Chapter 2

Total Syntheses of Ent-Kauranoids (–)-Trichorabdal A and (–)-Longikaurin E[†]

2.1 INTRODUCTION

In 2011, our group reported the total synthesis of the rearranged *ent*-Kauranoid maoecrystal Z. Key to the synthesis was a spirolactone intermediate that was prepared in good yield and excellent diastereoselectivity via a Ti(III)-mediated reductive coupling reaction. Given that several biologically active *ent*-kauranoids possess a spirocyclic lactone or lactol moiety, we set out to explore whether the spirolactone intermediate could be used for the synthesis of the more general 6,7-*seco* framework and its biogenetically related 7,20-epoxy type frameworks. This chapter introduces the state of the art prior to and concurrent with our synthetic efforts. A detailed account of our total

[†] The research discussed within this chapter was completed in collaboration with Dr. John T. S. Yeoman.

syntheses of (–)-trichorabdal A and (–)-longikaurin E via a common intermediate is described. This work, taken together with our synthesis of (–)-maoecrystal Z, represents a unified synthetic strategy to access structurally distinct *ent*-kauranoid natural products.

2.2 PREVIOUS AND CONCURRENT SYNTHETIC EFFORTS

Synthetic efforts relating to 6,7-*seco*-*ent*-kauranoids are discussed in this section with the aim of contextualizing our synthetic efforts with prior state of the art. Several syntheses of *ent*-kauranoid natural products followed our communication on the total synthesis of (–)-trichorabdal A and (–)-longikaurin E;[1] for the sake of brevity, these syntheses will not be reviewed in this section.

2.2.1 *Fujita's Relay Synthesis of Enmein*

In light of their compelling biological activity and structural complexity, several research groups have reported total syntheses of 6,7-seco-*ent*-kauranoids. Perhaps the most challenging synthetic aspect of these diterpenoids is the formation of the two quaternary centers, which include the C8 quaternary center and the C10 quaternary center contained within the central spirolactone. As early as 1974, Fujita reported the total synthesis of enmein (**15**) through an optically active relay compound (Figure 2.1).[2] In the synthesis, the C8 quaternary center was introduced via enolate alkylation. Thiol ether **37** was accessed in 12 steps from phenanthrene derivative **36.** Deprotection of thiol ether **37** and ozonolysis afforded a ketoaldehyde that underwent a sodium methoxide-mediated aldol reaction to form bicyclo[3.2.1]octane **38** of the *ent*-kaurene core. After

advancement to alkene **39**, ozonolysis cleaved the C6–C7 bond to form the 6,7-seco framework of **40**, which was advanced a further 18 steps to enmein (**15**).

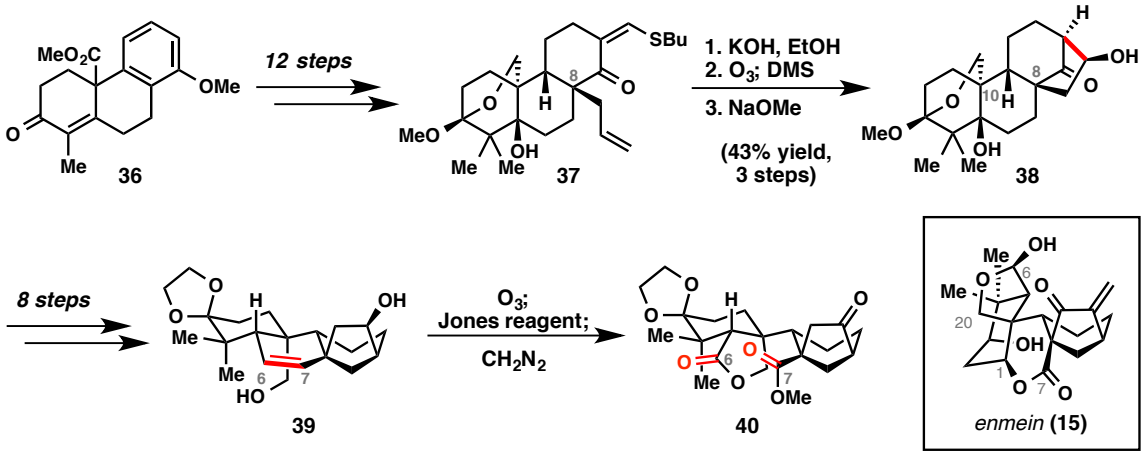


Figure 2.1. Key transformations in Fujita's relay synthesis of enmein (**15**).

2.2.2 *Mander's Synthesis of 15-Desoxyeffusin*

More than a decade later after Fujita's studies, Mander reported the synthesis of 15-desoxy derivatives of effusin and longikaurin C (Figure 2.2).[3] Similar to Fujita's strategy, oxidative cleavage of the C6–C7 bond of a lactol precursor provided access to the *seco-ent*-karanoid framework. To construct the bicyclo[3.2.1]octane, α-diazoketone **41** was treated with trifluoroacetic acid to afford dienone **42** through an intramolecular aromatic alkylation. A further 12 steps provided lactone **43**, which smoothly underwent intramolecular α-alkylation to furnish *ent*-kauranoid framework **44** after desilylation and oxidation. This intermediate was advanced to 15-desoxylongikaurin C (**45**), and oxidative cleavage of the C6–C7 bond upon exposure to periodic acid afforded the 6,7-*seco* type desoxyeffusin (**46**) in a biomimetic fashion. Notably, oxidation of C15 on both **45** and **46** to afford the corresponding natural products was not achieved at the time.

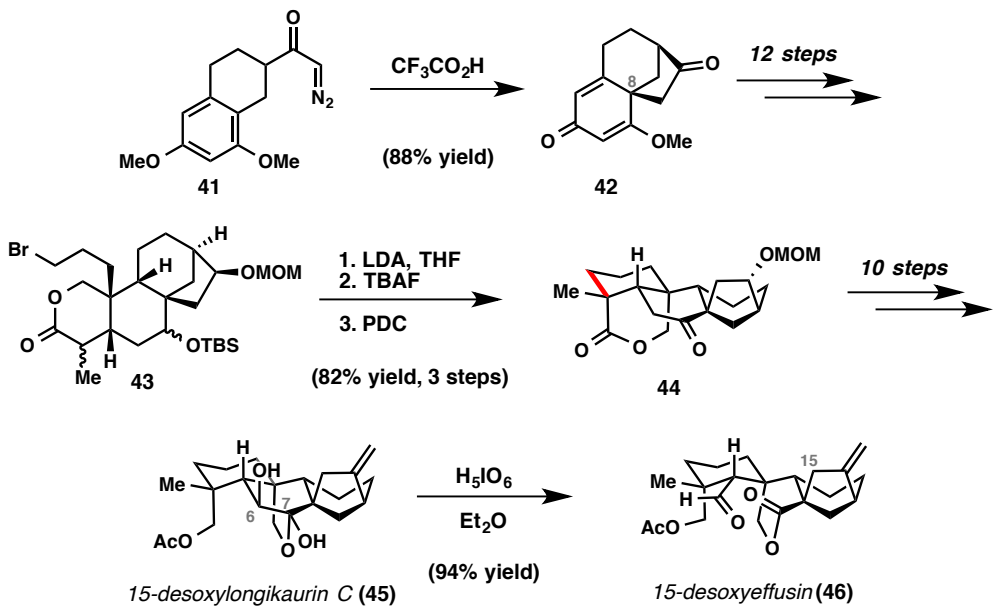


Figure 2.2. Mander's synthesis of 15-desoxy analogues.

2.2.3 *Zhai's Total Synthesis of Sculponeatin N*

Zhai and colleagues recently disclosed a concise total synthesis of sculponeatin N (**14**) that utilizes a radical cyclization to build the bicyclo[3.2.1]octane unit (Figure 2.3).[4] Beginning with known diester **47**, a silyl diene unit was appended, and a reduction/acylation sequence provided **48** as an intramolecular Diels–Alder cycloaddition precursor. Heating to 190 °C in the presence of a radical scavenger simultaneously constructed the B and C-rings, and after silylation, provided tricycle **49** in 76% yield over two steps. The C8 quaternary center of **51** was introduced via alkylation of the lactone with 2,3-dibromopropene (**50**). In a crucial step of the synthesis, exposure of **51** to triethylborane and tris(trimethylsilyl)silane rapidly furnished 6,7-*seco*-*ent*-kauranoid core **52**. Lastly, allylic oxidation and desilylation provided sculponeatin N (**14**) in just 13 steps from diester **47**.

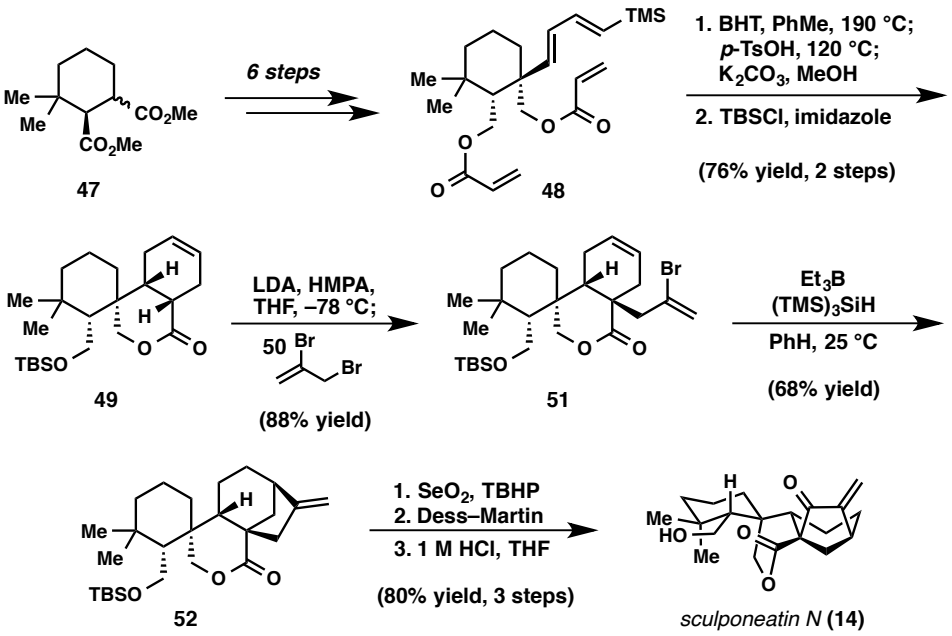


Figure 2.3. Zhai's total synthesis of sculponeatin N (**14**).

2.3 SYNTHETIC APPROACH

2.3.1 *Total Synthesis of (–)-Maoecrystal Z*

Our interest in the 6,7-seco-*ent*-kauranoids was piqued by maoecrystal Z (**17**), which possesses a unique rearranged skeleton.[5] In 2011, our group reported the total synthesis of (–)-maoecrystal Z (**17**) that featured, among other key steps, a dialdehyde cyclization cascade to form the tetracyclic core.[6] The synthetic strategy was partially guided by Fujita's studies that showed treatment of trichorabdal B (1**3**) initiated a retro-Dieckmann–aldol sequence to form the tetracyclic framework of **17**.[7] In the retrosynthetic analysis, **17** was envisioned to arise from a Sm^{II}-initiated cascade cyclization of **54** through Sm-enolate **53** (Figure 2.4). Dialdehyde **54** would arise from

alkylation with alkyl iodide **55** of the key spirolactone **56** that is found within the skeleton of many *ent*-kauranoids.

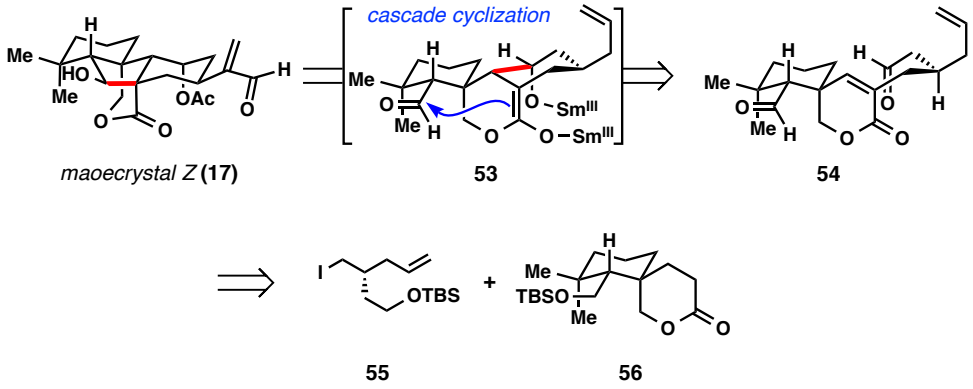


Figure 2.4. Retrosynthetic analysis of (–)-maoecrystal Z (**17**).

