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Studies towards the Total Synthesis of (–)-Caulerpenynol, a Toxic Sesquiterpenoid of the Green Seaweed *Caulerpa taxifolia*

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Dedicated to Prof. Maurice Santelli on the occasion of his 70th birthday

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The first diastereoselective synthesis of the antimicrobial and cytotoxic agent (–)-caulerpenynol (**2**) was achieved in relatively few steps from commercially available (*S*)-malic acid. Highlights of this synthesis include the nonracemization of the sensitive α-hydroxy ketone moiety and the proper choice of the protecting groups for critical last deprotection step.

Introduction

Some metabolites from tropical algae have been implicated in the chemical defense against grazing fish and invertebrates in herbivore-rich tropical waters[1] and have been proposed as an explanation for the unhindered proliferation of *Caulerpa taxifolia*, a tropical green seaweed, accidentally introduced into the Mediterranean. In comparison to other *Caulerpa* species in the tropics, *Caulerpa taxifolia* contains a large amount of caulerpenyne (**1**), a sesquiterpene isolated from 10 different species of *Caulerpa* and first identified from *Caulerpa prolifera*.[2] Among its biological activities, which are attributed to the diacetoxybutadiene moiety, caulerpenyne (**1**) inhibits the proliferation of the fibroblastic cell line BHK 21/C13 from baby hamster kidney and the division of sea urchin eggs.[3] The cytotoxicity was also demonstrated in various tumor cell lines,[4] and it was recently shown that caulerpenyne (**1**) has antiproliferative activity against the tumor cell line SK-N-SH and modifies the microtubule network.[5] In addition, several secondary metabolites were identified and could contribute to the toxicity of *C. taxifolia* from the Mediterranean (Figure 1). Among these metabolites, caulerpenynol (**2**) was isolated and identified in 1993 by Guerriero et al.[6] The antibacterial and cytotoxic activities of **2** were evaluated against prokaryotic marine bacteria and unicellular eukaryotes ciliate protists, and **2** proved to be the most active of the terpenes of *C. taxifolia* with the exception of two bacteria.[6]

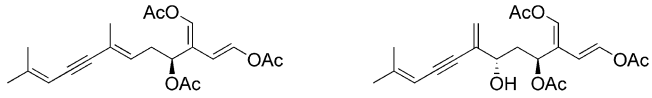

Figure 1. Caulerpenyne (**1**) and caulerpenynol (**2**).

Inspired by the pronounced biological activities of **2** and to provide material for a more extensive biological evaluation, we have undertaken the total synthesis of caulerpenynol (**2**). To the best of our knowledge, only a few synthetic transformations (epoxidation) from **1** to caulerpenynol (**2**) have been reported in the literature[6,7] but no total synthesis of **2** has been realized.

Herein is a full account of our preliminary communication, and we disclose results obtained during different approaches of the synthesis of **2**.[8]

Results and Discussion

The main structural features of **2** are a terminal 1,4-diacetoxybutadiene moiety, an enynene moiety, two chiral centers, and a 1,3-*anti*-diol moiety in which one alcohol function is protected as an acetate. As outlined in Scheme 1, our retrosynthetic scheme for synthesizing **2** called for the initial preparation of three fragments referred to as west, central, and east. We considered that the assembly of the three fragments could be obtained through two C–C coupling reactions. The first coupling was realized between alkynyllithium **3** (west fragment obtained from Fritsh–

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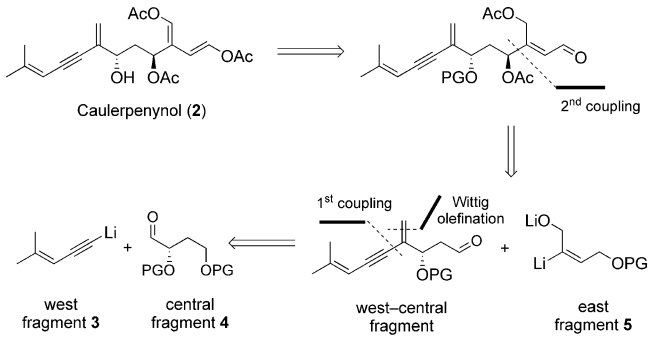
Buttenberg–Wiechell rearrangement) and aldehyde **4** (central fragment). The carbon skeleton was achieved through a second coupling between vinyllithium reagent **5** (east fragment obtained from a tin–lithium exchange reaction) and the corresponding west–central fragment.



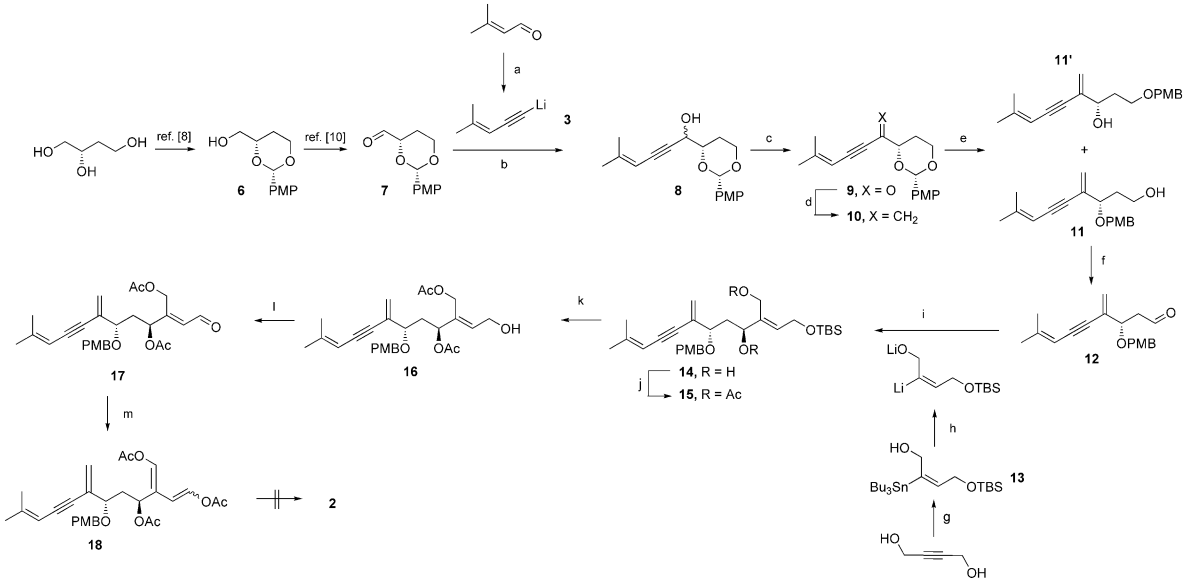
Scheme 1. Retrosynthetic scheme of (–)-caulerpenynol (**2**).

Synthesis of the central fragment (Scheme 2) started from commercially available (*S*)-butan-1,2,3-triol [or prepared on a large scale by reduction of (*S*)-malic acid], which was transformed in two steps, in high yield on a multigram scale into known ketal compound **6**.[9] First, (*S*)-butan-1,2,3-triol was protected as the tris-OTMS derivative followed by treatment with trimethylsilyl triflate and *p*-anisaldehyde to furnish acetal **6**. The alcohol function of **6** was then oxidized with Dess–Martin periodinane into unstable aldehyde **7**, which was immediately used for the next step without further purification.[10] Synthesis of the western fragment was performed by Corey–Fuchs alkynylation.[11] Commercially available 3,3-dimethylacrolein was first converted quantitatively into the known corresponding *gem*-dibromoalkene,[12] which after treatment with *n*BuLi (2 equiv.) generated alkynyllithium **3** through a Fritsch–Buttenberg–Wiechell rearrangement.

Construction of the carbon skeleton of (–)-caulerpenynol (**2**) started by a coupling reaction between central segment **7** and alkynyllithium **3** to furnish desired alcohol **8** in an 8:2 mixture of diastereomers. This mixture was then oxidized with Dess–Martin periodinane[13] to corresponding ketone **9**, which was then subjected to olefination under standard conditions to afford dienyne **10**. Regioselective reduction of *p*-methoxybenzylidene acetal **10** with DIBAL-H at –40 °C predominantly (78:22, 92%) gave *p*-methoxybenzyl ether **11** of the more-hindered secondary alcohol function. It is noteworthy that DIBAL-H must be cooled down to –78 °C before it is added to give better regioselectivity. The primary alcohol function of **11** was then oxidized with Dess–Martin periodinane into aldehyde **12**.

The remaining east fragment **13** was prepared in two steps from commercially available but-2-yn-1,4-diol through a palladium-catalyzed hydrostannation reaction to give quantitatively the known (*E*)-vinyltin reagent.[14,15] Subsequent selective protection of the less-hindered primary alcohol as a *tert*-butyldimethylsilyl ether furnished **13** in 64% overall yield for the two-step transformation.[15]

With the west–central and east fragments in hand, the carbon skeleton of caulerpenynol was achieved through a second coupling reaction between **12** and the vinyllithium reagent generated from the tin–lithium exchange reaction of **13**[16] to give diol **14** as a 6:4 mixture of diastereomers (64%). The diastereomers were separated by semipreparative HPLC, and the stereochemistry of major diastereomer **14** was determined by NOESY experiments conducted on the corresponding *p*-methoxybenzylidene acetal (obtained



Scheme 2. First approach to caulerpenynol (**2**). Reagents and conditions: (a) i. CBr_4, PPh_3, Zn, ii. *n*BuLi –78 °C; (b) –78 °C to r.t. (66% from **6**); (c) Dess–Martin periodinane, CH_2Cl_2 (91%); (d) $CH_2{=}PPh_3$, –40 to 0 °C (77%); (e) DIBAL-H, hexane, –80 to –40 °C (71%); (f) Dess–Martin periodinane, CH_2Cl_2 (82%); (g) i. Bu_3SnH, $PdCl_2(PPh_3)_2$, THF (99%); ii. TBDMSCl, DMF, 0 °C (65%); (h) MeLi·LiBr, –40 to –35 °C; (i) –78 °C, THF (64%); (j) Ac_2O, DMAP, pyridine (92%); (k) HF·pyridine, THF (77%); (l) Dess–Martin periodinane, CH_2Cl_2 (85%); (m) Ac_2O, DMAP, NEt_3, 80 °C (89%).

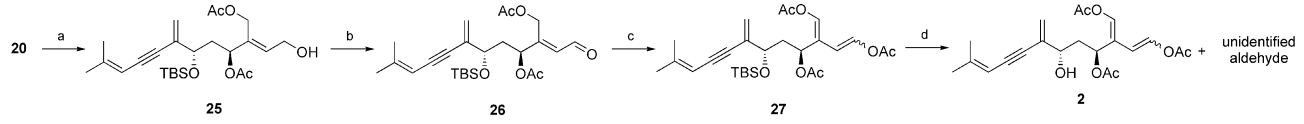
in 85% yield by oxidation of *p*-methoxybenzyl ether **14** with DDQ in anhydrous CH_2Cl_2).[17] At this stage, both hydroxy groups of the major *anti* isomer **14** were acylated by using acetic anhydride and a catalytic amount of DMAP in pyridine to give bisacetate **15**. Desilylation of primary TBS alcohol by HF·pyridine furnished desired alcohol **16**, which was then oxidized into aldehyde **17**. To generate the diacetoxybutadiene moiety, we employed conditions developed in our group[18] (NEt_3, DMAP, Ac_2O at 80 °C) and protected PMB caulerpenynol **18** was obtained as a 1:1 inseparable mixture of diastereomers. In order to complete the synthesis of caulerpenynol (**2**), the last step involved the removal of the PMB group. Unfortunately, the oxidative (DDQ or CAN) conditions failed to selectively provide caulerpenynol (**2**), which was never observed. Numerous unidentified byproducts were obtained that we attributed to the uncontrolled oxidation or cycloaddition reactions of the enynene and/or diacetoxybutadiene moieties.

