# Total Synthesis of (+)-18-*epi*-Latrunculol A: Development of a Synthetic Route

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S *Supporting Information*

ABSTRACT: The evolution of an enantioselective total synthesis of (+)-18-*epi*-latrunculol A, a congener of the marine-sponge-derived latrunculins A and B, is reported. Key steps include a late-stage Mitsunobu macrolactonization to construct the 16-membered macrolactone, a mild Carreira alkynylation to unite the northern and southern hemispheres, a diastereoselective, acid-mediated δ-hydroxy enone cyclization/equilibration sequence, and a functional-group-tolerant cross-metathesis to access the enone cyclization precursor.
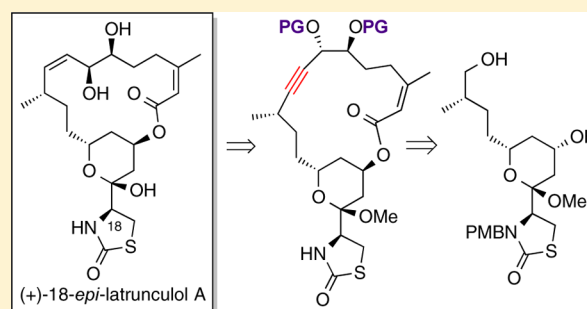
INTRODUCTION

The latrunculins constitute a family of macrolide natural products isolated from the taxologically unique marine sponges *Cacospongia mycofijiensis* and *Negombata magnifica* (Figure 1).[1,2]
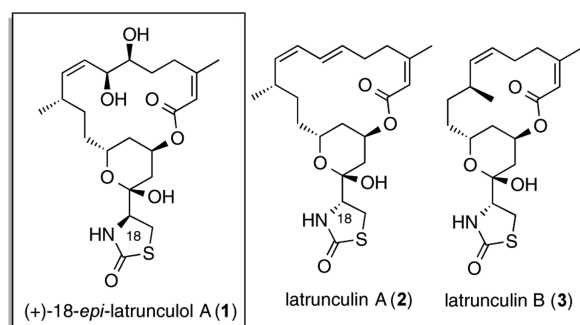

Figure 1. Latrunculin natural products.

that have been widely studied given of both their reversible inhibition of actin polymerization and their cytotoxicity against several human cancer cell lines.[3] Latrunculin A (**2**) in particular has served as an important molecular probe used to explore the biological implications of actin depolymerization,[4] and as such, it has been the target of several successful synthetic ventures.[5−13]

In 2008, Crews and co-workers reported the isolation, characterization, and initial biological assessment of a series of new, naturally occurring latrunculin analogues.[14] One compound, (+)-18-*epi*-latrunculol A (**1**), exhibited selective solid tumor cytotoxicity when tested against HCT-116 (5.5 μM) and MDA-MB-435 (>50 μM), but unlike the other members of the latrunculin family, **1** was *devoid* of the ability to inhibit actin polymerization. On the other hand, the parent compounds

(+)-latrunculin A (**2**) and B (**3**) demonstrate nonselective cytotoxicity profiles, thus limiting their use as chemotherapeutics.[15]

Given our longstanding interest in the latrunculins[5−7] and the intriguing biological profile of the epimeric latrunculin congener (+)-18-*epi*-latrunculol A (**1**), we undertook the development of a scalable total synthesis of (+)-**1** to confirm both the assigned structure and absolute stereochemistry and to provide sufficient quantities for additional biological evaluation.[16] Described herein is a full account of the evolution of the total synthesis of (+)-18-*epi*-latrunculol A (**1**), which led not only to (+)-**1** but also to the preparation of ca. 50 mg of the penultimate synthetic precursor for use in for future analogue development.

RESULTS AND DISCUSSION

While at the outset of this synthetic venture the total synthesis of (+)-18-*epi*-latrunculol A (**1**) had not been reported, effective total syntheses of the parent latrunculins A (**2**) and B (**3**) had been published by White,[12,13] Fürstner,[8−11] and our laboratory.[5−7] Not surprisingly, our synthetic strategy for (+)-18-*epi*-latrunculol A (**1**) was envisioned to exploit the lessons learned in our earlier syntheses, with important modifications to ensure efficient asymmetric access to the natural product (Scheme 1). Specifically, we envisioned a late-stage Mitsunobu macrolactonization[17] and either a Wittig olefination[18] or, given our earlier difficulties with the Wittig union for latrunculin A,[6,7] a nucleophilic addition protocol to construct the 16-membered macrolactone. The requisite southern hemisphere coupling partner **4** was in turn envisioned to be readily accessible from

Scheme 1. Retrosynthetic Analysis of (+)-1
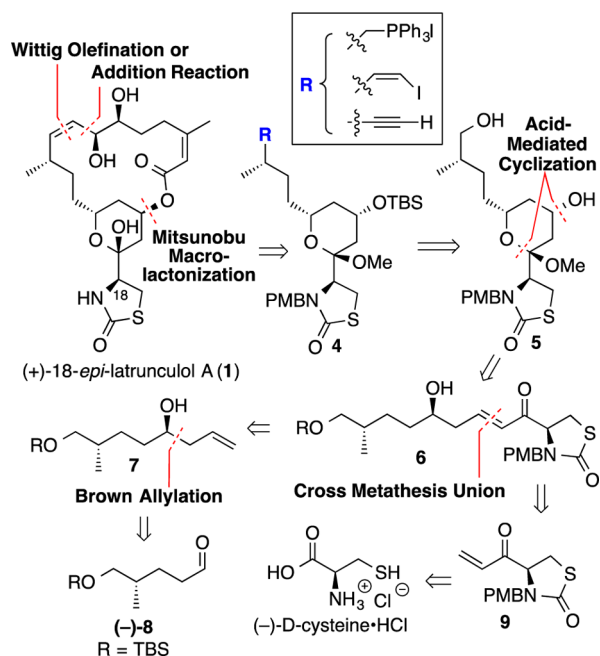
cyclic ketal **5** via a strategy level acid-mediated cyclization/equilibration of δ-hydroxy enone **6**.[5−8] The latter would be constructed through the aegis of a functional-group-compatible cross-metathesis reaction,[19,20] which was anticipated to circumvent both protecting group manipulation and oxidation, as required in all previous latrunculin syntheses.[5−13] The requisite cross-metathesis partners **7** and **9** in turn would arise from known aldehyde (−)-**8**[21] and D-cysteine, respectively.

In the synthetic direction, D-cysteine was converted to thiazolidinone (+)-**10** upon treatment with phenyl chloroformate followed by chemoselective N-protection with p-methoxybenzyl chloride, which provided (+)-**10** in a 65% yield for the two steps (Scheme 2). Acid (+)-**10** was then converted to the Weinreb amide, which upon treatment with freshly prepared vinylmagnesium bromide furnished enone (+)-**9** in 55% yield for the two steps. Quenching of the addition reaction with aqueous HCl was critical to obtain high yields of (+)-**9**. When saturated aqueous ammonium chloride was

Scheme 2. Synthesis of Enone (+)-9
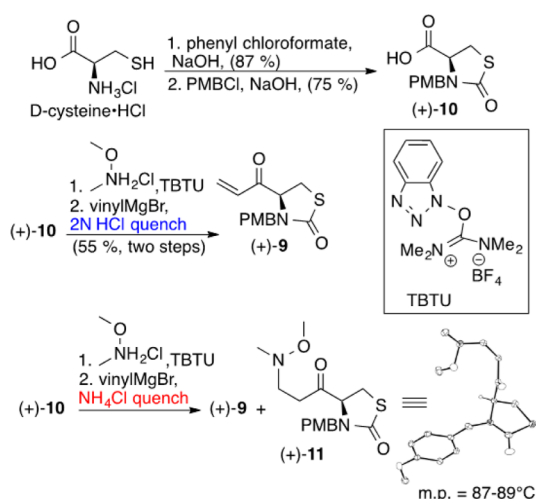
employed, a mixture of enone (+)-**9** and byproduct (+)-**11** was obtained, presumably via addition of the liberated hydroxylamine to the electrophilic enone.[22] The structure of (+)-**11** was confirmed by single-crystal X-ray analysis.

With gram quantities of enone (+)-**9** in hand, we turned to the construction of the remaining cross-metathesis partner (Scheme 3). Alcohol (−)-**13** was readily prepared utilizing a

Scheme 3. Synthesis of Enone (+)-6
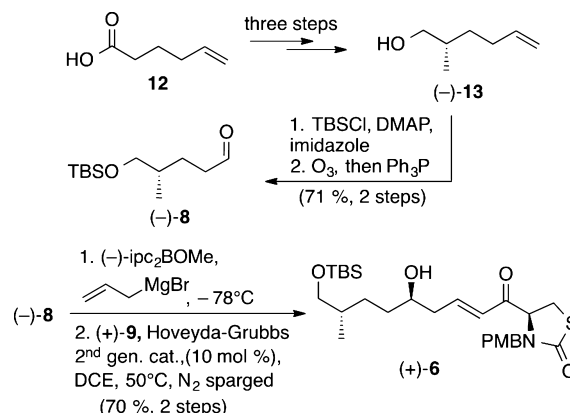
previously reported three-step sequence[23] beginning with commercially available 5-hexenoic acid (**12**). Alcohol (−)-**13** was then protected as the TBS ether, and subsequent ozonolysis of the terminal olefin provided known aldehyde (−)-**8**.[21] An asymmetric Brown allylation[24] followed to deliver the desired homoallylic alcohol, which was contaminated with small and variable amounts of the epimeric alcohol. Without separation, treatment of this mixture with 3 equiv of enone (+)-**9** and the Hoveyda−Grubbs second-generation catalyst to achieve cross-metathesis provided pure cyclization precursor (+)-**6** in 70% yield from (−)-**8** after standard flash column chromatography with 72% recovery of unreacted enone (+)-**9**.

The key acid-mediated cyclization was next achieved after extensive experimentation by subjecting δ-hydroxy enone (+)-**6** to a 1:1.3 (v/v) mixture of 6 N HCl and THF to furnish lactol (+)-**14** (Scheme 4). Upon standing, lactol (+)-**14** slowly

Scheme 4. Key Acid-Mediated Cyclization
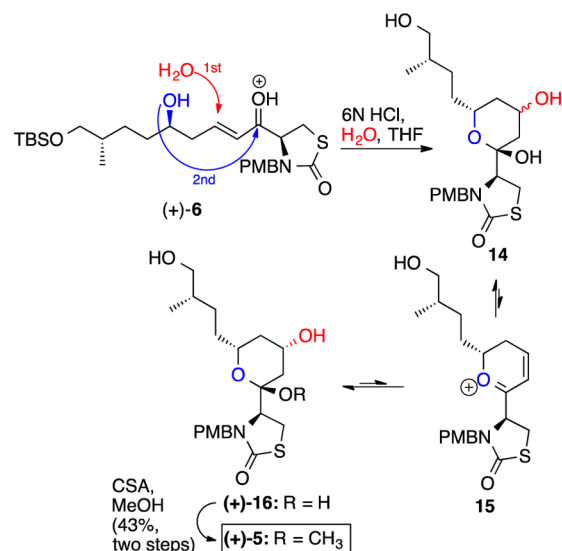
epimerized at room temperature; accordingly, the conversion to methyl ketal (+)-**5** was conducted immediately following the cyclization by treatment of lactol (+)-**14** with acidic methanol to provide (+)-**5** as a single diastereomer in 43% yield over two steps. Multiple byproducts and a small amount of the minor β-diastereomer accounted for the remaining mass balance of the acid-mediated cyclization of (+)-**6**. The mechanism proposed for the observed acid-mediated cyclization is depicted in Scheme 4. We reason that reversible formation of unsaturated oxonium intermediate **15** accounts for enrichment in the mixture of the diastereomeric secondary alcohols, thus providing the α-diastereomer (+)-**16** as the major product.[5−8]

Wittig olefination was next envisaged to unite the northern and southern hemispheres of (+)-18-*epi*-latrunculol A (**1**). However, we were cognizant of the challenges that a Wittig union had provided in the original synthesis of (+)-latrunculin A (**2**).[6,7] As indicated in our synthetic analysis, ketal (+)-**5** also held the promise of further elaboration to explore alternative coupling protocols (Scheme 5).

### Scheme 5. Envisioned Coupling Partners Arising from Ketal (+)-5
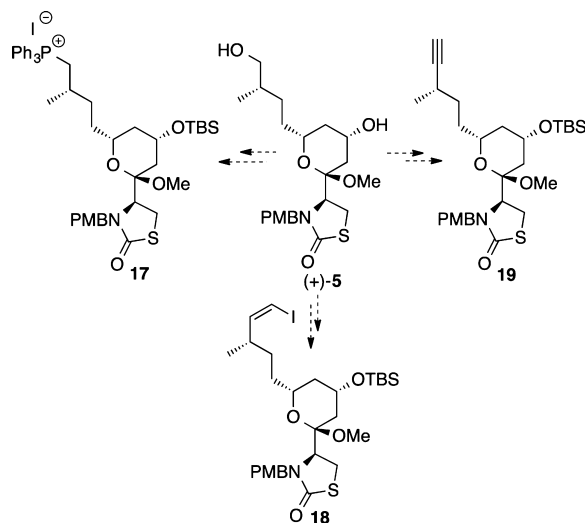
Proceeding with the Wittig olefination tactic, Wittig reagent (+)-**17** was prepared in three steps and 55% yield from (+)-**5** (Scheme 6). With (+)-**17** in hand, we explored the olefination protocol with benzaldehyde as a model coupling partner, employing NaHMDS to achieve deprotonation. Full conversion to a major product was observed, but to our surprise the product did not incorporate benzaldehyde; instead, phosphine oxide (+)-**21** was identified as the major product. Importantly, the reaction had been conducted under strictly anhydrous and deoxygenated conditions.[7,25,26] Nonetheless, all attempts afforded (+)-**21** as the major product, and no olefination was observed.