In the forward direction, (–)-γ-cyclogeraniol (**57**) was converted to the silyl ether and treated with *m*-CPBA to form epoxide **58** as an inconsequential mixture of diastereomers (Figure 2.5). After much optimization, it was found that spirolactone **56** could be accessed diastereoselectively through a titanocene-mediated coupling with trifluoroethyl acrylate. Alkylation and oxidation afforded enoate **59**, which was deprotected and treated with Dess–Martin periodinane to form the cyclization precursor, dialdehyde **54**. In the key step of the synthesis, exposure of dialdehyde **54** to SmI_2 and LiBr with *t*-BuOH as a proton source furnished a single diastereomer of tetracycle **60**. This reaction likely proceeds through ketyl formation at C12, undergoing radical cyclization and further reduction to form Sm-enolate **53** (see Figure 2.4). A subsequent aldol reaction affords the central 5-membered ring, overall providing two new rings and setting four stereocenters in a single step. Lastly, bis-acetylation to diacetate **61** followed

by ozonolysis and α-methylenation provided enal **62**, which was monodeprotected to afford maoecrystal Z (**17**).

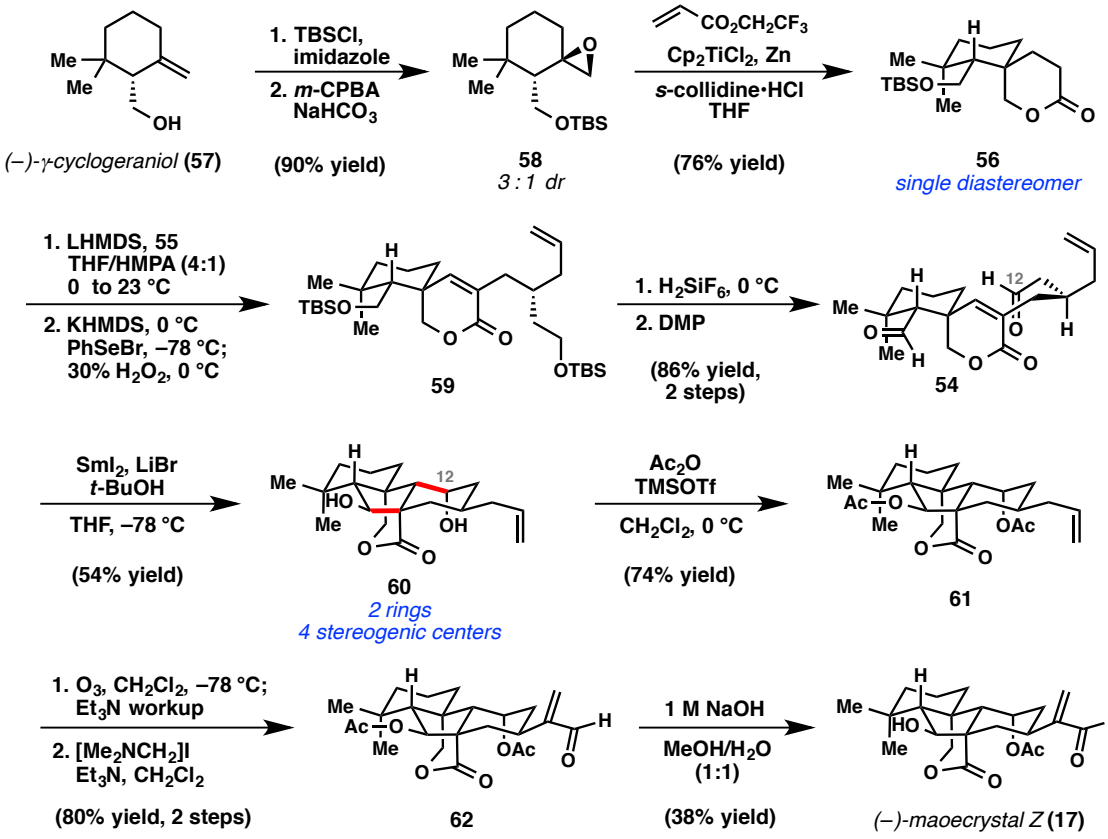


Figure 2.5. Total synthesis of (–)-maoecrystal Z (**17**).

Our group's total synthesis of (–)-maoecrystal Z (**17**) proceeded in 12 synthetic steps from (–)-γ-cyclogeraniol (**57**). The successful utilization of the key spirolactone **56** prompted our investigations to the biogenetically related *ent*-kauranoids (–)-trichorabdal A (**12**) and (–)-longikaurin E (**11**). Ultimately, spirolactone **56** would serve as an important building block for the completion of structurally distinct *ent*-kauranoid natural products.

2.3.2 *Retrosynthesis of (–)-Trichorabdal A and (–)-Longikaurin E*

Retrosynthetically, **11** and **12** were both envisioned to arise from *exo*-olefin **63** (Figure 2.6). To access (–)-longikaurin E (**11**), we hoped to forge the central oxabicyclo[2.2.2]octane via the reductive cyclization of a C6-aldehyde precursor.[8] The bicyclo[3.2.1]octane motif of **63** would arise through a transition metal-mediated oxidative cyclization reaction of silyl ketene acetal **64**. Although the oxidative cyclization of silyl enol ethers is well precedented,[9,10] there were no examples of transition metal-mediated oxidative cyclizations between silyl ketene acetals and simple olefins that generated all-carbon quaternary centers reported prior to our studies.[11] Mindful of this challenge, we were nonetheless eager to employ such a strategy for the assembly of this pivotal intermediate, as it was anticipated that the Sm(II)-mediated cyclization chemistry devised en route to (–)-maoecrystal Z (**17**) would enable the facile synthesis of tricycle **64** from aldehyde **65** and intermediate **59**. Thus, the strategy would enable the divergent synthesis of three architecturally unique *ent*-kauranoids via a common precursor.

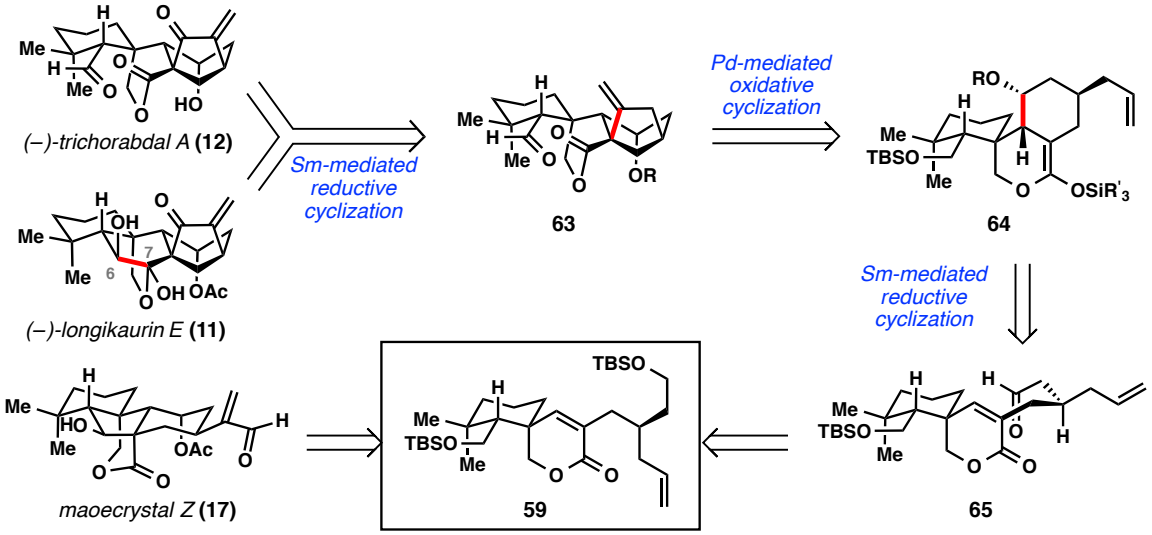


Figure 2.6. Retrosynthesis of (–)-trichorabdal A (**12**) and (–)-longikaurin E (**11**).

2.4 FORWARD SYNTHETIC EFFORTS

2.4.1 *Development of a Pd(II)-Mediated Oxidative Cyclization*

To investigate the proposed oxidative cyclization, we needed to prepare silyl ketene acetal **64** from enoate **59** (Figure 2.7). The more sterically accessible silyl ether of **59** was deprotected and oxidized to afford aldehyde **66**. Treatment with a mixture of SmI_2 and LiBr in THF in the presence of *t*-BuOH at low temperature formed the cyclization product **67** as a single diastereomer in 57% yield. MOM-protection of the secondary alcohol of **67** allowed for smooth conversion to silyl ketene acetal **64** upon deprotonation and trapping with TBSCl. It was found that use of silyl protecting groups gave lower yields of silyl ketene acetal **64**, presumably due to 1,3-diaxial interactions that made deprotonation at C8 challenging.

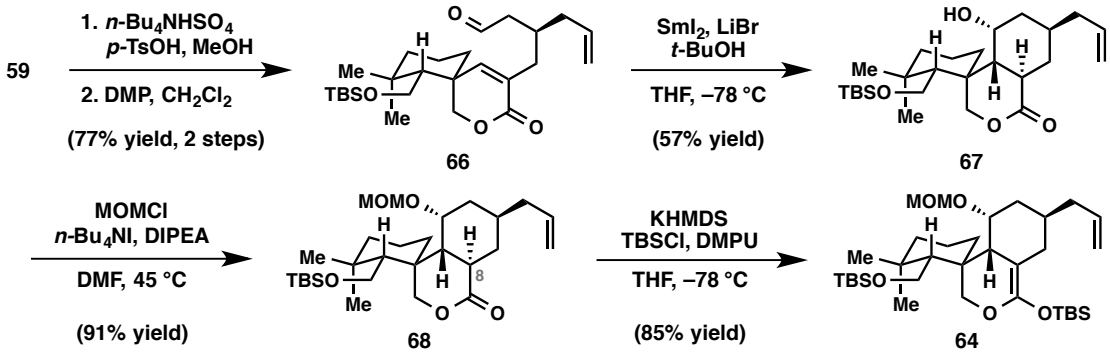
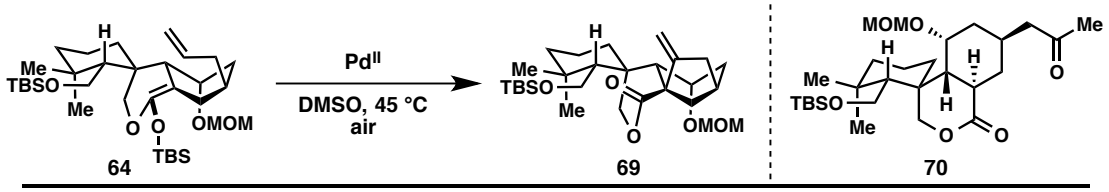


Figure 2.7. Preparation of silyl ketene acetal **64**.

With oxidative cyclization precursor **64** in hand, a survey of conditions for the key oxidative cyclization step was conducted. Upon exposure of **64** to 10 mol % $Pd(OAc)_2$ in DMSO at 45 °C under an air atmosphere, we were delighted to isolate tetracycle **69**, albeit in only 7% yield (Table 1, entry 1). Fortunately, the use of

stoichiometric $Pd(OAc)_2$ substantially improved both conversion and the yield of **69** (entry 2), and a survey of reaction conditions was conducted. The desired transformation does proceed in MeCN at ambient temperature (entry 3); however, increased side product formation is observed. Other solvents (e.g., PhMe, glyme, dioxane, *t*-BuOH, DMF) yielded only traces of **69**. Other palladium sources also performed poorly (entries 4–6): for example, the major product when using $PdCl_2$ and $AgBF_4$ (entry 6) was methyl ketone **70**, via Wacker oxidation. No desaturated products from Saegusa–Ito-type pathways were observed.[12]



Entry	Pd source (equiv)	Additive (equiv)	Yield 69 (%)[a]
1	$Pd(OAc)_2$ (0.1)	--	7
2	$Pd(OAc)_2$ (1.0)	--	35
3[b]	$Pd(OAc)_2$ (1.0)	--	28[c]
4	$Pd(TFA)_2$ (1.0)	--	19
5	$PdCl_2$ (1.0)	--	0
6	$PdCl_2$ (1.0)	$AgBF_4$ (2.0)	5[d]
7[e]	$Pd(OAc)_2$ (1.0)	H_2O (5.0)	38
8	$Pd(OAc)_2$ (1.0)	K_2CO_3 (5.0)	0
9	$Pd(OAc)_2$ (1.0)	AcOH (0.5)	56
10	$Pd(OAc)_2$ (0.1)	AcOH (0.5)	7
11	$Pd(OAc)_2$ (1.0)	AcOH (1.0)	31
12	$Pd(OAc)_2$ (1.0)	*p*-TsOH (0.5)	46
13	$Pd(OAc)_2$ (1.0)	BzOH (0.5)	32
14	$Pd(OAc)_2$ (1.0)	PivOH (0.5)	40

[a]Isolated yield. [b]Reaction conducted in MeCN at 23 °C. [c]Product isolated as an inseparable 4.3:1 mixture with an olefin isomerization side product. [d]13% yield of methyl ketone **70** was also isolated. [e]Run under a N_2 atmosphere.