As the *p*-methoxybenzyl protecting group does not seem to be the adequate protecting group for the last deprotection step of our synthesis, we decided to replace it by a *tert*-butyldimethylsilyl group that could be more readily removed. Replacement (Scheme 3) of the *p*-methoxybenzyl group by a *tert*-butyldimethylsilyl group was realized from **15** by routine protecting group interconversions. First of all, *p*-methoxybenzyl ether was deprotected by using DDQ in 5% aqueous CH_2Cl_2 to give corresponding secondary alcohol **19**, which was then protected as the silyl ether by TBSOTf and 2,6-lutidine at low temperature to furnished **20**.

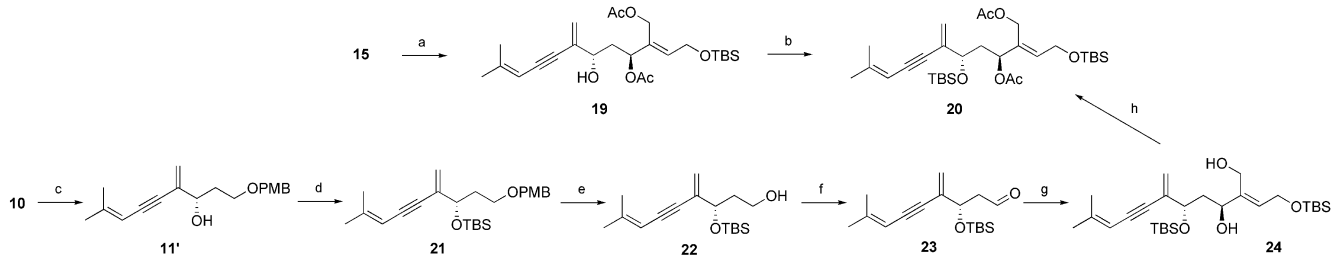
Another synthesis scheme (Scheme 3) was also used for the synthesis of TBS analog **20**. The *tert*-butyldimethylsilyl protecting group was introduced before the coupling between the west–central and east segments. The synthesis began with *p*-methoxybenzylidene acetal **10**, which can be reduced with $NaBH_3CN$/TMSCl in CH_3CN.[19] In comparison to reduction with DIBAL-H, the reduction reaction gave predominantly (9:1, 79%) *p*-methoxybenzyl ether **11′** of the less-hindered primary hydroxy group. Protection of the secondary hydroxy group by TBSOTf followed by oxidative deprotection of the *p*-methoxybenzyl ether function furnished desired alcohol **22** in a mixture with residual *p*-methoxybenzaldehyde. The primary alcohol function of **22** was then oxidized by using Dess–Martin periodinane into aldehyde **23**. Addition of the vinyllithium reagent generated by a tin–lithium exchange reaction on **13** gave desired diol **24** as a (6:4) mixture of diastereomers separable by column chromatography (30%). At this stage, both hydroxy groups of major *anti* isomer **24** were protected as the acetates to give bisacetate **20**.

Selective removal (Scheme 4) of the primary allylic TBS group in the presence of the hindered secondary TBS group was accomplished with a stock solution of HF·pyridine/THF/pyridine to furnish desired alcohol **25**.[20] The end of the synthesis was identical to the one previously described. Oxidation of primary alcohol **25** followed by transformation of aldehyde **26** into the diacetoxybutadienyl derivative led to a 45:55 mixture of TBS-protected caulerpenynol and TBS-protected *iso*-caulerpenynol (**27**). At this stage, we found that the cleavage of the TBS group of **27** also caused considerable problems. All attempts[21] to deprotect it with diluted HCl in THF, PPTS in ethanol, or TBAF in THF led only to starting material. In view of these difficulties, we were pleased to find that aqueous HF in CH_3CN gave better results. A 1:1 inseparable mixture of caulerpenynol (**2**) and *iso*-caulerpenynol (*iso*-**2**) was formed in low yield (40%). Along with the caulerpenynol derivatives, an aldehyde resulting from the hydrolysis of one enol acetate was obtained in 16% yield.

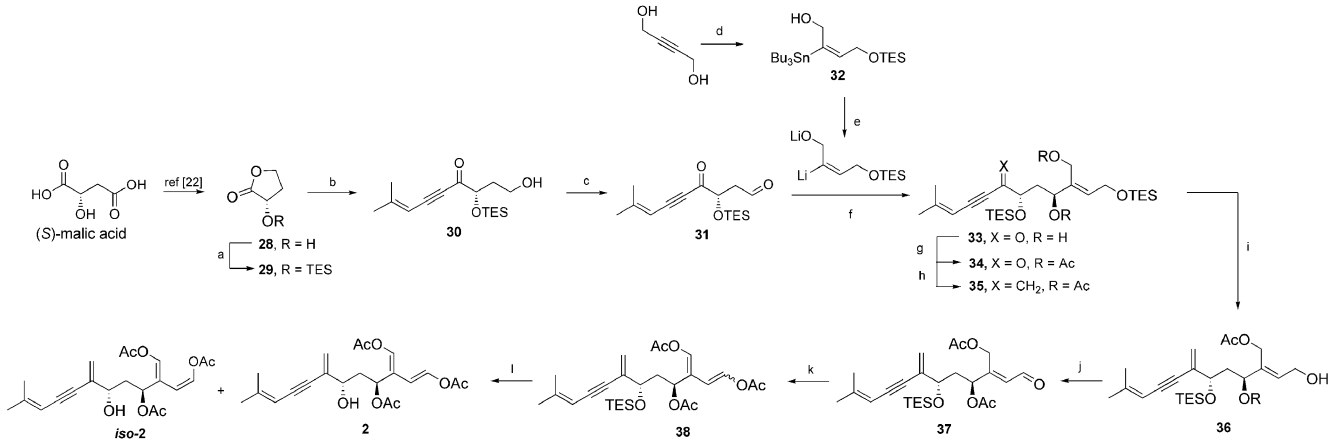
Even if the natural product was obtained, the last step is unsatisfactory and it is essential to consider the option for the ultimate deprotection very prudently. So we turned our attention to a triethylsilyl protecting group, which is more labile than the corresponding TBS group for the hydroxy



Scheme 4. Second approach to caulerpenynol (**2**). Reagents and conditions: (a) HF·pyridine/THF/pyridine, THF (86%); (b) Dess–Martin periodinane, CH_2Cl_2 (100%); (c) Ac_2O, DMAP, NEt_3, 80 °C (98%); (d) HF in water, CH_3CN.



Scheme 3. Synthesis of TBS analog **20**. Reagents and conditions: (a) DDQ, H_2O, CH_2Cl_2 (35–62%); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (71%); (c) $NaBH_3CN$/TMSCl, CH_3CN (79%); (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (97%); (e) DDQ, H_2O, CH_2Cl_2; (f) Dess–Martin periodinane, CH_2Cl_2 (85% over two steps), (g) **13**, MeLi·LiBr, –40 to –35 °C; (j) –78 °C, THF (30%); (h) Ac_2O, DMAP, pyridine (81%).



Scheme 5. Successful approach to caulerpenynol (**2**). Reagents and conditions: (a) TESCl, imidazole, DMAP, DMF (100%); (b) **3**, –78 °C to r.t. (73%); (c) Dess–Martin periodinane, CH_2Cl_2 (85%), (d) i. Bu_3SnH, $PdCl_2(PPh_3)_2$; ii. TESCl, NEt_3, –20 °C (53%); (e) MeLi·LiBr –78 to –40 °C; (f) –78 °C (43%, 7:3 mixture of diastereomers); (g) Ac_2O, DMAP, pyridine (81%); (h) $CH_2{=}PPh_3$, –80 to 0 °C (53%); (i) 2:1:10 mixture of AcOH/H_2O/THF,40 °C (88%); (j) Dess–Martin periodinane, CH_2Cl_2 (90%); (k) Ac_2O, DMAP, NEt_3, 80 °C (73%); (l) 3:2:1 mixture of AcOH/H_2O/THF, 45 °C (81%).

group needing protection. The beginning of the synthesis (Scheme 5) was slightly different and started from known lactone **28**.[22] First, (*S*)-malic acid was protected as an acetonide (2,2-dimethoxypropane, *p*-TsOH), and the carboxylic acid was then reduced to the alcohol by using BH_3–THF. This unstable product immediately rearranged into (*S*)-3-hydroxybutyrolactone (**28**) in the presence of *p*-TsOH. Lastly, the alcohol function of **28** was protected as the triethylsilyl ether to give new central fragment **29** (71% yield over four steps).

Construction of the carbon skeleton of (–)-caulerpenynol (**2**) started by a coupling reaction between central fragment **29** and alkynyllithium **3** to furnish corresponding alcohol **30**, which was then oxidized by using Dess–Martin periodinane to afford aldehyde **31**. The carbon skeleton of caulerpenynol was achieved through a second coupling reaction between **31** and a vinyllithium reagent generated by tin–lithium exchange reaction on **32** (obtained by selective protection of the less-hindered primary alcohol as triethylsilyl ether) to give diol **33** in 43% yield as a 7:3 mixture (based on ^{13}C NMR) of diastereomers separable by flash chromatography in favor of the *anti* diastereomer.[23] The stereochemistry of *anti*-diol **33** was confirmed by our previous results. ^1H and ^{13}C NMR spectra of **34**, obtained by protection of both hydroxy groups of major *anti* isomer **33** as the acetates, exactly matched those of TBS analog **20** (excepted alkyl silyl chain).[24]

Bisacetate **34** was subjected to an olefination reaction by using standard conditions to afford **35**. Selective cleavage of the primary allylic triethylsilyl ether in the presence of the secondary allylic triethylsilyl ether was performed with a 2:1:10 mixture of AcOH/H_2O/THF at 40 °C, furnishing desired primary alcohol **36**,[25] which was further oxidized with Dess–Martin periodinane into aldehyde **37**. The diacetoxybutadiene moiety was generated under basic conditions to give TES-protected caulerpenynol **38** in a 53:47 *E*/*Z* diastereomeric mixture. At last, a 3:2:1 mixture of AcOH/H_2O/THF at 45 °C was used to remove the triethylsilyl protecting group to afford cleanly a 52:48 diastereomeric mixture of caulerpenynol (**2**) and *iso*-caulerpenynol (*iso*-**2**) separable by HPLC.[26] The physical and spectroscopic data (mass, ^1H NMR, ^{13}C NMR, optical rotation) of our synthetic material are in complete agreement with those reported for the naturally derived caulerpenynol,[6,27] confirming our prediction of the relative and absolute configuration of *anti* diastereomer **33**.

Conclusions

In summary, the first diastereoselective synthesis of the antimicrobial and cytotoxic agent (–)-caulerpenynol (**2**) was achieved in relatively few steps from commercially available (*S*)-malic acid. Highlights of this synthesis include the nonracemization of the sensitive α-hydroxy ketone moiety and the proper choice of the protecting groups for the critical last deprotection step.

Experimental Section

1-[(2*S*,4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]-5-methylhex-4-en-2-yn-1-ol (8): To a solution of 1,1-dibromo-4-methylpent-1,3-diene[12] (6.4 g, 26.75 mmol) in THF (100 mL) was added *n*BuLi (2.5 M, 21.4 mL, 53.5 mmol) dropwise at –78 °C. The clear yellow solution was stirred at –78 °C for 1.5 h and then crude aldehyde **7** diluted in a minimum amount of THF was added by cannula. After warming to room temperature, the mixture was quenched with NH_4Cl/NH_4OH (8:2). The aqueous layer was extracted with EtOAc, and the combined organic layers were dried with Na_2SO_4, filtered, and then concentrated under vacuum. The crude alcohol was purified by column of chromatography (SiO_2; 4% NEt_3, petroleum ether/Et_2O, 5:5) to give a mixture (8:2) of two diastereomers (3.59 g) in 66% yield over two steps from **6**. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.62 (br. d, J = 13.4 Hz, 1 H, CH_2), 1.80 (s, 3 H, CH_3), 1.90 (s, 3 H, CH_3), 2.15 (qd, J = 13.4, 5.1 Hz, 1 H, CH_2), 2.71 (m,

1 H, OH), 3.78 (s, 3 H, CH_3), 3.85–4.01 (m, 2 H, CH_2 and CH), 4.31 (dd, J = 11.1, 5.1 Hz, 1 H, CH_2), 4.65 (br. s, 1 H, CH), 5.28 (br. s, 1 H, CH), 5.50 (s, 1 H, CH), 6.87 (br. d, J = 8.8 Hz, 2 H, 2×CH), 7.42 (br. d, J = 8.8 Hz, 2 H, 2×CH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.2 (CH_3), 24.8 (CH_3), 25.2 (CH_2), 55.3 (CH_3), 65.2 (CH), 66.7 (CH_2), 79.2 (CH), 84.4 (C), 87.9 (C), 101.3 (CH), 104.6 (CH), 113.6 (2×CH), 127.6 (2×CH), 130.9 (C), 149.8 (C), 160.1 (C) ppm. HRMS (ESI): calcd. for $C_{18}H_{23}O_4$ $[M + H]^+$ 303.1590; found 303.1596.

