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Enantioselective Total Synthesis and Structural Assignment of Callyspongiolide

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Abstract

We have elucidated the complete absolute configuration of callyspongiolide and unambiguously assigned its stereochemistry at the C-21 center through synthesis. Four stereoisomers of callyspongiolide were synthesized in a convergent and enantioselective manner. A late-stage Sonogashira coupling forges the diene-ynic side chain. Other notable reactions are Yonemitsu's variation of the Yamaguchi macrolactonization to cyclize an alkynic seco acid, highly *trans*-selective Julia-Kocienski olefination, CBS reduction to set the C-21 stereocenter, and methyl cuprate addition to an unsaturated pyranone to install the C-5 methyl center.

Introduction

The marine environment continues to be a treasure trove for structural and biological diversity, producing natural products with significant medicinal potential.^{1–4} To date, many clinically effective drugs as well as promising investigational drug candidates have emerged from marine sources.^{5, 6} Specifically, marine sponges of the genus *Callyspongia* have provided a variety of natural products that display intriguing biological properties.^{7–11} Proksch and co-workers recently reported the isolation of callyspongiolide (**1**, Figure 1) off the coast of Indonesia from the sponge, *Callyspongia* species.¹² Preliminary biological studies revealed that callyspongiolide displayed complete inhibition of the murine lymphoma cell line, L5178Y. It exhibited potent cytotoxicity against human Jurkat J16 T and Ramos B lymphocytes with IC₅₀ values of 70 nM and 60 nM, respectively. Furthermore, callyspongiolide induced increased levels of hypodiploid nuclei at EC₅₀ levels of 80 nM for Jurkat J16 T and 50 nM for Ramos B lymphocytes. The mechanism of action is intriguing as the addition of Q-VD-OPH did not reverse apoptosis, suggesting that the mode of action does not involve a caspase pathway. The callyspongiolide structure contains a 14-membered macrolactone bearing both *cis*- and *trans*-olefins with a branching carbamate functionality on the lactone ring. The macrolactone is conjoined to a bromophenol through a unique diene-ynic linker. The structure and relative stereochemistry was determined using detailed NMR and HRMS analysis. However, the relative stereochemistry of the C-21 stereocenter

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[†]Electronic Supplementary Information (ESI) available: ¹H- and ¹³C-NMR spectra of new compounds

was left unassigned. Also, the absolute configuration of the five stereogenic centers within the macrolactone was not determined.

The unique structural features as well as biological properties of callyspongiolide attracted our interest in structural elucidation and enantioselective synthesis to expedite structural variants for biological studies. To determine the absolute configuration of the macrolactone segment in relation to the stereocenter on the side chain, conceivably four possible stereoisomers need to be synthesized in a stereo-defined manner and compared to the natural product. We recently reported a convergent and enantioselective synthesis of both epimers at C-21 in the proposed structure of (+)-callyspongiolide, **1**.¹³ The absolute stereochemistry of each epimer at C-21 was assigned unambiguously using X-ray crystallographic analysis. Neither ¹H- or ¹³C-NMR analysis could differentiate between the two epimers of callyspongiolide **1**. However, the sign of our specific rotations as well as magnitude were different than the reported values for the natural callyspongiolide by Proksch and co-workers. Recently, Ye and co-workers reported the synthesis of four callyspongiolide diastereomers, assigned the stereochemical configuration of the natural product, and correlated to bioactivity.¹⁴ Herein we report an enantioselective synthesis of (–)-callyspongiolide (**2**) and reveal unequivocally the absolute stereochemical configuration of the natural product.

Results and discussion

Our synthetic strategy for callyspongiolide **2** is convergent and involves the union of macrolactone **3** and enyne segment **4** shown in Figure 2. These segments could be joined by a Sonogashira coupling or Julia olefination of the appropriately functionalized intermediates. For Sonogashira coupling, aldehyde **3** could be converted to requisite vinyl iodide by a Takai olefination. Synthesis of the *cis*-macrolactone can be carried out from the seco acid **5** using a similar strategy we developed for the synthesis of laulimalide.^{15–18} This entails a Yamaguchi macrolactonization of the seco acid followed by selective hydrogenation of the alkynic lactone to the *cis*-lactone. Construction of the seco acid **5** would be achieved by Julia olefination of an aldehyde derived from alcohol **6** as the key step. The δ -lactone **6** can be constructed from homoallylic alcohol **7**, which is readily available from the complementary aldehyde. The enyne side chain would be constructed through Wittig olefination of the corresponding aldehyde derived from olefin **8**. A Corey-Bakshi-Shibata (CBS) reduction of the corresponding ketone could set the absolute configuration of the benzylic alcohol in **8**.

Our synthesis of the macrocyclic core of callyspongiolide begins in Scheme 1. Aldehyde **11**¹⁹ was conveniently prepared from imide **10** following procedures reported by Evans and co-workers.²⁰ Brown asymmetric allylation²¹ of **11** afforded homoallylic alcohol **7** in 84% yield and 10:1 dr (by ¹H-NMR analysis). Treatment of **7** with acryloyl chloride provided **12** in 63% yield. Ring closing metathesis of the acrylate ester using Grubbs II gave pyranone **13** in 93% yield. Installation of the C-5 methyl substituent was achieved by stereoselective conjugate addition using Gillman's methyl cuprate at –78 °C,²² providing **14** in 93% yield. The TBDPS ether was removed to deliver the primary alcohol **6**, which was then subjected to DMP oxidation to furnish aldehyde **15**.

Our synthesis of the requisite sulfone for Julia olefination is shown in Scheme 2. Epoxy alcohol **17** was prepared via Sharpless epoxidation²³ of allyl alcohol **16** as described by Crimmins and co-workers.²⁴ The epoxide was opened stereo- and regioselectively using Gilman's methyl cuprate²⁵ at $-50\text{ }^{\circ}\text{C}$ to $-10\text{ }^{\circ}\text{C}$ followed by addition of NaIO_4 to give the corresponding 1,3-diol **18** in 76% yield. Chemoselective introduction of the 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfide provided thioether **19**, followed by silyl protection, resulted in sulfide **20** in 84% yield for the two-steps. Our initial attempts of ammonium molybdate- H_2O_2 oxidation were ineffective in advancing the second oxidation of the incipient sulfoxide to sulfone.²⁶ Instead, changing to the peracid *m*-CPBA carried out the full oxidation to sulfone **21** at $23\text{ }^{\circ}\text{C}$ in 88% yield.

We next sought to explore reaction conditions for the Julia-Kocienski olefination. As shown in Table 1, metallation of sulfone **21** using LiHMDS in THF at $-78\text{ }^{\circ}\text{C}$ followed by addition of aldehyde **15** furnished lactone **22** in 67% yield with a *trans/cis* ratio of 2:1 by ^1H -NMR (entry 1).^{27, 28} Switching the solvent to DME or base to KHMDS was detrimental to reaction conversion and yields (entries 2–4). In all cases, elimination of the silyl ether was observed as the major product. Corey and Rajendar recently observed slight increases in reaction yield and dramatic improvements in *E/Z* ratio with the addition of tetrabutylammonium bromide.²⁹ While no *cis*-isomer was detectable by ^1H NMR using KHMDS in THF at $-78\text{ }^{\circ}\text{C}$, reaction yields remained low (entry 5). The use of LiHMDS resulted in a modest improvement of 3:1 in *E/Z* ratio (entry 6). Interestingly, addition of tetrahexylammonium chloride enhanced selectivity to 5:1 (entry 7). However, nearly exclusive formation of the *trans*-olefin was observed using LiHMDS in DMF at $-60\text{ }^{\circ}\text{C}$ in the absence of an additive. In this case, lactone **22** was obtained in 76% yield with a *trans/cis* ratio of 27:1.

Our synthesis of the macrocyclic core is shown in Scheme 3. Treatment of lactone **22** with *N,O*-dimethylhydroxylamine hydrochloride in the presence of isopropylmagnesium chloride at $-20\text{ }^{\circ}\text{C}$ resulted in ring opening to form Weinreb amide **23**. Protection of the resulting alcohol initially proved difficult since TBSCl and imidazole in DCM or DMF resulted in silyl migrations. However, changing the base to triethylamine completely inhibited rearrangements and TBS ether **24** was obtained in 91% yield.³⁰ DIBAL-H reduction at $-78\text{ }^{\circ}\text{C}$ followed by Seyferth-Gilbert homologation using the Ohira-Bestmann reagent³¹ at $23\text{ }^{\circ}\text{C}$ provided terminal alkyne **25** in 90% for the two-steps. Alkyne **25** was then alkylated to form alkynyl ester **26** in quantitative yield. The secondary TES protecting group was removed and ester hydrolysis revealed an alkynyl seco acid.

We then explored formation of the macrocyclic core, the results of which are shown in Table 2. Standard Yamaguchi macrolactonization conditions³² were first attempted, but to our surprise, complete formation of the mixed anhydride was never observed (entry 1). Steglich³³ and Boden-Keck³⁴ conditions were more effective, albeit in low isolated yields of alkynyl lactone **27** (entries 2 and 3). Use of BOP-Cl³⁵ showed a modest improvement in reaction yield (entry 4). Alternatively, employing Yonemitsu's variation³⁶ of the Yamaguchi macrolactonization was most effective, whereby instead of preforming the mixed anhydride, a solution of seco acid is added directly to the cocktail of reagents. In this manner, alkynyl lactone **27** was obtained in 67% yield over three steps (entry 5).

The synthesis of vinyl iodide from macrolactone **27** is shown in Scheme 4. The conjugated alkyne was readily reduced to the *cis*-lactone using Lindlar catalyst under a hydrogen-filled balloon to provide **28** in near quantitative yield. Introduction of the carbamate moiety was achieved by first deprotection of the TBS ether with HF·py followed by treatment with chlorosulfonyl isocyanate at 0 °C to provide carbamate **30** in 96% yield. The primary alcohol was then unmasked using DDQ to give alcohol **31**. Oxidation of the resulting alcohol with DMP followed by Takai olefination³⁷ of the intermediate aldehyde provided vinyl iodide **32** in 60% yield over two-steps.

Our attention was then shifted to synthesis of the side chain, shown in Scheme 5. Commercially available 2-bromo-3-hydroxybenzaldehyde was protected as the TBS ether to provide silyl ether **33** in 98% yield. Reverse prenylation of aldehyde **33** using 3-methyl-2-butenylmagnesium chloride at 0 °C afforded racemic alcohol **34** in quantitative yield. The racemic alcohol was oxidized with PCC at 23 °C to provide ketone **35** in 93% yield. Enantioselective reduction of such *tert*-alkyl ketones is synthetically challenging as there is hardly any effective procedure that can provide high levels of enantioselectivity.

