Published in final edited form as:

Tetrahedron. 2008 May 19; 64(21): 4674–4699. doi:10.1016/j.tet.2008.02.001.

Enantioselective total synthesis of callipeltoside A: two approaches to the macrolactone fragment

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Abstract

The enantioselective total synthesis of callipeltoside A is described. Two syntheses of the macrolactone subunit are included: the first relies upon an Ireland–Claisen rearrangement to generate the trisubstituted olefin geometry and the second utilizes an enantioselective vinylogous aldol reaction for this purpose. Enantioselective syntheses of the sugar and chlorocyclopropane side chain fragments are also disclosed. The relative and absolute stereochemistry of this natural product was determined by fragment coupling with the two enantiomers of the side chain fragment.

1. Introduction

1.1. Background

In 1996, Minale and co-workers isolated minute quantities of callipeltoside A (**1**, Figure 1) from the lithistid sponge *Callipelta* sp.^{1a} This macrolide was the first reported member of a new class of marine natural products, characterized by several unique structural features. Appended to the fourteen-membered macrolactone, which contains a six-membered hemiketal, are a highly functionalized deoxyamino sugar (callipeltose) and a dienyne-trans-chlorocyclopropane side chain. Additional analyses of the sponge extracts revealed the presence of two further members of this family: callipeltosides B and C (Figure 1).^{1b} All three macrolides possess the macrolactone and side chain portions, but differ in their sugar subunits and glycoside linkages. Extensive NMR experiments were used to assign the relative stereochemical relationships in the macrolactone and sugar regions, however the relative stereochemistry of the side chain remained unresolved; moreover the absolute stereochemistry was not assigned. These stereochemical ambiguities, coupled with promising biological activity and lack of natural material (*vide infra*) make this molecule an attractive candidate for total synthesis. To date, four total syntheses and numerous approaches to the synthesis of various subunits have been reported.²

1.2. Biological investigations

Preliminary biological assays indicated that callipeltoside A exhibits moderate cytotoxicity against human bronchopulmonary non-small-cell lung carcinoma NSCLC-N6 and P388 cell lines (IC₅₀ values of 11.26 μg/mL and 15.26 μg/mL, respectively).^{1a} Flow cytometry assays

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of NSCLC-N6 cell line treated with callipeltoside A revealed *in vitro* inhibition of cell proliferation of the G1 phase. This cell cycle dependent effect may be induced by enzyme inhibition or terminal cell differentiation. No further biological investigations have been disclosed, perhaps due to the lack of an abundant source of the natural product.

1.3. Absolute stereochemistry: Celmer's rule

In 1986 Celmer compared published structures of macrolactone antibiotics and found that a majority of macrolides share two common characteristics: (1) they possess a D-configuration at the lactone-containing alkoxy stereocenter, and (2) the C₇ carbon is either unsubstituted ("classical macrolides") or has an L-OH substitution ("unusual macrolides"),³ although exceptions do exist. Since the proposed relative stereochemistry of callipeltoside did not follow both trends, we decided to pursue the stereoisomer that possesses the C₇ L-OH configuration, a more conserved trait amongst the "unusual macrolides". Based on the original NOESY data,^{1a} selection of this enantiomer of the macrolide dictates the stereochemistry of the sugar to be as illustrated in Figure 1. Synthesis of the two possible diastereomers **1a** and **1b**, that differ only in the configuration of the cyclopropyl group, would allow the absolute and relative stereochemistry of callipeltoside A to be unequivocally determined.

1.4. General synthesis plan

Our strategy involved disconnecting callipeltoside into three principal fragments: macrolactone **A**, callipeltose derivative **B**, and chlorocyclopropane side chain **C** (Scheme 1). A late-stage glycosylation would allow some flexibility should the stereochemical assignment of the sugar moiety prove to be invalid. The final fragment coupling was planned to be a Horner–Wadsworth–Emmons olefination of each enantiomer of phosphonate **C** to an appropriate aldehyde, a strategy that would allow a late-stage divergence of the synthesis to the two possible diastereomers.

2. Results and discussion

2.1. Synthesis of the macrolactone fragment: 1st generation

Our initial strategy for the synthesis of macrolactone fragment **A** focused on the construction of the trisubstituted olefin by an Ireland–Claisen rearrangement of an oxygenated enolate (Scheme 2). Rearrangement precursor **2** would be prepared from aldehyde **3**, which is available from β -ketoester **4**. The stereochemical array of substrate **4** can be derived from the stereochemistry of β -ketoimide **5** through a series of diastereoselective aldol reactions.

The synthesis began with the *anti*-selective aldol addition of the (*E*) boron enolate of β -ketoimide **5** to cinnamaldehyde (Scheme 3). This reaction, developed in these laboratories in 1992,⁴ led to the formation of aldol adduct **6** in excellent diastereoselectivity. Anti-selective reduction with tetramethylammonium triacetoxyborohydride⁵ formed diol **7**, which was converted to aldehyde **8** in three steps. Addition of Chan's diene **9**⁶ mediated by BF₃•OEt₂ gave the desired Felkin aldol adduct **10** as a single diastereomer. This high diastereoselectivity was expected due to the reinforcing stereochemical relationship in aldehyde **8**, which leads to a combination of Felkin and β -alkoxy control.⁷

β -Ketoester **10** was elaborated to aldehyde **11** by silylation, ketal hydrolysis, methylation and ozonolysis (Scheme 4). Isopropenylmagnesium bromide was then added under chelation control to form allylic alcohol **12** as a single diastereomer. Protecting group interconversion and acylation produced allylic ester **13**, the precursor to the key Ireland–Claisen rearrangement.⁸ Treatment of ester **13** with LiHMDS in the presence of TMSCl and triethylamine effected the Ireland–Claisen rearrangement to yield the desired acid **14** as a

single olefin isomer with the desired configuration at C₁₃.⁹ This compound was elaborated to seco-acid **15**, the precursor to the macrolactone fragment, in three steps. After considerable experimentation, it was found that the use of Murai's modified Yamaguchi macrolactonization conditions¹⁰ formed the desired macrolactone **16** in acceptable yield, thus completing the first generation synthesis of this fragment.

2.2. Synthesis of the macrolactone fragment: 2nd generation

While our initial strategy did lead to a successful synthesis of macrolactone **16**, late-stage protecting group issues coupled with the overall linearity of the route inspired us to explore the possibility of a more convergent synthesis of this fragment. Although two diastereoselective aldol reactions would still be used to prepare the C₅-C₉ stereopentad of seco-acid **17**, the aldol reaction with β -ketoimide **5** would occur at a later stage. This strategy suggested aldehyde **18** as a key fragment (Scheme 5). We hoped to develop a catalytic enantioselective synthesis of this aldehyde, wherein the trisubstituted olefin geometry and the configuration at C₁₃ would be defined in a single operation.

The key step envisioned for the enantioselective synthesis of aldehyde **18** was a vinylogous aldol reaction between silyl dienolate **19** and aldehyde **20**, catalyzed by a chiral Lewis acid. Previous studies from these laboratories have shown that bis(oxazolinyl)pyridine copper(II) complexes are effective catalysts for the vinylogous aldol reaction of (benzyloxy)acetaldehyde.¹¹ While these results provided a valuable precedent for development of the current reaction, the crucial issue of the product olefin geometry remained unaddressed in these cases.¹² Initially, addition of a solution of aldehyde **20** to a solution of silyl dienolate **19** in the presence of catalyst **21** as the bench stable dihydrate led to the formation of α,β -unsaturated ester **22** in low yield and enantioselectivity (Table 1, entry 1). Analysis of the unpurified reaction mixture indicated the presence of several products, many of which resulted from the addition of multiple equivalents of dienolate **19**. Oligomeric products have been observed previously in aldol reactions catalyzed by complex **21**, but in these cases multiple equivalents of aldehyde were incorporated.¹³ We hypothesized that these oligomers were the result of slow silyl transfer to the intermediate copper alkoxide, although slow addition of the aldehyde to the reaction mixture did not lead to an improvement in the current case (entry 2). Gratifyingly, simultaneous slow addition of separate solutions of substrates **19** and **20** to the catalyst solution allowed the isolation of desired ester **22** in excellent yield and enantioselectivity (entries 3 and 4).¹⁴ Ester **22** was readily converted to aldehyde **24** in three straightforward transformations in good yield (Scheme 6).

β -Ketoimide **5** had been shown to control the stereochemical course of the diastereoselective aldol reaction to form the C₈-C₉ bond in the first-generation synthesis (*vide supra*). Addition of aldehyde **24** to the boron enolate of β -ketoimide **5**, however, led to the formation of desired aldol adduct **25a** with a disappointing 1.2:1 diastereomeric ratio (Scheme 7, eq 1).¹⁵ Remarkably, reaction with enantiomeric aldehyde *ent*-**24** yielded adduct **25b** with excellent diastereoselectivity for the desired *anti-anti* diastereomer (eq 2). Taken together, these reactions document an unanticipated aldehyde facial bias resulting from the remote secondary silyloxy stereocenter at C₁₃.¹⁶ This result is surprising, since this stereocenter is five carbon atoms removed from the reaction site, and is further removed spatially due to the (*E*) configuration of the trisubstituted olefin. To probe the generality of this process, the (*E*) boron enolate of methyl isobutyl ketone was added to a series of aldehydes similar to **24** (Table 2).¹⁷ The results indicate that an *O*-silyl group is necessary at C₁₃, but the protecting group on the C₁₄-oxygen is not as important to selectivity.

Although aldol adduct **25b** possessed the undesired stereochemistry at C₁₃, we hoped to utilize this unexpected result by modifying our overall synthetic strategy. In the original plan, the C₁₃ hydroxyl group was to participate in a macrolactonization with retention of configuration; if, however, this center were to be inverted (e.g. under Mitsunobu conditions¹⁸) in concert with macrocyclization, the overall efficiency of the strategy would be maintained. Elaboration of aldol adduct **25b** to the requisite seco acid generally followed the precedent set by the first generation synthesis (Schemes 2 and 3), with a few notable differences. Aldol adduct **25b** was not stable to column chromatography, and was therefore subjected directly to the *anti*-selective reduction conditions utilized previously (Scheme 8).⁵ Unfortunately, the initial product of this reaction, cyclohexylboronic ester **26**, proved generally resistant to hydrolysis. Treatment of the unpurified boronic ester with diethanolamine, however, led to cleavage of the boronic ester with concomitant lactonization to form **27**.¹⁹ This lactone was readily converted to the Weinreb amide; diol protection and reduction with lithium aluminum hydride then provided aldehyde **28**.

Addition of Chan's diene to aldehyde **28** formed β -ketoester **29** as a single diastereomer (Scheme 9). Silylation with TBSOTf and 2,6-lutidine led to the formation of a mixture of acetonide **30** and lactol **31**, the latter formed via acetonide hydrolysis under the Lewis acidic reaction conditions.²⁰ Both compounds can be converted to the mixed methyl ketal **32** by stirring in methanol in the presence of a mild Brønsted acid such as pyridinium *para*-toluenesulfonate (PPTS), followed by methylation of the free hydroxyl with methyl triflate and 2,6-di-*tert*-butylpyridine (DTBP). The small quantity (<20%) of dihydropyran formed under these conditions can be converted to ketal **32** by resubjection to the solvolysis conditions. Selective deprotection of **32** was possible using tetrabutylammonium fluoride (TBAF).²¹ To allow for flexibility in the macrocyclization, two possible precursors were prepared: hydrolysis of the ester with lithium hydroxide yielded seco-acid **33**; alternatively, mesylation followed by hydrolysis provided mesylate **34**.

Attempts to cyclize seco-acid **33** directly using Mitsunobu conditions led either to the recovery of starting material, or elimination of the C₁₃-hydroxyl to form a conjugated diene. Cyclization of mesylate **34**, however, proved far more promising (Table 3). Initial subjection of mesylate **34** to cesium carbonate and DMAP at 70 °C led to the formation of the desired macrolactone, albeit in low yield (entry 1). Although variation of solvent and temperature did not lead to an improvement in yield (entries 2 and 3), replacement of DMAP with a crown ether (18-crown-6) allowed the isolation of macrocycle **35** in acceptable yield (entry 5). Overall, the second-generation synthesis of the macrocycle was accomplished in 16 steps and 8% overall yield, a significant improvement from the first generation synthesis (20 steps and 2% overall yield).

2.3. Synthesis of Callipeltose^{2p}

Our strategy for the synthesis of the sugar fragment **B** involved a convergent approach in which the key C_{2'}-C_{3'} bond is formed via diastereoselective addition of an oxygenated enolate to a methyl ketone (Scheme 10). According to the Zimmerman–Traxler transition state model,²² Felkin-selective addition of an (*E*) enolate should lead to the formation of the desired configuration of C_{2'} and C_{3'}.

Ketone **36** was prepared in 5 steps from D-threonine as shown in Scheme 11. Acid, amine and alcohol protection yielded ester **37**, which was converted to methyl ketone **36** via the intermediate Weinreb amide. While the addition of the lithium enolate of ethyl methoxyacetate to ketone **36** led exclusively to the formation of the desired Felkin configuration at C_{3'}, selectivity at C_{2'} was only 2:1, favoring the undesired syn configuration (Scheme 12).²³ While this result was likely due to formation of significant

quantities of the undesired (*E*) enolate, the diastereoselectivity could not be improved by the use of other amide bases (i.e. LiHMDS, LiTMP) or additives (i.e. HMPA).

Based on these results, the ester reaction partner was changed to the cyclic ester **39**, which can only form the desired (*Z*) enolate (Scheme 13). When the lithium enolate of this ester was added to ketone **36**, the desired aldol adduct **40** was formed in good yield and excellent stereoselectivity,²⁴ presumably via the indicated transition state (**ts1**).

Treatment of aldol adduct **40** with aqueous acetic acid effected removal of the acetone and cyclohexylidene ketals with concomitant lactonization, providing lactone **41** in good yield (Scheme 14). After considerable experimentation it was found that the C₂'-hydroxyl could be selectively methylated using Meerwein's salt and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP).²⁵ The resultant lactone was reduced and acetylated using Rychnovsky's one-pot procedure²⁶ to yield the six-membered acetate **42** as a 9:1 mixture of anomers. To allow for glycosidation flexibility, the anomeric acetate **42** was converted into both the trichloroacetimidate **43** and the thioglycosides **44** and **45**.

2.4. Synthesis of the Phosphonate Side Chain^{2s}

Due to the stereochemical ambiguity of the cyclopropane appendage (*vide infra*), it was crucial that a synthesis of the phosphonate fragment be amenable to either enantiomer. Our synthesis strategy (Scheme 15) involved installation of the phosphonate moiety by a Michaelis–Arbusov rearrangement.²⁷ Dibromoolefin **47** should serve as a suitable precursor to **46** using a transition metal coupling reaction with an appropriate vinyl metal species, followed by elimination. Dibromoolefin **46** is available from a Corey–Fuchs homologation²⁸ of aldehyde **48**. While it was known that the Charette cyclopropanation was possible with vinyl halides,²⁹ we hoped to develop a new method for the stereoselective construction of halocyclopropanes. To this end we envisioned the construction of aldehyde **48** via a directed cyclopropanation of a vinyl chloride.^{30,31}

The (*S*) enantiomer was initially selected for synthesis because it is derived from inexpensive D-mannitol. Cleavage of 1,2,5,6-di-*O*-cyclohexylidene-D-mannitol (**49**) using conditions developed by Schmid³² cleanly provided protected glyceraldehyde **50** (Scheme 16). Unfortunately, Takai olefination resulted in the formation of vinyl chloride **52** with moderate diastereoselection (87:13 (*E*):(*Z*)) and low yield (<40% from **49**). Furthermore, the two isomers were not readily separated by flash column chromatography. These results, coupled with the fact that the Takai olefination³³ requires the use of a large quantity of expensive, highly toxic chromium(II) chloride, led us to explore alternative approaches to vinyl chloride **52**. Masuda has reported the stereospecific electrophilic chlorination of vinylboranes formed *in situ* from alkynes, leading to the formation of (*E*) vinyl chlorides in good to excellent yields.³⁴ To test the viability of this reaction for the formation of **52**, aldehyde **50** was first homologated to alkyne **51** using Ohira's reagent (**53**).³⁵ Subjection of this alkyne to Masuda's conditions resulted in the formation of vinyl chloride **52** in good yield as a single olefin isomer.

Cyclopropanation of vinyl chloride **52** proved more difficult than was originally expected. This olefin, presumably due to its low nucleophilicity, proved resistant to Simmons–Smith cyclopropanation under various standard conditions. For example, less than 10% conversion was observed using either the Furukawa (Et₂Zn, CH₂I₂)³⁶ or Denmark (Et₂Zn, CH₂I₂, ZnI₂)³⁷ carbenoid variants. In our search for a more reactive carbenoid, we were attracted to a recent report by Shi wherein he found that the reactivity of zinc carbenoids could be markedly increased by the addition of one equivalent of a Brønsted acid.³⁸ In particular, the authors found that the addition of one equivalent of trifluoroacetic acid to diethylzinc prior

to the addition of diiodomethane led to the formation of a highly reactive carbenoid. This study did not, however, address the ability of this reactive carbenoid to participate in a diastereoselective cyclopropanation. Gratifyingly, subjection of vinyl chloride **52** to Shi's conditions resulted in the formation of cyclopropane **54** as a single diastereomer in good yield (eq 3).³⁹

(3)

Elaboration of cyclopropane **54** to dibromide **47** was accomplished as shown in Scheme 18. Removal of the cyclohexylidene ketal initially proved difficult due to reketalization during *in vacuo* concentration. When the methanolic reaction solution was washed with hexanes prior to concentration, however, the cyclohexanone dimethyl ketal was removed and diol **55** was isolated in good yield. Diol cleavage with potassium carbonate-buffered lead tetraacetate afforded the volatile aldehyde **48**, which was immediately treated with excess Corey–Fuchs reagent to cleanly afford dibromoolefin **47**.

Shen has reported a method for the direct formation of enynes from dibromides and vinylstannanes, catalyzed by Pd_2dba_2 in the presence of electron-rich triaryl phosphines and Hünig's base.⁴⁰ While this system did effect the coupling of dibromide **47** with stannanes **56**, enyne **46** was isolated in low yields (<50%), and separation of tin byproducts proved problematic (Scheme 18). Thus the possibility of separating the coupling and elimination steps were investigated. Roush has reported the stereoselective coupling of vinylboronic acids and dibromoolefins.⁴¹ Under thallium ethoxide-mediated coupling conditions, substitution occurs at the position of the sterically less encumbered (*E*) bromide. In this manner, treatment of a mixture of dibromide **47** and boronic acid **57**⁴² with a catalytic quantity of $\text{Pd}(\text{PPh}_3)_4$ in the presence of thallium ethoxide led to the clean formation of diene **58** in excellent yield. Conversion to the enyne was possible using a DBU-induced elimination of HBr .⁴³ Allylic alcohol **46** was then converted to the desired phosphonate by bromination followed by an Arbusov rearrangement.

Access to *ent*-**59** was possible from commercially available L-gulonic γ -lactone (Scheme 19). Periodate cleavage of the mono(cyclohexylidene ketal) **60** according to Schmid's conditions³² followed by homologation with Ohira's reagent (**53**) led to the formation of alkyne *ent*-**51**. This alkyne was then elaborated to phosphonate *ent*-**59** in an identical manner to that described previously (*vide supra*).

2.5. Fragment Assembly and Stereochemical Analysis

With efficient syntheses of all three fragments of callipeltoside A in hand, we were prepared to investigate fragment assembly. Contrary to the approach of others,^{2a,c} we envisioned glycosylation with an appropriate callipeltose derivative prior to coupling with the chlorocyclopropane side chain. The key advantage of this approach is that the two enantiomers of the side chain can be appended to a common intermediate in the penultimate step. Following TBAF deprotection of the C₅ silyl ether, macrolactone **61** was prepared for glycosylation (eq 4).

(4)

While trichloroacetimidate **43** was not an effective glycosyl donor for this system, thioglycoside **45** was found to be an excellent alternative (Table 4). It has been reported that thioglycosides serve as excellent glycosyl donors in the presence of N-iodosuccinimide (NIS) and triflic acid.⁴⁴ With the present system, however, these conditions led to a complex reaction mixture. Gratifyingly, when this system was buffered with 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) the formation of the desired glycoside bond was achieved in excellent yield when N-silyl donor **45** was used. It is worth noting that either anomer of **45** can be used, leading to the formation of a single product. The stereochemistry of product **62** was determined by NOESY analysis and by analysis of the coupling constants of the sugar protons. This result is consistent with nucleophilic attack on the *exo* face of the derived oxocarbenium ion as shown.

In preparation for the final fragment coupling, a Horner–Wadsworth–Emmons olefination, the glycosylated macrolactone was deprotected and the resulting primary alcohol oxidized to aldehyde **64** (Scheme 20). Although standard PMB deprotection conditions (DDQ, H₂O) led to mixtures of lactol and methyl ketal, performing the oxidative deprotection in a mixture of methanol and water led to the exclusive formation of lactol **63**. It was thus envisioned that by the use of excess phosphonate anion during the olefination reaction, an unprotected lactol could be used in the coupling process. To test this hypothesis, oxidation to aldehyde **64** was accomplished under Parikh–Doering conditions.⁴⁵ Gratifyingly, addition of excess lithium anion of phosphonate **59**, generated *in situ* with LiHMDS, to aldehyde **64** resulted in the formation of the desired dienyne **65** in moderate selectivity (3:1) for the desired (*E,E*) configuration (Scheme 21).⁴⁶ Although no conditions were found to directly improve this selectivity, exposure of the mixture to a catalytic quantity of iodine under ambient light led to a marked increase in the olefin ratio (*E,E*:*E,Z* 11:1).^{46b,f} Desilylation of **65** with buffered TBAF completed the synthesis of **1a** in 56% yield from alcohol **63**. This process was repeated using *ent*-**59**, yielding diastereomer **1b** in similar yield over the four-step sequence.

Diastereomers **1a** and **1b** were shown to exhibit essentially identical NMR spectral data, indicating the cyclopropane moiety is too remote to affect the overall conformation of these molecules. In addition, both spectra were in good agreement with the data reported for natural callipeltoside.⁴⁷ Fortuitously, the optical rotations of the two diastereomers were drastically different in both sign and magnitude. Diastereomer **1a** exhibited a rotation of -17 (c 0.19, MeOH), whereas diastereomer **1b** registered a value of $+140$ (c 0.05, MeOH). Natural callipeltoside A has a reported rotation of -17.6 (c 0.04, MeOH), thus we assigned the relative and absolute stereochemistry of callipeltoside A to be identical to that of diastereomer **1a**, in full agreement with the conclusions drawn by Trost and coworkers.^{2a,c}

3. Conclusions

The enantioselective total synthesis of callipeltoside A has been accomplished in 25 steps (longest linear sequence) and 4% overall yield. A series of key methodologies were developed during the course of this synthesis: (1) a diastereoselective addition of an

oxygenated enolate to a methyl ketone to prepare the densely functionalized callipeltose in a rapid and convergent manner; (2) a diastereoselective cyclopropanation of an electron-poor vinyl chloride using Shi's modified Simmons–Smith conditions; (3) a catalytic, enantioselective vinylogous aldol reaction to provide the trisubstituted olefin geometry and the C₁₃ configuration in a single operation; (4) a cesium carbonate-mediated cyclization with concomitant hydroxyl inversion to form the macrolactone; and (5) a buffered *N*-iodosuccinimide-mediated glycosylation to prepare the glycosyl bond of a system susceptible to Lewis acidic conditions. Moreover, an unusual remote 1,5-induction effect was observed in the addition of a (*E*) boron enolate to an α,β -unsaturated aldehyde. Based on spectral data and optical rotation, the synthesis confirmed the relative and absolute configuration of this marine macrolide.

