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Stereoselective total synthesis of *ent*-Hyptenolide

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A stereoselective total synthesis of *ent*-Hyptenolide is reported involving aymmetric allylation, Horner-Emmons-Wordsworth olefination, stereoselective *anti* reduction and RCM as the key steps.

Introduction

Hyptenolide (**1**, Figure 1), a new α-pyrone was recently isolated from the aerial parts of *Hyptis macrostachys* Benth.[1] The structure of **1** was deciphered by extensive NMR techniques and CD spectral data. The intriguing structural features of **1** includes a unique combination of a *trans* olefin (C3'/C4') in conjugation with *cis* olefin (C1'/C2') and the diene connected to the α-pyranone motif at C6. The distal end of the diene fragment is endowed with *anti*-diacetoxy propane moiety. Compound **1** showed selective spasmolytic effect in the guinea pig trachea and ileum.[1] In continuation with our interest in the synthesis of 5,6-dihydropyran-2-one[2] containing natural products, the hitherto unreported structural features of **1** coupled with its impressive bio-active profile encouraged us to undertake its total synthesis.

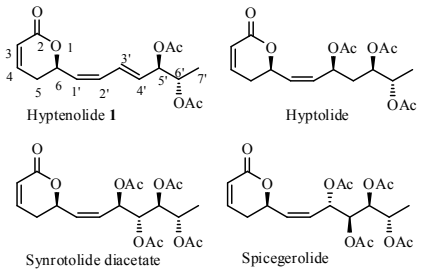
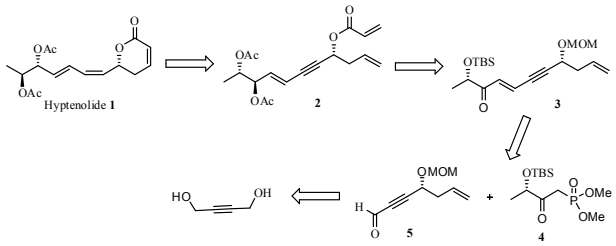


Figure 1. Structure of Hyptenolide and related pyranone polyacetates

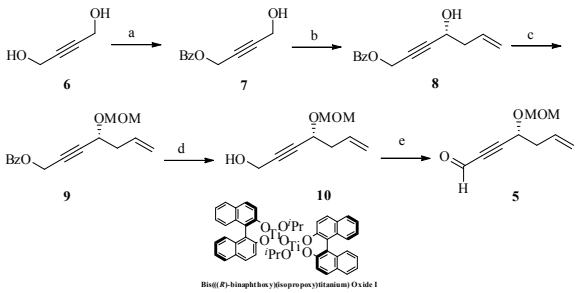
Results and discussion

The envisaged retrosynthetic analysis of compound **1** is depicted in Scheme 1. Accordingly, **1** could be obtained from diacetoxy acryloyl derivative **2** on RCM. Compound **2** in turn could be derived from enyne **3** upon few chemical transformations such as silyl deprotection, selective reduction, acetylation, MOM-deprotection followed by acryloylation. Further, compound **3** maybe assembled using the HEW-olefination reaction between chiral ynal **5** and chiral phosphonate **4**. Ynal **5** is conveniently drawn from commercially available 1,4-butyne diol involving Keck allylation to garner the stereogenic carbon and other sequential transformations like deprotection-oxidation reaction set. While phosphonate **4** itself was prepared from ethyl L-lactate by a reported procedure.[3]



Scheme 1. Retrosynthetic analysis of hyptenolide **1**

Accordingly, the synthesis began from the commercially available 1,4-butyne diol **6** (Scheme 2). Diol **6** on selective protection as its monobenzoate[4] under conventional reaction conditions followed by oxidation (IBX conditions) afforded the corresponding aldehyde which on Keck allylation[5] (*R*-BINOL/Ti(O^iPr_4)/$TiCl_4$/Ag_2O/allyltributyltin/CH_2Cl_2/-15 °C) provided the chiral propargylic alcohol **8** (75%). The absolute stereochemistry of the newly created stereogenic center was

