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Stereoselective total synthesis of (+)-hyptolide†

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Stereoselective synthesis of the naturally occurring 6-membered lactone hyptolide **1** is described. The main feature of the synthesis is the utility of the hitherto unexplored alkyne fragment derived from commercially available 3-butyn-1-ol (homopropargylic alcohol).

Introduction

In 1920, Gorter[1] reported the isolation of a crystalline lactone, (+)-hyptolide **1**, from leaves of *Hyptis pectinata*, a plant that is used in folk medicine. Various biological effects were found with its extracts, such as: analgesic, anti-inflammatory, and anti-microbial. The structure proposed was proved wrong when hyptolide was subjected to reinvestigation by Birch and Butler[2] in 1964. Later, the absolute configuration was established by Anders Kjaer *et al.*[3] by detailed ^{1}H and ^{13}C NMR spectroscopic studies and on the basis of single-crystal X-ray diffraction data as 6*R*-(1*Z*,3*S*,5*R*,6*S*)-5,6-dihydro-6-[3,5,6-tris(acetoxy)-1-heptenyl]-2*H*-pyran-2-one. Hyptolide (**1**) is structurally similar to other members of the polyhydroxy δ-pyranone natural product family such as spicigerolide (**2**),[4] synrotolide (**3**),[5] synargentolide A (**4**),[6] anamarine (**5**)[7] (Fig. 1). Earlier, two syntheses[8] were reported for the synthesis of (+)-hyptolide. While our manuscript was under preparation, a silicon tethered RCM route for hyptolide was published by Kumar and his co-workers.[9] As part of our continuing interest in the synthesis of natural products having δ-lactone rings,[10] we were interested in the synthesis of hyptolide. In the present communication, we disclose the stereoselective total synthesis of (+)-hyptolide from commercially available 3-butyn-1-ol.

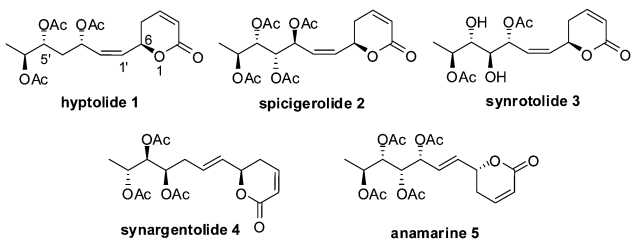
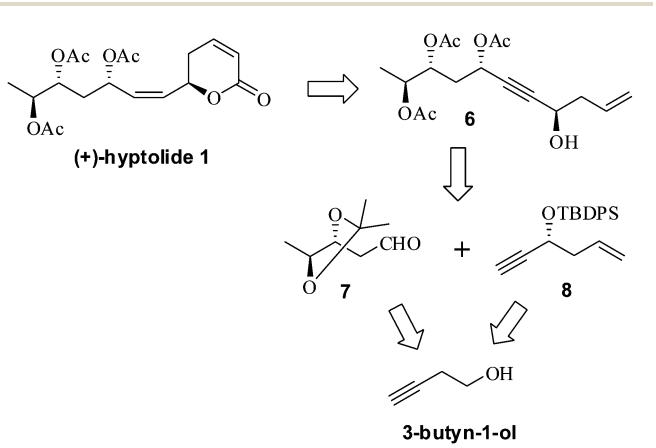


Fig. 1 Hyptolide type pyranone polyacetates.

Retrosynthetic analysis (Scheme 1) reveals that compound **1** could be synthesized from homoallylic alcohol **6** by acrylolyation followed by a RCM reaction and semihydrogenation of the triple bond. The compound **6** in turn can be synthesized from **7** and **8** by a coupling reaction. Whereas, the aldehyde **7** and alkyne **8** intermediates could be derived from 3-butyn-1-ol.

Results and discussion

Our synthetic endeavor began with the benzyl protected 2,3-epoxy alcohol **9** (Scheme 2) prepared from 3-butyn-1-ol similarly as reported for the preparation of PMB(*para*-methoxybenzyl) protected 2,3-epoxy alcohol.[11] We then turned our attention to the key step for the introduction of benzoate *via* nucleophilic epoxide ring opening with benzoic acid, which culminates in the creation of a C5′ chiral center of the molecule. Thus, regio- and stereoselective ring opening of ((2*S*,3*S*)-3-(2-(benzyloxy)ethyl)oxiran-2-yl)methanol **9** was



Scheme 1 Retrosynthesis.