4. Experimental section

4.1. General information

All non-aqueous reactions and distillations were carried out under an atmosphere of dry nitrogen in glassware that had been flame-dried under a stream of nitrogen. THF, CH₂Cl₂, toluene and Et₂O were purified by passage through a bed of activated alumina. All other reaction solvents were distilled from calcium hydride. Solvents used for extraction and chromatography were HPLC grade. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and ceric ammonium molybdate, anisaldehyde or potassium permanganate stain followed by heating. Chromatography on silica gel was performed using a forced flow of the indicated solvent system of EM Reagents silica gel (230–400 mesh). Unless otherwise stated, all isolated compounds were >95% as judged by ¹H NMR analysis. Infrared (IR) spectra were recorded as thin films on KBr plates on a Perkin Elmer 1600 series FT-IR spectrophotometer. ¹H NMR spectra were recorded at 20 °C on Varian Inova 500 spectrometer or Mercury 400 spectrometers. Data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz; integration). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. Ambiguous assignments were resolved on the basis of 2D-COSY experiments, and are listed according to the callipeltoside numbering system, except those of the side chain precursors. ¹³C NMR spectra were recorded at 20 °C on a Mercury 400 (100 MHz) spectrometer with proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. Mass spectra were obtained on JEOL AX-505 and SX-102 high resolution magnetic sector mass spectrometers by the Harvard University Mass Spectrometry Laboratory. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a sodium lamp, and are reported as follows: [α] _{λ} ^{t(°C)} (c (g/100 mL), solvent).

4.2. Synthetic procedures

4.2.1. (6*E*)-1-[(4*S*)-2-Oxo-4-benzyl(1,3-oxazolidin-3-yl)](2*S*,4*R*,5*R*)-5-hydroxy-2,4-dimethyl-7-phenylhept-6-ene-1,3-dione (6)—To a cooled (0 °C) solution of 3.0 g (10.4 mmol) β -ketoimide **5**⁴ in 120 mL of Et₂O was added 2.73 mL (12.5 mmol) of Cy₂BCl then 1.35 mL (12.5 mmol) of Et₃N. The resulting yellow suspension was stirred for 1 h at 0 °C, then cooled to –78 °C prior to the dropwise addition of 1.90 mL (15.0 mmol) of cinnamaldehyde. The reaction was stirred at –78 °C for 3 h, then allowed to warm to –20 °C over 1 h before addition of 100 mL of 2:1 MeOH:sat. NH₄Cl(aq). The mixture was stirred for an additional 10 min at 0 °C then poured into 300 mL of CH₂Cl₂ and 50 mL of H₂O. The aqueous layer was separated and extracted with an additional 200 mL of CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. The unpurified reaction mixture was triturated with 100 mL of Et₂O (overnight

stirring), and the mother liquor was removed by pipette. The resulting crystals were washed with 5 mL of cold Et₂O to provide 2.30 g (5.46 mmol, >20:1 dr) of the title compound. The mother liquor was concentrated and purified by flash column chromatography (20% EtOAc/hexanes) to provide an additional 921 mg (2.19 mmol, 10:1 dr) of the title compound. Combined yield: 74%, 20:1 dr. [α]_D²³ +77.4 (*c* 1.0, CH₂Cl₂); IR (neat) 3027, 2991, 2938, 1778, 1692, 1453, 1359, 1213, 1120, 1073, 1049, 1005, 751, 695 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.19 (m, 10H), 6.61 (d, *J* = 15.8 Hz, 1H), 6.17 (dd, *J* = 15.8, 7.4 Hz, 1H), 4.92 (q, *J* = 7.1 Hz, 1H), 4.80–4.71 (m, 1H), 4.39 (t, *J* = 7.7 Hz, 1H), 4.30–4.18 (m, 2H), 3.30 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.96 (dq, *J* = 8.0, 7.1 Hz, 1H), 2.78 (dd, *J* = 13.3, 9.6 Hz, 1H), 2.56 (br s, 1H), 1.50 (d, *J* = 7.3 Hz, 3H), 1.20 (d, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 211.1, 170.6, 153.5, 136.3, 135.0, 132.3, 129.5, 129.4, 128.9, 128.6, 127.9, 127.4, 126.5, 75.3, 66.4, 55.3, 52.8, 49.8, 37.9; exact mass calc. for C₂₅H₂₇O₅NNa[M+Na]⁺: 444.1787; found: 444.1787.

4.2.2. (6E)-1-[(4S)-2-Oxo-4-benzyl(1,3-oxazolidin-3yl)](2S,3S,4R,5R)-3,5-hydroxy-2,4-dimethyl-7-phenylhept-6-ene-1-one (7)—4.13 g Me₄NBH(OAc)₃ (15.7mmol) was dissolved in 15 mL of glacial acetic acid and 15 mL of CH₃CN and cooled to 0 °C. The aldol product **6** (1.32 g, 3.13mmol) was dissolved in 30 mL of CH₃CN and added to this solution at 0 °C and the reaction was stirred for 3 h. The mixture was then transferred via cannula to 300 mL of a rapidly stirring biphasic mixture of 1:1 CH₂Cl₂ and sat. NaHCO₃(aq). The mixture was stirred for 5 min and then placed in a separatory funnel. The organic phase was separated and the aqueous phase was extracted with 100 mL of CH₂Cl₂. The combined organic phases were washed with 50 mL of brine and the solvent was removed under reduced pressure. The crude product was dissolved three times in 100 mL of MeOH and the solvent was removed under reduced pressure to give 1.32 g (3.12mmol, 98%) of the title compound of sufficient purity to be used directly. [α]_D²³ +60.2 (*c* 1.0, EtOAc); IR (neat) 3027, 2973, 2920, 1779, 1693, 1454, 1389, 1351, 1212, 1113, 1052, 968, 749, 695 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.43–7.11 (m, 10H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.32 (dd, *J* = 6.4, 15.9 Hz, 1H), 4.66–4.74 (m, 1H), 4.42 (d, *J* = 10.4, 1H), 4.32 (t, *J* = 6.4, 1H), 4.02–4.18 (m, 3H), 3.18 (dd, *J* = 3.1, 13.4, 1H), 2.78 (dd, *J* = 9.3, 13.4, 1H), 1.78–1.89 (m, 1H), 1.12 (d, *J* = 6.9, 3H), 1.04 (d, *J* = 7.0, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 176.5, 153.3, 136.5, 135.0, 131.2, 130.7, 129.2, 128.6, 128.3, 128.2, 127.3, 127.0, 126.2, 75.4, 72.5, 66.0, 54.9, 40.7, 39.1, 37.5, 14.0, 9.7; Exact mass calc for C₂₅H₂₉O₅NNa, 446.1943; found, 446.1943.

4.2.3. 3-{2-[6-((1E)-2-Phenylvinyl)(4S,5R,6R)-2,2,5-trimethyl(1,3-dioxan-4-yl)](2S)propanoyl}(4S)-4-benzyl-1,3-oxazolidinone—To a solution of 1.10 g diol **7** (2.60 mmol) in 20 mL of 2,2-dimethoxypropane and 50 mL of acetone at rt was added 70 mg of PPTS (0.279 mmol). The resultant mixture was stirred for 1 h at rt. The reaction mixture was poured to 100 mL of Et₂O and 30 mL of 1 M NaHCO₃(aq) and the organic phase was separated. The organic phase was washed twice with 50 mL of H₂O and dried over MgSO₄. The solvent was removed under reduced pressure to give 1.14 g (2.46 mmol, 95%) of the title compound of sufficient purity to be used directly. [α]_D²³ +49.5 (*c* 2.3, EtOAc); IR (neat) 2984, 2936, 2918, 2352, 1779, 1699, 1454, 1384, 1220, 1112, 746 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.15–7.45 (m, 10H), 6.59 (d, *J* = 15.8 Hz, 1H), 6.26 (dd, *J* = 7.0, 15.8 Hz, 1H), 4.60–4.70 (m, 1H), 4.11–4.23 (m, 3H), 4.03–4.11 (m, 1H), 3.91 (t, *J* = 7.0, 1H), 3.27 (dd, *J* = 3.4, 13.4, 1H), 2.80 (dd, *J* = 9.6, 13.4, 1H), 1.89–2.00 (m, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.16 (d, *J* = 6.6, 3H), 1.01 (d, *J* = 6.8, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 175.2, 153.2, 136.5, 135.3, 131.0, 129.4, 128.8, 128.5, 128.4, 127.6, 127.2, 126.4, 101.0, 76.2, 70.9, 65.9, 55.3, 37.9, 37.8, 37.6, 24.5, 24.1, 13.2, 11.2; Exact mass calc for C₂₈H₃₃O₅NNa: 486.2256; found: 486.2256.

4.2.4. 2-[6-((1*E*)-2-Phenylvinyl)(4*S*,5*R*,6*R*)-2,2,5-trimethyl(1,3-dioxan-4-yl)](2*S*)-1-ethylthioprop-1-one—To a solution of 1.05 mL (14.2 mmol) of ethanethiol in 60 mL of THF (−78 °C) was added dropwise 6.88 mL of *n*-BuLi (1.47 M, 10.1 mmol). The reaction mixture was warmed to 0 °C and kept for 15 min at this temperature. A solution of 2.00 g (4.32 mmol) of the acetonide in 50 mL of THF (10 °C) was then added dropwise. The reaction mixture was stirred for 2 h at −5 °C to 0 °C and then poured to 150 mL of 0.5 M NaOH(aq) and 300 mL EtOAc. The organic phase was washed with 100 mL of brine and the combined organic phases were further extracted with 200 mL of EtOAc. The combined organic phases were dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography to give 1.26 g (3.62 mmol, 84%) of the title compound as a clear colorless oil. $[\alpha]_D^{23}$ −10.3 (*c* 1.6, EtOAc); IR (neat) 2986, 2934, 2878, 1688, 1651, 1495, 1452, 1379, 1222, 1182, 1156, 1050, 1025, 999, 967, 904, 885, 744, 693 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 7.18–8.25 (m, 5H), 6.58 (d, *J* = 15.9 Hz, 1H), 6.24 (dd, *J* = 7.0, 15.9 Hz, 1H), 4.16 (dd, *J* = 4.6, 10.8, 1H), 3.90 (t, *J* = 7.0, 1H), 2.80–2.92 (m, 2H), 2.70–2.80 (m, 1H), 1.83–1.94 (m, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.24 (t, *J* = 7.4, 3H), 1.08 (d, *J* = 6.9, 3H), 0.94 (d, *J* = 6.8, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 136.4, 130.8, 128.3, 128.3, 127.5, 126.0, 101.1, 76.0, 70.3, 49.0, 37.5, 24.3, 24.0, 22.9, 14.7, 13.9, 10.8; Exact mass calc for C₂₀H₂₉O₃S: 349.1831; found: 349.1831.

4.2.5. 2-[6-((1*E*)-2-Phenylvinyl)(4*S*,5*R*,6*R*)-2,2,5-trimethyl(1,3-dioxan-4-yl)](2*S*)-propanal (8)—To a cooled (−78 °C) solution of 1.20 g (3.45 mmol) of the thioester in 75 mL of toluene was added 5.43 mL of DIBAL-H (1 M solution in THF). The solution was stirred for 15 min at −78 °C and then quenched by the addition of 3 mL of EtOAc. Then 50 mL of 0.5 M Rochelle salt were added and the mixture was stirred for 2 h at rt. The organic phase was separated and the aqueous phase was extracted with 300 mL of Et₂O. The combined organic extracts were washed with 25 mL of brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by flash chromatography (12% EtOAc/hexanes) gave 827 mg (2.87 mmol, 83%) of the title compound as a clear, colorless oil. $[\alpha]_D^{23}$ −18.3 (*c* 1.0, EtOAc); IR (neat) 2985, 2936, 1729, 1454, 1380, 1222, 1155, 1030, 967, 886, 747 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) δ 9.70 (d, *J* = 3.1, 1H), 7.20–7.42 (m, 5H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.25 (dd, *J* = 6.9, 15.9 Hz, 1H), 4.11 (dd, *J* = 4.7, 10.8, 1H), 3.95–3.99 (m, 1H), 2.49–2.59 (m, 1H), 1.91–2.01 (m, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 1.00 (d, *J* = 6.7, 3H), 0.99 (d, *J* = 6.6, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 204.1, 131.1, 128.5, 128.2, 127.7, 126.4, 101.2, 76.2, 69.8, 46.0, 37.8, 24.6, 23.9, 11.1, 10.2; Exact mass calc for C₁₈H₂₈O₃N: 306.2069; found: 306.2069.

4.2.6. Methyl 6-[6-((1*E*)-2-phenylvinyl)(4*S*,5*R*,6*R*)-2,2,5-trimethyl(1,3-dioxan-4-yl)](5*S*,6*R*)-5-hydroxy-3-oxoheptanoate (10)—To a cooled (−78 °C) solution of 870 mg of aldehyde **8** (3.02 mmol) in 100 mL of toluene was added 2.20 mL of silyl dienyl ether **9**⁶ and then dropwise 496 mL of BF₃·OEt₂. After 10 min the reaction was quenched by the addition of 100 mL of sat. NaHCO₃(aq). The mixture was diluted with 100 mL of EtOAc and the layers were separated, the aqueous layer was extracted with 100 mL of EtOAc, the combined organic extracts were washed with brine, dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (25% EtOAc/hexanes) gave 1.05 g (2.60 mmol, 86%, dr 95:5) of the title compound as a clear, colorless oil. $[\alpha]_D^{23}$ −45.5 (*c* 1.5, EtOAc); IR (neat) 2985, 2936, 1729, 1454, 1380, 1222, 1155, 1030, 967, 886, 747 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 7.28–7.35 (m, 2H), 7.19–7.27 (m, 2H), 7.12–7.18 (m, 1H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.18 (dd, *J* = 6.9, 15.9 Hz, 1H), 4.29 (m, 1H), 3.82–3.91 (m, 2H), 3.67 (s, 3H), 3.48 (d, *J* = 15.6, 1H), 3.45 (d, *J* = 15.6, 1H), 2.96 (br. s, 1H), 2.74 (dd, *J* = 13.1, 8.4, 1H), 2.52 (dd, *J* = 13.1, 1.8, 1H), 1.78–1.87 (m, 1H), 1.66–1.74 (m, 1H), 1.40 (s, 3H), 1.35 (s, 3H), 0.88 (d, *J* = 6.7, 3H), 0.76 (d, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 136.6, 131.0, 128.7,

128.5, 128.4, 127.7, 126.5, 101.2, 76.5, 70.1, 68.0, 52.4, 49.8, 46.9, 38.1, 37.6, 25.1, 24.3, 11.2, 10.1; Exact mass calc for C₂₃H₃₂O₆Na: 427.2097; found: 427.2097.

4.2.7. Methyl 2-[6-((2*S*,1*R*)-2-hydroxy-1-methyl-3-oxopropyl)-(4*S*,5*S*,2*R*)-2-hydroxy-5-methyl-4-(*tert*-butyldimethylsilyloxy)perhydro-2*H*-pyran-2yl]acetate

—To a cooled solution (−78 °C) of 1050 mg (2.60 mmol) of **10** in 100 mL of CH₂Cl₂ was added dropwise 423 mL (3.60 mmol) of lutidine and 819 mL (3.57 mmol) of TBSOTf. After 20 min the reaction was quenched by addition of 80 mL of sat. NaHCO₃(aq) and the mixture was stirred for 30 min. The organic phase was separated and the aqueous phase was further extracted with 100 mL of EtOAc. The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated in vacuo. The unpurified reaction mixture was dissolved in 150 mL of MeOH and 74 mg of PPTS was added. After 56 h the reaction was quenched by addition of 400 mL of sat. NaHCO₃(aq). The mixture was diluted with 300 mL of Et₂O and the organic phase was separated. The aqueous phase was further extracted twice with 300 mL of Et₂O and the combined organic extracts were washed with brine (100 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (11% EtOAc/hexanes) gave 857 mg (1.74 mmol, 67%) of the title compound as a clear, colorless oil. [α]_D²³ −18.1 (*c* 1.0, EtOAc); IR (neat) 2933, 2856, 1742, 1642, 1546, 1530, 1462, 1381, 1320, 1252, 1076, 876, 835, 774, 748 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 7.20–7.45 (m, 5H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.18 (dd, *J* = 5.4, 15.9 Hz, 1H), 4.31 (t, *J* = 5.3, 1H), 3.76 (d, *J* = 10.6, 1H), 3.69 (s, 3H), 3.60–3.71 (m, 1H), 3.23 (s, 3H), 2.82 (br. s, 1H), 2.71 (d, *J* = 13.4, 1H), 2.52 (d, *J* = 13.4, 1H), 2.08 (dd, *J* = 4.4, 12.9, 1H), 1.88–1.94 (m, 1H), 1.70 (t, *J* = 12.4, 1H), 1.43–1.52 (m, 1H), 0.99 (d, *J* = 6.9, 3H), 0.88 (s, 9H), 0.86 (d, *J* = 6.5, 3H), 0.05 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 169.6, 136.9, 132.3, 130.8, 128.5, 127.4, 126.3, 99.3, 75.6, 69.9, 51.7, 48.5, 42.9, 41.9, 39.9, 38.7, 25.8, 12.6, 10.1, −4.1, −4.8; Exact mass calc for C₂₇H₄₄O₆SiNa: 515.2805; found: 515.2805.

4.2.8. Methyl 2-[6-((2*S*,1*R*)-2-methoxy-1-methyl-3-oxopropyl)-(4*S*,5*S*,2*R*)-2-methoxy-5-methyl-4-(*tert*-butyldimethylsilyloxy)perhydro-2*H*-pyran-2yl]acetate (11**)**

—To a solution of 120 mg (0.244 mmol) of the alcohol in 3.0 mL of CH₂Cl₂ was added 750 mg (3.66 mmol) of 2,6-di-*tert*-butyl-4-methylpyridine and 200 mL (1.77 mmol) of MeOTf. The solution was stirred for 14 h at rt and 3 mL of MeOH were added to quench excess MeOTf. The solution was stirred for 30 min and then poured into 50 mL of sat. NaHCO₃(aq) and diluted with 100 mL of Et₂O. The organic phase was separated and the aqueous phase was further extracted with 50 mL of Et₂O and the combined organic extracts were washed with brine, dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (5% EtOAc/hexanes) yielded 101 mg (0.200 mmol, 82%) of the title compound and approx. 10 mg of the derived dihydropyran, which can be converted into the title compound by stirring in MeOH/PPTS. To a cooled solution (−78 °C) of 50 mg (0.100 mmol) of the olefin in 10 mL of CH₂Cl₂ and 5 mL of MeOH was added O₃ for 3 min (the reaction mixture turned blue after 2 min). Then 15 drops of Me₂S were added and the reaction mixture was slowly warmed to rt overnight. The mixture was poured into 50 mL of sat. NaHCO₃(aq) and 50 mL of EtOAc and the organic phase was separated. The aqueous phase was further extracted with 50 mL of EtOAc and the combined organic extracts were dried over MgSO₄, filtrated and concentrated. Purification by flash chromatography (17% EtOAc/hexanes) gave 35 mg (0.081 mmol, 81%) of the title compound as a clear, colorless oil. [α]_D²³ −86.9 (*c* 0.4, EtOAc); IR (neat) 2955, 2932, 2857, 1744, 1463, 1438, 1379, 1318, 1252, 1222, 1190, 1150, 1070, 1033, 1006, 837, 775 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) δ 9.58 (d, *J* = 4.4, 1H), 3.62–3.72 (m, 1H), 3.68 (s, 3H), 3.63 (dd, *J* = 1.8, 10.7, 1H), 3.50 (dd, *J* = 4.4, 8.9, 1H), 3.34 (s, 3H), 3.21 (s, 3H), 2.63 (s, 2H), 2.14 (dd, *J* = 4.7, 12.9, 1H), 2.03–2.11 (m, 1H), 1.69 (dd, *J* = 10.8, 13.1, 1H), 1.40–1.50 (m, 1H), 0.91 (s, 9H), 0.88 (d, *J* = 6.6, 3H), 0.84 (d, *J* = 7.0, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.6,

99.1, 86.5, 72.1, 70.3, 57.7, 51.6, 47.9, 43.0, 41.7, 39.4, 34.8, 25.8, 18.0, 12.4, 7.5, -4.1, -4.7; Exact mass calc for $C_{21}H_{40}O_7SiNa$: 455.2441; found: 455.2441.

4.2.9. Methyl 2-[6-((2S,3S,1R)-3-hydroxy-2-methoxy-1,4-dimethylpent-4-enyl)-(4S,5S,2R)-2-methoxy-5-methyl-4-(tert-butyldimethylsilyloxy)perhydro-2H-pyran-2-yl]acetate (12)—A cooled solution of 1.89 mL of 2-magnesiumbromopropene (0.5 M in THF) was diluted with 5 mL of THF and transferred via cannula to a cooled solution (-78 °C) of 210 mg (0.486 mmol) of aldehyde **11** in 5 mL of THF. After 15 min at -78 °C the reaction was quenched by addition of 25 mL of $NaHCO_3(aq)$. The mixture was diluted with 10 mL of EtOAc and the organic phase was separated. The aqueous phase was extracted twice with 20 mL of EtOAc and the combined organic extracts were washed with 10 mL brine, dried over $MgSO_4$, concentrated in vacuo to give 225 mg (0.474 mmol, 98%) of the title compound as a clear, colorless oil of sufficient purity to be used directly. $[\alpha]_D^{23}$ -54.1 (c 0.4, EtOAc); IR (neat) 2929, 2856, 1744, 1440, 1378, 1316, 1251, 1079, 1038, 897, 837, 775 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 5.30 (s, 1H), 4.94 (dd, J = 1.3, 2.8, 1H), 4.06 (br. d, J = 1.8, 1H), 3.66 (s, 3H), 3.60–3.70 (m, 1H), 3.56 (dd, J = 1.1, 10.7, 1H), 3.41 (s, 3H), 3.36 (dd, J = 1.8, 8.7, 1H), 3.24 (s, 3H), 2.63 (d, J = 12.8, 1H), 2.60 (d, J = 12.8, 1H), 2.11 (dd, J = 4.6, 12.9, 1H), 1.95–2.05 (m, 1H), 1.80 (s, 3H), 1.67 (dd, J = 10.9, 12.9, 1H), 1.38–1.50 (m, 1H), 0.87 (s, 9H), 0.85–0.87 (m, 6H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 146.4, 111.0, 99.1, 82.0, 73.7, 73.3, 70.3, 59.9, 51.5, 48.6, 42.6, 42.1, 40.0, 35.8, 25.8, 19.4, 18.0, 13.0, 9.9, -4.1, -4.7; Exact mass calc for $C_{24}H_{46}O_7SiNa$: 497.2910; found: 497.2911.