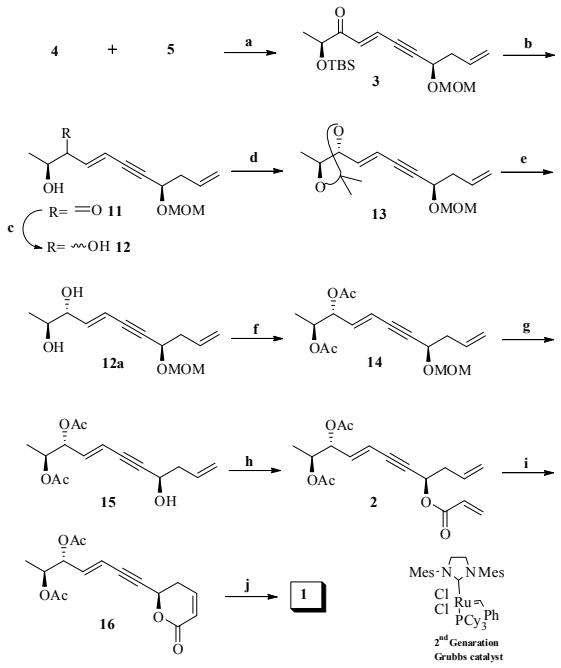


Scheme 2. *Reagents and conditions* : a) Ref. 4; b) i) IBX, DMSO, CH_2Cl_2, 0 °C-rt, 90%, ii) **I**, allyltributyltin (1.1 equiv), CH_2Cl_2, -15 °C, 36h (75%); c) MOM-Cl, DIPEA, dry CH_2Cl_2, 0°C–rt, 4h, 88%; d) K_2CO_3, CH_3OH, 0 °C-rt, 80%; e) IBX, DMSO, CH_2Cl_2, 0 °C-rt, 90%.

established using literature analogy and assigned as '*R*'.[6] Next, protection of the secondary hydroxyl group as its MOM-ether (MOM-Cl/DIPEA/CH_2Cl_2/0 °C to rt) furnished compound **9** (88%). Subsequent hydrolysis (K_2CO_3/MeOH/0 °C-rt) of the

benzoate **9** released the primary hydroxyl group to afford **10** (80%) in order to facilitate its oxidation (IBX/DMSO/CH_2Cl_2/0 °C to rt) and thus generate the crucial ynal fragment **5** (90%).

Another synthon, chiral phosphonate **4** was accessed using a reported procedure.[3] Having the phosphonate **4** in hand, Horner-Emmons-Wordsworth olefination reaction was performed between phosphonate **4** and ynal **5** (Scheme 3) to result in enyne **3** (60%) as the separable *E*-isomer (>85%) as the major isomer. The *E*-geometry was ascertained from the ^{1}H NMR spectrum wherein the newly formed olefinic protons resonated at δ 6.98 ppm as a doublet (J = 15.8 Hz, 1H) and another at δ 6.78 ppm as a dd (J =1.8, 15.8 Hz, 1H). The other terminal olefinic protons



Schme 3. *Reagents and conditions* : a) Cs_2CO_3, MeCN, -15 °C, 45 min., 60%; b) PPTS, MeOH, 0 °C–rt, 12h, 78%; c) $ZnBH_4$, THF, 0 °C, 0.5h, 89%; d) 2,2 DMP, PPTS, CH_2Cl_2, 0 °C-rt, 73%; e) 60% aq.AcOH, 6h, rt, 87%; f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C-rt, 90%; g) $TiCl_4$, CH_2Cl_2, 0 °C, 1h, 80%; h) Acryloyl chloride, Et_3N, DMAP, dry CH_2Cl_2, 0 °C, 1h, 82%; i) Grubbs'-II, dry CH_2Cl_2, rt, 12h, 65%; j) H_2, Pd-$CaCO_3$ (Lindlar's catalyst), Quinoline, EtOAc, 20 min, 90%.

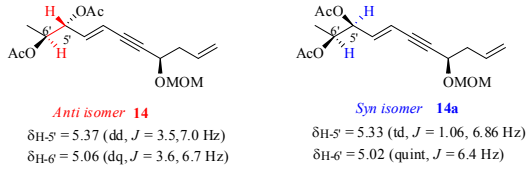


Figure 2. Comapritive ^{1}H NMR data of *anti*- and *syn*-isomeric diacetates **14** and **14a**.

