

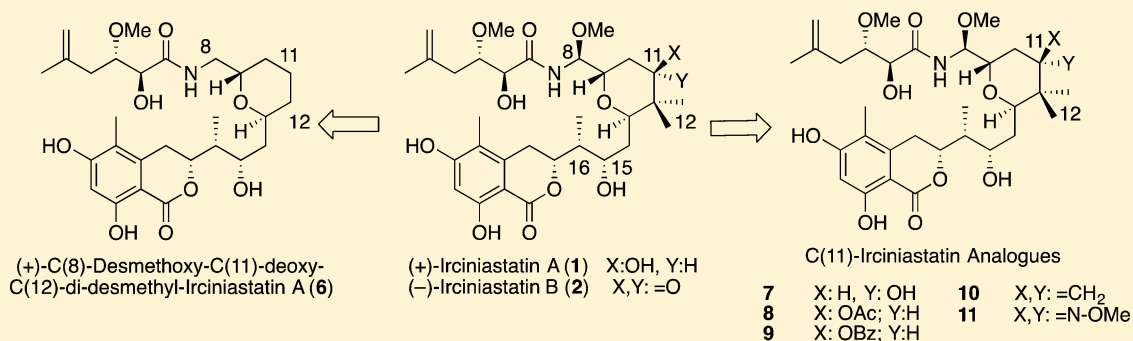
Design, Synthesis, and Evaluation of Irciniastatin Analogues: Simplification of the Tetrahydropyran Core and the C(11) Substituents

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Supporting Information



ABSTRACT: The design, synthesis, and biological evaluation of irciniastatin A (1) analogues, achieved by removal of three synthetically challenging structural units, as well as by functional group manipulation of the C(11) substituent of both irciniastatins A and B (1 and 2), has been achieved. To this end, we first designed a convergent synthetic route toward the diminutive analogue (+)-C(8)-desmethoxy-C(11)-deoxy-C(12)-didesmethylirciniastatin (6). Key transformations include an acid-catalyzed 6-*exo*-tet pyran cyclization, a chiral Lewis acid mediated aldol reaction, and a facile amide union. The absolute configuration of 6 was confirmed via spectroscopic analysis (CD spectrum, HSQC, COSY, and ROESY NMR experiments). Structure–activity relationship (SAR) studies of 6 demonstrate that the absence of the three native structural units permits access to analogues possessing cytotoxic activity in the nanomolar range. Second, manipulation of the C(11) position, employing late-stage synthetic intermediates from our irciniastatin syntheses, provides an additional five analogues (7–11). Biological evaluation of these analogues indicates a high functional group tolerance at position C(11).

INTRODUCTION

The irciniastatins (Figure 1), potent architecturally intriguing marine cytotoxins, have attracted considerable interest due to their highly selective profiles toward numerous cancer cell lines. Irciniastatin A and irciniastatin B ((+)-1 and (–)-2) were initially isolated by Pettit,¹ followed within months by psymberin independently isolated by Crews;² the latter was confirmed to be (+)-irciniastatin A (1). We have retained the family name irciniastatin, given the initial isolation and naming by Pettit.

Structurally related to the irciniastatins are congeners from the pederin family (e.g., 3).^{3,4} Common features of the pederin family are the acid-labile *N,O*-aminal group, in conjunction with the highly substituted 2,6-*trans*-tetrahydropyran core. The dihydroisocoumarin motif, however, was only found in the irciniastatins.⁴ Despite the structural similarities, (+)-irciniastatin A (1) was initially reported to display significant differential activities (>10000-fold) against a wide range of cancer cell lines,

which was not observed for other members of the pederin family.² Taken together, the initial structural and biological studies suggest that the observed differential cytotoxicity of the irciniastatins might arise via a novel mode of action.

Although (+)-irciniastatin A (1) and (–)-irciniastatin B (2) possess almost identical chemical structures, (–)-irciniastatin B (2) is reported to be 10 times more cytotoxic in comparison to (+)-irciniastatin A (1) against three cell lines: human pancreas (BXP-3), breast (MCF-7), and glioblastoma (SF268).¹ The disparity in biological activity between 1 and 2, given only a single oxidation state difference at C(11), is further enhanced by a report from a group at Schering-Plough, in conjunction with their synthetic venture, that the C(11)-deoxy congener 4 was 3–10 times more cytotoxic than (+)-irciniastatin A (1). This observation suggests that the hydroxyl group at C(11) is

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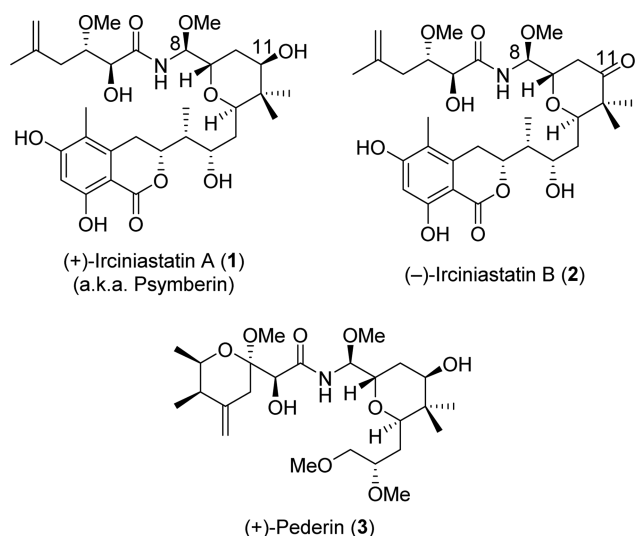


Figure 1. Structures of the irciniastatins and pederin.

not required for high potency (Figure 2).⁵ Of equal interest, from the perspective of design, Floreancig and co-workers reported that C(8)-desmethoxyirciniastatin A (5) also retained high levels of cytotoxicity similar to those for (+)-irciniastatin A (1), which in turn implies that the presence of the C(8)-N,O-aminal is also not a requirement to preserve biological activity (Figure 2).⁶

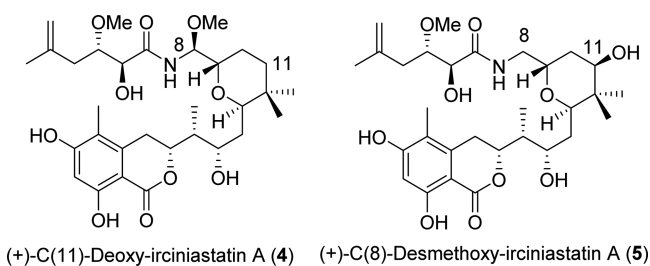


Figure 2. Previously synthesized irciniastatin analogues.

Further biological evaluation of irciniastatin A (1) led Usui and co-workers to report that treatment of human leukemia Jurkat cells initiates apoptosis by triggering stress-activated protein kinases such as JNK and p38.⁷ Subsequently in 2012 the De Brabander and Roth groups performed a forward genetic screen in *C. Elegans*, identifying the main molecular target of (+)-irciniastatin A (1) to be the ribosome, which is also targeted by the pederins. These studies further revealed that the cross-resistance of an irciniastatin-resistant mutant strain did not occur with mycalamide A, a member of the pederin family, thereby suggesting two distinct binding modes.⁸ Adding to the intrigue of these compounds, De Brabander and Roth reported that “totally synthetic” (+)-irciniastatin A (1) did not display the differential cytotoxicity that had been reported earlier by the Crews group.^{2,8} We also note that Kataoka and co-workers reported that (+)-irciniastatin A (1) inhibits protein translation with kinetics different from that of other translation inhibitors such as acetoxycycloheximide, cytotrienin A, and deoxyinvaleanol.^{9,10} Finally and very recently, Usui and co-workers suggested that the irciniastatins are similar to mycalamide B, another member of the pederin family, that binds to the E-site of the ribosome to inhibit protein translation.¹¹

Given the interesting biological profiles, the unusual structural features, and the limited abundance of the irciniastatins, the synthetic community has invested considerable effort directed at the total synthesis of these natural products and related congeners. Indeed, since their initial isolation in 2004, seven syntheses of (+)-irciniastatin A (1) have been reported.^{6,12–17} These efforts include the seminal total synthesis and structural confirmation by DeBrabander and co-workers,¹² the late-stage, three-component union by the Floreancig group leading to the shortest synthesis to date (14-step longest linear sequence),⁶ and our 2008 synthesis of (+)-irciniastatin A (1).¹⁴ The total synthesis of the more active of the two irciniastatin congeners, (-)-irciniastatin B (2), was subsequently completed in our laboratory in 2012¹⁸ via augmentation of our earlier synthesis of (+)-irciniastatin A (1)¹⁴ and then recently by Iwabuchi and co-workers (2015).¹¹ In view of the continuing synthetic and biological interest in the irciniastatins, we undertook the design, synthesis, and biological evaluation of a structurally diminutive congener of the irciniastatins (6; Figure 3), as well as several C(11)-irciniastatin analogues (7–11, Figure 3), available from late-stage intermediates in our total synthesis campaigns.

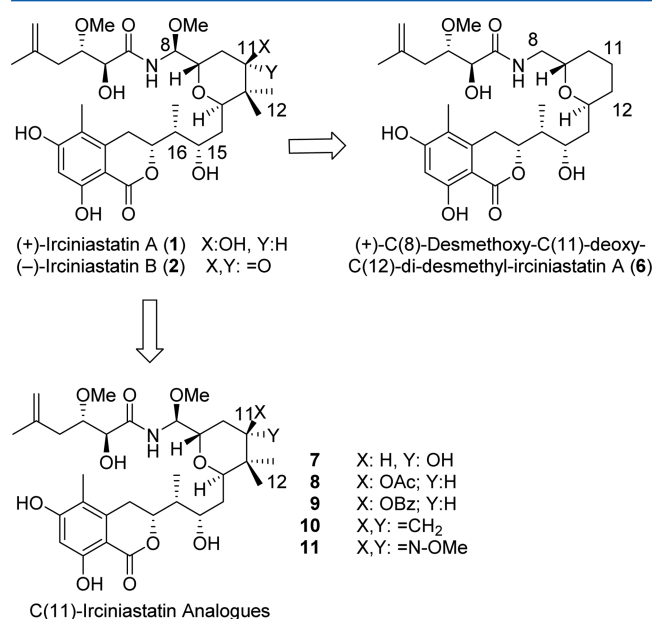


Figure 3. Proposed irciniastatin analogues.

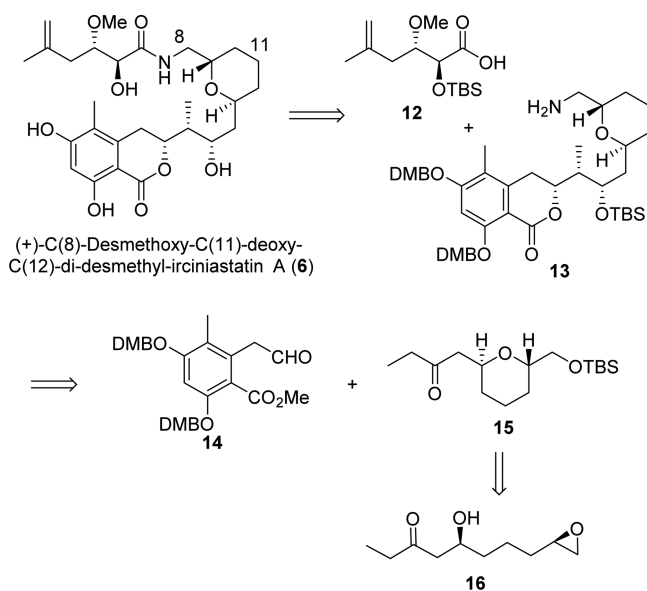
Our design strategy for the proposed diminutive form of (+)-irciniastatin A (1) began with retaining the 2,6-*trans*-tetrahydropyran core, which is conserved across all active members of the pederin families. However, in planning a synthetic route that would permit the rapid construction of diverse analogues, the dense functionality of the pyran ring posed a considerable challenge. Our initial strategy therefore was to remove the C(12)-*gem*-dimethyl unit in the tetrahydropyran core. The consequence on biological activity of removing the dimethyl group had not until our work (*vide infra*) been determined, although Floreancig and co-workers did propose that this structural unit minimizes the activation energy required to adopt a favorable active-site binding conformation.⁶ We also chose to remove the C(8)-methoxy group of the N,O-aminal as well as the C(11)-hydroxy group, given that the removal of both groups in other congeners had

not led to significant loss of biological activity.^{5,6} Removal of the C(8)-methoxy group of the *N,O*-aminal unit would also permit a more facile synthesis. Taken together, these structural modifications held the promise for more ready access to potentially highly active irciniastatin analogues. We thus identified C(8)-desmethoxy-C(11)-deoxy-C(12)-didesmethylirciniastatin **6** as our initial target. In addition, to probe the SAR at C(11) of the native irciniastatin structure, we also undertook manipulation of several late-stage intermediates reported earlier in our total synthesis of (–)-irciniastatin B (**2**) (Figure 3).¹⁸ We envision that such analogues would add further insights to the SAR of the tetrahydropyran core and in turn provide direction for the future design of accessible, potentially potent irciniastatin analogues.

RESULTS AND DISCUSSION

Synthesis of C(8)-Desmethoxy-C(11)-deoxy-C(12)-didesmethylirciniastatin (6). From a synthetic perspective, we envisioned that analogue **6** would arise via the union of side chain **12**, featuring a TBS protecting group instead of the earlier utilized SEM ether^{14,18} with primary amine **13**. The latter was prepared via a stereoselective *syn*-aldol union between aldehyde **14**,¹⁸ possessing robust 3,4-dimethoxybenzyl groups that had proven effective in our synthesis of (–)-irciniastatin B (**2**),¹⁸ and pyran **15** (Scheme 1). Pyran **15** in turn would be constructed via a 6-*exo*-tet cyclization of epoxide **16** available in six steps from commercially available material.

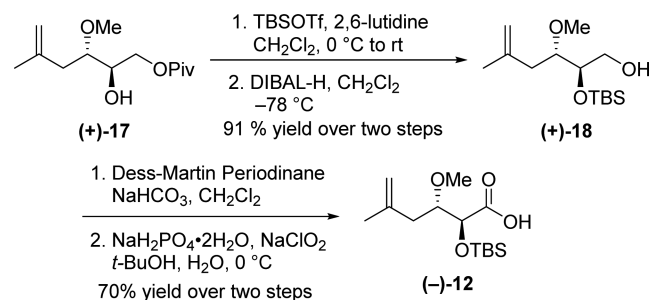
Scheme 1. Retrosynthetic Analysis for C(8)-Desmethoxy-C(11)-deoxy-C(12)-didesmethylirciniastatin (6)



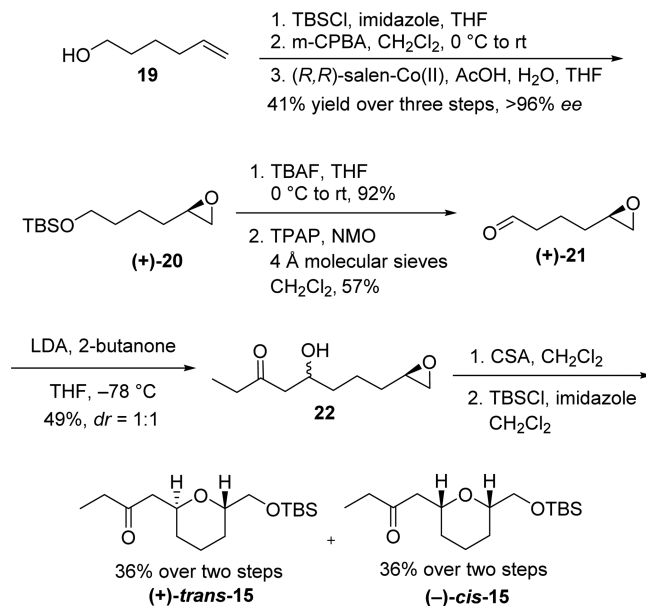
We began the synthesis of acid (–)-**12** by protection of alcohol (+)-**17**,¹⁹ prepared previously in our synthesis of irciniastatins as the TBS ether, followed by reductive removal of the pivalate group to furnish (+)-**18** (Scheme 2). A two-step oxidation sequence yielded the desired acid (–)-**12** in 70% yield for the two steps.