4.2.10. Prop-2-enyl-2-[6-((2S,3S,1R)-3-hydroxy-2-methoxy-1,4-dimethylpent-4-enyl)(2S,4S,5S)-2-methoxy-5-methyl-4-(1,1,2,2-tetramethyl-1-sila-propoxy)perhydro-2H-pyran-2-yl]acetate—A 1 M solution of LiOH in H_2O (14 mL) was added to a solution of 333 mg (0.70 mmol) of alcohol **12** in 28 mL of methanol and 28 mL of THF at rt. The resulting homogeneous reaction was stirred vigorously overnight. The volatile solvents were removed *in vacuo*, and the residual oil was diluted with H_2O and acidified to pH <2 with 6 M $HCl(aq)$. The aqueous layer was extracted with 3×100 mL of Et_2O . The combined organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The resulting yellow oil was used directly in the next reaction without further purification. The yellow oil containing the acid was dissolved in 0.70 mL of DMF at rt. 63 μL (0.73 mmol) of freshly distilled allyl bromide and 119 mg (0.36 mmol) of solid Cs_2CO_3 were added to the reaction solution, and the resulting mixture was stirred overnight at rt. The reaction was quenched with sat. $NH_4Cl(aq)$ and extracted with 3×20 mL of Et_2O . The combined organic layers were washed with H_2O and brine to remove DMF. The organic layer was then dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to afford 270 mg (0.54 mmol, 77% yield, 2 steps) of desired product as a colorless oil. $[\alpha]_D^{23}$ -56.6 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2 , film) 2954, 2933, 2858, 2369, 1739, 1462, 1374, 1313, 1251, 1218, 1082, 1036, 1008, 938, 891, 836, 775 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95–5.85 (m, 1H); 5.32 (ddt, J = 1.5, 2.9, 17.2 Hz, 1H); 5.22 (ddt, J = 1.5, 2.6, 10.5 Hz, 1H); 5.16 (d, J = 0.7 Hz, 1H); 4.94 (dd, J = 1.5, 2.9 Hz, 1H); 4.57 (ddt, J = 1.1, 1.5, 5.9 Hz, 2H); 4.01 (d, J = 6.2 Hz, 1H); 3.68–3.62 (m, 1H); 3.56 (dd, J = 1.5, 10.6 Hz, 1H); 3.41 (s, 3H); 3.37 (dd, J = 1.8, 8.4 Hz, 1H); 3.25 (s, 3H); 2.66 (s, 2H); 2.55 (d, 1H); 2.13 (dd, J = 4.8, 12.8 Hz, 1H); 2.04–1.96 (m, 1H); 1.80 (s, 3H); 1.67 (dd, J = 11.0, 12.8 Hz, 1H); 1.46–1.39 (m, 1H); 0.88 (s, 9H); 0.87 (d, J = 6.6 Hz, 3H); 0.84 (d, J = 4.0 Hz, 3H); 0.04 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.3, 146.7, 132.3, 118.6, 111.3, 99.4, 82.2, 73.9, 73.7, 70.6, 65.5, 60.3, 48.9, 43.0, 42.5, 40.3, 36.1, 26.1, 19.8, 18.3, 13.3, 10.3, -3.8, -4.4; Exact mass calcd. for $C_{26}H_{48}O_7Si$ $[M+Na]^+$: 523.3126; found: 523.3145 (ES).

4.2.11. (1S)-1-((1S,2S)-2-((3S,4S,6S)-6-Methoxy-3-methyl-6-[(prop-2-enyloxy-carbonyl)-methyl]-4-(1,1,2,2-tetramethyl-1-silapropoxy)perhydro-2H-pyran-2-yl)-1-methoxypropyl)-2-methylprop-2-enyl-2-[(3,4-dimethoxyphenyl)methoxy]acetate (13)—195 mg (0.86 mmol) of dimethoxy(benzyloxy) acetic acid was added to a solution of 270 mg (0.54 mmol) of alcohol in 5.0 mL of dry CH₂Cl₂ under N₂. The resulting solution was cooled to 0 °C and 223 mg (1.08 mmol) of DCC was added to the reaction mixture. The ice bath was removed to allow the reaction to warm to rt over 15 minutes. After addition of 33 mg (0.27 mmol) of DMAP to the suspension, the reaction was stirred at rt overnight. The reaction mixture was diluted with EtOAc and then filtered through a plug of Celite. The filtrate was concentrated *in vacuo*. Purification by flash chromatography (column neutralized with 20% EtOAc/hexane + 0.1% Et₃N; eluted with 20% EtOAc/hexanes) afforded 345 mg (0.49 mmol, 90%) of the title compound as a clear oil. [α]_D²³ –53.8 (c 0.7, CH₂Cl₂); IR (CH₂Cl₂, film) 3087, 2954, 2851, 1739, 1518, 1465, 1420, 1376, 1261, 1241, 1194, 1160, 1125, 1087, 1032, 1010, 837, 776 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.92–6.79 (m, 3H); 5.93–5.84 (m, 1H); 5.36 (s, 1H); 5.31 (ddt, *J* = 1.5, 2.9, 17.0 Hz, 1H); 5.21 (ddt, *J* = 1.5, 2.6, 10.6 Hz, 1H); 5.00–4.93 (m, 2H); 4.60–4.51 (m, 4H); 4.15 (d, *J* = 1.5 Hz, 2H); 3.86 (s, 3H); 3.85 (s, 3H); 3.63 (dt, *J* = 4.0, 10.3 Hz, 1H); 3.57 (dd, *J* = 1.1, 10.6 Hz, 1H); 3.49 (dd, *J* = 2.2, 9.2 Hz, 1H); 3.40 (s, 3H); 3.24 (s, 3H); 2.68 (d, *J* = 13.5 Hz, 1H); 2.63 (d, *J* = 13.5 Hz, 1H); 2.12 (dd, *J* = 4.8, 12.8 Hz, 1H); 1.95–1.88 (m, 1H); 1.84 (s, 3H); 1.64 (dd, *J* = 11.0, 12.8 Hz, 1H); 1.45–1.35 (m, 1H); 0.86 (s, 9H); 0.81 (d, *J* = 6.6 Hz, 3H); 0.76 (d, *J* = 7.0 Hz, 3H); 0.04 (s, 6H); ¹³C NMR (100.6 MHz, CDCl₃) δ 169.5, 168.9, 149.0, 148.8, 141.3, 131.9, 129.4, 120.7, 118.2, 111.9, 111.2, 110.7, 99.0, 80.9, 76.2, 73.1, 72.9, 70.2, 66.5, 65.1, 58.9, 55.8, 55.7, 48.6, 42.6, 42.1, 39.7, 35.2, 25.8, 20.1, 17.9, 12.9, 9.1, –4.1, –4.8; Exact mass calcd. for C₃₇H₆₀O₁₁Si [M+Na]⁺: 731.3782; found: 731.3803 (ES).

4.2.12. (4E)(2R,6R,7R)-7-((3S,4S,6S)-6-Methoxy-3-methyl-6-[prop-2-enyloxy-carbonyl)methyl]-4-(1,1,2,2-tetramethyl-1-silapropoxy)perhydro-2H-pyran-2-yl)-2-[(3,4-dimethoxyphenyl)methoxy]-6-methoxy-4-methyloct-4-enoic acid (14)—A 0.5 M solution of LiHMDS was prepared by adding 93 μL (1.9 M, 0.18 mmol) of *n*-BuLi to a solution of 50 μL (0.24 mmol) of hexamethyldisilazane in 0.33 mL of THF at –78 °C under N₂. The solution was stirred at –78 °C for 30 minutes then at 0 °C for 15 min. The LiHMDS solution was then added dropwise to a solution of 42 mg (0.06 mmol) of ester **13** in 0.59 mL THF at –100 °C under N₂. The resulting mixture was stirred at –100 °C for 30 min. Meanwhile, in a separate flame dried flask, 22 μL (0.18 mmol) of TMSCl was added to 25 μL (0.18 mmol) of Et₃N at rt. The cloudy mixture was filtered through a 0.45 μm filter and added to the lithium enolate reaction. The reaction solution was stirred at –100 °C for another hour before gradually warming to rt overnight. The light yellow reaction solution was quenched with 3 mL of Et₂O and 1 mL of 0.1 N HCl(aq). The heterogeneous mixture was vigorously stirred at rt for 5 min. Following the addition of 30 mL of Et₂O and 10 mL of 0.1 M HCl, the layers were separated. The organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (linear gradient, 60 → 100% EtOAc/hexanes; then 85:10:5 EtOAc/*i*-PrOH/H₂O) provided 25.7 mg (0.037 mmol, 61%) of the title compound as a clear oil. [Silica gel chromatography was performed in this experiment to fully characterize the product even though this purification method also caused some decomposition of the material and gave a lower yield.] [α]_D²³ –3.9 (c 1.1, CH₂Cl₂); IR (CH₂Cl₂, film) 2954, 2933, 2923, 2862, 2369, 2348, 2328, 1733, 1718, 1703, 1687, 1518, 1503, 1467, 1421, 1256, 1159, 1082, 1031, 836 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.87–6.81 (m, 3H); 5.95–5.85 (m, 1H); 5.33 (ddt, *J* = 1.5, 17.2 Hz, 1H); 5.22 (ddt, *J* = 1.5, 10.3 Hz, 1H); 5.07 (d, *J* = 9.5 Hz, 1H); 4.63–4.56 (m, 3H); 4.44 (d, *J* = 11.4 Hz, 1H); 4.14 (dd, *J* = 5.9, 7.0 Hz, 1H); 3.87 (s, 6H); 3.72 (d, *J* = 10.6 Hz, 1H); 3.66 (m, 1H); 3.23 (s, 3H); 3.19 (dd, *J* = 10.3, 12.8 Hz, 1H); 3.12 (s, 3H); 2.71 (d, *J* = 13.6 Hz, 1H); 2.64 (d, *J* =

13.5 Hz, 1H); 2.57 (m, 2H); 2.15 (dd, J = 4.8, 12.8 Hz, 1H); 1.71 (s, 3H); 1.67 (m, 2H); 1.41-1.37 (m, 1H); 0.87 (s, 9H); 0.82 (d, J = 6.6 Hz, 3H); 0.69 (d, J = 7.0 Hz, 3H); 0.05 (s, 6H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 176.0, 169.1, 149.0, 148.9, 135.5, 132.0, 129.5, 129.1, 121.0, 118.3, 111.4, 110.8, 98.8, 76.2, 72.6, 71.6, 70.6, 65.2, 55.9, 55.8, 55.2, 47.7, 43.3, 42.8, 42.2, 39.9, 38.5, 25.9, 18.0, 17.1, 12.4, 8.6, -4.1, -4.8.

4.2.13. Prop-2-enyl-2-(6-((3*E*)(1*R*,2*R*,6*RS*,4*S*,5*S*)-2-methoxy-5-methyl-4-(1,1,2,2-tetramethyl-1-silapropoxy)perhydro-2H-pyran-2-yl)acetate—

To a solution of 5.80 mg (8.20 μmol) of acid **14** in 82 μL of CH_2Cl_2 was added 1.50 μL (19.7 μmol) of ethanethiol, 2.30 μL (16.40 μmol) of triethylamine, and 2.40 mg (94.0 μmol) of BOP-Cl. The resulting solution was stirred for 10 min at 0 $^\circ\text{C}$ and then at rt for 5 h. The reaction was quenched with 2 mL of H_2O and extracted with 3×10 mL of CHCl_3 . The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash chromatography (10 $\rightarrow$ 20% EtOAc/hexanes) afforded 3.9 mg (5.17 μmol , 63%) of the title compound as a clear oil. TLC R_f = 0.59 (30% EtOAc/hexanes); $[\alpha]_D^{23}$ +36.4 (c 0.7, CH_2Cl_2); IR (CH_2Cl_2 , film) 2954, 2933, 2862, 1739, 1682, 1595, 1518, 1464, 1421, 1380, 1323, 1263, 1159, 1144, 1081, 1032, 1005, 933, 837, 776 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.94-6.81 (m, 3H); 5.95-5.85 (m, 1H); 5.32 (ddt, J = 1.5, 17.2 Hz, 1H); 5.22 (ddt, J = 1.5, 10.3 Hz, 1H); 5.02 (d, J = 8.8 Hz, 1H); 4.65 (d, J = 11.0 Hz, 1H); 4.57 (d, J = 5.1 Hz, 2H); 4.38 (d, J = 11.0 Hz, 1H); 4.08 (t, J = 6.6 Hz, 1H); 3.88 (s, 3H); 3.87 (s, 3H); 3.88-3.83 (m, 1H); 3.72 (dd, J = 1.8, 10.6 Hz, 1H); 3.66 (ddd, J = 4.8, 9.5 Hz, 1H); 2.88 (q, J = 7.3 Hz, 2H); 2.70 (d, J = 13.5 Hz, 1H); 2.63 (d, J = 13.2 Hz, 1H); 2.49 (d, J = 7.0 Hz, 1H); 2.15 (dd, J = 4.8, 12.8 Hz, 1H); 1.69 (d, J = 1.1 Hz, 3H); 1.69-1.59 (m, 2H); 1.42-1.35 (m, 1H); 1.26 (t, J = 7.3 Hz, 3H); 0.88 (s, 9H); 0.81 (d, J = 6.6 Hz, 3H); 0.67 (d, J = 7.3 Hz, 3H); 0.05 (s, 6H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 203.4, 169.1, 148.9, 148.8, 135.6, 134.7, 132.0, 129.6, 129.5, 129.4, 120.9, 118.3, 111.5, 110.8, 98.8, 83.2, 73.1, 71.5, 70.6, 65.2, 55.9, 55.8, 55.2, 47.7, 44.1, 43.4, 42.2, 39.9, 38.5, 25.9, 22.4, 18.0, 17.2, 14.6, 12.3, 8.7, -4.1, -4.7; Exact mass calcd. for $\text{C}_{39}\text{H}_{64}\text{O}_{10}\text{SSi}$ $[\text{M}+\text{Na}]^+$: 775.3862; found: 775.3887 (ES).

4.2.14. Prop-2-enyl-2-[6-((3*E*)(1*R*,2*R*,6*R*)-7-ethylthio-6-hydroxyl-2-methoxy-1,4-dimethyl-7-oxohept-3-enyl)(2*S*,4*S*,5*S*)-2-methoxy-5-methyl-4-(1,1,2,2-

tetramethyl-1-silapropoxy)perhydro-2H-pyran-2-yl]acetate—66.5 mg (0.088 mmol) of the thioester was dissolved in 8.1 mL of CH_2Cl_2 and 0.9 mL of MeOH at rt. Addition of 40.0 mg (0.176 mmol) of DDQ to the reaction produced a clear green solution. After stirring at rt overnight, the mixture turned to a clear yellow solution. The reaction was quenched with 20 mL of sat. $\text{NaHCO}_3(\text{aq})$ and extracted with 3×30 mL of Et_2O . The combined organic layer were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc/hexanes) afforded 42.1 mg (0.070 mmol, 79%) of the title compound. $[\alpha]_D^{23}$ +13.3 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2 , film) 3481, 2957, 2928, 2849, 2365, 2945, 1738, 1677, 1461, 1377, 1313, 1264, 1219, 1140, 1081, 1027, 933, 834, 775 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.94-5.87 (m, 1H); 5.30 (dd, J = 1.5, 17.2 Hz, 1H); 5.22 (dd, J = 1.1, 10.3 Hz, 1H); 5.08 (d, J = 9.5 Hz, 1H); 4.57 (d, J = 5.5 Hz, 2H); 4.37-4.32 (m, 1H); 3.97-3.87 (m, 1H); 3.73 (dd, J = 1.5, 10.6 Hz, 1H); 3.66 (ddd, J = 4.0, 8.9 Hz, 1H); 3.24 (s, 3H); 3.16 (s, 3H); 2.90 (q, J = 7.3 Hz, 2H); 2.67 (d, J = 2.6 Hz, 2H); 2.67-2.60 (m, 1H); 2.37 (dd, J = 9.2, 13.9 Hz, 1H); 2.14 (dd, J = 4.4, 13.2 Hz, 1H); 1.85-1.63 (m, 2H); 1.75 (s, 3H); 1.42-1.36 (m, 1H); 1.26 (t, J = 7.3 Hz, 3H); 0.87 (s, 9H); 0.83 (d, J = 6.6 Hz, 3H); 0.70 (d, J = 7.0 Hz, 3H); 0.05 (s, 6H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 203.9, 169.4, 135.9, 132.3, 130.7, 118.6, 99.2, 76.0, 72.0, 70.9, 65.5, 56.3, 55.7, 48.0, 45.7, 43.6, 42.5, 40.2, 38.8, 26.2, 23.1, 18.3, 17.3, 14.8, 12.7, 9.0, -3.8, -4.4; Exact mass calcd. for $\text{C}_{30}\text{H}_{54}\text{O}_8\text{SSi}$ $[\text{M}+\text{Na}]^+$: 625.3206; found: 625.3205 (FAB).

4.2.15. 2-[6((3E)(1R,2R,6R)-7-Ethylthio-6-hydroxy-2-methoxy-1,4-dimethyl-7-oxohept-3-enyl)(2S,4S,5S)-2-methoxy-5-methyl-4-(1,1,2,2-tetramethyl-1-silapropoxy) perhydro-2H-pyran-2-yl]acetic acid (15)—16.1 mg (0.066 mmol) of the thioester was dissolved in 0.27 mL of dry THF at rt under N₂. 3.10 mg (2.70 μmol) of palladium tetrakis(triphenylphosphine), 33.0 μL (0.243 mmol) of triethylamine, and 9.20 μL (0.243 mmol) of formic acid were then added to the reaction. After 4 h of stirring at rt, the volatile solvents were removed *in vacuo* and dried under reduced pressure. Purification by two column flash chromatography (column 1 to remove impurities: linear gradient 50 → 80% EtOAc/hexanes; column 2 to remove residual Pd(Ph₃)₄ salts: 10 → 30% EtOAc/hexane + 1% AcOH) afforded 9.1 mg (0.040 mmol, 60%) of the title compound. [α]_D²³ +5.0 (c 0.4, CH₂Cl₂); IR (CH₂Cl₂, film) 3382, 2932, 2857, 1713, 1682, 1439, 1384, 1316, 1257, 1148, 1122, 1081, 1031, 1007, 837, 776, 724 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.10 (d, *J* = 9.5 Hz, 1H); 4.35 (dd, *J* = 4.0, 9.2 Hz, 1H); 3.91 (m, 2H); 3.67 (ddd, *J* = 4.4, 9.9 Hz, 1H); 3.26 (s, 3H); 3.18 (s, 3H); 2.91 (q, *J* = 7.7 Hz, 2H); 2.84 (d, *J* = 15.0 Hz, 1H); 2.66 (m, 1H); 2.61 (d, *J* = 15.4 Hz, 1H); 2.38 (dd, *J* = 9.2, 14.3 Hz, 1H); 2.09 (dd, *J* = 4.8, 12.8 Hz, 1H); 1.78 (m, 1H); 1.75 (d, *J* = 1.1 Hz, 3H); 1.65 (dd, *J* = 6.2, 16.1 Hz, 1H); 1.52 (m, 1H); 1.27 (t, *J* = 7.32 Hz, 3H); 0.87 (s, 9H); 0.86 (d, *J* = 6.6 Hz, 3H); 0.79 (d, *J* = 7.3 Hz, 3H); 0.06 (s, 3H); 0.05 (s, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ 203.9, 171.7, 136.3, 130.0, 99.2, 77.7, 76.0, 73.1, 70.3, 55.7, 48.6, 45.6, 43.2, 42.3, 40.2, 38.6, 26.0, 23.1, 18.2, 17.3, 14.8, 12.6, 9.4, -3.9, -4.6; Exact mass calcd. for C₂₇H₅₀O₈SSi [M+Na]⁺: 585.2893; found: 585.2899 (ES).

4.2.16. (1S, 12S, 13S, 5R, 9R, 10R)-5-(Ethylthiocarbonyl)-1,9-dimethoxy-7,10,12-trimethyl-4,15-dioxo-13-(1,1,2,2-tetramethyl-1-silapropoxy)-bicyclo[9.3.1]pentadec-7-en-3-one (16)—At room temperature, 5.80 mg (10.3 μmol) of seco acid **15** was dissolved in 0.34 mL of THF. 6.40 μL (41.2 μmol) of trichlorobenzoic acid and 14.0 μL (82.6 μmol) of diisopropylethylamine were then added to the reaction. After stirring at rt overnight, the resulting anhydride mixture was diluted with 2.6 mL of toluene. The mixture was added *via* syringe pump to a solution of 47.0 mg (0.381 mmol) of DMAP in 3.9 mL of toluene at 70 °C over 2 h. An additional 2 mL of toluene rinse was then added *via* syringe pump. The reaction mixture was stirred for at least an additional 30 min before cooling to rt. The volatile solvents were removed *in vacuo*, and the resulting oil was purified by flash chromatography (10% EtOAc/hexane) to afford 1.2 mg of the title compound and 2.0 mg of the derived dihydropyran, which can be reketalyzed with 0.1 eq PPTS and 0.05 M MeOH (6.1 μmol, 59% combined yield). [α]_D²³ +115 (c 0.1, CH₂Cl₂); IR (CH₂Cl₂, film) 2944, 2923, 2872, 1744, 1682, 1462, 1380, 1333, 1251, 1231, 1185, 1144, 1072, 1005, 867, 836, 769 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.44 (dd, *J* = 2.9, 12.7 Hz, 1H); 5.34 (d, *J* = 9.8 Hz, 1H); 3.88 (dd, *J* = 2.0, 10.3 Hz, 1H); 3.54 (d, *J* = 10.3 Hz, 1H); 3.46 (ddd, *J* = 3.9, 10.3 Hz, 1H); 3.27 (s, 3H); 3.22 (s, 3H); 2.89 (q, *J* = 7.3 Hz, 2H); 2.69 (d, *J* = 12.7 Hz, 1H); 2.65 (m, 1H); 2.61 (d, *J* = 12.2 Hz, 1H); 2.44 (dd, *J* = 12.7 Hz, 1H); 2.20 (m, 1H); 2.14 (dd, *J* = 4.4, 13.7 Hz, 1H); 1.65 (s, 3H); 1.44 (m, 1H); 1.28 (m, 4H); 1.01 (d, 3H, *J* = 6.8 Hz, 3H); 0.91 (m, 12H); 0.07 (s, 3H); 0.06 (s, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ 199.6, 168.6, 132.1, 128.3, 100.3, 81.6, 80.5, 80.2, 75.7, 70.2, 56.4, 51.6, 43.5, 43.4, 40.9, 40.5, 38.4, 26.0, 23.0, 18.2, 15.4, 14.6, 13.1, -3.9, -4.5; Exact mass calcd. for C₂₇H₄₈O₇SSi [M+Na]⁺: 567.2790; found: 567.2788 (ES).

4.2.17. Ethyl (2E)(5S)-5-hydroxy-6-[(4-methoxyphenyl)methoxy]-3-methylhex-2-enoate (ent-22)—A solution of 581 mg (0.618 mmol, 2.5 mol %) of Cu(S,S)PhPyBox•2SbF₆•2H₂O¹¹ in 25 mL of CH₂Cl₂ was precooled to -78 °C. Solutions of 4.45 g (24.7 mmol) of *p*-methoxy(benzyloxy)acetaldehyde **20** and 5.95 g (29.7 mmol) of silyl ketene acetal **19** each in 12 mL of CH₂Cl₂ were added simultaneously over 20 hours using a syringe pump, maintaining the reaction vessel at -78 °C. After the addition was

complete, the cold reaction solution was filtered through a silica plug with a rinse of 200 mL of Et₂O. The solvent was removed *in vacuo* and the unpurified reaction mixture was diluted with 100 mL of EtOAc and 5 mL of 1 M HCl(aq) was added. After vigorous stirring for 45 minutes, the reaction mixture was poured into 100 mL of sat. NaHCO₃(aq). The organic layer was removed and the aqueous layer was extracted with 3 × 100 mL of CH₂Cl₂. The combined organic layers were washed with brine (100 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Flash column chromatography (25% EtOAc/hexanes) yielded 7.06 g (22.9 mmol, 93%) of the title compound as a clear, colorless oil. TLC R_f 0.15 (20% EtOAc/hexanes); [α]_D²³ −1.47 (*c* 8.61, CH₂Cl₂); IR (neat) 3475, 2936, 1713, 1647, 1613, 1513, 1248, 1151 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.73 (q, *J* = 1.1 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.46 (d, *J* = 11.4 Hz, 1H), 4.14 (q, *J* = 7.3 Hz, 2H), 4.05–3.99 (m, 1H), 3.81 (s, 3H), 3.47 (dd, *J* = 9.5, 3.7 Hz, 1H), 3.33 (dd, *J* = 9.5, 7.0 Hz, 1H), 2.34–2.21 (m, 2H), 2.19 (d, *J* = 1.1 Hz, 3H), 1.27 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.4, 159.3, 155.7, 129.8, 118.1, 113.8, 73.5, 73.1, 68.2, 59.6, 55.3, 44.6, 18.9, 14.3; exact mass calc. for C₁₇H₂₄O₅: 309.1702; found: 309.1708 (EI); assay of enantiomeric excess: HPLC (Chiracel AD column; 5% ¹PrOH in hexanes; 0.5 mL/min); t_r (minor) = 45.84 min.; t_r (major) = 51.00 min; 95% ee.

