure of atropurpuran 2.1 and diterpenoid alkaloids with the fused double bicyclo[2.2.2]octane skeleton.................................................................................150

Figure 2.2: Ball and stick representation of the X-ray crystal structure of azotricycle 2.92...............................................................................................................................172

List of Schemes

Scheme 1.1: Proposed biosynthesis of maoecrystal V...............................................5

Scheme 1.2: Thomson’s synthesis of the skeletal core of maoecrystal V using an intermolecular Diels-Alder reaction.................................................................7

Scheme 1.3: Singh’s synthesis of the bicyclo[2.2.2]octane core of maoecrystal V using an intramolecular Diels-Alder reaction triggered by an oxidative Alder-Becker dearomatization.................................................................8

Scheme 1.4: Zakarian’s synthesis of the THF ring via Rh(II) C-H insertion chemistry and of the bicyclo[2.2.2]octane of maoecrystal V using an intramolecular Diels-Alder reaction facilitated by an oxidative dearomatization.................................9

Scheme 1.5: Nicolaou and Chen’s synthesis of the pentacyclic framework of maoecrystal V, epimeric at C5 through a Diels-Alder reaction with a bis-alkylation forming the lactone.................................................................10

Scheme 1.6: Chen’s synthesis of the four of the five rings of maoecrystal V with correct stereochemistry at C5 via directed hydrogenation.................................11
Scheme 1.7: Trauner's non Diels-Alder synthesis for the bicyclo[2.2.2]octane framework of maoecrystal V.................................................................12

Scheme 1.8: Baran's oxidative Wessely dearomatization/Diels-Alder strategy for the synthesis of the bicyclo[2.2.2]octane framework of maoecrystal V...............................13

Scheme 1.9: Li and Yang's synthesis of the exocyclic dienophile 1.64 for an intramolecular Diels-Alder reaction en route to maoecrystal V..............................................14

Scheme 1.10: Li and Yang's oxidative dearomatization/Diels-Alder route to synthesize maoecrystal V........................................................................................................15

Scheme 1.11: Danishefsky's synthesis of the carbocyclic skeleton of maoecrystal V albeit epimeric at C5 via a Diels-Alder reaction en route to synthesize maoecrystal V.................................................................17

Scheme 1.12: Intermediates en route to Danishefsky's synthesis of maoecrystal V; epimerization and functionalization .................................................................18

Scheme 1.13: Last two steps of Danishefsky's synthesis of maoecrystal V; epoxidation and semi-pinacol rearrangement .................................................................19

Scheme 1.14: Initial base induced cyclization cascade proposal ..............................................21

Scheme 1.15: Proposed hydroxide induced cyclization cascade sequence ......................22

Scheme 1.16: Undesired reactivity of ketoaldehyde 1.94.....................................................23

Scheme 1.17: Second generation proposal toward maoecrystal V using Diels-Alder ..........................................................................................................................24

Scheme 1.18: Third generation proposal toward maoecrystal V relying on an intramolecular cationic ring cyclization and reverse prenylation ................................24

Scheme 1.19: A stereoconvergent aldol-lactonization reaction forms the bicyclo[2.2.2]octane core ....................................................................................................26

Scheme 1.20: Lewis acid catalysis gave a mixture of undesired reverse prenylation products ...........................................................................................................27

Scheme 1.21: BBr₃ promoted reverse prenylation giving the undesired diastereomer 1.124 ..................................................................................................................28

Scheme 1.22: Rhodium carbenoid promoted C-H insertion forms the tetrahydrofuran ring with undesired stereochemistry at C5 ..................................................28
Scheme 1.23: Rhodium carbenoid promoted C-H insertion forms undesired pentacycle 1.136..........................................................30

Scheme 1.24: Rhodium carbenoid C-H insertion forms desired pentacycle 1.138 in low yield.................................................................31

Scheme 1.25: Rhodium Rh₂(R-BTPCP)₄ forms desired pentacycle 1.138 in acceptable yield...........................................................................32

Scheme 1.26: Revised synthetic proposal to maoecrystal V from pentacycle 1.14...33

Scheme 1.27: Proposed route to enantiomerically pure (-)-1.105 from (+)-limonene oxide........................................................................34

Scheme 1.28: Synthetic route to enantiomerically pure 1.149 from (+)-limonene oxide........................................................................35

Scheme 1.29: Acid catalyzed aldol-lactonization provides two diastereomers of bicyclo[2.2.2]octane; (-)-1.105 and 1.155........................36

Scheme 1.30: Isomerization of undesired bicyclo[2.2.2]octane 1.155.................37

Scheme 1.31: Ketalization and diazo-transfer reactions to produce 1.157...........38

Scheme 1.32: Boron trifluoride promotes cyanohydrin formation from undesired face of C₈........................................................................40

Scheme 1.33: Tenative assignment for 1.162 in cyanohydrin formation from undesired face of C₈.................................................................41

Scheme 1.34: Proposed protecting group shield steering of facial selectivity of cyanide addition to C₈.............................................................42

Scheme 1.35: Preparation of C₁₅ TES-protected alcohol 1.167. .........................43

Scheme 1.36: Diastereomeric Weinreb amide-nitriles 1.168 and epi-1.168. ....... 43

Scheme 1.37: Functionalization of Weinreb 1.168 amide to keto-aldehyde 1.143 through lactone 1.170...............................................................44

Scheme 1.38: Conversion keto-aldehyde 1.143 to cyclohexenone 1.144..........45

Scheme 1.39: Aldol-Pinner hypothesis to install final ring of maoecrystal V........46

Scheme 1.40: Hydrolysis of nitrile 1.144 to amide 1.174....................................46
Scheme 1.41: Reduction/oxidation sequence to make aldehyde 1.176 and acid 1.173

Scheme 1.42: Proposed intermolecular aldol leading to lactol to make maocystal V

Scheme 1.43: Attempted aldol and alkylation of 1.176 or 1.180

Scheme 1.44: Preparation of methylester 1.183 and silylprotected species 1.184

Scheme 1.45: Proposed lactone trap for a reversible aldol reaction

Scheme 1.46: Protection of the C15 hydroxyl group

Scheme 1.47: Alkylation to make chloromethylester 1.191

Scheme 1.48: Formation of doubly alkylated methane “dimer-acetal” 1.192

Scheme 1.49: Proposed molecules to reduce the 1,3-diaxial steric crowding during alkylation

Scheme 1.50: Synthesis of close analogues of maocystal V, both with and without enone

Scheme 2.1: Wang’s proposed biogenetic pathway of atropurpruan 2.1

Scheme 2.2: Hsung’s preparation of the BCD ring system of atropurpuran

Scheme 2.3: Kobayashi’s rapid entry into the entire carbocyclic framework of atropurpuran

Scheme 2.4: Proposed synthesis of atropurpuran 2.1 via a cascade of [4+2] cycloadditions

Scheme 2.5: Attempt to synthesize pyrone with two pendant enone groups 2.33

Scheme 2.6: Observation of arene 2.35

Scheme 2.7: Electrocyclic ring formation/Diels-Alder cascade proposal

Scheme 2.8: Synthesis of triene 2.36 to test the electrocyclization/Diels-Alder proposal

Scheme 2.9: Observation of electrocyclization then rapid isomerization to conjugated diene 2.44
Scheme 2.10: Proposal to stop isomerization to allow Diels-Alder with \( \alpha \)-methyl group................................................................. 159

Scheme 2.11: Synthesis of homoannular diene with pendant dienophile \( \text{2.46} \)............. 160

Scheme 2.12: Unintentional (a) and intentional (b) synthesis of heteroannular diene \( \text{2.52} \)........................................................................................................................................ 161

Scheme 2.13: Synthesis of a fused double bicyclo[2.2.2]octane \( \text{2.58} \)............. 162

Scheme 2.14: Possible modifications to efficiently make fused double bicyclo[2.2.2]octane framework that were ultimately not pursued................. 163

Scheme 2.15: Kim’s radical cyclization chemistry................................................................. 164

Scheme 2.16: Proposed cascading sequence to generate a fused double bicyclo[2.2.2]octane skeleton using radical addition into arylsulfonyl hydrazones.......................................................................................................................... 165

Scheme 2.17: Synthesis of keto-aldehyde \( \text{2.76} \) via a stepwise Lawton annulation................................................................. 166

Scheme 2.18: An unexpected C-C insertion and skeletal rearrangement product \( \text{2.79} \)........................................................................................................................................ 167

Scheme 2.19: Synthesis of keto-aldehyde compounds \( \text{2.83a-d} \)......................... 167

Scheme 2.20: Keto-aldehydes \( \text{2.83a-d} \) underwent sulfonylhydrazone formation and C-C insertion.......................................................................................................................... 168

Scheme 2.21: (a) Kabalka’s base promoted tosyldihydrazone coupling with tributylborane. (b) An example of Barluenga’s tosyldihydrazone boronic acid coupling................................................................................................. 169

Scheme 2.22: Plausible mechanism for C-C bond insertion to form \( \text{2.84-a} \)......... 170

Scheme 2.23: Synthesis of monocyclic keto-aldehyde \( \text{2.89} \) from known ester \( \text{2.87} \)........................................................................................................................................ 171

Scheme 2.24: An unexpected transformation of keto-aldehydes \( \text{2.89} \) and \( \text{2.90} \) .... 171

Scheme 2.25: Plausible pathway(s) to azotricycle \( \text{2.92} \)........................................................................................................................................ 173
List of Tables

Table 1.1: Selective and highly potent cytotoxicity of maoecrystal V......................... 4
Table 1.2: Effects of Rh$_2$(BTPCP)$_4$ enantiomer on yield of C-H insertion of 1.157... 39
Table 1.3: Attempts at performing a bisalkylation to form lactone ring..................... 52

List of Spectra

$^1$H-NMR of Compound 1.143 (CDCl$_3$)...........................................................................93
$^{13}$C-NMR of Compound 1.143 (CDCl$_3$)...........................................................................93
IR of Compound 1.143 (neat).............................................................................................94
$^1$H-NMR of Compound 1.144 (CDCl$_3$)...........................................................................95
$^{13}$C-NMR of Compound 1.144 (CDCl$_3$)...........................................................................95
IR of Compound 1.144 (neat).............................................................................................96
$^1$H-NMR of Compound 1.151 (CDCl$_3$)...........................................................................97
$^{13}$C-NMR of Compound 1.151 (CDCl$_3$)...........................................................................97
$^1$H-NMR of Compound 1.152 (CDCl$_3$)...........................................................................98
$^{13}$C-NMR of Compound 1.152 (CDCl$_3$)...........................................................................98
IR of Compound 1.152 (neat)............................................................................................99
$^1$H-NMR of Compound 1.105 (CDCl$_3$).........................................................................100
$^{13}$C-NMR of Compound 1.105 (CDCl$_3$).........................................................................100
IR of Compound 1.105 (neat)...........................................................................................101
Chiral GC Data for Compound 1.105............................................................................102
$^1$H-NMR of Compound 1.155 (CDCl$_3$).........................................................................104
$^{13}$C-NMR of Compound 1.155 (CDCl$_3$).........................................................................104
IR of Compound 1.155 (neat)................................................................. 105

$^1$H-NMR of Compound 1.156 (CDCl$_3$)...................................................... 106

$^{13}$C-NMR of Compound 1.156 (CDCl$_3$)...................................................... 106

IR of Compound 1.156 (neat)........................................................................ 107

$^1$H-NMR of Compound 1.157 (CDCl$_3$)...................................................... 108

$^{13}$C-NMR of Compound 1.157 (CDCl$_3$)...................................................... 108

IR of Compound 1.157 (neat)........................................................................ 109

$^1$H-NMR of Compound 1.158 (CDCl$_3$)...................................................... 110

$^{13}$C-NMR of Compound 1.158 (CDCl$_3$)...................................................... 110

IR of Compound 1.158 (neat)........................................................................ 111

$^1$H-NMR of Compound 1.162 (CDCl$_3$)...................................................... 112

$^{13}$C-NMR of Compound 1.162 (CDCl$_3$)...................................................... 112

$^1$H-NMR of Compound 1.167 (CDCl$_3$)...................................................... 113

$^{13}$C-NMR of Compound 1.167 (CDCl$_3$)...................................................... 113

IR of Compound 1.167 (neat)........................................................................ 114

$^1$H-NMR of Compound 1.168 (CDCl$_3$)...................................................... 115

$^{13}$C-NMR of Compound 1.168 (CDCl$_3$)...................................................... 115

IR of Compound 1.168 (neat)........................................................................ 116

$^1$H-NMR of Compound epi-1.168 (CDCl$_3$).................................................. 117

$^{13}$C-NMR of Compound epi-1.168 (CDCl$_3$).................................................. 117

$^1$H-NMR of Compound 1.169 (CDCl$_3$)...................................................... 118

$^{13}$C-NMR of Compound 1.169 (CDCl$_3$)...................................................... 118

IR of Compound 1.169 (neat)........................................................................ 119
$^1$H-NMR of Compound 1.170 (CDCl$_3$) ................................................................. 120

$^{13}$C-NMR of Compound 1.170 (CDCl$_3$) ................................................................. 120

IR of Compound 1.170 (neat) ..................................................................................... 121

$^1$H-NMR of Compound 1.173 (CDCl$_3$) ................................................................. 122

$^{13}$C-NMR of Compound 1.173 (CDCl$_3$) ................................................................. 122

HSQC NMR of Compound 1.173 (CDCl$_3$) ............................................................. 123

IR of Compound 1.173 (neat) ..................................................................................... 123

$^1$H-NMR of Compound 1.174 (CDCl$_3$) ................................................................. 124

$^{13}$C-NMR of Compound 1.174 (CDCl$_3$) ................................................................. 124

HSQC NMR of Compound 1.174 (CDCl$_3$) ............................................................. 125

$^1$H-NMR of Compound 1.176 (CDCl$_3$) ................................................................. 126

$^{13}$C-NMR of Compound 1.176 (CDCl$_3$) ................................................................. 126

$^1$H-NMR of Compound 1.180 (CDCl$_3$) ................................................................. 127

$^{13}$C-NMR of Compound 1.180 (CDCl$_3$) ................................................................. 127

HSQC NMR of Compound 1.180 (CDCl$_3$) ............................................................. 128

IR of Compound 1.180 (neat) ..................................................................................... 128

$^1$H-NMR of Compound 1.183 (CDCl$_3$) ................................................................. 129

$^{13}$C-NMR of Compound 1.183 (CDCl$_3$) ................................................................. 129

HSQC NMR of Compound 1.183 (CDCl$_3$) ............................................................. 130

IR of Compound 1.183 (neat) ..................................................................................... 130

$^1$H-NMR of Compound 1.184 (CDCl$_3$) ................................................................. 131

$^{13}$C-NMR of Compound 1.184 (CDCl$_3$) ................................................................. 131

$^1$H-NMR of Compound 1.188 (CDCl$_3$) ................................................................. 132

xvii
$^1\text{H}$-NMR of Compound 2.30 (CDCl$_3$) ........................................................................................................ 218

$^1\text{H}$-NMR of Compound 2.32 (CDCl$_3$) ........................................................................................................ 219

$^1\text{H}$-NMR of Compound 2.35 (CDCl$_3$) ........................................................................................................ 220

$^{13}\text{C}$-NMR of Compound 2.35 (CDCl$_3$) ........................................................................................................ 220

HSQC NMR of Compound 2.35 (CDCl$_3$) ........................................................................................................ 221

$^1\text{H}$-NMR of Compound 2.36 (CDCl$_3$) ........................................................................................................ 222

$^{13}\text{C}$-NMR of Compound 2.36 (CDCl$_3$) ........................................................................................................ 222

HSQC NMR of Compound 2.36 (CDCl$_3$) ........................................................................................................ 223

$^1\text{H}$-NMR of Compound 2.40 (CDCl$_3$) ........................................................................................................ 224

$^{13}\text{C}$-NMR of Compound 2.40 (CDCl$_3$) ........................................................................................................ 224

$^1\text{H}$-NMR of Compound 2.42 (CDCl$_3$) ........................................................................................................ 225

$^{13}\text{C}$-NMR of Compound 2.42 (CDCl$_3$) ........................................................................................................ 225

$^1\text{H}$-NMR of Compound 2.44 (CDCl$_3$) ........................................................................................................ 226

$^{13}\text{C}$-NMR of Compound 2.44 (CDCl$_3$) ........................................................................................................ 226

HSQC NMR of Compound 2.44 (CDCl$_3$) ........................................................................................................ 227

$^1\text{H}$-NMR of Compound 2.46 (CDCl$_3$) ........................................................................................................ 228

$^{13}\text{C}$-NMR of Compound 2.46 (CDCl$_3$) ........................................................................................................ 228

$^1\text{H}$-NMR of Compound 2.51 (CDCl$_3$) ........................................................................................................ 229

$^{13}\text{C}$-NMR of Compound 2.51 (CDCl$_3$) ........................................................................................................ 229

$^1\text{H}$-NMR of Compound 2.52 (CDCl$_3$) ........................................................................................................ 230

$^{13}\text{C}$-NMR of Compound 2.52 (CDCl$_3$) ........................................................................................................ 230

HSQC NMR of Compound 2.52 (CDCl$_3$) ........................................................................................................ 231

$^1\text{H}$-NMR of Compound 2.53 (toluene-d$_8$) ................................................................................................ 232
13C-NMR of Compound 2.53 (toluene-d8) ................................................................. 232

1H-NMR of Compound 2.55 (toluene-d8) ............................................................... 233

13C-NMR of Compound 2.55 (toluene-d8) ............................................................... 233

1H-NMR of Compound 2.58 (CDCl3) ....................................................................... 234

13C-NMR of Compound 2.58 (CDCl3) ....................................................................... 234

HSQC NMR of Compound 2.58 (CDCl3) ................................................................. 235

COSY NMR of Compound 2.58 (CDCl3) ................................................................. 235

1H-NMR of Compound 2.72 (CDCl3) ....................................................................... 236

13C-NMR of Compound 2.72 (CDCl3) ....................................................................... 236

1H-NMR of Compound 2.73 (CDCl3) ....................................................................... 237

13C-NMR of Compound 2.73 (CDCl3) ....................................................................... 237

1H-NMR of Compound 2.74 (CDCl3) ....................................................................... 238

13C-NMR of Compound 2.74 (CDCl3) ....................................................................... 238

1H-NMR of Compound 2.75 (CDCl3) ....................................................................... 239

13C-NMR of Compound 2.75 (CDCl3) ....................................................................... 239

1H-NMR of Compound 2.76 (CDCl3) ....................................................................... 240

13C-NMR of Compound 2.76 (CDCl3) ....................................................................... 240

HSQC NMR of Compound 2.76 (CDCl3) ................................................................. 241

1H-NMR of Compound 2.77 (CDCl3) ....................................................................... 242

13C-NMR of Compound 2.77 (CDCl3) ....................................................................... 242

HSQC NMR of Compound 2.77 (CDCl3) ................................................................. 243

1H-NMR of Compound 2.79 (CDCl3) ....................................................................... 244

13C-NMR of Compound 2.79 (CDCl3) ....................................................................... 244
HSQC NMR of Compound 2.29 (CDCl₃) ................................................................. 245
IR of Compound 2.29 (neat) ................................................................. 245
¹H-NMR of Compound 2.81-b (CDCl₃) ................................................................. 246
¹³C-NMR of Compound 2.81-b (CDCl₃) ................................................................. 246
IR of Compound 2.81-b (neat) ................................................................. 247
¹H-NMR of Compound 2.81-c (CDCl₃) ................................................................. 248
¹³C-NMR of Compound 2.81-c (CDCl₃) ................................................................. 248
¹H-NMR of Compound 2.81-d (CDCl₃) ................................................................. 249
¹³C-NMR of Compound 2.81-d (CDCl₃) ................................................................. 249
IR of Compound 2.82-a (neat) ................................................................. 250
¹H-NMR of Compound 2.82-a (CDCl₃) ................................................................. 250
¹³C-NMR of Compound 2.82-a (CDCl₃) ................................................................. 250
IR of Compound 2.82-a (neat) ................................................................. 251
¹H-NMR of Compound 2.82-b (CDCl₃) ................................................................. 252
¹³C-NMR of Compound 2.82-b (CDCl₃) ................................................................. 252
IR of Compound 2.82-b (neat) ................................................................. 253
¹H-NMR of Compound 2.82-c (CDCl₃) ................................................................. 254
¹³C-NMR of Compound 2.82-c (CDCl₃) ................................................................. 254
IR of Compound 2.82-c (neat) ................................................................. 255
¹H-NMR of Compound 2.82-d (CDCl₃) ................................................................. 256
¹³C-NMR of Compound 2.82-d (CDCl₃) ................................................................. 256
¹H-NMR of Compound 2.83-a (CDCl₃) ................................................................. 257
¹³C-NMR of Compound 2.83-a (CDCl₃) ................................................................. 257
¹H-NMR of Compound 2.83-b (CDCl₃) ................................................................. 258
<table>
<thead>
<tr>
<th>Compound</th>
<th>NMR Type</th>
<th>CDCl$_3$</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$^{13}$C-NMR</td>
<td>2.83-b</td>
<td>258</td>
</tr>
<tr>
<td></td>
<td>$^{1}$H-NMR</td>
<td>2.83-c</td>
<td>259</td>
</tr>
<tr>
<td></td>
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HSQC NMR of Compound 2.91 (CDCl₃) ................................................................. 272
COSY NMR of Compound 2.91 (CDCl₃) ................................................................. 272
IR of Compound 2.91 (neat) .................................................................................. 273
¹H-NMR of Compound 2.92 (CDCl₃) ..................................................................... 274
¹³C-NMR of Compound 2.92 (CDCl₃) ..................................................................... 274
HSQC NMR of Compound 2.92 (CDCl₃) ................................................................. 275
COSY NMR of Compound 2.92 (CDCl₃) ................................................................. 275
HMBC NMR of Compound 2.92 (CDCl₃) ............................................................... 276
IR of Compound 2.92 (neat) .................................................................................. 276
List of Abbreviations

°C  
degrees celsius

9-BBN  
9-borabicyclo[3.3.1]nonane

Å  
angstrom

Ac  
acetyl

AcCl  
acetyl chloride

ACN  
acetonitrile

ACS  
American Chemical Society

AcOH  
acetic acid

AIBN  
azobisisobutyronitrile

anhy  
anhydrous

aq  
aqueous

Anal.  
analytical

APT  
attracted proton test

atm  
atmosphere

BHT  
3,5-di-tert-butyl-4-hydroxytoluene

Bn  
benzyl

BOM  
benzyloxymethyl

BRSM  
based on recovered starting material

br  
broad

n-BuLi  
n-butyl lithium

t-BuLi  
t-butyl lithium

BuOH  
butyl alcohol

c  
concentration

°C  
degrees Celsius

calcd  
calculated

CAS  
chemical abstract services

cm  
centimeters

cm\(^{-1}\)  
wave numbers

CSA  
camphor sulfonic acid
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<th>Abbreviation</th>
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<tr>
<td>CPTS</td>
<td>collidinium $p$-toluenesulfonate</td>
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<tr>
<td>Cy$_3$P</td>
<td>tricyclohexyl phosphine</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
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<tr>
<td>DA</td>
<td>Diels-Alder</td>
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<tr>
<td>DABCO®</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
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<td>DBU</td>
<td>1,8-diazabicycloundecene-7-ene</td>
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<td>DCC</td>
<td>1,3-dicyclohexylcarbodiimide</td>
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<tr>
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<td>dichloromethane</td>
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<td>DIBAL-H</td>
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<td>dimethylacetamide</td>
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<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
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<td>dimethyldioxirane</td>
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<td>dimethylformamide</td>
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<td>Dess-Martin periodinane</td>
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<td>dimethyl sulfide</td>
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<td>dimethyl sulfoxide</td>
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<td>1-ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
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<td>EI</td>
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<td>bis(trimethylsilyl)amine</td>
</tr>
<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>Hz</td>
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<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
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<td>infrared</td>
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<tr>
<td>J</td>
<td>coupling constant</td>
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<td>potassium t-butoxide</td>
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<td>L</td>
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<td>LAH</td>
<td>lithium aluminum hydride</td>
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<td>lithium diisopropylamide</td>
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<td>lithium bis-(trimethylsilyl)amide</td>
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<td>MOMCl</td>
<td>methoxymethyl chloride</td>
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MsCl  methanesulfonyl chloride
N  normal
NaH  sodium hydride
nOe  nuclear Overhauser effect
NBS  N-bromosuccinamide
NBSA  o-nitrobenzenesulfonylazide
NIS  N-iodosuccinimide
NMO  4-methylmorpholine N-oxide
NMP  N-methyl-2-pyrrolidone
NMR  nuclear magnetic resonance
obs  observed
o-DCB  ortho-dichlorobenzene
p  pentet (quintet)
PCC  pyridinium chlorochromate
Ph  phenyl
PhH  benzene
PhCF₃  α,α,α-trifluorotoluene
PhMe  toluene
PPh₃  triphenylphosphine
ppm  parts per million
PPTS  pyridinium para-toluenesulfonate
psi  pounds per square inch
p-TsOH  para-toluenesulfonic acid
Pyr  pyridine
q  quartet
quant.  Quantitative
quin  quintet
RT  room temperature
RCM  ring closing metathesis
s  singlet

xxvii
SFC
supercritical fluid chromatography
sat
saturated

TBAF
tetrabutylammonium fluoride
TBS
$\text{tert}$-butyldimethylsilyl
TBSOTf
$\text{tert}$-butyldimethylsilyl trifluoromethanesulfonate
TEA
triethylamine
TEMPO
$(2,2,6,6$-$\text{tetramethylpiperidin-1-yl$)$oxyl
TES
triethylsilyl
TESCl
triethylsilyl chloride
TESOTf
triethylsilyl trifluoromethanesulfonate
TFA
trifluoroacetic acid
TFDO
methyl(trifluoromethyl)dioxirane
Tf$_2$O
trifluoroacetic anhydride
THF
tetrahydrofuran
TIPS
triisopropylsilyl
TLC
thin layer chromatography
TMS
trimethylsilyl
TMSCl
trimethylsilyl chloride
TMSCN
trimethylsilyl cyanide
TMSI
trimethylsilyl iodide
TsN$_3$
$\text{para}$-toluenesulfonyl azide
Tol
$\text{para}$-toluene
UHP
urea hydrogen peroxide
UV
ultraviolet
General Methods

All reactions were carried out under a nitrogen or an argon atmosphere unless otherwise indicated. Acetonitrile, benzene, dichloromethane, dimethyl sulfoxide, tetrahydrofuran, toluene and triethylamine were deoxygenated and dried by argon sparging and passing through activated alumina columns. α,α,α-Trifluorotoluene was distilled under nitrogen from CaH and stored over 3 or 4Å molecular sieves. Other commercially available reagents were used without purification unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm Whatman silica gel plates with fluorescent indicator using UV light. Development of the plates was accomplished by using basic potassium permanganate, ceric ammonium molybdate or p-anisaldehyde stain. Flash chromatography was performed using silica gel (32-63 µm) from Dynamic Absorbents, Inc.

Nuclear magnetic resonance (NMR) spectra were obtained on 400 MHz Varian, 300 MHz or 500 MHz Bruker spectrometers. ¹H-NMR spectra are referenced to the residual proton solvent peak (CDCl₃ = 7.26 ppm; C₆D₆ = 7.16 ppm; toluene-d₈ = 7.09). ¹³C-NMR (APT) spectra are referenced to the deuterated solvent signal (CDCl₃ = 77.16 ppm; C₆D₆ = 128.06 ppm; toluene-d₈ = 137.86). The multiplicities are abbreviated as follows; s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, br = broad signal. High-resolution mass spectrometry was obtained on an Agilent 6210 high-resolution time of flight LC/MS using electrospray ionization (ESI+). FT-IR spectra were obtained on a Thermo Electron Corporation
Nicolet 6700 FTIR equipped with a diamond tip [30,000 to 200 cm\(^{-1}\)]. Optical rotations were obtained on a Perkin-Elmer 341 polarimeter.
Chapter 1

Efforts towards a total synthesis of enantiopure maecrystal V
1.1 Discovery and identification of maocrystal V

The widely distributed southwestern Chinese perennial shrub, *Isodon eriocalyx* (Dunn.) Hara is used in traditional folk medicine to treat ailments such as sore throat, inflammation, influenza and hypertension.\(^1,2\) Known to be a rich source of *ent*-kauranoid diterpene compounds with various oxygenation and cleavage patterns, *Isodon eriocalyx* has drawn chemists to study its extracts in order to identify the bioactive components.\(^3\) In doing such, over 30 new *ent*-kauranoid compounds having the core skeletal framework shown in Figure 1.1 have been identified. The compounds in Figure 1.2 are representative *ent*-kauranoids that show modest antitumor (1.1 and 1.2) or antibacterial (1.3 and 1.4) activity.\(^1,3\)

![ent-kaurane skeleton and ent-kaurane numbering](image)

**Figure 1.1:** Core skeletal framework for *ent*-kauranes with and without numbering. Bicyclo[3.2.1]octane highlighted in blue.

![Representative ent-kauranoids with antitumor (1.1, 1.2) and antibacterial activity (1.3, 1.4)](image)

**Figure 1.2:** Representative *ent*-kauranoids with antitumor (1.1, 1.2) and antibacterial activity (1.3, 1.4).
In the 1990’s as part of an ongoing search for anticancer diterpenoid compounds from the genus *Isodon* plants of the Labiatae family, Sun and coworkers isolated 5 mg of a bioactive diterpenoid molecule from 11.9 kg of dried leaves of *Isodon eriocalyx* (0.000042% overall yield). Using IR, NMR and HRMS data, they proposed an uncommon skeletal framework for the 19-carbon ent-kauranoid 16-\((R)\)-methyl-1,15-dioxo-6,7-seco-6-nor-15(8→9)-abeo-5,8-epoxy-ent-kaur-2-en-7,20-oilde and trivially named it maoecrystal V (1.5). Approximately ten years later, a successful single crystal X-ray diffraction experiment verified their proposal and the unique structure was disclosed in late 2004.\(^2\)

![maoecrystal V (1.5)](image)

**Figure 1.3:** Structure of maoecrystal V with carbon numbering.

Figures 1.1 and 1.2 depict a commonly found trait in many *ent*-kauranoids, namely a bicyclo[3.2.1]octane as part of their skeletal core (blue highlight). In contrast, maoecrystal V (1.5) has the unique feature of containing a bicyclo[2.2.2]octane in the pentacyclic skeleton. The central, sterically congested tetrahydrofuran ring, trans-fused cyclohexenone moiety and the spirocyclic \(\delta\)-lactone provide the framework for six stereogenic centers which include two vicinal all carbon quaternary centers (C9 and C10) as part of a run of four contiguous
stereocenters (C₈, C₉, C₁₀ and C₅). Maoecrystal V (1.5) is considered the most highly modified ent-kauranoid isolated from the Isodon species.²

The complexity of this molecule is enough to inspire synthetic chemists to their apply their craft. However, adding to the intrigue of this diterpenoid, Sun and coworkers also demonstrated that maoecrystal V (1.5) is selectively cytotoxic against HeLa ovarian cancer cells in a five human tumor cell assay. As shown in Table 1.1, maoecrystal V (1.5) shows poor activity in four out of the five tumor cells assayed, but impressively has an IC₅₀ = 0.02 µg/mL (60 nM) against the cervical cancer cells. No further studies on the mechanism of action or the cellular target have been disclosed.

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<th>A549</th>
<th>BGC-823</th>
<th>CNE</th>
<th>HeLa</th>
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<td>maoecrystal V</td>
<td>6.43 x 10⁴</td>
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<td>1.47 x 10⁴</td>
<td>nd¹</td>
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<td>1.61</td>
<td>0.25</td>
<td>2.31</td>
<td>0.99</td>
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</table>

¹ Not determined.

Table 1.1: Selective and highly potent cytotoxicity of maoecrystal V.
Cell lines: K562 = myelogeneous leukemia; A549 human carcinomic alveolar basal epithelial; BGC-823 = human gastric carcinoma; CNE = human nasopharyngeal carcinoma; HeLa = human cervical cancer

1.2 Proposed biosynthesis

A biogenetic pathway to maoecrystal V (1.5) starting from the commonly occurring 7,20-epoxy-ent-kaurane (1.6) was proposed.⁴ As shown in Scheme 1.1, oxidative cleavage of between C₆ and C₇ of 1.6 would provide aldehyde/lactone 1.7.
Stereoretentive Baeyer-Villager type oxidation with hydrolysis of the resultant formyl ester would provide C$_5$ secondary alcohol 1.8 and the loss of the C$_6$ carbon fragment leaving nineteen carbons in the skeleton. A skeletal rearrangement, including a 1,2-carbon shift, triggered by hydride abstraction at C$_9$ proceeding through carbocation 1.9 would provide the requisite pentacyclic framework 1.10 upon tetrahydrofuran ring formation. Reduction at C$_{17}$ of the exocyclic methylene followed by oxidation to the cyclohexenone ring would provide maoecrystal V (1.5).