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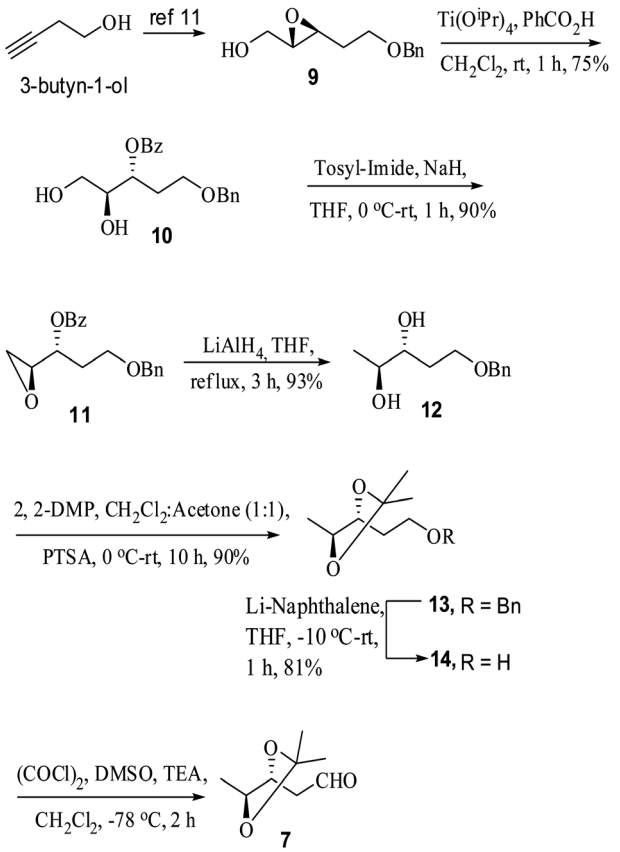
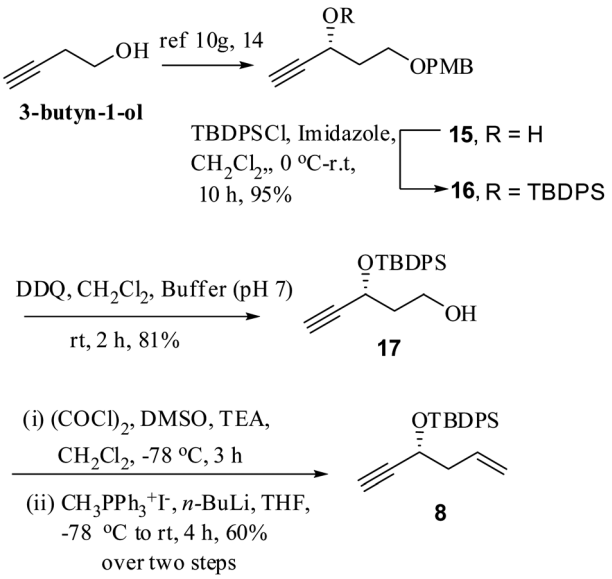
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of all compounds. See DOI: 10.1039/c3ra45042b



Scheme 2 Synthesis of aldehyde **7**.



Scheme 3 Synthesis of chiral propargylic alcohol **8**.

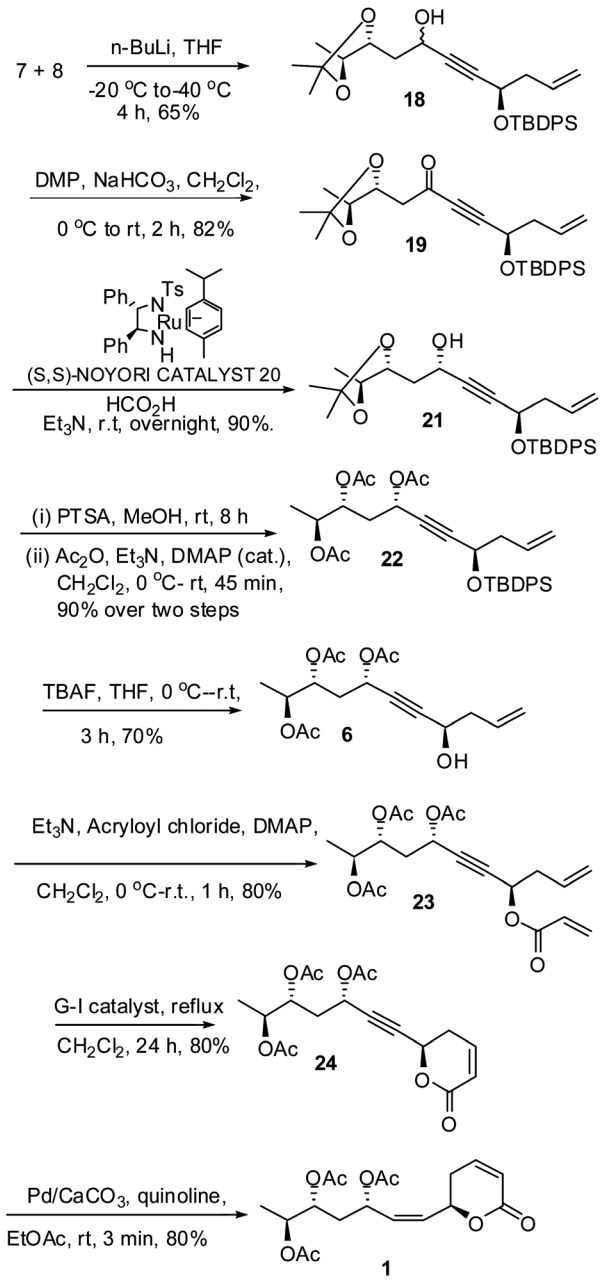
achieved at C-3 with benzoic acid and $Ti(OiPr)_4$ within 1 h in CH_2Cl_2,[12] affording a 75% yield of the benzoate diol **10**. The diol **10** was converted into epoxide **11** in 90% yield by following the Forsyth protocol.[13] Lithium aluminium hydride reduction of epoxide **11** delivered terminal methyl compound **12**. The diol **12** having *anti*-configuration was protected as an acetonide **13** followed by removal of benzyl group resulted in primary alcohol **14**. Swern oxidation of **14** led to the formation of aldehyde **7**.

The synthesis of hitherto unexplored alkyne fragment **8** began by converting commercially available 3-butyn-1-ol (homopropargylic alcohol) to the known PMB protected chiral propargylic alcohol **15** following a reported procedure (Scheme 3).[10g,14a–c] The free secondary hydroxyl group of the latter was protected as silyl ether **16** and DDQ-mediated oxidative cleavage of the PMB (*para*-methoxybenzyl) ether produced primary alcohol **17**. Swern oxidation of alcohol afforded aldehyde followed by one-carbon Wittig olefination (*n*-BuLi, $CH_3PPh_3^+I^-$, dry THF) to furnish key intermediate **8**.