Construction of the tetrahydropyran core of the union partner **15** was envisioned via a cyclization tactic, similar to what was developed in our syntheses of (+)-irciniastatin A (**1**) and (–)-irciniastatin B (**2**): namely, a 6-*exo*-tet cyclization involving epoxide **22** (Scheme 3). To access epoxide **22**, we

Scheme 2. Synthesis of Acid Side Chain (–)-**12**



Scheme 3. Synthesis of Tetrahydropyran **15**



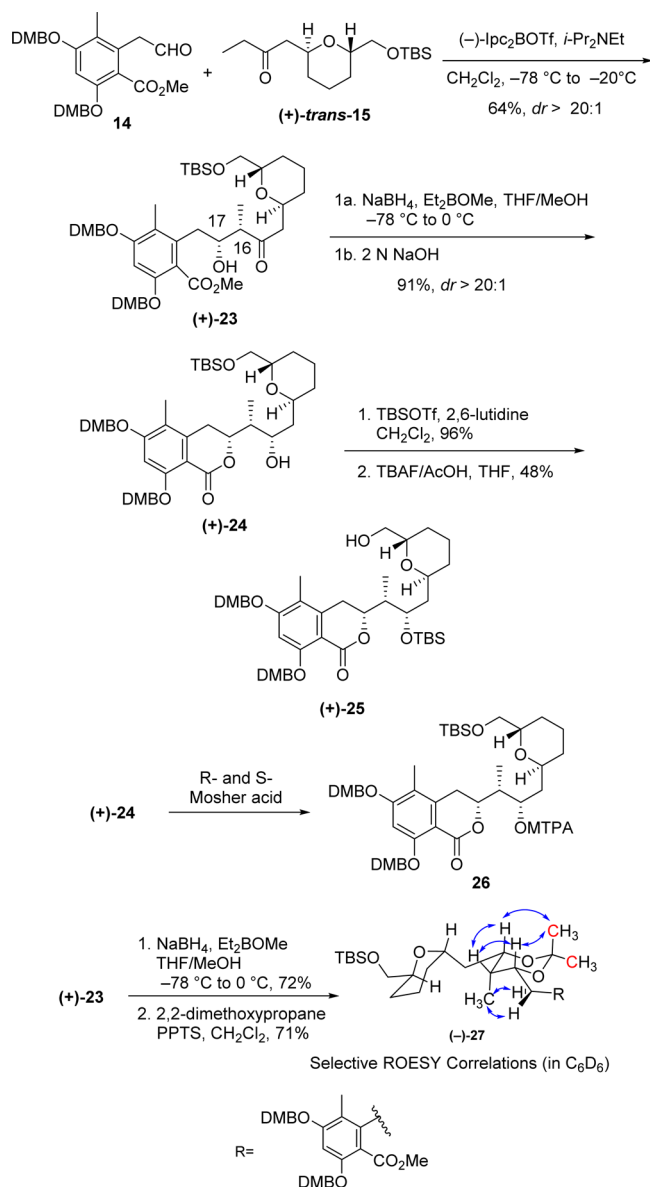
first constructed (+)-**20** from the commercially available unsaturated alcohol **19**, protected as a TBS ether, followed by epoxidation (*m*-CPBA) and a Jacobsen hydrolytic kinetic resolution (HKR).^{20–22} The TBS ether was then removed and the resulting alcohol subjected to modified Ley oxidation conditions²³ to furnish aldehyde (+)-**21**. We next set out to unite 2-butanone with aldehyde (+)-**21** via a base-mediated aldol reaction to arrive at alcohol **22**. Not surprisingly, a 1:1 mixture of diastereomers was observed, which proved separable via chromatography at a later step (vide infra).

For the proposed cyclization step, alcohol **22** was treated with a catalytic amount of camphorsulfonic acid (CSA), which furnished exclusively the tetrahydropyran ring via what we envision to be a 6-*exo*-tet pathway. Although both 6-*exo*-tet and 7-*endo*-tet pathways are feasible,^{24,25} we reason that the 6-*exo*-tet pathway dominates due to a combination of a favored six-membered-ring transition state and the enhanced stabilization of partial positive charge on the internal carbon over the terminal carbon of the epoxide. Protection of the resulting primary alcohol then permitted chromatographic separation of the *trans* and *cis* isomers of **15**, each available in 36% yield for the two steps. Stereochemical assignments of the diastereomers were established via 2D NMR analysis (NOESY; see Supporting Information) (Scheme 3). We note that, although construction of alcohol **22** was not stereoselective, we have identified a rapid and economical route to (+)-*trans*-**15** and

(-)-*cis*-**15**, thereby holding the potential for a variety of future diastereomeric irciniastatin analogues.

We turned next to the union of aldehyde **14**¹⁸ with 2,6-*trans*-tetrahydropyran (+)-**15** (Scheme 4). Preliminary experiments

Scheme 4. Fragment Union and Stereochemical Assignment



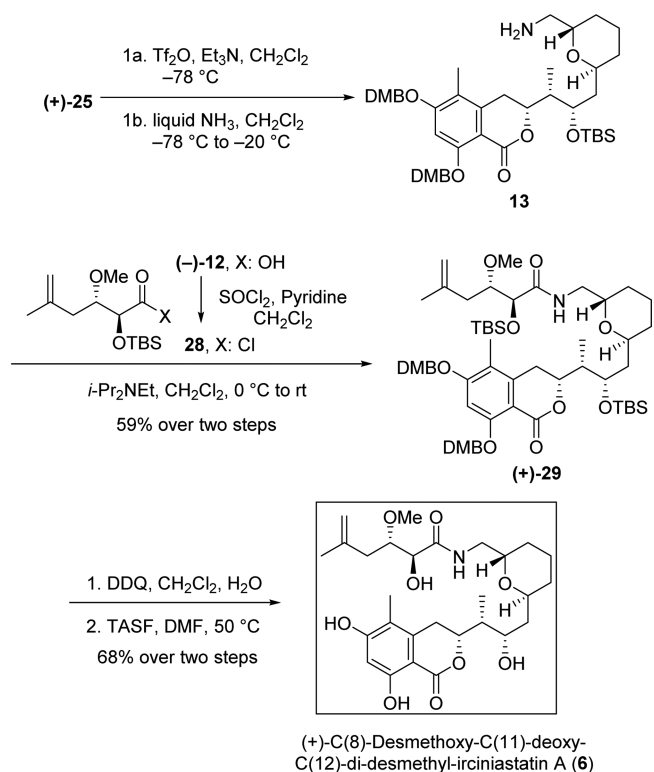
demonstrated that the Lewis acid Cl₂BPh, previously employed in our irciniastatin A and B syntheses,^{14,26} led to the undesirable loss of the TBS groups. More importantly, given the absence of the *gem*-dimethyl unit present in our previous irciniastatin syntheses, the substrate-controlled reaction proceeded with poor diastereoselectivity due to potential conformational changes in the transition state of the aldol union. However, upon screening several Lewis acids, we discovered that the Paterson boron reagent²⁷ (-)-Ipc₂BOTf furnished the desired aldol product (+)-**23** in 64% isolated yield, with both excellent diastereoselectivity (dr > 20:1) and enantioselectivity (vide infra) under the reagent-controlled conditions. It is noteworthy that the success of the reagent-controlled diastereoselective aldol reaction offers the potential to provide all four stereoisomers at C(16) and C(17) of (+)-**23**,

from which more irciniastatin congeners could be prepared for future SAR studies.

Reduction²⁸ of (+)-**23** under chelation-controlled conditions with concomitant lactonization upon treatment with aqueous sodium hydroxide solution (2 N) led to lactone (+)-**24** in 91% yield with excellent dr (>20:1). To confirm the stereochemistry of (+)-**24**, we performed a Mosher ester analysis²⁹ on (+)-**24**, as well as extensive NMR experiments on the derived acetonide (-)-**27** (¹H, ¹³C, HSQC, COSY, ROESY), thereby establishing both the desired *syn* 1,3-diol configuration on the basis of the diagnostic method pioneered by Evans³⁰ and Rychnovsky,³¹ as well as the requisite absolute configuration. The absolute stereochemical configuration of (+)-**24** was further supported by matching the CD spectrum of (+)-**24** with late-stage intermediates employed in our earlier synthesis of (-)-irciniastatin B (**2**) (see the Supporting Information, Figure 1). Alcohol (+)-**24** was then protected as the TBS ether followed by selective removal of the primary TBS group by treatment with TBAF buffered with acetic acid to furnish primary alcohol (+)-**25**.

With advanced alcohol (+)-**25** in hand, introduction of the primary amine was now required to permit union with acid **12** (Scheme 5). Initial attempts employing either reductive

Scheme 5. Amide Coupling and Completion of (+)-C(8)-Desmethoxy-C(11)-deoxy-C(12)-didesmethylirciniastatin (**6**)



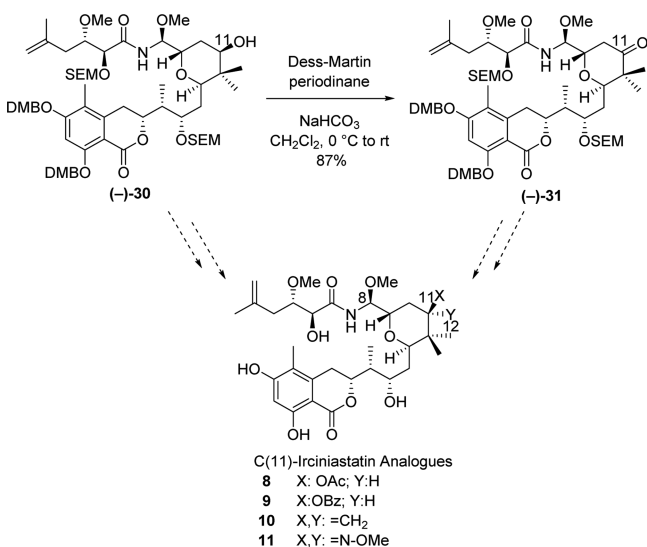
amination or Mitsunobu conditions,³² however, failed to provide the desired amine **13**. After considerable optimization, amination of (+)-**25** was eventually achieved by triflation of the primary alcohol followed by treatment with liquid ammonia, the product of which was carried forward to the amide coupling step without further purification. We note that, in previous total syntheses of (+)-irciniastatin A (**1**) and (-)-irciniastatin B (**2**), significant experimentation was required to effect the difficult

amide union, given the sterically hindered Teoc-protected *N,O*-aminal moiety.^{14–16,18} As anticipated, amide formation employing primary amine **13** now proceeded in a more straightforward manner; reaction of **13** and acid chloride **28**, the latter derived in situ from acid (–)-**12** via treatment with SOCl_2 , led to (+)-**29** in a combined yield of 59%. A two-stage deprotection sequence, employing DDQ, followed by treatment with TASF completed the synthesis of (+)-*C*(8)-desmethoxy-*C*(11)-deoxy-*C*(12)-didesmethylirciniastatin (**6**).

In summary, this convergent strategy now permits access to an irciniastatin analogue (**6**), absent three structural features in comparison to the natural products. The advantages of this synthetic venture include facile union of advanced intermediates and the potential to access multiple diastereomeric intermediates that hold the promise for future stereochemically diverse irciniastatin analogues.

Synthesis of *C*(11)-Irciniastatin Analogues 7–11. *epi-C*(11)-Irciniastatin A (**7**), as described in our recent report on total synthesis of (–)-irciniastatin B (**2**),¹⁹ was readily available via the direct reduction of (–)-irciniastatin B (**2**). Construction of other *C*(11)-irciniastatin analogues (**8–11**) could be accessed by manipulating late-stage synthetic irciniastatin A and B intermediates. Critical to the success of the latter venture was the availability of alcohol (–)-**30** (Scheme 6), which could

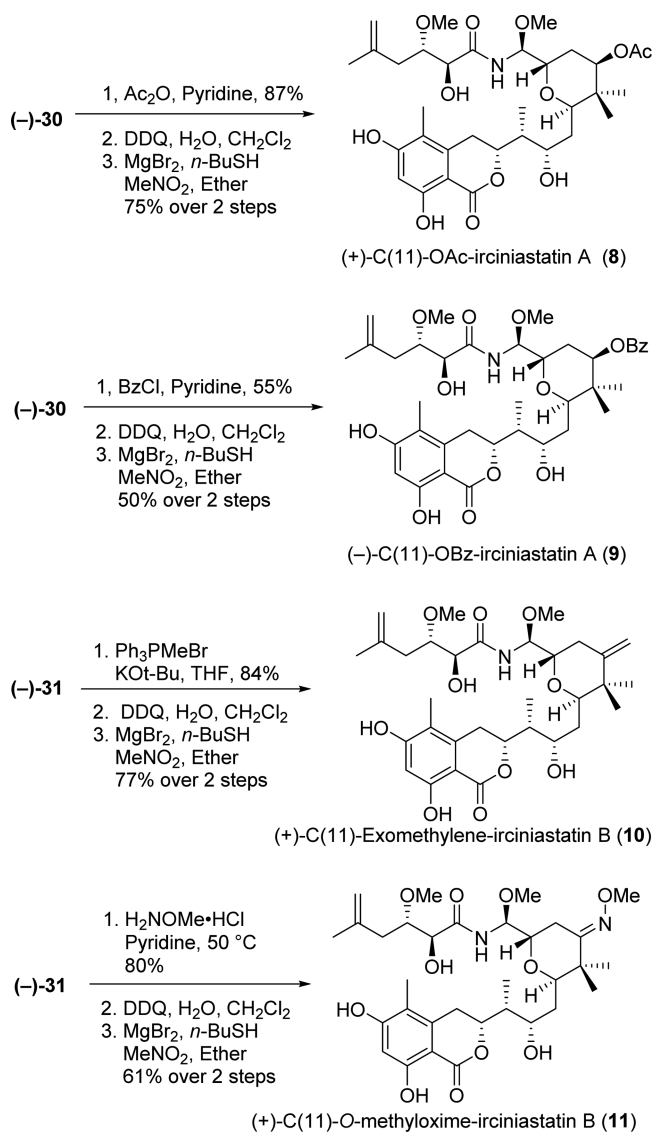
Scheme 6. Synthetic Strategy to *C*(11)-Irciniastatin Analogues 8–11



be readily oxidized chemoselectively to ketone (–)-**31** and then differentially functionalized to generate a small collection of analogues (Scheme 6). It is worth noting that selective modification at the *C*(11) position of **30** and **31** is hampered by the presence of the neighboring *gem*-dimethyl group, as well as the overall instabilities of the molecules owing to the presence of the *N,O*-aminal, which limited the number of possible functional group manipulations that could be employed to generate analogues.