Table 2.1. Reaction optimization of the oxidative cyclization of **64.**

High variability in both the yield and purity of **69** upon attempts to increase reaction scale beyond a few milligrams prompted an examination of the roles of adventitious water and Brønsted acid. Indeed, similar reaction conditions with water and Brønsted acid have been used to promote Wacker-type oxidation of terminal olefins.[13] Control experiments demonstrated that water had little effect on product formation (entry 7), whereas the addition of bases such as K_2CO_3 inhibits the reaction (entry 8). On the other hand, the use of 0.5 equiv AcOH as an additive afforded **69** in 56% yield (entry 9) with a much cleaner reaction profile, a result reproducible on preparative scales. Neither an increased amount of AcOH nor the use of other acids examined were found to further improve the yield. To the best of our knowledge, this represents the first example of a Pd-mediated oxidative cyclization of a silyl ketene acetal to generate an all-carbon quaternary center.

2.4.2 *Total Synthesis of (–)-Trichorabdal A*

Having now established the carbon framework present in many 6,7-*seco*-*ent*-kauranoids, the remaining steps for the synthesis of **12** included installation of the *exo*-enone and C6 aldehyde. Ozonolysis of **69** and subsequent α-methylenation using bis(dimethylamino)methane and acetic anhydride delivered β-ketolactone **72** (Figure 2.8).[14] Notably, the analogous two-step procedure using Eschenmoser's salt provided significantly diminished yields of **72**. Exposure to 6 M aqueous HCl in dioxane at 45 °C smoothly effected global deprotection, and selective oxidation of the C6 primary alcohol was accomplished using catalytic TEMPO and $PhI(OAc)_2$,[15] delivering (–)-trichorabdal A (**12**).[16]

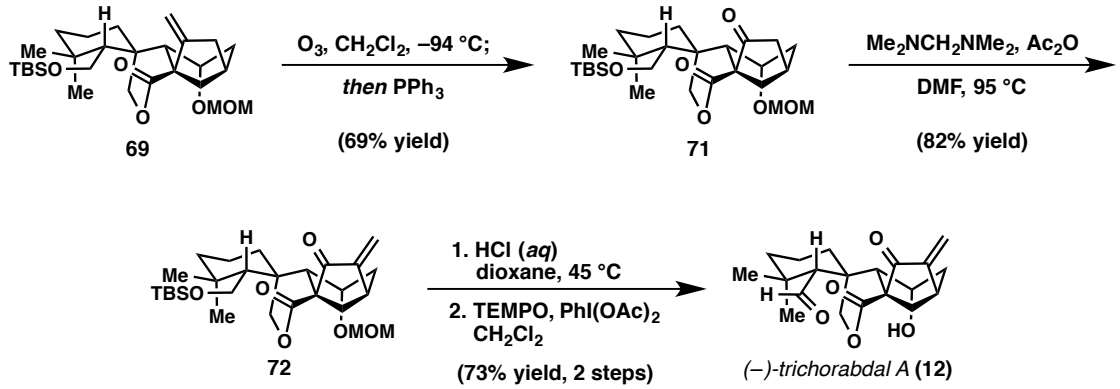


Figure 2.8. Total synthesis of (–)-trichorabdal A (**12**).

2.4.3 *Total Synthesis of (–)-Longikaurin E*

With the synthesis of **12** complete, we turned our attention to the aldehyde-lactone reductive coupling required for the synthesis of (–)-longikaurin E (**11**). Treatment of *exo*-olefin **69** with 6 M aqueous HCl in dioxane at 45 °C resulted in global deprotection to afford diol **73**; subsequent oxidation with catalytic TEMPO and $PhI(OAc)_2$ likewise proceeded smoothly (Figure 2.9). Aldehyde **74** was acetylated using acetic anhydride and DMAP to furnish **75**, and a screen of reaction parameters for the proposed reductive cyclization was conducted.

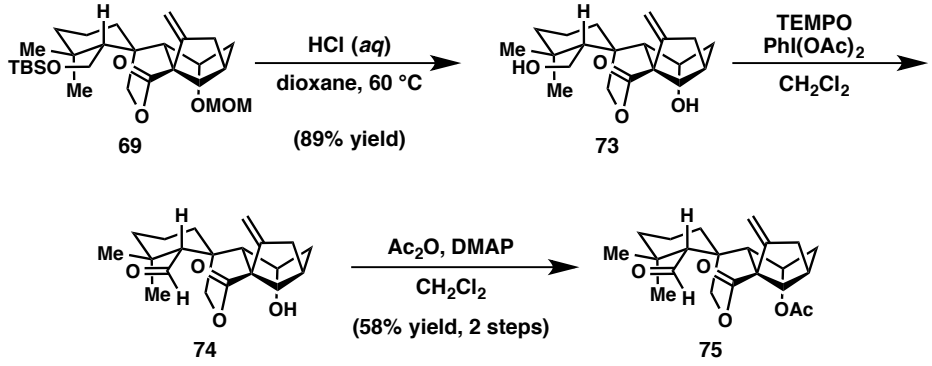
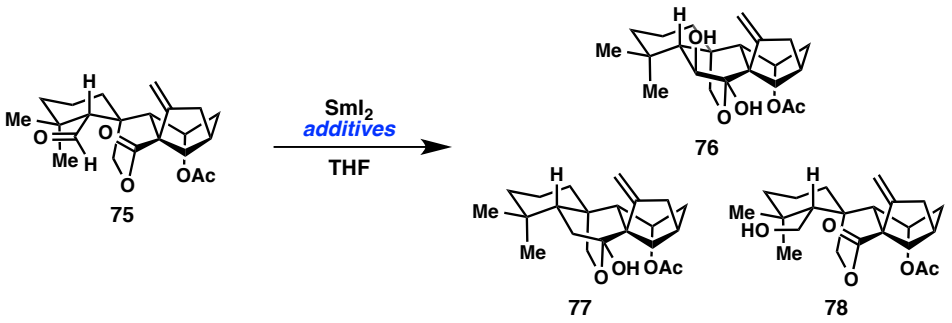


Figure 2.9. Synthesis of aldehyde-lactone **75**.



Entry	Equivs SmI_2	Additives (equivs)	Temperature (°C)	Yield[a] (brsm)
1	5.0	LiCl (50), *t*-BuOH (1.0)	–78	no reaction
2	5.0	LiBr (50), *t*-BuOH (1.0)	–78	no reaction
3	5.0	*t*-BuOH (1.0)	–78	no reaction
4	5.0	HMPA (50), *t*-BuOH (1.0)	–78	0%[b]
5	5.0	LiCl (50), *t*-BuOH (1.0)	0	54% **78**
6	5.0	LiBr (50), *t*-BuOH (1.0)	0	38% **78**
7	5.0	*t*-BuOH (1.0)	0	25% **76** (100%)
8	2.2	--	23	55% **76** (75%)
9	2.4	--	23	55% **76** (62%)
10[c]	5.0	*t*-BuOH (1.0)	23	72% **77**

[a]Isolated yield. [b]Complex mixture. [c]Run to full consumption of **75**.

Table 2.2. Optimization of Sm-mediated pinacol-type coupling.

Surprisingly, treatment of aldehyde-lactone **75** with LiCl, LiBr, or no lithium salt in the presence of *t*-BuOH at –78 °C (Table 2.2, entries 1–3) led to recovery of starting material, while use of a bulkier additive, HMPA, resulted in a complex mixture of products (entry 4). The use of lithium salts with *t*-BuOH at higher temperature induced reduction of the aldehyde to alcohol **78** with no recovered starting material (entries 5–6). Fortunately, omitting the lithium salts at 0 °C gave 20% yield of desired hydroxyl-lactol **76** (entry 7). Further raising the temperature to 23 °C improved conversion, while utilizing less equivalents of SmI_2, and excluding the proton source lowered the amount of

side-products. Overall, this resulted in a 55% isolated yield of the desired product (**76**), along with 27% yield of recovered starting material (entry 8). The remainder of the mass balance was attributed to C6-deoxy lactol **77** and over-reduction side products. Attempts to push the reaction to completion, for example by raising the equivalents of SmI_2, resulted in larger amounts of side-product **77** (entry 9). In fact, running the reaction to full consumption of **75** gave lactol **77** in 72% yield (entry 10).

Completion of the total synthesis from hydroxyl-lactol **76** proceeded via ozonolysis and α-methylenation under previously described conditions (Figure 2.10). Notably, a significant amount of an epoxide product was observed in the ozonolysis of **76**. Formation of this epoxide was suppressed by using lower temperatures, down to –94 °C. Lastly, α-methylenation of ketone **79** delivered (–)-longikaurin E (**11**) in 67% yield.[17] This represents the first total synthesis of a 7,20-epoxy-*ent*-kauranoid natural product.

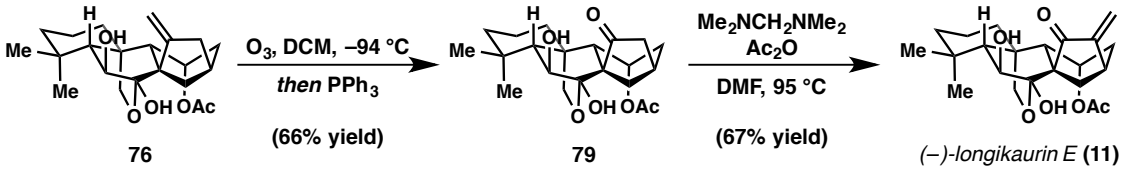


Figure 2.10. Total synthesis of (–)-longikaurin E (**11**).

2.5 CONCLUDING REMARKS

In summary, a unified synthetic strategy to prepare three unique *ent*-kauranoid frameworks from unsaturated lactone **59** has been established. The first total synthesis of (–)-trichorabdal A (**12**) and (–)-longikaurin E (**11**) proceeded in 15 and 17 steps and 3.2% and 1.0% overall yield, respectively, from (–)-γ-cyclogeraniol (**57**). The pivotal transformations that enabled these syntheses include a new Pd^{II}-mediated oxidative

cyclization of a silyl ketene acetal (**64**) to form an all-carbon quaternary center, as well as a Sm^{II}-mediated pinacol-type coupling to forge the oxabicyclo[2.2.2]octane of **11**. Taken with our group's total synthesis of (–)-maoecrystal Z (**17**), we have demonstrated the synthetic utility of single-electron chemistry in diastereoselectively forming vicinal stereocenters in complex polycyclic systems and have also established a non-biomimetic synthetic relationship among three architecturally distinct *ent*-kaurane diterpenoids.

2.6 EXPERIMENTAL SECTION

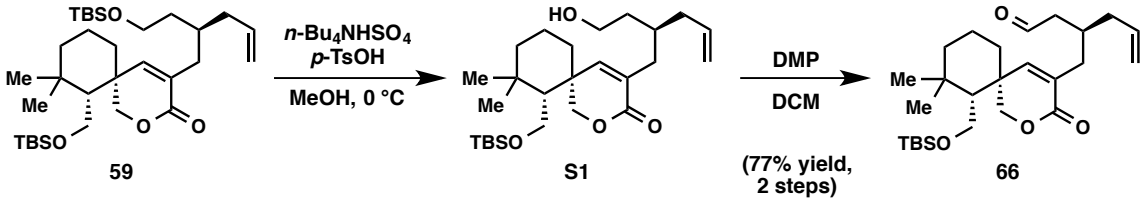
2.6.1 *Materials and Methods*

Unless otherwise stated, reactions were performed under an inert atmosphere (dry N_2 or Ar) with freshly dried solvents utilizing standard Schlenk techniques. Glaswarewas oven-dried at 120 °C for a minimum of four hours, or flame-dried utilizing a Bunsen burner under high vacuum. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), *tert*-butyl methyl ether (TBME), benzene (PhH), and toluene (PhMe) were dried by passing through activated alumina columns. Triethylamine (Et_3N) and *N,N*-Diisopropylethylamine (DIPEA) were distilled over calcium hydride, 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) and hexamethylphosphor-amide (HMPA) were distilled over calcium hydride under reduced pressure, and dimethylsulfoxide (DMSO) was dried over 4 Å MS for at least 48 hours 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 staining. Flash column chromatography was performed using silica gel (SiliaFlash® P60, particle size 40-63 microns [230 to 400 mesh]) 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 Bruker Avance III HD with Prodigy cryoprobe (at 400 MHz and 101 MHz respectively), a Varian 400 MR (at 400 MHz and 101 MHz, respectively), 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, $\delta = 7.26$) and $CDCl_3$ (^{13}C, $\delta = 77.0$). Data for

^{1}H 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).