We chose to explore Corey's CBS reduction^{38, 39} of ketone **35** to introduce the C-21 center and the results are shown in Table 3. Initial reduction of the hindered ketone using 0.1 equivalent of (*S*)-Me-CBS and 2 equivalents of borane dimethylsulfide (BMS) in PhMe at 0 °C gave alcohol (*S*)-**34** in 14% yield with 95% *ee* by HPLC analysis using a chiral column (entry 1). While the reaction yield was marginal, the reduction exhibited excellent stereoselectivity. The amount of catalyst appeared to directly correlate with the amount of product formed. We increased catalyst loading to 25% and then 50% and this led to improvement of 24% and 59% yield for alcohol (*S*)-**34**, respectively (entries 2 and 3). We presumed that the catalyst-product complex was not dissociating,⁴⁰ thereby preventing further catalytic reduction. However, addition of 1 equivalent of catalyst showed no improvement (entry 4). Reducing the temperature to –30 °C was detrimental to the reaction (entry 5) and increasing to room temperature⁴¹ appeared to promote hydroboration of the terminal alkene (entry 6). Switching to catecholborane may have prevented this side reaction but was unable to promote reduction under all conditions screened (entry 7). Neither THF or DCM proved to be effective (entries 8 and 9).⁴² We elected to carry out reduction with 0.5 equivalent of Me-CBS catalyst and borane dimethylsulfide to provide optically active alcohol (*S*)-**34** in 59% yield and observed enantioselectivity of 99% *ee* (entry 3).

Protection of the hindered alcohol was achieved using TESOTf to give TES ether (*S*)-**8** in 96% yield but subsequent ozonolysis of the terminal olefin resulted in silyl deprotections. However, Nicolaou's conditions⁴³ for oxidative cleavage of olefins smoothly gave the corresponding aldehyde. Wittig olefination using the commercially available triphenylphosphonium bromide **37** followed by global deprotection provided enyne (*S*)-**4**. In a similar manner, enyne (*R*)-**4** was prepared by employing the (*R*)-Me-CBS catalyst during enantioselective reduction. We have previously established the stereochemical outcome of reduction using both enantiomers of the CBS catalyst by X-ray crystallography.¹³

To ascertain stereochemical identity of the C-21 chiral center as well as determine absolute configuration, we carried out the coupling of vinyl iodide **32** with optically active enyne **4** as

shown in Scheme 6. Sonogashira coupling between vinyl iodide **32** and either enantiomer of enyne **4** proceeded smoothly to afford callyspongiolide (*R*)-**2** and (*S*)-**2** in very good yields (82% and 75% yield, respectively). The ¹H- and ¹³C-NMR spectra of these diastereomers were identical and the structural assignment for the C-21 stereogenic carbon could not be made based upon the NMRs. However, the specific rotation of our HPLC purified (>98% purity) synthetic callyspongiolide (*R*)-**2** {[α]_D²⁰ = −25.5 (c 0.1, MeOH)} displayed the same sign and similar magnitude to the reported value {[α]_D²⁰ = −12.5 (c 0.1, MeOH)}.¹² On the other hand, callyspongiolide (*S*)-**2** showed a value significantly larger in magnitude {[α]_D²⁰ = −182 (c 0.1, MeOH)}.

In order to make an unambiguous assignment in absolute configuration of the natural product, two other stereoisomers have been prepared as shown in Scheme 7. For the synthesis of callyspongiolide (*S*)-**1** and (*R*)-**1**, homoallylic alcohol *ent*-**7** and epoxyalcohol *ent*-**17** were converted to vinyl iodide *ent*-**32** as previously reported.¹³ Sonogashira coupling with either enantiomer of enyne **4** provided callyspongiolide (*S*)-**1** and (*R*)-**1** in very good yield (79% and 82% yield, respectively). The ¹H- and ¹³C-NMR spectra could not differentiate between the epimers and comparison of specific rotations were necessary. Our HPLC purified (>98% pure) epimeric synthetic callyspongiolide (*S*)-**1** and (*R*)-**1** displayed specific rotation values {[α]_D²⁰ = +24.5 (c 0.1, MeOH) for (*S*)-**1**; [α]_D²⁰ = +159 (c 0.1, MeOH) for (*R*)-**1**} which were opposite in sign but equal magnitude to their respective enantiomers. Of specific note, both synthetic callyspongiolide enantiomers have shown comparable magnitude of rotation which is higher than the reported values.^{12,14} We therefore, assigned the absolute configuration and the C-21 stereocenter of the natural callyspongiolide same as the synthetic callyspongiolide (*R*)-**2**.

Conclusions

In summary, callyspongiolide is an exciting new molecule that displays potent cytotoxic properties against various cancer cell lines. The molecule was isolated recently in a small quantity and complete structural elucidation, particularly the absolute configuration of all six chiral centers with relation to the C-21 center, could not be carried out unambiguously during isolation and structure studies. We have elucidated the complete absolute configuration of callyspongiolide and assigned its stereochemistry at the C-21 center through synthesis. Initially, we have carried out the synthesis and assignment of two unnatural isomers of callyspongiolide but have now synthesized all four possible stereoisomers enantioselectively. C-21 epimers (*S*)-**1** and (*R*)-**2** are enantiomeric, as are (*S*)-**2** and (*R*)-**1**. After comparison of all data, synthetic callyspongiolide (*R*)-**2** corresponds to the natural product. Our synthetic callyspongiolide (>98% purity by HPLC) showed a higher magnitude of specific rotation than reported values. Our convergent synthesis involved Sonogashira coupling of a vinyl iodide with two enyne enantiomers to give the corresponding C-21 epimers. The synthesis of the macrolactone unit highlights a Yonemitsu-modified Yamaguchi macrolactonization of an alkynic acid followed by catalytic hydrogenation to form the sensitive *cis*-lactone. Furthermore, the synthesis features a highly *trans*-selective Julia-Kocienski olefination to set the C₁₀-C₁₁ *trans*-olefin and an

enantioselective CBS reduction to provide both C-21 epimers in high enantiomeric purity. The current work will continue to provide access to structural variants of callyspongiolide. Further synthesis and biological studies are ongoing in our laboratories.

Experimental Section

Chemicals and reagents were purchased from commercial suppliers and used without further purification. Anhydrous solvents were obtained as follows: dichloromethane and toluene from calcium hydride, diethyl ether and tetrahydrofuran from sodium/benzophenone, and methanol from activated magnesium. All other solvents were reagent grade. All moisture-sensitive reactions were either carried out in flame or oven-dried (120 °C) glassware under an argon atmosphere. TLC analysis was conducted using glass-backed thin-layer silica gel chromatography plates (60 Å, 250 µm thickness, F-254 indicator). Column chromatography was performed using Silicycle 230–400 mesh, 60 Å pore diameter silica gel. ¹H and ¹³C NMR spectra were recorded on either Bruker DRX-500, Bruker AV500HD, or Bruker AvanceIII-800 spectrometers. Chemical shift (δ values) are reported in parts per million and are referenced to the residual solvent signal (CDCl₃ ¹H singlet = 7.26, ¹³C triplet = 77.16; DMSO-d₆ ¹H quintet = 2.50, ¹³C septet = 39.52). Characteristic splitting patterns due to spin-spin coupling are identified as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sex = sextet, sep = septet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, dq = doublet of quartets, brs = broad singlet. All coupling constants are measured in hertz (Hz). Optical rotations were recorded on a Perkin Elmer 341 polarimeter. HPLC data was collected using a system composed of an Agilent 1100 series degasser, quaternary pump, thermostatable column compartment, variable wavelength detector, and Agilent 1200 series autosampler and fraction collector controlled by Chemstation software. HRMS spectra were recorded at the Purdue University Department of Chemistry Mass Spectrometry Center.

(4*R*,6*R*)-7-((*tert*-Butyldiphenylsilyl)oxy)-6-methylhept-1-en-4-ol (7)

To a clear solution of borinic ester (17.1661 g, 54.3 mmol, 1.5 equiv) in Et₂O (160 mL) at 0 °C was slowly added allylmagnesium bromide (1 M Et₂O, 50 mL, 50.0 mmol, 1.4 equiv). The ice bath was removed and flask left stirring 1.5 h. The flask was then cooled to −78 °C and a clear solution of aldehyde (12.1041 g, 35.5 mmol) in Et₂O (80 mL) was added slowly via cannula, producing a white mixture. The reaction was carefully quenched with methanol (11 mL) after 1 h, treated with 3 M NaOH (28 mL) and 30% H₂O₂ (55 mL), then left stirring overnight. The crude product was extracted with EA (x3), washed with brine and dried over Na₂SO₄. The isopinocampheol was removed via Kugelrohr distillation (120 °C, 10 torr). Purification by flash chromatography (3% EA/HX) gave 16.2013 g of alcohol (84% yield, 10:1 dr) as a clear oil. *R*_f = 0.14 (5% EA/HX); ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.66–7.69 (m, 4H), 7.37–7.46 (m, 6H), 5.78–5.88 (m, 1H), 5.10–5.15 (m, 2H), 3.74–3.80 (m, 1H), 3.50–3.58 (m, 2H), 2.14–2.30 (m, 3H), 1.91 (sex, 1H), 1.59 (ddd, *J* = 14.0, 7.6, 4.4 Hz, 1H), 1.42 (ddd, *J* = 14.1, 8.4, 5.7 Hz, 1H), 1.07 (s, 9H), 0.94 (d, *J* = 6.9, 3H); ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 135.8, 135.7, 135.2, 133.7, 129.8, 127.8, 117.9, 68.9, 68.7, 42.3, 41.3, 32.5, 27.0, 19.4, 17.9; HRMS-ESI (+) *m/z* calc'd for C₂₄H₃₄O₂Si [M+Na]⁺: 405.2226, found 405.2215; [α]_D²⁰ −0.8 (*c* 1.33, CHCl₃).

(4*R*,6*R*)-7-((*tert*-Butyldiphenylsilyl)oxy)-6-methylhept-1-en-4-yl acrylate (12)

To a clear solution of alcohol (8.2849 g, 21.7 mmol) in DCM (140 mL) at 0 °C was slowly added Et₃N (15 mL, 108 mmol, 5.0 equiv) and acryloyl chloride (5.3 mL, 65.2 mmol, 3 equiv) sequentially. After 30 min, silica gel was added and the mixture was concentrated via rotary evaporation. Purification by flash chromatography (3% EA/HX) gave 5.9427 g of acrylate ester (63% yield) as a clear oil. R_f = 0.4 (5% EA/HX); ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.64–7.68 (m, 4H), 7.36–7.45 (m, 6H), 6.36 (dd, J = 17.3, 1.5 Hz, 1H), 6.08 (dd, J = 17.3, 10.4 Hz, 1H), 5.71–5.82 (m, 2H), 5.03–5.10 (m, 3H), 3.46–3.54 (m, 2H), 2.26–2.39 (m, 2H), 1.69–1.87 (m, 2H), 1.40–1.46 (m, 1H), 1.06 (s, 9H), 0.97 (d, J = 6.7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 165.9, 135.7, 134.0, 133.7, 130.5, 129.7, 129.0, 127.7, 117.9, 72.5, 68.3, 39.0, 37.0, 32.8, 27.0, 19.5, 17.5; HRMS-ESI (+) m/z calc'd for C₂₇H₃₆O₃Si [M+Na]⁺: 459.2332, found 459.2328; $[\alpha]_D^{20}$ –8.4 (c 3.07, CHCl₃).

