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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**, Fig. 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 14-membered macrolactone, which contains a 6-membered hemiketal, are a highly functionalized deoxyamino sugar (callipeltose) and a dienyne-*trans*-chlorocyclopropane side chain. Additional analysis of the sponge extracts revealed the presence of two further members of this family: callipeltosides B and C (Fig. 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.

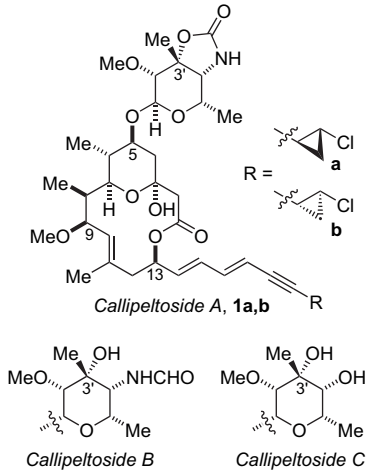

Figure 1. The structures of callipeltosides A–C.

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 (IC_{50} values of 11.26 and 15.26 μg/mL, respectively).[1a] Flow

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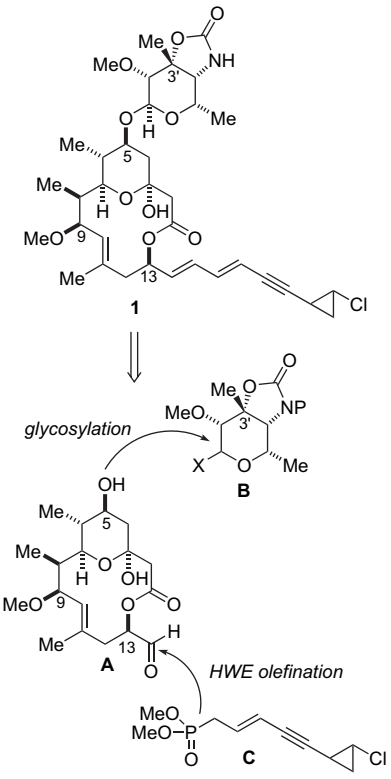
cytometry assays of NSCLC-N6 cell line treated with callipeltoside A revealed in vitro inhibition of cell proliferation of the G1 phase. This cell cycle dependent effect may be induced by enzyme inhibition or terminal cell differentation. No further biological investigations have been disclosed, perhaps 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 C_7 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 C_7 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 incorrect. 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.



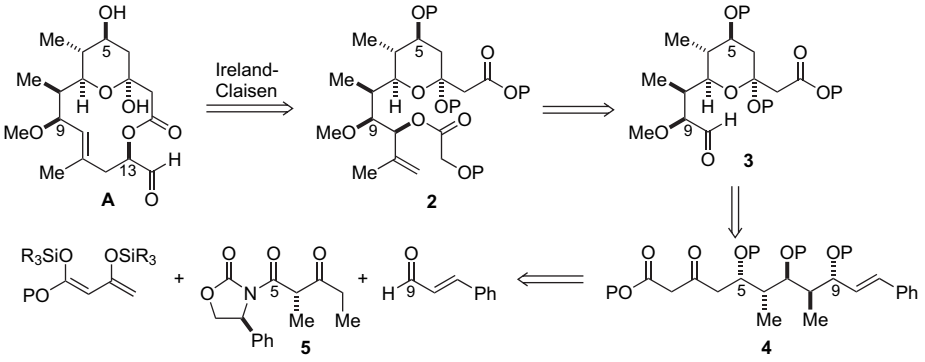
Scheme 1. General synthesis strategy.

2. Results and discussion

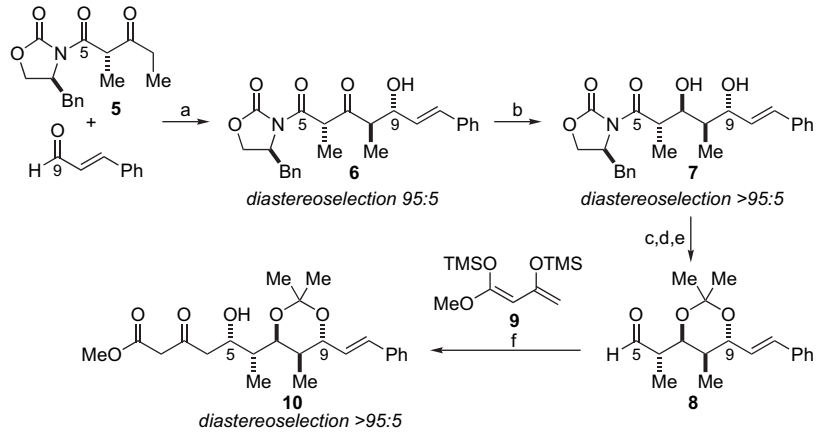
2.1. Synthesis of the macrolactone fragment: first generation

Our initial approach to 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). Rearrangment 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 triacetoxyborohydride[5] formed diol **7**, which was converted to aldehyde **8** in three steps. Addition of Chan's diene **9**[6] mediated by $BF_3\cdot OEt_2$ gave the desired Felkin aldol adduct **10** as a single diastereomer. This high diastereoselectivity was expected due to the reinforcing stereochemical



Scheme 2. First-generation retrosynthetic plan for macrolactone fragment.



Scheme 3. Reaction conditions: (a) Cy_2BCl, $EtNMe_2$, −78 to −20 °C, 78%; (b) $Me_4NBH(OAc)_3$, AcOH, CH_3CN, 0 °C, 98%; (c) $(MeO)_2CMe_2$, PPTS, acetone, rt; (d) LiSEt, THF, −5 to 0 °C; (e) DIBAL-H, toluene, −78 °C, 66% (three steps); (f)$BF_3{\cdot}OEt_2$, toluene, −78 °C, 86%.

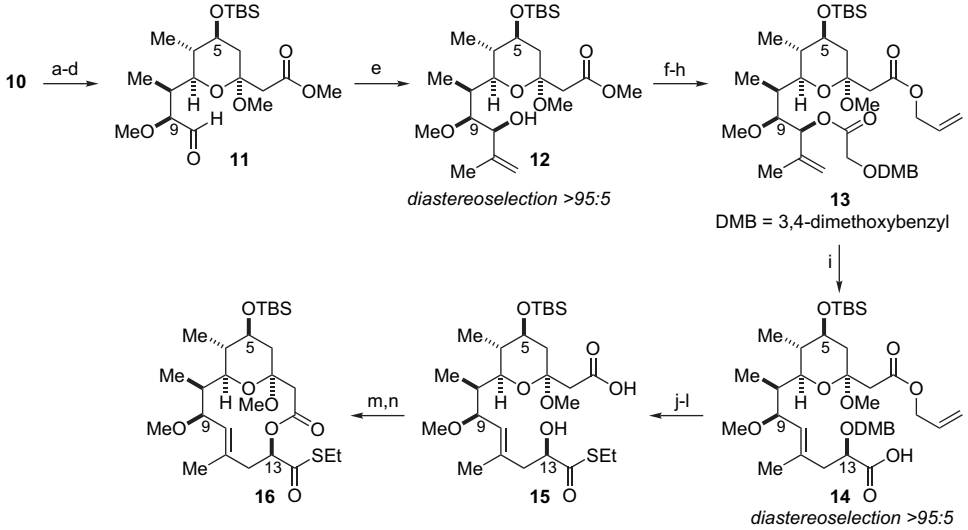
relationship in aldehyde **8**, which leads to a combination of Felkin and β-alkoxy control.[7]

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 C_{13}.[9] This compound was then transformed in three steps to seco-acid **15**, the precursor to the macrolactone subunit. After considerable experimentation, it was found that the use of Murai's modified Yamaguchi macrolactonization conditions[10] formed the desired macrolactone **16** in acceptable yield, thus completing the first-generation synthesis of this fragment.

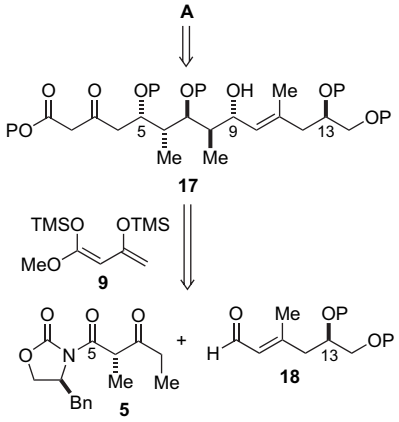
2.2. Synthesis of the macrolactone fragment: second generation

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 led 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 C_{13} 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

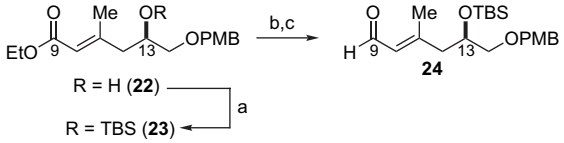


Scheme 4. Reaction conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (b) PPTS, MeOH, rt, 67% (two steps); (c) MeOTf, DTBMP, CH_2Cl_2, rt, 82%; (d) O_3, CH_2Cl_2, MeOH, −78°C, then Me_2S, rt, 82%; (e) isopropenylmagnesium bromide, THF, −78 °C, 79%; (f) LiOH, MeOH, THF, H_2O, rt; (g) Cs_2CO_3, allyl bromide, DMF, rt, 77% (two steps); (h) $DMBOCH_2COOH$, DCC, CH_2Cl_2, 0 °C, then DMAP, rt, 90%; (i) LiHMDS, $TMSCl{\cdot}Et_3N$, 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) $Pd(PPh_3)_4$, HCO_2H, Et_3N, THF, rt, 60%; (m) 2,4,6-$Cl_3C_6H_2COCl$, $^iPr_2NEt$, THF, rt, then DMAP, toluene, 70 °C; (n) PPTS, MeOH, rt, 59% (two steps).



Scheme 5. Second-generation retrosynthetic plan for macrolactone fragment.

