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Total Synthesis and Biological Evaluation of Irciniastatin A (a.k.a. Psymberin) and Irciniastatin B

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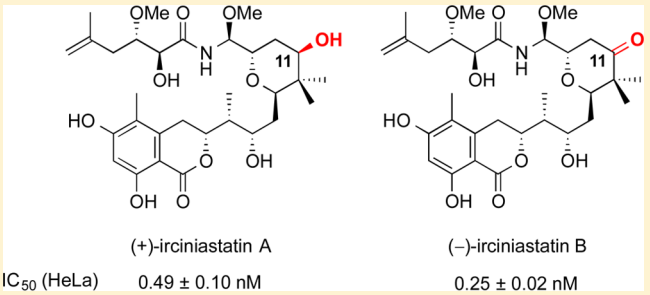
Supporting Information

ABSTRACT: Irciniastatin A (a.k.a. psymberin) and irciniastatin B are members of the pederin natural product family, which have potent antitumor activity and structural complexity. Herein, we describe a full account of our total synthesis of (+)-irciniastatin A and (−)-irciniastatin B. Our synthesis features the highly regioselective Eu(OTf)$_3$-catalyzed, DTBMP-assisted epoxide ring opening reaction with MeOH, which enabled a concise synthesis of the C1−C6 fragment, extensive use of AZADO (2-azaadamantane *N*-oxyl) and its related nitroxyl radical/oxoammonium salt-catalyzed alcohol oxidation throughout the synthesis, and a late-stage assembly of C1−C6, C8−C16, and C17−C25 fragments. In addition, for the synthesis of (−)-irciniastatin B, we achieved the C11-selective control of the oxidation stage via regioselective deprotection and AZADO-catalyzed alcohol oxidation. The synthetic irciniastatins showed high levels of cytotoxic activity against mammalian cells. Furthermore, chemical footprinting experiments using synthetic compounds revealed that the binding site of irciniastatins is the E-site of the ribosome.



INTRODUCTION

In 2004, (+)-irciniastatin A (**1**) and (−)-irciniastatin B (**2**) were isolated by Pettit and co-workers[1] from the marine sponge *Ircinia ramosa*. Independently, psymberin was isolated by Crews and co-workers[2] from the marine sponge *Psammocinia* in the same year (Figure 1). These two reports revealed that these natural products possessed a complex molecular architecture consisting of an unstable *N*,*O*-aminal moiety, a highly substituted 2,6-*trans*-tetrahydropyran skeleton, and either nine or eight stereogenic centers. At that time, Crews assumed that irciniastatin A and psymberin are identical; however, the stereochemistry of both compounds was not determined completely.

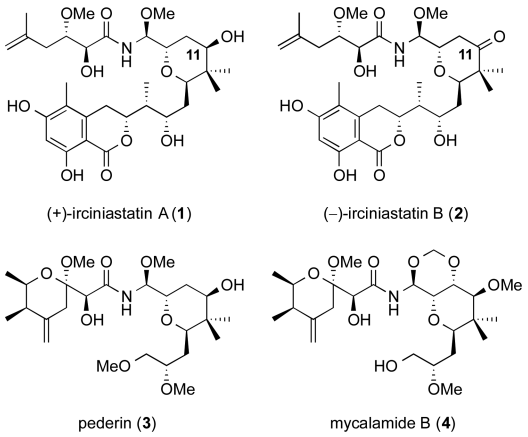


Figure 1. Pederin-type natural products.

In 2005, the first total synthesis of (+)-irciniastatin A (**1**) was accomplished by De Brabander and co-workers,[3] who established the absolute configuration of (+)-**1** and demonstrated that (+)-irciniastatin A and psymberin possess identical structures. After this pioneering synthesis, 7 total syntheses[4] including the synthesis by our laboratory,[4d] 2 formal syntheses,[5] and 10 synthetic studies[6] have been reported.

Besides their fascinating structures, both (+)-irciniastatin A (**1**) and (−)-irciniastatin B (**2**) show strong inhibitory activity against a series of human cancer cell lines at the nanomolar level.[1] Interestingly, these two congeners possess different values of activity against several human cancer cell lines,[1] although these structures were considered to differ only in the oxidation level at C11. Subsequently, some analogues of **1** were

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synthesized and tested for their biological activities,[4d,e,g,7] which gave highly potent derivatives and biological insights.[8]

However, compared with those of (+)-irciniastatin A (**1**), the structural and biological details of (−)-irciniastatin B (**2**) have not been intensively investigated. In 2012, Smith and co-workers achieved the first total synthesis and determination of the absolute configuration of (−)-irciniastatin B (**2**),[9] which is the only example of total synthesis.

To shed light on the impact of C11 oxidation level on their biological activity,[10] we explored efficient synthetic routes to irciniastatins. Herein, we provide a full account of our work including the total synthesis of (+)-irciniastatin A (**1**) and (−)-irciniastatin B (**2**). Subsequently, we describe the binding mode of irciniastatins on the ribosome, which might induce the inhibition of protein translation.

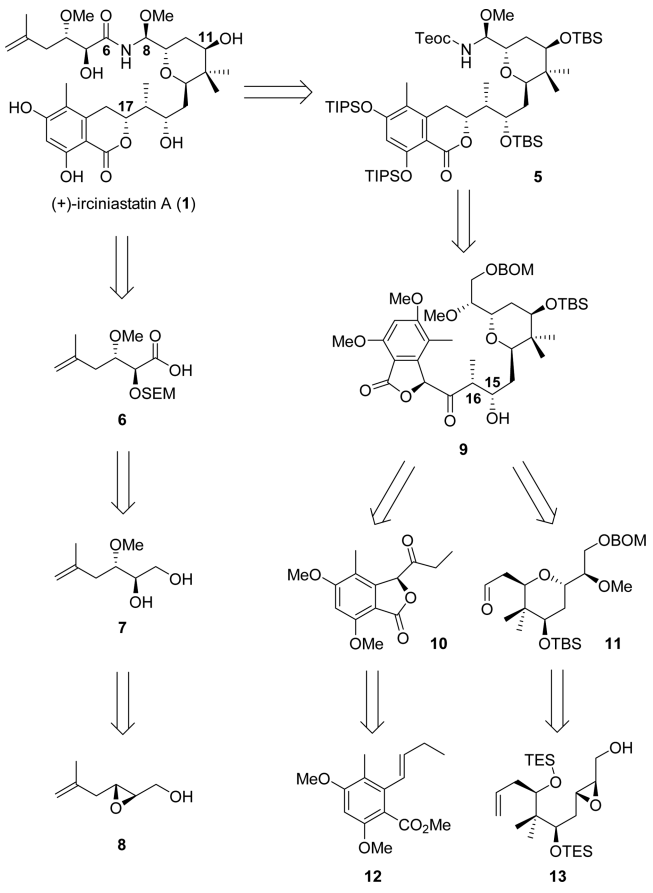
RESULTS AND DISCUSSION

Total Synthesis of (+)-Irciniastatin A (1). Considering stereochemical complexity and structural clarity, coupled with our assumption that irciniastatins would be only distinguished by the oxidation stage at C11, we set (+)-irciniastatin A as the first goal of our synthetic venture. Our first-generation retrosynthetic analysis of (+)-irciniastatin A (**1**) is depicted in Scheme 1. **1** was disconnected at the amide bond, leading to the protected hemiaminal **5** and the C1−C6 acyclic side chain **6**. For the installation of the hemiaminal functionality in **5**, we relied on the Curtius rearrangement approach developed by Smith and co-workers.[4b,9] The key intermediate **5** was conceived to be transformed from **9** via a diastereoselective reduction of the aldol moiety and a reductive translactonization. We envisioned that **9** would be united via a substrate-controlled aldol reaction of the C16−C25 ketone fragment **10** and the C8−C15 tetrahydropyran fragment **11**. We envisioned synthesizing not only both fragments **6** and **11** but also their enantiomers and diastereomers for future SAR study; we decided to adopt the "Sharpless asymmetric epoxidation−regioselective epoxide ring opening" sequence as a key maneuver.[11] 1,2-Diol **7** would be synthesized via a Lewis acid mediated regioselective ring opening from 2,3-epoxy alcohol **8**, which could be easily obtained using the Sharpless asymmetric epoxidation reaction. Independently, tetrahydropyran unit of **11** would be constructed in the same manner from epoxy alcohol **13**. The aldol counterpart **10** would be accessed from *E*-alkene **12** via the Sharpless asymmetric dihydroxylation, γ-lactonization, and oxidation of the resultant alcohol.

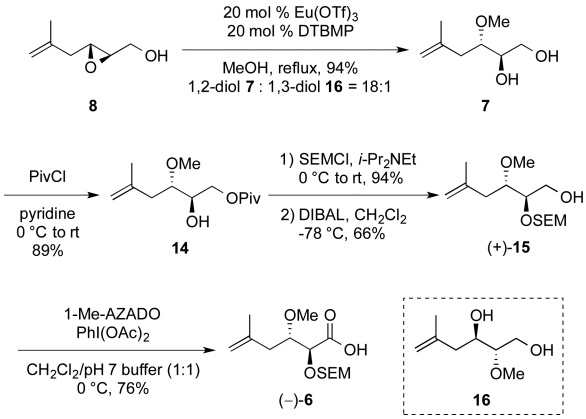
The synthesis of side chain **6** began with the regioselective ring opening of the known 2,3-epoxy alcohol (+)-**8**[12] with MeOH (Scheme 2). The Ti(O-*i*-Pr)$_4$-mediated nucleophilic ring opening of 2,3-epoxy alcohols was developed by Sharpless and co-workers, which provides 3-substituted-1,2-diol derivatives.[13] Initially, we tried this condition, but the yield and selectivity were unsatisfactory, giving the desired 1,2-diol **7** and undesired 1,3-diol **16** (54% yield, **7**:**16** = 3:1) as an inseparable mixture. After extensive screening of the reaction conditions, we found that the combined use of catalytic amounts of Eu(OTf)$_3$ and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) gave the desired 1,2-diol **7** in high yield and regioselectivity. In addition, we also found that this catalytic method can be applied to various epoxy alcohols and nucleophiles (alcohols, thiols, and amines).[14] The 1,2-diol **7** was converted to primary alcohol (+)-**15** via a protection−deprotection sequence. Oxidation of (+)-**15** using 1-Me-AZADO/PhI(OAc)$_2$[15] provided carboxylic acid (−)-**6**.

Access to the 2,6-*trans*-tetrahydropyran fragment **11** began with the known epoxy alcohol (+)-**17**,[16] which was prepared from (−)-pantolactone (Scheme 3). Protection of the primary alcohol (+)-**17** as the THP ether, followed by regioselective ring opening of epoxide with lithium acetylide and BF$_3$·OEt$_2$,[17] furnished the secondary alcohol **18**. Removal of the THP group and the subsequent TEMPO-catalyzed oxidation gave aldehyde (+)-**19** selectively. A diastereoselective allylation of (+)-**19** using allyltributylstannane in the presence of MgBr$_2$[18] produced diol (+)-**20** with high selectivity. Protecting group manipu-

Scheme 1. First-Generation Retrosynthetic Analysis of (+)-Irciniastatin A (1)



Scheme 2. Synthesis of Carboxylic Acid (−)-6



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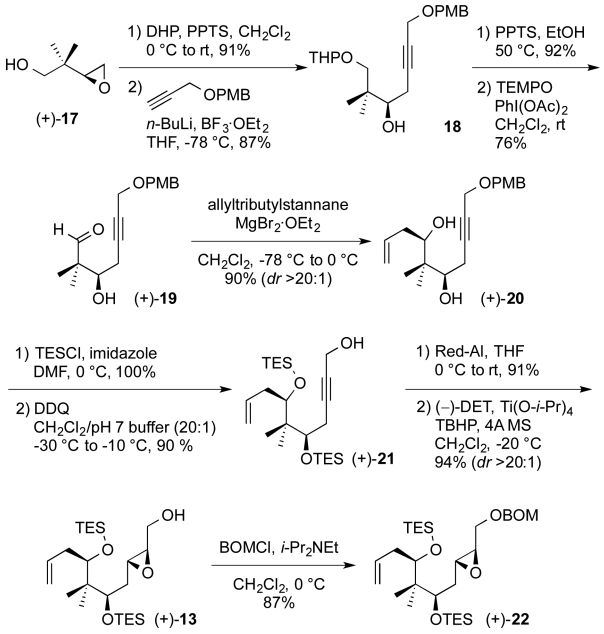
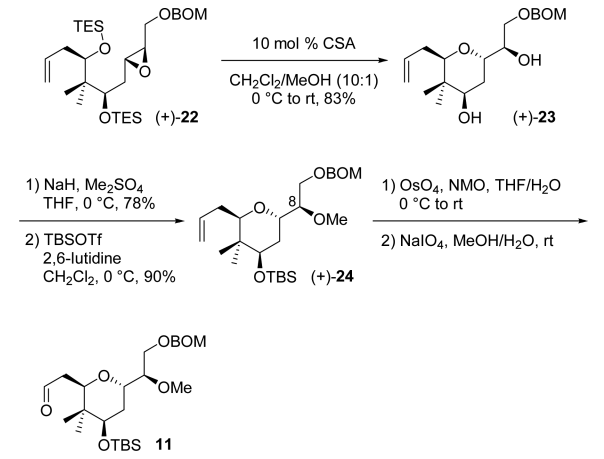
Scheme 3. Synthesis of Tetrahydropyran Precursor (+)-22



lation, followed by (*E*)-selective reduction of the alkyne, furnished the corresponding allyl alcohol, which was then converted to the epoxide (+)-**22** through the Sharpless asymmetric epoxidation and protection of the primary alcohol.

We then focused on the epoxide ring opening–tetrahydropyran ring formation using (+)-**22** (Scheme 4). Fortunately,

Scheme 4. Concise Synthesis of 2,6-*trans*-Tetrahydropyran Fragment 11



we found that the catalytic amount of camphorsulfonic acid (CSA) simultaneously promoted the removal of the TES group and oxy-cyclization to furnish the 2,6-*trans*-tetrahydropyran (+)-**23**.[19] For regioselective methylation of the C8 hydroxyl group, four types of conditions were screened: (1) KOH/MeI (64% yield), (2) *t*BuOK/MeI (39% yield), (3) DTBMP/MeOTf (complex mixtures), and (4) NaH/Me_2SO_4 (78%), indicating that bulkiness of the methylating reagent was important. Protection of the C11 hydroxyl group and the oxidative cleavage of the terminal alkene gave the desired aldehyde **11**.

Synthesis of the requisite left-wing fragment (+)-**10** began with the installation of a methyl group onto **26** to give **27** via an electrophilic methoxymethylation of the benzene nuclei and the following hydrogenolytic cleavage of the methoxy group (Scheme 5). The remaining phenolic group was triflated to give **28**, the Suzuki–Miyaura coupling of which with alkenyl boronate **29** in the presence of $Pd(PPh_3)_4$ and K_3PO_4 in dioxane at 100 °C gave **12** in 83% yield. Upon treatment with Sharpless AD-mix-α, the *E*-alkene **12** furnished γ-lactone (+)-**30** in 88% (>99% ee after recrystallization) via the enantioselective dihydroxylation and concomitant lactonization. 1-Me-AZADO-catalyzed oxidation[15] of (+)-**30** using PhI(OAc)$_2$ gave ketone (+)-**10** without losing enantiomeric integrity.

Having secured both the coupling partners, we next examined the aldol reaction to construct the C15–C16 bond. Disappointingly, our attempt was hampered by the highly acidic nature of the C18-methine proton, which caused a facile scrambling of enolates generated from (+)-**10**, impairing the enantiomeric purity. Worse still, a model study using nonanal with lithium enolate, generated *in situ* from the ketone (+)-**10** and LDA in THF at −78 °C, gave exclusively C18-aldol **31**, indicating the pronounced reactivity of the C18-enolate in the aldol reaction compared with the C16-enolate. These observations led us to alter our synthetic plan shown in Scheme 6.

Thus, the projected key intermediate **5** was disconnected in a retro-aldol fashion into the C17–C25 aldehyde fragment **32** and the C8–C16 tetrahydropyran fragment **33** in light of successful precedents by De Brabander[3,4g] and Smith.[4b,9] The requisite ketone **33** would be prepared from the aldehyde **11** via nucleophilic introduction of an ethyl group.

To install the ethyl ketone moiety, **11** was treated with ethylmagnesium bromide, followed by 1-Me-AZADO oxidation,[15] to give ketone (+)-**34** in good yield (Scheme 7). To complete the synthesis of the tetrahydropyran fragment, one-pot oxidation conditions developed in our laboratory[20] were utilized for the construction of the carboxylic acid moiety. Thus, deprotection of the BOM ether gave the corresponding primary alcohol, which was oxidized using 1-Me-AZADO$^+BF_4^-$/$NaClO_2$, followed by treatment with benzyl bromide, to provide the desired central fragment (+)-**33**.

With the fragment (+)-**33** in hand, we examined the coupling reaction of (+)-**33** with the aldehyde **32**.[3] Treatment of (+)-**33** with dichlorophenylborane[21] provided the *Z*-enolate, and the addition of **32** provided the aldol product (+)-**35** with high diastereoselectivity (Scheme 8).[22] Subsequent diastereoselective reduction of the C15 ketone (+)-**35** with $NaBH_4$ in the presence of Et_3B, followed by lactonization, provided dihydroisocoumarin (+)-**36**. The benzyl ester moiety in (+)-**36** was then converted to a carboxylic acid via hydrogenation, which was subjected to a Curtius sequence using 2-(trimethylsilyl)ethanol as a nucleophile to give Teoc-protected hemiaminal (+)-**5** in high yield.