appeared at their expected shifts. Next, we envisaged an *anti*-reduction of the accompanying keto group in enyne **3** would lead us to the total carbon framework with rightly positioned stereogenic centers. Firstly, desilylation of **3** (PPTS/MeOH/0 °C-rt) was effected to give the hydroxy ketone derivative **11** (78%). However, reduction[7] ($ZnBH_4$/THF/0 °C) of **11** offered an chromatographically inseparable diastereomeric mixture **12** (89% combined yield) in favor of the *anti*-isomer (4:1, *anti*:*syn*) as the major compound. The diastereomeric ratio of **12** was determined from the ^{1}H NMR spectrum by measuring the integration of the separable protons. For instance, while the terminal methyl protons of the minor isomer resonated at δ 1.19 ppm as a doublet (J = 6.4 Hz, 0.75H), the same protons for the major isomer resonated at δ 1.14 ppm as doublet (J = 6.4 Hz, 3H). Also, one of the olefinic protons for the minor isomer resonated at δ 6.19 ppm as a dd (J = 6.13, 15.8 Hz, 0.25H) while the corresponding proton for the major isomer resonated at δ 6.11 ppm as a dd (J = 6.1, 15.8 Hz, 1H). The relative stereochemistry of the major isomer was initially assigned as *anti* based on literature precedence.[3,7] Thankfully, the diastereomeric mixture **12** could be chromatographically separated on its conversion to acetonide **13** (2,2 DMP/PPTS/CH_2Cl_2/0 °C to rt, 73%). As envisioned and to continue with the synthesis, optically pure *anti*-isomer (**12a**) was necessary. Hence, deprotection of the acetonide group was carried out under acidic conditions (60% aq. AcOH) to afford optically pure diol **12a** (87%) that was diacetylated (Ac_2O/Et_3N/DMAP/CH_2Cl_2/0 °C to rt) to **14** (90%). In order to conclusively establish the *anti*-stereochemistry of the diol **12a**, we conducted few more experiments. For example, keto compound **3** was subjected to Luche reduction[8] followed by TBS-deprotection to afford *syn*-diol exclusively in 92% yield which was acetylated to afford **14a** (90%) under conventional conditions. Likewise, the minor isomer obtained during the chromatographic separation of **13** was also converted into its diacetate after few transformations such as acetonide group deprotection followed by acetylation. Next, the comparative ^{1}H NMR study of the thus obtained diacetates was made which showed a complete match, thus unequivocally establishing their *syn* diol relationship. Having ascertained the relatively stereochemistry of minor isomer, a comparison of ^{1}H NMR data of **14** and **14a** was also taken up (Figure 2). Herein the two spectra displayed differences, notably the allylic proton H5' in *anti*-isomer resonated downfield (δ 5.37 ppm) than its *syn* counter part (δ 5.33 ppm) in accordance with the literature report.[9] Thus, the major compound **14** was conclusively proved as the *anti*-isomer drawing inference from all the above observations and its stereogenic carbon C5' was assigned as '*R*'. Additionally, the absolute stereochemistry of the newly created stereogenic center was confirmed later through the synthesis.

Furthermore, diacetate **14** on deprotection of MOM group under Lewis acid conditions ($TiCl_4$/CH_2Cl_2/0 °C) provided the homoallyl alcohol derivative **15** (80%). Subsequent acryloylation of **15** (acryloyl chloride/Et_3N/DMAP/CH_2Cl_2/0 °C) afforded **2** (82%) which on Grubbs' catalyst[10] assisted RCM (G-II/CH_2Cl_2/rt) resulted in the ring-closed product **16** (65%). Finally, partial hydrogenation of **16** under Lindlar's conditions gave the target compound **1** (90%).

All the spectral data of synthetic **1** matched[1,11] with the reported data excepting the specific rotation {Synthetic **1**: $[\alpha]_D^{20}$ = -45.8 (*c* 0.2, $CHCl_3$); Natural **1**[1]: $[\alpha]_D^{20}$ = +45.0 (*c* 0.001, $CHCl_3$)}, which showed an opposite sign of rotation implying the synthesis of an enantiomer.

Conclusion

In summary, we accomplished the total synthesis of *ent*-Hyptenolide in an overall yield of 3.9% from **7** using aymmetric allylation, Horner-Emmons-Wordsworth olefination, stereoselective *anti* reduction and RCM as the key steps.