1-[(2*S*,4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]-5-methylhex-4-en-2-yn-1-one (9): To a stirred solution of alcohol **8** (6.57 g, 21.72 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added Dess–Martin periodinane (11 g, 26.07 mmol) and pyridine (2.6 mL, 30.41 mmol). The reaction mixture was stirred at room temperature and followed by TLC. After disappearance of the starting material, the mixture was poured into a saturated aqueous $Na_2S_2O_3$/$NaHCO_3$ solution (1 L, 1:1). After stirring for 10 min, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried with Na_2SO_4, and then concentrated under vacuum. The crude product was purified by column of chromatography (SiO_2; 4% NEt_3, petroleum ether/Et_2O, 5:5) to give **9** (5.95 g) in 91% yield. $[\alpha]_D^{21}$ = –14.2 (c = 1, CH_2Cl_2). M.p. 95–100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.89 (br. s, 3 H, CH_3), 1.91 (s, 3 H, CH_3), 1.94–2.12 (m, 2 H, CH_2), 3.81 (s, 3 H, CH_3), 4.01 (td, J = 11.5, 3.0 Hz, 1 H, CH_2), 4.34 (ddd, J = 11.5, 4.9, 1.3 Hz, 1 H, CH_2), 4.44 (dd, J = 11.5, 3.0 Hz, 1 H CH), 5.45 (br. s, 1 H, CH), 5.55 (s, 1 H, CH), 6.88 (br. d, J = 8.8 Hz, 2 H, 2×CH), 7.47 (br. d, J = 8.8 Hz, 2 H, 2×CH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.1 (CH_3), 25.6 (CH_3), 27.8 (CH_2), 55.4 (CH_3), 66.8 (CH_2), 81.6 (CH), 89.3 (C), 95.2 (C), 101.2 (CH), 103.7 (CH), 113.6 (2×CH), 127.7 (2×CH), 130.6 (C), 160.2 (C), 160.3 (C), 185.3 (C) ppm. HRMS (ESI): calcd. for $C_{18}H_{21}O_4$ $[M + H]^+$ 301.1434; found 301.1434.

(2*S*,4*S*)-2-(4-Methoxyphenyl)-4-(5-methyl-1-methylenehex-4-en-2-ynyl)-1,3-dioxane (10): To a solution of CH_3PPh_3I (215 mg, 0.53 mmol) in dry THF (2 mL) was added, at –40 °C, dropwise *n*BuLi (2.5 M in hexanes, 0.192 mL, 4.8 mmol). The solution was warmed up to 0 °C for 2 h and recooled to –50 °C. Ketone **9** (80 mg, 0.27 mmol) dissolved in a minimum amount of THF was added by cannula. The mixture was warmed up to room temperature and quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated aqueous NaCl solution, dried with Na_2SO_4, and then concentrated. The crude product was purified by column of chromatography (SiO_2; 4% NEt_3, petroleum ether/Et_2O, 8:2) to give **10** (61.3 mg) in 77% yield. $[\alpha]_D^{21}$ = –32.3 (c = 1, CH_2Cl_2). M.p. 41 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84 (br. s, 3 H, CH_3), 1.93 (s, 3 H, CH_3), 1.89–2.04 (m, 2 H, CH_2), 3.80 (s, 3 H, CH_3), 4.01 (td, J = 11.5, 3.2 Hz, 1 H, CH_2), 4.27–4.38 (m, 2 H, CH_2 and CH), 5.40 (br. s, 1 H, CH), 5.47 (br. s, 1 H, CH_2), 5.55 (s, 1 H, CH), 5.63 (br. s, 1 H, CH_2), 6.89 (br. d, J = 8.8 Hz, 2 H, 2×CH), 7.46 (br. d, J = 8.8 Hz, 2 H, 2×CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 25.0 (CH_3), 31.1 (CH_2), 55.4 (CH_3), 67.1 (CH_2), 78.2 (CH), 89.2 (C), 89.4 (C), 101.2 (CH), 105.2 (CH), 113.6 (2×CH), 119.5 (CH_2), 127.6 (2×CH), 131.2 (C), 132.0 (C), 149.4 (C), 160.0 (C) ppm. HRMS (ESI): calcd. for $C_{19}H_{23}O_3$ $[M + H]^+$ 299.1641; found 299.1641.

(3*S*)-3-(4-Methoxybenzyloxy)-8-methyl-4-methylenenon-7-en-5-yn-1-ol (11): To a stirred solution of dioxane **10** (600 mg, 2.01 mmol) in hexane (85 mL) was added at –80 °C, DIBAL-H (1.5 M in toluene, 8.04 mL, 12.06 mmol) precooled to –80 °C. The solution was warmed to –40 °C and stirred overnight. The mixture was carefully quenched with a few drops of methanol and then by a saturated aqueous Rochel salt solution and diluted with EtOAc. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried with $MgSO_4$ and then concentrated under vacuum. The crude product was purified by column of chromatography (SiO_2; petroleum ether/Et_2O, 7:3 to 0:10) to give a 78:22 separable mixture of two isomers (555 mg) in 91% yield. Major isomer **11**: $[\alpha]_D^{21}$ = –102.8 (c = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.83 (s, 3 H, CH_3), 1.92 (s, 3 H, CH_3), 1.87–2.08 (m, 2 H, CH_2), 2.43 (m, 1 H, OH), 3.67–3.80 (m, 2 H, CH_2), 3.79 (s, 3 H, CH_3), 4.05 (dd, J = 8.5, 4.3 Hz, 1 H, CH, H2), 4.28 (d, J = 11.3 Hz, 1 H, CH_2), 4.60 (d, J = 11.3 Hz, 1 H, CH_2), 5.40 (br. s, 1 H, CH), 5.46 (br. s, 1 H, CH_2), 5.53 (br. s, 1 H, CH_2), 6.87 (br. d, J = 8.5 Hz, 2 H, 2×CH), 7.26 (br. d, J = 8.5 Hz, 2 H, 2×CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 25.0 (CH_3), 37.2 (CH_2), 55.3 (CH_3), 60.7 (CH_2), 70.2 (CH_2), 80.6 (CH), 89.0 (C), 89.8 (C), 105.1 (CH), 113.9 (2×CH), 121.3 (CH_2), 129.7 (2×CH), 130.0 (C), 132.1 (C), 149.8 (C), 159.3 (C) ppm. HRMS (ESI): calcd. for $C_{19}H_{25}O_3$ $[M + H]^+$ 301.1798; found 301.1810.

(3*S*)-3-(4-Methoxybenzyloxy)-8-methyl-4-methylenenon-7-en-5-yn-1-al (12): To a stirred solution of alcohol **11** (2.4 g, 7.99 mmol) in CH_2Cl_2 (190 mL) at 0 °C was added Dess–Martin periodinane (4.04 g, 9.59 mmol). The reaction mixture was stirred at room temperature and followed by TLC. After disappearance of the starting material, the mixture was poured into a saturated aqueous $Na_2S_2O_3$/$NaHCO_3$ solution (400 mL, 1:1). After stirring for 10 min, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried with Na_2SO_4, and then concentrated under vacuum. The crude aldehyde was purified by column of chromatography (SiO_2; petroleum ether/Et_2O, 7:3) to give **12** (1.95 g) in 82% yield. $[\alpha]_D^{23}$ = –74.6 (c = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84 (s, 3 H, CH_3), 1.92 (s, 3 H, CH_3), 2.68 (ddd, J = 16.4, 4.3, 1.7 Hz, 1 H, CH_2), 2.84 (ddd, J = 16.4, 8.5, 2.5 Hz, 1 H CH_2), 3.79 (s, 3 H, CH_3), 4.32 (d, J = 11.3 Hz, 1 H, CH_2), 4.35 (dd, J = 8.5, 4.3 Hz, 1 H, CH_2), 4.59 (d, J = 11.3 Hz, 1 H, CH_2), 5.40 (br. s, 1 H, CH), 5.52 (s, 1 H, CH_2), 5.55 (br. s, 1 H, CH), 6.86 (br. d, J = 8.7 Hz, 2 H, 2×CH), 7.25 (br. d, J = 8.7 Hz, 2 H, 2×CH), 9.74 (br. d, J = 2.5, 1.7 Hz, CH, 1 Hd) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 25.0 (CH_3), 48.6 (CH_2), 55.3 (CH_3), 70.3 (CH_2), 76.3 (CH), 88.5 (C), 90.3 (C), 105.0 (CH), 113.9 (2×CH), 121.7 (CH_2), 129.7 (2×CH), 129.9 (C), 131.2 (C), 150.0 (C), 159.4 (C), 200.7 (CH) ppm. HRMS (ESI): calcd. for $C_{19}H_{23}O_3$ $[M + H]^+$ 299.1641; found 299.1642.

(3*S*,5*S*,*E*)-2-[2-(*tert*-Butyldimethylsilyloxy)ethylidene]-5-(4-methoxybenzyloxy)-10-methyl-6-methyleneundec-9-en-7-yne-1,3-diol (14): To a solution of (*E*)-vinyltin reagent **13**[15] (2.7 g, 5.49 mmol) in THF (85 mL) at –40 °C was added dropwise MeLi·LiBr (2.2 M, 5 mL, 10.99 mmol). The reaction mixture was warmed to –35 °C and stirred until disappearance of the starting material (1 h). The mixture was cooled to –90 °C, aldehyde **12** (1.366 g, 4.58 mmol) diluted in a minimum amount of THF was then added dropwise. The solution was kept at –90 °C for 2 h and then quenched with a saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. The crude product was then purified by flash chromatography (petroleum ether/Et_2O, 4:6) to give a 6:4 mixture of diastereomers (1.456 g) in 64% yield. The two diastereomers were separated by chiral semipreparative HPLC. Major diastereomer **14**: $[\alpha]_D^{25}$ = –41.8 (c = 1, CH_2Cl_2). M.p. 40–44 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.10 (s, 6 H, 2×CH_3), 0.92 (s, 9 H, 3×CH_3), 1.85 (s, 3 H, CH_3), 1.93 (s, 3 H, CH_3), 2.02–2.07 (m, 2 H, CH_2), 2.87 (m, 1 H, OH), 2.97 (m, 1 H, OH), 3.82

(s, 3 H, CH_3), 4.13–4.18 (m, 3 H, CH and CH_2), 4.25–4.28 (m, 3 H, CH_2 and CH_2), 4.43–4.47 (m, 1 H, CH), 4.60 (d, J = 11.1 Hz, 1 H, CH_2), 5.41 (br. s, 1 H, CH), 5.51 (s, 1 H, CH_2), 5.55 (br. s, 1 H, CH_2), 5.73 (t, J = 6.0 Hz, 1 H, CH), 6.90 (br. d, J = 8.7 Hz, 2 H, 2×CH), 7.29 (br. d, J = 8.7 Hz, 2 H, 2×CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.1 (2×CH_3), 18.4 (C), 21.3 (CH_3), 25.0 (CH_3), 26.0 (3×CH_3), 40.0 (CH_2), 55.4 (CH_3), 58.7 (CH_2), 59.6 (CH_2), 70.6 (CH_2), 73.0 (CH), 79.0 (CH), 89.2 (C), 89.9 (C), 105.1 (CH), 114.0 (2×CH), 121.0 (CH_2), 128.3 (CH), 129.8 (2×CH), 130.0 (C), 131.9 (C), 142.7 (C), 149.8 (C), 159.5 (C) ppm. MS (ESI+): m/z = 518 $[M + NH_4]^+$. HRMS (ESI): calcd. for $C_{29}H_{45}O_5Si$ $[M + H]^+$ 501.3030; found 501.3030.