For the synthesis of **1**, the stage was set to examine the coupling of (+)-**5** with the acylic chain (−)-**6**. Initially, we tried the coupling using the acyl chloride derivative from (−)-**6**, but we only observed decomposition of acid chloride. We assumed that these results were due to instability of acid chloride compounds in this condition. After intensive effort, we found that the choice of the protecting group of alcohol in (−)-**6** was important,[23] and Smith's protocol[4b,9] was the only successful method of this coupling reaction. Finally, the deprotection of all of the protecting groups using TASF provided (+)-irciniastatin A [(+)-**1**] in 53% yield. We used this synthetic route for the

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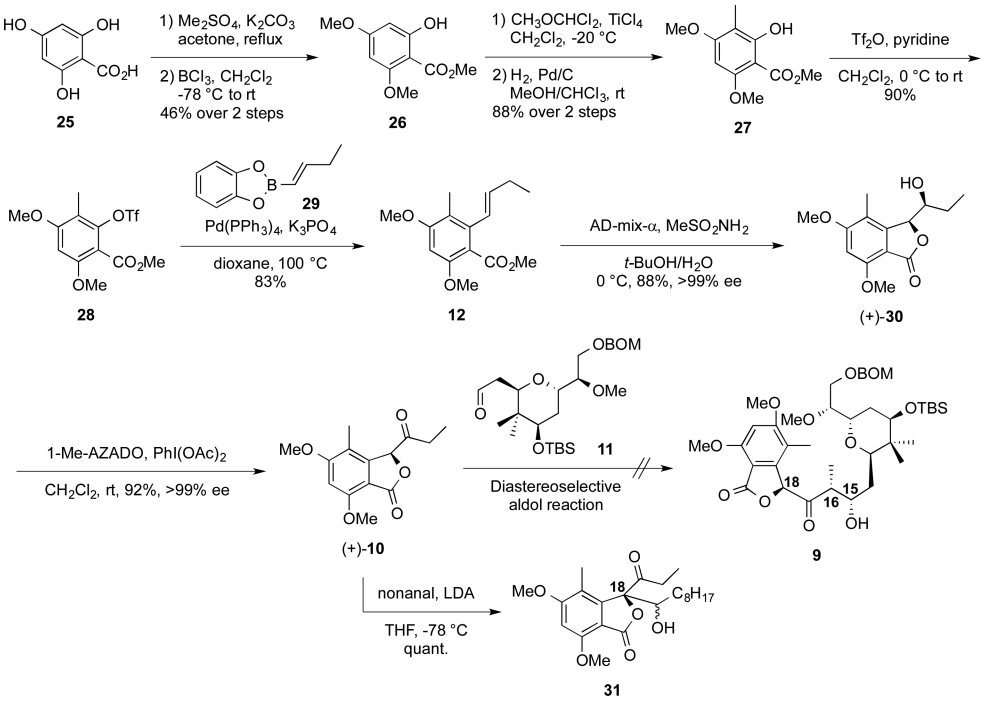
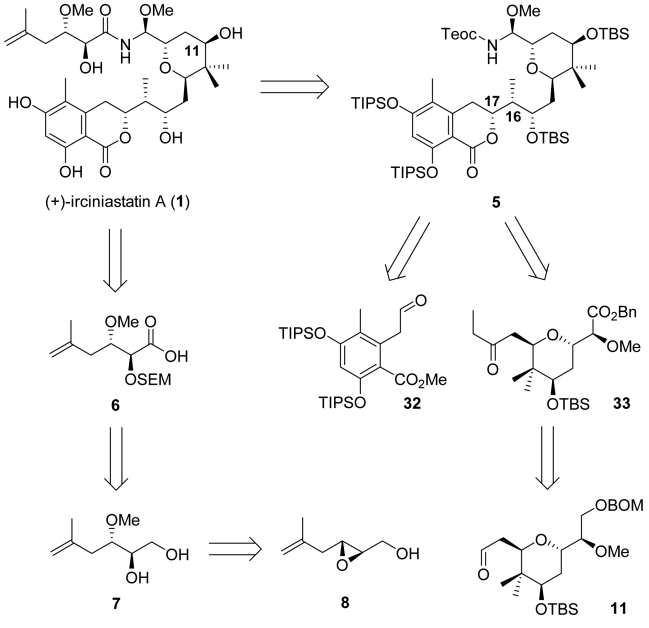
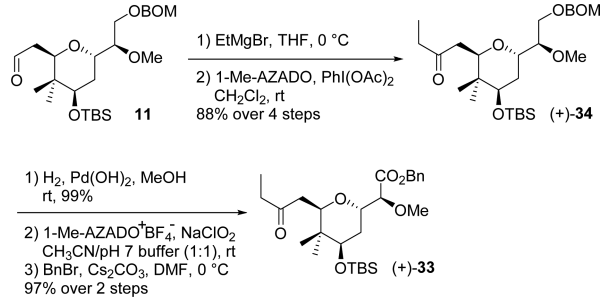
Scheme 5. Synthesis of Left Fragment (+)-10 and Attempts at Aldol Reaction



Scheme 6. Alternative Synthetic Strategy



Scheme 7. Concise Synthesis of Tetrahydropyran Fragment (+)-33



synthesis of unnatural (−)-irciniastatin A [(−)-**1**] and (+)-alkymberin [(+)-**39**] for our biological studies.[4d]

Total Synthesis of (−)-Irciniastatin B (2). Toward the total synthesis of (−)-irciniastatin B (**2**), we initially ambitioned the direct conversion strategy from (+)-irciniastatin A [(+)-**1**] (Scheme 9). Thus, we anticipated that the C11 hydroxyl group would be the most sterically hindered among the hydroxyl groups of irciniastatin A (**1**), thereby resisting protection by a hindered silyl group. Indeed, the treatment of (+)-**1** with 7 equiv of TBSOTf gave tetrakis-TBS ether together with pentakis-TBS ether. After chromatographic separation, the tetrakis-TBS ether was oxidized by AZADO[15] to furnish the ketone. However, extensive structural analysis revealed that the product was not **41** but (+)-**40** having the unexpected C15-carbonyl moiety instead of C11.[24] This result could be due to the decrease in the nucleophilicity of the C15-hydroxy group via the intramolecular hydrogen bonding effect. Because the direct conversion from irciniastatin A to B was difficult, we decided to develop an alternative strategy toward the synthesis of **2**.

For the synthesis of (−)-irciniastatin B (**2**), we considered that the oxidation of C11 should be conducted at the late stage of the synthesis of **2**. In fact, Smith and co-workers reported that the 2,6-*trans*-tetrahydropyran-4-one core was very unstable under basic conditions.[9] The synthesis of new tetrahydropyran fragment (+)-**44** for (−)-irciniastatin B (**2**) commenced from the functional group manipulation of diol (+)-**23** (Scheme 10). Upon the selective methylation of the C8 hydroxy group, and the deprotection of the benzyloxymethyl group using $LiBF_4$,[25] (+)-**23** was converted to diol (+)-**42**, the remaining two hydroxyl groups of which were protected by benzyl ether to give (−)-**43** in 80% yield. Next, the ketone (+)-**44** was synthesized via a four-step sequence, as in the synthesis of (+)-**33**.

With (+)-**44** in hand, we examined the aldol coupling with the aldehyde **32** (Scheme 11). Also in this case, dichlor-

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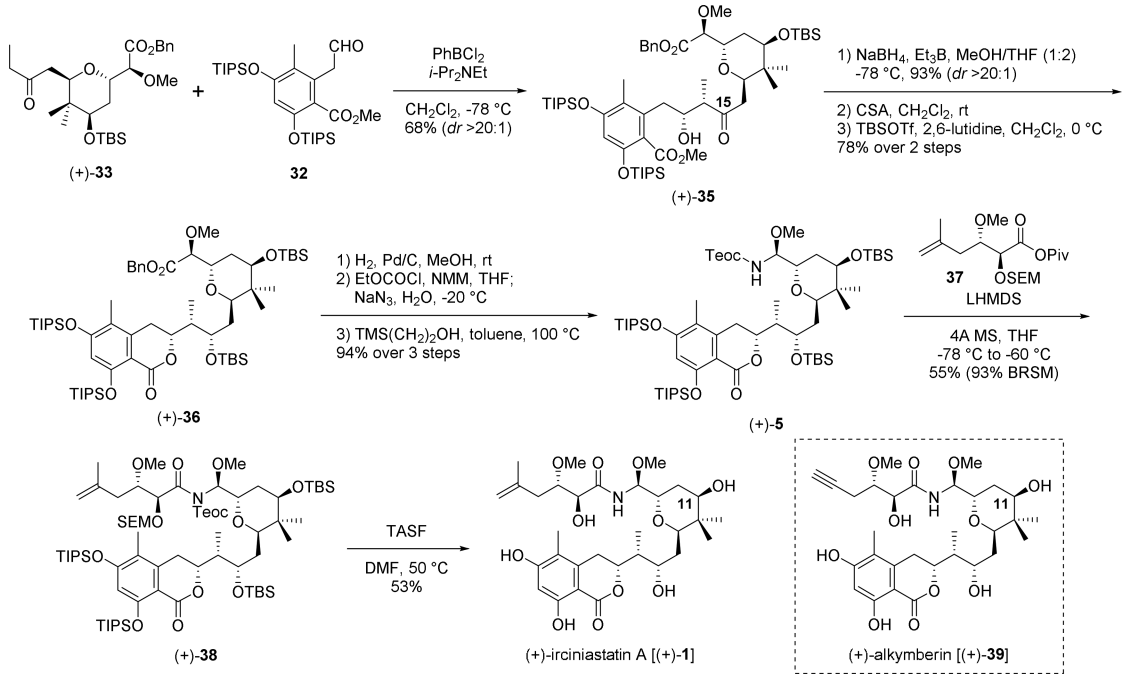
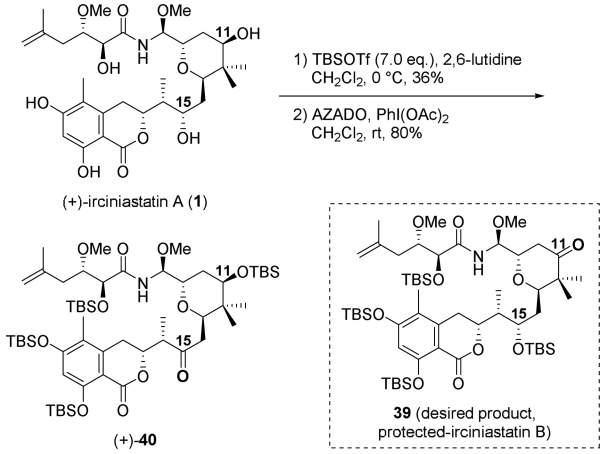
J. Org. Chem. 2015, 80, 12333−12350

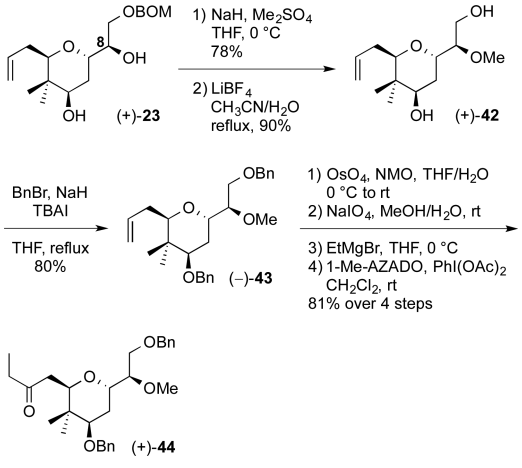
Scheme 8. Total Synthesis of (+)-Irciniastatin A [(+)-1]



Scheme 9. Attempted Direct Conversion of Irciniastatin A (1) to B (2)



Scheme 10. Synthesis of Fragment (+)-44



ophenylborane[21] was the best Lewis acid for the coupling, which gave (+)-**45** with good diastereoselectivity. Reduction of (+)-**45** with $NaBH_4$ in the presence of Et_2BOMe provided the 1,3-*syn* diol product, which was converted to lactone (+)-**46** in 78% over 2 steps. We then focused on the selective oxidation of the primary alcohol to the corresponding carboxylic acid. After screening, we found that the selective one-pot oxidation proceeded smoothly using the salt of DMN-AZADO[26] (1,5-dimethyl-9-azanoradamantane *N*-oxyl), which gave (+)-**48** in 81% yield. Note that the same oxidative conversion using $TEMPO^+BF_4^-$ catalyst resulted in a modest yield of (+)-**48** (12 h, 56% yield). Subsequent Curtius rearrangement, followed by the protection of the C11 alcohol as a TES ether, furnished Teoc-protected hemiaminal (+)-**50**. The final fragment union of (+)-**50** with the acyclic side chain **37** was achieved using the same conditions as those for the synthesis of (+)-**38**. The selective deprotection of the TES ether of (+)-**51** using 1 M HCl, followed by AZADO oxidation,[15] gave protected irciniastatin B (+)-**52**. Finally, global deprotection using TASF provided (−)-irciniastatin B (**2**). However, there were some slight differences in ^1H and ^{13}C NMR spectra and the optical rotation value between the (−)-**2** isolated by Pettit and co-workers[1] and our synthetic (−)-**2**.

Nevertheless, all of the spectral data for our synthetic (−)-**2** were in full agreement with the data reported by Smith and co-workers.[9] Thus, we concluded that the structure and absolute configuration of our synthetic (−)-**2** are correct. In addition, we confirmed that our synthetic (−)-**2** possessed the desired 2,6-*trans*-tetrahydropyran-4-one core by 2D-NOE correlations.[27]

Biological Studies of Irciniastatins A and B. Synthetic irciniastatins A and B were evaluated for their cytotoxicity against mammalian cell lines (Table 1). As we previously reported,[28] (+)-irciniastatin A [(+)-**1**] showed potent cytotoxicity, but (−)-irciniastatin B [(−)-**2**] showed more potent cytotoxicity. We previously reported that (+)-irciniastatin A [(+)-**1**] inhibited protein translation and cell cycle progression in the G1 phase in Jurkat cells. As expected, both irciniastatins

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Scheme 11. Total Synthesis of (−)-Irciniastatin B [(−)-2]

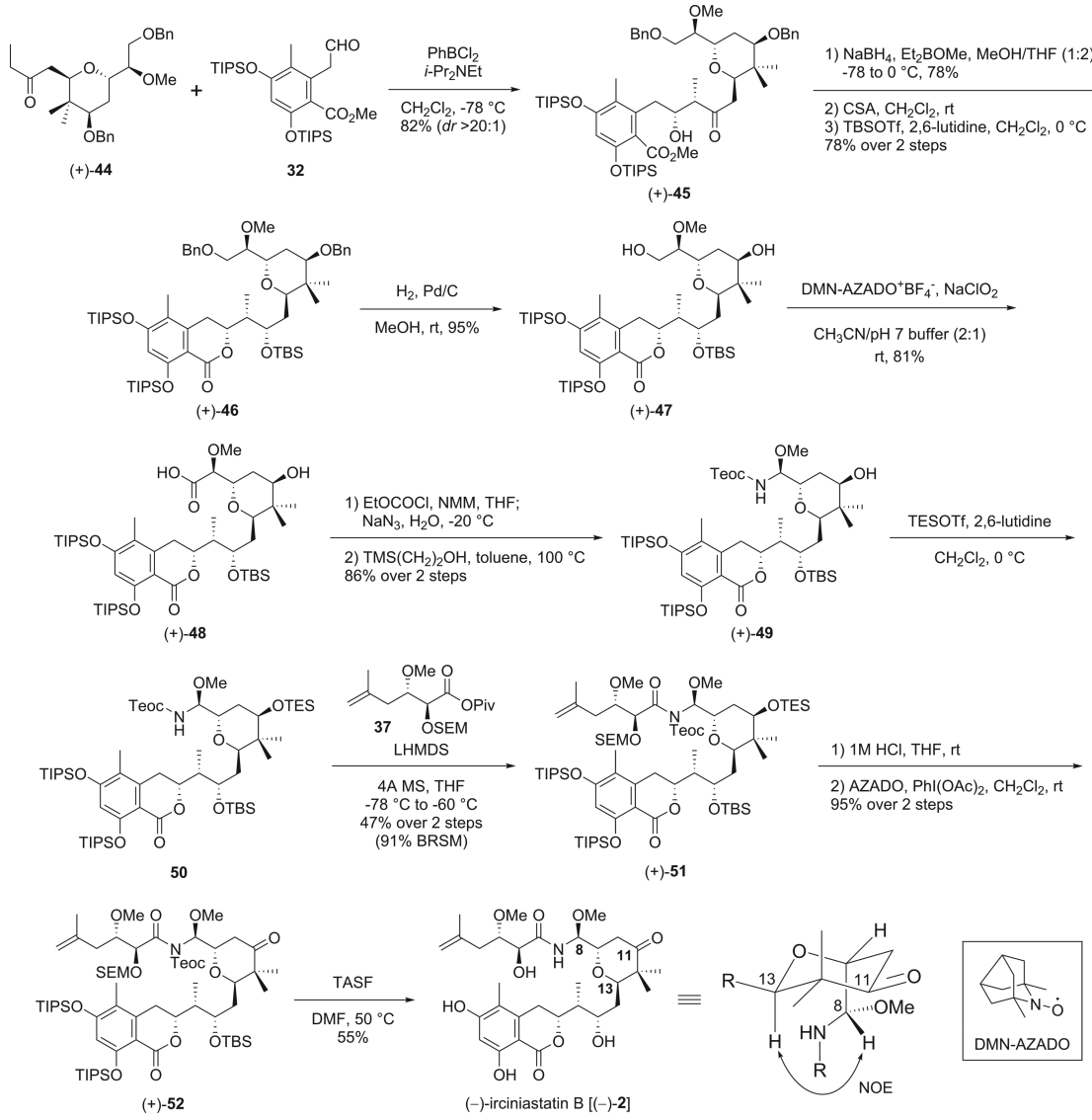

Table 1. IC_{50} Value for Cytotoxicity against Mammalian Cells[a]

	IC_{50} (nM)			
	HeLa	3Y1	MCAS	SKOV3
irciniastatin A	0.49 ± 0.10	1.24 ± 0.40	1.36 ± 0.37	0.34 ± 0.03
irciniastatin B	0.25 ± 0.02	0.41 ± 0.04	0.61 ± 0.08	0.16 ± 0.00

[a]Exponentially growing cells were treated with various concentrations of irciniastatins A and B for 48 h (HeLa and 3Y1) or 72 h (MCAS and SKOV3). Cell viability was determined by WST-8. Values are expressed as mean ± deviation of two independent experiments (MCAS and SKOV3), or mean ± SD of three independent experiments (HeLa and 3Y1).

A and B also potently inhibited protein translation in HeLa and 3Y1 cells and cell cycle progression in G1 phase in 3Y1 cells (Tables 2 and 3). These results strongly suggest that (−)-irciniastatin B [(−)-**2**] as well as (+)-irciniastain A [(+)-**1**] is a potent protein translation inhibitor.

Chemical footprinting has been used to map the binding site of translation inhibitors, and mycalamide B (**4**), another pederin-type translation inhibitor, has given rise to a footprint at the E-site of the 60S ribosomal subunit.[29] Therefore, we next investigated whether (+)-irciniastatin A [(+)-**1**] and (−)-irciniastatin B [(−)-**2**] also bind in the same site to the mycalamide B-binding site.

Purified yeast ribosomes were incubated with each compound, followed by treatment with dimethyl sulfate (DMS). Footprints were obtained with extracted ribosome RNA by primer extension using avian myeloblastosis virus (AMV) reverse transcriptase. As shown in Figure 2, a specific methylation of C2765 on the 25S rRNA (corresponding to C3993 on 28S rRNA in mammalian cells) of the large subunit by DMS treatment was seen in DMSO samples, and this methylation was inhibited by pretreatment with 100 nM (+)-irciniastatin A [(+)-**1**], (−)-irciniastatin B [(−)-**2**], and cycloheximide (CHX). These results strongly suggested that (+)-irciniastatin A [(+)-**1**] and (−)-irciniastatin B [(−)-**2**] bind

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Table 2. IC_{50} Value for Protein Synthesis of 3Y1 and HeLa Cells[a]

	IC_{50} (nM)	
	HeLa	3Y1
irciniastatin A	3.84 ± 0.13	3.05 ± 0.33
irciniastatin B	0.98 ± 0.06	0.71 ± 0.04

[a]Exponentially growing 3Y1 and HeLa cells were treated with various concentrations of irciniastatins A and B for 2 h, followed by [methyl-^{3}H] methionine treatment for 2 h. Radioactivity in acid-insoluble fractions was determined. Values are expressed as mean ± deviation of two independent experiments.

Table 3. Distribution of DNA Content in 3Y1[a]

		DNA content (%)		
	concentration (nM)	2C	2−4C	4C
control	0.0	63.7	25.6	10.7
irciniastatin A	1.0	78.5	15.5	6.0
irciniastatin B	0.3	77.0	16.9	6.1

[a]Exponentially growing 3Y1 cells were treated with irciniastatins A and B at indicated concentrations for 18 h, and the distribution of DNA content and relative cell number were determined.

in the same site to the mycalamide B-binding site, the E-site of ribosome.

Taken together, the results strongly suggest that (+)-irciniastatin A [(+)-**1**] and (−)-irciniastatin B [(−)-**2**] bind in the E-site of the 60S ribosomal subunit and inhibit protein translation.

CONCLUSION

We have accomplished the divergent total synthesis of (+)-irciniastatin A [(+)-**1**] and (−)-irciniastatin B [(−)-**2**] using "Sharpless asymmetric epoxidation−regioselective epoxide ring opening" chemistry as a key maneuver. In the synthesis of the side chain, we have demonstrated an effective protocol for regioselective epoxide ring opening reaction using Eu(OTf)$_3$/DTBMP, which realized the shortest (eight steps from commercially available propargyl alcohol) synthesis of this fragment reported to date. The convergent synthetic routes were developed via a late-stage assembly of C1−C6, C8−C16, and C17−C25 fragments. In the total synthesis of (−)-irciniastatin B, we achieved the C11-selective control of the oxidation stage via expedient functional group transformations and AZADO-catalyzed alcohol oxidation. Eight of nine stereocenters (for irciniastatin A)/seven of eight stereocenters (for irciniastatin B), except for one derived from (−)-pantolactone, were constructed employing Sharpless asymmetric epoxidation or substrate control transformations. Although our synthetic routes rely on frequent use of protecting groups (for irciniastatin A, 11 steps out of a total of 31 steps were allocated for protection/deprotection reaction; for irciniastatin B, 12 steps out of a total of 33 steps), the robust sequence allowed giving a sufficient amount of irciniastatins for biological evaluation.

The biological studies using synthetic compounds showed a high level of cytotoxic activity against mammalian cells. Furthermore, chemical footprinting experiments revealed that the binding site of irciniastatins is the E-site of the ribosome.