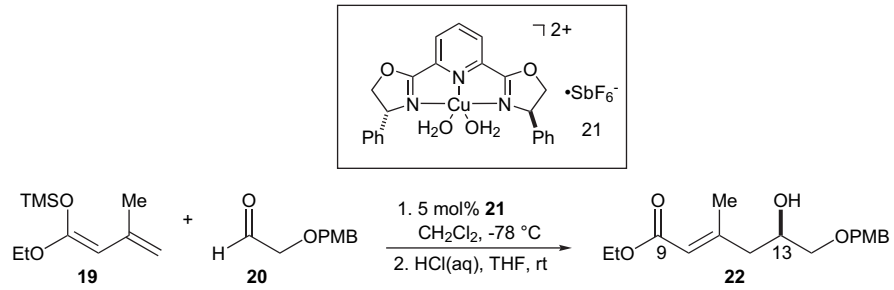
acid. Previous studies from these laboratories have shown that bis(oxazolinyl)pyridine copper(II) complexes are effective catalysts for the vinylogous aldol reaction of (benzyloxy)acetaldehyde.[11] While these results provided a valuable precedent for development of the current reaction, the crucial 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). Fortunately, simultaneous slow addition of separate solutions of substrates **19** and **20** to the catalyst solution allowed the isolation of the 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).



Scheme 6. Reaction conditions: (a) TBSCI, imid, DMF, rt; (b) $LiAlH_4$, Et_2O, 0 °C to rt; (c) SO_3·Py, Et_3N, DMSO, CH_2Cl_2, 0 °C, 75% (three steps).

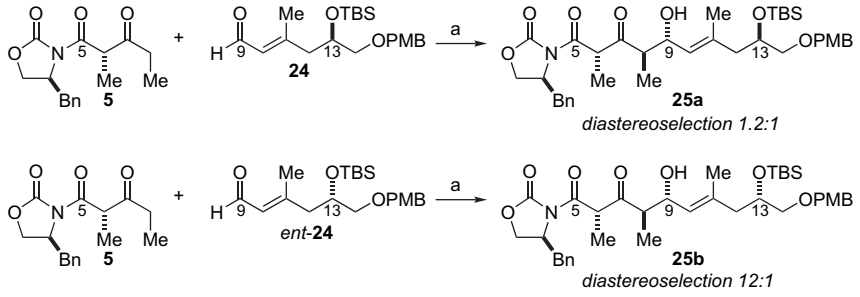
β-Ketoimide **5** had been shown to control the stereochemical course of the diastereoselective aldol reaction to form the C_8–C_9 bond in the first-generation synthesis (vide supra). Addition of aldehyde **24** to the boron enolate of β-ketoimide **5**, however, led to the formation of the desired aldol 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 C_{13}.[16] This result was quite 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 C_{13}, but the protecting group on the C_{14}-oxygen is not as important to selectivity.

Table 1
Optimization of vinylogous aldol reaction[a]



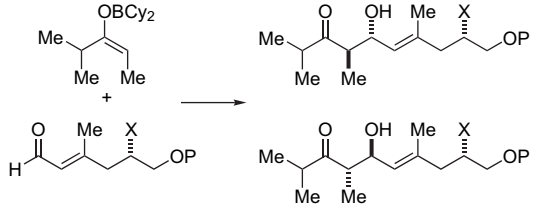
Entry	Conditions	Yield of 22 (%)	Enantioselectivity (% ee)	Olefin selectivity (*E*/*Z*)
1	Rapid addition of **20**	27	80	11:1
2	Slow addition of **20**	29	59	21:1
3	Slow addition of **19** and **20**	99	97	>50:1
4[b]	Slow addition of **19** and **20**	93	95	>50:1

[a] 0.5 mmol scale.
[b] 25 mmol scale, 2.5 mol % **21**.



Scheme 7. Reaction conditions: (a) **5**, Cy_2BCl, $EtNMe_2$, Et_2O, 0 °C, RCHO, −78 °C.

Table 2
Generality of 1,5-induction



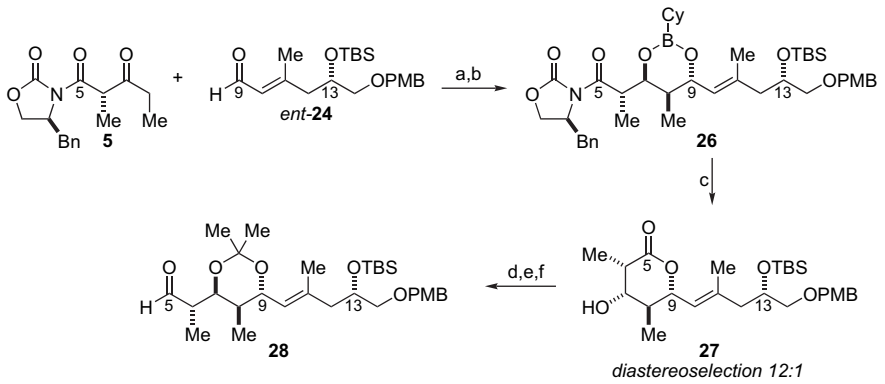
Entry	X	P	Diastereoselection[a]
1	OTBS	PMB	3.0:1
2	OTBS	TBDPS	2.4:1
3	OPMB	PMB	1.3:1
4	Me	PMB	1:1
5	^{i}Pr	PMB	1.2:1

[a] Determined by ^{1}H NMR analysis.

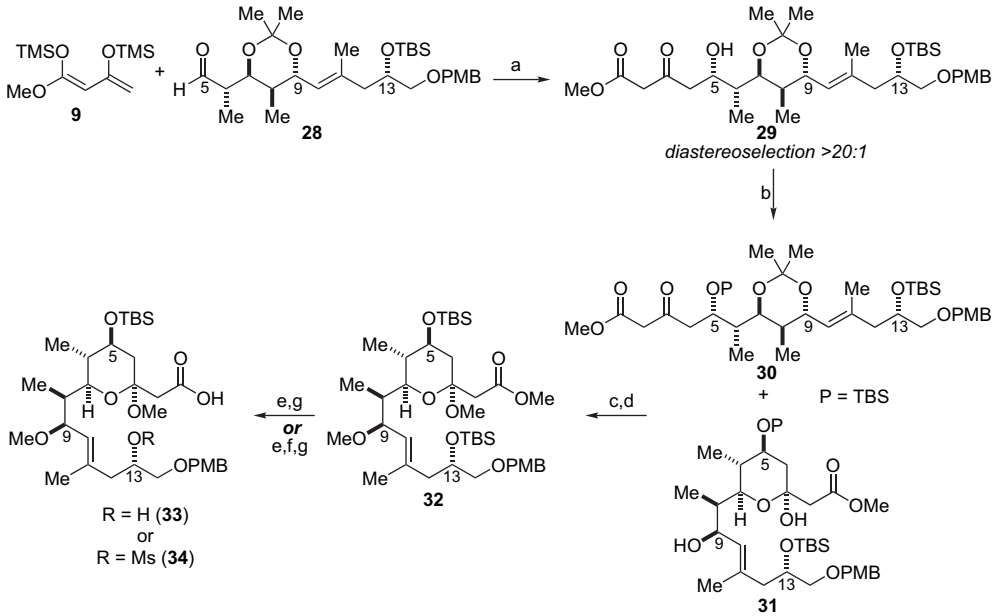
Although aldol adduct **25b** possessed the undesired stereochemistry at C_{13}, we hoped to utilize this unexpected result by modifying our overall synthesis strategy. In the original plan, the C_{13} hydroxyl group was to participate in a macrolactonization with retention of configuration; if, however, this center were to be inverted (e.g., under Mitsunobu conditions[18]) 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 acid 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 to either the recovery of starting material or elimination of the C_{13}-hydroxyl to form a conjugated diene. Cyclization of mesylate **34**, however, proved far more promising



Scheme 8. Reaction conditions: (a) **5**, Cy_2BCl, $EtNMe_2$, 0 °C, then *ent*-**24**, −78 °C; (b) $Me_4NB(OAc)_3$, MeCN, AcOH, 0 °C; (c) $HN(CH_2CH_2OH)_2$, EtOAc, rt, 86% (three steps); (d) HNMe(OMe)·HCl, $AlMe_3$, CH_2Cl_2, 0 °C to rt; (e) $Me_2C(OMe)_2$, PPTS, acetone, rt; (f) $LiAlH_4$, Et_2O, rt, 72% (three steps).

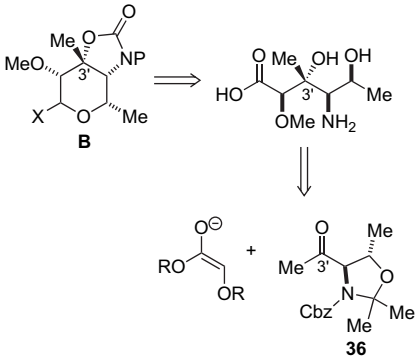


Scheme 9. Reaction conditions: (a) $BF_3 \cdot OEt_2$, toluene, −90 °C, 88%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 88%, 1.1:1 **30/31**; (c) PPTS, MeOH, rt, 91%; (d) MeOTf, DTBP, CH_2Cl_2, rt, then PPTS, MeOH, rt, 63%; (e) TBAF, THF, rt; (f) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C; (g) LiOH, H_2O, THF, rt, 70% (two steps for **33**) or 68% (three steps for **34**).

(Table 3). Initial treatment of mesylate **34** with 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).

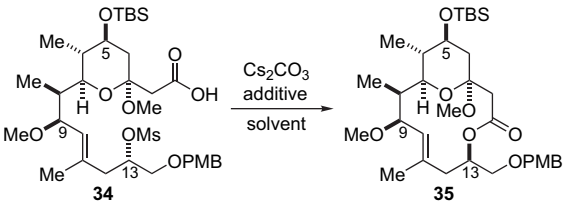
2.3. Synthesis of callipeltose[2p]

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 $C_{3'}$.



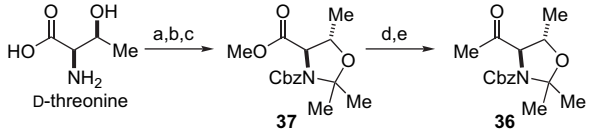
Scheme 10. Retrosynthetic analysis of callipeltose.