Scheme 1.1: Proposed biosynthesis of maoecrystal V.

1.3 Previous synthetic efforts-Literature

The unique and complex structure of maoecrystal V coupled with its selective cytotoxicity has sparked significant interest in the synthetic organic chemical community. Six labs have disclosed synthetic efforts to make the molecule and two were successful in achieving racemic total syntheses. Li and Yang accomplished this goal first in 2010,$^5$a followed by the Danishefsky lab in 2012.$^6$a The following sections will provide a summary of the work disclosed in the literature, as well as
prior efforts from the Sorensen lab. Throughout this thesis, the carbon numbering system depicted in Figure 1.3 will be applied to all intermediates according to the location that corresponding carbon would be found in the natural product.

To date, all of the published chemistry directed at synthesizing maoecrystal V (1.5) has been racemic. It will become apparent that the favored strategy in the chemical community to generate maoecrystal V (1.5) has been [4+2] cycloaddition chemistry, usually in an intramolecular fashion, often in tandem with a dearomatization to provide the requisite diene. In fact, all but one of the reported efforts to synthesize maoecrystal V (1.5) employ a Diels-Alder based strategy to install the bicyclo[2.2.2]octane core. Even our lab’s initial approach to the total synthesis of maoecrystal V (1.5) employed a [4+2] strategy.⁷

The Thomson lab at Northwestern approached maoecrystal V (1.5), by targeting an intermolecular Diels-Alder to form the bicyclo[2.2.2]octane (Scheme 1.2).⁸ The cross conjugated diene 1.12 formed from the Nazarov cyclization of 1.11, was reduced in 1,2 fashion with DIBAL-H to provide a diene intermediate (not shown), which then participated in a diastereoselective intermolecular Diels-Alder reaction with nitroethylene to afford bicyclo[2.2.2]octene 1.13. After epimerization at C₁₅, hydrogenation and oxidation led to ketone 1.14; a Rubottom oxidation then provided α-hydroxy ketone 1.15. Unfortunately, the group was not successful in achieving a directed remote oxidation at C₅ to form the desired tetrahydrofuran ring (1.16).
Scheme 1.2: Thomson’s synthesis of the skeletal core of maoecrystal V using an intermolecular Diels-Alder reaction.

Singh and coworkers employed a tandem Alder-Becker sodium periodate dearomatization/intramolecular Diels-Alder reaction to generate the bicyclo[2.2.2]octane framework (Scheme 1.3). Treatment of phenol 1.17 with aqueous sodium periodate provided the intermediate diene 1.18, which subsequently underwent an intramolecular Diels-Alder reaction upon heating, forging the bicyclo[2.2.2]octene 1.19. Zinc metal reduction of the epoxide followed by Jones oxidation with concurrent decarboxylation gave the bicyclo[2.2.2]octene 1.21 containing the desired δ-lactone. Hydrogenation of this alkene provided 1.22 with three of the five rings in the skeletal core of maoecrystal V (1.5).
Scheme 1.3: Singh’s synthesis of the bicyclo[2.2.2]octane core of maoecrystal V using an intramolecular Diels-Alder reaction triggered by an oxidative Alder-Becker dearomatization.

By focusing on the creation of the tetrahydrofuran via Rh(II) carbenoid C-H insertion chemistry, the Zakarian lab achieved the desired stereochemistry for what would become the C5 carbon in the natural product (Scheme 1.4). Diazoester 1.23 was efficiently converted to tetrahydrofuran 1.24 upon treatment with Rh2(OAc)4. Alkylation, reduction and treatment with methylmagnesium bromide provided monoprotected catechol 1.26. Oxidative dearomatization with PhI(O2CCF3)2 provided protected o-quinone 1.27. Acylation with acryloyl chloride provided substrate 1.28 for an intramolecular Diels-Alder. The bicyclo[2.2.2]octane core was achieved by heating diene 1.28 in the presence of butylated hydroxytoluene (BHT) to provide 1.29 in excellent yield. The authors propose that the total synthesis of maoecrystal V (1.5) could be achieved in part by carbon-carbon bond cleavage forming 1.30 followed by subsequent acylradical cyclization to form the δ-lactone ring in 1.31.
Scheme 1.4: Zakarian’s synthesis of the THF ring via Rh(II) C-H insertion chemistry and of the bicyclo[2.2.2]octane of maoecrystal V using an intramolecular Diels-Alder reaction facilitated by an oxidative dearomatization.

Scheme 1.5 shows a Diels-Alder strategy from the labs of Nicolaou and Chen that ultimately provided all five rings present in maoecrystal V (1.5) although epimeric at C5 in the skeletal framework.\textsuperscript{11a} The silyloxy diene with attached vinyl ether 1.32 afforded the bicyclo[2.2.2]octane 1.33 after heating in toluene and deprotection with aqueous acid. Hypervalent iodine dearomatization provides the monoprotected p-quinone 1.34. Multi-step reduction gave a diol that contained a cyclohexane ring with the undesired stereochemistry at C5 (not shown). Compound 1.35 was realized after double benzylation of the diol. Unmasking of the ketone, Tebbe olefination, Simmons-Smith cyclopropanation and hydrogenolysis provided cyclopropane diol 1.36. Dess-Martin oxidation to the dione, platinum-catalyzed
hydrogenation of the cyclopropyl group, and Saegusa oxidation to the enone were achieved affording compound 1.37. δ-Lactone 1.39 was formed by basic hydrolysis of the methyl ester followed by dialkylation using chloriodomethane in the presence of KOtBu and 18-crown-6 ether in low yield.

Scheme 1.5: Nicolaou and Chen’s synthesis of the pentacyclic framework of maoecrystal V, epimeric at C5 through a Diels-Alder reaction with a bis-alkylation forming the lactone.

The Chen lab ultimately set the desired stereochemistry at C5 by a diastereoselective reduction of ketone 1.41, which was derived from 1.34, at C1 with L-selectride followed by unmasking of the carbonyl at C4 1.43, (Scheme 1.6).11

Directed hydrogenation with palladium gave the cyclohexane ring with the correct stereochemistry at C5 (1.44). Following an Wittig olefination, cyclopropanation and hydrogenation sequence, the authors created four of the five rings of maoecrystal V
(1.5), excluding for the δ-lactone, with correct stereochemistry at C₅ as shown in compound 1.46. There was no mention of the fate of this advanced intermediate.

![Scheme 1.6](image)

**Scheme 1.6:** Chen's synthesis of the four of the five rings of maoecrystal V with correct stereochemistry at C₅ via directed hydrogenation.

The only strategy in the literature that relies on a non-Diels-Alder approach came from the Trauner lab (Scheme 1.7). They showed that bicyclo[2.2.2]octane 1.48 was achieved by an intramolecular aldol reaction of keto-aldehyde 1.47 followed by silyl protection of the resulting hydroxy group. After diastereoselective vinyl addition to the ketone, lactonization provided the tricycle 1.49. A sequence of steps provided the double aldol product 1.50, which upon ozonolysis was trapped as the tetracycle 1.51 that maps directly onto the natural product.
Scheme 1.7: Trauner’s non Diels-Alder synthesis for the bicyclo[2.2.2]octane framework of maoecrystal V.

The Baran lab showed a strategy for making maoecrystal V (1.5) via an intramolecular Diels-Alder reaction enabled by a Wessely lead-catalyzed oxididative dearomatization.\textsuperscript{13} Shown in Scheme 1.8, the aryl bismuth reagent 1.53 was coupled with the keto-aldehyde 1.52, by way of Barton coupling. Chemoselective reduction of the resulting formyl group, acylation of the primary alcohol and deprotecton of the phenol compound provided hemiacetal 1.54. Treatment with Pb(OAc)$_4$ gave the requisite diene 1.55 through oxidative dearomatization, which upon heating in o-dichlorobenzene afforded all but the tetrahydrofuran ring of maoecrystal V (1.5) as shown in compound 1.56.
Scheme 1.8: Baran’s oxidative Wessely dearomatization/Diels-Alder strategy for the synthesis of the bicyclo[2.2.2]octane framework of maoecrystal V.

Concurrent to the Baran work, the groups of Li and Yang published a strategy based on the same concept of employing an intramolecular Diels-Alder reaction enabled by lead (IV) oxidative dearomatization to form the skeleton of maoecrystal V.\textsuperscript{5b} According to Baran, the author, Li, was a postdoctoral associate in his lab during the time that they were investigating the previously described chemistry. Controversy aside, this strategy eventually led to the first successful racemic synthesis of maoecrystal V (1.5).\textsuperscript{5a}

Starting from unconjugated enone 1.57, β-ketoester 1.58 was formed using sodium hydride and dimethylcarbonate (Scheme 1.9). The following oxidative lead aryl coupling with 1.59 was accomplished in excellent yield. Sequential reduction of β-ketoester 1.60 was performed to make cis-diol 1.61. EDCI promoted esterification yielded β-phosphonate ester 1.62. After diazotization with tosylazide and DBU, rhodium (II) acetate catalyzed O-H insertion provided cyclic ether 1.63. This
phosphate ester then reacted with KOTBu and paraformaldehyde in a Horner-Wadsworth-Emmons reaction providing an exocyclic enone. TFA deprotection reveals phenol 1.64.

Scheme 1.9: Li and Yang’s synthesis of the exocyclic dienophile 1.64 for an intramolecular Diels-Alder reaction en route to maecrystal V.

In an ambitious two-step sequence to form the entire pentacyclic skeleton, the authors relied on a lead(IV)acetate Wessely oxidative acetoxylation of 1.64 to generate a diene (not shown, Scheme 1.10). Superheating the crude diene to 145 °C in toluene provided the desired Diels-Alder adduct as a mixture of separable
diastereomers (favoring the undesired exo-products 1.66 over the desired endo-product 1.65). Allylic bromination of cyclohexene 1.65 with NBS, followed by trapping the allylic radical generated from tributylin hydride with TEMPO gave an allylic TEMPO adduct (not shown). Zn/AcOH reduction gave allylic alcohol 1.67.

![Scheme 1.10](image)

**Scheme 1.10:** Li and Yang’s oxidative dearomatization/Diels-Alder route to synthesize maecrystal V.

At this stage, samarium diiodide reduction of the acetate group led to an epimerization of the α-methyl group at C₁₆. Chemoselective hydrogenation with Lindlar’s catalyst gave allylic alcohol 1.68 with a saturated bicyclo[2.2.2]octane ring. The authors finally isolated racemic maecrystal V (1.5) (2.8 mg) by oxidizing the allylic hydroxyl group with Dess-Martin periodinane followed by epimerizing the α-
methyl group at C_{16} with DBU to give a separable 1:1 mixture of the desired natural product 1.5 and C_{16}-epi-maoecrystal V (not shown). There was no mention of confirming the observed selective cytotoxicity reported by Sun and coworkers.

Li and Yang’s 17-step sequence was accomplished in 1% overall yield, an impressive accomplishment in total synthesis especially when compared to the attempts previously discussed. Although there is room for improvement in the key Diels-Alder step, the brevity of the sequence helps to alleviate this shortcoming in light of the recently reported second total synthesis from the Danishefsky lab (vide infra).

The initial efforts to synthesize maoecrystal V (1.5) in the Danishefsky lab were among the first published in 2009. They expanded on their efforts in 2011 and in 2012 the published a route to provide the natural product. The successful route will be discussed below.

By employing an intramolecular Diels-Alder strategy, Danishefsky and Peng impressively installed four of the five carbocyclic rings in only six steps. However, installing the tetrahydrofuran ring with the correct stereochemistry at C_5 and the need to fully functionalize the pentacyclic skeleton posed significant challenges.

Through a five-step sequence of alkylation, reduction, oxidation, acylation and enolate protection, ester 1.69 and vinylogous acid chloride 1.70 were combined to provide silyloxy diene 1.71 with pendant enone (Scheme 1.11). By heating 1.70 in a sealed tube in toluene followed by fluoride-assisted removal of the silyl ether, bicyclo[2.2.2]octene 1.72, complete with δ-lactone and both quaternary carbons (C_{10} and C_9) was realized. Selective nucleophilic epoxidation of enone 1.72 followed
by opening of the epoxide with magnesium iodide provided a vicinal iodohydrin (not shown). Reduction of the carbon-iodide bond using tributyltinhydride under radical conditions gave alcohol 1.73. The authors achieved chemoselective epoxidation of the C₄-C₅ alkene using m-chloroperoxybenzoic acid and subsequently opened the epoxide under acidic conditions to provide 1.74, noting that the tetrahydrofuran ring has the undesired stereochemistry at C₅.

Scheme 1.11: Danishefsky’s synthesis of the carbocyclic skeleton of maoecrystal V albeit epimeric at C₅ via a Diels-Alder reaction en route to synthesize maoecrystal V.

As shown in Scheme 1.12, Danishefsky and Peng epimerized the stereocenter at C₅ in a twelve-step sequence to provide 1.78. Beginning with 1.74, acetate protection followed by sodium borohydride reduction yielded an inconsequential mixture of epimeric alcohols at C₁₆ (1:1, not shown). Methoxymethyl protection of the mixture of alcohols followed by removal of the acetate group provided alcohol 1.75. Using m-chloroperoxybenzoic acid and Dess-Martin periodinane, a cyclohexenenone/alcohol was established, which was subsequently protected with an acetate group (1.76). In order to ablate the stereocenter at C₅, thiophenol
conjugatively added into the enone, creating a β-thiophenoxy ketone that underwent 1,2-reduction to a β-thiophenoxy alcohol with sodium borohydride. Desulfurization under Raney-nickel catalysis followed by dehydration using methanesulfonyl chloride and dimethylaminopyridine (DMAP) produced glycal 1.77. Removal of the acetate moiety followed by epoxidation with dimethyldioxirane and subsequent semipinacol rearrangement with BF₃•OEt₂ provided the pentacycle 1.78, which had the correct stereochemistry at C₅.

![Scheme 1.12](image)

**Scheme 1.12:** Intermediates *en route* to Danishefsky’s synthesis of maocystal V; epimerization and functionalization.

Olefination of the C₄ ketone 1.78 using Lambardo’s conditions followed by Simmons-Smith cyclopropanation afforded compound 1.79. Double oxidation using pyridinium chlorochromate followed by platinum oxide-catalyzed hydrogenation of
the cyclopropane yielded dione 1.80 which contains the geminal dimethyl group at C₄. Chemoselective olefination using the Lombardo reagent followed by acid-catalyzed isomerization provided alkene 1.81 as a bicyclo[2.2.2]octene. A Saegusa oxidation installed the requisite enone functionality in molecule 1.82.

![Chemical structure](image)

**Scheme 1.13**: Last two steps of Danishefsky's synthesis of maoecrystal V; epoxidation and semi-pinacol rearrangement.

As shown in the first step of Scheme 1.13, the authors observed epoxidation of alkene 1.82 using trifluorodimethyldioxirane (TFDO), albeit in an unselective 1:1 diastereomeric ratio. Fortunately, epoxides 1.83 and 1.84 were separable and treatment of compound 1.83 with BF₃•OEt₂ at room temperature induced epoxide opening and subsequent 1,2-hydride shift to provide racemic maoecrystal V (1.5). There was no comment about retesting the biological activity of the synthetic material.
Both syntheses of maecrystal V (1.5) are impressive feats of organic chemistry. However, both show that there are significant challenges to an expedient synthesis of the enantiopure natural product. Both teams had difficulty either in efficiency or in the stereocontrol of creating the densely substituted tetrahydrofuran ring. These two labs have company in the synthetic community because most groups attempting a synthesis have not adequately solved the challenging tetrahydrofuran ring installation. Although glaringly obvious in the Danishefsky route, the Li and Yang route also contained redox or functional group manipulations in more than half of the steps. These necessary, yet undesirable, transformations lengthen both routes. Additionally, neither group has proposed a method to render these routes either enantioselective or enantiospecific.

1.4 Previous synthetic efforts-Sorensen Lab

Shortly after the initial disclosure of the highly potent, selective cytotoxicity and the fascinating structure, the Sorensen laboratory began pursuit of a total synthesis of maecrystal V (1.5). Postdoctoral associate William Chain and graduate student Douglas McLeod led the initial efforts, which employed, at least in part, a Diels-Alder strategy.\(^7\) Graduate student Mathew Naylor joined the project and has been pursuing a similar Diels-Alder approach; however, since that work is still in progress, it will not be discussed here. With a keen interest in synthesizing the molecule after the departure of McLeod, graduate student Jillan Spangler began a non Diels-Alder approach to the molecule.\(^{14}\) Postdoctoral associate Lorenz Herdeis
quickly joined the effort. These results of the Chain/McLeod and the initial Spangler/Herdeis approaches are described below.

**Scheme 1.14:** Initial base induced cyclization cascade proposal.

The first proposed route (Scheme 1.14) would take advantage of an intermolecular Diels-Alder with diene 1.85 and dimethylacetylene dicarboxylate (DMAD, 1.86) providing a bicyclo[2.2.2]octadiene 1.87 after triflation. This would allow for a carbonylative Stille palladium cross coupling with vinyl stannane 1.88 to provide enone 1.89. The key cyclization cascade sequence, triggered by basic hydrolysis of the methyl esters, was proposed to generate the pentacyclic framework in molecule 1.90, *(vide infra)*. A decarboxylation would provide enone/alkene 1.82. To finish the total synthesis, the lab proposed the same epoxidation/semipinacol transformation sequence that the Danishefsky lab had not yet brought to fruition (see Scheme 1.13).

The cyclization cascade depicted in Scheme 1.15 would be initiated by basic hydrolysis of the methyl ester groups of 1.89. If the C7 containing carboxylate of
1.91 would participate in an intramolecular alkoxy Michael addition into the enone at C$_{20}$, one could imagine formation of intermediate enolate 1.92. An intramolecular aldol between C$_{10}$ and C$_{5}$ would then be possible to form intermediate β-hydroxylate 1.93. Finally, a second hetero-Michael addition into the α,β-unsaturated acid at C$_{8}$ would give rise to the pentacyclic molecule 1.90 containing an extraneous carboxylate group at C$_{14}$.

![Diagram of proposed reaction sequence (Scheme 1.15)](attachment:reaction_sequence.png)

Scheme 1.15: Proposed hydroxide induced cyclization cascade sequence.

To test this hypothesis, McLeod and Chain built model ketoaldehyde 1.94, (Scheme 1.16). Although this molecule lacked the unit of unsaturation between C$_{2}$ and C$_{3}$, it allowed for the study of the proposed hetero-Michael-aldol-hetero-Michael cascade sequence. To their dismay, treating aldehyde 1.94 with a variety of hydroxide reagents did not lead to the desired pentacyclic framework, but only to the spirocyclic ketal 1.97. McLeod postulates that the aldehyde is susceptible to
nucleophilic addition by hydroxide forming hemiacetal 1.95, which, in turn, forms anion 1.96; lactonization then generated the undesired spiroketal product 1.97.

Scheme 1.16: Undesired reactivity of ketoaldehyde 1.94.

Fearful that this undesired reactivity would also be encountered using an unsaturated intermediate along the proposed synthetic route, a second-generation synthetic proposal was pursued. Without completely abandoning the knowledge gained from the initially investigated route, a Diels Alder-lactonization-hetero-Michael cascade followed by an eventual hydride transfer-vinylogous-aldol approach was proposed and investigated. Scheme 1.17 depicts the second planned strategy. If diene-triol 1.98 could undergo an intermolecular Diels-Alder reaction, it was assumed that lactonization followed by hetero-Michael addition to form the tetracyclic structure 1.100 would logically occur through 1.99. Advancing alcohol 1.100 to the tetracycle with pendant allenone 1.101 would allow for the testing of the hypothesis that an appropriate Lewis acid could induce a 1,5-hydride shift from
the C₅ to the C₃ carbon. The resulting zwitterionic enolate-oxocarbenium (1.102) could then participate in a vinylogous aldol reaction generating enone 1.103 containing the pentacyclic skeleton of maoecrystal V (1.5). Using the same end game strategy of decarboxylation, epoxidation and semi-pinacol rearrangement as previously proposed could provide maoecrystal V.

Scheme 1.17: Second generation proposal toward maoecrystal V using Diels-Alder.

Synthetic efforts produced compound 1.101. Nonetheless, after exhaustive experimental investigation, McLeod observed neither intramolecular nor intermolecular hydride abstraction.

Also intrigued by the chemical complexity, the lack of stereocontrol in the literature efforts and the desire to further investigate the biological activity of maoecrystal V (1.5), Jillian Spangler and Dr. Lorenz Herdeis embarked on a markedly different approach to the natural product. The strategy, outlined in Scheme 1.18, would not rely on a Diels-Alder reaction to generate the bicyclo[2.2.2]octane fragment but rather an intramolecular aldol-lactonization
sequence. The proposal began with an acid catalyzed aldol-lactonization of keto-aldehyde 1.104 to provide bicyclo[2.2.2]octane-lactone 1.105. The desired diastereomer depicted was expected to form due to the rapid epimerization of the stereocenters at C9 and C16 under acidic conditions. Cyanohydrin formation at C8 (1.106) followed by THF ring formation with a leaving group at C5 would give rise to nitrile 1.107. A reverse cationic prenylation would afford compound 1.108. Hydrolysis of nitrile 1.108 to a carboxylic acid followed by lactone opening from a metallo-vinyl addition would provide acid 1.109. After oxidation of the secondary alcohol, ring-closing metathesis would provide cyclohexenenone 1.110. Installation of the final δ-lactone would be achieved by a bis-alkylation of 1.110 to provide maoecrystal V (1.5).

Scheme 1.18: Third generation proposal toward maoecrystal V relying on an intramolecular cationic ring cyclization and reverse prenylation.
Spangler and Herdeis found that known ester 1.112, which came from an alkylation of cyclohexenone 1.111, participates in a Sakurai reaction with crotyltrimethylsilane 1.113 to provide a variable diastereotopic mixture of cyclohexanone 1.114 (Scheme 1.19). Ozonolysis of the olefin with reductive workup provided the ketoaldehyde 1.104, also as a mixture of inconsequential diastereomers. Inspired by the work of Kitahara, an intramolecular aldol of 1.104 with subsequent lactonization provides racemic bicyclo[2.2.2]octane as a single X-ray confirmed diastereomer. Even though, crotyltrimethyl silane provides the desired bicyclo[2.2.2]octane 1.105, Spangler and Herdeis used commercially available allyltrimethylsilane in an analogous sequence to provide bicyclo[2.2.2]octane 1.115 which lacks the methyl group at C16 as a more scalable and overall more crystalline model system.

Scheme 1.19: A stereoconvergent aldol-lactonization reaction forms the bicyclo[2.2.2]octane core.

* By the time the racemic aldol-lactonization work was complete, the work by the Trauner group had not been published. Our lab did not have great concern for scientific overlap because even though the two strategies to make the bicyclo[2.2.2]octane ring are remarkably similar, subsequent strategies diverge markedly.
Through synthetic effort ketal 1.116 was achieved. However, attempts at Lewis acid reverse prenylation did not lead to desired tetrahydrofuran 1.122 (Scheme 1.20). Reactivity was observed from Lewis acid ring opening of ketal 1.116 through undesired oxocarbenium 1.117, leading to a complex mixture of regioisomeric prenylation species 1.118, enol ether 1.119 and ketal epimer 1.120.

Scheme 1.20: Lewis acid catalysis gave a mixture of undesired reverse prenylation products.

A second oxocarbenium strategy to generate the THF ring with the prenyl group at C5 began by making acetal 1.123, (Scheme 1.21). An extensive evaluation of Lewis acids showed that BBr3 and Hünig’s base were uniquely successful at opening the ketal to an oxonium that participates in an intramolecular aldol to make tetrahydrofuran 1.124. Unfortunately, X-ray crystallography of the p-bromobenzyl ester 1.125 showed that the C5 carbon was produced as the undesired stereoisomer.
Scheme 1.21: BBr₃ promoted reverse prenylation giving the undesired diastereomer 1.124.

Because the only successful reverse prenylation experiment provided the tetrahydrofuran ring with the undesired stereochemistry at C₅, a new approach was needed. One solution would be to form the tetrahydrofuran ring via rhodium carbenoid C-H insertion chemistry. Scheme 1.22 depicts an initial attempt to employ such a strategy.

Scheme 1.22: Rhodium carbenoid promoted C-H insertion forms the tetrahydrofuran ring with undesired stereochemistry at C₅.

Using Noyori’s conditions, treatment of ketone 1.115 with bis-trimethylsilyl neopentyl glycol (1.125) and trimethylsilyl trifluoromethanesulfonate (TMSOTf)
gently yielded cyclic ketal 1.126. An interesting feature of this strategy is that the carbons in the ketal were to be incorporated into the final molecule. Cyanide addition using trimethylsilyl cyanide (TMSCN) in the presence of BF$_3$·OEt$_2$ gave rise to cyanohydrin 1.127 with excellent diastereoselectivity. Protection of the primary alcohol as a p-bromobenzoyl ester followed by diazo-transfer provided the diazolactone 1.130. When the diazolactone was subjected to 1 mol% Rh$_2$(esp)$_2$, the tetrahydrofuran containing tetracycle 1.131 was formed in good yield as a single diastereomer. However, in yet another disappointment, the C$_5$ stereogenic center was shown to be epimeric to the natural product via X-ray crystallography.

Undiscouraged and with high confidence, Spangler and Herdeis devised a modified rhodium catalyzed C-H insertion strategy that should favor the desired tetrahydrofuran formation. In Scheme 1.23, hydrolysis of cyanohydrin 1.132, under forcing microwave conditions generated carboxylic acid 1.133. Mesylation of the primary alcohol followed by heating induced lactonization to form compound 1.134. Treatment with LiHMDS and o-nitrobenzenesulfonyl azide 1.129 formed diazolactone 1.135. This ε-lactone was believed to have a high propensity for insertion into the C$_5$-H bond to form the desired THF ring due to two factors. Namely, the inductive withdrawing effect of the acetate group should deactivate insertion into the C$_3$-H bond and entropy should favor insertion into the C$_5$-H bond to make the 5-membered THF ring. To great disappointment, even after a evaluation of a multitude of Rh(II) and other metal catalysts, only the product from C$_3$-H insertion was observed. This was attributed to significant conformational rigidity of

29
the system. Nuclear Overhauser experiments indicated that the C\textsubscript{3}-H might be locked into close proximity to C\textsubscript{10} before diazotization.

Scheme 1.23: Rhodium carbenoid promoted C-H insertion forms undesired pentacycle 1.136.

A third, slightly modified C-H insertion strategy gave a sliver of hope that the generation of the THF ring with the correct stereochemistry at C\textsubscript{5} in scalable quantities would be possible, (Scheme 1.24). Ketal 1.126 was subjected to diazo transfer conditions to give tetracycle diazolactone 1.137. Subjecting this diazolactone species to Rh\textsubscript{2}(OAc)\textsubscript{4} or Rh\textsubscript{2}(esp)\textsubscript{2} in DCM at 0 °C provided ~20% of a 4.2:1 diastereomeric mixture of C\textsubscript{5}-H:C\textsubscript{3}-H insertion products, as well as a decomposition product (not shown). The generation of desired pentacycle 1.138, although in low yields and moderate diastereoselectivity provided evidence to continue on this route for the total synthesis of maoecrystal V (1.5).
Scheme 1.24: Rhodium carbenoid C-H insertion forms desired pentacycle 1.138 in low yield.

1.5 Results and discussion†

Even though the two racemic syntheses have been accomplished, neither Li and Yang nor Danishefsky report any confirmatory data on the originally reported selective cytotoxicity of maoecrystal V (1.5). Due to both the lack of follow up investigation on the biological activity and the absence of an enantioselective synthesis, we continued striving for our goal of making enantiopure maoecrystal V (1.5). We also believed that by using organic synthesis, the opportunity to design and test new molecules that resemble maoecrystal V (1.5) would arise. Subjecting intermediates and newly designed compounds to biological assays such as the National Cancer Institute 60 Human Tumor Cell Line Assay (NCI60) was a worthwhile secondary goal of the project.

After Dr. Jillian Spangler defended her thesis, she had assumed the role of a postdoctoral associate in the Sorensen lab in order to optimize the Rh-carbenoid insertion reaction that yielded compound 1.138, (Scheme 1.24). During the short

† Much of this work was done in collaboration with Dr. Lorenz Herdeis and some with Dr. Jillian Spangler.
timeframe she remained, valiant effort and a bit of good fortune in a small gift of catalyst yielded an enabling key step to facilitate the advancement of the project. We evaluated a small library of Rh(II) catalyst (most were a gift from the labs of Prof. Huw M. Davies of Emory University) in the C-H insertion step. Gratifyingly, one enantiopure catalyst, \( \text{Rh}_2(R\text{-BTPCP})_4 \), which was undisclosed by Davies at the time, showed desired reactivity. Based on small-scale NMR yield calculations, desired C\textsubscript{5}-H insertion species \textbf{1.138} was the major product in \( \text{CH}_2\text{Cl}_2 \) and PhCF\textsubscript{3}, (Scheme 1.25). (Note: vinyl ether \textbf{1.140} was assigned through crude NMR, however it was not isolable).

![Scheme 1.25](image)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>NMR Yield</th>
<th>\textbf{1.138}</th>
<th>\textbf{1.139}</th>
<th>\textbf{1.140}</th>
</tr>
</thead>
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<td>( \text{CH}_2\text{Cl}_2 )</td>
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<td>6</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>PhCF\textsubscript{3}</td>
<td>85%</td>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

\textbf{Scheme 1.25}: Rhodium \( \text{Rh}_2(R\text{-BTPCP})_4 \) forms desired pentacycle \textbf{1.138} in acceptable yield.

Encouraged by the ability to make \textbf{1.138} with the THF ring having the desired C\textsubscript{5} configuration, we decided to continue pursuing the originally proposed non-Diels-Alder route in Scheme 1.18 but with some modification. Scheme 1.26 depicts a possible path forward from THF species \textbf{1.141}. Cyanation at C\textsubscript{8} would provide cyanohydrin \textbf{1.142}. Methylation with ring opening of the lactone followed
by primary alcohol oxidation could provide keto-aldehyde 1.143. An aldol condensation/β-elimination reaction would provide cyclohexenone 1.144. Hydrolysis of the nitrile followed by oxidation of the secondary hydroxyl group would provide diketo-acid 1.110. Again, in the final step, we envisioned a bis-alkylation with a dihalomethane to provide the natural product maecrystal V.

**Scheme 1.26:** Revised synthetic proposal to maecrystal V from pentacycle 1.141.

While much of the previous work was being developed, we devised an enantiospecific synthesis of bicyclo[2.2.2]octane-lactone 1.105. Since it is known that racemic keto-aldehyde 1.104 participates in the aldol-lactonization sequence to provide racemic compound 1.105 as a single diastereomer (see Scheme 1.19), the C₁₃ stereogenic center would provide absolute stereocontrol for the transformation. Rather than attempting an enantioselective addition of metallo-crotyl species to either achiral 1.111 or racemic 1.112, the initial strategy relied on identifying a readily available, naturally occurring compound with the C₁₃ center already existing.
in the correct stereoconfiguration. Fortunately, the readily available monoterpenes (+)-limonene (R-limonene) was ideal in this regard; the C\textsubscript{13} carbon is delivered by nature with the desired configuration allowing for a possible total synthesis of enantiopure maecrystal V (1.5). Further investigation showed that the mixture of cis and trans epoxides sold as (+)-limonene oxide 1.145 would be more appropriate. The initial proposal in Scheme 1.27 began by hydroboration/oxidation\textsuperscript{17} of the isopropenyl group of 1.145 to provide primary alcohol 1.146 as a complex diastereomeric mixture. A base-induced elimination reaction would then convert the mixture of epoxides (1.146) to the mixture of diols (1.147). Double oxidation would provide exocyclic enone-aldehyde 1.148. Vinylogous cyanide addition would give cyanoketo-aldehyde 1.149 as an analogous substrate to the racemic ester-keto-aldehyde 1.104. It was presumed that an acid catalyzed aldol lactonization with nitrile 1.149 would behave in a similar manner as the ester except with loss of ammonia to provide bicyclo[2.2.2]octane (−)-1.105 as a single, enantiomerically pure diastereomer.

Scheme 1.27: Proposed route to enantiomerically pure (−)-1.105 from (+)-limonene oxide.
Although the three-step sequence of hydroboration/oxidation-elimination-double oxidation of limonene oxide to make keto-aldehyde 1.146 was achieved, the molecule was unstable and led to unsatisfactory results in further functionalization. To remedy the situation, an alteration of the sequence proved to be satisfactory.

