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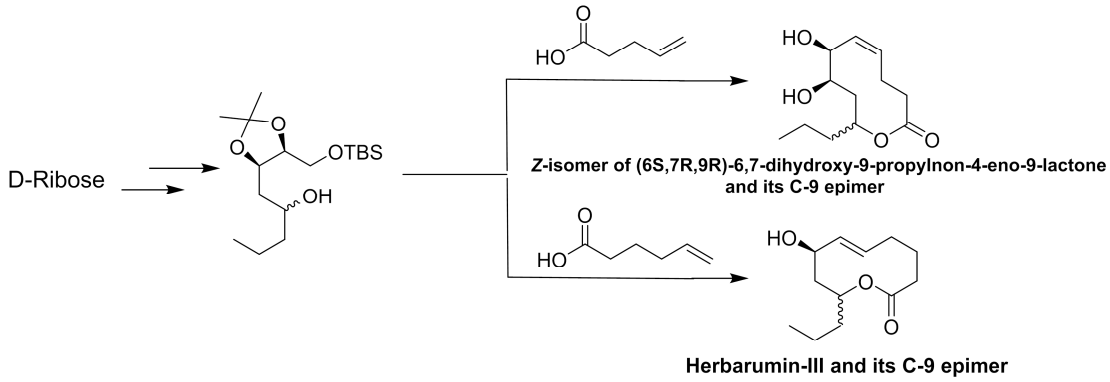
Lingaiah Maram[a], Raghavendar Reddy Parigi[a] and Biswanath Das*[a]



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ABSTRACT

A new and efficient strategy has been developed for the stereoselective total synthesis of nonenolides: (*Z*)-isomer of (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone, herbarumin-III and their C-9 epimers starting from D (-) ribose. The synthesis includes the coupling of the alcohol and acid fragments of the molecules, employing Yamaguchi esterification protocol followed by intramolecular ring closure metathesis. The method has efficiently constructed the ten-membered lactone skeleton of the compounds with proper stereogenic centers containing appropriate functionalities.

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1. Introduction

Natural nonenolides are 10-membered lactonic compounds with interesting structural features and important pharmacological activities. They have been discovered as the common chemical constituents of several fungi.[1] These compounds are found to contain various functionalities in different stereoconfigurations and to exhibit impressive biological properties such as anticancer, antifungal, antimalarial, antibacterial and phytotoxic activities.[2] The term phytotoxicity refers to the toxic effect of compounds on plant growth and the nonenolides with phytotoxic activity have been isolated from various sources.[3]

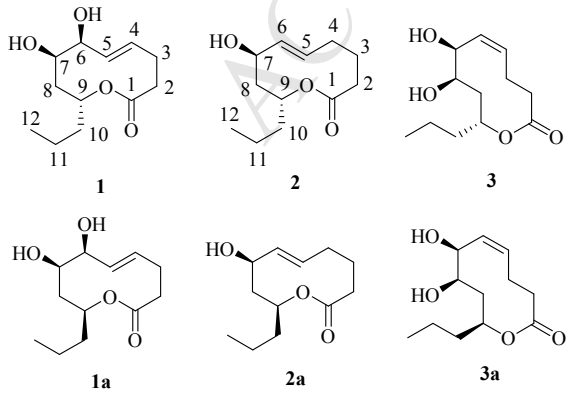

Figure 1. Structures of phyotoxic nonenolides and their C-9 epimers.

The novel phytotoxic nonenolide, (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone (**1**) (Figure 1) was obtained from solid cultures of the endophytic fungus *Phomopsis sp.* HCCB03520, together with three known compounds.[4] The compound **1** showed activity on germination and radicle growth of *Medicago sativa*, *Trifoliumhybridum*, and *Buchloe dactyloides*. The IC_{50} values of **1** on germination of *Medicago sativa*, *Trifolium hybridum*, and *Buchloe dactyloides* were 15.8, 24.2, and 31.2 µg/ml, and for radicle growth of these plants were 31.9, 63.3, 130.9 µg/ml, respectively, and the compound is less active then positive control [2-(2, 4-dichlorophenoxy) acetic acid (IC_{50}: 1.5, 1.6, and 1.2 µg/ml for germination, and 3.7, 7.4, 1.5 µg/ml for radicle growth)]. Earlier the synthesis of the (*Z*)-isomer of (6*R*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone (**3**) was accomplished.[5] We have now planned for the synthesis of **1**, but we have achieved the synthesis of its *Z*-isomer **3** and also for the first time the synthesis of the C-9 epimer (**3a**) of **3** through a common route.

Another phytotoxic nonenolide, namely (7*R*,9*R*)-7-hydroxy-9-propyl-5-nonen-9-olide which was designated with the trivial name herbarumin-III (**2**) (Figure 1) was isolated from reinvestigation of the fermentation broth and mycelium of the fungus *Phoma herbarum*.[6] The compound **2** interacted with bovine-brain calmodulin and inhibited the activation of the calmodulin dependent enzyme cAMP phosphodiesterase. It showed relevant phytotoxic effects (IC_{50}: 2 x 10^{-5} M) and inhibited radicle growth with higher potency than 2, 2-dichlorophenoxyacetic acid (IC_{50}: 2 x 10^{-4} M), used as positive control. Some syntheses of the herbarumin-III have been achieved but our approach is effective and different from earlier

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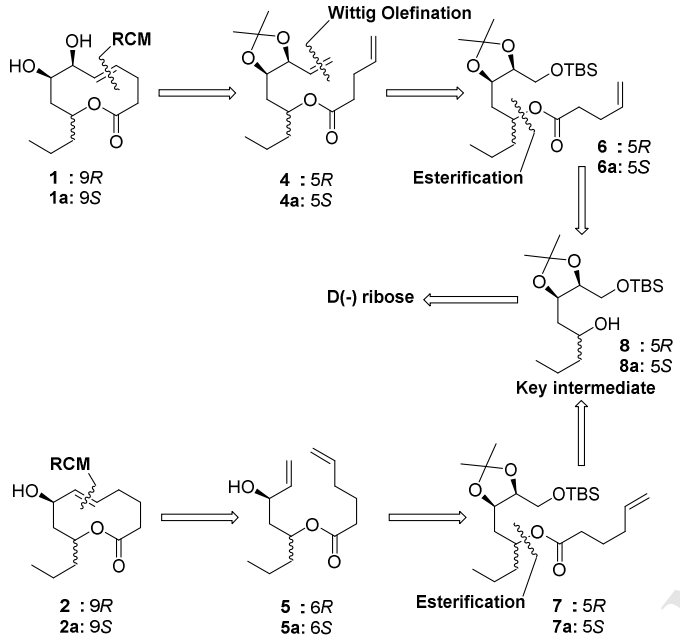
reports.[7] However, for the first time we have accomplished the synthesis of C-9 epimer (**2a**) of herbarumin-III (**2**).

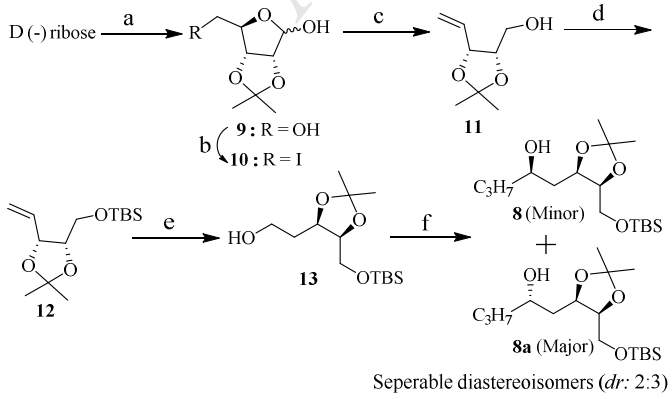
2. Results and Discussions

In continuation of our work[8] on the stereoselective construction of bioactive natural products we have realized that **1**, **2** and their C-9 epimers **1a**, **2a** can be synthesized from the dienes **4**, **5** and **4a**, **5a** respectively (Scheme 1). The dienes **4**, **4a** and **5**, **5a** in turn, can be prepared from the esters **6**, **6a** and **7**, **7a** while the esters **6**, **6a** and **7**, **7a** from the diastereoisomeric alcohols **8** and **8a**. Both the alcohols **8**, **8a** can be generated from the D (-) ribose which is commercially available.



