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Cis Selective RCM Study to the 14-Membered Cyclic Subunit of Bielschowskysin

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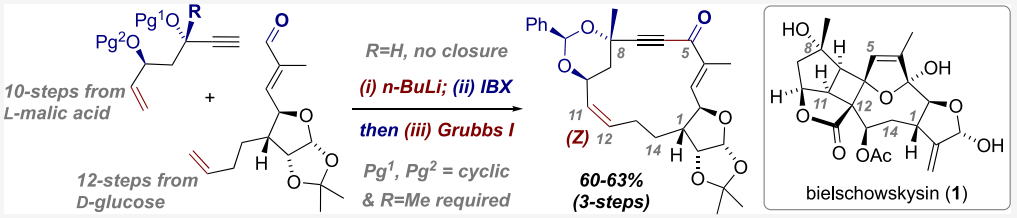

ABSTRACT: A concise, (Z)-selective ring-closing metathesis (RCM) route to the 14-membered carbocycle of bielschowskysin is detailed using naturally occurring chiral starting materials. Unproductive RCM substrates were attributed to alkyne chelation of the ruthenium catalyst and steric disadvantages within the cembranoid precursors, which was eventually circumvented by using cyclic diol benzylidene protection involving a C8-quaternary carbinol center.

INTRODUCTION

Ring-closing metathesis (RCM) is a powerful method to form macrocyclic frameworks of natural products.[1,2] In complex cases, it remains a challenge to predispose the macrocyclic precursor to selective ring closure in both electronic and conformational senses. Such difficulties were observed, for example, in the synthesis of the macrocycles of roseophilin[3] and the plecomacrolides.[4] Despite additional geometric issues in forming alkene macrocycles, especially to achieve cis-selectivity, RCM is an elegant way to access even the most challenging of natural product frameworks.[5] Although relatively scarce in the assembly of complex cembranolides, relevant reports to our current study of bielschowskysin (**1**), a highly oxygenated tricyclo[9.3.0.0^{2,10}]tetradecane isolated from *Pseudopterogorgia kallos*,[6] include the total synthesis of deoxypukalide and sarcophytonolide C.[7,8]

To date, a series of model studies to bielschowskysin **1** have been reported (Figure 1).[9] Sulikowski and our group independently reported the synthesis of the bicyclo[3.2.0]-heptane core based on a biomimetic transannular [2 + 2] photocycloaddition to construct the cyclobutane ring (Figure 1a,b, respectively).[9a,b] Nicolaou et al. reported an expedient synthesis of the first 14-carbon framework of **1** through RCM and transannular [2 + 2] studies (Figure 1c).[9c] Mulzer and co-workers disclosed a nonphotochemical strategy to the bicyclo[3.2.0]heptane core structure of bielschowskysin, featuring the all-carbon quaternary center at C12 for the first time (Figure 1d).[9d] The same position was targeted by Ghosh et al. in their stereocontrolled approach to the bicyclic core through Cu(I)-catalyzed intramolecular [2 + 2] cycloaddition (Figure 1e).[9h]

Stoltz and co-workers pursued a strategically different approach to the cyclobutane core of **1** by heterolytic ring expansion of a strained cyclopropane.[9e] Mulzer's group showcased an advanced [2 + 2]-photoadduct bearing a vinyl bromide and exo-methylene that underwent an atypical acetoxy-carbocyclization with Pd(OAc)$_2$ to form a 13-membered homolog of **1** (Figure 1g).[9f] Roche, West, and co-workers used a biomimetic approach to report the hemisynthesis of the bielschowskyane skeleton.[9i] Recently, Sarlah's group explored the stepwise cyclobutane formation from the tricyclic ring system.[9j]

RESULTS AND DISCUSSION

Herein, we extend our previous macrocyclic findings[9g] to a practical, cis-selective RCM assembly of the 14-membered cembrane carbocycle (**2**) of bielschowskysin (Figure 1i). This key step conveniently installs a double bond between C11 and C12, allowing for a subsequent intramolecular [2 + 2] photocycloaddition step. To access a linear precursor for macrocyclization *via* RCM, a convergent route was envisioned by disconnection at C6−C5. This is planned through addition of an alkyne onto a conjugate aldehyde. In order to develop a more practical approach to synthesize the bielschowskysin

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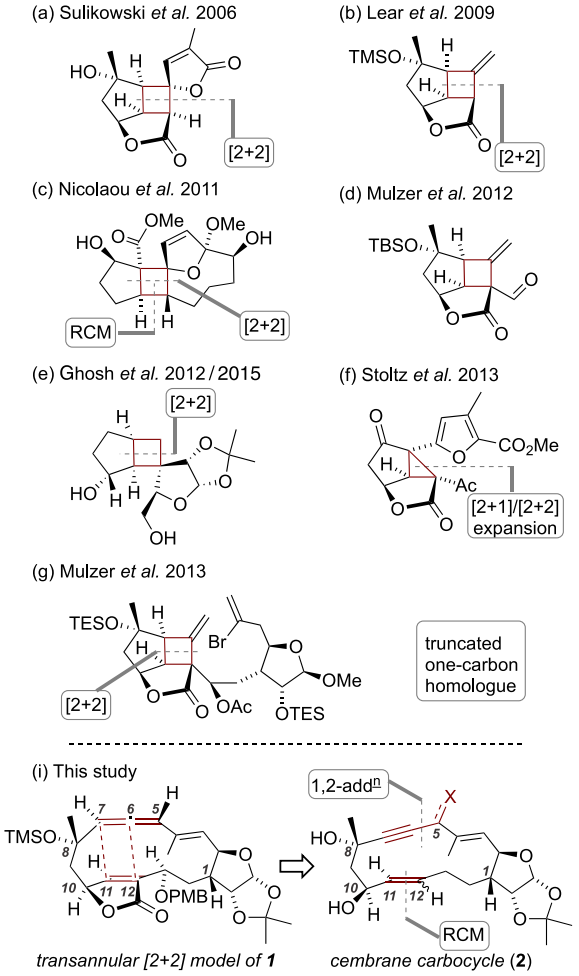
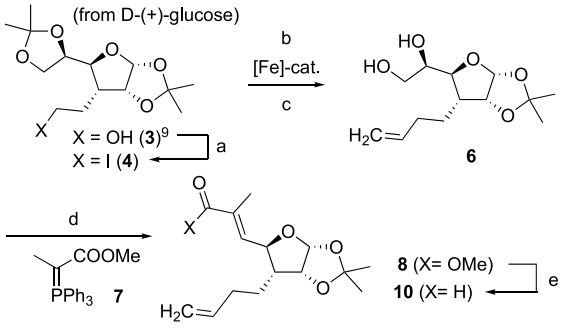


Figure 1. Key model studies of bielschowskysin **1**, proposed [2 + 2]-transannular model, and cembrane carbocycle target **2**.

carbon skeleton, we decided to use naturally occurring chiral compounds as starting materials. Alcohol **3** was synthesized as previously reported[9g] (in five steps from D-(+)-glucose) and subsequently treated under Appel conditions to afford alkyl iodide **4** in 94% yield (Scheme 1). Vinylation at this stage required a convenient sp^3–sp^2 cross coupling method using

Scheme 1. Synthesis of Aldehyde 10[a]



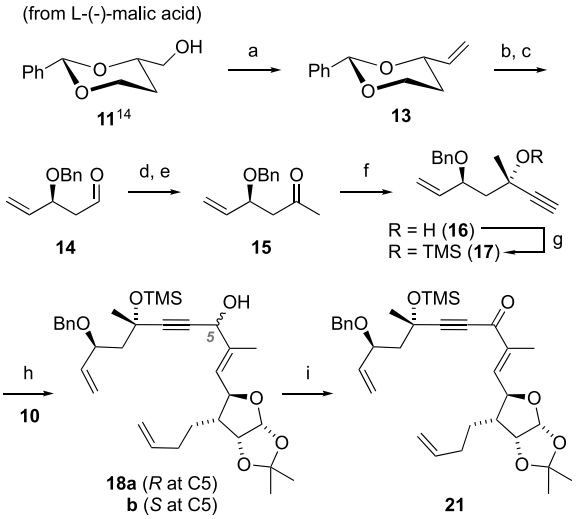
[a]Reagents and conditions: (a) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C to rt, 94%. (b) $Fe(acac)_3$ (20 mol%), $H_2C{=}CHMgBr$, HMTA, TMEDA, THF, −20 °C to 0 °C, 1 h, 69%. (c) 60% AcOH in H_2O, rt, 12 h, 70%. (d) (i) $NaIO_4$, H_2O, MeOH, rt, 15 min and (ii) **7**, CH_2Cl_2, rt, 12 h, 70%, over 2 steps. (e) (i) DIBAL-H, CH_2Cl_2, −78 °C to rt over 4 h, 88% and (ii) DMP, 2 h, CH_2Cl_2, rt, 94%.

the acetylacetonato iron(III) complex with HMTA and TMEDA as ligands, which proceeded under mild conditions at 0 °C and quickly completed within 30–60 min.[10−12]

Selective removal of the exocyclic acetal by 60% aqueous acetic acid gave diol **6**. Oxidative cleavage of vicinal diol to a sensitive aldehyde and subsequent Wittig homologation produced conjugate ester **8**. DIBAL-H reduction of ester and following DMP oxidation gave conjugated aldehyde **10**.[13]

Synthesis of the chiral propargylic alcohol **16** fragment started from known dioxane-carbinol **11**, obtained from commercially available (L)-(−)-malic acid in two steps (Scheme 2).[14] Swern oxidation and immediate Takai–Nozaki

Scheme 2. Synthesis of First-Generation RCM Precursors[a]



[a]Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C and (ii) Zn, CH_2I_2, $PbCl_2$, $Ti(i\text{-}PrO)_4$, CH_2Cl_2, 0 °C to rt, 61% (2 steps). (b) DIBAL-H, CH_2Cl_2, 0 °C, 90%. (c) DMP, CH_2Cl_2, 2 h, 86%. (d) MeMgBr, ether, 2 h, −78 °C. (e) PCC, CH_2Cl_2, 95% (2 steps). (f) $HC{\equiv}CMgBr$, ether, −78 °C to rt, 2 h, 67% (anti/syn = 3:1). (g) TMSCl, Et_3N, CH_2Cl_2, 0 °C, 96%. (h) EtMgBr, THF, −20 °C to rt, 2 h, (anti/syn = 1.4:1), 83%. (i) IBX, EA, reflux, 4 h, 82%.

olefination of the crude aldehyde gave the alkene **13**.[15] Reductive ring opening by DIBAL-H,[16] selectively at less hindered side of acetal, and DMP oxidation of resulting primary alcohol afforded aldehyde **14**. Methylmagnesium bromide addition followed by PCC oxidation resulted in the methyl ketone **15** in good yield. Nucleophilic addition onto this ketone by ethynylmagnesium bromide gave propargylic alcohols in a 3:1 ratio favoring the anti-alcohol **16**,[17] which was protected as its corresponding TMS ether **17** (Scheme 2). C–C bond-forming alkyne addition was then brought about by *in situ* preparation of alkynylmagnesium bromide; subsequent addition onto aldehyde **10** afforded alcohols **18a** and **18b**. A series of RCM substrates bearing a protected alcohol were prepared: **19**, **20a,** and **20b** (Scheme 3). In addition, these alcohols **18a**/**b** were oxidized to give ketone **21** as another RCM substrate.

