Chapter 2

Development of a Synthetic Strategy for Ent-Kauranoid Natural Products: Total Synthesis of (–)-Maoecrystal Z[†]

2.1 INTRODUCTION

Maoecrystal Z, isolated in 2006 by Han *et al.*,[1] is one of the most highly modified naturally occurring *ent*-kauranoids obtained from *Isodon* plants. Its compact and densely functionalized tetracyclic ring system comprises six vicinal stereogenic centers, including two all-carbon quaternary centers. Similar to many *Isodon* diterpenoids, maoecrystal Z possesses a central, spiro-fused lactone as well as an α,β-unsaturated carbonyl, a pharmacophore present in other bioactive *ent*-kauranoid natural products. Cognizant of this structural homology, we sought to develop a unified strategy that would enable access to maoecrystal Z and other distinct *ent*-kauranoid architectures. The development and execution of the first stage in our synthetic plan is discussed in detail below.

[†] Portions of this chapter were reproduced from the following communication: Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 14964. The research discussed was completed in collaboration with Jacob Y. Cha, a postdoctoral researcher in the Reisman Laboratory.

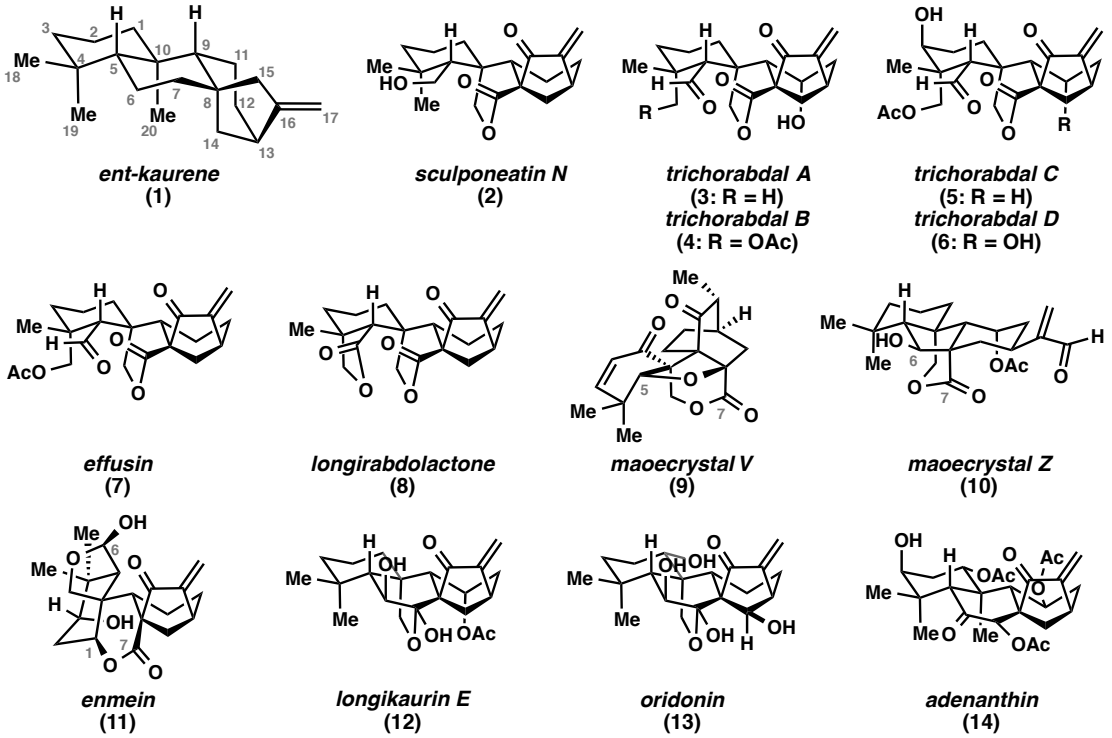


Figure 2.1. *Ent*-kaurene and selected *Isodon* diterpenoids.

2.1.1 Structure and Synthetic Challenges

The 6,7-*seco*-*ent*-kauranoids number approximately 100 out of more than 600 diterpenoids isolated from *Isodon* plants in a century of study (see Figure 2.1).[2,3] Natural products with this characteristic polycyclic framework are believed to arise through C6–C7 oxidative cleavage of a derivative of *ent*-kaurene (**1**),[4] and their structures can be further categorized into two subclasses: spiro-lactone type (7,20-lactone type, *e.g.*, **2**–**10**) and enmein type (1,7-lactone type, see **11**).[3g–i,5] Although the rearranged spiro-lactone framework of maoecrystal Z (**10**) is unique among naturally occurring diterpenoids, this ring system was previously observed during the course of isolation studies on a more representative 6,7-*seco*-*ent*-kauranoid, trichorabdal B (**4**). In a 1981 communication, Fujita and coworkers describe the treatment of **4** with dilute sodium hydroxide in

methanol, which effects a skeletal rearrangement to methyl ester **92** (see Figure 2.2), an oxidized congener of **10**.[3c] The authors proposed a mechanism of methoxide-promoted retro-Dieckmann fragmentation and subsequent aldol ring closure; a similar pathway is likely the origin of **10**.[1]

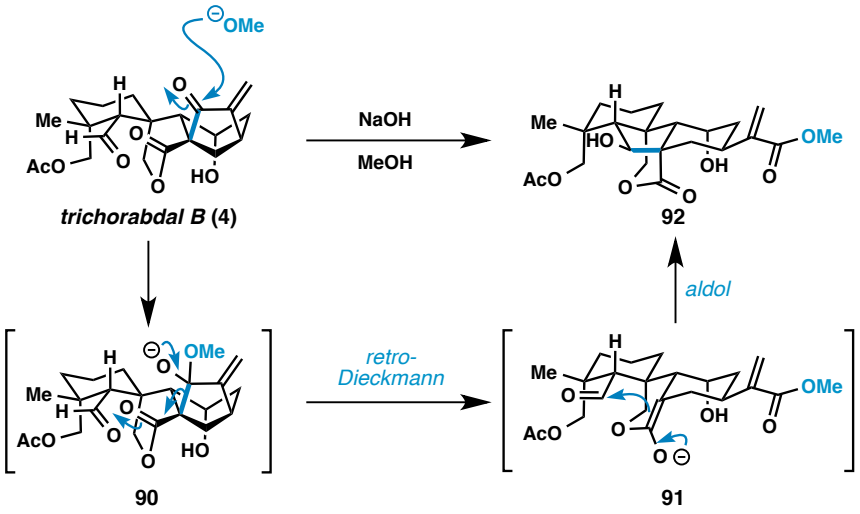


Figure 2.2. Retro-Dieckmann/aldol sequence observed by Fujita.

A principal challenge in the synthesis of maoecrystal Z (**10**) and other spiro-lactone type 6,7-*seco*-*ent*-kauranoids lies in the congested nature of the multiple vicinal stereocenters about the spiro ring junction at C10. In particular, **10** possesses two stereogenic quaternary carbons among six vicinal stereocenters adjacent to yet a third quaternary carbon. The high level of difficulty in constructing such compact, stereochemically complex architectures is evident in both recent efforts toward (±)-maoecrystal V (**9**)[6] and the few prior studies on other 6,7-*seco*-*ent*-kauranoids,[7] as discussed in the preceding chapter. Consequently, these frameworks remain formidable targets in asymmetric total synthesis.

2.1.2 Biological Activity

The known biological activities of *Isodon* diterpenoids[2] include highly selective anti-inflammatory,[8] anticancer[3f,9] and antibacterial properties.[10] Maoecrystal Z (**10**) has shown modest cytotoxicity against multiple human tumor cell lines (K562 leukemia, MCF-7 breast, and A2780 ovarian);[1] however, little is known of its molecular targets or mode of action. In contrast, the *ent*-kauranoid oridonin (**13**) has been found to act as a potent noncompetitive inhibitor of NF-κB transcriptional activity via a novel mechanism.[8] Additionally, a recent study has revealed that adenanthin (**14**) selectively inhibits two isoforms of the peroxiredoxin enzymes and also displays in vivo activity in a murine model of acute promyelocytic leukemia,[9b] suggesting that the cytotoxicity of **14** and other *ent*-kauranoids may occur by a unique target-selective mechanism. A unified strategy to access the *ent*-kauranoids maoecrystal Z (**10**), trichorabdal A (**3**) and longikaurin E (**12**) could potentially be applied to the preparation of synthetic derivatives of **12**–**14** to enable more thorough mode of action studies. Thus, an initial synthetic route toward **10** was an appealing goal.

2.1.3 Synthetic Approach

In our initial synthetic planning, we conceived of two principal retrosynthetic disconnections for the formation of the C and D rings of **10** (see Figure 2.3). Firstly, we envisioned that the five-membered C ring and the C8 all-carbon quaternary stereocenter could be constructed via an intramolecular aldol cyclization, a strategic decision guided in part by Fujita's studies on **4**,[3c] (Figure 2.2) which suggest that a precursor such as **93** would likely undergo an aldol cyclization under mild conditions to form the C ring of **10**.

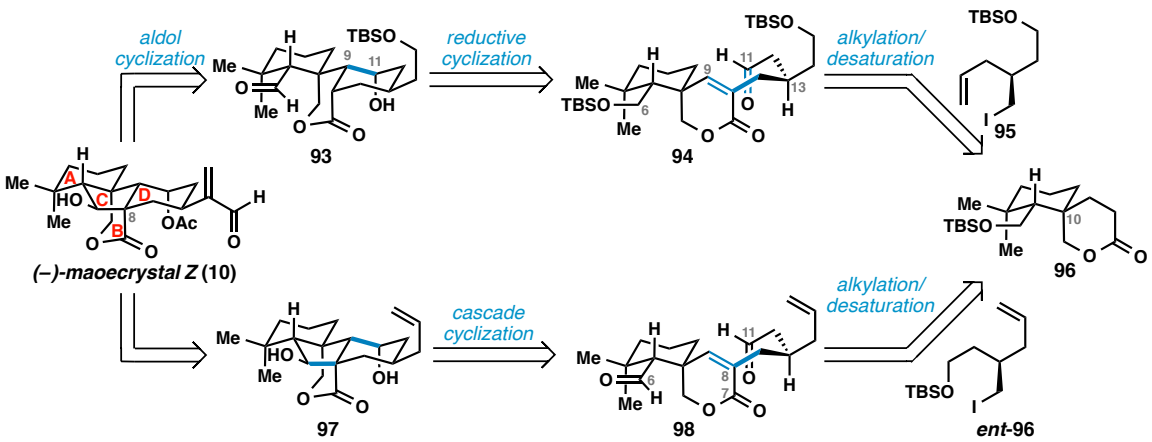


Figure 2.3. Retrosynthetic analysis for maoecrystal Z.

Secondly, it was anticipated that the six-membered D ring could be prepared from an aldehyde-enoate (*e.g.*, **94**) by a Sm-mediated ketyl-olefin reductive cyclization.[11] We hypothesized that C–C bond formation would proceed by addition of the C11 ketyl radical to the more sterically accessible enoate face, opposite to C6, which is further reinforced by the equatorially disposed siloxyethyl group of the C13 stereocenter (see **94**). Whereas this stereochemical preference was expected to result in the correct configuration at C9, the corresponding C11 alcohol configuration was difficult to predict based on conformational analysis alone. Aldehyde **94** could be convergently prepared from spirolactone **96** and alkyl iodide **95** via sequential alkylation, desaturation, and ozonolysis.

Alternate to the stepwise sequence outlined above, we recognized that it might be possible to execute both cyclizations as part of a single tandem cascade process. Recent studies by Procter and colleagues[12] have demonstrated the utility of SmI_2 for the reductive cascade cyclizations of dialdehyde substrates in order to rapidly construct polycyclic frameworks, as exemplified by their recent total synthesis of (+)-pleuromutilin.[13] In this regard, maoecrystal Z could be simplified to diol **97**, which we

hypothesized could arise from dialdehyde **98** via such a cascade. We anticipated that ketyl radical formation at the C6 aldehyde would be kinetically disfavored due to the steric encumbrance imposed by two adjacent quaternary centers; therefore, enoate addition of the C11 ketyl with desired facial selectivity (vide supra) was expected to provide the D ring. Subsequently, a second single-electron reduction would afford the C7–C8 enolate, poised to undergo aldol cyclization in accord with the precedent of Fujita's isolation studies. If the issues of chemo- and diastereoselectivity prove tractable, the proposed cascade cyclization would rapidly increase structural complexity, building two new rings and diastereoselectively setting four new stereogenic centers in a single step. Conveniently, substrates for both the stepwise and cascade approaches can be readily accessed from spirolactone **96** and either enantiomer of alkyl iodide **95**. We also expected that spirolactone **96**, possessing the C10 spirocyclic quaternary center present in many bioactive *ent*-kauranoids, would serve as a valuable synthon for efforts toward trichorabdal A (**3**) and longikaurin E (**12**) as part of a unified strategy (Figure 2.4).

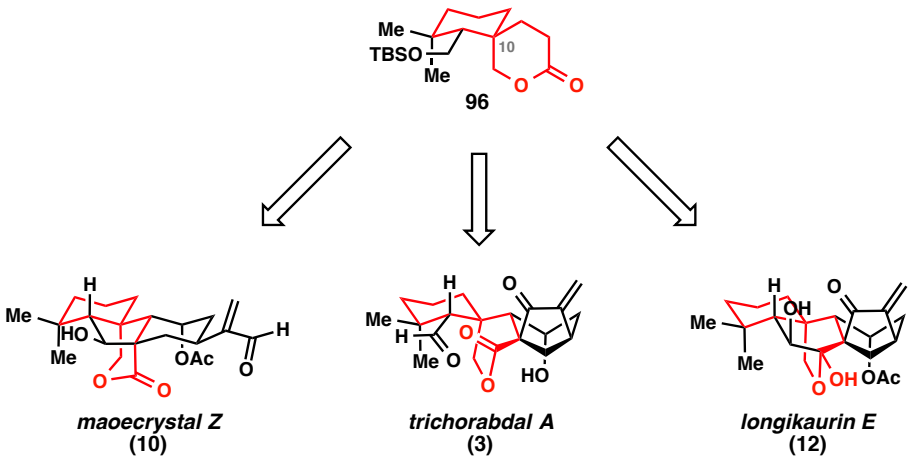


Figure 2.4. A unified strategy for *ent*-kauranoid total synthesis.

2.2 FORWARD SYNTHETIC EFFORTS

The following section describes the varied strategies explored, reactions examined, and experiments conducted in order to achieve the total synthesis of (–)-maoecrystal Z.[14]

2.2.1 Synthesis of a Common Spirolactone

In the forward sense, our initial objectives were to prepare spirolactone **96** and set the central C10 quaternary stereocenter. A known synthetic sequence employing a classical resolution with (*R*)-(–)-*α*-methylbenzylamine (**103**) was used to prepare (–)-*γ*-cyclogeraniol (**104**, Figure 2.5).[15] Protection of **104** as the *tert*-butyldimethylsilyl (TBS) ether, followed by exposure to *m*-chloroperoxybenzoic acid (*m*-CPBA) afforded epoxide **106** as a 3:1 mixture of diastereomers. Treatment of a mixture of **106** and methyl acrylate with Gansäuer's modified conditions[16] (Table 2.1, entry 1) for the radical epoxide-olefin coupling developed by Nugent and RajanBabu[17] resulted in formation of spirolactone **96** in 28% yield. Although the yield was modest, we were delighted to find that lactone **96** was diastereomerically pure and possessed the desired stereochemical configuration at C10, as confirmed by single crystal X-ray diffraction of desilylated lactone **109** (see Figure 2.6). The major side product isolated under unoptimized conditions was allylic alcohol **108**, potentially arising from epoxide **106** via Lewis acid-promoted rearrangement or a Ti^{III}-mediated radical disproportionation process.[18]

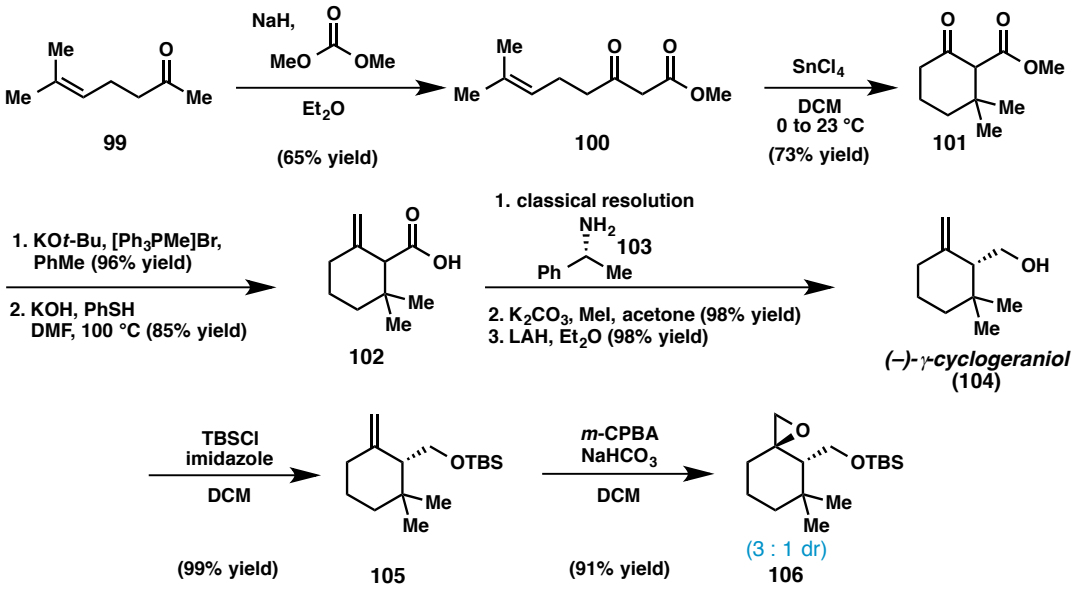
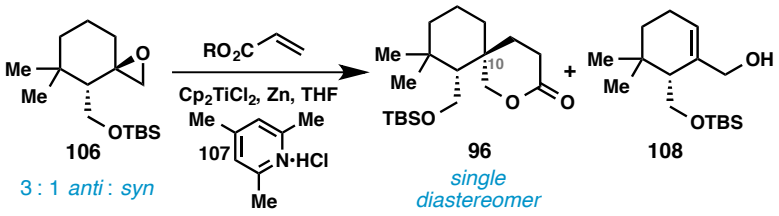


Figure 2.5. Synthesis of epoxide **106**.