Scheme 1. Retrosynthesis of **1**, **2** and their C-9 epimers **1a** and **2a**

The present synthesis was initiated by converting D (-) ribose (Scheme 2) into the iodo compound **10** via the formation of the primary alcohol **9** following reported methods.[9] The iodo compound **10** was reacted with Zn and AcOH (cat.) in MeOH under reflux to generate the olefinic aldehyde, which was not isolated but simultaneously reacted with $NaBH_4$ in MeOH to afford the alcohol **11**.[10] The hydroxyl group in **11** was protected as TBS to afford the **12**. The TBS ether **12** on treatment with $(c\text{-Hex})_2BH$[11] in THF followed by oxidation with H_2O_2/NaOH afforded the alcohol **13**. The alcohol **13** was oxidized with $SO_3.Py$[12] to generate the corresponding aldehyde and the crude aldehyde was immediately treated with the Grignard reagent, C_3H_7MgBr to produce the diastereoisomeric alcohols **8** and **8a** (*dr: 2:3*). Both the alcohols were separated by column chromatography and utilized for subsequent steps.



Scheme 2. Synthesis of alcohol **8** and its diastereomer **8a**

Reagents and conditions: (a) acetone, Cat. H_2SO_4, r.t., 4 h, 96%; (b) Ph_3P, Iodine, Imidazole, toluene, reflux, 2 h, 94% ; (c) Zn, MeOH, AcOH (cat.), reflux, 2 h then $NaBH_4$, MeOH, 0 ^oC-r.t., 4 h, 86% (for two steps); (d) TBS-Cl, imidazole, CH_2Cl_2, 0 ^oC-r.t., 2 h, 96%; (e) $(c\text{-Hex})_2BH$, THF, 0 ^oC-r.t., 2 h, then 30% aq. H_2O_2, 20% aq. NaOH, 0 ^oC-r.t., 8 h, 84%; (f) $SO_3.Py$, CH_2Cl_2, DMSO (3:1), Et_3N, 0 ^oC, 1 h then C_3H_7MgBr in THF, THF, 0 ^oC-r.t., 4 h, 96% (for two steps).

The absolute stereochemistry of the newly generated stereogenic center in compound **8a** bearing the hydroxyl group was determined by preparing the *S* and *R*-MTPA (α-Methoxy-α-trifluoromethylphenyl acetic acid) esters by a modified Mosher's method[13] and found to have (*S*)- configuration at C-5 (Figure 2). The negative chemical shift difference to the left side of the MTPA plane and the positive chemical shift differences to the right side of the MTPA plane indicated that the hydroxyl stereochemistry has (*S*)-configuration (Figure 2). Consequently, the stereochemistry of the same group in **8** is of *R*-configuration. These configurations of both **8** and **8a** were further confirmed by their subsequent transformations by coupling with the acid fragments into the target molecules.

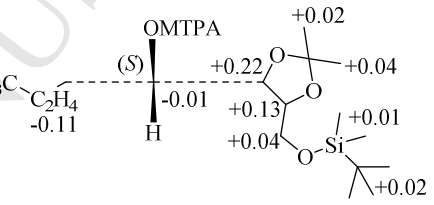


Figure 2: Determination of absolute configuration and $\Delta\delta$ values for the (*S*) and (*R*)-MTPA ester derivatives of **8a** ($\Delta\delta = \delta_S - \delta_R$).

After successful achievement of the diastereomeric alcohols **8** and **8a**, they were individually esterified with 4-pentenoic acid under Yamaguchi esterification protocol[14] to afford the esters **6** and **6a** (Scheme 3). The TBS ether group of esters **6** and **6a** was separately cleaved with TBAF to form the alcohols **14** and **14a** respectively. The alcohols **14** and **14a** were oxidized with $SO_3.Py$[12] and the generated corresponding aldehydes were subjected to C-1 Wittig olefination with Ph_3PCH_3Br in the presence of NaHMDS to yield the dienes **4** and **4a** required for the synthesis of the nonenolide **1**. The dienes **4** and **4a** were individually, subjected to intramolecular ring closing metathesis using Grubbs' II-generation catalyst[15] (**A**) and it was observed that both the dienes **4** and **4a** afforded the cyclization products **15** and **15a** respectively in high yields. Finally, deprotection of the acetonide group of **15** and **15a** was carried out with 4 *N* HCl in CH_3CN to furnish the (*Z*)-isomer (**3**) of the nonenolide **1** (from **15**) and also the (*Z*)-isomer (**3a**) of the C-9 epimer **1a** (from **15a**).

In the present synthesis compounds **15** and **15a** were formed with an olefinic double bond having *Z*-stereochemistry. These two compounds, **15** and **15a** were subsequently converted into **3** and **3a** respectively. The compound **15** is a known molecule, previously synthesized by our group[5b] and also by another group.[5a] Its structure was settled earlier from its spectral (^1H, ^{13}C and 2D NMR) studies. We have now established the structures of our presently synthesized compounds, **15** and **15a** by comparison of the spectral (^1H and ^{13}C NMR) values with those reported for the former.[5] In the ^1H NMR spectra of both the compounds the coupling constant between two olefinic protons was around 10.0 Hz (for **15**, 10.2 Hz and for **15a**, 10.5 Hz) indicating clearly the *Z*- configuration of the double bond present in these compounds.

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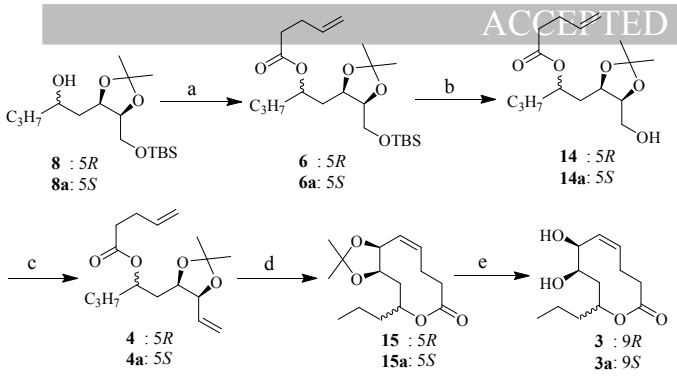
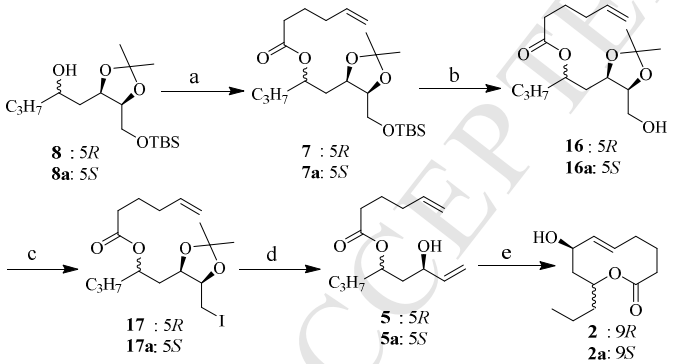


Scheme 3. Synthesis of (*Z*) isomer of (6*S*, 7*R*, 9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone (**3**) and its C-9 epimer (**3a**)

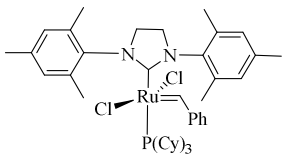
Reagents and conditions: (a) 4-pentenoic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 0 °C to r.t., 6 h, 96%; (b) TBAF (1 M in THF), THF, 0 °C to r.t., 4 h, 94%; (c) SO_3.Py, CH_2Cl_2, DMSO (3:1), Et_3N, 0 ^oC, 1 h then Ph_3PCH_3Br, NaHMDS, THF, 0 ^oC-r.t., 8 h, 84% (for two steps); (d) Grubbs' II (cat.), CH_2Cl_2, reflux, 12 h, 92%; (e) CH_3CN, 4 *N* HCl, 0 °C to r.t., 2 h, 90%.

The diastereomeric alcohols **8** and **8a** were successfully utilized for synthesis of herbarumin-III and its C-9 epimer (Scheme 4). The alcohols were individually esterified with 5-hexenoic acid under Yamaguchi esterification protocol[14] to afford the esters **7** and **7a** respectively. The TBS ether group of the esters **7** and **7a** was separately cleaved with TBAF to form the alcohols **16** and **16a** which were converted into the iodo compounds **17** and **17a** by treatment with iodine, Ph_3P and imidazole in THF.[16] Next, the iodo compounds **17** and **17a** were reacted[17] with Zn in EtOH under reflux to produce the dienes **5** (from **17**) and **5a** (from **17a**). The intramolecular ring-closing metathesis (RCM)[16a] of **5** and **5a** individually by using Grubbs' II-generation catalyst (**A**) afforded the herbarumin-III (**2**)[18] and its C-9 epimer (**2a**) respectively.