The TES ether diene precursors **20a** (*R* at C5) and **20b** (*S* at C5) did not respond to RCM conditions using Grubbs II (**24**) or Hoveyda–Grubbs II (**25**) catalysts and, each time, the starting material was recovered. Treatment of ketone **21** (carbonyl at C5) with the Grubbs I catalyst (**23**)[18] also only provided the recovered starting material. However, treatment of the methyl ether **19** with either Grubbs II or Hoveyda–

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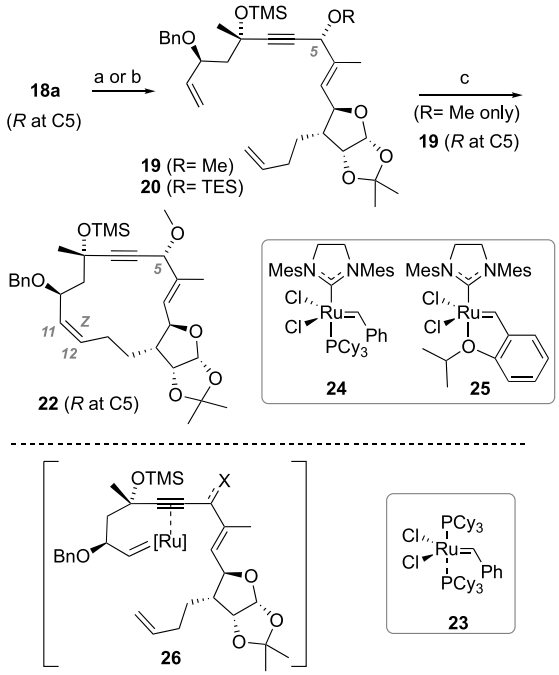
Scheme 3. First-Generation RCM Study with Unproductive Cyclization Precursors[a]



[a]Reagents and conditions: (a) NaH, MeI, THF, 0 °C to rt, 3 h, 85%. (b) TESOTf, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h, 82−87%. (c) 20 mol % of **24** or **25**, degassed toluene, reflux, 2 h, 5%.

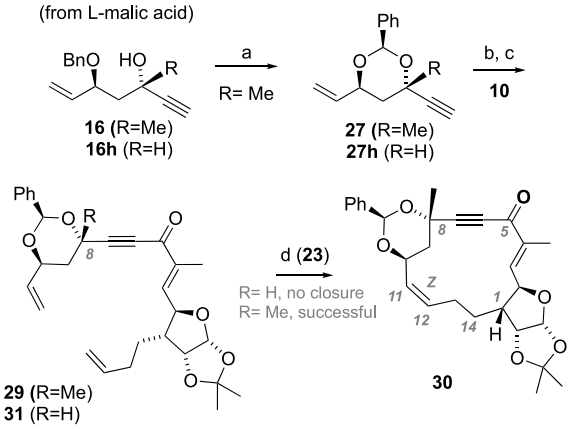
Grubbs II in refluxing toluene brought about ring closure to **22** in 5% isolated yield (Scheme 3). NOESY correlation analysis of the macrocycle **22** showed that the newly formed C11−C12 double bond is *Z*-configured.[19]

The inactivity of RCM substrates **20** (OTES at C5) and **21** (ketone at C5) toward metathesis and low yield, in the case of **19** (OMe at C5), could be explained by possible unproductive chelating events between ruthenium and the triple bond (Scheme 3, **26**). Such complexes can be relatively stable, as observed for some alkyne-chelated ruthenium alkylidene complexes,[20] and thereby consume the catalyst irreversibly and stop the reaction partially or completely.[21]

Based on these results, we modified the RCM substrate, so that unproductive chelation modes would be largely avoided. Cyclic acetal protection of the 1,3-diol moiety of the alkyne fragment was thus targeted in the benzylidene substrates **29** and **31** (Scheme 4). Following our previous synthetic route, we first synthesized the terminal alkyne **27** by DDQ-mediated oxidation of **16**. Acetylide-based coupling with aldehyde **10** followed by the oxidation of the resulting secondary alcohol gave the ynone **29** (R = Me) as the RCM substrate for the study.

Confirming our hypothesis mentioned above, as supported by DFT calculations,[19] treatment of this ring-constrained substrate **29** with the Grubbs I catalyst **23** generated the macrocycle **30** in good yield with exclusive *Z* configuration at the newly formed carbon−carbon double bond (Scheme 4). When CuI was added as an additive to facilitate catalytic turnover for alkyne substrates, similar yields were obtained.[22] Further RCM studies with substrate **31** (R = H) supports the idea that steric hindrance around the alkyne carbons is important for a successful ruthenium-based olefinic ring closure. Thus, the steric hindrance generated by quaternary

Scheme 4. Successful RCM to the Cembrane Carbocycle[a]



[a]Reagents and conditions: (a) DDQ, CH_2Cl_2, rt, 3 h, yield for 27−86%; for 27 h-81%. (b) *n*-BuLi, THF, then **10**, −78 °C to rt, 2 h, 80%. (c) IBX, EA, reflux, 4 h, 95%. (d) **23** (20 mol %), CH_2Cl_2 (*c* = 0.5 mM), 12 h, reflux, 79% without CuI (83% with CuI).

C8 is proposed to block ruthenium from binding to the alkyne.[23] When we used the RCM substrate **31** (R = H), lacking the methyl group in C8, only the starting material was recovered. In this case, the addition of CuI as an additive still afforded no reaction and, using $Ti(OiPr)_4$,[24] led to partial decomposition of the starting material.

In summary, we achieved a practical, straightforward RCM entry to the cembranoid macrocycle **30** of bielschowskysin (**1**) in 15 steps from D-glucose (5.0% yield over a longest linear sequence). Although DFT calculations provided insights into alternative RCM precursors and outcomes,[19] this 14-carbon macrocycle lends itself to various transannular closures and functional diversifications, whereby synthetic elaboration to bielschowskysin (−)-**1** and other biosynthetically related furanocembranes are conceivable (e.g., plumarellide, verrillin, rameswaralide, and providencin).[25]

EXPERIMENTAL SECTION

General Information. All reactions were performed in oven-dried glassware under a nitrogen or argon atmosphere unless otherwise noted. All solvents used in the reactions were purified before use. Dry CH_2Cl_2 was distilled from CaH_2, and dry tetrahydrofuran (THF) and diethyl ether were distilled from sodium and benzophenone. All commercially available compounds were used without purification. The reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm 2E Merck silica gel plates (60F-254) under a 254 nm UV lamp and stained by aqueous ceric ammonium molybdate solution or $KMnO_4$ solution. Flash chromatography was performed on silica gel 60. ^1H and ^{13}C NMR spectra were recorded on Bruker AVANCE 300 MHz (AV300) and Bruker AVANCE 500 MHz (AV500) spectrometers at an ambient atmosphere.

General Techniques and Methods. All nonaqueous reactions were performed in flame dried glassware under a nitrogen or argon atmosphere unless stated otherwise. All solvents used in the reactions were purified before use. Dichloromethane (CH_2Cl_2) was distilled over CaH_2 and dry diethyl ether (Et_2O), and THF was distilled from sodium/benzophenone. All commercially available compounds were used as received without further purification. 4 Å molecular sieves were activated by heating at 120−140 °C under high vacuum for 4 h before storing in a dry desiccator. The reactions were monitored by TLC carried out on 0.25 mm 2E Merck silica gel plates (60F-254) under a 254 nm UV lamp and stained by aqueous ceric ammonium molybdate solution or $KMnO_4$ solution. Flash chromatography was performed on silica gel 60 (0.040—0.063 mm). ^1H and ^{13}C NMR

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spectra were recorded on Bruker ACF (300 MHz) and Bruker AMX500 (500 MHz) NMR spectrometers at an ambient atmosphere. 2D NMR was performed on a Bruker AMX500 (500 MHz) NMR spectrometer. Chemical shifts are reported in δ (ppm) and calibrated using residual undeuterated solvents as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet, m = multiplet, and br = broad. ^{1}H NMR coupling constants (J) are reported in Hertz (Hz), and mass spectra were obtained on Finnigan MAT95XL-T and Micromass VG7035 double-focusing mass spectrometers. High-resolution ESI mass spectra were obtained on a Shimadzu LCMS-IT-TOF spectrometer. Infrared spectra were recorded on a Perkin-Elmer FT 1600 spectrometer.

*(3aR,5S,6R,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxlan-4-yl)-6-(2-iodo ethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole (**4**).* Triphenyl phosphine (7.10 g, 27.05 mmol, 1.3 equiv) and imidazole (2.20 g, 32.3 mmol, 1.5 equiv) were dissolved in dry CH_2Cl_2 (90 mL) and stirred for 10 min at room temperature under a N_2 atmosphere. The contents were cooled using ice bath, and then, iodine (3.17 g, 24.97 mmol, 1.2 equiv) as a solid was added in one portion and slowly warmed to room temperature over 10−15 min. Alcohol **3**[9] (6 g, 20.81 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added, and the reaction mixture was stirred for 1 h at room temperature for the completion of reaction. The reaction volume was reduced approximately to 50 mL using the rotary evaporator. Diethyl ether was added to precipitate triphenylphosphine oxide, the precipitate was filtered, and the solvent was distilled under vacuo. The residue was purified by flash column chromatography (gradient 5−10% ethyl acetate/hexane) to afford the iodide **4** (7.80 g, 94%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.77 (d, J = 3.75 Hz, 1H), 4.66 (t, J = 4.40 Hz, 1H), 4.08 (dd, J = 8.2, 6.3 Hz, 1H), 4.01 (dd, J = 12.0, 6.9 Hz, 1H), 3.91 (dd, J = 8.2, 5.1 Hz, 1H), 3.80−3.77 (m, 1H), 3.43−3.38 (m, 1H), 3.28−3.23 (m, 1H), 2.26−2.18 (m, 1H), 2.14−2.04 (m, 2H), 1.49 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 111.9, 109.6, 104.9, 81.3, 80.6, 77.5, 67.4, 48.8, 29.0, 26.7, 26.6, 26.3, 25.2, 4.6; HRMS (ESI) (m/z): [M + Na]$^+$ calcd for $C_{14}H_{23}INaO_5$, 421.0488; found, 421.0477.

