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A unified strategy for the synthesis of (−)-maoecrystal Z, (−)-trichorabdal A, and (−)-longikaurin E

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ABSTRACT

Herein we describe in full our investigations that led to the completion of the first total syntheses of (−)-maoecrystal Z, (−)-trichorabdal A, and (−)-longikaurin E. The unified strategy employs a Ti^{III}-mediated reductive epoxide coupling to rapidly prepare a key spirolactone. Highly diastereoselective Sm^{II}-mediated reductive cyclizations and a Pd^{II}-mediated oxidative cyclization enable the construction of three architecturally distinct *ent*-kauranoid frameworks from this common intermediate.

1. Introduction

The folk medicine traditions of China and Japan have long made use of *Isodon* plants as remedies for inflammation, gastric and respiratory infections, cancer, and other maladies; consequently, it should come as no surprise that these plants have proven to be a rich source of bioactive diterpenoids (see Fig. 1).[1,2] As early as 1958, investigations of *Isodon japonica* led to the isolation of enmein (**8**),[2h–j] later confirmed as a 6,7-seco-*ent*-kauranoid by X-ray crystallography.[3] In the years hence, continued studies have revealed many new and structurally diverse *ent*-kauranoids with highly selective anticancer and antibacterial properties (see Fig. 1). For example, trichorabdals A and B (**2** and **3**)[4] and **8**[5] have been found to display in vivo inhibition of Ehrlich ascites carcinoma in mice, and maoecrystals Z and V (**1** and **7**),[2a,g] longikaurin E (**4**),[6] and sculponeatin N (**6**),[2f] exhibit in vitro activity against several cancer cell lines. Notably, maoecrystal V (**7**) and adenanthin (**5**) possess remarkable selectivity profiles: **7** displayed potent cytotoxicity against HeLa cells (IC_{50}=60 nM) but was essentially inactive against four other cell lines (IC_{50}>40 mM),[2g] while **5** was found to

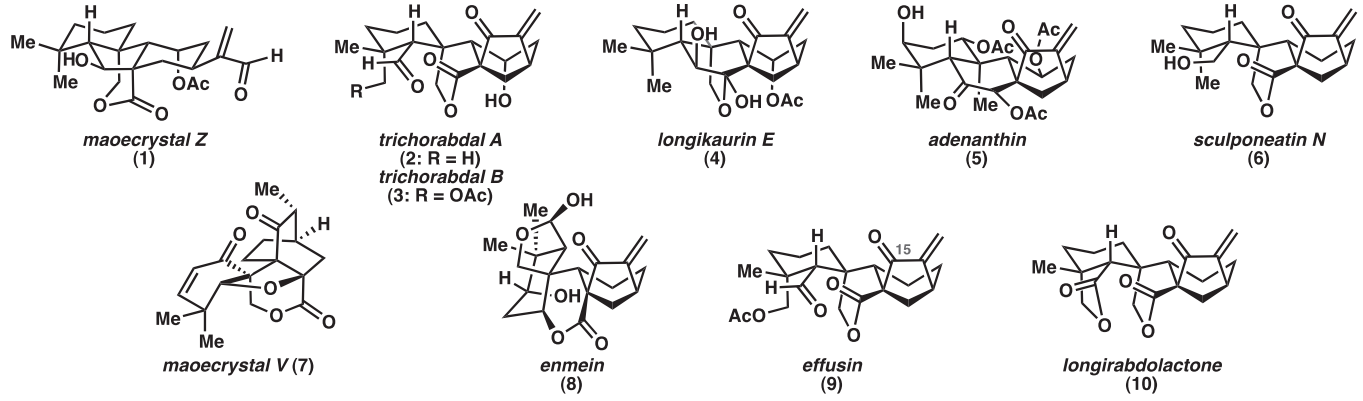

Fig. 1. Selected *Isodon* diterpenoids.

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selectively inhibit two isoforms of the peroxiredoxin enzymes and prolong survival in murine models of acute promyelocytic leukemia.[7]

Though comprised largely of *ent*-kauranoids, the more than 600 *Isodon* diterpenoids isolated to date are a highly diverse family, exhibiting numerous frameworks and oxidation patterns.[1] Many of the bioactive members share similar structural features, such as a central, spiro-fused lactone characteristic of the 7,20-lactone class of 6,7-seco-*ent*-kauranoids (e.g., **2**, **3**, **6**, **9**, **10**, see Fig. 1). Furthermore, some motifs, such as the α,β-unsaturated carbonyl, are often vital for biological activity: Fujita demonstrated that hydrogenation of various *ent*-kauranoids to their saturated derivatives significantly weakened (**3**)[4] or abolished (**8**)[5] antibacterial and antitumor activity; similarly, the dihydro derivative of **5** was found to be inactive.[7]

Despite the multitude of bioactive 6,7-seco-*ent*-kauranoids isolated and characterized since the 1970s, there have been strikingly few reports of synthetic studies. In 1986, Mander and co-workers reported a total synthesis of 15-desoxyeffusin,[8] and in 2003 disclosed a semisynthesis of longirabdolactone (**10**) from gibberellic acid.[9] Several research groups have reported efforts[10] toward maoecrystal V (**7**) since its structural elucidation in 2004, with completed total syntheses published by the laboratories of Yang,[11] Danishefsky,[12] and Zakarian.[13] Interest in 6,7-seco-*ent*-kauranoid targets has continued with two recent total syntheses of sculponeatin N (**6**).[14,15]

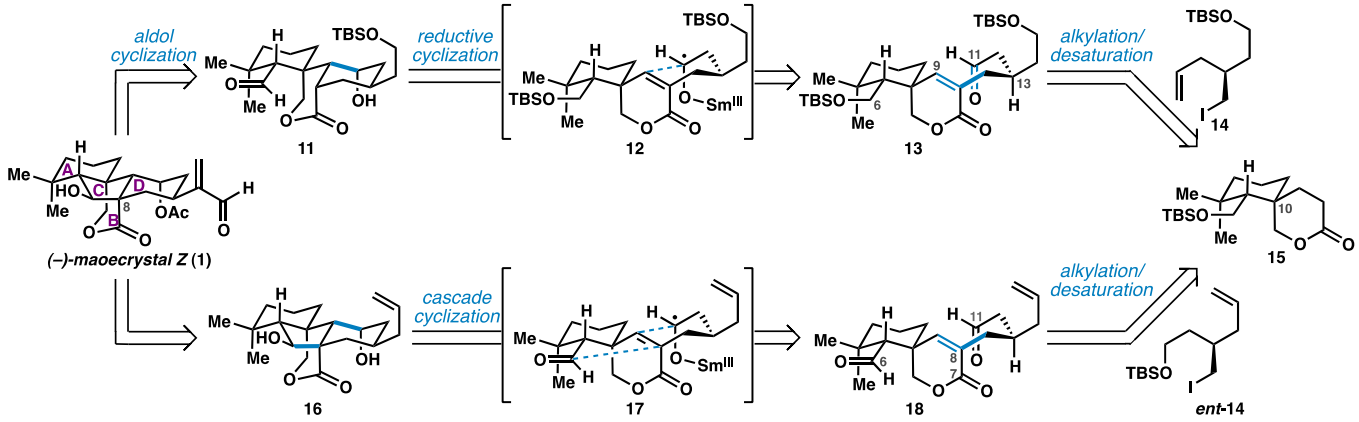
initial synthesis of **1** would yield valuable insights for the preparations of **2** and **4**.

These endeavors have resulted in the first total syntheses of three architecturally distinct *ent*-kauranoids: (−)-maoecrystal Z, (−)-trichorabdal A, and (−)-longikaurin E.[16] Described herein are the full details of our efforts and the experiments that brought about the development and successful execution of this universal synthetic strategy.

2. Results and discussion

2.1. Synthetic plan

In our initial synthetic planning, we conceived of two principal retrosynthetic disconnections for the formation of the C and D rings of **1** (see Scheme 1). Firstly, we envisioned that the five-membered C ring and the C8 all-carbon quaternary stereocenter could be constructed via an intramolecular aldol cyclization, a strategic decision guided in part by isolation studies on a related *ent*-kauranoid, trichorabdal B (**3**, Fig. 1). Fujita and co-workers describe the skeletal rearrangement of **3** to an oxidized congener of **1** via a methoxide-triggered retro-Dieckmann/aldol sequence.[2c] This finding suggests that a precursor such as **11** could undergo an intramolecular aldol cyclization under mild conditions to form the C ring of **1**.



Scheme 1. Retrosynthetic analysis for maoecrystal Z.

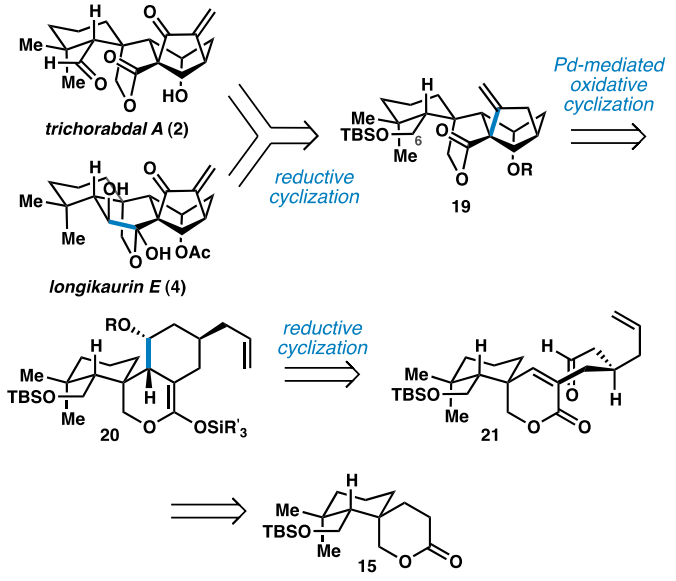
Our interests in the *ent*-kauranoids were initially piqued by maoecrystal Z (**1**). Isolated in 2006 as a minor constituent from *Isodon eriocalyx*,[2a] its densely functionalized, rearranged framework is unprecedented among seco-*ent*-kauranoid natural products and bears six contiguous stereogenic centers, including two all-carbon quaternary stereocenters. The structural complexity of its compact, tetracyclic ring system, in addition to its activity against human tumor cell lines (K562 leukemia, MCF-7 breast, A2780 ovarian), rendered **1** a compelling target for total synthesis. As a key design consideration, we sought to develop a strategy that would not only facilitate the preparation of **1**, but could also be modified to enable the synthesis of other bioactive *ent*-kauranoids such as trichorabdal A (**2**) and longikaurin E (**4**). Given the similarity of substitution and oxidation level about the A-rings of **1**, **2**, and **4**, (see Fig. 1) it was anticipated that a route passing through a common bicyclic spiro-fused lactone would be appropriate. If designed properly, such a route could be diverged at a late stage to provide access to the three distinct ring systems required. In undertaking this strategy, we envisioned that the chemical transformations and experiments devised during the

Secondly, it was anticipated that the six-membered D ring could be prepared from an aldehyde-enoate (e.g., **13**) by a Sm-mediated ketyl-olefin reductive cyclization.[17] We hypothesized that C–C bond formation would proceed by addition of the C11-ketyl radical to the more sterically accessible enoate face, opposite to C6, diastereoselectivity that should be further reinforced by the equatorially disposed siloxyethyl group of the C13 stereocenter (see conformation **12**). Whereas this stereochemical preference was expected to result in the correct configuration at C9, the corresponding C11 alcohol configuration was difficult to predict based on conformational analysis alone. Aldehyde **13** could be convergently prepared from spirolactone **15** and alkyl iodide **14** via sequential alkylation, desaturation, and ozonolysis.

Alternate to the stepwise sequence outlined above, we recognized that it might be possible to execute both cyclizations as part of a single tandem cascade process. Recent studies by Procter and co-workers[18] have demonstrated the utility of SmI_2 for the reductive cascade cyclizations of dialdehyde substrates in order to rapidly construct polycyclic frameworks, as exemplified by their recent total synthesis of (+)-pleuromutilin.[19] In this regard,

maoecrystal Z could be simplified to diol **16**, which we hypothesized could arise from dialdehyde **18** via such a cascade. We anticipated that ketyl radical formation at the C6-aldehyde would be kinetically less favorable due to the steric encumbrance imposed by two adjacent quaternary centers; therefore, enoate addition of the C11-ketyl with desired facial selectivity (vide supra) was expected to provide the D ring. Subsequently, a second single-electron reduction would afford the C7–C8 enolate, poised to undergo aldol cyclization in accord with the precedent of Fujita's isolation studies. If the issues of chemo- and diastereoselectivity prove tractable, the proposed cascade cyclization would rapidly increase structural complexity, building two new rings and diastereoselectively setting four new stereogenic centers in a single step. Conveniently, substrates for both the stepwise and cascade approaches can be readily accessed from spirolactone **15** and either enantiomer of alkyl iodide **14**. We also expected that spirolactone **15**, possessing the C10 spirocyclic quaternary center present in many bioactive *ent*-kauranoids, would serve as a valuable synthon for efforts toward trichorabdal A (**2**) and longikaurin E (**4**) as part of a unified strategy.

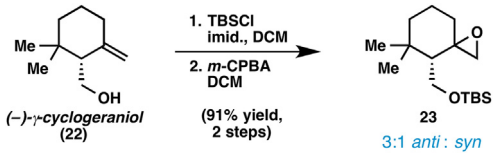
Retrosynthetically, **2** and **4** were both envisioned to be accessed from *exo*-olefin **19** (see Scheme 2). To access **4**, we hoped to forge the central oxabicyclo[2.2.2]octane via the reductive cyclization of a C6-aldehyde precursor. The bicyclo[3.2.1]octane motif of **19** would arise through a transition metal-mediated oxidative cyclization reaction of silyl ketene acetal **20**. Although the oxidative cyclization of silyl enol ethers is well precedented,[20,21] 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.[22] 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 **1** would enable the facile synthesis of tricycle **20** from the common spirolactone **15**.



Scheme 2. Retrosynthetic analysis for trichorabdal A and longikaurin E.

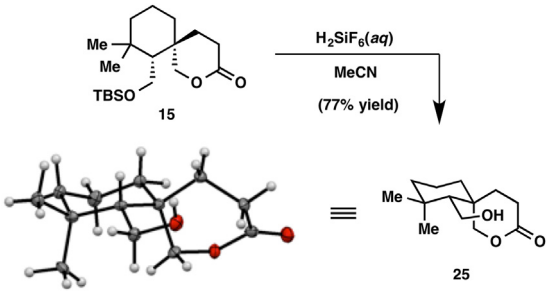
2.2. Preparation of a key spirolactone (15)

Our initial objectives were to prepare spirolactone **15** and set the central C10 quaternary stereocenter. Studies commenced with protection of (−)-γ-cyclogeraniol (**22**)[23] as the *tert*-butyldimethylsilyl (TBS) ether, followed by exposure to *m*-chloroperoxybenzoic acid (*m*-CPBA) to afford epoxide **23** as a 3:1 mixture of diastereomers (Scheme 3).



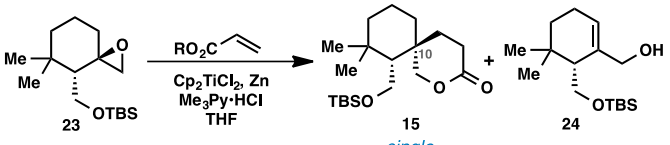
Scheme 3. Preparation of epoxide **23**.