We reasoned that the biological activity of analogues lacking the hydroxyl functionality at *C*(11) would be affected by lowering the polarity (i.e., the hydrogen-bond donating ability) of the substituents. Alcohol (–)-**30** (Scheme 7) was therefore treated with acetyl chloride to furnish the corresponding acetate in 87% yield. Subsequent global deprotection resulted in (–)-*C*(11)-OAc-irciniastatin A (**8**) in 75% yield for the two

Scheme 7. Construction of *C*(11)-Irciniastatin Analogues 8–11



steps. The larger derivative possessing a benzoate group at *C*(11) was synthesized in a similar fashion to provide (+)-*C*(11)-OBz-irciniastatin A (**9**) to probe the spatial requirements of the biological target at this position.

Next, we constructed the *C*(11)-irciniastatin B methylene and *O*-methyloxime congeners **10** and **11** via chemical manipulation of ketone (–)-**31**. We reasoned that an *exo*-methylene moiety at *C*(11) would not only provide a structural, though not electronic, bioisostere of the native ketone but also would increase the hydrophobicity of the molecule. To this end, Wittig methenylation³³ of ketone (–)-**31** followed by global deprotection provided (+)-*C*(11)-*exo*-methyleneirciniastatin B (**10**) (Scheme 7). We also envisioned that an *O*-methyloxime moiety at *C*(11) might be a suitable, extended bioisostere of the ketone.³⁴ In this case, although the electronic properties at *C*(11) might be similar to those of the ketone, the (+)-*C*(11)-*O*-methyloxime analogue **11** would now possess two potential hydrogen bond acceptor sites. Construction of **11** was readily achieved via reaction of *O*-methylhydroxylamine hydrochloride with ketone (–)-**31**, followed by global deprotection.

Biological Evaluation of the Irciniastatin Analogues.

Biological evaluation of the synthetic analogues was achieved by cell viability assays³⁵ against proliferative cell lines including A2058 (melanoma), H522-T1 (nonsmall cell lung cancer), and/or HCT-116 (colon cancer) (Tables 1 and 2). In addition,

Table 1. Antiproliferative IC₅₀ (nM) Values for (+)-Irciniastatin A (1) and (+)-C(8)-Desmethoxy-C(11)-deoxy-C(12)-didesmethylirciniastatin (6) against HCT-116 Cells

entry	compound	IC ₅₀ (HCT-116) (nM)
1	(+)-irciniastatin A (1)	0.2
2	(+)-C(8)-desmethoxy-C(11)-deoxy-C(12)-didesmethylirciniastatin (6)	160

we compared the resultant IC₅₀ value with the cytotoxicity data of analogues against quiescent IMR-90 immortalized human fibroblasts to measure selectivity, defined by the ratio IC₅₀(IMR-90):IC₅₀(tumor cell line). Analogues with high selectivity values would be viewed to have greater potential as a therapeutic drug lead.

We discovered that, even without the substituents found in the native pyran core of the irciniastatins, analogue 6 remarkably retained significant antiproliferative properties at the nanomolar level (IC₅₀ = 160 nM), albeit with an about 800-fold decrease in activity in comparison to (+)-irciniastatin A (1) in the same experiment (Table 1). Previous studies had revealed that removing C(8)-*N,O*-aminal decreased the cytotoxicity by around 10-fold in comparison to 1.^{5,6} Also of interest, Floreancig and co-workers have suggested that the *gem*-dimethyl group plays a key role in permitting the molecule to adopt an appropriate conformation for protein target binding, although an appropriate analogue to test this hypothesis had not been synthesized and evaluated.⁶ Pleasingly, our findings suggest that the combined removal of the C(12) *gem*-dimethyl group, the hydroxyl at C(11), and the methoxy group at C(8) leads to the diminutive analogue 6 that retains tumor cell growth inhibition in the nanomolar range, suggesting that although the *gem*-dimethyl group may well influence the activity of the irciniastatins, its presence is not necessary for significant tumor cell growth inhibition. On the basis of these initial results, the simple tetrahydropyran scaffold is an attractive structural motif to provide facile synthetic access to active irciniastatin analogues for future SAR studies.

Biological evaluation of irciniastatin analogues 7–11 further reveals that the C(11) position is highly tolerant of a variety of nonpolar functional groups with either the *R* or *S* configuration (Table 2). For example, *epi*-C(11)-irciniastatin A (7) displays

an activity profile similar to that of irciniastatin A (1). Functionalization of the C(11)-hydroxyl group to an acetyl or benzoyl group led to retention of cytotoxicity at the subnanomolar level, with benzoate 9 displaying about a 5-fold decrease in activity in comparison to both the acetate 8 and (+)-irciniastatin A (1). Interestingly, the C(11)-irciniastatin B analogues 10 and 11 with similar geometries (i.e., *exo*-methylene) and electronic properties (i.e., *O*-methyl oxime) at C(11) as in the natural product revealed significant cell growth inhibition properties. Although increasing the hydrophobicity of C(11), vis-à-vis the C(11) methylene congener, did not lead to an improvement in the cytotoxicity, the excellent functional group tolerance at C(11) holds the promise for ready conjugation at this site with biological probes to explore the mode of action of the irciniastatins.

It is important to note that in the assay data reported in Table 2, a change in the automation protocol for cell preparation and sample handling occurred from the earlier assay (Table 1). In particular, the control compound (+)-irciniastatin A (1) was less potent against the HCT-116 cell line (IC₅₀ = 4 nM vs IC₅₀ = 0.2 nM). We are however confident that the relative potencies in each assay (Tables 1 and 2) are reliable.

Finally, from the selectivity panel screen in Table 2, we note that (–)-irciniastatin B (2) appears to be more selective than (+)-irciniastatin A (1) across the three tested cell lines. Consistent with this result, the irciniastatin B C(11)-methylene and *O*-methyloxime analogues (10 and 11) possessed higher selectivities for inhibiting A2085 (melanoma) cell growth over nonproliferating IMR-90, in comparison both to (+)-irciniastatin A (1) and the two related acetate and benzoate congeners (8 and 9). The higher selectivity values suggest that the irciniastatin B scaffold, wherein the C(11) position resides in an oxidized state, holds greater potential as a therapeutic lead in comparison to (+)-irciniastatin A (1) and the corresponding C(11) analogues.

SUMMARY

In summary, we have exploited our earlier developed convergent synthetic strategy to the irciniastatins to access a series of novel, active totally synthetic analogues of these intriguing natural products, including the identification of a simplified central scaffold that permits retention of biological activity. As a further enrichment of the synthetic strategies toward the irciniastatins and their analogues, the synthesis of C(11)-deoxy-C(12)-didesmethylirciniastatin 6 features (A) rapid and economic access to both the *trans*- and *cis*-tetrahydropyran cores via a 6-*exo*-tet epoxide cyclization, (B) application of a diastereoselective aldol reaction mediated by a

Table 2. Proliferative Cell Growth Inhibition Assay and IMR-90 Cytotoxicity Assay IC₅₀ Values (nM) for (+)-Irciniastatin A (1), (–)-Irciniastatin B, and C(11)-Irciniastatin Analogues 7–11

entry	compound	IC ₅₀ (cell line) (nM) (IC ₅₀ (IMR-90):IC ₅₀ (cell line))			
		A2058	H522-T1	HCT-116	IMR-90
1	(+)-irciniastatin A (1)	0.4 (68)	1 (27)	4 (7)	27
2	(–)-irciniastatin B (2)	0.5 (114)	0.8 (71)	3 (19)	57
3	<i>epi</i> -C(11)-irciniastatin A (7)	0.4 (85)	0.9 (38)	3 (11)	34
4	(+)-C(11)-OAc-irciniastatin A (8)	0.4 (68)	0.7 (39)	2 (14)	27
5	(–)-C(11)-OBz-irciniastatin A (9)	2.7 (30)	5.4 (15)	NA	81
6	(+)-C(11)- <i>exo</i> -methylene irciniastatin B (10)	0.7 (68)	1.6 (31)	1 (49)	49
7	(+)-C(11)- <i>O</i> -methyloxime-irciniastatin B (11)	0.5 (92)	0.8 (58)	NA	46

chiral boron Lewis acid to provide potentially all four stereoisomers, and (C) direct access to primary amine (**13**) via triflation and ammonia substitution to permit installation of various side chains. Pleasingly, in cell viability assays, analogue **6** retained antiproliferative activity in the nanomolar range, demonstrating that the C(8)-*N,O*-aminal, C(11)-hydroxyl, and C(12)-*gem*-dimethyl groups are not essential for biological activity. In addition, manipulation of the C(11) position, employing late-stage intermediates derived from our total synthesis of the irciniastatins, permitted access to a series of C(11)-irciniastatin analogues **7–11**. The derived congeners display significant biological profiles, demonstrating high functional group tolerance at C(11). Of importance, the higher selectivity level was consistently observed with irciniastatin B derivatives oxidized at C(11), indicating that the C(11) oxidized tetrahydropyran core may serve as a better scaffold for lead development.

EXPERIMENTAL SECTION

Materials and Methods. Reactions were performed in either flame- or oven-dried glassware under a nitrogen atmosphere unless noted otherwise. Anhydrous diethyl ether (Et₂O), tetrahydrofuran (THF), dichloromethane (CH₂Cl₂), and toluene were obtained from a solvent purification system. Triethylamine, diisopropylethylamine, and pyridine were freshly distilled from calcium hydride under a nitrogen atmosphere. All chemicals were purchased from commercial vendors, unless otherwise referenced. Reactions were magnetically stirred unless stated otherwise and monitored by thin-layer chromatography (TLC) with 0.25 mm precoated silica gel plates. Silica gel chromatography was performed utilizing ACS grade solvents and silica gel. Preparatory TLC was performed using 500 μm precoated silica gel plates and ACS grade solvents. Medium pressure liquid chromatography was conducted by using a medium-pressure pump equipped with a high-pressure glass column (350 mm × 35 mm or 350 mm × 10 mm) packed with silica gel (standard grade, porosity 60 Å, particle size 32–63 μm).

Infrared spectra were obtained using a FT/IR plus spectrometer. Optical rotations were obtained using a polarimeter at 589 nm. CD spectra were obtained using a circular dichroism spectrometer in a 1 mm quartz cell. ¹H NMR spectra (500 MHz field strength) and ¹³C NMR spectra (125 MHz field strength) were obtained on a 500 MHz spectrometer or a cryomagnat (500 MHz/52 mm) with a 5 mm dual cryoprobe. Chemical shifts are reported relative to chloroform (δ 7.26), benzene (δ 7.16), or methanol (δ 3.31) for ¹H NMR spectra and chloroform (δ 77.16), benzene (δ 128.06), or methanol (δ 49.15) for ¹³C spectra. The following abbreviations are used to describe multiplicities in ¹H NMR spectra: s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), t (triplet), td (triplet of doublets), m (multiplet), q (quartet), and app (apparent). High-resolution mass spectra (HRMS) were measured on a LC-TOF mass spectrometer.

(2*R*,3*S*)-2-((*tert*-Butyldimethylsilyloxy)-3-methoxy-5-methylhex-5-en-1-yl) pivalate ((+)-18**).** To a solution of (2*R*,3*S*)-2-hydroxy-3-methoxy-5-methylhex-5-en-1-yl pivalate (+)-**17**¹⁹ (840 mg, 3.44 mmol) dissolved in CH₂Cl₂ (10 mL) at 0 °C were added 2,6-lutidine (0.78 mL, 6.71 mmol, 1.95 equiv) and TBSOTf (0.84 mL, 3.65 mmol, 1.06 equiv). After the reaction mixture was stirred for 1.5 h at room temperature, it was quenched with a saturated aqueous solution of NaHCO₃ (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, and concentrated in vacuo to yield crude (2*R*,3*S*)-2-((*tert*-butyldimethylsilyloxy)-3-methoxy-5-methylhex-5-en-1-yl) pivalate (+)-**18** (1.18 g) as a faint yellow oil: [α]_D²⁰ = +11.8 (c 3.5, CHCl₃); IR (neat) 3076, 2957, 2930, 2857, 1733, 1480, 1472, 1462, 1283, 1255, 1159, 1115, 836, 777 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.82 (br s, 1H), 4.79 (br s, 1H), 4.18 (dd, *J* = 11.5, 4.5 Hz, 1H), 4.05 (dd, *J* = 11.5, 5.3 Hz, 1H), 3.90 (ddd, *J* = 5.3, 4.5, 3.6 Hz, 1H), 3.40 (s, 3H), 3.43–3.35 (m, 1H), 2.30–2.16 (m, 2H), 1.78 (s, 3H), 1.22 (s, 9H),

0.90 (s, 9H), 0.09 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 178.5, 143.1, 112.6, 81.4, 72.2, 65.7, 58.7, 39.3, 38.9, 27.4, 26.6, 25.9, 22.9, 18.1, -4.6; HRMS (ES+) *m/z* 381.2442 [(*M* + Na)⁺; calcd for C₁₉H₃₈O₄SiNa 381.2437].

To a solution of (+)-**18** (1.18 g, azeotroped with benzene three times) in CH₂Cl₂ (30 mL) at -78 °C was added DIBAL-H (10.3 mL, 1 M in toluene, 3.13 equiv). The reaction mixture was stirred for 30 min at -78 °C and then quenched by addition of MeOH (5 mL). After the mixture was warmed to room temperature, a saturated aqueous solution of Rochelle's salt (20 mL) was added. The biphasic mixture was stirred for 1 h at room temperature to allow the organic layer to clear. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄, and concentrated in vacuo. The crude mixture was purified by column chromatography on SiO₂ (15% EtOAc/hexanes) to provide (+)-**18** (860 mg, 3.13 mmol, 91% yield over two steps) as a colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 4.81 (br s, 1H), 4.79 (br s, 1H), 3.74–3.60 (m, 3H), 3.43 (s, 3H), 3.41 (dd, *J* = 8.6, 4.6 Hz, 1H), 2.27 (dd, *J* = 14.3, 4.5 Hz, 1H), 2.22–2.14 (m, 2H), 1.78 (s, 3H), 0.9 (s, 9H), 0.09 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 143.0, 112.9, 81.9, 74.4, 64.0, 59.2, 40.3, 26.0, 22.9, 18.2, -4.4, -4.5. Extra analytical data are available in previously reported literature.³⁶

(2*S*,3*S*)-2-((*tert*-Butyldimethylsilyloxy)-3-methoxy-5-methylhex-5-enoic Acid ((-)-12**).** To a solution of (+)-**18** (220 mg, 0.80 mmol) in CH₂Cl₂ (70 mL) was added NaHCO₃ (150 mg, 1.79 mmol, 2.23 equiv) and Dess–Martin periodinane (374 mg, 0.88 mmol, 1.10 equiv). The reaction mixture was stirred for 30 min and quenched with a saturated aqueous solution of NaHCO₃ (30 mL). The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic layers were washed successively with a saturated aqueous solution of Na₂S₂O₃ (30 mL), a saturated aqueous solution of NaHCO₃ (30 mL), and brine (40 mL). The organic layer was then dried over MgSO₄ and concentrated in vacuo to afford crude (2*S*,3*S*)-2-((*tert*-butyldimethylsilyloxy)-3-methoxy-5-methylhex-5-enal ((-)-**12**; 220 mg) as a colorless oil: [α]_D²⁰ = -22.0 (c 0.2, CHCl₃); IR (neat) 2954, 2929, 2857, 1733, 1472, 1463, 1253, 1145, 1108, 898, 838, 779 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.59 (d, *J* = 1.1 Hz, 1H), 4.83 (br s, 2H), 4.14 (dd, *J* = 2.4, 1.1 Hz, 1H), 3.61 (dt, *J* = 7.0, 2.4 Hz, 1H), 3.40 (s, 3H), 2.31 (dd, *J* = 3.8, 7.2 Hz, 1H), 2.25 (dd, *J* = 13.7, 7.1 Hz, 1H), 1.68 (s, 3H), 0.94 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 203.7, 141.7, 114.5, 83.0, 78.6, 58.1, 38.6, 25.9, 22.7, 18.3, -4.7, -4.8. HRMS (ES+) *m/z* 295.1702 [(*M* + Na)⁺; calcd for C₁₄H₂₆O₃SiNa 295.1705].