Undeterred, we turned to the alternative coupling protocols that could be accessed quickly from ketal (+)-**5** (Scheme 5). Vinyl iodide **18** and/or alkyne **19**, for example, would permit the union of the derived vinyl or alkynyl organometallic reagents to a northern hemisphere in the form of an aldehyde. Toward this end, vinyl iodide (+)-**18** and terminal alkyne (+)-**19** were each constructed in three steps from ketal (+)-**5** (Scheme 7). First, chemoselective oxidation of the primary alcohol provided the corresponding aldehyde. Subsequent

Scheme 6. Model Wittig Olefination
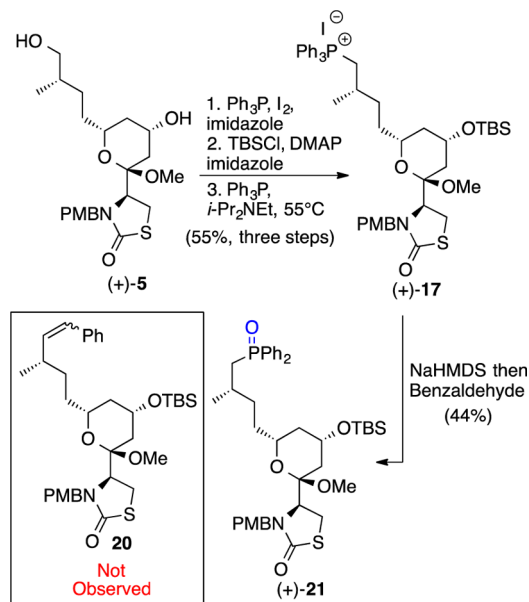
Scheme 7. Synthesis of Vinyl Iodide (+)-18 and Alkyne (+)-19
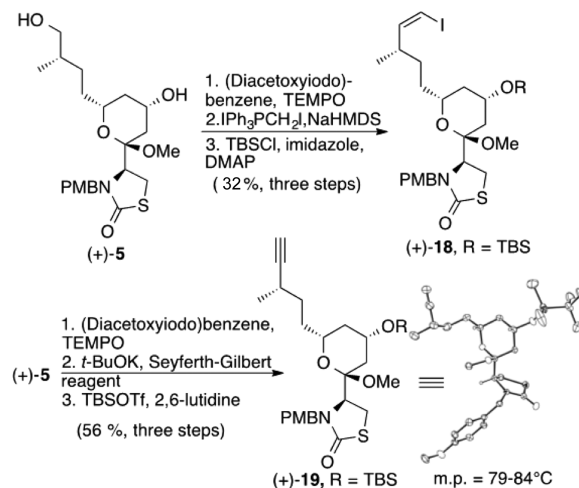
Stork−Zhao olefination[27] was followed by TBS protection of the secondary hydroxyl, which led to *cis*-vinyl iodide (+)-**18** in 32% yield over the three steps. Alternatively, application of the Seyferth−Gilbert reagent[28,29] delivered the terminal alkyne without epimerization of the α-stereocenter. Again, the secondary tetrahydropyran hydroxyl group was protected as a TBS ether to provide alkyne (+)-**19** in 56% yield from ketal (+)-**5**.

The requisite northern-hemisphere aldehyde (+)-**24** was next prepared in six steps from known alkynyl diol (−)-**22** (Scheme 8).[30] The synthesis began with the two-step chemoselective protection of (−)-**22**, which was followed by deprotonation of the alkynyl proton with *n*-BuLi and, in turn, addition of the resulting lithium acetylide to methyl chloroformate to deliver alkynoate (−)-**23**. Conjugate addition of Me₂CuLi then provided the *Z*-trisubstituted enoate, which was exposed to acetic acid-buffered TBAF to remove the primary TBS group. Interestingly, employing unbuffered TBAF to remove the TBS group led to complete isomerization of the trisubstituted enoate. Oxidation of the derived alcohol employing Parikh−
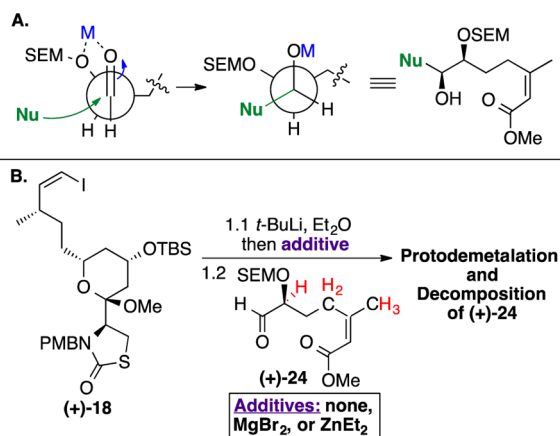
Scheme 8. Synthesis of Northern-Hemisphere Aldehyde (+)-24
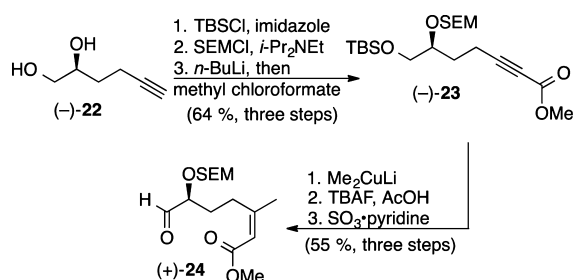
Doering conditions[31] then provided the requisite northern-hemisphere aldehyde (+)-**24** in a yield of 35% over the six steps.

On the basis of the transition state outlined in Scheme 9A, we reasoned that the chelation-controlled addition of a vinyl

**Scheme 9. Attempted Chelation-Controlled Addition of (+)-18 to (+)-24**

nucleophile, prepared via metalation of vinyl iodide (+)-**18**, to aldehyde (+)-**24** would lead to the desired *syn* stereochemistry. Somewhat surprisingly, however, addition of various metalated species derived from (+)-**18** to aldehyde (+)-**24** resulted only in protodemetalation and aldehyde decomposition (Scheme 9B). Presumably the decomposition of (+)-**24** is due to facile deprotonation of the acidic α- and/or γ-protons of the enoate (shown in red in Scheme 9) upon treatment with the strongly basic nucleophiles.

Aware of the pronounced base sensitivity of aldehyde (+)-**24**, we explored a Carreira alkynylation[32] employing alkyne (+)-**19**. The mild nature of the alkynylzinc nucleophile employed in this reaction was anticipated to circumvent decomposition. Pleasingly, after brief optimization of the Carreira alkynylation, the desired union of the northern and southern hemispheres was achieved to funish (+)-**25** in 95% yield, impressively as a single diastereomer (Scheme 10). Of considerable importance, prolonged drying of the Zn(OTf)$_2$ proved to be critical for the success of this union. The stereochemistry of the newly formed propargylic alcohol was confirmed via conversion to acetonide (+)-**26**, with the latter structure assigned by 2D NMR analysis. The NOE correlation illustrated in Scheme 10 proved particularly diagnostic.

With construction of the carbon skeleton of (+)-**18**-*epi*-latrunculol A (**1**) now achieved, we turned to the requisite

Scheme 10. Coupling of the Northern and Southern Hemispheres
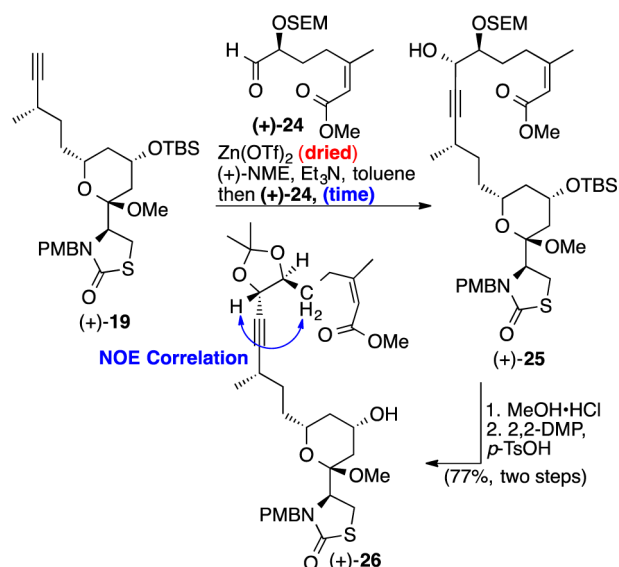
Conditions	Observations
1) Zn(OTf)$_2$ (flame dried)	No Reaction
2) Zn(OTf)$_2$ (dried overnight) Reaction Time: ca. 12 h	69 % (+)-**25**
3) Zn(OTf)$_2$ (dried overnight) Reaction Time: ca. 3 d	95 % (+)-**25**

alkyne semireduction. This transformation proved most difficult. No reduction was observed when (+)-**25** was subjected to either the Lindlar[33] or P-2 nickel boride[34] catalyst under a hydrogen atmosphere. To determine whether the steric environment of the internal alkyne was precluding the metal coordination necessary for hydrogenation, we turned to molecular mechanics calculations employing the MM2 force field. On the basis of these calculations as well as examination of a physical model of (+)-**25**, we discovered that in spite of the linear geometry of the alkyne, intermediate (+)-**25** could in fact attain the requisite orientation for the key Mitsunobu macrolactonization. With this scenario in mind as well as with the expectation that semireduction of an alkyne in a 16-membered macrolactone might be enhanced by ring strain,[11] we proceeded with the synthesis of the envisioned alkyne-containing seco acid. Propargyl alcohol (+)-**25** was protected as the SEM ether to maintain rotational freedom of the northern hemisphere (Scheme 11). Removal of the TBS ether was

Scheme 11. Synthesis of Seco Acid (+)-27
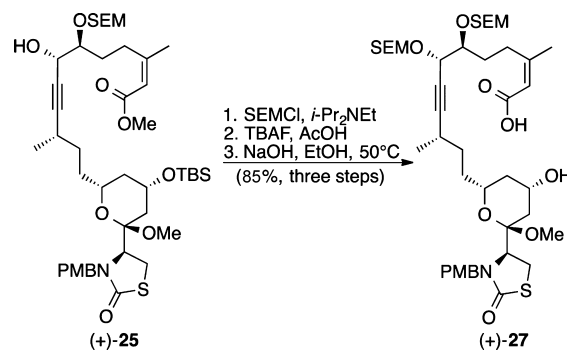
achieved by employing acetic acid-buffered TBAF. Hydrolysis of the methyl ester followed by warming of the ester to 50 °C with NaOH in ethanol provided the alkyne-containing seco acid (+)-**27** in 85% yield from (+)-**25**.

The anticipated Mitsunobu macrolactonization was then attempted by addition of triphenylphosphine and diisopropyl azodicarboxylate (DIAD) to seco acid (+)-**27** (Scheme 12).

**Scheme 12. Macrolactonization and Thiazolidinone Deprotection**
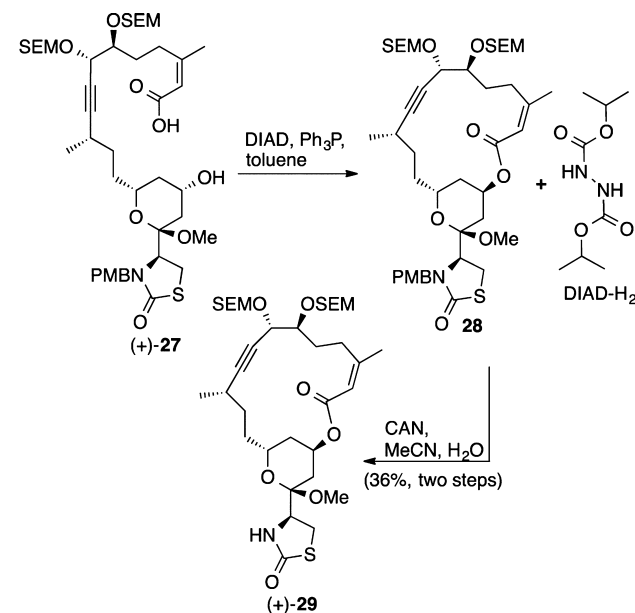
Although no reaction was observed in THF, toluene provided full conversion to macrolactone **28** and the reduced DIAD byproduct (DIAD-H$_2$), which unfortunately proved to be inseparable via standard silica gel chromatography. Treatment of the mixture with ceric ammonium nitrate (CAN) in aqueous acetonitrile pleasingly removed the PMB group to furnish deprotected macrolactone (+)-**29** in 36% yield from (+)-**27**, which could be readily purified via flash chromatography. A similar Mitsunobu macrolactonization employed in the original Smith synthesis of (+)-latrunculin A (**2**), although yielding a similarly 16-membered macrolactone in a 31% yield,[6] proved to be completely unworkable in this case because of the incompatible conditions required for removal of the PMB protecting group. Fürstner and co-workers observed similar decompositions of their late-stage macrolactones when attempting to remove the robust PMB protecting group and likewise required a protecting group interchange before completing their total synthesis of (+)-latrunculin A (**2**).[11] Presumably the macrolactone in (+)-**29** is more stable toward the strong oxidizing conditions required to remove the PMB group because (+)-**29** lacks the conjugated diene moiety present in the advanced (+)-latrunculin A (**2**) intermediates.

