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Synthesis of the *ABC* Framework of Tamulamides A and B

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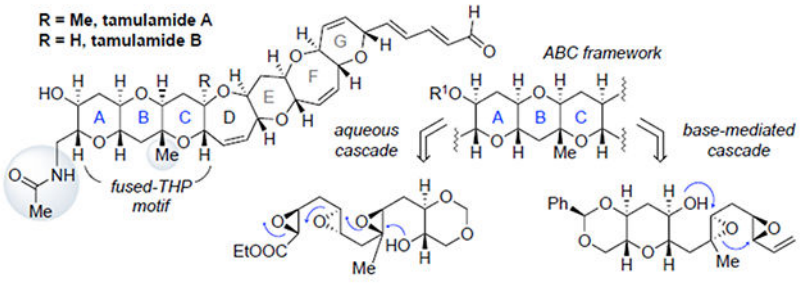
Abstract

Synthesis of the fused tetrahydrofuran motif comprising the *ABC* rings of the marine ladder polyethers tamulamides A and B has been achieved via two different polyepoxide cascade strategies. Investigations into a triepoxide cascade under aqueous conditions revealed the importance of the electronic nature of the cascade end-group with this initial approach. Ultimately, a diepoxide cascade under basic conditions proved most successful, providing the *ABC* tetrahydropyran triad in 41% yield.

Graphical Abstract



Keywords

natural products; polyethers; cascade reactions; epoxide openings; oxygen heterocycles

1. INTRODUCTION

Tamulamides A (**1**) and B (**2**) are two members of the marine ladder polyether (MLP) class of natural products, a family of compounds which have attracted the attention of chemists and biologists alike over the past three decades (Scheme 1a).[1] Isolated in 2010 from *K. brevis* cultures, the tamulamides feature seven fused rings and 15 stereogenic centers and differ only in the substituent off the central D ring (tamulamide A, R = Me; tamulamide B, R

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ASSOCIATED CONTENT

Supporting Information Available. Copies of ^{1}H- and ^{13}C- spectra for selected compounds and the X-ray structure of compound **23**. Crystallographic data for **23** is available on the Cambridge Crystallographic Data Center (CCDC) (# 1812239).

The authors declare no competing financial interest.

= H).[2] These natural products appear to possess similar antagonistic activity as brevenal, binding at the same voltage sensitive sodium channels (tamulamide A, K_i = 2.5 μM; tamulamide B, K_i = 210 nM) but exhibiting no significant ichthyotoxicity at even the highest levels tested.[2] The antagonistic nature of these polyethers provides opportunities for therapeutic applications, such as in the case of brevenal which was recently investigated as a treatment of mucociliary disorders such as cystic fibrosis.[3] The biological relevance of this class of natural products as a whole is well established with many polyethers displaying antifungal,[4] anticancer[5] and antibiotic activity.[6]

The construction of poly-tetrahydropyran (THP) fragments found in MLPs has been inspired by the proposed biosynthesis of these natural products, in which an epoxide-opening cascade furnishes the polyether in a single dramatic step.[7] Though elegant, this synthetic strategy suffers from regioselectivity issues. The cyclization of electronically-unbiased epoxides for example, shows preference for *exo* rather than *endo*-opening, resulting in the undesired, smaller-ring THF products under acidic,[8] basic[9] and neutral conditions (Scheme 1b).[10] Over the past several years, our group has developed a number of single-epoxide cyclizations and polyepoxide cascades which proceed in an *endo*-selective fashion. Among our efforts is the development of directing-group free cascades that use THP or 1,3-dioxane templates.[11,12] The latter, in particular, can provide greatly-enhanced *endo* selectivity, with the 6-membered THP product favored under basic, acidic or neutral water conditions.

Herein we evaluate two epoxide-opening cascade approaches to access the *ABC* core of tamulamides A and B. As shown in Scheme 1a, this segment of the molecule features three fused THP rings, an amide side-chain, and a methyl group at the *BC* ring junction. Specifically, we examine a 1,3-dioxane-templated cascade reaction of **4** (Approach 1, Scheme 1c) and a non-templated, base-mediated strategy starting from **5** (Approach 2, Scheme 1c). Previous studies in our group have revealed that both the electronic and steric nature of substituents greatly influence a polyepoxide cascade outcome and efficiency.[13] Thus, the methyl substituent and the identity of the functional groups R^2 and R^3 of **4** and **5** respectively, necessitated particular consideration in the present work.

2. RESULTS AND DISCUSSION

Our investigations commenced with the synthesis of polyepoxide **4** in order to investigate Approach 1 (Scheme 1c). An Alder ene[14,15] reaction of linear fragment **6** and 1,3-dioxane template **7** was envisioned to provide access to the core structure of **4** (Scheme 2a). This intermediate could then undergo late-stage derivatization of the cascade-end R^2 group (**4a** = $(CH)_2COOEt$ or **4b** = CH_2N_3) to access the acetamide on the *A* ring (Scheme 1a). As shown in Scheme 2b, the synthesis of **4** began with the propargylation of (*S*)-(−) glyceraldehyde acetonide to provide alcohol **8**[16] as a 4:1 mixture of diastereomers. This ratio was subsequently improved to 94:6 through careful chromatography. Removal of the acetonide protecting group of **8** with DOWEX resin furnished a 1, 2, 3 triol. The 1,3 diol was then reprotected as a benzylidene acetal, and subsequent silyl protection and methylation provided **9**. Exchange of the benzylidene acetal for the more robust methylene acetal completed the installation of the 1,3-dioxane template onto alkyne **7**. For the synthesis of **11a**, Alder-ene coupling of **7** proceeded with the tosylated derivative of known alkene **10**.[17]

Subsequent reaction with sodium azide then furnished diene **11a** with moderate linear to branched selectivity. Towards the synthesis of **11b**, Alder-ene coupling of **10** and **7** proceeded in good yield. Oxidation of the epoxy alcohol followed by installation of the enoate group then furnished **11b**. For both **11a** and **11b**, subsequent Shi epoxidation[18] installed the remaining epoxides, and silyl deprotection provided triepoxide cascade precursors **4a** and **4b**, respectively.

As summarized in Table 1, the success of the 1,3-dioxane-templated cascade reaction of triepoxide **4** to generate **12** varied depending on the conditions and identity of the R^2 group. Initial attempts to promote the cascade reaction of **4a** ($R^2 = CH_2N_3$) led to a mixture of **12** and **13** under neutral water conditions (Table 1, entry 1).[19] Though encouraging to observe the formation of the desired all-*endo* product **12**, the major product was **13**, resulting from *exo* cyclization of the last ring. An extended reaction time of two weeks was required for completion of the cascade. In addition, the combined isolated yield of **12** and **13** was low (*ca.* 47%), with the mass balance suspected to be non-specific epoxide hydrolysis products due to the lengthy reaction period.

Alternatively, a rapid reaction was observed when **4a** was exposed to acidic conditions[20] and resulted in the formation of **13** in 20% yield, and the isolation of the precursor to product **14** with the final epoxide in place in 80% yield (Table 1, entry 2). These two products formed via the *exo* cyclization of the last and second epoxides, respectively. Although ultimately unproductive, this result indicated that under acidic conditions, the cyclization to form the *C* ring was occurring with high *endo* selectivity, presumably due to stabilization provided by the methyl directing group.[13] Notably, both the reaction rate (1 day versus 14 days) and mass balance (quantitative versus ~50%) improved under acidic conditions relative to neutral-water conditions. Aiming to capitalize on these observations, we subsequently envisioned an initial cyclization of **4a** under acidic conditions to form the THP *C* ring (Scheme 3). Assuming the cascade reaction could be halted after this first cyclization through the use of cold temperatures and shorter reaction times, the resulting diad template **15** could then be treated to aqueous conditions to enhance the endo-selectivity of the final two cyclizations and provide product **12**.[21] In practice, treatment of **4a** with (±)-CSA at –78 °C for 10 min resulted in quantitative formation of **15** ($R^2 = CH_2N_3$). Subsequent treatment of **15** to mildly acidic water conditions for 7 days, indeed provided **12** ($R^2 = CH_2N_3$), but as a 1:2 ratio of **12** to **13** determined by ^{1}H NMR (Table 1, entry 3). Attempts to improve the reaction outcome by treating **15** to non-aqueous conditions proved to be less favorable, as no detectable formation of the desired all-*endo* product **12** was observed (data not shown).

The results from these preliminary investigations suggested that the inductively electron-withdrawing nature of the azide R^2 group on **4a** was inhibiting selective *endo* opening of the final epoxide.[2] Thus, we transitioned to triepoxide **4b** featuring the relatively weaker electron-withdrawing enoate R^2 group (i.e. $R^2 = (CH)_2CO_2Et$) that could also be further elaborated to the desired amide side-chain present in the tamulamides.[23] As shown in Table 1, entry 4, treatment of **4b** to acidic conditions provided a 1:1.6 ratio of isolated yields for the desired all-*endo* product **12** ($R^2 = (CH)_2CO_2Et$) to the undesired product **14** (R^2 =

$(CH)_2CO_2Et$). Product **14** is proposed to result from *exo* then *endo* cyclization of the second and third epoxides, respectively. As the desired *endo*-cyclization of the final two epoxides again proved challenging under acidic conditions, we chose to apply our interrupted cascade strategy used for **4a** as described in Table 1, entry 3. Treatment of **4b** with (±)-CSA at low temperatures provided **15** ($R^2 = (CH)_2CO_2Et$) in quantitative yield. Subjection of **15** to neutral water conditions at elevated temperatures for 4 days resulted in exclusive formation of the desired all-*endo* product **12** ($R^2 = (CH)_2CO_2Et$), with no detectable formation of *exo*-cyclized product **14** (Table 1, entry 5). Although this cascade reaction proved highly regioselective, the yield of this transformation was only 7% over three steps (i.e. formation of **15**, epoxide-opening cascade reaction, acylation for ease of product identification).