4.2.18. Ethyl (2E)(5S)-6-[(4-methoxyphenyl)methoxy]-3-methyl-5-(*tert*-butyldimethylsiloxy) hex-2-enoate (*ent*-23)—2.68 g (39.4 mmol) of imidazole and 2.55 g (23.6 mmol) of TBSCl were added to a solution of 6.06 g (19.7 mmol) alcohol *ent*-22 in 125 mL of anhydrous DMF and the resulting solution was stirred for 11 hours at rt. The solution was then diluted with 300 mL of 1:1 hexanes:Et₂O and washed with 3 × 300 mL of 1:1 H₂O:brine. The aqueous layers were back extracted with 300 mL of 1:1 hexanes:Et₂O, and the combined organic fractions were dried (Na₂SO₄) and concentrated *in vacuo* to provide 8.31 g (19.7 mmol, quant.) of the title compound as a clear, colorless oil. TLC R_f 0.6 (EtOAc/hexanes); [α]_D²³ −17.0 (*c* 6.4, MeOH); IR (neat) 2930, 2857, 1716, 1514, 1250, 1223, 1151, 836 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.69 (br s, 1H), 4.44 (s, 2H), 4.19–4.09 (m, 2H), 4.00–3.95 (m, 1H), 3.81 (s, 3H), 3.38 (dd, *J* = 9.3, 5.4 Hz, 1H), 3.31 (dd, *J* = 9.8, 5.9 Hz, 1H), 2.40 (dd, *J* = 13.2, 4.4 Hz, 1H), 2.22 (dd, *J* = 13.2, 7.8 Hz, 1H), 2.17 (d, *J* = 1.0 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H) 0.848 (s, 9H) 0.02 (s, 3H), 0.00 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.6, 159.1, 156.3, 130.3, 129.3, 118.5, 113.7, 74.1, 73.0, 69.8, 59.4, 55.3, 46.3, 25.8, 19.4, 18.1, 14.3, −4.5, −5.0; exact mass calc. for C₂₃H₃₈O₅Si+NH₄: 440.2833; found: 440.2840 (CI).

4.2.19. (2E)(5S)-6-[(4-Methoxyphenyl)methoxy]-3-methyl-5-(*tert*-butyldimethylsiloxy)hex-2-en-1-ol—8.07 g (19.1 mmol) of *ent*-23 was dissolved in 80 mL of Et₂O and cooled to 0 °C. 20 mL (1.0 M, 20 mmol) of a solution of LiAlH₄ in Et₂O was added dropwise over 5 minutes, and the resulting solution was warmed to rt and stirred for 1 hour. The reaction mixture was then cooled to 0 °C and quenched by the slow sequential addition of 0.76 mL of H₂O, 0.76 mL of 15% NaOH(aq) and 2.28 mL of H₂O. Once the precipitate became white, the resulting slurry was filtered through Celite with a 3 × 100 mL Et₂O rinse. Concentration *in vacuo* provided 6.54 g (17.2 mmol, 90%) of the title compound as a clear colorless oil. TLC R_f 0.1 (20% EtOAc/hexanes); [α]_D²³ −2.86 (*c* 4.9, CH₂Cl₂); IR (neat) 3329, 2929, 2858, 1613, 1514, 1472, 1249, 1099, 1036, 776 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) δ 7.25 (d, *J* = 8.8 Hz, 2H) 6.87 (d, *J* = 8.8 Hz, 2H), 5.42 (br t, *J* = 6.8 Hz, 1H), 4.44 (s, 2H), 4.16–4.08 (m, 2H), 3.96–3.91 (m, 1H), 3.81 (s, 3H), 3.37–3.31 (m, 2H), 2.27 (dd, *J* = 13.7, 5.1 Hz, 1H) 2.14 (dd, *J* = 13.7, 7.3 Hz, 1H), 1.68 (s, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.1, 136.3, 130.4, 129.2, 126.5, 113.7, 74.2, 72.9, 70.1, 59.4, 55.2, 44.9, 25.8, 18.2, 16.9, −4.4, −4.7; exact mass calc. for C₂₁H₃₆O₄Si+Na: 403.2281; found: 403.2278 (FAB).

4.2.20. (2E)(5S)-6-[(4-Methoxyphenyl)methoxy]-3-methyl-5-(*tert*-butyldimethylsiloxy)hex-2-enal (*ent*-24)—A solution of 6.89 g (18.1 mmol) of the alcohol in 100 mL of CH₂Cl₂ and 26.5 mL of DMSO was cooled to 0 °C and 10.1 mL (72.4 mmol) of Et₃N followed by 5.76 g (36.2 mmol) of SO₃•pyr were added. After stirring for 4 hours at 0 °C, the reaction mixture was diluted with 400 mL of 1:1 hexanes:Et₂O and washed with 400 mL each of 10:1 brine:H₂O, 1:1 brine:H₂O, conc. CuSO₄(aq) and H₂O. The aqueous fractions were back extracted with 400 mL of 1:1 hexanes:Et₂O, and then the combined organic fractions were dried (Na₂SO₄) and concentrated *in vacuo* to yield a green oil. Flash column chromatography (10% EtOAc/hexanes) provided 5.15 g (13.6 mmol, 83%) of the title compound as a clear colorless oil. TLC R_f 0.4 (EtOAc/hexanes); [α]_D²³ −3.33 (c 0.52, CH₂Cl₂); IR (neat) 2929, 2856, 1874, 1514, 1249, 1103, 836 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) δ 9.97 (d, *J* = 8.3 Hz, 1H), 7.25–7.23 (m, 2H), 6.89–6.87 (m, 2H), 5.91–5.89 (m, 1H), 4.44 (s, 2H), 4.06–3.98 (m, 1H), 3.81 (s, 3H), 3.40 (dd, *J* = 9.8, 5.4 Hz, 1H), 3.30 (dd, *J* = 9.8, 6.3 Hz, 1H), 2.48 (dd, *J* = 13.2, 3.9 Hz, 1H), 2.32 (dd, *J* = 13.2, 8.3 Hz, 1H), 2.19 (d, *J* = 1.5 Hz, 3H), 0.84 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 190.9, 160.9, 159.2, 130.1, 129.9, 129.3, 113.8, 73.9, 73.0, 70.0, 55.3, 45.9, 25.7, 18.4, 18.1, −4.5, −4.9.

4.2.21. 6-[(1E)(4S)-5-[(4-Methoxyphenyl)methoxy]-2-methyl-4-(*tert*-butyldimethylsiloxy)pent-1-enyl] (3S,4S,5S,6R)-4-hydroxy-3,5-dimethyl-3H-4,5,6-trihydropyran-2-one (27)—To a cooled (0 °C) solution of 1.79 g (6.19 mmol) of β-ketoimide **5**⁴ in 70 mL of Et₂O were added 1.78 mL (8.12 mmol) of dicyclohexylboron chloride and 0.88 mL (8.12 mmol) of EtNMe₂. Almost immediately the solution became yellow with the concomitant formation of a white precipitate. This mixture was stirred for 1 hour at 0 °C, and then chilled to −78 °C. 1.80 g (4.77 mmol) of aldehyde *ent*-24 was added by syringe, and the mixture was stirred for 2 hours at −78 °C and then transferred to a −20 °C freezer for 1 hour. The reaction was quenched by the addition of 60 mL of 2:1 MeOH:sat. NH₄Cl(aq) and the mixture was warmed to rt. This heterogeneous mixture was diluted with 200 mL of H₂O and extracted with 3 × 200 mL of CH₂Cl₂. The organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The resulting yellow oil was diluted with 15 mL of CH₃CN and added via cannula to a cooled (0 °C) solution of 6.28 g (23.9 mmol) of Me₄NBH(OAc)₃ in 15 mL of AcOH and 15 mL of CH₃CN. The resulting yellow solution was stirred for 2 hours at 0 °C and then transferred via cannula to a vigorously stirring mixture of 400 mL of sat. NaHCO₃(aq) and 200 mL of CH₂Cl₂. After stirring for 30 minutes, the layers were separated and the aqueous layer was further extracted with 2 × 150 mL of CH₂Cl₂. The combined organic fractions were dried (Na₂SO₄) and concentrated *in vacuo*. To the resulting yellow oil were added 50 mL of EtOAc and 11 mL of diethanolamine, and the resulting suspension was stirred vigorously for 3 hours. The reaction mixture was then diluted with 200 mL of EtOAc and washed with 3 × 200 mL of 10:1 H₂O:brine and 200 mL of brine. The aqueous layers were back extracted with 200 mL of EtOAc, the combined organic fractions were dried (Na₂SO₄) and concentrated *in vacuo*. HPLC analysis of the unpurified reaction mixture (Zorbax SiO₂ column, 30% EtOAc in hexanes, 1.0 mL/min) shows a diastereomeric ratio of 12:1 [*t*_R(major) = 18.3 min; *t*_R(minor) = 16.2 min]. Flash column chromatography (5% → 50% EtOAc/hexanes; linear gradient) provided 1.61 g (3.27 mmol, 69% from aldehyde *ent*-24) of the title compound as a single diastereomer. [α]_D²³ +35.6 (c 0.32, CH₂Cl₂); IR (neat) 3472, 2929, 1729, 1514, 1249, 1105, 1105, 834, 777 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.19 (br d, *J* = 9.5 Hz, 1H), 4.52 (t, *J* = 9.5 Hz, 1H), 4.44 (s, 2H), 3.95–3.93 (m, 1H), 3.80 (s, 3H), 3.78 (t, *J* = 3.7 Hz, 1H), 3.33 (br d, *J* = 5.4, 2H), 2.74–2.72 (m, 1H), 2.34 (dd, *J* = 13.2, 5.9 Hz, 1H), 2.20 (dd, *J* = 13.7, 5.9 Hz, 1H), 1.79–1.75 (m, 1H), 1.73 (d, *J* = 1.0 Hz, 3H), 1.28 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.0, 159.0, 139.8, 130.4, 129.3, 124.6,

113.7, 77.7, 75.2, 73.5, 72.9, 70.2, 55.3, 44.7, 43.2, 39.2, 25.8, 18.1, 18.0, 15.4, 11.1, -4.5, -4.8; exact mass calc. for $C_{27}H_{44}O_6Si+H^+$: 493.2985; found: 493.2984 (ES).

4.2.22. 2-(6-((1E)(4S)-5-[(4-Methoxyphenyl)methoxy]-2-methyl-4-(*tert*-butyldimethylsiloxy) pent-1-enyl)(4S,5R,6R)-2,2,5-trimethyl(1,3-dioxan-4-yl)) (2S)-N-methoxy-N-methyl-propanamide—

To a cooled (0 °C) solution of *N,O*-dimethylhydroxylamine•HCl (1.53 g, 15.7 mmol) in 50 mL of CH_2Cl_2 was added neat $AlMe_3$ (1.51 mL, 15.7 mmol) dropwise over 10 minutes. The heterogeneous mixture became homogeneous after stirring for 1 hour at 0 °C, at which point a solution of 1.55 g (3.15 mmol) of lactone **27** in 10 mL of CH_2Cl_2 was added via cannula. The resulting solution was stirred for 16 hours at 0 °C → rt. The reaction was quenched by the slow addition of 100 mL of sat. Rochelle's salt (aq), and stirring until both layers became clear (3 hours). The mixture was diluted with an extra 100 mL of sat. Rochelle's salt (aq) and extracted with 4 × 200 mL of EtOAc. The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. The unpurified oil was diluted with 60 mL of acetone and 30 mL of dimethoxypropane, 80 mg (0.32 mmol) of PPTS was added and the resulting solution was stirred for 2.5 hours at rt. 5 mL of sat. $NaHCO_3$ (aq) was added, and the mixture was poured into 200 mL of H_2O . The product was extracted with 3 × 150 mL of CH_2Cl_2 , dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (20% EtOAc/hexanes) yielded 1.32 g (2.22 mmol, 70% from lactone **27**) of the title compound as a clear, colorless oil. TLC R_f 0.3 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ -7.61 (*c* 0.57, CH_2Cl_2); IR (neat) 2934, 2856, 1664, 1514, 1383, 1249, 1103, 1025, 836 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.27 (br d, *J* = 8.3 Hz, 1H), 4.46 (d, *J* = 10.1 Hz, 1H), 4.42 (d, *J* = 10.1 Hz, 1H), 4.04 (dd, *J* = 10.7, 4.9 Hz, 1H), 3.98 (dd, *J* = 8.8, 7.8 Hz, 1H), 3.95-3.93 (m, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.33 (d, *J* = 4.9 Hz, 2H), 3.19 (br s, 3H), 3.16 (br s, 1H), 2.31 (dd, *J* = 13.7, 5.6 Hz, 1H), 2.14 (dd, *J* = 13.7, 6.3 Hz, 1H), 1.79-1.75 (m, 1H), 1.72 (d, *J* = 1.5 Hz, 3H), 1.29 (s, 3H), 1.28 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 137.0, 130.5, 129.1, 127.7, 113.6, 100.7, 74.2, 72.9, 71.5, 70.5, 70.4, 61.2, 55.2, 45.2, 38.3, 35.1, 32.0, 25.9, 24.4, 24.0, 18.1, 17.6, 13.2, 11.2, -4.5, -4.8; exact mass calc. for $C_{32}H_{55}NO_7Si+H^+$: 594.3826; found 594.3834 (ES).

4.2.23. 2-(6-((1E)(4S)-5-[(4-Methoxyphenyl)methoxy]-2-methyl-4-(*tert*-butyldimethylsiloxy) pent-1-enyl)(4S,5R,6R)-2,2,5-trimethyl(1,3-dioxan-4-yl)) (2S)propanal (28**)**—

A solution of 180 mg (0.303 mmol) of the Weinreb amide in 20 mL of EtOAc was chilled to 0 °C and 300 μ L (1.0 M, 0.300 mmol) of a solution of $LiAlH_4$ in Et_2O was added via syringe. The mixture was warmed to rt, and followed closely by TLC analysis (30% EtOAc/hexanes). After 30 minutes, an additional 50 μ L of the $LiAlH_4$ solution was added, and then 15 minutes later an additional 15 μ L was added. After a total of 60 minutes, TLC analysis showed complete reaction and 5 mL of EtOAc was added. 50 mL of sat. aqueous Rochelle's salt was added and the mixture was stirred vigorously for 3 hours. The aqueous layer was then extracted with 3 × 100 mL of CH_2Cl_2 . The combined organic fractions were dried (Na_2SO_4), filtered and concentrated *in vacuo* to provide 160 mg (0.299 mmol, 99%) of the title compound as a clear, colorless oil of sufficient purity to be used directly. TLC R_f 0.7 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ -10.6 (*c* 0.66, CH_2Cl_2); IR (neat) 2933, 2856, 1732, 1613, 1514, 1380, 1249, 1100, 836 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) δ 9.67 (d, *J* = 3.4 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 5.25 (br d, *J* = 8.3, 1H), 4.46 (d, *J* = 12.4 Hz, 1H), 4.43 (d, *J* = 12.4 Hz, 1H), 4.05-4.02 (m, 2H), 3.96-3.92 (m, 1H), 3.80 (s, 3H), 2.53-2.46 (m, 1H), 2.32 (dd, *J* = 13.7, 5.9 Hz, 1H), 2.14 (dd, *J* = 13.2, 6.8 Hz, 1H), 1.83-1.76 (m, 1H), 1.73 (d, *J* = 1.0 Hz, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz,

CDCl₃) δ 204.5, 159.1, 137.5, 130.5, 129.2, 127.3, 113.7, 101.0, 74.1, 72.9, 71.4, 70.2, 70.0, 55.2, 46.1, 45.2, 38.9, 25.9, 24.5, 23.7, 18.2, 17.6, 11.1, 10.3, -4.5, -4.8.

4.2.24. Methyl 6-(6-((1E)(4S)-5-[(4-methoxyphenyl)methoxy]-2-methyl-4-(*tert*-butyldimethylsiloxy)pent-1-enyl)(4R,5R,6R)-2,2,5-trimethyl(1,3-dioxan-4-yl)) (5S,6R)-5-hydroxy-3-oxoheptanoate (29)—A solution of 807 mg (1.51 mmol) of aldehyde **28** in 60 mL of toluene was chilled to an internal temperature of -90 °C in a toluene/N₂(l) bath. A solution of 1.18 g (4.53 mmol) of freshly prepared Chan's Diene **9⁶** in 5 mL of toluene was added via cannula. 230 μ L (1.81 mmol) of neat BF₃•OEt₂ was then added over 5 minutes, and the mixture was stirred for 45 minutes, maintaining the internal temperature below -85 °C. 5 mL of sat. NaHCO₃(aq) was then added and the mixture was warmed to rt. The mixture was diluted with 100 mL of EtOAc, then washed with 100 mL of H₂O and 100 mL of brine. The aqueous layers were back extracted with 100 mL of EtOAc, the combined organic extracts were dried (Na₂SO₄) and the solvent was removed *in vacuo*. Flash column chromatography (10% → 50% EtOAc/hexanes; linear gradient) yielded 869 mg (1.34 mmol, 88%) of the title compound as a clear colorless oil. TLC R_f 0.1 (30% EtOAc/hexanes); [α]_D²³ -33.9 (c 0.84, CH₂Cl₂); IR (neat) 3496, 2932, 2856, 1750, 1716, 1514, 1249, 1089, 836 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.24 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.24 (br d, *J* = 8.8 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.30 (br d, *J* = 10.3 Hz, 1H), 4.00 (t, *J* = 8.3 Hz, 1H), 3.98-3.92 (m, 1H), 3.87 (dd, *J* = 10.7, 4.4 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.53 (d, *J* = 1.5 Hz, 2H), 3.33 (d, *J* = 5.4 Hz, 2H), 2.80 (dd, *J* = 16.4, 10.5 Hz, 1H), 2.58 (dd, *J* = 16.4, 2.2 Hz, 1H), 2.31 (dd, *J* = 13.7, 5.9 Hz, 1H), 2.14 (dd, *J* = 13.7, 6.8 Hz, 1H), 1.80-1.74 (m, 2H), 1.72 (s, 3H), 1.39 (s, 3H₂), 1.38 (s, 3H), 0.87 (s, 9H), 0.81 (t, *J* = 6.8 Hz, 6H), 0.03 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 203.2, 167.5, 159.0, 137.3, 130.5, 129.2, 127.5, 113.7, 100.9, 74.1, 72.9, 71.5, 70.4, 70.3, 68.6, 55.2, 52.4, 49.8, 46.7, 45.2, 39.1, 37.4, 25.9, 25.0, 24.1, 18.2, 14.6, 11.1, 10.5, -4.5, -4.8; exact mass calc. for C₃₅H₅₈O₉Si+Na: 673.3748; found: 673.3755 (FAB).

4.2.25. Methyl 2-(6-((3E)(6S,1R,2R)-2-methoxy-7-[(4-methoxyphenyl)methoxy]-1,4-di-methyl- 6-(*tert*-butyldimethylsiloxy)hept-3-enyl)(2S,4S,5S,6S)-2-methoxy-5-methyl-4-(*tert*-butyldimethylsiloxy)-2H-3,4,5,6-tetrahydropyran-2-yl)acetate (32)—230 μ L (1.97 mmol) of 2,6-Lutidine was added to a cooled (-78 °C) solution of 826 mg (1.27 mmol) of alcohol **29** in 28 mL of CH₂Cl₂. A solution of 438 μ L (1.91 mmol) of TBSOTf in 2.0 mL of CH₂Cl₂ was then added via syringe over 5 minutes. After stirring for an additional 15 minutes at -78 °C, 5 mL of sat. NaHCO₃ (aq) was added and the mixture was allowed to warm to rt. An additional 100 mL of CH₂Cl₂ was added, and then the organic layer was washed with 100 mL of H₂O, 100 mL of 1 M NaHSO₄ (aq) and 100 mL of brine. The aqueous layers were back extracted with 100 mL of CH₂Cl₂, the combined organic layers were dried (Na₂SO₄) and the solvent was removed *in vacuo*. Flash column chromatography (0% → 40% EtOAc/hexanes; linear gradient) to yield 434 mg (0.567 mmol) β -ketoester **30** and 401 mg (0.543 mmol) lactol **31** (combined yield: 88%). The β -ketoester and lactol obtained from the previous step (1.11 mmol total) were diluted with 60 mL of MeOH and 30 mg (0.11 mmol) of PPTS was added. After stirring for 10 hours at rt, the reaction was quenched by the addition of 2 mL of sat. NaHCO₃(aq). The mixture was diluted with 200 mL of H₂O, and the desired product was extracted with 7 × 200 mL of CH₂Cl₂. The extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo* to yield 745 mg (1.01 mmol, 91%) of the desired alcohol of sufficient purity for the next step. To a solution of 745 mg (1.01 mmol) of this alcohol in 60 mL of CH₂Cl₂ was added 4.54 mL (20.2 mmol) of 2,6-di-*tert*-butylpyridine followed by 1.14 mL (10.1 mmol) of methyl triflate. After stirring for 20 hours at rt, the reaction was quenched by the addition of 5 mL of MeOH. The reaction solution was then poured in to 200 mL of sat. NaHCO₃(aq) and extracted with 3 × 200 mL of CH₂Cl₂. The combined organic extracts

were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (2% $\rightarrow$ 14% EtOAc/hexanes; linear gradient; 0.2% Et_3N added during column packing) yielded 303 mg of the title compound, as well as 151 mg of a 2:1 mixture of the title compound and the derived dihydropyran. This mixture was converted into pure **32** by stirring with PPTS (5 mg) in MeOH (10 mL) for 10 hours. Overall yield: 474 mg (0.800 mmol, 63%). TLC R_f 0.7 (20% EtOAc/hexanes); $[\alpha]_D^{23}$ -15.9 (c 0.36, CH_2Cl_2); IR (neat) 2954, 2930, 2856, 1745, 1514, 1463, 1250, 1083, 836 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) 7.24 (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 4.95 (br d, $J = 8.8$ Hz, 1H), 4.44 (s, 2H), 4.00 (m, 1H), 3.88 (t, 9.8 Hz, 1H), 3.80 (s, 3H), 3.72 (dd, $J = 10.7$, 2.0 Hz, 1H), 3.69-3.64 (m, 1H), 3.66 (s, 3H), 3.39 (dd, $J = 9.8$, 4.6 Hz, 1H), 3.33 (dd, $J = 9.8$, 6.3 Hz, 1H), 3.24 (s, 3H), 3.13 (s, 3H), 2.66 (d, $J = 13.2$ Hz, 1H), 2.63 (d, $J = 13.7$ Hz, 1H), 2.34 (dd, $J = 13.7$, 6.8 Hz, 1H), 2.25 (dd, $J = 13.7$, 4.9 Hz, 1H), 2.12 (dd, $J = 12.9$, 4.6 Hz, 1H), 1.72 (d, $J = 1.0$ Hz, 3H), 1.69-1.64 (m, 2H), 1.43-1.37 (m, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.84 (d, $J = 6.2$ Hz, 3H), 0.64 (d, $J = 6.8$ Hz, 3H), 0.06 (s, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.9, 159.0, 137.6, 130.5, 129.2, 128.5, 113.6, 98.8, 77.2, 73.8, 73.0, 71.7, 70.6, 70.6, 55.3, 55.2, 51.5, 47.6, 45.1, 43.3, 42.0, 39.9, 38.6, 25.9, 18.1, 18.0, 17.8, 12.4, 8.7, -4.1 , -4.4 , -4.7 ; exact mass calcd for $\text{C}_{40}\text{H}_{72}\text{O}_9\text{Si}_2+\text{Na}$: 775.4613; found: 775.4605 (FAB).