(*R*)-6-((*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropyl)-5,6-dihydro-2*H*-pyran-2-one (13)

A deep violet solution of diene (5.8200 g, 13.3 mmol) and Grubbs II catalyst (355.1 mg, 0.418 mmol, 3 mol %) in DCM (800 mL) was heated to reflux. After 3.5 h, the reaction was quenched with the addition of ethyl vinyl ether (400 μ L) and left stirring 1 h. The crude product was concentrated onto silica gel and purified by flash chromatography (10% EA/HX) to give 5.0861 g of diene (93% yield) as a clear oil. R_f = 0.2 (10% EA/HX); ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.63–7.67 (m, 4H), 7.36–7.45 (m, 6H), 6.83 (ddd, J = 9.7, 5.4, 3.1 Hz, 1H), 6.00 (ddd, J = 9.7, 2.3, 1.2 Hz, 1H), 4.39–4.46 (m, 1H), 3.58 (dd, J = 10.1, 5.1 Hz, 1H), 3.53 (dd, J = 10.0, 5.5 Hz, 1H), 2.17–2.33 (m, 2H), 1.95 (sex, J = 6.7 Hz, 1H), 1.79 (ddd, J = 14.0, 7.1, 5.2 Hz, 1H), 1.63–1.70 (m, 1H), 1.06 (s, 9H), 0.98 (d, J = 6.8 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 164.6, 145.0, 135.71, 135.69, 133.8, 133.7, 129.8, 127.8, 121.5, 76.7, 68.1, 38.7, 31.9, 29.9, 27.0, 19.4, 17.6; HRMS-ESI (+) m/z calc'd for C₂₅H₃₂O₃Si [M+Na]⁺: 431.2019, found 431.2009; $[\alpha]_D^{20}$ +47.8 (c 2.32, CHCl₃).

(4*S*,6*R*)-6-((*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropyl)-4-methyltetrahydro-2*H*-pyran-2-one (14)

MeLi (3.1 M DEM, 15.8 mL, 49.0 mmol, 4 equiv) was slowly added to a tan suspension of CuI (4.6671 g, 24.5 mmol, 2.0 equiv) in Et₂O (100 mL) at 0 °C to give a clear solution. After stirring 30 min, the flask was cooled to –78 °C and a clear solution of lactone (5.0051 g, 12.2 mmol) in Et₂O (20 mL) was added slowly via cannula. After 3 h, the reaction was quenched with sat. NH₄Cl and flask warmed to rt. The crude product was extracted with EA (x3), washed in brine and dried over MgSO₄. Purification by flash chromatography (10% EA/HX) gave 4.8305 g of lactone (93% yield) as a clear oil. R_f = 0.3 (15% EA/HX); ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.63–7.67 (m, 4H), 7.36–7.45 (m, 6H), 4.39–4.46 (m, 1H), 3.58 (dd, J = 10.0, 3.6 Hz, 1H), 3.51 (dd, J = 9.9, 5.7 Hz, 1H), 2.54 (dd, J = 16.0, 5.5 Hz, 1H), 2.11–2.19 (m, 1H), 2.08 (dd, J = 16.0, 9.2 Hz, 1H), 1.92 (sex, J = 6.7, 1H), 1.67–1.75 (m, 2H), 1.48–1.60 (m, 2H), 1.04–1.07 (m, 12H), 0.97 (d, J = 6.8 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 172.7, 135.72, 135.70, 133.9, 133.8, 129.8, 127.8, 76.0, 68.2, 39.4, 37.6, 35.5, 32.1, 27.0, 23.9, 21.7, 19.4, 17.7; HRMS-ESI (+) m/z calc'd for C₂₆H₃₆O₃Si [M+Na]⁺: 447.2332, found 447.2321; $[\alpha]_D^{20}$ –23.3 (c 1.55, CHCl₃).

(4S,6R)-6-((R)-3-Hydroxy-2-methylpropyl)-4-methyltetrahydro-2H-pyran-2-one (6)

TBAF (1 M THF, 14.7 mL, 14.7 mmol, 1.3 equiv) was added slowly to a clear solution of silyl ether (4.8017 g, 11.3 mmol) in THF (60 mL). The reaction was quenched with sat. NH_4Cl after 45 min. The crude product was extracted with EA (x3), washed in brine and dried over Na_2SO_4 . Purification by flash chromatography (50% EA/HX) gave 1.8041 g of alcohol (86% yield) as a clear oil. $R_f = 0.15$ (50% EA/HX); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 4.55 (sep, $J = 4.6$ Hz, 1H), 3.55 (dd, $J = 10.7, 5.5$ Hz, 1H), 3.50 (dd, $J = 10.7, 6.0$ Hz, 1H), 2.51–2.60 (m, 1H), 2.11–2.22 (m, 2H), 1.91 (sex, $J = 6.6$ Hz, 1H), 1.76 (ddd, $J = 15.0, 8.8, 6.3$ Hz, 1H), 1.55–1.68 (m, 3H), 1.08 (d, $J = 6.6$ Hz, 3H), 0.96 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 172.7, 75.8, 67.5, 39.3, 37.6, 35.5, 32.2, 23.9, 21.6, 17.3; HRMS-ESI (+) m/z calc'd for $\text{C}_{10}\text{H}_{18}\text{O}_3$ $[\text{M}+\text{Na}]^+$: 209.1154, found 209.1150; $[\alpha]_{\text{D}}^{20} -55.9$ (c 0.583, CHCl_3).

(R)-2-Methyl-3-((2R,4S)-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)propanal (15)

To a clear solution of alcohol (1.8041 g, 9.69 mmol) in DCM (50 mL) at 0 °C was added portionwise NaHCO_3 (4.0704 g, 48.5 mmol, 5 equiv) and DMP (8.2195 g, 19.4 mmol, 2.0 equiv) sequentially. The ice bath was removed after 10 min. After 1.5 h, the reaction was slowly quenched with a 1:1 solution of sat. $\text{NaHCO}_3/\text{Na}_2\text{S}_2\text{O}_3$ solution and left stirring 10 min. The crude product was extracted with DCM (x3), washed in sat. NaHCO_3 and brine, then dried over Na_2SO_4 . Purification through a short silica plug (40% EA/HX) gave 1.6043 g of aldehyde (90% yield) as a clear oil. $R_f = 0.4$ (50% EA/HX); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 9.67 (s, 1H), 4.47 (tt, $J = 9.6, 3.7$ Hz, 1H), 2.74–2.83 (m, 1H), 2.55 (dd, $J = 15.4, 4.7$ Hz, 1H), 2.11–2.24 (m, 1H), 1.97 (ddd, $J = 14.4, 9.2, 3.2$ Hz, 1H), 1.76 (ddd, $J = 14.1, 9.4, 6.7$ Hz, 1H), 1.58–1.67 (m, 2H), 1.18 (d, $J = 7.5$ Hz, 3H), 1.08 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 204.0, 172.3, 75.2, 42.6, 37.5, 36.5, 35.6, 24.0, 21.5, 14.6; HRMS-ESI (+) m/z calc'd for $\text{C}_{10}\text{H}_{16}\text{O}_3$ $[\text{M}+\text{Na}]^+$: 207.0997, found 207.0993; $[\alpha]_{\text{D}}^{20} -22.3$ (c 0.520, CHCl_3).

(2S,3S)-4-((4-Methoxybenzyl)oxy)-2-methylbutane-1,3-diol (18)

MeLi (3.1 M DEM, mL, mmol, 6.0 equiv) was slowly added to a tan suspension of CuI (8.3432 g, 43.8 mmol, 2.2 equiv) in Et_2O (50 mL) at 0 °C to give a clear solution. After stirring 15 min, the flask was cooled to –50 °C and a clear solution of epoxy alcohol (4.4126 g, 19.7 mmol) in THF (30 mL) added slowly via cannula to produce a white mixture. After 30 min, the reaction was quenched with sat. NH_4Cl and flask warmed to rt. The mixture was filtered through celite and filter cake thoroughly washed with Et_2O . The solution was then washed with NH_4OH (x2) and brine. The aqueous washes were diluted with brine and extracted with EA (x3), combined with prior organic layer and dried over Na_2SO_4 . To a biphasic mixture of 1,2- and 1,3-diols in $\text{Et}_2\text{O}/\text{H}_2\text{O}$ (2:1, 40 mL) at 0 °C was added NaIO_4 (2.1124 g, 9.87 mmol, 0.5 equiv). The ice bath was removed after 10 min. After 5 h, the reaction was diluted with brine and layers separated. The crude product was extracted with EA (x3), combined with the prior organic layer, then dried over Na_2SO_4 . Purification by flash chromatography (50 to 60% EA/HX) gave 3.5722 g of diol (76% yield) as a clear oil. $R_f = 0.1$ (50% EA/HX); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.25 (d, $J = 8.7$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 4.45–4.52 (m, 2H), 3.80 (s, 3H), 3.71 (td, $J = 7.5, 3.0$ Hz, 1H)

3.60–3.67 (m, 2H), 3.56 (dd, J = 9.6, 3.1 Hz, 1H), 3.41 (dd, J = 9.6, 7.3 Hz, 1H), 3.11 (brs, 2H), 1.76–1.84 (m, 1H), 0.85 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 159.5, 129.9, 129.6, 114.0, 75.5, 73.2, 72.7, 67.3, 55.4, 37.6, 13.8; HRMS-ESI (+) m/z calc'd for $\text{C}_{13}\text{H}_{20}\text{O}_4$ $[\text{M}+\text{Na}]^+$: 263.1260, found 263.1255; $[\alpha]_{\text{D}}^{20}$ +9.3 (c 1.82, DCM).

(2S,3R)-1-((4-Methoxybenzyl)oxy)-3-methyl-4-((1-phenyl-1H-tetrazol-5-yl)thio)butan-2-ol (19)

To a clear solution of diol (3.5722 g, 14.9 mmol), thiol (3.2033 g, 18.0 mmol, 1.2 equiv), and PPh_3 (4.7242 g, 18.0 mmol, 1.2 equiv) in THF (150 mL) at -20°C was added DIAD (3.5 mL, 17.8 mmol, 1.2 equiv) slowly. After 1 h, the reaction was quenched with H_2O (1 mL) and concentrated onto silica gel. Purification by flash chromatography (30% EA/HX) gave 5.8680 g of sulfide (99% yield) as a clear oil. R_f = 0.1 (25% EA/HX); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.51–7.59 (m, 5H), 7.25 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.52 (d, J = 11.5 Hz, 1H), 4.47 (d, J = 11.5 Hz, 1H), 3.80 (s, 3H), 3.70 (dd, J = 11.4, 4.2 Hz, 1H), 3.59–3.66 (m, 2H), 3.43–3.50 (m, 2H), 3.16 (brs, 1H), 2.13–2.22 (m, 1H), 1.02 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 159.4, 155.2, 133.8, 130.2, 130.0, 129.9, 129.6, 124.0, 114.0, 73.3, 73.2, 72.0, 55.4, 37.3, 36.5, 15.9; HRMS-ESI (+) m/z calc'd for $\text{C}_{20}\text{H}_{24}\text{N}_4\text{O}_3\text{S}$ $[\text{M}+\text{Na}]^+$: 423.1467, found 423.1458; $[\alpha]_{\text{D}}^{20}$ –0.05 (c 2.23, CHCl_3).