![Scheme 1.28: Synthetic route to enantiomerically pure 1.149 from (+)-limonene oxide.]

As shown in Scheme 1.28, the known LDA base promoted elimination reaction produced a diastereomeric mixture of allylic alcohols (1.150). The crude mixture was converted to allylic ethyl carbonate 1.151 by capping with ethyl chloroformate in the presence of pyridine in 83% yield over two steps. This mixture of diastereomers participated in an efficient palladium-catalyzed \( \pi \)-allyl cyanation to converge on the single \( R \)-enantiomer of diene-nitrile \(+\)-1.152 in 90% yield. Diene \(+\)-1.152 was subjected to thexylborane to induce intermolecular followed by intramolecular hydroboration, forming the intermediate 2-borabicyclo[3.3.1]nonane 1.153 as a mixture of epimers at \( C_{16} \). The intermediate
borabicycle was oxidized using urea-hydrogen peroxide (UHP) to minimize hydrolysis of the nitrile to water soluble diol 1.154 in 87% over two steps. Oxidation of both the primary and allylic alcohols using the conditions reported by Swern21 led to keto-aldehyde 1.149 as a mixture of isomers in high yield. This five-step sequence was scalable starting with an input of 100 g of (+)-limonene oxide 1.145 with reproducible yields, although a scientist should be mindful of the dangers caused by the acute toxicity and the required amount of trimethylsilylcyanide if repeating the sequence.

When the keto-aldehyde-nitrile 1.149 was subjected to the same aldol-lactonization conditions as keto-aldehyde-ester 1.104 (2N HCl in actone, 60°C),22 desired reactivity was observed but with significant side products as indicated by crude 1H and 13C NMR spectra. As shown in Scheme 1.29, a cleaner reaction profile was observed by heating with 6N HCl (aq) in toluene to 110 °C in a sealed vessel. The desired enantiopure bicyclo[2.2.2]octane (–)-1.105 was isolated in 55% yield along with 22% yield of undesired diastereomer 1.155. Chiral GC analysis determined that (–)-1.105 had an er = 99.4:0.6.

![Scheme 1.29](image)

Scheme 1.29: Acid catalyzed aldol-lactonization provides two diastereomers of bicyclo[2.2.2]octane; (–)-1.105 and 1.155.
Heating undesired isomer 1.155 with 2N HCl in actone showed that reversible lactone opening, epimerization of C₁₆, and aldol-lactonization allowed for equilibration of the diasteromers (2:1 favoring desired (−)-1.105 to undesired 1.155). As shown in Scheme 1.30, refluxing with 6N HCl in toluene for 1 day almost imperceptibly improved the ratio to 2.6:1 and gave a 49% yield of the desired bicyclo[2.2.2]octane. If forced, the diastereomeric ratio could be improved to 5.6:1 (¹H NMR) by refluxing in toluene and 6N HCl for 6 days. With enough iteration, this isomerization process could funnel most of the undesired material into desired bicyclo[2.2.2]octane (−)-1.105.

![Scheme 1.30: Isomerization of undesired bicyclo[2.2.2]octane 1.155.](image)

Enantiopure bicyclo[2.2.2]octane 1.105 was converted to ketal 1.156 in excellent yield using the mild Noyori conditions (Scheme 1.31). For larger scale needed some improvement. In her thesis, Spangler describes the optimized diazo-transfer reaction, which works well on less than 50 mg scale. She and Dr. Herdeis found that strict temperature control at -78 °C was absolutely necessary to prevent azide transfer. On a larger scale, a dry ice/acetone bath did not allow for robust reaction, as a two-degree temperature rise would fail to produce the desired diazo species. A simple remedy to allow conversion of larger amounts of lactone 1.156 to the desired compound 1.157 was discovered. By cooling the reaction bath between
-110 to -100°C (MeOH/N₂) and diluting the THF mixture to prevent crystallization of the lithium enolate at the lower temperature, batches of up to 10 g of the lactone 1.156 have been converted to the α-diazolactone 1.157.

Scheme 1.31: Ketalization and diazo-transfer reactions to produce 1.157.

Since we obtained enantiomerically pure diazo species (-)-1.157, we needed to determine if the enantiopure Rh₂(R-BTPCP)₄ catalyst would be a match or mismatch for efficient C-H insertion to provide pentacycle 1.158. Experiments were executed to determine the effect of a single enantiomer catalyst on C-H insertion of both racemic and enantiopure diazo-compound 1.157. Table 1.2 depicts the results. Although the catalyst loading was 10x different, entries 1 and 2 show that either antipode of Rh₂(BTPCP)₄ gave approximately the same amount of desired C-H insertion product for racemic starting material 1.157. It became apparent that the R enantiomer rhodium catalyst was markedly less efficient than the S catalyst when using the enantiopure diazospecies (-)-1.157 as evidenced by entries 3 and 4 where 1.4 mol% loading led to 35% and 72% isolated yield respectively. A matched case of enantiopure substrate and enantiopure catalyst existed. Entries 5 through 8 show an ascending scale of substrate input of (-)-1.157 from 60 mg up to 1.57 g. In executing these reactions, (-)-1.157 was dissolved in dry degassed α,α,α-trifluorotoluene (BTF) and portions of Rh₂(S-BTPCP)₄ were added in dry degassed
portions of BTF via airtight syringe or canula. When the reaction was observed to slow progression or stall, a new portion of catalyst was added. Purification of product 1.158 by silica and crystallography was simplified by the complete consumption of the starting material 1.157. Catalyst loading for the matched case was as low at 0.2 mol% and up to 0.5 mol% each with a 70% or more chemical yield.

![Reaction Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Scale mg</th>
<th>Diazo description</th>
<th>Catalyst</th>
<th>Loading mol %</th>
<th>Yield %</th>
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<td>(+/-)</td>
<td>R</td>
<td>0.11</td>
<td>45</td>
</tr>
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<td>(-)</td>
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<td>8</td>
<td>1565</td>
<td>(-)</td>
<td>S</td>
<td>0.50</td>
<td>70</td>
</tr>
</tbody>
</table>

Table 1.2: Effects of Rh₂(BTPC)₄ enantiomer on yield of C-H insertion of 1.157.

Having the synthetic knowledge to achieve the pentacyclic compound 1.158 with THF ring in the requisite configuration at C₅, we could now investigate the strategies to make both the cyclohexenone and the δ-lactone rings. To proceed, we attempted cyanide addition to des-methyl-ketal 1.138 at C₈ with TMSCN and borontrifluoride, (Scheme 1.33). This experiment produced an unexpected result in
that Lewis acid promoted cyanation occurred, however the resulting cyanohydrin had undesired stereochemistry at C₈ as depicted in 1.159. We did not observe 1.160. This was verified by X-ray crystallography of the p-bromobenzoyl ester 1.161, (Figure 1.4). As previously seen, the facial selectivity was reversed when the THF ring was not formed. (See cyanation of 1.126 to 1.131, Scheme 1.22, verification of stereoconfiguration was by X-ray of compound 1.131).

Scheme 1.32: Boron trifluoride promotes cyanohydrin formation from undesired face of C₈.

Figure 1.4: X-ray crystal structure of 1.161 indicating undesired stereochemistry at C₈.

Because the C₁₆-methyl group points away from the C₈ ketal in 1.158, we assumed that it would likely have very little influence in directing an addition to the desired face. In order to have a reference compound containing the undesired stereochemistry at C₈, we subjected compound 1.158 to TMSCN and BF₃·OEt₂ and
tentatively assigned the product **1.162** to have the same undesired *trans* stereochemistry to the primary alcohol (Scheme 1.33). Changing solvents (CH₂Cl₂, CH₃CN, PhCH₃), Lewis acid (TiCl₄, TMSOTf, ZnI₂), or cyanide reagent (TBSCN, *t*-butyl-isonitrile, dimethylaluminum cyanide) led to either no reaction or the same tentatively assigned undesired cyanohydrin **1.162**.

![Scheme 1.33: Tentative assignment for **1.162** in cyanohydrin formation from undesired face of C₈.](image)

After this setback of undesired facial selectivity, we hypothesized that it might be possible to use the C₁₅ oxygen to block nucleophilic addition of the undesired face of C₈, (Scheme 1.34). If the lactone in **1.158** could be opened with vinyl or methyl magnesium bromide and the resulting hydroxyl protect with a group large enough to overhang C₈ as in **1.163**, it might be possible to shield the undesired face of the intermediary oxocarbenium **1.164**. This could ensure nucleophilic delivery from the opposite face of C₈ giving desired cyanohydrin **1.165**.
Scheme 1.34: Proposed protecting group shield steering of facial selectivity of cyanide addition to C8.

Addition of methylmagnesium bromide in an attempt to open lactone 1.158 produced a lactol and not the desired $\gamma$-hydroxy methylketone. Fortunately, we did observe lactone opening upon treatment of 1.158 with excess magnesium bromide salt of N,O-dimethylhydroxyl amine, forming the $\gamma$-hydroxy Weinreb amide 1.166, (Scheme 1.35). Initial experiments showed that during rotary evaporation of the organic layers from workup, we infuriatingly observed rapid reversion to the starting lactone. We believed the reverse reaction was likely due to increasing the concentration of the residual Lewis acidic magnesium salts upon reduction in volume. Extra aqueous washes to remove the magnesium salts alleviated this undesired ring formation. Immediately after isolation, the crude alcohol was treated with 2,6-lutidine and triethylsilyl trifluoromethanesulfonate (TESOTf) to generate the Weinreb amide-silyloxy species 1.167.
Scheme 1.35: Preparation of C_{15} TES-protected alcohol 1.167.

In Scheme 1.36, subjecting ketal 1.167 with the overhanging triethylsilyloxy group at C\textsubscript{15} with TMSCN and boron trifluoride led to cyanide addition at C\textsubscript{8} but also loss of the triethylsilyl protecting group in the tentatively assigned amide 1.168. We wanted to confirm facial selectivity but X-ray analysis eluded us. We made Weinreb amide epi-1.168 from the likely assigned undesired cyanohydrin 1.162 and observed the same connectivity, but different NMR spectra. This supports the conclusion that we made the desired diastereomer 1.168, (Scheme 1.35). Definitive crystallographic analysis has not been executed.

Scheme 1.36: Diastereomeric Weinreb amide-nitriles 1.168 and epi-1.168.
We hoped that addition of methyl Grignard reagent or methyl lithium to the Weinreb amide 1.168 would generate methyl ketone 1.169. However, it became apparent that this species was resistant to external nucleophiles. No addition was observed even after heating to reflux in THF with excess methyllithium. In a two-step sequence, methyl ketone 1.169 was realized. We observed formation of lactone 1.170 upon treatment of 1.168 with p-toluenesulfonic or methanesulfonic acid in toluene or benzene. At 0 °C in diethyl ether, methyl magnesium bromide added to the lactone 1.170 to form methyl-ketone-diol 1.169, presumably as a magnesium salt, which immediately precipitated from the solution. The yield of the methyl ketone 1.169 was slightly variable at ~60%, (~91% BRSM) and unreacted lactone 1.170 was easily recovered from each of these reactions. Chemoselective oxidation of the primary alcohol 1.169 to the aldehyde 1.143 was achieved using TEMPO and trichlorocyanuric acid as oxidant in methylene chloride at RT in 79% yield.25

Scheme 1.37: Functionalization of Weinreb 1.168 amide to keto-aldehyde 1.143 through lactone 1.170.
Under $p$-toluenesulfonic acid in toluene, keto-aldehyde 1.143 undergoes intramolecular aldol followed by elimination to generate the $trans$-fused cyclohexenone 1.144. This reaction established the fourth of five rings found in the natural product in 51-65% yield, (Scheme 1.38).

![Scheme 1.38: Conversion keto-aldehyde 1.143 to cyclohexenone 1.144.](image)

Having the lactone ring of maoecrystal V left to install, we investigated the feasibility of forming it through the introduction of the C$_{20}$ carbon-oxygen fragment between C$_{10}$ to and C$_{7}$ in various oxidation states and functional groups. Our initially proposed bis-alkylation strategy (Scheme 1.25) would require a carboxylic acid at C$_{7}$; however, by isolating the C$_{7}$ nitrile compound 1.144, the opportunity arose to attempt an intermolecular aldol-intermolecular Pinner reaction to form the final lactone ring. Scheme 1.39 depicts the possible reaction of nitrile 1.144 with acid and formaldehyde followed by subsequent hydrolysis producing the pentacyclic skeleton of 1.172. We hypothesized that protic acid could both activate the nitrile to nucleophilic addition and catalyze tautomerization to the enol, which could facilitate the desired transformation. This idea was very appealing, as it would quickly build the last ring of maoecrystal V (1.5). Unfortunately, all attempts under various acidic sources (TFA, HCl in ether or dioxane) and different sources of formaldehyde (paraformaldehyde, trioxane) did not afford the desired reaction.
Scheme 1.39: Aldol-Pinner hypothesis to install final ring of maoecrystal V.

We were undiscouraged by the lack of success with the aldol-Pinner attempts as we still had the bis-alkylation strategy to investigate. We hoped that hydrolysis of nitrile 1.144 to carboxylic acid 1.173 could be accomplished under simple acidic or basic conditions (LiOH, LiOOH). Sadly, no hydrolysis was observed with aqueous acid and basic hydrolysis led to decomposition. NMR evidence suggested that β-elimination, opening the THF ring and loss of cyanide as the major pathway. Fortunately, heating 1.144 for several days in ethanol and water in the presence of Parkins’ platinum catalyst,27 primary amide 1.174 was isolated in 48% yield. However, all attempts (acid, base, oxidative ie N₂O₄) to convert the amide into the acid were unsuccessful.

Scheme 1.40: Hydrolysis of nitrile 1.144 to amide 1.174.
To obtain carboxylic acid 1.173 which was needed to investigate the proposed final bis-alkylation strategy, we relied on a reduction oxidation sequence. In Scheme 1.41, reduction of the carbonyl and cyano groups of 1.144 with diisobutylaluminum hydride (DIBAl-H) at -78 °C in toluene led to aldehyde 1.175 as an inconsequential diastereomeric mixture of allylic alcohols at C$_1$. Without purification, oxidation to the enone using barium manganate gave keto-aldehyde 1.176 in 85% over two steps.$^{28}$ Oxidation of the formyl group of 1.176 using Pinnick conditions led to the carboxylic acid 1.173.$^{29}$

Scheme 1.41: Reduction/oxidation sequence to make aldehyde 1.176 and acid 1.173.

We capitalized on the opportunity to use the intermediate aldehyde 1.176 in attempts at forming the lactone ring. Scheme 1.42 shows this proposal. If the enolate 1.177 could form, we investigated the possibility of introducing formaldehyde between C$_{10}$ and C$_7$ through an intermolecular aldol, which could possibly form the
six-membered lactol 1.179. We envisioned that a separate double oxidation step could transform lactol 1.179 to maoecrystal V (1.5).

Scheme 1.42: Proposed intermolecular aldol leading to lactol to make maoecrystal V.

Unfortunately, after a series of experiments in THF at -78 °C using either lithium diisopropylamide or potassium hydride as base to generate the enolate and anhydrous monomeric formaldehyde (Schlosser method or from BtCH2OH),30,31 we did not observe the desired transformation (Scheme 1.42). Temperatures higher than -60 °C led to decomposition.

Although it was tempting to conclude that the aldol product or resulting lactol under basic conditions would just prefer to retro aldol, returning to starting material, the possibility that alkylation was not occurring was more likely the correct explanation. More evidence that alkylation was difficult is shown in Scheme 1.43. After triethylysilyl protection of the C15 hydroxyl group with TESCl and
imidazole in DMF, we attempted to irreversibly alkylate at C10 with KH and ICH2Cl to no avail.

**Scheme 1.43**: Attempted aldol and alkylation of 1.176 or 1.180.

Although evidence was mounting that nucleophilic addition was not occurring, we installed an irreversible trap for the process in case alkylation with formaldehyde was proceeding, but was reversible. We treated acid 1.173 with TMSCHN2 in methanol to create the methyl ester 1.183 in good yield followed by the protection of the silylether 1.184 (Scheme 1.44).

**Scheme 1.44**: Preparation of methylester 1.183 and silylprotected species 1.184.

If enolate 1.185 of methyl ester 1.184 could form with base and then add into formaldehyde on the correct face 1.186, the lactone could form, reducing the
possibility of retro aldol (Scheme 1.44). Unfortunately, we observed that treating methyl ester 1.184 with KH and anhydrous formaldehyde in THF from -78 °C to room temperature did not lead to the desired lactone. We were also unable to alkylate 1.184 at C10 with ICH2Cl. There was evidence that with KH in THF at temperatures above -60 °C, deprotonation was occurring. NMR and mass spectral data for the decomposition products support β-elimination although attempts to perform deuterium exchange at C10 have been unsuccessful, leading only to decomposition.

Scheme 1.45: Proposed lactone trap for a reversible aldol reaction.

In final attempts at making the lactone through intermolecular alkylation at C10, we focused the originally proposed bis-alkylation strategy deciding to use acid 1.173, as this would avoid epimerizing the C16 methyl of acid 1.110. To avoid undesired alkylation of the C15 hydroxy group of 1.173, it would need to be protected. Scheme 1.46 shows the synthesis of both the MOM and triethylsilyl protected species. Firstly, Pinnick oxidation of TES-ether/aldehyde 1.180 provided
the Tes-ether/acid 1.188. A sequence of alkylation of the both the C$_{15}$ hydroxy and the C$_{7}$ acid followed by deprotection of the MOM ester with MeOH and water with heat provided the C$_{15}$ MOM ether-acid 1.190.

Scheme 1.46: Protection of the C$_{15}$ hydroxyl group.

Having the C$_{15}$ hydroxyl 1.173, MOM ether 1.190 and TES ether 1.188 in hand, we attempted to achieve bis-alkylation of these compounds at both C$_{10}$ and the carboxylic acid oxygen using chloroiodomethane. Table 1.3, shows the results of these experiments. Room temperature experiments using DBU (>10 equiv) and DMF led only to monoalkylation of the acid, *vide infra*. We observed the same product for entries 3 and 4 using KOTBu or KHMDS with 18-crown-6 ether as additive in THF. For entry 2, the use of LDA gave only recovered starting material. The use of KH led only to decomposition of the starting material after warming to RT and no significant discernable product was isolated.
It became apparent that an alkylation strategy including the bis-alkylation strategy, which had been employed previously in Chen and Nicoloau's model system with incorrect stereochemistry at C₅, was not successful with our substrates. The absence of evidence for an efficient intermolecular alkylation event between C₁₀ and formaldehyde or ICH₂Cl forced us to accept the possibility that failure of installing the quaternary center was due, at least in part, to 1,3-diaxial interactions with the C₁₉ methyl and C₇ carbon in each of the above cases (nitrile, aldehyde, and methyl ester), (Figure 1.5).

**Table 1.3**: Attempts at performing a bisalkylation to form lactone ring.

<table>
<thead>
<tr>
<th>Entry</th>
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<td>DMF</td>
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<td>CICH₂-ester</td>
</tr>
<tr>
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</tr>
<tr>
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<td>KOtBu</td>
<td>18-crown-6</td>
<td>THF</td>
<td>70°C</td>
<td>CICH₂-ester</td>
</tr>
<tr>
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<td>KHMDS</td>
<td>18-crown-6</td>
<td>THF</td>
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<td>CICH₂-ester</td>
</tr>
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<td>KH</td>
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</tr>
</tbody>
</table>

**Figure 1.5**: 1,3-diaxial steric interactions that may prevent alkylation.
In an attempt to overcome the intermolecular alkylation issues, we investigated the possibility of an intramolecular alkylation using chloromethyl ester 1.191. We reasoned that with enolate formation between C1 and C10, the intermolecular alkylation forging the C10-C20 bond and the final lactone ring for maoecrystal V (1.5) was possible. As shown in Table 1.3 and Scheme 1.47, 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) promoted the alkylation of carboxylic acid 1.173 at 23 °C with chloroiodomethane to provide the chloromethyl ester 1.191 in up to 52% yield.

![Scheme 1.47: Alkylation to make chloromethylester 1.191.]

Initial studies showed that the chloromethyl ester was prone to hydrolysis. Using K OtBu, 18-crown-6 ether, THF and 4Å mol sieves the only product we observed was the carboxylic acid 1.173. We observed the same hydrolysis for NaH in DMF. Resubjecting the chloromethyl ester 1.191 to the initial alkylation conditions with increased heat (DBU in DMF, 50 °C) led to a compound that was consistent with double alkylation of the dihalomethane 1.192, (Scheme 1.48). We postulated that hydrolysis was occurring through advantageous water and the resulting acid quickly alkylated the remaining chloromethyl ester forming the “dimer-acetal” 1.192.
Scheme 1.48: Formation of doubly alkylated methane “dimer-acetal” 1.192.

Upon deeper investigation, we also observed the doubly alkylated methane 1.192 during the initial chloromethyl ester formation. Unfortunately, we did not observe the lactone ring in the above experiments. We also did not observe the desired lactone ring using LiHMDS in THF with Bu₄NI as additive nor with MgBr₂·OEt₂ and iPr₂NEt in CH₂Cl₂. We postulate that the lack of desired reactivity is due to the likelihood that the chloromethyl ester preferentially exists in the s-trans-conformer rather than the requisite s-cis-conformer needed for alkylation. This also may be due to the 1,3-diaxial steric interaction with the C₁⁹ methyl group.

It would be interesting to test the 1,3-diaxial steric interaction hypothesis by creating a system where the C₁⁹ methyl is absent in any or all of these lactone ring annulation strategies. Scheme 1.49 shows some ideas to reduce the steric interaction. One could imagine making compound 1.193 via C-H insertion on the simple propylene glycol ketal and advancing it to 1.194, which by design would lack the geminal dimethyl groups at C₄. If the last δ-lactone ring forms via one of the strategies previously discussed, one might be able to employ a strategy using an exocyclic alkene at C₄ such as 1.196 to make maocrystal V (1.5).
Scheme 1.49: Proposed molecules to reduce the 1,3-diaxial steric crowding during alkylation.

Although our efforts have not yet provided maoecrystal V, we would still like to aid in the fundamental understanding of the selective cytotoxicity reported by Sun and coworkers. Some of the benefits of the science of organic natural product synthesis are the analogous compounds that can be made. Our studies provided the opportunity to make interesting enantiopure maoecrystal V-like molecules that if investigated in a biological setting may demonstrate similar activity to the natural product.

Scheme 1.50 shows the reactions used to transform alcohol 1.183 into molecules that even more closely resemble maoecrystal V. By treating 1.183 with Dess-Martin periodinane,32 diketone 1.199 was formed in high yield. Hopefully this molecule, dubbed maoecrystal V-des-lactone has biological activity to similar the natural product. We have postulated that the cytotoxic activity of maoecrystal V may arise from the enone functionality by covalent binding in a biological setting. To test this hypothesis, we wanted to make the saturated version 1.201. Hydrogenation of 1.183 with palladium on carbon, gave cyclohexanone 1.200 in
high yield. By treating 1.200 with Dess-Martin periodinane, diketone 1.201 was formed in high yield. As of writing, we have submitted the compounds in Scheme 1.50 to the NCI in order to test the biological activity in the 60 human tumor cell assay.

![Scheme 1.50: Synthesis of close analogues of maoecrystal V, both with and without enone.](image_url)

### 1.6 Conclusions

Even though our goal of synthesizing maoecrystal V (1.5) is still elusive, this project has spawned some very interesting strategies and chemistry. Firstly, we sourced the enantiospecificity of our route from nature. Conversion of readily available enantiopure (+)-limonene oxide to a keto-aldehyde-nitrile provided the element of absolute stereocontrol for the aldol-lactonization chemistry to generate the bicyclo[2.2.2]octane portion of the natural product. We discovered a rhodium carbenoid C-H insertion reaction that created the tetrahydrofuran ring of maoecrystal V with the appropriate stereochemistry with the added benefit of
incorporating the all the atoms of a simple ketal. We also found that the efficiency of C-H insertion was improved by using a matched enantiopure catalyst with the enantiopure diazolactone. Facial selectivity of cyanide addition was accomplished by the introduction a protecting group that shields addition from the undesired face of the oxocarbenium. Additionally, we made four out of the five rings of maoecrystal V with exquisite stereocontrol over all the elements. Finally, we made analogues of the natural product to attempt to aid the biological understanding of the cyctotoxicity of the natural product. There is a wealth of knowledge built into this project and we still believe that the C-H insertion strategy will be key to an enantiospecific synthesis of maoecrystal V.
1.7 Experimental Details

Butyllithium 2.5M in hexanes (320 ml, 0.800 mol, 1.18 equiv) was added over 45 min to diisopropylamine (81.04 g, 0.801 mol, 1.18 equiv) in Et₂O (708 g, 992 ml) at 0 °C. Then (+)-limone oxide (mix of cis and trans) (103.0 g, 0.677 mol, 1.0 equiv) in was added and the reaction was allowed to warm to rt in the icebath over 16h. The reaction mixture was cooled to 0 °C then quenched with sat NH₄Cl (200 ml) and H₂O (100 ml). The layers were separated and the organic layer was washed first with HCl 0.2M (200 ml) and then with sat NaCl (200 ml). The organic layer was dried over Na₂SO₄, filtered and concentrated to a residue then placed under vacuum for 16 hr. The crude oil was dissolved in THF (550 ml) and pyridine (105 ml) and cooled to 0 °C. Ethyl chloroformate (150 ml, 171 g, 1.58 mol) was added over 4 h in portions and the mixture was stirred 13 h while warming to rt. The reaction was quenched with HCl 1M (150 ml) and the layers were separated. The organic was washed with half-saturated NaCl (160 ml) then sat NaCl (150 ml) and dried over Na₂SO₄, filtered and concentrated to a residue. The crude red oil was distilled under vacuum (full vaccum Welch pump, 90-100 °C) to provide the diastereomeric mixture of allylic carbonates as a yellow translucent oil (125.8 g, 83% over two steps.)
$^{1}$H NMR (500 MHz, Chloroform-d) $\delta$ 5.24 (s, 0.6H), 5.07 (m, 1H), 5.02 (s, 0.6H), 4.91 (s, 0.6H), 4.85 (s, 1H), 4.79 (s, 1H), 4.75 to 4.63 (m, 3.6H), 4.26 to 4.14 (m, 3.2H), 2.5 to 2.4 (m, 1.6H), 2.41 to 2.35 (m, 0.6H), 2.30 to 2.22 (m, 1.6H), 2.22 to 2.15 (m, 1.6H), 2.16 to 2.05 (m, 1.6H), 1.92 to 1.78 (m, 1.6H), 1.74 to 1.67 (m, 4.8H), 1.66 to 1.52 (m, 1.6H), 1.47 to 1.35 (m, 1H), 1.35 to 1.19 (m, 7.2 H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 154.7, 154.6, 148.9, 148.1, 145.8, 144.7, 113.4, 109.6, 109.3, 105.2, 78.3, 77.3, 64.13, 63.9, 43.8, 38.7, 38.5, 36.9, 33.9, 32.5, 32.4, 30.6, 21.0, 20.9, 14.4.
Under a nitrogen atmosphere, the allylic carbonate mixture 1.151 (45.61 g, 0.203 mol, 1.0 equiv) and trimethylsilylcyanide (43.76 g, 0.441 mol, 2.17 equiv) were dissolved in THF (386 g). Tetrakistriphenylphosphine palladium (12.0 g, 0.010 mol, 0.051 equiv) was added and the reaction was refluxed for 2 days. The reaction was cooled to 20°C and EtOAc (400 mL) was added. Solid sodium carbonate (53 g) was added followed by addition of H₂O (500 g) and stirred for 45 mins. The layers were separated and the organic layer was washed with saturated NaHCO₃ (300 mL) then dried over MgSO₄, filtered and concentrated to a residue. Distillation under full vacuum (~0.1 mm Hg, bp = 72 °C) provided the desired product (29.31 g, 90% yield) as a pale yellow oil.

¹H NMR (500 MHz, Chloroform-d) δ 5.80 (br s, 1H), 4.74 (br s, 1H), 4.70 (br s, 1H), 3.00 (s, 2H), 2.21-1.90 (m, 5H), 1.89-1.82 (m, 1H), 1.73 (s, 3H), 1.56 -1.42 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 149.16, 126.80, 125.94, 117.82, 109.15, 40.45, 30.55, 28.57, 27.35, 25.51, 20.90. IR (neat) cm⁻¹ 2918, 2837, 2248, 1643, 1435, 1375, 1146, 886. HRMS calculated for calc C₁₁H₁₆N [M+H]+ 162.1283 found 162.1268 (ESI +). Rotation (CH₂Cl₂) [α]²₃D = +95.1.
2,3-Dimethyl-2-butene (48.81 g, 0.580 mol, 1.15 equiv) was added to a 0°C solution of borane•THF (550 ml of a 1.0M solution in THF, 0.550 mol, 1.09 equiv) and stirred 1.5h. Then (R)-2-(4-(prop-1-en-2-yl)cyclohex-1-enyl)acetonitrile (+)-1.152 (81.04 g, 0.503 mol, 1.0 equiv) in THF (270 mL) was added over 10 min to the resulting thexylborane. The solution was warmed to 23 °C over 1.5 hr then cooled to 0 °C. The reaction was quenched with a solution of saturated aqueous sodium bicarbonate (25ml) and water (75ml). Then urea hydrogen peroxide (180 g, 1.91 mol, 3.8 equiv) was added in small portions (10-20 g) over 45 min allowing the reaction mixture to cool after each addition due to the observed exotherm. After stirring for 1 hr, the THF was removed by rotary evaporation and EtOAc (500 ml) was added. The resulting colorless precipitate was removed by filtration then washed with EtOAc. The resulting organic layer was separated from the aqueous layer and washed with saturated NaCl (3 x 25ml). The aqueous layers were combined and washed 5x with 50 mL CH₂Cl₂. The organic layers were dried over Na₂SO₄, filtered and reduced to a residue. Purification of the crude material was accomplished by silica chromatography using a gradient of 25 to 50% acetone in hexanes providing 1.154 as a ~1:1 mixture of diastereomers as a viscous yellow oil (86.50 g, 0.438 mol, 87% yield).
$^1$H NMR (500 MHz, Chloroform-d) $\delta$ 3.56 (m, 1H), 3.49 (apparent dt, $J = 11.0, 6.0$ Hz, 1H), 3.36 (apparent dq, $J = 10.4, 5.0$ Hz, 1H), 2.62 (apparent ddd, $J = 16.7, 3.9, 1.5$ Hz, 1H), 2.51 (apparent ddd, $J = 16.8, 7.2, 1.0$ Hz, 1H), 2.35 to 2.26 (m, 1H), 2.01 to 1.90 (m, 2H), 1.85 (s, 1H), 1.68 (apparent tt, $J = 12.1, 2.7$ Hz, 1H), 1.63 to 1.48 (m, 3H), 1.31 to 1.19 (m, 1H), 1.19 to 0.98 (m, 2H), 0.88 (apparent t, $J = 6.6$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl₃) $\delta$ 119.1, 73.0, 72.9, 65.9, 65.9, 41.8, 41.7, 40.1, 40.1, 39.9, 37.7, 37.6, 37.5, 29.9, 29.8, 29.5, 27.2, 20.6, 20.6, 13.5, 13.3.
Oxalyl chloride (25.73 g, 0.203 mol, 2.61 equiv) was dissolved in CH$_2$Cl$_2$ (110 mL) and cooled to -78 °C. Dry DMSO (25 mL, 0.352 mol, 4.52 equiv) was added to the reaction over 25 min. Diol 1.152 (15.35 g, 0.078 mol, 1.0 equiv) dissolved in DCM (100 mL) was added over 10 min resulting in a thin white slurry. After 25 mins, triethylamine (57 mL, 0.408 mol, 5.24 equiv) was added and the mixture became a thick white slurry. After 30 min at -78 °C the mixture was warmed to rt. Water (150 mL) was added and the layers were split. The aqueous layer was extracted with DCM and the organics were combined and reduced to a residue. EtOAc was added and the organic layer was washed with water followed by saturated brine and dried over Na$_2$SO$_4$. The solution was filtered and concentrated to a residue leaving the desired product (14.77 g, 98%) as a pale oil.

