Chapter 3

Applications of a Unified Synthetic Strategy: Total Syntheses of (–)-Trichorabdal A and (–)-Longikaurin E[†]

3.1 INTRODUCTION

Having completed our initial objective, the total synthesis of maoecrystal Z, we sought access to additional distinct *ent*-kauranoid architectures. It was envisioned that a unified strategy would be a powerful tool for the synthesis of *ent*-kauranoid natural product analogs to further the exploration of novel biological properties discussed in the previous chapter. The route developed achieves the rapid synthesis of an unsaturated spirolactone intermediate, which possesses functional handles suitable for elaboration to trichorabdal A and longikaurin E. The divergent preparation of these bioactive *Isodon* diterpenoids from this key intermediate is described below.

[†] Portions of this chapter have been reproduced from the following communication: Yeoman, J. T. S.; Mak, V. W.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 11764. The research discussed was completed in collaboration with Victor W. Mak, a graduate student in the Reisman Laboratory.

3.1.1 Synthetic Considerations

Reported in 1982, the structure of trichorabdal A (**3**) is a prototypic 6,7-*seco*-*ent*-kauranoid (see Figure 3.1).[1] Its characteristic *exo*-methylene cyclopentanone contrasts with the acyclic enal of maoecrystal Z (**10**), though it exhibits a similar level of structural complexity. However, the structure of longikaurin E (**12**), disclosed in 1981, is that of the parent *ent*-kauranoid, with a C6–C7 bond extant.[2] In the retrosynthetic sense, we envisioned that both **3** and **12** could be accessible from *exo*-olefin **143**. To access **12**, we

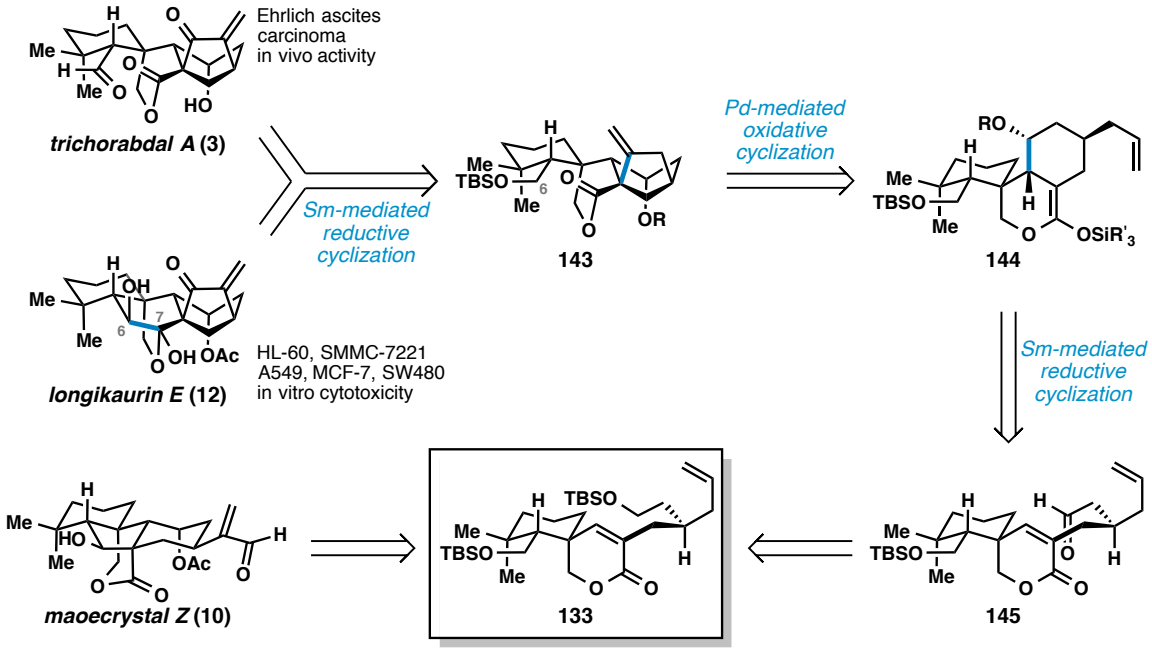


Figure 3.1. Retrosynthetic analysis for trichorabdal A (**3**) and longikaurin E (**12**).

hoped to forge the central oxabicyclo[2.2.2]octane via the reductive cyclization of a C6-aldehyde precursor.[3] In a key step, the bicyclo[3.2.1]octane motif of **143** would arise through an oxidative cyclization. Although this transformation is well established for silyl enol ethers,[4,5] we anticipated that use of a silyl ketene acetal such as **144** might prove more challenging: prior to our studies, there were no reported examples of transition metal-mediated oxidative cyclization reactions between silyl ketene acetals and simple

olefins to generate all-carbon quaternary centers.[6] Nonetheless, this disconnection was appealing as **144** could be obtained following Sm^{II}-mediated reductive cyclization of an aldehyde (**145**) derived from bis-silyl ether **133**, previously synthesized in five steps from (–)-γ-cyclogeraniol (**104**) en route to maoecrystal Z.[7]