Treatment of a mixture of **23** and methyl acrylate with Gansäuer's modified conditions[24] (Table 1, entry 1) for the radical epoxide–olefin coupling developed by Nugent and RajanBabu[25] resulted in formation of spirolactone **15** in 28% yield. Although the yield was modest, we were delighted to find that lactone **15** was diastereomerically pure and possessed the correct stereochemical configuration at C10, as confirmed by single crystal X-ray diffraction of desilylated lactone **25** (Scheme 4). The major side product isolated under unoptimized conditions was allylic alcohol **24**, potentially arising from epoxide **23** via Lewis acid-promoted rearrangement or a Ti^{III}-mediated radical disproportionation process.[26]



Scheme 4. Stereochemical confirmation of spirolactone **15**.

Table 1
Optimization of synthesis of spirolactone **15**



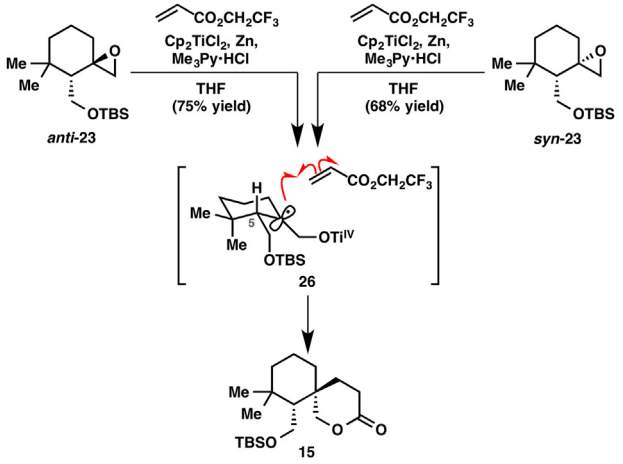
Entry	R (equiv)	Cp_2TiCl_2 (equiv)	Zn (equiv)	$Me_3Py{\cdot}HCl$ (equiv)	Yield **15**[a] (%)
1	CH_3 (3.0)	0.5	2.0	2.5	28
2	CH_3 (10.0)	2.0	3.0	5.0	35
3	CH_3 (10.0)	2.0[b]	3.0	3.0	44
4	CH_3 (10.0)	1.6[c]	3.0	3.0	61
5	CH_3 (10.0)	1.6[c]	1.5	3.0	58
6	CH_2CF_3 (10.0)	1.6[c]	1.5	3.0	76
7	CH_2CF_3 (5.0)	1.6[c]	1.5	3.0	74
8	CH_2CF_3 (3.0)	1.6[c]	1.5	3.0	62

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

Encouraged by this result, we began a survey of reaction parameters in order to obtain more synthetically useful quantities of **15**. Use of a large excess (10 equiv) of methyl acrylate and a full stoichiometric quantity of Cp_2TiCl_2 furnished **15** in 35% yield (Table 1, entry 2); further modest increases were realized using portionwise addition protocols for Cp_2TiCl_2 (entries 3–5). Combining a portionwise addition protocol with a more electrophilic

coupling partner, 2,2,2-trifluoroethyl acrylate, enabled the isolation of lactone **15** in 76% yield (entry 6).[27] Additionally, we were pleased to observe only a slight decrease to 74% yield when 5 equiv acrylate was used (entry 7). Under the optimized conditions, formation of allylic alcohol side product **24** was minimal.

As expected, chromatographic separation of *anti*- and *syn*-**23** and independent subjection of each to the optimized reductive coupling conditions furnished lactone **15** as a single diastereomer in 75% and 68% yields, respectively, supporting the intermediacy of radical **26** (Scheme 5). The major diastereomer (*anti*-**23**) was also found to be reduced by Ti^{III} more quickly: when a reaction employing a 2.3:1 *anti*/*syn* mixture of **23** was run to 56% conversion, unreacted **23** was recovered as a 1.3:1 mixture. The high diastereoselectivity observed for this transformation is proposed to derive from approach of the acrylate partner *syn* to the C5 proton of **26**, minimizing nonbonding interactions with the adjacent siloxy and axial methyl substituents. With the initial all-carbon quaternary stereocenter set and gram quantities of key lactone **15** in hand, we were poised to investigate its elaboration to maoecrystal Z (**1**).



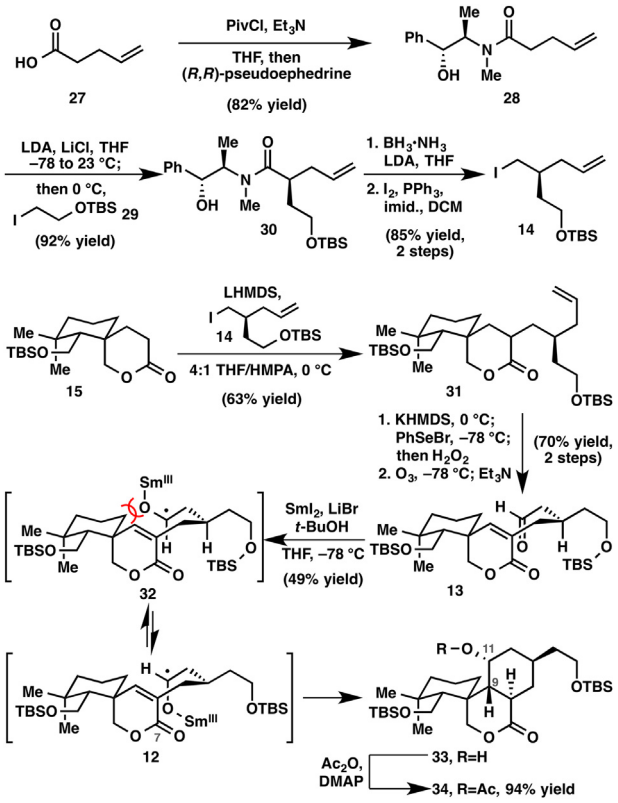
Scheme 5. Control experiments demonstrate epoxide coupling is stereoconvergent.

2.3. Pursuit of a stepwise cyclization

Though our ultimate goal was to employ a Sm^{II}-mediated dialdehyde cascade cyclization to access the core of **1**, we elected to first pursue a stepwise route in order to investigate the efficiency and selectivity of each ring-forming step in isolation. Toward this end, chiral alkyl iodide **14** was prepared according to Myers's asymmetric alkylation protocol.[28] Pent-4-enoic acid (**27**) was converted to pseudoephedrine amide **28**, which was alkylated with *tert*-butyl(2-iodoethoxy)dimethylsilane (**29**) to furnish amide **30** in 92% yield and >20:1 dr (see Scheme 6). Reductive cleavage of the auxiliary using lithium amidoborane provided the primary alcohol, readily converted to enantioenriched alkyl iodide **14** following treatment with iodine and triphenylphosphine.

Moving forward, alkylation of lactone **15** with iodide **14** proceeded upon treatment with lithium hexamethyldisilazide (LHMDS) to afford **31** in 63% yield as an inconsequential mixture of diastereomers. Formation of the phenyl selenide followed by oxidation and elimination delivered the unsaturated lactone, whose terminal alkene was chemoselectively ozonolyzed to afford aldehyde **13**, the targeted ketyl-olefin cyclization precursor.

Initial attempts to prepare tricycle **33** using SmI_2 in THF at 0 °C effected rapid decomposition of **13**, with only traces of the desired product observed by NMR analysis of the crude reaction mixture. Studies by Procter and others have demonstrated that the use of



Scheme 6. Synthesis and Sm^{II}-mediated reductive cyclization of aldehyde **13**.

additives, especially lithium halide salts, can have dramatic effects on the outcome of reactions employing SmI_2.[29] A survey of reaction parameters revealed that the addition of LiCl or LiBr was critical for the desired reactivity. Using a tenfold excess of LiBr relative to SmI_2 and 1 equiv *tert*-butanol (*t*-BuOH) as a proton source, secondary alcohol **33** was obtained in 49% yield. Following treatment with acetic anhydride and 4-dimethylaminopyridine (DMAP), stereochemical analysis of acetate **34** by 1- and 2-D NMR techniques revealed that the configuration of the C9 and C11 stereocenters was correct for elaboration to **1** and other *ent*-kauranoids.[30] The high selectivity for this diastereomer is proposed to result from reaction via ketyl conformation **12**. Whereas conformation **32** is destabilized by the nonbonding interaction between the Sm-ketyl and A-ring methylene, the sp^2 hybridization of C7 appears to alleviate potentially unfavorable 1,3-diaxial interactions present in conformation **12**.

Successful construction of tricycle **33** confirmed the viability of a Sm^{II}-mediated reductive cyclization as the first step in the proposed cascade. In principle, enal installation and aldol cyclization would complete the synthesis of **1**; we therefore continued to advance **34** in order to examine the requisite aldol step. Desilylation with fluorosilicic acid followed by Dess–Martin oxidation[31] furnished dialdehyde **36** (see Scheme 7). Methylenation was accomplished using Eschenmoser's salt[32] and triethylamine to yield enal **37**, isomeric to maoecrystal Z (**1**) and lacking only the C8–C6 bond. Unfortunately, considerable experimentation with a variety of acids and bases failed to promote the desired intramolecular aldol cyclization. NMR analysis of the crude reaction mixtures led us to hypothesize that undesired transesterifications or skeletal rearrangements were occurring due to competitive aldehyde enolization. However, it was also suspected that non-productive reactivity of the enal was giving rise to additional side products. In order to more effectively probe the aldol reactivity, a substrate lacking the enal was prepared.

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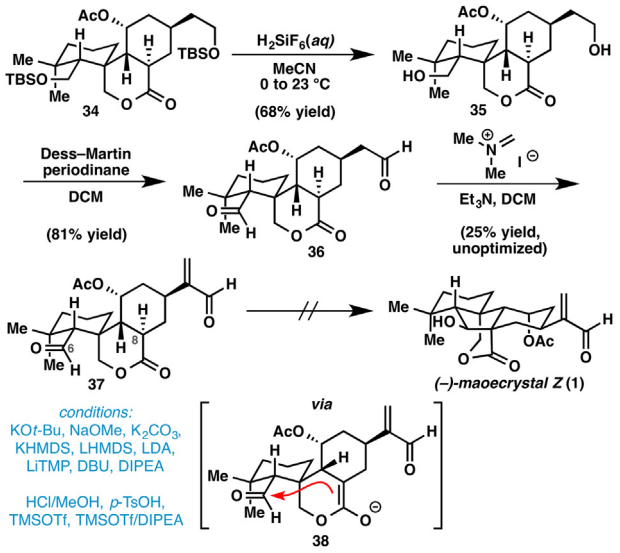
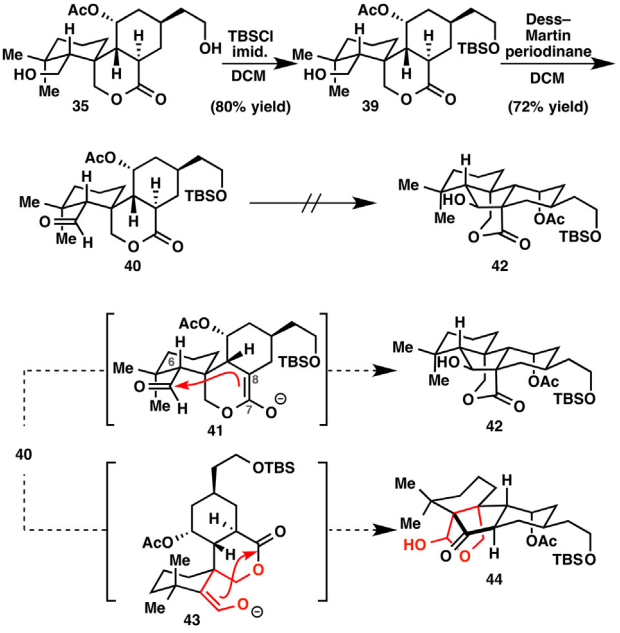


Scheme 7. Initial efforts toward an aldol cyclization.

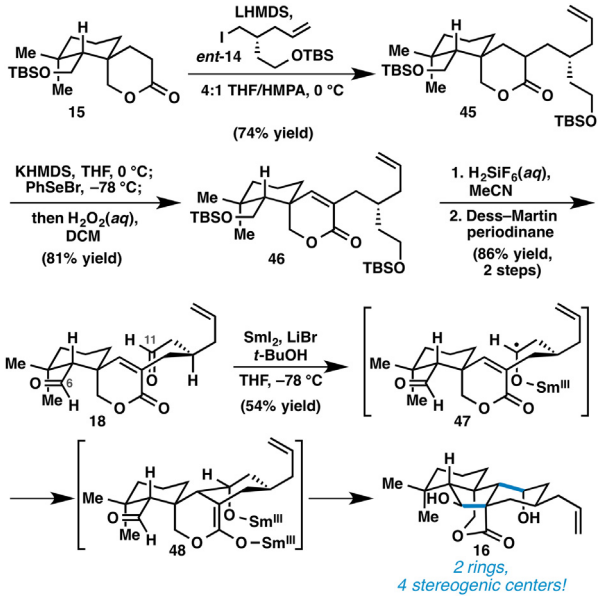
Thus, diol **35** was selectively monosilylated using TBSCl and imidazole. TBS ether **39** was then oxidized using Dess–Martin periodinane to furnish an aldol substrate (**40**) lacking the reactive enal motif (see Scheme 8). However, the desired aldol cyclization (**40**→**42**) was not observed, and similar rearrangement products as observed with dialdehyde **37** were detected. The predominant reactivity pathway is proposed to be aldehyde enolization resulting in skeletal rearrangement by the mechanism shown in Scheme 8 (**40**→**44**).[33]



Scheme 8. Synthesis and undesired reactivity of aldehyde **40**.

2.4. Synthesis of (−)-maoecrystal Z via cascade cyclization

Although our inability to conjoin C6 and C8 was somewhat disheartening, we recognized that the issue of enolization site selectivity is obviated in the proposed reductive cascade cyclization. We therefore turned our attention to the synthesis of a dialdehyde cyclization substrate. Alkyl iodide *ent*-**14** was prepared from the (*S*,*S*)-pseudoephedrine amide and coupled to lactone **15** as before (see Scheme 9). A similar selenation/selenoxide elimination sequence followed by global desilylation and Dess–Martin oxidation furnished dialdehyde **18** in good overall yield. Thus, we were poised to investigate the crucial dialdehyde cyclization cascade.



Scheme 9. Reductive cascade cyclization of dialdehyde **18**.

In the event, treatment of **18** with SmI_2 and LiBr in the presence of *t*-BuOH at −78 °C provided tetracyclic diol **16** in 54% yield *as a single diastereomer*. Indeed, C11-ketyl radical cyclization occurs with excellent chemoselectivity and stereocontrol to form putative Sm^{III} enolate **48** following a second single-electron reduction. Enolate **48** then undergoes aldol cyclization with the proximal C6-aldehyde to forge the second all-carbon quaternary stereocenter and the complete carbon skeleton of maoecrystal Z. Importantly, all four new stereocenters possess the correct configuration for advancement to the natural product, as determined by thorough NMR analysis.[30] In addition to the steric congestion about C6 imposed by two quaternary centers, a second explanation for the observed chemoselectivity lies in the proposed reversibility of Sm-ketyl formation from aldehydes.[29d] Though both ketyls may form, a thermodynamically favorable 6-*endo*-cyclization by the C11-ketyl (relative to a reversible 4-*exo*-cyclization of the C6-ketyl), followed by a second, irreversible one-electron reduction to give the Sm-enolate could result in funneling of **18** to diol **16**. The major side product of this transformation appeared to be the tricycle resulting from ketyl-olefin cyclization followed by enolate protonation.