We next undertook global deprotection to remove both SEM protecting groups with concomitant hydrolysis of the ketal (Scheme 13). Extensive experimentation culminated in the use of aqueous acetic acid with catalytic camphorsulfonic acid (CSA) at 50 °C to provide the penultimate alkyne (+)-**30**. Although the global deprotection was achieved, removal of the SEM groups required extended reaction times (>12 h) at elevated temperature (50 °C), which resulted in varying
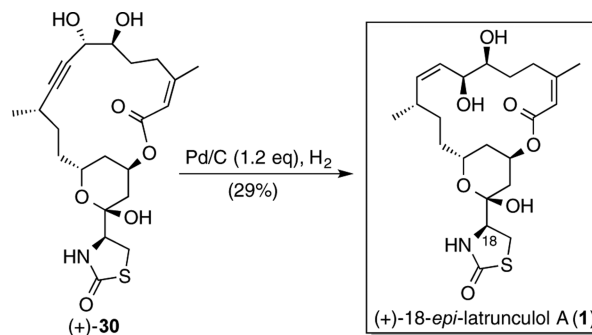
Scheme 13. Global Deprotection of Macrolactone (+)-29
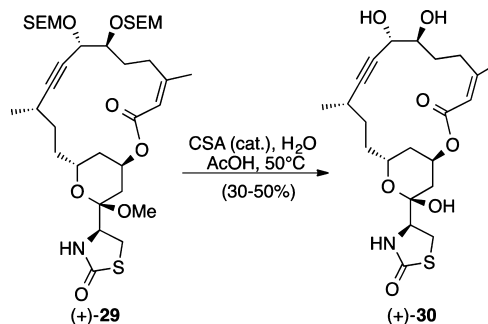
degrees of decomposition as well as inconsistent yields of (+)-**30** ranging from ca. 30% to 50%.

While moderate in yield, the global deprotection provided sufficient alkyne (+)-**30** to evaluate the final semireduction (Scheme 14). Again, semireduction employing either the

Scheme 14. Semireduction of Alkyne (+)-30

Lindlar or P-2 nickel boride catalyst under a hydrogen atmosphere did not proceed. Other reduction conditions, including Wilkinson's catalyst,[35] homogeneous palladium-catalyzed transfer hydrogenation, Adams' catalyst,[36] and a two-step hydroboration/protodeborylation sequence, also proved ineffective;[37] no reaction, over-reduction, and/or decomposition of starting material resulted. Ultimately we discovered that a catalytic quantity of palladium on carbon, without a poisoning agent, delivered the semireduction product, albeit with incomplete consumption of alkyne (+)-**30**. Fortunately, the use of 1.2 equiv of Pd/C (10 wt %) did eventually provide full conversion, but only a 29% isolated yield of (+)-18-*epi*-latrunculol A (**1**) was obtained.

The spectral data of synthetic (+)-18-*epi*-latrunculol A (**1**), including the ^{1}H NMR (500 MHz), HRMS parent ion identification, and chiroptic properties, proved identical in all respects to those reported for natural (+)-18-*epi*-latrunculol A (**1**).[14] Importantly, the observation of identical chiroptic properties for synthetic (+)-**1** permitted the assignment of the absolute stereochemistry of (+)-18-*epi*-latrunculol A (**1**). The ^{13}C NMR spectrum, however, proved problematic. When taken in acetone-d_6 as reported by Crews, the carbon resonances, while identical in chemical shift to those reported for natural (+)-18-*epi*-latrunculol A (**1**), appeared doubled in several cases, a hallmark of course of a diastereomeric mixture (Figure 2A). On the other hand, when the ^{13}C NMR spectrum of synthetic (+)-18-*epi*-latrunculol A (**1**) was taken in CDCl$_3$ instead of acetone-d_6, the spectrum revealed the correct number of chemical shifts required for (+)-**1**. Tracing the
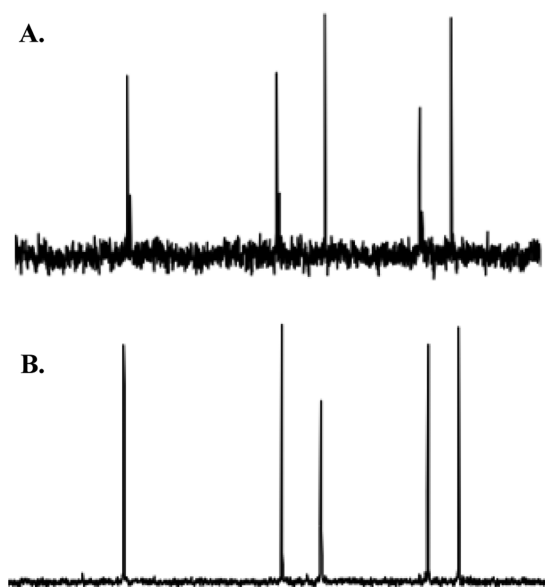
Figure 2. ^{13}C NMR spectra (60−80 ppm) of synthetic (+)-18-*epi*-latrunculol A (**1**) in (A) acetone-d_6 and (B) acetone-d_6 with added D_2O.

problem back to acetone-d_6, we observed both H_2O and DHO peaks in the ^1H NMR spectrum and thus speculated that a deuterium equilibrium exchange had occurred to account for the mixture observed in the ^{13}C NMR spectrum. Taking extreme care to introduce the acetone-d_6 under a strictly nitrogen atmosphere greatly reduced the amount of H_2O and DHO, and although the doubled peaks were still observable, they were considerably reduced (Figure 2A). Importantly, upon addition of D_2O to the NMR sample in acetone-d_6, the doubled carbon resonances were converted to a single set of resonances for deuterated 18-*epi*-latrunculol A (**1**) (Figure 2B; see the Supporting Information for the NMR spectra of deuterated 18-*epi*-latrunculol A).

With conclusive evidence that the first total synthesis, structural confirmation, and absolute configuration assignment of (+)-18-*epi*-latrunculol A (**1**) had been achieved, we returned to the optimization of the global deprotection and final semireduction to facilitate a preparatively useful synthesis of the natural product. Toward this end, we elected to explore an acetonide group to protect the vicinal diol, as such a group exchange would result in the same overall step count as in the bis-SEM sequence and, importantly, the acetonide was anticipated to be more acid-labile.[38]

Treatment of (+)-**25** with acidic methanol as described earlier (Scheme 10) removed both the SEM and TBS protecting groups while maintaining the mixed methyl ketal. The vicinal diol was in turn protected chemoselectively as the acetonide to provide (+)-**26** in 77% yield over the two steps. Upon hydrolysis of the methyl ester, the Mitsunobu macro-lactonization and subsequent PMB removal proceeded in a yield comparable to that in the SEM-protected sequence of intermediates to furnish macrolactone (+)-**31** in 35% yield from the methyl ester (Scheme 15). We were then particularly pleased to find that global deprotection delivered the penultimate alkyne (+)-**30** in 86% yield after only 2 h.

The low yield of the final semireduction was reasoned to be a consequence of the excess adsorbing carbon solid support (Scheme 14). Pleasingly, a change to barium carbonate as a less

Scheme 15. Revised Diol Protection and Semireduction
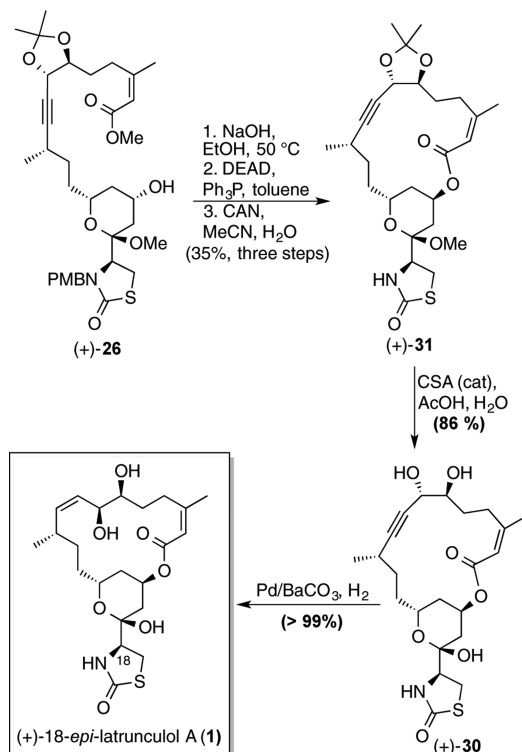
adsorbent solid support provided the semireduction of (+)-**30** in nearly quantitative yield, although a stoichiometric quantity of palladium was still required (Scheme 15). Synthetic (+)-18-*epi*-latrunculol A (**1**) was thus available upon semihydrogenation in 86% overall yield for the final two steps, a marked improvement from the previous protecting group strategy.

■ SUMMARY

We have reported here the total synthesis, structural validation, and assignment of the relative and absolute stereochemistry of (+)-18-*epi*-latrunculol A (**1**), exploiting a longest linear sequence of 20 steps from commercially available 5-hexenoic acid. Key steps in the successful route include a functional-group-compatible cross-metathesis reaction that avoids protection and oxidation steps required in all previous latrunculin synthetic ventures, an acid-mediated cyclization/equilibration sequence, an effective Carreira alkynylation, and a late-stage Mitsunobu macrolactonization. In addition, judicious selection of diol protection and successful optimization of the alkyne semireduction now permits access to synthetic (+)-18-*epi*-latrunculol A (**1**). Biological evaluation of the natural product and synthetic intermediates and further development of the tandem cyclization/equilibration of *trans-δ*-hydroxy enones are currently underway and will be reported in due course.

■ EXPERIMENTAL SECTION

Materials and Methods. Reactions were carried out in flame-dried or oven-dried glassware under a nitrogen atmosphere unless noted otherwise. Anhydrous diethyl ether (Et_2O), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and toluene were obtained from a solvent purification system. All of the commercially available reagents were used without purification unless otherwise noted. Triethylamine, diisopropylethylamine, and pyridine were freshly distilled from calcium hydride under a nitrogen atmosphere. Reactions were magnetically stirred unless stated otherwise and monitored by thin-layer

chromatography (TLC) with 0.25 mm Silacycle precoated silica gel plates. Silica gel chromatography was performed utilizing ACS-grade solvents and silica gel from either Silacycle or Sorbent Technologies. Infrared spectra were obtained using an FT-IR spectrometer. Optical rotations were obtained using a polarimeter. All melting points were obtained on a melting point apparatus and are uncorrected. ^{1}H NMR spectra (500 MHz field strength) and ^{13}C NMR spectra (125 MHz field strength) were obtained on a 500 MHz spectrometer or a cryomagnet (500 MHz/52 mm) with a 5 mm dual cryoprobe. Chemical shifts are reported relative to chloroform (δ 7.27) or acetone (δ 2.05) for ^{1}H NMR spectra and chloroform (δ 77.23) or acetone (δ 206.68, 29.92) for ^{13}C spectra. High-resolution mass spectrometry (HRMS) was performed on an LC-TOF mass spectrometer.

(S)-3-(4-Methoxybenzyl)-2-oxothiazolidine-4-carboxylic Acid [(+)-10]. To a solution of D-cysteine hydrochloride hydrate (25 g, 142.34 mmol) in an aqueous sodium hydroxide solution (28.47 g of NaOH, 140 mL of H$_2$O) cooled to 0 °C was added phenyl chloroformate (39 mL, 313.15 mmol) in toluene (60 mL) dropwise via an addition funnel. After the addition was complete, the reaction mixture was allowed to warm to room temperature, where it was stirred overnight and then quenched with toluene (60 mL) and H$_2$O (60 mL). The aqueous layer was washed with toluene (3 × 50 mL). The aqueous layer was acidified by dropwise addition of 1 N HCl to pH < 1, and the solution was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo to provide a white solid that was used without further purification.

To a solution of the previously obtained white solid in H$_2$O (14 mL), DMSO (48 mL), and NaOH (11.1 g, 278 mmol) cooled to 0 °C was added p-methoxybenzyl chloride (25 mL, 184.4 mmol) dropwise. After the addition was complete, the ice−water bath was removed and the reaction mixture was stirred at room temperature for 14 h. The reaction mixture became cloudy with a white precipitate. The reaction mixture was partitioned between diethyl ether (50 mL) and 0.5 N NaOH(aq) (50 mL). The aqueous layer was separated and washed with diethyl ether (2 × 50 mL). The aqueous layer was acidified to pH < 1 by dropwise addition of 6 N HCl to the stirring basic aqueous solution. The cloudy white mixture was extracted with EtOAc (3 × 75 mL) and concentrated in vacuo to yield (+)-**10** (16.0 g, 59.86 mmol, 65% over two steps) as a brown oil. $[\alpha]_D^{21}$ +53.2 (c 0.36, CHCl$_3$); IR (neat, cm^{-1}) 2934, 1740, 1612, 1514, 1444, 1396, 1248; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.20 (d, J = 8.3 Hz, 2H), 6.89 (d, J = 8.3 Hz, 2H), 5.15 (d, J = 14.5 Hz, 1H), 4.20 (dd, J = 2.8, 8.3 Hz, 1H), 4.02 (d, J = 15.7 Hz, 1H), 3.81 (s, 3H), 3.54 (dd, J = 9.3, 11.7 Hz, 1H), 3.42 (dd, J = 2.8, 12.3 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 174.5, 172.0, 159.7, 130.1, 127.5, 114.6, 59.0, 55.6, 47.6, 29.2; HRMS (ESI-TOF) m/z (M − H)$^-$ calcd for C$_{12}$H$_{12}$NO$_4$S 266.0487, found 266.0475.