The crude material (-)-**12** (220 mg) was dissolved in *t*-BuOH/H₂O (3/1, 20 mL) and cooled to 0 °C. To the reaction mixture were added NaH₂PO₄·2H₂O (235 mg, 1.51 mmol, 1.89 equiv), 2-methyl-2-butene (4.60 mL, 43.3 mmol, 54.1 equiv), and NaClO₂ (235 mg, 80 wt %, 2.08 mmol, 2.60 equiv). The reaction mixture was stirred for 10 min and then poured into H₂O (20 mL), diluted with EtOAc (40 mL), and acidified with 10% citric acid to pH 4. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, and concentrated in vacuo. The crude mixture was purified by column chromatography on SiO₂ (25% EtOAc/hexanes) to provide acid (-)-**12** (160 mg, 0.555 mmol, 70% over two steps) as a colorless oil: [α]_D²⁰ = -4.8 (c 0.6, CHCl₃); IR (neat) 2929, 2852, 1727, 1465, 1357, 1253, 1154, 838, 777 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.86 (br s, 1H), 4.82 (br s, 1H), 4.44 (d, *J* = 2.1 Hz, 1H), 3.66 (ddd, *J* = 7.9, 5.6, 2.1 Hz, 1H), 3.44 (s, 3H), 2.33 (dd, *J* = 14.3, 8.1 Hz, 1H), 2.19 (dd, *J* = 14.3, 5.5 Hz, 1H), 1.77 (s, 3H), 0.96 (s, 9H), 0.19 (s, 3H), 0.15 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.9, 141.7, 113.7, 81.9, 73.8, 58.5, 38.0, 25.9, 22.8, 18.3, -4.5, -5.4. HRMS (ES+) *m/z* 311.1643 [(*M* + Na)⁺; calcd for C₁₄H₂₆O₄SiNa 311.1655].

***tert*-Butyldimethyl(4-(oxiran-2-yl)butoxy)silane ((±)-**20**).** To a solution of 5-hexenol **19** (21.0 g, 0.210 mol) in THF (350 mL) were added imidazole (15.9 g, 0.233 mol, 1.11 equiv) and TBSCl (33.4 g, 0.222 mol, 1.06 equiv). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with H₂O (80 mL) and extracted with EtOAc (3 × 150 mL). The combined

organic layers were dried over MgSO_4 and concentrated in vacuo to afford the crude *tert*-butyl(hex-5-en-1-yloxy)dimethylsilane (45.0 g).

The crude material (45.0 g) was then dissolved in CH_2Cl_2 (500 mL), cooled to 0 °C, and treated with *m*-CPBA (77% purity, 54.9 g, 0.245 mol, 1.17 equiv) in three equal portions over a period of 30 min. The reaction mixture was warmed to room temperature and was stirred overnight. The reaction vessel was cooled to 0 °C and the mixture filtered through a pad of Celite. The filtrate was poured into a mixture of a saturated aqueous solution of NaHCO_3 (200 mL) and a saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (200 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic layers were dried over MgSO_4 and concentrated in vacuo to afford (\pm)-**20** (45.0 g) as a colorless oil.

(R)-tert-Butyldimethyl(4-(oxiran-2-yl)butoxy)silane ((+)-20). (R,R)-(-)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (1.20 g, 1.99 mmol, 0.01 equiv) was activated by stirring with AcOH (0.47 mL, 8.21 mmol, 0.04 equiv) in an open flask for 30 min. The crude epoxide (\pm)-**20** (45.0 g) and THF (2.6 mL) was added to the catalyst mixture. Then reaction mixture was cooled to 0 °C, and H_2O (1.96 mL, 109 mmol, 0.56 equiv) was introduced. The reaction mixture was warmed to room temperature. After 8 h, the crude mixture was purified via distillation (65 °C, 0.025 Torr) to provide (+)-**20** as a colorless oil (20.0 g, 87.0 mmol, 41% yield over three steps). An enantiomeric excess (ee) of >96% was determined by ^{19}F NMR of the corresponding R and S Mosher esters on secondary alcohol/azide derived from reacting (+)-**20** with sodium azide.²⁰ All spectroscopic analysis matched the reported literature except for optical rotation, while the optical rotation of the *S* enantiomer was reported to be -4.4 (c 1.00, CHCl_3):²² $[\alpha]_{\text{D}}^{20} = +4.8$ (c 3.2, CHCl_3); IR (neat) 2929, 2857, 1472, 1255, 1100, 836, 775 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.62 (t, $J = 6.1$ Hz, 2H), 2.90 (m, 1H), 2.74 (dd, $J = 5.0, 4.0$ Hz, 1H), 2.46 (dd, $J = 5.1, 2.7$ Hz, 1H), 1.63–1.43 (m, 6H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 63.1, 52.4, 47.2, 32.7, 32.4, 26.1, 22.5, 18.5, -5.2 ; HRMS (ES+) m/z 231.1747, [(M + H)⁺; calcd for $\text{C}_{16}\text{H}_{23}\text{O}$ 231.1749].

(R)-4-(Oxiran-2-yl)butan-1-ol ((+)-S3). To a solution of (+)-**20** (3.0 g, 13.0 mmol) in THF (60 mL) was added TBAF (20 mL 1 M in THF, 20.0 mmol, 1.54 equiv) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h before quenching with a saturated aqueous solution of NaHCO_3 (20 mL). The mixture was extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed with brine (30 mL), dried over MgSO_4 , and concentrated in vacuo. The crude mixture was purified by column chromatography on SiO_2 (75% to 100% diethyl ether/hexanes) to provide (+)-**S3** (1.4 g, 12.0 mmol, 92% yield) as a colorless oil: $[\alpha]_{\text{D}}^{20} = +13.0$ (c 4.7, CHCl_3); IR (neat) 3399 (br), 2937, 2864, 1411, 1057, 880 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.65 (m, 2H), 2.91 (m, 1H), 2.74 (dd, $J = 5.0, 4.0$ Hz, 1H), 2.47 (dd, $J = 5.0, 2.7$ Hz, 1H), 1.69–1.46 (m, 6H), 0.09 (t, $J = 5.1$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 62.8, 52.4, 47.2, 32.5, 32.3, 22.4; HRMS (ES+) m/z 117.0923 [(M + H)⁺; calcd for $\text{C}_6\text{H}_{13}\text{O}_2$ 117.0916].

(R)-4-(oxiran-2-yl)butanal ((+)-21). A suspension of NMO/TPAP in CH_2Cl_2 was made by mixing NMO (378 mg, 3.23 mmol, 1.50 equiv), 4 Å molecular sieves (1.1 g), and TPAP (39 mg, 0.11 mmol, 0.05 equiv) in CH_2Cl_2 (4 mL). A solution of (+)-**S3** (250 mg, 2.15 mmol) in CH_2Cl_2 (1 mL) was added to the NMO/TPAP suspension over 20 min via syringe pump. After addition was complete, the reaction mixture was stirred for 2 h and the mixture was diluted with pentanes (4 mL). Without concentration, the entire reaction mixture was directly purified via flash chromatography (50% diethyl ether/pentanes) to provide (+)-**21** as a colorless liquid (140 mg, 1.23 mmol, 57% yield). Aldehyde (+)-**21** was found to be volatile and unstable and was used in the next step as soon as possible: $[\alpha]_{\text{D}}^{20} = +11.5$ (c 2.5, CHCl_3); IR (neat) 3421 (br), 2925, 2854, 2726, 1723, 1456, 1260, 1102, 664 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.78 (m, 1H), 2.91 (m, 1H), 2.75 (dd, $J = 4.9, 4.0$ Hz, 1H), 2.60–2.48 (m, 2H), 2.47 (dd, $J = 5.0, 2.7$ Hz, 1H), 1.89–1.72 (m, 2H), 1.74–1.61 (m, 1H), 1.54–1.46 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 202.1, 52.0, 47.0, 43.5, 31.8, 18.7; HRMS (ES+) m/z 115.0739 [(M + H)⁺; calcd for $\text{C}_6\text{H}_{11}\text{O}_2$ 115.0759].

5-Hydroxy-8-((R)-oxiran-2-yl)octan-3-one (22). To a solution of 2-butanone (1.34 mL, 15 mmol, 1.70 equiv) in THF (8 mL) was added dropwise a freshly prepared solution of LDA (15 mmol, 1.70 equiv) in THF (72 mL) at -78 °C. The reaction mixture was stirred for 30 min at -78 °C. A solution of aldehyde (+)-**21** (1.0 g, 8.8 mmol) in THF (10 mL) was then added dropwise at -78 °C. The reaction mixture was stirred for another 30 min before being quenched with pH 7 phosphate buffer (20 mL). The mixture was extracted with EtOAc (3 × 70 mL), and the combined organic layers were washed with brine (40 mL), dried over MgSO_4 , and concentrated in vacuo. The crude mixture was purified by column chromatography on SiO_2 (25% to 50% EtOAc/hexanes) to provide **22** (810 mg, 4.3 mmol, 49% yield, dr = 1:1) as a colorless oil and an inseparable mixture of diastereomers.

1-(6-(((tert-Butyldimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)butan-2-one (15). To a solution of **22** (dr = 1:1) (1.34 g, 7.2 mmol) in CH_2Cl_2 (134 mL) was added CSA (332 mg, 1.43 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature for 2 h and was quenched by addition of a saturated aqueous solution of NaHCO_3 (40 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (40 mL), dried over MgSO_4 , and concentrated in vacuo to afford a mixture of *trans*- and *cis*-pyran isomers. To a solution of the crude pyran mixture in CH_2Cl_2 (70 mL) were added 2,6-lutidine (3.25 mL, 28.2 mmol, 3.9 equiv) and TBSOTf (2.0 mL, 8.7 mmol, 1.2 equiv) at 0 °C. The reaction mixture was stirred for 30 min, quenched with a saturated aqueous solution of NaHCO_3 (50 mL), and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO_4 , and concentrated in vacuo. The two diastereomers were separated by MPLC on SiO_2 (8% EtOAc/hexanes) to provide (+)-*trans*-**15** (778 mg, 2.6 mmol, 36% yield over two steps) and (–)-*cis*-**15** (780 mg, 2.6 mmol, 36% yield over two steps) as colorless oils. The stereochemical configuration was determined by NOE NMR analysis on each isomer. Pyran (+)-*trans*-**15**: $[\alpha]_{\text{D}}^{20} = +26.8$ (c 4.5, CHCl_3); IR (neat) 2932, 2856, 1715, 1256, 1102, 836, 776 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) 4.25 (m, 1H), 3.73 (m, 1H), 3.66 (dd, $J = 10.1, 5.5$ Hz, 1H), 3.60 (dd, $J = 10.1, 6.6$ Hz, 1H), 2.66 (dd, $J = 15.5, 8.0$ Hz, 1H), 2.49 (dq, $J = 7.3, 1.7$ Hz, 2H), 2.42 (dd, $J = 15.1, 5.6$ Hz, 1H), 1.74–1.59 (m, 4H), 1.50–1.40 (m, 1H) 1.40–1.31 (m, 1H), 1.04 (t, $J = 7.3$ Hz, 3H), 0.89 (s, 9H), 0.049 (s, 3H), 0.046 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 210.1, 72.2, 68.99, 64.7, 46.6, 36.8, 30.1, 26.5, 26.1, 18.5, 18.4, 7.7, -5.2 , -5.3 ; HRMS (ES+) m/z 323.2018 [(M + Na)⁺; calcd for $\text{C}_{16}\text{H}_{32}\text{O}_3\text{NaSi}$ 323.2018]. Pyran (–)-*cis*-**15**: $[\alpha]_{\text{D}}^{20} = -16.9$ (c 3.8, CHCl_3); IR (neat) 2930, 2857, 1716, 1254, 1078, 836, 777 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.78 (m, 1H) 3.60 (dd, $J = 10.3, 5.5$ Hz, 1H), 3.45 (dd, $J = 10.3, 5.5$ Hz, 1H), 3.40 (m, 1H), 2.65 (dd, $J = 15.3, 7.7$ Hz, 1H), 2.53–2.43 (m, 1H), 2.39 (dd, $J = 15.3, 5.1$ Hz, 1H), 1.88–1.81 (m, 1H), 1.67–1.46 (m, 4H), 1.28–1.08 (m, 2H), 1.03 (t, $J = 7.3$ Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 210.3, 78.6, 74.4, 66.9, 49.4, 37.1, 31.8, 27.9, 26.1, 23.2, 18.5, 7.7, -5.1 , -5.2 ; HRMS (ES+) m/z 301.2198 [(M + H)⁺; calcd for $\text{C}_{16}\text{H}_{33}\text{O}_3\text{Si}$ 301.2199].

Ketone (+)-23. Freshly prepared (–)-Ipc₂BOTf²⁷ (0.57 mL, ca. 0.88 M in hexanes, 1.2 equiv) was diluted with CH_2Cl_2 (0.8 mL). To the resulting solution was added *i*-Pr₂NEt (0.15 mL, 0.858 mmol, 2.0 equiv) at -78 °C. The reaction mixture was stirred for 15 min, and then a solution of (+)-*trans*-**15** (130 mg, 0.433 mmol) in CH_2Cl_2 (0.8 mL) was added. The reaction mixture was stirred at -78 °C for 1 h and then warmed to -20 °C and stirred for an additional 2 h. The boron-enolate solution was then cooled to -78 °C, and a solution of aldehyde **14** (295 mg, 0.562 mmol, 1.3 equiv) in CH_2Cl_2 (0.8 mL) was added. The reaction mixture was stirred for 2 h at -78 °C before it was warmed to -20 °C and stirred for an additional 16 h. The reaction was quenched with pH 7 phosphate buffer (3 mL), warmed to room temperature, and diluted with diethyl ether (3 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 3 mL). The combined organic layers were concentrated to remove the majority of the solvent in vacuo. The crude boronic ester was dissolved in MeOH/THF (5 mL, 1/1), and to the mixture was added pH 7 phosphate buffer (2 mL) and cold H_2O_2 (50% w/v, 2 mL) dropwise at

0 °C. The reaction mixture was warmed to room temperature and was stirred for 90 min. The reaction mixture was extracted by EtOAc (3 × 10 mL), and the combined organic layers were washed with a saturated aqueous solution of NaHCO₃ (20 mL) and brine (30 mL), dried over MgSO₄, and concentrated in vacuo. The crude mixture was purified by column chromatography on SiO₂ (40% EtOAc/hexanes) to provide (+)-23 (230 mg, 0.279 mmol, 64%, dr >20:1) as a white amorphous solid: $[\alpha]_D^{20} = +23.8$ (c 3.5, CHCl₃); IR (neat) 3437 (br), 2957, 3000, 2934, 2856, 1707, 1592, 1517, 1463, 1265, 1159, 1099, 1028, 837, 762 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.93 (m, 3H), 6.91–6.80 (m, 3H), 6.49 (s, 1H), 5.00 (d_{A,B}, J = 16.7 Hz, 1 H), 4.99 (d_{A,B}, J = 16.7 Hz, 1 H), 4.95 (s, 2H), 4.30–4.22 (m, 1H), 4.09–4.00 (m, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.75–3.69 (m, 1H), 3.68–3.57 (m, 3H), 2.92 (dd, J = 16.1, 7.1 Hz, 1H), 2.86 (dd, J = 14.2, 3.2 Hz, 1H), 2.65–2.55 (m, 2H), 2.18 (s, 3H), 1.75–1.62 (m, 4H), 1.49–1.40 (m, 1H), 1.40–1.34 (m, 1H), 1.20 (d, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 212.3, 170.7, 158.9, 155.0, 149.2, 149.1, 148.9, 148.8, 136.8, 129.33, 129.26, 119.8, 119.6, 119.0, 117.60, 111.1, 111.0, 110.6, 110.5, 97.4, 72.2, 71.7, 71.0, 70.4, 68.5, 64.5, 55.97, 55.94, 55.92, 55.90, 52.9, 52.6, 46.5, 35.6, 30.0, 26.4, 26.0, 18.4, 18.3, 11.6, 11.4, -5.2, -5.3; HRMS (ES+) *m/z* 847.4068 [(M + Na)⁺; calcd for C₄₅H₆₄O₁₂NaSi 847.4065].