Table 3
Cyclization of mesylate **34**



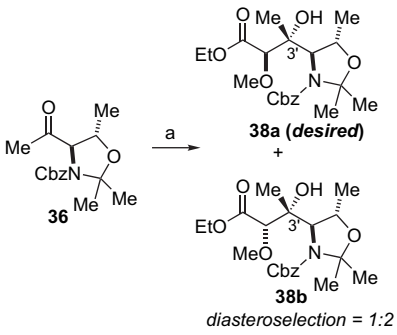
Entry	Additive	Solvent	Temp (°C)	Yield
1	DMAP	Toluene	70	33%
2	DMAP	Toluene	40	NR
3	None	DMF	40	NR
4	18-C-6	Toluene	70	(40% conv.)
5	18-C-6	Toluene	110	67%

Ketone **36** was prepared in five 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 the formation of significant quantities of the



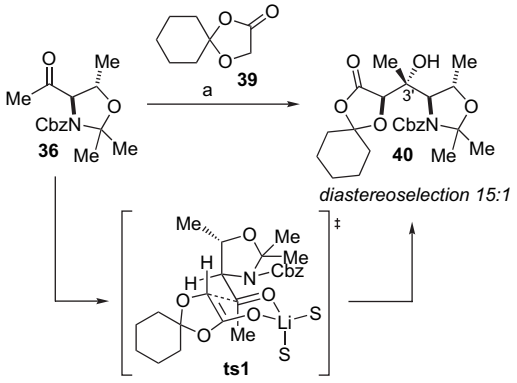
Scheme 11. Reaction conditions: (a) NaOH, CbzCl, MeCN, H_2O; (b) MeI, K_2CO_3, DMF; (c) TsOH, $Me_2C(OMe)_2$, acetone, 93% (three steps); (d) ^{i}PrMgCl, MeONHMe·HCl, THF, 93%; (e) MeMgBr, THF, 69%.

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).



Scheme 12. Reaction conditions: (a) $MeOCH_2CO_2Et$, LDA, THF, −78 °C, 56%.

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**).

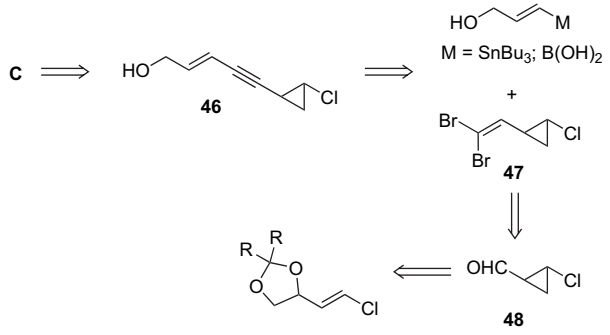


Scheme 13. Reaction conditions: (a) LDA, THF, −50 °C, 89%.

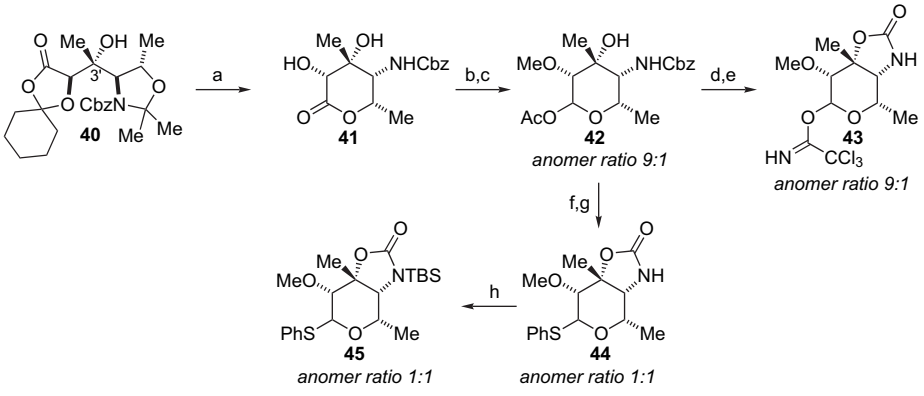
Treatment of aldol adduct **40** with aqueous acetic acid effected removal of the acetonide and cyclohexylidene ketals with concomitant lactonization, providing lactone **41** in good yield (Scheme 14). After considerable experimentation, it was found that the $C_{2'}$-hydroxyl could be selectively methylated 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 procedure[26] 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 homologation[28] 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]

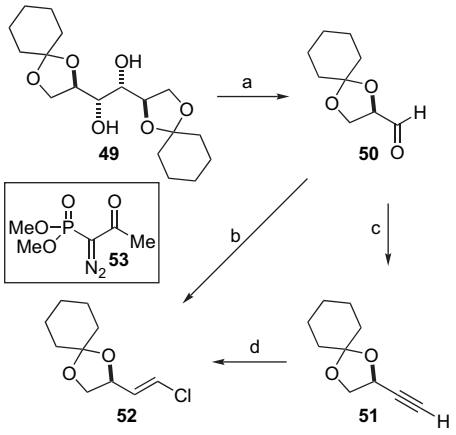


Scheme 15. Strategy for the construction of the side chain fragment.



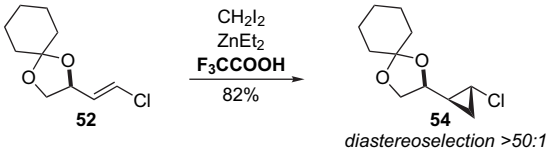
Scheme 14. Reaction conditions: (a) AcOH, 71%; (b) $Me_3O\cdot BF_4$, DTBMP, CH_2Cl_2, rt, 82%; (c) DIBAL-H, CH_2Cl_2, Ac_2O, DMAP, Py, 93%; (d) NaH, THF; (e) DBU, Cl_3CCN, 51% (two steps); (f) $BF_3\cdot OEt_2$, PhSH, CH_2Cl_2, 81%; (g) NaH, THF, 97%; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 92%.

The (*S*)-enantiomer was initially selected for the 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 Schmid and Bradley[32] 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 olefination[33] requires the use of a large quantity of chromium(II) chloride, led us to explore alternative approaches to vinyl chloride **52**. Masuda and co-workers have reported the stereospecific electrophilic chlorination of vinylboranes formed in situ from the hydroboration of 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.



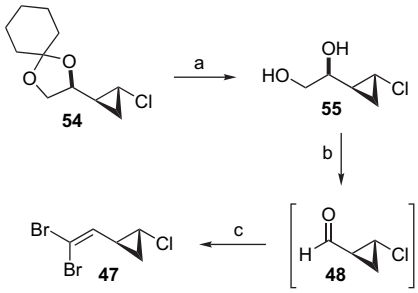
Scheme 16. Reaction conditions: (a) KIO_4, $KHCO_3$, THF/H_2O, rt; (b) $CrCl_2$, $CHCl_3$, THF, 70 °C, <40% (from **49**), 87:13 *E*/*Z*; (c) **53**, K_2CO_3, MeOH, 94% (from **49**); (d) (i) Sia_2BH, THF, −15 to 0 °C, THF; (ii) $CuCl_2$, H_2O, HMPT, THF, 0−70 °C, 70%, >20:1 *E*/*Z*.

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 (Et_2Zn, CH_2I_2)[36] or Denmark (Et_2Zn, CH_2I_2, ZnI_2)[37] carbenoid variants. In our search for a more reactive carbenoid, we were attracted to a recent report by Shi and co-workers wherein he found that the reactivity of zinc carbenoids could be markedly increased by the addition of 1 equiv of a Brønsted acid.[38] In particular, the authors found that the addition of 1 equiv 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]



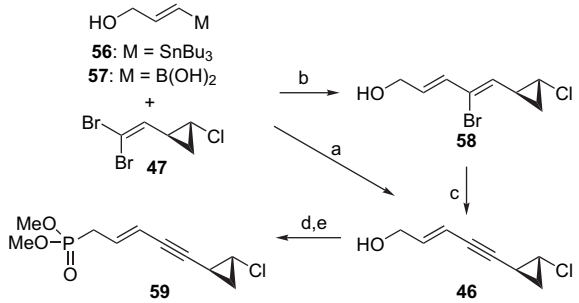
(3)

Elaboration of cyclopropane **54** to dibromide **47** was accomplished as shown in Scheme 17. Removal of 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, 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**.



Scheme 17. Reaction conditions: (a) Dowex resin, MeOH, rt, 82%; (b) $Pb(OAc)_4$, K_2CO_3, CH_2Cl_2, rt; (c) PPh_3, CBr_4, CH_2Cl_2, 94% (two steps).

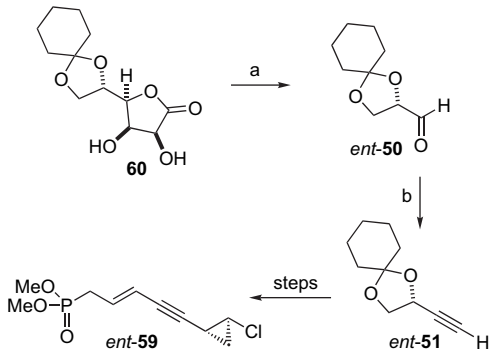
Shen and Wang have reported a method for the direct formation of enynes from dibromides and vinylstannanes, catalyzed by Pd_2dba_2 in the presence of electron-rich triaryl phosphines and Hünig's base.[40] While this system did effect the coupling of dibromide **47** with stannanes **56**, enyne **46** 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 was investigated. Roush



Scheme 18. Reaction conditions: (a) **56**, 2.5 mol % Pd_2dba_3, 15 mol % P(*p*-$C_6H_4OMe)_3$, $^iPr_2NEt$, <50%; (b) 10 mol % $Pd(PPh_3)_4$, TlOEt, THF/H_2O, rt, 93%; (c) DBU, toluene, 110 °C, 99%; (d) CBr_4, PPh_3, CH_2Cl_2, −40 °C, 94%; (e) $P(OMe)_3$, 100 °C, 80%.

and co-workers have 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 $Pd(PPh_3)_4$ 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 rearrangment.

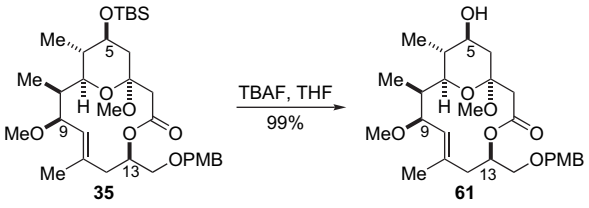
Access to *ent*-**59** was possible from commercially available L-gulonic γ-lactone (Scheme 19). Periodate cleavage of the mono(cyclohexylidene ketal) **60** according to Schmid's conditions[32] followed by homologation with Ohira's reagent (**53**) led to the formation of alkyne *ent*-**51**. This alkyne was then elaborated to phosphonate *ent*-**59** in an identical manner to that described previously (vide supra).