*(3aR,5S,6R,6aR)-6-(But-3-en-1-yl)-5-((R)-2,2-dimethyl-1,3-dioxo-lan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole (**6**).* Iodide **4** (0.77 g, 1.93 mmol) was charged into a 50 mL RBF and dried azeotropically with anhydrous THF (2×) and flushed with argon gas. Freshly predried $Fe(acac)_3$ (0.136 g, 0.39 mmol, 20 mol %) and HMTA (0.054 g, 0.39 mmol, 20 mol %) were added, and the septum-sealed RBF with contents inside was kept under high vacuum for 5 min and subsequently flushed with argon (three cycles). TMEDA (0.12 mL, 0.774 mmol, 40 mol %) was added, and the contents were dissolved by the addition of anhydrous THF (10 mL) and cooled to −20 °C. Vinylmagnesium bromide (1 M in THF, 2.9 mL, 2.9 mmol, 1.5 equiv) was added over 15 min to the stirring solution at −20 °C with the aid of a syringe pump (10 mL/h).[11,12] After completion of the addition, the reaction mixture was stirred for additional 1 h at 0 °C, diluted with diethyl ether, and quenched by the slow addition of 1 M HCl. The aqueous layer was extracted with diethyl ether, and then combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product. The crude was passed through a silica-gel column (gradient 10% ethyl acetate/hexane) to provide the olefin acetonide **5** (0.4 g, 69%) as colorless oil. The acetonide **5** (0.32 g, 1.07 mmol) was dissolved in 60% AcOH/H_2O (10 mL) and allowed to stir at room temperature for 12 h. Upon completion of exocyclic acetal hydrolysis (TLC monitoring), toluene was added and concentrated in vacuo. The resulting syrup was purified by flash column chromatography (gradient 30−50% ethyl acetate/hexane) to provide the diol **6** (0.194 g, 70%) as a faint yellow syrup. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.85−5.77 (m, 1H), 5.74 (d, J = 3.15 Hz, 1H) 5.07−5.03 (m, 1H), 4.98 (d, J = 10.1 Hz, 1H), 4.62 (m, 1H), 3.89 (dd, J = 10.1, 3.8 Hz, 1H), 3.72−3.69 (m, 3H) 2.87 (s, br, 1H, OH), 2.62 (s, br, 1H, OH), 2.31−2.24 (m, 1H), 2.13−2.05 (m, 1H), 1.98−1.90 (m, 1H), 1.78−1.70 (m, 1H), 1.63−1.57 (m, 1H), 1.49 (s, 3H), 1.32 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 138.2, 115.0, 111.7, 104.6, 82.8, 81.0, 72.7, 63.3, 45.6, 31.7, 26.7, 26.3, 24.2. HRMS (ESI) (m/z): [M + Na]$^+$ calcd for $C_{13}H_{22}NaO_5$, 281.1365; found, 281.1358.

*Methyl (E)-3-((3aR,5R,6R,6aR)-6-(But-3-en-1-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-methylacrylate (**8**).* The diol **6** (0.32 g, 1.24 mmol, 1.0 equiv) was dissolved in MeOH (6 mL) and $NaIO_4$ (0.4 g, 1.86 mmol, 1.5 equiv) and in H_2O (1.5 mL) was added slowly at room temperature. White precipitate formation began immediately with an exothermic reaction. After stirring for 15 min, the solution was filtered through a fritted sintered funnel, and the solid was washed several times with MeOH and CH_2Cl_2. The filtrate was diluted with CH_2Cl_2 and washed with brine, and again, the aqueous layer was extracted with CH_2Cl_2 (3×). The combined dichloromethane was dried over anhydrous Na_2SO_4, and the solvent reduced approximately to a 50% volume using the rotary evaporator to afford the crude aldehyde in CH_2Cl_2 solution. Yield **7** (0.43 g, 1.24 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added to the crude aldehyde in CH_2Cl_2, and the reaction mixture was allowed to stir at room temperature for 12 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (gradient 10−15% ethyl acetate/hexane) to isolate **8** (0.25 g, 70%) as a syrup. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.53, (d, J = 8.8 Hz, 1H), 5.80 (d, J = 3.8 Hz, 1H), 5.78−5.70 (m, 1H), 5.00−4.93 (m, 2H), 4.61 (t, J = 4.4 Hz, 1H), 4.54 (t, J = 10.1 Hz, 1H), 3.71 (s, 3H), 2.23−2.16 (m, 1H), 2.06−1.99 (m, 1H), 1.88 (s, 3H), 1.81−1.75 (m, 1H), 1.70−1.63 (m, 1H), 1.50 (s, 3H), 1.30−1.26 (m, 4H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 167.8, 138.1, 137.9, 131.2, 114.9, 111.5, 105.2, 80.5, 77.4, 51.8, 49.7, 31.6, 26.6, 26.1, 23.3, 13.3 HRMS (ESI) (m/z): [M + Na]$^+$ calcd for $C_{16}H_{24}NaO_5$, 319.1521; found, 319.1516.

*(E)-3-((3aR,5R,6R,6aR)-6-(But-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-methylacrylaldehyde (**10**).*[13] To a stirring solution of conjugated ester **8** (0.34 g, 1.12 mmol, 1.0 equiv) in dry CH_2Cl_2 (5 mL) at −78 °C, DIBAL-H (3.1 mL, 3.1 mmol, 2.67 equiv, 1 M in cyclohexane) was added over 10 min. The reaction contents were allowed to warm to room temperature in the dry ice bath over 4 h. The reaction was quenched by the addition of saturated aqueous Rochelle salt (sodium potassium tartrate) dropwise (6 mL) and stirred vigorously for 30 min at room temperature, during which the gray cloud appeared in the water layer. The solution was diluted with ether, the aqueous layer was extracted with ether (3×), and the combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude syrup was purified by flash column chromatography (gradient 20−30% ethyl acetate/hexane) to provide the desired allylic alcohol **9** (0.27 g, 88%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.84−5.76 (m, 1H), 5.81−5.80 (d, J = 3.8 Hz, 1H), 5.38 (dd, J = 8.8, 1.3 Hz, 1H), 5.04 (dd, J = 17.0, 1.30 Hz, 1H), 4.98−4.96 (m, 1H), 4.62 (t, J = 4.4 Hz, 1H), 4.53 (t, J = 9.5 Hz, 1H), 4.05 (s, 2H), 2.27−2.22 (m, 1H), 2.10−2.03 (m, 1H), 1.74 (s, 3H, Me), 1.72−1.63 (m, 2H), 1.54 (s, 3H, Me), (contains $CDCl_3$-H_2O 5H), 1.37−1.30 (m, 4H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 141.3, 138.3, 122.5, 114.9, 111.3, 104.9, 80.7, 77.4, 67.8, 49.78, 31.8, 26.7, 26.3, 23.4, 14.3. To the stirring solution of allylic alcohol **9** (0.43 g, 1.58 mmol, 1.0 equiv) in dry CH_2Cl_2 (10 mL) was added the Dess−Martin periodinane (DMP) reagent (1.0 g, 2.38 mmol, 1.5 equiv) at room temperature and the reaction was allowed to continue for 2 h at room temperature. Upon complete conversion of allylic alcohol, the reaction mixture was filtered through a celite bed and concentrated on a rotary evaporator. The crude residue was purified by flash column chromatography (gradient 10−20% ethyl acetate/hexane) to provide conjugated aldehyde **10** (0.4 g, 94%) as a colorless syrup. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.46 (s, 1H), 6.29 (dd, J = 8.2, 1.3 Hz, 1H), 5.87 (d, J = 3.1 Hz, 1H), 5.80−5.72 (m, 1H), 5.02 (dd, J = 17.1, 1.9 Hz 1H), 4.98 (dd, J = 10.1, 1.3 Hz, 1H), 4.73 (t, J = 10.1 Hz, 1H), 4.68 (t, J = 4.4 Hz, 1H), 2.35−2.20 (m, 1H), 2.10−2.02 (m, 1H), 1.90−1.84 (m, 1H), 1.81 (d, J = 1.3 Hz, 3H), 1.78−1.70 (m, 1H), 1.54 (m, 3H), 1.35 (s, 3H), 1.33−1.26 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 194.6, 149.0, 141.1, 137.7, 115.2, 111.8, 105.4,

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80.5, 77.3, 49.9, 31.6, 26.6, 26.2, 23.4, 10.1. HRMS (ESI) (m/z): [M + Na]$^+$ calcd for $C_{15}H_{22}NaO_4$, 289.1416; found, 289.1407.