Experimental section

Reactions were carried out under N_2 in dry solvents. All reactions were monitored by tlc and silica-coated plates were visualized by exposure to ultraviolet light and/or α-naphthol charring. Organic solutions were dried (Na_2SO_4) and concentrated below 40 ^oC under reduced pressure in a Büchi rotary evaporator. All column chromatographic (CC) separations were performed using silica gel (SiO_2; 60-120 mesh) with EtOAc and hexane as eluents. Tlc was performed on Merck 60 F254 silica gel plates. Yields refer to chromatographically and spectroscopically (^{1}H- and ^{13}C-NMR) homogeneous material. Air-sensitive reagents were transferred by syringe and double-ended needle. Optical rotations were measured on Anton Paar mcp-200 polarimeter and ^{1}H NMR and ^{13}C NMR spectra were recorded on Avance 300 or Avance 500 MHz nuclear magnetic resonance spectrometers. Chemical shifts were reported as (δ) in parts per million (ppm) with respect to internal TMS. Coupling constants J values are given in Hz. High-resolution mass spectra (HRMS) were obtained using either a TOF or a double focusing spectrometer.

(*R*)-4-Hydroxyhept-6-en-2-yn-1-yl benzoate (**8**)

To an ice-cooled solution of IBX (9.94 g, 35.52 mmol) in DMSO (8.39 mL, 107.56 mmol) and CH_2Cl_2 (45 mL), was added a solution of alcohol **7** (4.5 g, 23.68 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 2 h and then filtered through a Celite pad and washed with CH_2Cl_2 (3 x 30 mL). The organic filtrate was sequentially washed with H_2O, brine and later dried (Na_2SO_4) and concentrated *in vacuo*. The crude aldehyde (4.0 g, 90%, viscous liquid) was immediately subjected to the next reaction without further purification.

To a stirred solution of $TiCl_4$ (1 M solution in CH_2Cl_2, 2.1 mL, 2.1 mmol) in dry CH_2Cl_2 (40 mL) was added $Ti(O^iPr)_4$ (1.82 mL, 6.40 mmol) at 0 ^oC under N_2. The solution was allowed to warm to room temperature. After 1 h, (*R*)-Binaphthol (2.43 g, 8.49 mmol) was added at room temperature and the solution was stirred for 3 h. The mixture was cooled to 0 ^oC, and treated with silver(I) oxide (0.98 g, 4.25 mmol). The reaction mixture was allowed to warm to room temperature, and stirred there for 5 h under exclusion of direct light to furnish chiral bisTi(IV) oxide (*R*,*R*)-I was treated with aldehyde (4.0 g, 21.27 mmol) and allyltributyltin (7.17 mL, 21.66 mmol) at -15 ^oC. The whole mixture was warmed to 0 ^oC and allowed to stir for 36 h. The reaction mixture was quenched with saturated $NaHCO_3$, and extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were washed with brine, dried (Na_2SO_4), concentrated, and the residue was purified by column chromatography (EtOAc:*n*-hexane, 3:7) to give the allylated product **8** (3.63 g, 75%) as yellow liquid.

$[\alpha]_D^{20}$ = -2.44 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (dd, *J* = 1.3, 8.3 Hz, 2H), 7.58 (m, 1H), 7.48-7.43 (m, 2H), 5.88 (m, 1H), 5.23-5.17 (m, 2H), 4.96 (d, *J* = 1.6 Hz, 2H), 4.49 (t, *J* = 6.1 Hz, 1H), 2.52-2.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 133.2, 132.7, 129.7, 129.4, 128.3, 119.1, 87.1, 79.2, 61.5, 52.7, 41.8; HRMS: *m/z* calcd for $C_{14}H_{18}O_3N$ $[M+NH_4]^+$: 248.1281; found: 248.1273.

(*R*)-4-(Methoxymethoxy)hept-6-en-2-yn-1-yl benzoate (**9**)

To compound **8** (3.5 g, 15.21 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C, were successively added DIPEA (7.8 mL, 60.46 mmol), catalytic DMAP and MOMCl (1.82 mL, 22.75 mmol). The mixture was stirred for 4 h at room temperature, then the reaction was quenched by adding water (20 mL) and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were washed with brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude material was purified by column chromatography (EtOAc:*n*-hexane, 2:8) to afford product **9** (3.66 g, 88%) as an colorless liquid.

$[\alpha]_D^{20}$ = + 71.0 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.1 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 5.89 (m, 1H), 5.23-5.08 (m, 2H), 5.0-4.90 (m, 3H), 4.61 (d, *J* = 6.7 Hz, 1H), 4.43 (t, *J* = 6.4 Hz, 1H), 3.38 (s, 3H), 2.52 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 133.2, 133.2, 129.7, 129.5, 128.3, 118.0, 94.1 85.0, 79.9, 65.1, 55.6, 52.6, 39.8; HRMS: *m/z* calcd for $C_{16}H_{22}O_4N$ $[M+NH_4]^+$: 292.1543; found: 292.1535.