Scheme 3: Synthesis of herbarumin-III (**2**) and its C-9 epimer (**2a**)

Reagents and conditions: (a) 5-hexenoic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 0 °C to r.t., 6 h, 94%; (b) TBAF (1 M in THF), THF, 0 °C to r.t., 4 h, 96%; (c) Ph_3P, I_2, imidazole, THF, 0 ^oC-r.t., 2 h, then Zn, EtOH, reflux, 4 h, 94% (for two steps) (d) Grubbs' II (cat.), CH_2Cl_2, reflux, 12 h, 90%.



(**A**)
Grubbs' II generation catalyst

3. Conclusion

In conclusion, we have described the stereoselective total synthesis of (*Z*)-isomer of a novel phytotoxic nonenolide, (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone and herbarumin-III along with their C-9 epimers through a common route. The C-9 epimers have been synthesized here for the first time. The inexpensive and commonly available D (-) ribose has been used as the starting material. The Grignard addition, Yamaguchi esterification and intramolecular ring-closing metathesis are important steps involved in the present synthesis.

4. Experimental Section

4. 1. General methods

^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on Bruker (Avance) 300 MHz (^1H) and 75 MHz (^{13}C) and Varian Unity (Innova) 500 MHz (^1H) and 125 MHz (^{13}C) spectrometers at ambient temperature. Chemical shifts are reported in ppm relative to TMS as internal standard. IR spectra were recorded using a Perkin-Elmer Infrared-683 spectrophotometer with KBr optics. ESI-MS were obtained on a VG-Autospec Micro mass instrument and HRMS (ESI) on an Exactive Orbitrap mass spectrometer (Thermo Scientific, USA). Optical rotations were measured on a Jasco Dip 360 digital Polari meter. Silica gel F_{254} plates were used for thin-layer chromatography (TLC) in which the spots were examined under UV light and then developed using Iodine vapor. All the reagents and solvents were of reagent grade and used without further purification unless otherwise stated. Column chromatography was carried on silica gel (60–120 mesh) packed in glass columns.

4.1.1. tert-Butyl (((4S, 5R)-2, 2-Dimethyl-5-vinyl-1, 3-dioxolan-4-yl) methoxy) dimethylsilane (**12**): To a stirred solution of alcohol **11** (6.0 g, 37.97 mmol) and imidazole (7.74 g, 113.92) in CH_2Cl_2 at 0 ^oC was added the TBS-Cl (6.3 g, 41.72 mmol) and stirring was continued at room temperature for 2 h. After completion of the reaction as monitored by TLC, reaction was quenched with H_2O (5 mL) and worked up with CH_2Cl_2 (2 x 15 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo, the crude product was purified by a silica gel column chromatography (60–120 mesh) using hexane/AcOEt (98:2) to obtain pure compound **12** (9.91 g, 98%) as colorless oil; IR (KBr): 2931, 2858, 1468, 1253, 1098, 838, 777 cm^{-1}; $[\alpha]D^{27}$ - 12.00 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.96-5.80 (1H, m), 5.34 (1H, d, J = 16.9 Hz), 5.21 (1H, d, J = 10.3 Hz), 4.61 (1H, t, J = 6.7 Hz), 4.19 (1H, q, J = 6.7 Hz), 3.60 (2H, d, J = 6.0 Hz), 1.47 (3H, s), 1.36 (3H, s), 0.88 (9H, s), 0.04 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.6, 117.7, 108.5, 78.6, 78.4, 62.2, 27.8, 25.8, 25.3, 18.2, -5.4; MS (ESI): *m/z* = 295 $[M+Na]^+$; HRMS (ESI): calcd for $C_{14}H_{29}O_3Si$ $[M+H]^+$: 273.3839; found: 273.3832.

4.1.2. 2-((4R, 5S)-5-(((tert-Butyldimethylsilyl) oxy) me-thyl)-2, 2-dimethyl-1, 3-dioxolan-4-yl) ethanol (**13**): To a stirred solution of alkene **12** (6.0 g, 22.05 mmol) in dry THF (20 mL) at 0 ^oC, $[c\text{-}Hex)_2BH]$ dicyclohexylborane (17.64 mL, 26.47 mmol, 1.5 M in THF) was added slowly. The mixture was stirred at room temperature for 12 h. Then it was cooled to 0 ^oC and treated with aq. NaOH (11.2 mL, 110.25 mmol, 10 M aqueous solution) followed by H_2O_2 (4.2 mL, 110.30 mmol, 50% aqueous solution). The reaction mixture was stirred for 2 h at room temperature. Aq. NH_4Cl was added and the reaction mixture was extracted with AcOEt (2 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (60–120

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mesh) using hexane/AcOEt (90:10) to afford compound **13** (5.43 g, 85%) as a colorless liquid; IR (KBr): 3454, 2931, 2858, 1467, 1253, 1099, 839 cm^{-1}; $[\alpha]D^{27}$ -2.10 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 4.35 (1H, m), 4.17-4.09 (1H, m), 3.88-3.82 (1H, m), 3.85 (1H, m), 3.67 (1H, dd, *J* =12.0, 10.0 Hz), 3.0 (1H, dd, *J* = 12.0, 5.0 Hz), 2.58 (1H, brs), 1.96-1.84 (2H, m), 1.42 (3H, s), 1.35 (3H, s), 0.89 (9H, s), 0.07 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 107.8, 77.7 (2C), 61.7, 61.2, 31.1, 28.1, 25.8, 25.4, 18.3, -5.4, -5.5; MS (ESI): *m/z* = 313 $[M+Na]^+$; HRMS (ESI): calcd for $C_{14}H_{31}O_4Si$ $[M+H]^+$: 291. 8353; found: 291. 8349.

4.1.3. (R)-1-((4R, 5S)-5-(((tert-Butyldimethylsilyl) oxy) methyl)-2, 2-dimethyl-1, 3-dioxolan-4-yl) pentan-2-ol (**8**): To a stirred solution of compound **13** (5.0 g, 17.24 mmol) in a mixture of CH_2Cl_2/DMSO (3:1, 40 mL) at 0 ^oC, Et_3N (12.0 mL, 86.13 mmol) and SO_3.Py (13.79 g, 86.20 mmol) were added simultaneously under N_2 condition. The resulting solution was stirred at same temperature for 1 h. After completion of the reaction monitored by TLC, the reaction mixture was diluted with cold H_2O (15 mL) and the organic layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude aldehyde was used directly after flash chromatography for the next reaction.

To a stirred solution of aldehyde (4.96 g, 17.22 mmol) in dry THF (10 mL) was added *n*-propyl magnesium bromide (1.5 M solution in THF) at 0 ^oC and stirred for 6 h at the same temperature. After completion of the reaction as monitored by TLC, the reaction was quenched with saturated aq. NH_4Cl (15 mL) at 0 ^oC. The reaction mixture was worked up with AcOEt (3 x 20 mL), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by a silica gel column chromatography (60–120 mesh) using hexane/AcOEt (97:3) to obtain pure compounds **8** (2.52 g, 7.59 mmol) and **8a** (3.08 g, 9.27 mmol) as colourless liquids (5.60 g, 16.86 mmol, *dr = 2:3*, 98% (for two steps)).

Spectral data of compound (**8**): IR (KBr): 3453, 2931, 2859, 1463, 1254, 1095, 837, 776 cm^{-1}; $[\alpha]D^{27}$ -5.62 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.39-4.34 (1H, m), 4.15-4.10 (1H, m), 3.86-3.80 (1H, m), 3.67-3.59 (2H, m), 3.36 (1H, brs), 1.82 (1H, dt, *J* = 15.0, 6.0 Hz), 1.67-1.58 (2H, m), 1.56-1.49 (1H, m), 1.48-1.37 (4H, m), 1.34 (3H, s), 1.25 (1H, brs), 0.93 (3H, t, *J* = 7.1 Hz), 0.88 (9H, s), 0.06 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 108.3, 77.8, 71.3, 68.2, 61.6, 39.5, 35.6, 30.3, 28.0, 25.8, 18.7, 14.1, -5.4, -5.5; MS (ESI): *m/z* = 355 $[M+Na]^+$; HRMS (ESI): calcd for $C_{17}H_{37}O_4Si$ $[M+H]^+$: 333. 1992; found: 333. 1987.