*(2S,4S)-2-Phenyl-4-vinyl-1,3-dioxane (**13**).* To a stirring solution of dry CH_2Cl_2 (10 mL) was added oxalyl chloride (2.1 mL, 24.8 mmol, 1.6 equiv) under argon an atmosphere and cooled to −78 °C using a dry ice bath. Anhydrous DMSO (3.3 mL, 46.0 mmol, 3.0 equiv) was added drop-wise to the abovementioned solution. The stirring was continued for 20 min and then, **11**[14] (3.0 g, 15.4 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) was added. The reaction was allowed to proceed for 30 min at −78 °C, triethyl amine (10.0 mL, 72.0 mmol, 4.7 equiv) was added dropwise at −78 °C, and the resulting cloudy solution was stirred for additional 15 min after which it was quenched by the slow addition of water. The biphasic mixture was allowed to warm to room temperature, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude aldehyde **12** was dried azeotropically using dry THF, which then carried forward for the next step reaction without purification. **Takai−Nozaki olefination:**[15] CH_2I_2 (12.5 mL, 154.4 mmol, 10.0 equiv) was added dropwise to a solution of freshly activated Zn dust (10 g, 154.4 mmol, 10.0 equiv) and $PbCl_2$ (0.43 g, 1.54 mmol, 0.1 equiv) in THF (40 mL) for 15 min with constant stirring under argon. The reaction becomes vigorous with effervescence and reached reflux within 10 min from the point of CH_2I_2 addition. Then, the reaction was cooled by arranging an external ice bath as soon as effervescence started, and the grayish solution was stirred at room temperature after effervescence ceases. After 1 h, Ti(i-OPr)$_4$ (4.4 mL, 15.2 mmol, 1.0 equiv) was added and allowed to stir for 30 min at room temperature, and the crude 2-phenyl-1,3-dioxane-4-carbaldehyde **12** in THF (6 mL) was added to the greenish reaction solution. The reaction was continued overnight, diluted with ether, and quenched by the addition of 1 M HCl (50 mL). The layers were separated, the aqueous layer was extracted with ether (2 × 30 mL), and the combined organic fractions were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (gradient 1−5% Et_2O/hexane) to furnish 2-phenyl-4-vinyl-1,3-dioxane **13** (1.8 g, 61%) exclusively as a transparent colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55−7.52 (m, 2H), 7.40−7.34 (m, 3H), 6.00−5.93 (m, 1H), 5.59 (s, 1H), 5.38−5.34 (m, 1H), 5.21−5.18 (m, 1H), 4.41−4.36 (m, 1H), 4.30 (ddd, J = 11.4, 5.0, 1.3 Hz, 1H), 4.04−3.99 (m, 1H), 1.99−1.91 (m, 1H), 1.64−1.60 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 138.5, 137.8, 128.7, 128.1, 126.1, 115.5, 101.1, 77.5, 66.8, 31.1. HRMS (ESI) (m/z): [M + Na]$^+$ calcd for $C_{12}H_{14}NaO_2$, 213.0891; found, 213.0886.

*(S)-3-(Benzyloxy)pent-4-enal (**14**).* DIBAL-H (25 mL, 1 M in cyclohexane, 25 mmol, 1.5 equiv) was added slowly dropwise[16] to a solution of 2-phenyl-4-vinyl-1,3-dioxane **13** (3.2 g, 16.8 mmol. 1.0 equiv) in CH_2Cl_2 (40 mL) at 0 °C, and the reaction was allowed to warm gradually to room temperature over 5 h. Upon completion, the reaction was quenched by the slow addition of 1 M HCl solution, after 15 min of stirring cloudy clumps disappeared from the organic phase. The aqueous phase was extracted with ether (2×), and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (gradient 15−30% ethyl acetate/hexane) to furnish (*S*)-3-(benzyloxy)pent-4-en-1-ol **13a** (2.9 g, 90%) exclusively as a transparent oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36−7.27 (m, 5H), 5.84−5.77 (m, 1H), 5.29−5.28 (m, 2H), 4.63 (d, J = 11.4 Hz, 1H), 4.37 (d, J = 12.0 Hz, 1H), 4.02 (td, J = 8.2, 4.4 Hz, 1H), 3.81−3.71 (m, 2H), 2.45 (s, br, 1H, OH), 1.92−1.85 (m, 1H), 1.82−1.76 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 138.1, 138.1, 128.4, 127.7, 127.6, 117.4, 79.7, 70.2, 60.4, 37.76; HRMS (ESI) (m/z): [M + Na]$^+$ calcd for $C_{12}H_{16}NaO_2$, 215.1048; found, 215.1036. To the stirring solution of (*S*)-3-(benzyloxy)pent-4-en-1-ol **13a** (2.5 g, 13 mmol, 1.0 equiv) and $NaHCO_3$ (10.9 g, 130 mmol, 10.0 equiv) in dry CH_2Cl_2 (40 mL) was added DMP (11 g, 26 mmol, 2.0 equiv) at room temperature, and the reaction was continued for 2 h at room temperature. The reaction contents were filtered through a celite pad, washed with CH_2Cl_2, and concentrated on a rotary evaporator, and the residue was purified by flash column chromatography (gradient 2−5% ethyl acetate/hexane) to provide (*S*)-3-(benzyloxy)pent-4-enal **14** (2.12 g, 86%) as a colorless syrup. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.76−9.75 (m, 1H), 7.36−7.27 (m, 5H), 5.85−5.78 (m, 1H), 5.36−5.30 (m, 2H), 4.62 (d, J = 11.4 Hz, 1H), 4.40 (d, J = 12 Hz, 1H), 4.36−4.32 (m, 1H), 2.74 (ddd, J = 16.4, 8.2, 2.5 Hz, 1H), 2.56 (ddd, J = 16.4, 5.1, 1.9 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 200.6, 137.9, 136.9, 128.3, 128.3, 127.7, 127.6, 118.2, 75.3, 70.3, 49.0. HRMS (ESI) (m/z): [M + Na]$^+$ calcd for $C_{12}H_{14}NaO_2$, 213.0891; found, 213.0888.

*(S)-4-(Benzyloxy)hex-5-en-2-one (**15**).* To a stirring solution of (*S*)-3-(benzyloxy)pent-4-enal **14** (0.54 g, 2.84 mmol, 1.0 equiv) in anhydrous ether (15 mL) at −78 °C was added MeMgBr (2.0 mL, 3 M in Et_2O, 6 mmol, 2.1 equiv). After 2 h of stirring, the reaction mixture at −78 °C was quenched by the slow addition of 1 M HCl (15 mL). The aqueous phase was extracted with ether (2 × 10 mL), and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue obtained as a mixture of two diastereomers (0.44 g) subjected to the next step without purification. The mixture of secondary alcohol (440 mg, 2.13 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (10 mL) followed by the addition of PCC (690 mg, 3.2 mmol, 1.5 equiv) at room temperature. The resulting dark orange-black reaction mixture was stirred overnight, carefully filtered through a celite pad, and concentrated the filtrate using the rotary evaporator. The thick darker reside was purified by flash column chromatography (gradient 10−15% ethyl acetate/hexane) to furnish (*S*)-4-(benzyloxy)hex-5-en-2-one **15** (0.410 g, 95%) as a colorless syrup. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34−7.27 (m, 5H), 5.81−5.74 (m, 1H), 5.33−5.25 (m, 2H), 4.57 (d, J = 11.4 Hz, 1H), 4.37 (d, J = 11.4 Hz, 1H), 4.31−4.27 (m, 1H), 2.85−2.80 (m, 1H), 2.53 (dd, J = 15.8, 4.4 Hz, 1H), 2.16 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 206.4, 138.1, 137.4, 128.3, 127.7, 127.5, 117.6, 76.5, 70.5, 49.4, 31.0; HRMS (ESI) (m/z): [M + Na]$^+$ calcd for $C_{13}H_{16}NaO_2$, 227.1048; found, 227.1045.

*(5S)-5-(Benzyloxy)-3-methylhept-6-en-1-yn-3-ol (**16**).* To a stirring solution of methyl ketone **15** (0.410 g, 2.0 mmol, 1.0 equiv) in anhydrous ether (20 mL) at −78 °C was added ethynylmagnesium bromide (20 mL, 0.5 M in THF, 10 mmol, 5.0 equiv). Then, the reaction mixture was allowed to warm slowly to room temperature over 2 h and quenched by the addition of 1 M HCl (15 mL). The aqueous phase was extracted with ether (2×), and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (gradient 10−15% ethyl acetate in hexanes) to furnish diastereomeric ethynyl carbinols, (3*S*,5*S*)-5-(benzyloxy)-3-methylhept-6-en-1-yn-3-ol **16**[17] (0.31 g, 67%) and (3*R*,5*S*)-5-(benzyloxy)-3-methylhept-6-en-1-yn-3-ol **16s** (0.10 g, 22%) (dr = 3:1) as a colorless syrup. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34−7.29 (m, 5H), 5.90−5.84 (m, 1H), 5.34−5.29 (m, 2H), 4.62 (d, J = 12.0 Hz, 1H), 4.36 (d, J = 11.4 Hz, 1H), 4.23−4.19 (m, 1H), 3.68 (s, 1H), 2.43 (s, 1H), 2.23 (dd, J = 14.5, 8.8 Hz, 1H), 1.92 (dd, J = 14.8, 3.8 Hz, 1H) 1.51 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 138.0, 137.5, 128.4, 128.0, 127.8, 118.2, 87.9, 78.2, 70.8, 70.2, 66.9, 47.3, 29.6. (ESI) (m/z): [M + Na]$^+$ calcd for $C_{15}H_{18}NaO_2$, 253.1204; found, 253.1197. (3*R*,5*S*)-5-(Benzyloxy)-3-methylhept-6-en-1-yn-3-ol (**16s**); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36−7.26 (m, 5H, Ph), 5.83−5.75 (m, 1H), 5.35−5.28 (m, 2H), 4.91 (s 1H, OH), 4.63 (d, J = 11.4 Hz, 1H), 4.56−4.52 (m, 1H), 4.44 (d, J = 10.8 Hz, 1H), 2.43 (s, 1H), 1.97 (dd, J = 14.8, 11.5 Hz, 1H), 1.78 (dd, J = 14.5, 2.5 Hz, 1H), 1.48 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 137.3, 137.3, 128.4, 128.2, 127.8, 117.9, 87.3, 80.3, 71.4, 70.7, 67.4, 47.1, 30.4; HRMS (ESI) (m/z): [M + Na]$^+$ calcd for $C_{15}H_{18}NaO_2$, 253.1204; found, 253.1196.