2.6.2 *Preparative Procedures and Spectroscopic Data*

Preparation of aldehyde 66:



To a solution of enoate **59** (1.94 g, 3.43 mmol) in 35 mL MeOH cooled to 0 °C was added *n*-Bu_4NHSO_4 (128 mg, 0.378 mmol, 0.11 equiv) and *p*-TsOH (26 mg, 0.14 mmol, 0.04 equiv). After stirring at 0 °C for 1.5 h, the reaction mixture was diluted with sat. $NaHCO_3$ (25 mL) and concentrated *in vacuo* to remove MeOH. The aqueous layer was then extracted with EtOAc (3 x 15 mL). The combined organic extracts were then washed with brine (15 mL), dried over Na_2SO_4, and concentrated *in vacuo* to provide crude alcohol **S1**. Crude **S1** was immediately dissolved in DCM (35 mL) and Dess–Martin periodinane (2.91 g, 6.87 mmol, 2.0 equiv) was added. After stirring at ambient

temperature for 30 min, sat. $NaHCO_3$ (20 mL) and sat. $Na_2S_2O_3$ (20 mL) were added and the biphasic mixture was stirred vigorously until both layers became clear (20 min). The layers were separated and the aqueous phase was extracted with DCM (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (10 to 12% EtOAc/Hex) to provide aldehyde **66** as a clear gum (1.18 g, 77% yield from **59**).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.71 (t, *J* = 2.0 Hz, 1H), 6.39 (s, 1H), 5.78 – 5.66 (m, 1H), 5.09 – 4.99 (m, 2H), 4.48 (dd, *J* = 11.2, 1.9 Hz, 1H), 4.40 (dd, *J* = 11.2, 1.4 Hz, 1H), 3.81 – 3.71 (m, 2H), 2.48 – 2.26 (m, 4H), 2.20 – 2.10 (m, 2H), 2.01 (dt, *J* = 13.9, 7.6 Hz, 1H), 1.84 (d, *J* = 13.6 Hz, 1H), 1.69 – 1.49 (m, 2H), 1.48 – 1.39 (m, 2H), 1.25 (td, *J* = 13.0, 4.3 Hz, 1H), 1.14 (td, *J* = 13.0, 4.4 Hz, 1H), 1.01 (s, 3H), 0.89 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 202.5, 164.8, 155.6, 135.6, 126.2, 117.6, 69.9, 61.3, 55.5, 47.3, 42.0, 39.7, 38.6, 36.0, 33.1, 33.0, 32.8, 32.1, 25.8, 23.2, 18.3, 18.1, -5.5, -5.6.

FTIR (thin film/NaCl): 3421, 3076, 2927, 2855, 2716, 1728, 1713, 1471, 1393, 1255, 1164, 1150, 1104, 1068, 995, 913, 838, 776 cm^{-1}.

HRMS: (MM: ESI–APCI) calc'd for $C_{26}H_{45}O_4Si$ $[M + H]^+$ 449.3082, found 449.3067.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –33.4° (*c* = 1.23, $CHCl_3$).

An analytical sample of alcohol **S1** was obtained (63% yield) by SiO_2 chromatography (30% EtOAc/Hex):

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.37 (s, 1H), 5.73 (dddd, *J* = 16.8, 10.4, 7.7, 6.5 Hz, 1H), 5.07 – 4.98 (m, 2H), 4.51 (dd, *J* = 11.3, 2.1 Hz, 1H), 4.41 (dd, *J* = 11.3, 1.5 Hz, 1H), 3.83 – 3.71 (m, 3H), 3.67 (dt, *J* = 11.0, 6.4 Hz, 1H), 2.36 (ddd, *J* = 13.9, 5.6, 1.3 Hz, 1H), 2.16 – 2.07 (m, 1H), 2.04 (dd, *J* = 14.0, 8.2 Hz, 1H), 2.01 – 1.92 (m, 2H), 1.91 – 1.78 (m, 2H), 1.66 – 1.49 (m, 3H), 1.49 – 1.34 (m, 3H), 1.32 – 1.21 (m, 1H), 1.21 – 1.09 (m, 1H), 1.02 (s, 3H), 0.92 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H);

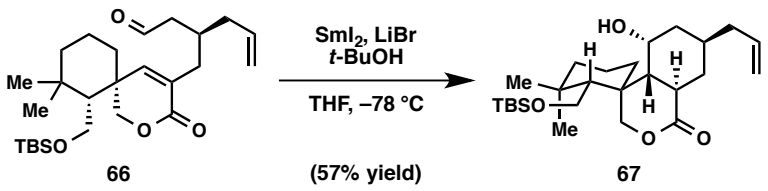
^{13}C NMR (126 MHz, $CDCl_3$): δ 165.2, 154.6, 136.3, 127.6, 116.8, 70.0, 61.5, 60.6, 55.6, 42.1, 40.0, 38.2, 35.7, 35.3, 33.3, 33.3, 33.0, 32.8, 25.8, 23.3, 18.4, 18.0, -5.5, -5.6;

FTIR (thin film/NaCl): 3447, 3074, 2952, 2928, 2856, 1718, 1472, 1462, 1395, 1363, 1256, 1165, 1150, 1105, 1069, 995, 909, 838, 776;

HRMS: (MM: ESI–APCI) calc'd for $C_{26}H_{47}O_4Si$ $[M + H]^+$ 451.3238, found 451.3251.

$[\alpha]_D^{25}$ = –44.6° (*c* = 1.21, $CHCl_3$);

Preparation of tricycle 67:



Fresh SmI_2 was prepared according to the following procedure:[18] 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 solution of aldehyde **66** (0.676 g, 1.51 mmol) and *t*-BuOH (0.145 mL, 1.51 mmol, 1.0 equiv) in 150 mL THF was cooled to –78 °C. Inside a glovebox, a separate flame-dried flask was charged with LiBr (3.27 g, 38 mmol, 25 equiv), removed from the glovebox, and to this flask was added freshly prepared 0.1 M SmI_2 in THF (38 mL, 3.8 mmol, 2.5 equiv) and stirred vigorously for 2 min. While stirring continued, the resulting homogenous purple solution was added to the aldehyde solution via cannula. After 45 min at –78 °C, sat. $NaHCO_3$ (60 mL), sat. $Na_2S_2O_3$ (60 mL) and Rochelle salt (10 g) were added, and the mixture was extracted with EtOAc (3 x 80 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (9 to 12% EtOAc/Hex) to afford tricycle **67** as a white foam (0.385 g, 57% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.80 – 5.68 (m, 1H), 5.04 – 4.94 (m, 2H), 4.55 (br s, 1H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.24 (dd, *J* = 11.5, 1.4 Hz, 1H), 3.72 (dd, *J* = 11.4, 4.1 Hz, 1H), 3.67 (dd, *J* = 11.3, 3.3 Hz, 1H), 2.85 (td, *J* = 12.3, 3.4 Hz, 1H), 2.45 (dtd, *J* = 13.2, 3.6, 2.0 Hz, 1H), 2.04 – 1.84 (m, 5H), 1.79 – 1.71 (m, 2H), 1.69 (t, *J* = 3.8 Hz, 1H), 1.56 – 1.36 (m, 4H), 1.27 (td, *J* = 12.7, 4.9 Hz, 1H), 1.09 (ddd, *J* = 14.2, 12.5, 2.2 Hz, 1H), 1.01 (s, 3H), 0.98 (t, *J* = 12.0 Hz, 1H), 0.88 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

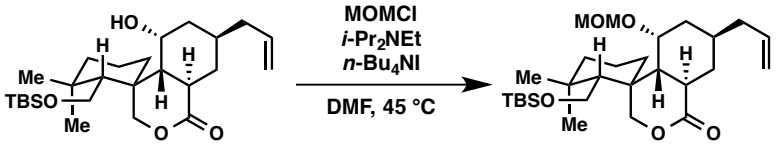
^{13}C NMR (126 MHz, $CDCl_3$): δ 174.2, 136.2, 116.3, 73.2, 65.5, 60.0, 51.5, 46.6, 41.9, 40.9, 40.8, 39.5, 35.4, 35.1, 34.1, 33.7, 30.6, 27.8, 25.9, 23.6, 18.4, 18.1, -5.5, -5.6.

FTIR (thin film/NaCl): 3461, 3075, 2927, 2856, 1716, 1471, 1463, 1394, 1362, 1256, 1220, 1064, 1046, 994, 911, 837, 776, 734 cm^{-1}.

HRMS: (MM: ESI–APCI) calc'd for $C_{26}H_{47}O_4Si$ $[M + H]^+$ 451.3238, found 451.3236.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –11.3° (*c* = 2.26, $CHCl_3$).

Preparation of MOM ether 68:



67 (91% yield) 68

A solution of tricycle **67** (0.315 g, 0.699 mmol), *n*-Bu_4NI (26 mg, 70 μmol, 0.1 equiv), DIPEA (0.73 mL, 4.2 mmol, 6.0 equiv), and MOMCl (92% tech., 0.29 mL, 3.5 mmol, 5.0 equiv) in 3.5 mL DMF was heated to 45 °C. After stirring for 6 h at 45 °C, the reaction mixture was cooled to room temperature and diluted with sat. $NaHCO_3$ (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (7 to 9% EtOAc/Hex) to afford methoxymethyl ether **68** as a clear gum (0.315 g, 91% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.81 – 5.69 (m, 1H), 5.05 – 4.98 (m, 1H), 4.98 (t, *J* = 1.2 Hz, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 4.62 (d, *J* = 6.7 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.37 (dt, *J* = 3.7, 1.8 Hz, 1H), 4.24 (dd, *J* = 11.4, 1.4 Hz, 1H), 3.74 (dd, *J* = 11.4, 4.1 Hz, 1H), 3.67 (dd, *J* = 11.4, 3.3 Hz, 1H), 3.40 (s, 3H), 2.87 (td, *J* = 12.3, 3.5 Hz, 1H), 2.47 (dtd, *J* = 13.1, 3.7, 2.1 Hz, 1H), 2.09 – 1.86 (m, 5H), 1.86 – 1.72 (m, 2H), 1.69 (t, *J* = 3.7 Hz, 1H), 1.64 – 1.40 (m, 4H), 1.28 – 1.18 (m, 1H), 1.08 – 0.96 (m, 4H), 0.90 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H).

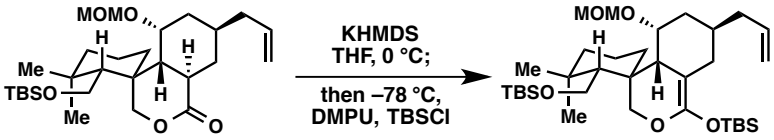
^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 136.2, 116.3, 95.1, 73.3, 71.4, 59.8, 56.3, 51.4, 47.0, 42.1, 40.8, 39.6, 36.4, 36.1, 35.3, 34.1, 33.9, 31.2, 27.4, 25.9, 23.5, 18.3, 18.1, -5.5, -5.6.

FTIR (thin film/NaCl): 3074, 2951, 2927, 2855, 1731, 1472, 1462, 1389, 1361, 1256, 1202, 1149, 1085, 1063, 1045, 918, 838, 776 cm^{-1}.

HRMS: (MM: ESI–APCI) calc'd for $C_{28}H_{51}O_5Si$ $[M + H]^+$ 495.3500, found 495.3510.

$[\alpha]_D^{25}$ = –22° (*c* = 0.76, $CHCl_3$).

Preparation of silyl ketene acetal 64:



68 **(85% yield)** **64**

*Note: 1-methyl-2-pyrrolidinone (NMP; distilled from CaH_2) can be readily substituted for DMPU affording identical product yields.