Spectral data of compound (**8a**): IR (KBr): 3460, 2931, 2957, 2859, 1463, 1380, 1254, 1094, 838, 775 cm^{-1}; $[\alpha]D^{27}$ -4.16 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.43 (1H, q, *J* = 7.0 Hz), 4.20-4.16 (1H, m), 3.80-3.73 (1H, m), 3.67 (1H, dd, *J* = 12.0, 10.0 Hz), 3.56 (1H, dd, *J* = 12.0, 6.0 Hz), 2.73 (1H, brs), 1.91-1.84 (1H, m), 1.80-1.71 (1H, m), 1.53-1.42 (2H, m), 1.40 (4H, m), 1.35 (4H, m), 0.93 (3H, t, *J* = 7.0 Hz), 0.90 (9H, s), 0.09 (6H, s) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 107.2, 77.7, 75.2, 69.2, 61.8, 40.5, 35.5, 28.1, 25.9, 25.4, 18.9, 14.0, -5.5; MS (ESI): *m/z* = 355 $[M+Na]^+$; HRMS (ESI): calcd for $C_{17}H_{36}O_4Si$ $[M+H]^+$: 333.1992; found:333.1985.

4.1.4. (R)-1-((4R, 5S)-5-(((tert-Butyldimethylsilyl) oxy) methyl)-2, 2-dimethyl-1, 3-dioxolan-4-yl) pentan-2-yl pent-4-enoate (**6**): To a stirred solution of 4-pentenoic acid (0.30 g, 3.03 mmol) in toluene (5 mL) were added Et_3N (0.52 mL, 3.79 mmol) and 2, 4, 6- $Cl_3C_6H_2COCl$ (0.51 mL, 3.28 mmol) at 0 ^oC. The reaction mixture was stirred for 1 h at 0 ^oC and a solution of alcohol **8** (0.84 g, 2.53 mmol) and DMAP (227 mg, 1.86 mmol) in toluene (5.0 mL) were then added to the above solution at 0 ^oC. The resulting mixture was stirred at room temperature for 8 h. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with saturated aq. $NaHCO_3$ at 0 ^oC and the reaction mixture was extracted with AcOEt (3 x 10 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (60-120 mesh) using hexane/AcOEt (90:10) to give compound **6** (1.00 g, 96%) as a colorless oil; IR (KBr): 2957, 2859, 1734, 1466, 1254, 1100, 839, 778 cm^{-1}; $[\alpha]D^{27}$ +10.55 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.92-5.75 (1H, m), 5.19-4.96 (3H, m), 4.24-4.15 (1H, m), 4.10-4.02 (1H, m), 3.68-3.53 (2H, m), 2.40 (4H, s), 1.96-1.79 (2H, m), 1.61-1.52 (2H, m), 1.44-1.32 (4H, m), 1.32-1.24 (4H, m), 0.96-0.83 (12H, m), 0.06 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 136.8, 115.2, 107.9, 77.6, 74.7, 72.0, 61.7, 36.7, 33.8, 33.6, 28.9, 28.1, 25.4, 25.8, 18.3, 13.9, -5.4, -5.5; MS (ESI): *m/z* = 437 $[M+Na]^+$; HRMS (ESI): calcd for $C_{22}H_{43}O_5Si$ $[M+H]^+$: 415.2635; found:415.2629.

4.1.5. (S)-1-((4R, 5S)-5-(((tert-Butyldimethylsilyl) oxy) methyl)-2, 2-dimethyl-1, 3-dioxolan-4-yl) pentan-2-yl pent-4-enoate (**6a**): To a stirred solution of 4-pentenoic acid (0.22 g, 2.24 mmol) in toluene (3 mL) were added Et_3N (0.39 mL, 2.80 mmol) and 2, 4, 6- $Cl_3C_6H_2COCl$ (0.38 mL, 2.42 mmol) at 0 ^oC. The reaction mixture was stirred for 0.5 h at 0 ^oC and a solution of alcohol **8a** (0.62 g, 1.86 mmol) and DMAP (100 mg, 1.86 mmol) in toluene (5.0 mL) were then added to the above solution at 0 ^oC. The resulting mixture was stirred at room temperature for 8 h. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with sat. $NaHCO_3$ at 0 ^oC and the reaction mixture was extracted with AcOEt (2 x 10 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (60-120 mesh) using hexane/AcOEt (90:10) to give compound **6a** (0.76 g, 98%) as a colorless oil; IR (KBr): 2932, 2860, 1736, 1645, 1374, 1252, 1097, 840, 777 cm^{-1}; $[\alpha]D^{27}$ +22.00 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.91-5.74 (1H, m), 5.16-4.96 (3H, m), 4.20-4.12 (1H, m), 4.04 (1H, q, *J* = 5.6 Hz), 3.68-3.55 (2H, m), 2.44-2.32 (4H, brs), 1.92-1.81 (1H, m), 1.80-1.67 (1H, m), 1.66-1.47 (3H, m), 1.39 (3H, s), 1.36-1.23 (4H, m), 0.95-0.84 (12H, m), 0.06 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 136.7, 115.3, 107.9, 77.5, 73.7, 71.8, 61.7, 37.1, 33.8, 29.0, 28.1, 25.8, 25.4, 18.3, 13.9, -5.4, -5.5; MS (ESI): *m/z* = 437 $[M+Na]^+$; HRMS (ESI): calcd for $C_{22}H_{43}O_5Si$ $[M+H]^+$: 415.2635; found: 415.2627.

4.1.6. (R)-1-((4R, 5S)-5-(Hydroxymethyl)-2, 2-dimethyl-1, 3-dioxolan-4-yl) pentan-2-yl pent-4-enoate (**14**): To a stirred solution of ester **6** (0.9 g, 2.17 mmol) in THF was added TBAF (2.6 mL, 1.2 equv) (1M in THF) at 0 ^oC and stirring was continued for 4 h at room temperature until TLC showed complete conversion of the starting material. The reaction mixture was quenched with water and the organic layer was extracted with AcOEt (3 x 10 mL). The organic extract was dried over anhydrous Na_2SO_4, and evaporated. The crude reaction mixture was purified by silica gel column chromatography (60-120 mesh) using hexane/AcOEt (80:20) as an eluent to provide the compound **14** (0.64 g, 98%) as a clear oil; IR (KBr): 3457, 2932, 2874, 1731, 1375, 1217, 1044, 916 cm^{-1}; $[\alpha]D^{27}$ -2.66 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.88-5.78 (1H, m), 5.11-5.04 (2H, m), 5.01 (1H, dd, *J* = 1.2, 10.2 Hz), 4.25-4.20 (1H, m), 4.15 (1H, q, *J* = 6.0 Hz), 3.61 (2H, d, *J* = 6.0 Hz), 2.44-2.34 (4H, m), 1.93-1.84 (1H, m), 1.79-1.73 (1H, m), 1.63-1.54 (2H, m), 1.46 (3H, s), 1.40-1.23 (6H, m), 0.91 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.7, 136.6, 115.3, 77.7, 74.0, 71.6, 61.3, 36.1, 33.7, 33.5, 28.7, 28.0, 25.3, 18.3, 13.7; MS (ESI): *m/z*

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= 323 $[M+Na]^+$; HRMS (ESI): calcd for $C_{16}H_{29}O_5$ $[M+H]^+$: 300.1145; found: 300.1139.