4.2.26. Methyl-2-(6-((3E)(6S,1R,2R)-6-hydroxy-2-methoxy-7-[(4-methoxyphenyl)methoxy]-1,4-dimethylhept-3-enyl)(2S,4S,5S)-2-methoxy-5-methyl-4-(tert-butyldimethylsilyl-oxy)perhydro-2H-pyran-2-yl)acetate—To a solution of 61.2 mg (0.081 mmol) of **32** in 1.6 mL of THF was added 0.49 mL (0.486 mmol, 1.0 M in THF) of TBAF at rt. After stirring for 40 min, the reaction was quenched with 1.0 mL of sat. $\text{NH}_4\text{Cl}(\text{aq})$ solution and extracted with 3×10 mL of EtOAc. The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (linear gradient, 40 $\rightarrow$ 80% EtOAc/hexanes) afforded 36.5 mg (0.058 mmol, 71%) of the title compound as clear, colorless oil, along with 4.0 mg (7%) of starting material and 6.5 mg (15%) of bis-desilylated product. TLC R_f 0.6 (60% EtOAc/hexanes); $[\alpha]_D^{23}$ -24.6 (c 0.23, CH_2Cl_2); IR (CH_2Cl_2 , film) 3477, 2930, 2856, 1738, 1612, 1517, 1464, 1438, 1375, 1317, 1248, 1080, 1037, 837, 774 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.29 (m, 2H), 6.91 (d, $J = 8.8$ Hz, 2H), 5.01 (d, $J = 9.8$ Hz, 1H), 4.51 (s, 2H), 4.00-3.97 (m, 1H), 3.92 (dd, $J = 9.8$ Hz, 1H), 3.83 (s, 3H), 3.75 (dd, $J = 1.45$, 9.3 Hz, 1H), 3.69 (s, 3H), 3.72-3.67 (m, 1H), 3.51 (dd, $J = 3.4$, 9.3 Hz, 1H), 3.36 (dd, $J = 7.3$, 9.3 Hz, 1H), 3.26 (s, 3H), 3.16 (s, 3H), 2.69 (d, $J = 13.7$ Hz, 1H), 2.65 (d, $J = 13.2$ Hz, 1H), 2.30-2.25 (m, 2H), 2.15 (dd, $J = 4.9$, 12.7 Hz, 1H), 1.72 (m, 2H), 1.60 (s, 3H), 1.43 (m, 1H), 0.91 (s, 9H), 0.87 (d, $J = 6.3$ Hz, 3H), 0.68 (d, $J = 6.8$ Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.1, 159.5, 137.4, 130.2, 129.6, 128.8, 114.1, 99.0, 77.4, 74.0, 73.3, 71.9, 70.9, 68.8, 55.5, 51.8, 47.9, 44.0, 43.5, 42.2, 40.1, 38.8, 26.1, 18.3, 17.4, 12.6, 8.9, -3.8 , -4.5 ; exact mass calc. for $\text{C}_{34}\text{H}_{58}\text{O}_9\text{Si}$ $[\text{M}+\text{NH}_4]^+$: 656.4194; found: 656.4197 (ES).

4.2.27. 2-(6-((3E)(6S,1R,2R)-2-Methoxy-7-[(4-methoxyphenyl)methoxy]-1,4-dimethyl-6-(methylsulfonyloxy)hept-3-enyl)(2S,4S,5S)-2-methoxy-5-methyl-4-(tert-butyldi-methylsilyloxy)perhydro-2H-pyran-2-yl)acetic acid (34)—To a solution of the 34.0 mg (0.053 mmol) of alcohol in 0.53 mL of CH_2Cl_2 at 0°C was added 0.010 mL (0.069 mmol) of triethylamine, 2.0 mg (0.017 mmol) of DMAP, and 0.005 mL (0.069 mmol) of mesyl chloride. After stirring for 4 h at 0°C , the reaction was quenched with 1.0 mL of sat. $\text{NH}_4\text{Cl}(\text{aq})$ and extracted with 3×10 mL of EtOAc. The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The clear oil residue was directly used in the next reaction without further purification. To a solution of mesylate in 2.2 mL of THF and 2.2 mL of MeOH was added 1.1 mL of 1.0 M solution of $\text{LiOH}(\text{aq})$ at rt. After vigorously stirring the resulting mixture overnight, the reaction was quenched with 20 mL of sat. $\text{NH}_4\text{Cl}(\text{aq})$ solution and extracted with 20 mL of EtOAc. The

aqueous layer was acidified to pH <2 with 1 M HCl and back extracted with 3 × 20 mL of EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5% MeOH/CH₂Cl₂) afforded 36.8 mg (0.050 mmol, 95%) of desired product **34** as a clear, colorless oil. TLC R_f 0.5 (40% EtOAc/hexanes); [α]_D²³ –19.6 (c 0.95, CH₂Cl₂); IR (CH₂Cl₂, film) 3145, 2924, 2860, 1735, 1712, 1613, 1514, 1464, 1360, 1250, 1174, 1081, 1035, 918, 837, 776 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.23 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.03 (d, *J* = 9.2 Hz, 1H), 4.96–4.92 (m, 1H), 4.47 (s, 2H), 3.85 (dd, *J* = 9.5 Hz, 1H), 3.80 (s, 3H), 3.70–3.64 (m, 2H), 3.56 (d, *J* = 5.1 Hz, 2H), 3.25 (s, 3H), 3.15 (s, 3H), 3.01 (s, 3H), 2.79 (d, *J* = 14.3 Hz, 1H), 2.62 (d, *J* = 14.3 Hz, 1H), 2.51 (dd, *J* = 7.0, 13.9 Hz, 1H), 2.41 (dd, *J* = 6.6, 14.3 Hz, 1H), 2.11 (dd, *J* = 4.8, 13.2 Hz, 1H), 1.74 (s, 3H), 1.76–1.68 (m, 1H), 1.62 (dd, *J* = 11.0, 12.8 Hz, 1H), 0.88 (s, 9H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.67 (d, *J* = 7.3 Hz, 3H), 0.05 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 172.3, 159.6, 135.5, 130.2, 129.7, 129.6, 114.2, 99.1, 80.3, 77.5, 73.3, 72.8, 71.2, 70.4, 55.8, 55.5, 48.4, 43.2, 42.7, 42.2, 40.2, 39.0, 38.7, 26.1, 18.2, 17.2, 12.6, 9.2, –3.9, –4.5; exact mass calc. for C₃₄H₅₈O₁₁SSi [M+NH₄]⁺: 720.3813; found: 720.3806 (ES).

4.2.28. (1S,11S,12S,13S,5R,9R,10R)-1,9-Dimethoxy-5-[(4-methoxyphenyl)methoxy]-7,10,12-trimethyl-4,15-dioxo-13-(tert-butyl)dimethylsilyloxy)bicyclo[9.3.1]pentadec-7-en-3-one (35)—To a solution of 36.8 mg (0.052 mmol) of acid **34** in 35.0 mL of toluene was added 102 mg (0.310 mmol) of freshly grounded cesium carbonate and 34.4 mg (0.130 mmol) of 18-crown-6. The resulting mixture was heated to reflux (110 °C) for 5 h then gradually cooled to rt. The reaction was quenched with 50 mL of sat. NH₄Cl(aq) and extracted with 3 × 100 mL of EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (neutralized column with 20% EtOAc/hexanes + 0.1 % triethylamine; eluted with 20% EtOAc/hexanes) afforded 21.2 mg (0.035 mmol, 67%) of desired product **35** as a white amorphous solid. TLC R_f 0.7 (40% EtOAc/hexanes); [α]_D²³ –17.5 (c 0.35, CH₂Cl₂); IR (CH₂Cl₂, film) 2931, 2850, 1729, 1612, 1514, 1462, 1361, 1303, 1250, 1168, 1140, 1075, 1040, 1005, 889, 835, 774 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.25 (d, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.29 (d, *J* = 9.3 Hz, 1H), 5.29 (m, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.44 (d, *J* = 11.7 Hz, 1H), 3.89 (dd, *J* = 2.4, 9.8 Hz, 1H), 3.81 (s, 3H), 3.51 (m, 4H), 3.29 (s, 3H), 3.22 (s, 3H), 2.60 (d, *J* = 12.7 Hz, 1H), 2.44 (d, *J* = 12.2 Hz, 1H), 2.41 (dd, *J* = 12.2, 13.2 Hz, 1H), 2.25 (d, *J* = 13.2 Hz, 1H), 2.19 (m, 1H), 2.12 (dd, *J* = 4.4, 13.2 Hz, 1H), 1.64 (s, 3H), 1.48 (m, 1H), 1.25 (m, 1H), 1.00 (d, *J* = 7.3 Hz, 3H), 0.89 (m, 12H), 0.07 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 169.0, 159.5, 133.5, 130.4, 129.5, 126.9, 114.0, 110.3, 80.6, 77.4, 76.7, 72.9, 71.7, 70.3, 69.8, 55.5, 55.2, 51.6, 43.7, 42.7, 41.1, 40.5, 26.1, 26.0, 18.2, 15.8, 13.1, –3.9, –4.6; exact mass calc. for C₃₃H₅₄O₈Si [M+Na]⁺: 629.3486; found: 629.3484 (ES).

4.2.29. Phenylmethyl-(5S,4R)-4-(methoxycarbonyl)-2,2,5-trimethyl-1,3-oxazolidine-3-carboxylate (37)—To a suspension of 5.0 g (42 mmol) of D-Threonine in 50 mL of acetonitrile was slowly added a solution of 50 mL (50 mmol) of 1 M NaOH(aq) at room temperature. The reaction mixture was cooled to 0 °C and then 6.0 mL (42 mmol) of benzoyl chloride was added. Solid Na₂CO₃ was used to maintain reaction pH at 10. Once the pH level had stabilized, another 0.60 mL of benzoyl chloride was added. The reaction was allowed to warm gradually overnight. After 12 h of stirring at room temperature, the reaction was concentrated *in vacuo* to remove as much solvent as possible. The residual oil was acidified to pH ~2 with 6.0 M HCl(aq). The aqueous solution was extracted with 3 × 100 mL of EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The clear oil residue was used directly for the next reaction without further purification. To a solution of the threonine acid in 39 mL of dimethylformamide was

added solid 6.4 g (46 mmol) of K_2CO_3 . The reaction mixture was cooled to 0 °C after which 5.2 mL (84 mmol) of methyl iodide was added. After 30 min of stirring at 0 °C, the ice bath was removed and the reaction mixture was allowed to warm gradually overnight. After 12 h of stirring at room temperature, the solid K_2CO_3 was filtered and the filtrate was diluted with EtOAc. The organic solution was washed with H_2O and brine, then dried over Na_2SO_4 and filtered. The volatile solvents were removed *in vacuo*, and dried under reduced pressure to afford a white solid. The solid was used directly for the next step without further purification. To a solution of threonine methyl ester in 140 mL of benzene was added 10 mL (84 mmol) of dimethoxypropane and 112 mg (0.59 mmol) of *p*-toluenesulfonic acid monohydrate at room temperature. The reaction mixture was stirred for 12 h. The reaction flask was refitted with a 24/40 joint short-path distillation head and methanol was azeotropically removed by slow distillation at 70–80 °C over 4 h to remove about 70 mL of reaction solution. After allowing the remaining mixture to cool to room temperature, the reaction was quenched with saturated $NaHCO_3$ solution. The aqueous layer was back extracted with 2 x 100 mL of Et_2O . The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The clear, colorless oil was dried under reduced pressure overnight to afford 12 g (39.1 mmol, 93%, 3 steps) of the title compound. ^1H NMR indicated that the oil was purely desired product and did not need further purification. $[\alpha]_D^{23} +45.1$ (*c* 0.7, CH_2Cl_2); IR (CH_2Cl_2 , film) 2985, 2954, 1755, 1722, 1712, 1408, 1348, 1258, 1203, 1169, 1129, 1073, 766, 697 cm^{-1} ; ^1H NMR (500 MHz, $DMSO-d_6$, 100 °C) δ 7.37–7.31 (m, 5H); 5.65–5.03 (m, 2H); 4.16 (dq, *J* = 5.9, 6.8 Hz, 1H); 4.01 (d, *J* = 6.8 Hz, 1H); 3.59 (s, 3H); 1.56 (s, 3H); 1.51 (s, 3H); 1.32 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $DMSO-d_6$, 110 °C) δ 169.6, 150.9, 135.8, 127.7, 127.3, 127.0, 94.2, 73.3, 65.9, 65.0, 51.4, 26.3, 23.9; Exact mass calcd. for $C_{16}H_{21}O_5N$ $[M+NH_4]^+$: 325.1420; found: 325.1566 (CI).

4.2.30. Phenylmethyl-(5*S*,4*R*)-4-(*N*-methoxy-*N*-methyl-carbamoyl)-2,2,5-trimethyl-1,3-oxazolidine-3-carboxylate—To a cooled suspension of 0.79 g (8.1 mmol) of *N,O*-dimethylhydroxyamine hydrogen chloride in 50 mL of THF in a flame dried flask under N_2 was added 8.2 mL (2.0 M solution in THF) of isopropylmagnesium chloride. The resulting mixture was stirred at –78 °C for 5 min, then a solution of 1.0 g (3.3 mmol) of ester **37** in 15 mL of THF was added. The reaction was stirred for at –78 °C for an additional 3 min before transferring the reaction flask to a –40 °C bath. After stirring overnight at –40 °C, the reaction was quenched with 50 mL of sat. $NH_4Cl(aq)$ and extracted with 3 x 100 mL of EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to yield 1.0 g (3.07 mmol, 93%) of threonine weinreb amide as a clear, slightly yellow oil. TLC R_f = 0.23 (30% EtOAc/hexanes); $[\alpha]_D^{23} +34.6$ (*c* 0.8, CH_2Cl_2); IR (CH_2Cl_2 , film) 2984, 2940, 2900, 1714, 1674, 1409, 1350, 1269, 1250, 1176, 1120, 1173, 997, 865, 766, 743, 699 cm^{-1} ; ^1H NMR (500 MHz, $DMSO-d_6$, 115 °C) δ 7.39–7.31 (m, 5H); 5.08–5.03 (m, 2H); 4.50 (d, *J* = 6.3 Hz, 1H); 4.12 (dq, *J* = 6.3, 5.9 Hz, 1H); 3.57 (br s, 3H); 3.09 (s, 3H); 1.61 (s, 3H); 1.57 (s, 3H); 1.35 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100.6 MHz, $DMSO-d_6$, 20 °C, mixture of rotamers) δ 170.1, 170.0, 152.9, 151.8, 136.3, 136.1, 129.2, 128.8, 128.7, 128.6, 128.5, 128.3, 128.1, 127.7, 127.1, 95.5, 95.0, 75.0, 74.5, 67.6, 67.5, 65.4, 63.5, 62.9, 61.4, 60.7, 53.7, 32.5, 32.1, 28.1, 26.9, 25.2, 24.1, 19.2, 19.1; Exact mass calcd. for $C_{17}H_{24}N_2O_5$ $[M+H]^+$: 337.1685; found: 337.1763 (ES). Room temperature ^1H and ^{13}C NMR spectra are comparable to those reported in Vuljanic, T.; Kihlberg, J.; Somfai, P. *J. Org. Chem.* **1998**, *63*, 279–286.

4.2.31. Phenylmethyl-(5*S*,4*R*)-4-Acetyl-2,2,5-trimethyl-1,3-oxazolidine-3-carboxylate (36**)**—To a cooled solution (–40 °C) of 12.5 g (37.1 mmol) of the Weinreb amide in 124 mL THF, was slowly added the first portion of methylmagnesium bromide (12.3 mL, 3.0 M solution in Et_2O). After stirring for 1 h at –40 °C, a second portion of methylmagnesium bromide (12.3 mL, 3.0 M solution in Et_2O) was added. The reaction was

allowed to gradually warm to room temperature and stirred overnight. The reaction mixture changed from a cloudy gray suspension to a clear yellow solution. The reaction was quenched with 80 mL of sat. $\text{NH}_4\text{Cl}(\text{aq})$ and extracted with 3×150 mL of EtOAc. The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification *via* flash chromatography (linear gradient, 20 $\rightarrow$ 30% EtOAc/hexane) afforded 7.44 g (25.6 mmol, 69%) of **36** as a clear, slightly yellow oil. TLC R_f = 0.60 (30% EtOAc/hexane); $[\alpha]_D^{23} +33.6$ (c 0.88, CH_2Cl_2); IR (CH_2Cl_2 , film) 2985, 2936, 1714, 1455, 1409, 1349, 1250, 1216, 1126, 1074 cm^{-1} ; ^1H NMR (500 MHz, DMSO-d_6 , 115 $^\circ\text{C}$) δ 7.39-7.32 (m, 5H); 5.08 (s, 2H); 4.11-4.07 (m, 2H); 2.08 (s, 3H); 1.57 (s, 3H); 1.54 (s, 3H); 1.34 (d, J = 5.4 Hz, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6 , 110 $^\circ\text{C}$) δ 204.8, 152.4, 134.0, 129.0, 128.6, 128.4, 95.2, 73.5, 72.4, 67.2, 27.6, 26.9, 25.7, 19.7; Exact mass calcd. for $\text{C}_{16}\text{H}_{21}\text{NO}_4[\text{M}+\text{H}]^+$: 292.1471; found: 292.1549 (ES).

4.2.32. Ethyl (2S,3S)-3-((4S,5R)-2,2,5-trimethyl-3-[benzyloxycarbonyl](1,3-oxazolidin-4-yl))-3-hydroxy-2-methoxybutanoate (38a) and Ethyl (3S,2R)-3-((4S,5R)-2,2,5-trimethyl-3-[benzyloxycarbonyl](1,3-oxazolidin-4-yl))-3-hydroxy-2-methoxybutanoate (38b)—To a cooled solution (0 $^\circ\text{C}$) of 0.07 mL (0.54 mmol) of diisopropylamine in 0.68 mL of THF was added a solution of 0.23 mL (2.2 M) of *n*-BuLi in hexanes. The resulting mixture was stirred for an additional 30 min at 0 $^\circ\text{C}$ and then cooled to -78 $^\circ\text{C}$. To form the enolates, 0.06 mL (0.51 mmol) of ethyl methoxyacetate was added and the reaction mixture was stirred for an addition 30 min at -78 $^\circ\text{C}$ before slow addition of a solution of 100 mg (0.34 mmol) of methyl ketone **36** in 0.20 mL of THF to produce a light yellow mixture. The mixture stirred in a -78 $^\circ\text{C}$ cryocool for 2 days and quenched with sat. $\text{NH}_4\text{Cl}(\text{aq})$. The biphasic mixture was extracted with 3×5 mL of MTBE. The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by Semi-prep HPLC on Zorbax Sil column (20% EtOAc/hexane; 21 mL/min; 268 nm) afforded aldol adducts **38a** (20 mg, 0.068 mmol, 20%) and **38b** (36 mg, 0.121 mmol, 36%). **Minor product (38a)**: $[\alpha]_D^{23} -12.8$ (c 1.0, CHCl_3); IR (CHCl_3 , film) 3349, 2986, 2937, 1741, 1701, 1674, 1457, 1406, 1348, 1212, 1182, 1115, 1091, 1031, 669 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3 , 57 $^\circ\text{C}$) δ 7.38-7.30 (m, 5H); 5.25 (d, J = 12.3 Hz, 1H); 5.12 (d, J = 12.3 Hz, 1H); 4.60-4.55 (m, 1H); 4.21 (q, J = 7.1 Hz, 2H); 3.97 (d, J = 3.3 Hz, 1H); 3.79 (s, 1H); 3.32 (s, 1H); 3.31 (s, 3H); 1.61 (s, 3H); 1.56 (s, 3H); 1.33 (d, J = 6.3 Hz, 3H); 1.28 (t, J = 7.1 Hz, 3H); 1.25 (s, 3H); Exact mass calcd. for $\text{C}_{21}\text{H}_{31}\text{NO}_7[\text{M}+\text{Na}]^+$: 432.2101; found: 432.1998 (FAB). **Major product (38b)**: $[\alpha]_D^{23} +2.7$ (c 1.7, CHCl_3); IR (CHCl_3 , film) 3549, 3497, 2986, 2944, 1749, 1728, 1702, 1454, 1401, 1345, 1256, 1200, 1114, 1092, 1051, 1028 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3 , 57 $^\circ\text{C}$) δ 7.36-7.26 (m, 5H); 5.22 (d, J = 12.3 Hz, 1H); 5.11 (d, J = 12.3 Hz, 1H); 4.56 (q, J = 6.6 Hz, 1H); 4.23-4.18 (m, 3H); 3.85 (s, 1H); 3.39 (s, 3H); 3.02 (s, 1H); 1.62 (s, 3H); 1.57 (s, 3H); 1.35 (d, J = 6.5 Hz, 3H); 1.29 (t, J = 7.1 Hz, 2H); 1.16 (s, 3H); Exact mass calcd. for $\text{C}_{21}\text{H}_{31}\text{NO}_7[\text{M}+\text{Na}]^+$: 432.2101; found: 432.1998 (FAB).

4.2.33. Phenylmethyl-4-[(1R)-1-((2S)-1,4-dioxo-3-oxospiro[4.5]dec-2-yl)-1-hydroxyethyl]-(5S,4R)-2,2,5-trimethyl-1,3-oxazolidine-3-carboxylate (40)—In a flame-dried flask under Ar, a solution of 2.0 mL (14 mmol) of diisopropylamine in 14 mL of THF was cooled to 0 $^\circ\text{C}$. Slowly, 7.0 mL (1.92 M solution in hexane) of *n*-BuLi was added and the reaction mixture was stirred for 15 min. The resulting solution of LDA was cooled to -50 $^\circ\text{C}$, after which a solution of 2.1 g (13.5 mmol) of dioxolanone **39** in 41 mL of THF was slowly added. Reaction mixture turned bright yellow after stirring at -50 $^\circ\text{C}$ for 15 min. The reaction mixture was then cooled to -78 $^\circ\text{C}$, after which a -78 $^\circ\text{C}$ solution of 0.80 g (2.8 mmol) of ketone **36** in 11 mL of THF was added. The reaction was stirred for 2 h while slowly warming to -30 $^\circ\text{C}$ prior to quenching by the addition of 30 mL of sat. $\text{NH}_4\text{Cl}(\text{aq})$. The resulting biphasic mixture was stirred vigorously and then extracted with 3×80 mL of

EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc/hexanes) afforded 0.97 g (10.8 mmol, 80%) of aldol adduct **40** as clear, colorless oil. TLC R_f = 0.23 (2.5% Et₂O/CH₂Cl₂); [α]_D²³ +5.5 (c 0.2, CH₂Cl₂); IR (CH₂Cl₂, film) 3494, 2941, 2867, 1790, 1704, 1454, 1403, 1347, 1267, 1214, 1109, 944, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, 58 °C) δ 7.37-7.32 (m, 5H); 5.20 (d, *J* = 12.2 Hz, 1H); 5.14 (d, *J* = 12.2 Hz, 1H); 4.54-4.52 (m, 1H); 4.38 (s, 1H); 4.16 (d, *J* = 2.4 Hz, 1H); 1.81-1.24 (m, 10H); 1.64 (s, 3H); 1.59 (s, 3H); 1.37 (d, *J* = 6.9 Hz, 3H); 1.24 (s, 3H); ¹³C NMR (100.6 MHz, CDCl₃, 58 °C) δ 171.9, 154.9, 136.3, 130.9, 128.7, 128.4, 111.4, 96.0, 76.6, 74.9, 73.0, 69.3, 67.7, 36.4, 35.7, 29.7, 27.4, 24.6, 23.2, 23.1, 20.5; Exact mass calcd. for C₂₄H₃₃NO₇ [M+H]⁺: 228.2335; found: 228.2351 (ES).

