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

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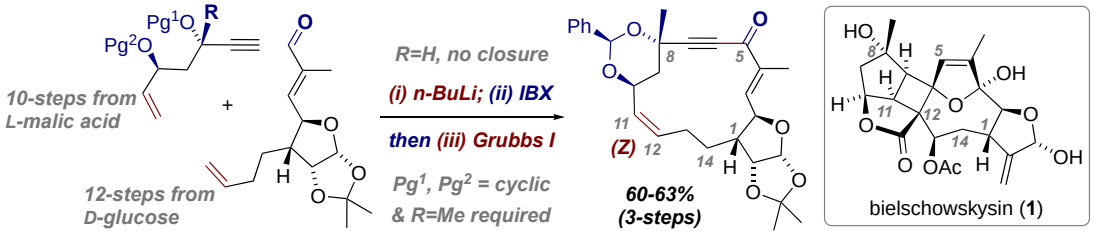
Dedicated in memory of Professor Christopher Abell

Supporting Information Placeholder



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 centre.

▪ 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 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 framework.[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 and 1b, 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 non-photochemical 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 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 group used biomimetic approach to report the hemisynthesis of bielschowskyane skeleton.[9i] Recently, Sarlah group explored the stepwise cyclobutane formation from 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] photo cycloaddition 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 bielschowskysin carbon skeleton, we decided to use naturally occurring chiral compounds as starting materials. Alcohol **3** was synthesized as previously reported[9g]

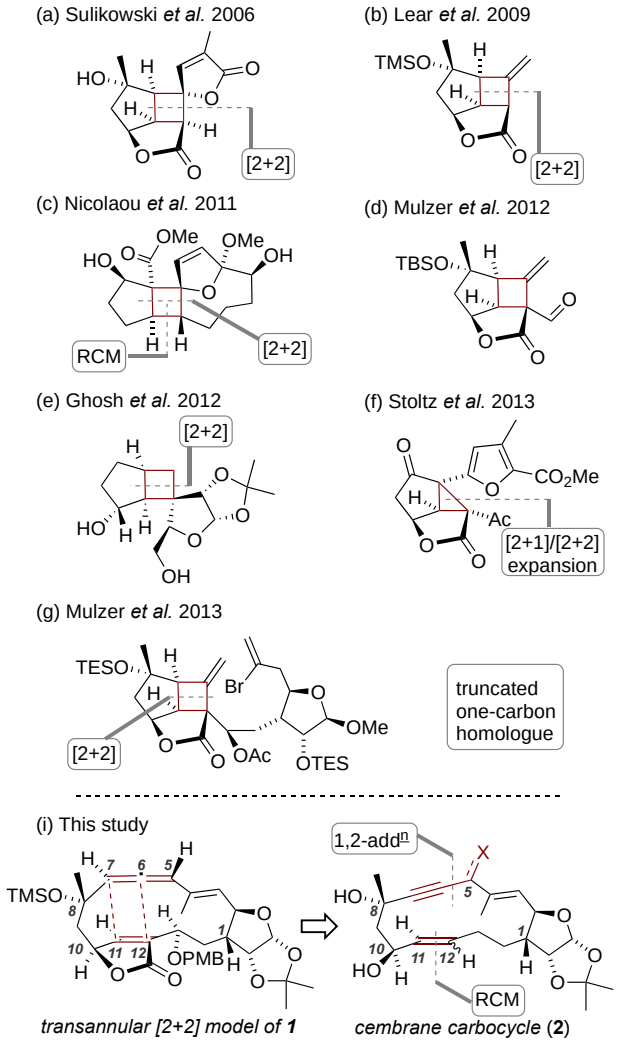
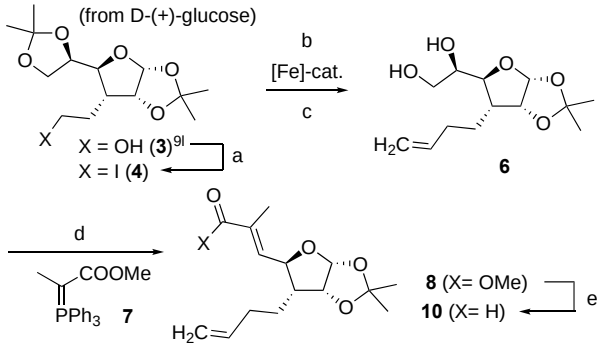


Figure 1. Key model studies of bielschowskysin **1**, proposed [2+2]-transannular model and cembrane carbocycle target **2**.