(S)-4-Acryloyl-3-(4-methoxybenzyl)thiazolidin-2-one [(+)-9]. To a solution of acid (+)-**10** (16 g, 59.86 mmol) in CH$_2$Cl$_2$ (200 mL) was added i-Pr$_2$NEt (31.4 mL, 179.58 mmol) N,O-dimethylhydroxylamine hydrochloride (9.93 g, 179.58 mmol), and then TBTU (28.8 g, 89.79 mmol) portionwise. The reaction mixture became cloudy with a white precipitate and was stirred overnight. The reaction mixture was quenched with 1.2 N HCl (100 mL), and the biphasic mixture was extracted with CH$_2$Cl$_2$ (4 × 100 mL). The combined organic layers were washed with 0.5 N NaOH (100 mL) and then concentrated in vacuo. The crude mixture was purified via column chromatography on SiO$_2$ (60% EtOAc/hexanes) to provide Weinreb amide (+)-**S1** (for structures **S1−S11** see the Supporting Information) (15.35 g, 49.46 mmol, 83%) as a brown oil. $[\alpha]_D^{21}$ +76.1 (c 1, CHCl$_3$); IR (neat, cm^{-1}) 2935, 1678, 1513, 1444, 1393, 1303; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.16 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.15 (d, J = 15.3 Hz, 1H), 4.40 (dd, J = 5.7, 8.1 Hz, 1H), 3.85 (d, J = 14.9 Hz, 1H), 3.80 (s, 3H), 3.47 (dd, J = 8.9, 11.3 Hz, 1H), 3.38 (s, 3H), 3.21 (s, 3H), 3.16 (dd, J = 4.8, 11.3 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 172.5, 169.4, 159.6, 130.3, 127.9, 114.4, 61.5, 57.7, 55.5, 47.2, 32.8, 28.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for C$_{14}$H$_{18}$N$_2$NaO$_4$S 333.0885, found 333.0887.

To a solution of Weinreb amide (+)-**S1** (316 mg, 1.018 mmol) in THF (3 mL) cooled to 0 °C was added dropwise a solution of freshly prepared vinylmagnesium bromide in THF (2.1 M, 2.5 mL). The reaction mixture was stirred for 15 min before it was slowly poured into stirring 2 N HCl (10 mL) at room temperature and extracted with CH$_2$Cl$_2$ (3 × 15 mL). The combined organic layers were washed with a saturated aqueous solution of NaHCO$_3$, dried over Na$_2$SO$_4$, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO$_2$ (60% EtOAc/hexanes) to provide (+)-**9** (181 mg, 0.653 mmol, 64%) as a yellow oil. $[\alpha]_D^{21}$ +69.4 (c 0.75, CHCl$_3$); IR (neat, cm^{-1}) 1672, 1612, 1513, 1248, 1175; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.12 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 6.49 (dd, J = 11.1, 17.4 Hz, 1H), 6.36 (dd, J = 1.0, 17.0 Hz, 1H), 5.90 (dd, J = 1.0, 10.5 Hz, 1H), 5.07 (d, J = 14.7 Hz, 1H), 4.34 (dd, J = 4.6, 9.3 Hz, 1H), 3.83 (d, J = 15.1 Hz, 1H), 3.80 (s, 3H), 3.51 (dd, J = 9.7, 11.9 Hz, 1H), 3.14 (dd, J = 4.6, 11.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.4, 172.0, 159.7, 131.7, 131.4, 130.2, 127.4, 114.4, 63.7, 55.4, 47.4, 27.9; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for C$_{14}$H$_{15}$NNaO$_3$S 300.0670, found 300.0684.

(S)-4-(3-(Methoxy(methyl)amino)propanoyl)-3-(4-methoxybenzyl)thiazolidin-2-one [(+)-11]. Orange crystalline solid, melting point 87−89 °C; $[\alpha]_D^{21}$ +40.9 (c 1.0, CHCl$_3$); IR (neat, cm^{-1}) 2935, 1724, 1674, 1611, 1513; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.13 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.06 (d, J = 13.9 Hz, 1H), 4.19 (dd, J = 5.2, 9.3 Hz, 1H), 3.86 (d, J = 13.3 Hz, 1H), 3.80 (s, 3H), 3.51 (dd, J = 10.3, 11.3 Hz, 1H), 3.43 (s, 3H), 3.18 (dd, J = 4.0, 12.3 Hz, 1H), 2.97−2.83 (m, 2H), 2.66 (t, J = 6.3 Hz, 2H), 2.57 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 205.4, 171.9, 159.7, 130.1, 127.6, 114.5, 65.2, 60.0, 55.5, 54.8, 47.5, 45.0, 36.9, 27.9; HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for C$_{16}$H$_{23}$N$_2$O$_4$S 339.1379, found 339.1374.

(S)-5-((tert-Butyldimethylsilyl)oxy)-4-methylpentanal [(−)-8]. To a solution of alcohol (−)-**13**[23] (1 g, 8.76 mmol) in CH$_2$Cl$_2$ (30 mL) at RT was added imidazole (775 mg, 11.39 mmol) followed by TBSCl (1.39 g, 9.2 mmol). The clear reaction mixture became cloudy with a white precipitate. After 30 min, 0.5 M HCl (20 mL) and CH$_2$Cl$_2$ (20 mL) were added. The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (2 × 20 mL). The combined organic layers were washed with a saturated aqueous solution of NaHCO$_3$ (10 mL) and brine (10 mL) sequentially and then dried over Na$_2$SO$_4$, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO$_2$ (5% Et$_2$O/hexanes) to provide (−)-**S2** (1.804 g, 7.89 mmol, 90%) as a clear oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.91−5.75 (m, 1H), 5.02 (dd, J = 17.1, 1.7 Hz, 1H), 4.95 (app d, J = 10 Hz, 1H), 3.46 (dd, J = 5.9, 9.5 Hz, 1H), 3.39 (dd, J = 6.7, 9.5 Hz, 1H), 2.20−2.08 (m, 1H), 2.07−1.95 (m, 1H), 1.70−1.58 (m, 1H), 1.57−1.46 (m, 1H), 1.23−1.11 (m, 1H), 0.91 (s, 9H), 0.89 (d, J = 6.7 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 139.5, 114.3, 68.5, 35.5, 32.6, 31.5, 26.2, 18.6, 16.8, −5.1.

Ozone was bubbled through a solution of olefin (−)-**S2** (3.98 g, 17.42 mmol) in CH$_2$Cl$_2$ (60 mL) at −78 °C until the reaction mixture appeared blue (3 h). A stream of nitrogen was then bubbled through the reaction mixture until the reaction mixture was again clear and no blue color remained. Triphenylphosphine (4.71 g, 17.94 mmol) was then added in one portion at −78 °C, and after the addition the reaction mixture was allowed to warm to RT and stirred overnight. Et$_3$N-buffered silica (stirred with 2 mL of Et$_3$N and 100 mL of hexanes) was added, and the mixture was concentrated in vacuo. The crude mixture, adsorbed onto Et$_3$N-buffered silica, was purified via column chromatography on SiO$_2$ (100% hexanes to 5% Et$_2$O/hexanes) to provide (−)-**8** (3.15 g, 13.67 mmol, 79%) as a clear oil.

The spectral data matched those previously reported.[21] ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.82−9.72 (m, 1H), 3.43 (s, 2H), 2.53−2.38 (m, 2H), 1.83−1.73 (m, 1H), 1.68−1.57 (m, 1H), 1.50−1.39 (m, 1H), 0.98−0.81 (m, 12H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 203.0, 68.0, 41.9, 35.5, 26.1, 25.7, 18.5, 16.7, −5.2, −5.2.

(S)-4-((5R,8S,E)-9-((tert-Butyldimethylsilyl)oxy)-5-hydroxy-8-methylnon-2-enoyl)-3-(4-methoxybenzyl)thiazolidin-2-one [(+)-6]. To a solution of (−)-B-Methoxydiisopinocampheylborane (3.72 g, 11.8 mmol) in Et$_2$O (29 mL) at 0 °C was added a 1 M solution of allylmagnesium bromide in Et$_2$O (11.8 mL, 11.8 mmol). After the

addition was complete, the ice bath was removed and the reaction mixture was stirred for 1 h at RT. The mixture was cooled to −78 °C, and a solution of aldehyde (−)-**8** (2.58 g, 11.2 mmol) in Et$_2$O (10 mL) was added dropwise down the side of the flask; additional Et$_2$O (5 mL) was used to wash any residual aldehyde. The reaction mixture was stirred at −78 °C for 3 h and then allowed to slowly warm to RT overnight, after which NaOH (3 N, 8 mL) and H$_2$O$_2$ (30% w/w, 3 mL) were added and the mixture was refluxed for 2 h. After cooling, the mixture was extracted with Et$_2$O (2 × 100 mL), and the combined organic layers were dried over Na$_2$SO$_4$, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO$_2$ (10% EtOAc/hexanes) to provide the allylic alcohol (3.10 g) contaminated with a minor amount of the epimeric alcohol, which was used in next reaction without further purification.

To a portion of the allylic alcohol mixture (197 mg) in DCE (4 mL) was added (+)-**9** (600 mg, 2.16 mmol, 3 equiv), and the mixture was sparged with N$_2$ for 20 min. Hoveyda−Grubbs second-generation catalyst (45 mg, 0.072 mmol, 10 mol %) was then added at RT, after which N$_2$ sparging was resumed and the reaction mixture was heated to 50 °C. After 3 h 20 min, charcoal (ca. 50 mg) was added, and the reaction mixture was stirred for 1 h. Silica (ca. 1 g) was then added, and the solvent was removed in vacuo. The crude mixture was purified via column chromatography on SiO$_2$ (10% EtOAc/CH$_2$Cl$_2$) to provide (+)-**6** [262 mg, 0.502 mmol, 70% from aldehyde (−)-**8**] and recovered (+)-**9** (287 mg, 1.04 mmol, 72% recovery). (+)-**6**: $[\alpha]_D^{21}$ +66.7 (c 0.93, CHCl$_3$); IR (neat) 3459, 2929, 2856, 1682, 1514, 1250; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.12 (d, J = 8.7 Hz, 2H), 7.03 (dt, J = 15.5, 6.9 Hz, 1H), 6.84 (d, J = 7.9 Hz, 2H), 6.27 (d, J = 15.9 Hz, 1H), 5.04 (d, J = 15.7 Hz, 1H), 4.30 (dd, J = 4.6, 9.3 Hz, 1H), 3.84 (d, J = 15.9 Hz, 1H), 3.79 (s, 3H), 3.76−3.70 (m, 1H), 3.49 (dd, J = 9.3, 11.7 Hz, 1H), 3.43 (d, J = 5.9 Hz, 2H), 3.14 (dd, J = 4.8, 10.1 Hz, 1H), 2.47−2.39 (m, 1H), 2.38−2.28 (m, 1H), 1.90−1.81 (m, 1H), 1.66−1.59 (m, 1H), 1.59−1.52 (m, 2H), 1.51−1.39 (m, 1H), 1.18−1.09 (m, 1H), 0.91−0.86 (m, 12H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.0, 172.2, 159.6, 148.1, 130.2, 127.6, 127.0, 114.4, 71.1, 68.3, 64.1, 55.5, 47.5, 40.6, 35.9, 35.1, 29.3, 28.2, 26.1, 18.5, 17.0, −5.2, −5.2; HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for C$_{27}$H$_{44}$NO$_5$SSi 522.2709, found 522.2688.

(S)-4-((2R,4S,6R)-2,4-Dihydroxy-6-((S)-4-hydroxy-3-methylbutyl)-tetrahydro-2H-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one [(+)-16]. To a solution of enone (+)-**6** (25 mg, 0.048 mmol) in THF (0.28 mL) was added 6 N HCl (0.21 mL) dropwise at 20 °C. After the reaction mixture was stirred for 19 h, a saturated aqueous solution of NaHCO$_3$ (5 mL) was added, followed by extraction with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were dried over Na$_2$SO$_4$, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO$_2$ (100% EtOAc) to provide lactol (+)-**16** (16 mg) as a yellow oil with minor impurities that was used in the following reaction without further purification. $[\alpha]_D^{21}$ +30.0 (c 1.0, CHCl$_3$); IR (neat) 3370, 2934, 1650, 1513, 1444, 1400; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.2 (d, J = 8.2 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 5.16 (d, J = 14.9 Hz, 1H), 4.45 (d, J = 14.3 Hz, 1H), 4.19−4.11 (m, 1H), 3.93−3.85 (m, 1H), 3.81 (s, 3H), 3.64 (dd, J = 5.2, 7.7 Hz, 1H), 3.45 (d, J = 5.7 Hz, 2H), 3.29−3.23 (m, 2H), 2.15 (dd, J = 4.1, 12.0 Hz, 1H), 2.0 (d, J = 12 Hz, 1H), 1.89 (bs, 2H), 1.66−1.53 (m, 4H), 1.35−1.11 (m, 3H), 0.92 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 174.3, 159.4, 129.8, 128.8, 114.4, 100.5, 70.0, 68.1, 64.7, 64.5, 55.5, 48.4, 40.5, 38.9, 35.9, 33.1, 29.1, 26.7, 16.7; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for C$_{21}$H$_{31}$NNaO$_6$S 448.1770, found 448.1782.