*((3S,5S)-5-(Benzyloxy)-3-methylhept-6-en-1-yn-3-yloxy)-trimethylsilane (**17**).* To a stirring solution of (3*S*,5*S*)-5-(benzyloxy)-3-methylhept-6-en-1-yn-3-ol **16** (0.115 g, 0.50 mmol, 1.0 equiv) and Et_3N (350 μL, 2.5 mmol, 5.0 equiv) in dry CH_2Cl_2 (5 mL) at 0 °C was added TMSOTf (230 μL, 1.25 mmol, 2.5 equiv) and stirred overnight at room temperature. The reaction mixture was quenched with H_2O, and the aqueous layer was extracted with ether. The combined organic fractions were washed with brine, dried over

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anhydrous Na_2SO_4, and filtered, and the ether was removed under reduced pressure. The yellow residue was purified by flash column chromatography (gradient 0−5% ethyl acetate/hexane) to give TMS ether **17** (0.15 g, 96%) exclusively as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37−7.31 (m, 4H, Ph), 7.28−7.25 (m, 1H, Ph), 5.87−5.79 (m, 1H), 5.27−5.20 (m, 2H), 4.56 (d, J = 11.4 Hz, 1H), 4.39 (d, J = 11.4 Hz, 1H), 4.13−4.08 (m, 1H), 2.44 (s, 1H), 2.13 (dd, J = 14.5, 6.3 Hz, 1H), 1.95 (dd, J = 14.5, 5.05 Hz, 1H), 1.54 (s, 3H), 0.19 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 139.2, 138.7, 128.2, 127.3, 116.3, 88.4, 77.2, 72.3, 70.0, 67.7, 50.1, 31.2, 1.8; HRMS (ESI) (m/z): [(M + Na)]$^+$ calcd for $C_{15}H_{18}NaO_2$, 253.1204; found, 253.1196.

*(3R,6S,8S,E)-8-(Benzyloxy)-1-((3aR,5R,6R,6aR)-6-(but-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2,6-dimethyl-6-(trimethylsilyloxy)deca-1,9-dien-4-yn-3-ol (**18a**).* To a stirring solution of alkyne **17** (0.234 g, 0.56 mmol, 1.0 equiv) in dry THF at −20 °C was added EtMgBr (250 μL, 3 M in THF, 0.76 mmol, 1.35 equiv), and the reaction was warmed to room temperature and then refluxed (using oil bath)at 50 °C for 1 h. The contents were cooled again to −20 °C, and aldehyde **10** (0.150 g, 0.56 mmol, 1.0 equiv) in dry THF was slowly added to the reaction mixture. The reaction was gradually warmed to room temperature over 2 h, quenched by the slow addition of saturated NH_4Cl, and extracted with ether (3×). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (gradient 20−35% ethyl acetate/hexane) to yield separable diastereomeric allylic alcohols **18a** (0.157 g) and **18b** (0.110 g) as colorless syrups (267 mg, 83% overall yield; dr = 1.4:1) with the recovery of starting materials. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34−7.24 (m, 5H), 5.83−5.74 (m, 3H), 5.52 (d, J = 8.9 Hz, 1H), 5.25−5.19 (m, 2H), 5.03 (dd, J = 17.1, 1.9 Hz, 1H), 4.96 (dd, J = 10.1, 1.3 Hz, 1H), 4.72 (s, br, 1H, OH), 4.62−4.60 (t, J = 4.4 Hz, 1H), 4.54 (d, J = 11.4 Hz, 1H) 4.50 (t, J = 9.5 Hz, 1H), 4.35 (d, J = 11.4 Hz, 1H), 4.07 (q, J = 6.3 Hz, 1H), 2.27−2.21 (m, 1H), 2.10 (dd, J = 14.2, 6.3 Hz, 1H), 2.06−2.02 (m, 1H), 1.93−1.90 (m, 1H), 1.80 (m, 1H), 1.80 (s, 3H, Me), 1.74−1.62 (m, 3H), 1.54 (s, 3H, Me), 1.50 (s, 3H, Me), 1.33 (s, 3H, Me), 0.15 (s, 9H, TMS); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 139.8, 139.2, 138.6, 138.2, 128.2, 127.7, 127.3, 124.7, 116.4, 114.9, 111.3, 105.0, 90.7, 82.5, 80.6, 77.4, 77.2, 69.9, 67.8, 67.1, 50.2, 49.7, 31.7, 31.2, 26.6, 26.2, 23.4, 13.6, 1.9. Note that four carbon peaks were submerged with other peaks; HRMS (ESI) (m/z): [M + Na]$^+$ calcd for $C_{33}H_{48}NaO_6Si$, 591.3118; found, 591.3118.

*(3S,6S,8S,E)-8-(Benzyloxy)-1-((3aR,5R,6R,6aR)-6-(but-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2,6-dimethyl-6-(trimethylsilyloxy)deca-1,9-dien-4-yn-3-ol (**18b**).* ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34−7.24 (m, 5H), 5.84−5.74 (m, 3H), 5.48 (d, J = 8.9 Hz, 1H), 5.25−5.19 (m, 2H), 5.03 (dq, J = 17.0, 1.9 Hz, 1H), 4.98−4.95 (m, 1H), 4.76 (d, J = 5.05 Hz, 1H), 4.62−4.60 (m, 1H), 4.54 (d, J = 11.4 Hz, 1H), 4.52−4.48 (m, 1H), 4.36 (d, J = 12.0 Hz, 1H), 4.07 (q, J = 6.3 Hz, 1H), 2.27−2.20 (m, 1H), 2.10 (dd, J = 14.5, 6.3 Hz, 1H), 2.08−2.03 (m, 1H), 1.94−1.90 (m, 1H), 1.81 (s, 3H, Me), 1.72−1.63 (m, 3H), 1.54 (s, 3H, Me), 1.50 (s, 3H, Me), 1.34−1.32 (m, 4H), 0.15 (m, 9H, TMS); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 140.0, 139.2, 138.7, 138.2, 128.2, 127.7, 127.3, 125.5, 125.0, 116.4, 114.9, 111.3, 105.0, 90.7, 82.5, 80.6, 77.5, 77.2, 69.9, 67.8, 67.4, 50.2, 49.7, 31.7, 31.2, 30.3, 29.6, 26.7, 26.3, 23.4, 13.2, 1.9. Note that a carbon peak was submerged with other peaks; HRMS (ESI) (m/z): [M + Na]$^+$ calcd for $C_{33}H_{48}NaO_6Si$, 591.3118; found, 591.3124.

*((3S,5S,8R,E)-3-(Benzyloxy)-10-(3aR,5R,6R,6aR)-6-(but-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-8-methoxy-5,9-dimethyldeca-1,9-dien-6-yn-5-yloxy)trimthylsila-ne (**19**).* NaH (60% in mineral oil, 10 mg, 0.25 mmol, 2.6 equiv) was added to the stirring solution of **18a** (0.055 g, 0.097 mmol, 1.0 equiv) and MeI (15 μL, 0.24 mmol, 2.5 equiv) in dry THF (3 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. Upon completion, the reaction was diluted with ether (15 mL) and quenched with H_2O. The aqueous layer was extracted with ether (2×), and the combined organic fractions were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (gradient 2−5% ethyl acetate/hexane) to obtain methyl ether **19** (0.048 g, 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33−7.24 (m, 5H), 5.82−5.74 (m, 3H), 5.49 (d, J = 8.9 Hz, 1H), 5.24−5.19 (m, 2H), 5.02 (dd, J = 17.1, 1.9 Hz, 1H), 4.96 (d, J = 10.1 Hz, 1H), 4.62−4.60 (m, 1H), 4.55−4.49 (m, 2H), 4.37−4.34 (m, 2H), 4.08 (q, J = 6.4 Hz, 1H), 3.30 (s, 3H, OMe), 2.27−2.21 (m, 1H), 2.10 (dd, J = 14.5, 6.3 Hz, 1H), 2.06−2.02 (m, 1H), 1.93 (dd, J = 14.2, 4.4 Hz, 1H), 1.76 (s, 3H, Me), 1.73−1.65 (m, 2H), 1.54 (s, 3H, Me), 1.52 (s, 3H, Me), 1.34−1.32 (m, 1H), 1.33 (s, 3H, Me), 0.15 (s, 9H, TMS); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 139.1, 138.7, 138.2, 137.74, 128.2, 127.7, 127.2, 126.3, 116.3, 114.9, 111.3, 105.0, 91.5, 80.6, 77.4, 75.8, 69.9, 67.9, 55.5, 50.3, 49.8, 31.7, 31.3, 26.7, 26.3, 23.4, 13.5, 1.8. Note that six carbon peaks were submerged with other peaks; HRMS (ESI) (m/z): [M + Na]$^+$ calcd for $C_{34}H_{50}NaO_6Si$, 605.3274; found, 605.3271.

*(4S,7R)-4-((S)-2-(Benzyloxy)but-3-enyl)-7-((E)-1-((3aR,5R,6-R,6aR)-6-(but-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]-dioxol-5-yl)prop-1-en-2-yl)-9,9-diethyl-2,2,4-trimethyl-3,8-dioxa-2,9-disilaundec-5-yne (**20a**).* To a stirring solution of **18a** or **18b** (0.025 g, 0.044 mmol, 1.0 equiv) and triethyl amine (15 μL, 0.11 mmol, 2.5 equiv) in dry CH_2Cl_2 (3 mL) at 0 °C was added TESOTf (33 μL, 0.11 mmol, 2.5 equiv). The reaction mixture was warmed to room temperature and stirred for 2 h under the inert atmosphere. Upon completion, the reaction was diluted with ether (15 mL) and quenched with H_2O. The aqueous layer was extracted with ether (2×), and the combined organic fractions were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (gradient 2−5% ethyl acetate/hexane) to obtain methyl ether **20a** (82%) or **20b** (87%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34−7.23 (m, 5H), 5.87−5.73 (m, 3H), 5.41 (d, J = 9.5 Hz, 1H), 5.22 (m, 1H), 5.18 (dd, J = 10.1, 1.3 Hz, 1H), 5.02 (dd, J = 17.0, 1.85 Hz, 1H), 4.96 (d, J = 10.1 Hz, 1H), 4.73 (s, 1H), 4.61 (t, J = 3.8 Hz, 1H), 4.53−4.47 (m, 2H), 4.35 (d, J = 11.35 Hz, 1H), 4.08 (dd, J = 12.0, 6.3, Hz, 1H), 2.27−2.21 (m, 1H), 2.06 (dd, J = 14.5, 6.3 Hz, 1H), 2.05−2.01 (m, 1H), 1.93−1.89 (m, 1H), 1.77 (d, J = 1.25 Hz, 3H, Me), 1.69−1.64 (m, 2H), 1.55−1.53 (m, 1H), 1.53 (s, 3H, Me), 1.50 (s, 3H, Me), 1.33 (s, 3H, Me), 0.95 (t, J = 8.15 Hz, 9H, TES), 0.65−0.59 (m, 6H, TES), 0.15 (s, 9H, TMS). HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{39}H_{62}NaO_6Si_2$, 705.3983; found, 705.4005.