Scheme 1. Synthesis of aldehyde 10



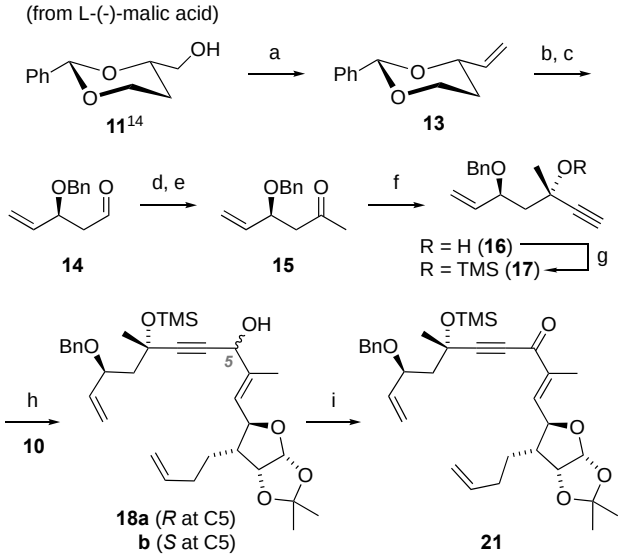
Reagents & Conditions: (a) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C to rt, 94 %. (b) Fe(acac)$_3$ (20 mol%), H_2C=CHMgBr, HMTA, TMEDA, THF, –20 °C to 0 °C, 1 h, 69 %. (c) 60 % AcOH in H_2O, rt, 12 h, 70 %. (d) i. $NaIO_4$, H_2O, MeOH, rt, 15 min.; ii. **7**, CH_2Cl_2, rt, 12 h, 70 %, over 2 steps. (e) i.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

(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 *sp3-sp2* cross coupling method using 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 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 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 favouring 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.

Scheme 2. Synthesis of first-generation RCM precursors

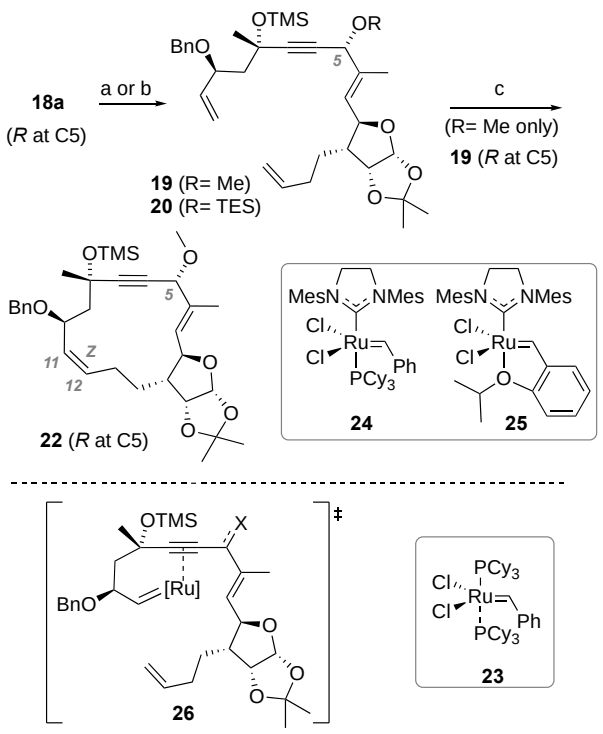


Reagents & Conditions: (a) i. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C; ii. Zn, CH_2I_2, $PbCl_2$, Ti(*i*-PrO)$_4$, CH_2Cl_2, 0 °C to rt, 61 % (2 steps). (b) DIBAL–H, CH_2Cl_2, 0 °C, 90 %. (c) DMP, CH_2Cl_2, 2 h, 86 % (d) MeMgBr, ether, 2 h, –78 °C. (e) PCC, CH_2Cl_2, 95 % (2 steps). (f) HC≡CMgBr, ether, –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 %.

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, starting material was recovered. Treatment of ketone **21** with Grubbs I catalyst

(**23**)[18] also only provided the recovered starting material. However, treatment of

Scheme 3. First generation RCM study with unproductive cyclization precursors



Reagents & 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 %.