(S)-4-((2R,4S,6R)-4-Hydroxy-6-((S)-4-hydroxy-3-methylbutyl)-2-methoxytetrahydro-2H-pyran-2-yl)-3-(4-methoxybenzyl)thiazol-idin-2-one [(+)-5]. To a solution of lactol (+)-**16** (16 mg) with minor impurities in MeOH (0.4 mL) was added camphorsulfonic acid (1 mg, 0.004 mmol), and the reaction mixture was stirred overnight at RT. The reaction was quenched with a saturated aqueous solution of NaHCO$_3$ (5 mL), which was followed by extraction with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were dried over Na$_2$SO$_4$, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO$_2$ (80% EtOAc/hexanes) to

provide (+)-**5** [9 mg, 0.021 mmol, 43% from enone (+)-**6**] as a clear oil. $[\alpha]_D^{21}$ +46.1 (c 0.95, CHCl$_3$); IR (neat) 3411, 2933, 1655, 1513, 1452, 1396, 1248; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.15 (d, J = 9.1 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 5.24 (d, J = 15.1 Hz, 1H), 4.22 (d, J = 14.9 Hz, 1H), 4.13−4.03 (m, 1H), 3.95 (dd, J = 4.8, 10.3 Hz, 1H), 3.81 (s, 3H), 3.56−3.49 (m, 1H), 3.46 (t, J = 5.7 Hz, 1H), 3.41−3.26 (m, 2H), 3.02 (s, 3H), 2.11 (dd, J = 4.6, 11.9 Hz, 1H), 1.99 (d, J = 11.7 Hz, 1H), 1.73−1.43 (m, 8H), 1.29−1.16 (m, 1H), 1.15−1.07 (m, 1H), 0.91 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 173.4, 159.2, 128.8, 128.6, 114.3, 102.6, 70.5, 68.1, 64.8, 57.0, 55.4, 47.9, 46.9, 40.2, 37.8, 35.8, 33.1, 28.9, 26.4, 16.6; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for C$_{22}$H$_{33}$NNaO$_6$S 462.1926, found 462.1912.

((S)-4-((2R,4S,6R)-4-((tert-Butyldimethylsilyl)oxy)-6-methoxy-6-((S)-3-(4-methoxybenzyl)-2-oxothiazolidin-4-yl)tetrahydro-2H-pyran-2-yl)-2-methylbutyl)triphenylphosphonium iodide [(+)-17]. To a solution of methyl ketal (+)-**5** (165 mg, 0.375 mmol) in CH$_2$Cl$_2$ (4 mL) were added imidazole (153 mg, 2.25 mmol), triphenyl phosphine (296 mg, 1.13 mmol), and finally iodine (248 mg, 0.975 mmol), and the reaction mixture was stirred overnight at RT. A 1:1 mixture of a 10% aqueous solution of Na$_2$S$_2$O$_3$ (5 mL) and a saturated aqueous solution of sodium bicarbonate (5 mL) was added to quench the reaction mixture. To the resulting biphasic solution was added additional CH$_2$Cl$_2$ (5 mL), and the organic layer was removed. The aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 5 mL), and the combined organic layers were dried over Na$_2$SO$_4$, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO$_2$ (40% EtOAc/hexanes) to provide the primary iodide (172 mg, 0.313 mmol, 84%) as a clear oil that was used directly in the next reaction.

To a solution of the prepared primary iodide (170 mg, 0.31 mmol) in CH$_2$Cl$_2$ (3 mL) was added imidazole (53 mg, 0.78 mmol), DMAP (19 mg, 0.16 mmol), and then TBSCl (71 mg, 0.47 mmol) portionwise. After the reaction mixture was stirred overnight, a saturated aqueous solution of sodium bicarbonate (10 mL) was added to quench the reaction mixture. To the resulting biphasic solution was added additional CH$_2$Cl$_2$ (15 mL), and the organic layer was removed. The aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 15 mL), and the combined organic layers were dried over Na$_2$SO$_4$, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO$_2$ (10% EtOAc/hexanes) to provide the TBS-ether (175 mg, 0.264 mmol, 84%) as a clear oil that was used directly in the next reaction.

To a solution of the TBS-ether (108 mg, 0.163 mmol) in acetonitrile (2 mL) were added triphenylphosphine (640 mg, 2.44 mmol) and i-Pr$_2$NEt (0.2 mL, 1.14 mmol), and the reaction mixture was heated to 55 °C for 48 h and then concentrated in vacuo to afford an orange oil that was purified via filtration through a short pad of SiO$_2$. Washing with EtOAc to remove residual triphenylphosphine and triphenylphosphine oxide followed by washing with 5% MeOH in CH$_2$Cl$_2$ provided Wittig reagent (+)-**17** as an orange foam (118 mg, 0.13 mmol, 78%). $[\alpha]_D^{21}$ +24.6 (c 1.0, CHCl$_3$); IR (neat, cm^{-1}) 2927, 1667, 1512, 1438; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90−7.82 (m, 4H), 7.71−7.61 (m, 8H), 7.55 (t, J = 7.7 Hz, 1H), 7.50−7.44 (m, 2H), 7.16 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 5.15 (d, J = 16.1 Hz, 1H), 4.19 (d, J = 16.1 Hz, 1H), 4.02−3.86 (m, 2H), 3.81 (s, 3H), 3.76−3.63 (m, 2H), 3.40 (t, J = 9.6 Hz, 1H), 3.27−3.18 (m, 2H), 2.84 (s, 3H), 1.86 (dd, J = 4.5, 13.5 Hz, 1H), 1.86−1.78 (m, 1H), 1.77−1.65 (m, 4H), 1.58−1.47 (m, 3H), 1.25−1.18 (m, 1H), 1.04 (d, J = 6.4 Hz, 3H), 0.87, (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 173.5, 159.3, 135.2, 133.9 (d, J = 9.6 Hz), 132.3 (d, J = 11.8 Hz), 132.1, 130.6 (d, J = 11.8 Hz), 129.0, 128.8 (d, J = 3.2 Hz), 128.6, 119.5, 118.8, 114.4, 102.6, 69.8, 65.2, 57.0, 55.6, 48.3, 46.9, 37.8, 33.7 (d, J = 10.2 Hz), 33.3, 30.3, 29.9, 29.8 (d, J = 3.3 Hz), 26.5, 26.1, 21.0 (d, J = 8.7 Hz), 18.2, −4.3, −4.4; HRMS (ESI-TOF) m/z (M)$^+$ calcd for C$_{46}$H$_{61}$NO$_5$PSSi 798.3777, found 798.3763.

(S)-4-((2R,4S,6R)-4-((tert-Butyldimethylsilyl)oxy)-6-((S)-4-(diphe-nylphosphoryl)-3-methylbutyl)-2-methoxytetrahydro-2H-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one [(+)-21]. To a solution of Wittig reagent (+)-**17** (5 mg, 5 μmol) in THF (0.1 mL) at 0 °C was slowly added NaHMDS (1M, 50 μL), which turned the reaction

mixture red. After the reaction mixture was stirred at 0 °C for 10 min, benzaldehyde (10 μL, 10 mg, 0.01 mmol) was added. After 5 min of stirring, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (5 mL). To the resulting biphasic solution was added additional CH_2Cl_2 (5 mL), and the organic layer was removed. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO_2 (40% EtOAc/hexanes) to provide (+)-**21** with an unidentified contaminant. The mixture was then further purified via preparative TLC (250 μm, 60% EtOAc/hexanes) to provide (+)-**21** (1.6 mg, 2.2 μmol, 44%) as a clear film. $[\alpha]_D^{21}$ +33.0 (c 0.11, CHCl₃); IR (neat, cm⁻¹) 2926, 2854, 1673, 1514, 1459, 1386; ¹H NMR (500 MHz, CDCl₃) δ 7.76−7.69 (m, 4H), 7.52−7.36 (m, 6H), 7.15 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 5.19 (d, J = 15.6 Hz, 1H), 4.21 (d, J = 15.6 Hz, 1H), 3.96 (sept, J = 5.9 Hz, 1H), 3.83 (dd, J = 4.4, 9.3 Hz, 1H), 3.81 (s, 3H), 3.37−3.20 (m, 3H), 2.88 (s, 3H), 2.31−2.22 (m, 1H), 2.12−2.11 (m, 1H), 2.08−1.96 (m, 1H), 1.87 (dd, J = 4.7, 13.1 Hz), 1.72 (app dt, J = 2.2, 12.8 Hz, 1H), 1.55 (dd, J = 10.4, 13.1 Hz, 2H), 1.47−1.33 (m, 2H), 1.15 (q, J = 12.7 Hz, 2H), 0.98 (d, J = 6.7 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 173.6, 159.0, 131.6, 131.6, 130.7 (d, J = 10.4 Hz), 130.6 (d, J = 9.5 Hz), 128.8, 128.7 (d, J = 5.3 Hz), 128.6 (d, J = 5.6 Hz), 128.5, 114.1, 102.5, 69.9, 65.1, 57.0, 55.3, 47.7, 46.7, 40.8, 37.6, 37.1, 36.5, 34.0, 32.7, 29.7, 28.1 (d, J = 3.4 Hz), 26.3, 25.9, 21.5 (d, J = 8.3 Hz), 18.1, −4.5, −4.6. HRMS (ESI-TOF) m/z (M + H)⁺ calcd for $C_{40}H_{57}NO_6PSSi$ 738.3414, found 738.3427.

(S)-4-((2R,4S,6R)-4-((tert-Butyldimethylsilyl)oxy)-6-((S,Z)-5-iodo-3-methylpent-4-en-1-yl)-2-methoxytetrahydro-2H-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one [(+)-18]. To a solution of ketal (+)-**5** (400 mg, 0.91 mmol) in CH_2Cl_2 (9 mL) cooled to 0 °C was added TEMPO (21 mg, 0.137 mmol) followed by (diacetoxyiodo)-benzene (264 mg, 0.819 mmol) portionwise. After 12 h, the reaction mixture was partitioned between CH_2Cl_2 (10 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO_2 (60% EtOAc/hexanes) to provide hydroxy aldehyde (+)-**S3** (286 mg, 0.654 mmol, 72%) as a clear oil. $[\alpha]_D^{21}$ +40.9 (c 0.39, CHCl₃); IR (neat) 3438, 2929, 2845, 1721, 1669, 1612, 1513, 1456, 1395; ¹H NMR (500 MHz, CDCl₃) δ 9.59 (d, J = 1.6 Hz, 1H), 7.14 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.22 (d, J = 15.3 Hz, 1H), 4.21 (d, J = 14.9 Hz, 1H), 4.07 (sept, J = 4.2 Hz, 1H), 3.96 (dd, J = 3.2, 9.3 Hz, 1H), 3.80 (s, 3H), 3.58−3.48 (m, 1H), 3.43−3.27 (m, 2H), 3.00 (s, 3H), 2.32 (q, J = 7.1 Hz, 1H), 2.10 (dd, J = 5.2, 12.5 Hz, 1H), 1.97 (d, J = 12.7 Hz, 2H), 1.93−1.77 (m, 1H), 1.65 (t, J = 11.1 Hz, 1H), 1.53 (q, J = 7.5 Hz, 2H), 1.40−1.30 (m, 1H), 1.29−1.15 (m, 2H), 1.10 (d, J = 7.1 Hz, 3H), 0.91−0.75 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 204.8, 173.5, 159.2, 128.7, 128.6, 114.3, 102.7, 70.1, 64.5, 56.9, 55.4, 47.8, 46.8, 46.3, 40.1, 37.7, 33.0, 26.4, 26.3, 13.6; HRMS (ESI-TOF) m/z (M + H)⁺ calcd for $C_{22}H_{32}NO_6S$ 438.1950, found 438.1938.

To a solution of IPh_3PCH_2I (1.26 g, 2.38 mmol) in THF (24 mL) was added NaHMDS (1 M, 1.9 mL) at RT, and the reaction mixture was stirred for ca. 1 min and then cooled to −60 °C. HMPA (0.66 mL, 3.81 mmol) was added, and the reaction mixture was further cooled to −78 °C, after which hydroxy aldehyde (+)-**S3** (104 mg, 0.24 mmol) in THF (ca. 1 mL) was added dropwise. After 1 h of stirring at −78 °C, the reaction mixture was quenched by the addition of a saturated aqueous solution of ammonium chloride (5 mL). The biphasic mixture was extracted with diethyl ether (3 × 5 mL), and the combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO_2 (45−50% EtOAc/hexanes) to provide the hydroxyvinyl iodide (60 mg, 0.107 mmol, 45%) as a brown foam that was used directly in the next reaction.

To a solution of the hydroxy vinyl iodide (60 mg, 0.11 mmol) in CH_2Cl_2 (0.4 mL) were added imidazole (15 mg, 0.214 mmol), DMAP (7 mg, 0.054 mmol), and finally TBSCl (24 mg, 0.16 mmol), and the resulting mixture was stirred at RT overnight. The reaction was

incomplete after 14 h, so again imidazole (15 mg, 0.214 mmol), DMAP (7 mg, 0.054 mmol), and finally TBSCl (24 mg, 0.16 mmol) were added. After 12 h, a saturated aqueous solution of sodium bicarbonate (ca. 5 mL) was added to quench the reaction. The biphasic mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO_2 (30% EtOAc/hexanes) to provide vinyl iodide (+)-**18** (74 mg, 0.11 mmol, quant.) as an oil. $[\alpha]_D^{21}$ +15.4 (c 0.14, CHCl₃); IR (neat, cm⁻¹) 2927, 2856, 1676, 1513, 1457, 1389; ¹H NMR (500 MHz, CDCl₃) δ 7.16 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.15 (d, J = 7.1 Hz, 1H), 5.88 (dd, J = 7.4, 9.0 Hz, 1H), 5.20 (d, J = 15.3 Hz, 1H), 4.26 (d, J = 15.4 Hz, 1H), 4.02 (sept, J = 5.0 Hz, 1H), 3.95 (dd, J = 4.0, 9.3 Hz, 1H), 3.81 (s, 3H), 3.56−3.50 (m, 1H), 3.39−3.29 (m, 2H), 3.04 (s, 3H), 2.50 (quin, J = 6.0 Hz, 1H), 1.92 (dd, J = 1.4, 4.9 Hz, 1H), 1.81 (dt, J = 2.3, 12.4 Hz, 1H), 1.59 (dd, J = 10.5, 13.0 Hz, 1H), 1.52−1.36 (m, 5H), 1.24 (d, J = 12.2 Hz, 2H), 0.98 (d, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.076 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 173.8, 159.2, 146.5, 129.0, 128.8, 114.4, 102.8, 81.2, 70.0, 65.4, 57.5, 55.5, 48.0, 47.1, 41.0, 39.4, 38.1, 33.2, 31.9, 29.9, 26.5, 26.1, 19.6, 18.3, −4.3, −4.4; HRMS (ESI-TOF) m/z (M + Na)⁺ calcd for $C_{29}H_{46}INNaO_5SSi$ 698.1808, found 698.1774.