*(4S,7S)-4-((S)-2-(Benzyloxy)but-3-enyl)-7-((E)-1-((3aR,5R,6R,6aR)-6-(but-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-prop-1-en-2-yl)-9,9-diethyl-2,2,4-trimethyl-3,8-dioxa-2,9-disilaun-dec-5-yne (**20b**).* ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34−7.25 (m, 5H), 5.84−5.73 (m, 3H), 5.40 (d, J = 8.9 Hz, 1H), 5.23 (m, 1H), 5.18 (dd, J = 10.1, 1.25 Hz, 1H), 5.02 (dd, J = 17.0, 1.9 Hz, 1H), 4.95 (d, J = 9.5 Hz, 1H), 4.74 (s, 1H), 4.60 (t, J = 3.8 Hz, 1H), 4.53 (d, J = 11.9 Hz, 1H), 4.49 (t, J = 9.5 Hz, 1H), 4.36 (d, J = 11.4 Hz, 1H), 4.10 (dd J = 12.0, 6.3 Hz, 1H), 2.25−2.18 (m, 1H), 2.07 (dd J = 13.9, 6.3 Hz, 1H), 2.05−2.01 (m, 1H), 1.92 (dd, J = 14.5, 5.0 Hz, 1H), 1.78 (s, 3H), 1.70−1.65 (m, 2H), 1.54 (s, 3H, Me), 1.49 (s, 3H, Me), 1.35−1.31 (m, 1H), 1.33 (s, 3H, Me), 0.95 (t, J = 8.2 Hz, 9H), 0.67−0.58 (m, 6H, TES), 0.14 (s, 9H, TMS); ^{13}C{^{1}H} NMR ($CDCl_3$,125 MHz): δ 140.8, 139.2, 138.7, 138.2, 128.2, 127.7, 127.2, 123.9, 116.0, 114.9, 111.2, 105.0, 88.9, 83.6, 80.6, 77.6, 77.3, 70.0, 67.9, 67.6, 50.2, 49.9, 31.8, 31.2, 26.6, 26.3, 23.4, 12.9, 6.7, 4.7, 1.8; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{39}H_{62}NaO_6Si_2$, 705.3983; found, 705.4003.

*Macrocyclization by RCM (**22**).* Grubbs II catalyst **24** or **25** (0.015 mmol, 20 mol %) in degassed toluene (10 mL) was added to a refluxing (using oil bath) solution of diene **19** (0.045 g, 0.077 mmol, 1.0 equiv) in degassed toluene (0.1 mM) over 2 h *via* the syringe pump. Upon complete addition, the reaction was refluxed (using oil bath) for a further 30 min followed by distillation of the solvent under reduced pressure. The residue was purified by flash column chromatography to isolate macrocycle **22**[19] (0.002 g, 5%) along with other trace unidentified products and unreacted starting materials (15−25%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34−7.30

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(m, 5H), 5.85 (d, J = 8.85 Hz, 1H), 5.81 (d, J = 5.05 Hz 1H), 5.79 (d, J = 3.75 Hz, 1H), 5.58−5.52 (m, 1H), 4.60−4.54 (m, 4H), 4.50−4.44 (m, 2H), 4.11 (s, br, 1H), 3.27 (s, 3H, OMe), 2.24 (d, J = 2.5 Hz, 1H), 2.24−2.17 (m, 2H), 1.93−1.84 (m, 3H), 1.84 (d, J = 1.25 Hz, 3H, Me), 1.56−5.54 (m, 7H), 1.33 (s, 3H, Me); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 138.8, 137.0, 132.8, 129.0, 128.3, 127.9, 127.6, 127.4, 111.3, 104.9, 93.4, 82.8, 80.9, 77.2, 75.7, 74.1, 70.7, 67.2, 53.9, 47.4, 33.1, 29.5, 26.8, 26.3, 23.2, 15.2, 1.8. Note that five carbon peaks were submerged with other peaks; MS (ESI): 577.2 $[M + Na]^+$; HRMS (ESI) (m/z): $[M + Na]^+$ calcd for $C_{32}H_{46}NaO_6Si$, 577.2961; found, 577.2962.

(6S,8S,E)-8-(Benzyloxy)-1-((3aR,5R,6R,6aR)-6-but-3-en-1-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2,6-dimethyl-6-((trimethylsilyl)oxy)deca-1,9-dien-4-yn-3-one (**21**). To a solution of alkynol **18a**/**b** (0.050 g, 0.088 mmol, 1.0 equiv) in ethyl acetate (5 mL) was added IBX (0.049 g, 0.176 mmol, 2.0 equiv). The reaction mixture was refluxed (using oil bath) for 5 h, then cooled to room temperature, and filtered through a medium glass frit. The filter cake was washed with ethyl acetate, the combined filtrate was concentrated, and the resulting residue was purified by flash chromatography (2−10% ethyl acetate/hexane) to afford compound **21** (0.041 g, 82%) as colorless oil. R_f = 0.65 (25% ethyl acetate/hexane); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33−7.32 (m, 5H), 6.84 (d, J = 8.2 Hz, 1H), 5.84 (d, J = 3.2 Hz, 1H), 5.81−5.76 (m, 3H), 5.28−5.22 (m, 3H), 5.05−4.98 (m, 3H), 4.69−4.65 (m, 2H), 4.56 (d, J = 12.0 Hz, 1H), 4.36 (d, J = 11.4 Hz, 1H), 4.11−4.09 (m, 1H), 2.20−2.17 (m, 2H), 2.09−2.00 (m, 2H), 1.86 (s, 3H), 1.59 (s, 3H), 1.55 (s, 3H), 1.35 (s, 3H), 0.18 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 179.5, 144.9, 140.2, 138.7, 138.5, 137.8, 128.3, 127.8, 127.4, 117.1, 115.2, 111.8, 105.4, 96.9, 81.2, 80.6, 77.8, 77.3, 70.0, 68.0, 50.0, 49.7, 31.9, 31.7, 31.6, 30.7, 29.7, 29.3, 26.7, 26.3, 23.4, 11.6, 1.8; HRMS (ESI) (m/z): $[M + Na]^+$ calcd for $C_{33}H_{46}NaO_6Si$, 589.2956; found, 589.2979.

(2R,4S,6S)-4-Ethynyl-2-phenyl-6-vinyl-1,3-dioxane (**27h**). To a stirring solution of benzyl ether **16h** (0.35 g, 1.62 mmol, 1.0 equiv) in dry DCM (15 mL) was added DDQ (0.40 g, 1.78 mmol, 1.1 equiv), and the reaction mixture was held at room temperature for 3 h. The reaction solution was filtered through a celite pad, diluted with DCM (25 mL), and washed with saturated $NaHCO_3$. The aqueous layer was extracted with DCM (2×), and the combined organic fractions were washed with brine (25 mL), dried over anhydrous Na_2SO_4, and removed the solvent under reduced pressure. The orange-red residue was purified by flash column chromatography (gradient 2−5% diethyl ether/hexane) to furnish benzylidene acetal **27h** as colorless oil (0.28 g, 81%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.51−7.50 (m, 2H), 7.38−7.34 (m, 3H), 6.14 (s, 1H), 5.99−5.88 (m, 1H), 5.41−5.35 (m, 1H), 5.24−5.19 (m, 1H), 5.07−5.05 (m, 1H), 4.78−4.74 (m, 1H), 2.67 (s, 1H), 2.19−2.09 (m, 1H), 1.80−1.74 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ; 138.1, 137.2, 128.8, 128.2, 126.7, 126.2, 116.0, 95.8, 80.8, 76.5, 73.5, 64.1, 35.3. Note that an aromatic carbon was submerged with other peaks; HRMS (ESI) (m/z): $[M + Na]^+$ calcd for $C_{14}H_{14}NaO_2$, 237.0891; found, 237.0885.

(E)-1-((3aR,5R,6R,6aR)-6-(But-3-en-1-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-methyl-5-((2R,4S,6S)-2-phenyl-6-vinyl-1,3-dioxan-4-yl)pent-1-en-4-yn-3-one (**31**). To a solution of alkynol **28h** (0.15 g, 0.31 mmol, 1.0 equiv) in ethyl acetate (10 mL) was added IBX (0.18 g, 0.62 mmol, 2.0 equiv). After the resulting mixture was refluxed (using oil bath) for 4 h, the reaction was cooled to room temperature and filtered through a medium glass frit. The filter cake was washed with ethyl acetate, the combined filtrates were concentrated, and the resulting residue was purified by flash chromatography (2−10% ethyl acetate/hexane) to afford compound alkynone **31** as colorless oil (0.056 g) in 95% yield. R_f = 0.56 (20% ethyl acetate/hexane); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.52−7.50 (m, 2H), 7.38−7.35 (m, 3H), 6.97 (d, J = 8.9 Hz, 1H), 6.10 (s, 1H), 5.94−5.88 (m, 1H), 5.81−5.75 (m, 1H), 5.82 (d, J = 3.2 Hz, 1H), 5.38 (d, J = 17.7 Hz, 1H), 5.23−5.21 (m, 2H), 5.05−4.96 (m, 2H), 4.73−4.64 (m, 3H), 2.24−2.21 (m, 2H), 2.08−2.01 (m, 1H), 1.90 (s, 3H), 1.88−1.86 (m, 2H), 1.77−1.70 (m, 2H), 1.56 (s, 3H), 1.36 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 179.1, 145.8, 140.2, 137.7, 137.7, 136.7, 129.1, 128.2, 126.3, 116.5, 115.3, 111.9, 105.4, 96.9, 89.8, 84.6, 80.6, 77.7, 76.7, 74.0, 64.3, 50.0, 34.6, 31.6, 26.7, 26.2, 23.4, 11.6; HRMS (m/z): $[M + Na]^+$ calcd for $C_{29}H_{34}O_6Na$, 501.2248; found, 501.2234.