(3*S*,5*S*,*E*)-2-[2-(*tert*-Butyldimethylsilyloxy)ethylidene]-5-(4-methoxybenzyloxy)-10-methyl-6-methyleneundec-9-en-7-yne-1,3-diyl Diacetate (15): A solution of *trans*-diol **14** (0.660 g, 1.32 mmol), acetic anhydride (0.495 mL, 5.27 mmol), and DMAP (80 mg, 0.65 mmol) in pyridine (14 mL) was stirred overnight. The mixture was quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with diethyl ether, and the organic layers were washed with saturated aqueous $CuSO_4$ solution and water, dried with $MgSO_4$, and concentrated under vacuum. The crude product was purified by column of chromatography (SiO_2; petroleum ether/Et_2O, 8:2) to give **15** (0.720 g) in 93% yield. $[\alpha]_D^{21}$ = –54.7 (c = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 6 H, 2×CH_3), 0.87 (s, 9 H, 3×CH_3), 1.83 (s, 3 H, CH_3), 1.90 (s, 3 H, CH_3), 1.91 (s, 3 H, CH_3), 1.96–2.00 (m, 2 H, CH_2), 2.00 (s, 3 H, CH_3), 3.79 (s, 3 H, CH_3), 3.79–3.86 (m, 1 H, CH), 4.20 (d, J = 11.3 Hz, 1 H, CH_2), 4.27 (br. d, J = 5.9 Hz, 2 H, CH_2), 4.54 (d, J = 11.3 Hz, 1 H, CH_2), 4.58 (s, 2 H, CH_2), 5.39 (br. s, 1 H, CH), 5.42 (br. s, 1 H, CH_2), 5.45 (m, 1 H, CH), 5.50 (br. s, 1 H, CH_2), 5.81 (t, J = 5.9 Hz, 1 H, CH), 6.84 (br. d, J = 8.5 Hz, 2 H, 2×CH), 7.23 (br. d, J = 8.5 Hz, 2 H, 2×CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.1 (2×CH_3), 18.3 (C), 20.8 (CH_3), 21.1 (CH_3), 21.2 (CH_3), 24.9 (CH_3), 25.9 (3×CH_3), 39.8 (CH_2), 55.3 (CH_3), 59.6 (2×CH_2), 70.0 (CH_2), 72.5 (CH), 77.0 (CH), 89.1 (C), 89.7 (C), 105.3 (CH), 113.8 (2×CH), 121.1 (CH_2), 129.9 (2×CH), 130.2 (C), 132.3 (C), 133.3 (C), 133.8 (CH), 149.5 (C), 159.3 (C), 169.9 (C), 170.7 (C) ppm. MS (ESI+): m/z = 602 $[M + NH_4]^+$. HRMS (ESI): calcd. for $C_{33}H_{52}NO_7Si$ $[M + NH_4]^+$ 602.3507; found 602.3504.

(3*S*,5*S*,*E*)-2-(2-Hydroxyethylidene)-5-(4-methoxybenzyloxy)-10-methyl-6-methyleneundec-9-en-7-yne-1,3-diyl Diacetate (16): To a stirred solution of **15** (92 mg, 0.157 mmol) in THF (2 mL) was added HF·pyridine complex (140 μL). The reaction mixture was stirred at room temperature and followed by TLC. After disappearance of the starting material (3 h), the mixture was concentrated under vacuum and then purified by column of chromatography (SiO_2; petroleum ether/EtOAc, 6:4) to give **16** (57 mg) in 77% yield. $[\alpha]_D^{24}$ = –64.5 (c = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.83 (br. s, 3 H, CH_3), 1.90 (br. s, 3 H, CH_3), 1.91 (br. s, 3 H, CH_3), 1.91–2.03 (m, 2 H, CH_2), 2.01 (s, 3 H, CH_3), 3.78 (s, 3 H, CH_3), 3.78–3.85 (m, 1 H, CH), 4.18–4.22 (m, 3 H, CH_2 and CH_2), 4.54 (d, J = 11.5 Hz, 1 H, CH_2), 4.58 (d, J = 12.5 Hz, 1 H, CH_2), 4.70 (d, J = 12.5 Hz, 1 H, CH_2), 5.39 (br. s, 1 H, CH), 5.43 (m, 2 H, CH and CH_2), 5.50 (br. s, 1 H, CH_2), 5.91 (J = 6.7 Hz, 1 H, CH), 6.85 (br. d, J = 8.5 Hz, 2 H, 2×CH), 7.23 (br. d, J = 8.5 Hz, 2 H, 2×CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (CH_3), 21.1 (CH_3), 21.2 (CH_3), 25.0 (CH_3), 40.0 (CH_2), 55.4 (CH_3), 58.5 (CH_2), 59.5 (CH_2), 70.0 (CH_2), 72.4 (CH), 76.9 (CH), 89.1 (C), 89.8 (C), 105.2 (CH), 113.8 (2×CH), 121.2 (CH_2), 130.0 (2×CH), 130.2 (C), 132.1 (C), 132.3 (C), 135.6 (CH), 149.7 (C), 159.3 (C), 170.1 (C), 171.2 (C) ppm.

(3*S*,5*S*,*E*)-5-(4-Methoxybenzyloxy)-10-methyl-6-methylene-2-(2-oxoethylidene)undec-9-en-7-yne-1,3-diyl Diacetate (17): To a stirred solution of alcohol **16** (45 mg, 0.0956 mmol) in CH_2Cl_2 (3 mL) was added at 0 °C Dess–Martin periodinane (48 mg, 0.115 mmol). The mixture was stirred at room temperature and followed by TLC. After disappearance of the starting material (2 h), the solution was poured into a saturated aqueous $Na_2S_2O_3$/$NaHCO_3$ solution (5 mL, 1:1). After stirring for 10 min, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried with Na_2SO_4, and then concentrated under vacuum. The crude aldehyde was purified by column of chromatography (SiO_2; petroleum ether/ether, 1:1) to give **17** (38 mg) in 85% yield. $[\alpha]_D^{26}$-56.5 (c = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.83 (br. s, 3 H, CH_3), 1.85–1.95 (m, 1 H, CH_2), 1.90 (br. s, 3 H, CH_3), 1.92 (br. s, 3 H, CH_3), 2.01–2.10 (m, 1 H, CH_2), 2.03 (br. s, 3 H, CH_3), 3.79 (s, 3 H, CH_3), 3.85 (dd, J = 10.0, 2.6 Hz, 1 H, CH), 4.19 (d, J = 11.5 Hz, 1 H, CH_2), 4.56 (d, J = 11.5 Hz, 1 H, CH_2), 5.00 (d, J = 14.0 Hz, 1 H, CH_2), 5.09 (d, J = 14.0 Hz, 1 H, CH_2), 5.39 (br. s, 1 H, CH), 5.45–5.52 (m, 3 H, CH and CH_2), 6.05 (d, J = 7.2 Hz, 1 H, CH), 6.85 (br. d, J = 8.5 Hz, 2 H, 2×CH), 7.21 (br. d, J = 8.5 Hz, 2 H, 2×CH), 10.04 (d, J = 7.2 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 20.8, 21.2, 25.0, 39.7, 55.4, 59.4, 70.0, 71.0, 76.3, 88.9, 90.0, 105.1, 113.9 (2 C), 121.4, 128.1, 129.9, 130.0 (2 C), 131.9, 149.9, 156.1, 159.4, 169.9, 171.4, 190.5 ppm.

(4*S*,6*S*,*Z*)-3-(Acetoxymethylene)-6-(4-methoxybenzyloxy)-11-methyl-7-methylenedodeca-1,10-dien-8-yne-1,4-diyl Diacetate (18): In a dry Schlenk tube, a solution of **17** (36 mg, 0.0768 mmol), DMAP (9.3 mg, 0.0768 mmol), NEt_3 (1 mL), and acetic anhydride (21.6 μL, 0.23 mmol) was stirred at 80 °C and monitored by TLC. After disappearance of the starting material (3 h), the mixture was concentrated under vacuum. The crude product was purified by flash chromatography (SiO_2; petroleum ether/EtOAc, 8:2) to give a 52:48 mixture (35 mg) of **18** and *iso*-**18** in 89% yield. Data for **18**: ^{1}H NMR (500 MHz, C_6D_6): δ = 1.44 (br. s, 3 H, CH_3), 1.45 (br. s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 1.55 (s, 3 H, CH_3), 1.56 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 1.64 (s, 3 H, CH_3), 1.71 (s, 3 H, CH_3), 1.82 (br. s, 3 H, CH_3), 1.86 (br. s, 3 H, CH_3), 2.24–2.30 (m, 2 H, 2×CH_2), 2.41–2.46 (m, 1 H, CH_2), 2.60–2.66 (m, 1 H, CH_2), 3.31 (s, 3 H, CH_3), 3.32 (s, 3 H, CH_3), 4.11 (dd, J = 9.8, 3.0 Hz, 1 H, CH), 4.14 (dd, J = 10.0, 2.8 Hz, 1 H, CH), 4.30–4.34 (m, 2 H, 2×CH_2), 4.65 (m, 2 H, 2×CH_2), 5.08 (d, J = 7.2 Hz, 1 H, CH), 5.37–5.41 (m, 4 H, 2×CH and CH_2), 5.52 (br. s, 1 H, CH_2), 5.56 (br. s, 1 H, CH_2), 5.75 (d, J = 12.7 Hz, 1 H, CH), 6.61 (dd, J = 10.6, 3.1 Hz, 1 H, CH), 6.65 (dd, J = 10.4, 3.3 Hz, 1 H, CH), 6.81 (br. d, J = 8.0 Hz, 4 H, 2×CH_2), 7.30–7.34 (m, 6 H), 7.93 (d, J = 12.7 Hz, 1 H, CH), 8.12 (s, 1 H, CH) ppm.

(3*S*,5*S*,*E*)-2-[2-(*tert*-Butyldimethylsilyloxy)ethylidene]-5-hydroxy-10-methyl-6-methyleneundec-9-en-7-yne-1,3-diyl Diacetate (19): To a stirred solution of **15** (82 mg, 0.0141 mmol) in 5% aqueous CH_2Cl_2 (2.9 mL) was added DDQ (31.9 mg, 0.0141 mmol) at 0 °C. The solution was stirred at room temperature and followed by TLC. After disappearance of the starting material (3 h), the mixture was filtered through Celite and concentrated under vacuum. The crude product was purified by column of chromatography (SiO_2; petroleum ether/Et_2O, 7:3) to give **19** (41 mg) in 62% yield. $[\alpha]_D^{19}$ = –34.1 (c = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, 2×CH_3); 0.88 (s, 9 H, 3×CH_3), 1.82 (br. s, 3 H, CH_3), 1.82–1.90 (m, 1 H, CH_2), 1.90 (br. s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 2.06–2.18 (m, 1 H, CH_2), 2.52 (m, 1 H, OH), 4.12 (br. d, J = 8.9 Hz, 1 H, CH), 4.30 (d, J = 5.9 Hz, 2 H, CH_2), 4.63 (s, 2 H, CH_2), 5.38 (br. s, 1 H, CH), 5.40 (br. s, 1 H, CH_2), 5.48–5.52 (m, 2 H, CH and CH_2), 5.86 (t, J = 5.9 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.2 (2×CH_3), 18.2 (C), 20.8 (CH_3),

21.0 (CH_3), 21.1 (CH_3), 24.8 (CH_3), 25.9 ($3\times CH_3$), 40.7 (CH_2), 59.5 ($2\times CH_2$), 70.5 (CH), 72.7 (CH), 88.9 (C), 90.0 (C), 105.1 (CH), 119.2 (CH_2), 133.1 (C), 134.0 (CH), 134.5 (C), 149.3 (C), 170.6 (C), 170.7 (C) ppm. MS (ESI+): m/z = 482 $[M + NH_4]^+$. HRMS (ESI): calcd. for $C_{25}H_{44}NO_6Si$ $[M + NH_4]^+$ 482.2932; found 482.2930.