(S)-4-((2R,4S,6R)-4-((tert-Butyldimethylsilyl)oxy)-2-methoxy-6-((S)-3-methylpent-4-yn-1-yl)tetrahydro-2H-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one [(+)-19]. To a 1.0 M solution of t-BuOK in THF (4.6 mL, 4.6 mmol) cooled to −78 °C was added Seyferth−Gilbert reagent (789 mg, 5.26 mmol) in THF (7 mL) down the side of the reaction vessel. The reagent was washed with THF (3 mL), and the reaction mixture turned yellow-orange but remained transparent. After 25 min, aldehyde (+)-**S3** (1.15 g, 2.63 mmol) in THF (10 mL) was added to the solution dropwise and then washed with additional THF (5 mL). The yellow-orange reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (15 mL) and CH_2Cl_2 (20 mL) at −78 °C. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO_2 (50% EtOAc/hexanes) to provide alkyne (+)-**S4** (852 mg, 1.97 mmol, 75%) as a white foam. $[\alpha]_D^{21}$ +52.8 (c 0.23, CHCl₃); IR (neat) 3416, 2931, 1670, 1513; ¹H NMR (500 MHz, CDCl₃) δ 7.14 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.22 (d, J = 16.1 Hz, 1H), 4.22 (d, J = 15.5 Hz, 1H), 4.07 (sept, J = 4.8 Hz, 1H), 3.95 (dd, J = 4.2, 7.9 Hz, 1H), 3.80 (s, 3H), 3.58−3.47 (m, 1H), 3.43−3.28 (m, 2H), 3.01 (s, 3H), 2.48−2.32 (m, 1H), 2.10 (dd, J = 4.2, 12.7 Hz, 1H), 2.04 (d, J = 2.6 Hz, 1H), 1.98 (d, J = 14.9 Hz, 1H), 1.81−1.68 (m, 1H), 1.67−1.54 (m, 3H), 1.49−1.35 (m, 1H), 1.30−1.20 (m, 1H), 1.17 (d, J = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 173.6, 159.2, 128.8, 128.7, 114.4, 102.7, 88.6, 70.0, 68.9, 64.7, 57.1, 55.5, 47.9, 46.9, 40.3, 37.9, 33.4, 32.5, 26.4, 25.9, 21.1; HRMS (ESI-TOF) m/z (M + H)⁺ calcd for $C_{23}H_{32}NO_5S$ 434.2001, found 434.2007.

To a solution of alkyne (+)-**S4** (270 mg, 0.623 mmol) in CH_2Cl_2 (2.1 mL) was added 2,6-lutidine (0.14 mL, 1.246 mmol). The reaction mixture was cooled to 0 °C, and TBSOTf (0.17 mL, 0.747 mmol) was added dropwise. After 1 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL), and 0.5 N HCl (5 mL) was added, The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO_2 (30% EtOAc/hexanes) to provide (+)-**19** (341 mg, 0.623 mmol, near quant.) as white crystals. $[\alpha]_D^{21}$ +16.7 (c 0.69, CHCl₃); mp 79−84 °C; IR (neat) 3307, 2930, 2856, 1731, 1675, 1513; ¹H NMR (500 MHz, CDCl₃) δ 7.16 (d, J = 8.3 Hz, 2H), 6.87 (d, J = 8.9 Hz, 2H), 5.20 (d, J = 15.3 Hz, 1H), 4.26 (d, J = 15.9 Hz, 1H), 4.08−3.97 (m, 1H), 3.94 (dd, J = 4.6, 9.7 Hz, 1H), 3.85−3.76 (m, 3H), 3.56−3.46 (m, 1H), 3.34 (s, 2H), 2.47−2.36 (m, 1H), 2.04 (d, J = 2.2 Hz, 1H), 1.92 (dd, J = 4.4, 12.9 Hz, 1H), 1.87−1.80 (m, 1H), 1.76−1.67 (m, 1H), 1.62−1.55 (m, 5H), 1.46−1.37 (m, 1H), 1.31−1.21 (m, 2H), 1.18 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 173.7, 159.2, 128.9, 128.7, 114.3, 102.7, 88.7, 69.7, 68.9, 65.4, 57.4, 55.5, 47.9, 47.0, 40.9, 38.0,

33.4, 32.5, 26.4, 26.0, 25.9, 21.1, 18.2; HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for $C_{29}H_{46}NO_5SSi$ 548.2866, found 548.2878.

Methyl (S)-7-((tert-Butyldimethylsilyl)oxy)-6-((2-(trimethylsilyl)-ethoxy)methoxy)hept-2-ynoate [(−)-23]. To a solution of diol (−)-22[30] (0.9 g, 7.89 mmol) in CH_2Cl_2 (80 mL) was added imidazole (1.61 g, 23.67 mmol). The resulting mixture was cooled to 0 °C, and TBSCl (1.19 g, 7.89 mmol) was added portionwise. The ice bath was removed after 30 min, and the reaction mixture was stirred at room temperature. After 14 h, 0.5 N HCl (40 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The organic layers were combined, washed sequentially with a saturated aqueous solution of $NaHCO_3$ and brine, dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO_2 (20% to 100% EtOAc/hexanes) to provide (−)-S5 (1.58 g, 6.9 mmol, 88%) as a brown oil. $[\alpha]_D^{21}$ −1.1 (c 0.15, CHCl$_3$); IR (neat, cm^{-1}) 3447, 3313, 2118, 1738, 1471, 1256, 1121; ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.79 (sept, J = 4.2 Hz, 1H), 3.66 (dd, J = 3.6, 9.7 Hz, 1H), 3.45 (dd, J = 7.1, 9.9 Hz, 1H), 2.36 (dt, J = 2.1, 7.1 Hz, 2H), 1.97 (t, J = 2.6 Hz, 1H), 1.72−1.57 (m, 2H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 84.2, 70.7, 68.7, 67.1, 31.8, 26.1, 18.5, 15.0, −5.2, −5.2; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{12}H_{24}NaO_2Si$ 251.1443, found 251.1441.

To a solution of TBS ether (−)-S5 (556 mg, 2.43 mmol) in CH_2Cl_2 (8 mL) were added i-Pr$_2$NEt (1.7 mL, 9.72 mmol) and SEMCl (0.52 mL, 72.92 mmol) dropwise. An exit needle was placed through the septum to allow the smoky atmosphere to clear. After 14 h, a saturated aqueous solution of $NaHCO_3$ (20 mL) was added to quench the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with 10% citric acid (50 mL), dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was filtered through a pad of SiO_2 to yield a yellow oil that was used without further purification.

To a solution of the previously obtained yellow oil in THF (8 mL) cooled to −78 °C was added a solution of n-BuLi in THF (2.4M, 1.5 mL) dropwise. After 20 min of stirring, methyl chloroformate (0.33 mL, 4.13 mmol) was added dropwise. The reaction mixture was stirred for 1 h, and the dry ice bath was removed. After 3 h of stirring, Et$_2$O (10 mL) was added, followed by a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO_2 (5% ether/hexanes) to provide (−)-23 (737 mg, 1.77 mmol, 73% over two steps) as a free-flowing oil. $[\alpha]_D^{21}$ −36.6 (c 1.0, CHCl$_3$); IR (neat, cm^{-1}) 2953, 2239, 1718, 1435, 1253; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.78 (d, J = 6.7 Hz, 1H), 4.71 (d, J = 6.5 Hz, 1H), 3.76 (s, 3H), 3.71−3.53 (m, 5H), 2.53−2.44 (m, 2H), 1.93−1.81 (m, 1H), 1.80−1.71 (m, 1H), 0.95 (t, J = 8.3 Hz, 2H), 0.89 (s, 9H), 0.06 (s, 6H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 154.4, 94.9, 89.6, 73.2, 65.6, 65.3, 52.7, 30.1, 26.1, 18.5, 18.3, 15.0, −1.2, −5.2, −5.2; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{20}H_{40}NaO_5Si_2$ 439.2312, found 439.2296.

Methyl (S,Z)-3-Methyl-7-oxo-6-((2-(trimethylsilyl)ethoxy)meth-oxy)hept-2-enoate [(+)-24]. To a suspension of CuI (322 mg, 1.69 mmol) in THF (8 mL) cooled to 0 °C was added a solution of MeLi in Et$_2$O (0.4M, 2.25 mL, 3.38 mmol) dropwise, and the reaction mixture turned orange and then clear. After 45 min of stirring, the Me$_2$CuLi solution was cooled to −78 °C, and a solution of alkynoate (−)-23 (587 mg, 1.41 mmol) in THF (8 mL) was added. After 2 h, pH 7 buffer (10 mL) and MeOH (2 mL) were added, and then the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO_2 (10% ether/hexanes) to provide enoate (−)-S6 (351 mg, 0.81 mmol, 58%) as an oil. $[\alpha]_D^{21}$ −6.8 (c 0.67, CHCl$_3$); IR (neat, cm^{-1}) 2953, 2929, 2858, 1722, 1649, 1250; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.67 (s, 1H), 4.82 (d, J = 7.5 Hz, 1H), 4.74 (d, J = 6.7 Hz, 1H), 3.71−3.59 (m, 6H), 3.67 (s, 3H), 2.81−2.63 (m, 2H), 1.90 (s, 3H), 1.79−1.70 (m, 1H), 1.64−1.59 (m, 1H), 0.96−0.94 (m, 1H), 0.90 (s, 9H), 0.05 (br s, 6H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 166.8, 160.8, 116.1, 94.9, 78.5, 65.8, 65.3, 51.0,

30.3, 29.7, 26.1, 25.3, 18.5, 18.3, −1.2, −5.2, −5.2; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{21}H_{44}NaO_5Si_2$ 455.2625, found 455.2638.

To a solution of enoate (−)-S6 (351 mg, 0.811 mmol) in THF (8 mL) was added a solution of TBAF in THF (1 M, 1.6 mL) that was premixed with AcOH (0.12 mL). After 14 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL), and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO_2 (20% EtOAc/hexanes) to provide (+)-S7 (257 mg, 0.807 mmol, 99%) as an oil. $[\alpha]_D^{21}$ +41.7 (c 0.39, CHCl$_3$); IR (neat, cm^{-1}) 3443, 2951, 2891, 1719, 1647, 1436, 1248; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.75−5.64 (m, 1H), 4.82 (d, J = 7.3 Hz, 1H), 4.70 (d, J = 6.7 Hz, 1H), 3.84−3.74 (m, 1H), 3.68 (s, 3H), 3.64−3.54 (m, 4H), 2.79−2.68 (m, 1H), 2.68−2.55 (m, 1H), 1.91 (s, 3H), 1.76−1.58 (m, 2H), 1.04−0.90 (m, 2H), 0.03 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 166.9, 160.6, 116.2, 95.5, 82.2, 65.9, 65.5, 51.1, 30.1, 29.6, 25.4, 18.4, −1.3; HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for $C_{15}H_{31}O_5Si$ 319.1941, found 319.1940.

To a solution of alcohol (+)-S7 (149 mg, 0.468 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C were added i-Pr$_2$NEt (0.41 mL, 2.34 mmol) and DMSO (0.33 mL, 4.68 mmol). SO$_3$·pyridine (223 mg, 1.4 mmol) was then added in one portion. After 15 min, the reaction mixture was diluted with CH_2Cl_2 (10 mL), and a saturated aqueous solution of $NaHCO_3$ (10 mL) was added. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was purified via short column chromatography on SiO_2 (30% EtOAc/hexanes) to provide aldehyde (+)-24 (144 mg, 0.455 mmol, 97%) as a brown oil. $[\alpha]_D^{21}$ +5.2 (c 1.3, CHCl$_3$); IR (neat) 2952, 1719, 1650, 1437, 1378, 1249, 1193; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.66 (d, J = 1.58 Hz, 1H), 5.70 (s, 1H), 4.82 (d, J = 7.13 Hz, 1H), 4.75 (d, J = 6.94 Hz, 1H), 3.94 (ddd, J = 7.13, 5.15, 1.39 Hz, 1H), 3.71−3.82 (m, 1H), 3.68 (s, 3H), 3.58−3.67 (m, 1H), 2.73−2.83 (m, 1H), 2.62−2.72 (m, 1H), 1.90 (s, 3H), 1.78−1.89 (m, 2H), 0.93 (s, 2H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 202.9, 166.7, 159.3, 116.8, 95.3, 82.4, 66.1, 51.1, 29.2, 28.6, 25.3, 18.2, −1.3; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{15}H_{28}NaO_5Si$ 339.1604, found 339.1605.