At this point, we were set to couple the appropriate fragments to generate the carbon frame work of hyptolide. Formation of the chiral propargyl alcohol **21** was envisioned by lithiated alkyne **8** coupling to the aldehyde **7** followed by adopting an oxidation/selective reduction protocol. Alkyne **8** on reaction with *n*-BuLi followed by coupling of the generated lithium acetylide with aldehyde **7** afforded a mixture of propargylic alcohols **18** (65%), which on oxidation with Dess–Martin Periodinane (DMP) gave ynone **19** in 82% yield (Scheme 4).

Initially, our efforts towards the reduction of **19** to the corresponding hydroxy compound **21** were not fruitful under CBS conditions. Use of 1 M solution of $BH_3 \cdot DMS$ at −40 °C gave low yields of the reduced product. Whereas, using conc. $BH_3 \cdot DMS$ solution either in dry toluene or THF furnished the alcohol (**21**) as a diastereomeric mixture in 6 : 4 ratio however, the ketone functionality was reduced with Noyori's catalyst Ru[(1*S*,2*S*)-*p*-TsNCH(Ph)CH(Ph)NH](η6-*p*-cymene) (**20**)[15] in HCOOH affording **21** in 90% yield and 95% de.[16] Then, we tried to minimize the use of protecting groups by maintaining the oxygenated functional groups as acetates. Thus, hydrolytic cleavage of acetonide protecting group in **21** leading to a triol, which was acetylated *in situ* with acetic anhydride in the presence of NEt_3 and DMAP to form the triacetate **22** in 90% yield for the two steps. The alcohol **22** was transformed into its acrylic ester **23** in 80% yield by treating with acryloyl chloride, catalytic amounts of DMAP and triethylamine in CH_2Cl_2. Ring closing metathesis[17] reaction of **23** in refluxing DCM for 24 h using 10 mol% first generation Grubbs' catalyst, bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride produced the lactone **24** in 80% yield.

We envisioned that partial hydrogenation of the triple bond using Lindlar's catalyst in EtOAc would provide hyptolide. However, this reaction was base as well as time sensitive, maybe it is attributed for the presence of three OAc groups. Hydrogenation using $Pd/BaSO_4$ for 10 min resulted in fully saturated compound by reduction of triple bond and lactone double bond. Use of $Pd/CaCO_3$ in 10 min also resulted in partial hydrogenation of the triple bond to the *Z*-olefin of along with reduction of the lactone double bond. However, reducing the time to 3 min in the presence of $Pd/CaCO_3$ provided the target lactone, (+)-hyptolide (**1**) by achieving the partial hydrogenation



Scheme 4 Synthesis of hyptolide **1**.

of the triple bond to the *Z*-olefin in 90% yield. The synthetic (+)-hyptolide (**1**) spectroscopic data was identical to that of the natural product.

Overall yields 7.14%, 15.34% and 20.27% reported respectively by Marco & Carda *et al.*,[8a] Chakraborty *et al.*[8c] and Kumar *et al.*[9] for previous synthetic routes.

Conclusion

We have successfully completed the total synthesis of (+)-hyptolide from 3-butyn-1-ol with an overall yield of 7.08% relying on regioselective epoxide opening, sharpless asymmetric epoxidation, aldehyde alkyne coupling and ring-closing metathesis reactions as key steps.

Experimental section

All the solvents and reagents were purified by standard techniques, reactions were performed in oven-dried round bottom flasks; crude products were purified by column chromatography on silica gel (60–120 mesh). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to an methanolic acidic solution of *p*-anisaldehyde on a hot plate (~250 °C). Organic solutions were concentrated on rotary evaporator at 40–45 °C. IR spectra were recorded on Perkin–Elmer 683, Thermo Nicolet Nexus 670 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on a Varian Gemini 200, Bruker AV-300 and Varian Innova 500 NMR spectrometer. Chemical shifts were reported in parts per million (ppm) with respect to internal TMS. Coupling constants (*J*) are quoted in Hertz (Hz). s, br s, d, dd, ddd, dt, t, q, qt and m refer to singlet, broad singlet, doublet, doublet of doublet, doublet of doublet of doublet, triplet, quartet, quintet and multiplet, respectively. The optical rotations were measured on a Perkin Elmer-343 polarimeter. The diastereomeric excess of the products were measured by HPLC using Shimadzu LC-20AT series with XDB C18, 150 × 4.6, 5U column. Mass spectra were recorded on Micromass VG-7070H mass spectrometer for ESI and EI are given in mass-to-charge (*m*/*z*). High-resolution mass spectra (HRMS) [ESI] were obtained using either a TOF or a double focusing spectrometer.