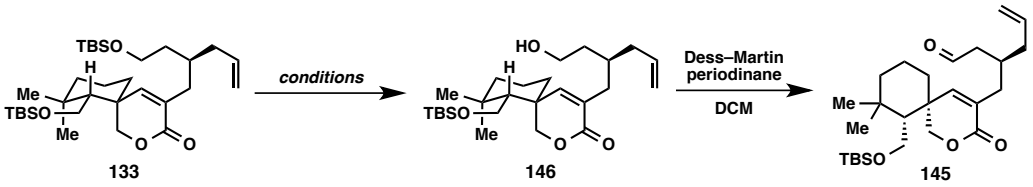
3.2 FORWARD SYNTHETIC EFFORTS

The following section describes the experiments conducted in order to achieve the total syntheses of (–)-trichorabdal A and (–)-longikaurin E.[8]

3.2.1 Development of a Key Pd^{II}-Mediated Oxidative Cyclization

As described in the retrosynthetic analysis, our initial objective was the elaboration of bis-silyl ether **133** to a suitable silyl ketene acetal substrate for the proposed oxidative cyclization reaction. Toward this end, cleavage of the more sterically accessible TBS ether could be accomplished under a variety of conditions (see Table 3.1). The use of *n*-Bu_4NHSO_4 and *p*-TsOH in methanol at 0 °C [9] (entry 3) provided optimal chemoselectivity for the desired desilylation; immediate treatment of crude alcohol **146** with Dess–Martin periodinane[10] furnished the highest yields of aldehyde **145**. Exposure of **145** to SmI_2 with LiBr and *t*-BuOH as additives effected reductive cyclization, providing a single diastereomer of tricyclic alcohol **147** in 57% yield (see Figure 3.2).[11] Protection of **147** as the methoxymethyl ether (**148**) proceeded smoothly, and subsequent deprotonation with KHMDS followed by addition of TBSCl at –78 °C delivered silyl ketene acetal **149**. Use of the MOM ether protecting group was found to be critical for silyl ketene acetal formation: use of silicon-based groups in the protection of **147** resulted

in poor yields for the ketene acetal forming step, and efforts to disilylate **147** were likewise unfruitful. As the C11 alcohol is *syn* to the enolizable proton, we hypothesize that large silyl ether groups sterically obstruct the desired deprotonation.



entry	conditions	temp (°C)	yield 145 (%)[a]
1	3:1:1 AcOH/THF/H_2O	23	68
2	4:1:1 THF/TFA/H_2O	0	55
3	*n*-Bu_4NHSO_4, *p*-TsOH, MeOH	0	77

[a]Isolated yield.

Table 3.1. Survey of conditions for selective deprotection/oxidation of **133**.

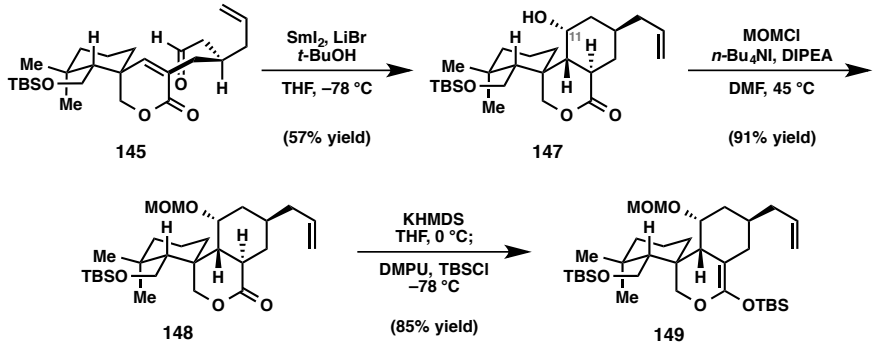
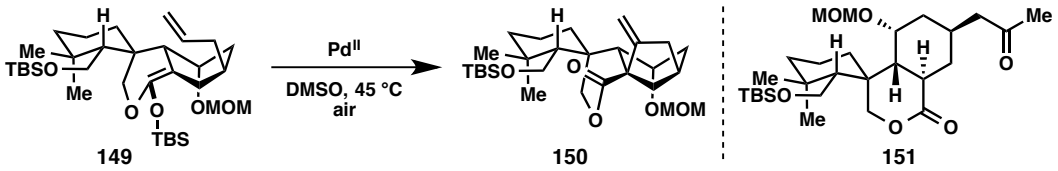


Figure 3.2. Synthesis of silyl ketene acetal **149**.