To a solution of KHMDS (0.106 g, 0.534 mmol, 2.0 equiv) in 5 mL THF cooled to 0 °C was added MOM ether **68** (0.132 g, 0.267 mmol) dropwise as a solution in THF (3 mL + 1 mL rinse). After stirring at 0 °C for 30 min, the reaction mixture was cooled to –78 °C and DMPU (1.0 mL) was added dropwise. After stirring 5 min, TBSCl (80 mg in 1 mL THF, 0.53 mmol, 2.0 equiv) was added and cooling was maintained at –78 °C. After 1 h, the reaction mixture was warmed to 0 °C, diluted with ice-cold pentane (10 mL) and ice-cold sat. $NaHCO_3$ (5 mL). The layers were separated and the aqueous was extracted with ice-cold pentane (2 x 5 mL). The combined organic layers were washed

with brine (3 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on Florisil (3% EtOAc/Hex with 0.5% Et_3N) to afford silyl ketene acetal **64** as a clear gum (0.139 g, 85% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.77 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.02 – 4.93 (m, 2H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.04 (dd, *J* = 11.4, 2.9 Hz, 1H), 3.99 (d, *J* = 10.3 Hz, 1H), 3.92 (dt, *J* = 3.8, 1.8 Hz, 1H), 3.84 (dd, *J* = 10.4, 1.5 Hz, 1H), 3.81 (dd, *J* = 11.4, 2.6 Hz, 1H), 3.36 (s, 3H), 2.69 (ddd, *J* = 13.2, 4.3, 2.1 Hz, 1H), 2.22 (s, 1H), 2.15 (dq, *J* = 13.8, 2.7 Hz, 1H), 2.02 – 1.87 (m, 2H), 1.79 – 1.66 (m, 2H), 1.59 – 1.39 (m, 4H), 1.31 – 1.15 (m, 2H), 1.05 (s, 3H), 1.02 (s, 3H), 1.00 – 0.93 (m, 2H), 0.93 (s, 9H), 0.90 (s, 9H), 0.13 (s, 6H), 0.03 (s, 3H), 0.03 (s, 3H).

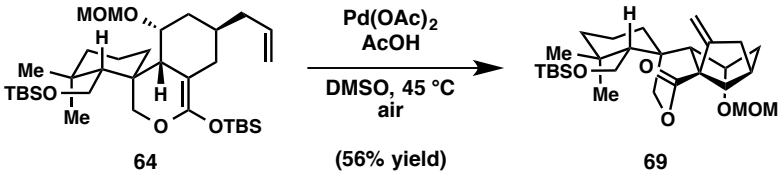
^{13}C NMR (126 MHz, $CDCl_3$): δ 148.5, 137.2, 115.5, 95.8, 82.8, 74.7, 71.9, 61.7, 56.3, 50.1 (br), 45.8, 41.2, 38.5 (br), 38.2, 37.7, 33.8, 33.6, 32.9, 32.8, 30.4 (br), 28.1, 26.0, 25.8, 19.5, 18.1, 18.0, -4.2, -4.4, -5.7, -5.9.

FTIR (thin film/NaCl): 3075, 2952, 2929, 2857, 1713, 1472, 1463, 1361, 1250, 1166, 1150, 1099, 1047, 1035, 989, 910, 870, 839, 783 cm^{-1}.

HRMS: (MM: ESI–APCI) calc'd for $C_{34}H_{65}O_5Si_2$ $[M + H]^+$ 609.4365, found 609.4354.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –82.6° (*c* = 1.50, $CHCl_3$).

Preparation of tetracycle 69:



A solution of silyl ketene acetal **64** (0.139 g, 0.228 mmol), $Pd(OAc)_2$ (52 mg, 0.23 mmol, 1.0 equiv), and AcOH (6.9 mg in 0.10 mL DMSO, 0.11 mmol, 0.5 equiv) in 9 mL DMSO was heated to 45 °C in an open flask. After stirring under air for 6 h at 45 °C, the reaction mixture was cooled to room temperature, diluted with 1M HCl (10 mL) and extracted with Et_2O (4 x 6 mL). The combined organic extracts were washed with brine (3 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (7 to 9% EtOAc/Hex) to afford tetracycle **69** as a clear gum (63 mg, 56% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.98 (s, 1H), 4.94 (s, 1H), 4.65 (d, *J* = 6.7 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.53 (s, 2H), 4.13 (q, *J* = 4.4 Hz, 1H), 3.79 (dd, *J* = 11.4, 5.0 Hz, 1H), 3.71 (dd, *J* = 11.7, 2.0 Hz, 1H), 3.40 (s, 3H), 2.68 (d, *J* = 5.0 Hz, 1H), 2.58 (d, *J* = 16.6 Hz, 1H), 2.47 – 2.42 (m, 2H), 2.30 – 2.22 (m, 2H), 2.19 (d, *J* = 16.3 Hz, 1H), 1.89 (dd, *J* = 11.8, 3.9 Hz, 1H), 1.78 (d, *J* = 14.0 Hz, 1H), 1.73 – 1.68 (m, 1H), 1.49 – 1.41 (m, 3H), 1.37 (dd, *J* = 14.5, 4.5 Hz, 1H), 1.30 – 1.24 (m, 1H), 1.02 (s, 3H), 0.94 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.4, 157.0, 106.1, 96.0, 72.9, 71.5, 60.7, 56.1, 53.4, 52.2, 52.1, 42.9, 42.4, 41.4, 35.9, 35.8, 34.4, 34.4, 30.9, 30.6, 25.9, 23.7, 18.3, 18.2, -5.5, -5.5.

FTIR (thin film/NaCl): 3583, 2926, 2853, 1739, 1464, 1388, 1252, 1232, 1147, 1082, 1046, 837, 776 cm^{-1}.

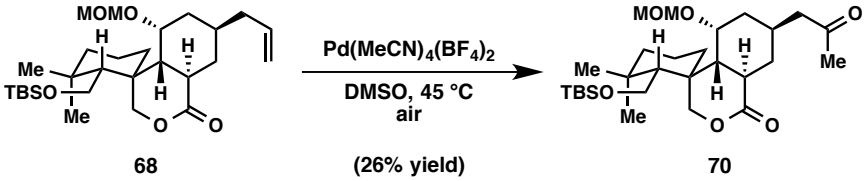
HRMS: (MM: ESI–APCI) calc'd for $C_{28}H_{49}O_5Si$ $[M + H]^+$ 493.3344, found 493.3355.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +23.0° (*c* = 0.305, $CHCl_3$).

Optimization of reaction parameters: General procedure for oxidative cyclization of 64 to 69 (Table 2.1).

A vial was charged with silyl ketene acetal **64** (10 mg, 16 μmol), Pd(II) salt, additive, and solvent (0.65 mL), placed under an atmosphere of O_2, N_2, or air, and heated to the desired temperature. Following the cessation of reaction progress as indicated by LC-MS or TLC analysis, the mixture was cooled to room temperature and diluted with 1M HCl (1 mL) and Et_2O (1 mL). The layers were separated and the aqueous layer was extracted further with Et_2O (3 x 0.5 mL). The combined organic extracts were washed with brine (0.5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (7 to 9% EtOAc/Hex) to afford pure tetracycle **69**.

Preparation of methyl ketone 70:



68 **(26% yield)** **70**

*Note: Methyl ketone **70** was initially isolated as a side product during optimization experiments for the conversion of **64** to **69** (Table 2.1, entry 6, 13% yield). Independent preparation was accomplished using the following procedure.

A solution of MOM ether **68** (16 mg, 32 μmol) and $Pd(MeCN)_4(BF_4)_2$ (14 mg, 32 μmol, 1.0 equiv) in DMSO (1.3 mL) was heated at 45 °C in an open vial. After stirring under air for 3 h, the reaction mixture was cooled to room temperature and diluted with 1M HCl (2 mL) and extracted with Et_2O (3 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 (10 to 20% EtOAc/Hex) to afford methyl ketone **70** as a clear gum (4.3 mg, 26% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.76 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 6.8 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.37 (dt, *J* = 3.8, 1.8 Hz, 1H), 4.25 (dd, *J* = 11.4, 1.4 Hz, 1H), 3.74 (dd, *J* = 11.4, 4.0 Hz, 1H), 3.67 (dd, *J* = 11.4, 3.3 Hz, 1H), 3.45 (s, 3H), 2.94 (td, *J* = 12.3, 3.6 Hz, 1H), 2.46 – 2.37 (m, 2H), 2.38 – 2.23 (m, 2H), 2.13 (s, 3H), 2.09 (dq, *J* = 14.1, 3.2 Hz, 1H), 1.99 – 1.88 (m, 2H), 1.81 – 1.73 (m, 1H), 1.68 (t, *J* = 3.7 Hz, 1H), 1.59 – 1.42 (m, 4H), 1.29 – 1.19 (m, 1H), 1.11 – 1.03 (m, 1H), 1.02 (s, 3H), 0.90 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H).

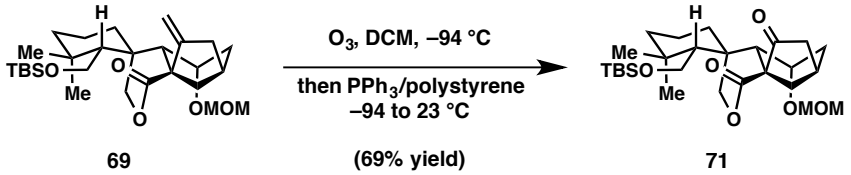
^{13}C NMR (126 MHz, $CDCl_3$): δ 207.5, 173.6, 95.0, 73.4, 70.7, 59.9, 56.5, 51.4, 50.1, 46.8, 42.1, 39.6, 36.3, 36.0, 35.3, 34.1, 33.9, 30.5, 27.4, 27.1, 25.9, 23.6, 18.4, 18.1, -5.5, -5.5.

FTIR (thin film/NaCl): 2951, 2926, 2855, 1732, 1716, 1471, 1463, 1361, 1251, 1206, 1148, 1084, 1063, 1045, 918, 837, 776 cm^{-1}.

HRMS: (MM: ESI–APCI) calc'd for $C_{28}H_{51}O_6Si$ $[M + H]^+$ 511.3449, found 511.3465.

$[\alpha]_D^{25}$ = –15° (*c* = 0.22, $CHCl_3$).

Preparation of ketolactone 71:



69 (69% yield) **71**

A solution of tetracycle **69** (30.0 mg, 60.9 μmol) in 6 mL DCM was cooled to –94 °C (liq. N_2/acetone) at which time ozone was gently bubbled through the solution (O_2 flow rate = 1/8 L/min, 1 setting on ozone generator) for 10 min. The solution was purged with argon for 5 min, polystyrene-bound PPh_3 (3 mmol/g loading, 200 mg, 0.61 mmol, 10 equiv) was then added. The reaction was slowly warmed to room temperature over 30 min. After stirring for 3 h, the suspension was filtered through celite and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (15 to 20% EtOAc/Hex) to afford ketolactone **71** as a clear gum (20.9 mg, 69% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.69 (d, *J* = 6.7 Hz, 1H), 4.61 (d, *J* = 6.7 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.27 (br s, 1H), 3.69 (d, *J* = 11.3 Hz, 1H), 3.64 (dd, *J* = 11.7, 6.1 Hz, 1H), 3.41 (s, 3H), 2.83 (d, *J* = 10.8 Hz, 1H), 2.73 – 2.62 (m, 2H), 2.48 (ddd, *J* = 18.4, 6.9, 1.4 Hz, 1H), 2.44 – 2.31 (m, 2H), 2.13 (dd, *J* = 18.4, 3.7 Hz, 1H), 2.07 (t, *J* = 13.1 Hz, 1H), 1.75 – 1.65 (m, 2H), 1.53 – 1.37 (m, 3H), 1.32 (dd, *J* = 15.4, 4.4 Hz, 1H), 1.29 – 1.21 (m, 1H), 1.03 (s, 3H), 0.88 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

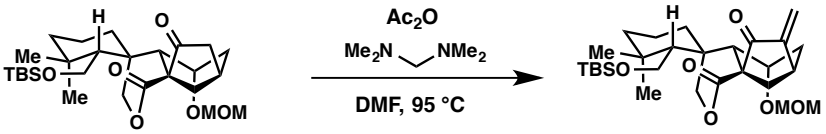
^{13}C NMR (126 MHz, $CDCl_3$): δ 214.1, 171.3, 96.2, 72.9, 70.0, 60.4, 57.4, 56.4, 51.4, 48.2, 47.1, 43.1, 42.5, 35.2, 34.3, 34.2, 32.5, 29.1, 27.1, 25.9, 23.6, 18.2, 18.0, -5.5, -5.5.

FTIR (thin film/NaCl): 2952, 2928, 2856, 1750, 1726, 1471, 1464, 1390, 1236, 1148, 1094, 1047, 959, 945, 915, 838, 778 cm^{-1}.