5-(((2R,3S)-4-((4-Methoxybenzyl)oxy)-2-methyl-3-((triethylsilyl)oxy)butyl)thio)-1-phenyl-1H-tetrazole (20)

Et_3N (6.1 mL, 43.8 mmol, 3 equiv) and TESOTf (6.6 mL, 29.2 mmol, 2.0 equiv) were added sequentially to a clear solution of alcohol (5.8680 g, 14.7 mmol) in DCM (100 mL) at 0°C . The reaction was quenched with sat. NaHCO_3 after 1 h and flask warmed to rt. The crude product was extracted with DCM (x3), washed in brine, and dried over MgSO_4 . Purification by flash chromatography (5% EA/HX) gave 6.4060 g of sulfide (85% yield) as a clear oil. R_f = 0.6 (25% EA/HX); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.50–7.60 (m, 5H), 7.24 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.44 (s, 2H), 3.80–3.84 (m, 1H), 3.80 (s, 3H), 3.64 (dd, J = 12.8, 4.8 Hz, 1H), 3.50 (dd, J = 9.7, 6.1 Hz, 1H), 3.43 (dd, J = 9.6, 5.5 Hz, 1H), 3.29 (dd, J = 12.9, 7.9 Hz, 1H), 2.20–2.28 (m, 1H), 1.06 (d, J = 6.9 Hz, 3H), 0.92 (t, J = 8.0 Hz, 9H), 0.53–0.62 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 159.3, 155.2, 133.9, 130.3, 130.1, 129.8, 129.5, 124.0, 113.9, 74.4, 73.2, 72.3, 55.4, 36.4, 35.9, 16.3, 7.0, 5.1; HRMS-ESI (+) m/z calc'd for $\text{C}_{26}\text{H}_{38}\text{N}_4\text{O}_3\text{SSi}$ $[\text{M}+\text{Na}]^+$: 537.2332, found 537.2322; $[\alpha]_{\text{D}}^{20}$ –8.11 (c 2.28, CHCl_3).

5-(((2R,3S)-4-((4-Methoxybenzyl)oxy)-2-methyl-3-((triethylsilyl)oxy)butyl)sulfonyl)-1-phenyl-1H-tetrazole (21)

To a clear solution of sulfide (6.4060 g, 12.4 mmol) in DCM (60 mL) was added portionwise NaHCO_3 (4.7225 g, 56.2 mmol, 4.5 equiv) and m -CPBA (70 wt %, 9.3405 g, 37.9 mmol, 3.1 equiv) sequentially. After 13 h, the flask was cooled to 0°C and carefully quenched with sat. NaHCO_3 . The crude product was extracted with DCM (x3), washed in brine and dried over MgSO_4 . Purification by flash chromatography (5% EA/HX) gave 5.9878 g of sulfone (88% yield) as a clear oil. R_f = 0.3 (10% EA/HX); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.56–7.68 (m, 5H), 7.23 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.42 (s, 2H), 4.10 (dd,

$J = 14.9, 2.8 \text{ Hz, 1H}$), 3.82 (td, $J = 6.1, 2.8 \text{ Hz, 1H}$) 3.80 (s, 3H), 3.47 (dd, $J = 14.8, 9.4 \text{ Hz, 1H}$), 3.37–3.43 (m, 2H), 2.52–2.60 (m, 1H), 1.19 (d, $J = 6.9 \text{ Hz, 3H}$), 0.92 (t, $J = 8.0 \text{ Hz, 9H}$), 0.54–0.61 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 159.4, 154.1, 133.3, 131.5, 130.0, 129.8, 129.6, 125.4, 113.9, 74.3, 73.2, 71.5, 57.9, 55.4, 31.6, 17.3, 7.0, 5.0; HRMS-ESI (+) m/z calc'd for $\text{C}_{26}\text{H}_{38}\text{N}_4\text{O}_5\text{SSi}$ $[\text{M}+\text{Na}]^+$: 569.2230, found 569.2215; $[\alpha]_{\text{D}}^{20} -3.87$ (c 2.38, CHCl_3).

(4*S*,6*R*)-6-((2*R*,5*S*,6*S*, *E*)-7-((4-Methoxybenzyl)oxy)-2,5-dimethyl-6-((triethylsilyl)oxy)hept-3-en-1-yl)-4-methyltetrahydro-2*H*-pyran-2-one (22)

LHMDS (1 M THF, 7.7 mL, 7.7 mmol, 1.46 equiv) was slowly added to a clear solution of sulfone (4.2208 g, 7.92 mmol, 1.5 equiv) in DMF (40 mL) at -60°C to give a light-orange solution. After stirring 30 min, a clear solution of aldehyde (972.1 mg, 5.28 mmol) in DMF (10 mL) was added dropwise via cannula. After 1.5 h, the reaction was quenched with sat. NH_4Cl and flask warmed to rt. The crude product was diluted with H_2O (100 mL) and extracted with EA (x4), washed in brine, and dried over Na_2SO_4 . Purification by flash chromatography (10% EA/HX) gave 2.0242 g of lactone (76% yield, 27:1 *trans/cis*) as a clear oil. $R_f = 0.5$ (25% EA/HX); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.23 (d, $J = 8.7 \text{ Hz, 2H}$), 6.87 (d, $J = 8.7 \text{ Hz, 2H}$), 5.42 (dd, $J = 15.5, 8.2 \text{ Hz, 1H}$), 5.15 (dd, $J = 15.5, 8.3 \text{ Hz, 1H}$), 4.44 (d, $J = 11.6 \text{ Hz, 1H}$), 4.33–4.40 (m, 2H), 3.80 (s, 3H), 3.71 (td, $J = 5.8, 3.2 \text{ Hz, 1H}$), 3.32 (dd, $J = 9.4, 5.8 \text{ Hz, 1H}$), 3.27 (dd, $J = 9.3, 5.8 \text{ Hz, 1H}$), 2.50–2.55 (m, 1H), 2.38–2.46 (m, 1H), 2.30–2.38 (m, 1H), 2.06–2.20 (m, 2H), 1.63–1.76 (m, 2H), 1.46 (ddd, $J = 14.2, 5.9, 4.1 \text{ Hz, 1H}$), 1.29 (ddd, $J = 13.8, 9.9, 3.4 \text{ Hz, 1H}$), 1.04 (d, $J = 6.6 \text{ Hz, 3H}$), 0.99 (d, $J = 7.0 \text{ Hz, 3H}$), 0.97 (d, $J = 6.8 \text{ Hz, 3H}$), 0.93 (t, $J = 8.0 \text{ Hz, 9H}$), 0.54–0.63 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 172.7, 159.2, 135.2, 131.7, 130.7, 129.3, 113.8, 75.6, 75.1, 73.0, 72.9, 55.4, 24.0, 21.7, 21.6, 17.3, 7.1, 5.2; HRMS-ESI (+) m/z calc'd for $\text{C}_{29}\text{H}_{48}\text{O}_5\text{Si}$ $[\text{M}+\text{Na}]^+$: 527.3169, found 527.3162; $[\alpha]_{\text{D}}^{20} -76.9$ (c 0.800, CHCl_3).

(3*S*,5*R*,7*R*,10*S*,11*S*, *E*)-5-Hydroxy-*N*-methoxy-12-((4-methoxybenzyl)oxy)-*N*,3,7,10-tetramethyl-11-((triethylsilyl)oxy)dodec-8-enamide (23)

To clear mixture of lactone (1.0171 g, 2.02 mmol) and $\text{MeNH}(\text{OMe})\cdot\text{HCl}$ (304.6 mg, 3.12 mmol, 1.5 equiv) in THF (15 mL) at -20°C was added $i\text{PrMgCl}$ (2 M THF, 3.6 mL, 7.20 mmol, 3.6 equiv) slowly. After 45 min the reaction was quenched with sat. NH_4Cl and flask warmed to rt. The crude product was extracted with EA (x3), washed in brine, and dried over Na_2SO_4 . Purification by flash chromatography (30% EA/HX) gave 1.0762 g of Weinreb amide (94% yield) as a clear oil. $R_f = 0.2$ (30% EA/HX); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.24 (d, $J = 8.6 \text{ Hz, 2H}$), 6.87 (d, $J = 8.7 \text{ Hz, 2H}$), 5.42 (dd, $J = 15.5, 7.8 \text{ Hz, 1H}$), 5.24 (dd, $J = 15.5, 8.0 \text{ Hz, 1H}$), 4.42 (d, $J = 11.6, 1\text{H}$), 4.37 (d, $J = 11.5 \text{ Hz, 1H}$), 3.80 (s, 3H), 3.71 (td, $J = 5.7, 3.4 \text{ Hz, 1H}$), 3.66 (s, 3H), 3.58 (sep, $J = 4.3 \text{ Hz, 1H}$), 3.35 (dd, $J = 9.5, 5.6 \text{ Hz, 1H}$), 3.29 (dd, $J = 9.5, 5.9 \text{ Hz, 1H}$), 3.17 (s, 3H), 2.68 (brs, 1H), 2.39–2.48 (m, 1H), 2.22–2.39 (m, 4H), 1.38–1.47 (m, 2H), 1.27–1.36 (m, 2H), 0.91–1.00 (m, 18H), 0.54–0.62 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 159.2, 136.2, 130.7, 130.4, 129.4, 113.8, 75.2, 73.03, 72.97, 67.1, 61.3, 55.4, 45.9, 44.7, 40.4, 38.9, 33.7, 32.3, 26.0, 21.7, 21.6, 16.9, 7.1, 5.2; HRMS-ESI (+) m/z calc'd for $\text{C}_{31}\text{H}_{55}\text{NO}_6\text{Si}$ $[\text{M}+\text{Na}]^+$: 588.3697, found 588.3689; $[\alpha]_{\text{D}}^{20} -15.0$ (c 0.547, CHCl_3).

(3*S*,5*R*,7*R*,10*S*,11*S*, *E*)-5-((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-12-((4-methoxybenzyl)oxy)-*N*,3,7,10-tetramethyl-11-((triethylsilyl)oxy)dodec-8-enamide (24)

To a clear solution of alcohol (1.0762 g, 1.90 mmol) in DMF (19 mL) at 0 °C was added Et₃N (0.8 mL, 5.74 mmol, 3.0 equiv) and TBSCl (573.3 mg, 3.80 mmol, 2.0 equiv) sequentially. The ice bath was removed after 10 min. Following 1.5 h, the reaction was highly diluted with H₂O. The crude product was extracted with EA (x3), washed in brine, and dried over Na₂SO₄. Purification by flash chromatography (10% EA/HX) gave 1.1786 g of Weinreb amide (91% yield) as a clear oil. *R*_f = 0.2 (30% EA/HX); ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.24 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.41 (dd, *J* = 15.6, 8.1 Hz, 1H), 5.23 (dd, *J* = 15.6, 7.8 Hz, 1H), 4.39 (s, 2H), 3.80 (s, 3H), 3.69–3.77 (m, 2H), 3.66 (s, 3H), 3.37 (dd, *J* = 9.5, 5.2 Hz, 1H), 3.31 (dd, 9.4, 6.1 Hz, 1H), 3.17 (s, 3H), 2.42 (dd, *J* = 15.2, 5.5 Hz, 1H), 2.21–2.35 (m, 3H), 2.05–2.15 (m, 1H), 1.42–1.51 (m, 2H), 1.28–1.37 (m, 2H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.91–0.96 (m, 15H), 0.88 (s, 9H), 0.54–0.62 (m, 6H), 0.06 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 173.9, 159.2, 136.6, 130.8, 130.2, 129.3, 113.8, 75.3, 73.5, 73.0, 69.1, 61.3, 55.4, 45.6, 44.5, 40.8, 39.8, 33.2, 32.2, 26.8, 26.1, 22.2, 20.3, 18.2, 17.4, 7.1, 5.2, –3.7, –4.0; HRMS-ESI (+) *m/z* calc'd for C₃₇H₆₉NO₆Si₂ [M+Na]⁺: 702.4562, found 702.4550; [α]_D²⁰ –19.3 (*c* 0.880, CHCl₃).