(R)-4-(Methoxymethoxy)hept-6-en-2-yn-1-ol (**10**)

To stirred solution of **9** (3.2 g, 11.11 mmol) in MeOH (35 mL) was added potassium carbonate solid (2.3 g, 16.66 mmol) at 0 ^oC and allowed it to stir at room temperature. After stirring for 3 h, solvent MeOH was removed under reduced pressure. The crude residue was washed with water (3 x 20 mL) and extracted with EtOAc (2 x 50 mL). The organic layer was dried (Na_2SO_4), concentrated and purified by column chromatography (EtOAc:*n*-hexane, 3.5:6.5) to obtain alcohol **10** (1.56 g, 80%) as a colorless liquid.

$[\alpha]_D^{20}$= +90.0 (*c* 4.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (m, 1H), 5.23-5.09 (m, 2H), 4.94 (d, *J* = 6.7 Hz, 1H), 4.61 (d, *J* = 6.7 Hz, 1H), 4.42 (t, *J* = 6.4 Hz, 1H), 4.30 (d, *J* = 0.94 Hz, 2H), 3.38 (s, 3H), 2.50 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.2, 117.9, 93.9, 84.3, 83.5, 65.2, 55.6, 50.7, 39.9; *m/z:* $C_9H_{18}O_3N$ $(M+NH_4)^+$: 188.

(5*R*,11*S*,*E*)-5-Allyl-11,13,13,14,14-pentamethyl-2,4,12-trioxa-13-silapentadec-8-en-6-yn-10-one (**3**)

To an ice-cooled solution of IBX (3.45 g, 12.32 mmol) in DMSO (3.21 mL, 41.15 mmol) and CH_2Cl_2 (20 mL), was added a solution of alcohol **10** (1.40 g, 8.23 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 2 h and then filtered through a Celite pad and washed with CH_2Cl_2 (3 x 30 mL). The combined organic filtrates were washed with H_2O (2 x 10 mL)

and brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude aldehyde **5** (1.24 g, 90%) was immediately subjected to the next reaction without further purification.

Cs_2CO_3 (2.37 g, 7.29 mmol) was added to a solution of **4** (1.13 g, 3.64 mmol) in MeCN (10 mL), and was stirred for 45 min at room temperature. The reaction mixture was cooled to -15 ^oC and a solution of the aldehyde **5** (1.24 g, 7.29 mmol) in MeCN (10 mL) was added drop wise and stirred for 45 min at the same temperature. After completion of the reaction, it was cautiously quenched by addition of saturated citric acid (10 mL), poured into water (30 mL), and extracted with diethyl ether (3 x 50 mL). Combined organic layers were washed with brine (2 x 20 mL) and dried (Na_2SO_4). Evaporation of solvent gave the crude residue, which was purified by column chromatography using (EtOAc:*n*-hexane,1:9) as eluent to furnish **3** (*E*-isomer, 1.54 g, 60%) as a light yellow oil.

$[\alpha]_D^{20}$= +17.7 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98 (d, *J* = 15.8 Hz, 1H), 6.78 (dd, *J* = 1.6, 16.0 Hz, 1H), 5.88 (m, 1H), 5.22-5.13 (m, 2H), 4.91 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.55 (td, *J* = 1.6, 6.5 Hz, 1H), 4.26 (q, *J* = 6.8 Hz, 1H), 3.39 (s, 3H), 2.60-2.50 (m, 2H), 1.30 (d, *J* = 6.7 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.5, 132.9, 132.5, 123.5, 118.2, 97.1, 94.3, 83.9 ,74.2, 65.7, 55.7, 39.7, 25.7, 20.9, 18.1, -4.8, -5.0; HRMS: *m/z* calcd for $C_{19}H_{33}O_4Si$ $[M+H]^+$: 353.2142; found: 353.2181.

(2*S*,8*R*,*E*)-2-Hydroxy-8-(methoxymethoxy)undeca-4,10-dien-6-yn-3-one (11)

To a stirred solution of **3** (1.2 g, 3.40 mmol) in MeOH (20 mL) was added PPTS (1.71 g, 6.81mmol) at room temperature and it was stirred for 12 h. After completion of the reaction (monitored by tlc), MeOH was evaporated under vacuum and the reaction mixture was diluted with CH_2Cl_2 (20 mL). Solid $NaHCO_3$ was added to the reaction mixture and was stirred for further 15 min. The reaction mixture was then filtered through a short pad of Celite and was washed with CH_2Cl_2 (3 x 20 mL) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (EtOAc:*n*-hexane,3:7) to obtain alcohol **11** (0.632 g, 78%) as a colorless oil.