HRMS: (MM: ESI–APCI) calc'd for $C_{27}H_{47}O_6Si$ $[M + H]^+$ 495.3136, found 495.3147.

$[\alpha]_D^{25}$ = +8.2° (*c* = 0.99, $CHCl_3$).

Preparation of enone 72:



71 **72**

A solution of ketolactone **71** (19.2 mg, 38.8 μmol), bis(dimethylamino)methane (0.40 mL, 2.9 mmol, 75 equiv), acetic anhydride (0.40 mL, 4.2 mmol, 109 equiv) and 0.40 mL DMF was heated to 95 °C in a sealed vial. After stirring at 95 °C for 1 h, the reaction mixture was cooled to room temperature, diluted with sat. $NaHCO_3$ (1 mL) and extracted with DCM (3 x 1 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (0.5 mL) and brine (0.5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (10 to 15% EtOAc/Hex) to afford enone **72** as a clear gum (16.1 mg, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.98 (s, 1H), 5.46 (s, 1H), 4.69 (d, *J* = 6.7 Hz, 1H), 4.61 (d, *J* = 6.7 Hz, 1H), 4.60 (d, *J* = 11.5 Hz, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 4.24 (br s, 1H), 3.66 (d, *J* = 11.4 Hz, 1H), 3.58 (dd, *J* = 11.4, 6.1 Hz, 1H), 3.42 (s, 3H), 3.13 (ddt, *J* = 9.6, 5.0, 1.0 Hz, 1H), 2.85 (d, *J* = 12.1 Hz, 1H), 2.68 (s, 1H), 2.45 (dd, *J* = 15.2, 9.3 Hz, 1H), 2.31 (dd, *J* = 12.3, 4.7 Hz, 1H), 1.93 (t, *J* = 13.8 Hz, 1H), 1.75 (d, *J* = 14.4 Hz, 1H), 1.68

(d, J = 5.1 Hz, 1H), 1.58 (dd, J = 15.1, 4.7 Hz, 1H), 1.54 – 1.39 (m, 3H), 1.30 – 1.20 (m, 1H), 1.03 (s, 3H), 0.88 (s, 3H), 0.84 (s, 9H), 0.01 (s, 3H), -0.02 (s, 3H).

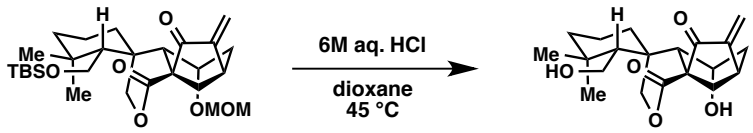
^{13}C NMR (126 MHz, $CDCl_3$): δ 201.0, 171.3, 150.0, 118.1, 96.4, 73.0, 69.3, 60.4, 56.9, 56.4, 51.9, 48.0, 43.7, 42.5, 36.9, 34.4, 34.3, 34.3, 29.7, 29.6, 26.0, 23.7, 18.3, 18.0, -5.6, -5.6.

FTIR (thin film/NaCl): 2952, 2928, 2855, 1744, 1719, 1462, 1389, 1366, 1261, 1235, 1147, 1122, 1092, 1047, 989, 932, 838, 778 cm^{-1}.

HRMS: (MM: ESI–APCI) calc'd for $C_{28}H_{47}O_6Si$ $[M + H]^+$ 507.3136, found 507.3145.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +27.6° (c = 1.02, $CHCl_3$).

Preparation of diol S2:



72 (99% yield) **S2**

To a solution of enone **72** (16.1 mg, 31.8 μmol) in 0.90 mL dioxane was added 0.70 mL 6M HCl (*aq*), and the mixture was stirred at 45 °C. After 75 min, the reaction mixture was cooled to room temperature, carefully diluted with sat. $NaHCO_3$ (3 mL) and DCM (3 mL) and stirred until cessation of bubbling (10 min). The layers were separated and the aqueous layer was extracted with DCM (3 x 2 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (1 mL) and brine (1 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (50 to 65% EtOAc/Hex) to afford diol **S2** as a white solid (11.0 mg, 99% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.01 (s, 1H), 5.48 (s, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.55 (br s, 1H), 4.32 (dd, *J* = 11.4, 1.2 Hz, 1H), 3.79 (dd, *J* = 11.4, 1.8 Hz, 1H), 3.65 (dd, *J* = 11.4, 6.3 Hz, 1H), 3.16 (ddt, *J* = 8.8, 4.9, 1.1 Hz, 1H), 3.00 (d, *J* = 12.2 Hz, 1H), 2.65 (d, *J* = 3.2 Hz, 1H), 2.31 (ddd, *J* = 12.2, 4.8, 1.4 Hz, 1H), 2.14 (ddd, *J* = 15.1, 8.9, 1.9 Hz, 1H), 2.11 – 2.01 (m, 1H), 1.87 – 1.79 (m, 2H), 1.76 (d, *J* = 6.1 Hz, 1H), 1.56 – 1.43 (m, 4H), 1.37 – 1.27 (m, 2H), 1.07 (s, 3H), 0.88 (s, 3H).

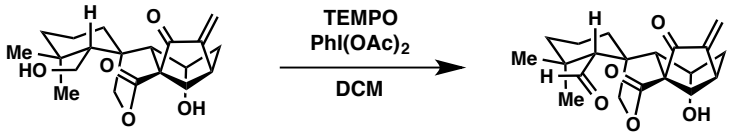
^{13}C NMR (126 MHz, $CDCl_3$): δ 201.3, 171.2, 149.7, 118.2, 69.5, 66.1, 60.1, 56.8, 51.7, 47.3, 43.4, 42.0, 34.6, 34.3, 33.9, 30.2, 30.1, 29.7, 24.0, 18.1.

FTIR (thin film/NaCl): 3434, 2921, 2848, 1734, 1700, 1457, 1390, 1357, 1260, 1124, 1039, 1021, 928, 836, 749 cm^{-1}.

HRMS: (MM: ESI–APCI) calc'd for $C_{20}H_{29}O_5$ $[M + H]^+$ 349.2010, found 349.2014.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +14° (*c* 0.16, $CHCl_3$).

Preparation of (–)-trichorabdal A (12):



S2 **(74% yield)** *(–)-trichorabdal A* **(12)**

To a solution of diol **S2** (11.0 mg, 31.6 μmol) in 1.6 mL DCM was added 2,2,6,6-tetramethylpiperidine 1-oxyl (1.0 mg, 6.3 μmol, 0.1 equiv) and iodobenzene diacetate (14.2 mg, 44.2 μmol, 1.4 equiv). After stirring for 3.5 h at ambient temperature, the reaction mixture was diluted with sat. $NaHCO_3$ (0.5 mL) and sat. $Na_2S_2O_3$ (0.5 mL). The layers were separated, 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, filtered

through a small plug of silica gel, and concentrated *in vacuo*. The crude residue was purified by preparative reverse phase HPLC (40 to 70% MeCN/H_2O, 10 minute gradient, t_R=6.8 min) to afford (–)-trichorabdal A (**12**) as a white solid (8.1 mg, 74% yield).

^{1}H NMR (600 MHz, pyridine-d_5, at 60 °C): δ 10.06 (d, *J* = 4.3 Hz, 1H), 6.49 (s, 1H), 6.01 (s, 1H), 5.38 (s, 1H), 5.12 (d, *J* = 11.4 Hz, 1H), 4.88 – 4.64 (m, 1H), 4.65 – 4.60 (m, 1H), 3.46 (d, *J* = 11.8 Hz, 1H), 3.13 (dd, *J* = 8.9, 4.6 Hz, 1H), 2.91 (d, *J* = 4.3 Hz, 1H), 2.64 – 2.57 (m, 1H), 2.48 – 2.38 (m, 3H), 2.04 – 1.95 (m, 1H), 1.78 (dd, *J* = 14.8, 5.0 Hz, 1H), 1.68 – 1.59 (m, 1H), 1.52 – 1.42 (m, 2H), 1.27 – 1.19 (m, 1H), 1.04 (s, 3H), 0.99 (s, 3H);

^{13}C NMR (126 MHz, pyridine-d_5, at 60 °C): δ 205.3, 201.5, 171.1, 150.9, 117.6, 70.8, 65.0, 60.9 (br), 56.9 (br), 47.9 (br), 42.7 (br), 42.1, 40.3 (br), 35.3, 34.3, 32.4, 31.6, 28.6, 25.9 (br), 18.7.

FTIR (thin film/NaCl): 3467, 2922, 2849, 1744, 1711, 1647, 1490, 1459, 1391, 1349, 1271, 1238, 1180, 1124, 1079, 1038, 1024, 928, 850, 730 cm^{-1}.

HRMS: (MM: ESI–APCI) calc'd for $C_{20}H_{27}O_5$ $[M + H]^+$ 347.1853, found 347.1837.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –61° (*c* 0.12, EtOH).

^{1}H NMR comparison table for trichorabdal A (**12**).

Natural*[16] (400 MHz, C_5D_5N, 40 °C) δ (ppm)	**Natural** mult	**Natural** *J* (Hz)	**Synthetic** (600 MHz, C_5D_5N, 60 °C) δ (ppm)	**Synthetic** mult	**Synthetic** *J* (Hz)	Δ (ppm)
10.03	d, 1H	3	10.06	d, 1H	4.3	+0.03
6.05	s, 1H	-	6.01	s, 1H	-	–0.04
5.35	s, 1H	-	5.38	s, 1H	-	+0.03
5.10	ABq, 1H	12	5.12	d, 1H	11.4	+0.02
4.71	ABq, 1H	12	4.72	m, 1H	-	+0.01
4.60	m, 1H	-	4.62	m, 1H	-	+0.02
3.45	d, 1H	12	3.46	d, 1H	11.8	+0.01
3.12	dd, 1H	10,4	3.13	dd, 1H	8.9, 4.6	+0.01
2.90	d, 1H	3	2.91	d, 1H	4.3	+0.01
1.00	s, 3H	-	1.04	s, 3H	-	+0.04
0.95	s, 3H	-	0.99	s, 3H	-	+0.04

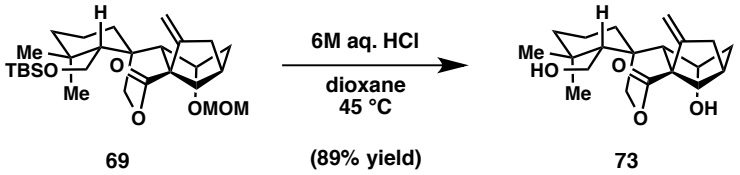
***** No further ^{1}H signals were reported.

^{13}C NMR comparison table for trichorabdal A (**12**).**

Natural[16] (100 MHz, C_5D_5N, 60 °C) δ (ppm)	**Synthetic** (126 MHz, C_5D_5N, 60 °C) δ (ppm)	Δ (ppm)
204.5	205.3	+0.8
200.7	201.5	+0.8
169.5	171.1	+0.6
150.6	150.9	+0.3
117.1	117.6	+0.5
70.7	70.8	+0.1
64.9	65.0	+0.1
60.7	60.9	+0.2
56.7	56.9	+0.2
47.8	47.9	+0.1
42.7	42.7	0.0
42.0	42.1	+0.1
40.3	40.3	0.0
35.2	35.3	+0.1
34.2	34.3	+0.1
32.3	32.4	+0.1
31.5	31.6	+0.1
28.4	28.6	+0.2
26.0	25.9	–0.1
18.6	18.7	+0.1

****** It should be noted that conformational flexibility of the natural product results in significant broadening of some carbon signals, even at elevated temperatures. For discussion of the conformational equilibria of these structures, see Osawa et al.[16]

Preparation of diol 73:



69 (89% yield) **73**

To a solution of tetracycle **69** (59.2 mg, 0.120 mmol, 1.0 equiv) in 3.7 mL dioxane was added 2.8 mL 6M HCl(*aq*). The resulting solution was heated to 45 °C and stirred for 30 min. The reaction mixture was then cooled to 0 °C and diluted with sat. $NaHCO_3$ (10 mL) and DCM (10 mL) and stirred until bubbling ceased (15 min). The layers were separated, and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (40 to 50% EtOAc/Hex) to provide diol **73** (35.9 mg, 89% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.98 – 4.95 (m, 2 H), 4.46 (br s, 2H), 4.40 (dtd, *J* = 6.6, 5.2, 3.6 Hz, 1H), 3.87 (dt, *J* = 11.5, 4.5 Hz, 1H), 3.82 (dt, *J* = 11.5, 2.9 Hz, 1H), 2.64 (d, *J* = 5.2 Hz, 1H), 2.60 (ddt, *J* = 16.6, 5.4, 2.6 Hz, 1H), 2.52 – 2.43 (m, 2H), 2.37 (td, *J* = 13.3, 4.3 Hz, 1H), 2.26 (br s, 1 H), 2.22 (dq, *J* = 16.2, 2.0 Hz, 1H), 1.97 (dtd, *J* = 14.2, 6.4, 1.2 Hz, 1H), 1.90 (t, *J* = 3.6 Hz, 1H), 1.88 – 1.81 (m, 3H), 1.66 (ddt, *J* = 14.2, 5.2, 1.9 Hz, 1H), 1.52 – 1.41 (m, 3H), 1.31 (ddd, *J* = 14.1, 13.1, 4.3 Hz, 1H), 1.05 (s, 3H), 0.92 (s, 3H).