(2S,4S,6S)-4-Ethynyl-4-methyl-2-phenyl-6-vinyl-1,3-dioxane (**27**). To a stirring solution of benzyl ether **16** (0.070 g, 0.3 mmol, 1.0 equiv) in dry DCM (5 mL) was added DDQ (0.076 g, 0.33 mmol, 1.1 equiv), and the reaction mixture was held at room temperature for 3 h. The reaction solution was filtered through a celite pad, diluted with DCM (10 mL), and washed with saturated $NaHCO_3$. The aqueous layer was extracted with DCM (2×), and the combined organic fractions were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and removed the solvent under reduced pressure. The orange-red residue was purified by flash column chromatography (gradient 2−5% diethyl ether/hexane) to furnish benzylidene acetal **27** as colorless oil (0.060 g, 86%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.55−7.37 (m, 2H, Ph), 7.35−7.31 (m, 3H, Ph), 6.06 (s, 1H), 5.96−5.89 (m, 1H), 5.39−5.35 (m, 1H), 5.21−5.18 (m, 1H), 4.68−4.64 (m, 1H), 2.64 (s, 1H), 1.86 (dd, J = 2.6, 13.25 Hz, 1H), 1.74 (dd, J = 12.6, 11.4 Hz, 1H), 1.62 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 138.3, 137.3, 128.7, 128.1, 126.3, 115.8, 96.8, 83.9, 74.9, 74.4, 70.1, 42.4, 29.7.; HRMS (ESI) (m/z): $[M + Na]^+$ calcd for $C_{15}H_{16}NaO_2$, 251.1048; found, 251.1039.

(E)-1-((3aR,5R,6R,6aR)-6-(But-3-en-1-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-methyl-5-((2R,4S,6S)-4-methyl-2-phenyl-6-vinyl-1,3-dioxan-4-yl)pent-1-en-4-yn-3-one (**29**). To a solution of alkyne **27** (0.100 g, 0.44 mmol, 1.7 equiv) in dry THF (2 mL) was added n-BuLi (0.25 mL, 0.39 mmol, 1.6 M in hexane, 1.5 equiv) at −78 °C. The reaction mixture was warmed to room temperature and allowed to react for 30 min. After recooling the reaction to −78 °C, a solution of aldehyde **10** (70 mg, 0.26 mmol, 1.0 equiv) in dry THF (2 mL) was added. The resulting solution was warmed to room temperature over 2 h and quenched with saturated NH_4Cl solution after completion. The aqueous solution was extracted with CH_2Cl_2, and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (15−20% ethyl acetate/hexane) to afford the product **28** as a mixture of diastereomers, 104 mg in 80% yield. R_f = 0.27 (25% ethyl acetate/hexane); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.54−7.51 (m, 2H), 7.36−7.34 (m, 3H), 6.01 (s, 1H), 5.98−5.72 (m, 3H), 5.62−5.58 (m, 1H), 5.39−5.32 (m, 1H), 5.19 (d, J = 17.5 Hz, 1H), 5.02−4.96 (m, 2H), 4.88 (d, J = 9.4 Hz, 1H), 4.62−4.53 (m, 3H), 5.19 (d, J = 17.5 Hz, 1H), 2.25−1.98 (m, 4H), 1.88 (s, 3H), 1.77−1.74 (m, 3H), 1.69 (s, 3H), 1.60 (s, 3H), 1.34 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 139.9, 138.3, 138.1, 137.2, 128.7, 128.1, 126.3, 125.4, 125.2, 115.8, 115.0, 111.4, 104.9, 96.8, 86.2, 85.6, 80.7, 74.5, 70.3, 67.3, 67.2, 49.7, 42.4, 31.7, 31.6, 29.7, 26.7, 26.2, 23.5, 13.5; HRMS (ESI) (m/z): $[M + Na]^+$ calcd for $C_{30}H_{38}NaO_6$, 517.2561; found, 517.2557; To a solution of alkynol **28** (0.060 g, 0.12 mmol, 1.0 equiv) in ethyl acetate (5 ml) was added IBX (0.067 g, 0.24 mmol, 2.0 equiv). After the resulting mixture was refluxed (using oil bath) for 4 h, the reaction was cooled to room temperature and filtered through a medium glass frit. The filter cake was washed with ethyl acetate, the combined filtrates were concentrated, and the resulting residue was purified by flash chromatography (2−10% ethyl acetate/hexane) to afford compound alkynone **29** as colorless oil (0.056 g) in 95% yield. R_f = 0.58 (20% ethyl acetate/hexane); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.58−7.55 (m, 2H), 7.49−4.47 (m, 3H), 6.95 (d, J = 1.3, 1H), 6.03 (s, 1H), 5.93−5.87 (m, 1H), 5.80 (d, J = 3.2 Hz, 1H), 5.79−5.73 (m, 1H), 5.37 (d, J = 17.7 Hz, 1H), 5.21 (d, J = 9.5 Hz, 1H), 5.04−4.99 (m, 2H), 4.70 (t, J = 8.8 Hz, 1H), 4.65−4.63 (m, 1H), 4.60−4.57 (m, 1H), 2.23−2.21 (m, 1H), 2.09−2.02 (m, 1H), 1.97 (dd, J = 13.2, 1.9 Hz, 1H), 1.91 (s, 3H), 1.89−1.78 (m, 4H), 1.68 (s, 3H), 1.56 (s, 3H), 1.36 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 179.3, 145.6, 140.2, 137.8, 137.7, 136.7, 129.0, 128.2, 126.4, 116.3, 115.3, 111.9, 105.4, 97.7, 92.7, 83.3, 80.6, 77.7, 74.7, 70.5, 49.9, 41.8, 31.5, 29.0, 26.7, 26.2, 23.6, 11.6; HRMS (ESI) (m/z): $[M + Na]^+$ calcd for $C_{30}H_{36}NaO_6$, 515.2404; found, 515.2390.

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*Macrocyclization by RCM (**30**).* To a solution of **29** (20 mg, 0.041 mmol, 1.0 equiv) in degassed CH_2Cl_2 (80 mL) was added a solution of Grubbs I catalyst **23** (6 mg, 0.008 mmol, 20 mol %) in 2.0 mL of degassed CH_2Cl_2, and the reaction was placed under reflux for 12 h using oil bath. After cooling the reaction to room temperature, column filtration of the reaction mixture removed most ruthenium impurity and the resulting filtrate was concentrated and purified by flash chromatography (2−10% ethyl acetate/hexane) to afford compound **30** as colorless oil (15 mg) in 79% yield. R_f = 0.42 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.51−7.48 (m, 2H), 7.36−7.32 (m, 3H), 6.92 (d, J = 8.2 Hz, 1H), 5.98 (s, 1H), 5.82 (d, J = 3.8, 1H), 5.68−5.66 (m, 1H), 5.56−5.54 (m, 1H), 5.11 (t, J = 9.5, 1H), 4.72−4.68 (m, 1H), 4.63−4.61 (m, 1H), 2.38−2.35 (m, 1H), 2.23−2.20 (m, 1H), 2.03 (s, 3H), 1.90−1.81 (m, 5H), 1.65 (s, 3H), 1.56 (s, 3H), 1.35 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 179.1, 144.0, 143.7, 137.6, 134.2, 129.3, 129.0, 128.2, 126.3, 111.8, 104.6, 98.1, 93.3, 84.9, 83.8, 78.0, 71.1, 47.9, 44.0, 34.6, 31.5, 27.4, 26.7, 26.1, 24.9, 22.6, 14.0, 11.3; HRMS (ESI) (m/z): [M + Na]$^+$ calcd for $C_{28}H_{32}NaO_6$, 487.2091; found, 487.2083.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02984.

Experimental procedures, compound characterization, and NMR spectra, including the characterization of **30** and DFT macrocyclization studies with associated data (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated in memory of Professor Christopher Abell.

■ REFERENCES

(1) Reviews on olefin metathesis: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. Ring-Closing Metathesis and Related Processes in Organic Synthesis. *Acc. Chem. Res.* **1995**, *28*, 446−452. (b) Fürstner, A. Olefin Metathesis and Beyond. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (c) Hoveyda, A. H.; Zhugralin, A. R. The remarkable metal-catalysed olefin metathesis reaction. *Nature* **2007**, *450*, 243−251. (d) Kress, S.; Blechert, S. Asymmetric catalysts for stereocontrolled olefin metathesis reactions. *Chem. Soc. Rev.* **2012**, *41*, 4389−4408. (e) Ogba, O. M.; Warner, N. C.; O'Leary, D. J.; Grubbs, R. H. Recent advances in ruthenium-based olefin metathesis. *Chem. Soc. Rev.* **2018**, *47*, 4510−4544.

(2) Olefin metathesis in total synthesis: (a) de Weghe, P.; Eustache, J. The application of olefin metathesis to the synthesis of biologically active macrocyclic agents. *Curr. Top. Med. Chem.* **2005**, *5*, 1495−1519. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Metathesis Reactions in Total Synthesis. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490−4527. (c) Gradillas, A.; Pérez-Castells, J. Macrocyclization by Ring-Closing Metathesis in the Total Synthesis of Natural Products: Reaction Conditions and Limitations. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086−6101. (d) Fürstner, A. Metathesis in total synthesis. *Chem. Commun.* **2011**, *47*, 6505−6511. (e) Lei, X.; Li, H. Selective alkene metathesis in the total synthesis of complex natural product. *Top. Curr. Chem.* **2012**, *327*, 163−196.

(3) (a) Kim, S. H.; Figueroa, I.; Fuchs, P. L. Application of the grubbs ring-closing metathesis for the construction of a macrocyclic ansa-bridge. Synthesis of the tricyclic core of roseophilin. *Tetrahedron Lett.* **1997**, *38*, 2601−2604. (b) Fürstner, A.; Gastner, T.; Weintritt, H. A Second Generation Synthesis of Roseophilin and Chromophore Analogues. *J. Org. Chem.* **1999**, *64*, 2361−2366. (c) Bamford, S. J.; Luker, T.; Speckamp, W. N.; Hiemstra, H. Enantioselective Formal Total Synthesis of Roseophilin. *Org. Lett.* **2000**, *2*, 1157−1160.

(4) Lu, K.; Huang, M.; Xiang, Z.; Liu, Y.; Chen, J.; Yang, Z. Development of a Concise and Diversity-Oriented Approach for the Synthesis of Plecomacrolides via the Diene-Ene RCM. *Org. Lett.* **2006**, *8*, 1193−1196.

(5) Selected reports on stereoselective issues in olefin metathesis to macrocycles: (a) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. Synthesis of macrocyclic natural products by catalyst-controlled stereoselective ring-closing metathesis. *Nature* **2011**, *479*, 88−93. (b) Wang, Y.; Jimenez, M.; Sheehan, P.; Zhong, C.; Hung, A. W.; Tam, C. P.; Young, D. W. Selective Access to Trisubstituted Macrocyclic E- and Z-Alkenes from the Ring-Closing Metathesis of Vinylsiloxanes. *Org. Lett.* **2013**, *15*, 1218−1221.