4.2.34. *N*-((2*S*,3*R*,4*R*,5*R*)-4,5-Dihydroxy-2,4-dimethyl-6-oxo(3,4,5-trihydro-2H-pyran-3-yl))(phenylmethoxy) carboxamide (41**)**—To 204 mg (0.46 mmol) of the aldol adduct **40** was added a 4 mL of 60% AcOH(aq). The reaction flask was fitted with a reflux condenser and the reaction mixture was heated to 70 °C. After stirring for 16 h at 70 °C, the reaction was cooled to room temperature. Acetic acid was azeotropically removed with 3 × 35 mL of heptane to afford a white solid. Residual acetic acid was removed by washing with sat. NaHCO₃(aq) and extraction with EtOAc. Purification by flash chromatography (linear gradient, 50 → 60% EtOAc/hexanes) afforded 101 mg (0.33 mmol, 71%) of **41** as a white solid. TLC R_f = 0.27 (60% EtOAc/hexanes); [α]_D²³ -74.8 (c 0.9, CH₂Cl₂); IR (KBr) 3593, 3539, 3426, 3364, 2985, 2933, 1739, 1694, 1525, 1343, 1230, 1127, 1040, 967, 746, 702 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 7.39-7.29 (m, 5H); 5.12 (dd, *J* = 4.0, 12.2 Hz, 2H); 4.73 (dq, *J* = 5.9, 6.2 Hz, 1H); 4.45 (s, 1H); 4.03 (d, *J* = 5.1 Hz, 1H); 1.37 (s, 3H); 1.25 (d, *J* = 6.2 Hz, 3H); ¹³C NMR (100.6 MHz, CD₃OD) δ 174.2, 157.9, 137.1, 128.3, 127.9, 127.6, 73.7, 72.7, 72.9, 66.6, 59.6, 23.5, 14.8; Exact mass calcd. for C₁₅H₁₉NO₆ [M+H]⁺: 310.1291; found: 310.1302 (ES).

4.2.35. *N*-((2*S*,3*R*,4*R*,5*R*)-4-Hydroxy-5-methoxy-2,4-dimethyl-6-oxo(3,4,5-trihydro-2H-pyran-3-yl))(phenylmethoxy)carboxamide—In a flame-dried flask, 500 mg (1.6 mmol) of lactone **41** was dissolved in 81 mL of CH₂Cl₂. While under N₂, 719 mg (4.9 mmol) of Meerwein's reagent (Me₃O•BF₄) was added followed by 1.5 g (7.3 mmol) of 2,6-di-*tert*-butyl-4-methyl pyridine. The reaction mixture was stirred at room temperature for 2 days, after which the reaction was quenched with 80 mL of sat. NaHCO₃. The layers were separated and the aqueous layer was further extracted with 2 × 100 mL of CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford a yellow solid. Purification by trituration with 10 mL of 20% EtOAc/hexanes afforded 429 mg (1.3 mmol, 82%) of the title compound as a fine white powder. The expensive 2,6-di-*tert*-butyl-4-methyl pyridine can be recovered by flash chromatography of mother liquor from trituration. TLC R_f = 0.29 (60% EtOAc/hexanes); [α]_D²³ -26.2 (c 0.8, CH₂Cl₂); IR (CH₂Cl₂, film) 3428, 2995, 2940, 1755, 1711, 1502, 1232, 1205, 1165, 1128, 1043 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.32 (m, 5H); 5.66 (d, *J* = 9.5 Hz, 1H); 5.16 (d, *J* = 12.2 Hz, 1H); 5.10 (d, *J* = 12.1 Hz, 1H); 4.57 (m, 1H); 4.06 (dd, *J* = 4.4, 9.5 Hz, 1H); 3.80 (s, 1H); 3.64 (s, 3H); 2.78 (s, 1H); 1.48 (s, 3H); 1.34 (d, *J* = 6.2 Hz, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ 169.6, 157.2, 136.4, 128.8, 128.6, 128.5, 128.2, 82.0, 74.4, 72.3, 67.4, 60.4, 56.6, 53.7; Exact mass calcd. for C₁₆H₂₁NO₆ [M]⁺: 323.1369; found: 323.1359 (EI).

4.2.36. (2*S*,6*S*,3*R*,4*R*,5*R*)-4-Hydroxy-3-methoxy-4,6-dimethyl-5-[(phenylmethoxy)carbonylamino] perhydro-2H-pyran-2-yl acetate (42**)**—In a flame-dried flask, 200 mg (0.62 mmol) of the lactone methyl ether was dissolved in 3.1 mL of CH₂Cl₂ and cooled to -78 °C under N₂. 2.2 mL (1.0 M in toluene) of a solution of DIBAL-H was added. After stirring at -78 °C for 1 h, 150 μL (1.9 mmol) of pyridine, 83

mg of DMAP in 1.4 mL of CH₂Cl₂, and 234 μ L (2.5 mmol) of acetic anhydride were added sequentially. After stirring at –66 °C overnight, the reaction flask was transferred to a 0 °C bath and stirred for an additional 2 h. The reaction was quenched with 8.0 mL of 1.0 M Rochelle's Salt solution, 2.0 mL of sat. NH₄Cl(aq), and 2.0 mL of EtOAc. The mixture was stirred vigorously for 30 min or until both organic and aqueous layers became clear. The layers were separated and the aqueous layer was further extracted with 3 $\times$ 20 mL of EtOAc. The organic layers were combined, and dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (linear gradient, 40 $\rightarrow$ 50% EtOAc/hexanes) afforded 210 mg (0.58 mmol, 93%) of anomeric acetate **42** in a 9:1 anomeric ratio (based on ¹H NMR spectral analysis) as a clear, colorless oil. TLC R_f = 0.29 (40% EtOAc/hexanes); IR (CH₂Cl₂, film) 3417, 2984, 2939, 1726, 1513, 1331, 1311, 1226, 1102, 1045, 861, 740, 700 cm^{–1}; ¹H NMR (400 MHz, CDCl₃, major anomer) δ 7.38–7.30 (m, 5H); 5.78 (s, 1H); 5.67 (d, *J* = 10.6 Hz, 1H); 5.17 (d, *J* = 12.1 Hz, 1H); 5.06 (d, *J* = 12.1 Hz, 1H); 3.89 (dq, *J* = 1.5, 6.2 Hz, 1H); 3.62 (s, 3H); 3.24 (s, 1H); 2.16 (s, 3H); 1.41 (s, 3H); 1.21 (d, *J* = 6.2 Hz, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ 169.2, 157.3, 136.7, 128.7, 128.4, 128.2, 92.8, 84.0, 71.3, 70.1, 67.2, 62.8, 58.7, 23.2, 21.3, 17.1; Exact mass calcd. for C₁₈H₂₅NO₇ [M+NH₄]⁺: 385.1975; found 385.1964 (CI).

4.2.37. (5*S*,1*R*,2*R*,6*R*)-7-Aza-2-methoxy-1,5-dimethyl-4,9-dioxo-3-(2,2,2-Trichloro-1-iminoethoxy)bicyclo [4.3.0]nonan-8-one (43**)**—In a flame-dried flask, 12 mg (0.033 mmol) of a mixture of anomeric acetates **42** was dissolved in 0.40 mL of THF and cooled to 0 °C under N₂. After stirring for 30 min at 0 °C, the reaction mixture was warmed to room temperature and stirred for 2 h. After the mixture turned into yellow suspension, the reaction was quenched with 10 mg of solid NH₄Cl and concentrated *in vacuo*. To ensure complete quenching, the resulting oil was further diluted with 10 mL of wet CHCl₃ and concentrated *in vacuo*. In a flame-dried flask, the unpurified lactol was dissolved in 0.2 mL of trichloroacetonitrile and 0.4 mL of CH₂Cl₂ at room temperature. Dropwise, 5 μ L (0.033 mmol) DBU was added and the reaction mixture immediately darkened to a red-brown color after 10 min of stirring. After stirring at room temperature for 1.5 h, the reaction mixture was concentrated *in vacuo*. The reaction mixture must be purified immediately after the reaction to avoid product decomposition. Purification by flash chromatography (linear gradient, 60 $\rightarrow$ 100% EtOAc/hexanes, each batch of eluent contained 1 vol% Et₃N) afforded 6.1 mg (0.017 mmol, 51%) of trichloroacetimidate **43** as a yellow solid. TLC R_f = 0.21 (80% EtOAc/hexanes); [α]_D²³ –17.2 (*c* 0.2, CH₂Cl₂); IR (CH₂Cl₂, film) 3303, 2933, 1749, 1713, 1667, 1631, 1374, 1266, 1107, 1050, 974, 912, 794, 640 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) δ 8.71 (s, 1H); 6.21 (d, *J* = 6.2 Hz, 1H); 5.45 (br s, 1H); 4.11 (dq, *J* = 2.2, 6.2 Hz, 1H); 3.61 (d, *J* = 5.9 Hz, 1H); 3.59 (s, 3H); 3.47 (d, *J* = 1.5 Hz, 1H); 1.64 (s, 1H); 1.21 (d, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ 160.7, 157.8, 98.9, 91.2, 81.6, 80.2, 66.1, 61.1, 61.0, 23.5, 15.7.

4.2.38. *N*-((2*S*,3*S*,4*R*,5*R*)-4-Hydroxy-5-methoxy-2,4-dimethyl-6-phenylthio-perhydro-2H-pyran-3-yl)(phenylmethoxy)carboxamide—To a solution of 0.33 g (0.90 mmol) of anomeric acetates **42** in 3.6 mL of CH₂Cl₂ was added 0.19 mL (1.80 mmol) of thiophenol and 0.34 mL (2.70 mmol) of BF₃•OEt₂ at 0 °C. The resulting solution was stirred overnight and gradually warmed to room temperature. The reaction was quenched with 10 mL of sat. NaHCO₃(aq) and extracted with 3 $\times$ 30 mL of EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. Purification by flash chromatography (30% $\rightarrow$ 40% EtOAc/Hexane) afforded 0.30 g (0.73 mmol, 81%) of the title compound as a 1:1 mixture of anomers. IR (CH₂Cl₂, film) 3564, 3418, 2982, 2937, 2834, 1731, 1714, 1514, 1504, 1454, 1316, 1226, 1090, 736, 693 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) **Anomer α** : δ 7.38 (m, 10H); 5.54 (s, 1H); 5.19 (d, *J* = 12.4 Hz, 1H); 5.08 (d, *J* = 12.1 Hz, 1H); 4.48 (dq, *J* = 1.5, 6.2 Hz, 1H); 3.67 (d, *J* = 10.6 Hz, 1H); 3.43 (s, 3H); 3.24 (s,

1H); 1.56 (s, 3H); 1.21 (d, $J = 6.2$ Hz, 3H); **Anomer β** : δ 7.38 (m, 10H); 5.78 (d, $J = 10.6$ Hz, 1H); 5.19 (d, $J = 12.1$ Hz, 1H); 5.07 (d, $J = 12.1$ Hz, 1H); 4.87 (d, $J = 1.1$ Hz, 1H); 3.79 (dq, $J = 1.5, 6.2$ Hz, 1H); 3.69 (s, 3H); 3.63 (d, $J = 10.6$ Hz, 1H); 3.29 (s, 1H); 1.37 (s, 3H); 1.23 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100.6 MHz, CD_3Cl_3) **Anomer α** : δ 157.2, 136.8, 135.5, 131.4, 129.4, 128.8, 128.39, 128.38, 127.8, 85.5, 84.8, 68.7, 67.1, 66.6, 59.3, 59.0, 24.1, 17.4; **Anomer β** : δ 157.5, 136.6, 135.1, 131.3, 129.3, 128.7, 128.4, 128.2, 127.7, 87.7, 86.4, 73.7, 70.6, 67.2, 63.6, 58.9, 23.6, 17.8; Exact mass calcd. for $\text{C}_{22}\text{H}_{27}\text{NSO}_5$ $[\text{M}+\text{H}]^+$: 418.1610; found: 418.1688 (ES).

4.2.39. (5S,1R,2R,6R)-7-aza-2-methoxy-1,5-dimethyl-4,9-dioxa-3-phenylthio-bicyclo[4.3.0]nonan-8-one (44)—To a suspension of 101 mg (4.20 mmol) of neat NaH in 17 mL of THF was added a solution of 0.70 g (1.68 mmol) of the thioglycosides in 17 mL THF at 0 °C. The reaction was stirred overnight while gradually warmed to room temperature. The reaction was quenched with 890 mg of solid NH_4Cl and 0.096 mL of glacial acetic acid. The resulting mixture was diluted with CH_3Cl and filtered through a fritted funnel to remove solid NH_4Cl . The filtrate was concentrated *in vacuo* and then triturated with 20% EtOAc/hexanes for 10 min. Filtration of the mixture afforded a solid enriched in one anomer. The filtrate was concentrated *in vacuo* and then purified by flash chromatography (10% acetone/ CH_2Cl_2) to afford a colorless oil enriched in the other anomer. The isolated solid and oil gave a combined yield of 0.50 g (1.63 mmol, 97%). IR (CH_2Cl_2 , film) 3270, 2983, 2933, 2873, 2248, 1760, 1584, 1481, 1440, 1385, 1306, 1263, 1219, 1122, 1081, 1060, 1024, 972, 911, 734, 692, 658 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) **Anomer α** : δ 7.38 (m, 5H); 6.48 (s, 1H); 5.29 (d, $J = 8.1$ Hz, 1H); 4.04 (dq, $J = 1.8, 6.6$ Hz, 1H); 3.67 (s, 3H); 3.41 (d, $J = 1.8$ Hz, 1H); 3.28 (d, $J = 8.1$ Hz, 1H); 1.59 (s, 3H); 1.14 (d, $J = 6.6$ Hz, 3H); **Anomer β** : δ 7.39 (m, 5H); 6.11 (s, 1H); 4.62 (d, $J = 1.1$ Hz, 1H); 3.66 (s, 3H); 3.60 (dq, $J = 2.2, 6.6$ Hz, 1H); 3.45 (d, $J = 2.2$ Hz, 1H); 3.35 (s, 1H); 1.52 (s, 3H); 1.38 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) **Anomer α** : δ 159.0, 132.1, 131.6, 129.2, 127.8, 86.7, 82.6, 81.4, 64.8, 62.2, 61.2, 23.8, 15.8; **Anomer β** : δ 159.5, 135.4, 131.4, 129.2, 127.7, 87.3, 82.8, 81.6, 70.7, 63.6, 60.8, 23.0, 18.1; Exact mass calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 310.1113; found: 310.1115 (ES).

4.2.40. (5S,1R,2R,6R)-7-Aza-2-methoxy-1,5-dimethyl-4,9-dioxa-3-phenylthio-7-(1,1,2,2-tetramethyl-1-silapropyl)bicyclo[4.3.0]nonan-8-one (45)—To a solution of 10.0 mg (0.032 mmol) of thioglycosides **44** in 0.11 mL of CH_2Cl_2 was added 0.010 mL (0.083 mmol) of 2,6-lutidine and 0.015 mL (0.064 mmol) of TBSOTf at 0 °C. The reaction was stirred for 1 h at 0 °C and then the reaction was warmed to room temperature. After an additional 5 h of stirring, the reaction was quenched with 5.0 mL solution of sat. $\text{NaHCO}_3(\text{aq})$ and extracted with 3×10 mL of EtOAc. The combined organic layer were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc/hexane) afforded 12.6 mg (0.029 mmol, 92% yield) of a mixture of thioglycoside **45**. **Anomer α** : $[\alpha]_{\text{D}}^{23} -213.5$ (c 0.8, CH_2Cl_2); IR (CH_2Cl_2 , film) 2934, 2857, 1728, 1584, 1477, 1440, 1366, 1249, 1210, 1108, 1083, 1024, 838, 805, 689 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.52-7.49 (m, 2H); 7.32-7.25 (m, 3H); 5.28 (d, $J = 8.1$ Hz, 1H); 4.05 (dq, $J = 2.6, 6.6$ Hz, 1H); 3.65 (s, 3H); 3.41 (d, $J = 2.6$ Hz, 1H); 3.28 (d, $J = 8.1$ Hz, 1H); 1.55 (s, 3H); 1.18 (d, $J = 6.6$ Hz, 3H); 1.02 (s, 9H); 0.39 (s, 3H); 0.20 (s, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 161.2, 134.2, 132.1, 129.1, 127.7, 86.9, 82.7, 81.7, 66.5, 65.1, 62.0, 27.9, 23.0, 20.4, 17.5, -3.6, -3.8; Exact mass calcd. for $\text{C}_{21}\text{H}_{33}\text{NO}_4\text{SSi}$ $[\text{M}+\text{H}]^+$: 424.1978; found: 424.1976 (ES). **Anomer β** : $[\alpha]_{\text{D}}^{23} +70.5$ (c 1.0, CH_2Cl_2); IR (CH_2Cl_2 , film) 2941, 2849, 1726, 1585, 1473, 1443, 1367, 1251, 1200, 1119, 1068, 1023, 835, 805, 785, 739, 640 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.52 (d, $J = 7.3$ Hz, 2H); 7.30-7.26 (m, 3H); 5.48 (d, $J = 5.1$ Hz, 1H); 4.11 (dq, $J = 5.1, 7.0$ Hz, 1H); 3.70 (d, $J = 5.1$ Hz, 1H); 3.58 (d, $J = 5.1$ Hz, 1H); 3.56 (s, 3H); 1.52 (s, 3H); 1.42 (d, $J = 7.0$ Hz, 3H); 1.01

(s, 9H); 0.41 (s, 3H); 0.19 (s, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 161.1, 136.9, 131.0, 129.1, 127.1, 85.1, 80.4, 79.8, 70.8, 63.7, 61.0, 27.9, 27.6, 25.9, 20.3, 17.1, -4.0, -4.1; Exact mass calcd. for $\text{C}_{21}\text{H}_{33}\text{NO}_4\text{SSi}$ $[\text{M}+\text{H}]^+$: 424.1978; found: 424.1973 (ES).

4.2.41. (2S)-2-Ethynyl-1,4-dioxaspiro[4.5]decane (51)—A solution of 1.28 g (3.75 mmol) of **49** in 2 mL of THF was added dropwise via syringe to a mixture of 949 mg (4.13 mmol) of KIO_4 and 37 mg (0.370 mmol) of KHCO_3 in 6 mL of H_2O . The resulting slurry was stirred vigorously for 3 h at rt. The mixture was then filtered, and the filter cake was rinsed with 16 mL of EtOAc and 6 mL of H_2O . The aqueous layer was saturated with NaCl, and the biphasic mixture refiltered. The layers were separated, and the aqueous layer was extracted with 20 mL of EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The unpurified aldehyde **50** was then diluted with 70 mL of MeOH, and 2.18 g (15.8 mmol) of K_2CO_3 was added. A solution of 1.73 g (15.8 mmol) of **53**⁴⁸ in 8 mL of MeOH was prepared, and this solution was added to the reaction mixture via cannula (2 mL MeOH rinse). The mixture became homogeneous upon stirring vigorously at rt overnight. The alkyne was extracted from the MeOH with 3×80 mL of hexanes, followed by washing the combined hexanes extracts with 100 mL of H_2O . These extracts were then dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 1.17 g (7.04 mmol, 94%) the title compound as a clear, colorless oil. $[\alpha]_{\text{D}}^{23} +35.5$ (c 0.40, CH_2Cl_2); IR (neat) 3290, 2937, 2120, 1450, 1162, 1103, 1042 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.74 (td, $J = 6.3, 2.0$ Hz, 1H), 4.19 (dd, $J = 7.8, 6.3$ Hz, 1H), 3.97 (dd, $J = 7.8, 6.3$ Hz, 1H), 2.51 (d, $J = 2.0$ Hz, 1H), 1.72-1.37 (m, 10H); ^{13}C NMR (100 MHz, CDCl_3) δ 111.1, 81.5, 73.7, 69.4, 64.8, 35.6, 35.3, 24.9, 23.8.

4.2.42. 2-((1E)-2-Chlorovinyl(2S)-1,4-dioxaspiro[4.5]decane (52)—A solution of 1.74 mL (16.4 mmol) of 2-methyl-2-butene in 7.0 mL of THF was chilled to -15°C , followed by addition of 8.19 mL (1.0 M, 8.19 mmol) of $\text{BH}_3 \cdot \text{THF}$. The resulting colorless solution was stirred for 30 min at -15°C and then 1.5 hours at 0°C , followed by recooling to -15°C . A solution of 1.36 g (8.18 mmol) of **51** in 5.0 mL of THF was then added via cannula (2.0 mL THF rinse), and the mixture was stirred at -15°C for 30 min and 0°C for 3 h. 8.0 mL of hexamethylphosphoramide, 2.64 g (19.6 mmol) of CuCl_2 , 176 μL (9.77 mmol) of H_2O and 7.0 mL of THF were then added sequentially. The resulting orange-brown solution was then stirred for 1 h at 0°C , 8 h at rt, and 4 h at 70°C . 4.08 g (26.5 mmol) of $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$, 7.0 mL of H_2O and 7.0 mL of THF were then added, and the resulting heterogeneous mixture was stirred for 5 h at rt. The mixture was diluted with 100 mL of Et_2O and washed with 50 mL of sat. $\text{NH}_4\text{Cl}(\text{aq})$ and 70 mL of brine. The aqueous layers were extracted with an additional 20 mL of Et_2O , and the combined organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo*. Flash column chromatography (1 $\rightarrow$ 4% Et_2O /hexanes; linear gradient) yielded 1.16 g (5.70 mmol, 70%) of the title compound as a clear, colorless oil. $[\alpha]_{\text{D}}^{23} +23.5$ (c 0.32, CH_2Cl_2); IR (neat) 2937, 2863, 1621, 1448, 1162, 1102, 933; ^1H NMR (500 MHz, CDCl_3) δ 6.33 (dd, $J = 13.2, 1.0$ Hz, 1H), 5.96 (dd, $J = 13.2, 7.3$ Hz, 1H), 4.56 (dddd, $J = 7.3, 7.3, 6.3, 1.0$ Hz, 1H), 4.13 (dd, $J = 7.3, 6.3$ Hz, 1H), 3.66 (dd, $J = 8.3, 6.3$ Hz, 1H), 1.75-1.30 (m, 10H); ^{13}C NMR (100 MHz, CDCl_3) δ 131.8, 122.1, 110.6, 74.6, 68.9, 36.4, 35.5, 25.3, 24.1, 24.1.

4.2.43. (2S)-2-((1S,2R)-2-Chlorocyclopropyl)-1,4-dioxaspiro[4.5]decane (54)—A solution of 5.31 mL (51.8 mmol) of Et_2Zn in 300 mL of CH_2Cl_2 was prepared in a 3-necked flask fitted with an Ar inlet, and chilled to 0°C . A solution of 3.99 mL (51.8 mmol) of CF_3COOH in 20 mL of CH_2Cl_2 was added dropwise over 20 min via syringe, followed by stirring for 20 min at 0°C . To the resulting slurry, a solution of 4.17 mL (51.8 mmol) of CH_2I_2 in 10 mL of CH_2Cl_2 was added via cannula. The resulting mixture became homogeneous upon stirring for 20 min at 0°C . A solution of 2.00 g (9.87 mmol) of **52** in 10

mL of CH₂Cl₂ was then added via cannula, followed by removal of the ice bath and stirring for 4 h at rt. The reaction was quenched by the addition of 100 mL of sat. NH₄Cl(aq) and stirring for 30 min. The biphasic mixture was poured into an additional 200 mL of sat. NH₄Cl(aq), and the organic layer removed. The aqueous layer was extracted with an additional 2 × 200 mL of CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄), filtered, and the solvent removed *in vacuo*. Flash column chromatography (1 → 6% Et₂O/hexanes; linear gradient) afforded 1.75 g (82%, 8.07 mmol) of the title compound as a clear, colorless oil. $[\alpha]_D^{23}$ -42.8 (*c* 0.64, CH₂Cl₂); IR (neat) 2936, 2863, 1716, 1449, 1366, 1164, 1102, 1041, 927 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.13 (dd, *J* = 8.3, 6.3 Hz, 1H), 3.96 (ddd, *J* = 6.8, 6.3, 5.9 Hz, 1H), 3.70 (dd, *J* = 8.3, 6.8 Hz, 1H), 3.00 (ddd, *J* = 7.3, 3.9, 3.4 Hz, 1H), 1.64-1.34 (m, 11H), 1.11 (ddd, *J* = 7.3, 6.3, 6.3 Hz, 1H) 1.04 (ddd, *J* = 9.8, 6.3, 3.9 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 109.6, 74.7, 68.6, 36.1, 35.0, 29.7, 25.0, 24.5, 23.9, 23.7, 12.6.