$^1$H NMR (500 MHz, Chloroform-d) δ 9.68 (d, $J = 1.7$ Hz, 1H), 9.67 (d, $J = 1.8$ Hz, 1H), 2.77 to 2.64 (m, 5H), 2.56 to 2.37 (m, 10H), 2.36 to 2.17 (m, 6H), 2.02 (apparent dt, $J = 13.6, 2.9$ Hz, 2H), 1.97 to 1.88 (m, 2H), 1.75 to 1.61 (m, 3H), 1.61 to 1.45 (m, 3H), 1.3 to 1.95 (m, 1H), 1.19 (d, $J = 7.2$ Hz, 3H), 1.16 (d, $J = 7.2$ Hz, 4H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 207.2, 207.1, 203.3, 203.3, 118.5, 50.8, 50.7, 46.4, 46.4, 45.5, 44.0, 39.7, 39.6, 31.8, 31.7, 29.3, 27.4, 17.8, 10.2, 10.0.
Keto-aldhyde-nitrile 1.149 (11.03 g, 0.057 mmol) was dissolved in toluene (180 mL) and 6N HCl (90 mL) in a Teflon sealed vessel and heated to 100 °C for 6 hr. After cooling to rt, EtOAc (20 mL) was added and the layers were separated. The organic layer was washed with water (3x 50 mL) and once with saturated NaCl (50 ml). The first aqueous layer was back extracted with EtOAc and the organics were combined, dried over Na2SO4, filtered and concentrated to a residue. The crude red oil was purified by silica gel chromatography (gradient of 4:1 to 1:1 Hexane:EtOAc) provided the desired product as white solids (6.18 g, 56%). A sample was dissolved in 15:1 Hexanes:EtOAc with heat, then allowed to cool providing colorless crystals mp = 117-118 °C. (Note: The undesired isomer 1.155 was isolated from this procedure, 2.40 g, 22%)
This is the undesired diastereomer from the procedure for compound (–)-1.105.

Keto-aldhyde-nitrile 1.149 (11.03 g, 0.057 mmol) was dissolved in toluene (180 mL) and 6N HCl (90 mL) in a Teflon sealed vessel and heated to 100 °C for 6 hr. After cooling to rt, EtOAc (20 mL) was added and the layers were separated. The organic layer was washed with water (3x 50 mL) and once with saturated NaCl (50 ml). The first aqueous layer was back extracted with EtOAc and the organics were combined, dried over Na2SO4, filtered and concentrated to a residue. The crude red oil was purified by silica gel chromatography (gradient of 4:1 to 1:1 Hexane:EtOAc) provided the product as white solids (2.40 g, 22%). (Note: Desired isomer (–)-1.105 was isolated from this procedure, 6.18 g, 56%).

$^1$H NMR (500 MHz, Chloroform-d) δ 3.90 (d, $J = 7.3$ Hz, 1H), 2.85 (d, $J = 17.4$ Hz, 1H), 2.45 (dt, $J = 19.1, 2.3$ Hz, 1H), 2.19 (d, $J = 17.4$ Hz, 1H), 2.09-1.96 (m, 3H), 1.96-1.87 (m, 1H), 1.61 (d, $J = 8.0$ Hz, 2H), 1.23 (d, $J = 6.9$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl₃) δ 209.8, 175.5, 85.5, 53.2, 40.3, 35.0, 34.6, 34.2, 27.0, 23.2, 18.7. IR (neat) cm⁻¹ 2972, 2948, 2929, 2881, 1783, 1722, 1458, 1222, 1212, 1171, 1024, 921, 832, 534, 518, 461. HRMS calculated for C11H15O3 [M+H]$^+$ = 195.1016, found 195.1038 (ESI+).
Ketone (-)-**1.105** (22.07 g, 0.114 mol, 1.0 equiv) and *bis*-trimethylsilyl neopentyl glycol (43.03 g, 0.173 mol, 1.5 equiv) were dissolved in DCM (314 g) and cooled to 0 °C. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (6 mL, 0.033 mol, 0.29 equiv) was added and the reaction was allowed to warm in the ice bath to RT over 17 hr. The reaction was quenched into sat. NaHCO3 (350 mL) then the layers were separated. The organic layer was washed with water (3x 110 mL), dried over Na2SO4, filtered and concentrated to a residue and dried *in vacuo* leaving the desired ketal (31.71 g, 99.6%) as colorless solids. A small sample was recrystallized in hexanes yielding colorless crystals, mp = 150-151 °C.

**1H NMR** (500 MHz, Chloroform-d) δ 3.82 (d, J = 8.1 Hz, 1H), 3.63 (d, J = 11.6 Hz, 1H), 3.56 (d, J = 11.5 Hz, 1H), 3.33 (ddd, J = 11.7, 7.7, 2.8 Hz, 2H), 2.91 (d, J = 16.9 Hz, 1H), 2.27 (ddd, J = 13.2, 4.6, 2.6 Hz, 1H), 2.12-2.03 (m, 2H), 1.99 (q, J = 7.2 Hz, 1H), 1.78 - 1.67 (m, 1H), 1.67 - 1.61 (m, 1H), 1.57 (dd, J = 13.2, 2.0 Hz, 1H), 1.49 - 1.39 (m, 1H), 1.30 (ddd, J = 12.8, 10.7, 1.8 Hz, 1H), 1.16 (s, 3H), 1.12 (d, J = 6.9 Hz, 3H), 0.70 (s, 3H).

**13C NMR** (126 MHz, CDCl3) δ 178.0, 100.6, 88.6, 70.4, 69.0, 46.3, 35.9, 34.9, 34.7, 33.3, 30.2, 25.6, 22.9, 22.4, 20.6, 17.8. IR (neat) cm⁻¹ 2954, 2871, 1777, 1471, 1129, 1104, 1051, 1013, 854, 616. HRMS calculated for C₁₆H₂₅O₄ [M+H]+ = 281.1753, found 281.1785 (ESI+). Rotation (CH₂Cl₂) [α]²₃°D = +23.6
Ketal (⁺)-1.156 (1.40 g, 5.0 mmol, 1.0 equiv) was dissolved in THF (70 mL) and cooled to 0 °C. LiHMDS 1.0M in THF (10 ml, 10.0 mmol, 2.0 equiv) was added. After 1 hr at 0 °C, the reaction mixture was cooled in a liquid nitrogen/MeOH cold bath. Then o-nitrobenzenesulfonyl azide (1.483 g, 6.5 mmol, 1.3 equiv) in THF (50 mL) was added over 45 min. The reaction mixture was stirred for 30 min, then quenched into 2M citric acid buffer pH = 4 (110 mL). As it warmed to rt, the mixture turned yellow. The layers were separated and the aqueous layer was extracted with EtOAc (40 mL). The organic layers were combined, washed with water (3x 40 mL), dried over Na₂SO₄, filtered and concentrated to a residue. The crude yellow solids were purified by silica gel chromatography with a gradient of pure toluene to 4% EtOAc in toluene giving the desired diazo-compound (1.092 g, 71%) as yellow solids.

¹H NMR (500 MHz, Chloroform-d) δ 3.75 (d, J = 8.8 Hz, 1H), 3.64 (d, J = 11.4 Hz, 1H), 3.52 (d, J = 11.2 Hz, 1H), 3.40 (dd, J = 11.4, 2.8 Hz, 1H), 3.32 (dd, J = 11.2, 2.8 Hz, 1H), 2.33 (ddd, J = 13.1, 4.6, 2.6 Hz, 2H), 2.22 (ddd, J = 12.7, 10.6, 7.5 Hz, 1H), 2.06 (p, J = 7.1 Hz, 1H), 1.84-1.73 (m, 1H), 1.70-1.59 (m, 3H), 1.54 (m, 1H), 1.16 (s, 3H), 1.11 (d, J = 6.8 Hz, 3H), 0.72 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 172.1, 101.3, 86.7, 70.7, 69.2, 50.1, 34.9, 34.1, 33.3, 30.2, 24.2, 22.3, 20.3, 17.3. IR (neat) cm⁻¹ 2960, 2869,
2091, 1736, 1378, 1237, 1132, 1111, 1025, 732. HRMS calculated for $C_{16}H_{23}N_2O_4$

Diazocompound (-)-1.157 (0.915 g, 2.99 mmol) was dissolved in argon sparged benzotrifluoride (PhCF₃) 25ml and the resulting solution sparged with argon subsurface for 10 min then cooled to 0 °C. Meanwhile the catalyst Rh₂[(S)-BTPCP]₄ (5.3 mg, 0.003 mmol, 0.01 equiv) was separately dissolved in PhCF₃ (1.0 mL) and sparged with argon then added to the main solution. After 17 hr 2.7 mg Rh₂[(S)-BTPCP]₄ in argon sparged PhCF₃ (1 mL) was added. After 41 hr 2.6 mg Rh₂[(S)-BTPCP]₄ in argon sparged PhCF₃ (1 mL) was added. (Total catalyst = 10.6 mg, 0.2 mol%). After 4 more hours the starting material was consumed and the solvent was evaporated. The crude material was purified by silica chromatography with a gradient 10:1 to 3:1 hexanes:EtOAc yielding the desired product as a colorless oil (0.644 g, 77%).

¹H NMR (500 MHz, Chloroform-d) δ 4.14 (d, J = 1.9 Hz, 1H), 3.92 (d, J = 8.0 Hz, 1H), 3.45 (dd, J = 11.5, 2.0 Hz, 1H), 3.37 (d, J = 11.5 Hz, 1H), 2.94 (s, 1H), 2.06 -1.87 (m, 4H), 1.87 - 1.77 (m, 1H), 1.68 - 1.54 (m, 4H), 1.26 (s, 3H), 1.17 (d, J = 6.9 Hz, 3H), 0.85 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 179.7, 106.6, 92.2, 91.0, 71.8, 48.7, 46.2, 42.5, 38.9, 33.8, 32.2, 26.2, 24.1, 22.0, 19.7, 18.8. IR (neat) cm⁻¹ 2937, 2881, 2753, 1208, 1028, 956, 842, 653. HRMS calculated for C₁₆H₂₃O₄ [M+H] = 279.15963, found 279.16051 (ESI +). Rotation (CH₂Cl₂) [α]²₃ = -94.8.
Compound 1.162

Ketal 1.158 (9 mg, 0.032 mmol) in acetonitrile (1 mL) at 0 °C was treated with TMSCN (9 µL, 0.064 mmol, 2.0 equiv) and BF$_3$•OEt$_2$ (8 µL, 0.064 mmol, 2.0 equiv). After 1 hr, the reaction was quenched with sat NaHCO$_3$ the extracted with DCM 3x. The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated. The crude material was purified by silica chromatography eluting with hexane:EtOAc 2:1 to give the desired product as a clear film (9 mg, 96%).

$^1$H NMR (500 MHz, Chloroform-d) δ 4.52 (d, $J$ = 3.8 Hz, 1H), 4.07 (d, $J$ = 7.3 Hz, 1H), 3.56 to 3.46 (m, 2H), 2.87 (m, 2H), 2.57 (ddd, $J$ = 13.7, 5.1, 2.1 Hz, 1H), 2.13 to 2.07 (m, 1H), 1.95 (dd, $J$ = 13.5, 7.2 Hz, 2H), 1.82 (t, $J$ = 4.9 Hz, 1H), 1.77 (q, $J$ = 10.1, 9.0 Hz, 1H), 1.62 to 1.54 (m, 1H), 1.51 (dd, $J$ = 13.6, 10.1 Hz, 1H), 1.23 (d, $J$ = 6.8 Hz, 3H), 1.00 (s, 3H), 0.97 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 177.9, 121.5, 92.5, 84.4, 79.8, 70.6, 55.0, 47.9, 38.4, 35.6, 34.6, 34.4, 23.2, 20.9, 20.7, 20.6, 17.6.
Isopropylmagnesium bromide 2.0 M in THF (12 ml, 0.024 mol, 12.0 equiv) was added to N,O-dimethylhydroxylamine hydrochloride (1.17 g, 0.012 mol, 6 equiv) in THF (20 mL) at 0 °C. After 1 hr, the reaction mixture was cooled to -78 °C and ketal (-)-1.158 (0.557 g, 0.002 mol) in THF (6 ml) was added to the mixture. The reaction was warmed to -20 °C then quenched with sat NH₄Cl (20 ml) and H₂O (5 ml). The mixture was extracted with DCM (50 ml) and the layers separated. The organic layer was washed with water (3x 50 mL), dried over Na₂SO₄, filtered and concentrated to almost to a residue. The residue was dissolved in DCM (20ml) then 2,6-lutidine (1.85 ml, 0.016 mmol, 8.0 equiv) and triethylsilyltrifluoromethane sulfonate (1.86 mL, 0.008 mol, 4.0 equiv) was added. The reaction mixture was quenched into sat NaHCO₃ and the layers were separated. The organic layer was washed with sat NaHCO₃, dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was purified by silica chromatography eluting with a gradient of 10:1 to 3:1 hexanes:EtOAc leaving the desired Weinreb-amide as colorless solids (0.520 g, 57%).

¹H NMR (500 MHz, Chloroform-d) δ 4.70 (s, 1H), 3.67 (s, 2H), 3.63 (d, J = 11.4 Hz, 1H), 3.55 (dd, J = 11.3, 1.5 Hz, 1H), 3.52 (s, 1H), 3.23 (s, 2H), 2.79 (d, J = 2.0 Hz, 1H),
1.91 (dd, $J = 13.3$, 5.1 Hz, 1H), 1.83 (d, $J = 13.3$ Hz, 1H), 1.76 - 1.56 (m, 5H), 1.55 - 1.45 (m, 1H), 1.31 (s, 2H), 1.04 (d, $J = 7.3$ Hz, 2H), 0.95 (t, $J = 8.0$ Hz, 6H), 0.68 (s, 2H), 0.57 (q, $J = 8.1$ Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.7, 106.8, 84.5, 78.5, 74.1, 59.8, 54.3, 49.2, 43.7, 40.4, 32.8, 32.1, 31.6, 25.2, 25.0, 22.1, 19.9, 19.9, 7.4, 5.6. IR (neat) cm$^{-1}$ 2955, 2910, 2874, 1670, 1460, 1378, 1103, 1075, 1018, 1006, 963, 818, 728. HRMS calculated for C$_{24}$H$_{44}$NO$_5$Si [M+H]$^+$ = 454.29833, found 454.29780 (ESI +). Rotation (CH$_2$Cl$_2$) $[\alpha]^{23}_D = +20.2$
Weinreb amide 1.168 (150 mg, 0.331 mmol, 1.0 equiv) was dissolved in DCM then cooled to 0 °C. Trimethylsilyl cyanide (88µl, 0.660 mmol, 2.0 equiv) then BF₃•OEt₂ (84 µl, 0.663 mmol, 2.0 equiv) were added. The reaction was quenched with sat NaHCO₃ (6 ml) and H₂O (1 ml). The layers were split and the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to a residue. The crude solids were purified by silica chromatography eluting with 1:1 hexanes:EtOAc to give the desired compound as colorless solids (79 mg, 65%).

¹H NMR (500 MHz, Chloroform-d) δ 4.77 (d, J = 10.4 Hz, 1H), 4.57 (d, J = 3.8 Hz, 1H), 3.88 (d, J = 10.4 Hz, 1H), 3.79 (s, 3H), 3.55 (d, J = 11.1 Hz, 1H), 3.37 (d, J = 10.4 Hz, 1H), 3.29 to 3.27 (m, 2H), 3.26 (s, 3H), 2.56 (dd, J = 13.7, 5.2 Hz, 1H), 2.10 (s, 1H), 2.01 (d, J = 13.7 Hz, 1H), 1.90 to 1.75 (m, 6H), 1.75 to 2.65 (m, 1H), 1.44 to 1.35 (m, 1H), 1.06 (s, 3H), 1.05 (d, J = 7.0 Hz, 4H), 0.84 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 172.8, 123.0, 91.4, 81.6, 78.3, 70.7, 61.8, 53.5, 47.7, 42.9, 40.3, 39.3, 32.8, 30.6, 27.4, 21.5, 20.3, 19.9 18.8. IR (neat) cm⁻¹ 3433, 2959, 2877, 1634, 1474, 1185, 1113, 1054, 999, 732, 647.
Isopropylmagnesium bromide 1.5 M in THF (29 µl, 0.043 mmol, 10 equiv) was added to N,O-dimethylhydroxylamine hydrochloride (2 mg, 0.021 mmol, 5 equiv) in THF (0.5 mL) at -20 °C and warmed to rt over 1 hr then added to a solution of lactone-nitrile 1.162 (1.3 mg, 0.0043 mmol, 1.0 equiv) in THF (0.5 mL) at -20 °C. The mixture was warmed to RT, quenched with NH₄Cl and extracted with EtOAc. The crude material was purified by silica chromatography 3:2 EtOAc:hexanes leaving the desired compound as a clear film (~1mg).

¹H NMR (500 MHz, Chloroform-d) δ 4.94 (d, J = 8.3 Hz, 1H), 3.70 (s, 3H), 3.61 (dd, J = 11.3, 8.0 Hz, 1H), 3.41 (dd, J = 11.5, 3.8 Hz, 1H), 3.38 to 3.30 (m, 1H), 3.18 (s, 3H), 2.64 (d, J = 8.2 Hz, 1H), 2.48 (ddd, J = 13.9, 5.1, 2.5 Hz, 1H), 2.39 (dd, J = 8.8, 4.4 Hz, 1H), 1.98 (dt, J = 14.6, 7.0 Hz, 2H), 1.89 (d, J = 11.4 Hz, 1H), 1.79 (d, J = 13.9 Hz, 1H), 1.14 (d, J = 6.7 Hz, 3H), 1.06 (s, 3H), 0.85 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 174.3, 123.3, 87.7, 76.3, 70.9, 60.8, 54.3, 45.9, 42.1, 38.2, 37.6, 34.1, 32.4, 30.0, 20.9, 20.7, 20.2, 16.9.
Lactone 1.171 (46 mg, 0.146 mmol, 1.0 equiv) was dissolved in dry Et₂O (15 mL) and cooled to 0 °C. Then methylmagnesium bromide 3.0M in Et₂O (130 µL, 0.39 mmol, 2.6 equiv) was added to the solution and white precipitate formed immediately. After 45 min, the reaction mixture was allowed to warm to rt and held for 2 h. The cloudy mixture was quenched with sat NH₄Cl and water. The layers were separated and the aqueous layer was extracted with Et₂O twice. The organic layers were combined, dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was purified by silica chromatography eluting with 3:1 to 2:1 hexane:EtOAc leaving the desired methylketone as colorless solids (25 mg, 52%, 85% BRSM). Recovered starting material lactone (18 mg, 39% recovery).

¹H NMR (500 MHz, Chloroform-d) δ 4.67 (d, J = 10.4 Hz, 1H), 3.61 (d, J = 10.3 Hz, 1H), 3.55 (d, J = 4.3 Hz, 1H), 3.46 (dd, J = 10.9, 4.1 Hz, 1H), 3.35 (dd, J = 10.9, 6.3 Hz, 1H), 3.16 (dd, J = 4.3, 2.1 Hz, 1H), 2.56 (dd, J = 13.8, 5.3 Hz, 1H), 2.32 (s, 3H), 2.02 to 1.94 (m, 2H), 1.92 to 1.78 (m, 3H), 1.75 to 1.69 (m, 2H), 1.44 (ddd, J = 13.1, 10.5, 7.9 Hz, 1H), 1.04 (d, J = 7.2 Hz, 3H), 0.99 (s, 3H), 0.90 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 209.8, 122.7, 91.0, 81.2, 78.0, 70.3, 59.2, 53.5, 43.2, 40.2, 39.0, 33.2, 30.5, 27.1, 21.5, 20.7, 19.8, 18.8. IR (neat) cm⁻¹ 3500, 2956, 294, 2854, 1701, 1464, 1378, 1364, 1282, 1182, 1086, 1058, 1040, 977. HRMS calculated for C₁₈H₂₈NO₄⁺ [M+H]⁺ = 322.20128, found 322.20261 (ESI+)
Weinreb amide 1.168 (70 mg, 0.191 mmol) and \( p \)-toluenesulfonic acid monohydrate (12.2 mg, 0.064 mmol, 0.34 equiv) was heated to 100 °C in toluene (4ml) for 17 h. The reaction mixture was cooled to rt, filtered and concentrated to a residue. The crude material was purified by silica chromatography with a gradient of 6:1 to 3:1 hexane:EtOAc providing the desired lactone as colorless solids (41 mg, 71%).

\[^1\text{H} \text{NMR (500 MHz, Chloroform-d)} \delta 4.73 (d, J = 12.5 \text{ Hz}, 1\text{H}), 4.28 (\text{br S}, 1\text{H}), 4.07 (d, J = 12.0 \text{ Hz}, 1\text{H}), 4.00 (d, J = 12.0 \text{ Hz}, 1\text{H}), 2.95 (d, J = 12.5 \text{ Hz}, 1\text{H}), 2.61 (dd, J = 13.9, 5.5 \text{ Hz}, 1\text{H}), 2.04 (d, J = 5.3 \text{ Hz}, 1\text{H}), 1.99 (d, J = 13.9 \text{ Hz}, 1\text{H}), 1.91 - 1.79 (m, 3\text{H}), 1.79 - 1.67 (m, 3\text{H}), 1.23 (s, 3\text{H}), 1.17 (s, 3\text{H}), 1.11 (d, J = 7.3 \text{ Hz}, 3\text{H}). \]^13\text{C NMR (126 MHz, CDCl}_3) \delta 171.1, 122.5, 87.8, 82.9, 80.0, 75.1, 48.1, 47.3, 45.4, 39.9, 35.4, 30.8, 27.8, 26.6, 19.5, 18.3. \text{IR (neat cm}^{-1} \text{) 3486, 2959, 1752, 1466, 1141, 1024, 915, 732. HRMS calculated for C}_{17}\text{H}_{24}\text{NO}_4 [\text{M+H}]^+ = 306.16998, \text{found 306.17028 (ESI +).} \]
Methylketone-diol 1.170 (95 mg, 0.296 mmol, 1.0 equiv) and trichlorocyanuric acid (171 mg, 0.736 mmol, 2.5 equiv) were dissolved in DCM (13 mL). (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl [TEMPO] (9.5 mg, 0.061 mmol, 0.21 equiv) was then added and the solution turned orange. After 2 h, the mixture, a thin white slurry, was gravity filtered through Celite and concentrated to a residue. The crude material was twice purified by silica chromatography eluting first with 3:1 then 6:1 hexane:EtOAc leaving the desired aldehyde as colorless solids (75 mg, 79%).

$^1$H NMR (500 MHz, Chloroform-d) δ 9.59 (s, 1H), 4.85 (d, $J = 10.2$ Hz, 1H), 3.53 (d, $J = 4.6$ Hz, 1H), 3.36 (d, $J = 10.1$ Hz, 1H), 3.17 (dd, $J = 4.5$, 2.0 Hz, 1H), 2.56 (dd, $J = 13.8$, 5.3 Hz, 1H), 2.32 (s, 3H), 2.03 to 1.92 (m, 2H), 1.91 to 1.78 (m, 3H), 1.73 (m, 1H), 1.44 (ddd, $J = 13.1$, 10.6, 7.8 Hz, 1H), 1.14 (s, 7H), 1.04 (d, $J = 7.2$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 208.8, 205.1, 122.1, 88.5, 81.5, 77.8, 59.1, 53.7, 49.9, 43.2, 40.0, 33.3, 30.4, 26.9, 19.8, 19.2, 18.8. IR (neat) cm$^{-1}$ 3517, 2957, 2919, 2850, 1762, 1725, 1466, 1364, 1283, 1182, 1083, 1021, 975, 889, 702, 651, 601. HRMS calculated for C$_{18}$H$_{28}$NO$_4$ [M+H]$^+$ = 320.1862, found 320.1857(ESI +)
Keto-aldehyde **1.143** (100 mg, 0.313 mmol) and *p*-toluenesulfonic acid monohydrate (16 mg, 0.094 mmol, 0.3 equiv) were heated to reflux in toluene (23 mL) for 7 h. The reaction was cooled to rt and quenched with sat NaHCO₃ (6 ml) and the layers were separated. The organic layer was washed with water, then brine, and dried over Na₂SO₄. The crude material was purified by silica chromatography 6:1 to 4:1 hexane:EtOAc leaving the desired enone as colorless solids (48 mg, 51%).

**1H NMR** (500 MHz, Chloroform-d) δ 6.55 (d, *J* = 10.0 Hz, 1H), 5.82 (d, *J* = 10.0 Hz, 1H), 4.80 (d, *J* = 13.0 Hz, 1H), 4.22 (d, *J* = 5.0 Hz, 1H), 2.99 (d, *J* = 13.0 Hz, 0H), 2.60 (dd, *J* = 13.9, 5.5 Hz, 1H), 1.95 (d, *J* = 13.9 Hz, 1H), 1.92 (d, *J* = 5.7 Hz, 1H), 1.88 to 1.75 (m, 4H), 1.75 to 1.67 (m, 2H), 1.28 (s, 3H), 1.24 (s, 3H), 1.12 (d, *J* = 7.3 Hz, 3H).

**13C NMR** (126 MHz, CDCl₃) δ 197.4, 158.1, 128.1, 122.6, 88.7, 81.7, 53.4, 47.8, 45.6, 40.4, 39.9, 30.9, 27.3, 26.9, 19.6, 18.4, 17.9. IR (neat) cm⁻¹ 3487, 2960, 2874, 1690, 1465, 1578, 1026, 913, 732, 647. HRMS calculated for C₁₇H₂₃O₃ [M+H]⁺ = 302.1757, found 302.1756 (ESI +).
Aldehyde **1.177** (81 mg, 0.266 mmol), 2-methyl-2-butene (1ml), and NaH₂PO₄ 1.0M aq (1.93ml) were dissolved in tBuOH (9 ml). NaClO₂ 1M aq (0.80 ml, 0.80 mmol, 3.0 equiv) was added and stirred for 2 h. The reaction mixture was quenched with citric acid pH=4 buffer 0.5 M aq (9 ml) and DCM (20 ml) was added. The layers were separated and the aqueous layer was extracted with DCM (4x15 ml). All organic layers were combined, dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was purified on silica gel eluting with a gradient of 6:1 to 1:1 hexane:EtOAc. The desired material was isolated as a colorless solid (55 mg, 65%).

**1H NMR** (500 MHz, Chloroform-d) δ 6.47 (d, J = 10.0 Hz, 1H), 5.80 (d, J = 10.0 Hz, 1H), 4.87 (d, J = 12.9 Hz, 1H), 4.22 (d, J = 1.8 Hz, 1H), 3.48 (d, J = 12.9 Hz, 1H), 4.22 (d, J = 1.8 Hz, 1H), 2.84 (dd, J = 14.0, 5.8 Hz, 1H), 2.26 to 2.17 (m, 1H), 1.85 to 1.69 (m, 3H), 1.64 to 1.52 (m, 2H), 1.36 to 1.23 (m, 1H), 1.21 (s, 3H), 1.12 (d, J = 7.3 Hz, 3H), 1.04 (s, 3H). **13C NMR** (126 MHz, CDCl₃) δ 199.0, 177.1, 157.8, 128.3, 87.9, 87.0, 47.7, 46.8, 40.4, 37.2, 31.1, 27.5, 24.4, 19.7, 19.1, 17.9. (note: a carbon is obscured by the solvent peak CDCl₃ 76.91, which is observable in the HSQC). **13C NMR** (126 MHz, CD₃CN) δ 199.7, 174.6, 158.8, 129.1, 88.4, 87.7, 77.5, 52.8, 48.6, 47.5, 41.0, 37.9, 32.2, 27.9, 25.7, 20.1, 20.0, 18.4. **IR (neat) cm⁻¹** 3472, 2962, 1686, 1466, 1376, 1171, 1031, 909, 731. **HRMS** calculated for [M+H] C₁₈H₂₅O₅⁺ = 321.1697, found (ESI +) 321.1696. Rotation (CH₂Cl₂) [α]²³D = -127.2
Diisobutylaluminum hydride 1.5 M in toluene (110 ul, 0.165 mmol, 3.5 equiv) was added dropwise to a -78 °C solution of enone-nitrile 1.144 (14.3 mg, 0.047 mmol) in toluene (2.5 ml). After 1hr, the reaction was quenched with MeOH (0.5 ml) and with 10% citric acid (1 ml). The reaction was warmed to RT and the layers were separated. The aqueous layer was extracted with DCM (4x2 mL). The combined organics were dried over Na₂SO₄, filtered and rotovapped. Purification on silica gel eluting with a gradient of 6:1 to 2:1 hexane:EtOAc provided a mixture of allylic alcohols 1.176 (13.2 mg, 91%).

The allylic alcohols 1.176 (12.9 mg, 0.042 mmol) and BaMnO₄ 90% (169 mg, 0.594 mmol, 14 equiv) were stirred in DCM (3 ml) at 35 °C for 24 h. The mixture was filtered through Celite and the solvent was removed in vacuo. The crude material was purified by silica chromatography with a gradient 6:1 to 2:1 hexane:EtOAc giving desired aldehyde as colorless film (7.6 mg, 59%).

$^1$H NMR (500 MHz, Chloroform-d) δ 9.54 (s, 1H), 6.52 (d, J = 10.0 Hz, 1H), 5.83 (d, J = 10.0 Hz, 1H), 4.94 (d, J = 13.1 Hz, 1H), 4.16 (d, J = 4.3 Hz, 1H), 2.99 (d, J = 13.0 Hz, 1H), 2.56 (dd, J = 13.7, 5.5 Hz, 1H), 1.84 to 1.47 (m, 8H), 1.25 (s, 3H), 1.12 (s, 3H), 1.10 (d, J = 7.3 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl₃) δ 198.2, 196.6, 157.9, 128.3, 87.8, 86.5, 76.8, 52.6, 46.8, 46.4, 40.3, 33.4, 31.2, 27.4, 24.0, 19.6, 18.2, 18.1.
Nitrile 1.144 (15.5 mg, 0.514 mmol) and Parkins’ catalyst (12mg, 0.028 mmol, 0.54 equiv) were heated to 80 °C in a mixture of EtOH (2.5 ml) and H₂O (0.2 ml) for 3 d. The reaction was cooled to rt and the solvent was removed in vacuo. The crude material was purified by silica chromatography with a gradient of 3:1 to 1:1 hexane:EtOAc providing the desired amide as a colorless film (7.7 mg, 48%).

¹H NMR (500 MHz, Chloroform-d) δ 6.43 (d, J = 10.0 Hz, 1H), 5.98 (s, 1H), 5.78 (d, J = 10.0 Hz, 1H), 5.04 (s, 1H), 4.82 (d, J = 13.1 Hz, 1H), 4.12 (d, J = 9.2 Hz, 1H), 3.24 (d, J = 13.0 Hz, 1H), 2.74 (m, 1H), 2.37 (dd, J = 13.9, 5.5 Hz, 1H), 1.87 (d, J = 14.0 Hz, 1H), 1.78 (s, 1H), 1.70 (d, J = 7.8 Hz, 1H), 1.50 (d, J = 16.5 Hz, 2H), 1.22 (s, 3H), 1.13 (d, J = 7.3 Hz, 3H), 1.10 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 198.8, 178.5, 157.4, 128.3, 87.5, 86.6, 77.7, 51.8, 47.5, 46.9, 40.3, 31.8, 27.5, 23.6, 19.9, 19.3, 17.7.
Aldehyde 1.176 (7.6 mg, 0.025 mmol), triethylsilyl chloride (63 µl, 0.375 mmol, 15 equiv) and imidazole (36 mg, 0.53 mmol, 21 equiv) were heated to 80 °C in DMF (0.4 ml) for 2 hr. The solvent was removed in vacuo and the crude material was purified by silica chromatography eluting with 20:1 to 10:1 hexane:EtOAc. Desired product was isolated as a colorless film (7 mg, 67%).