With silyl ketene acetal **149** in hand, we sought to explore the proposed oxidative cyclization to form the bicyclo[3.2.1]octane present in trichorabdal A (**3**) and longikaurin E (**12**). Upon exposure of **149** to 10 mol % $Pd(OAc)_2$ in DMSO at 45 °C under an air atmosphere, we were delighted to isolate tetracycle **150**, albeit in only 7% yield (Table 3.2, entry 1). Fortunately, the use of stoichiometric $Pd(OAc)_2$ substantially improved both conversion and the yield of **150** (entry 2), and a survey of reaction conditions was conducted. The desired transformation does proceed in MeCN at ambient temperature

(entry 3); however, an increased level of olefin isomerization side products is observed. All other solvents tested (e.g., PhMe, glyme, dioxane, *t*-BuOH, DMF) yielded only traces of **150**; other palladium sources also performed quite poorly (entries 4–6). Less coordinating counterions for palladium appear to skew the distribution of products toward that of Wacker oxidation: the major product when using $PdCl_2$ and $AgBF_4$ (entry 6) was methyl ketone **151**. No desaturated products from Saegusa–Ito-type pathways were observed.[12]



149 150 151

entry	Pd source (equiv)	additive (equiv)	yield 150 (%)[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 **151** was also isolated. [e]Run under a N_2 atmosphere.

Table 3.2. Reaction optimization for the formation of **150**.

High variability in both the yield and purity of **150** upon attempts to increase reaction scale beyond a few milligrams prompted an examination of the roles of adventitious water and Brønsted acid. 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 **150** 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 further improved the yield.

While the exact role of the acid additive remains unclear, we observe that formation of palladium black is strongly suppressed, a likely cause of the reduction in side product formation. In studies on a Pd^{II} catalytic system for aerobic alcohol oxidation, Sigman and colleagues observe a rate increase with the addition of AcOH, possibly due to a switch in the rate- and turnover-limiting step from *β*-hydride elimination to reoxidation.[13] In our system, there are two likely reaction pathways (Figure 3.3) to form *exo*-olefin **150**: one, olefin coordination and direct displacement by the ketene acetal nucleophile (**149** to **152**) to afford a Pd^{II}-alkyl species (**153**), releasing **150** upon *β*-hydride elimination; and two, transmetalation to afford a Pd^{II}-enolate, which may undergo a *syn*-palladation pathway via its C-bound tautomer (**155** to **153**), followed by *β*-hydride elimination to release the product (**150**). While our system does not appear to undergo catalytic turnover, limited NMR studies have suggested that olefin insertion or *β*-hydride elimination may be sluggish in our system. The addition of AcOH likely influences various equilibria and dynamic processes such as ligand exchange, transmetalation, olefin insertion, and enolate tautomerization, all of which could affect the reaction rate or mechanism. Irrespective of the role of AcOH, to the best of our knowledge, this transformation represents the first example of a Pd-mediated oxidative cyclization of a silyl ketene acetal to generate an all-carbon quaternary center.

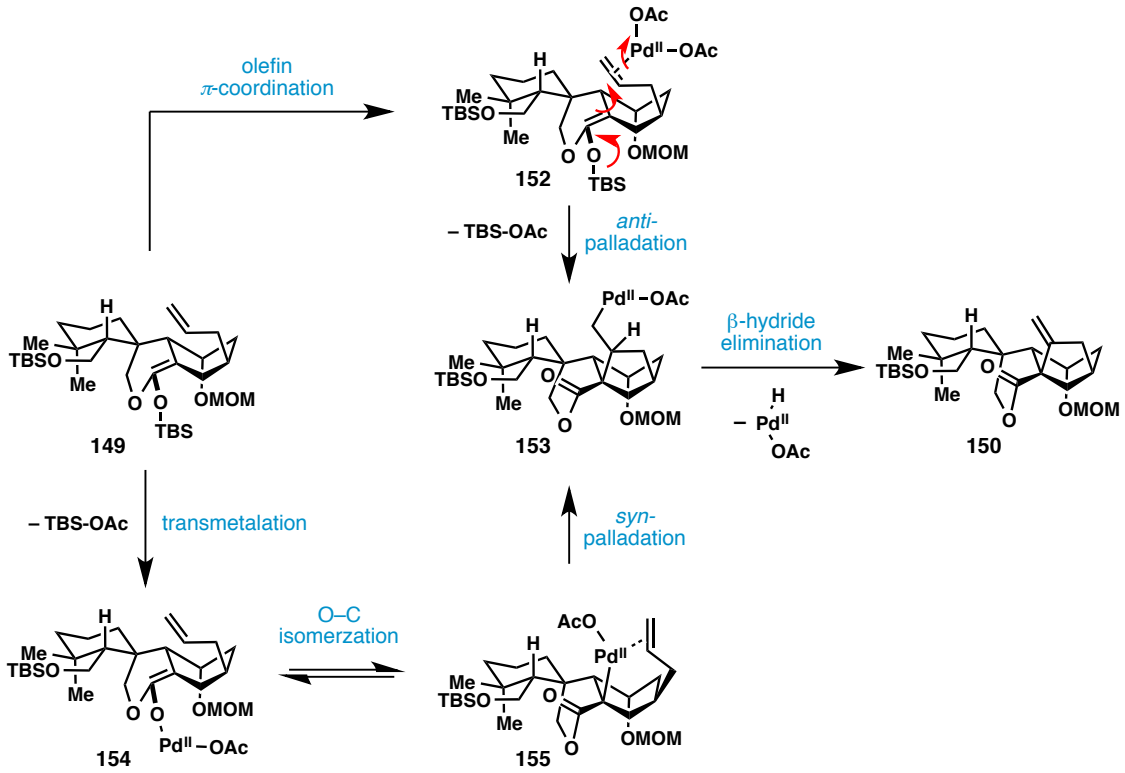
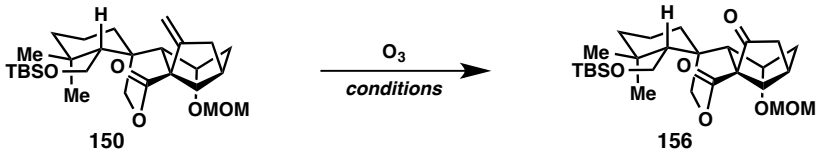


Figure 3.3. Mechanistic pathways for the formation of **150** from **149**.