Scheme 19. Reaction conditions: (a) KIO_4, $KHCO_3$, THF/H_2O, rt; (b) **53**, K_2CO_3, MeOH, rt, 77% (two steps).

2.5. Fragment assembly and stereochemical analysis

With efficient syntheses of all the 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 C_5 silyl ether, macrolactone **61** was prepared for glycosylation (Eq. 4).

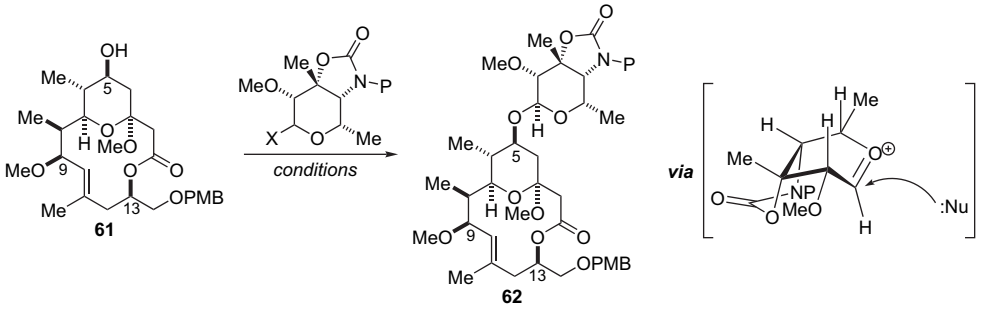


(4)

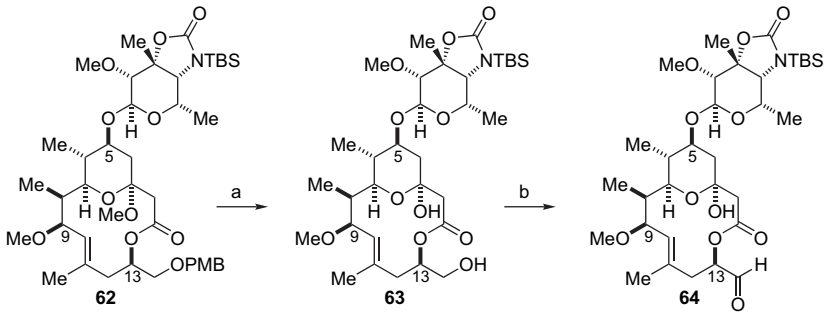
While trichloroacetimidate **43** was not an effective glycosyl donor for this system, thioglycoside **45** was found to be an excellent alternative (Table 4). It has been reported that thioglycosides serve as excellent glyocosyl donors in the presence of *N*-iodosuccinimide (NIS) and triflic acid.[44] 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, H_2O) 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

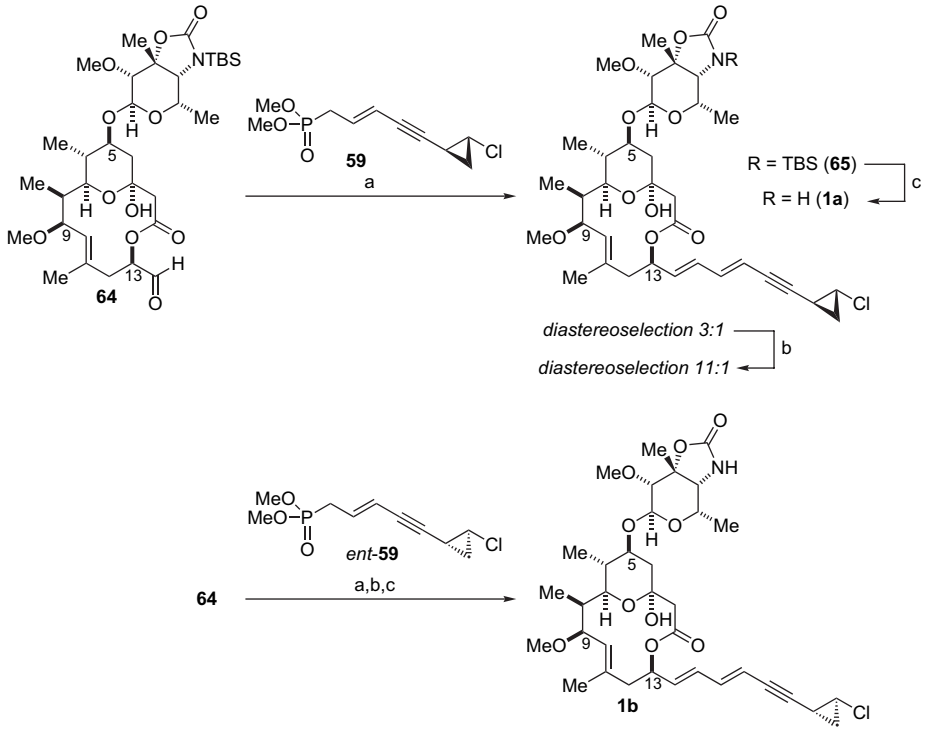
Table 4
Glycosylation of alcohol **61**



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%



Scheme 20. Reaction conditions: (a) DDQ, CH_2Cl_2, MeOH, H_2O, 83%; (b) $SO_3\cdot Py$, Et_3N, 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**.

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] Fortunately, 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 dramatically 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 co-workers.[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 C_{13} 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 an (*E*)-boron enolate to an α,β-unsaturated aldehyde. Based on the 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, CH_2Cl_2, toluene, and Et_2O 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 of 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 ^{1}H NMR analysis. Infrared (IR) spectra were recorded as thin films on KBr plates on a Perkin Elmer 1600 series FT-IR spectrophotometer. ^{1}H 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 hertz; integration). Chemical shifts are reported in parts per million 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. ^{13}C NMR spectra were recorded at 20 °C on a Mercury 400 (100 MHz) spectrometer with proton decoupling. Chemical shifts are reported in parts per million 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: $[\alpha]_\lambda^{t\,(^\circ C)}$ (*c* (g/100 mL), solvent).

4.2. Experimental procedures

4.2.1. (6E)-1-[(4S)-2-Oxo-4-benzyl(1,3-oxazolidin-3-yl)]-(2S,4R,5R)-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 Et_2O were added 2.73 mL (12.5 mmol) of Cy_2BCl and then 1.35 mL (12.5 mmol) of Et_3N. The resulting yellow suspension was stirred for 1 h at 0 °C and then cooled to −78 °C prior to the dropwise addition of 1.90 mL (15.0 mmol) of cinnamaldehyde. The reaction mixture was stirred at −78 °C for 3 h and then allowed to warm to −20 °C over 1 h before the addition of 100 mL of 2:1 MeOH/satd NH_4Cl (aq). The mixture was stirred for an additional 10 min at 0 °C, and then poured into 300 mL of CH_2Cl_2 and 50 mL of H_2O. The aqueous layer was separated and extracted with an additional 200 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The unpurified reaction mixture was triturated with 100 mL of Et_2O (overnight stirring) and the mother liquor was removed by pipette. The resulting crystals were washed with 5 mL of cold Et_2O 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. $[\alpha]_D^{23}$ +77.4 (*c* 1.0, CH_2Cl_2); IR (neat) 3027, 2991, 2938, 1778, 1692, 1453, 1359, 1213, 1120, 1073, 1049, 1005, 751, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{25}H_{27}O_5NNa[M+Na]^+$: 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**)

$Me_4NBH(OAc)_3$ (4.13 g, 15.7 mmol) was dissolved in 15 mL of glacial acetic acid and 15 mL of CH_3CN and cooled to 0 °C. The aldol product **6** (1.32 g, 3.13 mmol) was dissolved in 30 mL of CH_3CN and added to this solution at 0 °C and the reaction mixture was stirred for 3 h. The mixture was then transferred via cannula to 300 mL of a rapidly stirring biphasic mixture of 1:1 CH_2Cl_2 and satd $NaHCO_3$ (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 CH_2Cl_2. 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 (3.12 mmol, 98%) of the title compound of sufficient purity

to be used directly. $[\alpha]_D^{23}$ +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, $CDCl_3$) 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 Hz, 1H), 4.32 (t, *J*=6.4 Hz, 1H), 4.02–4.18 (m, 3H), 3.18 (dd, *J*=3.1, 13.4 Hz, 1H), 2.78 (dd, *J*=9.3, 13.4 Hz, 1H), 1.78–1.89 (m, 1H), 1.12 (d, *J*=6.9 Hz, 3H), 1.04 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{25}H_{29}O_5NNa$: 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 into 100 mL of Et_2O and 30 mL of 1 M $NaHCO_3$ (aq), and the organic phase was separated. The organic phase was washed twice with 50 mL of H_2O and dried over $MgSO_4$. 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. $[\alpha]_D^{23}$ +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, $CDCl_3$) 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 Hz, 1H), 3.27 (dd, *J*=3.4, 13.4 Hz, 1H), 2.80 (dd, *J*=9.6, 13.4 Hz, 1H), 1.89–2.00 (m, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.16 (d, *J*=6.6 Hz, 3H), 1.01 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{28}H_{33}O_5NNa$: 486.2256; found: 486.2256.

4.2.4. 2-[6-((1E)-2-Phenylvinyl)(4S,5R,6R)-2,2,5-trimethyl-(1,3-dioxan-4-yl)](2S)-1-ethylthiopropan-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 of 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 $MgSO_4$ 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, $CDCl_3$) 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 Hz, 1H), 3.90 (t, *J*=7.0 Hz, 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 Hz, 3H), 1.08 (d, *J*=6.9 Hz, 3H), 0.94 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{20}H_{29}O_3S$: 349.1831; found: 349.1831.

*4.2.5. 2-[6-((1E)-2-Phenylvinyl)(4S,5R,6R)-2,2,5-trimethyl-(1,3-dioxan-4-yl)](2S)-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 was 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 Et_2O. The combined organic extracts were washed with 25 mL of brine, dried over $MgSO_4$, 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, $CDCl_3$) δ 9.70 (d, *J*=3.1 Hz, 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 Hz, 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 Hz, 3H), 0.99 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{18}H_{28}O_3N$: 306.2069, found: 306.2069.