4.1.7. (S)-1-((4R, 5S)-5-(Hydroxymethyl)-2, 2-dimethyl-1, 3-dioxolan-4-yl) pentan-2-yl pent-4-enoate (**14a**): To a stirred solution of ester **6a** (0.7 g, 1.69 mmol) in THF was added TBAF (2.0 mL, 1.2 equv) (1M in THF) at 0 ^oC and stirring was continued for 6 h at room temperature until TLC showed complete conversion of the starting material. The reaction mixture was quenched with water and the organic layer was extracted with AcOEt (3 x 10 mL). The organic extract was dried over anhydrous Na_2SO_4, and evaporated. The crude reaction mixture was purified by silica gel column chromatography (60-120 mesh) using hexane/AcOEt (80:20) as an eluent to provide the compound **14a** (0.49 g, 96%) as a clear oil; IR (KBr): 3420, 2928, 2873, 1728, 1376, 1376, 1180, 1066, 916 cm^{-1}; $[\alpha]D^{27}$ -1.42 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.87-5.77 (1H, m), 5.10-5.02 (2H, m), 5.01 (1H, dd, *J* = 1.2, 10.2 Hz), 4.20-4.15 (1H, m), 4.13-4.08 (1H, m), 3.66-3.56 (2H, m), 2.42-2.34 (4H, m), 2.01 (1H, brs), 1.85-1.78 (1H, m), 1.75-1.68 (1H, m), 1.63-1.50 (2H, m), 1.44 (3H, s), 1.39-1.24 (5H, m), 0.90 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 136.6, 115.5, 108.1, 77.6, 73.5, 71.8, 61.6, 37.0, 33.7, 28.9. 28.0, 25.6, 18.3, 13.9; MS (ESI): *m/z* = 323 $[M+Na]^+$; HRMS (ESI): calcd for $C_{16}H_{29}O_5$ $[M+H]^+$: 301.1145; found: 301.1141.

4.1.8. (R)-1-((4R, 5S)-2, 2-Dimethyl-5-vinyl-1, 3-dioxolan-4-yl) pentan-2-yl pent-4-enoate (**4**): To a stirred solution of compound **14** (0.6 g, 2.0 mmol) in a mixture of CH_2Cl_2/DMSO (3:1, 15 mL) at 0 ^oC, Et_3N (1.39 mL, 10.0 mmol) and SO_3.Py (1.6 g, 10.0 mmol) were added simultaneously under N_2 atm. The resulting reaction mixture was stirred at same temperature for 1 h. After completion of the reaction as monitored by TLC, the reaction mixture was diluted with cold water (5 mL) and the organic layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude aldehyde (0.56 g, 96%) was used directly after flash chromatography for the next reaction.

Methyltriphenylphosphonium bromide (1.43 g, 4.0 mmol) was thoroughly flame dried and anhydrous THF (15 mL) was added and the resulting suspension was cooled to 0 °C prior to the drop wise addition of NaHMDS in THF (1.6 M in THF) (5.0 mL, 4.10 mmol). The resulting gold suspension was warmed to 25 °C for 30 min and re-cooled to -10 °C prior to the addition of above aldehyde (0.56 g, 1.87 mmol) in anhydrous THF (5 mL). The reaction was stirred at room temperature for 10 h, as judged by TLC, and quenched by the addition of saturated aq. NH_4Cl (10 ml). The mixture was then extracted with Et_2O (4 x 10 mL), washed sequentially with H_2O (15 mL) and saturated aq. NaCl (3 x 10 mL) and then dried over anhydrous Na_2SO_4. Removal of solvents under reduced pressure followed by flash column chromatography (60-120 mesh) using hexane/AcOEt (90:10) gave compound **4** (0.49 g, 84%) as a colorless oil; IR (KBr): 2959, 2932, 1732, 1380, 1243, 1174, 1051, 926 cm^{-1}; $[\alpha]D^{27}$ -13.33 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.90-5.72 (2H, m), 5.38-5.21 (2H, m), 5.10-4.98 (3H, m), 4.49 (1H, t, *J* = 7.0 Hz), 4.19 (1H, t, *J* = 7.0 Hz), 2.40 (4H, s), 1.80 (1H, m), 1.68-1.51 (2H, m), 1.48 (3H, s), 1.41-1.20 (6H, m), 0.90 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 136.7, 134.2, 118.7, 115.4, 108.3, 79.8, 75.0, 71.4, 36.4, 35.0, 28.9, 28.2, 25.6, 18.4, 13.8; MS (ESI): *m/z* = 319 $[M+Na]^+$; HRMS (ESI): calcd for $C_{17}H_{29}O_4$ $[M+H]^+$: 297. 3833; found: 297. 3828.

4.1.9. (S)-1-((4R, 5S)-2, 2-Dimethyl-5-vinyl-1, 3-dioxolan-4-yl) pentan-2-yl pent-4-enoate (**4a**): To a stirred solution of compound **14a** (0.4 g, 1.33 mmol) in a mixture of CH_2Cl_2/DMSO (3:1, 15 mL) at 0 ^oC, Et_3N (0.93 mL, 6.62 mmol) and SO_3.Py (1.06 g, 6.62 mmol) were added simultaneously under N_2 condition. The resulting reaction mixture was stirred at same temperature for 1 h. After completion of the reaction as monitored by TLC, the reaction mixture was diluted with cold water (5 mL) and the organic layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude aldehyde (0.36 g, 96%) was used directly after flash chromatography for the next reaction.

Methyltriphenylphosphonium bromide (0.96 g, 2.68 mmol) was thoroughly flame dried and anhydrous THF (10 mL) was added and the resulting suspension was cooled to 0 °C prior to the drop wise addition of NaHMDS in THF (1.6 M) (3.5 mL, 2.75 mmol). The resulting gold suspension was warmed to 25 °C for 30 min and re-cooled to -10 °C prior to the addition of above aldehyde (0.36 g, 1.20 mmol) solution in anhydrous THF (5 mL). The reaction was stirred at room temperature for 12 h, as judged by TLC, and quenched by the addition of saturated aq. NH_4Cl (10 ml). The mixture was then extracted with Et_2O (2 x 10 mL), washed sequentially with H_2O (15 mL) and saturated aq. NaCl (3 x 5 mL) and then dried over anhydrous Na_2SO_4. Removal of solvents under reduced pressure followed by flash column chromatography (60-120 mesh) using hexane/AcOEt (90:10) gave compound **4a** (0.33 g, 86%) as a colorless oil; IR (KBr): 2961, 2930, 1734, 1639, 1376, 1172, 1048, 922, 769 cm^{-1}; $[\alpha]D^{27}$ -17.53 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.95-5.71 (2H, m), 5.38-5.22 (2H, m), 5.14-4.96 (3H, m), 4.48 (1H, t, *J* = 6.4 Hz), 4.22-4.10 (1H, m), 2.39 (4H, s), 1.73-1.51 (3H, m), 1.47 (3H, s), 1.41-1.20 (6H, m), 0.91 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 136.7, 134.2, 118.3, 115.4, 108.3, 79.5, 74.6, 71.7, 37.0, 35.1, 33.7, 29.0, 28.2, 25.6, 18.3, 13.9; MS (ESI): *m/z* = 319 $[M+Na]^+$; HRMS (ESI): calcd for $C_{17}H_{29}O_4$ $[M+H]^+$: 297. 3833; found: 297. 3825.

4.1.10. (3aR, 5R, 11aS, Z)-2, 2-Dimethyl-5-propyl-4, 5, 8, 9-tetrahydro-3aH-[1, 3]dioxolo[4, 5d]oxecin-7(11aH)-one (**15**): Grubbs' II generation catalyst (45 mg, 0.05 mmol) was dissolved in dry, deoxygenated CH_2Cl_2 (120 mL). After heating the solution to reflux, diene **4** (0.08 g, 0.27 mmol) dissolved in dry, deoxygenated CH_2Cl_2 (80 mL) was added drop wise over 30 min. The reaction mixture was refluxed for 12 h at 50 ^oC. After completion of the reaction (by TLC), the mixture was concentrated in vacuo, and the residue was purified by column chromatography (60-120 mesh) using hexane/AcOEt (80:20) to afford pure **15** (0.059 g, 82%) as a white solid; IR (KBr): 2958, 2932, 1736, 1245, 1067, 976, 878, 762 cm^{-1}; $[\alpha]D^{27}$ -33.12 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.60 (1H, td, *J* = 10.2, 5.1 Hz), 5.48 (1H, t, *J* = 10.2 Hz), 5.19-5.14 (1H, m), 5.04-4.99 (1H, m), 4.41 (1H, m), 2.77-2.67 (1H, m), 2.64-2.58 (1H, m), 2.34-2.24 (1H, m), 2.10-1.99 (2H, m), 1.90-1.84 (1H, m), 1.78-1.69 (1H, m), 1.66-1.51 (2H, m), 1.49 (3H, s), 1.40 (3H, s), 1.38-1.24 (1H, m), 0.94 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 129.5, 129.4, 107.2, 74.6, 74.0, 70.3, 34.0, 33.4, 31.5, 28.5, 26.1, 22.5, 19.3, 13.7; MS (ESI): *m/z* = 291 $[M+Na]^+$; HRMS (ESI): calcd for $C_{15}H_{25}O_4$ $[M+H]^+$: 269.2435; found: 269.2429.