3.2.2 Synthesis of (–)-Trichorabdal A

Having now established the carbon framework present in many 6,7-*seco*-*ent*-kauranoids, the remaining steps for transformation to **3** include installation of the *exo*-enone and C6 aldehyde. Initial ozonolyses of **150** employed a triethylamine workup, resulting in the isolation of only 33% yield of desired *β*-ketolactone **156**, and poor overall mass recovery (Table 3.3, entry 1). This finding suggested a marked sensitivity to base, compared with intermediates bearing the maoecrystal Z framework. A brief survey of solvents and workup parameters revealed that triphenylphosphine provided most rapid decomposition of the ozonide to ketolactone **156**. Use of triphenylphosphine supported on polystyrene for easy removal and product purification, combined with a lower reaction temperature of –94 °C increased the yield of **156** to 69% (entry 6). Notably, a further

slight increase could be realized by lowering the reaction temperature to –116 °C and switching solvents to bromoethane (entry 7).



entry	solvent	temp (°C)	workup reagent (equiv)	yield 156 (%)[a]
1	DCM	–78	Et_3N (20)	33
2	DCM	–78	Me_2S (25)	52
3	DCM	–78	thiourea (10)	51
4	DCM	–78	PPh_3 (10)	63
5	DCM	–78	PPh_3/polystyrene (10)	63
6	DCM	–94[b]	PPh_3/polystyrene (10)	69
7	EtBr	–116[c]	PPh_3/polystyrene (10)	71
8	pentane[d]	–116[c]	PPh_3/polystyrene (10)	64

[a]Isolated yield. [b]Acetone/N_2(*liq*) bath. [c]EtOH/N_2(*liq*) bath. [d]Ozonide of **150** insoluble in pentane, DCM added with workup reagents.

Table 3.3. Optimization of ozonolysis of **150**.

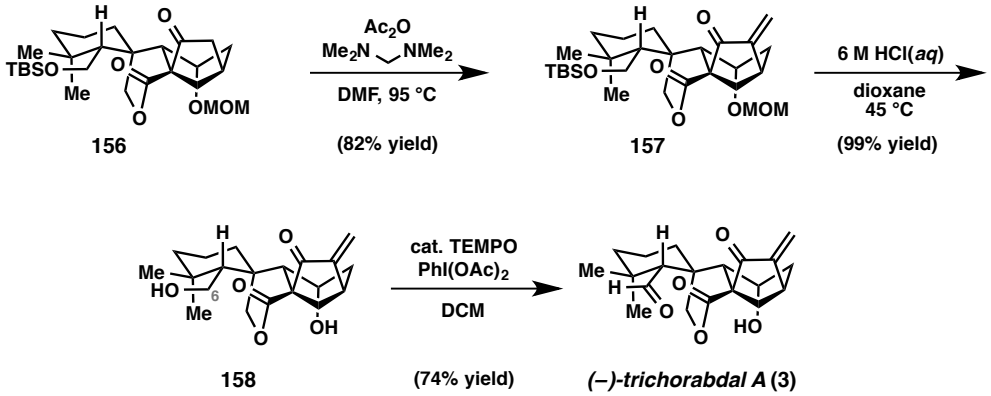


Figure 3.4. Completion of total synthesis of (–)-trichorabdal A (**3**).

Enone **157** was obtained in 82% yield upon treatment of **156** with bis(dimethylamino)methane and acetic anhydride (Figure 3.4).[14] Two-step protocols

using a strong base and Eschenmoser's salt provided significantly diminished yields of **157**. 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 (**3**).[16]

3.2.3 Synthesis of (–)-Longikaurin E

With the synthesis of **3** complete, we turned our attention to the aldehyde-lactone reductive coupling required for the synthesis of longikaurin E (**12**). Treatment of *exo*-olefin **150** with 6 M aqueous HCl in dioxane at 45 °C resulted in global deprotection to afford diol **159**; subsequent oxidation with catalytic TEMPO and $PhI(OAc)_2$ likewise proceeded smoothly (see Figure 3.5). Aldehyde **160** was acetylated using acetic anhydride and DMAP to furnish **161**, and a screen of reaction parameters for the proposed reductive cyclization was conducted.