With access to the core, completion of the synthesis of **1** necessitated acetylation of the C11 carbinol and enal installation (see Scheme 10). Unfortunately, treatment of diol **16** with acetic anhydride and DMAP effected acetylation of only the C6 carbinol. Use of excess reagents or higher temperatures provided low yields of diacetate **50**, delivering and significant quantities of translactonization product **51**. Sequences of C6 monoprotection, C11 acetylation, and C6 deprotection did not prove fruitful, often resulting in complex mixtures of products. Unable to realize a selective C11 monoacetylation, we opted to advance diacetate **50** toward the natural product. Diacetylation was accomplished smoothly using acetic anhydride and TMSOTf. Ozonolysis of **50**, followed by Eschenmoser methylenation of the resulting aldehyde provided acetyl-maoecrystal Z (**52**). Removal of the C6 acetate was best accomplished using sodium hydroxide in aqueous methanol, providing (−)-maoecrystal Z in 38% yield, and in 12 synthetic steps from (−)-γ-cyclogeraniol (**22**).[34]

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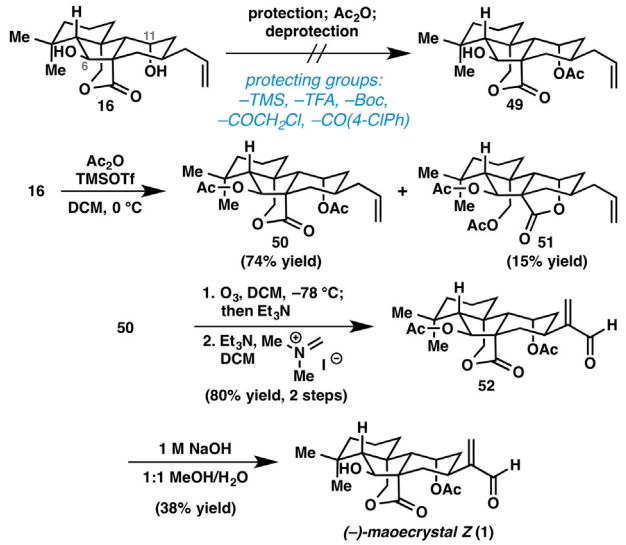
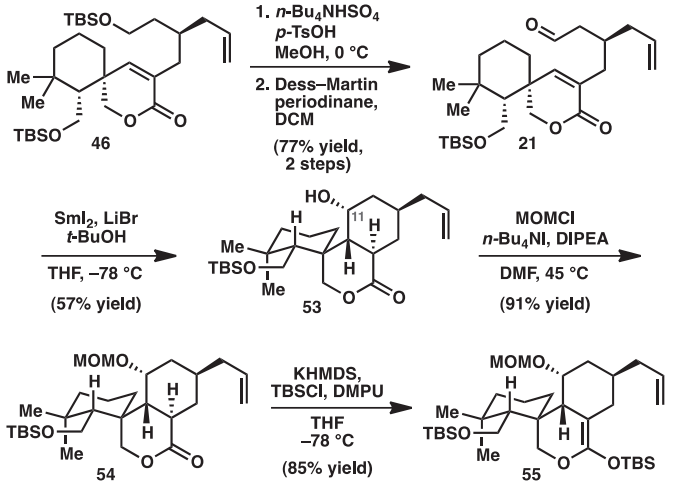


Scheme 10. Completion of the synthesis of (−)-maoecrystal Z (**1**).

2.5. Synthesis of (−)-trichorabdal A

Having achieved our first synthetic objective, we aimed to establish the utility of spirolactone **15** for the preparation of additional *Isodon* diterpenoids. In particular, our focus shifted toward trichorabdal A (**2**). Structurally elucidated by Node and co-workers in 1982, **2** bears the bridging cyclopentanone characteristic of *ent*-kauranoids and was found to inhibit tumor growth in vivo in mice and exhibit in vitro cytotoxicity toward HeLa cells.[2b] As described in the retrosynthetic analysis, the bicyclo[3.2.1]octane of **2** was envisioned to arise via a Pd^{II}-mediated oxidative cyclization of a tricyclic silyl ketene acetal precursor. In order to test this hypothesis, we advanced bis-silyl ether **46** toward a suitable cyclization substrate (Scheme 11).

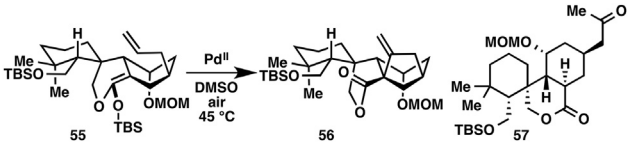


Scheme 11. Synthesis of silyl ketene acetal **55**.

Selective cleavage of the more accessible TBS ether was accomplished with *p*-TsOH and n-Bu_4NHSO_4 in methanol at 0 °C;[35] immediate treatment of the crude alcohol with Dess–Martin periodinane provided aldehyde **21** in 77% yield. Reductive cyclization of **21** was effected by exposure to SmI_2 with LiBr and *t*-BuOH as additives, providing a single diastereomer of tricyclic alcohol **53** in 57% yield. Protection of **53** as the methoxymethyl ether (**54**) proceeded smoothly, and subsequent deprotonation with potassium hexamethyldisilazide (KHMDS) followed by addition of TBSCl at low temperature delivered silyl ketene acetal **55**. Use of the MOM ether protecting group was found to be critical for silyl ketene acetal formation: use of silicon-based protecting groups resulted in poor yields for the ketene acetal forming step, and attempts to disilylate alcohol **53** or trap its Sm-enolate precursor were likewise unfruitful.

With silyl ketene acetal **55** in hand, we sought to explore the proposed oxidative cyclization to form the bicyclo[3.2.1]octane present in trichorabdal A (**2**) and longikaurin E (**4**). Upon exposure of **55** to 10 mol % $Pd(OAc)_2$ in DMSO at 45 °C under an air atmosphere, we were delighted to isolate tetracycle **56**, albeit in only 7% yield (Table 2, entry 1). Fortunately, the use of stoichiometric $Pd(OAc)_2$ substantially improved both conversion and the yield of **56** (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 **56**. 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 **57**, via Wacker oxidation. No desaturated products from Saegusa–Ito-type pathways were observed.[36]

Table 2
Reaction optimization of the preparation of **56**



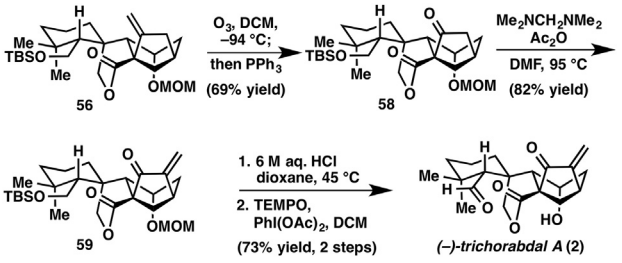
Entry	Pd source (equiv)	Additive (equiv)	Yield **56**[a] (%)
1	$Pd(OAc)_2$ (0.1)	—	7
2	$Pd(OAc)_2$ (1.0)	—	35
3[b]	$Pd(OAc)_2$ (1.0)	—	28[c]
4	$Pd(TFA)_2$ (1.0)	—	19
5	$PdCl_2$ (1.0)	—	0
6	$PdCl_2$ (1.0)	$AgBF_4$ (2.0)	5[d]
7[e]	$Pd(OAc)_2$ (1.0)	H_2O (5.0)	38
8	$Pd(OAc)_2$ (1.0)	K_2CO_3 (5.0)	0
9	$Pd(OAc)_2$ (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] Yield: 13% of methyl ketone **57** was also isolated.
[e] Run under a N_2 atmosphere.

High variability in both the yield and purity of **56** 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 **56** 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.

Having now established the carbon framework present in many 6,7-seco-*ent*-kauranoids, the remaining steps for transformation to **2** included installation of the *exo*-enone and C6-aldehyde.

Ozonolysis of **56** and subsequent α-methylenation using bis(dimethylamino)methane and acetic anhydride[37] delivered β-ketolactone **59** (see Scheme 12). Notably, the analogous two-step procedure using Eschenmoser's salt[30] provided significantly diminished yields of **59**. 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 $PhI(OAc)_2$,[38] delivering (−)-trichorabdal A (**2**).[39]

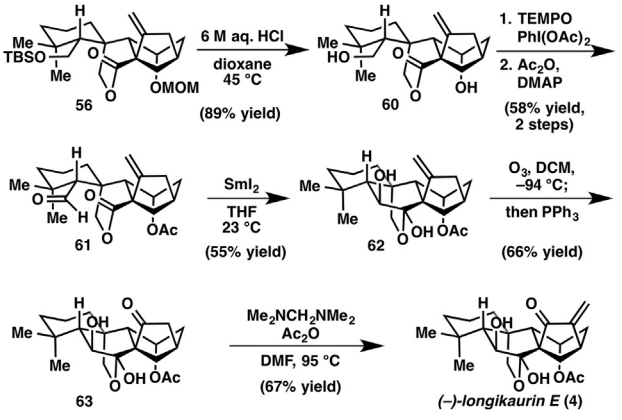


Scheme 12. Completion of the synthesis of (−)-trichorabdal A (**2**).

2.6. Synthesis of (−)-longikaurin E

Following completion of the synthesis of **2** via the proposed oxidative cyclization reaction, attention turned to the elaboration of tetracycle **56** to (−)-longikaurin E (**4**). First isolated in 1981 from *Rabdosia longituba*,[2d] **4** displays antibacterial activity and cytotoxicity against multiple human tumor cell lines (HL-60 leukemia, SMMC-7221 liver, A549 lung, MCF-7 breast, and SW480 colon).[6] Unlike **1** and **2**, which have undergone biosynthetic oxidative cleavage to afford their 6,7-seco-*ent*-kauranoid skeletons, the *ent*-kauranoid **4** possesses a C6–C7 bond as part of a central oxabicyclo[2.2.2]octane. Whereas conversion of key *exo*-olefin **56** to **2** took place by a sequence of relatively straightforward functional group manipulations, preparation of **4** from this same intermediate would require an uncommon reductive cyclization of an aldehyde-lactone precursor. As SmI_2 is known to facilitate the pinacol-type coupling of a variety of bis-carbonyl substrates, including ketoesters, we wished to investigate its application to the synthesis of **4**.[40] To this end, we sought to access aldehyde-lactone **61**.

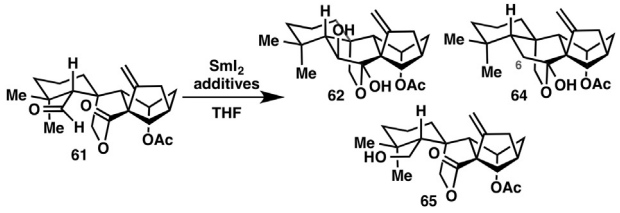
Treatment of *exo*-olefin **56** with 6 M aqueous HCl in dioxane at 45 °C resulted in global deprotection to afford diol **60**; subsequent oxidation with catalytic TEMPO and $PhI(OAc)_2$ likewise proceeded smoothly (see Scheme 13). Acetylation using acetic anhydride and DMAP furnished aldehyde-lactone **61**, and a screen of reaction parameters for the proposed reductive cyclization was conducted.



Scheme 13. Synthesis of (−)-longikaurin E (**4**).

Unexpectedly, exposure of **61** to SmI_2 with LiBr and *t*-BuOH at −78 °C (Table 3, entry 1) led to recovery of starting material. Whereas addition of HMPA was unfruitful (entry 2), increasing the reaction temperature to 0 °C resulted in reduction to primary alcohol **65** when employing LiCl or LiBr additives (entries 3 and 4). Gratifyingly, exclusive use of SmI_2 at ambient temperature provided the desired hydroxy-lactol (**62**) in 55% yield, along with 27% yield of recovered **61** (entry 5). Interestingly, attempts to push the reaction to full conversion did not improve the yield of **62**. Instead, C6-deoxylactol **64** was isolated, resulting from Sm-mediated α-deoxygenation of the ketone tautomer of **62** (entry 7).[41] With the oxabicyclo[2.2.2]octane in hand, ozonolysis of **62** and α-methylenation under previously described conditions yielded (−)-longikaurin E (Scheme 13).[42]

Table 3
Reaction optimization for preparation of **62**



Entry	SmI_2 (equiv)	Additives (equiv)	Temp (°C)	Yield[a] (brsm)
1	5.0	LiBr (50) *t*-BuOH (1.0)	−78	No rxn
2	5.0	HMPA (50)	−78	0%[b]
3	5.0	LiCl (50) *t*-BuOH (1.0)	0	54% **65**
4	5.0	LiBr (50) *t*-BuOH (1.0)	0	38% **65**
5	2.0	—	23	55% **62** (75%)
6	2.4	—	23	55% **62** (62%)
7[c]	5.0	*t*-BuOH (1.0)	23	72% **64**

[a] Isolated yield.
[b] Complex mixture.
[c] Run to full consumption of **61**.

3. Conclusion

In summary, a unified synthetic strategy has enabled the first total syntheses of three *ent*-kauranoid natural products, (−)-maoecrystal Z, (−)-trichorabdal A, and (−)-longikaurin E, from (−)-γ-cyclogeraniol in 12, 15, and 17 synthetic steps, respectively. Prior to the divergence point of this route, key unsaturated lactone **46** was prepared in five steps using a highly diastereoselective Ti^{III}-mediated reductive epoxide coupling. Other pivotal transformations employed were a Sm^{II}-mediated dialdehyde cascade cyclization, a Pd^{II}-mediated oxidative cyclization, and a Sm^{II}-mediated pinacol-type coupling of an aldehyde-lactone. Our synthetic efforts conspicuously demonstrate the utility of single-electron chemistry for the diastereoselective preparation of vicinal stereogenic centers within complex polycyclic systems and have also established a non-biomimetic synthetic relationship among three architecturally distinct *ent*-kaurane diterpenoids.

4. Experimental section

4.1. General

Unless otherwise stated, reactions were performed at ambient temperature under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (DCM), acetonitrile (MeCN), and dimethylformamide (DMF) were dried by passing through activated alumina columns. Methanol (MeOH) was

distilled over magnesium methoxide, 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 4 Å MS for at least 48 h 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 F_{254} pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or $KMnO_4$ staining. Flash column chromatography was performed as described by Still and coworkers[43] 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 5 μm column (9.4×250 mm). Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected.