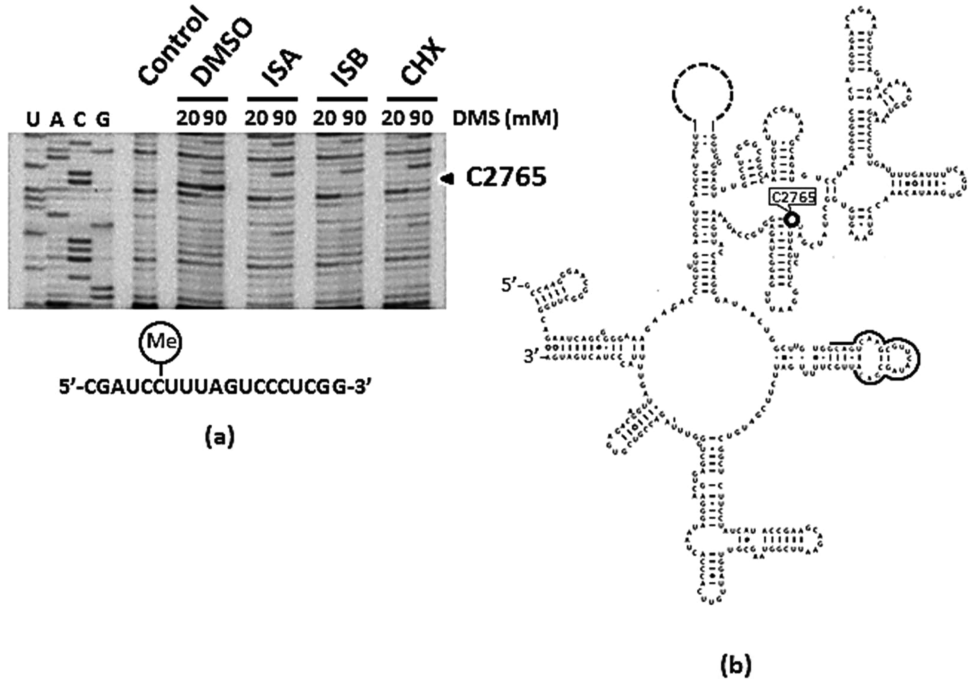

Figure 2. Inhibition of protein synthesis by binding to the E-site of the 60S subunit: The chemical footprinting of irciniastatins A and B. Ribosomes were incubated with 100 nM solutions of the compounds as indicated and methylated with DMS. Extracted rRNAs were subjected to reverse transcription. (a) rRNA not treated with DMS was the control. The [^{32}P]-labeled DNA was resolved on a denaturing polyacrylamide gel. (b) Secondary structure of the 25S LSU domain V (nucleotides 2365−2423 and 2607−2994). The primer hybridized with extracted rRNA is underlined. The binding site (C2765) in domain V of the 25S rRNA is indicated.

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EXPERIMENTAL SECTION

General Procedure. All reactions were carried out under an argon atmosphere with dehydrated solvents under anhydrous conditions, unless otherwise noted. Dehydrated THF and CH_2Cl_2 were purchased and other solvents were dehydrated and distilled according to standard protocols. Reagents were obtained from commercial suppliers and used without further purification, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates ($60F_{254}$). Column chromatography was performed on Silica gel 60N (spherical, neutral, 63-210 μm), and flash column chromatography was performed on Silica gel 60N (spherical, neutral, 40−50 μm). Optical rotations were measured at rt, using the sodium D line. Infrared spectra were obtained at 4.0 cm^{-1} resolution and are reported in wavenumbers. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded using 400 or 600 MHz spectrometers. The chemical shifts (δ) are given from TMS (0.00 ppm) in $CDCl_3$ and from the residual nondeuterated solvent peak in methanol-d4 (methanol-d4:3.30 ppm) as internal standards. Coupling constants (J) are reported in hertz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, sept = septet, br = broad. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a 100 or 150 MHz spectrometer. The chemical shifts are given from $CDCl_3$ (77.0 ppm) and methanol-d4 (49.0 ppm) as internal standards. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded using electron impact (EI) with a magnetic sector or time-of-flight mass analyzer, or by fast atom bombardment (FAB) with a magnetic sector or time-of-flight mass analyzer, or by electrospray ionization (ESI) with an ion-trap mass analyzer. HPLC was performed using a UV/vistbl1 detector at 254 nm.

(2*R*,3*S*)-3-Methoxy-5-methylhex-5-ene-1,2-diol 7. To a solution of epoxy alcohol **8**[12] (708 mg, 5.53 mmol) in MeOH (28 mL) was added 2,6-di-*tert*-butyl-4-methylpyridine (227 mg, 1.11 mmol), followed by $Eu(OTf)_3$ (780 mg, 1.11 mmol), and the reaction was stirred for 19 h at 70 °C. After cooling of the reaction, sat. $NaHCO_3$ (15 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 2/1) gave diol **7** (835 mg, 5.22 mmol, 94%) as a pair of regioisomers (1,2-diol **7**:1,3-diol **16** = 18:1 determined by ^1H NMR spectrum).

7: IR (neat): 3390, 2936, 1648, 1446, 1214, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.84 (brs, 1H), 4.80 (brs, 1H), 3.84−3.77 (m, 1H), 3.73−3.67 (m, 2H), 3.54 (dt, J = 6.6, 4.1 Hz, 1H), 3.47 (s, 3 × 1/19H), 3.43 (s, 3 × 18/19H), 2.70 (d, J = 6.3 Hz, 1H), 2.44−2.41 (m, 1H), 2.38 (dd, J = 14.1, 6.8 Hz, 1H), 2.18 (dd, J = 14.3, 6.5 Hz, 1H), 1.79 (s, 3H); MS (EI) calculated for $C_7H_{13}O_2$ $[M - CH_3O]^+$: 129.0916, found 129.0894.

(2*R*,3*S*)-2-Hydroxy-3-methoxy-5-methylhex-5-en-1-yl Pivalate 14. To a solution of diol **7** (205 mg, 1.28 mmol) in pyridine (2.6 mL) was added PivCl (0.173 mL, 1.41 mmol) at 0 °C. The reaction was allowed to warm to rt, and after 2 h, the reaction was cooled to 0 °C and Et_2O (3 mL) was added. Sat. $NaHCO_3$ (3 mL) was then added, and the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/8) gave pivalate ester **14** (276 mg, 1.13 mmol, 89%) as a pair of regioisomers.

14: IR (neat): 3479, 2973, 2828, 1730, 1460, 1285, 1164, 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.78 (s, 1H), 4.76 (s, 1H), 4.18 (dd, J = 11.2, 3.6 Hz, 1H), 4.11 (dd, J = 11.2, 6.4 Hz, 1H), 3.85−3.82 (m, 2H), 3.40−3.36 (m, 1H), 3.35 (s, 3H), 2.27 (dd, J = 14.4, 7.6 Hz, 1H), 2.21 (dd, J = 14.8, 5.2 Hz, 1H), 1.74 (s, 3H), 1.17 (s, 9H); MS (EI) calculated for $C_{13}H_{24}O_4$ $[M]^+$: 244.1675, found 244.1703.

(2*R*,3*S*)-3-Methoxy-5-methyl-2-((2-(trimethylsilyl)ethoxy)-methoxy)hex-5-en-1-yl Pivalate 53. To a solution of pivalate ester **14** (276 mg, 1.13 mmol) in CH_2Cl_2 (3.8 mL) was added *i*-Pr_2NEt (0.494 mL, 2.83 mmol), followed by SEMCl (0.400 mL, 2.26 mmol), at 0 °C, and the reaction was allowed to warm to rt. After stirring for 4 h, the reaction was cooled to 0 °C and sat. NH_4Cl (3 mL) was added. The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/20) gave SEM-ether **53** (399 mg, 1.07 mmol, 94%) as a pair of regioisomers.

53: IR (neat): 2955, 1733, 1249, 1159, 1106, 1059, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.82 (brs, 1H), 4.79 (brs, 1H), 4.77 (d, J = 7.2 Hz, 1H), 4.74 (d, J = 7.2 Hz, 1H), 4.30 (dd, J = 11.6, 4.0 Hz, 1H), 4.12 (dd, J = 11.6, 6.4 Hz, 1H), 3.83 (dt, J = 6.4, 4.0 Hz, 1H), 3.69 (dt, J = 10.0, 6.4 Hz, 1H), 3.60 (dt, J = 10.0, 6.8 Hz, 1H), 3.50 (ddd, J = 7.2, 5.2, 4.0 Hz, 1H), 3.40 (s, 3H), 2.28−2.26 (m, 2H), 1.78 (s, 3H), 1.20 (s, 9H), 0.95−0.90 (m, 2H), 0.00 (s, 9H); MS (FAB) calculated for $C_{19}H_{39}O_5Si$ $[M + H]^+$: 375.2548, found 375.2567.

(2*R*,3*S*)-3-Methoxy-5-methyl-2-((2-(trimethylsilyl)ethoxy)-methoxy)hex-5-en-1-ol (+)-15. To a solution of SEM ether **53** (399 mg, 1.07 mmol) in CH_2Cl_2 (5.3 mL) was added DIBAL (1.0 M in toluene, 2.35 mL, 2.35 mmol) at −78 °C. After 10 min, the reaction was quenched with MeOH (0.6 mL). The reaction was allowed to warm to rt, and EtOAc (6 mL) and sat. Rochelle's salt (6 mL) were added. After 1 h, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/6) gave alcohol (+)-**15** (204 mg, 0.704 mmol, 66%) as a colorless oil.

(+)-**15**: $[\alpha]_D^{23}$ +34.3 (c 1.98, $CHCl_3$); IR (neat): 3454, 2952, 1649, 1445, 1376, 1250, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.80 (s, 1H), 4.80 (d, J = 7.2 Hz, 1H), 4.76 (s, 1H), 4.68 (d, J = 6.8 Hz, 1H), 3.77−3.68 (m, 3H), 3.68−3.55 (m, 2H), 3.48 (dt, J = 9.6, 4.4 Hz, 1H), 3.39 (s, 3H), 3.24 (dd, J = 7.2, 4.4 Hz, 1H), 2.30 (dd, J = 14.4, 7.6 Hz, 1H), 2.20 (dd, J = 14.8, 5.2 Hz, 1H), 1.76 (s, 3H), 0.94 (t, J = 8.4 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.3, 112.9, 95.3, 82.2, 80.7, 65.7, 62.3, 58.3, 39.2, 22.7, 18.0, −1.6 ; MS (FAB) calculated for $C_{14}H_{31}O_4Si$ $[M + H]^+$: 291.1992, found 291.1979.

(2*S*,3*S*)-3-Methoxy-5-methyl-2-((2-(trimethylsilyl)ethoxy)-methoxy)hex-5-enoic Acid (−)-6. To a solution of alcohol (+)-**15** (90.1 mg, 0.311 mmol) in CH_2Cl_2/pH 7 buffer (1.0 mL/1.0 mL) was added 1-Me-AZADO (10.3 mg, 0.0621 mmol) and $PhI(OAc)_2$ (300 mg, 0.932 mmol) at 0 °C. After 2 h, the reaction was quenched with sat. $Na_2S_2O_3$ and allowed to warm to rt. After 1 h, the mixture was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/1) gave carboxylic acid (−)-**6** (71.5 mg, 0.235 mmol, 76%) as a colorless oil.

(−)-**6**: $[\alpha]_D^{23}$ −24.4 (c 0.53, $CHCl_3$); IR (neat): 2953, 1725, 1649, 1377, 1250, 1110, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.84 (s, 1H), 4.81 (s, 1H), 4.79 (s, 2H), 4.40 (d, J = 2.8 Hz, 1H), 3.75 (ddd, J = 8.4, 5.6, 3.2 Hz, 1H), 3.68 (dd, J = 9.2, 8.0 Hz, 1H), 3.44 (s, 3H), 2.40 (dd, J = 14.4, 8.0 Hz, 1H), 2.28 (dd, J = 14.4, 4.2 Hz, 1H), 1.77 (s, 3H), 0.92 (m, 2H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.6, 141.6, 113.3, 94.8, 80.7, 75.9, 66.1, 58.1, 38.5, 22.7, 18.0, − 1.4 ; MS (FAB) calculated for $C_{14}H_{28}O_5SiNa$ $[M + Na]^+$: 327.1604, found 327.1585.

2-(2-Methyl-2-((*S*)-oxiran-2-yl)propoxy)tetrahydro-2*H*-pyran 54. To a solution of the epoxide (+)-**17** (16.6 g, 143 mmol) in CH_2Cl_2 (143 mL) was added DHP (16.9 mL, 186 mmol), followed by PPTS (7.17 g, 28.5 mmol), at 0 °C. After stirring for 10 h, DHP (3.90 mL, 42.8 mmol) was added, and the mixture was stirred for 1.5 h. The reaction was quenched with Et_3N and water. The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification by column chromatography (EtOAc/Hexane 1/10) gave THP ether **54** (25.9 g, 130 mmol, 91%) as a pair of diastereomers.

54: IR (neat): 2942, 1477, 1351, 1201, 1122, 1065, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.59 (m, 1H), 3.87−3.81 (m, 1H), 3.61 (d, J = 9.2 Hz, 0.5H), 3.56 (dd, J = 9.2 Hz, 0.5H), 3.54−3.49 (m, 1H), 3.18 (d, J = 9.2 Hz, 0.5H), 3.11 (d, J = 9.2 Hz, 0.5H), 2.95−2.91 (m, 1H), 2.68−2.64 (m, 2H), 1.87−1.78 (m, 1H), 1.76−1.64 (m, 1H), 1.64−1.50 (m, 4H), 0.93 (s, 1.5H), 0.93 (s, 1.5H), 0.90 (s, 1.5H), 0.90 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 98.6, 98.2, 73.9, 73.6, 61.4, 61.2, 56.9, 56.7, 43.5, 34.4, 34.4, 30.2, 30.2, 25.2, 20.2, 20.1, 20.0, 19.9,

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19.0, 18.9 ; MS (EI) calculated for $C_{11}H_{19}O_3$ $[M - H]^+$: 199.1334, found 199.1335.

(3*R*)-7-((4-Methoxybenzyl)oxy)-2,2-dimethyl-1-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-5-yn-3-ol 18. To a solution of *p*-methoxybenzyl propargyl ether (792 mg, 4.50 mmol) in THF (6.5 mL) was added *n*-BuLi (1.56 M in hexane, 2.88 mL, 4.50 mmol) at −78 °C. The reaction was allowed to stir at 0 °C for 1.5 h. The solution was cooled to −78 °C, and $BF_3{\cdot}OEt_2$ (0.560 mL, 4.50 mmol) was added dropwise. After 30 min, epoxide **54** (300 mg, 1.50 mmol) was dissolved in THF (1 mL) and added dropwise to the reaction mixture. After 1 h, the reaction was quenched with Et_3N (1.0 mL) and sat. $NaHCO_3$ (5 mL) and stirred at rt for 1 h. The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/4) gave alkyne **18** (491 mg, 1.31 mmol, 87%) as a pair of diastereomers.

18: IR (neat): 3467, 2942, 2871, 1612, 1514, 1249, 1074, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.28 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.59 (t, J = 3.4 Hz, 0.5H), 4.55−4.53 (m, 2.5H), 4.16−4.14 (m, 2H), 3.86−3.79 (m, 4H), 3.72−3.68 (m, 1.5H), 3.60 (d, J = 9.5 Hz, 0.5H), 3.54−3.51 (m, 1H), 3.35 (brs, 0.5H), 3.28 (d, J = 9.8 Hz, 0.5H), 3.19 (d, J = 9.5 Hz, 0.5H), 3.13 (brs, 0.5H), 2.56−2.46 (m, 1H), 2.42−2.34 (m, 1H), 1.79−1.68 (m, 2H), 1.62−1.51 (m, 4H), 0.96 (s, 1.5H), 0.95 (s, 1.5H), 0.94 (s, 1.5H), 0.93 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.3, 129.7, 129.7, 128.6, 113.9, 113.8, 99.4, 99.0, 85.1, 84.9, 76.2, 75.9, 75.8, 75.7, 71.1, 71.1, 65.0, 62.7, 62.0, 57.4, 57.4, 55.3, 55.2, 38.3, 38.1, 30.6, 30.4, 25.3, 25.3, 22.9, 22.6, 22.4, 22.4, 19.7, 19.6, 19.2, 19.2 ; MS (EI) calculated for $C_{17}H_{23}O_4$ $[M - C_5H_9O]^+$: 291.1596, found 291.1582.

(*R*)-7-((4-Methoxybenzyl)oxy)-2,2-dimethylhept-5-yne-1,3-diol (+)-55. To a solution of alkyne **18** (3.18 g, 8.45 mmol) in EtOH (42 mL) was added PPTS (425 mg, 1.69 mmol), and the reaction was stirred for 19 h at 70 °C. After cooling of the reaction, sat. $NaHCO_3$ (20 mL) was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/2) gave diol (+)-**55** (2.27 g, 7.78 mmol, 92%) as a colorless oil.

(+)-**55**: $[\alpha]_D^{28}$ +24.4 (c 1.18, $CHCl_3$); IR (neat): 3411, 2958, 2225, 1612, 1514, 1250, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.51 (s, 2H), 4.14 (t, J = 2.2 Hz, 1H), 3.80 (s, 3H), 3.69 (dd, J = 9.5, 3.2 Hz, 1H), 3.52 (d, J = 11.0 Hz, 1H), 3.44 (d, J = 11.0 Hz, 1H), 3.05 (brs, 1H), 2.92 (brs, 1H), 2.49 (ddt, J = 16.7, 3.2, 2.2 Hz, 1H), 2.38 (ddt, J = 16.7, 9.5, 2.2 Hz, 1H), 0.90 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.3, 129.6, 129.4, 113.8, 84.2, 78.3, 76.9, 71.6, 71.3, 57.3, 55.2, 38.3, 23.0, 22.2, 18.5 ; MS (EI) calculated for $C_{17}H_{24}O_4$ $[M]^+$: 292.1675, found 292.1659.

(*R*)-3-Hydroxy-7-((4-methoxybenzyl)oxy)-2,2-dimethylhept-5-ynal (+)-19. To a solution of diol (+)-**55** (20.0 g, 68.5 mmol) in CH_2Cl_2 (69 mL) was added $PhI(OAc)_2$ (28.7 g, 89.0 mmol), followed by TEMPO (1.61 g, 10.3 mmol). After stirring for 7 h at rt, $PhI(OAc)_2$ (4.41 g, 13.7 mmol) and TEMPO (530 mg, 3.42 mmol) were added, and the reaction was stirred for 1 h. The reaction was then diluted with Et_2O (70 mL) and quenched with sat. $Na_2S_2O_3$ (70 mL) at 0 °C. After stirring for 1 h, the mixture was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/3) gave aldehyde (+)-**19** (15.1 g, 51.9 mmol, 76%) as a colorless oil.

(+)-**19**: $[\alpha]_D^{25}$ +24.3 (c 1.38, $CHCl_3$); IR (neat): 3438, 2937, 2235, 1723, 1612, 1250, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.57 (s, 1H), 7.27 (d, J = 8.4 Hz, 2H), 6.89−6.86 (m, 2H), 4.51 (s, 2H), 4.13 (t, J = 2.2 Hz, 1H), 3.92 (dd, J = 9.3, 3.7 Hz, 1H), 3.81 (s, 3H), 2.50 (ddt, J = 16.7, 3.7, 2.2 Hz, 1H), 2.39 (ddt, J = 16.7, 9.3, 2.2 Hz, 1H), 1.11 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.3, 159.3, 129.6, 129.4, 113.8, 83.1, 79.0, 73.4, 71.3, 57.2, 55.2, 49.7, 22.9, 18.8, 16.7 ; MS (EI) calculated for $C_{17}H_{22}O_4$ $[M]^+$: 290.1518, found 290.1504.