(2*S*,3*R*)-5-(Benzyloxy)-1,2-dihydroxypentan-3-yl benzoate (10)

To a stirred solution of epoxy alcohol **9** (7 g, 33.65 mmol) in dry CH_2Cl_2 (35 mL) containing benzoic acid nuleophile (4.51 g, 37.09 mmol), Ti(O-*i*-Pr)$_4$ (15.0 mL, 50.52 mmol) was added at room temperature. The mixture was stirred for 1 h at the same temperature. After completion of the reaction, as determined by TLC, the reaction mixture was cooled to 0 °C and quenched with dropwise addition of saturated aqueous $NaHCO_3$ (20 mL). The resulting milky solution was stirred vigorously for 10 h and then filtered through a pad of Celite (CH_2Cl_2 rinse) and extracted with ethyl acetate (4 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (4 : 6, EtOAc–hexane) to afford **10** (8.32 g, 25.24 mmol, 75%) as a viscous liquid. $[\alpha]_D^{25}$ = +7.4 (*c* 1.1, $CHCl_3$); IR (KBr): 3420, 2867, 1715, 1275, 1112, 1070, 713 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$):δ 8.01–7.98 (m, 2H), 7.60–7.56 (m, 1H), 7.46–7.41 (m, 2H), 7.37–7.22 (m, 5H), 5.24–5.20 (m, 1H), 4.51 (ABq, *J* = 17.5, 11.7 Hz, 2H), 3.85–3.80 (m, 1H), 3.74–3.63 (m, 2H), 3.62–3.56 (m, 2H), 2.64 (br s, 1H), 2.27–2.19 (m, 1H), 2.17–2.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 137.5, 133.2, 129.6, 128.3, 127.7, 73.2, 72.6, 7 2.2, 66.0, 62.8, 30.9; HRMS (ESI) for $C_{19}H_{22}O_5Na$ $[M + Na]^+$ found 353.13594, calcd 353.13531.

(*R*)-3-(Benzyloxy)-1-((*S*)-oxiran-2-yl)propyl benzoate (11)

To a stirred solution of 60% sodium hydride dispersion in mineral oil (1.45 g, 60.41 mmol) in THF (17 mL) was added the diol **10** (8.0 g, 24.24 mmol) followed by tosyl-imidazole (10.76 g,

48.46 mmol), and the mixture was stirred for 1 h at 0 °C. After completion of reaction, water was added and extracted with EtOAc (3 × 50 mL). The combined organic fraction was dried over anhydrous Na_2SO_4, and solvent was removed under reduced pressure. The residue was purified on silica gel column chromatography (3 : 7 EtOAc–hexane) to afford the epoxide **11** (6.8 g, 21.8 mmol, 90%) as colorless oil. $[\alpha]_D^{25} = +14.8$ (*c* 1.0, $CHCl_3$); IR (KBr): 1721, 1269, 1107, 711 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.03–7.99 (m, 2H); 7.59–7.54 (m, 1H); 7.46–7.41 (m, 2H); 7.34–7.20 (m, 5H); 5.21 (td, J = 8.0, 4.8 Hz, 1H), 4.48 (ABq, $\Delta\delta AB = 0.02$, $JAB = 11.9$ Hz, 2H), 3.67–3.58 (m, 2H); 3.18–3.15 (m, 1H); 2.83 (dd, J = 5.0 Hz, 1H); 2.79 (dd, J = 5.0 Hz, 1H); 2.18–2.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.5, 137.9, 132.9, 129.5, 128.2, 128.1, 127.5, 127.4, 72.9, 70.8, 65.7, 52.3, 45.4, 31.2; HRMS (ESI) for $C_{19}H_{20}O_4Na$ $[M + Na]^+$ found 335.12538, calcd 335.12476.

(2*S*,3*R*)-5-(Benzyloxy)pentane-2,3-diol (12)

To a stirred suspension of $LiAlH_4$ (2.41 g, 63.42 mmol) in anhydrous THF (15 mL) at 0 °C was added dropwise a solution of terminal epoxide **11** (6.6 g, 21.15 mmol) in anhydrous THF (30 mL). The reaction mixture was allowed to warm to 25 °C and stirred for 3 h. Reaction mixture was then cooled to 0 °C and quenched with dropwise addition of saturated aqueous Na_2SO_4 (20 mL). The precipitate formed was filtered and washed with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (4 : 6, EtOAc–hexane) to afford **12** (4.12 g, 19.62 mmol, 93%) as a viscous liquid. $[\alpha]_D^{25} = -8.2$ (*c* 0.8, $CHCl_3$); IR (KBr): 3417, 2867, 1367, 1075, 741, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.39–7.28 (m, 5H), 4.54 (s, 2H), 3.83–3.73 (m, 2H), 3.72–3.66 (m, 2H), 3.29 (br s, 1H), 1.90–1.80 (m, 1H), 1.77–1.70 (m, 1H), 1.16 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.6, 128.4, 127.7, 127.6, 74.5, 73.2, 69.9, 68.8, 30.5, 17.4; HRMS (ESI) for $C_{12}H_{18}O_3Na$ $[M + Na]^+$ found 233.11482, calcd 233.11458.

(4*R*,5*S*)-4-(2-(Benzyloxy)ethyl)-2,2,5-trimethyl-1,3-dioxolane (13)

2,2-Dimethoxypropane (3.96 mL, 38.07 mmol) and catalytic PTSA (0.4 g, 2.32 mmol) were added successively to a solution of diol **12** (4 g, 19.04 mmol) in a mixture of CH_2Cl_2 : Me_2CO (1 : 1) (40 mL). The solution was stirred for 10 h at room temperature and then quenched with solid $NaHCO_3$. The crude compound was concentrated *in vacuo* and purified by column chromatography (1 : 9, EtOAc–hexane) to afford the acetonide product **13** (4.52 g, 18.08 mmol, 90%) as a colorless liquid. $[\alpha]_D^{25} = +30.5$ (*c* 1.0, $CHCl_3$); IR (KBr): 2983, 1374, 1217, 1089, 771, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.25 (m, 5H), 4.52 (ABq, J = 16.1, 11.9 Hz, 2H), 4.29–4.19 (m, 2H), 3.67–3.58 (m, 2H), 1.82–1.72 (m, 2H), 1.44 (s, 3H), 1.33 (s, 3H), 1.15 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.2, 128.0, 127.3, 127.2, 74.7, 73.3, 72.8, 67.1, 30.1, 28.3, 25.6, 15.3; HRMS (ESI) for $C_{15}H_{22}O_3Na$ $[M + Na]^+$ found 273.14612, calcd 273.14540.