$^1$H NMR (500 MHz, Chloroform-d) δ 9.52 (s, 1H), 6.52 (d, $J = 10.0$ Hz, 1H), 5.83 (d, $J = 10.0$ Hz, 1H), 4.94 (d, $J = 13.1$ Hz, 1H), 4.20 (d, $J = 1.5$ Hz, 1H), 2.94 (d, $J = 13.1$ Hz, 1H), 2.54 (dd, $J = 13.2$, 5.6 Hz, 1H), 1.77 to 1.69 (m, 3H), 1.69 to 1.64 (m, 2H), 1.49 (tdd, $J = 9.7$, 3.8, 1.7 Hz, 1H), 1.22 (s, 3H), 1.10 (s, 3H), 1.08 (d, $J = 7.2$ Hz, 3H), 0.93 (t, $J = 7.9$ Hz, 9H), 0.57 (qd, $J = 7.9$, 4.3 Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 197.7, 196.1, 157.9, 128.4, 87.1, 86.5, 77.1, 52.7, 47.2, 44.9, 40.0, 32.4, 31.0, 27.3, 23.8, 19.5, 18.4, 18.0, 7.2, 5.3. IR (neat) cm$^{-1}$ 2957, 2876, 1726, 1694, 1465, 1375, 1106, 1075, 1007, 812, 737, 724. HRMS calculated for [M+H] C$_{24}$H$_{39}$O$_4$Si$^+$ = 419.26121, found (ESI +) 419.25916.
Trimethylsilyldiazomethane 2.0M in Et₂O (0.300 ml, 0.600 mmol, 7 equiv) was dropwise added to a RT solution of carboxylic acid \textbf{1.174} (27.7 mg, 0.0865 mmol) in MeOH (2.5 ml). The solvent was removed \textit{in vacuo} and the crude product was purified on silica gel eluting with a gradient of 6:1 to 4:1 hexane:EtOAc. Desired methyl ester was isolated as a colorless film (25.6 mg, 87%).

\begin{align*}
^{1}H \text{ NMR} \, (500 \text{ MHz, Chloroform-d}) & \delta 6.45 \,(d, \, J = 9.9 \text{ Hz}, \, 1H), \, 5.78 \,(d, \, J = 10.0 \text{ Hz}, \, 1H), \\
4.82 \,(d, \, J = 12.9 \text{ Hz}, \, 1H), \, 4.21 \,(s, \, 1H), \, 3.73 \,(s, \, 3H), \, 3.57 \,(d, \, J = 12.9 \text{ Hz}, \, 1H), \, 2.87 \,(dd, \, J = 13.9, \, 5.8 \text{ Hz}, \, 1H), \\
2.20 \,(dd, \, J = 11.9, \, 9.8 \text{ Hz}, \, 1H), \, 1.81 \, \text{to} \, 1.66 \,(m, \, 3H), \, 1.58 \, \text{to} \, 1.47 \,(m, \, 2H), \, 1.18 \,(s, \, 3H), \, 1.10 \,(d, \, J = 7.3 \text{ Hz}, \, 3H), \, 0.98 \,(s, \, 3H). \\
^{13}C \text{ NMR} \, (126 \text{ MHz, CDCl}_3) & \delta 199.2, \, 173.0, \, 157.7, \, 128.3, \, 87.7, \, 87.0, \, 77.0, \, 52.3, \, 51.8, \, 47.9, \, 46.9, \, 40.3, \, 37.3, \, 31.1, \\
27.5, \, 24.4, \, 19.7, \, 19.0, \, 17.7. \text{IR (neat) cm}^{-1} \, 3488, \, 2954, \, 2873, \, 1727, \, 1684, \, 1591, \, 1465, \\
1375, \, 1237, \, 1170, \, 1030, \, 1017, \, 911, \, 730. \text{HRMS calculated for } C_{19}H_{27}O_5 \, [M+H]^+ = 335.1853, \text{found 335.1862 (ESI+). Rotation (CH}_2Cl_2) \, [\alpha]^{23}_D = -109.1. 
\end{align*}
Methyl ester 1.183 (3.0 mg, 9 µmol), imidazole (17.8 mg, 269 µmol, 29 equiv) and triethylsilyl chloride (20 µl, 119 µmol, 13 equiv) were combined in DMF (0.5 ml) and heated to 80 °C for 24 hr. The reaction mixture was cooled to rt and the solvent was removed in vacuo. The crude material was purified on silica gel eluting with a gradient of 20:1 to 10:1 hexanes:EtOAc to provide the desired silyl ether as a colorless film (3.8 mg, 95%).

^1H NMR (500 MHz, Chloroform-d) δ 6.46 (d, J = 10.0 Hz, 1H), 5.78 (d, J = 10.0 Hz, 1H), 4.82 (d, J = 12.9 Hz, 1H), 4.27 (s, 1H), 3.72 (s, 3H), 3.53 (d, J = 12.9 Hz, 1H), 2.83 (dd, J = 13.3, 5.8 Hz, 1H), 2.17 (m, 1H), 1.84 (d, J = 12.9 Hz, 1H), 1.77 to 1.68 (m, 2H), 1.56 to 1.46 (m, 2H), 1.16 (s, 3H), 1.08 (d, J = 6.9 Hz, 3H), 0.97 (s, 3H), 0.92 (t, J = 7.9 Hz, 8H), 0.55 (qd, J = 7.8, 4.7 Hz, 6H). ^13C NMR (126 MHz, CDCl₃) δ 198.9, 173.0, 157.8, 128.3, 87.1, 87.0, 77.2, 52.2, 51.9, 48.3, 45.5, 40.0, 36.1, 30.9, 27.4, 24.3, 19.5, 19.2, 17.8, 7.2, 5.3.
Aldehyde 1.180 (7 mg, 0.017 mmol), 2-methyl-2-butene (0.82 ml), and NaH$_2$PO$_4$ 1.0 M aq (0.167 ml, 0.167, 10 equiv) were dissolved in tBuOH (0.8 ml). NaClO$_2$ 1 M aq (66 µl, 0.066 mmol, 4.0 equiv) was added and stirred for 40 min. The reaction mixture was quenched with citric acid pH=4 buffer 0.5 M aq (0.8 ml) and extracted with DCM (3x 2 ml). All organic layers were combined, dried over Na$_2$SO$_4$, filtered and concentrated to a residue. The crude material was purified on silica gel eluting with a gradient of 6:1 to 1:1 hexane:EtOAc. The desired material was isolated as a colorless solid (4.7 mg, 64%).

$^1$H NMR (500 MHz, Chloroform-d) δ 6.47 (d, $J = 10.0$ Hz, 1H), 5.79 (d, $J = 10.0$ Hz, 1H), 4.86 (d, $J = 12.9$ Hz, 1H), 4.26 (d, $J = 1.2$ Hz, 1H), 3.44 (d, $J = 12.9$ Hz, 1H), 2.79 (dd, $J = 13.5$, 5.9 Hz, 1H), 2.21 to 2.11 (m, 1H), 1.86 (d, $J = 13.4$ Hz, 1H), 1.74 (m, 3H), 1.65 to 1.55 (m, 4H), 1.18 (s, 3H), 1.09 (d, $J = 7.2$ Hz, 3H), 1.01 (s, 3H), 0.92 (t, $J = 7.9$ Hz, 9H), 0.55 (qd, $J = 7.9$, 4.5 Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 198.6, 176.8, 157.8, 128.3, 87.2, 87.1, 77.2, 51.8, 48.2, 45.4, 40.1, 36.1, 30.9, 27.4, 24.3, 19.5, 19.2, 17.9, 7.2, 5.3.
Carboxylic acid-alcohol 1.173 (7.8 mg, 0.024 mmol) and tetrabutylammonium iodide (15 mg, 0.041 mmol, 1.7 equiv) were dissolved in DCM (1.5 ml). Diisopropylethyl amine (222 µl, 1.27 mmol, 52 equiv) and methoxymethyl chloride (186 µl, 2.45 mmol) were added and the reaction was heated to 40 °C for 1.5h. The solvent was evaporated in vacuo and the crude material was purified on silica gel eluting with a gradient of 10:1 to 6:1 hexane:EtOAc. The desired product was isolated as a colorless film. (6.7 mg, 67%).

$^1$H NMR (500 MHz, Chloroform-d) $\delta$ 6.47 (d, $J = 10.0$ Hz, 1H), 5.78 (d, $J = 10.0$ Hz, 1H), 5.32 (d, $J = 5.9$ Hz, 1H), 5.26 (d, $J = 5.9$ Hz, 1H), 4.74 (d, $J = 12.9$ Hz, 1H), 4.58 (d, $J = 6.6$ Hz, 1H), 4.51 (d, $J = 6.6$ Hz, 1H), 4.07 (d, $J = 1.6$ Hz, 1H), 3.58 (d, $J = 12.9$ Hz, 1H), 3.52 (s, 3H), 3.29 (s, 3H), 2.87 (dd, $J = 13.7, 6.1$ Hz, 1H), 2.27 (m, 1H), 1.87 (ddd, $J = 7.2, 3.5, 1.8$ Hz, 1H), 1.82 to 1.72 (m, 2H), 1.64 to 1.53 (m, 2H), 1.20 (s, 3H), 1.12 (d, $J = 7.4$ Hz, 3H), 1.00 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 198.8, 171.5, 158.0, 128.2, 96.4, 90.9, 87.8, 87.3, 82.7, 57.9, 56.5, 51.8, 47.60, 43.0, 40.3, 36.5, 30.9, 27.6, 24.7, 19.9, 19.4, 17.9.
Compound 1.190

Methoxylmethyl ester 1.189 (6.7 mg, 0.0164 mmol) was dissolved in MeOH (0.6 ml) and H₂O (0.4 ml) and heated to 90 °C for 18h. The reaction mixture was concentrated to a residue then purified on silica gel eluting with a gradient of 3:1 to 1:1 to 1:2 hexanes:EtOAc. The desired acid was isolated as a colorless film (3.0 mg, 50%)

¹H NMR (500 MHz, Chloroform-d) δ 6.48 (d, J = 10.0 Hz, 1H), 5.78 (d, J = 10.0 Hz, 1H), 4.77 (d, J = 12.9 Hz, 1H), 4.59 (d, J = 6.5 Hz, 1H), 4.51 (d, J = 6.6 Hz, 1H), 4.06 (d, J = 1.6 Hz, 1H), 3.48 (d, J = 12.9 Hz, 1H), 3.29 (s, 3H), 2.82 (dd, J = 13.8, 6.0 Hz, 1H), 2.24 (dd, J = 12.7, 10.0 Hz, 1H), 1.90 1.82 (m, 1H), 1.83 to 1.74 (m, 1H), 1.65 to 1.55 (m, 4H), 1.37 to 1.28 (m, 1H), 1.22 (s, 3H), 1.12 (d, J = 7.3 Hz, 3H), 1.04 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 198.6, 176.4, 157.9, 128.2, 96.4, 87.8, 87.0, 82.7, 56.5, 51.8, 47.5, 43.0, 40.3, 36.6, 30.9, 27.7, 24.8, 19.9, 19.3, 17.9.
Carboxylic acid 1.173 (6.2 mg, 0.019 mmol) was dissolved in DMF (0.5 ml). DBU (6.4 µl, 0.043 mmol, 2.2 equiv) followed by chloriodomethane (2 µl, 0.027 mmol, 1.4 equiv) were added and stirred at RT. The reaction was quenched with NH₄Cl, and extracted with EtOAc (3x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was purified by silica chromatography eluting with a gradient of 6:1 to 1:1 hexane:EtOAc. The chloromethyl ester was isolated as a colorless film (3.2 mg, 44%).

¹H NMR (500 MHz, Chloroform-d) δ 6.47 (d, ̂J = 10.0 Hz, 1H), 5.83 to 5.79 (m, 2H), 5.73 (d, ̂J = 5.9 Hz, 1H), 4.85 (d, ̂J = 12.9 Hz, 1H), 4.25 (s, 1H), 3.50 (d, ̂J = 13.0 Hz, 1H), 2.84 (dd, ̂J = 14.1, 5.9 Hz, 1H), 2.25 to 2.17 (m, 1H), 1.84 to 1.65 (m, 3H), 1.19 (s, 3H), 1.11 (d, ̂J = 7.3 Hz, 3H), 1.00 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 198.8, 170.0, 157.8, 128.3, 88.1, 86.9, 76.8, 69.3, 51.7, 48.1, 46.8, 40.3, 36.9, 31.0, 27.5, 24.3, 19.7, 19.1, 17.9.
This is the same procedure for making chloromethyl ester 1.191.

Carboxylic acid 1.173 (6.2 mg, 0.019 mmol) was dissolved in DMF (0.5 ml). DBU (6.4 µl, 0.043 mmol, 2.2 equiv) followed by chloriodomethane (2 µl, 0.027 mmol, 1.4 equiv) were added and stirred at RT. The reaction was quenched with NH₄Cl, and extracted with EtOAc (3x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was purified by silica chromatography eluting with a gradient of 6:1 to 1:1 hexane:EtOAc. The acetal “dimer” was isolated as a colorless film (2.2 mg, 35%). [Note: The 2 proton singlet at 5.88 is the acetal signal]

¹H NMR (500 MHz, Chloroform-d) δ 6.47 (d, J = 10.0 Hz, 2H), 5.88 (s, 2H), 5.80 (d, J = 10.0 Hz, 2H), 4.84 (d, J = 12.9 Hz, 2H), 4.24 (s, 2H), 3.51 (d, J = 12.9 Hz, 2H), 2.82 (dd, J = 14.1, 5.7 Hz, 2H), 2.17 (t, J = 10.8 Hz, 2H), 1.19 (s, 6H), 1.10 (d, J = 7.1 Hz, 6H), 1.01 (s, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 198.9, 170.8, 157.8, 128.3, 88.0, 87.0, 80.5, 76.8, 51.7, 48.0, 46.8, 40.4, 37.0, 31.0, 27.5, 24.4, 19.7, 19.0, 17.9.
Enone **1.183** (9.5 mg, 0.028 mmol) and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one [Dess-Martin periodinane] (15 mg, 0.036, 1.3 equiv) were dissolved in DCM (2 ml) and stirred at rt for 1 h. The reaction was quenched with 20% Na$_2$S$_2$O$_3$ (1 ml) and sat NaHCO$_3$ (1 ml). The layers were separated and the aqueous was extracted with DCM. The combined organics were dried over Na$_2$SO$_4$, filtered and concentrated to a residue. The crude material was purified by silica chromatography eluting with 6:1 to 3:1 hexane:EtOAc leaving the desired dione as a colorless film (9 mg, 96%).

$^1$H NMR (500 MHz, Chloroform-d) $\delta$ 6.48 (d, $J = 10.0$ Hz, 1H), 5.89 (d, $J = 10.0$ Hz, 1H), 4.20 (d, $J = 12.4$ Hz, 1H), 3.77 (s, 3H), 3.20 (d, $J = 12.4$ Hz, 1H), 2.87 (dd, $J = 14.5$, 5.3 Hz, 1H), 2.46 (dd, $J = 14.3$, 10.2 Hz, 1H), 2.30 (q, $J = 6.1$, 5.1 Hz, 1H), 2.15 to 2.01 (m, 2H), 1.91 (t, $J = 12.4$ Hz, 1H), 1.66 (dd, $J = 13.5$, 9.3 Hz, 2H), 1.26 (d, $J = 7.5$ Hz, 3H), 1.18 (s, 3H), 1.02 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 212.3, 196.6, 172.9, 156.8, 128.4, 86.3, 85.9, 58.1, 52.6, 49.1, 48.4, 39.3, 39.2, 32.6, 27.1, 21.2, 18.8, 18.3, 16.0. IR (neat) cm$^{-1}$ 2929, 2876, 1725, 1691, 1450, 1327, 1246, 1106, 1020, 922, 795, 731. HRMS calculated for C$_{19}$H$_{25}$O$_5$ [M+H]$^+$ = 333.1697, found 333.1696 (ESI +). Rotation (CH$_2$Cl$_2$) $[\alpha]^{23}_D = -90.5$. 

90
Enone 1.183 (11.2 mg, 0.034 mmol) was dissolved in Et₂O (2 ml). Palladium on Carbon 10 wt% [Pd/C 10 wt%] (10.5 mg, 0.01 mmol, 0.29 equiv) and hydrogen (H₂, 1 atm balloon with needle) were added and stirred for 2.25 h. The reaction was filtered and the solvent was removed in vacuo leaving the desired product as colorless solids (11.2 mg, 99%).

¹H NMR (500 MHz, Chloroform-d) δ 4.54 (d, J = 12.8 Hz, 1H), 4.30 (d, J = 5.3 Hz, 1H), 3.74 (s, 3H), 3.62 (d, J = 12.8 Hz, 1H), 2.83 (dd, J = 14.0, 5.8 Hz, 1H), 2.38 to 2.29 (m, 1H), 2.23 to 2.16 (m, 1H), 2.13 (dd, J = 13.2, 9.9 Hz, 1H), 1.77 (d, J = 7.1 Hz, 1H), 1.74 to 1.65 (m, 2H), 1.62 (ddt, J = 10.6, 6.6, 4.0 Hz, 2H), 1.56 to 1.38 (m, 3H), 1.15 (dt, J = 13.6, 9.9 Hz, 1H), 1.09 (d, J = 7.1 Hz, 3H), 1.08 (s, 3H), 0.93 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 209.4, 173.2, 90.2, 86.8, 77.2, 54.0, 52.3, 48.1, 46.6, 39.4, 37.5, 37.2, 35.2, 31.0, 28.5, 24.3, 19.8, 19.1, 18.4. IR (neat) cm⁻¹: 3495, 2951, 2873, 1713, 1457, 1364, 1208, 1016, 916, 730. HRMS calculated for C₁₉H₂₉O₅ [M+H]+ = 337.2010, found 337.2015 (ESI +). Rotation (CH₂Cl₂) [α]D²³ = −69.3.
Cyclohexanone-alcohol 1.200 (4 mg, 0.012 mmol) and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one [Dess-Martin periodinane] (13 mg, 0.031, 2.6 equiv) were dissolved in DCM (2.3 ml) and stirred at rt for 2.5 h. The reaction was quenched with 20% Na$_2$S$_2$O$_3$ (1 ml) and sat NaHCO$_3$ (1 ml). The layers were separated and the aqueous was extracted with DCM. The combined organics were dried over Na$_2$SO$_4$, filtered and concentrated to a residue. The crude material was purified by silica chromatography eluting with 6:1 hexane:EtOAc leaving the desired dione as a colorless film (3.3 mg, 83%).

$^1$H NMR (500 MHz, Chloroform-d) δ 4.03 (d, $J$ = 12.3 Hz, 1H), 3.77 (s, 3H), 3.14 (d, $J$ = 12.3 Hz, 1H), 2.82 (dd, $J$ = 14.6, 5.3 Hz, 1H), 2.45 to 2.36 (m, 2H), 2.32 to 2.18 (m, 2H), 2.12 to 1.98 (m, 2H), 1.89 (t, $J$ = 12.3 Hz, 1H), 1.68 to 1.52 (m, 4H), 1.25 (d, $J$ = 7.5 Hz, 3H), 1.08 (s, 3H), 0.95 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 212.4, 206.7, 173.0, 87.5, 85.9, 58.0, 52.5, 50.9, 49.1, 39.4, 37.9, 36.2, 34.0, 32.6, 28.4, 20.9, 18.9, 18.9, 16.0. IR (neat) cm$^{-1}$ 2929, 1728, 1457, 1246, 1209, 1159, 1078, 1022, 995. HRMS calculated for C$_{19}$H$_{27}$O$_5$ [M+H]$^+$ = 335.1853, found 335.1856 (ESI +).
1.8 Spectroscopic Data

$^1$H-NMR of Compound 1.143 (CDCl$_3$)

$^{13}$C-NMR of Compound 1.143 (CDCl$_3$)
IR of Compound 1.143 (neat)


$^1$H-NMR of Compound 1.144 (CDCl$_3$)

$^{13}$C-NMR of Compound 1.144 (CDCl$_3$)
IR of Compound 1.144 (neat)
$^1$H-NMR of Compound 1.151 (CDCl$_3$)

$^{13}$C-NMR of Compound 1.151 (CDCl$_3$)
$^1$H-NMR of Compound 1.152 (CDCl$_3$)

$^{13}$C-NMR of Compound 1.152 (CDCl$_3$)
IR of Compound 1.152 (neat)
$^1$H-NMR of Compound 1.105 (CDCl$_3$)

$^{13}$C-NMR of Compound 1.105 (CDCl$_3$)
IR of Compound 1.105 (neat)
Chiral GC Data for Compound **1.105**

Gas chromatography (GC) was performed on an Agilent 7890A series instrument equipped with a split-mode capillary injection system and flame ionization detectors. Enantiomeric ratios were determined using a J&W Scientific Cyclodex-B (30 mm x 0.25mm) column. Flow rate and temperature = 1ml/min @ 180 °C isothermic.

**Racemate 1.105**

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(-)-1.105

er = 99.449 : 0.551

Area Percent Report

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Use Multiplier & Dilution Factor with ISIDs

Signal 1: FID2 E, Back Signal

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$^1$H-NMR of Compound 1.155 (CDCl$_3$)

$^{13}$C-NMR of Compound 1.155 (CDCl$_3$)
IR of Compound 1.155 (neat)
$^1$H-NMR of Compound **1.156** (CDCl$_3$)

![NMR spectrum](image)

$^{13}$C-NMR of Compound **1.156** (CDCl$_3$)

![NMR spectrum](image)
IR of Compound **1.156** (neat)
$^1$H-NMR of Compound 1.157 (CDCl$_3$)

$^{13}$C-NMR of Compound 1.157 (CDCl$_3$)
IR of Compound 1.157 (neat)
$^1$H-NMR of Compound 1.158 (CDCl$_3$)

$^{13}$C-NMR of Compound 1.158 (CDCl$_3$)
IR of Compound 1.158 (neat)
$^{1}$H-NMR of Compound 1.162 (CDCl$_3$)

$^{13}$C-NMR of Compound 1.162 (CDCl$_3$)
$^1$H-NMR of Compound **1.167** (CDCl$_3$)

$^{13}$C-NMR of Compound **1.167** (CDCl$_3$)
IR of Compound 1.167 (neat)
$^1$H-NMR of Compound **1.168** (CDCl$_3$)

$^{13}$C-NMR of Compound **1.168** (CDCl$_3$)
IR of Compound 1.168 (neat)
$^1$H-NMR of Compound epi-1.168 (CDCl$_3$)

$^{13}$C-NMR of Compound epi-1.168 (CDCl$_3$)
$^1$H-NMR of Compound 1.169 (CDCl$_3$)

$^{13}$C-NMR of Compound 1.169 (CDCl$_3$)
IR of Compound 1.169 (neat)
$^1$H-NMR of Compound 1.170 (CDCl₃)

$^{13}$C-NMR of Compound 1.170 (CDCl₃)
IR of Compound 1.170 (neat)
$^{1}$H-NMR of Compound 1.173 (CDCl$_3$)

![H-NMR spectrum](image)

$^{13}$C-NMR of Compound 1.173 (CDCl$_3$)

![C-NMR spectrum](image)
HSQC NMR of Compound 1.173 (CDCl₃)

IR of Compound 1.173 (neat)
$^1$H-NMR of Compound 1.174 (CDCl$_3$)

$^{13}$C-NMR of Compound 1.174 (CDCl$_3$)
HSQC NMR of Compound 1.174 (CDCl$_3$)
\(^1\)H-NMR of Compound 1.176 (CDCl\(_3\))

\(^{13}\)C-NMR of Compound 1.176 (CDCl\(_3\))
$^1$H-NMR of Compound **1.180** (CDCl$_3$)

$^{13}$C-NMR of Compound **1.180** (CDCl$_3$)
HSQC NMR of Compound 1.180 (CDCl$_3$)

IR of Compound 1.180 (neat)
$^1$H-NMR of Compound 1.183 (CDCl$_3$)

$^{13}$C-NMR of Compound 1.183 (CDCl$_3$)
HSQC NMR of Compound 1.183 (CDCl₃)

IR of Compound 1.183 (neat)
$^1$H-NMR of Compound 1.184 (CDCl$_3$)

$^{13}$C-NMR of Compound 1.184 (CDCl$_3$)
$^1$H-NMR of Compound **1.188** (CDCl$_3$)

$^{13}$C-NMR of Compound **1.188** (CDCl$_3$)
$^{1}$$H$-NMR of Compound 1.189 (CDCl$_3$)

$^{13}$$C$-NMR of Compound 1.189 (CDCl$_3$)
$^1$H-NMR of Compound 1.190 (CDCl$_3$)

$^{13}$C-NMR of Compound 1.190 (CDCl$_3$)
$^1$H-NMR of Compound 1.191 (CDCl$_3$)

$^{13}$C-NMR of Compound 1.191 (CDCl$_3$)
HSQC NMR of Compound 1.191 (CDCl₃)
$^1$H-NMR of Compound 1.192 (CDCl$_3$)

$^{13}$C-NMR of Compound 1.192 (CDCl$_3$)
$^1$H-NMR of Compound **1.199** (CDCl$_3$)

$^{13}$C-NMR of Compound **1.199** (CDCl$_3$)
HSQC NMR of Compound 1.199 (CDCl₃)

IR of Compound 1.199 (neat)
$^1$H-NMR of Compound **1200** (CDCl$_3$)

![1H-NMR Spectrum](image1)

$^{13}$C-NMR of Compound **1200** (CDCl$_3$)

![13C-NMR Spectrum](image2)
IR of Compound 1.200 (neat)
$^1$H-NMR of Compound **1.201** (CDCl$_3$)

![H-NMR spectrum of Compound 1.201](image)

$^{13}$C-NMR of Compound **1.201** (CDCl$_3$)

![C-NMR spectrum of Compound 1.201](image)
HSQC NMR of Compound 1.201 (CDCl₃)

IR of Compound 1.201 (neat)
1.9 References


(b) Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. *Org. Lett.* **2009**, *11*, 4770-4773.


7 McLeod, D. D. PhD. Dissertation, Princeton University, **2010**.


14 Spangler, J. E. PhD. Dissertation (Chapter 3), Princeton University, **2011**.

15 For a reviews on C-H insertion see:


Chapter 2

Efforts towards a total synthesis of atropurpuran and the discovery of skeletal rearrangements.
2.1 Discovery and identification of atropurpuran

The tubers of Aconitum species are used in traditional Chinese ‘Cao-Wu’ medicine for the treatment of pain and neurological disorders.\(^1\) These plants are widely distributed in the northern hemisphere and are known for the production of structurally diverse diterpenoid alkaloids with a wide range of bioactivities.\(^2\) In 2008, after investigation of roots from Aconitum hemsleyanum var. atropurpureum collected from Mount Emei in the Sichuan Provence of China, Wang and coworkers disclosed the discovery of a novel diterpene,\(^3\) a rare non-alkaloid find for the Aconitum genus.\(^4\) Their extraction process yielded 12 mg of atropurpuran (2.1, Figure 2.1) as colorless needles from 2.4 kg of dried root material. This diterpene contains a tetracyclo[5.3.3.0\(^4,9\),0\(^4,12\)]tridecane skeleton, which is the fusion of two bicyclo[2.2.2]octane units, certainly a rare and intriguing find in nature. Although the fused double bicyclo[2.2.2]octane is exceedingly uncommon, atropurpuran (2.1) shares the architecture with three known alkaloids isolated from a related plant, Aconitum arcuatum.\(^5\) Shown also in Figure 2.1, arcutin (2.2), arcutinine (2.3) and arcutinidine (2.4) have hydrated C\(_{1\cdots10}\) alkene, the 1-pyrroline ring instead of the C\(_{19}\) aldehyde and C\(_6\) ketone as well as differing substitution on the C\(_{15}\) hydroxyl group. Even though they are structurally interesting, no biological studies have been reported for any of these molecules.
2.2 Proposed biogenetic synthesis

Scheme 2.1 shows Wang’s poorly evidenced, yet still proposed biogenetic pathway of atropurpuran (2.1).\(^3\) Beginning with hetidane-type terpene precursor 2.5, fragmentation of the C\(_{13}\)-C\(_{14}\) bond would yield dialdehyde 2.6. An overall loss of H\(_2\) and ethylene would allow for formation of hemi-quinone 2.7. A Michael addition of hydroxide would form dienolate 2.8, which would then participate in a Diels-Alder reaction with ethylene forming bicyclo[2.2.2]octane 2.9. Dehydration of the tertiary alcohol would provide cyclohexene 2.10, which can participate in an intramolecular aldol reaction. After the reduction of the hydroxyl group at C\(_{13}\) and the installation of a hydroxyl at C\(_{15}\), atropurpuran (2.1) would be realized.

\[\text{Figure 2.1: Structure of atropurpuran (2.1) and diterpenoid alkaloids with the fused double bicyclo[2.2.2]octane skeleton.}\]
Scheme 2.1: Wang’s proposed biogenetic pathway of atropurpuran 2.1.

2.3 Literature efforts to make atropurpuran

We were intrigued by the structures of these molecules and started a program to synthesize atropurpuran (2.1). When we initiated this project in 2009, no studies had been reported in the literature even though arcutin (2.2) was known since 2000. Since our program began, there have been two reports on synthetic efforts toward atropurpuran 2.1. An impressive first report came in 2011 from the Kobayashi group at the Tokyo University of Science and second appeared in 2012 from the Hsung group at the University of Wisconsin.\textsuperscript{6,7}

In a short effort, the Hsung group employed an extension of their 1,3-hydrogen shift/6π-electrocyclization/intramolecular Diels-Alder chemistry to form the BCD rings of atropurpuran 2.1\textsuperscript{7,8} In Scheme 2.2, chiral auxiliary allenamide 2.12 was treated with camphor sulfonic acid (CSA) to induce a 1,3-hydrogen shift to create the conjugated triene 2.13. In the presence of titanium (IV) isopropoxide in toluene at 110 °C, a 6π-electrocyclization generated diene 2.14. This amidodiene
underwent an intramolecular Diels-Alder reaction at 185 °C in decane over 48 hr to provide bicyclo[2.2.2]octene 2.15 in 73% yield over three steps as a 2:1 diastereotopic mixture of *endo*-isomers. Facially selective dimethyldioxirane (DMDO) epoxidation to give 2.16 followed by hydrolysis yielded the BCD ring system of atropurpuran (2.1) with an epimeric hydroxy group at C15 in 85% over two steps.

**Scheme 2.2:** Hsung’s preparation of the BCD ring system of atropurpuran.

The efforts by the Kobayashi lab are far more comprehensive. Using an oxidative dearomatization/Diels-Alder strategy, they synthesized the entire carbocyclic framework of atropurpuran 2.1. As shown in Scheme 2.3, allylmagnesium bromide addition into tetralone 2.18 yields tertiary alcohol 2.19. Exposure of the phenol to (diacetoxyiodo)benzene in methanol provides the masked *ortho*-benzoquinone 2.20, which upon heating undergoes an intramolecular Diels-Alder reaction to form the fused double bicyclo[2.2.2]octene 2.21 in 79% yield. Next, the terminal alkenes participate in ring-closing metathesis using Grubbs’ type-
II catalyst\(^9\) in high efficiency to give cyclohexene \(2.22\). Hydrogenation of both alkenes followed by triflation and elimination provide the pentacyclic skeleton of atropurpuran \(2.1\) shown in molecule \(2.23\). This impressive sequence shows a rapid entry into the complex framework, but has yet to be translated into the natural product.\(^{\dagger}\)

![Scheme 2.3: Kobayashi’s rapid entry into the entire carbocyclic framework of atropurpuran.](image)

### 2.4 Results and Discussion\(^5\)

Our initial retrosynthetic proposal for atropurpuran (\(2.1\)) is shown in Scheme 2.4. The natural product could arise from a diastereoselective epoxidation/elimination sequence from alkene \(2.24\). We postulated that \(2.24\) could arise from a

\(^{\dagger}\) The Kobayashi work was published about a year after we initiated our efforts on atropurpuran. It will become apparent that these efficiencies should be lauded. We decided to pursue a radical based ring closing strategy based partly on the above results.

\(^5\) The pyrone work was done in collaboration with Dr. John Malona.
diastereoselective ring annulation strategy on diketone 2.25. Disconnecting the molecule in this manner reveals symmetry in the natural product. The fused double bicyclo[2.2.2]octane-dione 2.25 could arise from an intramolecular Diels-Alder reaction between the diene and enone fragments of 2.26. A second proposed disconnection via a Diels-Alder-retro [4+2] (loss of carbon dioxide) led us to attempt to make the bis-enone/pyrone 2.27 to investigate this proposed three-step cascade sequence.\textsuperscript{10}

\[ \text{Diels-Alder} \]

\[ \text{Retro [4+2]} \]

\[ \text{Diels-Alder} \]

\[ \text{Epoxidation} \]

\[ \text{Annulation} \]

atropurpuran 2.24 2.25

\[ \text{2.27} \]

\[ \text{2.26} \]

\textbf{Scheme 2.4:} Proposed synthesis of atropurpuran 2.1 via a cascade of [4+2] cycloadditions.

Our initial foray into the investigation of the proposed three-step cascade sequence begins in Scheme 2.5 with efforts to make a dienone similar to 2.27. Beginning with known carboxylic acid/pyrone 2.28,\textsuperscript{11} a borane reduction in the presence of triethylborane provided a low yield (25\%) of the primary alcohol 2.29. Mesylation with methanesulfonyl chloride and pyridine in CH\textsubscript{2}Cl\textsubscript{2} provided 2.30 in
excellent yield. A nucleophilic substitution reaction with commercially available allyl dimethylmalonate 2.31 provided the diester pyrone 2.32. Unfortunately, our attempts to convert the diester into the bis-enone species 2.33 (i.e. addition of vinyl metal species) were not met with success.

Scheme 2.5: Attempt to synthesize pyrone with two pendant enone groups 2.33.