Methyl (6S,7S,10S,Z)-12-((2R,4S,6R)-4-((tert-Butyldimethylsilyl)-oxy)-6-methoxy-6-((S)-3-(4-methoxybenzyl)-2-oxothiazolidin-4-yl)-tetrahydro-2H-pyran-2-yl)-7-hydroxy-3,10-dimethyl-6-((2-(trimeth-ylsilyl)ethoxy)methoxy)dodec-2-en-8-ynoate [(+)-25]. To Zn(OTf)$_2$ (dried by stirring overnight at 120 °C under high vacuum, 1.12 g, 3.078 mmol) were added (+)-NME (azeotroped three times with toluene, 600 mg, 3.35 mmol) and triethylamine (distilled prior to use, 0.46 mL, 3.35 mmol) in toluene (3.5 mL). The reaction mixture was stirred vigorously for 3 h. Alkyne (+)-19 (300 mg, 0.548 mmol) in toluene (1.3 mL) was then added, and the mixture was stirred for 3 h. Aldehyde (+)-24 (95 mg, 0.300 mmol) was then added in toluene (0.5 mL), and the reaction mixture was stirred at RT overnight. The mixture was portioned between a saturated aqueous solution of NH_4Cl (10 mL) and EtOAc (10 mL), and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO_2 (20% EtOAc/hexanes) to provide alcohol (+)-25 (247 mg, 0.287 mmol, 95%) as a clear oil. $[\alpha]_D^{21}$ +51.5 (c 0.79, CHCl$_3$); IR (neat) 3440, 2951, 1719, 1678, 1513; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.15 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.67 (s, 1H), 5.19 (d, J = 15.3 Hz, 1H), 4.88 (d, J = 7.1 Hz, 1H), 4.69 (d, J = 6.9 Hz, 1H), 4.28 (d, J = 6.9 Hz, 1H), 4.24 (d, J = 15.3 Hz, 1H), 4.01 (sept, J = 5.0 Hz, 1H), 3.93 (dd, J = 4.0, 9.5 Hz, 1H), 3.79 (s, 3H), 3.77−3.69 (m, 1H), 3.69−3.59 (m, 4H), 3.53−3.46 (m, 2H), 3.38−3.28 (m, 2H), 2.99 (s, 3H), 2.90−2.82 (m, 1H), 2.64−2.55 (m, 1H), 2.49−2.40 (m, 1H), 1.95−1.89 (m, 2H), 1.88 (d, J = 1.0 Hz, 3H), 1.83−1.76 (m, 1H), 1.75−1.63 (m, 2H), 1.63−1.51 (m, 3H), 1.45−1.36 (m, 1H), 1.29−1.20 (m, 2H), 1.14 (s, 3H), 0.99−0.92 (m, 2H), 0.88 (s, 9H), 0.07 (s, 6H), 0.01 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 173.7, 166.7, 160.1, 159.2, 128.9, 128.7, 116.4, 114.3, 102.8, 96.3, 90.5, 84.7, 79.3,

69.8, 66.2, 65.6, 65.4, 57.3, 55.5, 51.0, 47.8, 47.0, 41.0, 37.9, 33.5, 32.5, 30.2, 29.5, 26.5, 26.1, 26.0, 25.1, 21.0, 18.3, 18.2, −1.3, −4.3, −4.4; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{44}H_{73}NNaO_{10}SSi_2$ 886.4391, found 886.4396.

Methyl (Z)-5-((4S,5S)-5-((S)-5-((2R,4S,6R)-4-Hydroxy-6-methoxy-6-((S)-3-(4-methoxybenzyl)-2-oxothiazolidin-4-yl)tetrahydro-2H-pyran-2-yl)-3-methylpent-1-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-methylpent-2-enoate [(+)-26]. To propargyl alcohol (+)-**25** (43 mg, 0.0498 mmol) was added MeOH·HCl (1.5%) (0.7 mL) followed by CH₂Cl₂ (0.5 mL) to rinse the sides of the flask. After 3.5 h of stirring at RT, a saturated aqueous solution of NaHCO₃ (5 mL) was added to quench the reaction. The resulting mixture was extracted with CH₂Cl₂ (2 × 20 mL). The combined organic layers were dried over Na₂SO₄, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO₂ (80% to 100% EtOAc/hexanes) to provide (+)-**S8** (27 mg, 0.0436 mmol, 88%) as a clear oil. $[\alpha]_D^{21}$ +58.0 (*c* 1.0, CHCl₃); IR (neat) 3423, 2945, 1651, 1513, 1442, 1395; ¹H NMR (500 MHz, CDCl₃) δ 7.15 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.83−5.72 (m, 1H), 5.23 (d, *J* = 16.2 Hz, 1H), 4.22 (d, *J* = 15.5 Hz, 1H), 4.19 (br s, 1H), 4.12−4.05 (m, 1H), 4.03 (d, *J* = 3.4 Hz, 1H), 3.95 (dd, *J* = 2.6, 8.9 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.59−3.50 (m, 1H), 3.50−3.43 (m, 1H), 3.42−3.29 (m, 2H), 3.19−3.09 (m, 1H), 3.00 (s, 3H), 2.81 (d, *J* = 2.8 Hz, 1H), 2.45 (q, *J* = 6.1 Hz, 1H), 2.32 (quin, *J* = 5.5 Hz, 1H), 2.11 (dd, *J* = 3.2, 12.1 Hz, 1H), 1.97 (d, *J* = 14.3 Hz, 1H), 1.91−1.88 (m, 3H), 1.66 (br s, 2H), 1.63 (br s, 3H), 1.60−1.55 (m, 2H), 1.47−1.39 (m, 1H), 1.25−1.20 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 173.5, 168.2, 160.0, 159.3, 128.8, 128.7, 117.2, 114.4, 102.7, 90.7, 79.2, 73.6, 70.0, 66.3, 64.8, 57.1, 55.5, 51.6, 47.9, 46.9, 40.3, 37.9, 33.4, 32.6, 30.8, 29.3, 26.4, 26.1, 24.9, 21.1; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{32}H_{45}NNaO_9S$ 642.2713, found 642.2715.

To a solution of (+)-**S8** (27 mg, 0.0436 mmol) in 2,2-dimethoxypropane (1 mL) were added acetone (0.2 mL) and a small crystal of *p*-TsOH·H₂O. After the reaction mixture was stirred for 30 min at RT, a saturated aqueous solution of NaHCO₃ (5 mL) was added to quench the reaction. The resulting mixture was extracted with CH₂Cl₂ (2 × 20 mL). The combined organic layers were dried over Na₂SO₄, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO₂ (40% EtOAc/hexanes) to provide acetonide (+)-**26** (25 mg, 0.0379 mmol, 87%) as a clear oil. $[\alpha]_D^{21}$ +27.5 (*c* 1.0, CHCl₃); IR (neat) 3447, 2944, 1715, 1673, 1513, 1444, 1379; ¹H NMR (500 MHz, CDCl₃) δ 7.15 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.76−5.63 (m, 1H), 5.23 (d, *J* = 16.6 Hz, 1H), 4.29 (dd, *J* = 1.6, 7.3 Hz, 1H), 4.22 (d, *J* = 15.1 Hz, 1H), 4.11−4.02 (m, 1H), 4.02−3.91 (m, 2H), 3.80 (s, 3H), 3.68 (s, 3H), 3.58−3.48 (m, 1H), 3.42−3.29 (m, 2H), 3.00 (s, 3H), 2.88−2.77 (m, 1H), 2.71−2.60 (m, 1H), 2.46 (q, *J* = 6.1 Hz, 1H), 2.10 (dd, *J* = 5.0, 12.7 Hz, 1H), 1.97 (s, 1H), 1.91 (d, *J* = 1.0 Hz, 3H), 1.81−1.72 (m, 3H), 1.71−1.65 (m, 1H), 1.62 (s, 3H), 1.60−1.56 (m, 1H), 1.44 (s, 3H), 1.40 (s, 3H), 1.25−1.19 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 173.5, 166.8, 160.0, 159.3, 128.9, 128.7, 116.4, 114.4, 109.8, 102.7, 91.2, 81.8, 77.9, 70.9, 69.9, 64.8, 57.1, 55.5, 51.1, 47.9, 46.9, 40.3, 37.8, 33.4, 32.5, 31.1, 29.8, 27.4, 26.6, 26.4, 26.1, 25.4, 21.0; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{35}H_{49}NNaO_9S$ 682.3026, found 682.3026.

(6S,7S,10S,Z)-12-((2R,4S,6R)-4-Hydroxy-6-methoxy-6-((S)-3-(4-methoxybenzyl)-2-oxothiazolidin-4-yl)tetrahydro-2H-pyran-2-yl)-3,10-dimethyl-6,7-bis((2-(trimethylsilyl)ethoxy)methoxy)dodec-2-en-8-ynoic Acid [(+)-27]. To a solution of propargylic alcohol (+)-**25** (208 mg, 0.241 mmol) and *i*-PrNEt₂ in CH₂Cl₂ (0.8 mL) was added SEMCl dropwise. After 36 h, 0.5 N HCl (5 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were dried over Na₂SO₄, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO₂ (12% EtOAc/hexanes) to provide bis-SEM ether (+)-**S9** (210 mg, 0.211 mmol, 88%) as a clear oil. $[\alpha]_D^{21}$ +98.1 (*c* 0.3, CHCl₃); IR (neat) 2951, 2895, 1719, 1681, 1513, 1456; ¹H NMR (500 MHz, CDCl₃) δ 7.15 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 5.65 (s, 1H), 5.19 (d, *J* = 15.3 Hz, 1H), 4.91 (d, *J* = 7.1 Hz, 1H), 4.85 (d, *J* = 8.3 Hz, 1H), 4.75 (d, *J* = 7.3 Hz, 1H), 4.66 (d, *J* = 7.1 Hz, 1H), 4.45

(d, *J* = 4.8 Hz, 1H), 4.24 (d, *J* = 16.4 Hz, 1H), 4.02 (sept, *J* = 4.6 Hz, 1H), 3.94 (dd, *J* = 3.6, 9.1 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 7H), 3.57−3.44 (m, 2H), 3.39−3.27 (m, 2H), 2.98 (s, 3H), 2.86−2.77 (m, 1H), 2.71−2.61 (m, 1H), 2.48−2.39 (m, 1H), 1.89 (br s, 1H), 1.90−1.85 (m, 3H), 1.86−1.76 (m, 1H), 1.55 (br s, 6H), 1.44−1.36 (m, 1H), 1.25−1.20 (m, 1H), 1.14 (d, *J* = 6.7 Hz, 3H), 0.97−0.92 (m, 4H), 0.89 (s, 9H), 0.07 (s, 6H), 0.03−0.01 (m, 18H); ¹³C NMR (125 MHz, CDCl₃) δ 173.8, 166.6, 160.4, 159.2, 128.9, 128.7, 116.2, 114.4, 102.8, 95.6, 92.4, 91.3, 79.7, 77.2, 69.8, 68.4, 65.6, 65.5, 65.4, 57.2, 55.5, 51.0, 47.8, 47.0, 41.0, 37.9, 33.6, 32.7, 29.9, 29.7, 26.5, 26.2, 26.1, 25.2, 21.2, 18.3, −1.2, −4.2, −4.4; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{50}H_{87}NNaO_{11}SSi_3$ 1016.5205, found 1016.5207.

To a solution of bis-SEM ether (+)-**S9** (346 mg, 0.348 mmol) in THF (1.5 mL) was added a premixed solution of TBAF in THF (1 M, 3.5 mL, 3.5 mmol) and acetic acid (52 mg, 0.87 mmol) at room temperature. After 14 h, a saturated aqueous solution of NH₄Cl (10 mL) was added, and the biphasic mixture was extracted with CH₂Cl₂ (3 × 40 mL). The combined organic layers were dried over Na₂SO₄, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO₂ (40% EtOAc/hexanes) to provide alcohol (+)-**S10** (305 mg, 0.347 mmol, quant.) as a clear oil. $[\alpha]_D^{21}$ +50.8 (*c* 0.2, CHCl₃); IR (neat) 3458, 2950, 1718, 1675, 1513, 1249; ¹H NMR (500 MHz, CDCl₃) δ 7.14 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.66 (s, 1H), 5.23 (d, *J* = 16.1 Hz, 1H), 4.90 (d, *J* = 6.7 Hz, 1H), 4.85 (d, *J* = 6.7 Hz, 1H), 4.74 (d, *J* = 7.1 Hz, 1H), 4.66 (d, *J* = 6.5 Hz, 1H), 4.46 (d, *J* = 4.0 Hz, 1H), 4.21 (d, *J* = 15.5 Hz, 1H), 4.11−4.02 (m, 1H), 3.95 (dd, *J* = 3.3, 9.2 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 7H), 3.57−3.48 (m, 2H), 3.41−3.29 (m, 2H), 3.00 (br s, 3H), 2.80 (dt, *J* = 6.1, 11.9 Hz, 1H), 2.69 (dt, *J* = 5.7, 10.9 Hz, 1H), 2.49−2.40 (m, 1H), 2.10 (dd, *J* = 5.0, 12.9 Hz, 1H), 1.96 (d, *J* = 12.1 Hz, 1H), 1.88 (s, 3H), 1.84−1.74 (m, 2H), 1.68−1.55 (m, 4H), 1.45−1.37 (m, 1H), 1.22−1.18 (m, 1H), 1.14 (d, *J* = 6.7 Hz, 3H), 0.97−0.90 (m, 4H), 0.83−0.78 (m, 1H), 0.01 (d, *J* = 2.4 Hz, 18H); ¹³C NMR (125 MHz, CDCl₃) δ 173.5, 166.8, 160.4, 159.3, 128.8, 128.7, 116.2, 114.4, 102.7, 95.6, 92.4, 91.3, 79.6, 69.9, 68.4, 65.6, 65.6, 64.7, 57.0, 55.5, 51.0, 47.8, 40.3, 37.8, 33.5, 32.6, 29.9, 29.7, 26.4, 26.1, 25.3, 21.2, 18.3, −1.2, −1.2; HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for $C_{44}H_{74}NO_{11}SSi_2$ 880.4521, found 880.4525.