(4*R*,6*R*)-10-((4-Methoxybenzyl)oxy)-5,5-dimethyldec-1-en-8-yne-4,6-diol (+)-20. To a solution of $MgBr{\cdot}OEt_2$ (405 mg, 1.57 mmol) in CH_2Cl_2 (2.0 mL) was added aldehyde (+)-**19** (207 mg, 0.713 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C. After stirring for 30 min, allyltributylstannane (0.490 mL, 1.57 mmol) was added, and the reaction was allowed to stir at 0 °C. After 12 h, the reaction was quenched with sat. $NaHCO_3$ (3 mL) and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/3) gave 4*R*-alcohol (+)-**20** (214 mg, 0.644 mmol, 90%, *dr* > 20:1) as a colorless oil.

(+)-**20**: $[\alpha]_D^{24}$ +30.0 (c 1.74, $CHCl_3$); IR (neat): 3399, 2965, 2225, 1612, 1513, 1250, 1062 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.27 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.92−5.82 (m, 1H), 5.18−5.14 (m, 2H), 4.51 (s, 2H), 4.14 (t, J = 2.2 Hz, 2H), 3.81 (s, 0.06H), 3.80 (s, 2.94H), 3.76 (dt, J = 9.2, 3.9 Hz, 1H), 3.66 (ddd, J = 10.5, 3.9, 2.2 Hz, 1H), 2.49 (ddt, J = 16.6, 3.9, 2.2 Hz, 1H), 2.43 (ddt, J = 16.6, 9.0, 2.2 Hz, 1H), 2.33 (m, 1H), 2.15 (m, 1H), 0.94 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 135.9, 129.5, 129.4, 117.5, 113.6, 84.4, 77.9, 76.7, 76.6, 71.2, 57.3, 55.2, 40.1, 36.4, 22.9, 20.8, 20.5 ; MS (FAB) calculated for $C_{20}H_{27}O_4$ $[M - H]^+$: 331.1909, found 331.1889.

(4*R*,6*R*)-4,6-Bistriethylsilyloxy-5,5-dimethyl-10-(4-methoxybenzyloxy)-1-decen-8-yne (+)-56. To a solution of diol (+)-**20** (17.2 g, 51.8 mmol) in DMF (52 mL) was added imidazole (17.6 g, 259.1 mmol), followed by TESCl (21.7 mL, 123 mmol), at 0 °C. After stirring for 1.5 h, the reaction was quenched with sat. $NaHCO_3$ (25 mL). The mixture was extracted with Et_2O, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/30) gave TES-ether (+)-**56** (28.9 g, 51.6 mmol, 100%) as a colorless oil.

(+)-**56**: $[\alpha]_D^{25}$ +17.4 (c 1.83, $CHCl_3$); IR (neat): 2954, 1613, 1513, 1463, 1249, 1078, 1007 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.28 (d, J = 8.8 Hz, 2H), 6.90−6.86 (m, 2H), 5.85 (ddt, J = 18.0, 9.5, 7.2 Hz, 1H), 5.07−5.00 (m, 2H), 4.51 (s, 2H), 4.13 (t, J = 2.2 Hz, 2H), 3.81 (s, 3H), 3.76 (dd, J = 7.1, 4.8 Hz, 1H), 3.64 (dd, J = 7.6, 3.4 Hz, 1H), 2.50 (ddt, J = 17.3, 4.2, 2.0 Hz, 1H), 2.36−2.25 (m, 2H), 2.14 (m, 1H), 0.97 (t, J = 7.8 Hz, 9H), 0.95 (t, J = 7.8 Hz, 9H), 0.87 (s, 6H), 0.70 (q, J = 7.8 Hz, 6H), 0.60 (t, J = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.3, 137.1, 129.7, 129.5, 126.2, 113.7, 85.8, 77.4, 77.3, 76.4, 71.0, 57.4, 55.1, 44.4, 38.0, 23.7, 19.9, 19.7, 7.0, 5.6, 5.5 ; MS (EI) calculated for $C_{30}H_{51}O_4Si_2$ $[M - C_2H_5]^+$: 531.3326, found 531.3350.

(5*R*,7*R*)-5,7-Bistriethylsilyloxy-6,6-dimethyl-9-decen-2-yn-1-ol (+)-21. To a solution of bis-TES ether (+)-**56** (16.9 g, 30.1 mmol) in CH_2Cl_2/pH 7 buffer (143 mL/7.2 mL) was added DDQ (10.3 g, 45.2 mmol) at −30 °C, and the reaction was allowed to stir at 0 °C. After 13 h, the reaction was quenched with sat. $Na_2S_2O_3$ (100 mL) and stirred for 1 h at rt. The reaction mixture was filtered through a pad of Celite, followed by washing with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/20) gave alcohol (+)-**21** (11.9 g, 27.0 mmol, 90%) as a colorless oil.

(+)-**21**: $[\alpha]_D^{25}$ +21.3 (c 1.06, $CHCl_3$); IR (neat): 3327, 2955, 2227, 1640, 1459, 1415, 1238, 1079, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.85 (ddt, J = 17.3, 8.9, 6.8 Hz, 1H), 5.08−5.01 (m, 2H), 4.24 (dt, J = 6.0, 2.2 Hz, 2H), 3.74 (dt, J = 7.0, 4.1 Hz, 1H), 3.64 (dd, J = 7.5, 3.4 Hz, 1H), 2.48 (ddt, J = 17.1, 4.1, 2.2 Hz, 1H), 2.33 (ddd, J = 14.7, 3.4, 1.7 Hz, 1H), 2.26 (ddt, J = 17.1, 7.0, 2.2 Hz, 1H), 2.15 (m, 1H), 1.43 (t, J = 6.0 Hz, 1H), 0.98 (t, J = 8.0 Hz, 9H), 0.96 (t, J = 7.3 Hz, 9H), 0.83 (s, 3H), 0.83 (s, 3H), 0.68 (q, J = 7.3 Hz, 6H), 0.60 (q, J = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.2, 116.2, 85.4, 79.7, 77.4, 76.4, 51.4, 44.4, 38.0, 23.7, 20.0, 19.7, 7.1, 7.0, 7.0, 5.6, 5.4 ; MS (EI) calculated for $C_{22}H_{43}O_3Si_2$ $[M - C_2H_5]^+$: 411.2751, found 411.2739.

(5*R*,7*R*,*E*)-5,7-Bistriethylsilyloxy-6,6-dimethyl-2,9-decadien-1-ol (+)-57. To a solution of alcohol (+)-**21** (786 mg, 1.79 mmol) in THF (7.9 mL) was added Red-Al (1.8 M in toluene, 1.98 mL, 3.57

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J. Org. Chem. 2015, 80, 12333−12350

mmol) at 0 °C, and the reaction was allowed to stir at rt. After stirring for 3 h, the reaction was quenched with H_2O (1 mL) at 0 °C and stirred for 1 h at rt. The reaction mixture was filtered through a pad of Celite, followed by washing with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/20) gave allyl alcohol (+)-**57** (718 mg, 1.62 mmol, 91%) as a colorless oil.

(+)-**57**: $[\alpha]_D^{22}$ +28.4 (c 0.65, $CHCl_3$); IR (neat): 3330, 2955, 2877, 1459, 1415, 1238, 1076, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.85 (ddt, J = 19.0, 10.7, 7.2 Hz, 1H), 5.78−5.61 (m, 2H), 5.05−5.01 (m, 2H), 4.11 (d, J = 5.6 Hz, 2H), 3.62−3.58 (m, 2H), 2.28−2.20 (m, 2H), 2.14−2.07 (m, 2H), 0.98 (t, J = 3.6 Hz, 18H), 0.86 (s, 6H), 0.63 (q, J = 3.6 Hz, 6H), 0.59 (q, J = 3.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.2, 131.4, 130.5, 116.2, 77.4, 77.3, 63.8, 44.5, 37.8, 36.1, 19.8, 19.8, 7.09, 5.63 ; MS (FAB) calculated for $C_{24}H_{51}O_3Si_2$ $[M + H]^+$: 443.3377, found 443.3394.

(2*R*,3*R*,5*R*,7*R*)-5,7-Bistriethylsilyloxy-6,6-dimethyl-2,3-epoxy-9-decen-1-ol (+)-13. To freshly activated 4 Å molecular sieves (1.0 g) in CH_2Cl_2 (2.4 mL) was added (−)-DET (39.6 mg, 0.192 mmol) in CH_2Cl_2 (0.1 mL). The solution was cooled to −20 °C, and $Ti(OiPr)_4$ (0.0380 mL, 0.128 mmol) was added, followed by TBHP (3.11 M solution in CH_2Cl_2, 0.823 mL, 2.56 mmol). The reaction was stirred for 1 h, and then a solution of allyl alcohol (+)-**57** (567 mg, 1.28 mmol) in CH_2Cl_2 (0.1 mL) was added. After 2 h, the reaction was quenched with a 6:1 mixture of acetone/water (2.8 mL) and stirred for 1 h at rt. The reaction mixture was filtered through a pad of Celite, followed by washing with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/12) gave epoxy alcohol (+)-**13** (554 mg, 1.21 mmol, 94%, dr > 20:1) as a colorless oil.

(+)-**13**: $[\alpha]_D^{30}$ +46.4 (c 0.61, $CHCl_3$); IR (neat): 3436, 2955, 1639, 1459, 1415, 1239, 1078, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.84 (ddt, J = 15.3, 8.1, 6.8 Hz, 1H), 5.05−4.99 (m, 2H), 3.94 (ddd, J = 12.2, 6.1, 2.4 Hz, 1H), 3.81 (dd, J = 9.0, 2.4 Hz, 1H), 3.63 (ddd, J = 12.2, 6.1, 4.4 Hz, 1H), 3.48 (dd, J = 7.6, 3.4 Hz, 1H), 3.11 (dt, J = 7.6, 2.8 Hz, 1H), 2.94 (dt, J = 4.0, 2.4 Hz, 1H), 2.26−2.22 (m, 1H), 2.14−2.06 (m, 1H), 1.78 (ddd, J = 14.4, 9.0, 3.7 Hz, 1H), 1.62 (t, J = 6.1 Hz, 1H), 1.38 (ddd, J = 14.1, 7.8, 2.4 Hz, 1H), 0.99 (t, J = 7.8 Hz, 9H), 0.95 (t, J = 8.1 Hz, 9H), 0.88 (s, 3H), 0.85 (s, 3H), 0.66 (q, J = 8.1 Hz, 6H), 0.66 (q, J = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.9, 116.2, 77.6, 75.1, 61.6, 59.7, 54.0, 44.0, 37.6, 35.1, 20.0, 19.9, 7.2, 7.2, 5.7, 5.6 ; MS (FAB) calculated for $C_{24}H_{51}O_4Si_2$ $[M + H]^+$: 459.3326, found 459.3304.

(4*R*,6*R*,8*R*,9*R*)-10-(Benzyloxymethoxy)-4,6-bistriethylsilyloxy-5,5-dimethyl-8,9-epoxy-1-decene (+)-22. To a solution of epoxy alcohol (+)-**13** (2.35 g, 5.13 mmol) in CH_2Cl_2 (10 mL) was added i-Pr_2NEt (3.59 mL, 20.5 mmol), followed by BOMCl (1.41 mL, 10.3 mmol), at 0 °C. After stirring for 5.5 h, the reaction was quenched with sat. $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/40−1/20) gave BOM ether (+)-**22** (2.59 g, 4.47 mmol, 87%) as a colorless oil.

(+)-**22**: $[\alpha]_D^{26}$ +37.8 (c 0.49, $CHCl_3$); IR (neat): 2954, 1457, 1077, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35−7.28 (m, 5H), 5.83 (ddt, J = 17.1, 10.0, 7.1 Hz, 1H), 5.02 (d, J = 15.4 Hz, 1H), 5.00 (d, J = 9.8 Hz, 1H), 4.78 (s, 2H), 4.62 (s, 2H), 3.84−3.80 (m, 2H), 3.58 (dd, J = 11.5, 5.6 Hz, 1H), 3.46 (dd, J = 7.6, 3.4 Hz, 1H), 3.02 (dt, J = 8.1, 2.9 Hz, 1H), 2.95 (ddd, J = 5.4, 2.9 Hz, 1H), 2.23 (m, 1H), 2.09 (m, 1H), 1.79 (ddd, J = 12.7, 9.3, 3.4 Hz, 1H), 1.33 (ddd, J = 14.2, 7.8, 2.2 Hz, 1H), 0.98 (t, J = 8.1 Hz, 9H), 0.95 (t, J = 7.8 Hz, 9H), 0.88 (s, 3H), 0.84 (s, 3H), 0.66 (q, J = 8.1 Hz, 6H), 0.59 (q, J = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.7, 137.0, 128.4, 127.9, 127.7, 116.2, 94.7, 77.6, 75.1, 69.4, 68.0, 58.0, 54.2, 44.0, 37.5, 35.1, 19.9, 19.8, 7.1, 7.1, 5.6, 5.5 ; MS (EI) calculated for $C_{30}H_{53}O_5Si_2$ $[M - C_2H_5]^+$: 549.3432, found 549.3449.

(2*R*,4*R*,6*S*)-2-Allyl-6-((1*R*)-2-(benzyloxymethoxy)-1-hydroxyethyl)-3,3-dimethyl-4-hydroxytetrahydropyran (+)-23. To a solution of BOM ether (+)-**22** (476 mg, 0.823 mmol) in CH_2Cl_2/MeOH (4.1 mL/0.4 mL) was added CSA (19.0 mg, 0.0823 mmol) at 0 °C. After stirring for 19 h, the reaction was quenched with sat. $NaHCO_3$ (1.0 mL) and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/1) gave diol (+)-**23** (238 mg, 0.680 mmol, 83%) as a colorless oil.

(+)-**23**: $[\alpha]_D^{26}$ +41.7 (c 0.94, $CHCl_3$); IR (neat): 3421, 2942, 1640, 1454, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36−7.29 (m, 5H), 5.82 (ddt, J = 17.1, 10.3, 6.8 Hz, 1H), 5.05 (ddd, J = 17.1, 3.4, 1.5 Hz, 1H), 4.99 (ddd, J = 10.3, 2.0, 1.0 Hz, 1H), 4.81 (d, J = 6.6 Hz, 1H), 4.79 (d, J = 6.6 Hz, 1H), 4.63 (s, 2H), 3.94 (m, 1H), 3.84 (dd, J = 10.6, 2.9 Hz, 1H), 3.81 (dd, J = 5.4, 4.0 Hz, 1H), 3.63 (dd, J = 9.5, 4.0 Hz, 1H), 3.59 (dd, J = 10.6, 6.6 Hz, 1H), 3.23 (dd, J = 10.7, 2.7 Hz, 1H), 2.64 (brs, 1H), 2.35 (m, 1H), 2.22 (m, 1H), 2.11 (dt, J = 13.4, 4.0 Hz, 1H), 1.74 (ddd, J = 13.4, 9.5, 5.4 Hz, 1H), 0.99 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.6, 136.8, 128.6, 128.0, 127.9, 116.4, 95.6, 79.5, 72.3, 70.7, 70.7, 69.9, 69.1, 38.4, 33.7, 29.7, 23.9, 14.8 ; MS (EI) calculated for $C_{20}H_{30}O_5$ $[M]^+$: 350.2093, found 350.2108.

(2*R*,4*R*,6*S*)-2-Allyl-6-((1*R*)-2-(benzyloxymethoxy)-1-methoxyethyl)-3,3-dimethyl-4-hydroxytetrahydropyran (+)-58. To a solution of diol (+)-**23** (121 mg, 0.344 mmol) in THF (3.4 mL) was added NaH (60%, 34.4 mg, 0.861 mmol) at 0 °C. After stirring for 30 min, Me_2SO_4 (0.0390 mL, 0.413 mmol) was added, and the reaction was stirred at 0 °C. After 2 h, the reaction was quenched with sat. NH_4Cl (2 mL) and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/8−1/4) gave methyl ether (+)-**58** (97.4 mg, 0.267 mmol, 78%) as a colorless oil.

(+)-**58**: $[\alpha]_D^{29}$ +33.3 (c 0.80, $CHCl_3$); IR (neat): 3467, 2935, 1640, 1454, 1100, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36−7.27 (m, 5H), 5.84 (ddt, J = 17.1, 10.1, 7.0 Hz, 1H), 5.04 (dd, J = 17.1, 1.5 Hz, 1H), 4.98 (d, J = 10.1 Hz, 1H), 4.79 (s, 2H), 4.63 (s, 2H), 3.95 (ddd, J = 8.9, 6.1, 3.0 Hz, 1H), 3.90 (dd, J = 11.0, 2.2 Hz, 1H), 3.81 (dd, J = 5.4, 3.9 Hz, 1H), 3.73 (dd, J = 9.5, 4.2 Hz, 1H), 3.64 (dd, J = 11.0, 5.5 Hz, 1H), 3.59 (dd, J = 10.6, 4.8 Hz, 1H), 3.53 (ddd, J = 8.9, 4.8, 2.2 Hz, 1H), 3.47 (s, 3H), 3.20 (dd, J = 9.9, 2.7 Hz, 1H), 2.31−2.18 (m, 2H), 2.06 (dt, J = 13.4, 3.0 Hz, 1H), 1.75 (dt, J = 13.4, 10.6, 6.1 Hz, 1H), 1.44 (brs, 1H), 0.99 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.9, 136.7, 128.4, 127.9, 127.6, 116.3, 95.1, 79.1, 78.6, 72.5, 69.9, 69.4, 66.6, 58.4, 38.6, 33.8, 29.6, 23.5, 13.8 ; MS (EI) calculated for $C_{18}H_{27}O_5$ $[M - C_3H_5]^+$: 323.1859, found 323.1841.

(2*R*,4*R*,6*S*)-2-Allyl-6-((1*R*)-2-(benzyloxymethoxy)-1-methoxyethyl)-3,3-dimethyl-4-*tert*-butyldimethylsilyloxytetrahydropyran (+)-24. To a solution of methyl ether (+)-**58** (177 mg, 0.487 mmol) in CH_2Cl_2 (2.4 mL) was added 2,6-lutidine (0.170 mL, 1.46 mmol), followed by TBSOTf (0.168 mL, 0.730 mmol), at 0 °C. After stirring for 30 min, the reaction was quenched with sat. $NaHCO_3$ (1 mL). The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/40−1/20) gave TBS ether (+)-**24** (209 mg, 0.438 mmol, 90%) as a colorless oil.

(+)-**24**: $[\alpha]_D^{29}$ +18.5 (c 1.24, $CHCl_3$); IR (neat): 2954, 1640, 1471, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36−7.27 (m, 5H), 5.83 (ddt, J = 16.8, 10.0, 6.8 Hz, 1H), 5.02 (d, J = 16.8 Hz, 1H), 4.96 (dd, J = 10.0, 1.0 Hz, 1H), 4.79 (s, 2H), 4.63 (s, 2H), 3.92−3.86 (m, 2H), 3.63 (dd, J = 10.7, 5.4 Hz, 1H), 3.56−3.50 (m, 2H), 3.49 (s, 3H), 3.23 (dd, J = 10.5, 2.4 Hz, 1H), 2.40 (m, 1H), 2.19 (dd, J = 14.4, 6.8 Hz, 1H), 1.94 (dt, J = 13.9, 4.4 Hz, 1H), 1.70 (ddd, J = 13.9, 9.3, 5.4 Hz, 1H), 1.44 (brs, 1H), 0.94 (s, 3H), 0.90 (s, 9H), 0.88 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.8, 137.0, 128.3, 127.8, 127.6, 115.9, 95.1, 79.7, 79.3, 73.0, 69.3, 69.0, 67.2, 58.5, 38.8, 33.8,

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J. Org. Chem. 2015, 80, 12333−12350

30.2, 25.9, 24.5, 18.1, 15.8, −4.1, −4.9 ; MS (EI) calculated for $C_{27}H_{46}O_5Si$ $[M]^+$: 478.3115, found 478.3118.

2-((2*R*,4*R*,6*S*)-6-((*R*)-2-((Benzyloxy)methoxy)-1-methoxyethyl)-4-((*tert*-butyldimethylsilyl)oxy)-3,3-dimethyltetrahydro-2*H*-pyran-2-yl)acetaldehyde 11. To a solution of TBS ether (+)-**24** (500 mg, 1.05 mmol) in THF/H_2O (10 mL/1 mL) was added NMO (184 mg, 1.57 mmol), followed by OsO_4 (0.196 M solution in THF, 0.0530 mL, 0.0105 mmol), at 0 °C, and the reaction was allowed to stir at rt. After stirring for 10.5 h, the reaction was quenched with sat. $Na_2S_2O_3$ (1 mL) and stirred for 1 h at rt. The mixture was extracted with EtOAc, and the combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration afforded a crude diol. To a solution of the diol in MeOH/H_2O (18.8 mL/2.1 mL) was added $NaIO_4$ (335 mg, 1.57 mmol), and the mixture was stirred at rt. After 30 min, EtOAc (30 mL) and H_2O (10 mL) were added. The mixture was extracted with EtOAc, and the combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration afforded aldehyde **11** as a colorless oil.