At the time Dr. Malona left the project, we were not able to synthesize a dienone/pyrone such as 2.33. However, it soon became apparent that the first two fundamental steps of the proposed Diels-Alder/retro [4+2]/Diels-Alder could be investigated using the pyrone with pendant allyl group 2.32. Even though an allyl group would be less activated than an electon deficient enone in an intramolecular Diels-Alder reaction with this diene, it might react with thermal instigation. As shown in Scheme 2.6, heating 2.32 in toluene-d₈ to reflux for 5 days provided arene 2.35. This product is the logical result of a [4+2] cycloaddition that provided intermediate 2.33, which underwent loss of carbon dioxide in a retro [4+2] cycloaddition, which then oxidized to the arene 2.35, likely due to advantageous
oxygen. Knowing that the first two fundamental steps of the three-step cascade reaction proposal were possible, the feasibility of the last step needed to be determined.

![Scheme 2.6: Observation of arene 2.35.](image)

Since the viability of the last intramolecular Diels-Alder step of the proposed three-step cascade was undefined, a dieneophile would need to be attached to a diene similar to 2.34. Scheme 2.7, shows a proposal for testing the last step. Triene 2.36 could undergo a 6π-electrocyclic-ring formation to generate racemic diene 2.37. This intermediate diene could then participate in an intramolecular Diels-Alder reaction with one of the pendant allyl groups previously installed, thereby providing the fused double bicyclo[2.2.2]octane framework.

![Scheme 2.7: Electrocyclic ring formation/Diels-Alder cascade proposal.](image)
Scheme 2.8 shows the synthetic setup to test this hypothesis. The known cyclohexenone 2.39\textsuperscript{12} was treated with lithium diisopropylamide and allyl bromide to make the bis-allyl cyclohexenone 2.40 in 78\% yield, then aqueous HCl unmasked the dione 2.41 in quantitative yield. This was followed by treating dione 2.41 with trifluoromethanesulfonyl anhydride and pyridine at -78 °C to make the desired vinyl triflate species 2.42 in 61\% efficiency. To avoid uncontrolled electrocyclization, a room temperature palladium catalyzed Suzuki reaction\textsuperscript{13} with known boronic ester diene 2.43\textsuperscript{14} using tricyclohexylphosphine provided the test substrate triene 2.36 in 30\% yield.

![Scheme 2.8: Synthesis of triene 2.36 to test the electrocyclization/Diels-Alder proposal.](image)

The desired triene 2.36 was dissolved in toluene-d\textsubscript{8} and placed in a Teflon sealed J. Young NMR tube. The solution was deoxygenated by a cycle of freezing, pumping and thawing under nitrogen. The reaction was heated to 140 °C and followed by \textsuperscript{1}H NMR, 13C NMR, COSY, and HSQC, (Scheme 2.9). The starting material was consumed and the NMR was distinct. It was apparent that the major product was not the desired fused double bicyclo[2.2.2]octane 2.38, but rather the
conjugated dienone 2.44. The product of electrocyclization 2.37 was inferred due to lack of observation in the NMR spectra. Whether the isomerization to the conjugated dienone 2.44 was a suprafacial 1,5-hydride shift or the result of advantageous acid or base, the transformation was faster than the desired Diels-Alder reaction. This result materialized the significant improbability of achieving all three steps of the proposed three-step cascade using a pyrone with pendant dienophiles because the last step would likely fail.

Scheme 2.9: Observation of electrocyclization then rapid isomerization to conjugated dienone 2.44.

Even with this disappointing outcome, the possibility of the making of a fused double bicyclo[2.2.2]octane ring system using this intramolecular Diels-Alder strategy still beckoned. One simple way stop the isomerization of 2.37 to 2.44 was to replace the α-proton with a methyl group. Although this would install an extraneous carbon for atropurpuran 2.1, if the skeletal system were realized with an α-methyl, we would search to identify a more easily removable moiety. Scheme
2.10, depicts the proposal with triene 2.45. An electrocyclic ring formation would provide the homoannular diene 2.46 which should not isomerize to the conjugated dienone. Diene 2.46 could then participate in the desired Diels-Alder reaction to provide bicyclo[2.2.2]octane 2.47.

Scheme 2.10: Proposal to stop isomerization to allow Diels-Alder with α-methyl group.

On careful examination of the skeletal framework of 2.46, it became apparent that it could be synthesized from the Wieland-Miescher ketone 2.48, (Scheme 2.11). This observation allowed the avoidance of the capricious reaction to make boronic ester diene 2.43. Scheme 2.11 depicts the synthesis of 2.46 starting from the Wieland-Miescher ketone 2.48. Known protection of the enone carbonyl of 2.48 using collidine p-toluenesulfonate (CPTS) and ethylene glycol formed ketal 2.49 with isomerized alkene. Treatment with LDA and a slight excess amount of allyl bromide led to a mixture of mono and diallylated ketone products. Diallylketone 2.50 was isolated in 18% yield, which was enough to execute the remainder of the sequence. Deprotection of the ketal with isomerization of the double bond revealed the enone 2.51 in excellent yield. Treatment of enone 2.51 with KHMSDS and perfluorobutanesulfonyl fluoride yielded the vinyl nonaflate 2.52.
in 84% yield. A tetrakis(tribenzylyphosphine) palladium cross-coupling reaction with trimethylaluminum led to the homoannular diene 2.46 in 14% yield.

Scheme 2.11: Synthesis of homoannular diene with pendant dienophile 2.46.

Unfortunately, heating homoannular diene 2.46 in sealed NMR tube in toluene-d₈ to 120 °C did not lead to the desired fused double bicyclo[2.2.2]octane 2.47, but rather the heteroannular diene 2.53, (Scheme 2.12a). This was confirmed by independent synthesis of 2.53 by making the thermodynamic dienyl triflate 2.54 by treating the diallyl Weiland-Mieschler ketone 2.51 with 2,6-lutidine and trifluromethanesulfonyl anhydride (Tf₂O) followed by cross coupling with trimethylaluminum with tetrakis(tribenzylyphosphine) palladium as catalyst, (Scheme 2.12b). It should also be noted that 2.46 rapidly isomerized to 2.53 during workup, after isolation or upon treatment with p-toluenesulfonic acid in toluene.
Again a rapid isomerization, this time to the heteroannular diene 2.53, was faster than the desired Diels-Alder reaction. Since a fused double bicyclo[2.2.2]octane was still desired, exchanging the methyl on the diene for a silyloxy group could raise the energy of the HOMO of the diene enough to increase the rate of Diels-Alder reaction over the isomerization. Scheme 2.13 shows the result of this hypothesis. By treating 2.51 with KHMDS and TBSOTf at -78 °C in THF, the homoannular silyloxydiene 2.55 with pendant allyl dienophile was isolated in 80% yield. Next diene 2.55 was heated to 140 °C in toluene-d₈ in a sealed NMR tube for 19 hours. After NMR indicated the complete conversion of starting material, the crude mixture was exposed to trifluoroacetic acid (TFA) affording the fused double bicyclo[2.2.2]octane dione 2.58 in 21% yield and the diallyl Wieland-Mieschler ketone 2.51, likely through the protonation and isomerization of heteroannular diene 2.57. Although the efficiency was low and the angular methyl group was extraneous for the natural product, this was the first synthetic fused double bicyclo[2.2.2]octane.
Even though we were pleased at forming a fused double bicyclo[2.2.2]octane, we evaluated the Diels-Alder strategy in the context of synthesizing atropurpuran 2.1. In order to continue using the strategy, obstacles would need to be overcome. Firstly, a more easily removable group than the methyl would need to be installed. We considered using a methyl carboxylate that could be removed via Barton radical decarboxylation conditions. Secondly, the rate of desired Diels-Alder reaction would have to be increased relative to the observed undesired heteroannular diene isomerization. This could be accomplished by lowering the LUMO of the dienophile by addition of electron withdrawing groups. Superficially, one might assume that installing a conjugated proximal ketone carbonyl would accomplish this goal, however based on a physical model, the ketone and alkene would need to adopt an orthogonal conformation in the Diels-Alder transition state, breaking any π-induced electron withdrawing. To lower the LUMO in the transition state while keeping the molecule symmetrical, we proposed adding a distal methyl ester to the dienophile.
These proposals would result in a molecule such as 2.59 and if successful, molecule 2.60. However, the setup costs to make such a molecule were undesirable, therefore this strategy was not pursued further.

**Scheme 2.14**: Possible modifications to efficiently make fused double bicyclo[2.2.2]octane framework that were ultimately not pursued.

![Scheme 2.14](image)

An alternate strategy that would employ a radical cyclization cascade was proposed. Sunggak Kim demonstrated the cyclization protocol of adding an alkyl radical into an arylsulfonyl hydrazone or an Eshenmosher iminoaziridine which then fragments to form a new radical that is propagated or captured with another electrophile.\(^{16,17,18}\) For example, Scheme 2.15 shows that the linear alkyl bromide with mesitylsulfonyl hydrazone 2.61 forms a carbon centered radical at the terminal carbon after bromine abstraction. The alkyl radical then engages the sulfonyl hydrazone forming a cyclohexanone. The hydrazone then fragments generating a new secondary radical, which abstracts a hydrogen atom from tributyltin hydride forming 2.62. A similar alkyl iodide with the Eschenmoser type
aziridylimine 2.63 undergoes the same process, but intercepts methyl acrylate 2.64 before hydrogen abstraction, generating 2.65.

\[
\begin{align*}
\text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \quad \text{Br} \quad 2.61 \quad \text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \quad 2.62 \\
\text{N} \quad \text{N} \quad \text{NSO}_2\text{Mes} \quad \text{nBuSnH} \quad \text{AIBN} \quad 58\% \quad \text{N} \quad \text{N} \quad \text{Ph} \quad \text{CO}_2\text{CH}_3 \quad 2.63 \quad 2.64 \quad \text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \quad 2.65 \\
\end{align*}
\]

**Scheme 2.15**: Kim’s radical cyclization chemistry.

We proposed a cascade sequence to capitalize on this behavior of radicals and arylsulfonfonyl hydrazones to make the skeletal framework of atropurpuran 2.1. Shown in Scheme 2.16, heating vinyl iodide/bis-arylsulfonfonylhydrazone 2.66 in the presence of tributyltin hydride using azobisisobutyronitrile (AIBN) as initiator could form the rapidly inverting vinyl radical 2.67. The vinyl radical could then engage the proximal arylsulfonfonyl hydrazone forming a bicyclo[2.2.2]octene ring, which upon hydrazone fragmentation would produce nitrogen, an arylsulfinic acid and a new carbon-based tertiary radical 2.68. This tertiary radical could then add into the remaining arylsulfonfonyl hydrazone followed by a similar fragmentation to provide the secondary alkyl radical 2.69. The final radical would abstract hydrogen from tributyltinhydride to propagate the reaction and produce fused double bicyclo[2.2.2]octane 2.70.
Scheme 2.16: Proposed cascading sequence to generate a fused double bicyclo[2.2.2]octane skeleton using radical addition into arylsulfonyl hydrazones.

Scheme 2.17 shows the synthesis of the keto-aldehyde substrate 2.77. Takai-Utimoto chromium mediated olefination\textsuperscript{20} of ketone 2.71 produced vinyl iodide 2.72 in modest yield. Hydrolysis of the ketal gave cyclohexanone 2.73 in 63% yield. Lawton annulation using enamine alkylation is known to have poor diastereoselectivity for substituents at C\textsubscript{4} of cyclohexanones;\textsuperscript{21} thus a two-step procedure was implemented. A low temperature alkylation with low temperature quench followed by enamine ring closure gave the bicyclo[3.3.1]nonanone 2.75. Treatment of 2.75 with LiHMDS and allylbromide provided unsaturated ester 2.76. Osmium tetroxide mediated dihydroxylation\textsuperscript{22} followed by lead (IV) acetate oxidative cleavage provided the desired keto-aldehyde 2.77 in 50% yield over two steps.
Scheme 2.17: Synthesis of keto-aldehyde 2.76 via a stepwise Lawton annulation.

By treating keto-aldehyde 2.77 with one equivalent of 2,4,6-trimethylbenzenesulfonyl hydrazide in THF to form the mesitylsulfonyl hydrazone, a few unexpected observations were made. Namely TLC (3:1 Hexane:Ethyl acetate) analysis before rotary evaporation was ultraviolet light active with Rf <0.2. After concentrating to a residue by rotary evaporation, the Rf increased to 0.55 and the spot was no longer ultraviolet light active. $^1$H and $^{13}$C NMR clearly indicated that the compound was no longer symmetrical and no aryl fragment was present in the final product. No N-H stretch was observed by IR spectroscopy. Scheme 2.18 shows the result of this reaction as the skeletal rearranged product 2.79 with an effective carbon–carbon insertion of the aldehyde carbon between the $\alpha$-carbon and the ketone carbon.
Scheme 2.18: An unexpected C-C insertion and skeletal rearrangement product 2.79.

Realizing that this was an interesting unknown transformation, a small collection of related compounds were synthesized and subjected to the similar reaction conditions. Scheme 2.18 shows the unoptimized syntheses of four keto-aldehyde substrates. Cycloalkylketone 2.80 was subjected to a Lawton type annulation using either pyrrolidine or potassium tert-butoxide. The resulting bicycle 2.81 was allylated with LiHMDS in THF. Ozonolysis with reductive dimethyl sulfide workup or dihydroxylation/oxidative cleavage gave the keto-aldehyde 2.83.

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Scheme 2.19: Synthesis of keto-aldehyde compounds 2.83a-d.

Keto-aldehydes 2.83 a-d, were treated with either 2,4,6-trimethylbenzenesulfonyl hydrazide in THF (2.83 a-b) or p-toluensulfonyl hydrazide in CDCl_3 (2.83 c-d) to form the aryl sulfonyl hydrazone, Scheme 2.19.
After the starting material was consumed (TLC analysis), the solvent was evaporated from 2.83 a-b and the residue was dissolved in CDCl₃. Off gassing was immediately observed from the reaction with 2.83-a forming the skeletal rearranged product 2.84-a. Mild heating to 60 °C was needed to effect the rearrangement with 2.83-b and 2.83-c noting that the rearrangement with 2.83-c was regiospecific for the migration of the tertiary carbon. The bicyclo[3.3.1]nonanone with methyl groups flanking the ketone 2.83-d needed to be heated to 100 °C in toluene-d₈ in order to rearrange to 2.84-d. Yields were between 49 -75% and not optimized.

**Scheme 2.20:** Keto-aldehydes 2.83a-d underwent sulfonylhydrazone formation and C-C insertion.

In terms of mechanistic insight, there are recent relevant examples of tosylsulfonylhydrazones behaving as nucleophiles under basic conditions. Kabalka
and coworkers demonstrated intermolecular nucleophilicity with benzaldehyde derived arylsulfonylhydrazones under basic conditions with tributylboron and a subsequent 1,2 alkyl shift, (Scheme 2.21a). The alkyl boron could then be oxidized or protodeborolated (not shown). The Barluenga lab elaborated this concept to couple tosylhydrazones with boronic acids under basic conditions, (Scheme 2.21b.)

![Scheme 2.21: (a) Kabalka's base promoted tosylhydrozone coupling with tributylborane. (b) An example of Barluenga's tosylhydrazone boronic acid coupling.](image)

It is understandable that the deprotonated tosylhydrazones in the examples above are nucleophilic due to their anionic nature. Barluenga proposes elimination of the sulfinic acid to generate a diazocompound that immediately adds to the boronic acid or further decomposes to a carbene, then adds to the boronic acid. Under our non-basic conditions, an initial elimination of the arylsulfinic acid to make the diazospecies may be less likely. A plausible mechanistic explanation for
the conversion of keto-aldehyde such as 2.83-a to C-C inserted product 2.84-a is depicted in Scheme 2.22. Upon condensation of the mesitylhydrazide with the formyl group of 2.83-a, mesitylhydrazone 2.85 is formed. One can imagine a six-membered transition state where the ketone carbonyl might be activated to nucleophilic addition of the hydrazone carbon by internal protonation from the N-H of the sulfonylamine, in a formal aza-ene type reaction. The resulting bicyclo[2.2.2]octane with the tertiary alcohol 2.86 would then participate in an arylsulfonylhydrazone fragmentation with a concurrent semi-pinacol shift to produce ketone 2.84-a, releasing nitrogen (N₂) and mesitylsulfinic acid. This may be reminiscent of the Tiffaneau-Demjanov rearrangement. Whether the fragmentation occurs simultaneously or stepwise is of great interest but has not yet been determined.

Scheme 2.22: Plausible mechanism for C-C bond insertion to form 2.84-a.
The desire to apply this reaction to other substrates led to the discovery of yet another interesting reaction. Scheme 2.23 shows the synthesis of a truncated enolizable keto-aldehyde substrate, 2.89, that we hoped would also participate in the C-C bond insertion reaction. Ethyl ester 2.87 was allylated with LiHMDS and allylbromide. After acid catalyzed ketal removal, cyclohexanone 2.88 was realized in 47% over two steps. Ozonolysis of the alkene gave the monocyclic keto-aldehyde 2.89.

Scheme 2.23: Synthesis of monocyclic keto-aldehyde 2.89 from known ester 2.87.

Scheme 2.24 shows the results of treating truncated monocyclic keto-aldehydes 2.89 and 2.90 with p-toluenesulfonyl hydrazide in CDCl₃. It was clear by ¹H NMR that the aldehyde peak disappeared quickly but more interestingly, the ¹³C NMR showed that both carbonyls disappeared upon heating to 60 °C. After purification by silica chromatography, the spectral data indicated that an unexpected ring system had formed. Using X-ray crystallographic analysis (Figure 2.2), the structure was finally fully deciphered to be the azo-tricycle 2.92 shown.

Scheme 2.24: An unexpected transformation of keto-aldehydes 2.89 and 2.90.
The conversion of the keto-aldehydes to the azocompounds 2.91 and 2.92 was certainly unexpected. Due to a lack of thorough experimentation, this may be more difficult to explain mechanistically. However, Scheme 2.25 depicts a possible pathway to arrive at 2.92. Combining keto-aldehyde 2.90 with tosylsulfonyl hydrazide forms the hydrazone 2.93, which can be in equilibrium with the enol tautomer 2.94. Either through a polar mechanism of two nucleophilic additions (path a) or less likely through a [3+2] cycloaddition (path b) the tricycle 2.96 can be formed. Through an overall loss of water and a shift of the sulfinic group, tricyclic azo-sulfone 2.92 can be formed. This is an interesting novel transformation that warrants deeper experimental study into the scope and mechanism.
Scheme 2.25: Plausible pathway(s) to azotricycle 2.92.

2.5 Conclusions

Studying the diterpene molecule atropurpuran 2.1 as an object for synthesis led to some very interesting observations. The initially proposed three-step cascade to make the fused double bicyclo[2.2.2]octane was likely destined to fail on the last step of the cascade due to undesired isomerization to a fully conjugated dienone. With the addition of an extraneous methyl group, the isomerization to a conjugated dienone that would doom the original proposal was stopped. However, this led to the discovery of a second undesired homoannular to heteroannular diene isomerization that impeded the desired Diels-Alder reaction. By employing a more electron rich silyloxydiene, a fused double bicyclo[2.2.2]octane was finally realized, albeit in low yield. Finally, during the investigating of a radical ring cyclization approach to making the skeletal framework of atropurpuran 2.1, a novel C-C insertion and rearrangement reaction was discovered. Furthermore, while
investigating the C-C insertion reaction, another novel chemical transformation was observed. The two new reactions are much more scientifically interesting than the originally investigated plans to make the natural product. Unfortunately the efforts to study the new reactions were far from comprehensive, which leaves ample opportunity to investigate the scope, mechanistic insight and chemistry of the resulting products.
2.6 Experimental Details

Borane•dimethylsulfide (2.31 g, 30.4 mmol) was added to a solution of carboxylic acid 2.28 (4.65 g, 27.7 mmol) in 50 ml THF and stirred for 2d at rt. The thick orange slurry was quenched with H₂O (25 ml) then made slightly basic with 1N NaOH and stirred for 20 min. The mixture was extracted with EtOAc. The aqueous layer was made slightly acidic using 1 N HCl then extracted twice with EtOAc. The combined organics were washed with H₂O, sat NaCl and dried over Na₂SO₄. The mixture was filtered and concentrated to a residue. Crude material was purified by silica chromatography eluting with 4:1 EtOAc:hexane then 1:1 MeOH:EtOAc giving the desired alcohol (1.064 g, 25%).

¹H NMR (500 MHz, Chloroform-d) δ 5.97 (s, 1H), 5.94 (d, J = 7.3 Hz, 1H), 3.91 (dt, J = 9.9, 3.6 Hz, 1H), 2.69 (q, J = 6.1 Hz, 2H), 2.11 (d, J = 4.9 Hz, 2H).
Alcohol 2.29 (0.610 g, 3.96 mmol), and pyridine (0.48 ml, 5.96 mmol, 1.5 equiv) methanesulfonyl chloride (0.58 ml, 7.49 mmol, 1.9 equiv) were dissolved in DCM (10 ml) and stirred at rt for 18 h. Additional methanesulfonyl chloride (0.3 ml, 3.88 mmol, 0.9 equiv) was added and stirred 24 hr. The reaction mixture was concentrated to a residue then dissolved in EtOAc. The organic layer was washed with pH 7 buffer, then saturated NaCl, dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was purified on silica gel eluting with a gradient of 50 to 90% EtOAc in hexane. Desired product was isolated as a colorless oil (0.823 g, 94%).

¹H NMR (500 MHz, Chloroform-d) δ 6.02 (s, 1H), 5.98 (s, 1H), 4.50 (t, J = 6.1 Hz, 2H), 3.01 (s, 3H), 2.91 (t, J = 6.1 Hz, 2H), 2.15 (d, J = 1.2 Hz, 3H).
NaH 60% in oil (0.17 ml, 0.428 mmol) was washed with dry hexane then suspended in dry THF (5 ml). The allylmalonate 2.31 (73.8 mg, 0.428 mmol) and the mesylate 2.30 (82.9 mg, 0.357 mmol) were added and stirred until complete. The reaction was quenched with NH₄Cl and extracted with EtOAc. Purification by silica chromatography eluting with 1:1 hexane:EtOAc gave the desired product as a clear oil (35.4 mg, 32%).

¹H NMR (501 MHz, Toluene-d₈) δ 5.65 to 5.52 (m, 2H), 5.13 (s, 1H), 4.97 (d, J = 7.9 Hz, 1H), 4.94 (s, 1H), 3.30 (s, 6H), 2.65 (d, J = 7.4 Hz, 2H), 2.20 (s, 4H), 1.35 (s, 3H).
Pyrone 2.32 (7.0 mg, 0.023 mmol) was dissolved in toluene-d₈ (0.5 ml) and heated to 110 °C for 5 days with intermittent NMR analysis. The solvent was removed and the crude material was purified on silica gel elution with 20% EtOAc in hexane. The arene product was isolated as a colorless film (4 mg, 67%).

¹H NMR (501 MHz, Chloroform-d) δ 7.01 (d, J = 7.8 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H), 6.87 (s, 1H), 3.72 (s, 6H), 3.23 (s, 2H), 2.79 (t, J = 6.8 Hz, 2H), 2.31 (t, J = 6.8 Hz, 2H), 2.27 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 171.9, 135.6, 134.3, 130.3, 129.2, 128.7, 127.0, 53.7, 52.8, 34.4, 28.3, 25.9, 21.0. HRMS calculated for C₁₅H₁₈NaO₄⁺ [M+Na]⁺ = 285.10973, found = 285.10964.
In an oven dried vial with Teflon septa, palladium (II) acetate (7.3 mg), KF (75 mg), vinyl triflate 2.42 (96.0 mg, 0.296 mmol) and the vinyl boronate ester 2.43 (67.7 mg, 0.349 mmol) were evacuated and backfilled with argon. THF (1 ml) and tricyclohexylphosphine (11.2 mg) were added and the reaction mixture was stirred at 23 °C. The mixture was filtered through a silica plug using EtOAc then concentrated to a residue. Purification on silica gel gave desired triene as a yellow film (21.5 mg, 30%).

$^1$H NMR (500 MHz, Chloroform-d) δ 6.75 (dd, $J = 17.4$, 10.9 Hz, 1H), 6.09 (s, 1H), 5.88 (s, 1H), 5.71 (dddd, $J = 16.8$, 10.6, 8.1, 6.5 Hz, 2H), 5.41 (d, $J = 17.4$ Hz, 1H), 5.23 (d, $J = 10.9$ Hz, 1H), 5.17 to 5.02 (m, 5H), 2.51 to 2.45 (m, 2H), 2.41 (dd, $J = 14.2$, 6.5 Hz, 2H), 2.20 (dd, $J = 14.2$, 8.2 Hz, 2H), 2.08 (s, 1H), 1.98 (d, $J = 1.2$ Hz, 3H), 1.94 (t, $J = 7.0$, 2H). $^{13}$C NMR (126 MHz, Tol-d8) δ 196.7, 161.2, 139.4, 135.1, 134.7, 131.4, 127.6, 118.7, 117.3, 42.8, 34.4, 30.8, 21.0. HRMS calc for C$_{17}$H$_{23}$O$^+$ [M+H]$^+$ = 243.17434, found 243.17441 (ESI+).
Butyllithium 2.5M in hexane (9.56 ml, 23.9 mmol) was added to a -78 °C solution of diisoproplamine (3.37 ml, 23.9 mmol) in THF (24 ml). After 30 min, cyclohexenone 2.39 (4.15 g, 19.9 mmol) was added. After 15 min, allylbromide (2.2 ml, 25.6 mmol) was added and the reaction mixture was warmed to rt in the dry ice bath and held for 20 h. The reaction was quenched with half-saturated NH₄Cl (40 ml), washed with sat NaCl, dried over Na₂SO₄, filtered and concentrated to a residue. The crude orange oil was distilled (150 °C, 2mm) to provide the desired product as a pale yellow oil (3.86 g, 78%).

¹H NMR (500 MHz, Chloroform-d) δ 5.73 (ddddd, J = 16.5, 10.6, 7.8, 7.0 Hz, 2H), 5.26 (s, 1H), 5.07 (q, J = 1.2 Hz, 2H), 5.06 to 5.02 (m, 2H), 3.57 (d, J = 6.5 Hz, 2H), 2.43 (t, J = 6.4 Hz, 2H), 2.40 (ddt, J = 13.9, 7.0, 1.2 Hz, 2H), 2.17 (ddt, J = 13.9, 7.8, 1.2 Hz, 2H), 2.01 (septet, J = 6.7 Hz, 1H), 1.85 (t, J = 6.4 Hz, 2H), 0.96 (d, J = 6.8 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 202.4, 176.3, 134.4, 118.1, 101.9, 74.9, 46.5, 39.8, 29.0, 27.9, 25.9, 19.2. HRMS calculated for C₁₆H₂₅O₂⁺ [M+H]⁺ = 249.18491, found 249.18490.
Compound \textbf{2.40} (3.21 g, 12.9 mmol) was dissolved in THF (25 ml), H\textsubscript{2}O (3 ml) and HCl 6M (3 ml), then stirred at 40 °C for 3h. EtOAc (20 ml) and H\textsubscript{2}O (10 ml) were added. The layers were separated and the organic layer was washed with sat NaCl, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and rotovapped leaving the diketone product \textbf{2.41} as a waxy solid (2.48 g, 100%).

Diketone \textbf{2.41} (0.973 g, 5.06 mmol) and pyridine (0.810 ml, 10.1 mmol) were dissolved in DCM (20 ml) at -78 °C. Trifluoromethanesulfonic anhydride (1.02 ml, 6.07 mmol) was added over 2 min. After 1hr, the reaction was warmed to 0 °C, then HCl 0.5M (10 ml) and Et\textsubscript{2}O (30 ml) were added. The layers were separated. The organic layer was washed with H\textsubscript{2}O (20 ml), half saturated K\textsubscript{2}CO\textsubscript{3} (20 ml) and saturated NaCl (20 ml), then dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated to a residue. The crude material was purified on silica gel eluting with 20:1 hexanes:EtOAc providing the desired vinyl triflate (1.00 g, 61%).

\textsuperscript{1}H NMR (500 MHz, Chloroform-d) \(\delta\) 6.11 (s, 1H), 5.74 (dddd, \(J = 16.9, 10.2, 8.0, 6.8\) Hz, 2H), 5.24 to 5.14 (m, 4H), 2.50 (t, \(J = 7.0\) Hz, 2H), 2.48 (ddt, \(J = 7.3, 6.8, 1.3\) Hz, 2H), 2.30 (ddt, \(J = 14.0, 8.0, 1.0\) Hz, 2H), 2.01 (dd, \(J = 7.5, 6.4\) Hz, 2H). \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 197.3, 170.6, 131.8, 120.5, 118.3 (q, \(J_{C:F} = 320.3\) Hz), 117.6, 42.7, 41.1, 33.8, 28.7.
In a Teflon sealed J.Young NMR tube, triene 2.36 (11 mg, 0.045 mmol) in toluene-d$_8$ was cycled through freezing, pumping and thawing with nitrogen backfill (7x) then heated to 140 °C for 24 hr. The reaction was monitored by $^1$H and $^{13}$C NMR and not purified.

$^1$H NMR (500 MHz, Toluene-d8) δ 5.74 (dt, $J$ = 2.9, 1.5 Hz, 1H), 5.54 (dddd, $J$ = 16.5, 9.7, 8.1, 6.6, 1.5 Hz, 2H), 4.98 to 4.85 (m, 4H), 2.55 (t, $J$ = 9.4 Hz, 2H), 2.31 (ddd, $J$ = 7.5, 6.5, 1.5 Hz, 2H), 2.15 (ddt, $J$ = 14.1, 6.6, 1.5 Hz, 2H), 1.91 (ddd, $J$ = 14.2, 8.0, 1.0 Hz, 2H), 1.77 (ddt, $J$ = 10.7, 8.1, 1.4 Hz, 2H), 1.62 (ddd, $J$ = 8.2, 6.4, 1.5 Hz, 2H), 1.58 (s, 3H). $^{13}$C NMR (126 MHz, Tol) δ 195.7, 153.7, 146.3, 135.1, 120.5, 118.7, 118.4, 42.9, 34.3, 30.5, 28.9, 24.1, 20.7.
Under argon, tetrakis(triphenylphosphine) palladium (22 mg, 0.019 mmol) was added to a solution of vinyl nonaflate 2.52 (513 mg, 0.95 mmol) in THF (5 ml). Then trimethylaluminum 2.0 M in toluene (0.95 ml, 1.90 mmol) was added and the reaction was stirred for 19 h. The mixture was quenched with sat NaHCO₃ and Et₂O and aqueous Rochelle’s salt was added and stirred. The layers were separated and the organic layer was washed with sat NaCl and dried over Na₂SO₄, filtered and concentrated to a residue. Purification on silica gel eluting with 40:1 to 10:1 hexane:EtOAc provided the homoannular diene (35 mg, 14%). This compound begins to isomerize immediately after isolation and was heated in toluene-d₈ to an attempt to achieve the Diels-Alder reaction (see synthesis of 2.53).
Butyllithium 2.5M in hexane (5.6ml, 14 mmol) was added to diisopropylamine (2.0ml, 14.2 mmol) in THF (24 ml) at -78 °C. After 10 min, ketone 2.49 (2.41 g, 10.82 mmol) was added. After 45 min, allylbromide (1.21 ml, 14.1 mmol) was added and the reaction mixture was warmed to rt and held for 3h. The reaction was quenched with half-saturated brine (25 ml) and EtOAc (15ml) was added. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was purified by silica chromatography eluting with 10:1 to 6:1 hexane:EtOAc giving the diallyl species 2.50 (0.600 g, 18%).

The ketal 2.50 (0.517 g, 1.71 mmol) was dissolved in THF (8 ml) and H₂O (1.8 ml), then HCl 2M (1.0 ml) was added and the mixture was stirred at 50 °C for 6hr. EtOAc (15ml) was added and the layers were separated. The organic layer was washed with H₂O, sat NaCl, dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was dried in vacuo giving the desired species 2.51 (0.44 g, 100%).