Diol (+)-S4. To a solution of ketone (+)-23 (26 mg, 0.032 mmol) in THF/MeOH (0.53 mL, 3/1) at -78 °C was added Et₂BOMe (0.12 mL, 1 M in THF, 3.8 equiv). The reaction mixture was stirred for 30 min, followed by the addition of NaBH₄ (10 mg, 0.26 mmol, 8.1 equiv). The reaction mixture was stirred for 2 h at -78 °C and then warmed to 0 °C and stirred for an additional 2 h. The reaction mixture was then quenched by slow addition of pH 7 phosphate buffer/MeOH mixture (2 mL, 1/1 v/v) and H₂O₂ (0.5 mL, 30% aqueous solution). The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was diluted with EtOAc, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 4 mL), and the combined organic layers were washed with brine (10 mL), dried over MgSO₄, and concentrated in vacuo. The crude mixture was purified by column chromatography on SiO₂ (50% EtOAc/hexanes) to provide the diol (+)-S4 (19 mg, 23.0 μmol, 72% yield) as an off-white foam, which was dried to be a white amorphous solid: $[\alpha]_D^{20} = +20.3$ (c 0.7, CHCl₃); IR (neat) 3462 (br), 2930, 1724, 1591, 1516, 1463, 1264, 1159, 1028, 837, 763 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 7.02–6.99 (m, 1H), 6.86–6.81 (m, 3H), 6.58 (dd, J = 8.0, 5.3 Hz, 2H), 6.48 (s, 1H), 4.90 (d_{A,B}, J = 11.9 Hz, 1H), 4.87 (d_{A,B}, J = 11.9 Hz, 1H), 4.76 (br s, 2H), 4.54–4.49 (m, 1H), 4.38 (s, 1H), 4.08 (d, J = 2.4 Hz, 1H), 4.02 (d, J = 10.0 Hz, 1H), 3.77–3.67 (m, 1H), 3.68 (s, 3H), 3.62–3.57 (m, 1H), 3.55 (dd, J = 10.2, 8.0 Hz, 1H), 3.52 (s, 3H), 3.44 (s, 3H), 3.41 (s, 3H), 3.40 (s, 3H), 3.35–3.27 (m, 2H), 3.17 (dd, J = 13.6, 6.1 Hz, 1H), 2.55 (s, 3H), 2.03 (dt, J = 14.3, 10.5 Hz, 1H), 1.72–1.66 (m, 1H), 1.40–1.20 (m, 10H), 1.31 (d, J = 6.9 Hz, 3H), 1.09–0.97 (m, 2H), 0.95 (s, 9H), 0.85–0.78 (m, 1H), 0.04 (s, 3H), 0.03 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 170.5, 159.3, 155.7, 150.8, 150.7, 150.3, 150.2, 139.0, 130.4, 130.2, 120.4, 120.1, 120.0, 119.7, 112.4, 112.3, 112.0, 111.8, 97.8, 78.0, 77.0, 74.1, 71.8, 71.4, 71.0, 65.3, 56.0, 55.89, 55.87, 52.3, 43.1, 37.2, 37.1, 30.7, 30.6, 26.7, 26.4, 19.2, 18.8, 12.6, 7.0, -4.96, -5.01; HRMS (ES+) *m/z* 849.4199 [(M + Na)⁺; calcd for C₄₅H₆₆O₁₂NaSi 849.4221].

Acetal (-)-27. To a solution of diol (+)-S4 (8.0 mg, 9.7 μmol) in CH₂Cl₂ (150 μL) were added 2,2-dimethoxypropane (150 μL) and a catalytic amount of PPTS. The reaction mixture was stirred for 1 h at room temperature, quenched with a saturated aqueous solution of NaHCO₃ (3 mL), and extracted with CH₂Cl₂ (3 × 3 mL). The combined organic layers were washed with brine (5 mL), dried over MgSO₄, and concentrated in vacuo. The crude mixture was purified by column chromatography on SiO₂ (25% EtOAc/hexanes) to provide (-)-27 (6.0 mg, 6.9 μmol, 71% yield) as a white foam: $[\alpha]_D^{20} = -2.3$ (c 0.5, CHCl₃); IR (neat) 2932, 1724, 1592, 1517, 1462, 1264, 1159, 1029, 837 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 7.03 (d, J = 2.0 Hz, 1H), 6.89–6.82 (m, 3H), 6.59 (t, J = 8.0 Hz, 2H), 6.49 (s, 1H), 4.90 (s, 2H), 4.75 (s, 2H), 4.40 (dt, J = 8.1, 3.0 Hz, 1H), 4.12 (ddd, J = 7.8, 6.4, 2.1 Hz, 1H), 3.99–3.92 (m, 1H), 3.80–3.76 (m, 1H), 3.73 (s,

3H), 3.75–3.71 (m, 1H), 3.65 (dd, J = 9.9, 6.6 Hz, 1H), 3.54 (s, 3H), 3.44 (s, 3H), 3.41 (s, 3H), 3.40 (s, 3H), 3.31 (dd, J = 14.2, 8.2 Hz, 1H), 2.85 (dd, J = 14.3, 3.4 Hz, 1H), 2.50 (s, 3H), 2.16 (m, 1H), 1.62–1.49 (m, 3H), 1.48 (s, 3H), 1.42 (m, 4H), 1.28 (s, 3H), 1.21–1.11 (m, 1H), 1.09 (d, J = 6.7 Hz, 3H), 0.98 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 169.7, 159.0, 155.6, 150.8, 150.7, 150.4, 150.2, 139.1, 130.4, 130.1, 120.6, 120.1, 119.9, 119.6, 112.4, 112.3, 112.2, 111.9, 99.4, 97.7, 76.0, 71.7, 71.4, 70.98, 70.91, 69.0, 66.1, 56.0, 55.89, 55.87, 52.1, 36.4, 36.1, 35.3, 30.62, 30.57, 30.0, 27.7, 26.5, 19.9, 19.0, 18.9, 12.7, 6.0, -4.76, -4.83; HRMS (ES+) *m/z* 889.4567 [(M + Na)⁺; calcd for C₄₈H₇₀O₁₂NaSi 889.4534].

Lactone (+)-24. To a solution of alcohol (+)-23 (330 mg, 0.400 mmol) in THF (6.3 mL) and MeOH (2.1 mL) cooled to -78 °C was added Et₂BOMe (1.35 mL, 1 M in THF, 3.4 equiv). The reaction mixture was stirred for 30 min, and NaBH₄ (126 mg, 3.33 mmol, 8.3 equiv) was added. The reaction mixture was stirred for 2 h at -78 °C and then warmed to 0 °C and stirred for an additional 2 h. The reaction mixture was then quenched with a 2 N aqueous solution of NaOH (13.5 mL). The reaction mixture was stirred at room temperature for 1 h and then extracted with EtOAc (3 × 4 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, and concentrated in vacuo. The crude mixture was purified via flash chromatography on SiO₂ (50% EtOAc/hexanes) to provide (+)-24 (288 mg, 0.362 mmol, 91% yield) as a white amorphous solid: $[\alpha]_D^{20} = +28.8$ (c 3.0, CHCl₃); IR (neat) 3490 (br), 3006, 2934, 2856, 1710, 1593, 1517, 1463, 1265, 1160, 1139, 1087, 1029, 837, 754, 665 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.34 (d, J = 1.9 Hz, 1H), 6.97–6.91 (m, 3H), 6.88 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 6.53 (s, 1H), 5.18 (d_{A,B}, J = 11.9 Hz, 1H), 5.11 (d_{A,B}, J = 11.9 Hz, 1H), 5.00 (app s, 2H), 4.40 (ddd, J = 12.0, 5.3, 2.6 Hz, 1H), 4.17–4.12 (m, 1H), 4.05–4.01 (m, 1H), 3.97 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.85 (m, 1H), 3.70 (dd, J = 10.4, 7.9 Hz, 1H), 3.56 (dd, J = 10.4, 4.7 Hz, 1H), 3.00 (dd, J = 16.5, 2.7 Hz, 1H), 2.88 (dd, J = 16.5, 12.0 Hz, 1H), 2.11 (s, 3H), 2.09–1.99 (m, 1H), 1.92–1.83 (m, 1H), 1.73–1.54 (m, 4H), 1.47–1.20 (m, 3H), 1.12 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.04 (br s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 163.8, 161.1, 160.2, 149.4, 149.3, 149.1, 148.6, 142.1, 129.5, 128.8, 120.1, 119.0, 116.0, 111.1, 110.9, 110.7, 110.5, 107.8, 97.8, 78.6, 73.9, 72.3, 71.9, 71.0, 70.4, 64.4, 56.1, 56.03, 56.00, 55.99, 42.6, 36.8, 30.7, 29.5, 26.0, 18.7, 18.4, 11.2, 10.0, -5.25, -5.34; HRMS (ES+) *m/z* 817.3958 [(M + Na)⁺; calcd for C₄₄H₆₂O₁₁NaSi 817.3959].

MTPA Esters (R)-26 and (S)-26. (R)-26. To a solution of (+)-24 (5.4 mg, 6.8 μmol) in CH₂Cl₂ (150 μL) were added stock solutions of R-(+)-MTPA-OH (60 μL, 0.1 g/mL in CH₂Cl₂, 3.8 equiv), DCC (50 μL, 0.1 g/mL in CH₂Cl₂, 3.6 equiv), and DMAP (30 μL, 0.1 g/mL in CH₂Cl₂, 3.6 equiv). The reaction mixture was stirred for 8 h. The reaction mixture was directly loaded on preparatory TLC (500 μm, 60% EtOAc/hexanes) for purification to provide R-MTPA-methyl ester 26 (3.4 mg, 3.4 μmol, 50%) as a white amorphous powder: $[\alpha]_D^{20} = +66.6$ (c 0.3, CHCl₃); IR (neat) 2929, 2854, 1742, 1718, 1593, 1517, 1463, 1265, 1244, 1161, 1080, 1027, 837, 732 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.43 (d, J = 7.7 Hz, 2H), 7.32 (d, J = 1.9 Hz, 1H), 7.24–7.11 (m, 3H), 6.98–6.90 (m, 3H), 6.88 (d, J = 7.8 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 5.48–5.39 (m, 1H), 5.17 (d_{A,B}, J = 11.9 Hz, 1H), 5.11 (d_{A,B}, J = 11.9 Hz, 1 H), 5.04 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87–3.82 (m, 1H), 3.79–3.71 (m, 2H), 3.66 (dd, J = 10.1, 5.2 Hz, 1H), 3.60 (dd, J = 10.1, 6.9 Hz, 1H), 3.53 (s, 3H), 2.93 (dd, J = 16.3, 2.4 Hz, 1H), 2.56 (dd, J = 16.2, 12.1 Hz, 1H), 2.09–2.11 (m, 2H), 2.11 (s, 3H), 1.78–1.70 (m, 1H), 1.70–1.53 (m, 4H), 1.51–1.46 (m, 1H), 1.38–1.30 (m, 1H), 1.08 (d, J = 6.8 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 165.9, 162.9, 161.1, 160.1, 149.3, 149.2, 149.0, 148.5, 140.9, 132.1, 129.4, 129.2, 128.6, 128.3, 126.8, 119.9, 118.9, 115.9, 111.0, 110.7, 110.5, 110.4, 107.4, 97.7, 77.4, 77.2, 74.5, 71.8, 70.8, 70.3, 68.3, 64.1, 56.0, 55.90, 55.88, 55.85, 55.5, 39.4, 34.7, 30.1, 29.7, 29.6, 26.1, 25.9, 18.3, 18.2, 11.0, 9.9, -5.3, -5.4; HRMS (ES+) *m/z* 1033.4341 [(M + Na)⁺; calcd for C₅₄H₆₉O₁₃NaSiF₃ 1033.4346].

(S)-26. In an entirely analogous fashion, (S)-(-)-MTPA-OH was used to produce the S-MTPA-methyl ester 26 (4.6 mg, 4.6 μmol, 67%)

as a white amorphous solid: $[\alpha]_D^{20} = +24.4$ (c 0.4, CHCl_3); IR (neat) 2929, 2855, 1741, 1716, 1593, 1517, 1463, 1266, 1244, 1161, 1080, 1027, 837, 738 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.48–7.42 (m, 2H), 7.33 (d, $J = 1.9$ Hz, 1H), 7.29–7.21 (m, 3H), 6.95 (m, 3H), 6.88 (d, $J = 7.9$ Hz, 1H), 6.84 (d, $J = 7.9$ Hz, 1H), 6.56 (s, 1H), 5.46–5.38 (m, 1H), 5.18 ($d_{\text{A,B}}$, $J = 11.9$ Hz, 1 H), 5.11 ($d_{\text{A,B}}$, $J = 11.9$ Hz, 1 H), 5.06–5.00 (m, 2H), 4.10 (ddd, $J = 12.1, 6.4, 2.3$ Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.75–3.70 (m, 1H), 3.69–3.60 (m, 2H), 3.53 (dd, $J = 10.2, 6.5$ Hz, 1H), 3.46 (s, 3H), 2.92 (dd, $J = 16.3, 2.5$ Hz, 1H), 2.65 (dd, $J = 16.3, 12.2$ Hz, 1H), 2.29–2.20 (m, 1H), 2.12–2.05 (m, 1H), 2.06 (s, 3H), 1.70–1.68 (m, 1H), 1.63–1.53 (m, 4H), 1.48–1.40 (m, 1H), 1.34–1.27 (m, 1H), 1.12 (d, $J = 6.8$ Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.6, 163.6, 161.7, 160.7, 149.9, 149.8, 149.6, 149.1, 141.5, 132.3, 130.1, 129.8, 129.2, 129.0, 128.0, 120.5, 119.4, 116.54, 111.6, 111.3, 111.1, 111.0, 108.0, 98.3, 78.2, 77.8, 75.7, 72.5, 71.4, 70.9, 68.2, 64.6, 56.6, 56.51, 56.48, 56.5, 55.9, 39.6, 34.8, 30.7, 30.3, 30.3, 26.7, 26.5, 19.0, 18.9, 11.6, 10.7, –4.7, –4.8; HRMS (ES+) m/z 1033.4371 [(M + Na) $^+$]; calcd for $\text{C}_{54}\text{H}_{69}\text{O}_{13}\text{NaSiF}_3$ 1033.4357].