4.2. Experimental procedures and data of synthetic intermediates

4.2.1. Epoxide ***23***. To a solution of (*R*)-(−)-γ-cyclogeraniol (**22**)[23] (2.42 g, 15.7 mmol, 1.0 equiv) in DCM (150 mL) was added imidazole (2.67 g, 39.2 mmol, 2.5 equiv) then TBSCl (3.07 g, 20.4 mmol, 1.3 equiv). The resulting suspension was vigorously stirred for 1 h then diluted with H_2O (75 mL). The layers were separated and the aqueous layer was extracted with DCM (3×25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (0–10% EtOAc/Hex) to provide the TBS ether (4.17 g, 99% yield). $[\alpha]_D^{25}$ −19.6 (*c* 0.74, $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$): δ 4.79 (m, 1H), 4.64 (m, 1H), 3.80 (dd, *J*=10.2, 4.8 Hz, 1H), 3.71 (dd, *J*=10.1, 7.8 Hz, 1H), 2.17–2.04 (m, 2H), 1.95 (dd, *J*=7.7, 4.8 Hz, 1H), 1.57–1.43 (m, 1H), 1.29–1.25 (m, 1H), 0.96 (s, 3H), 0.89 (s, 9H), 0.88 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.4, 109.4, 62.0, 55.9, 37.7, 34.2, 33.6, 29.0, 26.0, 25.9, 23.5, 18.3, −5.4; IR (NaCl/thin film): 2953, 2929, 2905, 2856, 1648, 1472, 1463, 1386, 1362, 1256, 1104, 888, 837, 774 cm^{-1}; HRMS ($APCI^+$) calcd for $C_{16}H_{33}OSi$ $[M+H]^+$ 269.2295, found 269.2293.

The TBS ether (4.03 g, 15.0 mmol, 1.0 equiv) was dissolved in DCM (150 mL) and to this solution at 0 °C was added solid $NaHCO_3$ (6.30 g, 75.0 mmol, 5.0 equiv) then 85% *m*-CPBA (9.14 g, 45.0 mmol, 3.0 equiv). The ice bath was removed and the resulting suspension was allowed to warm to rt and stir for an additional 1 h and then diluted with satd $Na_2S_2O_3$ (75 mL) and satd $NaHCO_3$ (75 mL) and stirred for 20 min. The layers were separated and the organic layer was washed with one additional portion of satd $Na_2S_2O_3$ (75 mL) and satd $NaHCO_3$ (75 mL). The combined aqueous extracts were then extracted with DCM (3×50 mL) and the combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated in vacuo. The resulting crude residue was chromatographed on SiO_2 (40–100% $CHCl_3$/Hex) to provide epoxide **23** (3.89 g, 91% combined yield).

*4.2.1.1. Data for anti-****23****.* $[\alpha]_D^{25}$ −26.4 (*c* 1.57, $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$): δ 3.72 (dd, *J*=10.3, 5.0 Hz, 1H), 3.67 (dd, *J*=10.4, 7.3 Hz, 1H), 2.68 (d, *J*=4.9 Hz, 1H), 2.51 (d, *J*=4.9 Hz, 1H), 1.83–1.72 (m, 2H), 1.60–1.56 (m, 1H), 1.45 (m, *J*=3.9 Hz, 1H), 1.29–1.20 (m, 2H), 1.15–1.13 (m, 1H), 1.10 (s, 3H), 0.92 (s, 3H), 0.87 (s, 9H), 0.03 (d, *J*=0.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 61.3, 58.9, 52.2, 36.3, 34.1, 30.9, 28.6, 27.6, 25.9, 20.0, 18.1, −5.6; IR (NaCl/thin film): 2952, 2930, 2857, 1472, 1463, 1389, 1366, 1256, 1095, 837, 775 cm^{-1}; HRMS ($APCI+$) calcd for $C_{16}H_{33}O_2Si$ $[M+H]^+$ 285.2244, found 285.2239.

*4.2.1.2. Data for syn-****23****.* $[\alpha]_D^{25}$ +11.7 (*c* 1.57, $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$): δ 3.69 (dd, *J*=10.5, 3.4 Hz, 1H), 3.51 (dd, *J*=10.5, 5.8 Hz, 1H), 2.80 (d, *J*=5.1 Hz, 1H), 2.48 (d, *J*=5.1 Hz, 1H), 1.75–1.67 (m, 1H), 1.60–1.52 (m, 3H), 1.48–1.41 (m, 1H), 1.29–1.22 (m, 2H), 1.00 (s, 3H), 0.91 (s, 3H), 0.86 (s, 9H), 0.03 (d, *J*=2.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 59.8, 58.3, 54.1, 52.1, 38.4, 34.8, 33.1, 29.5, 25.9, 24.9, 20.6, 18.1, −5.40, −5.42; IR (NaCl/thin film): 2929, 2856, 1469, 1426, 1221, 1050, 836, 728 cm^{-1}; HRMS ($APCI^+$) calcd for $C_{16}H_{33}O_2Si$ $[M+H]^+$ 285.2244, found 285.2242.

4.2.2. Spirolactone ***15*** *and allylic alcohol* ***24***. To a stirred solution of epoxide **23** (~3:1 mixture of diastereomers, 2.94 g, 10.3 mmol, 1.0 equiv) in THF (50 mL) were then added 2,4,6-collidine hydrochloride (4.89 g, 31.0 mmol, 3.0 equiv), 2,2,2-trifluoroethyl acrylate (13.1 mL, 103 mmol, 10.0 equiv), and activated zinc dust (1.01 g, 15.5 mmol, 1.5 equiv). Titanocene dichloride (513 mg, 2.06 mmol, 0.2 equiv) was then added every 3 h for 24 h (4.10 g, 16.5 mmol, 1.6 equiv overall) and then diluted with satd NH_4Cl (50 mL) and Et_2O (30 mL). The biphasic mixture was then filtered through a small pad of Celite and the layers were separated. The aqueous layer was extracted with Et_2O (3×30 mL) and the combined organic extracts were dried over Na_2SO_4, filtered through a small pad of silica gel, and concentrated in vacuo. The resulting crude residue was chromatographed on SiO_2 (5–20% EtOAc/Hex) to provide spirolactone **15** (2.67 g, 76% yield).

4.2.2.1. Data for lactone ***15***. $[\alpha]_D^{25}$ +35.7 (*c* 0.975, $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$): δ 4.43 (dd, *J*=11.7, 1.5 Hz, 1H), 4.38 (d, *J*=12.0 Hz, 1H), 3.87–3.81 (m, 2H), 2.57 (ddd, *J*=16.4, 9.2, 7.0 Hz, 1H), 2.47 (dt, *J*=16.6, 6.2 Hz, 1H), 2.34 (dt, *J*=13.7, 6.8 Hz, 1H), 1.96 (dtd, *J*=13.5, 3.6, 1.5 Hz, 1H), 1.59–1.48 (m, 3H), 1.45–1.37 (m, 2H), 1.29–1.23 (m, 2H), 1.10–1.03 (m, 1H), 1.01 (s, 3H), 0.89 (s, 9H), 0.87 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 71.2, 60.4, 56.5, 42.1, 36.7, 36.3, 33.9, 33.7, 33.0, 28.6, 25.9, 23.8, 18.5, 18.0, −5.55, −5.56; IR (NaCl/thin film): 2952, 2928, 2856, 1753, 1462, 1253, 1091, 1050, 838, 776 cm^{-1}; HRMS ($APCI^+$) calcd for $C_{19}H_{37}O_3Si$ $[M+H]^+$ 341.2506, found 341.2494.

4.2.2.2. Data for alcohol ***24***. ^1H NMR (500 MHz; $CDCl_3$): δ 5.71 (t, *J*=3.3 Hz, 1H), 4.16 (br dd, *J*=12.3, 6.4 Hz, 1H), 3.93 (br dd, *J*=12.3, 6.1 Hz, 1H), 3.90 (dd, *J*=10.0, 3.2 Hz, 1H), 3.57 (dd, *J*=10.0, 8.1 Hz, 1H), 3.36 (t, *J*=6.5 Hz, 1H), 2.08–1.95 (m, 3H), 1.43 (dt, *J*=13.4, 6.8 Hz, 1H), 1.28 (td, *J*=13.1, 6.7 Hz, 1H), 0.95 (s, 3H), 0.91 (s, 9H), 0.88 (s, 3H), 0.09 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.7, 125.1, 67.7, 64.3, 48.7, 33.8, 31.5, 28.3, 25.9, 25.0, 22.8, 18.2, −5.47, −5.50; IR (NaCl/thin film): 3351, 2954, 2928, 2857, 1472, 1388, 1361, 1256, 1135, 1105, 1056, 1034, 1006, 996, 937, 893, 882, 837, 774 cm^{-1}; HRMS (MM: ESI-APCI) calcd for $C_{16}H_{33}O_2Si$ $[M+H]^+$ 285.2244, found 285.2241.

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*4.2.3. Deprotected spirolactone **25**.* To a solution of spirolactone **15** (103 mg, 0.30 mmol, 1.0 equiv) in MeCN (4 mL) was added 20–25 wt % H_2SiF_6 (0.4 mL, 0.68 mmol, 2.2 equiv). The solution was stirred until LC/MS (or TLC) indicated full consumption of starting material (30 min). The reaction mixture was diluted with satd $NaHCO_3$ (10 mL) and EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (50–90% EtOAc/Hex) to provide lactone **25** (53 mg, 77% yield). Crystals suitable for X-ray analysis were obtained by layering a nearly saturated solution of **25** (53 mg) in DCM (ca. 0.4 mL) with isooctane. ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.37 (dd, J=11.7, 1.2 Hz, 1H), 4.27 (dd, J=11.7, 1.5 Hz, 1H), 3.89 (dd, J=11.5, 3.8 Hz, 1H), 3.85 (dd, J=11.5, 4.7 Hz, 1H), 2.58 (ddd, J=16.8, 7.9, 7.1 Hz, 1H), 2.50 (ddd, J=16.8, 7.4, 6.3 Hz, 1H), 2.36 (dt, J=14.2, 7.1 Hz, 1H), 2.01–1.93 (m, 1H), 1.57–1.48 (m, 2H), 1.48–1.40 (m, 2H), 1.35–1.22 (m, 2H), 1.14–1.06 (m, 1H), 1.04 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 173.2, 71.2, 60.4, 57.2, 41.9, 36.6, 36.3, 33.9, 33.6, 33.1, 28.4, 23.2, 18.4; IR (NaCl/thin film): 3393, 2976, 2920, 2868, 1722, 1447, 1384, 1332, 1282, 1250, 1158, 1135, 1077, 1053, 1034, 984, 940, 833, 731 cm^{-1}; HRMS (MM: ESI-APCI) calcd for $C_{13}H_{23}O_3$ $[M+H]^+$ 227.1642, found 227.1640; mp=110–111 °C.

*4.2.4. Pseudoephedrine amide **28**.* *NOTE: The enantiomeric series can similarly be prepared using (*S*,*S*)-pseudoephedrine in the following procedures (compound **27**→compound **14**) for the preparation of *ent*-**14**.

To a solution of 4-pentenoic acid (**27**) (4.0 mL, 39.2 mmol, 1.0 equiv) in THF (200 mL) at 0 °C was added Et_3N (16.3 mL, 117.6 mmol, 3.0 equiv) then pivaloyl chloride (5.8 mL, 5.7 mmol, 1.2 equiv) dropwise causing a white suspension to develop, which was then vigorously stirred for 1 h at rt. In a separate flame-dried flask, (*R*,*R*)-pseudoephedrine (8.42 g, 51.0 mmol, 1.3 equiv) was dissolved in THF (200 mL) and Et_3N (16.3 mL, 117.6 mmol, 3.0 equiv). The resulting clear solution was transferred via cannula to the solution of the mixed anhydride and stirred for 6 h at 23 °C and then diluted with satd $NaHCO_3$ (300 mL) and EtOAc (300 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3×200 mL) and the combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated in vacuo. The resulting crude residue was chromatographed on SiO_2 (30–60% EtOAc/Hex) to provide amide **28** (7.95 g, 82% yield). $[\alpha]_D^{25}$ −105.6 (*c* 1.15, $CHCl_3$); ^{1}H NMR (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$): δ 7.41–7.21 (m, 5H), 5.92–5.74 (m, 1H), 5.10–4.92 (m, 2H), 4.61–4.43 (m, 2H), 4.32* (br, 1H), 3.99* (m, 1H), 3.20* (s, 1H), 2.90* (s, 3H), 2.81 (s, 3H), 2.60–2.49* (m, 1H), 2.49–2.26 (m, 4H), 1.07 (d, J=6.8 Hz, 3H), 0.97* (d, J=6.8 Hz, 3H); ^{13}C NMR (2:1 rotamer ratio, 126 MHz, $CDCl_3$): δ 174.4, 173.3, 142.3, 141.4, 137.8, 137.3, 128.5, 128.2, 128.2, 127.5, 126.8, 126.4, 115.1, 114.9, 76.3, 75.3, 58.2, 33.4, 32.8, 32.4, 29.6, 29.3, 28.9, 26.8, 15.3, 14.4; IR (NaCl/thin film): 3381, 3063, 3028, 2977, 2924, 1620, 1480, 1452, 1405, 1315, 1257, 1200, 1120, 1050, 1027, 912, 838, 758, 701 cm^{-1}; HRMS (MM: ESI-APCI) calcd for $C_{15}H_{22}NO_2$ $[M+H]^+$ 248.1645, found 248.1644.

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

*4.2.5. Alkylated amide **30**.* A flame-dried flask in a glove box was charged with lithium chloride (4.95 g, 116.7 mmol, 6.0 equiv) and then removed from the glove box. To this flask were then added diisopropylamine (6.3 mL, 44.7 mmol, 2.3 equiv) and THF (40 mL). The resulting suspension was cooled to −78 °C, and a solution of *n*-BuLi in hexanes (2.6 M, 15.7 mL, 40.8 mmol, 2.1 equiv) was added via cannula. The suspension was warmed briefly to 0 °C and then recooled to −78 °C. An ice-cooled solution of amide **28** (4.81 g, 19.5 mmol, 1.0 equiv) in THF (40 mL) was then added to the reaction flask via cannula. The reaction mixture was stirred at −78 °C for 1 h, at 0 °C for 15 min, and at 25 °C for 5 min, and finally cooled to 0 °C, whereupon *tert*-butyl(2-iodoethoxy)dimethylsilane (**29**) (8.35 g, 29.2 mmol, 1.5 equiv) in THF (20 mL) was added via cannula. The mixture was stirred at 0 °C for 15 min and then diluted with satd NH_4Cl (100 mL) and EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (15–45% EtOAc/Hex) to provide alkylated amide **30** (7.26 g, 92% yield). $[\alpha]_D^{25}$ −53.3 (*c* 1.24, $CHCl_3$); ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$): δ 7.39–7.21 (m, 5H), 5.80–5.67 (m, 1H), 5.11–4.93 (m, 2H), 4.59 (t, J=6.8 Hz, 1H), 4.55–4.30 (m, 2H), 4.22–4.14* (m, 1H), 3.79–3.65 (m, 1H), 3.61–3.52 (m, 1H), 3.35 (ddd, J=10.5, 8.6, 4.2 Hz, 1H), 3.27* (br d, J=3.6 Hz, 1H), 3.22–3.11* (m, 1H), 3.04–2.92 (m, 1H), 2.89* (s, 3H), 2.88 (s, 3H), 2.44–2.31 (m, 1H), 2.24–2.09 (m, 2H), 1.91* (br, 1H), 1.80–1.71 (m, 1H), 1.70–1.52 (m, 2H), 1.10 (d, J=6.8 Hz, 3H), 0.92* (d, J=6.8 Hz, 1H), 0.88* (s, J=2.8 Hz, 9H), 0.85 (s, 9H), 0.07* (s, 3H), 0.06* (s, 3H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (3:1 rotamer ratio, 126 MHz, $CDCl_3$): δ 177.5, 175.9, 142.3, 141.4, 135.9, 128.6, 128.2, 128.1, 127.5, 127.0, 126.3, 116.6, 76.1, 75.3, 61.8, 60.2, 58.9 (br), 58.1, 38.2, 38.0, 37.4, 36.8, 35.6, 35.5, 33.1 (br), 29.6, 26.8, 26.0, 25.8, 18.5, 18.1, 15.8, 14.4, −5.20, −5.24, −5.42, −5.44; IR (NaCl/thin film): 3391, 3064, 3029, 2955, 2928, 2856, 1619, 1472, 1452, 1409, 1305, 1256, 1100, 1083, 1052, 1005, 913, 835, 810, 775, 701 cm^{-1}; HRMS (MM: ESI-APCI) calcd for $C_{23}H_{40}NO_3Si$ $[M+H]^+$ 406.2772, found 406.2765.