Encouraged by this result, we began a survey of reaction parameters in order to obtain more synthetically useful quantities of **96**. Use of a large excess (10 equiv) of methyl acrylate and a full stoichiometric quantity of Cp_2TiCl_2 furnished **96** in 35% yield (Table 2.1, entry 2); further modest increases were realized using portionwise addition protocols for Cp_2TiCl_2 (entries 3–5). Combining a portionwise addition protocol with a more electrophilic coupling partner, 2,2,2-trifluoroethyl acrylate, enabled the isolation of lactone **96** in 76% yield (entry 6). Additionally, we were pleased to observe only a slight decrease to 74% yield when 5 equiv acrylate were used (entry 7). Under the optimized conditions, formation of allylic alcohol side product **108** was minimal. We conjecture that the poor yields observed when using methyl acrylate are due to the slow release of methanol into the reaction mixture during lactonization, resulting in coordination and inhibition of the titanium center. This effect is reduced through use of 2,2,2-trifluoroethyl acrylate and the corresponding release of more weakly coordinating trifluoroethanol.



entry	R (equiv)	Cp_2TiCl_2 equiv	Zn equiv	2,4,6-collidine•HCl (107) equiv	Yield 96 (%)[a]
1	CH_3 (3.0)	0.5	2.0	2.5	28
2	CH_3 (10.0)	2.0	3.0	5.0	35
3	CH_3 (10.0)	2.0[b]	3.0	3.0	44
4	CH_3 (10.0)	1.6[c]	3.0	3.0	61
5	CH_3 (10.0)	1.6[c]	1.5	3.0	58
6	CH_2CF_3 (10.0)	1.6[c]	1.5	3.0	76
7	CH_2CF_3 (5.0)	1.6[c]	1.5	3.0	74
8	CH_2CF_3 (3.0)	1.6[c]	1.5	3.0	62

[a]Isolated yield. [b]Added in two 1.0 equiv portions every 12 h. [c]Added in 0.2 equiv portions over 24 h.

Table 2.1. Optimization of the synthesis of spirolactone **96**.

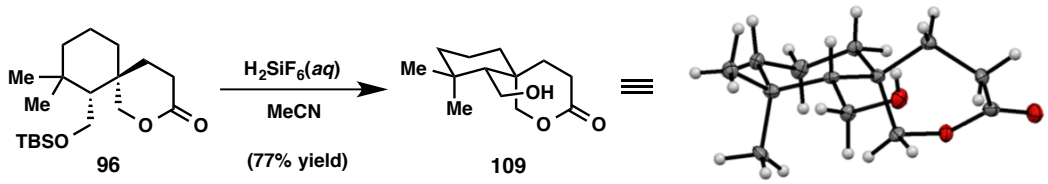


Figure 2.6. Stereochemical confirmation of spirolactone **96**.

As expected, chromatographic separation of *anti*- and *syn*-**106** and independent subjection of each to the optimized reductive coupling conditions furnished lactone **96** as a single diastereomer in 75% and 68% yield, respectively, supporting the intermediacy of radical **110** (Figure 2.7). The major diastereomer (*anti*-**106**) was also found to be consumed more quickly: when a reaction employing a 2.3:1 *anti/syn* mixture of **106** was run to 56% conversion, unreacted **106** was recovered as a 1.3:1 mixture. The high diastereoselectivity observed for this transformation is proposed to derive from approach of the acrylate partner *syn* to the C5 proton of **110**, minimizing nonbonding interactions with the adjacent siloxy and axial methyl substituents. With the initial all-carbon

quaternary stereocenter set and gram quantities of key lactone **96** in hand, we were poised to investigate its elaboration to maoecrystal Z (**10**).

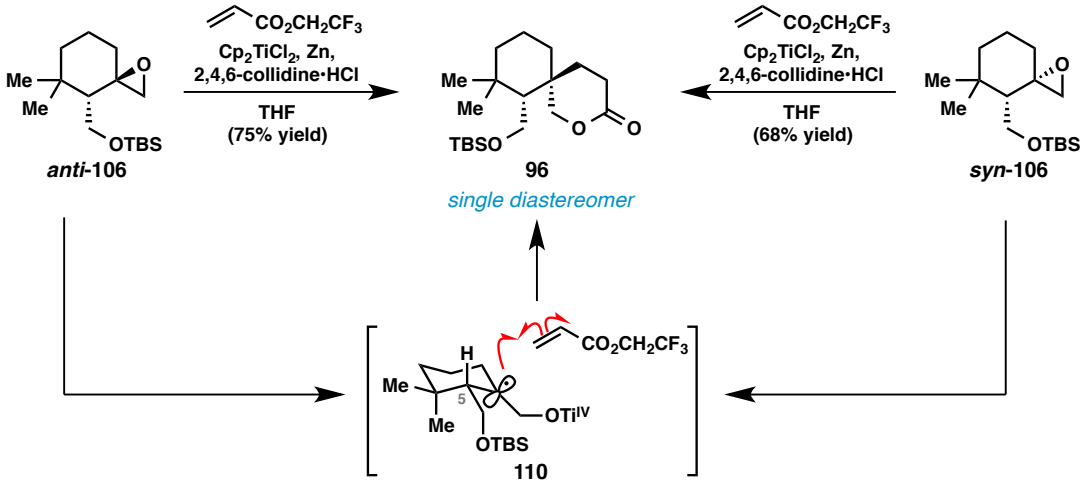


Figure 2.7. Control experiments demonstrate epoxide coupling is stereoconvergent.

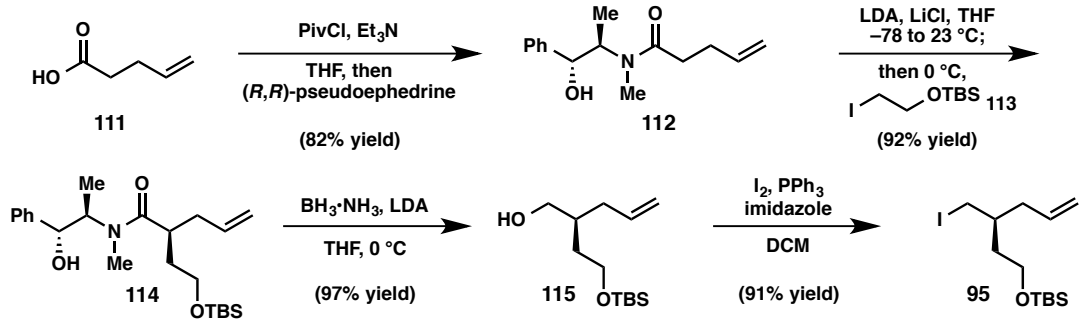


Figure 2.8. Synthesis of chiral alkyl iodide **95** via Myers alkylation protocol.

2.2.2 Pursuit of a Stepwise Cyclization

Though our ultimate ambition was to employ a Sm^{II}-mediated dialdehyde cascade cyclization to access the core of **10**, we elected to first pursue a stepwise route in order to investigate the efficiency and selectivity of each ring-forming step in isolation. Toward this end, alkyl iodide **95** was prepared according to Myers's asymmetric alkylation protocol.[19] Pent-4-enoic acid (**111**) was converted to pseudoephedrine amide **112**, which was alkylated with *tert*-butyl(2-iodoethoxy)dimethylsilane (**113**) to furnish amide **114** in

92% yield and >20:1 dr (Figure 2.8). Reductive cleavage of the auxiliary using lithium amidoborane provided the primary alcohol (**115**), readily converted to enantioenriched alkyl iodide **95** following treatment with iodine and triphenylphosphine.

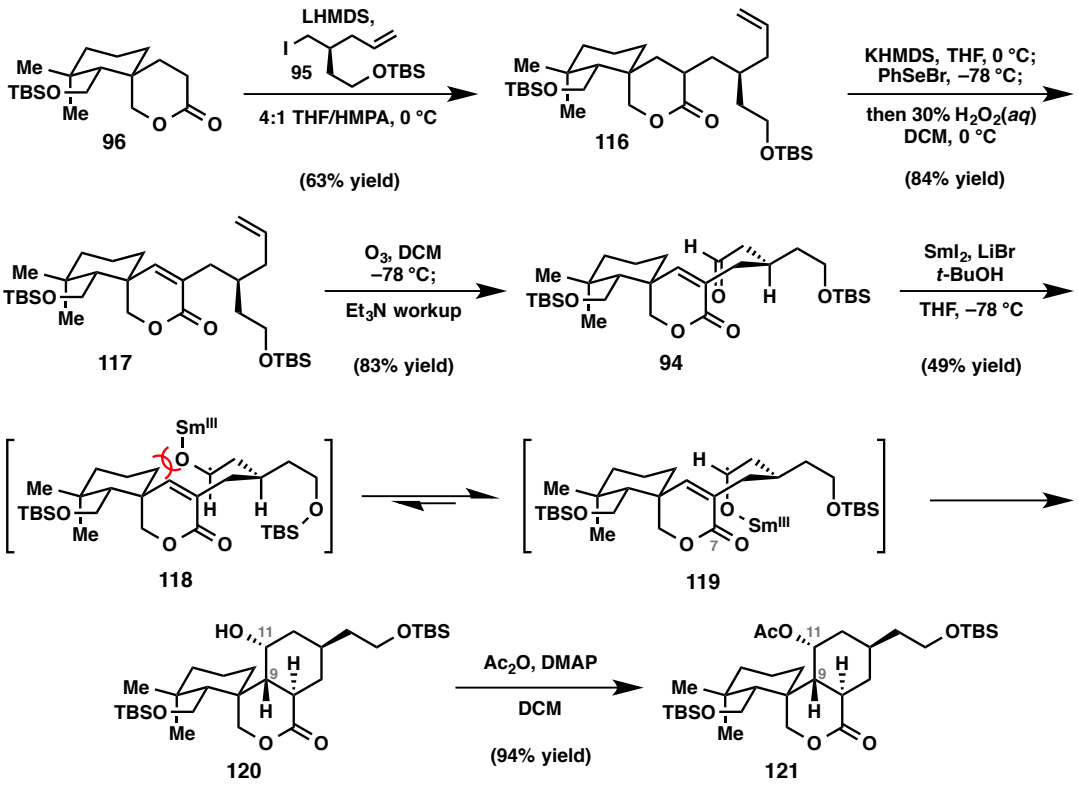


Figure 2.9. Synthesis and Sm^{II}-mediated reductive cyclization of aldehyde **94**.

Moving forward, alkylation of lactone **96** with iodide **95** proceeded upon treatment with lithium LHMDS to afford **116** in 63% yield as an inconsequential mixture of diastereomers (see Figure 2.9). The requisite desaturation of **116** was accomplished by deprotonation with KHMDS and phenylselenation at low temperature, followed by oxidation of the phenyl selenide and elimination. Alternative methods for installing the *α,β*-unsaturation, including the Saegusa–Ito protocol, [20] IBX, [21] and *N-tert*-butylphenylsulfinimidoyl chloride[22] were found to be ineffective. The terminal olefin of **117** was chemoselectively ozonolyzed to afford aldehyde **94**, the targeted ketyl-olefin

cyclization precursor.

Initial attempts to prepare tricycle **120** using SmI_2 in THF at 0 °C effected rapid decomposition of **94**, with only traces of the desired product observed by NMR analysis of the crude reaction mixture. Studies by Procter and others have demonstrated that the use of additives, especially lithium halide salts, can have dramatic effects on the outcome of reactions employing SmI_2.[23] A survey of reaction parameters revealed that the addition of LiCl or LiBr was critical for the desired reactivity. Using a tenfold excess of LiBr relative to SmI_2 and 1 equiv *tert*-butanol (*t*-BuOH) as a proton source, secondary alcohol **120** was obtained in 49% yield. Following treatment with acetic anhydride and 4-dimethylaminopyridine (DMAP), stereochemical analysis of acetate **121** by 1- and 2-D NMR techniques revealed that the configurations of the C9 and C11 stereocenters were correct for elaboration to **10** and other *ent*-kauranoids. The high selectivity for this diastereomer is proposed to result from reaction via ketyl conformation **119**. Whereas conformation **118** is destabilized by the nonbonding interaction between the Sm-ketyl and A-ring methylene, the sp^2 hybridization of C7 appears to alleviate potentially unfavorable 1,3-diaxial interactions present in conformation **119**.

Successful construction of tricycle **120** confirmed the viability of a Sm^{II}-mediated reductive cyclization as the first step in the proposed cascade. In principle, enal installation and aldol cyclization would complete the synthesis of **10**; we therefore continued to advance **121** in order to examine the requisite aldol step. Desilylation with fluorosilicic acid followed by Dess–Martin oxidation[24] furnished dialdehyde **123** (Figure 2.10). Methylenation was accomplished using Eschenmoser's salt[25] and triethylamine to yield enal **124**, isomeric to maoecrystal Z (**10**) and lacking only the C8–C6 bond.

Unfortunately, considerable experimentation with a variety of acids and bases in order to effect an intramolecular aldol cyclization did not furnish detectable quantities of **10**. NMR analysis of the crude reaction mixtures suggested that **124** had suffered undesired transesterifications or skeletal rearrangements due to competitive aldehyde enolization. Moreover, it was suspected that non-productive reactions of the enal of **124** were giving rise to additional side products. In order to more effectively probe the aldol reactivity, we chose to prepare a less functionalized aldehyde substrate.

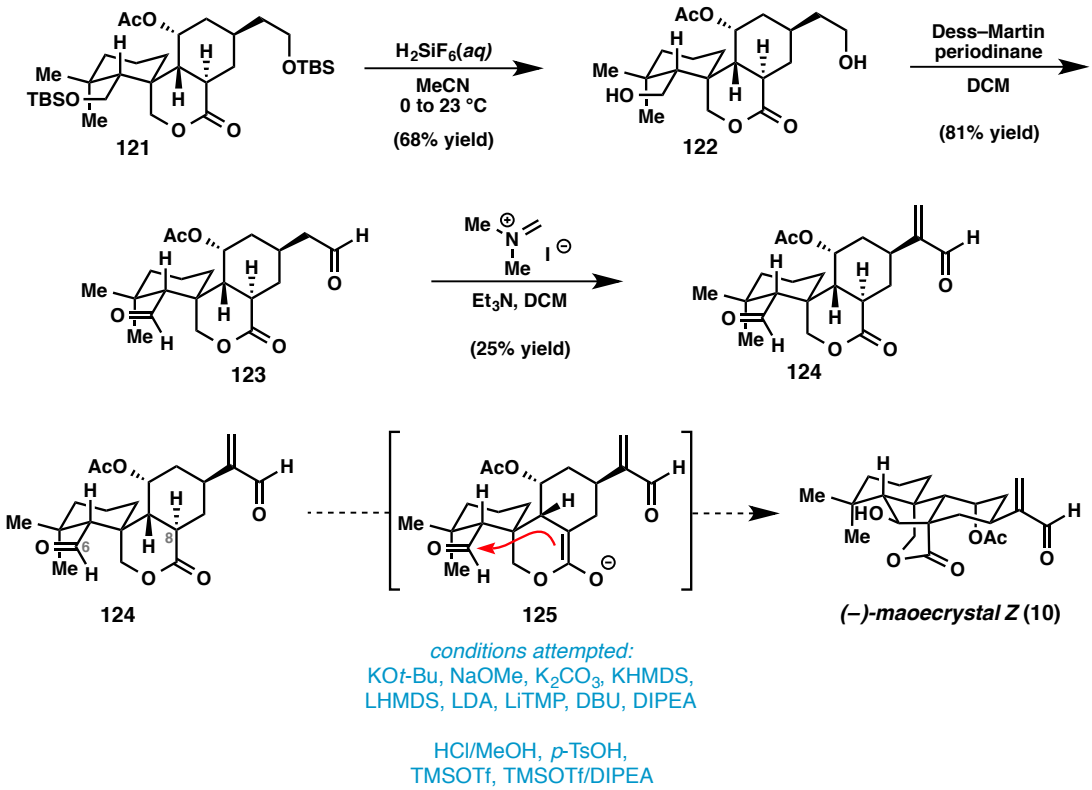


Figure 2.10. Initial efforts toward an aldol cyclization.