Bis-TBS Ether (+)-55. To a solution of (+)-24 (170 mg, 0.214 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added 2,6-lutidine (127 μL , 1.10 mmol, 5.1 equiv) and TBSOTf (120 μL , 0.52 mmol, 2.5 equiv). After 3 h, the reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 (10 mL) and extracted with CH_2Cl_2 (3 \times 10 mL). The combined organic layers were washed successively with an aqueous solution of HCl (10 mL, 1 N), a saturated aqueous solution of NaHCO_3 (20 mL), and brine (20 mL). The organic layer was dried over MgSO_4 and concentrated in vacuo. The crude mixture was purified via flash chromatography on SiO_2 (35% EtOAc/hexanes) to provide (+)-55 (187 mg, 0.206 mmol, 96%) as a white amorphous solid: $[\alpha]_D^{20} = +28.3$ (c 1.7, CHCl_3); IR (neat) 2951, 2931, 2856, 1712, 1593, 1517, 1463, 1264, 1160, 1139, 1080, 1030, 836, 774, 754 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.33 (d, $J = 1.9$ Hz, 1H), 6.99–6.91 (m, 3H), 6.91–6.81 (m, 2H), 6.53 (s, 1H), 5.18 ($d_{\text{A,B}}$, $J = 11.9$ Hz, 1 H), 5.11 ($d_{\text{A,B}}$, $J = 11.9$ Hz, 1 H), 5.01 ($d_{\text{A,B}}$, $J = 11.3$ Hz, 1 H), 4.99 (d, $J = 11.3$ Hz, 1 H), 4.32 (ddd, $J = 12.1, 7.0, 2.4$ Hz, 1H), 4.02–3.94 (m, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.87–3.82 (m, 1H), 3.70–3.62 (m, 2H), 3.60–3.52 (m, 1H), 3.05 (dd, $J = 16.4, 2.5$ Hz, 1H), 2.68 (dd, $J = 16.4, 12.1$ Hz, 1H), 2.10 (s, 3H), 1.87 (ddd, $J = 14.0, 8.3, 5.4$ Hz, 1H), 1.70–1.59 (m, 5H), 1.42 (m, 1H), 1.32 (m, 1H), 1.10 (d, $J = 6.8$ Hz, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.7, 161.1, 160.2, 149.4, 149.3, 149.1, 148.6, 141.7, 129.5, 128.9, 120.1, 119.0, 115.8, 111.2, 111.0, 110.8, 110.6, 108.0, 97.8, 78.6, 72.0, 71.0, 70.4, 70.3, 68.3, 64.6, 56.2, 56.1, 56.04, 56.02, 41.4, 37.5, 30.5, 30.4, 26.8, 26.1, 26.0, 18.6, 18.5, 18.1, 11.3, 10.6, –3.8, –4.4, –5.1, –5.2; HRMS (ES+) m/z 931.4810 [(M + Na) $^+$]; calcd for $\text{C}_{50}\text{H}_{76}\text{O}_{11}\text{NaSi}_2$ 931.4824].

Alcohol (+)-25. To a solution of (+)-55 (250 mg, 0.275 mmol) in THF (4.15 mL) at 0 °C was added a stock solution of TBAF and acetic acid in THF (4.15 mL; recipe for stock solution 1.4 mL of TBAF (1 M in THF), 64 μL of AcOH, and 2.74 mL of THF). The reaction mixture was warmed to room temperature and stirred for 10 h. The reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 (10 mL) and extracted with EtOAc (3 \times 10 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO_4 , and concentrated in vacuo. The crude mixture was purified via flash chromatography on SiO_2 (30% to 80% EtOAc/hexanes) to provide recovered (+)-S3 (115 mg, 0.126 mmol, 46%) and alcohol (+)-25 (105 mg, 0.132 mmol, 48%) as a white amorphous solid: $[\alpha]_D^{20} = +23.6$ (c 2.0, CHCl_3); IR (neat) 3487 (br), 2932, 2856, 1710, 1593, 1517, 1463, 1264, 1159, 1083, 1029, 836, 810, 754 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.32 (d, $J = 1.9$ Hz, 1H), 6.99–6.90 (m, 4H), 6.87 (d, $J = 8.1$ Hz, 1H), 6.83 (d, $J = 8.6$ Hz, 1H), 6.53 (s, 1H), 5.18 ($d_{\text{A,B}}$, $J = 11.9$ Hz, 1 H), 5.11 ($d_{\text{A,B}}$, $J = 11.9$ Hz, 1 H), 5.02 ($d_{\text{A,B}}$, $J = 11.3$ Hz, 1 H), 5.00 ($d_{\text{A,B}}$, $J = 11.3$ Hz, 1 H), 4.33 (ddd, $J = 11.9, 6.7, 2.4$ Hz, 1H), 4.07–3.99 (m, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.94–3.87 (m, 1H), 3.79–3.72 (m, 1H), 3.70–3.62 (m, 1H), 3.49–3.41 (m, 1H), 3.03 (dd, $J = 16.4, 2.5$ Hz, 1H), 2.71 (dd, $J = 16.4, 12.0$ Hz, 1H), 2.10 (s, 3H), 2.09–2.04 (m,

1H), 2.00 (dd, $J = 8.2, 3.7$ Hz, 1H), 1.94 (ddd, $J = 14.2, 9.0, 5.3$ Hz, 1H), 1.70–1.56 (m, 4H), 1.40–1.30 (m, 2H), 1.10 (d, $J = 6.8$ Hz, 3H), 0.85 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.5, 161.2, 160.2, 149.4, 149.3, 149.1, 148.6, 141.5, 129.5, 128.8, 120.1, 119.1, 115.9, 111.2, 110.9, 110.8, 110.6, 107.9, 97.9, 78.5, 71.4, 71.0, 70.4, 69.9, 68.2, 64.1, 56.2, 56.06, 56.04, 56.03, 41.3, 36.6, 30.2, 29.8, 26.4, 25.9, 18.6, 18.2, 11.2, 10.3, –3.7, –4.4; HRMS (ES+) m/z 817.3950 [(M + Na) $^+$]; calcd for $\text{C}_{44}\text{H}_{62}\text{O}_{11}\text{NaSi}$ 817.3959].

Amine 13. To a solution of (+)-25 (23 mg, 0.029 mmol) in CH_2Cl_2 (2 mL) at –78 °C were added Et_3N (23 μL , 0.164 mmol, 5.6 equiv) and Ti_2O (184 μL , 50 $\mu\text{L}/\text{mL}$ in CH_2Cl_2 , 0.055 mmol, 1.9 equiv). The reaction mixture was stirred for 1 h and diluted with CH_2Cl_2 (2 mL). The resulting mixture was treated with condensed anhydrous ammonia (4 mL) at –20 °C and was stirred for 3 h. The system was warmed to 0 °C to ensure residual ammonia was evaporated and then diluted with EtOAc (4 mL) and an aqueous solution of NaOH (1 N, 10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 \times 10 mL). The combined organic layers were washed with brine (15 mL), dried over MgSO_4 , and concentrated in vacuo to provide amine 13 (23 mg) as a brown foam. Crude amine 13 was carried forward without further purification.

Acid Chloride 28. To a solution of acid (–)-12 (35 mg, 0.12 mmol) in CH_2Cl_2 (0.72 mL) were added pyridine (50 μL , 0.62 mmol, 5.2 equiv) and thionyl chloride (35 μL , 0.48 mmol, 4.0 equiv) at 0 °C. After addition, the reaction mixture was stirred at room temperature for 2 h and then concentrated under a stream of N_2 followed by vacuum (ca. 0.02 mmHg). After removal of CH_2Cl_2 , the residue was suspended in toluene (1 mL). The upper layer clear solution was transferred to another flask and dried in vacuo immediately for the next step.

Amide (+)-29. The crude acid chloride 28 was dissolved in CH_2Cl_2 (0.5 mL), followed by addition of *i*-Pr $_2\text{NEt}$ (52 μL , 0.30 mmol, 10 equiv) and a solution of crude amine 13 (23 mg) in CH_2Cl_2 (0.5 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 2 h before it was warmed to room temperature for another 2 h. The reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 (3 mL) and extracted with EtOAc (3 \times 5 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 , and concentrated in vacuo. The crude mixture was purified via flash chromatography on SiO_2 (66% EtOAc/hexanes) to provide amide (+)-29 (18 mg, 0.017 mmol, 59% over two steps) as a white amorphous solid: $[\alpha]_D^{20} = +1.8$ (c 0.7, CHCl_3); IR (neat) 3429, 1714, 2856, 1714, 1675, 1593, 1517, 1463, 1262, 1160, 1139, 1083, 1029, 836, 776, 731 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.32 (d, $J = 2.0$ Hz, 1H), 7.01–6.90 (m, 4H), 6.87 (dd, $J = 7.9$ Hz, 1H), 6.83 (dd, $J = 8.3$ Hz, 1H), 6.54 (s, 1H), 5.17 ($d_{\text{A,B}}$, $J = 11.6$ Hz, 1 H), 5.11 ($d_{\text{A,B}}$, $J = 11.6$ Hz, 1 H), 5.02 ($d_{\text{A,B}}$, $J = 11.3$ Hz, 1 H), 4.98 ($d_{\text{A,B}}$, $J = 11.3$ Hz, 1 H), 4.74 (br s, 1H), 4.70 (br s, 1H), 4.38 (d, $J = 1.8$ Hz, 1H), 4.30 (ddd, $J = 12.2, 6.9, 2.4$ Hz, 1H), 3.96 (m, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87–3.84 (m, 1H), 3.74–3.63 (m, 2H), 3.48 (ddd, $J = 12.1, 7.3, 4.6$ Hz, 1H), 3.37 (s, 3H), 3.17 (dt, $J = 13.5, 4.6$ Hz, 1H), 3.04 (dd, $J = 16.4, 2.5$ Hz, 1H), 2.71 (dd, $J = 16.4, 12.2$ Hz, 1H), 2.24 (dd, $J = 14.7, 9.1$ Hz, 1H), 2.10 (s, 3H), 2.05–1.94 (m, 2H), 1.88–1.72 (m, 2H), 1.69 (s, 3H), 1.66–1.51 (m, 5H), 1.42–1.32 (m, 2H), 1.11 (d, $J = 6.8$ Hz, 3H), 0.92 (s, 9H), 0.85 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.8, 163.5, 161.3, 160.3, 149.5, 149.4, 149.2, 148.7, 142.7, 141.6, 129.5, 128.8, 120.2, 119.1, 115.8, 112.6, 111.2, 111.0, 110.8, 110.6, 107.9, 97.8, 81.9, 78.1, 77.4, 74.0, 71.0, 70.9, 70.5, 69.3, 69.1, 57.9, 56.2, 56.14, 56.11, 56.10, 42.5, 42.4, 37.5, 35.5, 30.9, 28.3, 27.8, 26.1, 26.0, 22.8, 18.4, 18.3, 18.2, 11.4, 11.0, –3.9, –4.1, –4.3, –5.3; HRMS (ES+) m/z 1064.5953 [(M + H) $^+$]; calcd for $\text{C}_{58}\text{H}_{90}\text{NO}_{13}\text{Si}_2$ 1064.5951].

(+)-C(8)-Desmethoxy-C(11)-deoxy-C(12)-didesmethylirici-niastanin A (6). To a solution of amide (+)-29 (3.9 mg, 3.7 μmol) in CH_2Cl_2 (330 μL) were added H_2O (40 μL) and a suspension of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (73 μL , 0.1 g/mL in CH_2Cl_2 , 8.7 equiv). The reaction mixture was stirred for 8 h, and the reaction progress was monitored by LC-MS. After removal of the

two DMB ethers, the reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 (1 mL) and the biphasic mixture was stirred vigorously for an additional 30 min. The reaction mixture was diluted with CH_2Cl_2 (1 mL), and the layers were separated. The organic layer was washed with a saturated aqueous solution of NaHCO_3 (3×2 mL) and brine (5 mL), dried over Na_2SO_4 , and concentrated in vacuo to provide crude bis-phenol as a faint yellow oil. The bis-phenol was dissolved in DMF (0.8 mL) in a plastic vial, followed by addition of TAS-F (22 mg, 22 equiv). The reaction mixture was warmed to 50 °C and stirred for 24 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (1 mL) and extracted with EtOAc (5×2 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 , and concentrated in vacuo. The crude mixture was purified by preparatory TLC (500 μm , 95% EtOAc/hexanes) to provide irciniastatin analogue (+)-6 (1.35 mg, 2.5 μmol , 68% over two steps) as a white amorphous solid: $[\alpha]_{\text{D}}^{20} = +7.6$ (c 0.2, CHCl_3); IR (neat) 3361 (br), 2926, 2855, 1655, 1618, 1542, 1462, 1378, 1252, 1171, 1105 cm^{-1} ; ^1H NMR (500 MHz, CD_3OD) δ 6.25 (s, 1H), 4.74 (br s, 1H), 4.71 (br s, 1H), 4.52 (ddd, $J = 12.0, 5.9, 3.2$ Hz, 1H), 4.32 (d, $J = 2.9$ Hz, 1H), 4.03–3.94 (m, 2H), 3.93–3.86 (m, 1H), 3.67 (dt, $J = 9.4, 3.3$ Hz, 1H), 3.57 (dd, $J = 13.7, 8.8$ Hz, 1H), 3.34 (s, 3H), 3.23 (dd, $J = 13.8, 4.5$ Hz, 1H), 3.09 (dd, $J = 16.6, 3.2$ Hz, 1H), 2.90 (dd, $J = 16.6, 12.0$ Hz, 1H), 2.28 (ddd, $J = 14.6, 9.3, 1.0$ Hz, 1H), 2.07 (s, 3H), 2.06–2.02 (m, 1H), 1.98–1.87 (m, 1H), 1.86–1.78 (m, 1H), 1.74–1.65 (m, 8H), 1.48–1.32 (m, 2H), 1.12 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.8, 172.4, 164.5, 163.7, 144.0, 141.0, 115.2, 113.0, 101.4, 101.3, 82.5, 82.0, 72.4, 71.9, 71.3, 70.8, 57.6, 43.3, 41.7, 39.3, 38.3, 31.1, 29.3, 28.4, 22.9, 19.3, 10.7, 9.6; HRMS (ES+) m/z 558.2670 [(M + Na) $^+$]; calcd for $\text{C}_{28}\text{H}_{41}\text{NO}_9\text{Na}$ 558.2679.