11: IR (neat): 2954, 1727, 1524, 1234, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.66 (d, J = 2.4 Hz, 1H) 7.29−7.19 (m, 5H), 4.71 (d, J = 1.2 Hz, 1H), 4.55 (d, J = 1.2 Hz, 1H), 4.61 (s, 1H), 3.89−3.84 (m, 1H), 3.72 (dd, J = 10.6, 3.0 Hz, 1H), 3.59−3.53 (m, 1H), 3.45−3.39 (m, 4H), 3.21 (d, J = 9.6 Hz, 1H), 2.87−2.80 (m, 1H), 2.42 (m, J = 16.4 Hz, 1H), 1.94−1.88 (m, 1H), 1.64−1.58 (m, 1H), 0.90 (s, 3H), 0.85 (s, 9H), 0.82 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.7, 137.9, 128.3, 127.8, 127.5, 95.0, 79.8, 74.9, 72.8, 69.4, 68.6, 66.7, 58.4, 43.7, 38.0, 30.1, 25.9, 24.7, 18.1, −4.2, −4.9; MS (EI) calculated for $C_{22}H_{35}O_6Si$ $[M - C_4H_9]^+$: 423.2203, found 423.2227.

Methyl 4,6-Dimethoxy-2-hydroxybenzoate 26. To a solution of 2,4,6-trihydroxybenzoic acid (**25**) (10.0 g, 53.2 mmol) in acetone (177 mL) was added K_2CO_3 (44.1 g, 319 mmol), followed by Me_2SO_4 (30.2 mL, 319 mmol), and the mixture was heated to reflux. After stirring for 22 h, the reaction mixture was filtered through a pad of Celite, followed by washing with EtOAc. Then, concentration afforded a crude trimethyl ether. To a solution of the crude trimethyl ether in CH_2Cl_2 (106 mL) was added BCl_3 (1.0 M solution, 79.8 mL, 79.8 mmol) at −78 °C, and the reaction was allowed to stir at 0 °C. After stirring for 5 h, the reaction was quenched with 10% HCl aq. and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/8) gave phenol **26** (5.16 g, 24.3 mmol, 46% over 2 steps) as a white solid.

26: mp: 111−112 °C; IR (neat): 1638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 12.03 (s, 1H), 6.11 (d, J = 2.5 Hz, 1H), 5.97 (d, J = 2.5 Hz, 1H), 3.92 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.6, 166.0, 165.3, 162.1, 96.6, 93.4, 91.5, 56.0, 55.4, 52.2 ; MS (EI) calculated for $C_{10}H_{12}O_5$ $[M]^+$: 212.0685, found 212.0692.

Methyl 4,6-Dimethoxy-2-hydroxy-3-methylbenzoate 27. To a solution of phenol **26** (5.16 g, 24.3 mmol) in CH_2Cl_2 (81 mL) was added 1,1-dichlorodimethyl ether (4.40 mL, 48.6 mmol), followed by $TiCl_4$ (8.00 mL, 72.9 mmol), at −20 °C. After stirring for 1 h, the reaction was quenched with 10% HCl aq. and the mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration afforded a crude benzaldehyde. To a solution of the crude benzaldehyde in MeOH/$CHCl_3$ (54 mL/27 mL) was added 10% Pd-C (1.17 g) and hydrogenated (H_2, 1 atm). After 38 h, the catalyst was filtered through a pad of Celite, followed by washing with EtOAc. The combined organic layers were concentrated. Purification by column chromatography (EtOAc/Hexane 1/8) gave methylbenzene **27** (4.83 g, 21.4 mmol, 88%) as a white solid.

27: mp: 153−154 °C; IR (neat): 2950, 1729, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 12.04 (s, 1H), 5.99 (s, 1H), 3.92 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 162.7, 162.1, 160.5, 105.7, 96.5, 87.0, 56.1, 55.4, 52.1, 7.4 ; MS (EI) calculated for $C_{11}H_{14}O_5$ $[M]^+$: 226.0841, found 226.0828.

Methyl 4,6-Dimethoxy-3-methyl-2-trifluoromethanesulfonyloxybenzoate 28. To a solution of methylbenzene **27** (82.1 mg, 0.363 mmol) in CH_2Cl_2 (1.8 mL) was added pyridine (70.0 μL, 0.871 mmol), followed by Tf_2O (0.0730 mL, 0.436 mmol), at 0 °C. After stirring for 4 h, the reaction was quenched with sat. $NaHCO_3$ and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/3) gave triflate **28** (117 mg, 0.327 mmol, 90%) as a white solid.

28: mp: 113−114 °C; IR (neat): 1735, 1621 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.46 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 160.5, 157.3, 145.3, 118.3 (q, J = 318 Hz), 113.2, 109.5, 94.8, 56.6, 56.0, 52.5, 9.6 ; MS (EI) calculated for $C_{12}H_{13}F_3O_7S$ $[M]^+$: 358.0334, found 358.0336.

Methyl 2-(1-Butenyl)-4,6-dimethoxy-3-methylbenzoate 12. A solution of boronic acid ester **29** (1.14 g, 6.54 mmol) in 1,4-dioxane (16 mL) was first sonicated. To triflate **28** (1.17 g, 3.27 mmol), K_3PO_4 (1.39 g, 6.54 mmol), and $Pd(PPh_3)_4$ (378 mg, 0.327 mmol) was added a solution of boronic acid ester in 1,4-dioxane at rt. After stirring at 100 °C for 12 h, the reaction was quenched with 1 M NaOH aq. and the reaction mixture was filtered through a pad of Celite, followed by washing with EtOAc. The mixute was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/8) gave alkene **12** (717 mg, 2.71 mmol, 83%) as a colorless oil.

12: IR (neat): 1731, 1588 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.36 (d, J = 15.8 Hz, 1H), 6.36 (s, 1H), 5.76 (dt, J = 15.8, 6.8 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 2.16 (dq, J = 7.6, 6.8 Hz, 3H), 1.04 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.1, 158.8, 155.3, 137.7, 137.6, 125.6, 116.8, 115.8, 93.8, 56.1, 55.6, 51.9, 29.3, 13.6, 11.6 ; MS (EI) calculated for $C_{15}H_{20}O_4$ $[M]^+$: 264.1362, found 264.1351.

(3*S*)-5,7-Dimethoxy-3-[(1*S*)-1-hydroxypropyl]-4-methylphthalide (+)-30. To a solution of phenol AD-mix-α (530 mg, 1.4 g/mmol) in *t*-BuOH/H_2O (1.5 mL/1.5 mL) was added $MeSO_2NH_2$ (36.0 mg, 0.379 mmol) at 0 °C. After stirring for 30 min, alkene **12** (100 mg, 0.379 mmol) was added, and the reaction was stirred for 108 h. Then, the reaction was quenched with sat. $Na_2S_2O_3$ and the crude was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/4) and then recrystallization gave phthalide (+)-**30** (89.0 mg, 0.335 mmol, 88%, 99% ee) as a white solid. The enantiomeric excess was determined by HPLC analysis.

(+)-**30**: $[\alpha]_D^{31}$ +77.7 (c 1.45, $CHCl_3$); mp: 178−179 °C; IR (neat): 3469, 1739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.42 (s, 1H), 5.34 (s, 1H), 4.01 (t, J = 7.6 Hz, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 2.16 (dq, J = 7.6, 7.3 Hz, 3H), 2.12 (s, 3H), 1.09 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.9, 164.0, 158.0, 148.8, 111.9, 106.0, 94.5, 80.9, 72.1, 55.9, 55.8, 27.6, 10.9, 10.3 ; MS (EI) calculated for $C_{14}H_{18}O_5$ $[M]^+$: 266.1154, found 266.1136.

(3*S*)-5,7-Dimethoxy-4-methyl-3-(1-oxopropyl)-phthalide (+)-10. To a solution of phthalide (+)-**30** (54.6 mg, 0.205 mmol, 99% ee) in CH_2Cl_2 (0.38 mL) was added $PhI(OAc)_2$ (78.7 mg, 0.244 mmol), followed by 1-Me-AZADO (7.80 mg, 0.0470 mmol), at 0 °C. After stirring for 5 h at rt, the reaction was then diluted with Et_2O (1 mL) and quenched with sat. $Na_2S_2O_3$ (1 mL) at 0 °C. After stirring for 1 h, the crude was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/2) and then recrystallization gave ketone (+)-**10** (49.7 mg, 0.188 mmol, 92%, 99% ee) as a white solid. The enantiomeric excess was determined by HPLC analysis.

(+)-**10**: $[\alpha]_D^{24}$ +241 (c 0.66, $CHCl_3$); mp: 130−131 °C; IR (neat): 1768, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.46 (s, 1H), 5.58 (s, 1H), 4.01 (s, 3H), 3.94 (s, 3H), 3.81 (s, 3H), 2.61 (dq, J = 18.8, 7.5 Hz, 1H), 2.19 (dq, J = 18.8, 7.1 Hz, 1H), 2.08 (s, 3H), 0.97 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.8, 168.2, 164.5, 158.4, 145.0, 114.0, 103.9, 95.2, 83.3, 56.1, 56.1, 29.5, 10.7, 7.1; MS (EI) calculated for $C_{14}H_{16}O_5$ $[M]^+$: 264.0998, found 264.0984.

(3*R*)-3-(1-Hydroxynonyl)-5,7-dimethoxy-4-methyl-3-propionylphthalide 31. To a solution of LDA in THF (1.24 mL, 0.390 mmol) was added ketone (+)-**10** (87.0 mg, 0.329 mmol) in THF at

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−78 °C. After stirring for 30 min, nonanal (95.0 mg, 0.658 mmol) was added. After 2 h at −78 °C, the reaction was quenched with sat. NH_4Cl at 0 °C. The crude was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/2) gave aldol **31** (134 mg, 0.329 mmol, quant., mixture of diastereomer) as a white solid.

31: IR (neat): 3464, 1759, 1725, 1614, 1597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, major diastereomer) δ: 6.48 (s, 1H), 4.81 (dt, J = 9.6, 2.4 Hz, 1H), 4.02 (s, 3H), 3.95 (s, 3H), 2.69 (dq, J = 13.2, 5.6 Hz, 1H), 2.27 (dq, J = 13.2, 5.6 Hz, 1H), 2.16 (s, 3H), 2.04 (d, J = 9.6 Hz), 1.47−1.45 (m, 1H), 1.32−1.14 (m, 12H), 0.97 (t, J = 7.2 Hz, 3H), 0.84 (t, J = 6.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.7, 166.2, 164.8, 163.4, 160.6, 158.7, 158.1, 130.6, 121.9, 114.4, 100.0, 95.3, 83.1, 71.8, 71.5, 56.6, 56.2, 56.1, 44.8, 44.0, 33.9, 33.9, 33.5, 31.8, 29.5, 29.3, 29.2, 29.2, 29.2, 29.0, 29.0, 25.9, 25.4, 24.6, 22.6, 14.0, 11.1, 10.9, 10.3, 10.0 ; MS (EI) calculated for $C_{23}H_{34}O_6$ $[M]^+$: 406.2355, found 406.2353.

(2*R*,4*R*,6*S*)-6-((1*R*)-2-(Benzyloxymethoxy)-1-methoxyethyl)-3,3-dimethyl-2-(2-oxobutyl)-4-*tert*-butyldimethylsilyloxytetrahydropyran (+)-34. To a solution of EtMgBr (0.300 M solution in THF, 20.9 mL, 6.27 mmol) was added the crude aldehyde **11** dropwise at 0 °C. After stirring for 30 min, the reaction was quenched with sat. NH_4Cl (5 mL) and the mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration afforded a crude ethyl alcohol. To a solution of the ethyl alcohol in CH_2Cl_2 (5.2 mL) was added $PhI(OAc)_2$ (404 mg, 1.25 mmol), followed by 1-Me-AZADO (17.4 mg, 0.105 mmol), at rt. After stirring for 16 h, the reaction was then diluted with Et_2O (10 mL) and quenched with sat. $Na_2S_2O_3$ (10 mL) at 0 °C. After stirring for 1 h at rt, the mixture was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/10) gave ketone (+)-**34** (467 mg, 0.919 mmol, 88% over 4 steps) as a colorless oil.

(+)-**34**: $[\alpha]_D^{24}$ +22.0 (c 3.60, $CHCl_3$); IR (neat): 2931, 1716, 1472, 1254, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37−7.26 (m, 5H), 4.78 (d, J = 6.4 Hz, 1H), 4.75 (d, J = 6.4 Hz, 1H), 4.61 (s, 1H), 3.92−3.79 (m, 3H), 3.63−3.52 (m, 3H), 3.48 (s, 3H), 2.78 (dd, J = 16.0, 9.8 Hz, 1H), 2.43−2.38 (m, 3H), 1.96 (dt, J = 13.6, 4.0 Hz, 1H), 1.68 (ddd, J = 14.8, 9.6, 5.6 Hz, 1H), 1.00 (t, J = 7.2 Hz, 3H), 0.91 (s, 9H), 0.91 (s, 3H), 0.86 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.4, 138.1, 128.3, 127.9, 127.5, 95.1, 79.0, 75.7, 72.8, 69.5, 69.2, 66.3, 58.3, 42.3, 38.3, 37.3, 29.9, 25.8, 24.2, 18.0, 15.5, 7.6, −4.2, −5.0 ; MS (EI) calculated for $C_{28}H_{48}O_6Si$ $[M]^+$: 508.3220, found 508.3201.

(2*R*,4*R*,6*S*)-3,3-Dimethyl-6-((1*R*)-2-hydroxy-1-methoxyethyl)-2-(2-oxobutyl)-4-*tert*-butyldimethylsilyloxytetrahydropyran (+)-59. To a solution of ketone (+)-**34** (339 mg, 0.667 mmol) in MeOH (3.3 mL) was added 20% $Pd(OH)_2$ (33.9 mg, 10% w/w) and hydrogenated (H_2, 1 atm). After 40 min, the catalyst was filtered through a pad of Celite, followed by washing with EtOAc. The combined organic layers were concentrated. Purification by column chromatography (EtOAc/Hexane 1/4) gave alcohol (+)-**59** (257 mg, 0.663 mmol, 99%) as a colorless oil.

(+)-**59**: $[\alpha]_D^{25}$ +23.9 (c 1.59, $CHCl_3$); IR (neat): 3467, 2955, 1715, 1471, 1362, 1254, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.81 (m, 2H), 3.71 (d, J = 12.0 Hz, 1H), 3.60 (brs, 1H), 3.56 (dd, J = 8.0, 4.0 Hz, 1H), 3.42 (s, 3H), 3.29 (dt, J = 8.0, 3.6 Hz, 1H), 2.90 (dd, J = 16.0, 10.0 Hz, 1H), 2.61 (brs, 1H), 2.42 (m, 3H), 1.85 (dt, J = 14.0, 4.8 Hz, 1H), 1.67 (ddd, J = 13.6, 8.0, 4.8 Hz, 1H), 1.01 (t, J = 7.2 Hz, 1H), 0.90 (s, 3H), 0.87 (s, 9H), 0.83 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.1, 81.0, 79.3, 72.8, 69.0, 60.8, 58.0, 42.2, 38.0, 37.0, 30.8, 25.8, 24.7, 18.0, 17.1, 7.6, −4.3, −5.0 ; MS (EI) calculated for $C_{20}H_{41}O_5Si$ $[M + H]^+$: 389.2723, found 389.2761.

(2*R*,4*R*,6*S*)-6-((1*S*)-1-Benzyloxycarbonyl-1-methoxymethyl)-3,3-dimethyl-2-(2-oxobutyl)-4-*tert*-butyldimethylsilyloxytetrahydropyran (+)-33. To a solution of alcohol (+)-**59** (20.9 mg, 0.0538 mmol) in MeCN/pH 7 buffer (0.27 mL/0.27 mL) was added $NaClO_2$ (80%, 18.3 mg, 0.161 mmol), followed by 1-Me-AZADO$^+BF_4^-$ (1.36 mg, 0.00538 mmol), at rt. After stirring for 30 min, the reaction was quenched with 2-methyl-2-butene (1 mL). The mixture was extracted with EtOAc, and the combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration afforded a crude carboxylic acid. To a solution of the crude carboxylic acid in DMF (1.1 mL) was added Cs_2CO_3 (35.1 mg, 0.108 mmol), followed by BnBr (0.0255 mL, 0.215 mmol), at 0 °C. After stirring for 1 h, the reaction was diluted with Et_2O (3 mL) and quenched with sat. NH_4Cl (2 mL). The crude was extracted with Et_2O, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/20−1/8) gave benzyl ester (+)-**33** (25.6 mg, 0.0520 mmol, 97% over 2 steps) as a colorless oil.

(+)-**33**: $[\alpha]_D^{24}$ +11.5 (c 1.30, $CHCl_3$); IR (neat): 2955, 1747, 1717, 1461, 1255, 1100, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.39−7.29 (m, 5H), 5.23 (d, J = 12.2 Hz, 1H), 5.20 (d, J = 12.2 Hz, 1H), 4.12 (q, J = 6.1 Hz, 1H), 4.03 (dd, J = 9.5, 3.6 Hz, 1H), 3.95 (d, J = 6.1 Hz, 1H), 3.64 (dd, J = 7.6, 3.6 Hz, 1H), 3.39 (s, 3H), 2.85 (dd, J = 15.4, 9.3 Hz, 1H), 2.50 (dd, J = 15.4, 3.4 Hz, 1H), 2.42 (q, J = 7.3 Hz, 2H), 1.92 (ddd, J = 13.9, 6.4, 3.9 Hz, 1H), 1.60 (ddd, J = 13.2, 7.2, 4.8 Hz, 1H), 1.02 (t, J = 7.3 Hz, 3H), 0.94 (s, 3H), 0.90 (s, 9H), 0.83 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.6, 170.4, 135.4, 128.3, 128.1, 128.0, 82.6, 76.8, 72.7, 69.6, 66.5, 58.3, 42.2, 37.8, 36.8, 30.0, 25.7, 24.6, 17.9, 17.3, 7.6, −4.5, −5.1; MS (EI) calculated for $C_{27}H_{44}O_6Si$ $[M]^+$: 492.2907, found 492.2911

(*S*)-Benzyl 2-((2*S*,4*R*,6*R*)-Tetrahydro-5,5-dimethyl-6-((3*S*,4*R*)-4-hydroxy-3-methyl-5-(6-methyl-2-methyloxycarbonyl-3,5-bistriisopropylsilyloxyphenyl)-2-oxopentyl)-4-*tert*-butyldimethylsilyloxy-2*H*-pyran-2-yl)-2-methoxyacetate (+)-35. A solution of ketone (+)-**33** (69.7 mg, 0.142 mmol) in CH_2Cl_2 (2.0 mL) was cooled to −78 °C, and $PhBCl_2$ (44.1 μL, 0.340 mmol) was added. After stirring for 20 min, *i*-Pr_2NEt (74.2 μL, 0.425 mmol) was added dropwise. After stirring for 1 h at −78 °C, aldehyde **32** (91.2 mg, 0.170 mmol) in CH_2Cl_2 (0.8 mL) was added to the boron enolate dropwise. After stirring for 1 h at −78 °C, the reaction was quenched with MeOH (3 mL) and sat. $NaHCO_3$ (3 mL). The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/8) gave aldol (+)-**35** (99.1 mg, 0.0964 mmol, 68%, *dr* > 20:1) as a white foam.