2-((4*R*,5*S*)-2,2,5-Trimethyl-1,3-dioxolan-4-Yl)ethanol (14)

To a stirred solution of naphthalene (13.82 g, 107.96 mmol) in THF (30 mL) were added lithium granules (0.88 g, 125.71 mmol) at room temperature, and the solution was allowed to stir at room temperature for 45 min to generate Li naphthalenide. To the resulting dark green solution was added benzyl ether **13** (4.5 g, 18.0 mmol) at −10 °C, and the mixture was allowed to stir at the same temperature for 1 h, quenched with aqueous NH_4Cl, extracted into EtOAc (3 × 50 mL), dried over Na_2SO_4, concentrated, and purified on silica gel (3 : 7 EtOAc–hexane) to give alcohol **14** (2.3 g, 14.37 mmol, 81%) as a colorless liquid. $[\alpha]_D^{25} = +25.5$ (*c* 0.6, $CHCl_3$); IR (KBr): 3423, 2984, 1376, 1246, 1218, 1085, 1058, 1005, 853 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.35–4.21 (m, 2H), 3.87–3.79 (m, 2H), 2.49 (br s, 1H), 1.85–1.71 (m, 1H), 1.65–1.54 (m, 1H), 1.47 (s, 3H), 1.19 (d, J = 6.0 HZ, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 107.6, 76.5, 73.5, 60.5, 32.0, 28.2, 25.6, 15.2; HRMS (ESI) for $C_8H_{16}O_3Na$ $[M + Na]^+$ found 183.0995, calcd 183.0992.

2-((4*R*,5*S*)-2,2,5-Trimethyl-1,3-dioxolan-4-yl)acetaldehyde (7)

To a stirred solution of oxalyl chloride (2.33 mL, 27.55 mmol) in dry CH_2Cl_2 (15 mL) at −78 °C, dry DMSO (3.9 mL, 55.0 mmol) was added dropwise. After 30 min, alcohol **14** (2.2 g, 13.75 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving a copious white precipitate. After stirring for 2 h at −78 °C, Et_3N (10.97 mL, 82.42 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to rt. The reaction mixture was then diluted with water (20 mL) and expected with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with water (15 mL), brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford the aldehyde **7**, which was directly used for further reaction without purification.

(*R*)-*tert*-Butyl(5-(4-methoxybenzyloxy)pent-1-yn-3-yloxy) diphenylsilane (16)

Imidazole (3.7 g, 54.41 mmol), and TBDPSCl (7.5 ml, 27.27 mmol) were added to a stirred solution of compound **15** (6.0 g, 27.2 mmol) in CH_2Cl_2 (35 mL) at 0 °C. Stirring was continued for 10 h and then the mixture was diluted with CH_2Cl_2 (20 mL). Evaporation of the solvent under reduced pressure followed by column chromatography (1 : 9, EtOAc–hexane) afforded the silyl ether **16** (11.87 g, 25.91 mmol, 95%) as a colorless liquid. $[\alpha]_D^{25} = +11.8$ (*c* 0.7, $CHCl_3$); IR (KBr): 2931, 2857, 1512, 1246, 1108, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.75–7.65 (m, 4H), 7.44–7.33 (m, 6H), 7.15 (d, J = 8.6 HZ, 2H), 6.84 (d, J = 8.6 HZ, 2H), 4.5679 (td, J = 6.4, 1.9 Hz, 1H), 4.30 (s, 2H), 3.80 (s, 3H), 3.63–3.55 (m, 2H), 2.28 (d, J = 2.1 HZ, 1H), 2.07–1.94 (m, 2H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.0, 136.0, 135.8, 134.7, 129.7, 129.6, 129.5, 129.1, 127.6, 127.5, 127.3, 113.6, 84.5, 72.9, 72.4, 65.9, 61.0, 55.2, 38.4, 26.8, 19.2; HRMS (ESI) for $C_{29}H_{34}O_3NaSi$ $[M + Na]^+$ found 481.21694, calcd 481.21619.

(*R*)-3-(*tert*-Butyldiphenylsilyloxy)pent-4-yn-1-ol (17)

Compound **16** (11.89 g, 25.76 mmol) was taken in 30 mL of CH_2Cl_2 : pH 7 buffer (9 : 1), DDQ (6.43 g, 28.32 mmol) was added to it, and the solution was stirred for 2 h at room temperature. The reaction mixture was filtered off and the filtrate was washed with 5% $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purified by silica gel column chromatography (2 : 8, EtOAc–hexane) to afford **17** as a light yellow colored liquid (7.04 g, 20.82 mmol, 81%). $[\alpha]_D^{25} = +33.8$ (*c* 0.6, $CHCl_3$); IR (KBr): 3301, 2957, 2933, 2859, 1108, 1050, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.75 (dt, $J = 6.7$, 1.3 Hz, 2H), 7.70 (dt, $J = 6.5$, 1.3 Hz, 2H), 7.44 (dt, $J = 7.4$, 2.4 Hz, 2H), 7.41–7.37 (m, 4H), 4.59 (td, $J = 5.3$, 2.1 Hz, 1H), 3.96–3.88 (m, 1H), 3.81–3.74 (m, 1H), 2.36 (d, $J = 2.1$ Hz, 1H), 2.02–1.96 (m, 1H), 1.89–1.82 (m, 1H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 135.9, 135.6, 129.8, 129.7, 127.6, 127.3, 83.9, 73.6, 62.0, 59.1, 39.9, 26.7, 19.1; HRMS (ESI) for $C_{21}H_{26}O_2NaSi$ $[M + Na]^+$ found 361,15943 calcd 361.15887.