*4.2.6. Methyl 6-[6-((1E)-2-phenylvinyl)(4S,5R,6R)-2,2,5-trimethyl(1,3-dioxan-4-yl)](5S,6R)-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 were added 2.20 mL of silyl dienyl ether **9**[6] and then dropwise 496 mL of $BF_3 \cdot OEt_2$. After 10 min, the reaction was quenched by the addition of 100 mL of satd $NaHCO_3$ (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 $MgSO_4$, 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, $CDCl_3$) 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 Hz, 1H), 3.45 (d, *J*=15.6 Hz, 1H), 2.96 (br s, 1H), 2.74 (dd, *J*=13.1, 8.4 Hz, 1H), 2.52 (dd, *J*=13.1, 1.8 Hz, 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 Hz, 3H), 0.76 (d, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{23}H_{32}O_6Na$: 427.2097, found: 427.2097.

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

To a cooled solution (−78 °C) of 1050 mg (2.60 mmol) of **10** in 100 mL of CH_2Cl_2 were 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 the addition of 80 mL of satd $NaHCO_3$ (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 $MgSO_4$, 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 the addition of 400 mL of satd $NaHCO_3$ (aq). The mixture was diluted with 300 mL of Et_2O and the organic phase was separated. The aqueous phase was further extracted twice with 300 mL of Et_2O and the combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, 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. $[\alpha]_D^{23}$ −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}; ^{1}H NMR (400 MHz, $CDCl_3$) 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 Hz, 1H), 3.76 (d, *J*=10.6 Hz, 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 Hz, 1H), 2.52 (d, *J*=13.4 Hz, 1H), 2.08 (dd, *J*=4.4, 12.9 Hz, 1H), 1.88−1.94 (m, 1H), 1.70 (t, *J*=12.4 Hz, 1H), 1.43−1.52 (m, 1H), 0.99 (d, *J*=6.9 Hz, 3H), 0.88 (s, 9H), 0.86 (d, *J*=6.5 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{27}H_{44}O_6SiNa$: 515.2805; found: 515.2805.

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

To a solution of 120 mg (0.244 mmol) of the alcohol in 3.0 mL of CH_2Cl_2 were 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 was added to quench excess MeOTf. The solution was stirred for 30 min, and then poured into 50 mL of satd $NaHCO_3$ (aq) and diluted with 100 mL of Et_2O. The organic phase was separated and the aqueous phase was further extracted with 50 mL of Et_2O and the combined organic extracts were washed with brine, dried over $MgSO_4$, 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 CH_2Cl_2 and 5 mL of MeOH was added O_3 for 3 min (the reaction mixture turned blue after 2 min). Then 15 drops of Me_2S was added and the reaction mixture was slowly warmed to rt overnight. The mixture was poured into 50 mL of satd $NaHCO_3$ (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 $MgSO_4$, 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. $[\alpha]_D^{23}$ −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}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (d, *J*=4.4 Hz, 1H), 3.62−3.72 (m, 1H), 3.68 (s, 3H), 3.63 (dd, *J*=1.8, 10.7 Hz, 1H), 3.50 (dd, *J*=4.4, 8.9 Hz, 1H), 3.34 (s, 3H), 3.21 (s, 3H), 2.63 (s, 2H), 2.14 (dd, *J*=4.7, 12.9 Hz, 1H), 2.03−2.11 (m, 1H), 1.69 (dd, *J*=10.8, 13.1 Hz, 1H), 1.40−1.50 (m, 1H), 0.91 (s, 9H), 0.88 (d, *J*=6.6 Hz, 3H), 0.84 (d, *J*=7.0 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd 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-2yl]-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 the 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 $MgSO_4$, and 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}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (s, 1H), 4.94 (dd, *J*=1.3, 2.8 Hz, 1H), 4.06 (br d, *J*=1.8 Hz, 1H), 3.66 (s, 3H), 3.60−3.70 (m, 1H), 3.56 (dd, *J*=1.1, 10.7 Hz, 1H), 3.41 (s, 3H), 3.36 (dd, *J*=1.8, 8.7 Hz, 1H), 3.24 (s, 3H), 2.63 (d, *J*=12.8 Hz, 1H), 2.60 (d, *J*=12.8 Hz, 1H), 2.11 (dd, *J*=4.6, 12.9 Hz, 1H), 1.95−2.05 (m, 1H), 1.80 (s, 3H), 1.67 (dd, *J*=10.9, 12.9 Hz, 1H), 1.38−1.50 (m, 1H), 0.87 (s, 9H), 0.85−0.87 (m, 6H), 0.05 (s, 6H); ^{1}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 calcd 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 mixture 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 satd 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, two steps) of the 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-dimethoxy-phenyl)methoxy]acetate (**13**)*

Dimethoxy(benzyloxy) acetic acid (195 mg, 0.86 mmol) was added to a solution of 270 mg (0.54 mmol) of alcohol in 5.0 mL of dry CH_2Cl_2 under N_2. 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 min. After addition of 33 mg (0.27 mmol) of DMAP to the suspension, the reaction mixture 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% Et_3N; eluted with 20% EtOAc/hexanes) afforded 345 mg (0.49 mmol, 90%) of the title compound as a clear oil. $[\alpha]_D^{23}$ −53.8 (*c* 0.7, CH_2Cl_2); IR (CH_2Cl_2, 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, $CDCl_3$) 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 $C_{37}H_{60}O_{11}Si$ $[M+Na]^+$: 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 N_2. The solution was stirred at −78 °C for 30 min and 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 N_2. 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 Et_3N 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 Et_2O and 1 mL of 0.1 N HCl (aq). The heterogenous mixture was vigorously stirred at rt for 5 min. Following the addition of 30 mL of Et_2O and 10 mL of 0.1 M HCl, the layers were separated. The organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (linear gradient, 60→100% EtOAc/hexanes, then 85:10:5 EtOAc/*i*-PrOH/H_2O) 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.] $[\alpha]_D^{23}$ −3.9 (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2, 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, $CDCl_3$) 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-{(3E)(1R,2R,6R)-6-[(3,4-dimethoxyphenyl)methoxy]-7-ethylthio-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)acetate

To a solution of 5.80 mg (8.20 μmol) of acid **14** in 82 μL of CH_2Cl_2 were 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 °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→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}; ^{1}H 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 $C_{39}H_{64}O_{10}SSi$ $[M+Na]^+$: 775.3862, found: 775.3887 (ES).

4.2.14. Prop-2-enyl-2-[6-((3E)(1R,2R,6R)-7-ethylthio-6-hydroxyl-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]acetate

Thioester (66.5 mg, 0.088 mmol) 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 satd $NaHCO_3$ (aq) and extracted with 3×30 mL of Et_2O. The combined organic layers 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}; ^{1}H 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 $C_{30}H_{54}O_8SSi$ $[M+Na]^+$: 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**)*

Thioester (16.1 mg, 0.066 mmol) was dissolved in 0.27 mL of dry THF at rt under N_2. Palladium tetrakistriphenylphosphine (3.10 mg, 2.70 μmol), 33.0 μL (0.243 mmol) of triethylamine, and 9.20 μL (0.243 mmol) of formic acid were then added to the reaction mixture. 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 $Pd(Ph_3)_4$ salts: 10→30% EtOAc/hexane+1% AcOH) afforded 9.1 mg (0.040 mmol, 60%) of the title compound. $[\alpha]_D^{23}$ +5.0 (*c* 0.4, CH_2Cl_2); IR (CH_2Cl_2, film) 3382, 2932, 2857, 1713, 1682, 1439, 1384, 1316, 1257, 1148, 1122, 1081, 1031, 1007, 837, 776, 724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 $C_{27}H_{50}O_8SSi$ $[M+Na]^+$: 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-dioxa-13-(1,1,2,2-tetramethyl-1-silapropoxy)-bicyclo[9.3.1]pentadec-7-en-3-one (**16**)

At rt, 5.80 mg (10.3 μmol) of seco-acid **15** was dissolved in 0.34 mL of THF. Trichlorobenzoic acid (6.40 μL, 41.2 μmol) and 14.0 μL (82.6 μmol) of diisopropylethylamine were then added to the reaction mixture. 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, followed by a rinse of the syringe with 2 mL of toluene. 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 reketalized with 0.1 equiv PPTS and 0.05 M MeOH (6.1 μmol, 59% combined yield). $[\alpha]_D^{23}$ +115 (*c* 0.1, CH_2Cl_2); IR (CH_2Cl_2, film) 2944, 2923, 2872, 1744, 1682, 1462, 1380, 1333, 1251, 1231, 1185, 1144, 1072, 1005, 867, 836, 769 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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, *J*=6.8 Hz, 3H), 0.91 (m, 12H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 $C_{27}H_{48}O_7SSi$ $[M+Na]^+$: 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·$2SbF_6$·$2H_2O$[11] in 25 mL of CH_2Cl_2 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 CH_2Cl_2 were added simultaneously over 20 h 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 Et_2O. 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 min, the reaction mixture was poured into 100 mL of satd $NaHCO_3$ (aq). The organic layer was removed and the aqueous layer was extracted with 3×100 mL of CH_2Cl_2. The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), 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); $[\alpha]_D^{23}$ −1.47 (*c* 8.61, CH_2Cl_2); IR (neat) 3475, 2936, 1713, 1647, 1613, 1513, 1248, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{17}H_{24}O_5$: 309.1702, found: 309.1708 (EI); assay of enantiomeric excess: HPLC (Chiracel AD column, 5% ^{i}PrOH 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**)

Imidazole (2.68 g, 39.4 mmol) 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 h at rt. The solution was then diluted with 300 mL of 1:1 hexanes/Et_2O and washed with 3×300 mL of 1:1H_2O/brine. The aqueous layers were back extracted with 300 mL of 1:1 hexanes/Et_2O, and the combined organic fractions were dried (Na_2SO_4) 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); $[\alpha]_D^{23}$ −17.0 (*c* 6.4, MeOH); IR (neat) 2930, 2857, 1716, 1514, 1250, 1223, 1151, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{23}H_{38}O_5Si+NH_4$: 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