¹H NMR (500 MHz, Chloroform-d) δ 5.89 (s, 1H), 5.68 (ddt, J = 17.3, 10.1, 7.3 Hz, 1H), 5.57 (ddt, J = 17.3, 10.1, 7.3 Hz, 1H), 5.17 to 4.98 (m, 4H), 2.80 (dtd, J = 16.6, 7.1, 2.1 Hz, 1H), 2.58 (dt, J = 17.0, 6.8 Hz, 1H), 2.53 to 2.45 (m, 2H), 2.42 (ddd, J = 17.5, 5.1, 2.8 Hz, 1H), 2.32 (dd, J = 14.1, 7.2 Hz, 1H), 2.29 to 2.23 (m, 2H), 2.11 (dd, J = 14.1, 7.5

Compound 2.51
Hz, 1H), 1.99 (dt, \( J = 14.3, 7.1 \) Hz, 1H), 1.91 (td, \( J = 14.0, 5.3 \) Hz, 1H), 1.78 (dt, \( J = 14.1, 6.6 \) Hz, 1H), 1.38 (s, 3H). \(^{13}\text{C} \) NMR (126 MHz, CDCl\(_3\)) \( \delta \) 214.0, 198.2, 165.8, 133.4, 132.8, 125.7, 119.4, 119.1, 50.8, 48.9, 40.8, 40.3, 33.5, 31.4, 27.9, 27.1, 23.3. HRMS calculated for \( \text{C}_{17}\text{H}_{23}\text{O}_2^+ \) [M+H]\(^+\) = 259.16926, found 259.16782.
A solution of ketone 2.51 (258 mg, 1.0 mmol) in THF (5 ml) was added to a -78 °C solution of KHMDS 0.5M in toluene (2.4 ml, 1.2 mmol) and held for 30 min. Then perfluorobutanesulfonyl fluoride (0.196 ml, 1.1 mmol) was added and held for 2h. The reaction was quenched at -78 °C with sat NaHCO₃ and extracted with Et₂O. The organic layer was washed with sat NaCl, dried over Na₂SO₄, filtered, concentrated to a residue and dried in vacuo giving the desired vinyl nonaflate (454 mg, 84%).

¹H NMR (500 MHz, Chloroform-d) δ 5.72 to 5.56 (m, 4H), 5.13 to 5.01 (m, 4H), 2.72 to 2.62 (m, 1H), 2.58 (dd, J = 17.9, 6.9 Hz, 1H), 2.50 to 2.37 (m, 3H), 2.30 (dd, J = 13.9, 7.3 Hz, 1H), 2.13 (dd, J = 13.9, 7.8 Hz, 1H), 1.90 (ddd, J = 14.1, 6.6, 5.0 Hz, 1H), 1.76 (ddd, J = 14.4, 10.1, 4.8 Hz, 1H), 1.22 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 215.04, 147.65, 145.18, 133.53, 133.21, 119.21, 119.07, 115.08, 111.74, 50.84, 46.47, 41.15, 40.62, 32.20, 29.20, 25.80, 22.60.
Ketone 2.51 (129 mg, 0.5 mmol) in DCM (2.7 ml) was combined with 2,6-lutidine (216 µl, 1.9 mmol) and trifluoromethanesulfonic anhydride (114 µl, 0.68 mmol) and stirred at rt for 2h. The reaction was quenched with sat NaHCO₃ and Et₂O was added. The organic layer was washed with sat NaCl, dried over Na₂SO₄, filtered and concentrated to a residue. The vinyl triflate 2.54 (128 mg, 66%) was isolated after silica chromatography 20:1 to 10:1 hex:EtOAc. Under argon, the vinyl triflate 2.54 (111 mg, 0.28 mmol) was dissolved in THF (1.4 ml). Tetrakistriphenylphosphine palladium (16 mg, 0.014 mmol) followed by trimethylaluminum 2.0M in toluene (280 µl, 0.56 mmol) were added. After 21 h, the reaction mixture was quenched with sat NaHCO₃, then EtOAc and aqueous Rochelle’s salt were added and stirred. The organic layer was separated, washed with sat NaCl, dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was purified on silica gel eluting with 100:0 to 20:1 hexanes:EtOAc giving the desired heteroannular diene (41 mg, 56%).

^1H NMR (500 MHz, Toluene-d₈) δ 5.79 10 5.67 (m, 1H), 5.57 (dddd, J = 16.7, 10.1, 8.2, 6.6 Hz, 1H), 5.34 (dd, J = 7.2, 2.2 Hz, 1H), 5.04 to 4.82 (m, 3H), 2.68 (ddt, J = 13.5, 5.9, 1.5 Hz, 1H), 2.44 (d, J = 16.7 Hz, 1H), 2.17 to 2.10 (m, 2H), 1.97 (dt, J = 13.6, 7.4 Hz, 2H), 1.83 (dd, J = 17.1, 7.4 Hz, 1H), 1.66 (dd, J = 18.0, 5.6 Hz, 1H), 1.56 (s, 3H), 1.42 (td, J = 12.7, 5.6 Hz, 1H), 0.98 (s, 3H). ^13C NMR (126 MHz, Tol) δ 215.27, 139.79, 187
135.19, 134.74, 133.96, 123.78, 118.52, 118.08, 117.92, 49.74, 44.71, 41.47, 40.28, 30.62, 27.31, 23.30, 21.18. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 217.5, 139.2, 135.5, 134.7, 133.5, 123.2, 118.4, 118.4, 49.9, 44.7, 41.3, 40.0, 30.3, 30.2, 27.3, 23.5, 21.2.

Compound **2.46** (6 mg, 0.023 mmol) was heated to in toluene-d$_8$ (0.75 ml). Below are $^1$H NMR spectra from bottom to top at T=0 min, 25 min, 3.75 hr, 7hr and independently synthesised **2.53**.
A solution of ketone 2.51 (334 mg, 1.29 mmol) in THF (3 ml) was added to a -78 °C solution of KHMDS 0.5M in toluene (2.84 ml, 1.42 mmol) in THF (3 ml) and held for 30 min. Then t-butyldimethylsilyltrifluoromethane sulfonate (0.326 ml, 1.42 mmol) was added and held for 1h. The reaction was quenched at -78 °C with sat NaHCO₃ (4 ml) and H₂O (1 ml) and extracted with EtOAc. The organic layer was washed with H₂O, sat NaCl, dried over Na₂SO₄, filtered, and concentrated to a residue. The crude material was purified on Et₃N-pretreated slurry packed silica gel eluting with 40:1 hexane:EtOAc yielding the silyloxydiene 2.55 as a yellow oil (386 mg, 80%).

¹H NMR (500 MHz, Toluene-d8) δ 5.66 to 5.54 (m, 2H), 5.52 (s, 1H), 5.03 to 4.86 (m, 4H), 4.70 (dt, J = 5.9, 2.5 Hz, 1H), 2.49 to 2.41 (m, 2H), 2.38 (ddt, J = 13.7, 6.8, 1.3 Hz, 1H), 2.31 to 2.19 (m, 2H), 2.17 to 2.09 (m, 2H), 2.05 to 1.98 (m, 3H), 1.56 to 1.40 (m, 2H), 1.14 (s, 3H), 0.96 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H). ¹³C NMR (126 MHz, Tol) δ 214.8, 148.1, 144.4, 134.5, 134.1, 121.0, 118.4, 118.2, 98.7, 50.5, 46.9, 41.3, 40.9, 32.9, 30.0, 25.8, 25.8, 25.7, 22.1.
Diene 2.55 (21 mg, 0.056 mmol) was dissolved in toluene-d₈ (0.65 ml) and heated in a sealed NMR tube in a 140 °C oil bath for 19 h. The starting material peaks were absent in the NMR, so the solution was concentrated to a residue. Then the mixture was dissolved in DCM (0.2 ml) and trifluoroacetic acid (0.2 ml) was added. The solution was concentrated to a residue and purified on silica gel. The desired fused double bicyclo[2.2.2]octane 2.58 was isolated (3 mg, 21%) with ketone 2.51 as the major side product (~4 mg, ~25%)

^1^H NMR (500 MHz, Chloroform-d) δ 5.77 (ddt, J = 17.4, 10.3, 7.4 Hz, 1H), 5.08 to 4.98 (m, 2H), 2.39 (dd, J = 14.5, 3.4 Hz, 1H), 2.35 (d, J = 19.1 Hz, 1H), 2.31 to 2.19 (m, 2H), 2.18 (dd, J = 13.5, 10.7 Hz, 1H), 2.12 (dd, J = 14.0, 7.8 Hz, 1H), 1.99 to 1.89 (m, 2H), 1.80 (ddd, J = 13.4, 10.6, 2.8 Hz, 1H), 1.75 to 1.58 (m, 2H), 1.57 to 1.50 (m, 2H), 1.35 (dt, J = 13.6, 2.4 Hz, 1H), 1.27 to 1.21 (m, 2H), 1.09 (s, 3H). ^13^C NMR (126 MHz, CDCl₃) δ 221.7, 215.5, 134.4, 117.9, 46.8, 45.7, 44.3, 44.2, 42.5, 38.9, 37.3, 34.8, 34.0, 27.1, 26.0. IR (neat) cm⁻¹ 2927, 2868, 1710, 1455, 998, 914, 734. HRMS calc for C₁₇H₂₃O₂⁺ [M+H]⁺ = 259.16926, found 259.17005
Ketone 2.71 (1.23 g, 6.67 mmol) was azeotropically dried by distilling under reduced pressure with benzene (2x 20ml) then dissolved in THF (20 ml) and iodoform (5.21 g, 13.2 mmol). Meanwhile a slurry of chromium (II) chloride (6.52 g, 53.1 mmol, 8 equiv) was prepared and cooled to 0 °C under argon in THF (20 ml). The ketone/iodoform solution was dropwise added the slurry over 30 min then warmed to rt and stirred for 18 h. The reaction mixture was quenched with NaHCO₃ (20 ml) and H₂O (20 ml). The mixture was extracted with EtOAc (40 ml), then the organic layer was washed with half-saturated NaHCO₃ (2x 20 ml), half-saturated brine (2x 20 ml) and brine. The organic layer was dried over Na₂SO₄, filtered, concentrated to a residue and purified on silica gel eluting with a gradient of 20:1 to 10:1 hexane:EtOAc giving the desired vinyl iodide as an oil (0.970 g, 47%).

¹H NMR (501 MHz, Chloroform-d) δ 5.97 (s, 1H), 3.94 (s, 4H), 2.18 (tt, \( J = 7.9, 3.4 \) Hz, 1H), 1.82 (s, 3H), 1.80 to 1.75 (m, 2H), 1.73 to 1.67 (m, 2H), 1.61 to 1.54 (m, 4H). ¹³C NMR (126 MHz, CDCl₃) δ 210.8, 150.1, 76.2, 46.2, 41.0, 31.3, 22.7.
Ketal **2.72** (0.970 g, 3.15 mmol) was heated to 50 °C in THF (10 ml) and HCl 1M (5 ml) for 30 min. The reaction was extracted with EtOAc (10 ml) and washed with sat NaHCO₃ and sat NaCl, then dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was purified on silica gel eluting with a gradient of 20:1 to 10:1 hexanes:EtOAc giving the desired ketone as a colorless oil (0.540 g, 65%).

**$^1$H NMR** (500 MHz, Chloroform-d) δ 6.08 (s, 1H), 2.63 (tt, $J$ = 11.9, 2.8 Hz, 1H), 2.46 to 2.40 (m, 1H), 2.37 (dd, $J$ = 14.5, 5.7 Hz, 1H), 2.06 (ddd, $J$ = 13.0, 5.8, 3.0 Hz, 2H), 1.86 (s, 3H), 1.72 (qd, $J$ = 12.7, 5.3 Hz, 3H). **$^{13}$C NMR** (126 MHz, CDCl₃) δ 210.8, 150.1, 76.2, 46.2, 41.0, 31.3, 22.7. IR (neat) cm⁻¹ 2963, 2931, 2866, 1695, 1267, 1149, 940, 789, 659, 486. HRMS calculated for C₉H₁₄IO⁺ [M+H]⁺ = 265.00838, found 265.00768.
Ketone 2.73 (520 mg, 1.97 mmol) was added to a -78 °C solution of lithium diisopropylamide (2.36 mmol) in THF (5 ml), then warmed to 0°C, then cooled to -78 °C. Ethyl 2-(bromomethyl)acrylate (0.300 ml, 2.17 mmol) was added via syringe and stirred for 2 hr. The reaction was quenched at -78 °C with H2O (3 ml) then extracted into EtOAc. The organic layer was washed with sat NaCl, dried over Na2SO4, filtered and concentrated to a residue. The crude material (~6:1 diastereomeric ratio) was purified on silica gel eluting with 20:1 to 10:1 hexane:EtOAc giving the desired single diastereomeric product (346 mg, 47%).

1H NMR (500 MHz, Chloroform-d) δ 6.22 (s, 1H), 6.10 (s, 1H), 5.59 (s, 1H), 4.20 (q, \( J = 6.9 \) Hz, 2H), 2.83 to 2.71 (m, 2H), 2.72 to 2.63 (m, 1H), 2.56 to 2.45 (m, 1H), 2.45 to 2.3 (m, 2H), 2.02 to 1.88 (m, 3H), 1.86 (s, 3H), 1.84 to 1.71 (m, 1H), 1.30 (t, \( J = 7.2 \) Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 212.5, 166.8, 149.3, 137.9, 127.3, 76.4, 61.1, 47.8, 41.1, 38.2, 35.2, 33.3, 30.6, 23.0, 14.4.
Compound 2.74 (346 mg, 0.919 mmol) was mixed with pyrrolidine (75 µl, 0.92 mmol), triethylamine (130 µl, 0.92 mmol) in acetonitrile (5 ml) at 65 °C for 2d. The reaction was quenched with HCl 1M (2.5 ml), solid NaCl to saturate and extracted with EtOAc thrice. The combined organic layers were washed with sat NaHCO₃, sat NaCl, dried over Na₂SO₄, filtered and condensed to a residue. The crude material was purified on silica gel eluting with 15:1 to 10:1 hexanes:EtOAc giving desired diastereomer bicyclo[3.3.1]nonane (212 mg, 61%).

\[
\begin{align*}
\text{Compound 2.75} \\
\text{CO}_2\text{Et} \\
\text{CH}_3
\end{align*}
\]

1H NMR (400 MHz, Chloroform-d) δ 6.13 (quin, \(J = 1.0\) Hz, 1H), 4.14 (q, \(J = 7.1\) Hz, 2H), 3.17 (tt, \(J = 12.6, 4.3\) Hz, 1H), 2.59 (apparent d, \(J = 10.0\) Hz, 2H), 2.50 to 2.39 (m, 2H), 2.35 (dt, \(J = 13.3, 5.1\) Hz, 1H), 2.14 (td, \(J = 13.1, 2.6\) Hz, 2H), 2.02 to 1.92 (m, 2H), 1.90 to 1.81 (m, 2H), 1.84 (d, \(J = 1.0\) Hz, 3H). 13C NMR (126 MHz, CDCl₃) δ 219.3, 174.4, 148.7, 77.0, 61.0, 42.9, 39.9, 36.9, 36.7, 32.4, 22.9, 14.3.
Compound **2.76** (181 mg, 0.481 mmol) in THF (1.6 ml) was added to a -78°C solution of LiHMDS 1.0M in THF (0.722 ml, 0.722 mmol) and stirred for 30min. Allyl bromide (64 µl, 0.739 mmol) was then added and the reaction was wamed to 0 °C. After 30 min, the reaction was quenched at 0 °C with sat NH₄Cl and extracted with EtOAc. The organic layer was washed with H₂O, sat NaCl, dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was purified on silica gel with 10:1 hexanes:EtOAc giving the desired product as colorless solids (140 mg, 70%).

**1H NMR** (501 MHz, Chloroform-d) δ 6.09 (s, 1H), 5.59 (ddt, J = 17.3, 10.1, 7.3 Hz, 1H), 5.07 (d, J = 9.8 Hz, 1H), 5.03 (d, J = 17.0 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.13 (tt, J = 12.6, 4.5 Hz, 1H), 2.54 (apparent d, J = 8.4 Hz, 2H), 2.43 to 2.35 (m, 2H), 2.35 to 2.24 (m, 4H), 2.03 to 1.95 (m, 2H), 1.88 (td, J = 13.3, 3.3 Hz, 2H), 1.81 (d, J = 1.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H). **13C NMR** (126 MHz, CDCl₃) δ 221.5, 175.9, 148.6, 133.2, 119.3, 77.0, 61.2, 43.2, 42.3, 41.4, 37.2, 36.8, 22.7, 14.4. HRMS calculated for C₁₇H₂₄IO₄⁺ [M+H]⁺ = 419.07138, found 419.07172.
Compound 2.76 (113 mg, 0.271 mmol) was stirred with N-methylmorpholine-N-oxide (73 mg, 0.542 mmol) in DCM (3.3 ml) at rt. Then osmium tetroxide 4 wt% in water (63 mg, 0.010mmol, 0.02 equiv) was added and stirred for 6.5 hr. The reaction was quenched with half-saturated Na$_2$S$_2$O$_3$ then extracted with DCM (3x 2ml). The combined organics were dried over, Na$_2$SO$_4$, filtered and condensed to a residue. The resulting orange film was dissolved in DCM (2 ml), then lead (IV) acetate (127 mg, 0.286 mmol) was added and stirred for 45 min. The resulting solution was adsorbed onto silica by rotary evaporation then purified by silica gel chromatography eluting with 3:1 hexane:EtOAc giving the desired aldehyde as pale orange solids (58 mg, 51% 2-steps).

$^1$H NMR (501 MHz, Chloroform-d) $\delta$ 9.62 (s, 1H), 6.13 (s, 1H), 4.17 (q, $J$ = 7.1 Hz, 2H), 3.20 (tt, $J$ = 12.7, 4.4 Hz, 1H), 2.77 (s, 2H), 2.60 to 2.50 (m, 4H), 2.38 to 2.27 (m, 2H), 2.04 to 1.97 (m, 2H), 1.89 (td, $J$ = 13.6, 3.0 Hz, 2H), 1.82 (d, $J$ = 1.0 Hz, 3H), 1.24 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 221.3, 199.0, 175.2, 148.2, 77.3, 61.6, 49.2, 41.9, 41.4, 40.5, 37.3, 36.8, 22.8, 14.2. IR (neat) cm$^{-1}$ 2906, 2819, 1726, 1710, 1452, 1200, 1068, 1029, 933, 781, 682, 507, 461. HRMS calculated for C$_{17}$H$_{24}$IO$_4^+$ [M+H]$^+$ = 419.07138, found 419.07172.
Keto-aldehyde 2.77 (8.6 mg, 20.6 µmol) and 2,4,6-trimethylbenzenesulfonyl hydrazide (4.4 mg, 20.5 µmol) were dissolved in THF (0.5 ml) and stirred for 45 min. Then the solvent was removed by rotary evaporation. The crude material was analyzed by NMR in CDCl₃, then purified on silica gel eluting with 6:1 up to 3:1 hexane:EtoAc. The C-C/skeletal rearranged product was isolated as a colorless oil (6.3 mg, 76%).

¹H NMR (500 MHz, Chloroform-d) δ 6.08 (s, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.87 to 2.72 (m, 4H), 2.38 to 2.27 (m, 2H), 2.17 (ddd, J = 13.5, 11.3, 2.1 Hz, 1H), 1.99 (dt, J = 13.3, 2.3 Hz, 1H), 1.90 (ddd, J = 14.3, 7.5, 2.7 Hz, 2H), 1.77 (s, 3H), 1.74 (d, J = 7.4 Hz, 1H), 1.65 (dt, J = 12.0, 5.4 Hz, 1H), 1.60 (s, 3H), 1.55 (dd, J = 13.5, 2.9 Hz, 1H), 1.39 (dd, J = 14.5, 12.7 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.25 (s, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 214.4, 175.5, 150.8, 77.0, 61.0, 54.9, 48.6, 44.1, 41.4, 40.2, 36.7, 36.7, 35.3, 33.6, 33.5, 22.1, 14.3. IR (neat) cm⁻¹ 2919, 2853, 1716, 1448, 1366, 1250, 1186, 1061. HRMS calculated C₁₇H₂₄IO₃⁺ [M+H]⁺ = 403.07646, found 403.07789.
1-(1-cyclohepten-1-yl)-pyrrolidine (680 mg, 3.63 mmol), made from condensing pyrrolidine with cycloheptanone, was dissolved in acetonitrile (6ml) with triethylamine (0.58 ml, 4.1 mmol) and ethyl 2-(bromomethyl)acrylate (0.800 mg, 4.14 mmol) and heated to 65 °C for 2 days. The reaction was quenched with HCl 1M, extracted with EtOAc, washed with H₂O, then sat NaCl, dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was purified by silica chromatography elution with 10:1 hexane:EtOAc giving the desired product (473 mg, 51%).

¹H NMR (500 MHz, Chloroform-d) δ 4.13 (q, J = 7.1 Hz, 1H), 2.63 (p, J = 6.6 Hz, 2H), 2.49 (tt, J = 11.2, 6.6 Hz, 1H), 2.19 to 2.09 (m, 4H), 1.93 (dddd, J = 13.3, 9.8, 7.4, 3.3 Hz, 2H), 1.79 to 1.71 (m, 2H), 1.55 (ddt, J = 16.5, 5.3, 3.4 Hz, 2H), 1.49 to 1.39 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 218.1, 175.3, 60.8, 46.9, 38.4, 31.1, 30.7, 26.2, 14.3. IR (neat) cm⁻¹ 2927, 2858, 1712, 1447, 1377, 1304, 1234, 1181, 1155, 1038, 928, 857. HRMS calculated for C₁₂H₂₀NaO₃⁺ [M+Na]⁺ = 247.13047, found 247.13034.
Compound 2.81-c

2-Methylcyclohexanone (449 mg, 4.0 mmol), KOTBu 1.0 M in THF (8.0 ml, 8.0 mmol) and ethyl 2-(bromomethyl)acrylate (0.804 mg, 4.16 mmol) were heated to 65 °C for 24 h. The reaction was quenched with HCl 2M, extracted with EtOAc, washed with H₂O, then sat NaCl, dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was purified by silica chromatography elution with 10:1 to 6:1 hexane:EtOAc giving the desired product (167 mg, 19%).

¹H NMR (500 MHz, Chloroform-d) δ 4.12 (qd, J = 7.1, 1.2 Hz, 2H), 3.49 (tt, J = 12.5, 5.9 Hz, 1H), 2.55 (s, 1H), 2.31 to 1.99 (m, 5H), 1.91 (t, J = 13.1 Hz, 1H), 1.82 to 1.72 (m, 2H), 1.66 to 1.56 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 0.99 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 219.9, 174.8, 60.9, 46.0, 45.7, 43.8, 42.1, 38.3, 36.5, 34.3, 24.5, 21.5, 14.4.
2,6-Dimethylcyclohexanone (504 mg, 4.0 mmol), KOtBu 1.0 M in THF (8.0 ml, 8.0 mmol) and ethyl 2-(bromomethyl)acrylate (0.804 mg, 4.16 mmol) were heated to 65 °C for 24 h. The reaction was quenched with NH₄Cl, extracted with EtOAc, washed with H₂O, then sat NaCl, dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was purified by silica chromatography elution with 10:1 to 6:1 hexane:EtOAc giving the desired product (166 mg, 17%).

^1H NMR (500 MHz, Chloroform-d) δ 4.11 (q, J = 7.1 Hz, 2H), 3.57 (tt, J = 13.0, 5.9 Hz, 1H), 2.22 to 2.15 (m, 2H), 2.08 to 2.00 (m, 2H), 1.90 (ddd, J = 14.9, 12.9, 2.1 Hz, 2H), 1.80 to 1.70 (m, 2H), 1.57 (dddd, J = 14.0, 6.8, 4.9, 2.0 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.00 (s, 6H). ^13C NMR (126 MHz, CDCl₃) δ 219.8, 174.9, 60.9, 45.8, 43.8, 42.2, 38.4, 24.8, 21.6, 14.3. IR (neat) cm⁻¹ 2968, 2927, 2850, 1730, 1711, 1451, 1378, 1293, 1176, 1031, 879, 655. HRMS calculated for C₁₄H₂₃O₃⁺ [M+H]^⁺ = 239.16417, found 239.16410.
Compound **281-a** (388 mg, 1.85 mmol) in THF (6 ml) at -78 °C was treated with LiHMDS 1.0M in THF (2.2 ml, 2.2mmol, 1.19 equiv) and stirred for 45 min. Allyl bromide (210 µl, 2.43 mmol, 1.3 equiv) was added and the reaction was warmed to 0 °C for 1 h. The mixture was quenched with NH₄Cl, extracted with EtOAc, washed with H₂O, then sat NaCl, dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was purified by silica chromatography eluting with 10:1 hexane:EtOAc giving the desired product (280 mg, 60.6%).

\(^1\)H NMR (500 MHz, Chloroform-d) \(\delta\) 5.59 (ddt, \(J = 17.3, 10.1, 7.3\) Hz, 1H), 5.08 to 4.99 (m, 2H), 4.15 (q, \(J = 7.1\) Hz, 2H), 2.51 (d, \(J = 9.3\) Hz, 3H), 2.34 (dd, \(J = 14.7, 3.2\) Hz, 2H), 2.29 to 2.21 (m, 4H), 2.11 to 1.99 (m, 1H), 1.97 (d, \(J = 13.3\) Hz, 3H), 1.85 (tt, \(J = 13.2, 3.9\) Hz, 2H), 1.48 (ddt, \(J = 14.2, 4.6, 2.2\) Hz, 1H), 1.26 (t, \(J = 7.1\) Hz, 3H). \(^13\)C NMR (126 MHz, CDCl₃) \(\delta\) 222.9, 176.0, 133.4, 119.0, 61.0, 43.5, 43.3, 41.3, 37.5, 36.5, 15.7, 14.4. IR (neat) cm\(^{-1}\) 2932, 2858, 1720, 1447, 1209, 1128, 1038, 921. HRMS calculated for \(\text{C}_{15}\text{H}_{23}\text{O}_3\)\(^+\) [M+H]\(^+\) = 251.16417, found 251.16367.
Compound 281-b (112 mg, 0.5 mmol) in THF (1.4 ml) at -78 °C was treated with 
LiHMDS 1.0M in THF (0.6 ml, 0.6 mmol, 1.2 equiv) and stirred for 45 min. Allyl 
bromide (55 µl, 0.64 mmol, 1.3 equiv) was added and the reaction was warmed to 0 
°C for 1 hr. The reaction was quenched with NH₄Cl, extracted with EtOAc, washed 
with H₂O, then sat NaCl, dried over Na₂SO₄, filtered and concentrated to a residue. 
The crude material was purified by silica chromatography eluting with 10:1 
hexane:EtOAc giving the desired product (87 mg, 66%).

¹H NMR (500 MHz, Chloroform-d) δ 5.59 (ddt, J = 17.3, 10.1, 7.3 Hz, 1H), 5.12 to 4.96 
(m, 2H), 4.15 (q, J = 7.1 Hz, 2H), 2.62 (p, J = 6.5 Hz, 2H), 2.34 to 2.24 (m, 4H), 2.02 
(dd, J = 14.2, 8.4 Hz, 2H), 1.91 (ddt, J = 13.1, 9.9, 5.2 Hz, 2H), 1.74 (td, J = 9.8, 3.7 Hz, 
2H), 1.57 to 1.49 (m, 2H), 1.43 (dtd, J = 13.1, 9.7, 9.1, 3.5 Hz, 2H), 1.26 (t, J = 7.1 Hz, 
3H). ¹³C NMR (126 MHz, CDCl₃) δ 218.6, 176.5, 133.5, 118.7, 60.9, 44.8, 44.0, 41.3, 
35.0, 31.0, 25.9, 14.4. IR (neat) cm⁻¹ 2930, 2860, 1716, 1444, 1213, 1138, 1033, 919, 
860, 776. HRMS calculated for C₁₆H₂₅O₃⁺ [M+H]⁺ = 265.17982, found 265.17962.
Compound 281-c (130 mg, 0.58 mmol) in THF (2 ml) at -78 °C was treated with LiHMDS 1.0M in THF (0.7 ml, 0.7 mmol, 1.2 equiv) and stirred for 1 h. Allyl bromide (60 µl, 0.64 mmol, 1.2 equiv) was added and the reaction was warmed to rt after 1 hr. The reaction was quenched with NH₄Cl, extracted with EtOAc, washed with H₂O, then sat NaCl, dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was purified by silica chromatography eluting with 20:1 to 10:1 hexane:EtOAc giving the desired product (52 mg, 34%).

¹H NMR (500 MHz, Chloroform-d) δ 5.57 (dddd, J = 17.2, 10.2, 8.0, 6.5 Hz, 1H), 5.09 to 4.95 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 2.59 (dd, J = 8.8, 3.9 Hz, 1H), 2.54 (d, J = 14.6 Hz, 1H), 2.32 to 2.14 (m, 4H), 2.09 – 1.90 (m, 2H), 1.90 – 1.75 (m, 3H), 1.55 to 1.44 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.05 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 222.8, 175.9, 133.5, 119.1, 60.9, 45.8, 44.2, 44.2, 43.9, 43.5, 41.2, 37.3, 36.3, 26.0, 17.3, 14.4. IR (neat) cm⁻¹ 2926, 2857, 1711, 1451, 1210, 1041, 919, 637. HRMS calculated for C₁₆H₂₅O₃⁺ [M+H]⁺ = 265.17982, found 265.18013.
Compound 281-d (314 mg, 1.32 mmol) in THF (5 ml) at -78 °C was treated with LiHMDS 1.0 M in THF (1.58 ml, 1.58 mmol, 1.2 equiv) and stirred for 1 h. Allyl bromide (150 µl, 1.73 mmol, 1.3 equiv) was added and the reaction was warmed to rt in a dry ice/acetone bath overnight. The reaction was quenched with NH₄Cl, extracted with EtOAc, washed with H₂O, then sat NaCl, dried over Na₂SO₄, filtered and concentrated to a residue. The crude material was purified by silica chromatography eluting with 20:1 to 10:1 hexane:EtOAc giving the desired product (211 mg, 58%).

¹H NMR (500 MHz, Chloroform-d) δ 5.55 (ddt, J = 17.2, 10.1, 7.2 Hz, 1H), 5.04 (d, J = 9.4 Hz, 1H), 5.00 (d, J = 17.0 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 2.49 (d, J = 14.9 Hz, 2H), 2.14 (d, J = 7.2 Hz, 2H), 1.96 (tdd, J = 14.2, 11.2, 6.5 Hz, 1H), 1.89 to 1.79 (m, 4H), 1.47 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.07 (s, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 222.5, 175.9, 133.6, 119.1, 60.9, 45.7, 44.3, 44.1, 41.2, 26.3, 18.7, 14.4. IR (neat) cm⁻¹ 2964, 2850, 1725, 1709, 1452, 1379, 1210, 1161, 1125, 1038, 1000, 918. HRMS calculated for C₁₇H₂₇O₃⁺ [M+H]+ = 279.19547, found 279.19523.
Ozone was bubbled into a solution of compound 2.82-a (276 mg, 1.10 mmol) in DCM (2 ml) and MeOH (2 ml) at -78 °C after the solution turned blue nitrogen was bubbled into the solution until it was colorless. Then dimethylsulfide (1 ml) was added and the reaction was warmed to rt and stirred until the secondary ozonide was consumed. The solution was then concentrated to a residue and dried in vacuo. The desired keto-aldehyde was isolated after purification on silica gel 10:1 to 3:1 hexane:EtOAc as a colorless waxy solid (210 mg, 76%).

\[ ^1 \text{H NMR} (500 \text{ MHz}, \text{Chloroform-d}) \delta 9.62 \text{ (s, 1H)}, 4.15 \text{ (q, } J = 7.1 \text{ Hz, 2H)}, 2.75 \text{ (s, 2H), 2.53 \text{ (d, } J = 9.9 \text{ Hz, 2H), 2.48 \text{ (dd, } J = 14.8, 3.2 \text{ Hz, 2H), 2.31 to 2.21 \text{ (m, 2H), 2.20 to 2.05 \text{ (m, 1H), 1.98 \text{ (d, } J = 12.8 \text{ Hz, 2H), 1.85 \text{ (tt, } J = 13.6, 4.0 \text{ Hz, 2H), 1.51 \text{ (ddt, } J = 14.4, 4.7, 2.4 \text{ Hz, 1H), 1.23 \text{ (t, } J = 7.1 \text{ Hz, 3H).}}}
\]

\[ ^{13} \text{C NMR} (126 \text{ MHz, CDCl}_3) \delta 222.5, 199.2, 175.4, 61.5, 49.1, 42.9, 40.8, 37.6, 36.9, 15.3, 14.2. \text{IR (neat) cm}^{-1} 2932, 2858, 1715, 1454, 1200, 1081, 1023. \text{HRMS calculated for } C_{14}H_{21}O_4^+ [M+H]^+ = 253.14344, \text{found 253.14276.} \]
Compound **2.82-b** (85 mg, 0.322 mmol) was stirred with N-methylmorpholine-N-oxide (87 mg, 0.644 mmol) in DCM (3 ml) at rt. Then osmium tetroxide 4 wt% in water (70 mg, 0.011 mmol, 0.03 equiv) was added and stirred for 2 hr. The reaction was quenched with half-saturated Na$_2$S$_2$O$_3$ then extracted with DCM (3x 2ml). The combined organics were dried over Na$_2$SO$_4$, filtered and condensed to a residue. The resulting orange film was dissolved in DCM (2 ml), then lead (IV) acetate (160 mg, 0.361 mmol) was added and stirred for 45 min. The resulting solution was adsorbed onto silica by rotary evaporation then purified by silica gel chromatography eluting with 3:1 hexane:EtOAc giving the desired aldehyde as pale orange solids (37 mg, 43% 2-steps).