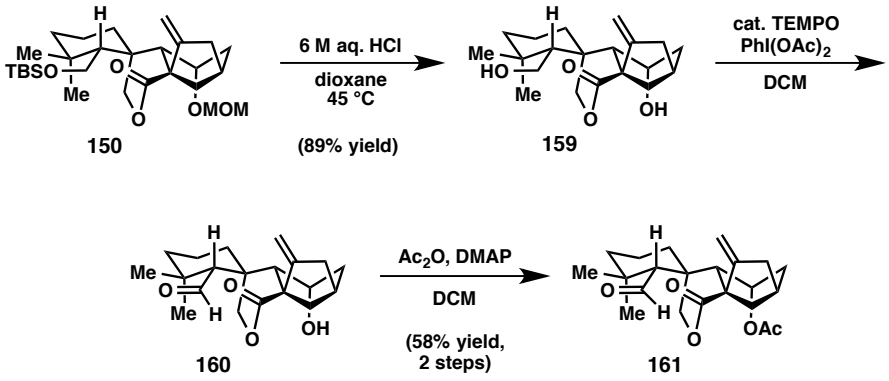
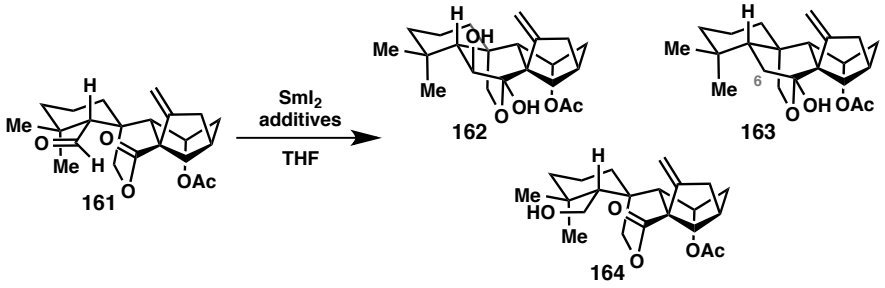


Figure 3.5. Advancement of *exo*-olefin **150** to aldehyde-lactone **161**.



entry	SmI_2 equiv	additives (equiv)	temp (°C)	yield[a] (brsm)
1	5.0	LiBr (50) *t*-BuOH (1.0)	–78	no reaction
2	5.0	HMPA (50)	–78	0%[b]
3	5.0	LiCl (50) *t*-BuOH (1.0)	0	54% **164**
4	5.0	LiBr (50) *t*-BuOH (1.0)	0	38% **164**
5	2.0	--	23	55% **162** (75%)
6	2.4	--	23	55% **162** (62%)
7[c]	5.0	*t*-BuOH (1.0)	23	72% **161**

[a]Isolated yield. [b]Complex mixture. [c]Run to full consumption of **161**.

Table 3.4. Survey of reaction paramters for conversion of **161** to **162**.

Exposure of **161** to SmI_2 with LiBr and *t*-BuOH at –78 °C (Table 3.4, entry 1) unexpectedly led to recovery of starting material. Whereas addition of HMPA effected swift decomposition of **161** (entry 2), increasing the reaction temperature to 0 °C resulted in reduction to primary alcohol **164** when employing LiCl or LiBr additives (entries 3 and 4). Gratifyingly, exclusive use of SmI_2 at ambient temperature provided the desired hydroxy-lactol (**162**) in 55% yield, along with 27% yield of recovered **161** (entry 5). Interestingly, attempting to push the reaction to full conversion did not improve the yield of **162**; instead, over-reduction to C6-deoxylactol **163** was observed (entry 7). It is presumed that warmer temperatures enable the ketyl radical intermediate to attain the necessary conformation for cyclization; omission of additives precludes competitive

over-reduction (to **164**) and α-deoxygenation (to **163**) processes, favoring cyclization product **162**. With the oxabicyclo[2.2.2]octane in hand, ozonolysis of **162** and α-methylenation under previously described conditions revealed (–)-longikaurin E (Figure 3.6).

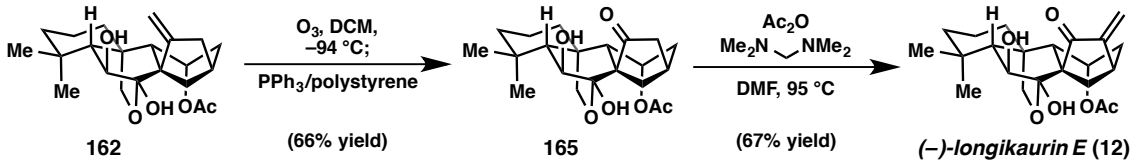


Figure 3.6. Completion of the synthesis of (–)-longikaurin E (**12**).

3.3 CONCLUDING REMARKS

In summary, a unified strategy has enabled the first total syntheses of the *ent*-kauranoid natural products (–)-trichorabdal A (**3**) and (–)-longikauin E (**12**) in 15 and 17 steps from (–)-γ-cyclogeraniol (**104**), and in 3.2% and 1.0% overall yield. Key to the success of our approach is the development of a Pd^{II}-mediated silyl ketene acetal oxidative cyclization reaction to install the bridgehead all-carbon quaternary stereocenter of **3** and **12**, and the use of a Sm^{II}-mediated reductive coupling to construct the C6–C7 bond of **12**. These transformations, taken together with those described in the previous chapter, constitute a diverging route that has established a synthetic relationship among three architecturally distinct *ent*-kaurane diterpenoids by enabling their total syntheses from one common spirolactone.