As a means of improving the yield of **12**, we next explored the base-mediated cascade shown in Approach 2, Scheme 1c. While the regioselectivity of epoxide-opening cascades are governed by electronic effects under Lewis or Brensted acid conditions, base-mediated epoxide openings are more sensitive to steric considerations, resulting in attack of the epoxide at the most sterically accessible site.[24] Given the methyl substitution pat-tem of the proposed cascade precursor **16** (Scheme 4a), a highly *endo*-selective cascade under basic conditions was thus envisioned. A vinyl cascade-end group was incorporated into **16**, as it has been previously shown competent in *endo*-selective base-mediated cascades.[25]

As shown in Scheme 4a, **16** was proposed to originate from diene **17**, which in turn could be prepared via a B-alkyl Suzuki of exocyclic olefin **18** and an appropriately-modified diene fragment such as **19**. This convergent approach was suspected to bode well for the scalability of **16**, and in-turn the base-mediated cascade to provide **12**. Though significant precedent exists within the MLP literature for the coupling of an exocyclic olefin such as **18** with an enol phosphate,[26] or a vinyl triflate,[27] to the best of our knowledge an allyl halide coupling partner has not been examined. Studies from the Johnson group in 1997 illustrated that an endocyclic vinyl bromide is a competent electrophilic partner in a Suzuki coupling to an exocyclic olefin en route to aza-*C*-disaccharide derivatives.[28] Towards this end, the synthesis of diene **19** commenced with a copper-mediated allylation of propargyl alcohol with allylic bromide **20**.[29] Though this reaction proceeded in modest yield (*ca.* 45%), attempts to optimize proved unsuccessful. Subsequent reduction of alkyne **21** occurred without any trace of vinyl bromide reduction to provide diene **19**. Notably, a route involving direct coupling of allyl bromide **20** with a metal alkene containing suitably protected allylic alcohol provided consistently lower yields of diene **19**. Suzuki coupling of diene **19** and exocyclic olefin **18**[30,31] proceeded in moderate yield with no need for protection of the allylic alcohol to furnish diene **22**. Sharpless and Shi epoxidations, followed by installation of the vinyl group and desilylation provided **16** in 19 steps (LLS).

As shown in Table 2, entry 1, treatment of **16** to pH 11 phosphate buffer at room temperature for 7 days led to an encouraging 2:1 ratio of isolated all-*endo* product **23** to undesired **24**. The desired all-*endo* product **23** was isolated in 21% yield. An increased reaction rate and further improvement in yield was observed by increasing the reaction temperature to 70 °C, providing **23** in 41% yield, which corresponds to an approximate 64% yield per epoxide-

opening (Table 2, entry 2). The structure of this *ABC* intermediate was confirmed by X-ray crystallography (Figure S1 and S2).

3. CONCLUSION

In conclusion, two strategies towards the THP triad of the *ABC* core of tamulamides A and B have been examined. In the first approach, an interrupted triepoxide cascade with an enoate cascade-end group provided the desired *ABC* framework in 7% yield. The second approach involved a base-mediated diepoxide cascade and provided the desired all-*endo* product in a much improved 41% yield. Future work will focus on the synthesis of the *DEFG* fragment and completion of the synthesis of the tamulamides A and B.

4. EXPERIMENTAL SECTION

General Information.

Unless otherwise specified, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon under anhydrous conditions with magnetic stirring. Dichloromethane, tetrahydrofuran (THF), Et_2O, benzene, dioxane and triethylamine were purified via an SG Water USA solvent column system. Reactions in water utilized deionized water (pH 7) without further purification. $Ti(OiPr)_4$ and was distilled from CaH_2 and stored over molecular sieves under argon. All reagents were commercially obtained and used without further purification, unless noted otherwise. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230–400 mesh) or Biotage® Isolera flash purification system on SNAP KP-Sil, HP-Sil or Ultra columns (silica gel, average particle size 50, 25, 25 μm respectively). ^1H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded at ambient temperature. ^1H NMR spectra were obtained at 500 MHz using a JEOL ECZ-500 or a Varian Inova-500 spectrometer or at 400 MHz using a Bruker AVANCE-400 spectrometer. ^{13}C NMR spectra were obtained at 125 MHz using a JEOL or a Varian Inova-500 spectrometer or at 100 MHz using a Bruker AVANCE-400 spectrometer. NMR spectra were obtained in $CDCl_3$, or C_6D_6. The ^1H NMR data are reported as follows: chemical shift in parts per million (ppm) from an internal standard of residual chloroform (7.27 ppm) or benzene (7.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant in hertz (Hz), and integration (H). Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of an internal standard of residual chloroform (77.2 ppm) or benzene (128.4 ppm). Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000 FT-IR or an Agilent Cary 630 FTIR Spectrometer. High-resolution mass spectra (HR-MS) were acquired on a Bruker Daltronics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer at the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical rotations were measured using a Jasco Model 1010 digital polarimeter at 589 nm. X-ray structures were collected on a Siemens three-circle Platform Diffractometer coupled to a Brucker-APEX CCD detector at the MIT Department of Chemistry X-Ray Diffraction Facility.

(((2*S*,4*R*,5*S*)-4-(but-2-yn-1-yl)-2-phenyl-1,3-dioxan-5-yl)oxy)(*tert*-butyl)diphenylsnane (9).

Alcohol **8**[16] (2.38 g, 14.0 mmol, 1.00 equiv) was dissolved in deionzed H2O (30 mL) and DOWEX-WX8-400 resin (2.38 g) was added. A reflux condensor was attached and the reaction was heated to 70 °C for 70 min after which the mixture was cooled to ambient temparture and filtered. The solvent was evaporated *in vacuo* and the resulting triol was carried onto the next step without further purification. Benzaldehyde dimethyl acetal (4.62 mL, 30.7 mmol) was added to a solution of the above triol in CH_2Cl_2 (28 mL). Following the addition of (±)-CSA (650 mg, 2.79 mmol, 20 mol%) the reaction stirred at ambient temperature for 16 h, after which triethylamine (1.95 mL, 14.0 mmol) was added and solvent was evaporated *in vacuo*. Purification via flash chromatography (0-100% EtOAc in hexanes) furnished (2*S*,4*R*,5*S*)-2-phenyl-4-(prop-2-yn-1-yl)-1,3-dioxan-5-ol as an oil (1.10 g, 5.04 mmol, 36% over two steps). To a solution of the benyzylidene acetal (1.10 g, 5.04 mmol) in DMF (25 mL) was added imidazole (1.03 g, 15.1 mmol) and TBDPSCl (1.96 g, 7.56 mmol) and the reaction was stirred at ambient temperature for 16 h, after which point an additional batch of imidazole (343 mg) and TBDPSCl (650 mg) were added. After an additional 4 h, the solvent was evaporated *in vacuo* and the residue was partitioned between EtOAc (20 mL) and H_2O (20 mL). Purification via flash chromatography (0-100% EtOAc in hexanes) furnished *tert*-butyldiphenyl(((2*S*,4*R*,5*S*)-2-phenyl-4-(prop-2-yn-1-yl)-1,3-dioxan-5-yl)oxy)silane (2.09 g, 4.59 mmol, 91%). The protected alkyne (1.00 g, 2.18 mmol) was azeotropically dried with benzene (10 mL) into a reaction flask that was subsequently dried under vacuum (~ 1 torr) for 1 h. The residue was then dissolved in THF (22 mL), cooled to –78 °C and *n*-BuLi (2.17 mL, 2 M in hexanes, 4.37 mmol) was added and the reaction was stirred for 5 min. Once the reaction was transferred to a 0 °C bath, methyl iodide (0.41 mmol, 6.56 mmol, previously neutralized by running through a plug of alumina) was added and the reaction was allowed to stir as the ice bath expired. After 90 min, the reaction was quenched by the addition of sat. $NaHCO_{3(aq)}$ (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3x) and combined organic extracts were washed with brine, dried over Na_2SO_4, and solvent was evaporated *in vacuo*. Purification via flash chromatography (0–100% EtOAc in hexanes) provided alkyne **9** as an oil (645 mg, 1.37 mmol, 62%): $[\alpha]^{23}D$ = +4.8 (*c* = 0.8, $CHCl_3$); FT-IR (thin film, cm^{-1}): 2857, 1461, 1217; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.69 (m, 2H), 7.67 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.49 – 7.43 (m, 4H), 7.42 – 7.37 (m, 4H), 7.34 – 7.30 (m, 3H), 5.49 (s, 1H), 3.90 (dd, *J* = 10.5, 4.7 Hz, 1H), 3.86 – 3.76 (m, 2H), 3.58 (dd, *J* = 10.6, 9.3 Hz, 1H), 2.74 (dp, *J* = 16.8, 2.6 Hz, 1H), 2.55 – 2.46 (m, 1H), 1.76 (t, *J* = 2.5 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 135.9, 130.2, 130.1, 128.9, 128.3, 128.0, 127.9, 126.3, 101.0, 80.9, 75.2, 71.5, 66.5, 27.1, 22.5, 19.5, 3.9; HRMS (ESI, *m/z*): $[M+NH_4]^+$ calcd for $C_{30}H_{34}O_3Si$, 488.2615; found 488.2636.

(((4*R*,5*S*)-4-(but-2-yn-1-yl)-1,3-dioxan-5-yl)oxy)(*tert*-butyl)diphenylsilane (7).