For this purpose, diol **122** could be selectively monosilylated using TBSCl and imidazole. TBS ether **126** was then oxidized using Dess–Martin periodinane to furnish an aldol substrate (**127**) lacking the reactive enal motif (Figure 2.11). The stereochemical configuration of this aldehyde was confirmed by single crystal X-ray diffraction. Once

again, the desired aldol cyclization (**127** to **129**) was not observed, and similar rearrangement products as observed with dial **124** were detected. The predominant reactivity pathway resulting from treatment of **127** with KHMDS at –78 °C is proposed to be aldehyde enolization resulting in skeletal rearrangement to hemiacetal **131** by the mechanism shown in Figure 2.11.[26]

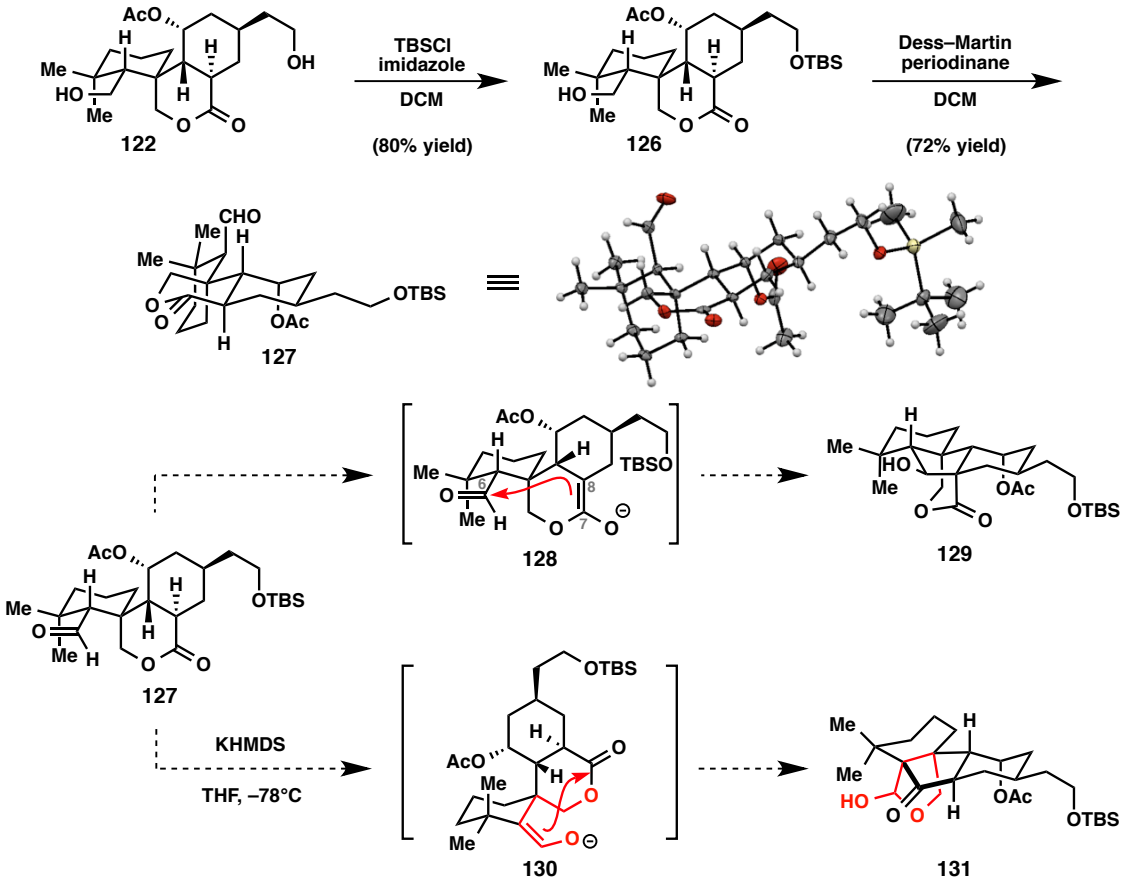


Figure 2.11. Synthesis and undesired reactivity of simplified aldol substrate **127**.

2.2.3 Synthesis of (–)-Maoecrystal Z via Cascade Cyclization

Although our continued inability to conjoin C6 and C8 was somewhat disheartening, it was recognized that the issue of enolization site selectivity is obviated in the proposed reductive cascade cyclization. We therefore turned our attention to the synthesis of a

dialdehyde cyclization substrate. Alkyl iodide *ent*-**95** was prepared from the analogous (*S*,*S*)-pseudoephedrine amide and coupled to lactone **96** as before (see Figure 2.12). Phenylselenation and selenoxide elimination followed by global desilylation and Dess–Martin oxidation furnished dialdehyde **98** in good overall yield. Thus, we were poised to investigate the crucial dialdehyde cyclization cascade.

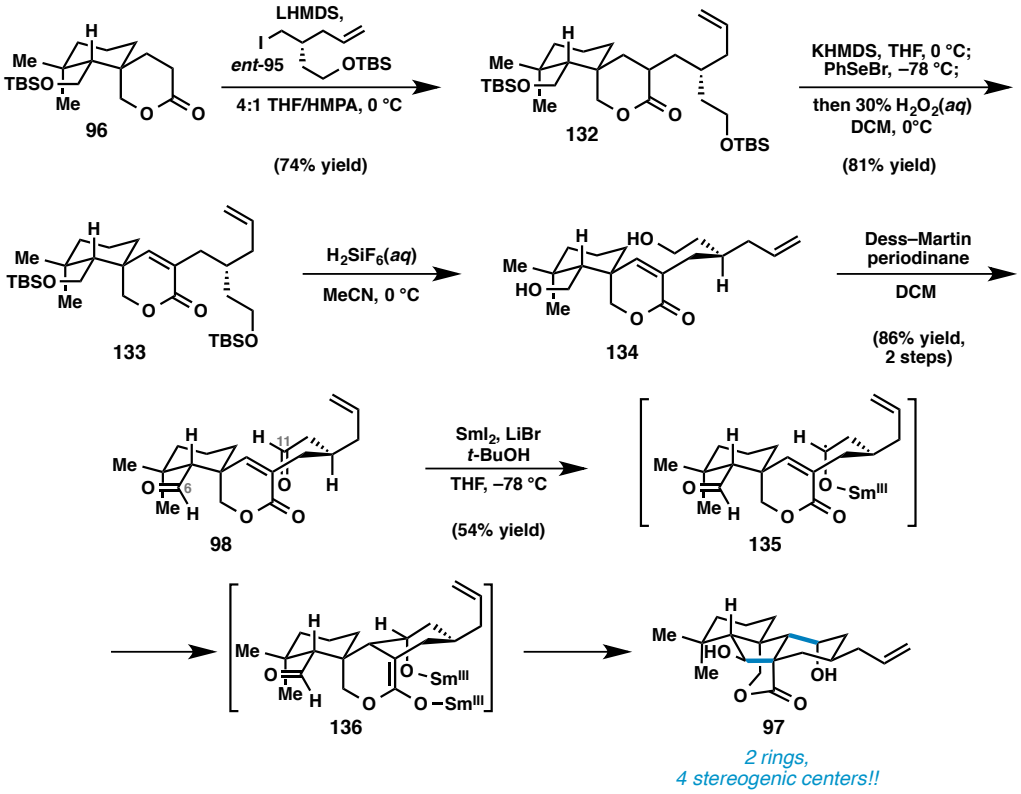


Figure 2.12. Synthesis and reductive cascade cyclization of aldehyde **98**.

In the event, treatment of **98** with SmI_2 and LiBr in the presence of *t*-BuOH at –78 °C provided tetracyclic diol **97** in 54% yield *as a single diastereomer*. Indeed, C11 ketyl radical cyclization occurs with excellent chemoselectivity and stereocontrol to form putative Sm^{III} enolate **136** following a second single electron reduction. Enolate **136** then undergoes aldol cyclization with the proximal C6 aldehyde to forge the second all-carbon quaternary stereocenter and the complete carbon skeleton of maoecrystal Z. Importantly,

all four new stereocenters possess the correct configuration for advancement to the natural product, as determined by thorough 1- and 2-D NMR analysis. In addition to the steric congestion about C6 imposed by two quaternary centers, a second explanation for the observed chemoselectivity lies in the proposed reversibility of Sm-ketyl formation from aldehydes.[23d] Though both ketyls may form, a thermodynamically favorable 6-*endo*-cyclization by the C11-ketyl (as opposed to a reversible 4-*exo*-cyclization of the C6-ketyl), followed by a second, irreversible single-electron reduction to give the Sm^{III} enolate would result in funneling of intermediates to diol **97** via aldol cyclization. The major side product of this transformation appeared to be the tricycle resulting from ketyl-olefin cyclization followed by enolate protonation.

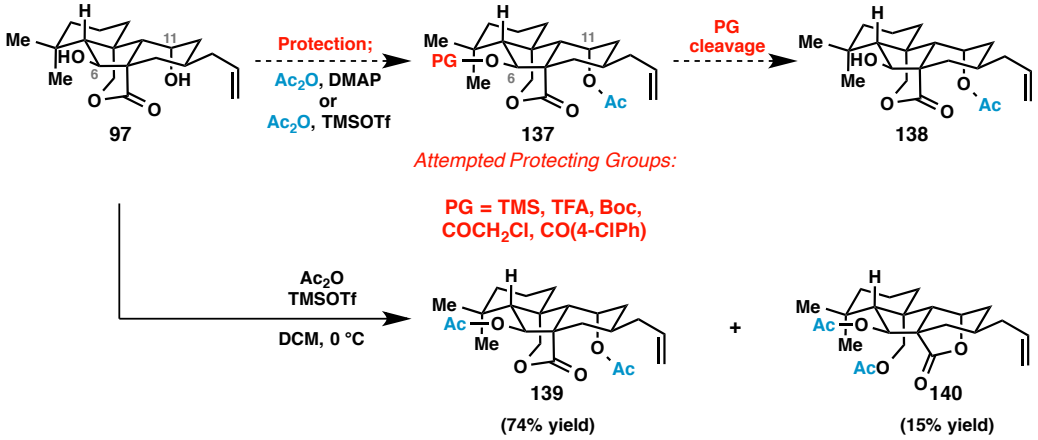


Figure 2.13. Efforts toward the acetylation of diol **97**.

With access to the core, completion of the synthesis of **10** necessitated acetylation of the C11 carbinol (see Figure 2.13) and enal installation. Unfortunately, treatment of diol **97** with acetic anhydride and DMAP effected acetylation of only the C6 carbinol, and more forcing conditions provided low yields of bis-acetate **139** and significant quantities of translactonization product **140**. Thus, several protecting groups were evaluated for a sequential protection/acetylation/deprotection scheme (see **137**, Figure 2.13). However,

use of these groups did not prove fruitful, frequently resulting in increased levels of rearrangement, low yields of **137**, or poor selectivity during protecting group removal, and often in complex mixtures. We were *in no case* able to achieve serviceable yields of **138** over the desired sequence.

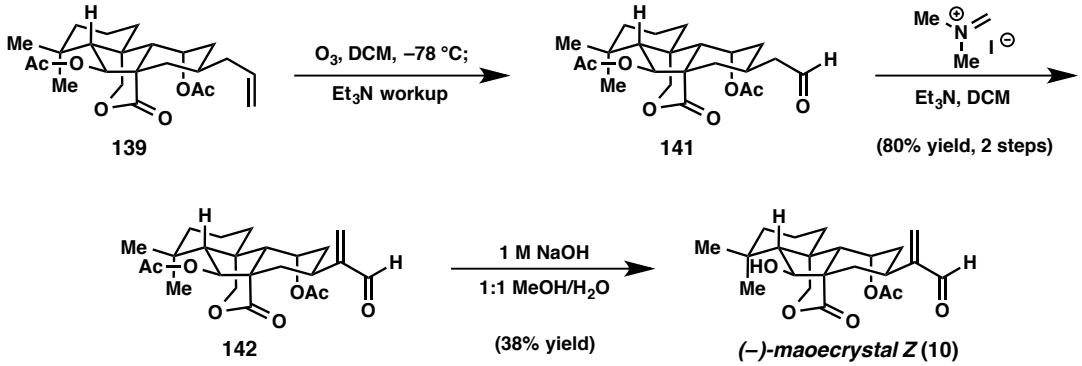


Figure 2.14. Completion of the synthesis of (–)-maoecrystal Z.

After numerous attempts to realize a selective C11 monoacetylation, we opted to advance bis-acetate **139** toward the natural product. Bis-acetylation was accomplished smoothly using Ac_2O and TMSOTf. Ozonolysis of **139** (see Figure 2.14), followed by Eschenmoser methylenation of the resulting aldehyde (**141**) provided acetyl-maoecrystal Z (**142**). A survey of conditions (Table 2.2) revealed that removal of the unneeded C6 acetate was best accomplished using sodium hydroxide in aqueous methanol, providing (–)-maoecrystal Z in 38% yield (12 steps and 4.3% overall from **104**).[27]

entry	conditions	maoecrystal Z[a]	diol	C6 acetate
1	1 M NaOH, 1:1 MeOH/H_2O	44	28	28
2	1 M NaOH, 1:4 MeOH/H_2O	20	78	2
3	1 M NaOH, EtOH	20	80	0
4	1 M NaOH, THF	0	100	0
5	Pyridine, H_2O	no reaction	--	--
6	Otera's catalyst	no reaction	--	--

[a]Relative product ratios as determined by crude ^{1}H NMR analysis.

Table 2.2. Survey of hydrolysis conditions for acetyl-maoecrystal Z (**124**).

2.3 CONCLUDING REMARKS

In summary, the first total synthesis of (–)-maoecrystal Z (**10**) is described. Essential to our strategy was the use of a Ti^{III}-mediated reductive epoxide coupling reaction for the rapid assembly of a single diastereomer of bicyclic spirolactone **96**. Early-stage construction of the A-B bicycle and central C10 all-carbon quaternary stereocenter, present in many other *ent*-kauranoid natural products, allowed later transformations to proceed in high diastereoselectivity. In a second key transformation, a Sm^{II}-mediated dialdehyde cascade cyclization furnished a single diastereomer of the tetracyclic core of **10** while simultaneously forging four of its seven stereogenic centers. The chemical transformations developed for this efficient and concise route enable the synthesis of **10** in just 12 synthetic steps from (–)-γ-cyclogeraniol (**104**) and also find broad utility in the syntheses of (–)-trichorabdal A and (–)-longikaurin E from unsaturated lactone **133**, described in Chapter 3.

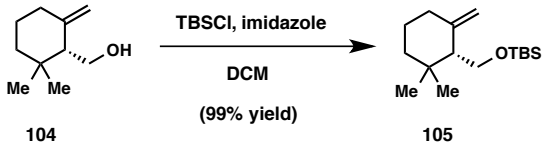
2.4 EXPERIMENTAL SECTION

2.4.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (DCM), and acetonitrile (MeCN) were dried by passing through activated alumina columns. Methanol (MeOH) was distilled over magnesium methoxide, Triethylamine (Et_3N) and Diisopropylamine (*i*-Pr_2NH) were distilled over calcium hydride, and hexamethylphosphoramide (HMPA) was distilled over calcium hydride under reduced pressure prior to use. Unless otherwise stated, chemicals and reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, $KMnO_4$, or CAM staining. Flash column chromatography was performed as described by Still et al.[28] using silica gel (particle size 0.032-0.063) purchased from Silicycle. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 126 MHz, respectively) or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, δ = 7.26), or pyridine (^1H, δ = 8.71, most downfield signal), and $CDCl_3$ (^{13}C, δ = 77.0) or pyridine (^{13}C, δ = 149.9, center peak of most downfield signal). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode. Preparative HPLC was performed with an Agilent 1100 Series HPLC utilizing an Agilent Eclipse XDB-C18 5μm column (9.4 x 250 mm). Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected.