Compound *ent*-**23** (8.07 g, 19.1 mmol) was dissolved in 80 mL of Et_2O and cooled to 0 °C. A solution of $LiAlH_4$ in Et_2O (20 mL, 1.0 M, 20 mmol) was added dropwise over 5 min, and the resulting solution was warmed to rt and stirred for 1 h. The reaction mixture was then cooled to 0 °C and quenched by the slow sequential addition of 0.76 mL of H_2O, 0.76 mL of 15% NaOH (aq), and 2.28 mL of H_2O. Once the precipitate became white, the resulting slurry was filtered through Celite with a 3×100 mL Et_2O 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); $[\alpha]_D^{23}$ −2.86 (*c* 4.9, CH_2Cl_2); IR (neat) 3329, 2929, 2858, 1613, 1514, 1472, 1249, 1099, 1036, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{21}H_{36}O_4Si$+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 CH_2Cl_2 and 26.5 mL of DMSO was cooled to 0 °C and 10.1 mL (72.4 mmol) of Et_3N followed by 5.76 g (36.2 mmol) of SO_3·Py was added. After stirring for 4 h at 0 °C, the reaction mixture was diluted with 400 mL of 1:1 hexanes/Et_2O and washed with 400 mL each of 10:1 brine/H_2O, 1:1 brine/H_2O, concd $CuSO_4$ (aq), and H_2O. The aqueous fractions were back extracted with 400 mL of 1:1 hexanes/Et_2O, and then the combined organic fractions were dried (Na_2SO_4) 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); $[\alpha]_D^{23}$ −3.33 (c 0.52, CH_2Cl_2); IR (neat) 2929, 2856, 1874, 1514, 1249, 1103, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 Et_2O were added 1.78 mL (8.12 mmol) of dicyclohexylboron chloride and 0.88 mL (8.12 mmol) of $EtNMe_2$. Almost immediately the solution became yellow with the concomitant formation of a white precipitate. This mixture was stirred for 1 h at 0 °C, and then chilled to −78 °C. Aldehyde *ent*-**24** (1.80 g, 4.77 mmol) was added by syringe, and the mixture was stirred for 2 h at −78 °C and then transferred to a −20 °C freezer for 1 h. The reaction was quenched by the addition of 60 mL of 2:1 MeOH/satd NH_4Cl (aq) and the mixture was warmed to rt. This hetereogeneous mixture was diluted with 200 mL of H_2O and extracted with 3×200 mL of CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The resulting yellow oil was diluted with 15 mL of CH_3CN and added via cannula to a cooled (0 °C) solution of 6.28 g (23.9 mmol) of $Me_4NBH(OAc)_3$ in 15 mL of AcOH and 15 mL of CH_3CN. The resulting yellow solution was stirred for 2 h at 0 °C and then transferred via cannula to a vigorously stitrring mixture of 400 mL of satd $NaHCO_3$ (aq) and 200 mL of CH_2Cl_2. After stirring for 30 min, the layers were separated and the aqueous layer was further extracted with 2×150 mL of CH_2Cl_2. The combined organic fractions were dried (Na_2SO_4) 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 h. The reaction mixture was then diluted with 200 mL of EtOAc and washed with 3×200 mL of 10:1H_2O/brine and 200 mL of brine. The aqueous layers were back extracted with 200 mL of EtOAc, and the combined organic fractions were dried (Na_2SO_4) and concentrated in vacuo. HPLC analysis of the unpurified reaction mixture (Zorbax SiO_2 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 (linear gradient, 5→50% EtOAc/hexanes) provided 1.61 g (3.27 mmol, 69% from aldehyde *ent*-**24**) of the title compound as a single diastereomer. $[\alpha]_D^{23}$ +35.6 (c 0.32, CH_2Cl_2); IR (neat) 3472, 2929, 1729, 1514, 1249, 1105, 1105, 834, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 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 Hz, 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd 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-methylpropanamide

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 min. The hetereogeneous mixture became homogeneous after stirring for 1 h 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 h at 0 °C→rt. The reaction was quenched by the slow addition of 100 mL of satd Rochelle's salt (aq) and stirred until both layers became clear (3 h). The mixture was diluted with an extra 100 mL of satd Rochelle's salt (aq) and extracted with 4×200 mL of EtOAc. The comined 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 h at rt. Satd $NaHCO_3$ (aq) (5 mL) 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 chromatagraphy (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}; ^{1}H 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 calcd 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 μL (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 min, an additional 50 μL of the $LiAlH_4$ solution was added and then 15 min later an additional 15 μL was added. After a total of 60 min, TLC analysis showed completion reaction and 5 mL of EtOAc was added. Satd Rochelle's salt (aq) (50 mL) was added and the mixture was stirred vigorously for 3 h. 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}; ^{1}H 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 Hz, 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, $CDCl_3$) 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/N_2(l) bath. A solution of 1.18 g (4.53 mmol) of freshly prepared Chan's diene **9**[6] in 5 mL of toluene was added via cannula. Neat $BF_3\cdot OEt_2$ (230 μL, 1.81 mmol) was then added over 5 min and the mixture was stirred for 45 min, maintaining the internal temperature below −85 °C. Satd $NaHCO_3$ (aq) (5 mL) was then added and the mixture was warmed to rt. The mixture was diluted with 100 mL of EtOAc, and then washed with 100 mL of H_2O and 100 mL of brine. The aqueous layers were back extracted with 100 mL of EtOAc, the combined organic extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. Flash column chromatography (linear gradient, 10→50% EtOAc/hexanes) yielded 869 mg (1.34 mmol, 88%) of the title compound as a clear colorless oil. TLC R_f 0.1 (30% EtOAc/hexanes); $[\alpha]_D^{23}$ −33.9 (*c* 0.84, CH_2Cl_2); IR (neat) 3496, 2932, 2856, 1750, 1716, 1514, 1249, 1089, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 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, 3H), 1.38 (s, 3H), 0.87 (s, 9H), 0.81 (t, J=6.8 Hz, 6H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{35}H_{58}O_9Si+Na$: 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**)*

2,6-Lutidine (230 μL, 1.97 mmol) was added to a cooled (−78 °C) solution of 826 mg (1.27 mmol) of alcohol **29** in 28 mL of CH_2Cl_2. A solution of 438 μL (1.91 mmol) of TBSOTf in 2.0 mL of CH_2Cl_2 was then added via syringe over 5 min. After stirring for an additional 15 min at −78 °C, 5 mL of satd $NaHCO_3$ (aq) was added and the mixture was allowed to warm to rt. An additional 100 mL of CH_2Cl_2 was added, and then the organic layer was washed with 100 mL of H_2O, 100 mL of 1 M $NaHSO_4$ (aq), and 100 mL of brine. The aqueous layers were back extracted with 100 mL of CH_2Cl_2, the combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. Flash column chromatography (linear gradient, 0→40% EtOAc/hexanes) yielded 434 mg (0.567 mmol) of β-ketoester **30** and 401 mg (0.543 mmol) of 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 h at rt, the reaction was quenched by the addtion of 2 mL of satd $NaHCO_3$ (aq). The mixture was diluted with 200 mL of H_2O and the desired product was extracted with 7×200 mL of CH_2Cl_2. The extracts were dried (Na_2SO_4), 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 CH_2Cl_2 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 h at rt, the reaction was quenched by the addition of 5 mL of MeOH. The reaction solution was then poured into 200 mL of satd $NaHCO_3$ (aq) and extracted with 3×200 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (linear gradient, 2→14% EtOAc/hexanes, 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 h. 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 $C_{40}H_{72}O_9Si_2$+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-butyldimethylsilyloxy)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 satd NH_4Cl (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→80% EtOAc/hexanes) afforded 36.5 mg (0.058 mmol, 71%) of the title compound as a clear colorless oil, along with 4.0 mg (7%) of the 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 calcd for $C_{34}H_{58}O_9Si$ $[M+NH_4]^+$: 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-butyldimethylsilyloxy)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 were 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 satd NH_4Cl (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 LiOH (aq) at rt. After vigorously stirring the resulting mixture overnight, the reaction was quenched with 20 mL of satd NH_4Cl (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 Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (5% MeOH/CH_2Cl_2) afforded 36.8 mg (0.050 mmol, 95%) of the desired product **34** as a clear colorless oil. TLC R_f 0.5 (40% EtOAc/hexanes); $[\alpha]_D^{23}$ −19.6 (*c* 0.95, CH_2Cl_2); IR (CH_2Cl_2, film) 3145, 2924, 2860, 1735, 1712, 1613, 1514, 1464, 1360, 1250, 1174, 1081, 1035, 918, 837, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{34}H_{58}O_{11}SSi$ $[M+NH_4]^+$: 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-dioxa-13-(tert-butyldimethylsilyloxy)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 were 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 and then gradually cooled to rt. The reaction was quenched with 50 mL of satd NH_4Cl (aq) and extracted with

3×100 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 20% EtOAc/hexanes+0.1% triethylamine, eluted with 20% EtOAc/hexanes) afforded 21.2 mg (0.035 mmol, 67%) of the desired product **35** as a white amorphous solid. TLC R_f 0.7 (40% EtOAc/hexanes); $[\alpha]_D^{23}$ −17.5 (*c* 0.35, CH_2Cl_2); IR (CH_2Cl_2, film) 2931, 2850, 1729, 1612, 1514, 1462, 1361, 1303, 1250, 1168, 1140, 1075, 1040, 1005, 889, 835, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{33}H_{54}O_8Si$ $[M+Na]^+$: 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 rt. The reaction mixture was cooled to 0 °C and then 6.0 mL (42 mmol) of benzoyl chloride was added. Solid Na_2CO_3 was used to maintain the reaction pH at 10. Once the pH level had stabilized, another 0.60 mL of benzoyl chloride was added. The reaction mixture was allowed to warm gradually overnight. After 12 h of stirring at rt, the reaction mixture 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 Na_2SO_4, filtered, and concentrated in vacuo. The clear oil residue was used directly for the next reaction without futher purification. To a solution of 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 rt, 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 were added 10 mL (84 mmol) of dimethoxypropane and 112 mg (0.59 mmol) of *p*-toluenesulfonic acid monohydrate at rt. 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 rt, the reaction was quenched with saturated $NaHCO_3$ solution. The aqueous layer was back extracted with 2×100 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%, three steps) of the title compound. ^1H NMR indicated that the oil was purely the desired product and did not need futher 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-(5S,4R)-4-(N-methoxy-N-methylcarbamoyl)-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 and then a solution of 1.0 g (3.3 mmol) of ester **37** in 15 mL of THF was added. The reaction mixture was stirred 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 satd NH_4Cl (aq) and extracted with 3×100 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)[48] 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)[48] 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).