(5*S*,6*S*,9*R*,11*R*, *E*)-3,3-Diethyl-5-(((4-methoxybenzyl)oxy)methyl)-6,9,13,13,14,14-hexamethyl-11-((*R*)-2-methylpent-4-yn-1-yl)-4,12-dioxo-3,13-disilapentadec-7-ene (25)

DIBAL-H (1 M HX, 3.5 mL, 3.50 mmol, 1.5 equiv) was slowly added to a clear solution of Weinreb amide (1.5687 g, 2.31 mmol) in THF (20 mL) at –78 °C. After 1 h, the reaction was quenched with a few drops of MeOH, potassium sodium tartrate and flask warmed to rt. Following 1.5 h of vigorous stirring, the crude product was extracted with EA (x3), washed in brine, and dried over Na₂SO₄. Purification by flash chromatography (5% EA/HX) gave 1.4325 g of aldehyde as a clear oil. To a clear solution of aldehyde (1.4325 g, 2.31 mmol) in MeOH (20 mL) was added K₂CO₃ (1.1101 g, 8.03 mmol, 3.5 equiv) and Ohira-Bestmann reagent (0.4 mL, 2.67 mmol, 1.2 equiv) sequentially to form a yellow mixture. The reaction was quenched with H₂O after 2 h. The crude product was extracted with EA (x3), washed in brine, and dried over Na₂SO₄. Purification by flash chromatography (3% EA/HX) gave 1.2788 g of alkyne (90% yield over 2-steps) as a clear oil. *R*_f = 0.5 (5% EA/HX); ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.40 (dd, *J* = 15.6, 8.2 Hz, 1H), 5.24 (dd, *J* = 15.6, 7.7 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 3H), 3.69–3.76 (m, 2H), 3.37 (dd, *J* = 9.4, 5.4 Hz, 1H), 3.31 (dd, *J* = 9.4, 6.0 Hz, 1H), 2.22–2.36 (m, 2H), 2.20 (ddd, *J* = 16.6, 5.1, 2.7 Hz, 1H), 2.08 (ddd, *J* = 16.7, 7.0, 2.7 Hz, 1H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.78 (sex, *J* = 6.6 Hz, 1H), 1.51–1.57 (m, 1H), 1.29–1.43 (m, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.92–0.96 (m, 12H), 0.55–0.63 (m, 6H), 0.064 (s, 3H), 0.057 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 159.2, 136.6, 130.8, 130.1, 129.3, 113.8, 83.2, 75.2, 73.4, 73.1, 69.5, 69.0, 55.4, 45.1, 44.2, 40.7, 33.2, 29.0, 26.1, 26.0, 21.8, 20.1, 18.2, 17.5, 7.1, 5.2, –3.9; HRMS-ESI (+) *m/z* calc'd for C₃₆H₆₄O₄Si₂ [M+Na]⁺: 639.4241, found 639.4234; [α]_D²⁰ –10.3 (*c* 0.702, CHCl₃).

Ethyl (5*R*,7*R*,9*R*,12*S*,13*S*, *E*)-7-((*tert*-butyldimethylsilyl)oxy)-14-((4-methoxybenzyl)oxy)-5,9,12-trimethyl-13-((triethylsilyl)oxy)tetradec-10-en-2-ynoate (26)

To a clear solution of alkyne (1.2788 g, 2.07 mmol) in THF (20 mL) at -78°C was added *n*-BuLi (1.6 M HX, 1.7 mL, 2.72 mmol, 1.3 equiv) slowly. After stirring 20 min, ClCO_2Et (0.6 mL, 6.28 mmol, 3.0 equiv) was added slowly. The reaction was quenched with sat. NH_4Cl after 1 h and flask warmed to rt. The crude product was extracted with EA (x3), washed in brine, and dried over Na_2SO_4 . Purification by flash chromatography (3% EA/HX) gave 1.3975 g of alkynyl ester (quantitative) as a clear oil. $R_f = 0.3$ (5% EA/HX); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.24 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.39 (dd, $J = 15.6$, 8.1 Hz, 1H), 5.23 (dd, $J = 15.6$, 7.6 Hz, 1H), 4.41 (d, $J = 11.5$, 1H), 4.38 (d, $J = 11.5$ Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 3.80 (s, 3H), 3.68–3.76 (m, 2H), 3.36 (dd, $J = 9.4$, 5.4 Hz, 1H), 3.30 (dd, $J = 9.3$, 5.9 Hz, 1H), 2.37 (dd, $J = 17.1$, 5.0 Hz, 1H), 2.32 (td, $J = 7.4$, 3.2 Hz, 1H), 2.18–2.28 (m, 2H), 1.82–1.92 (m, 1H), 1.48–1.55 (m, 1H), 1.32–1.41 (m, 3H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.00 (d, $J = 7.1$ Hz, 3H), 0.99 (d, $J = 7.3$ Hz, 3H), 0.91–0.97 (m, 12H), 0.88 (s, 9H), 0.54–0.62 (m, 6H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 159.2, 153.9, 136.5, 130.8, 130.2, 129.3, 113.8, 88.2, 75.2, 74.5, 73.3, 73.1, 68.9, 61.9, 55.4, 44.9, 44.1, 40.7, 33.2, 28.7, 26.3, 26.1, 21.7, 20.3, 18.2, 17.5, 14.2, 7.1, 5.2, -3.9 ; HRMS-ESI (+) m/z calc'd for $\text{C}_{39}\text{H}_{68}\text{O}_6\text{Si}_2$ $[\text{M}+\text{Na}]^+$: 711.4453, found 711.4448; $[\alpha]_{\text{D}}^{20} -6.10$ (c 0.853, CHCl_3).

(6*R*,8*R*,10*R*,13*S*,14*S*, *E*)-8-((*tert*-Butyldimethylsilyl)oxy)-14-(((4-methoxybenzyl)oxy)methyl)-6,10,13-trimethyloxacyclotetradec-11-en-3-yn-2-one (27)

PPTS (177.4 mg, 0.706 mmol, 0.3 equiv) was added in one portion to a clear solution of TES-ether (1.3975 g, 2.07 mmol) in EtOH (20 mL) at 0°C . After 15 h, the reaction was quenched with sat. NaHCO_3 and flask warmed to rt. The crude product was extracted with EA (x3), washed in brine, and dried over Na_2SO_4 . $\text{LiOH}\cdot\text{H}_2\text{O}$ (867.8 mg, 20.7 mmol, 10 equiv) was added in a single portion to a cloudy solution of alkynyl ester (1.1610 mg, 2.07 mmol) in THF/ H_2O (2:1, 20 mL) to give a yellow mixture. After 22 h, the reaction was quenched with 1 N HCl. The crude product was extracted with EA (x3), washed in brine, and dried over Na_2SO_4 . To a cloudy mixture of 2,4,6-trichlorobenzoyl chloride (220 μL , 1.41 mmol, 1.6 equiv), DMAP (56.1 mg, 0.459 mmol, 0.5 equiv), and DIPEA (750 μL , 4.31 mmol, 4.8 equiv) in PhMe (165 mL) was added a clear solution of seco acid (1.1319 g, 2.07 mmol) in PhMe (15 mL) slowly via cannula to give a faint-yellow mixture. After 3 h, the reaction was quenched with sat. NaHCO_3 . The crude product was extracted with EA (x3), washed in brine, and dried over Na_2SO_4 . Purification by flash chromatography (3% EA/HX) gave 1.3975 g of alkynyl lactone (67% yield over 3-steps) as a clear oil. $R_f = 0.2$ (5% EA/HX); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.25 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.22 (dd, $J = 15.0$, 9.3 Hz, 1H), 5.08 (dd, $J = 15.0$, 9.6 Hz, 1H), 4.69 (ddd, $J = 10.5$, 4.1, 2.5 Hz, 1H), 4.56 (d, $J = 11.8$ Hz, 1H), 4.38 (d, $J = 11.8$ Hz, 1H), 4.10–4.15 (m, 1H), 3.80 (s, 3H), 3.65 (dd, $J = 11.3$, 2.5 Hz, 1H), 3.58 (dd, $J = 11.3$, 4.3 Hz, 1H), 2.54–2.63 (m, 1H), 2.39 (dd, $J = 16.4$, 3.2 Hz, 1H), 2.22–2.32 (m, 1H), 2.07–2.17 (m, 1H), 1.98 (dd, $J = 16.5$, 10.7 Hz, 1H), 1.35–1.50 (m, 3H), 1.24 (ddd, $J = 13.8$, 11.1, 2.0 Hz, 1H), 0.90–0.95 (m, 9H), 0.88 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 159.4, 153.3, 139.5, 130.1, 129.5, 113.9, 90.4, 78.0, 75.3, 73.0, 71.0, 68.7, 55.4, 48.2, 47.9, 39.3, 34.8,

28.6, 27.0, 26.2, 23.9, 23.7, 18.5, 17.3, -2.9, -3.1; HRMS-ESI (+) m/z calc'd for $C_{31}H_{48}O_5Si$ $[M+Na]^+$: 551.3169, found 551.3156; $[\alpha]_D^{20} +1.73$ (c 0.880, $CHCl_3$).

(3Z,6R,8R,10R,11E,13S,14S)-8-((*tert*-Butyldimethylsilyl)oxy)-14-(((4-methoxybenzyl)oxy)methyl)-6,10,13-trimethyloxacyclotetradeca-3,11-dien-2-one (28)

A black mixture of alkynyl lactone (212.0 mg, 0.401 mmol), quinoline (55 μ L, 0.465 mmol, 1.2 equiv), and catalyst (97.7 mg) in EA/1-hexene (1:1, 4 mL) was flushed with Ar (x5), H_2 (x5), and left vigorously stirring under an H_2 balloon. The reaction was filtered through celite after 2 h and filter cake thoroughly rinsed with EA. Purification by flash chromatography (3% EA/HX) gave 212.3 g of *cis*-lactone (quantitative) as a clear oil. R_f = 0.2 (5% EA/HX); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.25 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.21 (td, J = 12.3, 3.8 Hz, 1H), 5.92 (dd, J = 11.6, 2.1 Hz, 1H), 5.16 (dd, J = 15.1, 9.3 Hz, 1H), 5.03 (dd, J = 15.1, 9.2 Hz, 1H), 4.94 (ddd, J = 10.3, 4.4, 2.6 Hz, 1H), 4.56 (d, J = 11.8 Hz, 1H), 4.40 (d, J = 11.8 Hz, 1H), 3.80 (s, 3H), 3.69 (td, J = 14.1, 5.6 Hz, 1H), 3.52–3.60 (m, 2H), 3.48 (t, J = 9.7 Hz, 1H), 2.36–2.45 (m, 1H), 2.15–2.24 (m, 1H), 2.00–2.11 (m, 1H), 1.93 (dq, J = 14.3, 3.0 Hz, 1H), 1.26–1.35 (m, 2H), 1.01–1.08 (m, 1H), 1.00 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 0.83–0.93 (m, 12H), 0.14 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 165.6, 159.3, 145.9, 137.6, 132.0, 130.3, 129.4, 122.2, 113.9, 74.6, 73.0, 69.7, 68.6, 55.4, 47.8, 44.9, 39.5, 34.7, 31.2, 27.6, 26.2, 22.9, 20.2, 18.5, 17.4, -3.0, -3.3; HRMS-ESI (+) m/z calc'd for $C_{31}H_{50}O_5Si$ $[M+Na]^+$: 553.3326, found 553.3319; $[\alpha]_D^{20} -37.1$ (c 0.647, $CHCl_3$).