2.4.2 Preparative Procedures and Spectroscopic Data

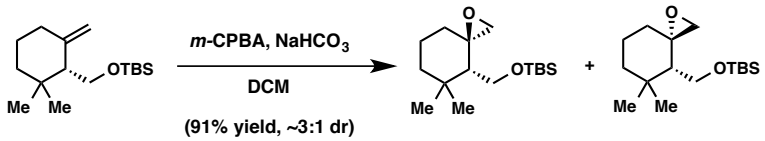
Preparation of TBS ether 105.



104 105

To a solution of (*R*)-(–)-γ-cyclogeraniol (**104**) (2.42 g, 15.7 mmol, 1.0 equiv) in DCM (150 mL) was added imidazole (2.67 g, 39.2 mmol, 2.5 equiv) then TBSCl (3.07 g, 20.4 mmol, 1.3 equiv). The resulting suspension was vigorously stirred for 1 h then diluted with H_2O (75 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (0 to 10% EtOAc/Hex) to provide TBS ether **105** (4.17 g, 99% yield). $[\alpha]_D^{25}$ = –19.6° (*c* 0.74, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.79 (m, 1H), 4.64 (m, 1H), 3.80 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.71 (dd, *J* = 10.1, 7.8 Hz, 1H), 2.17 – 2.04 (m, 2H), 1.95 (dd, *J* = 7.7, 4.8 Hz, 1H), 1.57 – 1.43 (m, 1H), 1.29 – 1.25 (m, 1H), 0.96 (s, 3H), 0.89 (s, 9H), 0.88 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.4, 109.4, 62.0, 55.9, 37.7, 34.2, 33.6, 29.0, 26.0, 25.9, 23.5, 18.3, -5.4; IR (NaCl/thin film): 2953, 2929, 2905, 2856, 1648, 1472, 1463, 1386, 1362, 1256, 1104, 888, 837, 774 cm^{-1}; HRMS (APCI+) calc'd for $C_{16}H_{33}OSi$ $[M + H]^+$ 269.2295, found 269.2293.

Preparation of epoxide 106.



105 *anti*-106 (3:1) *syn*-106

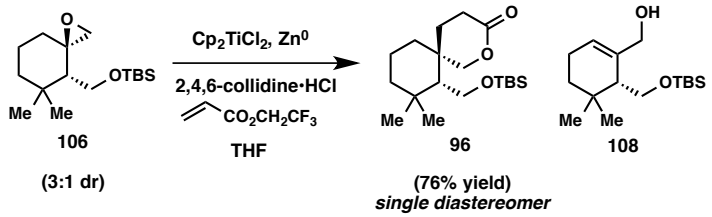
To a solution of olefin **105** (4.03 g, 15.0 mmol, 1.0 equiv) in CH_2Cl_2 (150 mL) at 0 ºC was added solid $NaHCO_3$ (6.30 g, 75.0 mmol, 5.0 equiv) then 85% *m*-CPBA (9.14 g, 45.0 mmol, 3.0 equiv). The ice bath was removed and the resulting suspension was allowed to warm to rt and stir

for an additional 1 h and then diluted with sat. $Na_2S_2O_3$ (75 mL) and sat. $NaHCO_3$ (75 mL) and stirred for 20 min. The layers were separated and the organic layer was washed with one additional portion of sat. $Na_2S_2O_3$ (75 mL) and sat. $NaHCO_3$ (75 mL). The combined aqueous extracts were then extracted with DCM (3 x 50 mL) and the combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The resulting crude residue was chromatographed on SiO_2 (40 to 100% $CHCl_3$/Hex) to provide epoxide **106** (3.89 g, 91% combined yield).

Data for *anti*-**106**: $[\alpha]_D^{25}$ = –26.4° (*c* 1.57, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.72 (dd, *J* = 10.3, 5.0 Hz, 1H), 3.67 (dd, *J* = 10.4, 7.3 Hz, 1H), 2.68 (d, *J* = 4.9 Hz, 1H), 2.51 (d, *J* = 4.9 Hz, 1H), 1.83 – 1.72 (m, 2H), 1.60 – 1.56 (m, 1H), 1.45 (m, *J* = 3.9 Hz, 1H), 1.29 – 1.20 (m, 2H), 1.15 – 1.13 (m, 1H), 1.10 (s, 3H), 0.92 (s, 3H), 0.87 (s, 9H), 0.03 (d, *J* = 0.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 61.3, 58.9, 52.2, 36.3, 34.1, 30.9, 28.6, 27.6, 25.9, 20.0, 18.1, -5.6; IR (NaCl/thin film): 2952, 2930, 2857, 1472, 1463, 1389, 1366, 1256, 1095, 837, 775 cm^{-1}; HRMS (APCI+) calc'd for $C_{16}H_{33}O_2Si$ $[M + H]^+$ 285.2244, found 285.2239.

Data for *syn*-**106**: $[\alpha]_D^{25}$ = +11.7° (*c* 1.57, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.69 (dd, *J* = 10.5, 3.4 Hz, 1H), 3.51 (dd, *J* = 10.5, 5.8 Hz, 1H), 2.80 (d, *J* = 5.1 Hz, 1H), 2.48 (d, *J* = 5.1 Hz, 1H), 1.75 – 1.67 (m, 1H), 1.60 – 1.52 (m, 3H), 1.48 – 1.41 (m, 1H), 1.29 – 1.22 (m, 2H), 1.00 (s, 3H), 0.91 (s, 3H), 0.86 (s, 9H), 0.03 (d, *J* = 2.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 59.8, 58.3, 54.1, 52.1, 38.4, 34.8, 33.1, 29.5, 25.9, 24.9, 20.6, 18.1, -5.40, -5.42; IR (NaCl/thin film): 2929, 2856, 1469, 1426, 1221, 1050, 836, 728 cm^{-1}; HRMS (APCI+) calc'd for $C_{16}H_{33}O_2Si$ $[M + H]^+$ 285.2244, found 285.2242.

Preparation of spirolactone 96.



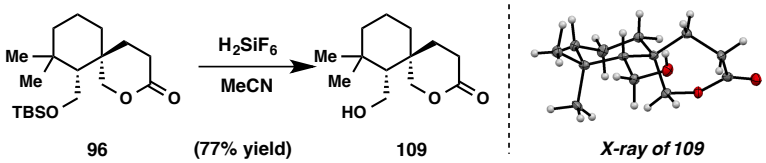
To a stirred solution of epoxide **106** (~3:1 mixture of diastereomers, 2.94 g, 10.3 mmol, 1.0 equiv) in THF (50 mL) was then added 2,4,6-collidine hydrochloride (4.89 g, 31.0 mmol, 3.0 equiv), 2,2,2-trifluoroethyl acrylate (13.1 mL, 103 mmol, 10.0 equiv), and activated zinc dust (1.01 g, 15.5 mmol, 1.5 equiv). Titanocene dichloride (513 mg, 2.06 mmol, 0.2 equiv) was then added every 3 h for 24 h (4.10 g, 16.5 mmol, 1.6 equiv overall) and then diluted with sat. NH_4Cl (50 mL) and Et_2O (30 mL). The biphasic mixture was then filtered through a small pad of Celite and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic extracts were dried over Na_2SO_4, filtered through a small pad of silica gel, and concentrated *in vacuo*. The resulting crude residue was chromatographed on SiO_2 (5 to 20% EtOAc/Hex) to provide spirolactone **96** (2.67 g, 76% yield).

Data for lactone **96**: $[\alpha]_D^{25}$ = +35.7° (*c* 0.975, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.43 (dd, *J* = 11.7, 1.5 Hz, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 3.87 – 3.81 (m, 2H), 2.57 (ddd, *J* = 16.4, 9.2, 7.0 Hz, 1H), 2.47 (dt, *J* = 16.6, 6.2 Hz, 1H), 2.34 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.96 (dtd, *J* = 13.5, 3.6, 1.5 Hz, 1H), 1.59 – 1.48 (m, 3H), 1.45 – 1.37 (m, 2H), 1.29 – 1.23 (m, 2H), 1.10 – 1.03 (m, 1H), 1.01 (s, 3H), 0.89 (s, 9H), 0.87 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 71.2, 60.4, 56.5, 42.1, 36.7, 36.3, 33.9, 33.7, 33.0, 28.6, 25.9, 23.8, 18.5, 18.0, -5.55, -5.56; IR (NaCl/thin film): 2952, 2928, 2856, 1753, 1462, 1253, 1091, 1050, 838, 776 cm^{-1}; HRMS (APCI+) calc'd for $C_{19}H_{37}O_3Si$ $[M + H]^+$ 341.2506, found 341.2494.

Data for alcohol **108**: ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.71 (t, *J* = 3.3 Hz, 1H), 4.16 (br dd, *J* = 12.3, 6.4 Hz, 1H), 3.93 (br dd, *J* = 12.3, 6.1 Hz, 1H), 3.90 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.57 (dd, *J* =

10.0, 8.1 Hz, 1H), 3.36 (t, *J* = 6.5 Hz, 1H), 2.08 – 1.95 (m, 3H), 1.43 (dt, *J* = 13.4, 6.8 Hz, 1H), 1.28 (td, *J* = 13.1, 6.7 Hz, 1H), 0.95 (s, 3H), 0.91 (s, 9H), 0.88 (s, 3H), 0.09 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.7, 125.1, 67.7, 64.3, 48.7, 33.8, 31.5, 28.3, 25.9, 25.0, 22.8, 18.2, -5.47, -5.50; IR (NaCl/thin film): 3351, 2954, 2928, 2857, 1472, 1388, 1361, 1256, 1135, 1105, 1056, 1034, 1006, 996, 937, 893, 882, 837, 774 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{16}H_{33}O_2Si$ $[M + H]^+$ 285.2244, found 285.2241.

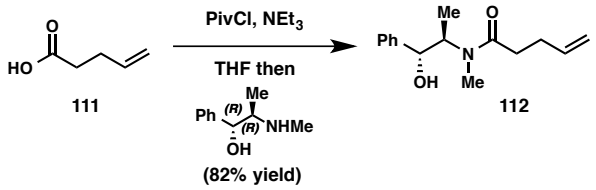
Preparation of lactone 109.



To a solution of spirolactone **96** (103 mg, 0.30 mmol, 1.0 equiv) in MeCN (4 mL) at rt was added 20-25 wt% H_2SiF_6 (0.4 mL, 0.68 mmol, 2.2 equiv). The solution was stirred until LC/MS (or TLC) indicated full consumption of starting material (30 min). The reaction mixture was diluted with sat. $NaHCO_3$ (10 mL) and EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (50-90% EtOAc/Hex) to provide lactone **109** (53 mg, 77% yield). Crystals suitable for X-ray analysis were obtained by layering a nearly saturated solution of spirocycle **109** (53 mg) in CH_2Cl_2 (ca. 0.4 mL) with isooctane: ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.37 (dd, *J* = 11.7, 1.2 Hz, 1H), 4.27 (dd, *J* = 11.7, 1.5 Hz, 1H), 3.89 (dd, *J* = 11.5, 3.8 Hz, 1H), 3.85 (dd, *J* = 11.5, 4.7 Hz, 1H), 2.58 (ddd, *J* = 16.8, 7.9, 7.1 Hz, 1H), 2.50 (ddd, *J* = 16.8, 7.4, 6.3 Hz, 1H), 2.36 (dt, *J* = 14.2, 7.1 Hz, 1H), 2.01 – 1.93 (m, 1H), 1.57 – 1.48 (m, 2H), 1.48 – 1.40 (m, 2H), 1.35 – 1.22 (m, 2H), 1.14 – 1.06 (m, 1H), 1.04 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 173.2, 71.2, 60.4, 57.2, 41.9, 36.6, 36.3, 33.9, 33.6, 33.1, 28.4, 23.2, 18.4; IR (NaCl/thin

film): 3393, 2976, 2920, 2868, 1722, 1447, 1384, 1332, 1282, 1250, 1158, 1135, 1077, 1053, 1034, 984, 940, 833, 731 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{13}H_{23}O_3$ $[M+H]^+$ 227.1642, found 227.1640; mp = 110–111 ºC.

Preparation of Myers amide 112.



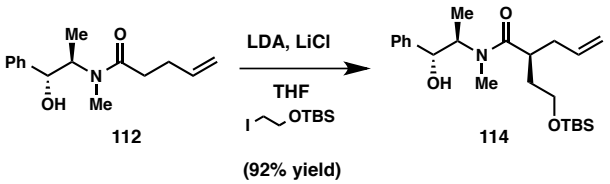
*NOTE: The enantiomeric series can similarly be prepared using (*S*,*S*)-pseudoephedrine in the following procedures (compound **111** → compound **95**) for the preparation of *ent*-**95**.

To a solution of 4-pentenoic acid (4.0 mL, 39.2 mmol, 1.0 equiv) in THF (200 mL) at 0 ºC was added Et_3N (16.3 mL, 117.6 mmol, 3.0 equiv) then pivaloyl chloride (5.8 mL, 5.7 mmol, 1.2 equiv) dropwise causing a white suspension to develop, which was then vigorously stirred for 1 h at rt. In a separate flame dried flask, (*R*,*R*)-pseudoephedrine (8.42 g, 51.0 mmol, 1.3 equiv) was dissolved in THF (200 mL) and NEt_3 (16.3 mL, 117.6 mmol, 3.0 equiv). The resulting clear solution was transferred via cannula to the solution of the mixed anhydride and stirred for 6 h at rt and then diluted with sat. $NaHCO_3$ (300 mL) and EtOAc (300 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 200 mL) and the combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The resulting crude residue was chromatographed on SiO_2 (30 to 60% EtOAc/Hex) to provide amide **112** (7.95 g, 82% yield). $[\alpha]_D^{25} = -105.6°$ (*c* 1.15, $CHCl_3$); ^1H NMR (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$): δ 7.41 – 7.21 (m, 5H), 5.92 – 5.74 (m, 1H), 5.10 – 4.92 (m, 2H), 4.61 – 4.43 (m, 2H), 4.32* (br, 1H), 3.99* (m, 1H), 3.20* (s, 1H), 2.90* (s, 3H), 2.81 (s, 3H), 2.60 – 2.49* (m, 1H), 2.49 – 2.26 (m, 4H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.97* (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (2:1 rotamer ratio, 126 MHz, $CDCl_3$): δ 174.4, 173.3, 142.3,

141.4, 137.8, 137.3, 128.5, 128.2, 128.2, 127.5, 126.8, 126.4, 115.1, 114.9, 76.3, 75.3, 58.2, 33.4, 32.8, 32.4, 29.6, 29.3, 28.9, 26.8, 15.3, 14.4; IR (NaCl/thin film): 3381, 3063, 3028, 2977, 2924, 1620, 1480, 1452, 1405, 1315, 1257, 1200, 1120, 1050, 1027, 912, 838, 758, 701 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{15}H_{22}NO_2$ $[M + H]^+$ 248.1645, found 248.1644.

Rotation for opposite enantiomeric series: $[\alpha]_D^{25}$ = +99.8° (*c* 0.92, $CHCl_3$).

Preparation of alkylated Myers amide 114.