(*R*)-*tert*-Butyl(hex-5-en-1-yn-3-yloxy)diphenylsilane (8)

To a stirred solution of oxalyl chloride (3.5 mL, 41.41 mmol) in dry CH_2Cl_2 (30 mL) at −78 °C, dry DMSO (5.88 mL, 82.81 mmol) was added drop wise. After 30 min, alcohol **17** (7.0 g, 20.71 mmol) in CH_2Cl_2 (25 mL) was added over 10 min giving a copious white precipitate. After stirring for 2 h at −78 °C, Et_3N (16.53 mL, 124.22 mmol) was added slowly and stirred for 30 min allowing the reaction mixture warm to rt. The reaction mixture was then diluted with water (20 mL) and CH_2Cl_2 (3 × 60 mL). The combined organic layer was washed with water (30 mL), brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford the aldehyde, which was directly used as such for further reaction.

To a stirred suspension of methyltriphenylphosphonium iodide (13.37 g, 33.09 mmol) in dry THF (35 mL) at −78 °C, *n*-BuLi in hexane (2.0 M, 12.41 mL, 24.82 mmol) was added drop wise under an N_2 atmosphere and allowed to return to room temperature. After 45 min, the reaction mixture was again cooled to−78 °C and the aldehyde compound (5.56 g, 16.54 mmol) dissolved in dry THF (20 mL) was added dropwise and stirred for another 45 min. The reaction mixture was quenched with saturated NH_4Cl solution (15 mL) at 0 °C and extracted with diethyl ether (2 × 40 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (1 : 9, EtOAc–hexane) to afford pure compound **8** (3.31 g, 9.91 mmol, 60% over two steps) as a pale yellow liquid. $[\alpha]_D^{25} = +16.2$ (*c* 1.0, $CHCl_3$); IR (KBr): 2933, 2858, 1109, 1082, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.77–7.66 (m, 4H), 7.48–7.32 (m, 6H), 5.91–5.76 (m, 1H), 5.10–5.00 (m, 2H), 4.37 (td, $J = 5.2$, 2.2 Hz, 1H), 2.50–2.35 (m, 2H), 2.34 (d, $J = 1.5$, Hz, 1H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 135.9, 135.8, 133.2, 129.7, 129.6, 127.5, 127.4, 117.9, 84.4, 73.0, 63.3, 42.7, 26.8, 19.2; anal. calcd for $C_{22}H_{26}OSi$: C, 78.99; H, 7.83%; found: C, 78.60; H, 7.77%.

(*R*)-5-(*tert*-Butyldiphenylsilyloxy)-1-((4*R*,5*S*)-2,2,5-trimethyl-1,3-dioxolan-4-yl)oct-7-en-3-yn-2-one (19)

To a stirred solution of alkyne **8** (2 g, 5.98 mmol) in dry THF (20 mL) was slowly added *n*-BuLi (2.0 M, 4.5 mL, 8.98 mmol, solution in hexanes) at −20 °C under N_2. The reaction mixture was stirred for 30 min at −78 °C, and a solution of compound **7** (1.13 g, 7.15 mmol) in dry THF (15 mL) was added dropwise with stirring. The mixture was kept at −40 °C for 2 h and then allowed to warm to rt for 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and extracted with EtOAc, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane–EtOAc = 75 : 25) to afforded alcohol **18** as a 1 : 1 mixture of diastereomers (determined by chiral HPLC analysis) in approximately 65% yield.

To the above obtained alcohol **18** (1.8 g, 3.65 mmol) in 20 mL of dry CH_2Cl_2, Dess–Martin periodinate (2.32 g, 5.46 mmol) and $NaHCO_3$ (0.92 g, 10.95 mmol) were added at 0 °C and stirred for 2 h. After completion of the reaction, the reaction was quenched with aqueous sodium thiosulfate solution (6 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The reaction mixture was extracted with CH_2Cl_2 (2 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (3 : 7, EtOAc–hexane) to afford **19** (1.46 g, 2.97 mmol, 82%) as a yellow liquid. $[\alpha]_D^{25} = +50.1$ (*c* 0.5, $CHCl_3$); IR (KBr): 2983, 2924, 2860, 1679, 1109, 1083, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.76–7.65 (m, 4H), 7.46–7.35 (m, 6H), 5.91–5.74 (m, 1H), 5.16–5.05 (m, 2H), 4.56–4.44 (m, 2H), 4.29 (t, $J = 6.0$ Hz, 1H), 2.66–2.35 (m, 4H), 1.41 (s, 3H), 1.32 (s, 3H), 1.12–1.03 (m, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 184.2, 135.8, 135.7, 134.4, 130.0, 129.8, 129.5, 118.6, 107.7, 92.8, 83.7, 73.4, 73.0, 63.3, 46.1, 41.9, 28.2, 26.7, 25.6, 19.2, 15.2; HRMS (ESI) for $C_{30}H_{38}O_4NaSi$ $[M + Na]^+$ found 513.24316, calcd 513.24268.