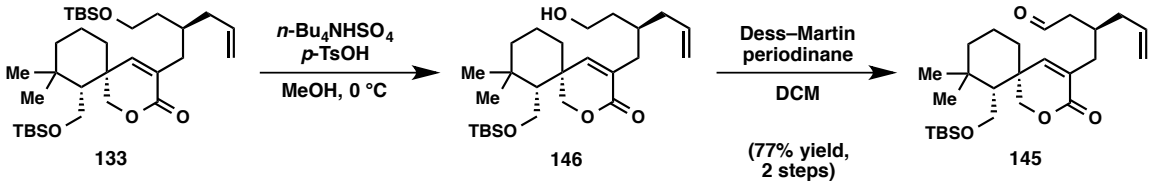
3.4 EXPERIMENTAL SECTION

3.4.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (DCM), and dimethylformamide (DMF) 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(1*H*)-pyrimidinone (DMPU) and hexamethylphosphoramide (HMPA) were distilled over calcium hydride under reduced pressure, and dimethylsulfoxide (DMSO) was dried over 4ÅMS 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. Flash column chromatography was performed as described by Still et al.[17] using silica gel (particle size 0.032-0.063) purchased from Silicycle or Florisil (100-200 mesh) purchased from Sigma-Aldrich. 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).

3.4.2 Preparative Procedures and Spectroscopic Data

Preparation of aldehyde 145.

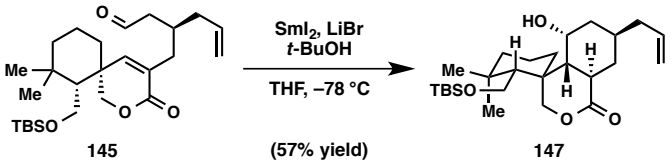


To a solution of enoate **133** (1.94 g, 3.43 mmol) in 35 mL MeOH cooled to 0 °C was added *n*-Bu_4NHSO_4 (128 mg, 0.378 mmol, 0.11 equiv) and *p*-TsOH (26 mg, 0.14 mmol, 0.04 equiv). After stirring at 0 °C for 1.5 h, the reaction mixture was diluted with sat. $NaHCO_3$ (25 mL) and concentrated *in vacuo* 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 **146**. Crude **146** 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 **145** as a clear gum (1.18 g, 77% yield from **133**). $[\alpha]_D^{25}$ = –33.4° (*c* 1.23, $CHCl_3$); ^{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.

An analytical sample of alcohol **146** was obtained (63% yield) by SiO_2 chromatography (30% EtOAc/Hex). $[\alpha]_D^{25}$ = –44.6° (*c* 1.21, $CHCl_3$); ^1H 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.

Preparation of tricycle 147.



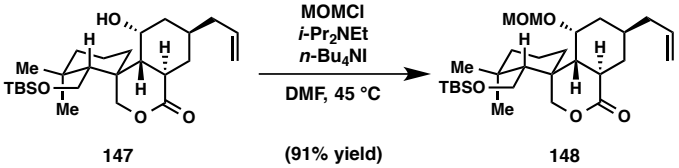
145 147

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 **145** (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 **17** as a white foam (0.385 g, 57% yield). $[\alpha]_D^{25}$ = –11.3° (*c* 2.26, $CHCl_3$); ^{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.

Preparation of MOM ether 148.

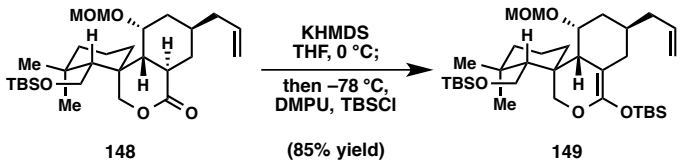


147 **(91% yield)** **148**

A solution of tricycle **147** (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 **148** as a clear gum (0.315 g, 91% yield). $[\alpha]_D^{25} = -22°$ (*c* 0.76, $CHCl_3$); ^1H 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.

Preparation of silyl ketene acetal 149.



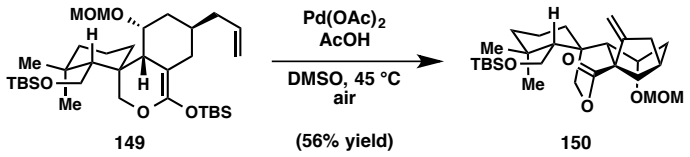
148 (85% yield) 149

*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 **148** (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 **149** as a clear gum (0.139 g, 85% yield). $[\alpha]_D^{25}$ = –82.6° (*c* 1.50, $CHCl_3$); ^1H 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.

Preparation of tetracycle 150.