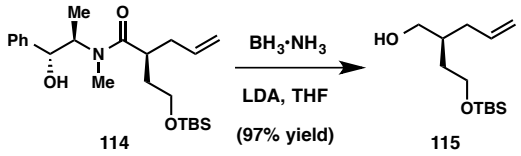


A flame-dried flask in a glove box was charged with lithium chloride (4.95 g, 116.7 mmol, 6.0 equiv) and then removed from the glove box. To this flask was then added diisopropylamine (6.3 mL, 44.7 mmol, 2.3 equiv) and THF (40 mL). The resulting suspension was cooled to –78 °C, and a solution of *n*-BuLi in hexanes (2.6 M, 15.7 mL, 40.8 mmol, 2.1 equiv) was added via cannula. The suspension was warmed briefly to 0 °C and then recooled to –78 °C. An ice-cooled solution of amide 1**12** (4.81 g, 19.5 mmol, 1.0 equiv) in THF (40 mL) was then added to the reaction flask via cannula. The reaction mixture was stirred at –78 °C for 1 h, at 0 °C for 15 min, and at 25 °C for 5 min, and finally cooled to 0 °C, whereupon *tert*-butyl(2-iodoethoxy)dimethylsilane (8.35 g, 29.2 mmol, 1.5 equiv) in THF (20 mL) was added via cannula. The mixture was stirred at 0 °C for 15 min and then diluted with sat. NH_4Cl (100 mL) and EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (15 to 45% EtOAc/Hex) to provide alkylated amide **114** (7.26 g, 92% yield). $[\alpha]_D^{25}$ = –53.3° (*c* 1.24, $CHCl_3$); ^1H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$): δ 7.39 – 7.21 (m,

5H), 5.80 – 5.67 (m, 1H), 5.11 – 4.93 (m, 2H), 4.59 (t, J = 6.8 Hz, 1H), 4.55 – 4.30 (m, 2H), 4.22 – 4.14* (m, 1H), 3.79 – 3.65 (m, 1H), 3.61 – 3.52 (m, 1H), 3.35 (ddd, J = 10.5, 8.6, 4.2 Hz, 1H), 3.27* (br d, J = 3.6 Hz, 1H), 3.22 – 3.11* (m, 1H), 3.04 – 2.92 (m, 1H), 2.89* (s, 3H), 2.88 (s, 3H), 2.44 – 2.31 (m, 1H), 2.24 – 2.09 (m, 2H), 1.91* (br, 1H), 1.80 – 1.71 (m, 1H), 1.70 – 1.52 (m, 2H), 1.10 (d, J = 6.8 Hz, 3H), 0.92* (d, J = 6.8 Hz, 1H), 0.88* (s, J = 2.8 Hz, 9H), 0.85 (s, 9H), 0.07* (s, 3H), 0.06* (s, 3H), 0.01 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (3:1 rotamer ratio, 126 MHz, $CDCl_3$): δ 177.5, 175.9, 142.3, 141.4, 135.9, 128.6, 128.2, 128.1, 127.5, 127.0, 126.3, 116.6, 76.1, 75.3, 61.8, 60.2, 58.9 (br), 58.1, 38.2, 38.0, 37.4, 36.8, 35.6, 35.5, 33.1 (br), 29.6, 26.8, 26.0, 25.8, 18.5, 18.1, 15.8, 14.4, -5.20, -5.24, -5.42, -5.44; IR (NaCl/thin film): 3391, 3064, 3029, 2955, 2928, 2856, 1619, 1472, 1452, 1409, 1305, 1256, 1100, 1083, 1052, 1005, 913, 835, 810, 775, 701 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{23}H_{40}NO_3Si$ $[M + H]^+$ 406.2772, found 406.2765.

Rotation for opposite enantiomeric series: $[\alpha]_D^{25}$ = +46.3° (c 0.60, $CHCl_3$).

Preparation of alcohol 115.



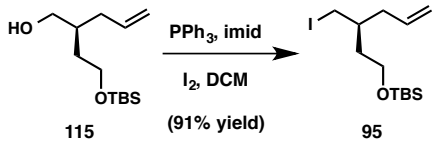
A solution of *n*-BuLi in hexanes (2.6 M, 18.9 mL, 49.0 mmol, 3.9 equiv) was added to a solution of diisopropylamine (7.4 mL, 52.8 mmol, 4.2 equiv) in THF (50 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, then warmed to 0 °C, and held at that temperature for 10 min. Borane-ammonia complex (90% technical grade, 1.73 g, 50.3 mmol, 4.0 equiv) was carefully added in one portion, and the suspension was stirred at 0 °C for 15 min and then was warmed to 23 °C. After 15 min, the suspension was recooled to 0 °C. A solution of amide **114** (5.10 g, 12.6 mmol, 1.0 equiv) in THF (40 mL, followed by a 10 mL rinse) was added

via cannula. The reaction mixture was then warmed to rt, held at that temperature for 4 h, and then cooled to 0 °C where excess hydride was quenched by the careful addition of sat. NH_4Cl (100 mL). The mixture was stirred for 30 min at 0 °C and then extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (5 to 35% EtOAc/Hex) to provide alcohol **115** (2.98 g, 97% yield). $[\alpha]_D^{25}$ = –8.4° (*c* 0.93, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.81 – 5.73 (m, 1H), 5.05 – 4.99 (m, 2H), 3.78 – 3.74 (m, 1H), 3.64 (ddd, *J* = 10.5, 8.1, 3.8 Hz, 1H), 3.60 (m, 1H), 3.48 – 3.44 (m, 1H), 3.18 (d, *J* = 5.2 Hz, 1H), 2.11 (dtd, *J* = 14.0, 7.0, 1.1 Hz, 1H), 2.05 – 1.99 (m, 1H), 1.76 – 1.71 (m, 1H), 1.70 – 1.64 (m, 1H), 1.52 (dtd, *J* = 14.5, 8.0, 4.2 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 136.9, 116.2, 65.9, 61.8, 39.4, 36.4, 35.0, 25.8, 18.2, -5.48, -5.50; IR (NaCl/thin film): 3351, 2954, 2928, 2857, 1640, 1472, 1256, 1093, 835, 775 cm^{-1}; HRMS (APCI+) calc'd for $C_{13}H_{29}O_2Si$ $[M + H]^+$ 245.1931, found 245.1928.

Rotation for opposite enantiomeric series: $[\alpha]_D^{25}$ = +10.8° (*c* 1.30, $CHCl_3$).

Conversion to the Mosher ester was accomplished by treatment of alcohol **115** (17 mg, 0.07 mmol, 1 equiv) with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (40 μL, 0.21 mmol, 3.0 equiv) and 4-DMAP (34 mg, 0.28 mmol, 4.0 equiv) in CH_2Cl_2 (2 mL) at rt for 1 h. The solution was diluted with sat. $NaHCO_3$ (2 mL) and stirred for 20 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL), dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo* to afford the corresponding crude Mosher ester in >20:1 dr (determined by ^{1}H NMR analysis of the crude reaction mixture).

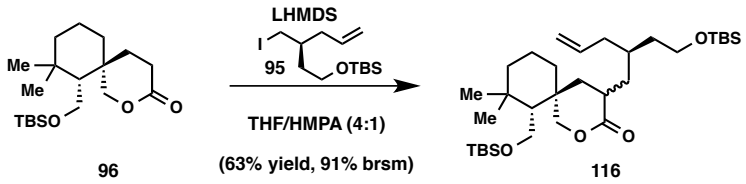
Preparation of iodide 95.



Imidazole (1.82 g, 26.8 mmol, 3.0 equiv) and I_2 (2.22 g, 8.7 mmol, 0.98 equiv) were added sequentially to a solution of PPh_3 (2.22 g, 8.5 mmol, 0.95 equiv) in CH_2Cl_2 (80 mL) at rt. A solution of alcohol **115** (2.18 g, 8.9 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added to the resulting suspension via cannula. The reaction was stirred at rt for 2 h and then diluted with sat. $Na_2S_2O_3$ (30 mL) and sat. $NaHCO_3$ (30 mL) and then stirred for 15 min. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (0-10% EtOAc/Hex) to provide iodide **95** (2.88 g, 91% yield). $[\alpha]_D^{25}$ = +4.1° (*c* 1.215, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.71 (dddd, *J* = 17.0, 10.2, 7.6, 6.8 Hz, 1H), 5.13 (ddt, *J* = 17.0, 2.0, 1.4 Hz, 1H), 5.10 – 5.04 (m, 1H), 3.68 – 3.62 (m, 2H), 3.32 (dd, *J* = 9.8, 4.0 Hz, 1H), 3.28 (dd, *J* = 9.8, 4.6 Hz, 1H), 2.19 – 2.11 (m, 1H), 2.11 – 2.02 (m, 1H), 1.62 – 1.44 (m, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 135.6, 117.2, 60.4, 38.6, 36.9, 35.2, 25.9, 18.3, 15.9, -5.33, -5.35; IR (NaCl/thin film): 3077, 2954, 2928, 2856, 1641, 1471, 1462, 1439, 1388, 1360, 1256, 1100, 1043, 1005, 940, 916, 835, 775, 665 cm^{-1}; HRMS (APCI+) calc'd for $C_{13}H_{27}OSi$ $[M - I]^+$ 227.1826, found 227.1824.

Rotation for opposite enantiomeric series: $[\alpha]_D^{25}$ = –4.7° (*c* 0.565, $CHCl_3$).

Preparation of alkylated lactone 116.



96 116

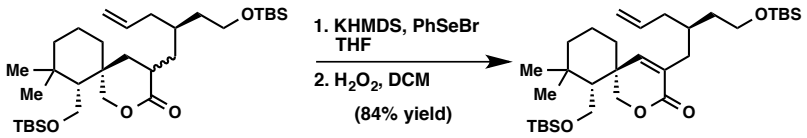
To a solution of **96** (507 mg, 1.49 mmol, 1.0 equiv) and **95** (633 mg, 1.79 mmol, 1.1 equiv) in (4:1) THF/HMPA (8 mL) at 0 °C was added a solution of LHMDS (274 mg, 1.64 mmol, 1.1 equiv) in THF (2.0 mL followed by a 1.0 mL rinse). The resulting solution was stirred for an additional 3 h at 0 °C and then diluted with sat. $NaHCO_3$ (50 mL) and Et_2O (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 25 mL) and the combined organic extracts were washed with H_2O (3 x 40 mL) and brine (1 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (5 to 20% EtOAc/Hex) to provide alkylated lactone **116** (532 mg, 63% isolated yield) as a mixture of diastereomers and recovered **96** (140 mg).

Data for less polar diastereomer: $[\alpha]_D^{25}$ = +28.5° (*c* 0.39, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.82 – 5.72 (m, 1H), 5.07 – 4.99 (m, 2H), 4.41 – 4.33 (m, 2H), 3.88 (ddd, *J* = 24.8, 11.3, 3.6 Hz, 2H), 3.69 – 3.56 (m, 2H), 2.56 (td, *J* = 13.4, 6.8 Hz, 1H), 2.24 (dt, *J* = 15.6, 7.8 Hz, 1H), 2.08 (dd, *J* = 7.1, 5.9 Hz, 2H), 1.88 (ddd, *J* = 21.0, 14.9, 4.4 Hz, 2H), 1.82 – 1.73 (m, 1H), 1.63 – 1.36 (m, 6H), 1.24 (ddd, *J* = 10.6, 8.2, 5.3 Hz, 2H), 1.20 – 1.12 (m, 1H), 1.12 – 1.02 (m, 1H), 1.00 (s, 3H), 0.93 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.08 (d, *J* = 3.6 Hz, 6H), 0.03 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.2, 136.1, 116.6, 69.1, 61.0, 60.5, 57.1, 42.3, 41.6, 38.5, 38.1, 36.6, 35.8, 34.7, 34.2, 33.1, 31.1, 26.0, 25.9, 24.2, 18.5, 18.3, 18.0, -5.29, -5.31, -5.41, -5.46; IR (NaCl/thin film) 3075, 2953, 2928, 2856, 1752, 1639, 1472, 1463, 1388, 1361, 1256, 1163, 1096, 1061, 1024, 1005, 910, 837, 775 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{32}H_{63}O_4Si_2$ $[M + H]^+$ 567.4259, found 567.4278.

Data for more polar diastereomer: $[\alpha]_D^{25}$ = –22.0° (*c* 1.69, $CHCl_3$); ^{1}H NMR (500 MHz;

$CDCl_3$): δ 5.78 – 5.66 (m, 1H), 5.06 – 4.95 (m, 2H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.20 (d, *J* = 11.8 Hz, 1H), 3.83 – 3.72 (m, 2H), 3.72 – 3.58 (m, 2H), 2.61 – 2.50 (m, 1H), 2.19 – 2.11 (m, 1H), 2.06 (t, *J* = 13.2 Hz, 1H), 2.01 – 1.82 (m, 3H), 1.72 – 1.18 (m, 10H), 1.18 – 1.06 (m, 1H), 1.01 (s, 3H), 0.96 – 0.78 (m, 21H), 0.06 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.3, 136.6, 116.5, 72.9, 60.7, 60.6, 55.5, 41.7, 39.8, 38.6, 37.0, 36.0, 35.8, 35.6, 34.7, 33.8, 33.1, 31.1, 26.0, 25.9, 23.8, 18.4, 18.3, 18.0, -5.27, -5.31, -5.50, -5.55; IR (NaCl/thin film): 3076, 2953, 2928, 2856, 1749, 1640, 1471, 1463, 1389, 1361, 1256, 1169, 1092, 1005, 911, 837, 775 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{32}H_{63}O_4Si_2$ $[M + H]^+$ 567.4259, found 567.4252.

Preparation of unsaturated lactone 117.

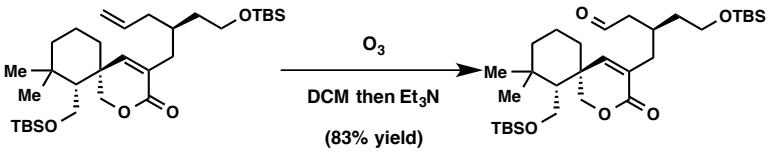


116 **117**

To a solution of KHMDS (105 mg, 0.53 mmol, 1.2 equiv) in THF (6 mL) at 0 °C was added **116** (1.5:1 mixture of diastereomers, 246 mg, 0.43 mmol, 1.0 equiv) in THF (3 mL followed by a 1 mL rinse) dropwise via cannula. The resulting clear solution was allowed to stir at 0 ºC for 30 min then at rt for 15 min. The solution was re-cooled to –78 °C, at which time, a solution of PhSeBr (114 mg, 0.48 mmol, 1.1 equiv) in THF (3 mL followed by a 1 mL wash) at –78 °C was slowly added dropwise via cannula. The resulting pale yellow solution was allowed to stir for 15 min at –78 ºC and then diluted with sat. $NaHCO_3$ (15 mL). The mixture was diluted with Et_2O (30 mL) and H_2O (30 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 15 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude residue was diluted with CH_2Cl_2 (6 mL) and cooled to 0 °C. To this was added 30 wt% H_2O_2 (0.3 mL, 2.9 mmol, 6.8 equiv) and stirred for 30 min. The reaction mixture was diluted with H_2O (15 mL) and the layers were separated. The aqueous layer

was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with sat. $NaHCO_3$ (1 x 10 mL), dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (0 to 15% EtOAc/Hex) to afford unsaturated lactone **117** (206 mg, 84% yield). $[\alpha]_D^{25} = -29.2°$ (*c* 0.51, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.36 (s, 1H), 5.81 – 5.69 (m, 1H), 5.03 (br s, 1H), 5.02 – 4.98 (m, 1H), 4.47 (dd, *J* = 11.2, 2.0 Hz, 1H), 4.36 (dd, *J* = 11.2, 1.2 Hz, 1H), 3.79 – 3.72 (m, 2H), 3.65 (t, *J* = 6.6 Hz, 2H), 2.19 (dd, *J* = 7.2, 0.9 Hz, 2H), 2.10 – 1.98 (m, 2H), 1.93 – 1.83 (m, 2H), 1.67 – 1.38 (m, 6H), 1.26 (td, *J* = 13.0, 3.9 Hz, 1H), 1.19 – 1.11 (m, 1H), 1.02 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.04 (s, 6H), 0.03 (d, *J* = 1.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.9, 154.2, 136.5, 127.2, 116.5, 69.8, 61.4, 61.1, 55.6, 42.1, 39.7, 37.6, 36.2, 35.1, 33.2, 33.1, 33.0, 32.9, 26.0, 25.9, 23.3, 18.4, 18.3, 18.1, -5.28, -5.31, -5.50, -5.55; IR (NaCl/thin film): 2953, 2928, 2856, 1723, 1472, 1463, 1389, 1361, 1256, 1164, 1150, 1101, 1030, 1005, 938, 837, 776, 665 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{32}H_{61}O_4Si_2$ $[M + H]^+$ 565.4103, found 565.4083.

Preparation of aldehyde 94.

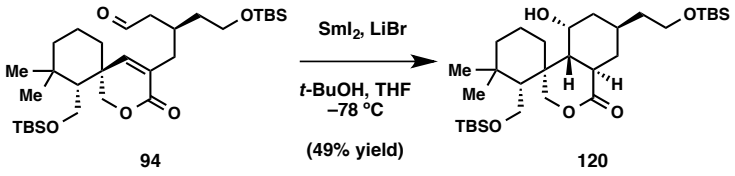


117 **94**

A solution of olefin **117** (108 mg, 0.19 mmol, 1.0 equiv) in DCM (4 mL) was cooled to –78 ºC, at which time, ozone was gently bubbled through the solution (O_2 flow rate = 1/8 L/min, 0 setting on ozonator) until LC/MS (or TLC) indicated full consumption of starting material (ca. 20 min). The solution was purged with N_2 for 3 min then Et_3N (1.3 mL, 9.33 mmol, 50 equiv) was slowly added dropwise. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stirred until LC/MS indicated complete conversion of the ozonide to the aldehyde (ca. 30 min), filtered through a small plug of silica gel, and concentrated *in vacuo*.