(3Z,6R,8R,10R,11E,13S,14S)-8-Hydroxy-14-(((4-methoxybenzyl)oxy)methyl)-6,10,13-trimethyloxacyclotetradeca-3,11-dien-2-one (29)

HFpy (70% HF, 0.4 mL) was added slowly to a clear solution of silyl ether (214.0 mg) in MeOH (4 mL) at 0 °C. The reaction was carefully quenched with sat. $NaHCO_3$ and flask warmed to rt. The crude product was extracted with EA (x3), washed in brine, and dried over Na_2SO_4 . Purification by flash chromatography (20% EA/HX) gave 150.4 mg of alcohol (90% yield) as a clear oil. R_f = 0.2 (25% EA/HX); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.25 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.27 (dd, J = 11.7, 3.5 Hz, 1H), 5.94 (dd, J = 11.6, 2.5 Hz, 1H), 5.15 (dd, J = 15.0, 9.5 Hz, 1H), 5.01 (dd, J = 15.0, 9.4 Hz, 1H), 4.94 (ddd, J = 10.4, 4.6, 2.6 Hz, 1H), 4.56 (d, J = 11.8 Hz, 1H), 4.41 (d, J = 11.8 Hz, 1H), 3.76–3.85 (m, 3H), 3.52–3.60 (m, 2H), 3.40 (t, J = 10.8 Hz, 1H), 2.38–2.47 (m, 1H), 2.22–2.31 (m, 1H), 2.10–2.19 (m, 1H), 1.94 (dq, J = 14.7, 2.8 Hz, 1H), 1.53–1.63 (brs, 1H), 1.34 (dd, J = 11.9, 4.0 Hz, 1H), 1.26 (dd, J = 10.2, 2.0 Hz, 1H), 1.05 (d, J = 7.0 Hz, 3H), 0.97–1.03 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 166.0, 159.4, 146.1, 137.1, 132.5, 130.2, 129.5, 122.2, 113.9, 74.7, 73.0, 69.6, 66.1, 55.4, 46.2, 43.1, 39.8, 34.6, 31.3, 27.3, 22.5, 20.2, 17.6; HRMS-ESI (+) m/z calc'd for $C_{25}H_{36}O_5$ $[M+Na]^+$: 439.2461, found 439.2456; $[\alpha]_D^{20} -41.9$ (c 0.253, $CHCl_3$).

(2S,3S,4E,6R,8R,10R,12Z)-2-(((4-Methoxybenzyl)oxy)methyl)-3,6,10-trimethyl-14-oxooxacyclotetradeca-4,12-dien-8-yl carbamate (30)

To a clear solution of alcohol (150.4 mg, 0.361 mmol) in DCM (4 mL) at 0 °C was added chlorosulfonyl isocyanate (45 μ L) dropwise. After 15 min, the reaction was treated with THF/H₂O (4:1, 2 mL) and ice bath removed. The reaction was quenched with sat. NaHCO₃ after 5 h. The crude product was extracted with EA (x3), washed in brine, and dried over Na₂SO₄. Purification by flash chromatography (35% EA/HX) gave 159.4 mg of alcohol (96% yield) as a clear oil. R_f = 0.2 (5% EA/HX); ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.25 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.13 (td, J = 12.1, 3.3 Hz, 1H), 5.95 (dd, J = 11.6, 2.2 Hz, 1H), 5.31 (dd, J = 15.0, 9.6 Hz, 1H), 4.98–5.07 (m, 2H), 4.45–4.60 (m, 4H), 4.39 (d, J = 11.8 Hz, 1H), 3.80 (s, 3H), 2.71–3.79 (m, 1H), 3.52–3.61 (m, 2H), 2.41–2.51 (m, 1H), 2.03–2.13 (m, 1H), 1.96 (dq, J = 14.8, 2.7 Hz, 1H), 1.83–1.92 (m, 1H), 1.45–1.56 (m, 2H), 1.02–1.10 (m, 1H), 1.01 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 165.4, 159.3, 156.7, 143.8, 136.4, 133.1, 130.3, 129.5, 122.8, 113.9, 74.6, 72.9, 71.5, 69.4, 55.4, 44.4, 41.4, 39.4, 34.0, 31.6, 27.5, 22.5, 20.3, 17.5; HRMS-ESI (+) m/z calc'd for C₂₆H₃₇NO₆ [M+Na]⁺: 482.2519, found 482.2510; $[\alpha]_D^{20}$ –11.7 (c 0.480, CHCl₃).

(2S,3S,4E,6R,8R,10R,12Z)-2-(Hydroxymethyl)-3,6,10-trimethyl-14-oxooxacyclotetradeca-4,12-dien-8-yl carbamate (31)

DDQ (94.7 mg, 0.417 mmol, 2 equiv) was added in one portion to a clear/yellow biphasic mixture of PMB-ether (93.6 mg, 0.204 mmol) in DCM/pH 7 phosphate buffer (9:1, 4 mL) to give a green mixture. After 3 h the reaction was quenched with sat. NaHCO₃. The crude product was extracted with EA (x3), washed in brine, and dried over Na₂SO₄. Purification by flash chromatography (75% EA/HX) gave 52.3 mg of alcohol (75% yield) as a white amorphous solid. R_f = 0.2 (70% EA/HX); ¹H NMR (500 MHz, CDCl₃) δ (ppm): 6.17 (td, J = 12.0, 3.4 Hz, 1H), 5.93 (dd, J = 11.6, 2.5 Hz, 1H), 5.34 (dd, J = 15.0, 9.5 Hz, 1H), 5.03 (dd, J = 15.0, 9.3 Hz, 1H), 4.93 (ddd, J = 10.4, 4.9, 2.4 Hz, 1H), 4.59 (t, J = 10.9 Hz, 1H), 4.50 (brs, 2H), 3.69–3.88 (m, 3H), 2.39–2.48 (m, 1H), 2.04–2.14 (m, 1H), 1.96 (dq, J = 14.9, 2.7 Hz, 1H), 1.85–1.93 (m, 1H), 1.72 (t, J = 5.9 Hz, 1H), 1.47–1.55 (m, 2H), 1.04–1.10 (m, 2H), 1.03 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 165.6, 156.8, 144.7, 136.3, 133.1, 122.3, 76.8, 71.4, 63.2, 44.4, 41.5, 39.1, 34.0, 31.7, 27.5, 22.4, 20.3, 17.5; HRMS-ESI (+) m/z calc'd for C₁₈H₂₉NO₅ [M+Na]⁺: 362.1944, found 362.1935; $[\alpha]_D^{20}$ +4.08 (c 0.147, CHCl₃).

(2S,3S,4E,6R,8R,10R,12Z)-2-((E)-2-Iodovinyl)-3,6,10-trimethyl-14-oxooxacyclotetradeca-4,12-dien-8-yl carbamate (32)

To a clear solution of alcohol (52.3 mg, 0.154 mmol) in DCM (3 mL) at 0 °C was added NaHCO₃ (90.5 mg, 1.08 mmol, 7 equiv) and DMP (130.4 mg, 0.307 mmol, 2 equiv) sequentially. The reaction was quenched with sat. NaHCO₃ and Na₂S₂O₃ after 1.5 h and left vigorously stirring 10 min. The crude product was extracted with DCM (x3), washed in brine, and dried over Na₂SO₄. Purification through a short silica plug (50% EA/HX) gave 38.0 mg of aldehyde as a white amorphous solid. A yellow solution of aldehyde (38.0 mg, 0.113 mmol) and CHI₃ (133.3 mg, 0.339 mmol, 3 equiv) in THF (2 mL) was slowly

transferred via cannula to a green suspension of CrCl_2 (138.8 mg, 1.13 mmol, 10 equiv) in THF (1 mL) to give a dark maroon mixture. After 1 h the reaction was quenched with H_2O . The crude product was extracted with EA (x3), washed in brine, and dried over Na_2SO_4 . Purification through a short silica plug (40% EA/HX) gave 43.0 mg of vinyl iodide (60% yield over 2-steps) as a white amorphous solid. $R_f = 0.2$ (25% EA/HX); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 6.44–6.51 (m, 2H), 6.12 (td, $J = 12.2, 3.4$ Hz, 1H), 5.86 (dd, $J = 11.6, 2.4$ Hz, 1H), 5.27 (dd, $J = 15.0, 9.4$ Hz, 1H), 5.17 (ddd, $J = 10.4, 5.1, 2.6$ Hz, 1H), 5.03 (dd, $J = 15.0, 9.3$ Hz, 1H), 4.61 (brs, 2H), 4.57 (t, $J = 11.0$ Hz, 1H), 3.64 (ddd, $J = 15.0, 12.8, 5.0$ Hz, 1H), 2.17–2.26 (m, 1H), 2.04–2.12 (m, 1H), 1.95 (dq, $J = 15.0, 2.8$ Hz, 1H), 1.83–1.91 (m, 1H), 1.43–1.52 (m, 2H), 1.02–1.10 (m, 2H), 1.00 (d, $J = 7.0$ Hz, 3H), 0.94 (d, $J = 6.8$ Hz, 3H), 0.91 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 164.7, 156.8, 143.8, 143.5, 137.0, 132.4, 122.4, 81.6, 77.8, 71.0, 44.4, 42.3, 41.4, 34.0, 31.7, 27.4, 22.4, 20.3, 17.5; further spectroscopic data was not collected due to concern of decomposition.

2-Bromo-3-((*tert*-butyldimethylsilyl)oxy)benzaldehyde (33)

To a grey mixture of 2-bromo-3-hydroxybenzaldehyde (2.0692 g, 10.3 mmol) in DCM (50 mL) at 0°C was added DIPEA (3.5 mL, 20.1 mmol, 2 equiv) and TBSCl (1.9755 g, 13.1 mmol, 1.3 equiv) sequentially to produce a yellow solution. The ice bath was removed after 5 min. The reaction was quenched with sat. NH_4Cl after 4 h. The crude product was extracted with DCM (x3), washed in brine, and dried over MgSO_4 . Purification by flash chromatography (3% EA/HX) gave 3.1808 g of TBS phenol (98% yield) as a low-melting clear liquid. $R_f = 0.4$ (5% EA/HX); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 10.41 (d, $J = 0.8$ Hz, 1H), 7.52 (dd, $J = 7.7, 1.6$ Hz, 1H), 7.28 (td, $J = 8.0, 0.8$ Hz, 1H), 7.10 (dd, $J = 8.0, 1.6$ Hz, 1H), 1.07 (s, 9H), 0.28 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 192.6, 153.5, 135.3, 128.2, 125.4, 122.3, 120.6, 25.9, 18.6, -4.0 .