(+)-**35**: $[\alpha]_D^{23}$ +35.2 (c 2.61, $CHCl_3$); IR (neat): 3452, 2947, 2867, 1730, 1589, 1469, 1259, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38−7.29 (m, 5H), 6.26 (s, 1H), 5.24 (d, J = 12.0 Hz, 1H), 5.11 (d, J = 12.0 Hz, 1H), 4.14 (q, J = 5.6 Hz, 1H), 4.09 (dd, J = 9.2, 2.8 Hz, 1H), 4.03 (m, 1H), 3.98 (d, J = 5.6 Hz, 1H), 3.83 (s, 3H), 3.65 (dd, J = 7.6, 4.8 Hz, 1H), 3.50 (m, 1H), 3.39 (s, 3H), 3.02 (dd, J = 16.4, 9.2 Hz, 1H), 2.82 (dd, J = 14.0, 3.2 Hz, 1H), 2.67 (dt, J = 12.9, 6.4 Hz, 1H), 2.58−2.49 (m, 2H), 2.16 (s, 3H), 1.93 (ddd, J = 13.2, 6.0, 4.4 Hz, 1H), 1.59 (ddd, J = 13.2, 7.6, 5.6 Hz, 1H), 1.24 (m, 6H), 1.17 (d, J = 6.8 Hz, 3H), 1.11−1.06 (m, 36H), 0.94 (s, 3H), 0.89 (s, 9H), 0.85 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.0, 170.8, 170.5, 155.9, 151.3, 136.6, 135.5, 128.4, 128.2, 128.1, 120.5, 119.7, 107.3, 82.6, 76.4, 72.8, 71.4, 69.9, 66.6, 58.5, 53.1, 52.2, 42.4, 37.8, 36.0, 29.9, 25.8, 24.6, 18.0, 18.0, 17.9, 17.2, 13.2, 13.1, 12.3, 11.3, −4.4, −5.0 ; MS (FAB) calculated for $C_{55}H_{93}O_{10}Si_3$ $[M - CH_3O]^+$: 997.6077, found 997.6046.

(*S*)-Benzyl 2-((2*S*,4*R*,6*R*)-Tetrahydro-6-((2*S*,3*S*,4*R*)-2,4-bishydroxy-3-methyl-5-(6-methyl-2-methyloxycarbonyl-3,5-bistriisopropylsilyloxyphenyl)-pentyl)-5,5-dimethyl-4-*tert*-butyldimethylsilyloxy-2*H*-pyran-2-yl)-2-methoxyacetate (+)-60. To a solution of THF/MeOH (3.5 mL/5.2 mL) was added Et_3B (1.0 M solution in hexane, 2.62 mL, 2.62 mmol). After stirring for 1 h, the reaction was cooled to −70 °C and aldol (+)-**35** (539 mg, 0.524 mmol) in THF (7.0 mL) was added. After stirring for 30 min at −70 °C, $NaBH_4$ (198 mg, 5.24 mmol) was added, and the reaction was stirred for 16 h. The reaction was quenched with a mixture of MeOH/sat. NH_4Cl/30% aq. H_2O_2 (15 mL/15 mL/15 mL), and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification

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by column chromatography (EtOAc/Hexane 1/12−1/8) gave diol (+)-**60** (503 mg, 0.488 mmol, 93%, *dr* > 20:1) as a white foam.

(+)-**60**: $[\alpha]_D^{22}$ +14.8 (c 2.42, $CHCl_3$); IR (neat): 3490, 2947, 2867, 1732, 1589, 1468, 1258, 1165, 1100, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38−7.29 (m, 5H), 6.25 (s, 1H), 5.29 (d, *J* = 12.4 Hz, 1H), 5.18 (d, *J* = 12.0 Hz, 1H), 4.19 (dt, *J* = 9.6, 4,8 Hz, 1H), 4.01−3.99 (m, 2H), 3.87−3.83 (m, 4H), 3.73 (brs, 2H), 3.55−3.52 (m, 2H), 3.37 (s, 3H), 2.80 (ddd, *J* = 18.0, 14.0, 6.0 Hz, 2H), 2.19 (s, 3H), 1.92 (dt, *J* = 14.0, 4.4 Hz, 1H), 1.87−1.81 (dt, *J* = 14.4, 9.6 Hz, 1H), 1.65 (ddd, *J* = 14.4, 9.6, 5.6 Hz, 1H), 1.51 (dt, *J* = 6.8, 2.0 Hz, 1H), 1.45 (d, *J* = 14.4 Hz, 1H), 1.25 (sept, *J* = 7.6 Hz, 3H), 1.23 (sept, *J* = 7.6 Hz, 3H), 1.11−1.06 (m, 36H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.85 (s, 3H), 0.84 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 170.3, 155.6, 151.1, 137.1, 135.4, 128.5, 128.2, 120.7, 120.1, 107.1, 81.6, 81.5, 75.3, 72.2, 71.2, 66.9, 58.4, 52.1, 41.9, 38.9, 36.2, 33.5, 29.9, 25.8, 24.1, 18.1, 17.9, 15.5, 13.2, 13.1, 12.6, 6.1, −4.3, −4.9; MS (FAB) calculated for $C_{55}H_{95}O_{10}Si_3$ $[M - CH_3O]^+$: 999.6233, found 999.6224.

(*S*)-Benzyl 2-((2*S*,4*R*,6*R*)-Tetrahydro-6-((2*S*,3*S*)-3-((3*R*)-6,8-bistriisopropylsilyloxy-5-methyl-3,4-dihydroisocoumarinyl)-3-methyl-2-*tert*-butyldimethylsilyloxypropyl)-5,5-dimethyl-4-*tert*-butyldimethylsilyloxy-2*H*-pyran-2-yl)-2-methoxyacetate (+)-36. To a solution of diol (+)-**60** (98.0 mg, 0.0951 mmol) in CH_2Cl_2 (1.0 mL) was added CSA (2.21 mg, 0.00951 mmol) at rt. After stirring for 2 h, the reaction was quenched with sat. $NaHCO_3$ (1 mL) and the crude was extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration afforded the crude lactone. To a solution of crude lactone in CH_2Cl_2 (0.5 mL) was added 2,6-lutidine (0.0665 mL, 0.571 mmol), followed by TBSOTf (0.0655 mL, 0.285 mmol), at 0 °C. After stirring for 2 h, the reaction was diluted with Et_2O (2 mL) and quenched with sat. $NaHCO_3$ (1 mL). The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/40−1/20) gave TBS-ether (+)-**36** (82.1 mg, 0.0738 mmol, 78% over 2 steps) as a white foam.

(+)-**36**: $[\alpha]_D^{25}$ +48.9 (c 0.98, $CHCl_3$); IR (neat): 2947, 2892, 2867, 1727, 1591, 1568, 1472, 1353, 1249, 1172, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38−7.29 (m, 5H), 6.32 (s, 1H), 5.26 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 4.20−4.11 (m, 3H), 3.97 (d, *J* = 5.2 Hz, 1H), 3.62 (dd, *J* = 7.2, 4.4 Hz, 1H), 3.43 (d, *J* = 6.8 Hz, 1H), 3.39 (s, 3H), 3.08 (d, *J* = 16.0 Hz, 1H), 2.64 (dd, *J* = 16.4, 12.4 Hz, 1H), 2.10 (s, 3H), 2.01−1.90 (m, 3H), 1.69 (dd, *J* = 14.0, 10.4 Hz, 1H), 1.58 (m, 1H), 1.36−1.24 (m, 6H), 1.14−1.08 (m, 39H), 0.93 (s, 3H), 0.89 (s, 9H), 0.84 (s, 3H), 0.78 (s, 6H), 0.05 (s, 6H), 0.03 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 163.3, 158.4, 157.2, 141.3, 135.3, 128.4, 128.3, 128.2, 118.0, 110.4, 109.7, 83.3, 79.3, 77.1, 72.9, 69.8, 69.0, 66.6, 58.7, 39.9, 38.1, 33.5, 30.2, 25.9, 25.8, 25.0, 18.1, 18.0, 18.0, 16.9, 13.3, 11.9, 8.6, −3.4, −4.3, −4.9 ; MS (FAB) calculated for $C_{61}H_{109}O_{10}Si_4$ $[M + H]^+$: 1113.7098, found 1113.7126.

(2*R*,4*R*,6*S*)-2-((2*S*,3*S*)-3-((3*R*)-6,8-Bistriisopropylsilyloxy-5-methyl-3,4-dihydroisocoumarinyl)-3-methyl-2-*tert*-butyldimethylsilyloxypropyl)-3,3-dimethyl-6-((*S*)-methoxy-(*N*-(2-(trimethylsilyl)ethoxycarbonyl)amino)-methyl)-4-*tert*-butyldimethylsilyloxytetrahydropyran (+)-5. To a solution of TBS-ether (+)-**36** (272 mg, 0.244 mmol) in MeOH (2.4 mL) was added 10% Pd-C (27.2 mg, 10% w/w) and hydrogenated (H_2, 1 atm). After 1 h, the catalyst was filtered through a pad of Celite, followed by washing with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration afforded a crude carboxylic acid. To a solution of the crude carboxylic acid in THF (4.9 mL) was added NMM (0.0537 mL, 0.489 mmol), followed by EtOCOCl (0.0468 mL, 0.489 mmol), at −20 °C. After stirring for 20 min, NaN_3 (79.3 mg, 1.22 mmol) in H_2O (0.5 mL) was added to the reaction. After 20 min, $NaHCO_3$ (1 mL) was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$, and toluene (4.9 mL) was added. Filtration and concentration afforded a toluene solution of the crude acyl azide. This solution was heated to 100 °C and stirred for 30 min. The reaction mixture was cooled to rt, and 2-(trimethylsilyl)ethanol (0.350 mL, 2.44 mmol) was added. After stirring for 17 h at 100 °C, the reaction was cooled to rt and the solvent was evaporated. Purification by column chromatography (EtOAc/Hexane 1/20) gave Teoc-protected hemiaminal (+)-**5** (262 mg, 0.230 mmol, 94% over 3 steps) as a white foam.

(+)-**5**: $[\alpha]_D^{21}$ +41.2 (c 0.66, $CHCl_3$); IR (neat): 2950, 2895, 2867, 1727, 1592, 1568, 1472, 1353, 1250, 1173, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.30 (s, 1H), 5.45 (d, *J* = 8.0 Hz, 1H), 4.80 (d, *J* = 8.0 Hz, 1H), 4.21−4.10 (m, 4H), 4.00 (d, *J* = 6.4 Hz, 1H), 3.57 (brs, 1H), 3.36−3.34 (m, 4H), 3.03 (d, *J* = 12.8 Hz, 1H), 2.59 (dd, *J* = 12.8, 9.6 Hz, 1H), 2.27 (t, *J* = 10.8 Hz, 1H), 2.09 (s, 3H), 1.94 (t, *J* = 4.8 Hz, 1H), 1.81 (t, *J* = 8.8 Hz, 1H), 1.61 (dd, *J* = 18.0, 9.6 Hz, 1H), 1.46 (dt, *J* = 11.2, 4.8 Hz, 1H), 1.34−1.25 (m, 6H), 1.12−1.08 (m, 36H), 1.05 (d, *J* = 5.2 Hz, 3H), 0.96 (s, 3H), 0.89 (s, 9H), 0.87 (m, 2H), 0.85 (s, 3H), 0.77 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.00 (s, 9H), −0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4, 158.6, 157.4, 156.9, 141.3, 118.0, 110.5, 109.7, 84.2, 79.3, 77.4, 73.4, 68.6, 67.5, 63.4, 55.9, 39.5, 37.4, 32.5, 31.5, 29.9, 26.5, 26.0, 25.8, 20.7, 18.1, 18.0, 17.9, 17.6, 13.2, 13.1, 11.8, 8.7, −1.5, −3.5, −4.5, −4.9, −5.1; MS (FAB) calculated for $C_{56}H_{108}O_{10}NSi_5$ $[M - C_3H_7]^+$: 1094.6820, found 1094.6835.

(+)-11,15-Bis-*tert*-butyldimethylsilyl-21,23-bistriisopropylsilyl-7-*N*-(2-(trimethylsilyl)ethoxycarbonyl)-5-(trimethylsilyl)-ethoxymethylirciniastatin A (+)-38. To a solution of carboxylic acid (−)-**6** (24.8 mg, 0.0814 mmol) in CH_2Cl_2 (0.41 mL) was added *i*-Pr_2NEt (0.0156 mL, 0.0895 mmol), followed by PivCl (0.0105 mL, 0.0854 mmol), at 0 °C. After stirring for 30 min, the reaction was quenched with sat. $NaHCO_3$ (1 mL). The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The unpurified mixed anhydride **37** was azeotroped with benzene (3 × 1 mL), placed on the vacuum pump for 30 min, and then dissolved in THF (0.7 mL). To a solution of a Teoc-protected hemiaminal (+)-**5** (61.7 mg, 0.0542 mmol) in THF (1.1 mL) was added activated 4 Å molecular sieves (108 mg) and the solution of the mixed anhydride **37**. The mixture was cooled to −78 °C, and LHMDS (1.6 M solution in THF, 0.136 mL, 0.217 mmol) was added. After stirring for 30 min, the reaction was allowed to warm to −60 °C and stirred for 6.5 h. Sat. NH_4Cl (2 mL) was added, and the reaction was allowed to warm to rt. The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/40−1/20) gave amide (+)-**38** (42.2 mg, 0.0297 mmol, 55%, 93% BRSM) as a colorless oil.

(+)-**38**: $[\alpha]_D^{21}$ +41.2 (c 0.66, $CHCl_3$); IR (neat): 2950, 2895, 2867, 1727, 1592, 1568, 1472, 1353, 1250, 1173, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.30 (s, 1H), 5.65 (d, *J* = 4.0 Hz, 1H), 5.15 (d, *J* = 3.6 Hz, 1H), 4.77 (d, *J* = 7.6 Hz, 1H), 4.67 (d, *J* = 5.2 Hz, 1H), 4.61 (d, *J* = 5.2 Hz, 1H), 4.32−4.29 (m, 3H), 4.17 (ddd, *J* = 9.2, 6.4, 1.2 Hz, 1H), 4.11 (dt, *J* = 8.0, 2.8 Hz, 1H), 3.65 (ddd, *J* = 7.2, 3.6, 2.0 Hz, 1H), 3.61−3.52 (m, 3H), 3.35 (s, 3H), 3.27 (s, 3H), 3.16 (d, *J* = 7.6 Hz, 1H), 3.06 (dd, *J* = 13.2, 1.2 Hz, 1H), 2.86 (dd, *J* = 13.2, 10.0 Hz, 1H), 2.30 (dd, *J* = 12.0, 7.6 Hz, 1H), 2.23−2.18 (m, 4H), 2.02 (m, 1H), 1.96 (m, 1H), 1.80 (m, 1H), 1.77 (s, 3H), 1.75−1.61 (m, 2H), 1.35−1.24 (m, 6H), 1.13−1.08 (m, 39H), 1.04 (m, 2H), 0.90 (s, 12H), 0.83 (m, 2H), 0.81 (s, 3H), 0.76 (s, 9H), 0.06−0.04 (s, 15H), −0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.6, 163.5, 158.5, 157.3, 154.3, 142.7, 141.9, 118.3, 112.7, 110.5, 109.6, 95.1, 88.3, 81.0, 79.5, 75.4, 74.3, 72.7, 69.0, 66.0, 65.9, 58.0, 56.5, 40.3, 39.0, 38.8, 35.0, 30.3, 30.0, 29.7, 25.9, 25.8, 24.0, 22.8, 18.1, 18.0, 18.0, 17.6, 13.6, 13.3, 13.1, 12.0, 8.8, −1.5, −1.6, −3.3, −4.2, −4.9, −5.0 ; MS (FAB) calculated for $C_{70}H_{134}O_{14}NSi_6$ $[M - C_3H_7]^+$: 1380.8420, found 1380.8413.

(+)-Irciniastatin A/Psymberin [(+)-1]. To a solution of amide (+)-**38** (13.3 mg, 9.32 μmol) in DMF (0.9 mL) was added TASF (102 mg, 0.373 mmol), and the reaction was heated to 50 °C. After stirring for 16 h, the reaction was quenched with sat. NH_4Cl (1 mL) and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/1−2/1) gave (+)-irciniastatin A/psymberin [(+)-**1**] (3.02 mg, 4.96 μmol, 53%) as a white solid.

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(+)-**1**: $[\alpha]_D^{25}$ +26.6 (c 0.11, $CHCl_3$); IR (neat): 3378, 2927, 1656, 1619, 1519, 1462, 1376, 1253, 1173, 1106, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 11.1 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 5.45 (dd, J = 8.0, 7.2 Hz, 1H), 4.80 (s, 2H), 4.53 (dt, J = 9.2, 3.2 Hz, 1H), 4.41 (s, 1H), 4.35 (s, 1H), 4.30 (m, 1H), 3.94 (d, J = 8.4 Hz, 1H), 3.88 (m, 1H), 3.74 (m, 1H), 3.67 (dd, J = 8.4, 4.8 Hz, 1H), 3.54 (d, J = 8.4 Hz, 3H), 3.38 (s, 6H), 2.88 (dd, J = 13.2, 2.8 Hz, 1H), 2.81 (dd, J = 13.2, 10.0 Hz, 1H), 2.38 (dd, J = 11.2, 6.8 Hz, 1H), 2.18 (dd, J = 11.6, 3.2 Hz, 1H), 2.07 (m, 1H), 2.03 (s, 3H), 1.88−1.78 (m, 2H), 1.75 (s, 3H), 1.63 (m, 1H), 1.10 (d, J = 6.0 Hz, 3H), 0.97 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.4, 173.6, 170.5, 161.1, 142.0, 139.7, 113.2, 113.0, 101.6, 101.3, 81.9, 80.6, 79.6, 78.3, 73.9, 73.1, 73.1, 71.4, 57.9, 56.3, 42.7, 38.8, 37.6, 32.2, 29.7, 28.5, 23.1, 22.7, 13.6, 10.5, 9.2; MS (FAB) calculated for $C_{30}H_{44}O_{10}N$ $[M - CH_3O]^+$: 578.2965, found 578.2967.

(+)-5,11,21,23-Tetrakis-*tert*-butyldimethylsilylirciniastatin A (+)-61. To a solution of (+)-irciniastatin A [(+)-**1**] (10.9 mg, 0.0179 mmol) in CH_2Cl_2 (1.8 mL) was added 2,6-lutidine (29.2 μL, 0.251 mmol) and TBSOTf (28.8 μL, 0.125 mmol) at 0 °C. After stirring for 1 h, the reaction was quenched with sat. $NaHCO_3$ (0.6 mL) and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/20−1/10) gave TBS-ether (+)-**61** (6.80 mg, 6.38 μmol, 36%) as a colorless oil.

(+)-**61**: $[\alpha]_D^{21}$ +28.0 (c 0.05, $CHCl_3$); IR (neat): 2932, 2359, 1728, 1684, 1472, 1253, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.09 (d, J = 10.0 Hz, 1H), 6.28 (s, 1H), 5.28 (dd, J = 10.0, 5.5 Hz, 1H), 4.79 (s, 1H), 4.75 (s, 1H), 4.40 (d, J = 1.5 Hz, 1H), 4.26 (ddd, J = 11.5, 7.4, 2.6 Hz, 1H), 4.00−3.92 (m, 2H), 3.68 (ddd, J = 9.3, 3.4, 1.5 Hz, 1H), 3.63 (s, 1H), 3.54 (dd, J = 7.8, 3.4 Hz, 1H), 3.35 (s, 3H), 3.21 (s, 3H), 3.11 (dd, J = 16.3, 2.7 Hz, 1H), 2.77 (dd, J = 16.6, 11.7 Hz, 1H), 2.32 (dd, J = 14.6, 9.7 Hz, 1H), 2.13 (s, 3H), 2.10−2.01 (m, 2H), 1.87 (ddd, J = 13.6, 6.8, 4.0 Hz, 1H), 1.80 (dt, J = 7.2, 2.0 Hz, 1H), 1.73 (s, 3H), 1.60 (m, 2H), 1.10 (d, J = 6.8 Hz, 4H), 1.04−0.89 (m, 42H), 0.25−0.03 (m, 21H), −0.01 (s, 3H); MS (ESI) calculated for $C_{55}H_{103}O_{11}NNaSi_4$ $[M + Na]^+$: 1088.6500, found 1088.6486.