(3*S*,5*S*,*E*)-5-(*tert*-Butyldimethylsilyloxy)-2-[2-(*tert*-butyldimethylsilyloxy)ethylidene]-10-methyl-6-methyleneundec-9-en-7-yne-1,3-diyl Diacetate (20)

Method A: To a stirred solution of alcohol **19** (54 mg, 0.115 mmol) in CH_2Cl_2 (2 mL) was added at 0 °C 2,6-lutidine (27 μL, 0.230 mmol) followed by TBSOTf (32 μL, 0.138 mmol). After stirring for 1 h at room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated aqueous NaCl solution, dried with Na_2SO_4, and then concentrated under vacuum. The crude product was purified by column of chromatography (SiO_2; petroleum ether/Et_2O, 9:1) to give **20** (47 mg) in 71% yield.

Method B: A solution of diol **25** (15 mg, 0.0303 mmol), acetic anhydride (12 μL, 0.0.121 mmol), and DMAP (0.185 mg, 1.51 μmol) in pyridine (0.5 mL) was stirred at room temperature. After disappearance of the starting material (4 h), the mixture was quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with diethyl ether, and the organic layers were washed with saturated aqueous $CuSO_4$ solution and water, dried with $MgSO_4$, and then concentrated under vacuum. The crude product was purified by column of chromatography (SiO_2; petroleum ether/Et_2O, 9:1) to give **20** (16.1 mg) in 92% yield. $[\alpha]_D^{22}$ = –30.8 (c = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.01 (s, 6 H, $2\times CH_3$), 0.05 (s, 6 H, $2\times CH_3$), 0.88 (s, 9 H, $3\times CH_3$), 0.90 (s, 9 H, $3\times CH_3$), 1.76–1.87 (m, 1 H, CH_2), 1.83 (s, 3 H, CH_3), 1.92 (s, 3 H, CH_3), 1.96–2.13 (m, 1 H, CH_2), 2.03 (br. s, 6 H, CH_3), 4.20 (br. d, J = 8.9 Hz, 1 H, CH), 4.29 (d, J = 5.7 Hz, 2 H, CH_2), 4.58 (d, J = 12.5 Hz, 1 H, CH_2), 4.63 (d, J = 12.5 Hz, 1 H, CH_2), 5.30 (br. d, J = 10.4 Hz, 1 H, CH), 5.35 (br. s, 1 H, CH_2), 5.38 (br. s, 1 H, CH), 5.43 (br. s, 1 H, CH_2), 5.79 (t, J = 5.7 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.3 (CH_3), –5.0 ($2\times CH_3$), –4.3 (CH_3), 18.2 (C), 18.4 (C), 21.0 (CH_3), 21.2 (CH_3), 21.3 (CH_3), 25.0 (CH_3), 25.9 ($6\times CH_3$), 42.6 (CH_2), 59.7 (CH_2), 60.0 (CH_2), 71.9 (CH), 72.6 (CH), 89.6 (C), 89.9 (C), 105.4 (CH), 119.2 (CH_2), 133.0 (CH), 134.0 (C), 135.7 (C), 149.2 (C), 170.1 (C), 170.8 (C) ppm. MS (ESI+): m/z = 596 $[M + NH_4]^+$. HRMS (ESI): calcd. for $C_{31}H_{58}NO_6Si_2$ $[M + NH_4]^+$ 596.3797; found 596.3797.

(3*S*)-1-(4-Methoxybenzyloxy)-8-methyl-4-methylenenon-7-en-5-yn-3-ol (11′): To a stirred solution of **10** (1 g, 3.35 mmol) in CH_3CN (67 mL) was added molecular sieves (4 Å, 433 mg). The solution was stirred at room temperature for 5 min. After cooling to 0 °C, $NaBH_3CN$ (1.26 g, 20.1 mmol) followed by TMSCl (2.55 mL, 20.1 mmol) was added. The mixture was stirred at 0 °C until disappearance of the starting material and then concentrated under vacuum. The mixture was diluted with water, extracted with EtOAc, dried with $MgSO_4$, and then concentrated. The crude product was purified by column of chromatography (SiO_2; petroleum ether/Et_2O, 6:4) to give a 1:9 separable mixture of two isomers (**11**/**11′**, 787 mg) in 79% yield. Major isomer **11′**: $[\alpha]_D^{21}$ = –17.5 (c = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.82 (s, 3 H, CH_3), 1.90 (s, 3 H, CH_3), 1.90–2.14 (m, 2 H, CH_2), 3.40 (br. d, J = 4.5 Hz, 1 H, OH), 3.57–3.73 (m, 2 H, CH_2), 3.78 (s, 3 H, CH_3), 4.35 (m, 1 H, CH), 4.43 (s, 2 H, CH_2), 5.38 (br. s, 1 H, CH), 5.43 (br. s, 1 H, CH_2), 5.54 (s, 1 H, CH), 6.87 (br. d, J = 8.5 Hz, 2 H, $2\times CH$), 7.24 (br. d, J = 8.5 Hz, 2 H, $2\times CH$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (CH_3), 24.8 (CH_3), 35.2 (CH_2), 55.1 (CH_3), 67.8 (CH_2), 72.8 (CH_2), 73.1 (CH), 89.4 (C), 89.5 (C), 105.1 (CH), 113.8 ($2\times CH$), 119.2 (CH_2), 129.3 ($2\times CH$), 130.0 (C), 134.5 (C), 149.0 (C), 159.2 (C) ppm. HRMS (ESI): calcd. for $C_{19}H_{25}O_3$ $[M + H]^+$ 301.1798; found 301.1799.

(*S*)-*tert*-Butyl[1-(4-methoxybenzyloxy)-8-methyl-4-methylenenon-7-en-5-yn-3-yloxy]dimethylsilane (21): To a stirred solution of alcohol **11′** (712 mg, 2.37 mmol) in dry CH_2Cl_2 (21 mL) was added, at 0 °C, 2,6-lutidine (0.552 mL, 4.74 mmol) then TBDMSOTf (0.628 mL, 2.84 mmol). The mixture was stirred at 0 °C until disappearance of the starting material (2 h) and then quenched with saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with Et_2O, and the combined organic phases washed with saturated aqueous NaCl solution, dried with $MgSO_4$, and concentrated. The crude product was purified by column of chromatography (SiO_2; petroleum ether/Et_2O, 9:1) to yield 957 mg (97%). $[\alpha]_D^{23}$ = –16.7 (c = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 3 H, CH_3), 0.08 (s, 3 H, CH_3), 0.92 (s, 9 H, $3\times CH_3$), 1.83 (s, 3 H), 1.92 (s, 3 H, CH_3), 1.94–2.08 (m, 2 H, CH_2), 3.48–3.64 (m, 2 H, CH_2), 3.81 (s, 3 H, CH_3), 4.34 (dd, J = 7.7, 4.3 Hz, 1 H, CH), 4.41 (d, J = 11.3 Hz, 1 H, CH_2), 4.46 (d, J = 11.3 Hz, 1 H, CH_2), 5.36 (br. s, 1 H, CH), 5.39 (br. s, 1 H, CH_2), 5.44 (s, 1 H, CH), 6.89 (br. d, J = 8.7 Hz, 2 H, $2\times CH$), 7.28 (br. d, J = 8.7 Hz, 2 H, $2\times CH$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.0 (CH_3), –4.5 (CH_3), 18.3 (C), 21.2 (CH_3), 24.9 (CH_3), 25.9 ($3\times CH_3$), 37.3 (CH_2), 55.3 (CH_3), 66.5 (CH_2), 72.3 (CH_2), 72.7 (CH), 89.5 (C), 89.8 (C), 105.4 (CH), 113.8 ($2\times CH$), 119.0 (CH_2), 129.4 ($2\times CH$), 130.9 (C), 135.8 (C), 148.9 (C), 159.2 (C) ppm. MS (ESI+): m/z = 432 $[M + NH_4]^+$. HRMS (ESI): calcd. for $C_{25}H_{39}O_3Si$ $[M + H]^+$ 415.2663; found 415.2660.

(3*S*)-3-(*tert*-Butyldimethylsilyloxy)-8-methyl-4-methylenenon-7-en-5-ynal (23): To a stirred solution of **21** (423 mg, 1.02 mmol) in 5% aqueous CH_2Cl_2 (4 mL) was added DDQ (255 mg, 1.12 mmol) at 0 °C. The solution was stirred at 0 °C and followed by TLC. After disappearance of the starting material (4 h), the mixture was filtered through Celite and concentrated. The crude product was purified by column chromatography (SiO_2; petroleum ether/Et_2O, 8:2) to yield 380 mg of an inseparable mixture of **22** and anisaldehyde. To a stirred solution of alcohol **22** and anisaldeyde (380 mg) in CH_2Cl_2 (31 mL) was added at 0 °C Dess–Martin periodinane (545 mg, 1.29 mmol). The mixture was stirred at room temperature and followed by TLC. After disappearance of the starting material (2 h), the solution was poured into a saturated aqueous $Na_2S_2O_3$/$NaHCO_3$ solution (55 mL, 1:1). After stirring for 10 min, the layers were separated, and the aqueous layer was extracted with Et_2O. The organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried with Na_2SO_4, and concentrated under vacuum. The crude aldehyde was purified by column of chromatography (SiO_2; petroleum ether/Et_2O, 9:1) to give **23** (254 mg) in 85% yield over two steps. $[\alpha]_D^{23}$ = –50.7 (c = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 3 H, CH_3), 0.08 (s, 3 H, CH_3), 0.89 (s, 9 H, $3\times CH_3$), 1.83 (s, 3 H, CH_3), 1.91 (s, 3 H, CH_3), 2.65 (ddd, J = 15.9, 4.4, 2.3 Hz, 1 H, CH_2), 2.77 (ddd, J = 15.9, 6.8, 2.6 Hz, 1 H CH_2), 4.65 (br. d, J = 6.8, 4.4 Hz CH, 1 Hd), 5.38 (br. s, 1 H, CH), 5.44 (br. s, 1 H, CH_2), 5.56 (s, 1 H, CH), 9.79 (t, J = 2.3 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.1 (CH_3), –4.6 (CH_3), 18.2 (C), 21.2 (CH_3), 25.0 (CH_3), 25.8 ($3\times CH_3$), 50.4 (CH_2), 70.9 (CH), 89.0 (C), 90.4 (C), 105.1 (CH), 119.6 (CH_2), 134.2 (C), 149.7 (C), 201.5 (CH) ppm. MS (ESI+): m/z = 342 $[M + NH_4 + MeOH]^+$. HRMS (ESI): calcd. for $C_{17}H_{29}O_2Si$ $[M + H]^+$ 293.1931; found 293.1926.

(3*S*,5*S*,*E*)-5-(*tert*-Butyldimethylsilyloxy)-2-[2-(*tert*-butyldimethylsilyloxy)ethylidene]-10-methyl-6-methyleneundec-9-en-7-yne-1,3-diol

(24): To a solution of vinyltin reagent **13**[15] (584 mg, 1.19 mmol) in THF (18.4 mL) was added at –40 °C MeLi·LiBr (2.2 M, 1.08 mL, 2.38 mmol). The mixture was stirred at –35 °C until disappearance of the starting material. The mixture was then cooled to –80 °C and aldehyde **23** (365 mg, 1.25 mmol), diluted in a minimum amount of THF, was added at –80 °C. The reaction was followed by TLC (2 h). The mixture was quenched with saturated NH_4Cl aqueous solution. The aqueous layer was extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. The crude product was purified by column of chromatography (SiO_2; petroleum ether/Et_2O, 9:1 to 6:4) to yield 117 mg (30%). Major isomer: $[\alpha]_D^{24} = -7.5$ (c = 1, CH_2Cl_2). M.p. 65 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 6 H, 2 × CH_3), 0.08 (s, 3 H, CH_3), 0.12 (s, 3 H, CH_3), 0.88 (s, 9 H, 3 × CH_3), 0.92 (s, 9 H, 3 × CH_3), 1.81 (s, 3 H, CH_3), 1.88 (s, 3 H, CH_3), 1.95–2.05 (m, 2 H, CH_2), 3.02 (br. s, 1 H, OH), 3.66 (br. s, 1 H, OH), 4.17 (br. s, 2 H, CH2), 4.27 (d, J = 6.0 Hz, 2 H, CH_2), 4.47 (br. d, J = 8.3 Hz, 1 H, CH), 4.53 (m, 1 H, CH), 5.35 (br. s, 1 H, CH), 5.49 (s, 1 H, CH_2), 5.55 (br. s, 1 H, CH_2), 5.69 (t, J = 6.0 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.2 (CH_3), –5.1 (2 × CH_3), –4.7 (CH_3), 18.3 (C), 18.4 (C), 21.3 (CH_3), 25.0 (CH_3), 25.9 (3 × CH_3), 26.0 (3 × CH_3), 40.8 (CH_2), 58.9 (CH_2), 59.7 (CH_2), 73.1 (CH), 74 (CH), 89.4 (C), 90.0 (C), 105.2 (CH), 119.8 (CH_2), 128.0 (CH), 133.5 (C), 142.5 (C), 149.4 (C) ppm. MS (ESI+): m/z = 512 $[M + NH_4]^+$. HRMS (ESI): calcd. for $C_{27}H_{51}O_4Si_2$ $[M + H]^+$ 495.3320; found 495.3320.