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

*4.2.6. Iodide **14**.* A solution of *n*-BuLi in hexanes (2.6 M, 18.9 mL, 49.0 mmol, 3.9 equiv) was added to a solution of diisopropylamine (7.4 mL, 52.8 mmol, 4.2 equiv) in THF (50 mL) at −78 °C. The resulting solution was stirred at −78 °C for 10 min, then warmed to 0 °C, and held at that temperature for 10 min. Borane–ammonia complex (90% technical grade, 1.73 g, 50.3 mmol, 4.0 equiv) was carefully added in one portion, and the suspension was stirred at 0 °C for 15 min and then was warmed to 23 °C. After 15 min, the suspension was recooled to 0 °C. A solution of amide **30** (5.10 g, 12.6 mmol, 1.0 equiv) in THF (40 mL, followed by a 10 mL rinse) was added via cannula. The reaction mixture was then warmed to 23 °C, held at that temperature for 4 h, and then cooled to 0 °C where excess hydride was quenched by the careful addition of satd NH_4Cl (100 mL). The mixture was stirred for 30 min at 0 °C and then extracted with Et_2O (3×50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through a small plug of silica gel, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (5–35% EtOAc/Hex) to provide the primary alcohol (2.98 g, 97% yield). $[\alpha]_D^{25}$ −8.4 (*c* 0.93, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.81–5.73 (m, 1H), 5.05–4.99 (m, 2H), 3.78–3.74 (m, 1H), 3.64 (ddd, J=10.5, 8.1, 3.8 Hz, 1H), 3.60 (m, 1H), 3.48–3.44 (m, 1H), 3.18 (d, J=5.2 Hz, 1H), 2.11 (dtd, J=14.0, 7.0, 1.1 Hz, 1H), 2.05–1.99 (m, 1H), 1.76–1.71 (m, 1H), 1.70–1.64 (m, 1H), 1.52 (dtd, J=14.5, 8.0, 4.2 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 136.9, 116.2, 65.9, 61.8, 39.4, 36.4, 35.0, 25.8, 18.2, −5.48, −5.50; IR (NaCl/thin film): 3351, 2954, 2928, 2857, 1640, 1472, 1256, 1093, 835, 775 cm^{-1}; HRMS ($APCI^+$) calcd for $C_{13}H_{29}O_2Si$ $[M+H]^+$ 245.1931, found 245.1928.

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

The primary alcohol (2.18 g, 8.9 mmol, 1.0 equiv) was dissolved in DCM (15 mL). In a separate flask, imidazole (1.82 g, 26.8 mmol, 3.0 equiv) and I_2 (2.22 g, 8.7 mmol, 0.98 equiv) were added sequentially to a solution of PPh_3 (2.22 g, 8.5 mmol, 0.95 equiv) in

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DCM (80 mL). The solution of primary alcohol was added to the resulting suspension via cannula. The reaction mixture was stirred for 2 h and then diluted with satd $Na_2S_2O_3$ (30 mL) and satd $NaHCO_3$ (30 mL) and then stirred for 15 min. The layers were separated and the aqueous layer was extracted with diethyl ether (3×30 mL). The combined organic extracts were dried over $MgSO_4$, filtered through a small plug of silica gel, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (0–10% EtOAc/Hex) to provide iodide **14** (2.88 g, 91% yield). $[\alpha]_D^{25}$ +4.1 (*c* 1.215, $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$): δ 5.71 (dddd, *J*=17.0, 10.2, 7.6, 6.8 Hz, 1H), 5.13 (ddt, *J*=17.0, 2.0, 1.4 Hz, 1H), 5.10–5.04 (m, 1H), 3.68–3.62 (m, 2H), 3.32 (dd, *J*=9.8, 4.0 Hz, 1H), 3.28 (dd, *J*=9.8, 4.6 Hz, 1H), 2.19–2.11 (m, 1H), 2.11–2.02 (m, 1H), 1.62–1.44 (m, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 135.6, 117.2, 60.4, 38.6, 36.9, 35.2, 25.9, 18.3, 15.9, −5.33, −5.35; IR (NaCl/thin film): 3077, 2954, 2928, 2856, 1641, 1471, 1462, 1439, 1388, 1360, 1256, 1100, 1043, 1005, 940, 916, 835, 775, 665 cm^{-1}; HRMS ($APCI^+$) calcd for $C_{13}H_{27}OSi$ $[M-I]^+$ 227.1826, found 227.1824.

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

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

4.2.7. Alkylated lactone ***31***. To a solution of lactone **15** (507 mg, 1.49 mmol, 1.0 equiv) and iodide **14** (633 mg, 1.79 mmol, 1.1 equiv) in (4:1) THF/HMPA (8 mL) at 0 °C was added a solution of LHMDS (274 mg, 1.64 mmol, 1.1 equiv) in THF (2.0 mL followed by a 1.0 mL rinse). The resulting solution was stirred for and additional 3 h at 0 °C and then diluted with satd $NaHCO_3$ (50 mL) and Et_2O (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×25 mL) and the combined organic extracts were washed with H_2O (3×40 mL) and brine (1×50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (5–20% EtOAc/Hex) to provide alkylated lactone **31** (532 mg, 63% isolated yield) as a mixture of diastereomers and recovered **15** (140 mg).

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

4.2.7.2. Data for more polar diastereomer. $[\alpha]_D^{25}$ −22.0 (*c* 1.69, $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$): δ 5.78–5.66 (m, 1H), 5.06–4.95 (m, 2H), 4.48 (d, *J*=11.8 Hz, 1H), 4.20 (d, *J*=11.8 Hz, 1H), 3.83–3.72 (m, 2H), 3.72–3.58 (m, 2H), 2.61–2.50 (m, 1H), 2.19–2.11 (m, 1H), 2.06 (t, *J*=13.2 Hz, 1H), 2.01–1.82 (m, 3H), 1.72–1.18 (m, 10H), 1.18–1.06 (m, 1H), 1.01 (s, 3H), 0.96–0.78 (m, 21H), 0.06 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.3, 136.6, 116.5, 72.9, 60.7, 60.6, 55.5, 41.7, 39.8, 38.6, 37.0, 36.0, 35.8, 35.6, 34.7, 33.8, 33.1, 31.1, 26.0, 25.9, 23.8, 18.4, 18.3, 18.0, −5.27, −5.31, −5.50, −5.55; IR (NaCl/thin film): 3076, 2953, 2928, 2856, 1749, 1640, 1471, 1463, 1389, 1361, 1256, 1169, 1092, 1005, 911, 837, 775 cm^{-1}; HRMS (MM: ESI–APCI) calcd for $C_{32}H_{63}O_4Si_2$ $[M+H]^+$ 567.4259, found 567.4252.

4.2.8. Aldehyde ***13***. To a solution of KHMDS (105 mg, 0.53 mmol, 1.2 equiv) in THF (6 mL) at 0 °C was added **31** (1.5:1 mixture of diastereomers, 246 mg, 0.43 mmol, 1.0 equiv) in THF (3 mL followed by a 1 mL rinse) dropwise via cannula. The resulting clear solution was allowed to stir at 0 °C for 30 min then at rt for 15 min. The solution was recooled to −78 °C, at which time, a solution of PhSeBr (114 mg, 0.48 mmol, 1.1 equiv) in THF (3 mL followed by a 1 mL wash) precooled at −78 °C was slowly added dropwise via cannula. The resulting pale yellow solution was allowed to stir for 15 min at −78 °C and then diluted with satd $NaHCO_3$ (15 mL). The mixture was diluted with Et_2O (30 mL) and H_2O (30 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3×15 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude residue was diluted with DCM (6 mL) and cooled to 0 °C. To this was added 30 wt % H_2O_2 (0.3 mL, 2.9 mmol, 6.8 equiv) and stirred for 30 min. The reaction mixture was diluted with H_2O (15 mL) and the layers were separated. The aqueous layer was extracted with DCM (3×10 mL) and the combined organic extracts were washed with satd $NaHCO_3$ (1×10 mL), dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (0–15% EtOAc/Hex) to afford the unsaturated lactone (206 mg, 84% yield). $[\alpha]_D^{25}$ −29.2 (*c* 0.51, $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$): δ 6.36 (s, 1H), 5.81–5.69 (m, 1H), 5.03 (br s, 1H), 5.02–4.98 (m, 1H), 4.47 (dd, *J*=11.2, 2.0 Hz, 1H), 4.36 (dd, *J*=11.2, 1.2 Hz, 1H), 3.79–3.72 (m, 2H), 3.65 (t, *J*=6.6 Hz, 2H), 2.19 (dd, *J*=7.2, 0.9 Hz, 2H), 2.10–1.98 (m, 2H), 1.93–1.83 (m, 2H), 1.67–1.38 (m, 6H), 1.26 (td, *J*=13.0, 3.9 Hz, 1H), 1.19–1.11 (m, 1H), 1.02 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.04 (s, 6H), 0.03 (d, *J*=1.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.9, 154.2, 136.5, 127.2, 116.5, 69.8, 61.4, 61.1, 55.6, 42.1, 39.7, 37.6, 36.2, 35.1, 33.2, 33.1, 33.0, 32.9, 26.0, 25.9, 23.3, 18.4, 18.3, 18.1, −5.28, −5.31, −5.50, −5.55; IR (NaCl/thin film): 2953, 2928, 2856, 1723, 1472, 1463, 1389, 1361, 1256, 1164, 1150, 1101, 1030, 1005, 938, 837, 776, 665 cm^{-1}; HRMS (MM: ESI-APCI) calcd for $C_{32}H_{61}O_4Si_2$ $[M+H]^+$ 565.4103, found 565.4083.

The unsaturated lactone (108 mg, 0.19 mmol, 1.0 equiv) was dissolved in DCM (4 mL) and cooled to −78 °C, at which time, ozone was gently bubbled through the solution (O_2 flow rate=1/8 L/min, 0 setting on ozonator) until LC/MS (or TLC) indicated full consumption of starting material (ca. 20 min). The solution was purged with N_2 for 3 min then Et_3N (1.3 mL, 9.33 mmol, 50 equiv) was slowly added dropwise. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stirred until LC/MS indicated complete conversion of the ozonide to the aldehyde (ca. 30 min), filtered through a small plug of silica gel, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (5–25% EtOAc/Hex) to afford aldehyde **13** (90 mg, 83% yield). $[\alpha]_D^{25}$ −29.8 (*c* 0.37, $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$): δ 9.73 (t, *J*=1.8 Hz, 1H), 6.40 (s, 1H), 4.48 (dd, *J*=11.2, 1.5 Hz, 1H), 4.40 (d, *J*=11.2 Hz, 1H), 3.80–3.72 (m, 2H), 3.67 (t, *J*=6.2 Hz, 2H), 2.49–2.33 (m, 4H), 2.15 (dd, *J*=13.8, 7.5 Hz, 1H), 1.85 (br d, *J*=13.6 Hz, 1H), 1.65–1.41 (m, 7H), 1.29–1.23 (m, 3H), 1.15 (td, *J*=13.0, 4.2 Hz, 2H), 1.02 (s, 3H), 0.89 (s, 3H), 0.88 (d, *J*=0.8 Hz, 9H), 0.87 (d, *J*=0.7 Hz, 9H), 0.04 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 202.8, 164.8, 155.5, 126.1, 69.9, 61.3, 60.8, 55.5, 47.8, 42.0, 39.6, 36.9, 36.2, 33.2, 33.0, 32.9, 29.8, 26.0, 25.9, 23.3, 18.4, 18.2, 18.1, −5.37, −5.39, −5.50, −5.54; IR (NaCl/thin film): 2953, 2928, 2856, 1723, 1472, 1388, 1361, 1255, 1150, 1096, 836, 775, 665 cm^{-1}; HRMS (MM: ESI-APCI) calcd for $C_{31}H_{59}O_5Si_2$ $[M+H]^+$ 567.3896, found 567.3915.

4.2.9. Tricycle ***33***. Fresh SmI_2 was prepared according to the following procedure:[44] 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 (~0.1 M in SmI_2) was allowed to settle for at least 10 min prior to use. This protocol was also used on half-scale as necessary to provide 25 mL SmI_2 solution.

A flame-dried flask in a glove box was charged with LiBr (333 mg, 3.84 mmol, 25.0 equiv) and then removed from the glove box. A freshly prepared solution of 0.1 M SmI_2 (3.84 mL, 0.384 mmol, 2.5 equiv) was then added to the flask containing LiBr and stirred until no visible white solids were apparent and a dark purple homogeneous solution emerged (ca. 5 min). The $SmBr_2$ mixture was transferred dropwise via cannula to a solution of aldehyde **13** (87 mg, 0.15 mmol, 1.0 equiv) and a solution of *t*-BuOH in THF (1.0 M, 0.15 mL, 0.15 mmol, 1.0 equiv) in THF (15 mL) at −78 °C. The reaction mixture was allowed to stir at −78 °C until LC/MS (or TLC) indicated full consumption starting material (ca. 1 h). The reaction mixture was quenched with satd $NaHCO_3$ (10 mL), satd $Na_2S_2O_3$ (10 mL), and Rochelle salt (2 g), and extracted with EtOAc (3×15 mL). The combined organic extracts were washed once with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (10–12% EtOAc/Hex) to afford tricycle **33** as a white foam (42.3 mg, 49% yield). $[\alpha]_D^{25}$ −6.1 (*c* 0.56, $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$): δ 4.57 (br s, 1H), 4.48 (d, *J*=11.4 Hz, 1H), 4.24 (d, *J*=11.4 Hz, 1H), 3.75–3.63 (m, 4H), 2.86 (td, *J*=12.3, 3.3 Hz, 1H), 2.47 (d, *J*=14.6 Hz, 1H), 1.99–1.93 (m, 2H), 1.78 (br d, *J*=13.6 Hz, 1H), 1.71 (t, *J*=3.5 Hz, 1H), 1.54–1.39 (m, 6H), 1.30 (dd, *J*=12.6, 4.8 Hz, 1H), 1.16–0.98 (m, 7H), 0.894 (s, 3H), 0.887 (s, 18H) 0.05 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 73.3, 65.7, 60.8, 60.1, 51.7, 46.7, 42.0, 41.4, 39.6, 39.5, 35.5, 35.4, 34.2, 33.8, 27.9, 27.5, 26.0, 25.9, 23.6, 18.4, 18.3, 18.2, −5.26, −5.28, −5.46, −5.50; IR (NaCl/thin film): 3469, 2927, 2856, 1726, 1471, 1462, 1389, 1360, 1256, 1091, 836, 775 cm^{-1}; HRMS (MM: ESI–APCI) calcd for $C_{31}H_{61}O_5Si_2$ $[M+H]^+$ 569.4052, found 569.4037.