To a solution of alkyne **9** (630 mg, 1.33 mmol) in MeOH (11 mL) was added $TsOH{\cdot}H_2O$ (50 mg, 0.26 mmol, 20 mol%). The reaction was stirred at ambient temperature for 2 h, after which triethylamine (0.186 mL, 1.34 mmol) was added and the solvent was evaporated *in vacuo*. The residue was purified via flash chromatography (0-100% EtOAc in hexanes) to furnish (2*S*,3*R*)-2-((*tert*-butyldiphenylsilyl)oxy)hept-5-yne-1,3-diol (234 mg, 0.62 mmol,

46%). The TBDPS protected diol (230 mg, 0.601 mmol) was azeotropically dried with benzene (5 mL) into a reaction flask that was subsequently dried under vacuum (~ 1 torr) for 1 h. The residue was dissolved in CH_2Cl_2 (2.4 mL) and dimethoxymethane (0.085 mL, 0.961 mmol) and $BF_3{\cdot}OEt_2$ (0.118 mL, 0.961 mmol) were added at ambient temperature. After 80 min, the reaction was quenched by the addition of sat. $NaHCO_{3(aq)}$ (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (3x) and combined organic extracts were washed with brine, dried over Na_2SO_4, and solvent was evaporated *in vacuo*. Purification via flash chromatography (0–100% EtOAc in hexanes) furnished alkyne **7** (174 mg, 0.44 mmol, 73%): $[\alpha]^{23}D$ = +413.4 (*c* = 0.4, $CHCl_3$); FT-IR (thin film, cm^{-1}): 1472, 1171; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.67 (m, 2H), 7.67 – 7.62 (m, 2H), 7.49 – 7.43 (m, 2H), 7.43 – 7.36 (m, 4H), 4.96 (dd, *J* = 6.1, 0.9 Hz, 1H), 4.58 (d, *J* = 6.1 Hz, 1H), 3.79 (ddd, *J* = 10.6, 5.1, 1.0 Hz, 1H), 3.71 (ddd, *J* = 9.9, 8.8, 5.1 Hz, 1H), 3.53 (ddd, *J* = 9.1, 6.5, 3.0 Hz, 1H), 3.32 (t, *J* = 10.2 Hz, 1H), 2.69 (dt, *J* = 16.9, 2.7 Hz, 1H), 2.44 (ddt, *J* = 16.9, 4.0, 2.5 Hz, 1H), 1.77 (t, *J* = 2.5 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, CDCf) δ 136.0, 135.9, 133.8, 132.8, 130.2, 130.1, 128.0, 127.8, 93.5, 80.7, 77.7, 74.8, 71.4, 66.5, 27.1,21.2, 19.4, 14.4, 3.9; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd for $C_{24}H_{30}O_3Si$, 417.1856; found 417.1856.

ethyl (*E*)-3-((2*S*,3*S*)-3-((2*E*,5*E*)-7-((4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-1,3-dioxan-4-yl)-5-methylhepta-2,5-dien-1-yl)oxiran-2-yl)acrylate (11b).

((2*S*,3*S*)-3-(but-3-en-1-yl)oxiran-2-yl)methanol **10**[17] (170 mg, 1.32 mmol) and alkyne **7** (261 mg, 0.66 mmol) were dissolved in acetone (1.32 mL) and the mixture was purged by bubbling with argon for 5 min. To the reaction mixture was added $CpRu(MeCN)_3PF_6$ (23 mg, 0.0529 mmol) in three portions, separated by 15 min of stirring. After the last addition, the reaction was stirred for 16 min and the solvent was evaporated *in vacuo*. The crude residue was purified via flash chromatography (0-100% of a 1:1 mixture of EtOAc and CH2O2 in hexanes) to furnish the product as a mixture of linear and branched regiosiomers (5:1 l/b, 251 mg, 0.482 mmol, 73%). This mixture was further purified using the same solvent gradient above to furnish the desired linear product, ((2*S*,3*S*)-3-((2*E*,5*E*)-7-((4*R*,5*S*)-5-((tert-butyldiphenylsilyl)oxy)-1,3-dioxan-4-yl)-5-methylhepta-2,5-dien-1-yl)oxiran-2-yl)methanol (>95:5 l/b, 124 mg, 0.237 mmol, 35%). The above linear diene (124 mg, 0.237 mmol) was azeotropically dried with benzene into a flask and dried under vacuum (~1 torr) for 20 min. Following dissoluiton in CH_2Cl_2 (4.7 mL), DMSO (0.948 mL, 13.3 mmol) and triethylamine (0.33 mL, 2.37 mmol) were added and the mixture was cooled to 0 °C before the addition of pyridine·SO_3 (151 mg, 0.948 mmol). The ice bath was removed and the reaction stirred while warming to ambient temperature. After 80 min, TLC indicated consumption of the starting material and Ph_3PCHCO_2Et (165 mg, 0.474 mmol) was added. After stirring at ambient temperature for 20 min, the reaction was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The aqeuous layer was extracted with CH2O2 (3x) and combined organic extracts were washed with brine, dried over Na_2SO_4, and solvent was evaporated *in vacuo*. Purification via flash chromatography (0–100% EtOAc in hexanes) provided diene **11b** as an oil (9:1 *E/Z*, 113 mg, 0.191 mmol, 80%): $[\alpha]^{23}D$ = −1.7 (*c* = 0.92, $CHCl_3$); FT-IR (thin film, cm^{-1}): 2961, 1718, 1655, 1186; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.66 (m, 2H), 7.64 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.48– 7.43 (m, 2H), 7.39 (tdd, *J* = 8.1, 2.9, 1.1 Hz, 4H), 6.69 (dd, *J* = 15.7, 7.1 Hz, 1H), 6.14 (dd, *J* = 15.7, 0.9 Hz, 1H), 5.53 (dtt, *J*

= 14.5, 6.5, 1.1 Hz, 1H), 5.43 (dtt, *J* = 14.8, 6.8, 1.2 Hz, 1H), 5.21 (tq, *J* = 6.7, 1.4 Hz, 1H), 4.90 (dd, *J* = 6.0, 0.9 Hz, 1H), 4.53 (d, *J* = 6.0 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.83 (ddd, *J* = 10.7, 5.0, 1.0 Hz, 1H), 3.55 (ddd, *J* = 9.9, 8.7, 5.0 Hz, 1H), 3.43 (td, *J* = 8.9, 2.6 Hz, 1H), 3.35 – 3.28 (m, 1H), 3.25 (ddd, *J* = 7.1, 2.1, 0.8 Hz, 1H), 2.96 (td, *J* = 5.3, 2.0 Hz, 1H), 2.69 (d, *J* = 6.7 Hz, 2H), 2.65 – 2.57 (m, 1H), 2.37 (tdd, *J* = 6.7, 5.5, 1.2 Hz, 2H), 1.99 (dddd, *J* = 14.5, 7.9, 6.6, 3.4 Hz, 1H), 1.52 (d, *J* = 1.3 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 144.7, 136.0, 136.0, 135.9, 133.8, 133.1, 132.5, 130.2, 130.1, 128.0, 127.9, 125.0, 123.9, 120.8, 93.5, 82.6, 71.6, 67.6, 60.85, 60.78, 55.9, 43.1, 34.9, 30.5, 27.1, 19.4, 16.5, 14.4; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd for $C_{35}H_{46}O_6Si$, 613.2956; found 613.2970.

ethyl (*E*)-3-((2*S*,3*S*)-3-(((2*S*,3*S*)-3-(((2*S*,3*S*)-3-(((4*R*,5*S*)-5-hydroxy-1,3-dioxan-4-yl)methyl)-2-methyloxiran-2-yl)methyl)oxiran-2-yl)methyl)oxiran-2-yl)acrylate (4b).

Diene **11b** (87.8 mg, 0.148 mmol) was dissolved in DMM/MeCN (2:1, 6.66 mL) and ent-Chiral Shi ketone catalyst (38.2 mg, 0.147 mmol), a solution of 0.05 M $Na_2B_4O_7{\cdot}10H_2O$ in 4 x 10^{-4} Na_2EDTA (4.44 mL) and *n*-$BuHSO_4$ (25.0 mg, 0.074 mmol) were added and the solution was cooled to 0 °C. The reaction was stirred vigorously, open to air, while a solution of Oxone® (2.97 mL, 0.594 mmol, 0.20 M in 4 x 10^{-4} M aqueous Na_2EDTA) and K_2CO_3 (2.97 mL, 2.67 mmol, 0.89 M in H_2O) were added simultaneously via syringe pump over the course of 60 min. After 15 min, 30 min and 45 min, an additional batch of ent-Shi catalyst (38.2 mg, 0.147 mmol each time) was added. The reaction was allowed to stir for an additional 30 min at 0 °C, after which point it was diluted with EtOAc (10 mL) and H2O (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and combined organic layers were washed with brine, dried over Na_2SO_4, and solvent was evaporated *in vacuo*. The crude residue was purified via flash chromatography (0–100% EtOAc in hexanes) to furnish ethyl (*E*)-3-((2*S*,3*S*)-3-(((2*S*,3*S*)-3-(((2*S*,3*S*)-3-(((4*R*,5*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-1,3-dioxan-4-yl)methyl)-2-methyloxiran-2-yl)methyl)oxiran-2-yl)methyl)oxiran-2-yl)acrylate (3:1 d.r., 58.6 mg, 0.094 mmol, 63%) which was carried on as a mixture of diasteromers.