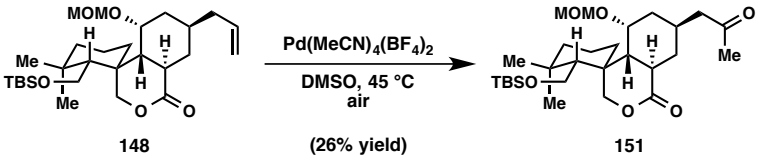


A solution of silyl ketene acetal **149** (0.139 g, 0.228 mmol), $Pd(OAc)_2$ (52 mg, 0.23 mmol, 1.0 equiv), and AcOH (6.9 mg in 0.10 mL DMSO, 0.11 mmol, 0.5 equiv) in 9 mL DMSO was heated to 45 °C in an open flask. After stirring under air for 6 h at 45 °C, the reaction mixture was cooled to room temperature, 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 **150** as a clear gum (63 mg, 56% yield). $[\alpha]_D^{25}$ = +23.0° (*c* 0.305, $CHCl_3$); ^{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.

Optimization of reaction parameters: General procedure for oxidative cyclization of 149 to 150 (Table 3.2).

A vial was charged with silyl ketene acetal **149** (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 **150**.

Preparation of methyl ketone 151.

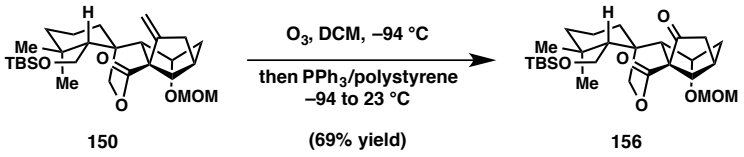


*Note: Methyl ketone **151** was initially isolated as a side product during optimization experiments for the conversion of **149** to **150** (Table 3.2, entry 6, 13% yield). Independent preparation was accomplished using the following procedure.

A solution of MOM ether **148** (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 **151** as a clear gum (4.3 mg, 26% yield). $[\alpha]_D^{25}$ = –15° (*c* 0.22, $CHCl_3$); ^{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.

Preparation of ketolactone 156.

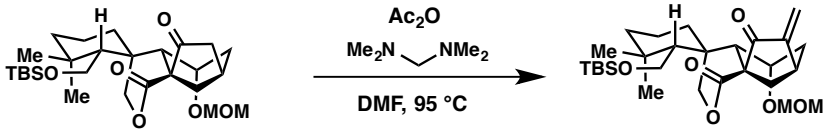


150 (69% yield) **156**

A solution of tetracycle **150** (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 **156** as a clear gum (20.9 mg, 69% yield). $[\alpha]_D^{25}$ = +8.2° (*c* 0.99, $CHCl_3$); ^{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.

Preparation of enone 157.

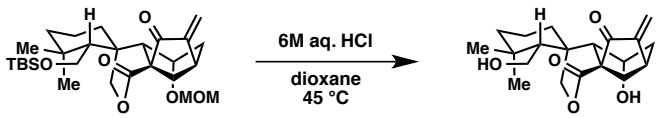


156 **157**

A solution of ketolactone **156** (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 **157** as a clear gum (16.1 mg, 82% yield). $[\alpha]_D^{25}$ = +27.6° (*c* 1.02, $CHCl_3$); ^{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.

Preparation of diol 158.

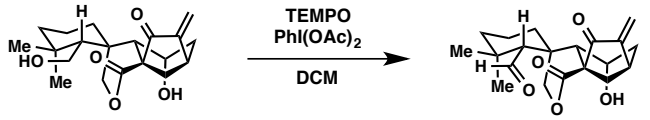


157 (99% yield) **158**

To a solution of enone **157** (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 **158** as a white solid (11.0 mg, 99% yield). $[\alpha]_D^{25}$ = +14° (*c* 0.16, $CHCl_3$); ^{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.

Preparation of (–)-trichorabdal A (3).



158 (74% yield) *(–)-trichorabdal A* (3)

To a solution of diol **158** (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 (**3**) as a white solid (8.1 mg, 74% yield). $[\alpha]_D^{25}$ = –61° (*c* 0.12, EtOH); ^{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.

^{1}H NMR comparison table for trichorabdal A (**3**).

Natural* [16a] (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

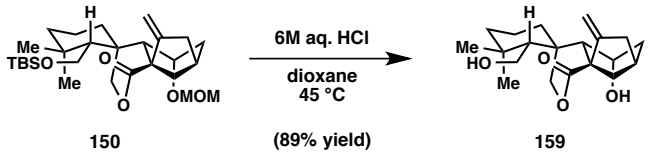
***** No further ^{1}H signals were reported.

^{13}C NMR comparison table for trichorabdal A (**3**).**

Natural[2] (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.[16c]

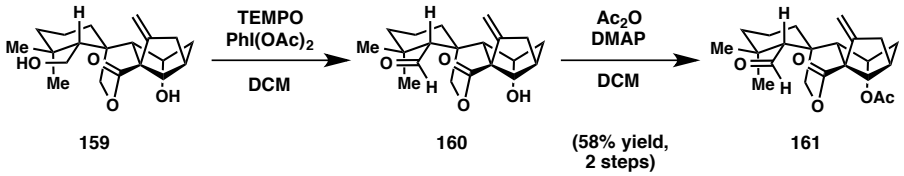
Preparation of diol 159.