4.2.10. Acetate ***34***. To a solution of tricycle **33** (41.9 mg, 73.6 μmol, 1.0 equiv) in DCM (3.5 mL) was added Ac_2O (49 μL, 0.515 mmol, 7.0 equiv) and then 4-DMAP (45 mg, 0.37 mmol, 5.0 equiv). The solution was stirred until LC/MS (or TLC) indicated complete consumption of starting material (1.5 h), at which time, the reaction mixture was diluted with satd $NaHCO_3$ (4 mL) and CH_2Cl_2 (2 mL) and stirred for 30 min. The layers were separated and the aqueous layer was extracted with DCM (3×3 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (7% EtOAc/Hex) to afford acetate **34** (42.1 mg, 94% yield). $[\alpha]_D^{25}$ −19.6 (*c* 0.44, $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$): δ 5.61 (br s, 1H), 4.46 (d, *J*=11.6 Hz, 1H), 4.37 (d, *J*=11.6 Hz, 1H), 3.75 (qd, *J*=10.2, 4.0 Hz, 2H), 3.63 (t, *J*=6.5 Hz, 2H), 2.84 (td, *J*=12.3, 3.5 Hz, 1H), 2.49 (dd, *J*=13.2, 2.0 Hz, 1H), 2.19 (dd, *J*=12.8, 0.7 Hz, 1H), 2.05 (s, 3H), 1.98–1.94 (m, 2H), 1.89–1.78 (m, 2H), 1.60–1.33 (m, 7H), 1.16 (td, *J*=12.9, 4.2 Hz, 1H), 1.10–0.99 (m, 4H), 0.899 (s, 9H), 0.881 (s, 3H), 0.876 (s, 9H), 0.07 (d, *J*=2.3 Hz, 6H), 0.03 (d, *J*=3.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 169.8, 73.1, 68.59, 60.33, 60.26, 51.4, 46.0, 42.2, 39.43, 39.36, 37.2, 36.5, 35.2, 34.1, 33.8, 30.3, 28.1, 28.0, 25.95, 25.91, 23.5, 21.6, 18.3, 18.24, −5.3, −5.42, −5.47; IR (NaCl/thin film): 2954, 2928, 2957, 1737, 1472, 1464, 1389, 1370, 1236, 1089, 837, 776 cm^{-1}; HRMS (MM: ESI–APCI) calcd for $C_{33}H_{63}O_6Si_2$ $[M+H]^+$ 611.4158, found 611.4152.

4.2.11. Diol ***35***. To a solution of acetate **34** (41.9 mg, 68.6 μmol) in 1.5 mL MeCN at 0 °C was added 20–25 wt % aqueous H_2SiF_6 (0.20 mL, 0.34 mmol, 5.0 equiv). After stirring at 0 °C for 15 min, the ice bath was removed and the mixture allowed to warm to ambient temperature. After 60 min, satd $NaHCO_3$ (2 mL) and EtOAc (2 mL) were carefully added. After cessation of bubbling, the layers were separated and the aqueous layer was extracted with EtOAc (2×2 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (50–100% EtOAc/Hex) to afford diol **35** as a clear gum (17.9 mg, 68% yield). $[\alpha]_D^{25}$ −9.1 (*c* 0.62, $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$): δ 5.64 (dt, *J*=3.9, 1.8 Hz, 1H), 4.44 (d, *J*=11.6 Hz, 1H), 4.34 (dd, *J*=11.6, 1.2 Hz, 1H), 3.86 (dd, *J*=11.9, 3.0 Hz, 1H), 3.78 (dd, *J*=11.8, 6.5 Hz, 1H), 3.69 (t, *J*=6.6 Hz, 2H), 2.86 (td, *J*=12.3, 3.5 Hz, 1H), 2.55–2.47 (m, 1H), 2.31 (dd, *J*=12.8, 1.6 Hz, 1H), 2.08 (s, 3H), 1.98–1.76 (m, 3H), 1.66 (dd, *J*=6.5, 3.0 Hz, 1H), 1.57–1.31 (m, 8H), 1.23–1.07 (m, 3H), 1.05 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 170.0, 72.9, 68.8, 60.3, 60.2, 51.5, 46.2, 42.1, 39.3, 39.1, 37.2, 36.4, 34.7, 33.9, 33.8, 28.2, 28.0, 23.2, 21.7, 18.2; IR (NaCl/thin film): 3429, 2925, 2873, 1728, 1459, 1390, 1371, 1237, 1208, 1071, 1031, 967, 916, 731 cm^{-1}; HRMS (MM: ESI-APCI) calcd for $C_{21}H_{35}O_6$ $[M+H]^+$ 383.2428, found 383.2432.

4.2.12. Dialdehyde ***36***. To a solution of diol **35** (12.4 mg, 32.4 μmol) in 0.7 mL DCM was added Dess–Martin periodinane (55 mg, 0.13 mmol, 4.0 equiv). After stirring for 15 min, the reaction mixture was diluted with satd $NaHCO_3$ (1 mL) and satd $Na_2S_2O_3$ (1 mL) and stirred vigorously until the layers became clear (ca. 20 min). The layers were then separated and the aqueous layer was extracted with DCM (3×1 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (33–50% EtOAc/Hex) to afford dialdehyde **36** (9.9 mg, 81% yield). $[\alpha]_D^{25}$ −8.4 (*c* 0.50, $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$): δ 9.93 (d, *J*=3.9 Hz, 1H), 9.75 (t, *J*=1.3 Hz, 1H), 5.41 (dt, *J*=3.9, 2.1 Hz, 1H), 4.66 (d, *J*=11.7 Hz, 1H), 4.40 (d, *J*=11.7 Hz, 1H), 2.86 (td, *J*=12.4, 3.5 Hz, 1H), 2.47–2.37 (m, 2H), 2.35 (dd, *J*=6.1, 1.4 Hz, 1H), 2.34–2.27 (m, 1H), 2.26 (d, *J*=3.9 Hz, 1H), 2.11 (s, 3H), 2.01 (dd, *J*=12.9, 1.9 Hz, 1H), 1.99–1.93 (m, 1H), 1.84–1.76 (m, 1H), 1.66–1.48 (m, 4H), 1.39–1.29 (m, 1H), 1.24–1.18 (m, 1H), 1.17 (s, 3H), 1.16–1.10 (m, 1H), 1.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.3, 200.7, 172.3, 169.8, 71.7, 68.1, 62.3, 49.8, 45.0, 41.1, 40.6, 36.7, 36.1, 33.9, 33.6, 33.3, 27.6, 26.0, 23.3, 21.5, 18.2; IR (NaCl/thin film): 2952, 2929, 2873, 2735, 1732, 1454, 1442, 1392, 1372, 1234, 1204, 1073, 1030, 914, 836, 731 cm^{-1}; HRMS (MM: ESI-APCI) calcd for $C_{21}H_{31}O_6$ $[M+H]^+$ 379.2115, found 379.2107.

4.2.13. Enal ***37***. A solution of dialdehyde **36** (9.8 mg, 26 μmol) in 1.5 mL DCM was prepared in a glove box. *N*,*N*-Dimethylmethyleneiminium iodide (48 mg, 0.26 mmol, 10 equiv) and Et_3N (55 μL, 0.39 mmol, 15 equiv) were added and the mixture was stirred for 10 h. After removal from the glove box, the reaction mixture was diluted with satd $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3×1 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (25–35% EtOAc/Hex) to afford enal **37** as a white solid (2.5 mg, 25% yield). $[\alpha]_D^{25}$ −16 (*c* 0.12, $CHCl_3$); ^1H NMR (600 MHz; $CDCl_3$): δ 9.95 (d, *J*=3.9 Hz, 1H), 9.50 (s, 1H), 6.25 (s, 1H), 6.04 (s, 1H), 5.47 (dt, *J*=4.0, 2.1 Hz, 1H), 4.69 (d, *J*=11.7 Hz, 1H), 4.41 (d, *J*=11.7 Hz, 1H), 2.97–2.87 (m, 2H), 2.43 (dq, *J*=13.1, 3.2 Hz, 1H), 2.28 (d, *J*=3.9 Hz, 1H), 2.14 (s, 3H), 2.10–2.03 (m, 1H), 2.01 (dq, *J*=14.1, 2.9 Hz, 1H), 1.83 (dt, *J*=13.8, 3.6 Hz, 1H), 1.66–1.50 (m, 3H), 1.42–1.20 (m, 4H), 1.18 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.4, 193.8, 172.3, 169.8, 152.5, 133.6, 71.8, 68.1, 62.4, 45.0, 41.1, 40.7, 36.4, 35.4, 33.6, 33.3, 32.6, 29.2, 27.7, 23.3, 21.6, 18.3; IR (NaCl/thin film): 2917, 2849, 1734, 1685, 1457, 1373, 1235, 1030 cm^{-1}; HRMS

(MM: ESI-APCI) calcd for $C_{22}H_{31}O_6$ $[M+H]^+$ 391.2115, found 391.2135.

*4.2.14. TBS ether **39**.* To a solution of diol **35** (13.1 mg, 34.2 μmol) in 1.0 mL DCM were added imidazole (5.8 mg, 86 μmol, 2.5 equiv) and TBSCl (5.1 mg as a solution in DCM, 0.10 mL, 34 μmol, 1.0 equiv). After stirring for 20 min, the reaction mixture was diluted with satd $NaHCO_3$ (1 mL). The layers were separated and the aqueous layer was extracted with DCM (2×1 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (25–35% EtOAc/Hex) to afford TBS ether **39** as a clear gum (13.5 mg, 80% yield). $[\alpha]_D^{25}$ −8.0 (*c* 0.62, $CHCl_3$); ^{1}H NMR (600 MHz; $CDCl_3$): δ 5.63 (dt, *J*=3.7, 2.0 Hz, 1H), 4.43 (d, *J*=11.6 Hz, 1H), 4.34 (dd, *J*=11.6, 1.3 Hz, 1H), 3.86 (dt, *J*=11.8, 3.3 Hz, 1H), 3.79 (ddd, *J*=11.6, 6.4, 4.9 Hz, 1H), 3.62 (t, *J*=6.5 Hz, 2H), 2.85 (td, *J*=12.3, 3.5 Hz, 1H), 2.47 (dtd, *J*=13.2, 3.7, 2.0 Hz, 1H), 2.30 (dd, *J*=12.7, 1.6 Hz, 1H), 2.06 (s, 3H), 2.00–1.76 (m, 3H), 1.66 (dd, *J*=6.5, 3.0 Hz, 1H), 1.63 (br s, 1H), 1.53–1.32 (m, 6H), 1.23–1.06 (m, 3H), 1.05 (s, 3H), 0.87 (s, 9H), 0.86 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 169.9, 72.9, 68.9, 60.3, 60.3, 51.6, 46.3, 42.1, 39.3, 39.2, 36.9, 36.5, 35.0, 33.9, 33.8, 28.2, 27.9, 25.9, 23.2, 21.6, 18.2, 18.2, −5.3, −5.3; IR (NaCl/thin film): 2952, 2927, 2856, 1733, 1472, 1462, 1388, 1370, 1237, 1206, 1099, 1034, 835, 775 cm^{-1}; HRMS (MM: ESI-APCI) calcd for $C_{27}H_{49}O_6Si$ $[M+H]^+$ 497.3293, found 497.3286.

*4.2.15. Aldehyde **40**.* To a solution of TBS ether **39** (12.2 mg, 24.6 μmol) in 0.6 mL DCM was added Dess–Martin periodinane (21 mg, 49 μmol, 2.0 equiv). After stirring for 40 min, the reaction mixture was diluted with satd $NaHCO_3$ (1 mL) and satd $Na_2S_2O_3$ (1 mL). The layers were separated and the aqueous layer was extracted with DCM (3×1 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (15–20% EtOAc/Hex) to afford aldehyde **40** as a white solid (8.8 mg, 72% yield). Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution of aldehyde **40** in Et_2O. $[\alpha]_D^{25}$ −6.6 (*c* 0.39, $CHCl_3$); ^{1}H NMR (600 MHz; $CDCl_3$): δ 9.94 (d, *J*=3.9 Hz, 1H), 5.41 (dt, *J*=3.9, 2.0 Hz, 1H), 4.65 (d, *J*=11.7 Hz, 1H), 4.42 (d, *J*=11.6 Hz, 1H), 3.62 (t, *J*=6.3 Hz, 2H), 2.80 (td, *J*=12.3, 3.4 Hz, 1H), 2.39 (dq, *J*=13.4, 3.0 Hz, 1H), 2.30 (d, *J*=3.8 Hz, 1H), 2.07 (s, 3H), 2.01–1.94 (m, 2H), 1.91–1.82 (m, 1H), 1.80 (dt, *J*=13.8, 3.7 Hz, 1H), 1.65–1.30 (m, 6H), 1.20 (td, *J*=13.1, 4.5 Hz, 1H), 1.16 (s, 3H), 1.11–1.02 (m, 5H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.2, 172.8, 169.8, 71.8, 68.6, 62.3, 60.1, 45.4, 41.1, 40.6, 39.0, 36.9, 36.3, 34.2, 33.7, 33.3, 27.6, 27.5, 25.9, 23.3, 21.5, 18.3, 18.2, −5.4; IR (NaCl/thin film): 2953, 2927, 2855, 1735, 1711, 1472, 1371, 1388, 1239, 1203, 1102, 1044, 834, 775 cm^{-1}; HRMS (MM: ESI-APCI) calcd for $C_{27}H_{47}O_6Si$ $[M+H]^+$ 495.3136, found 495.3132. Mp=129–131 °C.

*4.2.16. Alkylated lactone **45**.* To a solution of lactone **15** (205 mg, 0.60 mmol, 1.0 equiv) and *ent*-**14** (236 mg, 0.67 mmol, 1.1 equiv) in (4:1) THF/HMPA (3 mL) at 0 °C was added a solution of LHMDS (274 mg, 1.64 mmol, 1.1 equiv) in (4:1) THF/HMPA (2 mL followed by a 1 mL rinse). The resulting solution was stirred for an additional 3 h at 0 °C and then diluted with satd $NaHCO_3$ (20 mL) and Et_2O (30 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×10 mL) and the combined organic extracts were washed with H_2O (3×20 mL) and brine (1×20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (0–20% EtOAc/Hex) to provide lactone **45** (253 mg, 74% yield) as a mixture of diastereomers and recovered **15** (28 mg).

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

4.2.16.2. Data for more polar diastereomer. $[\alpha]_D^{25}$ −37.6 (*c* 0.48, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, *J*=16.8, 10.5, 7.1 Hz, 1H), 5.08–4.99 (m, 2H), 4.50 (d, *J*=11.8 Hz, 1H), 4.13 (d, *J*=11.8 Hz, 1H), 3.83–3.75 (m, 2H), 3.62 (t, *J*=6.8 Hz, 2H), 2.61–2.56 (m, 1H), 2.13–1.99 (m, 3H), 1.99–1.95 (m, 2H), 1.76–1.67 (m, 1H), 1.63–1.37 (m, 5H), 1.31–1.18 (m, 4H), 1.18–1.10 (m, 1H), 1.02 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.16 to −0.09 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 136.2, 116.6, 73.0, 61.1, 60.8, 55.1, 41.6, 40.0, 37.4, 37.2, 37.0, 36.5, 35.4, 34.8, 33.8, 33.1, 31.1, 26.0, 25.9, 18.5, 18.3, 18.0, −5.25, −5.26, −5.50, −5.55; IR (NaCl/thin film): 2952, 2927, 2856, 1751, 1471, 1462, 1387, 1360, 1255, 1168, 1151, 1094, 1062, 1005, 953, 938, 910, 836, 774 cm^{-1}; HRMS (MM: ESI–APCI) calcd for $C_{32}H_{63}O_4Si_2$ $[M+H]^+$ 567.4259, found 567.4265.