The crude residue was chromatographed on SiO_2 (5 to 25% EtOAc/Hex) to afford aldehyde **94** (90 mg, 83% yield). $[\alpha]_D^{25}$ = –29.8° (*c* 0.37, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.73 (t, *J* = 1.8, 1H), 6.40 (s, 1H), 4.48 (dd, *J* = 11.2, 1.5, 1H), 4.40 (d, *J* = 11.2, 1H), 3.80 – 3.72 (m, 2H), 3.67 (t, *J* = 6.2 Hz, 2H), 2.49 – 2.33 (m, 4H), 2.15 (dd, *J* = 13.8, 7.5, 1H), 1.85 (br d, *J* = 13.6, 1H), 1.65 – 1.41 (m, 7H), 1.29 – 1.23 (m, 3H), 1.15 (td, *J* = 13.0, 4.2, 2H), 1.02 (s, 3H), 0.89 (s, 3H), 0.88 (d, *J* = 0.8, 9H), 0.87 (d, *J* = 0.7, 9H), 0.04 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 202.8, 164.8, 155.5, 126.1, 69.9, 61.3, 60.8, 55.5, 47.8, 42.0, 39.6, 36.9, 36.2, 33.2, 33.0, 32.9, 29.8, 26.0, 25.9, 23.3, 18.4, 18.2, 18.1, -5.37, -5.39, -5.50, -5.54; IR (NaCl/thin film): 2953, 2928, 2856, 1723, 1472, 1388, 1361, 1255, 1150, 1096, 836, 775, 665 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{31}H_{59}O_5Si_2$ $[M + H]^+$ 567.3896, found 567.3915.

Preparation of tricycle 120.

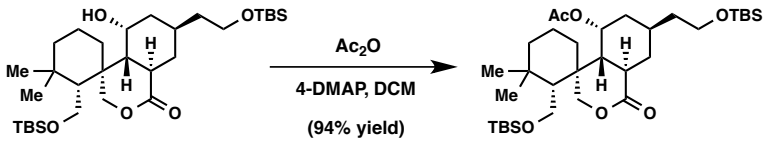


Fresh SmI_2 was prepared according to the following procedure[29]: A flame-dried flask was charged with finely ground samarium (Aldrich, 1.30 g, 8.64 mmol, 1.7 equiv) and was briefly flame-dried *in vacuo*. Once cooled, THF (50 mL) was added under argon followed by diiodoethane (1.40 g, 4.96 mmol, 1.0 equiv) with vigorous stirring for 3 h at ambient temperature. The deep blue solution (~0.1M in SmI_2) was allowed to settle for at least 10 min prior to use.

A flame-dried flask in a glove box was charged with LiBr (333 mg, 3.84 mmol, 25.0 equiv) and then removed from the glove box. A freshly prepared solution of 0.1M SmI_2 (3.84 mL, 0.384 mmol, 2.5 equiv) was then added to the flask containing LiBr and stirred until no visible white solids were apparent and a dark purple homogeneous solution emerged (ca. 5 min). The $SmBr_2$ mixture was transferred dropwise via cannula to a solution of aldehyde **94** (87 mg, 0.15 mmol,

1.0 equiv) and a solution of *t*-BuOH in THF (1.0 M, 0.15 mL, 0.15 mmol, 1.0 equiv) in THF (15 mL) at –78 °C. The reaction mixture was allowed to stir at –78 °C until LC/MS (or TLC) indicated full consumption starting material (ca. 1 h). The reaction mixture was quenched with sat. $NaHCO_3$ (10 mL), sat. $Na_2S_2O_3$ (10 mL), and Rochelle salt (2 g), and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed once with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (10 to 12% EtOAc/Hex) to afford tricycle **120** as a white foam (42.3 mg, 49% yield). $[\alpha]_D^{25}$ = –6.1° (*c* 0.56, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.57 (br s, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.24 (d, *J* = 11.4 Hz, 1H), 3.75-3.63 (m, 4H), 2.86 (td, *J* = 12.3, 3.3 Hz, 1H), 2.47 (d, *J* = 14.6 Hz, 1H), 1.99 – 1.93 (m, 2H), 1.78 (br d, *J* = 13.6 Hz, 1H), 1.71 (t, *J* = 3.5 Hz, 1H), 1.54 – 1.39 (m, 6H), 1.30 (dd, *J* = 12.6, 4.8 Hz, 1H), 1.16 – 0.98 (m, 7H), 0.894 (s, 3H), 0.887 (s, 18 H) 0.05 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 73.3, 65.7, 60.8, 60.1, 51.7, 46.7, 42.0, 41.4, 39.6, 39.5, 35.5, 35.4, 34.2, 33.8, 27.9, 27.5, 26.0, 25.9, 23.6, 18.4, 18.3, 18.2, -5.26, -5.28, -5.46, -5.50; IR (NaCl/thin film): 3469, 2927, 2856, 1726, 1471, 1462, 1389, 1360, 1256, 1091, 836, 775 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{31}H_{61}O_5Si_2$ $[M + H]^+$ 569.4052, found 569.4037.

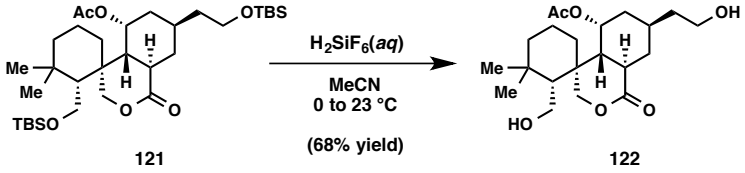
Preparation of acetate 121.



To a solution of tricycle **120** (41.9 mg, 73.6 μmol, 1.0 equiv) in DCM (3.5 mL) at rt was added Ac_2O (49 μL, 0.515 mmol, 7.0 equiv) and then 4-DMAP (45 mg, 0.37 mmol, 5.0 equiv). The solution was stirred until LC/MS (or TLC) indicated complete consumption of starting material (1.5 h), at which time, the reaction mixture was diluted with sat. $NaHCO_3$ (4 mL) and CH_2Cl_2 (2 mL) and stirred for 30 min. The layers were separated and the aqueous layer was

extracted with DCM (3 x 3 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (7% EtOAc/Hex) to afford acetate **121** (42.1 mg, 94% yield). $[\alpha]_D^{25}$ = –19.6° (*c* 0.44, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.61 (br s, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 3.75 (qd, *J* = 10.2, 4.0 Hz, 2H), 3.63 (t, *J* = 6.5 Hz, 2H), 2.84 (td, *J* = 12.3, 3.5 Hz, 1H), 2.49 (dd, *J* = 13.2, 2.0 Hz, 1H), 2.19 (dd, *J* = 12.8, 0.7 Hz, 1H), 2.05 (s, 3H), 1.98-1.94 (m, 2H), 1.89 – 1.78 (m, 2H), 1.60 – 1.33 (m, 7H), 1.16 (td, *J* = 12.9, 4.2 Hz, 1H), 1.10-0.99 (m, 4H), 0.899 (s, 9H), 0.881 (s, 3H), 0.876 (s, 9H), 0.07 (d, *J* = 2.3 Hz, 6H), 0.03 (d, *J* = 3.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 169.8, 73.1, 68.59, 60.33, 60.26, 51.4, 46.0, 42.2, 39.43, 39.36, 37.2, 36.5, 35.2, 34.1, 33.8, 30.3, 28.1, 28.0, 25.95, 25.91, 23.5, 21.6, 18.3, 18.24, -5.3, -5.42, -5.47; IR (NaCl/thin film): 2954, 2928, 2957, 1737, 1472, 1464, 1389, 1370, 1236 1089, 837, 776 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{33}H_{63}O_6Si_2$ $[M + H]^+$ 611.4158, found 611.4152.

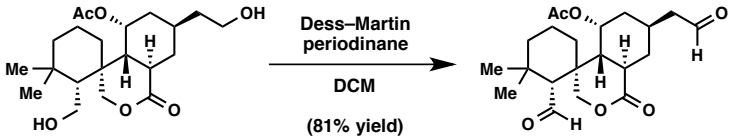
Preparation of diol 122.



To a solution of tricycle **121** (41.9 mg, 68.6 μmol) in 1.5 mL MeCN at 0 °C was added 20-25 wt% aq. H_2SiF_6 (0.20 mL, 0.34 mmol, 5.0 equiv). After stirring at 0 °C for 15 min, the ice bath was removed and the mixture allowed to warm to ambient temperature. After 60 min, sat. $NaHCO_3$ (2 mL) and EtOAc (2 mL) were carefully added. After cessation of bubbling, the layers were separated and the aqueous layer was extracted with EtOAc (2 x 2 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (50 to 100% EtOAc/Hex) to afford diol **122** as a

clear gum (17.9 mg, 68% yield). $[\alpha]_D^{25}$ = –9.1° (*c* 0.62, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.64 (dt, *J* = 3.9, 1.8 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.34 (dd, *J* = 11.6, 1.2 Hz, 1H), 3.86 (dd, *J* = 11.9, 3.0 Hz, 1H), 3.78 (dd, *J* = 11.8, 6.5 Hz, 1H), 3.69 (t, *J* = 6.6 Hz, 2H), 2.86 (td, *J* = 12.3, 3.5 Hz, 1H), 2.55 – 2.47 (m, 1H), 2.31 (dd, *J* = 12.8, 1.6 Hz, 1H), 2.08 (s, 3H), 1.98 – 1.76 (m, 3H), 1.66 (dd, *J* = 6.5, 3.0 Hz, 1H), 1.57 – 1.31 (m, 8H), 1.23 – 1.07 (m, 3H), 1.05 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 170.0, 72.9, 68.8, 60.3, 60.2, 51.5, 46.2, 42.1, 39.3, 39.1, 37.2, 36.4, 34.7, 33.9, 33.8, 28.2, 28.0, 23.2, 21.7, 18.2; IR (NaCl/thin film): 3429, 2925, 2873, 1728, 1459, 1390, 1371, 1237, 1208, 1071, 1031, 967, 916, 731 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{21}H_{35}O_6$ $[M + H]^+$ 383.2428, found 383.2432.

Preparation of dialdehyde 123.

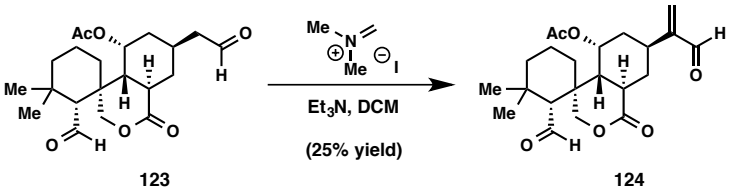


122 123

To a solution of diol **122** (12.4 mg, 32.4 μmol) in 0.7 mL DCM was added Dess–Martin periodinane (55 mg, 0.13 mmol, 4.0 equiv). After stirring for 15 min, the reaction mixture was diluted with sat. $NaHCO_3$ (1 mL) and sat. $Na_2S_2O_3$ (1 mL) and stirred vigorously until the layers became clear (ca. 20 min). The layers were then separated and the aqueous layer was extracted with DCM (3 x 1 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (33 to 50% EtOAc/Hex) to afford dialdehyde **123** (9.9 mg, 81% yield). $[\alpha]_D^{25}$ = –8.4° (*c* 0.50, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.93 (d, J = 3.9 Hz, 1H), 9.75 (t, *J* = 1.3 Hz, 1H), 5.41 (dt, *J* = 3.9, 2.1 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.40 (d, *J* = 11.7 Hz, 1H), 2.86 (td, *J* = 12.4, 3.5 Hz, 1H), 2.47 – 2.37 (m, 2H), 2.35 (dd, *J* = 6.1, 1.4 Hz, 1H), 2.34 – 2.27 (m, 1H), 2.26 (d, *J* = 3.9 Hz, 1H), 2.11 (s, 3H), 2.01 (dd, *J* = 12.9, 1.9 Hz, 1H), 1.99 – 1.93 (m, 1H), 1.84 – 1.76 (m, 1H), 1.66 –

1.48 (m, 4H), 1.39 – 1.29 (m, 1H), 1.24 – 1.18 (m, 1H), 1.17 (s, 3H), 1.16 – 1.10 (m, 1H), 1.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.3, 200.7, 172.3, 169.8, 71.7, 68.1, 62.3, 49.8, 45.0, 41.1, 40.6, 36.7, 36.1, 33.9, 33.6, 33.3, 27.6, 26.0, 23.3, 21.5, 18.2; IR (NaCl/thin film): 2952, 2929, 2873, 2735, 1732, 1454, 1442, 1392, 1372, 1234, 1204, 1073, 1030, 914, 836, 731 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{21}H_{31}O_6$ $[M + H]^+$ 379.2115, found 379.2107.

Preparation of enal 124.

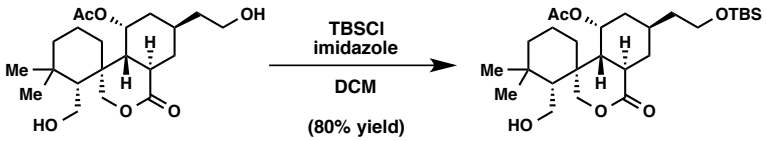


123 **124**

A solution of dialdehyde **123** (9.8 mg, 26 μmol) in 1.5 mL DCM was prepared in a glove box. *N*,*N*-dimethylmethyleneiminium iodide (48 mg, 0.26 mmol, 10 equiv) and Et_3N (55 μL, 0.39 mmol, 15 equiv) were added and the mixture was stirred for 10 h. After removal from the glovebox, the reaction mixture was diluted with sat. $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 1 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (25 to 35% EtOAc/Hex) to afford enal **124** as a white solid (2.5 mg, 25% yield). $[\alpha]_D^{25}$ = –16° (*c* 0.12, $CHCl_3$); ^{1}H NMR (600 MHz; $CDCl_3$): δ 9.95 (d, *J* = 3.9 Hz, 1H), 9.50 (s, 1H), 6.25 (s, 1H), 6.04 (s, 1H), 5.47 (dt, *J* = 4.0, 2.1 Hz, 1H), 4.69 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 11.7 Hz, 1H), 2.97 – 2.87 (m, 2H), 2.43 (dq, *J* = 13.1, 3.2 Hz, 1H), 2.28 (d, *J* = 3.9 Hz, 1H), 2.14 (s, 3H), 2.10 – 2.03 (m, 1H), 2.01 (dq, *J* = 14.1, 2.9 Hz, 1H), 1.83 (dt, *J* = 13.8, 3.6 Hz, 1H), 1.66 – 1.50 (m, 3H), 1.42 – 1.20 (m, 4H), 1.18 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.4, 193.8, 172.3, 169.8, 152.5, 133.6, 71.8, 68.1, 62.4, 45.0, 41.1, 40.7, 36.4, 35.4, 33.6, 33.3, 32.6, 29.2, 27.7, 23.3, 21.6, 18.3; IR (NaCl/thin film): 2917, 2849, 1734, 1685, 1457, 1373, 1235, 1030 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{22}H_{31}O_6$ $[M + H]^+$ 391.2115,

found 391.2135.

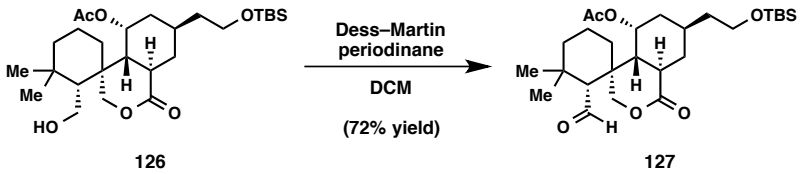
Preparation of silyl ether 126.



122 **126**

To a solution of diol **122** (13.1 mg, 34.2 µmol) in 1.0 mL DCM was added imidazole (5.8 mg, 86 µmol, 2.5 equiv) and TBSCl (5.1 mg as a solution in DCM, 0.10 mL, 34 µmol, 1.0 equiv). After stirring for 20 min, the reaction mixture was diluted with sat. $NaHCO_3$ (1 mL). The layers were separated and the aqueous layer was extracted with DCM (2 x 1 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (25 to 35% EtOAc/Hex) to afford silyl ether **126** as a clear gum (13.5 mg, 80% yield). $[\alpha]_D^{25}$ = –8.0° (*c* 0.62, $CHCl_3$); ^{1}H NMR (600 MHz; $CDCl_3$): δ 5.63 (dt, *J* = 3.7, 2.0 Hz, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.34 (dd, *J* = 11.6, 1.3 Hz, 1H), 3.86 (dt, *J* = 11.8, 3.3 Hz, 1H), 3.79 (ddd, *J* = 11.6, 6.4, 4.9 Hz, 1H), 3.62 (t, *J* = 6.5 Hz, 2H), 2.85 (td, *J* = 12.3, 3.5 Hz, 1H), 2.47 (dtd, *J* = 13.2, 3.7, 2.0 Hz, 1H), 2.30 (dd, *J* = 12.7, 1.6 Hz, 1H), 2.06 (s, 3H), 2.00 – 1.76 (m, 3H), 1.66 (dd, *J* = 6.5, 3.0 Hz, 1H), 1.63 (br s, 1H), 1.53 – 1.32 (m, 6H), 1.23 – 1.06 (m, 3H), 1.05 (s, 3H), 0.87 (s, 9H), 0.86 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 169.9, 72.9, 68.9, 60.3, 60.3, 51.6, 46.3, 42.1, 39.3, 39.2, 36.9, 36.5, 35.0, 33.9, 33.8, 28.2, 27.9, 25.9, 23.2, 21.6, 18.2, 18.2, -5.3, -5.3; IR (NaCl/thin film): 2952, 2927, 2856, 1733, 1472, 1462, 1388, 1370, 1237, 1206, 1099, 1034, 835, 775 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{27}H_{49}O_6Si$ $[M + H]^+$ 497.3293, found 497.3286.