4.1.11. (3aR, 5S, 11aS, Z)-2, 2-Dimethyl-5-propyl-4, 5, 8, 9-tetrahydro-3aH-[1, 3]dioxolo[4, 5 d]oxecin-7(11aH)-one (**15a**): Grubbs' II generation catalyst (34 mg, 0.04 mmol) was dissolved in dry, deoxygenated CH_2Cl_2 (100 mL). After heating the solution to reflux, diene **4a** (0.08 g, 0.27 mmol) dissolved in dry, deoxygenated CH_2Cl_2 (60 mL) was added dropwise over 30 min. The reaction mixture was refluxed for 9 h at 50 ^oC. After completion of the reaction (by TLC), the mixture was concentrated in vacuo, and the residue was purified by column

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chromatography (60-120 mesh) using hexane/AcOEt (80:20) to afford pure **15a** (0.06 g, 84%) as a yellow oil; IR (KBr): 2958, 2930, 1735, 1379, 1245, 1169, 1067, 878, 769 cm^{-1}; $[\alpha]D^{27}$ -50.83 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.72 (1H, td, *J* = 10.5, 7.0 Hz), 5.60 (1H, t, *J* = 10.5 Hz), 5.10 (1H, m), 4.71 (1H, dd, *J* = 10.5, 7.0 Hz), 4.31 (1H, q, *J* = 7.0 Hz), 2.71-2.56 (1H, m), 2.44-2.20 (3H, m), 2.19-2.07 (1H, m), 1.99-1.90 (2H, m), 1.72-1.54 (2H, m), 1.47 (3H, s), 1.40-1.19 (4H, m), 0.91 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 131.1, 129.0, 107.2, 77.9, 72.9, 71.5, 37.4, 36.0, 34.2, 28.1, 25.3, 24.1, 18.5, 13.7; MS (ESI): *m/z* = 291 $[M+Na]^+$; HRMS (ESI): calcd for $C_{15}H_{25}O_4$ $[M+H]^+$: 269.2435; found: 269.2430.

4.1.12. (4Z, 6S, 7R, 9R)-6, 7-Dihydroxy-9-propylnon-4-eno-9-lactone (**3**): To a solution of compound **15** (0.045 g, 0.17 mmol) in CH_3CN (5 mL) was added aq. HCl (4*N*, 0.5 mL) at 0 ºC. The resulting mixture was stirred for 6 h at room temperature and then added solid $NaHCO_3$. The reaction mixture was filtered through a pad of Celite and washed with AcOEt (10 mL). The filtrate was dried over anhydrous Na_2SO_4 and concentrated. The product was purified by silica gel column chromatography (60-120 mesh) using hexane/AcOEt (70:30) to afford the pure compound **3** (0.034 g, 91%) as a yellow oil; IR (KBr): 3400, 2958, 2927, 1728, 1452, 1250, 1163, 1066, 911, 722 cm^{-1}; $[\alpha]D^{27}$ +10.00 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.73-5.64 (2H, m), 5.02-4.95 (1H, m), 4.80 (1H, dd, *J* = 6.4, 2.4 Hz), 4.19 (1H, td, *J* = 11.2, 3.5 Hz), 2.86-2.74 (1H, m), 2.61 (1H, qd, *J* = 14.9, 3.5, 1.3 Hz), 2.31-2.22 (1H, m), 2.13-2.06 (1H, m), 1.89-1.75 (2H, m), 1.73-1.63 (1H, m), 1.59-1.50 (1H, m), 1.47-1.18 (5H, m), 0.94 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 130.7, 128.3, 71.3, 69.8, 68.3, 35.2, 33.7, 29.6, 23.2, 19.2, 13.6; MS (ESI): *m/z* = 251 $[M+Na]^+$; HRMS (ESI): calcd for $C_{12}H_{21}O_4$ $[M+H]^+$: 229.0968; found: 229. 0965.

4.1.13. (4Z, 6S, 7R, 9S)-6, 7-Dihydroxy-9-propylnon-4-eno-9-lactone (**3a**): To a solution of compound **15a** (0.05 g, 0.19 mmol) in CH_3CN (5 mL) was added aq. HCl (4*N*, 0.5 mL) at 0 ºC. The resulting mixture was stirred for 4 h at room temperature and then added solid $NaHCO_3$. The reaction mixture was filtered through a pad of Celite and washed with AcOEt (15 mL). The filtrate was dried over anhydrous Na_2SO_4 and concentrated. The product was purified by silica gel column chromatography (60-120 mesh) using hexane/AcOEt (70:30) to afford the pure compound **3a** (0.038 g, 89%) as a yellow oil; IR (KBr): 3421, 2929, 2874, 1723, 1263, 1152, 1026, 770 cm^{-1}; $[\alpha]D^{27}$ -26.66 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.93-5.72 (2H, m), 4.85-4.71 (1H, m), 4.30 (1H, dd, *J* = 9.8, 3.0 Hz), 4.09-3.97 (1H, m), 2.69-2.53 (1H, m), 2.46-2.23 (2H, m), 2.21-1.99 (1H, m), 1.96-1.82 (1H, m), 1.78-1.63 (1H, m), 1.60-1.46 (2H, m), 1.43-1.20 (4H, m), 0.91 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 130.7, 129.1, 72.5, 72.4, 67.8, 37.8, 37.7, 34.1, 24.3, 18.5, 13.8; MS (ESI): *m/z* = 251 $[M+Na]^+$; HRMS (ESI): calcd for $C_{12}H_{21}O_4$ $[M+H]$+: 229.0968; found: 229.0961.

4.1.14. (R)-1-((4R, 5S)-5-(((tert-Butyldimethylsilyl) oxy) methyl)-2, 2-dimethyl-1, 3-dioxolan-4-yl) pentan-2-yl hex-5-enoate (**7**): To a stirred solution of 5-hexenoic acid (0.36 g, 3.12 mmol) in toluene (5 mL) were added Et_3N (0.43 mL, 3.12 mmol) and 2, 4, 6- $Cl_3C_6H_2COCl$ (0.48 mL, 3.12 mmol) at 0 ^oC. The reaction mixture was stirred for 1 h at 0 ^oC and a solution of alcohol **8** (0.70 g, 2.08 mmol) and DMAP (220 mg, 1.86 mmol) in toluene (5.0 mL) was then added to the above solution at 0 ^oC. The resulting mixture was stirred at room temperature for 8 h. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with saturated aq. $NaHCO_3$ at 0 ^oC and the reaction mixture was extracted with AcOEt (3 x 10 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (60-120 mesh) using hexane/AcOEt (90:10) to give compound **7** (0.86 g, 96%) as a colorless oil; IR (KBr): 2957, 2929, 1733, 1464, 1251, 1100, 840, 778 cm^{-1}; $[\alpha]D^{27}$ +10.00 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.79 (1H, m), 5.12 (1H, m), 5.04 (1H, m), 5.01 (1H, m), 4.20 (1H, m), 4.06 (1H, m), 3.62 (1H, dd, *J* = 12.0, 10.0 Hz), 3.58 (1H, dd, *J* = 12.0, 5.0 Hz), 2.38 (1H, t, *J* = 7.0 Hz), 2.31 (1H, t, *J* = 7.0 Hz), 2.14-2.08 (2H, m), 1.94-1.81 (2H, m), 1.78-1.70 (2H, m), 1.59-1.52 (2H, m), 1.40 (3H, s), 1.38-1.24 (4H, m), 0.93-0.86 (12H, m), 0.06 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 137.7, 115.2, 107.9, 77.6, 74.7, 71.9, 61.7, 36.2, 33.9, 33.6, 33.1, 28.1, 25.8, 25.4, 25.1, 18.4, 13.9, -5.4, -5.5; MS (ESI): *m/z* = 451 $[M+Na]^+$; HRMS (ESI): calcd for $C_{23}H_{45}O_5Si$ [M+H]+: 429.1798; found: 429.1792.