*4.2.17. Unsaturated lactone **46**.* To a solution of KHMDS (73 mg, 0.37 mmol, 1.2 equiv) in THF (6 mL) at 0 °C was added lactone **45** (1.5:1 mixture of diastereomers, 172 mg, 0.30 mmol, 1.0 equiv) in THF (3 mL followed by a 1 mL rinse) dropwise via cannula. The resulting clear solution was allowed to stir at 0 °C for 30 min then at rt for 15 min. The solution was re-cooled to −78 °C, at which time, a solution of PhSeBr (79 mg, 0.33 mmol, 1.1 equiv) in THF (3 mL followed by a 1 mL wash) pre-cooled at −78 °C was slowly added dropwise via cannula. The resulting pale yellow solution was allowed to stir for 15 min at −78 °C and then diluted with satd $NaHCO_3$ (15 mL) and Et_2O (30 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×15 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude residue was diluted with DCM (4 mL) and cooled to 0 °C. To this was added 30 wt % H_2O_2 (0.2 mL, 1.96 mmol, 6.5 equiv) and stirred for 30 min. The reaction mixture was diluted with H_2O (15 mL) and the layers were separated. The aqueous layer was extracted with DCM (3×10 mL) and the combined organic extracts were washed with satd $NaHCO_3$ (1×10 mL), dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (0–15% EtOAc/Hex) to afford unsaturated lactone **46** (139 mg, 81% yield). $[\alpha]_D^{25}$ −22.7 (*c* 0.45, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.35 (s, 1H), 5.80–5.71 (m, 1H), 5.05–4.97 (m, 2H), 4.48 (dd, *J*=11.2, 1.5 Hz, 1H), 4.41 (d, *J*=11.3 Hz, 1H), 3.78 (d, *J*=4.5 Hz, 2H), 3.64 (td, *J*=6.9, 3.0 Hz, 2H), 2.19 (qd, *J*=12.5, 7.2 Hz, 2H), 2.04–2.02 (m, 2H), 1.85 (m, 2H), 1.60–1.39 (m, 7H), 1.26 (td, *J*=13.0, 3.8 Hz, 1H), 1.15 (td, *J*=13.3, 4.1 Hz, 1H), 1.02 (s, 3H), 0.92 (s, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.04 (d, *J*=0.6 Hz, 6H), 0.03 (d, *J*=0.5 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8, 154.3, 136.5, 127.4, 116.5, 70.0, 61.5, 61.2, 55.5, 42.2, 39.8, 37.9, 36.0, 35.6, 33.3, 33.2, 33.02, 32.98, 26.0, 25.9, 23.4, 18.5, 18.3, 18.1, −5.26, −5.29, −5.53, −5.58; IR (NaCl/thin film): 2952, 2927, 2856, 1722, 1471, 1462, 1388, 1360, 1255, 1164, 1149, 1096, 1005, 909, 836, 774, 662 cm^{-1}; HRMS (MM: ESI-APCI) calcd for $C_{32}H_{61}O_4Si_2$ $[M+H]^+$ 565.4103, found 565.4116.

*4.2.18. Dialdehyde **18**.* To a solution of unsaturated lactone **46** (130 mg, 0.23 mmol, 1.0 equiv) in MeCN (4 mL) at 0 °C was added

20–25 wt % H_2SiF_6 (0.5 mL, 0.85 mmol, 3.7 equiv). The solution was stirred until LC/MS (or TLC) indicated full consumption of starting material (2 h). The reaction mixture was diluted with satd $NaHCO_3$ (5 mL) and EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated in vacuo. The resulting crude residue was redissolved in DCM (8 mL) and cooled to 0 °C. To the solution was added Dess–Martin periodinane (293 mg, 0.69 mmol, 3.0 equiv), and after 2 h, an additional portion of DMP was added (293 mg, 0.69 mmol, 3.0 equiv). The solution was stirred for an additional 1 h and LC/MS had indicated full consumption of starting material. The reaction mixture was diluted with satd $Na_2S_2O_3$ (15 mL) and satd $NaHCO_3$ (10 mL) and stirred for 20 min. The layers were separated and the organic layer was again stirred with with satd $Na_2S_2O_3$ (15 mL) and satd $NaHCO_3$ (10 mL) for 20 min and the layers were separated. The organic layer was washed with H_2O (20 mL) and the combined aqueous extracts were back extracted with DCM_2 (3×15 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (10–35% EtOAc/Hex) to provide **18** (66 mg, 86% yield from **46**). $[\alpha]_D^{25}$ −20.3 (*c* 1.07, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.92 (d, *J*=3.0 Hz, 1H), 9.73 (t, *J*=1.8 Hz, 1H), 6.32 (s, 1H), 5.78–5.70 (m, 1H), 5.09–5.03 (m, 2H), 4.56 (d, *J*=11.3 Hz, 1H), 4.40 (dd, *J*=11.3, 1.4 Hz, 1H), 2.43–2.15 (m, 6H), 2.04 (dt, *J*=14.2, 7.1 Hz, 1H), 1.88 (dt, *J*=13.7, 3.5 Hz, 1H), 1.66 (ddt, *J*=11.3, 7.5, 3.8 Hz, 2H), 1.57–1.53 (m, 3H), 1.34–1.20 (m, 2H), 1.13 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 203.2, 202.6, 164.3, 151.3, 135.6, 128.2, 117.6, 70.1, 64.2, 47.4, 40.3, 39.0, 38.4, 35.5, 32.8, 32.3, 32.1, 31.8, 23.7, 18.0; IR (NaCl/thin film): 2928, 2849, 1719, 1461, 1442, 1390, 1370, 1294, 1163, 1148, 1112, 1072, 1031, 915 cm^{-1}; HRMS (MM: ESI-APCI) calcd for $C_{20}H_{29}O_4$ $[M+H]^+$ 333.2060, found 333.2068.

*4.2.19. Tetracycle **16**.* To a solution of dialdehyde **18** (28.0 mg, 84.2 μmol, 1.0 equiv) in THF (8 mL) were added LiBr in THF (1.0 M, 85 μL, 850 μmol, 10.1 equiv) and *t*-BuOH in THF (0.1 M, 85 μL, 85 μmol, 1.0 equiv) and the solution was cooled to −78 °C. A separate flask was flame-dried containing LiBr (219 mg, 2.52 mmol, 30 equiv) and to this was added freshly prepared (see Section 4.2.9) 0.1 M SmI_2 (2.5 mL, 250 μmol, 3.0 equiv) and stirred for 10 min. The resulting stirring purple solution was cannulated into the dialdehyde solution and stirred for 10 min. The reaction mixture was diluted with satd $NaHCO_3$ (10 mL), satd $Na_2S_2O_3$ (10 mL), H_2O (5 mL), then Rochelle salt (1.0 g) was added and then diluted with EtOAc (20 mL) and stirred for 15 min. The layers were separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica, and concentrated in vacuo. The crude residue was purified by preparative reverse-phase HPLC (40–60% MeCN/H_2O, 20 min gradient, t_R=13.5 min) to afford tetracycle **16** (15.2 mg, 54% yield). $[\alpha]_D^{25}$ −54.6 (*c* 0.25, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.80 (ddt, *J*=17.1, 10.1, 7.1, 1H), 5.05–5.00 (m, 2H), 4.58 (dd, *J*=11.3, 1.0, 1H), 4.52 (dd, *J*=11.3, 2.0, 1H), 4.36 (br s, 1H), 3.97 (dd, *J*=7.0, 4.1, 1H), 2.28–2.10 (m, 3H), 1.99 (m, 1H), 1.86–1.82 (m, 2H), 1.78 (dtd, *J*=14.2, 3.6, 1.7, 1H), 1.62–1.45 (m, 6H), 1.38 (d, *J*=7.0, 1H), 1.27–1.10 (m, 3H), 1.08 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 136.6, 116.3, 78.5, 74.0, 72.2, 66.1, 54.4, 51.5, 42.9, 41.6, 41.1, 41.0, 34.0, 32.7, 32.6, 32.2, 28.2, 21.3, 19.3. IR (NaCl/thin film): 3395, 2930, 2876, 1713, 1337, 1163, 1041, 913 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{20}H_{31}O_4$ $[M+H]^+$ 335.2217, found 335.2220.

*4.2.20. Diacetate **50** and γ-lactone **51**.* To a solution of tetracycle **16** (5.2 mg, 15.6 μmol, 1.0 equiv) in DCM (2 mL) at 0 °C were added Ac_2O (45 μL, 476.1 μmol, 30 equiv) and TMSOTf (20 μL, 110.5 μmol, 7.1 equiv). The resulting solution was stirred at 0 °C until LC/MS (or TLC) indicated complete consumption of starting material (5 min). The reaction mixture was diluted with satd $NaHCO_3$ (5 mL) and additional DCM (5 mL) and stirred for 30 min. The layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated in vacuo. The crude residue was purified by preparative reverse-phase HPLC (50–75% MeCN/H_2O, 20 min gradient, t_R=15.3 min for **50**, t_R=16.7 min for **51**) to afford diacetate **50** (4.8 mg, 74% yield) and γ-lactone **51** (1.0 mg, 15% yield).

*4.2.20.1. Data for desired diacetate **50**.* $[\alpha]_D^{25}$ −106.7 (*c* 0.11, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.77–5.69 (m, 1H), 5.37 (dt, *J*=3.5, 1.9 Hz, 1H), 5.20 (d, *J*=7.6 Hz, 1H), 5.01–4.97 (m, 2H), 4.62 (dd, *J*=11.9, 1.8 Hz, 1H), 3.98 (dd, *J*=12.0, 1.0 Hz, 1H), 2.27–2.24 (m, 1H), 2.09–1.94 (m, 8H), 1.82–1.79 (m, 1H), 1.66–1.60 (m, 4H), 1.50–1.40 (m, 1H), 1.32–1.17 (m, 4H), 1.08 (s, 3H), 1.08–1.02 (m, 1H), 0.90–0.83 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 170.0, 169.4, 135.9, 116.5, 73.2, 71.4, 67.7, 62.9, 53.3, 51.3, 42.7, 41.2, 40.7, 36.4, 32.9, 32.7, 32.4, 32.2, 28.6, 21.3, 21.0, 20.8, 19.1; IR (NaCl/thin film): 2955, 1745, 1641, 1444, 1368, 1230, 1153, 1103, 1029, 920 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{24}H_{35}O_6$ $[M+H]^+$ 419.2428, found 419.2425.

*4.2.20.2. Data for translactonized acetate **51**.* ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.75 (d, *J*=10.4 Hz, 1H), 5.73–5.65 (m, 1H), 5.04–4.99 (m, 2H), 4.88 (d, *J*=4.4 Hz, 1H), 4.18 (d, *J*=12.5 Hz, 1H), 3.84 (d, *J*=12.8 Hz, 1H), 2.21–2.16 (m, 1H), 2.11–2.07 (m, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 2.02–1.92 (m, 2H), 1.81 (dd, *J*=12.6, 6.0 Hz, 1H), 1.74 (s, 1H), 1.68–1.51 (m, 4H), 1.51–1.46 (m, 1H), 1.37–1.32 (m, 1H), 1.21–1.12 (m, 2H), 1.03 (td, *J*=13.0, 4.2 Hz, 1H), 0.90 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.8, 170.5, 169.7, 135.5, 116.9, 76.0, 73.2, 65.8, 63.0, 63.0, 54.7, 44.1, 41.7, 40.3, 36.7, 35.7, 35.3, 33.0, 32.8, 30.9, 21.6, 21.1, 20.9, 19.1; IR (NaCl/thin film): 2930, 2868, 1775, 1771, 1742, 1739, 1733, 1640, 1447, 1378, 1367, 1234, 1165, 1122, 1035, 937, 915 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{24}H_{35}O_6$ $[M+H]^+$ 419.2428, found 419.2433.

*4.2.21. Acetyl-maoecrystal Z (**52**).* A solution of diacetate **50** (4.8 mg, 11.5 μmol, 1.0 equiv) in DCM (2 mL) was cooled to −78 °C, at which time, ozone was gently bubbled through the solution (O_2 flow rate=1/8 L/min, 0 setting on ozonator) until LC/MS (or TLC) indicated full consumption of starting material (3 min). The solution was purged with N_2 for 3 min then Et_3N (100 μL, 717.5 μmol, 62.6 equiv) was slowly added dropwise. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stirred until LC/MS indicated complete conversion of the ozonide to the aldehyde (30 min), filtered through a small plug of silica gel, and concentrated in vacuo. The crude residue was azeotroped with heptane and placed under high vacuum for 20 min, and then dissolved in DCM (2 mL). To this was added Et_3N (50 μL, 358.7 μmol, 31.3 equiv) and the reaction flask was then taken into a glove box. *N*,*N*-Dimethylmethyleneiminium iodide (42.4 mg, 229.2 μmol, 20 equiv) was added to the solution and stirred at rt for 12 h. The reaction mixture was diluted with satd $NaHCO_3$ (5 mL) and additional DCM (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic extracts were dried over Na_2SO_4, filtered through a small plug of silica gel, and concentrated in vacuo. The crude residue was purified by preparative reverse-phase HPLC (40–60% MeCN/H_2O, 20 min gradient, t_R=14.5 min) to afford enal **52** (4.0 mg, 80% yield from **50**). $[\alpha]_D^{25}$ −67.9 (*c* 0.12, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.50 (d, *J*=0.7 Hz, 1H), 6.26 (s, 1H), 6.00 (d, *J*=1.1 Hz, 1H), 5.40 (d, *J*=1.5 Hz, 1H), 5.21 (d, *J*=6.8 Hz, 1H), 4.64 (d, *J*=11.9 Hz, 1H), 4.00 (d, *J*=12.0 Hz, 1H), 3.10 (t, *J*=12.6 Hz, 1H), 2.22 (dt, *J*=12.5, 1.7 Hz, 1H), 2.09 (d, *J*=1.4 Hz, 3H), 2.05 (d, *J*=1.5 Hz, 3H), 2.01–1.96 (m, 1H), 1.82 (d, *J*=12.9 Hz, 1H), 1.77 (s, 1H), 1.66–1.44 (m, 6H), 1.31 (td, *J*=13.2, 3.4 Hz, 1H), 1.21 (td, *J*=13.4, 4.0 Hz, 1H), 1.09 (s,

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3H), 0.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.0, 172.6, 169.9, 169.4, 152.3, 134.8, 73.3, 71.5, 67.4, 62.8, 52.8, 51.1, 42.9, 41.2, 35.0, 32.9, 32.7, 32.3, 30.3, 29.8, 21.3, 21.0, 20.8, 19.1; IR (NaCl/thin film): 2958, 1737, 1680, 1367, 1225, 1158, 1031 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{24}H_{33}O_7$ $[M+H]^+$ 433.2221, found 433.2217.