*4.2.31. Phenylmethyl-(5S,4R)-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 mixture was allowed to gradually warm to rt 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 satd NH_4Cl (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→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 °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 °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 $C_{16}H_{21}NO_4$ $[M+H]^+$: 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-oxa-zolidin-4-yl)}-3-hydroxy-2-methoxybutanoate (**38b**)*

To a cooled solution (0 °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 °C and then cooled to −78 °C. To form the enolates, 0.06 mL (0.51 mmol) of ethyl methoxyacetate was added and the reaction mixture was stirred for an additional 30 min at −78 °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 was stirred in a −78 °C cryocool for 2 days and quenched with satd NH_4Cl (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 °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 $C_{21}H_{31}NO_7$ $[M+Na]^+$: 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 °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 $C_{21}H_{31}NO_7$ $[M+Na]^+$: 432.2101, found: 432.1998 (FAB).

*4.2.33. Phenylmethyl-4-[(1R)-1-((2S)-1,4-dioxa-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 °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 °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 °C for 15 min. The reaction mixture was then cooled to −78 °C, after which a −78 °C solution of 0.80 g (2.8 mmol) of ketone **36** in 11 mL of THF was added. The reaction mixture was stirred for 2 h while slowly warming to −30 °C prior to quenching by the addition of 30 mL of satd NH_4Cl (aq). The resulting biphasic mixture was stirred vigorously and then extracted with 3×80 mL of EtOAc. The combined organic layers were dried over Na_2SO_4, 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 a clear colorless oil. TLC R_f=0.23 (2.5% Et_2O/CH_2Cl_2); $[\alpha]_D^{23}$ +5.5 (*c* 0.2, CH_2Cl_2); IR (CH_2Cl_2, film) 3494, 2941, 2867, 1790, 1704, 1454, 1403, 1347, 1267, 1214, 1109, 944, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 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); ^{13}C NMR (100.6 MHz, $CDCl_3$, 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 $C_{24}H_{33}NO_7$ $[M+H]^+$: 228.2335, found: 228.2351 (ES).

*4.2.34. N-((2S,3R,4R,5R)-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 rt. Acetic acid was azeotropically removed with 3×35 mL of heptane to afford a white solid. Residual acetic acid was removed by washing with satd $NaHCO_3$ (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); $[\alpha]_D^{23}$ −74.8 (*c* 0.9, CH_2Cl_2); IR (KBr) 3593, 3539, 3426, 3364, 2985, 2933, 1739, 1694, 1525, 1343, 1230, 1127, 1040, 967, 746, 702 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) 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); ^{13}C NMR (100.6 MHz, CD_3OD) 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 $C_{15}H_{19}NO_6$ $[M+H]^+$: 310.1291, found: 310.1302 (ES).

4.2.35. N-((2S,3R,4R,5R)-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 CH_2Cl_2. While under N_2, 719 mg (4.9 mmol) of Meerwein's reagent ($Me_3O\cdot BF_4$) was added followed by 1.5 g (7.3 mmol) of 2,6-di-*tert*-butyl-4-methylpyridine. The reaction mixture was stirred at rt for 2 days, after which the reaction was quenched with 80 mL of satd $NaHCO_3$. The layers were separated and the aqueous layer was further extracted with 2×100 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, 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-methylpyridine can be recovered by flash chromatography of mother liquor from trituration. TLC R_f=0.29 (60% EtOAc/hexanes); $[\alpha]_D^{23}$ −26.2 (c 0.8, CH_2Cl_2); IR (CH_2Cl_2, film) 3428, 2995, 2940, 1755, 1711, 1502, 1232, 1205, 1165, 1128, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 $C_{16}H_{21}NO_6$ $[M]^+$: 323.1369, found: 323.1359 (EI).

4.2.36. (2S,6S,3R,4R,5R)-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 lactone methyl ether was dissolved in 3.1 mL of CH_2Cl_2 and cooled to −78 °C under N_2. A solution of DIBAL-H (2.2 mL, 1.0 M in toluene) 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 CH_2Cl_2, and 234 μL (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 satd NH_4Cl (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 3×20 mL of EtOAc. The organic layers were combined, and dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (linear gradient, 40→50% EtOAc/hexanes) afforded 210 mg (0.58 mmol, 93%) of anomeric acetate **42** in a 9:1 anomeric ratio (based on ^{1}H NMR spectral analysis) as a clear colorless oil. TLC R_f=0.29 (40% EtOAc/hexanes); IR (CH_2Cl_2, film) 3417, 2984, 2939, 1726, 1513, 1331, 1311, 1226, 1102, 1045, 861, 740, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 $C_{18}H_{25}NO_7$ $[M+NH_4]^+$: 385.1975, found: 385.1964 (CI).

4.2.37. (5S,1R,2R,6R)-7-Aza-2-methoxy-1,5-dimethyl-4,9-dioxa-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 N_2. After stirring for 30 min at 0 °C, the reaction mixture was warmed to rt and stirred for 2 h. After the mixture turned into yellow suspension, the reaction was quenched with 10 mg of solid NH_4Cl and concentrated in vacuo. To ensure complete quenching, the resulting oil was further diluted with 10 mL of wet $CHCl_3$ 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 CH_2Cl_2 at rt. Dropwise 5 μL (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 rt 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→100% EtOAc/hexanes, each batch of eluent contained 1 vol % Et_3N) afforded 6.1 mg (0.017 mmol, 51%) of trichloroacetimidate **43** as a yellow solid. TLC R_f=0.21 (80% EtOAc/hexanes); $[\alpha]_D^{23}$ −17.2 (c 0.2, CH_2Cl_2); IR (CH_2Cl_2, film) 3303, 2933, 1749, 1713, 1667, 1631, 1374, 1266, 1107, 1050, 974, 912, 794, 640 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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-((2S,3S,4R,5R)-4-Hydroxy-5-methoxy-2,4-dimethyl-6-phenylthioperhydro-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 CH_2Cl_2 were added 0.19 mL (1.80 mmol) of thiophenol and 0.34 mL (2.70 mmol) of $BF_3\cdot OEt_2$ at 0 °C. The resulting solution was stirred overnight and gradually warmed to rt. The reaction was quenched with 10 mL of satd $NaHCO_3$ (aq) and extracted with 3×30 mL of EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (30→40% EtOAc/hexane) afforded 0.30 g (0.73 mmol, 81%) of the title compound as a 1:1 mixture of anomers. IR (CH_2Cl_2, film) 3564, 3418, 2982, 2937, 2834, 1731, 1714, 1514, 1504, 1454, 1316, 1226, 1090, 736, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *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 $C_{22}H_{27}NSO_5$ $[M+H]^+$: 418.1610, found: 418.1688 (ES).

4.2.39. (5S,1R,2R,6R)-7-Aza-2-methoxy-1,5-dimethyl-4,9-dioxa-3-phenylthiobicyclo[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 rt. 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}; ^{1}H 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 $C_{15}H_{19}NO_4S$ $[M+H]^+$: 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 were 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 mixture was stirred for 1 h at 0 °C and then the reaction mixture was warmed to rt. After an additional 5 h of stirring, the reaction was quenched with 5.0 mL solution of satd $NaHCO_3$ (aq) and extracted with 3×10 mL of EtOAc. The combined organic layers 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*: $[\alpha]_D^{23}$ −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}; ^{1}H 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 $C_{21}H_{33}NO_4SSi$ $[M+H]^+$: 424.1978, found: 424.1976 (ES). *Anomer β*: $[\alpha]_D^{23}$ +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}; ^{1}H 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 $C_{21}H_{33}NO_4SSi$ $[M+H]^+$: 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**[49] 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 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%) of the title compound as a clear colorless oil. $[\alpha]_D^{23}$ +35.5 (*c* 0.40, CH_2Cl_2); IR (neat) 3290, 2937, 2120, 1450, 1162, 1103, 1042 cm^{-1}; ^{1}H 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 the addition of 8.19 mL (1.0 M, 8.19 mmol) of $BH_3 \cdot THF$. The resulting colorless solution was stirred for 30 min at −15 °C and then for 1.5 h 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 at 0 °C for 3 h. Hexamethylphosphoramide (8.0 mL), 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, for 8 h at rt, and for 4 h at 70 °C. $NaBO_3 \cdot 4H_2O$ (4.08 g, 26.5 mmol), 7.0 mL of H_2O, and 7.0 mL of THF were then added, and the resulting heterogenous mixture was stirred for 5 h at rt. The mixture was diluted with 100 mL of Et_2O and washed with 50 mL of satd NH_4Cl (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 (linear gradient, 1→4% Et_2O/hexanes) yielded 1.16 g (5.70 mmol, 70%) of the title compound as a clear colorless oil. $[\alpha]_D^{23}$ +23.5 (*c* 0.32, CH_2Cl_2); IR (neat) 2937, 2863, 1621, 1448, 1162, 1102, 933; ^{1}H 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 CH_2Cl_2 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 satd NH_4Cl (aq) and stirring for 30 min. The biphasic mixture was poured into an additional 200 mL of satd NH_4Cl (aq), and the organic layer removed. The aqueous layer was extracted with an additional 2×200 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent removed in vacuo. Flash column chromatography (linear gradient, 1→6% Et_2O/hexanes) 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, CH_2Cl_2); IR (neat) 2936, 2863, 1716, 1449, 1366, 1164, 1102, 1041, 927 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 (linear gradient, 60→100% EtOAc/hexanes) 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, CH_2Cl_2); IR (neat) 3378, 2925, 1094, 1036 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.0, 66.2, 29.7, 24.5, 12.7; exact mass calcd for $C_5H_9ClO_2$ $[M+NH_4]^+$: 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 CH_2Cl_2 was added 2.63 g (19.0 mmol) of K_2CO_3 and the resulting slurry was chilled to 0 °C. $Pb(OAc)_4$ (1.94 g, 4.38 mmol) 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 CBr_4 was added to 30 mL of CH_2Cl_2 in a separate flask (flask B) and chilled to 0 °C. PPh_3 (9.99 g, 38.1 mmol) was added in five 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 CH_2Cl_2 rinse. The resulting red solution was stirred for 2 h 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 Et_2O. 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, CH_2Cl_2); IR (neat) 3006, 2924, 1432, 1360, 1279, 936, 781 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 H_2O was