(3*S*,5*S*,*E*)-5-(*tert*-Butyldimethylsilyloxy)-2-(2-hydroxyethylidene)-10-methyl-6-methyleneundec-9-en-7-yne-1,3-diyl Diacetate (25): To a stirred solution of **20** (62 mg, 0.107 mmol) in THF (4 mL) was added HF·pyridine/pyridine/THF (4 mL, 1:2:4). The mixture was stirred for 1 h at room temperature and then quenched with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried with Na_2SO_4 and then concentrated under vacuum. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 8:2) to give **25** (1.456 g) in 86% yield. $[\alpha]_D^{22} = -35.8$ (c = 1, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = –0.01 (s, 3 H, CH_3), 0.00 (s, 3 H, CH_3), 0.89 (s, 9 H, 3 × CH_3), 1.73–1.82 (m, 1 H, CH_2), 1.81 (s, 3 H, CH_3), 1.90 (s, 3 H, CH_3), 1.96–2.09 (m, 1 H, CH_2), 2.03 (br. s, 6 H, 2 × CH_3), 2.36 (m, 1 H, OH), 4.14–4.27 (m, 3 H, CH and CH_2), 4.55 (d, J = 12.5 Hz, 1 H, CH_2), 4.75 (d, J = 12.5 Hz, 1 H, CH_2), 5.28 (br. d, J = 10.8 Hz, 1 H, CH), 5.33 (br. s, 1 H, CH_2), 5.36 (br. s, 1 H, CH), 5.42 (br. s, 1 H, CH_2), 5.88 (t, J = 6.9 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.4 (CH_3), –4.3 (CH_3), 18.2 (C), 21.0 (CH_3), 21.1 (CH_3), 21.2 (CH_3), 25.0 (CH_3), 25.9 (3 × CH_3), 42.7 (CH_2), 58.3 (CH_2), 59.8 (CH_2), 71.7 (CH), 72.3 (CH), 89.5 (C), 89.9 (C), 105.3 (CH), 119.1 (CH_2), 130.9 (CH), 135.6 (C), 136.3 (C), 149.3 (C), 170.2 (C), 171.3 (C) ppm. MS (ESI+): m/z = 482 $[M + NH_4]^+$.

(3*S*,5*S*,*E*)-5-(*tert*-Butyldimethylsilyloxy)-10-methyl-6-methylene-2-(2-oxoethylidene)undec-9-en-7-yne-1,3-diyl Diacetate (26): To a stirred solution of alcohol **25** (43 mg, 0.0925 mmol) in CH_2Cl_2 (2.6 mL) was added at 0 °C Dess–Martin periodinane (47 mg, 0.111 mmol). The mixture was stirred at room temperature and followed by TLC. After disappearance of the starting material (2 h), the solution was poured into a saturated aqueous $Na_2S_2O_3$/$NaHCO_3$ solution (5 mL, 1:1). After stirring for 10 min, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried with Na_2SO_4, and then concentrated under vacuum. The crude aldehyde was purified by column of chromatography (SiO_2; petroleum ether/EtOAc, 8:2) to give **26** (42.6 mg) in quantitative yield. $[\alpha]_D^{22} = -16.3$ (c = 1, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ = 0.06 (s, 3 H, CH_3), 0.10 (s, 3 H, CH_3), 1.01 (s, 9 H, 3 × CH_3), 1.47 (br. s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 1.73 (s, 3 H, CH_3), 1.85 (br. s, 3 H, CH_3), 2.01 (dd, J = 7.4, 5.3 Hz, 2 H, CH_2), 4.37–4.41 (m, 1 H, CH), 4.58 (d, J = 14 Hz, 1 H, CH_2), 4.95 (d, J = 14 Hz, 1 H, CH_2), 5.39–5.42 (m, 3 H, CH and CH_2), 5.56–5.60 (m, 1 H, CH), 6.11 (d, J = 7.2 Hz, 1 H, CH), 9.93 (d, J = 7.2 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = –5.3 (CH_3), –4.2 (CH_3), 18.4 (C), 20.2$_6$ (CH_3), 20.3 (CH_3), 21.1 (CH_3), 24.6 (CH_3), 26.0 (3 × CH_3), 42.6 (CH_2), 59.0 (CH_2), 71.0 (CH), 72.2 (CH), 89.9 (C), 90.9 (C), 105.8 (CH), 119.4 (CH_2), 128.1 (CH), 136.1 (C), 149.4 (C), 156.0 (C), 169.4 (C), 169.6 (C), 189.6 (C) ppm. MS (ESI+): m/z = 482 $[M + NH_4]^+$.

(4*S*,6*S*,*Z*)-3-(Acetoxymethylene)-6-(4-*tert*-butyldimethylsiloxy)-11-methyl-7-methylenedodeca-1,10-dien-8-yne-1,4-diyl Diacetate (27): In a dry Schlenk tube, a solution of **26** (16.5 mg, 0.0357 mmol), DMAP (4.4 mg, 0.0357 mmol), NEt_3 (1 mL), and acetic anhydride (10 μL, 0.107 mmol) was stirred under an atmosphere of argon at 80 °C and monitored by TLC. After disappearance of the starting material (1 h), the mixture was concentrated under vacuum. The crude product was purified by flash chromatography (SiO_2; petroleum ether/EtOAc, 9:1) to give a 45:55 mixture (17.6 mg) of **27** and *iso*-**27** in 98% yield. ^1H NMR (300 MHz, C_6D_6): δ = 0.14–0.17 (m, 12 H, 12H, 6 × CH_3), 1.05 (s, 9 H, 3 × CH_3), 1.06 (s, 9 H, 3 × CH_3), 1.44 (br. s, 3 H, CH_3), 1.46 (br. s, 3 H, CH_3), 1.57 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 1.70 (s, 3 H, CH_3), 1.73 (s, 3 H, CH_3), 1.75 (s, 3 H, CH_3), 1.82 (m, 6 H, 2 × CH_3), 1.86 (br. s, 3 H, CH_3), 2.01–2.11 (m, 2 H, 2 × CH_2), 2.39–2.48 (m, 1 H, CH_2), 2.61–2.70 (m, 1 H, CH_2), 4.48 (dd, J = 9.6, 2.6 Hz, 1 H, CH), 4.53 (dd, J = 9.8, 2.5 Hz, 1 H, CH), 5.06 (d, J = 7.4 Hz, 1 H, CH), 5.36–5.46 (m, 6 H, 2 × CH and 2 × CH_2), 5.73 (d, J = 12.8 Hz, 1 H, CH), 6.32–6.40 (m, 2 H, 2 × CH), 7.30 (d, J = 7.4 Hz, 1 H, CH), 7.34 (s, 1 H, CH), 7.92 (d, J = 12.8 Hz, 1 H, CH), 8.17 (s, 1 H, CH) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = –4.1$_4$ (CH_3), –4.10 (CH_3), 18.43 (2 C), 20.0 (2 × CH_3), 20.1 (CH_3), 20.2 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 21.0 (CH_3), 21.1 (CH_3), 24.6 (2 × CH_3), 26.16 (3 × CH_3), 41.7 (CH_2), 42.0 (CH_2), 66.9 (CH), 67.1 (CH), 72.2 (CH), 72.4 (CH), 90.1$_1$ (C), 90.1$_3$ (C), 90.7 (C), 90.8 (C), 103.6 (CH), 106.0 (2 × CH), 110.1 (CH), 118.1 (C), 119.2 (CH_2), 119.3 (CH_2), 120.0 (C), 128.4 (CH), 134.5 (CH), 135.4 (CH), 136.3 (C), 136.5 (C), 137.1 (CH), 137.7 (CH), 148.9 (C), 149.0 (C), 166.6 (C), 166.7 (C), 166.8 (C), 167.2 (C), 169.1 (C), 169.2 (C) ppm. MS (ESI+): m/z = 522 $[M + NH_4]^+$.

(3*S*)-3-Triethylsilanyloxydihydrofuran-2(3*H*)-one (29): To a stirred solution of alcohol **28** (2.5 g, 24.48 mmol) in DMF (23 mL) was added imidazole (3.67 g, 53.87 mmol), DMAP (299 mg, 2.45 mmol), and TESCl (4.98 mL, 29.38 mmol). The solution was stirred at room temperature for 5 h and then quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl solution, dried with Na_2SO_4, and then concentrated under vacuum. The crude product was purified by column of chromatography (SiO_2; 3% NEt_3, petroleum ether/Et_2O, 7:3 to 6:4) to give **29** (5.3 g) in quantitative yield. $[\alpha]_D^{22} = -36.3$ (c = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.60–0.69 (m, 6 H, 3 × CH_2), 0.90–0.98 (m, 9 H, 3 × CH_3), 2.11–2.25 (m, 1 H, CH_2), 2.39–2.49 (m, 1 H, CH_2), 4.11–4.20 (m, 1 H, CH_2), 4.30–4.40 (m, 2 H, CH_2 and CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.7 (3 × CH_2), 6.6 (3 × CH_3), 32.5 (CH_2), 64.8 (CH_2), 68.00 (CH), 176.00 (C) ppm. HRMS (ESI): calcd. for $C_{10}H_{24}NO_3Si$ $[M + NH_4]^+$ 234.1519; found 234.1515.

(3*S*)-1-Hydroxy-8-methyl-3-(triethylsilyloxy)non-7-en-5-yn-4-one (30): To a solution of 1,1-dibromo-4-methylpent-1,3-diene[12]

(7.31 g, 30.46 mmol) in THF (130 mL) was added dropwise, at –78 °C, *n*-butyllithium (2.5 M in hexanes, 24.4 mL, 61 mmol). The solution was stirred at –78 °C for 1.5 h and then transferred by cannula to lactone **7** (6 g, 27.73 mmol) in THF (130 mL) at –78 °C. After warming to –20 °C, the mixture was quenched with a 9:1 mixture of saturated aqueous NH_4Cl solution and aqueous 33% NH_4OH solution. The aqueous phase was extracted with EtOAc. The combined organic layers were dried with Na_2SO_4, filtered, and then concentrated under vacuum. The crude alcohol was purified by column of chromatography (SiO_2; 3% NEt_3, petroleum ether/Et_2O, 7:3 to 6:4) to give **30** (5.04 g) in 61% yield. $[\alpha]_D^{22} = -56.3$ (c = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.63 (q, J = 7.9 Hz, 6 H, 3 × CH_2), 0.95 (t, J = 7.9 Hz, 9 H, 3 × CH_3), 1.89 (br. s, 3 H, CH_3), 1.99 (br. s, 3 H, CH_3), 1.97–2.05 (m, 2 H, CH_2), 2.24 (m, 1 H, OH), 3.76 (t, J = 5.6 Hz, 2 H, CH_2), 4.39 (br. d, J = 5.1, 6.8 Hz, CH, 1 Hd), 5.42 (br. s, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.8 (3 × CH_2), 6.8 (3 × CH_3), 22.0 (CH_3), 25.6 (CH_3), 36.9 (CH_2), 59.4 (CH_2), 77.5 (CH, C3), 89.6 (C), 94.3 (C), 103.7 (CH), 159.2 (C), 189.8 (C) ppm. HRMS (ESI): calcd. for $C_{16}H_{29}O_3Si$ $[M + H]^+$ 297.1880; found 297.1879.