To a solution of the protected triepoxide (3:1 d.r., 35.3 mg, 0.056 mmol) in THF (0.283 mL) at 0 °C, was added a freshly prepared solution of TBAF·$3H_2O$ (0.089 mL, 0.085 mmol, 1.00 M in THF). The ice bath was removed and the reaction was allowed to warm to ambient temperature with stirring over 60 min. The reaction mixture was loaded directly onto a silica gel column for purification (10–100% EtOAc in hexanes, silica was buffered with 1% Et3N in hexanes) to furnish triepoxide **4b** as an oil (3:1 d.r., 17.3 mg, 0.045 mmol, 79%): $[\alpha]^{23}D$ = −140 (*c* = 0.86, $CHCl_3$); FT-IR (thin film, cm^{-1}): 3427, 1716, 1654, 1171); ^{1}H NMR (500 MHz, C6D6) δ 6.70 (dd, *J* = 15.7, 7.0 Hz, 1H), 6.12 (dd, *J* = 15.7, 0.7 Hz, 1H), 4.95 (dd, *J* = 6.1, 0.9 Hz, 1H), 4.33 (d, *J* = 6.1 Hz, 1H), 4.05 (ddd, *J* = 10.7, 5.2, 1.0 Hz, 1H), 3.98 (q, *J* = 7.1 Hz, 2H), 3.64 (tt, *J* = 9.6, 4.8 Hz, 1H), 3.35 (dt, *J* = 9.5, 4.9 Hz, 1H), 3.17 (t, *J* = 10.3 Hz, 1H), 3.12 (t, *J* = 6.0 Hz, 1H), 2.78 (ddd, *J* = 7.0, 2.0, 0.7 Hz, 1H), 2.65 (ddd, *J* = 6.4, 5.4, 2.1 Hz, 1H), 2.57 (ddd, *J* = 7.1, 4.3, 2.0 Hz, 1H), 2.47 (ddd, *J* = 6.4, 5.3, 2.1 Hz, 1H), 2.29 (d, *J* = 5.7 Hz, 1H), 1.94 (dd, *J* = 6.0, 4.9 Hz, 2H), 1.49 (dd, *J* = 8.6, 5.8 Hz, 2H), 1.46 – 1.40 (m, 1H), 1.27 – 1.23 (m, 1H), 1.22 (s, 3H), 0.95 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 165.8, 144.8, 124.6, 93.8, 80.7, 71.8, 65.8, 60.9,58.9, 58.4, 56.3, 55.5, 55.1, 41.7, 35.4,

31.7, 17.6, 14.5; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd for $C_{19}H_{28}O_8$, 407.1678; found 407.1654.

ethyl (E)-3-((4a*S*,5a*R*,6a*S*,8*R*,9*S*,10a*R*,11a*S*,12a*R*)-9-acetoxy-5a-methyldodecahydropyrano[2″,3″:5′,6′]pyrano[2′,3′:5,6]pyrano[3,2-d][1,3]dioxin-8-yl)acrylate (12).

Triepoxide **4b** (14.6 mg, 0.0379 mmol) was azeotropically dried with benzene (5 mL into a flask and dried under vacuum (~ 1 torr) for 20 min. The residue was dissolved in CH2O2 (1.36 mL), cooled to – 78 °C, and the reaction stirred at this temperature for 10 min. A freshly prepared solution of (±)-CSA (0.1 M in CH_2O_2, 379 μL, 0.0379 mmol) was added at the same temperature. After 30 min, the reaction was quenched at – 78 °C by the addition of triethylamine (5.1 μL, 0.0759 mmol) and the reaction was stirred for 10 min at this temperature. After removing the reaction to stir in a room temperature water bath for 10 min, the solvent was evaporated *in vacuo* to yield intermediate **15** ($R^2 = (CH)_2COOEt$) which was carried on without further purification. The intermediate (**15**, $R^2 = (CH)_2COOEt$) was azeotropically dried with benzene (3 x 5 mL) to remove any residual organic solvent. To the vial was added pH 7 buffer (1.89 mL, 0.10 M KP_i), the reaction was capped, sealed with Teflon tape and heated at 70 °C with vigorous stirring for 4 d. The reaction was subsequently cooled to rt, and solvent was evaporated *in vacuo*. The residue was dissolved in pyridine (0.271 mL) and acetic anhydride (36 μL, 0.379 mmol) was added and the reaction was stirred at ambient temperature for 16 h. Solvent was evaporated *in vacuo* and the reaction mixture was loaded directly onto a silica gel column for purification (10–100% EtOAc in hexanes, silica was buffered with 1% Et_3N in hexanes) to furnish the all-*endo* cascade product **12** ($R^2 = (CH)_2CO_2Et$, 1.1 mg, 0.0025 mmol, 7% over three steps): $[\alpha]^{23}D$ = + 4.8 (*c* = 0.05, CHCf); FT-IR (thin film, cm^{-1}): 2864, 1381, 1266, 1038; ΄H NMR (500 MHz, C_6D_6) δ 7.20 (dd, *J* = 15.7, 4.6 Hz, 1H), 6.39 (dd, *J* = 15.7, 1.6 Hz, 1H), 4.93 (d, *J* = 6.0 Hz, 1H), 4.77 – 4.68 (m, 1H), 4.29 (d, *J* = 6.1 Hz, 1H), 4.08 (dd, *J* = 10.1, 4.6 Hz, 1H), 3.98 (q, *J* = 7.2 Hz, 2H), 3.67 – 3.63 (m, 1H), 3.60 (dt, *J* = 9.6, 4.8 Hz, 1H), 3.24 (t, *J* = 10.0 Hz, 1H), 3.03 – 2.96 (m, 1H), 2.95 – 2.89 (m, 2H), 2.79 (ddd, *J* = 11.7, 9.3, 3.9 Hz, 1H), 2.54 (dt, *J* = 11.3, 4.4 Hz, 1H), 2.16 (dt, *J* = 11.4, 4.0 Hz, 1H), 2.08 (dd, *J* = 11.5,4.6 Hz, 1H), 1.79 (q, *J* = 11.7 Hz, 1H), 1.54 (t, *J* = 11.6 Hz, 1H), 1.50 (s, 3H), 1.38 (q, *J* = 11.3 Hz, 1H),1.00 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 169.3, 166.2, 143.4, 123.6, 110.5, 94.4, 80.4, 79.2, 78.7, 78.1, 77.3, 74.6, 70.8, 70.4, 67.3, 60.9, 43.4, 36.0, 31.2, 20.6, 16.5, 14.5, 2.7; HRMS (DART, *m/z*): $[M+H]^+$ calcd for $C_{21}H_{30}O_9$, 427.1963; found 427.1979.

(*E*)-6-bromohept-5-en-2-yn-1-ol (21):

Propargyl alcohol (0.20 mL, 3.51 mmol) was dissolved in THF (8.70 mL) and cooled to 0 °C. Dropwise addition of *n*-butyllithium (0.86 M in THF, 8.16 mL) was followed by a period of stirring at 0 °C for 1 h. Subsequently, solid CuI (73.5 mg, 0.386 mmol) was added and the reaction was stirred at 0 °C for another 30 min. A solution of allyl bromide **20**[29] (760 mg, 3.55 mmol) in THF (8.90 mL) was then added, and the reaction was allowed to stir for 16 h while warming to ambient temperature. The reaction was quenched by the careful addition of sat. $NH_4Cl_{(aq)}$ (10 mL) and Et_2O (10 mL). The aqueous layer was extracted with Et_2O (3x) and combined organic extracts were washed with brine, dried over Na_2SO_4, and

solvent was evaporated *in vacuo*. Purification via flash chromatography (5–28% EtOAc in hexanes) provided **21** (303 mg, 1.60 mmol, 45%): FT-IR (thin film, cm $^{-1}$): 3312, 1652; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (tq, *J* = 7.4, 1.4 Hz, 1H), 4.26 (t, *J* = 2.2 Hz, 2H), 2.95 (dtt, *J* = 7.4, 2.2, 1.0 Hz, 2H), 2.25 (q, *J* = 1.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.2, 121.9, 82.6, 79.2, 51.5, 23.4, 19.5; HRMS (DART, m/z): $[M+NH_4]^+$ calcd for C_7H_9BrO, 206.0175; found 206.0174.

(2*E*,5*E*)-6-bromohepta-2,5-dien-1-ol (19).

To a solution of lithium aluminum hydride (91.2 mg, 2.40 mmol) in THF (2.40 mL) at 0 °C was added enyne **21** (303 mg, 1.60 mmol, 1.00 equiv) in THF (2.40 mL) dropwise. The reaction was stirred at 0 °C for 15 min, after which the ice bath was removed. After stirring at rt for 16 h, the reaction was quenched by the slow addition of 1 M HCl (2 mL) and Et2O (2 mL). The aqueous layer was extracted with Et_2O (3 x 5mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and solvent was evaporated *in vacuo*. Purification by flash chromatography (10–80% EtOAc in hexanes) furnished diene **19** as an oil (246 mg, 1.28 mmol, 70%) as a clear oil: FT-IR (thin film, cm $^{-1}$): 3403, 1670; ^{1}H NMR (500 MHz, C_6D_6) δ 5.78 (tq, *J* = 7.7, 1.4 Hz, 1H), 5.33 (m, 1H), 5.25 (m, 1H), 3.74 (m, 2H), 2.31 (m, 2H), 1.88, (q, *J* = 1.0 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 131.3, 130.1, 128.1, 121.0, 63.4, 32.5, 23.3; HRMS (DART, m/z): $[M-H]^+$ calcd for $C_7H_{11}BrO$, 188.9910; found 188.9929.

tert-butyldimethyl(((2*R*,4a*R*,7*R*,8a*S*)-6-methylene-2-phenylhexahydropyrano[3,2-d][1,3]dioxm-7-yl)oxy)silane (18).