1-(2-Bromo-3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2,2-dimethylbut-3-en-1-ol (34)

3-Methyl-2-butenylmagnesium chloride (1 M THF, 15 mL, 15.0 mmol, 1.5 equiv) was added slowly to a clear solution of aldehyde (3.1698 g, 10.1 mmol) in THF (50 mL) at 0°C to give a grey solution. The reaction was quenched with sat. NH_4Cl after 30 min and flask warmed to rt. The crude product was extracted with EA (x3), washed in brine, and dried over Na_2SO_4 . Purification by flash chromatography (3% EA/HX) gave 3.8732 g of racemic alcohol (quantitative) as a clear oil. $R_f = 0.3$ (5% EA/HX); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.15 (t, $J = 7.9$ Hz, 1H), 7.08 (dd, $J = 7.8, 1.6$ Hz, 1H), 6.81 (dd, $J = 7.9, 1.6$ Hz, 1H), 6.03 (dd, $J = 17.5, 10.8$ Hz, 1H), 5.12–5.15 (m, 2H), 5.07 (dd, $J = 17.5, 1.3$ Hz, 1H), 1.99 (brs, 1H), 1.12 (s, 3H), 1.05 (s, 9H), 1.03 (s, 3H), 0.25 (s, 3H), 0.23 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 152.3, 144.9, 142.4, 127.0, 122.2, 119.1, 118.2, 114.0, 78.0, 43.6, 26.0, 24.8, 21.5, 18.6, -4.0 , -4.1 ; HRMS-ESI (+) m/z calc'd for $\text{C}_{18}\text{H}_{29}\text{BrO}_2\text{SiNa}$ [$\text{M} + \text{Na}$] $^+$: 407.1018, found 407.1008. Chiral HPLC: Chiralpak IC3 (250 x 4.6 mm), 5% IPA/HX, flow = 0.5 mL/min, $T = 20^\circ\text{C}$, UV = 254 nm, $R_t(S) = 8.0$ min, $R_t(R) = 9.3$ min.

1-(2-Bromo-3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2,2-dimethylbut-3-en-1-one (35)

To a cloudy suspension of alcohol (2.4435 g, 6.34 mmol) and SiO_2 (2.8888 g) in DCM (32 mL) was added PCC (2.0503 g, 9.51 mmol, 1.5 equiv) portionwise. After 12 h, the reaction was filtered through celite and the filter cake washed with DCM. Purification by flash

chromatography (3% EA/HX) gave 2.2594 g of ketone (93% yield) as a clear oil. R_f = 0.4 (5% EA/HX); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.14 (t, J = 7.8 Hz, 1H), 6.85 (dd, J = 8.1, 1.4 Hz, 1H), 6.70 (dd, J = 7.6, 1.4 Hz, 1H), 6.02 (dd, J = 17.4, 10.6 Hz, 1H), 5.16 (dd, 10.2, 0.6 Hz, 1H), 5.13 (dd, J = 3.5, 0.7 Hz, 1H), 1.36 (s, 6H), 1.04 (s, 9H), 0.25 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 208.8, 153.1, 144.5, 142.4, 127.8, 120.1, 119.0, 114.6, 111.2, 51.3, 25.9, 24.3, 18.5, -4.1.

(S)-1-(2-Bromo-3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2,2-dimethylbut-3-en-1-ol ((S)-34)

To a faint-yellow solution of ketone (1.2356 g, 3.22 mmol) and (*S*)-Me-CBS (447.3 mg, 1.61 mmol, 0.5 equiv) in PhMe (30 mL) at 0 °C was added BMS (2 M THF, 3.2 mL, 6.40 mmol, 2.0 equiv) dropwise. After 2 h, the reaction was quenched with MeOH dropwise, flask warmed to room temperature, and concentrated via rotary evaporation. Purification by flash chromatography (5% EA/HX) gave 720.5 mg of alcohol (58% yield) as a clear oil. All spectroscopic data was identical to that of the racemic alcohol **34**; $[\alpha]_{\text{D}}^{20}$ -50.8 (*c* 1.85, CHCl_3); Chiral HPLC: Chiralpak IC3 (250 × 4.6 mm), 5% IPA/HX, flow = 0.5 mL/min, T = 20 °C, UV = 254 nm, R_t major = 7.9 min, R_t minor = 9.3 min.

(R)-1-(2-Bromo-3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2,2-dimethylbut-3-en-1-ol ((R)-34)

Prepared in the same manner as alcohol (*S*)-**34** above employing (*R*)-Me-CBS catalyst. $[\alpha]_{\text{D}}^{20}$ +49.2 (*c* 2.13, CHCl_3).

(S)-((1-(2-Bromo-3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2,2-dimethylbut-3-en-1-yl)oxy)triethylsilane ((S)-8)

To a clear solution of alcohol (153.7 mg, 0.399 mmol) in DCM (3 mL) at 0 °C was added Et_3N (170 μL , 1.22 mmol, 3.1 equiv) and TESOTf (135 μL , 0.597 mmol, 1.5 equiv) sequentially. After 30 min, the reaction was quenched with sat. NaHCO_3 and flask warmed to rt. The crude product was extracted with DCM (x3), washed in brine, and dried over MgSO_4 . Purification by flash chromatography (2% EA/HX) gave 191.3 mg (96% yield) of TES ether as a clear oil. R_f = 0.7 (5% EA/HX); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.09 (d, J = 4.8 Hz, 2H), 6.76–6.80 (m, 1H), 6.08 (dd, J = 17.6, 10.9 Hz, 1H), 5.06 (s, 1H), 4.94 (dd, J = 10.8, 1.3 Hz, 1H), 4.84 (dd, J = 17.6, 1.2 Hz, 1H), 1.07 (s, 3H), 1.05 (s, 9H), 1.00 (s, 3H), 0.83 (t, J = 8.0 Hz, 9H), 0.39–0.52 (m, 6H), 0.22 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 151.8, 145.1, 143.9, 126.5, 123.5, 118.9, 117.9, 112.1, 79.1, 43.8, 26.1, 24.3, 22.6, 18.6, 6.9, 4.9, -4.0, -4.1; $[\alpha]_{\text{D}}^{20}$ -18.64 (*c* 0.103, CHCl_3).

(R)-((1-(2-Bromo-3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2,2-dimethylbut-3-en-1-yl)oxy)triethylsilane ((R)-8)

Prepared in the same manner as TES ether (*S*)-**8** above. $[\alpha]_{\text{D}}^{20}$ +17.69 (*c* 1.45, CHCl_3).

(S, E)-2-Bromo-3-(1-hydroxy-2,2-dimethylhex-3-en-5-yn-1-yl)phenol ((S)-4)

To a clear solution of olefin (238.9 mg, 0.478 mmol) in acetone/ H_2O (5 mL) was added 2,6-lutidine (110 μL , 0.944 mmol, 2.0 equiv), NMO (115.2 mg, 0.983 mmol, 2.1 equiv), and OsO_4 (4% in H_2O , 0.6 mL, 0.094 mmol, 0.2 equiv) sequentially. The yellow solution was

left stirring overnight while covered with aluminum foil. After 12 h, $\text{PhI}(\text{OAc})_2$ (240.2 mg, 0.746 mmol, 1.6 equiv) was added and reaction left stirring additional 30 min. The reaction was quenched with $\text{Na}_2\text{S}_2\text{O}_3$ and left vigorously stirring 15 min. The crude product was extracted with EA (x3), washed in brine, and dried over Na_2SO_4 . Purification by flash chromatography (3% EA/HX) gave 224.0 mg of aldehyde as a clear oil. To a cream-colored suspension of phosphonium bromide (822.0 mg, 1.81 mmol, 4.0 equiv) in THF (10 mL) at -78°C was added LHMDs (1 M THF, 1.8 mL, 1.80 mmol, 4.0 equiv) slowly. After 10 min, the flask was warmed to -40°C for an additional 30 min, then re-cooled to -78°C . A clear solution of aldehyde (224.0 mg, 0.447 mmol) in THF (5 mL) was then added slowly via cannula. The flask was then slowly warmed to room temperature and left stirring overnight. After 12 h, the reaction was quenched with sat. NH_4Cl . The crude product was extracted with EA (x3), washed in brine, and dried over Na_2SO_4 . Purification by flash chromatography (3% EA/HX) gave 272.2 mg of TMS-enyne as a clear oil with a 7:1 trans/cis ratio as determined by ^1H NMR. To a clear solution of tri-silyl ether (272.2 mg, 0.478 mmol) in THF (5 mL) was added TBAF (1 M THF, 2.4 mL, 2.40 mmol, 5.0 equiv) slowly. After 20 h, the reaction was quenched with sat. NH_4Cl . The crude product was extracted with EA (x3), washed in brine, and dried over Na_2SO_4 . Purification by flash chromatography (15% EA/HX) gave 72.0 mg (51% yield over 3-steps) of enyne as a clear oil. R_f = 0.2 (15% EA/HX); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.24 (t, J = 8.0 Hz, 1H), 7.03 (dd, J = 7.8, 1.2 Hz, 1H), 6.98 (dd, J = 8.1, 1.4 Hz, 1H), 6.45 (d, J = 16.5 Hz, 1H), 5.67 (s, 1H), 5.42 (dd, J = 16.4, 2.2 Hz, 1H), 5.00 (s, 1H), 2.85 (d, J = 2.2 Hz, 1H), 1.94 (brs, 1H), 1.56 (brs, 1H), 1.14 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 151.9, 151.6, 141.1, 128.2, 121.4, 115.3, 112.8, 108.1, 82.6, 78.5, 77.0, 43.6, 24.3, 21.9; HRMS-ESI (+) m/z calc'd for $\text{C}_{14}\text{H}_{14}\text{BrO}$ $[\text{M}+\text{Na}]^+$: 277.0228, found 277.0214; $[\alpha]_{\text{D}}^{20}$ -98.47 (c 0.330, CHCl_3).

(*R, E*)-2-Bromo-3-(1-hydroxy-2,2-dimethylhex-3-en-5-yn-1-yl)phenol ((*R*)-4)

Prepared in the same manner as enyne (*S*)-4 above. $[\alpha]_{\text{D}}^{20}$ $+100.6$ (c 0.867, CHCl_3).