$[\alpha]_D^{20}$= +64.2 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (dd, *J* = 1.8, 15.8 Hz, 1H), 6.63 (d, *J* = 15.8 Hz, 1H), 5.87 (m, 1H), 5.22-5.14 (m, 2H), 4.91 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.56 (td, *J* = 1.6, 6.4 Hz, 1H), 4.42 (q, *J* = 7.0 Hz, 1H), 3.39 (s, 3H), 2.60-2.50 (m, 2H), 1.40 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.8, 132.8, 132.2, 124.7, 118.4, 98.8, 94.3, 83.1,71.8, 65.6, 55.7, 39.6, 19.9; HRMS: *m/z* calcd for $C_{13}H_{18}O_4Na$ $[M+Na]^+$: 261.1097; found: 261.1106.

(4*R*,5*S*)-4-((*R*,*E*)-5-(Methoxymethoxy)octa-1,7-dien-3-yn-1-yl)-2,2,5-trimethyl-1,3 dioxolane (13)

To a solution of zinc borohydride (4.2 M solution in THF, 0.56 mL, 2.39 mmol) was added drop wise a solution of ketone **11** (0.570 g, 2.39 mmol) in dry THF (10 mL), at 0 ^oC and under N_2. It was stirred for 30 min. the mixture was quenched with sat. aq. NH_4Cl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (EtOAc:*n*-hexane, 1:1) gave the 4:1 diastereomeric mixture of diol **12** (0.511 g, 89 %) as colorless liquid.

To a solution of diol **12** (0.460 g, 1.91 mmol) in dry CH_2Cl_2 (5 mL), 2,2-dimethoxy propane (0.47 mL, 4.5 mmol) and PPTS (0.048 g, 0.19 mmol) were added at 0 °C. The mixture was stirred at room temperature for 3 h. Next, solid $NaHCO_3$ was added to the reaction mixture and was stirred for further 15 min and filtered. Removal of solvent and purification by column chromatography (EtOAc:*n*-hexane, 2:8) gave the required *anti*-isomer **13** (0.394 g, 73%) as a colorless liquid.

$[\alpha]_D^{20}$= +55.2 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.05 (dd, *J* = 7.1, 15.8 Hz, 1H), 5.90 (m, 1H), 5.79 (dt, *J* = 1.1, 15.8 Hz,1H), 5.23-5.10 (m, 2H), 4.94 (d, *J* = 6.7 Hz, 1H), 4.61 (d, *J* = 6.7 Hz, 1H), 4.55-4.45 (m, 2H), 4.35 (*quint*, *J* = 6.4 Hz, 1H), 3.38 (s, 3H), 2.52 (t, *J* = 6.7 Hz, 2H), 1.49 (s, 3H), 1.36 (s, 3H), 1.16 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.5, 133.4, 117.8, 111.9, 108.3, 94.0, 88.3, 83.6, 78.8, 74.1, 65.6, 55.6, 40.0, 28.0, 25.4, 16.0; *m/z:* $C_{16}H_{24}O_4Na$$[M+Na]^+$: 303.

(2*S*,3*R*,8*R*,*E*)-8-(Methoxymethoxy)undeca-4,10-dien-6-yne-2,3-diol (12a)

To a solution of **13** (0.3 g, 1.07 mmol) was added 3 mL of aqueous 60% acetic acid at room temperature and it was stirred for 6 h. After completion of the reaction, it was cautiously quenched by addition of solid $NaHCO_3$, filtered and washed with EtOAc (3 x 10 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (EtOAc:*n*-hexane, 1:1) to obtain diol **12a** (0.223 g, 87% yield) as a colorless liquid.