A solution of tert-butyldimethyl(((2*R*,4a*R*,7*R*,8a*S*)-6-methylene-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)silane[31] (555 mg, 1.47 mmol) in a mixture of CH_2Cl_2 (12.3 mL) and MeOH (2.45 mL) was cooled to −78 °C and ozone was bubbled through the reaction mixture. After 15 min, the solution was a persistent blue color, at which point the ozone was removed and nitrogen gas was bubbled through the solution. Once the blue color had faded, $NaBH_4$ (279 mg, 7.36 mmol) was added and the reaction was removed from the cooling bath and allowed to warm to rt with stirring for 16 h. Following addition of sat. $NH_4Cl_{(aq)}$ (10 mL) and Et_2O (10 mL), the aqueous layer was separated and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography purification (6–50% EtOAc in hexanes) furnished ((2*R*,4a*R*,6S,7*R*,8a*S*)-7-((tert-butyldimethylsilyl)oxy)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-6-yl)methanol (476 mg, 1.25 mmol, 85%). To a solution of the primary alcohol (476 mg, 1.25 mmol) in THF (6.25 mL) was added PPh_3 (394 mg, 1.50 mmol) and imidazole (204 mg, 3.00 mmol). Following cooling to – 40 °C, iodine (381 mg, 1.50 mmol) was added and the reaction was removed from the cooling bath and allowed to warm to rt with stirring over the course of 90 min. The mixture was quenched by the addition of $Na_2S_2O_3$ (10% w/v, 10 mL) and Et_2O (10 mL). The aqueous layer was extracted with Et_2O (3 x 15 mL) and combined organic layers were washed with brine, dried over Na_2SO_4, and solvent was evaporated *in vacuo*. The residue was purified via flash chromatography (2–20% EtOAc in hexanes) to provide *tert*-butyl(((2*R*,4a*R*,6*R*,7*R*,8a*S*)-6-(iodomethyl)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)dimethylsilane (563 mg, 1.15 mmol, 91%). A solution of the primary iodide (504 mg, 1.03 mmol) in THF (5.10 mL)

was cooled to 0 °C. Solid KO*t*-Bu (231 mg, 2.06 mmol) was added at 0 °C, and the reaction stirred for 20 min at this temperature before being quenched by the addition of H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and the solvent was evacuated *in vacuo*. Purification by flash chromatography (110% EtOAc in hexanes) yielded **18** as an oil (318 mg, 0.877 mmol, 85%): $[\alpha]^{24}D$ = +21.7 (*c* = 0.645, $CHCl_3$); FT-IR (thin film, cm $^{-1}$): 1660, 1462, 1215; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.4, 2.3 Hz, 2H), 7.30–7.23 (m, 3H), 5.44 (s, 1H), 4.60 (d, *J* = 1.7 Hz, 1H), 4.56 (d, *J* = 1.8 Hz, 1H), 4.28 (dd, *J* = 10.4, 4.9 Hz, 1H), 4.14 (ddt, *J* = 10.6, 5.4, 1.8 Hz, 1H), 3.70–3.56 (m, 2H), 3.45 (ddd, *J* = 10.1, 9.1, 4.9 Hz, 1H), 2.37–2.28 (m, 1H), 1.72 (q, *J* = 11.2 Hz, 1H), 0.83 (s, 9H), 0.02 (s, 6H), 0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 137.4, 129.3, 128.53, 128.51, 126.3, 101.9, 93.7, 76.2, 74.1, 69.4, 67.1, 39.2, 25.9, 18.3, −4.7, −4.8; HRMS (DART, m/z): $[M+H]^+$ calcd for $C_{20}H_{30}O_4Si$, 363.1986; found 363.1972.

(2*E*,5*E*)-7-((2*R*,4a*R*,6*S*,7*R*,8a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-6-yl)-6-methylhepta-2,5-dien-1-ol (22).

Exocyclic olefin **18** (62.3 mg, 0.172 mmol) was azeotropically dried with benzene (5 mL) in a reaction vessel which was subsequently dried under vacuum (~ 1 torr) for 1 h. The vessel was backfilled with argon and a solution of 9-borabicylo[3.3.1]nonane dimer (52.0 mg, 0.430 mmol) in THF (3.66 mL) was added. The reaction aged for 3 h at rt, at which point an aqueous solution of K_3PO_4 was added (0.228 mL, 3 M in H_2O), degassed by sparging with nitrogen for 15 min. After 15 min of stirring at room temperature, the flask was quickly opened and solid [1,1'-bis(diphenylphosphino)ferrocene]palladium(II)dichloromethane adduct (14.0 mg, 0.0170 mmol) was added. A solution of diene **19** (65.6 mg, 0.343 mmol) in DMF (2.60 mL, degassed by sparging with nitrogen for 15 min) was then added and the reaction was allowed to stir for 16 h at room temperature with vigorous stirring. After this period, it was partitioned between Et_2O (10 mL) and H_2O (10 mL). The aqueous layer was extracted with Et_2O (4 x 15 mL), and the combined organic layers were washed with $LiCl_{(aq)}$ (5% w/w, 10 mL) and brine (10 mL), dried over Na_2SO_4 and solvent was evaporated *in vacuo*. The tawny brown gel was then dissolved in THF (1.15 mL) and H_2O (1.15 mL) and solid $NaBO_3{\cdot}4H_2O$ (264 mg, 1.72 mmol) was added, and the mixture was allowed to stir vigorously at rt for 2 h. The mixture was then partitioned and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and solvent was evaporated *in vacuo*. The residue was purified via flash chromatography (8–66% EtOAc in hexanes) to furnish THP-diene **22** as an oil (54.2 mg, 88% by weight contaminated with primary alcohol side product, 0.100 mmol, 58%): $[\alpha]^{24}D$ = −35.5 (*c* = 1.20, $CHCl_3$); FT-IR (thin film, cm $^{-1}$): 3387, 3037, 1684, 1456. ^1H NMR (500 MHz, $CDCl_3$) δ 7.50–7.46 (m, 2H), 7.39–7.31 (m, 3H), 5.73–5.61 (m, 2H), 5.50 (s, 1H), 5.22 (t, *J* = 7.3 Hz, 1H), 4.28 (dd, *J* = 10.6, 4.9 Hz, 1H), 4.12–4.08 (m, 2H), 3.83–3.78 (m, 1H), 3.78–3.74 (m, 1H), 3.66 (t, *J* = 10.2 Hz, 1H), 3.55–3.40 (m, 1H), 3.34–3.29 (m, 1H), 2.78 (t, *J* = 6.2 Hz, 2H), 2.57 (d, *J* = 14.3 Hz, 1H), 2.39 (dt, *J* = 11.5, 4.5 Hz, 1H), 1.97 (dd, *J* = 14.4, 9.8, 1H), 1.75–1.67 (m, 1H), 1.65 (s, 3H), 0.89 (s, 9H), 0.08 (s, 9H); ^{13}C NMR(125 MHz, $CDCl_3$) δ 137.7, 134.0, 131.8, 129.3, 129.0, 128.5, 126.4, 123.6, 101.9, 81.8, 76.6, 73.24, 70.7, 69.6, 64.0, 41.9, 39.2, 30.9, 25.9, 18.1, 16.6, −3.8, −4.5; HRMS (DART, m/z): $[M+NH_4]^+$ calcd for $C_{27}H_{42}O_5Si$, 492.3140; found 492.3145.

((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(((2*R*,4a*R*,6*S*,7*R*,8a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-6-yl)methyl)-3-methyloxiran-2-yl)methyl)oxiran-2-yl)methanol:

Into a flame-dried round bottom flask in a glovebox, 4Å molecular sieves (58.2 mg, activated by heating for 2 d at 200 °C at ~1 torr) were added, and the flask was subsequently removed from the glovebox and placed under an atmosphere of argon. Following the addition of CH_2Cl_2 (2.20 mL), the flask was cooled to −20 °C and D-(−)-DET (6.30 μL, 0.0367 mmol), Ti(O^iPr)$_4$ (9.00 μL, 0.0306 mmol) and TBHP (0.0740 mL, 0.408 mmol, 5.5 M in decane) were added. The mixture was allowed to stir at −20 °C for 30 min. Following transfer and azeotropic drying with benzene (5.00 mL) into a flame-dried pear-shaped flask, THP-diene **22** (97.0 mg, 0.204 mmol) was dried under reduced pressure, backfilled with argon, and dissolved in CH_2Cl_2 (0.725 mL). This solution was added to the mixture at −20 °C, and the reaction was maintained at this temperature for 16 h. The reaction was then poured into a solution of tartaric acid (20.4 mg, 0.136 mmol) and $FeSO_4 \cdot 7H_2O$ (68.0 mg, 0.245 mmol) in water (1.00 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min, and subsequently partitioned and further diluted with water (5 mL). The aqueous layer was extracted with Et_2O (3x 10 mL), and the combined organic layers were transferred to an Erlenmeyer flask. To this solution, 30% w/v NaOH in brine (1.00 mL) was added and the mixture was stirred vigorously for 45 min at rt. The solution was then transferred to a separatory funnel, washed with brine (10 mL), dried over Na_2SO_4, and solvent was evaporated *in vacuo*. Purification via flash chromatography (10-80% EtOAc in hexanes) provided the epoxy alcohol (>20:1 d.r., 65.0 mg, 0.132 mmol, 65%). The epoxy alcohol (64.1 mg, 0.130 mmol) was dissolved in DMM/MeCN (2:1, 5.85 mL). Chiral Shi ketone catalyst (16.7 mg, 0.0647 mmol), a solution of 0.05 M $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} Na_2EDTA (3.90 mL) and n-$BuHSO_4$ (22.0 mg, 0.0650 mmol) were added and the solution was cooled to 0 °C. The reaction was stirred vigorously, open to air, while a solution of Oxone® (2.60 mL, 0.520 mmol, 0.20 M in 4 x 10^{-4} M aqueous Na_2EDTA) and K_2CO_3 (2.60 mL, 2.34 mmol, 0.890 M in H_2O) were added simultaneously via syringe pump over the course of 60 min. After 15 min, 30 min and 45 min of reacting, an additional batch of Shi catalyst (16.7 mg, 0.0647 mmol each time) was added. The reaction was allowed to stir for an additional 30 min at 0 °C, after which point it was diluted with EtOAc (10 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and solvent was evaporated *in vacuo*. The crude residue was purified via flash chromatography (12–100% EtOAc in hexanes) to furnish the title diepoxy alcohol, ((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(((2*R*,4a*R*,6*S*,7*R*,8a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-6-yl)methyl)-3-methyloxiran-2-yl)methyl)oxiran-2-yl)methanol (3:1 d.r., 66.0 mg, 0.130 mmol, quantitative yield): $[\alpha]^{24}D = -30.8$ (*c* = 0.480, $CHCl_3$); FT-IR (thin film, cm^{-1}): 3489, 1456. ^1H NMR (500 MHz, $CDCl_3$) δ 7.50–7.46 (m, 2H), 7.40–7.33 (m, 3H), 5.51 (s, 1H), 4.32 (dd, *J* = 10.4, 4.9 Hz, 1H), 3.93 (dq, *J* = 12.7, 2.6 Hz, 1H), 3.72 – 3.63 (m, 2H), 3.53 (ddd, *J* = 11.8, 8.9, 4.1 Hz, 1H), 3.45 (ddd, *J* = 10.6, 8.8, 4.6 Hz, 1H), 3.41–3.32 (m, 2H), 3.16 (ddt, *J* = 6.8, 4.4, 1.9 Hz, 1H), 3.00 (dq, *J* = 4.3, 2.2 Hz, 1H), 2.94 (dd, *J* = 6.9, 5.5 Hz, 1H), 2.40 (dt, *J* = 11.5, 4.3 Hz, 1H), 2.08 (dd, *J* = 14.6, 1.7 Hz, 1H), 1.92–1.78 (m, 2H), 1.77–1.67 (m, 1H), 1.63 (dd, *J* = 14.7, 9.9 Hz, 1H), 1.32 (s, 3H), 0.88 (s, 9H), 0.08 (d, *J* = 0.8 Hz, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 129.3, 128.6, 126.4, 101.9,