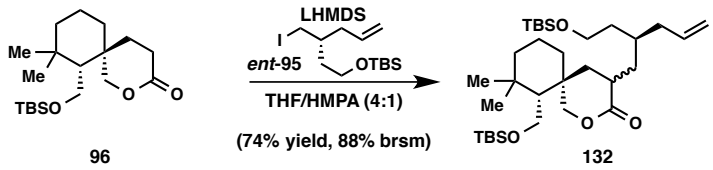
Preparation of aldehyde 127.



126 127

To a solution of silyl ether **126** (12.2 mg, 24.6 μmol) in 0.6 mL DCM was added Dess–Martin periodinane (21 mg, 49 μmol, 2.0 equiv). After stirring for 40 min, the reaction mixture was diluted with sat. $NaHCO_3$ (1 mL) and sat. $Na_2S_2O_3$ (1 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 1 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (15 to 20% EtOAc/Hex) to afford aldehyde **127** as a white solid (8.8 mg, 72% yield). Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution of aldehyde **127** in Et_2O. $[\alpha]_D^{25}$ = –6.6° (*c* 0.39, $CHCl_3$); ^{1}H NMR (600 MHz; $CDCl_3$): δ 9.94 (d, *J* = 3.9 Hz, 1H), 5.41 (dt, *J* = 3.9, 2.0 Hz, 1H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 3.62 (t, *J* = 6.3 Hz, 2H), 2.80 (td, *J* = 12.3, 3.4 Hz, 1H), 2.39 (dq, *J* = 13.4, 3.0 Hz, 1H), 2.30 (d, *J* = 3.8 Hz, 1H), 2.07 (s, 3H), 2.01 – 1.94 (m, 2H), 1.91 – 1.82 (m, 1H), 1.80 (dt, *J* = 13.8, 3.7 Hz, 1H), 1.65 – 1.30 (m, 6H), 1.20 (td, *J* = 13.1, 4.5 Hz, 1H), 1.16 (s, 3H), 1.11 – 1.02 (m, 5H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.2, 172.8, 169.8, 71.8, 68.6, 62.3, 60.1, 45.4, 41.1, 40.6, 39.0, 36.9, 36.3, 34.2, 33.7, 33.3, 27.6, 27.5, 25.9, 23.3, 21.5, 18.3, 18.2, –5.4 ; IR (NaCl/thin film): 2953, 2927, 2855, 1735, 1711, 1472, 1371, 1388, 1239, 1203, 1102, 1044, 834, 775 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{27}H_{47}O_6Si$ [M + H]$^+$ 495.3136, found 495.3132. mp = 129–131 °C.

Preparation of lactone 132.



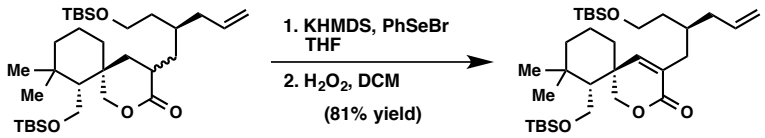
To a solution of **96** (205 mg, 0.60 mmol, 1.0 equiv) and ***ent*-95** (236 mg, 0.67 mmol, 1.1 equiv) in (4:1) THF/HMPA (3 mL) at 0 °C was added a solution of LHMDS (274 mg, 1.64 mmol, 1.1 equiv) in (4:1) THF/HMPA (2 mL followed by a 1 mL rinse). The resulting solution was stirred for an additional 3 h at 0 °C and then diluted with sat. $NaHCO_3$ (20 mL) and Et_2O (30 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were washed with H_2O (3 x 20 mL) and brine (1 x 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (0 to 20% EtOAc/Hex) to provide lactone **132** (253 mg, 74% yield) as a mixture of diastereomers and recovered **96** (28 mg).

Data for less polar diastereomer: $[\alpha]_D^{25}$ = +27.6° (*c* 1.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 – 5.67 (m, 1H), 5.06 – 4.96 (m, 2H), 4.46 (dd, *J* = 11.6, 1.1 Hz, 1H), 4.35 (d, *J* = 11.6 Hz, 1H), 3.95 – 3.86 (m, 2H), 3.71 – 3.63 (m, 2H), 2.61 – 2.57 (m, 1H), 2.22 (dd, *J* = 14.1, 7.0 Hz, 1H), 2.11 – 1.97 (m, 2H), 1.95 – 1.88 (m, 1H), 1.83 (ddd, *J* = 13.9, 7.7, 6.5 Hz, 1H), 1.79 – 1.69 (m, 1H), 1.64 – 1.35 (m, 5H), 1.29 – 1.16 (m, 3H), 1.11 – 1.01 (m, 2H), 1.00 (s, 3H), 0.94 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.20 – -0.09 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 136.6, 116.5, 69.2, 60.7, 60.5, 56.9, 42.4, 41.5, 38.6, 38.2, 36.1, 35.7, 34.9, 34.3, 33.0, 31.8, 26.0, 25.9, 24.3, 18.5, 18.3, 17.9, -5.31, -5.35, -5.43, -5.47; IR (NaCl/thin film): 2952, 2927, 2856, 1749, 1471, 1462, 1387, 1360, 1255, 1163, 1092, 1060, 1023, 994, 910, 836, 774 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{32}H_{63}O_4Si_2$ $[M+H]^+$ 567.4259, found 567.4278.

Data for more polar diastereomer: $[\alpha]_D^{25}$ = –37.6° (*c* 0.48, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 16.8, 10.5, 7.1 Hz, 1H), 5.08 – 4.99 (m, 2H), 4.50 (d, *J* = 11.8 Hz, 1H),

4.13 (d, *J* = 11.8 Hz, 1H), 3.83-3.75 (m, 2H), 3.62 (t, *J* = 6.8 Hz, 2H), 2.61 – 2.56 (m, 1H), 2.13 – 1.99 (m, 3H), 1.99 – 1.95 (m, 2H), 1.76 – 1.67 (m, 1H), 1.63 – 1.37 (m, 5H), 1.31 – 1.18 (m, 4H), 1.18 – 1.10 (m, 1H), 1.02 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.16 – -0.09 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 136.2, 116.6, 73.0, 61.1, 60.8, 55.1, 41.6, 40.0, 37.4, 37.2, 37.0, 36.5, 35.4, 34.8, 33.8, 33.1, 31.1, 26.0, 25.9, 18.5, 18.3, 18.0, -5.25, -5.26, -5.50, -5.55; IR (NaCl/thin film): 2952, 2927, 2856, 1751, 1471, 1462, 1387, 1360, 1255, 1168, 1151, 1094, 1062, 1005, 953, 938, 910, 836, 774 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{32}H_{63}O_4Si_2$ $[M+H]^+$ 567.4259, found 567.4265.

Preparation of unsaturated lactone 133.

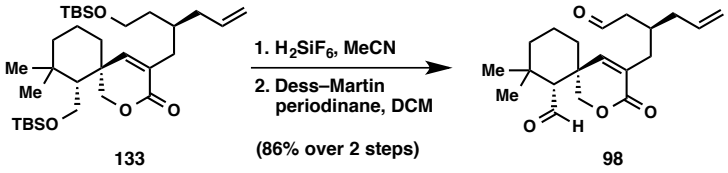


132 **133**

To a solution of KHMDS (73 mg, 0.37 mmol, 1.2 equiv) in THF (6 mL) at 0 °C was added **132** (1.5:1 mixture of diastereomers, 172 mg, 0.30 mmol, 1.0 equiv) in THF (3 mL followed by a 1 mL rinse) dropwise via cannula. The resulting clear solution was allowed to stir at 0 ºC for 30 min then at rt for 15 min. The solution was re-cooled to –78 °C, at which time, a solution of PhSeBr (79 mg, 0.33 mmol, 1.1 equiv) in THF (3 mL followed by a 1 mL wash) at –78 °C was slowly added dropwise via cannula. The resulting pale yellow solution was allowed to stir for 15 min at –78 ºC and then diluted with sat. $NaHCO_3$ (15 mL) and Et_2O (30 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude residue was diluted with DCM (4 mL) and cooled to 0 °C. To this was added 30 wt% H_2O_2 (0.2 mL, 1.96 mmol, 6.5 equiv) and stirred for 30 min. The reaction mixture was diluted with H_2O (15 mL) and the layers were separated. The aqueous layer was extracted with DCM (3 x 10 mL) and

the combined organic extracts were washed with sat. $NaHCO_3$ (1 x 10 mL), dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (0 to 15% EtOAc/Hex) to afford unsaturated lactone **133** (139 mg, 81% yield). $[\alpha]_D^{25}$ = –22.7° (*c* 0.45, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.35 (s, 1H), 5.80 – 5.71 (m, 1H), 5.05-4.97 (m, 2H), 4.48 (dd, *J* = 11.2, 1.5 Hz, 1H), 4.41 (d, *J* = 11.3 Hz, 1H), 3.78 (d, *J* = 4.5 Hz, 2H), 3.64 (td, *J* = 6.9, 3.0 Hz, 2H), 2.19 (qd, *J* = 12.5, 7.2 Hz, 2H), 2.04 – 2.02 (m, 2H), 1.85 (m, 2H), 1.60 – 1.39 (m, 7H), 1.26 (td, *J* = 13.0, 3.8 Hz, 1H), 1.15 (td, *J* = 13.3, 4.1 Hz, 1H), 1.02 (s, 3H), 0.92 (s, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.04 (d, *J* = 0.6 Hz, 6H), 0.03 (d, *J* = 0.5 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8, 154.3, 136.5, 127.4, 116.5, 70.0, 61.5, 61.2, 55.5, 42.2, 39.8, 37.9, 36.0, 35.6, 33.3, 33.2, 33.02, 32.98, 26.0, 25.9, 23.4, 18.5, 18.3, 18.1, -5.26, -5.29, -5.53, -5.58; IR (NaCl/thin film): 2952, 2927, 2856, 1722, 1471, 1462, 1388, 1360, 1255, 1164, 1149, 1096, 1005, 909, 836, 774, 662 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{32}H_{61}O_4Si_2$ $[M+H]^+$ 565.4103, found 565.4116.

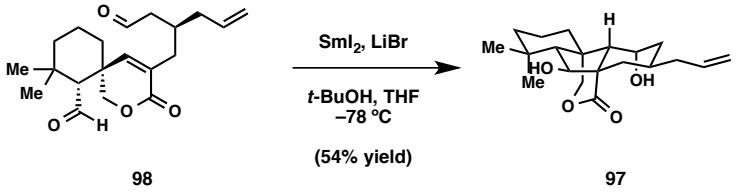
Preparation of dialdehyde 98.



To a solution of unsaturated lactone **133** (130 mg, 0.23 mmol, 1.0 equiv) in MeCN (4 mL) at 0 ºC was added 20-25 wt% H_2SiF_6 (0.5 mL, 0.85 mmol, 3.7 equiv). The solution was stirred until LC/MS (or TLC) indicated full consumption of starting material (2 h). The reaction mixture was diluted with sat. $NaHCO_3$ (5 mL) and EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The resulting crude residue was redissolved in DCM (8 mL) and cooled to 0 ºC. To the solution was added

Dess-Martin periodinane (293 mg, 0.69 mmol, 3.0 equiv), and after 2 h, an additional portion of DMP was added (293 mg, 0.69 mmol, 3.0 equiv). The solution was stirred for an additional 1 h and LC/MS had indicated full consumption of starting material. The reaction mixture was diluted with sat. $Na_2S_2O_3$ (15 mL) and sat. $NaHCO_3$ (10 mL) and stirred for 20 min. The layers were separated and the organic layer was again stirred with with sat. $Na_2S_2O_3$ (15 mL) and sat. $NaHCO_3$ (10 mL) for 20 min and the layers were separated. The organic layer was washed with H_2O (20 mL) and the combined aqueous extracts were back extracted with DCM_2 (3 x 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (10 to 35% EtOAc/Hex) to provide **98** (66 mg, 86% yield from **133**). $[\alpha]_D^{25}$ = –20.3° (*c* 1.07, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.92 (d, *J* = 3.0 Hz, 1H), 9.73 (t, *J* = 1.8 Hz, 1H), 6.32 (s, 1H), 5.78 – 5.70 (m, 1H), 5.09 – 5.03 (m, 2H), 4.56 (d, *J* = 11.3 Hz, 1H), 4.40 (dd, *J* = 11.3, 1.4 Hz, 1H), 2.43 – 2.15 (m, 6H), 2.04 (dt, *J* = 14.2, 7.1 Hz, 1H), 1.88 (dt, *J* = 13.7, 3.5 Hz, 1H), 1.66 (ddt, *J* = 11.3, 7.5, 3.8 Hz, 2H), 1.57 – 1.53 (m, 3H), 1.34 – 1.20 (m, 2H), 1.13 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 203.2, 202.6, 164.3, 151.3, 135.6, 128.2, 117.6, 70.1, 64.2, 47.4, 40.3, 39.0, 38.4, 35.5, 32.8, 32.3, 32.1, 31.8, 23.7, 18.0; IR (NaCl/thin film): 2928, 2849, 1719, 1461, 1442, 1390, 1370, 1294, 1163, 1148, 1112, 1072, 1031, 915 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $C_{20}H_{29}O_4$ $[M+H]^+$ 333.2060, found 333.2068.

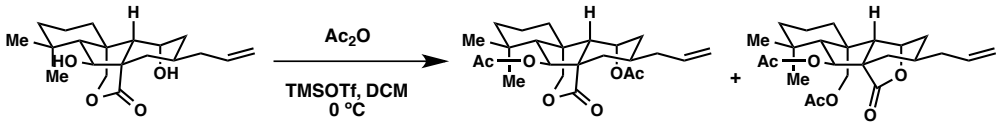
Preparation of tetracycle 97.



To a solution of dialdehyde **98** (28.0 mg, 84.2 μmol, 1.0 equiv) in THF (8 mL) was added LiBr in THF (1.0 M, 85 μL, 850 μmol, 10.1 equiv) and *t*-BuOH in THF (0.1 M, 85 μL, 85 μmol,

1.0 equiv) and the solution was cooled to –78 ºC. A separate flask was flame dried containing LiBr (219 mg, 2.52 mmol, 30 equiv) and to this was added freshly prepared 0.1 M SmI_2 (2.5 mL, 250 μmol, 3.0 equiv) and stirred for 10 min. The resulting stirring purple solution was cannulated into the dialdehyde solution and stirred for 10 min. The reaction mixture was diluted with sat. $NaHCO_3$ (10 mL), sat. $Na_2S_2O_3$ (10 mL), H_2O (5 mL), then Rochelle salt (1.0 g) was added and then diluted with EtOAc (20 mL) and stirred for 15 min. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica, and concentrated *in vacuo*. The crude residue was purified by preparative reverse phase HPLC (40 to 60% MeCN/H_2O, 20 minute gradient, t_R=13.5 min) to afford tetracycle **97** (15.2 mg, 54% yield). $[\alpha]_D^{25}$ = –54.6° (*c* 0.25, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.80 (ddt, *J* = 17.1, 10.1, 7.1, 1H), 5.05 – 5.00 (m, 2H), 4.58 (dd, *J* = 11.3, 1.0, 1H), 4.52 (dd, *J* = 11.3, 2.0, 1H), 4.36 (br s, 1H), 3.97 (dd, *J* = 7.0, 4.1, 1H), 2.28 – 2.10 (m, 3H), 1.99 (m, 1H), 1.86 – 1.82 (m, 2H), 1.78 (dtd, *J* = 14.2, 3.6, 1.7, 1H), 1.62 – 1.45 (m, 6H), 1.38 (d, *J* = 7.0, 1H), 1.27 – 1.10 (m, 3H), 1.08 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 136.6, 116.3, 78.5, 74.0, 72.2, 66.1, 54.4, 51.5, 42.9, 41.6, 41.1, 41.0, 34.0, 32.7, 32.6, 32.2, 28.2, 21.3, 19.3. IR (NaCl/thin film): 3395, 2930, 2876, 1713, 1337, 1163, 1041, 913 cm^{-1}; HRMS (ESI+) calc'd for $C_{20}H_{31}O_4$ $[M + H]^+$ 335.2217, found 335.2220.