$^1$H NMR (500 MHz, Chloroform-d) $\delta$ 9.65 (s, 1H), 4.16 (q, $J=7.1$ Hz, 2H), 2.73 (s, 2H), 2.65 to 2.56 (m, 2H), 2.50 (dd, $J=14.5, 6.6$ Hz, 2H), 2.05 to 1.96 (m, 2H), 1.96 to 1.89 (m, 2H), 1.82 to 1.69 (m, 2H), 1.60 to 1.50 (m, 2H), 1.49 to 1.38 (m, 2H), 1.24 (t, $J=7.1$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 218.0, 199.4, 176.0, 61.5, 49.5, 45.1, 41.8, 35.7, 30.8, 25.9, 14.2. IR (neat) cm$^{-1}$ 2931, 2861, 1706, 1175, 907, 727. HRMS calculated for C$_{15}$H$_{23}$O$_4$ [M+H]$^+$ = 267.15909, found 267.15943.
Ozone was bubbled into a solution of compound 2.82-c (51 mg, 0.193 mmol) in DCM (1 ml) at -78 °C after the solution turned blue nitrogen was bubbled into the solution until it was colorless. Then dimethylsulfide (1ml) was added and the reaction was warmed to rt, then concentrated to a residue and dried in vacuo. The desired keto-aldehyde was isolated after purification on silica gel 10:1 to 3:1 hexane:EtOAc as a colorless waxy solid (36 mg, 71%).

\(^{1}\)H NMR (500 MHz, Chloroform-d) δ 9.61 (s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 2.72 to 2.58 (m, 4H), 2.43 (dd, J = 14.6, 3.6 Hz, 1H), 2.25 (ddd, J = 14.3, 10.8, 3.2 Hz, 1H), 2.08 (tdd, J = 15.3, 7.5, 2.1 Hz, 1H), 1.95 (apparent d, J = 13.1 Hz, 1H), 1.90 to 1.71 (m, 3H), 1.59 to 1.45 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.02 (d, J = 3.0 Hz, 3H). \(^{13}\)C NMR (126 MHz, CDCl₃) δ 222.6, 199.2, 175.3, 61.5, 48.7, 45.9, 44.7, 44.1, 43.2, 41.3, 37.4, 36.8, 26.1, 17.0, 14.2. IR (neat) cm⁻¹ 2929, 2856, 1711, 1455, 1379, 1207, 1082, 1022. HRMS calculated for C₁₅H₂₃O₄⁺ [M+H]⁺ = 267.15909, found 267.15890 (ESI+).
Ozone was bubbled into a solution of compound 2.82-d (194 mg, 0.697 mmol) in DCM (4 ml) at -78 °C after the solution turned blue nitrogen was bubbled into the solution until it was colorless. Then dimethylsulfide (2 ml) was added and the reaction was warmed to rt, then concentrated to a residue and dried in vacuo. The desired keto-aldehyde was isolated after purification on silica gel 10:1 to 6:1 hexane:EtOAc as a colorless solid (143 mg, 73%).

$^1$H NMR (500 MHz, Chloroform-d) $\delta$ 9.60 (s, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 2.65 (d, $J = 14.4$ Hz, 2H), 2.59 (s, 2H), 2.04 (qt, $J = 13.6$, 4.4 Hz, 1H), 1.84 (d, $J = 13.8$ Hz, 4H), 1.54 (d, $J = 14.5$ Hz, 1H), 1.46 (td, $J = 13.3$, 4.0 Hz, 2H), 1.23 (t, $J = 7.1$ Hz, 3H), 1.05 (s, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 222.6, 199.3, 175.3, 61.4, 48.4, 45.7, 44.5, 44.2, 41.5, 26.4, 18.5, 14.2. IR (neat) cm$^{-1}$ 2991, 2965, 2927, 2855, 1736, 1723, 1700, 1451, 1390, 1333, 1256, 1193, 1158, 1116, 1072, 1028, 963, 885, 767, 624. HRMS calculated for C$_{16}$H$_{25}$O$_4^+$ [M+H]$^+$ = 281.17474, found 281.17469.
Keto-aldehyde 2.83-a (22 mg, 87 µmol) and 2,4,6-trimethylbenzenesulfonyl hydrazide (17.8 mg, 83 µmol) were dissolved in THF (0.5 ml) and stirred for 45 min. Then the solvent was removed by rotary evaporation. The crude material was then dissolved in CDCl₃ and bubbling was observed. The material was analyzed by NMR, then purified on silica gel eluting with 6:1 up to 3:1 hexane:EtOAc. The C-C inserted/skeletal rearranged product was isolated as a colorless oil (15.5 mg, 75%).

¹H NMR (501 MHz, Chloroform-d) δ 4.14 (q, J = 7.1 Hz, 2H), 2.81 to 2.67 (m, 3H), 2.34 to 2.22 (m, 2H), 2.09 (ddd, J = 13.7, 11.5, 2.4 Hz, 1H), 1.96 (d, J = 13.3 Hz, 1H), 1.90 to 1.72 (m, 4H), 1.72 to 1.55 (m, 2H), 1.50 (tdd, J = 12.9, 5.5, 2.7 Hz, 1H), 1.3 to 1.2 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 214.9, 175.9, 60.9, 54.8, 45.1, 40.3, 36.2, 35.3, 33.2, 31.9, 28.1, 19.2, 14.3. IR cm⁻¹ 2923, 2857, 1714, 1448, 1276, 1237, 1183, 1060. HRMS calculated for C₁₄H₂₁O₃⁺ [M+H]⁺ = 237.14852, found 237.14834 (ESI+).
Keto-aldehyde **2.83-b** (17 mg, 64 µmol) and 2,4,6-trimethylbenzenesulfonyl hydrazide (13.7 mg, 83 µmol) were dissolved in THF (0.5 ml) and stirred for 30 min. Then the solvent was removed by rotary evaporation. The crude material was then dissolved in CDCl₃ and analyzed by NMR. The NMR tube with sample was heated to 60 °C for 1 h, then concentrated to a residue and purified on silica gel eluting with 10:1 up to 6:1 hexane:EtOAc. The C-C insertion/skeletal rearranged product was isolated as a colorless oil (10.2 mg, 64%).

**1H NMR** (500 MHz, Chloroform-d) δ 4.15 (q, J = 7.1 Hz, 2H), 2.78 to 2.65 (m, 2H), 2.47 to 2.37 (m, 1H), 2.36 (ddd, J = 13.5, 11.3, 2.0 Hz, 1H), 2.27 (dt, J = 12.3, 3.4 Hz, 1H), 2.17 (dddd, J = 15.0, 11.1, 6.9, 3.7 Hz, 1H), 2.14 to 2.06 (m, 1H), 1.90 (t, J = 13.3 Hz, 2H), 1.84 to 1.79 (m, 3H), 1.73 to 1.63 (m, 3H), 1.62 to 1.54 (m, 1H), 1.42 (dd, J = 19.0, 9.5, 4.6 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H). **13C NMR** (126 MHz, CDCl₃) δ 220.3, 176.4, 60.9, 55.2, 48.7, 42.1, 40.7, 40.0, 39.6, 38.7, 37.5, 28.3, 24.9, 23.5, 14.3. IR cm⁻¹ 2923, 2871, 1723, 1698, 1450, 1230, 1201, 1065, 741. HRMS calculated for C₁₅H₂₃O₅⁺ [M+H]⁺ = 251.16417, found 251.16394 (ESI+).
Keto-aldehyde 2.83-c (10 mg, 38 µmol) and p-toluenesulfonyl hydrazide (7.2 mg, 39 µmol) were dissolved in CDCl₃ (0.5 ml) and stirred for 1.5 h with intermittent analysis by NMR. The NMR tube with sample was heated to 60 °C for 1 h, then concentrated to a residue and purified on silica gel eluting with 10:1 up to 6:1 hexane:EtOAc. The C-C insertion/skeletal rearranged product was isolated as a colorless film (6.0 mg, 64%).

¹H NMR (500 MHz, Chloroform-d) δ 4.15 (q, J = 7.1 Hz, 2H), 2.86 to 2.79 (m, 1H), 2.71 (q, J = 8.4 Hz, 1H), 2.25 (ddd, J = 12.5, 5.9, 3.0 Hz, 1H), 2.10 to 2.00 (m, 2H), 1.95 (apparent t, J = 13.0 Hz, 2H), 1.86 to 1.74 (m, 3H), 1.42 to 1.22 (m, 6H), 1.15 (s, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 215.8, 175.9, 60.9, 54.7, 49.5, 47.0, 43.6, 41.1, 39.7, 36.2, 33.3, 29.9, 29.7, 28.1, 20.0, 14.4. IR (neat) cm⁻¹ 2918, 2850, 1726, 1710, 1448, 1250, 1189, 1068, 1046. HRMS calculated for C₁₅H₂₃O₃⁺ [M+H]⁺ = 251.16417, found 251.16485 (ESI+).
Keto-aldehyde **2.83-d** (13 mg, 46 µmol) and *p*-toluenesulfonyl hydrazide (9.1 mg, 49 µmol) were dissolved in CDCl$_3$ (0.75 ml) and stirred for 30 min and NMR analysis indicated hydrozone formation. The sample was heated to 60 °C for 1h and NMR analysis indicated no significant reaction. The solvent was removed by rotary evaporation. The crude material was then dissolved in toluene-d$_8$ and analyzed by NMR. The NMR tube with sample was heated to 105 °C for 2h, then concentrated to a residue and purified on silica gel eluting with 10:1 hexane:EtOAc. A second silica gel column eluting with 20:1 hexane:EtOAc provided the desired C-C insertion/skeletal rearranged product as a colorless oil (6 mg, 49%).

$^1$H NMR (501 MHz, Chloroform-d) δ 4.15 (q, $J = 7.1$ Hz, 2H), 2.47 to 2.33 (m, 2H), 2.19 (dd, $J = 13.3$, 2.0 Hz, 1H), 2.08 (dd, $J = 14.4$, 2.6 Hz, 1H), 1.91 (dd, $J = 14.4$, 2.0 Hz, 1H), 1.87 to 1.77 (m, 1H), 1.76 (dd, $J = 12.3$, 2.4 Hz, 1H), 1.69 (dd, $J = 13.3$, 2.0 Hz, 1H), 1.60 (m, 2H), 1.49 (dt, $J = 14.8$, 3.5 Hz, 1H), 1.44 to 1.37 (m, 2H), 1.30 (m, 1H), 1.27 (t, $J = 7.1$ Hz, 2H), 1.16 (s, 3H), 1.13 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 216.0, 175.8, 62.3, 60.9, 50.9, 46.8, 44.3, 43.4, 42.3, 39.6, 38.1, 37.7, 33.0, 29.6, 22.0, 14.4. IR (neat) cm$^{-1}$ 2925, 2866, 1725, 1707, 1449, 1377, 1237, 1165, 1071. HRMS calculated for C$_{16}$H$_{25}$O$_3^+$ [M+H]$^+$ = 265.17982, found 265.17988.
LiHMDS 1.0M in THF (6.0 ml, 6.0 mmol) was added to a 0 °C solution of ketal/ester 1.87 (1.087 g, 5.07 mmol) in THF (10 ml). After 5 min, allyl bromide (0.52 ml, 6.0 mmol) was added. After 2 h, the reaction was quenched with NH₄Cl, extracted with EtOAc, washed with H₂O, and then concentrated to a residue. The residue was dissolved in THF (10 ml) and HCl 2N (10 ml) and heated to 40 °C for 45 min. EtOAc was added and the layers were separated. The organic layer was washed with sat NaHCO₃, H₂O, sat NaCl, then dried over Na₂SO₄, filtered and concentrated to a residue. The crude oil was purified by silica chromatography eluting with 10:1 to 6:1 hexane:EtOAc yielding the desired product (0.502 g, 47% over 2-steps).

¹H NMR (500 MHz, Chloroform-d) δ 5.77 to 5.64 (m, 1H), 5.12 to 5.01 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 2.50 to 2.37 (m, 4H), 2.37 to 2.26 (m, 4H), 1.67 (dd, J = 11.7, 5.3 Hz, 2H), 1.28 (t, J = 6.8 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 211.4, 175.0, 132.8, 118.8, 61.0, 46.4, 44.0, 38.5, 33.4, 14.5. IR (neat) cm⁻¹ 2957, 1714, 1442, 1201, 1109, 1024, 918. HRMS calculated for C₁₂H₁₉O₃⁺ [M+H]⁺ = 211.13287, found 233.11482.
Ozone was bubbled into a solution of compound 2.88 (212 mg, 1.01 mmol) in DCM (1 ml) at -78 °C after the solution turned blue, nitrogen was bubbled into the solution until it was colorless. Then dimethylsulfide (1ml) was added and the reaction was warmed to rt, then concentrated to a residue. Due to incomplete reduction of the secondary ozonide, the mixture was dissolved in dimethylsulfide (2 ml), and held for 16 hr. The reaction was then concentrated to a residue. The desired keto-aldehyde was isolated after purification on silica gel 6:1 to 3:1 hexane:EtOAc as a colorless waxy solid (126 mg, 59%).

\[ \text{Compound 2.89} \]

\( ^1H \) NMR (501 MHz, Chloroform-d) \( \delta \) 9.74 (t, \( J = 1.4 \) Hz, 1H), 4.23 (q, \( J = 7.1 \) Hz, 1H), 2.78 (d, \( J = 1.5 \) Hz, 1H), 2.56 (ddd, \( J = 16.3, 11.4, 5.8 \) Hz, 2H), 2.45 (dt, \( J = 10.9, 4.3 \) Hz, 2H), 2.33 (dt, \( J = 15.4, 4.7 \) Hz, 2H), 1.83 to 1.75 (m, 2H), 1.28 (t, \( J = 7.1 \) Hz, 2H). \( ^{13}C \) NMR (126 MHz, CDCl\(_3\)) \( \delta \) 210.2, 199.4, 174.5, 61.6, 51.8, 43.1, 37.9, 33.6, 14.3. IR (neat) cm\(^{-1}\) 2958, 1709, 1192, 1019. HRMS calculated for C\(_{11}\)H\(_{17}\)O\(_4\)Na\(^+\) [M+Na]\(^+\) = 235.09408, found 235.09451.
Keto-aldehyde \textbf{2.89} (9.5 mg, 45 \( \mu \)mol) and \( p \)-toluenesulfonyl hydrazide (8.3 mg, 45 \( \mu \)mol) were dissolved in CDCl\(_3\) (0.7 ml) and stirred for 30 min then the sample was heated to 65 °C for 2h. The solvent was removed by rotary evaporation. The crude material was purified on two silica gel columns eluting with 3:1 to 1:1 hexane:EtOAc giving the azo-compound as a film. (8 mg, 49%).

\( ^1H \) NMR (500 MHz, Chloroform-d) \( \delta \) 7.91 (d, \( J = 8.2 \) Hz, 2H), 7.40 (d, \( J = 8.0 \) Hz, 2H), 5.44(dd, \( J = 10, 7.7 \) Hz, 1H), 4.12 (q, \( J = 7.1 \) Hz, 2H), 3.07 (dd, \( J = 7.1, 4.9 \) Hz, 1H), 2.47 (s, 3H), 2.37 to 2.29 (m, 1H), 2.24 (dd, \( J = 14.8, 8.0 \) Hz, 1H), 2.11 to 2.01 (m, 2H), 1.98 (dd, \( J = 12.8, 4.6 \) Hz, 1H), 1.81 to 1.67 (m, 2H), 1.23 (t, \( J = 7.1 \) Hz, 3H), 0.83 (td, \( J = 14.7, 6.5 \) Hz, 1H). \( ^{13}C \) NMR (126 MHz, CDCl\(_3\)) \( \delta \) 174.7, 145.9, 132.5, 130.5, 129.9, 110.6, 91.3, 61.3, 47.4, 42.0, 37.5, 33.3, 27.1, 22.6, 21.9, 14.3, 14.3. IR (neat) cm\(^{-1}\) 2974, 1725, 1596, 1454, 1322, 1286, 1195, 1151, 1063, 816, 677, 598, 536. HRMS calc for \( C_{18}H_{25}N_2O_4S^+ \) [M+H]\(^+\) = 363.13730, found 363.13730 (ESI+).
Keto-aldehyde **2.90**\(^{27}\) (7 mg, 50 µmol) and \(p\)-toluenesulfonyl hydrazide (9.3 mg, 50 µmol) were dissolved in CDCl\(_3\) (0.7 ml) and stirred for 30 min then the sample was heated to 60 °C for 5h. The solvent was removed by rotary evaporation and the crude material was purified by silica gel chromatography eluting with 6:1 to 3:1 hexane:EtOAc giving the azotricycle as colorless solids. (7.7 mg, 53%).

\(^1\)H NMR (500 MHz, Chloroform-d) \(\delta\) 7.91 (d, \(J = 7.9\) Hz, 2H), 7.38 (d, \(J = 7.7\) Hz, 2H), 5.36 (apparent t, 1H), 2.98 (apparent t, 1H), 2.46 (s, 3H), 2.22 to 2.12 (m, 1H), 2.07 to 1.89 (m, 3H), 1.84 (dt, \(J = 17.2, 8.9\) Hz, 1H), 1.66 (dd, \(J = 14.3, 6.8\) Hz, 1H), 1.60 to 1.50 (m, 2H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 145.6, 132.7, 130.5, 129.8, 111.2, 92.2, 39.0, 37.5, 31.5, 30.1, 24.6, 22.6, 21.9. IR (neat) cm\(^{-1}\) 2944, 1596, 1452, 1317, 1291, 1148, 815, 673, 593, 536. HRMS calc for C\(_{15}\)H\(_{19}\)N\(_2\)O\(_2\)S\(^2\) [M+H]\(^+\) = 291.11617, found 291.11599 (ESI+).
2.7 Spectroscopic Data

$^1$H-NMR of Compound 2.29 (CDCl$_3$)
$^1$H-NMR of Compound 2.30 (CDCl$_3$)
$^1$H-NMR of Compound 2.32 (CDCl$_3$)

![NMR Spectrum](image)

**Molecular Structure**:
- $\text{H}_2\text{CO}_2\text{C}$
- $\text{CO}_2\text{CH}_3$
- $\text{CH}_3$
\textsuperscript{1}H-NMR of Compound 2.35 (CDCl\textsubscript{3})

\textsuperscript{13}C-NMR of Compound 2.35 (CDCl\textsubscript{3})
HSQC NMR of Compound 2.35 (CDCl₃)
$^{1}$H-NMR of Compound 2.36 (CDCl$_3$)

$^{13}$C-NMR of Compound 2.36 (CDCl$_3$)
HSQC NMR of Compound 2.36 (CDCl₃)
$^{1}$H-NMR of Compound **2.40** (CDCl$_3$

\[
\text{[Diagram of 1H-NMR spectrum for Compound 2.40]}\n\]

$^{13}$C-NMR of Compound **2.40** (CDCl$_3$

\[
\text{[Diagram of 13C-NMR spectrum for Compound 2.40]}\n\]
$^1$H-NMR of Compound 2.42 (CDCl$_3$)

$^{13}$C-NMR of Compound 2.42 (CDCl$_3$)
$^{1}$H-NMR of Compound 2.44 (CDCl$_3$)

$^{13}$C-NMR of Compound 2.44 (CDCl$_3$)
HSQC NMR of Compound 2.44 (CDCl3)
$^1$H-NMR of Compound 2.46 (CDCl$_3$)

$^{13}$C-NMR of Compound 2.46 (CDCl$_3$)
$^1$H-NMR of Compound 2.51 (CDCl$_3$)

![1H-NMR Spectrum](image)

$^{13}$C-NMR of Compound 2.51 (CDCl$_3$)

![13C-NMR Spectrum](image)
$^1$H-NMR of Compound 2.52 (CDCl$_3$)

$^{13}$C-NMR of Compound 2.52 (CDCl$_3$)
HSQC NMR of Compound 2.52 (CDCl₃)
$^1$H-NMR of Compound 2.53 (toluene-d$_8$)

$^{13}$C-NMR of Compound 2.53 (toluene-d$_8$)
$^1$H-NMR of Compound 2.55 (toluene-d$_8$)

$^{13}$C-NMR of Compound 2.55 (toluene-d$_8$)
$^1$H-NMR of Compound 2.58 (CDCl$_3$)

$^{13}$C-NMR of Compound 2.58 (CDCl$_3$)
HSQC NMR of Compound 2.58 (CDCl₃)

COSY NMR of Compound 2.58 (CDCl₃)
1H-NMR of Compound 2.72 (CDCl₃)

13C-NMR of Compound 2.72 (CDCl₃)
$^1$H-NMR of Compound **2.73** (CDCl$_3$)

$^{13}$C-NMR of Compound **2.73** (CDCl$_3$)
$^1$H-NMR of Compound 2.74 (CDCl$_3$)

$^{13}$C-NMR of Compound 2.74 (CDCl$_3$)
$^1$H-NMR of Compound 2.75 (CDCl$_3$)

$^{13}$C-NMR of Compound 2.75 (CDCl$_3$)
$^1$H-NMR of Compound 2.76 (CDCl$_3$)

$^{13}$C-NMR of Compound 2.76 (CDCl$_3$)
HSQC NMR of Compound 2.76 (CDCl₃)
$^{1}$H-NMR of Compound 2.77 (CDCl$_3$)

$^{13}$C-NMR of Compound 2.77 (CDCl$_3$)
HSQC NMR of Compound 2.77 (CDCl₃)
$^1$H-NMR of Compound 2.79 (CDCl$_3$)

$^{13}$C-NMR of Compound 2.79 (CDCl$_3$)
HSQC NMR of Compound 2.29 (CDCl₃)

IR of Compound 2.29 (neat)
$^1$H-NMR of Compound 2.81-b (CDCl$_3$)

$^{13}$C-NMR of Compound 2.81-b (CDCl$_3$)
IR of Compound 2.81-b (neat)
$^1$H-NMR of Compound 2.81-c (CDCl₃)

$^{13}$C-NMR of Compound 2.81-c (CDCl₃)
$^1$H-NMR of Compound 2.81-d (CDCl$_3$)

$^{13}$C-NMR of Compound 2.81-d (CDCl$_3$)
$^1$H-NMR of Compound 2.82-a (CDCl$_3$)

$^{13}$C-NMR of Compound 2.82-a (CDCl$_3$)
IR of Compound 2.82-a (neat)
$^1$H-NMR of Compound 2.82-b (CDCl$_3$)

$^{13}$C-NMR of Compound 2.82-b (CDCl$_3$)
IR of Compound **2.82-b** (neat)
$^1$H-NMR of Compound 2.82-c (CDCl$_3$)

$^{13}$C-NMR of Compound 2.82-c (CDCl$_3$)
IR of Compound 2.82-c (neat)
$^1$H-NMR of Compound **2.82-d** (CDCl$_3$)

$^{13}$C-NMR of Compound **2.82-d** (CDCl$_3$)
$^1$H-NMR of Compound 2.83-a (CDCl$_3$)

$^{13}$C-NMR of Compound 2.83-a (CDCl$_3$)
$^1$H-NMR of Compound 2.83-b (CDCl$_3$)

$^{13}$C-NMR of Compound 2.83-b (CDCl$_3$)
$^1$H-NMR of Compound 2.83-c (CDCl$_3$)

$^{13}$C-NMR of Compound 2.83-c (CDCl$_3$)
IR of Compound 2.83-c (neat)
$^1$H-NMR of Compound 2.83-d (CDCl$_3$)

$^{13}$C-NMR of Compound 2.83-d (CDCl$_3$)
$^1$H-NMR of Compound 2.84-a (CDCl$_3$)

$^{13}$C-NMR of Compound 2.84-a (CDCl$_3$)
HSQC NMR of Compound 2.84-a (CDCl$_3$)
$^1$H-NMR of Compound 2.84-b (CDCl$_3$)

$^{13}$C-NMR of Compound 2.84-b (CDCl$_3$)
HSQC NMR of Compound 2.84-b (CDCl₃)
$^1$H-NMR of Compound 2.84-c (CDCl$_3$)

$^{13}$C-NMR of Compound 2.84-c (CDCl$_3$)
IR of Compound 2.84-c (neat)
$^1$H-NMR of Compound 2.84-d (CDCl$_3$)

$^{13}$C-NMR of Compound 2.84-d (CDCl$_3$)
$^1$H-NMR of Compound 2.88 (CDCl$_3$)

$[^{13}$C-NMR of Compound 2.88 (CDCl$_3$)
$^1$H-NMR of Compound 2.89 (CDCl$_3$)

$^{13}$C-NMR of Compound 2.89 (CDCl$_3$)
$^1$H-NMR of Compound 2.91 (CDCl$_3$)

$^{13}$C-NMR of Compound 2.91 (CDCl$_3$)
HSQC NMR of Compound 2.91 (CDCl₃)

COSY NMR of Compound 2.91 (CDCl₃)
IR of Compound 2.91 (neat)
$^1$H-NMR of Compound 2.92 (CDCl$_3$)

$^{13}$C-NMR of Compound 2.92 (CDCl$_3$)
HSQC NMR of Compound 2.92 (CDCl₃)

COSY NMR of Compound 2.92 (CDCl₃)
HMBC NMR of Compound 2.92 (CDCl₃)

IR of Compound 2.92 (neat)
2.9 References


Tiffeneau, M.; Tchoubar, B. Compt. rend. 1937, 205, 1411-1413.


Appendix: X-ray Crystallographic Data for Compound 1.92

Computing details

Program(s) used to solve structure: SHELXS97 (Sheldrick, 1990); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997).

p212121

Crystal data

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<tr>
<th>C_{15}H_{18}N_{2}O_{2}S</th>
<th>V = 1412.87 (11) Å³</th>
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<tr>
<td>? , ?</td>
<td>F(000) = 616</td>
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<td>a = 10.4882 (5) Å</td>
<td>D_α = 1.365 Mg m⁻³</td>
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<td>b = 10.7720 (5) Å</td>
<td>Cu Kα radiation, λ = 1.54178 Å</td>
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<td>c = 12.5056 (5) Å</td>
<td>μ = 2.06 mm⁻¹</td>
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<td>α = 90°</td>
<td>T = 296 K</td>
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<td>β = 90°</td>
<td>××mm</td>
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<td>γ = 90°</td>
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Data collection

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<tr>
<td>10869 measured reflections</td>
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<tr>
<td>2214 independent reflections</td>
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<td>2177 reflections with $I &gt; 2\sigma(I)$</td>
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Refinement

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<th>Hydrogen site location: inferred from neighbouring sites</th>
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<td>Least-squares matrix: full</td>
<td>H atoms treated by a mixture of independent and constrained refinement</td>
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<tr>
<td>$R[F^2 &gt; 2\sigma(F^2)] = 0.026$</td>
<td>$w = 1/[\sigma^2(F_o^2) + (0.0442P)^2 + 0.1176P]$ where $P = (F_o^2 + 2F_c^2)/3$</td>
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<tr>
<td>$wR(F^2) = 0.070$</td>
<td>$(\Delta/\sigma)_{\text{max}} = 1.600$</td>
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<tr>
<td>$S = 1.07$</td>
<td>$\Delta\rho_{\text{max}} = 0.16 \text{ e Å}^{-3}$</td>
</tr>
<tr>
<td>2214 reflections</td>
<td>$\Delta\rho_{\text{min}} = -0.17 \text{ e Å}^{-3}$</td>
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<td>183 parameters</td>
<td>Extinction correction: SHELXL, $Fc^* = kFc[1+0.001xFc^2\lambda^2/\sin(2\theta)]^{1/4}$</td>
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<tr>
<td>0 restraints</td>
<td>Extinction coefficient: 0.0000 (8)</td>
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<td>Secondary atom site location: difference Fourier map</td>
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Special details

**Geometry.** All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

**Refinement.** Refinement of $F^2$ against ALL reflections. The weighted $R$-factor $wR$ and goodness of fit $S$ are based on $F^2$, conventional $R$-factors $R$ are based on $F$, with $F$ set to zero for negative $F^2$. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for
calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on $F^2$ are statistically about twice as large as those based on $F$, and R-factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å$^2$)

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<th>z</th>
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\[
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C11 & -0.18440 (16) & -0.90394 (18) & -0.08178 (15) & 0.0481 (4) \\
H12A & -0.2372 & -0.9494 & -0.1269 & 0.058^* \\
C12 & -0.32114 (17) & -0.71565 (18) & -0.46862 (15) & 0.0492 (4) \\
H13A & -0.3311 & -0.9494 & 0.08178 (15) & 0.0481 (4) \\
C13 & -0.09202 (15) & -0.82620 (15) & -0.12393 (13) & 0.0408 (4) \\
H15A & 0.0286 & -0.7280 & 0.0980 & 0.061^* \\
C15 & -0.19246 (15) & -0.71591 (15) & -0.31435 (13) & 0.0370 (4) \\
\end{array}
\]

Atomic displacement parameters (Å\(^2\))

\[
\begin{array}{ccccccc}
 & U^{11} & U^{22} & U^{33} & U^{12} & U^{13} & U^{23} \\
S & 0.0357 (2) & 0.0458 (2) & 0.0389 (2) & 0.00316 (15) & -0.00150 (16) & -0.00139 (16) \\
O1 & 0.0579 (7) & 0.0463 (7) & 0.0515 (7) & 0.0083 (5) & -0.0040 (6) & -0.0064 (5) \\
O2 & 0.0355 (6) & 0.0695 (8) & 0.0479 (7) & -0.0006 (6) & 0.0013 (5) & 0.0007 (6) \\
N1 & 0.0376 (7) & 0.0485 (8) & 0.0457 (8) & -0.0019 (6) & -0.0006 (6) & 0.0011 (6) \\
N2 & 0.0433 (7) & 0.0524 (8) & 0.0567 (9) & -0.0056 (7) & -0.0075 (7) & -0.0009 (7) \\
C1 & 0.0592 (11) & 0.0596 (11) & 0.0576 (12) & 0.0012 (9) & -0.0163 (9) & 0.0072 (10) \\
C2 & 0.0565 (11) & 0.0429 (9) & 0.0699 (13) & 0.0059 (9) & -0.0106 (9) & -0.0097 (9) \\
C3 & 0.0568 (10) & 0.0583 (11) & 0.0548 (11) & -0.0071 (9) & 0.0035 (9) & 0.0103 (10) \\
C4 & 0.0454 (9) & 0.0541 (10) & 0.0479 (10) & -0.0042 (8) & -0.0032 (8) & 0.0110 (8) \\
C5 & 0.0654 (12) & 0.0818 (14) & 0.0475 (12) & -0.0015 (11) & -0.0021 (9) & 0.0077 (10) \\
C6 & 0.0610 (11) & 0.0446 (10) & 0.0619 (12) & -0.0010 (9) & -0.0090 (9) & 0.0111 (9) \\
C7 & 0.0409 (8) & 0.0551 (11) & 0.0453 (10) & -0.0077 (7) & -0.0025 (7) & 0.0032 (8) \\
C8 & 0.0507 (9) & 0.0460 (9) & 0.0499 (10) & 0.0025 (7) & -0.0093 (8) & -0.0109 (9) \\
C9 & 0.0454 (9) & 0.0509 (10) & 0.0448 (10) & 0.0077 (8) & -0.0045 (8) & 0.0063 (8) \\
C10 & 0.0454 (9) & 0.0468 (10) & 0.0374 (9) & -0.0005 (7) & 0.0006 (7) & -0.0004 (7) \\
C11 & 0.0441 (9) & 0.0511 (10) & 0.0491 (10) & -0.0075 (8) & -0.0086 (8) & 0.0048 (8) \\
C12 & 0.0531 (10) & 0.0540 (10) & 0.0403 (9) & -0.0032 (8) & -0.0129 (8) & -0.0022 (8) \\
C13 & 0.0373 (8) & 0.0447 (8) & 0.0403 (9) & 0.0037 (7) & -0.0044 (7) & 0.0036 (7) \\
C14 & 0.0468 (9) & 0.0608 (11) & 0.0456 (10) & -0.0049 (8) & -0.0091 (8) & -0.0029 (8) \\
C15 & 0.0348 (8) & 0.0399 (8) & 0.0364 (8) & -0.0017 (7) & -0.0032 (6) & -0.0007 (7) \\
\end{array}
\]

Geometric parameters (Å, °)

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S—O1 & 1.4316 (13) & C3—C6 & 1.523 (3) \\
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\]
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<th>Distance (Å)</th>
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