80.4, 76.6, 73.2, 70.5, 69.6, 61.6, 60.6, 59.7, 59.1, 58.3, 53.3, 40.2, 39.1, 31.6, 25.9, 18.1, −3.8, −4.5; HRMS (ESI, m/z): $[M+Na]^+$ calcd for $C_{27}H_{42}O_7Si$, 529.2592; found 529.2600.

(2*R*,4a*R*,6*S*,7*R*,8a*S*)-6-(((2*R*,3*R*)-2-methyl-3-(((2*R*,3*R*)-3-vinyloxiran-2-yl)methyl)oxiran-2-yl)methyl)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-ol (16):

The above diepoxy alcohol (as a 3:1 mixture of diastereomers, 66.0 mg, 0.130 mmol) was azeotropically dried with benzene (1 mL) in a reaction vessel and dried under vacuum (~1 torr) for 30 minutes. The vessel was backfilled with argon, CH_2Cl_2 (4.30 mL) was added and the reaction was cooled to 0 °C. Solid $NaHCO_3$ (54.6 mg, 0.650 mmol) was added, followed by Dess–Martin periodinane (110 mg, 0.260 mmol). After stirring at 0 °C for 5 min, the ice bath was removed and the reaction was allowed to warm to ambient temperature over 40 min. The reaction was quenched by the addition of sat. $NaHCO_{3\,(aq)}$ (3.25 mL) and sat. $Na_2S_2O_{3\,(aq)}$ (3.25 mL). Additional CH_2Cl_2 (3.25 mL) was added, the reaction was stirred for 10 min and subsequently partitioned. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were washed with $NaHCO_3$ (5 mL) and brine (5 mL). Following drying with Na_2SO_2 and evaporation of solvent *in vacuo*, the resulting aldehyde was carried on without purification. Solid methyltriphenylphosphonium bromide (139 mg, 0.390 mmol) was briefly flame dried, cooled under vacuum (~1 torr) and the vessel was backfilled with argon. The phosphonium salt was dissolved in THF (1.00 mL) and cooled to 0 °C. To a flame-dried pear shaped flask which was taken into the glovebox, was added solid NaHMDS (66.7 mg, 0.364 mmol). The flask was removed from the glovebox and the solid was dissolved in THF (3.00 mL). This NaHMDS solution was added to the phosphonium salt at 0 °C, and the reaction was stirred at this temperature for 1 h. The aldehyde from above had been azeotropically dried with benzene (1 mL) into a flame-dried flask and dried under vacuum (~1 torr) for about 30 min. This aldehyde was dissolved in THF (3.4 mL) and added to the reaction mixture at 0 °C. After stirring at this temperature for 10 min, the reaction was quenched by the addition of H_2O (2 mL) and Et_2O (2 mL). The reaction mixture was partitioned, the aqueous layer was extracted with Et_2O (3 x 2 mL) and combined organic layers were washed with brine, dried over Na_2SO_4 and solvent was evaporated in vacuo. The crude residue was purified via flash chromatography (5–50% EtOAc in hexanes) to furnish *tert*-butyldimethyl(((2*R*,4a*R*,6*S*,7*R*,8a*S*)-6-(((2*R*,3*R*)-2-methyl-3-(((2*R*,3*R*)-3-vinyloxiran-2-yl)methyl)oxiran-2-yl)methyl)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)silane (46.8 mg, 0.930 mg, 72% over two steps). To a solution of the above described vinyl diepoxide (46.8 mg, 0.0930 mmol, 1.00 equiv) in THF (0.46 mL) at 0 °C, was added a freshly prepared solution of $TBAF{\cdot}3H_2O$ (0.19 mL, 0.186 mmol, 1.00 M in THF). The ice bath was removed and the reaction was allowed to warm to ambient temperature with stirring over 50 min. The reaction mixture was loaded directly onto a silica gel column for purification (10–100% EtOAc in hexanes, silica was buffered with 1% Et_3N in hexanes) to furnish the vinyl diepoxide cascade precursor **16** as an oil (3:1 d.r., 30.7 mg, 0.0790 mmol, 85%): $[\alpha]^{25}D$ = +1.16 (*c* = 0.225, $CHCl_3$); FT-IR (thin film, cm^{-1}): 3459, 2981, 1067, 753; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.7, 1.9 Hz, 2H), 7.42–7.34 (m, 3H), 5.65–5.57 (m, 1H), 5.53 (s, 1H), 5.51 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.31 (dt, *J* = 10.2, 1.0 Hz, 1H), 4.31 (dd, *J* = 10.4, 4.9 Hz, 1H), 3.72–3.62 (m, 2H), 3.57 (dtd, *J* = 11.7, 9.8, 9.4, 4.2 Hz, 1H), 3.38–3.33 (m, 2H), 3.20 (dd, *J* = 7.4, 2.2 Hz, 1H), 3.05–3.01 (m, 2H), 2.50 (dt, *J* = 11.5, 4.3 Hz, 1H), 2.20 (dd, *J* = 15.2, 3.0 Hz, 1H), 1.96–1.90 (m,

1H), 1.86–1.75 (m, 2H), 1.70 (q, *J* = 11.4 Hz, 1H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, CDCh) δ 137.6, 135.3, 129.3, 128.5, 126.4, 119.9, 101.9, 80.3, 73.6, 69.5, 69.1, 60.0, 59.8, 58.8, 57.7, 40.2, 38.0, 31.7, 18.0; HRMS (ESI, m/z): $[M+Na]^+$ calcd for $C_{22}H_{28}O_6$, 411.1778; found 411.1779.

(2*R*,4a*R*,5a*S*,6a*R*,8*S*,9*R*,10a*S*,11a*R*,12a*S*)-6a-methyl-2-phenyl-8-vinyldodecahydropyrano[2″,3″:5′,6′]pyrano[2′,3′:5,6]pyrano[3,2-d][1,3]dioxin-9-ol (23) and 5-((2*R*,4a*R*,5a*S*,8a*R*,9a*S*)-7-methyl-2-phenyloctahydrofuro[2′,3′:5,6]pyrano[3,2-d][1,3]dioxm-7-yl)-2-vinyltetrahydrofuran-3-oland (24).