150 (89% yield) **159**

To a solution of tetracycle **150** (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 **159** (35.9 mg, 89% yield). $[\alpha]_D^{25}$ = –28° (*c* 0.66, $CHCl_3$); ^{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.

Preparation of acetate 161.

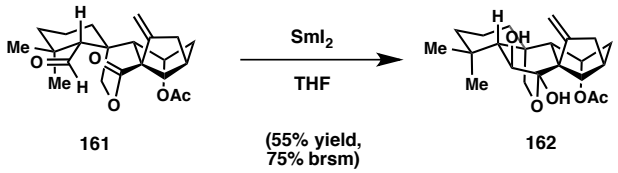


To a solution of diol **159** (35.2 mg, 0.105 mmol, 1.0 equiv) in DCM (5.3 mL) was added $PhI(OAc)_2$ (47.6 mg, 0.148 mmol, 1.4 equiv) and 2,2,6,6-tetramethylpiperidine 1-oxyl (3.3 mg, 21 μmol, 0.20 equiv). The resulting solution was stirred for 4.5 h, and then diluted with sat. $Na_2S_2O_3$ (20 mL). 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 **160**. The crude residue was chromatographed on SiO_2 (25% EtOAc/Hex) to provide 25.4 mg **160** (~85% purity, contaminated with ketoaldehyde from over-oxidation). Impure **160** 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 **161** (22.8 mg, 58% yield from **159**). $[\alpha]_D^{25}$ = –6.9° (*c* 0.42, $CHCl_3$); ^{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.

An analytical sample of aldehyde **160** was obtained (65% yield) by preparative reverse phase HPLC (45% to 70% MeCN/H_2O, 10 minute gradient, t_R = 7.0 min). $[\alpha]_D^{25}$ = –65.4° (*c* 0.37, $CHCl_3$); ^1H 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.

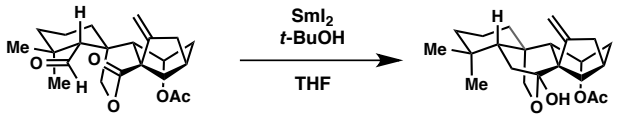
Preparation of hydroxylactol 162.



161 (55% yield, 75% brsm) **162**

To a solution of **161** (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 **161** (1.2 mg, 27% yield) and hydroxylactol **162** (2.4 mg, 55% yield). $[\alpha]_D^{25}$ = –47.2° (*c* 0.30, $CHCl_3$); ^{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.

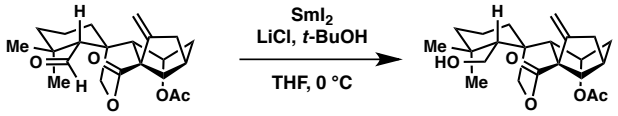
Preparation of lactol 163.



161 **(72% yield)** **163**

To a solution of aldehyde **161** (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 **163** (3.6 mg, 72% yield). $[\alpha]_D^{25}$ = –135° (*c* 0.30, $CHCl_3$); ^{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.

Preparation of primary alcohol 164.



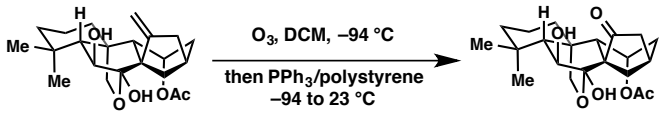
161 (54% yield) **164**

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 **161** (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 **164** (0.7 mg, 54% yield). $[\alpha]_D^{25} = -7.5°$ (*c* 0.16, $CHCl_3$); ^{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.

General procedure for reductive cyclization of aldehyde 161 (Table 3.4).

To a flask charged with aldehyde **161** (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 **162**, lactol **163**, primary alcohol **164**, or recovered aldehyde **161**.

Preparation of ketolactol 165.

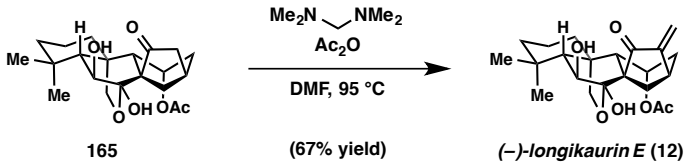


162 **(66% yield)** **165**

A solution of lactol **162** (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 **165** (2.9 mg, 66% yield). $[\alpha]_D^{25}$ = –86° (*c* 0.30, $CHCl_3$); ^{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.

Preparation of (–)-longikaurin E (12).



To a solution of **165** (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 (**12**) (1.8 mg, 67% yield). $[\alpha]_D^{25}$ = –51° (*c* 0.30, C_5H_5N); $[\alpha]_D^{25}$ = –39° (*c* 0.17, $CHCl_3$); ^{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.

^{1}H NMR comparison table for longikaurin E (**12**).

Natural*[2a] ($CDCl_3$) 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 (**12**).

Natural*[2a] ($CDCl_3$) 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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