$[\alpha]_D^{20}$= +88.9 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.16 (dd, *J* = 6.2, 16.0 Hz, 1H), 5.96-5.76 (m, 2H), 5.22-5.10 (m, 2H), 4.94 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.8 Hz, 1H), 4.49 (dt, *J* = 1.5, 6.4 Hz, 1H), 4.14 (m, 1H), 3.88 (m, 1H), 3.38 (s, 3H), 2.52 (t, *J* = 6.6 Hz, 2H), 1.14 (d, *J* = 6.42 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.1, 133.3, 117.9, 111.6, 94.0, 88.3, 83.6 ,75.4, 70.0, 65.6, 55.6, 40.0, 17.4; HRMS: *m/z* calcd for $C_{13}H_{20}O_4Na$ $[M+Na]^+$: 263.1253; found: 263.1262.

(2*S*,3*R*,8*R*,*E*)-8-(Methoxymethoxy)undeca-4,10-dien-6-yne-2,3-diyl diacetate (14)

To a solution of diol **12a** (0.170 g, 0.708 mmol) in dry CH_2Cl_2 (6 mL), pyridine (0.17 mL, 2.15 mmol), Ac_2O (0.2 mL, 1.96 mmol) and DMAP (cat.) were added slowly. The mixture was then stirred for 2 h at room temperature. After completion of the reaction (tlc monitoring), the mixture was extracted with EtOAc (2 x 10 mL), and the combined organic layer was washed with brine (5 mL), dried (Na_2SO_4), concentrated and purified by column chromatography (EtOAc:*n*-hexane, 2:8) to furnish **14** (0.206 g, 90%) as a viscous liquid.

$[\alpha]_D^{20}$ = +36.3 (*c* 1.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.05 (dd, *J* = 7.0, 16.0 Hz, 1H), 5.89 (m, 1H), 5.79 (d,

J = 16.0 Hz, 1H), 5.37 (dd, *J* = 3.5, 7.0 Hz, 1H), 5.20-5.12 (m, 2H), 5.06 (dq, *J* = 3.6, 6.7, Hz, 1H), 4.92 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 6.86 Hz, 1H), 4.49 (t, *J* = 6.4 Hz, 1H), 3.38 (s, 3H), 2.55-2.48 (m, 2H), 2.08 (s, 3H), 2.05 (s, 3H), 1.20 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 169.6, 136.3, 133.2, 117.9, 113.9, 94.0, 89.3, 82.9, 74.4, 70.1, 65.4, 55.5, 39.9, 21.0, 20.8, 15.0; HRMS: *m/z* calcd for $C_{17}H_{24}O_6Na$ $[M+Na]^+$: 347.1465; found: 347.1475.

(2*S*,3*R*,8*R*,*E*)-8-Hydroxyundeca-4,10-dien-6-yne-2,3-diyl diacetate (15)

To a stirred solution of compound **14** (0.160 g, 0.493 mmol) in dryCH_2Cl_2 (20 mL) was added $TiCl_4$ (1 M solution in CH_2Cl_2, 0.396 mL, 0.396 mmol) at 0 °C and the reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with solid $NaHCO_3$ (0.050 g) and filtered. The solvent was removed under reduced pressure. The residue was purified by column chromatography (EtOAc:*n*-hexane, 4:6) to afford **15** (0.110 g, 80%) as a colorless liquid.

$[\alpha]_D^{20}$ = -5.8 (*c* 2.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.05 (dd, *J* = 7.0, 16.0 Hz, 1H), 5.88 (m, 1H), 5.79 (dt, *J* = 1.5, 16.0 Hz, 1H), 5.37 (ddd, *J* = 1.2, 3.6, 7.0 Hz, 1H), 5.22 (m, 1H), 5.19 (t, *J* = 1.0 Hz, 1H), 5.07 (dq, *J* = 3.5, 6.5Hz, 1H), 4.54 (t, *J* = 5.4 Hz, 1H), 2.52-2.47 (m, 2H), 2.08 (s, 3H), 2.05 (s, 3H), 1.20 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 169.7, 136.4, 132.7, 119.1, 113.9, 91.4, 82.3, 74.5, 70.2, 61.8, 41.9, 21.0, 20.9, 15.1; HRMS: *m/z* calcd for $C_{15}H_{24}O_5N$ $[M+NH_4]^+$: 298.1649; found: 298.1658.

(2*S*,3*R*,8*R*,*E*)-8-(Acryloyloxy)undeca-4,10-dien-6-yne-2,3-diyl diacetate (2)

Acryloyl chloride (0.027mL, 0.306 mmol) was added drop wise under N_2 to a stirred solution of **15** (0.080 g, 0.285 mmol), and Et_3N (0.047 mL, 0.46 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at 0 °C for 1 h. After completion, the mixture was poured into brine (5 mL), and extracted with CH_2Cl_2 (2 x 10 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography(EtOAc:*n*-hexane, 2:8) to afford the corresponding acrylic ester **2** (0.078 g, 82%) as a yellow color oil.