(2*S*,3*S*)-*N*-((*S*)-((2*S*,4*R*,6*R*)-6-((*S*)-3-((*R*)-6,8-Bis((*tert*-butyldimethylsilyl)oxy)-5-methyl-1-oxoisochroman-3-yl)-2-oxobutyl)-4-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyltetrahydro-2*H*-pyran-2-yl)(methoxy)methyl)-2-((*tert*-butyldimethylsilyl)oxy)-3-methoxy-5-methylhex-5-enamide (+)-40. To a solution of TBS-ether (+)-**61** (7.00 mg, 6.60 μmol) in CH_2Cl_2 (0.66 mL) were added $PhI(OAc)_2$ (7.5 mg, 0.0200 mmol) and AZADO (2.2 mg, 0.0100 mmol). After stirring for 7 h, the reaction was then diluted with CH_2Cl_2 (3 mL) and quenched with sat. $Na_2S_2O_3$ (2.5 mL) at 0 °C. After stirring for 30 min at rt, the mixture was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by preparative TLC (EtOAc/Hexane 1/4) gave ketone (+)-**40** (5.60 mg, 5.30 μmol, 80%) as a colorless oil.

(+)-**40**: $[\alpha]_D^{21}$ +44.3 (c 0.22, $CHCl_3$); IR (neat): 3169, 2929, 2863, 2360, 1741, 1685, 1589, 1496, 1462, 1251, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.14 (d, J = 10.0 Hz, 1H, N-7), 6.29 (s, 1H, C-22), 5.16 (dd, J = 10.4, 3.6 Hz, 1H, C-8), 4.78 (d, J = 13.2 Hz, 2H, C-1), 4.50−4.44 (m, 2H, C-5, C-17), 4.08 (dd, J = 7.3, 4.3 Hz, 1H, C-13), 3.94 (m, 1H, C-9), 3.75 (ddd, J = 9.2, 4.0, 2.0 Hz, 1H, C-4), 3.62 (dd, J = 4.8, 2.4 Hz, 1H, C-11), 3.39 (s, 3H), 3.33 (s, 3H), 3.04 (dd, J = 17.4, 7.7 Hz, 1H), 2.96−2.88 (m, 3H, C-16, C-18), 2.55 (dd, J = 16.5, 11.6, 1H, C-18), 2.33 (dd, J = 14.5, 9.1 Hz, 1H, C-3), 2.15 (dd, J = 15.0, 3.4 Hz, 1H, C-3), 2.00 (s, 3H), 1.80 (m, 1H), 1.74 (s, 3H), 1.58−1.49 (m, 1H), 1.31 (d, J = 6.8 Hz, 4H), 1.26 (s, 2H), 1.03−0.85 (m, 42H), 0.25−0.22 (m, 12H), 0.15 (s, 3H), 0.07−0.05 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.7, 172.5, 142.6, 140.7, 118.8, 112.6, 110.6, 110.1, 82.4, 81.3, 76.0, 74.4, 73.2, 58.0, 56.1, 50.8, 43.0, 37.9, 37.5, 31.0, 30.0, 29.7, 26.0, 25.9, 25.8, 25.7, 22.8, 18.5, 18.3, 18.2, 18.0, 13.3, 11.7, −4.2, −4.2, −4.3, −4.4, −4.5, −4.9, −5.2 ; MS (ESI) calculated for $C_{55}H_{101}O_{11}NNaSi_4$ $[M + Na]^+$: 1086.6344, found 1086.6335.

(2*R*,4*R*,6*S*)-2-Allyl-6-((*R*)-2-hydroxy-1-methoxyethyl)-3,3-dimethyltetrahydro-2*H*-pyran-4-ol (+)-42. To a solution of BOM-ether (+)-**23** (203 mg, 0.557 mmol) in CH_3CN/H_2O (5.6 mL/0.3 mL) was added $LiBF_4$ (783 mg, 8.35 mmol) at rt. The reaction mixture was stirred at reflux for 3 h. The mixture was quenched with sat. $NaHCO_3$ (15 mL). The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/4−1/1) gave diol (+)-**42** (123 mg, 0.501 mmol, 90%) as a white solid.

(+)-**42**: $[\alpha]_D^{22}$ +12.3 (c 0.71, $CHCl_3$); IR (neat): 3734, 3388, 2148, 1683, 1558, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.83 (ddt, J = 16.8, 10.0, 7.2 Hz, 1H), 5.08 (dd, J = 16.8, 10.0 Hz, 2H), 3.92 (ddd, J = 8.7, 4.2, 4.0 Hz, 1H), 3.77 (dd, J = 12.0, 4.2 Hz, 1H), 3.69 (dd, J = 12.0, 4.0 Hz, 1H), 3.62 (dd, J = 9.1, 4.4 Hz, 1H), 3.45 (s, 3H), 3.35 (ddd, J = 8.7, 4.4, 4.4 Hz, 1H), 3.27 (dd, J = 10.8, 2.5 Hz, 1H), 2.43 (m, 1H), 2.22 (m, 2H), 2.00 (ddd, J = 13.6, 4.4, 4.4 Hz, 1H), 1.79 (ddd, J = 13.6, 9.1, 4.4 Hz, 1H), 1.64 (brs, 1H) 1.25 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ: 138.2, 116.5, 81.4, 80.7, 61.8, 58.9, 39.6, 34.9, 30.4, 28.2, 25.9, 23.9 ; MS (EI) calculated for $C_{10}H_{19}O_4$ $[M - C_3H_5]^+$: 203.1283, found 203.1277.

(2*R*,4*R*,6*S*)-2-Allyl-4-(benzyloxy)-6-((*R*)-2-(benzyloxy)-1-methoxyethyl)-3,3-dimethyltetrahydro-2*H*-pyran (−)-43. To a solution of diol (+)-**42** (14.7 mg, 0.0602 mmol) in THF (0.6 mL) was added NaH (12.0 mg, 0.301 mmol), followed by TBAI (2.2 mg, 6.02 μmol) and BnBr (0.0357 mL, 0.301 mmol), at rt. The reaction mixture was stirred at reflux for 2 h. The mixture was quenched with sat. NH_4Cl (2 mL). The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/40−1/20) gave Bn-ether (−)-**43** (20.4 mg, 0.0479 mmol, 80%) as a colorless oil.

(−)-**43**: $[\alpha]_D^{22}$ −0.98 (c 0.51, $CHCl_3$); IR (neat): 2863, 1639, 1454, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34−7.28 (m, 10H), 5.74 (ddt, J = 17.2, 10.4, 6.8 Hz, 2H), 4.97 (m, 2H), 4.64 (d, J = 12.4 Hz, 1H), 4.57 (d, J = 12.2 Hz, 1H), 4.50 (d, J = 12.2 Hz, 1H), 4.41 (d, J = 12.4 Hz, 1H), 3.89 (m, 1H), 3.75 (m, 1H), 3.48−3.45 (m, 2H), 3.45 (s, 3H), 3.27 (dd, J = 9.0, 4.0 Hz, 1H), 3.21 (dd, J = 10.6, 2.6 Hz, 1H) 2.38 (m, 1H), 2.18 (dd, J = 13.6, 6.8 Hz, 1H), 2.07 (dt, J = 14.0, 4.0 Hz, 1H), 1.78 (m, 1H), 0.99 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.0, 128.3, 128.3, 128.2, 127.6, 127.6, 127.5, 127.5, 127.4, 116.0, 87.7, 79.7, 79.1, 73.5, 71.1, 70.4, 70.3, 58.8, 38.3, 33.6, 25.5, 25.5 ; MS (EI) calculated for $C_{35}H_{40}O_6$ $[M]^+$: 556.2825, found 556.2840.

1-((2*R*,4*R*,6*S*)-4-(Benzyloxy)-6-((*R*)-2-(benzyloxy)-1-methoxyethyl)-3,3-dimethyltetrahydro-2*H*-pyran-2-yl)butan-2-one (+)-44. To a solution of Bn-ether (−)-**43** (117 mg, 0.276 mmol) in THF/H_2O (2.8/0.3 mL) was added NMO (48.6 mg, 0.415 mmol), followed by OsO_4 (0.196 M solution in THF, 0.028 mL, 5.53 μmol), at 0 °C. The reaction mixture was stirred at rt for 12 h. The mixture was quenched with sat. $Na_2S_2O_3$ (3 mL) and stirred for 1 h at rt. The mixture was extracted with EtOAc, and the combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration afforded a crude diol. To a solution of the diol in $MeOH/H_2O$ (5.0 mL/0.6 mL) was added $NaIO_4$ (88.7 mg, 0.415 mmol), and the mixture was stirred at rt. After 1 h, EtOAc and H_2O were added. The mixture was extracted with EtOAc, and the combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration afforded a crude aldehyde. To a solution of EtMgBr (1.0 M solution in THF, 1.66 mL, 1.66 mmol) was added the crude aldehyde dropwise at 0 °C. After stirring for 1 h, the reaction was quenched with sat. NH_4Cl (6 mL) and the mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration afforded a crude ethyl alcohol. To a solution of the ethyl alcohol in CH_2Cl_2 (0.6 mL) was added $PhI(OAc)_2$ (134 mg, 0.415 mmol), followed by 1-Me-AZADO (4.6 mg, 0.0276 mmol), at rt. After stirring for 3 h, the reaction was then diluted with Et_2O (3 mL) and quenched with sat. $Na_2S_2O_3$ (1.5 mL) at 0 °C. After stirring for 1 h at rt, the mixture was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/8) gave ketone (+)-**44** (102 mg, 0.224 mmol, 81% over 4 steps) as a colorless oil.

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J. Org. Chem. 2015, 80, 12333−12350

(+)-**44**: $[\alpha]_D^{27}$ +2.3 (c 0.61, $CHCl_3$); IR (neat): 2933, 2872, 2359, 1714, 1453, 1363, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36−7.27 (m, 10H), 4.65 (d, J = 12.0 Hz, 1H), 4.53 (s, 2H), 4.41 (d, J = 11.6 Hz, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.66 (d, J = 8.0 Hz, 1H), 3.47−3.43 (m, 2H), 3.43 (s, 3H), 3.31 (dd, J = 9.2, 4.0 Hz, 1H), 2.79 (dd, J = 15.6, 10.0 Hz, 1H), 2.41 (m, 3H), 2.08 (dt, J = 13.6, 4.4 Hz, 1H), 1.78 (m, 1H), 1.00 (t, J = 7.2 Hz, 3H), 0.97 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.5, 138.8, 138.6, 128.3, 128.3, 128.2, 127.6, 127.5, 127.5, 127.4, 79.3, 78.9, 76.0, 73.4, 71.0, 69.0, 58.4, 42.1, 37.8, 37.4, 25.4, 24.2, 7.6 ; MS (EI) calculated for $C_{28}H_{38}O_5$ $[M]^+$: 454.2719, found 454.2698.

Methyl 2-((2*R*,3*S*)-5-((2*R*,4*R*,6*S*)-4-(Benzyloxy)-6-((*R*)-2-(benzyloxy)-1-methoxyethyl)-3,3-dimethyltetrahydro-2*H*-pyran-2-yl)-2-hydroxy-3-methyl-4-oxopentyl)-3-methyl-4,6-bis((triisopropylsilyl)oxy)benzoate (+)-45. A solution of ketone (+)-**44** (68.0 mg, 0.150 mmol) in CH_2Cl_2 (2.2 mL) was cooled to −78 °C, and $PhBCl_2$ (70.0 μL, 0.539 mmol) was added. After stirring for 4 min, *i*-Pr_2NEt (0.117 mL, 0.673 mmol) was added dropwise. After stirring for 1 h at −78 °C, aldehyde **32** (200.6 mg, 0.374 mmol) in CH_2Cl_2 (0.8 mL) was added to the boron enolate dropwise. After stirring for 1 h at −78 °C, the reaction was quenched with the mixture of MeOH/pH 7 buffer (5.0/5.0 mL). After 15 min at −78 °C, sat. $NaHCO_3$ aq. was added to neutralize the reaction mixture to pH 7, and the mixture was stirred for 1 h at 0 °C. The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/15−1/8) gave aldol (+)-**45** (121 mg, 0.122 mmol, 82%) as a white foam.

(+)-**45**: $[\alpha]_D^{25}$ +21.4 (c 0.69, $CHCl_3$); IR (neat): 2945, 2867, 1708, 1589, 1467, 1416, 1342, 1265, 1193, 1166, 1071, 919 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37−7.24 (m, 10H), 6.26 (s, 1H), 4.65 (d, J = 12.2 Hz, 1H), 4.52 (s, 1H), 4.41 (d, J = 12.2 Hz, 1H), 4.03 (m, 1H), 3.91 (m, 1H), 3.87 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 3.68 (dd, J = 10.8, 2.4 Hz, 1H), 3.53 (m, 2H), 3.47−3.40 (m, 1H), 3.42 (s, 3H), 3.31 (dd, J = 10.0, 4.0 Hz, 1H), 2.90 (dd, J = 16.4, 9.6 Hz, 1H), 2.81 (dd, J = 14.4, 3.2 Hz, 1H), 2.66 (t, J = 6.0 Hz, 1H), 2.53−2.44 (m, 2H), 2.15 (s, 3H), 2.15−2.10 (m, 1H), 1.72 (m, 1H), 1.23 (sept, J = 7.6 Hz, 6H), 1.14−1.06 (m, 39H), 0.97 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.5, 171.1, 156.1, 151.6, 138.7, 138.6, 136.6, 128.3, 128.3, 128.2, 127.6, 127.5, 127.5, 127.3, 120.6, 119.8, 107.4, 78.8, 77.3, 77.2, 77.0, 76.7, 75.3, 73.4, 71.4, 70.9, 69.2, 58.5, 53.5, 52.3, 42.2, 37.8, 35.9, 25.3, 23.9, 18.0, 17.9, 13.2, 13.0, 12.3, 11.1; MS (FAB) calculated for $C_{56}H_{87}O_9Si_2$ $[M - CH_3O]^+$: 959.5889, found 959.5894.

Methyl 2-((2*R*,3*S*,4*S*)-5-((2*R*,4*R*,6*S*)-4-(Benzyloxy)-6-((*R*)-2-(benzyloxy)-1-methoxyethyl)-3,3-dimethyltetrahydro-2*H*-pyran-2-yl)-2,4-dihydroxy-3-methylpentyl)-3-methyl-4,6-bis((triisopropylsilyl)oxy)benzoate (+)-62. To a solution of aldol (+)-**45** (296 mg, 0.299 mmol) in THF/MeOH (3.3 mL/1.2 mL) cooled to −78 °C was added Et_2BOMe (1.0 M solution in THF, 0.60 mL, 0.598 mmol). After stirring for 1 h, to the reaction was added $NaBH_4$ (56.5 mg, 1.49 mmol). After 1 h, the reaction mixture was warmed to 0 °C. After 1.5 h, the reaction was quenched with a mixture of EtOAc/H_2O (4.0/4.0 mL) and MeOH/30% aq. H_2O_2 (6.5/6.5 mL) and stirred for 1 h. The mixture was extracted with EtOAc, and the combined organic layers were treated with solid $Na_2S_2O_3$ to destroy any remaining peroxide. The organic layer was then filtered and washed with sat. $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/8−1/6) gave diol (+)-**62** (231 mg, 0.232 mmol, 78%) as a white foam.

(+)-**62**: $[\alpha]_D^{26}$ +5.9 (c 0.21, $CHCl_3$); IR (neat): 3471, 2944, 2866, 1727, 1588, 1466, 1341, 1259, 1164, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.33−7.26 (m, 10H), 6.26 (s, 1H), 4.63 (d, J = 12.4 Hz, 1H), 4.58 (d, J = 12.4 Hz, 1H), 4.50 (d, J = 12.4 Hz, 1H), 4.41 (d, J = 12.4 Hz, 1H), 4.10−4.06 (m, 1H), 3.95 (s, 2H), 3.82 (s, 3H), 3.70 (dt, J = 10.4, 2.8 Hz, 1H), 3.54 (dd, J = 10.8, 4.0 Hz, 1H), 3.47−3.40 (m, 1H), 3.40 (s, 3H), 3.26 (dd, J = 8.8, 3.2 Hz, 1H), 2.78 (d, J = 6.4 Hz, 2H), 2.17 (s, 3H), 2.08−2.05 (m, 1H), 1.95−1.91 (m, 1H), 1.73−1.66 (m, 1H), 1.59 (s, 2H), 1.48−1.43 (m, 2H), 1.26 (sept, J = 7.6 Hz, 6H), 1.11−1.06 (m, 36H), 0.98−0.93 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.7, 158.7, 157.4, 140.8, 139.0, 138.3, 128.3, 128.2, 127.5, 127.5, 127.3, 127.3, 117.9, 109.9, 109.3, 79.7, 78.2, 77.3, 77.2, 77.0, 76.7, 76.5, 73.6, 71.1, 70.6, 69.8, 59.1, 43.8, 37.7, 29.8, 25.9, 25.2, 25.0, 18.1, 18.0, 18.0, 13.3, 13.1, 11.7, 10.4, −4.1, −4.7 ; MS (FAB) calculated for $C_{57}H_{92}O_{10}Si_2$ $[M - H]^+$: 991.6045, found 991.6082.

(*R*)-3-((2*S*,3*S*)-4-((2*R*,4*R*,6*S*)-4-(Benzyloxy)-6-((*R*)-2-(benzyloxy)-1-methoxyethyl)-3,3-dimethyltetrahydro-2*H*-pyran-2-yl)-3-((*tert*-butyldimethylsilyl)oxy)butan-2-yl)-5-methyl-6,8-bis((triisopropylsilyl)oxy)isochroman-1-one (+)-46. To a solution of diol (+)-**62** (254 mg, 0.255 mmol) in CH_2Cl_2 (5.1 mL) was added CSA (6.0 mg, 0.0255 mmol) at 0 °C. After stirring for 30 min, the reaction was quenched with sat. $NaHCO_3$ (1.5 mL) and the crude was extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration afforded the crude lactone. To a solution of crude lactone in CH_2Cl_2 (5.1 mL) was added 2,6-lutidine (0.12 mL, 1.022 mmol), followed by TBSOTf (0.12 mL, 0.511 mmol), at 0 °C. After stirring for 1 h, the reaction was diluted with Et_2O (2 mL) and quenched with sat. $NaHCO_3$ (2 mL). The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/20−1/15) gave TBS-ether (+)-**46** (213 mg, 0.198 mmol, 78% over 2 steps) as a white foam.

(+)-**46**: $[\alpha]_D^{27}$ +36.3 (c 0.14, $CHCl_3$); IR (neat): 2945, 2866, 1725, 1590, 1567, 1471, 1351, 1244, 1169, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.42−7.28 (m, 10H), 6.38 (s, 1H), 4.67 (d, J = 12.0 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.24 (t, J = 9.2 Hz, 1H), 4.17−4.14 (m, 1H), 4.05−4.03 (m, 1H), 3.76 (dd, J = 10.4, 4.0 Hz, 1H), 3.64 (dd, J = 10.0, 5.2 Hz, 1H), 3.53−3.51 (m, 1H), 3.53 (s, 3H), 3.42−3.36 (m, 2H), 3.06 (d, J = 16.4 Hz, 1H), 2.58 (dd, J = 16.0, 12.0 Hz, 1H), 2.30−2.20 (m, 1H), 2.12 (s, 3H), 2.08−2.00 (m, 2H), 1.84−1.80 (m, 1H), 1.67 (t, J = 11.2 Hz, 1H), 1.37 (sept, J = 7.6 Hz, 6H), 1.20−1.11 (m, 39H), 1.07 (s, 3H), 1.01 (s, 3H), 0.81 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 158.7, 157.5, 141.1, 138.8, 138.2, 128.3, 128.3, 128.2, 127.7, 127.5, 127.4, 117.9, 110.4, 109.8, 81.5, 80.1, 79.2, 73.4, 71.7, 69.8, 68.9, 58.9, 39.7, 37.6, 32.7, 29.9, 25.9, 25.7, 25.6, 18.0, 17.9, 13.2, 13.1, 13.0, 11.9, 8.7, −3.6, −5.0 ; MS (FAB) calculated for $C_{59}H_{95}O_9Si_3$ $[M - C_3H_7]^+$: 1031.6284, found 1031.6305.