Preparation of bis-acetate 139.



97 139 (74% yield) 140 (15% yield)

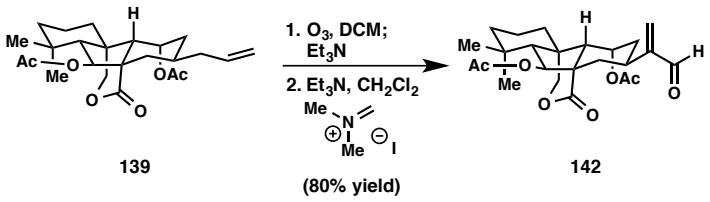
To a solution of tetracycle **97** (5.2 mg, 15.6 μmol, 1.0 equiv) in DCM (2 mL) at 0 ºC was added Ac_2O (45 μL, 476.1 μmol, 30 equiv) and TMSOTf (20 μL, 110.5 μmol, 7.1 equiv). The resulting solution was stirred at 0 ºC until LC/MS (or TLC) indicated complete consumption of starting material (5 min). The reaction mixture was diluted with sat. $NaHCO_3$ (5 mL) and additional DCM (5 mL) and stirred for 30 min. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was purified by preparative reverse phase HPLC (50 to 75% MeCN/H_2O, 20 minute gradient, t_R=15.3 min for **139**, t_R=16.7 min for **140**) to afford bis-acetate **139** (4.8 mg, 74% yield) and γ-lactone **140** (1.0 mg, 15% yield).

Data for desired bis-acetate **139**: $[\alpha]_D^{25}$ = –106.7° (*c* 0.11, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.77-5.69 (m, 1H), 5.37 (dt, *J* = 3.5, 1.9 Hz, 1H), 5.20 (d, *J* = 7.6 Hz, 1H), 5.01-4.97 (m, 2H), 4.62 (dd, *J* = 11.9, 1.8 Hz, 1H), 3.98 (dd, *J* = 12.0, 1.0 Hz, 1H), 2.27 – 2.24 (m, 1H), 2.09 – 1.94 (m, 8H), 1.82 – 1.79 (m, 1H), 1.66 – 1.60 (m, 4H), 1.50 – 1.40 (m, 1H), 1.32 – 1.17 (m, 4H), 1.08 (s, 3H), 1.08 – 1.02 (m, 1H), 0.90 – 0.83 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 170.0, 169.4, 135.9, 116.5, 73.2, 71.4, 67.7, 62.9, 53.3, 51.3, 42.7, 41.2, 40.7, 36.4, 32.9, 32.7, 32.4, 32.2, 28.6, 21.3, 21.0, 20.8, 19.1; IR (NaCl/thin film): 2955, 1745, 1641, 1444, 1368, 1230, 1153, 1103, 1029, 920 cm^{-1}; HRMS (ESI+) calc'd for $C_{24}H_{35}O_6$ $[M + H]^+$ 419.2428, found 419.2425.

Data for translactonized acetate **140**: ^{1}H-NMR (500 MHz; $CDCl_3$): δ 5.75 (d, *J* = 10.4 Hz,

1H), 5.73 – 5.65 (m, 1H), 5.04-4.99 (m, 2H), 4.88 (d, J = 4.4 Hz, 1H), 4.18 (d, J = 12.5 Hz, 1H), 3.84 (d, J = 12.8 Hz, 1H), 2.21 – 2.16 (m, 1H), 2.11 – 2.07 (m, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 2.02-1.92 (m, 2H), 1.81 (dd, J = 12.6, 6.0 Hz, 1H), 1.74 (s, 1H), 1.68-1.51 (m, 4H), 1.51 – 1.46 (m, 1H), 1.37 – 1.32 (m, 1H), 1.21 – 1.12 (m, 2H), 1.03 (td, J = 13.0, 4.2 Hz, 1H), 0.90 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.8, 170.5, 169.7, 135.5, 116.9, 76.0, 73.2, 65.8, 63.0, 63.0, 54.7, 44.1, 41.7, 40.3, 36.7, 35.7, 35.3, 33.0, 32.8, 30.9, 21.6, 21.1, 20.9, 19.1; IR (NaCl/thin film): 2930, 2868, 1775, 1771, 1742, 1739, 1733, 1640, 1447, 1378, 1367, 1234, 1165, 1122, 1035, 937, 915 cm^{-1}; HRMS (ESI+) calc'd for $C_{24}H_{35}O_6$ $[M + H]^+$ 419.2428, found 419.2433.

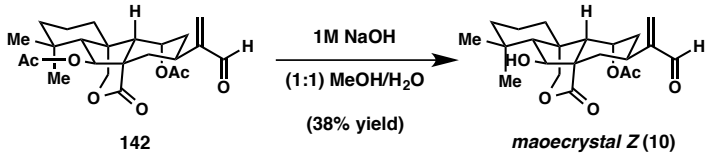
Preparation of enal 142.



A solution of bis-acetate **139** (4.8 mg, 11.5 μmol, 1.0 equiv) in DCM (2 mL) was cooled to – 78 ºC, at which time, ozone was gently bubbled through the solution (O_2 flow rate = 1/8 L/min, 0 setting on ozonator) until LC/MS (or TLC) indicated full consumption of starting material (3 min). The solution was purged with N_2 for 3 min then Et_3N (100 μL, 717.5 μmol, 62.6 equiv) was slowly added dropwise. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stirred until LC/MS indicated complete conversion of the ozonide to the aldehyde (30 min), filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was azeotroped with heptane and placed under high vacuum for 20 min, and then dissolved in DCM (2 mL). To this was added Et_3N (50 μL, 358.7 μmol, 31.3 equiv) and the reaction flask was then taken into a glove box. *N*,*N*-dimethylmethyleneiminium iodide (42.4 mg, 229.2 μmol, 20 equiv) was added to the solution and stirred at rt for 12 h. The reaction mixture was diluted with sat. $NaHCO_3$ (5 mL) and additional DCM (5 mL). The layers

were separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was purified by preparative reverse phase HPLC (40 to 60% MeCN/H_2O, 20 minute gradient, t_R=14.5 min) to afford enal **142** (4.0 mg, 80% yield from **139**). $[\alpha]_D^{25}$ = –67.9° (*c* 0.12, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.50 (d, *J* = 0.7 Hz, 1H), 6.26 (s, 1H), 6.00 (d, *J* = 1.1 Hz, 1H), 5.40 (d, *J* = 1.5 Hz, 1H), 5.21 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 11.9 Hz, 1H), 4.00 (d, *J* = 12.0 Hz, 1H), 3.10 (t, *J* = 12.6 Hz, 1H), 2.22 (dt, *J* = 12.5, 1.7 Hz, 1H), 2.09 (d, *J* = 1.4 Hz, 3H), 2.05 (d, *J* = 1.5 Hz, 3H), 2.01 – 1.96 (m, 1H), 1.82 (d, *J* = 12.9 Hz, 1H), 1.77 (s, 1H), 1.66-1.44 (m, 6H), 1.31 (td, *J* = 13.2, 3.4 Hz, 1H), 1.21 (td, *J* = 13.4, 4.0 Hz, 1H), 1.09 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.0, 172.6, 169.9, 169.4, 152.3, 134.8, 73.3, 71.5, 67.4, 62.8, 52.8, 51.1, 42.9, 41.2, 35.0, 32.9, 32.7, 32.3, 30.3, 29.8, 21.3, 21.0, 20.8, 19.1; IR (NaCl/thin film): 2958, 1737, 1680, 1367, 1225, 1158, 1031 cm^{-1}; HRMS (ESI+) calc'd for $C_{24}H_{33}O_7$ $[M + H]^+$ 433.2221, found 433.2217.

Preparation of (–)-maoecrystal Z (10).



To a suspension of enal **142** (2.9 mg, 6.7 μmol, 1.0 equiv) in 1:1 MeOH/H_2O (600 μL) at rt was added enough CH_2Cl_2 (ca. 200 μL) to afford a slightly cloudy solution. To this was added 1M NaOH (15 μL, 15 μmol, 2.2 equiv) and the solution was stirred for 1 h. An additional portion of 1M NaOH was then added (15 μL, 15 μmol, 2.2 equiv) and the solution was allowed to stir for an additional 2.5 h, at which time, LC/MS indicated complete consumption of starting material. AcOH (50 μL) was then added to neutralize the excess base. The reaction mixture was directly loaded onto a preparative reverse-phase HPLC column and purified (40 to 60% MeCN/H_2O, 20 minute gradient, t_R=8.3 min) to afford (–)-maoecrystal Z (**10**) (1.0 mg, 38% yield). $[\alpha]_D^{25} = -91.2°$ (*c* 0.05, MeOH); ^{1}H NMR (500 MHz; d_5-pyridine): δ 9.53 (s, 1H), 6.21 (s, 1H), 5.87 (s, 1H), 5.56 (td, *J* = 3.9, 2.0 Hz, 1H), 4.65 (dd, *J* = 11.8, 1.8 Hz, 1H), 4.38 (dd, *J* = 7.2, 5.5 Hz, 1H), 4.13 (dd, *J* = 12.0, 1.2 Hz, 1H), 3.61 (tt, *J* = 12.8, 3.3, 1H), 2.74 (ddd, *J* = 12.8, 3.5, 1.7 Hz, 1H), 2.23 (dtd, *J* = 13.9, 3.6, 1.8, 1H), 2.04 (t, *J* = 12.7, 1H), 2.03 (s, 3H), 1.89 (t, *J* = 2.0 1H), 1.67 (d, *J* = 6.8 Hz, 1H), 1.61 (dt, *J* = 12.9, 3.2 Hz, 1H), 1.46 (m, 1H), 1.41 (m, 1H and OH), 1.38 (m, 2H), 1.23 (s, 3H), 1.17 (m, 2H), 1.05 (s, 3H); ^{13}C NMR (126 MHz, d_5-pyridine) δ 194.3, 175.4, 169.9, 154.2, 133.8, 73.9, 71.9, 68.4, 66.0, 53.1, 52.3, 42.7, 41.8, 36.3, 34.5, 33.0, 32.3, 31.7, 28.9, 21.3, 21.1, 19.6; IR (NaCl/thin film): 3434, 2925, 2854, 1742, 1710, 1688, 1464, 1258, 1165, 1096, 838, 777 cm^{-1}; HRMS (ESI+) calc'd for $C_{22}H_{31}O_6$ $[M + H]^+$ 391.2115, found 391.2112.

^{1}H NMR (500 MHz; $CDCl_3$): δ 9.52 (s, 1H), 6.30 (d, *J* = 1.0 Hz, 1H), 6.02 (s, 1H), 5.41 (td, *J* = 4.0, 2.0 Hz, 1H), 4.61 (dd, *J* = 12.0, 2.0 Hz, 1H), 4.04 (dd, *J* = 7.1, 4.6 Hz, 1H), 4.00 (dd, *J* = 12.0, 1.2 Hz, 1H), 3.16 (tt, *J* = 12.6, 3.6, 1H), 2.30 (ddd, *J* = 12.6, 3.5, 1.8 Hz, 1H), 2.09 (s, 3H), 2.04 (dtd, *J* = 14.0, 3.5, 2.0 Hz, 1H), 1.87 (d, *J* = 4.4 Hz, -O**H**), 1.80 (dt, *J* = 13.2, 3.3, 1H), 1.74

(t, J = 2.0 Hz, 1H), 1.63 (t, J = 12.7 Hz, 1H), 1.61 (m, 2H), 1.46 (qt, J = 13.4, 3.8 Hz, 1H), 1.42 (br d, J = 6.9 Hz, 1H), 1.38 (ddd, J = 14.2, 12.9, 2.2 Hz, 1H), 1.29 (td, J = 13.2, 4.0 Hz, 1H), 1.23 (td, J = 13.5, 4.2 Hz, 1H), 1.08 (s, 3H), 1.06 (s, 3H).

^{1}H NMR comparison table of maoecrystal Z (**10**)

Natural (400 MHz)			**Synthetic** (500 MHz)			Δ (ppm)
δ	mult	*J* (Hz)	δ	mult	*J* (Hz)	
9.53	s, 1H	-	9.53	s, 1H	-	0.00
6.21	s, 1H	-	6.21	s, 1H	-	0.00
5.87	s, 1H	-	5.87	s, 1H	-	0.00
5.56	br s, 1H	-	5.56	td, 1H	3.9, 2.0	0.00
4.65	d, 1H	12.0	4.65	dd, 1H	11.8, 1.8	0.00
4.35	t, 1H	7.0	4.38	dd, 1H	7.2, 5.5	+0.03
4.13	d, 1H	12.0	4.13	dd, 1H	12.0, 1.2	0.00
3.60	br t, 1H	12.4	3.61	tt, 1H	12.8, 3.3	+0.01
2.73	dd, 1H	12.8, 1.6	2.74	ddd, 1H	12.8, 3.5, 1.7	+0.01
2.22	br d, 1H	13.6	2.23	dtd, 1H	13.9, 3.6, 1.8	+0.01
2.05	m, 1H	-	2.04	t, 1H	12.7	–0.01
2.03	s, 3H	-	2.03	s, 3H	-	0.00
1.89	s, 1H	-	1.89	t, 1H	2.0	0.00
1.65	d, 1H	7.0	1.67	d, 1H	6.8	+0.02
1.61	br d, 1H	13.2	1.61	dt, 1H	12.9, 3.2	0.00
1.47	m, 1H	-	1.46	m, 1H	-	–0.01
1.43	m, 1H	-	1.41	m, 1H and OH	-	–0.02
1.37	m, 2H	-	1.38	m, 2H	-	+0.01
1.23	s, 3H	-	1.23	s, 3H	-	0.00
1.17*	m, 1H*	-	1.17*	m, 2H*	-	0.00
1.12	m, 1H	-	-	-	-	-
1.05	s, 3H	-	1.05	s, 3H	-	0.00

*We did not observe a proton at 1.12 ppm, but rather, the proton located at 1.17 ppm integrated to 2 protons.

^{13}C NMR comparison table

Natural (δ at 400 MHz)	**Synthetic** (δ at 500 MHz)	Δ (ppm)
194.5	194.3	–0.2
175.7	175.4	–0.3
170.1	169.9	–0.2
154.5	154.2	–0.3
134.0	133.8	–0.2
74.2	73.9	–0.3
72.1	71.9	–0.2
68.6	68.4	–0.2
66.3	66.0	–0.3
53.3	53.1	–0.2
52.6	52.3	–0.3
42.9	42.7	–0.2
42.1	41.8	–0.3
36.5	36.3	–0.2
34.8	34.5	–0.3
33.2	33.0	–0.2
32.5	32.3	–0.2
31.9	31.7	–0.2
29.2	28.9	–0.3
21.6	21.3	–0.3
21.4	21.1	–0.3
19.7	19.6	–0.1

Natural (δ at 400 MHz)	**Synthetic** (δ at 500 MHz)	Δ (ppm)	**Synthetic** (δ at 500 MHz)**	Δ (ppm)**
194.5	194.3	–0.2	194.5	0.0
175.7	175.4	–0.3	175.7	0.0
170.1	169.9	–0.2	170.1	0.0
154.5	154.2	–0.3	154.4	–0.1
134.0	133.8	–0.2	134.0	0.0
74.2	73.9	–0.3	74.1	–0.1
72.1	71.9	–0.2	72.1	0.0
68.6	68.4	–0.2	68.6	0.0
66.3	66.0	–0.3	66.2	–0.1
53.3	53.1	–0.2	53.3	0.0
52.6	52.3	–0.3	52.5	–0.1
42.9	42.7	–0.2	42.9	0.0
42.1	41.8	–0.3	42.1	0.0
36.5	36.3	–0.2	36.5	0.0
34.8	34.5	–0.3	34.7	–0.1
33.2	33.0	–0.2	33.2	0.0
32.5	32.3	–0.2	32.5	0.0
31.9	31.7	–0.2	31.9	0.0
29.2	28.9	–0.3	29.1	–0.1
21.6	21.3	–0.3	21.6	0.0
21.4	21.1	–0.3	21.3	–0.1
19.7	19.6	–0.1	19.8	+0.1

**Rightmost peak of the most downfield signal of C_5D_5N referenced to δ 149.9 ppm.

By referencing the rightmost peak of the most downfield signal of C_5D_5N at δ 149.9 ppm, we obtained carbon shift values that were in better agreement with the literature.

2.5 NOTES AND REFERENCES

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(26) We were unfortunately unable to isolate a clean sample of **131** but tentatively assigned its structure as the hemiacetal shown in Figure 2.11 based on crude ^{1}H NMR and LC–MS data. See Appendix 1.

(27) Spectroscopic data obtained were consistent with isolation data reported by Han and coworkers.[1]

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