prepared. After three freeze–pump–thaw cycles, 740 mg (0.476 mmol) of $Pd(PPh_3)_4$ was added and the mixture was stirred for 5 min at rt. To the yellow solution was added 606 μL (8.56 mmol) of TlOEt 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 Et_2O and 50 mL of 1 M $NaHSO_4$ (aq), and the biphasic mixture was filtered through Celite with a 3×50 mL Et_2O rinse. An additional 150 mL of 1 M $NaHSO_4$ (aq) was added, the layers were separated, and the aqueous layer was extracted with 2×300 mL of Et_2O. The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting yellow oily solid was diluted with 50 mL of EtOAc and reconcentrated in the presence of SiO_2. Flash column chromatography (dry load, 20 → 40% EtOAc/hexanes) afforded the title compound; however, the presence of $Pd(PPh_3)_4$ 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 CH_2Cl_2 and 500 mg of cystein and 50 mL of H_2O were added, and the mixture was stirred vigorously for 30 min. The organic layer was washed with 100 mL of satd $NaHCO_3$ (aq) and the combined aqueous layers were then further extracted with 2×100 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), 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); $[\alpha]_D^{23}$ −96.7 (*c* 0.14, CH_2Cl_2); IR (neat) 3346, 3052, 2863, 1729, 1648, 1616, 1373, 1265, 1094, 949, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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 Hz, 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.0, 129.0, 124.9, 62.5, 34.2, 25.1, 18.3; exact mass calcd for $C_8H_{10}BrClO$ $[M]^+$: 235.9604, found: 235.9602 (EI).

4.2.47. (2E)-5-((1S,2R)-2-Chlorocylcopropyl)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 h 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 H_2O and 200 mL of satd $CuSO_4$ (aq), and the aqueous layers were then extracted with an additional 200 mL of EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash column chromatography (linear gradient, 10 → 25% EtOAc/hexanes) afforded 822 mg (5.20 mmol, 99%) of the title compound as a clear colorless oil. TLC R_f 0.6 (50% EtOAc/hexanes); $[\alpha]_D^{23}$ −252 (*c* 0.70, CH_2Cl_2);[50] IR (neat) 3354, 3015, 2925, 2857, 2220, 1718, 1636, 1432, 1258, 1095, 954, 688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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 (br, 1H, OH), 1.30–1.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 110.2, 89.5, 76.3, 62.9, 34.2, 19.1, 11.8; exact mass calcd for C_8H_9ClO $[M]^+$: 156.0342, found: 156.0330 (EI).

4.2.48. (1S,2R)-1-((E)-5-Bromopent-3-en-1-ynyl)-2-chlorocyclopropane

To a solution of 100 mg (0.640 mmol) of alcohol **46** in 5.0 mL of CH_2Cl_2 was added 276 mg (0.832 mmol) of PPh_3 and the resulting solution was chilled to −40 °C. CBr_4 (218 mg, 0.832 mmol) was then added in a single portion and the reaction mixture was stirred for 2 h at −40 °C. Following dilution with 20 mL of 1:1 hexanes/Et_2O, the organic layer was washed with 20 mL of H_2O and 20 mL of brine, and the aqueous layers were further extracted with 20 mL of 1:1 hexanes/Et_2O. The combined organic fractions were dried (Na_2SO_4), 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); $[\alpha]_D^{23}$ −204 (*c* 0.60, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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**)

Bromide (131 mg, 0.596 mmol) 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 h. Upon cooling to rt, EtOAc was used to transfer the reaction mixture to a flask and the mixture was concentrated in vacuo. Purification by flash column chromatography (linear gradient, 40 → 70% EtOAc/hexane), 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); $[\alpha]_D^{23}$ −161 (*c* 0.58, CH_2Cl_2); IR (neat) 2954, 2852, 2221, 1734, 1458, 1259, 1028, 811, 687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.01–5.94 (m, 1H), 5.58–5.54 (m), 3.74 (d, *J*=10.7 Hz, 6H), 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{10}H_{15}ClO_3P$ $[(M+H)^+]$: 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) of L-gulonic-γ-lactone in 100 mL of DMF were added 25.6 mL (168 mmol) of cyclohexanone dimethyl ketal and 400 mg (1.72 mmol) of CSA. The mixture, which became homogeneous after ~2 h, was stirred for 24 h at rt. About 1 mL of Et_3N 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. $[\alpha]_D^{23}$ +26.3 (*c* 0.98, CH_3OH); ^1H NMR (500 MHz, CD_3OD) 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); ^{13}C NMR (100 MHz, CD_3OD) 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 calcd for $C_{12}H_{18}O_6$ $[M^+]$: 258.1104, found: 258.1106 (EI).

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

Lactone **60** (13.7 g, 53.0 mmol) 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 KIO_4 and 11.7 g (117 mmol) of $KHCO_3$ in 95 mL H_2O at such a rate that the internal temperature was maintained below 27 °C. After 3 h, 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 (Na_2SO_4), 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 K_2CO_3 was added. A solution of 12.3 g (64.1 mmol) of **53**[49] 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 rt overnight. Alkyne was extracted from MeOH with 6×500 mL of hexanes followed by washing the combined hexanes extracts with 500 mL of H_2O. These extracts were then dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography (30% CH_2Cl_2/hexanes) provided 6.74 g (40.6 mmol, 77%) of the title compound as a clear colorless oil. $[\alpha]_D^{23}$ −35.2 (*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.

*4.2.52. (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 mixture was diluted with 10 mL of EtOAc and quenched with 10 mL of satd 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→60% EtOAc/hexanes) afforded 6.8 mg (0.014 mmol, 99% yield) of the desired product **61** as a 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 $C_{27}H_{40}O_8$ $[M+NH_4]^+$: 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-dioxa-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**, and flame and oven dried 4 Å 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) of 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 mixture was stirred overnight and allowed to gradually warm to rt. The deep red reaction mixture was quenched with 5.0 mL solution of satd $NaHCO_3$ (aq) and extracted with 3×20 mL of EtOAc. The combined organic layers were washed with 10.0 mL of satd $Na_2S_2O_3$ (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→40% EtOAc/hexanes) afforded 10.0 mg (0.025 mmol, 95% yield) of the 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 calcd 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-dioxa-8-oxo-7-(tert-butyldimethylsilyl)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 μmol) of glycosylated macrolactone **62** in 0.34 mL of CH_2Cl_2 were 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 satd $NaHCO_3$ (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→60% EtOAc/hexanes) afforded 4.9 mg (7.3 μmol, 83% yield) of the 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 calcd 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-dioxa-8-oxo-7-(tert-butyldimethylsilyl)-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 °C. A premixed solution of 53.0 mg (0.330 mmol) of $SO_3\cdot Py$ in 0.37 mL of DMSO was then added to the reaction mixture at 0 °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→60% EtOAc/hexanes) afforded 7.1 mg of the desired product **64**. In order to avoid aldehyde epimerization or decomposition, the colorless oil was used directly for the next step without further characterization. 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 °C. Freshly prepared solution of LiHMDS (0.066 mL, 0.5 M in THF, 0.033 mmol) was added to the phosphonate solution and stirred for 10 min at −78 °C. To the resulting yellow reaction mixture was added the aldehyde solution at −78 °C. The reaction mixture was stirred for an additional hour at −78 °C and then allowed to gradually warm to rt. The red mixture was quenched with 10 mL of satd 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→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 CH_2Cl_2 and then five drops (approx. 0.020 mL) of a solution of I_2 (1.8 mg in 1.0 mL of CH_2Cl_2) 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 satd $Na_2S_2O_3$ (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); $[\alpha]_D^{23}$ −49.8 (*c* 0.27, CH_2Cl_2); IR (CH_2Cl_2, film) 3454, 2931, 2869, 1727, 1363, 1363, 1250, 1224, 1178, 1101, 1066, 1024, 840, 804 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{41}H_{62}NO_{10}SiCl$ $[M+NH_4]^+$: 809.4175, found: 809.4157 (ES).

*4.2.56. 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-dioxa-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 and then quenched with 5.0 mL of satd $NaHCO_3$ (aq) and extracted with 3×20 mL of CH_2Cl_2. 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 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/H_2O), 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); $[\alpha]_D^{23}$ −14.2 (*c* 0.06, MeOH); IR (CH_2Cl_2, film) 3444−3269, 2982, 2921, 1758, 1742, 1701, 1665−1578, 1373, 1342, 1224, 1173, 1096, 1055, 1024, 968 cm^{-1}; ^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, *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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{35}H_{48}NO_{10}Cl$ $[M+Na]^+$: 700.2864, found: 700.2850 (ES).

*4.2.57. 5-[(1E,3E)-6-((1R,2S)-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-dioxa-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 (**1b**)*

A solution of 7.7 mg (0.031 mmol) of phosphonate *ent*-**59** in 700 μL of THF was chilled to 0 °C and 156 μL (0.2 M in THF/hexanes) of a freshly prepared LiHMDS solution was added. After stirring for 15 min, this mixture was chilled to −78 °C, and a solution of 7.0 mg (0.010 mmol) of aldehyde **64** in 300 μL of THF was added down the side of the flask via syringe. The reaction mixture was allowed to slowly warm to rt overnight, and was then poured into 10 mL of satd NH_4Cl (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 μL of an iodine solution (1.8 mg/mL in CH_2Cl_2) was added. Upon stirring for 1 h under ambient light, the mixture was poured into 10 mL of 0.5 M $Na_2S_2O_3$ (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→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 μL of THF, and 20 μL of acetic acid and 24 μL of TBAF solution (1.0 M in THF) were added. After stirring for 45 min, the mixture was poured into 10 mL of satd $NaHCO_3$ (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% (three steps)) of the title compound as an amorphous solid. The product was further purified using analytical HPLC Zorbax C18 (4.6 mm ID×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).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.02.001.

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