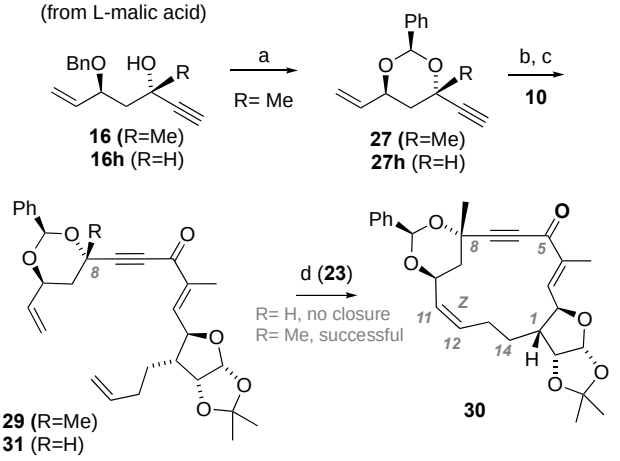
the methyl ether **19** with either Grubbs II or Hoveyda-Grubbs II in refluxing toluene brought about ring closure to **22** in 5 % isolated yield (Scheme 3). NOESY correlation analysis of the macrocycle **22** showed that the newly formed C11-C12 double bond is Z configured.[19]

The inactivity of RCM substrates **20** (OTES at C5) and **21** (carbonyl at C5) towards metathesis and low yield, in the case of **19** (MeO 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 oxidation of the resulting secondary alcohol gave the ynone **29** (R = Me) as the RCM substrate for study.

Confirming our hypothesis above, as supported by DFT calculations,[19] treatment of this ring-constrained substrate **29** with 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 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 starting material was recovered. In this case, the addition of CuI as additive still afforded no reaction, and using $Ti(OiPr)_4$[24] led to partial decomposition of the starting material.

Scheme 4. Successful RCM to cembrane carbocycle



Reagents & Conditions: (a) DDQ, CH_2Cl_2, rt, 3 h, yield for 27-86 %; for 27h-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).

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 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, providencin).[25]

▪ EXPERIMENTAL SECTION

General information: All reactions were performed in oven-dried glassware under 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 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 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) spectrometer at ambient atmosphere.

General techniques & methods: All non-aqueous reactions were performed in flame dried glassware under 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), tetrahydrofuran (THF) was distilled from sodium/benzophenone. All commercially available compounds were used as received without further purification. 4Å molecular sieves were activated by heating at 120-140 °C under high vacuum for 4h before storing in a dry desiccator. The reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm 2E Merck silica gel plates (60F-254) under 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 spectra were recorded on Bruker ACF (300 MHz) and Bruker AMX500 (500 MHz) NMR spectrometer at ambient atmosphere. 2D NMR was performed on 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, br=broad. ^1H NMR coupling constants (*J*) are reported in Hertz (Hz), Mass spectra were obtained on Finnigan MAT95XL-T and Micromass VG7035 double focusing mass spectrometer. High resolution ESI mass spectra were obtained on a Shimadzu LCMS-IT-TOF spectrometer. Infrared spectra were recorded on 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 N_2 atmosphere. The contents were cooled using ice-bath, then iodine (3.17 g, 24.97 mmol, 1.2 equiv) as solid was added in one portion and slowly warmed to room temperature over 10-15 min. Alcohol **3**[9l] (6 g, 20.81 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added and the reaction mixture was stirred for one hour at room temperature for the completion of reaction. The reaction volume was reduced approximately to 50 mL using rotary evaporator. Diethyl ether was added to precipitate triphenylphosphine oxide, the precipitate was filtered, and the solvent 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. ^1H 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); $^{13}C\{1H\}$ 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): $[M+Na]^+$ Calculated 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-dioxolan-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 (2x) and flushed with argon gas. Freshly pre-dried $Fe(acac)_3$ (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, the contents dissolved by addition of anhydrous THF (10 mL) and cooled to –20 °C. Vinylmagnesium bromide (1M 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 syringe pump (10 mL/h).[11,12] After completion of the addition, the reaction mixture was stirred for additional one hour at 0 °C, diluted with diethyl ether, quenched by slow addition of 1M HCl. The aqueous layer was extracted with diethyl ether, then combined organic fractions washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to a give crude product. The crude was passed through 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 hr. 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. ^1H 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, 3.8Hz, 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); $^{13}C\{1H\}$ 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): $[M+Na]^+$ Calculated 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-methylacry late (**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) 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 fritted sintered funnel and the solid washed several times with MeOH and CH_2Cl_2. The filtrate was diluted with CH_2Cl_2, washed with brine and again the aqueous layer extracted with CH_2Cl_2 (3x). The combined dichloromethane was dried over anhydrous Na_2SO_4 and the solvent reduced approximately to 50% volume using rotary evaporator to afford the crude aldehyde in CH_2Cl_2 solution. Ylide **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 allowed to stir at room temperature for 12 hrs. The solvent was removed under reduced pressure and the residue purified by flash column chromatography (gradient 10-15% ethyl acetate/hexane) to isolate **8** (0.25 g, 70 %) as a syrup. ^1H 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); $^{13}C\{1H\}$ 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): $[M+Na]^+$ Calculated 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-methylacrylaldhyde (**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, 1M in cyclohexane) was added over 10 min. The reaction contents were allowed to warm to room temperature in the dry ice bath over 4 hrs. The reaction was quenched by addition of saturated aqueous Rochelle salt (sodium potassium tartrate) drop wise (6 mL) and stirred vigorously for 30 min at room temperature, during which the gray cloud appeared in water layer. The solution was diluted with ether, the aqueous layer was extracted with ether (3x) and the combined organic fractions 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{1H} 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 Dess-Martin periodinane (DMP) reagent (1.0 g, 2.38 mmol, 1.5 equiv) at room temperature and the reaction allowed to continue for two hours 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{1H} NMR ($CDCl_3$, 125 MHz): δ 194.6, 149.0, 141.1, 137.7, 115.2, 111.8, 105.4, 80.5, 77.3, 49.9, 31.6, 26.6, 26.2, 23.4, 10.1. HRMS (ESI) (m/z): $[M+Na]^+$ Calculated for $C_{15}H_{22}NaO_4$ 289.1416; Found, 289.1407.