*4.2.22. (−)-Maoecrystal Z (**1**).* To a suspension of enal **52** (2.9 mg, 6.7 μmol, 1.0 equiv) in 1:1 MeOH/H_2O (600 μL) was added enough DCM (ca. 200 μL) to afford a slightly cloudy solution. To this was added 1 M NaOH (15 μL, 15 μmol, 2.2 equiv) and the solution was stirred for 1 h. An additional portion of 1 M NaOH was then added (15 μL, 15 μmol, 2.2 equiv) and the solution was allowed to stir for an additional 2.5 h, at which time, LC/MS indicated complete consumption of starting material. AcOH (50 μL) was then added to neutralize the excess base. The reaction mixture was directly loaded onto a preparative reverse-phase HPLC column and purified (40–60% MeCN/H_2O, 20 min gradient, t_R=8.3 min) to afford (−)-maoecrystal Z (**1**) (1.0 mg, 38% yield). $[\alpha]_D^{25}$ −91.2 (*c* 0.05, MeOH); ^{1}H NMR (500 MHz; pyridine-d_5): δ 9.53 (s, 1H), 6.21 (s, 1H), 5.87 (s, 1H), 5.56 (td, *J*=3.9, 2.0 Hz, 1H), 4.65 (dd, *J*=11.8, 1.8 Hz, 1H), 4.38 (dd, *J*=7.2, 5.5 Hz, 1H), 4.13 (dd, *J*=12.0, 1.2 Hz, 1H), 3.61 (t, *J*=12.8, 3.3, 1H), 2.74 (ddd, *J*=12.8, 3.5, 1.7 Hz, 1H), 2.23 (dtd, *J*=13.9, 3.6, 1.8, 1H), 2.04 (t, *J*=12.7, 1H), 2.03 (s, 3H), 1.89 (t, *J*=2.0 1H), 1.67 (d, *J*=6.8 Hz, 1H), 1.61 (dt, *J*=12.9, 3.2 Hz, 1H), 1.46 (m, 1H), 1.41 (m, 1H and OH), 1.38 (m, 2H), 1.23 (s, 3H), 1.17 (m, 2H), 1.05 (s, 3H); ^{13}C NMR (126 MHz, pyridine-d_5) δ 194.3, 175.4, 169.9, 154.2, 133.8, 73.9, 71.9, 68.4, 66.0, 53.1, 52.3, 42.7, 41.8, 36.3, 34.5, 33.0, 32.3, 31.7, 28.9, 21.3, 21.1, 19.6; IR (NaCl/thin film): 3434, 2925, 2854, 1742, 1710, 1688, 1464, 1258, 1165, 1096, 838, 777 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{22}H_{31}O_6$ $[M+H]^+$ 391.2115, found 391.2112.

^{1}H NMR (500 MHz; $CDCl_3$): δ 9.52 (s, 1H), 6.30 (d, *J*=1.0 Hz, 1H), 6.02 (s, 1H), 5.41 (td, *J*=4.0, 2.0 Hz, 1H), 4.61 (dd, *J*=12.0, 2.0 Hz, 1H), 4.04 (dd, *J*=7.1, 4.6 Hz, 1H), 4.00 (dd, *J*=12.0, 1.2 Hz, 1H), 3.16 (t, *J*=12.6, 3.6, 1H), 2.30 (ddd, *J*=12.6, 3.5, 1.8 Hz, 1H), 2.09 (s, 3H), 2.04 (dtd, *J*=14.0, 3.5, 2.0 Hz, 1H), 1.87 (d, *J*=4.4 Hz, −O*H*), 1.80 (dt, *J*=13.2, 3.3 Hz, 1H), 1.74 (t, *J*=2.0 Hz, 1H), 1.63 (t, *J*=12.7 Hz, 1H), 1.61 (m, 2H), 1.46 (qt, *J*=13.4, 3.8 Hz, 1H), 1.42 (br d, *J*=6.9 Hz, 1H), 1.38 (ddd, *J*=14.2, 12.9, 2.2 Hz, 1H), 1.29 (td, *J*=13.2, 4.0 Hz, 1H), 1.23 (td, *J*=13.5, 4.2 Hz, 1H), 1.08 (s, 3H), 1.06 (s, 3H).

*4.2.23. Aldehyde **21**.* To a solution of enoate **46** (1.94 g, 3.43 mmol) in 35 mL MeOH cooled to 0 °C were 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 satd $NaHCO_3$ (25 mL) and concentrated in vacuo to remove MeOH. The aqueous layer was then extracted with EtOAc (3×15 mL). The combined organic extracts were then washed with brine (15 mL), dried over Na_2SO_4, and concentrated in vacuo to provide the crude alcohol. The crude residue 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, satd $NaHCO_3$ (20 mL) and satd $Na_2S_2O_3$ (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 (3×15 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 (10–12% EtOAc/Hex) to provide aldehyde **21** as a clear gum (1.18 g, 77% yield from **46**). $[\alpha]_D^{25}$ −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) calcd for $C_{26}H_{45}O_4Si$ $[M+H]^+$ 449.3082, found 449.3067.

An analytical sample of the intermediate alcohol was obtained (63% yield) by SiO_2 chromatography (30% EtOAc/Hex). $[\alpha]_D^{25}$ −44.6 (*c* 1.21, $CHCl_3$); ^{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) calcd for $C_{26}H_{47}O_4Si$ $[M+H]^+$ 451.3238, found 451.3251.

*4.2.24. Tricycle **53**.* A solution of aldehyde **21** (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 glove box, a separate flame-dried flask was charged with LiBr (3.27 g, 38 mmol, 25 equiv), removed from the glove box, and to this flask was added freshly prepared (see Section 4.2.9) 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, satd $NaHCO_3$ (60 mL), satd $Na_2S_2O_3$ (60 mL), and Rochelle salt (10 g) were added, and the mixture was extracted with EtOAc (3×80 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 (9–12% EtOAc/Hex) to afford tricycle **53** 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) calcd for $C_{26}H_{47}O_4Si$ $[M+H]^+$ 451.3238, found 451.3236.

*4.2.25. MOM ether **54**.* A solution of tricycle **53** (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 satd $NaHCO_3$ (5 mL) and extracted with Et_2O (3×5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (7–9% EtOAc/Hex) to afford methoxymethyl ether **54** as a clear gum (0.315 g, 91% yield). $[\alpha]_D^{25}$ −22 (*c* 0.76, $CHCl_3$); ^{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) calcd for $C_{28}H_{51}O_5Si$ $[M+H]^+$ 495.3500, found 495.3510.

*4.2.26. Silyl ketene acetal **55**.* 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 **54** (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 for 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 satd $NaHCO_3$ (5 mL). The layers were separated and the aqueous was extracted with ice-cold pentane (2×5 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 **55** as a clear gum (0.139 g, 85% yield). $[\alpha]_D^{25}$ −82.6 (*c* 1.50, $CHCl_3$); ^{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) calcd for $C_{34}H_{65}O_5Si_2$ $[M+H]^+$ 609.4365, found 609.4354.

*4.2.27. Tetracycle **56**.* A solution of silyl ketene acetal **55** (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 1 M HCl (10 mL), and extracted with Et_2O (4×6 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 (7–9% EtOAc/Hex) to afford tetracycle **56** 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) calcd for $C_{28}H_{49}O_5Si$ $[M+H]^+$ 493.3344, found 493.3355.

*4.2.28. General procedure for oxidative cyclization of **55** to **56** (Table 2).* A vial was charged with silyl ketene acetal **55** (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 1 M HCl (1 mL) and Et_2O (1 mL). The layers were separated and the aqueous layer was extracted further with Et_2O (3×0.5 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 (7–9% EtOAc/Hex) to afford pure tetracycle **56**.

*4.2.29. Methyl ketone **57**.* *Note: Methyl ketone **57** was initially isolated as a side product during optimization experiments for the conversion of **55** to **56** (Table 2, entry 6, 13% yield). Independent preparation of was accomplished using the following procedure.

A solution of MOM ether **54** (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 1 M HCl (2 mL) and extracted with Et_2O (3×2 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 (10–20% EtOAc/Hex) to afford methyl ketone **57** 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) calcd for $C_{28}H_{51}O_6Si$ $[M+H]^+$ 511.3449, found 511.3465.

*4.2.30. Ketolactone **58**.* A solution of tetracycle **56** (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 mixture 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 (15–20% EtOAc/Hex) to afford ketolactone **58** 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) calcd for $C_{27}H_{47}O_6Si$ $[M+H]^+$ 495.3136, found 495.3147.

*4.2.31. Enone **59**.* A solution of ketolactone **58** (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 satd $NaHCO_3$ (1 mL), and extracted with DCM (3×1 mL). The combined organic extracts were washed with satd $NaHCO_3$ (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 (10–15% EtOAc/Hex) to afford enone **59** as a clear gum (16.1 mg, 82% yield). $[\alpha]_D^{25}$ +27.6 (*c* 1.02, $CHCl_3$); ^1H 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) calcd for $C_{28}H_{47}O_6Si$ $[M+H]^+$ 507.3136, found 507.3145.

*4.2.32. (−)-Trichorabdal A (**2**).* To a solution of enone **59** (16.1 mg, 31.8 μmol) in 0.90 mL dioxane was added 0.70 mL 6 M HCl (aqueous), and the mixture was stirred at 45 °C. After 75 min, the reaction mixture was cooled to room temperature, carefully diluted with satd $NaHCO_3$ (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 (3×2 mL). The combined organic extracts were washed with satd $NaHCO_3$ (1 mL) and brine (1 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (50–65% EtOAc/Hex) to afford the corresponding diol as a white solid (11.0 mg, 99% yield). $[\alpha]_D^{25}$ +14 (*c* 0.16, $CHCl_3$); ^1H 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) calcd for $C_{20}H_{29}O_5$ $[M+H]^+$ 349.2010, found 349.2014.

The diol (11.0 mg, 31.6 μmol) was dissolved in 1.6 mL DCM, and 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) were added. After stirring for 3.5 h at ambient temperature, the reaction mixture was diluted with satd $NaHCO_3$ (0.5 mL) and satd $Na_2S_2O_3$ (0.5 mL). The layers were separated, the aqueous layer was extracted with DCM (3×1 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 (40–70% MeCN/H_2O, 10 min gradient, t_R=6.8 min) to afford (−)-trichorabdal A (**2**) as a white solid (8.1 mg, 74% yield). $[\alpha]_D^{25}$ −61 (*c* 0.12, EtOH); ^1H 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) calcd for $C_{20}H_{27}O_5$ $[M+H]^+$ 347.1853, found 347.1837.

*4.2.33. Diol **60**.* To a solution of tetracycle **56** (59.2 mg, 0.120 mmol, 1.0 equiv) in 3.7 mL dioxane was added 2.8 mL 6 M HCl (aqueous). 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 satd $NaHCO_3$ (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 (3×20 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 (40–50% EtOAc/Hex) to provide diol **60** (35.9 mg, 89% yield). $[\alpha]_D^{25}$ −28 (*c* 0.66, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 4.98–4.95 (m, 2H), 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, 1H), 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^+) calcd for $C_{20}H_{31}O_4$ $[M+H]^+$ 335.2217, found 335.2228.

*4.2.34. Aldehyde-lactone **61**.* To a solution of diol **60** (35.2 mg, 0.105 mmol, 1.0 equiv) in DCM (5.3 mL) were 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 satd $Na_2S_2O_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with DCM (3×20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to provide the crude aldehyde. The crude residue was chromatographed on SiO_2 (25% EtOAc/Hex) to provide 25.4 mg aldehyde (~85% purity, contaminated with ketoaldehyde from over-oxidation). Following dissolution in DCM (7.6 mL), 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 satd $NaHCO_3$ (20 mL) and DCM (20 mL). The layers were separated, and the aqueous layer was extracted with DCM (3×10 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 aldehyde-lactone **61** (22.8 mg, 58% yield from **60**). $[\alpha]_D^{25}$ −6.9 (*c* 0.42, $CHCl_3$); ^1H 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^+) calcd for $C_{22}H_{31}O_5$ $[M+H]^+$ 375.2166, found 375.2175.

An analytical sample of the intermediate aldehyde was obtained (65% yield) by preparative reverse-phase HPLC (45–70% MeCN/H_2O, 10 min 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$^+$) calcd for $C_{20}H_{29}O_4$ $[M+H]^+$ 333.2060, found 333.2070.

4.2.35. Hydroxy-lactol ***62****.* To a solution of aldehyde **61** (4.4 mg, 12 μmol, 1.0 equiv) in THF (0.27 mL) was added freshly prepared (see Section 4.2.9) 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 satd $NaHCO_3$ (1 mL), satd $Na_2S_2O_3$ (1 mL), and DCM (2 mL). The layers were separated, and the aqueous layer was extracted with DCM (3×2 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (17%–25% EtOAc/Hex) to provide recovered **61** (1.2 mg, 27% yield) and hydroxy-lactol **62** (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$^+$) calcd for $C_{20}H_{29}O_3$ $[M-OAc]^+$ 317.2111, found 317.2119.

4.2.36. Ketolactol ***63****.* A solution of lactol **62** (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 mixture 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 **63** (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$^+$) calcd for $C_{21}H_{31}O_6$ $[M+H]^+$ 379.2115, found 379.2123.

*4.2.37. (−)-Longikaurin E (****4****).* To a solution of ketolactol **63** (2.6 mg, 6.9 μmol, 1.0 equiv) in DMF (0.23 mL) were 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 1 M HCl (2 mL) and extracted with Et_2O (3×4 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 (**4**) (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$^+$) calcd for $C_{22}H_{31}O_6$ $[M+H]^+$ 391.2115, found 391.2125.

4.2.38. General procedure for reductive cyclization of aldehyde ***61*** *(Table 3).* To a flask charged with aldehyde **61** (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. If required, an oven-dried vial in a glove box was charged with LiCl or LiBr (170 μmol, 50 equiv), sealed, and removed from the glove box. Freshly prepared (see Section 4.2.9) 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 mixture was allowed to stir at the indicated temperature until the appearance of a yellow solution (35–55 min). At this point, the reaction mixture was diluted with satd NaHCO (1 mL), satd $Na_2S_2O_3$ (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 (3×2 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%–33% EtOAc/Hex) to afford hydroxy-lactol **62**, lactol **64**, primary alcohol **65**, and/or recovered aldehyde **61**.

4.2.38.1. Lactol ***64****.* To a solution of aldehyde **61** (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 (see 4.2.9) 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 satd $NaHCO_3$ (5 mL), satd $Na_2S_2O_3$ (5 mL), and DCM (10 mL). The layers were separated and the aqueous layer was extracted with DCM (3×10 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (25%–33% EtOAc/Hex) to provide lactol **64** (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$^+$) calcd for $C_{20}H_{29}O_2$ $[M-OAc]^+$ 301.2162, found 301.2164.

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4.2.38.2. Primary alcohol ***65***. Freshly prepared (see Section 4.2.9) 0.1 M SmI_2 (0.17 mL, 17 μmol, 5.0 equiv) was added directly to a vial charged (in a glove box) 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 **61** (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 satd $NaHCO_3$ (1 mL), satd $Na_2S_2O_3$ (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 (3×2 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was chromatographed on SiO_2 (20–25% EtOAc/Hex) to afford alcohol **65** (0.7 mg, 54% yield). $[\alpha]_D^{25}$ −7.5 (*c* 0.16, $CHCl_3$); ^1H 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^+) calcd for $C_{20}H_{29}O_3$ $[M-OAc]^+$ 317.2117, found 317.2105.

4.3. X-ray crystallographic data

Crystallographic data for **25** and **40** have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Copies of these data may be obtained free of charge from http://www.ccdc.cam.ac.uk/products/csd/request/ by quoting the publication citation and deposition number, #837088 for **25** and #830951 for **40**.

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Supplementary data

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