Acetate (+)-S6. To a solution of alcohol (–)-30 (7.0 mg, 6 μmol) in pyridine (0.42 mL) was added acetic anhydride (0.18 mL) dropwise. The reaction mixture was stirred for 7.5 h at room temperature. The reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 and extracted with EtOAc (3×0.5 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The crude mixture was purified via flash chromatography on SiO_2 (40% to 45% EtOAc/hexanes) to furnish acetate (+)-S6 (6.3 mg, 5.1 μmol , 87%) as a colorless oil: $[\alpha]_{\text{D}}^{20} = +5.3$ (c 0.5, CHCl_3); IR (neat) 3391, 2925, 2858, 1716, 1687, 1592, 1516, 1462, 1371, 1249, 1150 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.31 (ap s, 1H), 7.23 (d, $J = 9.7$ Hz, 1H), 6.98–6.92 (m, 3 H), 6.87 (d, $J = 8.7$ Hz, 1H), 6.83 (d, $J = 8.0$ Hz, 1H), 6.54 (s, 1H), 5.16 ($d_{\text{A,B}}$, $J = 11.5$ Hz, 1H), 5.10 ($d_{\text{A,B}}$, $J = 12.3$ Hz, 1H), 5.07 (d, $J = 10.6$ Hz, 1H), 4.98 (s, 2H), 4.87 (app t, $J = 3.9$ Hz, 1H), 4.82 (d, $J = 6.8$ Hz, 1H), 4.78 (s, 1H), 4.77 (s, 1H), 4.71 (app t, $J = 7.6$ Hz, 2H), 4.63 (d, $J = 7.2$ Hz, 1H), 4.38 (app s, 1H), 4.31 (m, 1H), 4.00 (dd, $J = 9.6, 2.9$ Hz, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.76–3.71 (m, 2H), 3.58 (dd, $J = 10.0, 6.9$ Hz, 1H), 3.56–3.49 (m, 2H), 3.49–3.44 (m, 1H), 3.37 (s, 3H), 3.31 (s, 3H), 3.23 (d, $J = 15.4$ Hz, 1H), 2.67 (dd, $J = 16.4, 12.8$ Hz, 1H), 2.36 (dd, $J = 14.6, 8.8$ Hz, 2H), 2.20 (dd, $J = 14.5, 4.3$ Hz, 1H), 2.14 (s, 3H), 2.11 (m, 1H), 2.08 (s, 3H), 1.83–1.74 (m, 2H), 1.71 (s, 3H), 1.57 (ddd, $J = 18.2, 7.9, 4.1$ Hz, 1H), 1.16 (d, $J = 6.8$ Hz, 3H), 1.05 (s, 3H), 0.95–0.90 (m, 1H), 0.88 (s, 3H), 0.86–0.84 (m, 1H), 0.86–0.79 (ddd, $J = 17.5, 11.5, 5.9$ Hz, 1H), 0.74–0.69 (ddd, $J = 17.7, 11.7, 5.9$ Hz, 1H), 0.01 (s, 9H), –0.11 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.2, 170.3, 163.7, 161.3, 160.4, 149.6, 149.4, 149.3, 148.8, 142.4, 142.1, 129.6, 128.9, 120.2, 119.2, 116.2, 113.0, 111.3, 111.1, 111.0, 110.8, 108.1, 97.9, 94.8, 94.4, 81.7, 81.5, 79.3, 75.6, 74.5, 71.2, 70.5, 66.2, 65.7, 58.0, 56.4, 56.2, 56.08, 56.07, 56.0, 39.3, 38.4, 36.4, 30.2, 30.0, 29.9, 29.6, 27.9, 26.1, 22.9, 21.4, 20.2, 18.13, 18.10, 11.4, 9.7, –1.2, –1.4; HRMS (ES+) m/z 1212.6318 [(M + H) $^+$]; calcd for $\text{C}_{63}\text{H}_{98}\text{NO}_{18}\text{Si}_2$ 1212.6322.

C(11)-OAc-irciniastatin A (+)-8. To a solution of fully protected acetate (+)-S6 (5.1 mg, 4.2 μmol) in CH_2Cl_2 (50 μL) and H_2O (15 μL) was added a suspension of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1 mL, 0.33 M in CH_2Cl_2 , 8 equiv). After 10 h, the reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 and extracted with EtOAc (5×0.5 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in

vacuo. The crude mixture was purified via flash chromatography on SiO_2 (50% EtOAc/hexanes) to afford a 1/2 mixture of the desired bis-phenol and 3,4-dimethoxybenzaldehyde, respectively. The mixture was treated with a stock solution of $\text{MgBr}_2/n\text{-BuSH}/\text{MeNO}_2$ in Et_2O (0.155 mL; 25 equiv of MgBr_2 , and 25 equiv of $n\text{-BuSH}$; stock solution 57.4 mg of MgBr_2 , 33 μL of $n\text{-BuSH}$, 62 μL of MeNO_2 , and 0.62 mL of Et_2O). After 9 h, the reaction mixture was diluted with EtOAc, quenched with a saturated aqueous solution of NaHCO_3 , and extracted with EtOAc (5×0.5 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The crude mixture was purified via flash chromatography on SiO_2 40% to 80% EtOAc/hexanes with 5% v/v triethylamine to afford (+)-C(11)-OAc-irciniastatin A (+)-8 (1.9 mg, 3.1 μmol , 75% over two steps) as a white amorphous solid: $[\alpha]_{\text{D}}^{20} = +3.9$ (c 0.15, CHCl_3); IR (neat) 3372, 2923, 2850, 1737, 1661, 1617, 1515, 1461, 1373, 1251, 1172, 1108, 1071 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 11.15 (s, 1H), 7.17 (d, $J = 9.7$ Hz, 1H), 6.59 (bs, 1H), 6.30 (s, 1H), 5.43 (dd, $J = 10.3, 1.6$ Hz, 1H), 4.89 (dd, $J = 9.3, 4.4$ Hz, 1H), 4.81 (s, 1H), 4.80 (s, 1H), 4.59 (ddd, $J = 11.8, 8.3, 3.8$ Hz, 1H), 4.43 (app bs, 1H), 4.24 (br s, 1H), 3.97–3.90 (m, 2H), 3.77–3.74 (m, 2H), 3.65 (d, $J = 10.5$ Hz, 1H), 3.44–3.35 (m, 1H), 3.40 (s, 3H), 3.39 (s, 3H), 2.91–2.80 (m, 2H), 2.37 (dd, $J = 14.6, 8.8$ Hz, 1H), 2.18 (dd, $J = 14.8, 3.9$ Hz, 1H), 2.10 (s, 3H), 2.03 (s, 3H), 1.91 (m, 2H), 1.83–1.78 (m, 1H), 1.76 (s, 3H), 1.63 (d, $J = 15.0$ Hz, 1H), 1.11 (d, $J = 7.1$ Hz, 3H), 0.97 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.3, 170.7, 162.5, 161.1, 142.2, 140.0, 113.3, 113.2, 101.9, 101.5, 82.6, 80.6, 79.4, 79.0, 74.0, 73.4, 72.8, 71.8, 58.0, 56.7, 56.1, 42.8, 37.6, 37.5, 31.9, 29.9, 28.7, 27.1, 24.1, 22.9, 21.4, 10.7, 9.6; HRMS (ES+) m/z 674.3155 [(M + Na) $^+$]; calcd for $\text{C}_{33}\text{H}_{49}\text{NO}_{12}\text{Na}$ 674.3152.

Benzoate (+)-S7. To a solution of alcohol (–)-30 (6.0 mg, 5 μmol) in pyridine (0.30 mL) was added benzoyl chloride (30 μL , 0.43 mmol, 85 equiv) dropwise. The reaction mixture was stirred for 1 h at room temperature. Additional benzoyl chloride (50 μL) was added, and the reaction mixture was stirred for an additional 30 min. The reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 and extracted with EtOAc (3×0.5 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The crude mixture was purified via flash chromatography on SiO_2 (30% to 40% EtOAc/hexanes) to furnish benzoate (+)-S7 (3.6 mg, 0.003 mmol, 55%) as a white amorphous solid: $[\alpha]_{\text{D}}^{20} = +12.8$ (c 0.3, CH_2Cl_2); IR (neat) 3454, 3351, 2954, 2926, 2855, 1729, 1438, 1251, 1157, 1101, 1066, 1011, 1066, 833, 772 cm^{-1} ; ^1H NMR (500 MHz, CD_3OD) δ 8.17–8.00 (m, 3H), 7.59 (t, $J = 8.3$ Hz, 1H), 7.49 (t, $J = 7.7$ Hz, 2H), 7.26 (s, 1 H), 7.08 (s, 1 H), 6.97 (d, $J = 8.3$ Hz, 1 H), 6.94 (s, 2 H), 6.89 (d, $J = 8.4$ Hz, 1 H), 6.74 (s, 1 H), 5.22 (dd, $J = 5.7, 5.2$ Hz, 1 H), 5.20 ($d_{\text{A,B}}$, $J = 12.7$ Hz, 1 H), 5.16–5.14 (m, 1 H), 5.14 ($d_{\text{A,B}}$, $J = 12.7$ Hz, 1 H), 5.09 (app s, 2 H), 4.76–4.68 (m, 6 H), 4.42 (ddd, $J = 10.9, 5.4, 1.7$ Hz, 1 H), 4.28 (d, $J = 3.2$ Hz, 1 H), 4.04 (m, 1 H), 3.93 (m, 1 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.82 (bs, 6 H), 3.70 (ddd, $J = 10.0, 10.0, 6.5$ Hz, 1 H), 3.63 (m, 2H), 3.62–3.60 (m, 3 H), 3.38 (s, 3 H), 3.24 (s, 3 H), 2.79 (dd, $J = 16.6, 12.6$ Hz, 1 H), 2.30 (dd, $J = 14.7, 9.0$ Hz, 1 H), 2.20 (d, $J = 3.4$ Hz, 1 H), 2.17 (s, 3 H), 2.14 (dd, $J = 8.3, 4.5$ Hz, 1 H), 2.11 (dd, $J = 6.5, 2.9$ Hz, 1 H), 1.99 (m, 1 H), 1.90–1.85 (m, 1 H), 1.69 (s, 3 H), 1.15 (d, $J = 6.8$ Hz, 3 H), 1.11 (s, 3 H), 1.05 (s, 3 H), 0.88–0.78 (m, 3 H), 0.68 (ddd, $J = 13.4, 11.4, 5.6$ Hz, 1 H), –0.04 (s, 9 H), –0.13 (s, 9 H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.9, 173.8, 167.5, 166.4, 163.3, 162.1, 150.8, 150.8, 150.7, 150.2, 143.8, 143.4, 136.1, 134.6, 133.9, 131.7, 131.6, 131.2, 130.8, 130.7, 130.4, 129.6, 121.6, 120.9, 117.2, 113.5, 113.0, 112.8, 112.7, 112.4, 107.8, 99.1, 96.0, 95.5, 83.0, 82.9, 82.7, 80.7, 78.51, 78.46, 78.3, 76.7, 71.7, 71.5, 67.1, 66.8, 58.5, 57.0, 56.63, 56.60, 40.7, 39.7, 38.4, 32.4, 31.3, 28.2, 25.6, 23.2, 19.11, 19.05, 11.8, 9.4, –1.1, –1.3; high resolution mass spectrum (ES+) m/z 1296.6295 [(M + Na) $^+$]; calcd for $\text{C}_{68}\text{H}_{99}\text{NO}_{18}\text{Si}_2\text{Na}$ 1296.6298.

(–)-C(11)-OBz-irciniastatin A (–)-9. To a solution of fully protected benzoate (+)-S7 (3.6 mg, 2.8 μmol) in CH_2Cl_2 (100 μL) and H_2O (18 μL) was added a suspension of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (80 μL , 0.29 M in CH_2Cl_2 , 8 equiv). After 10 h, the reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 and extracted with EtOAc (5×0.5 mL). The combined

organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The crude mixture was purified via flash chromatography on SiO_2 (50% EtOAc/hexanes) to afford a 1/2 mixture of the desired bis-phenol and 3,4-dimethoxybenzaldehyde, respectively. The mixture was treated with a stock solution of $\text{MgBr}_2/n\text{-BuSH/MeNO}_2$ in Et_2O (0.140 mL; 25 equiv of MgBr_2 and 25 equiv of $n\text{-BuSH}$; stock solution 89.9 mg of MgBr_2 , 36 μL of $n\text{-BuSH}$, 100 μL of MeNO_2 , and 0.98 mL of Et_2O). After 9.5 h, the reaction mixture was diluted with EtOAc and quenched with a saturated aqueous solution of NaHCO_3 and extracted with EtOAc (5×0.5 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The crude mixture was purified via flash chromatography on SiO_2 (40% to 50% EtOAc/hexanes) to afford (+)-*C*(11)-OBz-irciniastatin A (–)–9 (1.0 mg, 1.4 μmol , 50% over two steps) as a white amorphous solid: $[\alpha]_{\text{D}}^{20} = -13.7$ (c 0.08, CHCl_3); IR (neat) 3372, 2943, 1726, 1663, 1599, 1446, 1377, 1253, 1114 cm^{-1} ; $^1\text{H NMR}$ (500 MHz, C_6D_6) δ 11.93 (bs, 1H), 8.17 (d, $J = 7.5$ Hz, 3H), 7.10 (t, $J = 7.5$ Hz, 2H), 6.31 (s, 1H), 5.67 (t, $J = 8.3$ Hz, 1H), 5.27 (dd, $J = 9.9$, 4.4 Hz, 1H), 5.04 (s, 1H), 4.92 (s, 1H), 4.61 (bs, 1H), 4.33 (m, 3H), 4.17 (d, $J = 9.7$ Hz, 1H), 3.91 (ddd, $J = 4.0$, 3.5, 3.5 Hz, 1H), 3.73 (d, $J = 10.4$ Hz, 1H), 3.59 (bs, 1H), 3.32 (s, 3H), 3.25 (s, 3H), 2.63 (d, $J = 16.3$ Hz, 1H), 2.65–2.51 (ddd, $J = 12.4$, 12.4, 8.7 Hz, 1H), 2.46 (dd, $J = 14.0$, 4.6 Hz, 2H), 2.26 (m, 1H), 2.02 (s, 3H), 1.93 (m, 1H), 1.79 (s, 3H), 1.58 (bs, 1H), 1.46 (d, $J = 13.9$ Hz, 1H), 1.06 (d, $J = 6.6$ Hz, 3H), 0.96 (s, 3H), 0.79 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, C_6D_6) δ 173.7, 170.9, 165.7, 163.2, 161.8, 142.6, 140.1, 133.2, 130.9, 129.9, 128.8, 127.5, 113.6, 113.5, 102.0, 101.6, 82.2, 81.5, 80.1, 78.9, 74.3, 73.8, 73.5, 57.8, 56.3, 43.1, 38.1, 37.8, 33.0, 32.4, 30.2, 30.1, 28.4, 27.2, 23.1, 14.4, 10.6, 9.2; HRMS (ES+) m/z 736.3286 [(M + Na)⁺; calcd for $\text{C}_{38}\text{H}_{51}\text{NO}_{12}\text{Na}$ 736.3309].