Vinyl diepoxide **16** (as a 3:1 mixture of diastereomers, 7.00 mg, 0.018 mmol, 1.00 equiv) was dried azeotropically with benzene (2 mL) in a flame-dried scintillation vial. The reaction vessel was dried on vacuum (~1 torr) for 1 h to remove any remaining organic solvent. To the vial was added pH 11 buffer (0.90 mL, 0.10 M KP_i), the reaction was capped, sealed with Teflon tape and heated at 70 °C with vigorous stirring for 48 h. The reaction was subsequently cooled to rt, and solvent was evaporated under a stream of nitrogen gas. Purification via flash chromatography (10–100% EtOAc in hexanes) furnished desired all-*endo* product **23** (2.1 mg, 0.005 mmol, 41% based on d.r. of starting material) and **24** (2.5 mg, 0.006 mmol, 47% based on d.r. of starting material). Data for **23**: $[\alpha]^{23}D = -42.1$ (*c* = 0.065, $CHCl_3$); FT-IR (thin film, cm^{-1}): 3434, 2930, 1647, 1457, 1175; ^{1}H NMR (500 MHz, C_6D_6) δ 7.67–7.63 (m, 2H), 7.21–7.18 (m, 2H), 7.14–7.11 (m, 1H), 5.84 (ddd, *J* = 17.1, 10.6, 6.2 Hz, 1H), 5.33 (s, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 5.05 (dd, *J* = 10.4, 1.8 Hz, 1H), 4.23 (dd, *J* = 10.3, 4.6 Hz, 1H), 3.78 (dd, *J* = 9.4, 6.3 Hz, 1H), 3.51–3.47 (m, 1H), 3.31–3.18 (m, 2H), 3.17–3.13 (m, 1H), 3.12–3.02 (m, 3H), 2.48 (dt, *J* = 11.0, 3.9 Hz, 1H), 2.22 (dd, *J* = 11.4, 4.1 Hz, 1H), 2.15 (dt, *J* = 11.8, 4.3 Hz, 1H), 1.77 (q, *J* = 11.1 Hz, 1H), 1.70 (t, *J* = 11.3 Hz, 1H), 1.63 (q, *J* = 11.7 Hz, 1H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 138.9, 137.4, 129.4, 127.1, 117.6, 110.5, 102.3, 80.3, 79.6, 78.1, 78.0, 76.4, 74.8, 70.8, 69.8, 44.0, 35.9, 33.9, 16.4; HRMS (DART, *m/z*): $[M+H]^+$ calcd for $C_{22}H_{28}O_6$, 389.1959; found 389.1942. Data for **24**: $[\alpha]^{23}D = -26.8$ (*c* = 0.04, $CHCl_3$); FT-IR (thin film, cm^{-1}): 3462, 2974, 1646, 1456, 1072; ^{1}H NMR (400 MHz, C_6D_6) δ 7.67–7.61 (m, 2H), 7.22–7.18 (m, 2H), 7.14–7.11 (m, 1H), 5.63 (ddd, *J* = 17.2, 10.6, 5.0 Hz, 1H), 5.28–5.23 (m, 2H), 4.99 (dt, *J* = 10.5, 1.8 Hz, 1H), 4.43–4.41 (m, 1H), 4.28 (dd, *J* = 10.3, 4.7 Hz, 1H), 3.87 (dd, *J* = 8.4, 5.9 Hz, 1H), 3.83 (br s, 1H), 3.61 (ddd, *J* = 11.5, 9.2, 3.7 Hz, 1H), 3.52 (t, *J* = 10.2 Hz, 1H), 3.34 (td, *J* = 9.6, 4.6 Hz, 1H), 3.26 (ddd, *J* = 11.2, 9.2, 6.6 Hz, 1H), 3.04 (ddd, *J* = 10.8, 9.0, 4.1 Hz, 1H), 2.94 (d, *J* = 8.4 Hz, 1H), 2.44 (dt, *J* = 10.6, 3.9 Hz, 1H), 1.90–1.79 (m, 2H), 1.69–1.55 (m, 3H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 138.9, 137.8, 129.3, 127.1, 115.5, 102.4, 88.1, 85.4, 84.1, 81.2, 79.2, 78.1, 75.8, 75.5, 69.9, 37.3, 36.2, 35.4, 26.3; HRMS (DART, *m/z*): $[M+H]^+$ calcd for $C_{22}H_{28}O_6$, 389.1959; found 389.1963.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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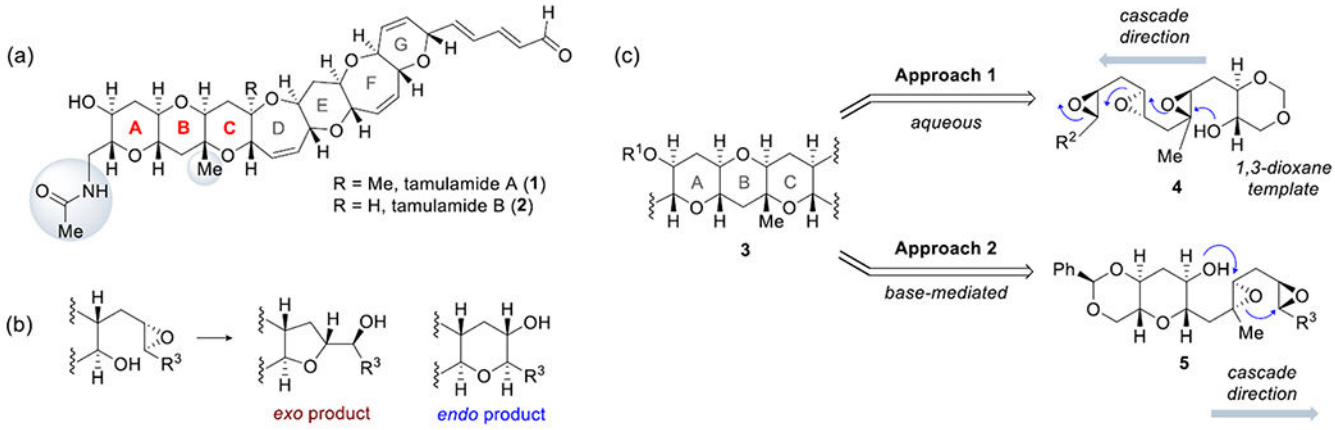
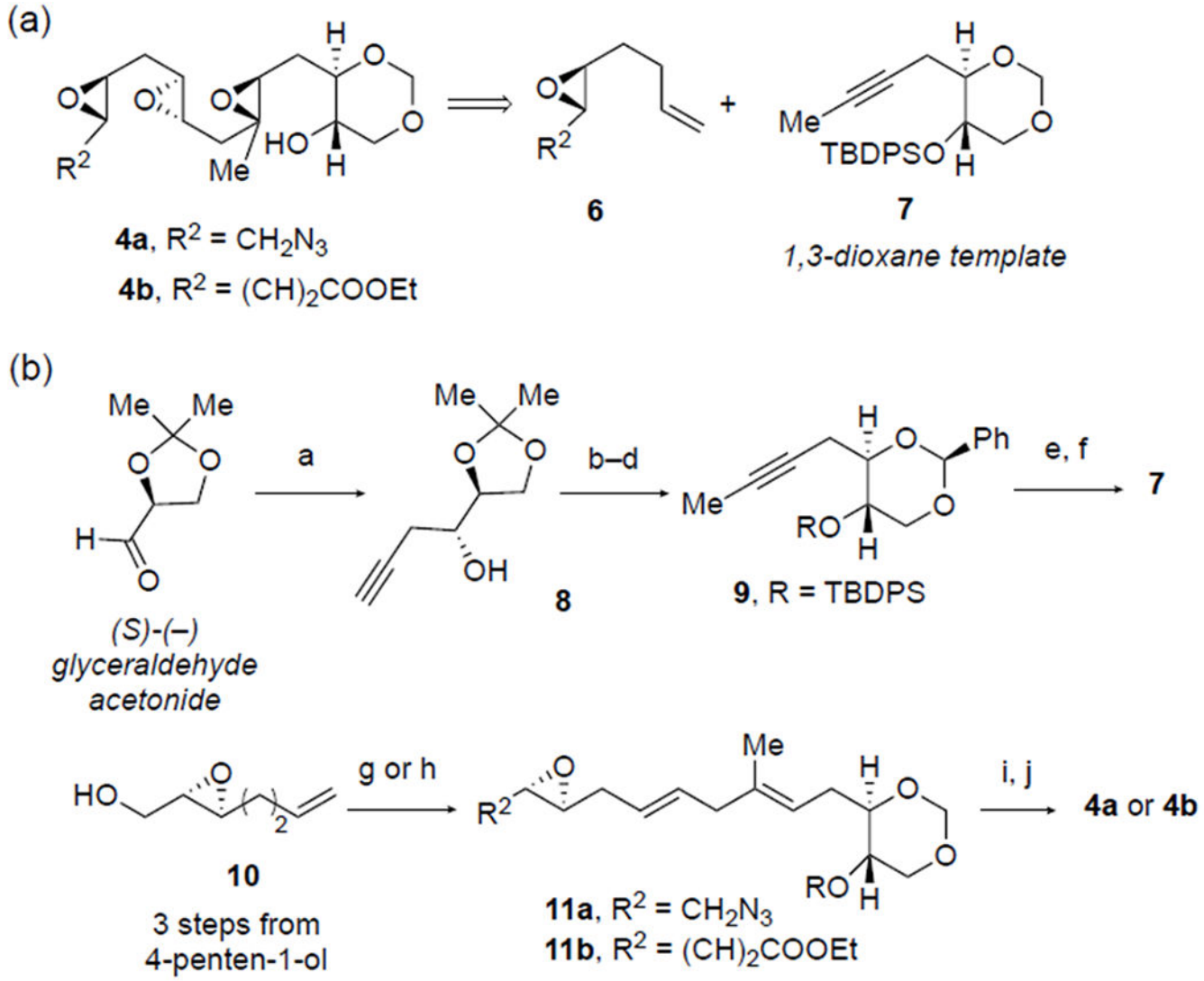


SCHEME 1.

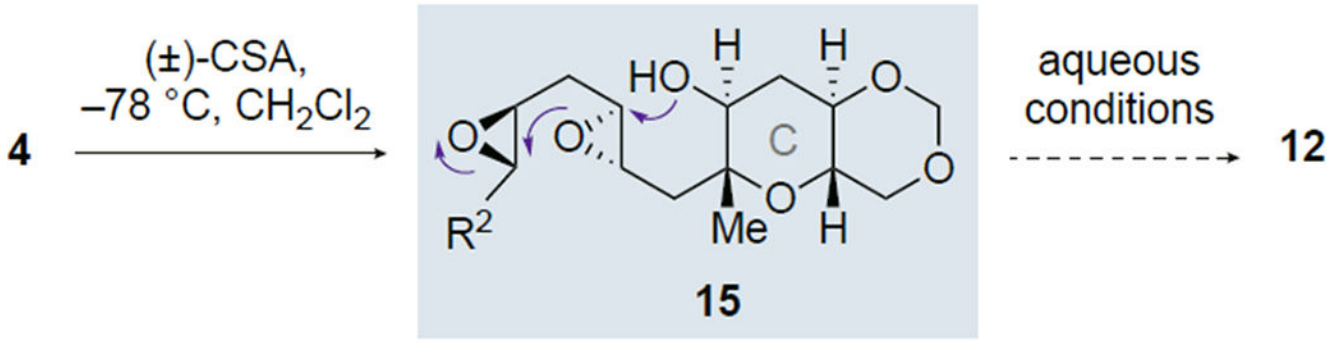
(a) Tamulamides A (1) and B (2). (b) Illustration of *exo* and *endo* product formation in an epoxideopening reaction. (b) Proposed strategies to access the *ABC* core of tamulamides A and B.