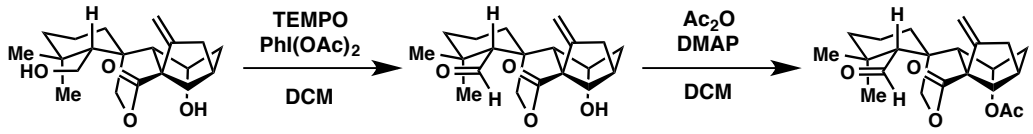
^{13}C NMR (126 MHz, $CDCl_3$): δ 175.5, 156.1, 106.3, 71.7, 66.4, 60.6, 54.0, 53.0, 51.4, 42.5, 41.7, 40.4, 39.7, 36.5, 34.4, 34.1, 31.5, 31.4, 23.5, 18.4.

FTIR (NaCl/thin film): 3246, 2929, 2872, 2848, 1734, 1459, 1388, 1353, 1298, 1242, 1087, 1044, 1023, 997, 989 cm^{-1}.

HRMS: (ESI+) calc'd for $C_{20}H_{31}O_4$ $[M + H]^+$ 335.2217, found 335.2228.

$[\alpha]_D^{25}$ = –28° (*c* = 0.66, $CHCl_3$).

Preparation of acetate 75.



To a solution of diol **73** (35.2 mg, 0.105 mmol, 1.0 equiv) in DCM (5.3 mL) was added $PhI(OAc)_2$ (47.6 mg, 0.148 mmol, 1.4 equiv) and 2,2,6,6-tetramethylpiperidine 1-oxyl (3.3 mg, 21 μmol, 0.20 equiv). The resulting solution was stirred for 4.5 h, and then diluted with sat. $Na_2S_2O_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide crude aldehyde **74**. The crude residue was chromatographed on SiO_2 (25% EtOAc/Hex) to provide 25.4 mg **74** (~85% purity, contaminated with ketoaldehyde from over-oxidation). Impure **74** was dissolved in DCM (7.6 mL), and Ac_2O (36 μL, 0.38 mmol, 5.0 equiv) and DMAP (93 mg, 0.76 mmol, 10 equiv) were added. The solution was stirred at ambient temperature until TLC indicated full consumption of starting material (30 min). The reaction mixture was then diluted with sat. $NaHCO_3$ (20 mL) and DCM (20 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was

chromatographed on SiO_2 (20% EtOAc/Hex) to provide acetate **75** (22.8 mg, 58% yield from **73**).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.93 (d, *J* = 4.4 Hz, 1H), 5.27 (q, *J* = 5.0 Hz, 1H), 4.99 (m, 2H), 4.84 (br d, *J* = 9.3 Hz, 1H), 4.68 (d, *J* = 11.8 Hz, 1H), 2.65 – 2.54 (m, 1H), 2.46 (q, *J* = 6.1 Hz, 1H), 2.39 (d, *J* = 4.4 Hz, 1H), 2.33 – 2.17 (m, 3H), 2.07 (s, 3H), 2.01 – 1.87 (m, 3H), 1.82 – 1.67 (m, 1H), 1.66 – 1.49 (m, 3H), 1.28 – 1.16 (m, 2H), 1.14 (s, 3H), 1.04 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 205.1, 174.2, 169.7, 155.0, 107.3, 70.4, 67.7, 62.5, 53.2, 51.9, 41.9, 41.7, 40.4, 36.5, 36.1, 34.5, 33.7, 30.6, 29.6, 23.8, 21.8, 18.2.

FTIR (NaCl/thin film): 3079, 2953, 2849, 2751, 1735, 1712, 1654, 1462, 1371, 1231, 1085, 1071, 1036, 914 cm^{-1}.

HRMS: (ESI+) calc'd for $C_{22}H_{31}O_5$ $[M + H]^+$ 375.2166, found 375.2175.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –6.9° (*c* = 0.42, $CHCl_3$).

An analytical sample of aldehyde **74** was obtained (65% yield) by preparative reverse phase HPLC (45% to 70% MeCN/H_2O, 10 minute gradient, t_R = 7.0 min).

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.95 (d, *J* = 5.4 Hz, 1H), 4.99 (s, 1H), 4.95 (t, *J* = 2.4 Hz, 1H), 4.88 (br s, 1H), 4.71 (d, *J* = 11.8 Hz, 1H), 4.25 (dq, *J* = 5.4, 3.5 Hz, 1H), 2.64 (d, *J* = 5.4 Hz, 1H), 2.59 – 2.53 (m, 1H), 2.51 – 2.47 (m, 1H), 2.46 – 2.35 (m, 2H), 2.17 (dq, *J* = 16.3, 2.0 Hz, 1H), 2.00 (d, *J* = 3.0 Hz, 1H), 1.96 (dt, *J* = 13.5, 6.6 Hz, 1H), 1.90 –

1.82 (m, 2H), 1.63 – 1.54 (m, 4H), 1.50 (dt, *J* = 13.2, 3.5 Hz, 1H), 1.31 (m, 1H), 1.18 (s, 3H), 1.00 (s, 3H).

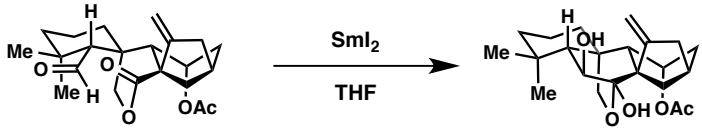
^{13}C NMR (126 MHz, $CDCl_3$): δ 206.6, 174.9, 155.5, 107.6, 71.3, 66.0, 63.4, 53.5, 53.5, 41.9, 41.2, 40.6, 39.5, 36.2, 34.4, 33.6, 31.4, 29.9, 23.6, 18.4.

FTIR (NaCl/thin film): 3467, 2990, 2946, 2844, 2717, 1718, 1653, 1465, 1390, 1280, 1233, 1201, 1117, 1088, 1025, 881 cm^{-1}.

HRMS: (ESI+) calc'd for $C_{20}H_{29}O_4$ $[M + H]^+$ 333.2060, found 333.2070.

$[\alpha]_D^{25}$ = –65.4° (*c* = 0.37, $CHCl_3$).

Preparation of hydroxylactol 76:



75 **(55% yield, 75% brsm)** **76**

To a solution of **75** (4.4 mg, 12 μmol, 1.0 equiv) in THF (0.27 mL) was added freshly prepared 0.1 M SmI_2 (0.23 mL, 23 μmol, 2.0 equiv). The solution was stirred until the reaction turned from blue to green (ca. 1.5 h). The reaction mixture was then diluted with sat. $NaHCO_3$ (1 mL), sat. $Na_2S_2O_3$ (1 mL), and DCM (2 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 x 2 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (17% to 25% EtOAc/Hex) to provide recovered **75** (1.2 mg, 27% yield) and hydroxylactol **76** (2.4 mg, 55% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.16 – 6.14 (m, 1H), 5.14 (ddd, *J* = 5.8, 4.1, 1.9 Hz, 1H), 5.11 (dd, *J* = 2.6, 1.2 Hz, 1H), 4.23 (dd, *J* = 9.1, 1.9 Hz, 1H), 4.10 (dd, *J* = 9.1, 1.8 Hz, 1H), 4.03 (dd, *J* = 7.3, 1.9 Hz, 1H), 2.59 (s, 1H), 2.50 – 2.42 (m, 2H), 2.40 (d, *J* = 1.9 Hz, 1H), 2.29 (dt, *J* = 8.9, 4.2 Hz, 1H), 2.17 – 2.09 (m, 2H), 2.06 (s, 3H), 1.75 (dt, *J* = 5.7, 1.5 Hz, 1H), 1.67 (dd, *J* = 11.7, 3.6 Hz, 1H), 1.51 – 1.41 (m, 3H), 1.39 – 1.32 (m, 3H), 1.27 – 1.22 (m, 2H), 1.12 (s, 3H), 1.09 (s, 3H).

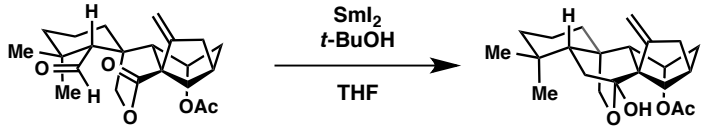
^{13}C NMR (126 MHz, $CDCl_3$): δ 169.9, 155.2, 113.0, 97.5, 75.4, 69.3, 69.1, 62.0, 57.3, 53.7, 46.7, 41.3, 37.2, 34.4, 34.2, 34.0, 33.6, 29.9, 27.2, 22.6, 22.0, 18.5.

FTIR (NaCl/thin film): 3436, 2927, 2851, 1733, 1648, 1443, 1376, 1264, 1237, 1210, 1073, 1029 cm^{-1}.

HRMS: (ESI+) calc'd for $C_{20}H_{29}O_3$ $[M - OAc]^+$ 317.2111, found 317.2119.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –47.2° (*c* = 0.30, $CHCl_3$).

Preparation of lactol 77:



75 **(72% yield)** **77**

To a solution of aldehyde **75** (5.0 mg, 13 μmol, 1.0 equiv) in THF (1.3 mL) was added *t*-BuOH (1.3 μL, 13 μmol, 1.0 equiv) and freshly prepared 0.1 M SmI_2 (0.67 mL, 67 μmol, 5.0 equiv) dropwise over 1 min. The resulting solution was stirred until the reaction turned from blue to green (ca. 6 h), and then diluted with sat. $NaHCO_3$ (5 mL), sat. $Na_2S_2O_3$ (5 mL), and DCM (10 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 10 mL). The organic extracts were dried over Na_2SO_4,

filtered, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (25% to 33% EtOAc/Hex) to provide lactol **77** (3.6 mg, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.18 (dd, *J* = 2.7, 1.5 Hz, 1H), 5.14 (td, *J* = 6.0, 1.6 Hz, 1H), 4.92 – 4.90 (m, 1H), 4.23 (s, 2H), 2.60 (dd, *J* = 13.9, 11.1 Hz, 1H), 2.56 (ddt, *J* = 15.6, 5.1, 2.3 Hz, 1H), 2.41 (s, 1H), 2.40 (ddt, *J* = 11.9, 3.2, 1.0 Hz, 1H), 2.29 (dt, *J* = 9.6, 4.7 Hz, 1H), 2.15 (ddt, *J* = 15.7, 9.5, 1.3 Hz, 1H), 2.12 (ddt, *J* = 15.7, 3.0, 1.5 Hz, 1H), 2.06 (s, 3H), 1.91 (dd, *J* = 14.0, 8.6 Hz, 1H), 1.64 (ddt, *J* = 11.6, 4.0, 1.0 Hz, 1H), 1.58 (d, *J* = 5.3 Hz, 1H), 1.52 – 1.47 (m, 2H), 1.45 – 1.32 (m, 3H), 1.29 (dtd, *J* = 13.7, 3.3, 1.5 Hz, 1H), 1.19 (td, *J* = 13.4, 5.1 Hz, 1H), 1.11 (td, *J* = 12.7, 4.0 Hz, 1H), 1.10 (s, 3H), 0.89 (s, 3H).

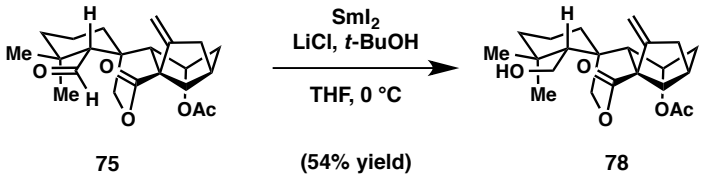
^{13}C NMR (126 MHz, $CDCl_3$): δ 170.1, 156.7, 105.5, 97.3, 69.1, 68.8, 61.1, 53.4, 49.2, 45.3, 40.8, 37.3, 36.0, 33.9, 33.7, 32.7, 32.0, 30.4, 27.1, 22.0, 21.1, 18.6.