Olefin (–)–S8. To a solution of PPh_3MeBr (75.4 mg, 0.211 mmol) in THF (0.46 mL) was added KO-*t*-Bu (0.20 mL, 0.20 mmol) to provide a yellow solution, which was stirred for 5 min. The solution (40 μL , 0.32 M in THF, 2.5 equiv) was added to a separate vial containing a solution of ketone (–)–31 (6.0 mg, 5.1 μmol) in THF (0.26 mL), and the yellow reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with water and extracted with EtOAc (4×0.5 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The crude mixture was purified via flash chromatography on SiO_2 (40% EtOAc/hexanes) to furnish olefin (–)–S8 (5.0 mg, 4.3 μmol , 84%) as a white amorphous oil: $[\alpha]_{\text{D}}^{20} = -3.4$ (c 0.4, CHCl_3); IR (neat) 3422, 2951, 1715, 1686, 1592, 1515, 1463, 1417, 1378, 1246, 1157, 1083, 1027 cm^{-1} ; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.41 (d, $J = 9.7$ Hz, 1H), 7.31 (app s, 1H), 6.97–6.93 (m, 3H), 6.87 (d, $J = 8.5$ Hz, 1H), 6.88 (d, $J = 8.3$ Hz, 1H), 6.54 (s, 1H), 5.17 ($d_{\text{A,B}}$, $J = 11.7$ Hz, 1H), 5.10 ($d_{\text{A,B}}$, $J = 11.7$ Hz, 1H), 5.03 (d, $J = 19.9$ Hz, 1H), 4.98 (s, 2H), 4.87 (d, $J = 5.5$ Hz, 1H), 4.86 (s, 1H), 4.78 (app s, 2H), 4.70 (d, $J = 13.6$ Hz, 1H), 4.64 ($d_{\text{A,B}}$, $J = 7.0$ Hz, 1H), 4.60 ($d_{\text{A,B}}$, $J = 6.8$ Hz, 1H), 4.42 (app s, 1H), 4.22 (ap t, $J = 10.8$ Hz, 1H), 3.96 (m, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.80–3.74 (m, 2H), 3.58 (ddd, $J = 9.7$, 9.7, 6.4 Hz, 1H), 3.53–3.48 (m, 2H), 3.42 (dd, $J = 11.0$, 5.3 Hz, 1H), 3.40 (s, 3H), 3.30 (s, 3H), 3.23 (d, $J = 16.1$ Hz, 1H), 2.64 (dd, $J = 16.2$, 12.3 Hz, 1H), 2.38 (dd, $J = 14.9$, 9.0 Hz, 1H), 2.30–2.22 (m, 2H), 2.13 (s, 3H), 2.06–1.97 (m, 2H), 1.72 (s, 3H), 1.66–1.63 (m, 1H), 1.19 (s, 3H), 1.16 (d, $J = 6.7$ Hz, 3H), 0.99 (s, 3H), 0.95–0.86 (m, 2H), 0.84–0.78 (ddd, $J = 14.0$, 12.0, 5.6 Hz, 1H), 0.75–0.67 (ddd, $J = 13.8$, 12.2, 6.1 Hz, 1H), 0.01 (s, 9H), –0.10 (s, 9H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 171.5, 163.8, 161.3, 160.4, 149.6, 149.4, 149.3, 148.8, 148.3, 142.4, 142.1, 129.6, 128.9, 120.2, 119.2, 116.1, 113.0, 111.3, 111.1, 111.0, 110.8, 109.7, 108.2, 97.9, 94.9, 94.7, 81.6, 81.5, 79.7, 79.4, 74.6, 72.2, 71.2, 70.5, 66.1, 65.5, 58.1, 56.3, 56.2, 40.2, 39.5, 38.4, 33.8, 29.9, 28.7, 27.5, 23.2, 23.0, 18.2, 11.4, 9.6, –1.2, –1.4; HRMS (ES+) m/z 1188.6088 [(M + Na)⁺; calcd for $\text{C}_{62}\text{H}_{95}\text{NO}_{16}\text{Si}_2\text{Na}$ 1188.6087].

(C11)-exo-Methyleirciniastatin B (+)–10. To a solution of olefin (–)–S8 (5.0 mg, 4.3 μmol) in CH_2Cl_2 (0.05 mL) and H_2O (15 μL) was added a suspension of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1 mL, 0.34 M in CH_2Cl_2 , 8.0 equiv). After 11.5 h, the reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 and extracted with EtOAc (5×0.5 mL). The combined

organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The crude mixture was purified via flash chromatography (50% EtOAc/hexanes) to afford a 1/2 mixture of the desired bis-phenol and 3,4-dimethoxybenzaldehyde, respectively. The mixture was treated with a stock solution of $\text{MgBr}_2/n\text{-BuSH/MeNO}_2$ in Et_2O (0.20 mL; 25 equiv of MgBr_2 , 25 equiv of $n\text{-BuSH}$; stock solution: 42.3 mg of MgBr_2 , 18 μL of $n\text{-BuSH}$, 46 μL of MeNO_2 , and 0.46 mL of Et_2O). After 10 h, the reaction mixture was diluted with EtOAc and quenched with a saturated aqueous solution of NaHCO_3 and extracted with EtOAc (5×0.5 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The crude mixture was purified via flash chromatography on SiO_2 (40% to 80% EtOAc/hexanes with 5% v/v triethylamine) to afford (+)-*C*(11)-exo-methyleirciniastatin A (+)–10 (2.0 mg, 3.3 μmol , 77% over two steps) as a white amorphous solid: $[\alpha]_{\text{D}}^{20} = +12.7$ (c 0.17, CHCl_3); IR (neat) 3379, 2921, 1732, 1659, 1623, 1514, 1454, 1379, 1254, 1109 cm^{-1} ; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 11.15 (s, 1H), 7.28 (d, $J = 10.3$, 6.7 Hz, 1H), 6.68 (bs, 1H), 6.30 (s, 1H), 5.28 (dd, $J = 10.3$, 6.7 Hz, 1H), 4.87 (s, 2H), 4.81 (s, 1H), 4.79 (s, 1H), 4.52 (ddd, $J = 4.0$, 16.4, 8.0 Hz, 1H), 4.45 (d, $J = 3.0$ Hz, 1H), 4.01 (d, $J = 10.1$ Hz, 1H), 3.92–3.88 (m, 2H), 3.77–3.74 (ddd, $J = 12.7$, 9.4, 3.8 Hz, 1H), 3.63 (d, $J = 10.7$ Hz, 1H), 3.40 (s, 3H), 3.35 (s, 3H), 3.34–3.31 (m, 1H), 2.93–2.80 (m, 2H), 2.52 (dd, $J = 14.2$, 5.4 Hz, 1H), 2.42–2.35 (m, 2H), 2.16 (dd, $J = 3.9$, 14.8 Hz, 1H), 2.02 (s, 3H), 1.88 (m, 1H), 1.79 (dd, $J = 10.6$, 2.8 Hz, 1H), 1.75 (s, 3H), 1.55 (d, $J = 14.5$ Hz, 1H), 1.14 (s, 3H), 1.10 (d, $J = 7.0$ Hz, 3H), 1.06 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 173.3, 170.7, 162.5, 161.2, 148.2, 142.2, 140.0, 113.4, 113.2, 110.0, 101.7, 101.5, 83.4, 80.6, 80.2, 79.1, 73.9, 73.2, 72.7, 58.0, 56.5, 43.0, 39.9, 37.5, 33.0, 32.1, 28.5, 25.0, 22.9, 21.7, 10.7, 9.5; HRMS (ES–) m/z 606.3280 [(M – H)[–]; calcd for $\text{C}_{32}\text{H}_{48}\text{NO}_{10}$ 606.3278].

O-Methyloxime (+)–S9. To a solution of (–)–31 (6.0 mg, 5.1 μmol) in pyridine (0.3 mL) was added methoxyamine hydrochloride (8.8 mg, 0.105 mmol, 20.6 equiv), and the reaction mixture was warmed to 50 °C. After 2 h, the reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 and extracted with EtOAc (3×0.5 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The crude mixture was purified via flash chromatography on SiO_2 (35% to 40% EtOAc/hexanes) to furnish O-methyloxime (+)–S9 (4.9 mg, 4.1 μmol , 80%) as an odorless oil: $[\alpha]_{\text{D}}^{20} = +11.3$ (c 0.4, CH_2Cl_2); IR (neat) 3421, 2930, 1715, 1680, 1593, 1516, 1462, 1378, 1247, 1157, 1029 cm^{-1} ; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.36 (d, $J = 10.1$ Hz, 1H), 7.31 (d, $J = 1.9$ Hz, 1H), 6.98–6.93 (m, 3H), 6.87 (d, $J = 8.7$ Hz, 1H), 6.83 (d, $J = 8.3$ Hz, 1H), 6.54 (s, 1H), 5.17 ($d_{\text{A,B}}$, $J = 12.1$ Hz, 1H), 5.10 ($d_{\text{A,B}}$, $J = 11.8$ Hz, 1H), 5.05 (dd, $J = 10.1$, 1.2 Hz, 1H), 4.98 (s, 2H), 4.84 ($d_{\text{A,B}}$, $J = 6.5$ Hz, 1H), 4.79 (s, 1H), 4.77 (s, 1H), 4.69 ($d_{\text{A,B}}$, $J = 6.4$ Hz, 1H), 4.65 ($d_{\text{A,B}}$, $J = 6.4$ Hz, 1H), 4.60 ($d_{\text{A,B}}$, $J = 7.3$ Hz, 1H), 4.40 (d, $J = 2.3$ Hz, 1H), 4.22 (ddd, $J = 11.5$, 8.5, 2.2 Hz, 1H), 4.02 (dd, $J = 3.5$, 12.1 Hz, 1H), 3.97–3.93 (m, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.81 (s, 3H), 3.78–3.73 (m, 2H), 3.60–3.54 (m, 2H), 3.53–3.48 (ddd, $J = 11.7$, 9.6, 5.6 Hz, 1H), 3.44–3.43 (ddd, $J = 11.6$, 9.9, 5.8 Hz, 1H), 3.40 (s, 3H), 3.30 (s, 3H), 3.20 (dd, $J = 16.6$, 5.4 Hz, 1H), 3.07 (dd, $J = 15.3$, 4.0 Hz, 1H), 2.67 (dd, $J = 16.6$, 12.3 Hz, 1H), 2.38 (dd, $J = 14.7$, 8.8 Hz, 1H), 2.23 (dd, $J = 14.3$, 4.5 Hz, 1H), 2.16–2.07 (m, 1H), 2.12 (s, 3H), 1.98–1.92 (m, 1H), 1.88 (dd, $J = 15.0$, 12.3 Hz, 1H), 1.75 (ddd, $J = 14.5$, 10.3, 3.8 Hz, 1H), 1.72 (s, 3H), 1.24 (s, 3H), 1.16 (d, $J = 6.7$ Hz, 3H), 1.03 (s, 3H), 0.96–0.85 (m, 2H), 0.82–0.76 (ddd, $J = 13.7$, 11.4, 5.4 Hz, 1H), 0.74–0.68 (ddd, $J = 13.4$, 11.7, 5.7 Hz, 1H), 0.00 (s, 9H), –0.10 (s, 9H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 171.5, 163.8, 161.3, 160.3, 158.2, 149.4, 149.3, 149.2, 148.7, 142.3, 141.9, 129.5, 128.8, 120.2, 119.1, 115.9, 113.1, 111.1, 110.9, 110.8, 110.6, 107.9, 97.6, 95.0, 94.7, 81.4, 81.3, 79.7, 79.5, 74.6, 71.0, 70.4, 70.4, 66.1, 65.6, 61.5, 58.0, 56.3, 56.2, 56.04, 56.00, 55.99, 40.6, 39.5, 38.3, 29.9, 29.8, 29.2, 27.2, 23.4, 22.9, 21.5, 18.1, 18.0, 11.4, 9.6, –1.2, –1.4; HRMS (ES+) m/z 1219.6161 [(M + Na)⁺; calcd for $\text{C}_{62}\text{H}_{96}\text{N}_2\text{O}_{17}\text{Si}_2\text{Na}$ 1219.6145].

(C11)-O-Methyloximeirciniastatin B (+)–11. To a solution of O-methyloxime (+)–S9 (4.9 mg, 4.1 μmol) in CH_2Cl_2 (0.160 mL) and H_2O (26 μL) was added a suspension of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1 mL, 0.33 M in CH_2Cl_2 , 8 equiv). After 11 h, the

reaction mixture was quenched with a saturated aqueous solution of NaHCO₃ and extracted with EtOAc (3 × 0.5 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo to afford a 2/1 mixture of the desired bis-phenol and 3,4-dimethoxybenzaldehyde, respectively. The crude mixture was carried forward without further purification. The mixture of bis-phenol and 3,4-dimethoxybenzaldehyde (1/2 mixture) was treated with a stock solution of MgBr₂/*n*-BuSH/MeNO₂ in Et₂O (0.200 mL; 25 equiv of MgBr₂, 25 equiv of *n*-BuSH; stock solution 47.4 mg of MgBr₂, 28 μL of *n*-BuSH, 50 μL of MeNO₂, and 0.52 mL of Et₂O). After 10 h, the reaction mixture was diluted with EtOAc, and quenched with a saturated aqueous solution of NaHCO₃ and extracted with EtOAc (5 × 0.5 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The crude mixture was purified via flash chromatography on water-washed SiO₂ (50 g of SiO₂ washed with H₂O (500 mL) and then MeOH (500 mL), EtOAc (500 mL), hexanes (500 mL) and dried under vacuum overnight (30% to 50% to 70% EtOAc/hexanes with 5% v/v triethylamine) to afford (+)-C(11)-O-methylxime-irciniastatin B (+)-11 (1.6 mg, 2.5 μmol, 61% over two steps) as a white amorphous solid: $[\alpha]_D^{20} = +24.8$ (*c* 0.14, CH₂Cl₂); IR (neat) 3370, 2920, 2857, 1658, 1262, 1171, 1071 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 11.12 (s, 1H), 7.32 (d, *J* = 10.0 Hz, 1H), 6.30 (s, 1H), 5.49 (br s, 1H), 5.13 (dd, *J* = 10.2, 6.8 Hz, 1H), 4.81 (s, 1H), 4.78 (s, 1H), 4.52 (ddd, *J* = 11.2, 3.9, 3.9 Hz, 1H), 4.45 (d, *J* = 2.7 Hz, 1H), 4.03 (d, *J* = 2.7 Hz, 1H), 3.97 (dt, *J* = 12.5, 6.2 Hz, 1H), 3.86 (s, 3H), 3.78–3.76 (ddd, *J* = 9.3, 3.5 Hz, 1H), 3.73 (d, *J* = 11.3 Hz, 2H), 3.39 (s, 3H), 3.36 (s, 3H), 2.91–2.80 (m, 3H), 2.70 (dd, *J* = 14.7, 5.3 Hz, 1H), 2.37 (dd, *J* = 14.7, 9.4 Hz, 1H), 2.14 (dd, *J* = 14.8, 3.7 Hz, 1H), 2.09 (s, 3H), 1.89 (m, 2H), 1.80 (dd, *J* = 15.0, 10.8 Hz, 1H), 1.75 (s, 3H), 1.59 (d, *J* = 15.0 Hz, 1H), 1.18 (s, 3H), 1.12 (app s, 3H), 1.10 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 173.3, 170.8, 162.4, 161.4, 158.0, 142.1, 139.9, 113.5, 113.3, 101.5, 83.5, 80.5, 80.4, 79.9, 73.1, 72.7, 72.4, 61.7, 57.9, 56.9, 42.8, 40.7, 37.5, 32.4, 32.1, 29.9, 28.4, 23.7, 22.8, 20.9, 10.7, 9.2; HRMS (ES+) *m/z* 659.3156 [(M + Na)⁺; calcd for C₃₂H₄₈N₂O₁₁Na 659.3156].

■ ASSOCIATED CONTENT

● Supporting Information

These materials are available free of charge via the Internet at The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02771.

CD and ¹H and ¹³C NMR spectroscopic data of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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