4.1.15. (S)-1-((4R, 5S)-5-(((tert-Butyldimethylsilyl) oxy) methyl)-2, 2-dimethyl-1, 3-dioxolan-4 yl) pentan-2-yl hex-5-enoate (**7a**): To a stirred solution of 5-hexenoic acid (0.26 g, 2.26 mmol) in toluene (5 mL) were added Et_3N (0.31 mL, 2.26 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.35 mL, 2.25 mmol) at 0 ^oC. The reaction mixture was stirred for 1 h at 0 ^oC and a solution of alcohol **8a** (0.50 g, 1.50 mmol) and DMAP (200 mg, 1.86 mmol) in toluene (5.0 mL) was then added to the above solution at 0 ^oC and the resulting mixture was stirred at room temperature for 8 h. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with saturated aq. $NaHCO_3$ at 0 ^oC and the reaction mixture was extracted with AcOEt (3 x 10 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (60-120 mesh) using hexane/AcOEt (90:10) to give compound **7a** (0.63 g, 96%) as a colorless oil; IR (KBr): 2957, 2932, 1736, 1639, 1376, 1250, 1098, 839, 776 cm^{-1}; $[\alpha]D^{27}$ +7.85 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.86-5.70 (1H, m), 5.14-5.03 (1H, m), 5.02-4.95 (1H, m), 4.20-4.17 (1H, m), 4.05 (1H, q, *J* = 5.6 Hz), 3.65-3.57 (2H, m), 2.30 (2H, t, *J* = 7.0 Hz), 2.09 (2H, q, *J* = 7.0 Hz), 1.92-1.81 (1H, m), 1.80-1.66 (3H, m), 1.65-1.52 (4H, m), 1.39 (3H, s), 1.36-1.24 (4H, m), 0.96-0.85 (12H, m), 0.06 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1, 137.5, 115.0, 107.6, 77.4, 74.5, 71.6, 61.5, 36.0, 33.7, 32.9, 28.0, 25.6, 25.2, 23.9, 18.2, 13.7, -5.5; MS (ESI): *m/z* = 451 $[M+Na]^+$; HRMS (ESI): calcd for $C_{23}H_{45}O_5Si$ $[M+H]^+$: 429.1798; found: 429.1790.

4.1.16. (R)-1-((4R, 5S)-5-(Hydroxymethyl)-2, 2-dimethyl-1, 3-dioxolan-4-yl) pentan-2-yl hex-5-enoate (**16**): To a stirred solution of compound **7** (0.80 g, 1.86 mmol) in anhydrous THF was added 5 mL of TBAF (2.24 mL, 1.0 M solution in THF) at 0 ^oC and the reaction mixture was stirred at room temperature for 1 h. The solvent was then concentrated in vacuo. The crude residue was purified by column chromatography (60-120 mesh) using hexane/AcOEt (80:20) to afford the primary alcohol **16** (0.54 g, 92%) as a pale yellow oil; IR (KBr): 3445, 2960, 2935, 1731, 1380, 1220, 1046, 913, 773 cm^{-1}; $[\alpha]D^{27}$ -12.00 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.86-5.70 (1H, m), 5.13-4.95 (3H, m), 4.27-4.08 (2H, m), 3.61 (2H, d, *J* = 5.4 Hz), 2.31 (2H, t, *J* = 7.5 Hz), 2.10 (2H, q, *J* = 7.0 Hz), 1.95-1.82 (1H, m), 1.81-1.67 (3H, m), 1.62-1.51 (2H, m), 1.46 (3H, s), 1.42-1.22 (6H, m), 0.91 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 137.6, 115.3, 108.1, 77.7, 74.0, 71.5, 61.5, 36.2, 33.8, 33.6, 33.0, 28.1, 25.3, 24.0, 18.5, 13.8; MS (ESI): *m/z* = 337 $[M+Na]^+$; HRMS (ESI): calcd for $C_{17}H_{31}O_5$ $[M+H]^+$: 315.2459; found: 315.2451.

4.1.17. (S)-1-((4R, 5S)-5-(Hydroxymethyl)-2, 2-dimethyl-1, 3-dioxolan-4-yl) pentan-2-yl hex-5-enoate (**16a**): To a stirred solution of compound **7a** (0.60 g, 1.40 mmol) in anhydrous THF was added 5 mL of TBAF (1.7 mL, 1.0 M solution in THF) at 0 ^oC and the reaction mixture was stirred at room temperature for 1

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h. The solvent was then removed in vacuo. The crude residue was purified by column chromatography (60-120 mesh) using hexane/AcOEt (80:20) to afford the primary alcohol **16a** (0.42 g, 96 %) as a pale yellow oil; IR (KBr): 3455, 2959, 2931, 1733, 1459, 1376, 1219, 1048, 994 cm^{-1}; $[\alpha]D^{27}$ -3.75 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.83-5.72 (1H, m), 5.03-4.97 (3H, m), 4.21-4.16 (1H, m), 4.13-4.09 (1H, m), 3.68-3.57 (2H, m), 2.31 (2H, t, *J* = 7.3 Hz), 2.10 (2H, q, *J* = 7.1 Hz), 1.86-1.79 (1H, m), 1.77-1.69 (3H, m), 1.67-1.51 (3H, m), 1.45 (3H, s), 1.41-1.28 (4H, m), 1.25 (1H, brs), 0.91 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 137.6, 115.3, 108.0, 77.6, 73.5, 71.6, 61.6, 37.0, 33.7, 33.6, 33.0, 28.1, 25.4, 24.1, 18.4, 13.9; MS (ESI): *m/z* = 337 $[M+Na]^+$; HRMS (ESI): calcd for $C_{17}H_{30}O_5$ $[M+H]^+$: 315.2459; found: 315.2453.

4.1.18. (R)-1-((4R, 5R)-5-(Iodomethyl)-2, 2-dimethyl-1, 3-dioxolan-4-yl) pentan-2-yl hex-5-enoate (**17**): To a solution of **16** (0.5 g, 1.59 mmol) in anhydrous THF (10 mL) were added Ph_3P (0.52 g, 1.99 mmol), imidazole (0.16 g, 2.38 mmol), and iodine (0.48 g, 1.91 mmol) simultaneously at 0 ^oC. The mixture was stirred at room temperature for 3 h. When the reaction was complete as monitored by TLC, the mixture was diluted with H_2O (10 mL), and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and saturated aq. $Na_2S_2O_3$ (10 mL), dried over anhydrous Na_2SO_4 and the organic layer was concentrated in vacuo. Column chromatography of the residue (60-120 mesh) using hexane/AcOEt (96:4) gave the iodide **17** (0.36 g, 0.65 mmol, 96%) as a colorless oil; IR (KBr): 2958, 1732, 1458, 1458, 1376, 1220, 1170, 1057, 913 cm^{-1}; $[\alpha]D^{27}$ +5.83 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.86-5.71 (1H, m), 5.16-5.04 (2H, m), 5.03-4.96 (1H, m), 4.33 (1H, q, *J* = 6.4 Hz), 4.24-4.15 (1H, m), 3.19-3.06 (2H, m), 2.31 (2H, t, *J* = 7.3 Hz), 2.10 (2H, q, *J* = 6.9 Hz), 1.92-1.67 (3H, m), 1.65-1.54 (3H, m), 1.47 (3H, s), 1.44-1.24 (5H, m), 0.92 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 137.6, 115.3, 108.7, 78.2, 74.9, 71.3, 35.8, 33.8, 33.6, 33.1, 28.4, 25.7, 24.0, 18.4, 13.9, 3.4; MS (ESI): *m/z* = 447 $[M+Na]^+$; HRMS (ESI): calcd for $C_{17}H_{30}IO_4$ [M+H]+: 425.1753; found: 425.1748.