(6) Marrero, J.; Rodríguez, A. D.; Baran, P.; Raptis, R. G.; Sánchez, J. A.; Ortega-Barria, E.; Capson, T. L. Bielschowskysin, a Gorgonian-Derived Biologically Active Diterpene with an Unprecedented Carbon Skeleton. *Org. Lett.* **2004**, *6*, 1661−1664.

(7) Ring closing metathesis strategies to cembranolides: (a) Donohoe, T. J.; Ironmonger, A.; Kershaw, N. M. Synthesis of (-)-(Z)-deoxypukalide. *Angew. Chem., Int. Ed.* **2008**, *47*, 7314−7316. (b) Takamura, H.; Iwamoto, K.; Nakao, E.; Kadota, I. Total Synthesis of Two Possible Diastereomers of (+)-Sarcophytonolide C and Its Structural Elucidation. *Org. Lett.* **2013**, *15*, 1108−1111.

(8) Alternative synthetic studies to cembranoid natural products: (a) Marshall, J. A.; Van Devender, E. A. Synthesis of (−)-Deoxypukalide, the Enantiomer of a Degradation Product of the Furanocembranolide Pukalide. *J. Org. Chem.* **2001**, *66*, 8037−8041. (b) Wipf, P.; Soth, M. J. Synthesis of the C(1)−C(18) Segment of Lophotoxin and Pukalide. Control of 2-Alkenylfuran (E/Z)-Configuration. *Org. Lett.* **2002**, *4*, 1787−1790. (c) Tsubuki, M.;

Takahashi, K.; Sakata, K.; Honda, T. Studies toward the Synthesis of Furanocembrane Bipinnatin J: Synthesis of a 2,3,5-Trisubstituted Furfuryl Ether Intermediate. *Heterocycles* **2005**, *65*, 531−540. (d) Cases, M.; Gonzalez-Lopez de Turiso, F.; Hadjisoteriou, M. S.; Pattenden, G. Synthetic studies towards furanocembrane diterpenes. A total synthesis of bis-deoxylophotoxin. *Org. Biomol. Chem.* **2005**, *3*, 2786−2804. (e) Roethle, P. A.; Hernandez, P. T.; Trauner, D. Exploring Biosynthetic Relationships among Furanocembranoids: Synthesis of (−)-Bipinnatin J, (+)-Intricarene, (+)-Rubifolide, and (+)-Isoepilophodione B. *Org. Lett.* **2006**, *8*, 5901−5904. (f) Huang, Q.; Rawal, V. H. Total Synthesis of (±)-Bipinnatin. *J. Org. Lett.* **2006**, *8*, 543−545. (g) Tang, B.; Bray, C. D.; Pattenden, G. Total synthesis of (+)-intricarene using a biogenetically patterned pathway from (−)-bipinnatin J, involving a novel transannular [5+2] (1,3-dipolar) cycloaddition. *Org. Biomol. Chem.* **2009**, *7*, 4448−4457. (h) Tang, B.; Bray, C. D.; Pattenden, G.; Rogers, J. Total synthesis of (ρ)-Z-deoxypukalide, a furanobutenolide-based cembranoid isolated from the pacific octocoral Leptogorgia spp. *Tetrahedron* **2010**, *66*, 2492−2500.

(9) Synthetic studies of bielschowskysin (**1**): (a) Doroh, B.; Sulikowski, G. A. Progress toward the Total Synthesis of Bielschowskysin: A Stereoselective [2 + 2] Photocycloaddition. *Org. Lett.* **2006**, *8*, 903−906. (b) Miao, R.; Gramani, S. G.; Lear, M. J. Stereocontrolled entry to the tricyclo[3.3.0]oxoheptane core of bielschowskysin by a [2+2] cycloaddition of an allene-butenolide. *Tetrahedron Lett.* **2009**, *50*, 1731−1733. (c) Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. An Expedient Synthesis of a Functionalized Core Structure of Bielschowskysin. *Angew. Chem., Int. Ed.* **2011**, *50*, 5149−5152. (d) Farcet, J.-B.; Himmelbauer, M.; Mulzer, J. A Non-Photochemical Approach to the Bicyclo[3.2.0]heptane Core of Bielschowskysin. *Org. Lett.* **2012**, *14*, 2195−2197. (e) Meyer, M. E.; Phillips, J. H.; Ferreira, E. M.; Stoltz, B. M. Use of a palladium(II)-catalyzed oxidative kinetic resolution in synthetic efforts toward bielschowskysin. *Tetrahedron* **2013**, *69*, 7627−7635. (f) Himmelbauer, M.; Farcet, J.-B.; Gagnepain, J.; Mulzer, J. Palladium-Catalyzed Carbo-oxygenation: The Bielschowskysin Case. *Org. Lett.* **2013**, *15*, 3098−3101. (g) Yang, E. G.; Sekar, K.; Lear, M. J. A macrolactonisation approach to the cembrane carbocycle of bielschowskysin. *Tetrahedron Lett.* **2013**, *54*, 4406−4408. (h) Jana, A.; Mondal, S.; Ghosh, S. Studies towards the synthesis of bielschowskysin. Construction of the highly functionalized bicyclo[3.2.0]heptane segment. *Org. Biomol. Chem.* **2015**, *13*, 1846−1859. (i) Scesa, P.; Wangpaichitr, M.; Savaraj, N.; West, L.; Roche, S. P. A Kinetic Dearomatization Strategy for an Expedient Biomimetic Route to the Bielschowskysin Skeleton. *Angew. Chem., Int. Ed.* **2018**, *57*, 1316−1321. (j) Nesic, M.; Kincanon, M. M.; Ryffel, D. B.; Sarlah, D. A new approach towards the synthesis of bielschowskysin: Synthesis and photochemistry of an advanced macrocyclic enedione intermediate. *Tetrahedron* **2020**, *76*, 131318. and references therein.

(10) Diederich, F.; de Meijer, A. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: New York, 2004.

(11) Cahiez, G.; Duplais, C.; Moyeux, A. Iron-Catalyzed Alkylation of Alkenyl Grignard Reagents. *Org. Lett.* **2007**, *9*, 3253−3254.

(12) Formation of the alkene via this coupling method was exclusive on small scale reaction, however, larger scales gave side-products due to competing β-hydride elimination-disproportionation processes along with the intended cross-coupling.

(13) Georges, M.; Fraser-Reid, B. Controlled Access to Furanose Precursors Related to Sesquiterpene Lactones. *J. Org. Chem.* **1985**, *50*, 5754−5758.

(14) Tsuri, T.; Kamata, S. An Efficient and Stereocontrolled Synthesis of Platelet Activating Factor from (S)-(-)-Malic Acid. *Tetrahedron Lett.* **1985**, *26*, 5195−5198.

(15) Takai-Nozaki olefination: (a) Okazoe, T.; Hibino, J.-I.; Takai, K.; Nozaki, H. Chemoselective Methylenation with a Methylene dianion Synthon. *Tetrahedron Lett.* **1985**, *26*, 5581−5584. (b) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. A Novel Catalytic Effect of Lead on the Reduction of a Zinc Carbenoid with Zinc Metal Leading to a Geminal Dizinc Compound. Acceleration of the Wittig-Type Olefination with the $RCHX_2$-$TiCl_4$-Zn Systems by Addition of Lead. *J. Org. Chem.* **1994**, *59*, 2668−2670.

(16) Ito, M.; Kibayashi, C. Chiral Preparation of (R)- and (S)-3-(Benzyloxy)-4,4-dimethyl-1-pentene. *Synthesis* **1993**, 137−140.

(17) Syn & anti relationships were established by DDQ mediated benzylidene formation and comparing to that of authentic samples.

(18) For the synthesis of sterically nondemanding disubstituted alkene via RCM, Grubbs I catalyst is preferred to its second generation catalyst due to its higher selectivity and stability Va, P.; Roush, W. R. Total Synthesis of Amphidinolide E. *J. Am. Chem. Soc.* **2006**, *128*, 15960−15961.

(19) The macrocycles **22** and **30** were confirmed by ^{1}H-, ^{13}C-NMR and LC-MS; the *Z* configuration of the double bond was confirmed by 2D NOESY analysis and was anticipated for **19** on the basis of *ab initio* studies at the B3LYP/6-31G(d) DFT level (see Supporting Information).

(20) Wang, K.-P.; Yun, S. Y.; Lee, D.; Wink, D. J. Structure and Reactivity of Alkyne-Chelated Ruthenium Alkylidene Complexes. *J. Am. Chem. Soc.* **2009**, *131*, 15114−15115.

(21) For examples of unproductive ruthenium chelate complexes see: (a) Fürstner, A.; Langemann, K. Total Syntheses of (+)-Ricinelaidic Acid Lactone and of (-)-Gloeosporone Based on Transition-Metal-Catalyzed C-C Bond Formations. *J. Am. Chem. Soc.* **1997**, *119*, 9130−9136. (b) Lin, Y. A.; Chalker, J. M.; Davis, B. G. Olefin Metathesis for Site-Selective Protein Modification. *ChemBioChem* **2009**, *10*, 959−969.

(22) Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. Rate Enhanced Olefin Cross-Metathesis Reactions: The Copper Iodide Effect. *J. Org. Chem.* **2011**, *76*, 4697−4702.

(23) Evans, P. A.; Cui, J.; Gharpure, S. J.; PolosukhinZhang, A. H. Enantioselective Total Synthesis of the Potent Antitumor Agent (-)-Mucocin Using a Temporary Silicon-Tethered Ring-Closing Metathesis Cross-Coupling Reaction. *J. Am. Chem. Soc.* **2003**, *125*, 14702−14703.

(24) Yang, Q.; Xiao, W.; Yu, Z. Lewis Acid Assisted Ring-Closing Metathesis of Chiral Diallylamines: An Efficient Approach to Enantiopure Pyrrolidine Derivatives. *Org. Lett.* **2005**, *7*, 871−874.

(25) Craig, R. A., II; Stoltz, B. M. Polycyclic Furanobutenolide-Derived Cembranoid and Norcembranoid Natural Products: Biosynthetic Connections and Synthetic Efforts. *Chem. Rev.* **2017**, *117*, 7878−7909.

https://doi.org/10.1021/acs.joc.0c02984
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