(2*S*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-1-((4*R*,5*S*)-2,2,5-trimethyl-1,3-dioxolan-4-yl)oct-7-en-3-yn-2-ol (21)

To a mixture of propargyl ketone **19** (1.0 g, 2.04 mmol) in formic acid (0.77 mL, 20.21 mmol) and triethylamine (1.13 mL, 8.15 mmol) were added at room temperature an aliquant amount of the stock solution of the RuCl[*N*-(tosyl)-(1,2-diphenylethylenediamine)(*p*-cymene)] complex 0.0337 M in CH_2Cl_2 (1.51 mL, 0.051 mmol), prepared according to ref. 15. The reaction mixture was stirred at room temperature for overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (3 : 7, EtOAc–hexane) to afford chiral propargyl alcohol **21** (0.9 g, 1.82 mmol, 90%) as a light yellow colored liquid. $[\alpha]_D^{25} = +54.6$ (*c* 0.9, $CHCl_3$); IR (KBr): 3448, 2933, 2892, 1109, 1081, 705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.77–7.73 (m, 2H), 7.72–7.68 (m, 2H), 7.45–7.34 (m, 6H), 5.91–5.81 (m, 1H), 5.11–5.04 (m, 2H), 4.47 (td, $J = 6.1$, 1.3 Hz, 1H), 4.42–4.37 (m, 1H), 4.25–4.18 (m, 1H), 4.10–4.04 (m, 1H), 2.52–2.38 (m, 2H), 1.83–1.67 (m, 2H), 1.43 (s, 3H), 1.31 (s, 3H), 1.12 (d, $J = 6.4$ Hz, 3H), 1.06 (s, 9H); ^{13}C

NMR ($CDCl_3$, 125 MHz): δ 135.9, 135.7, 133.5, 129.7, 129.5, 127.5, 127.2, 117.7, 107.8, 85.4, 73.4, 76.1, 73.4, 63.5, 61.1, 42.7, 37.6, 28.3, 26.7, 25.6, 19.2, 15.2; HRMS (ESI) for $C_{30}H_{40}O_4NaSi$ $[M + Na]^+$ found 515.25881, calcd 515.25707.

(2*S*,3*R*,5*S*,8*R*)-8-(*tert*-Butyldiphenylsilyloxy) undec-10-en-6-yne-2,3,5-triyl triacetate (22)

To a stirred solution of compound **21** (0.8 g, 1.62 mmol) in a MeOH (20 mL) and was added PTSA (0.2 g, 1.16 mmol) under N_2, then the mixture was stirred at room temperature for 8 h. The mixture was quenched with solid $NaHCO_3$ (0.2 g) and filtered, the solvent was removed under reduced pressure and the crude triol was directly used for the next step without further purification.

Anhydrous Et_3N (0.92 mL, 6.63 mmol), Ac_2O (0.33 mL, 3.23 mmol), and DMAP (10 mg, 0.082 mmol) were added to a solution of triol (0.5 g, 1.10 mmol) in anhydrous CH_2Cl_2 (15 mL) under nitrogen atmosphere at room temperature. The mixture was stirred at room temperature for 45 min. The solvent was removed under reduced pressure, and the mixture was purified by silica gel column chromatography (2 : 8, EtOAc–hexane) to afford **22** (0.57 g, 0.98 mmol, 90% over two steps) as a light yellow colored liquid.$[\alpha]_D^{25}$ = +16.0 (*c* 0.9, $CHCl_3$); IR (KBr): 1745, 1370, 1228, 1109, 1079, 1023, 702 cm; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (dd, J = 7.9 Hz, 2H), 7.67 (dd, J = 7.9 Hz, 2H), 7.44–7.35 (m, 6H), 5.86–5.76 (m, 1H), 5.31 (td, J = 5.9, 1.3 Hz, 1H), 5.09–5.02 (m, 4H), 4.39 (td, J = 6.5, 1.2 Hz, 1H), 2.47–2.35 (m, 2H), 2.03 (s, 3H), 2.02 (s, 3H), 2.0 (s, 3H), 1.28–1.24 (m, 2H), 1.17 (d, J = 6.4 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.1, 169.9, 169.4, 135.9, 135.7, 133.2, 129.7, 129.5, 127.5, 127.3, 117.9, 87.0, 81.1, 71.4, 70.0, 63.3, 61.2, 42.5, 33.9, 26.7, 21.0, 20.8, 19.2, 15.2; HRMS (ESI) for $C_{33}H_{42}O_7NaSi$ $[M + Na]^+$ found 601.25920, calcd 601.25842.

(2*S*,3*R*,5*S*,8*R*)-8-Hydroxyundec-10-en-6-yne-2,3,5-triyl triacetate (6)

A 1 M solution of TBAF in THF (1.73 mL, 1.73 mmol) was added to a solution of compound **22** (0.5 g, 0.86 mmol) in dry THF (15 mL) at 0 °C. The mixture was stirred at room temperature for 3 h. After completion of the reaction, the mixture was diluted with EtOAc (15 mL). The combined organic layers were washed with sat. NaCl, and the mixture was extracted with ethyl acetate (3 × 10 mL). The organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the mixture was purified by silica gel column chromatography (3 : 7, EtOAc–hexane) to afford **6** (0.2 g, 0.58 mmol, 70%) as a colorless liquid. $[\alpha]_D^{25}$ = −21.5 (*c* 0.7, CHCl3); IR (KBr): 3465, 1741, 1372, 1230, 1024 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.94–5.78 (m, 1H), 5.45 (dq, J = 5.4, 1.5 Hz, 1H), 5.31–5.03 (m, 4H), 4.43 (t, J = 5.4 Hz, 1H), 2.62 (brs, 1H), 2.50–2.42 (m, 2H), 2.19–2.10 (m, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 2.02–1.92 (m, 1H), 1.22 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.4, 170.1, 169.5, 132.7, 118.8, 87.4, 80.8, 71.2, 70.4, 61.3, 61.2, 41.7, 34.1, 21.0, 20.9, 20.8, 14.7; HRMS (ESI) for $C_{17}H_{24}O_7Na$ $[M + Na]^+$ found 363.14142 calcd 363.14077.