(*R*)-3-((2*S*,3*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-((2*R*,4*R*,6*S*)-4-hydroxy-6-((*R*)-2-hydroxy-1-methoxyethyl)-3,3-dimethyltetrahydro-2*H*-pyran-2-yl)butan-2-yl)-5-methyl-6,8-bis((triisopropylsilyl)oxy)isochroman-1-one (+)-47. To a solution of TBS-ether (+)-**46** (73.9 mg, 0.0687 mmol) in MeOH (1.4 mL) was added 10% Pd-C (7.4 mg, 10% w/w) and hydrogenated (H_2, 1 atm). After 5 h, the catalyst was filtered through a pad of Celite, followed by washing with EtOAc and concentrated. Purification by column chromatography (EtOAc/Hexane 1/4−1/2) gave diol (+)-**47** (58.4 mg, 0.0653 mmol, 95%) as a white foam.

(+)-**47**: $[\alpha]_D^{27}$ +58.3 (c 0.53, $CHCl_3$); IR (neat): 3440, 2947, 2868, 1705, 1591, 1567, 1472, 1411, 1386, 1353, 1248, 1172, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.28 (s, 1H), 4.27−4.19 (m, 2H), 4.04 (d, J = 12.0 Hz, 1H), 3.83 (dt, J = 9.2, 4.8 Hz, 1H), 3.63−3.61 (m, 2H), 3.53 (s, 3H), 3.45 (ddd, J = 12.0, 6.0, 2.6 Hz, 1H), 3.37 (brs, 1H), 3.21 (d, J = 10.4 Hz, 1H), 2.96 (dd, J = 16.4, 2.0 Hz, 1H), 2.74 (dd, J = 16.8, 12.8 Hz, 1H), 2.08 (s, 3H), 2.02−1.91 (m, 3H), 1.77−1.65 (m, 2H), 1.48 (brs, 1H), 1.29 (sept, J = 7.2 Hz, 6H), 1.11−1.07 (m, 36H), 1.04 (s, 3H), 0.95 (s, 3H), 0.88 (s, 3H), 0.83 (s, 9H), 0.08 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.1, 159.0, 157.7, 141.6, 118.1, 109.7, 109.5, 80.8, 79.4, 75.8, 72.5, 67.9, 62.2, 59.0, 39.8, 38.0, 34.5, 30.4, 29.1, 25.9, 25.8, 24.1, 18.0, 18.0, 17.9, 13.3, 13.1, 11.7, 8.6, −3.2, −4.7 ; MS (ESI) calculated for $C_{48}H_{91}O_9Si_3$ $[M + H]^+$: 895.5965, found 895.5941.

(*S*)-2-((2*S*,4*R*,6*R*)-6-((2*S*,3*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-((*R*)-5-methyl-1-oxo-6,8-bis((triisopropylsilyl)oxy)isochroman-3-yl)butyl)-4-hydroxy-5,5-dimethyltetrahydro-2*H*-pyran-2-yl)-2-methoxyacetic Acid (+)-48. To a solution of the diol (+)-**47** (17.6 mg, 0.0196 mmol) in CH_3CN/pH 7 buffer (0.4/0.2 mL) were added $NaClO_2$ (80%) (6.7 mg, 0.0588 mmol) and DMN-

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AZADO$^+BF_4^-$ (1.0 mg, 3.92 μmol). After 4.5 h, 2-methyl-2-butene (2 mL) and sat. NH_4Cl (1 mL) were added. The mixture was extracted with $CHCl_3$, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/2, then $CHCl_3$/MeOH 10%) gave carboxylic acid (+)-**48** (14.4 mg, 0.0158 mmol, 81%) as a white foam.

(+)-**48**: $[\alpha]_D^{28}$ +62.8 (c 0.96, $CHCl_3$); IR (neat): 3404, 2947, 2868, 1727, 1704, 1591, 1567, 1472, 1411, 1386, 1353, 1173, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.29 (s, 1H), 4.45 (dd, J = 11.0, 3.8 Hz, 1H), 4.25 (dq, J = 13.0, 2.8 Hz, 1H), 4.19−4.14 (m, 1H), 3.77 (d, J = 8.4 Hz, 1H), 3.70 (dd, J = 5.6, 3.2 Hz, 1H), 3.46−3.42 (m, 1H), 3.42 (s, 3H), 2.97 (dd, J = 16.8, 13.2 Hz, 1H), 2.85 (dd, J = 16.6, 2.6 Hz, 1H), 2.42 (t, J = 11.2 Hz, 1H), 2.17 (t, J = 6.6 Hz, 1H), 2.07 (s, 3H), 2.00−1.94 (m, 1H), 1.87−1.84 (m, 1H), 1.55 (dt, J = 10.8, 3.2 Hz, 1H), 1.30 (sept, J = 8.0 Hz, 6H), 1.34−1.26 (m, 1H), 1.13−1.08 (m, 36H), 1.03 (s, 3H), 0.97 (d, J = 7.2 Hz, 3H), 0.93 (s, 3H), 0.88 (s, 9H), 0.15 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.4, 166.2, 159.3, 157.8, 142.2, 118.1, 109.2, 109.2, 83.1, 79.8, 72.6, 68.1, 66.4, 58.2, 37.2, 36.9, 33.4, 31.7, 28.2, 26.1, 25.8, 18.0, 18.0, 18.0, 17.9, 13.2, 13.1, 11.7, 8.1, −3.1, −4.5 ; MS (ESI) calculated for $C_{48}H_{89}O_{10}Si_3$ $[M + H]^+$: 909.5764, found 909.5765.

2-(Trimethylsilyl)ethyl ((*S*)-((2*S*,4*R*,6*R*)-6-((2*S*,3*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-((*R*)-5-methyl-1-oxo-6,8-bis((triisopropylsilyl)oxy)isochroman-3-yl)butyl)-4-hydroxy-5,5-dimethyltetrahydro-2*H*-pyran-2-yl)(methoxy)methyl)-carbamate (+)-49. To a solution of carboxylic acid (+)-**47** (8.6 mg, 9.46 μmol) in THF (0.4 mL) was added NMM (3.1 μL, 0.028 mmol), followed by EtOCOCl (2.7 μL, 0.028 mmol), at −20 °C. After stirring for 20 min, NaN_3 (3.7 mg, 0.057 mmol) in H_2O (0.023 mL) was added to the reaction. After 30 min, sat. $NaHCO_3$ (0.5 mL) was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$, and toluene (0.4 mL) was added. Filtration and concentration afforded a toluene solution of the crude acyl azide. This solution was heated to 100 °C and stirred for 1 h. The reaction mixture was cooled to rt, and 2-(trimethylsilyl)ethanol (0.014 mL, 0.095 mmol) was added. After stirring for 2.5 h at 100 °C, the reaction was cooled to rt and the solvent was evaporated. Purification by column chromatography (EtOAc/Hexane 1/8−1/4) gave Teoc-protected hemiaminal (+)-**49** (8.3 mg, 8.13 μmol, 86% over 2 steps) as a white foam.

(+)-**49**: $[\alpha]_D^{26}$ +111.4 (c 0.51, $CHCl_3$); IR (neat): 3447, 2947, 2867, 2360, 1707, 1590, 1567, 1472, 1352, 1248, 1173, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.30 (s, 1H), 5.42 (d, J = 9.2 Hz, 1H), 4.86 (d, J = 7.6 Hz, 1H), 4.21−4.17 (m, 3H), 4.11 (t, J = 7.0 Hz, 1H), 4.01 (brs, 1H), 3.66 (brs, 1H), 3.40−3.37 (m, 1H), 3.37 (s, 3H), 3.01 (d, J = 16.0 Hz, 1H), 2.62 (dd, J = 16.8, 12.0 Hz, 1H), 2.35−2.27 (m, 1H), 2.11 (s, 3H), 1.98−1.87 (m, 2H), 1.30 (sept, J = 7.6 Hz, 6H), 1.12−1.05 (m, 42H), 1.00 (s, 3H), 0.91 (s, 6H), 0.79 (s, 9H), 0.01 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5, 158.6, 157.4, 141.4, 118.0, 110.4, 109.7, 84.1, 79.3, 79.3, 72.6, 68.6, 68.3, 63.4, 55.9, 39.6, 37.2, 32.8, 30.7, 29.8, 25.8, 25.7, 25.6, 18.0, 17.6, 17.5, 14.2, 13.3, 13.2, 13.2, 13.1, 11.9, 8.8, −1.6, −3.4, −5.1; MS (ESI) calculated for $C_{53}H_{101}NO_{10}NaSi_4$ $[M + Na]^+$: 1046.6395, found 1046.6373.

2-(Trimethylsilyl)ethyl ((*S*)-((2*S*,4*R*,6*R*)-6-((2*S*,3*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-((*R*)-5-methyl-1-oxo-6,8-bis-((triisopropylsilyl)oxy)isochroman-3-yl)butyl)-5,5-dimethyl-4-((triethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl) (methoxy)-methyl)((2*S*,3*S*)-3-methoxy-5-methyl-2-((2-(trimethylsilyl)-ethoxy)methoxy)hex-5-enoyl)carbamate (+)-51. To a solution of hemiaminal (+)-**49** (33.6 mg, 0.0328 mmol) in CH_2Cl_2 (0.8 mL) was added 2,6-lutidine (0.019 mL, 0.163 mmol), followed by TESOTf (0.019 mL, 0.082 mmol), at 0 °C. After stirring for 2 h, the reaction was quenched with sat. $NaHCO_3$ (1 mL). The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/40−1/20) gave give TES-ether **50** with unknown byproducts, which was taken on to the next step without further purification.

To a solution of a TES-ether **50** in THF (0.7 mL) was added activated 4 Å molecular sieves (80 mg). The mixture was cooled to −78 °C, and LHMDS (1.0 M solution in THF, 0.13 mL, 0.131 mmol) was added. After stirring for 20 min, the solution of the mixed anhydride **37** was added. After stirring for 30 min, the reaction was allowed to warm to −60 °C and stirred for 1.5 h. Sat. NH_4Cl (2 mL) was added, and the reaction was allowed to warm to rt. The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/40−1/20) gave amide (+)-**51** (21.8 mg, 0.0153 mmol, 47%, 91% BRSM) as a white foam.

(+)-**51**: $[\alpha]_D^{26}$ +81.2 (c 0.65, $CHCl_3$); IR (neat): 2951, 2868, 1727, 1590, 1568, 1471, 1411, 1351, 1248, 1172, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.34 (s, 1H), 5.68 (d, J = 4.4 Hz, 1H), 5.19 (d, J = 4.4 Hz, 1H), 4.81 (d, J = 8.0 Hz, 1H), 4.70 (d, J = 6.4 Hz, 1H), 4.65 (d, J = 6.4 Hz, 1H), 4.36−4.32 (m, 3H), 4.19−4.15 (m, 2H), 3.69−3.67 (m, 1H), 3.65−3.60 (m, 3H), 3.38 (s, 3H), 3.31 (s, 3H), 3.20 (d, J = 9.6 Hz, 1H), 3.11 (dd, J = 17.2 Hz, 1H), 2.90 (dd, J = 17.2, 12.8 Hz, 1H), 2.34−2.26 (m, 2H), 2.22 (s, 3H), 2.08−1.98 (m, 3H), 1.81−1.73 (m, 7H), 1.33 (sept, J = 7.6 Hz, 6H), 1.17−0.96 (m, 45H), 0.90 (s, 3H), 0.88 (s, 3H), 0.83 (s, 9H), 0.64 (q, J = 8.0 Hz, 6H), 0.12−0.03 (m, 30H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.5, 158.5, 157.3, 154.3, 142.7, 141.9, 118.3, 112.6, 110.5, 109.6, 95.0, 81.0, 79.6, 76.7, 75.5, 72.7, 69.0, 66.0, 65.9, 58.1, 56.5, 40.3, 39.0, 38.7, 25.8, 24.0, 22.8, 18.0, 18.0, 17.6, 13.3, 13.1, 12.0, 8.7, 6.9, 5.1, −1.5, −1.6, − 3.3,−4.9 ; MS (ESI) calculated for $C_{73}H_{141}NO_{14}Si_6Na$ $[M + Na]^+$: 1446.8860, found 1446.8835.

(+)-15-*tert*-Butyldimethylsilyl-21,23-bistriisopropylsilyl-7-*N*-(2-(trimethylsilyl)ethoxycarbonyl)-5-(trimethylsilyl)ethoxy-methylirciniastatin B (+)-52. To a solution of amide (+)-**51** (9.5 mg, 6.67 μmol) in THF (0.3 mL) was added 1 M HCl (0.020 mL, 0.020 mmol) at 0 °C. After stirring for 3 h at rt, the reaction was quenched with sat. $NaHCO_3$ (1 mL). The mixture was extracted with EtOAc, and the combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration afforded a crude alcohol. To a solution of the alcohol in CH_2Cl_2 (0.3 mL) were added $PhI(OAc)_2$ (6.5 mg, 0.020 mmol) and AZADO (0.50 mg, 3.34 μmol). After stirring for 1 h at rt, the reaction was quenched with sat. $Na_2S_2O_3$ (0.5 mL). After stirring for 30 min, the mixture was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (EtOAc/Hexane 1/10−1/8) gave ketone (+)-**52** (8.3 mg, 6.34 μmol, 95% over 2 steps) as a white foam.

(+)-**52**: $[\alpha]_D^{27}$ +58.9 (c 0.32, $CHCl_3$); IR (neat): 2947, 2360, 1725, 1590, 1469, 1353, 1247, 1172, 1083 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 6.33 (s, 1H), 5.65 (d, J = 4.2 Hz, 1H), 5.07 (d, J = 5.4 Hz, 1H), 4.82 (s, 1H), 4.78 (s, 1H), 4.70 (s, 2H), 4.41−4.28 (m, 4H), 4.25−4.20 (m, 1H), 3.83 (dd, J = 9.6, 2.4 Hz, 1H), 3.67−3.58 (m, 3H), 3.41 (s, 3H), 3.31 (s, 3H), 3.09 (d, J = 16.2 Hz, 1H), 2.88 (dd, J = 15.0, 6.6 Hz, 1H), 2.79 (dd, J = 12.6, 4.2 Hz, 1H), 2.63 (dd, J = 15.0, 6.0 Hz, 1H), 2.30 (d, J = 6.0 Hz, 2H), 2.19 (s, 3H), 2.05−2.00 (m, 1H), 1.77 (s, 3H), 1.73−1.71 (m, 2H), 1.56 (s, 3H), 1.32 (sept, J = 7.6 Hz, 6H), 1.16−1.12 (m, 39H), 1.05 (s, 3H), 0.90−0.82 (m, 13H), 0.10−0.04 (m, 24H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 211.8, 174.4, 163.4, 158.7, 153.9, 142.6, 141.6, 112.9, 110.4, 109.8, 94.7, 90.1, 81.1, 78.8, 68.8, 66.6, 65.9, 58.1, 57.4, 49.1, 40.8, 39.0, 38.9, 38.3, 34.1, 30.2, 29.8, 25.8, 23.1, 22.3, 19.2, 18.1, 18.1, 18.0, 17.6, 13.3, 13.2, 12.1, 9.2, −1.6, −3.3, −4.7 ; MS (ESI) calculated for $C_{67}H_{126}NO_{14}Si_5$ $[M + H]^+$: 1308.8019, found 1308. 7990.

(−)-Irciniastatin B [(−)-2]. To a solution of ketone (+)-**52** (7.0 mg, 5.35 μmol) in DMF (0.3 mL) was added TASF (73.6 mg, 0.267 mmol) in DMF (0.1 mL), and the reaction was heated to 50 °C. After stirring for 10 h, the reaction was quenched with sat. NH_4Cl (1 mL) and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography ($CHCl_3$/MeOH 1%−2%) gave (−)-irciniastatin B [(−)-**2**] (1.78 mg, 2.93 μmol, 55%) as a white foam.

(−)-**2**: $[\alpha]_D^{27}$ −26.9 (c 0.089, MeOH) {$[\alpha]_D^{20}$ −28.7 (c 0.2, MeOH)[9]}; IR (neat): 3357, 2927, 1714, 1656, 1618, 1508, 1380, 1251, 1089 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 11.13 (s, 1H), 7.30 (d, J = 10.2 Hz, 1H), 6.27 (s, 1H), 5.17 (dd, J = 9.6, 6.0 Hz, 1H), 4.79

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J. Org. Chem. 2015, 80, 12333−12350

(s, 1H), 4.76 (s, 1H), 4.54 (dd, J = 8.4, 4.8 Hz, 1H), 4.41 (s, 1H), 4.18 (q, J = 6.0 Hz, 1H), 4.06 (d, J = 10.2 Hz, 1H), 3.98 (dd, J = 11.4, 1.2 Hz, 1H), 3.75−3.72 (m, 1H), 3.70 (brs, 1H), 3.60 (brs, 1H), 3.36 (s, 3H), 3.35(s, 3H), 2.95−2.88 (m, 2H), 2.64 (d, J = 7.2 Hz, 1H), 2.34 (dd, J = 15.0, 8.4 Hz, 1H), 2.12−2.10 (m, 1H), 2.07 (s, 3H), 1.89 (m, 1H), 1.83−1.80 (m, 1H), 1.73 (s, 3H), 1.63−1.60 (m, 1H), 1.14 (s, 3H), 1.10 (d, J = 7.8 Hz, 3H), 1.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 176.4, 173.6, 170.5, 161.1, 142.0, 139.7, 113.2, 113.0, 101.6, 101.3, 81.9, 80.6, 79.6, 78.3, 73.9, 73.1, 73.1, 71.4, 57.9, 56.3, 42.7, 38.8, 37.6, 32.2, 29.7, 28.5, 23.1, 22.7, 13.6, 10.5, 9.2 ; MS (ESI) calculated for $C_{31}H_{46}NO_{11}$ $[M + H]^+$: 608.3065, found 608.3057.

Toxicity. Cell survival was determined by a WST-8 assay kit. HeLa, 3Y1, MCAS, and SKOV3 cells (3×10^3 cells/well) were seeded onto 96-well plates and incubated overnight. Then, cells were treated with various concentrations of irciniastatins A and B. After 48 h incubation, 10 μL of WST-8 reagent was added to the culture. After 2 h incubation, the absorbance at 450 nm was measured with an iMark microplate reader (BioRad Laboratories, Inc.). The number of living cells (% control) was calculated with the following formula: (each absorbance − absorbance of blank well)/(absorbance of 0 μM well − absorbance of blank well) × 100.

Protein Synthesis Assay. HeLa and 3Y1 cells (1.25×10^4 cells/well) were seeded onto a 24-well plate in Dulbecco's modified MEM (DMEM) supplemented with 10% FCS and incubated overnight. Then, cells were treated with various concentrations of irciniastatins A and B for 2 h, followed by [methyl-^{3}H] methionine (finally 3.7 kBq/mL) addition. After 2 h incubation, the cells were washed with PBS once, and ice-cold 5% TCA was added. Acid-insoluble fractions were solubilized by 0.25 M NaOH, and the radioactivity was determined using an LS 6500 liquid scintillation counter (Beckman Coulter Inc., Brea, CA).

Chemical Footprinting Assay.[30] 80S ribosomes were purified from yeast strain BY4741 by two cycled ultracentrifugation through sucrose cushions. 60 pmol of ribosomes, with a total volume of 80 μL, was treated with each compound for 5 min at 25 °C. After drug treatment, 20 μL of DMS was added to final 20 mM or 90 mM, and reacted for 5 min at 37 °C. The reaction was quenched, and rRNA was extracted by Phe/Chl extraction. 2.0 μg of rRNA treated with each drug was mixed with ^{32}P labeled primer (TGTCGCTAT-GAACGCTTGACTG, annealing at 2853−2832 base of yeast 25S rRNA), and annealed by heating to 60 °C for 20 min and cooling on ice for 5 min. Then, primer extension was performed using AMV reverse transcriptase for 45 min at 43 °C. The reaction was stopped by adding 2 × loading buffer (98% formamide, 10 mM EDTA, 0.1% xylene cyanol, 0.1% bromophenol blue) and heating to 90 °C for 10 min. These samples were loaded onto 8% polyacrylamide sequencing gel, and separated by 1600 V electrophoresis for 2 h. The gel was dried, and ^{32}P radioactivity was measured by Typhoon 8600.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02256.

^{1}H and ^{13}C spectral data of compounds and HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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