Callyspongiolide (*S*)-2

To a yellow solution of vinyl iodide (14.5 mg, 0.031 mmol) and (*S*)-enyne (13.7 mg, 0.046 mmol, 1.5 equiv) in degassed PhMe (4 mL) was added CuI (1.3 mg, 0.007 mmol, 0.2 equiv) and pyrrolidine (5 μL , 0.060 mmol, 1.9 equiv) sequentially to give a faint-red solution. After 5 min, $\text{Pd}(\text{PPh}_3)_4$ (3.7 mg, 0.003 mmol, 0.1 equiv) was added to produce a faint-yellow solution. After 45 min, the reaction was passed through a silica plug and eluted with Et_2O . Purification by flash chromatography (35% EA/HX) afforded 14.8 mg of callyspongiolide (*S*)-2 (75% yield) as a yellow residue. R_f = 0.14 (40% EA/HX); ^1H NMR (500 MHz, DMSO) δ (ppm): 10.07 (s, 1H), 7.13 (t, J = 7.9 Hz, 1H), 6.81–6.85 (m, 2H), 6.36 (d, J = 16.4 Hz, 1H), 6.13 (td, J = 12.1, 3.3 Hz, 1H), 6.06 (dd, J = 15.8, 7.7 Hz, 1H), 5.93–5.97 (m, 2H), 5.52 (d, J = 4.4 Hz, 1H), 5.45 (dd, J = 16.3, 2.1 Hz, 1H), 5.22 (dd, J = 15.0, 9.3 Hz, 1H), 5.09 (dd, J = 10.2, 7.9 Hz, 1H), 5.05 (dd, J = 15.1, 9.1 Hz, 1H), 4.89 (d, J = 4.4 Hz, 1H), 4.47 (t, J = 10.8 Hz, 1H), 3.42 (ddd, J = 15.0, 12.4, 4.9 Hz, 1H), 2.19–2.28 (m, 1H), 1.95–2.05 (m, 1H), 1.86 (dq, J = 14.8, 2.7 Hz, 1H), 1.69–1.79 (m, 1H), 1.32–1.44 (m, 2H), 1.00–1.07 (m, 2H), 1.04 (s, 3H), 0.97 (d, J = 7.2 Hz, 3H), 0.95 (s, 3H), 0.89 (d, J = 6.9 Hz,

3H), 0.87 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ (ppm): 164.2, 156.7, 153.3, 151.6, 143.2, 142.5, 139.6, 136.4, 132.0, 126.9, 122.3, 120.1, 114.4, 113.4, 111.7, 106.8, 90.5, 86.4, 76.6, 75.7, 68.3, 44.2, 43.1, 41.8, 41.1, 33.3, 31.3, 26.9, 24.1, 22.5, 22.0, 19.9, 17.5; HRMS-ESI (+) m/z calc'd for $\text{C}_{33}\text{H}_{42}\text{BrNO}_6$ $[\text{M}+\text{Na}]^+$: 650.2094, found 650.2087; $[\alpha]_{\text{D}}^{20}$ -182.0 (c 0.100, MeOH).

Callyspongiolide (*R*)-2

To a yellow solution of vinyl iodide (12.7 mg, 0.028 mmol) and (*R*)-enyne (13.7 mg, 0.046 mmol, 1.6 equiv) in degassed PhMe (3 mL) was added CuI (1.3 mg, 0.007 mmol, 0.2 equiv) and pyrrolidine (5 μL , 0.060 mmol, 2.1 equiv) sequentially to give a faint-red solution. After 5 min, $\text{Pd}(\text{PPh}_3)_4$ (3.4 mg, 0.003 mmol, 0.1 equiv) was added to produce a faint-yellow solution. After 45 min, the reaction was passed through a silica plug and eluted with Et_2O . Purification by flash chromatography (35% EA/HX) afforded 14.1 mg of callyspongiolide (*R*)-2 (82% yield) as a white amorphous solid. R_f = 0.14 (40% EA/HX); ^1H NMR (500 MHz, DMSO) δ (ppm): 10.07 (s, 1H), 7.13 (t, J = 7.9 Hz, 1H), 6.81–6.85 (m, 2H), 6.36 (d, J = 16.4 Hz, 1H), 6.13 (td, J = 12.1, 3.3 Hz, 1H), 6.06 (dd, J = 15.8, 7.7 Hz, 1H), 5.93–5.97 (m, 2H), 5.52 (d, J = 4.4 Hz, 1H), 5.45 (dd, J = 16.3, 2.0 Hz, 1H), 5.22 (dd, J = 15.0, 9.3 Hz, 1H), 5.09 (dd, J = 10.0, 7.8 Hz, 1H), 5.05 (dd, J = 15.0, 9.1 Hz, 1H), 4.89 (d, J = 4.4 Hz, 1H), 4.47 (t, J = 10.8 Hz, 1H), 3.42 (ddd, J = 15.0, 12.4, 4.9 Hz, 1H), 2.18–2.28 (m, 1H), 1.95–2.05 (m, 1H), 1.86 (dq, J = 14.9, 2.5 Hz, 1H), 1.69–1.79 (m, 1H), 1.32–1.44 (m, 2H), 1.00–1.07 (m, 2H), 1.04 (s, 3H), 0.97 (d, J = 7.3 Hz, 3H), 0.95 (s, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ (ppm): 164.2, 156.7, 153.3, 151.6, 143.2, 142.5, 139.6, 136.4, 132.0, 126.9, 122.3, 120.1, 114.4, 113.4, 111.7, 106.8, 90.5, 86.4, 76.6, 75.7, 68.3, 44.2, 43.1, 41.8, 41.1, 33.3, 31.3, 26.9, 24.1, 22.4, 22.0, 19.9, 17.5; HRMS-ESI (+) m/z calc'd for $\text{C}_{33}\text{H}_{42}\text{BrNO}_6$ $[\text{M}+\text{Na}]^+$: 650.2094, found 650.2090; $[\alpha]_{\text{D}}^{20}$ -25.5 (c 0.102, MeOH).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Structures of callyspongiolide isomers

Figure 2.
Retrosynthetic analysis of callyspongiolide

Scheme 1.

Synthesis of aldehyde **15**. Reagents and Conditions: (a) (+)-Ipc₂Ballyl, Et₂O, -78 °C, (84%, 10:1 dr); (b) acryloyl chloride, Et₃N, DCM, 0 °C, (63%); (c) Grubbs II (5 mol%), DCM, 42 °C, (93%); (d) Me₂CuLi₂I, Et₂O, -78 °C, (93%); (e) TBAF, THF, (86%); (f) DMP, NaHCO₃, DCM, 0 °C, (90%). Ip_c₂Ballyl = *B*-allyldiisopinocampheylborane; DMP = Dess-Martin periodinane.

Scheme 2.

Synthesis of sulfone **21**. Reagents and Conditions: (a) $\text{Me}_2\text{CuLi}_2\text{I}$, Et_2O , -50 to -10 $^\circ\text{C}$, then NaIO_4 , $\text{Et}_2\text{O}/\text{H}_2\text{O}$ (2:1), (76%); (b) PTSH, DIAD, PPh_3 , THF, -20 $^\circ\text{C}$, (99%); (c) TESOTf, Et_3N , DCM, 0 $^\circ\text{C}$, (85%); (d) *m*-CPBA, NaHCO_3 , DCM, (88%). PTSH = 1-phenyl-1*H*-tetrazole-5-thiol; DIAD = diisopropyl azodicarboxylate.

Scheme 3.

Synthesis of alkynyl ester **27**. Reagents and Conditions: (a) MeNH(OMe)HCl , $i\text{-PrMgCl}$, THF, $-20\text{ }^{\circ}\text{C}$, (94%); (b) TBSCl, Et_3N , DMF, (91%); (c) DIBAL-H, THF, $-78\text{ }^{\circ}\text{C}$; (d) Ohira-Bestmann reagent, K_2CO_3 , MeOH, (90%, 2-steps); (e) $n\text{-BuLi}$, ClCO_2Et , THF, $-78\text{ }^{\circ}\text{C}$, (quantitative); (f) PPTS, EtOH, $0\text{ }^{\circ}\text{C}$; (g) LiOH, THF- H_2O (2:1), $23\text{ }^{\circ}\text{C}$; (h) conditions in Table 2. DMF = *N,N*-dimethylformamide; DIBAL-H = diisobutylaluminum hydride; ClCO_2Et = ethyl chloroformate.

Scheme 4.

Synthesis of vinyl iodide **32**. Reagents and Conditions: (a) H_2 , Lindlar catalyst, quinoline, EtOAc/1-hexene (10:1), (quantitative); (b) HF·py, MeOH, 0 °C, (90%); (c) ClSO_2NCO , DCM, 0 °C, (96%); (d) DDQ, DCM, pH 7 phosphate buffer (1:1), (75%); (e) DMP, NaHCO_3 , DCM; (f) CrCl_2 , CHI_3 , THF, (60%, 2-steps). ClSO_2NCO = chlorosulfonyl isocyanate.

Scheme 5.

Synthesis of enynes *(S)*- and *(R)*-4. Reagents and Conditions: (a) TBSCl, DIPEA, DCM, (98%); (b) 3-methyl-2-butenylmagnesium chloride, THF, 0 °C, (quantitative); (c) PCC, DCM, (93%); (d) *(S)*-Me-CBS, BMS, PhMe, 0 °C, (59%); (e) TESOTf, Et₃N, DCM, 0 °C, (96%); (f) OsO₄, NMO, 2,6-lutidine, then PhI(OAc)₂; (g) **36**, LiHMDS, THF, -78 °C to rt; (h) TBAF, THF, (51% 3-steps). BMS = borane dimethylsulfide.

Scheme 6.

Synthesis of callyspongiolide (*R*)- and (*S*)-2. Reagents and Conditions: (a) Pd(PPh₃)₄, CuI, pyrrolidine, PhMe [82% for (*R*)-2, 75% for (*S*)-2].

Scheme 7.

Synthesis of callyspongiolide (*S*)- and (*R*)-**1**. Reagents and Conditions: (a) Pd(PPh₃)₄, CuI, pyrrolidine, PhMe, [79% for (*S*)-**1**, 82% for (*R*)-**1**].

Table 1

Julia-Kocienski olefination conditions

Entry	Solvent	Base	Additive	Temperature	Yield	trans/cis
1	THF	LiHMDS	-	-78 °C	67%	2:1
2	DME	LiHMDS	-	-78 °C	trace	2.2:1
3	DME	KHMDS	-	-78 °C	decomposed	-
4	THF	KHMDS	-	-78 °C	30%	12.5:1
5	THF	KHMDS	(C ₆ H ₁₃) ₄ N ⁺ Br ⁻	-78 °C	15%	100:0
6	THF	LiHMDS	(C ₆ H ₁₃) ₄ N ⁺ Br ⁻	-78 °C	72%	3:1
7	THF	LiHMDS	(C ₄ H ₉) ₄ N ⁺ Cl ⁻	-78 °C	62%	5:1
8	DMF	LiHMDS	-	-60 °C	76%	27:1

Table 2

Macrolactonization conditions

Entry	Conditions	Product
1	i) $\text{Cl}_3\text{C}_6\text{H}_2\text{COCl}$ Et_3N , THF ii) DMAP, PhMe	Incomplete Formation of Mixed Anhydride
2	DCC, CSA, DMAP DCM	27%
3	DCC, DMAP DCM	33%
4	BOP-Cl, DIPEA, DMAP DCM	46%
5	$\text{Cl}_3\text{C}_6\text{H}_2\text{COCl}$ DIPEA, DMAP PhMe	67%

Table 3

Stereoselective CBS reduction of ketone **35**.

Entry	CBS	Borane	Solvent	Temp (°C)	Yield (%)	ee (%)
1	(S)-Me-CBS (0.1 equiv.)	BMS	PhMe	0	14	95
2	(S)-Me-CBS (0.25 equiv.)	BMS	PhMe	0	24	>99
3	(S)-Me-CBS (0.5 equiv.)	BMS	PhMe	0	59	>99
4	(S)-Me-CBS (1 equiv.)	BMS	PhMe	0	56	>99
5	(S)-Me-CBS (0.5 equiv.)	BMS	PhMe	-30	trace	nd
6	(S)-Me-CBS (0.5 equiv.)	BMS	PhMe	rt	29	96
7	(S)-Me-CBS (0.5 equiv.)	CB	PhMe	0	NR	-
8	(S)-Me-CBS (0.5 equiv.)	BMS	THF	0	14	97
9	(S)-Me-CBS (0.5 equiv.)	BMS	DCM	0	trace	nd