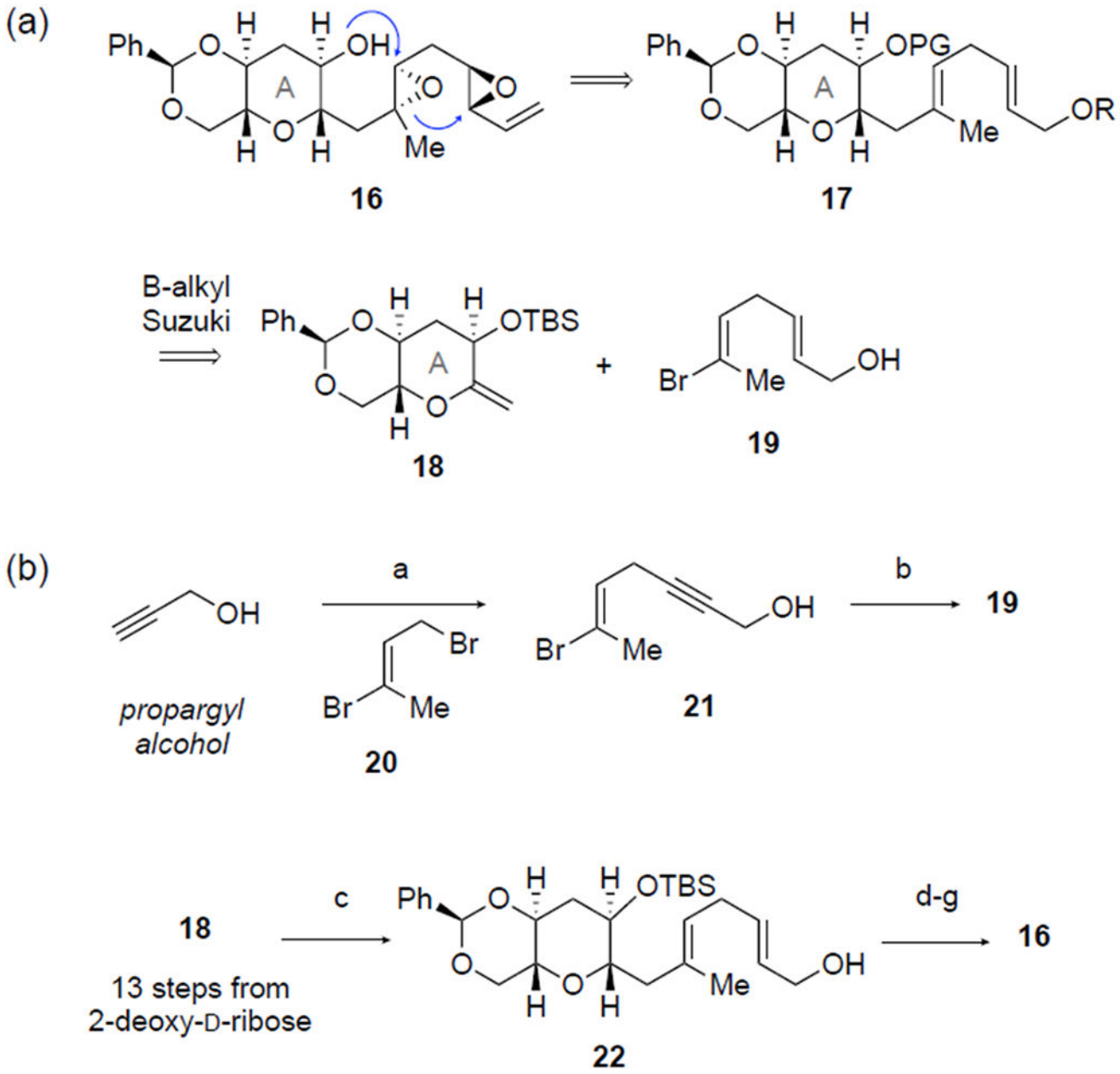
SCHEME 2.

(a) Retrosynthetic analysis of **4**. (b) Synthesis of cascade precursors **4a** ($R^2 = CH_2N_3$) and **4b** ($R^2 = (CH)_2COOEt$).

Reagents and conditions: a) propargyl bromide, Zn dust, 1:1 DMF/Et_2O, 98%, 4:1 d.r. enriched to 94:6; b) 1. DOWEX-WX8-400 resin; 2. benzyaldehyde dimethyl acetal, (±)-CSA, 36% over 2 steps; c) TBDPSCl, imid., 91%; d) MeI, *n*-BuLi, 62%; e) $TsOH \cdot H_2O$, 46%; f) Dimethoxymethane (DMM), $BF_3 \cdot OEt_2$, 73%; g) 1. TsCl, Et_3N, CH_2Cl_2, 72% 2. **7**, $CpRu(MeCN)_3 \cdot PF_6$ (8 mol %) acetone, rt, 53% 9:2 l/b; 3. NaN_3, DMF, 75%; h) 1. **7**, $CpRu(MeCN)_3 \cdot PF_6$ (8 mol %) acetone, rt, 73%, 5:1 l/b; 2. DMSO, Et_3N, $SO_3 \cdot$pyr, CH_2Cl_2 then Ph_3PCHCO_2Et, 80%, 9:1 *E/Z*; i) $Na_2B_4O_7$, ent-Shi cat., Oxone, K_2CO_3, *n*-Bu_4NHSO_4, 2:1 DMM/MeCN ; j) TBAF, THF, **4a**, 62% over two steps, **4b**, 50% over two steps.



SCHEME 3.
Proposed formation of 12.



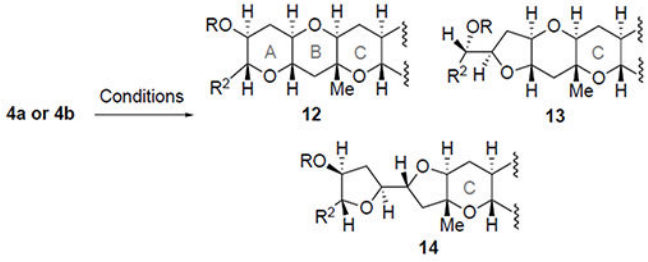
SCHEME 4.

Synthesis of cascade precursor **16**.

Reagents and conditions: a) n-BuLi, 0 °C, 30 min then **20**, Cu(I) I, 30 min, 45%; b) LAH, 0 °C to rt 16 h, 70%; c) 9-BBN–H, K_3PO_4, then **19**, $PdCl_2$(dppf) 58%; d) 1. TBHP, Ti(O*i*-Pr)$_4$, D-(−)-DET, 65%, >20:1 d.r.; e) $Na_2B_4O_7$, Shi cat., Oxone, K_2CO_3, n-Bu_4NHSO_4, quant, 3:1 d.r; f) 1. Dess–Martin periodinane, $NaHCO_3$, NaHMDS, Ph_3PMeBr, 72% over 2 steps; g) TBAF, 85%.

TABLE 1.

Cascade results of triepoxide **4a** ($R^2 = CH_2N_3$) and **4b** ($R^2 = (CH)_2COOEt$).



Entry	SM	Conditions	R	12:13:14
1	**4a**	pH 7,[a] 14 d, 70 °C; AC_2O, pyridine	Ac	7 : 40 : 0[b]
2	**4a**	(±)-CSA, CH_2Cl_2, rt, 24 h	H	0 : 20 : 0[b]
3	**4a**	1. (±)-CSA, −78 °C, CH_2Cl_2 2. pH 5.5,[a] 70 °C, 7 d; Ac_2O, pyridine	Ac	1 : 2 : <0.1 [c]
4	**4b**	(±)-CSA, rt, CH_2Cl_2; Ac_2O, pyridine	Ac	10 : 0 : 16 [b]
5	**4b**	1. (±)-CSA, −78 °C, CH_2Cl_2 2. pH 7, 70 °C, 4 d; Ac_2O, pyridine	Ac	7 : 0 : 0 [b]

[a] 0.1 M KPi buffer.

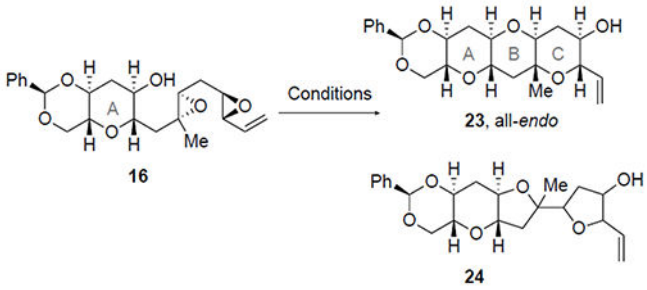
[b] Isolated product yields.

[c] Ratio determined by ^1H NMR.

SM = starting material.

TABLE 2.

Basic aqueous cascade results of **16**.



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Entry	Conditions	Isolated Yields (%)	
		23	24
1	pH 11,[a] rt, 7 d	21	10
2	pH 11,[a] 70 °C, 2 d	41	47

[a]0.1 M KPi buffer.