(3*S*)-8-Methyl-4-oxo-3-(triethylsilyloxy)non-7-en-5-ynal (31): To a stirred solution of alcohol **30** (1.5 g, 5.06 mmol) in CH_2Cl_2 (45 mL) was added at 0 °C Dess–Martin periodinane (2.55 g, 6.04 mmol). The mixture was stirred at room temperature and followed by TLC. After disappearance of the starting material (2 h), the solution was poured into a saturated aqueous $Na_2S_2O_3$/$NaHCO_3$ solution (255 mL, 1:1). After stirring for 10 min, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried with Na_2SO_4, and then concentrated under vacuum. The crude aldehyde was purified by column of chromatography (SiO_2; 3% NEt_3, petroleum ether/Et_2O, 8:2) to give **31** (1.27 g) in 85% yield. $[\alpha]_D^{20} = -46.4$ (c = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.63 (q, J = 8.0 Hz, 6 H, 3 × CH_2), 0.94 (t, J = 8.0 Hz, 9 H, 3 × CH_3), 1.91 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3), 2.80–2.83 (m, 2 H, CH_2), 4.68 (br. t, J = 5.8 Hz, 1 H, CH), 5.43 (br. s, 1 H, CH), 9.78 (br. t, J = 1.4 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.8 (3 × CH_2), 6.8 (3 × CH_3), 22.1 (CH_3), 25.6 (CH_3), 48.2 (CH_2), 74.3 (CH), 89.4 (C), 95.0 (C), 103.6 (CH), 159.8 (C), 188.0 (C), 199.08 (CH) ppm. MS (ESI+): m/z = 295 $[M + H]^+$. HRMS (ESI): calcd. for $C_{16}H_{27}O_3Si$ $[M + H]^+$ 295.1723; found 295.1723.

(*E*)-4-Triethylsilyloxy-2-tributylstannylbut-2-en-1-ol (32): To a solution of (*E*)-2-tributylstannylbut-2-en-1-ol[15] (9.66 g, 25.61 mmol) in THF (105 mL) at –20 °C was added NEt_3 (7.13 mL, 51.22 mmol) and TESCl (4.33 mL, 25.61 mmol). The solution was stirred at –20 °C and followed by TLC. After disappearance of the starting material (4 h) the reaction was quenched with water, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under vacuum. The crude alcohol was purified by column of chromatography (SiO_2; 3% NEt_3, petroleum ether/Et_2O, 9:1) to give **32** (6.62 g) in 53% yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.62 (q, J = 7.7 Hz, 6 H, 3 × CH_2), 0.86–0.99 (m, 24 H, 6 × CH_3, 3 × CH_2), 1.25–1.37 (m, 6 H, 6 × CH_2), 1.44–1.55 (m, 6 H, 6 × CH_2), 1.82 (br. t, J = 5.4 Hz, 1 H, OH), 4.22 (br. d, J = 5.5 Hz, $^4J_{Sn,H}$ = 16 Hz, 2 H, CH_2), 4.34 (m, $^3J_{Sn,H}$ = 37 Hz, 2 H, CH_2), 5.72 (br. t, J = 5.4 Hz, $^3J_{Sn,H}$ = 69 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.6 (3 × CH_2), 6.9 (3 × CH_3), 7.9, ($^1J_{Sn,C}$ = 332 Hz, 3 × CH_2), 13.8 (3 × CH_2), 27.2 ($^3J_{Sn,C}$ = 58 Hz, 3 × CH_2), 29.3 ($^2J_{Sn,C}$ = 19 Hz, 3 × CH_2), 60.5 (CH_2), 63.8 ($^2J_{Sn,C}$ = 24 Hz, CH_2), 138.9 ($^2J_{Sn,C}$ = 19 Hz, CH), 147.5 (C) ppm. HRMS (ESI): calcd. for $C_{22}H_{49}O_2SiSn$ $[M + H]^+$ 493.2522; found 493.2534.

(7*S*,9*S*,*E*)-9-Hydroxy-10-(hydroxymethyl)-2-methyl-7,12-bis(triethylsilyloxy)dodeca-2,10-dien-4-yn-6-one (33): To a solution of vinyl tin **32** (1.08 g, 2.21 mmol) in THF (31 mL) at –78 °C was added dropwise MeLi·LiBr (2.0 mL, 4.41 mmol, 2.2 M in Et_2O). The reaction mixture was warmed to –35 °C. The mixture was then cooled to –78 °C and aldehyde **31** (620 mg, 2.1 mmol) diluted in minimum of THF was added dropwise at –78 °C. The solution was kept at –78 °C for 1 h and then quenched with a 9:1 mixture of saturated aqueous NH_4Cl solution and aqueous 33% NH_4OH solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography (SiO_2; 3% NEt_3, petroleum ether/Et_2O, 6:4) to give a 7:3 separable mixture of diastereomers **34** (444 mg) in 43% yield. Major diastereomer **33**: $[\alpha]_D^{21} = -32.8$ (c = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.55–0.68 (m, 12 H, 6 × CH_2), 0.91–0.99 (m, 18 H, 6 × CH_3), 1.90 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3), 2.00–2.15 (m, 2 H, CH_2), 4.17 (br. d, J = 2.5 Hz, 2 H, CH_2), 4.25 (d, J = 5.6 Hz, 2 H, CH_2), 4.41 (d, J = 9.2 Hz, 1 H, CH), 4.51 (br. d, J = 4.3, 6.6 Hz, CH, 1 Hd), 5.43 (br. s, 1 H, CH), 5.71 (t, J = 5.6 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.4 (CH_2), 4.8 (CH_2), 6.8 (3 × CH_3), 22.0 (CH_3), 25.6 (CH_3), 40.1 (CH_2), 58.6 (CH_2), 59.1 (CH_2), 72.8 (CH), 77.4 (CH), 89.7 (C), 94.5 (C), 103.7 (CH), 128.5 (CH), 142.4 (C), 159.4 (C), 189.4 (C) ppm. MS (ESI+): m/z = 514 $[M + NH_4]^+$. HRMS (ESI): calcd. for $C_{26}H_{52}NO_5Si_2$ $[M + NH_4]^+$ 514.3378; found 514.3378.

(3*S*,5*S*,*E*)-10-Methyl-6-oxo-5-(triethylsilyloxy)-2-[2-(triethylsilyloxy)ethylidene]undec-9-en-7-yne-1,3-diyl Diacetate (34): A solution of diol **33** (70 mg, 0.141 mmol), acetic anhydride (53 μL, 0.563 mmol), and DMAP (1.7 mg, 0.014 mmol) in pyridine (2 mL) was stirred at room temperature. After disappearance of the starting material (4 h), the mixture was quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with diethyl ether and the organic layers were washed with saturated aqueous $CuSO_4$ solution and water, dried with $MgSO_4$, and then concentrated under vacuum. The crude product was purified by column of chromatography (SiO_2; 3% NEt_3, petroleum ether/Et_2O, 85:15) to give **34** (66 mg) in 81% yield. $[\alpha]_D^{19} = -31.5$ (c = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.53–0.63 (m, 12 H, 6 × CH_2), 0.92 (t, J = 7.9 Hz, 9 H, 3 × CH_3), 0.93 (t, J = 7.9 Hz, 9 H, 3 × CH_3), 1.74–1.87 (m, 1 H, CH_2), 1.91 (s, 3 H, CH_3), 2.01–2.02 (m, 9 H, 3 × CH_3), 2.06–2.20 (m, 1 H, CH_2), 4.23 (dd, J = 9.8, 2.8 Hz, 1 H, CH), 4.27 (d, J = 5.9 Hz, 2 H, CH_2), 4.57 (d, J = 12.7 Hz, 1 H, CH_2), 4.62 (d, J = 12.7 Hz, 1 H, CH_2), 5.31 (br. d, J = 10.6, 1.9 Hz, CH, 1 Hd), 5.44 (br. s, 1 H, CH), 5.83 (t, J = 5.9 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.5 (CH_2), 4.8 (CH_2), 6.8 (3 × CH_3), 20.9 (CH_3), 21.1 (CH_3), 22.0 (CH_3), 25.6 (CH_3), 39.6 (CH_2), 59.2 (CH_2), 59.7 (CH_2), 71.9 (CH), 76.0 (CH), 89.4 (C), 94.2 (C), 103.7 (CH), 133.4 (C), 133.7 (CH), 159.3 (C), 169.9 (C), 170.7 (C), 189.4 (C) ppm. MS (ESI+): m/z = 598 $[M + NH_4]^+$. HRMS (ESI): calcd. for $C_{30}H_{56}NO_7Si_2$ $[M + NH_4]^+$ 598.3589; found 598.3584.

(3*S*,5*S*,*E*)-10-Methyl-6-oxo-5-(triethylsilyloxy)-2-[2-(triethylsilyloxy)ethylidene]undec-9-en-7-yne-1,3-diyl Diacetate (35): To a stirred solution of CH_3PPh_3Br (307 mg, 0.860 mmol) in THF (0.7 mL) was added *t*BuOK (77 mg, 0.69 mmol) in THF (0.7 mL). The solution was stirred at 0 °C for 30 min and then cooled to –78 °C. Ketone **34** (100 mg, 0.172 mmol) diluted in THF (1 mL) was then added. The solution was warmed up to 0 °C and then quenched with water. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried with Na_2SO_4 and then concentrated under vacuum. The crude product was purified by column of chromatography (SiO_2; 3% NEt_3, petroleum ether/Et_2O, 9:1) to

give **35** (52 mg) in 53% yield. $[\alpha]_D^{19}$ = –34.0 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.57 (q, *J* = 8.12 Hz, 12 H, 6 × CH_2), 0.93 (t, *J* = 8.1 Hz, 9 H, 6 × CH_3), 1.74–1.87 (m, 1 H, CH_2), 1.81 (s, 3 H, CH_3), 1.90 (s, 3 H, CH_3), 1.95–2.08 (m, 1 H, CH_2), 2.01 (m, 6 H, 2 × CH_3), 4.20 (dd, *J* = 9.1, 2.7 Hz, 2 H, CH), 4.27 (d, *J* = 6.0 Hz, 2 H, CH_2), 4.56 (d, *J* = 12.5 Hz, 1 H, CH_2), 4.62 (d, *J* = 12.5 Hz, 1 H, CH_2), 5.29–5.37 (m, 3 H, CH_2 and 2 × CH), 5.43 (br. s, 1 H, CH_2), 5.80 (t, *J* = 6.0 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.5 (3 × CH_2), 4.9 (3 × CH_2), 6.8 (3 × CH_3), 6.9 (3 × CH_3), 20.9 (CH_3), 21.1 (CH_3), 21.2 (CH_3), 25.0 (CH_3), 42.32 (CH_2), 59.3 (CH_2), 59.8 (CH_2), 72.0 (CH), 72.7 (CH), 89.5 (C), 89.9 (C), 105.4 (CH), 119.1 (CH_2), 133.1 (CH), 133.9 (C), 135.7 (C), 149.2 (C), 170.0 (C), 170.8 (C) ppm. MS (ESI+): *m*/*z* = 596 $[M + NH_4]^+$. HRMS (ESI): calcd. for $C_{31}H_{58}NO_6Si_2$ $[M + NH_4]^+$ 596.3797; found 596.3790.