To a vigorously stirring solution of (+)-**S10** (24 mg, 0.027 mmol) in EtOH (2.5 mL) at room temperature was added 1 M NaOH (1 mL). The reaction mixture was then stirred at 50 °C for 24 h. EtOH was removed in vacuo, and 1 N HCl (5 mL) was added. The mixture was extracted with CH₂Cl₂ (3 × 10 mL), and the combined organic layers were dried over Na₂SO₄, decanted, and concentrated in vacuo. The crude mixture was purified by filtration through a SiO₂ plug with EtOAc to yield seco acid (+)-**27** (23 mg, 0.027 mmol, 97%) as a clear oil. $[\alpha]_D^{21}$ +56.0 (*c* 0.5, CHCl₃); IR (neat) 3420, 2951, 2891, 1679, 1513, 1249; ¹H NMR (500 MHz, CDCl₃) δ 7.14 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.68 (s, 1H), 5.22 (d, *J* = 16.1 Hz, 1H), 4.90 (d, *J* = 7.5 Hz, 1H), 4.84 (d, *J* = 8.7 Hz, 1H), 4.73 (d, *J* = 7.3 Hz, 1H), 4.66 (d, *J* = 7.5 Hz, 1H), 4.45 (d, *J* = 5.9 Hz, 1H), 4.21 (d, *J* = 13.5 Hz, 1H), 4.10−4.01 (m, 1H), 3.95 (dd, *J* = 3.8, 9.5 Hz, 1H), 3.79 (s, 3H), 3.76−3.59 (m, 4H), 3.53 (d, *J* = 6.1 Hz, 2H), 3.42−3.28 (m, 2H), 2.98 (s, 3H), 2.84−2.75 (m, 1H), 2.75−2.65 (m, 1H), 2.50−2.40 (m, 1H), 2.13−2.07 (m, 1H), 2.00−1.94 (m, 1H), 1.95−1.88 (m, 3H), 1.89−1.80 (m, 1H), 1.80−1.49 (m, 5H), 1.45−1.39 (m, 1H), 1.23−1.18 (m, 1H), 1.17−1.11 (m, 3H), 0.98−0.89 (m, 4H), 0.01 (d, *J* = 3.6 Hz, 18H); ¹³C NMR (125 MHz, CDCl₃) δ 173.7, 170.1, 163.0, 159.2, 128.8, 128.7, 116.0, 114.4, 102.7, 95.6, 92.4, 91.4, 79.6, 69.8, 68.5, 65.6, 65.6, 64.8, 60.6, 57.1, 55.5, 47.8, 46.9, 40.0, 37.6, 33.4, 29.8, 29.8, 26.4, 26.1, 25.6, 21.2, 21.2, 18.2, 14.4, −1.2, −1.2; HRMS (ESI-TOF) m/z (M - H)$^-$ calcd for $C_{43}H_{71}NO_{11}SSi_2$ 864.4208, found 864.4224.

Bis-SEM Lactone (+)-29. To a solution of *seco*-acid (+)-**27** (139 mg, 0.1605 mmol), and triphenylphosphine (210 mg, 0.8023 mmol) in toluene (16 mL) cooled to 0 °C was added DIAD dropwise. After 14 h, SiO₂ was added, and the solvent was removed in vacuo. The crude reaction mixture (adsorbed on SiO₂) was purified via column chromatography on SiO₂ (20% EtOAc/hexanes) to provide a macrolactone (140 mg, mixture of macrolactone and DIAD-H₂) as a clear oil that was used directly in the next reaction.

To a solution of the macrolactone from the previous step (70 mg) in MeCN (6.4 mL) and H_2O (1.6 mL) cooled to 0 °C was added CAN (176 mg, 0.321 mmol) in one portion, which turned the reaction mixture orange. The ice bath was removed after the addition, and the reaction mixture was stirred vigorously. After 1.5 h, a saturated aqueous solution of $NaHCO_3$ (10 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO_2 (25% EtOAc/hexanes) to provide lactone (+)-**29** (21 mg, 0.029 mmol, 36% over two steps) as an oil. $[\alpha]_D^{21}$ +20.7 (c 0.2, $CHCl_3$); IR (neat) 3358, 3193, 2924, 2853, 1684, 1463, 1377, 1263; ^1H NMR (500 MHz, $CDCl_3$) δ 5.68 (s, 1H), 5.45 (s, 1H), 5.10 (br s, 1H), 4.91 (t, J = 6.3 Hz, 2H), 4.76 (d, J = 8.5 Hz, 1H), 4.68 (d, J = 6.7 Hz, 1H), 4.26 (d, J = 8.7 Hz, 1H), 4.15–4.03 (m, 2H), 3.80–3.67 (m, 2H), 3.63–3.52 (m, 3H), 3.40 (dd, J = 8.7, 12.7 Hz, 1H), 3.36–3.29 (m, 1H), 3.28 (s, 3H), 2.72 (dt, J = 5.2, 10.7 Hz, 2H), 2.34 (dt, J = 5.2, 11.7 Hz, 1H), 2.28 (d, J = 15.7 Hz, 1H), 1.96–1.91 (m, 1H), 1.88 (s, 2H), 1.82–1.74 (m, 2H), 1.71–1.63 (m, 2H), 1.58–1.48 (m, 2H), 1.33–1.28 (m, 1H), 1.18 (d, J = 6.7 Hz, 4H), 1.00–0.89 (m, 5H), 0.03 (d, J = 10.5 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 167.3, 154.4, 118.5, 99.4, 96.3, 92.8, 90.3, 80.5, 78.8, 70.7, 66.9, 66.0, 65.6, 63.7, 57.7, 48.6, 35.9, 33.0, 31.6, 30.9, 30.8, 29.9, 29.7, 24.6, 24.3, 21.5, 18.3, 18.2; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{35}H_{61}NNaO_9SSi_2$ 750.3527, found 750.3529.

Acetonide-Protected Macrolactone (+)-31. To a solution of acetonide (+)-**26** (13 mg, 0.0227 mmol) in ethanol (1.7 mL) was added an aqueous solution of NaOH (1M, 0.7 mL) dropwise. The reaction mixture was stirred overnight at 50 °C and then concentrated under reduced pressure to give ca. 5 mL. An aqueous solution of HCl (1 N, 5 mL) was then added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was purified via SiO_2 plug (EtOAc) to provide the seco acid (13 mg, 0.0227 mmol, near quant.) as a clear oil that was used in the next reaction without further purification.

To a solution of the seco acid (72 mg, 0.112 mmol) in toluene (11 mL) was added Ph_3P (147 mg, 0.56 mmol) followed by a 60% solution of DEAD in toluene (227 mg, 0.78 mmol) dropwise at RT. After the reaction mixture was stirred overnight, SiO_2 (ca. 3 g) was added, and the solvent was removed in vacuo. The crude mixture was purified via column chromatography on SiO_2 (17.5% to 20% EtOAc/hexanes) to provide a macrolactone as a mixture contaminated with reduced DEAD (90 mg), which was used in the next reaction without further purification.

The next reaction was split into three batches.

Batch 1. To a solution of the macrolactone mixture obtained from the previous step (10 mg) in MeCN (1.3 mL) and H_2O (0.3 mL) was added CAN (35 mg, 0.064 mmol) in one portion, which turned the reaction mixture orange. The reaction mixture was stirred vigorously at RT. After 1 h, a saturated aqueous solution of $NaHCO_3$ (10 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo.

Batch 2. To a solution of the macrolactone mixture obtained from the previous step (34 mg) in MeCN (4.3 mL) and H_2O (1.1 mL) was added CAN (119 mg, 0.217 mmol) in one portion, which turned the reaction mixture orange. The reaction mixture was stirred vigorously at RT. After 1 h 40 min, a saturated aqueous solution of $NaHCO_3$ (10 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo.

Batch 3. To a solution of the macrolactone mixture obtained from the previous step (46 mg) in MeCN (5.6 mL) and H_2O (1.4 mL) was added CAN (161 mg, 0.293 mmol) in one portion, which turned the reaction mixture orange. The reaction mixture was stirred vigorously at RT. After ca. 1 h 30 min, a saturated aqueous solution of $NaHCO_3$ (10 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo.

The crude mixtures from batches 1, 2, and 3 were combined and then purified via column chromatography on SiO_2 (17% EtOAc/hexanes) to provide lactone (+)-**31** (20 mg, 0.0394 mmol, 35% over three steps) as a film. $[\alpha]_D^{21}$ +105.1 (c 0.58, $CHCl_3$); IR (neat) 3273, 2935, 1697, 1456, 1378; ^1H NMR (500 MHz, $CDCl_3$) δ 5.66 (s, 1H), 5.53 (s, 1H), 5.18–5.14 (m, 1H), 4.19 (d, J = 9.1 Hz, 1H), 4.15 (t, J = 11.5 Hz, 1H), 4.07 (t, J = 7.9 Hz, 1H), 3.88–3.78 (m, 1H), 3.44–3.36 (m, 1H), 3.36–3.30 (m, 1H), 3.29 (s, 3H), 2.82–2.74 (m, 1H), 2.70 (dt, J = 5.4, 11.7 Hz, 1H), 2.53 (dt, J = 5.2, 11.3 Hz, 1H), 2.26 (d, J = 14.5 Hz, 1H), 1.90 (d, J = 0.8 Hz, 3H), 1.84 (m, 4H), 1.64 (s, 3H), 1.61–1.53 (m, 2H), 1.45 (s, 3H), 1.41 (s, 3H), 1.19 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 166.8, 154.9, 118.6, 109.9, 99.4, 90.7, 82.5, 77.9, 70.7, 66.7, 64.7, 57.7, 48.7, 36.1, 32.5, 31.0, 30.9, 30.9, 29.7, 29.3, 27.3, 26.7, 24.7, 24.5, 20.8; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{26}H_{37}NNaO_7S$ 530.2188, found 530.2184.

Penultimate Macrolactone (+)-30. To a solution of macrolactone (+)-**31** (7 mg, 0.0138 mmol) in acetic acid (2.5 mL) and H_2O (1.1 mL) was added camphorsulfonic acid (2 mg). The reaction mixture was stirred at 50 °C. After 1 h, TLC analysis indicated the reaction to be complete. Acetic acid was removed in vacuo, and a saturated aqueous solution $NaHCO_3$ (10 mL) was added. The cloudy aqueous mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was purified via column chromatography on SiO_2 (75% EtOAc/hexanes) to provide triol (+)-**30** (5.4 mg, 0.0138 mmol, 86%) as a white foam. $[\alpha]_D^{21}$ +90.3 (c 0.39, $CHCl_3$); IR (neat) 3395, 2924, 1681, 1279; ^1H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.71 (s, 1H), 5.21 (s, 1H), 4.27 (t, J = 11.6 Hz, 1H), 4.09 (d, J = 7.7 Hz, 1H), 3.85 (t, J = 7.8 Hz, 1H), 3.48 (t, J = 8.5 Hz, 1H), 3.42–3.31 (m, 2H), 2.84 (td, J = 5.3, 11.4 Hz, 1H), 2.70–2.63 (m, 1H), 2.35 (td, J = 5.0, 12.1 Hz, 1H), 2.17 (d, J = 14.6 Hz, 1H), 1.99 (d, J = 13.5 Hz, 1H), 1.90 (s, 3H), 1.83–1.48 (m, 8H), 1.3–1.27 (m, 1H), 1.25 (bs, 2H), 1.17 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 166.8, 156.0, 117.8, 96.6, 90.4, 80.0, 75.9, 68.3, 66.9, 62.8, 62.7, 35.5, 32.5, 32.2, 32.0, 30.8, 29.9, 29.2, 24.5, 23.7, 21.3; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{22}H_{31}NNaO_7S$ 476.1719, found 476.1711.

(+)-18-epi-Latrunculol A (1). To a solution of triol (+)-**30** (2 mg, 0.0044 mmol) in EtOAc (0.3 mL) was added Pd on $BaCO_3$ (20 mg). The reaction flask was evacuated and refilled with H_2 three times and then stirred at RT under a balloon of H_2. After 4 h 30 min, a sample of the reaction mixture was filtered through Celite, and LC–MS analysis indicated the reaction to be complete. The reaction mixture was filtered through a pad of Celite with EtOAc and CH_2Cl_2, and the solvent was removed in vacuo. Residual catalyst was observed, so the crude mixture was filtered through a clean pad of Celite with CH_2Cl_2 to afford (+)-**1** (2 mg, 0.0044 mmol, near quant.) as a white foam. $[\alpha]_D^{21}$ +21.3 (c 0.12, MeOH); IR (neat, cm^{-1}) 3418, 2926, 2855, 1681, 1444, 1383, 1289; ^1H NMR (500 MHz, CD_3COCD_3) δ 6.58 (s, 1H), 5.63 (t, J = 10.5 Hz, 1H), 5.54 (s, 1H), 5.15 (bs, 1H), 5.05 (t, J = 10.9 Hz, 1H), 4.87 (s, 1H), 4.39–4.28 (m, 2H), 3.91 (t, J = 7.8 Hz, 1H), 3.58 (d, J = 6.2 Hz, 1H), 3.46 (d, J = 7.4 Hz, 1H), 3.43 (dd, J = 2.4, 8.1 Hz, 2H), 3.40–3.33 (m, 1H), 2.79–2.73 (m, 1H), 2.68 (td, J = 3.6, 11.8 Hz, 1H), 1.53–1.40 (m, 2H), 1.10–1.02 (m, 1H), 0.93 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 174.1, 166.7, 158.8, 136.6, 132.4, 118.7, 97.3, 76.7, 70.2, 68.1, 63.9, 62.5, 36.8, 35.4, 33.2, 32.5, 32.2, 31.9, 29.7, 29.1, 25.6, 23.2; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{22}H_{33}NNaO_7S$ 478.1875, found 478.1861.

See the Supporting Information for deuterated 18-epi-latrunculol A (**S11**).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectral data of all compounds (including **S1–S11**) and crystallographic data for compounds (+)-**11** and (+)-**19** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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