*(2S,4S)-2-phenyl-4-vinyl-1,3-dioxane (**13**):* To the stirring dry CH_2Cl_2 (10 mL) was added oxalyl chloride (2.1 mL, 24.8 mmol, 1.6 equiv) under argon atmosphere and cooled to –78 °C using dry ice bath. Anhydrous DMSO (3.3 mL, 46.0 mmol, 3.0 equiv) was added drop wise to the above solution. The stirring was continued for 20 min then **11**[14] (3.0 g, 15.4 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) added. The reaction was allowed to proceed for 30 min at –78 °C, triethyl amine (10.0 mL, 72.0 mmol, 4.7 equiv) added dropwise at –78 °C and the resulting cloudy solution stirred for additional 15 min after which quenched by 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 (3x) 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 eq uiv) in THF (40 mL) for 15 min with constant stirring under argon. The reaction become 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 stirred at room temperature after effervescence ceases. After one hour, Ti(*i*-OPr)$_4$ (4.4 mL, 15.2 mmol, 1.0 equiv) was added, allowed to sir for 30 min at room temperature and the crude 2-phenyl-1,3-dioxane-4-carbaldehyde **12** in THF (6 mL) added to the greenish reaction solution. The reaction was continued overnight, diluted with ether, quenched by addition of 1M HCl (50 mL). The layers were separated, the aqueous layer extracted with ether (2x30 mL) and the combined organic fractions 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{1H} 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): $[M+Na]^+$ Calculated for $C_{12}H_{14}NaO_2$ 213.0891; Found, 213.0886.

*(S)-3-(benzyloxy)pent-4-enal (**14**):* DIBAL-H (25 mL, 1M in cyclohexane, 25 mmol, 1.5 equiv) was added slowly drop wise[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 five hrs. Upon completion, the reaction was quenched by slow addition of 1M HCl solution, after 15min of stirring cloudy clumps disappeared from the organic phase. The aqueous phase was extracted with ether (2x) 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{1H} 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*): $[M+Na]^+$ Calculated 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) aet room temperature and the reaction was continued for two hours at room temperature. The reaction contents were filtered through a celite pad, washed with CH_2Cl_2, concentrated on a rotary evaporator and the residue 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{1H} 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*): $[M+Na]^+$ Calculated 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, 3M in Et_2O, 6 mmol, 2.1 equiv). After two hours of stirring the reaction mixture at –78 °C was quenched by slow addition of 1M HCl (15 mL). The aqueous phase was extracted with ether (2x10 mL) and the combined extracts washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue obtained as mixture of two diastereomers (0.44 g) subjected to 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 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 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{1H} 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]+ Calculated for C13H16NaO2 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 two hours and quenched by addition of 1M HCl (15 mL). The aqueous phase was extracted with ether (2x) 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, (3S,5S)-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{1H} 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*): $[M+Na]^+$ Calculated 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}HNMR ($CDCl_3$, 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{1H} 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]+ Calculated for C15H18NaO2 253.1204; Found, 253.1196.