(3*S*,5*S*,*E*)-2-(2-Hydroxyethylidene)-10-methyl-6-methylene-5-(triethylsilyloxy)undec-9-en-7-yne-1,3-diyl Diacetate (36): To a stirred solution of **35** (89 mg, 0.154 mmol) in THF (7 mL) was added a mixture of H_2O (700 μL) and AcOH (1.4 mL) dropwise. The mixture was warmed to 40 °C and stirred for 12 h. The mixture was then cooled to 0 °C and poured slowly into a suspension of $NaHCO_3$ (3 g) in water (20 mL). The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried with Na_2SO_4, and then concentrated under vacuum. The crude product was purified by column of chromatography (SiO_2; 3% NEt_3, petroleum ether/EtOAc, 1:1) to give **36** (63 mg) in 88% yield. $[\alpha]_D^{18}$ = –36.9 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.52–0.60 (m, 6 H, 3 × CH_2), 0.93 (t, *J* = 7.9 Hz, 9 H, 3 × CH_3), 1.74–1.87 (m, 1 H, CH_2), 1.81 (s, 3 H, CH_3), 1.90 (s, 3 H, CH_3), 1.96–2.09 (m, 1 H, CH_2), 2.02 (br. s, 6 H, 2 × CH_3), 2.37 (m, 1 H, OH), 4.14–4.27 (m, 3 H, CH and CH_2), 4.55 (d, *J* = 12.5 Hz, 1 H, CH_2), 4.74 (d, *J* = 12.5 Hz, 1 H, CH_2), 5.28 (dd, *J* = 10.4, 1.8 Hz, 1 H, CH), 5.34 (br. s, 1 H, CH_2), 5.36 (br. s, 1 H, CH), 5.43 (br. s, 1 H, CH_2), 5.88 (t, *J* = 6.8 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.9 (3 × CH_2), 6.9 (3 × CH_3), 21.0 (CH_3), 21.1 (CH_3), 21.2 (CH_3), 25.0 (CH_3), 42.5 (CH_2), 58.4 (CH_2), 59.7 (CH_2), 71.9 (CH), 72.5 (CH), 89.5 (C), 89.9 (C), 105.3 (CH), 119.1 (CH_2), 131.2 (CH), 135.6 (C), 136.1 (C), 149.3 (C), 170.2 (C), 171.2 (C) ppm. MS (ESI+): *m*/*z* = 482 $[M + NH_4]^+$. HRMS (ESI): calcd. for $C_{25}H_{44}NO_6Si$ $[M + NH_4]^+$ 482.2932; found 482.2929.

(3*S*,5*S*,*E*)-10-Methyl-6-methylene-2-(2-oxoethylidene)-5-(triethylsilyloxy)undec-9-en-7-yne-1,3-diyl Diacetate (37): To a stirred solution of alcohol **36** (58 mg, 0.125 mmol) in CH_2Cl_2 (4 mL) was added at 0 °C Dess–Martin periodinane (63 mg, 0.15 mmol). The mixture was stirred at room temperature and followed by TLC. After disappearance of the starting material (2 h), the solution was poured into a saturated aqueous $Na_2S_2O_3$/$NaHCO_3$ solution (7 mL, 1:1). After stirring for 10 min, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried with Na_2SO_4, and then concentrated under vacuum. The crude aldehyde was purified by column of chromatography (SiO_2; 3% NEt_3, petroleum ether/EtOAc, 7:3) to give **37** (51 mg) in 89% yield. $[\alpha]_D^{19}$ = –18.7 (*c* = 1, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ = 0.60–0.68 (m, 6 H, 3 × CH_2), 1.01 (t, *J* = 7.9 Hz, 9 H, 3 × CH_3), 1.46 (br. s, 3 H, CH_3), 1.64 (s, 3 H, CH_3), 1.72 (s, 3 H, CH_3), 1.84 (br. s, 3 H, CH_3), 2.00–2.04 (m, 2 H, CH_2), 4.40–4.44 (m, 1 H, CH), 4.62 (d, *J* = 13.6 Hz, 1 H, CH_2), 4.93 (d, *J* = 13.6 Hz, 1 H, CH_2), 5.39–5.44 (m, 3 H, CH and CH_2), 5.58–5.62 (m, 1 H, CH), 6.10 (br. d, *J* = 7.4 Hz, 1 H, CH), 9.93 (d, *J* = 7.4 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 5.2 (3 × CH_2), 7.1 (3 × CH_3), 20.2 (CH_3), 20.3 (CH_3), 21.1 (CH_3), 24.6 (CH_3), 42.5 (CH_2), 59.0 (CH_2), 71.1 (CH), 72.3 (CH), 89.9 (C), 90.9 (C), 105.8 (CH), 119.4 (CH_2), 128.1 (CH), 135.2 (C), 149.4 (C), 156.0 (C), 19.4 (C), 169.6 (C), 189.5 (CH) ppm. MS (ESI+): *m*/*z* = 480 $[M + NH_4]^+$. HRMS (ESI): calcd. for $C_{25}H_{42}NO_6Si$ $[M + NH_4]^+$ 480.2775; found 480.2774.

(3*S*,5*S*,*Z*)-2-(2-Acetoxyvinyl)-10-methyl-6-methylene-5-(triethylsilyloxy)undeca-1,9-dien-7-yne-1,3-diyl Diacetate (38): In a dry Schlenk tube, a solution of **37** (50 mg, 0.108 mmol), DMAP (13 mg, 0.108 mmol), NEt_3 (0.67 mL), and acetic anhydride (30 μL, 0.324 mmol) was stirred under an atmosphere of argon at 80 °C and monitored by TLC. After disappearance of the starting material (3 h), the mixture was concentrated under vacuum. The crude product was then purified by flash chromatography (SiO_2; 3% NEt_3, petroleum ether/EtOAc, 7:3) to give a 53:47 mixture (40 mg) of **38** and *iso*-**38** in 89% yield. ^1H NMR (300 MHz, C_6D_6): δ = 0.68–0.77 (m, 12 H, 6 × CH_2), 1.05–1.11 (m, 18 H, 6 × CH_3), 1.43 (br. s, 3 H, CH_3), 1.45 (br. s, 3 H, CH_3), 1.56 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3), 1.73 (br. s, 6 H, 2 × CH_3), 1.81 (br. s, 6 H, 2 × CH_3), 1.86 (br. s, 3 H, CH_3), 2.00–2.16 (m, 2 H, 2 × CH_2), 2.42–2.51 (m, 1 H, CH_2), 2.62–2.72 (m, 1 H, CH_2), 4.50–4.58 (m, 2 H, 2 × CH), 5.08 (d, *J* = 7.4 Hz, 1 H, CH), 5.35–5.48 (m, 6 H, 6 × CH), 5.74 (d, *J* = 12.7 Hz, 1 H, CH), 6.36–6.44 (m, 2 H, 2 × CH_2), 7.31 (d, *J* = 7.4 Hz, 1 H, CH), 7.34 (s, 1 H, CH), 6.10 (br. d, *J* = 7.4 Hz, 1 H, CH), 7.93 (d, *J* = 12.7 Hz, 1 H, CH), 8.17 (s, 1 H, CH) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 5.3_2 (3 × CH_2), 5.3_4 (3 × CH_2), 7.3 (6 × CH_3), 20.0 (3 × CH_3), 20.1 (CH_3), 20.5 (CH_3), 20.7 (CH_3), 21.0 (CH_3), 21.1 (CH_3), 24.6 (2 × CH_3), 41.7 (CH_2), 42.0 (CH_2), 67.0 (CH), 67.2 (CH), 72.5 (CH), 72.6 (CH), 90.1_1 (C), 90.1_4 (C), 90.7 (C), 90.8 (C), 103.7 (CH), 106.1 (CH), 110.2 (CH), 118.2 (C), 119.2 (CH_2), 119.3 (CH_2), 120.1 (C), 128.4 (CH), 134.6 (CH), 135.3 (CH), 136.4 (C), 136.6 (C), 137.2 (CH), 137.7 (CH), 148.9 (C), 149.0 (C), 166.6 (C), 166.8 (C), 166.9 (C), 167.2 (C), 169.1 (C), 169.2 (C) ppm. MS (ESI+): *m*/*z* = 522 $[M + NH_4]^+$. HRMS (ESI): calcd. for $C_{27}H_{44}NO_7Si$ $[M + NH_4]^+$ 522.2881; found 522.2880.

Caulerpenynol (2): To a stirred solution of **38** (20 mg, 0.0396 mmol) in THF (640 μL) was added a mixture of AcOH (2 mL) and H_2O (1 mL). The solution was then heated at 45 °C and followed by TLC. After disappearance of the starting material (2 h) the mixture was poured into an aqueous solution of $NaHCO_3$ (3 g). The aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried with Na_2SO_4, and then concentrated under vacuum. The crude product was purified by column of chromatography (SiO_2; 3% NEt_3, petroleum ether/EtOAc, 1:1) to give a 52:48 mixture of **2** and *iso*-**2** (12.5 mg) in 81% yield separable by HPLC.[26] Caulerpenynol (**2**): $[\alpha]_D^{25}$ = –48.6 (*c* = 0.105, EtOH), ref.[6] $[\alpha]_D^{20}$ = –53.7 (*c* = 0.095, EtOH). ^1H NMR (500 MHz, C_6D_6): δ = 1.46 (br. s, 3 H, CH_3), 1.57 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 1.71 (s, 3 H, CH_3), 1.84 (br. s, 3 H, CH_3), 2.00 (ddd, *J* = 14.5, 9.6, 3.4 Hz, 1 H, CH_2), 2.69 (ddd, *J* = 14.5, 10.4, 3.2 Hz, 1 H, CH_2), 4.30 (br. d, *J* = 9.6 Hz, 1 H, CH), 5.39 (br. s, 1 H, CH), 5.46 (br. s, 1 H, CH), 5.53 (br. s, 1 H, CH), 5.77 (d, *J* = 12.7 Hz, 1 H, CH), 6.53 (dd, *J* = 10.4, 3.4 Hz, 1 H, CH), 7.30 (s, 1 H, CH), 7.92 (d, *J* = 12.7 Hz, 1 H, CH) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 19.87 (CH_3), 19.98 (CH_3), 20.46 (CH_3), 21.07 (CH_3), 24.59 (CH_3), 40.74 (CH_2), 67.15 (CH), 70.92 (CH), 89.95 (C), 90.72 (C), 105.91 (CH), 109.93 (CH), 119.15 (CH_2), 119.92 (C), 134.46 (CH), 135.48 (C), 137.34 (CH), 149.06 (C), 166.73 (C), 167.24 (C), 170.00 (C) ppm. *iso*-**2**: $[\alpha]_D^{25}$ = –33.2 (*c* = 0.295, EtOH), ^1H NMR (500 MHz, C_6D_6): δ = 1.45 (br. s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 1.64 (s, 3 H, CH_3), 1.66 (s, 3 H, CH_3), 1.80 (br. s, 3 H, CH_3), 1.98 (ddd, *J* = 14.2, 9.6, 3.4 Hz, 1 H, CH_2), 2.53 (ddd, *J* = 14.2, 10.4, 3.0 Hz, 1 H, CH_2), 4.30 (br. d, *J* = 9.6 Hz,

1 H, CH), 5.12 (d, J = 7.3 Hz, 1 H, CH), 5.36 (br. s, 1 H, CH), 5.48 (br. s, 1 H, CH), 5.58 (br. s, 1 H, CH), 6.57 (dd, J = 10.4, 3.4 Hz, 1 H, CH), 7.31 (d, J = 7.3 Hz, 1 H, CH), 8.10 (s, 1 H, CH) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 20.00 (CH_3), 20.57 (CH_3), 21.04 (CH_3), 24.57 (CH_3), 40.99 (CH_2), 67.13 (CH), 70.89 (CH), 90.03 (C), 90.57 (C), 103.83 (CH), 105.88 (CH), 118.07 (C), 119.30 (CH_2), 135.33 (CH), 135.52 (C), 137.73 (CH), 149.10 (C), 166.84 (C), 166.97 (C), 170.14 (C) ppm.

Supporting Information (see footnote on the first page of this article): Synthetic procedures, NMR spectroscopic data, spectra for all synthesized compounds, comparison of NMR spectroscopic data for original and synthesized caulerpenynol (**2**).

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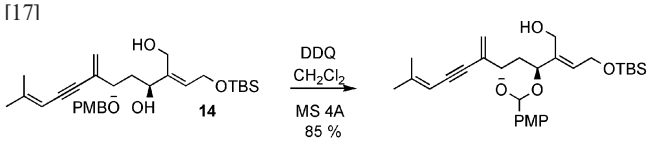

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[27] See Supporting Information for an NMR spectroscopic comparison between natural and synthetic caulerpenynol.

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