4.2.44. (1S)-1-((1S,2R)-2-Chlorocyclopropyl)ethane-1,2-diol (55)—To a solution of 430 mg (1.98 mmol) of **54** in 70 mL of MeOH was added 4.0 g of Dowex 50WX8-100 resin, and the resulting slurry was stirred vigorously for 3 h at rt. The resin was removed by filtration, and rinsed with 3 × 10 mL of MeOH. Cyclohexanone dimethyl ketal was then removed by washing the MeOH solution with 3 × 100 mL of hexanes. Concentration of the MeOH layer *in vacuo*, followed by purification by flash column (60 → 100% EtOAc/hexanes; linear gradient) afforded 228 mg (1.67 mmol, 84%) of the title compound as a clear, colorless oil. TLC *R_f* = 0.2 (50% EtOAc/hexanes); $[\alpha]_D^{23}$ -67.4 (*c* 0.37, CH₂Cl₂); IR (neat) 3378, 2925, 1094, 1036 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.81 (ddd, *J* = 6.3, 5.9, 3.4 Hz, 1H), 3.62 (ddd, *J* = 7.3, 6.3, 5.9 Hz, 1H), 3.49 (dddd, *J* = 7.3, 6.8, 3.9, 3.4 Hz, 1H), 3.00 (ddd, *J* = 7.3, 3.9, 3.4 Hz, 1H), 2.14 (br d, *J* = 3.9 Hz, 1H), 1.94 (t, *J* = 5.9 Hz, 1H), 1.35 (dddd, *J* = 9.8, 6.8, 6.3, 3.4 Hz, 1H), 1.10 (ddd, *J* = 7.3, 6.3, 6.3 Hz, 1H), 1.04 (ddd, *J* = 9.8, 6.3, 3.9 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 72.0, 66.2, 29.7, 24.5, 12.7; exact mass calc. for C₅H₉ClO₂ [M+NH₄]⁺: 154.0635; found: 154.0635 (CI).

4.2.45. 2-((1S,2R)-2-Chlorocyclopropyl)-1,1-dibromoethene (47)—To a solution of 520 mg (3.81 mmol) of **55** in 30 mL of CH₂Cl₂ was added 2.63 g (19.0 mmol) of K₂CO₃, and the resulting slurry was chilled to 0 °C. 1.94 g (4.38 mmol) of Pb(OAc)₄ was added in one portion, and the mixture was stirred vigorously for 30 min at 0 °C (flask A). Meanwhile, 6.31 g (19.0 mmol) of CBr₄ was added to 30 mL of CH₂Cl₂ in a separate flask (flask B) and chilled to 0 °C. 9.99 g (38.1 mmol) of PPh₃ was added in 5 equal portions to flask B, producing a bright red solution, which was stirred for 20 min at 0 °C. The contents of flask A were then filtered through Celite directly into flask B with a 2 × 5 mL CH₂Cl₂ rinse. The resulting red solution was stirred for 2 hours at 0 °C to rt. The solution was poured into 100 mL of ice-cold pentane, and filtered through a silica plug with 300 mL of Et₂O. Removal of the solvent *in vacuo* and flash column chromatography (pentane) afforded 930 mg (3.57 mmol, 94%) of the title compound as a clear, colorless oil. TLC *R_f* = 0.6 (pentane); $[\alpha]_D^{23}$ -80.5 (*c* 0.71, CH₂Cl₂); IR (neat) 3006, 2924, 1432, 1360, 1279, 936, 781 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.83 (d, *J* = 9.3 Hz, 1H), 3.06 (ddd, *J* = 6.8, 3.9, 3.4 Hz, 1H), 2.02 (dddd, *J* = 9.8, 9.3, 6.8, 3.4 Hz, 1H), 1.36 (ddd, *J* = 9.8, 6.3, 3.9 Hz, 1H), 1.14 (ddd, *J* = 6.8, 6.8, 6.3 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 137.1, 89.6, 33.0, 26.0, 17.5.

4.2.46. 5-((1S,2R)-2-Chlorocyclopropyl)(4Z,2E)-4-bromopenta-2,4-diene-1-ol (58)—A solution of 2.42 g (23.7 mmol) of **47** and 1.24 g (4.75 mmol) of **57** in 75 mL of THF and 25 mL of H₂O was prepared. After three freeze-pump-thaw cycles, 740 mg (0.476 mmol) of Pd(PPh₃)₄ was added, and the mixture was stirred for 5 min at rt. To the yellow solution was added 606 μL (8.56 mmol) of TIOEt dropwise, resulting in the immediate formation of a yellow precipitate. After stirring for 30 min at rt, the reaction mixture was

poured into 200 mL of Et₂O and 50 mL of 1 M NaHSO₄(aq), and the biphasic mixture was filtered through Celite with a 3 × 50 mL Et₂O rinse. An additional 150 mL of 1 M NaHSO₄(aq) was added, the layers were separated, and the aqueous layer was extracted with 2 × 300 mL of Et₂O. The combined organic fractions were dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting yellow oily solid was diluted with 50 mL of EtOAc, and re-concentrated in the presence of SiO₂. Flash column chromatography (dry load, 20 → 40% EtOAc/hexanes) afforded the title compound, however the presence of Pd(PPh₃)₄ was evident due to the appearance of yellow solids upon concentration, and aromatic peaks in the ¹H NMR spectrum. To remove the remaining palladium species, the mixture was diluted with 100 mL of CH₂Cl₂ and 500 mg of cysteine and 50 mL of H₂O were added, and the mixture was stirred vigorously for 30 minutes. The organic layer was washed with 100 mL of sat. NaHCO₃(aq), and the combined aqueous layers were then further extracted with 2 × 100 mL of CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo* to provide 1.05 g (4.42 mmol, 93%) of the title compound as a light yellow oil. TLC R_f 0.5 (50% EtOAc/hexanes); [α]_D²³ -96.7 (*c* 0.14, CH₂Cl₂); IR (neat) 3346, 3052, 2863, 1729, 1648, 1616, 1373, 1265, 1094, 949, 739 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.26 (d, *J* = 14.6 Hz, 1H), 6.21 (dt, *J* = 14.6, 4.4 Hz, 1H), 5.39 (d, *J* = 9.3, 1H), 4.32 (d, *J* = 4.4, 2H), 3.09 (ddd, *J* = 7.3, 4.4, 3.4 Hz, 1H), 3.34 (dddd, *J* = 9.8, 9.3, 6.3, 3.4 Hz, 1H), 1.51 (br s, 1H), 1.43 (ddd, *J* = 9.8, 6.3, 4.8 Hz, 1H), 1.16 (ddd, *J* = 7.3, 6.3, 6.3 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 133.0, 129.0, 124.9, 62.5, 34.2, 25.1, 18.3; exact mass calc. for C₈H₁₀BrClO [M]⁺: 235.9604; found: 235.9602 (EI).

4.2.47. (2*E*)-5-((1*S*,2*R*)-2-Chlorocyclopropyl)pent-2-en-4-yn-1-ol (46)—A solution of 1.25 g (5.26 mmol) of **58** and 5.51 mL (36.8 mmol) of DBU in 50 mL of toluene was prepared in a 100 mL flask fitted with a reflux condenser. The resulting solution was heated to 110 °C for 20 hours during which time a brown oil separated from the solution. The mixture was cooled to rt and diluted with 200 mL of EtOAc. This solution was washed with 2 × 200 mL of H₂O and 200 mL of sat. CuSO₄(aq), and the aqueous layers were then extracted with an additional 200 mL of EtOAc. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Flash column chromatography (10 → 25% EtOAc/hexanes; linear gradient) afforded 822 mg (5.20 mmol, 99%) of the title compound as a clear, colorless oil. TLC R_f 0.6 (50% EtOAc/hexanes); [α]_D²³ -252 (*c* 0.70, CH₂Cl₂); IR (neat) 3354, 3015, 2925, 2857, 2220, 1718, 1636, 1432, 1258, 1095, 954, 688 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.18 (dt, *J* = 15.6, 5.4 Hz, 1H), 5.68 (dq, *J* = 15.6, 2.0 Hz, 1H), 4.19 (dd, *J* = 5.4, 2.0 Hz, 2H), 3.17 (m, 1H), 1.78 (m, 1H), 1.39 (b, 1H, OH), 1.30-1.24 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 141.5, 110.2, 89.5, 76.3, 62.9, 34.2, 19.1, 11.8; exact mass calc. for C₈H₉ClO [M]⁺: 156.0342; found: 156.0330 (EI).

4.2.48. (1*S*,2*R*)-1-((*E*)-5-Bromo-pent-3-en-1-ynyl)-2-chloro-cyclopropane—To a solution of 100 mg (0.640 mmol) of alcohol **46** in 5.0 mL of CH₂Cl₂ was added 276 mg (0.832 mmol) of PPh₃, and the resulting solution was chilled to -40 °C. 218 mg (0.832 mmol) of CBr₄ was then added in a single portion and the reaction was stirred for 2 hours at -40 °C. Following dilution with 20 mL of 1:1 hexanes:Et₂O, the organic layer was washed with 20 mL of H₂O and 20 mL of brine, and the aqueous layers were further extracted with 20 mL of 1:1 hexanes:Et₂O. The combined organic fractions were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (dry load; pentane) provided 131 mg (0.596 mmol, 94%) of the title compound as a clear, colorless oil. TLC R_f 0.2 (hexanes); [α]_D²³ -204 (*c* 0.60, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 6.19 (dt, *J* = 15.6, 7.8 Hz, 1H), 5.70-5.66 (m, 1H), 3.96 (dd, *J* = 7.8, 0.9 Hz, 2H), 3.20-3.17 (m, 1H), 1.79-1.77 (m, 1H), 1.31-1.28 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 137.8, 114.2, 91.6, 75.7, 34.2, 31.6, 19.2, 11.8.

4.2.49. [(2E)-5-((1S,2R)-2-Chlorocyclopropyl)pent-2-en-4-ynyl]dimethoxyphosphino-1-one (59)

—131 mg (0.596 mmol) of the bromide was dissolved in 1.2 mL of P(OMe)₃ in a sealed tube, and the resulting solution was heated to 100 °C for 5 hours. Upon cooling to room temperature, EtOAc was used to transfer the reaction mixture to a flask, and the mixture was concentrated *in vacuo*. Purification by flash column chromatography (40 → 70% EtOAc:hex; linear gradient), followed by evacuating the residue obtained at high vacuum (~200 mtorr) until no further P(OMe)₃ was present by NMR, provided 119 mg (0.478 mmol, 80%) of the title compound as a clear, colorless oil. TLC R_f 0.1 (70% EtOAc/hexanes); [α]_D²³ -161 (c 0.58, CH₂Cl₂); IR (neat) 2954, 2852, 2221, 1734, 1458, 1259, 1028, 811, 687 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.01-5.94 (m, 1H), 5.58-5.54 (m), 3.74 (d, *J* = 10.7 Hz, 6 H), 3.17-3.14 (m, 1H), 2.64 (ddd, *J* = 22.9, 7.8, 1.5 Hz, 2H), 1.77-1.74 (m, 1H), 1.30-1.24 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 131.8 (d, *J* = 13.0 Hz), 114.4 (d, *J* = 15.3 Hz), 89.3, 76.3 (d, *J* = 6.1 Hz), 52.8 (d, *J* = 6.9 Hz), 34.1, 30.1 (d, *J* = 40.4 Hz), 19.1, 11.8; exact mass calc. for C₁₀H₁₅ClO₃P [(M+H)⁺]: 249.0447; found: 249.0445.

4.2.50. 5-((2R)-1,4-Dioxaspiro[4.5]dec-2-yl)(3S,5S,4R)-3,4,5-trihydroxy-3,4,5-trihydrofuran-2-one (60)

—To a suspension of 20.0 g (112 mmol) L-gulonic-γ-lactone in 100 mL of DMF was added 25.6 mL (168 mmol) of cyclohexanone dimethylketal and 400 mg (1.72 mmol) of CSA. The mixture, which became homogeneous after ~2 hours, was stirred for 24 hours at rt. About 1 mL of Et₃N was then added, and the solution was concentrated under high vacuum (<1 torr) at rt to 60 °C. While the resulting oil was still hot, a stir bar and 300 mL of toluene were added. The resulting mixture was cooled to rt with vigorous stirring, at which point a white solid precipitated from the solution. The solid was filtered, rinsed with 30 mL of toluene and evacuated under high vacuum (~200 mtorr), which provided 26.1 g (101 mmol, 90%) of the title compound as a white solid of sufficient purity to be used directly. [α]_D²³ +26.3 (c 0.98, CH₃OH); ¹H NMR (500 MHz, CD₃OD) δ 4.48 (d, *J* = 4.9 Hz, 1H), 4.42-4.39 (m, 1H), 4.34 (dd, *J* = 8.3, 3.4 Hz, 1H), 4.31 (dd, *J* = 4.9, 2.9 Hz, 1H), 4.18 (dd, *J* = 8.8, 6.3 Hz, 1H), 3.82 (dd, *J* = 8.8, 6.8 Hz, 1H), 1.64-1.40 (m, 10H); ¹³C NMR (100 MHz, CD₃OD) δ 177.9, 111.7, 83.6, 76.4, 71.8, 70.8, 65.7, 37.4, 35.9, 26.2, 24.9, 24.8; exact mass calc. for C₁₂H₁₈O₆ [M⁺]: 258.1104; found: 258.1106 (EI).

4.2.51. (2R)-2-Ethynyl-1,4-dioxaspiro[4.5]decane (ent-51)

—13.7 g (53.0 mmol) of lactone **60** was suspended in 90 mL of THF, and this “milky” solution was added dropwise via addition funnel to a solution of 26.9 g (117 mmol) of KIO₄ and 11.7 g (117 mmol) of KHCO₃ in 95 mL H₂O at such a rate that the internal temperature was maintained below 27 °C. After three hours, the suspension was filtered, and the filter cake was rinsed with 2 × 25 mL of EtOAc. The aqueous fraction was saturated with NaCl, and the mixture was refiltered. The layers were then separated, and the aqueous layer was further extracted with 50 mL of EtOAc. The combined organic fractions were dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The unpurified aldehyde *ent-50* was then diluted with 500 mL of MeOH, and 15.4 g (111 mmol) of K₂CO₃ was added. A solution of 12.3 g (64.1 mmol) of **53**⁴⁸ in 20 mL of MeOH was prepared, and this solution was added to the reaction mixture via cannula (5 mL MeOH rinse). The mixture became homogeneous upon stirring vigorously at room temperature overnight. The alkyne was extracted from the MeOH with 6 × 500 mL of hexanes, followed by washing the combined hexanes extracts with 500 mL of H₂O. These extracts were then dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% CH₂Cl₂/hexanes) provided 6.74 g (40.6 mmol, 77%) of the title compound as a clear, colorless oil. [α]_D²³ -35.2 (c 0.40, CH₂Cl₂); IR (neat) 3290, 2937, 2120, 1450, 1162, 1103, 1042 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.74 (td, *J* = 6.3, 2.0 Hz, 1H), 4.19 (dd, *J* = 7.8, 6.3 Hz, 1H), 3.97 (dd, *J* = 7.8, 6.3 Hz, 1H),

2.51 (d, J = 2.0 Hz, 1H), 1.72–1.37 (m, 10H); ^{13}C NMR (100 MHz, CDCl_3) δ 111.1, 81.5, 73.7, 69.4, 64.8, 35.6, 35.3, 24.9, 23.8.

4.2.52. (1S,13S,5R,9R,10R,11R,12R)-13-Hydroxy-1,9-dimethoxy-5-[(4-methoxyphenyl)-methoxy]-7,10,12-trimethyl-4,15-dioxabicyclo[9.3.1]pentadec-7-en-3-one (61)—To a solution of 8.6 mg (0.014 mmol) of macrolactone **35** in 0.28 mL of THF was added 0.084 mL (1.0 M in THF) of TBAF at rt. After stirring for 8 h, the reaction was diluted with 10 mL of EtOAc and quenched with 10 mL of sat. NH_4Cl (aq) solution. The aqueous layer was back extracted with 2×10 mL of EtOAc and then the combined organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (neutralized with 20% EtOAc/hexane + 0.1% triethylamine; eluted with 50 $\rightarrow$ 60% EtOAc/hexanes) afforded 6.8 mg (0.014 mmol, 99% yield) of desired product **61** as clear, colorless oil. TLC R_f 0.1 (40% EtOAc/hexanes); $[\alpha]_D^{23}$ -24.1 (c 0.34, CH_2Cl_2); IR (CH_2Cl_2 , film) 3450, 2966, 2924, 1724, 1614, 1588, 1514, 1461, 1440, 1356, 1319, 1298, 1245, 1182, 1129, 1082, 1029, 998, 819 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.25 (m, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.30 (d, J = 9.3 Hz, 1H), 5.30 (m, 1H), 4.53 (d, J = 11.7 Hz, 1H), 4.44 (d, J = 11.7 Hz, 1H), 3.90 (dd, J = 2.4, 10.3 Hz, 1H), 3.81 (s, 3H), 3.53 (m, 4H), 3.30 (s, 3H), 3.22 (s, 3H), 2.63 (d, J = 12.7 Hz, 1H), 2.47 (d, J = 12.7 Hz, 1H), 2.38 (dd, J = 12.7 Hz, 1H), 2.26 (m, 3H), 1.65 (s, 3H), 1.37 (m, 1H), 1.25 (m, 1H), 1.01 (d, J = 7.3 Hz, 3H), 0.98 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.9, 159.4, 133.6, 130.3, 129.5, 126.8, 114.0, 100.1, 80.4, 76.6, 73.0, 71.7, 69.8, 69.7, 55.5, 55.3, 51.6, 43.6, 42.7, 40.6, 40.4, 38.3, 15.9, 14.4, 12.7; exact mass calcd. for $\text{C}_{27}\text{H}_{40}\text{O}_8$ $[\text{M}+\text{NH}_4]^+$: 510.3067; found: 510.3069 (ES).

4.2.53. (1S,11S,13S,5R,9R,10R,12R)-13-[(5S,1R,2R,3R,6R)-7-Aza-2-methoxy-1,5-dimethyl-4,9-dioxo-8-oxo-7-(*tert*-butyldimethylsilyl)bicyclo[4.3.0]non-3-yloxy]-1,9-dimethoxy-5-[(4-methoxyphenyl)-methoxy]methyl-7,10,12-trimethyl-4,15-dioxabicyclo[9.3.1]pentadec-7-en-3-one (62)—To a suspension of 11.0 mg (0.026 mmol) of thioglycoside **45**, 6.60 mg (0.013 mmol) of alcohol acceptor **61**, flame and oven dried 4Å MS in 2.5 mL of CH_2Cl_2 was added 6.7 mg (0.033 mmol) of 2,6-di-*tert*-butyl-4-methylpyridine at rt and stirred for 50 min. The resulting mixture was cooled to -15°C , and then 5.80 mg (0.026 mmol) NIS and 0.046 mL (0.005 mmol) of a premixed solution of TfOH/ CH_2Cl_2 (from a stock solution of 0.020 mL TfOH in 2.0 mL CH_2Cl_2) were added. The reaction was stirred overnight and allowed to gradually warm to rt. The deep red reaction mixture was quenched with 5.0 mL solution of sat. NaHCO_3 (aq) and extracted with 3×20 mL of EtOAc. The combined organic layers were washed with 10.0 mL of sat. $\text{Na}_2\text{S}_2\text{O}_3$ (aq), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (neutralized column with 20% EtOAc/hexanes + 0.1 % triethylamine; eluted with 30 $\rightarrow$ 40% EtOAc/hexanes) afforded 10.0 mg (0.025 mmol, 95% yield) of desired product **62** as a colorless oil. TLC R_f 0.6 (EtOAc/hexanes); $[\alpha]_D^{23}$ -60.9 (c 0.18, CH_2Cl_2); IR (CH_2Cl_2 , film) 2932, 2870, 1731, 1612, 1462, 1364, 1245, 1100, 1064, 1023, 836, 805 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.37 (m, 2H), 6.88 (d, J = 8.3 Hz, 2H), 5.34–5.30 (m, 1H), 5.27 (d, J = 10.3 Hz, 1H), 4.79 (d, J = 6.3 Hz, 1H), 4.54 (d, J = 11.7 Hz, 1H), 4.44 (d, J = 11.7 Hz, 1H), 3.91–3.89 (m, 2H), 3.81 (s, 3H), 3.66–3.55 (m, 1H), 3.59 (s, 3H), 3.53 (dd, J = 5.4, 10.3 Hz, 1H), 3.50 (dd, J = 4.4, 10.3 Hz, 1H), 3.44 (dd, J = 4.4, 11.2 Hz, 1H), 3.35 (d, J = 2.4 Hz, 1H), 3.30 (s, 3H), 3.23 (m, 1H), 3.22 (s, 3H), 2.61 (d, J = 12.7 Hz, 1H), 2.43 (d, J = 12.7 Hz, 1H), 2.40–2.33 (m, 2H), 2.26–2.19 (m, 2H), 1.65 (s, 3H), 1.51 (s, 3H), 1.55–1.48 (m, 1H), 1.29–1.24 (m, 1H), 1.16 (d, J = 6.3 Hz, 3H), 1.03 (s, 9H), 1.00 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.3 Hz, 3H), 0.41 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 168.5, 161.1, 159.2, 133.4, 130.1, 129.3, 126.5, 113.8, 102.1, 99.8, 82.1, 82.0, 80.3, 77.2, 76.3, 72.7, 71.4, 69.5, 65.8, 65.4, 65.2, 61.4, 55.3, 55.0, 53.4, 51.6, 43.1, 42.4,

38.5, 27.7, 22.4, 20.2, 17.3, 15.6, 15.3, 12.6, -3.8, -4.0; exact mass calc. for $C_{42}H_{67}NO_{12}Si$ $[M+NH_4]^+$: 823.4776; found: 823.4777 (ES).

4.2.54. (1S, 13S, 5R, 9R, 10R, 12R)-13-[(3S, 5S, 1R, 2R, 6R)-7-Aza-2-methoxy-1,5-dimethyl-4,9-dioxo-8-oxo-7-(tert-butylidimethylsilyl)bicyclo[4.3.0]non-3-yloxy]-1-hydroxy-5-(hydroxymethyl)-9-methoxy-7,10,12-trimethyl-4,15-dioxabicyclo[9.3.1]pentadec-7-en-3-one (63)—

To a solution of 7.1 mg (8.8 μ mol) of glycosylated macrolactone **62** in 0.34 mL of CH_2Cl_2 was added 0.068 mL of MeOH, 0.27 mL of deionized H_2O , and 10.0 mg (0.044 mmol) of DDQ. The resulting mixture was stirred vigorously overnight at rt. The deep red reaction mixture was quenched with 1.0 mL of H_2O , diluted with 10.0 mL of EtOAc, and washed with 10.0 mL sat. $NaHCO_3$ (aq). The aqueous layer was back extracted with 2×10 mL of EtOAc. The combined organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (neutralized column with 50% EtOAc/hexanes; eluted with 50 $\rightarrow$ 60% EtOAc/hexanes) afforded 4.9 mg (7.3 μ mol, 83% yield) of desired product **63** as a colorless oil. TLC R_f 0.3 (60% EtOAc/hexanes); $[\alpha]_D^{23}$ -69.3 (c 0.25, CH_2Cl_2); IR (CH_2Cl_2 , film) 3433, 2941, 2859, 1727, 1706, 1368, 1322, 1250, 1224, 1177, 1106, 1065, 1024, 839, 803 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) δ 5.46-5.41 (m, 1H), 5.32 (d, J = 9.3 Hz, 1H), 4.95 (d, J = 2.4 Hz, 1H), 4.87 (d, J = 6.3 Hz, 1H), 3.93 (dq, J = 2.4, 6.3 Hz, 1H), 3.84-3.72 (m, 3H), 3.67 (dd, J = 2.4, 10.3 Hz, 1H), 3.61 (s, 3H), 3.36 (d, J = 2.9 Hz, 1H), 3.27-3.25 (m, 1H), 3.26 (s, 3H), 2.53 (d, J = 13.2 Hz, 1H), 2.47 (d, J = 12.7 Hz, 1H), 2.35-2.22 (m, 4H), 1.76 (s, 3H), 1.55-1.49 (m, 1H), 1.53 (s, 3H), 1.36 (ddd, J = 2.0, 2.4, 11.2 Hz, 1H), 1.19 (d, J = 6.8 Hz, 3H), 1.05 (s, 9H), 1.01 (d, J = 1.0 Hz, 3H), 0.99 (s, 3H), 0.42 (s, 3H), 0.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 161.2, 132.6, 127.7, 102.0, 95.4, 82.4, 80.0, 77.7, 77.4, 75.2, 73.0, 65.6, 65.5, 65.1, 61.5, 55.5, 44.9, 43.3, 42.6, 38.8, 37.0, 27.9, 22.7, 20.4, 17.6, 16.4, 12.5, 6.7, -3.5, -3.8; exact mass calc. for $C_{33}H_{57}NO_{11}Si$ $[M+Na]^+$: 694.8951; found: 694.3600 (FAB).