FTIR (NaCl/thin film): 3402, 2929, 1729, 1646, 1444, 1366, 1236, 1210, 1182, 1101, 1044, 915 cm^{-1}.

HRMS: (ESI+) calc'd for $C_{20}H_{29}O_2$ $[M - OAc]^+$ 301.2162, found 301.2164.

$[\alpha]_D^{25}$ = –135° (*c* = 0.30, $CHCl_3$).

Preparation of primary alcohol 78:



75 **(54% yield)** **78**

Freshly prepared 0.1 M SmI_2 (0.17 mL, 17 μmol, 5.0 equiv) was added directly to a vial charged with LiCl (7.2 mg, 170 μmol, 50 equiv) and stirred until the solution had turned emerald green and all solids were dissolved (< 10 min). The resulting solution was added dropwise via cannula into a solution of aldehyde **75** (1.3 mg, 3.5 μmol, 1.0 equiv) and a solution of *t*-BuOH in THF (0.01 M, 0.35 mL, 3.5 μmol, 1.0 equiv) stirring at 0 °C. Stirring continued until the reaction turned yellow (35 min). The reaction mixture was diluted with sat. $NaHCO_3$ (1 mL), sat. $Na_2S_2O_3$ (1 mL), and H_2O (0.5 mL), then Rochelle salt (100 mg) and EtOAc (2 mL) were added. The layers were separated, and the aqueous layer extracted with EtOAc (3 x 2 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (20 to 25% EtOAc/Hex) to afford alcohol **78** (0.7 mg, 54% yield).

^{1}H NMR (500 MHz; $CDCl_3$): δ 5.47 (ddd, *J* = 5.4, 4.5, 3.4 Hz, 1H), 4.96 (t, *J* = 2.4 Hz, 1H), 4.90 (t, *J* = 1.9 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 3.82 (d, *J* = 11.8 Hz, 1H), 3.73 (dt, *J* = 10.9, 4.7 Hz, 1H), 2.81 (d, *J* = 4.3 Hz, 1H), 2.65 (ddt, *J* = 16.8, 5.8, 2.7 Hz, 1H), 2.45 (q, *J* = 6.8 Hz, 1H), 2.36 (dd, *J* = 11.9, 2.7 Hz, 1H), 2.24 (dq, *J* = 16.9, 2.2 Hz, 1H), 2.08 – 2.02 (m, 1H), 2.07 (s, 3H), 1.99 (dd, *J* = 12.2, 4.8 Hz, 1H), 1.86 (d, *J* = 13.6 Hz, 1H), 1.67 – 1.57 (m, 2H), 1.53 – 1.45 (m, 4H), 1.28 – 1.24 (m, 1H), 1.19 (td, *J* = 14.3, 5.3 Hz, 1H), 1.05 (s, 3H), 0.90 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.7, 170.1, 156.5, 105.2, 70.4, 68.0, 60.3, 53.3, 52.4, 51.2, 42.8, 42.4, 40.9, 37.4, 35.8, 34.3, 34.2, 30.2, 30.0, 23.7, 21.9, 18.1.

IR (NaCl/thin film): 3463, 2951, 2925, 2868, 2848, 1737, 1729, 1651, 1460, 1447, 1388, 1372, 1233, 1181, 1083, 1021 cm^{-1}.

HRMS: (ESI+) calc'd for $C_{20}H_{29}O_3$ $[M - OAc]^+$ 317.2117, found 317.2105.

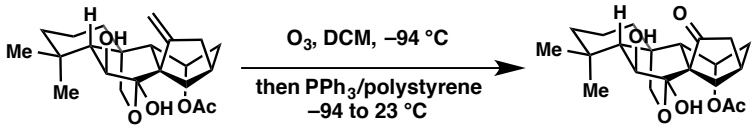
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –7.5° (*c* = 0.16, $CHCl_3$).

General procedure for reductive cyclization of aldehyde 75 (Table 2.2):

To a flask charged with aldehyde **75** (1.3 mg, 3.5 μmol, 1.0 equiv) was added one of the following: 0.35 mL THF; 0.35 mL 10 mM *t*-BuOH /THF solution (3.5 μmol, 1.0 equiv); 0.35 mL THF and 30 uL HMPA (0.175 mmol, 50 equiv) and maintained at the indicated temperature. Inside a glove box, an oven-dried vial was charged with LiCl or LiBr (170 μmol, 50 equiv) or naught, and removed from the glove box, or not. Freshly prepared 0.1 M SmI_2 was added directly to the reaction vessel dropwise, or to the vial containing LiX, which was stirred for 1–10 min until all solids were dissolved, and the resulting solution then added dropwise via cannula to the reaction vessel. Following addition of SmI_2 or SmI_2/LiX, the reaction was allowed to stir at the indicated temperature until the appearance of a yellow solution (35–55 min). At this point, the reaction was diluted with sat. NaHCO (1 mL), sat. $Na_2S_2O_3$ (1 mL), and H_2O (0.5 mL), and Rochelle salt (100 mg) and EtOAc (2 mL) were added. The layers were separated, and the aqueous extracted with EtOAc (3 x 2 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was

chromatographed on SiO_2 (17% to 33% EtOAc/Hex) to afford hydroxylactol **76**, lactol **77**, primary alcohol **78**, or recovered aldehyde **75**.

Preparation of ketolactol 79:



76 **(66% yield)** **79**

A solution of lactol **76** (4.4 mg, 12 μmol, 1.0 equiv) in DCM (2 mL) was cooled to –94 °C (liq. N_2/acetone), and ozone was gently bubbled through the solution (O_2 flow rate = 1/8 L/min, 1 setting on ozone generator) for 10 min. The solution was purged with argon for 10 min, and then polystyrene-bound PPh_3 (3 mmol/g loading, 39 mg, 0.12 mmol, 10 equiv) was added. After 25 min, the reaction was warmed to 0 °C and stirred for 30 min, and finally warmed to room temperature and stirred for an additional 30 min. The solution was filtered through a pad of celite and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (33% EtOAc/Hex) to afford ketolactol **79** (2.9 mg, 66% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.63 (d, *J* = 12.0 Hz, 1H), 5.24 (td, *J* = 4.9, 1.4 Hz, 1H), 4.16 (dd, *J* = 9.4, 1.9 Hz, 1H), 4.09 (dd, *J* = 9.3, 1.7 Hz, 1H), 3.79 (dd, *J* = 12.0, 7.5 Hz, 1H), 3.53 (s, 1H), 2.71 (ddd, *J* = 12.4, 4.0, 1.3 Hz, 1H), 2.70 – 2.65 (m, 1H), 2.50 (ddd, *J* = 18.7, 7.1, 1.6 Hz, 1H), 2.30 – 2.24 (m, 2H), 2.18 (dd, *J* = 18.6, 4.0 Hz, 1H), 2.10 (s, 3H), 1.59 (dd, *J* = 4.9, 1.2 Hz, 1H), 1.54 – 1.42 (m, 3H), 1.38 – 1.33 (m, 2H), 1.26 – 1.21 (m, 3H), 1.13 (s, 3H), 1.11 (s, 3H).

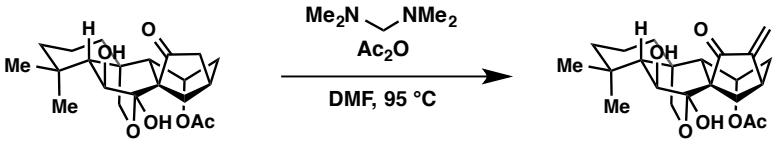
^{13}C NMR (126 MHz, $CDCl_3$): δ 222.7, 169.7, 94.8, 74.7, 68.9, 68.1, 59.6, 58.8, 53.6, 49.3, 41.3, 36.9, 35.9, 33.9, 33.7, 30.6, 29.1, 25.9, 22.5, 21.9, 18.3.

FTIR (NaCl/thin film): 3338, 2924, 2870, 1728, 1446, 1373, 1306, 1238, 1212, 1061, 1021, 939 cm^{-1}.

HRMS: (ESI+) calc'd for $C_{21}H_{31}O_6$ $[M + H]^+$ 379.2115, found 379.2123.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –86° (*c* = 0.30, $CHCl_3$).

Preparation of (–)-longikaurin E (11):



79 **(67% yield)** *(–)-longikaurin E* **(11)**

To a solution of **79** (2.6 mg, 6.9 μmol, 1.0 equiv) in DMF (0.23 mL) was added bis(dimethylamino) methane (0.23 mL, 1.7 mmol, 240 equiv) and Ac_2O (0.23 mL, 2.1 mmol, 300 equiv), and the resulting mixture was stirred at 95 °C for 45 min in a sealed vial. After cooling to room temperature, the solution was diluted with 1M HCl (2 mL) and extracted with Et_2O (3 x 4 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was chromatographed on SiO_2 (33% EtOAc/Hex) to afford (–)-longikaurin E (**11**) (1.8 mg, 67% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.00 (t, *J* = 0.9 Hz, 1H), 5.84 (d, *J* = 12.0 Hz, 1H), 5.47 (t, *J* = 0.8 Hz, 1H), 5.27 (ddd, *J* = 5.5, 4.5, 1.1 Hz, 1H), 4.13 (dd, *J* = 9.3, 1.4 Hz, 1H), 4.10 (dd, *J* = 9.3, 1.9 Hz, 1H), 3.87 (dd, *J* = 12.0, 8.1 Hz, 1H), 3.53 (s, 1H), 3.13 (dd, *J* = 9.4, 4.7 Hz, 1H), 2.71 (dd, *J* = 12.3, 0.8 Hz, 1H), 2.31 (ddd, *J* = 16.2, 9.3, 1.0 Hz, 1H),

2.21 (ddd, *J* = 12.2, 4.6, 1.2 Hz, 1H), 2.11 (s, 3H), 1.79 (ddt, *J* =16.0, 5.5, 1.1 Hz, 1H), 1.62 (d, *J* = 4.0 Hz, 1H), 1.51 – 1.42 (m, 2H), 1.39 – 1.33 (m, 2H), 1.32 – 1.20 (m, 3H), 1.15 (s, 3H), 1.13 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 208.4, 169.7, 151.7, 118.5, 95.0, 74.8, 69.1, 68.0, 58.5, 58.5, 53.7, 41.4, 38.0, 37.1, 34.1, 33.7, 33.6, 31.3, 26.3, 22.8, 21.9, 18.4.

FTIR (NaCl/thin film): 3270, 2953, 2918, 2854, 1727, 1714, 1644, 1504, 1372, 1373, 1264, 1241, 1167, 1057, 940 cm^{-1}.

HRMS: (ESI+) calc'd for $C_{22}H_{31}O_6$ $[M + H]^+$ 391.2115, found 391.2125.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –51° (*c* = 0.30, C_5H_5N); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = –39° (*c* = 0.17, $CHCl_3$).

^{1}H NMR comparison table for longikaurin E (**11**).

Natural*[17] ($CDCl_3$) δ (ppm)	**Natural** mult	**Natural** *J* (Hz)	**Synthetic** ($CDCl_3$, 500 MHz) δ (ppm)	**Synthetic** mult	**Synthetic** *J* (Hz)	Δ (ppm)
5.26	dd, 1H	4.5, 4.5	5.27	ddd, 1H	5.5, 4.5, 1.1	+0.01
4.11	br s, 2H	-	4.13 4.10	dd, 1H dd, 1H	9.3, 1.4 9.3, 1.9	-
3.91	dd, 1H	12, 8	3.87	dd, 1H	12.0, 8.1	–0.04
2.09	s, 3H	-	2.11	s, 3H	-	+0.02
1.71 – 1.88	m**	-	1.79	ddt, 1H	16.0, 5.5, 1.1	-
1.62	m**	-	1.62	d, 1H	4.0	0.00
1.25	m**	-	1.20 – 1.32	m, 3H	-	-
1.14	s, 3H	-	1.15	s, 3H	-	+0.01
1.12	s, 3H	-	1.13	s, 3H	-	+0.01

^{13}C NMR comparison table for longikaurin E (**11**).

Natural* [17] ($CDCl_3$) δ (ppm)	**Synthetic** ($CDCl_3$, 126 MHz) δ (ppm)	Δ (ppm)
208.4	208.4	0.0
169.6	169.7	+0.1
151.7	151.7	0.0
118.2	118.5	+0.3
95.0	95.0	0.0
74.5	74.8	+0.3
68.9	69.1	+0.2
68.1	68.0	–0.1

* No further ^{1}H or ^{13}C signals were reported.
** Integrations not reported.

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