$[\alpha]_D^{20}$ = +0.17 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.45 (d, *J* = 17.3 Hz, 1H), 6.18-6.04 (m, 2H), 5.90-5.75 (m, 3H), 5.59 (t, *J* = 6.4 Hz, 1H), 5.37 (dd, *J* = 3.5, 6.8 Hz, 1H), 5.22-5.13 (m, 2H), 5.06 (m, 1H), 2.59 (t, *J* = 6.5 Hz, 2H), 2.08 (s, 3H), 2.05 (s, 3H), 1.20 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 169.7, 164.9, 137.0, 131.9, 131.5, 127.9, 118.8, 113.5, 87.8, 82.9, 74.4, 70.1, 63.6, 39.0, 21.0, 20.8, 15.0; HRMS: *m/z* calcd for $C_{18}H_{22}O_6Na$ $[M+Na]^+$: 357.1308; found: 357.1320.

(2*S*,3*R*,*E*)-7-((*R*)-6-Oxo-3,6-dihydro-2H-pyran-2-yl)hept-4-en-6-yne-2,3-diyl diacetate (16)

To a solution of compound **2** (0.040 g, 0.119 mmol) in CH_2Cl_2 (40 mL) was added Grubbs' second generation catalyst (0.01 g, 0.0117 mmol) at room temperature. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated and the crude product was purified by column chromatography (EtOAc:*n*-hexane, 4:6) to give lactone **16** (0.023 g, 65%) as a pale-yellow oil.

$[\alpha]_D^{20}$ = -0.36 (*c* 0.17, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89 (m, 1H), 6.18-6.05 (m, 2H), 5.77 (d, *J* = 16.0 Hz, 1H), 5.40-5.28 (m, 2H), 5.07 (dq, *J* = 3.5, 6.4 Hz, 1H), 2.73-2.65 (m, 2H), 2.09 (s, 3H), 2.06 (s, 3H), 1.20 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 169.7, 162.4, 143.8, 138.0, 121.5, 112.9, 86.3, 83.6, 74.3, 70.1, 67.3, 30.0, 21.0, 20.9, 15.1; HRMS: *m/z* calcd for $C_{16}H_{18}O_6Na$ $[M+Na]^+$: 329.0995; found: 329.1009.

(2*S*,3*R*,4*E*,6*Z*)-7-((*R*)-6-Oxo-3,6-dihydro-2H-pyran-2-yl)hepta-4,6-diene-2,3-diyl diacetate {*ent*-Hyptenolide 1}

To a solution of **16** (0.009 g, 0.0294 mmol) in EtOAc (2 mL), one drop of quinoline and Lindlar's catalyst ($Pd/CaCO_3$, catalytic amount) were added and the mixture was stirred at room temperature under H_2 for 20 min. After completion of the reaction, the mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (EtOAc:*n*-hexane, 1:1) to afford **1** (0.008 g, 90%) as an oil.

$[\alpha]_D^{20}$ = -45.8 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (ddd, *J* = 2.8, 5.4, 9.9 Hz, 1H), 6.51 (tdd, *J* = 1.0, 11.2, 15.1 Hz, 1H), 6.17 (br. t, *J* = 11.3 Hz, 1H), 6.08 (ddd, *J* = 1.2, 2.2, 9.7 Hz, 1H), 5.76 (dd, *J* = 7.1, 15.2 Hz, 1H), 5.64 (dd, *J* = 8.6, 10.8 Hz, 1H), 5.45 (ddd, *J* = 1.0, 3.3, 7.1 Hz, 1H), 5.35 (m, 1H), 5.07 (dq, *J* = 3.5, 6.5 Hz, 1H), 2.48-2.32 (m, 2H), 2.10 (s, 3H), 2.05 (s, 3H), 1.21 (d , *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 169.9, 163.6, 144.5, 131.1, 130.3, 128.5, 128.1, 121.6, 74.5, 73.7, 70.4, 29.7, 21.1, 21.0, 14.9; HRMS: *m/z* calcd for $C_{16}H_{20}O_6Na$ $[M+Na]^+$: 331.1152; found: 331.1161.

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References and Notes

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11. For all the spectral data please see the Supplementary Information.