*((3S,5S)-5-(benzyloxy)-3-methylhept-6-en-1-yn-3-yloxy)trimethylsilane (**17**)*: To a stirring solution of (3S,5S)-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 anhydrous Na_2SO_4, filtered and the ether 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{1H} 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]$^+$ Calculated 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, 3M in THF, 0.76 mmol, 1.35 equiv) and the reaction warmed to room temperature, then refluxed (using oil bath)at 50 °C for one hour. The contents were cooled again to – 20 °C, 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 two hours, quenched by slow addition of saturated NH_4Cl and extracted with ether (3x). 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{1H} 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: Four carbon peaks were submerged with other peaks; HRMS (ESI) (m/z): $[M+Na]^+$ Calculated 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{1H} 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: A carbon peak was submerged with other peaks; HRMS (ESI) (m/z): $[M+Na]^+$ Calculated 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 three hours. Upon completion, the reaction was diluted with ether (15 mL) and quenched with H_2O. The aqueous layer was extracted with ether (2x), the combined organic fractions 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{1H} 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: six carbon peaks were submerged with other peaks; HRMS (ESI) (m/z): $[M+Na]^+$ Calculated 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,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-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 two hours under the inert atmosphere. Upon completion, the reaction was diluted with ether (15 mL) and quenched with H2O. The aqueous layer was extracted with ether (2x), the combined organic fractions 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]+ Calculated for C39H62NaO6Si2 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-disilaundec-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{1H} 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]+ Calculated for C39H62NaO6Si2 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 two hours *via* 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 material (15-25%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34-7.30 (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: five carbon peaks were submerged with other peaks; MS (ESI): 577.2 $[M+Na]^+$; HRMS (ESI) (m/z): $[M+Na]^+$ Calculated 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 five hours, then cooled to room temperature and filtered through a medium glass frit. The filter cake was washed with ethyl acetate, concentrated the combined filtrate and the resulting residue 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): δ7.33-7.32 (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): $[M+Na]^+$ Calculated 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 three hours. The reaction solution was filtered through a celite pad, diluted with DCM (25 mL), and washed with saturated NaHCO3. The aqueous layer was extracted with DCM (2x) and the combined organic fractions 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%). ^{1}H 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: An aromatic carbon was submerged with other peaks; HRMS (ESI) (m/z): $[M+Na]^+$ Calculated 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 four hours, the reaction was cooled to room temperature and filtered through a medium glass frit. The filter cake was washed with ethyl acetate, and 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); ^{1}H NMR ($CDCl_3$, 500 MHz): δ7.52-7.50 (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): $[M+Na]^+$ Calculated 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 three hours. 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 (2x) and the combined organic fractions 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%). ^{1}H 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): $[M+Na]^+$ Calculated 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 minutes. After re-cooling 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 two hours and quenched with saturated NH_4Cl solution after completion. The aqueous solution was extracted with CH_2Cl_2, the combined organic extracts 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 mixture of diastereomers, 104 mg in 80% yield. R_f = 0.27 (25 % ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ7.54-7.51 (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): $[M+Na]^+$ Calculated 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 four hours, the reaction was cooled to room temperature and filtered through a medium glass frit. The filter cake was washed with ethyl acetate, and 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); ^{1}H NMR ($CDCl_3$, 500 MHz): δ7.58-7.55 (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): $[M+Na]^+$ Calculated for $C_{30}H_{36}NaO_6$ 515.2404; Found 515.2390.

*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 degassed CH_2Cl_2 and the reaction was placed under

reflux for 12h 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{1H} 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): $[M+Na]^+$ Calculated for $C_{28}H_{32}NaO_6$ 487.2091; Found 487.2083.

▪ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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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