(2*S*,3*R*,5*S*,8*R*)-8-(Acryloyloxy)undec-10-en-6-yne-2,3,5-triyl triacetate (23)

Acryloyl chloride (0.058 mL, 0.74 mmol) was added drop wise under N_2 to a solution of alcohol **6** (0.17 g, 0.5 mmol), Et_3N (0.13 mL, 1.0 mmol), and DMAP (5 mg, 0.041 mmol) in anhyd CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 1 h until the reaction was complete (TLC). The mixture was then poured into brine and extracted with CH_2Cl_2 (2 × 10 mL). The organic phases were washed with 1 M aq. HCl (5 mL) and brine (8 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography (2 : 8, EtOAc–hexane) to give **23** (0.15 g, 0.38 mmol, 80%) as a light yellow liquid. $[\alpha]_D^{25}$ = +10.8 (*c* 0.7, $CHCl_3$); IR (KBr): 2984, 2930, 1733, 1228, 1181, 1083, 1024 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.47 (dd, J = 30.6, 17.2 Hz, 1H), 6.18–6.08 (m, 1H), 5.90–5.75 (m, 2H), 5.53–5.43 (m, 2H), 5.19–5.06 (m, 4H), 2.56 (t, J = 6.5 Hz, 2H), 2.19–2.09 (m, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03–1.96 (m, 1H), 1.20 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$,75 MHz): δ 170.2, 170.1, 169.5, 164.8, 131.6, 127.8, 118.9, 83.3, 81.9, 71.3, 70.1, 63.0, 61.1, 38.8, 33.9, 21.0, 20.9, 15.2; HRMS (ESI) for $C_{20}H_{26}O_8Na$ $[M + Na]^+$ found 417.15199 calcd 417.15074.

(2*S*,3*R*,5*S*)-7-((*R*)-6-oxo-3,6-Dihydro-2*H*-pyran-2-yl)hept-6-yne-2,3,5-triyl triacetate (24)

Grubbs' first-generation catalyst (0.033 g, 0.0415 mmol) was added to a solution of **23** (0.1 g, 0.25 mmol) in anhyd. CH_2Cl_2 (25 mL) at 0 °C, and the mixture was allowed to warm to room temperature over 24 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure and the residue was purified by column chromatography (5 : 5, EtOAc–hexane) to give **24** (0.073 g, 0.19 mmol, 80%) as a colorless liquid. $[\alpha]_D^{25}$ = −4.0 (*c* 0.3, $CHCl_3$); IR (KBr): 2924, 2853, 1739, 1374, 1231, 1049, 1025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 (dt, J = 9.7, 4.2 Hz, 1H), 6.08 (dt, J = 9.9, 1.8 Hz, 1H), 5.40 (dddd, J = 14.8, 9.1, 5.4, 1.3 Hz, 1H), 5.21 (td, J = 7.0, 1.2 Hz, 1H), 5.17 (dt, J = 10.2, 3.0 Hz, 1H), 5.08–5.03 (m, 1H), 2.70–2.65 (m, 2H), 2.17–2.10 (m, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.03–1.96 (m, 1H), 1.2 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.2, 169.5, 162.2, 144.1, 121.3, 82.7, 82.4, 71.1, 70.2, 66.7, 60.9, 33.8, 30.9, 21.0, 20.9, 20.8, 15.1; HRMS (ESI) for $C_{18}H_{22}O_8Na$ $[M + Na]^+$ found 398.12069 calcd 389.12062.

6*R*-(1*Z*,3*S*,5*R*,6*S*)-5,6-Dihydro-6-[3,5,6-tris(acetoxy)-1-heptenyl]-2*H*-pyran-2-one (hyptolide) (1)

To solution of compound **24** (0.04 g, 0.10 mmol) in EtOAc (10 mL), one drop of quinoline and Lindlar's catalyst (Pd/$CaCO_3$) were added and stirred at room temperature under H_2 atm for 3 min. After completion of the reaction, the reaction mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified on silica gel column chromatography (ethyl acetate–hexane, 5 : 5) to give hyptolide **1** (32 mg, 0.087 mmol, 80%) as a solid, mp 83–87 °C, (ref. 3 m.p. 87–88 °C); $[\alpha]_D^{25}$ = +12.5 (*c* 0.7, $CHCl_3$); {ref. 3 $[\alpha]_D^{25}$ = +11.2 (*c* = 0.6, CHCl3)}. IR (KBr): 1738, 1373, 1238,

1045 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.91–6.86 (m, 1H), 6.07–6.03 (m, 1H), 5.81–5.76 (m, 1H), 5.57–5.50 (m, 2H), 5.32–5.25 (m, 1H), 5.02–4.96 (m, 1H), 4.92 (dt, J = 9.4, 3.2 Hz, 1H), 2.48–2.38 (m, 2H), 2.10–2.06 (m, 4H), 2.05 (s, 3H), 2.03 (s, 3H), 1.87–1.80 (m, 1H), 1.20 (d, J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.5, 170.2, 165.0, 163.3, 144.5, 131.2, 130.7, 121.5, 73.8, 70.9, 70.4, 66.5, 34.8, 30.9, 21.2, 21.1, 21.0, 14.7; HRMS (ESI) for $C_{18}H_{24}O_8Na$ $[M + Na]^+$ found 391.13634 calcd 391.13530.

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