4.1.19. (S)-1-((4R, 5R)-5-(Iodomethyl)-2, 2-dimethyl-1, 3-dioxolan-4-yl) pentan-2-yl hex-5 enoate (**17a**): To a solution of **16a** (0.4 g, 1.27 mmol) in anhydrous THF (10 mL) were added Ph_3P (0.42 g, 1.59 mmol), imidazole (0.130 g, 1.91 mmol), and iodine (0.39 g, 1.52 mmol) simultaneously at 0 ^oC. The mixture was stirred at room temperature for 3 h. When the reaction was complete as monitored by TLC, the mixture was diluted with H_2O (10 mL), and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and saturated aq. $Na_2S_2O_3$ (10 mL), dried over anhydrous Na_2SO_4 and the organic layer was concentrated in vacuo. Column chromatography of the crude residue (60-120 mesh) using hexane/ AcOEt (96:4) afforded the pure iodide **17a** (0.53 g, 98%) as a colorless oil; IR (KBr): 2958, 2827, 1731, 1375, 1169, 1056, 913 cm^{-1}; $[\alpha]D^{27}$ -25.12 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.83-5.74 (1H, m), 5.11-4.97 (3H, m), 4.31-4.25 (1H, m), 4.15-4.10 (1H, m), 3.21-3.11 (2H, m), 2.33-2.28 (2H, m), 2.10 (2H, q, *J* = 7.0 Hz), 1.84-1.69 (3H, m), 1.66-1.51 (3H, m), 1.45 (3H, s), 1.40-1.24 (4H, m), 1.25 (1H, brs), 0.92 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, CDCl3): δ 173.0, 137.6, 115.4, 108.5, 78.2, 74.5, 71.2, 37.0, 33.7, 33.0, 28.4, 25.7, 24.1, 18.4, 13.9, 3.8; MS (ESI): *m/z* = 447 $[M+Na]^+$; HRMS (ESI): calcd for $C_{17}H_{30}IO_4$ $[M+H]^+$: 425.1753; found: 425.1746.

4.1.20. (4R, 6R)-6-Hydroxyoct-7-en-4-yl hex-5-enoate (**5**): To a solution of iodide **17** (0.60 g, 1.41 mmol) in 95% EtOH (15 mL) was added Zn dust (0.46 g, 7.07 mmol) at room temperature and the mixture was stirred at 80 °C for 3 h (TLC monitoring). When the reaction was complete, the reaction mixture was allowed to keep at room temperature and filtered through a short pad of Celite and the Celite pad was washed with AcOEt (2 x 15 mL) and the solvent was evaporated. Column chromatography of the residue (60-120 mesh) using hexane/AcOEt (70:30) furnished **5** (0.31 g, 92%) as a colorless oil; IR (KBr): 3445, 2959, 2930, 1732, 1458, 1248, 1175, 997, 916, 760 cm^{-1}; $[\alpha]D^{27}$ +1.28 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.90-5.73 (2H, m), 5.23 (1H, d, *J* = 17.2 Hz), 5.11 (1H, d, *J* = 10.3 Hz), 5.06-4.97 (3H, m), 4.26-4.16 (1H, m), 2.37-2.25 (2H, m), 2.09 (2H, q, *J* = 7.1 Hz), 2.01 (1H, brs), 1.90-1.78 (1H, m), 1.77-1.69 (2H, m), 1.68-1.63 (1H, brs), 1.62-1.50 (1H, m), 1.47-1.40 (1H, m), 1.40-1.28 (1H, m), 1.25 (1H, brs), 0.91 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5, 140.5, 137.6, 115.3, 114.9, 71.5, 70.5, 41.5, 36.7, 33.8, 33.0, 24.0, 13.8; MS (ESI): *m/z* = 263 $[M+Na]^+$; HRMS (ESI): calcd for $C_{14}H_{25}O_3$ $[M+H]^+$: 241.3839; found: 241.3831.

4.1.21. (4S, 6R)-6-Hydroxyoct-7-en-4-yl hex-5-enoate (**5a**): To a solution of iodide **17a** (0.50 g, 1.18 mmol) in 95% EtOH (15 mL) was added Zn dust (0.38 g, 5.90 mmol) at room temperature and the mixture was stirred at 80 °C for 3 h (TLC monitoring). When the reaction was complete, the reaction mixture was allowed to keep at room temperature and filtered through a short pad of Celite washed with AcOEt (2 x 15 mL) and the solvent was evaporated. Column chromatography of the residue (60-120 mesh) using hexane/AcOEt (70:30) furnished pure compound **5a** (0.26 g, 94%) as a colorless oil; IR (KBr): 3450, 2959, 2929, 1729, 1642, 1178, 994, 754 cm^{-1}; $[\alpha]D^{27}$ -6.66 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.90-5.74 (2H, m), 5.27 (1H, dt, *J* = 17.2, 3.0 Hz), 5.13-5.07 (2H, m), 5.06-4.98 (2H, m), 4.05 (1H, m), 2.36 (2H, t, *J* = 7.3 Hz), 2.11 (2H, q, *J* = 7.1 Hz), 1.76 (2H, q, *J* = 7.6 Hz), 1.73-1.65 (1H, m), 1.65-1.58 (3H, m), 1.56-1.47 (1H, m), 1.39-1.24 (2H, m), 0.91 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.7, 139.9, 137.5, 115.5, 114.4, 71.0, 68.4, 42.4, 36.9, 33.7, 33.0, 24.1, 18.6, 13.8; MS (ESI): *m/z* = 263 $[M+Na]^+$; HRMS (ESI): calcd for $C_{14}H_{25}O_3$ $[M+H]^+$: 241.3839; found: 241.3834.

4.1.22. (7R,9R)-7-Hydroxy-9-propyl-5-nonen-9-olide (Herbarumin-III) (**2**): Grubbs' II generation catalyst (45 mg, 0.05 mmol) was dissolved in dry, deoxygenated CH_2Cl_2 (120 mL). After heating the solution to reflux, diene **5** (0.08 g, 0.33 mmol) dissolved in dry, deoxygenated CH_2Cl_2 (80 mL) was added drop wise over 30 min. The reaction mixture was refluxed for 12 h at 50 ^oC. After completion of the reaction (monitored by TLC), the mixture was concentrated in vacuo, and the residue was purified by column chromatography (60-120 mesh) using hexane/AcOEt (70:30) to afford the pure compound **2** (0.059 g, 84%) as a light yellow oil. IR (KBr): 3461, 2927, 2855, 1728, 1440, 1203, 1094, 986, 771 cm^{-1}; $[\alpha]D^{27}$ +28.00 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.63 (1H, dt, J = 17.0, 1.5 Hz), 5.50-5.41 (1H, m), 5.29-5.22 (1H, m), 4.41 (1H, m), 2.44-2.34 (1H, m), 2.32-2.25 (1H, m), 2.17-2.06 (1H, m), 2.05-1.92 (3H, m), 1.89-1.69 (3H, m), 1.58-1.49 (1H, m), 1.45-1.37 (1H, m), 1.36-1.23 (2H, m), 0.89 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8, 134.5, 124.7, 67.9, 67.7, 40.5, 37.3, 34.5, 33.6, 25.9, 18.3, 13.7; MS (ESI): *m/z* = 235 $[M+Na]^+$; HRMS (ESI): calcd for $C_{12}H_{21}O_3$ $[M+H]^+$: 213.3003; found: 213.2994.

4.1.23. (7R,9S)-7-Hydroxy-9-propyl-5-nonen-9-olide (C-9 epimer of Herbarumin-III) (**2a**): Grubbs' II generation catalyst (45 mg, 0.05 mmol) was dissolved in dry, deoxygenated CH_2Cl_2 (120 mL). After heating the solution to reflux, diene **5a** (0.08 g, 0.33 mmol) dissolved in dry, deoxygenated CH_2Cl_2 (80 mL) was added drop wise over 30 min. The reaction mixture was refluxed

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for 12 h at 50 °C. After completion of the reaction (monitored by TLC), the mixture was concentrated in vacuo, and the residue was purified by column chromatography (60-120 mesh) using hexane, AcOEt (70:30) to afford the pure compound **2a** (0.056 g, 80%) as a light yellow oil; IR (KBr): 3444, 2958, 2930, 1727, 1364, 1211, 1113, 1029, 974, 932 cm^{-1}; $[\alpha]D^{27}$ -14.20 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.52-5.42 (1H, m), 5.08-5.02 (1H, m), 4.11-4.05 (1H, m), 2.36-2.29 (2H, m), 2.07-1.92 (2H, m), 1.91-1.84 (1H, m), 1.84-1.77 (1H, m), 1.77-1.68 (1H, m), 1.64-1.50 (4H, m), 1.49-1.41 (1H, m), 1.38-1.23 (2H, m), 0.90 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.5, 135.8, 131.2, 72.7, 70.9, 41.4, 37.7, 34.6, 33.4, 29.7, 26.3, 18.3, 13.8; MS (ESI): *m/z* = 235 $[M+Na]^+$; HRMS (ESI): calcd for $C_{12}H_{21}O_3$ $[M+H]^+$: 213.3003; found: 213.2998.

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Supporting Information

Supplementary data associated with this article can be found, in the online version.

References and notes

†Part 87 in the series, "Synthetic studies on natural products"

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