4.2.55. 5-[(1E,3E)-6-((1S,2R)-2-Chlorocyclopropyl)hexa-1,3-dien-5-ynyl](1S, 11S, 13S, 5R, 9R, 10R, 12R)-13-[(3S,5S,1R,2R,6R)-7-aza-2-methoxy-1,5-dimethyl-4,9-dioxo-8-oxo-7-(tert-butylidimethylsilyl)-bicyclo[4.3.0]non-3-yloxy]-1-hydroxy-9-methoxy-7,10,12-trimethyl-4,15-dioxabicyclo[9.3.1]pentadec-7-en-3-one (65)—

To a solution of 7.3 mg (0.011 mmol) of alcohol **63** in 0.91 mL of CH_2Cl_2 and 0.37 mL of DMSO was added 0.046 mL (0.330 mmol) of triethylamine at 0 $^{\circ}C$. A premixed solution of 53.0 mg (0.330 mmol) of $SO_3 \cdot$ pyridine in 0.37 mL of DMSO was then added to the reaction mixture at 0 $^{\circ}C$. After stirring for 4 h, the reaction was quenched with 5.0 mL of brine and extracted with 3×20 mL of EtOAc. The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (neutralized column with 50% EtOAc/hexanes + 0.1 % triethylamine; eluted with 50 $\rightarrow$ 60% EtOAc/hexanes) afforded 7.1 mg of desired product **64**. In order to avoid aldehyde epimerization or decomposition, the colorless oil was used directly for the next step without further characterization. The aldehyde **64** was dissolved in 0.22 mL of THF. In a separate flask, 8.1 mg (0.033 mmol) of phosphonate side chain **59** was dissolved in 1.6 mL of THF and cooled to -78 $^{\circ}C$. 0.066 mL (0.5 M in THF, 0.033 mmol) of a freshly prepared solution of LiHMDS was added to the phosphonate solution and stirred for 10 min at -78 $^{\circ}C$. To the resulting yellow reaction mixture was added the aldehyde solution at -78 $^{\circ}C$. The reaction was stirred for an additional hour at -78 $^{\circ}C$ and then allowed to gradually warm to rt. The red mixture was quenched with 10 mL of sat. NH_4Cl (aq) and extracted with 3×20 mL of EtOAc. The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash chromatography (neutralized column with 30% EtOAc/hexanes + 0.1 % triethylamine; eluted with 30 $\rightarrow$ 40% EtOAc/hexanes) afford 5.4 mg of product **65**

(*E:Z* = 3:1). The isomeric mixture was immediately dissolved in 1.6 mL of CH₂Cl₂ and then 5 drops (approx. 0.020 mL) of a solution of I₂ (1.8 mg in 1.0 mL of CH₂Cl₂) was added. The resulting slightly pink colored solution was stirred for 1 h at rt with regular hood light. The reaction was quenched with 5.0 mL of sat. Na₂S₂O₃(aq) and extracted with 3 × 10 mL of EtOAc to afford 5.4 mg (0.0069 mmol, 63%) of **65** as an amorphous white solid (*E:Z* = 11:1). TLC R_f 0.8 (60% EtOAc/hexanes); [α]_D²³ -49.8 (*c* 0.27, CH₂Cl₂); IR (CH₂Cl₂, film) 3454, 2931, 2869, 1727, 1363, 1363, 1250, 1224, 1178, 1101, 1066, 1024, 840, 804 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.48 (dd, *J* = 10.7, 15.6 Hz, 1H), 6.27 (dd, *J* = 10.7, 15.1 Hz, 1H), 5.82 (dd, *J* = 6.3, 7.3 Hz, 1H), 5.76 (dd, *J* = 6.3, 15.1 Hz, 1H), 5.57 (dd, *J* = 1.5, 15.6 Hz, 1H), 5.30 (d, *J* = 9.8 Hz, 1H), 4.90 (d, *J* = 2.4 Hz, 1H), 4.84 (d, *J* = 6.3 Hz, 1H), 3.90 (dq, *J* = 2.4, 6.3 Hz, 1H), 3.80 (dd, *J* = 2.4, 9.3 Hz, 1H), 3.78 (dt, *J* = 2.4, 10.3 Hz, 1H), 3.59 (s, 3H), 3.34 (d, *J* = 2.4 Hz, 1H), 3.24 (s, 3H), 3.23 (m, 1H), 3.18 (m, 1H), 2.51 (d, *J* = 12.7 Hz, 1H), 2.43 (d, *J* = 13.2 Hz, 1H), 2.26 (m, 4H), 1.80 (m, 1H), 1.73 (s, 3H), 1.51 (s, 3H), 1.49 (m, 1H), 1.30 (m, 3H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.03 (s, 9H), 0.97 (d, *J* = 6.8 Hz, 6H), 0.40 (s, 3H), 0.20 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.9, 161.2, 140.4, 133.0, 132.5, 131.1, 128.0, 112.7, 102.1, 95.4, 92.5, 82.4, 82.3, 80.0, 77.4, 75.2, 71.6, 65.6, 65.5, 61.5, 55.5, 47.1, 45.0, 43.3, 38.8, 37.0, 34.5, 29.9, 27.9, 22.7, 20.4, 19.5, 17.6, 16.3, 12.5, 12.3, 6.7, -3.5, -3.8; exact mass calc. for C₄₁H₆₂NO₁₀SiCl [M+NH₄]⁺: 809.4175; found: 809.4157 (ES).

4.2.56. 5-[(1*E*,3*E*)-6-((1*S*,2*R*)-2-Chlorocyclopropyl)hexa-1,3-dien-5-ynyl](1*S*, 11*S*, 13*S*, 5*R*, 9*R*, 10*R*, 12*R*)-13-((3*S*, 5*S*, 1*R*, 2*R*, 6*R*)-7-aza-2-methoxy-1,5-dimethyl-4,9-dioxo-8-oxobicyclo[4.3.0]non-3-yloxy)-1-hydroxy-9-methoxy-7,10,12-trimethyl-4,15-dioxabicyclo[9.3.1]pentadec-7-en-3-one (1a)—

To a solution of 5.4 mg (0.0068 mmol) of *N*-TBS callipeltoside (**65**) in 1.1 mL of THF and 0.057 mL of glacial acetic acid was added 0.068 mL (1.0 M in THF) TBAF at rt. The resulting mixture was stirred for 30 min then quenched with 5.0 mL of sat. NaHCO₃(aq) and extracted with 3 × 20 mL of CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (neutralized column with 50% EtOAc/hexanes + 0.1% triethylamine; eluted with 60 → 80% EtOAc/hexanes) afforded 4.1 mg (0.0061 mmol, 89%) of callipeltoside A as a white amorphous solid. The product was further purified using analytical HPLC Zorbax C18 (4.6 mm ID × 25 cm) column (82% MeOH/H₂O), 1.0 mL/min, 272 nm; (*Z*) isomer t_r = 12.7 min; (*E*) isomer t_r = 14.2 min. TLC R_f 0.2 (80% EtOAc/hexanes); [α]_D²³ -14.2 (*c* 0.06, MeOH); IR (CH₂Cl₂, film) 3444-3269, 2982, 2921, 1758, 1742, 1701, 1665-1578, 1373, 1342, 1224, 1173, 1096, 1055, 1024, 968 cm⁻¹; ¹H NMR (500 MHz, CD₃OD) δ 6.50 (dd, *J* = 10.7, 15.6 Hz, 1H), 6.33 (dd, *J* = 10.7, 14.2 Hz, 1H), 5.83 (m, *J* = 6.3 Hz, 1H), 5.80 (m, 1H), 5.64 (dd, *J* = 2.0, 15.1 Hz, 1H), 5.26 (d, *J* = 9.8 Hz, 1H), 4.71 (d, *J* = 6.3 Hz, 1H), 3.95 (dq, *J* = 2.0, 6.3 Hz, 1H), 3.88 (dd, *J* = 2.4, 9.3 Hz, 1H), 3.72 (m, *J* = 4.8 Hz, 1H), 3.63 (dd, *J* = 2.4, 10.3 Hz, 1H), 3.59 (s, 3H), 3.44 (d, *J* = 2.0 Hz, 1H), 3.42 (d, *J* = 5.9 Hz, 1H), 3.24 (m, 1H), 3.21 (s, 3H), 2.52 (d, *J* = 12.7 Hz, 1H), 2.46 (d, *J* = 13.2 Hz, 1H), 2.30 (m, 2H), 2.21 (m, 2H), 1.79 (m, 1H), 1.74 (s, 3H), 1.50 (s, 3H), 1.49 (m, 1H), 1.39 (t, *J* = 11.7 Hz, 1H), 1.27 (m, 2H), 1.08 (d, *J* = 6.3 Hz, 3H), 0.99 (d, *J* = 6.3 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.9, 161.1, 141.6, 134.4, 134.3, 132.0, 128.4, 113.5, 103.7, 96.6, 92.8, 83.9, 83.0, 81.4, 78.7, 78.4, 76.4, 72.7, 65.3, 62.7, 62.0, 55.4, 47.8, 46.0, 44.5, 39.9, 38.2, 35.1, 23.0, 19.8, 16.3, 15.9, 12.8, 12.7, 6.8; exact mass calc. for C₃₅H₄₈NO₁₀Cl [M+Na]⁺: 700.2864; found: 700.2850 (ES).

4.2.57. 5-[(1*E*,3*E*)-6-((1*R*,2*S*)-2-Chlorocyclopropyl)hexa-1,3-dien-5-ynyl](1*S*, 11*S*, 13*S*, 5*R*, 9*R*, 10*R*, 12*R*)-13-((3*S*, 5*S*, 1*R*, 2*R*, 6*R*)-7-aza-2-methoxy-1,5-dimethyl-4,9-dioxo-8-oxobicyclo[4.3.0]non-3-yloxy)-1-hydroxy-9-methoxy-7,10,12-trimethyl-4,15-dioxo-bicyclo[9.3.1]pentadec-7-en-3-one (1b)—

A solution of 7.7 mg (0.031 mmol) of phosphonate *ent*-**59** in 700 μ L of THF was chilled to 0 °C and 156 μ L (0.2 M in THF/hexanes) of a freshly prepared LiHMDS solution was added. After stirring for 15 minutes, this mixture was chilled to –78 °C, and a solution of 7.0 mg (0.010 mmol) of aldehyde **64** in 300 μ L of THF was added down the side of the flask via syringe. The reaction mixture was allowed to slowly warm to room temperature overnight, and was then poured into 10 mL of sat. $\text{NH}_4\text{Cl}(\text{aq})$. The desired product was extracted with 3×10 mL of EtOAc, and the organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/hexanes; 0.2% Et_3N added during packing) provided 4.0 mg of the desired dienyne as a 3:1 mixture of *E:E* to *Z:E* isomers. This mixture was dissolved in 1.5 mL of CH_2Cl_2 and 18 μ L of an iodine solution (1.8 mg/mL in CH_2Cl_2) was added. Upon stirring for 1 hour under ambient light, the mixture was poured into 10 mL of 0.5 M $\text{Na}_2\text{S}_2\text{O}_3(\text{aq})$ and extracted with 3×10 mL of EtOAc. The extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (0 $\rightarrow$ 50% EtOAc/hexanes; 0.2% Et_3N added during packing) provided 3.5 mg of the desired dienyne with an enhanced 11:1 olefin ratio. The protected dienyne was then dissolved in 400 μ L of THF, and 20 μ L of acetic acid and 24 μ L of TBAF solution (1.0 M in THF) was added. After stirring for 45 minutes, the mixture was poured into 10 mL of sat. $\text{NaHCO}_3(\text{aq})$ and extracted with 3×10 mL of CH_2Cl_2 . The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography provided 3.0 mg (0.0044 mmol, 43% (3 steps)) of the title compound as an amorphous solid. The product was further purified using analytical HPLC Zorbax C18 (4.6 mm ID $\times$ 25 cm) column (82% MeOH/ H_2O), 1.0 mL/min, 272 nm; (*Z*) isomer t_r = 12.7 min; (*E*) isomer t_r = 14.2 min. $[\alpha]_D^{23} +140$ (c 0.05, MeOH); ^1H NMR (500 MHz, CD_3OD) δ 6.50 (dd, J = 10.7, 15.6 Hz, 1H), 6.33 (dd, J = 10.7, 14.2 Hz, 1H), 5.83 (m, 1H), 5.80 (m, 1H), 5.64 (dd, J = 2.0, 15.1 Hz, 1H), 5.26 (d, J = 9.8 Hz, 1H), 4.70 (d, J = 6.3 Hz, 1H), 3.95 (dq, J = 2.0, 6.3 Hz, 1H), 3.87 (dd, J = 2.4, 9.3 Hz, 1H), 3.72 (m, 1H), 3.64 (dd, J = 2.4, 10.3 Hz, 1H), 3.59 (s, 3H), 3.44 (d, J = 2.0 Hz, 1H), 3.42 (d, J = 5.9 Hz, 1H), 3.25 (m, 1H), 3.21 (s, 3H), 2.52 (d, J = 12.7 Hz, 1H), 2.46 (d, J = 13.2 Hz, 1H), 2.30 (m, 2H), 2.21 (m, 2H), 1.79 (m, 1H), 1.74 (s, 3H), 1.50 (s, 3H), 1.49 (m, 1H), 1.39 (t, J = 11.7 Hz, 1H), 1.27 (m, 2H), 1.08 (d, J = 6.3 Hz, 3H), 0.99 (d, J = 6.3 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support was provided by NIH (GM33328-18), NSF and Merck Research Laboratories.

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Figure 1.
The structures of Callipeltoside A, B and C

Scheme 1.
General synthesis strategy

Scheme 2.
First generation retrosynthetic plan for macrolactone fragment

Scheme 3.

Reaction conditions: (a) Cy_2BCl , EtNMe_2 , -78 to -20 $^\circ\text{C}$, 78%; (b) $\text{Me}_4\text{NBH}(\text{OAc})_3$, AcOH , CH_3CN , 0 $^\circ\text{C}$, 98%; (c) $(\text{MeO})_2\text{CMe}_2$, PPTS, acetone, rt; (d) LiSEt , THF, -5 to 0 $^\circ\text{C}$; (e) DIBAL-H , toluene, -78 $^\circ\text{C}$, 66% (3 steps); (f) $\text{BF}_3\cdot\text{OEt}_2$, toluene, -78 $^\circ\text{C}$, 86%.

Scheme 4.

Reaction conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2 , -78°C ; (b) PPTS, MeOH, rt, 67% (2 steps); (c) MeOTf, DTBMP, CH_2Cl_2 , rt, 82%; (d) O_3 , CH_2Cl_2 , MeOH, -78°C then Me_2S , rt, 82%; (e) isopropenylmagnesium bromide, THF, -78°C , 79%; (f) LiOH, MeOH, THF, H_2O , rt; (g) Cs_2CO_3 , allyl bromide, DMF, rt, 77% (2 steps); (h) DMBOCH₂COOH, DCC, CH_2Cl_2 , 0°C then DMAP, rt, 90%; (i) LiHMDS, $\text{TMSCl}\cdot\text{Et}_3\text{N}$, THF, -100°C to rt, 61%; (j) EtSH, BOPCl, Et_3N , CH_2Cl_2 , 0°C to rt, 63%; (k) DDQ, MeOH, rt, 79%; (l) $\text{Pd}(\text{PPh}_3)_4$, HCO_2H , Et_3N , THF, rt, 60%; (m) 2,4,6- $\text{Cl}_3\text{C}_6\text{H}_2\text{COCl}$, $i\text{Pr}_2\text{NEt}$, THF, rt then DMAP, toluene, 70°C ; (n) PPTS, MeOH, rt, 59% (2 steps).

Scheme 5.
Second generation retrosynthetic plan for macrolactone fragment

Scheme 6.

Reaction conditions: (a) TBSCl, imid, DMF, rt; (b) LiAlH₄, Et₂O, 0 °C to rt; (c) SO₃•pyr, Et₃N, DMSO, CH₂Cl₂, 0 °C, 75% (3 steps).

Scheme 8.

Reaction conditions: (a) **5**, Cy_2BCl , EtNMe_2 , 0°C then *ent*-**24**, -78°C ; (b) $\text{Me}_4\text{NB}(\text{OAc})_3$, MeCN , AcOH , 0°C ; (c) $\text{HN}(\text{CH}_2\text{CH}_2\text{OH})_2$, EtOAc , rt, 86% (3 steps); (d) $\text{HNMe}(\text{OMe})\cdot\text{HCl}$, AlMe_3 , CH_2Cl_2 , 0°C to rt; (e) $\text{Me}_2\text{C}(\text{OMe})_2$, PPTS, acetone, rt; (f) LiAlH_4 , Et_2O , rt, 72% (3 steps).

Scheme 9.

Reaction conditions: (a) $\text{BF}_3 \cdot \text{OEt}_2$, toluene, -90°C , 88%; (b) TBSOTf, 2,6-lut, CH_2Cl_2 , -78°C , 88%, 1.1:1 **30:31**; (c) PPTS, MeOH, rt, 91%; (d) MeOTf, DTBP, CH_2Cl_2 , rt then PPTS, MeOH, rt, 63%; (e) TBAF, THF, rt; (f) MsCl, Et_3N , DMAP, CH_2Cl_2 , 0°C ; (g) LiOH, H_2O , THF, rt, 70% (2 steps; for **33**) or 68% (3 steps; for **34**)

Scheme 10.
Retrosynthetic Analysis of Callipeltose

Scheme 11.

Reaction conditions: (a) NaOH, CbzCl, MeCN, H₂O; (b) MeI, K₂CO₃, DMF; (c) TsOH, Me₂C(OMe)₂, acetone, 93% (3 steps); (d) ⁱPrMgCl, MeONHMe•HCl, THF, 93%; (e) MeMgBr, THF, 69%.

Scheme 12.

Reaction conditions: (a) $\text{MeOCH}_2\text{CO}_2\text{Et}$, LDA, THF, -78°C , 56%.

Scheme 13.

Reaction conditions: (a) LDA, THF, -50°C , 89%.

Scheme 14.

Reaction conditions: (a) AcOH, 71%; (b) $\text{Me}_3\text{O}\cdot\text{BF}_4$, DTBMP, CH_2Cl_2 , rt, 82%; (c) DIBAL-H, CH_2Cl_2 ; Ac_2O , DMAP, pyr, 93%; (d) NaH, THF; (e) DBU, Cl_3CCN , 51% (2 steps); (f) $\text{BF}_3\cdot\text{OEt}_2$, PhSH, CH_2Cl_2 , 81%; (g) NaH, THF, 97%; (h) TBSOTf, 2,6-lut, CH_2Cl_2 , 92%.

Scheme 16.

Reaction conditions: (a) KIO_4 , KHCO_3 , THF/ H_2O , rt; (b) CrCl_2 , CHCl_3 , THF, $70\text{ }^\circ\text{C}$, <40% (from **49**), 87:13 (E):(Z); (c) **53**, K_2CO_3 , MeOH, 94% (from **49**); (d) (i) Si_2BH , THF, -15 to $0\text{ }^\circ\text{C}$, THF; (ii) CuCl_2 , H_2O , HMPT, THF, 0 to $70\text{ }^\circ\text{C}$, 70%, >20:1 (E):(Z).

Scheme 17.

Reaction conditions: (a) Dowex resin, MeOH, rt, 82%; (b) Pb(OAc)₄, K₂CO₃, CH₂Cl₂, rt; (c) PPh₃, CBr₄, CH₂Cl₂, 94% (2 steps).

Scheme 18.

Reaction conditions: (a) **56**, 2.5 mol% Pd_2dba_3 , 15 mol% $\text{P}(p\text{-C}_6\text{H}_4\text{OMe})_3$, $i\text{Pr}_2\text{NEt}$, <50%;
 (b) 10 mol% $\text{Pd}(\text{PPh}_3)_4$, TIOEt , $\text{THF}/\text{H}_2\text{O}$, rt, 93%; (c) DBU, toluene, 110 °C, 99%; (d)
 CBr_4 , PPh_3 , CH_2Cl_2 , -40 °C, 94%; (e) $\text{P}(\text{OMe})_3$, 100 °C, 80%.

Scheme 19.

Reaction conditions: (a) KIO_4 , KHCO_3 , THF/ H_2O , rt; (b) **53**, K_2CO_3 , MeOH, rt, 77% (2 steps).

Scheme 20.

Reaction conditions: (a) DDQ, CH_2Cl_2 , MeOH, H₂O, 83%; (b) $\text{SO}_3 \cdot \text{pyr}$, Et₃N, DMSO, CH_2Cl_2 , 0 °C to rt

Scheme 21.

Reaction conditions: (a) LiHMDS, -78°C to rt; (b) I_2 , CH_2Cl_2 , rt; (c) TBAF, AcOH, THF, rt, 56% (for **1a**) and 43% (for **1b**) from alcohol **63**

Table 1

Optimization of vinylogous aldol reaction^a

Entry	Conditions	Yield of 22 (%)	Enantioselectivity (%ee)	Olefin selectivity (<i>E</i> : <i>Z</i>)
1	rapid addition of 20	27	80	11:1
2	slow addition of 20	29	59	21:1
3	slow addition of 19 and 20	99	97	>50:1
4 ^b	slow addition of 19 and 20	93	95	>50:1

^a 0.5 mmol scale;^b 25 mmol scale, 2.5 mol% **21**

Table 2

Generality of 1,5-induction

Entry	X	P	Diastereoselection ^a
1	OTBS	PMB	3.0:1
2	OTBS	TBDPS	2.4:1
3	OPMB	PMB	1.3:1
4	Me	PMB	1:1
5	iPr	PMB	1.2:1

^aDetermined by ¹H NMR analysis

Table 3**Cyclization of mesylate **34****

Entry	Additive	Solvent	Temp	Yield
1	DMAP	toluene	70 °C	33%
2	DMAP	toluene	40 °C	NR
3	none	DMF	40 °C	NR
4	18-C-6	toluene	70 °C	(40% conv.)
5	18-C-6	toluene	110 °C	67%

Table 4

Glycosylation of alcohol **61**

Entry	Sugar	X	P	Conditions	Result
1	43	OC(=NH)CCl ₃	H	TMSOTf, 0 °C	Decomposition
2	44	SPh	H	NIS, TfOH	Decomposition
3	45	SPh	TBS	NIS, TfOH	<50%
4	45	SPh	TBS	NIS, TfOH, DTBMP	95%